TABLET FORMULATIONS OF RBP4 INHIBITORS AND METHODS OF USE

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 63/282,540 filed on November 23, 2021, which is incorporated by reference in its entirety.

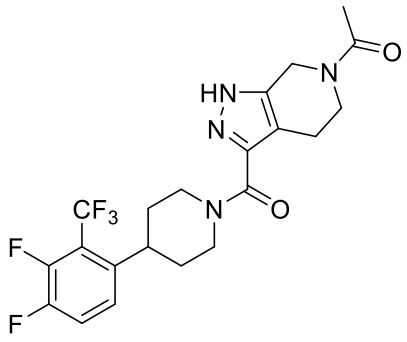
BACKGROUND

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

BRIEF SUMMARY

[0002a] In an aspect of the present disclosusre, there is provided a tablet pharmaceutical composition comprising:

(i) a compound having the structure



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

(ii) hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), or both in an amount of 1-10% by weight;

(iii) a disintegrant in an amount of about 0.01% to about 5% by weight; and

(iv) a diluent.

[0002b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising any one of the formulas set forth below:

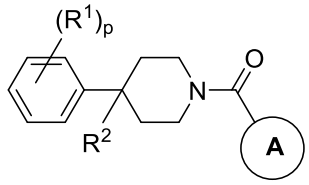
Formula	Ingredient % weight in Tablet						
	Compound 1	CCNa	HPC	MCC	LMH	CSD	Magnesium Stearate
1	5	0.75	6	43.25	43.5	0.5	1
2	7	0.75	3	44.25	43.5	0.5	1
3	10	0.75	3	43.25	41.5	0.5	1
4	15	0.75	3	39.5	40.25	0.5	1
13	5	0.75	6	43.75	43.75	0.75	0
14	7	0.75	6	42.75	42.75	0.75	0
15	5	0.75	3	45.75	44.75	0.75	0
16	5	0.75	4	44.75	44.75	0.75	0
17	5	0.75	8	42.75	42.75	0.75	0
19	5	0.75	6	43.75	43.75	0.5	0.25
20	7	0.75	6	42.75	42.75	0.5	0.25
21	5	0.75	3	45.75	44.75	0.5	0.25
22	5	0.75	4	44.75	44.75	0.5	0.25
23	5	0.75	8	42.75	42.75	0.5	0.25
25	5	0.75	3	43.25	43.25	0.5	2
26	7	0.75	3	43.25	43.25	0.75	2
27	10	0.75	3	42	42	0.25	2
28	15	0.75	3	39	39.75	0.5	2
29	5	1	6	43.25	43.25	0.5	1
30	7	1	6	43.25	41.25	0.5	1

Formula	Ingredient % weight in Tablet						
	Compound 1	CCNa	HPMC	MCC	LMH	CSD	Magnesium Stearate
31	5	0.75	6	43.25	43.5	0.5	1
32	7	0.75	3	44.25	43.5	0.5	1
33	10	0.75	3	43.25	41.5	0.5	1
34	15	0.75	3	39.5	40.25	0.5	1
43	5	0.75	6	43.75	43.75	0.75	0
44	7	0.75	6	42.75	42.75	0.75	0
45	5	0.75	3	45.75	44.75	0.75	0
46	5	0.75	4	44.75	44.75	0.75	0
47	5	0.75	8	42.75	42.75	0.75	0
49	5	0.75	6	43.75	43.75	0.5	0.25
50	7	0.75	6	42.75	42.75	0.5	0.25
51	5	0.75	3	45.75	44.75	0.5	0.25
52	5	0.75	4	44.75	44.75	0.5	0.25
53	5	0.75	8	42.75	42.75	0.5	0.25
54	5	0.75	0	46.75	46.75	0.5	0.25
55	5	0.75	3	43.25	43.25	0.5	2
56	7	0.75	3	43.25	43.25	0.75	2
57	10	0.75	3	42	42	0.25	2
58	15	0.75	3	39	39.75	0.5	2
59	5	1	6	43.25	43.25	0.5	1
60	7	1	6	43.25	41.25	0.5	1

[0003] Provided herein are formulations for lowering serum or plasma concentrations of RBP4.

[0004] Provided herein are tablet pharmaceutical compositions comprising:

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



Formula (I)

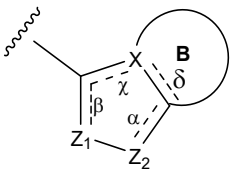
wherein:

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

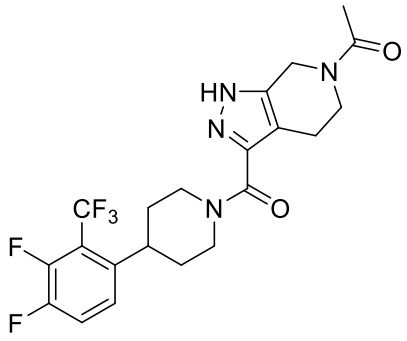
B is a substituted or unsubstituted fused 5-, 6-, or 7- membered ring structure; and

CLAIMS

We Claim:

1. A tablet pharmaceutical composition comprising:

(i) a compound having the structure



, or a pharmaceutically acceptable salt, crystalline, solvate, polymorph, or N-oxide thereof; and

(ii) hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), or both in an amount of 1-10% by weight;

(iii) a disintegrant in an amount of about 0.01% to about 5% by weight; and

(iv) a diluent.

