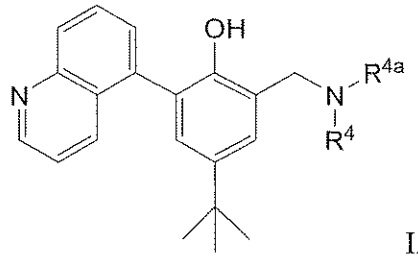
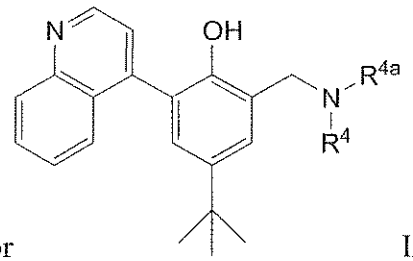


IA-6,

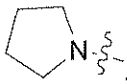


IA-7,



or IA-8,

wherein each quinolinyl or isoquinolinyl of IA-4, IA-5, IA-6, IA-7, or IA-8 is optionally substituted with 1, 2, or 3 R^5.

19. The compound of any one of claims 12 to 18, wherein each R^5 is independently $-CF_3$, F, Cl, Br, $-NH_2$, $-OC_{1-6}$alkyl, -CN, $-N(CH_3)_2$, , C_{1-10}alkyl, C_{1-10}alkylsulfonyl, or $-C_{3-6}$cycloalkyl.

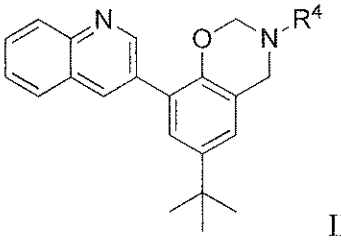
20. A pharmaceutical composition comprising a compound of any one of claims 1 to 19 and a pharmaceutically acceptable carrier or diluent.

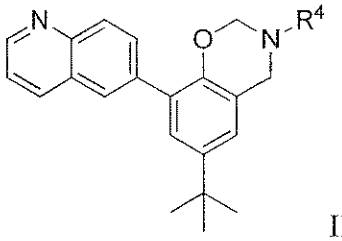
21. ~~A method for treating malaria in a patient comprising administering to the patient~~ Use of a compound of any one of claims claim 1 to 19 in the manufacture of a medicament for treating malaria in a patient.

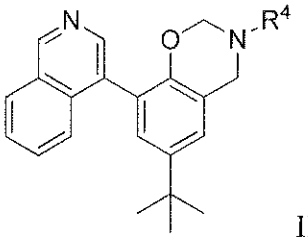
22. The ~~method~~ use according to claim 21 wherein the compound of Formula I is co-administered with at least one agent that is Amodiaquine, Arteether, Arteflene, Artemether, Artemisinin, Artesunate, Atovaquone, Chloroquine, Clindamycin, Dihydroartemisinin, Doxycycline, Halofantrine, Lumefantrine, Mefloquine, Pamaquine, Piperaquine, Primaquine, Proguanil, Pyrimethamine, Pyronaridine, Quinine, Tafenoquin, or a combination thereof.

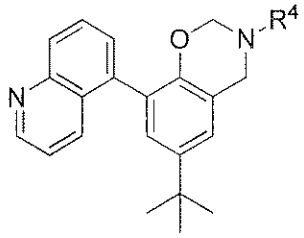
23. A compound of Formula II:

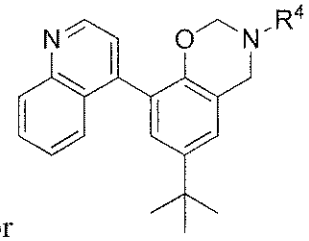
39. The compound of any one of claims 33 to 37, wherein the compound of formula IIA is:


IIA-4,

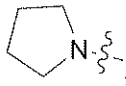

IIA-5,


IIA-6,


IIA-7, or


IIA-8,

wherein each quinolinyl or isoquinolinyl of IIA-4, IIA-5, IIA-6, IIA-7, or IIA-8 is optionally substituted with 1, 2, or 3 R^5.

40. The compound of any one of claims 33 to 39, wherein each R^5, if present, is $-CF_3$, F, Cl, Br, $-NH_2$, $-OC_{1-6}$alkyl, -CN, $-N(CH_3)_2$, , C_{1-10}alkyl, C_{1-10}alkylsulfonyl, or $-C_{3-6}$cycloalkyl.

41. A pharmaceutical composition comprising a compound of any one of claims 23 to 40 and a pharmaceutically acceptable carrier or diluent.

42. ~~A method for treating malaria in a patient comprising administering to the patient~~ Use of a compound of any one of claims claim 23 to 40 in the manufacture of a medicament for treating malaria in a patient.

43. The ~~method~~ use according to claim 42 wherein the compound of Formula II is co-administered with at least one agent that is Amodiaquine, Arteether, Arteflene, Artemether, Artemisinin, Artesunate, Atovaquone, Chloroquine, Clindamycin, Dihydroartemisinin, Doxycycline, Halofantrine, Lumefantrine, Mefloquine, Pamaquine, Piperaquine, Primaquine, Proguanil, Pyrimethamine, Pyronaridine, Quinine, Tafenoquin, or a combination thereof.

a significant problem in the treatment of malaria. The WHO recommends artemisinins in combination with other classes of antimalarials (artemisinin-based combination therapies (ACTs)) as the first line treatment for malaria caused by *P. falciparum*. The emergence of *P. falciparum* resistant to artemisinins, confirmed on the Cambodia-Thailand border in 2009 and suspected in parts of Myanmar and Vietnam, highlights the critical need for new malaria drugs from novel chemical classes.

