Bioorg. Med. Chem. Lett. 121 (2025) 130143

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Oxime functionalized Chalcones: Unveiling a new class of Chalcones with potent Antiplasmodial activity against blood-stages of *Plasmodium falciparum* in culture

Reeta Chaudhary [a], Ayushee [b], Vinoth Rajendran [c,*], T.M. Rangarajan [d,*]

[a] Department of Chemistry, Shivaji College, University of Delhi, New Delhi, India
[b] Department of Chemistry, University of Delhi, Delhi, India
[c] Department of Microbiology, School of Life Sciences, Pondicherry University, Puducherry 605014, India
[d] Department of Chemistry, Sri Venkateswara College, University of Delhi, New Delhi, India

A B S T R A C T

The *Plasmodium falciparum* parasite, which is responsible for malaria, has developed resistance to several first-line antimalarial drugs. To address this issue, researchers have been developing novel hybrid molecules that can inhibit parasite growth. In this study, a total of 38 chalcone oxime ethers, consisting of four different types, were evaluated for *in vitro* blood-stage antiplasmodial activity against *P. falciparum* (3D7) using SYBR green I assay. The four classes of oxime ethers showed promising to moderate antiplasmodial activity. At least one molecule from each class was potent, with the IC_{50} values of less than 5 μg/mL. Among the four classes, chalcone-chalconeoxime ethers (CCOE) were the most effective, with the IC_{50} values of 1.55 μg/mL and 1.4 μg/mL for **CCOE-2** and **CCOE-5**, respectively. The most potent molecules, **CKOE-13**, **COAE-2**, **CCOE-2**, and **CCOE-5**, were tested against the chloroquine-resistant strain *P. falciparum* (INDO) exhibited IC_{50} values of less than 5 μg/mL. Notably, the most potent molecules did not induce hemolysis at concentrations up to 50 μg/mL. These findings highlight a new class of chalconeoxime ethers as potent antiplasmodial agents, warranting further exploration of their biological activities.

Malaria is a disease caused by the protozoan parasite *P. falciparum*, which infects both hepatocytes and red blood cells.[1] According to the World Malaria Report 2023, there are 249 million cases and 608,000 deaths worldwide.[2] Unfortunately, the COVID-19 pandemic has led to a 5 % increase in global malaria cases.[3] Although chemotherapy remains the primary treatment for malaria, the emergence of drug-resistant parasites has diminished the efficacy of clinical antimalarial drugs.[4,5] The efficacy of malarial vaccines is limited, offering only partial protection.[6] These findings highlight the urgent need for the development of new therapeutic molecules that can effectively combat malarial parasites.

The bio-precursors of flavonoids, also called chalcones (1,3-diaryl-2-propen-1-ones), or α,β-unsaturated carbonyl compounds, are a fascinating class of compounds that are used in medicine,[7,8] synthesis,[9] and material chemistry[10,11] with diverse characteristics and applications. Chalcones only class of compounds that have a broad spectrum of biological and chemotherapeutic activities, such as anti-inflammatory,[12] anticancer,[13,14] antibacterial,[15,16] antileishmanial,[16] antioxidant,[17] antifungal,[18] and antitubercular activities,[19] owing to their nearly planar structure and extended conjugation that allows chalcones to easily bind with protein thiol groups by Michael-type reactivity.[20,21] One of the main reasons for the huge attraction of chalcones among chemists is the ease of synthesis of chalcones with vast structural diversity, which can be transformed into various heterocycles and other compounds.[7–9,12–21] Our group introduced a new method for accessing chalcone derivatives from bromo-chalcones as precursors *via* Pd-catalyzed C—O cross-coupling reactions[22–26] with potent antiplasmodial effects[25] and potent monoamine oxidase-B (MAO-B) inhibitory effect.[27] Among the oxygen nucleophiles that we have coupled with bromo-chalcones, oximes have attracted our much attention because of their pharmaceutical importance as antibiotics (cefmenoxime,[28] aztreonam,[29] roxithromycin[30]), anti-inflammatory (Ridogrel),[31] antifungal (oxiconazole),[32] and neuroleptic properties.[33] In addition, some previously reported chalcone oxime ethers showed excellent antiplasmodial[25] and MAO-B inhibitory activities[34] (Fig. 1).

Consequently, given the significance of discovering new compounds for effective antiplasmodial treatment, we conducted a study that evaluated the antiplasmodial activity of our previously synthesized chalcone-ketoxime,-aldoxime, and -chalcone oxime ethers[24,26] against blood-stage parasites of drug-sensitive and drug-resistant *P. falciparum*.

A total of 38 chalcone oxime ethers were synthesized by Pd-catalyzed C—O cross-coupling reactions between the corresponding bromo-

* Corresponding authors.
E-mail addresses: vinoth.avj@gmail.com (V. Rajendran), rt.m@svc.ac.in (T.M. Rangarajan).

https://doi.org/10.1016/j.bmcl.2025.130143
Received 2 October 2024; Received in revised form 23 January 2025; Accepted 14 February 2025
Available online 18 February 2025