

SMALL MOLECULE MODULATORS OF MAS AND MRGD RECEPTORS**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] The present application claims benefit of U.S. Provisional Application No. 63/599,411, filed on November 15, 2023, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] Described herein are small molecule compounds that can be used as modulators of the G-protein coupled receptors Mas and MrgD. Such compounds can be used for treating diseases and disorders, including the exemplary diseases and disorders described herein.

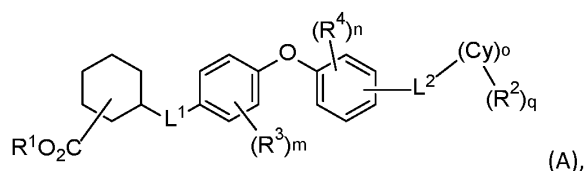
BACKGROUND

[0003] Mas-related G protein-coupled receptor D (MrgD), first identified in sensory neurons of mouse dorsal root ganglion, as well as Mas have been demonstrated to be involved in or related to several diseases and disorders, including cancer, cardiovascular disease, renal disease, inflammation, neuromotor disease, and metabolic disease or disorders. Thus, modulation of the G-protein coupled receptors Mas and MrgD becomes important in treating such diseases and disorders. There remains a need for new compounds, including new small molecule compounds, for the development of effective therapies targeting modulation of these receptors.

SUMMARY OF THE INVENTION

[0004] The present invention relates to small molecule compounds and pharmaceutically acceptable forms thereof that are potent modulators (e.g., agonists or activators) of the G-protein coupled receptors Mas and MrgD. Also described herein are compositions (e.g., pharmaceutical compositions) comprising compounds and pharmaceutically acceptable forms described herein, as well as uses of the compounds, pharmaceutically acceptable forms thereof, and compositions in methods for treating diseases and disorders, including those described herein.

[0005] In one aspect, the invention features a method of treating a disease or disorder, where said method comprises administering to a subject in need thereof a compound having a structure according to Formula (A),



or a pharmaceutically acceptable salt thereof, wherein

each of **R**¹ and **R**⁵ is independently H or C₁-C₆ alkyl;

R² is independently H, OH, or (CH₂)_pCO₂R⁵;

R³ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶;

R⁴ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶, or two **R**⁴ on adjacent carbons combine to form a heteroaryl moiety, or one **R**⁴ combines with **R**^{7B} to form a heteroaryl moiety;

L¹ is independently a covalent bond, C(O), C(O)NR^{7A}, or NR^{7A}C(O);

L² is independently a covalent bond, CH₂, C(O), NR^{7B}, C(O)NR^{7B}, or NR^{7B}C(O);

R⁶ is independently C₆-C₁₀ aryl or 5- to 10-membered heteroaryl;

each **R**^{7A} is independently H or C₁-C₆ alkyl;

each **R**^{7B} is independently H or C₁-C₆ alkyl, or **R**^{7B} combines with **R**⁴ to form a heteroaryl moiety;

X¹ is independently a covalent bond, O, or CH₂;

Cy is independently C₅-C₁₀ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

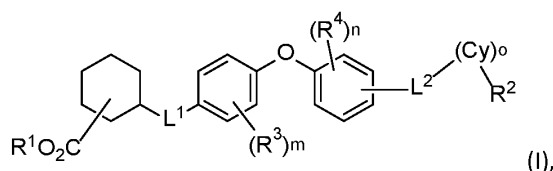
each of **m**, **n**, and **o** is independently 0, 1, or 2;

p is independently 0 or 1; and

q is independently 0, 1, 2, or 3, and

wherein the disease or disorder is one that benefits from modulation Mas or MrgD receptors.

[0006] In embodiments, a compound of Formula (A) has a structure according to Formula (I)



or a pharmaceutically acceptable salt thereof, wherein

each of R^1 and R^5 is independently H or C_1 - C_6 alkyl;

R^2 is independently H or $(CH_2)_pCO_2R^5$;

R^3 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1-R^6 ;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1-R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

L^1 is independently a covalent bond, $C(O)$, $C(O)NR^{7A}$, or $NR^{7A}C(O)$;

L^2 is independently a covalent bond, CH_2 , $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7A} is independently H or C_1 - C_6 alkyl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

Cy is independently C_5 - C_{10} cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

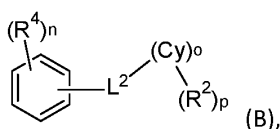
each of m , n , and o is independently 0, 1, or 2; and

p is independently 0 or 1.

and

wherein the disease or disorder is one that benefits from modulation Mas or MrgD receptors.

[0007] In another aspect, the invention features a method of treating a disease or disorder, where said method comprises administering to a subject in need thereof a compound having a structure according to Formula (B),



or a pharmaceutically acceptable salt thereof, wherein

R^2 is independently H, OH, or $(CH_2)_pCO_2R^5$;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1-R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

R^5 is independently H or C_1 - C_6 alkyl;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7B} is independently H or C_1-C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

L^2 is independently a covalent bond, C(O), NR^{7B} , C(O) NR^{7B} , or $NR^{7B}C(O)$;

Cy is independently C_5-C_7 cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of n and o is independently 0, 1, or 2;

p is independently 0, 1, 2, or 3, and

wherein the disease or disorder is one that benefits from modulation Mas or MrgD receptors.

[0008] In embodiments, a disease or disorder is cancer, cardiomyopathy, cardiovascular disease (e.g., stroke), renal disease, inflammation, a metabolic disease or disorder, preeclampsia, peripheral vascular disease, fibrotic disease, endothelial disease, hemorrhagic fever, malaria, muscular dystrophy, Marfan syndrome, radiation sickness, or sarcopenia.

[0009] In embodiments, a disease or disorder is cancer.

[00010] In embodiments, a disease or disorder is cardiomyopathy.

[00011] In embodiments, a disease or disorder is cardiovascular disease. In embodiments, a cardiovascular disease is selected from hypertension, heart failure, stroke, atherosclerosis, and aortic aneurysm.

[00012] In embodiments, a disease or disorder is renal disease. In embodiments, a renal disease is renal dysfunction.

[00013] In embodiments, a disease or disorder is inflammation.

[00014] In embodiments, a disease or disorder is metabolic disease or disorder. In embodiments, a metabolic disease or disorder is diabetes.

[00015] In embodiments, a disease or disorder is preeclampsia.

[00016] In embodiments, a disease or disorder is peripheral vascular disease.

[00017] In embodiments, a disease or disorder is fibrotic disease.

[00018] In embodiments, a disease or disorder is endothelial disease.

[00019] In embodiments, a disease or disorder is hemorrhagic fever. In embodiments, a hemorrhagic fever is Ebola disease.

[00020] In embodiments, a disease or disorder is Malaria. In embodiments, a Malaria is severe Malaria. In embodiments, a Malaria is cerebral Malaria.

[00021] In embodiments, a disease or disorder is muscular dystrophy.

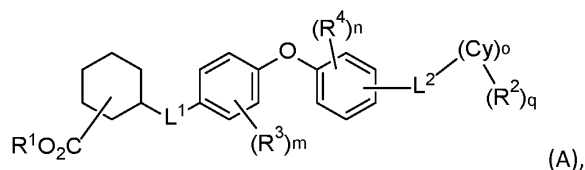
[00022] In embodiments, a disease or disorder is Marfan syndrome.

[00023] In embodiments, a disease or disorder is radiation sickness.

[00024] In embodiments, a disease or disorder is sarcopenia.

[00025] In embodiments, a disease or disorder is stroke.

[00026] In another aspect, the present invention provides a method of modulating glucose metabolism, where the method comprises administering to a subject in need thereof a compound having a structure according to Formula (A),



or a pharmaceutically acceptable salt thereof, wherein

each of R^1 and R^5 is independently H or C_1 - C_6 alkyl;

R^2 is independently H, OH, or $(CH_2)_pCO_2R^5$;

R^3 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1 - R^6 ;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1 - R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

L^1 is independently a covalent bond, $C(O)$, $C(O)NR^{7A}$, or $NR^{7A}C(O)$;

L^2 is independently a covalent bond, CH_2 , $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7A} is independently H or C_1 - C_6 alkyl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

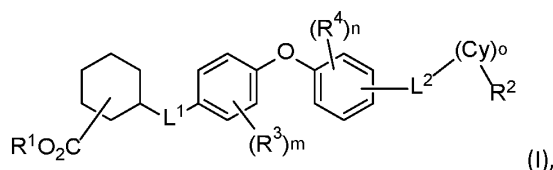
Cy is independently C₅-C₁₀ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of **m**, **n**, and **o** is independently 0, 1, or 2;

p is independently 0 or 1; and

q is independently 0, 1, 2, or 3.

[00027] In embodiments, a compound of Formula (A) has a structure according to Formula (I)



or a pharmaceutically acceptable salt thereof, wherein

each of **R¹** and **R⁵** is independently H or C₁-C₆ alkyl;

R² is independently H or (CH₂)_pCO₂R⁵;

R³ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶;

R⁴ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶, or two **R⁴** on adjacent carbons combine to form a heteroaryl moiety, or one **R⁴** combines with **R^{7B}** to form a heteroaryl moiety;

L¹ is independently a covalent bond, C(O), C(O)NR^{7A}, or NR^{7A}C(O);

L² is independently a covalent bond, CH₂, C(O), NR^{7B}, C(O)NR^{7B}, or NR^{7B}C(O);

R⁶ is independently C₆-C₁₀ aryl or 5- to 10-membered heteroaryl;

each **R^{7A}** is independently H or C₁-C₆ alkyl;

each **R^{7B}** is independently H or C₁-C₆ alkyl, or **R^{7B}** combines with **R⁴** to form a heteroaryl moiety;

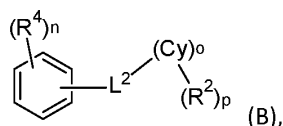
X¹ is independently a covalent bond, O, or CH₂;

Cy is independently C₅-C₁₀ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of **m**, **n**, and **o** is independently 0, 1, or 2; and

p is independently 0 or 1.

[00028] In another aspect, the present invention provides a method of modulating glucose metabolism, where the method comprises administering to a subject in need thereof a compound having a structure according to Formula (B),



or a pharmaceutically acceptable salt thereof, wherein

R^2 is independently H, OH, or $(CH_2)_pCO_2R^5$;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1 - R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

R^5 is independently H or C_1 - C_6 alkyl;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

L^2 is independently a covalent bond, $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

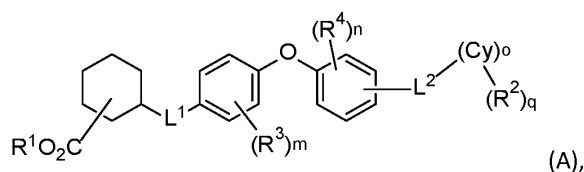
Cy is independently C_5 - C_7 cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of n , and o is independently 0, 1, or 2; and

p is independently 0, 1, 2, or 3.

[00029] In embodiments, a subject has diabetes.

[00030] In another aspect, the present invention provides a method of treating a cerebrovascular disease or disorder, where the method comprises administering to a subject in need thereof a compound having a structure according to Formula (A),



or a pharmaceutically acceptable salt thereof, wherein

each of R^1 and R^5 is independently H or C_1 - C_6 alkyl;

R^2 is independently H, OH, or $(CH_2)_pCO_2R^5$;

R^3 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1 - R^6 ;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1 - R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

L^1 is independently a covalent bond, $C(O)$, $C(O)NR^{7A}$, or $NR^{7A}C(O)$;

L^2 is independently a covalent bond, CH_2 , $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7A} is independently H or C_1 - C_6 alkyl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

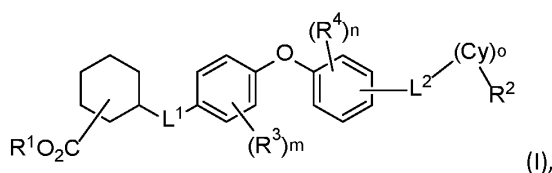
Cy is independently C_5 - C_{10} cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of m , n , and o is independently 0, 1, or 2;

p is independently 0 or 1; and

q is independently 0, 1, 2, or 3.

[00031] In embodiments, a compound of Formula (A) has a structure according to Formula (I)



or a pharmaceutically acceptable salt thereof, wherein

each of R^1 and R^5 is independently H or C_1 - C_6 alkyl;

R^2 is independently H or $(CH_2)_pCO_2R^5$;

R^3 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1 - R^6 ;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1 - R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

L^1 is independently a covalent bond, $C(O)$, $C(O)NR^{7A}$, or $NR^{7A}C(O)$;

L^2 is independently a covalent bond, CH_2 , $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7A} is independently H or C_1 - C_6 alkyl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

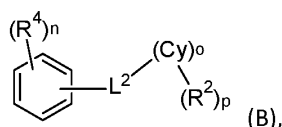
X^1 is independently a covalent bond, O, or CH_2 ;

Cy is independently C_5 - C_{10} cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of **m**, **n**, and **o** is independently 0, 1, or 2; and

p is independently 0 or 1.

[00032] In another aspect, the present invention provides a method of treating a cerebrovascular disease or disorder, where the method comprises administering to a subject in need thereof a compound having a structure according to Formula (B),



or a pharmaceutically acceptable salt thereof, wherein

R^2 is independently H, OH, or $(CH_2)_pCO_2R^5$;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1-R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

R^5 is independently H or C_1 - C_6 alkyl;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

L^2 is independently a covalent bond, $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

Cy is independently C_5 - C_7 cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

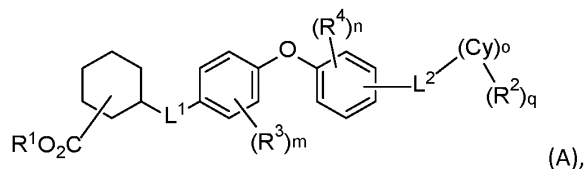
each of **n** and **o** is independently 0, 1, or 2; and

p is independently 0, 1, 2, or 3.

[00033] In embodiments, a cerebrovascular disease or condition is stroke.

[00034] In embodiments, a cerebrovascular disease or condition is ischemic stroke, hemorrhagic stroke, or a combination thereof.

[00035] In another aspect, the present invention provides a method of treating a neurological disease or disorder, said method comprising administering to a subject in need thereof a compound having a structure according to Formula (A),



or a pharmaceutically acceptable salt thereof, wherein

each of **R**¹ and **R**⁵ is independently H or C₁-C₆ alkyl;

R² is independently H, OH, or (CH₂)_pCO₂R⁵;

R³ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶;

R⁴ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶, or two **R**⁴ on adjacent carbons combine to form a heteroaryl moiety, or one **R**⁴ combines with **R**^{7B} to form a heteroaryl moiety;

L¹ is independently a covalent bond, C(O), C(O)NR^{7A}, or NR^{7A}C(O);

L² is independently a covalent bond, CH₂, C(O), NR^{7B}, C(O)NR^{7B}, or NR^{7B}C(O);

R⁶ is independently C₆-C₁₀ aryl or 5- to 10-membered heteroaryl;

each **R**^{7A} is independently H or C₁-C₆ alkyl;

each **R**^{7B} is independently H or C₁-C₆ alkyl, or **R**^{7B} combines with **R**⁴ to form a heteroaryl moiety;

X¹ is independently a covalent bond, O, or CH₂;

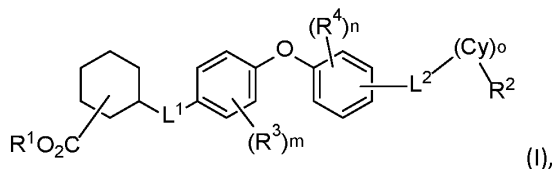
Cy is independently C₅-C₁₀ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of **m**, **n**, and **o** is independently 0, 1, or 2;

p is independently 0 or 1; and

q is independently 0, 1, 2, or 3.

[00036] In embodiments, a compound of Formula (A) has a structure according to Formula (I)



or a pharmaceutically acceptable salt thereof, wherein

each of **R**¹ and **R**⁵ is independently H or C₁-C₆ alkyl;

R^2 is independently H or $(CH_2)_pCO_2R^5$;

R^3 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1-R^6 ;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1-R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

L^1 is independently a covalent bond, CH_2 , $C(O)$, $C(O)NR^{7A}$, or $NR^{7A}C(O)$;

L^2 is independently a covalent bond, $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7A} is independently H or C_1 - C_6 alkyl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

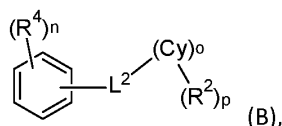
X^1 is independently a covalent bond, O, or CH_2 ;

Cy is independently C_5 - C_{10} cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of m , n , and o is independently 0, 1, or 2; and

p is independently 0 or 1.

[00037] In another aspect, the present invention provides a method of treating a neurological disease or disorder, said method comprising administering to a subject in need thereof a compound having a structure according to Formula (B),



or a pharmaceutically acceptable salt thereof, wherein

R^2 is independently H, OH, or $(CH_2)_pCO_2R^5$;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1-R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

R^5 is independently H or C_1 - C_6 alkyl;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

L^2 is independently a covalent bond, $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

Cy is independently C₅-C₇ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of **n** and **o** is independently 0, 1, or 2; and

p is independently 0, 1, 2, or 3.

[00038] In embodiments, each of **R**¹ and **R**⁵ is independently H.

[00039] In embodiments, **m** and **n** are both 0.

[00040] In embodiments, one of **m** and **n** is 1, and the other is 0.

[00041] In embodiments, **R**³ is independently methyl and/or **R**⁴ is independently methyl, isopropyl, or benzyl.

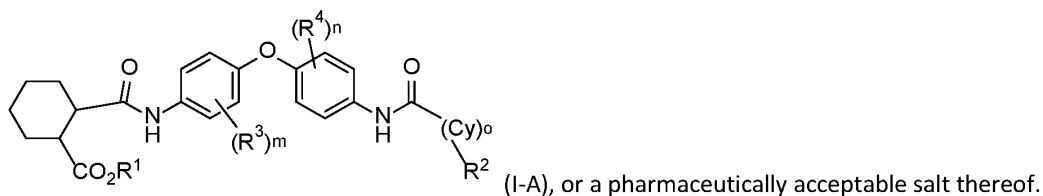
[00042] In embodiments, **L**¹ is a covalent bond, **o** is 0, and **R**² is H.

[00043] In embodiments, **L**¹ is NHC(O) and **o** is 1.

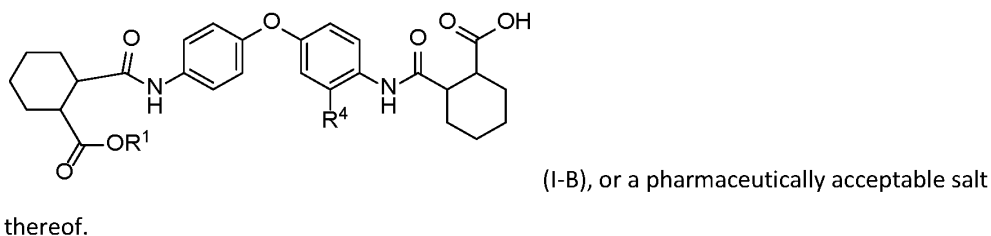
[00044] In embodiments, **Cy** is phenyl.

[00045] In embodiments, **Cy** is cyclohexyl.

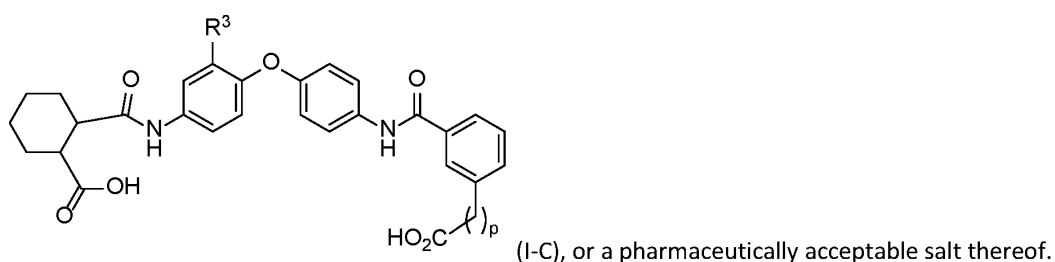
[00046] In embodiments, a compound of Formula (I) has a structure according to Formula (I-A),



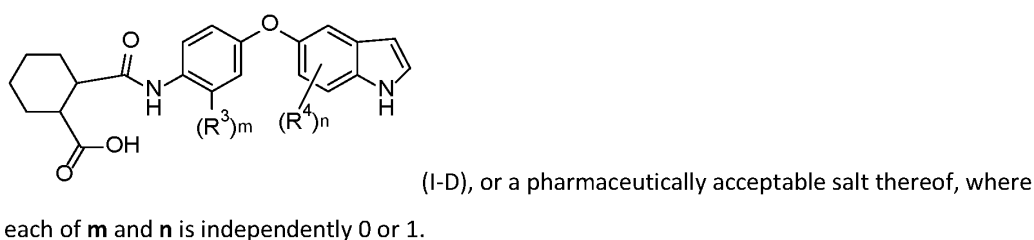
[00047] In embodiments, a compound of Formula (I) has a structure according to Formula (I-B),



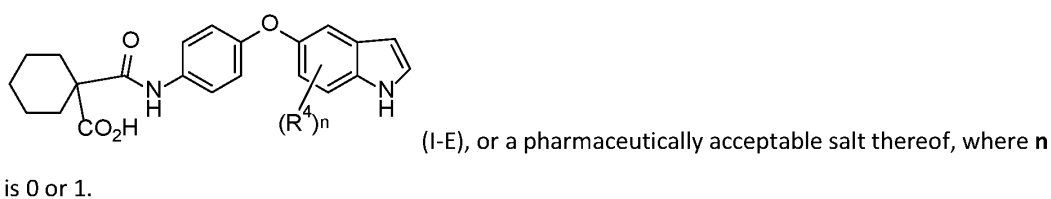
[00048] In embodiments, a compound of Formula (I) has a structure according to Formula (I-C),



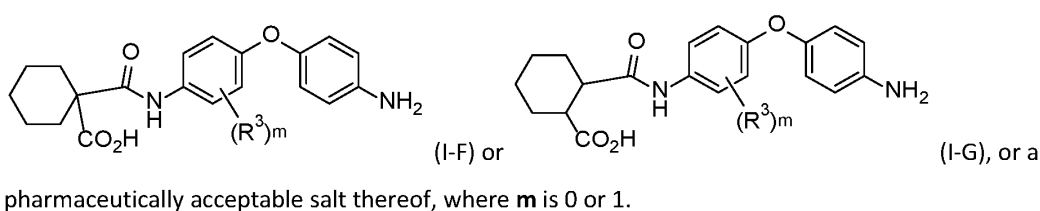
[00049] In embodiments, a compound of Formula (I) has a structure according to Formula (I-D),



[00050] In embodiments, a compound of Formula (I) has a structure according to Formula (I-E),



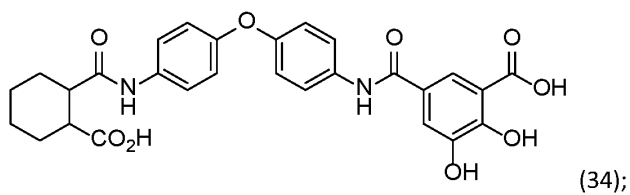
[00051] In embodiments, a compound of Formula (I) has a structure according to Formula (I-F) or (I-G),



[00052] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.

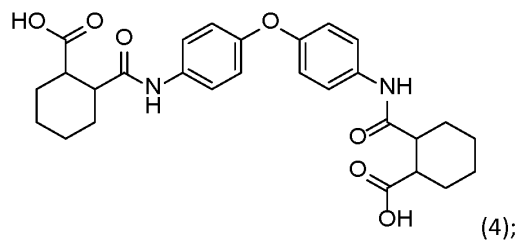
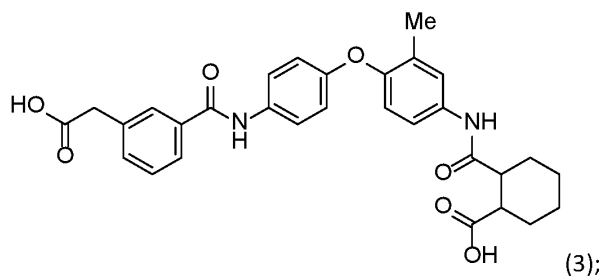
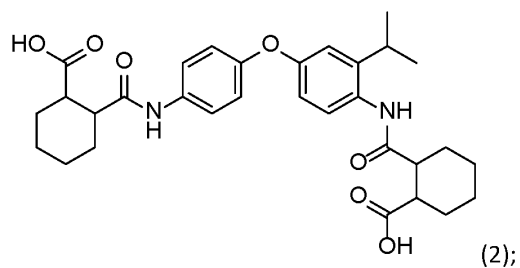
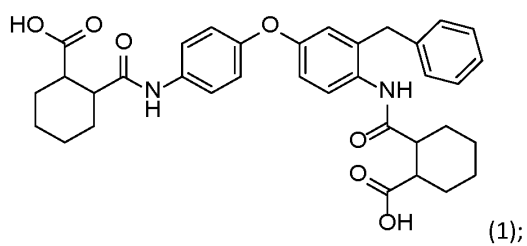
[00053] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.

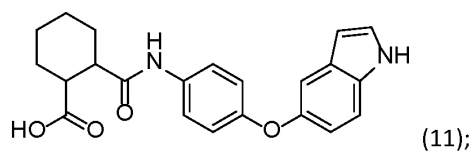
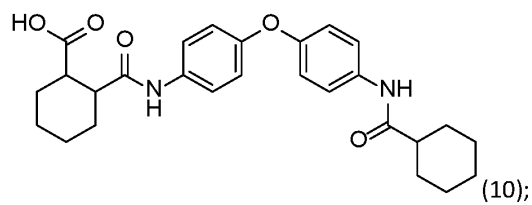
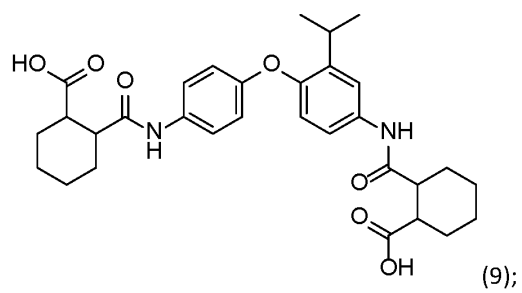
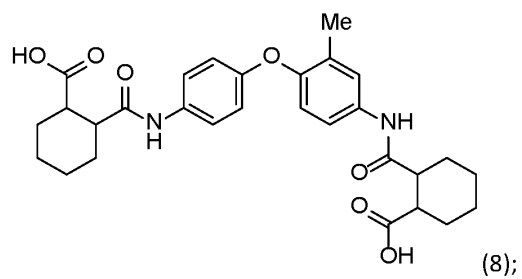
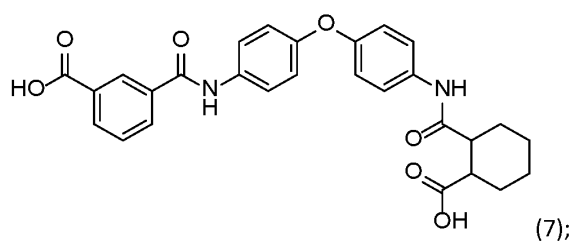
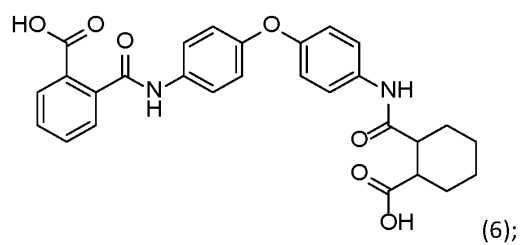
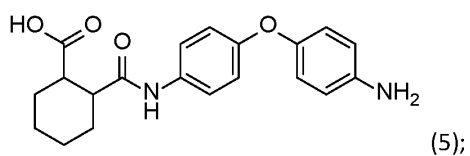
[00054] In embodiments, a compound of Formula (A) is selected from the group consisting of:

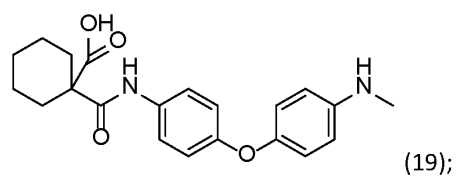
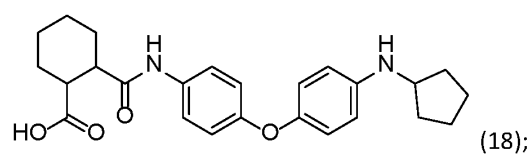
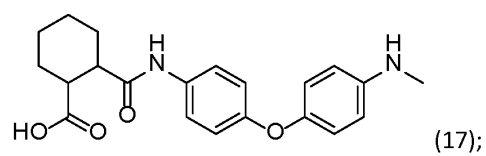
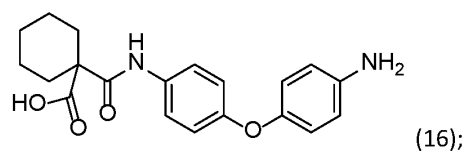
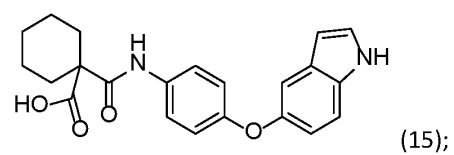
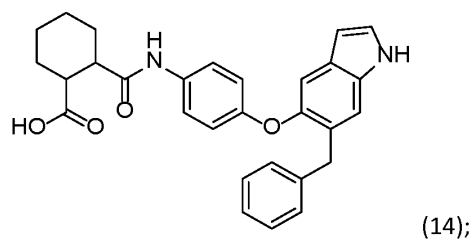
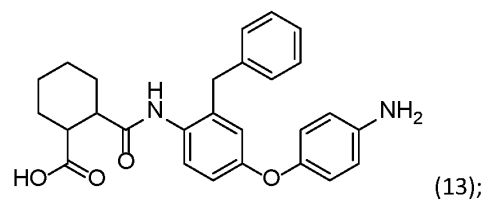
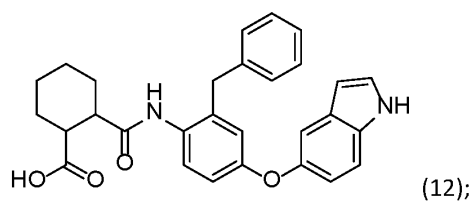


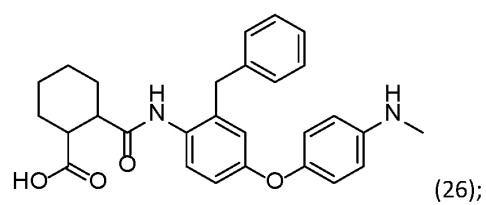
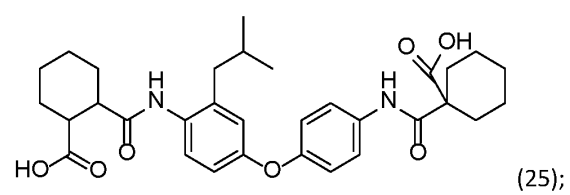
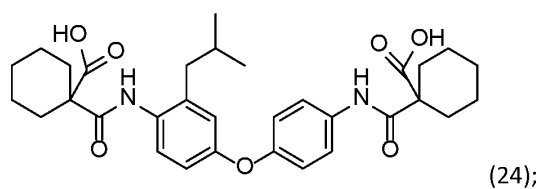
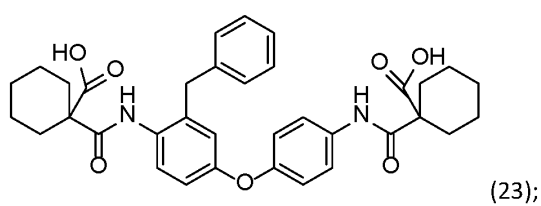
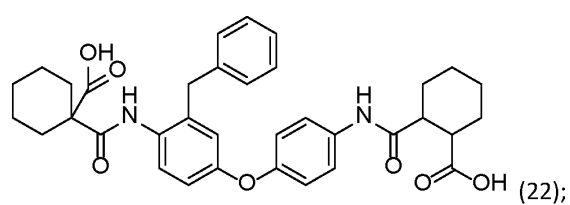
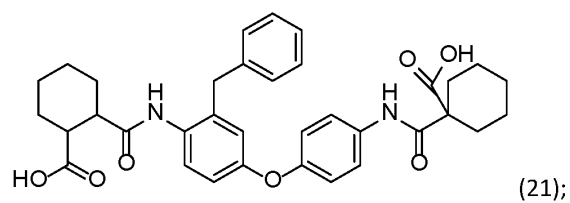
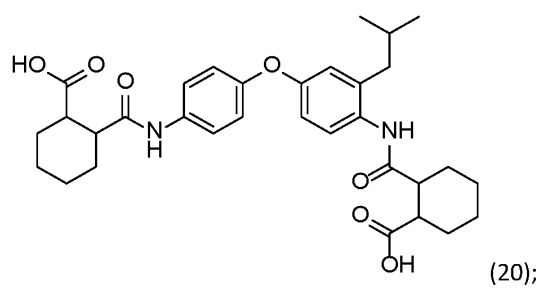
or a pharmaceutically acceptable salt thereof.

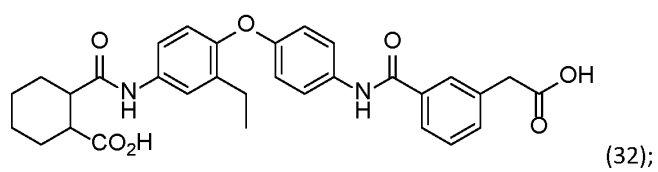
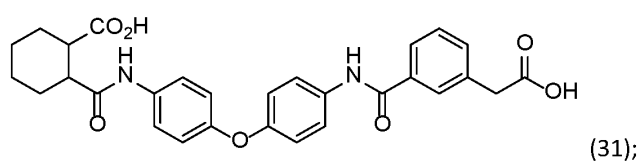
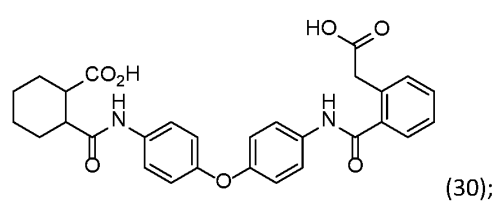
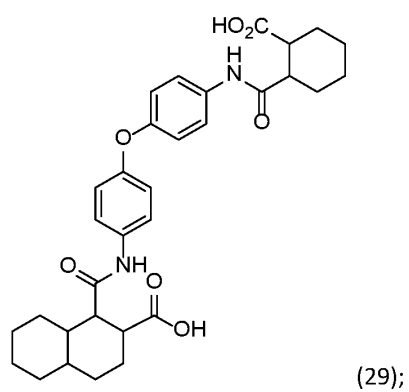
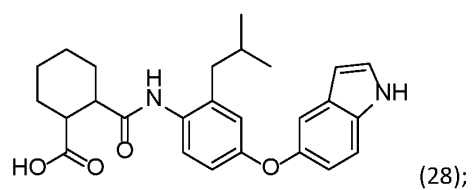
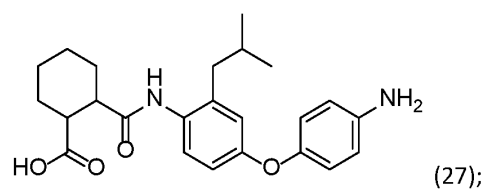
[00055] In embodiments, a compound of Formula (I) is selected from the group consisting of:



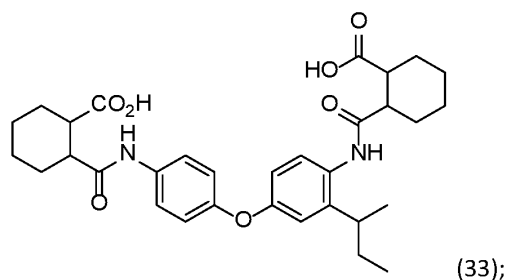






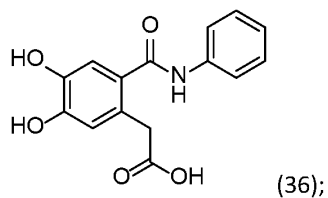
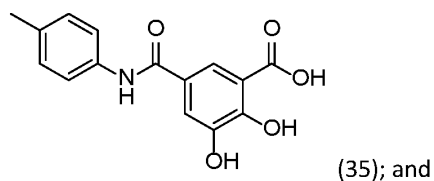


and



or a pharmaceutically acceptable salt thereof.

[00056] In embodiments, a compound of Formula (B) is selected from the group consisting of:



or a pharmaceutically acceptable salt thereof

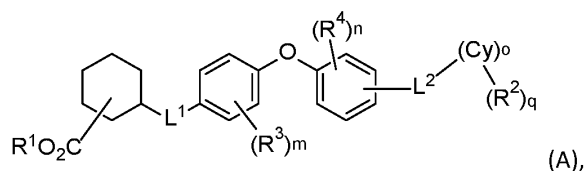
[00057] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.

[00058] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.

[00059] In embodiments, a method described herein comprises the administration of a pharmaceutically acceptable salt of the compound.

[00060] In another aspect, the present invention provides a pharmaceutical composition comprising:

(1) a therapeutically effective amount of a compound having a structure according to Formula (A),



or a pharmaceutically acceptable salt thereof, wherein

each of R^1 and R^5 is independently H or C_1 - C_6 alkyl;

R^2 is independently H, OH, or $(CH_2)_pCO_2R^5$;

R^3 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1 - R^6 ;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1 - R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

L^1 is independently a covalent bond, $C(O)$, $C(O)NR^{7A}$, or $NR^{7A}C(O)$;

L^2 is independently a covalent bond, CH_2 , $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7A} is independently H or C_1 - C_6 alkyl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

Cy is independently C_5 - C_{10} cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of m , n , and o is independently 0, 1, or 2;

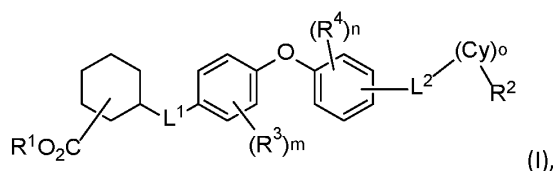
p is independently 0 or 1; and

q is independently 0, 1, 2, or 3; and

(2) a pharmaceutically acceptable excipient.

[00061] In embodiments, a pharmaceutical composition comprising:

(1) a therapeutically effective amount of a compound having a structure according to Formula (I),



or a pharmaceutically acceptable salt thereof, wherein

each of **R¹** and **R⁵** is independently H or C₁-C₆ alkyl;

R² is independently H or (CH₂)_pCO₂R⁵;

R³ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶;

R⁴ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶, or two **R⁴** on adjacent carbons combine to form a heteroaryl moiety, or one **R⁴** combines with **R^{7B}** to form a heteroaryl moiety;

L¹ is independently a covalent bond, C(O), C(O)NR^{7A}, or NR^{7A}C(O);

L² is independently a covalent bond, CH₂, C(O), NR^{7B}, C(O)NR^{7B}, or NR^{7B}C(O);

R⁶ is independently C₆-C₁₀ aryl or 5- to 10-membered heteroaryl;

each **R^{7A}** is independently H or C₁-C₆ alkyl;

each **R^{7B}** is independently H or C₁-C₆ alkyl, or **R^{7B}** combines with **R⁴** to form a heteroaryl moiety;

X¹ is independently a covalent bond, O, or CH₂;

Cy is independently C₅-C₁₀ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of **m**, **n**, and **o** is independently 0, 1, or 2; and

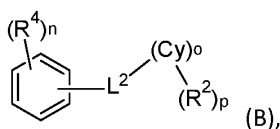
p is independently 0 or 1;

and

(2) a pharmaceutically acceptable excipient.

[00062] In another aspect, the present invention provides a pharmaceutical composition comprising:

(1) a therapeutically effective amount of a compound having a structure according to Formula (B),



or a pharmaceutically acceptable salt thereof, wherein

R^2 is independently H, OH, or $(CH_2)_pCO_2R^5$;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1-R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

R^5 is independently H or C_1 - C_6 alkyl;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

L^2 is independently a covalent bond, $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

Cy is independently C_5 - C_7 cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of n and o is independently 0, 1, or 2; and

p is independently 0, 1, 2, or 3;

and

(2) a pharmaceutically acceptable excipient.

[00063] In embodiments, each of R^1 and R^5 is independently H.

[00064] In embodiments, m and n are both 0.

[00065] In embodiments, one of m and n is 1, and the other is 0.

[00066] In embodiments, R^3 is independently methyl and/or R^4 is independently methyl, isopropyl, or benzyl.

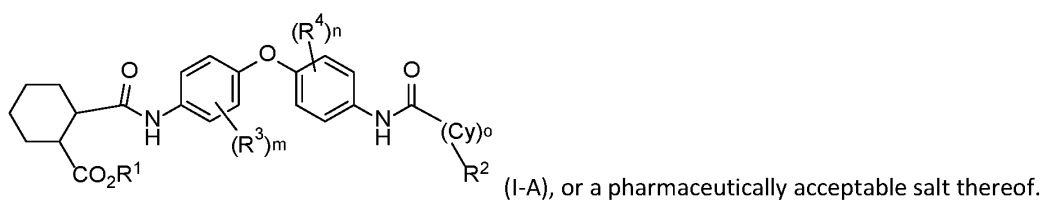
[00067] In embodiments, L^1 is a covalent bond, o is 0, and R^2 is H.

[00068] In embodiments, L^1 is $NHC(O)$ and o is 1.

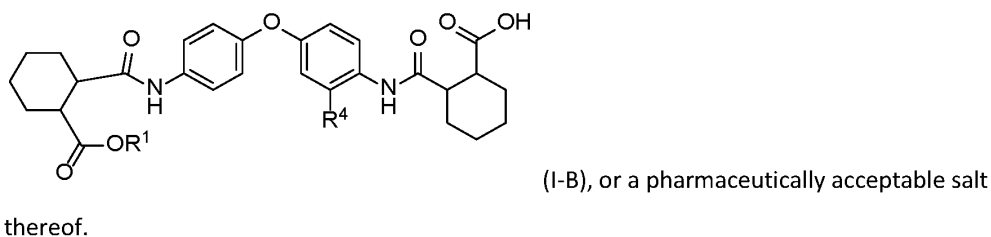
[00069] In embodiments, Cy is phenyl.

[00070] In embodiments, Cy is cyclohexyl.

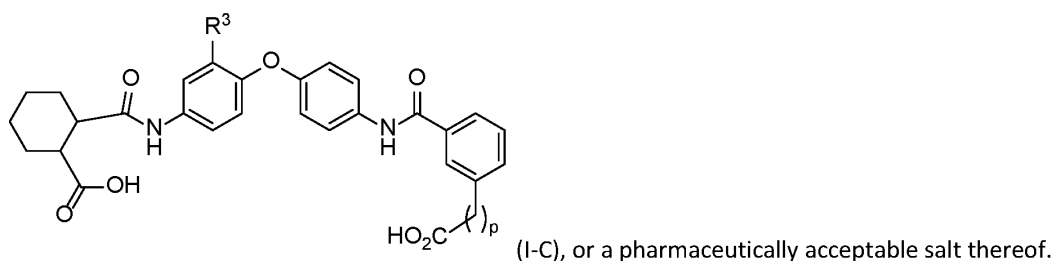
[00071] In embodiments, a compound of Formula (I) has a structure according to Formula (I-A),



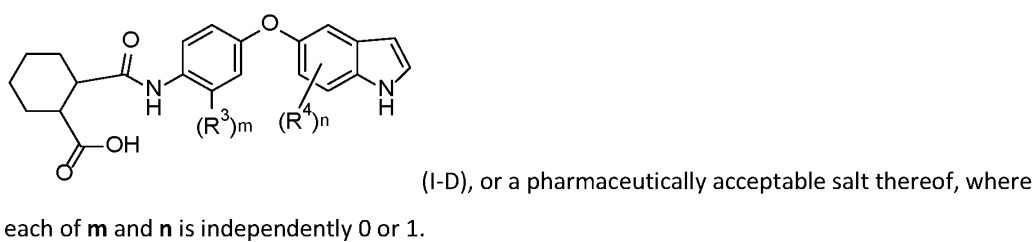
[00072] In embodiments, a compound of Formula (I) has a structure according to Formula (I-B),



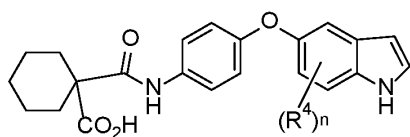
[00073] In embodiments, a compound of Formula (I) has a structure according to Formula (I-C),



[00074] In embodiments, a compound of Formula (I) has a structure according to Formula (I-D),



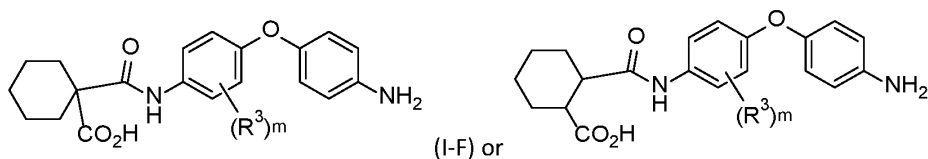
[00075] In embodiments, a compound of Formula (I) has a structure according to Formula (I-E),



(I-E), or a pharmaceutically acceptable salt

thereof, where **n** is 0 or 1.

[00076] In embodiments, a compound of Formula (I) has a structure according to Formula (I-F) or (I-G),

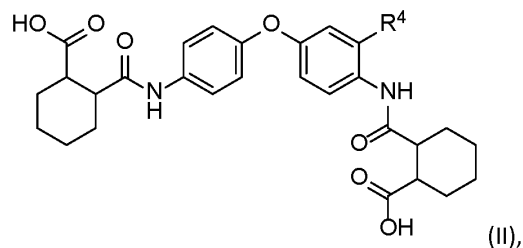


(I-G), or a pharmaceutically acceptable salt thereof, where **m** is 0 or 1.

[00077] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.

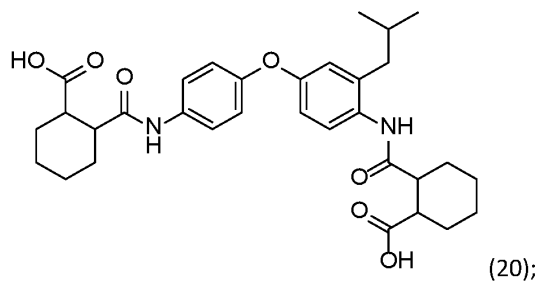
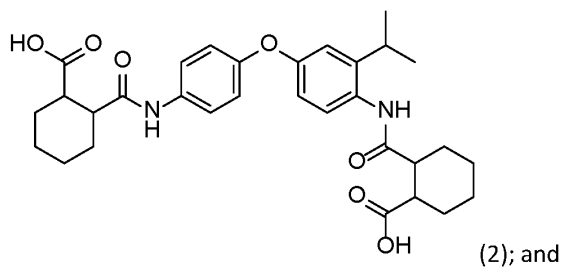
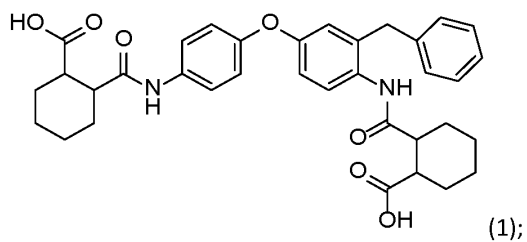
[00078] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.

