# Ian GILBERT, *et al.*
# DDD107498 vs Malaria

http://www.sciencealert.com/new-drug-has-the-potential-to-ward-off-malaria-with-a-single-dose
**18 JUN 2015**

## New drug has the potential to ward off malaria with a single dose

And it'll cost less than $1 per dose.

Lab tests have highlighted the potential of a new drug to treat malaria in affected patients, prevent it from spreading, and ward off future infections with a single dose. Developed by chemists at Dundee University in Scotland and the not-for-profit group Medicines for Malaria Venture, the drug acts against each of the life stages of the malaria parasite, making it a promising option for those already infected and as a vaccination.

"There are other compounds being developed for malaria, but relatively few of [these] have reached the stage we're at," lead researcher Ian Gilbert said in a press release. "What's most exciting is the number of potential attributes, such as the ability to give it in a single dose which will mean that medics can make sure a patient completes the treatment."

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Named DDD107498, the drug has been in development since 2009, and was made using one of almost 4,700 compounds tested for effectiveness against malaria at the Drug Discovery Unit (DDU) facilities in the UK.

In tests with mice and other lab animals, the researchers report that the drug identified and attacked the protein involved in the production of various vital enzymes and proteins in the malaria parasite's cells throughout all stages of its lifecycle, which prevented the spread and development of the disease. The parasite was successfully cleared from both the blood and livers of the affected animals.

"The compound we have discovered works in a different way to all other antimalarial medicines on the market or in clinical development, which mean that it has great potential to work against current drug-resistant parasites," one of the team, Kevin Read, said in the release. "It targets part of the machinery that makes proteins within the parasite that causes malaria."

The results have been published in Nature.

According to Steve Connor at The Guardian, the first phase of clinical trials will begin in the coming months, and if the drug makes it to the market, will likely be sold for less than $1 a dose, "which is considered the maximum price that the poorest affected countries can afford", he says.

As David Reddit, CEO of Medicines for Malaria Venture, pointed out to BBC News, malaria threatens half the world's population - the half that can least afford treatment and vaccination against it, so a cheap, one-off medication could be the most promising option in development. "DDD107498 is an exciting compound since it holds the promise to not only treat but also protect these vulnerable populations," he said.

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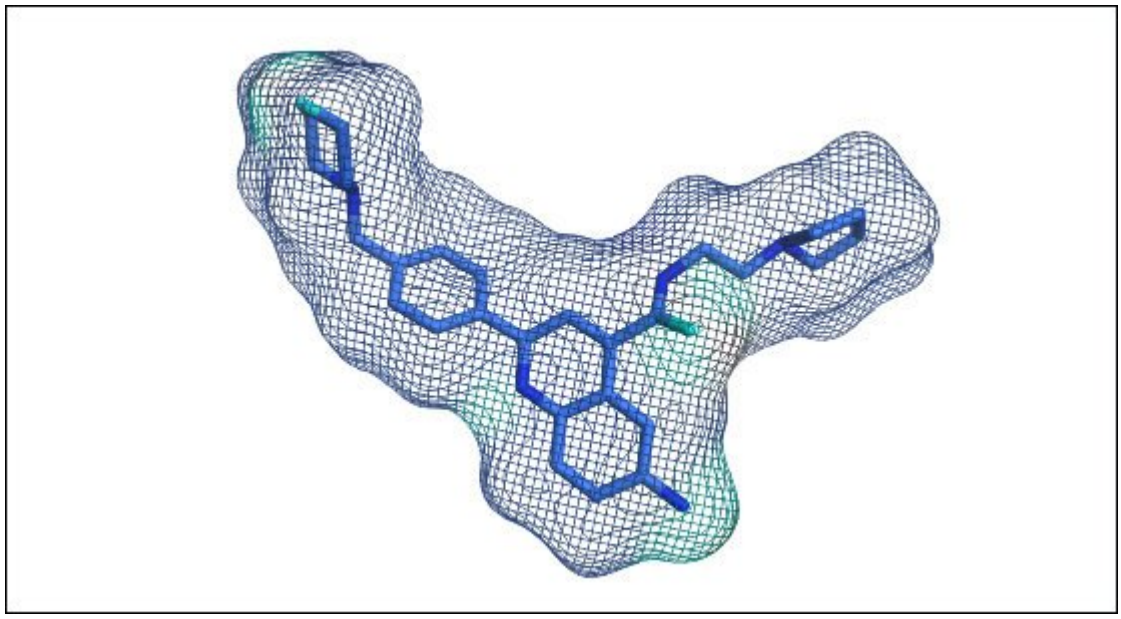
**https://www.youtube.com/watch?v=I2qHc4YTDSg**

**Video by Drug Discovery Unit at the University of Dundee**



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**http://www.dundee.ac.uk/news/2015/discovery-of-a-novel-antimalarial-compound-published-in-nature.php**
**17 Jun 2015**

**Discovery of a novel antimalarial compound published in Nature**

**by Roddy Isles**

**Potential new anti-malarial drug developed at Drug Discovery Unit**

Professor Ian Gilbert and Dr Kevin Read explain how a new compound developed at the Drug Discovery Unit at the University of Dundee has the potential to treat malaria sufferers with just a single dose and also prevent the spread and transmission of the disease.

