FORMULATIONS OF RBP4 INHIBITORS AND METHODS OF USE

CROSS REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/871,622 filed July 8, 2019, which application is incorporated herein by reference in its entirety.

BACKGROUND

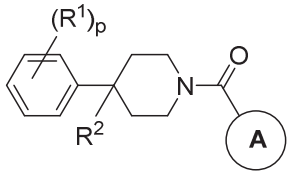
[0002] A need exists in the medicinal arts for the effective treatment of visual diseases and disorders associated with retinol-binding protein 4 (RBP4).

CROSS-REFERENCE TO RELATED APPLICATIONS

[0003] This application claims priority to U.S. Provisional Application No. 62/871,622, filed on July 8, 2019, the disclosure of which is hereby incorporated by reference in its entirety.

BRIEF SUMMARY OF THE ~~INVENTION~~DISCLOSURE

[0004] In one aspect, provided herein is a pharmaceutical composition comprising a compound of Formula (I), a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof:



Formula (I)

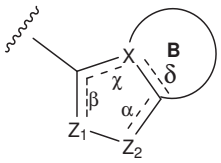
wherein:

each R^1 is independently halogen, haloalkyl, or alkyl;

R^2 is -H, -OH, or halogen;

p is 0, 1, 2, 3, 4, or 5;

A has the structure:



wherein:

α, β, χ, and δ are each independently absent or present, and when present each is a bond;

X is C;

Z_1 is S, O, or N;

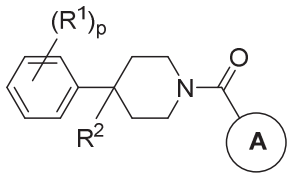
Z_2 is S, O, N, or NR^3;

R^3 is H, C_1-C_4 alkyl, or oxetane; and

B is a substituted or unsubstituted fused 5-, 6-, or 7- membered ring structure;

wherein the composition comprises a solid dispersion comprising a dispersion polymer.

[0004a] In one aspect, provided herein is a nanosuspension pharmaceutical composition comprising: a compound of Formula (I), a pharmaceutically acceptable salt, crystalline, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof:



Formula (I)

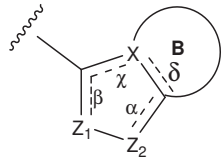
wherein:

each R^1 is independently halogen, haloalkyl, or alkyl;

R^2 is -H, -OH, or halogen;

p is 0, 1, 2, 3, 4, or 5;

A has the structure:



wherein:

α, β, χ, and δ are each independently absent or present, and when present each is a bond;

X is C;

Z_1 is S, O, or N;

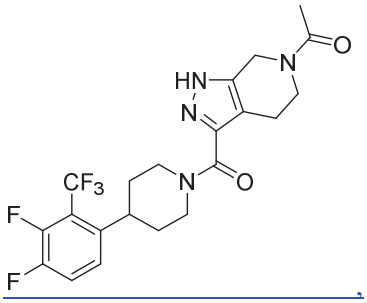
Z_2 is S, O, N, or NR^3;

R^3 is H, C_1-C_4 alkyl, or oxetane; and

B is a substituted or unsubstituted fused 5-, 6-, or 7- membered ring structure;

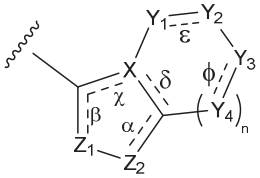
wherein the compound of Formula (I) is suspended in a pharmaceutically acceptable solvent.

[0004b] In one aspect, provided herein is a polymorph of a compound of Formula (I) having the structure



wherein the polymorph exhibits an x-ray powder diffraction pattern having at least three characteristic peaks expressed in degrees two theta (+/- 0.5 degree theta) at 6.7, 9.3, 14.1, 17.2, 23.5, 27.1, and/or 29.0.

