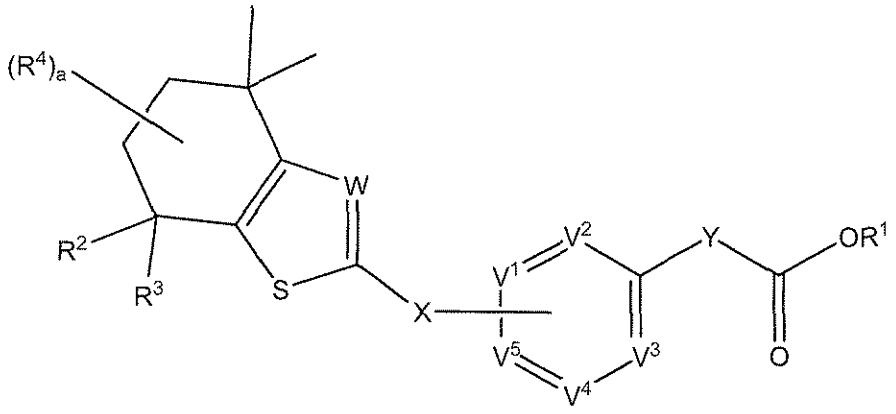
~~STATEMENT OF INVENTION~~SUMMARY

The present ~~invention~~ disclosure provides a compound of formula (I):



Formula (I)

wherein:

R^1 is selected from the group consisting of H, C_1-C_6alkyl and a carboxylic acid protecting group;

R^2 and R^3 are independently selected from the group consisting of H and C_1-C_6alkyl;

each R^4 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_2-C_{12}alkenyloxy, optionally substituted C_2-C_{12}alkynyloxy, optionally substituted C_2-C_{10}heteroalkyloxy, optionally substituted C_3-C_{12}cycloalkyloxy, optionally substituted C_3-C_{12}cycloalkenyloxy, optionally substituted C_2-C_{12}heterocycloalkyloxy, optionally substituted C_2-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18}aryloxy, optionally substituted C_1-C_{18}heteroaryloxy, optionally substituted C_1-C_{12}alkylamino, SR^5, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$, NR^5COR^5, NR^5COOR^5, $NR^5SO_2R^5$, $NR^5CONR^5R^5$, NR^5R^5, and acyl, or two R^4 on the same carbon atom when taken together form a =O substituent or a group of formula =NOH, or two R^4 on adjacent carbon atoms when taken together form a double bond;

optionally substituted C_2-C_{12}alkynyloxy, optionally substituted C_2-C_{10}heteroalkyloxy, optionally substituted C_3-C_{12}cycloalkyloxy, optionally substituted C_3-C_{12}cycloalkenyloxy, optionally substituted C_2-C_{12}heterocycloalkyloxy, optionally substituted C_2-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18}aryloxy, optionally substituted C_1-C_{18}heteroaryloxy, optionally substituted C_1-C_{12}alkylamino, SR^5, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$, NR^5COR^5, NR^5COOR^5, $NR^5SO_2R^5$, $NR^5CONR^5R^5$, NR^5R^5, and acyl, or R^7 when taken together with the carbon atom to which it is attached forms a cyclic moiety with a substituent on X;

R^8 is a bond to X,

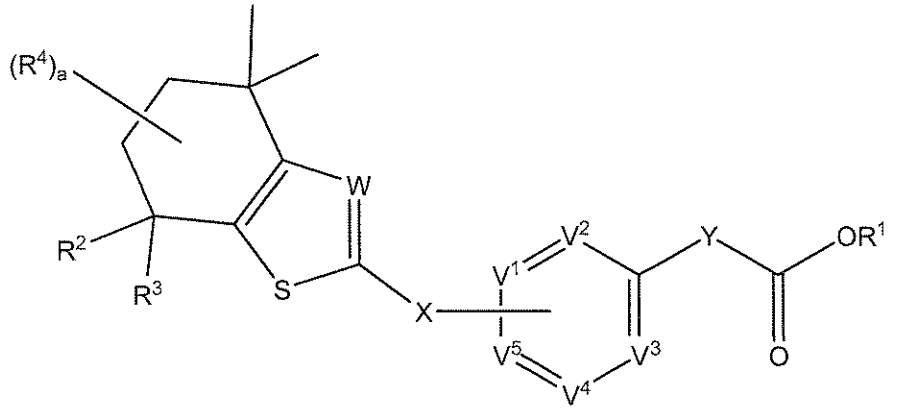
Y is a bond or a linking group;

W is selected from the group consisting of N and CR^9;

R^9 is selected from H and C_1-C_6alkyl;

or a pharmaceutically acceptable salt thereof.

In one aspect, there is provided a compound of formula (I):



Formula (I)

wherein:

R^1 is selected from the group consisting of H, C_1-C_6alkyl and a carboxylic acid protecting group;

R^2 and R^3 are independently selected from the group consisting of H and C_1-C_6alkyl;

each R^4 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_2-C_{12}alkenyloxy, optionally substituted C_2-C_{12}alkynyloxy, optionally substituted C_2-C_{10}heteroalkyloxy, optionally substituted C_3-C_{12}cycloalkyloxy, optionally substituted C_3-C_{12}cycloalkenyloxy, optionally substituted C_2-C_{12}heterocycloalkyloxy, optionally substituted C_2-C_{12}heterocycloalkenyloxy, optionally substituted C_6-C_{18}aryloxy, optionally substituted C_1-C_{18}heteroaryloxy, optionally substituted C_1-C_{12}alkylamino, SR^5, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$, NR^5COR^5, NR^5COOR^5, $NR^5SO_2R^5$, $NR^5CONR^5R^5$, NR^5R^5, and acyl, or two R^4 on the same carbon atom when taken together form a =O substituent or a group of formula =NOH, or two R^4 on adjacent carbon atoms when taken together form a double bond;

wherein each R^5 is independently selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{10}heteroalkyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_6-C_{18}aryl, and optionally substituted C_1-C_{18}heteroaryl;

a is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

wherein X is selected from the group consisting of a bond, –O-, -S-, $-NR^{10}$-, $NR^{10}C(=O)$-, $-C(=R^{11})$- and $-(CR^{12}R^{13})_b$-;

wherein R^{10} is selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl,optionally substituted C_6-C_{18}aryl,optionally substituted C_1-C_{18}heteroaryl,optionally substituted C_3-C_{12}cycloalkylC_1-C_{12}alkyl, optionally substituted C_2-C_{12}heterocycloalkylC_1-C_{12}alkyl, optionally substituted C_6-C_{18}aryl C_1-C_{12}alkyl, optionally substituted C_1-C_{18}heteroarylC_1-C_{12}alkyl, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$ and acyl;

wherein R^{11} is selected from the group consisting of O, NR^{14}, NOR^{14} and $CR^{14}R^{15}$, wherein each R^{14} and R^{15} is independently selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_2-C_{12}heteroalkyl, optionally

substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl,optionally substituted C_6-C_{18}aryl,optionally substituted C_1-C_{18}heteroaryl,optionally substituted C_3-C_{12}cycloalkylC_1-C_{12}alkyl, optionally substituted C_2-C_{12}heterocycloalkylC_1-C_{12}alkyl, optionally substituted C_6-C_{18}aryl C_1-C_{12}alkyl, optionally substituted C_1-C_{18}heteroarylC_1-C_{12}alkyl, and acyl;

each R^{12} and R^{13} is independently selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl,optionally substituted C_6-C_{18}aryl,optionally substituted C_1-C_{18}heteroaryl,optionally substituted C_3-C_{12}cycloalkylC_1-C_{12}alkyl, optionally substituted C_2-C_{12}heterocycloalkylC_1-C_{12}alkyl, optionally substituted C_6-C_{18}aryl C_1-C_{12}alkyl, optionally substituted C_1-C_{18}heteroarylC_1-C_{12}alkyl, and acyl, or R^{12} and R^{13} on the same carbon atom when taken together form a cyclic moiety,

b is an integer selected from the group consisting of 0, 1, 2,3 and 4;

V^2, V^3 and V^4 are each independently selected from the group consisting of N and CR^6;

each R^6 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_2-C_{12}alkenyloxy, optionally substituted C_2-C_{12}alkynyloxy, optionally substituted C_2-C_{10}heteroalkyloxy, optionally substituted C_3-C_{12}cycloalkyloxy, optionally substituted C_3-C_{12}cycloalkenyloxy, optionally substituted C_2-C_{12}heterocycloalkyloxy, optionally substituted C_2-C_{12}heterocycloalkenyloxy, optionally substituted C_6-C_{18}aryloxy, optionally substituted C_1-C_{18}heteroaryloxy, optionally substituted C_1-C_{12}alkylamino, SR^5, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$, NR^5COR^5, NR^5COOR^5, $NR^5SO_2R^5$, $NR^5CONR^5R^5$, NR^5R^5, and acyl;

V^1 and V^5 are selected from the group consisting of N, CR^7 and CR^8 such that one of V^1 and V^5 is CR^8 and the other is N or CR^7;

R^7 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl,

optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_2-C_{12}alkenyloxy, optionally substituted C_2-C_{12}alkynyloxy, optionally substituted C_2-C_{10}heteroalkyloxy, optionally substituted C_3-C_{12}cycloalkyloxy, optionally substituted C_3-C_{12}cycloalkenyloxy, optionally substituted C_2-C_{12}heterocycloalkyloxy, optionally substituted C_2-C_{12}heterocycloalkenyloxy, optionally substituted C_6-C_{18}aryloxy, optionally substituted C_1-C_{18}heteroaryloxy, optionally substituted C_1-C_{12}alkylamino, SR^5, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$, NR^5COR^5, NR^5COOR^5, $NR^5SO_2R^5$, $NR^5CONR^5R^5$, NR^5R^5, and acyl, or R^7 when taken together with the carbon atom to which it is attached forms a cyclic moiety with a substituent on X;

R^8 is a bond to X,

Y is a bond;

W is selected from the group consisting of N and CR^9;

R^9 is selected from H and C_1-C_6alkyl;

or a pharmaceutically acceptable salt thereof.

In a further aspect, ~~the invention relates to~~there is provided a pharmaceutical composition ~~containing~~ including a compound ~~of the invention~~as described herein and a pharmaceutically acceptable diluent, excipient or carrier.

~~In yet an even further aspect the invention relates to~~Disclosed is a method of prevention or treatment of a condition in a mammal comprising administration of an effective amount of a compound of the ~~invention~~disclosure. In one embodiment the condition is a condition that can be prevented or treated by activation of RXR.

In one aspect, there is provided use of a compound as described herein in the preparation of a medicament.

~~In yet an even further aspect the invention relates to~~Also disclosed is the use of a compound of the disclosure~~invention~~ in the preparation of a medicament for the treatment of a condition in a mammal. In one embodiment the condition is a condition that can be prevented or treated by activation of RXR.

~~In yet an even further aspect still the invention relates to~~Further disclosed is the use of a compound of the disclosure~~invention~~ for the treatment of a condition in a mammal. In one embodiment the condition is a condition that can be prevented or treated by activation of RXR.

Examples of conditions that may be treated include cancers, dermatological disorders, respiratory and pulmonary system disorders, metabolic disorders, inflammatory diseases, renal diseases, autoimmune diseases and neurodegenerative diseases.

Examples of cancers include Breast Cancer, pancreatic cancer, Cutaneous T-cell lymphoma (relapsed or refractory cutaneous T-cell lymphoma), Lung cancer, Liver cancer (hepatocellular carcinoma), Kaposi's Sarcoma (AIDS related Kaposi's sarcoma), Cutaneous T-cell lymphoma, promyelocytic leukemia, Skin cancer (basal cell carcinoma), Non-small cell Lung Cancer, Kidney cancer (advanced renal cell cancer), Gastrointestinal (stomach) cancer (advanced aerodigestive tract cancer), Mesothelioma, and Non-small-cell lung cancer.

Examples of dermatological disorders include Dermatitis (severe chronic hand eczema in adults), Psoriasis (Severe Plaque Psoriasis), Psoriasis (moderate to severe psoriasis) and alopecia.

Examples of respiratory and pulmonary system disorers include Bronchial Metaplasia and Pulmonary Fibrosis (Fibrosis).

Examples of metabolic diseases include Pre diabetes, Type 2 diabetes, Obesity, Hypercholesteriolemia, Hypertriglyceridemia, Hypertension, Dyslipidemia, hyperinsulinaemia, Liver diseases, NASH, and Atherosclerosis.

Examples of inflammatory disorders include oxidative stress, Renal fibrosis, Hepatic diseases such as steatosis, steatohepatitis (alcoholic and non alcoholic), Hepatic fibrosis and cirrhosis, autoimmune diseases and Experimental autoimmune encephalomyelitis.

An example of a neurodegenerative disorder is alzheimers disease.

Examples of other conditions that may be treated include obesity and cardiovascular disease.

The compounds of the disclosure~~invention~~ may also be used to provide a number of beneficial effects to a mammal. Examples of beneficial effects that may be provided include increasing muscle endurance, improving cardiac function and achieving an exercise mimetic effect.

Accordingly, in another aspect, ~~the invention provides~~there is provided use of a compound as described herein in the preparation of a medicament for increasing muscle endurance in a mammal. Also provided is a method of increasing muscle endurance in a mammal, the method comprising administering an effective amount of a compound of the disclosure~~invention~~.

Accordingly, in another aspect, ~~the invention provides~~there is provided use of a compound as described herein in the preparation of a medicament for improving cardiac function in a mammal. Also provided is a method of improving cardiac function in a mammal, the method comprising administering an effective amount of a compound of the disclosure~~invention~~. Examples of cardiac function that may be improved include stroke work, stroke volume, ejection fraction and ventricular refilling.

Accordingly, in another aspect, ~~the invention provides~~there is provided use of a compound as described herein in the preparation of a medicament for achieving an exercise mimetic effect in a mammal. Also provided is a method of achieving an exercise mimetic effect in a mammal, the method comprising administering an effective amount of a compound of the disclosure~~invention~~.

These and other teachings of the disclosure~~invention~~ are set forth herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A shows cholesterol retention in neuronal cells treated with compound 40.

Figure 1B shows reduced oxidative stress (ROS) levels in neuronal cells treated with compound 40.

Figure 1C shows caspase activity in neuronal cells treated with compound 40.

Figure 1D shows ABCA1 expression in neuronal cells treated with compound 40.

Figure 1E shows ABCG1 expression in neuronal cells treated with compound 40.

Figure 2A shows reduced oxidative stress (ROS) levels in astrocytes treated with compound 40.

Figure 2B shows IL6 levels in astrocytes treated with compound 40.

Figure 2C shows IL6 expression in astrocytes treated with compound 40.

Figure 2D shows IL1B expression in astrocytes treated with compound 40.

Figure 2E shows COX2 expression in astrocytes treated with compound 40.

Figure 2F shows MCP1 expression in astrocytes treated with compound 40.

Figure 3A shows MiA PaCa2 cell line growth on cells treated with compound 40.

Figure 3B shows the results of a cell proliferation assay (BrdU incorporation) of MiA PaCa2 cell line growth on cells treated with compound 40.

Figure 4A shows reduced oxidative stress (ROS) levels in MiA PaCa2 treated with compound 40.

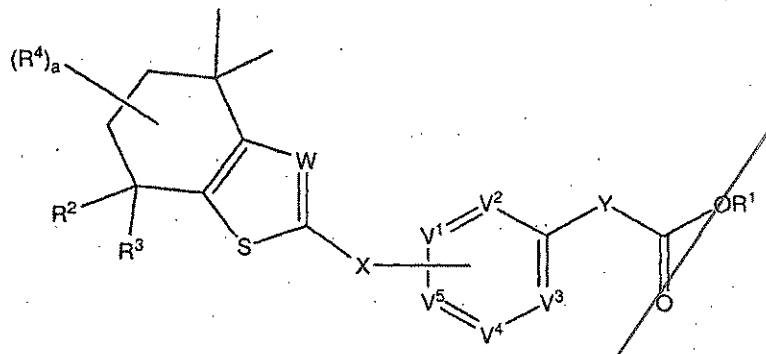
Figure 4B shows caspase levels in MiA PaCa2 treated with compound 40.

Figure 4C shows a cell death ELISA in MiA PaCa2 treated with compound 40.

Figure 5A shows impact of compound 40 on cell proliferation of MCF7 cells.

Claims

1. A compound of formula (I):



Formula (I)

wherein:

R^1 is selected from the group consisting of H, C_1-C_6alkyl and a carboxylic acid protecting group;

R^2 and R^3 are independently selected from the group consisting of H and C_1-C_6alkyl;

each R^4 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_2-C_{12}alkenyloxy, optionally substituted C_2-C_{12}alkynyloxy, optionally substituted C_2-C_{10}heteroalkyloxy, optionally substituted C_3-C_{12}cycloalkyloxy, optionally substituted C_3-C_{12}cycloalkenyloxy, optionally substituted C_2-C_{12}heterocycloalkyloxy, optionally substituted C_2-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18}aryloxy, optionally substituted C_1-C_{18}heteroaryloxy, optionally substituted C_1-C_{12}alkylamino, SR^5, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$, NR^5COR^5, NR^5COOR^5, $NR^5SO_2R^5$, $NR^5CONR^5R^5$, NR^5R^5, and acyl, or two R^4 on the same carbon atom when taken together form a =O substituent or a group of formula =NOH, or two R^4 on adjacent carbon atoms when taken together form a double bond;

wherein each R^5 is independently selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{10}heteroalkyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_6-C_{18}aryl, and optionally substituted C_1-C_{18}heteroaryl;

a is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

X is a bond or a linking group;

V^2, V^3 and V^4 are each independently selected from the group consisting of N and CR^6;

each R^6 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_2-C_{12}alkenyloxy, optionally substituted C_2-C_{12}alkynyloxy, optionally substituted C_2-C_{10}heteroalkyloxy, optionally substituted C_3-C_{12}cycloalkyloxy, optionally substituted C_3-C_{12}cycloalkenyloxy, optionally substituted C_2-C_{12}heterocycloalkyloxy, optionally substituted C_2-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18}aryloxy, optionally substituted C_1-C_{18}heteroaryloxy, optionally substituted C_1-C_{12}alkylamino, SR^5, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$, NR^5COR^5, NR^5COOR^5, $NR^5SO_2R^5$, $NR^5CONR^5R^5$, NR^5R^5, and acyl;

V^1 and V^5 are selected from the group consisting of N, CR^7 and CR^8 such that one of V^1 and V^5 is CR^8 and the other is N or CR^7;

R^7 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_2-C_{12}alkenyloxy,

optionally substituted C_2-C_{12}alkynyloxy, optionally substituted C_2-C_{10}heteroalkyloxy, optionally substituted C_3-C_{12}cycloalkyloxy, optionally substituted C_3-C_{12}cycloalkenyloxy, optionally substituted C_2-C_{12}heterocycloalkyloxy, optionally substituted C_2-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18}aryloxy, optionally substituted C_1-C_{18}heteroaryloxy, optionally substituted C_1-C_{12}alkylamino, SR^5, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$, NR^5COR^5, NR^5COOR^5, $NR^5SO_2R^5$, $NR^5CONR^5R^5$, NR^5R^5, and acyl, or R^7 when taken together with the carbon atom to which it is attached forms a cyclic moiety with a substituent on X;

R^8 is a bond to X,
Y is a bond or a linking group;

W is selected from the group consisting of N and CR^9;

R^9 is selected from H and C_1-C_6alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 is H.