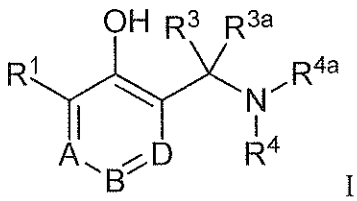
[0006] Since the original work of Burckhalter (Burckhalter, J. H., et al., J. Am. Chem. Soc. 1946, 68, 1894-1901 and J. Am. Chem. Soc. 1948, 70, 1363-1373), aminoalkyl phenols have been studied extensively as antimalarial agents (See Wiselogle, F. Y., Ed.; Survey of Antimalarial Drugs, 1941-1945, Vols. I and II, Edwards Bros., Ann Arbor, Mich., and Duncan, W. G., et al., J. Med. Chem. 1969, 12, 711-712). Optimization of the original α-(dialkylamino)-o-cresol template led to the identification of WR-194,965 (Schmidt, L. H., et al., Antimicrobial Agents and Chemotherapy 1978, 14, 672-679, Peters, W., et al., Annals of Tropical Medicine & Parasitology 1984, 78, 561-565, and 1984, 78, 567-579) which was profiled in human clinical trials (Karle, J. M., et al., Antimicrobial Agents and Chemotherapy 1988, 32, 540-546). Further modifications involved addition of the known antimalarial 4-aminoquinoline moiety to the aminoalkyl phenol template and led to the identification of antimalarial compounds such as Amodiaquine (Burckhalter, J. H., et al., J. Am. Chem. Soc. 1948, 70, 1363-1373) and Tebuquine (Werbel, L. M., et al., J. Med. Chem. 1986, 29, 924-939). Recently, 3,5-disubstituted-2-aminoalkylphenols with antimalarial activity have been reported (U.S. Pat. No. 7,589,127, issued Sep. 15, 2009 and Powles, M. A., et al., Antimicrobial Agents and Chemotherapy 2012, 56, 2414-2419).

[0007] New antimalarial compounds with exceptional potency, high activity against resistant strains, and good safety profiles are still needed.

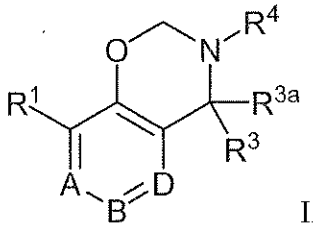
SUMMARY

[0008] The present ~~invention~~ disclosure relates to compounds and compositions for the treatment of malaria, including drug resistant malaria. The compounds of this ~~invention~~ disclosure are antiprotozoal agents effective *in vitro* and *in vivo* against protozoa of the genus Plasmodium (*P. falciparum, P. bergei*, etc.), the infectious agent responsible for malaria.

[0009] The present invention is directed in aspects to compounds of Formula I and Formula II:



I



II

and pharmaceutically acceptable salts, enantiomers, and diastereoisomers thereof, wherein

R^1 is heteroaryl attached through a carbon atom of the heteroaryl ring, optionally substituted with 1, 2, or 3 R^5;

A, B and D are independently are CH, CR^2 or N, provided that at least one of A, B, or D is CR^2;

R^2 is C_{1-10} alkyl, C_{1-10} haloalkyl, halo, cyano, C_{3-10} cycloalky, C_{1-6} alkylsulfonyl, C_{6-10} aryl, optionally substituted with 1, 2, or 3 R^5, or heteroaryl attached through a carbon atom of the heteroaryl ring optionally substituted with 1, 2, or 3 R^5;

R^3 and R^{3a} independently are hydrogen, C_{1-10} alkyl, C_{1-10} haloalkyl, or C_{3-10} cycloalkyl;

R^4 and R^{4a} independently are hydrogen, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{3-10} cycloalkyl, C_{1-10}alkC_{3-10}cycloalkyl, or C_{1-10}alkNR^7R^{7a}, wherein R^7 and R^{7a} are independently H or C_{1-10}alkyl; or

R^4 and R^{4a}, together with the nitrogen through which they are attached, form a heterocyclic ring of 4 to 7 ring atoms, where one carbon ring atom may be optionally replaced with NR^6, O, S, or SO_2, and where any carbon ring atom may be optionally substituted with C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, or C_{3-10} cycloalkyl;

each R^5 is independently halo, cyano, hydroxy, C_{1-10} alkyl, C_{1-10} haloalkyl, C_{1-10} alkoxy, C_{1-10} haloalkoxy, C_{3-10} cycloalky, C_{3-10} cycloalkoxy, amino, C_{1-10} alkylamino, C_{1-10} dialkylamino, C_{3-10} cycloalkyamino, pyrrolidinyl, C_{1-10} alkylsulfonyl, sulfamoyl, C_{1-10} alkylsulfamoyl or C_{1-10} dialkylsulfamoyl; and

R^6 is C_{1-10} alkyl, C_{1-10} haloalkyl, C_{3-10} cycloalkyl, or acetyl.

The present invention is directed in other aspects to pharmaceutical compositions comprising a compound as disclosed herein and a pharmaceutically acceptable carrier or diluent.

The present invention is directed in other aspects to the use of a compound as disclosed herein in the manufacture of a medicament for treating malaria in a patient.

Methods of treating malaria using compounds of the invention, as well as methods of making the compounds of the invention, are also described.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0010] It is to be understood that this invention is not limited to the specific products, methods, conditions or parameters described and / or shown herein, and that the terminology used herein is for the purpose of describing particular embodiments by way of example only and is not intended to be limiting of any claimed invention. Similarly, unless specifically stated otherwise, any description as to a possible mechanism or mode of action or reason for