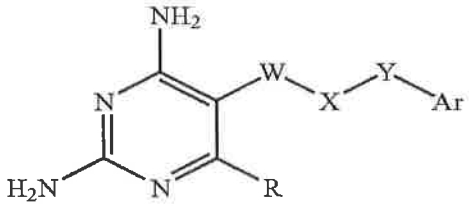
CLAIMS

We claim:

1. A compound of Formula I:

(I)



wherein R is hydrogen or C_{1-4} alkyl,

W—X—Y is $O(CH_2)_{2-4}O$; Ar is an optionally substituted aromatic ring selected from the group consisting of phenyl and naphthyl, or an optionally substituted heteroaromatic ring selected from the group consisting of quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pyridyl, indolyl, triazolyl, benzoxazolyl, benzimidazolyl, indolinyl and benzotriazolyl; wherein

when Ar is an aromatic ring, it is optionally substituted by at least one group selected from the group consisting of benzoxazolyl, carboxyl, carboxyalkylC(1-3), carboxyalkylC(1-3)oxy, alkylC(1-3)oxycarbonylalkylC(1-3), alkylC(1-3)oxycarbonylalkylC(1-3)oxy, tetrazolyl, tetrazolylalkylC(1-3) and tetrazolylalkylC(1-3)oxy; and Ar is optionally substituted by additional substituents; or a pharmaceutically acceptable salt or substituted derivative thereof.

2. The compound of claim **1**, wherein R is C_{1-4} alkyl.

3. The compound of claim **1**, wherein R is ethyl.

4. The compound of claim **1**, wherein Ar is substituted by at least one group selected from the group consisting of benzoxazolyl, nitro, carboxyl, carboxyalkylC(1-3), carboxyalkylC(1-3)oxy, alkylC(1-3)oxycarbonylalkylC(1-3), alkylC(1-3)oxycarbonylalkylC(1-3)oxy, tetrazolyl,

tetrazolylalkylC(1-3) and tetrazolylalkylC(1-3)oxy, Ar is further substituted at one or more available positions with at least one group selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, trifluoromethyl, aryl, substituted aryl, halogen, amino, substituted amino, alkoxy, aryloxy, hydroxyl and nitro.

5. The compound of claim **4**, wherein Ar is 4-quinolinyl or substituted 4-quinolinyl.

6. The compound of claim **1**, wherein R is ethyl, W—X—Y is $O(CH_2)_3O$ and Ar is quinolinyl or substituted 4-quinolinyl.

7. The compound of claim **2**, wherein Ar is substituted by at least one group selected from the group consisting of benzoxazolyl, nitro, carboxyl, carboxyalkylC(1-3), carboxyalkylC(1-3)oxy, alkylC(1-3)oxycarbonylalkylC(1-3), alkylC(1-3)oxycarbonylalkylC(1-3)oxy, tetrazolyl, tetrazolylalkylC(1-3) and tetrazolylalkylC(1-3)oxy, Ar is further substituted at one or more available positions with at least one group selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, trifluoromethyl, aryl, substituted aryl, halogen, amino, substituted amino, alkoxy, aryloxy, hydroxyl and nitro.

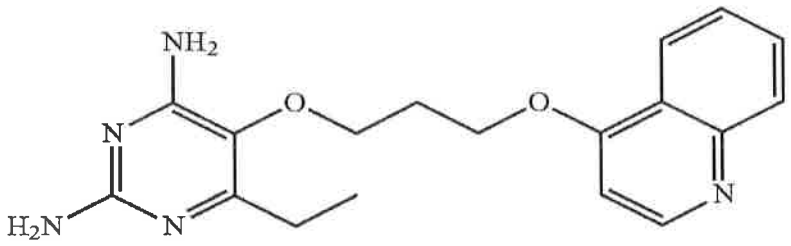
8. The compound of claim **1** wherein said Ar is quinolinyl or substituted 4-quinolinyl.

9. The compound of claim **3**, wherein Ar is substituted by at least one group selected from the group consisting of benzoxazolyl, nitro, carboxyl, carboxyalkylC(1-3), carboxyalkylC(1-3)oxy, alkylC(1-3)oxycarbonylalkylC(1-3), alkylC(1-3)oxycarbonylalkylC(1-3)oxy, tetrazolyl, tetrazolylalkylC(1-3) and tetrazolylalkylC(1-3)oxy, Ar is further substituted at one or more available positions with at least one group selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, trifluoromethyl, aryl, substituted aryl, halogen, amino, substituted amino, alkoxy, aryloxy, hydroxyl and nitro.