3. A compound according to claim 1 or 2 wherein Y is a bond.

4. A compound according to any one of claims 1 to 3 wherein a is 0.

5. A compound according to any one of claims 1 to 4 wherein R^2 and R^3 are C_1-C_6alkyl.

6. A compound according to any one of claims 1 to 5 wherein R^2 and R^3 are methyl.

7. A compound according to any one of claims 1 to 6 whereln W is N.

8. A compound according to any one of claims 1 to 6 wherein W is CR^9.

9. A compound according to claim 8 where R^9 is methyl.

10. A compound according to any one of claims 1 to 9 wherein X is selected from the group consisting of a bond, –O-, -S-, $-NR^{10}$-, $NR^{10}C(=O)$-, $-C(=R^{11})$- and $-(CR^{12}R^{13})_b$-;

wherein R^{10} is selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_3-C_{12}cycloalkylC_1-C_{12}alkyl, optionally substituted C_2-C_{12}heterocycloalkylC_1-C_{12}alkyl, optionally substituted C_6-C_{18}aryl C_1-C_{12}alkyl, optionally substituted C_1-C_{18}heteroarylC_1-C_{12}alkyl, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$ and acyl;

wherein R^{11} is selected from the group consisting of O, NR^{14}, NOR^{14} and $CR^{14}R^{15}$, wherein each R^{14} and R^{15} is independently selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_2-C_{12}heteroalkyl, *optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally* substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_3-C_{12}cycloalkylC_1-C_{12}alkyl, optionally substituted C_2-C_{12}heterocycloalkylC_1-C_{12}alkyl, optionally substituted C_6-C_{18}aryl C_1-C_{12}alkyl, optionally substituted C_1-C_{18}heteroarylC_1-C_{12}alkyl, and acyl;

each R^{12} and R^{13} is independently selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_3-C_{12}cycloalkylC_1-C_{12}alkyl, optionally substituted C_2-C_{12}heterocycloalkylC_1-C_{12}alkyl, optionally substituted C_6-C_{18}aryl C_1-C_{12}alkyl, optionally substituted C_1-C_{18}heteroarylC_1-C_{12}alkyl, and acyl, or R^{12} and R^{13} on the same carbon atom when taken together form a cyclic moiety or R^{12} and R^{13} on adjacent carbon atoms when taken together form a double bond;

b is an integer selected from the group consisting of 0, 1, 2,3 and 4;

11. A compound according to claim 10 wherein X is $-NR^{10}-$

12 A compound according to claim 11 wherein R^{10} is selected from the group consisting of H, C_1-C_{12}alkyl, and C_3-C_{12}cycloalkylC_1-C_{12}alkyl.

13 A compound according to any one of claims 1 to 12 wherein V^2 is CR^6.

14. A compound according to any one of claims 1 to 13 wherein V^3 is CR^6.

15. A compound according to any one of claims 1 to 14 wherein V^5 is CR^6.

16. A compound according to any one of claims 1 to 15 wherein V^4 is CR^6.

17. A compound according to any one of claims 1 to 15 wherein V^4 is N.

18. A compound according to any one of claims 1 to 17 wherein V^1 is CR^6.

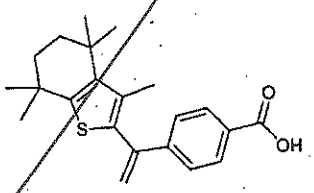
19. A compound according to any one of claims 1 to 17 wherein V^1 is N.

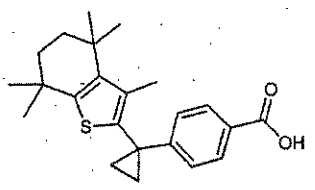
20. A compound according to any one of the proceeding claims wherein each R^6 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, C_1-C_{12}alkyl and C_1-C_{12}alkyloxy.

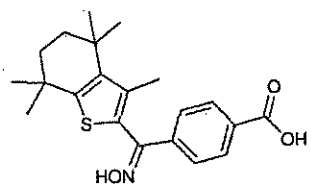
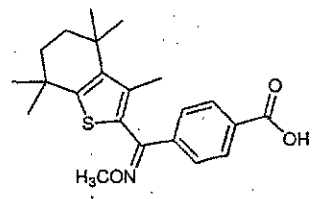
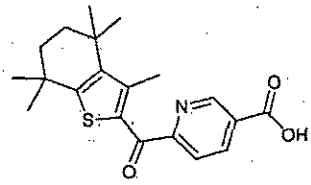
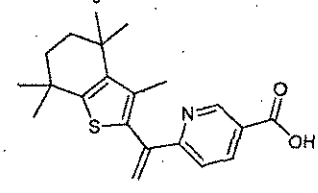
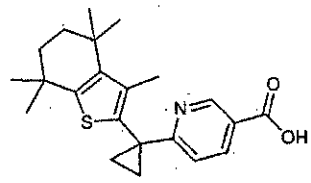
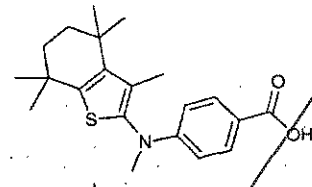
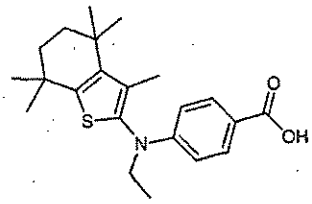
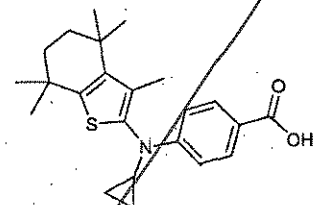
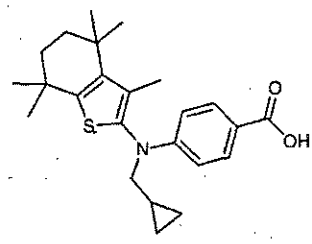
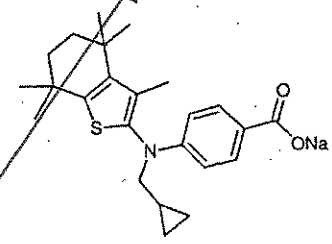
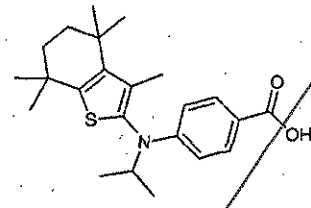
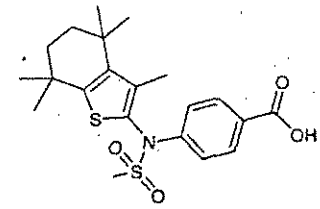
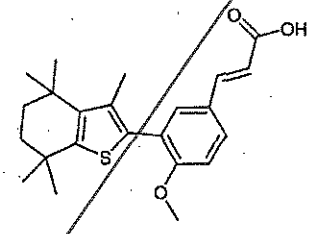
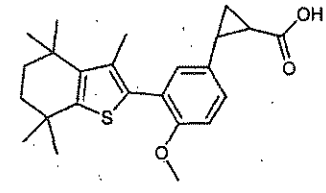
21. A compound according to any one of the proceeding claims wherein each R^6 is independently selected from the group consisting of H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $(CH_2)_3CH_3$, Cl, Br, F, I, OH, NO_2, NH_2, CN, OCH_3, $OCH_2CH_2CH_3$, CF_3, and OCF_3.

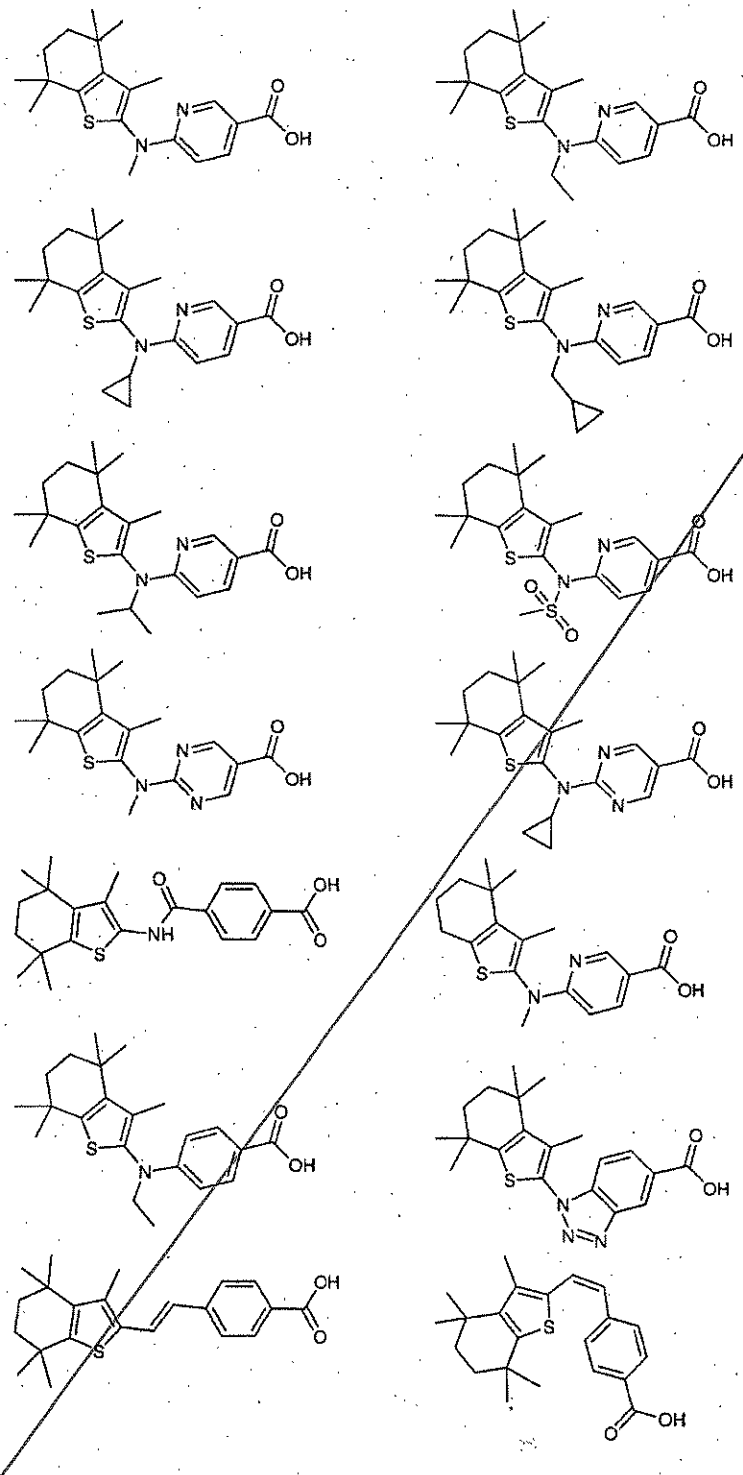
22. A compound according to claim 1 wherein each optional substituent is independently selected from the group consisting of H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $(CH_2)_3CH_3$, Cl, Br, F, I, OH, NO_2, NH_2, CN, OCH_3, $OCH_2CH_2CH_3$, CF_3, and OCF_3.

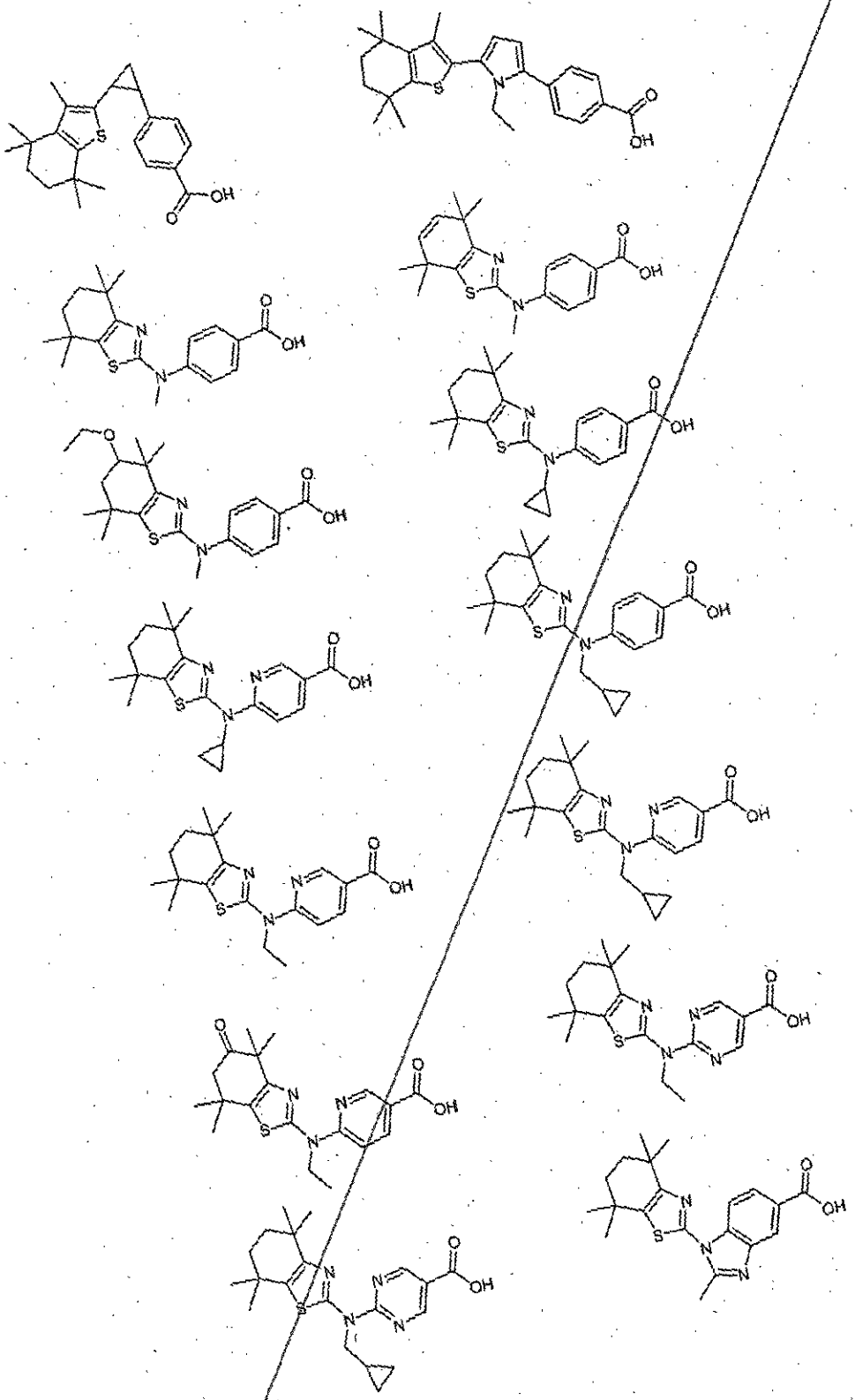
23. A compound according to claim 1 selected from the group consisting of

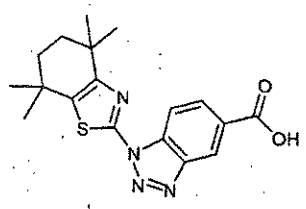
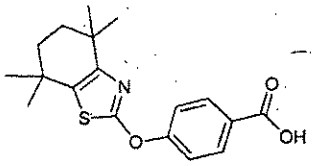
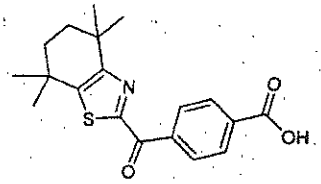
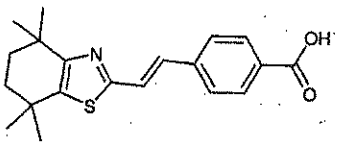
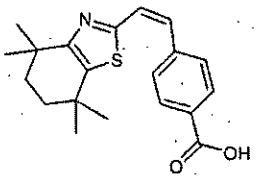
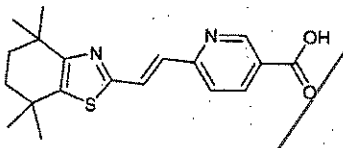
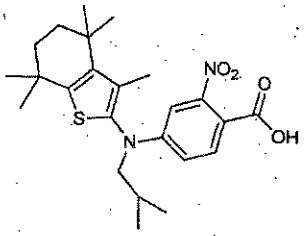
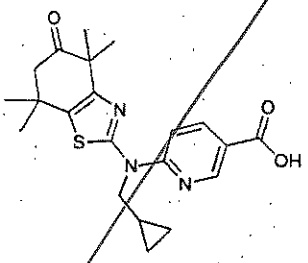
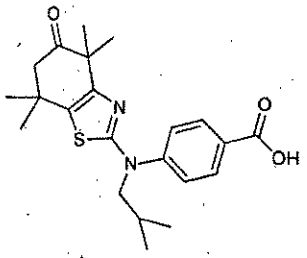
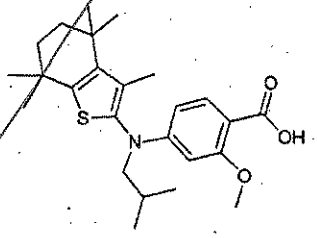
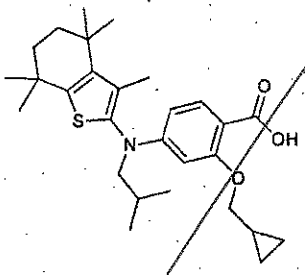
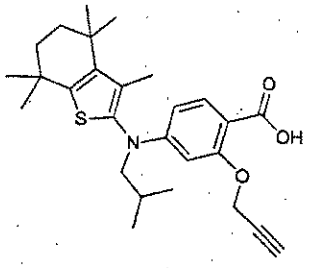


