

LIVER X RECEPTOR (LXR) MODULATORS

This application claims the benefit of priority of U.S. Provisional Appl. No. 61/873,746, filed September 4, 2013, which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Liver X receptor (LXR) activation is associated with inflammation, hyperproliferative and/or disordered skin barrier differentiation. LXR activation also modulates multiple pathways underlying the etiology and pathology of skin aging.

SUMMARY OF THE INVENTION

Described herein are compounds of Formula I, IA, IB, II, IIA, IIB, III, IIIA, IIIB, IV, IVA, and IVB, pharmaceutical compositions that include such compounds, and methods of use thereof, for modulating LXR. ~~Disclosed~~~~In one aspect~~ is the topical administration of at least one liver X receptor (LXR) modulator described herein to the skin of a mammal in the treatment of dermal diseases, disorders or conditions.

Provided herein are methods and compositions comprising topical administration of a *liver X receptor (LXR) modulator for treatment of dermal diseases, disorders or conditions*. Dermal diseases, disorders or conditions include, but are not limited to, skin aging, scarring, psoriasis, dermatitis, eczema, urticaria, rosacea, burns, acne, or any other condition described herein. Dermal diseases or disorders also refer to pigmentary disorders including but not limited to vitiligo. Dermal diseases also refer to skin malignancies and cancer, including melanoma and metastatic forms of these diseases.

In another embodiment is the use of a compound of Formula I, IA, IB, II, IIA, IIB, III, IIIA, IIIB, IV, IVA, and IVB, or a pharmaceutically acceptable salt, in the manufacture of a *medicament for the treatment of a disease, disorder, or condition that would benefit from LXR modulation* (such as any of the methods described herein). In another embodiment is the a compound of Formula I, IA, IB, II, IIA, IIB, III, IIIA, IIIB, IV, IVA, and IVB, or a pharmaceutically acceptable salt, for use in treatment of the treatment of a disease, disorder,

or condition that would benefit from LXR modulation (such as any of the methods described herein).

Accordingly, provided herein are methods and compositions for maintenance of the dermal barrier and/or normalization of the dermal barrier and/or reducing injury to the dermal barrier and/or regeneration of the dermal barrier.

~~Disclosed in one aspect provided herein~~ is a method for treating the epidermis of a mammalian subject suffering from a perturbed epidermal barrier function, said method comprising topically administering to said epidermis a topical composition comprising an active ingredient that is an activator of the liver X receptor (LXR), said active ingredient being present in a concentration that is effective in enhancing barrier development.

~~Disclosed in another aspect, provided herein~~ is a method for treating the epidermis or mucous membrane of a terrestrial mammalian subject suffering from a condition of disturbed differentiation or excess proliferation, said method comprising topically administering to said epidermis or mucous membrane a topical composition comprising an active ingredient that is an activator of the liver X receptor (LXR), said active ingredient being present in a concentration that is effective in enhancing barrier development.

In some embodiments of the methods or compositions described above, the activator of LXR is a compound of Formula I, IA, IB, II, IIA, IIB, III, IIIA, IIIB, IV, IVA, and IVB as described herein. In some embodiments of the methods or compositions described above, the concentration of said active ingredient in the topical composition is from about 0.1 μ M to 100 μ M.

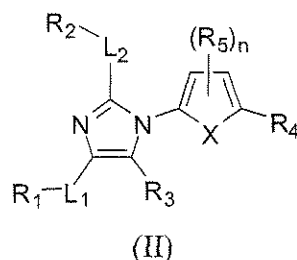
~~Disclosed in one aspect~~ is the use of a LXR modulator in the manufacture of a topical formulation for use in the treatment of a dermal disease, disorder or condition in a mammal.

~~Disclosed in one aspect~~ is the use of a LXR modulator and a second therapeutic agent in the manufacture of a topical formulation for use in the treatment of a dermal disease, disorder or condition in a mammal.

~~Disclosed in another aspect~~ is a compound of Formula (I):

S-. In another embodiment of the aforementioned embodiments is a compound of Formula I wherein X is -CH=CH-.

~~Disclosed~~In another aspect is a compound of Formula (II):



wherein:

X is -O-, -S-, or -C(R₆)=C(R₆)-;

L₁ is a bond, C₁-C₆alkyl, or C₁-C₆heteroalkyl; wherein C₁-C₆alkyl and C₁-C₆heteroalkyl are optionally substituted with at least one R₇;

L₂ is a C₁-C₆alkyl, or C₁-C₆heteroalkyl;

R₁ is -C(=O)OR₈;

R₂ is hydrogen, -OR₉, -N(R₉)₂, -C(=O)R₉, -C(=O)N(R₉)₂, -C(=N-OH)R₉, -C(=S)N(R₉)₂, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, or optionally substituted heterocycloalkyl;

R₃ is hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R₄ is aryl or heteroaryl; wherein aryl and heteroaryl are substituted with at least one R₁₁;

each R₅ is independently halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R₆ is independently hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R₇ is independently C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;

each R₈, each R₉, and each R₁₀ are each independently hydrogen, C₁-C₆alkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, aryl, or heteroaryl;

each R₁₁ is independently halogen, nitro, -OR₁₀, -N(R₁₀)₂, -CN, -C(=O)R₁₀, -C(=O)OR₁₀, -C(=O)N(R₁₀)₂, -NR₁₀C(=O)R₁₀, -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, -SO₂N(R₁₀)₂, -C(=O)OCH₂SCH₃, optionally substituted C₁-C₆alkyl, optionally substituted C₃-C₈cycloalkyl,

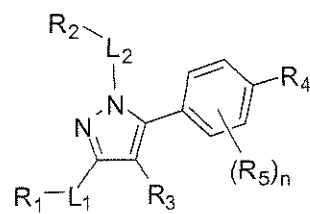
optionally substituted C₁-C₆haloalkyl, optionally substituted C₁-C₆heteroalkyl, optionally substituted -C₁-C₆alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl; and

n is 0-2;

5 or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof.

In another embodiment is a compound of Formula II wherein L₁ is a bond. In another embodiment is a compound of Formula II wherein L₁ is C₁-C₆alkyl optionally substituted with at least one R₇. In another embodiment is a compound of Formula II wherein L₁ is -CH₂-. In a further embodiment is a compound of Formula II wherein R₁ is -C(=O)OR₈, and R₈ is C₁-C₆alkyl or C₁-C₆heteroalkyl. In a further embodiment is a compound of Formula II wherein L₂ is C₁-C₆alkyl. In a further embodiment is a compound of Formula II wherein R₂ is hydrogen. In another embodiment of the aforementioned embodiments is a compound of Formula II wherein R₄ is phenyl substituted with one R₁₁. In another embodiment of the
15 aforementioned embodiments is a compound of Formula II wherein R₄ is phenyl substituted with one R₁₁, R₁₁ is -SO₂R₁₀, and R₁₀ is C₁-C₆alkyl. In another embodiment of the aforementioned embodiments is a compound of Formula II wherein R₄ is phenyl substituted with at least two R₁₁. In another embodiment of the aforementioned embodiments is a compound of Formula II wherein R₄ is phenyl substituted with at least two R₁₁ and each R₁₁
20 is independently halogen, optionally substituted C₁-C₆alkyl, -SO₂R₁₀, -NR₁₀SO₂R₁₀, or -SO₂N(R₁₀)₂. In another embodiment of the aforementioned embodiments is a compound of Formula II wherein n is 0. In another embodiment of the aforementioned embodiments is a compound of Formula II wherein R₃ is hydrogen. In another embodiment of the aforementioned embodiments is a compound of Formula II wherein R₃ is halogen. In
25 another embodiment of the aforementioned embodiments is a compound of Formula II wherein X is -O-. In another embodiment of the aforementioned embodiments is a compound of Formula II wherein X is -S-. In another embodiment of the aforementioned embodiments is a compound of Formula II wherein X is -CH=CH-.

In one aspect, there is provided compound of Formula (III):



(III)

or a pharmaceutically acceptable salt thereof, wherein:

L₁ is a bond;

L₂ is a C₁-C₆alkyl, or C₁-C₆heteroalkyl;

R₁ is -C(=O)OR₈;

R₂ is hydrogen, -OR₉, -N(R₉)₂, -C(=O)R₉, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, or optionally substituted heterocycloalkyl;

R₃ is hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R₄ is aryl or heteroaryl; wherein aryl and heteroaryl are substituted with at least one

R₁₁;

each R₅ is independently halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R₇ is independently C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;

R₈ is hydrogen, C₁-C₆alkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, aryl, or heteroaryl;

R₉ is hydrogen, C₁-C₆alkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, aryl, or heteroaryl;

each R₁₀ are each independently hydrogen, C₁-C₆alkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, aryl, or heteroaryl;

each R₁₁ is independently halogen, nitro, -OR₁₀, -N(R₁₀)₂, -CN, -C(=O)R₁₀, -C(=O)OR₁₀, -C(=O)N(R₁₀)₂, -NR₁₀C(=O)R₁₀, -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, -SO₂N(R₁₀)₂, -C(=O)OCH₂SCH₃, optionally substituted C₁-C₆alkyl, optionally substituted C₃-C₈cycloalkyl, optionally substituted C₁-C₆haloalkyl, optionally substituted C₁-C₆heteroalkyl, optionally substituted -C₁-C₆alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;
and

n is 0-4.

Also provided is a compound of Formula (III):

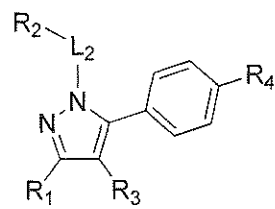
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n is 0-4;

or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof.

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In another aspect, there is provided a compound of Formula (IV):



(IV)

wherein:

R₁ is C₁-C₆ alkyl or C₂-C₆ alkenyl, wherein said C₁-C₆ alkyl is optionally substituted by 1, 2, 3, or 4 substituents independently selected from hydroxy, C₁-C₄ alkoxy, and C₁-C₄ haloalkoxy;

L₂ is a C₁-C₆ alkyl;

R₂ is C(=O)OR₉;

R₃ is hydrogen or C₁-C₆alkyl;

R₄ is phenyl substituted with at least one R₁₁;

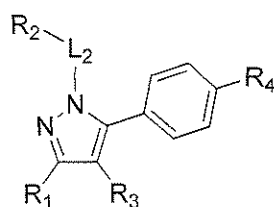
each R₉ is independently hydrogen or C₁-C₆alkyl;

each R₁₀ is independently hydrogen or C₁-C₆alkyl; and

each R₁₁ is independently halogen, nitro, -OR₁₀, -N(R₁₀)₂, -CN, -C(=O)R₁₀, -C(=O)OR₁₀, -C(=O)N(R₁₀)₂, -NR₁₀C(=O)R₁₀, -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, -SO₂N(R₁₀)₂, -C(=O)OCH₂SCH₃, C₁-C₆alkyl, or C₁-C₆ haloalkyl, wherein said C₁-C₆ alkyl is optionally substituted by 1, 2, 3, or 4 substituents independently selected from cyano, hydroxy, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, amino, C₁-C₄ alkylamino, and di(C₁-C₄ alkyl)amino;

provided that at least one R₁₁ is -NR₁₀C(=O)R₁₀, -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, or -SO₂N(R₁₀)₂.