[0005] In certain ~~embodiment~~examples, A has the structure



wherein:

n is 0, 1, or 2;

α, β, χ, δ, ε, and ϕ are each independently absent or present, and when present each is a bond;

Z_1 is S, O, or N;

Z_2 is S, O, N or NR^3,

wherein R^3 is H, C_1-C_4 alkyl, or oxetane;

X is C;

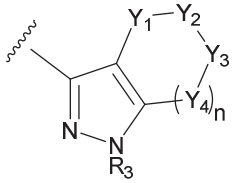
Y_1, Y_2, Y_3 and each occurrence of Y_4 are each independently CR^4, $C(R^5)_2$, NR^6, O, N, SO_2, or –(C=O)-, wherein:

R^4 is H, halogen, C_1-C_{10} alkyl, C_1-C_{10} cycloalkyl, -O(C_1-C_{10} alkyl), -C(O)OH, -C(O)O(C_1-C_{10} alkyl), -C(O)NH_2, -C(O)NH (C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_2$, -NHC(O)NH(C_1-C_{10} alkyl), -NHC(O)N(C_1-C_4 alkyl)$_2$, -SO_2NH(C_1-C_{10} alkyl), -SO_2N(C_1-C_{10} alkyl)$_2$, -CN, or -CF_3;

R^5 is H or C_1-C_{10} alkyl; and

R^6 is H, C_1-C_{10} alkyl, C_3-C_6 cycloalkyl, -(C_1-C_{10} alkylene)CF_3, -(C_1- C_{10} alkylene)OCH_3, -(C_1-C_{10} alkylene)-halogen, -SO_2(C_1-C_{10} alkyl), -SO_2(C_1-C_{10} alkylene) -CF_3, -SO_2(C_1-C_{10} alkylene)OCH_3, -SO_2(C_1-C_{10} alkylene)-halogen, -C(O)(C_1-C_{10} alkyl), -C(O)(C_1-C_{10} alkylene)CF_3, -C(O)(C_1-C_{10} alkylene)OCH_3, -C(O)(C_1-C_{10} alkylene)-halogen, -C(O)NH(C_1-C_{10} alkyl), -C(O)N(C_1-C_{10} alkyl)$_2$, -(C_1-C_{10} alkyl)C(O)OH, -C(O)NH_2, or oxetane.

[0006] In certain ~~embodiment~~examples, A has the structure



wherein:

n is 0;

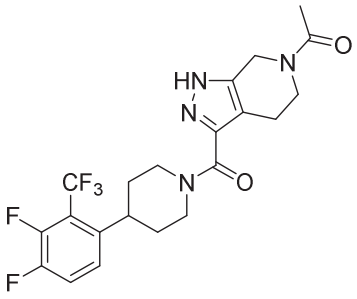
R^3 is H, C_1-C_4 alkyl, or oxetane;

Y_1 and Y_3 are each CH_2 or $C(CH_3)_2$;

Y_2 is O, SO_2, or NR^6; and

R^6 is H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, -(C_1-C_4 alkylene)CF_3, -(C_1-C_4 alkylene)OCH_3, -(C_1-C_4 alkylene)-halogen, -SO_2(C_1-C_4 alkyl), -SO_2(C_1-C_4 alkylene)CF_3, -SO_2(C_1-C_4 alkylene)OCH_3, -SO_2(C_1-C_4 alkylene)-halogen, -C(O)(C_1-C_4 alkyl), -C(O)(C_1-C_4 alkylene)CF_3, -C(O)(C_1-C_4 alkylene)OCH_3, -C(O)(C_1-C_4 alkylene)-halogen, -C(O)NH(C_1-C_4 alkyl), -C(O)N(C_1-C_4 alkyl)$_2$, -(C_1-C_4 alkylene)C(O)OH, -$C(O)NH_2$, or oxetane.

[0007] In certain ~~embodiment~~examples, the compound of Formula (I) has the structure:



, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof.

[0008] In certain ~~embodiment~~examples, the compound of Formula (I) is effective to reduce RBP4 concentrations in dosages forms of 1 to 200mg or 5 to 25mg. In certain ~~embodiment~~examples, the compound of Formula (I) is a micronized crystalline. In certain ~~embodiment~~examples, the compound of Formula (I) is a polymorph exhibiting an x-ray powder diffraction pattern having at least three characteristic peaks expressed in degrees two theta (+/- 0.5 degree theta) at 6.7, 9.3, 14.1, 17.2, 23.5, 27.1, and/or 29.0.