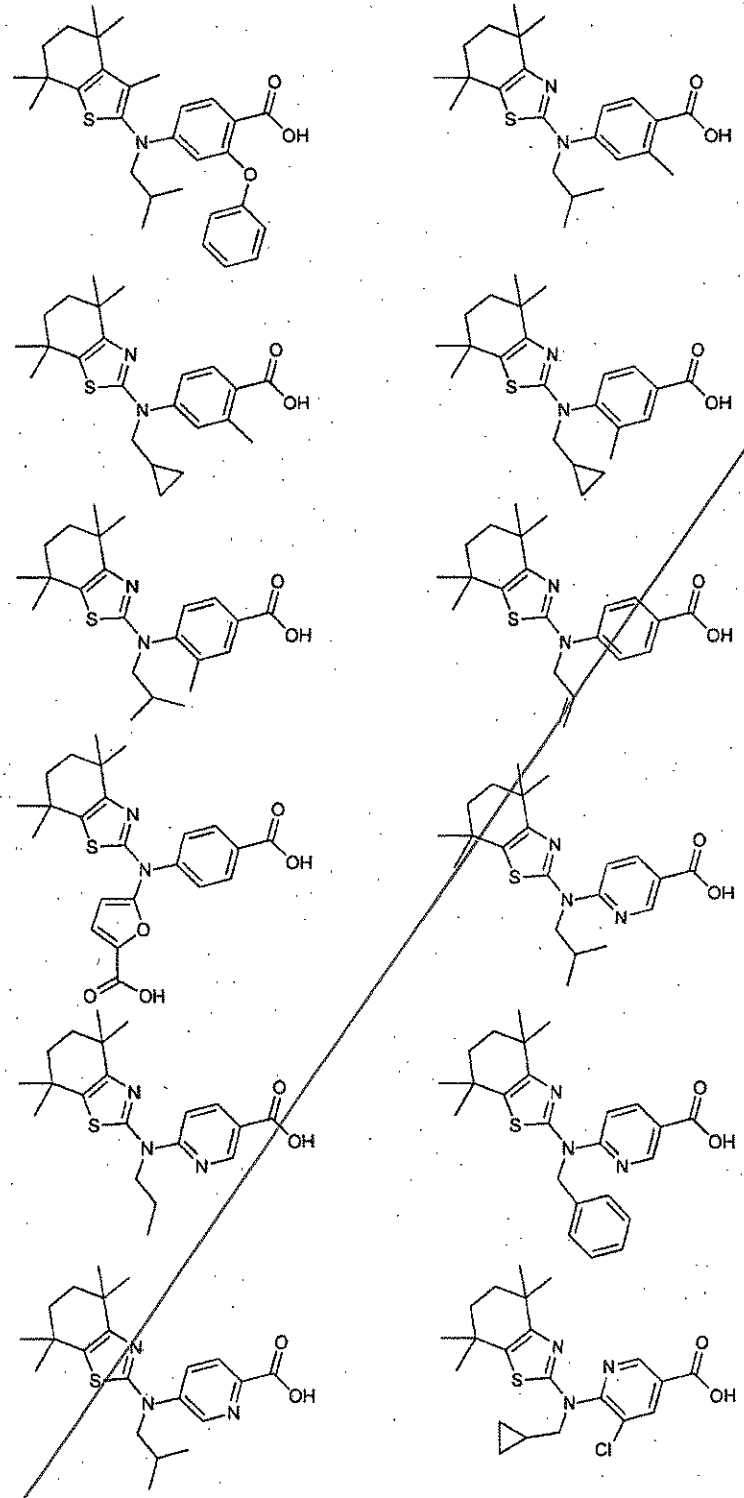


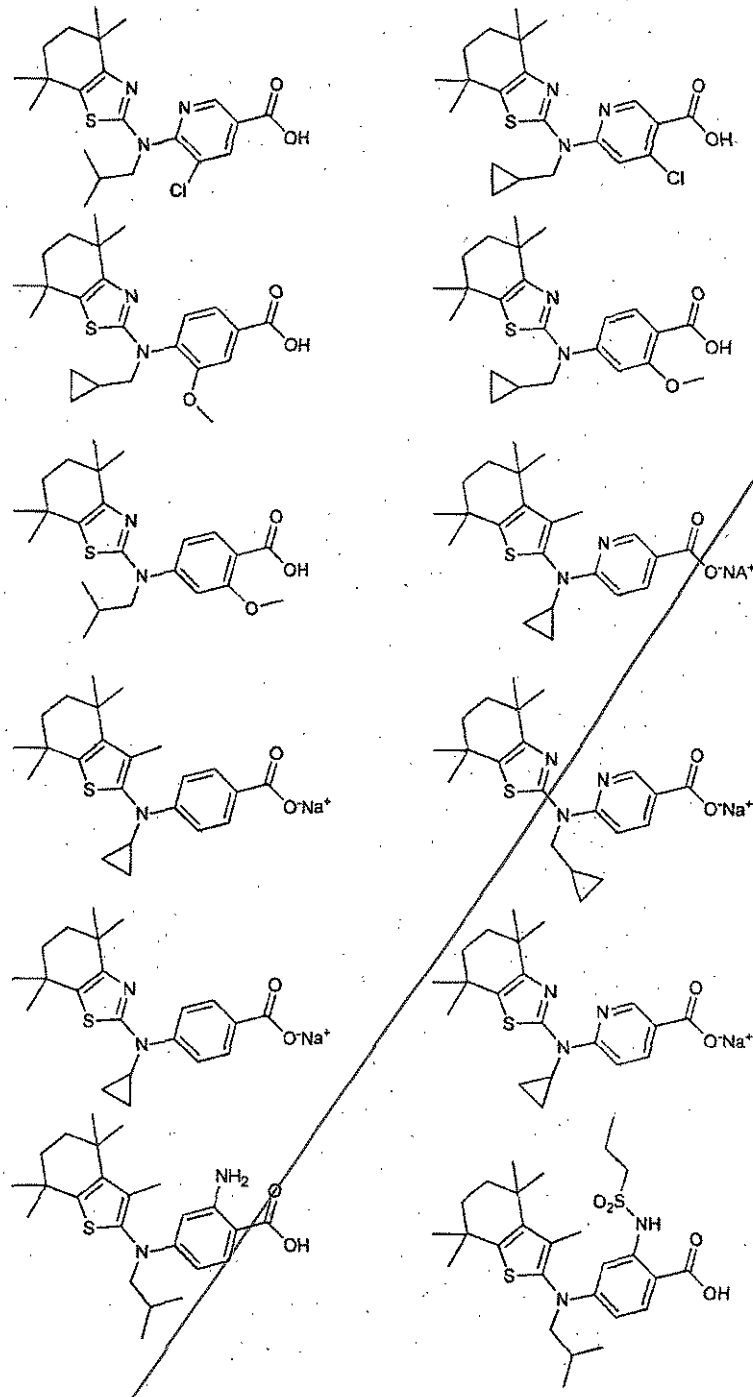















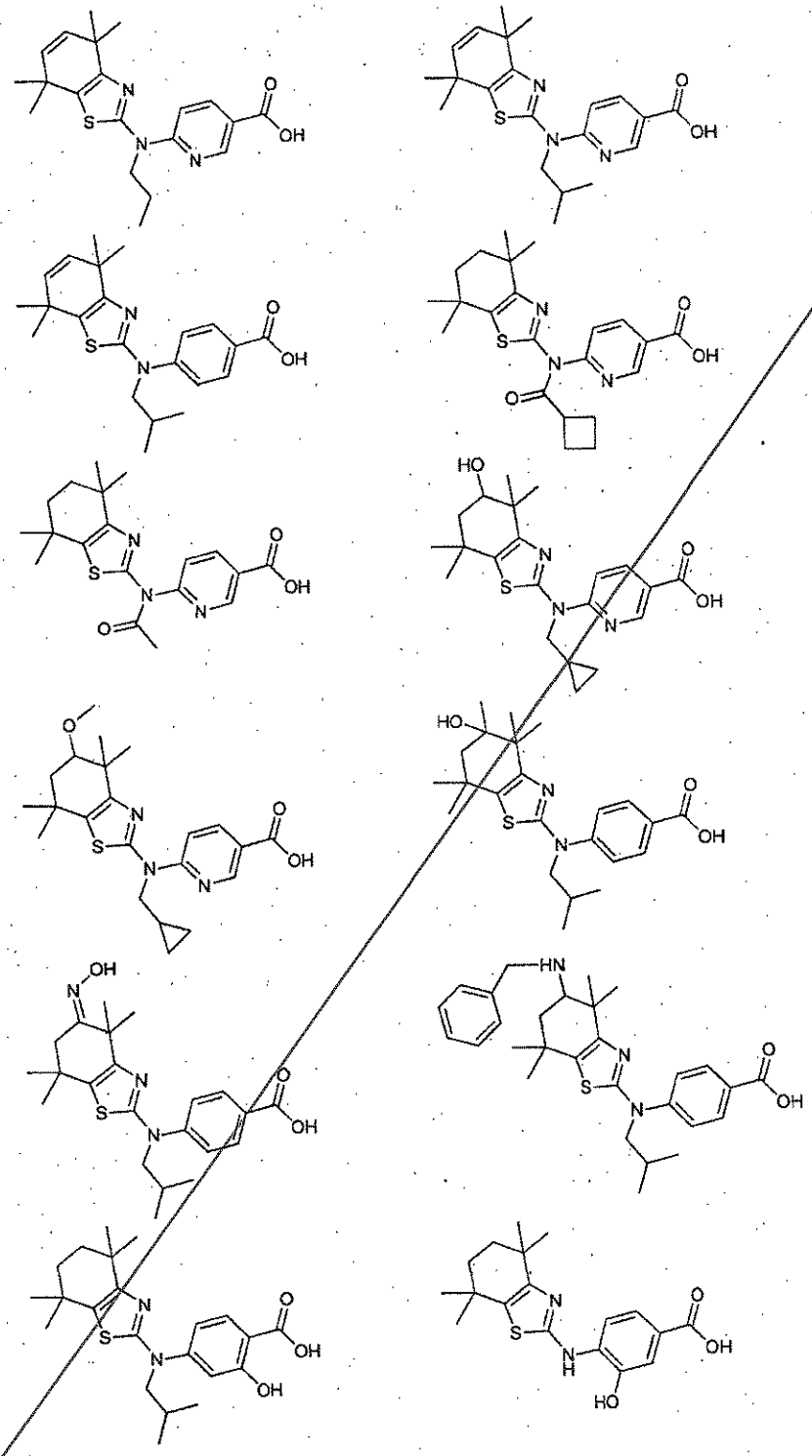


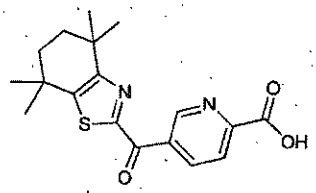
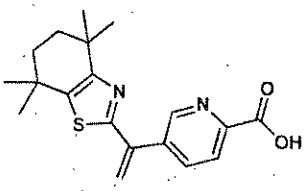
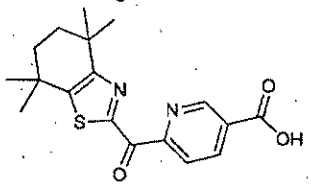
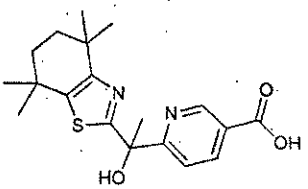
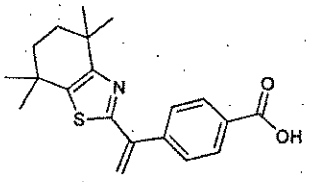
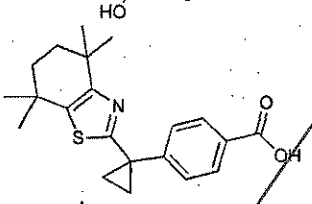
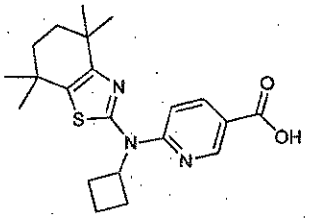
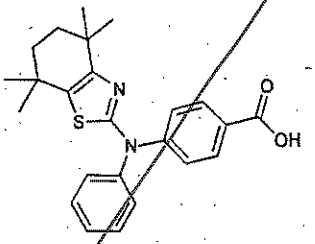
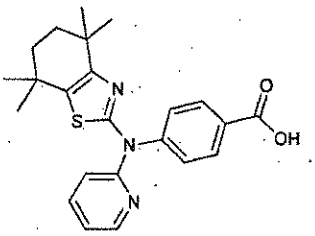
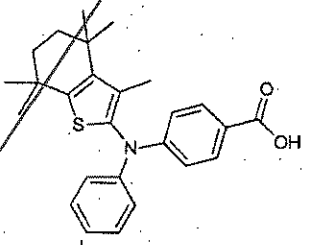
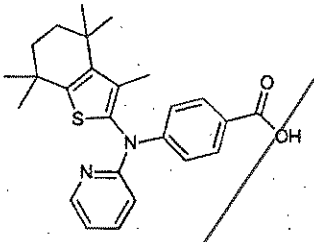
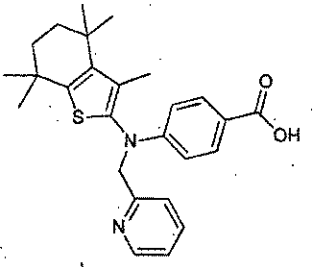
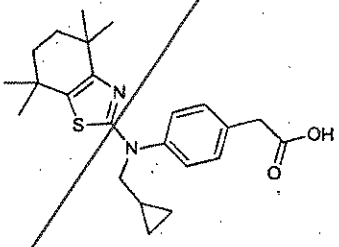
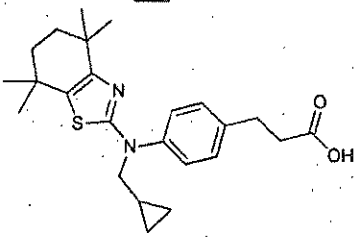


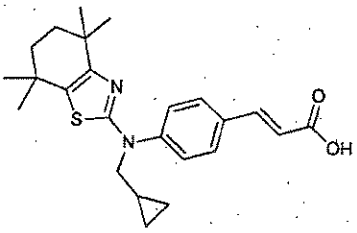
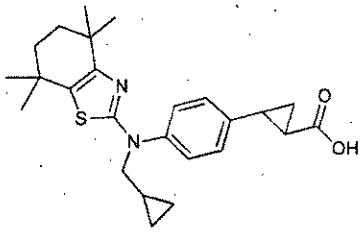



















or pharmaceutically acceptable salt, or prodrug thereof.

24. A pharmaceutical composition including a compound according to any one of claims 1 to 12 and a pharmaceutically acceptable diluent, excipient or carrier.

25. A method of prevention or treatment of a condition in a mammal, the method comprising administering an effective amount of a compound according to any one of claims 1 to 23.

26. A method according to claim 25 wherein the condition can be prevented or treated by activation of RXR

27. A method according to claim 23 wherein the condition is selected from the group consisting of Cancers such as premalignant and malignant hyperproliferative diseases such as cancers of the breast, pancreas, skin, prostate, cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, Liver, oral cavity, pancreas, blood and lymphatic system, metaplasias, dysplasias, neoplasias, leukoplakias and papillomas of the mucous membranes and in the treatment of Kaposis sarcoma, Cutaneous T Cell Lymphoma, promyelocytic leukemia, Non-Small-Cell Lung Cancer, Kidney Cancer (Advanced Renal Cell Cancer), Gastrointestinal Cancer, Mesothelioma, Bronchial Metaplasia; Skin disorders such as Dermatitis (Severe Chronic Hand Eczema in Adults) Psoriasis (Severe Plaque Psoriasis), Alopecia (Hair Loss), actinic keratoses, arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis, ichthyoses and other keratinization and hyperproliferative disorders of the skin, eczema, atopic dermatitis, Darriers disease, lichen planus, prevention and reversal of glucocorticoid damage (steroid atrophy), as a topical anti-microbial, as skin pigmentation agents and to treat and reverse the effects of age and photo damage to the skin; Metabolic Diseases such as diabetes, Type II Diabetes, Obesity, Hyperglycemia, Hypercholesterimia, Hypertriglyceridimia; hyperinsulinaemia, Cardio vascular Diseases including diseases associated with lipid metabolism such as dyslipidemias, lipodystrophy, prevention of restenosis and as an agent to increase the level of circulating tissue plasminogen activator (TPA), NASH, Steatosis, Steatohepatitis, Cirrhosis; liver disease, renal diseases including chronic kidney disease,

Fibrosis including Pulmonary fibrosis, renal fibrosis and liver fibrosis, Eye disorders such as proliferative vitreoretinopathy (PVR), retinal detachment, dry eye and other corneopathies, autoimmune diseases and Inflammatory Diseases, inflammation, oxidative stress, pulmonary fibrosis, ileitis, colitis and Krohn's disease; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Amyotrophic Lateral Sclerosis (ALS), Multiple sclerosis, improper pituitary function, including insufficient production of growth hormone, modulation of apoptosis, including both the induction of apoptosis and inhibition of T-Cell activated apoptosis, restoration of hair growth, restoration of cardiac function, restoration of muscle function and multiple sclerosis.