DisclosedIn another aspect is a compound of Formula (IV):



(IV)

wherein:

R₁ is C₁-C₆ alkyl or C₂-C₆ alkenyl, wherein said C₁-C₆ alkyl is optionally substituted by
 5 1, 2, 3, or 4 substituents independently selected from hydroxy, C₁-C₄ alkoxy, and C₁-C₄
 haloalkoxy;

L₂ is a C₁-C₆ alkyl;

R₂ is C(=O)OR₉;

R₃ is hydrogen or C₁-C₆alkyl;

10 R₄ is phenyl substituted with at least one R₁₁;

each R₉ is independently hydrogen or C₁-C₆alkyl;

each R₁₀ is independently hydrogen or C₁-C₆alkyl; and

each R₁₁ is independently halogen, nitro, -OR₁₀, -N(R₁₀)₂, -CN, -C(=O)R₁₀, -

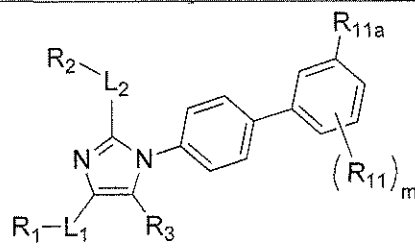
C(=O)OR₁₀, -C(=O)N(R₁₀)₂, -NR₁₀C(=O)R₁₀, -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, -SO₂N(R₁₀)₂, -

15 C(=O)OCH₂SCH₃, C₁-C₆alkyl, or C₁-C₆ haloalkyl, wherein said C₁-C₆ alkyl is optionally
 substituted by 1, 2, 3, or 4 substituents independently selected from cyano, hydroxy, C₁-C₄
 alkoxy, C₁-C₄ haloalkoxy, amino, C₁-C₄ alkylamino, and di(C₁-C₄ alkyl)amino;

provided that at least one R₁₁ is -NR₁₀C(=O)R₁₀, -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, or -
 SO₂N(R₁₀)₂;

20 or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or
 pharmaceutically acceptable prodrug thereof.

In another aspect there is provided a compound of Formula (IA):



(IA)

wherein:

L_1 and L_2 are each independently a bond, C_1 - C_6 alkyl, or C_1 - C_6 heteroalkyl; wherein C_1 - C_6 alkyl and C_1 - C_6 heteroalkyl are optionally substituted with at least one R_7 ;

R_1 is halogen, $-CF_3$, $-OR_8$, $-N(R_8)_2$, $-C(=O)R_8$, $-C(=O)OR_8$, $-C(=O)N(R_8)_2$, $-C(=N-OH)R_8$, $-C(=S)N(R_8)_2$, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, or optionally substituted C_2 - C_7 heterocycloalkyl;

R_2 is $-C(=O)OR_9$;

R_3 is hydrogen, halogen, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

each R_7 is independently C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_1 - C_6 haloalkyl, C_1 - C_6 heteroalkyl, $-C_1$ - C_6 alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;

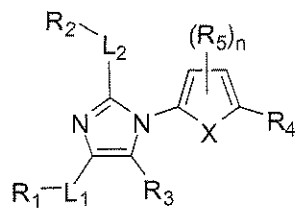
each R_8 , each R_9 , and each R_{10} are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, $-C_1$ - C_6 alkyl-aryl, aryl, or heteroaryl;

m is 0 or 1;

R_{11a} is $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$;

each R_{11} is independently halogen, nitro, $-OR_{10}$, $-N(R_{10})_2$, $-CN$, $-C(=O)R_{10}$, $-C(=O)OR_{10}$, $-C(=O)N(R_{10})_2$, $-NR_{10}C(=O)R_{10}$, $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, $-SO_2N(R_{10})_2$, $-C(=O)OCH_2SCH_3$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted $-C_1$ - C_6 alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl; or a pharmaceutically acceptable salt thereof.

In another aspect, there is provided a compound of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof, wherein:

X is $-C(R_6)=C(R_6)-$;

L₁ is a bond, C₁-C₆alkyl, or C₁-C₆heteroalkyl; wherein C₁-C₆alkyl and C₁-C₆heteroalkyl are optionally substituted with at least one R₇;

L₂ is a C₁-C₆alkyl, or C₁-C₆heteroalkyl;

R₁ is $-C(=O)OR_8$;

R₂ is hydrogen, $-OR_9$, $-N(R_9)_2$, $-C(=O)R_9$, $-C(=O)N(R_9)_2$, $-C(=N-OH)R_9$, $-C(=S)N(R_9)_2$, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, or optionally substituted heterocycloalkyl;

R₃ is hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R₄ is aryl or heteroaryl; wherein aryl and heteroaryl are substituted with at least one R₁₁;

each R₅ is independently halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R₆ is independently hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R₇ is independently C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, $-C_1-C_6$ alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;

each R₈, each R₉, and each R₁₀ are each independently hydrogen, C₁-C₆alkyl, C₁-C₆heteroalkyl, $-C_1-C_6$ alkyl-aryl, aryl, or heteroaryl;

each R₁₁ is independently halogen, nitro, $-OR_{10}$, $-N(R_{10})_2$, $-CN$, $-C(=O)R_{10}$, $-C(=O)OR_{10}$, $-C(=O)N(R_{10})_2$, $-NR_{10}C(=O)R_{10}$, $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, $-SO_2N(R_{10})_2$, $-C(=O)OCH_2SCH_3$, optionally substituted C₁-C₆alkyl, optionally substituted C₃-C₈cycloalkyl, optionally substituted C₁-C₆haloalkyl, optionally substituted C₁-C₆heteroalkyl, optionally substituted $-C_1-C_6$ alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;

and
n is 0-2.

In another aspect, there is provided a pharmaceutical composition comprising a compound of any one of the Formulae described herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

~~Disclosed in another aspect~~ is a pharmaceutical composition comprising a compound of Formula I, IA, IB, II, IIA, IIB, III, IIIA, IIIB, IV, IVA, and IVB, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

~~In another aspect~~, there is provided use of a compound according to any one of the Formulae described herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a dermal disease, disorder or condition selected from skin aging, scarring, psoriasis, dermatitis, eczema, urticaria, rosacea, burns, and acne in a mammal.

~~Disclosed in another aspect~~ is a method of treating a disease, disorder or condition in a mammal that would benefit from LXR modulation comprising administering to the mammal a compound of Formula I, IA, IB, II, IIA, IIB, III, IIIA, IIIB, IV, IVA, and IVB, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof.

In a further embodiment is a method of treating a disease, disorder or condition in a mammal that would benefit from LXR modulation comprising administering to the mammal a compound of Formula I, IA, IB, II, IIA, IIB, III, IIIA, IIIB, IV, IVA, and IVB, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof; wherein the disease, disorder or condition in a mammal is a dermal disease, disorder or condition selected from skin aging, scarring, psoriasis, dermatitis, eczema, urticaria, rosacea, burns, and acne.

~~In another aspect~~, there is provided a method of modulating LXR activity comprising contacting LXR, or portion thereof, with a compound according to any one of the Formulae described herein, or a pharmaceutically acceptable salt thereof.

~~Disclosed in another aspect~~ is a method of modulating LXR activity comprising contacting LXR, or portion thereof, with a compound of Formula I, IA, IB, II, IIA, IIB, III, IIIA, IIIB, IV, IVA, and IVB, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof.

INCORPORATION BY REFERENCE

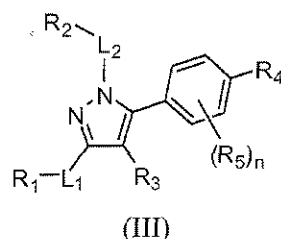
All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

LXR was first described by Willy, P. J., et al., "LXR, a nuclear receptor that defines a distinct retinoid response pathway," Genes & Development 9:1033-1045 (Cold Spring Harbor Laboratory Press).

WHAT IS CLAIMED IS:

1. A compound of Formula (III):



or a pharmaceutically acceptable salt thereof, wherein:

L₁ is a bond, C₁-C₆alkyl, or C₁-C₆heteroalkyl; wherein C₁-C₆alkyl and C₁-C₆heteroalkyl are optionally substituted with at least one R₇;

L₂ is a C₁-C₆alkyl, or C₁-C₆heteroalkyl;

R₁ is -C(=O)OR₈;

R₂ is hydrogen, -OR₉, -N(R₉)₂, -C(=O)R₉, -C(=O)N(R₉)₂, -C(=N-OH)R₉, -C(=S)N(R₉)₂, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, or optionally substituted heterocycloalkyl;

R₃ is hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R₄ is aryl or heteroaryl; wherein aryl and heteroaryl are substituted with at least one R₁₁;

each R₅ is independently halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R₇ is independently C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;

R₈ is hydrogen, C₁-C₆alkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, aryl, or heteroaryl;

R₉ is hydrogen, C₁-C₆alkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, aryl, or heteroaryl;

each R₁₀ are each independently hydrogen, C₁-C₆alkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, aryl, or heteroaryl;

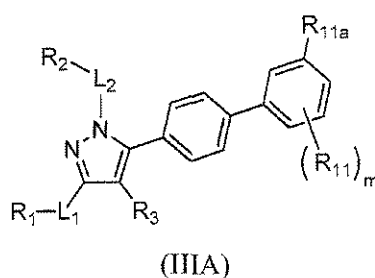
each R₁₁ is independently halogen, nitro, -OR₁₀, -N(R₁₀)₂, -CN, -C(=O)R₁₀, -C(=O)OR₁₀, -C(=O)N(R₁₀)₂, -NR₁₀C(=O)R₁₀, -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, -SO₂N(R₁₀)₂, -C(=O)OCH₂SCH₃, optionally substituted C₁-C₆alkyl, optionally substituted C₃-C₈cycloalkyl,

optionally substituted C₁-C₆haloalkyl, optionally substituted C₁-C₆heteroalkyl, optionally substituted -C₁-C₆alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;
and

n is 0-4.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein L₂ is a C₁-C₆alkyl and R₂ is hydrogen.
3. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein -L₂-R₂ is isobutyl.
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt thereof, wherein L₁ is a bond.
5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R₁ is -C(=O)OR₈, and R₈ is hydrogen or C₁-C₆alkyl.
6. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt thereof, wherein R₁ is -C(=O)OR₈, and R₈ is ethyl.
7. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R₁ is C(=O)OR₈, R₈ is C₁-C₆alkyl, L₁ is a bond, L₂ is a C₁-C₆alkyl, and R₂ is hydrogen.
8. The compound of any one of claims 1-7, or a pharmaceutically acceptable salt thereof, wherein n is 0.
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R₄ is phenyl substituted with at least one R₁₁.