10. The compound of claim **9**, wherein said Ar is quinolinyl or substituted 4-quinolinyl.

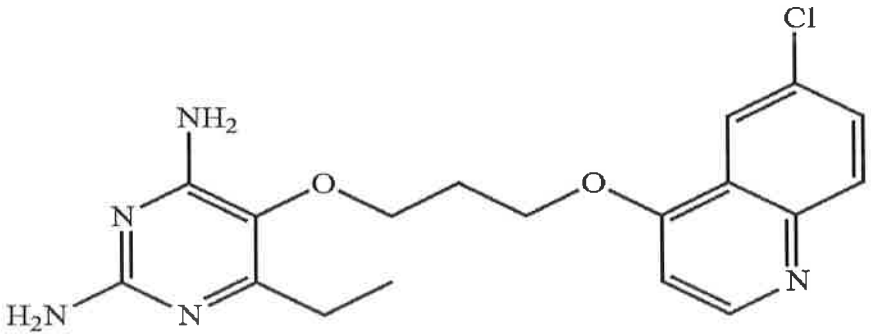
11. The compound of claim **4**, wherein W-X-Y is $O(XCH_2)_{2-4}O$.

12. The compound of claim **1**, wherein said compound is is the following compound or a pharmaceutically acceptable salt thereof of the following compound:



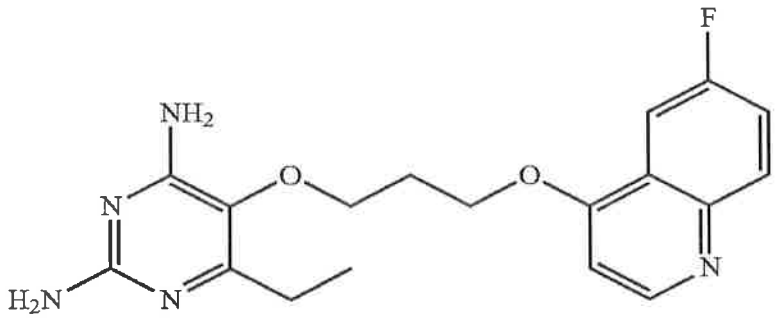
2,4-diamino-6-ethyl-5-(3-(quinolin-4-yloxy)propoxy)pyrimidine.

13. The compound of claim **1**, wherein said compound is the following compound, or a pharmaceutically acceptable salt thereof of the following compound:



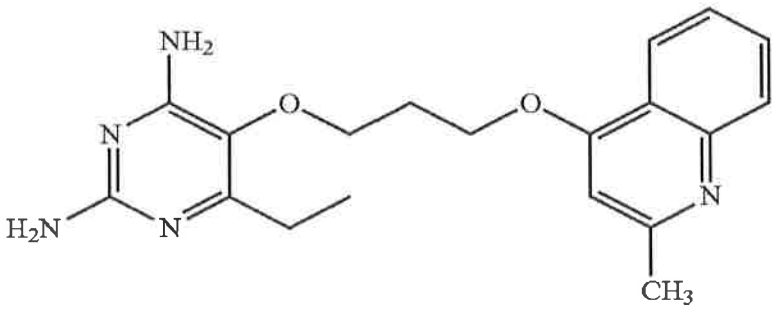
2,4-diamino-6-ethyl-5-(3-(6-chloro-quinolin-4-yloxy) propoxy)pyrimidine.

14. The compound of claim **1**, wherein said compound is as follows, or a pharmaceutically acceptable salt thereof of the following compound:



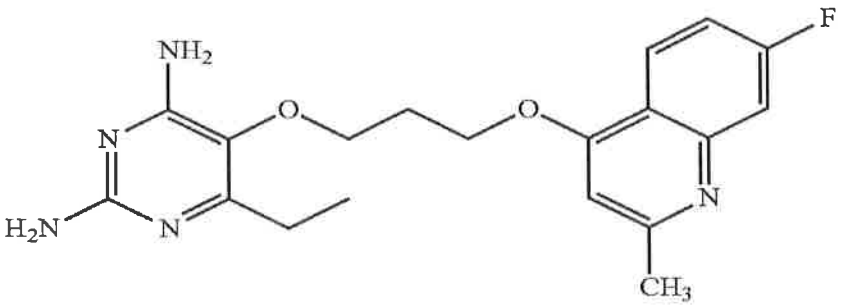
2,4-diamino-6-ethyl-5-(3-(6-fluoro-quinolin-4-yloxy) propoxy)pyrimidine.

