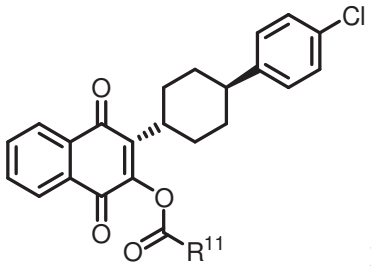
BRIEF SUMMARY OF THE INVENTION

[0005a] In one aspect provided herein is pharmaceutical composition comprising:

(i) an oil; and

(ii) a compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (III)

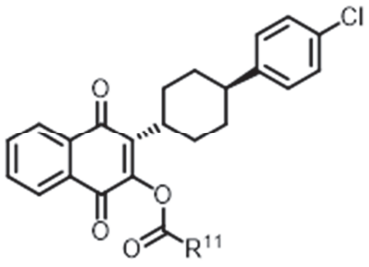
wherein:

R^{11} is a C_1-C_6 alkyl.

[0005b] In one aspect provided herein is the use of a pharmaceutical composition as described herein for the preparation of a medicament for treatment or prevention of malaria, wherein the medicament is to be administered to the subject.

[0005c] In one aspect provided herein is the use of an effective amount of a compound as described herein in the manufacture of a medicament for killing or inhibiting the growth of a Plasmodium species such as Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, or Plasmodium knowlesi.

[0005d] In one aspect provided herein is a pharmaceutical suspension comprising nanoparticles or microparticles of a crystalline compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:

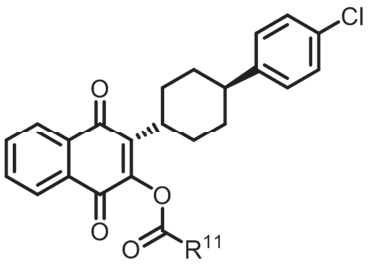


Formula (III)

wherein: R^{11} is C_1-C_6 alkyl.

[0005e] In one aspect provided herein is the use of a pharmaceutical suspension as described herein for the preparation of a medicament for treatment or prevention of malaria, wherein the medicament is to be administered to a subject.

[0005f] In one aspect provided herein is a compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:

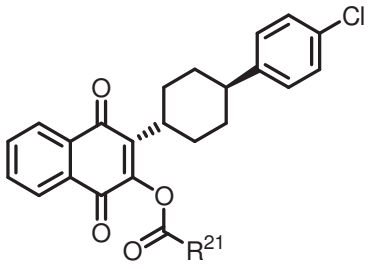


Formula (III)

wherein:

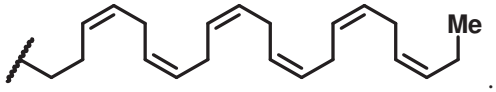
R^{11} is C_6 alkyl.

[0006] Described herein are compounds of Formula (IV) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



wherein R^{21} is optionally substituted C_3-C_{30}alkenyl or optionally substituted C_2-C_{30}alkynyl.

[0007] In a compound of Formula (IV), R^{21} may be C_3-C_{30}alkenyl. In a compound of Formula (IV), R^{21} may be C_6-C_{30}alkenyl. In a compound of Formula (IV), R^{21} may be C_6-C_{25}alkenyl. In a compound of Formula (IV), R^{21} may be C_{15}-C_{25}alkenyl. In a compound of Formula (IV), R^{21} may be



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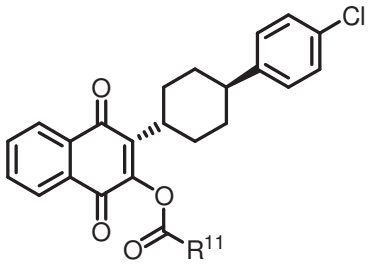
[0008] Also described herein is a pharmaceutical composition comprising:

(i) an oil; and

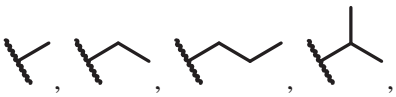
(ii) a compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (III)

wherein:

R^{11} is a lipophilic moiety.

