FEBRIFUGINE ANALOGUES: PROMISING ANTIMALARIAL AGENTS

SURENDER PARLAPALLY

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ABSTRACT

Halofuginone is an analog of febrifugine—an alkaloid originally isolated from the plant Dichroafebrifuga. During recent years, halofuginone has attracted much attention because of its wide range of beneficial biological activities, which encompass malaria, cancer, and fibrosis-related and autoimmune diseases. At present two modes of halofuginone actions have been described: (1) Inhibition of Smad3 phosphorylation downstream of the TGFβ signaling pathway results in inhibition of fibroblasts-to-myofibroblasts transition and fibrosis. (2) Inhibition of prolyl-tRNA synthetase (ProRS) activity in the blood stage of malaria and inhibition of Th17 cell differentiation thereby inhibiting inflammation and the autoimmune reaction by activation of the amino acid starvation and integrated stress responses. This review deals with the history and origin of this natural product, its synthesis, its known modes of action, and it's various biological activities in pre-clinical animal models and in humans.

Keywords: malaria; fibrosis; inflammation; autoimmunity; Th-17; apoptosis

INTRODUCTION

Malaria is a life-threatening disease caused by protozoa of the genus Plasmodium and remains one of the world's greatest public health problems. Half of population in the world is at the risk of malaria, especially in tropical and subtropical areas. The widely-spread disease is transmitted through the bite of infected female Anopheles mosquitoes, leading to over one million deaths from malaria every year. Most of the deaths are attributed to the parasite species Plasmodium falciparum, which can kill patients in hours. When it gets into the human body, P. falciparum can be able to modify the surface of infected red blood cells by interposing parasite proteins. The enzymes (cysteine and aspartic proteinases) break down hemoglobin into amino-acids and heme. All the amino-acid contents are used to build parasite proteins, while only a small portion of heme is merged into parasite hemoproteins, and the rest of heme is detoxified (polymerized) catalyzed by parasite enzyme. Many drugs such as chloroquine and other traditional antimalarials have been investigated for their efficacy in the treatment of malaria, but strains of P. falciparum that are resistant to some of these drugs have appeared. Hence, it is important to discover new medicines for malaria, and many drugs especially isolated from medical plants have been investigated for their efficacy in the treatment of malaria.

In order to develop new drugs or explain how molecular properties of the drugs can be related to biological activity, the quantitative structure-activity relationship (QSAR) approach is usually used to describe how a given biological activity varies as a function of the molecular descriptors based on molecular structures. Ojha & Roy reviewed the QSAR reports published in previous literatures and some pharmacophore models and docking studies of ant malarial drugs, and tried to address the physical and chemical properties and structural characteristics required for antimalarial activity in different chemical classes. In addition, docking studies of antimalarial compounds against different targets were reviewed to explore patterns of interaction at the molecular level, with a focus on the existing knowledge of QSAR and pharmacophore models for different classes of antimalarial drugs.

Identification of bioactive small molecules and confirmation of their activity is crucial for both academic research and pharmaceutical applications. The plant kingdom provides a reservoir of natural products that play highly significant roles in drug discovery and development. Thus, biodiversity represents an unlimited source of novel chemical entities that offer promise as novel, efficacious and safe therapies for various diseases. There is a current perception that bioactive compounds are obtained through computer-modeling, bioinformatics, chemical genetics, high-throughput screening, and other drug-discovery methods. However, the history of science contains many cases in which serendipity prevailed where other approaches failed, and halofuginone—an analog of febrifugine, an alkaloid originally isolated from the plant Dichroafebrifuga—is an excellent example of a bioactive molecule discovered by serendipity. In this review we will describe the history and origin of this natural product, its synthesis, its known modes of action, and it's various biological activities in preclinical animal models and in humans.

