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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 falcipuram 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 anti-plasmodial 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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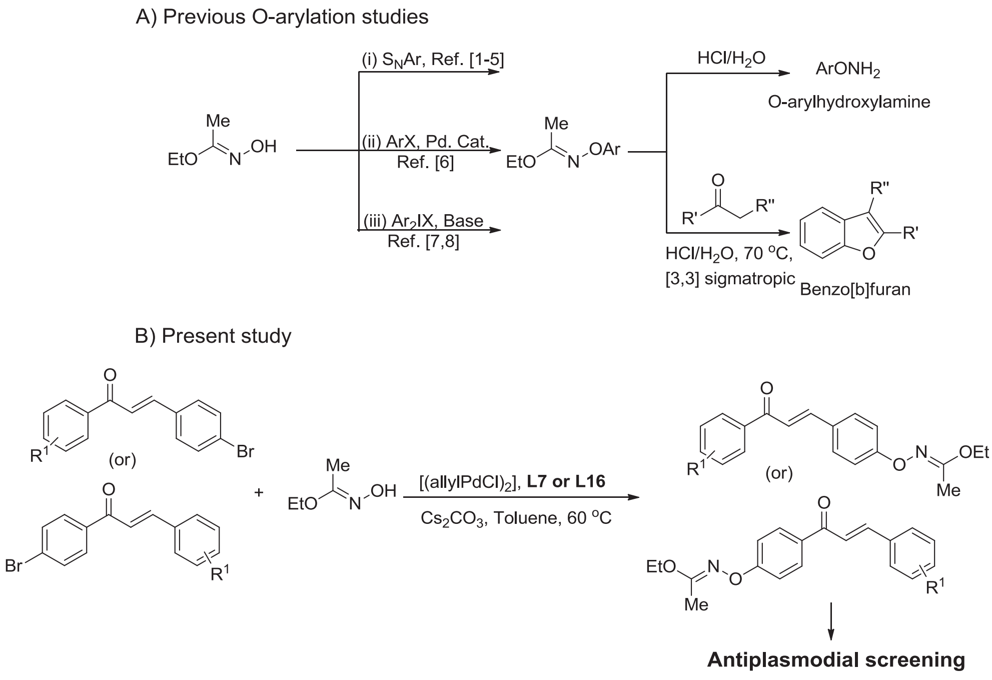


Scheme 1. Coupling of EAcHO with aryl halides (A) and bromo-chalcones (B).

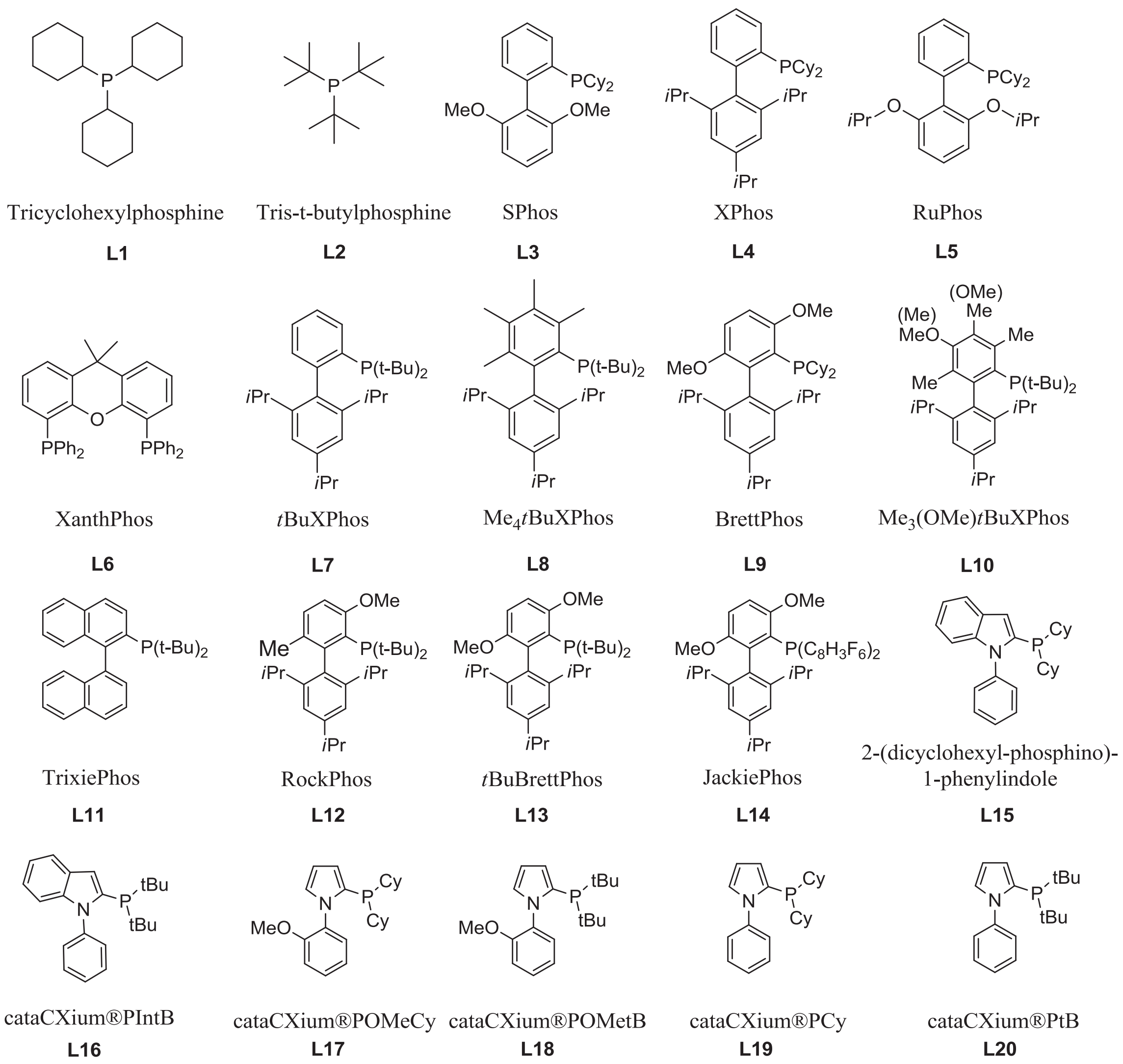
degradation, succinate ubiquinone reductase, cyclin-dependent protein kinases, and plasmepsin II [23,24]. Antiplasmodial research is still an active area of research and there is a huge demand for developing new antiplasmodial agents which receive considerable attention among medicinal chemists due to high mortality of malarial infection and, more to the point, the development of clinical resistance to currently available antiplasmodial drugs [23,24].

A scanty report is available on bromo-chalcones used as a coupling partner in Pd-catalyzed cross-coupling reactions to synthesize new chalcones derivatives. Recently, A. G. Correa first reported the Pd-catalyzed coupling of bromo-chalcones with arylboronic acids [25]. Later, W. Chen demonstrated Pd-catalyzed coupling of bromo-chalcones with different carbon nucleophiles [26]. Subsequently, our group has also developed the methodology for Pd-catalyzed cross-coupling reactions of bromo-chalcones with oxygen nucleophiles [27–31]. To the best of our knowledge, no methodology is reported for the coupling of bromo-chalcones with EAcHO (Scheme 1B). Since the aryl derivatives of EAcHO could be converted into benzofuran derivatives (Scheme 1A) [6–9], this methodology would kindle the chemists' interest due to the recent finding of benzofuran-chalcone hybrids which would be considered as potential candidates for Alzheimer's Disease [20]. Herein, we report a novel methodology for Pd-catalyzed coupling of bromo-chalcones with EAcHO and their antiplasmodial effect on the growth of *P. falciparum* (3D7) in culture.

