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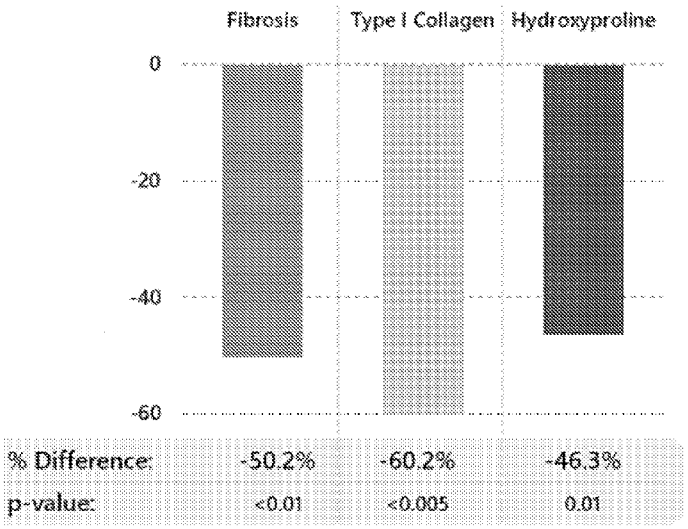


Figure 7

(57) Abstract: The present disclosure is directed to methods of treating fibrotic conditions by administration of TRβ agonists. The disclosure provides methods wherein the abnormal deposition of extracellular matrix components, such as collagen, keratin, or elastin, is reduced, either through interaction of TRβ agonists with TGF-β –dependent inflammatory pathways, or by other mechanisms, thereby ameliorating fibrotic symptoms.

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[Continued on next page]

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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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COMPOSITIONS FOR THE TREATMENT OF FIBROSIS

FIELD

[0001] The compositions and methods of the present disclosure relate generally to the field of treatments for fibrotic disease.

BACKGROUND

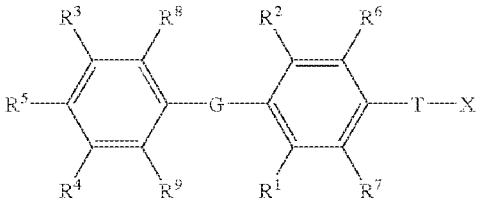
[0002] Fibrosis is a pathogenic hallmark of a vast number of conditions, implicating a wide variety of tissues, among them the liver (e.g., non-alcoholic steatohepatitis, glycogen storage disease type IX, cirrhosis), the lung (e.g., chronic interstitial lung disease, pneumoconiosis, silicosis, emphysema, fibrosing lung diseases, idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia), the vasculature (e.g., diffuse interstitial fibrosis; atherosclerosis), the heart (e.g., cardiac fibrosis; atrial fibrosis; endomyocardial fibrosis), the skin (e.g., keloid lesions, nephrogenic systemic fibrosis, scleroderma), joints and interstitial tissues (e.g., arthrofibrosis, Dupuytren's disease), the pancreas (e.g., pancreatitis), the mouth (e.g., fibrous proliferative lesions of the oral cavity), the gut (e.g., fibrosing strictures, for example, related to Crohn's disease), the brain (glial scarring, leptomeningeal fibrosis associated with bacterial meningitis). Fibrosis may also result from environmental insults or a variety of injuries, such as, for example, exposure to ionizing radiation (such as during cancer treatments), as a result of cystic rupture in the breast, (causing palpable lesions in mammary tissue), and generally as a result of overdeposition of collagen following a wound or tissue insult, such as after injury or surgery.

[0003] While some types of fibrosis involve underlying genetic predispositions (e.g., Dupuytren's disease), most types involve prolonged inflammation of the affected tissue (e.g., hepatic fibroses and pneumoconial fibroses). Symptoms may be as minor as pruritis and aesthetic concerns (e.g., in the case of keloid lesions of the skin) or as significant as pulmonary failure and death (e.g., as terminal symptoms of pulmonary fibroses and cardiac fibroses). While fibrosis is essentially irreversible once established, treatments exist to slow

the progression of various fibrotic conditions, or to ameliorate fibrosis or fibrotic conditions. Current antifibrotic treatments include anti-inflammatory compounds such as pirfenidone and fibroblast growth factor receptor antagonist nintedanib. For dermal and subdermal fibroses, examples of current therapies include surgery, phototherapy and injections of *Clostridium histolyticum* collagenase. However, due to the irreversible nature of the various fibroses, as well as the limited efficacy of current therapies, there remains a need for additional therapeutic approaches to this class of conditions.

SUMMARY

[0004] Disclosed herein are methods of treating fibroses, fibrotic conditions or fibrotic symptoms in a subject in need thereof comprising administering to said subject at least one compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

G is selected from the group consisting of —O—, —S—, —S(=O)—, —S(=O)$_2$—, —Se—, —CH_2—, —CF_2—, —CHF—, —C(O)—, —CH(OH)—, —CH(C_1-C_4 alkyl)-, —CH(C_1-C_4 alkoxy)-, —C(=CH_2)—,—NH—, and —N(C_1-C_4 alkyl)-;

T is selected from the group consisting of —(CR^a_2)$_k$—, —CR^b=CR^b—(CR^a_2)$_n$—, —(CR^a_2)$_n$—CR^b=CR^b—, —(CR^a_2)—CR^b=CR^b—(CR^a_2)—, —O(CR^b_2)(CR^a_2)$_n$—, —S(CR^b_2)(CR^a_2)n—, N(R^c)(CR^b_2)(CR^a_2)$_n$—, N(R^b)C(O)(CR^a_2)$_n$, —C(O)(CR^a_2)$_m$—, —(CR^a_2)$_m$C(O)—, —(CR^a_2)C(O)(CR^a_2)$_n$, —(CR^a_2)$_n$C(O)(CR^a_2)—, and —C(O)NH(CR^b_2)(CR^a_2)$_p$—;

k is an integer from 1-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

each R^a is independently selected from the group consisting of hydrogen, optionally substituted —C_1-C_4 alkyl, halogen, —OH, optionally substituted —O—C_1-C_4 alkyl, —OCF_3, optionally substituted —S—C_1-C_4 alkyl, —NR^bR^c, optionally substituted —C_2-C_4 alkenyl, and optionally substituted —C_2-C_4 alkynyl; with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom;

each R^b is independently selected from the group consisting of hydrogen and optionally substituted —C_1-C_4 alkyl;

each R^c is independently selected from the group consisting of hydrogen and optionally substituted —C_1-C_4 alkyl, optionally substituted —C(O)—C_1-C_4 alkyl, and —C(O)H;

R^1, and R^2 are each independently selected from the group consisting of halogen, optionally substituted —C_1-C_4 alkyl, optionally substituted —S—C_1-C_3 alkyl, optionally substituted —C_2-C_4 alkenyl, optionally substituted —C_2-C_4 alkynyl, —CF_3, —OCF_3, optionally substituted—O—C_1-C_3 alkyl, and cyano;

R^6, R^7, R^8, and R^9 are each independently selected from the group consisting of are each independently selected from the group consisting of hydrogen, halogen, optionally substituted —C C_1-C_4 alkyl, optionally substituted —S—C_1-C_3 alkyl, optionally substituted —C_2-C_4 alkenyl, optionally substituted —C_2-C_4 alkynyl, —CF_3, —OCF_3, optionally substituted—O—C_1-C_3 alkyl, and cyano; or R^6 and T are taken together along with the carbons they are attached to form a ring of 5 to 6 atoms including 0 to 2 heteroatoms independently selected from —NR^i—, —O—, and —S—, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; and X is attached to this ring by a direct bond to a ring carbon, or by —(CR^a_2)— or —C(O)— bonded to a ring carbon or a ring nitrogen;

R^i is selected from the group consisting of hydrogen, —C(O)C_1-C_4 alkyl, —C_1-C_4 alkyl, and —C_1-C_4—aryl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, halogen, —CF_3, —OCF_3, cyano, optionally substituted —C_1-C_{12} alkyl, optionally substituted —C_2-C_{12} alkenyl, optionally substituted —C_2-C_{12} alkynyl, —SR^d, —S(=O)R^e, —$S(=O)_2R^e$, —

$S(=O)_2NR^fR^g$, —C(O)OR^h, —C(O)R^e, —$N(R^b)C(O)NR^fR^g$, —$N(R^b)S(=O)_2R^e$, —$N(R^b)S(=O)_2NR^fR^g$, and —NR^fR^g;

each R^d is selected from the group consisting of optionally substituted —C_1-C_{12} alkyl, optionally substituted —C_2-C_{12} alkenyl, optionally substituted —C_2-C_{12} alkynyl, optionally substituted —$(CR^b_2)_n$ aryl, optionally substituted —$(CR^b_2)_n$ cycloalkyl, optionally substituted —$(CR^b_2)_n$ heterocycloalkyl, and —C(O)NR^fR^g;

each R^e is selected from the group consisting of optionally substituted —C_1-C_{12} alkyl, optionally substituted —C_2-C_{12} alkenyl, optionally substituted —C_2-C_{12} alkynyl, optionally substituted —$(CR^a_2)_n$ aryl, optionally substituted —$(CR^a_2)_n$ cycloalkyl, and optionally substituted —$(CR^a_2)_n$ heterocycloalkyl;

R^f and R^g are each independently selected from the group consisting of hydrogen, optionally substituted —C_1-C_{12} alkyl, optionally substituted —C_2—C_{12} alkenyl, optionally substituted —C_2-C_{12} alkynyl, optionally substituted —$(CR^b_2)_n$ aryl, optionally substituted —$(CR^b_2)_n$ cycloalkyl, and optionally substituted —$(CR^b_2)_n$ heterocycloalkyl, or R^f and R^g may together form an optionally substituted heterocyclic ring, which may contain a second heterogroup selected from the group consisting of O, NR^C, and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted —C_1-C_4 alkyl, —OR^b, oxo, cyano, —CF_3, optionally substituted phenyl, and —C(O)OR^h;

each R^h is selected from the group consisting of optionally substituted —C_1-C_{12} alkyl, optionally substituted —C_2-C_{12} alkenyl, optionally substituted —C_2-C_{12} alkynyl, optionally substituted —$(CR^b_2)_n$ aryl, optionally substituted —$(CR^b_2)_n$ cycloalkyl, and optionally substituted —$(CR^b_2)_n$ heterocycloalkyl;

R^5 is selected from the group consisting of —OH, optionally substituted —OC_1-C_6 alkyl, $OC(O)R^e$, —$OC(O)OR^h$, —F, —$NHC(O)R^e$, —$NHS(=O)R^e$, —$NHS(=O)_2R^e$, —$NHC(=S)NH(R^h)$, and —$NHC(O)NH(R^h)$;

X is $P(O)YR^{11}Y'R^{11}$;

Y and Y′ are each independently selected from the group consisting of —O—, and —NR^v—;

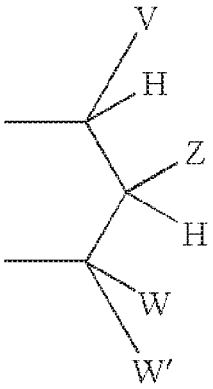
when Y and Y′ are —O—, R^{11} attached to —O— is independently selected from the group consisting of —H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloakyl wherein the cyclic moiety contains a carbonate or

thiocarbonate, optionally substituted -alkylaryl, —$C(R^Z)_2OC(O)NR^Z{}_2$, —NR^Z—C(O)—R^y, —$C(R^Z)_2$—OC(O)R^y, —$C(R^Z)_2$—O—C(O)OR^y, —$C(R^Z)_2OC(O)SR^y$, -alkyl-S—C(O)R^y, -alkyl-S—S-alkylhydroxy, and -alkyl-S—S—S-alkylhydroxy;

when Y and Y′ are —NR^V—, then R^{11} attached to —NR^V— is independently selected from the group consisting of —H, —$[C(R^Z)_2]_q$—$COOR^y$, —$C(R^X)_2COOR^Y$, —$[C(R^Z)_2]_q$—C(O)SR^y, and -cycloalkylene-$COOR^y$;

when Y is —O— and Y′ is NR^V, then R^{11} attached to —O— is independently selected from the group consisting of —H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloakyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, —$C(R^Z)_2OC(O)NR^Z{}_2$, —NR^Z—C(O)—R^y, —$C(R^Z)_2$—OC(O)R^y, —$C(R^Z)_2$—O—C(O)OR^y, —$C(R^Z)_2OC(O)SR^y$, -alkyl-S—C(O)R^y, -alkyl-S—S-alkylhydroxy, and -alkyl-S—S—S-alkylhydroxy; and R^{11} attached to —NR^V— is independently selected from the group consisting of H, —$[C(R^Z)_2]_q$—$COOR^y$, —$C(R^X)_2COOR^y$, —$[C(R^Z)_2]_q$—C(O)SR^y, and -cycloalkylene-$COOR^y$;

or when Y and Y′ are independently selected from —O— and NR^V, then together R^{11} and R^{11} are -alkyl-S—S-alkyl- to form a cyclic group, or together R^{11} and R^{11} are the group:



wherein:

V, W, and W′ are independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted aralkyl, heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, optionally substituted 1-alkenyl, and optionally substituted 1-alkynyl;

or together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, wherein 0-1 atoms are heteroatoms and the remaining atoms are carbon, substituted with hydroxy, acyloxy, alkylthiocarbonyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus;

or together V and Z are connected via an additional 3-5 atoms to form a cyclic group, wherein 0-1 atoms are heteroatoms and the remaining atoms are carbon, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

or together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

or together Z and W are connected via an additional 3-5 atoms to form a cyclic group, wherein 0-1 atoms are heteroatoms and the remaining atoms are carbon, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

or together W and W′ are connected via an additional 2-5 atoms to form a cyclic group, wherein 0-2 atoms are heteroatoms and the remaining atoms are carbon, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of —CHR^zOH, —$CHR^zOC(O)R^y$,—$CHR^zOC(S)R^y$, —$CHR^zOC(S)OR^y$, —$CHR^zOC(O)SR^y$, —$CHR^zOCO_2R^y$, —OR^z, —SR^z, —CHR^zN_3, —CH_2-aryl, —CH(aryl)OH, —$CH(CH{=}CR^z{}_2)OH$, —$CH(C{\equiv}CR^z)OH$, —R^z, —$NR^z{}_2$, —$OCOR^y$, —OCO_2R^y, —$SCOR^y$, —SCO_2R^y, —$NHCOR^z$, —$NHCO_2R^y$, —CH_2NH-aryl, —$(CH_2)q$—OR^z, and —$(CH_2)q$—SR^z;

q is an integer 2 or 3;

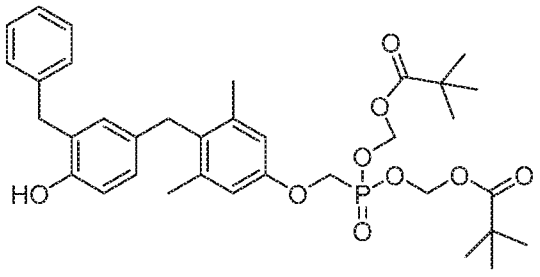
each R^z is selected from the group consisting of R^y and —H;

each R^y is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

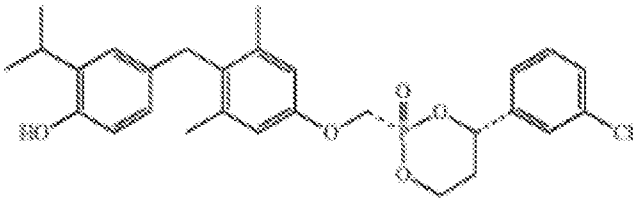
each R^x is independently selected from the group consisting of —H, and alkyl, or together R^x and R^x form a cyclic alkyl group; and

each R^v is selected from the group consisting of —H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl.

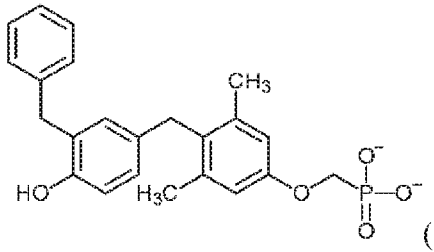
[0005] According to the methods and compositions described herein, the compound to be administered may comprise one or more of the compounds having a structure selected from the group consisting of:



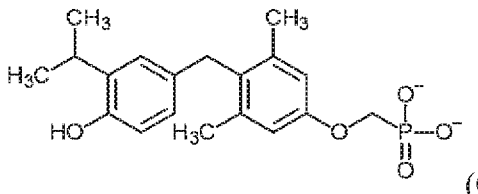
(Compound 1),



(Compound 2),



(Compound 3), and



(Compound 4); or pharmaceutically acceptable salts thereof.

[0006] According to the methods and compositions disclosed herein, the compounds described above may be administered to treat, ameliorate, prevent, or cure one or more fibrotic conditions selected from glycogen storage disease type III (GSD III), glycogen storage disease type VI (GSD VI), glycogen storage disease type IX (GSD IX), non-

alcoholic steatohepatitis (NASH), cirrhosis, hepatitis, scleroderma, alcoholic fatty liver disease, atherosclerosis, asthma, cardiac fibrosis, organ transplant fibrosis, muscle fibrosis, pancreatic fibrosis, bone-marrow fibrosis, liver fibrosis, cirrhosis of liver and gallbladder, fibrosis of the spleen, pulmonary fibrosis, idiopathic pulmonary fibrosis, diffuse parenchymal lung disease, idiopathic interstitial fibrosis, diffuse interstitial fibrosis, interstitial pneumonitis, desquamative interstitial pneumonia, respiratory bronchiolitis, interstitial lung disease, chronic interstitial lung disease, acute interstitial pneumonitis, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, lymphocytic interstitial pneumonia, pneumoconiosis, silicosis, emphysema, interstitial fibrosis, sarcoidosis, mediastinal fibrosis, cardiac fibrosis, atrial fibrosis, endomyocardial fibrosis, renal fibrosis, chronic kidney disease, Type II diabetes, macular degeneration, keloid lesions, hypertrophic scar, nephrogenic systemic fibrosis, injection fibrosis, complications of surgery, fibrotic chronic allograft vasculopathy and/or chronic rejection in transplanted organs, fibrosis associated with ischemic reperfusion injury, post-vasectomy pain syndrome, fibrosis associated with rheumatoid arthritis, arthrofibrosis, Dupuytren's disease, dermatomyositis-polymyositis, mixed connective tissue disease, fibrous proliferative lesions of the oral cavity, fibrosing intestinal strictures, Crohn's disease, glial scarring, leptomeningeal fibrosis, meningitis, systemic lupus erythematosus, fibrosis due to radiation exposure, fibrosis due to mammary cystic rupture, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, psoriasis, or symptoms or sequelae thereof, or other diseases or conditions resulting in the excessive deposition of extracellular matrix components, such as collagen, which may be affected by interventions within the TRβ pathway, or any combination thereof. The methods and compositions according to the present disclosure may comprise a primary fibrosis, or a condition in which said fibrosis, fibrotic condition or fibrotic symptom is secondary to or symptomatic of another condition.

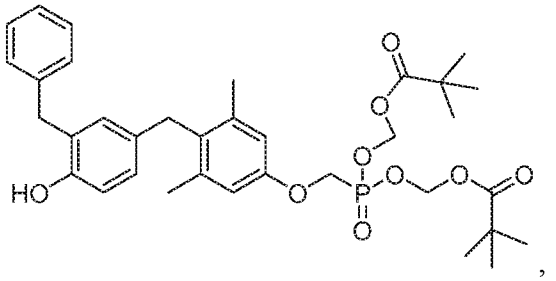
[0007] In some embodiments according to the methods and compositions as disclosed herein, said fibrosis, fibrotic condition or fibrotic symptom may comprise one or more of scleroderma, atherosclerosis, cardiac fibrosis, organ transplant fibrosis, muscle fibrosis, pancreatic fibrosis, bone-marrow fibrosis, liver fibrosis, fibrosis of the spleen, pulmonary fibrosis, idiopathic pulmonary fibrosis, idiopathic interstitial fibrosis, diffuse interstitial fibrosis, interstitial lung disease, chronic interstitial lung disease, pneumoconiosis,

silicosis, interstitial fibrosis, sarcoidosis, mediastinal fibrosis, cardiac fibrosis, atrial fibrosis, endomyocardial fibrosis, renal fibrosis, macular degeneration, keloid lesions, hypertrophic scar, nephrogenic systemic fibrosis, injection fibrosis, fibrotic complications of surgery, fibrotic chronic allograft vasculopathy, fibrosis associated with ischemic reperfusion injury, arthrofibrosis, Dupuytren's disease, fibrous proliferative lesions of the oral cavity, fibrosing intestinal strictures, glial scarring, leptomeningeal fibrosis, fibrosis due to radiation exposure, fibrosis due to mammary cystic rupture, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis or any combination thereof.

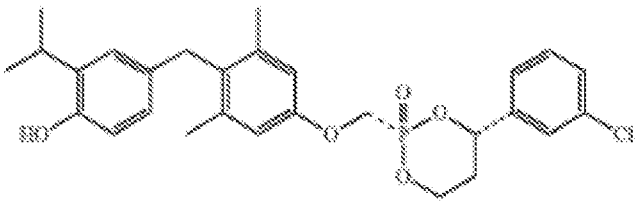
[0008] In some other embodiments, said fibrosis, fibrotic condition or fibrotic symptom may be secondary to one or more of glycogen storage disease type III (GSD III), glycogen storage disease type VI (GSD VI), glycogen storage disease type IX (GSD IX), non-alcoholic steatohepatitis (NASH), cirrhosis, hepatitis, scleroderma, alcoholic fatty liver disease, atherosclerosis, asthma, cirrhosis of the gallbladder, diffuse parenchymal lung disease, interstitial pneumonitis, desquamative interstitial pneumonia, respiratory bronchiolitis, interstitial lung disease, chronic interstitial lung disease, acute interstitial pneumonitis, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, lymphocytic interstitial pneumonia, emphysema, chronic kidney disease, Type II diabetes, macular degeneration, chronic rejection in transplanted organs, post-vasectomy pain syndrome, rheumatoid arthritis, dermatomyositis-polymyositis, mixed connective tissue disease, Crohn's disease, meningitis, systemic lupus erythematosus, or symptoms or sequelae thereof, or other diseases or conditions resulting in the excessive deposition of extracellular matrix components, such as collagen, which may be affected by interventions within the TRβ pathway, or any combination thereof.

[0009] In some other embodiments, said fibrosis, fibrotic condition or fibrotic symptom may comprise a symptom or sequela of GSD III, GSD IX, Non Alcoholic Steatohepatitis, cirrhosis of the liver or pancreas, Dupuytren's disease, scleroderma, idiopathic pulmonary fibrosis, or alcoholic fatty liver disease, or any combination thereof.

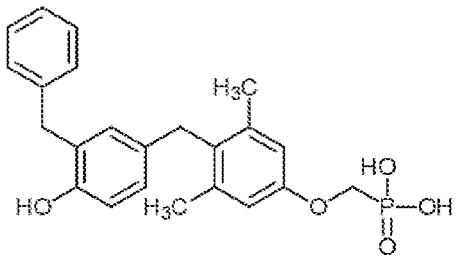
[0010] The methods and compositions of the present disclosure may further comprise a method of treating a fibrosis, a fibrotic condition or a fibrotic symptom in a subject, comprising administering one or more of



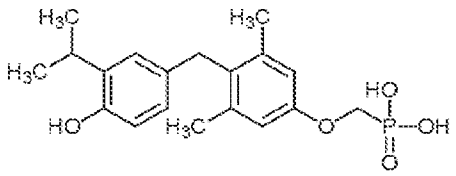
,



,



, or



,

to a subject in need thereof.

[0011] The methods and compositions according to the present disclosure further provide for the administration of one or more of the compounds listed above to a subject, wherein said subject has one or more conditions selected from glycogen storage disease type III (GSD III), glycogen storage disease type VI (GSD VI), glycogen storage disease type IX (GSD IX), hepatitis, scleroderma, atherosclerosis, asthma, cardiac fibrosis, organ transplant fibrosis, muscle fibrosis, pancreatic fibrosis, bone-marrow fibrosis, liver fibrosis, cirrhosis of the gallbladder, fibrosis of the spleen, pulmonary fibrosis, idiopathic pulmonary fibrosis, diffuse parenchymal lung disease, idiopathic interstitial fibrosis, diffuse interstitial fibrosis, interstitial pneumonitis, desquamative interstitial pneumonia, respiratory bronchiolitis,

interstitial lung disease, chronic interstitial lung disease, acute interstitial pneumonitis, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, lymphocytic interstitial pneumonia, pneumoconiosis, silicosis, emphysema, interstitial fibrosis, sarcoidosis, mediastinal fibrosis, cardiac fibrosis, atrial fibrosis, endomyocardial fibrosis, renal fibrosis, chronic kidney disease, Type II diabetes, macular degeneration, keloid lesions, hypertrophic scar, nephrogenic systemic fibrosis, injection fibrosis, complications of surgery, fibrotic chronic allograft vasculopathy and/or chronic rejection in transplanted organs, fibrosis associated with ischemic reperfusion injury, post-vasectomy pain syndrome, fibrosis associated with rheumatoid arthritis, arthrofibrosis, Dupuytren's disease, dermatomyositis-polymyositis, mixed connective tissue disease, fibrous proliferative lesions of the oral cavity, fibrosing intestinal strictures, Crohn's disease, glial scarring, leptomeningeal fibrosis, meningitis, systemic lupus erythematosus, fibrosis due to radiation exposure, fibrosis due to mammary cystic rupture, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, or symptoms or sequelae thereof, or other diseases or conditions resulting in the excessive deposition of extracellular matrix components, such as collagen, which may be affected by interventions within the TRβ pathway, or any combination thereof. The methods and compositions of the present disclosure contemplate said administration wherein the condition is a primary fibrosis, a secondary fibrosis, or a fibrotic symptom of a condition.

[0012] According to the methods and compositions of the present disclosure, a primary fibrosis may comprise one or more of scleroderma, atherosclerosis, cardiac fibrosis, organ transplant fibrosis, muscle fibrosis, pancreatic fibrosis, bone-marrow fibrosis, liver fibrosis, fibrosis of the spleen, pulmonary fibrosis, idiopathic pulmonary fibrosis, idiopathic interstitial fibrosis, diffuse interstitial fibrosis, interstitial lung disease, chronic interstitial lung disease, pneumoconiosis, silicosis, interstitial fibrosis, sarcoidosis, mediastinal fibrosis, cardiac fibrosis, atrial fibrosis, endomyocardial fibrosis, renal fibrosis, macular degeneration, keloid lesions, hypertrophic scar, nephrogenic systemic fibrosis, injection fibrosis, fibrotic complications of surgery, fibrotic chronic allograft vasculopathy, fibrosis associated with ischemic reperfusion injury, arthrofibrosis, Dupuytren's disease, fibrous proliferative lesions of the oral cavity, fibrosing intestinal strictures, glial scarring, leptomeningeal fibrosis,

fibrosis due to radiation exposure, fibrosis due to mammary cystic rupture, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis or any combination thereof.

[0013] According to the methods and compositions of the present disclosure, a secondary fibrosis may comprise a fibrosis associated with one or more of glycogen storage disease type III (GSD III), glycogen storage disease type VI (GSD VI), glycogen storage disease type IX (GSD IX), hepatitis, scleroderma, atherosclerosis, asthma, cirrhosis of the gallbladder, diffuse parenchymal lung disease, interstitial pneumonitis, desquamative interstitial pneumonia, respiratory bronchiolitis, interstitial lung disease, chronic interstitial lung disease, acute interstitial pneumonitis, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, lymphocytic interstitial pneumonia, emphysema, chronic kidney disease, Type II diabetes, macular degeneration, chronic rejection in transplanted organs, post-vasectomy pain syndrome, rheumatoid arthritis, dermatomyositis-polymyositis, mixed connective tissue disease, Crohn's disease, meningitis, systemic lupus erythematosus, or symptoms or sequelae thereof, or other diseases or conditions resulting in the excessive deposition of extracellular matrix components, such as collagen, which may be affected by interventions within the TRβ pathway, or any combination thereof.

