(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 February 2005 (03.02.2005)

PCT

(10) International Publication Number
WO 2005/010202 A2

(51) International Patent Classification[7]: C12Q

(21) International Application Number: PCT/US2004/023010

(22) International Filing Date: 16 July 2004 (16.07.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/488,057 16 July 2003 (16.07.2003) US

(71) Applicant *(for all designated States except US)*: **LIGAND PHARMACUETICALS INCORPORATED** [US/US]; 10275 Science Center Drive, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **MAPES, Christopher** [US/US]; 8255 Pasadena Avenue, La Mesa, CA 91941 (US). **CHEN, Jyun-Hung** [—/US]; 7614 Palmilla Drive, #58, San Diego, CA 92122 (US). **MICHELLYS, Pierre** [FR/US]; 10824 Pablado Road, #221, San Diego, CA 92127 (US).

(74) Agent: **SEIDMAN, Stephanie, L.**; Fish & Richardson P.C., 12390 El Camino Real, San Diego, CA 92130 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHENYL ACETIC ACID DERIVATIVES AS HEPATOCYTE NUCLEAR FACTOR 4α (HNF-4α) MODULATOR COMPOUNDS

(57) Abstract: The present invention is directed to hepatocyte nuclear factor 4 α (HNF-4 α) receptor modulator compounds. This invention is also directed to pharmaceutical agents comprising such compounds as well as methods of using such compounds and pharmaceutical agents for modulating HNF-4 α receptors as well as processes mediated by HNF-4 α receptors. Also provided are methods of making such compounds and pharmaceutical agents, as well as intermediates used in their synthesis.

WO 2005/010202 A2

PHENYL ACETIC ACID DERIVATIVES AS HEPATOCYTE NUCLEAR FACTOR 4α (HNF-4α) MODULATOR COMPOUNDS

RELATED APPLICATIONS

[001] This application claims the benefit of priority of U.S. Provisional Application Ser. No. 60/488,057 filed July 16, 2003, the entire disclosure of which is incorporated herein by reference.

TECHNICAL FIELD

[002] This invention relates to compounds that bind to and/or modulate hepatocyte nuclear factor 4α receptors and to methods for making and using such compounds.

BACKGROUND

[003] Hepatocyte nuclear factor 4α (HNF-4α) has been described as a member of the steroid/thyroid superfamily of transcription factors that is expressed in liver, kidney, intestine and pancreas. Sladek, F.M., Zhong, W., Lai, E., and Darnell, J.E. (1990) *Genes Dev.* **4**, 2353-2365; Miquerol, L., Lopez, S., Cartier, N., Tulliez, M., Raymondjean, M., and Kahn, A. (1994) *J. Biol. Chem.* **269**, 8944-8951. No ligand has been identified at present and therefore HNF-4α is referred to as an orphan member of the intracellular receptor family (3-5). Tsai, M.J., and O'Malley, B.W. (1994) *Annu. Rev. Biochem.* **63**, 451-486; Mangelsdorf, D.J. and Evans, R.M. (1995) *Cell* **83**, 841-850; Kastner, P., Mark, M., and Chambon, P. (1995) *Cell* **83**, 859-869.

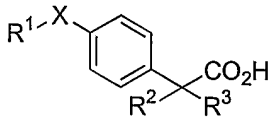
[004] HNF-4α has been described as being capable of activating transcription in tissue culture cells under certain conditions. Kou *et al.*, (1992) *Nature* **355**:457-461; Ladias *et al.*, (1992) *J. Biol. Chem.* **267**:15849-15860; Mietus-Snyder *et al.*, (1992) *Mol.*

Cell. Biol. **12:**1708-1718; Metzger *et al.*, (1993) *J. Biol. Chem.* **268:**16831-16838. It has been suggested that HNF-4α plays a role in one or more metabolic pathways, including glucose and lipid homeostasis. Ladias *et al.*, (1992) *J. Biol. Chem.* **267:**15849-15860; Mietus-Snyder *et al.*, (1992) *Mol. Cell. Biol.* **12:**1708-1718; Metzger *et al.*, (1993) *J. Biol. Chem.* **268:**16831-16838; Yamagata *et al.*, (1996) *Nature* **384:**458-460; Stoffel & Duncan (1997) *Proc. Natl. Acad. Sci. U.S.A.* **94:**13209-13214.

[005] Certain mutations of HNF-4α result in defective function of the endocrine pancreas and maturity-onset diabetes of the young (MODY1), suggesting that HNF-4 α plays a role in metabolic gene regulation. Yamagata *et al.*, (1996) *Nature* **384:**458-460. Liver-specific knockouts demonstrate that HNF-4α plays a role in liver development and function. Li *et al.*, (2000) *Genes & Dev.* **14:**464-474; Hayhurst *et al.*, (2001) *Mol. Cell. Biol.* **21:**1393-1403; Fraser *et al.*, (1998) *Nuc. Acids Res.* **26:**2702-2707.

SUMMARY OF THE INVENTION

[006] In certain embodiments, the present invention provides a compound of formula I:



I

and pharmaceutically acceptable salts, esters, amides, and prodrugs thereof,

wherein:

R^1 is selected from a C_1-C_{10} alkyl optionally substituted with one or more halogens, C_2-C_{10} alkenyl optionally substituted with one or more halogens, C_2-C_{10}

alkynyl optionally substituted with one or more halogens, a C_5-C_8 carbocyclic ring optionally substituted with one or more R^4, and a five to eight membered heterocyclic ring optionally substituted with one or more R^4;

R^2 and R^3 are each independently selected from H, oxygen and a halogen; or

R^2 and R^3 taken together form an oxygen;

R^4 is selected from H, halogen, a C_1-C_4 optionally substituted with one or more halogens, a C_2-C_4 alkenyl optionally substituted with one or more halogens, a C_2-C_4 alkynyl optionally substituted with one or more halogens, a C_1-C_4 alkoxy optionally substituted with one or more halogens, a C_1-C_4 thioalkyl optionally substituted with a nitro group and/or one or more halogens, a C_2-C_4 thioalkenyl optionally substituted with a nitro group and/or one or more halogens, a C_2-C_4 thioalkynyl optionally substituted with a nitro group and/or one or more halogens; and

X is selected from methylene, oxygen, sulfur and null.

[007] In certain embodiments, the invention provides a pharmaceutical agent comprising a pharmaceutically acceptable carrier and a compound of Formula I.

[008] In certain embodiments, the invention provides a method of treating a patient comprising administering to said patient a pharmaceutical agent comprising a pharmaceutically acceptable carrier and a pharmaceutically effective amount of a compound of Formula I.

[009] In certain embodiments, the invention provides a selective HNF-4α modulator of Formula I. In certain embodiments, the invention provides an HNF-4α selective binding agent of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

[010] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention claimed. As used herein, the singular includes the plural unless specifically stated otherwise. As used herein, "or" means "and/or" unless stated otherwise. Furthermore, use of the term "including" as well as other forms, such as "includes," and "included," is not limiting.

[011] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described. All documents, or portions of documents, cited in the application including, but not limited to, patents, patent applications, articles, books, manuals, and treatises are hereby expressly incorporated by reference in their entirety for any purpose.

Definitions

[012] Unless specific definitions are provided, the nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, medicinal chemistry and pharmaceutical chemistry described herein are those known in the art. Standard chemical symbols are used interchangeably with the full names represented by such symbols. Thus, for example, the terms "hydrogen" and "H" are understood to have identical meaning. Standard techniques may be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients. Standard techniques may be used for recombinant DNA methodology, oligonucleotide synthesis, tissue

culture and transformation (*e.g.*, electroporation, lipofection). Reactions and purification techniques may be performed *e.g.*, using kits according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The foregoing techniques and procedures may be generally performed according to conventional methods well known in the art and as described in various general or more specific references that are cited and discussed throughout the present specification. *See e.g.*, Sambrook *et al. Molecular Cloning: A Laboratory Manual* (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)), which is incorporated herein by reference in its entirety.

[013] As used herein, the following terms are defined with the following meanings:

[014] The term "selective binding compound" refers to a compound that selectively binds to any portion of one or more target receptors.

[015] The term "selective HNF-4α receptor binding compound" refers to a compound that selectively binds to any portion of an HNF-4α receptor.

[016] The term "selectively binds" refers to the ability of a selective binding compound to bind to a target receptor with greater affinity than it binds to a non-target receptor. In certain embodiments, selective binding refers to binding to a target with an affinity that is at least 10, 50, 100, 250, 500, or 1000 times greater than the affinity for a non-target.

[017] The term "target receptor" refers to a receptor or a portion of a receptor capable of being bound by a selective binding compound. In certain embodiments, a target receptor is an HNF-4α receptor.

[018] The term "modulator" refers to a compound that alters or elicits an activity of a molecule. For example, a modulator may cause an increase or decrease in the magnitude of a certain activity of a molecule compared to the magnitude of the activity in the absence of the modulator. In certain embodiments, a modulator is an inhibitor, which decreases the magnitude of one or more activities of a molecule. In certain embodiments, an inhibitor completely prevents one or more activities of a molecule. In certain embodiments, a modulator is an activator, which increases the magnitude of at least one activity of a molecule. In certain embodiments the presence of a modulator results in an activity that does not occur in the absence of the modulator.

[019] The term "selective modulator" refers to a compound that selectively modulates a target activity.

[020] The term "selective HNF-4 α receptor modulator" refers to a compound that selectively modulates at least one activity associated with an HNF-4a receptor.

[021] The term "selectively modulates" refers to the ability of a selective modulator to modulate a target activity to a greater extent than it modulates a non-target activity.

[022] The term "target activity" refers to a biological activity capable of being modulated by a selective modulator. Certain exemplary target activities include, but are not limited to, changes in binding affinity, signal transduction, enzymatic activity, transcription of one or more genes, tumor growth, changes in blood glucose concentration, and inflammation or inflammation-related processes.

[023] The term "receptor-mediated activity" refers to any biological activity that results, either directly or indirectly, from binding of a ligand to a receptor.

[024] The term "agonist" refers to a compound, the presence of which results in a biological activity of a receptor that is the same as the biological activity resulting from the presence of a naturally occurring ligand for the receptor.

[025] The term "partial agonist" refers to a compound the presence of which results in a biological activity of a receptor that is of the same type as that resulting from the presence of a naturally occurring ligand for the receptor, but of a lower magnitude.

[026] The term "antagonist" refers to a compound, the presence of which results in a decrease in the magnitude of a biological activity of a receptor. In certain embodiments, the presence of an antagonist results in complete inhibition of a biological activity of a receptor. The term "alkyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain alkyl radical having from 1 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having from 1 to about 6 carbon atoms as well as those having from 1 to about 4 carbon atoms. Examples of alkyl radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, tert-amyl, pentyl, hexyl, heptyl, octyl and the like.

[027] The term "alkenyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more carbon-carbon double-bonds and having from 2 to about 18 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon double bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, 1,4-butadienyl and the like.

[028] The term "alkynyl," alone or in combination, refers to an optionally substituted straight-chain or branched-chain hydrocarbon radical having one or more

carbon-carbon triple-bonds and having from 2 to about 12 carbon atoms. The term also includes substituted straight-chain or branched-chain alkyl radicals having one or more carbon-carbon tyriple bonds and having from 2 to about 6 carbon atoms as well as those having from 2 to about 4 carbon atoms. Examples of alkynyl radicals include ethynyl, propynyl, butynyl and the like.

[029] In certain embodiments, an alkyl comprises 1 to 20 carbon atoms (whenever it appears herein, a numerical range such as "1 to 20" refers to each integer in the given range; *e.g.*, "1 to 20 carbon atoms" means that an alkyl group may comprise only 1 carbon atom, 2 carbon atoms, 3 carbon atoms, etc., up to and including 20 carbon atoms, although the term "alkyl" also includes instances where no numerical range of carbon atoms is designated).

[030] The terms "lower alkyl", "lower alkenyl" and "lower alkynyl" refer to radicals comprising 1 to 6 carbon atoms. The term "medium alkyl" refers to an alkyl comprising 7 to 12 carbon atoms. An alkyl may be designated as "C_1-C_4 alkyl" or similar designations. By way of example only, "C_1-C_4 alkyl", "C_1-C_4 alkenyl" and"C_1-C_4 alkynyl" indicate a radical having one, two, three, or four carbon atoms (*e.g.*, methyl, ethyl, propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, t-butyl, ethenyl, propenyl, butenyl, ethynyl, propynyl, and butynyl).