2. Results and discussion

2.1. Chemistry-methodology

We started off our work with the screening of ligands for the coupling of EAcHO with bromo-chalcone, (*E*)-3-(4-bromophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one, as model substrate. To find a suitable ligand(s) for this process, the commercially available Buchwald type and Beller type ligands used are shown in Fig. 1. The ligand screening reaction was carried out under the standard conditions such as 1.0 mol % of [$Pd_2(dba)_3$], 2.5 mol % of ligands (**L1**-**L20**) and 1.5 eq. of Cs_2CO_3 as base in toluene solvent at 60 °C under argon atmosphere. The results of ligand screening are summarized in Table 1. Of the twenty ligands screened for the coupling of model substrate with EAcHO, only three ligands, **L7**, **L16** and **L20** gave the coupling product in good yield with 98% conversion. The only Buchwald ligand, *t*BuXPhos (**L7**) was successful in the coupling reaction with 71% yield. The other two Beller type ligands, cataCXium®PIntB (**L16**) and cataCXium®PtB (**L20**) were also found to be successful in the coupling reaction for the first time. The successful coupling of bromobenzene with EAcHO reported by Buchwald [6] using *t*BuBrettPhos (**L13**) ligand was failed to couple our model substrate with EAcHO under these reaction conditions. Therefore, we decided to screen the palladium sources with these promising ligands and the results are summarized in Table 2. The Pd-catalysts, $Pd(OAc)_2$ and $Pd(PPh_3)_4$, with both the ligands **L7** and **L16** did not facilitate the coupling reaction of model substrate with EAcHO (Entries 1–4). The model reaction using the catalyst combinations [(π-cinnamylPdCl)$_2$]/**L7** or **L16** ligand gave the coupling product only in 68% and 56% yield respectively (Entries 5 and 6). The reaction using the catalyst combination of [(π-allyl)PdCl]$_2$/*t*BuXPhos ligand (**L7**) gave the desired product with a slight rise of yield, 78% (Entry 7), comparted to [$Pd_2(dba)_3$] system [6]. The supporting ligand Me$_4$*t*BuXPhos (**L8**) with [(π-allyl)PdCl]$_2$, though successful in the coupling of phenyl bromide with EAcHO in 70% conversion shown by Buchwald [6], failed to facilitate the coupling of bromo-chalcone with EAcHO (Entry 8). The ligands BrettPhos (**L9**) and RockPhos (**L12**) facilitated the reaction to some extent and gave the desired product in poor yield (Entries 9 and 10). The ligand *t*BuBrettPhos (**L13**), a successful ligand in the coupling of phenyl bromide with EAcHO [6], facilitated the coupling reaction only with [(π-allyl)PdCl]$_2$ (Entry 11) as good as *t*BuXPhos ligand (**L7**). The catalyst system comprised of [(π-allyl)PdCl]$_2$/cataCXium®PIntB (**L16**) gave the desired product in lower yield (Entry 12) than the yield obtained by the catalyst system [$Pd_2(dba)_3$]/cataCXium®PIntB (**L16**) (Table 1, Entry 16). The solvent 1,4-dioxane was also found to be a good solvent of choice for the coupling reaction, gave the desired product in good yield, 76%, (Entry 13). Based on the optimization results (Tables 1 and 2), although *t*BuBrettPhos (**L13**) ligand gave the similar result [6], the [(π-allyl)PdCl]$_2$/*t*BuXPhos (**L7**) catalyst system has been chosen as a best catalyst system with respect to comparably low prize of ligand **L7**. Having the best catalyst system and the reaction conditions in hand, we further explored the coupling of EAcHO with different bromo-chalcones bearing the bromine substitution on



Tricyclohexylphosphine **L1**; Tris-t-butylphosphine **L2**; SPhos **L3**; XPhos **L4**; RuPhos **L5**

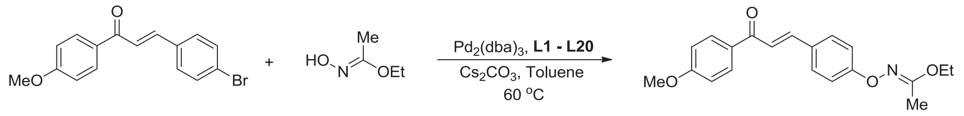
XanthPhos **L6**; *t*BuXPhos **L7**; Me$_4$*t*BuXPhos **L8**; BrettPhos **L9**; Me$_3$(OMe)*t*BuXPhos **L10**

TrixiePhos **L11**; RockPhos **L12**; *t*BuBrettPhos **L13**; JackiePhos **L14**; 2-(dicyclohexyl-phosphino)-1-phenylindole **L15**

cataCXium®PIntB **L16**; cataCXium®POMeCy **L17**; cataCXium®POMetB **L18**; cataCXium®PCy **L19**; cataCXium®PtB **L20**

Fig. 1. Structure of ligands used for Pd-catalyzed C−O cross-coupling reaction.

Table 1
Ligand screen for the Pd-catalyzed coupling of (*E*)-3-(4-bromophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one with EAcHO.[a]



Entry	Ligand	Conv.	Yield	Entry	Ligand	Conv.	Yield
1	**L1**	ND	NR	11	**L11**	51.0	54[c]
2	**L2**	ND	NR	12	**L12**	ND	NR
3	**L3**	ND	NR	13	**L13**	ND	NR
4	**L4**	ND	NR	14	**L14**	42.0	43[c]
5	**L5**	ND	NR	15	**L15**	ND	NR
6	**L6**	ND	NR	16	**L16**	**98**	**72**[b]
7	**L7**	**98**	**71**[b]	17	**L17**	ND	NR
8	**L8**	ND	NR	18	**L18**	92	48[b]
9	**L9**	42.0	32[c]	19	**L19**	ND	NR
10	**L10**	ND	NR	20	**L20**	**98**	**70**[b]

[a] Reaction Conditions: (*E*)-3-(4-bromophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (0.35 mmol, 1.0 eq.), EAcHO (0.7 mmol, 2.0 eq.), Cs_2CO_3 (0.52 mmol, 1.5 eq.), [$Pd_2(dba)_3$] (1.0 mol %), Ligand, **L1**-**L20** (2.5 mol %), toluene (2.0 mL), 60 °C, Ar atm., Reaction time, 3 h.

[b] Isolated yield.

[c] Yield & Conv. calculated based on ^{1}H NMR. NR = No Reaction. ND = Not Determined.

Table 2
Palladium source screening for Pd-catalyzed coupling of (*E*)-3-(4-bromophenyl)-1-(4- methoxyphenyl)prop-2-en-1-one with EAcHO.[a]

Entry	Pd Source (1.0 mol %)	**Ligand** (2.5 mol %)	Conv. (%)[b]	Yield (%)[b]
1	$Pd(OAc)_2$	**L7**	ND	NR
2	$Pd(OAc)_2$	**L16**	ND	NR
3	$Pd(PPh_3)_4$	**L7**	ND	NR
4	$Pd(PPh_3)_4$	**L16**	ND	NR
5	[(π-cinnamylPdCl)$_2$]	**L7**	98	68
6	[(π-cinnamylPdCl)$_2$]	**L16**	90	56
7	[(π-allyl)PdCl]$_2$	**L7**	**95**	**78**
8	[(π-allyl)PdCl]$_2$	**L8**	ND	NR
9	[(π-allyl)PdCl]$_2$	**L9**	52	45
10	[(π-allyl)PdCl]$_2$	**L12**	32	25
11	[(π-allyl)PdCl]$_2$	**L13**	**90**	**75**
12	[(π-allyl)PdCl]$_2$	**L16**	95	66
13	[(π-allyl)PdCl]$_2$	**L7**	**95**	**76**[c]

[a] Reaction Conditions: (*E*)-3-(4-bromophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (0.35 mmol, 1.0 eq.), EAcHO (0.7 mmol, 2.0 eq.), Cs_2CO_3 (0.52 mmol, 1.5 eq.), Pd-catalyst (1.0 mol %), Ligand (2.5 mol %), toluene (2.0 mL), 60 °C, Ar atm.

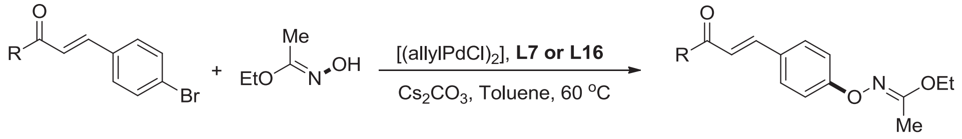
[b] Based on the isolated compound.