[0014] According to the methods and compositions of the present disclosure, a primary fibrosis may comprise a symptom or sequela of GSD III, GSD IX, cirrhosis of the pancreas, Dupuytren's disease, scleroderma, idiopathic pulmonary fibrosis, or alcoholic fatty liver disease, or any combination thereof.

[0015] According to the methods and compositions of the present disclosure, the compositions to be administered may further comprise one or more pharmaceutically acceptable excipients, and may be formulated for oral, intravenous, intraarterial, intestinal, rectal, vaginal, nasal, pulmonary, topical, intradermal, transdermal, transbuccal, translingual, sublingual, or opthalmic administration, or any combination thereof.

[0016] According to the methods and compositions of the present disclosure, a subject to which the compositions listed above are to be administered may show abnormal or excessive deposition of collagen type 1, 1a, or III. In some embodiments according to the methods and compositions of the present disclosure, administration of said composition results in the prevention, amelioration, or cure of said fibrosis, fibrotic condition, or fibrotic

symptom, and may further result in the reduction in the amount of extracellular matrix proteins present in one or more tissues of said subject. In some embodiments, said reduction in the amount of extracellular matrix proteins present in one or more tissues of said subject may comprise a reduction in the amount of collagen present in one or more tissues of said subject, and may further comprise a reduction in the amount of Type I, Type Ia, or Type III collagen present in one or more tissues of said subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0017] Figure 1 shows total liver hydroxyproline content in mice following 8 weeks of treatment with vehicle, low dose Compound 2 (see Example 1), high dose Compound 2 (see Example 1), Compound 1, or elafibranor (control). Compound 2-treated animals show lower total liver hydroxyproline levels than control-treated or mock-treated animals.

[0018] Figure 2 shows representative images of liver stained with Picro-Sirius Red (to visualize collagen I and III deposition, red stain) at the end of the treatment period following 8 weeks of treatment with vehicle, low dose Compound 2 (see Example 1), high dose Compound 2 (see Example 1), Compound 1, or elafibranor (control) (magnification 10x, scale bar = 200 μm).

[0019] Figure 3 shows representative images of liver stained with anti-type I collagen (col1a1) (Southern Biotech, Cat. 131001) at the end of the treatment period following 8 weeks of treatment with vehicle, low dose Compound 2 (see Example 1), high dose Compound 2 (see Example 1), Compound 1, or elafibranor (control) (magnification 20x, scale bar = 100 μm).

[0020] Figure 4 shows total Liver ColA1 content post-biopsy following 8 weeks of treatment with vehicle, low dose Compound 2 (see Example 1), high dose Compound 2 (see Example 1), Compound 1, or elafibranor (control). Compound 2-treated animals show lower total liver ColA1 content than control-treated or mock-treated animals.

[0021] Figure 5 shows liver Picro-Sirius Red (PSR) staining, post-biopsy, as determined by histological quantitative assessment following 8 weeks of treatment with vehicle, low dose Compound 2 (see Example 1), high dose Compound 2 (see Example 1), Compound 1, or elafibranor (control). Total (mg/liver) liver collagen 1 and 3 were determined by morphometry following Picro-Sirius Red staining. Liver sections from Compound-1-treated animals showed lower PSR staining than those from mock-treated animals; liver sections from Compound 2-treated animals showed lower PSR staining than control-treated or mock-treated animals. Data expressed as mean ± SEM (n=11-12).

[0022] Figure 6 shows the percent reduction in total liver triglycerides, cholesterol, and lipids as well as the percent reduction in NAS for Compound 2-treated animals vs. vehicle-treated controls following 8 weeks of dosing with Compound 2 in a diet-induced mouse model of NASH (See Example 6).

[0023] Figure 7 shows the percent reduction in liver fibrosis for Compound 2-treated animals vs. vehicle-treated controls following 8 weeks of dosing with Compound 2 in a diet-induced mouse model of NASH (See Example 6). Liver fibrosis is assessed in terms of fibrosis score, the level of Type I collagen present, and the level of hydroxyproline present in post-treatment liver samples.

[0024] Figure 8 shows the percent reduction in pro-fibrogenic gene expression for Compound 2-treated animals vs. vehicle-treated controls following 8 weeks of dosing with Compound 2 in a diet-induced mouse model of NASH (See Example 6). Pro-fibrogenic gene expression is assessed in terms of the levels of expression of Cola1, Col3a1, αSMA, and Galectin 1 in post-treatment liver samples.

DETAILED DESCRIPTION

[0025] The present disclosure provides compounds and methods for treating fibrosis, fibrotic conditions, or fibrotic symptoms by administering thyroid hormone receptor-β (TRβ) agonists. In some embodiments, such fibrosis, fibrotic conditions, or

conditions giving rise to fibrotic symptoms may include glycogen storage disease type III (GSD III), glycogen storage disease type VI (GSD VI), glycogen storage disease type IX (GSD IX), non-alcoholic steatohepatitis (NASH), cirrhosis, hepatitis, scleroderma, alcoholic fatty liver disease, atherosclerosis, asthma, cardiac fibrosis, organ transplant fibrosis, muscle fibrosis, pancreatic fibrosis, bone-marrow fibrosis, liver fibrosis, cirrhosis of liver and gallbladder, fibrosis of the spleen, scleroderma, pulmonary fibrosis, idiopathic pulmonary fibrosis, diffuse parenchymal lung disease, idiopathic interstitial fibrosis, diffuse interstitial fibrosis, interstitial pneumonitis, desquamative interstitial pneumonia, respiratory bronchiolitis, interstitial lung disease, chronic interstitial lung disease, acute interstitial pneumonitis, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, lymphocytic interstitial pneumonia, pneumoconiosis, silicosis, emphysema, interstitial fibrosis, sarcoidosis, mediastinal fibrosis, cardiac fibrosis, atrial fibrosis, endomyocardial fibrosis, renal fibrosis, chronic kidney disease, Type II diabetes, macular degeneration, keloid lesions, hypertrophic scar, nephrogenic systemic fibrosis, injection fibrosis, complications of surgery, fibrotic chronic allograft vasculopathy and/or chronic rejection in transplanted organs, fibrosis associated with ischemic reperfusion injury, post-vasectomy pain syndrome, fibrosis associated with rheumatoid arthritis, arthrofibrosis, Dupuytren's disease, dermatomyositis-polymyositis, mixed connective tissue disease, fibrous proliferative lesions of the oral cavity, fibrosing intestinal strictures, Crohn's disease, glial scarring, leptomeningeal fibrosis, meningitis, systemic lupus erythematosus, fibrosis due to radiation exposure, fibrosis due to mammary cystic rupture, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, or symptoms or sequelae thereof, or other diseases or conditions resulting in the excessive deposition of extracellular matrix components, such as collagen, which may be affected by interventions within the TRβ pathway. Such conditions may be associated with inflammation and/or injury, and further may involve responses mediated by TGF-β-dependent pathways which can be modulated by thyroid hormones (see, e.g., Alfonso-Merino et al., Proc. Nat. Acad. Sci. 113(24):E3451-60 (2016), which is incorporated herein for its disclosure of the ability of thyroid hormones to modulate TGF-β signaling and related fibrosis in mice). Because TGF-β-dependent pathways are implicated in fibroblast differentiation and the stimulation of collagen production, and thyroid hormones such as T3 and T4 may impinge on these pathways via the TRβ receptor, the present

disclosure provides compositions and methods for the prevention, amelioration, or reduction in collagen deposition in one or more tissues of a subject by administering TRβ agonist compounds.

Definitions

[0026] The term "mammal" is used in its usual biological sense. Thus, it specifically includes humans and non-human mammals such as dogs, cats, horses, donkeys, mules, cows, domestic buffaloes, camels, llamas, alpacas, bison, yaks, goats, sheep, pigs, elk, deer, domestic antelopes, and non-human primates as well as many other species.

[0027] "Subject" as used herein, means a human or a non-human mammal including but not limited to a dog, cat, horse, donkey, mule, cow, domestic buffalo, camel, llama, alpaca, bison, yak, goat, sheep, pig, elk, deer, domestic antelope, or a non-human primate selected for treatment or therapy.

[0028] "Subject suspected of having" means a subject exhibiting one or more clinical indicators of a disease or condition. In certain embodiments, the disease or condition is one or more fibroses, fibrotic conditions, or fibrotic symptoms. In certain embodiments, the disease or condition is scleroderma. In certain embodiments, the disease or condition is non-alcoholic steatohepatitis. In certain embodiments, the disease or condition is cirrhosis. In certain embodiments, the disease or condition is non-alcoholic fatty liver disease. In certain embodiments, the disease or condition is idiopathic pulmonary fibrosis. In certain embodiments, the disease or condition is atherosclerosis. In certain embodiments, the disease or condition is hepatitis, alcoholic fatty liver disease, asthma, cardiac fibrosis, organ transplant fibrosis, muscle fibrosis, pancreatic fibrosis, bone-marrow fibrosis, liver fibrosis, cirrhosis of liver and gallbladder, fibrosis of the spleen, scleroderma, pulmonary fibrosis, diffuse parenchymal lung disease, idiopathic interstitial fibrosis, diffuse interstitial fibrosis; interstitial pneumonitis, desquamative interstitial pneumonia, respiratory bronchiolitis, interstitial lung disease, chronic interstitial lung disease, acute interstitial pneumonitis, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, lymphocytic interstitial pneumonia, pneumoconiosis, silicosis, emphysema, interstitial fibrosis, sarcoidosis, mediastinal fibrosis, cardiac fibrosis, atrial fibrosis, endomyocardial fibrosis, renal fibrosis, chronic kidney disease, Type II diabetes, macular

degeneration, keloid lesions, hypertrophic scar, nephrogenic systemic fibrosis, injection fibrosis, complications of surgery, fibrotic chronic allograft vasculopathy and/or chronic rejection in transplanted organs, fibrosis associated with ischemic reperfusion injury, post-vasectomy pain syndrome, fibrosis associated with rheumatoid arthritis, arthrofibrosis, Dupuytren's disease, dermatomyositis-polymyositis, mixed connective tissue disease, fibrous proliferative lesions of the oral cavity, fibrosing intestinal strictures, Crohn's disease, glial scarring, leptomeningeal fibrosis, meningitis, systemic lupus erythematosus, fibrosis due to radiation exposure, fibrosis due to mammary cystic rupture, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, or symptoms or sequelae thereof, or other diseases or conditions resulting in the excessive deposition of extracellular matrix components.

[0029] As used herein, "fibrosis" refers to the abnormal deposition of extracellular matrix proteins. Such proteins include but are not limited to collagen, elastin, fibronectin, laminin, keratin, keratin, keratin sulfate, fibrin, perlecan, agrin, or agrecan. As used herein, "collagen" refers to any one of the subtypes of collagen, including but not limited to Type I, II, III, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, XIV, XV, XVI, XVII, or XVIII. Exemplary collagen types and subtypes especially include Type I, Type Ia, Type II, Type III, Type IV, and Type V. As used herein, fibrosis may occur by itself or as a symptom or sequela of another condition. As used herein, fibrosis may result from a genetic condition, a genetic predisposition, an environmental insult, an injury, healing of an injury, an autoimmune condition, or a chronic inflammation, a chronic inflammatory condition, or another condition leading to abnormal or excessive deposition of extracellular matrix components. Fibrosis as referred to herein may be assessed by assaying for, or determining the presence or level of, one or more biomarkers. Biomarkers for the presence of fibrosis include, but are not limited to, expression of the Cola1, Col3a1, αSMA, and/or Galectin1 genes or any combination or product thereof. Diagnosis or assessment of fibrosis may further be made by determination of the presence or level of type I collagen and/or hydroxyproline or any combination or product thereof. Diagnosis or assessment of fibrosis may also be made by histological, histochemical, or immunohistochemical analysis of one or more samples from a subject.

[0030] "Glycogen storage disease" means any one or more of a group of disorders marked by dysfunction in the synthesis, transport, or utilization of glycogen,

generally due to the loss of a necessary enzyme activity. Glycogen storage diseases are generally classified by type according to their symptoms and etiologies. Known types include GSD type 0 (aglycogenesis, glycogen synthase deficiency); GSD type 1 (von Gierke disease, glucose-6-phosphatase translocase/transporter deficiency, GSD I); GSD type 2 (Pompe disease, alpha-1-4-glucosidase deficiency, GSD II); GSD type 3 (Cori disease, Forbes disease, limit dextrinosis, debranching enzyme disease; amylo-1-6-glucosidase deficiency due to loss of glucosidase, and/or transferase activity, GSD III); GSD type 4 (Andersen disease, glycogen phosphorylase deficiency, brancher deficiency, amylopectinosis, glycogen branching enzyme deficiency; amylo-1,4 to 1,6 transglucosidase deficiency, GSD IV); GSD type 5 (McArdle disease; glycogen phosphorylase (muscle type) deficiency, GSD V); GSD type 6 (Hers disease; glycogen phosphorylase E (liver type) deficiency, GSD VI); GSD type 7 (Tarui disease; phosphofructokinase deficiency, GSD VII); GSD type 8, 9 (GSD with phosphorylase activation system defects; phosphorylase kinase (liver or muscle isoforms) deficiency, GSD VIII and GSD IX); GSD type 10 (cyclic AMP-dependent kinase deficiency, GSD X); GSD type 11 (Fanconi-Bickel syndrome; glucose transporter type 2 (GLUT2) deficiency, GSD XI); and GSD type 12 (aldolase A deficiency, GSD XII). Subtypes of glycogen storage diseases are also known, in particular GSD 1a, which results from mutations in the gene for glucose-6-phosphatase (G6PC) and leads to, among other symptoms, the excess accumulation of glycogen and lipids in liver tissue, hepatomegaly, hepatic adenomas, and hepatocellular carcinoma. Symptoms of glycogen storage diseases may include elevated or reduced blood sugar, insulin insensitivity, myopathies, as well as hepatic symptoms such as steatosis, hyperlipidemia, hypercholesterolemia, cardiomegaly, hepatomegaly, fibrosis, cirrhosis, hepatocellular adenoma, and hepatocellular carcinoma. Symptoms may also include insulin insensitivity, elevated or reduced blood glucose, renal dysfunction, and/or fibrosis.

[0031] "Subject in need thereof" means a subject identified as in need of a therapy or treatment.

[0032] A therapeutic effect relieves, to some extent, one or more of the symptoms of a disease or disorder, and includes curing the disease or disorder. "Curing" means that the symptoms of active disease are eliminated. However, certain long-term or permanent effects of the disease may exist even after a cure is obtained (such as extensive tissue damage).

[0033] "Treat," "treatment," or "treating," as used herein refers to administering a pharmaceutical composition for prophylactic and/or therapeutic purposes. The term "prophylactic treatment" refers to treating a patient who does not yet have the relevant disease or disorder, but who is susceptible to, or otherwise at risk of, a particular disease or disorder, whereby the treatment reduces the likelihood that the patient will develop the disease or disorder. The term "therapeutic treatment" refers to administering treatment to a patient already having a disease or disorder.

[0034] "Preventing" or "prevention" refers to delaying or forestalling the onset, development or progression of a condition or disease for a period of time, including weeks, months, or years.

[0035] "Amelioration" means a lessening of severity of at least one indicator of a condition or disease. In certain embodiments, amelioration includes a delay or slowing in the progression of one or more indicators of a condition or disease. The severity of indicators may be determined by subjective or objective measures which are known to those skilled in the art.

[0036] "Modulation" means a perturbation of function or activity. In certain embodiments, modulation means an increase in gene expression. In certain embodiments, modulation means a decrease in gene expression. In certain embodiments, modulation means an increase or decrease in total serum levels of a specific protein. In certain embodiments, modulation means an increase or decrease in free serum levels of a specific protein. In certain embodiments, modulation means an increase or decrease in total serum levels of a specific non-protein factor. In certain embodiments, modulation means an increase or decrease in free serum levels of a specific non-protein factor. In certain embodiments, modulation means an increase or decrease in total bioavailability of a specific protein. In certain embodiments, modulation means an increase or decrease in total bioavailability of a specific non-protein factor.

[0037] "Administering" means providing a pharmaceutical agent or composition to a subject, and includes, but is not limited to, administering by a medical professional and self-administering.

[0038] Administration of the compounds disclosed herein or the pharmaceutically acceptable salts thereof can be via any of the accepted modes of administration for agents

that serve similar utilities including, but not limited to, orally, subcutaneously, intravenously, intranasally, topically, transdermally, intraperitoneally, intramuscularly, intrapulmonarilly, vaginally, rectally, or intraocularly. Oral and parenteral administrations are customary in treating the indications that are the subject of the preferred embodiments.

[0039] "Parenteral administration," means administration through injection or infusion. Parenteral administration includes, but is not limited to, subcutaneous administration, intravenous administration, intramuscular administration, intraarterial administration, and intracranial administration.

[0040] "Subcutaneous administration" means administration just below the skin.

[0041] "Intravenous administration" means administration into a vein.

[0042] "Intraarterial administration" means administration into an artery.

[0043] The term "agent" includes any substance, molecule, element, compound, entity, or a combination thereof. It includes, but is not limited to, e.g., protein, polypeptide, peptide or mimetic, small organic molecule, polysaccharide, polynucleotide, and the like. It can be a natural product, a synthetic compound, or a chemical compound, or a combination of two or more substances.

[0044] "Pharmaceutical agent" means a substance that provides a therapeutic effect when administered to a subject.

[0045] "Pharmaceutical composition" means a mixture of substances suitable for administering to an individual that includes a pharmaceutical agent. For example, a pharmaceutical composition may comprise a modified oligonucleotide and a sterile aqueous solution.

[0046] "Active pharmaceutical ingredient" means the substance in a pharmaceutical composition that provides a desired effect.

[0047] The term "pharmaceutically acceptable salt" refers to salts that retain the biological effectiveness and properties of the compounds with which they are associated and, which are not biologically or otherwise undesirable. In many cases, the compounds herein are capable of forming acid and/or base salts by virtue of the presence of phenol and/or phosphonate groups or groups similar thereto. One of ordinary skill in the art will be aware that the protonation state of any or all of these compounds may vary with pH and ionic character of the surrounding solution, and thus the present disclosure contemplates multiple

charge states of each compound. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum, and the like; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like, specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. Many such salts are known in the art, as described in WO 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein in its entirety).

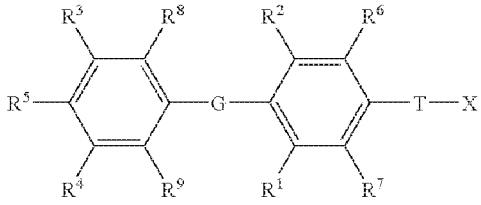
[0048] "Solvate" refers to the compound formed by the interaction of a solvent and an EPI, a metabolite, or salt thereof. Suitable solvates are pharmaceutically acceptable solvates including hydrates.

[0049] The term "atherosclerosis" refers to a condition characterized by irregularly distributed lipid deposits in the intima of large and medium-sized arteries wherein such deposits provoke fibrosis and calcification. Atherosclerosis raises the risk of angina, stroke, heart attack, or other cardiac or cardiovascular conditions.

Compounds

[0050] In some embodiments, the TRβ agonists for use as described herein include compounds according to Formula I:

Formula I:



wherein:

G is selected from the group consisting of —O—, —S—, —S(=O)—, —S(=O)$_2$—, —Se—, —CH_2—, —CF_2—, —CHF—, —C(O)—, —CH(OH)—, —CH(C_1-C_4 alkyl)-, —CH(C_1-C_4 alkoxy)-, —C(=CH_2)—,—NH—, and —N(C_1-C_4 alkyl)-;

T is selected from the group consisting of —($CR^a_{2)k}$—, —CR^b=CR^b—(CR^a_2)$_n$—, —(CR^a_2)$_n$—CR^b=CR^b—, —(CR^a_2)—CR^b=CR^b—(CR^a_2)—, —O(CR^b_2)(CR^a_2)$_n$—, —S(CR^b_2)(CR^a_2)n—, N(R^c)(CR^b_2)(CR^a_2)$_n$—, N(R^b)C(O)(CR^a_2)$_n$, —C(O)(CR^a_2)$_m$—, —(CR^a_2)$_m$C(O)—, —(CR^a_2)C(O)(CR^a_2)$_n$, —(CR^a_2)$_n$C(O)(CR^a_2)—, and —C(O)NH(CR^b_2)(CR^a_2)$_p$—;

k is an integer from 1-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

each R^a is independently selected from the group consisting of hydrogen, optionally substituted —C_1-C_4 alkyl, halogen, —OH, optionally substituted —O—C_1-C_4 alkyl, —OCF_3, optionally substituted —S—C_1-C_4 alkyl, —NR^bR^c, optionally substituted —C_2-C_4 alkenyl, and optionally substituted —C_2-C_4 alkynyl; with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom;

each R^b is independently selected from the group consisting of hydrogen and optionally substituted —C_1-C_4 alkyl;

each R^c is independently selected from the group consisting of hydrogen and optionally substituted —C_1-C_4 alkyl, optionally substituted —C(O)—C_1-C_4 alkyl, and —C(O)H;

R^1, and R^2 are each independently selected from the group consisting of halogen, optionally substituted —C_1-C_4 alkyl, optionally substituted —S—C_1-C_3 alkyl, optionally

substituted —C_2-C_4 alkenyl, optionally substituted —C_2-C_4 alkynyl, —CF_3, —OCF_3, optionally substituted—O—C_1-C_3 alkyl, and cyano;

R^6, R^7, R^8, and R^9 are each independently selected from the group consisting of are each independently selected from the group consisting of hydrogen, halogen, optionally substituted —C C_1-C_4 alkyl, optionally substituted —S—C_1-C_3 alkyl, optionally substituted —C_2-C_4 alkenyl, optionally substituted —C_2-C_4 alkynyl, —CF_3, —OCF_3, optionally substituted—O—C_1-C_3 alkyl, and cyano; or R^6 and T are taken together along with the carbons they are attached to form a ring of 5 to 6 atoms including 0 to 2 heteroatoms independently selected from —NR^i—, —O—, and —S—, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; and X is attached to this ring by a direct bond to a ring carbon, or by —(CR^a_2)— or —C(O)— bonded to a ring carbon or a ring nitrogen;

R^i is selected from the group consisting of hydrogen, —C(O)C_1-C_4 alkyl, —C_1-C_4 alkyl, and —C_1-C_4—aryl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, halogen, —CF_3, —OCF_3, cyano, optionally substituted —C_1-C_{12} alkyl, optionally substituted —C_2-C_{12} alkenyl, optionally substituted —C_2-C_{12} alkynyl, —SR^d, —S(=O)R^e, —$S(=O)_2R^e$, —$S(=O)_2NR^fR^g$, —C(O)OR^h, —C(O)R^e, —$N(R^b)C(O)NR^fR^g$, —$N(R^b)S(=O)_2R^e$, —$N(R^b)S(=O)_2NR^fR^g$, and —NR^fR^g;

each R^d is selected from the group consisting of optionally substituted —C_1-C_{12} alkyl, optionally substituted —C_2-C_{12} alkenyl, optionally substituted —C_2-C_{12} alkynyl, optionally substituted —$(CR^b_2)_n$ aryl, optionally substituted —$(CR^b_2)_n$ cycloalkyl, optionally substituted —$(CR^b_2)_n$ heterocycloalkyl, and —C(O)NR^fR^g;

each R^e is selected from the group consisting of optionally substituted —C_1-C_{12} alkyl, optionally substituted —C_2-C_{12} alkenyl, optionally substituted —C_2-C_{12} alkynyl, optionally substituted —$(CR^a_2)_n$ aryl, optionally substituted —$(CR^a_2)_n$ cycloalkyl, and optionally substituted —$(CR^a_2)_n$ heterocycloalkyl;

R^f and R^g are each independently selected from the group consisting of hydrogen, optionally substituted —C_1-C_{12} alkyl, optionally substituted —C_2—C_{12} alkenyl, optionally substituted —C_2-C_{12} alkynyl, optionally substituted —$(CR^b_2)_n$ aryl, optionally substituted —

$(CR^b_2)_n$ cycloalkyl, and optionally substituted —$(CR^b_2)_n$ heterocycloalkyl, or R^f and R^g may together form an optionally substituted heterocyclic ring, which may contain a second heterogroup selected from the group consisting of O, NR^C, and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted —C_1-C_4 alkyl, —OR^b, oxo, cyano, —CF_3, optionally substituted phenyl, and —$C(O)OR^h$;

each R^h is selected from the group consisting of optionally substituted —C_1-C_{12} alkyl, optionally substituted —C_2-C_{12} alkenyl, optionally substituted —C_2-C_{12} alkynyl, optionally substituted —$(CR^b_2)_n$ aryl, optionally substituted —$(CR^b_2)_n$ cycloalkyl, and optionally substituted —$(CR^b_2)_n$ heterocycloalkyl;

R^5 is selected from the group consisting of —OH, optionally substituted —OC_1-C_6 alkyl, $OC(O)R^e$, —$OC(O)OR^h$, —F, —$NHC(O)R^e$, —$NHS(=O)R^e$, —$NHS(=O)_2R^e$, —$NHC(=S)NH(R^h)$, and —$NHC(O)NH(R^h)$;

X is $P(O)YR^{11}Y'R^{11}$;

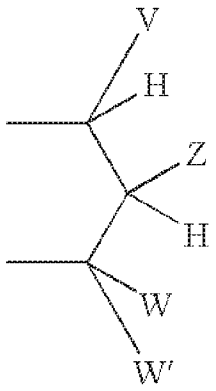
Y and Y′ are each independently selected from the group consisting of —O—, and —NR^v—; when Y and Y′ are —O—, R^{11} attached to —O— is independently selected from the group consisting of —H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloakyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, —$C(R^z)_2OC(O)NR^z_2$, —NR^z—$C(O)$—R^y, —$C(R^z)_2$—$OC(O)R^y$, —$C(R^z)_2$—O—$C(O)OR^y$, —$C(R^z)_2OC(O)SR^y$, -alkyl-S—$C(O)R^y$, -alkyl-S—S-alkylhydroxy, and -alkyl-S—S—S-alkylhydroxy;

when Y and Y′ are —NR^v—, then R^{11} attached to —NR^v— is independently selected from the group consisting of —H, —$[C(R^z)_2]_q$—$COOR^y$, —$C(R^x)_2COOR^Y$, —$[C(R^z)_2]_q$—$C(O)SR^y$, and -cycloalkylene-$COOR^y$;

when Y is —O— and Y′ is NR^v, then R^{11} attached to —O— is independently selected from the group consisting of —H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloakyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, —$C(R^z)_2OC(O)NR^z_2$, —NR^z—$C(O)$—R^y, —$C(R^z)_2$—$OC(O)R^y$, —$C(R^z)_2$—O—$C(O)OR^y$, —$C(R^z)_2OC(O)SR^y$, -alkyl-S—$C(O)R^y$, -alkyl-S—S-alkylhydroxy, and -alkyl-S—S—S-alkylhydroxy; and R^{11} attached to —NR^v— is independently selected from the group

consisting of H, —[$C(R^Z)_2$]$_q$—$COOR^y$, —$C(R^x)_2COOR^y$, —[$C(R^Z)_2$]$_q$—$C(O)SR^y$, and -cycloalkylene-$COOR^y$;

or when Y and Y′ are independently selected from —O— and NR^v, then together R^{11} and R^{11} are -alkyl-S—S-alkyl- to form a cyclic group, or together R^{11} and R^{11} are the group:



wherein:

V, W, and W′ are independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted aralkyl, heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, optionally substituted 1-alkenyl, and optionally substituted 1-alkynyl;

or together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, wherein 0-1 atoms are heteroatoms and the remaining atoms are carbon, substituted with hydroxy, acyloxy, alkylthiocarbonyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus;

or together V and Z are connected via an additional 3-5 atoms to form a cyclic group, wherein 0-1 atoms are heteroatoms and the remaining atoms are carbon, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

or together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

or together Z and W are connected via an additional 3-5 atoms to form a cyclic group, wherein 0-1 atoms are heteroatoms and the remaining atoms are carbon, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

or together W and W′ are connected via an additional 2-5 atoms to form a cyclic group, wherein 0-2 atoms are heteroatoms and the remaining atoms are carbon, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of —CHR^zOH, —$CHR^zOC(O)R^y$,—$CHR^zOC(S)R^y$, —$CHR^zOC(S)OR^y$, —$CHR^zOC(O)SR^y$, —$CHR^zOCO_2R^y$, —OR^z, —SR^z, —CHR^zN_3, —CH_2-aryl, —CH(aryl)OH, —$CH(CH{=}CR^z{}_2)OH$, —$CH(C{\equiv}CR^z)OH$, —R^z, —$NR^z{}_2$, —$OCOR^y$, —OCO_2R^y, —$SCOR^y$, —SCO_2R^y, —$NHCOR^z$, —$NHCO_2R^y$, —CH_2NH-aryl, —$(CH_2)q$—OR^z, and —$(CH_2)q$—SR^z;

q is an integer 2 or 3;

each R^z is selected from the group consisting of R^y and —H;

each R^y is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

each R^x is independently selected from the group consisting of —H, and alkyl, or together R^x and R^x form a cyclic alkyl group;

each R^v is selected from the group consisting of —H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl;

and pharmaceutically acceptable salts thereof.

