

LIVER X RECEPTOR (LXR) MODULATORS

This application claims the benefit of priority of U.S. Provisional No. 61/873,755, filed September 4, 2013, which is incorporated herein by reference in its entirety.

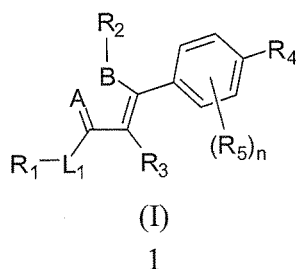
BACKGROUND OF THE INVENTION

5 Liver X receptor (LXR), 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)), is a member of the nuclear hormone superfamily and consists of two subtypes, LXR alpha and LXR beta. LXR modulates a variety of physiological responses including inflammation in various tissues and cell types, regulation of cholesterol absorption, 10 cholesterol elimination (bile acid synthesis), and transport of cholesterol from peripheral tissues via plasma lipoproteins to the liver. LXR also regulates genes involved in glucose metabolism, cholesterol metabolism in the brain and apolipoproteins such as ApoE and its isoforms, that are implicated in cellular differentiation and apoptosis, inflammation, neurodegenerative disease, and infectious diseases (Geyeregger, R. et al., *Cell. Mol. Life Sci.* 2006, 63:524-539). LXR also 15 regulates genes, including ApoE, in melanoma cells and melanocytes (Lim, K.M., et al., *J Invest Dermatol.* (2013) 133(4):1063-71) and thus is also a therapeutic target for treatment of certain types of cancers.

SUMMARY OF THE INVENTION

20 Described herein are compounds of Formula I, IA, IB, IC, II, IIA, or IIB, pharmaceutical compositions that include such compounds, and methods of use thereof, for modulating LXR. In one ~~aspect-embodiment~~ is the administration of at least one LXR modulator described herein to a mammal in the treatment of diseases, disorders or conditions that would benefit from LXR modulation.

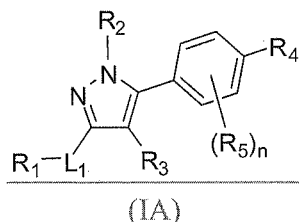
In one ~~aspect-embodiment~~ is a compound of Formula (I):



embodiment is a compound of Formula I wherein R_1 is $-\text{CF}_3$. In another embodiment is a compound of Formula I wherein R_1 is $-\text{C}(=\text{O})\text{R}_8$. In another embodiment is a compound of Formula I wherein R_1 is $-\text{C}(=\text{O})\text{R}_8$, and R_8 is $\text{C}_1\text{-C}_6$ alkyl. In another embodiment is a compound of Formula I wherein R_1 is $\text{C}(=\text{O})\text{N}(\text{R}_9)_2$. In another embodiment of the aforementioned

5 embodiments is a compound of Formula I wherein R_2 is $\text{C}_1\text{-C}_6$ alkyl. In another embodiment of the aforementioned embodiments is a compound of Formula I wherein R_2 is isobutyl. In another embodiment of the aforementioned embodiments is a compound of Formula I wherein R_3 is hydrogen. In another embodiment of the aforementioned embodiments is a compound of Formula I wherein R_3 is halogen.

10 In one aspect is a compound of Formula (IA):



or a pharmaceutically acceptable salt thereof, wherein:

L_1 is a bond, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_1\text{-C}_6$ heteroalkyl;

R_1 is $-\text{OR}_9$, $-\text{N}(\text{R}_9)_2$, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_1\text{-C}_6$ haloalkyl, $\text{C}_2\text{-C}_9$ heterocycloalkyl, $-\text{C}(=\text{O})\text{R}_8$, or $-\text{C}(=\text{O})\text{N}(\text{R}_9)_2$;

R_2 is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_3\text{-C}_8$ cycloalkyl, or $-\text{C}_1\text{-C}_6$ alkyl- $\text{C}_3\text{-C}_8$ cycloalkyl;

R_3 is hydrogen, halogen, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_1\text{-C}_6$ haloalkyl;

R_4 is aryl or heteroaryl; wherein aryl or heteroaryl is substituted with at least one R_{11} ;

each R_5 is independently halogen, $\text{C}_1\text{-C}_6$ alkyl, or $\text{C}_1\text{-C}_6$ haloalkyl;

R_8 is $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_2\text{-C}_6$ alkenyl, $\text{C}_1\text{-C}_6$ haloalkyl, $-\text{C}_1\text{-C}_6$ alkyl-aryl, aryl, or heteroaryl;

