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[Continued on next page]

(54) Title: ANTI-FOLATE ANTIMALARIALS WITH DUAL-BINDING MODES AND THEIR PREPARATION

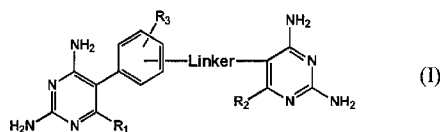
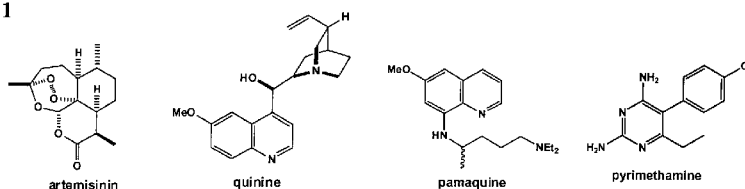


Fig. 1



(57) **Abstract:** The present invention is anti-folate antimalarials with dual-binding modes of the general formula (I) [refer to structure in the abstract] wherein R_1 and R_2 which may be the same or different are independently selected from methyl or ethyl or alkyl-phenyl, R_3 is independently hydrogen, halide, lower alkyl substituted with ester, carboxylic, amide, and ether. Linker is $X(CH_2)_nY$ wherein X and Y which may be the same or different are independently selected from oxygen, carbon, nitrogen, substituted phenyl where n is an integer from 1 to 2-6, or pharmaceutically acceptable salts therefore. The anti-folate antimalarials with dual-binding modes act as novel inhibitors with good inhibition constants against wild-type, double (C59R+S108N), triple (N51+C59R+S108N), and quadruple (N51+C59R+S108N+I164L) mutant enzymes. The compounds are also effective against wild type (Tm4/S.2) and mutants (K1CB1, W2, Csl-2 and V1/S) malaria parasites.



DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT,
LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE,
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A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/496 (2012.01)

USPC - 514/275

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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USPC - 514/275; 544/296, 323, 324

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatBase, Google Patents, PubMed Central, Sure Chem Open

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2009/0099220 A1 (YUTHAVONG et al) 16 April 2009 (16.04.2009) entire document	1-5
A	US 2004/0180913 A1 (YUTHAVONG et al) 16 September 2004 (16.09.2004) entire document	1-5
A	NZILA et al. 'Preclinical evaluation of the antifolate QN254, 5-chloro-N'6'-(2,5-dimethoxy-benzyl)-quinazoline-2,4,6-triamine, as an antimalarial drug candidate'. <i>Antimicrobial Agents and Chemotherapy</i> 54(6): 2603-2610, June 2010. Article retrieved from PubMed Central. Retrieved on [24.09.2012]. <URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2876411/pdf/1526-09.pdf > entire document	1-5
A	NDUATI et al. 'Effect of folate derivatives on the activity of antifolate drugs used against malaria and cancer'. <i>Parasitol Res</i> 102:1227-1234, 9 February 2008. Article retrieved from PubMed Central. Retrieved on [24.09.2012]. <URL: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2292483/pdf/436_2008_Article_897.pdf > entire document	1-5
A	US 4,232,023 A (DICK et al) 04 November 1980 (04.11.1980) entire document	1-5

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