[00079] In another aspect, the present invention provides a compound having a structure according to Formula (II),



or a pharmaceutically acceptable salt thereof, wherein **R⁴** is C₂-C₆ alkyl or benzyl.

[00080] In embodiments, a compound of Formula (II) is selected from the group consisting of:



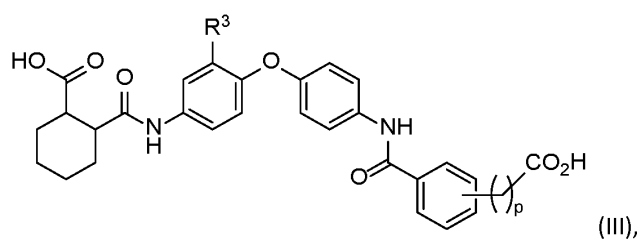
or a pharmaceutically acceptable salt thereof.

[00081] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.

[00082] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.

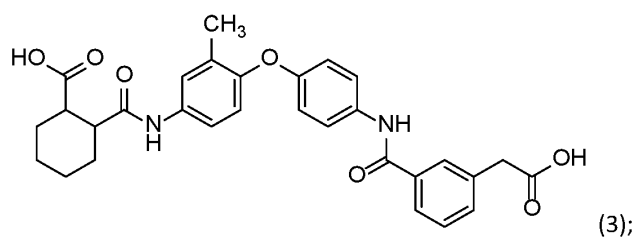
[00083] In embodiments, the invention features a pharmaceutically acceptable salt of the compound of Formula (II).

[00084] In another aspect, the present invention provides a compound having a structure according to Formula (III),



or a pharmaceutically acceptable salt thereof, wherein R^3 is C_1 - C_6 alkyl, and p is 0 or 1.

[00085] In embodiments, the compound of Formula (III) is selected from the group consisting of:



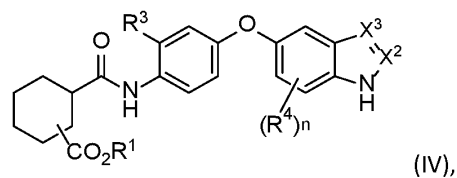
or a pharmaceutically acceptable salt thereof.

[00086] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.

[00087] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.

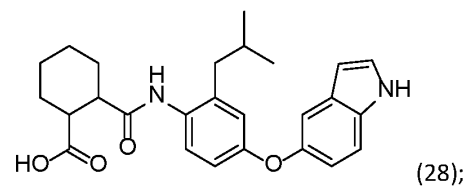
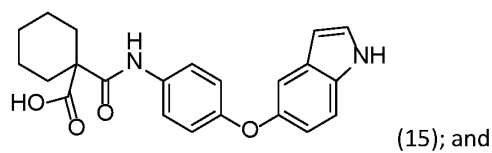
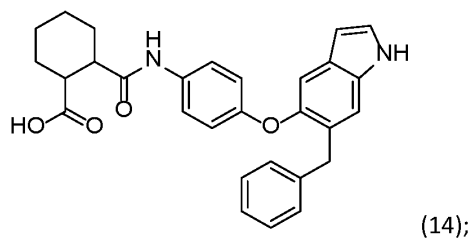
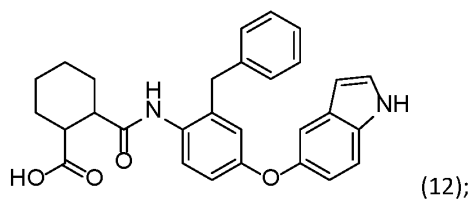
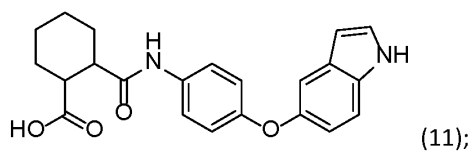
[00088] In embodiments, the invention features a pharmaceutically acceptable salt of a compound of Formula (III).

[00089] In another aspect, the present invention provides a compound having a structure according to Formula (IV),



or a pharmaceutically acceptable salt thereof, wherein R^1 is H or C_1 - C_6 alkyl, R^3 is H or C_1 - C_6 alkyl optionally substituted by phenyl, R^4 is C_1 - C_6 alkyl or benzyl, each of X^2 and X^3 is independently N or CH, and n is 0 or 1.

[00090] In embodiments, a compound of Formula (IV) is selected from the group consisting of:



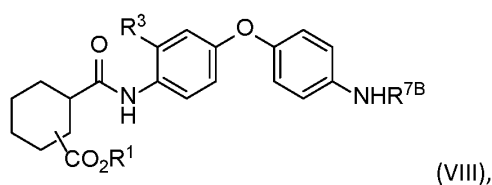
or a pharmaceutically acceptable salt thereof.

[00091] In embodiments substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.

[00092] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.

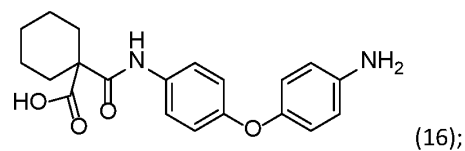
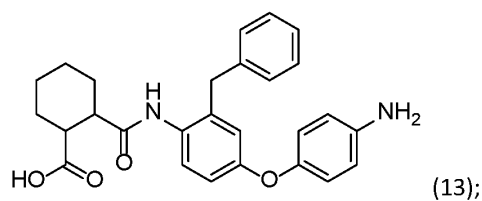
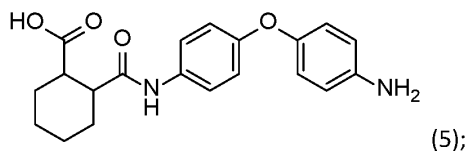
[00093] In embodiments, the invention features a pharmaceutically acceptable salt of the compound of Formula (IV).

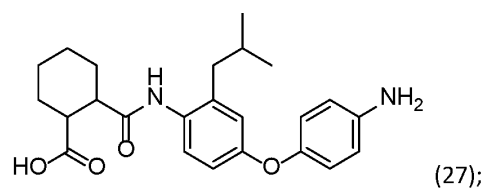
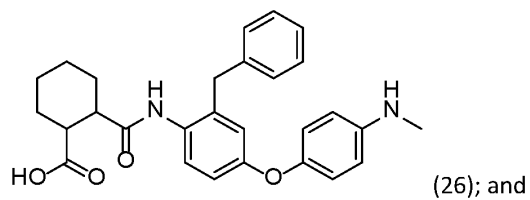
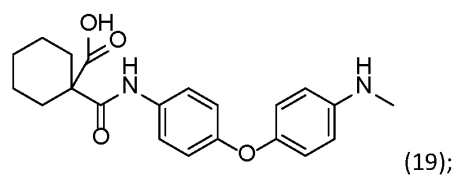
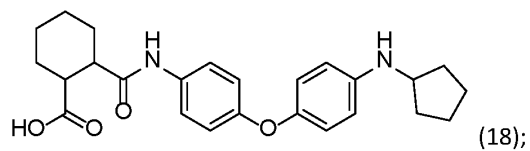
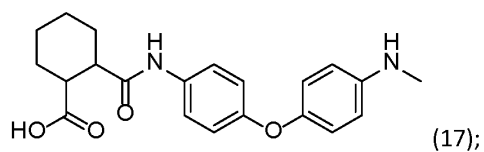
[00094] In another aspect, the present invention provides a compound having a structure according to Formula (VIII),



or a pharmaceutically acceptable salt thereof, wherein R^1 is H or C_1 - C_6 alkyl, R^3 is H or C_1 - C_6 alkyl optionally substituted by phenyl, and R^{7B} is H or C_1 - C_6 alkyl.

[00095] In embodiments, a compound of Formula (VIII) is selected from the group consisting of:



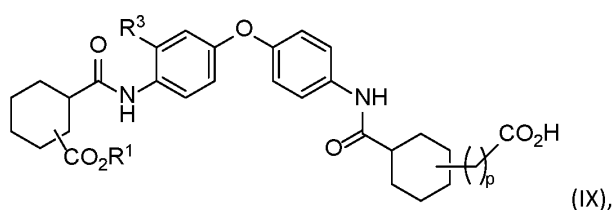


[00096] or a pharmaceutically acceptable salt thereof. In embodiments substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.

[00097] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.

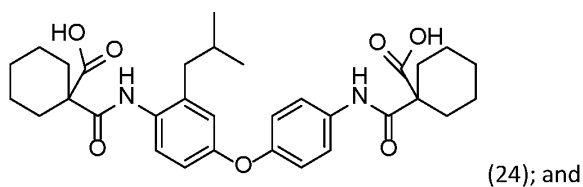
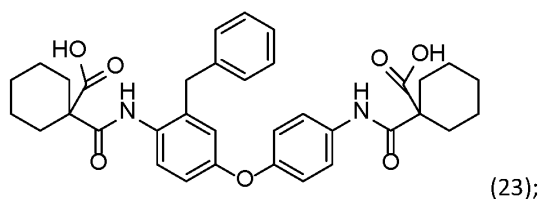
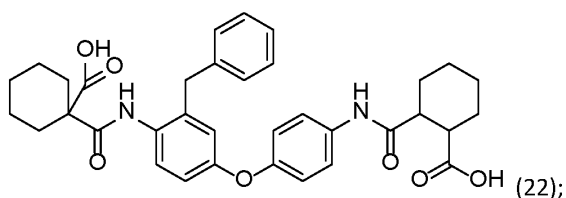
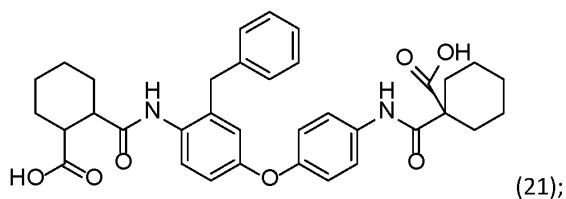
[00098] In embodiments, the invention features a pharmaceutically acceptable salt of the compound of Formula (VIII).

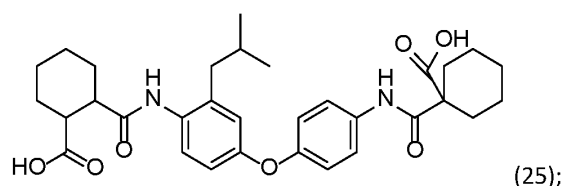
[00099] In another aspect, the present invention provides a compound having a structure according to Formula (IX),



or a pharmaceutically acceptable salt thereof, wherein R^1 is H or C_1 - C_6 alkyl, R^3 is C_2 - C_6 alkyl optionally substituted by phenyl, and p is 0 or 1.

[000100] In embodiments, a compound of Formula (X) is selected from the group consisting of:





or a pharmaceutically acceptable salt thereof.

[000101] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.

[000102] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.

[000103] In embodiments, the invention features a pharmaceutically acceptable salt of the compound of Formula (IX).

[000104] Other features, objects, and advantages of the present invention are apparent in the detailed description that follows. It should be understood, however, that the detailed description, while indicating embodiments of the present invention, is given by way of illustration only, not limitation. Various changes and modifications within the scope of the invention will become apparent to those skilled in the art from the detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

[000105] The drawings are for illustration purposes only, not for limitation.

[000106] **FIG. 1** depicts a study of Compound (4) and the peptide angiotensin-(1-7) in a diabetic mouse model.

[000107] **FIG. 2** depicts a study of Compound (3)-*trans* and angiotensin-(1-7) in Mesangial cells.

[000108] **FIG. 3** depicts receptor-binding studies of Compound (5).

[000109] **FIGS. 4A-4D** depict studies of Compound (1)-*cis/cis* and an angiotensin-(1-7) peptide (TXA127) in a preclinical stroke model, showing outcomes in neuroscore (**FIG. 4A**), forelimb placement test (**FIG. 4B**), stepping test (**FIG. 4C**), and body swing test (**FIG. 4D**).

[000110] FIGS. 5A-5D depict studies of Compound (5) and an angiotensin-(1-7) peptide (TXA127) in a preclinical stroke model, showing outcomes in neuroscore (FIG. 5A), forelimb placement test (FIG. 5B), stepping test (FIG. 5C), and body swing test (FIG. 5D).

[000111] FIG. 6 depicts studies of Compound (1) (labeled with M13B) and three concentrations of Compound (5) (labeled with M13A) in stroke. For each of D-2, D-8, D-15, D-22, and D-29, the data corresponding to 1M, 2M, 3M, 4M, 5M, 5M, 6M, 7M, 8M, 9M, and 10M cohorts are presented sequentially in the grouping from left to right.

[000112] FIG. 7 depicts studies of Compound (1) (labeled with M13B) and two concentrations of Compound (3) (labeled with M13D) in stroke. For each of D-2, D-8, D-15, D-22, and D-29, the data corresponding to 1M, 2M, 3M, 4M, 5M, 5M, and 6M cohorts are presented sequentially in the grouping from left to right.

[000113] FIG. 8 depicts studies of Compound (34) (labeled with M13(2)12), Compound (35) (labeled with M13(2)13), Compound (5) (labeled with M13(2)9), and Compound (1) (labeled with M13(2)20) in colony formation assay of A498 cells.

[000114] FIG. 9 depicts cell numbers from colony formation studies using compounds according to Compound (6) (labeled with M13(1)7) and Compound (5) (labeled with M13(2)9).

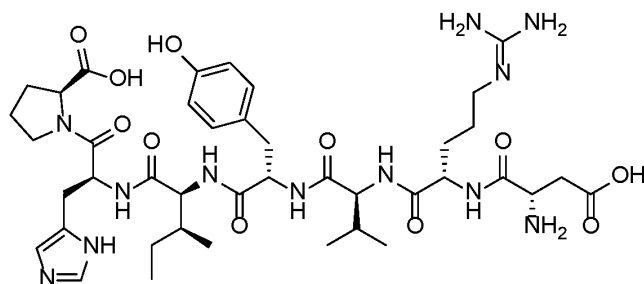
[000115] FIG. 10 depicts studies of compounds of Formula (A) (labeled with M13 (Compound (4)), M13(2)9 (Compound (5)), and M13(2)20 (Compound (1))) in HUVEC cell tube formation assay.

[000116] FIG. 11 depicts studies of compounds of Formula (A) (labeled with M13(2)12 (Compound (34)), M13 (Compound (4)), M13(2)1 (Compound (9)), M13(2)4 (Compound (33)), M13(2)9 (Compound (5)), and M13(2)20 (Compound (1))), and compounds of Formula (B) (labeled with M13(2)13 (Compound (35)) and M13(2)15 (Compound (36))) in Ussing chamber.

[000117] FIG. 12 depicts studies of compounds of Formula (A) (labeled with M13 (Compound (4)) and M13(2)20 (Compound (1))), endogenous agonist (labeled with EA) and solvent in in Ussing chamber.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[000118] Angiotensin-(1-7) is an endogenous heptapeptide component of the renin-angiotensin system (RAS) having the following structure.



Angiotensin-(1-7)

[000119] Angiotensin-(1-7) can bind to the G-protein coupled MrgD and Mas receptors, which results in various therapeutic effects, including use for treating various non-limiting diseases and disorders including but not limited to atherosclerosis, aortic aneurysm, cancer, cardiac dysfunction, diabetes mellitus, heart failure, obesity, renal disease and dysfunction.

[000120] The present invention relates to small molecule compounds which are structurally distinct from Angiotensin-(1-7) but nonetheless are potent modulators of the Mas and MrgD G-protein coupled receptors. The small molecules described herein can be therapeutically effective in the treatment of diseases and conditions that benefit from Angiotensin-(1-7) therapy, and exemplary therapeutic uses are described herein. Thus, described herein are small molecule Mas/MrgD modulators, compositions (e.g., pharmaceutical compositions) comprising compounds and pharmaceutically acceptable forms described herein, as well as uses of the compounds, pharmaceutically acceptable forms thereof, and compositions in methods for treating diseases and disorders, including those described herein.

[000121] Exemplary formulas and compounds are described herein. Also provided herein are exemplary embodiments of structural features which may be present in any formula described herein. Any exemplary embodiment of a structural feature may occur in combination with any other exemplary structural feature described herein. Further, and unless otherwise indicated herein, any description of a formula or compound also includes any pharmaceutically acceptable forms of the compound, including but not limited to any pharmaceutically acceptable salts, hydrates, solvates, isomers, polymorphs, prodrugs, and isotopically labeled derivatives of disclosed formulas and compounds.

[000122] Various aspects of the invention are described in detail in the following sections. The use of sections is not meant to limit the invention. Each section can apply to any aspect of the invention. In this application, the use of “or” means “and/or” unless stated otherwise.

Definitions

[000123] In order for the present invention to be more readily understood, certain terms are first defined below. Additional definitions for the following terms and other terms are set forth throughout the specification.

[000124] As used in this application, the terms “about” and “approximately” are used as equivalents. Any numerals used in this application with or without about/approximately are meant to cover any normal fluctuations appreciated by one of ordinary skill in the relevant art.

[000125] *Animal:* As used herein, the term “animal” refers to any member of the animal kingdom. In embodiments, “animal” refers to humans, at any stage of development. In embodiments, “animal” refers to non-human animals, at any stage of development. In certain embodiments, the non-human animal is a mammal (*e.g.*, a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, and/or a pig). In embodiments, animals include, but are not limited to, mammals, birds, reptiles, amphibians, fish, insects, and/or worms. In embodiments, an animal may be a transgenic animal, genetically-engineered animal, and/or a clone.

[000126] *Approximately or about:* As used herein, the term “approximately” or “about,” as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In certain embodiments, the term “approximately” or “about” refers to a range of values that fall within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less in either direction (greater than or less than) of the stated reference value unless otherwise stated or otherwise evident from the context (except where such number would exceed 100% of a possible value).

[000127] *Biologically active:* As used herein, the phrase “biologically active” refers to a characteristic of any agent that has activity in a biological system, and particularly in an organism. For instance, an agent that, when administered to an organism, has a biological effect on that organism, is considered to be biologically active.

[000128] *Brain Condition* – as used herein, a “brain condition” is any disease, disorder or event that results in damage and/or dysfunction of at least a portion of a subject’s brain. Non-limiting

examples of brain conditions include: stroke (both ischemic and hemorrhagic), , and traumatic brain injury.

[000129] *Carrier or diluent:* As used herein, the terms “carrier” and “diluent” refers to a pharmaceutically acceptable (e.g., safe and non-toxic for administration to a human) carrier or diluting substance useful for the preparation of a pharmaceutical formulation. Exemplary diluents include sterile water, bacteriostatic water for injection (BWFI), a pH buffered solution (e.g. phosphate-buffered saline), sterile saline solution, Ringer's solution or dextrose solution.

[000130] *Dosage form:* As used herein, the terms “dosage form” and “unit dosage form” refer to a physically discrete unit of a therapeutic agent for the patient to be treated. Each unit contains a predetermined quantity of active material calculated to produce the desired therapeutic effect. It will be understood, however, that the total dosage of the composition will be decided by the attending physician within the scope of sound medical judgment.

[000131] *Dosing regimen:* A “dosing regimen” (or “therapeutic regimen”), as that term is used herein, is a set of unit doses (typically more than one) that are administered individually to a subject, typically separated by periods of time. In embodiments, a given therapeutic agent has a recommended dosing regimen, which may involve one or more doses. In embodiments, a dosing regimen comprises a plurality of doses each of which are separated from one another by a time period of the same length; in embodiments, a dosing regime comprises a plurality of doses and at least two different time periods separating individual doses. In embodiments, the therapeutic agent is administered continuously over a predetermined period. In embodiments, the therapeutic agent is administered once a day (QD) or twice a day (BID).

[000132] *Functional equivalent or derivative:* As used herein, the term “functional equivalent” or “functional derivative” denotes, in the context of a functional derivative of an amino acid sequence, a molecule that retains a biological activity (either function or structural) that is substantially similar to that of the original sequence. A functional derivative or equivalent may be a natural derivative or is prepared synthetically. Exemplary functional derivatives include amino acid sequences having substitutions, deletions, or additions of one or more amino acids, provided that the biological activity of the protein is conserved. The substituting amino acid desirably has chemico-physical properties which are similar to that of the substituted amino acid. Desirable similar chemico-physical properties include, similarities in charge, bulkiness, hydrophobicity, hydrophilicity, and the like.

[000133] *Improve, increase, or reduce:* As used herein, the terms “improve,” “increase” or “reduce,” or grammatical equivalents, indicate values that are relative to a baseline measurement, such as a measurement in the same individual prior to initiation of the treatment described herein, or a measurement in a control subject (or multiple control subject) in the absence of the treatment described herein. A “control subject” is a subject afflicted with the same form of disease as the subject being treated, who is about the same age as the subject being treated.

[000134] *In vitro:* As used herein, the term “*in vitro*” refers to events that occur in an artificial environment, *e.g.*, in a test tube or reaction vessel, in cell culture, *etc.*, rather than within a multi-cellular organism.

[000135] *In vivo:* As used herein, the term “*in vivo*” refers to events that occur within a multi-cellular organism, such as a human and a non-human animal. In the context of cell-based systems, the term may be used to refer to events that occur within a living cell (as opposed to, for example, *in vitro* systems).

[000136] *Isolated:* As used herein, the term “isolated” refers to a substance and/or entity that has been (1) separated from at least some of the components with which it was associated when initially produced (whether in nature and/or in an experimental setting), and/or (2) produced, prepared, and/or manufactured by the hand of man. Isolated substances and/or entities may be separated from at least about 10%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 98%, about 99%, substantially 100%, or 100% of the other components with which they were initially associated. In embodiments, isolated agents are more than about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, about 99%, substantially 100%, or 100% pure. As used herein, a substance is “pure” if it is substantially free of other components. As used herein, the term “isolated cell” refers to a cell not contained in a multi-cellular organism.

[000137] *Patient:* As used herein, the term “patient” or “subject” refers to any organism to which a provided composition may be administered, *e.g.*, for experimental, diagnostic, prophylactic, cosmetic, and/or therapeutic purposes. Typical patients include animals (*e.g.*, mammals such as mice, rats, rabbits, non-human primates, and/or humans). In embodiments, a patient is a human. A human includes pre- and post-natal forms.

[000138] *Pharmaceutically acceptable:* The term “pharmaceutically acceptable,” as used herein, refers to substances that, within the scope of sound medical judgment, are suitable for use in

contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio. Accordingly, pharmaceutically acceptable relates to substances that are not biologically or otherwise undesirable, *i.e.*, the material can be administered to an individual along with the relevant active compound without causing clinically unacceptable biological effects or interacting in a deleterious manner with any of the other components of the pharmaceutical composition in which it is contained.

[000139] *Pharmaceutically acceptable form*: Unless otherwise indicated herein, any description of a formula or compound also includes any pharmaceutically acceptable forms of the compound. As used herein, a “pharmaceutically acceptable form” of a disclosed formula or compound includes, but is not limited to, pharmaceutically acceptable salts, hydrates, solvates, isomers, polymorphs, prodrugs, and isotopically labeled derivatives of disclosed formulas and compounds. In embodiments, a “pharmaceutically acceptable form” includes, but is not limited to, pharmaceutically acceptable salts, isomers, prodrugs and isotopically labeled derivatives of disclosed compounds. In embodiments, a “pharmaceutically acceptable form” includes, but is not limited to, pharmaceutically acceptable salts, stereoisomers, prodrugs and isotopically labeled derivatives of disclosed compounds. In certain embodiments, the pharmaceutically acceptable form is a pharmaceutically acceptable salt of a disclosed formula or compound as described herein.

[000140] *Pharmaceutically acceptable salt*: Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge *et al.*, describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences* (1977) 66:1–19. Pharmaceutically acceptable salts of the compounds of this invention include those derived from suitable inorganic and organic acids and bases. Examples of pharmaceutically acceptable, nontoxic acid addition salts are salts of an amino group formed with inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, and perchloric acid or with organic acids such as acetic acid, oxalic acid, maleic acid, tartaric acid, citric acid, succinic acid, or malonic acid, or by using other methods used in the art such as ion exchange. Other pharmaceutically acceptable salts include adipate, alginate, ascorbate, aspartate, benzenesulfonate, benzoate, bisulfate, borate, butyrate, camphorate, camphorsulfonate, citrate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, formate, fumarate, glucoheptonate, glycerophosphate, gluconate, hemisulfate, heptanoate, hexanoate, hydroiodide, 2-hydroxy-ethanesulfonate, lactobionate, lactate, laurate, lauryl sulfate, malate, maleate, malonate, methanesulfonate, 2-naphthalenesulfonate, nicotinate, nitrate, oleate, oxalate, palmitate, pamoate, pectinate, persulfate, 3-phenylpropionate, phosphate, picrate, pivalate, propionate, stearate,

succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate, undecanoate, valerate salts, and the like. Salts derived from appropriate bases include alkali metal, alkaline earth metal, ammonium and $N^+(C_{1-4}\text{-alkyl})_4$ salts. Representative alkali or alkaline earth metal salts include sodium, lithium, potassium, calcium, magnesium, and the like. Further pharmaceutically acceptable salts include, when appropriate, nontoxic ammonium, quaternary ammonium, and amine cations formed using counterions such as halide, hydroxide, carboxylate, sulfate, phosphate, nitrate, sulfonate, and aryl sulfonate. Further pharmaceutically acceptable salts include salts formed from the quaternization of an amine using an appropriate electrophile, *e.g.*, an alkyl halide, to form a quaternized alkylated amino salt.

[000141] *Prodrug*: Pharmaceutically acceptable forms of any compound described herein can include prodrugs. As used herein, the term “prodrug” refers to compounds that are transformed *in vivo* to yield a disclosed compound or any other pharmaceutically acceptable form of the compound. In embodiments, a prodrug may be inactive when administered to a subject but may be converted *in vivo* to an active compound, for example, by hydrolysis. See, *e.g.*, Bundgaard, H., *Design of Prodrugs* (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam). A discussion of prodrugs is provided in Higuchi, T., et al., “Pro-drugs as Novel Delivery Systems,” *A.C.S. Symposium Series*, Vol. 14, and in *Bioreversible Carriers in Drug Design*, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated in full by reference herein. Prodrugs can typically be prepared using well known methods, such as those described in *Burger's Medicinal Chemistry and Drug Discovery*, 172-178, 949-982 (Manfred E. Wolff ed., 5th ed., 1995), and *Design of Prodrugs* (H. Bundgaard ed., Elsevier, New York, 1985). The term “prodrug” is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a subject.

[000142] Prodrugs of compounds described herein may be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to provide a compound described herein (*i.e.*, the parent active compound). Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of an alcohol or acetamide, formamide and benzamide derivatives of an amine functional group in the active compound and the like. Other examples of prodrugs include compounds that comprise $-\text{NO}$, $-\text{NO}_2$, $-\text{ONO}$, or $-\text{ONO}_2$ moieties.

[000143] *Prevent*: As used herein, the term “prevent” or “prevention”, when used in connection with the occurrence of a disease, disorder, and/or condition, refers to reducing the risk of developing the disease, disorder and/or condition. See the definition of “risk.”

[000144] *Risk*: As will be understood from context, a “risk” of a disease, disorder, and/or condition comprises a likelihood that a particular individual will develop a disease, disorder, and/or condition (e.g., stroke). In embodiments, risk is expressed as a percentage. In embodiments, risk is from 0,1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90 up to 100%. In embodiments risk is expressed as a risk relative to a risk associated with a reference sample or group of reference samples. In embodiments, a reference sample or group of reference samples have a known risk of a disease, disorder, condition and/or event (e.g., stroke). In embodiments a reference sample or group of reference samples are from individuals comparable to a particular individual. In embodiments, relative risk is 0,1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more.

[000145] *Subject*: As used herein, the term “subject” refers to a human or any non-human animal (e.g., mouse, rat, rabbit, dog, cat, cattle, swine, sheep, horse or primate). A human includes pre- and post-natal forms. In many embodiments, a subject is a human being. A subject can be a patient, which refers to a human presenting to a medical provider for diagnosis or treatment of a disease. The term “subject” is used herein interchangeably with “individual” or “patient.” A subject can be afflicted with or is susceptible to a disease or disorder but may or may not display symptoms of the disease or disorder.

[000146] *Substantially*: As used herein, the term “substantially” refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term “substantially” is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[000147] *Therapeutically effective amount*: As used herein, the term “therapeutically effective amount” of a therapeutic agent means an amount that is sufficient, when administered to a subject suffering from or susceptible to a disease, disorder, and/or condition, to treat, diagnose, prevent, and/or delay the onset of the symptom(s) of the disease, disorder, and/or condition. It will be appreciated by those of ordinary skill in the art that a therapeutically effective amount is typically administered via a dosing regimen comprising at least one unit dose.

[000148] *Treating:* As used herein, the term “treat,” “treatment,” or “treating” refers to any method used to partially or completely alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of and/or reduce incidence of one or more symptoms or features of a particular disease, disorder, and/or condition. Treatment may be administered to a subject who does not exhibit signs of a disease and/or exhibits only early signs of the disease for the purpose of decreasing the risk of developing pathology associated with the disease.

[000149] *Stability:* As used herein, the term “stable” refers to the ability of the therapeutic agent to maintain its therapeutic efficacy (e.g., all or the majority of its intended biological activity and/or physiochemical integrity) over extended periods of time. The stability of a therapeutic agent, and the capability of the pharmaceutical composition to maintain stability of such therapeutic agent, may be assessed over extended periods of time (e.g., for at least 1, 3, 6, 12, 18, 24, 30, 36 months or more). In certain embodiments, pharmaceutical compositions described herein have been formulated such that they are capable of stabilizing, or alternatively slowing or preventing the degradation, of one or more therapeutic agents formulated therewith. In the context of a formulation a stable formulation is one in which the therapeutic agent therein essentially retains its physical and/or chemical integrity and biological activity upon storage and during processes (such as freeze/thaw, mechanical mixing and lyophilization).

[000150] *Subject:* As used herein, the term “subject” refers to a human or any non-human animal (e.g., mouse, rat, rabbit, dog, cat, cattle, swine, sheep, horse or primate). A human includes pre- and post-natal forms. In many embodiments, a subject is a human being. A subject can be a patient, which refers to a human presenting to a medical provider for diagnosis or treatment of a disease. The term “subject” is used herein interchangeably with “individual” or “patient.” A subject can be afflicted with or is susceptible to a disease or disorder but may or may not display symptoms of the disease or disorder.

[000151] *Substantially:* As used herein, the term “substantially” refers to the qualitative condition of exhibiting total or near-total extent or degree of a characteristic or property of interest. One of ordinary skill in the biological arts will understand that biological and chemical phenomena rarely, if ever, go to completion and/or proceed to completeness or achieve or avoid an absolute result. The term “substantially” is therefore used herein to capture the potential lack of completeness inherent in many biological and chemical phenomena.

[000152] *Suffering from:* An individual who is “suffering from” a disease, disorder, and/or condition has been diagnosed with or displays one or more symptoms of the disease, disorder, and/or condition.

[000153] *Susceptible to:* An individual who is “susceptible to” a disease, disorder, and/or condition has not been diagnosed with the disease, disorder, and/or condition. In embodiments, an individual who is susceptible to a disease, disorder, and/or condition may not exhibit symptoms of the disease, disorder, and/or condition. In embodiments, an individual who is susceptible to a disease, disorder, condition, or event (for example, ischemic stroke) may be characterized by one or more of the following: (1) a genetic mutation associated with development of the disease, disorder, and/or condition; (2) a genetic polymorphism associated with development of the disease, disorder, and/or condition; (3) increased and/or decreased expression and/or activity of a protein associated with the disease, disorder, and/or condition; (4) habits and/or lifestyles associated with development of the disease, disorder, condition, and/or event (5) having undergone, planning to undergo, or requiring a transplant. In embodiments, an individual who is susceptible to a disease, disorder, and/or condition will develop the disease, disorder, and/or condition. In embodiments, an individual who is susceptible to a disease, disorder, and/or condition will not develop the disease, disorder, and/or condition.

[000154] *Therapeutically effective amount:* As used herein, the term “therapeutically effective amount” of a therapeutic agent means an amount that is sufficient, when administered to a subject suffering from or susceptible to a disease, disorder, and/or condition, to treat, diagnose, prevent, and/or delay the onset of the symptom(s) of the disease, disorder, and/or condition. It will be appreciated by those of ordinary skill in the art that a therapeutically effective amount is typically administered via a dosing regimen comprising at least one unit dose.

[000155] *Treating:* As used herein, the term “treat,” “treatment,” or “treating” refers to any method used to partially or completely alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of and/or reduce incidence of one or more symptoms or features of a particular disease, disorder, and/or condition. Treatment may be administered to a subject who does not exhibit signs of a disease and/or exhibits only early signs of the disease for the purpose of decreasing the risk of developing pathology associated with the disease.

[000156] The variable groups defined herein, *e.g.*, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, aryloxy, aryl, heterocycle and heteroaryl groups defined herein, whether used alone or as part of another group, can be optionally substituted unless otherwise indicated. In embodiments, a variable

group is unsubstituted. In embodiments, a variable group is substituted (e.g., comprising 1, 2, 3, 4, or 5 substituents (e.g., as described herein) and as valency and stability permits). Still further embodiments are described herein.

[000157] “Optional” or “optionally” means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances where it does not.

[000158] *Aliphatic*: As used herein, the term aliphatic refers to hydrocarbons and includes both saturated and unsaturated hydrocarbons. An aliphatic may be linear, branched, or cyclic. For example, C₁–C₂₀ aliphatics can include C₁–C₂₀ alkyls (e.g., linear or branched C₁–C₂₀ saturated alkyls), C₂–C₂₀ alkenyls (e.g., linear or branched C₄–C₂₀ dienyls, linear, or branched C₆–C₂₀ trienyls, and the like), and C₂–C₂₀ alkynyls (e.g., linear or branched C₂–C₂₀ alkynyls). C₁–C₂₀ aliphatics can include C₃–C₂₀ cyclic aliphatics (e.g., C₃–C₂₀ cycloalkyls, C₄–C₂₀ cycloalkenyls, or C₈–C₂₀ cycloalkynyls). In certain embodiments, the aliphatic may comprise one or more cyclic aliphatic and/or one or more heteroatoms such as oxygen, nitrogen, or sulfur and may optionally be substituted with one or more substituents such as alkyl, halo, alkoxyl, hydroxy, amino, aryl, ether, ester or amide. An aliphatic group is unsubstituted or substituted with one or more substituent groups as described herein. For example, an aliphatic may be substituted with one or more (e.g., 1, 2, 3, 4, 5, or 6 independently selected substituents) of halogen, -COR', -CO₂H, -CO₂R', -CN, -OH, -OR', -OCOR', -OCO₂R', -NH₂, -NHR', -N(R')₂, -SR' or -SO₂R', wherein each instance of R' independently is C₁–C₂₀ aliphatic (e.g., C₁–C₂₀ alkyl, C₁–C₁₅ alkyl, C₁–C₁₀ alkyl, or C₁–C₃ alkyl). In embodiments, R' independently is an unsubstituted alkyl (e.g., unsubstituted C₁–C₂₀ alkyl, C₁–C₁₅ alkyl, C₁–C₁₀ alkyl, or C₁–C₃ alkyl). In embodiments, R' independently is unsubstituted C₁–C₃ alkyl. In embodiments, the aliphatic is unsubstituted. In embodiments, the aliphatic does not include any heteroatoms.

[000159] *Alkyl*: As used herein, the term “alkyl” means acyclic linear and branched hydrocarbon groups, e.g., “C₁–C₂₀ alkyl” refers to alkyl groups having 1–20 carbons and “C₁–C₄ alkyl” refers to alkyl groups having 1–4 carbons. Alkyl groups include C₁–C₂₀ alkyl, C₁–C₁₅ alkyl, C₁–C₁₀ alkyl, C₁–C₄ alkyl, and C₁–C₃ alkyl). In embodiments, an alkyl group is C₁–C₄ alkyl. An alkyl group may be linear or branched. Examples of alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, etc. The term “lower alkyl” means an alkyl group straight chain or branched alkyl having 1 to 6 carbon atoms. Other alkyl groups will be readily apparent to those of skill in the art given the benefit of the present disclosure. An alkyl group may be unsubstituted or substituted with one or more substituent groups as

described herein. For example, an alkyl group may be substituted with one or more (*e.g.*, 1, 2, 3, 4, 5, or 6 independently selected substituents) of halogen, -COR', -CO₂H, -CO₂R', -CN, -OH, -OR', -OCOR', -OCO₂R', -NH₂, -NHR', -N(R')₂, -SR' or -SO₂R', wherein each instance of R' independently is C₁-C₂₀ aliphatic (*e.g.*, C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, C₁-C₄ alkyl, or C₁-C₃ alkyl). In embodiments, R' independently is an unsubstituted alkyl (*e.g.*, unsubstituted C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In embodiments, R' independently is unsubstituted C₁-C₃ alkyl. Non-limiting examples of alkyl groups include methyl, ethyl, n-propyl, *iso*-propyl, n-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, and the like. In embodiments, the alkyl is substituted (*e.g.*, with 1, 2, 3, 4, 5, or 6 substituent groups as described herein). In embodiments, an alkyl group is substituted with a-OH group and may also be referred to herein as a "hydroxyalkyl" group, where the prefix denotes the -OH group and "alkyl" is as described herein. In embodiments, an alkyl group is substituted with a-OR' group. Non-limiting examples of substituted alkyl groups include hydroxymethyl, chloromethyl, trifluoromethyl, aminomethyl, 1-chloroethyl, 2-hydroxyethyl, 1,2-difluoroethyl, 3-carboxypropyl, and the like. In substituent groups with multiple alkyl groups such as (C₁-C₆ alkyl)₂amino, the alkyl groups may be the same or different.

[000160] *Alkylene*: The term "alkylene," as used herein, represents a saturated divalent straight or branched chain hydrocarbon group and is exemplified by methylene, ethylene, isopropylene and the like. Likewise, the term "alkenylene" as used herein represents an unsaturated divalent straight or branched chain hydrocarbon group having one or more unsaturated carbon-carbon double bonds that may occur in any stable point along the chain, and the term "alkynylene" herein represents an unsaturated divalent straight or branched chain hydrocarbon group having one or more unsaturated carbon-carbon triple bonds that may occur in any stable point along the chain. In certain embodiments, an alkylene, alkenylene, or alkynylene group may comprise one or more cyclic aliphatic and/or one or more heteroatoms such as oxygen, nitrogen, or sulfur and may optionally be substituted with one or more substituents such as alkyl, halo, alkoxyl, hydroxy, amino, aryl, ether, ester or amide. For example, an alkylene, alkenylene, or alkynylene may be substituted with one or more (*e.g.*, 1, 2, 3, 4, 5, or 6 independently selected substituents) of halogen, -COR', -CO₂H, -CO₂R', -CN, -OH, -OR', -OCOR', -OCO₂R', -NH₂, -NHR', -N(R')₂, -SR' or -SO₂R', wherein each instance of R' independently is C₁-C₂₀ aliphatic (*e.g.*, C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In embodiments, R' independently is an unsubstituted alkyl (*e.g.*, unsubstituted C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In embodiments, R' independently is unsubstituted C₁-C₃ alkyl. In certain embodiments, an alkylene, alkenylene, or alkynylene is unsubstituted. In certain embodiments, an alkylene, alkenylene, or alkynylene does not include any heteroatoms.

[000161] *Alkenyl*: As used herein, “alkenyl” means any linear or branched hydrocarbon chains having one or more unsaturated carbon-carbon double bonds that may occur in any stable point along the chain, *e.g.*, “C₂-C₂₀ alkenyl” refers to an alkenyl group having 2–20 carbons. For example, an alkenyl group includes prop-2-enyl, but-2-enyl, but-3-enyl, 2-methylprop-2-enyl, hex-2-enyl, hex-5-enyl, 2,3-dimethylbut-2-enyl, and the like. In embodiments, the alkenyl comprises 1, 2, or 3 carbon-carbon double bond. In embodiments, the alkenyl comprises a single carbon-carbon double bond. In embodiments, multiple double bonds (*e.g.*, 2 or 3) are conjugated. An alkenyl group may be unsubstituted or substituted with one or more substituent groups as described herein. For example, an alkenyl group may be substituted with one or more (*e.g.*, 1, 2, 3, 4, 5, or 6 independently selected substituents) of halogen, -COR', -CO₂H, -CO₂R', -CN, -OH, -OR', -OCOR', -OCO₂R', -NH₂, -NHR', -N(R')₂, -SR' or -SO₂R', wherein each instance of R' independently is C₁-C₂₀ aliphatic (*e.g.*, C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In embodiments, R' independently is an unsubstituted alkyl (*e.g.*, unsubstituted C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In embodiments, R' independently is unsubstituted C₁-C₃ alkyl. In embodiments, the alkenyl is unsubstituted. In embodiments, the alkenyl is substituted (*e.g.*, with 1, 2, 3, 4, 5, or 6 substituent groups as described herein). In embodiments, an alkenyl group is substituted with a-OH group and may also be referred to herein as a “hydroxyalkenyl” group, where the prefix denotes the -OH group and “alkenyl” is as described herein. Nonlimiting examples of alkenyl groups include ethenyl, 3-propenyl, 1-propenyl (*also* 2-methylethenyl), isopropenyl (*also* 2-methylethen-2-yl), buten-4-yl, and the like. Nonlimiting examples of substituted alkenyl groups include 2-chloroethenyl (*also* 2-chlorovinyl), 4-hydroxybuten-1-yl, 7-hydroxy-7-methyloct-4-en-2-yl, 7-hydroxy-7-methyloct-3,5-dien-2-yl, and the like.

[000162] *Alkynyl*: As used herein, “alkynyl” means any hydrocarbon chain of either linear or branched configuration, having one or more carbon-carbon triple bonds occurring in any stable point along the chain, *e.g.*, “C₂-C₂₀ alkynyl” refers to an alkynyl group having 2–20 carbons. Examples of an alkynyl group include prop-2-ynyl, but-2-ynyl, but-3-ynyl, pent-2-ynyl, 3-methylpent-4-ynyl, hex-2-ynyl, hex-5-ynyl, *etc.* In embodiments, an alkynyl comprises one carbon-carbon triple bond. An alkynyl group may be unsubstituted or substituted with one or more substituent groups as described herein. For example, an alkynyl group may be substituted with one or more (*e.g.*, 1, 2, 3, 4, 5, or 6 independently selected substituents) of halogen, -COR', -CO₂H, -CO₂R', -CN, -OH, -OR', -OCOR', -OCO₂R', -NH₂, -NHR', -N(R')₂, -SR' or -SO₂R', wherein each instance of R' independently is C₁-C₂₀ aliphatic (*e.g.*, C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In embodiments, R' independently is an unsubstituted alkyl (*e.g.*, unsubstituted C₁-C₂₀ alkyl, C₁-C₁₅ alkyl, C₁-C₁₀ alkyl, or C₁-C₃ alkyl). In embodiments, R' independently is unsubstituted C₁-C₃ alkyl. In embodiments, the alkynyl is unsubstituted. In embodiments, the alkynyl is substituted (*e.g.*, with 1, 2, 3, 4, 5, or 6

substituent groups as described herein). Nonlimiting examples of alkynyl groups include ethynyl, prop-2-ynyl (*also* propargyl), propyn-1-yl, and 2-methyl-hex-4-yn-1-yl. Nonlimiting examples of substituted alkynyl groups include, 5-hydroxy-5-methylhex-3-ynyl, 6-hydroxy-6-methylhept-3-yn-2-yl, 5-hydroxy-5-ethylhept-3-ynyl, and the like.

[000163] *Alkoxy*: The term “alkoxy” refers to the group -O-alkyl, wherein the alkyl group is as defined above, including from 1 to 10 carbon atoms of a straight, branched, saturated cyclic configuration and combinations thereof, attached to the parent molecular structure through an oxygen. Examples include methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentoxy, cyclopropyloxy, cyclohexyloxy and the like. “Lower alkoxy” refers to alkoxy groups containing one to six carbons. In embodiments, C₁₋₄ alkoxy is an alkoxy group which encompasses both straight and branched chain alkyls of from 1 to 4 carbon atoms. Unless stated otherwise in the specification, an alkoxy group can be optionally substituted by one or more substituents (*e.g.*, as described herein for alkyl). The terms “alkenoxy” and “alkynoxy” mirror the above description of “alkoxy” wherein the prefix “alk” is replaced with “alken” or “alkyn” respectively, and the parent “alkenyl” or “alkynyl” terms are as described herein.

[000164] *Amide*: The term “amide” or “amido” refers to a chemical moiety with formula C(O)N(R')₂, -C(O)N(R')-, -NR'C(O)R', or -NR'C(O)-, where each R' is independently selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, aryl, arylalkyl, heteroaryl (bonded through a ring carbon), heteroarylalkyl, or heterocycloalkyl (bonded through a ring carbon), unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein, or two R' can combine with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring.

[000165] *Amino*: The term “amino” or “amine” refers to a -N(R')₂ group, where each R' is independently selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, aryl, arylalkyl, heteroaryl (bonded through a ring carbon), heteroarylalkyl, or heterocycloalkyl (bonded through a ring carbon), unless stated otherwise in the specification, each of which moiety can itself be optionally substituted as described herein, or two R' can combine with the nitrogen atom to form a 3-, 4-, 5-, 6-, or 7-membered ring. In embodiments, an amino group is -NHR', where R' is aryl (“arylamino”), heteroaryl (“heteroarylamino”), or alkyl (“alkylamino”).

[000166] *Aryl*: The term “aryl” used alone or as part of a larger moiety as in “aralkyl,” refers to a monocyclic, bicyclic, or tricyclic carbocyclic ring system having a total of six to fourteen ring members, wherein said ring system has a single point of attachment to the rest of the molecule,

wherein at least one ring in the system is aromatic, and wherein each ring in the system contains 4 to 7 ring members. In embodiments, an aryl group has 6 ring carbon atoms ("C₆ aryl," e.g., phenyl). In embodiments, an aryl group has 10 ring carbon atoms ("C₁₀ aryl," e.g., naphthyl such as 1-naphthyl and 2-naphthyl). In embodiments, an aryl group has 14 ring carbon atoms ("C₁₄ aryl," e.g., anthracyl). "Aryl" also includes ring systems wherein the aryl ring, as defined above, is fused with one or more carbocyclyl or heterocyclyl groups wherein the radical or point of attachment is on the aryl ring, and in such instances, the number of carbon atoms continue to designate the number of carbon atoms in the aryl ring system. Aryl groups can be unsubstituted or substituted. Exemplary aryls include phenyl, naphthyl, and anthracene. Aryl rings can be, for example, phenyl or naphthyl ring each optionally substituted with one or more moieties capable of replacing one or more hydrogen atoms. Non-limiting examples of aryl groups include: phenyl, naphthyl-1-yl, naphthyl-2-yl, 4-fluorophenyl, 2-hydroxyphenyl, 3-methylphenyl, 2-amino-4-fluorophenyl, 2-(*N,N*-diethylamino)phenyl, 2-cyanophenyl, 2,6-di-*tert*-butylphenyl, 3-methoxyphenyl, 8-hydroxynaphthyl-2-yl, 4,5-dimethoxynaphthyl-1-yl, and 6-cyano-naphthyl-1-yl. Aryl groups also include, for example, phenyl or naphthyl rings fused with one or more saturated or partially saturated carbon rings (e.g., bicyclo[4.2.0]octa-1,3,5-trienyl, indanyl), which can be substituted at one or more carbon atoms of the aromatic and/or saturated or partially saturated rings.

