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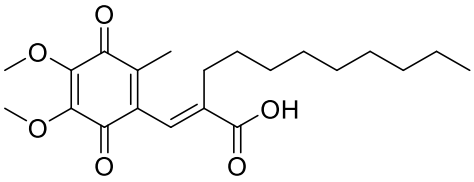
Improved dosing procedures for treating diabetic retinopathy, diabetic macular edema, and/or other diabetic retinal disorders and/or other disorders using the foregoing compound would benefit patients.

[0005] The present invention addresses this need and provides other related advantages.

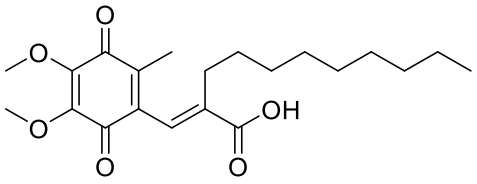
SUMMARY

[0005a] In a first aspect of the present disclosure, there is provided a use of a first therapeutic agent in the manufacture of a medicament for treating a diabetic retinal disease in a human patient, wherein about 480 mg to about 600 mg of the first therapeutic agent is to be orally administered to the human patient per day to thereby treat the diabetic retinal disease, and wherein the first therapeutic agent is a compound of Formula I or a pharmaceutically acceptable salt thereof:



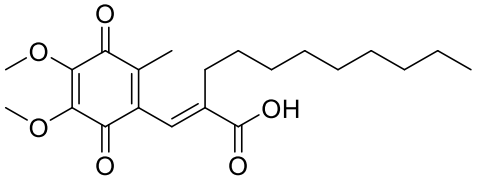
(I).

[0005b] In another aspect of the present disclosure, there is provided a use of a first therapeutic agent in the manufacture of a medicament for treating a diabetic retinal disease in a human patient, wherein from about 120 mg to about 600 mg of the first therapeutic agent is to be orally administered to the human patient per day to thereby treat the diabetic retinal disease, and wherein the first therapeutic agent is a compound of Formula I or a pharmaceutically acceptable salt thereof:



(I).

[0005c] In yet another aspect of the present disclosure, there is provided a use of a first therapeutic agent in the manufacture of a medicament for treating a disease or condition selected from wet age-related macular degeneration, dry age-related macular degeneration, retinal vein occlusion, geographic atrophy, retinal neovascularization, choroidal neovascularization, or corneal graft rejection, wherein from about 120 mg to about 600 mg of the first therapeutic agent is to be administered to the human patient per day to thereby treat the disease or condition, and wherein the first therapeutic agent is a compound of Formula I or a pharmaceutically acceptable salt thereof:



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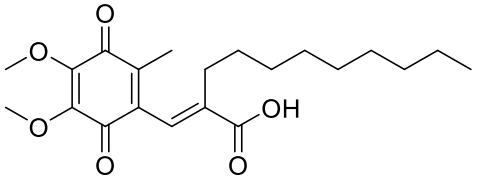
[0006] The present disclosure provides methods, compositions, and kits containing a first therapeutic agent that is a substituted 2,3-dimethoxyquinone of Formula I, or a pharmaceutically acceptable salt thereof, for treating patients suffering from diabetic retinopathy, diabetic macular edema, and/or other diabetic retinal disorders and/or other disorders. The methods generally comprise orally administering to a human patient in need thereof an amount of from about 120 mg to about 600 mg per day of a compound of Formula I or a pharmaceutically acceptable salt thereof:



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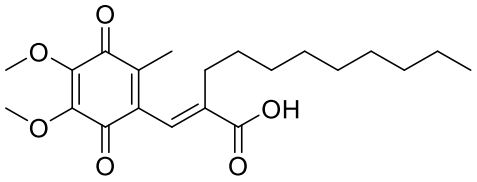
Exemplary more preferred examples comprise orally administering to a human patient in need thereof an amount of from about 480 mg to about 600 mg per day of a compound of Formula I or pharmaceutically acceptable salt thereof. Improvement in the patient's diabetic retinal disorder can be evaluated according to improvement in the patient's Diabetic Retinopathy Severity Score (DRSS), improvement in the patient's visual acuity, and other procedures described in the literature. Additional exemplary examples and examples of the present disclosure are described below.

