This invention relates to produgs based on artemisinin and to a method of manufacturing such produgs. The produgs of artemisinin according to the invention have the general structure A-B-M wherein A is a dihydroartemisinin moiety; B is a linking group; and M is a moiety selected from the group consisting of moieties derived from anti-malarial drugs other than artemisinin, in particular quinoline derivatives, and moieties derived from amine compounds. The invention further relates to the use of such produgs in the prevention and treatment of malaria and in the manufacture of a medicament for use in such treatment. This invention also relates to the oral and transdermal application of such produgs.
PRODRUGS OF ARTEMISININ

FIELD OF THE INVENTION
This invention relates to artemisinin-antimalarial mutual prodrugs and artemisinin analogue prodrugs.

INTRODUCTION
This invention relates to prodrugs based on artemisinin and to a method of manufacturing such prodrugs. This invention further relates to the use of such prodrugs in the prevention and treatment of malaria in mammals and in the manufacture of a medicament for use in such treatment. This invention also relates to the oral and transdermal application of such prodrugs.

BACKGROUND TO THE INVENTION
Malaria is one of the most widespread diseases in the world, particularly in the third-world countries and especially in sub-Saharan Africa. Currently, 300-500 million people worldwide have malaria. Each year 1 to 2 million people die of this infectious disease, and 75% of them are African children (Wongsrichanalai, Pickard et al., 2002). Vaccines to prevent people from contracting malaria are being developed, but no success has yet been reported. Chemotherapy treatment of current malaria patients is becoming more and more difficult because the malaria parasites, Plasmodium falciparum, causing the disease have developed widespread resistance to standard antimalarial drugs such as quinine and especially chloroquine (Wongsrichanalai, Pickard et al., 2002; Wilairatana, Krudsood et al., 2002; Winstanley, Ward et al., 2002).

In the early seventies, Chinese chemists reported the isolation and structure elucidation of the sesquiterpene 1,2,4-trioxane, artemisinin (quighaosu, 1; Figure 1), which is a highly active antimalarial component of the ancient Artemisia annua (sweet wormwood) Chinese herbal remedy for fevers (Klayman, 1985). This important discovery represented a breakthrough in finding an effective antimalarial that was not quinoline-based and, therefore, that was effective against multidrug-resistant malaria parasites. Chemical synthesis of a mono-deoxygenated version of artemisinin, dihydroartemisinin (4), established that the endoperoxide unit in this natural trioxane was essential for its high antimalarial potency (Klayman, 1993). Ever since, artemisinin as well as semi-synthetic derivatives and synthetic trioxanes have been used clinically. Sodium artesunate (2) is a succinic half ester of the reduced lactol form of artemisinin that, although prone to hydrolysis, is fast-acting, water-soluble, effective, and widely used in areas of the world where malaria is endemic (Barradell
and Fitton, 1995). China approved the oil-soluble artemether (3), and sodium artesunate as antimalarial drugs along with artemisinin itself in 1987.

Artemisinin (1), and its antimalarial derivatives, sodium artesunate (2), artemether (3) and 10-dihydroartemisinin (4).

As a class, trioxane compounds have proven unusually valuable for (a) their brisk and potent antimalarial activity, (b) their lack of resistance and cross-resistance with other antimalarials, and (c) their action against the gametocyte forms of the parasite responsible for infecting mosquitoes and thus for transmitting this infectious disease (Tang, Dong et al., 2004; Haynes and Krishna, 2004; Jefford, 2004; Ashley and White, 2005; Meunier, 2008). For these reasons, trioxanes are now considered an essential component of artemisinin combination therapy (ACT) against drug-resistant malaria (Gamer, 2004; World Health Organization, 2006). Several synthetic cyclic peroxides, trioxanes and trioxolanes show significant promise as antimalarial drugs because of their artemisinin-like activity (Jefford, 2007). In combination with other antimalarial drugs, sodium artesunate is currently the drug of choice in most third-world cases of malaria (White, Nosten et al., 1999).

Artemisinin combination treatment (ACT) is currently the treatment preferred by the WHO (World Health Organization, 2006). ACT unfortunately suffers from the following disadvantages:
(i) The very short half-lives of the artemisinin class of antimalarials (typically 1 to 2 hours) necessitate frequent dosing for several days in order to achieve sufficient exposure of the parasites to the drug, increasing cost and leading to poor compliance, which in turn leads to inadequate treatment and can drive resistance development.