The details of the discovery, properties and mechanism of action of a novel antimalarial compound, DDD107498, have been published in the journal Nature. DDD107498 has the potential to treat malaria patients in a single dose, including those with malaria parasites resistant to current

medications, and help reduce the transmission of the parasite.

The compound was identified through a collaboration between the University of Dundee's Drug Discovery Unit (DDU) and Medicines for Malaria Venture (MMV).

"The publication describes the discovery and profiling of this exciting new compound," said Professor Ian Gilbert, Head of Chemistry at the Drug Discovery Unit, who led the team that discovered the compound. "It reveals that DDD107498 has the potential to treat malaria with a single dose, prevent the spread of malaria from infected people, and protect a person from developing the disease in the first place.

"There is still some way to go before the compound can be given to patients. However we are very excited by the progress that we have made."

"Malaria continues to threaten almost half of the world's population – the half that can least afford it," said Dr David Reddy, MMV's CEO. "DDD107498 is an exciting compound since it holds the promise to not only treat but also protect these vulnerable populations. The collaboration to identify and progress the compound, led by the Drug Discovery Unit at the University of Dundee, drew on MMV's network of scientists from Melbourne to San Diego. The publication of the research is an important step and a clear testament to the power of partnership."

Dr Kevin Read, joint leader of the project, also based at the Drug Discovery Unit at Dundee, said, "New drugs are urgently needed to treat malaria, as resistance to the current gold-standard antimalarial drug is now considered a real threat. The compound we have discovered works in a different way to all other antimalarial medicines on the market or in clinical development, which means that it has great potential to work against current drug-resistant parasites. It targets part of the machinery that makes proteins within the parasite that causes malaria."

"The need for new antimalarial drugs is more urgent than ever before, with emerging strains of the parasite now showing resistance against the best available drugs," said Dr Michael Chew from the Wellcome Trust, which provides funding for the Dundee DDU and MMV. "These strains are already present at the Myanmar-Indian border and it's a race against time to stop resistance spreading to the most vulnerable populations in Africa. The discovery of this new antimalarial agent, which has shown remarkable potency against multiple stages of the malaria lifecycle, is an exciting prospect in the hunt for viable new treatments."

"Our partnership with MMV was critical to the progress of this compound," added Professor Ian Gilbert. "Dr Paul Willis at MMV and Sir Simon Campbell, a mentor from MMV's Expert Scientific Advisory Committee, gave invaluable input to the project. We have extensively profiled the compound, investigating its properties to understand how it works; this could not have been done without MMV's scientific input and support of its network of partners around the world.

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# US2015045354
# Anti-Malarial Agents

**Field of the Invention**

The present invention relates to a new class of quinoline-4-carboxamide compounds, to their use in medicine, to compositions containing them, to processes for their preparation and to intermediates used in such processes. In particular the present invention provides quinoline-4-carboxamide for use in the treatment of malaria. Background

In the undeveloped world, over 350 million people are at risk from neglected tropical diseases such as malaria, African sleeping sickness, Chagas disease and Leishmaniasis. Existing therapies to treat

such neglected tropical diseases are increasingly ineffective due to the development of resistance by the parasites that underpin these conditions to drugs used both in disease prevention and treatment.

Worldwide, an estimated 200 to 300 million malarial infections occur each year. Approximately 1 million people die each year from malaria and the disease is one of the world's biggest killers. Malaria is caused by an infection of the red blood cells with a tiny organism or parasite called protozoa. Five species of the protozoa Plasmodium are known to cause infection in humans: Plasmodium falciparum (Pf); Plasmodium vivax (Pv); Plasmodium ovale; Plasmodium malariae; and Plasmodium knowlesi. The injection of protozoa of Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, or Plasmodium malariae into the blood stream, is effected by a single source, the bite of the female Anopheles mosquito. Thus there is a need for agents which are effective against Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae and Plasmodium knowlesi infections. The most life-threatening form of malaria is attributable to blood cells infected with the Plasmodium falciparum parasite, and can cause kidney or liver failure, coma and death. About 2% of people infected with falciparum malaria die and with an estimated one child dying every 45 seconds from falciparum malarial infections the need for an effective treatment could not be higher. Thus there is a need for agents which are: effective against Plasmodium falciparum infections; effective against Plasmodium falciparum and Plasmodium vivax infections; effective against Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale and Plasmodium knowlesi infections. Plasmodium species require two hosts, human and mosquito for completion of its life- cycle. In humans the infection is initiated by the inoculation of sporozoites in the saliva of an infected mosquito. Once inside the body the sporozoites migrate to the liver and there infect hepatocytes where they differentiate, via the exoerythrocytic intracellular stage, into the merozoite stage which infects red blood cells to initiate cyclical replication in the asexual blood stage. The life-cycle is completed by the differentiation of a number of merozoites in the red blood cells into sexual stage gametocytes which are ingested by the mosquito, where they develop through a series of stages in the mid gut to produce sporozoites which migrate to the salivary gland.