2. The pharmaceutical composition of claim 1, wherein the disintegrant is selected from the group comprising agar-agar, algins, calcium carbonate, carboxymethylcellulose, cellulose, hydroxypropylcellulose, low substituted hydroxypropylcellulose, clays, croscarmellose sodium (CCNa), crospovidone, gums, magnesium aluminum silicate, methylcellulose, microcrystalline cellulose (MCC), polacrilin potassium, sodium alginate, sodium starch glycolate, maize starch, potato starch, tapioca starch, and combinations thereof.

3. The pharmaceutical composition of claim 2, wherein the disintegrant comprises CCNa, MCC, crospovidone, tapioca starch, or a combination thereof.

4. The pharmaceutical composition of claim 1, wherein the disintegrant comprises CCNa.

5. The pharmaceutical composition of claim 1, wherein the disintegrant comprises CCNa in an amount of about 0.75% by weight of the pharmaceutical composition.

6. The pharmaceutical composition of any one of claim 1-5, wherein the HPC or HPMC is about 6% by weight of the pharmaceutical composition.

7. The pharmaceutical composition of claim 1, wherein the disintegrant comprises about 0.75% of CCNa by weight of the pharmaceutical composition and the pharmaceutical composition comprises about 6% of HPC by weight.

8. The pharmaceutical composition of any one of claims 1-7, wherein the tablet comprises the diluent in an amount of from about 0.01% to about 99% by weight of the tablet pharmaceutical composition
9. The pharmaceutical composition of claim 8, wherein the diluent comprises MCC, lactose monohydrate (LMH), or both.
10. The pharmaceutical composition of any one of claims 1 to 9, further comprising an anti-adherent, and wherein the anti-adherent comprises colloidal silicon dioxide (CSD), magnesium stearate, or both.
11. The pharmaceutical composition of claim 10, wherein the anti-adherent comprises CSD in an amount of about 0.5% by weight of the tablet pharmaceutical composition and/or wherein the anti-adherent comprises magnesium stearate in an amount of about 1.0% by weight of the tablet pharmaceutical composition.
12. The pharmaceutical composition of any one of the preceding claims, wherein the dry weight of the pharmaceutical composition is from about 0.1 mg to about 400 mg.
13. The pharmaceutical composition of any one of claims 1-12, wherein the compound is about 1% to about 10% by weight of the tablet pharmaceutical composition.
14. The pharmaceutical composition of any one of claims 1-12, wherein the compound is about 5% by weight of the tablet pharmaceutical composition.
15. The pharmaceutical composition of any one of the preceding claims, wherein at least about 5%, 10%, 25%, 50%, 75%, 80%, 90%, 95%, or 100% of the pharmaceutical composition by weight has dissociated or dissolved after about 5 minutes, 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, or one hour when placed in an aqueous medium at about pH 7 and at 25°C.
16. The pharmaceutical composition of any one of the preceding claims, wherein at least about 5%, 10%, 25%, 50%, 75%, 80%, 90%, 95%, or 100% of the pharmaceutical composition by weight has dissociated or dissolved after about 5 minutes, 10 minutes, 20 minutes, 30 minutes, 40 minutes, 50 minutes, or one hour when placed in a simulated gastric fluid at 37°C.
17. A pharmaceutical composition comprising any one of the formulas set forth below:

Formula	Ingredient % weight in Tablet						
	Compound 1	CCNa	HPC	MCC	LMH	CSD	Magnesium Stearate
1	5	0.75	6	43.25	43.5	0.5	1
2	7	0.75	3	44.25	43.5	0.5	1
3	10	0.75	3	43.25	41.5	0.5	1
4	15	0.75	3	39.5	40.25	0.5	1
13	5	0.75	6	43.75	43.75	0.75	0
14	7	0.75	6	42.75	42.75	0.75	0
15	5	0.75	3	45.75	44.75	0.75	0
16	5	0.75	4	44.75	44.75	0.75	0
17	5	0.75	8	42.75	42.75	0.75	0
19	5	0.75	6	43.75	43.75	0.5	0.25
20	7	0.75	6	42.75	42.75	0.5	0.25
21	5	0.75	3	45.75	44.75	0.5	0.25
22	5	0.75	4	44.75	44.75	0.5	0.25
23	5	0.75	8	42.75	42.75	0.5	0.25
25	5	0.75	3	43.25	43.25	0.5	2
26	7	0.75	3	43.25	43.25	0.75	2
27	10	0.75	3	42	42	0.25	2
28	15	0.75	3	39	39.75	0.5	2
29	5	1	6	43.25	43.25	0.5	1
30	7	1	6	43.25	41.25	0.5	1

Formula	Ingredient % weight in Tablet						
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33	10	0.75	3	43.25	41.5	0.5	1
34	15	0.75	3	39.5	40.25	0.5	1
43	5	0.75	6	43.75	43.75	0.75	0
44	7	0.75	6	42.75	42.75	0.75	0
45	5	0.75	3	45.75	44.75	0.75	0
46	5	0.75	4	44.75	44.75	0.75	0
47	5	0.75	8	42.75	42.75	0.75	0
49	5	0.75	6	43.75	43.75	0.5	0.25
50	7	0.75	6	42.75	42.75	0.5	0.25
51	5	0.75	3	45.75	44.75	0.5	0.25
52	5	0.75	4	44.75	44.75	0.5	0.25
53	5	0.75	8	42.75	42.75	0.5	0.25
54	5	0.75	0	46.75	46.75	0.5	0.25
55	5	0.75	3	43.25	43.25	0.5	2
56	7	0.75	3	43.25	43.25	0.75	2
57	10	0.75	3	42	42	0.25	2
58	15	0.75	3	39	39.75	0.5	2
59	5	1	6	43.25	43.25	0.5	1
60	7	1	6	43.25	41.25	0.5	1

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