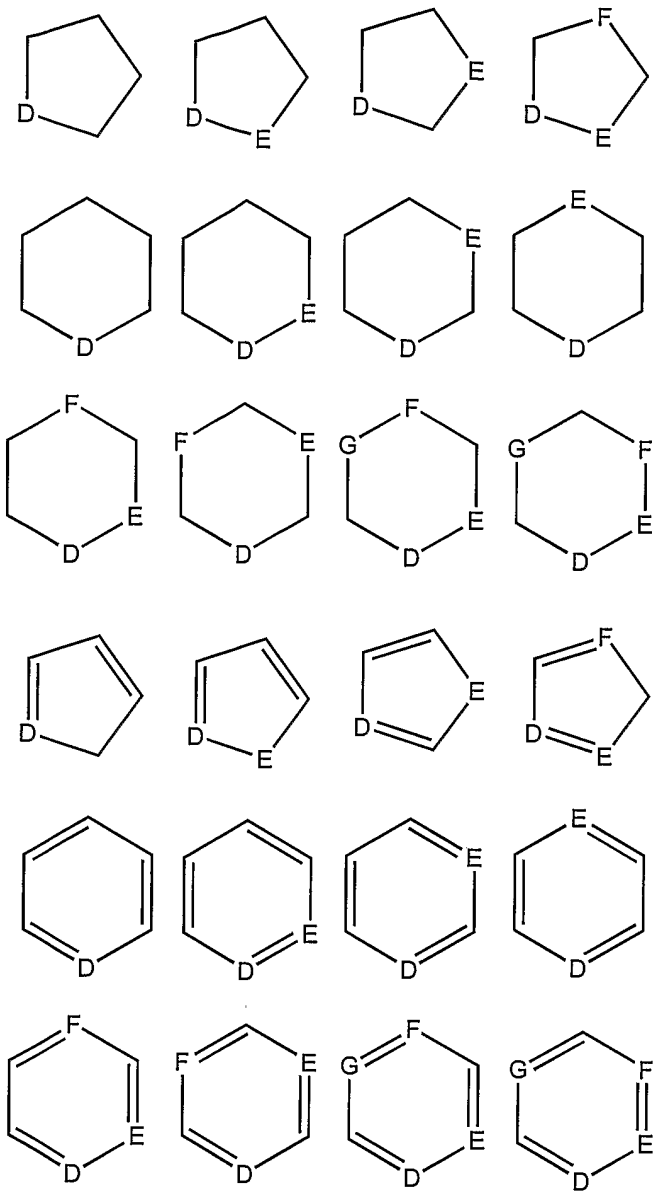
[031] The term "haloalkyl" refers to an alkyl in which at least one hydrogen atom is replaced with a halogen atom. In certain of the embodiments in which two or more hydrogen atom are replaced with halogen atoms, the halogen atoms are all the same as each other. In certain of such embodiments, the halogen atoms are not all the same as each other.

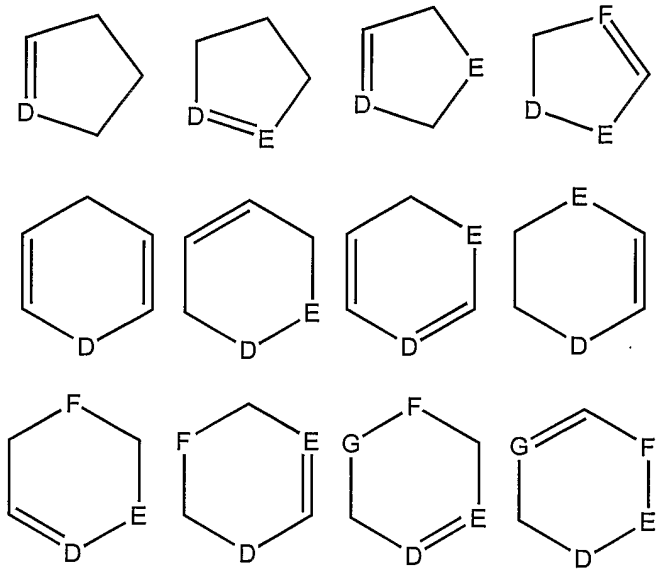
[032] The term "hetero" refers to a group comprising an alkyl and one or more heteroatoms. Certain heteroalkyls are acylalkyls, in which the one or more heteroatoms are outside of an alkyl chain. Examples of heteroalkyls, heteroalkenyls, and heteroalkynyls, include, but are not limited to, $CH_3C(=O)CH_2$-, $CH_3C(=O)CH_2CH_2$-, $CH_3CH_2C(=O)CH_2CH_2$-, $CH_3C(=O)CH_2CH_2CH_2$-, $CH_3OCH_2CH_2$-, CH_3NHCH_2-, and the like.

[033] The term "heterohaloalkyl" refers to a heteroalkyl in which at least one hydrogen atom is replaced with a halogen atom.

[034] The term "carbocycle" refers to a group comprising a covalently closed ring, wherein each of the atoms forming the ring is a carbon atom. Carbocylic rings may be formed by three, four, five, six, seven, eight, nine, or more than nine carbon atoms. Carbocycles may be optionally substituted.

[035] The term "heterocycle" refers to a group comprising a covalently closed ring wherein at least one atom forming the ring is a heteroatom. Heterocyclic rings may be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Any number of those atoms may be heteroatoms (*i.e.*, a heterocyclic ring may comprise one, two, three, four, five, six, seven, eight, nine, or more than nine heteroatoms). In heterocyclic rings comprising two or more heteroatoms, those two or more heteroatoms may be the same as or different from each other. Heterocycles may be optionally substituted. Binding to a heterocycle can be at a heteroatom or via a carbon atom. For example, binding for benzo-fused derivatives, may be via a carbon of the benzenoid ring. Examples of heterocycles include, but are not limited to the following:


D
D E
D E
F
D E
D
D E
D E
E
D
F
D E
F E
D
F
G E
D
G F
E
D



wherein D, E, F, and G each independently represent a heteroatom. Each of D, E, F, and G may be the same as or different from each other.

[036] The term "heteroatom" refers to an atom other than carbon or hydrogen. Heteroatoms are typically independently selected from oxygen, sulfur, nitrogen, and phosphorus, but are not limited to those atoms. In embodiments in which two or more heteroatoms are present, the two or more heteroatoms may all be the same, or some or all of the two or more heteroatoms may each be different from the others.

[037] The term "aromatic" refers to a group comprising a covalently closed ring having a delocalized π-electron system. Aromatic rings may be formed by five, six, seven, eight, nine, or more than nine atoms. Aromatics may be optionally substituted. Examples of aromatic groups include, but are not limited to phenyl, naphthalenyl, phenanthrenyl, anthracenyl, tetralinyl, fluorenyl, indenyl, and indanyl. The term aromatic includes, for example, benzenoid groups, connected via one of the ring-forming carbon atoms, and optionally carrying one or more substituents selected from an aryl, a

heteroaryl, a cycloalkyl, a non-aromatic heterocycle, a halo, a hydroxy, an amino, a cyano, a nitro, an alkylamido, an acyl, a C_{1-6} alkoxy, a C_{1-6} alkyl, a C_{1-6} hydroxyalkyl, a C_{1-6} aminoalkyl, a C_{1-6} alkylamino, an alkylsulfenyl, an alkylsulfinyl, an alkylsulfonyl, an sulfamoyl, and a trifluoromethyl. In certain embodiments, an aromatic group is substituted at one or more of the para, meta, and/or ortho positions. Examples of aromatic groups comprising substitutions include, but are not limited to, phenyl, 3-halophenyl, 4-halophenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-aminophenyl, 4-aminophenyl, 3-methylphenyl, 4-methylphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 4-trifluoromethoxyphenyl, 3-cyanophenyl, 4-cyanophenyl, dimethylphenyl, naphthyl, hydroxynaphthyl, hydroxymethylphenyl, (trifluoromethyl)phenyl, alkoxyphenyl, 4-morpholin-4-ylphenyl, 4-pyrrolidin-1-ylphenyl, 4-pyrazolylphenyl, 4-triazolylphenyl, and 4-(2-oxopyrrolidin-1-yl)phenyl.

[038] The term "aryl" refers to an aromatic group wherein each of the atoms forming the ring is a carbon atom. Aryl rings may be formed by five, six, seven, eight, nine, or more than nine carbon atoms. Aryl groups may be optionally substituted.

[039] The term "heteroaryl" refers to an aromatic group wherein at least one atom forming the aromatic ring is a heteroatom. Heteroaryl rings may be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Heteroaryl groups may be optionally substituted. Examples of heteroaryl groups include, but are not limited to, aromatic C_{3-8} heterocyclic groups comprising one oxygen or sulfur atom or up to four nitrogen atoms, or a combination of one oxygen or sulfur atom and up to two nitrogen atoms, and their substituted as well as benzo- and pyrido-fused derivatives, for example, connected via one of the ring-forming carbon atoms. In certain embodiments, heteroaryl groups are optionally substituted with one or more substituents, independently selected

from halo, hydroxy, amino, cyano, nitro, alkylamido, acyl, C_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} hydroxyalkyl, C_{1-6} aminoalkyl, C_{1-6} alkylamino, alkylsulfenyl, alkylsulfinyl, alkylsulfonyl, sulfamoyl, and trifluoromethyl. Examples of heteroaryl groups include, but are not limited to, unsubstituted and mono- or di-substituted derivatives of furan, benzofuran, thiophene, benzothiophene, pyrrole, pyridine, indole, oxazole, benzoxazole, isoxazole, benzisoxazole, thiazole, benzothiazole, isothiazole, imidazole, benzimidazole, pyrazole, indazole, tetrazole, quinoline, isoquinoline, pyridazine, pyrimidine, purine and pyrazine, furazan, 1,2,3-oxadiazole, 1,2,3-thiadiazole, 1,2,4-thiadiazole, triazole, benzotriazole, pteridine, phenoxazole, oxadiazole, benzopyrazole, quinolizine, cinnoline, phthalazine, quinazoline, and quinoxaline. In some embodiments, the substituents are halo, hydroxy, cyano, O-C_{1-6} alkyl, C_{1-6} alkyl, hydroxy-C_{1-6} alkyl, or amino-C alkyl.

[040] The term "non-aromatic ring" refers to a group comprising a covalently closed ring that does not have a delocalized π-electron system.

[041] The term "cycloalkyl", alone or in combination, refers to a monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety has from 3 to about 8 carbon atoms. Examples of cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.Cycloalkyl rings may be formed by three, four, five, six, seven, eight, nine, or more than nine carbon atoms. Cycloalkyls may be optionally substituted

[042] The term "non-aromatic heterocycle" refers to a group comprising a non-aromatic ring wherein one or more atoms forming the ring is a heteroatom. Non-aromatic heterocyclic rings may be formed by three, four, five, six, seven, eight, nine, or more than nine atoms. Non-aromatic heterocycles may be optionally substituted. In certain embodiments, non-aromatic heterocycles comprise one or more carbonyl or

thiocarbonyl groups such as, for example, oxo- and thio-containing groups. Examples of non-aromatic heterocycles include, but are not limited to, lactams, lactones, cyclic imides, cyclic thioimides, cyclic carbamates, tetrahydrothiopyran, 4H-pyran, tetrahydropyran, piperidine, 1,3-dioxin, 1,3-dioxane, 1,4-dioxin, 1,4-dioxane, piperazine, 1,3-oxathiane, 1,4-oxathiin, 1,4-oxathiane, tetrahydro-1,4-thiazine, 2H-1,2-oxazine, maleimide, succinimide, barbituric acid, thiobarbituric acid, dioxopiperazine, hydantoin, dihydrouracil, morpholine, trioxane, hexahydro-1,3,5-triazine, tetrahydrothiophene, tetrahydrofuran, pyrroline, pyrrolidine, pyrrolidone, pyrrolidione, pyrazoline, pyrazolidine, imidazoline, imidazolidine, 1,3-dioxole, 1,3-dioxolane, 1,3-dithiole, 1,3-dithiolane, isoxazoline, isoxazolidine, oxazoline, oxazolidine, oxazolidinone, thiazoline, thiazolidine, and 1,3-oxathiolane.

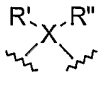
[043] The term "arylalkyl" refers to a group comprising an aryl group bound to an alkyl group.

[044] The term "carbocycloalkyl" refers to a group comprising a carbocyclic cycloalkyl ring. Carbocycloalkyl rings may be formed by three, four, five, six, seven, eight, nine, or more than nine carbon atoms. Carbocycloalkyl groups may be optionally substituted.

[045] The term "ring" refers to any covalently closed structure. Rings include, for example, carbocycles (*e.g.*, aryls and cycloalkyls), heterocycles (*e.g.*, heteroaryls and non-aromatic heterocycles), aromatics (*e.g.*, aryls and heteroaryls), and non-aromatics (*e.g.*, cycloalkyls and non-aromatic heterocycles). Rings may be optionally substituted. Rings may form part of a ring system.

[046] The term "ring system" refers to two or more rings, wherein two or more of the rings are fused. The term "fused" refers to structures in which two or more rings share one or more bonds.

[047] The substituent "R" appearing by itself and without a number designation refers to a substituent selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl (bonded through a ring carbon) and non-aromatic heterocycle (bonded through a ring carbon).

[048] The term "null" refers to a group being absent from a structure. For example, in the structure  , if X is C, then both R' and R" exist, but if X is N, then one of those R groups is null, meaning that only three groups are bound to the N.

[049] The term "O-carboxy" refers to a group of formula RC(=O)O-.

[050] The term "C-carboxy" refers to a group of formula -C(=O)OR.

[051] The term "acetyl" refers to a group of formula $-C(=O)CH_3$.

[052] The term "trihalomethanesulfonyl" refers to a group of formula $X_3CS(=O)_2-$ where X is a halogen.

[053] The term "cyano" refers to a group of formula -CN.

[054] The term "isocyanato" refers to a group of formula -NCO.

[055] The term "thiocyanato" refers to a group of formula -CNS.

[056] The term "isothiocyanato" refers to a group of formula -NCS.

[057] The term "sulfonyl" refers to a group of formula -S(=O)-R.

[058] The term "S-sulfonamido" refers to a group of formula $-S(=O)_2NR$.

[059] The term "N-sulfonamido" refers to a group of formula $RS(=O)_2NH-$.

[060] The term "trihalomethanesulfonamido" refers to a group of formula $X_3CS(=O)_2NR$-.

[061] The term "O-carbamyl" refers to a group of formula -OC(=O)-NR.

[062] The term "N-carbamyl" refers to a group of formula ROC(=O)NH-.

[063] The term "O-thiocarbamyl" refers to a group of formula -OC(=S)-NR.

[064] The term "N-thiocarbamyl" refers to a group of formula ROC(=S)NH-.

[065] The term "C-amido" refers to a group of formula $-C(=O)-NR_2$.

[066] The term "N-amido" refers to a group of formula RC(=O)NH-.