[0009] In the pharmaceutical composition comprising a compound of Formula (III), R^{11} may be optionally substituted C_1-C_{30}alkyl, optionally substituted C_2-C_{30}alkenyl, or optionally substituted C_2-C_{30}alkynyl. In the pharmaceutical composition comprising a compound of Formula (III), R^{11} may be optionally substituted C_1-C_{20}alkyl, optionally substituted C_2-C_{20}alkenyl, or optionally substituted C_2-C_{20}alkynyl. In the pharmaceutical composition comprising a compound of Formula (III), R^{11} may be C_1-C_6alkyl. In the pharmaceutical composition comprising a compound of Formula (III), R^{11} may be C_7-C_{30}alkyl. In the pharmaceutical composition comprising a compound of Formula (III), R^{11} may be R^{11} is is ,

malaria, the compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, comprised in the pharmaceutical composition is released from the pharmaceutical composition at a rate providing an average concentration of trans-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione in the blood plasma of said subject of at least about 1000 nM over about 13 weeks. In the method for the treatment or prevention of malaria, the method may further comprise administering an additional antimalarial agent. In the method for the treatment or prevention of malaria, the additional antimalarial agent is selected from artemisinin, artemisinin derivatives, atovaquone, proguanil, quinine, chloroquine, amodiaquine, pyrimethamine, doxycycline, clindamycin, mefloquine, primaquine, pyronaridine, halofantrine, or ELQ-300.

[0012a] Described herein is the use of a compound described herein or a pharmaceutical composition described herein for the preparation of a medicament for treatment or prevention of malaria, wherein the medicament is to be administered to the subject.

[0013] Described herein are methods of killing or inhibiting the growth of a Plasmodium species comprising contacting the species with an effective amount of a compound of Formula (IV). In the method of killing or inhibiting the growth of a Plasmodium species, the Plasmodium species is Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, or Plasmodium knowlesi.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] **FIG. 1** depicts the exposure of ELQ-300 following PO or IM dosing with Compound 2.

[0015] **FIG. 2A** depicts the percent protection following a sporozoite challenge at day 14 following IM administration of Compound 2 (3, 10, and 30 mg/kg).

[0016] **FIG. 2B** depicts the exposure of ELQ-300 in mouse following IM administration of Compound 2 (3, 10, and 30 mg/kg).

[0017] **FIG. 3A** depicts the exposure of ELQ-300 in rat following IM administration of Compound 2 (3.72 mg/kg in sesame oil).

[0018] **FIG. 3B** depicts the plasma exposure of ELQ-300 and Compound 2 in dog following IM administration of Compound 2 (20 mg/mL, 3% TPGS, 1% HPMC E5 suspension).

[0019] **FIG. 4A** depicts the exposure of ELQ-300 in mouse following IM administration of Compound 2, 4, 8, 9, and 10 (3 mg/kg, 1.5 mg/mL in sesame oil).

[0020] **FIG. 4B** depicts the exposure of ELQ-300 in mouse following IM administration of Compound 12, 13, 14, 16, 17, and 18 (3 mg/kg, 1.5 mg/mL in sesame oil).

[0021] **FIG. 5** depicts the characteristic X-ray diffraction pattern of the crystalline ELQ-300-Form IA.

[0022] **FIG. 6** depicts the characteristic X-ray diffraction pattern of the crystalline ELQ-300-Form IB.

[0023] **FIG. 7** depicts the characteristic X-ray diffraction pattern of the crystalline ELQ-300-Form II (first preparation).