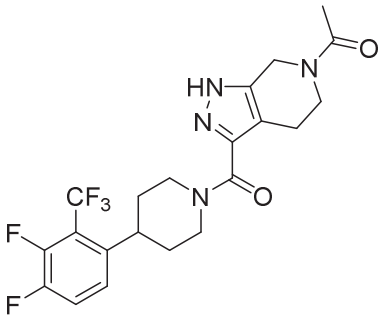
[0009] In certain ~~embodiment~~examples, the compound of Formula (I) is molecularly dispersed in the dispersion polymer. In certain ~~embodiment~~examples, the compound of Formula (I) is amorphous and molecularly dispersed in the dispersion polymer In some ~~embodiment~~examples, the compound of Formula (I) is amorphous within the dispersion polymer. In certain ~~embodiment~~examples, the dispersion polymer is selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose-acetate succinate (HPMC-AS or HPMCAS), hydroxypropyl cellulose (HPC), methyl

cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, hydroxyethyl ethyl cellulose, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinylpyrrolidone (PVP), polyethylene polyvinyl alcohol copolymers, polyoxyethylene-polyoxypropylene block copolymers, and combinations thereof. In certain ~~embodiment~~examples, the dispersion polymer is HPMC. In certain ~~embodiment~~examples, the dispersion polymer is HPMC-AS.

[0010] In certain ~~embodiment~~examples, the dispersion polymer comprises about 1-99% by weight of the solid dispersion. In certain ~~embodiment~~examples, the dispersion polymer comprises about 20-80% by weight of the solid dispersion. In certain ~~embodiment~~examples, the dispersion polymer comprises about 40-60% by weight of the solid dispersion. In certain ~~embodiment~~examples, the dispersion polymer comprises about 1-99% by weight, 20-80% by weight, or 40-60% by weight of the solid dispersion. In certain ~~embodiment~~examples, the compound of Formula (I) comprises about 1-99% by weight of the solid dispersion. In certain ~~embodiment~~examples, the compound of Formula (I) comprises 20-80% by weight of the solid dispersion. In certain ~~embodiment~~examples, the compound of Formula (I) comprises about 40-60% by weight of the solid dispersion. In certain ~~embodiment~~examples, the ratio of the compound of Formula (I):dispersion polymer is about 20:80 (w/w) in the solid dispersion. In certain ~~embodiment~~examples, the ratio of the compound of Formula (I):dispersion polymer is about 40:60 (w/w) in the solid dispersion. In certain ~~embodiment~~examples, the compound of Formula (I) comprises about 1-99% by weight, about 20-80% by weight, or about 40-60% by weight of the solid dispersion.

[0011] In certain ~~embodiment~~examples, the ratio of the compound of Formula (I):dispersion polymer is about 20:80 (w/w) in the solid dispersion. In certain ~~embodiment~~examples, the ratio of the compound of Formula (I):dispersion polymer is about 40:60 (w/w) in the solid dispersion.

[0012] In certain ~~embodiment~~examples, the compound of Formula (I) is



and the dispersion polymer is HPMC-AS.

[0013] In certain ~~embodiment~~examples, the dispersion polymer is HPMC-AS, M or HPMC-AS, H. In certain ~~embodiment~~examples, the dispersion polymer is HPMC-AS, M. In certain ~~embodiment~~examples, the dispersion polymer is HPMC-AS, H. In certain ~~embodiment~~examples, the dispersion polymer is HPMC-AS having an acetyl content from 7-11 wt%, a succinyl content from 10-14 wt%, a methoxyl content from 21-25

wt%, and a hydroxypropyl content from 5-9 wt%. In certain ~~embodiment~~examples, the dispersion polymer is HPMC-AS having an acetyl content from 10-14 wt%, a succinyl content from 4-8 wt%, a methoxyl content from 22-26 wt%, and a hydroxypropyl content from 6-10 wt%.