Many countries have been experiencing resurgence in malaria cases caused by Plasmodium falciparum due to the spread of parasites which are increasingly resistant to both chloroquine, the drug most widely used for prevention and treatment as well as newer, alternative treatments such as artesunate. See, Wellems et al, JID 2001 ;184 (15 September) and Noedl et al, N Engl J Med 2008; 359:2619-2620 (11 December). The development of new anti-malarial treatments is of great importance particularly given the rapid spread of parasite resistance even within newer artemisinin-based therapies.

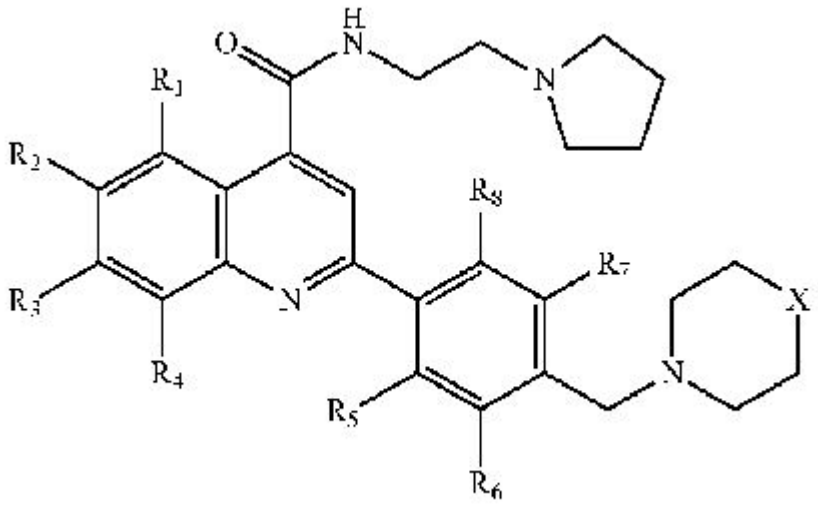
In the battle against the continued spread of both malarial infection and the parasite resistance to malaria compounds having the potential to both combat the infection and also impact upon the parasite growth cycle, particularly against gametocyte development and thereby impacting upon subsequent transmission potential, would be highly desirable.

A further strand in assisting effective treatment of malarial infections is the need for therapies which can be dosed efficiently in difficult conditions. As such, single-dose, oral, rectal or parenteral therapies, particularly sustained or modified release therapies would be of value.

Thus there is a need for new and effective anti-malarial agents. In particular there is a need for new anti-malarial agents which: are effective against drug-resistant parasites; are effective against drug-resistant Plasmodium falciparum infections such as for example Chloroquine-resistant Plasmodium falciparum infections; which are active against gametocytes; have transmission-blocking potential; which are active against liver stage; which can be used for single-dose treatment; and/or which can be used for prophylactic treatment.

The present invention provides a novel class of class of quinolone-4-carboxamide compounds Plasmodium falciparum 3D7 inhibitors having potential as anti-malarial agents. The novel class of quinolone-4-carboxamide compounds according to the present invention have potential for the

treatment of Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae and Plasmodium knowlesi infections. In particular the novel class of class of quinolone-4-carboxamide compounds according to the present invention have potential for the treatment of Plasmodium falciparum infections; Plasmodium falciparum and Plasmodium vivax infections; Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae and Plasmodium knowlesi infections. Desirable properties of compounds of formula (I) according to the present invention include: potency against Plasmodium falciparum 3D7; low toxicity in MRC-5 or HepG2 cells ; both desirable Plasmodium falciparum (Pf) 3D7 potency and low toxicity in MRC-5 or HepG2 ; desirable Plasmodium falciparum and Plasmodium vivax (Pv) activity against clinical isolates; desirable transmission blocking activity; gametocyte inhibitory potential; activity against dormant liver stage forms; good biopharmaceutical properties such as physical stability; good solubility profiles; appropriate metabolic stability; desirable ADME properties (adsorption, distribution, metabolism, excretion).

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