15. The compound of claim **1**, wherein said compound is the following compound, or a pharmaceutically acceptable salt thereof of the following compound:



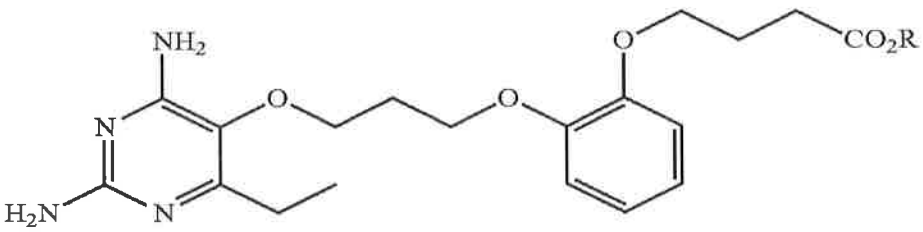
2,4-diamino-6-ethyl-5-(3-(2-methylquinolin-4-yloxy) propoxy)pyrimidine.

16. The compound of claim **1**, wherein said compound is the following compound, or a pharmaceutically acceptable salt thereof of the following compound:



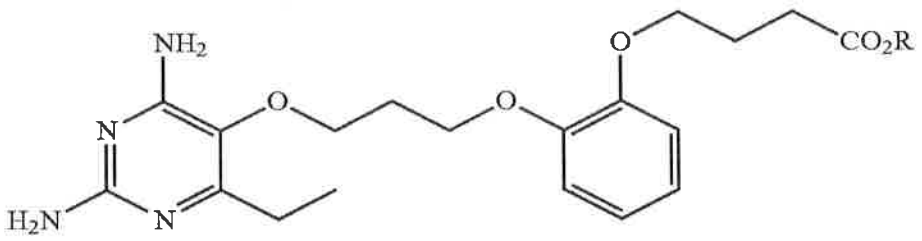
2,4-diamino-6-ethyl-5-(3-(7-fluoro-2-methylquinolin-4-yloxy)propoxy)pyrimidine.

17. The compound of claim **1**, wherein said compound is the following compound, or a pharmaceutically acceptable salt thereof of the following compound:



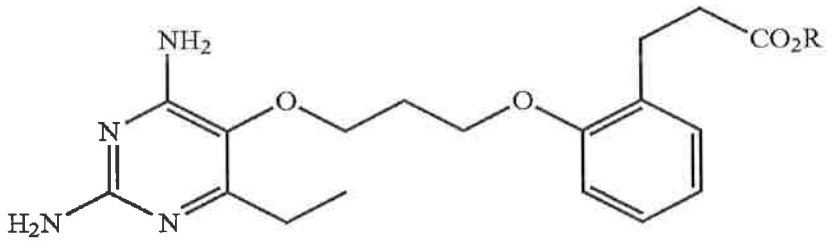
2,4-diamino-6-ethyl-5-(3-(2-(3-carboxypropoxy)phenoxy)propoxy)pyrimidine, wherein R is H.

18. The compound of claim **1**, wherein said compound is the following compound or a pharmaceutically acceptable salt thereof of the following compound:



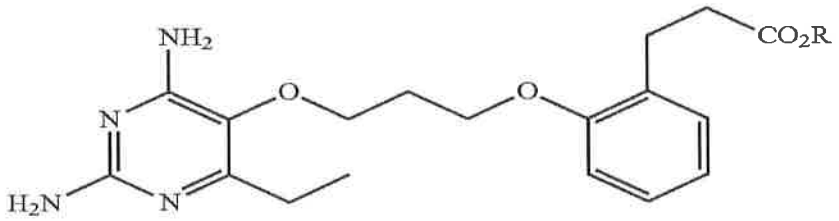
2,4-diamino-6-ethyl-5-(3-(2-(3-carboxypropoxy)phenoxy)propoxy)pyrimidine ethyl ester, wherein R is Et.

