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**SYNTHESIS AND ANTIMALARIAL
ACTIVITY OF
PYRROLO[3,2-F]QUINAZOLINE-1,3-DIAMINE
DERIVATIVES**

GOVERNMENT INTEREST

The invention described herein may be manufactured, used and licensed by or for the U.S. Government.

BACKGROUND OF THE INVENTION

1 Field of the Invention

The present invention relates to new compounds that are useful for the treatment of malaria. The compounds of the invention are pyrroloquinazolinediamine derivatives, namely alkyl derivatives, carbamate derivatives, succinimide derivatives, alkylcarboxamides derivatives, including acetamide, phthalimide, and all other amide and imide derivatives of the parent compound 1 and their analogs that are effective and less toxic for treatment of malaria, including but not limited to *P. falciparum* and *P. vivax* strains.

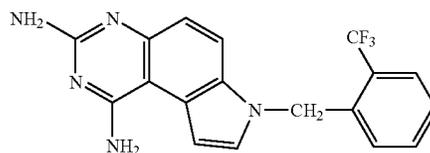
2 Brief Description of Related Art

The current global situation with respect to malaria indicates that about two billion people are exposed to the disease. Each year between 100 to 200 million new cases of infection are reported and approximately 1 to 2 million people die due to malaria [1, 2]. US ground troops suffered high percentage of casualties by malaria infection during the Vietnam War and recently among British and US soldiers deployed in Somalia, Africa [3]. The situation of malaria control is rapidly worsening mainly due to non-availability of effective drugs and development of drug resistance to the existing first line drugs [4, 5]. Furthermore, the usefulness of many newer antimalarial drugs was impaired by their side effects. Lethal hemolysis side effect was observed in glucose-6-phosphate dehydrogenase (G6PD) deficient recipients of 8-aminoquinoline drugs [6] (primaquine and tafenoquine) and CNS toxicity was problematic in the patients treated with mefloquine [7]. Therefore, there is an eminent need for new and safe antimalarial compounds to combat these parasites in the epidemic areas of the world.

Pyrroloquinazolinediamine derivatives were reported to possess anticancer, antimicrobial and antimalarial activities (See Ledig, et al. U.S. Pat. No. 4,118,561) [8]. Among the derivatives, WR227825 (1) is one of the most potent antimalarial agents ever reported [9]. This compound displayed not only high in vitro efficacy against *P. falciparum* with IC₅₀~0.01 ng/ml but also highly active against *P. berghei* in rodent model, with 100% curative oral dose between <0.1 to 4 mg/kg. However, Ledig, et al. WR227825 also exhibited high host toxicity, with subcutaneous LD₅₀ in mice at less than 20 mg/kg and produced deaths in Aotus monkey at doses less than 2 mg/kg [10]. The low therapeutic index of compound 1 has severely limited its value as an antimalarial agent. Nevertheless, the high efficacy and low therapeutic index of Ledig, et al., WR227825 make this compound an ideal lead for optimization to fabricate new derivatives with improvement in therapeutic index or deficiencies in preclinical/pharmacological profiles.

In addition to high host toxicity, the lead compound 1 is sparingly soluble in common organic solvents and water, a highly undesirable physical property for large scale synthesis and purification.

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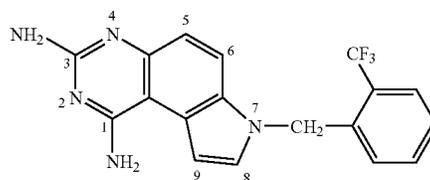
(WR227825)

What is needed is a composition that is effective against both drug sensitive and multi-drug resistant strains of malaria, especially *P. falciparum* and *P. vivax* and is substantially less toxic than WR 227825 so that it can be used safely in humans. What is also needed is a composition that is soluble in common organic solvents to facilitate the purification in a large scale synthesis of the composition. The parent compound 1 is sparingly soluble in either water or common organic solvents, which is a challenging problem to overcome during its large scale preparation.

The present invention solves the toxicity problems of the prior art by providing novel derivatives of WR227825 that have been found by the inventors to be substantially less toxic and more soluble in organic solvents than WR227825.

SUMMARY OF THE INVENTION

The present invention is directed to derivatives of:



(WR227825)

wherein the amino groups at 1 and 3 positions have been substituted to render the compound a carbamate derivative, succinimide derivative, alkyl derivatives and alkylcarboxamide derivative including acetamide, phthalimide, or all other amide and imide derivatives. The compound 1 has been further modified by replacing one of the amino groups at 1-position with a hydroxy function.

BRIEF DESCRIPTION OF THE FIGURES

FIGS. 1A-D are graphs showing parasitemia responses in individual rat infected with *P. berghe* ANKA: (A) vehicle control with 1% CMC suspension; (B) 5 mg/kg of WR288901 (3e) with 100% curative measurement; (C) 10 mg/kg of WR288901(3e) with 100% curative effect, and (D) 20 mg/kg of WR288901 (3e) with 100% curative measurement in all animals following daily intragastric administration for three days (at day 6, 7, and 8 post-inoculation) treatments (n=2-5).

DETAILED DESCRIPTION

In this invention, we have initially synthesized a series of alkylcarbamates of WR227825 (2a-m) as shown in Table 1. All of the carbamates prepared, except 2-chlorobenzylcar-