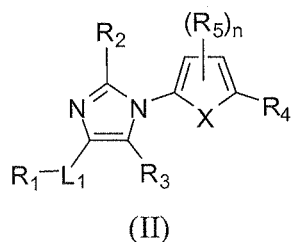
each R_9 is independently hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ heteroalkyl, $\text{C}_1\text{-C}_6$ haloalkyl, $-\text{C}_1\text{-C}_6$ alkyl-aryl, aryl, or heteroaryl;

each R_{10} is independently hydrogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ heteroalkyl, $-\text{C}_1\text{-C}_6$ alkyl-aryl, aryl, or heteroaryl;

each R_{11} is independently halogen, nitro, $-\text{OR}_{10}$, $-\text{N}(\text{R}_{10})_2$, $-\text{CN}$, $-\text{C}(=\text{O})\text{R}_{10}$, $-\text{C}(=\text{O})\text{OR}_{10}$, $-\text{C}(=\text{O})\text{N}(\text{R}_{10})_2$, $-\text{NR}_{10}\text{C}(=\text{O})\text{R}_{10}$, $-\text{NR}_{10}\text{SO}_2\text{R}_{10}$, $-\text{SOR}_{10}$, $-\text{SO}_2\text{R}_{10}$, $-\text{SO}_2\text{N}(\text{R}_{10})_2$, $-\text{C}(=\text{O})\text{OCH}_2\text{SCH}_3$, optionally substituted $\text{C}_1\text{-C}_6$ alkyl, optionally substituted $\text{C}_3\text{-C}_8$ cycloalkyl, optionally substituted $\text{C}_1\text{-C}_6$ haloalkyl, optionally substituted $\text{C}_1\text{-C}_6$ heteroalkyl, optionally substituted $-\text{C}_1\text{-C}_6$ alkyl-aryl, optionally substituted aryl, or optionally substituted heteroaryl; and

n is 0-4.

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



or a pharmaceutically acceptable salt thereof, wherein:

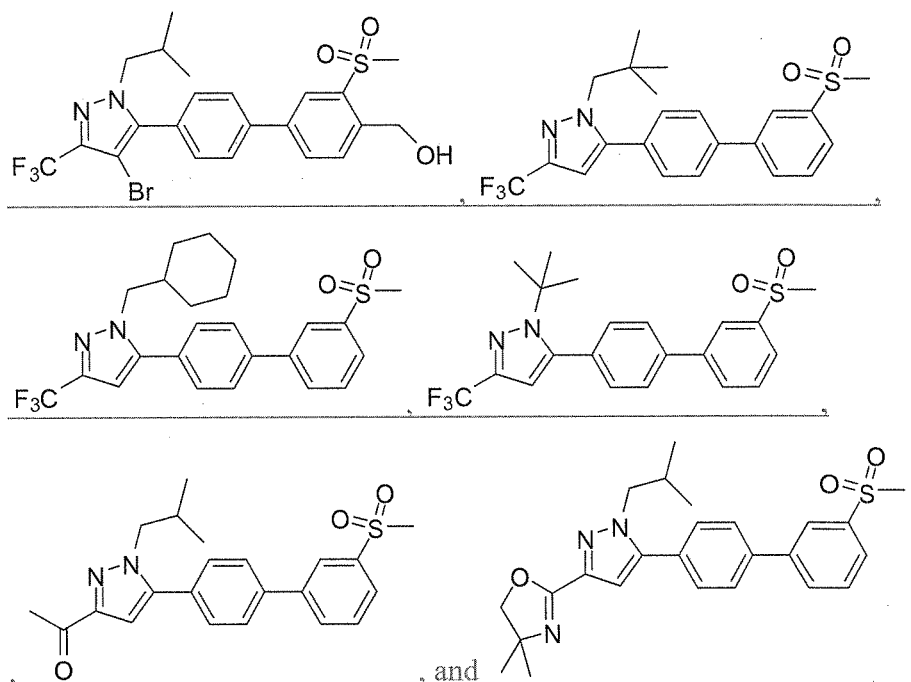
- 5 X is -O-, -S-, or -C(R₆)=C(R₆)-;
- L₁ is a bond, C₁-C₆alkyl, or C₁-C₆heteroalkyl;
- R₁ is -OR₉, -N(R₉)₂, C₁-C₆alkyl, C₂-C₆alkenyl, C₁-C₆haloalkyl, C₂-C₉heterocycloalkyl, -C(=O)R₈, or -C(=O)N(R₉)₂;
- R₂ is C₁-C₆alkyl, C₂-C₆alkenyl, C₃-C₈cycloalkyl, or -C₁-C₆alkyl-C₃-C₈cycloalkyl;
- 10 R₃ is hydrogen, halogen, C₁-C₆alkyl, or C₁-C₆haloalkyl;
- R₄ is aryl or heteroaryl; wherein aryl or heteroaryl is 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;
- R₈ is C₁-C₆alkyl, C₂-C₆alkenyl, C₁-C₆haloalkyl, -C₁-C₆alkyl-aryl, aryl, or heteroaryl;
- 15 each R₉ is independently hydrogen, C₁-C₆alkyl, C₁-C₆heteroalkyl, C₁-C₆haloalkyl, -C₁-C₆alkyl-aryl, aryl, or heteroaryl;
- each R₁₀ is 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, 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; and R₁ is -OH. 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 H. 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 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 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 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 is a compound selected from:



or a pharmaceutically acceptable salt thereof.