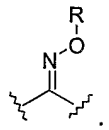
[067] The term "ester" refers to a chemical moiety with formula $-(R)_n$-COOR', where R and R' are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl (bonded through a ring carbon) and non-aromatic heterocycle (bonded through a ring carbon), where n is 0 or 1.

[068] The term "amide" refers to a chemical moiety with formula $-(R)_n$-C(O)NHR' or $-(R)_n$-NHC(O)R', where R and R' are independently selected from alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, heteroaryl (bonded through a ring carbon) and heteroalicyclic (bonded through a ring carbon), where n is 0 or 1. In certain embodiments, an amide may be an amino acid or a peptide.

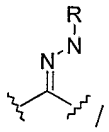
[069] The term "alkoxy," refers to an alkyl ether radical. Examples of alkoxy radicals include, but are not limited to, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like.

[070] The term "formyl" includes aldehydes attached to a compound via an alkyl, aryl, heteroaryl, arylalkyl or heteroarylalkyl group (*e.g.*, -alkyl-CHO, -aryl-CHO, -arylalkyl-CHO or –heteroarylalkyl-CHO, etc.).

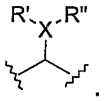
[071] The term "oxime" refers to a group of formula:



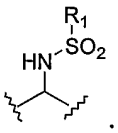
[072] The term "hydrazone" refers to a group of formula:



[073] The term "hydroxylamine" refers to a group of formula:



[074] The term sulfonamide refers to a group of formula:



[075] The term "halogen" includes F, Cl, Br and I

[076] The terms "amine," "hydroxy," and "carboxyl" include such groups that have been esterified or amidified. Procedures and specific groups used to achieve esterification and amidification are known to those of skill in the art and can readily be found in reference sources such as Greene and Wuts, *Protective Groups in Organic*

Synthesis, 3rd Ed., John Wiley & Sons, New York, NY, 1999, which is incorporated by reference herein in its entirety.

[077] Unless otherwise indicated, the term "optionally substituted," refers to a group in which none, one, or more than one of the hydrogen atoms has been replaced with one or more group(s) individually and independently selected from: alkyl, alkenyl, alkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, haloalkyl, haloalkenyl, haloalkynyl, heterohaloalkyl, cycloalkyl, cycloalkenyl, cycloalkynyl, aryl, arylalkyl, arylalkenyl, arylalkynyl, arylalkyl, heteroaryl, non-aromatic heterocycle, hydroxy, alkoxy, aryloxy, mercapto, alkylthio, alkenylthio, alkynylthio, arylthio, cyano, halo, carbonyl, thiocarbonyl, O-carbamyl, N-carbamyl, O-thiocarbamyl, N-thiocarbamyl, C-amido, N-amido, S-sulfonamido, N-sulfonamido, C-carboxy, O-carboxy, isocyanato, thiocyanato, isothiocyanato, nitro, silyl, trihalomethanesulfonyl, and amino, including mono- and di-substituted amino groups, and the protected derivatives of amino groups. Such protective derivatives (and protecting groups that may form such protective derivatives) are known to those of skill in the art and may be found in references such as Greene and Wuts, supra. In embodiments in which two or more hydrogen atoms have been substituted, the substituent groups may together form a ring.

[078] The term "carrier" refers to a compound that facilitates the incorporation of another compound into cells or tissues. For example, dimethyl sulfoxide (DMSO) is a commonly used carrier for improving incorporation of certain organic compounds into cells or tissues.

[079] The term "pharmaceutical agent" refers to a chemical compound or composition capable of inducing a desired therapeutic effect in a patient. In certain embodiments, a pharmaceutical agent comprises an active agent, which is the agent that

induces the desired therapeutic effect. In certain embodiments, a pharmaceutical agent comprises a prodrug. In certain embodiments, a pharmaceutical agent comprises inactive ingredients such as carriers, excipients, and the like.

[080] The term "therapeutically effective amount" refers to an amount of a pharmaceutical agent sufficient to achieve a desired therapeutic effect.

[081] The term "prodrug" refers to a pharmaceutical agent that is converted from a less active form into a corresponding more active form *in vivo*.

[082] The term "pharmaceutically acceptable" refers to a formulation of a compound that does not significantly abrogate biological activity, a pharmacological activity and/or other properties of the compound when the formulated compound is administered to a patient. In certain embodiments, a pharmaceutically acceptable formulation does not cause significant irritation to a patient.

[083] The term "co-administer" refers to administering more than one pharmaceutical agent to a patient. In certain embodiments, co-administered pharmaceutical agents are administered together in a single dosage unit. In certain embodiments, co-administered pharmaceutical agents are administered separately. In certain embodiments, co-administered pharmaceutical agents are administered at the same time. In certain embodiments, co-administered pharmaceutical agents are administered at different times.

[084] The term "patient" includes human and animal subjects.

[085] The term "substantially pure" means an object species (*e.g.*, compound) is the predominant species present (*i.e.*, on a molar basis it is more abundant than any other individual species in the composition). In certain embodiments, a substantially pure composition is a composition wherein the object species comprises at least about 50

percent (on a molar basis) of all species present. In certain embodiments, a substantially pure composition is a composition wherein the object species comprises more than about 80%, 85%, 90%, 95%, or 99% of all species present in the composition. In certain embodiments, a substantially pure object species is purified to essential homogeneity (contaminant species cannot be detected in the composition by conventional detection methods) wherein the composition consists essentially of the single object species.

[086] The term "tissue-selective" refers to the ability of a compound to modulate a biological activity in one tissue to a greater or lesser degree than it modulates a biological activity in another tissue. The biological activities modulated in the different tissues may be the same or they may be different. The biological activities modulated in the different tissues may be mediated by the same type of target receptor. For example, in certain embodiments, a tissue-selective compound may modulate an HNF-4α receptor-mediated biological activity in one tissue and fail to modulate, or modulate to a lesser degree, an HNF-4α receptor-mediated biological activity in another tissue type.

[087] The term "monitoring" refers to observing an effect or absence of any effect. In certain embodiments, cells are monitored after contacting those cells with a compound of the present invention. Examples of effects that may be monitored include, but are not limited to, changes in cell phenotype, cell proliferation, an HNF-4α receptor activity, or the interaction between an HNF-4α receptor and a natural binding partner.

[088] The term "cell phenotype" refers to physical or biological characteristics. Examples of characteristics that constitute phenotype included, but are not limited to, cell size, cell proliferation, cell differentiation, cell survival, apoptosis (cell death), or the

utilization of a metabolic nutrient (*e.g.*, glucose uptake). Certain changes or the absence of changes in cell phenotype are readily monitored using techniques known in the art.

[089] The term "cell proliferation" refers to the rate at which cells divide. The number of cells growing in a vessel can be quantified by a person skilled in the art (*e.g.*, by counting cells in a defined area using a light microscope, or by using laboratory apparatus that measure the density of cells in an appropriate medium). One skilled in that art can calculate cell proliferation by determining the number of cells in a sample at two or more times.

[090] The term "contacting" refers to bringing two or more materials into close enough proximity that they may interact. In certain embodiments, contacting can be accomplished in a vessel such as a test tube, a petri dish, or the like. In certain embodiments, contacting may be performed in the presence of additional materials. In certain embodiments, contacting may be performed in the presence of cells. In certain of such embodiments, one or more of the materials that are being contacted may be inside a cell. Cells may be alive or may dead. Cells may or may not be intact.

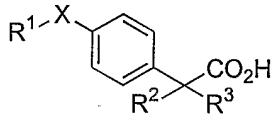
Certain compounds

[091] Certain compounds that bind to HNF-4α receptors and/or certain compounds that modulate an activity of such receptors play a role in health (*e.g.*, normal growth, development, and/or absence of disease). In certain embodiments, compounds of the present invention are useful for treating any of a variety of diseases or conditions.

[092] Certain compounds have been previously described as receptor modulators. See *e.g.*, U. S. Patent Nos. 6,462,038, 5,693,646; 6,380,207; 6,506,766; 5,688,810; 5,696,133; 6,569,896, 6,673,799; 4,636,505; 4,097,578; 3,847,988; U.S. Pat Application No. 10/209,461 (Pub. No. US 2003/0055094); International Patent

Application Nos. WO 01/27086& WO 02/22585; Zhi, *et al. Bioorganic & Med. Chem. Lett.* (2000) **10:**415-418; Pooley, *et al., J. Med. Chem.* (1998) **41:** 3461; Hamann, *et al. J. Med. Chem.* (1998) 41(4), 623; and Yin, *et al., Molecular Pharmacology*, 2003, **63:**211-223 the entire disclosures of which are incorporated by reference herein in their entirety. Certain cyclothiocarbamate analogues have been described as progesterone receptor modulators (*e.g.*, U.S. Pat. Nos. 6,436,929 and 6,509,334). Certain cyclocarbamate analogues have been described as progesterone receptor antagonists (*e.g.*, U.S. Pat. Nos. 6,306,851, 6,380,178, 6,441,019, 6,444,668, 6,509,334, and 6,566,358; Zhang, *et al. J. Med. Chem.* **45**:4379 (2002)).

[093] In certain embodiments, the invention provides a compound of formula I:



I

or a pharmaceutically acceptable sale, ester, amide, or prodrug thereof.

[094] In certain embodiments, R^1 is selected from a C_1-C_{10} alkyl optionally substituted with one or more halogens, a C_2-C_{10} alkenyl optionally substituted with one or more halogens, a C_2-C_{10} alkynyl optionally substituted with one or more halogens, a C_5-C_8 carbocyclic ring optionally substituted with one or more R^4, and a five to eight membered heterocyclic ring optionally substituted with one or more R^4, an optionally substituted C_1-C_{10} heteroalkyl, an optionally substituted C_2-C_{10} heteroalkenyl, an optionally substituted C_2-C_{10} heteroalkynyl, an optionally substituted C_1-C_{10} haloalkyl, an optionally substituted C_2-C_{10} haloalkenyl, an optionally substituted C_2-C_{10}

haloalkynyl, an optionally substituted C_1-C_{10} heterohaloalkyl, an optionally substituted C_2-C_{10} heterohaloalkenyl, an optionally substituted C_2-C_{10} heterohaloalkynyl, an optionally substituted C_3–C_{10} cycloalkyl, an optionally substituted C_3-C_{10} cycloalkenyl, an optionally substituted C_3-C_{10} cycloalkynyl, an optionally substituted C_3–C_{10} heterocycle, an optionally substituted C_3–C_8 aryl, and an optionally substituted C_3–C_8 heteroaryl. In certain embodiments, R^1 is an optionally substituted C_1-C_{10} alkyl, an optionally substituted C_2-C_{10} alkenyl, an optionally substituted C_2-C_{10} alkynyl, an optionally substituted C_2-C_{10} heteroalkyl, an optionally substituted C_2-C_{10} heteroalkenyl, an optionally substituted C_2-C_{10} heteroalkynyl, or an optionally substituted C_3–C_{10} cycloalkyl. In certain embodiments, R^1 is an optionally substituted C_1-C_{10} alkyl, an optionally substituted C_2-C_{10} alkenyl, an optionally substituted C_2-C_{10} alkynyl, an optionally substituted C_2-C_{10} heteroalkyl, an optionally substituted C_2-C_{10} heteroalkenyl, or an optionally substituted C_2-C_{10} heteroalkynyl. In certain of such embodiments, R^1 is selected from an optionally substituted C_2-C_{10} alkenyl, an optionally substituted C_2-C_{10} alkynyl, an optionally substituted C_2-C_{10} heteroalkenyl, an optionally substituted C_2-C_{10} heteroalkynyl, an optionally substituted C_3-C_{10} cycloalkenyl, and an optionally substituted C_3-C_{10} cycloalkynyl. In certain embodiments, R^1 is selected from an optionally substituted methyl, ethyl propyl isopropyl, butyl, sec-butyl, and tert-butyl.

[095] In certain embodiments, R^2 and R^3 are each independently selected from H, oxygen and a halogen. In certain embodiments, R^2 and R^3 taken together form an oxygen.

[096] In certain embodiments, R^4 is selected from H, a halogen, a C_1-C_4 alkyl optionally substituted with one or more halogens, a C_2-C_4 alkenyl optionally substituted with one or more halogens, a C_2-C_4 alkynyl optionally substituted with one or more

halogens, a C_1-C_4 alkoxy optionally substituted with one or more halogens, a C_1-C_4 thioalkyl optionally substituted with a nitro group and/or one or more halogens, a C_2-C_4 thioalkenyl optionally substituted with a nitro group and/or one or more halogens, a C_2-C_4 thioalkynyl optionally substituted with a nitro group and/or one or more halogens, an optionally substituted C_1-C_6 heteroalkyl, an optionally substituted an optionally substituted C_2-C_6 heteroalkenyl, an optionally substituted C_2-C_6 heteroalkynyl, an optionally substituted C_1-C_6 haloalkyl, an optionally substituted C_2-C_6 haloalkenyl, an optionally substituted C_2-C_6 haloalkynyl, an optionally substituted C_1-C_6 heterohaloalkyl, an optionally substituted C_2-C_6 heteroalkenyl, an optionally substituted C_2-C_6 heteroalkynyl, an optionally substituted C_3–C_8 cycloalkyl, an optionally substituted C_3-C_8 cycloalkenyl, an optionally substituted C_3-C_8 cycloalkynyl, an optionally substituted C_3–C_8 heterocycle, an optionally substituted C_3–C_8 aryl, an optionally substituted C_3–C_8 heteroaryl. In certain embodiments, R^4 is an optionally substituted C_1-C_4 alkyl, an optionally substituted C_2-C_4 alkenyl, an optionally substituted C_2-C_4 alkynyl, an optionally substituted C_2-C_8 heteroalkyl, an optionally substituted C_2-C_8 heteroalkenyl, an optionally substituted C_2-C_8 heteroalkynyl,, or an optionally substituted C_3–C_8 cycloalkyl. In certain embodiments, R^4 is an optionally substituted C_1-C_4 alkyl, an optionally substituted C_2-C_4 alkenyl, an optionally substituted C_2-C_4 alkynyl, an optionally substituted C_2-C_8 heteroalkyl, an optionally substituted C_2-C_8 heteroalkenyl, an optionally substituted C_2-C_8 heteroalkynyl, an optionally substituted C_3-C_8 cycloalkenyl, or an optionally substituted C_3-C_8 cycloalkynyl. In certain of such embodiments, R^4 is selected from an optionally substituted C_2-C_4 alkenyl, an optionally substituted C_2-C_4 alkynyl, an optionally substituted C_2-C_8 heteroalkenyl, an optionally substituted C_2-C_8 heteroalkynyl, an optionally substituted C_3-C_8 cycloalkenyl, and an

optionally substituted C_3-C_8 cycloalkynyl. In certain embodiments, R^4 is selected from an optionally substituted methyl, ethyl propyl isopropyl, butyl, sec-butyl, and tert-butyl. In certain of the embodiments where R^4 is a halogen, R^4 is F or Cl.