(ii) The only combination preparation available in South Africa, and in most of the world, is an artemether-lumefantrine combination (Co-Artem®; Novartis). A Chinese-developed drug (Artekin®) is currently under clinical development. Due to the high cost, availability and absorption kinetics of Co-Artem®, artesunate, combined with mefloquine is now becoming the standard recommended treatment for multidrug resistant *falciparum* malaria.

(iii) Artemether, a hydrophobic artemisinin derivative, has relatively low bioavailability and should be administered with a fatty meal, which is usually impractical in most areas where treatment is required.

(iv) No paediatric dosage form is yet available.

(v) Some isolated cases of resistance due to treatment with artemisinins alone instead of ACT have been reported.

A one-day treatment alternative overcoming the pharmacokinetic deficiencies of the artemisinin endoperoxides may address the bioavailability and compliance issues as well as cost implications. If the total exposure to the endoperoxide is the same as after normal dosing, toxicity due to prolonged exposure will be prevented. The principal idea is to change the therapeutic efficacy of the active pharmaceutical ingredient (API) by changing the pharmacokinetics thereof. This can be achieved by a) extending the duration of adequate exposure after a single dose by lengthening its half-life in the human body or b) by slowly releasing the absorbed compound or c) by targeting the compound to the parasite in its host cell or d) by increased delivery to the parasite itself.

Prodrugs have a long history as a means to stabilise, improve efficacy, bioavailability and delivery or to protect an active molecule (Testa, 2004; Etmayer, Amidon et al., 2004). Formation Rate Limited (FRL) metabolite kinetics occurs when a metabolite has a short half-life if it is administered as itself, but exhibits a longer half-life when formed in the body from a precursor or parent drug, as the half-life of the parent drug will govern the half-life of the metabolite (Houston, 1981; Testa, 2004).
This invention relates to two types of artemisinin prodrugs, viz: (a) artemisinin-antimalarial mutual prodrugs, and (b) artemisinin analogue prodrugs. Preliminary studies have shown promising results for these groups of compounds.

A prodrug with a suitable biological half-life and safety profile may be generated by varying the structure of the bridging segment between the two moieties. In the body, the result should then be the metabolic formation of one or two antimalarial drugs from a common prodrug according to controlled rate-limited kinetics of the artemisinin component.

The human skin, as the largest organ in the body, offers a favourable route for the administration of drugs and can be utilised as a very effective delivery system of medicines to the body. The benefits of transdermal above oral or intravenous administration of drugs have been well documented. The greatest advantages include a non-invasive treatment regimen, circumvention of first pass metabolism by the liver, avoiding negative effects on the gastrointestinal tract, better patient compliance, the potential for sustained release (useful for drugs with short biological half-lives requiring frequent oral or parenteral administration), controlled input kinetics (which are particularly indispensable for drugs with narrow therapeutic indices), more uniform plasma levels and quick interruption of treatment.

These benefits have led to the recent upsurge in research in the transdermal delivery of drugs. The skin, however, is an efficient barrier protecting the internal plasma from the harsh exterior. In order to penetrate the skin a drug molecule has to possess special characteristics. Much research has been conducted to improve the flux of drugs through the skin, concentrating primarily on decreasing the barrier function of the skin. A further approach is the use of penetration enhancers with permeation properties that can be delivered concurrently with the drug. Another feasible option is the synthesis of prodrugs having the same efficacy as the parent drug but with improved transdermal flux (Bonina, Puglia et al., 2001; Fourie, Breytenbach et al., 2004; Monene, Goosen et al., 2005).

OBJECT OF THE INVENTION

It is therefore an object of the present invention to provide anti-malarial prodrugs based on artemisinin and methods of manufacturing and uses of such derivatives with which the aforesaid disadvantages could be reduced and which are useful alternatives to the known substances.
SUMMARY OF THE INVENTION

According to the invention there are provided prodrugs of artemisinin of the general structure A-B-M

wherein
A is a dihydroartemisinin moiety;
B is a linking group; and
M is a moiety selected from the group consisting of moieties derived from anti-malarial drugs other than artemisinin and moieties derived from amine compounds,

provided that where M is quinine the linking group is linked to the quinine via the C₉ hydroxy group of the quinine.