[0051] In some embodiments, the compound of Formula I has the following provisos:

a) when G is —O—, T is —CH_2—, R^1 and R^2 are each bromo, R^3 is iso-propyl, R^4 is hydrogen, and R^5 is —OH, then X is not $P(O)(OH)_2$ or $P(O)(OCH_2CH_3)_2$;

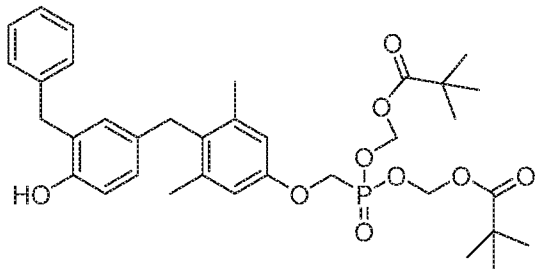
b) V, Z, W, W′ are not all —H; and

c) when Z is —R^z, then at least one of V, W, and W′ is not —H, alkyl, aralkyl, or heterocycloalkyl;

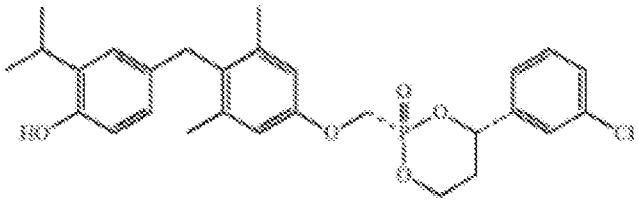
d) when G is —O—, T is —$(CH_2)_{1\text{-}4}$—, R^1 and R^2 are independently halogen, alkyl, and cycloalkyl, R^3 is alkyl, R^4 is hydrogen, and R^5 is —OH, then X is not —$P(O)(OH)_2$ or —$P(O)$(O-lower alkyl)$_2$; and

e) when G is —O—, R^5 is —NHC(O)R^e, —NHS(=O)$_{1-2}R^e$, —NHC(S)NH(R^b), or —NHC(O)NH(R^h), T is —$(CH_2)^m$-, —CH=CH—, —O$(CH_2)_{1-2}$—, or —NH$(CH_2)_{1-2}$—, then X is not —P(O)$(OH)_2$ or —P(O)(OH)NH_2.

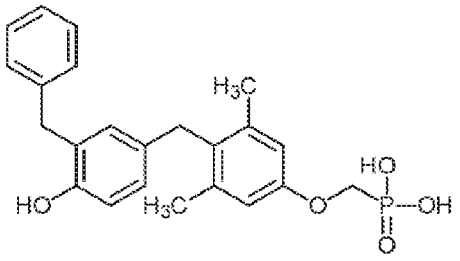
[0052] In some embodiments, the compound is selected from one or more of the following:



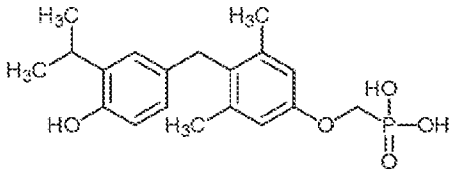
(Compound 1),



(Compound 2),



(Compound 3), or

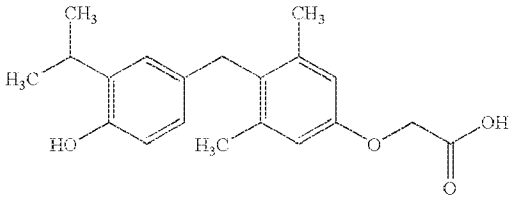
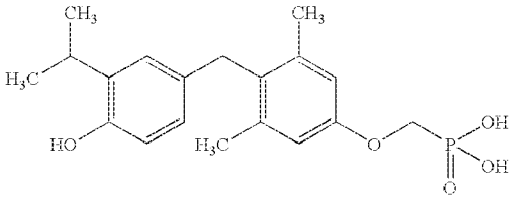
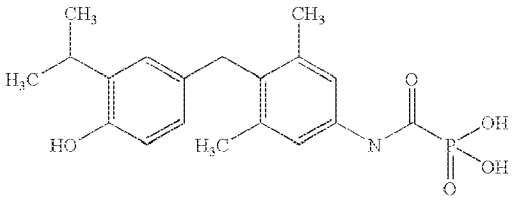
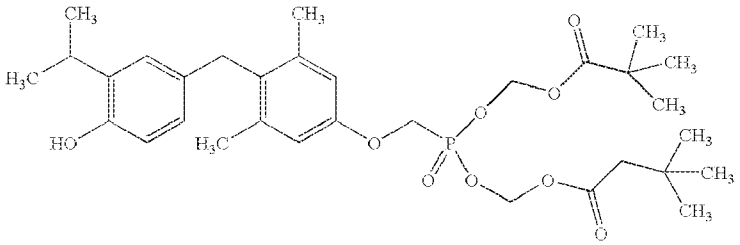
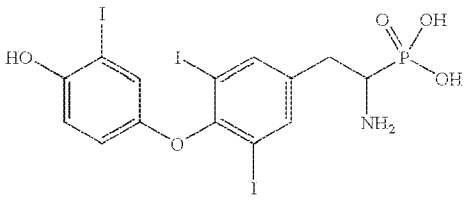
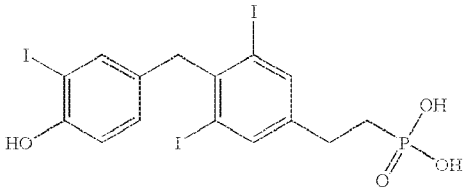
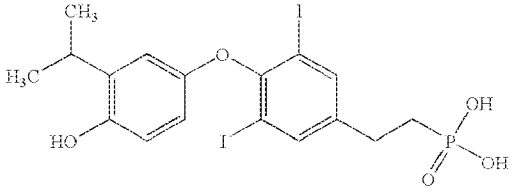


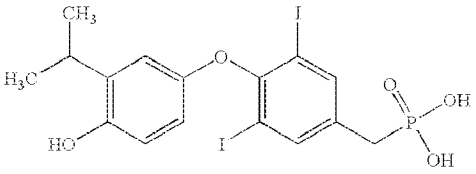
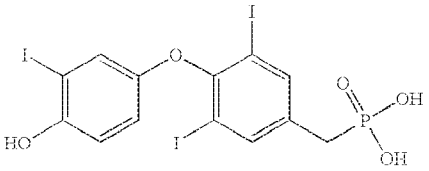
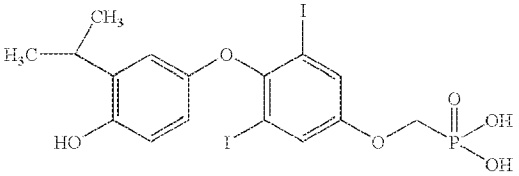
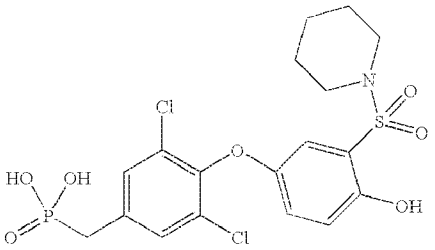
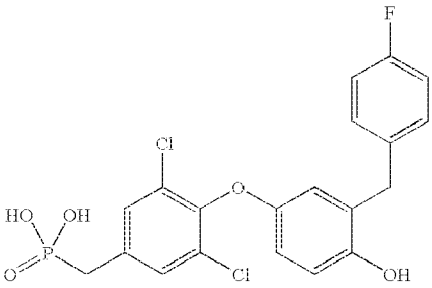
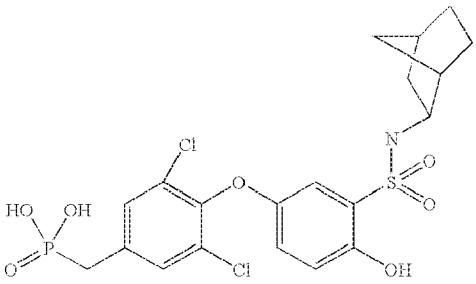
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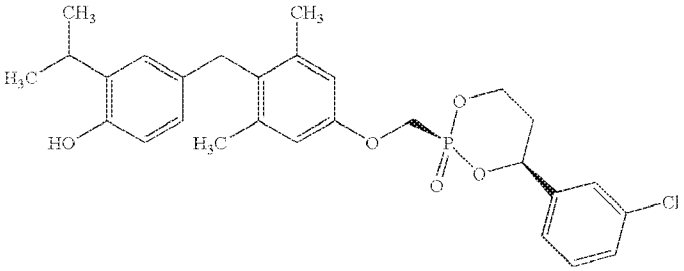
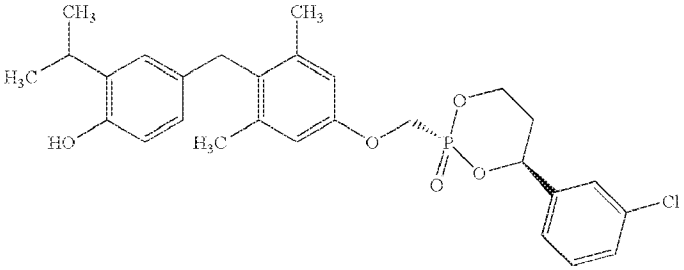
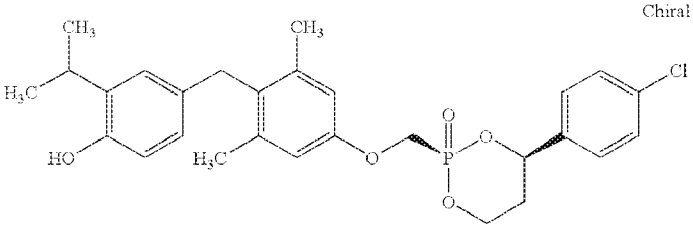
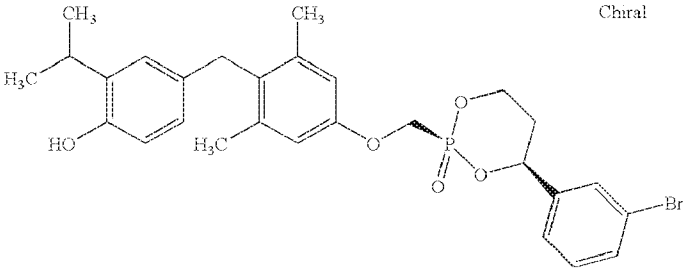
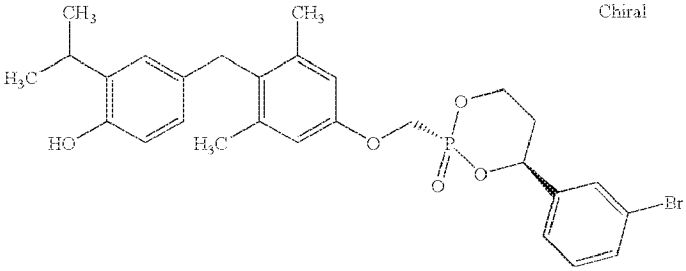
or pharmaceutically acceptable salts thereof.

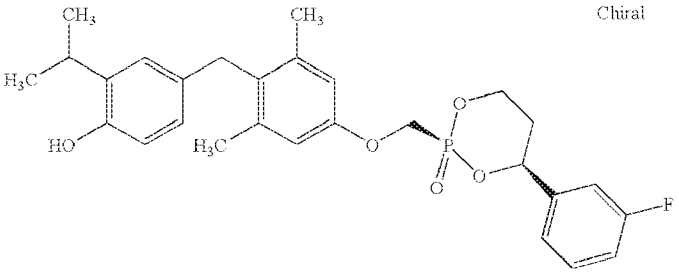
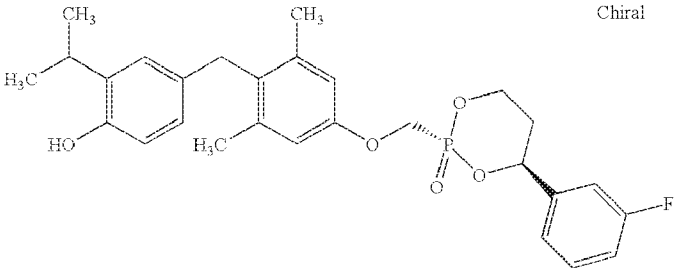
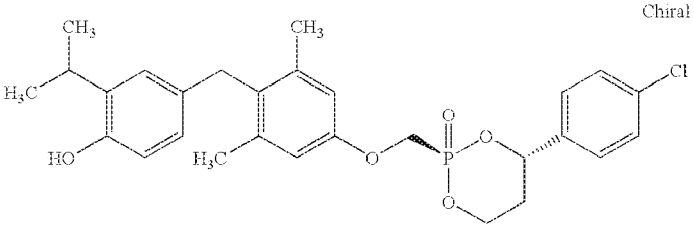
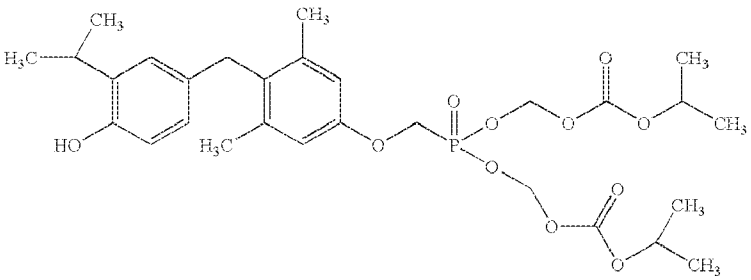
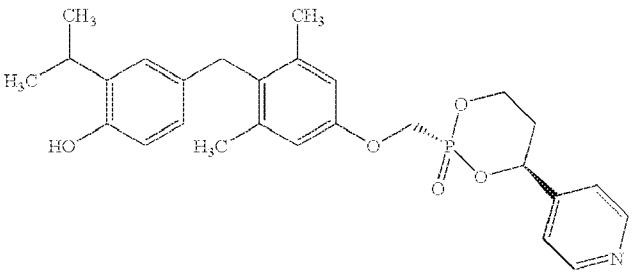
[0053] In other embodiments, the compound is selected from:

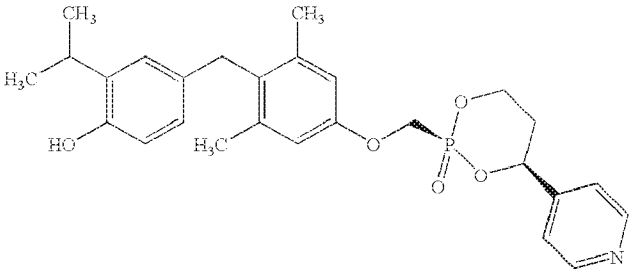
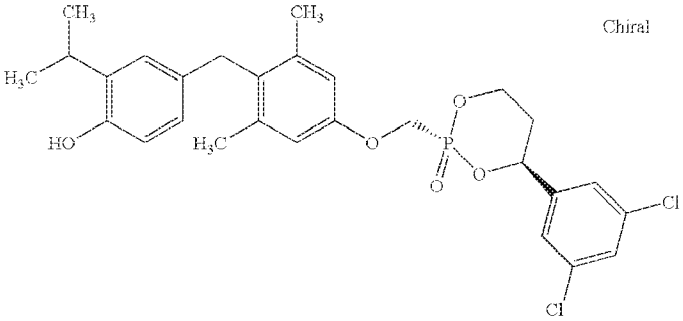
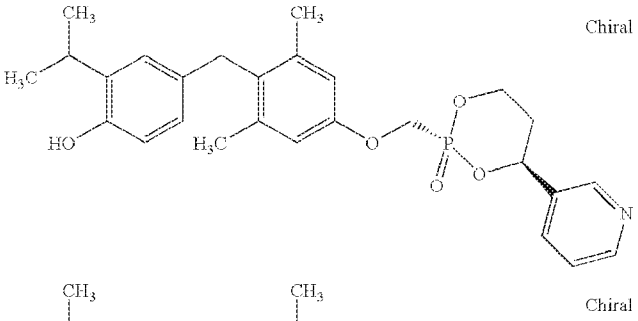
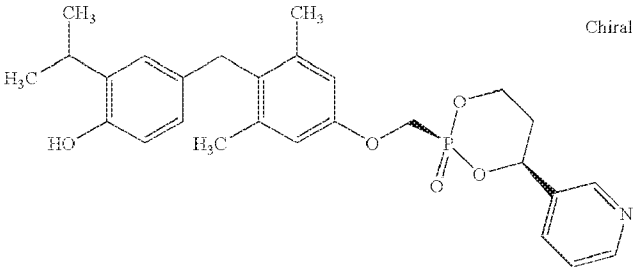
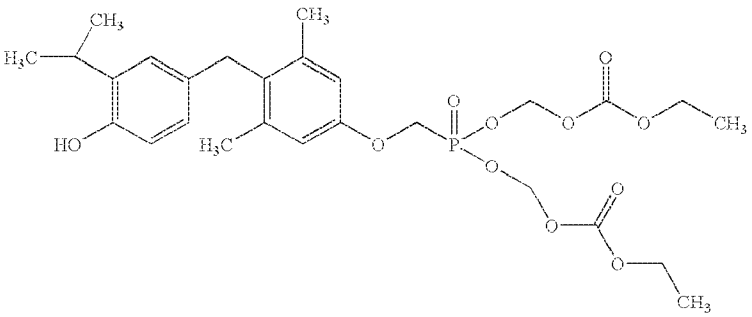
Structure Compound Number

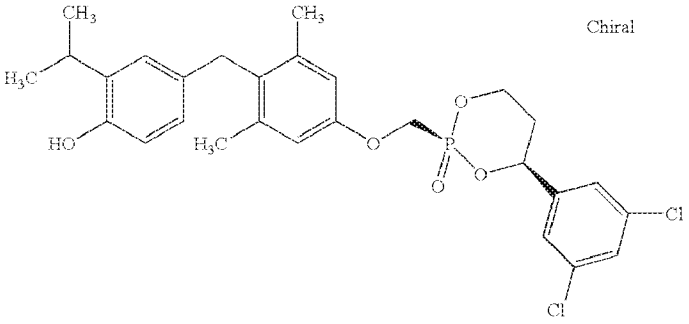
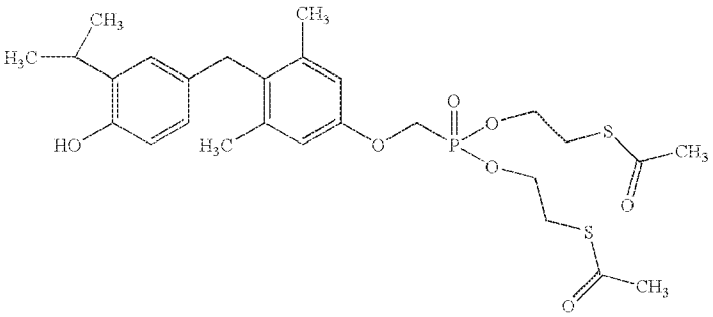
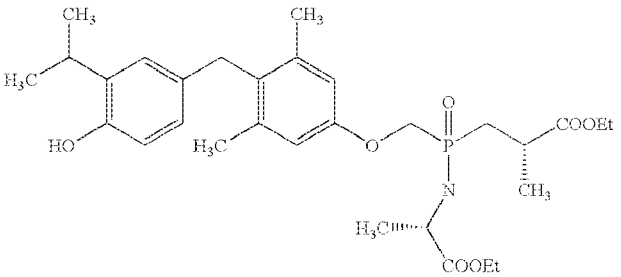
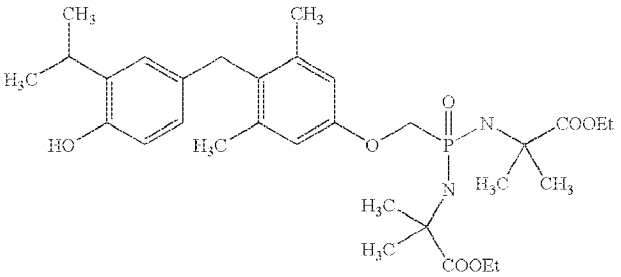
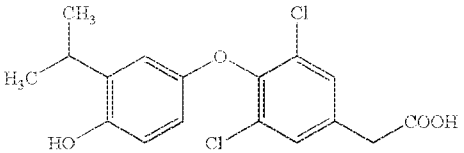
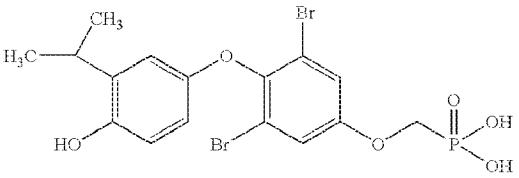
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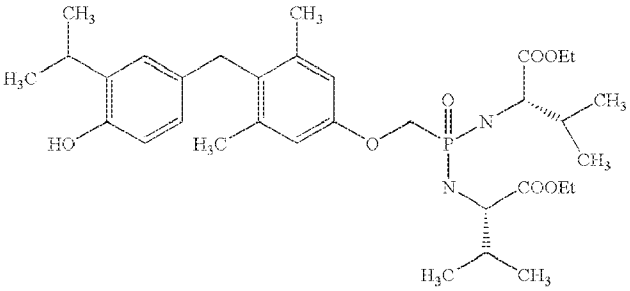
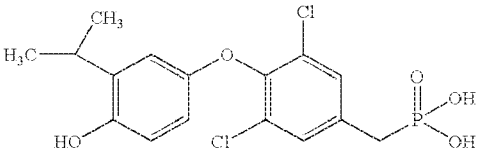
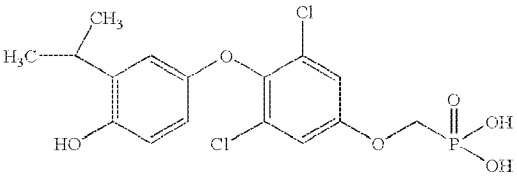
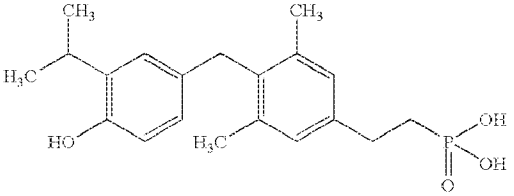
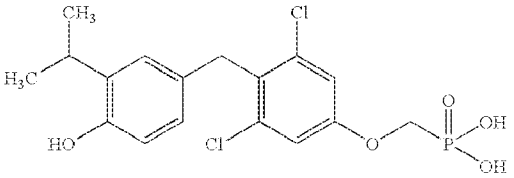
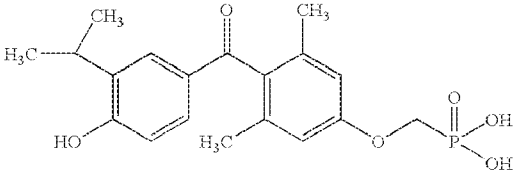
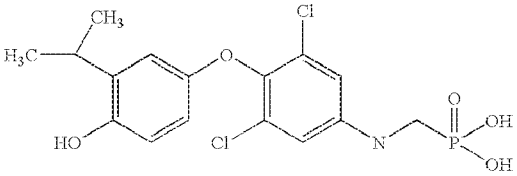
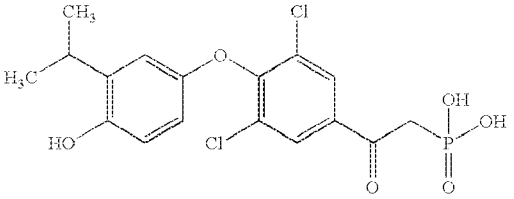
Structure	Compound Number
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	11
	10

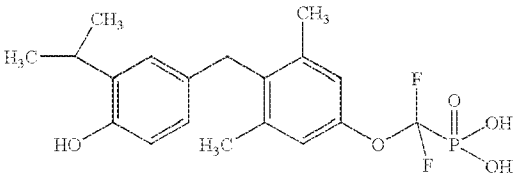
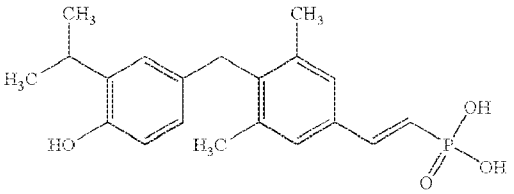
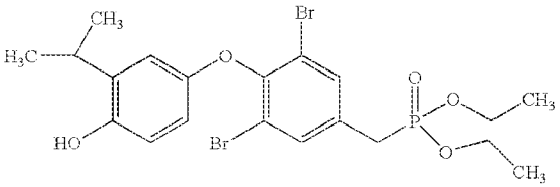
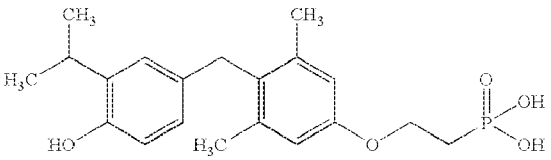
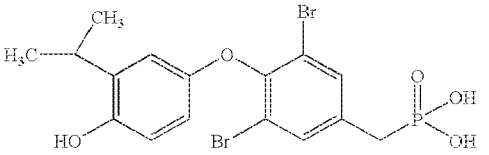
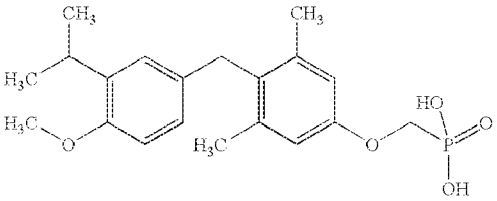
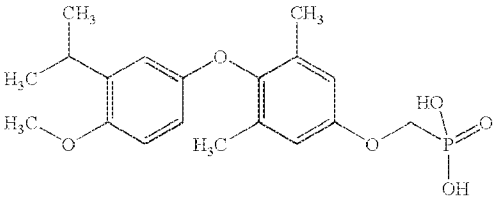
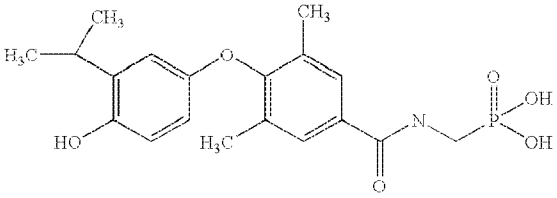
Structure	Compound Number
	cis-13-1
 Chiral	trans-13-1
 Chiral	cis-13-6
 Chiral	cis-13-2
	trans-13-2