[097] In certain embodiments, X is selected from methylene, oxygen, sulfur, or null.

[098] Certain compounds of the present inventions may exist as stereoisomers including, but not limited to, optical isomers. The present disclosure is intended to include all stereoisomers and both the racemic mixtures of such stereoisomers as well as the individual enantiomers that may be separated according to methods that are known in the art or that may be excluded by synthesis schemes known in the art designed to yield predominantly one enantomer relative to another.

[099] As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. In addition, two diastereomers which have a different configuration at only one chiral center are referred to herein as "epimers." The terms "racemate," "racemic mixture" or "racemic modification" refer to a mixture of equal parts of enantiomers.

[0100] The compounds of the present invention may be chiral, and it is intended that any enantiomers, as separated, pure or partially purified enantiomers or racemic mixtures thereof are included within the scope of the invention. Furthermore, when a

double bond or a fully or partially saturated ring system or more than one center of asymmetry or a bond with restricted rotatability is present in the molecule diastereomers may be formed. It is intended that any diastereomers, as separated, pure or partially purified diastereomers or mixtures thereof are included within the scope of the invention. Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms, which the compounds are able to form, are included within the scope of the present invention. Thus, as one skilled in the art knows, certain aryls may exist in tautomeric forms. The invention also includes tautomers, enantiomers and other stereoisomers of the compounds of Formula I. Such variations are contemplated to be within the scope of the invention.

[0101] The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (rectus) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" (sinister) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in "Nomenclature of Organic Compounds: Principles and Practice", (J.H. Fletcher, et al., eds., 1974) at pages 103-120.

[0102] The designation " " refers to a bond that protrudes forward out of the plane of the page.

[0103] The designation " " refers to a bond that protrudes backward out of the plane of the page.

[0104] The designation " ~~~ " refers to a bond wherein the stereochemistry is not defined.

[0105] The compounds of Formula I, when existing as a diastereomeric mixture, may be separated into diastereomeric pairs of enantiomers by, for example, fractional crystallization from a suitable solvent, for example methanol or ethyl acetate or a mixture thereof. The pair of enantiomers thus obtained may be separated into individual stereoisomers by conventional means, for example by the use of an optically active acid as a resolving agent. Alternatively, any enantiomer of a compound of Formula I may be obtained by stereospecific synthesis using optically pure starting materials or reagents of known configuration or through enantioselective synthesis.

[0106] The term "enantiomeric enrichment" as used herein refers to the increase in the amount of one enantiomer as compared to the other. A convenient method of expressing the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee," which is found using the following equation:

$$ee = \frac{E^1 - E^2}{E^1 + E^2} \times 100$$

[0107] wherein E^1 is the amount of the first enantiomer and E^2 is the amount of the second enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of 70:30 is achieved, the ee with respect to the first enantiomer is 40%. However, if the final ratio is 90:10, the ee with respect to the first enantiomer is 80%. An ee of greater than 90% is preferred, an ee of greater than 95% is most preferred and an ee of greater than 99% is most especially preferred. Enantiomeric enrichment is readily determined by one of ordinary skill in the art using standard techniques and

procedures, such as gas or high performance liquid chromatography with a chiral column. Choice of the appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is well within the knowledge of one of ordinary skill in the art. In addition, the specific stereoisomers and enantiomers of compounds of Formula I can be prepared by one of ordinary skill in the art utilizing well known techniques and processes, such as those disclosed by J. Jacques, *et al.*, "Enantiomers, Racemates, and Resolutions," John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen," Stereochemistry of Organic Compounds," (Wiley-Interscience 1994), and European Patent Application No. EP-A-838448, published April 29, 1998. Examples of resolutions include recrystallization techniques or chiral chromatography.

[0108] As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations.

[0109] The following table provides examples of certain variables from various Markush groups in this application. One of ordinary skill in the art will recognize that the variables may selected in any combination.

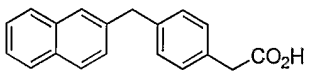
Table A. Table of Markush Groups by Variable

	Markush Group A	Markush Group B	Markush Group C	Markush Group D
R_1	C_1-C_{10} alkyl, C_2-C_{10} alkenyl, C_2-C_{10} alkynl, a carbocyclic ring, and a heterocyclic ring, wherein said alkyl, alkenyl, and alkynl groups are optionally substituted with one or more halogens, and said carbocyclic and heterocyclic rings are optionally substituted with one or more R_4;	C_2-C_8 alkyl, C_4-C_6 alkenyl, C_4-C_6 alkynl, a carbocyclic ring, and a heterocyclic ring, wherein said alkyl, alkenyl, and alkynl groups are optionally substituted with one or more halogens, and said carbocyclic and heterocyclic rings are optionally substituted with one or more R_4;	C_3-C_6 alkyl, and a C_5-C_8 carbocyclic ring, optionally substituted with one or more halogens, wherein said carbocyclic rings is optionally substituted with one or more R_4;	C_3-C_5 alkyl, and a C_5-C_8 carbocyclic ring, optionally substituted with one or more halogens, wherein said carbocyclic ring is optionally substituted with one or more R_4;
R_2	H, oxygen or halogen	H or oxygen		H
	R_2 and R_3 taken together form an oxygen			
R_3	H, oxygen or halogen	H or oxygen		H
	R_2 and R_3 taken together form an oxygen			
R_4	H, halogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynl, C_1-C_4 alkoxy, C_1-C_4 thioalkyl, C_2-C_4			H, C_2-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynl, and C_2-C_4 alkoxy

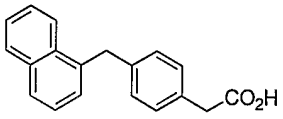
	Markush Group A	Markush Group B	Markush Group C	Markush Group D
	thioalkenyl, and C_2-C_4 thioalkynyl, wherein said alkyl, alkenyl, alkynyl, and alkoxy groups are optionally substituted with one or more halogens, and said thioalkyl, thioalkenly and thioalkynl groups are optionally substituted with a nitro group or one or more halogens;			
X	methylene, oxygen, sulfur or null	methylene	oxygen or sulfur	null

In certain embodiments, the invention provides compounds selected from:

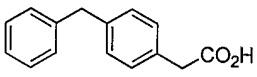
4-(2-naphthylmethyl) phenyl acetic acid (Compound 1)



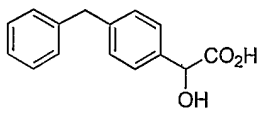
4-(1-naphthylmethyl) phenyl acetic acid (Compound 2)



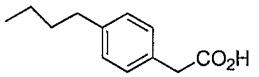
4-(benzyl)phenyl acetic acid (Compound 3)



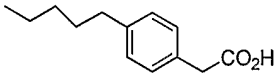
2-hydroxy-2-[4-(benzyl)phenyl]acetic acid (Compound 4)



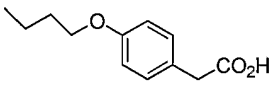
4-butyl phenyl acetic acid (Compound 5)



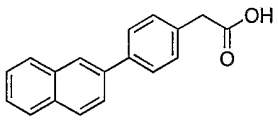
4-pentyl phenyl acetic acid (Compound 6)



4-butoxy phenyl acetic acid (Compound 7)



4-(2-naphthyl)phenyl acetic acid (Compound 8)



and pharmaceutically acceptable salts, esters, amides, and/or prodrugs of any of those compounds.

[0110] In certain embodiments, a compound of Formula I is a selective HNF-4α receptor modulator. In certain embodiments, a compound of Formula I is a selective HNF-4α receptor agonist. In certain embodiments, a compound of Formula I is a selective HNF-4α receptor antagonist. In certain embodiments, a compound of Formula

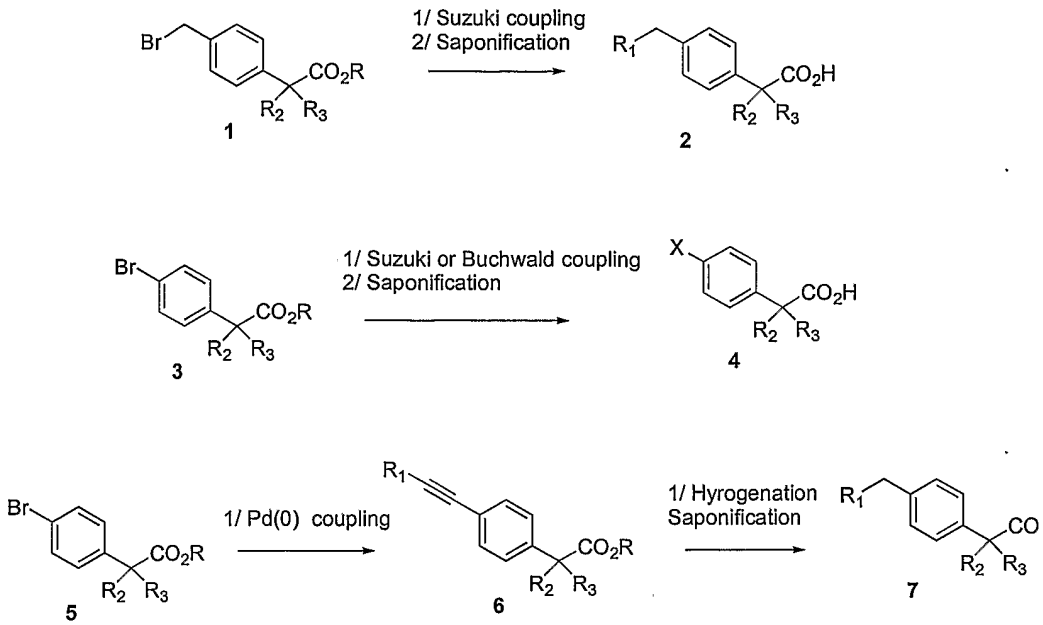
I is a selective HNF-4α receptor partial agonist. In certain embodiments, a compound of Formula I is a tissue-specific selective HNF-4α receptor modulator. In certain embodiments, a compound of Formula I is a gene-specific selective HNF-4α receptor modulator. In certain embodiments, a compound of Formula I is a selective HNF-4α receptor binding compound.

[0111] In certain embodiments, the present invention provides selective HNF-4α receptor modulators. In certain embodiments, the invention provides selective HNF-4α receptor binding agents. In certain embodiments, the invention provides methods of making and methods of using selective HNF-4α receptor modulators and/or selective HNF-4α binding agents. In certain embodiments, selective HNF-4α modulators are agonists, partial agonists, and/or antagonists for the HNF-4α receptor. In certain embodiments, the invention provides compounds that are selective for an HNF-4α receptor relative to a retinoic X receptor. In certain embodiments, the invention provides compounds that are selective for an HNF-4α receptor relative to an RXR by at least 8 times.

Certain Synthesis Methods

[0112] Certain synthesis schemes are now provided. The synthesis schemes are provide only to illustrate possible ways to make certain compounds of the invention and do not limit the invention in any way. One of skill in the art will recognize that compounds of the present invention may be synthesized through any of a variety of schemes using a variety of different starting materials.

SCHEME I



General procedure for Suzuki coupling (SCHEME I)

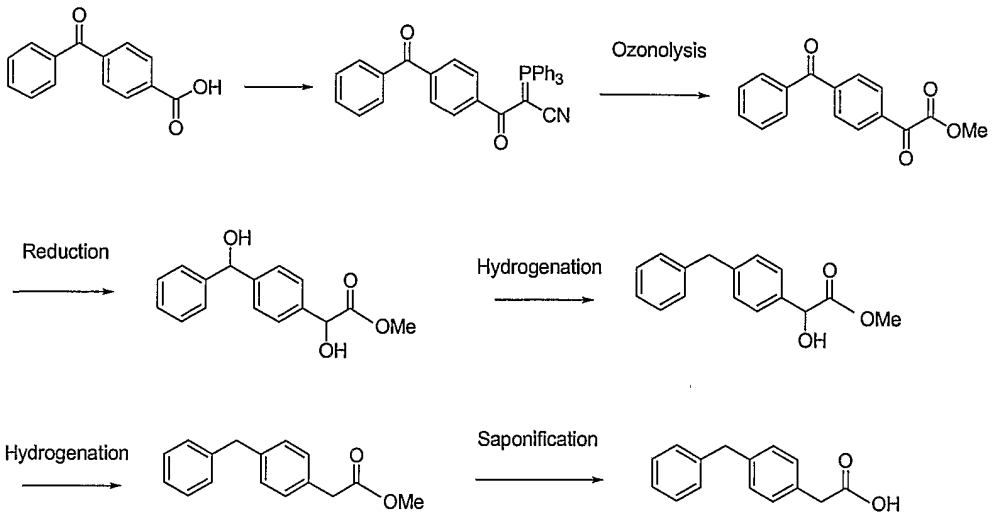
[0113] In a two neck round bottomed flask containing a magnetic stir bar and equipped with a reflux condenser is introduced one equivalent of bromo ester **1** or **3**, 1.5 equivalents of a desired boronic acid, 10 Molar % of substrate of tetrakistriphenylphosphine palladium ($Pd(PPh_3)_4$) followed by toluene (2 ml/mmol substrate), absolute EtOH (2 ml/mmol substrate) and 2N aqueous Na_2CO_3 solution (1 ml/mmol substrate). The mixture is flushed with nitrogen and stirred at reflux overnight and then cooled to room temperature. Water is added and the solution is extracted with EtOAc (3 times). The organic layers are collected, washed with brine and dried over $MgSO_4$. After filtration and removal of the solvents, the crude ester is purified over silica gel column chromatography (eluent: hexane/EtOAc) to afford the desired ethyl ester **2** or **4**.

