European Journal of Pharmacology ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

# Chloroquine-based hybrid molecules as promising novel chemotherapeutic agents

Vandana Srivastava [a,b], Hoyun Lee [a,b,*]

[a] Advanced Medical Research Institute of Canada, Health Sciences North, 41 Ramsey Lake Road, Sudbury, Ontario, Canada P3E 5J1
[b] Division of Medical Sciences, Northern Ontario School of Medicine, 935 Ramsey Lake Road, Sudbury, Ontario, Canada P3E 2C6

ARTICLE INFO

*Article history:*
Received 10 February 2015
Received in revised form
15 April 2015
Accepted 20 April 2015

*Chemical compounds studied in this article:*
Chloroquine (PubChem CID: 2719)
Artemisinin (PubChem CID: 68827)
NSC7092257 (PubChem CID: 398939)
SGI 1027 (PubChem CID: 24858111)

*Keywords:*
Chloroquine
Cancer
Hybrid molecule
Anticancer agent
Antimalarial agent
4-Aminoquinoline
4-Aminoquinoline (PubChem CID: 68476)

ABSTRACT

Chloroquine (CQ) has a broad spectrum of pharmacological activities including anticancer and anti-inflammatory, in addition to its well-known antimalarial activity. This very useful property of CQ may be rendered through a variety of different molecular and cellular mechanisms, including the induction of apoptosis, necrosis and lysosomal dysfunction. CQ alone may not be as effective as many well-known anticancer drugs; however, it often shows synergisticts when combined with other anticancer agents, without causing substantial ill-effects. To increase its pharmacological activity, scientists synthesized many different chloroquine derivatives by a repositioning approach, some of which show higher activities than the parental CQ. To further improve anticancer activity, medicinal chemists have recently been focusing on generating CQ hybrid molecules by joining, directly or through a linker, 4-aminoquinoline and other pharmacologically active phamarcophore(s). Indeed, some CQ hybrid molecules substantially improved anticancer activity while maintaining desirable CQ property, providing an excellent opportunity of developing effective and safe novel anticancer agents. Since the approach of developing CQ hybrid molecules has advanced much more in the antimalarial drug research, it can provide an excellent template for anticancer drug development. This review provides an overview of CQ-based hybrid molecules by focusing on: (1) the potential advantage of the hybrid approach in developing effective and safe anticancer agents; (2) what we can learn from the CQ hybrid approach used in the development of effective antimalarial agents; and (3) CQ hybrid molecules as potential anticancer agents in different categories classified based on their chemical compositions.





**Contents**



* Corresponding author at: Advanced Medical Research Institute of Canada, Health Sciences North, 41 Ramsey Lake Road, Sudbury, Ontario, Canada P3E 5J1. Tel.: +1 705 522 6237x2703.
*E-mail address:* hlee@amric.ca (H. Lee).

http://dx.doi.org/10.1016/j.ejphar.2015.04.048
0014-2999/

## 1. Introduction

Drug discovery is a quite challenging field in terms of time and financial investment. Average time to develop a new drug is approximately 12–15 years (Meunier, 2008) at an estimated cost of $161 million–$ 1.8 billion (USD), depending on the therapeutic areas (Morgan et al., 2011). Historically, the long process of drug discovery usually begins with random screening of chemical compounds with high potency of cell killing, which often associated with high side effects. More recently, this approach is being replaced with a rationalized drug design, often based on specific molecular targets, which has resulted in the successful development of a few effective drugs. However, in spite of intensive efforts by medicinal chemists to increase the selectivity and sensitivity of drugs towards established targets, many diseases still remains incurable. Furthermore, the use of target-based drugs often results in the rapid development of resistance to the drugs. Therefore, an effective and selective drug is always in great demand and new approaches must be developed to overcome drug side effects and emergence of drug resistance.