In one form of the invention the anti-malarial drug is a quinoline derivative. In this form of the invention the quinoline derivative is preferably selected from the group consisting of amodiaquine, n-bisethylamodiaquine, chloroquine, mefloquine, piperaquine, primaquine, pamaquine, quinine, isouquine, pyronaridine and tafenoquine.

Alternatively, the anti-malarial drug may be a drug effective in the treatment of malaria but not a quinoline derivative. In this form of the invention the drug may be selected from the group consisting of halofantrine, lumefantrine, proguanil (chlorguanide), cycloguanil and pyrimethamine or their pharmacophores.

In the form of the invention in which M is a moiety derived from an amine compound the amine compound is preferably selected from the group consisting of

1-amino-4-methylpiperazine,
1-amino-4-methylpiperazine,
1(3-aminopropyl)imidazole,
1-aminohydantoin,
1,2,4-triazole,
2,4-diamino-6-chloro-pyrimidine,
4-aminomorpholine,
4(2-aminoethyl)morpholine,
4(2-aminomethyl)morpholine,
4-amino-4H-1,2,4-triazole,
acethydrazide,
ethyl 1-piperazine,
N,N-dimethylethylenediamine, and
N-acetylenediamine.

The linking group may be selected from the group consisting of an amino group, a carbonoyl group and a carbamoyl group. It will be understood that the presence of a carbonoyl group as linking group in the A-B-M structure as defined above results in a carbonate-linked mutual prodrug of artemisin with a selected M moiety, while the presence of a carbamoyl group as linking group in the A-B-M structure as defined above results in a carbamate-linked mutual prodrug of artemisinin with a selected M moiety.

According to a first preferred embodiment of the invention there are provided carbonate-linked mutual prodrugs of artemisin with a quinoline derivative anti-malarial drug having a hydroxyl group in its structure and hence represented by the formula $R^2$-OH in which $R^2$ is the quinoline derivative moiety, which prodrugs have the structural formula I in which $R^2$ has the same meaning as in the quinoline derivative anti-malarial drug

![Carbonate-linked mutual prodrug](Image)

According to a second preferred embodiment of the invention there are provided carbamate-linked mutual prodrugs of artemisinin with a quinoline derivative anti-malarial drug having an amine group in its structure, and hence represented by the formula $R^1$-$NH_2$ in which $R^1$ is the quinoline derivative moiety, which prodrugs have the structural formula II in which $R^1$ has the same meaning as in the quinoline derivative anti-malarial drug

![Carbamate-linked mutual prodrug](Image)
Most preferably the artemisinin prodrugs of the invention are:

- Dihydroartemisinin-mefloquine prodrug (5)

- Dihydroartemisinin-proguanil pharmacophore

wherein $R'$ is a C$_2$ to C$_4$ hydrocarbylene chain

wherein R is a C$_2$ to C$_4$ hydrocarbylene chain

DHA-proguanil pharmacophore
Further according to the invention there is provided a method for the prevention and treatment of malaria in mammals, birds and/or reptiles including the step of administering to such mammal, bird and/or reptile a pharmaceutically effective amount of a prodrug according to the invention as defined above. In the method according to the invention the prodrug may be administered orally, transdermally or parenterally.

Also according to the invention there is provided for the use of a prodrug according to the invention as defined above in the manufacture of a medicament for the use in a method for the prevention or treatment of malaria in mammals, birds and/or reptiles. In the use according to the invention the medicament may be manufactured to be suitable to be administered orally, transdermally or by injection or infusion.

Also according to the invention there is provided a pharmaceutical composition comprising any of the prodrugs as defined above in combination with one or more pharmaceutically acceptable excipients.

According to yet another aspect of the invention there is provided a method for the preparation of artemisinin prodrugs substantially as herein described and exemplified.
The invention will now be described in more detail with reference to the following non-limiting examples.

All compounds are synthesised using standard organic chemical procedures (Furniss, Hannaford et al., 1987).