28. A method according to claim 27 wherein the condition is diabetes.

29. A method according to claim 28 wherein the condition is type II diabetes.

30. A method according to claim 27 wherein the condition is cancer.

31. The method of claim 27, wherein the condition is a disease of the liver.

32. A method according to claim 31 wherein the condition is nonalcoholic steatohepatitis. (NASH)

33. A method according to claim 27 wherein the condition is obesity.

34. A method according to claim 27 wherein the condition is cardiovascular disease.

35. A method of increasing muscle endurance in a mammal, the method comprising administering an effective amount of a compound according to any one of claims 1 to 23.

36. A method of improving cardiac function in a mammal, the method comprising administering an effective amount of a compound according to any one of claims 1 to 23.

37. A method of achieving an exercise mimetic effect in a mammal, the method comprising administering an effective amount of a compound according to any one of claims 1 to 23.

38. Use of a compound according to any one of claims 1 to 23 in the preparation of a medicament.

39. A use according to claim 38 wherein the medicament is for the treatment of a condition can be prevented or treated by activation of RXR

40. A use according to claim 38 wherein the condition is selected from the group consisting of Cancers such as premalignant and malignant hyperproliferative diseases such as cancers of the breast, pancreas, skin, prostate, cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, Liver, oral cavity, pancreas, blood and lymphatic system, metaplasias, dysplasias, neoplasias, leukoplakias and papillomas of the mucous membranes and in the treatment of Kaposis sarcoma, Cutaneous T Cell Lymphoma, promyelocytic leukemia, Non-Small-Cell Lung Cancer, Kidney Cancer (Advanced Renal Cell Cancer), Gastrointestinal Cancer, Mesothelioma, Bronchial Metaplasia; Skin disorders such as Dermatitis (Severe Chronic Hand Eczema in Adults) Psoriasis (Severe Plaque Psoriasis), Alopecia (Hair Loss), actinic keratoses, arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis, ichthyoses and other keratinization and hyperproliferative disorders of the skin, eczema, atopic dermatitis, Darriers disease, lichen planus, prevention and reversal of glucocorticoid damage (steroid atrophy), as a topical anti-microbial, as skin pigmentation agents and to treat and reverse the effects of age and photo damage to the skin; Metabolic Diseases such as diabetes, Type II Diabetes, Obesity, Hyperglycemia, Hypercholesterimia, Hypertriglyceridimia; hyperinsulinaemia, Cardio vascular Diseases including diseases associated with lipid metabolism such as dyslipidemias, lipodystrophy, prevention of restenosis and as an agent to increase the level of circulating tissue plasminogen activator (TPA), NASH, Steatosis, Steatohepatitis, Cirrhosis; liver disease, renal diseases including chronic kidney disease, Fibrosis including Pulmonary fibrosis, renal fibrosis and liver fibrosis, Eye disorders such as proliferative vitreoretinopathy (PVR), retinal detachment, dry eye and other corneopathies; autoimmune diseases and Inflammatory Diseases, inflammation, oxidative stress, pulmonary fibrosis, ileitis, colitis and Krohn's disease; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Amyotrophic Lateral Sclerosis (ALS), Multiple sclerosis, improper pituitary function, including insufficient production of growth hormone, modulation of apoptosis, including both the induction of apoptosis and inhibition of T-Cell activated apoptosis, restoration of hair growth, restoration of cardiac function, restoration of muscle function and multiple sclerosis.

41. A use according to claim 40 wherein the condition is diabetes.

42. A use according to claim 41 wherein the condition is type II diabetes.

43. A use according to claim 40 wherein the condition is cancer.

44. A use according to claim 40, wherein the condition is a disease of the liver.

45. A Use according to claim 44 wherein the condition is nonalcoholic steatohepatitis (NASH).

46. A use according to claim 40 wherein the condition is obesity.

47. A use according to claim 40 wherein the condition is cardiovascular disease.

48. Use of a compound according to any one of claims 1 to 23 in the preparation of a medicament for increasing muscle endurance in a mammal.

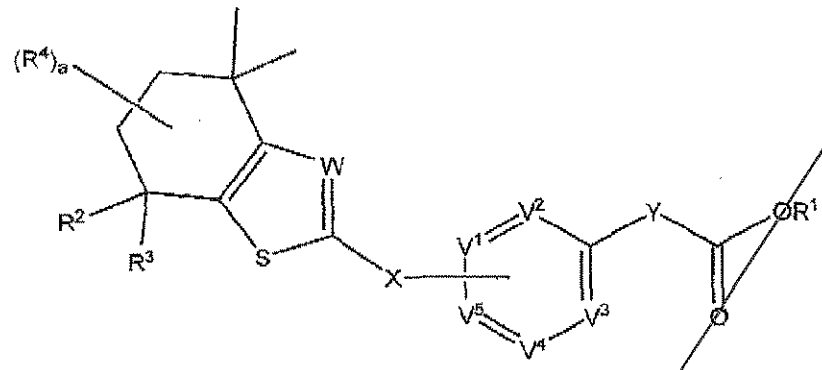
49. Use of a compound according to any one of claims 1 to 23 in the preparation of a medicament for improving cardiac function in a mammal.

50. Use of a compound according to any one of claims 1 to 23 in the preparation of a medicament for achieving an exercise mimetic effect in a mammal.

51. A compound according to claim 1 substantially as hereinbefore described with reference to any of the examples.

Claims

1. A compound of formula (I):



Formula (I)

wherein:

R^1 is selected from the group consisting of H, C_1-C_6alkyl and a carboxylic acid protecting group;

R^2 and R^3 are independently selected from the group consisting of H and C_1-C_6alkyl;

each R^4 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_2-C_{12}alkenyloxy, optionally substituted C_2-C_{12}alkynyloxy, optionally substituted C_2-C_{10}heteroalkyloxy, optionally substituted C_3-C_{12}cycloalkyloxy, optionally substituted C_3-C_{12}cycloalkenyloxy, optionally substituted C_2-C_{12}heterocycloalkyloxy, optionally substituted C_2-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18}aryloxy, optionally substituted C_1-C_{18}heteroaryloxy, optionally substituted C_1-C_{12}alkylamino, SR^5, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$, NR^5COR^5, NR^5COOR^5, $NR^5SO_2R^5$, $NR^5CONR^5R^5$, NR^5R^5, and acyl, or two R^4 on the same carbon atom when taken together form a =O substituent or a group of formula =NOH, or two R^4 on adjacent carbon atoms when taken together form a double bond;

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wherein each R^5 is independently selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{10}heteroalkyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_6-C_{18}aryl, and optionally substituted C_1-C_{18}heteroaryl;

a is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

wherein X is selected from the group consisting of a bond, –O–, -S-, -NR^{10}–, $NR^{10}C(=O)$-, -$C(=R^{11})$- and –$(CR^{12}R^{13})_b$-;

wherein R^{10} is selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_3-C_{12}cycloalkylC_1-C_{12}alkyl, optionally substituted C_2-C_{12}heterocycloalkylC_1-C_{12}alkyl, optionally substituted C_6-C_{18}aryl C_1-C_{12}alkyl, optionally substituted C_1-C_{18}heteroarylC_1-C_{12}alkyl, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$ and acyl;

wherein R^{11} is selected from the group consisting of O, NR^{14}, NOR^{14} and $CR^{14}R^{15}$, wherein each R^{14} and R^{15} is independently selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_3-C_{12}cycloalkylC_1-C_{12}alkyl, optionally substituted C_2-C_{12}heterocycloalkylC_1-C_{12}alkyl, optionally substituted C_6-C_{18}aryl C_1-C_{12}alkyl, optionally substituted C_1-C_{18}heteroarylC_1-C_{12}alkyl, and acyl;

each R^{12} and R^{13} is independently selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally

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substituted C_3-C_{12}cycloalkylC_1-C_{12}alkyl, optionally substituted C_2-C_{12}heterocycloalkylC_1-C_{12}alkyl, optionally substituted C_6-C_{18}aryl C_1-C_{12}alkyl, optionally substituted C_1-C_{18}heteroarylC_1-C_{12}alkyl, and acyl, or R^{12} and R^{13} on the same carbon atom when taken together form a cyclic moiety,

b is an integer selected from the group consisting of 0, 1, 2,3 and 4;

V^2, V^3 and V^4 are each independently selected from the group consisting of N and CR^6;

each R^6 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_2-C_{12}alkenyloxy, optionally substituted C_2-C_{12}alkynyloxy, optionally substituted C_2-C_{10}heteroalkyloxy, optionally substituted C_3-C_{12}cycloalkyloxy, optionally substituted C_3-C_{12}cycloalkenyloxy, optionally substituted C_2-C_{12}heterocycloalkyloxy, optionally substituted C_2-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18}aryloxy, optionally substituted C_1-C_{18}heteroaryloxy, optionally substituted C_1-C_{12}alkylamino, SR^5, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$, NR^5COR^5, NR^5COOR^5, $NR^5SO_2R^5$, $NR^5CONR^5R^5$, NR^5R^5, and acyl;

V^1 and V^5 are selected from the group consisting of N, CR^7 and CR^8 such that one of V^1 and V^5 is CR^8 and the other is N or CR^7;

R^7 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_2-C_{12}alkenyloxy, optionally substituted C_2-C_{12}alkynyloxy, optionally substituted C_2-C_{10}heteroalkyloxy, optionally substituted C_3-C_{12}cycloalkyloxy, optionally substituted C_3-C_{12}cycloalkenyloxy,

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optionally substituted C_2-C_{12}heterocycloalkyloxy, optionally substituted C_2-C_{12} heterocycloalkenyloxy, optionally substituted C_6-C_{18}aryloxy, optionally substituted C_1-C_{18}heteroaryloxy, optionally substituted C_1-C_{12}alkylamino, SR^5, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$, NR^5COR^5, NR^5COOR^5, $NR^5SO_2R^5$, $NR^5CONR^5R^5$, NR^5R^5, and acyl, or R^7 when taken together with the carbon atom to which it is attached forms a cyclic moiety with a substituent on X;

R^6 is a bond to X.

Y is a bond;

W is selected from the group consisting of N and CR^9;

R^9 is selected from H and C_1-C_6alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 is H.

3. A compound according to any one of claims 1 to 2 wherein a is 0.

4. A compound according to any one of claims 1 to 3 wherein R^2 and R^3 are C_1-C_6alkyl.

5. A compound according to any one of claims 1 to 4 wherein R^2 and R^3 are methyl.

6. A compound according to any one of claims 1 to 7 wherein W is N.

7. A compound according to any one of claims 1 to 7 wherein W is CR^9.

8. A compound according to claim 7 where R^9 is methyl.

9. A compound according to claim 1 wherein X is $-NR^{10}-$

10 A compound according to claim 9 wherein R^{10} is selected from the group consisting of H, C_1-C_{12}alkyl, and C_3-C_{12}cycloalkylC_1-C_{12}alkyl.

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11 A compound according to any one of claims 1 to 10 wherein V^2 is CR^6.

12. A compound according to any one of claims 1 to 11 wherein V^3 is CR^6.

13. A compound according to any one of claims 1 to 12 wherein V^5 is CR^6

14. A compound according to any one of claims 1 to 13 wherein V^4 is CR^6.

15. A compound according to any one of claims 1 to 13 wherein V^4 is N.

16. A compound according to any one of claims 1 to 15 wherein V^1 is CR^6.

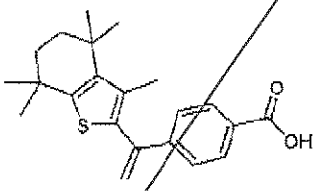
17. A compound according to any one of claims 1 to 15 wherein V^1 is N.

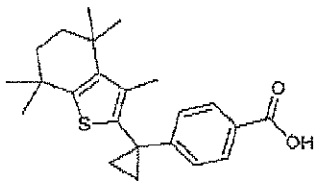
18. A compound according to any one of the proceeding claims wherein each R^6 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, C_1-C_{12}alkyl and C_1-C_{12}alkyloxy.

19. A compound according to any one of the proceeding claims wherein each R^6 is independently selected from the group consisting of H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $(CH_2)_3CH_3$, Cl, Br, F, I, OH, NO_2, NH_2, CN, OCH_3, $OCH_2CH_2CH_3$, CF_3, and OCF_3.

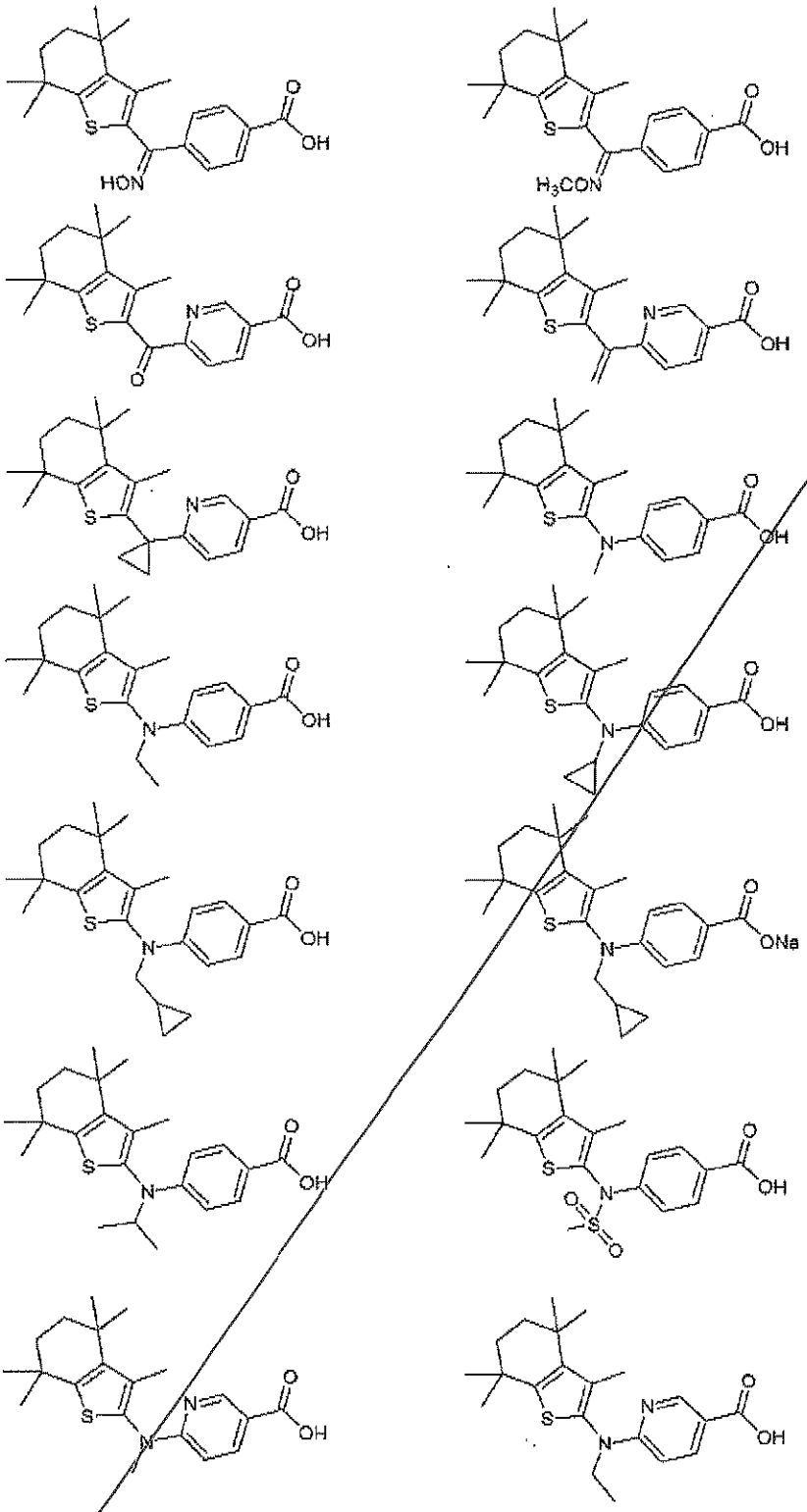
20 A compound according to claim 1 wherein each optional substituent is independently selected from the group consisting of H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $(CH_2)_3CH_3$, Cl, Br, F, I, OH, NO_2, NH_2, CN, OCH_3, $OCH_2CH_2CH_3$, CF_3, and OCF_3.