10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein at least one R_{11} is $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$.
11. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt thereof, wherein at least one R_{11} is $-SO_2R_{10}$.
12. The compound of claim 10 or 11, or a pharmaceutically acceptable salt thereof, wherein each R_{10} is independently C_1 - C_6 alkyl.
13. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt thereof, wherein R_4 is phenyl substituted with one R_{11} , wherein R_{11} is $-SO_2R_{10}$ and R_{10} is C_1 - C_6 alkyl; or R_4 is phenyl substituted with two R_{11} , and one R_{11} is $-SO_2R_{10}$ and one R_{11} is optionally substituted C_1 - C_6 alkyl.
14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt thereof, wherein "optionally substituted" means substituted by 1, 2, 3, or 4 substituents independently selected from halo, cyano, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, hydroxy, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, amino, C_1 - C_4 alkylamino, and di(C_1 - C_4 alkyl)amino.
15. The compound of any one of claims 1-8, wherein the compound is a compound of Formula (IIIA):



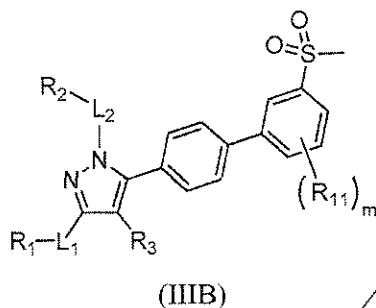
wherein:

m is 0 or 1; and

R_{11a} is $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$;

or a pharmaceutically acceptable salt thereof.

16. The compound of any one of claims 1-8, wherein the compound is a compound of Formula (IIIB):



wherein m is 0 or 1;

or a pharmaceutically acceptable salt thereof.

17. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

L_1 is a bond;

R_1 is $-C(=O)OR_8$;

R_8 is hydrogen or C_1 - C_6 alkyl;

L_2 is a C_1 - C_6 alkyl;

R_2 is hydrogen;

R_4 is phenyl substituted with at least one R_{11} ;

each R_{11} is independently C_1 - C_6 alkyl, $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-$

$SO_2N(R_{10})_2$; wherein said C_1 - C_6 alkyl is optionally substituted by 1 hydroxy;

provided that at least one R_{11} is $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$;

each R_{10} is independently C_1 - C_6 alkyl;

n is 0; and

R_3 is hydrogen.

18. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

L_1 is a bond;

R_1 is $-C(=O)OR_8$;

R₃ is hydrogen.

[illegible]R2-L2-c1nc(R1)c(R3)c(c1)-c2ccc(R4)cc2

(IV)

145

R₁ is C₁-C₆ alkyl or C₂-C₆ alkenyl, wherein said C₁-C₆ alkyl is optionally substituted by 1, 2, 3, or 4 substituents independently selected from hydroxy, C₁-C₄ alkoxy, and C₁-C₄ haloalkoxy;

L₂ is a C₁-C₆ alkyl;

R₂ is C(=O)OR₉;

R₃ is hydrogen or C₁-C₆alkyl;

R₄ is phenyl substituted with at least one R₁₁;

each R₉ is independently hydrogen or C₁-C₆alkyl;

each R₁₀ is independently hydrogen or C₁-C₆alkyl; and

each R₁₁ is independently halogen, nitro, -OR₁₀, -N(R₁₀)₂, -CN, -C(=O)R₁₀, -C(=O)OR₁₀, -C(=O)N(R₁₀)₂, -NR₁₀C(=O)R₁₀, -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, -SO₂N(R₁₀)₂, -C(=O)OCH₂SCH₃, C₁-C₆alkyl, or C₁-C₆ haloalkyl, wherein said C₁-C₆ alkyl is optionally substituted by 1, 2, 3, or 4 substituents independently selected from cyano, hydroxy, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, amino, C₁-C₄ alkylamino, and di(C₁-C₄ alkyl)amino;

provided that at least one R₁₁ is -NR₁₀C(=O)R₁₀, -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, or -SO₂N(R₁₀)₂.

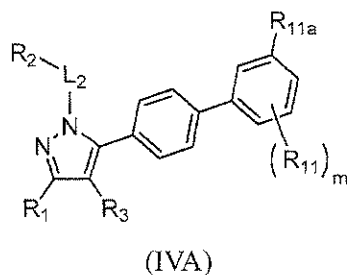
21. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein R₁ is C₂-C₄ alkenyl or C₁-C₃ alkyl, wherein said C₁-C₃ alkyl is optionally substituted by 1 hydroxy.

22. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein R₁ is -C(=CH₂)CH₃, isopropyl, or -C(CH₃)₂OH.

23. The compound of any one of claims 20-22, or a pharmaceutically acceptable salt thereof, wherein L₂ is -CH₂-.

24. The compound of any one of claims 20-22, or a pharmaceutically acceptable salt thereof, wherein -L₂-R₂ is -CH₂C(=O)OR₉, wherein R₉ is hydrogen or C₁-C₆ alkyl.

25. The compound of any one of claims 20-22, or a pharmaceutically acceptable salt thereof, wherein $-L_2-R_2$ is $-CH_2C(=O)OR_9$, wherein R_9 is hydrogen, methyl, or ethyl.
26. The compound of any one of claims 20-25, or a pharmaceutically acceptable salt thereof, wherein R_3 is hydrogen.
27. The compound of any one of claims 20-26, or a pharmaceutically acceptable salt thereof, wherein R_4 is phenyl substituted with at least one R_{11} .
28. The compound of any one of claims 20-27, or a pharmaceutically acceptable salt thereof, wherein at least one R_{11} is $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$.
29. The compound of any one of claims 20-27, or a pharmaceutically acceptable salt thereof, wherein at least one R_{11} is $-SO_2R_{10}$.
30. The compound of claim 28 or 29, or a pharmaceutically acceptable salt thereof, wherein each R_{10} is independently C_1-C_6 alkyl.
31. The compound of claim 28 or 29, or a pharmaceutically acceptable salt thereof, wherein each R_{10} is methyl.
32. The compound of any one of claims 20-26, or a pharmaceutically acceptable salt thereof, wherein R_4 is phenyl substituted with one R_{11} , wherein R_{11} is $-SO_2R_{10}$ and R_{10} is C_1-C_6 alkyl; or R_4 is phenyl substituted with two R_{11} , and one R_{11} is $-SO_2R_{10}$ and one R_{11} is optionally substituted C_1-C_6 alkyl.
33. The compound of any one of claims 20-26, wherein the compound is a compound of Formula (IVA):



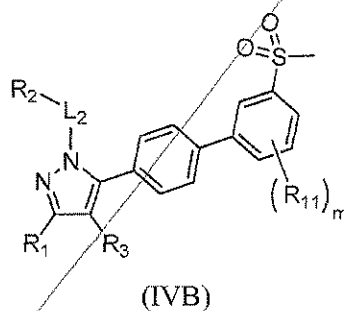
wherein:

m is 0 or 1; and

R_{11a} is -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, or -SO₂N(R₁₀)₂;

or a pharmaceutically acceptable salt thereof.

34. The compound of any one of claims 20-26, wherein the compound is a compound of Formula (IVB):



wherein m is 0 or 1;

or a pharmaceutically acceptable salt thereof.

35. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein:

R₁ is C₂-C₄ alkenyl or C₁-C₃ alkyl, wherein said C₁-C₃ alkyl is optionally substituted by 1 hydroxy;

-L₂-R₂ is -CH₂C(=O)OR₉;

R₉ is hydrogen or C₁-C₆ alkyl;

R₄ is phenyl substituted with at least one R₁₁;

each R₁₁ is independently C₁-C₆ alkyl, -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, or -SO₂N(R₁₀)₂; wherein said C₁-C₆ alkyl is optionally substituted by 1 hydroxy;

provided that at least one R_{11} is $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$; each R_{10} is independently C_1 - C_6 alkyl; and R_3 is hydrogen.

36. The compound of claim 20, or a pharmaceutically acceptable salt thereof, wherein: R_1 is C_2 - C_4 alkenyl or C_1 - C_3 alkyl, wherein said C_1 - C_3 alkyl is optionally substituted by 1 hydroxy;

$-L_2-R_2$ is $-CH_2C(=O)OR_9$;

R_9 is hydrogen or C_1 - C_6 alkyl;

R_4 is phenyl substituted with at least one R_{11} ;

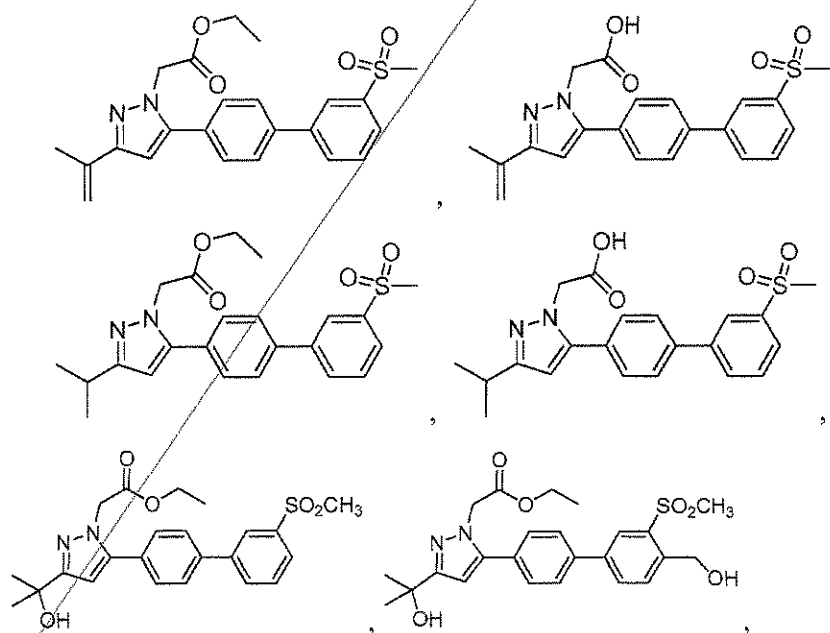
each R_{11} is independently C_1 - C_6 alkyl, $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$; wherein said C_1 - C_6 alkyl is optionally substituted by 1 hydroxy;