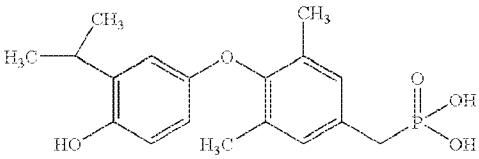
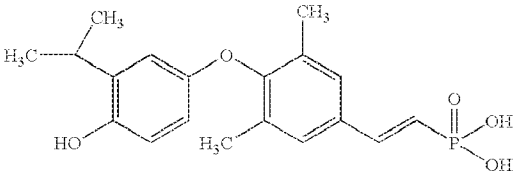
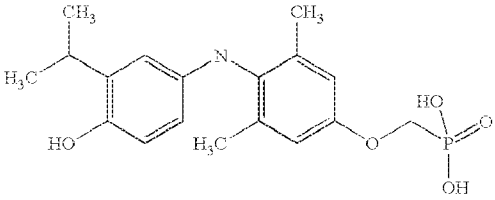
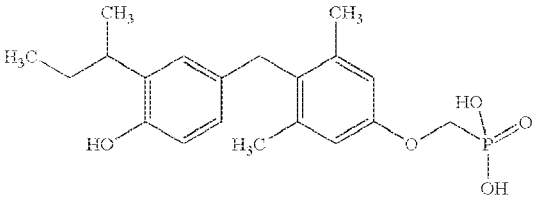
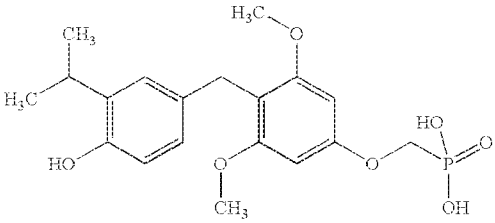
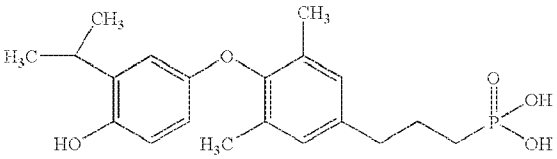
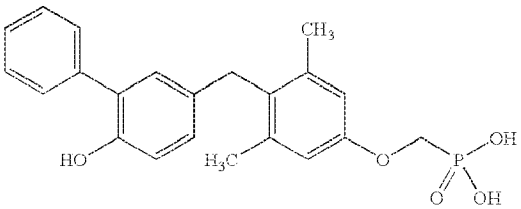
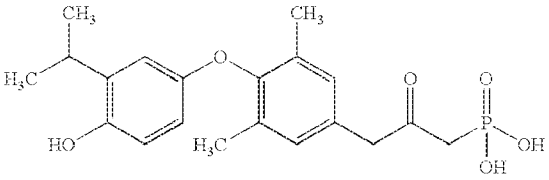
Structure	Compound Number
	cis-13-3
	trans-13-3
	trans-13-6
	12-3
	trans-13-5

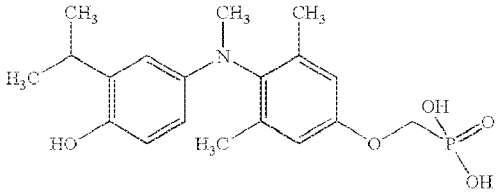
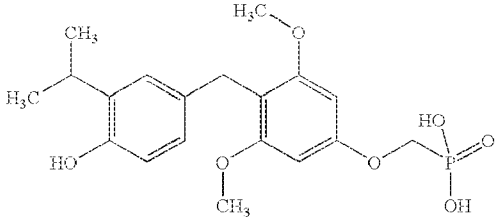
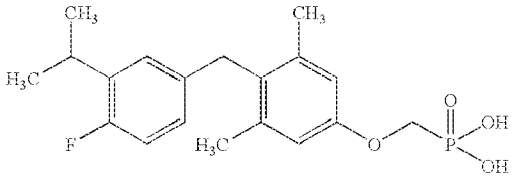
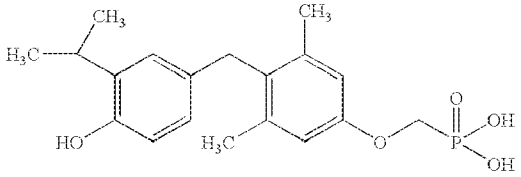
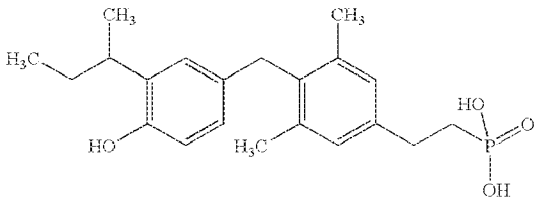
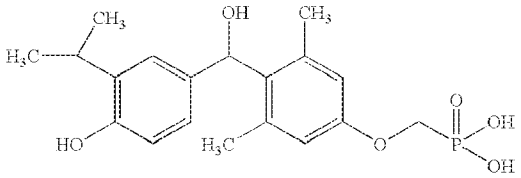
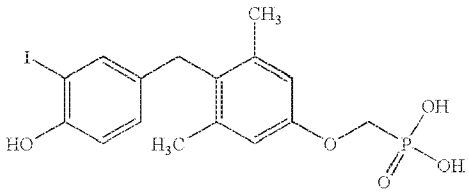
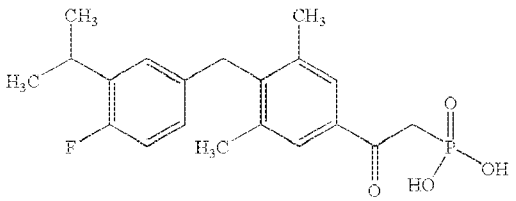
Structure	Compound Number
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 Chiral	trans-13-7
 Chiral	trans-13-4
	cis-13-4
	12-2

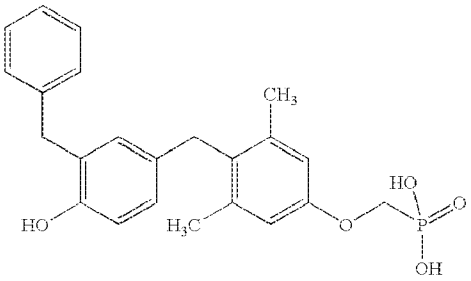
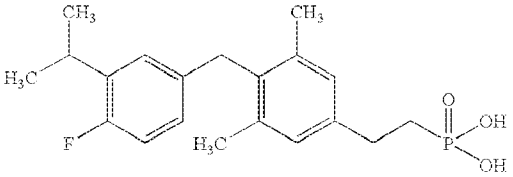
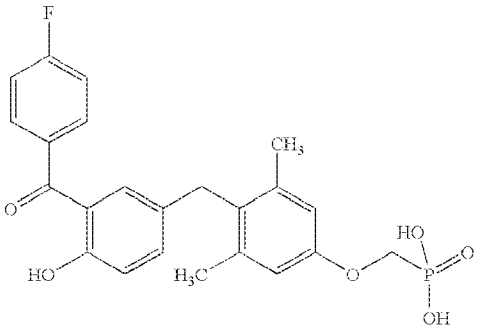
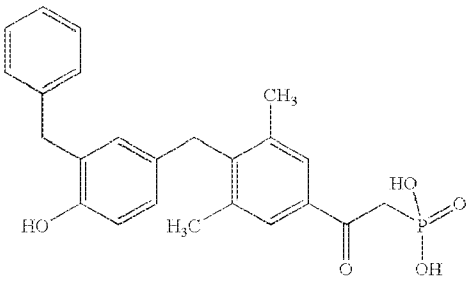
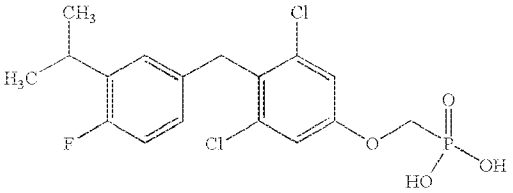
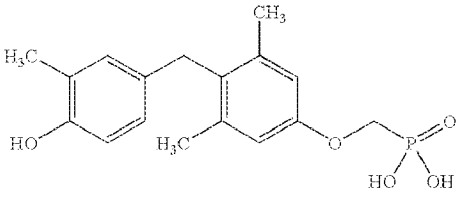
Structure	Compound Number
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	14
	15-1
	15-2
	18
	8-1

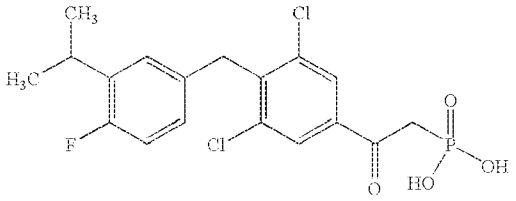
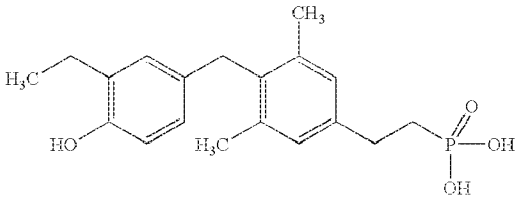
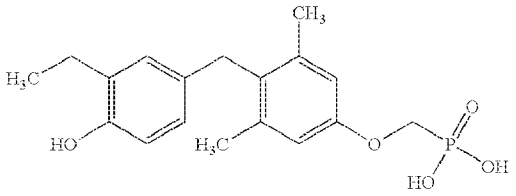
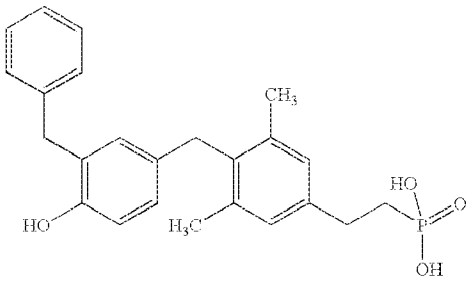
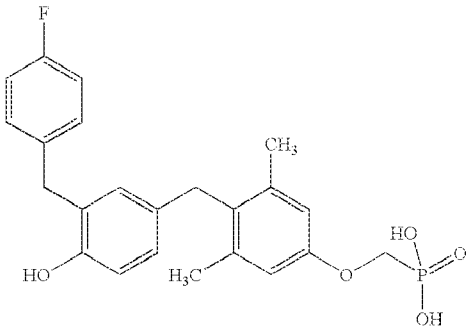
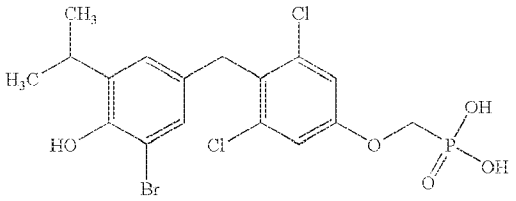
Structure	Compound Number
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	19
	8-2
	24-1
	7-5
	25
	22
	21

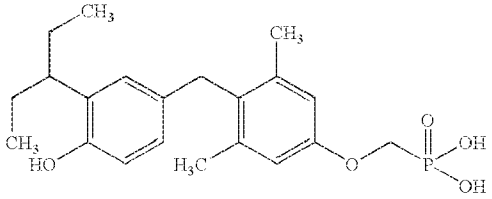
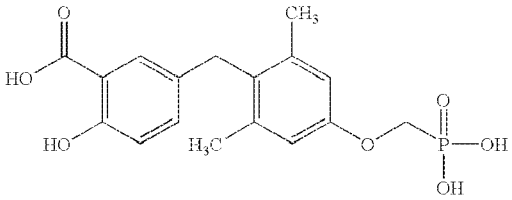
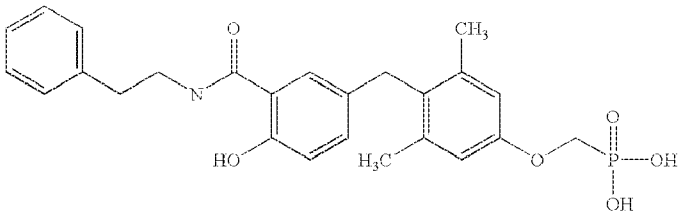
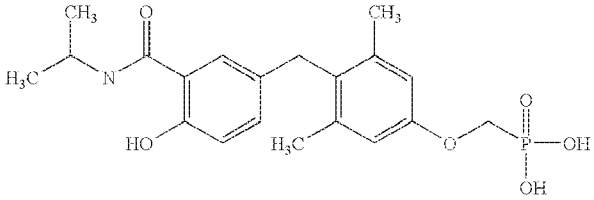
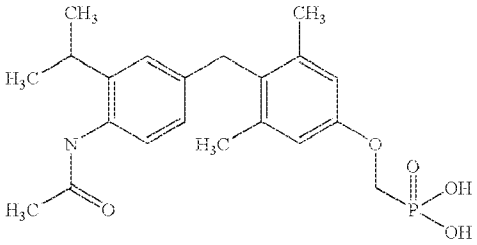
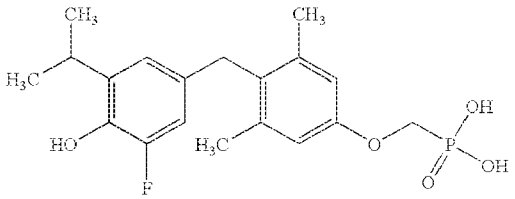
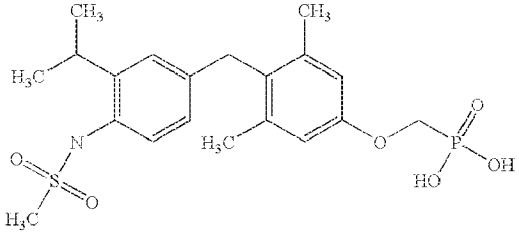
Structure	Compound Number
	7-6
	24-2
	19-1
	26
	19-2
	7-4
	30
	23

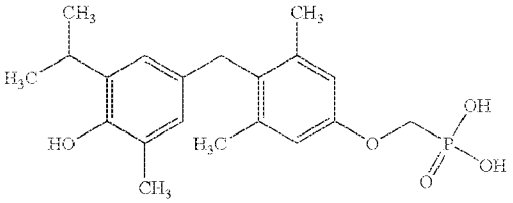
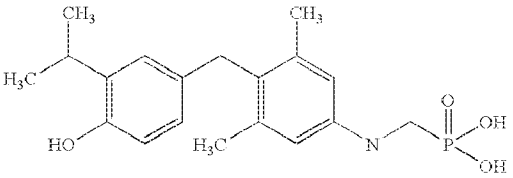
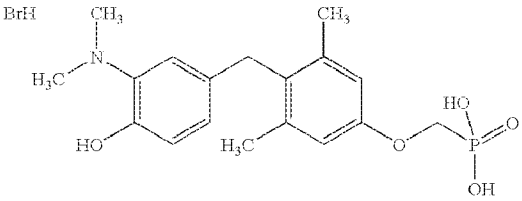
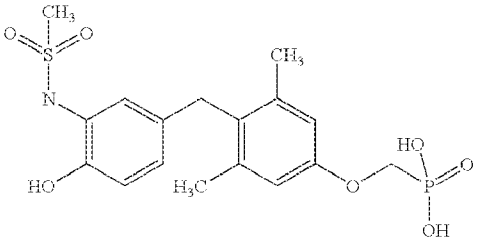
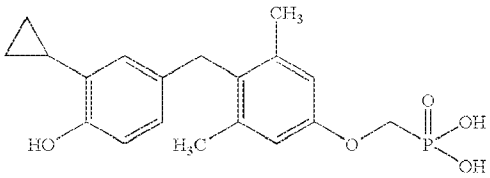
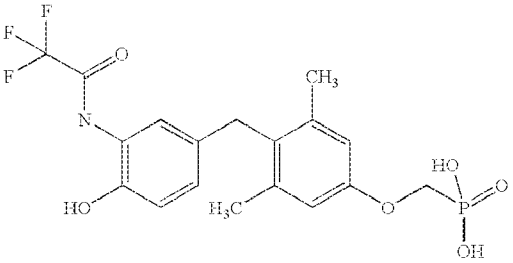
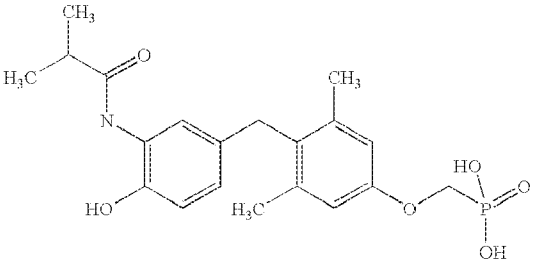
Structure	Compound Number
	19-3
	28
	20
	7-3
	7-2
	29
	7-1
	32

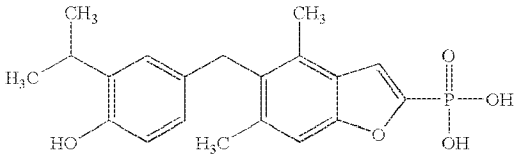
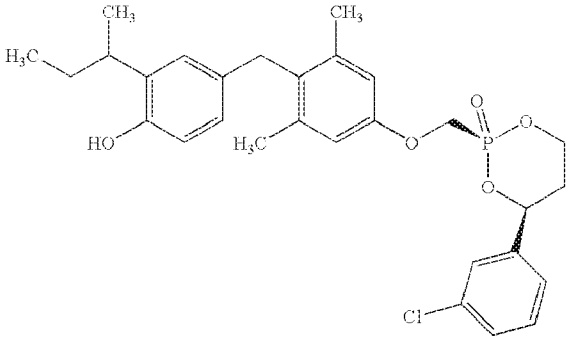
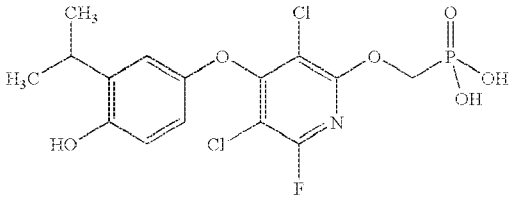
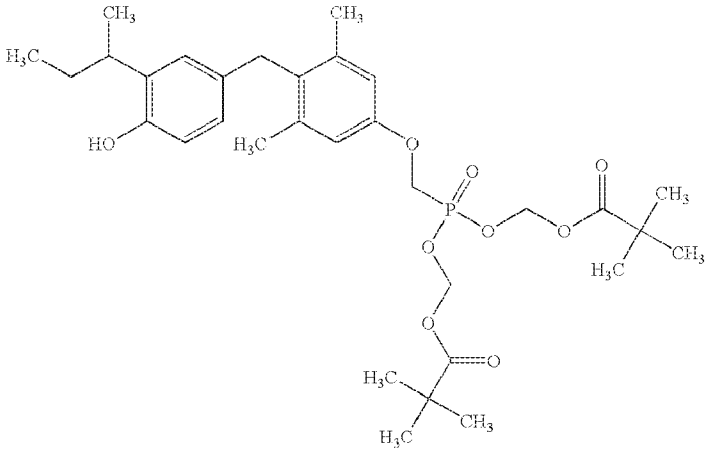
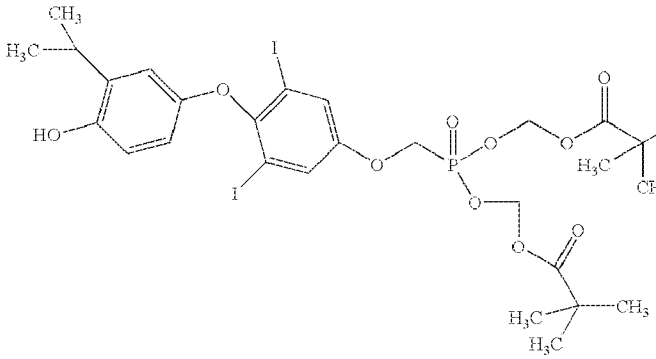
Structure	Compound Number
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	24
	27
	31
	24-3
	33
	34
	41-2

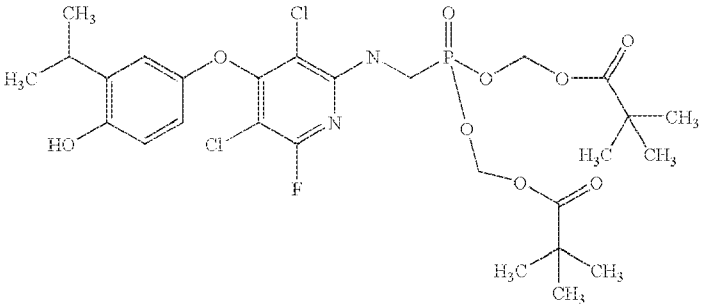
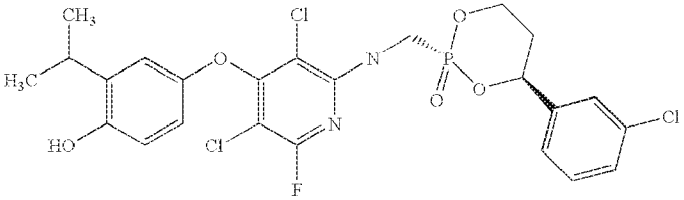
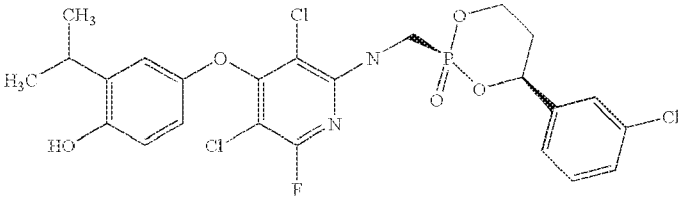
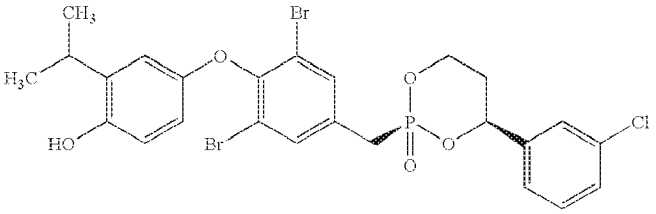
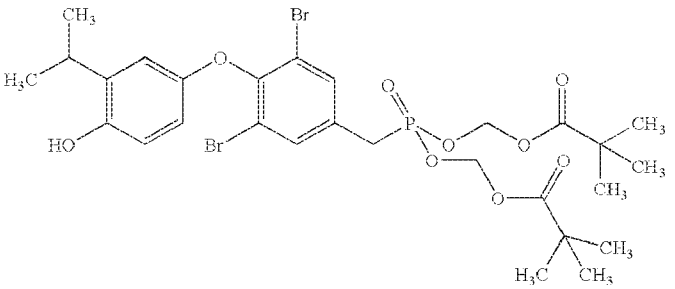
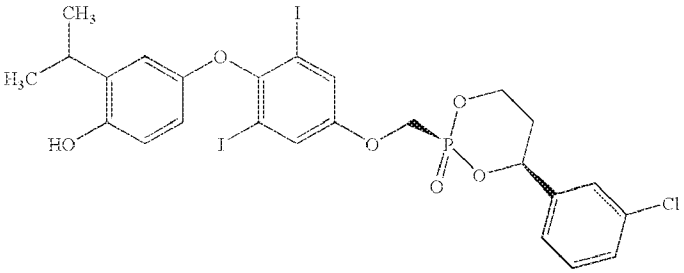
Structure	Compound Number
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	42-2
	39
	41
	27-2
	7-7

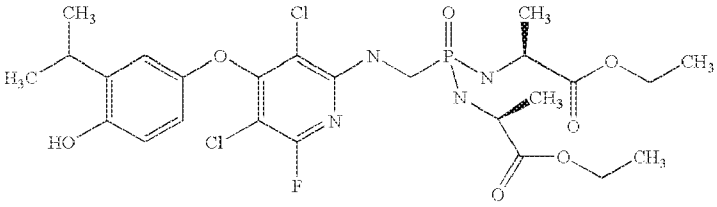
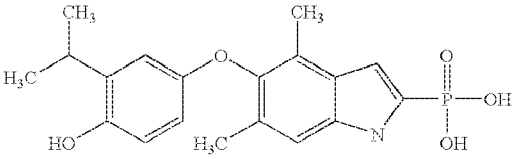
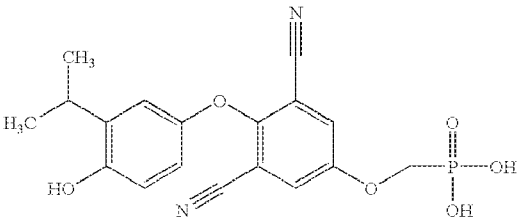
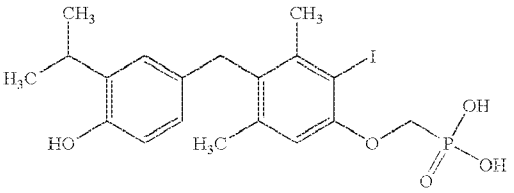
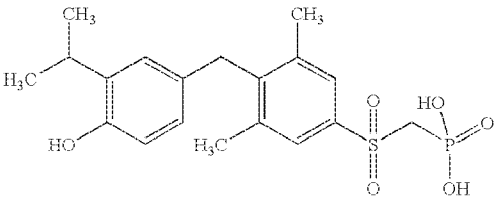
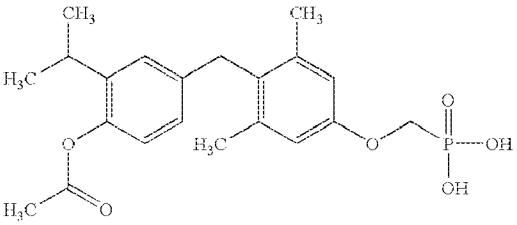
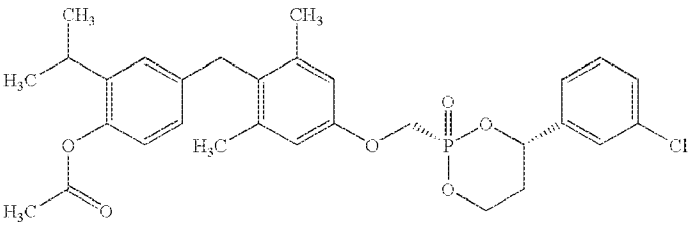
Structure	Compound Number
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	24-4
	7-8
	42
	40
	7-14