[0014] In certain ~~embodiment~~examples, the dispersion polymer comprises polyvinylpyrrolidone (PVP). In certain ~~embodiment~~examples, the PVP is present in a ratio with the compound of Formula (I) from about 10:1 to about 1:1. In certain ~~embodiment~~examples, the PVP is a present in a ratio with the compound of Formula (I) of about 2:1, about 3:1, or about 5:1. In certain ~~embodiment~~examples, the PVP has a molecular weight average molecular weight from about 7,000 Daltons to about 11,000 Daltons.

[0015] In certain ~~embodiment~~examples, the pharmaceutical composition further comprises a filler, a sweetener, a disintegrant, a wetting agent, a glidant, a lubricant, or a surfactant, or any combinations thereof. In certain ~~embodiment~~examples, the solid dispersion further comprises a filler, a sweetener, a disintegrant, a wetting agent, a glidant, a lubricant, or a surfactant, or any combinations thereof.

[0016] In certain ~~embodiment~~examples, the solid dispersion has an average particle size of less than 10 µm. In certain ~~embodiment~~examples, the solid dispersion has an average particle size of less than 20 µm. In certain ~~embodiment~~examples, the solid dispersion has an average particle size from about 10 µm to 20 µm. In certain ~~embodiment~~examples, the solid dispersion has an average particle size of less than 10 µm or less than 20 µm.

[0017] In one ~~aspect~~example, provided herein, is a nanosuspension pharmaceutical composition comprising a compound of Formula (I), a pharmaceutically acceptable salt, crystalline, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof, wherein the compound of Formula (I) is suspended in a pharmaceutically acceptable solvent. In some ~~embodiment~~examples, the compound of Formula (I) is Compound 1, or a pharmaceutically acceptable salt, crystalline, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof. In some ~~embodiment~~examples, the compound of Formula (I) is a polymorph exhibiting an x-ray powder diffraction pattern having at least three characteristic peaks expressed in degrees two theta (+/- 0.5 degree theta) at 6.7, 9.3, 14.1, 17.2, 23.5, 27.1, and/or 29.0. In some ~~embodiment~~examples, the concentration of the compound of Formula (I) is from about 1 mg/mL to about 50 mg/mL. In some ~~embodiment~~examples, the compound of Formula (I) is micronized. In some ~~embodiment~~examples, the compound of Formula (I) has an average particle size of less than 1000 nm.

[0018] In some ~~embodiment~~examples, the nanosuspension further comprises a surfactant. In some ~~embodiment~~examples, the surfactant comprises sodium dodecyl sulfate, a poloxamer, or a polysorbate. In some ~~embodiment~~examples, the nanosuspension further comprises an excipient. In some ~~embodiment~~examples, the excipient comprises hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose-acetate succinate (HPMC-AS), hydroxypropyl cellulose (HPC), methyl cellulose, hydroxyethyl

methyl cellulose, hydroxyethyl cellulose acetate, hydroxyethyl ethyl cellulose, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinylpyrrolidone (PVP), polyethylene polyvinyl alcohol copolymers, polyoxyethylene-polyoxypropylene block copolymers, or any combinations thereof. In some ~~embodiment~~examples, the excipient is present at a concentration from about 0.1% to about 5%.

[0019] In certain ~~embodiment~~examples, the pharmaceutical composition is encapsulated. In certain ~~embodiment~~examples, the pharmaceutical composition is in the form of a tablet. In certain ~~embodiment~~examples, the pharmaceutical composition is in the form of a capsule. In certain ~~embodiment~~examples, the pharmaceutical composition is a liquid formulation. In certain ~~embodiment~~examples, the pharmaceutical composition is formulated as an oral suspension.