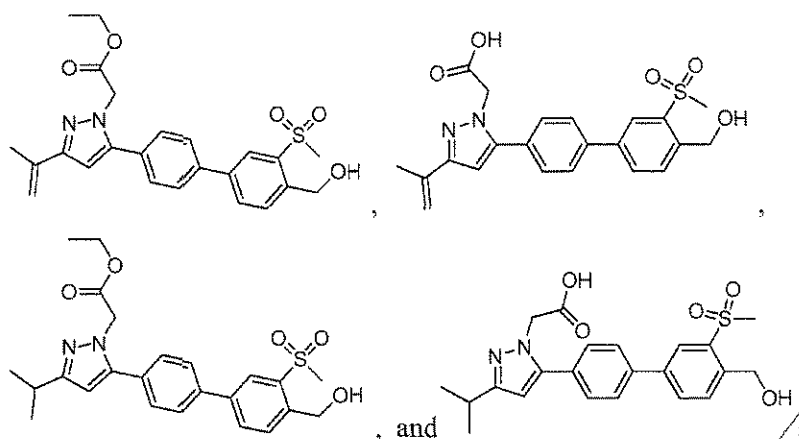
provided that at least one R_{11} is $-SO_2N(R_{10})_2$;

each R_{10} is independently C_1 - C_6 alkyl; and

R_3 is hydrogen.

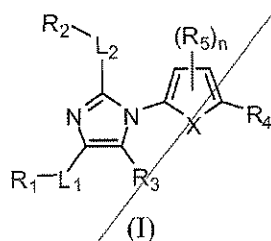
37. The compound of claim 20, selected from:





or a pharmaceutically acceptable salt thereof.

38. A compound of Formula (I):



wherein:

X is -O-, -S-, or -C(R₆)=C(R₆)-;

L₁ and L₂ are each independently a bond, C₁-C₆alkyl, or C₁-C₆heteroalkyl; wherein C₁-C₆alkyl and C₁-C₆heteroalkyl are optionally substituted with at least one R₇;

R₁ is halogen, -CF₃, -OR₈, -N(R₈)₂, -C(=O)R₈, -C(=O)OR₈, -C(=O)N(R₈)₂, -C(=N-OH)R₈, -C(=S)N(R₈)₂, C₁-C₆alkyl, C₁-C₆heteroalkyl, or optionally substituted C₂-C₇heterocycloalkyl;

R₂ is -C(=O)OR₉;

R₃ is hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R₄ is aryl or heteroaryl; wherein aryl and heteroaryl are substituted with at least one R₁₁;

each R₅ is independently halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R₆ is independently hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R₇ is independently C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;

each R₈, each R₉, and each R₁₀ are each independently hydrogen, C₁-C₆alkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, aryl, or heteroaryl;

each R₁₁ is independently halogen, nitro, -OR₁₀, -N(R₁₀)₂, -CN, -C(=O)R₁₀, -C(=O)OR₁₀, -C(=O)N(R₁₀)₂, -NR₁₀C(=O)R₁₀, -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, -SO₂N(R₁₀)₂, -C(=O)OCH₂SCH₃, optionally substituted C₁-C₆alkyl, optionally substituted C₃-C₈cycloalkyl, optionally substituted C₁-C₆haloalkyl, optionally substituted C₁-C₆heteroalkyl, optionally substituted -C₁-C₆alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl; and

n is 0-2;

or a pharmaceutically acceptable salt thereof.

39. The compound of claim 38, or a pharmaceutically acceptable salt thereof, wherein X is -S-.

40. The compound of claim 38, or a pharmaceutically acceptable salt thereof, wherein X is -CH=CH-.

41. The compound of claim 40, or a pharmaceutically acceptable salt thereof, wherein L₂ is -CH₂-.

42. The compound of any one of claims 40-41, or a pharmaceutically acceptable salt thereof, wherein R₂ is -C(=O)OR₉; and R₉ is hydrogen or C₁-C₆alkyl.

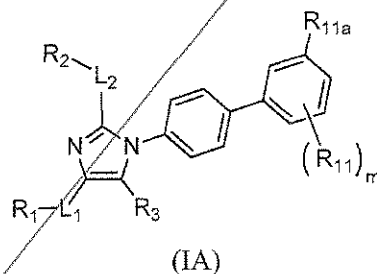
43. The compound of claim 42, or a pharmaceutically acceptable salt thereof, wherein R₉ is hydrogen, methyl or ethyl.

44. The compound of any one of claims 40-43, or a pharmaceutically acceptable salt thereof, wherein L_1 is a bond.
45. The compound of claim 44, or a pharmaceutically acceptable salt thereof, wherein R_1 is C_1 - C_6 alkyl or $-CF_3$.
46. The compound of any one of claims 40-43, or a pharmaceutically acceptable salt thereof, wherein L_1 is C_1 - C_6 alkyl; and R_1 is $-OR_8$.
47. The compound of any one of claims 40-43, or a pharmaceutically acceptable salt thereof, wherein $-L_1-R_1$ is isopropyl, $-CF_3$, and $-C(CH_3)_2OH$.
48. The compound of any one of claims 40-47, or a pharmaceutically acceptable salt thereof, wherein n is 0.
49. The compound of any one of claims 40-48, or a pharmaceutically acceptable salt thereof, wherein R_3 is hydrogen.
50. The compound of any one of claims 40-49, or a pharmaceutically acceptable salt thereof, wherein R_4 is phenyl substituted with at least one R_{11} .
51. The compound of any one of claims 40-50, or a pharmaceutically acceptable salt thereof, wherein at least one R_{11} is $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$.
52. The compound of any one of claims 40-50, or a pharmaceutically acceptable salt thereof, wherein at least one R_{11} is $-SO_2R_{10}$.
53. The compound of claim 51 or 52, or a pharmaceutically acceptable salt thereof, wherein each R_{10} is independently C_1 - C_6 alkyl.

54. The compound of any one of claims 40-49, or a pharmaceutically acceptable salt thereof, wherein R_4 is phenyl substituted with one R_{11} , wherein R_{11} is $-\text{SO}_2R_{10}$ and R_{10} is C_1 - C_6 alkyl; or R_4 is phenyl substituted with two R_{11} , and one R_{11} is $-\text{SO}_2R_{10}$ and one R_{11} is optionally substituted C_1 - C_6 alkyl.

55. The compound of any one of claims 40-54, or a pharmaceutically acceptable salt thereof, wherein "optionally substituted" means optionally substituted by 1, 2, 3, or 4 substituents independently selected from halo, cyano, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, hydroxy, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, amino, C_1 - C_4 alkylamino, and $\text{di}(\text{C}_1$ - C_4 alkyl)amino.

56. The compound of any one of claims 40-49, wherein the compound is a compound of Formula (IA):



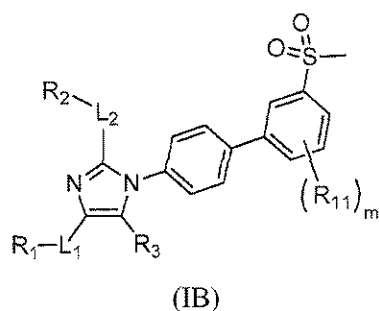
wherein:

m is 0 or 1; and

R_{11a} is $-\text{NR}_{10}\text{SO}_2R_{10}$, $-\text{SOR}_{10}$, $-\text{SO}_2R_{10}$, or $-\text{SO}_2\text{N}(\text{R}_{10})_2$;

or a pharmaceutically acceptable salt thereof.

57. The compound of any one of claims 40-49, wherein the compound is a compound of Formula (IB):



wherein m is 0 or 1;

or a pharmaceutically acceptable salt thereof.

58. The compound of claim 40, or a pharmaceutically acceptable salt thereof, wherein:

X is $-\text{CH}=\text{CH}-$;

L_2 is $\text{C}_1\text{-C}_6$ alkyl;

R_2 is $-\text{C}(=\text{O})\text{OR}_9$;

R_9 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

L_1 is a bond; and R_1 is $\text{C}_1\text{-C}_6$ alkyl or $-\text{CF}_3$; or

L_1 is $\text{C}_1\text{-C}_6$ alkyl; and R_1 is $-\text{OR}_8$;

R_4 is phenyl substituted with at least one R_{11} ;

each R_{11} is independently $\text{C}_1\text{-C}_6$ alkyl, $-\text{NR}_{10}\text{SO}_2\text{R}_{10}$, $-\text{SOR}_{10}$, $-\text{SO}_2\text{R}_{10}$, or $-\text{SO}_2\text{N}(\text{R}_{10})_2$; wherein said $\text{C}_1\text{-C}_6$ alkyl is optionally substituted by 1 hydroxy;

provided that at least one R_{11} is $-\text{NR}_{10}\text{SO}_2\text{R}_{10}$, $-\text{SOR}_{10}$, $-\text{SO}_2\text{R}_{10}$, or $-\text{SO}_2\text{N}(\text{R}_{10})_2$;

each R_{10} is independently $\text{C}_1\text{-C}_6$ alkyl;

n is 0; and

R_3 is hydrogen.