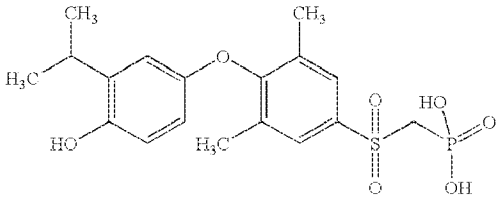
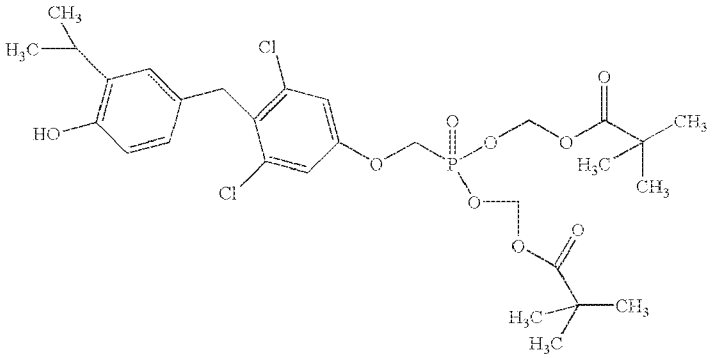
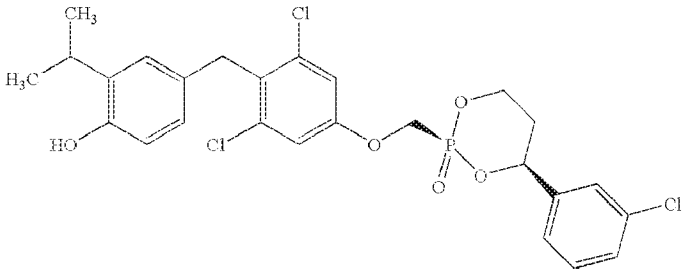
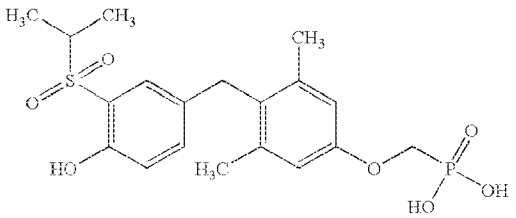
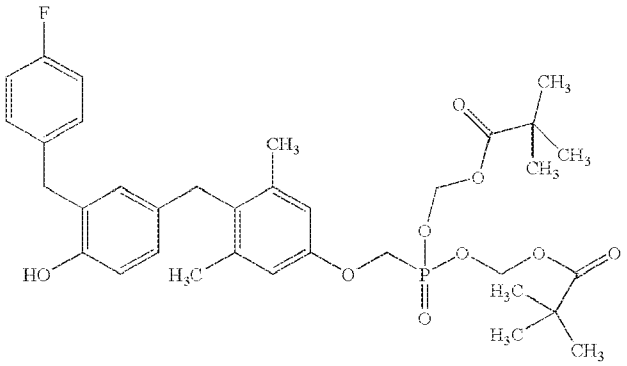
Structure	Compound Number
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	35
	37
	36
	7-12
	7-11
	7-13

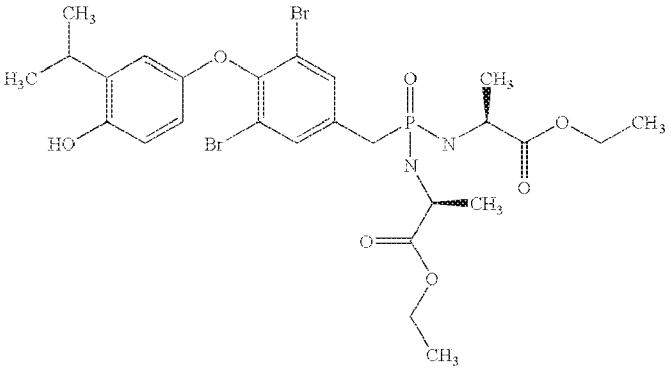
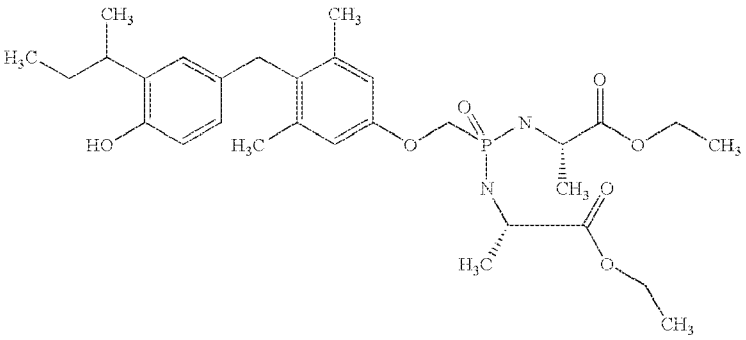
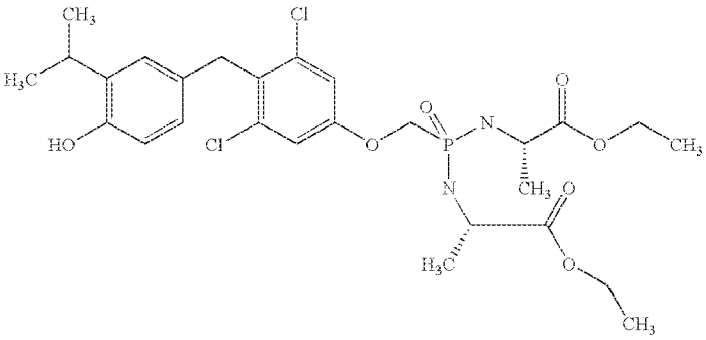
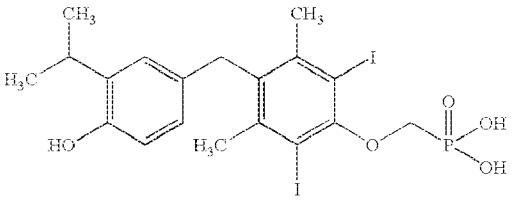
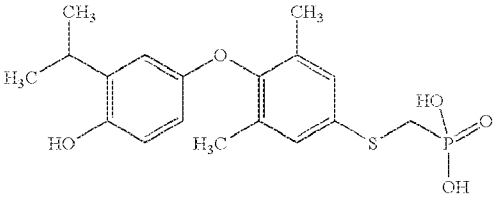
Structure	Compound Number
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	47
	49
	51-1
	48
	51-2
	51-3

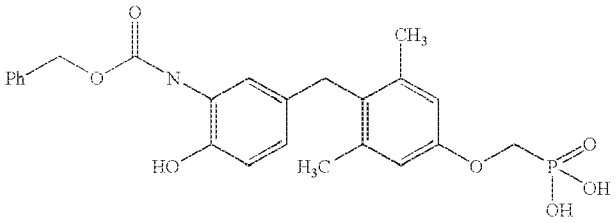
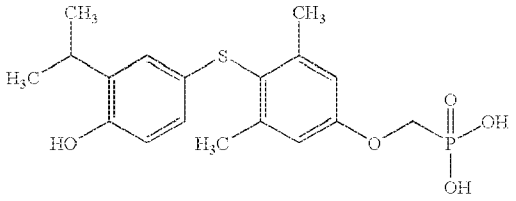
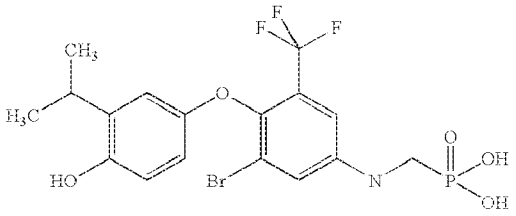
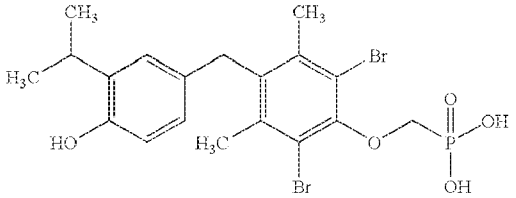
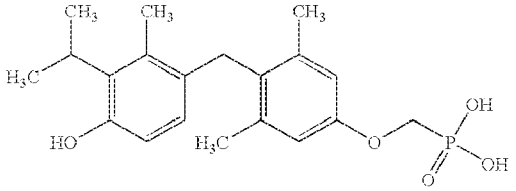
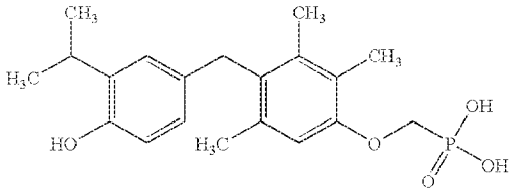
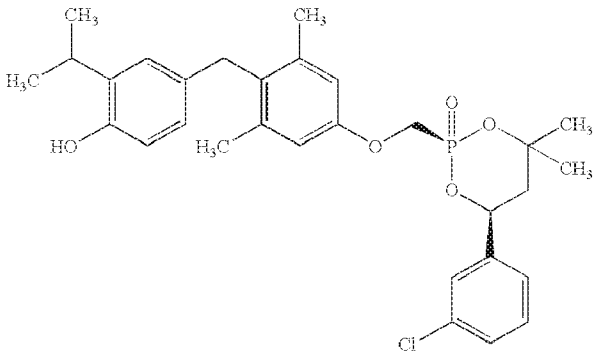
Structure	Compound Number
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	13-8
	57
	12-4
	12-7

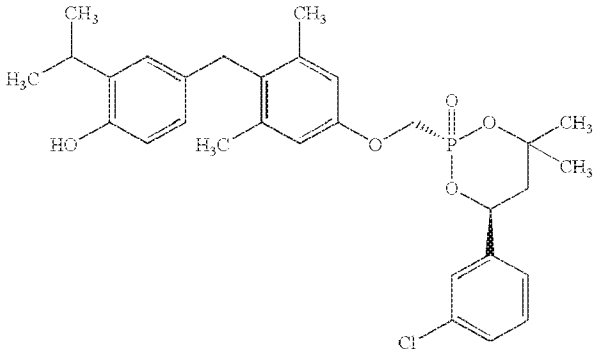
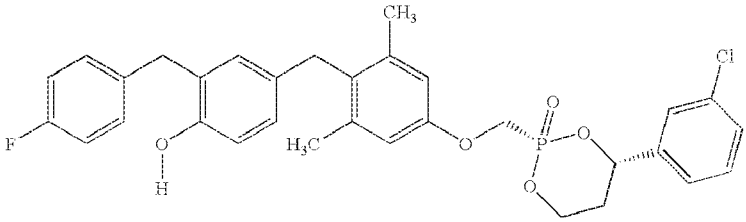
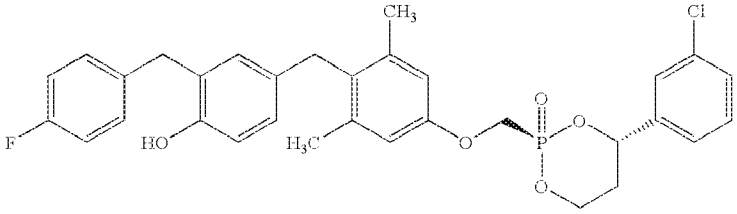
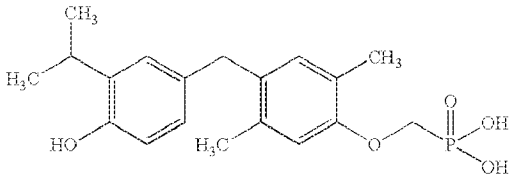
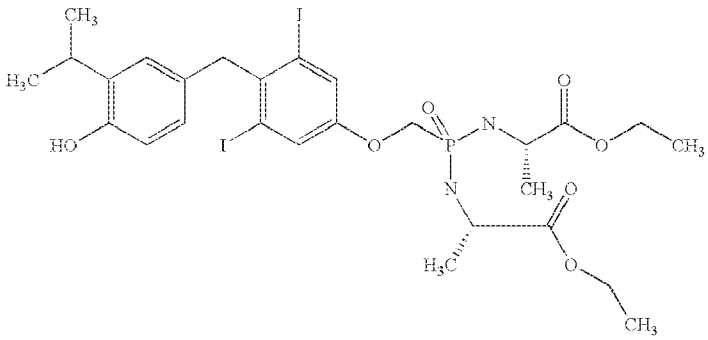
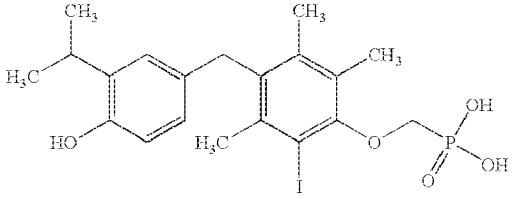
Structure	Compound Number
	12-9
	13-12-trans
	13-12-cis
	13-9
	12-5
	13-10

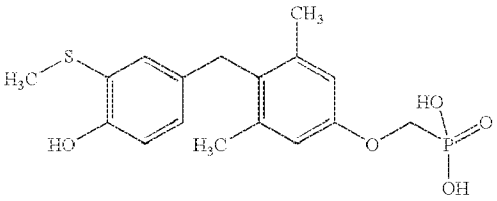
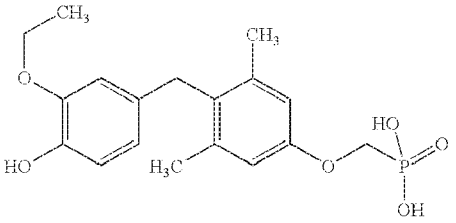
Structure	Compound Number
	15-6
	66
	56
	46
	52
	58
	59

Structure	Compound Number
	53
	12-8
	13-11
	44
	12-6

Structure	Compound Number
	15-5
	15-4
	15-7
	65-1
	54

Structure	Compound Number
	50
	43
	63
	65-2
	7-16
	61
	13-13-cis

Structure	Compound Number
	13-13-trans
	13-14-cis
	13-14-trans
	7-17
	15-8
	62

Structure	Compound Number
	55
	7-15

or pharmaceutically acceptable salts thereof.

[0054] The compounds described above may be prepared according to known methods, including those described in U.S. Patent No. 7,829,552, which is incorporated herein by reference in its entirety. Additional TRβ agonists are described in U.S. Patent No. 7,514,419; U.S. Application Publication No. 2009/002895; U.S. Application Publication No. 2010/0081634; U.S Application Publication No. 2012/0046364; and PCT Application Publication No. WO 2011/038207, all of which are incorporated herein by reference in their entirety.

Pharmaceutical Compositions

[0055] The compounds useful as described above can be formulated into pharmaceutical compositions for use in treatment of the conditions described herein. Standard pharmaceutical formulation techniques are used, such as those disclosed in Remington's The Science and Practice of Pharmacy, 21st Ed., Lippincott Williams & Wilkins (2005), incorporated herein by reference in its entirety. Accordingly, some embodiments include pharmaceutical compositions comprising: (a) a safe and therapeutically effective amount of a compound described herein, or pharmaceutically acceptable salts thereof; and (b) a pharmaceutically acceptable carrier, diluent, excipient or combination thereof.

[0056] The term "pharmaceutically acceptable carrier" or "pharmaceutically acceptable excipient" includes any and all solvents, diluents, emulsifiers, binders, buffers, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption

delaying agents and the like, or any other such compound as is known by those of skill in the art to be useful in preparing pharmaceutical formulations. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions. In addition, various adjuvants such as are commonly used in the art may be included. These and other such compounds are described in the literature, e.g., in the Merck Index, Merck & Company, Rahway, NJ. Considerations for the inclusion of various components in pharmaceutical compositions are described, e.g., in Gilman et al. (Eds.) (1990); Goodman and Gilman's: The Pharmacological Basis of Therapeutics, 8th Ed., Pergamon Press.

[0057] Some examples of substances, which can serve as pharmaceutically-acceptable carriers or components thereof, are sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and methyl cellulose; powdered tragacanth; malt; gelatin; talc; solid lubricants, such as stearic acid and magnesium stearate; calcium sulfate; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil, corn oil and oil of theobroma; polyols such as propylene glycol, glycerine, sorbitol, mannitol, and polyethylene glycol; alginic acid; emulsifiers, such as the TWEENS; wetting agents, such as sodium lauryl sulfate; coloring agents; flavoring agents; tableting agents, stabilizers; antioxidants; preservatives; pyrogen-free water; isotonic saline; and phosphate buffer solutions.

[0058] The choice of a pharmaceutically-acceptable carrier to be used in conjunction with the subject compound is determined by the way the compound is to be administered.

[0059] The compositions described herein are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition containing an amount of a compound that is suitable for administration to a subject, in a single dose, according to good medical practice. The preparation of a single or unit dosage form however, does not imply that the dosage form is administered once per day or once per course of therapy. A unit dosage form may comprise a single daily dose or a fractional sub-dose wherein several unit dosage forms are to be administered over the course of a day in order to complete a daily

dose. According to the present disclosure, a unit dosage form may be given more or less often that once daily, and may be administered more than once during a course of therapy. Such dosage forms may be administered in any manner consistent with their formulation, including orally, parenterally, and may be administered as an infusion over a period of time (e.g., from about 30 minutes to about 2-6 hours). While single administrations are specifically contemplated, the compositions administered according to the methods described herein may also be administered as a continuous infusion or via an implantable infusion pump.

[0060] The methods as described herein may utilize any of a variety of suitable forms for a variety of routes for administration, for example, for oral, nasal, rectal, topical (including transdermal), ocular, intracerebral, intracranial, intrathecal, intra-arterial, intravenous, intramuscular, or other parental routes of administration. The skilled artisan will appreciate that oral and nasal compositions include compositions that are administered by inhalation, and made using available methodologies. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in the art may be used. Pharmaceutically-acceptable carriers include, for example, solid or liquid fillers, diluents, hydrotropes, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the activity of the compound. The amount of carrier employed in conjunction with the compound is sufficient to provide a practical quantity of material for administration per unit dose of the compound. Techniques and compositions for making dosage forms useful in the methods described herein are described in the following references, all incorporated by reference herein: Modern Pharmaceutics, 4th Ed., Chapters 9 and 10 (Banker & Rhodes, editors, 2002); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1989); and Ansel, Introduction to Pharmaceutical Dosage Forms 8th Edition (2004).

[0061] Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent

granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents.

[0062] The pharmaceutically-acceptable carriers suitable for the preparation of unit dosage forms for peroral administration is well-known in the art. Tablets typically comprise conventional pharmaceutically-compatible adjuvants as inert diluents, such as calcium carbonate, sodium carbonate, mannitol, lactose and cellulose; binders such as starch, gelatin and sucrose; disintegrants such as starch, alginic acid and croscarmelose; lubricants such as magnesium stearate, stearic acid, microcrystalline cellulose, carboxymethyl cellulose, and talc. Tablets may also comprise solubilizers or emulsifiers, such as poloxamers, cremophor/Kolliphor®/Lutrol®, methylcellulose, hydroxypropylmethylcellulose, or others as are known in the art. Glidants such as silicon dioxide can be used to improve flow characteristics of the powder mixture. Coloring agents, such as the FD&C dyes, can be added for appearance. Sweeteners and flavoring agents, such as aspartame, saccharin, menthol, peppermint, and fruit flavors, are useful adjuvants for chewable tablets. Capsules typically comprise one or more solid diluents disclosed above. The selection of carrier components depends on secondary considerations like taste, cost, and shelf stability, which can be readily made by a person skilled in the art.

[0063] Peroral (PO) compositions also include liquid solutions, emulsions, suspensions, and the like. The pharmaceutically-acceptable carriers suitable for preparation of such compositions are well known in the art. Typical components of carriers for syrups, elixirs, emulsions and suspensions include ethanol, glycerol, propylene glycol, polyethylene glycol, liquid sucrose, sorbitol and water. For a suspension, typical suspending agents include methyl cellulose, sodium carboxymethyl cellulose, AVICEL RC-591, tragacanth and sodium alginate; typical wetting agents include lecithin and polysorbate 80; and typical preservatives include methyl paraben and sodium benzoate. Peroral liquid compositions may also contain one or more components such as sweeteners, flavoring agents and colorants disclosed above.

[0064] Such compositions may also be coated by conventional methods, typically with pH or time-dependent coatings, such that the subject compound is released in the gastrointestinal tract in the vicinity of the desired topical application, or at various times to

extend the desired action. Such dosage forms typically include, but are not limited to, one or more of cellulose acetate phthalate, polyvinylacetate phthalate, hydroxypropyl methyl cellulose phthalate, ethyl cellulose, Eudragit coatings, waxes and shellac.

[0065] Compositions described herein may optionally include other drug actives.

[0066] Other compositions useful for attaining systemic delivery of the subject compounds include sublingual, buccal and nasal dosage forms. Such compositions typically comprise one or more of soluble filler substances such as sucrose, sorbitol and mannitol; and binders such as acacia, microcrystalline cellulose, carboxymethyl cellulose and hydroxypropyl methyl cellulose. Glidants, lubricants, sweeteners, colorants, antioxidants and flavoring agents disclosed above may also be included.

[0067] A liquid composition, which is formulated for topical ophthalmic use, is formulated such that it can be administered topically to the eye. The comfort may be maximized as much as possible, although sometimes formulation considerations (e.g. drug stability) may necessitate less than optimal comfort. In the case that comfort cannot be maximized, the liquid may be formulated such that the liquid is tolerable to the patient for topical ophthalmic use. Additionally, an ophthalmically acceptable liquid may either be packaged for single use, or contain a preservative to prevent contamination over multiple uses.

[0068] For ophthalmic application, solutions or medicaments are often prepared using a physiological saline solution as a major vehicle. Ophthalmic solutions may preferably be maintained at a comfortable pH with an appropriate buffer system. The formulations may also contain conventional, pharmaceutically acceptable preservatives, stabilizers and surfactants.

[0069] Preservatives that may be used in the pharmaceutical compositions disclosed herein include, but are not limited to, benzalkonium chloride, PHMB, chlorobutanol, thimerosal, phenylmercuric, acetate and phenylmercuric nitrate. A useful surfactant is, for example, Tween 80. Likewise, various useful vehicles may be used in the ophthalmic preparations disclosed herein. These vehicles include, but are not limited to, polyvinyl alcohol, povidone, hydroxypropyl methyl cellulose, poloxamers, carboxymethyl cellulose, hydroxyethyl cellulose and purified water.

[0070] Tonicity adjustors may be added as needed or convenient. They include, but are not limited to, salts, particularly sodium chloride, potassium chloride, mannitol and glycerin, or any other suitable ophthalmically acceptable tonicity adjustor.

[0071] Various buffers and means for adjusting pH may be used so long as the resulting preparation is ophthalmically acceptable. For many compositions, the pH will be between 4 and 9. Accordingly, buffers include acetate buffers, citrate buffers, phosphate buffers and borate buffers. Acids or bases may be used to adjust the pH of these formulations as needed.

[0072] Ophthalmically acceptable antioxidants include, but are not limited to, sodium metabisulfite, sodium thiosulfate, acetylcysteine, butylated hydroxyanisole and butylated hydroxytoluene.

[0073] Other excipient components, which may be included in the ophthalmic preparations, are chelating agents. A useful chelating agent is edetate disodium, although other chelating agents may also be used in place or in conjunction with it.

[0074] For topical use, including for transdermal administration, creams, ointments, gels, solutions or suspensions, etc., containing the compound disclosed herein are employed. Topical formulations may generally be comprised of a pharmaceutical carrier, co-solvent, emulsifier, penetration enhancer, preservative system, and emollient.

[0075] For intravenous administration, the compounds and compositions described herein may be dissolved or dispersed in a pharmaceutically acceptable diluent, such as a saline or dextrose solution. Suitable excipients may be included to achieve the desired pH, including but not limited to NaOH, sodium carbonate, sodium acetate, HCl, and citric acid. In various embodiments, the pH of the final composition ranges from 2 to 8, or preferably from 4 to 7. Antioxidant excipients may include sodium bisulfite, acetone sodium bisulfite, sodium formaldehyde, sulfoxylate, thiourea, and EDTA. Other non-limiting examples of suitable excipients found in the final intravenous composition may include sodium or potassium phosphates, citric acid, tartaric acid, gelatin, and carbohydrates such as dextrose, mannitol, and dextran. Further acceptable excipients are described in Powell, et al., Compendium of Excipients for Parenteral Formulations, PDA J Pharm Sci and Tech 1998, 52 238-311 and Nema et al., Excipients and Their Role in Approved Injectable Products: Current Usage and Future Directions, PDA J. Pharm. Sci. Tech. 2011, 65 287-332, both of

which are incorporated herein by reference in their entirety. Antimicrobial agents may also be included to achieve a bacteriostatic or fungistatic solution, including but not limited to phenylmercuric nitrate, thimerosal, benzethonium chloride, benzalkonium chloride, phenol, cresol, and chlorobutanol.

[0076] The compositions for intravenous administration may be provided to caregivers in the form of one more solids that are reconstituted with a suitable diluent such as sterile water, saline or dextrose in water shortly prior to administration. In other embodiments, the compositions are provided in solution ready to administer parenterally. In still other embodiments, the compositions are provided in a solution that is further diluted prior to administration. In embodiments that include administering a combination of a compound described herein and another agent, the combination may be provided to caregivers as a mixture, or the caregivers may mix the two agents prior to administration, or the two agents may be administered separately.

[0077] The actual unit dose of the active compounds described herein depends on the specific compound, and on the condition to be treated. In some embodiments, the dose may be from about 0.01 mg/kg to about 120 mg/kg or more of body weight, from about 0.05 mg/kg or less to about 70 mg/kg, from about 0.1 mg/kg to about 50 mg/kg of body weight, from about 1.0 mg/kg to about 10 mg/kg of body weight, from about 5.0 mg/kg to about 10 mg/kg of body weight, or from about 10.0 mg/kg to about 20.0 mg/kg of body weight. In some embodiments, the dose may be less than 100 mg/kg, 90 mg/kg, 80 mg/kg, 70 mg/kg, 60 mg/kg, 50 mg/kg, 40 mg/kg, 30 mg/kg, 25 mg/kg, 20 mg/kg, 10 mg/kg, 7.5 mg/kg, 6 mg/kg, 5 mg/kg, 4 mg/kg, 3 mg/kg, 2.5 mg/kg, 1 mg/kg, 0.5mg/kg, 0.1 mg/kg, 0.05 mg/kg or 0.005 mg/kg of body weight. In some embodiments, the actual unit dose is 0.05, 0.07, 0.1, 0.3, 1.0, 3.0, 5.0, 10.0 or 25.0 mg/kg of body weight. Thus, for administration to a 70 kg person, the dosage range would be from about 0.1 mg to 70 mg, from about 1 mg to about 50 mg, from about 0.5 mg to about 10 mg, from about 1 mg to about 10 mg, from about 2.5 mg to about 30 mg, from about 35 mg or less to about 700 mg or more, from about 7 mg to about 600 mg, from about 10 mg to about 500 mg, or from about 20 mg to about 300 mg, or from about 200 mg to about 2000 mg. In some embodiments, the actual unit dose is 5 mg. In some embodiments the actual unit dose is 10 mg. In some embodiments, the actual unit dose is 25 mg. In some embodiments, the actual unit dose is 250 mg or less. In some embodiments, the

actual unit dose is 100 mg or less. In some embodiments, the actual unit dose is 70 mg or less.

[0078] Said compounds may also be incorporated into formulations for delivery outside the systemic circulation. Such formulations may include enteric-coated capsules, tablets, soft-gels, spray dried powders, polymer matrices, hydrogels, enteric-coated solids, crystalline solids, amorphous solids, glassy solids, coated micronized particles, liquids, nebulized liquids, aerosols, or microcapsules.

Methods of Administration

[0079] The compositions described above may be administered through any suitable route of administration, for example, by injection, such as subcutaneously, intramuscularly, intraperitoneally, intravenously, or intraarterially; topically, such as by cream, lotion, or patch; orally, such as by a pill, dissolved liquid, oral suspension, buccal film, or mouthrinse; nasally, such as by a nasal aerosol, powder, or spray; or ocularly, such as by an eye drop). In some embodiments, the composition may be administered one, twice, three times, our four times per day. In other embodiments, the composition may be administered once, twice, or three times per week. In other embodiments, the composition is administered every other day, every three days, or every four days. In other embodiments, the composition every other week, every three weeks, or every four weeks. In other embodiments, the composition is administered once per month or twice per month.

[0080] In some embodiments, an initial loading dose is administered which is higher than subsequent doses (maintenance doses). The dosage form or mode of administration of a maintenance dose may be different from that used for the loading dose. In any of the embodiments disclosed herein, a maintenance dose may comprise administration of the unit dosage form on any dosing schedule contemplated herein, including but not limited to, monthly or multiple times per month, biweekly or multiple times each two weeks, weekly or multiple times per week, daily or multiple times per day. It is contemplated within the present disclosure that dosing holidays may be incorporated into the dosing period of the maintenance dose. Such dosing holidays may occur immediately after the administration of the loading dose or at any time during the period of administration of the maintenance dose. In some embodiments, the loading dose is 300 mg or less; 250 mg or

less, 200 mg or less, 150 mg or less, or 100 mg or less. In some embodiments, the maintenance dose is 300 mg or less; 200 mg or less, 100 mg or less, 50 mg or less, 25 mg or less, 10 mg or less, 5 mg or less, or 1 mg or less.

