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Synthesis of novel chalcones through palladium-catalyzed C—O cross-coupling reaction of bromo-chalcones with ethyl acetohydroxamate and their antiplasmodial evaluation against *Plasmodium falciparum in vitro*

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ABSTRACT

An efficient method for palladium-catalyzed C—O cross-coupling of ethyl acetohydroxamate (EAcHO) with 4-bromo-chalcones has been developed to synthesize novel chalcones. The two supporting ligands, namely *t*BuXPhos (**L7**), and cataCXium®PIntB (**L16**) were found to be effective ligands towards the Pd-catalyzed C—O cross-coupling reaction to afford the desired product in moderate to excellent yields (50–99%). The coupled products were screened for *in vitro* blood stage antiplasmodial activity against *Plasmodium falciparum* (3D7) using the [^{3}H] hypoxanthine incorporation inhibition assay. Of the twenty two compounds screened, eleven showed good antiplasmodial activity with IC_{50} values ranging from 6–16 μg/mL. The selected active molecules **11**, **16**, **22**, (IC_{50} 12 μg/mL) and **19** (IC_{50} 6 μg/mL) were studied for their cytotoxic effect against HepG2 Cells (human hepatocellular liver carcinoma cell lines), showing the selectivity index (SI) values are greater than 4 except chalcone **22**. Our result demonstrates a methodology for synthesizing novel chalcones as a new class of antiplasmodial agent.

1. Introduction

Ethyl acetohydroxamate (EAcHO) is one of the important oxygen nucleophile for the preparation of ethyl aryloxyacetohydroxamates which have traditionally been synthesized, by Zinner's Method, via S_NAr type process with electron-deficient aryl systems under basic conditions (Scheme 1A (i)). However, the traditional method is suffered from harsh reaction conditions and limited substrate scope [1–5]. Earlier to Buchwald's report [6], no efficient method has been developed, albeit the ethyl aryloxyacetohydroxamates have been served as an important precursor for the synthesis of benzofurans and synthetically useful aryloxyamines [3–9]. In 2010, Buchwald and Maimone developed an efficient Pd-catalyzed O-arylation of EAcHO with aryl/heteroaryl halides and the coupled product could be converted into *O*-aryl hydroxylamines, and benzofurans in one pot (Scheme 1A (ii)) [6]. Lately, metal-free O-arylation of ethyl acetohydroxamate with diaryliodonium salts and subsequent benzofuran synthesis in one pot procedure has also been reported (Scheme 1A (iii)) [7,8].

Chalcones are one of the major classes of natural products with widespread distribution in plant kingdom [10] and have incessantly been paid a huge attention due to their simple chemistry and pervasive applications in medicinal [11,12], synthetic [13,14] and material chemistries [15]. However, chalcones hold a fascination for most medicinal chemists due to their wide spectrum of chemotherapeutic properties such as antileishmanial [16], anticancer [17], anti-inflammatory [18], antimalarial [19], as a potential curative agent in treating Alzheimer's disease [20–22] etc. With the advent of the natural Licochalcone A possessing antiplasmodial property, the synthesis and antiplasmodial screening of a large number of chalcone derivatives has been triggered. Chalcones' linear or nearly planar structure, an extended conjugation, is allowed to bind the chalcone perfectly into the active sites of *Trypanosoma* and *Plasmodium* cysteine proteases of the malarial parasites. However, the exact mechanism of parasite growth inhibition of different chalcones is not completely studied, while several studies, for unlike chalcones derivatives, indicate that inhibition of a parasite growth is mediated through induced permeation pathway of infected erythrocyte membrane, glutathione (GSH)-dependent haemin

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