19. The compound of claim **1**, wherein said compound is the following compound, or a pharmaceutically acceptable salt thereof:



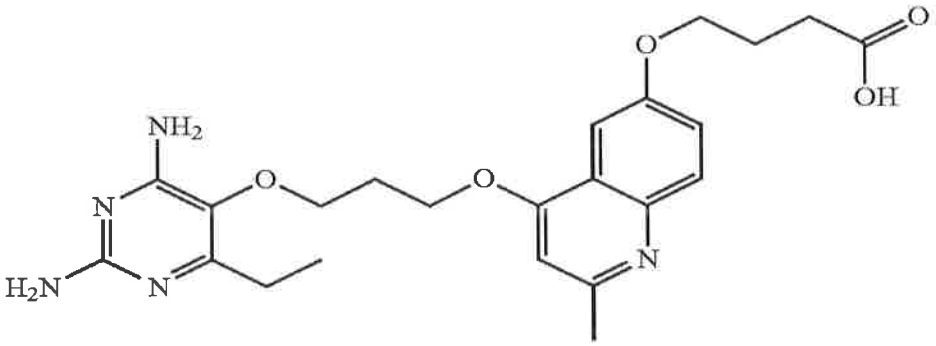
2,4-diamino-6-ethyl-5-(3-(2-(2-carboxyethyl)phenoxy)propoxy)pyrimidine ethyl ester, wherein R is Et.

20. The compound of claim **1**, wherein said compound is the following compound, or a pharmaceutically acceptable salt thereof of the following compound:



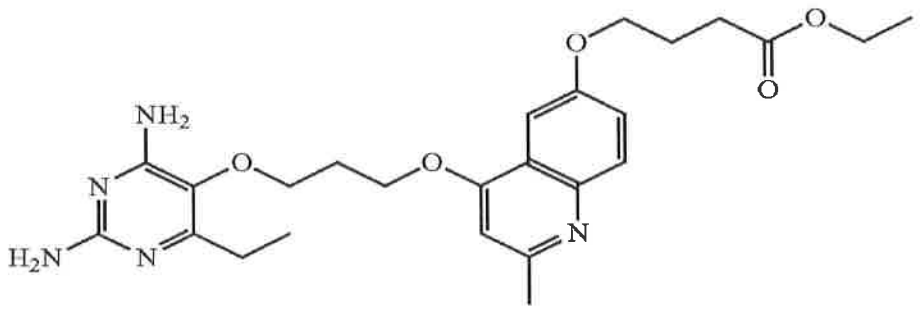
2,4-diamino-6-ethyl-5-(3-(2-(2-carboxyethyl)phenoxy) propoxy)pyrimidine, wherein R is H.

21. The compound of claim **1**, wherein said compound is the following compound, or a pharmaceutically acceptable salt thereof of the following compound:



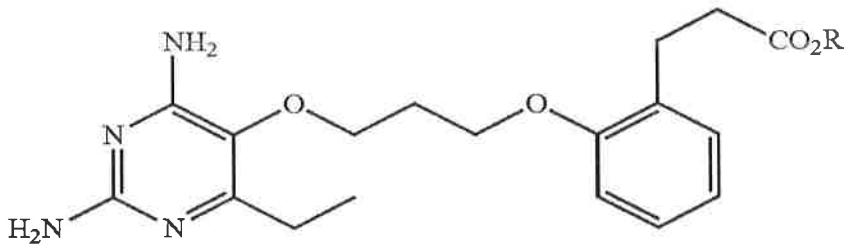
2,4-diamino-6-ethyl-5-(3-(6-(3-carboxypropoxy)-2-methylquinolin-4-yloxy)-propoxy)pyrimidine.

22. The compound of claim **1**, wherein said compound is the following compound, or a pharmaceutically acceptable salt thereof of the following compound:



2,4-diamino-6-ethyl-5-(3-(6-(3-carboxypropoxy)-2-methylquinolin-4-yloxy)-propoxy)pyrimidin ethyl ester.

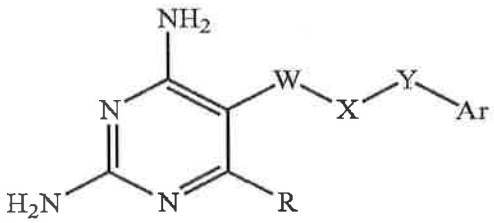
23. The compound according to claim **20**, wherein the compound is a pharmaceutically acceptable hydrochloride salt of the following compound:



2,4-diamino-6-ethyl-5-(3-(2-(2-carboxyethyl)phenoxy) propoxy)pyrimidine, wherein R is H.