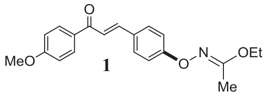
[c] Ethyl acetohydroxamate (3.0 eq.), 1,4-dioxane (2.0 mL).

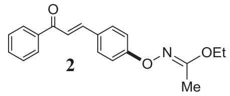
the 3-phenyl ring, (*E*)-3-(bromophenyl)-1-(substitutedphenyl)prop-2-en-1-ones as shown in Table 3. The [(π-allyl)PdCl]$_2$/*t*BuXPhos (**L7**) ligand system coupled the unsubstituted bromo-chalcone, (*E*)-3-(bromophenyl)-1-(phenyl)prop-2-en-1-one, with EAcHO to afford the coupled product **2** in 79% yield. The catalyst system also coupled the other (*E*)-3-(bromophenyl)-1-(substitutedphenyl)prop-2-en-1-ones, such as -1-(4-fluorophenyl)-, -1-(4-methylphenyl)-, -1-(2-methoxyphenyl)-, -1-(2-methylphenyl)-, and -1-(3-hydroxyphenyl)- with EAcHO to afford the desired coupled products, **3**–**6**, and **9** in good to excellent yields, whereas the catalyst system failed to couple the EAcHO with (*E*)-3-(4-bromophenyl)-1-(4-nitrophenyl)prop-2-en-1-one with little to no product, **7**. The chalcones, (*E*)-3-(4-bromophenyl)-1-(2,4-dimethoxyphenyl)prop-2-en-1-one and (*E*)-3-(4-bromophenyl)-1-(naphthalen-1-yl)prop-2-en-1-one were also effectively coupled with EAcHO by the catalyst system to afford the desired products **8** and **11** in 81% and 97% respectively. However, the catalyst system failed to couple the 3-bromo-chalcone, (*E*)-3-(3-bromophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one, and heteroarylchalcone, (*E*)-3-(4-bromophenyl)-1-(1H-pyrrol-2-yl)prop-2-en-1-one with EAcHO. The other successful ligand/catalyst systems such as [(π-allyl)PdCl]$_2$/*t*Bu-BrettPhos (**L13**) and [$Pd_2(dba)_3$]/cataCXium®PIntB (**L16**) were also tested in the scope of the reaction. The former catalyst system could couple the chalcones, (*E*)-3-(4-bromophenyl)-1-(4-fluorophenyl)prop-2-en-1-one with EAcHO, to afford the desired product **3** in moderate yield, 69%. The later catalyst system was also effective towards the coupling of EAcHO with 4-bromo-chalcones to afford the desired products **9** and **11** in 68% and 84% yields respectively.

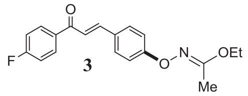
Alternatively, the coupling reactions were carried out with chalcones, bearing the bromine substitution on 1-phenyl ring, (*E*)-1-(4-bromophenyl)-3-(substitutedphenyl)prop-2-en-1-ones, with EAcHO and the results are given in Table 4. The [(π-allyl)PdCl]$_2$/*t*BuXPhos (**L7**) ligand system was successfully coupled the unsubstituted 4-bromo-chalcone, (*E*)-1-(4-bromophenyl)-3-(phenyl)prop-2-en-1-one, with EAcHO to afford the product **13** in excellent yield, 94%. The catalyst system was also successful in the coupling of substituted 4-bromo-chalcones, (*E*)-1-(4-bromophenyl)-3-(substitutedphenyl)prop-2-en-1-ones, such as -3-(4-methylphenyl)-, -3-(4-methoxyphenyl)-, -3-(4-benzyloxyphenyl)-, -3-(2-methoxyphenyl)-, -3-(3-methoxyphenyl)-, -3-(2,5-dimethoxyphenyl)-, -3-(3,4-dimethoxyphenyl)-, and -3-(3,4,5-

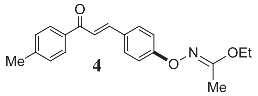
Table 3
Palladium-catalyzed C—O cross-coupling of EAcHO with (*E*)-3-(bromophenyl)-1-(substituted- phenyl)prop-2-en-1-ones.[a,b]




1
(**L7**, 78%, 3 h)


2
(**L7**, 79%, 23 h)


3
(**L7**, 88%, 1 h)
(**L13**, 69%, 6 h)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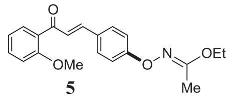
(**L7**, 74%, 3 h)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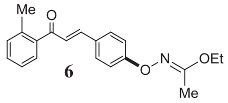
(**L7**, 75%, 3.5 h)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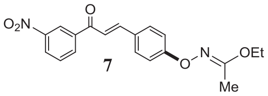
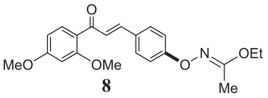
(**L7**, 73%, 6 h)


7
(**L7**, NR, 6 h)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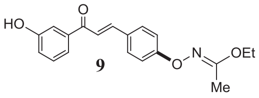
(**L7**, 81%, 24 h)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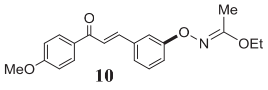
(**L7**, 99%, 2 h)
(**L16**, 68%, 2 h)[c]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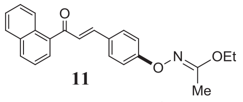
(**L7**, NR, 4 h)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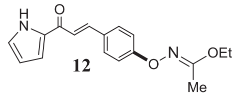
(**L7**, 97%, 2 h)
(**L16**, 84%, 2 h)[c]

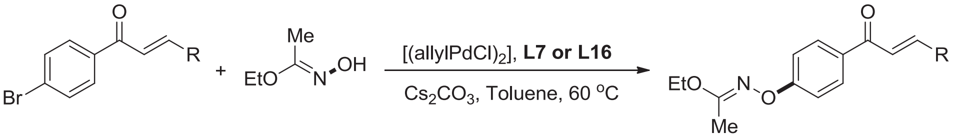

12
(**L7**, NR, 24 h)

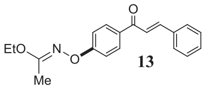
[a] Reaction conditions: Bromo-chalcones (0.5 mmol, 1 equiv.), Ethyl acetohydroxamate (1.0 mmol, 2.0 equiv.), Cs_2CO_3 (0.75 mmol, 1.5 equiv.), [$(allylPdCl)_2$] (1.0 mol %), Ligands (2.5 mol %), toluene (2.5 mL), Ar atm.

[b] Isolated yield.

[c] [$Pd_2(dba)_3$] (1.0 mol %), cataCXium®PIntB (**L16**).

Table 4
Palladium-catalyzed C—O cross-coupling of EAcHO with (*E*)-1-(bromophenyl)-3-(substituted- phenyl)prop-2-en-1-ones.[a,b]

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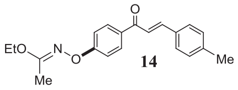
(**L7**, 94%, 1.3 h)
(**L16**, 87%, 2 h)[c]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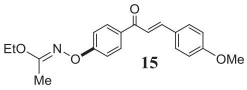
(**L7**, 80%, 3 h)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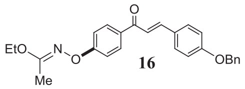
(**L7**, 88%, 2.5 h)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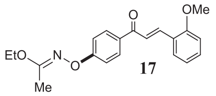
(**L7**, 65%, 4 h)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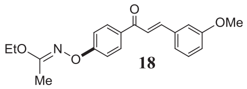
(**L7**, 50%, 6 h)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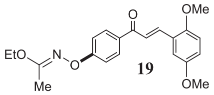
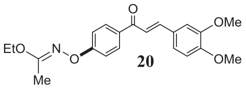
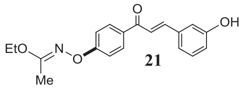
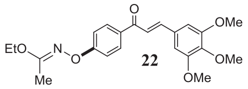
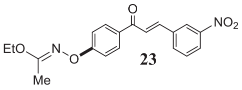
(**L7**, 91%, 24 h)

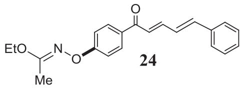

19
(**L7**, 83%, 1 h)

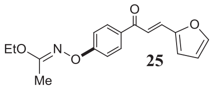

20
(**L7**, 90%, 1 h)
(**L16**, 90%, 1.5 h)[c]

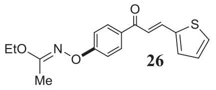

21
(**L7**, NR, 8 h)

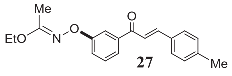

22
(**L7**, 93%, 2 h)
(**L16**, 70%, 24 h)[c]

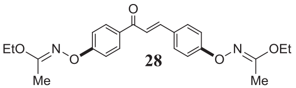

23
(**L7**, NR, 4 h)


24
(**L7**, 92%, 1 h)


25
(**L7**, 86%, 3 h)
(**L16**, 80%, 4 h)[c]


26
(**L7**, 84%, 6 h)


27
(**L7**, NR, 6 h)


28
(**L7**, 87%, 3 h)[d]

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[a] Reaction conditions: Bromo-chalcones (0.5 mmol, 1 equiv.), EAcHO (1.0 mmol, 2.0 equiv.), Cs$_2$CO$_3$ (0.75 mmol, 1.5 equiv.), [(allylPdCl)$_2$] (1.0 mol %), *t*BuXPhos (**L7**) (2.5 mol %), toluene (2.5 mL), Ar atm.

