wherein R^1, R^2, R^3 R^4, R^5, R^6, R^7 and R^8 are independently of each other selected from: H, Cl or F; wherein the pyrrolidinyl, morpholinyl or thiomorpholinyl dioxide heterocyclic groups are independently optionally substituted by one or more Cl, F or $-(C_1-C_3)$ alkyl groups; and

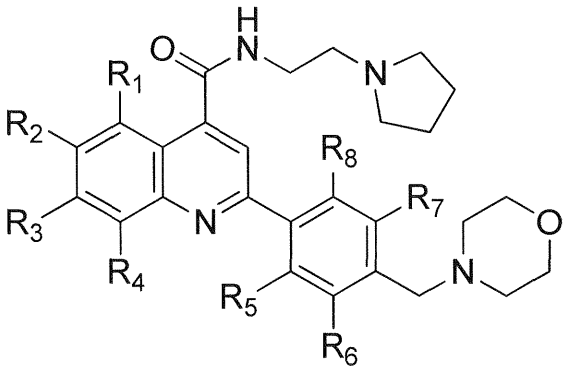
wherein X is –O- or $-SO_2-$;

or a pharmaceutically acceptable salt, hydrate, ~~solvate, isomer, prodrug~~ or polymorph thereof.

The present disclosure additionally provides compounds of formula (I) wherein wherein R^1, R^2, R^3 R^4, R^5, R^6, R^7 and R^8 are independently of each other selected from: H, Cl or F; wherein the pyrrolidinyl, morpholinyl or thiomorpholinyl dioxide heterocyclic groups are independently optionally substituted by one or more Cl, F or $-(C_1-C_3)$ alkyl groups; and

wherein X is –O- or $-SO_2-$; or a pharmaceutically acceptable salt, hydrate, ~~solvate, isomer, prodrug~~ or polymorph thereof.

Also disclosed are compounds of formula (I) wherein X is –O-, compounds of formula (IA):

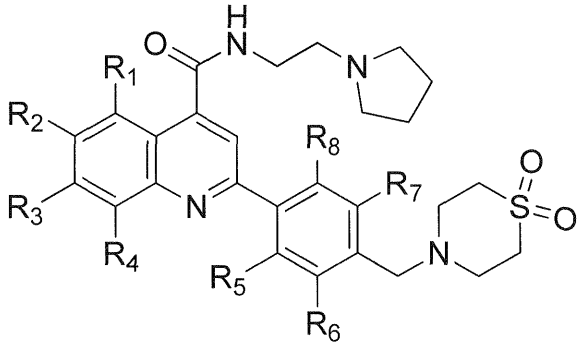


IA

or a pharmaceutically acceptable salt, hydrate, solvate, isomer, prodrug or polymorph thereof

wherein R^1, R^2, R^3 R^4, R^5, R^6, R^7 and R^8 are independently of each other selected from: H, Cl or F; and wherein the pyrrolidinyl or morpholinyl groups are independently optionally substituted by one or more Cl, F or $-(C_1-C_3)$ alkyl groups.

Also disclosed are compounds of formula (I) wherein X is $–SO_2-$, compounds of formula (IB):



IB

or a pharmaceutically acceptable salt, hydrate, solvate, isomer, prodrug or polymorph thereof

wherein R^1, R^2, R^3 R^4, R^5, R^6, R^7 and R^8 are independently of each other selected from: H, Cl or F; and wherein the pyrrolidinyl or thiomorpholinyl dioxide groups are independently optionally substituted by one or more Cl, F or $–(C_1-C_3)$ alkyl groups.

In another aspect, there is provided a pharmaceutical composition comprising a compound of formula (I) or pharmaceutically acceptable, salt, ~~solvate,~~ hydrate, ~~isomer, prodrug~~ or poymorph thereof, according to any preceding claim, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

In another aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable, salt, ~~solvate,~~ hydrate, ~~isomer, prodrug~~ or polymorph thereof according to any one of claims 1 to 10 for use as a medicament.

In yet another aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable, salt, ~~solvate,~~ hydrate, ~~isomer, prodrug~~ or polymorph thereof according to any one of claims 1 to 10 for use in the treatment of malaria.

Description

For the avoidance of doubt, all definitions provided herein apply equally to general formula (I), (IA) and (IB) as detailed hereinbefore. As such, reference to compounds of formula (I) includes compounds of formula (IA) and (IB).

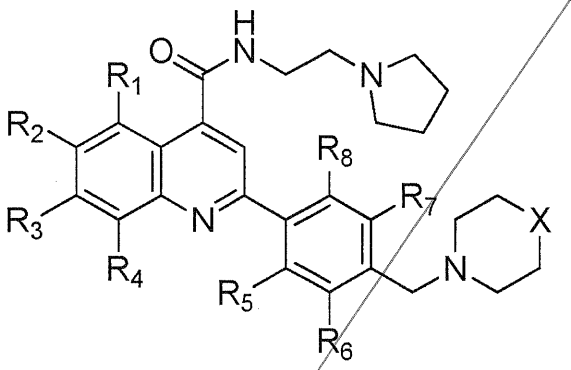
Scientific and technical terms used herein have the meanings with which they are commonly understood in the art unless specifically defined alternatively herein.