[000167] *Arylalkyl*: The term "arylalkyl" refers to an -(alkylene)-aryl radical where aryl and alkylene are as disclosed herein and which are optionally substituted by one or more of the exemplary substituent groups described herein. The "arylalkyl" group is bonded to the parent molecular structure through the alkylene moiety. The term "arylalkoxy" refers to an -O-[arylalkyl] radical (-O-[(alkylene)-aryl]), which is attached to the parent molecular structure through the oxygen. . Examples of arylalkyl groups include, for example, benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, fluorenylmethyl and the like.

[000168] *Arylene*: The term "arylene" as used herein refers to an aryl group that is divalent (that is, having two points of attachment to the molecule). Exemplary arylenes include phenylene (e.g., unsubstituted phenylene or substituted phenylene).

[000169] *Carbonyl*: The term "carbonyl" refers to a -C(=O)R', or -C(=O)- group, where R' is selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, aryl, arylalkyl, amino, hydroxyl, heteroaryl (bonded through a ring carbon), heteroarylalkyl, heterocycloalkyl (bonded through a ring carbon), unless stated other-wise in the specification, each of which moiety can itself be optionally substituted as described herein.

[000170] *Cyclic*: The term “cyclic” as used herein, refers to any covalently closed structure. Cyclic moieties include, for example, carbocycles (*e.g.*, aryls and cycloalkyls), heterocycles (*e.g.*, heteroaryls and heterocycloalkyls), aromatics (*e.g.*, aryls and heteroaryls), and non-aromatics (*e.g.*, cycloalkyls and heterocycloalkyls). In embodiments, cyclic moieties are optionally substituted. In embodiments, cyclic moieties form part of a ring system.

[000171] *Cycloaliphatic*: The term “cycloaliphatic” refers to a monocyclic or polycyclic radical that contains only carbon and hydrogen and can be saturated or partially unsaturated. A cycloaliphatic group may be substituted or unsubstituted. Fully saturated cycloaliphatics can be termed “cycloalkyl”. Partially unsaturated cycloalkyl groups can be termed “cycloalkenyl” if the carbocycle contains at least one double bond, or “cycloalkynyl” if the carbocycle contains at least one triple bond. Cycloaliphatic groups include groups having from 3 to 13 ring atoms (*e.g.*, C₃₋₁₃ cycloalkyl). Whenever it appears herein, a numerical range such as “3 to 10” refers to each integer in the given range, *e.g.*, “3 to 10 carbon atoms” means that the cycloaliphatic group (*e.g.*, cycloalkyl) can consist of 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, etc., up to and including 10 carbon atoms. The term “cycloaliphatic” also includes bridged and spiro-fused cyclic structures containing no heteroatoms. The term also includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of ring atoms) groups. Polycyclic cycloaliphatic groups include bicycles, tricycles, tetracycles, and the like. In embodiments, “cycloalkyl” can be a C₃₋₈ cycloalkyl group. In embodiments, “cycloalkyl” can be a C₃₋₅ cycloalkyl group. Illustrative examples of cycloaliphatic groups include but are not limited to the following moieties: C₃₋₆ cycloaliphatic groups include, without limitation, cyclopropyl (C₃), cyclobutyl (C₄), cyclopentyl (C₅), cyclopentenyl (C₅), cyclohexyl (C₆), cyclohexenyl (C₆), cyclohexadienyl (C₆) and the like. Examples of C₃₋₇ cycloaliphatic groups include norbornyl (C₇). Examples of C₃₋₈ cycloaliphatic groups include the aforementioned C₃₋₇ carbocyclyl groups as well as cycloheptyl (C₇), cycloheptadienyl (C₇), cycloheptatrienyl (C₇), cyclooctyl (C₈), bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, and the like. Examples of C₃₋₁₃ cycloaliphatic groups include the aforementioned C₃₋₈ carbocyclyl groups as well as octahydro-1H-indenyl, decahydronaphthalenyl, spiro[4.5]decanyl, and the like. Additional, nonlimiting examples of cycloaliphatic groups (including cycloalkyl groups) include: cyclopropyl, 2-methyl-cyclopropyl, cyclopropenyl, cyclobutyl, 2,3-dihydroxycyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctanyl, decalanyl, 2,5-dimethylcyclopentyl, 3,5-dichlorocyclohexyl, 4-hydroxycyclohexyl, 3,3,5-trimethylcyclohex-1-yl, octahydropentalenyl, octahydro-1H-indenyl, 3a,4,5,6,7,7a-hexahydro-3H-inden-4-yl, decahydroazulenyl; bicyclo[6.2.0]decanyl, decahydronaphthalenyl, dodecahydro-1H-fluorenyl, bicyclo-[2.1.1]hexanyl, bicyclo[2.2.1]heptanyl, bicyclo[3.1.1]heptanyl, 1,3-dimethyl[2.2.1]heptan-2-

yl, bicyclo[2.2.2]octanyl, and bicyclo[3.3.3]undecanyl. A "bicycloalkyl" group includes bridged cycloalkyl groups such as bicyclo[1.1.1]pentyl, bicyclo[2.1.1]heptane, adamantanyl, and norbornanyl; as well as spiro cycloalkyl groups include spiro[3.3]heptane and spiro[4.5]decane. A "heterobicycloalkyl" group is a bicycloalkyl comprising at least one heteroatom in the ring framework.

[000172] *Ester*: The term "ester" refers to a group of formula $-C(O)OR'$ or $-R'OC(O)-$, where R' is selected from alkyl, alkenyl, alkynyl, heteroalkyl (bonded through a chain carbon), cycloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, or heterocycloalkyl as described herein.

[000173] *Halogen*: As used herein, the term "halogen" shall mean chlorine, bromine, fluorine, and iodine.

[000174] *Haloalkyl*: The term "haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen. Haloalkyl groups include perhaloalkyl groups, wherein all hydrogens of an alkyl group have been replaced with halogens (e.g., $-CF_3$, CF_2CF_3). Haloalkyl groups can optionally be substituted with one or more substituents in addition to halogen. Examples of haloalkyl groups include, but are not limited to, fluoromethyl, dichloroethyl, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl groups.

[000175] *Haloalkoxy*: The term "haloalkoxy" refers to the group $-O$ -haloalkyl, wherein the haloalkyl group is as defined above. Examples of haloalkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, and pentafluoroethoxyl.

[000176] *Heteroalkyl*: The term "heteroalkyl" is meant a branched or unbranched alkyl, alkenyl, or alkynyl group as defined herein (including groups having from 1 to 14 carbon atoms) which also comprise at least one heteroatom (e.g., 1, 2, 3 or 4 heteroatoms) independently selected from the group consisting of N, O, S, and P. For example, "1- to 6-membered heteroalkyl" can encompass heteroalkyl groups having 1-6 atoms (e.g., carbon atoms and at least one heteroatom selected from N, O, S, and P) along the main chain of the group. In embodiments, heteroalkyls exclude peroxy ($O-O$) moieties. Heteroalkyls include tertiary amines, secondary amines, ethers, thioethers, amides, thioamides, carbamates, thiocarbamates, hydrazones, imines, phosphodiesteres, phosphoramidates, sulfonamides, and disulfides. A heteroalkyl group may optionally include monocyclic, bicyclic, or tricyclic rings, in which each ring desirably has three to six members. Examples of heteroalkyls include polyethers, such as methoxymethyl and ethoxyethyl. Accordingly, the term "heteroalkoxy"

refers to the group -O-heteroalkyl, where the group is attached to the parent molecular structure via the oxygen.

[000177] *Heteroalkylene*: The term “heteroalkylene” as used herein, represents a divalent form of a heteroalkyl group as described herein.

[000178] *Heteroaryl*: The term “heteroaryl,” as used herein, is defined herein as one or more rings having from 5 to 20 atoms wherein at least one atom in at least one ring is a heteroatom chosen from nitrogen (N), oxygen (O), or sulfur (S), and wherein further at least one of the rings that includes a heteroatom is aromatic, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. In embodiments, “heteroaryl” refers to a monocyclic, bicyclic, or tricyclic carbocyclic ring system having a total of six to fourteen ring members, wherein said ring system has a single point of attachment to the rest of the molecule, wherein at least one ring in the system is aromatic, wherein each ring in the system contains 4 to 7 ring members, and wherein at least one ring atom is a heteroatom such as, but not limited to, nitrogen, oxygen, or sulfur. In heteroaryl groups that include 2 or more fused rings, the non-heteroatom bearing ring may be a carbocycle (e.g., 6,7-Dihydro-5H-cyclopentapyrimidine) or aryl (e.g., benzofuranyl, benzothiophenyl, indolyl). Exemplary heteroaryl groups have from 5 to 14 ring atoms and contain from 1 to 5 ring heteroatoms independently selected from nitrogen (N), oxygen (O), or sulfur (S). One or more N or S atoms in a heteroaryl group can be oxidized. Heteroaryl groups can be unsubstituted or substituted. The term “N-containing heteroaryl” refers to heteroaryl groups which comprise at least one nitrogen in the ring system (e.g., a heteroaryl comprising 1, 2, or 3 nitrogen atoms). In embodiments, the foregoing groups, as derived from the groups listed above, are C-attached or N-attached where such is possible. Further, the term “heteroaryloxy” refers to the group -O-heteroaryl, where the group is attached to the parent molecular structure via the oxygen. Non-limiting examples of heteroaryl groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizynyl, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. Non-limiting examples of heteroaryl rings containing a single ring include: 1,2,3,4-tetrazolyl, [1,2,3]triazolyl, [1,2,4]triazolyl, triazinyl, thiazolyl, 1H-imidazolyl, oxazolyl, furanyl, thiophenyl, pyrimidinyl, 2-phenylpyrimidinyl, pyridinyl, 3-methylpyridinyl, and 4-dimethylaminopyridinyl. Non-limiting examples of heteroaryl rings containing 2 or more fused rings include: benzofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, cinnolinyl, naphthyridinyl,

phenanthridinyl, 7H-purinyl, 9H-purinyl, 6-amino-9H-purinyl, 5H-pyrrolo[3,2-*d*]pyrimidinyl, 7H-pyrrolo[2,3-*d*]pyrimidinyl, pyrido[2,3-*d*]pyrimidinyl, 2-phenylbenzo[*d*]thiazolyl, 1H-indolyl, 4,5,6,7-tetrahydro-1H-indolyl, quinoxalyl, 5-methylquinoxalyl, quinazolinyl, quinolinyl, 8-hydroxyquinolinyl, 1H-benzo[*d*]imidazol-2(3H)-onyl, 1H-benzo[*d*]imidazolyl, and isoquinolinyl. One non-limiting example of a heteroaryl group as described above is C₁-C₅ heteroaryl, which has 1 to 5 carbon ring atoms and at least one additional ring atom that is a heteroatom (preferably 1 to 4 additional ring atoms that are heteroatoms) independently selected from nitrogen (N), oxygen (O), or sulfur (S). Examples of C₁-C₅ heteroaryl include, but are not limited to, triazinyl, thiazol-2-yl, thiazol-4-yl, imidazol-1-yl, 1H-imidazol-2-yl, 1H-imidazol-4-yl, isoxazolin-5-yl, furan-2-yl, furan-3-yl, thiophen-2-yl, thiophen-4-yl, pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl, pyridin-2-yl, pyridin-3-yl, and pyridin-4-yl.

[000179] *Heteroarylene*: The term “heteroarylene,” as used herein, represents a divalent form of a heteroaryl group as described herein.

[000180] *Heteroarylalkyl*: The term “heteroarylalkyl” refers to an -(alkylene)-heteroaryl radical where heteroaryl and alkylene are as disclosed herein and which are optionally substituted by one or more of the exemplary substituent groups described herein. The “heteroarylalkyl” group is bonded to the parent molecular structure through the alkylene moiety. The term “heteroarylalkoxy” refers to an -O-[heteroarylalkyl] radical (-O-[(alkylene)-heteroaryl]), which is attached to the parent molecular structure through the oxygen.

[000181] *Heterocycloalkyl*: The term “heterocycloalkyl” or “heterocyclyl” as used herein, is a non-aromatic ring wherein at least one atom is a heteroatom such as, but not limited to, nitrogen, oxygen, sulfur, or phosphorus, and the remaining atoms are carbon, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. In embodiments, a “heterocycloalkyl” or “heterocyclyl” refers to groups containing one to four heteroatoms each selected from O, S and N, wherein each heterocycle group has from 4 to 10 atoms in its ring system, and with the proviso that the ring of said group does not contain two adjacent O or S atoms. Herein, whenever the number of carbon atoms in a heterocycle is indicated (*e.g.*, C₁-C₆-heterocycle), at least one other atom (the heteroatom) must be present in the ring. Designations such as “C₁-C₆-heterocycle” refer only to the number of carbon atoms in the ring and do not refer to the total number of atoms in the ring. In embodiments, it is understood that the heterocycle ring has additional heteroatoms in the ring. Designations such as “4-6-membered heterocycle” refer to the total number of atoms that are contained in the ring (*i.e.*, a four, five, or six membered ring, in which at least one atom is a carbon

atom, at least one atom is a heteroatom and the remaining two to four atoms are either carbon atoms or heteroatoms). In embodiments, in heterocycles that have two or more heteroatoms, those two or more heteroatoms are the same or different from one another. In embodiments, heterocycles are optionally substituted. In embodiments, binding to a heterocycle is at a heteroatom or via a carbon atom (i.e., in embodiments, the foregoing groups, as derived from the groups listed above, are C-attached or N-attached where such is possible). Examples of heterocycloalkyl groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidino, morpholino, thiomorpholino, thioxanyl, piperazinyl, azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, 2-pyrrolinyl, 3-pyrrolinyl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl and quinolizinyl. In embodiments, heterocyclic moieties having a single ring include: diazirinyl, aziridinyl, urazolyl, azetidiny, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolidinyl, isothiazolyl, isothiazolinyl, oxathiazolidinonyl, oxazolidinonyl, hydantoinyl, tetrahydrofuranyl, pyrrolidinyl, morpholinyl, piperazinyl, piperidinyl, dihydropyranyl, tetrahydropyranyl, piperidin-2-onyl (valerolactam), 2,3,4,5-tetrahydro-1H-azepinyl, 2,3-dihydro-1H-indole, and 1,2,3,4-tetrahydro-quinoline. Non-limiting examples of heterocyclic moieties having 2 or more rings include: hexahydro-1H-pyrroliziny, 3a,4,5,6,7,7a-hexahydro-1H-benzo[d]imidazolyl, 3a,4,5,6,7,7a-hexahydro-1H-indolyl, 1,2,3,4-tetrahydroquinolinyl, chromanyl, isochromanyl, indolinyl, isoindolinyl, and decahydro-1H-cycloocta[b]pyrrolyl. The heterocycloalkyl group can be substituted or unsubstituted. The heterocycle groups include benzo-fused ring systems and ring systems substituted with one or two oxo (=O) moieties such as pyrrolidin-2-one. In embodiments, depending on the structure, a heterocycle group is a monoradical or a diradical (i.e., a heterocyclene group). The heterocycles described herein are substituted or unsubstituted. In embodiments, a heterocycle is substituted with 0, 1, 2, 3, or 4 substituents independently selected from alkenyl, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkyl, alkylcarbonyl, alkylcarbonyloxy, alkylthio, alkylthioalkyl, alynyl, carboxy, cyano, formyl, haloalkoxy, haloalkyl, halogen, hydroxyl, hydroxyalkylene, mercapto, nitro, amino, and amido moieties.

[000182] *Substituted:* The term “substituted” is defined herein as a moiety, whether acyclic or cyclic, which has one or more hydrogen atoms replaced by a substituent or several (e.g., 1 to 10) substituents as defined herein below. The substituents are capable of replacing one or two hydrogen atoms of a single moiety at a time. In addition, these substituents can replace two hydrogen atoms on two adjacent carbons to form said substituent, new moiety or unit.

[000183] The variable groups defined herein, *e.g.*, alkyl, alkenyl, alkynyl, cycloalkyl, alkoxy, aryloxy, aryl, heterocycle and heteroaryl groups defined herein, whether used alone or as part of another group, can be optionally substituted. Optionally substituted groups will be so indicated.

[000184] *Moiety*: The term “moiety” refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[000185] *Nitro*: The term “nitro” refers to a -NO_2 group.

[000186] *Nitrogen protecting group*: In certain embodiments, the substituent present on a nitrogen atom is a nitrogen protecting group (also referred to as an amino protecting group or an N-protecting group). Nitrogen protecting groups are well known in the art and include those described in detail in *Protecting Groups in Organic Synthesis*, T. W. Greene and P. G. M. Wuts, 3rd edition, John Wiley & Sons, 1999, incorporated herein by reference.

[000187] For example, nitrogen protecting groups such as amide groups (*e.g.*, $\text{-C(=O)R}^{\text{aa}}$) include, but are not limited to, formamide, acetamide, chloroacetamide, trichloroacetamide, trifluoroacetamide, phenylacetamide, 3-phenylpropanamide, picolinamide, 3-pyridylcarboxamide, N-benzoylphenylalanyl derivative, benzamide, p-phenylbenzamide, o-nitrophenylacetamide, o-nitrophenoxyacetamide, acetoacetamide, (N'-dithiobenzoyloxyacylamino)acetamide, 3-(p-hydroxyphenyl)propanamide, 3-(o-nitrophenyl)propanamide, 2-methyl-2-(o-nitrophenoxy)propanamide, 2-methyl-2-(o-phenylazophenoxy)propanamide, 4-chlorobutanamide, 3-methyl-3-nitrobutanamide, o-nitrocinnamide, N-acetylmethionine derivative, o-nitrobenzamide and o-(benzoyloxymethyl)benzamide.

[000188] Nitrogen protecting groups such as carbamate groups (*e.g.*, $\text{-C(=O)OR}^{\text{aa}}$) include, but are not limited to, methyl carbamate, ethyl carbamate, 9-fluorenylmethyl carbamate (Fmoc), 9-(2-sulfo)fluorenylmethyl carbamate, 9-(2,7-dibromo)fluorenylmethyl carbamate, 2,7-di-t-butyl-[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl carbamate (DBD-Tmoc), 4-methoxyphenacyl carbamate (Phenoc), 2,2,2-trichloroethyl carbamate (Troc), 2-trimethylsilylethyl carbamate (Teoc), 2-phenylethyl carbamate (hZ), 1-(1-adamanty1)-1-methylethyl carbamate (Adpoc), 1,1-dimethyl-2-haloethyl carbamate, 1,1-dimethyl-2,2-dibromoethyl carbamate (DB-t-BOC), 1,1-dimethyl-2,2,2-trichloroethyl carbamate (TCBOC), 1-methyl-1-(4-biphenyl)ethyl carbamate (Bpoc), 1-(3,5-di-t-butylphenyl)-1-methylethyl carbamate (t-Bumeoc), 2-(2'-and 4'-pyridyl)ethyl carbamate (Pyoc), 2-(N,N-dicyclohexylcarboxamido)ethyl carbamate, t-butyl carbamate (BOC), 1-

adamantyl carbamate (Adoc), vinyl carbamate (Voc), allyl carbamate (Alloc), 1-isopropylallyl carbamate (Ipaoc), cinnamyl carbamate (Coc), 4-nitrocinnamyl carbamate (Noc), 8-quinolyl carbamate, N-hydroxypiperidinyl carbamate, alkylthio carbamate, benzyl carbamate (Cbz), p-methoxybenzyl carbamate (Moz), p-nitrobenzyl carbamate, p-bromobenzyl carbamate, p-chlorobenzyl carbamate, 2,4-dichlorobenzyl carbamate, 4-methylsulfinylbenzyl carbamate (MsZ), 9-anthrylmethyl carbamate, diphenylmethyl carbamate, 2-methylthioethyl carbamate, 2-methylsulfonyl ethyl carbamate, 2-(p-toluenesulfonyl)ethyl carbamate, [2-(1,3-dithianyl)]methyl carbamate (Dmoc), 4-methylthiophenyl carbamate (Mtpc), 2,4-dimethylthiophenyl carbamate (Bmpc), 2-phosphonioethyl carbamate (Peoc), 2-triphenylphosphonioisopropyl carbamate (Ppoc), 1,1-dimethyl-2-cyanoethyl carbamate, m-chloro-p-acyloxybenzyl carbamate, p-(dihydroxyboryl)benzyl carbamate, 5-benzisoxazolylmethyl carbamate, 2-(trifluoromethyl)-6-chromonylmethyl carbamate (Tcroc), m-nitrophenyl carbamate, 3,5-dimethoxybenzyl carbamate, o-nitrobenzyl carbamate, 3,4-dimethoxy-6-nitrobenzyl carbamate, phenyl(o-nitrophenyl)methyl carbamate, t-amyl carbamate, S-benzyl thiocarbamate, p-cyanobenzyl carbamate, cyclobutyl carbamate, cyclohexyl carbamate, cyclopentyl carbamate, cyclopropylmethyl carbamate, p-decyloxybenzyl carbamate, 2,2-dimethoxyacetylvinyl carbamate, o-(N,N-dimethylcarboxamido)benzyl carbamate, 1,1-dimethyl-3-(N,N-dimethylcarboxamido)propyl carbamate, 1,1-dimethylpropynyl carbamate, di(2-pyridyl)methyl carbamate, 2-furanylmethyl carbamate, 2-iodoethyl carbamate, isoborynl carbamate, isobutyl carbamate, isonicotinyl carbamate, p-(p'-methoxyphenylazo)benzyl carbamate, 1-methylcyclobutyl carbamate, 1-methylcyclohexyl carbamate, 1-methyl-1-cyclopropylmethyl carbamate, 1-methyl-1-(3,5-dimethoxyphenyl)ethyl carbamate, 1-methyl-1-(p-phenylazophenyl)ethyl carbamate, 1-methyl-1-phenylethyl carbamate, 1-methyl-1-(4-pyridyl)ethyl carbamate, phenyl carbamate, p-(phenylazo)benzyl carbamate, 2,4,6-tri-t-butylphenyl carbamate, 4-(trimethylammonium)benzyl carbamate, and 2,4,6-trimethylbenzyl carbamate.

[000189] Nitrogen protecting groups such as sulfonamide groups (e.g., $-S(=O)_2R^{aa}$) include, but are not limited to, p-toluenesulfonamide (Ts), benzenesulfonamide, 2,3,6-trimethyl-4-methoxybenzenesulfonamide (Mtr), 2,4,6-trimethoxybenzenesulfonamide (Mtb), 2,6-dimethyl-4-methoxybenzenesulfonamide (Pme), 2,3,5,6-tetramethyl-4-methoxybenzenesulfonamide (Mte), 4-methoxybenzenesulfonamide (Mbs), 2,4,6-trimethylbenzenesulfonamide (Mts), 2,6-dimethoxy-4-methylbenzenesulfonamide (iMds), 2,2,5,7,8-pentamethylchroman-6-sulfonamide (Pmc), methanesulfonamide (Ms), β -trimethylsilyl ethanesulfonamide (SES), 9-anthracenesulfonamide, 4-(4',8'-dimethoxynaphthylmethyl)benzenesulfonamide (DNMBS), benzylsulfonamide, trifluoromethylsulfonamide, and phenacylsulfonamide.

[000190] Other nitrogen protecting groups include, but are not limited to, phenothiazinyl-(10)-acyl derivative, N'-p-toluenesulfonylaminoacyl derivative, N'-phenylaminothioacyl derivative, N-benzoylphenylalanyl derivative, N-acetylmethionine derivative, 4,5-diphenyl-3-oxazolin-2-one, N-phthalimide, N-dithiasuccinimide (Dts), N-2,3-diphenylmaleimide, N-2,5-dimethylpyrrole, N-1,1,4,4-tetramethyldisilylazacyclopentane adduct (STABASE), 5-substituted 1,3-dimethyl-1,3,5-triazacyclohexan-2-one, 5-substituted 1,3-dibenzyl-1,3,5-triazacyclohexan-2-one, 1-substituted 3,5-dinitro-4-pyridone, N-methylamine, N-allylamine, N-[2-(trimethylsilyl)ethoxy]methylamine (SEM), N-3-acetoxypyrrolamine, N-(1-isopropyl-4-nitro-2-oxo-3-pyrroline-3-yl)amine, quaternary ammonium salts, N-benzylamine, N-di(4-methoxyphenyl)methylamine, N-5-dibenzosuberylamine, N-triphenylmethylamine (Tr), N-[(4-methoxyphenyl)diphenylmethyl]amine (MMTr), N-9-phenylfluorenylamine (PhF), N-2,7-dichloro-9-fluorenylmethyleneamine, N-ferrocenylmethylamino (Fcm), N-2-picolylamino N'-oxide, N-1,1-dimethylthiomethyleneamine, N-benzylideneamine, N-p-methoxybenzylideneamine, N-diphenylmethyleneamine, N-[(2-pyridyl)mesityl]methyleneamine, N-(N',N'-dimethylaminomethylene)amine, N,N'-isopropylidenediamine, N-p-nitrobenzylideneamine, N-salicylideneamine, N-5-chlorosalicylideneamine, N-(5-chloro-2-hydroxyphenyl)phenylmethyleneamine, N-cyclohexylideneamine, N-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine, N-borane derivative, N-diphenylborinic acid derivative, N-[phenyl(pentaacylchromium- or tungsten)acyl]amine, N-copper chelate, N-zinc chelate, N-nitroamine, N-nitrosoamine, amine N-oxide, diphenylphosphinamide (Dpp), dimethylthiophosphinamide (Mpt), diphenylthiophosphinamide (Ppt), dialkyl phosphoramidates, dibenzyl phosphoramidate, diphenyl phosphoramidate, benzenesulfenamide, o-nitrobenzenesulfenamide (Nps), 2,4-dinitrobenzenesulfenamide, pentachlorobenzenesulfenamide, 2-nitro-4-methoxybenzenesulfenamide, triphenylmethylsulfenamide, and 3-nitropyridinesulfenamide (Npys).

[000191] Whenever a term (*e.g.*, alkyl or aryl) or either of their prefix roots (*e.g.*, alk- or ar-) appear in a name of a substituent the name is to be interpreted as including those limitations provided herein. For example, affixing the suffix "-ene" to a group indicates the group is a divalent moiety, *e.g.*, arylene is the divalent moiety of aryl, heteroarylene is the divalent moiety of heteroaryl, cycloalkylene is the divalent moiety of cycloalkyl, heterocycloalkylene is the divalent moiety of heterocycloalkyl, or heterocyclelene is the divalent moiety of heterocyclyl. Similarly, affixing the suffix "-oxy" to a group indicates the group is attached to the parent molecular structure through an oxygen atom (-O-) (*e.g.*, cycloalkyloxy, benzyloxy, and the like).

[000192] *Administering:* The terms “administer”, “administration” and “administering” refer to providing a composition of the present invention (e.g., a recombinant gene therapy vector expressing alpha galactosidase) to a subject in need thereof (e.g., to a person suffering from the effects of Fabry disease).

[000193] The terms “individual,” “subject,” “subject in need thereof” and “patient,” used interchangeably herein, refer to a mammal, including, but not limited to, murines, simians, humans, mammalian farm animals, mammalian sport animals, and mammalian pets. In preferred embodiments, the individual is a human. In various embodiments, a subject or a subject in need thereof is a Fabry patient exhibiting one or more symptoms associated with peripheral neuropathy. *Therapeutically effective:* A “therapeutically effective” amount or dose or “sufficient/effective” amount or dose, is a dose that produces effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, e.g., Lieberman, *Pharmaceutical Dosage Forms* (vols. 1-3, 1992); Lloyd, *The Art, Science and Technology of Pharmaceutical Compounding* (1999); Pickar, *Dosage Calculations* (1999); and Remington: *The Science and Practice of Pharmacy*, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[000194] *Treatment:* As used herein, the term “treatment” or “therapy” generally means obtaining a desired physiologic effect. The effect may be prophylactic in terms of completely or partially preventing a disease or condition or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for an injury, disease or condition and/or amelioration of an adverse effect attributable to the injury, disease or condition and includes arresting the development or causing regression of a disease or condition. Treatment can also include prophylactic use to mitigate the effects of injury, should it occur. For example, in one aspect, the present invention includes pre-administration to mitigate damage prior to surgery involving the peripheral nervous system. Treatment can also refer to any delay in onset, amelioration of symptoms, improvement in patient survival, increase in survival time or rate, etc. The effect of treatment can be compared to an individual or pool of individuals not receiving the treatment.

Compounds of Formulas (A), (I)-(X), and (B)

[000195] The invention features compounds of Formulas (A) (e.g., Formulas (I)-(X)) and (B), including subformulas thereof as well as certain specifically described compounds (e.g., Compounds (1)-(36)), as well as pharmaceutically acceptable forms thereof. Compounds described herein are

suitable for pharmaceutical compositions and methods of use (e.g., methods of treating diseases and disorders), including the non-limiting exemplary embodiments described herein.

[000196] That is, certain exemplary formulas and compounds are described herein. Also provided herein are exemplary embodiments of structural features which may be present in any formula described herein. Any exemplary embodiment of a structural feature may occur in combination with any other exemplary structural feature described herein. Further, and unless otherwise indicated herein, any description of a formula or compound also includes any pharmaceutically acceptable forms of the compound, including but not limited to any pharmaceutically acceptable salts, hydrates, solvates, isomers, polymorphs, prodrugs, and isotopically labeled derivatives of disclosed formulas and compounds.

[000197] When any variable occurs more than one time in any constituent or in any formula, its definition in each occurrence is independent of its definition at every other occurrence (*e.g.*, in $N(R^9)_2$, each R^9 may be the same or different than the other). Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

[000198] Any formula given herein is intended to represent compounds having structures depicted by the structural formula as well as certain variations or forms. In particular, compounds of any formula given herein may have asymmetric centers and therefore exist in different enantiomeric forms. All optical isomers and stereoisomers of the compounds of the general formula, and mixtures thereof, are considered within the scope of the formula. Thus, any formula given herein is intended to represent a racemate, one or more enantiomeric forms, one or more diastereomeric forms, one or more atropisomeric forms, and mixtures thereof. Furthermore, certain structures may exist as geometric isomers (*i.e.*, cis and trans isomers), as tautomers, or as atropisomers. Additionally, any formula given herein is intended to embrace hydrates, solvates, and polymorphs of such compounds, and mixtures thereof.

[000199] Compounds described herein can comprise an asymmetric atom (also referred as a chiral center), and some of the compounds can comprise one or more asymmetric atoms or centers, which can thus give rise to optical isomers (enantiomers) and diastereomers. The present teachings and compounds disclosed herein include such enantiomers and diastereomers, as well as the racemic and resolved, enantiomerically pure R and S stereoisomers, as well as other mixtures of the R and S stereoisomers and pharmaceutically acceptable salts thereof. Optical isomers can be obtained in pure form by standard procedures known to those skilled in the art, which include, but are not limited to, diastereomeric salt formation, kinetic resolution, and asymmetric synthesis. The

present teachings also encompass cis and trans isomers of compounds containing alkenyl moieties (e.g., alkenes and imines). It is also understood that the present teachings encompass all possible regioisomers, and mixtures thereof, which can be obtained in pure form by standard separation procedures known to those skilled in the art, and include, but are not limited to, column chromatography, thin-layer chromatography, and high-performance liquid chromatography.

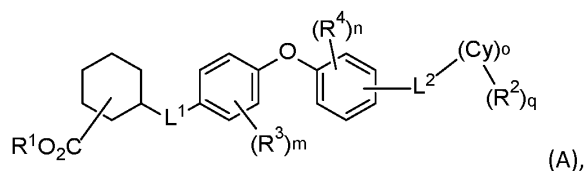
[000200] Compounds described herein can comprise atoms that exhibit their natural isotopic abundances, or one or more of the atoms may be artificially enriched in a particular isotope having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominately found in nature. The term “isotopologue” refers to a species that has the same chemical structure and formula as a specific compound provided herein, with the exception of the positions of isotopic substitution and/or level of isotopic enrichment at one or more positions, e.g., hydrogen vs. deuterium. The present invention is meant to include all suitable isotopic variations of the compounds of the compounds described herein. For example, different isotopic forms of hydrogen (H) include protium (^1H), deuterium (^2H), and tritium (^3H), as well as compositions enriched in isotopologues of any compound described herein.

[000201] In embodiments, one or more of the hydrogens of the compounds described herein is replaced by a deuterium. When a position is designated as “H” or “hydrogen”, the position is understood to have hydrogen at its natural abundance isotopic composition. When a position is designated as “ ^2H ” or “deuterium”, the position is understood to have deuterium at an abundance that is at least 3340 times greater than the natural abundance of deuterium, which is 0.015% (i.e., the term “ ^2H ” or “deuterium” indicates at least 50.1% incorporation of deuterium). Accordingly, the invention also features compositions enriched in deuterated compounds.

[000202] In embodiments, compositions of any compound provided herein may have an isotopic enrichment factor for each deuterium present at a site designated as a potential site of deuteration on the compound of at least 3500 (52.5% deuterium incorporation), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Formula (A)

[000203] In embodiments, a compound has a structure according to Formula (A),



or a pharmaceutically acceptable salt thereof, wherein each of **L¹**, **L²**, **R¹**, **R²**, **R³**, **R⁴**, **Cy**, **m**, **n**, **o**, and **q** is independently according to any embodiment, or combination of embodiments, as described herein.

[000204] In embodiments of Formula (A),

R¹ is independently H or C₁-C₆ alkyl

R² is independently H, OH, or (CH₂)_pCO₂R⁵;

R³ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶;

R⁴ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶, or two **R⁴** on adjacent carbons combine to form a heteroaryl moiety, or one **R⁴** combines with **R^{7B}** to form a heteroaryl moiety;

L¹ is independently a covalent bond, C(O), C(O)NR^{7A}, or NR^{7A}C(O);

X¹ is independently a covalent bond, O, or CH₂;

R⁵ is independently H or C₁-C₆ alkyl;

R⁶ is independently C₆-C₁₀ aryl or 5- to 10-membered heteroaryl;

each **R^{7A}** is independently H or C₁-C₆ alkyl;

each **R^{7B}** is independently H or C₁-C₆ alkyl, or **R^{7B}** combines with **R⁴** to form a heteroaryl moiety;

X¹ is independently a covalent bond, O, or CH₂;

L² is independently a covalent bond, CH₂, C(O), NR^{7B}, C(O)NR^{7B}, or NR^{7B}C(O);

Cy is independently C₅-C₁₀ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of **n** and **o** is independently 0, 1, or 2;

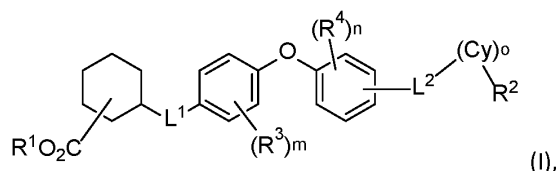
p is independently 0, 1, 2, or 3.

[000205] In embodiments, **L²** is independently a covalent bond, C(O), NR^{7B}, C(O)NR^{7B}, or NR^{7B}C(O).

[000206] In embodiments, **Cy** is independently C₅-C₇ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl.

Formula (I)

[000207] In embodiments, a compound has a structure according to Formula (I),



or a pharmaceutically acceptable salt thereof, wherein each of **L¹**, **L²**, **R¹**, **R²**, **R³**, **R⁴**, **Cy**, **m**, **n**, and **o** is independently according to any embodiment, or combination of embodiments, as described herein.

[000208] In embodiments of Formula (I),

each of **R¹** and **R⁵** is independently H or C₁-C₆ alkyl;

R² is independently H or (CH₂)_pCO₂R⁵;

R³ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶;

R⁴ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶, or two **R⁴** on adjacent carbons combine to form a heteroaryl moiety, or one **R⁴** combines with **R^{7B}** to form a heteroaryl moiety;

L¹ is independently a covalent bond, C(O), C(O)NR^{7A}, or NR^{7A}C(O);

L² is independently a covalent bond, CH₂, C(O), NR^{7B}, C(O)NR^{7B}, or NR^{7B}C(O);

R⁶ is independently C₆-C₁₀ aryl or 5- to 10-membered heteroaryl;

each **R^{7A}** is independently H or C₁-C₆ alkyl;

each **R^{7B}** is independently H or C₁-C₆ alkyl, or **R^{7B}** combines with **R⁴** to form a heteroaryl moiety;

X¹ is independently a covalent bond, O, or CH₂;

Cy is independently C₅-C₁₀ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of **m**, **n**, and **o** is independently 0, 1, or 2; and

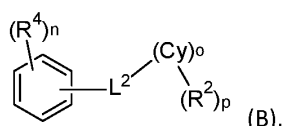
p is independently 0 or 1.

[000209] In embodiments, **L²** is independently a covalent bond, C(O), NR^{7B}, C(O)NR^{7B}, or NR^{7B}C(O).

[000210] In embodiments, **Cy** is independently C₅-C₇ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl

Formula (B)

[000211] In embodiments, a compound has a structure according to Formula (B),



or a pharmaceutically acceptable salt thereof, wherein each of **L²**, **R²**, **R⁴**, **Cy**, **n**, **o**, and **p** is independently according to any embodiment, or combination of embodiments, as described herein.

[000212] In embodiments of Formula (B),

R² is independently H, OH, or (CH₂)_pCO₂R⁵;

R⁴ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶, or two **R⁴** on adjacent carbons combine to form a heteroaryl moiety, or one **R⁴** combines with **R^{7B}** to form a heteroaryl moiety;

X¹ is independently a covalent bond, O, or CH₂;

R⁵ is independently H or C₁-C₆ alkyl;

R⁶ is independently C₆-C₁₀ aryl or 5- to 10-membered heteroaryl;

each **R^{7B}** is independently H or C₁-C₆ alkyl, or **R^{7B}** combines with **R⁴** to form a heteroaryl moiety;

L² is independently a covalent bond, C(O), NR^{7B}, C(O)NR^{7B}, or NR^{7B}C(O);

Cy is independently C₅-C₇ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of **n** and **o** is independently 0, 1, or 2;

p is independently 0, 1, 2, or 3.

[000213] In embodiments **R¹** is independently H.

[000214] In embodiments **R¹** is independently C₁-C₆ alkyl. In embodiments **R¹** is independently unsubstituted C₁-C₆ alkyl. In embodiments **R¹** is independently substituted C₁-C₆ alkyl.

[000215] In embodiments R^5 is independently H.

[000216] In embodiments R^5 is independently C_1-C_6 alkyl. In embodiments R^5 is independently unsubstituted C_1-C_6 alkyl. In embodiments R^5 is independently substituted C_1-C_6 alkyl.

[000217] In embodiments, R^2 is independently H.

[000218] In embodiments, R^2 is independently OH.

[000219] In embodiments, R^2 is independently $(CH_2)_pCO_2R^5$. In embodiments, p is independently 0. In embodiments, p is independently 1.

[000220] In embodiments R^3 is independently C_1-C_6 alkyl. In embodiments R^3 is independently unsubstituted C_1-C_6 alkyl. In embodiments R^3 is independently substituted C_1-C_6 alkyl.

[000221] In embodiments R^3 is independently 1- to 6-membered heteroalkyl. In embodiments R^3 is independently unsubstituted 1- to 6-membered heteroalkyl. In embodiments R^3 is independently substituted 1- to 6-membered heteroalkyl

[000222] In embodiments R^3 is independently X^1-R^6 .

[000223] In embodiments, X^1 is independently a covalent bond. In embodiments, R^6 is independently C_6-C_{10} aryl (e.g., phenyl) or 5- to 10-membered heteroaryl (e.g., indole). In embodiments, R^6 is unsubstituted. In embodiments, R^6 is substituted.

[000224] In embodiments, X^1 is independently O. In embodiments, R^6 is independently C_6-C_{10} aryl (e.g., phenyl) or 5- to 10-membered heteroaryl (e.g., indole). In embodiments, R^6 is unsubstituted. In embodiments, R^6 is substituted.

[000225] In embodiments, X^1 is independently CH_2 . In embodiments, R^6 is independently C_6-C_{10} aryl (e.g., phenyl) or 5- to 10-membered heteroaryl (e.g., indole). In embodiments, R^6 is unsubstituted. In embodiments, R^6 is substituted.

[000226] In embodiments, R^4 is independently C_1-C_6 alkyl. In embodiments R^4 is independently unsubstituted C_1-C_6 alkyl. In embodiments R^4 is independently substituted C_1-C_6 alkyl.

[000227] In embodiments R^4 is independently 1- to 6-membered heteroalkyl. In embodiments R^4 is independently unsubstituted 1- to 6-membered heteroalkyl. In embodiments R^4 is independently substituted 1- to 6-membered heteroalkyl

- [000228] In embodiments R^4 is independently X^1-R^6 .
- [000229] In embodiments, two R^4 on adjacent carbons combine to form a heteroaryl moiety (e.g., an indole).
- [000230] In embodiments, one R^4 combines with R^{7B} to form a heteroaryl moiety.
- [000231] In embodiments, L^1 is independently a covalent bond.
- [000232] In embodiments, L^1 is independently C(O).
- [000233] In embodiments, L^1 is independently C(O)NR^{7A}.
- [000234] In embodiments, L^1 is independently NR^{7A}C(O).
- [000235] In embodiments, L^2 is independently a covalent bond.
- [000236] In embodiments, L^2 is independently CH₂.
- [000237] In embodiments, L^2 is independently C(O).
- [000238] In embodiments, L^2 is independently NR^{7B}.
- [000239] In embodiments, L^2 is independently C(O)NR^{7B}.
- [000240] In embodiments, L^2 is independently NR^{7B}C(O).
- [000241] In embodiments, each R^{7A} is independently H. In embodiments, each R^{7A} is independently C₁-C₆ alkyl. In embodiments R^{7A} is independently unsubstituted C₁-C₆ alkyl. In embodiments R^{7A} is independently substituted C₁-C₆ alkyl.
- [000242] In embodiments, each R^{7B} is independently H. In embodiments, each R^{7B} is independently C₁-C₆ alkyl. In embodiments R^{7B} is independently unsubstituted C₁-C₆ alkyl. In embodiments R^{7B} is independently substituted C₁-C₆ alkyl.
- [000243] In embodiments, R^{7B} combines with R^4 to form a heteroaryl moiety.
- [000244] In embodiments, **Cy** is independently C₅-C₁₀ cycloalkyl (e.g., cyclopentyl, cyclohexyl, or decahydronaphthalenyl). In embodiments, **Cy** is unsubstituted. In embodiments, **Cy** is substituted.

[000245] In embodiments, **Cy** is independently C₅-C₇ cycloalkyl (e.g., cyclohexyl). In embodiments, **Cy** is unsubstituted. In embodiments, **Cy** is substituted.

[000246] In embodiments, **Cy** is independently 5- to 7-membered heterocyclyl. In embodiments, **Cy** is unsubstituted. In embodiments, **Cy** is substituted.

[000247] In embodiments, **Cy** is independently 5- to 6-membered heteroaryl. In embodiments, **Cy** is unsubstituted. In embodiments, **Cy** is substituted.

[000248] In embodiments, **Cy** is independently phenyl. In embodiments, **Cy** is unsubstituted. In embodiments, **Cy** is substituted.

[000249] In embodiments, **m** is independently 0.

[000250] In embodiments, **m** is independently 1.

[000251] In embodiments, **m** is independently 2.

[000252] In embodiments, **n** is independently 0.

[000253] In embodiments, **n** is independently 1.

[000254] In embodiments, **n** is independently 2.

[000255] In embodiments, **o** is independently 0.

[000256] In embodiments, **o** is independently 1.

[000257] In embodiments, **o** is independently 2.

[000258] In embodiments, **p** is independently 0.

[000259] In embodiments, **p** is independently 1.

[000260] In embodiments, **p** is independently 2.

[000261] In embodiments, **p** is independently 3.

[000262] In embodiments, **q** is independently 0.

[000263] In embodiments, **q** is independently 1.

- [000264] In embodiments, **q** is independently 2.
- [000265] In embodiments, **q** is independently 3.
- [000266] In embodiments, each of **R¹** and **R⁵** is independently H.
- [000267] In embodiments, **m** and **n** are both 0.
- [000268] In embodiments, one of **m** and **n** is 1, and the other is 0.
- [000269] In embodiments, **R³** is independently methyl and/or **R⁴** is independently methyl, isopropyl, or benzyl.
- [000270] In embodiments, **L¹** is a covalent bond, **o** is 0, and **R²** is H.
- [000271] In embodiments, **L¹** is NHC(O) and **o** is 1.
- [000272] In embodiments, **L²** is a covalent bond, **o** is 0, and **R²** is H.
- [000273] In embodiments, **L²** is CH₂, **o** is 1, and **R²** is H.
- [000274] In embodiments, **L²** is NHC(O) and **o** is 1.
- [000275] In embodiments, **L²** is NR^{7B}, **o** is 0, and **R²** is H.
- [000276] In embodiments, **L²** is NR^{7B}, **o** is 0, and **R²** is H.
- [000277] In embodiments, **L²** is NR^{7B}, **o** is 0, and **R²** is methyl.
- [000278] In embodiments, **L²** is NR^{7B}, **o** is 1, and **R²** is H.
- [000279] In embodiments, **R^{7B}** is H, **o** is 0, and **R²** is H.
- [000280] In embodiments, **R^{7B}** is methyl, **o** is 0, and **R²** is H.
- [000281] In embodiments, **R^{7B}** is H, **o** is 0, and **R²** is methyl.
- [000282] In embodiments, **R^{7B}** is H, **o** is 1, and **R²** is H.
- [000283] In embodiments, **Cy** is phenyl.
- [000284] In embodiments, **Cy** is cyclohexyl.

[000285] In embodiments, **Cy** is cyclopentyl.

[000286] In embodiments, **Cy** is decahydronaphthalenyl.

[000287] In embodiments, non-hydrogen groups on different carbons of the cyclohexyl moiety substituted by $-\text{CO}_2\text{R}^1$ are *cis* to each other (also referred to as a “*cis*-cyclohexyl”).

[000288] In embodiments, non-hydrogen groups on different carbons of the cyclohexyl moiety substituted by $-\text{CO}_2\text{R}^1$ are *trans* to each other (also referred to as a “*trans*-cyclohexyl”).

[000289] In embodiments where **Cy** is C_5 - C_{10} cycloalkyl (e.g., a cyclohexyl, a cyclopentyl, or decahydronaphthalene) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of on a **Cy** moiety are *cis* to each other (also referred to as a “*cis*-**Cy**”).

[000290] In embodiments where **Cy** is C_5 - C_7 cycloalkyl (e.g., a cyclohexyl or a cyclopentyl) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of on a **Cy** moiety are *cis* to each other (also referred to as a “*cis*-**Cy**”).

[000291] In embodiments where **Cy** is C_5 - C_{10} cycloalkyl (e.g., a cyclohexyl, a cyclopentyl, or decahydronaphthalene) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of a **Cy** moiety are *trans* to each other (also referred to as a “*trans*-**Cy**”).