[b] Isolated yield.

[c] [Pd$_2$(dba)$_3$] (1.0 mol %), **L16** (2.5 mol %).

[d] Dibromo-chalcone (0.5 mmol, 1 equiv.), EAcHO (2.0 mmol, 4.0 equiv.), Cs$_2$CO$_3$ (1.5 mmol, 3.0 equiv.), [(allylPdCl)$_2$] (2.0 mol %), *t*BuXPhos (**L7**) (5.0 mol %), toluene (2.5 mL), Ar atm.

trimethoxyphenyl)-, with EAcHO to afford the desired coupled products, **14–20** and **22** in moderate to excellent yields. Unfortunately, the catalyst system failed to couple the -3-(3-hydroxyphenyl)-, and -3-(3-nitrophenyl)-, to afford the desired products **21** and **23**. The cinnamyl chalcone, (2*E*,4*E*)-1-(4-bromophenyl)-5-phenylpenta-2,4-dien-1-one, and heteroaryl chalcones, (*E*)-1-(4-bromophenyl)-3-(furan-2-yl)prop-2-en-1-one and (*E*)-1-(4-bromophenyl)-3-(thiophen-2-yl)prop-2-en-1-one, were effectively coupled to afford the desired products **24**, **25**, and **26** in 92%, 86%, and 84% yields respectively. The catalyst system was ineffective towards the coupling of 3-bromo-chalcone, (*E*)-1-(3-bromophenyl)-3-(4-methylphenyl)prop-2-en-1-one, to afford the desired product **27**. This result reveals that the catalyst system purely direct the reductive elimination step through electronic pathway [27,28]. Finally, the catalyst system could effectively couple the dibromo-chalcone, (*E*)-1,3-bis(4-bromophenyl)prop-2-en-1-one, with EAcOH, to afford the desired product **28** in 87% yield. Similarly, the other catalyst system comprised of [Pd$_2$(dba)$_3$]/cataCXium®PIntB (**L16**) could also effectively facilitate the coupling reaction to afford the desired products **13**, **20**, **22**, and **25** in 87%, 90%, 70%, and 80% yields respectively. This is the first report for the catalyst system with **L16** ligand in the coupling of bromo-chalcones with EAcOH.

2.2. *Antiplasmodial activity of chalcones*

All the novel chalcones synthesized by Pd-catalyzed cross-coupling of bromo-chalcones with EAcHO (Scheme 1B, Tables 3 and 4) were screened for antiplasmodial activity using a [^{3}H] hypoxanthine-incorporation assay against *P. falciparum* (3D7) in culture. The 50% inhibitory concentration (IC$_{50}$) values on parasite growth for all chalcone series are given in Table 5. The standard antimalarial drugs chloroquine (CQ) and artemisinin (ART) were used as positive controls [32]. Almost all the synthesized chalcones exhibited a differential killing effect on the parasite, but none of them had better IC$_{50}$ values than CQ and ART. The chalcones with EAcHO substituted on 4-position of 3-phenyl ring (**1–6**, **8**, **9**, and **11**) showed acceptable inhibitory effects on the parasite growth. Particularly, the chalcones **1**, **5**, **6**, **8**, **9**, and **11** showed interesting antiplasmodial activity with IC$_{50}$ values ranging from 12 to 16 µg/mL. The chalcones with methoxy group on 1-phenyl ring (**1**, **5**, and **8**), irrespective of its position and number, showed interesting antiplasmodial activity, whereas the methyl group shows the position dependent activity. The chalcone with methyl group at 4-position of 1-phenyl ring (**4**) showed moderate antiplasmodial activity with an IC$_{50}$ value of 33 µg/mL, whereas those at 2-position (**6**) showed increased

Table 5

In vitro antiplasmodial activity of coupled products against *P. falciparum* (3D7).

No.	Chalcone	*P. falciparum* (3D7)	
		IC_{50} (μg/mL ± SEM)[a]	IC_{50} (μM ± SEM)
1.	**1**	16 ± 1.02	47.1 ± 0.85
2.	**2**	30 ± 0.65	96.9 ± 0.82
3.	**3**	> 40	> 112.1
4.	**4**	33 ± 1.58	102 ± 0.98
5.	**5**	14 ± 1.10	41.25 ± 0.85
6.	**6**	14 ± 0.63	43.29 ± 0.78
7.	**8**	16 ± 0.94	43.31 ± 0.42
8.	**9**	15 ± 1.05	46.10 ± 0.85
9.	**11**	**12 ± 0.75**	**33.38 ± 0.10**
10.	**13**	30 ± 0.34	96.97 ± 0.72
11.	**14**	26 ± 1.14	80.39 ± 0.98
12.	**15**	28 ± 0.88	82.50 ± 0.64
13.	**16**	**12 ± 1.20**	**28.88 ± 0.82**
14.	**17**	26 ± 0.50	76.60 ± 0.92
15.	**18**	14 ± 1.88	41.25 ± 1.12
16.	**19**	**6 ± 0.35**	**16.24 ± 0.52**
17.	**20**	14 ± 0.78	37.89 ± 0.90
18.	**22**	**12 ± 0.54**	**30.0 ± 0.84**
19.	**24**	> 40	> 119.26
20.	**25**	> 40	> 174.42
21.	**26**	28 ± 1.33	88.77 ± 0.89
22.	**28**	26 ± 0.95	63.34 ± 0.82
23.	Chloroquine (CQ)[b]	0.010 ± 0.5	0.031 ± 0.36
24.	Artemisinin (ART)[b]	0.021 ± 0.75	0.074 ± 0.45

[a] IC_{50} (μg/mL): concentration corresponding to 50% growth inhibition of parasite.

[b] Antimalarial control.

antiplasmodial activity with an IC_{50} value of 14 μg/mL. The other chalcones **2** and **3** showed moderate parasite killing effect. Among the nine chalcones synthesized, the naphthyl chalcones (**11**) was found to be most active with an IC_{50} value of 12 μg/mL.

We next examined the effect of EAcHO group substituted on 4-position of 1-phenyl ring (Table 5, **13–20**, **22**, **24–26**, and **28**) showed acceptable inhibitory effects on the parasite growth. Among these chalcones, eight chalcones (**13–15**, **17**, and **24–28**) showed moderate inhibitory effect on the parasite growth with the IC_{50} values ranging from 26 to 40 μg/mL. Only five chalcones (**16**, **18–20**, and **22**) showed interesting antiplasmodial activity.

The antiplasmodial activity of chalcones with mono methoxy group on 3-phenyl ring is position dependent. The methoxy group at 4- and 2-position (**15** and **17**) showed moderate activity, whereas those at 3-position (**18**) showed increased antiplasmodial activity with an IC_{50} value of 14 μg/mL. However, polymethoxy substituted chalcones (**19**, **20**, and **22**) showed improved antiplasmodial activity with IC_{50} values of 6 μg/mL, 14 μg/mL, and 12 μg/mL respectively. Also, the chalcone with benzyloxy group showed interesting inhibitory effect with an IC_{50} value 12 μg/mL. The cinnamyl (**24**), and heteroaryl (**25**, and **26**) chalcones possess moderate inhibitory effects on the parasite killing. Amongst all chalcones, the chalcone **19** showed most active towards the parasite killing effect with an IC_{50} value of 6 μg/mL. Interestingly, the synthesized novel chalcones are exhibited a highly comparable IC_{50} values with other chalcone derivatives and antimalarial agents in clinics [33–36].