Methods of Treatment

[0081] Some embodiments according to the methods and compositions of the present disclosure relate to a method for the reduction or prevention of the deposition of extracellular matrix proteins, comprising administering an effective amount of a compound described herein to a subject in need thereof. In some embodiments, said deposition of extracellular matrix proteins may comprise abnormal or excessive deposition of said proteins. In some embodiments, said extracellular matrix proteins may comprise one or more of collagen, keratin, elastin, or fibrin. In some embodiments, said extracellular matrix proteins may comprise collagen. In some embodiments, said extracellular matrix proteins may comprise Type I collagen. In some embodiments, said extracellular matrix proteins may comprise Collagen Type Ia. In some embodiments, said extracellular matrix proteins may comprise Type III collagen. Some embodiments according to the compositions and methods of the present disclosure relate to a method for the treatment of a fibrosis or its symptoms or sequelae, comprising administering an effective amount of a compound described herein to a subject in need thereof.

[0082] In some embodiments, the compounds and compositions comprising the compounds described herein can be used to treat a variety of conditions arising from fibrosis or inflammation, and specifically including those associated with abnormal collagen deposition. Example conditions include glycogen storage disease type III (GSD III), glycogen storage disease type VI (GSD VI), glycogen storage disease type IX (GSD IX), non-alcoholic steatohepatitis (NASH), cirrhosis, hepatitis, scleroderma, alcoholic fatty liver disease, atherosclerosis, asthma, cardiac fibrosis, organ transplant fibrosis, muscle fibrosis, pancreatic fibrosis, bone-marrow fibrosis, liver fibrosis, cirrhosis of liver and gallbladder, fibrosis of the spleen, pulmonary fibrosis, idiopathic pulmonary fibrosis, diffuse parenchymal lung disease, idiopathic interstitial fibrosis, diffuse interstitial fibrosis, interstitial pneumonitis, desquamative interstitial pneumonia, respiratory bronchiolitis, interstitial lung disease, chronic interstitial lung disease, acute interstitial pneumonitis, hypersensitivity

pneumonitis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, lymphocytic interstitial pneumonia, pneumoconiosis, silicosis, emphysema, interstitial fibrosis, sarcoidosis, mediastinal fibrosis, cardiac fibrosis, atrial fibrosis, endomyocardial fibrosis, renal fibrosis, chronic kidney disease, Type II diabetes, macular degeneration, keloid lesions, hypertrophic scar, nephrogenic systemic fibrosis, injection fibrosis, complications of surgery, fibrotic chronic allograft vasculopathy and/or chronic rejection in transplanted organs, fibrosis associated with ischemic reperfusion injury, post-vasectomy pain syndrome, fibrosis associated with rheumatoid arthritis, arthrofibrosis, Dupuytren's disease, dermatomyositis-polymyositis, mixed connective tissue disease, fibrous proliferative lesions of the oral cavity, fibrosing intestinal strictures, Crohn's disease, glial scarring, leptomeningeal fibrosis, meningitis, systemic lupus erythematosus, fibrosis due to radiation exposure, fibrosis due to mammary cystic rupture, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, or symptoms or sequelae thereof, or other diseases or conditions resulting in the excessive deposition of extracellular matrix components, such as collagen.

[0083] In some embodiments the methods of the present disclosure comprise methods for the treatment, amelioration, or prevention of a fibrotic condition. In some embodiments, said fibrotic condition may be secondary to another condition. In some embodiments, said fibrotic condition or primary condition may further comprise chronic inflammation of an organ, tissue, spatial region, or fluid-connected area of the body of a subject. In some embodiments, said inflammation may comprise activation of one or more TGF-beta dependent signaling pathways. In some embodiments, said TGF-β dependent signaling pathways may comprise one or more elements responsive to T3 or T4. In some embodiments, said fibrotic condition may comprise abnormal or excessive deposition of one or more of collagen, keratin, or elastin. In some embodiments, said fibrotic condition may comprise abnormal or excessive deposition of collagen. In some embodiments, said fibrotic condition may comprise abnormal or excessive deposition of Type I collagen. In some embodiments, said fibrotic condition may comprise abnormal or excessive deposition of Collagen Type Ia. In some embodiments, said fibrotic condition may comprise abnormal or excessive deposition of Type III collagen. In some embodiments said fibrotic condition may comprise one or more of glycogen storage disease type III (GSD III), glycogen storage

disease type VI (GSD VI), glycogen storage disease type IX (GSD IX), non-alcoholic steatohepatitis (NASH), cirrhosis, hepatitis, scleroderma, alcoholic fatty liver disease, atherosclerosis, asthma, cardiac fibrosis, organ transplant fibrosis, muscle fibrosis, pancreatic fibrosis, bone-marrow fibrosis, liver fibrosis, cirrhosis of liver and gallbladder, fibrosis of the spleen, scleroderma, pulmonary fibrosis, idiopathic pulmonary fibrosis, diffuse parenchymal lung disease, idiopathic interstitial fibrosis, diffuse interstitial fibrosis, interstitial pneumonitis, desquamative interstitial pneumonia, respiratory bronchiolitis, interstitial lung disease, chronic interstitial lung disease, acute interstitial pneumonitis, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, lymphocytic interstitial pneumonia, pneumoconiosis, silicosis, emphysema, interstitial fibrosis, sarcoidosis, mediastinal fibrosis, cardiac fibrosis, atrial fibrosis, endomyocardial fibrosis, renal fibrosis, chronic kidney disease, Type II diabetes, macular degeneration, keloid lesions, hypertrophic scar, nephrogenic systemic fibrosis, injection fibrosis, complications of surgery, fibrotic chronic allograft vasculopathy and/or chronic rejection in transplanted organs, fibrosis associated with ischemic reperfusion injury, post-vasectomy pain syndrome, fibrosis associated with rheumatoid arthritis, arthrofibrosis, Dupuytren's disease, dermatomyositis-polymyositis, mixed connective tissue disease, fibrous proliferative lesions of the oral cavity, fibrosing intestinal strictures, Crohn's disease, glial scarring, leptomeningeal fibrosis, meningitis, systemic lupus erythematosus, fibrosis due to radiation exposure, fibrosis due to mammary cystic rupture, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis. In some embodiments, said fibrotic condition may comprise one or more of GSD III, GSD IX, Non Alcoholic Steatohepatitis, cirrhosis of the liver and/or pancreas, scleroderma, idiopathic pulmonary fibrosis, psoriasis, alcoholic fatty liver disease, Dupuytren's disease, and/or any combination thereof.

[0084] According to the methods and compositions of the present disclosure, thyroid receptor agonists such as those disclosed herein, and especially including Compounds 1-4, may be administered to a subject for the treatment, amelioration, prevention, or cure of a fibrotic condition, or a condition for which fibrosis is a symptom or sequela. According to the methods and composition as disclosed herein, said fibrotic condition or condition having fibrosis as a sequela may further comprise chronic inflammation. According to the methods and compositions as disclosed herein, said fibrotic

condition or condition having fibrosis as a sequela may further comprise activation of one or more TGF-β dependent signaling pathways. According to the methods and compositions as disclosed herein, said fibrotic condition or condition having fibrosis as a sequela may further comprise activation and/or repression of one or more Thyroid Receptor Beta (TRβ) dependent signaling pathways. According to the methods and compositions as disclosed herein, said fibrotic condition or condition having fibrosis as a sequela may further comprise the involvement of signaling pathways responsive to triiodothyronine (T3), thyroxine (T4), any combination thereof, or mimetics thereof. According to the methods and compositions as disclosed herein, said fibrotic condition or condition having fibrosis as a sequela may further comprise the involvement of receptors responsive to T3, T4, any combination thereof, or mimetics thereof. In some embodiments according to the methods and compositions disclosed herein, said fibrotic condition or condition having fibrosis as a sequela may comprise the involvement of TRβ. In some embodiments according to the methods and compositions disclosed herein, said fibrotic condition or condition having fibrosis as a sequela may comprise one or more conditions which are prevented, ameliorated, or cured by the administration of one or more agonists of TRβ. In some embodiments according to the methods and compositions disclosed herein, said fibrotic condition or condition having fibrosis as a sequela may comprise one or more conditions which are prevented, ameliorated, or cured by the administration of one or more of Compounds 1-4. In some embodiments, said one or more agonists of TRβ, or said one or more of Compounds 1-4, may be coadministered with one or more active drug compounds and/or one or more excipients. In some embodiments, said one or more agonists of TRβ, or said one or more of Compounds 1-4, may be administered prior to, during, or after a surgical intervention, phototherapy, or ultrasound therapy. In some embodiments, said one or more agonists of TRβ, or said one or more of Compounds 1-4, may be coadministered with one or more of Pirfenidone, nintedanib, and/or a fibroblast growth factor receptor antagonist, and/or a collagenase, such as *Clostridium histolyticum* collagenase.

[0085] In some embodiments, the compositions and methods described herein provide compositions and methods for the treatment, amelioration, prevention or cure of collagen deposition. In some embodiments, said collagen deposition comprises and abnormal or excessive deposition of collagen. In some embodiments, said collagen

deposition may comprise abnormal or excessive deposition of Type I collagen. In some embodiments, said collagen deposition may comprise abnormal or excessive deposition of Collagen Type Ia. In some embodiments, said collagen deposition may comprise abnormal or excessive deposition of Type III collagen. According to the methods and compositions as disclosed herein, said collagen deposition may further comprise the involvement of receptors responsive to T3, T4, any combination thereof, or mimetics thereof. In some embodiments according to the methods and compositions disclosed herein, said collagen deposition may comprise the involvement of TRβ. In some embodiments according to the methods and compositions disclosed herein, said collagen deposition may be prevented, ameliorated, or cured by the administration of one or more agonists of TRβ. In some embodiments according to the methods and compositions disclosed herein, said collagen deposition may be prevented, ameliorated, or cured by the administration of one or more of Compounds 1-4. In some embodiments, said one or more agonists of TRβ, or said one or more of Compounds 1-4, may be coadministered with one or more active drug compounds and/or one or more excipients. In some embodiments, said one or more agonists of TRβ, or said one or more of Compounds 1-4, may be administered prior to, during, or after a surgical intervention, phototherapy, or ultrasound therapy. In some embodiments, said one or more agonists of TRβ, or said one or more of Compounds 1-4, may be coadministered with one or more of Pirfenidone, nintedanib, and/or a fibroblast growth factor receptor antagonist, and/or a collagenase, such as *Clostridium histolyticum* collagenase.

[0086] In some embodiments, administration of compounds 1-4, of compound 2, or of any of the compounds or compositions as disclosed herein results in a reduction in the expression of the Cola1, Col3a1, αSMA, and/or Galectin1 genes or any combination or product thereof in the subject to which said compound or composition is administered. In some embodiments, administration of compounds 1-4, of compound 2, or of any of the compounds or compositions as disclosed herein results in a reduction in the degree of fibrosis observable by histology, histochemistry, immunohistochemistry, or the like, and/or reduction s in the amount, accumulation, or distribution of type 1 collagen and/or hydroxyproline or any combination thereof in the subject to which said compound or composition is administered. In some embodiments, administration of compounds 1-4, of compound 2, or of any of the compounds or compositions as disclosed herein results in a reduction in total

serum lipids, total serum cholesterol, total serum triglycerides, total liver lipids, total liver cholesterol, total liver triglycerides, or any combination thereof.

The methods described herein are further illustrated by the following examples.

Example 1:

[0087] DIO-NASH mice were acclimatized for 3 weeks, with pre-treatment liver biopsy samples collected prior to acclimatization. Mice were randomly assigned to one of five dosing groups, with 12 mice per group. Assigned dosages were: Compound 2 (low): 3 mg/kg; Compound 2 (high): 10 mg/kg; Compound 1: 10 mg/kg; and Elafibranor (30 mg.kg). One group was mock treated with vehicle only as a control. Dosage forms were administered orally once per day. After 8 weeks, animals were sacrificed and liver samples were taken. Liver samples were assayed for total liver hydroxyproline, and subjected to immunohistochemical observation for fibrosis stage as well as the extent of ColaI (Collagen Type Ia) staining. As shown in Figure 1, Compound 2-treated animals show lower total liver hydroxyproline levels than control-treated or mock-treated animals. Since hydroxyproline is a significant component of collagen, and collagen is the most significant source of hydroxyproline in animal tissues, levels of hydroxyproline provide a reliable proxy for the presence of collagen in a sample.

[0088] Terminal liver biopsy samples were also subjected to histochemical staining and immunohistochemical staining. Representative images of liver stained with Picro-Sirius Red (to visualize collagen I and III deposition, red stain) at the end of the treatment period following 8 weeks of treatment with vehicle, low dose Compound 2, high dose Compound 2, Compound 1, or elafibranor are shown in Figure 2. As shown in Figure 5, total liver collagen (mg/liver) 1 and 3 was determined by morphometry following Picro-Sirius Red staining. Liver sections from Compound-1-treated animals showed lower PSR staining than those from mock-treated animals; liver sections from Compound 2-treated animals showed lower PSR staining than control-treated or mock-treated animals. Representative images of liver stained with anti-type I collagen (col1a1) (Southern Biotech, Cat. 131001) at the end of the treatment period following 8 weeks of treatment with vehicle, low dose Compound 2, high dose Compound 2, Compound 1, or elafibranor are shown in Figure 3. The extent of ColA1 content was calculated as the total liver ColA1 staining in

terminal liver biopsy samples. As shown in Figure 4, Compound 2-treated animals show lower total liver ColA1 content than control-treated or mock-treated animals.

[0089] Fibrosis scores were also calculated based on observation of terminal liver biopsy samples. Additionally, a higher proportion of animals treated with Compound 1 or Compound 2 showed a reduction in fibrosis score post-treatment than did mock treated animals. No Compound 2-treated animals showed increases in their fibrosis score post-treatment.

Example 2:

[0090] Pulmonary fibrosis is induced in healthy male Dunkin-Hartley guinea pigs by administering bleomycin intratracheally. Control subjects are developed by intratracheal administration of saline solution. After the establishment of pulomnary fibrosis in the bleomycin treated animals, test articles comprising any one of Compounds 1-4, or any other compound disclosed herein, are administered to each subject as appropriate for its formulation, daily or as appropriate, for 6-10 weeks. Unilateral lung biopsies are taken prior to the first administration of the test articles and again after sacrifice following the last administration of the test articles. Biopsy samples are analyzed as described in Example I, with the addition of immunohistochemical staining for type III collagen. Lungs from animals treated with the compounds disclosed herein, especially those animals treated with Compound 2, show reduced levels of hydroxyproline, decreased Collagen III staining, and decreased fibrosis score relative to the levels shown prior to the administration of the test articles. Mock treated animals show little or no reduction in fibrosis, hydroxyproline content, or Collagen III content.

Example 2:

[0091] Palmar fascia fibrosis is induced in nude mice by introducing fibroblasts from fibrotic cords of Dupuytren's disease patients as described in Stish, L. et al., BMC Musculoskelet. Disord. 16: 138-148 (2015) which is hereby incorporated by reference with respect to its description of the establishement of an animal model system for the study of palmar fascia fibrosis. After the establishment of palmar fascia fibrosis in the fibroblast treated animals, test articles comprising any one of Compounds 1-4, or any other compound

disclosed herein, are administered to each subject as appropriate for its formulation, daily or as appropriate, for 6-10 weeks. Unilateral forepaw biopsies are taken prior to the first administration of the test articles and again after sacrifice following the last administration of the test articles. Biopsy samples are analyzed as described in Example I, with the addition of immunohistochemical staining for type III collagen. Palmar fascia from animals treated with the compounds disclosed herein, especially those animals treated with Compound 2, show reduced levels of hydroxyproline, decreased Collagen III staining, and decreased fibrosis score relative to the levels shown prior to the administration of the test articles. Mock treated animals show little or no reduction in fibrosis, hydroxyproline content, or Collagen III content.

Example 3:

[0092] Hypertrophic skin lesions are induced in Sprague-Dawley Rats by subcutaneous injection of capsaicin asdescribed in Wallengren, J. et al., Skin Pharm. Appl. Skin Physiol. 15(3):154-165(2002), which is hereby incorporated by reference with respect to its description of the induction of hypertrophic skin lesions in rats; or in C57BL or other appropriate strain mice by subcutaneous administration of CCl_4 and/or bleomycin, as described in Alonso-Merino et al., Proc. Nat. Acad. Sci. 113(24):E3451-60 (2016), which is incorporated herein for its disclosure of the induction of fibrotic skin lesions in mice. After the establishment of hypertrophic skin lesions in the capsaicin, CCl_4 and/or bleomycin treated animals, test articles comprising any one of Compounds 1-4, or any other compound disclosed herein, are administered to each subject animal as appropriate for its formulation, daily or as appropriate, for 6-10 weeks. Skin biopsies from the injection site are taken prior to the first administration of the test articles and again after sacrifice following the last administration of the test articles. Biopsy samples are analyzed as described in Example I, with the addition of immunohistochemical staining for type III collagen. Injection site skin samples from animals treated with the compounds disclosed herein, especially those animals treated with Compound 2, show reduced levels of hydroxyproline, decreased Collagen III staining, and decreased fibrosis score relative to the levels shown prior to the administration of the test articles. Mock treated animals show little or no reduction in fibrosis, hydroxyproline content, or Collagen III content.

Example 4:

[0093] Glucose-6-phosphatase-α deficient mice that manifest GSD-3- like hepatic symptoms, including hypercholesterolemia and hyperlipidemia (Agl-/-, see e.g. Liu, K.M. et al., Mol. Genet. Metabol. 111(4):467-76 (2014)) are treated with test articles comprising any one of Compounds 1-4, or any other compound disclosed herein, administered to each subject as appropriate for its formulation, daily or as appropriate, for 6-10 weeks. Liver biopsies are taken prior to the first administration of the test articles and again after sacrifice following the last administration of the test articles. Biopsy samples are analyzed as described in Example I. Liver samples from animals treated with the compounds disclosed herein, especially those animals treated with Compound 2, show reduced levels of hydroxyproline, decreased Collagen I staining, and decreased fibrosis score relative to the levels shown prior to the administration of the test articles. Mock treated animals show little or no reduction in fibrosis, hydroxyproline content, or Collagen I content.

Example 5:

[0094] Phosphorylase kinase deficient mice that manifest GSD-8/9- like hepatic symptoms, including hypercholesterolemia and hyperlipidemia (PhKc-/-, see, e.g., Varsanyi, M. et al., Biochem. Genet. 18(3-4):247-61 (1980)), are treated with test articles comprising any one of Compounds 1-4, or any other compound disclosed herein, administered to each subject as appropriate for its formulation, daily or as appropriate, for 6-10 weeks. Liver biopsies are taken prior to the first administration of the test articles and again after sacrifice following the last administration of the test articles. Biopsy samples are analyzed as described in Example I. Liver samples from animals treated with the compounds disclosed herein, especially those animals treated with Compound 2, show reduced levels of hydroxyproline, decreased Collagen I staining, and decreased fibrosis score relative to the levels shown prior to the administration of the test articles. Mock treated animals show little or no reduction in fibrosis, hydroxyproline content, or Collagen I content.

Example 6:

[0095] Compound 2 was evaluated in a diet-induced NASH mouse model (See, e.g., Hansen, H. et al., Drug Discovery Today 22(17):1701-1718 (2017) which is hereby incorporated by reference with respect to its disclosure of diet-induced, genetic, chemical, and other NASH mouse models). Diet-driven NASH in this model does not rely on chemical/toxin effects to generate steatohepatitis/fibrosis. Animals were biopsied pre-study, and only animals with NASH and fibrosis were selected for study. Selected animals were acclimatized and randomized, with experimental groups of 11-12 animals per cohort receiving oral dosing of compound 2 according to the following schedules: Daily dosing for 8 weeks; or daily dosing for week 0-1 followed by weekly dosing for weeks 2-8. At week 8, animals were sacrificed and tissues analyzed. Plasma enzymes (P-ALT (alanine aminotransferase) and P-AST(aspartate aminotransferase)), total plasma triglycerides, and total plasma cholesterol were measured, and terminal necropsy of each liver was carried out, assaying total liver biochemistry including total liver triglycerides, and total liver cholesterol, as well as histological evaluation of NAFLD activity score (done pre- and post-treatment), fibrosis stage (also done pre- and post-treatment), steatosis, Col1a1 level, and galactin-3 level. Tissue samples were preserved for characterization using RNAseq; RNAseq was used to determine expression levels for genes showing differential expression in compound 2-treated vs. vehicle treated animals and/or genes known to be implicated in fibrosis. Significant reductions in liver triglycerides and cholesterol were observed in treatment groups relative to untreated controls. As shown in figure 6, total lipid content in the liver was reduced by approximately 80%, with similar reductions in plasma lipids and significant improvements in NAS scores. No significant toxicity was observed.

[0096] As shown in figure 7, significant reductions in fibrosis, type 1 collagen deposition, and hydroxyproline (50.2%, 60.2%, and 46.3%, respectively) were also seen relative to pre-treatment samples. Post-treatment, expression of pro-fibrotic genes Col1a1, Col3a1, αSMA, and Galectin 1 were reduced by 36.3%, 27.1%, 37%, and 64.7%, respectively (Figure 8), confirming the results observed by histology. Thus, 8-week dosing with compound 2 resulted in marked improvements in histological, biochemical, and genetic markers related to steatosis, fibrosis, and non-alcoholic steatohepatitis in a diet-induced NASH model.

[0097] With respect to the use of substantially any plural and/or singular terms herein, those having skill in the art can translate from the plural to the singular and/or from the singular to plural as is appropriate to the context and/or application. The various singular/plural permutations can be expressly set forth herein for sake of clarity.

[0098] It will be understood by those within the art that, in general, terms used herein, and especially in the appended claims (for example, bodies of the appended claims) are generally intended as "open" terms (for example, the term "including" should be interpreted as "including but not limited to," the term "having" should be interpreted as "having at least," the term "includes" should be interpreted as "includes but is not limited to," etc.). It will be further understood by those within the art that if a specific number of an introduced claim recitation is intended, such an intent will be explicitly recited in the claim, and in the absence of such recitation no such intent is present. For example, as an aid to understanding, the following appended claims can contain usage of the introductory phrases "at least one" and "one or more" to introduce claim recitations. However, the use of such phrases should not be construed to imply that the introduction of a claim recitation by the indefinite articles "a" or "an" limits any particular claim containing such introduced claim recitation to embodiments containing only one such recitation, even when the same claim includes the introductory phrases "one or more" or "at least one" and indefinite articles such as "a" or "an" (for example, "a" and/or "an" should be interpreted to mean "at least one" or "one or more"); the same holds true for the use of definite articles used to introduce claim recitations. In addition, even if a specific number of an introduced claim recitation is explicitly recited, those skilled in the art will recognize that such recitation should be interpreted to mean at least the recited number (for example, the bare recitation of "two recitations," without other modifiers, means at least two recitations, or two or more recitations). Furthermore, in those instances where a convention analogous to "at least one of A, B, and C, etc." is used, in general such a construction is intended in the sense one having skill in the art would understand the convention (for example, " a system having at least one of A, B, and C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). In those instances where a convention analogous to "at least one of A, B, or C, etc." is used, in general such a construction is intended in the sense one having skill in the

art would understand the convention (for example, " a system having at least one of A, B, or C" would include but not be limited to systems that have A alone, B alone, C alone, A and B together, A and C together, B and C together, and/or A, B, and C together, etc.). It will be further understood by those within the art that virtually any disjunctive word and/or phrase presenting two or more alternative terms, whether in the description, claims, or drawings, should be understood to contemplate the possibilities of including one of the terms, either of the terms, or both terms. For example, the phrase "A or B" will be understood to include the possibilities of "A" or "B" or "A and B."

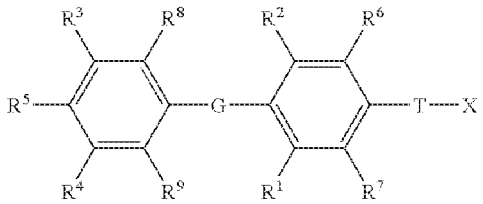
[0099] In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

[0100] As will be understood by one skilled in the art, for any and all purposes, such as in terms of providing a written description, all ranges disclosed herein also encompass any and all possible sub-ranges and combinations of sub-ranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as "up to," "at least," "greater than," "less than," and the like include the number recited and refer to ranges which can be subsequently broken down into sub-ranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 articles refers to groups having 1, 2, or 3 articles. Similarly, a group having 1-5 articles refers to groups having 1, 2, 3, 4, or 5 articles, and so forth.

[0101] While various aspects and embodiments have been disclosed herein, other aspects and embodiments will be apparent to those skilled in the art. The various aspects and embodiments disclosed herein are for purposes of illustration and are not intended to be limiting, with the true scope and spirit being indicated by the following claims.