59. The compound of claim 40, or a pharmaceutically acceptable salt thereof, wherein:

X is $-\text{CH}=\text{CH}-$;

L_2 is $\text{C}_1\text{-C}_6$ alkyl;

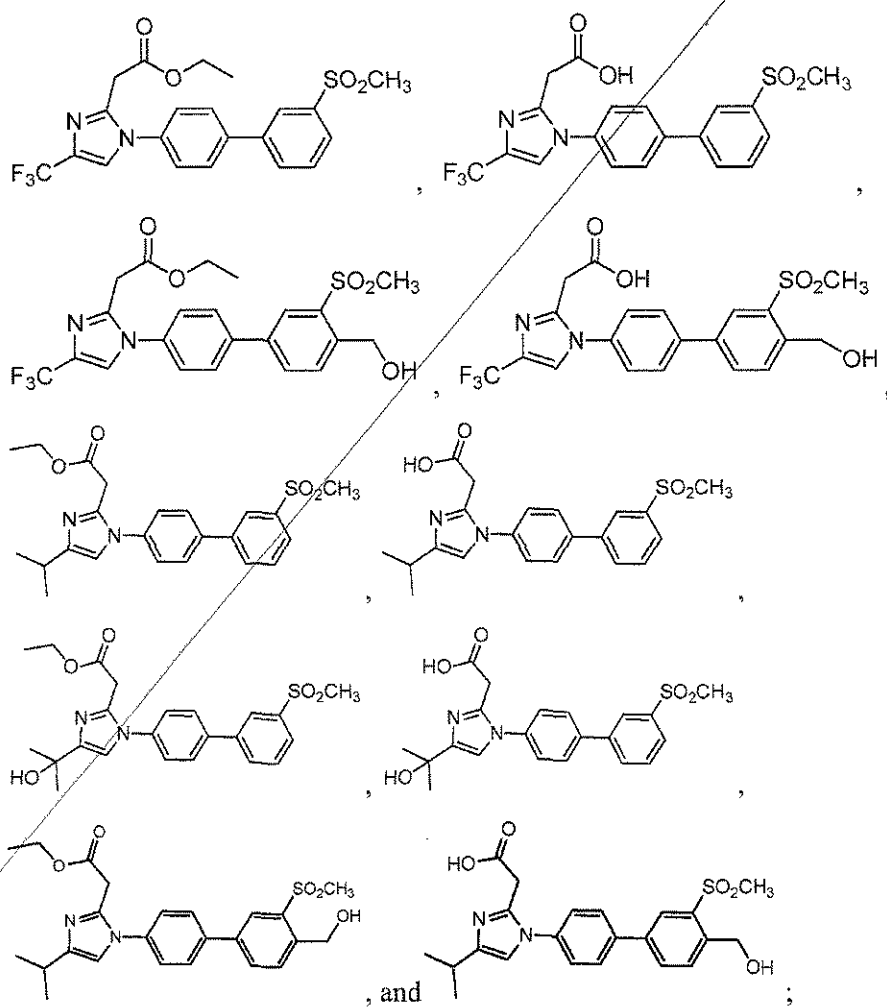
R_2 is $-\text{C}(=\text{O})\text{OR}_9$;

R_9 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

L_1 is a bond; and R_1 is $\text{C}_1\text{-C}_6$ alkyl or $-\text{CF}_3$; or

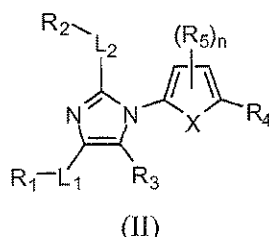
L_1 is C_1 - C_6 alkyl; and R_1 is $-OR_8$;
 R_4 is phenyl substituted with at least one R_{11} ;
 each R_{11} is independently C_1 - C_6 alkyl or $-SO_2R_{10}$; wherein said C_1 - C_6 alkyl is optionally substituted by 1 hydroxy;
 provided that at least one R_{11} is $-SO_2R_{10}$;
 each R_{10} is independently C_1 - C_6 alkyl;
 n is 0; and
 R_3 is hydrogen.

60. The compound of claim 40, selected from:



or a pharmaceutically acceptable salt thereof.

61. A compound of Formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

X is -O-, -S-, or -C(R₆)=C(R₆)-;

L₁ is a bond, C₁-C₆alkyl, or C₁-C₆heteroalkyl; wherein C₁-C₆alkyl and C₁-C₆heteroalkyl are optionally substituted with at least one R₇;

L₂ is a C₁-C₆alkyl, or C₁-C₆heteroalkyl;

R₁ is -C(=O)OR₈;

R₂ is hydrogen, -OR₉, -N(R₉)₂, -C(=O)R₉, -C(=O)N(R₉)₂, -C(=N-OH)R₉, -C(=S)N(R₉)₂, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, or optionally substituted heterocycloalkyl;

R₃ is hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R₄ is aryl or heteroaryl; wherein aryl and heteroaryl are substituted with at least one R₁₁;

each R₅ is independently halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R₆ is independently hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R₇ is independently C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;

each R₈, each R₉, and each R₁₀ are each independently hydrogen, C₁-C₆alkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, aryl, or heteroaryl;

each R₁₁ is independently halogen, nitro, -OR₁₀, -N(R₁₀)₂, -CN, -C(=O)R₁₀, -C(=O)OR₁₀, -C(=O)N(R₁₀)₂, -NR₁₀C(=O)R₁₀, -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, -SO₂N(R₁₀)₂, -C(=O)OCH₂SCH₃, optionally substituted C₁-C₆alkyl, optionally substituted C₃-C₈cycloalkyl,

optionally substituted C₁-C₆haloalkyl, optionally substituted C₁-C₆heteroalkyl, optionally substituted -C₁-C₆alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;
and

n is 0-2.

62. The compound of claim 61, or a pharmaceutically acceptable salt thereof, wherein X is -S-.

63. The compound of claim 61, or a pharmaceutically acceptable salt thereof, wherein X is -CH=CH-.

64. The compound of claim 63, or a pharmaceutically acceptable salt thereof, wherein L₁ is a bond.

65. The compound of claim 64, or a pharmaceutically acceptable salt thereof, wherein R₁ is a -C(=O)OR₈; and R₈ is hydrogen or C₁-C₆alkyl.

66. The compound of claim 65, or a pharmaceutically acceptable salt thereof, wherein R₈ is hydrogen, methyl, or ethyl.

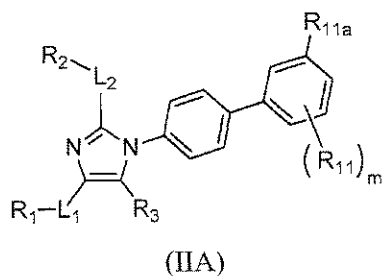
67. The compound of any one of claims 63-66, or a pharmaceutically acceptable salt thereof, wherein L₂ is C₁-C₆alkyl.

68. The compound of claim 67, or a pharmaceutically acceptable salt thereof, wherein R₂ is hydrogen.

69. The compound of any one of claims 63-66, or a pharmaceutically acceptable salt thereof, wherein -L₂-R₂ is isobutyl.

70. The compound of any one of claims 63-69, or a pharmaceutically acceptable salt thereof, wherein n is 0.
71. The compound of any one of claims 63-70, or a pharmaceutically acceptable salt thereof, wherein R_3 is hydrogen.
72. The compound of any one of claims 63-71, or a pharmaceutically acceptable salt thereof, wherein R_4 is phenyl substituted with at least one R_{11} .
73. The compound of any one of claims 63-72, or a pharmaceutically acceptable salt thereof, wherein at least one R_{11} is $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$.
74. The compound of any one of claims 63-72, or a pharmaceutically acceptable salt thereof, wherein at least one R_{11} is $-SO_2R_{10}$.
75. The compound of claim 73 or 74, or a pharmaceutically acceptable salt thereof, wherein each R_{10} is independently C_1 - C_6 alkyl.
76. The compound of any one of claims 63-71, or a pharmaceutically acceptable salt thereof, wherein R_4 is phenyl substituted with one R_{11} , wherein R_{11} is $-SO_2R_{10}$ and R_{10} is C_1 - C_6 alkyl; or R_4 is phenyl substituted with two R_{11} , and one R_{11} is $-SO_2R_{10}$ and one R_{11} is optionally substituted C_1 - C_6 alkyl.
77. The compound of any one of claims 63-76, or a pharmaceutically acceptable salt thereof, wherein "optionally substituted" means optionally substituted by 1, 2, 3, or 4 substituents independently selected from halo, cyano, C_1 - C_4 alkyl, C_2 - C_4 alkenyl, hydroxy, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, amino, C_1 - C_4 alkylamino, and $di(C_1$ - C_4 alkyl)amino.

78. The compound of any one of claims 63-71, wherein the compound is a compound of Formula (IIA):



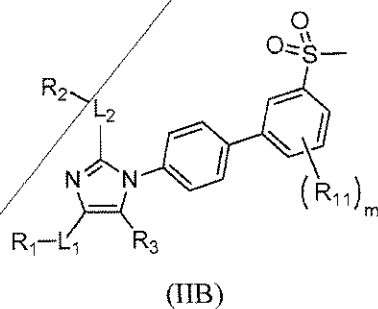
wherein:

m is 0 or 1; and

R_{11a} is -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, or -SO₂N(R₁₀)₂;

or a pharmaceutically acceptable salt thereof.

79. The compound of any one of claims 63-71, wherein the compound is a compound of Formula (IIB):



wherein m is 0 or 1;

or a pharmaceutically acceptable salt thereof.

80. The compound of claim 63, or a pharmaceutically acceptable salt thereof, wherein:

X is -CH=CH-;

R₁ is a -C(=O)OR₈; and R₈ is hydrogen or C₁-C₆alkyl;

L₂ is C₁-C₆alkyl;

R₂ is hydrogen;

R₄ is phenyl substituted with at least one R₁₁;

each R_{11} is independently C_1 - C_6 alkyl, $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$; wherein said C_1 - C_6 alkyl is optionally substituted by 1 hydroxy;
 provided that at least one R_{11} is $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$;
 each R_{10} is independently C_1 - C_6 alkyl;
 n is 0; and
 R_3 is hydrogen.