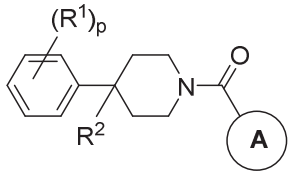
[0020] In another ~~aspect~~example is a method of treating an eye disease comprising administering a therapeutically effective amount of a pharmaceutical composition of any of the preceding claims to a subject in need thereof. In certain ~~embodiment~~examples, the eye disease is a disease characterized by excessive lipofuscin accumulation in the retina. In certain ~~embodiment~~examples, the disease characterized by excessive lipofuscin accumulation is Age-Related Macular Degeneration, dry (atrophic) Age-Related Macular Degeneration, Juvenile Macular Degeneration (Stargardt Disease), Best disease, adult vitelliform maculopathy, Geographic Atrophy, Stargardt-like macular dystrophy, diabetic retinopathy, or an ABCA4 gene associated retinal disease.

[0021] In another ~~aspect~~example is a method for lowering the serum concentration of RBP4 in a subject, comprising administering to the subject a therapeutically effective amount of a pharmaceutical composition. In certain ~~embodiment~~examples, the therapeutically effective amount of the pharmaceutical composition comprises about 0.1 mg to about 400 mg of the compound of Formula (I). In certain ~~embodiment~~examples, the therapeutically effective amount of the pharmaceutical composition comprises about 0.5 mg to about 400 mg of the compound of Formula (I). In certain ~~embodiment~~examples, the therapeutically effective amount of the pharmaceutical composition comprises about 0.5 mg to about 50 mg of the compound of Formula (I). In certain ~~embodiment~~examples, the therapeutically effective amount of the pharmaceutical composition comprises about 0.1 mg of the compound of Formula (I). In certain ~~embodiment~~examples, the therapeutically effective amount of the pharmaceutical composition comprises about 0.5 mg of the compound of Formula (I). In certain ~~embodiment~~examples, the therapeutically effective amount of the pharmaceutical composition comprises about 1 mg of the compound of Formula (I). In certain ~~embodiment~~examples, the therapeutically effective amount of the pharmaceutical composition comprises about 5 mg of the compound of Formula (I). In certain ~~embodiment~~examples, the therapeutically effective amount of the pharmaceutical composition comprises about 10 mg of the compound of Formula (I). In certain ~~embodiment~~examples, the therapeutically effective amount of the

pharmaceutical composition comprises about 25 mg of the compound of Formula (I). In certain ~~embodiment~~examples, the therapeutically effective amount of the pharmaceutical composition comprises about 50 mg of the compound of Formula (I). In certain ~~embodiment~~examples, the therapeutically effective amount of the pharmaceutical composition comprises about 100 mg of the compound of Formula (I). In certain ~~embodiment~~examples, the therapeutically effective amount of the pharmaceutical composition comprises about 200 mg of the compound of Formula (I). In certain ~~embodiment~~examples, the therapeutically effective amount of the pharmaceutical composition comprises about 400 mg of the compound of Formula (I). In certain ~~embodiment~~examples, the therapeutically effective amount of the pharmaceutical composition comprises about 0.1 mg, about 0.5 mg, about 1 mg, about 5 mg, about 10 mg, about 25 mg, about 50 mg, about 100 mg, about 200 mg, or about 400 mg of the compound of Formula (I).

[0022] In certain ~~embodiment~~examples, the pharmaceutical composition is administered one, two, three, or four times daily. In certain ~~embodiment~~examples, the pharmaceutical composition is administered daily, every other day, every other day 3 times a week, every 2 weeks, every 3 weeks, every 4 weeks, every 5 weeks, every 3 days, every 4 days, every 5 days, every 6 days, weekly, bi-weekly, 3 times a week, 4 times a week, 5 times a week, 6 times a week, once a month, twice a month, 3 times a month, once every 2 months, once every 3 months, once every 4 months, once every 5 months, or once every 6 months. In certain ~~embodiment~~examples, the pharmaceutical composition is administered once daily. In certain ~~embodiment~~examples, the pharmaceutical composition is administered orally. In certain ~~embodiment~~examples, the serum RBP4 concentration of the subject is reduced to below 1 μM after treatment.