Finally, the selected active molecules **11**, **16**, **19**, and **22** were studied for their cytotoxic effect in HepG2 cells and the results are given in Table 6. The selectivity index (SI) values for the selected active molecules, **11**, **16**, **19**, and **22** were calculated using the formula of IC_{50} value of normal cell line (HepG2)/IC_{50} value of *P. falciparum* (3D7), are 4.5, 8.3, 16.7, and 1.7 respectively. The compound **22** exhibited non-selective killing of the parasite with lower selectivity index of 1.7. The most active molecule **19** displayed higher SI values indicating lower cytotoxic effect towards HepG2 cells. As a result, the active molecule **19** is considered to be highly efficacious towards the inhibition of *P. falciparum* with greater selectivity.

Table 6

Cytotoxic effect on HepG2 cells and selectivity index (SI) of most active molecules (**11**, **16**, **19**, and **22**) *in vitro*.

Chalcone	Cytotoxicity (HepG2 Cells)		Selectivity index (SI)
	(μg/mL ± SEM)	(μM ± SEM)	
11	54 ± 1.12	150 ± 0.85	4.5
16	> 100	> 240	> 8.3
19	> 100	> 271	> 16.7
22	20 ± 0.65	50 ± 0.84	1.7

3. Experimental section

3.1. Analytical methods

NMR data were obtained on Jeol 400 MHz spectrometers. All compounds were characterized by ^1H, ^{13}C NMR (399.78 MHz, 100.5 MHz respectively), IR, and HRMS. Copies of ^1H and ^{13}C NMR spectra can be found in Supplementary Information. All ^1H and ^{13}C chemical shifts are reported in parts per million (ppm) and were measured relative to TMS or residual $CDCl_3$ solvent peak. FT-IR spectra were recorded on Bucker model RXI using KBr disc. HRMS (ESI) measurements were performed on Thermo Scientific Orbitrap Elite Hybrid Ion Trap-Orbitrap Mass Spectrometer. Melting points were recorded on Buchi M-560 instruments and were uncorrected. Yields referred to isolated compounds.

3.2. General procedure for the palladium-catalyzed cross-coupling of bromo-chalcones with ethyl acetohydroxamate

An oven dried 5.0 mL two-neck round bottomed flask was equipped with a magnetic stir bar, a rubber septum, condenser and an argon balloon on the top of the condenser with the aid of an adaptor. The flask was charged with Cs_2CO_3 and dried with hot air gun under vacuum. The R.B. flask was allowed to cool under argon atmosphere. Bromo-chalcones, Pd-source and ligand (**L7** or **L16**) were added in quick succession. The flask was then repeatedly evacuated and refilled with Ar gas for three times to maintain inert atm. To this, 2.0 mL of anhydrous toluene was added via syringe and again the flask was flushed with argon for three times. Ethyl acetohydroxamate was added to the reaction mixture via syringe and the flask was placed in a pre-heated oil bath at a temperature 60 °C. The reaction mixture was stirred vigorously until completion of the reaction (times mentioned in tables) as indicated by TLC analysis. The reaction mixture was allowed to cool to room temperature, and the crude product, obtained by usual water workup procedure, was purified by column chromatography on silica gel (230–400 mesh size) using 5–10% ethyl acetate in hexane as eluent. The solvent removal under reduced pressure afforded the desired compound was obtained as a yellow solid/viscous liquid.

3.2.1. Ethyl N-4-((E)-3-(4-methoxyphenyl)-3-oxo-prop-1-enyl) phenoxyethanimidate (1)

Yellow solid (Yield 78%); m.p. 105.4–107.4 °C. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.35–1.39 (t, 3H), 2.13 (s, 3H), 3.89 (s, 3H), 4.18–4.24 (q, 2H), 6.98 (d, 2H, J = 8.4 Hz), 7.18 (d, 1H, J = 8.4 Hz), 7.43 (d, 1H, J = 15.3 Hz), 7.53 (d, 1H, J = 10.6 Hz), 7.59 (d, 2H, J = 8.8 Hz), 7.78 (d, 1H, J = 15.2 Hz), 8.04 (d, 2H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 14.49, 14.52, 55.62, 63.24, 113.90, 114.36, 119.57, 128.35, 130.05, 130.84, 131.54, 144.17, 161.74, 163.37, 166.33, 188.99. FTIR (KBr) υ (cm^{-1}): 2977, 2918, 2847, 1913, 1647, 1596, 1500, 1420, 1375, 1313, 1249, 1221, 1172, 1112, 1017, 975, 828, 745, 675, 612, 566, 532. HRMS (ESI) calcd. for $C_{20}H_{21}NO_4$: $[M + H]^+$

340.1549; Found: 340.1553.

3.2.2. Ethyl N-4-((E)-3-oxo-3-phenylprop-1-enyl)phenoxyethanimidate (2)

Yellow solid (Yield 79%); m.p. 91.7–93.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.35–1.39 (t, 3H), 2.14 (s, 3H), 4.18–4.24 (q, 2H), 7.19 (d, 2H, J = 8.8 Hz), 7.42 (d, 1H, J = 15.7 Hz), 7.48–7.52 (t, 2H), 7.57 (d, 1H, J = 7.3 Hz), 7.60 (d, 2H, J = 8.7 Hz), 7.8 (d, 1H, J = 15.6 Hz), 8.01 (d, 2H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.47, 14.54, 63.25, 114.36, 114.42, 119.78, 128.14, 128.56, 130.19, 132.67, 138.68, 145.09, 161.91, 166.38, 190.84. IR (KBr) υ (cm^{-1}): 2977, 2919, 2850, 1895, 1653, 1996, 1499, 1412, 1370, 1314, 1246, 1210, 1155, 1057, 1012, 975, 904, 824, 772, 718, 686. HRMS (ESI) calcd. for $C_{19}H_{19}NO_3$: [M + H]$^+$ 310.1443; Found: 310.1442; [M + Na]$^+$ 332.1263; Found: 332.1257.

3.2.3. Ethyl N-4-((E)-3-(4-fluorophenyl)-3-oxo-prop-1-enyl) phenoxyethanimidate (3)

Yellow solid (Yield 88%); m.p. 95.1–96.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.35–1.39 (t, 3H), 2.14 (s, 3H), 4.18–4.24 (q, 2H), 7.15–7.20 (m, 4H), 7.39 (d, 1H, J = 15.7 Hz), 7.60 (d, 2H, J = 8.8 Hz), 7.80 (d, 1H, J = 15.3 Hz), 8.03–8.07 (q, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.49, 14.56, 63.27, 114.42, 115.80 (d, $^2J_{C\text{-}F}$ = 21.3 Hz), 119.22, 128.00, 130.25, 131.12 (d, $^3J_{C\text{-}F}$ = 9.1 Hz), 134.99, 145.30, 161.99, 164.33, 166.42, 189.11. IR (KBr) υ (cm^{-1}): 2977, 2917, 2850, 1906, 1654, 1596, 1566, 1500, 1415, 1372, 1314, 1209, 1157, 1109, 1052, 1019, 980, 900, 819, 670, 600, 570. HRMS (ESI) calcd. for $C_{19}H_{18}FNO_3$: [M + H]$^+$ 328.1349; Found: 328.1343; [M + Na]$^+$ 366.0908; Found: 366.0922.