81. The compound of claim 63, or a pharmaceutically acceptable salt thereof, wherein:

X is $-\text{CH}=\text{CH}-$;

R_1 is a $-\text{C}(=\text{O})\text{OR}_8$; and R_8 is hydrogen or C_1 - C_6 alkyl;

L_2 is C_1 - C_6 alkyl;

R_2 is hydrogen;

R_4 is phenyl substituted with at least one R_{11} ;

each R_{11} is independently C_1 - C_6 alkyl or $-SO_2R_{10}$; wherein said C_1 - C_6 alkyl is optionally substituted by 1 hydroxy;

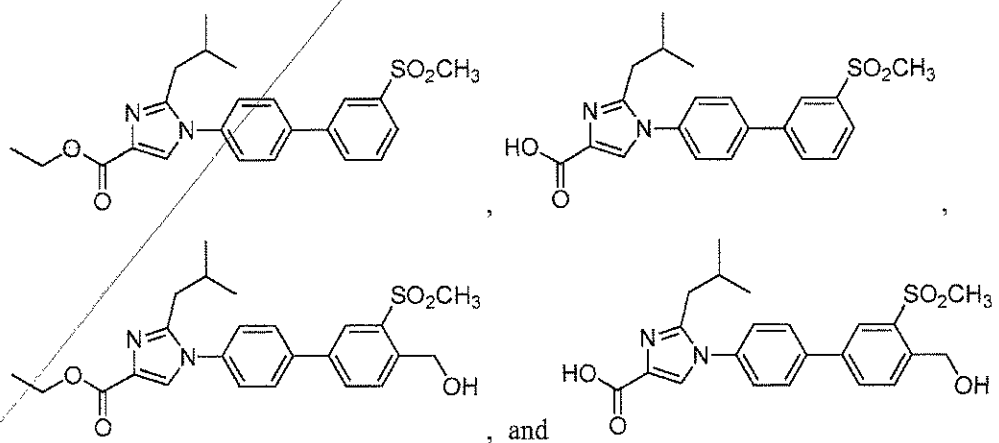
provided that at least one R_{11} is $-SO_2R_{10}$;

each R_{10} is independently C_1 - C_6 alkyl;

n is 0; and

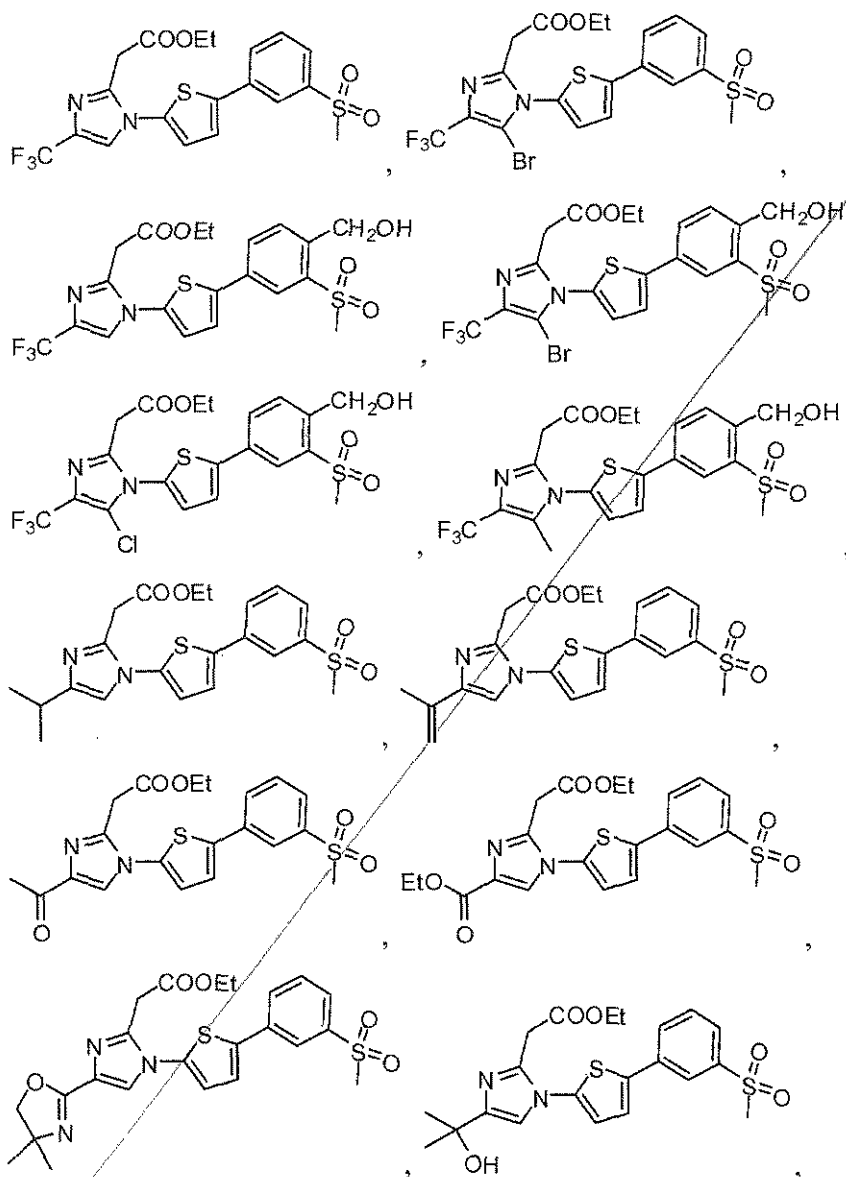
R_3 is hydrogen.

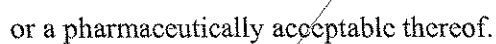
82. The compound of claim 63, selected from:



or a pharmaceutically acceptable salt thereof.

83. A compound selected from:





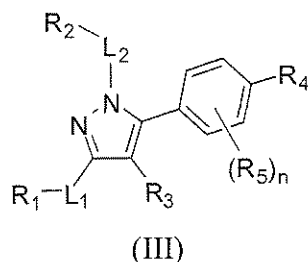
85. A method of treating a disease, disorder or condition in a mammal that would benefit from LXR modulation comprising administering to the mammal a compound according to any one of claims 1-83, or a pharmaceutically acceptable salt thereof.

86. The method of claim 85, wherein the disease, disorder or condition in a mammal is a dermal disease, disorder or condition selected from skin aging, scarring, psoriasis, dermatitis, eczema, urticaria, rosacea, burns, and acne.

87. A method of modulating LXR activity comprising contacting LXR, or portion thereof, with a compound according to any one of claims 1-83, or a pharmaceutically acceptable salt thereof.

WHAT IS CLAIMED IS:

1. A compound of Formula (III):



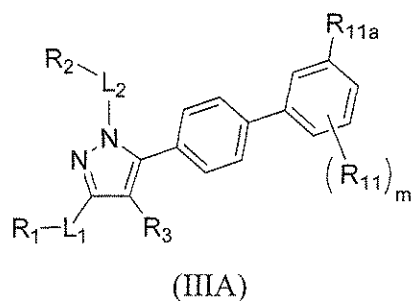
or a pharmaceutically acceptable salt thereof, wherein:

- L_1 is a bond;
- L_2 is a C_1 - C_6 alkyl, or C_1 - C_6 heteroalkyl;
- R_1 is $-C(=O)OR_8$;
- R_2 is hydrogen, $-OR_9$, $-N(R_9)_2$, $-C(=O)R_9$, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_1 - C_6 haloalkyl, or optionally substituted heterocycloalkyl;
- R_3 is hydrogen, halogen, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;
- R_4 is aryl or heteroaryl; wherein aryl and heteroaryl are substituted with at least one R_{11} ;
- each R_5 is independently halogen, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;
- each R_7 is independently C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_1 - C_6 haloalkyl, C_1 - C_6 heteroalkyl, $-C_1$ - C_6 alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;
- R_8 is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, $-C_1$ - C_6 alkyl-aryl, aryl, or heteroaryl;
- R_9 is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, $-C_1$ - C_6 alkyl-aryl, aryl, or heteroaryl;
- each R_{10} are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, $-C_1$ - C_6 alkyl-aryl, aryl, or heteroaryl;
- each R_{11} is independently halogen, nitro, $-OR_{10}$, $-N(R_{10})_2$, $-CN$, $-C(=O)R_{10}$, $-C(=O)OR_{10}$, $-C(=O)N(R_{10})_2$, $-NR_{10}C(=O)R_{10}$, $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, $-SO_2N(R_{10})_2$, $-C(=O)OCH_2SCH_3$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally

substituted -C₁-C₆alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;
and

n is 0-4.

2. The compound of claim 1, wherein the compound is a compound of Formula (IIIA):



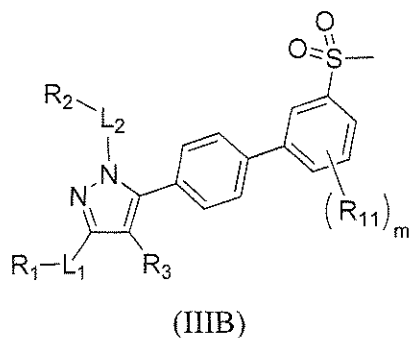
wherein:

m is 0 or 1; and

R_{11a} is -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, or -SO₂N(R₁₀)₂;

or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, wherein the compound is a compound of Formula (IIIB):



wherein m is 0 or 1;

or a pharmaceutically acceptable salt thereof.

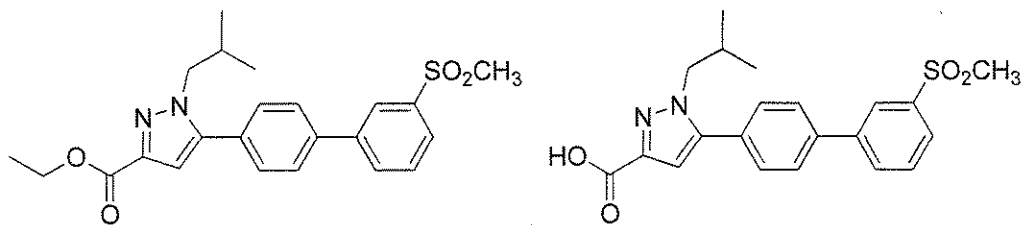
4. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

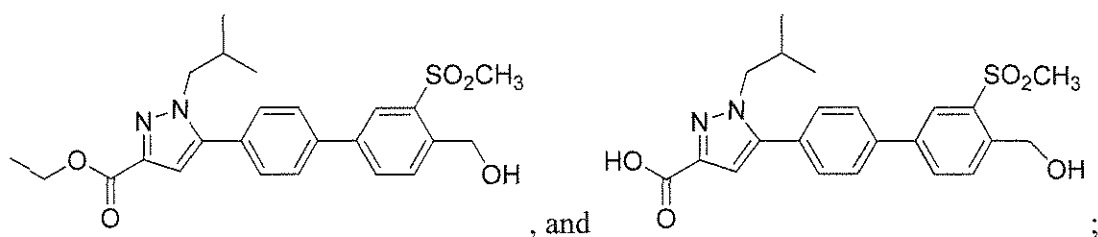
L₁ is a bond;

R₁ is -C(=O)OR₈;

R₈ is hydrogen or C₁-C₆alkyl.

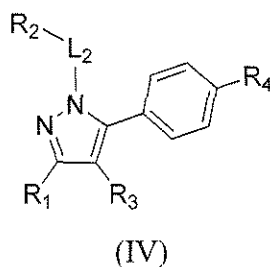
- L_2 is a C_1 - C_6 alkyl;
 R_2 is hydrogen;
 R_4 is phenyl substituted with at least one R_{11} ;
each R_{11} is independently C_1 - C_6 alkyl, $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$; wherein said C_1 - C_6 alkyl is optionally substituted by 1 hydroxy;
provided that at least one R_{11} is $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$;
each R_{10} is independently C_1 - C_6 alkyl;
 n is 0; and
 R_3 is hydrogen.
5. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:
 L_1 is a bond;
 R_1 is $-C(=O)OR_8$;
 R_8 is hydrogen or C_1 - C_6 alkyl.
 L_2 is a C_1 - C_6 alkyl;
 R_2 is hydrogen;
 R_4 is phenyl substituted with at least one R_{11} ;
each R_{11} is independently C_1 - C_6 alkyl, $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$; wherein said C_1 - C_6 alkyl is optionally substituted by 1 hydroxy;
provided that at least one R_{11} is $-SO_2N(R_{10})_2$;
each R_{10} is independently C_1 - C_6 alkyl;
 n is 0; and
 R_3 is hydrogen.
6. The compound of claim 1, selected from:





or a pharmaceutically acceptable salt thereof.