[0023] In another ~~aspect~~example, described herein, is a method of manufacturing a solid dispersion comprising the steps of adding a solvent to a vessel; adding a compound of Formula (I) or its pharmaceutically acceptable salt to the vessel; adding a dispersion polymer to the vessel to obtain a first mixture; mixing the first mixture until the compound of Formula (I) or its pharmaceutically acceptable salt and the dispersion polymer are dissolved in the solvent to obtain a first solution; and dry spraying the first solution to obtain a first solid; wherein the compound of Formula (I) has the structure:



Formula (I)

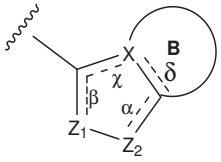
wherein:

each R^1 is independently halogen, haloalkyl, or alkyl;

R^2 is -H, -OH, or halogen;

p is 0, 1, 2, 3, 4, or 5;

A has the structure:



wherein:

α, β, χ, and δ are each independently absent or present, and when present each is a bond;

X is C;

Z_1 is S, O, or N;

Z_2 is S, O, N, or NR^3;

R^3 is H, C_1-C_4 alkyl, or oxetane; and

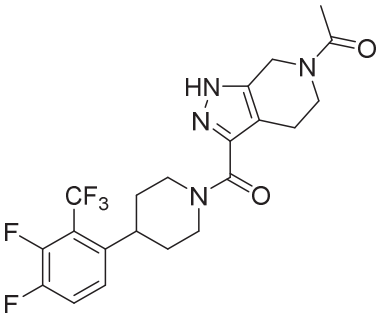
B is a substituted or unsubstituted fused 5-, 6-, or 7- membered ring structure;

wherein the composition comprises a solid dispersion comprising a dispersion polymer.

[0024] In certain ~~embodiment~~examples, the solvent comprises an organic solvent. In certain ~~embodiment~~examples, the solvent is selected from the group consisting of ethanol, methanol, acetone, isopropyl alcohol, n-butanol, tetrahydrofuran, dichloromethane, ethyl acetate, methyl acetate, acetonitrile, chloroform, carbon tetrachloride, benzene, toluene, diethyl ether, dioxane, pentane, hexane, cyclohexane, heptane, methyl *t*-butyl ether, petroleum ether, 1-propanol, and combinations thereof. In certain ~~embodiment~~examples, the solvent is 90:10 dichloromethane:methanol (v/v).

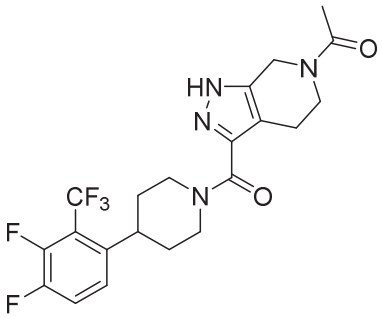
[0025] In certain ~~embodiment~~examples, the dispersion polymer selected from the group consisting of hydroxypropyl methylcellulose (HPMC), hydroxypropyl methylcellulose-acetate succinate (HPMC-AS), hydroxypropyl cellulose (HPC), methyl cellulose, hydroxyethyl methyl cellulose, hydroxyethyl cellulose acetate, hydroxyethyl ethyl cellulose, polyvinyl alcohol polyvinyl acetate copolymers, polyethylene glycol, polyethylene glycol polypropylene glycol copolymers, polyvinylpyrrolidone (PVP), polyethylene polyvinyl alcohol copolymers, polyoxyethylene-polyoxypropylene block copolymers, and combinations thereof. In certain ~~embodiment~~examples, the dispersion polymer is HPMC-AS. In certain ~~embodiment~~examples, the dispersion polymer is HPMC. In some ~~embodiment~~examples, the dispersion polymer is polyvinyl pyrrolidine.

[0026] In certain ~~embodiment~~examples, the compound of Formula (I) has the structure:



, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof. In certain ~~embodiment~~examples, the solvent comprises acetic acid, acetone, acetonitrile, benzene, tert-butyl alcohol, tert-butyl methyl ether, carbon tetrachloride, chloroform, cyclohexane, 1,2-dichloroethane, dichloromethane, diethyl ether, diglyme, 1,2,-dimethoxyethane, dimethyl acetamide, dimethylformamide, dimethyl sulfoxide, dioxane, ethanol, ethyl acetate, ethyl methyl ketone, ethylene glycol, hexanes, hexamethylphosphoramide, methanol, nitromethane, pentanes, 2-proponal, pyridine, tetrahydrofuran, toluene, xylenes, or any combination thereof.