[000292] In embodiments where **Cy** is C_5 - C_7 cycloalkyl (e.g., a cyclohexyl or a cyclopentyl) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of a **Cy** moiety are *trans* to each other (also referred to as a “*trans*-**Cy**”).

[000293] In embodiments, a compound of Formula (A), or any subformulas thereof, comprises a *cis*-cyclohexyl and a *cis*-**Cy** (e.g., a *cis*-cyclohexyl, a *cis*-cyclopentyl, or a *cis*-decahydronaphthalenyl).

[000294] In embodiments, a compound of Formula (A), or any subformulas thereof, comprises a *cis*-cyclohexyl and a *cis*-**Cy** (e.g., a *cis*-cyclohexyl or a *cis*-cyclopentyl).

[000295] In embodiments, a compound of Formula (A), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *trans*-**Cy** (e.g., a *trans*-cyclohexyl, a *trans*-cyclopentyl, or a *trans*-decahydronaphthalenyl).

[000296] In embodiments, a compound of Formula (A), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *trans*-**Cy** (e.g., a *trans*-cyclohexyl or a *trans*-cyclopentyl).

[000297] In embodiments, a compound of Formula (A), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *cis*-**Cy** (e.g., a *cis*-cyclohexyl, a *cis*-cyclopentyl, or a *cis*-decahydronaphthalenyl).

[000298] In embodiments, a compound of Formula (A), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *cis*-**Cy** (e.g., a *cis*-cyclohexyl or a *cis*-cyclopentyl).

[000299] In embodiments, a compound of Formula (A), or any subformulas thereof, comprises a *cis*-cyclohexyl and a *trans*-**Cy** (e.g., a *trans*-cyclohexyl, a *trans*-cyclopentyl, or a *trans*-decahydronaphthalenyl).

[000300] In embodiments, a compound of Formula (A), or any subformulas thereof, comprises a *cis*-cyclohexyl and a *trans*-**Cy** (e.g., a *trans*-cyclohexyl or a *trans*-cyclopentyl).

[000301] In embodiments, a compound of Formula (I), or any subformulas thereof, comprises a *cis*-cyclohexyl and a *cis*-**Cy** (e.g., a *cis*-cyclohexyl, a *cis*-cyclopentyl, or a *cis*-decahydronaphthalenyl).

[000302] In embodiments, a compound of Formula (I), or any subformulas thereof, comprises a *cis*-cyclohexyl and a *cis*-**Cy** (e.g., a *cis*-cyclohexyl or a *cis*-cyclopentyl).

[000303] In embodiments, a compound of Formula (I), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *trans*-**Cy** (e.g., a *trans*-cyclohexyl, a *trans*-cyclopentyl, or a *trans*-decahydronaphthalenyl).

[000304] In embodiments, a compound of Formula (I), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *trans*-**Cy** (e.g., a *trans*-cyclohexyl or a *trans*-cyclopentyl).

[000305] In embodiments, a compound of Formula (I), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *cis*-**Cy** (e.g., a *cis*-cyclohexyl, a *cis*-cyclopentyl, or a *cis*-decahydronaphthalenyl).

[000306] In embodiments, a compound of Formula (I), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *cis*-**Cy** (e.g., a *cis*-cyclohexyl or a *cis*-cyclopentyl).

[000307] In embodiments, a compound of Formula (I), or any subformulas thereof, comprises a *cis*-cyclohexyl and a *trans*-**Cy** (e.g., a *trans*-cyclohexyl, a *trans*-cyclopentyl, or a *trans*-decahydronaphthalenyl).

[000308] In embodiments, a compound of Formula (I), or any subformulas thereof, comprises a *cis*-cyclohexyl and a *trans*-Cy (e.g., a *trans*-cyclohexyl or a *trans*-cyclopentyl).

[000309] In embodiments, a compound of Formula (B), or any subformulas thereof, comprises a *cis*-cyclohexyl and a *cis*-Cy (e.g., a *cis*-cyclohexyl or a *cis*-cyclopentyl).

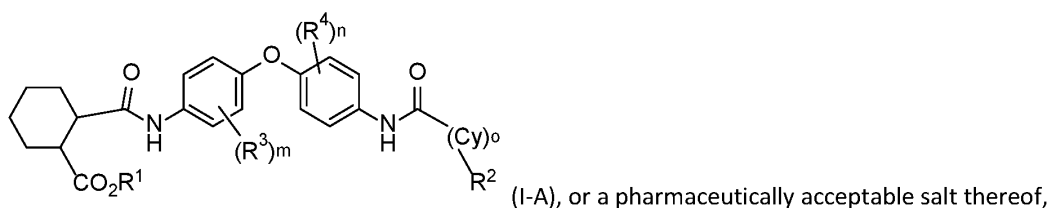
[000310] In embodiments, a compound of Formula (B), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *trans*-Cy (e.g., a *trans*-cyclohexyl or a *trans*-cyclopentyl).

[000311] In embodiments, a compound of Formula (B), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *cis*-Cy (e.g., a *cis*-cyclohexyl or a *cis*-cyclopentyl).

[000312] In embodiments, a compound of Formula (B), or any subformulas thereof, comprises a *cis*-cyclohexyl and a *trans*-Cy (e.g., a *trans*-cyclohexyl or a *trans*-cyclopentyl).

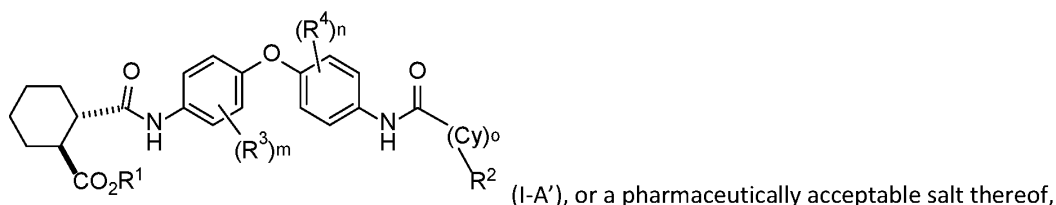
Formulas (I-A to I-G)

[000313] In embodiments, a compound of Formula (I) has a structure according to Formula (I-A),



wherein each of R^1 , R^2 , R^3 , R^4 , Cy , m , n , and o is independently according to any embodiment, or combination of embodiments, as described herein.

[000314] In embodiments, the substituents on the cyclohexyl moiety are *trans* to each other, e.g., according to Formula (I-A'),



wherein each of R^1 , R^2 , R^3 , R^4 , Cy , m , n , and o is independently according to any embodiment, or combination of embodiments, as described herein.

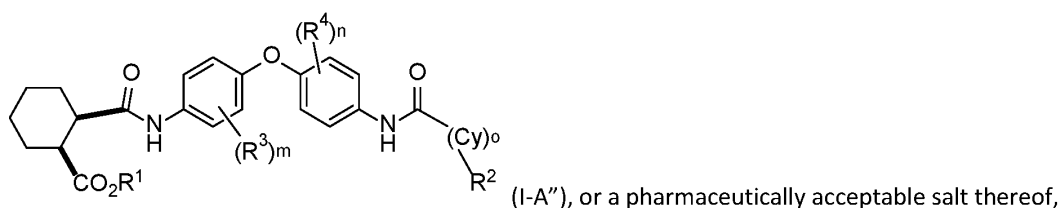
[000315] In embodiments where **Cy** is C₅-C₁₀ cycloalkyl (e.g., a cyclohexyl, a cyclopentyl, or decahydronaphthalenyl) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of on a **Cy** moiety are *cis* to each other (also referred to as a “*cis-Cy*”).

[000316] In embodiments where **Cy** is C₅-C₇ cycloalkyl (e.g., a cyclohexyl or a cyclopentyl) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of on a **Cy** moiety are *cis* to each other (also referred to as a “*cis-Cy*”).

[000317] In embodiments where **Cy** is C₅-C₁₀ cycloalkyl (e.g., a cyclohexyl, a cyclopentyl, or decahydronaphthalenyl) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of a **Cy** moiety are *trans* to each other (also referred to as a “*trans-Cy*”).

[000318] In embodiments where **Cy** is C₅-C₇ cycloalkyl (e.g., a cyclohexyl or a cyclopentyl) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of a **Cy** moiety are *trans* to each other (also referred to as a “*trans-Cy*”).

[000319] In embodiments, the substituents on the cyclohexyl moiety are *cis* to each other, e.g., according to Formula (I-A”),



wherein each of **R¹**, **R²**, **R³**, **R⁴**, **Cy**, **m**, **n**, and **o** is independently according to any embodiment, or combination of embodiments, as described herein.

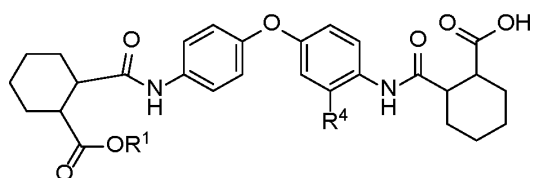
[000320] In embodiments where **Cy** is C₅-C₁₀ cycloalkyl (e.g., a cyclohexyl, a cyclopentyl, or a decahydronaphthalenyl) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of on a **Cy** moiety are *cis* to each other (also referred to as a “*cis-Cy*”).

[000321] In embodiments where **Cy** is C₅-C₇ cycloalkyl (e.g., a cyclohexyl or a cyclopentyl) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of on a **Cy** moiety are *cis* to each other (also referred to as a “*cis-Cy*”).

[000322] In embodiments where **Cy** is C₅-C₁₀ cycloalkyl (e.g., a cyclohexyl, a cyclopentyl, or a decahydronaphthalenyl) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of a **Cy** moiety are *trans* to each other (also referred to as a “*trans-Cy*”).

[000323] In embodiments where **Cy** is C₅-C₇ cycloalkyl (e.g., a cyclohexyl or a cyclopentyl) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of a **Cy** moiety are *trans* to each other (also referred to as a “*trans-Cy*”).

[000324] In embodiments, a compound of Formula (I) has a structure according to Formula (I-B),



(I-B), or a pharmaceutically acceptable salt

thereof, wherein each of **R**¹ and **R**⁴ is independently according to any embodiment as described herein.

[000325] In embodiments, the substituents on an individual cyclohexyl moiety are *cis* to each other.

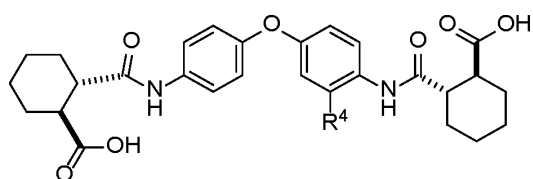
[000326] In embodiments, the substituents on an individual cyclohexyl moiety are *trans* to each other.

[000327] In embodiments, the substituents on each cyclohexyl moiety are *cis* to each other.

[000328] In embodiments, the substituents on each cyclohexyl moiety are *trans* to each other.

[000329] In embodiments, the substituents on one cyclohexyl moiety are *trans* to each other, and the substituents on the other cyclohexyl moiety are *cis* to each other.

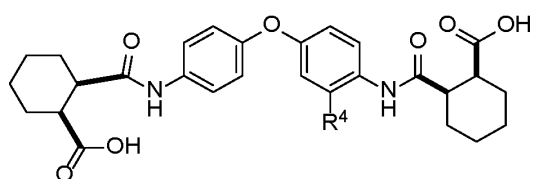
[000330] In embodiments, a compound of Formula (I) has a structure according to Formula (I-B'),



(I-B'), or a pharmaceutically acceptable salt

thereof, wherein **R**⁴ is independently according to any embodiment as described herein.

[000331] In embodiments, a compound of Formula (I) has a structure according to Formula (I-B''),

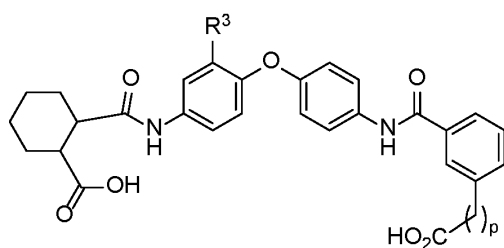


(I-B''), or a pharmaceutically acceptable salt

thereof, wherein R^4 is independently according to any embodiment as described herein.

[000332] In embodiments, the substituents on an individual cyclohexyl moiety are *trans* to each other.

[000333] In embodiments, a compound of Formula (I) has a structure according to Formula (I-C),



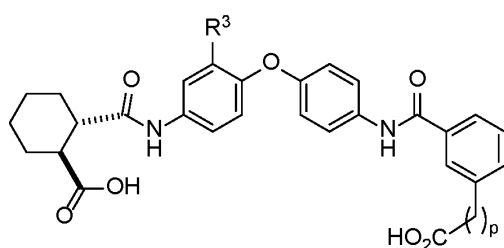
(I-C), or a pharmaceutically acceptable salt thereof,

wherein each of R^3 and p is independently according to any embodiment, or combination of embodiments described herein. In embodiments, p is independently 0 or 1.

[000334] In embodiments, the substituents on the cyclohexyl moiety are *cis* to each other.

[000335] In embodiments, the substituents on the cyclohexyl moiety are *trans* to each other.

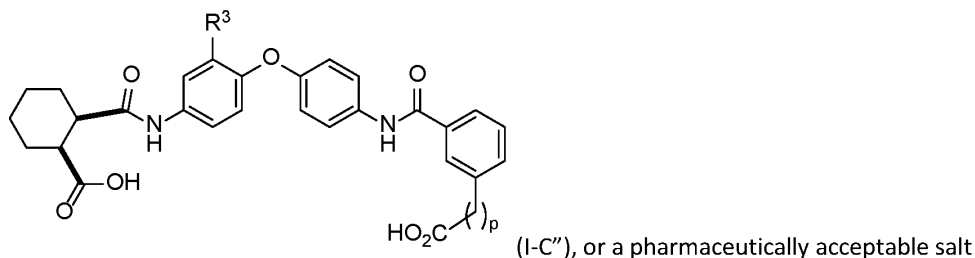
[000336] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other, e.g., according to Formula (I-C'),



(I-C'), or a pharmaceutically acceptable salt thereof,

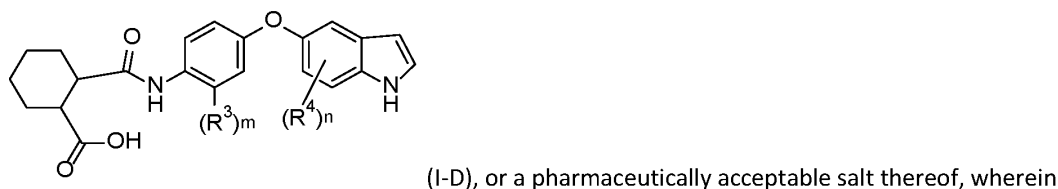
wherein each of R^3 and p is independently according to any embodiment, or combination of embodiments described herein. In embodiments, p is independently 0 or 1.

[000337] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other e.g., according to Formula (I-C''),



thereof, wherein each of R^3 and p is independently according to any embodiment, or combination of embodiments described herein. In embodiments, p is independently 0 or 1.

[000338] In embodiments, a compound of Formula (I) has a structure according to Formula (I-D),

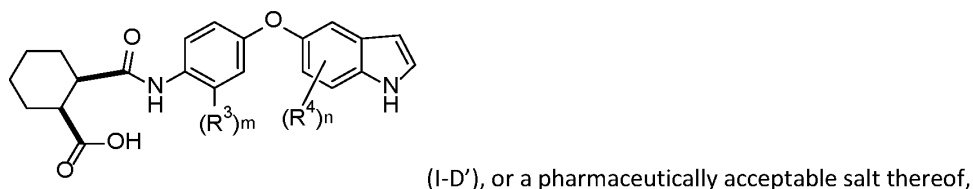


each of R^3 , R^4 , m , and n is independently according to any embodiment, or combination of embodiments described herein. In embodiments, each of m and n is independently 0 or 1. Where m is 0, a hydrogen is located at that position of the phenyl ring.

[000339] In embodiments, the substituents on the cyclohexyl moiety are *cis* to each other.

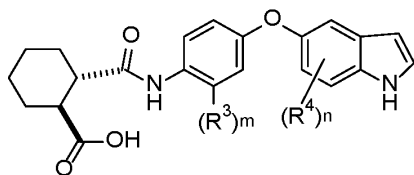
[000340] In embodiments, the substituents on the cyclohexyl moiety are *trans* to each other.

[000341] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other, e.g., according to Formula (I-D'),



wherein each of R^3 , R^4 , m , and n is independently according to any embodiment, or combination of embodiments described herein. In embodiments, each of m and n is independently 0 or 1. Where m is 0, a hydrogen is located at that position of the phenyl ring.

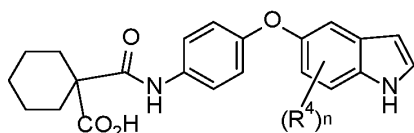
[000342] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other, e.g., according to Formula (I-D''),



(I-D''), or a pharmaceutically acceptable salt thereof,

wherein each of R^3 , R^4 , m , and n is independently according to any embodiment, or combination of embodiments described herein. In embodiments, each of m and n is independently 0 or 1. Where m is 0, a hydrogen is located at that position of the phenyl ring.

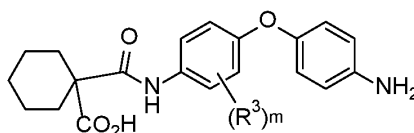
[000343] In embodiments, a compound of Formula (I) has a structure according to Formula (I-E),



(I-E), or a pharmaceutically acceptable salt thereof, wherein

each of R^4 and n is independently according to any embodiment, or combination of embodiments described herein. In embodiments, n is 0 or 1.

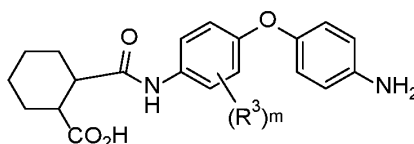
[000344] In embodiments, a compound of Formula (I) has a structure according to Formula (I-F),



(I-F), or a pharmaceutically acceptable salt thereof, wherein

each of R^3 and m is independently according to any embodiment, or combination of embodiments described herein. In embodiments, m is 0 or 1.

[000345] In embodiments, a compound of Formula (I) has a structure according to Formula (I-G),



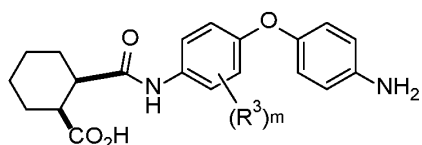
(I-G), or a pharmaceutically acceptable salt thereof, wherein

each of R^3 and m is independently according to any embodiment, or combination of embodiments described herein. In embodiments, m is 0 or 1.

[000346] In embodiments, the substituents on the cyclohexyl moiety are *cis* to each other.

[000347] In embodiments, the substituents on the cyclohexyl moiety are *trans* to each other.

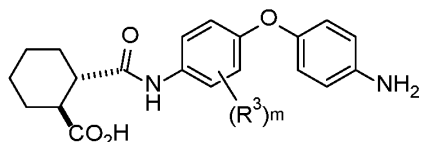
[000348] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other, e.g., according to Formula (I-G'),



(I-G'), or a pharmaceutically acceptable salt thereof,

wherein each of R^3 and m is independently according to any embodiment, or combination of embodiments described herein. In embodiments, m is 0 or 1.

[000349] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other, e.g., according to Formula (I-G''),

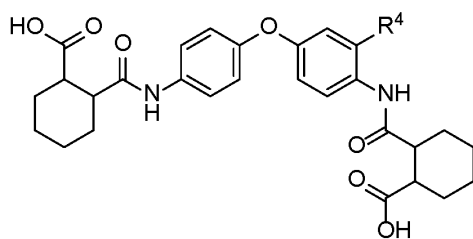


(I-G''), or a pharmaceutically acceptable salt thereof,

wherein each of R^3 and m is independently according to any embodiment, or combination of embodiments described herein. In embodiments, m is 0 or 1.

Formula (II)

[000350] In embodiments, a compound of Formula (I) has a structure according to Formula (II),



(II), or a pharmaceutically acceptable salt thereof,

wherein R^4 is according to any embodiment described herein. In embodiments, R^4 is C_2 - C_6 alkyl or benzyl.

[000351] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.

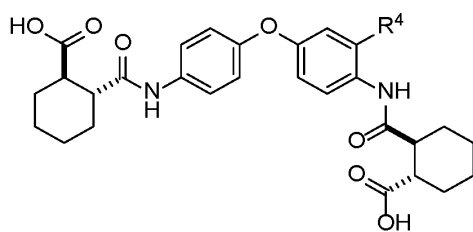
[000352] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.

[000353] In embodiments, a compound of Formula (II), or any subformulas thereof, comprises two *cis*-cyclohexyl groups.

[000354] In embodiments, a compound of Formula (II), or any subformulas thereof, comprises two *trans*-cyclohexyl groups.

[000355] In embodiments, a compound of Formula (II), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *cis*-cyclohexyl.

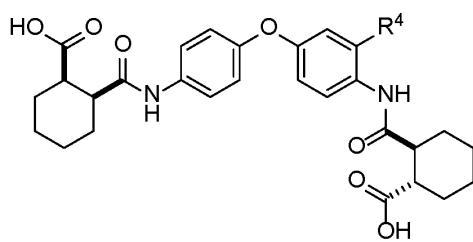
[000356] In embodiments, a compound of Formula (II) has a structure according to Formula (II-A),



(II-A), or a pharmaceutically acceptable salt thereof,

wherein R^4 is according to any embodiment described herein. In embodiments, R^4 is C_2 - C_6 alkyl or benzyl.

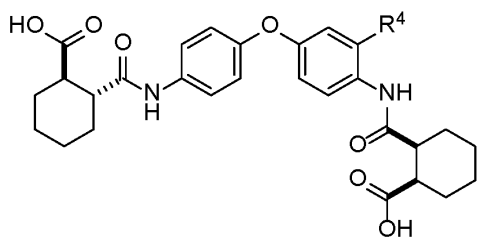
[000357] In embodiments, a compound of Formula (II) has a structure according to Formula (II-B),



(II-B), or a pharmaceutically acceptable salt thereof,

wherein R^4 is according to any embodiment described herein. In embodiments, R^4 is C_2 - C_6 alkyl or benzyl.

[000358] In embodiments, a compound of Formula (II) has a structure according to Formula (II-C),

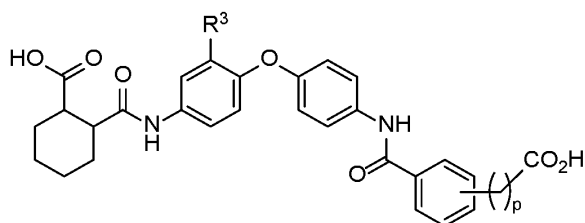


(II-C), or a pharmaceutically acceptable salt thereof,

wherein R^4 is according to any embodiment described herein. In embodiments, R^4 is C_2 - C_6 alkyl or benzyl.

Formula (III)

[000359] In embodiments, a compound of Formula (I) has a structure according to Formula (III),



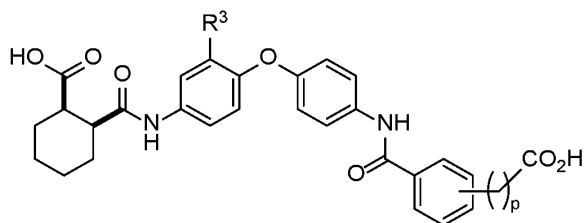
(III), or a pharmaceutically acceptable salt

thereof, wherein R^3 and p are each according to any embodiment described herein. In embodiments, R^3 is C_1 - C_6 alkyl, and p is 0 or 1.

[000360] In embodiments, a compound of Formula (III), or any subformulas thereof, comprises a *cis*-cyclohexyl group.

[000361] In embodiments, a compound of Formula (III), or any subformulas thereof, comprises a *trans*-cyclohexyl group.

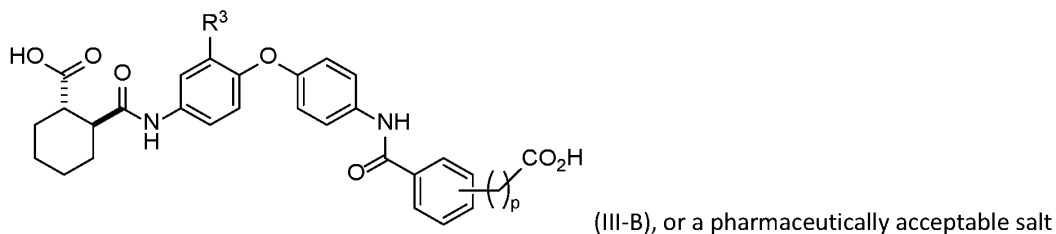
[000362] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other, e.g., a structure according to Formula (III-A),



(III-A), or a pharmaceutically acceptable salt

thereof, wherein R^3 and p are each according to any embodiment described herein. In embodiments, R^3 is C_1 - C_6 alkyl, and p is 0 or 1.

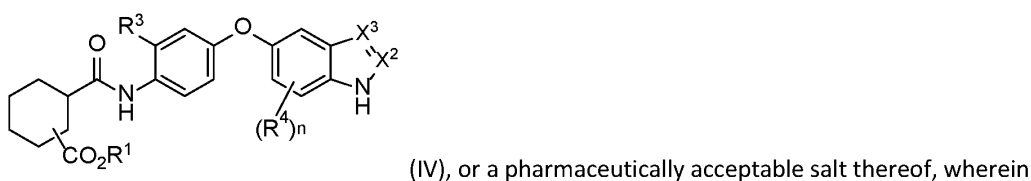
[000363] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other, e.g., a structure according to Formula (III-B),



thereof, wherein **R³** and **p** are each according to any embodiment described herein. In embodiments, **R³** is C₁-C₆ alkyl, and **p** is 0 or 1.

Formula (IV)

[000364] In embodiments, a compound of Formula (I) has a structure according to Formula (IV),

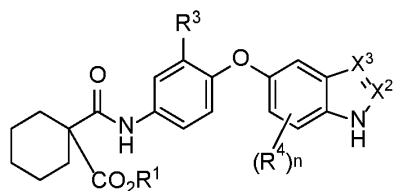


each of **R¹**, **R³**, **R⁴**, **X²**, **X³**, and **n** are each according to any embodiment described herein. In embodiments, **R¹** is H or C₁-C₆ alkyl, **R³** is H or C₁-C₆ alkyl optionally substituted by phenyl, **R⁴** is C₁-C₆ alkyl or benzyl, each of **X²** and **X³** is independently N or CH, and **n** is 0 or 1.

[000365] In embodiments, a compound of Formula (IV), or any subformulas thereof, comprises a *cis*-cyclohexyl group.

[000366] In embodiments, a compound of Formula (IV), or any subformulas thereof, comprises a *trans*-cyclohexyl group.

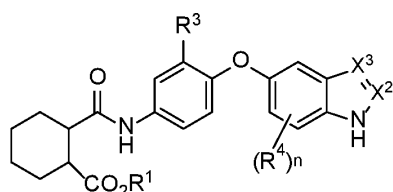
[000367] In embodiments, a compound of Formula (IV) has a structure according to Formula (IV-A),



(IV-A), or a pharmaceutically acceptable salt thereof, wherein

each of R^1 , R^3 , R^4 , X^2 , X^3 , and n are each according to any embodiment described herein. In embodiments, R^1 is H or C₁-C₆ alkyl, R^3 is H or C₁-C₆ alkyl optionally substituted by phenyl, R^4 is C₁-C₆ alkyl or benzyl, each of X^2 and X^3 is independently N or CH, and n is 0 or 1.

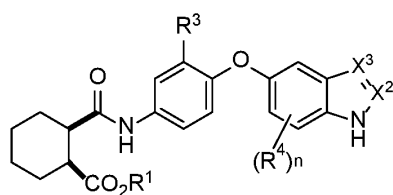
[000368] In embodiments, a compound of Formula (IV) has a structure according to Formula (IV-B),



(IV-B), or a pharmaceutically acceptable salt thereof, wherein

each of R^1 , R^3 , R^4 , X^2 , X^3 , and n are each according to any embodiment described herein. In embodiments, R^1 is H or C₁-C₆ alkyl, R^3 is H or C₁-C₆ alkyl optionally substituted by phenyl, R^4 is C₁-C₆ alkyl or benzyl, each of X^2 and X^3 is independently N or CH, and n is 0 or 1.

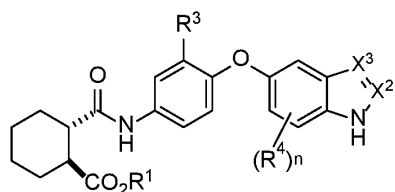
[000369] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other, e.g., a structure according to Formula (IV-B'),



(IV-B'), or a pharmaceutically acceptable salt thereof, wherein

each of R^1 , R^3 , R^4 , X^2 , X^3 , and n are each according to any embodiment described herein. In embodiments, R^1 is H or C₁-C₆ alkyl, R^3 is H or C₁-C₆ alkyl optionally substituted by phenyl, R^4 is C₁-C₆ alkyl or benzyl, each of X^2 and X^3 is independently N or CH, and n is 0 or 1.

[000370] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other, e.g., a structure according to Formula (IV-B''),

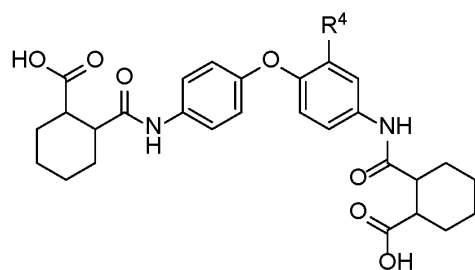


(IV-B''), or a pharmaceutically acceptable salt thereof, wherein

each of R^1 , R^3 , R^4 , X^2 , X^3 , and n are each according to any embodiment described herein. In embodiments, R^1 is H or C₁-C₆ alkyl, R^3 is H or C₁-C₆ alkyl optionally substituted by phenyl, R^4 is C₁-C₆ alkyl or benzyl, each of X^2 and X^3 is independently N or CH, and n is 0 or 1.

Formula (V)

[000371] In embodiments, a compound of Formula (I) has a structure according to Formula (V),



(V), or a pharmaceutically acceptable salt thereof,

wherein R^4 is according to any embodiment described herein. In embodiments, R^4 is C₁-C₆ alkyl or benzyl. In embodiments, R^4 is C₁-C₆ alkyl. In embodiments, R^4 is unsubstituted C₁-C₆ alkyl. In embodiments, R^4 is substituted C₁-C₆ alkyl. In embodiments, R^4 is benzyl.

[000372] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.

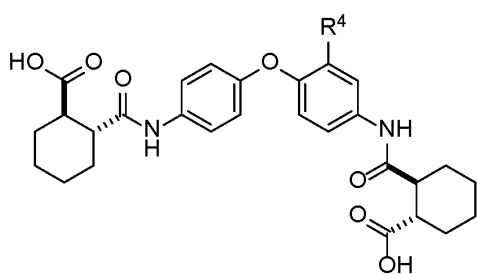
[000373] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.

[000374] In embodiments, the substituents on each cyclohexyl moiety are *cis* to each other.

[000375] In embodiments, the substituents on each cyclohexyl moiety are *trans* to each other.

[000376] In embodiments, the substituents on one cyclohexyl moiety are *trans* to each other, and the substituents on the other cyclohexyl moiety are *cis* to each other.

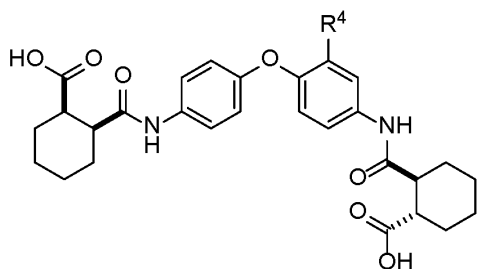
[000377] In embodiments, a compound of Formula (II) has a structure according to Formula (V-A),



(V-A), or a pharmaceutically acceptable salt thereof,

wherein R^4 is according to any embodiment described herein. In embodiments, R^4 is C_1 - C_6 alkyl or benzyl.

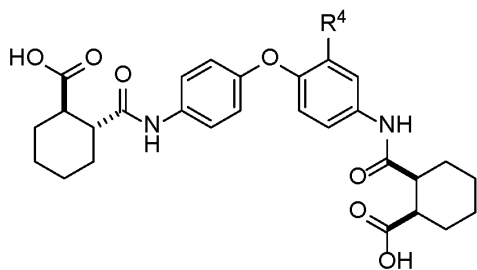
[000378] In embodiments, a compound of Formula (V) has a structure according to Formula (V-B),



(V-B), or a pharmaceutically acceptable salt thereof,

wherein R^4 is according to any embodiment described herein. In embodiments, R^4 is C_1 - C_6 alkyl or benzyl.

[000379] In embodiments, a compound of Formula (V) has a structure according to Formula (V-C),

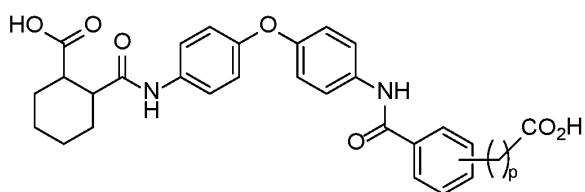


(V-C), or a pharmaceutically acceptable salt thereof,

wherein R^4 is according to any embodiment described herein. In embodiments, R^4 is C_1 - C_6 alkyl or benzyl.

Formula (VI)

[000380] In embodiments, a compound of Formula (I) has a structure according to Formula (VI),



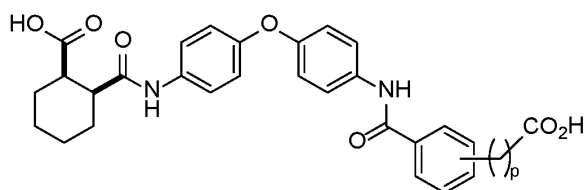
(VI), or a pharmaceutically acceptable salt

thereof, wherein p is according to any embodiment described herein. In embodiments, p is 0. In embodiments, p is 1.

[000381] In embodiments, a compound of Formula (VI), or any subformulas thereof, comprises a *cis*-cyclohexyl group.

[000382] In embodiments, a compound of Formula (VI), or any subformulas thereof, comprises a *trans*-cyclohexyl group.

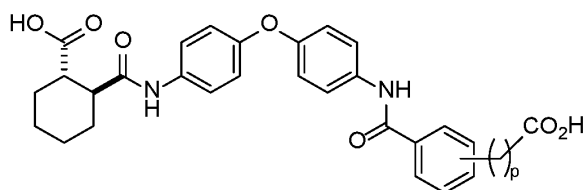
[000383] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other, e.g., a structure according to Formula (VI-A),



(VI-A), or a pharmaceutically acceptable salt

thereof, wherein p is according to any embodiment described herein. In embodiments, p is 0. In embodiments, p is 1.

[000384] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other, e.g., a structure according to Formula (VI-B),

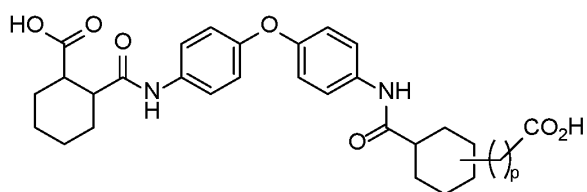


(VI-B), or a pharmaceutically acceptable salt

thereof, wherein p is according to any embodiment described herein. In embodiments, p is 0. In embodiments, p is 1.

Formula (VII)

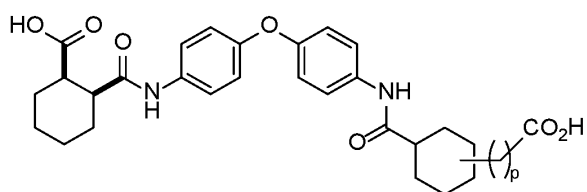
[000385] In embodiments, a compound of Formula (I) has a structure according to Formula (VII),



(VII), or a pharmaceutically acceptable salt

thereof, wherein **p** is according to any embodiment described herein. In embodiments, **p** is 0. In embodiments, **p** is 1.

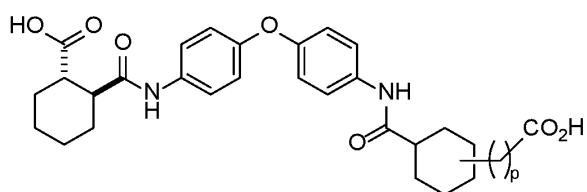
[000386] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other, e.g., a structure according to Formula (VII-A),



(VII-A), or a pharmaceutically acceptable

salt thereof, wherein **p** is according to any embodiment described herein. In embodiments, **p** is 0. In embodiments, **p** is 1.

[000387] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other, e.g., a structure according to Formula (VII-B),

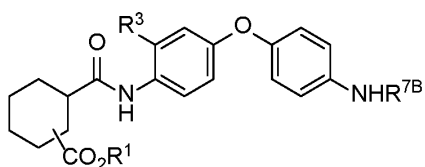


(VII-B), or a pharmaceutically acceptable salt

thereof, wherein **p** is according to any embodiment described herein. In embodiments, **p** is 0. In embodiments, **p** is 1.

Formula (VIII)

[000388] In embodiments, a compound of Formula (I) has a structure according to Formula (VIII),



(VIII), or a pharmaceutically acceptable salt thereof,

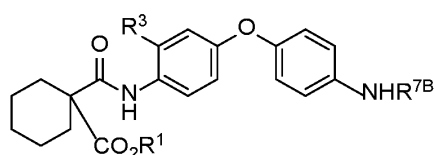
wherein each of **R¹**, **R³** and **R^{7B}** are each according to any embodiment described herein. In

embodiments, R^1 is H or C₁-C₆ alkyl, R^3 is H or C₁-C₆ alkyl optionally substituted by phenyl, and R^{7B} is H or C₁-C₆ alkyl.

[000389] In embodiments, a compound of Formula (VIII), or any subformulas thereof, comprises a *cis*-cyclohexyl group.

[000390] In embodiments, a compound of Formula (VIII), or any subformulas thereof, comprises a *trans*-cyclohexyl group.

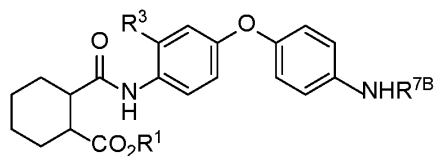
[000391] In embodiments, a compound of Formula (IV) has a structure according to Formula (VIII-A),



(VIII-A), or a pharmaceutically acceptable salt thereof,

wherein each of R^1 , R^3 and R^{7B} are each according to any embodiment described herein. In embodiments, R^1 is H or C₁-C₆ alkyl, R^3 is H or C₁-C₆ alkyl optionally substituted by phenyl, and R^{7B} is H or C₁-C₆ alkyl.

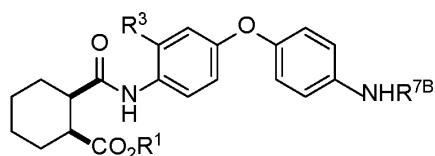
[000392] In embodiments, a compound of Formula (IV) has a structure according to Formula (VIII-B),



(VIII-B), or a pharmaceutically acceptable salt thereof,

wherein each of R^1 , R^3 and R^{7B} are each according to any embodiment described herein. In embodiments, R^1 is H or C₁-C₆ alkyl, R^3 is H or C₁-C₆ alkyl optionally substituted by phenyl, and R^{7B} is H or C₁-C₆ alkyl.

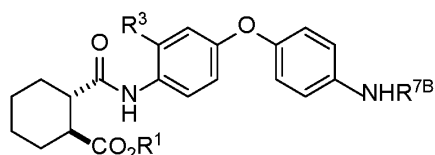
[000393] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other, e.g., a structure according to Formula (VIII-B'),



(VIII-B'), or a pharmaceutically acceptable salt thereof,

wherein each of R^1 , R^3 and R^{7B} are each according to any embodiment described herein. In embodiments, R^1 is H or C₁-C₆ alkyl, R^3 is H or C₁-C₆ alkyl optionally substituted by phenyl, and R^{7B} is H or C₁-C₆ alkyl.

[000394] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other, e.g., a structure according to Formula (VIII-B'),

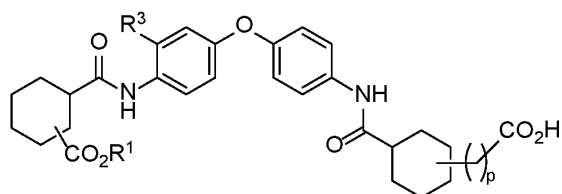


(VIII-B''), or a pharmaceutically acceptable salt thereof,

wherein each of R^1 , R^3 and R^{7B} are each according to any embodiment described herein. In embodiments, R^1 is H or C₁-C₆ alkyl, R^3 is H or C₁-C₆ alkyl optionally substituted by phenyl, and R^{7B} is H or C₁-C₆ alkyl.

Formula (IX)

[000395] In embodiments, a compound of Formula (I) has a structure according to Formula (IX),



(IX), or a pharmaceutically acceptable salt

thereof, wherein each of R^1 , R^3 and p are each according to any embodiment described herein. In embodiments, R^1 is H or C₁-C₆ alkyl, R^3 is C₂-C₆ alkyl optionally substituted by phenyl, and p is 0 or 1. In embodiments, R^1 is H, R^3 C₂-C₆ alkyl optionally substituted by phenyl, and p is 1.

[000396] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.

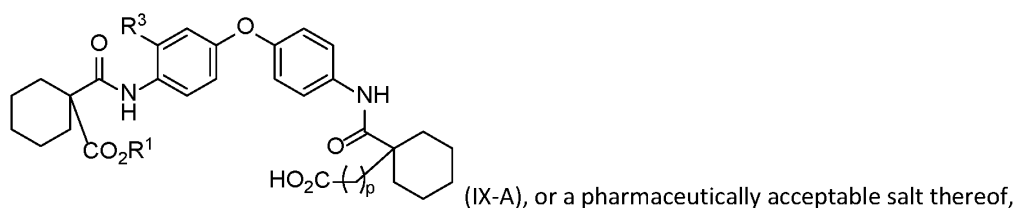
[000397] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.

[000398] In embodiments, a compound of Formula (IX), or any subformulas thereof, comprises two *cis*-cyclohexyl groups.

[000399] In embodiments, a compound of Formula (IX), or any subformulas thereof, comprises two *trans*-cyclohexyl groups.

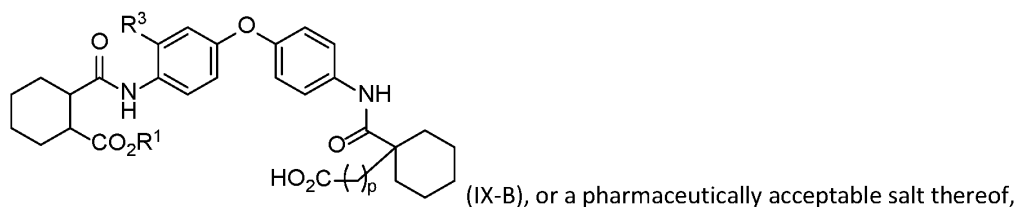
[000400] In embodiments, a compound of Formula (IX), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *cis*-cyclohexyl.

[000401] In embodiments, a compound of Formula (I) has a structure according to Formula (IX-A),



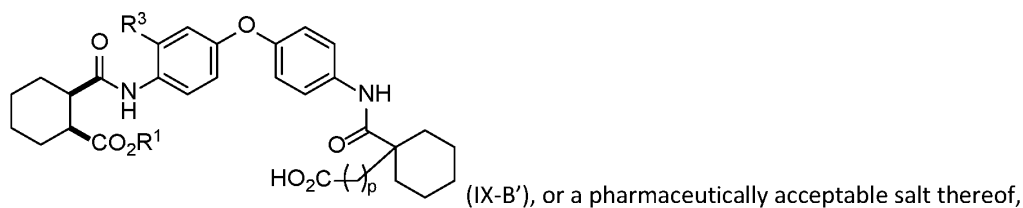
wherein each of R^1 , R^3 and p are each according to any embodiment described herein. In embodiments, R^1 is H or C₁-C₆ alkyl, R^3 is C₂-C₆ alkyl optionally substituted by phenyl, and p is 0 or 1. In embodiments, R^1 is H, R^3 C₂-C₆ alkyl optionally substituted by phenyl, and p is 1.

[000402] In embodiments, a compound of Formula (I) has a structure according to Formula (IX-B),



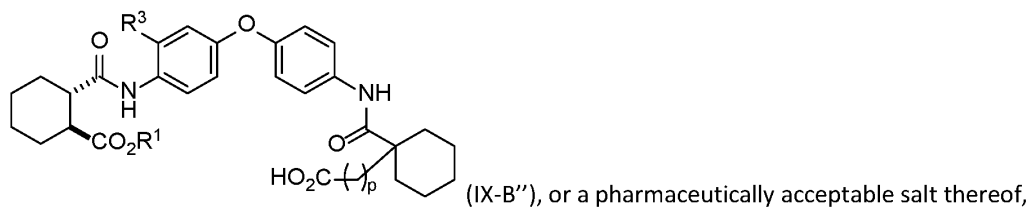
wherein each of R^1 , R^3 and p are each according to any embodiment described herein. In embodiments, R^1 is H or C₁-C₆ alkyl, R^3 is C₂-C₆ alkyl optionally substituted by phenyl, and p is 0 or 1. In embodiments, R^1 is H, R^3 C₂-C₆ alkyl optionally substituted by phenyl, and p is 1.

[000403] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other, e.g., a structure according to Formula (IX-B'),



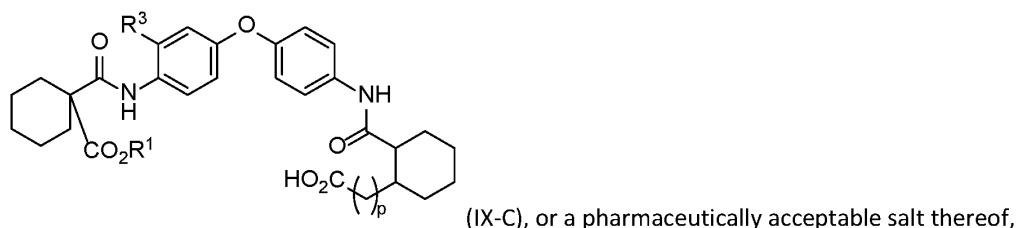
wherein each of R^1 , R^3 and R^{7B} are each according to any embodiment described herein. In embodiments, R^1 is H or C₁-C₆ alkyl, R^3 is C₂-C₆ alkyl optionally substituted by phenyl, and R^{7B} is H or C₁-C₆ alkyl.

[000404] In embodiments, substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other, e.g., a structure according to Formula (IX-B''),



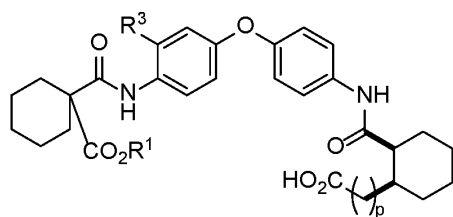
wherein each of R^1 , R^3 and R^{7B} are each according to any embodiment described herein. In embodiments, R^1 is H or C₁-C₆ alkyl, R^3 is C₂-C₆ alkyl optionally substituted by phenyl, and R^{7B} is H or C₁-C₆ alkyl.