7. A compound of Formula (IV):



wherein:

R_1 is C_1 - C_6 alkyl or C_2 - C_6 alkenyl, wherein said C_1 - C_6 alkyl is optionally substituted by 1, 2, 3, or 4 substituents independently selected from hydroxy, C_1 - C_4 alkoxy, and C_1 - C_4 haloalkoxy;

L_2 is a C_1 - C_6 alkyl;

R_2 is $C(=O)OR_9$;

R_3 is hydrogen or C_1 - C_6 alkyl;

R_4 is phenyl substituted with at least one R_{11} ;

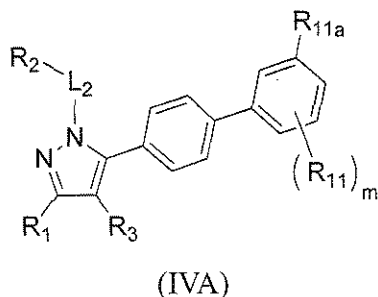
each R_9 is independently hydrogen or C_1 - C_6 alkyl;

each R_{10} is independently hydrogen or C_1 - C_6 alkyl; and

each R_{11} is independently halogen, nitro, $-OR_{10}$, $-N(R_{10})_2$, $-CN$, $-C(=O)R_{10}$, $-C(=O)OR_{10}$, $-C(=O)N(R_{10})_2$, $-NR_{10}C(=O)R_{10}$, $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, $-SO_2N(R_{10})_2$, $-C(=O)OCH_2SCH_3$, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl, wherein said C_1 - C_6 alkyl is optionally substituted by 1, 2, 3, or 4 substituents independently selected from cyano, hydroxy, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, amino, C_1 - C_4 alkylamino, and $di(C_1$ - C_4 alkyl)amino;

provided that at least one R_{11} is $-NR_{10}C(=O)R_{10}$, $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$.

8. The compound of claim 7, wherein the compound is a compound of Formula (IVA):



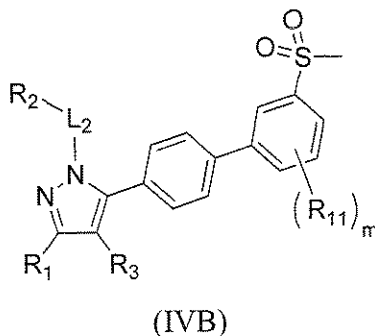
wherein:

m is 0 or 1; and

R_{11a} is -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, or -SO₂N(R₁₀)₂;

or a pharmaceutically acceptable salt thereof.

9. The compound of claim 7, wherein the compound is a compound of Formula (IVB):



wherein m is 0 or 1;

or a pharmaceutically acceptable salt thereof.

10. The compound of claim 7, or a pharmaceutically acceptable salt thereof, wherein:

R₁ is C₂-C₄ alkenyl or C₁-C₃ alkyl, wherein said C₁-C₃ alkyl is optionally substituted by 1 hydroxy;

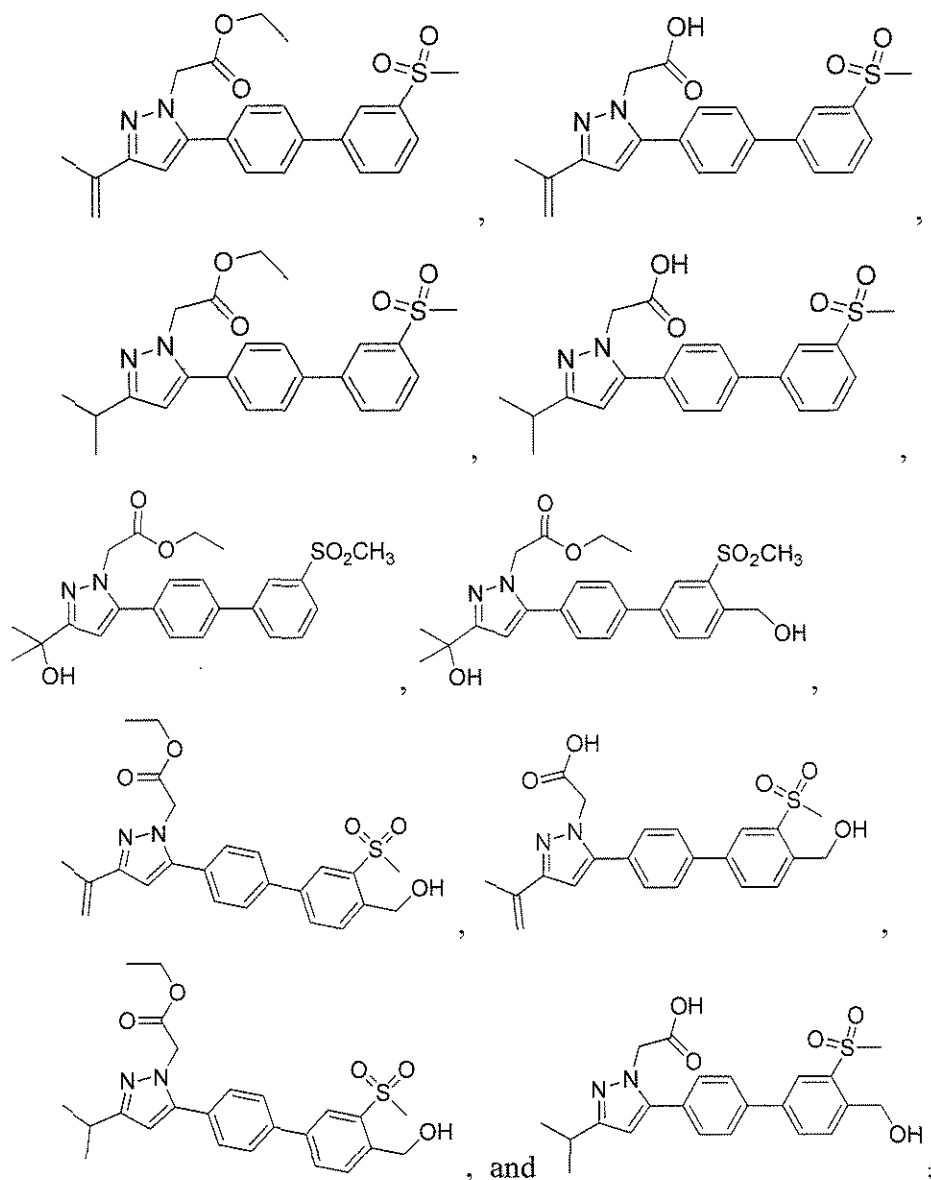
-L₂-R₂ is -CH₂C(=O)OR₉;

R₉ is hydrogen or C₁-C₆ alkyl;

R₄ is phenyl substituted with at least one R₁₁;

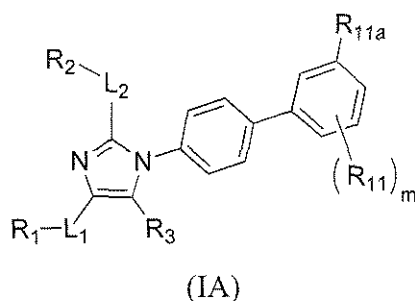
each R_{11} is independently C_1 - C_6 alkyl, $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$; wherein said C_1 - C_6 alkyl is optionally substituted by 1 hydroxy;
provided that at least one R_{11} is $-SO_2N(R_{10})_2$;
each R_{10} is independently C_1 - C_6 alkyl; and
 R_3 is hydrogen.

11. The compound of claim 7, selected from:



or a pharmaceutically acceptable salt thereof.

12. A compound of Formula (IA):



wherein:

L_1 and L_2 are each independently a bond, C_1 - C_6 alkyl, or C_1 - C_6 heteroalkyl; wherein C_1 - C_6 alkyl and C_1 - C_6 heteroalkyl are optionally substituted with at least one R_7 ;

R_1 is halogen, $-CF_3$, $-OR_8$, $-N(R_8)_2$, $-C(=O)R_8$, $-C(=O)OR_8$, $-C(=O)N(R_8)_2$, $-C(=N-OH)R_8$, $-C(=S)N(R_8)_2$, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, or optionally substituted C_2 - C_7 heterocycloalkyl;

R_2 is $-C(=O)OR_9$;

R_3 is hydrogen, halogen, C_1 - C_6 alkyl, or C_1 - C_6 haloalkyl;

each R_7 is independently C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, C_1 - C_6 haloalkyl, C_1 - C_6 heteroalkyl, $-C_1$ - C_6 alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;

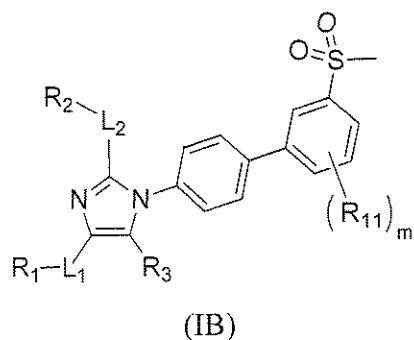
each R_8 , each R_9 , and each R_{10} are each independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, $-C_1$ - C_6 alkyl-aryl, aryl, or heteroaryl;

m is 0 or 1;

R_{11a} is $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, or $-SO_2N(R_{10})_2$;

each R_{11} is independently halogen, nitro, $-OR_{10}$, $-N(R_{10})_2$, $-CN$, $-C(=O)R_{10}$, $-C(=O)OR_{10}$, $-C(=O)N(R_{10})_2$, $-NR_{10}C(=O)R_{10}$, $-NR_{10}SO_2R_{10}$, $-SOR_{10}$, $-SO_2R_{10}$, $-SO_2N(R_{10})_2$, $-C(=O)OCH_2SCH_3$, optionally substituted C_1 - C_6 alkyl, optionally substituted C_3 - C_8 cycloalkyl, optionally substituted C_1 - C_6 haloalkyl, optionally substituted C_1 - C_6 heteroalkyl, optionally substituted $-C_1$ - C_6 alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl; or a pharmaceutically acceptable salt thereof.

