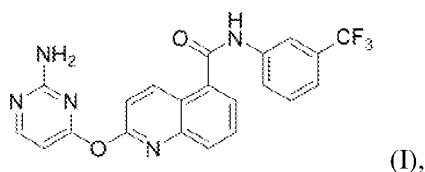


CLAIMS

WHAT IS CLAIMED IS:

1. A pharmaceutical composition, comprising:

(i) a compound of Formula (I):



or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof; and

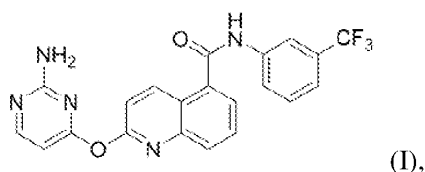
(ii) at least one pharmaceutically acceptable excipient,

wherein the pharmaceutical composition is in a dosage form for ophthalmic dosing or administration.

2. The composition of claim 1, wherein the dosage form is a suspension comprising fine particles of a compound of Formula (I), or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof.

3. A pharmaceutical composition, comprising:

(i) fine particles of a compound of Formula (I):



or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof; and

(ii) at least one pharmaceutically acceptable excipient,

wherein the pharmaceutical composition is formulated as a suspension.

4. The composition of claim 2 or 3, wherein the particles are micronized.

5. The composition of any one claims 2-4, wherein the particles of the compound of Formula (I), or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof have a diameter of from about 0.1 μm to about 40 μm .

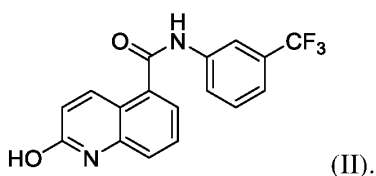
6. The composition of any one claims 2-5, wherein the particles of the compound of Formula (I), or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof have a diameter of from about 0.1 μm to about 10 μm .

7. The composition of any one claims 2-6, wherein the particles of the compound of Formula (I), or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof have a diameter of from about 0.3 μm to about 5 μm .
8. The composition of claim 4 or 5, wherein at least about 10% of the particles have a diameter of from about 0.1 μm to about 40 μm .
9. The composition of any one of claims 4, 5, or 8, wherein at least about 20% of the particles have a diameter of from about 0.1 μm to about 40 μm .
10. The pharmaceutical composition of any one of claims 4, 5, or 8-9, wherein at least about 30% of the particles have a diameter of from about 0.1 μm to about 40 μm .
11. The composition of any one of claims 4, 5, or 8-10, wherein at least about 40% of the particles have a diameter of from about 0.1 μm to about 40 μm .
12. The composition of any one of claims 4, 5, or 8-11, wherein at least about 50% of the particles have a diameter of from about 0.1 μm to about 40 μm .
13. The composition of any one of claims 4, 5, or 8-12, wherein at least about 60% of the particles have a diameter of from about 0.1 μm to about 40 μm .
14. The composition of any one of claims 4, 5, or 8-13, wherein at least about 70% of the particles have a diameter of from about 0.1 μm to about 40 μm .
15. The composition of any one of claims 4, 5, or 8-14, wherein at least about 80% of the particles have a diameter of from about 0.1 μm to about 40 μm .
16. The composition of any one of claims 4, 5, or 8-15, wherein at least about 90% of the particles have a diameter of from about 0.1 μm to about 40 μm .
17. The composition of any one of claims 4, 5, or 8-16, wherein at least about 95% of the particles have a diameter of from about 0.1 μm to about 40 μm .
18. The composition of any one of claims 1-4, wherein the particles have a D10 value of less than about 1 μm .
19. The composition of any one of claims 1-4, wherein the particles have a D50 value of less than about 5 μm .
20. The composition of any one of claims 1-4, wherein the particles have a D90 value of less than about 10 μm .
21. The composition of any one of claims 1-20, wherein the compound of Formula (I) or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof; is crystalline, microcrystalline, amorphous, or lyophilized.