[000405] In embodiments, a compound of Formula (I) has a structure according to Formula (IX-C),



wherein each of R^1 , R^3 and p are each according to any embodiment described herein. In embodiments, R^1 is H or C₁-C₆ alkyl, R^3 is C₂-C₆ alkyl optionally substituted by phenyl, and p is 0 or 1. In embodiments, R^1 is H, R^3 is C₂-C₆ alkyl optionally substituted by phenyl, and p is 1.

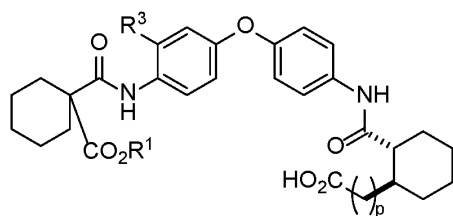
[000406] In embodiments, a compound of Formula (I) has a structure according to Formula (IX-C'),



(IX-C'), or a pharmaceutically acceptable salt thereof,

wherein each of R^1 , R^3 and p are each according to any embodiment described herein. In embodiments, R^1 is H or C_1 - C_6 alkyl, R^3 is C_2 - C_6 alkyl optionally substituted by phenyl, and p is 0 or 1. In embodiments, R^1 is H, R^3 is C_2 - C_6 alkyl optionally substituted by phenyl, and p is 1.

[000407] In embodiments, a compound of Formula (I) has a structure according to Formula (IX-C'),

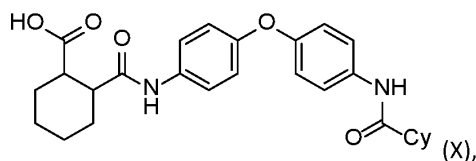


(IX-C''), or a pharmaceutically acceptable salt thereof,

wherein each of R^1 , R^3 and p are each according to any embodiment described herein. In embodiments, R^1 is H or C_1 - C_6 alkyl, R^3 is C_2 - C_6 alkyl optionally substituted by phenyl, and p is 0 or 1. In embodiments, R^1 is H, R^3 is C_2 - C_6 alkyl optionally substituted by phenyl, and p is 1.

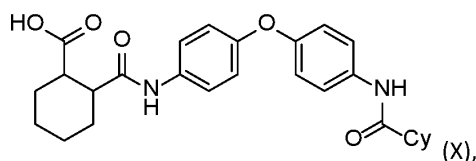
Formula (X)

[000408] In another aspect, the present invention provides a compound having a structure according to Formula (X),



or a pharmaceutically acceptable salt thereof, wherein **Cy** is independently C_5 - C_{10} cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl.

[000409] In another aspect, the present invention provides a compound having a structure according to Formula (X),



or a pharmaceutically acceptable salt thereof, wherein **Cy** is independently C₅-C₇ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl.

[000410] In embodiments, non-hydrogen groups on different carbons of the cyclohexyl moiety substituted by -CO₂H in Formula (X) are *cis* to each other (also referred to as a “*cis*-cyclohexyl”).

[000411] In embodiments, non-hydrogen groups on different carbons of the cyclohexyl moiety substituted by -CO₂H in Formula (X) are *trans* to each other (also referred to as a “*trans*-cyclohexyl”).

[000412] In embodiments where **Cy** is C₅-C₁₀ cycloalkyl (e.g., a cyclohexyl, a cyclopentyl, or a decahydronaphthalenyl) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of on a **Cy** moiety are *cis* to each other (also referred to as a “*cis*-**Cy**”).

[000413] In embodiments where **Cy** is C₅-C₇ cycloalkyl (e.g., a cyclohexyl or a cyclopentyl) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of on a **Cy** moiety are *cis* to each other (also referred to as a “*cis*-**Cy**”).

[000414] In embodiments where **Cy** is C₅-C₁₀ cycloalkyl (e.g., a cyclohexyl, a cyclopentyl, or a decahydronaphthalenyl) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of a **Cy** moiety are *trans* to each other (also referred to as a “*trans*-**Cy**”).

[000415] In embodiments where **Cy** is C₅-C₇ cycloalkyl (e.g., a cyclohexyl or a cyclopentyl) or 5- to 7-membered heterocyclyl, non-hydrogen groups on different carbons of a **Cy** moiety are *trans* to each other (also referred to as a “*trans*-**Cy**”).

[000416] In embodiments, a compound of Formula (X), or any subformulas thereof, comprises a *cis*-cyclohexyl and a *cis*-**Cy** (e.g., a *cis*-cyclohexyl, a *cis*-cyclopentyl, or a *cis*-decahydronaphthalenyl).

[000417] In embodiments, a compound of Formula (X), or any subformulas thereof, comprises a *cis*-cyclohexyl and a *cis*-**Cy** (e.g., a *cis*-cyclohexyl or a *cis*-cyclopentyl).

[000418] In embodiments, a compound of Formula (X), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *trans*-**Cy** (e.g., a *trans*-cyclohexyl, a *trans*-cyclopentyl, or a *trans*-decahydronaphthalenyl).

[000419] In embodiments, a compound of Formula (X), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *trans*-**Cy** (e.g., a *trans*-cyclohexyl or a *trans*-cyclopentyl).

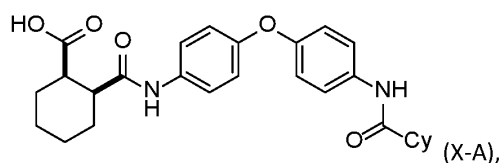
[000420] In embodiments, a compound of Formula (X), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *cis*-**Cy** (e.g., a *cis*-cyclohexyl, a *cis*-cyclopentyl, or a *cis*-decahydronaphthalenyl).

[000421] In embodiments, a compound of Formula (X), or any subformulas thereof, comprises a *trans*-cyclohexyl and a *cis*-**Cy** (e.g., a *cis*-cyclohexyl or a *cis*-cyclopentyl).

[000422] In embodiments, a compound of Formula (X), or any subformulas thereof, comprises a *cis*-cyclohexyl and a *trans*-**Cy** (e.g., a *trans*-cyclohexyl, a *trans*-cyclopentyl, or a *trans*-decahydronaphthalenyl).

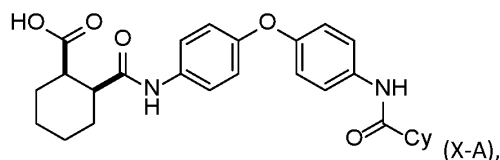
[000423] In embodiments, a compound of Formula (X), or any subformulas thereof, comprises a *cis*-cyclohexyl and a *trans*-**Cy** (e.g., a *trans*-cyclohexyl or a *trans*-cyclopentyl).

[000424] In another aspect, the present invention provides a compound having a structure according to Formula (X-A),



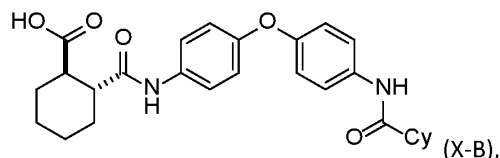
or a pharmaceutically acceptable salt thereof, wherein **Cy** is independently C₅-C₁₀ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl.

[000425] In another aspect, the present invention provides a compound having a structure according to Formula (X-A),



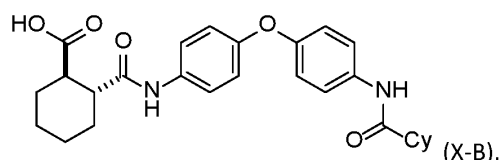
or a pharmaceutically acceptable salt thereof, wherein **Cy** is independently C₅-C₇ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl.

[000426] In another aspect, the present invention provides a compound having a structure according to Formula (X-B),



or a pharmaceutically acceptable salt thereof, wherein **Cy** is independently C₅-C₁₀ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl.

[000427] In another aspect, the present invention provides a compound having a structure according to Formula (X-B),



or a pharmaceutically acceptable salt thereof, wherein **Cy** is independently C₅-C₇ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl.

[000428] Similarly, the invention also features pharmaceutically acceptable salts of compounds described herein, including pharmaceutically acceptable salts (e.g., sodium salts) of any Compound described. In embodiments, a pharmaceutically acceptable salt is a mono-sodium salt (e.g., of a mono-acid or a di-acid described herein). In embodiments, a pharmaceutically acceptable salt is a di-sodium salt (e.g., of a di-acid described herein).

Exemplary Compounds

[000429] Exemplary compounds include those described throughout the present disclosure, as well as any pharmaceutically acceptable form thereof (e.g., a pharmaceutically acceptable salt thereof), including certain specifically-described compounds.

[000430] For example, non-limiting compounds of the invention include those of **Table 1**, as well as any pharmaceutically acceptable form thereof (e.g., a pharmaceutically acceptable salt thereof). Compounds of the invention include diastereomers of illustrative structures unless otherwise noted. Exemplary diastereomers of certain of Compounds (1)-(36) are also provided in **Table 1**. Similarly, the invention also features pharmaceutically acceptable salts of compounds described herein,

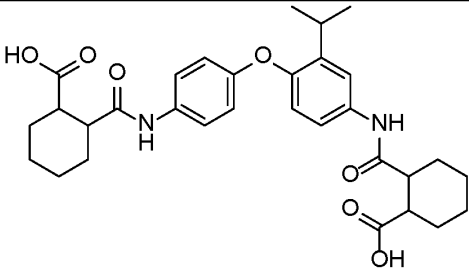
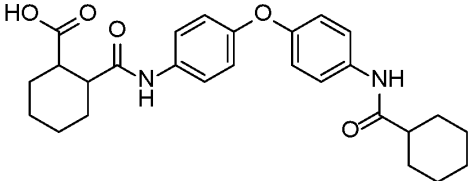
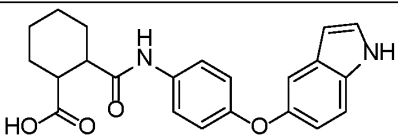
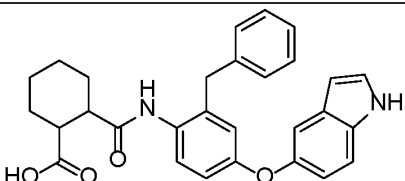
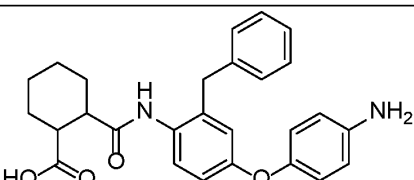
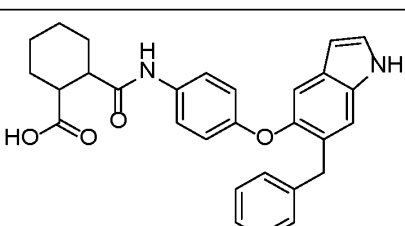
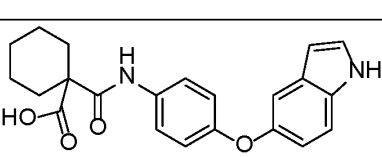
including pharmaceutically acceptable salts (e.g., sodium salts) of any Compound described in **Table 1**.

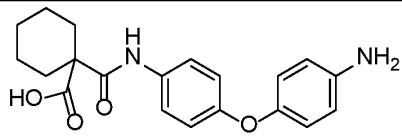
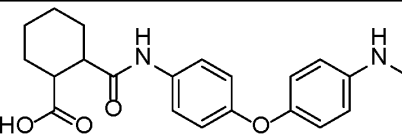
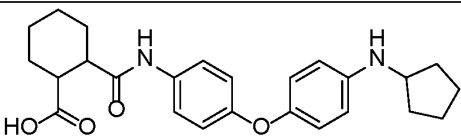
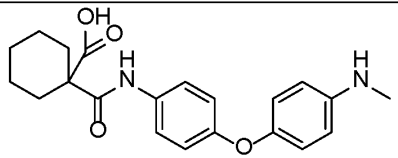
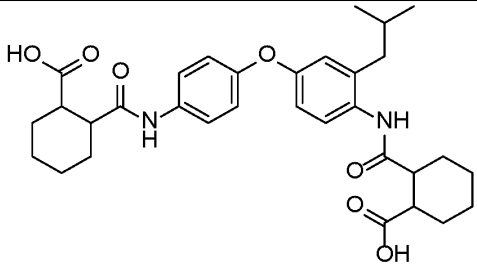
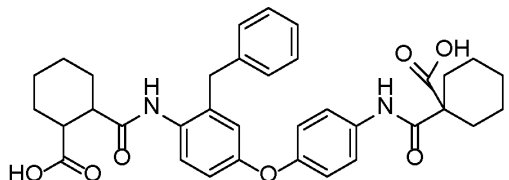
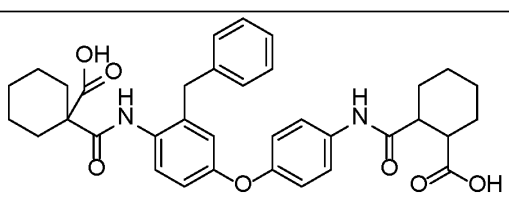
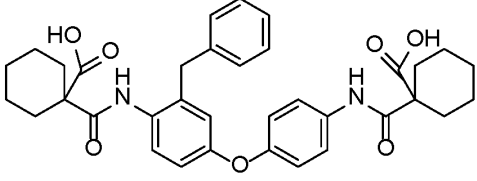
[000431] Additionally, if stereochemistry is not indicated, it is understood that the formula encompasses all permitted stereoisomers (e.g., enantiomers and diastereomers). As described elsewhere herein, non-hydrogen substituents on different carbon atoms of a ring (e.g., a cyclohexyl, a cyclopentyl, or a decahydronaphthalenyl) are understood to be *cis*- or *trans*- relative to each other, with certain non-limiting embodiments also identified in **Table 1**.

Table 1

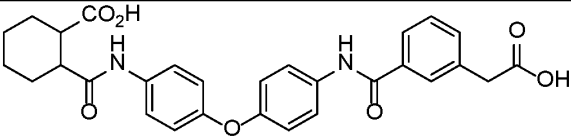
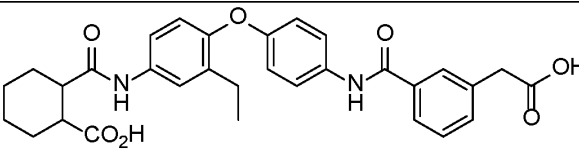
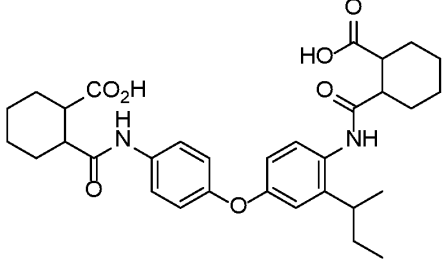
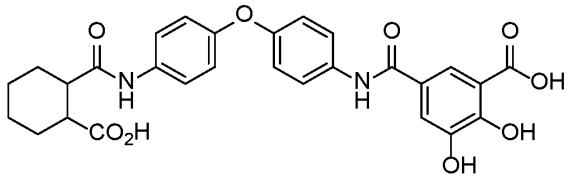
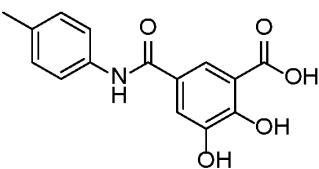
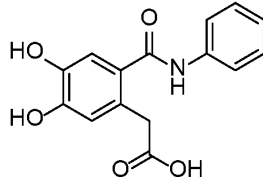
Name	Compound No.	Structure
M13(2)20 or M13B	(1)	
	<i>cis</i> -(1)	
	<i>cis</i> -(1)-disodium salt	
M13(2)2	(2)	

Name	Compound No.	Structure
M13(1)23	(3)	
M13	(4)	
M13(2)9 or M13A	(5)	
M13(1)7	(6)	
M13(1)12	(7)	
M13(1)15	(8)	

Name	Compound No.	Structure
M13(2)1	(9)	
M13(2)7	(10)	
M13(2)9-129	(11)	
M13(2)9-18	(12)	
M13(2)9-12	(13)	
M13(2)9-89	(14)	
M13(2)9-28	(15)	

Name	Compound No.	Structure
M13(2)9-6I	(16)	
M13(2)9G	(17)	
M13(2)9H	(18)	
M13(2)9I	(19)	
M13(2)20A	(20)	
M13(2)20B	(21)	
M13(2)20C	(22)	
M13(2)20D	(23)	

Name	Compound No.	Structure
M13(2)20E	(24)	
M13(2)20F	(25)	
M920D	(26)	
M920E	(27)	
M920F	(28)	
M13(1)1	(29)	
M13(1)2	(30)	

Name	Compound No.	Structure
M13(1)4	(31)	
M13(1)35	(32)	
M13(2)4	(33)	
M13(2)12	(34)	
M13(2)13	(35)	
M13(2)15	(36)	

[000432] In embodiments, a compound is Compound (1) (e.g., Compound *cis*-(1)), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (1) (e.g., Compound *cis*-(1)). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (1) (e.g., a sodium salt of Compound (1) such as a monosodium or a disodium salt of Compound (1)). In embodiments, a compound is a pharmaceutically acceptable salt of Compound *cis*-(1) (e.g., a sodium salt of Compound *cis*-(1) such as a monosodium or a disodium salt of Compound *cis*-(1)).

[000433] In embodiments, a compound is Compound (2), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (2). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (2) (e.g., a sodium salt of Compound (2) such as a monosodium or a disodium salt of Compound (2)).

[000434] In embodiments, a compound is Compound (3), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (3). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (3) (e.g., a sodium salt of Compound (3) such as a monosodium or a disodium salt of Compound (3)).

[000435] In embodiments, a compound is Compound (4), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (4). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (4) (e.g., a sodium salt of Compound (4) such as a monosodium or a disodium salt of Compound (4)).

[000436] In embodiments, a compound is Compound (5), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (5). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (5) (e.g., a sodium salt of Compound (5) such as a monosodium or a disodium salt of Compound (5)).

[000437] In embodiments, a compound is Compound (6), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (6). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (6) (e.g., a sodium salt of Compound (6) such as a monosodium or a disodium salt of Compound (6)).

[000438] In embodiments, a compound is Compound (7), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (7). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (7) (e.g., a sodium salt of Compound (7) such as a monosodium or a disodium salt of Compound (7)).

[000439] In embodiments, a compound is Compound (8), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (8). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (8) (e.g., a sodium salt of Compound (8) such as a monosodium or a disodium salt of Compound (8)).

[000440] In embodiments, a compound is Compound (9), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (9). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (9) (e.g., a sodium salt of Compound (9) such as a monosodium or a disodium salt of Compound (9)).

[000441] In embodiments, a compound is Compound (10), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (10). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (10) (e.g., a sodium salt of Compound (10) such as a monosodium or a disodium salt of Compound (10)).

[000442] In embodiments, a compound is Compound (11), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (11). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (11) (e.g., a sodium salt of Compound (11) such as a monosodium salt of Compound (11)).

[000443] In embodiments, a compound is Compound (12), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (12). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (12) (e.g., a sodium salt of Compound (12) such as a monosodium salt of Compound (12)).

[000444] In embodiments, a compound is Compound (13), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (13). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (13) (e.g., a sodium salt of Compound (13) such as a monosodium salt of Compound (13)).

[000445] In embodiments, a compound is Compound (14), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (14). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (14) (e.g., a sodium salt of Compound (14) such as a monosodium salt of Compound (14)).

[000446] In embodiments, a compound is Compound (15), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (15). In embodiments, a compound is a

pharmaceutically acceptable salt of Compound (15) (e.g., a sodium salt of Compound (15) such as a monosodium salt of Compound (15)).

[000447] In embodiments, a compound is Compound (16), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (16). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (16) (e.g., a sodium salt of Compound (16) such as a monosodium salt of Compound (16)).

[000448] In embodiments, a compound is Compound (17), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (17). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (16) (e.g., a sodium salt of Compound (17) such as a monosodium salt of Compound (17)).

[000449] In embodiments, a compound is Compound (18), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (18). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (18) (e.g., a sodium salt of Compound (18) such as a monosodium salt of Compound (18)).

[000450] In embodiments, a compound is Compound (19), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (19). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (19) (e.g., a sodium salt of Compound (19) such as a monosodium salt of Compound (19)).

[000451] In embodiments, a compound is Compound (20), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (20). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (20) (e.g., a sodium salt of Compound (20) such as a monosodium or a disodium salt of Compound (20)).

[000452] In embodiments, a compound is Compound (21), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (21). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (21) (e.g., a sodium salt of Compound (21) such as a monosodium or a disodium salt of Compound (21)).

[000453] In embodiments, a compound is Compound (22), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (22). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (22) (e.g., a sodium salt of Compound (22) such as a monosodium or a disodium salt of Compound (22)).

[000454] In embodiments, a compound is Compound (23), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (23). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (23) (e.g., a sodium salt of Compound (23) such as a monosodium or a disodium salt of Compound (23)).

[000455] In embodiments, a compound is Compound (24), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (24). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (24) (e.g., a sodium salt of Compound (24) such as a monosodium or a disodium salt of Compound (24)).

[000456] In embodiments, a compound is Compound (25), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (25). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (25) (e.g., a sodium salt of Compound (25) such as a monosodium or a disodium salt of Compound (25)).

[000457] In embodiments, a compound is Compound (26), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (26). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (26) (e.g., a sodium salt of Compound (26) such as a monosodium or a disodium salt of Compound (26)).

[000458] In embodiments, a compound is Compound (27), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (27). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (27) (e.g., a sodium salt of Compound (27) such as a monosodium or a disodium salt of Compound (27)).

[000459] In embodiments, a compound is Compound (28), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (28). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (28) (e.g., a sodium salt of Compound (28) such as a monosodium salt of Compound (28)).

[000460] In embodiments, a compound is Compound (29), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (29). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (29) (e.g., a sodium salt of Compound (29) such as a monosodium or a disodium salt of Compound (29)).

[000461] In embodiments, a compound is Compound (30), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (30). In embodiments, a compound is a

pharmaceutically acceptable salt of Compound (30) (e.g., a sodium salt of Compound (30) such as a monosodium or a disodium salt of Compound (30)).

[000462] In embodiments, a compound is Compound (31), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (31). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (31) (e.g., a sodium salt of Compound (31) such as a monosodium or a disodium salt of Compound (31)).

[000463] In embodiments, a compound is Compound (32), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (32). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (32) (e.g., a sodium salt of Compound (32) such as a monosodium or a disodium salt of Compound (32)).

[000464] In embodiments, a compound is Compound (33), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (33). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (33) (e.g., a sodium salt of Compound (33) such as a monosodium or a disodium salt of Compound (33)).

[000465] In embodiments, a compound is Compound (34), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (34). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (34) (e.g., a sodium salt of Compound (34) such as a monosodium or a disodium salt of Compound (34)).

[000466] In embodiments, a compound is Compound (35), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (35). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (35) (e.g., a sodium salt of Compound (35) such as a monosodium salt of Compound (35)).

[000467] In embodiments, a compound is Compound (36), or a pharmaceutically acceptable salt thereof. In embodiments, a compound is Compound (36). In embodiments, a compound is a pharmaceutically acceptable salt of Compound (36) (e.g., a sodium salt of Compound (36) such as a monosodium salt of Compound (36)).

Synthetic Methods

[000468] Compounds described herein can be prepared according to methods known in the art. Accordingly, disclosed compounds can generally be synthesized by an appropriate combination of generally well-known synthetic methods and radiosynthesis systems. Techniques useful in

synthesizing these chemical entities are both readily apparent and accessible to those of skill in the relevant art, based on the instant disclosure. Many of the optionally substituted starting compounds and other reactants are commercially available, e.g., from Aldrich Chemical Company (Milwaukee, Wis.) or can be readily prepared by those skilled in the art using commonly employed synthetic methodology.

[000469] For example, the exemplary synthetic methods described in the instant Examples can be used to prepare still other compounds of the invention.

Pharmaceutical Compositions

[000470] In another aspect, the invention features compositions comprising any compound described herein, or any pharmaceutically acceptable form thereof (e.g., any pharmaceutically acceptable salt thereof).

[000471] In one aspect, the invention features a pharmaceutical composition comprising (1) compound or pharmaceutically acceptable salt thereof as described herein (e.g., a compound according to any one of Formulas A (e.g., Formulas (I)-(X)) and (B) such as the compounds of Table 1 (including any one of Compounds (1)-(36)) and pharmaceutically acceptable salts thereof). In embodiments, a pharmaceutical composition further comprises (2) a pharmaceutically acceptable excipient.

[000472] In embodiments, a composition is a pharmaceutical composition.

[000473] In embodiments, a pharmaceutically acceptable form of a compound includes any pharmaceutically acceptable salts, hydrates, solvates, isomers, prodrugs, and isotopically labeled derivatives thereof.

[000474] In embodiments, a pharmaceutical composition comprises any compound described herein, or a pharmaceutically acceptable form thereof (e.g., a pharmaceutically acceptable salt thereof).

[000475] In embodiments, the invention features a pharmaceutically acceptable salt of a compound described herein, including for use in the compositions and methods described herein. Examples of such salts are acid addition salts formed with inorganic acids, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and the like. Salts may also be formed with organic acids such as, for example, acetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid, benzoic acid, tannic acid,

pamoic acid, alginic acid, polyglutamic acid, and the like. Salts formed from a cationic material may utilize the conjugate base of these inorganic and organic acids. Salts may also be formed with polyvalent metal cations such as zinc, calcium, bismuth, barium, magnesium, aluminum, copper, cobalt, nickel and the like or with an organic cation formed from N,N'-dibenzylethylenediamine or ethylenediamine, or combinations thereof (e.g., a zinc tannate salt). The non-toxic, physiologically acceptable salts are preferred.

[000476] The salts can be formed by conventional means such as by reacting the free acid or free base forms of the product with one or more equivalents of the appropriate acid or base in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is then removed in vacuo or by freeze-drying, or by exchanging the cations of an existing salt for another cation on a suitable ion exchange resin.

[000477] Compounds described herein and any pharmaceutically acceptable form thereof, may be formulated in pharmaceutical compositions. Such a pharmaceutical composition may be provided in a form suitable for administration to a subject, and may comprise one or more pharmaceutically acceptable carriers, one or more additional ingredients, or some combination of these. Accordingly, in embodiments, a compound or any pharmaceutically acceptable form thereof (e.g., any pharmaceutically acceptable salt thereof) described herein may be formulated for pharmaceutical use. In embodiments, pharmaceutically acceptable compositions comprise a therapeutically effective amount of one or more compounds described herein, or any pharmaceutically acceptable form thereof (e.g., a pharmaceutically acceptable salt), in any of the preceding embodiments, taken alone or formulated together with one or more pharmaceutically acceptable carriers (additives), excipient and/or diluents.

[000478] Pharmaceutical compositions that are useful in the methods of the invention may be suitably developed for inhalational, oral, rectal, vaginal, parenteral, topical, transdermal, pulmonary, intranasal, buccal, ophthalmic, intrathecal, transdermal, nasal, inhalation, endotrache, intravenous, subcutaneous, intramuscular, epidural injection, or another route of administration.

[000479] In embodiments, a pharmaceutical composition may be specially formulated for administration in solid or liquid form, e.g., drenches (aqueous or non-aqueous solutions or suspensions), tablets, sterile solutions, suspensions, sustained-release formulations, cream, ointment, controlled-release patch or spray.

[000480] In embodiments, the compositions of the invention are formulated using one or more pharmaceutically acceptable excipients or carriers. In one embodiment, the pharmaceutical compositions of the invention comprise a therapeutically effective amount of at least one compound of the invention, or any pharmaceutically acceptable form thereof (e.g., a pharmaceutically acceptable salt thereof) and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers, which are useful, include, but are not limited to, glycerol, water, saline, ethanol and other pharmaceutically acceptable salt solutions such as phosphates and salts of organic acids. Examples of these and other pharmaceutically acceptable carriers are described in Remington's Pharmaceutical Sciences (1991, Mack Publication Co., New Jersey), the entire disclosure of which is incorporated by reference herein for all purposes.

[000481] For the purposes of the present invention the term "excipient" and "carrier" are used interchangeably throughout the description of the present invention and said terms are defined herein as, "ingredients which are used in the practice of formulating a safe and effective pharmaceutical composition." "Pharmaceutically acceptable excipients and carriers" refer to any substance that is acceptable for use in pharmaceutical applications from a toxicological perspective and does not adversely interact with the active ingredient. Accordingly, pharmaceutically acceptable carriers are those that are compatible with the other ingredients in the composition and are biologically acceptable.

[000482] The formulator will understand that excipients are used primarily to serve in delivering a safe, stable, and functional pharmaceutical, serving not only as part of the overall vehicle for delivery but also as a means for achieving effective absorption by the recipient of the active ingredient. An excipient may fill a role as simple and direct as being an inert filler, or an excipient as used herein may be part of a pH stabilizing system or coating to insure delivery of the ingredients safely to the stomach. The formulator can also take advantage of the fact that the compounds of the present invention have improved cellular potency, pharmacokinetic properties, as well as improved oral bioavailability.

[000483] The formulations of the pharmaceutical compositions described herein may be prepared by any method known or hereafter developed in the art of pharmacology. In general, such preparatory methods include the step of bringing the active ingredient into association with a carrier or one or more other accessory ingredients, and then, if necessary or desirable, shaping or packaging the product into a desired single- or multi-dose unit.

[000484] To increase the effectiveness of compounds of the present teachings, it can be desirable to combine a compound with other agents effective in the treatment of the target disease. For example, other active compounds (i.e., other active ingredients or agents) effective in treating the target disease can be administered with compounds of the present teachings. The other agents can be administered at the same time or at different times than the compounds disclosed herein.

Kits and Packages

[000485] In another aspect, the present disclosure provides kits and commercial packages comprising one or more compounds described herein, or any pharmaceutically acceptable forms thereof (e.g., any pharmaceutically acceptable salts thereof), or pharmaceutical composition as described herein.

[000486] In embodiments, provided herein are kits. The kits can include a compound or pharmaceutically acceptable form thereof, or pharmaceutical composition as described herein, in suitable packaging, and written material that can include instructions for use, discussion of clinical studies, listing of side effects, and the like.

[000487] Kits are well suited for the delivery of solid oral dosage forms such as tablets or capsules. Such kits can also include information, such as scientific literature references, package insert materials, clinical trial results, and/or summaries of these and the like, which indicate or establish the activities and/or advantages of the pharmaceutical composition, and/or which describe dosing, administration, side effects, drug interactions, or other information useful to the health care provider. Such information can be based on the results of various studies, for example, studies using experimental animals involving in vivo models and studies based on human clinical trials.

Therapeutic Methods

[000488] Compounds of the present can be useful for the treatment or inhibition of a pathological condition or disorder in a mammal, for example, a human subject. The present teachings accordingly provide methods of treating or inhibiting a pathological condition or disorder by providing to a mammal a compound of the present teachings (including its pharmaceutically acceptable forms such as any pharmaceutically acceptable salt) or a pharmaceutical composition that includes one or more compounds of the present teachings in combination or association with pharmaceutically acceptable carriers. Compounds of the present teachings can be administered alone or in combination with other therapeutically effective compounds or therapies for the treatment or inhibition of the pathological condition or disorder.

[000489] Specifically, compounds described herein can effectively modulate Mas and MrgD receptors and are suitable for treating and preventing any diseases and disorders that benefit from modulation of these receptors. For example, compounds described herein can be effective in treating and preventing diseases and disorders that also benefit from Angiotensin-(1-7) therapy, which likewise binds to and modulates these receptors.

[000490] In accordance with the present disclosure, compounds described herein as well as any pharmaceutically acceptable forms thereof, or any pharmaceutical composition thereof, are used for treating diseases and/or disorders that are associated with modulation of Mas and MrgD receptors, such as those described herein.

[000491] In various embodiments, a compound or pharmaceutically acceptable salt thereof described herein is administered at a therapeutically effective amount. Generally, a therapeutically effective amount is sufficient to achieve a meaningful benefit to the subject (e.g., treating, modulating, curing, preventing and/or ameliorating the underlying disease or condition). In some particular embodiments, appropriate doses or amounts to be administered may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

Monotherapy and Combination Therapies

[000492] In embodiments, a compound described herein, or a pharmaceutically acceptable form thereof (e.g., a pharmaceutically acceptable salt thereof), or any pharmaceutical composition thereof, is administered as a monotherapy.

[000493] In embodiments, a compound described herein, or a pharmaceutically acceptable form thereof (e.g., a pharmaceutically acceptable salt thereof), or any pharmaceutical composition thereof, is administered in combination with one or more therapeutic agents (e.g., a second therapeutic agent) such as one or more antiviral agents and/or one or more immune modulators.

[000494] The term “in combination” means either a co-therapy or combination therapy, or a co-formulation in a single pharmaceutical form, or in a single commercial package, for example a kit or a blister of two or more active ingredients.

[000495] In embodiments, two or more compositions are administered simultaneously, sequentially, or at an interval period of time. In embodiments, one or more pharmaceutical compositions are administered simultaneously. In some cases, one or more pharmaceutical compositions are administered sequentially. In additional cases, one or more pharmaceutical

compositions are administered at an interval period of time (e.g., the first administration of a first pharmaceutical composition is on day one followed by an interval of at least 1, 2, 3, 4, 5, or more days prior to the administration of at least a second pharmaceutical composition.

[000496] Exemplary therapies that may be used in combination with one or more compounds described herein as a combination therapy include, but are not limited to, thrombolytic compounds, antioxidants or other reactive oxygen species agents, interferon beta-1a (e.g. Avonex, Rebif, CinnoVex, ReciGen), interferon beta-1b (Betaseron), glatiramer acetate (Copaxone), mitoxantrone (Novantrone), natalizumab (Tysabri), fingolimod (Gilenya), the first oral drug available, and Teriflunomide (Aubagio), or combinations thereof. In embodiments, combination therapy comprises administration of a therapeutic selected from: prednisolone or methyl-prednisolone; a PD1 inhibitors; a β blocker; a steroid, a tyrosine kinase inhibitor (e.g., axitinib or sunitinib), an anti-VEGF compound (e.g., bevacizumab), or a genetic therapy (e.g., genetic therapies for Duchenne Muscular Dystrophy such as viltolarsen).

Exemplary Indications

[000497] Compounds and pharmaceutically acceptable salts thereof described herein can be effective for treating the following exemplary, non-limiting diseases and disorders that benefit from modulation of Mas and/or MrgD receptors in a subject in need thereof.

[000498] In embodiments, a modulator of Mas and/or MrgD receptors is an agonist of the receptor(s).

[000499] In embodiments, a modulator of Mas and/or MrgD receptors is an activator of the receptor(s).

[000500] In one aspect, the invention features a method of treating a disease or disorder comprising administering to a subject in need thereof any compound or pharmaceutically acceptable salt thereof as described herein (e.g., a compound according to any one of Formulas (A) (e.g., Formulas (I)-(X)) and B such as the compounds of Table 1 (including any one of Compounds (1)-(36)) and pharmaceutically acceptable salts thereof).

[000501] In embodiments, a disease or disorder is one that benefits from modulation of Mas or MrgD receptors. In embodiments, a disease or disorder is cancer, cardiomyopathy, cardiovascular disease (e.g., stroke), renal disease (e.g., renal dysfunction), inflammation, a metabolic disease or disorder (e.g., diabetes), preeclampsia, peripheral vascular disease, fibrotic disease, endothelial

disease, hemorrhagic fever, malaria, muscular dystrophy, Marfan syndrome, radiation sickness, or sarcopenia. In embodiments, a disease or disorder is, heart failure, stroke, atherosclerosis, pulmonary fibrosis, and aortic aneurysm. In embodiments, a disease or disorder is stroke.

[000502] In one aspect, the invention features a method of modulating glucose metabolism comprising administering to a subject in need thereof any compound or pharmaceutically acceptable salt thereof as described herein (e.g., a compound according to any one of Formulas (A) (e.g., Formulas (I)-(X)) and (B) such as the compounds of Table 1 (including any one of Compounds (1)-(36)) and pharmaceutically acceptable salts thereof).

[000503] In one aspect, the invention features a method of treating a cerebrovascular disease or disorder comprising administering to a subject in need thereof any compound or pharmaceutically acceptable salt thereof as described herein (e.g., a compound according to any one of Formulas (A) (e.g., Formulas (I)-(X)) and (B) such as the compounds of Table 1 (including any one of Compounds (1)-(36)) and pharmaceutically acceptable salts thereof).

[000504] In one aspect, the invention features a method of treating a neurological disease or disorder comprising administering to a subject in need thereof any compound or pharmaceutically acceptable salt thereof as described herein (e.g., a compound according to any one of Formulas (A) (e.g., Formulas (I)-(X)) and (B) such as the compounds of Table 1 (including any one of Compounds (1)-(36)) and pharmaceutically acceptable salts thereof).

[000505] In embodiments, a compound or pharmaceutically acceptable salt thereof as described herein is an antihypertrophic.

[000506] In embodiments, a compound or pharmaceutically acceptable salt thereof as described herein is an antiarrhythmogenic.

[000507] In embodiments, a compound or pharmaceutically acceptable salt thereof as described herein is an antiatherogenic.

[000508] In embodiments, a compound or pharmaceutically acceptable salt thereof as described herein is an antifibrotic.

[000509] In embodiments, a compound or pharmaceutically acceptable salt thereof as described herein is an antithrombotic.

[000510] In embodiments, a disease or disorder is cardiovascular disease. In embodiments, a disease or disorder is hypertension. In embodiments, a disease or disorder is heart failure. In embodiments, a disease or disorder is atherosclerosis. In embodiments, a disease or disorder is aortic aneurysm.

[000511] In embodiments, a disease or disorder is cardiovascular disease, hypertension, heart failure, infection, alopecia, anemia, cytopenia, neural disease, inflammation, fibrosis, cancer, acute respiratory distress syndrome or wound healing (claimed). Also useful for treating gastrointestinal tract comprising oesophagitis, gastric ulcers, irritable bowel syndrome (IBS), hepatic disorders (e.g., hepatitis), gall bladder disease, and sepsis; respiratory tract infection comprising inflammatory disorders, such as asthma, and pneumonitis; kidney diseases comprising renal failure, and nephritis; atherosclerosis, arterial thrombosis, diabetic complications, angina, cardiac arrhythmias, and preeclampsia; and stroke.

[000512] In embodiments, a disease or disorder is pulmonary fibrosis.

[000513] In embodiments, a disease or disorder is renal disease (e.g., renal dysfunction).

[000514] In embodiments, a disease or disorder is inflammation.

[000515] In embodiments, a disease or disorder is a metabolic disease or disorder (e.g., diabetes). In embodiments, a disease or disorder is abnormal glucose metabolism.

[000516] In embodiments, a disease or disorder is a cerebrovascular disease or disorder.

[000517] In embodiments, a disease or disorder is stroke. In embodiments, a disease or disorder is ischemic stroke. In embodiments, a disease or disorder is hemorrhagic stroke.

[000518] In embodiments, a disease or disorder is neurological disease or disorder.

[000519] In embodiments, a disease or disorder is cancer.

[000520] In embodiments, a disease or disorder is fibrosis.

[000521] In embodiments, a disease or disorder is an ocular or ophthalmological disease or disorder (e.g., uveitis or glaucoma).

[000522] In embodiments, a disease or disorder is pain (e.g., nociceptive pain).

Cancer

[000523] In embodiments, a compound described herein, or any pharmaceutically acceptable salt thereof, is useful in methods of treating a cancer in a subject in need thereof.

[000524] In embodiments, provided herein are methods to treat cancer in a subject. In embodiments, provided are methods to prevent or reduce the likelihood of cancer occurring in a subject. In embodiments, provided are methods to prevent or reduce the likelihood of metastasis occurring in a subject. In embodiments, provided are methods of inhibiting cancer cell growth or proliferation in a subject, methods of inhibiting angiogenesis in a tissue, and methods of inhibiting fibrosis in a tissue. In embodiments, the method of treating cancer in a subject includes administering to the subject an effective amount of a compound or pharmaceutically acceptable salt thereof as described herein. In embodiments, administering a compound or pharmaceutically acceptable salt thereof as described herein inhibits cancer cell growth or proliferation in the subject. In embodiments, the cancer comprises cells that express the angiotensin-(1-7) receptor Mas and/or MrgD. In embodiments, administering a compound or pharmaceutically acceptable salt thereof as described herein prevents or reduces the likelihood of tumor growth, metastasis, or both tumor growth and metastasis. In embodiments, administering a compound or pharmaceutically acceptable salt thereof as described herein inhibits at least one of cancer cell growth or proliferation, angiogenesis, inflammation, or fibrosis. In embodiments, administering a composition or pharmaceutically acceptable salt thereof inhibits cell growth or proliferation of endothelial cells (in vivo, in vitro). In embodiments, administering a compound or pharmaceutically acceptable salt thereof as described herein inhibits collagen formation.

[000525] In embodiments, a cancer is adenocarcinoma, adenocarcinoma of the lung, acute myeloid leukemia ("AML"), acute lymphoblastic leukemia ("ALL"), adrenocortical carcinoma, anal cancer (e.g., squamous cell carcinoma of the anus), appendiceal cancer, B-cell derived leukemia, B-cell derived lymphoma, bladder cancer, brain cancer, breast cancer (e.g., triple negative breast cancer (TNBC)), cancer of the fallopian tube(s), cancer of the testes, cerebral cancer, cervical cancer (e.g., squamous cell carcinoma of the cervix), cholangiocarcinoma, choriocarcinoma, chronic myelogenous leukemia, a CNS tumor, colon cancer or colorectal cancer (e.g., colon adenocarcinoma), diffuse intrinsic pontine glioma (DIPG), diffuse large B cell lymphoma ("DLBCL"), embryonal rhabdomyosarcoma (ERMS), endometrial cancer, epithelial cancer, esophageal cancer (e.g., squamous cell carcinoma of the esophagus), Ewing's sarcoma, eye cancer (e.g., uveal melanoma), follicular lymphoma ("FL"), gallbladder cancer, gastric cancer, gastrointestinal cancer, glioma, head and neck cancer (e.g., squamous cell carcinoma of the head and neck (SCHNC)), a hematological cancer, hepatocellular cancer, Hodgkin's lymphoma

(HL)/primary mediastinal B-cell lymphoma, kidney cancer, kidney clear cell cancer, laryngeal cancer, leukemia, liver cancer, lung cancer (e.g., non-small cell lung cancer (NSCLC), small cell lung cancer, lung adenocarcinoma, or squamous cell carcinoma of the lung), lymphoma, melanoma, Merkel cell carcinoma, mesothelioma, monocytic leukemia, multiple myeloma, myeloma, a neuroblastic-derived CNS tumor (e.g., neuroblastoma (NB)), non-Hodgkin's lymphoma (NHL), oral cancer, osteosarcoma, ovarian cancer, ovarian carcinoma, pancreatic cancer, peritoneal cancer, primary peritoneal cancer, prostate cancer, relapsed or refractory classic Hodgkin's Lymphoma (cHL), rectal cancer, salivary gland cancer (e.g., a salivary gland tumor), sarcoma, skin cancer, small intestine cancer, stomach cancer, squamous cell carcinoma, squamous cell carcinoma of the penis, stomach cancer, T-cell derived leukemia, T-cell derived lymphoma, thymic cancer, a thymoma, thyroid cancer, uveal melanoma, urothelial cell carcinoma, uterine cancer (e.g., uterine endometrial cancer or uterine sarcoma), vaginal cancer (e.g., squamous cell carcinoma of the vagina), vulvar cancer (e.g., squamous cell carcinoma of the vulva), or Wilms tumor.

[000526] In embodiments, a cancer is bladder cancer, bone cancer, brain cancer, breast cancer, colon cancer, cervical cancer, endometrial cancer, fallopian tube cancer, gastrointestinal cancer, genitourinary cancer, head and neck cancer, hepatocellular carcinoma, leukemia, lung cancer, lymphoma, melanoma, liver cancer, ovarian cancer, pancreatic cancer, peritoneal cancer, prostate cancer, sarcoma, skin cancer, or testicular cancer. In some instances, a cancer expresses the Ang-(1-7) receptor Mas. In some cases, the Mas receptor is overexpressed in a cancer. In one example, a cancer is lung cancer. In another example, a cancer is breast cancer. In another example, a cancer is glioblastoma. In another example, a cancer is hepatocellular carcinoma. In another example, a cancer is prostate cancer. In another example, a cancer is sarcoma.

Cardiomyopathy

[000527] In embodiments, a compound described herein, or any pharmaceutically acceptable salt thereof, is useful in methods of treating a cardiomyopathy in a subject in need thereof.

[000528] Cardiomyopathy is a disease of the heart muscle, which makes it harder for the heart to fill with blood and to pump blood. Cardiomyopathy can lead to heart failure and may require heart transplantation. Cardiomyopathy can also cause abnormal heart rhythms. Genetic testing has increased our understanding of cardiomyopathies and has led to identification of specific genetic mutations that lead to the disease and detect mutation carriers even before the disease begins. Advanced imaging techniques can also identify problems with the heart muscle.

[000529] Cardiomyopathies are typically divided into two major groups based on predominant organ involvement (see Maron et al., *Circulation* 113(14):1807-16 (2006)). *Primary* cardiomyopathies (genetic, nongenetic, acquired) are those solely or predominantly confined to heart muscle and are relatively few in number. *Secondary* cardiomyopathies show pathological myocardial involvement as part of a large number and variety of generalized systemic (multiorgan) disorders. The frequency and degree of secondary myocardial involvement vary considerably among these diseases, some of which are exceedingly uncommon and for which the evidence of myocardial pathology may be sparse and reported in only a few patients.

[000530] Genetic cardiomyopathies include, but are not limited to, hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D), LV noncompaction, conduction system disease, ion channelopathies, Long-QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia (CPVT), short-QT syndrome (SQTS) and idiopathic ventricular fibrillation.

Hypertrophic Cardiomyopathy (HCM)

[000531] Hypertrophic Cardiomyopathy (HCM) is a clinically heterogeneous, but relatively common autosomal dominant genetic heart disease (1:500 of the general population for the disease phenotype recognized by echocardiography) that probably is the most frequently occurring cardiomyopathy.

[000532] HCM is typically characterized morphologically and defined by a hypertrophied, nondilated LV in the absence of another systemic or cardiovascular disease that is capable of producing the magnitude of wall thickening evident (e.g., systemic hypertension, aortic valve stenosis). Clinical diagnosis is customarily made with 2-dimensional echocardiography (or alternatively with cardiac magnetic resonance imaging) by detection of otherwise unexplained LV wall thickening, usually in the presence of a small LV cavity, after suspicion is raised by the clinical profile or as part of family screening.

[000533] When LV wall thickness is mild, differential diagnosis with physiological athlete's heart may arise. Furthermore, individuals harboring a genetic defect for HCM do not necessarily express clinical markers of their disease such as LV hypertrophy on echocardiogram, ECG abnormalities, or symptoms at all times during life, and ECG alterations can precede the appearance of hypertrophy. Indeed, virtually any LV wall thickness, even when within normal limits, is consistent with the presence of an HCM-causing mutant gene, and diagnosis can be made by laboratory DNA analysis. Furthermore, recognition of LV hypertrophy may be age related with its initial appearance delayed

well into adulthood (adult morphological conversion). Most HCM patients have the propensity to develop dynamic obstruction to LV outflow under resting or physiologically provokable conditions, produced by systolic anterior motion of the mitral valve with ventricular septal contact.