13. The compound of claim 12, wherein the compound is a compound of Formula (IB):



wherein m is 0 or 1;

or a pharmaceutically acceptable salt thereof.

14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein:

L_2 is C_1 - C_6 alkyl;

R_2 is $-C(=O)OR_9$;

R_9 is hydrogen or C_1 - C_6 alkyl;

L_1 is a bond; and R_1 is C_1 - C_6 alkyl or $-CF_3$; or

L_1 is C_1 - C_6 alkyl; and R_1 is $-OR_8$;

R_4 is phenyl substituted with at least one R_{11} ;

each R_{11} is independently C_1 - C_6 alkyl or $-SO_2R_{10}$; wherein said C_1 - C_6 alkyl is optionally substituted by 1 hydroxy;

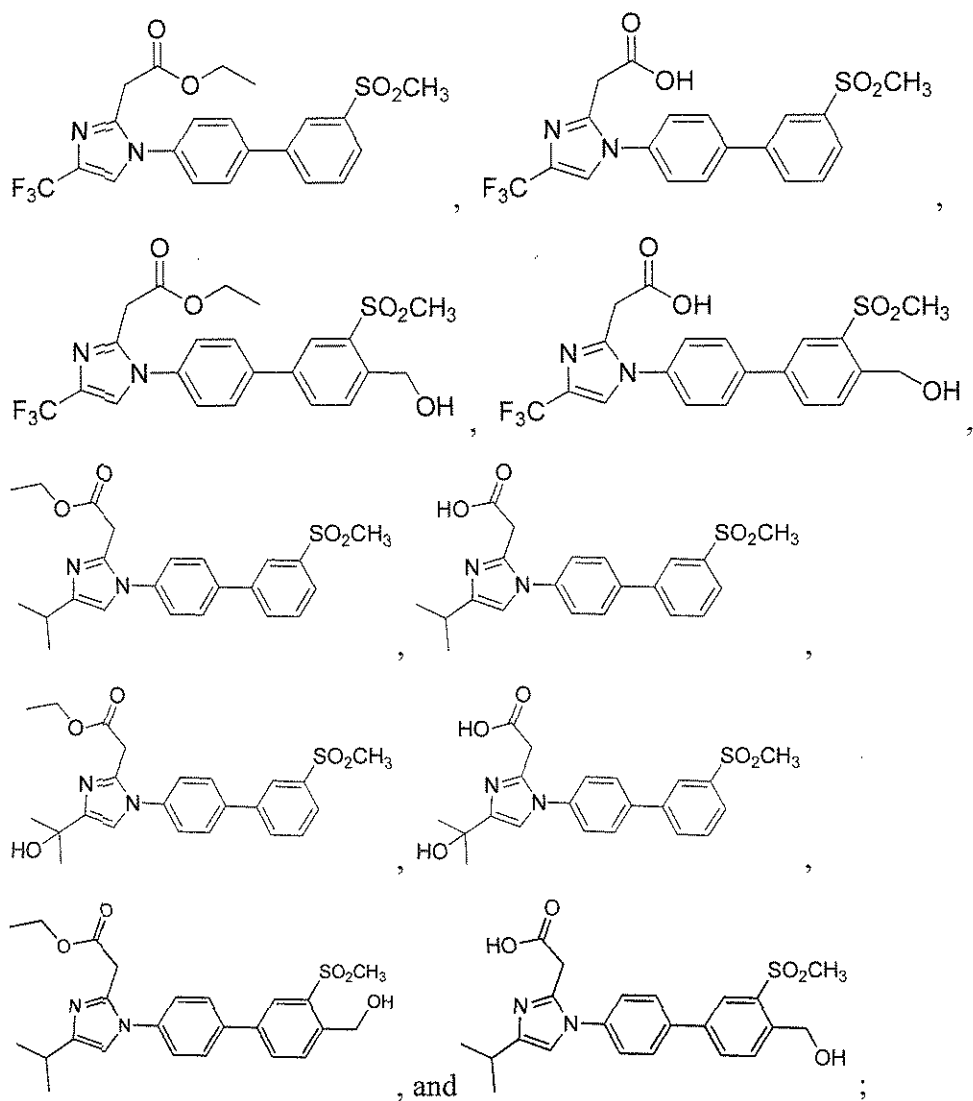
provided that at least one R_{11} is $-SO_2R_{10}$;

each R_{10} is independently C_1 - C_6 alkyl;

n is 0; and

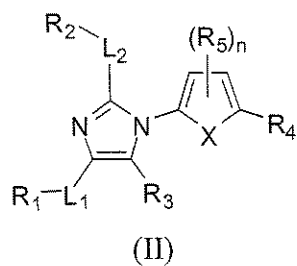
R_3 is hydrogen.

15. The compound of claim 12, selected from:



or a pharmaceutically acceptable salt thereof.

16. A compound of Formula (II):



or a pharmaceutically acceptable salt thereof, wherein:

X is $-C(R_6)=C(R_6)-$;

L₁ is a bond, C₁-C₆alkyl, or C₁-C₆heteroalkyl; wherein C₁-C₆alkyl and C₁-C₆heteroalkyl are optionally substituted with at least one R₇;

L₂ is a C₁-C₆alkyl, or C₁-C₆heteroalkyl;

R₁ is -C(=O)OR₈;

R₂ is hydrogen, -OR₉, -N(R₉)₂, -C(=O)R₉, -C(=O)N(R₉)₂, -C(=N-OH)R₉, -C(=S)N(R₉)₂, C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, or optionally substituted heterocycloalkyl;

R₃ is hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

R₄ is aryl or heteroaryl; wherein aryl and heteroaryl are substituted with at least one R₁₁;

each R₅ is independently halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R₆ is independently hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;

each R₇ is independently C₁-C₆alkyl, C₃-C₈cycloalkyl, C₁-C₆haloalkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;

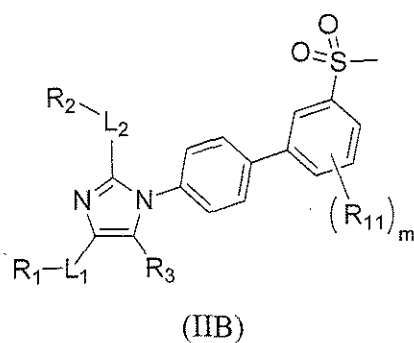
each R₈, each R₉, and each R₁₀ are each independently hydrogen, C₁-C₆alkyl, C₁-C₆heteroalkyl, -C₁-C₆alkyl-aryl, aryl, or heteroaryl;

each R₁₁ is independently halogen, nitro, -OR₁₀, -N(R₁₀)₂, -CN, -C(=O)R₁₀, -C(=O)OR₁₀, -C(=O)N(R₁₀)₂, -NR₁₀C(=O)R₁₀, -NR₁₀SO₂R₁₀, -SOR₁₀, -SO₂R₁₀, -SO₂N(R₁₀)₂, -C(=O)OCH₂SCH₃, optionally substituted C₁-C₆alkyl, optionally substituted C₃-C₈cycloalkyl, optionally substituted C₁-C₆haloalkyl, optionally substituted C₁-C₆heteroalkyl, optionally substituted -C₁-C₆alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl;

and

n is 0-2.

17. The compound of claim 16, wherein the compound is a compound of Formula (IIB):



wherein m is 0 or 1;

or a pharmaceutically acceptable salt thereof.

18. The compound of claim 17, or a pharmaceutically acceptable salt thereof, wherein:

X is $-\text{CH}=\text{CH}-$;

R_1 is a $-\text{C}(=\text{O})\text{OR}_8$; and R_8 is hydrogen or $\text{C}_1\text{-C}_6$ alkyl;

L_2 is $\text{C}_1\text{-C}_6$ alkyl;

R_2 is hydrogen;

R_4 is phenyl substituted with at least one R_{11} ;

each R_{11} is independently $\text{C}_1\text{-C}_6$ alkyl or $-\text{SO}_2\text{R}_{10}$; wherein said $\text{C}_1\text{-C}_6$ alkyl is optionally substituted by 1 hydroxy;

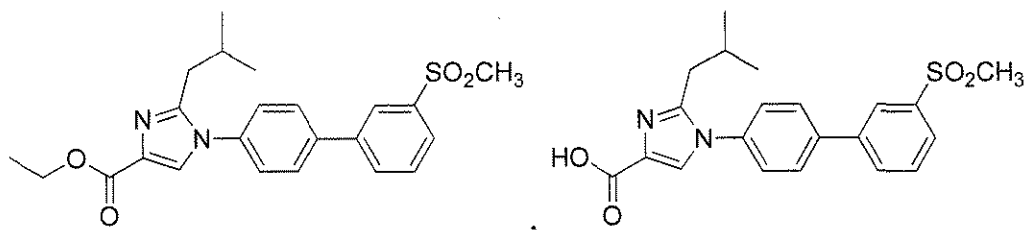
provided that at least one R_{11} is $-\text{SO}_2\text{R}_{10}$;

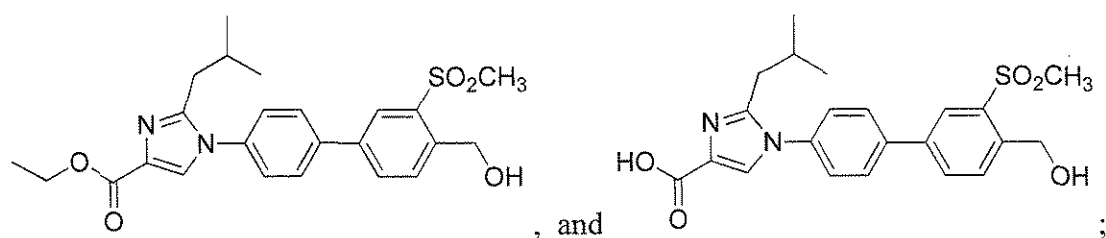
each R_{10} is independently $\text{C}_1\text{-C}_6$ alkyl;

n is 0; and

R_3 is hydrogen.

19. The compound of claim 16, selected from:





or a pharmaceutically acceptable salt thereof.

20. A pharmaceutical composition comprising a compound of any one of claims 1-19, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

21. Use of a compound according to any one of claims 1-19, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a dermal disease, disorder or condition selected from skin aging, scarring, psoriasis, dermatitis, eczema, urticaria, rosacea, burns, and acne in a mammal.

22. A method of modulating LXR activity comprising contacting LXR, or portion thereof, with a compound according to any one of claims 1-19, or a pharmaceutically acceptable salt thereof.