SCHEME II

General procedure for saponification (SCHEME II)

[0114] In a round-bottomed flask is added the desired ester followed by THF (5 ml/mmol substrate), MeOH (5 ml/mmol substrate) and 2N aqueous LiOH (excess). The solution is stirred at room temperature until completion and the solvents are removed under reduced pressure. The crude pasty mixture is acidified with 2N aqueous HCl (5 ml/ mmol substrate) and extracted twice with EtOAc. The organic layer is dried over $MgSO_4$, filtered and concentrated. The crude acid is recrystallized or purified by column chromatography (SiO_2; eluant: 1:1 ratio of ethyl acetate:hexane) to give the desired product.

SCHEME III



[0115] In certain embodiments, the invention provides a salt corresponding to any of the compounds provided herein. In certain embodiments, the invention provides a salt corresponding to a selective HNF-4α modulator. In certain embodiments, the invention provides a salt corresponding to a selective HNF-4α receptor binding agent. In certain embodiments, a salt is obtained by reacting a compound with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. In certain embodiments, a salt is obtained by reacting a compound with a base to form a salt such as an ammonium salt, an alkali metal salt, such as a sodium or a potassium salt, an alkaline earth metal salt, such as a calcium or a magnesium salt, a salt of organic bases such as dicyclohexylamine, N-methyl-D-glucamine, tris(hydroxymethyl)methylamine, and salts with amino acids such as arginine, lysine, and the like.

[0116] In certain embodiments, one or more carbon atoms of a compound of the present invention is replaced with silicon. *See e.g.*, WO 03/037905A1; Tacke & Zilch,

Endeavour, New Series **10**:191-197 (1986); Bains & Tacke, *Curr. Opin. Drug Discov. Devel.* **6**:526-43 (2003). In certain embodiments, compounds of the present invention comprising one or more silicon atoms possess certain desired properties, including, but not limited to, greater stability and/or longer half-life in a patient, when compared to the same compound in which none of the carbon atoms have been replaced with a silicon atom.

[0117] Protecting groups that may be used in the present invention include those that are commonly known to those skilled in the art, such groups include, but are not limited to TBDMS, TBS and Benzyl.

Certain Assays

[0118] In certain embodiments, compounds of the present invention are capable of modulating activity of HNF-4α receptors in a "co-transfection" assay (also called a "cis-trans" assay), which has been discussed previously. *See e.g.*, Evans *et al.*, *Science*, 240:889-95 (1988); U.S. Pat. Nos. 4,981,784 and 5,071,773; Pathirana *et al.*, *Mol. Pharm.* **47**:630-35 (1995)). Modulating activity in a co-transfection assay has been shown to correlate with *in vivo* modulating activity. Thus, in certain embodiments, such assays are predictive of *in vivo* activity. *See, e.g.*, Berger *et al.*, *J. Steroid Biochem. Molec. Biol.* **41**:773 (1992).

[0119] In certain co-transfection assays, two different co-transfection plasmids are prepared. In the first co-transfection plasmid, cloned cDNA encoding an intracellular receptor (*e.g.*, HNF-4α receptor) is operatively linked to a constitutive promoter (*e.g.*, the SV 40 promoter). In the second co-transfection plasmid, cDNA encoding a reporter protein, such as firefly luciferase (LUC), is operatively linked to a promoter that is

activated by a receptor-dependant activation factor. Both co-transfection plasmids are co-transfected into the same cells. Expression of the first co-transfection plasmid results in production of the intracellular receptor protein. Activation of that intracellular receptor protein (*e.g.*, by binding of an agonist) results in production of a receptor-dependant activation factor for the promoter of the second co-transfection plasmid. That receptor-dependant activation factor in turn results in expression of the reporter protein encoded on the second co-transfection plasmid. Thus, reporter protein expression is linked to activation of the receptor. Typically, that reporter activity can be conveniently measured (*e.g.*, as increased luciferase production).

[0120] Certain co-transfection assays can be used to identify agonists, partial agonists, and/or antagonists of intracellular receptors. In certain embodiments, to identify agonists, co-transfected cells are exposed to a test compound. If the test compound is an agonist or partial agonist, reporter activity is expected to be higher compared to co-transfected cells in the absence of the test compound. In certain embodiments, to identify antagonists, the cells are exposed to a known agonist (*e.g.*, the natural ligand for the receptor) in the presence and absence of a test compound. If the test compound is an antagonist, reporter activity is expected to be lower than that of cells exposed only to the known agonist.

[0121] In certain embodiments, compounds of the invention are used to detect the presence, quantity and/or state of receptors in a sample. In certain of such embodiments, samples are obtained from a patient. In certain embodiments, compounds are radio- or isotopically-labeled. For example, compounds of the present invention that selectively bind HNF-4α receptors may be used to determine the presence or amount of such receptors in a sample, such as cell homogenates and lysates.

[0122] In certain embodiments, the present invention provides for use of both CARLA and mammalian-2-hybrid assays, to characterize the *in vitro* profile of compounds of the invention on a HNF-4α receptor.

[0123] In certain embodiments, the present invention provides for use of $[H]^3$-[4-[(phenylhydrazino)(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)]benzoic acid] (Example 73) and/or $[H]^3$-4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethoxy-2-naphthalenyl]benzoyl benzoic acid (Example 3) as radioactive ligands for a binding assay.

Certain Pharmaceutical Agents

[0124] In certain embodiments, at least one selective HNF-4α receptor modulator, or pharmaceutically acceptable salt, ester, amide, and/or prodrug thereof, either alone or combined with one or more pharmaceutically acceptable carriers, forms a pharmaceutical agent. Techniques for formulation and administration of compounds of the present invention may be found for example, in "Remington's Pharmaceutical Sciences," Mack Publishing Co., Easton, PA, 18th edition, 1990.

[0125] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is prepared using known techniques, including, but not limited to mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or tabletting processes.

[0126] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is a liquid (*e.g.*, a suspension, elixir and/or solution). In certain of such embodiments, a liquid pharmaceutical agent comprising one or more compounds of the present invention is prepared using ingredients known in the art,

including, but not limited to, water, glycols, oils, alcohols, flavoring agents, preservatives, and coloring agents.

[0127] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is a solid (*e.g.*, a powder, tablet, and/or capsule). In certain of such embodiments, a solid pharmaceutical agent comprising one or more compounds of the present invention is prepared using ingredients known in the art, including, but not limited to, starches, sugars, diluents, granulating agents, lubricants, binders, and disintegrating agents.

[0128] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is formulated as a depot preparation. Certain of such depot preparations are typically longer acting than non-depot preparations. In certain embodiments, such preparations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. In certain embodiments, depot preparations are prepared using suitable polymeric or hydrophobic materials (for example an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[0129] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises a delivery system. Examples of delivery systems include, but are not limited to, liposomes and emulsions. Certain delivery systems are useful for preparing certain pharmaceutical agents including those comprising hydrophobic compounds. In certain embodiments, certain organic solvents such as dimethylsulfoxide are used.

[0130] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises one or more tissue-specific delivery

molecules designed to deliver the pharmaceutical agent to specific tissues or cell types. For example, in certain embodiments, pharmaceutical agents include liposomes coated with a tissue-specific antibody.

[0131] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises a co-solvent system. Certain of such co-solvent systems comprise, for example, benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. In certain embodiments, such co-solvent systems are used for hydrophobic compounds. A non-limiting example of such a co-solvent system is the VPD co-solvent system, which is a solution of absolute ethanol comprising 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant Polysorbate 80™, and 65% w/v polyethylene glycol 300. The proportions of such co-solvent systems may be varied considerably without significantly altering their solubility and toxicity characteristics. Furthermore, the identity of co-solvent components may be varied: for example, other surfactants may be used instead of Polysorbate 80™; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, *e.g.*, polyvinyl pyrrolidone; and other sugars or polysaccharides may substitute for dextrose.

[0132] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises a sustained-release system. A non-limiting example of such a sustained-release system is a semi-permeable matrix of solid hydrophobic polymers. In certain embodiments, sustained-release systems may, depending on their chemical nature, release compounds over a period of hours, days, weeks or months.

[0133] Certain compounds used in pharmaceutical agent of the present invention may be provided as pharmaceutically acceptable salts with pharmaceutically compatible counterions. Pharmaceutically compatible salts may be formed with many acids, including but not limited to hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc.

[0134] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention comprises an active ingredient in a therapeutically effective amount. In certain embodiments, the therapeutically effective amount is sufficient to prevent, alleviate or ameliorate symptoms of a disease or to prolong the survival of the subject being treated. Determination of a therapeutically effective amount is well within the capability of those skilled in the art.

[0135] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is formulated as a prodrug. In certain embodiments, prodrugs are useful because they are easier to administer than the corresponding active form. For example, in certain instances, a prodrug may be more bioavailable (*e.g.*, through oral administration) than is the corresponding active form. In certain instances, a prodrug may have improved solubility compared to the corresponding active form. In certain embodiments, a prodrug is an ester. In certain embodiments, such prodrugs are less water soluble than the corresponding active form. In certain instances, such prodrugs possess superior transmittal across cell membranes, where water solubility is detrimental to mobility. In certain embodiments, the ester in such prodrugs is metabolically hydrolyzed to carboxylic acid. In certain instances the carboxylic acid containing compound is the corresponding active form. In certain embodiments, a

prodrug comprises a short peptide (polyaminoacid) bound to an acid group. In certain of such embodiments, the peptide is metabolized to form the corresponding active form.

[0136] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is useful for treating a conditions or disorder in a mammalian, and particularly in a human patient. Suitable administration routes include, but are not limited to, oral, rectal, transmucosal, intestinal, enteral, topical, suppository, through inhalation, intrathecal, intraventricular, intraperitoneal, intranasal, intraocular and parenteral (*e.g.*, intravenous, intramuscular, intramedullary, and subcutaneous). In certain embodiments, pharmaceutical intrathecals are administered to achieve local rather than systemic exposures. For example, pharmaceutical agents may be injected directly in the area of desired effect (*e.g.*, in the renal or cardiac area).

[0137] In certain embodiments, a pharmaceutical agent comprising one or more compounds of the present invention is administered in the form of a dosage unit (*e.g.*, tablet, capsule, bolus, etc.). In certain embodiments, such dosage units comprise a selective a HNF-4α receptor modulator in a dose from about 1 μg/kg of body weight to about 50 mg/kg of body weight. In certain embodiments, such dosage units comprise a selective a HNF-4α receptor modulator in a dose from about 2 μg/kg of body weight to about 25 mg/kg of body weight. In certain embodiments, such dosage units comprise a selective a HNF-4α receptor modulator in a dose from about 10 μg/kg of body weight to about 5 mg/kg of body weight. In certain embodiments, pharmaceutical agents are administered as needed, once per day, twice per day, three times per day, or four or more times per day. It is recognized by those skilled in the art that the particular dose, frequency, and duration of administration depends on a number of factors, including,

without limitation, the biological activity desired, the condition of the patient, and tolerance for the pharmaceutical agent.

[0138] In certain embodiments, a pharmaceutical agent comprising a compound of the present invention is prepared for oral administration. In certain of such embodiments, a pharmaceutical agent is formulated by combining one or more compounds of the present invention with one or more pharmaceutically acceptable carriers. Certain of such carriers enable compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient. In certain embodiments, pharmaceutical agents for oral use are obtained by mixing one or more compounds of the present invention and one or more solid excipient. Suitable excipients include, but are not limited to, fillers, such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, and/or polyvinylpyrrolidone (PVP). In certain embodiments, such a mixture is optionally ground and auxiliaries are optionally added. In certain embodiments, pharmaceutical agents are formed to obtain tablets or dragee cores. In certain embodiments, disintegrating agents (*e.g.*, cross-linked polyvinyl pyrrolidone, agar, or alginic acid or a salt thereof, such as sodium alginate) are added.

[0139] In certain embodiments, dragee cores are provided with coatings. In certain of such embodiments, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to tablets or dragee coatings.

[0140] In certain embodiments, pharmaceutical agents for oral administration are push-fit capsules made of gelatin. Certain of such push-fit capsules comprise one or more compounds of the present invention in admixture with one or more filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In certain embodiments, pharmaceutical agents for oral administration are soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In certain soft capsules, one or more compounds of the present invention are be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

[0141] In certain embodiments, pharmaceutical agents are prepared for buccal administration. Certain of such pharmaceutical agents are tablets or lozenges formulated in conventional manner.