21. A compound according to claim 1 selected from the group consisting of



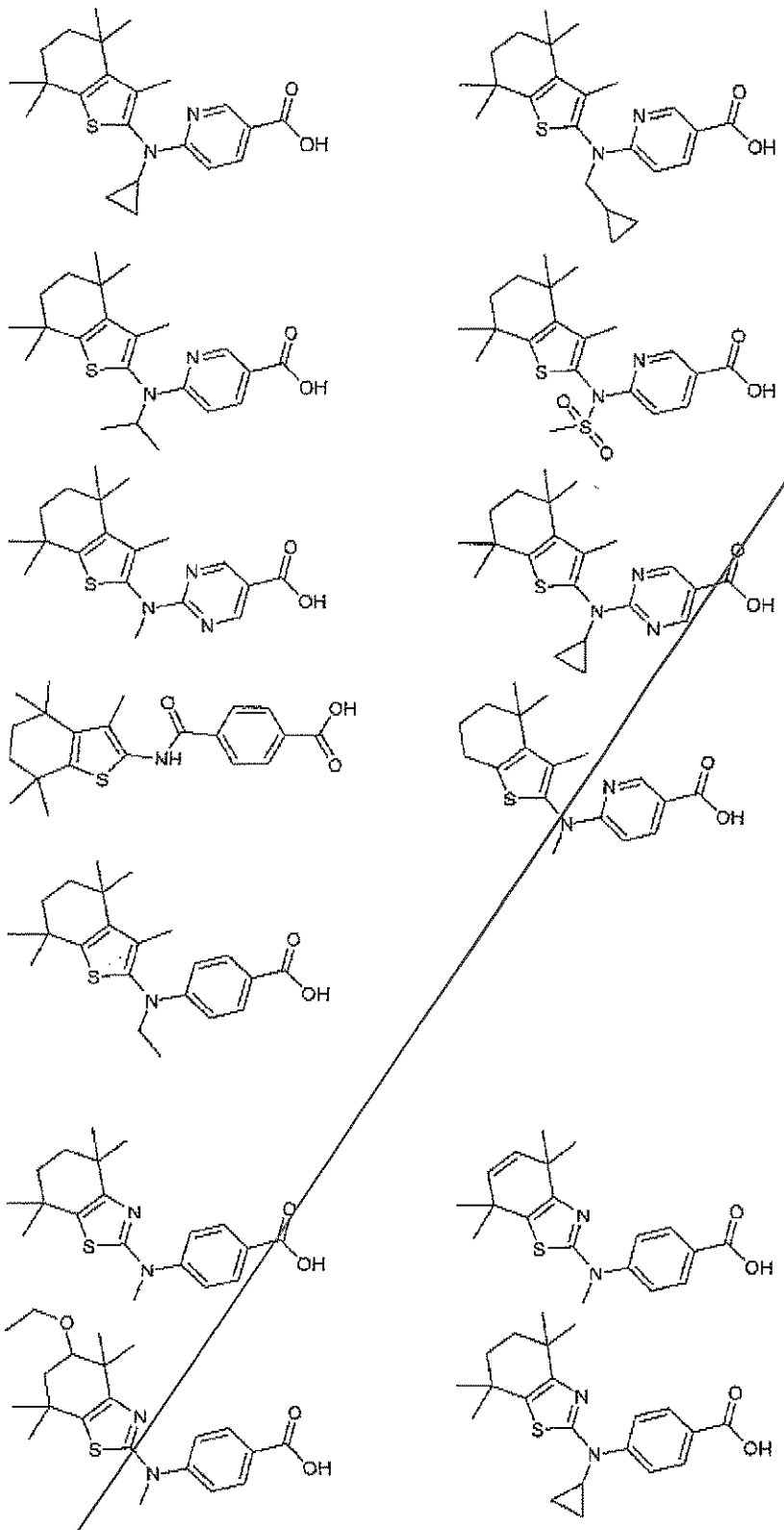


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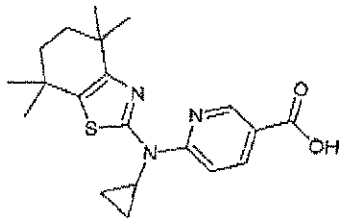
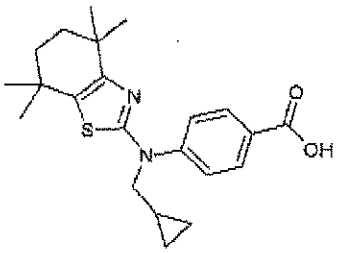
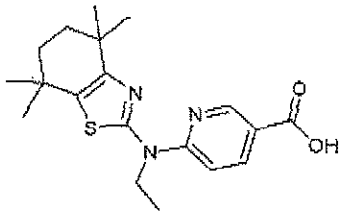
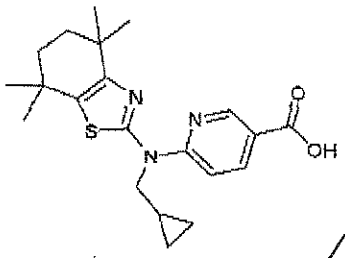
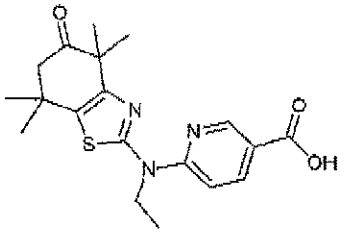
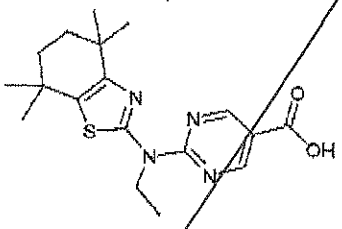
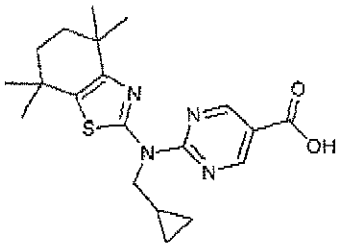
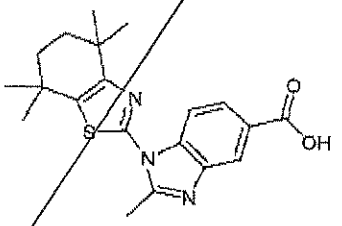
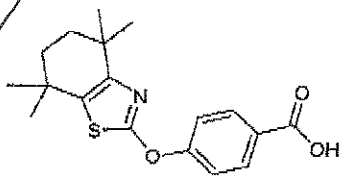
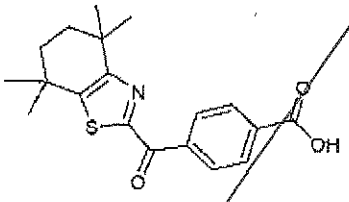
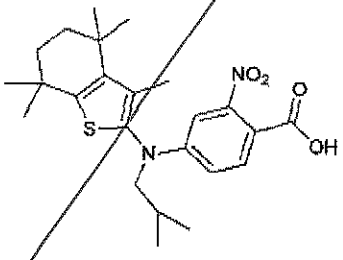
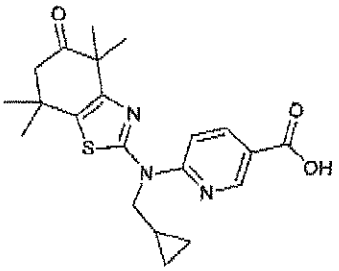
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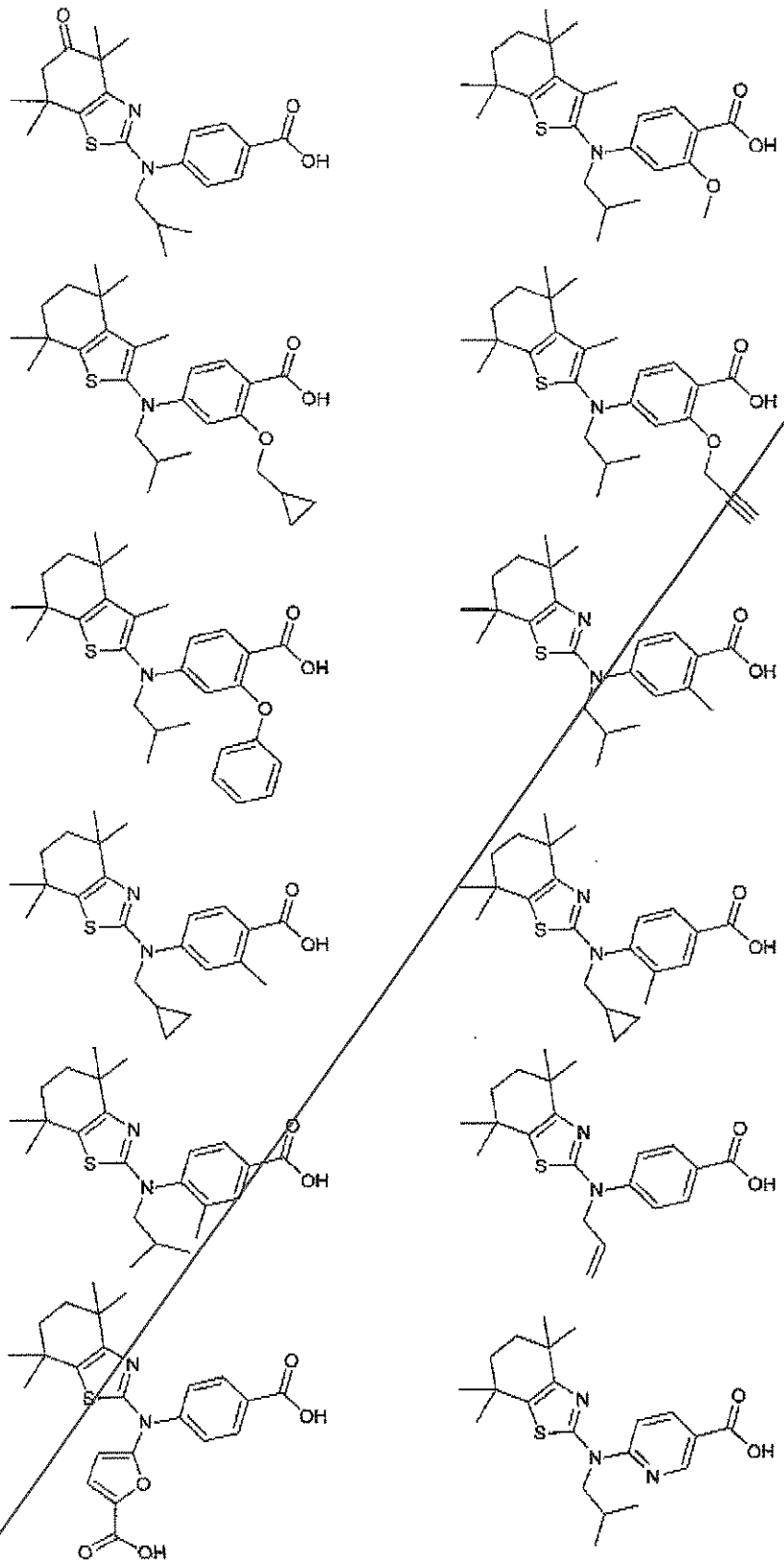


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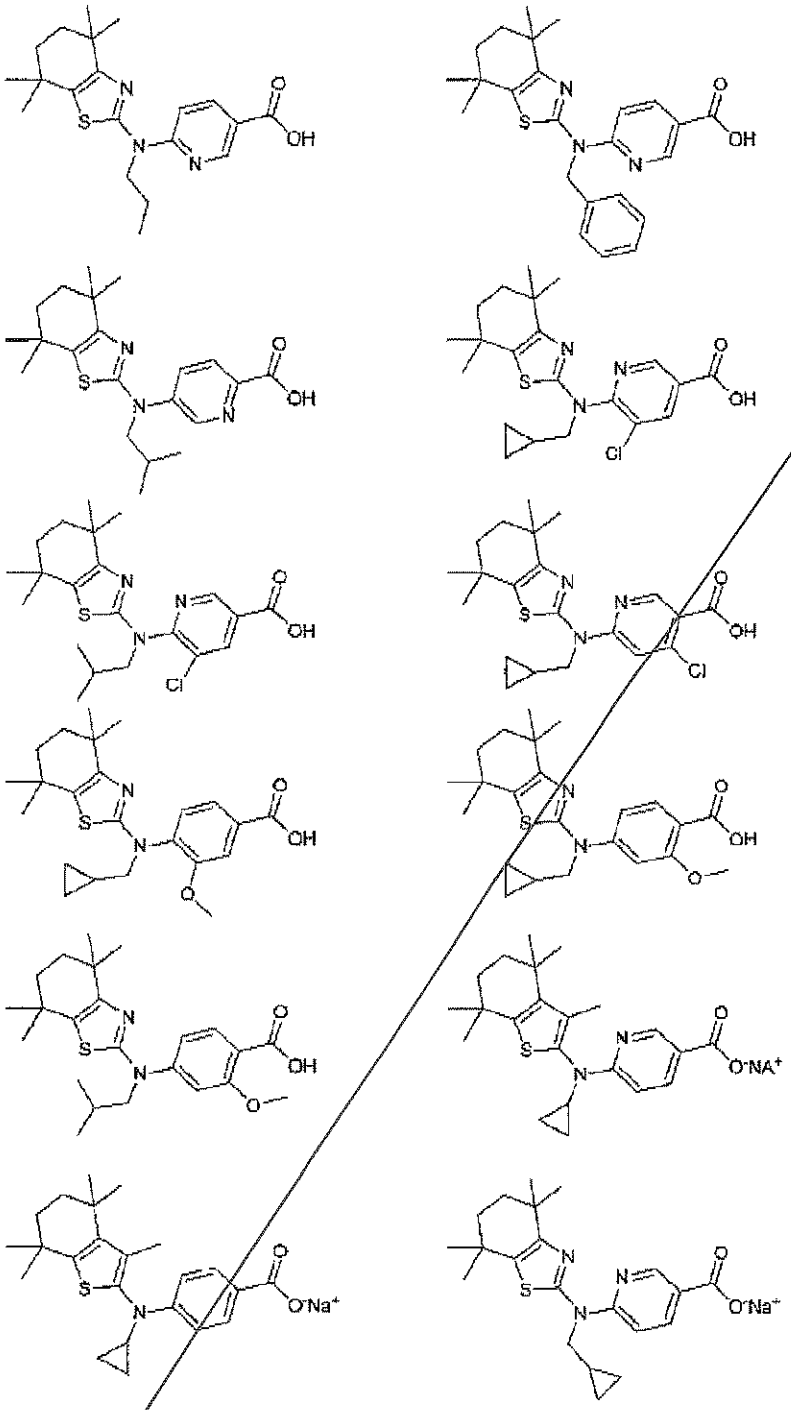













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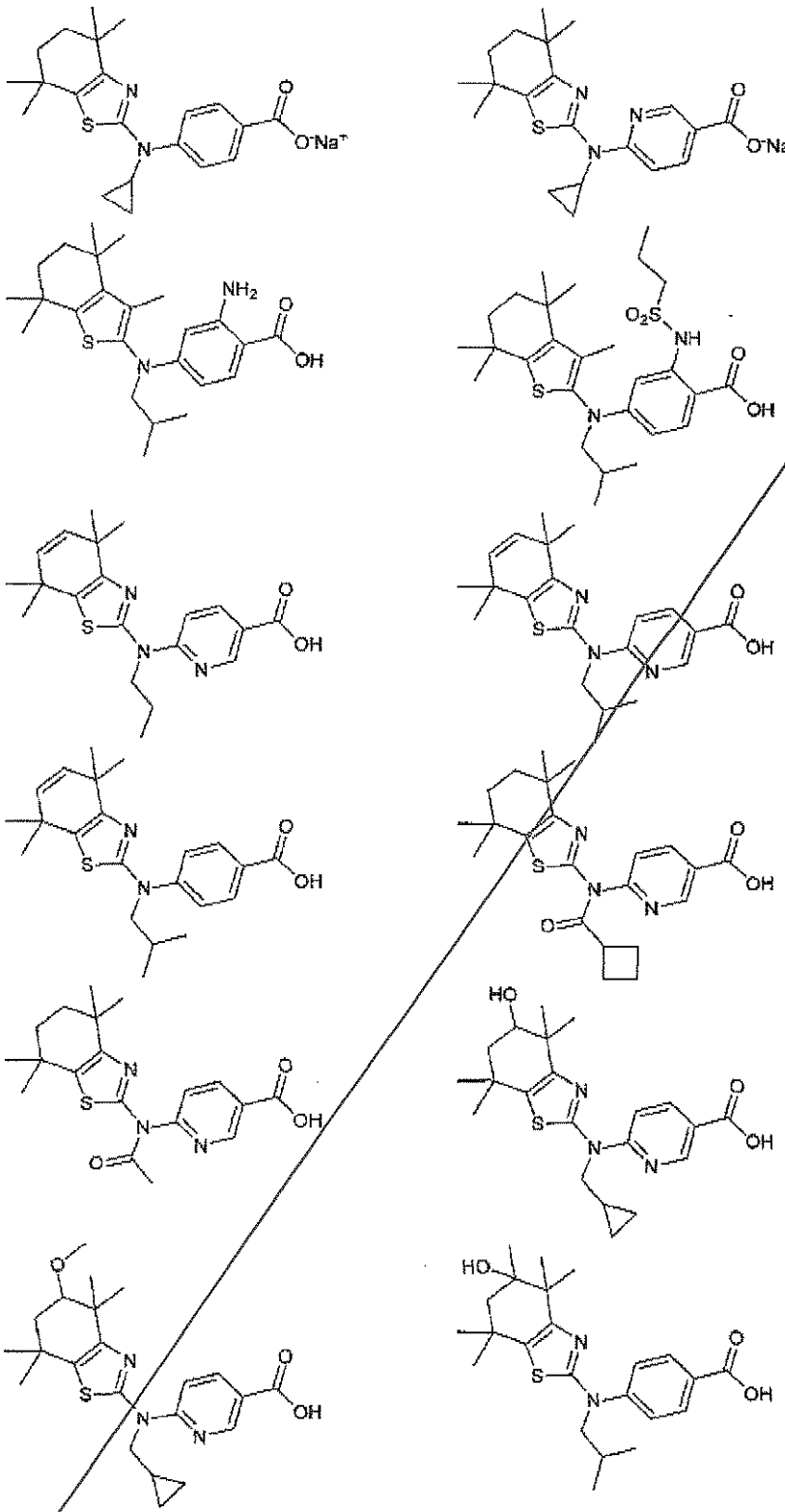