22. The composition of any one of claims 1-21 wherein the dosage form is a modified-release dosage form.
23. The composition of claim 22, wherein the modified-release dosage form is a delayed-release dosage form, an extended-release (ER) dosage form, or a targeted-release dosage form.
24. The composition of claim 23, wherein the ER dosage form is a sustained-release (SR) dosage form or controlled-release (CR) dosage form.
25. The composition of any one of claims 1-25, wherein The composition comprises from about 0.025% to about 2.0% w/v of a compound of Formula (I), or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof.
26. The composition of any one of claims 1-25, wherein The composition comprises from about 0.05% to about 0.5% w/v of a compound of Formula (I), or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof.
27. The composition of any one of claims 1-25, wherein the composition comprises from about 0.05% to about 0.15% w/v of a compound of Formula (I), or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof.
28. The composition of any one of claims 1-27, wherein the at least one pharmaceutically acceptable excipient is a diluent, buffering agent, suspending agent, solubilizer, emulsifier, antioxidant, pH adjusting agent, preservative, detackifier, anti-foaming agent, chelating agent, thickening agent, viscomodulator, tonicifier, colorant, opacifier, binder, filler, plasticizer, or any combination thereof.
29. The composition of claim 28, wherein the at least one pharmaceutically acceptable excipient is a suspending agent, a wetting agent, a pH adjuster, an anti-oxidant, an osmotic pressure regulator, or any combination thereof.
30. The composition of claim 29, wherein the suspending agent is a polymer.
31. The composition of claim 29 or 30, wherein the suspending agent is a carbomer homopolymer, carbomer copolymer, carbomer interpolymer, polycarbophil, a cellulose derivative, a polyvinyl alcohol, a povidone, a hyaluronic acid or a salt thereof, chondroitin sulfate, a natural gum, or any combination thereof.
32. The composition of claim 31, wherein the cellulose derivative is hydroxypropyl methylcellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, or any combination thereof.

33. The composition of claim 32, wherein the hydroxypropyl methylcellulose (HPMC) is K100, K4M, K15M, K100M, E4M, E10M, or any combination thereof.
34. The composition of any one of claims 30-33, wherein the suspending agent is hydroxypropyl methylcellulose (HPMC).
35. The composition of claim 34, wherein the hypromellose is HPMC E4M.
36. The composition of any one of claims 30-35, wherein the concentration of the suspending agent in the compositions is up to about 1% w/w.
37. The composition of any one of claims 30-36, wherein the concentration of the suspending agent in the formulation is up to about 0.5% w/w.
38. The composition of any one of claims 28-37, wherein the solubilizer is Kollophor® ELP, Kollophor® HS 15, or a combination thereof.
39. The composition of claim 38, wherein the solubilizer is Kollophor® HS 15.
40. The composition of claim 38 or 39, wherein the concentration of the solubilizer in the composition is up to about 5% w/w.
41. The composition of any one of claims 28-40, wherein the wetting agent is polyoxyl 15-hydroxystearate.
42. The composition of any one of claims 28-31, wherein the pH adjuster is a buffer.
43. The composition claim 42, wherein the buffer is a phosphate buffer or a hydrate thereof.
44. The composition claim 43, wherein the phosphate buffer is potassium phosphate or a hydrate thereof.
45. The composition of claim 44, wherein the phosphate buffer is sodium dihydrogen phosphate dihydrate ($\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$), di-sodium hydrogen phosphate dodecahydrate ($\text{Na}_2\text{HPO}_4 \cdot 12\text{H}_2\text{O}$), or a combination thereof.
46. The composition of any one of claims 28-45, wherein the osmotic pressure regulator is a salt.
47. The composition of claim 46, wherein the salt is sodium chloride.
48. The composition of claim 46 or 47, wherein the concentration of the osmotic pressure regulator in the composition is up to about 0.5% w/w.
49. The composition of any one of claims 28-48, wherein the anti-oxidant is a thiosulfate.
50. The composition of claim 49, wherein the thiosulfate is sodium thiosulfate.
51. The composition of claim 49 or 50, wherein the concentration of the anti-oxidant in the composition is up to about 0.2% w/w.

52. The composition of any one of claims 1-51, wherein the composition is stable for up to 24 months at a temperature of from about 20 °C to about 25 °C.
53. The composition of any one of claims 1-52, wherein the composition is substantially free of impurities.
54. The composition of any one of claims 1-53, wherein the composition is at least about 90% pure.
55. The composition of any one of claims 1-54, wherein the composition is at least about 95% pure.
56. The composition of any one of claims 1-55, wherein the composition is at least about 96% pure.
57. The composition of any one of claims 1-56, wherein the composition is at least about 97% pure.
58. The composition of any one of claims 1-57, wherein the composition is at least about 98% pure.
59. The composition of any one of claims 1-58, wherein the composition is at least about 99% pure.
60. The composition of any one of claims 1-59, wherein the composition is at least about 99.1%, about 99.2%, about 99.3%, about 99.4%, about 99.5%, about 99.6%, about 99.7%, about 99.8%, about 99.9%, or about 100% pure.
61. The composition of any one of claims 1-59, wherein the composition comprises up to about 2% w/w of total impurities.
62. The composition of any one of claims 1-59, wherein the composition comprises less than about 0.9% w/w, about 0.8% w/w, about 0.7% w/w, about 0.6% w/w, about 0.5% w/w, about 0.4% w/w, about 0.3% w/w, about 0.2% w/w, or about 0.1% w/w of total impurities.
63. The composition of claim 61 or 62, wherein the impurity is a degradant.
64. The composition of any one of claims 61-63, wherein the impurity comprises the compound of Formula (II):