[0142] In certain embodiments, a pharmaceutical agent is prepared for administration by injection (*e.g.*, intravenous, subcutaneous, intramuscular, etc.). In certain of such embodiments, a pharmaceutical agent comprises a carrier and is formulated in aqueous solution, such as water or physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. In certain embodiments, other ingredients are included (*e.g.*, ingredients that aid in solubility or serve as preservatives). In certain embodiments, injectable suspensions are prepared using appropriate liquid carriers, suspending agents and the like. Certain pharmaceutical agents for injection are presented in unit dosage form, *e.g.*, in ampoules or in multi-dose containers. Certain pharmaceutical agents for injection are suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. Certain solvents suitable for use in

pharmaceutical agents for injection include, but are not limited to, lipophilic solvents and fatty oils, such as sesame oil, synthetic fatty acid esters, such as ethyl oleate or triglycerides, and liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, such suspensions may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[0143] In certain embodiments, a pharmaceutical agent is prepared for transmucosal administration. In certain of such embodiments penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

[0144] In certain embodiments, a pharmaceutical agent is prepared for administration by inhalation. Certain of such pharmaceutical agents for inhalation are prepared in the form of an aerosol spray in a pressurized pack or a nebulizer. Certain of such pharmaceutical agents comprise a propellant, *e.g.*, dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In certain embodiments using a pressurized aerosol, the dosage unit may be determined with a valve that delivers a metered amount. In certain embodiments, capsules and cartridges for use in an inhaler or insufflator may be formulated. Certain of such formulations comprise a powder mixture of a compound of the invention and a suitable powder base such as lactose or starch.

[0145] In certain embodiments, a pharmaceutical agent is prepared for rectal administration, such as a suppositories or retention enema. Certain of such

pharmaceutical agents comprise known ingredients, such as cocoa butter and/or other glycerides.

[0146] In certain embodiments, a pharmaceutical agent is prepared for topical administration. Certain of such pharmaceutical agents comprise bland moisturizing bases, such as ointments or creams. Exemplary suitable ointment bases include, but are not limited to, petrolatum, petrolatum plus volatile silicones, lanolin and water in oil emulsions such as Eucerin™, available from Beiersdorf (Cincinnati, Ohio). Exemplary suitable cream bases include, but are not limited to, Nivea™ Cream, available from Beiersdorf (Cincinnati, Ohio), cold cream (USP), Purpose Cream™, available from Johnson & Johnson (New Brunswick, New Jersey), hydrophilic ointment (USP) and Lubriderm™, available from Pfizer (Morris Plains, New Jersey).

[0147] In certain embodiments, the formulation, route of administration and dosage for a pharmaceutical agent of the present invention can be chosen in view of a particular patient's condition. (See *e.g.*, Fingl *et al.* 1975, in "The Pharmacological Basis of Therapeutics", Ch. 1 p. 1). In certain embodiments, a pharmaceutical agent is administered as a single dose. In certain embodiments, a pharmaceutical agent is administered as a series of two or more doses administered over one or more days.

[0148] In certain embodiments, a pharmaceutical agent of the present invention is administered to a patient between about 0.1% and 500%, more preferably between about 25% and 75% of an established human dosage. Where no human dosage is established, a suitable human dosage may be inferred from ED_{50} or ID_{50} values, or other appropriate values derived from *in vitro* or *in vivo* studies.

[0149] In certain embodiments, a daily dosage regimen for a patient comprises an oral dose of between 0.1 mg and 2000 mg of a compound of the present invention. In

certain embodiments, a daily dosage regimen is administered as a single daily dose. In certain embodiments, a daily dosage regimen is administered as two, three, four, or more than four doses.

[0150] In certain embodiments, a pharmaceutical agent of the present invention is administered by continuous intravenous infusion. In certain of such embodiments, from 0.1 mg to 500 mg of a composition of the present invention is administered per day.

[0151] In certain embodiments, a pharmaceutical agent of the invention is administered for a period of continuous therapy. For example, a pharmaceutical agent of the present invention may be administered over a period of days, weeks, months, or years.

[0152] Dosage amount, interval between doses, and duration of treatment may be adjusted to achieve a desired effect. In certain embodiments, dosage amount and interval between doses are adjusted to maintain a desired concentration on compound in a patient. For example, in certain embodiments, dosage amount and interval between doses are adjusted to provide plasma concentration of a compound of the present invention at an amount sufficient to achieve a desired effect. In certain of such embodiments the plasma concentration is maintained above the minimal effective concentration (MEC). In certain embodiments, pharmaceutical agents of the present invention are administered with a dosage regimen designed to maintain a concentration above the MEC for 10-90% of the time, between 30-90% of the time, or between 50-90% of the time.

[0153] In certain embodiments in which a pharmaceutical agent is administered locally, the dosage regimen is adjusted to achieve a desired local concentration of a compound of the present invention.

[0154] In certain embodiments, a pharmaceutical agent may be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack may for example comprise metal or plastic foil, such as a blister pack. The pack or dispenser device may be accompanied by instructions for administration. The pack or dispenser may also be accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, may be the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. Compositions comprising a compound of the invention formulated in a compatible pharmaceutical carrier may also be prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

[0155] In certain embodiments, a pharmaceutical agent is in powder form for constitution with a suitable vehicle, *e.g.*, sterile pyrogen-free water, before use.

Certain Combination Therapies

[0156] In certain embodiments, one or more pharmaceutical agents of the present invention are co-administered with one or more other pharmaceutical agents. In certain embodiments, such one or more other pharmaceutical agents are designed to treat the same disease or condition as the one or more pharmaceutical agents of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat a different disease or condition as the one or more pharmaceutical agents of the present invention. In certain embodiments, such one or more other pharmaceutical agents are designed to treat an undesired effect of one or more

pharmaceutical agents of the present invention. In certain embodiments, one or more pharmaceutical agents of the present invention is co-administered with another pharmaceutical agent to treat an undesired effect of that other pharmaceutical agent. In certain embodiments, one or more pharmaceutical agents of the present invention and one or more other pharmaceutical agents are administered at the same time. In certain embodiments, one or more pharmaceutical agents of the present invention and one or more other pharmaceutical agents are administered at the different times. In certain embodiments, one or more pharmaceutical agents of the present invention and one or more other pharmaceutical agents are prepared together in a single formulation. In certain embodiments, one or more pharmaceutical agents of the present invention and one or more other pharmaceutical agents are prepared separately.

[0157] Examples of pharmaceutical agents that may be co-administered with a pharmaceutical agent of the present invention include, but are not limited to, analgesics (*e.g.*, acetaminophen); anti-inflammatory agents, including, but not limited to non-steroidal anti-inflammatory drugs (*e.g.*, ibuprofen, COX-1 inhibitors, and COX-2, inhibitors); salicylates; antibiotics; antivirals; antifungal agents; antidiabetic agents (*e.g.*, biguanides, glucosidase inhibitors, insulins, sulfonylureas, and thiazolidenediones); adrenergic modifiers; diuretics; hormones (*e.g.*, anabolic steroids, androgen, estrogen, calcitonin, progestin, somatostatin, and thyroid hormones); immunomodulators; muscle relaxants; antihistamines; osteoporosis agents (*e.g.*, biphosphonates, calcitonin, and estrogens); prostaglandins, antineoplastic agents; psychotherapeutic agents; sedatives; poison oak or poison sumac products; antibodies; and vaccines.

Certain Indications

[0158] In certain embodiments, the invention provides methods of treating a patient comprising administering one or more compounds of the present invention. Compounds of the present invention, including, but not limited to, pharmaceutically acceptable salts, solvates and hydrates, are expected to be effective in treating diseases or conditions that are mediated by HNF-4α. Therefore, in certain embodiments, compounds of the invention are effective in treating conditions that are mediated by HNF-4α, including, but not limited to, syndrome X, non-insulin dependent diabetes mellitus, cancer, obesity, cardiovascular disease and dyslipidemia. In certain embodiments, a patient is treated prophylactically to reduce or prevent the occurrence of a condition.

[0159] In certain embodiments, the present invention provides a method of lowering blood glucose levels in a mammal by administering to the patient a pharmaceutically effective amount of at least one compound of the present invention. In certain embodiments, the patient is a mammal. In certain embodiments, the patient is a human.

[0160] In certain embodiments, the present invention provides a method of lowering plasma triglycerides levels in a patient by administering to the mammal a pharmaceutically effective amount of at least one compound of the present invention. In certain embodiments, the patient is a mammal. In certain embodiments, the patient is a human.

[0161] In certain embodiments, the present invention provides a method of increasing insulin levels in a patient by administering to the mammal a pharmaceutically

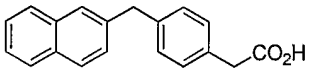
effective amount of at least one compound of the present invention. In certain embodiments, the patient is a mammal. In certain embodiments, the patient is a human.

EXAMPLES

[0162] The following examples, including experiments and results achieved, are provided for illustrative purposes only and are not to be construed as limiting the present invention.

Example 1

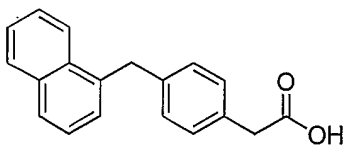
4-(2-naphthylmethyl) phenyl acetic acid (Compound 1)



[0163] 4-(2-naphthylmethyl) phenyl acetic acid was synthesized according to the general procedure for Suzuki coupling (SCHEME **I**) followed by saponification described as SCHEME **II** using ethyl-4-bromomethyl phenyl acetate and 2-naphthalene boronic acid as starting materials. 4-(2-naphthylmethyl) phenyl acetic acid was isolated as a white powder by recrystallization from EtOAc/hexanes. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (m, 3H), 7.63 (s, 1H), 7.44 (m, 2H), 7.31 (dd, J = 8.3 Hz, J = 1.5 Hz, 1H), 7.20 (d, J = 1.5 Hz, 4H), 4.12 (s, 2H), 3.62 (s, 2H).

Example 2

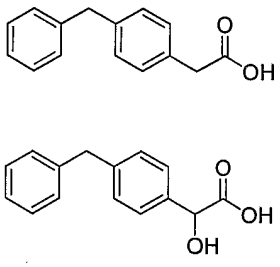
4-(1-naphthylmethyl) phenyl acetic acid (Compound 2)



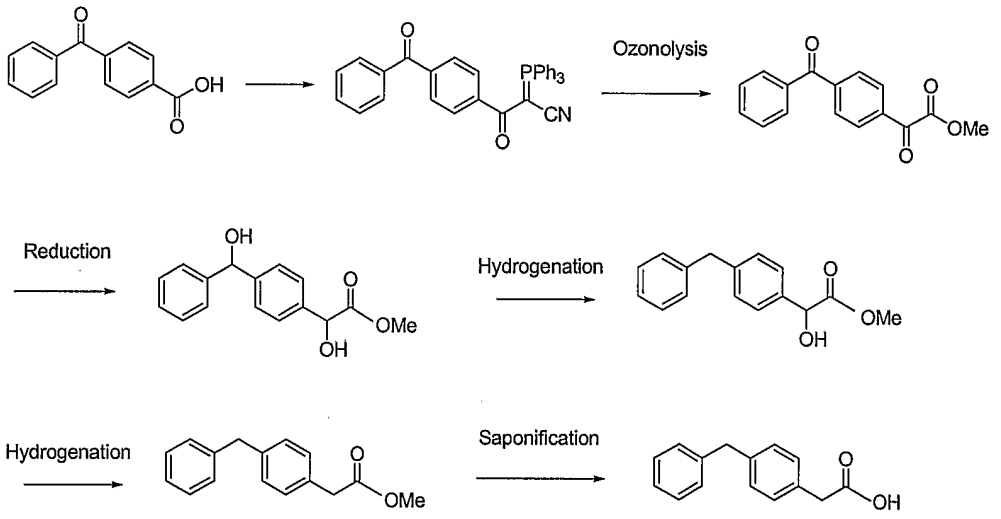
[0164] 4-(1-naphthylmethyl) phenyl acetic acid was synthesized according to the general procedure for Suzuki coupling (SCHEME **I**) followed by saponification described as SCHEME **II** using ethyl-4-bromomethyl phenyl acetate and 1-naphthalene boronic acid as starting materials. 4-(1-naphthylmethyl) phenyl acetic acid was isolated as a white powder by recrystallization from EtOAc/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 6.8 Hz, 1H), 7.86 (d, J = 2.3 Hz, 1H), 7.76 (d, J = 8.2 Hz 1H), 7.58 (m, 3H), 7.28 (d, *J* = 6.8 Hz, 1H), 7.17 (s, 4H), 4.43 (s, 2H), 3.59 (s, 2H).

Examples 3 and 4

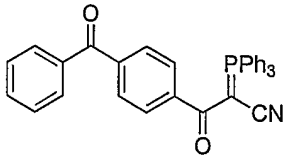
4-(benzyl)phenylacetic acid (Compound 3) and 2-Hydroxy-2-[4-(benzyl)phenyl]acetic acid (Compound 4)



[0165] Compounds 3 and 4 may be synthesized according to the following synthetic scheme (III):

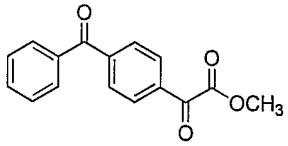


A. 1-Cyano-1-(triphenylphosphoranylidene)-2-oxo-2-[4-benzoylphenyl]ethane



[0166] To a solution of 4-benzoyl benzoic acid (4.0742 g, 18.0 mmol) in 100 mL of CH_2Cl_2 was added sequentially (cyanomethylene)triphenylphosphorane (8.14 g, 27.0 mmol), DMAP (2.20 g, 18.0 mmol) and triethylamine (7.60 mL, 54.0 mmol) followed by EDCI (4.1430 g, 21.6 mmol). The resulting mixture was stirred at 23° C for 24 hours. Following thin layer chromatography (TLC) analysis to confirm the completion of the reaction, the solvent was removed under reduced pressure. The residue was taken into 250 mL of ethyl acetate and washed with H_2O (3 x 150 mL) and brine (150 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was further purified by flash column chromatography (SiO_2, 5 x 20 cm, 1:1 ratio of ethyl acetate:hexane as eluant) to give 8.1135 g (88%, theo. 9.1758 g) of the desired product as a white solid. ^1H NMR (500 MHz, $CDCl_3$) 8.10(d, J=8.8 Hz, 2H), 7.85(d, J=8.8 Hz, 2H), 7.82 (m, 2H), 7.76-7.48(m, 16H).