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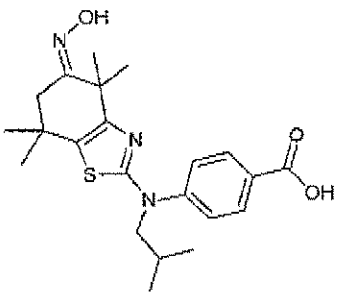
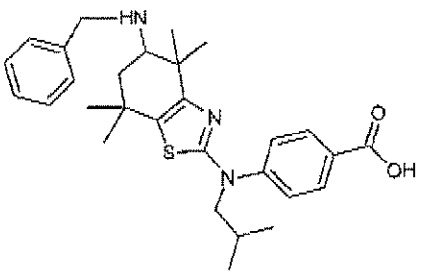
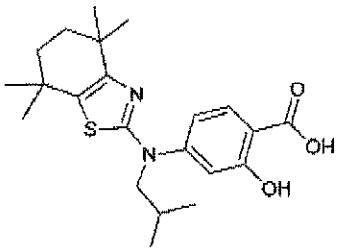
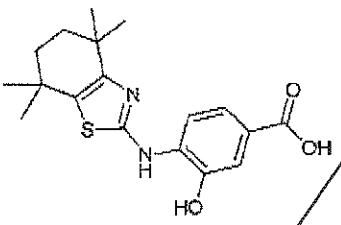
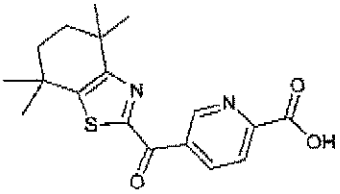
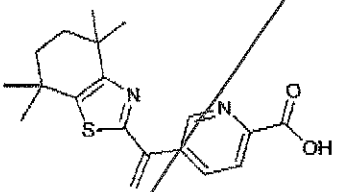
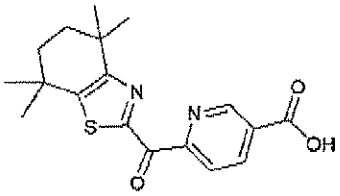
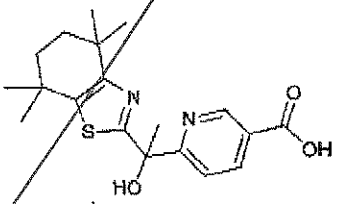
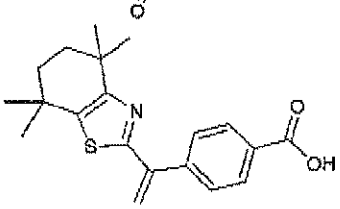
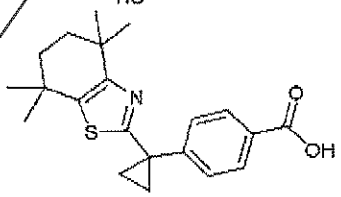
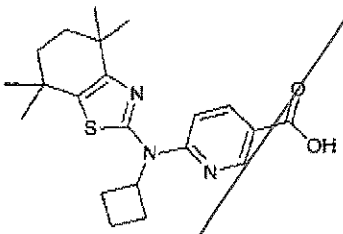
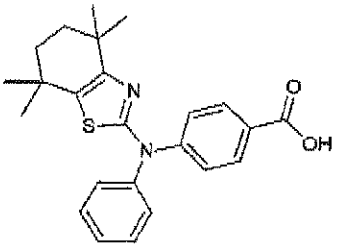
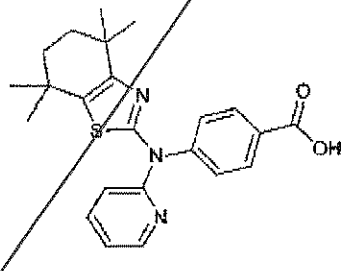
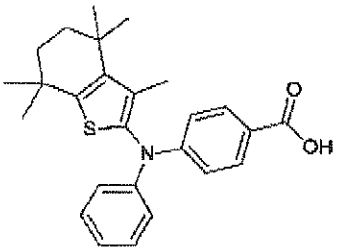
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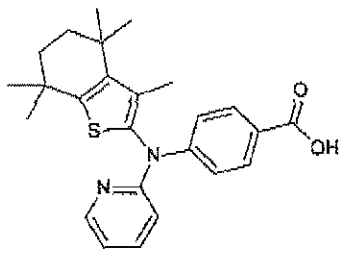
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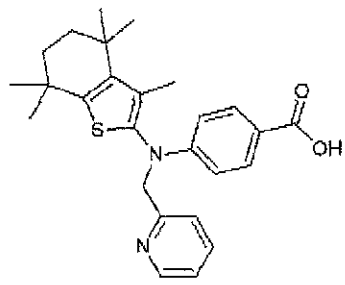


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or pharmaceutically acceptable salt, thereof.

22. A pharmaceutical composition including a compound according to any one of claims 1 to 21 and a pharmaceutically acceptable diluent, excipient or carrier.

23. A method of prevention or treatment of a condition in a mammal, the method comprising administering an effective amount of a compound according to any one of claims 1 to 21.

24. A method according to claim 23 wherein the condition can be prevented or treated by activation of RXR

25. A method according to claim 23 wherein the condition is selected from the group consisting of Cancers such as premalignant and malignant hyperproliferative diseases such as cancers of the breast, pancreas, skin, prostate, cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, Liver, oral cavity, pancreas, blood and lymphatic system, metaplasias, dysplasias, neoplasias, leukoplakias and papillomas of the mucous membranes and in the treatment of Kaposis sarcoma, Cutaneous T Cell Lymphoma, promyelocytic leukemia, Non-Small-Cell Lung Cancer, Kidney Cancer (Advanced Renal Cell Cancer), Gastrointestinal Cancer, Mesothelioma, Bronchial Metaplasia; Skin disorders such as Dermatitis (Severe Chronic Hand Eczema in Adults) Psoriasis (Severe Plaque Psoriasis), Alopecia (Hair Loss), actinic keratoses, arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis, ichthyoses and other keratinization and hyperproliferative disorders of the skin, eczema, atopic dermatitis, Darriers disease, lichen planus, prevention and reversal of glucocorticoid damage (steroid atrophy), as a topical anti-microbial, as skin pigmentation agents and to treat and reverse the effects of age and photo damage to the skin; Metabolic Diseases such as diabetes, Type II Diabetes, Obesity, Hyperglycemia, Hypercholesterimia, Hypertriglyceridimia; hyperinsulinaemia, Cardio vascular Diseases including diseases associated with lipid metabolism such as dyslipidemias, lipodystrophy, prevention of

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restenosis and as an agent to increase the level of circulating tissue plasminogen activator (TPA), NASH, Steatosis, Steatohepatitis, Cirrhosis; liver disease, renal diseases including chronic kidney disease, Fibrosis including Pulmonary fibrosis, renal fibrosis and liver fibrosis, Eye disorders such as proliferative vitreoretinopathy (PVR), retinal detachment, dry eye and other corneopathies; autoimmune diseases and Inflammatory Diseases, inflammation, oxidative stress, pulmonary fibrosis, ileitis, colitis and Krohn's disease; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Amyotrophic Lateral Sclerosis (ALS), Multiple sclerosis, improper pituitary function, including insufficient production of growth hormone, modulation of apoptosis, including both the induction of apoptosis and inhibition of T-Cell activated apoptosis, restoration of hair growth, restoration of cardiac function, restoration of muscle function and multiple sclerosis.

26. A method according to claim 25 wherein the condition is diabetes.

27. A method according to claim 25 wherein the condition is type II diabetes.

28. A method according to claim 25 wherein the condition is cancer.

29. The method of claim 25, wherein the condition is a disease of the liver.

30. A method according to claim 29 wherein the condition is nonalcoholic steatohepatitis. (NASH)

31. A method according to claim 25 wherein the condition is obesity.

32. A method according to claim 25 wherein the condition is cardiovascular disease.

33. A method of increasing muscle endurance in a mammal, the method comprising administering an effective amount of a compound according to any one of claims 1 to 21.

34. A method of improving cardiac function in a mammal, the method comprising administering an effective amount of a compound according to any one of claims 1 to 21.

35. A method of achieving an exercise mimetic effect in a mammal, the method comprising administering an effective amount of a compound according to any one of claims 1 to 21.

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36. Use of a compound according to any one of claims 1 to 21 in the preparation of a medicament.

37. A use according to claim 36 wherein the medicament is for the treatment of a condition can be prevented or treated by activation of RXR

38. A use according to claim 36 wherein the condition is selected from the group consisting of Cancers such as premalignant and malignant hyperproliferative diseases such as cancers of the breast, pancreas, skin, prostate, cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, Liver, oral cavity, pancreas, blood and lymphatic system, metaplasias, dysplasias, neoplasias, leukoplakias and papillomas of the mucous membranes and in the treatment of Kaposis sarcoma, Cutaneous T Cell Lymphoma, promyelocytic leukemia, Non-Small-Cell Lung Cancer, Kidney Cancer (Advanced Renal Cell Cancer), Gastrointestinal Cancer, Mesothelioma, Bronchial Metaplasia; Skin disorders such as Dermatitis (Severe Chronic Hand Eczema in Adults) Psoriasis (Severe Plaque Psoriasis), Alopecia (Hair Loss), actinic keratoses, arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis, ichthyoses and other keratinization and hyperproliferative disorders of the skin, eczema, atopic dermatitis, Darriers disease, lichen planus, prevention and reversal of glucocorticoid damage (steroid atrophy), as a topical anti-microbial, as skin pigmentation agents and to treat and reverse the effects of age and photo damage to the skin; Metabolic Diseases such as diabetes, Type II Diabetes, Obesity, Hyperglycemia, Hypercholesterimia, Hypertriglyceridimia; hyperinsulinaemia, Cardio vascular Diseases including diseases associated with lipid metabolism such as dyslipidemias, lipodystrophy, prevention of restenosis and as an agent to increase the level of circulating tissue plasminogen activator (TPA), NASH, Steatosis, Steatohepatitis, Cirrhosis; liver disease, renal diseases including chronic kidney disease, Fibrosis including Pulmonary fibrosis, renal fibrosis and liver fibrosis, Eye disorders such as proliferative vitreoretinopathy (PVR), retinal detachment, dry eye and other corneopathies; autoimmune diseases and Inflammatory Diseases, inflammation, oxidative stress, pulmonary fibrosis, ileitis, colitis and Krohn's disease; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Amyotrophic Lateral Sclerosis (ALS), Multiple sclerosis, improper pituitary function, including insufficient production of growth hormone, modulation of apoptosis, including both the induction of apoptosis and inhibition of T-Cell activated apoptosis, restoration of hair growth, restoration of cardiac function, restoration of muscle function and multiple sclerosis.

39. A use according to claim 38 wherein the condition is diabetes.

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40. A use according to claim 39 wherein the condition is type II diabetes.

41. A use according to claim 38 wherein the condition is cancer.

42 A use according to claim 38, wherein the condition is a disease of the liver.

43. A Use according to claim 42 wherein the condition is nonalcoholic steatohepatitis (NASH).

44. A use according to claim 38 wherein the condition is obesity.

45. A use according to claim38 wherein the condition is cardiovascular disease.

46. Use of a compound according to any one of claims 1 to 21 in the preparation of a medicament for increasing muscle endurance in a mammal.

47. Use of a compound according to any one of claims 1 to 21 in the preparation of a medicament for improving cardiac function in a mammal.

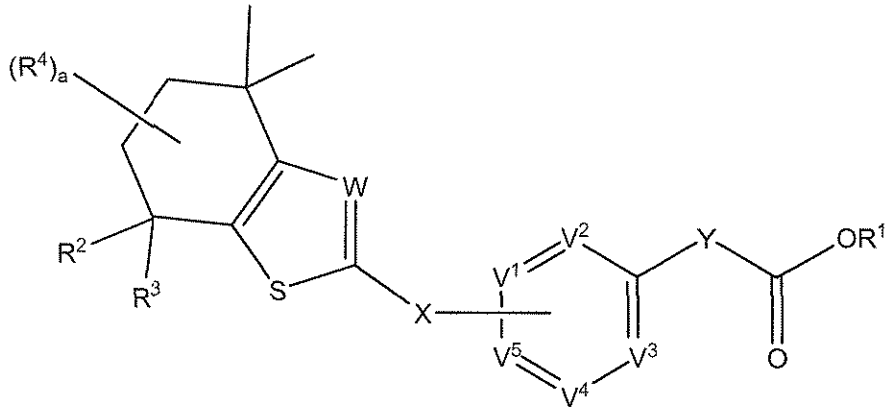
48. Use of a compound according to any one of claims 1 to 21 in the preparation of a medicament for achieving an exercise mimetic effect in a mammal.

49. A compound according to claim 1 substantially as hereinbefore described with reference to any of the examples.

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CLAIMS

1. A compound of formula (I):



Formula (I)

wherein:

R^1 is selected from the group consisting of H, C_1-C_6alkyl and a carboxylic acid protecting group;

R^2 and R^3 are independently selected from the group consisting of H and C_1-C_6alkyl;

each R^4 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_2-C_{12}alkenyloxy, optionally substituted C_2-C_{12}alkynyloxy, optionally substituted C_2-C_{10}heteroalkyloxy, optionally substituted C_3-C_{12}cycloalkyloxy, optionally substituted C_3-C_{12}cycloalkenyloxy, optionally substituted C_2-C_{12}heterocycloalkyloxy, optionally substituted C_2-C_{12}heterocycloalkenyloxy, optionally substituted C_6-C_{18}aryloxy, optionally substituted C_1-C_{18}heteroaryloxy, optionally substituted C_1-C_{12}alkylamino, SR^5, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$, NR^5COR^5, NR^5COOR^5, $NR^5SO_2R^5$, $NR^5CONR^5R^5$, NR^5R^5, and acyl, or two R^4 on the same carbon atom when taken together form a =O substituent or a group of formula =NOH, or two R^4 on adjacent carbon atoms when taken together form a double bond;

wherein each R^5 is independently selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{10}heteroalkyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_6-C_{18}aryl, and optionally substituted C_1-C_{18}heteroaryl;

a is an integer selected from the group consisting of 0, 1, 2, 3, and 4;

wherein X is selected from the group consisting of a bond, –O-, -S-, -NR^{10}-, $NR^{10}C(=O)$-, -$C(=R^{11})$- and –$(CR^{12}R^{13})_b$-;

wherein R^{10} is selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl,optionally substituted C_6-C_{18}aryl,optionally substituted C_1-C_{18}heteroaryl,optionally substituted C_3-C_{12}cycloalkylC_1-C_{12}alkyl, optionally substituted C_2-C_{12}heterocycloalkylC_1-C_{12}alkyl, optionally substituted C_6-C_{18}aryl C_1-C_{12}alkyl, optionally substituted C_1-C_{18}heteroarylC_1-C_{12}alkyl, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$ and acyl;

wherein R^{11} is selected from the group consisting of O, NR^{14}, NOR^{14} and $CR^{14}R^{15}$, wherein each R^{14} and R^{15} is independently selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl,optionally substituted C_6-C_{18}aryl,optionally substituted C_1-C_{18}heteroaryl,optionally substituted C_3-C_{12}cycloalkylC_1-C_{12}alkyl, optionally substituted C_2-C_{12}heterocycloalkylC_1-C_{12}alkyl, optionally substituted C_6-C_{18}aryl C_1-C_{12}alkyl, optionally substituted C_1-C_{18}heteroarylC_1-C_{12}alkyl, and acyl;

each R^{12} and R^{13} is independently selected from the group consisting of H, optionally substituted C_1-C_{12}alkyl, optionally substituted C_2-C_{12} alkenyl, optionally substituted C_2-C_{12} alkynyl, optionally substituted C_1-C_{12}haloalkyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl,optionally

substituted C_6-C_{18}aryl,optionally substituted C_1-C_{18}heteroaryl,optionally substituted C_3-C_{12}cycloalkylC_1-C_{12}alkyl, optionally substituted C_2-C_{12}heterocycloalkylC_1-C_{12}alkyl, optionally substituted C_6-C_{18}aryl C_1-C_{12}alkyl, optionally substituted C_1-C_{18}heteroarylC_1-C_{12}alkyl, and acyl, or R^{12} and R^{13} on the same carbon atom when taken together form a cyclic moiety,

b is an integer selected from the group consisting of 0, 1, 2,3 and 4;

V^2, V^3 and V^4 are each independently selected from the group consisting of N and CR^6;

each R^6 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_2-C_{12}alkenyloxy, optionally substituted C_2-C_{12}alkynyloxy, optionally substituted C_2-C_{10}heteroalkyloxy, optionally substituted C_3-C_{12}cycloalkyloxy, optionally substituted C_3-C_{12}cycloalkenyloxy, optionally substituted C_2-C_{12}heterocycloalkyloxy, optionally substituted C_2-C_{12}heterocycloalkenyloxy, optionally substituted C_6-C_{18}aryloxy, optionally substituted C_1-C_{18}heteroaryloxy, optionally substituted C_1-C_{12}alkylamino, SR^5, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$, NR^5COR^5, NR^5COOR^5, $NR^5SO_2R^5$, $NR^5CONR^5R^5$, NR^5R^5, and acyl;

V^1 and V^5 are selected from the group consisting of N, CR^7 and CR^8 such that one of V^1 and V^5 is CR^8 and the other is N or CR^7;

R^7 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, optionally substituted C_1-C_{12}alkyl, optionally substituted C_1-C_{12}haloalkyl optionally substituted C_2-C_{12}alkenyl, optionally substituted C_2-C_{12}alkynyl, optionally substituted C_2-C_{12}heteroalkyl, optionally substituted C_3-C_{12}cycloalkyl, optionally substituted C_3-C_{12}cycloalkenyl, optionally substituted C_2-C_{12}heterocycloalkyl, optionally substituted C_2-C_{12}heterocycloalkenyl, optionally substituted C_6-C_{18}aryl, optionally substituted C_1-C_{18}heteroaryl, optionally substituted C_1-C_{12}alkyloxy, optionally substituted C_2-

C_{12}alkenyloxy, optionally substituted C_2-C_{12}alkynyloxy, optionally substituted C_2-C_{10}heteroalkyloxy, optionally substituted C_3-C_{12}cycloalkyloxy, optionally substituted C_3-C_{12}cycloalkenyloxy, optionally substituted C_2-C_{12}heterocycloalkyloxy, optionally substituted C_2-C_{12}heterocycloalkenyloxy, optionally substituted C_6-C_{18}aryloxy, optionally substituted C_1-C_{18}heteroaryloxy, optionally substituted C_1-C_{12}alkylamino, SR^5, SO_3H, $SO_2NR^5R^5$, SO_2R^5, $SONR^5R^5$, SOR^5, COR^5, COOH, $COOR^5$, $CONR^5R^5$, NR^5COR^5, NR^5COOR^5, $NR^5SO_2R^5$, $NR^5CONR^5R^5$, NR^5R^5, and acyl, or R^7 when taken together with the carbon atom to which it is attached forms a cyclic moiety with a substituent on X;

R^8 is a bond to X,

Y is a bond;

W is selected from the group consisting of N and CR^9;

R^9 is selected from H and C_1-C_6alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^1 is H.