WHAT IS CLAIMED IS:

1. A method of treating fibrosis, a fibrotic condition or a fibrotic symptom in a subject in need thereof comprising administering to said subject in need thereof at least one compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein:

G is selected from the group consisting of —O—, —S—, —S(=O)—, —S(=O)$_2$—, —Se—, —CH_2—, —CF_2—, —CHF—, —C(O)—, —CH(OH)—, —CH(C_1-C_4 alkyl)-, —CH(C_1-C_4 alkoxy)-, —C(=CH_2)—,—NH—, and —N(C_1-C_4 alkyl)-;

T is selected from the group consisting of —(CR^a_2)$_k$—, —CR^b=CR^b—(CR^a_2)$_n$—, —(CR^a_2)$_n$—CR^b=CR^b—, —(CR^a_2)—CR^b=CR^b—(CR^a_2)—, —O(CR^b_2)(CR^a_2)$_n$—, —S(CR^b_2)(CR^a_2)n—, N(R^c)(CR^b_2)(CR^a_2)$_n$—, N(R^b)C(O)(CR^a_2)$_n$, —C(O)(CR^a_2)$_m$—, —(CR^a_2)$_m$C(O)—, —(CR^a_2)C(O)(CR^a_2)$_n$, —(CR^a_2)$_n$C(O)(CR^a_2)—, and —C(O)NH(CR^b_2)(CR^a_2)$_p$—;

k is an integer from 1-4;

m is an integer from 0-3;

n is an integer from 0-2;

p is an integer from 0-1;

each R^a is independently selected from the group consisting of hydrogen, optionally substituted —C_1-C_4 alkyl, halogen, —OH, optionally substituted —O—C_1-C_4 alkyl, —OCF_3, optionally substituted —S—C_1-C_4 alkyl, —NR^bR^c, optionally substituted —C_2-C_4 alkenyl, and optionally substituted —C_2-C_4 alkynyl; with the proviso that when one R^a is attached to C through an O, S, or N atom, then the other R^a attached to the same C is a hydrogen, or attached via a carbon atom;

each R^b is independently selected from the group consisting of hydrogen and optionally substituted —C_1-C_4 alkyl;

each R^c is independently selected from the group consisting of hydrogen and optionally substituted —C_1-C_4 alkyl, optionally substituted —C(O)—C_1-C_4 alkyl, and —C(O)H;

R^1, and R^2 are each independently selected from the group consisting of halogen, optionally substituted —C_1-C_4 alkyl, optionally substituted —S—C_1-C_3 alkyl, optionally substituted —C_2-C_4 alkenyl, optionally substituted —C_2-C_4 alkynyl, —CF_3, —OCF_3, optionally substituted—O—C_1-C_3 alkyl, and cyano;

R^6, R^7, R^8, and R^9 are each independently selected from the group consisting of are each independently selected from the group consisting of hydrogen, halogen, optionally substituted —C C_1-C_4 alkyl, optionally substituted —S—C_1-C_3 alkyl, optionally substituted —C_2-C_4 alkenyl, optionally substituted —C_2-C_4 alkynyl, —CF_3, —OCF_3, optionally substituted—O—C_1-C_3 alkyl, and cyano; or R^6 and T are taken together along with the carbons they are attached to form a ring of 5 to 6 atoms including 0 to 2 heteroatoms independently selected from —NR^i—, —O—, and —S—, with the proviso that when there are 2 heteroatoms in the ring and both heteroatoms are different than nitrogen then both heteroatoms have to be separated by at least one carbon atom; and X is attached to this ring by a direct bond to a ring carbon, or by —(CR^a_2)— or —C(O)— bonded to a ring carbon or a ring nitrogen;

R^i is selected from the group consisting of hydrogen, —C(O)C_1-C_4 alkyl, —C_1-C_4 alkyl, and —C_1-C_4—aryl;

R^3 and R^4 are independently selected from the group consisting of hydrogen, halogen, —CF_3, —OCF_3, cyano, optionally substituted —C_1-C_{12} alkyl, optionally substituted —C_2-C_{12} alkenyl, optionally substituted —C_2-C_{12} alkynyl, —SR^d, —S(=O)R^e, —$S(=O)_2R^e$, —$S(=O)_2NR^fR^g$, —C(O)OR^h, —C(O)R^e, —$N(R^b)C(O)NR^fR^g$, —$N(R^b)S(=O)_2R^e$, —$N(R^b)S(=O)_2NR^fR^g$, and —NR^fR^g;

each R^d is selected from the group consisting of optionally substituted —C_1-C_{12} alkyl, optionally substituted —C_2-C_{12} alkenyl, optionally substituted —C_2-C_{12} alkynyl, optionally substituted —(CR^b_2)$_n$ aryl, optionally substituted —(CR^b_2)$_n$ cycloalkyl, optionally substituted —(CR^b_2)$_n$ heterocycloalkyl, and —C(O)NR^fR^g;

each R^e is selected from the group consisting of optionally substituted —C_1-C_{12} alkyl, optionally substituted —C_2-C_{12} alkenyl, optionally substituted —C_2-C_{12} alkynyl, optionally

substituted —$(CR^a_2)_n$ aryl, optionally substituted —$(CR^a_2)_n$ cycloalkyl, and optionally substituted —$(CR^a_2)_n$ heterocycloalkyl;

R^f and R^g are each independently selected from the group consisting of hydrogen, optionally substituted —C_1-C_{12} alkyl, optionally substituted —C_2—C_{12} alkenyl, optionally substituted —C_2-C_{12} alkynyl, optionally substituted —$(CR^b_2)_n$ aryl, optionally substituted —$(CR^b_2)_n$ cycloalkyl, and optionally substituted —$(CR^b_2)_n$ heterocycloalkyl, or R^f and R^g may together form an optionally substituted heterocyclic ring, which may contain a second heterogroup selected from the group consisting of O, NR^C, and S, wherein said optionally substituted heterocyclic ring may be substituted with 0-4 substituents selected from the group consisting of optionally substituted —C_1-C_4 alkyl, —OR^b, oxo, cyano, —CF_3, optionally substituted phenyl, and —$C(O)OR^h$;

each R^h is selected from the group consisting of optionally substituted —C_1-C_{12} alkyl, optionally substituted —C_2-C_{12} alkenyl, optionally substituted —C_2-C_{12} alkynyl, optionally substituted —$(CR^b_2)_n$ aryl, optionally substituted —$(CR^b_2)_n$ cycloalkyl, and optionally substituted —$(CR^b_2)_n$ heterocycloalkyl;

R^5 is selected from the group consisting of —OH, optionally substituted —OC_1-C_6 alkyl, $OC(O)R^e$, —$OC(O)OR^h$, —F, —$NHC(O)R^e$, —$NHS(=O)R^e$, —$NHS(=O)_2R^e$, —$NHC(=S)NH(R^h)$, and —$NHC(O)NH(R^h)$;

X is $P(O)YR^{11}Y'R^{11}$;

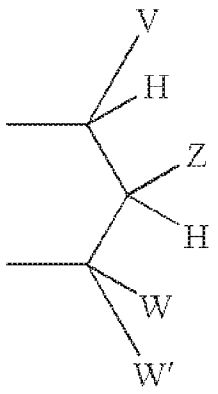
Y and Y′ are each independently selected from the group consisting of —O—, and —NR^v—; when Y and Y′ are —O—, R^{11} attached to —O— is independently selected from the group consisting of —H, alkyl, optionally substituted aryl, optionally substituted heterocycloalkyl, optionally substituted CH_2-heterocycloakyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, —$C(R^z)_2OC(O)NR^z_2$, —NR^z—C(O)—R^y, —$C(R^z)_2$—$OC(O)R^y$, —$C(R^z)_2$—O—$C(O)OR^y$, —$C(R^z)_2OC(O)SR^y$, -alkyl-S—$C(O)R^y$, -alkyl-S—S-alkylhydroxy, and -alkyl-S—S—S-alkylhydroxy;

when Y and Y′ are —NR^v—, then R^{11} attached to —NR^v— is independently selected from the group consisting of —H, —$[C(R^z)_2]_q$—$COOR^y$, —$C(R^x)_2COOR^Y$, —$[C(R^z)_2]_q$—$C(O)SR^y$, and -cycloalkylene-$COOR^y$;

when Y is —O— and Y′ is NR^v, then R^{11} attached to —O— is independently selected from the group consisting of —H, alkyl, optionally substituted aryl, optionally

substituted heterocycloalkyl, optionally substituted CH_2-heterocycloakyl wherein the cyclic moiety contains a carbonate or thiocarbonate, optionally substituted -alkylaryl, —$C(R^Z)_2OC(O)NR^Z{}_2$, —NR^Z—C(O)—R^Y, —$C(R^Z)_2$—$OC(O)R^Y$, —$C(R^Z)_2$—O—$C(O)OR^Y$, —$C(R^Z)_2OC(O)SR^Y$, -alkyl-S—C(O)R^Y, -alkyl-S—S-alkylhydroxy, and -alkyl-S—S—S-alkylhydroxy; and R^{11} attached to —NR^Y— is independently selected from the group consisting of H, —$[C(R^Z)_2]_q$—$COOR^Y$, —$C(R^X)_2COOR^Y$, —$[C(R^Z)_2]_q$—$C(O)SR^Y$, and -cycloalkylene-$COOR^Y$;

or when Y and Y′ are independently selected from —O— and NR^Y, then together R^{11} and R^{11} are -alkyl-S—S-alkyl- to form a cyclic group, or together R^{11} and R^{11} are the group:



wherein:

V, W, and W′ are independently selected from the group consisting of hydrogen, optionally substituted alkyl, optionally substituted aralkyl, heterocycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, optionally substituted 1-alkenyl, and optionally substituted 1-alkynyl;

or together V and Z are connected via an additional 3-5 atoms to form a cyclic group containing 5-7 atoms, wherein 0-1 atoms are heteroatoms and the remaining atoms are carbon, substituted with hydroxy, acyloxy, alkylthiocarbonyloxy, alkoxycarbonyloxy, or aryloxycarbonyloxy attached to a carbon atom that is three atoms from both Y groups attached to the phosphorus;

or together V and Z are connected via an additional 3-5 atoms to form a cyclic group, wherein 0-1 atoms are heteroatoms and the remaining atoms are carbon, that is fused to an aryl group at the beta and gamma position to the Y attached to the phosphorus;

or together V and W are connected via an additional 3 carbon atoms to form an optionally substituted cyclic group containing 6 carbon atoms and substituted with one substituent selected from the group consisting of hydroxy, acyloxy, alkoxycarbonyloxy, alkylthiocarbonyloxy, and aryloxycarbonyloxy, attached to one of said carbon atoms that is three atoms from a Y attached to the phosphorus;

or together Z and W are connected via an additional 3-5 atoms to form a cyclic group, wherein 0-1 atoms are heteroatoms and the remaining atoms are carbon, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

or together W and W′ are connected via an additional 2-5 atoms to form a cyclic group, wherein 0-2 atoms are heteroatoms and the remaining atoms are carbon, and V must be aryl, substituted aryl, heteroaryl, or substituted heteroaryl;

Z is selected from the group consisting of —CHR^zOH, —$CHR^zOC(O)R^y$, —$CHR^zOC(S)R^y$, —$CHR^zOC(S)OR^y$, —$CHR^zOC(O)SR^y$, —$CHR^zOCO_2R^y$, —OR^z, —SR^z, —CHR^zN_3, —CH_2-aryl, —CH(aryl)OH, —$CH(CH{=}CR^z{}_2)OH$, —$CH(C{\equiv}CR^z)OH$, —R^z, —$NR^z{}_2$, —$OCOR^y$, —OCO_2R^y, —$SCOR^y$, —SCO_2R^y, —$NHCOR^z$, —$NHCO_2R^y$, —CH_2NH-aryl, —$(CH_2)q$—OR^z, and —$(CH_2)q$—SR^z;

q is an integer 2 or 3;

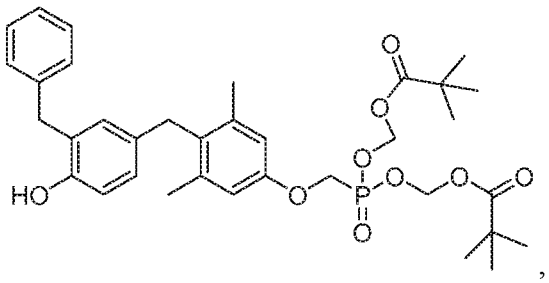
each R^z is selected from the group consisting of R^y and —H;

each R^y is selected from the group consisting of alkyl, aryl, heterocycloalkyl, and aralkyl;

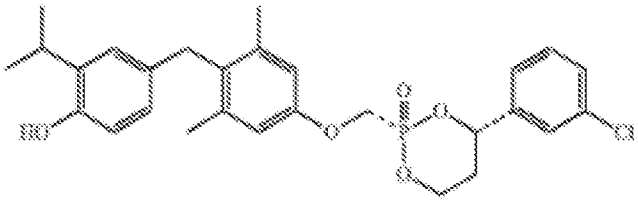
each R^x is independently selected from the group consisting of —H, and alkyl, or together R^x and R^x form a cyclic alkyl group; and

each R^y is selected from the group consisting of —H, lower alkyl, acyloxyalkyl, alkoxycarbonyloxyalkyl, and lower acyl.

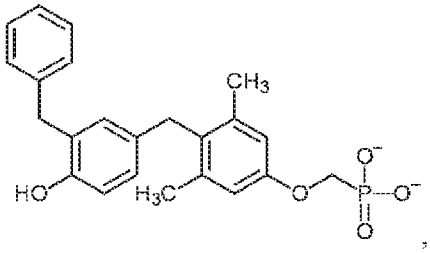
2. The method of Claim 1 wherein the compound to be administered comprises one or more of the compounds having a structure selected from the group consisting of:



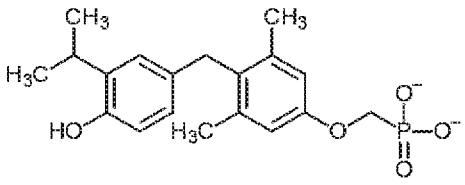
,



,



, and



; or pharmaceutically acceptable salts thereof.

3. The method of any of Claims 1-2 wherein said subject has one or more fibrotic conditions selected from glycogen storage disease type III (GSD III), glycogen storage disease type VI (GSD VI), glycogen storage disease type IX (GSD IX), non-alcoholic steatohepatitis (NASH), cirrhosis, hepatitis, scleroderma, alcoholic fatty liver disease, atherosclerosis, asthma, cardiac fibrosis, organ transplant fibrosis, muscle fibrosis, pancreatic fibrosis, bone-marrow fibrosis, liver fibrosis, cirrhosis of liver and gallbladder, fibrosis of the spleen, pulmonary fibrosis, idiopathic pulmonary fibrosis, diffuse parenchymal lung disease, idiopathic interstitial fibrosis, diffuse interstitial fibrosis, interstitial pneumonitis, desquamative interstitial pneumonia, respiratory bronchiolitis, interstitial lung disease, chronic interstitial lung disease, acute interstitial pneumonitis, hypersensitivity

pneumonitis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, lymphocytic interstitial pneumonia, pneumoconiosis, silicosis, emphysema, interstitial fibrosis, sarcoidosis, mediastinal fibrosis, cardiac fibrosis, atrial fibrosis, endomyocardial fibrosis, renal fibrosis, chronic kidney disease, Type II diabetes, macular degeneration, keloid lesions, hypertrophic scar, nephrogenic systemic fibrosis, injection fibrosis, complications of surgery, fibrotic chronic allograft vasculopathy and/or chronic rejection in transplanted organs, fibrosis associated with ischemic reperfusion injury, post-vasectomy pain syndrome, fibrosis associated with rheumatoid arthritis, arthrofibrosis, Dupuytren's disease, dermatomyositis-polymyositis, mixed connective tissue disease, fibrous proliferative lesions of the oral cavity, fibrosing intestinal strictures, Crohn's disease, glial scarring, leptomeningeal fibrosis, meningitis, systemic lupus erythematosus, fibrosis due to radiation exposure, fibrosis due to mammary cystic rupture, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, or symptoms or sequelae thereof, or other diseases or conditions resulting in the excessive deposition of extracellular matrix components, such as collagen, which may be affected by interventions within the TRβ pathway, or any combination thereof.

4. The method of any of Claims 1-3 wherein said fibrosis, fibrotic condition or fibrotic symptom is a primary fibrosis.

5. The method of any of Claims 1-4 wherein said fibrosis, fibrotic condition or fibrotic symptom is secondary to another condition.

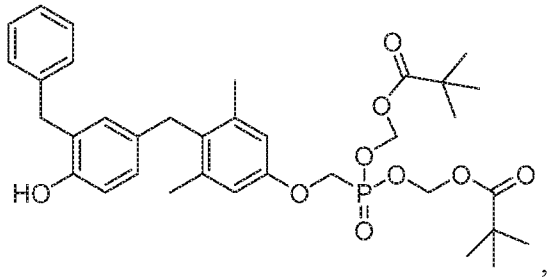
6. The method of any of Claims 1-5 wherein said fibrosis, fibrotic condition or fibrotic symptom comprises one or more of scleroderma, atherosclerosis, cardiac fibrosis, organ transplant fibrosis, muscle fibrosis, pancreatic fibrosis, bone-marrow fibrosis, liver fibrosis, fibrosis of the spleen, pulmonary fibrosis, idiopathic pulmonary fibrosis, idiopathic interstitial fibrosis, diffuse interstitial fibrosis, interstitial lung disease, chronic interstitial lung disease, pneumoconiosis, silicosis, interstitial fibrosis, sarcoidosis, mediastinal fibrosis, cardiac fibrosis, atrial fibrosis, endomyocardial fibrosis, renal fibrosis, macular degeneration, keloid lesions, hypertrophic scar, nephrogenic systemic fibrosis, injection fibrosis, fibrotic complications of surgery, fibrotic chronic allograft vasculopathy, fibrosis associated with

ischemic reperfusion injury, arthrofibrosis, Dupuytren's disease, fibrous proliferative lesions of the oral cavity, fibrosing intestinal strictures, glial scarring, leptomeningeal fibrosis, fibrosis due to radiation exposure, fibrosis due to mammary cystic rupture, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis or any combination thereof.

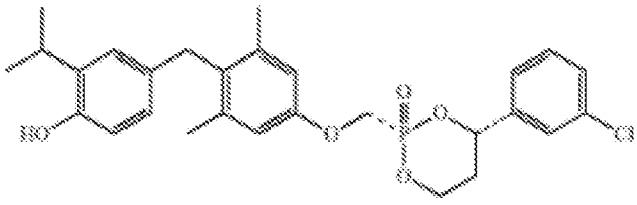
7. The method of any of Claims 1-3 or 5 wherein said fibrosis, fibrotic condition or fibrotic symptom is secondary to one or more of glycogen storage disease type III (GSD III), glycogen storage disease type VI (GSD VI), glycogen storage disease type IX (GSD IX), non-alcoholic steatohepatitis (NASH), cirrhosis, hepatitis, scleroderma, alcoholic fatty liver disease, atherosclerosis, asthma, cirrhosis of the gallbladder, diffuse parenchymal lung disease, interstitial pneumonitis, desquamative interstitial pneumonia, respiratory bronchiolitis, interstitial lung disease, chronic interstitial lung disease, acute interstitial pneumonitis, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, lymphocytic interstitial pneumonia, emphysema, chronic kidney disease, Type II diabetes, macular degeneration, chronic rejection in transplanted organs, post-vasectomy pain syndrome, rheumatoid arthritis, dermatomyositis-polymyositis, mixed connective tissue disease, Crohn's disease, meningitis, systemic lupus erythematosus, or symptoms or sequelae thereof, or other diseases or conditions resulting in the excessive deposition of extracellular matrix components, such as collagen, which may be affected by interventions within the TRβ pathway, or any combination thereof.

8. The method of any of Claims 1-7 wherein said fibrosis, fibrotic condition or fibrotic symptom is a symptom or sequela of GSD III, GSD VI, GSD IX, Non Alcoholic Steatohepatitis, cirrhosis of the liver or pancreas, Dupuytren's disease, scleroderma, idiopathic pulmonary fibrosis, or alcoholic fatty liver disease, or any combination thereof.

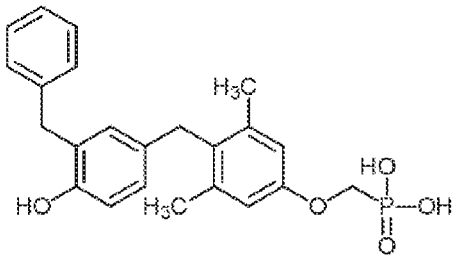
9. A method of treating a fibrosis, a fibrotic condition or a fibrotic symptom in a subject, comprising administering one or more compounds having a structure selected from the group consisting of:



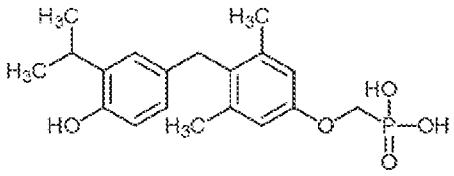
,



,



,



, or pharmaceutically acceptable salts thereof

to a subject in need thereof.

10. The method of Claim 9 wherein said subject has one or more conditions selected from glycogen storage disease type III (GSD III), glycogen storage disease type VI (GSD VI), glycogen storage disease type IX (GSD IX), hepatitis, scleroderma, atherosclerosis, asthma, cardiac fibrosis, organ transplant fibrosis, muscle fibrosis, pancreatic fibrosis, bone-marrow fibrosis, liver fibrosis, cirrhosis of the gallbladder, fibrosis of the spleen, pulmonary fibrosis, idiopathic pulmonary fibrosis, diffuse parenchymal lung disease, idiopathic interstitial fibrosis, diffuse interstitial fibrosis, interstitial pneumonitis, desquamative interstitial pneumonia, respiratory bronchiolitis, interstitial lung disease, chronic interstitial lung disease, acute interstitial pneumonitis, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, lymphocytic

interstitial pneumonia, pneumoconiosis, silicosis, emphysema, interstitial fibrosis, sarcoidosis, mediastinal fibrosis, cardiac fibrosis, atrial fibrosis, endomyocardial fibrosis, renal fibrosis, chronic kidney disease, Type II diabetes, macular degeneration, keloid lesions, hypertrophic scar, nephrogenic systemic fibrosis, injection fibrosis, complications of surgery, fibrotic chronic allograft vasculopathy and/or chronic rejection in transplanted organs, fibrosis associated with ischemic reperfusion injury, post-vasectomy pain syndrome, fibrosis associated with rheumatoid arthritis, arthrofibrosis, Dupuytren's disease, dermatomyositis-polymyositis, mixed connective tissue disease, fibrous proliferative lesions of the oral cavity, fibrosing intestinal strictures, Crohn's disease, glial scarring, leptomeningeal fibrosis, meningitis, systemic lupus erythematosus, fibrosis due to radiation exposure, fibrosis due to mammary cystic rupture, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis, or symptoms or sequelae thereof, or other diseases or conditions resulting in the excessive deposition of extracellular matrix components, such as collagen, which may be affected by interventions within the TRβ pathway, or any combination thereof.

11. The method of any of Claims 9-10 wherein said condition is a primary fibrosis.

12. The method of any of Claims 9-11 wherein said condition has fibrosis as a symptom.

13. The method of any of Claims 9-12 wherein said fibrosis, fibrotic condition or fibrotic symptom comprises one or more of scleroderma, atherosclerosis, cardiac fibrosis, organ transplant fibrosis, muscle fibrosis, pancreatic fibrosis, bone-marrow fibrosis, liver fibrosis, fibrosis of the spleen, pulmonary fibrosis, idiopathic pulmonary fibrosis, idiopathic interstitial fibrosis, diffuse interstitial fibrosis, interstitial lung disease, chronic interstitial lung disease, pneumoconiosis, silicosis, interstitial fibrosis, sarcoidosis, mediastinal fibrosis, cardiac fibrosis, atrial fibrosis, endomyocardial fibrosis, renal fibrosis, macular degeneration, keloid lesions, hypertrophic scar, nephrogenic systemic fibrosis, injection fibrosis, fibrotic complications of surgery, fibrotic chronic allograft vasculopathy, fibrosis associated with ischemic reperfusion injury, arthrofibrosis, Dupuytren's disease, fibrous proliferative lesions

of the oral cavity, fibrosing intestinal strictures, glial scarring, leptomeningeal fibrosis, fibrosis due to radiation exposure, fibrosis due to mammary cystic rupture, myelofibrosis, retroperitoneal fibrosis, progressive massive fibrosis or any combination thereof.

14. The method of any of Claims 9-13 wherein said fibrosis, fibrotic condition or fibrotic symptom comprises one or more of glycogen storage disease type III (GSD III), glycogen storage disease type VI (GSD VI), glycogen storage disease type IX (GSD IX), hepatitis, scleroderma, atherosclerosis, asthma, cirrhosis of the gallbladder, diffuse parenchymal lung disease, interstitial pneumonitis, desquamative interstitial pneumonia, respiratory bronchiolitis, interstitial lung disease, chronic interstitial lung disease, acute interstitial pneumonitis, hypersensitivity pneumonitis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, lymphocytic interstitial pneumonia, emphysema, chronic kidney disease, Type II diabetes, macular degeneration, chronic rejection in transplanted organs, post-vasectomy pain syndrome, rheumatoid arthritis, dermatomyositis-polymyositis, mixed connective tissue disease, Crohn's disease, meningitis, systemic lupus erythematosus, or symptoms or sequelae thereof, or other diseases or conditions resulting in the excessive deposition of extracellular matrix components, such as collagen, which may be affected by interventions within the TRβ pathway, or any combination thereof.

15. The method of any of Claims 9-14 wherein said fibrosis, fibrotic condition or fibrotic symptom is a symptom or sequela of GSD III, GSD VI, GSD IX, cirrhosis of the pancreas, Dupuytren's disease, scleroderma, idiopathic pulmonary fibrosis, or alcoholic fatty liver disease, or any combination thereof.

16. The method of any of Claims 1-15, comprising administering a composition comprising said compound and one or more pharmaceutically acceptable excipients.

17. The method of any of Claims 1-16 wherein said composition is formulated for oral, intravenous, intraarterial, intestinal, rectal, vaginal, nasal, pulmonary, topical, intradermal, transdermal, transbuccal, translingual, sublingual, or opthalmic administration, or any combination thereof.

18. The method of any of Claims 1-17 wherein said subject shows abnormal or excessive deposition of collagen.

19. The method of any of Claims 1-18 wherein said subject shows abnormal or excessive deposition of collagen type 1.

20. The method of any of Claims 1-19 wherein said subject shows abnormal or excessive deposition of collagen type 1a.

21. The method of any of Claims 1-20 wherein said subject shows abnormal or excessive deposition of collagen type III.

22. The method of any of Claims 1-21 wherein said administration of said compound results in the prevention, amelioration, or cure of said fibrosis, fibrotic condition, or fibrotic symptom.

23. The method of any of Claims 1-22 wherein said administration of said compound results in the reduction in the amount of extracellular matrix proteins present in one or more tissues of said subject.

24. The method of any of Claims 1-23 wherein said administration of said compound results in the reduction in the amount of collagen present in one or more tissues of said subject.

25. The method of any of Claims 1-24 wherein said administration of said compound results in the reduction in the amount of Type I, Type Ia, or Type III collagen present in one or more tissues of said subject.