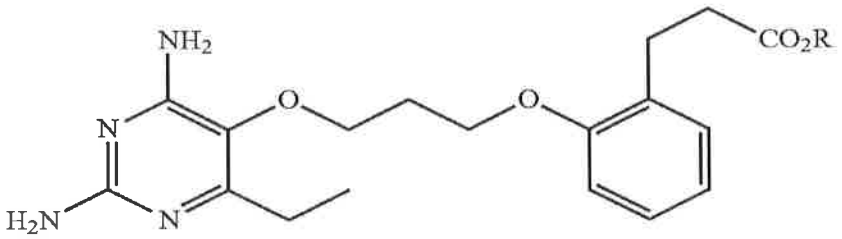
24. A pharmaceutical formulation comprising a compound of Formula (I):

(I)



wherein R is hydrogen or C_{1-4} alkyl,
W—X—Y is $O(CH_2)_{2-4}O$;
Ar is an optionally substituted aromatic ring selected from phenyl and naphthyl, or an optionally substituted heteroaromatic ring selected from the group consisting of quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pyridyl, indolyl, triazolyl, benzoxazolyl, benzimidazolyl, indolinyl and benzotriazolyl; wherein
when Ar is an aromatic ring, it is substituted by at least one group selected from the group consisting of benzoxazolyl, carboxyl, carboxyalkylC(1-3), carboxyalkylC(1-3)oxy, alkylC(1-3)oxycarbonylalkylC(1-3), alkylC(1-3)oxycarbonylalkylC(1-3)oxy, tetrazolyl, tetrazolylalkylC(1-3) and tetrazolylalkylC(1-3)oxy; and Ar is optionally substituted by additional substituents; or a pharmaceutically acceptable salt or substituted derivative thereof.

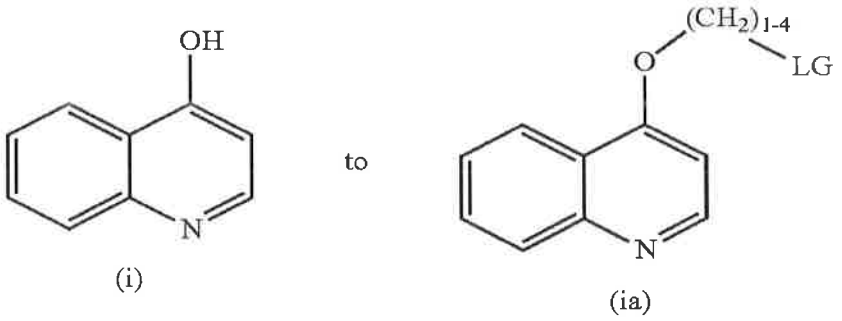
25. The pharmaceutical formulation according to claim **24**, wherein said compound is the following compound or a pharmaceutically acceptable hydrochloric acid salt thereof:



2,4-diamino-6-ethyl-5-(3-(2-(2-carboxyethyl)phenoxy) propoxy)pyrimidine, wherein R is H.

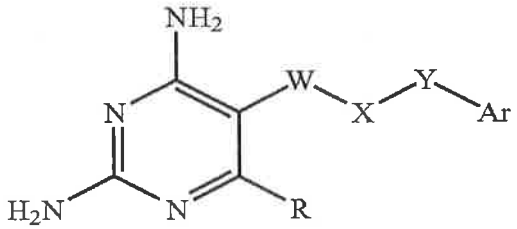
26. A method of synthesis, comprising the steps of: alkylating ArOH according to Scheme 1,

Scheme 1



wherein LG is a suitable leaving group and wherein said alkylation step is a step in the method of synthesizing of compounds of Formula (I):

(I)