[0007] One example of the present disclosure provides a method of treating a diabetic retinal disease in a human patient. The method comprises orally administering to a human patient in need thereof

a first therapeutic agent in an amount of from about 480 mg to about 600 mg per day, to thereby treat the diabetic retinal disease, wherein the first therapeutic agent is a compound of Formula I or a pharmaceutically acceptable salt thereof:



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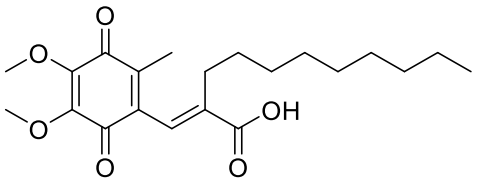
In certain examples, a first dose of the first therapeutic agent and a second dose of the first therapeutic agent are orally administered to the patient on the same day. In certain examples, the method further comprises administering to the patient a second therapeutic agent that is a vascular endothelial growth factor inhibitor. In certain examples, the diabetic retinal disease is diabetic retinopathy. In certain examples, the diabetic retinal disease is diabetic macular edema. Additional features of the method are described in the detailed description.

[0008] Another example of the present disclosure provides a method of treating a diabetic retinal disease in a human patient. The method comprises orally administering to a human patient in need thereof a first therapeutic agent in an amount of from about 120 mg to about 600 mg per day, to thereby treat the diabetic retinal disease, wherein the first therapeutic agent is a compound of Formula I or a pharmaceutically acceptable salt thereof:

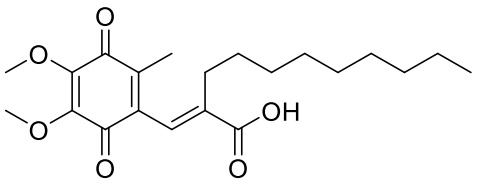


(I).

In certain examples, a first dose of the first therapeutic agent and a second dose of the first therapeutic agent are orally administered to the patient on the same day. In certain examples, the method further comprises administering to the patient a second therapeutic agent that is a vascular endothelial growth factor inhibitor. In certain examples, the diabetic retinal disease is diabetic retinopathy. In certain examples, the diabetic retinal disease is diabetic macular edema. Additional features of the method are described in the detailed description.

[0009] Another example of the present disclosure provides a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, for use in treating a diabetic retinal disease in a human patient according to a method described herein. Preferably, the pharmaceutical composition is formulated for oral administration.

[0010] Another example of the present disclosure provides a method of treating a disease or condition selected from wet age-related macular degeneration, dry age-related macular degeneration, retinal vein occlusion, geographic atrophy, retinal neovascularization, choroidal neovascularization, or corneal graft rejection. The method comprises orally administering to a human patient in need thereof a first therapeutic agent in an amount of from about 120 mg to about 600 mg per day, to thereby treat the disease or condition, wherein the first therapeutic agent is a compound of Formula I or a pharmaceutically acceptable salt thereof:



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BRIEF DESCRIPTION OF FIGURES

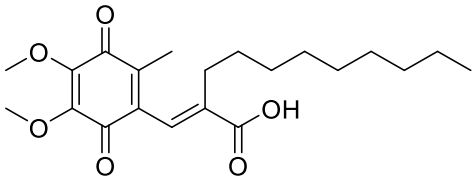
[0011] **Figure 1** depicts exemplary diabetic retinopathy severity scores (DRSS) and corresponding descriptions and retinal images.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The invention provides methods, compositions, and kits containing a first therapeutic agent that is a substituted 2,3-dimethoxyquinone of Formula I, or a pharmaceutically acceptable salt thereof, for treating patients suffering from diabetic retinopathy, diabetic macular edema, and/or other diabetic retinal disorders and/or other disorders. The methods generally comprise orally administering to a human patient in need thereof an amount of from about 120 mg to about 600 mg per day of a compound of Formula I or a pharmaceutically acceptable salt thereof:

Claims:

1. Use of a first therapeutic agent in the manufacture of a medicament for treating a diabetic retinal disease in a human patient, wherein about 480 mg to about 600 mg of the first therapeutic agent is to be orally administered to the human patient per day to thereby treat the diabetic retinal disease, and wherein the first therapeutic agent is a compound of Formula I or a pharmaceutically acceptable salt thereof:



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2. The use of claim 1, wherein the first therapeutic agent is a compound of Formula I.

