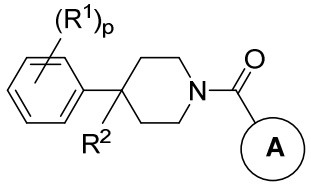
CLAIMS

We Claim:

1. A pharmaceutical composition comprising a solid dispersion, wherein the solid dispersion comprises:

(i) a compound of Formula (I), a pharmaceutically acceptable salt, crystalline, solvate, polymorph, prodrug, metabolite, N-oxide, stereoisomer, or isomer thereof:



Formula (I)

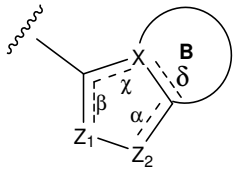
wherein:

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;

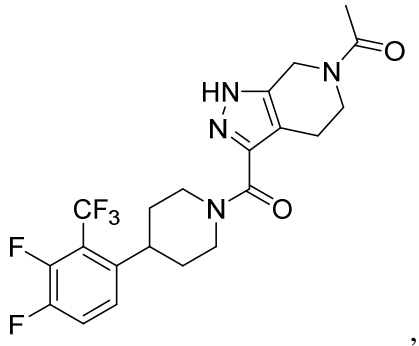
Z_2 is S, O, N, or NR^3;

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; and

(ii) a dispersion polymer.

2. The pharmaceutical composition of claim 1, wherein the compound of Formula (I) has the structure:



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

3. The pharmaceutical composition of any one of the preceding claims, wherein the compound of Formula (I) is effective to reduce RBP4 concentrations in dosages forms of 1 to 200mg or 5 to 25mg.

4. The pharmaceutical composition of any one of the preceding claims, wherein the compound of Formula (I) is amorphous and molecularly dispersed in 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.

5. The pharmaceutical composition of any one of the preceding claims, wherein the dispersion polymer comprises about 1-99% by weight, 20-80% by weight, or 40-60% by weight of the solid dispersion.

6. The pharmaceutical composition of any one of the preceding claims, wherein the ratio of the compound of Formula (I):dispersion polymer is about 20:80 (w/w) or about 40:60 (w/w) in the solid dispersion.

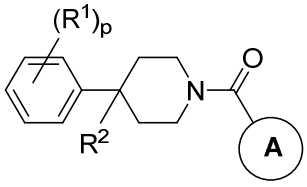
7. The pharmaceutical composition of claim 5 or 6, wherein the dispersion polymer is HPMC-AS having an acetyl content from 7-11 wt%, a succinyl content from 10-14 wt%, a methoxyl content from 21-25 wt%, and a hydroxypropyl content from 5-9 wt%.

8. The pharmaceutical composition of any one of claims 1-7, wherein the dispersion polymer comprises polyvinylpyrrolidone (PVP); wherein the PVP is present in a ratio with the compound of Formula (I) from about 10:1 to about 1:1.

9. The pharmaceutical composition of claim 8, wherein the PVP has a molecular weight average molecular weight from about 7,000 Daltons to about 11,000 Daltons.

10. 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)

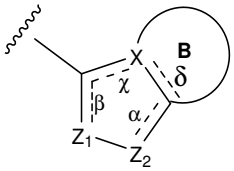
wherein:

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.

11. The nanosuspension pharmaceutical formulation of claim 10, wherein the concentration of the compound of Formula (I) is from about 1 mg/mL to about 50 mg/mL.

12. The nanosuspension pharmaceutical formulation of claim 10 or 11, wherein the compound of Formula (I) is micronized.

13. The nanosuspension pharmaceutical formulation of any one of claims 10-12, wherein the compound of Formula (I) has an average particle size of less than 1000 nm.

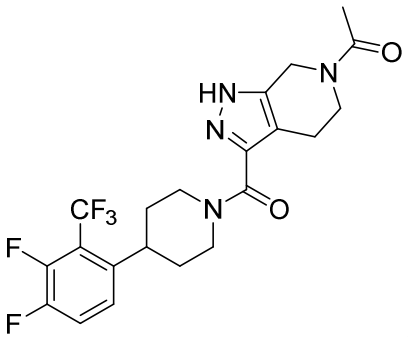
14. The nanosuspension pharmaceutical formulation of any one of claims 10-13, further comprising a surfactant, wherein the surfactant comprises sodium dodecyl sulfate, a poloxamer, or a polysorbate.

15. The nanosuspension pharmaceutical formulation of claim 14, wherein the surfacing is present at a concentration from about 0.01% to about 1%.

16. The nanosuspension pharmaceutical formulation of any one of claims 10-15, further comprising an excipient, wherein 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.

17. The nanosuspension pharmaceutical composition of claim 16, wherein the excipient is present at a concentration from about 0.1% to about 5%.

18. A polymorph of a compound of Formula (I) having the structure



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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.

19. The polymorph of claim 18, wherein the polymorph is crystalline.

20. The polymorph of any one of claims 18 or 19, wherein 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.