[000534] HCM is caused by a variety of mutations encoding contractile proteins of the cardiac sarcomere. Several mutant genes are associated with HCM, most commonly β -myosin heavy chain (the first identified) and myosin-binding protein C. The other genes appear to account for far fewer cases of HCM and include troponin T and I, regulatory and essential myosin light chains, titin, α -tropomyosin, α -actin, α -myosin heavy chain, and muscle LIM protein. This genetic diversity is compounded by considerable intragenic heterogeneity, with >400 individual mutations now identified. These most commonly are missense mutations but include insertions, deletions, and splice (split-site) mutations encoding truncated sarcomeric proteins. The characteristic diversity of the HCM phenotype is attributable to the disease-causing mutations and probably to the influence of modifier genes and environmental factors.

[000535] In addition, nonsarcomeric protein mutations in genes involved in cardiac metabolism have been reported to be responsible for primary cardiac glycogen storage diseases in older children and adults with a clinical presentation mimicking (or indistinguishable from) that of sarcomeric HCM. One of these conditions involves the gene encoding the γ -2-regulatory subunit of the AMP-activated protein kinase (PRKAG2), associated with variable degrees of LV hypertrophy and ventricular preexcitation. The other involves the gene encoding lysosome-associated membrane protein 2 (LAMP-2), resulting in Danon-type storage disease. Clinical manifestations are limited largely to the heart, usually with massive degrees of LV hypertrophy and ventricular preexcitation. These disorders are now part of a subgroup of previously described infiltrative forms of LV hypertrophy such as Pompe disease, a glycogen storage disease caused by α -1,4 glycosidase (acid maltase deficiency) in infants, and Fabry's disease, an X-linked recessive disorder of glycosphingolipid metabolism caused by a deficiency of the lysosomal enzyme α -galactosidase A, resulting in intracellular accumulation of glycosphingolipids.

[000536] A number of other diseases associated with LV hypertrophy involve prominent thickening of the LV wall, occurring mostly in infants and children ≤ 4 years of age, which may resemble or mimic typical HCM caused by sarcomere protein mutations. These cardiomyopathies include secondary forms such as Noonan syndrome, an autosomal dominant cardiofacial condition associated with a variety of cardiac defects (most commonly, dysplastic pulmonary valve stenosis

and atrial septal defect) resulting from mutations in PTPN11, a gene encoding the nonreceptor protein tyrosine phosphatase SHP-2 genes.

[000537] Other diseases in this category include, but are not limited to, mitochondrial myopathies resulting from mutations encoding mitochondrial DNA (including Kearns-Sayre syndrome) or mitochondrial proteins associated with ATP electron transport chain enzyme defects that alter mitochondrial morphology. Also included are metabolic myopathies representing ATP production and utilization defects involving abnormalities of fatty acid oxidation (acyl CoA dehydrogenase deficiencies) and carnitine deficiency, as well as infiltrative myopathies, i.e., glycogen storage diseases (type II; autosomal recessive Pompe disease), Hunter's and Hurler's diseases, and the transient and nonfamilial cardiomyopathy as part of generalized organomegaly, recognized in infants of insulin-dependent diabetic mothers. In older patients, a number of systemic diseases have been associated with hypertrophic forms of cardiomyopathy; these include Friedreich's ataxia, pheochromocytoma, neurofibromatosis, lentiginosis, and tuberous sclerosis.

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

[000538] ARVC/D is form of inheritable heart muscle disease, which involves predominantly the right ventricle with progressive loss of myocytes and fatty or fibrofatty tissue replacement, resulting in regional (segmental) or global abnormalities. Although frequently associated with myocarditis (enterovirus or adenovirus in some cases), ARVC/D is not considered a primary inflammatory cardiomyopathy. In addition, evidence of LV involvement with fibrofatty replacement, chamber enlargement.

[000539] ARVC/D has a broad clinical spectrum, usually presenting clinically with ventricular tachyarrhythmias (e.g., monomorphic ventricular tachycardia). Noninvasive clinical diagnosis may be confounding, without an easily obtained single test or finding that is definitively diagnostic, and generally requires an integrated assessment of electrical, functional, and anatomic abnormalities. Diagnosis often requires a high index of suspicion, frequently triggered by presentation with arrhythmias, syncope, or cardiac arrest, as well as global or segmental chamber dilatation or wall motion abnormalities.

[000540] Noninvasive tests used to diagnose ARVC/D, in addition to personal and family history, include 12-lead ECG, echocardiography, right ventricular angiography, cardiac magnetic resonance imaging, and computerized tomography. Endomyocardial biopsy from the right ventricular free wall is a sensitive diagnostic marker when fibrofatty infiltration is associated with surviving strands of myocytes. ECGs most commonly show abnormal repolarization with T-wave inversion in leads V1

through V3 and small-amplitude potentials at the end of the QRS complex (epsilon wave); Brugada syndrome—like right bundle-branch block and right precordial ST-segment elevation accompanied by polymorphic ventricular tachycardia also have been reported in a small subpopulation of ARVC/D patients.

[000541] In many cases, ARVC/D shows autosomal dominant inheritance, albeit often with incomplete penetrance. Autosomal dominant ARVC/D has been mapped to 8 chromosomal loci, with mutations identified thus far in 4 genes: the cardiac ryanodine receptor RyR2, which is also responsible for familial catecholaminergic polymorphic ventricular tachycardia (CPVT); desmoplakin; plakophilin-2; and mutations altering regulatory sequences of the transforming growth factor- β gene, which has a role in inflammation. Two recessive forms have been described in conjunction with palmoplantar keratoderma and woolly hair (Naxos disease) and with Carvajal syndrome, caused by mutations in junctional plakoglobin and desmoplakin, respectively. Although the function of desmosomal proteins to anchor intermediate filaments to desmosomes implicates ARVC/D as a primary structural abnormality, there is also a link to ion channel dysfunction.

LV Noncompaction

[000542] Noncompaction of ventricular myocardium is a congenital cardiomyopathy characterized by a distinctive (“spongy”) morphological appearance of the LV myocardium. Noncompaction involves predominantly the distal (apical) portion of the LV chamber with deep intertrabecular recesses (sinusoids) in communication with the ventricular cavity, resulting from an arrest in the normal embryogenesis. LV noncompaction (LVNC) may be an isolated finding or may be associated with other congenital heart anomalies such as complex cyanotic congenital heart disease.

[000543] Diagnosis can be made with 2-dimensional echocardiography, cardiac magnetic resonance imaging, or LV angiography. The natural history of LVNC includes LV systolic dysfunction and heart failure (and some cases of heart transplantation), thromboemboli, arrhythmias, sudden death, and diverse forms of remodeling. Both familial and nonfamilial cases have been described. In the isolated form of LVNC, ZASP (Z-line) and mitochondrial mutations and X-linked inheritance resulting from mutations in the G4.5 gene encoding tafazzin (including association with Barth syndrome in neonates) have been reported. Noncompaction associated with congenital heart disease has been shown to result from mutations in the α -dystrobrevin gene and transcription factor NKX2.5.

Cardiovascular, Cardiopulmonary, and Cardioprotective Indications

[000544] In embodiments, a compound described herein, or any pharmaceutically acceptable salt thereof, is useful in methods of treating a cardiovascular or cardiopulmonary disease or disorder in a subject in need thereof. In embodiments, a compound described herein, or any pharmaceutically acceptable salt thereof, has cardioprotective benefits in a subject in need thereof.

[000545] In embodiments, a compound described herein, or any pharmaceutically acceptable salt thereof, is useful in methods of treating a cardiovascular disease or disorder.

[000546] Exemplary cardiovascular diseases and disorders include cardiomyopathy, cardiac arrhythmia, heart failure, left ventricular dysfunction (LVD), myocardial fibrosis (MF), myocardial infarction or a conduction disorder.

[000547] In embodiments, a subject having a cardiovascular disease or disorder may be asymptomatic or symptomatic. Exemplary symptoms include palpitations, dizziness, edema (e.g., peripheral edema), ascites, or pleural effusion, or any combination thereof.

[000548] In embodiments, a disease or disorder is, heart failure, atherosclerosis, or aortic aneurysm.

[000549] In embodiments, a disease or disorder is heart failure.

[000550] In embodiments, a disease or disorder is acute myocardial infarction. In embodiments, a disease or disorder is acute congestive myocardial insufficiency. In embodiments, a disease or disorder is chronic congestive myocardial insufficiency.

[000551] In embodiments, a disease or disorder is acute myocardial infarction.

[000552] In embodiments, a disease or disorder is left ventricular hypertrophy.

[000553] In embodiments, a disease or disorder is cardiac hypertrophy.

[000554] In embodiments, a disease or disorder is vascular hypertrophy.

[000555] In embodiments, a disease or disorder is atherosclerosis. In embodiments, a disease or disorder is pulmonary fibrosis.

[000556] In embodiments, a disease or disorder is aortic aneurysm.

[000557] In embodiments, a disease or disorder is thrombosis.

[000558] In embodiments, a disease or disorder is thrombocytopenia.

[000559] In embodiments, a disease or disorder is coronary heart disease. In embodiments, a disease or disorder is angina pectoris. In embodiments, a disease or disorder is endothelial dysfunction or endothelial damage.

[000560] In embodiments, a disease or disorder is peripheral arterial disease (PAD).

[000561] In embodiments, a disease or disorder is primary autonomic failure.

[000562] In embodiments, a cardiovascular disease or disorder is cardiomyopathy. In embodiments, cardiomyopathy is dilated cardiomyopathy (DCM) such as ischemic, valvular, genetic, pediatric, or acquired DCM. In embodiments, cardiomyopathy is left ventricular non-compaction cardiomyopathy (LVNC).

[000563] In embodiments, a cardiovascular disease or disorder is cardiac arrhythmia. In embodiments, a cardiac arrhythmia is a ventricular arrhythmia. In embodiments, a cardiac arrhythmia is an atrial arrhythmia. In embodiments, a cardiac arrhythmia is sinus tachycardia (e.g., persistent or labile sinus tachycardia), ventricular tachycardia, atrial fibrillation, atrial flutter, atrioventricular block, or sinus sick disease. In embodiments, there is an abnormality in atrioventricular conduction.

[000564] In embodiments, a cardiovascular disease or disorder is myocardial fibrosis (MF).

[000565] In embodiments, a cardiovascular disease or disorder is heart failure (e.g., chronic heart failure or right-sided heart failure).

[000566] In embodiments, a cardiovascular disease or disorder is left ventricular dysfunction (LVD). In embodiments, LVD is low ventricular ejection fraction (e.g., less than or about 55%).

[000567] Therapeutic effects can be assessed by methods known in the art. For example, cardiac imaging techniques such as cardiac magnetic resonance imaging (CMR) can be used to assess cardiac function. In embodiments, CMR is used with gadolinium enhancement (e.g., CMR with late gadolinium enhancement). Still other exemplary methods include electrocardiography (ECG) or echocardiography (e.g., Doppler echocardiography), including echocardiography with myocardial strain analysis.

[000568] In embodiments, treatment of a cardiovascular disease or disorder results in improved cardiac function (e.g., compared to the cardiac function of a subject immediately prior to commencement of treatment).

[000569] In embodiments, treatment of a cardiovascular disease or disorder results in maintained cardiac function (e.g., compared to the cardiac function of a subject immediately prior to commencement of treatment).

[000570] In embodiments, treatment of a cardiovascular disease or disorder results in delaying the onset of a cardiovascular disease or disorder (e.g., compared to the cardiac function of a subject immediately prior to commencement of treatment).

[000571] In embodiments, treatment of a cardiovascular disease or disorder results in preventing a cardiovascular disease or disorder (e.g., compared to the cardiac function of a subject immediately prior to commencement of treatment).

Brugada Syndrome

[000572] In embodiments, a cardiovascular disease or disorder is Brugada syndrome.

[000573] The Brugada syndrome is associated with sudden cardiac death in young people. The syndrome is identified by a distinctive ECG pattern consisting of right bundle-branch block and coved ST-segment elevation in the anterior precordial leads (V1 through V3). The characteristic ECG pattern is often concealed and may be unmasked with the administration of sodium channel blockers, including ajmaline, flecainide, procainamide, and pilsicainide. Familial autosomal dominant and sporadic forms have been linked to mutations in an α -subunit of the cardiac sodium channel gene SCN5A (the same gene responsible for LQT3) in 20% of patients. Another locus has been reported on the short arm of chromosome 3.

[000574] Sudden unexplained nocturnal death syndrome, found predominantly in young Southeast Asian males is a disorder causing sudden death during sleep as a result of ventricular tachycardia/fibrillation. Some cases of sudden unexplained nocturnal death syndrome resulting from SCN5A gene mutations and Brugada syndrome have been shown to be phenotypically, genetically, and functionally the same disorder.

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

[000575] In embodiments, a cardiovascular disease or disorder is Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT).

[000576] CPVT is characterized by syncope, sudden death, polymorphic ventricular tachycardia triggered by vigorous physical exertion or acute emotion (usually in children and adolescents), a normal resting ECG, and the absence of structural cardiovascular disease. Family history of 1 or multiple sudden cardiac deaths is evident in 30% of cases. The resting ECG is unremarkable, except for sinus bradycardia and prominent U waves in some patients. The most typical arrhythmia of CPVT is bidirectional ventricular tachycardia presenting with an alternating QRS axis. The autosomal dominant form of the disease has been linked to the RyR2 gene encoding for the cardiac ryanodine receptor, a large protein that forms the calcium release channel in the sarcoplasmic reticulum that is essential for regulation of excitation–contraction coupling and intracellular calcium levels. An autosomal recessive form has been linked to CASQ2, a gene that encodes for calsequestrin, a protein that serves as a major calcium-binding protein in the terminal cisternae of the sarcoplasmic reticulum. Calsequestrin is bound to the ryanodine receptor and participates in the control of excitation–contraction coupling.

Conduction System Disease

[000577] In embodiments, a cardiovascular disease or disorder is a conduction system disease.

[000578] For example, Lenegre disease, also known as progressive cardiac conduction defect, is characterized by primary progressive development of cardiac conduction defects in the His-Purkinje system, leading to widening of the QRS complex, long pauses, and bradycardia that may trigger syncope. Sick sinus syndrome is phenotypically similar to progressive cardiac conduction defect. Familial occurrence of both syndromes has been reported with an autosomal dominant pattern of inheritance. An ion channelopathy, in the form of SCN5A mutations, is thought to contribute to these conduction system defects. Wolff-Parkinson-White syndrome is familial in some cases, but information about the genetic causes is unavailable.

Ion Channelopathies

[000579] In embodiments, a cardiovascular disease or disorder is an ion channelopathy disease or disorder.

[000580] Some uncommon inherited and congenital arrhythmia disorders are caused by mutations in genes encoding defective ionic channel proteins, governing cell membrane transit of sodium and potassium ions. These ion channel disorders include, but are not limited to, LQTS, short-QT syndrome (SQTS), Brugada syndrome, and CPVT. Nocturnal sudden unexplained death syndrome in young Southeast Asian males and Brugada syndrome are based on similar clinical and genetic profiles. A small proportion (5% to 10%) of sudden infant deaths also may be linked to ion

channelopathies, including LQTS, SQTs, and Brugada syndrome. Clinical diagnosis of the ion channelopathies often can be made by identification of the disease phenotype on standard 12-lead ECG.

Long-QT Syndrome (LQTS)

[000581] In embodiments, a cardiovascular disease or disorder is Long-QT Syndrome.

[000582] Long-QT Syndrome is characterized by prolongation of ventricular repolarization and QT interval (corrected for heart rate) on the standard 12-lead ECG, a specific form of polymorphic ventricular tachycardia (torsade des pointes), and a risk for syncope and sudden cardiac death. Phenotypic expression (on the ECG) varies considerably, and approximately 25% to 50% of affected family members may show borderline or even normal QT intervals.

[000583] Two patterns of inheritance have been described in LQTS: a rare autosomal recessive disease associated with deafness (Jervell and Lange-Nielsen syndrome), which is caused by 2 genes that encode for the slowly activating delayed rectifier potassium channel (KCNQ1 and KCNE1 [minK]), and the much more common autosomal dominant disease unassociated with deafness (Romano-Ward syndrome), which is caused by mutations in 8 different genes. These include KCNQ1 (KvLQT1, LQT1), KCNH2 (HERG, LQT2), SCN5A (Na1.5, LQT3), ANKB (LQT4), KCNE1 (minK, LQT5), KCNE2 (MiRP1, LQT6), KCNJ2 (Kir2.1, LQT7, Andersen's syndrome), and CACNA1C (Ca1.2, LQT8, Timothy syndrome). Of the 8 genes, 6 encode for cardiac potassium channels, 1 for the sodium channel (SCN5A, LQT3), and 1 for the protein ankyrin, which is involved in anchoring ion channels to the cellular membrane (ANKB).

Short-QT Syndrome (SQTs)

[000584] In embodiments, a cardiovascular disease or disorder is Short-QT Syndrome (SQTs).

[000585] SQTs is characterized by a short QT interval (<330 ms) on an ECG and a high incidence of sudden cardiac death resulting from ventricular tachycardia/fibrillation. Another distinctive ECG feature of SQTs is the appearance of tall peaked T waves similar to those encountered with hyperkalemia. The syndrome has been linked to gain-of-function mutations in KCNH2 (HERG, SQT1), KCNQ1 (KvLQT1, SQT2), and KCNJ2 (Kir2.1, SQT3), causing an increase in the intensity of I_{Kr} , I_{Ks} , and I_{Kl} , respectively.

Idiopathic Ventricular Fibrillation

[000586] In embodiments, a cardiovascular disease or disorder is Idiopathic Ventricular Fibrillation.

[000587] A subgroup of patients with sudden death appears in the literature with the designation of idiopathic ventricular fibrillation. However, it is likely that idiopathic ventricular fibrillation is not an independent disease entity but rather a conglomeration of conditions with normal gross and microscopic findings in which arrhythmic risk undoubtedly derives from molecular abnormalities, most likely ion channel mutations.

Cerebrovascular and Neurological Diseases and Diseases and Brain Condition

[000588] In embodiments, a compound described herein, or any pharmaceutically acceptable salt thereof, is useful in methods of treating a cerebrovascular or neurological disease in a subject in need thereof. In embodiments, a compound described herein, or any pharmaceutically acceptable salt thereof, is useful in methods of treating a brain condition in a subject in need thereof. In embodiments, a compound described herein, or any pharmaceutically acceptable salt thereof, has neuroprotective benefits in a subject in need thereof.

[000589] In embodiments, a disease or disorder is ischemic injury. In embodiments, a disease or disorder is reperfusion injury.

[000590] In embodiments, a disease or disorder is cerebral vascular accident.

[000591] In embodiments, a disease or disorder is cerebral ischemia.

Traumatic Brain Injury

[000592] In embodiments, a disease or disorder is traumatic brain injury (TBI).

[000593] Traumatic brain injury (TBI), a form of acquired brain injury, occurs when a sudden trauma causes damage to the brain. TBI can result when the head suddenly and violently hits an object (or vice versa), or when an object pierces the skull and enters brain tissue. Symptoms of a TBI can be mild, moderate, or severe, depending on the extent of the damage to the brain. A person with a mild TBI may remain conscious or may experience a loss of consciousness for a few seconds or minutes. Other symptoms of mild TBI include headache, confusion, lightheadedness, dizziness, blurred vision or tired eyes, ringing in the ears, bad taste in the mouth, fatigue or lethargy, a change in sleep patterns, behavioral or mood changes, and trouble with memory, concentration, attention, or thinking. A person with a moderate or severe TBI may show these same symptoms but may also

have a headache that gets worse or does not go away, repeated vomiting or nausea, convulsions or seizures, an inability to awaken from sleep, dilation of one or both pupils of the eyes, slurred speech, weakness or numbness in the extremities, loss of coordination, and increased confusion, restlessness, or agitation.

[000594] Treatments for TBI focus primarily on preventing further injury or complications. Primary concerns in treating TBI include insuring proper oxygen supply to the brain and the rest of the body, maintaining adequate blood flow, and controlling blood pressure. Often, the primary treatment a TBI sufferer receives post-stabilization is rehabilitation that involves individually tailored treatment programs in the areas of physical therapy, occupational therapy, speech/language therapy, psychology/psychiatry, and social support. Embodiments of the present invention provide a novel treatment for these patients.

Endothelial disease

[000595] In embodiments, a compound described herein, or any pharmaceutically acceptable salt thereof, is useful in methods of treating an endothelial disease in a subject in need thereof.

Fibrotic disease

[000596] In embodiments, a disease or disorder is fibrosis.

[000597] The present invention provides methods of treating various fibrotic diseases, disorders, or conditions as described in greater detail below.

[000598] As used herein, the term “fibrotic disorder” refers to any disease characterized by fibrosis, including but not limited to systemic sclerosis, multifocal fibrosclerosis, sclerodermatous graft-vs-host-disease, nephrogenic systemic fibrosis, organ specific fibrosis, and the like. Illustrative organ specific fibrotic disorders include, but are not limited to, pulmonary fibrosis, pulmonary hypertension, cystic fibrosis, asthma, chronic obstructive pulmonary disease, liver fibrosis, kidney fibrosis, NASH, and the like. Many fibrotic diseases, disorders or conditions have disordered and/or exaggerated deposition of extracellular matrix in affected tissues. Fibrosis may be associated with inflammation, occur as a symptom of underlying disease, and/or caused by surgical procedure or wound healing process. Unchecked fibrosis can result in destruction of the architecture of the underlying organ or tissue, commonly referred to as scarring.

[000599] Exemplary fibrotic disorders conditions are described below and elsewhere in the present disclosure.

[000600] For example, fibrosis of the lungs represents a debilitating and potentially fatal form of fibrosis. Treatment options for fibrosis in lung tissue are very limited. Once developed, scarring is permanent, and lung transplantation is often the only therapeutic option available.

[000601] Pulmonary fibrosis is characterized by progressive scarring of lung tissue accompanied by fibroblast proliferation, excessive accumulation of extracellular matrix proteins, and abnormal alveolar structure. The thickened and stiff tissue makes it difficult for lungs to work properly, leading to breathing problems such as shortness of breath, and can ultimately be fatal. Pulmonary fibrosis may be caused by acute lung injury, viral infection, exposure to toxins, radiation, chronic disease, medications, or may be idiopathic (i.e., an undiscovered underlying cause).

[000602] The classic findings in idiopathic pulmonary fibrosis show diffuse peripheral scarring of the lungs with small bubbles (known as bullae) adjacent to the outer lining of the surface of the lung, often at the bases of the lungs. Idiopathic pulmonary fibrosis often has a slow and relentless progression. Early on, patients often complain of a dry unexplained cough. Next, shortness of breath (dyspnea) sets in and worsens over time triggered by less and less activity. Eventually, the shortness of breath becomes disabling, limiting all activity and even occurring while sitting still. In rarer cases, the fibrosis can be rapidly progressive, with dyspnea and disability occurring in weeks to months of onset of the disease. This form of pulmonary fibrosis has been referred to as Hamman-Rich syndrome.

[000603] Pulmonary hypertension is marked by an increase in the blood pressure of the lung vasculature, including the pulmonary artery, pulmonary vein, and/or pulmonary capillaries. Abnormally high pressure strains the right ventricle of the heart, causing it to expand. Over time, the right ventricle can weaken and lose its ability to pump enough blood to the lungs, leading to the development of heart failure. Pulmonary hypertension can occur as a result of other medical conditions, such as chronic liver disease and liver cirrhosis; rheumatic disorders such as scleroderma or systemic lupus erythematosus (lupus); and lung conditions including tumors, emphysema, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis. Pulmonary fibrosis may lead to narrowing of pulmonary vasculature resulting in pulmonary hypertension.

[000604] Chronic Obstructive Pulmonary Disease (COPD) is a common lung disease that is often associated with chronic bronchitis or emphysema. Symptoms can often include cough, mucus build up, fatigue, wheezing, and respiratory infection.

[000605] Chronic bronchitis and emphysema are diseases of the lungs in which the airways become narrowed. This leads to a limitation of the flow of air to and from the lungs, causing shortness of breath (dyspnea). In clinical practice, COPD is defined by its characteristically low airflow on lung function tests.

[000606] Lung damage and inflammation in the large airways results in chronic bronchitis. In the airways of the lung, the hallmark of chronic bronchitis is an increased number (hyperplasia) and increased size (hypertrophy) of the goblet cells and mucous glands of the airway. As a result, there is more mucus than usual in the airways, contributing to narrowing of the airways and causing a cough with sputum. Microscopically there is infiltration of the airway walls with inflammatory cells. Inflammation is followed by scarring and remodeling that thickens the walls and also results in narrowing of the airways. As chronic bronchitis progresses, there is squamous metaplasia (an abnormal change in the tissue lining the inside of the airway) and fibrosis (further thickening and scarring of the airway wall). The consequence of these changes is a limitation of airflow and difficulty breathing.

[000607] Asthma is a chronic lung disease characterized by inflammation and constriction of the airways. Asthma causes recurring periods of wheezing, tightness of the chest, shortness of breath, and coughing. Swelling and overproduction of mucus can cause further airway constriction and worsening of symptoms. There is evidence that increased matrix degradation may occur in asthma, and this may contribute to mechanical changes in the airways in asthma (Roberts et al (1995) *Chest* 107:111S-117S, incorporated herein by reference in its entirety. Treatment of extracellular matrix degradation may ameliorate symptoms of asthma.

[000608] Cystic fibrosis is a recessive multi-system genetic disease characterized by abnormal transport of chloride and sodium across epithelium, leading to thick, viscous secretions in the lungs, pancreas, liver, intestine and reproductive tract. Cystic fibrosis is caused by a mutation in the gene for the protein cystic fibrosis transmembrane conductance regulator (CFTR). Lung disease results from clogging of the airways due to mucus build-up, decreased mucociliary clearance, and resulting inflammation, which can cause fibrotic injury and structural changes to the lungs. The fibrotic lung damage progresses over time leading some cystic fibrosis patients to require lung transplant.

[000609] When referring to cystic fibrosis, to “treat” or “treating” cystic fibrosis (CF) may mean accomplishing one or more of the following: (a) reducing inflammation in the subject; (b) limiting any increase in inflammation the subject; (c) reducing the severity of one or more CF symptoms; (d) limiting or preventing development of one or more CF symptoms; (e) inhibiting worsening of one or

more CF symptoms; and (f) limiting or preventing recurrence of one or more CF symptoms in subjects that were previously symptomatic for the relevant CF symptom.

[000610] Common symptoms of subjects suffering from cystic fibrosis include, but are not limited to, accumulation of thick mucus, copious phlegm production, frequent chest infections, frequent coughing, frequent shortness of breath, inflammation, decreased ability to exercise, opportunistic infections of the lung and sinus (including but not limited to *Staphylococcus aureus*, *Haemophilus influenzae*, *Mycobacterium avium*, and *Pseudomonas aeruginosa*), pneumonia, tuberculosis, bronchiectasis, hemoptysis, pulmonary hypertension (and resulting heart failure), hypoxia, respiratory failure, allergic bronchopulmonary aspergillosis, mucus in the paranasal sinuses, sinus infection, facial pain, fever, excessive nasal drainage, development of nasal polyps, cardiorespiratory complications, CF-related diabetes, rectal prolapse, pancreatitis, malabsorption, intestinal blockage, exocrine pancreatic insufficiency, bile duct blockage, and liver cirrhosis.

[000611] In some embodiments, the symptoms of cystic fibrosis comprise inflammation. In these embodiments, some methods within the scope of the invention may comprise treating inflammation, wherein a beneficial effect of treatment can be assessed by, for example, a reduction in inflammatory cell count in a relevant sample from the subject, such as bronchoalveolar lavage (BAL) fluid. In a non-limiting embodiment, the beneficial effect may be assessed by demonstrating a reduction in neutrophil count in BAL fluid from the subject. The excessive recruitment of neutrophils into the airways of patients with CF is a significant predictor of lung disease severity in CF and therefore is an important therapeutic target. Methods for measuring such cell counts are well known in the art, including but not limited to FACS techniques. Thus, in some embodiments, methods within the scope of the invention may comprise reducing inflammation in the subject. In some embodiments, the method may comprise reducing neutrophil cell count in BAL fluid from the subject compared to control. Any suitable control can be used for comparison, such as cystic fibrosis subjects not treated with the compound or pharmaceutically acceptable salt thereof. In some embodiments, a decrease in neutrophil count provides a clinical benefit to the subject. In various embodiments, the reduction in neutrophil count is at least 5%, 10%, 15%, 20%, 25%, 50%, or more compared to control.

[000612] In another embodiment, the beneficial effect of the therapeutic methods of the invention may be assessed by a reduction in one or more inflammatory biomarkers in a relevant sample from the subject, such as BAL fluid. In various non-limiting embodiments, the inflammatory biomarker may comprise or consist of one or more of IL1 β , KC, MIP2, IFN γ , TNF α , IL-6, MCP-1, and

IL-10 in BAL fluid. Methods for measuring the amount of such biomarkers are well known in the art, including but not limited to ELISAs. Thus, in this embodiment, the methods may further comprise the reducing an amount of one or more inflammatory biomarkers in a BAL sample from the subject compared to control.

[000613] Post-surgical adhesion formation is a common complication of surgery. The formation of adhesions, from mechanical damage, ischemia, and infections, can increase morbidity and mortality following surgery. Although refined surgical procedures can reduce the magnitude of adhesion formation, adhesions are rarely surgically removed and an effective adjunctive therapy is needed. Reducing the fibrosis associated with this process could reduce pain, obstruction and other complications of surgery and promote healing and recovery.

[000614] Wounds (i.e., lacerations, openings) in mammalian tissue result in tissue disruption and coagulation of the microvasculature at the wound face. Repair of such tissue represents an orderly, controlled cellular response to injury. Soft tissue wounds, regardless of size, heal in a similar manner. Tissue growth and repair are biologic systems wherein cellular proliferation and angiogenesis occur in the presence of an oxygen gradient. The sequential morphological and structural changes which occur during tissue repair have been characterized in detail and have in some instances been quantified (see e.g., Hunt, T.K., et al., "Coagulation and macrophage stimulation of angiogenesis and wound healing," in *The Surgical Wound*, pp. 1-18, ed. F. Dineen & G. Hildrick-Smith (Lea & Febiger, Philadelphia: 1981)). The cellular morphology consists of three distinct zones. The central avascular wound space is oxygen deficient, acidotic and hypercarbic, and has high lactate levels. Adjacent to the wound space is a gradient zone of local anemia (ischemia) which is populated by dividing fibroblasts. Behind the leading zone is an area of active collagen synthesis characterized by mature fibroblasts and numerous newly-formed capillaries (i.e., neovascularization). U.S. Patent Nos. 5,015,629 and 7,022,675 (each incorporated by reference herein) disclose methods and compositions for increasing the rate of wound repair.

[000615] Scar formation is a natural part of the healing process. Disorderly collagen synthesis and deposition in a wound can result in excessive, thick, or raised scar formation. Generally, the larger the wound, the longer it takes to heal and the greater the chance of a problematic scar.

[000616] There are several types of scars. Hypertrophic scars are raised, pinkish-red areas located inside the borders of the original injury. They are often described as itchy. In some cases, hypertrophic scars shrink and fade on their own. Keloids are raised, deep-red areas that tend to cover much more area than that of the original injury. Even when surgically removed, keloids tend to

recur. Atrophic scars are skin depressions, like those that sometimes form from severe acne. They are caused by inflammation that destroys the collagen during the rebuilding process, leaving an area of indentation.

[000617] Systemic sclerosis is a systemic connective tissue disease characterized by alterations of the microvasculature, disturbances of the immune system and by massive deposition of collagen and other matrix substances in the connective tissue. Systemic sclerosis is a clinically heterogeneous generalized disorder which affects the connective tissue of the skin and internal organs such as gastrointestinal tract, lungs, heart and kidneys. Reduction of fibrosis resulting from systemic sclerosis may ameliorate symptoms and/or prevent further complications in affected tissues.

[000618] Nonalcoholic steatohepatitis (NASH) is a common liver disease. It resembles alcoholic liver disease but occurs in people who drink little or no alcohol. The major feature in NASH is fat in the liver, along with inflammation and damage. Nevertheless, NASH can be severe and can lead to cirrhosis, in which the liver is permanently damaged and scarred and no longer able to work properly.

[000619] NASH is usually a silent disease with few or no symptoms. Patients generally feel well in the early stages and only begin to have symptoms—such as fatigue, weight loss, and weakness—once the disease is more advanced or cirrhosis develops. The progression of NASH can take years, even decades. The process can stop and, in some cases may even begin to reverse on its own without specific therapy. Or NASH can slowly worsen, causing scarring or fibrosis to appear and accumulate in the liver. As fibrosis worsens, cirrhosis develops in which the liver becomes seriously scarred, hardened, and unable to function normally. Not every person with NASH develops cirrhosis, but once serious scarring or cirrhosis is present, few treatments can halt the progression. A person with cirrhosis experiences fluid retention, muscle wasting, bleeding from the intestines, and liver failure. Liver transplantation is the only treatment for advanced cirrhosis with liver failure, and transplantation is increasingly performed in people with NASH. NASH ranks as one of the major causes of cirrhosis in America, behind hepatitis C and alcoholic liver disease.

[000620] Kidney (renal) fibrosis results from excessive formation of fibrous connective tissue in the kidney. Kidney fibrosis causes significant morbidity and mortality and leads to a need for dialysis or kidney transplantation. Fibrosis can occur in either the filtering or reabsorptive component of the nephron, the functional unit of the kidney. A number of factors may contribute to kidney scarring, particularly derangements of physiology involved in the autoregulation of glomerular filtration. This in turn leads to replacement of normal structures with accumulated extracellular matrix. A spectrum of changes in the physiology of individual cells leads to the production of numerous peptide and non-

peptide fibrogens that stimulate alterations in the balance between extracellular matrix synthesis and degradation to favor scarring.

Hepatic Diseases and Disorders

[000621] In embodiments, a compound described herein, or any pharmaceutically acceptable salt thereof, is useful in methods of treating a hepatic disease or disorder in a subject in need thereof.

[000622] In embodiments, a disease or disorder is Nonalcoholic steatohepatitis (NASH).

[000623] In embodiments, a disease or disorder is acute liver failure.

[000624] In embodiments, a disease or disorder is liver fibrosis.

[000625] In embodiments, a disease or disorder is cirrhosis.

Inflammation

[000626] In embodiments, a compound described herein, or any pharmaceutically acceptable salt thereof, is useful in methods of treating an inflammation in a subject in need thereof.

[000627] In embodiments, an inflammation is scleroderma.

[000628] In embodiments, an inflammation is inflammatory bowel disease (IBD).

[000629] In embodiments, an inflammation is acute pancreatitis.

[000630] In embodiments, an inflammation is rheumatoid arthritis.

[000631] In embodiments, an inflammation is acute respiratory distress syndrome.

[000632] In embodiments, an inflammation is asthma.

[000633] In embodiments, an inflammation is cirrhosis.

[000634] In embodiments, an inflammation is uveitis.

Hemorrhagic fevers

[000635] In embodiments, a compound described herein, or any pharmaceutically acceptable salt thereof, is useful in methods of treating a hemorrhagic fever in a subject in need thereof.

[000636] In embodiments, a hemorrhagic fever is Alkhurma hemorrhagic fever (AHF), Chapare hemorrhagic fever (CHHF), Crimean-Congo hemorrhagic fever (CCHF), Ebola disease, hantavirus pulmonary syndrome (HPS), or hemorrhagic fever with renal syndrome (HFRS).

[000637] In embodiments, a hemorrhagic fever is Ebola.

Malaria

[000638] In embodiments, compounds and pharmaceutically acceptable salts described herein can be used to treating a malaria in a subject in need thereof.

[000639] In embodiments, a malaria is severe malaria.

[000640] In embodiments, a malaria is cerebral malaria.

Metabolic Diseases and Disorders

[000641] In embodiments, compounds and pharmaceutically acceptable salts described herein can be used to treating or reducing risk of diseases, disorders, or conditions that cause elevated blood sugar levels (e.g., diabetes) in a subject in need thereof.

[000642] The blood sugar concentration in the blood in healthy individuals is normally maintained between 64.8 and 104.4 mg/dL (American Diabetes Association, “Standards of Medical Care in Diabetes—2010”, *Diabetes Care*, 33: S1-S61, 2010). The body tightly regulates blood sugar levels as part of metabolic homeostasis. Blood sugar levels fluctuate throughout the day, and are usually lowest in the morning, before the first meal of the day, and rise for an hour or two after meals.

[000643] Glucose is the primary source of sugar in the blood and is the primary source of energy for the body's cells. The hormone insulin, which is produced in the beta cells in the islets of Langerhans in the pancreas, allows cells of the body to take up glucose from the blood and store it as glycogen.

[000644] Many clinical methods exist for assaying blood sugar levels, including but not limited to, fasting blood sugar test, urine glucose test, two-hour postprandial blood sugar test, oral glucose tolerance test, intravenous glucose tolerance test, glycosylated hemoglobin test, self-monitoring of glucose levels via patient testing, and/or random blood sugar testing. The fasting blood sugar/blood glucose test is the most common test for initial assessment of the presence or risk for developing diabetes. The test requires that an individual abstains from eating for at least 8 hours prior to the test. Typically, up to 100 mg/dL is considered normal for a fasting blood glucose test. Subjects with levels between 100 mg/dL and 125 mg/dL are typically considered to have impaired fasting glucose,

or be pre-diabetic, and subjects with levels that are 126 mg/dL or greater are typically considered diabetic.

[000645] Typically, a glucose tolerance test is used for measuring blood sugar levels. Impaired glucose tolerance is generally diagnosed if the blood glucose level measured during a glucose tolerance test is in the range of 140 mg/dL (7.84 mM) to 199 mg/dL (11.1 mM). Diabetes is generally diagnosed if the measured blood glucose level is 200 mg/dL (11.2 mM) or higher. But, as physiological status fluctuates continually, no single glucose tolerance test is definitive, and treatment for reducing of blood glucose levels need not be predicated solely on the results of such testing.

[000646] In embodiments, a disease or disorder is a metabolic disease or disorder.

[000647] In embodiments, a disease or disorder is diabetes.

[000648] In embodiments, a disease or disorder is neuropathic diabetes.

[000649] In embodiments, a disease or disorder is related to diabetes (e.g., caused by or associated with diabetes). In embodiments, a disease or disorder is diabetic peripheral neuropathy.

[000650] In embodiments, a disease or disorder is abnormal glucose metabolism.

[000651] In embodiments, a disease or disorder is primary and secondary hyperaldosteronism.

[000652] In embodiments, a disease or disorder is insulin resistance.

[000653] In embodiments, a disease or disorder is obesity.

Diabetes

[000654] In embodiments, a compound or pharmaceutically acceptable salt thereof as described herein can be used for treating or reducing risk of Diabetes. Diabetes is well known in the art (American Diabetes Association, "Standards of Medical Care in Diabetes—2010", *Diabetes Care*, 33: S1-S61, 2010). Diabetes is a disease in which the body does not produce or respond to insulin correctly. The inability to produce or respond to insulin correctly characteristic of diabetes results in elevated blood sugar levels.

[000655] There are two major types of diabetes. Type 1 diabetes affects the islets of Langerhans, destroying the body's ability to produce insulin. Type I diabetes represents 10% of all diabetes cases and affects as many as 1 million people in the United States. Type 2 diabetes is a metabolic disorder

resulting from the body's inability to produce enough insulin or properly use the insulin produced. Roughly 90% of all diabetic individuals in the United States suffer from Type 2 diabetes. Other, less common forms of diabetes include gestational diabetes, in which pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy, monogenic diabetes, which behaves similarly to Type 1 diabetes and is caused by a single gene mutation, congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, and steroid diabetes induced by high doses of glucocorticoids.

[000656] In embodiments, a compound or pharmaceutically acceptable salt thereof as described herein can be used for treating Diabetes. Diabetes can be associated with a wide range of conditions and complications affecting various organs throughout the body and can severely compromise quality of life and can even be fatal. Therefore, there is a need in the art for effective means of treating and preventing the development and progression of diabetes and associated complications.

[000657] Elevated blood sugar levels are responsible for most of the symptoms associated with diabetes. Diabetes associated symptoms include, but are not limited to, polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger). A number of skin rashes which can occur in diabetes are collectively known as diabetic dermadromes. Long term complications of diabetes include damage to the blood vessels. Diabetes doubles the risk of cardiovascular disease. The main "macrovascular" diseases (related to atherosclerosis of larger arteries) are ischemic heart disease (angina and myocardial infarction), stroke and peripheral vascular disease. Diabetes also causes "microvascular" complications—damage to the small blood vessels. Diabetic nephropathy, the impact of diabetes on the kidneys, can lead to scarring changes in the kidney tissue, loss of small or progressively larger amounts of protein in the urine, and eventually chronic kidney disease requiring dialysis. Diabetic neuropathy is the impact of diabetes on the nervous system, most commonly causing numbness, tingling and pain in the feet and also increasing the risk of skin damage due to altered sensation. Together with vascular disease in the legs, neuropathy contributes to the risk of diabetes-related foot problems (such as diabetic foot ulcers) that can be difficult to treat and occasionally require amputation.

[000658] In embodiments, a compound or pharmaceutically acceptable salt thereof as described herein can be used for reducing risk of Diabetes. Risk factors associated with diabetes in general, and with the development of Type 2 diabetes in particular, include a family history of diabetes, belonging to certain ethnic or racial groups, a history of gestational diabetes, obesity, in particular, high levels of visceral or abdominal fat, a sedentary lifestyle, age, high blood pressure, schizophrenia, as well as

altered glucose metabolism, including impaired glucose tolerance (IGT) or prediabetes. Therefore, there is a need in the art for effective means of treating and preventing the development and progression of risk factors associated with diabetes.

[000659] Anti-diabetics traditionally used to treat Diabetes include insulin sensitizers including biguanides such as Metformin, Buformin and Phenformin, TZD's (PPAR) such as Pioglitazone, Rivoglitazone, Rosiglitazone and Troglitazone, dual PPAR agonists such as Aloglitazar, Muraglitazar and Tesaglitazar, or secretagogues including sulphonylureas such as Carbutamide, Chloropropamide, Gliclazide, Tolbutamide, Tolazamide, Glipizide, Glibenclamide, Glyburide, Glipidone, Glycypyramide and Glimepiride, Meglitinides/glinides (K+) such as Nateglinide, Repaglinide and Mitiglinide, GLP-1 analogs such as Exenatide, Liraglutide and Albiglutide, DPP-4 inhibitors such as Alogliptin, Linagliptin, Saxagliptin, Sitagliptin and Vildagliptin, insulin analogs or special formulations such as (fast acting) Insulin lispro, Insulin aspart, Insulin glulisine, (long acting) Insulin glargine, Insulin detemir), inhalable insulin—Exubra and NPH insulin, and others including alpha-glucosidase inhibitors such as Acarbose, Miglitol and Voglibose, amylin analogues such as Pramlintide, SGLT2 inhibitors such as Dapagliflozin, Remogliflozin and Sergliflozin as well as miscellaneous ones including Benfluorex and Tolrestat.

[000660] Insulin is the primary treatment for Type 1 diabetes and its use as a treatment for Type 2 diabetes is becoming more prevalent. Insulin is administered through a course of injections that need to be administered in a carefully scheduled fashion, often requiring daily or even multiple daily injections. Treatments requiring injections of insulin carry with them associated risks of hypoglycemia and hyperinsulinemia. Further, the success of such treatments is often compromised by lack of patient compliance, i.e., failure to follow the recommended treatment schedule. There is a need for courses of treatment that have improved ease of administration, increasing patient comfort as well as the likelihood of patient compliance.

Marfan Syndrome

[000661] In embodiments, compounds and pharmaceutically acceptable salts described herein can be used to treating a Marfan syndrome in a subject in need thereof.

Muscular Dystrophy

[000662] In embodiments, compounds and pharmaceutically acceptable salts described herein can be used to treating a muscular dystrophy in a subject in need thereof.

Radiation Sickness

[000663] In embodiments, compounds and pharmaceutically acceptable salts described herein can be used to treating a radiation sickness in a subject in need thereof.

Renal Diseases and Disorders

[000664] In embodiments, compounds and pharmaceutically acceptable salts described herein can be used to treating a renal diseases and disorders in a subject in need thereof.

[000665] In embodiments, a renal disease or disorder is renal dysfunction.

[000666] In embodiments, a renal disease or disorder is acute kidney injury.

[000667] In embodiments, a renal disease or disorder is chronic kidney disease.

[000668] In embodiments, a renal disease or disorder is glomerulonephritis.

[000669] In embodiments, a renal disease or disorder is glomerular sclerosis.

[000670] In embodiments, a renal disease or disorder is renal insufficiency.

[000671] In embodiments, a renal disease or disorder is nephropathies. In embodiments, a disease or disorder is kidney failure.

[000672] In embodiments, a renal disease or disorder is kidney (renal) fibrosis.

Sarcopenia

[000673] In embodiments, compounds and pharmaceutically acceptable salts described herein can be used to treating a sarcopenia in a subject in need thereof.

Stroke

[000674] In embodiments, compounds and pharmaceutically acceptable salts described herein can be used to treating a stroke in a subject in need thereof.

[000675] In embodiments, a stroke is an ischemic stroke.

[000676] In embodiments, a stroke is hemorrhagic stroke.

[000677] The brain is highly vulnerable to a disturbance in its oxygen supply. Anoxia and ischemia lasting only a few seconds can cause symptoms and if the condition persists for minutes, they can cause irreversible neuronal damage. Accordingly, stroke is a prominent cause of serious, long-term disability and a leading cause of death in the United States. Stroke is also a significant burden on the

medical industry, with total health costs for disability due to stroke being estimated at approximately \$53 billion annually.

[000678] There are two types of stroke: ischemic and hemorrhagic. Ischemic stroke involves an obstruction in one or more blood vessels that supply blood to brain tissue, for example, occlusion resulting from atherosclerotic thrombi, or embolism. Ischemic stroke (cerebral ischemia) represents approximately 88% of all strokes, making ischemic stroke one of the most common types of cerebrovascular injury. Ischemic conditions in the brain quickly lead to neuronal death, often leading to permanent sensorimotor deficits. A hemorrhagic stroke is defined herein as the accumulation of blood anywhere within the cranial vault. Hemorrhagic strokes may result from many causes, including injury resulting from an expanding hematoma, which can disrupt or distort tissue.

[000679] A stroke may cause a wide variety of symptoms and/or complications. Without wishing to be held to a particular theory, it is thought that the specific signs, symptoms and/or complications, as well as their severity and duration, may be determined by where the stroke occurs in a brain as well as how severe it is. Because the brain controls or modulates nearly every system in the body, the range of potential signs, symptoms and/or complications is vast. In some embodiments, the signs, symptoms, and/or complications arising from a stroke include one or more of neurological impairment, cognitive impairment, language impairment, emotional impairment (e.g., depression, anxiety), and motor impairment. According to various embodiments, exemplary, non-limiting signs, symptoms and/or complications of stroke include, but are not limited to: paralysis, memory loss, pain, seizure, dysphagia (difficulty swallowing), aphasia (loss of speech or language ability), dysarthria (difficulty articulating words), ataxia (lack of coordinated movements), depression, mood swings, and loss of vision. In some embodiments, paralysis is partial (e.g., limited to one muscle group, area of the body, and/or side of the body). In some embodiments, paralysis is substantially complete (e.g., affecting both sides of the body and most or all voluntary muscles below the neck). Those of skill in the art will be able to readily identify several additional signs, symptoms and/or complications of stroke, the treatment of each of which is contemplated as within the scope of the present invention.