In one aspect is a pharmaceutical composition comprising a compound as defined herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

- 5 In another ~~aspect~~ embodiment is a pharmaceutical composition comprising a pharmaceutically acceptable diluent, excipient, carrier or binder and a compound of Formula I, IA, IB, IC, II, IIA, or IIB, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof.

- 10 In another ~~aspect~~ 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, IC, II, IIA, or IIB, 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, IC, II, IIA, or IIB, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof; wherein the disease, disorder or condition in a mammal is increased lipid levels, increased cholesterol levels, low HDL-cholesterol, high LDL-cholesterol, atherosclerotic diseases, diabetes, non-insulin dependent diabetes mellitus, metabolic syndrome, dyslipidemia, sepsis, inflammatory diseases, infectious diseases, skin diseases, colitis, pancreatitis, cholestasis of the liver, fibrosis of the liver, psoriasis, Alzheimer's disease, Parkinson's disease, impaired/ improvable cognitive function, HIV, cancer including metastatic cancer and metastatic melanoma, and age related forms of macular degeneration (wet and dry forms).

In some embodiments 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, IC, II, IIA, or IIB, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof; wherein the disease, disorder or condition in a mammal is cancer. In some embodiments the cancer is malignant melanoma. In some embodiments the ApoE levels are reduced in the cancer. In some embodiments the method further comprises the administration of a second therapeutic agent. In some embodiments the second therapeutic agent is a BRAF inhibitor. In some embodiments the BRAF inhibitor is selected from PDC-4032, GSK2118436, and PLX-3603. In some embodiments the second therapeutic agent is sunitinib malate, sorafenib tosylate, imatinib

mesylate, or nilotinib hydrochloride monohydrate; or a combination thereof. In some embodiments of the aforementioned embodiments the mammal is a human.

In some embodiments 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, IC, II, IIA, or IIB, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof; wherein the disease, disorder or condition in a mammal is Alzheimer's disease.

In some embodiments 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, IC, II, IIA, or IIB, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof; wherein the disease, disorder or condition in a mammal is Parkinson's disease.

In one aspect is use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease, disorder or condition in a mammal that would benefit from LXR modulation.

~~In another one~~ embodiment is the use of a compound of Formula I, IA, IB, IC, II, IIA, or IIB 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 a compound of Formula I, IA, IB, IC, II, IIA, or IIB for use in the any of the methods described herein. In another embodiment is the use of a LXR modulator in the manufacture of a medicament for use in the treatment of a disease, disorder or condition in a mammal, wherein the disease, disorder or condition in a mammal is increased lipid levels, increased cholesterol levels, low HDL-cholesterol, high LDL-cholesterol, atherosclerotic diseases, diabetes, non-insulin dependent diabetes mellitus, metabolic syndrome, dyslipidemia, sepsis, inflammatory diseases, infectious diseases, skin diseases, colitis, pancreatitis, cholestasis of the liver, fibrosis of the liver, psoriasis, Alzheimer's disease, Parkinson's disease, impaired/improvable cognitive function, HIV, cancer including metastatic cancer and metastatic melanoma, acute macular degeneration, and age related forms of macular degeneration (wet and dry forms). In another embodiment is the use of a LXR modulator and a second therapeutic agent in the manufacture of a medicament for use in the treatment of a disease, disorder or condition in a mammal, wherein the disease, disorder or condition in a mammal is increased lipid levels, increased cholesterol levels, low HDL-cholesterol, high LDL-cholesterol, atherosclerotic diseases, diabetes, non-insulin dependent diabetes mellitus, metabolic syndrome, dyslipidemia,

sepsis, inflammatory diseases, infectious diseases, skin diseases, colitis, pancreatitis, cholestasis of the liver, fibrosis of the liver, psoriasis, Alzheimer's disease, Parkinson's disease, impaired/improvable cognitive function, HIV, cancer including metastatic cancer and metastatic melanoma, and age related forms of macular degeneration (wet and dry forms).

5 In one aspect is an *in vitro* method of modulating LXR activity comprising contacting LXR, or portion thereof, with a compound as defined herein, or a pharmaceutically acceptable salt thereof.

10 In another aspect one embodiment is a method of modulating LXR activity comprising contacting LXR, or portion thereof, with a compound of Formula I, IA, IB, IC, II, IIA, or IIB, or a pharmaceutically acceptable salt, pharmaceutically acceptable solvate, or pharmaceutically acceptable prodrug thereof.