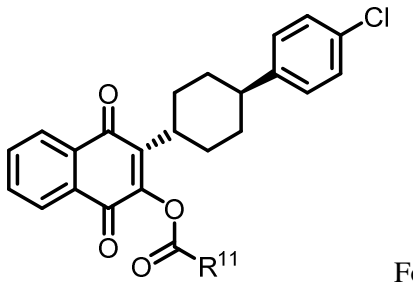
CLAIMS

We Claim:

1. A pharmaceutical composition comprising:

   (i) an oil; and

   (ii) a compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



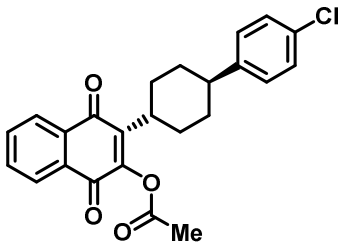
Formula (III)

   wherein:

   R^{11} is a C_1-C_6 alkyl.

2. The pharmaceutical composition of claim 1, wherein R^{11} is C_6 alkyl.

3. The pharmaceutical composition of claim 1, wherein the compound of Formula (III) is



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4. The pharmaceutical composition of any one of claims 1-3, wherein the oil is a vegetable oil.

5. The pharmaceutical composition of any one of claims 1-4, wherein the oil is selected from corn oil, peanut oil, sesame oil, olive oil, palm oil, safflower oil, soybean oil, cottonseed oil, rapeseed oil, sunflower oil and mixtures thereof.

6. The pharmaceutical composition of any one of claims 1-5, wherein the oil is sesame oil.

7. The pharmaceutical composition of any one of claims 1-6, wherein the concentration of the compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof is greater than about 50 mg/mL.

8. The pharmaceutical composition of any one of claims 1-7, wherein the concentration of the compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof is greater than about 100 mg/mL, in particular greater than about 200 mg/mL.

9. The pharmaceutical composition of any one of claims 1-6, wherein the concentration of the compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof is between about 20 mg/ml and about 300 mg/ml.

10. The pharmaceutical composition of any one of claims 1-9, further comprising surfactants, solubilizers, emulsifiers, preservatives, isotonicity agents, dispersing agents, wetting agents, fillers, solvents, buffers, stabilizers, lubricants, thickening agents, suspending agents, and any combinations thereof.

11. Use of a pharmaceutical composition of any one of claims 1-10 for the preparation of a medicament for treatment or prevention of malaria, wherein the medicament is to be administered to the subject.

12. The use of claim 11, wherein the medicament is to be administered by subcutaneous or intramuscular injection.

13. The use of claim 11 or 12, wherein the medicament is effective for sustained or controlled release.

14. The use of any one of claims 11-13, wherein the compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, comprised in the pharmaceutical composition is to be administered at a dose of about 5 to about 20 mg/day.

15. The use of any one of claims 11-14, wherein the compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, comprised in the pharmaceutical composition is released from the pharmaceutical composition over a period of a minimum of about 30 days after administration.

16. The use of any one of claims 11-15, wherein the compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, comprised in the pharmaceutical composition is released from the pharmaceutical composition at a rate providing an average concentration of trans-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-

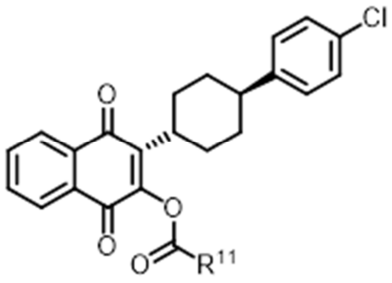
1,4-naphthalenedione in the blood plasma of said subject of at least about 200 nM, in particular of at least about 1000 nM over about 13 weeks.

17. The use of any one of claims 11-16, wherein said medicament is to be used in combination with an additional antimalarial agent.

18. The use of claim 17, wherein the additional antimalarial agent is selected from artemisinin, artemisinin derivatives, atovaquone, proguanil, quinine, chloroquine, amodiaquine, pyrimethamine, doxycycline, clindamycin, mefloquine, primaquine, pyronaridine, halofantrine, or ELQ-300.