[000680] While it can be difficult to accurately catalog every sign, symptom or complication in order to determine an accurate clinical picture of a stroke sufferer, several impairment and rating scales exist to aid medical personnel in determining the proper therapy(ies) for a patient as well as the effectiveness of therapy. Exemplary, non-limiting assessment/rating scales include, but are not

limited to: the National Institutes of Health Stroke Scale (NIHSS), the Canadian Neurological Scale, the Middle Cerebral Artery Neurological Score, Guy's Prognostic Score, the American Heart Association's Stroke Outcome Classification (AHA SOC), the Mini-Mental State Examination (MMSE), the Neurobehavioral Cognitive Status Examination (NCSE), the American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults, the Boston Diagnostic Aphasia Examination, the Center for Epidemiologic Studies Depression (CES-D) Scale, the Geriatric Depression Scale, the Basic Activities of Daily Living (BADL), the Instrumental Activities of Daily Living (IADL), the Functional Independence Measure (FIM), and the Barthel Index. Those of skill in the art will recognize additional rating scales that may be of use according to some embodiments.

Peripheral vascular disease

[000681] In embodiments, compounds and pharmaceutically acceptable salts described herein can be used to treating a peripheral vascular disease in a subject in need thereof.

Preeclampsia

[000682] In embodiments, compounds and pharmaceutically acceptable salts described herein can be used to treating a preeclampsia disease in a subject in need thereof.

Pulmonary Diseases and Disorders

[000683] In embodiments, a compound described herein, or any pharmaceutically acceptable salt thereof, is useful in methods of treating a pulmonary disease or disorder in a subject in need thereof.

[000684] In embodiments, a disease or disorder is pulmonary fibrosis.

[000685] In embodiments, a pulmonary disease or disorder is bronchitis, pulmonary fibrosis, asthma, acute respiratory distress syndrome, and pneumonia that results as a complication of infection by viruses including coronaviruses (CoVs), respiratory syncytial virus, avian influenza A H5N1, H1N1 virus and others, as well as other pathogens. In embodiments, said Coronaviruses include Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) and Coronavirus Disease 2019 (COVID-19).

[000686] In embodiments, a pulmonary disease or disorder is lung inflammation, pneumonia, acute lung injury, pulmonary hypertension, pulmonary fibrosis, and chronic obstructive pulmonary disease) and respiratory disease or conditions (e.g., respiratory infection, acute respiratory distress syndrome).

- [000687] In embodiments, a pulmonary disease or disorder is pulmonary hypertension.
- [000688] In embodiments, a pulmonary disease or disorder is Chronic Obstructive Pulmonary Disease (COPD).
- [000689] In embodiments, a pulmonary disease or disorder is chronic bronchitis.
- [000690] In embodiments, a pulmonary disease or disorder is emphysema.
- [000691] In embodiments, a pulmonary disease or disorder is asthma.
- [000692] In embodiments, a pulmonary disease or disorder is cystic fibrosis.
- [000693] In embodiments, a pulmonary disease or disorder is acute lung injury (ALI).
- [000694] In embodiments, a pulmonary disease or disorder is acute respiratory distress syndrome (ARDS).

EXAMPLES

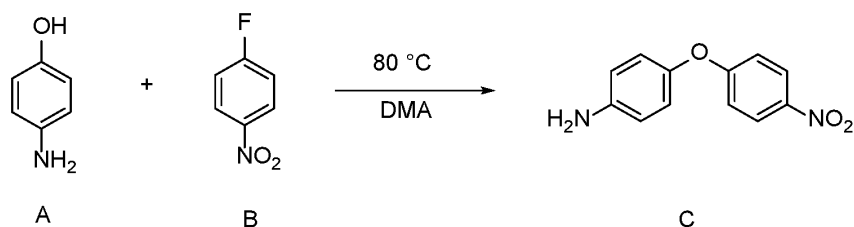
[000695] Exemplary features, objects, and advantages of the present invention are apparent in the examples that follow. It should be understood, however, that the examples, while indicating embodiments of the present invention, are given by way of illustration only, not limitation. Various changes and modifications within the scope of the invention will become apparent to those skilled in the art from the examples.

Example 1. Synthesis for Exemplary Compounds

[000696] Compounds (1)-(36) can be prepared according to methods known in the art. Exemplary methods and characterization data are provided below.

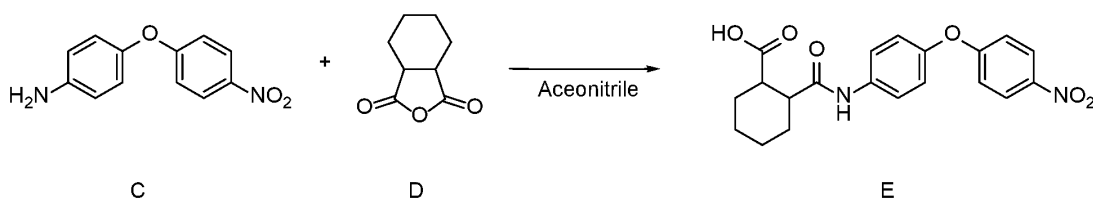
[000697] Compound (5) is synthesized according to the steps shown below.

[000698] Step 1.



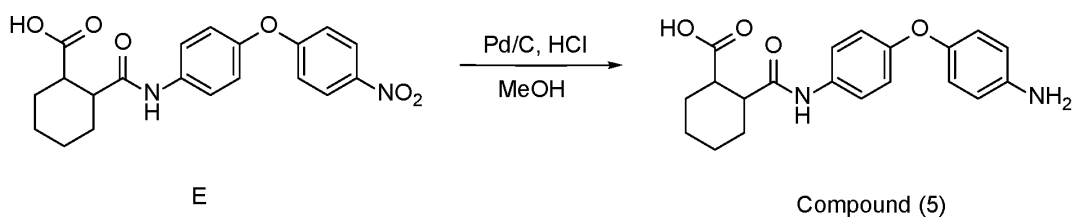
[000699] A suspension of A (1.09 g), B (1.41 g) and potassium carbonate (4.15 g) in dimethylacetamide (DMA) was stirred at 80 °C for 72h. After the reaction was deemed completion, water was added to the reaction mixture. C (2.3 g) was collected from precipitation.

[000700] Step 2.



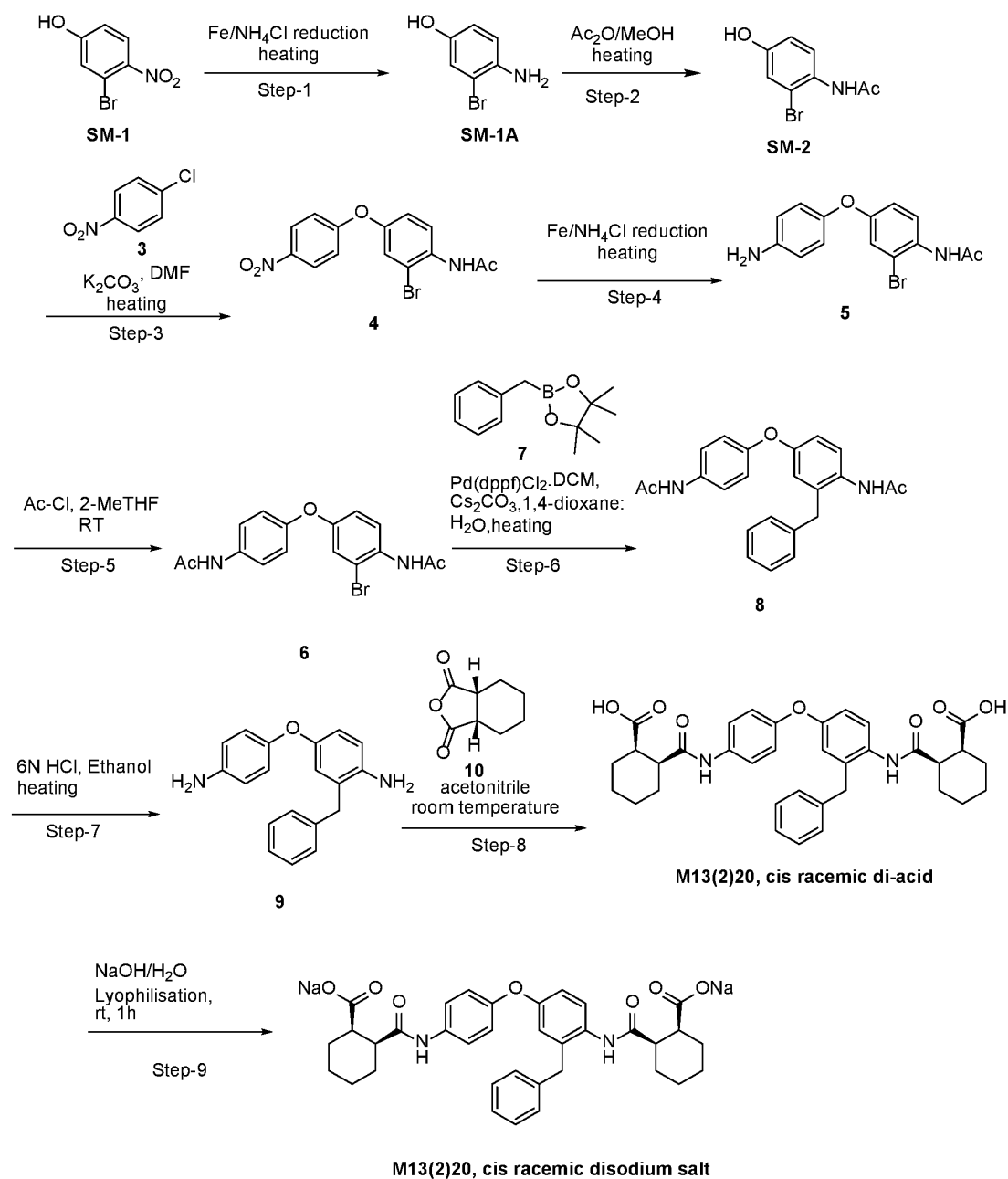
[000701] To a solution of C (230 mg) in acetonitrile was added D (154 mg) and the reaction mixture was stirred at room temperature for overnight. After the reaction was deemed completion, the reaction mixture was concentrated under reduced pressure and E (384 mg) was obtained.

[000702] Step 3.



[000703] E (384 mg) was dissolved in MeOH. To the resulting solution, aqueous HCl was added, followed by a suspension of Pd/C (containing 40 mg Pd) in water. The resulting mixture underwent a gas exchange with argon by evacuation under reduced pressure and backfilling with argon. The gas exchange process was repeated for three times. The resulting mixture underwent an additional gas exchange with hydrogen (H₂) by evacuation under reduced pressure and backfilling with hydrogen. The resulting suspension was stirred under H₂ for overnight. The resulting mixture underwent a gas exchange with argon for three times and the suspension was filtered with a pad of celite. The filtrate was concentrated under reduced pressure. The crude product was purified by prep-HPLC, followed by treatment with NaOH. The resulting material was further lyophilized to dryness, giving a mixture of Compound (5) (100 mg) and its corresponding sodium salt (94 mg).

[000704] The compounds (1)-(36) can also be synthesized through the below synthetic route.



[000705] **SM-1** is reduced to provide the **SM-1A**. The aniline derivative was acetylated to **SM-2**. Starting material **3** was *O*-arylated with **SM-2** to access intermediate **4**, which is reduced to provide intermediate **5**. Intermediate **5** is further acetylated to intermediate **6**, which is subjected to the Suzuki coupling to provide benzylated intermediate **8**. An exhaustive deprotection of the acetamidyl groups of intermediate **8** delivers free amine intermediate **9**, which is acetylated with compound **10**

to M13(2)20. At this point, the disodium salt of M13(2)2 can be prepared by treating with sodium base and subsequent lyophilization to afford disodium salt of M13(2)20.

[000706] Provided herein are characterization data for certain compounds of the synthetic route.

[000707] 4-amino-3-bromophenol **SM-1A** (8 g, 92.76 % Yield, brown solid): $^1\text{H NMR}$ (DMSO- d_6) δ : 8.79 (s, 1H), 6.78 (d, J = 2.8 Hz, 1H), 6.66 (d, J = 8.6 Hz, 1H), 6.55 (dd, J = 8.8, 2.4 Hz, 1H), 4.60 (s, 2H) ppm. **LCMS**: (ES+) 94.76%, m/z = 189.70 [M+H].

[000708] N-(2-bromo-4-hydroxyphenyl) acetamide **SM-2** (800 mg, 70 % Yield, brown solid): $^1\text{H NMR}$ (DMSO- d_6) δ : 9.78 (br s, 1H), 9.28 (s, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.00 (d, J = 2.4 Hz, 1H), 6.74 (dd, J = 8.8, 2.0 Hz, 1H), 2.00 (br s, 3H) ppm. **LCMS**: (ES+) 94.36%, m/z = 231.96 [M+H].

[000709] N-(2-bromo-4-(4-nitrophenoxy) phenyl) acetamide **4** (2.3 g, 75% Yield, pale-yellow solid): $^1\text{H NMR}$ (DMSO- d_6) δ : 9.52 (br s, 1H), 8.27 (d, J = 9.2 Hz, 2H), 7.66 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 2.4 Hz, 1H), 7.15-7.24 (m, 3H), 2.09 (s, 3H) ppm. **LCMS**: (ES+) 96.86%, m/z = 352.71 [M+H]

[000710] N-(4-(4-aminophenoxy)-2-bromophenyl) acetamide **5** (40 g, 87.4% Yield, pale pink solid): $^1\text{H NMR}$ (DMSO- d_6) δ : 9.40 (br s, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.04 (br s, 1H), 6.87 (d, J = 8.8 Hz, 1H), 6.75-6.83 (m, 2H), 6.60 (d, J = 8.8 Hz, 2H), 5.04 (s, 2H), 2.03 (s, 3H) ppm. **LCMS**: (ES+) 92.13%, m/z = 322.84 [M+H].

[000711] N-(4-(4-acetamido-3-bromophenoxy) phenyl) acetamide **6** (40 g, 88.4% Yield, brown gummy): $^1\text{H NMR}$ (DMSO- d_6) δ : 9.98 (s, 1H), 9.44 (br s, 1H), 7.58-7.64 (d, J = 8.8 Hz, 2H), 7.47 (d, J = 8.8 Hz, 1H), 7.19 (br s, 1H), 7.02 (d, J = 8.8 Hz, 2H), 6.95 (dd, J = 8.8, 2.4 Hz, 1H), 2.04 (br s, 6H) ppm. **LCMS**: (ES+) 93.14%, m/z = 364.94 [M+H].

[000712] N-(4-(4-acetamido-3-benzylphenoxy) phenyl) acetamide **8** (13 g, 90.08% Yield, off white solid): $^1\text{H NMR}$ (DMSO- d_6) δ : 7.53 (d, J = 8.8 Hz, 2H), 7.21-7.31 (m, 3H), 7.12-7.19 (m, 3H), 6.90 (d, J = 8.8 Hz, 2H), 6.69-6.75 (m, 2H), 3.91 (s, 2H), 2.01 (s, 3H), 1.94 (br s, 3H) ppm. **LCMS**: (ES+) 86.74%, m/z = 375.1 [M+H].

[000713] 4-(4-aminophenoxy)-2-benzylaniline **9** (8 g, 52 % Yield, off white solid): $^1\text{H NMR}$ (DMSO- d_6) δ : 7.24-7.30 (m, 2H), 7.14-7.22 (m, 3H), 6.56-6.62 (m, 3H), 6.46-6.53 (m, 4H), 4.76 (s, 2H), 4.60 (s, 2H), 3.75 (s, 2H) ppm. **LCMS**: (ES+) 94.70%, m/z = 291.67 [M+H].

[000714] *cis*-2-((4-(3-benzyl-4-(*cis*-2-carboxycyclohexane-1-carboxamido) phenoxy) phenyl)carbamoyl)cyclohexane-1-carboxylic acid **M13(2)20** (14 g, 71.0% Yield, off white solid): ^1H

NMR (DMSO-d₆) δ : 11.95 (br s, 2H), 9.70 (br s, 1H), 9.15 (br s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 6.8 Hz, 2H), 7.12-7.21 (m, 4H), 6.88 (d, J = 8.0 Hz, 2H), 6.69-6.77 (m, 2H), 3.82-3.98 (m, 2H), 2.92 (br s, 2H), 1.93-2.10 (m, 4H), 1.57-1.74 (m, 6H), 1.24-1.46 (m, 8H) ppm. **LCMS**: (ES+) 92.27%, m/z = 599.4 [M+H]. **HPLC**: 89.41 % Purity [method: Column: X-Select CSH C18 (4.6*150) mm 5u, Mobile Phase: A - 0.1% Formic acid in water: Acetonitrile (95:05), B – Acetonitrile].

[000715] Sodium *cis*-2-((4-(3-benzyl-4-(*cis*-2-carboxylatocyclohexane-1-carboxamido)phenoxy)phenyl) carbamoyl)cyclohexane-1-carboxylate **M13(2)20 cis racemic disodium salt** (18 g, 44.2% Yield, off white solid): ¹H NMR (DEUTERIUM OXIDE) δ : 7.42 (d, J = 9.0 Hz, 2H), 7.33-7.39 (m, 2H), 7.25-7.31 (m, 2H), 7.21 (d, J = 6.8 Hz, 2H), 7.12 (d, J = 9.2 Hz, 2H), 7.04-7.06 (m, 1H), 7.03 (s, 1H), 3.97 (s, 2H), 2.86-2.92 (m, 1H), 2.73-2.79 (m, 2H), 2.66 (dt, J = 7.6, 4.0 Hz, 1H), 1.99-2.13 (m, 3H), 1.73-1.93 (m, 3H), 1.54-1.72 (m, 5H), 1.47 (dd, J = 11.6, 6.0 Hz, 5H) ppm. **LCMS**: (ES+) 96.29%, m/z = 599.4 [M+ 2Na]. **HPLC**: 96.06 % purity [Column: X-Bridge C18 (4.6*150) mm 5u, Mobile Phase: A - 5mM Ammonium Bicarbonate in water, B – Acetonitrile].

[000716] The relative stereochemistry of **M13(2)20** was assigned by nuclear Overhauser effect experiment via the ¹H NMR spectroscopy.

Example 2. Comparison of small molecules and angiotensin-(1-7) in a diabetic mouse model

[000717] Unexpectedly, small molecule compounds described herein can show similar biological effects in disease models when compared to the peptide angiotensin-(1-7). For example, use of Compound (4) in a diabetic mouse model shows similar effects on blood glucose as compared to angiotensin-(1-7). See **FIG. 1**. In this model, the mice received five consecutive injections with streptozotocin (STZ) to destroy most of the pancreatic beta cells. Treatment with Ang-(1-7) or M13 began twenty-four hours after the last STZ injection.

Example 3. Receptor binding studies

[000718] Compounds described herein were also studied using Receptor-transferred HEK293 cells using intracellular cAMP as a readout. **Table 2** provides exemplary data from these studies, whereby 1 means 100% of the effect observed with 10⁻⁷M Ang-(1-7) and the numbers in brackets illustrate the most efficient concentrations.

[000719] **FIG. 2** shows that Compound (3) unexpectedly has a similar effect to angiotensin-(1-7) in Mesangial cells.

Table 2

Compound/Peptide	pcDNA	Mas	MrgD	AT2
Angiotensin-(1-7)	0	1 (10^{-7} M)	1 (10^{-7} M)	0
Compound (4)	0	1 (10^{-16} to 10^{-12} M)	1	0.5 (10^{-15} to 10^{-14} M)
Compound (3)	0	1 (10^{-14} M)	1 (10^{-15} M)	0

[000720] FIG. 3 depicts similar receptor-binding studies of Compound (5).

Example 4. Use of Compounds in Stroke Models

[000721] Compounds described herein also have been shown to be effective in pre-clinical stroke models. For example, Compound (1)-*cis/cis* has been shown to be effective in preclinical stroke models using rat when administered subcutaneously. Comparison to the effects of Angiotensin-(1-7) (TXA127) is also provided. See, for example, FIG. 4A (neuroscore), FIG. 4B (forelimb placement test), FIG. 4C (stepping test), and FIG. 4D (body swing test). Compound (5) has also been studied and shown effective in the same model: see, for example, FIG. 5A (neuroscore), FIG. 5B (forelimb placement test), FIG. 5C (stepping test), and FIG. 5D (body swing test).

[000722] Comparison of Compound (1) (labeled with M13B) and Compound (5) (labeled with M13A) has been tested in stroke. Neurological scores throughout the study (Averages $\pm$ SEM) are shown in FIG. 6.

[000723] Comparison of Compound (1) (labeled with M13B) and Compound (3) (labeled with M13D) has been tested in stroke. Neurological scores throughout the study (Averages $\pm$ SEM) are shown in FIG. 7.

[000724] Individual and group average NSS are presented in Table 3, based on treatment with TXA127, Compound (1) (labeled with M13B) and Compound (5) (labeled with M13A).

Table 3

Treatment Group (NS)	Day-8	Day-15	Day-22	Day-29
1M – 2M (TXA127 SC daily)	**	***	***	***
1M – 3M (TXA127 SC weekly)	*	***	***	*
1M – 4M (M13A SC 100 μ g/kg)	***	***	***	***
1M – 5M (M13A SC 3.2 μ g/kg)	*	***	***	***
1M – 6M (M13A SC 0.1 μ g/kg)	***	**	***	***
1M – 7M (M13B SC 200 μ g/kg)	***	***	***	***
1M – 8M (M13B SC 0.2 μ g/kg)	***	*	***	***

Treatment Group (NS)	Day-8	Day-15	Day-22	Day-29
1M – 9M (TXA127 PO 1 mg/kg)	NS	NS	***	***
1M – 10M (TXA127 PO 5 mg/kg)	***	NS	***	***

NS = Not significant.

Example 5. Colony Formation Studies

[000725] This example studies compounds of the invention in colony formation assays, which is a cell proliferation assay that can be used to study the propensity of individual cells to survive and propagate over periods of time.

[000726] For the colony formation assay, A498 cells were cultured in DMEM medium supplemented with 10% Fetal Bovine Serum and 1% Penicillin Streptomycin. The cells were seeded at 600 cell per well in six-well plates. The compounds were stored in a DMA 10^{-2} M stock solution, and later diluted with PBS to be used as treatment.

[000727] Starting from the following day, cells were treated with a range of concentrations (10^{-11} M to 10^{-7} M) of M13(2)9, M13(2)12, M13(2)13, and M13(2)20 daily, and DMA 10^{-9} M to 10^{-5} M was used as control. Each condition was evaluated in triplicate. After 14 days of treatment, cells were washed once with PBS after medium removal, stained with 0.5% crystal violet for 10 minutes at room temperature, and washed with distilled water. Once the plates were dried, the colonies were quantified. Number of colonies per well are depicted in **FIG. 8** and cell numbers are depicted in **FIG. 9**.

Example 6. Tube Formation Studies

[000728] This example studies compounds of the invention in tube formation assays, which can be used to evaluate the impact in angiogenesis as well as in other diseases.

[000729] For the tube formation assay, human umbilical vein endothelial cells (HUVEC cells) were thawed late afternoon without centrifugation, and seeded on a 75 cm² flask containing Endothelial Medium supplemented with 10% FBS. The next day, the medium was changed and 20mL of complete medium was added. The ECM gel aliquots were moved from -20°C to 4°C, and the 200 µL tips were placed at -20°C.

[000730] The next day, day 3, the medium from the cells was changed into empty medium (Endothelial Medium 0% FBS) and incubated for 1 hour. During the incubation time, 100 µL of ECM gel was added to the corresponding well on the 96-well plate without making bubbles, and incubated at 37°C. The compounds were prepared in a range of concentrations (10^{-11} M and 10^{-7} M).

[000731] After 1h incubation, the cells were washed two times with PBS and 2mL of Trypsin was added. Once the cells were detached, the Trypsin was neutralized using complete medium and the cells were centrifuge at 1100g for 2min at 25°C. Count the cells to seed 25000 cells in 200 μ L of medium.

[000732] The cells were treated with M13, M13(2)9, M13(2)20, and Ang-(1-7) at a concentration of 10^{-11} M and 10^{-7} M; 200 μ L of the treated cells were transferred onto the corresponding wells. After 4 hours, the cells were imaged placing the focus on the middle of the well. The results were analyzed using ImageJ. HUVEC cell tube formation assay is depicted in **FIG. 10**.

Example 7. Ussing Chamber Studies

[000733] This example studies compounds of the invention in Ussing Chamber studies, which can be used to evaluate, for example, epithelial barrier protection.

[000734] Intestinal preparations were mounted in Ussing chambers (exposed area of 0.12 cm²) with 8 ml of Krebs solution (95% O₂/5% CO₂, 37°C) in the basolateral and luminal reservoirs. Tissues were voltage-clamped at 0 mV using an automatic voltage clamp (EVC 4000, World Precision Instruments, Sarasota, Florida), and the short-circuit current (I_{sc}) required to maintain the potential at 0 mV was monitored as a reflection of the net active ion transport across the epithelium. To compromise the barrier function, 0.1 μ g of PTX (Pertussis toxin) was used, and after 10 minutes, the compounds were added to the chambers in a 10^{-11} and 10^{-7} M concentration as 10 minutes intervals, and EA (Endogenous agonist) was used as a control. The resistance was calculated using Ohms law. The experiments were carried out simultaneously in chambers connected to a PC equipped with DataTrax II software (WPI). The transepithelial electrical resistances from the Ussing chamber studies are depicted in **FIGS. 11 and 12**.

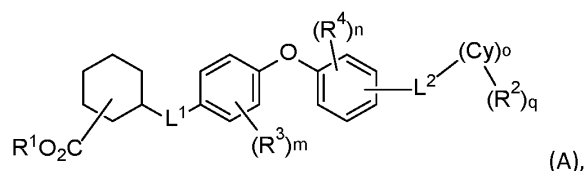
[000735] The data show that the instantly claimed compounds can act via Mas/MrgD in view of the lack of response from double knockout mice whereas a response is observed with the AT2 specific agonist EA.

EQUIVALENTS AND SCOPE

[000736] Those skilled in the art will recognize or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. The scope of the present invention is not intended to be limited to the above description, but rather is as set forth in the following claims.

CLAIMS

1. A method of treating a disease or disorder, said method comprising administering to a subject in need thereof a compound having a structure according to Formula (A),



or a pharmaceutically acceptable salt thereof, wherein

each of R^1 and R^5 is independently H or C_1 - C_6 alkyl;

R^2 is independently H, OH, or $(CH_2)_pCO_2R^5$;

R^3 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1-R^6 ;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1-R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

L^1 is independently a covalent bond, $C(O)$, $C(O)NR^{7A}$, or $NR^{7A}C(O)$;

L^2 is independently a covalent bond, CH_2 , $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7A} is independently H or C_1 - C_6 alkyl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

Cy is independently C_5 - C_{10} cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

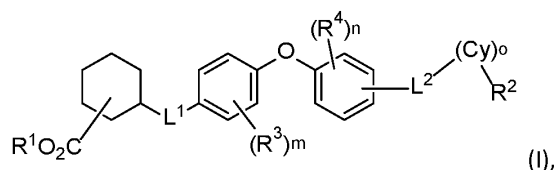
each of m , n , and o is independently 0, 1, or 2;

p is independently 0 or 1; and

q is independently 0, 1, 2, or 3, and

wherein the disease or disorder is one that benefits from modulation Mas or MrgD receptors.

2. The method of claim 1, wherein said compound has a structure according to Formula (I),



or a pharmaceutically acceptable salt thereof, wherein

each of R^1 and R^5 is independently H or C_1 - C_6 alkyl;

R^2 is independently H or $(CH_2)_pCO_2R^5$;

R^3 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1 - R^6 ;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1 - R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

L^1 is independently a covalent bond, $C(O)$, $C(O)NR^{7A}$, or $NR^{7A}C(O)$;

L^2 is independently a covalent bond, CH_2 , $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7A} is independently H or C_1 - C_6 alkyl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

Cy is independently C_5 - C_{10} cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

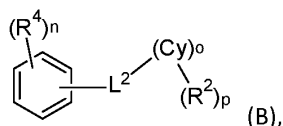
each of m , n , and o is independently 0, 1, or 2; and

p is independently 0 or 1.

and

wherein the disease or disorder is one that benefits from modulation of Mas or MrgD receptors

3. A method of treating a disease or disorder, said method comprising administering to a subject in need thereof a compound having a structure according to Formula (B),



or a pharmaceutically acceptable salt thereof, wherein

R^2 is independently H, OH, or $(CH_2)_pCO_2R^5$;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1 - R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

R^5 is independently H or C_1 - C_6 alkyl;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

L^2 is independently a covalent bond, $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

Cy is independently C_5 - C_7 cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

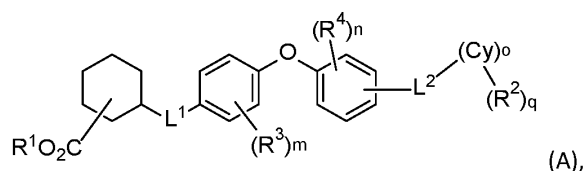
each of n and o is independently 0, 1, or 2;

p is independently 0, 1, 2, or 3, and

wherein the disease or disorder is one that benefits from modulation Mas or MrgD receptors.

4. The method of any one of claims 1-3, wherein the disease or disorder is cancer, cardiomyopathy, cardiovascular disease, renal disease, inflammation, a metabolic disease or disorder, preeclampsia, peripheral vascular disease, fibrotic disease, endothelial disease, hemorrhagic fever, malaria, muscular dystrophy, Marfan syndrome, radiation sickness, or sarcopenia.
5. The method of claim 4, wherein the disease or disorder is cancer.
6. The method of claim 4, wherein the disease or disorder is cardiomyopathy.
7. The method of claim 4, wherein the cardiovascular disease is selected from hypertension, heart failure, stroke, atherosclerosis, and aortic aneurysm.
8. The method of claim 4, wherein the renal disease is renal dysfunction.
9. The method of claim 4, wherein the disease or disorder is inflammation.
10. The method of claim 4, wherein the metabolic disease or disorder is diabetes.
11. The method of claim 4, wherein the disease or disorder is preeclampsia.
12. The method of claim 4, wherein the disease or disorder is peripheral vascular disease.

13. The method of claim 4, wherein the disease or disorder is fibrotic disease.
14. The method of claim 4, wherein the fibrotic disease is pulmonary fibrosis.
15. The method of claim 4, wherein the disease or disorder is endothelial disease.
16. The method of claim 4, wherein the hemorrhagic fever is Ebola disease.
17. The method of claim 4, wherein the malaria is severe malaria or cerebral malaria.
18. The method of claim 4, wherein the disease or disorder is muscular dystrophy.
19. The method of claim 4, wherein the disease or disorder is Marfan syndrome.
20. The method of claim 4, wherein the disease or disorder is radiation sickness.
21. The method of claim 4, wherein the disease or disorder is sarcopenia.
22. The method of claim 4, wherein the disease or disorder is stroke.
23. A method of modulating glucose metabolism, said method comprising administering to a subject in need thereof a compound having a structure according to Formula (A),



or a pharmaceutically acceptable salt thereof, wherein

each of **R**¹ and **R**⁵ is independently H or C₁-C₆ alkyl;

R² is independently H, OH, or (CH₂)_pCO₂R⁵;

R³ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶;

R⁴ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶, or two **R**⁴ on adjacent carbons combine to form a heteroaryl moiety, or one **R**⁴ combines with **R**^{7B} to form a heteroaryl moiety;

L¹ is independently a covalent bond, C(O), C(O)NR^{7A}, or NR^{7A}C(O);

L² is independently a covalent bond, CH₂, C(O), NR^{7B}, C(O)NR^{7B}, or NR^{7B}C(O);

R⁶ is independently C₆-C₁₀ aryl or 5- to 10-membered heteroaryl;

each **R**^{7A} is independently H or C₁-C₆ alkyl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

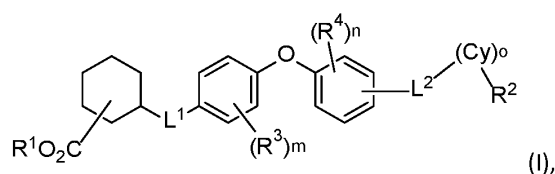
Cy is independently C_5 - C_{10} cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of **m**, **n**, and **o** is independently 0, 1, or 2;

p is independently 0 or 1; and

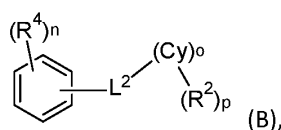
q is independently 0, 1, 2, or 3.

24. The method of claim 23, having a structure according to Formula (I),



or a pharmaceutically acceptable salt thereof.

25. A method of modulating glucose metabolism, said method comprising administering to a subject in need thereof a compound having a structure according to Formula (B),



or a pharmaceutically acceptable salt thereof, wherein

R^2 is independently H, OH, or $(CH_2)_pCO_2R^5$;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1 - R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

R^5 is independently H or C_1 - C_6 alkyl;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

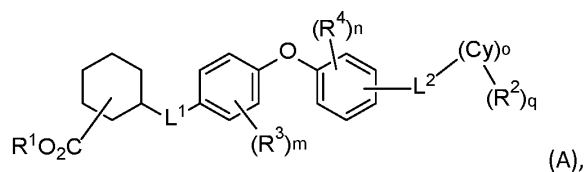
L^2 is independently a covalent bond, $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

Cy is independently C_5 - C_7 cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of **n**, and **o** is independently 0, 1, or 2; and

p is independently 0, 1, 2, or 3.

26. The method of any one of claims 23-25, wherein the subject has diabetes.
27. A method of treating a cerebrovascular disease or disorder, said method comprising administering to a subject in need thereof a compound having a structure according to Formula (A),



or a pharmaceutically acceptable salt thereof, wherein

each of **R**¹ and **R**⁵ is independently H or C₁-C₆ alkyl;

R² is independently H, OH, or (CH₂)_pCO₂R⁵;

R³ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶;

R⁴ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶, or two **R**⁴ on adjacent carbons combine to form a heteroaryl moiety, or one **R**⁴ combines with **R**^{7B} to form a heteroaryl moiety;

L¹ is independently a covalent bond, C(O), C(O)NR^{7A}, or NR^{7A}C(O);

L² is independently a covalent bond, CH₂, C(O), NR^{7B}, C(O)NR^{7B}, or NR^{7B}C(O);

R⁶ is independently C₆-C₁₀ aryl or 5- to 10-membered heteroaryl;

each **R**^{7A} is independently H or C₁-C₆ alkyl;

each **R**^{7B} is independently H or C₁-C₆ alkyl, or **R**^{7B} combines with **R**⁴ to form a heteroaryl moiety;

X¹ is independently a covalent bond, O, or CH₂;

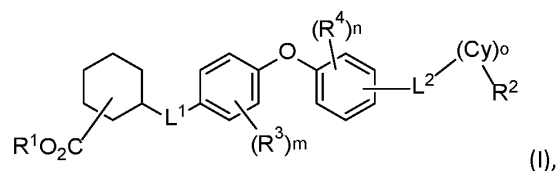
Cy is independently C₅-C₁₀ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of **m**, **n**, and **o** is independently 0, 1, or 2;

p is independently 0 or 1; and

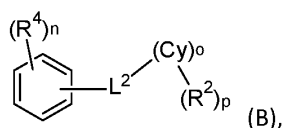
q is independently 0, 1, 2, or 3.

28. The method of claim 27, having a structure according to Formula (I),



or a pharmaceutically acceptable salt thereof.

29. A method of treating a cerebrovascular disease or disorder, said method comprising administering to a subject in need thereof a compound having a structure according to Formula (B),



or a pharmaceutically acceptable salt thereof, wherein

R^2 is independently H, OH, or $(CH_2)_pCO_2R^5$;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1-R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

R^5 is independently H or C_1 - C_6 alkyl;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

L^2 is independently a covalent bond, $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

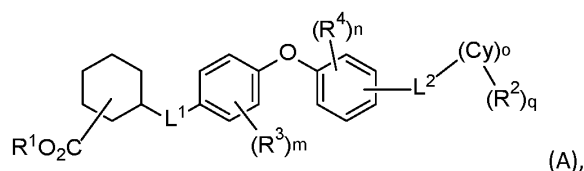
Cy is independently C_5 - C_7 cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of n and o is independently 0, 1, or 2; and

p is independently 0, 1, 2, or 3.

30. The method of any one of claims 27-29, wherein the cerebrovascular disease or condition is stroke.

31. The method of claim 30, wherein the cerebrovascular disease or condition is ischemic stroke, hemorrhagic stroke, or a combination thereof.
32. A method of treating a neurological disease or disorder, said method comprising administering to a subject in need thereof a compound having a structure according to Formula (A),



or a pharmaceutically acceptable salt thereof, wherein

each of **R**¹ and **R**⁵ is independently H or C₁-C₆ alkyl;

R² is independently H, OH, or (CH₂)_pCO₂R⁵;

R³ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶;

R⁴ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶, or two **R**⁴ on adjacent carbons combine to form a heteroaryl moiety, or one **R**⁴ combines with **R**^{7B} to form a heteroaryl moiety;

L¹ is independently a covalent bond, C(O), C(O)NR^{7A}, or NR^{7A}C(O);

L² is independently a covalent bond, CH₂, C(O), NR^{7B}, C(O)NR^{7B}, or NR^{7B}C(O);

R⁶ is independently C₆-C₁₀ aryl or 5- to 10-membered heteroaryl;

each **R**^{7A} is independently H or C₁-C₆ alkyl;

each **R**^{7B} is independently H or C₁-C₆ alkyl, or **R**^{7B} combines with **R**⁴ to form a heteroaryl moiety;

X¹ is independently a covalent bond, O, or CH₂;

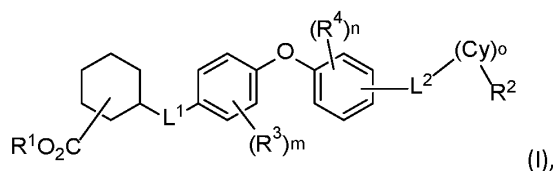
Cy is independently C₅-C₁₀ cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of **m**, **n**, and **o** is independently 0, 1, or 2;

p is independently 0 or 1; and

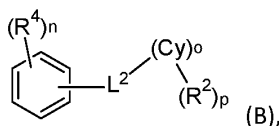
q is independently 0, 1, 2, or 3.

33. The method of claim 32, having a structure according to Formula (I),



or a pharmaceutically acceptable salt thereof.

34. A method of treating a neurological disease or disorder, said method comprising administering to a subject in need thereof a compound having a structure according to Formula (B),



or a pharmaceutically acceptable salt thereof, wherein

R^2 is independently H, OH, or $(CH_2)_pCO_2R^5$;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1-R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

R^5 is independently H or C_1 - C_6 alkyl;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

L^2 is independently a covalent bond, $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

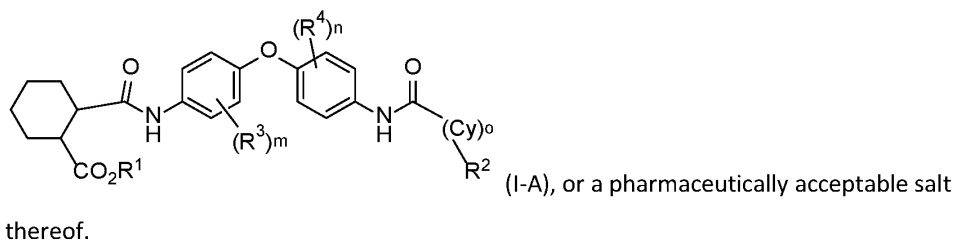
Cy is independently C_5 - C_7 cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of n and o is independently 0, 1, or 2; and

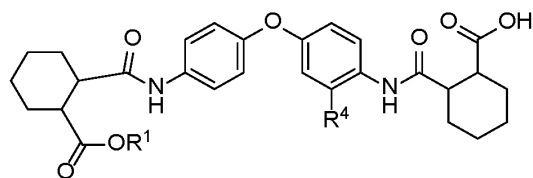
p is independently 0, 1, 2, or 3.

35. The method of any one of claims 1-34, wherein each of R^1 and R^5 is independently H.

36. The method of any one of claims 1-35, wherein
 m and n are both 0; or
 one of m and n is 1, and the other is 0.
37. The method of any one of claims 1-36, wherein R^3 is independently methyl and/or R^4 is independently methyl, isopropyl, or benzyl.
38. The method of any one of claims 1-37, wherein L^1 is a covalent bond, o is 0, and R^2 is H.
39. The method of any one of claims 1-37, wherein L^1 is $NHC(O)$ and o is 1.
40. The method of any one of claims 1-39, wherein L^2 is a covalent bond, o is 0, and R^2 is H.
41. The method of any one of claims 1-39, wherein L^2 is $NHC(O)$ and o is 1.
42. The method of any one of claims 1-39, wherein L^2 is NR^{7B} and o is 0 or 1.
43. The method of claim 42, wherein R^{7B} is H or C_1-C_6 alkyl.
44. The method of claim 42, wherein R^{7B} is H.
45. The method of claim 42, wherein R^{7B} is C_1-C_6 alkyl.
46. The method of claim 42, wherein R^{7B} combines with R^4 to form a heteroaryl moiety.
47. The method of any one of claims 1-46, wherein Cy is phenyl.
48. The method of any one of claims 1-46, wherein Cy is cyclohexyl.
49. The method of any one of claims 1-46, wherein Cy is cyclopentyl.
50. The method of any one of claims 1, 2, 4-24, 26-28, 30-33, and 35-49, wherein said compound has a structure according to Formula (I-A),

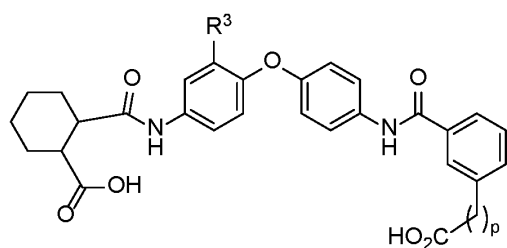


51. The method of any one of claims 1, 2, 4-24, 26-28, 30-33, and 35-49, wherein said compound has a structure according to Formula (I-B),



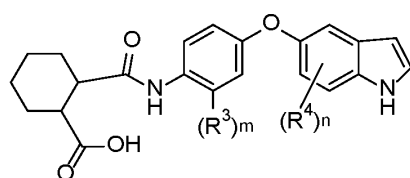
(I-B), or a pharmaceutically acceptable salt thereof.

52. The method of any one of claims 1, 2, 4-24, 26-28, 30-33, and 35-49, wherein said compound has a structure according to Formula (I-C),



(I-C), or a pharmaceutically acceptable salt thereof.

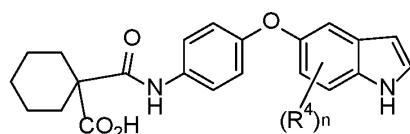
53. The method of any one of claims 1, 2, 4-24, 26-28, 30-33, and 35-49, wherein said compound has a structure according to Formula (I-D),



(I-D), or a pharmaceutically acceptable salt thereof,

wherein each of **m** and **n** is independently 0 or 1.

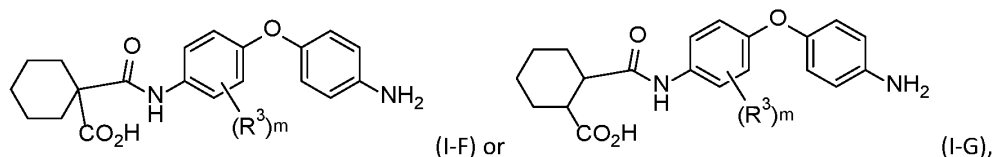
54. The method of any one of claims 1, 2, 4-24, 26-28, 30-33, and 35-49, wherein said compound has a structure according to Formula (I-E),



(I-E), or a pharmaceutically acceptable salt thereof,

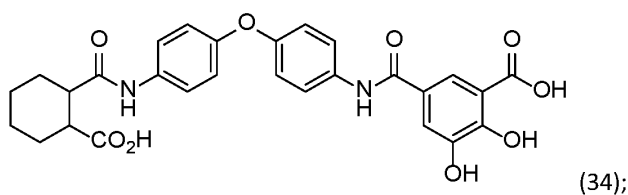
wherein **n** is 0 or 1.

55. The method of any one of claims 1, 2, 4-24, 26-28, 30-33, and 35-49, wherein said compound has a structure according to Formula (I-F) or (I-G),



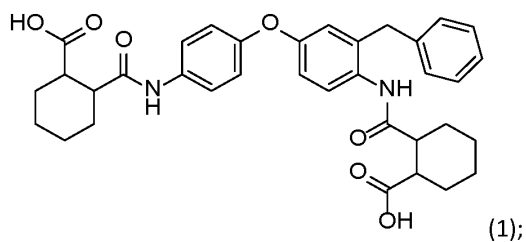
or a pharmaceutically acceptable salt thereof, wherein *m* is 0 or 1.