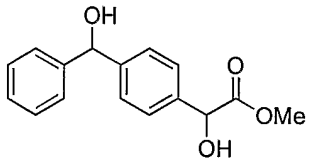
B. methyl 2-oxo-2-[4-benzoylphenyl]acetate



[0167] A solution of 1-cyano-1-(triphenylphosphoranylidene)-2-oxo-2-[4-benzoylphenyl]ethane (4.6770 g, 9.2 mmol) in 100 mL of a 1:1 ratio mixture of CH_2Cl_2:MeOH was cooled to –78° C in a dry ice/acetone bath. A stream of ozone was bubbled into the reaction mixture for 10 minutes until a blue colored solution persisted. The reaction mixture was allowed to slowly warm to 23° C, meanwhile a stream of nitrogen was bubbled into the solution to remove excess ozone. The solvent was then

removed under reduced pressure. The residue was taken into 40 mL of THF and treated with 10 mL of 1.0 M aqueous $AgNO_3$ solution. This mixture was stirred at 23° C for 24 hours, filtered through a pad of celite and the celite cake was rinsed with 200 mL of EtOAc. The filtrate was washed with H_2O (3x100 mL) and brine (100 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was further purified by flash column chromatography (SiO_2, 4 x 20 cm, 10% EtOAc/hexane as eluant) to give 0.8921 g (36%, theo. 2.4626 g) of the desired product as a pale yellow solid. ^1H NMR (500 MHz, $CDCl_3$) 8.17(d, J=8.8 Hz, 2H), 7.91(d, J=8.8 Hz, 2H), 7.83(m, 2H), 7.66(m, 1H), 7.53(m, 2H), 4.03 (s, 3H).

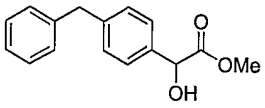
C. methyl 2-hydroxy-2-[4-[phenylhydroxymethyl]phenyl] acetate



[0168] A solution of methyl 2-oxo-2-[4-benzoylphenyl]acetate (0.6734g, 2.5 mmol) in 20 mL of a 1:1 ratio mixture of CH_2Cl_2:MeOH was treated with acetic acid (0.3015g, 5.0 mmol) and sodium cyanoborohydride (0.4732g, 7.5 mmol). The resulting mixture was stirred at 23° C for 3 hours, quenched with 50 mL of water and then extracted with 100 mL of EtOAc. The EtOAc extract was washed with H_2O (2x50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was further purified by flash column chromatography (SiO_2, 4 x 20 cm, 30% EtOAc/hexane as eluant) to give 0.6105 g (89%, theo. 0.6835 g) of the desired product as a white solid. ^1H NMR (500 MHz, DMSO-d_6)

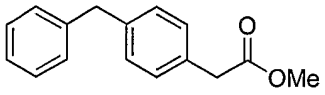
7.83(d, *J*=8.8 Hz, 2H), 7.81(m, 2H), 7.62(m, 1H), 7.58(d, *J*=8.3 Hz, 2H), 7.51(m, 2H), 5.30(d, *J*=3.9 Hz, 1H), 3.82(s, 3H), 3.57(d, *J*=5.4 Hz, 1H).

D. methyl 2-hydroxy-2-[4-[benzyl]phenyl] acetate



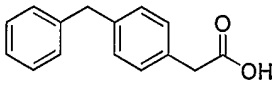
[0169] A solution of methyl 2-hydroxy-2-[4-[phenylhydroxymethyl]phenyl] acetate (0.6105 g, 2.2 mmol) in 25 mL of a 9:1 ratio mixture of EtOH:AcOH was treated with 10% palladium on carbon (65 mg). The resulting black suspension was stirred under hydrogen atmosphere (balloon pressure) at 23° C for 16 hours. The catalyst was removed by filtering through a pad of celite and the celite cake was rinsed with MeOH (100 mL) and CH_2Cl_2 (100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 4 x 20 cm, 20% ethyl acetate in hexane as eluant) to give 0.5459 g (95%, theo. 0.5746 g) product as a white solid. ^1H NMR (500 MHz, DMSO-d_6) 7.32(m, 4H), 7.22(m, 5H), 5.17 (d, *J*=3.9 Hz, 1H), 4.00(s, 2H), 3.78(s, 3H), 3.40 (d, *J*=5.3 Hz, 1H).

E. methyl 4-benzylphenylacetate



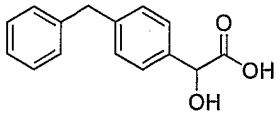
[0170] A solution of methyl 2-hydroxy-2-[4-[benzyl]phenyl] acetate (0.3688 g, 1.44 mmol) in 20 mL of a 1:1 ratio mixture of EtOH:AcOH was treated with 10% palladium on carbon (100 mg). The resulting black suspension was stirred under hydrogen atmosphere (balloon pressure) at 23° C for 24 hours. The catalyst was removed by filtering through a pad of celite and the celite cake was rinsed with MeOH (100 mL) and CH_2Cl_2 (100 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, 4 x 20 cm, 10% ethyl acetate in hexane as eluant) to give product 0.2981 g (86%, theo. 0.3458 g) as a white solid. ^1H NMR (500 MHz, DMSO-d_6) 7.22(m, 9H), 3.99 (s, 2H), 3.71(s, 3H), 3.62 (s, 2H).

F. 4-(benzyl)phenylacetic acid.



[0171] 4-(benzyl)phenylacetic acid was prepared by saponification of methyl 4-benzylphenylacetate according to the general procedure described above for Scheme II. ^1H NMR (500 MHz, DMSO-d_6) 11.30 (br. s, 1H), 7.35-7.15(m, 9H), 3.90 (s, 2H), 3.50(s, 2H).

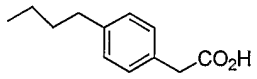
G. 2-Hydroxy-2-[4-(benzyl)phenyl]acetic acid.



[0172] A solution of methyl 2-hydroxy-2-[4-[benzyl]phenyl] acetate (61.8 mg, 0.24 mmol) in 15 mL of a 3:1:1 ratio mixture of THF:MeOH:H_2O was treated with lithium hydroxide monohydrate (101.2 mg, 2.40 mmol). The resulting mixture was heated to reflux for 20 hours. After TLC analysis indicating completion of the reaction, the mixture was acidified to pH 1 with 3.0 M aqueous HCl solution and extracted with ether (100 mL). The ether extract was washed with water (2 x 70 mL) and brine (70 mL). The ether layer was then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was further purified by recrystallization from a 9:1 ratio of hexane:ether mixture to provide 41.4 mg (71%, theo. 58.4 mg) desired product as a white solid. ^1H NMR (500 MHz, DMSO-d_6) 12.53(br. s, 1H), 7.35-7.15(m, 9H), 5.78(br. s, 1H), 4.97(s, 1H), 3.92(s, 2H).

Example 5

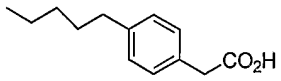
4-butyl phenyl acetic acid (Compound 5)



[0173] The compound of Example 5 was purchased as a custom synthesis compound, and was synthesized according to SCHEME **I**.

Example 6

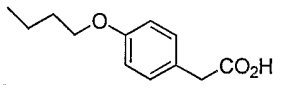
4-pentyl phenyl acetic acid (Compound 6)



[0174] The compound of Example 6 was purchased as a custom synthesis compound, synthesized according to SCHEME **I**.

Example 7

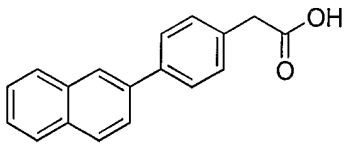
4-butoxy phenyl acetic acid (Compound 7)



[0175] This compound may be purchased from Lancaster Synthesis (Windham, NH) or Fluka (Buchs, Switzerland) or synthesized according to Scheme **II**.

Example 8

4-(2-naphthyl)phenyl acetic acid (Compound 8)

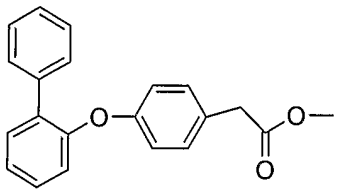


[0176] 4-(2-naphthyl) phenyl acetic acid was synthesized according to the general procedure for Suzuki coupling (SCHEME **I**) followed by saponification as described by Scheme **II** using methyl-4-bromo phenyl acetate and 2-naphthalene boronic acid as starting materials. 4-(2-naphthyl) phenyl acetic acid was isolated as a white

powder by recrystallization from EtOAc/hexanes. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (s, 1H), 7.89 (m, 3H), 7.73 (m, 1H), 7.70 (d, J = 8.2 Hz, 2H), 7.49 (m, 2H), 7.42(d, J = 8.2 Hz, 2H), 7.26 (s, 2H), 3.74 (s, 2H).

Example 9

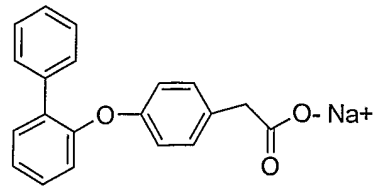
(4-(Biphenyl-2yloxy)-phenyl)-acetic acid methyl ester



[0177] Biphenyl-2-ol (0.171 g, 1.005 mmol), (4-Phenylboronic acid)-acetic acid-methyl ester (0.390g, 2.01 mmol), copper (II) acetate (0.182g, 1.005 mmol) and triethylamine (0.203 g, 2.01mmol) and 1 gram of powdered molecular sieves are suspended in dichloromethane (6.5 mL) and stirred for 16 hours. The solvent is removed under reduced pressure and the residue is columned using hexane :ethyl acetate (95:5) and increasing the polarity with hexane: ethyl acetate (9:1) to give the title compound (0.160 g,50 %) : (1 H NMR , 400 MHZ,CDCl3) : 7.55- 7.15 (m,9 H),7.17 (d, J=8.6 Hz,1H),7.01(d, J=6.9 HZ,1H),6.88 (d, J=7.8 HZ,2H),6.88 (d, J=7.8 Hz,2H),3.69 (s,3H),3.56 (s,2H)

Example 10

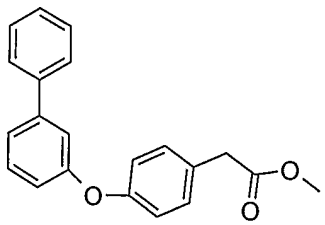
sodium (4-(biphenyl-2yl-oxy)-phenyl)-acetate



[0178] (4-(Biphenyl-2yloxy)-phenyl)-acetic acid methyl ester (0.095 g, 0.298 mmol) is dissolved in THF (5 mL) and lithium hydroxide (0.041g, 1.71 mmol) dissolved in water (2mL) is added and the reaction is heated at 55° C for 16 hours. The reaction is acidified with 1 N HCl and the reaction is extracted with ethyl acetate and washed with brine and dried over sodium sulfate. The organic layer is filtered and concentrated under reduced pressure to yield an oil. The oil is chromatographed on silica gel using dichloromethane: methanol (98:2) increasing the polarity with dichloromethane : methanol (94:6) to give an oil. The oil is dissolved in ethanol and added 1 N NaOH (0.3 mL) to give a precipitate. The precipitate is filtered off and dried to give the title compound. mass spectrum (m/e) : 303.3(M-1)

Example 11

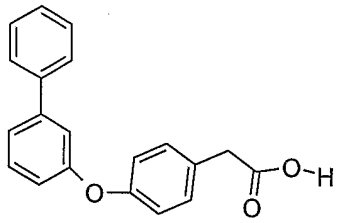
(4-(Biphenyl-3-yloxy)-phenyl)-acetic acid methyl ester



[0179] 3 –Biphenyl-boronic acid (0.386 g, 2 mmol), (4-Hydroxy-phenyl)-acetic acid methyl ester (0.166 g, 1 mmol), copper acetate (0.181 g, 1 mmol) , finely powdered molecular sieves (1 g) and triethyl amine (0.202 g, 2 mmol) were suspended in dichloromethane (6.5 mL) and stirred for 16 hours. The reaction is filtered through celite and the organics were removed under reduced pressure to give a residue. The residue was chromatographed on hexane : ethyl acetate (95:5) gradually increasing the polarity with hexane : ethyl acetate (9:1) to give the title compound (0.150 g, 24 5 % yield) (1 H-NMR,400 MHz,CDCl3) :δ 7.56 (d, J=7.9 Hz,2 H),δ7.42-7.35 (m,5 H),δ7.00 (m,3H),δ3.71(s, 3H),δ3.62 (s,2H)

Example 12

4-(Biphenyl-3-yloxy)-phenyl)-acetic acid



[0180] 4-(Biphenyl-3-yloxy)-phenyl)-acetic acid methyl ester (0.150 g, 0.471 mmol) was dissolved in THF (2mL) was added lithium hydroxide (0.033 g, 1.413 mmol) dissolved in water (1 mL). The reaction was heated at 55° C for 1 ½ hours. The reaction is acidified with 1 N HCl and extracted with ethyl acetate. The organic layers was dried with brine and dried over sodium sulfate. The organics were removed under reduced pressure to yield the title compound (0.095 g, 67 %). mass spectrum (m/e) : 303.1 (M-1)

Example 13

Binding Assays

[0181] Compounds of the invention were separately incubated with HNF-4α at varying concentrations in the presence of varying concentrations of radiolabeled methyl 4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl]benzoyl benzoate, which had been previously found to bind to HNF-4α, to determine the compound's binding affinity for HNF-4α. Binding affinity (K_i) for 3 compounds is provided in Table 1.