15 In one aspect is use of a compound as defined herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for modulating LXR activity, wherein the compound, or pharmaceutically acceptable salt thereof, is to be contacted with LXR.

15 **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.

20 **BRIEF DESCRIPTION OF THE FIGURES**

20 **Figure 1** shows ABCA1 gene expression analyzed by QT-PCR for Compound 4 as outlined in Example 13.

Figure 2 shows ABCG1 gene expression analyzed by QT-PCR for Compound 4 as outlined in Example 13.

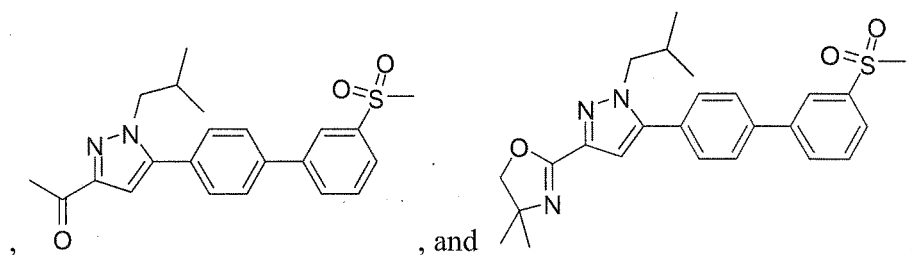
25 **Figure 3** shows IL1 β gene expression analyzed by QT-PCR for Compound 4 as outlined in Example 14.

Figure 4 shows α Syn gene expression analyzed by QT-PCR for Compound 4 as outlined in Example 15.

DETAILED DESCRIPTION OF THE INVENTION

30 **Metastatic Melanoma**

Expression levels of certain micro RNAs (miRNAs), including miRNA-1908, miRNA-199a-5p and miRNA-199a-3p and ApoE, including ApoE3 and ApoE4, correlate with the progression of malignant melanomas and metastatic disease as well as frequencies in other cancers (Tavazoie, S.F., et al., *Cell* (2012) 151:1-15). The discovery that the three miRNAs combinatorially target metastatic melanoma suppression establishes their potential as melanoma



or a pharmaceutically acceptable salt thereof.

60. A pharmaceutical composition comprising a compound according to any one of claims 1-59, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

61. ~~A method of treating a disease, disorder or condition in a mammal that would benefit from LXR modulation comprising administering to the mammal~~Use of a compound according to any one of claims 1-59, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a disease, disorder or condition in a mammal that would benefit from LXR modulation.

62. The ~~use method~~ of claim 61, wherein the disease, disorder or condition in a mammal is increased lipid levels, increased cholesterol levels, low HDL-cholesterol, high LDL-cholesterol, atherosclerotic diseases, diabetes, non-insulin dependent diabetes mellitus, metabolic syndrome, dyslipidemia, sepsis, inflammatory diseases, infectious diseases, skin diseases, colitis, pancreatitis, cholestasis of the liver, fibrosis of the liver, psoriasis, Alzheimer's disease, Parkinson's disease, impaired/ improvable cognitive function, HIV, cancer including metastatic cancer and metastatic melanoma, acute macular degeneration, and age related forms of macular degeneration (wet and dry forms).

63. The ~~use method~~ of claim 61, wherein the disease, disorder or condition is cancer.

64. The ~~use method~~ of claim 63, wherein the cancer is malignant melanoma.

65. The ~~use method~~ of claim 63, wherein ApoE levels are reduced in said cancer.

66. The ~~use method~~ of claim 62, ~~further comprising administering~~wherein the medicamen is to be administered with a second therapeutic agent.

67. The ~~use method~~ of claim 66, wherein the second therapeutic agent is a BRAF inhibitor.

68. The ~~use~~method of claim 67, wherein the BRAF inhibitor is selected from PDC-4032, GSK2118436, and PLX-3603.
69. The ~~use~~method of claim 66, wherein the second therapeutic agent is sunitinib malate, sorafenib tosylate, imatinib mesylate, or nilotinib hydrochloride monohydrate; or a combination thereof.
70. The ~~use~~method of any one of claims 61-69, wherein the mammal is a human.
71. The ~~use~~method of claim 61, wherein the disease, disorder or condition is Alzheimer's disease.
72. The ~~use~~method of claim 61, wherein the disease, disorder or condition is Parkinson's disease.
73. An *in vitro* method of modulating LXR activity comprising contacting LXR, or portion thereof, with a compound according to any one of claims 1-59, or a pharmaceutically acceptable salt thereof.
74. Use of a compound according to any one of claims 1-59, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for modulating LXR activity, wherein the compound, or pharmaceutically acceptable salt thereof, is to be contacted with LXR.