3. A compound according to any one of claims 1 to 2 wherein a is 0.

4. A compound according to any one of claims 1 to 3 wherein R^2 and R^3 are C_1-C_6alkyl.

5. A compound according to any one of claims 1 to 4 wherein R^2 and R^3 are methyl.

6. A compound according to any one of claims 1 to 7 wherein W is N.

7. A compound according to any one of claims 1 to 7 wherein W is CR^9.

8. A compound according to claim 7 where R^9 is methyl.

9. A compound according to claim 1 wherein X is $-NR^{10}-$

10 A compound according to claim 9 wherein R^{10} is selected from the group consisting of H, C_1-C_{12}alkyl, and C_3-C_{12}cycloalkylC_1-C_{12}alkyl.

11 A compound according to any one of claims 1 to 10 wherein V^2 is CR^6.

12. A compound according to any one of claims 1 to 11 wherein V^3 is CR^6.

13. A compound according to any one of claims 1 to 12 wherein V^5 is CR^8

14. A compound according to any one of claims 1 to 13 wherein V^4 is CR^6.

15. A compound according to any one of claims 1 to 13 wherein V^4 is N.

16. A compound according to any one of claims 1 to 15 wherein V^1 is CR^6.

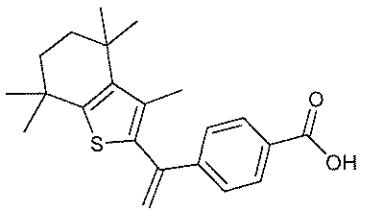
17. A compound according to any one of claims 1 to 15 wherein V^1 is N.

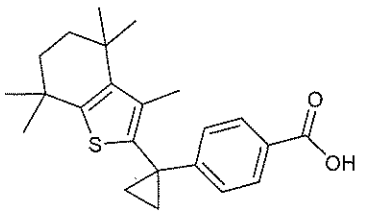
18. A compound according to any one of the proceeding claims wherein each R^6 is independently selected from the group consisting of H, halogen, OH, NO_2, CN, SH, NH_2, CF_3, OCF_3, C_1-C_{12}alkyl and C_1-C_{12}alkyloxy.

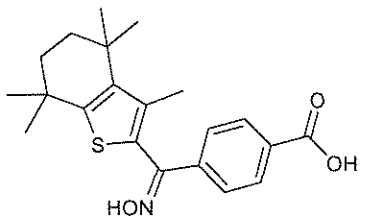
19. A compound according to any one of the proceeding claims wherein each R^6 is independently selected from the group consisting of H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $(CH_2)_3CH_3$, Cl, Br, F, I, OH, NO_2, NH_2, CN, OCH_3, $OCH_2CH_2CH_3$, CF_3, and OCF_3.

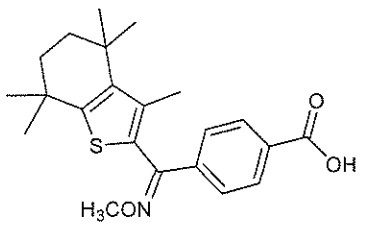
20 A compound according to claim 1 wherein each optional substituent is independently selected from the group consisting of H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $(CH_2)_3CH_3$, Cl, Br, F, I, OH, NO_2, NH_2, CN, OCH_3, $OCH_2CH_2CH_3$, CF_3, and OCF_3.

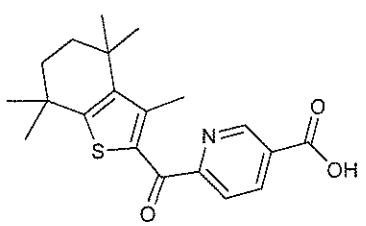
21. A compound according to claim 1 selected from the group consisting of