3. The use of claim 1 or 2, wherein a first dose of the first therapeutic agent and a second dose of the first therapeutic agent are to be orally administered to the patient on the same day.

4. The use of any one of claims 1-3, wherein about 600 mg of the first therapeutic agent is to be orally administered to the patient per day.

5. The use of claim 1 or 2, wherein about 360 mg of the first therapeutic agent is to be orally administered to the patient in the morning, and about 240 mg of the first therapeutic agent is to be orally administered to the patient in the evening.

6. The use of claim 1 or 2, wherein about 360 mg of the first therapeutic agent is to be orally administered to the patient, and then at a time that is from about 8 hours to about 16 hours later about 240 mg of the first therapeutic agent is to be orally administered to the patient.

7. The use of claim 1 or 2, wherein about 240 mg of the first therapeutic agent is to be orally administered to the patient in the morning, and about 360 mg of the first therapeutic agent is to be orally administered to the patient in the evening.

8. The use of claim 1 or 2, wherein about 240 mg of the first therapeutic agent is to be orally administered to the patient, and then at a time that is from about 8 hours to about 16 hours later about 360 mg of the first therapeutic agent is to be orally administered to the patient.

9. The use of claim 1 or 2, wherein about 300 mg of the first therapeutic agent is to be orally administered to the patient in the morning, and about 300 mg of the first therapeutic agent is to be orally administered to the patient in the evening.

10. The use of claim 1 or 2, wherein about 300 mg of the first therapeutic agent is to be orally administered to the patient, and then at a time that is from about 8 hours to about 16 hours later about 300 mg of the first therapeutic agent is to be orally administered to the patient.

11. The use of any one of claims 1-10, wherein if the patient experiences an adverse event due to the first therapeutic agent, then thereafter for a period of at least two days a reduced-daily amount of about 480 mg of the first therapeutic agent is to be orally administered to the patient per day.

12. The use of any one of claims 1-3, wherein about 480 mg of the first therapeutic agent is to be orally administered to a patient per day.

13. The use of claim 11 or 12, wherein about 240 mg of the first therapeutic agent is to be orally administered to the patient in the morning, and about 240 mg of the first therapeutic agent is to be orally administered to the patient in the evening.

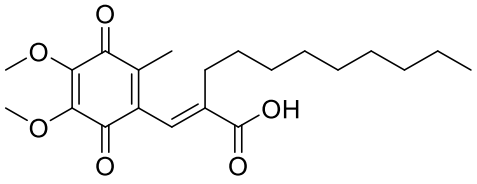
14. The use of claim 11 or 12, wherein about 240 mg of the first therapeutic agent is to be orally administered to the patient, and then at a time that is from about 8 hours to about 16 hours later about 240 mg of the first therapeutic agent is to be orally administered to the patient.

15. The use of any one of claims 1-10, wherein if the patient experiences an adverse event due to the first therapeutic agent, then thereafter for a period of at least two days a reduced-daily amount of about 300 mg of the first therapeutic agent is to be orally administered to the patient per day.

16. The use of claim 15, wherein the first therapeutic agent is to be orally administered to the patient in the morning.

17. Use of a first therapeutic agent in the manufacture of a medicament for treating a diabetic retinal disease in a human patient, wherein from about 120 mg to about 600 mg of the first therapeutic agent is to be orally administered to the human patient per day to thereby treat the diabetic retinal disease,

and wherein the first therapeutic agent is a compound of Formula I or a pharmaceutically acceptable salt thereof:



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18. The use of any one of claims 1-17, wherein the amount of the first therapeutic agent is to be orally administered to the patient daily for at least 4 weeks.

19. The use of any one of claims 1-17, wherein the amount of the first therapeutic agent is to be orally administered to the patient daily for at least 12 weeks.

20. The use of any one of claims 1-17, wherein the amount of the first therapeutic agent is to be orally administered to the patient daily for at least 24 weeks.

21. The use of any one of claims 1-20, wherein the first therapeutic agent is to be orally administered to the patient in the form of an extended-release pharmaceutical composition.

22. The use of any one of claims 1-21, wherein a second therapeutic agent that is an anti-inflammatory agent, anti-angiogenic agent, tyrosine kinase inhibitor, angiopoietin-2 inhibitor, and/or vascular endothelial growth factor inhibitor is to be further administered.