[0027] In another ~~aspect~~example, described herein, is a method for lowering the serum concentration of RBP4 in a subject, comprising administering to the subject a pharmaceutical composition comprising a therapeutically effective amount of a compound having the structure



, or a pharmaceutically acceptable salt, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof; wherein the pharmaceutical composition comprises the compound in an amount of about 10 mg; wherein the pharmaceutical composition is administered daily; and wherein the serum or plasma levels of RBP4 of the subject are reduced to below 1 μM.

[0028] In one ~~aspect~~example, provided herein, is a polymorph of Compound 1, wherein the polymorph exhibits an x-ray powder diffraction pattern having at least three characteristic peaks expressed in degrees two theta (+/- 0.5 degree theta) at 6.7, 9.3, 14.1, 17.2, 23.5, 27.1, and/or 29.0. In some ~~embodiment~~examples, the polymorph is crystalline. In some ~~embodiment~~examples, the polymorph exhibits an x-ray powder diffraction pattern having at least five characteristic peaks expressed in degrees two theta (+/- 0.5 degree theta) at 6.7, 9.3, 14.1, 17.2, 23.5, 27.1, and/or 29.0. In some ~~embodiment~~examples, the

polymorph exhibits an x-ray powder diffraction pattern having characteristic peaks expressed in degrees two theta (+/- 0.5 degree theta) at 6.7, 9.3, 14.1, 17.2, 23.5, 27.1, and/or 29.0. In some ~~embodiment~~examples, the polymorph is micronized. In some ~~embodiment~~examples, the polymorph has an average particle size of less than 20 μm, less than 10 μm, less than 1 μm, or less than 100 nm.

INCORPORATION BY REFERENCE

[0029] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference for the specific purposes identified herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0031] Fig. 1 illustrates a schematic of a mechanism of action for dry (atrophic) macular degeneration and Stargardt disease. Without being bound by theory, RBP4 transports retinol (a precursor to cytotoxic A2E) into the retina by way of the visual cycle. RBP4 inhibitors, such as Compound 1, are in some instances used to treat RBP4-related visual diseases and disorders.

[0032] Fig. 2 is a graph of bisretinoid A2E (pmol in the eye) and RBP4 (serum) levels for ABCA4-/-RDH8-/- mice either untreated, treated with vehicle, or treated with Compound 1. Mice treated with Compound 1 had an 80% reduction in bisretinoid accumulation ($p=0.003$; unpaired t-test).

[0033] Fig. 3 is a graph of outer nuclear layer (ONL) thickness (μm) as a function of distance (μm) from the optic nerve (ONH). ONL is the cell layer consisting of photoreceptor cell bodies (rods and cones). Dry AMD or STGD is often associated with thinning of the ONL and the loss of photoreceptor cells, indicating macular degeneration. ONL thickness was significantly decreased in the diseased group (abcd4/rdh8 knockout mice), as compared to the diseased group treated with Compound 1 wherein the ONL was preserved.

[0034] Fig. 4A is a graph of percent mean RBP4 reduction from baseline as a function of time (hours) for five cohorts comprising a total of 32 healthy adults in a randomized, double-blind, placebo-controlled Phase 1 clinical trial. Each cohort was given a single dose of 50 mg (Cohort 1), 100 mg (Cohort 2), 200 mg (Cohort 3), 400 mg (Cohort 4), 25 mg (Cohort 5) of Compound 1, or a placebo. Individuals receiving placebo were not included in the graph.

[0035] Fig. 4B is a graph of RBP4 concentration (ng/mL) as a function of time (hours) for five cohorts comprising a total of 32 healthy adults in a randomized, double-blind, placebo-controlled Phase 1 clinical trial. Each cohort was given a single dose of 50 mg (Cohort 1), 100 mg (Cohort 2),