**Example 1**
Artemisinin-quinoline based mutual prodrugs

**Scheme 1**: Synthesis of artemisinin-quinoline based mutual prodrugs

Bodansky’s (1955) method was used to activate DHA (see above) followed by the reaction with primaquine in THF at RT to exemplify the synthesis of artemisinin-quinoline based prodrugs. The reaction was followed by TLC. After completion, the solution was spun to dryness. The residue was dissolved in DCM and thoroughly washed with water, dried over MgSO₄ and purified by flash chromatography to afford the carbamate mutual prodrug.
Example 2
Artemisinin analogues

Scheme 2: Synthesis of artemisinin analogues

wherein H₂NR is any of 1-amino-4-methylpiperazine, 1-amino-4-methylpiperazine, 1(3-aminopropyl)imidazole, 1-amino hydantoin, 1,2,4-triazole, 2,4-diamino-6-chloro-pyrimidine 4-aminomorpholine, 4(2-aminoethyl)morpholine, 4(2-aminomethyl)morpholine, 4-amino-4H-1,2,4-triazole, acethydrazide, ethyl 1-piperazine, N,N-dimethyl ethylenediamine, and N-acetylethylenediamine and R thus the radical group originating from these mentioned amino compounds.

There are two methods for the activation of dihydroartemisinin with para-nitrobenzenesulfonylchloride:

1. Triethylamine (1.36 ml) is added to a solution of dihydroartemisinin (500 mg, 1.76 mmol) in DCM (21.4 ml). The solution is cooled to 0°C, and p-nitrobenzenesulfonylchloride (459.1 mg, 2.11 mmol) in DCM (6.02 ml) is added via an addition funnel. The reaction is stirred for 0.5h at 0°C and then for 4h at room temperature. The reaction mixture is filtered through Celite and diluted with DCM (60 ml). The filtrate is washed with H₂O (80 ml), sat. NaHCO₃ (80 ml) and H₂O (80 ml). The organic layer is dried. The reaction is monitored throughout with thin layer chromatography (Miller, Malkar et al., 2006).

2. Dihydroartemisinin (500 mg, 1.76 mmol) is dissolved in 30 ml THF/pyridine mixture (1/1, v/v). p-Nitrobenzenesulfonylchloride (459.1 mg, 2.11 mmol) is added to the solution and it is stirred for 12h at room temperature. The product is precipitated from cold diethyl ether and recrystallised from ethanol and dried under vacuum (Huh and Bae, 1999).
In the second step the activated dihydroartemisinin (2 mmol) is dissolved in a suitable solvent like dichloromethane, chloroform, THF or acetonitrile and the amino compound (2.1 mmol) dissolved in the same solvent is added dropwise with stirring at room temperature. The reaction is followed on TLC and heated to 60 °C if necessary. After completion of the reaction the solvent is removed under reduced pressure and the product is purified by column chromatography on silica gel.

Example 3
Artemisinin analogue with carbamoyl linking group

Using the same method as described in Example 1 an artemisinin analogue with a carbamoyl linking group may be made as set out in the reaction scheme below, in which R-NH₂ is again any of 1-amino-4-methylpiperazine, 1-amino-4-methylpiperazine, 1(3-aminopropyl)imidazole, 1-aminoimidazolidinone, 1,2,4-triazole, 2,4-diamino-6-chloropyrimidine 4-aminomorpholine, 4(2-aminoethyl)morpholine, 4(2-aminomethyl)morpholine, 4-amino-4H-1,2,4-triazole, acethydrazide, ethyl 1-piperazine, N,N-dimethylethlenediamine, and N-acetylenediamine and R thus the radical group originating from these mentioned compounds.

In the second step the activated dihydroartemisinin (2 mmol) is dissolved in a suitable solvent like dichloromethane, chloroform, THF or acetonitrile and the amino compound (2.1 mmol) dissolved in the same solvent is added dropwise with stirring at room temperature. The reaction is followed on TLC and heated to 60 °C if necessary. After completion of the reaction the solvent is removed under reduced pressure and the product is purified by column chromatography on silica gel.

The produced prodrugs were isolated and purified using column chromatography with the eluents as specified in the procedures. The products were analysed by ¹H- and ¹³C-NMR on a Varian Gemini-300 spectrometer in deuterated chloroform or dimethyl sulfoxide (DMSO). Infrared (IR) spectra were recorded on a Nicolet Magna-IR 550 spectrometer.
with KBr pellets and the melting points were determined by DSC on a Shimadzu DSC 50. Mass spectrometry (MS) was performed on an analytical VG 7070E mass spectrometer.

Example 4

Antiplasmodial activity of compounds according to the invention

1. Objective

To screen samples of four compounds according to the invention for in vitro antiplasmodial activity, namely compounds of the general formula

Sample DP6 - p-nitrophenylcarbonate artemisinin.
Sample MCL - 10-primaquiny1 artemisinin
Sample MS01 - 10-mφ hinolinylethylamino artemisinin
Sample MS08 - 10-(4-piperadiny1)methylamino artemisinin

and to compare such activity to the activity of CQ - chloroquine.