3.2.4. Ethyl N-4-((E)-3-oxo-3-(4-methylphenyl)prop-1-enyl) phenoxyethanimidate (4)

Yellow solid (Yield 74%); m.p. 73.5–76.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.35–1.39 (t, 3H), 2.13 (s, 3H), 2.43 (s, 3H), 4.18–4.24 (q, 2H), 7.18 (d, 2H, J = 8.8 Hz), 7.3 (d, 2H, J = 8.0 Hz), 7.42 (d, 1H, J = 15.7 Hz), 7.59 (d, 2H, J = 8.7 Hz), 7.79 (d, 1H, J = 15.6 Hz), 7.93 (d, 2H, J = 8.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.49, 14.53, 21.80, 63.24, 114.37, 119.79, 128.71, 129.40, 130.12, 132.31, 136.07, 143.47, 144.61, 161.81, 166.34, 190.28. IR (KBr) υ (cm^{-1}): 3029, 2978, 2919, 2851, 1912, 1652, 1594, 1566, 1500, 1411, 1373, 1315, 1246, 1214, 1158, 1113, 1055, 1006, 978, 903, 811, 736, 674, 644, 571. HRMS (ESI) calcd. for $C_{20}H_{21}NO_3$: [M + H]$^+$ 324.1600; Found: 324.1592; [M + Na]$^+$ 346.1419; Found: 346.1403.

3.2.5. Ethyl N-4-((E)-3-(2-methoxyphenyl)-3-oxo-prop-1-enyl) phenoxyethanimidate (5)

Yellow liquid (Yield 75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.35–1.38 (t, 3H), 2.12 (s, 3H), 3.89 (s, 3H), 4.17–4.22 (q, 2H), 7.0 (d, 1H, J = 8.3 Hz), 7.04 (d, 1H, J = 7.2 Hz), 7.15 (d, 1H, J = 8.8 Hz), 7.23 (d, 1H, J = 15.6 Hz), 7.41 (d, 1H, J = 15.7 Hz), 7.47 (d, 1H, J = 10.5 Hz), 7.53 (d, 2H, J = 8.8 Hz), 7.57 (d, 2H, J = 8.5 Hz), 7.6 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.49, 14.53, 55.88, 63.22, 111.69, 114.31, 120.78, 124.95, 128.30, 130.10, 130.30, 132.63, 143.89, 158.02, 161.70, 166.31, 193.49. IR (KBr) υ (cm^{-1}): 2978, 2921, 2846, 1896, 1649, 1595, 1498, 1428, 1410, 1380, 1314, 1242, 1203, 1161, 1113, 1021, 978, 904, 828, 758, 655, 606, 579. HRMS (ESI) calcd. for $C_{20}H_{21}NO_4$: [M + H]$^+$ 340.1549; Found: 340.1539; [M + Na]$^+$ 362.1368; Found: 362.1356.

3.2.6. Ethyl N-4-((E)-3-oxo-3-(2-methylphenyl)prop-1-enyl) phenoxyethanimidate (6)

Yellow liquid (Yield 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.34–1.38 (t, 3H), 2.12 (s, 3H), 2.43 (s, 3H), 4.17–4.22 (q, 2H), 7.0 (d, 1H, J = 15.9 Hz), 7.16 (d, 2H, J = 8.8 Hz), 7.27 (d, 2H, J = 8.0 Hz), 7.36 (d, 1H, J = 6.9 Hz), 7.41 (d, 1H, J = 15.6 Hz), 7.46 (d, 1H, J = 7.6 Hz), 7.5 (d, 2H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.48, 14.53, 20.24, 63.25, 114.39, 124.67, 125.54, 127.80, 128.05, 130.15, 130.29, 131.31, 136.79, 139.59, 146.36, 161.97, 166.39, 197.14. IR (KBr) υ (cm^{-1}): 2979, 2927, 2858, 1894, 1643, 1596, 1501, 1425, 1371, 1312, 1242, 1210, 1160, 1123, 1061, 1013, 979, 904, 829, 769, 734, 659, 576. HRMS (ESI) calcd. for $C_{20}H_{21}NO_3$: [M + H]$^+$ 324.1600; Found: 324.1601.

3.2.7. Ethyl N-4-((E)-3-(2,4-dimethoxyphenyl)-3-oxo-prop-1-enyl) phenoxyethanimidate (8)

Yellow solid (Yield 81%); m.p. 70.2–71.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.35–1.38 (t, 3H), 2.12 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 4.18–4.23 (q, 2H), 6.50 (s, 1H), 6.55–6.57 (q, 1H), 7.15 (d, 2H, J = 8.8 Hz), 7.38 (d, 1H, J = 15.6 Hz), 7.54 (d, 2H, J = 8.8 Hz), 7.65 (d, 1H, J = 15.6 Hz), 7.73 (d, 1H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.50, 55.67, 55.89, 63.21, 98.83, 105.19, 114.29, 122.68, 125.05, 128.72, 129.94, 132.85, 142.49, 160.37, 161.48, 164.06, 166.26, 190.93. IR (KBr) υ (cm^{-1}): 2920, 2845, 1886, 1648, 1601, 1497, 1462, 1418, 1372, 1317, 1244, 1208, 1160, 1110, 1020, 976, 903, 820, 646, 577. HRMS (ESI) calcd. for $C_{21}H_{23}NO_5$: [M + H]$^+$ 370.1654; Found: 370.1651; [M + Na]$^+$ 392.1474; Found: 392.1468.

3.2.8. Ethyl N-4-((E)-3-(3-hydroxyphenyl)-3-oxo-prop-1-enyl) phenoxyethanimidate (9)

Yellow solid (Yield 99%); m.p. 112.8–115.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.35–1.39 (t, 3H), 2.13 (s, 3H), 4.18–4.24 (q, 2H), 5.98 (s, 1H), 7.09 (d, 1H, J = 8.0 Hz), 7.18 (d, 2H, J = 8.8 Hz), 7.39 (d, 2H, J = 15.4 Hz), 7.56–7.60 (t, 4H), 7.8 (d, 1H, J = 15.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.49, 14.53, 63.28, 114.42, 115.30, 119.60, 120.32, 120.96, 128.02, 129.96, 130.35, 139.98, 145.69, 156.58, 162.04, 166.46, 190.99. FTIR (KBr) υ (cm^{-1}): 2983, 2917, 2849, 1652, 1573, 1499, 1445, 1371, 1313, 1242, 1111, 1049, 973, 902, 878, 827, 784, 735, 670, 616, 563. HRMS (ESI) calcd. for $C_{19}H_{19}NO_4$: [M + H]$^+$ 326.1392; Found: 326.1385; [M + Na]$^+$ 364.0951; Found: 364.0947.

3.2.9. Ethyl N-4-((E)-3-(naphthalen-1-yl)-3-oxo-prop-1-enyl) phenoxyethanimidate (11)

Yellow liquid (Yield 97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.34–1.38 (t, 3H), 2.13 (s, 3H), 3.89 (s, 3H), 4.17–4.22 (q, 2H), 7.16 (d, 2H, J = 3.4 Hz), 7.19 (d, 2H, J = 10.7 Hz), 7.50–7.58 (m, 6H), 7.74 (d, 1H, J = 8.0 Hz), 7.91 (d, 1H, J = 9.2 Hz), 7.99 (d, 1H, J = 8.0 Hz), 8.28 (d, 1H, J = 9.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.48, 14.55, 63.26, 114.40, 124.68, 125.05, 125.83, 126.53, 126.93, 127.43, 127.78, 128.52, 130.26, 130.63, 131.65, 133.94, 137.61, 146.45, 162.03, 166.41,196.32. FTIR (KBr) υ cm^{-1}): 3052, 2982, 2938, 1893, 1642, 1591, 1562, 1409, 1383, 1312, 1241, 1164, 1133, 1699, 1053, 977, 905, 830, 804, 778, 697, 655, 575. HRMS (ESI) calcd. for $C_{23}H_{21}NO_3$: [M + H]$^+$ 360.1600; Found: 360.1589; [M + K]$^+$ 398.1159; Found: 398.1144.