65. The composition of any one of claims 1-59, the composition comprises up to about 2.0% w/w of any individual impurity.
66. The composition of any one of claims 1-65, wherein the composition has a pH of from about 4.0 to about 9.0.
67. The composition of any one of claims 1-65, wherein the composition has a pH of from about 5.0 to about 8.0.
68. The composition of any one of claims 1-62, wherein the composition has a pH of from about 6.5 to about 8.0.
69. The composition of any one of claims 66-68, wherein the composition has a pH of from about 7.0 to about 8.0.
70. A method of preparing the composition of any one of claims 1-69, comprising:
- (i) micronizing the compound of Formula (I), or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof;
 - (ii) sterilizing the micronized compound of Formula (I), or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof; and
 - (iii) admixing a therapeutically effective amount of the compound of Formula (I), or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof with the least one pharmaceutically acceptable excipients.
71. The method of claim 70, wherein a suspension comprising particles of the compound of Formula (I), or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof is formed.
72. The method of claim 70 or 71, wherein the sterilization is performed before the admixing.
73. The method of claim 70 or 71, wherein the sterilization is performed after the admixing.
74. The method of any one of claims 70-73, wherein the sterilization is performed at a temperature of about 121 °C.
75. The method of any one of claims 70-74, wherein the sterilization is performed for a period of from about 20 to about 30 minutes.
76. A method for treating a disease or disorder associated with the abnormal proliferation of angiogenesis, comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-69.
77. The method of claim 76, wherein the disease or disorder associated with the abnormal proliferation of angiogenesis is caused by an abnormality of VEGFR2.

78. The method of claim 76, wherein the abnormal proliferation of angiogenesis is ocular angiogenesis.
79. The method of claim 76, wherein the abnormal proliferation of angiogenesis is choroidal angiogenesis.
80. The method according to claim 19, wherein the disease or disorder is wet macular degeneration, diabetic retinopathy or neovascular glaucoma, and the diseases associated with the abnormal proliferation of angiogenesis are wet macular degeneration, diabetic retinopathy or neovascular glaucoma.
81. A method for treating a disease or disorder caused by the abnormal protein kinases, comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-69.
82. The method of claim 81, wherein the protein kinase is VEGFR2, PDGFR- β , KIT, AURORA-B, FGFR2, SRC, JAK2 or P38- α .
83. The method of claim 82, wherein the protein kinase is VEGFR2, KIT or PDGFR- β .
84. A method of treating or preventing a disorder or disease, comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-69, wherein the disorder or disease is a neovascular disorder or disease, inflammatory disorder or disease, or a cancer.
85. A method of treating or preventing an ophthalmic disorder or disease, comprising administering to an eye of a subject in need thereof a therapeutically effective amount of the pharmaceutical composition of any one of claims 1-69.
86. The method of claim 85, wherein the ophthalmic disorder or disease affects function, clarity, and/or structure of the lens of the eye.
87. The method of claim 85, wherein the ophthalmic disorder or disease is wet macular degeneration, cataracts, presbyopia, nuclear sclerosis of the eye lens, Refsum disease, Smith-Lemli-Opitz syndrome (SLOS), Schnyder crystalline corneal dystrophy (SCCD), abetalipoproteinemia, familial hypobetalipoproteinemia, neovascularization, or cancer.
88. The method of claim 87, wherein the neovascularization is corneal neovascularization, iris neovascularization, or choroidal neovascularization.
89. The method of claim 88, wherein the ophthalmic disorder or disease is corneal neovascularization.

90. The method of any one of claims 76-89, wherein the subject has undergone a surgical procedure for treatment of the ophthalmic disorder or disease.
91. The method of any one of claims 76-90, wherein about 0.005 mg/mL to about 5.0 mg/mL of a pharmaceutical composition comprising the compound of Formula (I), or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof is administered to the eye of the subject.
92. The method of any one of claims 76-90, wherein about 0.01 mg/mL to about 4.0 mg/mL of a pharmaceutical composition comprising the compound of Formula (I), or an isotopic variant, tautomer, pharmaceutically acceptable salt, solvate, or hydrate thereof is administered to the eye of the subject.
93. The method of any one of claims 76-92, wherein the composition is administered the subject once per day, twice per day, three times per day, or four times per day.
94. The method of any one of claims 76-93, wherein the composition is administered the subject three times per day.
95. The method of any one of claims 76-94, wherein the administration is topical or by injection.