The modification of existing drugs is often the most cost effective and productive route of developing new drugs (Sullivan Jr. and Chong, 2007), among which a hybrid approach presents one of the most recent and promising strategies (Muregi and Ishih, 2010). A hybrid compound is usually created by linking, directly or through a linker, the structural domains of two or more compounds to make one effective drug (Fortin and Bérubé, 2013).

Chloroquine (CQ, Fig. 1), also known as Resochin, has been widely used to control malaria for over seven decades. The development of CQ was initially started from a natural product as its distance precursor quinine (Fig. 1) was isolated from the crude extracts of cinchona bark which had been used to treat fever and malaria for a long time. In 1891 Guttmann and Ehrlich used methylene blue (Fig. 1) to treat malaria patients (Gensini et al., 2007), this was the first synthetic molecule to be used as a drug in humans. Encouraging with this result, the Ehrlich group synthesized many similar compounds including quinacrine (Fig. 1) in 1931 (Krafts et al., 2012; Schirmer et al., 2011). Subsequently, Hans Andersag, a scientist at Bayer, created CQ by replacing the acridine ring of quinacrine with a quinoline ring (Hahn, 1975; Krafts et al., 2012). It turned out that CQ is comparatively well-tolerated antimalarial drug and even after decades of use, it is still a drug of choice for the control of malaria in many parts of the world. As summarized in Table 1, CQ is also used for the treatment of many other human diseases including microbial infections, inflammatory

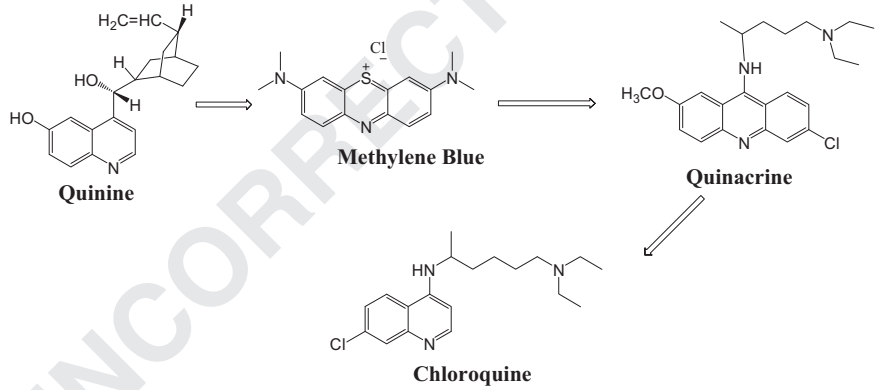


**Fig. 1.** Development of CQ from quinine.

**Table 1**
Use of chloroquine for other diseases.

| Disease | Reference |
|---|---|
| Anti-microbial | |
| Amebic hepatitis | Konan (1948) |
| Enhances antibacterial potency of ciprofloxacin | Adegbolagun et al. (2008) |
| Inhibits intracellular multiplication of *Legionella pneumophila* | Byrd and Horwitz (1991) |
| Revertes azole resistance in biofilm of *Candida albicans* | Shinde et al. (2013) |
| Anticryptococcal activity in murine model | Khan et al. (2005) |
| Anti-inflammatory | |
| Rheumatoid arthritis | http://www.hopkinsarthritis.org/arthritis-info/rheumatoid-arthritis<br>Thomé et al. (2013) |
| Antiviral | |
| Broad spectrum anti-HIV I and HIV II activity | Savarino et al. (2001, 2003) |
| Effective against avian influenza A H5N1 virus *in vitro* and *in vivo* | Naarding et al. (2007)<br>Yan et al. (2013) |
| Autoimmune disease | |
| Systemic lupus erythematosus (SLE) | Meinao et al. (1996)<br>Costedoat-Chalumeau et al. (2014) |



Please cite this article as: Srivastava, V., Lee, H., Chloroquine-based hybrid molecules as promising novel chemotherapeutic agents. Eur J Pharmacol (2015), http://dx.doi.org/10.1016/j.ejphar.2015.04.048