19. Use of an effective amount of a compound of any one of claims 1-6 in the manufacture of a medicament for killing or inhibiting the growth of a Plasmodium species such as Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, or Plasmodium knowlesi.

20. A pharmaceutical suspension comprising nanoparticles or microparticles of a crystalline compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:

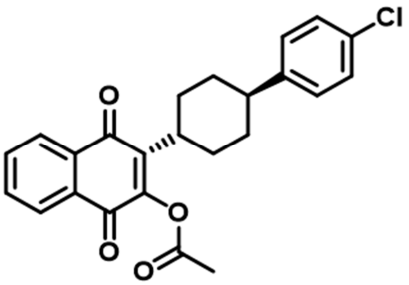


Formula (III)

wherein: R^{11} is C_1-C_6 alkyl.

21. The pharmaceutical suspension according to claim 20 wherein R^{11} is C_6 alkyl.

22. The pharmaceutical suspension according to claim 20, wherein the compound of Formula (III) is



or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

23. The pharmaceutical suspension according to any of claims 20-22, wherein the suspension comprises microparticles of a crystalline compound of Formula (III) with average particle size in the range of about 1 µm to about 50 µm.

24. The pharmaceutical suspension according to claim 23 wherein the suspension comprises microparticles of a crystalline compound of Formula (III) with average particle size in the range of about 5 µm to about 20 µm.

25. The pharmaceutical suspension according to any of claims 20-24, further comprising a pharmaceutically acceptable excipient selected from surfactants, solubilizers, emulsifiers, preservatives, isotonicity agents, dispersing agents, wetting agents, fillers, solvents, buffers, stabilizers, lubricants, thickening agents, suspending agents, and any combinations thereof.

26. The pharmaceutical suspension according to any one of claim 20-24, further comprising Synperonic® F108, dodecyl sodium sulfate (SLS), D-a-tocopheryl polyethylene glycol 1000 succinate (TPGS), hydroxypropyl methylcellulose (HPMC), and any combinations thereof.

27. The pharmaceutical suspension according to any one of claims 20-26, wherein the concentration of the crystalline compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof is between about 20 mg/mL and about 300 mg/mL.

28. The pharmaceutical suspension according to claim 27, wherein the concentration of the crystalline compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof is at least about 100 mg/mL.

29. Use of a pharmaceutical suspension of any one of claims 20-28 for the preparation of a medicament for treatment or prevention of malaria, wherein the medicament is to be administered to a subject.

30. The use of claim 29, wherein the pharmaceutical composition is to be administered by intramuscular injection.

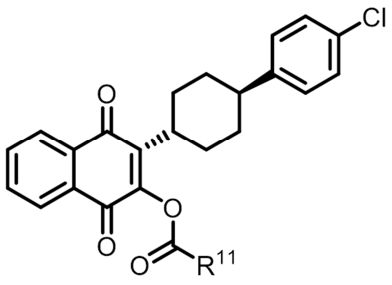
31. The use of any one of claims 29 or 30, wherein the pharmaceutical composition is effective for sustained or delayed release.

32. The use of any one of claims 29-31, wherein the compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof is released from the pharmaceutical suspension over a period of at least about twelve weeks after administration.

33. The use of any one of claims 29-31, wherein the compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof is released from the pharmaceutical suspension at a rate providing an average concentration of trans-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione in the blood plasma of said subject of at least about 200 nM, in particular of at least about 1000 nM, over about 13 weeks.

34. The use of any one of claims 29-31, wherein the compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof is to be administered with an additional antimalarial agent, in particular selected from artemisinin, artemisinin derivatives, proguanil, quinine, chloroquine, amodiaquine, pyrimethamine, doxycycline, clindamycin, mefloquine, primaquine, pyronaridine, halofantrine, or ELQ-300.

35. A compound of Formula (III) or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (III)

wherein:

R^{11} is C_6 alkyl.