REVIEW OF LITERATURE

RokhyatouSeck, Abdoulaye Gassama, Sandrine Cojean (2020) In order to prepare, at low cost, new compounds active against Plasmodium falciparum, The resulting compound library has been evaluated against chloroquine-sensitive (3D7) and chloroquine-resistant (W2) strains of P. falciparum. The most active molecules—compounds 12d (13.64 nM (3D7)), 13b (4.19 nM (3D7) and 13.30 nM (W2)), and 12a (11.6 nM (W2))—were comparable to chloroquine (22.38 nM (3D7) and 134.12 nM (W2)).

Yu Heng Ou, Chia Ming Chang (2020) Quantum chemical molecular descriptors representing different types of chemical reactivity was employed to investigate the antimalarial activities of 4-aminoquinoline, febrifugine, artemisinin and their derivatives. The quantitative structure-activity relationship results reveal that: (i) the antimalarial activities of 4-aminoquinoline compounds against the chloroquine-sensitive Plasmodium falciparum 3D7 strain are mainly affected by the electron flow and polarization interactions.

Yogesh Subhash Biradar, Swathi Bodupally, Harish Padh(2019) The objective of this study was to evaluate the in vitro antiplasmodial properties against malaria parasite in 15 plants mentioned in Indian traditional medicine texts. In vitro antiplasmodial activity of methanolic extracts obtained from Indian traditional medicinal plants was evaluated on Plasmodium falciparum of FCK2 and INDO strains using schizont maturation inhibition assay and parasite lactate dehydrogenase inhibition assay. A. zeylanica and E. ribes were the most promising extracts from this study and deserve further investigation of their antiplasmodial properties.

Shaun Smullen, Noel P. McLaughlin, Paul Evans (2017) The quinazolinone-containing 2,3-disubstituted piperidinesfebrifugine and isofebrifugine. Subsequently they have also been shown to be present in other plants belonging to the hydrangea family and various analogues of febrifugine have been prepared in attempts to tune biological properties. This review focuses on the literature associated with efforts dedicated towards uncovering the structures of febrifugine and isofebrifugine, the development of practical methods for their synthesis and the syntheses of structural analogues.

Selected Antimalarial Plants (2016) the book provides an overview of the disease malaria, epidemiology and implications on public health, the Plasmodium life cycle, and signs and symptoms associated with malaria. The book also provides an overview to research carried out on medicinal plants used for malaria, in particular ethnobotanical surveys, and an extensive compilation of more than 1800 medicinal plants reportedly used for malaria. Medicinal plants are important sources of novel chemical scaffolds, and Cinchona bark have revolutionized malaria chemotherapy and prophylaxis.

THE ORIGIN OF HALOFUGINONE AND ITS SYNTHESIS

In China, DichroafebrifugaLour. Which belongs to the Saxifragaceae family has been used for centuries against malarial fever. Extracts from either the roots or the leaves were effective for treating chicks infected with Plasmodium gallinaceum and in clinical cases of malaria. Among 600 plant extracts tested for their antimalarial effects, the extract of D. febrifuga was found to be one of the most effective. An active quinazoline-type alkaloid isolated from the roots and having the molecular structure C16H2103N3 was designated dichroin B, and later renamed febrifugine. The alkaloids febrifugine and its stereoisomer, isofebrifugine, have been identified as the active components of the plant, and both exhibited in vitro antimalarial activity against chloroquine-sensitive and chloroquine-resistant P. falciparum. Febrifugine was

found to be effective against P. vivax and more active than quinine against P. lophurae, P. gallinaceum, and P. cynomolgi. Because the high antimalarial activity was accompanied by gastrointestinal toxicity associated with, e.g., diarrhea, vomiting, and liver toxicity, the structure of febrifugine was used as a lead compound in the synthesis of some active molecules with lower toxicity that inhibited parasite growth both in vitro and in vivo.