23. The use of any one of claims 1-21, wherein a second therapeutic agent that is a vascular endothelial growth factor inhibitor is to be further administered.

24. The use of any one of claims 1-23, wherein the diabetic retinal disease is diabetic retinopathy.

25. The use of claim 24, wherein the diabetic retinopathy is mild diabetic retinopathy.

26. The use of claim 24, wherein the diabetic retinopathy is moderate diabetic retinopathy.

27. The use of claim 24, wherein the diabetic retinopathy is moderately severe to severe diabetic retinopathy.

28. The use of any one of claims 24-27, wherein the diabetic retinopathy is non-proliferative diabetic retinopathy.

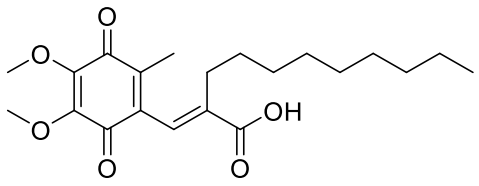
29. The use of any one of claims 24-27, wherein the diabetic retinopathy is proliferative diabetic retinopathy.

30. The use of any one of claims 1-23, wherein the diabetic retinal disease is diabetic macular edema.

31. The use of any one of claims 1-30, wherein the human patient is an adult human patient.

32. The use of any one of claims 1-30, wherein the first therapeutic agent reduces a symptom of diabetes.

33. Use of a first therapeutic agent in the manufacture of a medicament for treating a disease or condition selected from wet age-related macular degeneration, dry age-related macular degeneration, retinal vein occlusion, geographic atrophy, retinal neovascularization, choroidal neovascularization, or corneal graft rejection, wherein from about 120 mg to about 600 mg of the first therapeutic agent is to be administered to the human patient per day to thereby treat the disease or condition, and wherein the first therapeutic agent is a compound of Formula I or a pharmaceutically acceptable salt thereof:



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34. The use of claim 33, wherein the first therapeutic agent is a compound of Formula I.

35. The use of claim 33 or 34, wherein about 600 mg of the first therapeutic agent is to be orally administered to the patient per day.

36. The use of claim 33 or 34, wherein about 480 mg of the first therapeutic agent is to be orally administered to the patient per day.

37. The use of any one of claims 33-36, wherein a first dose of the first therapeutic agent and a second dose of the first therapeutic agent are to be orally administered to the patient on the same day.

38. The use of any one of claims 33-37, wherein the first therapeutic agent is to be orally administered to the patient in the morning.

39. The use of any one of claims 33-38, wherein the first therapeutic agent is to be orally administered to the patient in the evening.

40. The use of any one of claims 1-39, wherein the first therapeutic agent reduces any renal impairment experienced by the patient.

41. The use of any one of claims 1-40, wherein the first therapeutic agent achieves a neuroprotective effect.

42. The use of any one of claims 1-41, wherein any increase in blood plasma concentration of alanine aminotransferase due to the first therapeutic agent is no greater than 5%.

43. The use of any one of claims 1-42, wherein any increase in blood plasma concentration of aspartate aminotransferase due to the first therapeutic agent is no greater than 5%.

44. The use of any one of claims 1-43 wherein any reduction in glomerular filtration rate in the patient is no greater than 15%.

45. The use of any one of claims 1-44, wherein the incidence of any eye disorder due to the first therapeutic agent occurs no more frequently than one patient for every ten patients subjected to the same treatment.

46. The use of any one of claims 1-45, wherein the incidence of any eye disorder due to the first therapeutic agent occurs no more frequently than one patient for every twenty patients subjected to the same treatment.

47. The use of any one of claims 1-46, wherein the incidence of any gastrointestinal disorder due to the first therapeutic agent occurs no more frequently than one patient for every ten patients subjected to the same treatment.

48. The use of any one of claims 1-47, wherein the incidence of any nervous system disorder due to the first therapeutic agent occurs no more frequently than one patient for every twenty patients subjected to the same treatment.

49. The use of any one of claims 1-48, further characterized by achieving a reduction in blood plasma concentration of alanine aminotransferase due to the first therapeutic agent.

50. The use of any one of claims 1-49, further characterized by achieving a reduction in blood plasma concentration of aspartate aminotransferase due to the first therapeutic agent.