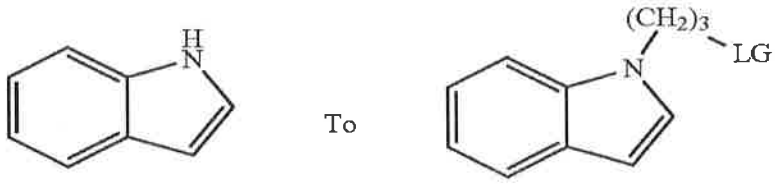


wherein R is hydrogen or C_{1-4} alkyl,
W is O or CH_2,
X is $(CH_2)_{2-4}$ and is optionally substituted with a hydroxyl group,
Y is CH_2, O, S, N(Z), wherein Z is H, acyl, alkyl, or aryl;
Ar is a substituted aromatic ring comprising phenyl or naphthyl, or an optionally substituted heteroaromatic ring selected from the group consisting of quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pyridyl, indolyl, triazolyl, benzoxazolyl, benzimidazolyl, indolinyl and benzotriazolyl; and wherein when Ar is an aromatic ring, it is substituted by at least one group selected from the group consisting of acyl, benzoxazolyl, nitro, carboxyl, carboxyalkylC(1-3), carboxyalkylC(1-3)oxy, alkylC(1-3)oxycarbonylalkylC(1-3), alkylC(1-3)oxycarbonylalkylC(1-3)oxy, tetrazolyl, tetrazolylalkylC(1-3) and

tetrazolylalkylC(1-3)oxy; and Ar is optionally substituted by additional substituents; or a pharmaceutically acceptable salt or substituted derivative thereof.

27. The method of synthesis according to claim **26**, wherein the alkylating step includes alkylating Ar according to Scheme 2,

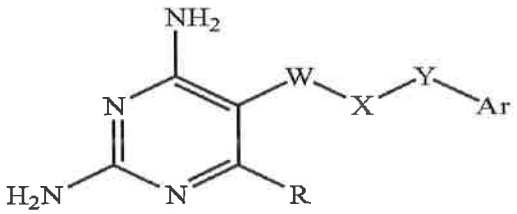
Scheme 2



(ii) (iia)

wherein LG is a suitable leaving group and wherein said alkylation step is a step in the method of synthesizing of compounds of Formula (I):

(I)



wherein R is hydrogen or C_{1-4} alkyl,
W is O or CH_2,
X is $(CH_2)_{2-4}$ and is optionally substituted with a hydroxyl group,

Y is CH_2, O, S, N(Z), wherein Z is H, acyl, alkyl, or aryl;

Ar is a substituted aromatic ring comprising phenyl or naphthyl, or an optionally substituted heteroaromatic ring selected from the group consisting of quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pyridyl, indolyl, triazolyl, benzoxazolyl, benzimidazolyl, indolinyl and benzotriazolyl; and wherein when Ar is an aromatic ring, it is substituted by at least one group selected from the group consisting of acyl, benzoxazolyl, nitro, carboxyl, carboxyalkylC(1-3), carboxyalkylC(1-3)oxy, alkylC(1-3)oxycarbonylalkylC(1-3), alkylC(1-3)oxycarbonylalkylC(1-3)oxy, tetrazolyl, tetrazolylalkylC(1-3) and

tetrazolylalkylC(1-3)oxy; and Ar is optionally substituted by additional substituents; or a pharmaceutically acceptable salt or substituted derivative thereof.

28. A method to treat a subject in need of treatment for malaria, which method comprises administering to said subject an effective amount of a compound of claim **1**.

29. The method of claim **28**, wherein the subject is a subject in need of treatment for a drug-resistant or non-resistant strain of malaria.

30. The method of claim **29**, wherein the drug-resistant strain of malaria is a strain that is resistant to at least one antifolate drug.

31. The method of claim **30**, wherein the drug-resistant strain of malaria is resistant to at least one antifolate drug selected from the group consisting of cycloguanil, chlorcycloguanil, pyrimethamine or other DHFR inhibitors.

32. The method of claim **30**, wherein the drug-resistant strain of malaria is an antifolate-resistant strain having one or more mutations in its DHFR protein sequence.

33. The method of claim **32**, wherein the antifolate-resistant strain of malaria has at least two mutations selected from the group consisting of 16(ala to val), 51(asn to ile), 59(cys to arg), 108(ser to asn), 108(ser to thr), and 164(ile to leu).

34. The method of claim **32**, wherein the antifolate-resistant strain of malaria has at least one mutation selected from the group consisting of 16(ala to val), 51(asn to ile), 59(cys to arg), 108(ser to asn), 108(ser to thr), and 164(ile to leu).