2. Methodology

The test samples were tested in triplicate on two separate occasions against chloroquine sensitive (CQS) strain of Plasmodium falciparum (D10). Continuous in vitro cultures of asexual erythrocyte stages of P. falciparum were maintained using a modified method of Trager and Jensen (1976). Quantitative assessment of antiplasmodial activity in vitro was determined via the parasite lactate dehydrogenase assay using a modified method described by Makler (1993).

The test samples were prepared to a 2mg/ml stock solution in 10% DMSO and sonicated to enhance solubility. Samples were tested as a suspension if not completely dissolved. Stock solutions were stored at -20°C. Further dilutions were prepared on the day of the experiment. Chloroquine (CQ) was used as the reference drug in all experiments. A full dose-response was performed for all compounds to determine the concentration inhibiting 50% of parasite growth (IC_{50}-value). Test samples were first tested at a starting concentration of 1000 ng/ml, which was then serially diluted 2-fold in complete medium to give 10 concentrations; with the lowest concentration being 2 ng/ml. The same dilution technique was used for all samples. Test samples were re-tested at a starting concentration of 100 ng/ml. The highest concentration of solvent to which the parasites were exposed to had no measurable effect on the parasite viability (data not shown). The
IC$_{50}$-values were obtained using a non-linear dose-response curve fitting analysis via Graph Pad Prism v.4.0 software.

3. Results

The results obtained are reflected in Table 1 below and in the accompanying graphs set out in Figures 1 and 2.

Table 1. *In vitro* antiplasmodial activity of test samples against *P. falciparum* (CQS) D10 strain.

<table>
<thead>
<tr>
<th>Sample code</th>
<th>IC$_{50}$ (ng/ml); n=2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP6*</td>
<td>46.32</td>
</tr>
<tr>
<td>MCL*</td>
<td>3.99</td>
</tr>
<tr>
<td>MS01</td>
<td>7.42</td>
</tr>
<tr>
<td>MS08</td>
<td>29.22</td>
</tr>
<tr>
<td>CQ</td>
<td>11.67 (n=3)</td>
</tr>
</tbody>
</table>

*Tested as a suspension

4. Discussion

The results showed that compounds MCL and MS01 were the most active with activity better than the reference drug CQ (Table 1). Compounds DP6 and MS08 also showed good activity.

The applicant foresees that the prodrugs in accordance with the present invention could be administered through oral and transdermal delivery systems. Transdermal delivery is advantageous in that it offers bypassing of the liver and possible first pass effects (presystemic metabolism) and could result in improved patient compliance, especially where patients can not tolerate orally administered medications. The ability of transdermal patches to provide a sustained release of drugs over a period of time helps to sustain the plasma drug levels at therapeutic concentrations, which are more difficult to obtain with oral or injectable drug therapy.

It will be appreciated that variations in detail are possible with prodrugs of artemisinin and methods of manufacturing and uses of such derivatives according to the invention without departing from the scope of this disclosure.
REFERENCES


CLAIMS

1. A prodrug of artemisinin of the general structure
   
   \[
   \text{A-B-M}
   \]
   wherein
   
   A is a dihydroartemisinin moiety;
   B is a linking group; and
   M is a moiety selected from the group consisting of moieties derived from anti-malarial drugs other than artemisinin and moieties derived from amine compounds, provided that where M is quinine the linking group is linked to the quinine via the C₉ hydroxy group of the quinine.

2. A prodrug according to claim 1 wherein M is a moiety selected from the group consisting of moieties derived from anti-malarial drugs which are quinoline derivatives.

3. A prodrug according to claim 2 wherein M is a moiety selected from the group consisting of moieties derived from amodiaquine, n-bisethylamodiaquine, chloroquine, mefloquine, piperaquine, primaquine, pamaquine, quinine, isoquine, pyronaridine and tafenoquine.

4. A prodrug according to claim 1 wherein M is a moiety selected from the group consisting of moieties derived from halofantrine, lumefantrine, proguanil (chlorguanide), cycloguanil and pyrimethamine or their pharmacophores.