Where two or more moieties are described as being "each independently" selected from a list of atoms or groups, this means that the moieties may be the same or different. The identity of each moiety is therefore independent of the identities of the one or more other moieties.

In the above definitions, unless otherwise indicated, alkyl groups having two or more carbon atoms, may be unsaturated or saturated, and are preferably saturated; alkyl groups having three or more carbon atoms, may be straight chain or branched chain. For example, a C_3 alkyl substituent can be in the form of normal-propyl (*n*-propyl), or iso-

Claims

1. A compound of formula I



I

wherein R^1, R^2, R^3 R^4, R^5, R^6, R^7 and R^8 are independently of each other selected from: H, Cl or F; wherein the pyrrolidinyl, morpholinyl or thiomorpholinyl dioxide heterocyclic groups are independently optionally substituted by one or more Cl, F or –(C_1-C_3) alkyl groups; and

wherein X is –O- or -SO_2- ;

or a pharmaceutically acceptable salt, hydrate, solvate, isomer, polymorph, or pro-drug thereof.

2. A compound according to claim 1 wherein X is –O-.

3. A compound according claim 1 or 2 wherein R^1 and R^2 are independently selected from H or F.

4. A compound according claim 1 or 2 wherein R^1 and R^2 are independently selected from H or Cl.

5. A compound according any of claims 1 or 4 wherein R^3 and R^4 are each independently selected from H or F.

6. A compound according to any of claims 1 to 5 wherein the quinoline ring is mono- or di-substituted with F or Cl or a mixture thereof.

7. A compound according to any of claims 1 to 6 wherein the phenyl ring is mono-, di- or tri- substituted with F or Cl or a mixture thereof.

8. A compound according to any of claims 1 to 7 wherein the phenyl ring is mono-substituted and wherein R^5 and/or R^8 are each independently selected from H or F.

9. A compound according to any of claims 1 to 5 wherein R^3 R^4, R^5, R^6 and R^7 are independently selected from H or F.

10. A compound according to claim 1 independently selected from:

6-Fluoro-2-[4-(morpholinomethyl)phenyl]-N-(2-pyrrolidin-1-ylethyl)quinoline-4-carboxamide;
6-Fluoro-2-[4-(morpholinomethyl)phenyl]-N-(2-pyrrolidin-1-ylethyl)quinoline-4-carboxamide fumaric acid salt;
6-chloro-2-[4-(morpholinomethyl)phenyl]-N-(2-pyrrolidin-1-ylethyl)quinoline-4-carboxamide;
2-[4-(morpholinomethyl)phenyl]-*N*-(2-pyrrolidin-1-ylethyl)quinoline-4-carboxamide;
6-fluoro-2-(3-fluoro-4-(morpholinomethyl)phenyl)-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide;
2-[4-(morpholinomethyl)phenyl]-*N*-(2-pyrrolidin-1-ylethyl)quinoline-4-carboxamide fumaric acid salt;
6-fluoro-2-(2-fluoro-4-(morpholinomethyl)phenyl)-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide;
2-(3,5-difluoro-4-(morpholinomethyl)phenyl)-6-fluoro-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide;
2-(4-((1,1-dioxidothiomorpholino)methyl)phenyl)-6-fluoro-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide;
2-(2,6-difluoro-4-(morpholinomethyl)phenyl-6-fluoro-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide;

2-(2,3-difluoro-4-(morpholinomethyl)phenyl-6-fluoro-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide;
2-(2-chloro-4-(morpholinomethyl)phenyl)-6-fluoro-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide;
2-(2-chloro-4-(morpholinomethyl)phenyl)-6-fluoro-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide fumaric acid salt;
or a pharmaceutically acceptable salt, hydrate, solvate, isomer, pro-drug or polymorph thereof.

11. A compound according to any preceding claim having *Pf* 3D7 functional potency of less than about 0.1 micromolar (μM), preferably less than about 0.05 micromolar (μM).

12. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable, salt, solvate, hydrate, isomer, prodrug or poymorph thereof, according to any preceding claim, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

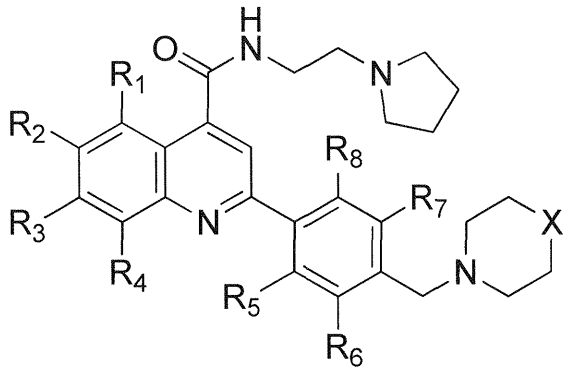
13. A pharmaceutical composition according to claim 11 including one or more additional therapeutic agents.