Co-transfection assay

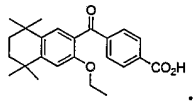
[0182] CV-1 cells (African green monkey kidney fibroblasts) were cultured in the presence of Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% charcoal resin-stripped fetal bovine serum (CH-FBS) then transferred to 96-well microtiter plates one day prior to transfection.

[0183] To determine HNF-4α receptor agonist and antagonist activity of the compounds of the present invention, the CV-1 cells were transiently transfected by FuGENE 6 transfection reagent in 175 cm2 flask with the following plasmids: pCMX-HNF-4αDF (3ug/flask), apoA1-LUC reporter (1ug/flask), and filler DNA (pcDNA; 3ug/flask). The receptor plasmid, pCMX-HNF-4αDF, contains the rat HNF-4α1 under constitutive control of the CMV promoter, as more fully described in J.D. Fraser *et al.*, **"DNA binding and transcription activation specificity of hepatocyte nuclear factor 4"** *NAR*, 26: 2702-2707 (1998).

[0184] The reporter plasmid, apoA1-LUC, contains the cDNA for firefly luciferase (LUC) under control of a multimerized HNF-4α response element (the A site

from the apo A1 promoter) linked to the TK minimal promoter. See *e.g.*, Fraser *et al.* supra. Twenty four after transfection the cells are harvested and plated in 96 well plates at 10,000 cells/well. Media containing one of the modulator compounds of the present invention in concentrations ranging from 10^{-10} to 10^{-5} M were added to the cells. Three to four replicates were used for each sample. Transfections and subsequent procedures were performed on a Biomek 1000 automated laboratory work station.

[0185] Samples containing 4-[5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-3-ethyloxy-2-naphthalenyl]benzoyl benzoic acid (LG0100695), which had previously been found to have agonist activity on HNF-4α, were included as a reference agonist. LG0100695 has the following structure:



[0186] After 24 hours, the cells were washed with PBS, lysed with a Triton X-100-based buffer and assayed for LUC activity using a NORTHSTAR HTS workstation.

[0187] The mean and standard error of the mean (SEM) of the luciferase response were calculated. Data were plotted as the response of the compound compared to the reference compounds over the range of the dose-response curve. For agonist experiments, the effective concentration that produced 50% of the maximum response (EC_{50}) was quantified. Agonist efficacy was a function (%) of LUC expression relative to the maximum LUC production by the reference agonist LG0100695. Antagonist activity was determined by testing the amount of LUC expression in the presence of no exogenous compound (just the endogenous ligand) as HNF-4α receptor agonist. The concentration of a test compound that inhibited 50% of LUC expression was quantified

(IC_{50}). In addition, the efficacy of antagonists was determined as a function (%) of maximal inhibition.

Table 1: Agonist, partial agonist, antagonist activity of HNF-4α receptor modulator compounds of present invention. Efficacy (%) for HNF-4α agonist was determined by comparing activity (*e.g.*, luciferase production) of putative agonist to that LG0100695. Efficacy (%) for HNF-4α antagonist was determined by the percentage amount by which the luciferase production is reduced (maximum concentration of antagonist) from the luciferase production without compound. NC = Not Calculated

Compounds	HNF-4α binding (ki, nM) CV-1 Cells	HNF-4α Agonist CV-1 Cells		HNF-4α Antagonist CV-1 Cells	
		% Efficacy	EC_{50} (nM)	% Efficacy	IC_{50} (nM
Example 1	NC	32	2647		
Example 2	3115	35	2838		
Example 3	604	30	2231		
Example 5	NC	50	2733		
Example 6	739	30	2953		
Example 7	NC	25	3106		

[0188] The present invention includes any combination of the various species and subgeneric groupings falling within the generic disclosure. This invention therefore includes the generic description of the invention with a proviso or negative limitation

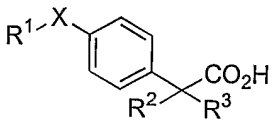
removing any subject matter from the genus, regardless of whether or not the excised material is specifically recited herein.

[0189] While in accordance with the patent statutes, description of the various embodiments and processing conditions have been provided, the scope of the invention is not to be limited thereto or thereby. Modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention.

[0190] Therefore, it will be appreciated that the scope of this invention is to be defined by the appended claims, rather than by the specific examples which have been presented merely to illustrate certain embodiments of the present invention.

What is claimed is:

1. A method for treating a patient having a disease or condition selected from the group of syndrome X non-insulin dependent diabetes mellitus, cancer, obesity, cardiovascular disease, dislipidemia, the method comprising administering to a patient a pharmaceutically effective amount of a compound of Formula I:



I

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein:

R^1 is selected from a C_1-C_{10} alkyl optionally substituted with one or more halogens, a C_2-C_{10} alkenyl optionally substituted with one or more halogens, a C_2-C_{10} alkynyl, optionally substituted with one or more halogens, a C_5-C_8 carbocyclic ring optionally substituted with one or more R^4, and a five to eight membered heterocyclic ring optionally substituted with one or more R^4;

R^2 and R^3 are each independently selected from H, oxygen and a halogen; or

R^2 and R^3 taken together form an oxygen;

R^4 is selected from H, halogen, a C_1-C_4 alkyl optionally substituted with one or more halogens, a C_2-C_4 alkenyl optionally substituted with one or more halogens, a C_2-C_4 alkynyl optionally substituted with one or more halogens, a C_1-C_4 alkoxy optionally substituted with one or more halogens, a C_1-C_4 thioalkyl optionally substituted with a nitro group and/or one or more halogens, a C_2-C_4 thioalkenyl optionally substituted with

a nitro group and/or one or more halogens, a C_2-C_4 thioalkynyl optionally substituted with a nitro group and/or one or more halogens; and

X is selected from methylene, oxygen, sulfur and null.

2. The method of claim 1, wherein X is O.

3. The method of claim 1, wherein X is S.

4. The method of claim 1, wherein R^1 is selected from the group of a C_2-C_8 alkyl optionally substituted with one or more halogens, a C_4-C_6 alkenyl optionally substituted with one or more halogens, a C_4-C_6 alkynl optionally substituted with one or more halogens, a C_5-C_8 carbocyclic ring optionally substituted with one or more R^4, and a heterocyclic ring optionally substituted with one or more R^4.

5. The method of claim 4, wherein R^1 is selected from the group of a C_3-C_5 alkyl and a carbocyclic ring optionally substituted with one or more R^4.

6. The method of claim 5, wherein R^4 is selected from H, a C_2-C_4 alkyl, a C_2-C_4 alkenyl, a C_2-C_4 alkynyl, and a C_2-C_4 alkoxy.

7. The method of claim 5, wherein R^2 is H.

8. The method of claim 7, wherein R^3 is H.

9. The method of claim 5, wherein R^2 and R^3 taken together form an oxygen.

10. The method of claim 9, wherein X is O.

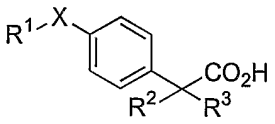
11. The method of claim 9, wherein X is S.

12. The method of claim 1, wherein said compound is selected from: 4-(2-naphthylmethyl) phenyl acetic acid; 4-(1-naphthylmethyl) phenyl acetic acid; 4-(benzyl) phenyl acetic acid; 2-hydroxy-2-[4-(benzyl)phenyl]acetic acid; 4-butyl phenyl acetic

acid; 4-pentyl phenyl acetic acid; 4-butoxy phenyl acetic acid; and 4-(2-naphthyl)phenyl acetic acid.

13. The method of claim 1, wherein said compound is selected from the group of: (4-(Biphenyl-2yloxy)-phenyl)-acetic acid methyl ester; Sodium (4-(biphenyl-2yl-oxy)-phenyl)-acetate; (4-(Biphenyl-3-yloxy)-phenyl)-acetic acid methyl ester; and 4-(Biphenyl-3-yloxy)-phenyl)-acetic acid.

14. A method of treating a HNF-4α receptor-mediated condition in an individual comprising administering to said individual a pharmaceutically active amount of a compound of Formula I:



I

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein:

R^1 is selected from a C_1-C_{10} alkyl optionally substituted with one or more halogens , a C_2-C_{10} alkenyl optionally substituted with one or more halogens, a C_2-C_{10} alkynyl optionally substituted with one or more halogens, a C_5-C_8 carbocyclic ring optionally substituted with one or more R^4, and a five to eight membered heterocyclic ring optionally substituted with one or more R^4;

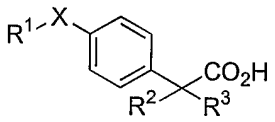
R^2 and R^3 are each independently selected from H, oxygen and a halogen; or

R^2 and R^3 taken together form an oxygen;

R^4 is selected from H, halogen, a C_1-C_4 alkyl optionally substituted with one or more halogens, a C_2-C_4 alkenyl optionally substituted with one or more halogens, a C_2-C_4 alkynyl optionally substituted with one or more halogens, a C_1-C_4 alkoxy optionally substituted with one or more halogens, a C_1-C_4 thioalkyl optionally substituted with a nitro group and/or one or more halogens, a C_2-C_4 thioalkenyl optionally substituted with a nitro group and/or one or more halogens, a C_2-C_4 thiokynyl optionally substituted with a nitro group and/or one or more halogens; and

X is selected from methylene, oxygen, sulfur and null.

15. A method of lowering blood glucose levels in an individual comprising administering to said individual a pharmaceutically effective amount of a compound represented by Formula I:



I

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein:

R^1 is selected from a C_1-C_{10} alkyl optionally substituted with one or more halogens, a C_2-C_{10} alkenyl optionally substituted with one or more halogens, a C_2-C_{10} alkynyl optionally substituted with one or more halogens, a C_5-C_8 carbocyclic ring optionally substituted with one or more R^4, and a five to eight membered heterocyclic ring optionally substituted with one or more R^4;

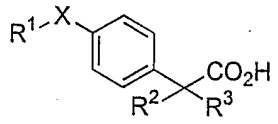
R^2 and R^3 are each independently selected from H, oxygen and a halogen; or

R^2 and R^3 taken together form an oxygen;

R^4 is selected from H, halogen, a C_1-C_4 alkyl optionally substituted with one or more halogens, a C_2-C_4 alkenyl optionally substituted with one or more halogens, a C_2-C_4 alkynyl optionally substituted with one or more halogens, a C_1-C_4 alkoxy optionally substituted with one or more halogens, a C_1-C_4 thioalkyl optionally substituted with a nitro group and/or one or more halogens, a C_2-C_4 thioalkenyl optionally substituted with a nitro group and/or one or more halogens, a C_2-C_4 alkynyl optionally substituted with a nitro group and/or one or more halogens; and

X is selected from methylene, oxygen, sulfur and null.

16. A method of lowering plasma triglycerides levels in an individual comprising administering to said individual a pharmaceutically effective amount of a compound represented by Formula I:



I

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein:

R^1 is selected from a C_1-C_{10} alkyl optionally substituted with one or more halogens, a C_2-C_{10} alkenyl optionally substituted with one or more halogens,a C_2-C_{10} alkynyl optionally substituted with one or more halogens, a C_5-C_8 carbocyclic ring

optionally substituted with one or more R^4, and a five to eight membered heterocyclic ring optionally substituted with one or more R^4;

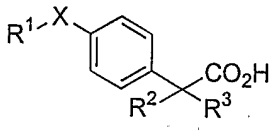
R^2 and R^3 are each independently selected from H, oxygen and a halogen; or

R^2 and R^3 taken together form an oxygen;

R^4 is selected from H, halogen, a C_1-C_4 alkyl optionally substituted with one or more halogens, a C_2-C_4 alkenyl optionally substituted with one or more halogens, a C_2-C_4 alkynyl optionally substituted with one or more halogens, a C_1-C_4 alkoxy optionally substituted with one or more halogens, a C_1-C_4 thioalkyl optionally substituted with a nitro group and/or one or more halogens, a C_2-C_4 thioalkenyl optionally substituted with a nitro group and/or one or more halogens, a C_2-C_4 thioalkynyl optionally substituted with a nitro group and/or one or more halogens; and

X is selected from methylene, oxygen, sulfur and null.

17. A method of increasing insulin blood level in an individual comprising administering to said individual a pharmaceutically effective amount of a compound represented by I:



I

or a pharmaceutically acceptable salt, ester, amide, or prodrug thereof,

wherein:

R^1 is selected from a C_1-C_{10} alkyl optionally substituted with one or more halogens, a C_2-C_{10} alkenyl optionally substituted with one or more halogens, a C_2-C_{10} alkynyl optionally substituted with one or more halogens, a C_5-C_8 carbocyclic ring optionally substituted with one or more R^4, and a five to eight membered heterocyclic ring optionally substituted with one or more R^4;

R^2 and R^3 are each independently selected from H, oxygen and a halogen; or

R^2 and R^3 taken together form an oxygen;

R^4 is selected from H, halogen, a C_1-C_4 alkyl optionally substituted with one or more halogens, a C_2-C_4 alkenyl optionally substituted with one or more halogens, a C_2-C_4 alkynyl optionally substituted with one or more halogens, a C_1-C_4 alkoxy optionally substituted with one or more halogens, a C_1-C_4 thioalkyl optionally substituted with a nitro group and/or one or more halogens, a C_2-C_4 thioalkenyl optionally substituted with a nitro group and/or one or more halogens, a C_2-C_4 thioalkynyl optionally substituted with a nitro group and/or one or more halogens; and

X is selected from methylene, oxygen, sulfur and null.