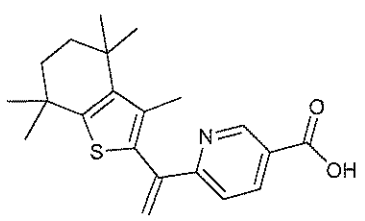


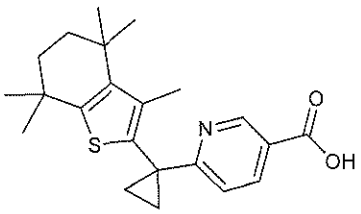


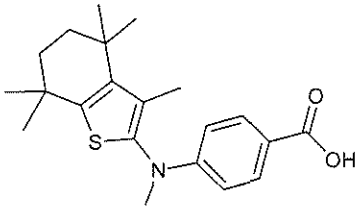


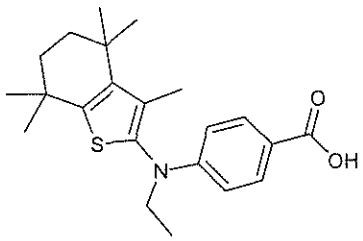


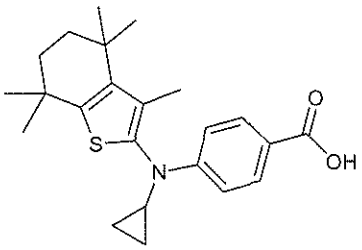


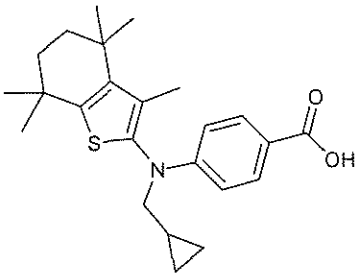


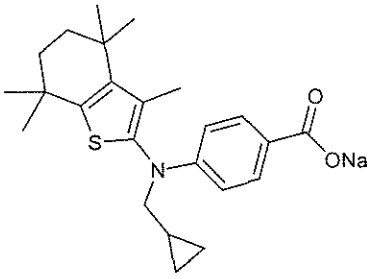


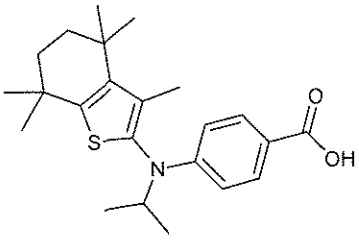


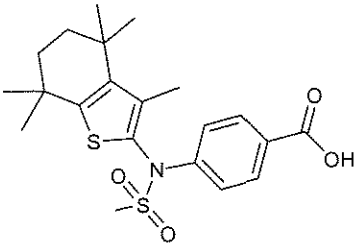


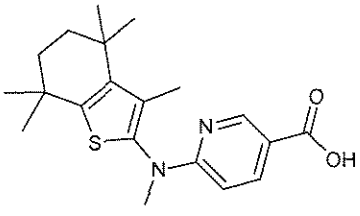


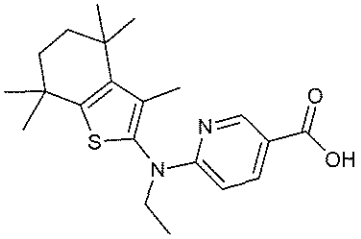


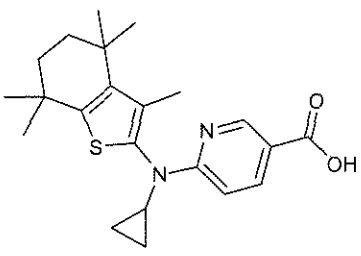


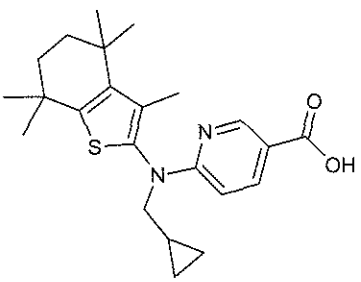


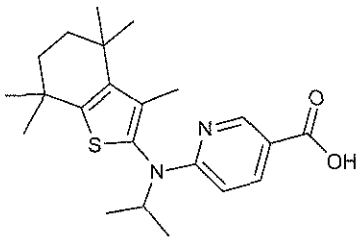


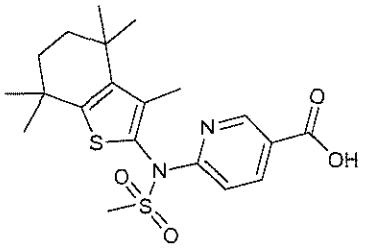


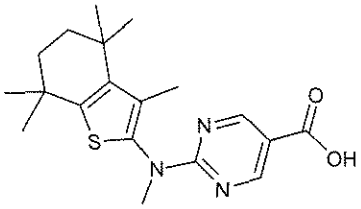


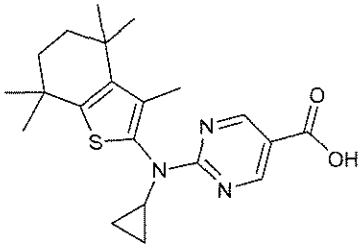


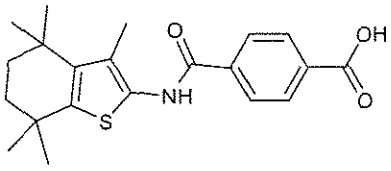


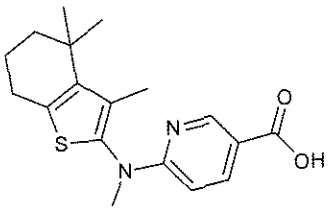


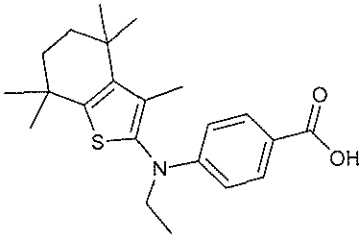


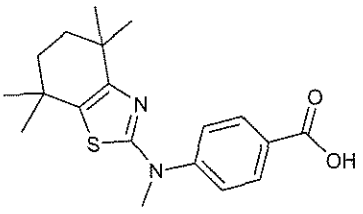


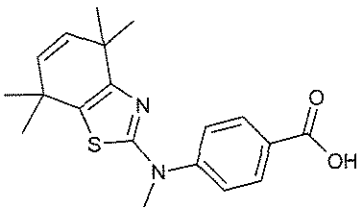


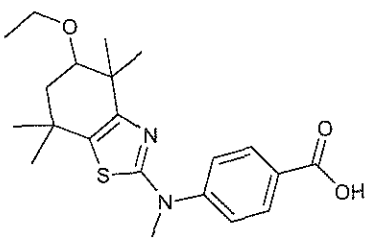


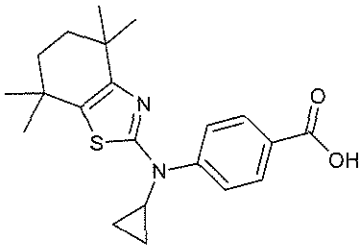


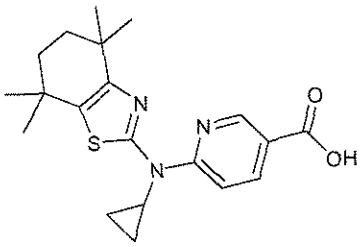


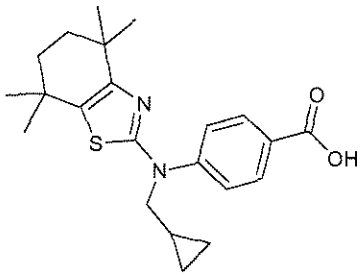


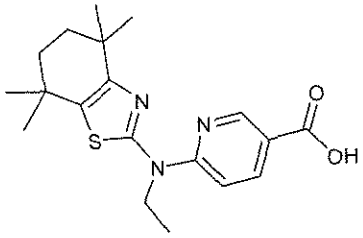


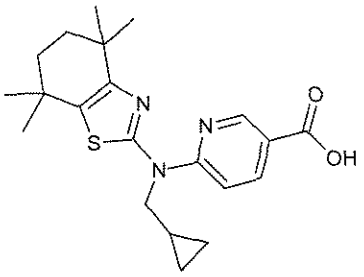


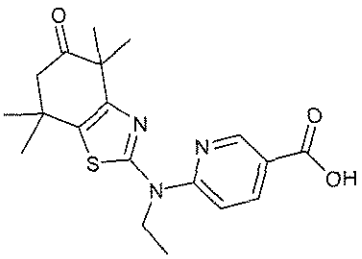


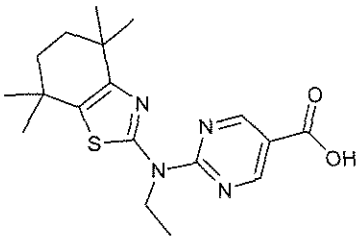


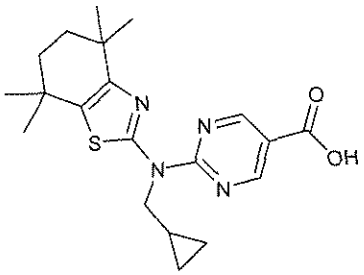


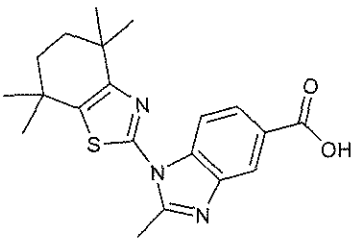


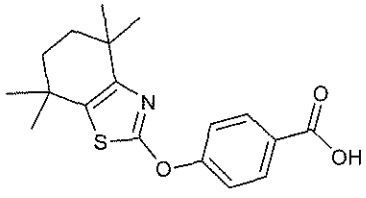


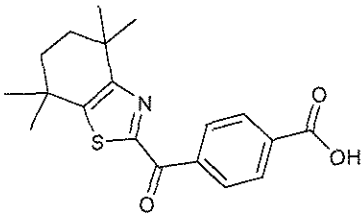


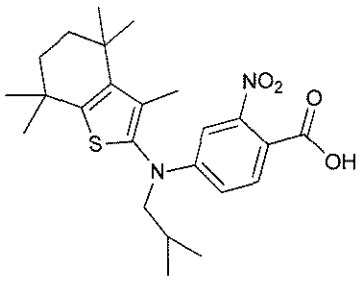


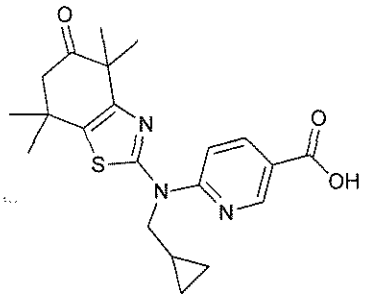


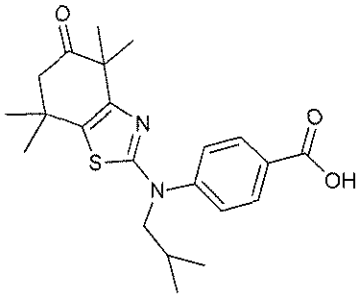


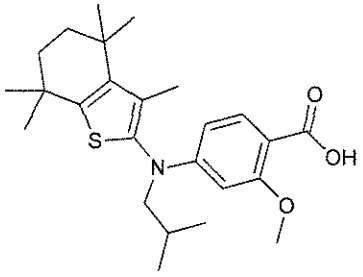


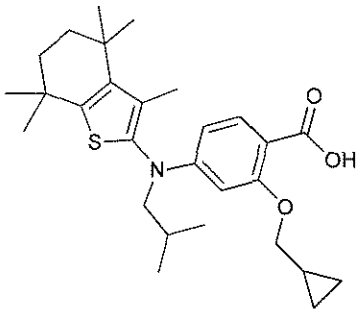


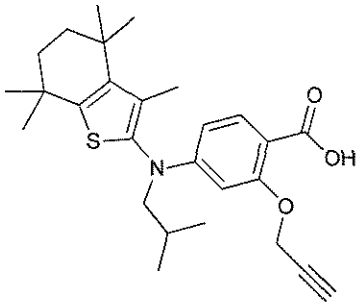


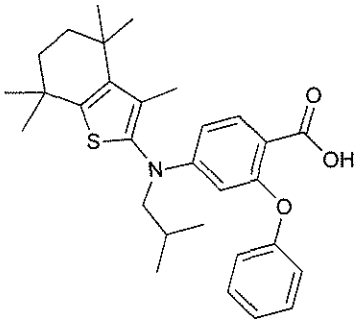


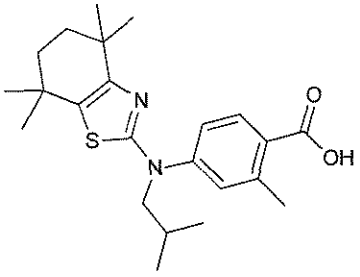


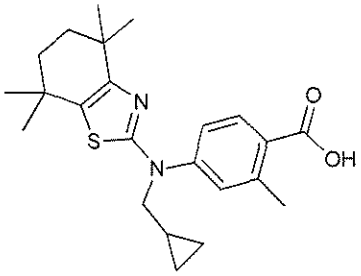


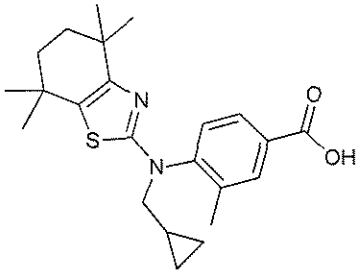


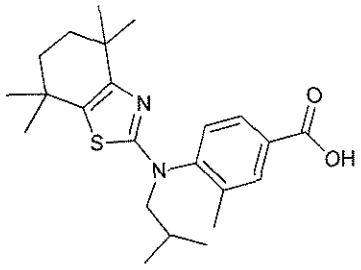


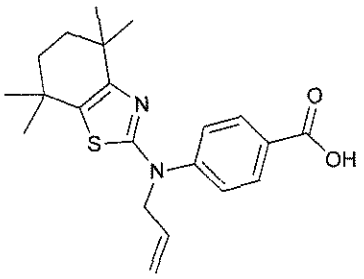


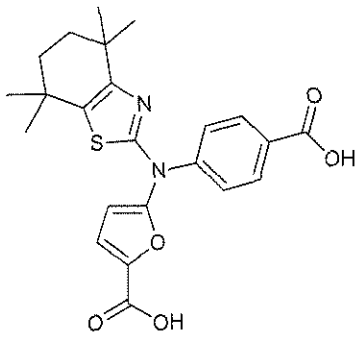


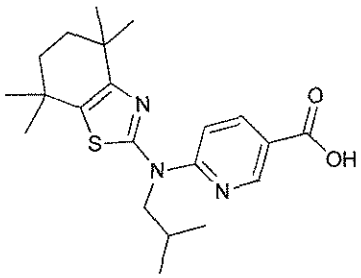


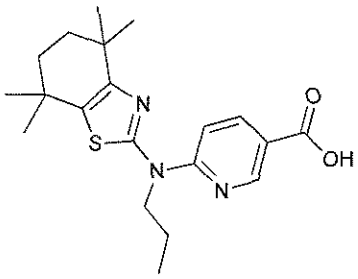


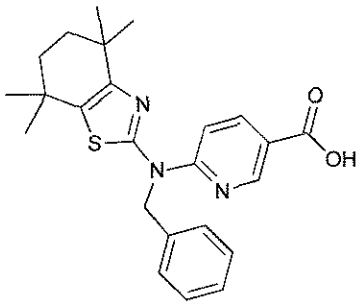


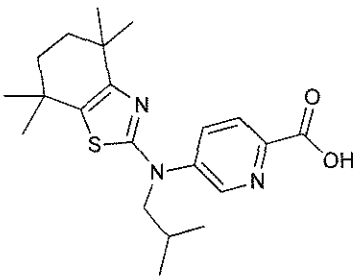


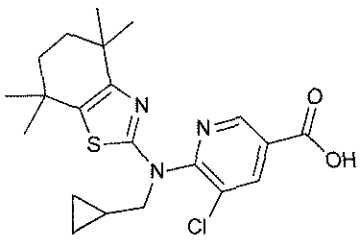


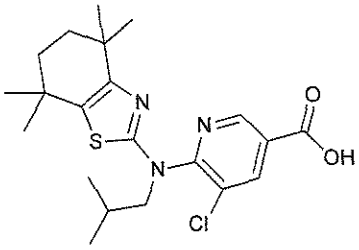


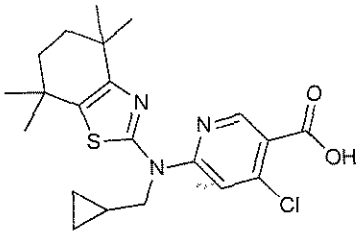


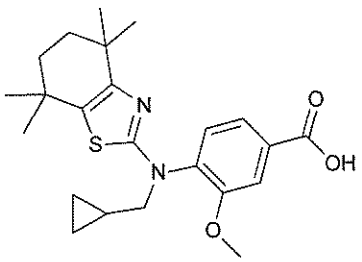


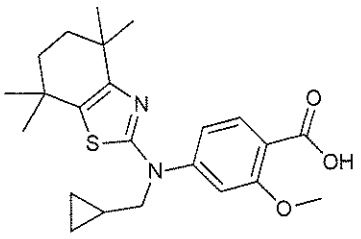


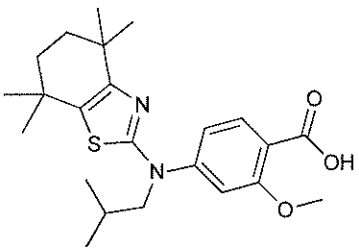


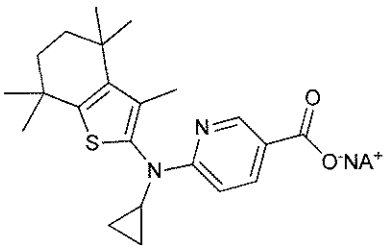


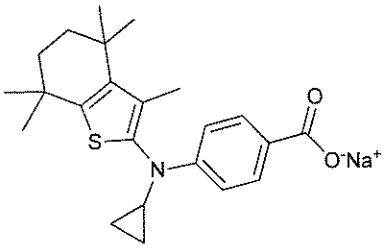


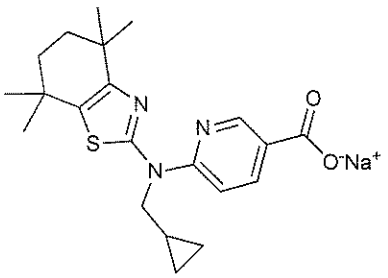


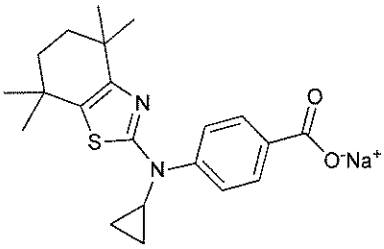


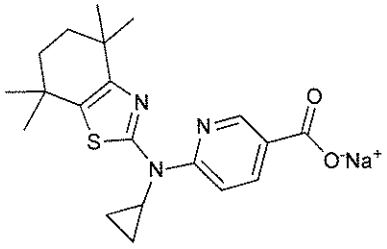


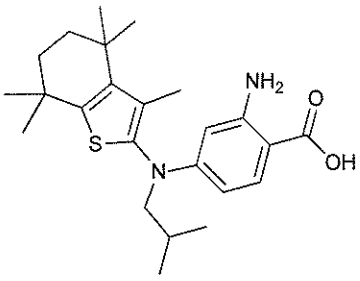


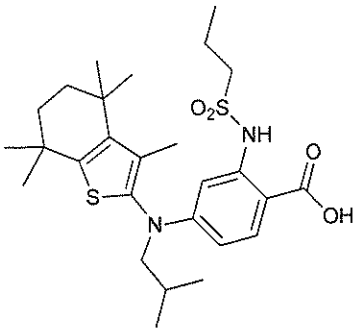


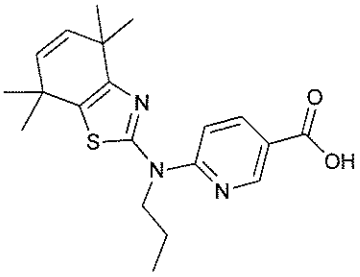


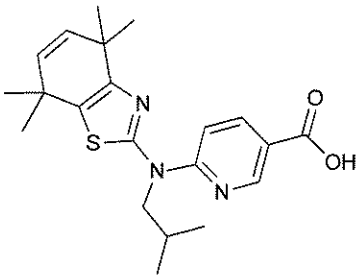


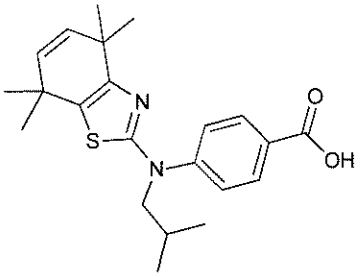


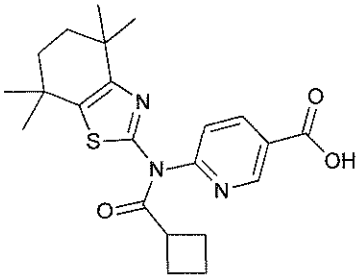


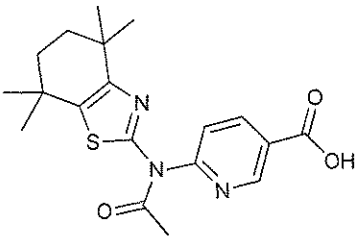


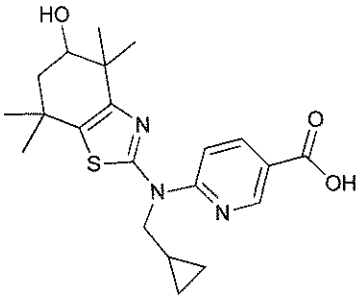


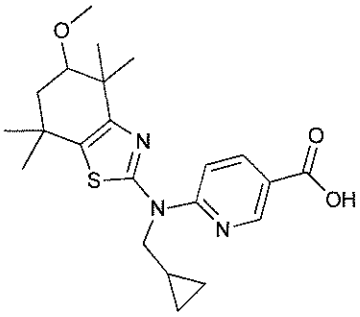


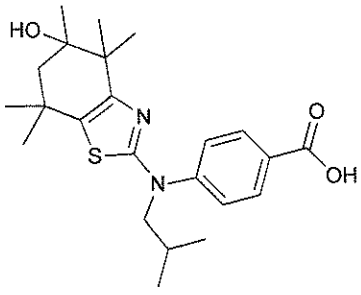


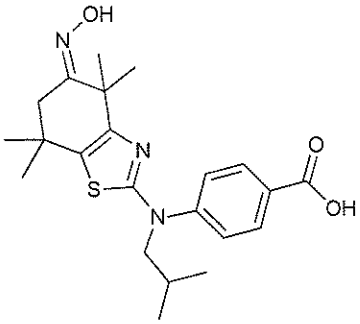


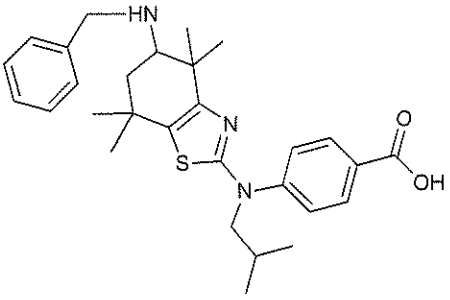


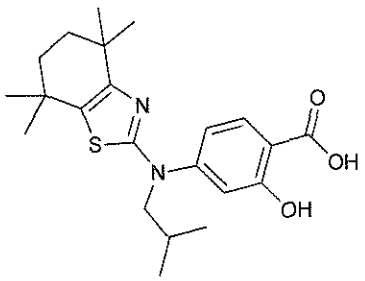


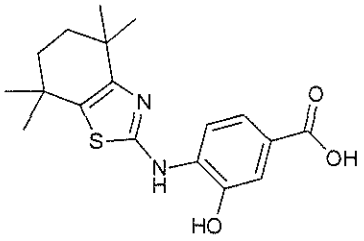


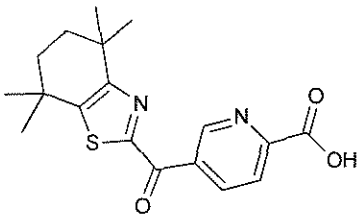


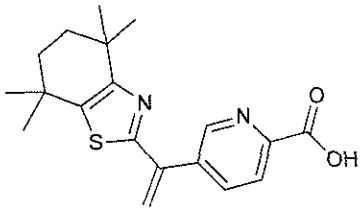


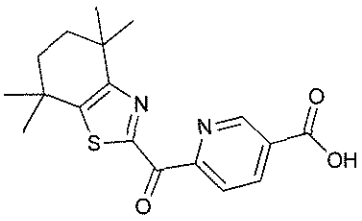


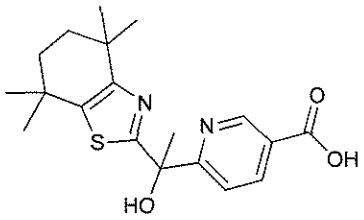


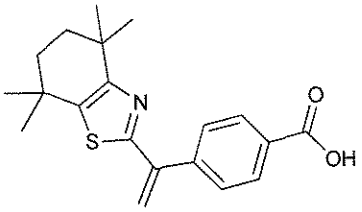


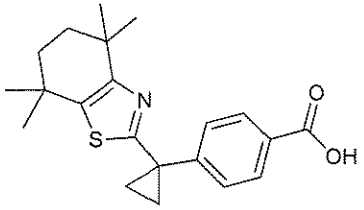


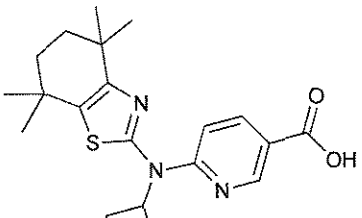


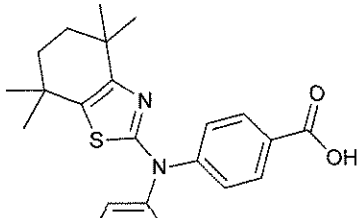


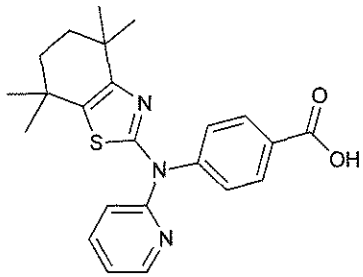


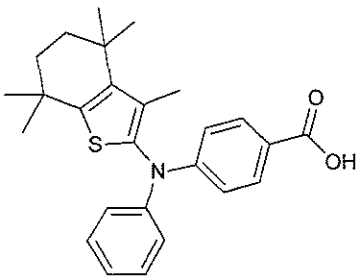


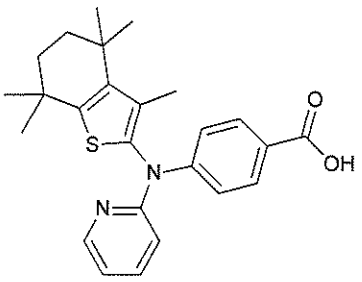


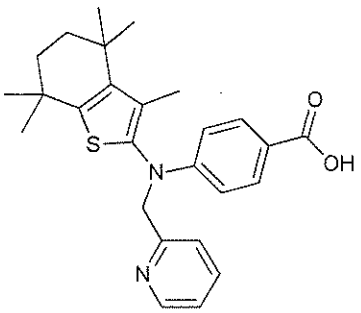












or pharmaceutically acceptable salt, thereof.

22. A pharmaceutical composition including a compound according to any one of claims 1 to 21 and a pharmaceutically acceptable diluent, excipient or carrier.

23. Use of a compound according to any one of claims 1 to 21 in the preparation of a medicament.

24. A use according to claim 23 wherein the medicament is for the treatment of a condition can be prevented or treated by activation of RXR

25. A use according to claim 23 wherein the condition is selected from the group consisting of Cancers such as premalignant and malignant hyperproliferative diseases such as cancers of the breast, pancreas, skin, prostate, cervix, uterus, colon, bladder, esophagus, stomach, lung, larynx, Liver, oral cavity, pancreas, blood and lymphatic system, metaplasias, dysplasias, neoplasias, leukoplakias and papillomas of the mucous membranes and in the treatment of Kaposis sarcoma, Cutaneous T Cell Lymphoma, promyelocyticleukemia, Non-Small-Cell Lung Cancer, Kidney Cancer (Advanced Renal Cell Cancer), Gastrointestinal Cancer, Mesothelioma, Bronchial Metaplasia; Skin disorders such as Dermatitis (Severe Chronic Hand Eczema in Adults) Psoriasis (Severe Plaque Psoriasis), Alopecia (Hair Loss), actinic keratoses, arsenic keratoses, inflammatory and non-inflammatory acne, psoriasis, ichthyoses and other keratinization and hyperproliferative disorders of the skin, eczema, atopic dermatitis, Darriers disease, lichen planus, prevention and reversal of glucocorticoid damage (steroid atrophy), as a topical anti-microbial, as skin pigmentation agents and to treat and reverse the effects of age and photo damage to the skin; Metabolic Diseases such as diabetes, Type II Diabetes, Obesity, Hyperglycemia, Hypercholesterimia, Hypertriglyceridimia; hyperinsulinaemia, Cardio vascular Diseases including diseases associated with lipid

metabolism such as dyslipidemias, lipodystrophy, prevention of restenosis and as an agent to increase the level of circulating tissue plasminogen activator (TPA), NASH, Steatosis, Steatohepatitis, Cirrhosis; liver disease, renal diseases including chronic kidney disease, Fibrosis including Pulmonary fibrosis, renal fibrosis and liver fibrosis, Eye disorders such as proliferative vitreoretinopathy (PVR), retinal detachment, dry eye and other corneopathies; autoimmune diseases and Inflammatory Diseases, inflammation, oxidative stress, pulmonary fibrosis, ileitis, colitis and Krohn's disease; neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and Amyotrophic Lateral Sclerosis (ALS), Multiple sclerosis, improper pituitary function, including insufficient production of growth hormone, modulation of apoptosis, including both the induction of apoptosis and inhibition of T-Cell activated apoptosis, restoration of hair growth, restoration of cardiac function, restoration of muscle function and multiple sclerosis.

26. A use according to claim 25 wherein the condition is diabetes.

27. A use according to claim 26 wherein the condition is type II diabetes.

28. A use according to claim 25 wherein the condition is cancer.

29 A use according to claim 25, wherein the condition is a disease of the liver.

30. A Use according to claim 29 wherein the condition is nonalcoholic steatohepatitis (NASH).

31. A use according to claim 25 wherein the condition is obesity.

32. A use according to claim 25 wherein the condition is cardiovascular disease.

33. Use of a compound according to any one of claims 1 to 21 in the preparation of a medicament for increasing muscle endurance in a mammal.

34. Use of a compound according to any one of claims 1 to 21 in the preparation of a medicament for improving cardiac function in a mammal.

35. Use of a compound according to any one of claims 1 to 21 in the preparation of a medicament for achieving an exercise mimetic effect in a mammal.