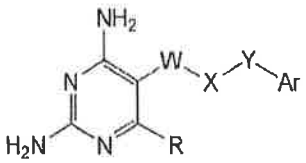
35. The method of claim **32**, wherein the antifolate-resistant strain of malaria has at least one mutation selected from the group consisting of 16(ala to val) and 108(ser to thr).

36. The method of claim **28**, wherein the treatment is an oral treatment.

CLAIMS

We claim:

1. A compound of Formula I:



(I)

wherein

R is hydrogen or C_{1-4} alkyl;

W is O or CH_2;

X is $(CH_2)_{2-4}$ and is optionally substituted with a hydroxyl group;

Y is CH_2, O, S, or N(Z), wherein Z is H or optionally substituted acyl, alkyl, or aryl;

Ar is a substituted aromatic ring comprising phenyl or naphthyl, or an optionally substituted heteroaromatic ring selected from the group consisting of quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, pyridyl, indolyl, triazolyl, benzoxazolyl, benzimidazolyl, indolinyl and benzotriazolyl; wherein

when Ar is an aromatic ring, it is substituted by at least one group selected from the group consisting of acyl, benzoxazolyl, nitro, carboxyl, carboxyalkylC(1-3), carboxyalkylC(1-3)oxy, alkylC(1-3)oxycarbonylalkylC(1-3), alkylC(1-3)oxycarbonylalkylC(1-3)oxy, tetrazolyl, tetrazolylalkylC(1-3) and tetrazolylalkylC(1-3)oxy; and Ar is optionally substituted by additional substituents; or a pharmaceutically acceptable salt or substituted derivative thereof.

2. The compound of claim 1, wherein R is C_{1-4} alkyl.

3. The compound of claim 1, wherein R is ethyl.

4. The compound of claim 1, wherein Ar is substituted at one or more available positions with at least one group selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, trifluoromethyl, aryl, substituted aryl, halogen, amino, substituted amino, alkoxy, aryloxy, hydroxyl and nitro.

5. The compound of claim 4, wherein W-X-Y is $O(CH_2)_{2-4}O$.

6. The compound of claim 5, wherein said Ar is quinolinyl or substituted 4-quinolinyl.

7. The compound of claim 6, wherein W-X-Y is $O(CH_2)_{3-5}O$.

8. The compound of claim 4, wherein W-X-Y is $O(CH_2)_{2-4}S$ or $O(CH_2)_{2-4}NZ$.

9. The compound of claim 8, wherein said Ar is quinolinyl or substituted 4-quinolinyl.

10. The compound of claim 9, wherein W-X-Y is $O(CH_2)_{3-5}O$.

11. The compound of claim 1, wherein R is ethyl, W-X-Y is $O(CH_2)_3O$, and Ar is quinolinyl or substituted 4-quinolinyl.

12. The compound of claim 11, wherein said Ar is quinolinyl or substituted 4-quinolinyl.

13. The compound of claim 12, wherein W-X-Y is $O(CH_2)_{3-5}O$.

14. The compound of claim 4, wherein W-X-Y is $O(CH_2)_{2-4}$.

15. The compound of claim 14, wherein said Ar is quinolinyl or substituted 4-quinolinyl.

16. The compound of claim 15, wherein W-X-Y is $O(CH_2)_{3-5}O$.

17. The compound of claim 2, wherein Ar is substituted at one or more available positions with at least one group selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted

cycloalkyl, trifluoromethyl, aryl, substituted aryl, halogen, amino, substituted amino, alkoxy, aryloxy, hydroxyl and nitro.

18. The compound of claim 17, wherein W-X-Y is $O(CH_2)_{2-4}O$.

19. The compound of claim 18, wherein said Ar is quinolinyl or substituted 4-quinolinyl.

20. The compound of claim 19, wherein W-X-Y is $O(CH_2)_{3-5}O$.

21. The compound of claim 17, wherein W-X-Y is $O(CH_2)_{2-4}S$.

22. The compound of claim 21, wherein said Ar is quinolinyl or substituted 4-quinolinyl.

23. The compound of claim 22, wherein W-X-Y is $O(CH_2)_{3-5}O$.

24. The compound of claim 17, wherein W-X-Y is $O(CH_2)_{2-4}NZ$.

25. The compound of claim 24, wherein said Ar is quinolinyl or substituted 4-quinolinyl.

26. The compound of claim 25, wherein W-X-Y is $O(CH_2)_{3-5}O$.

27. The compound of claim 17, wherein W-X-Y is $O(CH_2)_{2-4}$.

28. The compound of claim 27, wherein said Ar is quinolinyl or substituted 4-quinolinyl.

29. The compound of claim 28, wherein W-X-Y is $O(CH_2)_{3-5}O$.

30. The compound of claim 3, wherein Ar is substituted at one or more available positions with at least one group selected from the group consisting of alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, trifluoromethyl, aryl, substituted aryl, halogen, amino, substituted amino, alkoxy, aryloxy, hydroxyl and nitro.