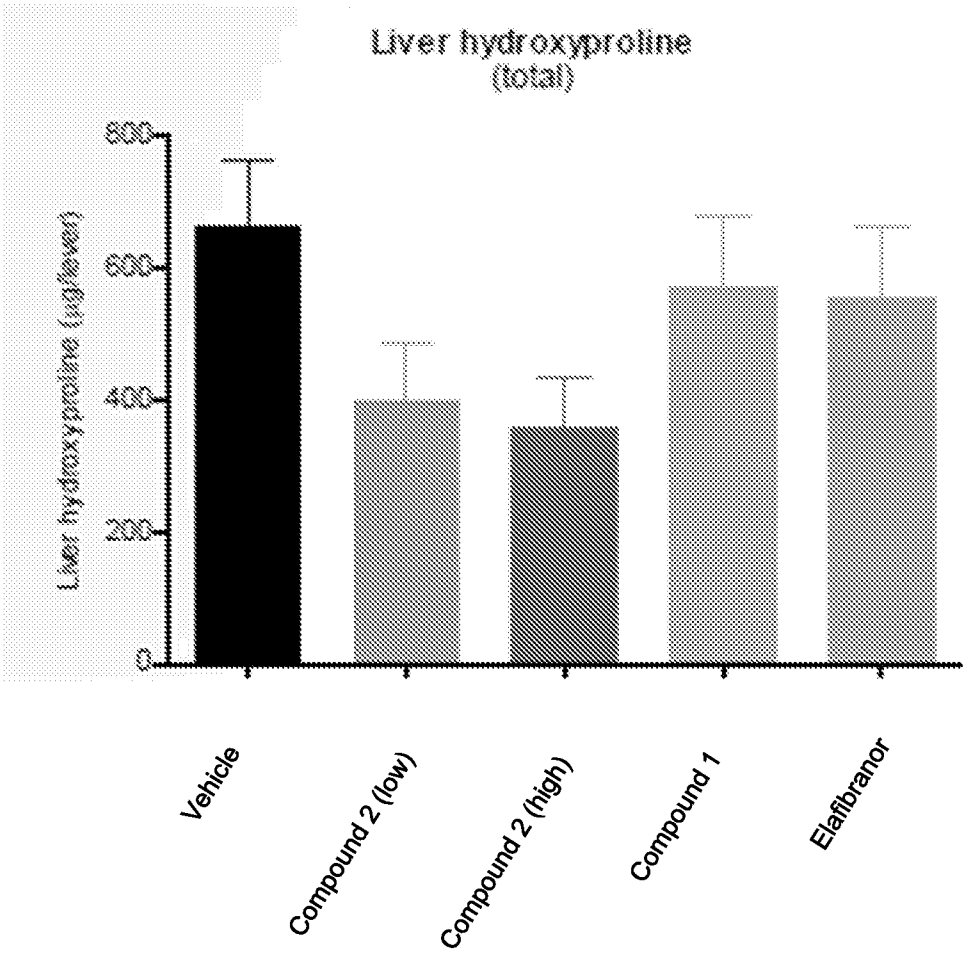
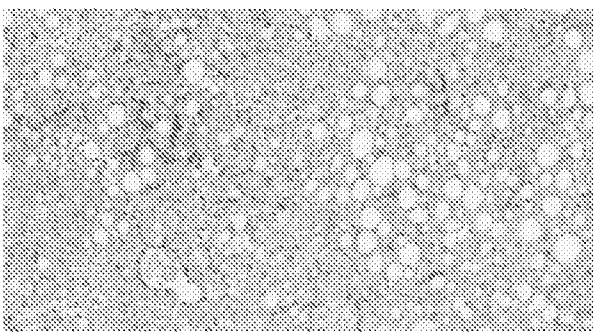
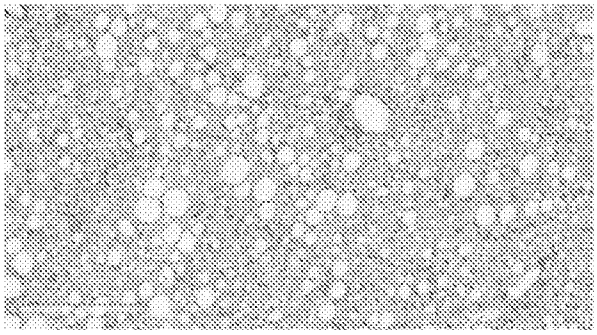

Liver hydroxyproline
(total)
Liver hydroxyproline (µg/liver)
800
600
400
200
0
Vehicle
Compound 2 (low)
Compound 2 (high)
Compound 1
Elafibranor

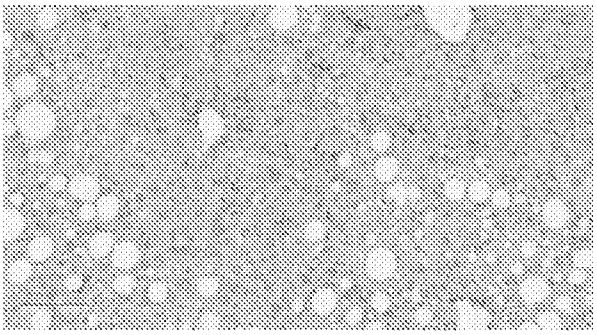
Figure 1



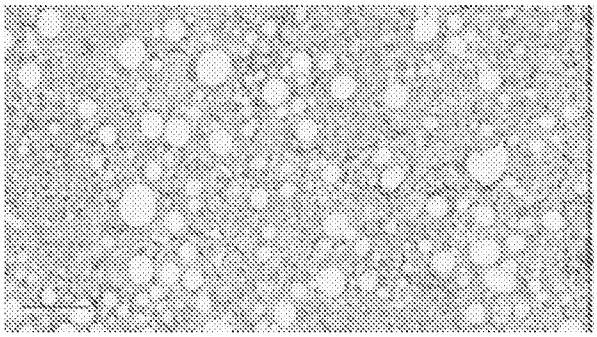
Vehicle



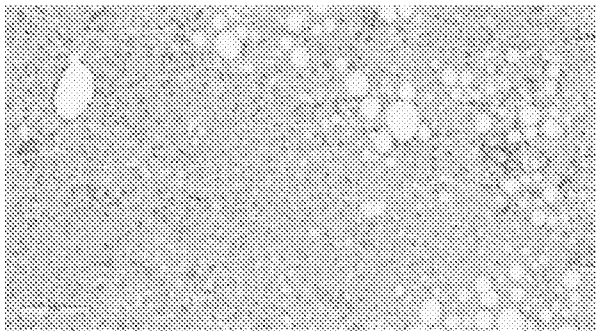
Compound 2 (low)



Compound 2 (high)

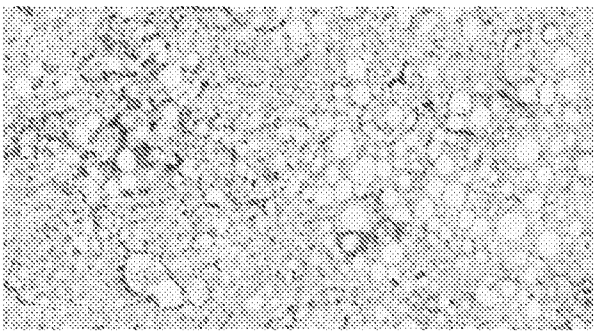


Compound 1

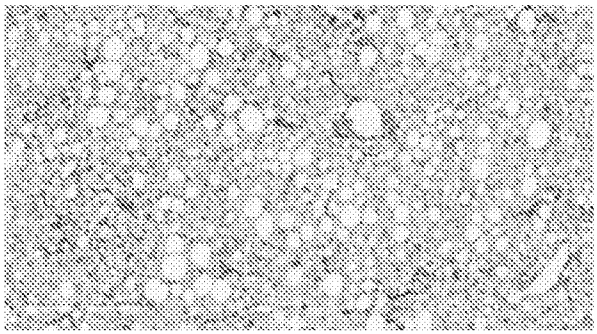


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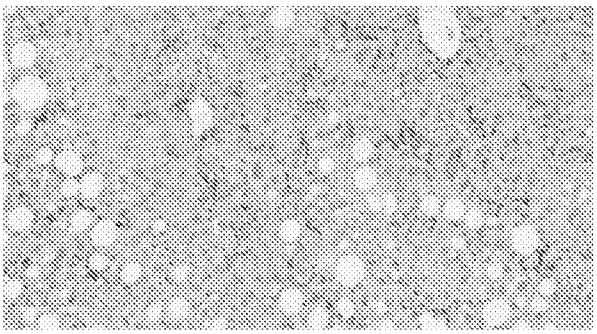
Figure 2



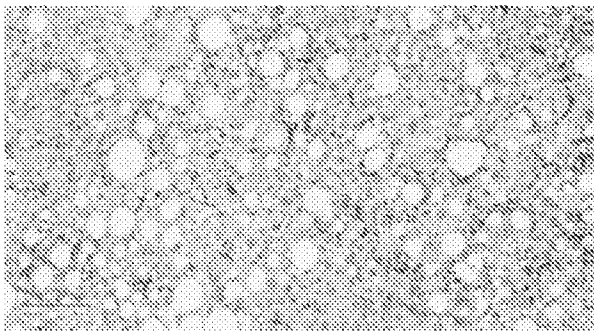
Vehicle



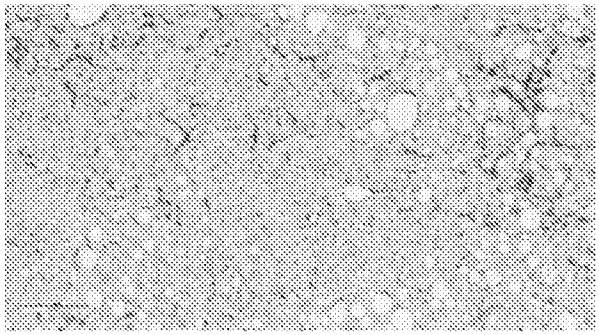
Compound 2 (low)



Compound 2 (high)



Compound 1



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Figure 3

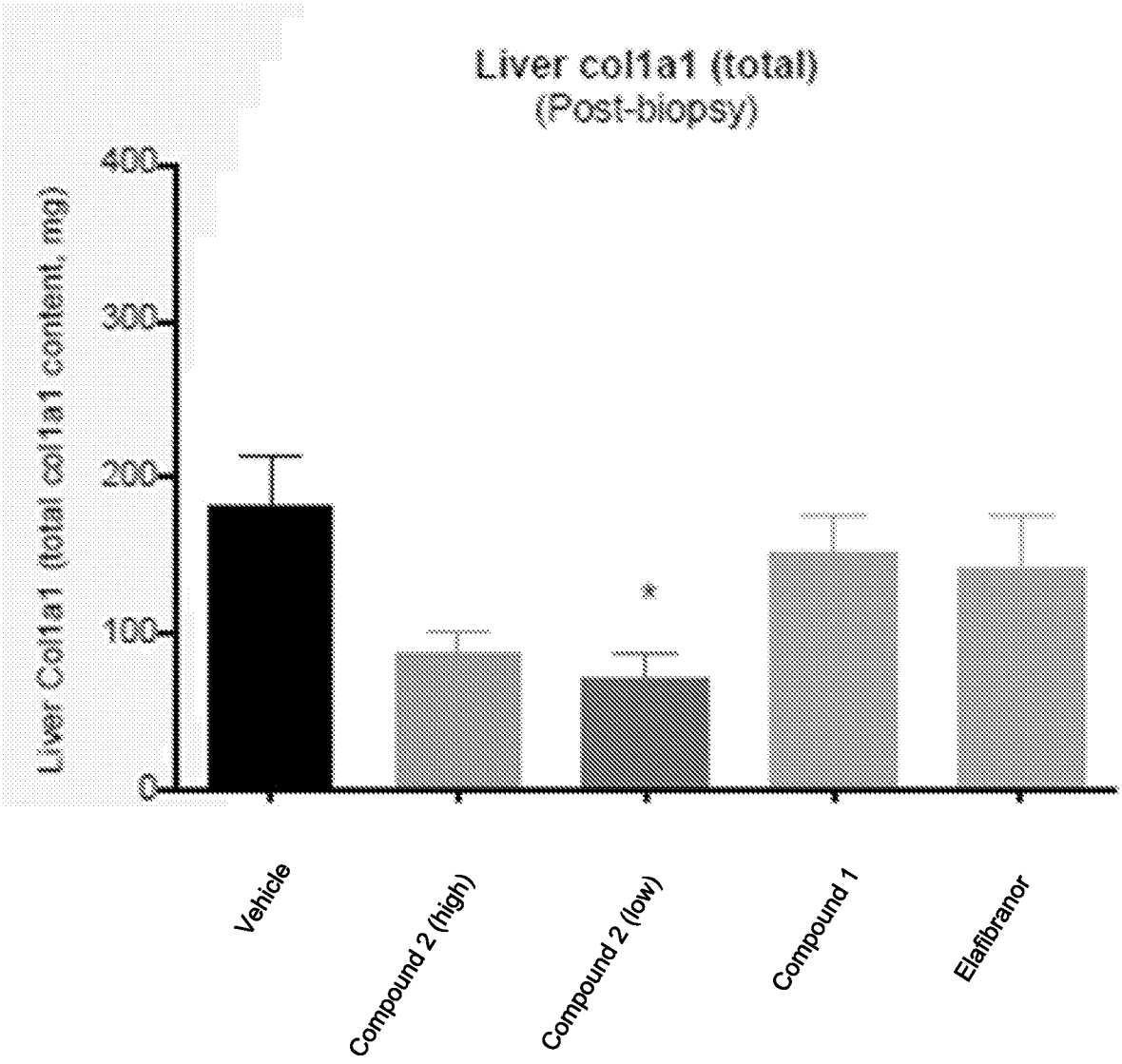

Liver col1a1 (total)
(Post-biopsy)
Liver Col1a1 (total col1a1 content, mg)
400
300
200
100
0
*
Vehicle
Compound 2 (high)
Compound 2 (low)
Compound 1
Elafibranor

Figure 4

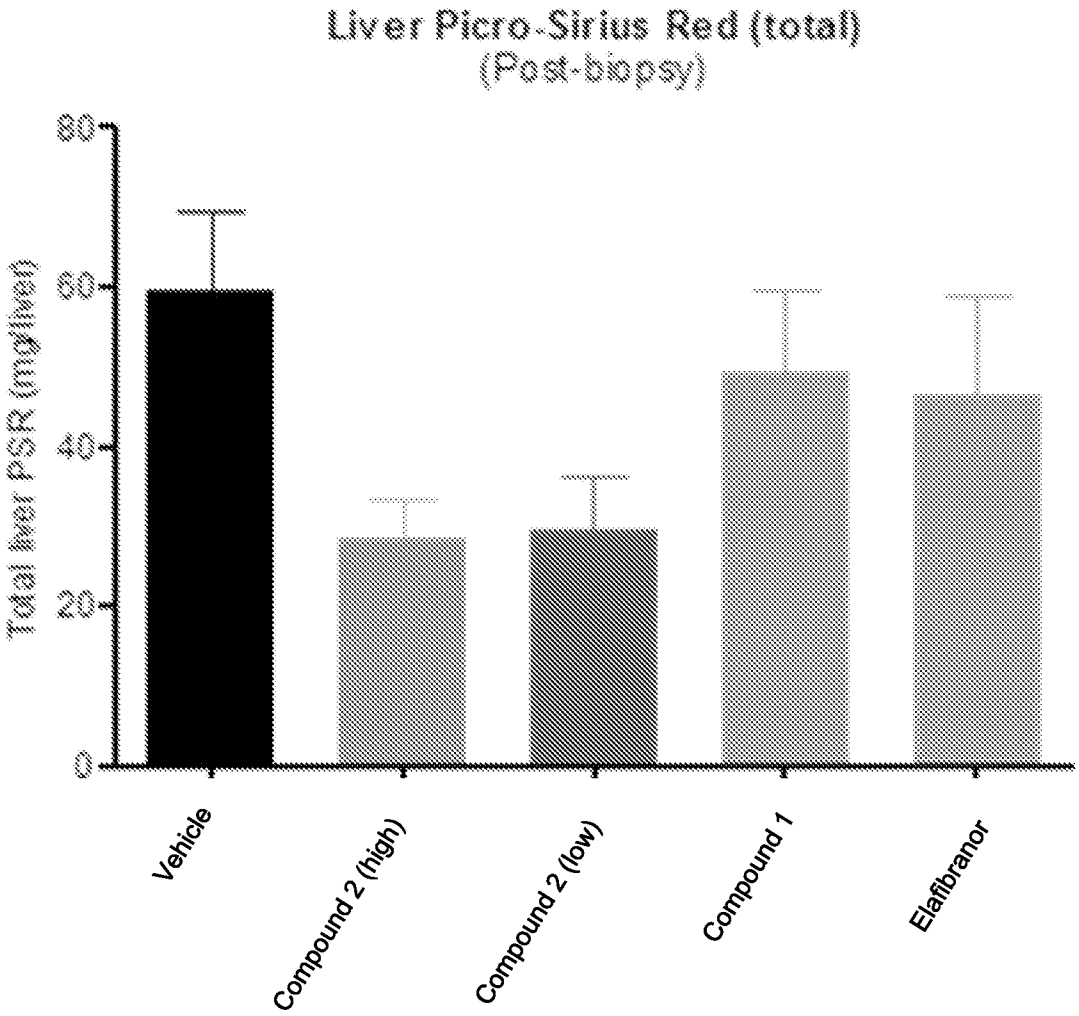

Liver Picro-Sirius Red (total)
(Post-biopsy)
Total liver PSR (mg/liver)
80
60
40
20
0
Vehicle
Compound 2 (high)
Compound 2 (low)
Compound 1
Elafibranor

Figure 5

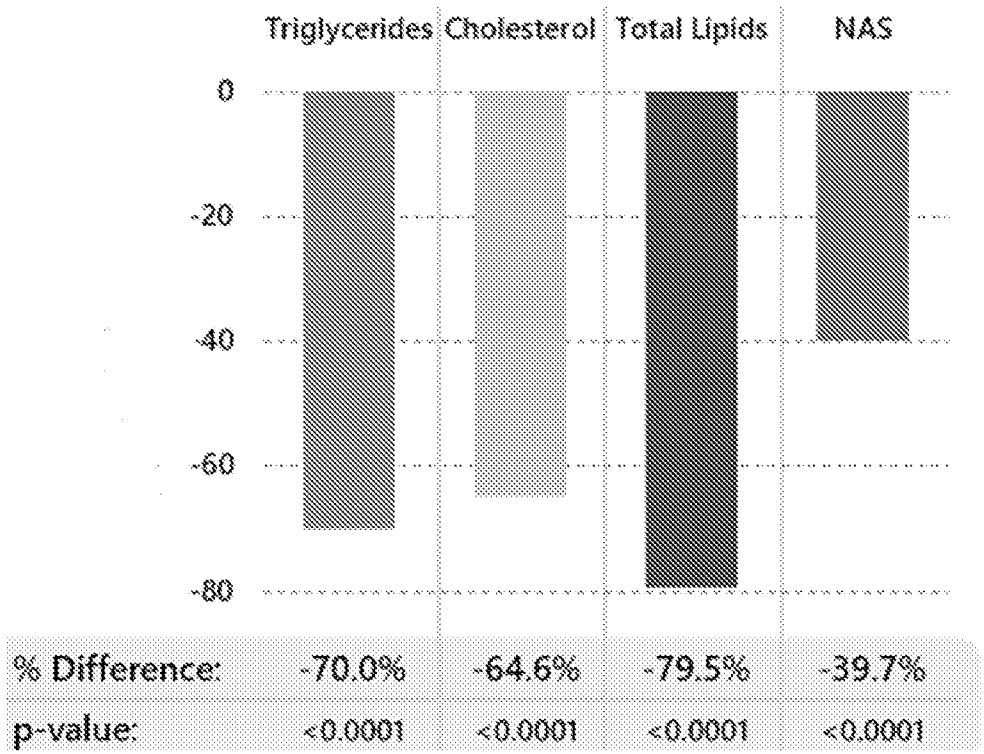

Triglycerides
Cholesterol
Total Lipids
NAS
0
-20
-40
-60
-80
% Difference:
-70.0%
-64.6%
-79.5%
-39.7%
p-value:
<0.0001
<0.0001
<0.0001
<0.0001

Figure 6

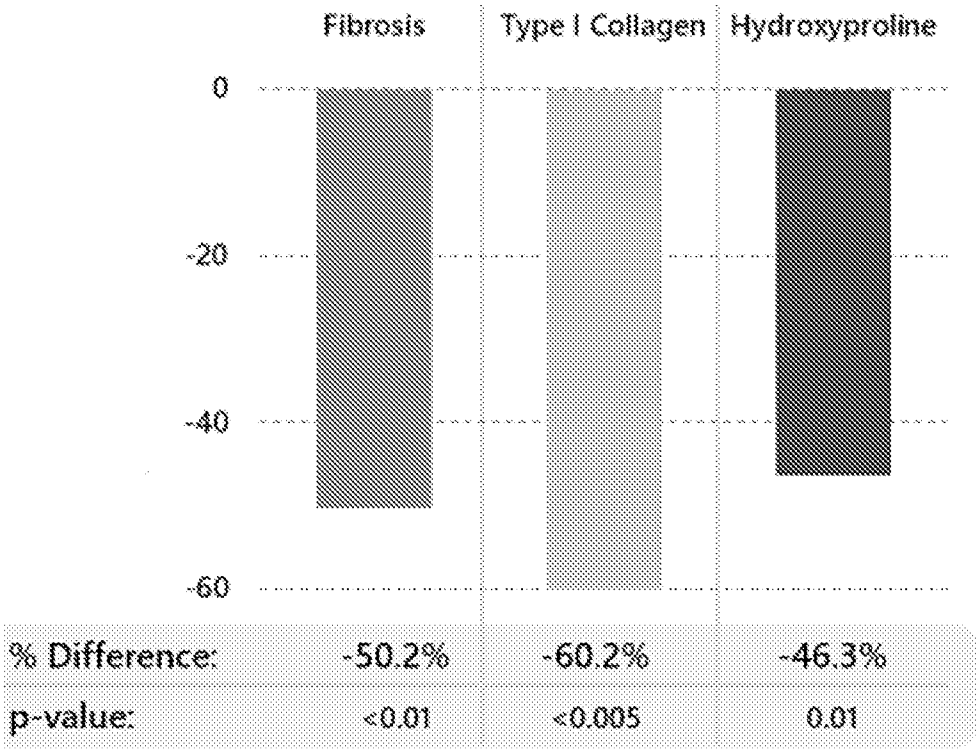
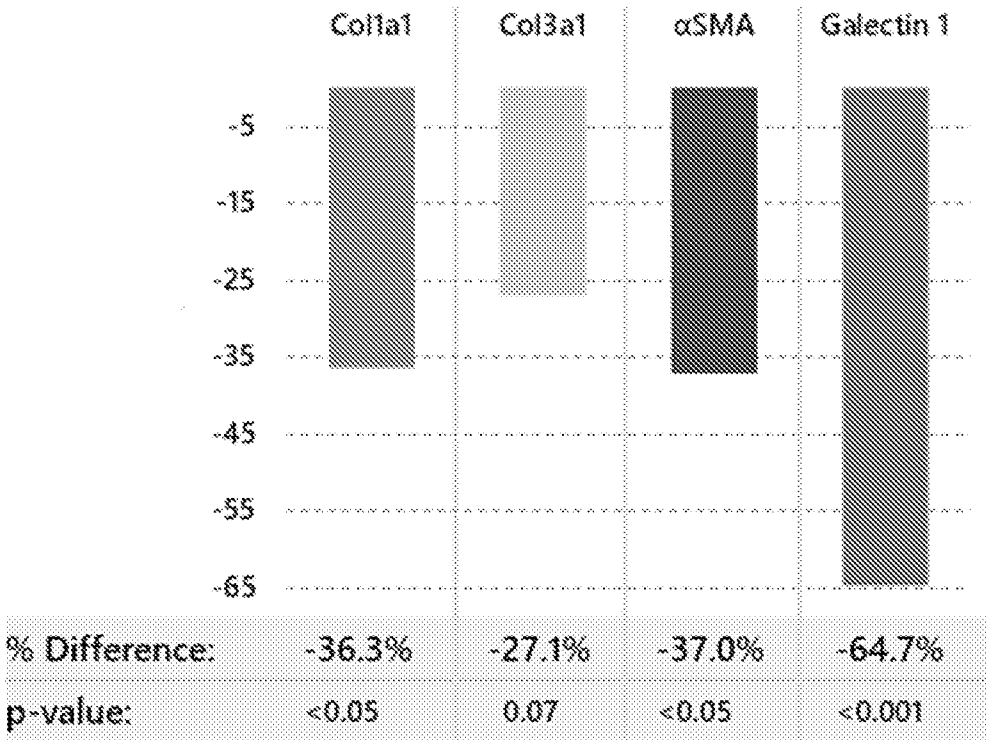

Fibrosis
Type I Collagen
Hydroxyproline
0
-20
-40
-60
% Difference:
-50.2%
-60.2%
-46.3%
p-value:
<0.01
<0.005
0.01

Figure 7



	Col1a1	Col3a1	αSMA	Galectin 1
% Difference:	-36.3%	-27.1%	-37.0%	-64.7%
p-value:	<0.05	0.07	<0.05	<0.001

Figure 8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/035909

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/662 (2006.01) A61K 31/665 (2006.01) A61P 1/16 (2006.01) A61P 19/04 (2006.01)

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)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, Epoque; Databases: Registry, Medline, CAplus, WPIDS, Biosis, Embase, EPODOC, WPIAP, TXTE cluster; structure search based on Formula I; Keywords: thyroid hormone receptor agonist, fibrosis, fibrous connective tissue, fibroma, fibrotic, cirrhosis, cirrhotic, scleroderma, scar, scarred, scarring, liver, hepatic, extracellular matrix, ECM protein, connective tissue, collagen, elastin, fibronectin, laminin, keratin, fibrin, perlecan, agrin, agrecan, deposit, lay down, laid down, formation, collagen, hydroxyproline, non-alcoholic fatty liver, NAFLD, fatty liver disease, non-alcoholic steatohepatitis, NASH, MB07811, VK2809, MB07344 & like terms; Registry numbers: 852948-13-1, 852947-39-8; Databases: AusPat, PatentScope, Espacenet, PubMed, Scholar.google.com, IP Australia Internal databases; Name Applicant and inventor search, and keywords: fibrosis, fibrotic, thyroid, hormone, VK2809, MB07811

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	Documents are listed in the continuation of Box C	

[X] Further documents are listed in the continuation of Box C [X] 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
2 August 2018	02 August 2018
Name and mailing address of the ISA/AU	**Authorised officer**
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA Email address: pct@ipaustralia.gov.au	Ross Heisey AUSTRALIAN PATENT OFFICE (ISO 9001 Quality Certified Service) Telephone No. +61262833185

INTERNATIONAL SEARCH REPORT C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		International application No. **PCT/US2018/035909**
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	CABLE, E.E., et al., "Reduction of Hepatic Steatosis in Rats and Mice After Treatment with a Liver-Targeted Thyroid Hormone Receptor Agonist", Hepatology, 2009, vol. 49, pages 407-417 Abstract; page 408, LH col., last paragraph; paragraph bridging pages 412-413; Figs. 1, 4-5 paragraph bridging pages 412-413; Figs. 1, 4-5	1-3, 5-10, 12-17, 22 1-25
Y	WO 2006/128058 A2 (METABASIS THERAPEUTICS, INC.) 30 November 2006 Abstract; para. 0038, 0048, 0190, 0266-0268; Compounds 7, cis-13-1; Examples A-D; claims 31-32	1-25
Y	WO 2006/128055 A2 (METABASIS THERAPEUTICS, INC.) 30 November 2006 Abstract; para. 0037-0038, 0164-0167; Examples 7, 13, 38; Compounds 7, 13-1-cis, 38	1-25
Y	WO 2006/128056 A2 (METABASIS THERAPEUTICS, INC.) 30 November 2006 Abstract; para. 0037-0038, 0150-0153; Examples 7, 13, 38; Compounds 7, 13-1-cis, 38	1-25
Y	ALONSO-MERINO, E., et al., "Thyroid hormones inhibit TGF-β signaling and attenuate fibrotic responses", PNAS, 2016, vol. 113(24), pages E3451-E3460 Abstract; page E3451, LH and RH col.; Figs. 7-10; Description at pages E3457-E3459	1-25
P,X	REUTERS Market News, "BRIEF-Viking Therapeutics says statistically significant reductions in fibrosis, liver collagen, after 8 weeks of VK2809 treatment", [retrieved from Internet on 28 July 2018] <URL: https://www.reuters.com/article/brief-viking-therapeutics-says-statistic/brief-viking-therapeutics-says-statistically-significant-reductions-in-fibrosis-liver-collagen-after-8-weeks-of-vk2809-treatment-idUSFWN1J308Y> Published online 6 June 2017. Whole document, in particular, Summary, bullet points	1-18, 22, 24
P,X	LIAN, B., "Evaluation of the Thyroid Receptor Agonist VK2809 on Liver Disease in DIO-NASH Mice", Hepatology, October 2017, vol. 66, No. Suppl. 1, Sp. Iss. SI, page 1038A, Abstract 1958 Whole document, in particular, Background, Results	1-17, 22
P,X	WO 2018/094265 A2 (VIKING THERAPEUTICS, INC.) 24 May 2018 Abstract; para. 0041, 0092, Examples 5-11; claims 2, 7	1-3, 5-10, 12-25

INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2018/035909**

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Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
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		AU 2006249350 B2	16 Feb 2012
		CA 2606499 A1	30 Nov 2006
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		JP 2008542301 A	27 Nov 2008
		MX 2007014502 A	07 Feb 2008
		US 2009232879 A1	17 Sep 2009
		US 2017112864 A1	27 Apr 2017
WO 2006/128055 A2	30 November 2006	WO 2006128055 A2	30 Nov 2006
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		EP 1689383 B1	31 Oct 2012
		EP 1891080 A2	27 Feb 2008
		EP 2428516 A1	14 Mar 2012
		JP 2007512359 A	17 May 2007
		JP 2008545710 A	18 Dec 2008
		KR 20060109926 A	23 Oct 2006
		MX 2007014493 A	07 Feb 2008
		RU 2006117986 A	27 Dec 2007
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		WO 2005051298 A2	09 Jun 2005

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INTERNATIONAL SEARCH REPORT Information on patent family members	International application No. **PCT/US2018/035909**

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Patent Document/s Cited in Search Report		**Patent Family Member/s**	
Publication Number	**Publication Date**	**Publication Number**	**Publication Date**
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		AU 2006249348 A1	30 Nov 2006
		AU 2006249348 B2	24 May 2012
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		RU 2007148927 A	10 Jul 2009
		US 2009028925 A1	29 Jan 2009
WO 2018/094265 A2	24 May 2018	WO 2018094265 A2	24 May 2018

End of Annex

Due to data integration issues this family listing may not include 10 digit Australian applications filed since May 2001.