3.2.10. Ethyl N-4-cinnamoylphenoxyethanimidate (13)

Yellow solid (Yield 94%); m.p. 71.3–73.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.36–1.40 (t, 3H), 2.15 (s, 3H), 4.20–4.25 (q, 2H), 7.24 (d, 2H, J = 8.8 Hz), 7.41–7.42 (t, 3H) 7.56 (d, 1H, J = 15.6 Hz), 7.64–7.66 (q, 2H), 7.81 (d, 1H, J = 15.7 Hz), 8.04 (d, 2H, J = 8.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$,): δ 14.48, 14.58, 63.32, 113.76, 122.15, 128.49, 129.05, 130.43, 130.77, 131.60, 135.27, 144.01, 163.59, 166.63, 188.94. FTIR (KBr) υ (cm^{-1}): 2978, 2917, 2848, 1650, 1602, 1498, 1447, 1373, 1313, 1246, 1213, 1157, 1111, 1054, 976, 906, 838, 762, 693, 667, 630, 598, 560. HRMS (ESI) calcd. for $C_{19}H_{19}NO_3$: [M + H]$^+$ 310.1443; Found: 310.1443; [M + K]$^+$ 348.1002; Found: 348.1013.

3.2.11. Ethyl N-4-((E)-3-(4-methylphenyl)acryloyl)phenoxyethanimidate (14)

Yellow solid (Yield 80%); m.p. 97.1–99.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.36–1.40 (t, 3H), 2.15 (s, 3H), 3.39 (s, 3H), 4.20–4.25(q, 2H), 7.23 (d, 3H, J = 8.9 Hz), 7.50–7.56 (t, 3H), 7.79 (d, 1H, J = 15.6 Hz), 8.03 (d, 2H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.49, 14.59, 21.67, 63.32, 113.73, 121.13, 128.52, 129.80, 130.73, 131.73, 132.52, 140.92, 144.12, 163.51, 166.62, 189.08. FTIR (KBr) υ (cm^{-1}): 2982, 2918, 2851, 1920, 1648, 1595, 1503, 1447, 1416, 1373, 1328, 1300, 1213, 1155, 1112, 1048, 1016, 974, 901, 839, 740, 664, 635, 598. HRMS (ESI) calcd. for $C_{20}H_{21}NO_3$: $[M + H]^+$ 324.1600; Found: 324.1594; $[M + Na]^+$ 346.1419; Found: 346.1408.

3.2.12. *Ethyl N-4-((E)-3-(4-methoxyphenyl)acryloyl) phenoxyethanimidate **(15)***

Yellow solid (Yield 98%); m.p. 96.7–98.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.36–1.40 (t, 3H), 2.15 (s, 3H), 3.86 (s, 3H), 4.20–4.25 (q, 2H), 6.94 (d, 2H, J = 8.8 Hz), 7.23 (d, 3H, J = 8.8 Hz), 7.44 (d, 1H, J = 15.2 Hz), 7.61 (d, 2H, J = 8.4 Hz), 7.78 (d, 1H, J = 15.8 Hz), 8.03 (d, 2H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.48, 14.59, 55.54, 63.31, 113.69, 114.49, 119.80, 127.98, 130.23, 130.65, 131.85, 143.86, 161.59, 163.42, 166.59, 189.00. FTIR (KBr) υ (cm^{-1}): 2959, 2916, 2845, 1896, 1649, 1595, 1504, 1427, 1371, 1316, 1297, 1255, 1217, 1151, 1114, 1056, 1022, 980, 903, 816, 743, 673, 628, 593, 551. HRMS (ESI) calcd. for $C_{20}H_{21}NO_4$: $[M + H]^+$ 340.1549; Found: 340.1545; $[M + Na]^+$ 362.1368; Found: 362.1358.

3.2.13. *Ethyl N-4-((E)-3-(4-(benzyloxy)phenyl)acryloyl) phenoxyethanimidate **(16)***

Yellow solid (Yield 65%); m.p. 80.5–83.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.36–1.40 (t, 3H), 2.15 (s, 3H), 4.20–4.25 (q, 2H), 5.12 (s, 2H), 7.01 (d, 2H, J = 8.8 Hz), 7.23 (d, 2H, J = 8.8 Hz), 7.34–7.46 (m, 6H), 7.61 (d, 2H, J = 8.8 Hz), 7.77 (d, 1H, J = 15.5 Hz), 8.02 (d, 2H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.49, 14.59, 63.32,70.24, 113.71, 115.39, 119.94, 127.64, 128.32, 128.82, 130.25, 130.67, 131.85, 136.59, 143.80, 160.77, 163.45, 166.61, 189.00. FTIR (KBr) υ (cm^{-1}): 2985, 1918, 2850, 1890, 1648, 1595, 1505, 1466, 1420, 1375, 1314, 1294, 1313, 1153, 1112, 1051, 1013, 978, 905, 826, 739, 695, 599, 589. HRMS (ESI) calcd. for $C_{26}H_{25}NO_4$: $[M + H]^+$ 416.1862; Found: 416.1858; $[M + K]^+$ 454.1421; Found: 454.1425.

3.2.14. *Ethyl N-4-((E)-3-(2-methoxyphenyl)acryloyl) phenoxyethanimidate **(17)***

Yellow solid (Yield 50%); m.p. 92.9–94.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.36–1.40 (t, 3H), 2.15 (s, 3H), 3.86 (s, 3H), 4.20–4.25 (q, 2H), 6.94 (d, 2H, J = 8.8 Hz), 7.23 (d, 2H, J = 8.8 Hz), 7.44 (d, 1H, J = 15.7 Hz), 7.6 (d, 2H, J = 8.7 Hz), 7.78 (d, 1H, J = 15.6 Hz), 8.02 (d, 2H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.48, 14.58, 55.54, 63.31, 113.71, 114.51, 119.83, 128.00, 130.23, 130.66, 131.87, 143.87, 161.61, 163.43, 166.59, 189.01. FTIR (KBr) υ (cm^{-1}): 2921, 2850, 1895, 1648, 1593, 1504, 1468, 1428, 1321, 1313, 1253, 1216, 1152, 1114, 1055, 1021, 979, 903, 817, 742, 674, 628, 593. HRMS (ESI) calcd. for $C_{20}H_{21}NO_4$: $[M + H]^+$ 340.1549; Found: 340.1540; $[M + Na]^+$ 362.1368; Found: 362.1356.

3.2.15. *Ethyl N-4-((E)-3-(3-methoxyphenyl)acryloyl) phenoxyethanimidate **(18)***

Yellow liquid (Yield 91%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.36–1.40 (t, 3H), 2.15 (s, 3H), 3.86 (s, 3H), 4.20–4.25 (q, 2H), 6.94–6.97 (q, 1H), 7.16 (s, 1H), 7.24 (d, 3H, J = 8.8 Hz), 7.32–7.35 (t, 1H), 7.53 (d, 1H, J = 15.6 Hz), 7.76 (d, 1H, J = 15.7 Hz), 8.03 (d, 2H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.48, 14.59, 55.49, 63.33, 113.50, 113.77, 116.17, 121.14, 122.47, 130.05, 130.79, 131.57, 136.66, 143.93, 160.05, 163.61, 166.65, 188.95. FTIR (KBr) υ (cm^{-1}): 2980, 2920, 2843, 1653, 1601, 1496, 1409, 1386, 1322, 1259, 1215, 1157, 1110, 1043, 978, 911, 829, 771, 738, 668, 638, 576. HRMS (ESI) calcd. for $C_{20}H_{21}NO_4$: $[M + H]^+$ 340.1549; Found: 340.1540; $[M + Na]^+$ 362.1368; Found: 362.1375.

3.2.16. *Ethyl N-4-((E)-3-(2,5-dimethoxyphenyl)acryloyl) phenoxyethanimidate **(19)***

Brown liquid (Yield 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.36–1.39 (t, 3H), 2.15 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.20–4.25 (q, 2H), 6.86–6.93 (m, 2H), 7.17 (d, 1H, J = 3.0 Hz), 7.23 (d, 2H, J = 8.8 Hz), 7.6 (d, 1H, J = 16.1 Hz), 8.02 (d, 1H, J = 8.8 Hz), 8.06 (d, 1H, J = 15.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.46, 14.55, 55.94, 56.22, 63.28, 112.54, 113.66, 113.85, 117.00, 123.18, 124.84, 130.77, 131.78, 139.36, 153.36, 153.58, 163.41, 166.55, 189.51. FTIR (KBr) υ (cm^{-1}): 3062, 2982, 2942, 2838, 1651, 1598, 1498, 1466, 1421, 1377, 1314, 1219, 1158, 1114, 1048, 978, 905, 830, 753, 715, 672, 635, 599, 569. HRMS (ESI) calcd. for $C_{21}H_{23}NO_5$: $[M + H]^+$ 370.1654; Found: 370.1662; $[M + K]^+$ 408.1213; Found: 408.1226.