31. The compound of claim 30, wherein W-X-Y is $O(CH_2)_{2-4}O$.

32. The compound of claim 31, wherein said Ar is quinolinyl or substituted 4-quinolinyl.

33. The compound of claim 32, wherein W-X-Y is $O(CH_2)_{3-5}O$.

34. The compound of claim 30, wherein W-X-Y is $O(CH_2)_{2-4}S$.

35. The compound of claim 34, wherein said Ar is quinolinyl or substituted 4-quinolinyl.

36. The compound of claim 35, wherein W-X-Y is $O(CH_2)_{3-5}O$.

37. The compound of claim 30, wherein W-X-Y is $O(CH_2)_{2-4}NZ$.

38. The compound of claim 37, wherein said Ar is quinolinyl or substituted 4-quinolinyl.

39. The compound of claim 38, wherein W-X-Y is $O(CH_2)_{3-5}O$.

40. The compound of claim 30, wherein W-X-Y is $O(CH_2)_{2-4}$.

41. The compound of claim 40, wherein said Ar is quinolinyl or substituted 4-quinolinyl.

42. The compound of claim 41, wherein W-X-Y is $O(CH_2)_{3-5}O$.

43. A method to treat a subject in need of treatment for malaria, which method comprises administering to said subject an effective amount of a compound of claim 1.

44. The method of claim 43, wherein the subject is a subject in need of treatment for a drug-resistant or non-resistant strain of malaria.

45. The method of claim 44, wherein the drug-resistant strain of malaria is a strain that is resistant to at least one antifolate drug.

46. The method of claim 45, wherein the drug-resistant strain of malaria is resistant to at least one antifolate drug selected from the group consisting of cycloguanil, chlorcycloguanil, pyrimethamine or other DHFR inhibitors.

47. The method of claim 45, wherein the drug-resistant strain of malaria is an antifolate-resistant strain having one or more mutations in its DHFR protein sequence.

48. The method of claim 47, wherein the antifolate-resistant strain of malaria has at least two mutations selected from the group consisting of 16(Ala→Val), 51(Asn→Ile), 59(Cys→Arg), 108(Ser→Asn), 108(Ser→Thr), and 164(Ile→Leu).

49. The method of claim 47, wherein the antifolate-resistant strain of malaria has at least one mutation selected from the group consisting of 16(Ala→Val), 51(Asn→Ile), 59(Cys→Arg), 108(Ser→Asn), 108(Ser→Thr), and 164(Ile→Leu).

50. The method of claim 47, wherein the antifolate-resistant strain of malaria has at least one mutation selected from the group consisting of 16(Ala→Val) and 108(Ser→Thr).

51. The method of claim 43, wherein the treatment is an oral treatment.

52. The compound of claim 1, wherein said compound is P113, or a pharmaceutically acceptable salt thereof.

53. The compound of claim 1, wherein said compound is P149, or a pharmaceutically acceptable salt thereof.

54. The compound of claim 1, wherein said compound is P153, or a pharmaceutically acceptable salt thereof.

55. The compound of claim 1, wherein said compound is P154, or a pharmaceutically acceptable salt thereof.

56. The compound of claim 1, wherein said compound is P157, or a pharmaceutically acceptable salt thereof.

57. The compound of claim 1, wherein said compound is P135, or a pharmaceutically acceptable salt thereof.

58. The compound of claim 1, wherein said compound is P217, or a pharmaceutically acceptable salt thereof.

59. The compound of claim 1, wherein said compound is P195, or a pharmaceutically acceptable salt thereof.

60. The compound of claim 1, wherein said compound is P218, or a pharmaceutically acceptable salt thereof.

61. The compound of claim 1, wherein said compound is P169, or a pharmaceutically acceptable salt thereof.

62. The compound of claim 1, wherein said compound is P219, or a pharmaceutically acceptable salt thereof.