14. A compound of formula (I) or a pharmaceutically acceptable, salt, solvate, hydrate, isomer, prodrug or polymorph thereof according to any one of claims 1 to 10 for use as a medicament.

15. A compound of formula (I) or a pharmaceutically acceptable, salt, solvate, hydrate, isomer, prodrug or polymorph thereof according to any one of claims 1 to 10 for use in the treatment of malaria.

Claims

1. A compound of formula I



I

wherein R^1, R^2, R^3 R^4, R^5, R^6, R^7 and R^8 are independently of each other selected from: H, Cl or F; wherein the pyrrolidinyl, morpholinyl or thiomorpholinyl dioxide heterocyclic groups are independently optionally substituted by one or more Cl, F or $-(C_1\text{-}C_3)$ alkyl groups; and

wherein X is –O- or $-SO_2-$;

or a pharmaceutically acceptable salt, hydrate, or polymorph thereof.

2. A compound according to claim 1 wherein X is –O-.

3. A compound according claim 1 or 2 wherein R^1 and R^2 are independently selected from H or F.

4. A compound according claim 1 or 2 wherein R^1 and R^2 are independently selected from H or Cl.

5. A compound according any of claims 1 or 4 wherein R^3 and R^4 are each independently selected from H or F.

6. A compound according to any of claims 1 to 5 wherein the quinoline ring is mono- or di-substituted with F or Cl or a mixture thereof.

7. A compound according to any of claims 1 to 6 wherein the phenyl ring is mono-, di- or tri- substituted with F or Cl or a mixture thereof.

8. A compound according to any of claims 1 to 7 wherein the phenyl ring is mono-substituted and wherein R^5 and/or R^8 are each independently selected from H or F.

9. A compound according to any of claims 1 to 5 wherein R^3 R^4, R^5, R^6 and R^7 are independently selected from H or F.

10. A compound according to claim 1 independenly selected from:

6-Fluoro-2-[4-(morpholinomethyl)phenyl]-N-(2-pyrrolidin-1-ylethyl)quinoline-4-carboxamide;
6-Fluoro-2-[4-(morpholinomethyl)phenyl]-N-(2-pyrrolidin-1-ylethyl)quinoline-4-carboxamide fumaric acid salt;
6-chloro-2-[4-(morpholinomethyl)phenyl]-N-(2-pyrrolidin-1-ylethyl)quinoline-4-carboxamide;
2-[4-(morpholinomethyl)phenyl]-*N*-(2-pyrrolidin-1-ylethyl)quinoline-4-carboxamide;
6-fluoro-2-(3-fluoro-4-(morpholinomethyl)phenyl)-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide;
2-[4-(morpholinomethyl)phenyl]-*N*-(2-pyrrolidin-1-ylethyl)quinoline-4-carboxamide fumaric acid salt;
6-fluoro-2-(2-fluoro-4-(morpholinomethyl)phenyl)-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide;
2-(3,5-difluoro-4-(morpholinomethyl)phenyl)-6-fluoro-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide;
2-(4-((1,1-dioxidothiomorpholino)methyl)phenyl)-6-fluoro-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide;
2-(2,6-difluoro-4-(morpholinomethyl)phenyl-6-fluoro-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide;
2-(2,3-difluoro-4-(morpholinomethyl)phenyl-6-fluoro-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide;
2-(2-chloro-4-(morpholinomethyl)phenyl)-6-fluoro-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide;

2-(2-chloro-4-(morpholinomethyl)phenyl)-6-fluoro-N-(2-(pyrrolidin-1-yl)ethyl)quinoline-4-carboxamide fumaric acid salt;
or a pharmaceutically acceptable salt, hydrate, or polymorph thereof.

11. A compound according to any preceding claim having *Pf* 3D7 functional potency of less than about 0.1 micromolar (μM), preferably less than about 0.05 micromolar (μM).

12. A pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable, salt, hydrate, or polymorph thereof, according to any preceding claim, together with one or more pharmaceutically acceptable carriers, diluents or excipients.

13. A pharmaceutical composition according to claim 12 including one or more additional therapeutic agents.

14. A compound of formula (I) or a pharmaceutically acceptable, salt, hydrate, or polymorph thereof according to any one of claims 1 to 10 for use as a medicament.

15. A compound of formula (I) or a pharmaceutically acceptable, salt, hydrate, or polymorph thereof according to any one of claims 1 to 10 for use in the treatment of malaria.