In addition, synthesis of a series of febrifugine derivatives as antimalarial drugs was performed by structural modifications at the quinazoline ring, the linker, or the piperidine ring, and antimalarial drug-discovery models were developed for screening and predicting efficacious febrifugine analogs. It has been demonstrated that most febrifugine analogs bearing a modified or unmodified 4- quinazolinone moiety are active, but analogs produced through modification of the side chain attached to the N3 position of the 4-quinazolinone ring have proved to be ineffective. Furthermore, a synthetically prepared racemic febrifugine was reported to be about half as effective as natural febrifugine. These results suggested that the 4-quinazolinone moiety, the nitrogen atom of the piperidine ring, and the hydroxyl group are necessary for the antimalarial activity, and that the absolute configuration of these functional groups plays an important role.

Halofuginone {7-bromo-6-chloro-3-[3-(3-hydroxy-2-piperidinyl)-2-oxopropyl]-4(3H)-quinazolinone} (Figure 1) is one of the febrifugine analogs used worldwide in commercial poultry production. Halofuginone hydrobromide is an FDA–approved feed additive for prevention of coccidiosis in broiler chickens and growing turkeys; also, other halofuginone salts are used against protozoan parasites in cattle. As in febrifugine, the piperidine ring was found to be essential for halofuginone activity. Because of the high interest in febrifugine and its analogs, including halofuginone, as antimalarial drugs, many reports on their synthesis was published during the years, to cite just a few). Some of the early synthesis procedures encountered various problems because of uncertainty regarding the absolute stereochemistry. It was found that under certain conditions febrifugine and isofebrifugine could interconvert. Recently, an elegant review was published that described the chemical complexity of the molecules involved and the problems encountered during the synthesis of febrifugine, isofebrifugine and halofuginone

STRUCTURAL ANALOGUES OF FEBRIFUGINE

In the 1970s, the synthesis and evaluation of analogues of febrifugine as potential antimalarial drugs demonstrated that the 4-quinazolinone moiety, the nitrogen atom of the piperidine ring and the hydroxyl group are essential for antimalarial activity (Fishman & Cruickshank, 1970; Chien& Cheng, 1970). It was also demonstrated that the absolute configuration of the compound is important since only modest activity is reported for the unnatural enantiomer (Hewitt et al., 1952). Mono- or disubstitution by certain groups on the quinazoline ring system, particularly at positions 5, 6, and 7, resulted in increased antimalarial activity and, in some cases, also increased the chemotherapeutic index.

The methylene dioxyphenyl group was found frequently in natural products and reported to possess some interesting biological activities. Based on this information Chien& Cheng (1970) prepared some 5,6-, 6,7-, and the 7,8- methylenedioxy derivatives (3) of febrifugine and related compounds. These analogues found to be active against Plasmodium berghei. Their toxicity in mice is much lower than that of febrifugine. The therapeutic indices of these compounds are comparable with those of the parent compound.

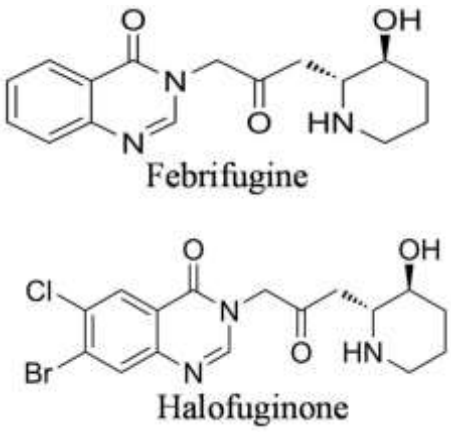

Figure 1: Structure of febrifugine and halofuginone

Compounds	X
4a	H
4b	OCH_3
4c	OH

Researcher prepared 3-[β-keto- - ɣ (3-hydroxy-2-pyridyl)propyl]-4-quinazolone (4a-c), in which the piperidine ring of the side chain has been replaced by pyridine. Compounds 4a-c was assayed against in P. beryhei mice and in chicks, no antimalarial activity was observed. However, the chemical and pharmacological characteristics of 1 encouraged medicinal chemists to pursue suitable lead compounds based on 1 for the development of novel anti malarial drugs.