5. A prodrug according to claim 1 wherein M is a moiety selected from the group consisting of moieties derived from an amine compound selected from the group consisting of
   1-aminopropyl)imidazole,
   1-aminopropyl)imidazole,
   13-aminopropyl)imidazole,
   1aminohydantoin,
   1,2,4-triazole,
   2,4-diamino-6-chloro-pyrimidine,
   4-aminomorpholine,
   4(2-aminoethyl)morpholine,
   4(2-aminomethyl)morpholine,
   4-aminomorpholine,
acethydrazide,
ethyl 1-piperazine,
N,N-dimethylethylenediamine, and
N-acetylenediamine.

6. A prodrug according to claim 1 the linking group is selected from the group consisting of an amino group, a carbonoyl group and a carbamoyl group.

7. A prodrug according to claim 1 which is a carbonate-linked mutual prodrug of artemisinin with a quinoline derivative anti-malarial drug having a hydroxyl group in its structure and represented by the formula $R^2$-OH in which $R^2$ is the quinoline derivative moiety, which prodrug has the structural formula I in which $R^2$ has the same meaning as in the quinoline derivative anti-malarial drug.

\[
\begin{align*}
\text{carbonate-linked mutual prodrug} \\
\text{I.}
\end{align*}
\]

8. A prodrug according to claim 1 which is a carbamate-linked mutual prodrug of artemisinin with a quinoline derivative anti-malarial drug having an amine group in its structure and represented by the formula $R^1$-$NH_2$ in which $R^1$ is the quinoline derivative moiety, which prodrugs have the structural formula II in which $R^1$ has the same meaning as in the quinoline derivative anti-malarial drug.

\[
\begin{align*}
\text{carbamate-linked mutual prodrug} \\
\text{II.}
\end{align*}
\]

9. An artemisinin prodrug according to claim 1 which is a compound represented by any one of the following structural formulae.
dihydroartemisinin-mefloquine πe prodrug (5)

wherein \( R' \) is a C\(_2\) to C\(_4\) hydrocarbylene chain

DHA-proguine πil pharmacophore

wherein R is a C\(_2\) to C\(_4\) hydrocarbylene chain
wherein R is a C₂ to C₄ hydrocarbylene chain

10. A method for the prevention or treatment of malaria in mammals, birds or reptiles including the step of administering to such mammal, bird or reptile a pharmaceutically effective amount of a prodrug according to any one of claims 1 to 9.

11. The use of a prodrug according to any one of claims 1 to 9 in the manufacture of a medicament for the use in a method for the prevention or treatment of malaria in mammals, birds or reptiles and wherein the medicament is manufactured to be suitable to be administered orally, transdermal or by injection or infusion.

12. A prodrug according to any one of claims 1 to 9 for use in a method for the prevention or treatment of malaria in mammals, birds or reptiles.

13. A pharmaceutical composition comprising any of the prodrugs according to any of claims 1 to 9 in combination with one or more pharmaceutically acceptable excipients.

14. A method for the preparation of a artemisinin-quinoline based mutual prodrugs comprising the steps of activating dihydroartemisinin by Bodansky's (1955) method and reacting the activated dihydroartemisinin with a quinoline based drug selected from the group consisting of amodiaquine, n-bisethylamodiaquine, chloroquine, mefloquine, piperaquine, primaquine, pamaquine, quinine, isoquine, pyronaridine and tafenoquine. in THF at room temperature and separating the resultant mutual prodrug from the reaction mixture.
15. A method for the preparation of an artemisinin analogue comprising the steps of activating dihydroartemisinin with para-nitrobenzenesulfonylchloride, and reacting the activated dihydroartemisinin with a compound selected from the group of compounds consisting of 1-amino-4-methylpiperazine, 1-amino-4-methylpiperazine, 1(3-aminopropyl)imidazole, 1-aminohydantoin, 1,2,4-triazole, 2,4-diamino-6-chloropyrimidine, 4-aminomorpholine, 4(2-aminoethyl)morpholine, 4(2-aminomethyl)morpholine, 4-amino-4H-1,2,4-triazole, acethydrazide, ethyl 1-piperazine, N,N-dimethylethylenediamine, and N-acetylethylethylenediamine, wherein the reaction is carried out in a solvent selected from dichloromethane, chloroform, THF and acetonitrile, and separating the resultant artemisinin analogue from the reaction mixture.
Figure 1. Dose-response curves of test samples against the CQS D10 strain of *P. falciparum*.
Figure 2. Dose-response curves of Chloroquine against the CQS D10 strain of *P. falciparum*