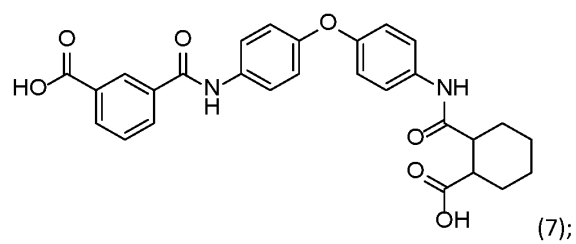
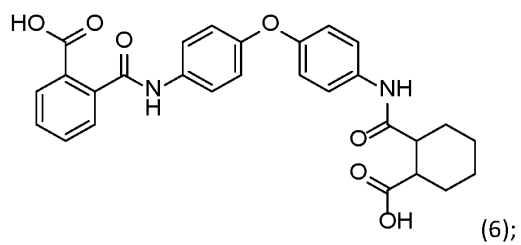
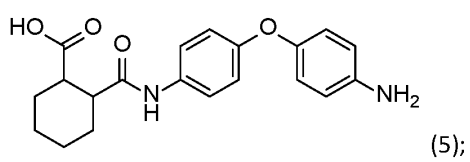
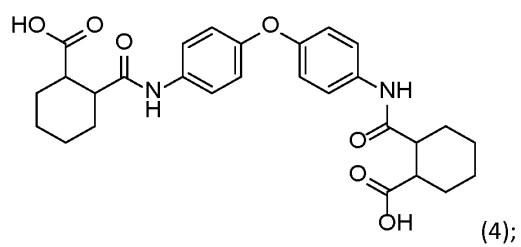
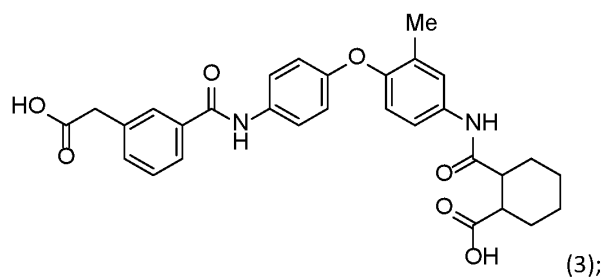
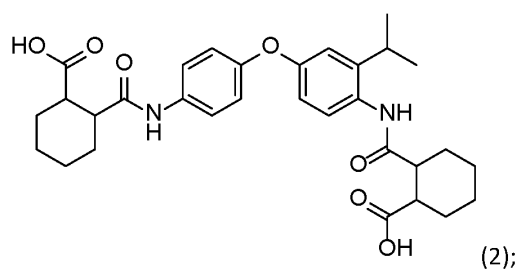
56. The method of any one of claims 50-55, wherein substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.
57. The method of any one of claims 50-55, wherein substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.
58. The method of any one of claims 1, 4-23, 26, 27, 30-32, and 35-49, wherein the compound of Formula (A) is selected from the group consisting of:

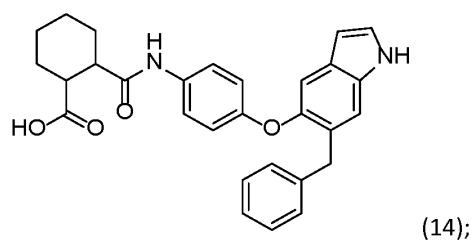
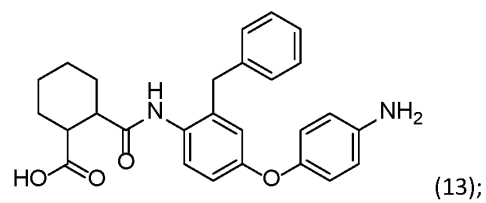
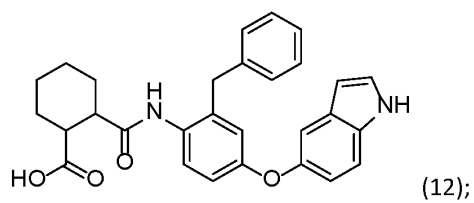
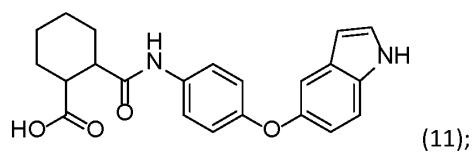
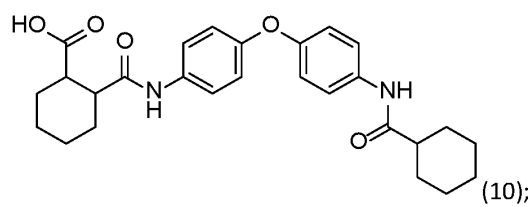
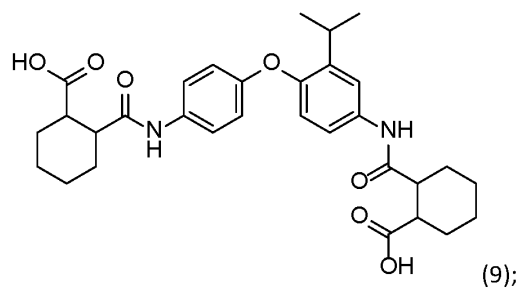
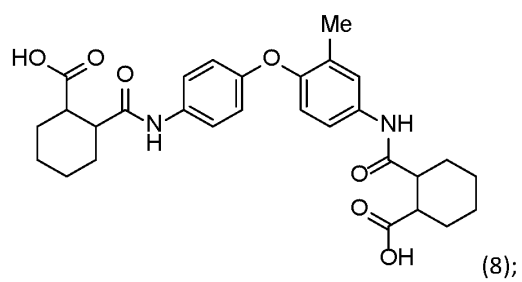


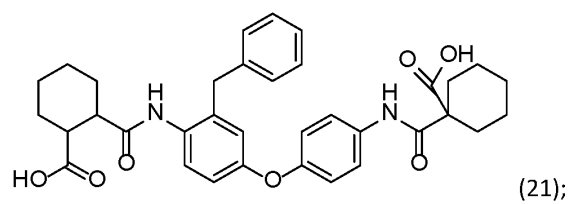
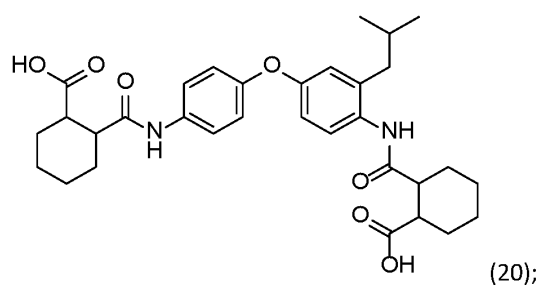
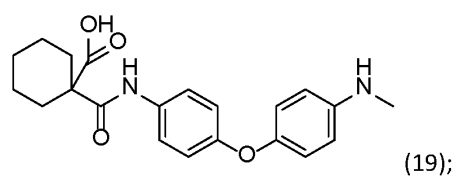
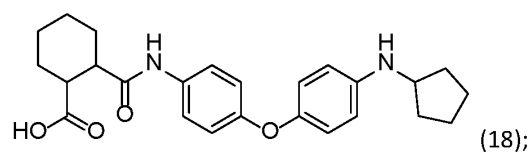
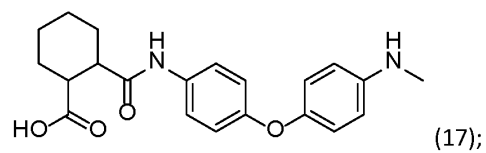
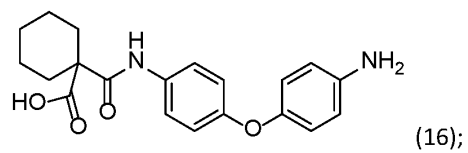
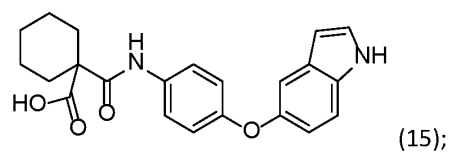
or a pharmaceutically acceptable salt thereof.

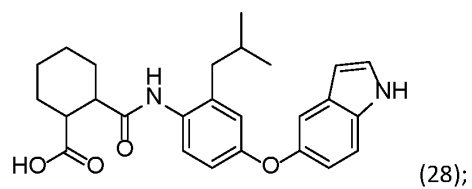
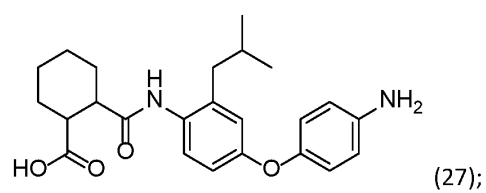
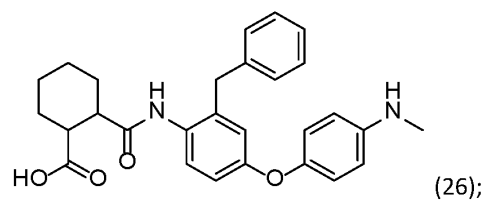
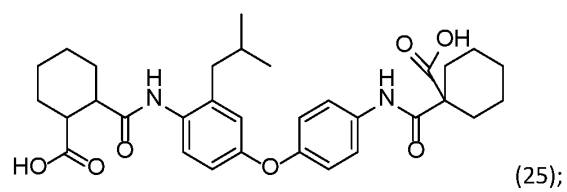
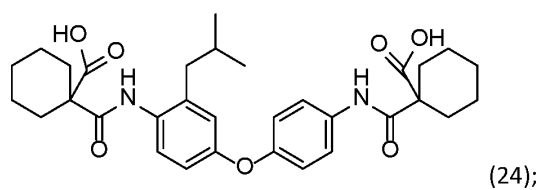
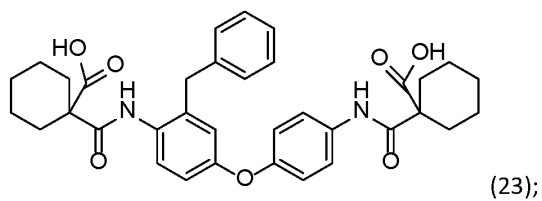
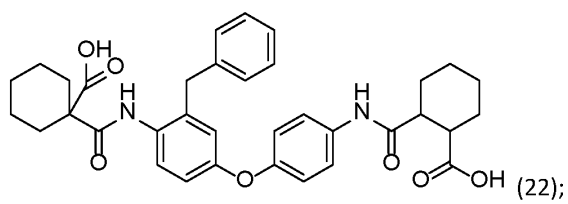
59. The method of any one of claims 2, 4-22, 24, 26, 28, 30, 31, 33, and 35-49, wherein the compound of Formula (I) is selected from the group consisting of:

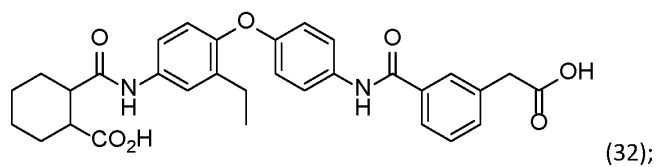
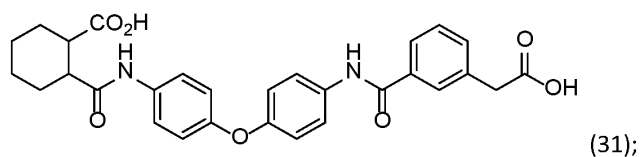
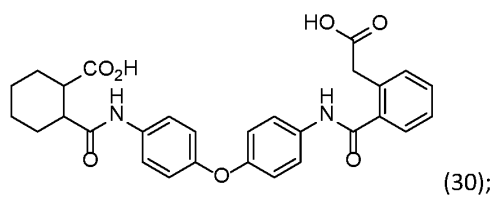
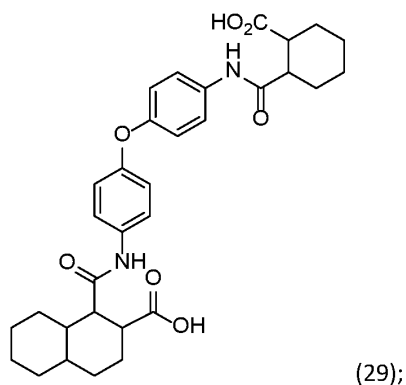




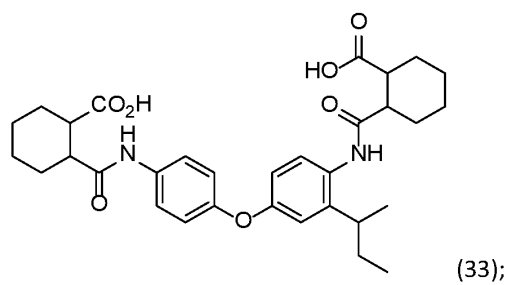






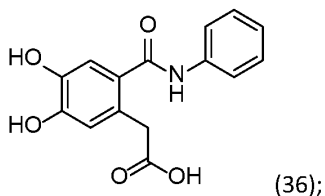
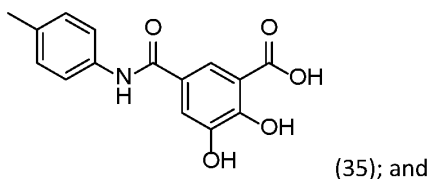


and



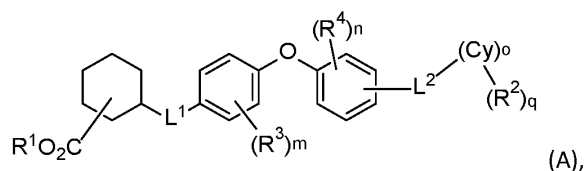
or a pharmaceutically acceptable salt thereof.

60. The method of any one of claims 3, 4-22, 25, 26, 29-31, and 34-49, wherein the compound of Formula (B) is selected from the group consisting of:



or a pharmaceutically acceptable salt thereof.

61. The method of any one of claims 58-60, wherein substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.
62. The method of any one of claims 58-60, wherein substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.
63. The method of any one of claims 1-62, comprising the administration of a pharmaceutically acceptable salt of the compound.
64. A pharmaceutical composition comprising:
 - (1) a therapeutically effective amount of a compound having a structure according to Formula (A),



or a pharmaceutically acceptable salt thereof, wherein

each of **R**¹ and **R**⁵ is independently H or C₁-C₆ alkyl;

R² is independently H, OH, or (CH₂)_pCO₂R⁵;

R³ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶;

R⁴ is independently C₁-C₆ alkyl, 1- to 6-membered heteroalkyl, or X¹-R⁶, or two **R**⁴ on adjacent carbons combine to form a heteroaryl moiety, or one **R**⁴ combines with **R**^{7B} to form a heteroaryl moiety;

L¹ is independently a covalent bond, C(O), C(O)NR^{7A}, or NR^{7A}C(O);

L^2 is independently a covalent bond, CH_2 , $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7A} is independently H or C_1 - C_6 alkyl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

Cy is independently C_5 - C_{10} cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of **m**, **n**, and **o** is independently 0, 1, or 2;

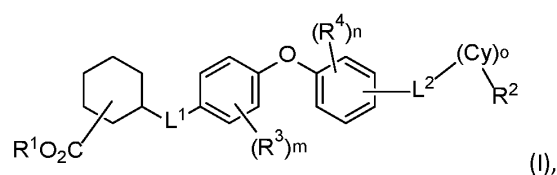
p is independently 0 or 1; and

q is independently 0, 1, 2, or 3; and

(2) a pharmaceutically acceptable excipient.

65. The pharmaceutical composition of claim 64, comprising:

(1) a therapeutically effective amount of a compound having a structure according to Formula (I),



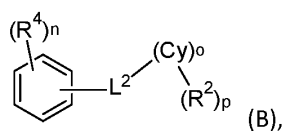
or a pharmaceutically acceptable salt thereof;

and

(2) a pharmaceutically acceptable excipient.

66. A pharmaceutical composition comprising:

(1) a therapeutically effective amount of a compound having a structure according to Formula (B),



or a pharmaceutically acceptable salt thereof, wherein

R^2 is independently H, OH, or $(CH_2)_pCO_2R^5$;

R^4 is independently C_1 - C_6 alkyl, 1- to 6-membered heteroalkyl, or X^1 - R^6 , or two R^4 on adjacent carbons combine to form a heteroaryl moiety, or one R^4 combines with R^{7B} to form a heteroaryl moiety;

X^1 is independently a covalent bond, O, or CH_2 ;

R^5 is independently H or C_1 - C_6 alkyl;

R^6 is independently C_6 - C_{10} aryl or 5- to 10-membered heteroaryl;

each R^{7B} is independently H or C_1 - C_6 alkyl, or R^{7B} combines with R^4 to form a heteroaryl moiety;

L^2 is independently a covalent bond, $C(O)$, NR^{7B} , $C(O)NR^{7B}$, or $NR^{7B}C(O)$;

Cy is independently C_5 - C_7 cycloalkyl, 5- to 7-membered heterocyclyl, 5- to 6-membered heteroaryl or phenyl;

each of n and o is independently 0, 1, or 2; and

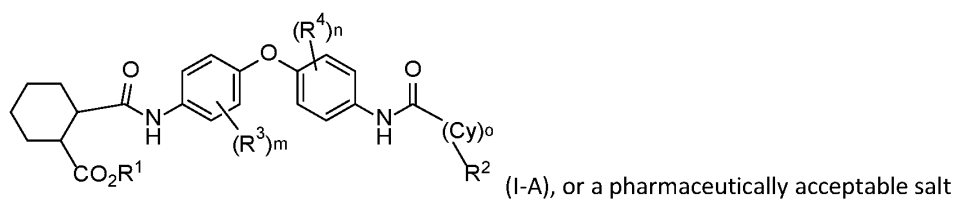
p is independently 0, 1, 2, or 3;

and

(2) a pharmaceutically acceptable excipient.

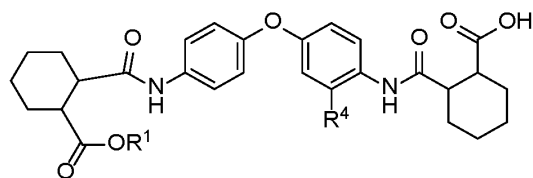
67. The pharmaceutical composition of any one of claims 64-66, wherein each of R^1 and R^5 is independently H.
68. The pharmaceutical composition of any one of claims 64-67, wherein m and n are both 0; or one of m and n is 1, and the other is 0.
69. The pharmaceutical composition of any one of claims 64-68, wherein R^3 is independently methyl and/or R^4 is independently methyl, isopropyl, or benzyl.
70. The pharmaceutical composition of any one of claims 64-69, wherein L^1 is a covalent bond, o is 0, and R^2 is H.
71. The pharmaceutical composition of any one of claims 64-69, wherein L^1 is $NHC(O)$ and o is 1.
72. The pharmaceutical composition of any one of claims 64-69, wherein L^2 is independently a covalent bond.
73. The pharmaceutical composition of any one of claims 64-69, wherein L^2 is independently $C(O)$.
74. The pharmaceutical composition of any one of claims 64-69, wherein L^2 is independently NR^{7B} .

75. The pharmaceutical composition of any one of claims 64-69, wherein L^2 is independently $C(O)NR^{7B}$.
76. The pharmaceutical composition of any one of claims 64-69, wherein L^2 is independently $NR^{7B}C(O)$.
77. The pharmaceutical composition of any one of claims 64-76, wherein R^{7A} is H or C_1 - C_6 alkyl.
78. The pharmaceutical composition of any one of claims 64-77, wherein R^{7B} is H or C_1 - C_6 alkyl.
79. The pharmaceutical composition of claims 78, wherein R^{7B} is H.
80. The pharmaceutical composition of any one of claims 64-78, wherein R^{7B} combines with R^4 to form a heteroaryl moiety.
81. The pharmaceutical composition of any one of claims 64-80, wherein **Cy** is 5- to 6-membered heteroaryl.
82. The pharmaceutical composition of any one of claims 64-80, wherein **Cy** is phenyl.
83. The pharmaceutical composition of any one of claims 64-80, wherein **Cy** is cyclohexyl.
84. The pharmaceutical composition of any one of claims 64-80, wherein **Cy** is cyclopentyl.
85. The pharmaceutical composition of claim 65, wherein said compound has a structure according to Formula (I-A),



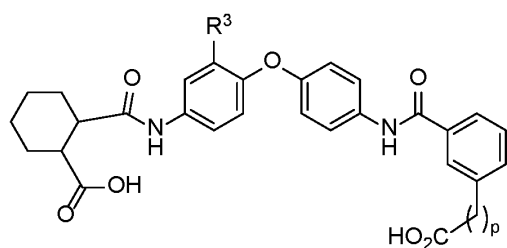
thereof.

86. The pharmaceutical composition of claim 65, wherein said compound has a structure according to Formula (I-B),



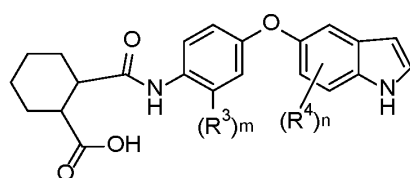
(I-B), or a pharmaceutically acceptable salt thereof.

87. The pharmaceutical composition of claim 65, wherein said compound has a structure according to Formula (I-C),



(I-C), or a pharmaceutically acceptable salt thereof.

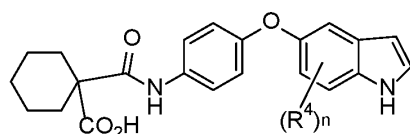
88. The pharmaceutical composition of claim 65, wherein said compound has a structure according to Formula (I-D),



(I-D), or a pharmaceutically acceptable salt thereof,

wherein each of **m** and **n** is independently 0 or 1.

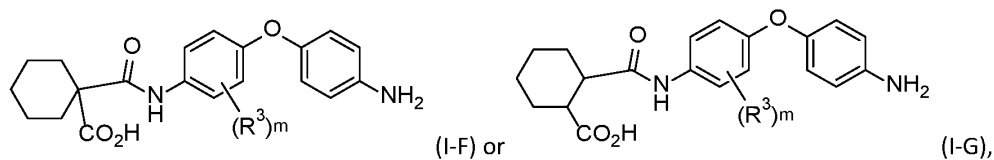
89. The pharmaceutical composition of claim 65, wherein said compound has a structure according to Formula (I-E),



(I-E), or a pharmaceutically acceptable salt thereof,

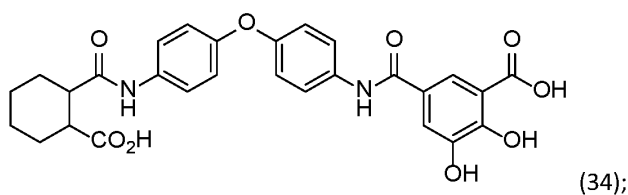
wherein **n** is 0 or 1.

90. The pharmaceutical composition of claim 65, wherein said compound has a structure according to Formula (I-F) or (I-G),



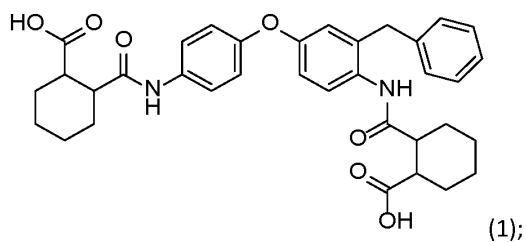
or a pharmaceutically acceptable salt thereof, wherein m is 0 or 1.

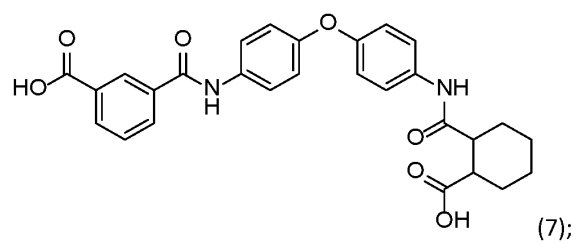
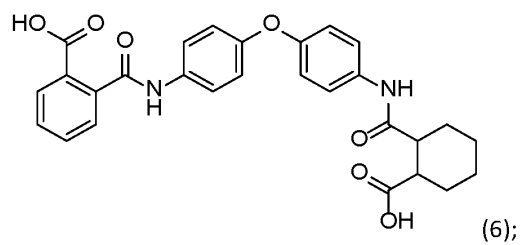
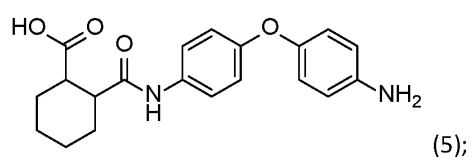
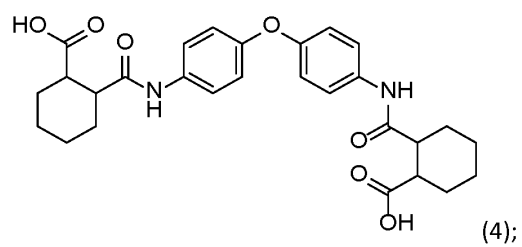
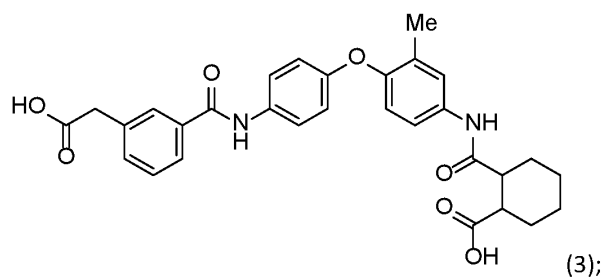
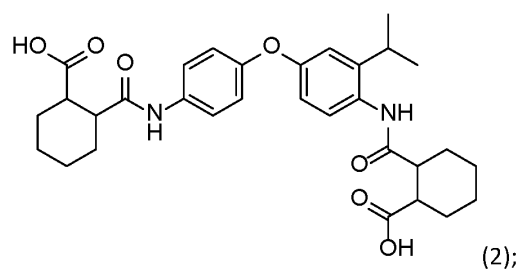
91. The pharmaceutical composition of any one of claims 85-90, wherein substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.
92. The pharmaceutical composition of any one of claims 85-90, wherein substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.
93. The pharmaceutical composition of claim 64, wherein the compound of Formula (A) is selected from the group consisting of:

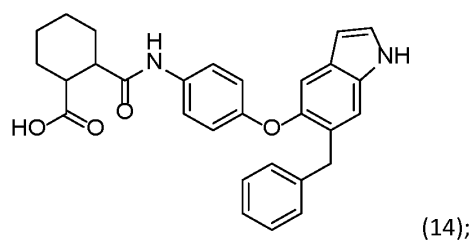
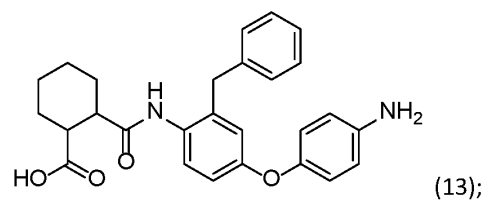
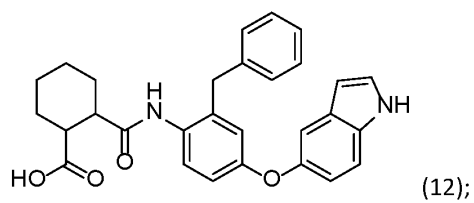
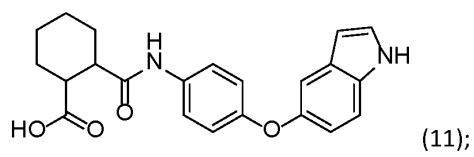
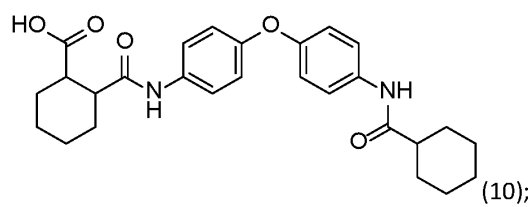
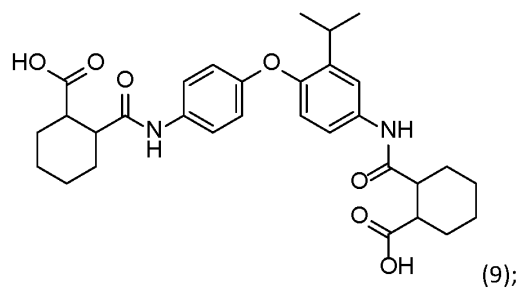
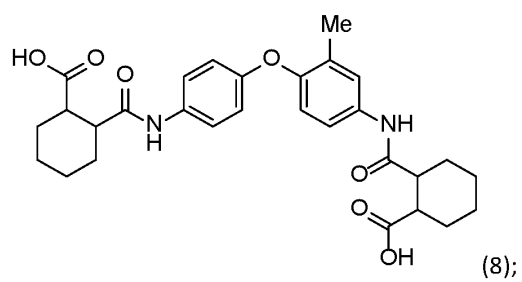


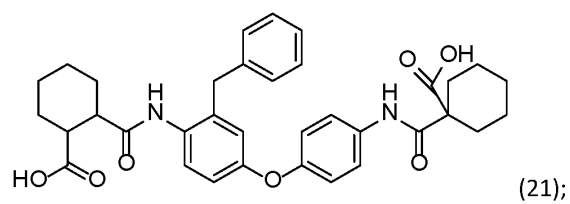
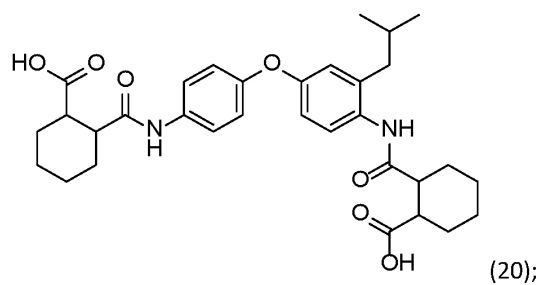
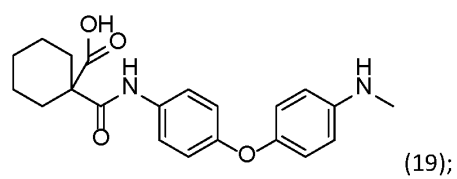
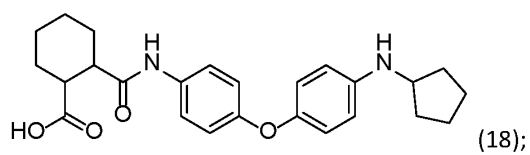
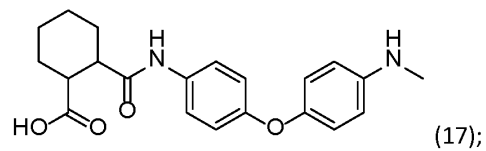
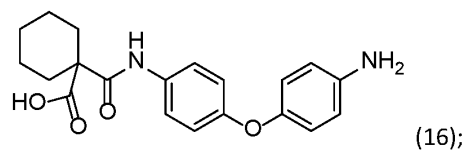
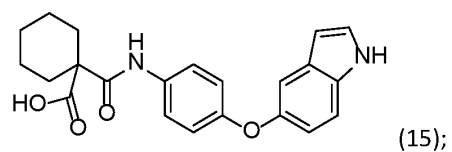
or a pharmaceutically acceptable salt thereof

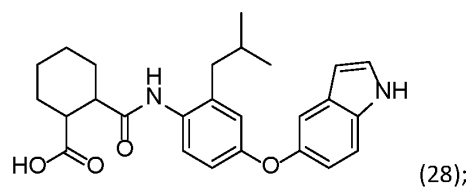
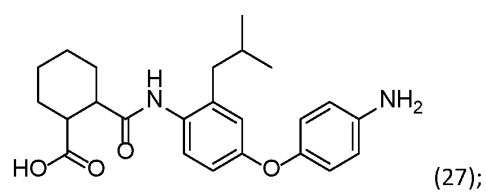
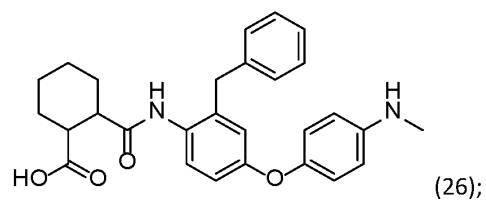
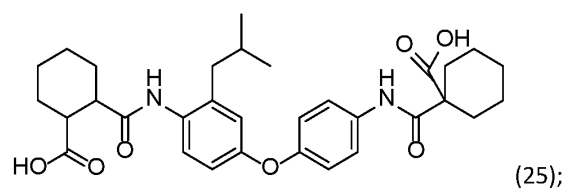
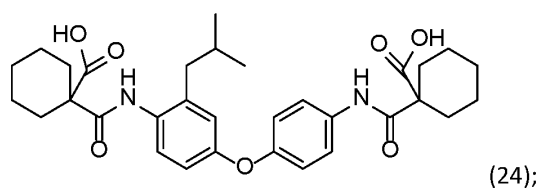
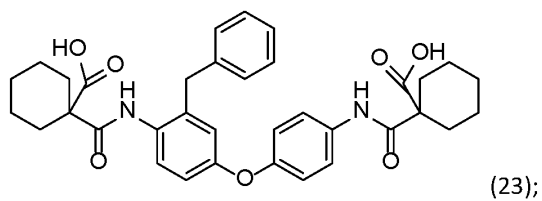
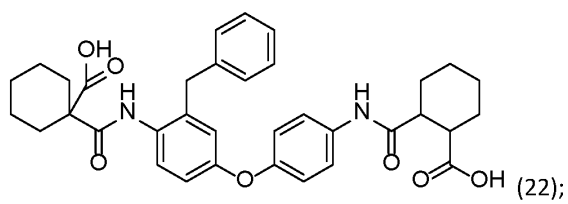
94. The pharmaceutical composition of claim 65, wherein the compound of Formula (I) is selected from the group consisting of:

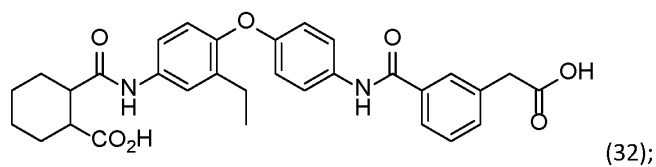
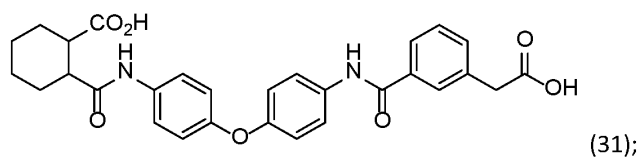
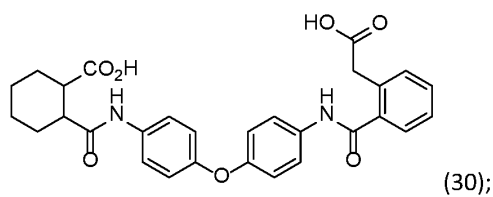
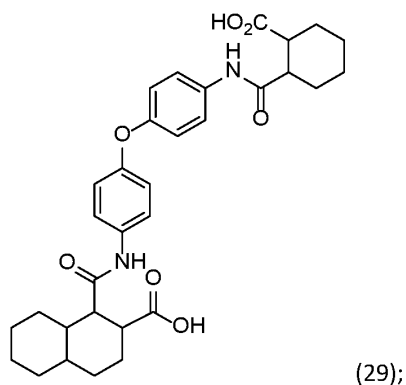




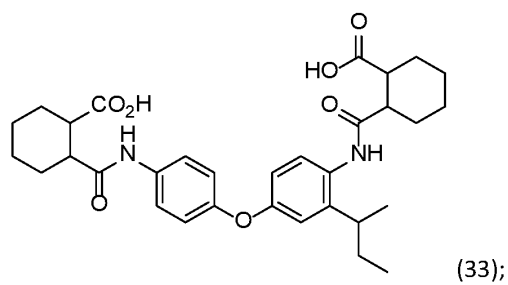






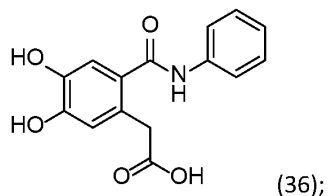
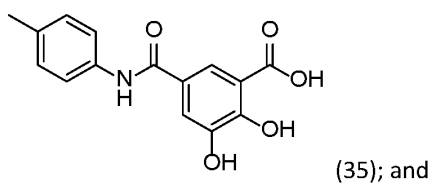


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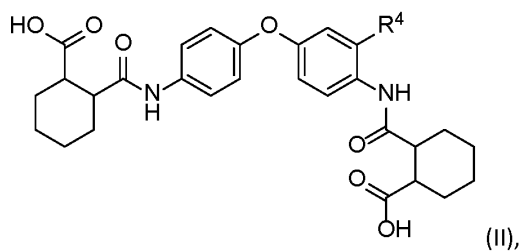
or a pharmaceutically acceptable salt thereof.

95. The pharmaceutical composition of claim 66, wherein the compound of Formula (B) is selected from the group consisting of:



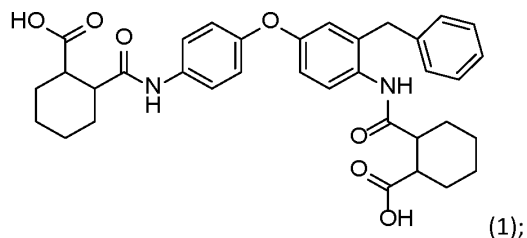
or a pharmaceutically acceptable salt thereof

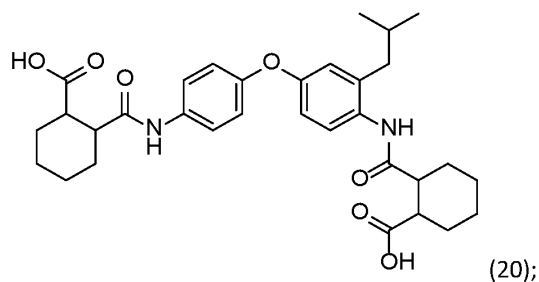
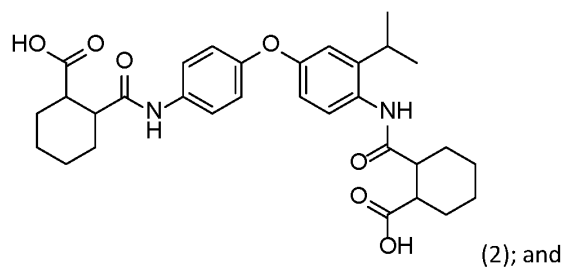
96. The pharmaceutical composition of any one of claims 93-95, wherein substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.
97. The pharmaceutical composition of any one of claims 93-95, wherein substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.
98. The pharmaceutical composition of any one of claims 64-97, comprising a pharmaceutically acceptable salt of the compound.
99. A compound having a structure according to Formula (II),



or a pharmaceutically acceptable salt thereof, wherein R^4 is C_2 - C_6 alkyl or benzyl.

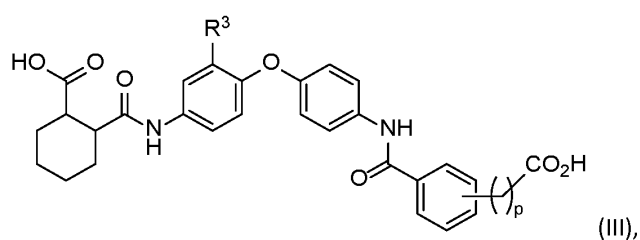
100. The compound of claim 99, selected from the group consisting of:





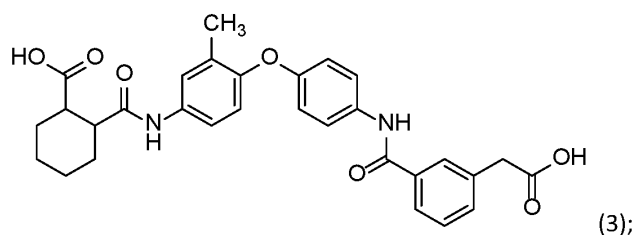
or a pharmaceutically acceptable salt thereof.

101. The compound of claim 99 or 100, wherein substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.
102. The compound of claim 99 or 100, wherein substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.
103. A pharmaceutically acceptable salt of the compound of any one of claims 99-102.
104. A compound having a structure according to Formula (III),



or a pharmaceutically acceptable salt thereof, wherein R^3 is C_1 - C_6 alkyl, and p is 0 or 1.

105. The compound of claim 104, selected from the group consisting of:



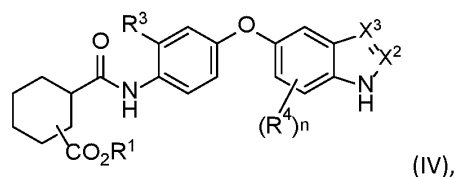
or a pharmaceutically acceptable salt thereof.

106. The compound of claim 104 or 105, wherein substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.

107. The compound of claim 104 or 105, wherein substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.

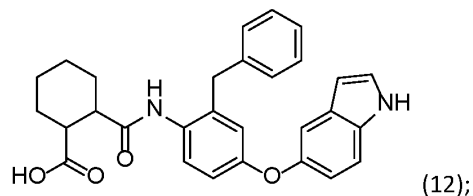
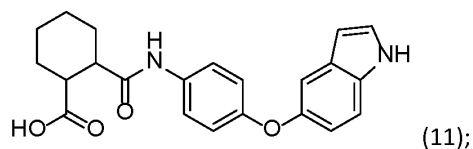
108. A pharmaceutically acceptable salt of the compound of any one of claims 104-107.

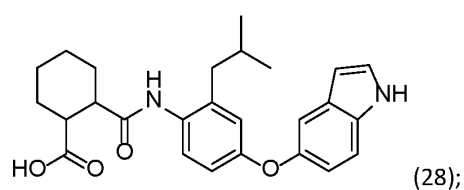
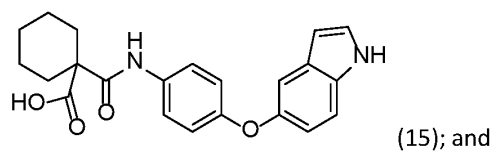
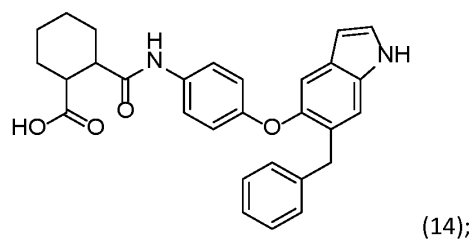
109. A compound having a structure according to Formula (IV),



or a pharmaceutically acceptable salt thereof, wherein R^1 is H or C₁-C₆ alkyl, R^3 is H or C₁-C₆ alkyl optionally substituted by phenyl, R^4 is C₁-C₆ alkyl or benzyl, each of X^2 and X^3 is independently N or CH, and n is 0 or 1.

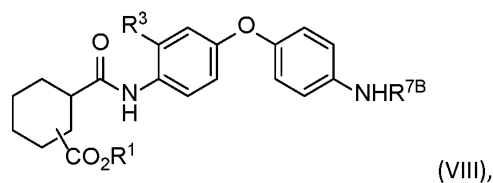
110. The compound of claim 109, selected from the group consisting of:





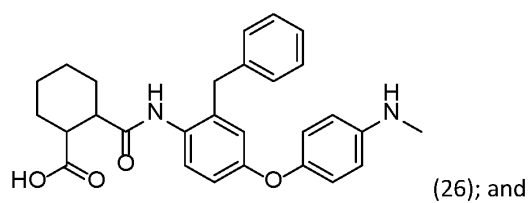
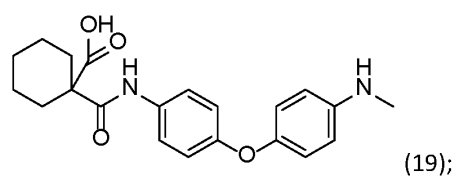
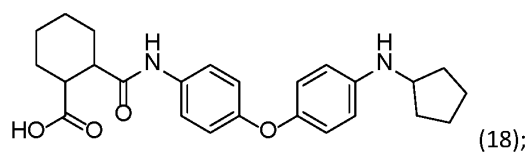
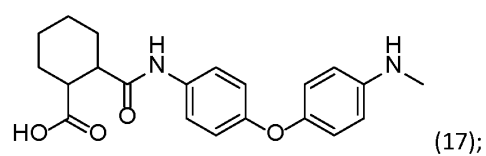
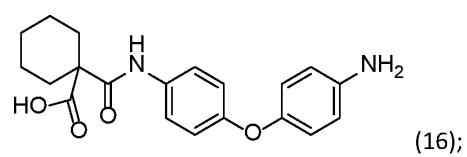
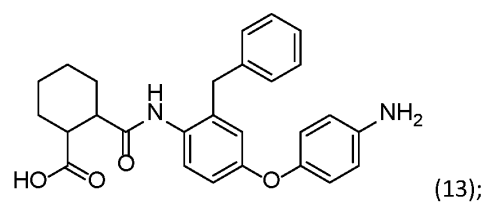
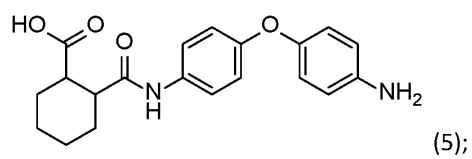
or a pharmaceutically acceptable salt thereof.

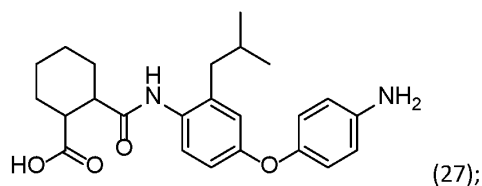
111. The compound of claim 109 or 110, wherein substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.
112. The compound of claim 109 or 110, wherein substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.
113. A pharmaceutically acceptable salt of the compound of any one of claims 109-112.
114. A compound having a structure according to Formula (VIII),



or a pharmaceutically acceptable salt thereof, wherein R^1 is H or C_1 - C_6 alkyl, R^3 is H or C_1 - C_6 alkyl optionally substituted by phenyl, and R^{7B} is H or C_1 - C_6 alkyl.

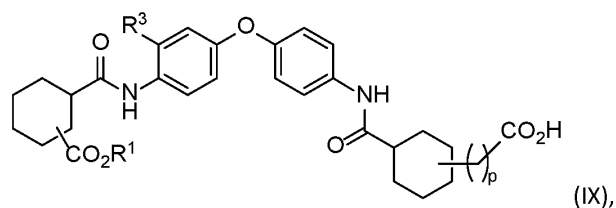
115. The compound of claim 114, selected from the group consisting of:





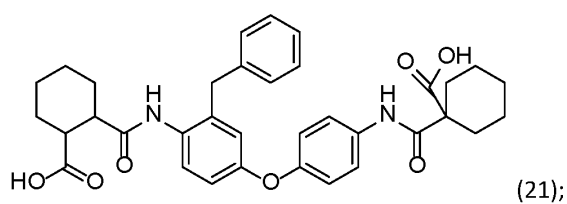
or a pharmaceutically acceptable salt thereof.

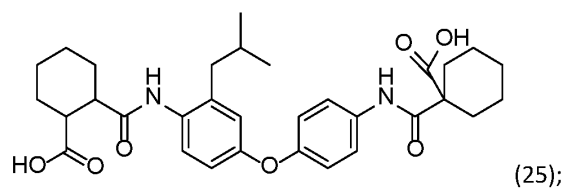
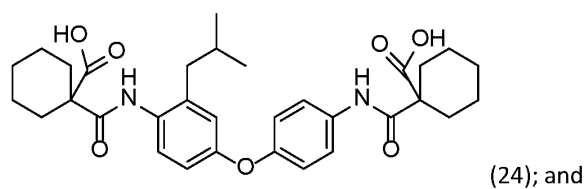
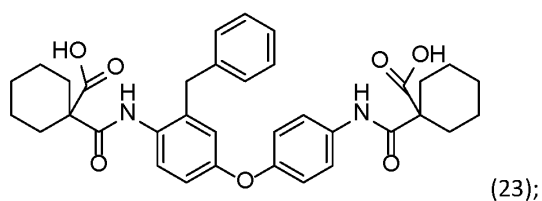
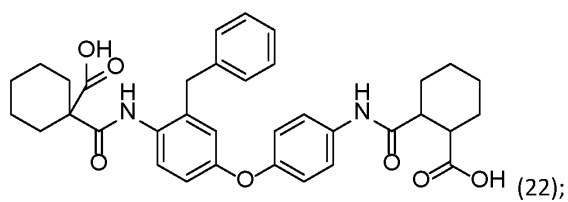
116. The compound of claim 114 or 115, wherein substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.
117. The compound of claim 114 or 115, wherein substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.
118. A pharmaceutically acceptable salt of the compound of any one of claims 114-117.
119. A compound having a structure according to Formula (IX),



or a pharmaceutically acceptable salt thereof, wherein R^1 is H or C_1 - C_6 alkyl, R^3 is C_2 - C_6 alkyl optionally substituted by phenyl, and p is 0 or 1.

120. The compound of claim 119, selected from the group consisting of:





or a pharmaceutically acceptable salt thereof.

121. The compound of claim 119 or 120, wherein substituents on adjacent carbons of a cyclohexyl ring are *cis* to each other.
122. The compound of claim 119 or 120, wherein substituents on adjacent carbons of a cyclohexyl ring are *trans* to each other.
123. A pharmaceutically acceptable salt of the compound of any one of claims 119-122.