HALOFUGINONE AS AN ANTIMALARIA THERAPY

The malarial burden of mortality and morbidity continues to rise in several developing countries in Africa, South America, and Asia. Malaria-related deaths remain alarmingly high, partly because of emergence of drug-resistant strains of malaria parasites. Thus, there is a constant need for novel high-efficacy antimalarial therapies that affect various stages in the parasite life-cycle. Of a series of febrifugine analogs halofuginone was the most active against P. falciparum growth in vitro, and displayed curative effects in P. berghei-infected mice. Chemicals with antimalarial effects showed differing patterns against ring stages, trophozoites, and schizonts of P. falciparum in culture, whereas halofuginone acted with equal speed on all 3 stages. Halofuginone affects both the asymptomatic liver stage that is the first stage of the Plasmodium parasite's life cycle as well as sporozoite propagation within liver cells and the blood stage that elicits characteristic malaria symptoms.

In the liver stage, halofuginone inhibited the P. berghei sporozoite load in HepG2 cells, with an IC50 value of 17 nM, without affecting sporozoite traversal. Analysis of the structure/activity relationships indicated that the addition of bromide on the quinazoline ring preserved the antimalarial efficacy of halofuginone and lowered its cytotoxicity for the host cells. The antimalaria mode of action of febrifugine and its analogs probably involved interaction with prolyl-tRNA synthetase (ProRS) in the blood stage. Halofuginone was found to inhibit ProRS activity causing intracellular accumulation of uncharged tRNA and mimicking reduced cellular proline availability. This function requires ATP that directly locks onto and orients two parts of halofuginone onto human ProRS, so that one part of halofuginone mimics bound proline and the other mimics the 3' end of bound tRNA. Halofuginone interacted strongly with the prolyl-tRNA synthetase of P. falciparum, which is resident exclusively in the parasite's cytoplasm, within the asexual blood stage in a non-competitive binding mode. The antimalarial activity of synthesized febrifugine and halofuginone analogs was determined by using in vitro assays: against chloroquine-sensitive and -resistant P. falciparum strains for susceptibility; and against two mammalian cell lines—neuronal cell line NG108 and macrophage cell line J774—for cytotoxicity. The IC_{50}s of halofuginone were observed to be the best among the synthesized derivatives of febrifugine

CONCLUSION

In recent years a lot of attention was focused on halofuginone and its analogs, in light of its wide range of beneficial biological activities against malaria, parasitic, and fibrosis-related diseases, and as an inhibitor of solid and plasma-cell cancers, and Th17-mediated inflammatory autoimmune diseases.However, on the other hand, there are some discrepancies that do not fit these models: halofuginone's effect of apoptosis, which is usually associated with minimal inflammation; the diversity in apoptosis in differing cell types; inhibition or activation of the NF-κB pathway in different cancer cells, the disparity in blocking Smad3 phosphorylation in smooth muscle cells and in balloon-injured rat carotid arteries, modulation of the expression of some ECM remodeling proteins without affecting TGFβ signaling. Moreover, the effects of halofuginone on autoimmune disease models are cytoprotective, which suggests that enhancement of apoptosis or decrease of proliferation

are not likely to be the molecular mechanism employed by halofuginone in this case. It should be noted that halofuginone did not result from any drug discovery program, and its structure was not designed specifically for any of its biological activities. All the preclinical and clinical studies that involved halofuginone have been conducted on racemic material. Thus, a specifically designed chemistry approach that uses halofuginone as an advanced lead structure, together with in vivo biological assays will help to decipher its mode of action, on the one hand, and, on the other hand, will lead to a new and much needed arsenal of drug candidates that may be more specific with respect to the various biological actions, better tolerated, and more efficacious.

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