3.2.17. *Ethyl N-4-((E)-3-(3,4-dimethoxyphenyl)acryloyl) phenoxyethanimidate **(20)***

Yellow solid (Yield 90%); m.p. 74.3–75.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.36–1.39 (t, 3H), 2.15 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H), 4.20–4.25 (q, 2H), 6.90 (d, 1H, J = 8.3 Hz), 7.17 (s, 1H), 7.24 (d, 2H, J = 8.8 Hz), 7.41 (d, 1H, J = 15.2 Hz), 7.76 (d, 1H, J = 15.2 Hz), 8.03 (d, 2H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.47, 14.55, 56.13, 63.31, 110.34, 111.33, 113.74, 120.20, 123.06, 128.31, 130.67, 131.87, 144.17, 149.42, 151.40, 163.48, 166.59, 189.03. FTIR (KBr) υ (cm^{-1}): 2967, 2935, 2845, 2595, 1648, 1593, 1510, 1448, 1414, 1378, 1330, 1309, 1253, 1210, 1160, 1132, 1019, 973, 905, 829, 804, 595, 560. HRMS (ESI) calcd. for $C_{21}H_{23}NO_5$: $[M + H]^+$ 370.1654; Found: 370.1660; $[M + Na]^+$ 392.1477; Found: 392.1477.

3.2.18. *Ethyl N-4-((E)-3-(3,4,5-trimethoxyphenyl)acryloyl) phenoxyethanimidate **(22)***

Yellow solid (Yield 93%); m.p. 125.3–127.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.36–1.39 (t, 3H), 2.15 (s, 3H), 3.90 (s, 3H), 3.93 (s, 6H), 4.19–4.25 (q, 2H), 6.86 (s, 2H), 7.24 (d, 2H, J = 8.7 Hz), 7.43 (d, 1H, J = 15.7 Hz), 7.71 (d, 1H, J = 15.6 Hz), 8.03 (d, 2H, J = 8.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.47, 14.59, 56.34, 61.14, 63.31, 105.64, 113.75, 121.52, 130.76, 131.61, 140.31, 144.20, 153.59, 163.57, 166.64, 188.94. FTIR (KBr) υ (cm^{-1}): 2972, 2929, 2839, 1651, 1601, 1501, 1456, 1373, 1316, 1279, 1247, 1212, 1153, 1128, 1030, 976, 906, 817, 684, 593. HRMS (ESI) calcd. for $C_{22}H_{25}NO_6$: $[M + H]^+$ 400.1760; Found: 400.1756; $[M + Na]^+$ 438.1319; Found: 438.1313.

3.2.19. *Ethyl N-4-((2E,4E)-5-phenylpenta-2,4-dienoyl) phenoxyethanimidate **(24)***

Yellow solid (Yield 92%); m.p. 116.2–117.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.36–1.39 (t, 3H), 2.14 (s, 3H), 4.20–4.25 (q, 2H), 7.02 (d, 2H, J = 8.7 Hz), 7.12 (d, 1H, J = 15.1 Hz), 7.22 (d, 2H, J = 8.8 Hz), 7.32–7.39 (p, 3H), 7.51 (d, 2H, J = 8.4 Hz), 7.57–7.63 (m, 1H), 7.99 (d, 2H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.48, 14.58, 63.32, 113.71, 125.52, 127.24, 127.36, 125.97, 129.21, 130.64, 131.62, 136.36, 141.44, 144.05, 163.49, 166.61, 188.61. FTIR (KBr) υ (cm^{-1}): 2984, 2915, 2849, 1648, 1591, 1495, 1449, 1417, 1375, 1351, 1314, 1246, 1196, 1153, 1108, 1050, 1005, 974, 898, 818, 759, 732, 687, 638, 596. HRMS (ESI) calcd. for $C_{21}H_{21}NO_3$: $[M + H]^+$ 336.1600; Found: 336.1596.

3.2.20. *Ethyl N-4-((E)-3-(furan-2-yl)acryloyl)phenoxyethanimidate **(25)***

Yellow liquid (Yield 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.36–1.39 (t, 3H), 2.14 (s, 3H), 4.19–4.25 (q, 2H), 6.50–6.52 (m, 1H), 6.7 (d, 1H, J = 3.4 Hz), 7.23 (d, 2H, J = 8.8 Hz), 7.48 (d, 1H, J = 15.3 Hz), 7.52 (s, 1H), 7.59 (d, 1H, J = 15.8 Hz), 8.04 (d, 2H, J = 8.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.48, 14.59, 63.32, 112.73, 113.74, 115.89, 119.44, 130.06, 130.70, 131.57, 144.80, 152.00, 163.57, 166.62, 188.31. FTIR (KBr) υ (cm^{-1}): 2982, 2925, 2852, 1737, 1653, 1600, 1502, 1476, 1346, 1319, 1226, 1193, 1158, 1111, 1057, 1009, 976, 907, 880, 832, 813, 747, 692, 630, 594. HRMS

(ESI) calcd. for $C_{17}H_{17}NO_4$: $[M + H]^+$ 300.1236; Found: 300.1230; $[M + Na]^+$ 338.0795; Found: 338.0793.

*3.2.21. Ethyl N-4-((E)-3-(thiophen-2-yl)acryloyl)phenoxyethanimidate **(26)***

Yellow solid (Yield 84%); m.p. 76.1–78.3 °C. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.36–1.39 (t, 3H), 2.13 (s, 3H), 4.19–4.25 (q, 2H), 7.08–7.10 (q, 1H), 7.23 (d, 2H, $J = 8.7$ Hz), 7.34–7.41 (m, 3H), 7.93 (d, 1H, $J = 15.2$ Hz), 8.02 (d, 2H, $J = 8.7$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.46, 14.59, 63.32, 113.72, 120.86, 128.48, 130.67, 131.48, 131.84, 131.92, 136.47, 140.76, 163.58, 166.61, 188.30. FTIR (KBr) υ (cm^{-1}): 2977, 2917, 2849, 1925, 1653, 1597, 1573, 1499, 1420, 1368, 1321, 1281, 1235, 1153, 1111, 1030, 969, 903, 814, 715, 671, 580. HRMS (ESI) calcd. for $C_{17}H_{17}NO_3S$: $[M + H]^+$ 316.1007; Found: 316.1006; $[M + Na]^+$ 338.0827; Found: 338.0824.

*3.2.22. Compound **(28)** [37]*

Yellow solid (Yield 87%); m.p. 91.7–93.3 °C. ^1H NMR (400 MHz, $CDCl_3$): δ ppm 1.35–1.40 (sx, 6H), 2.13 (s, 3H), 2.15 (s, 3H), 4.19–4.25 (m, 4H), 7.18 (d, 2H, $J = 8.7$ Hz), 7.23 (d, 2H, $J = 8.7$ Hz), 7.44 (d, 1H, $J = 15.7$ Hz), 7.59 (d, 2H, $J = 8.8$ Hz), 7.78 (d, 1H, $J = 15.6$ Hz), 8.02 (d, 2H, $J = 8.8$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 14.49, 14.58, 63.23, 63.31, 113.68, 114.34, 119.67, 128.38, 130.03, 130.65, 131.89, 144.08, 161.69, 163.39, 166.31, 166.56, 189.06. FTIR (KBr) υ (cm^{-1}): 2984, 2925, 2852, 1896, 1650, 1596, 1499, 1449, 1421, 1375, 1315, 1244, 1212, 1155, 1112, 1052, 979, 903, 818, 670, 638, 575. HRMS (ESI) calcd. for $C_{23}H_{26}N_2O_5$: $[M + H]^+$ 411.1920; Found: 311.1917; $[M + Na]^+$ 449.1479; Found: 449.1473.

3.3. Biological evaluation

3.3.1. In vitro culture of P. falciparum

The test molecules were evaluated against drug-susceptible *P. falciparum* (3D7) obtained from National Institute of Malaria Research (NIMR, New Delhi, India). The strain of *P. falciparum* was maintained by serial passages in human red blood cells (RBCs) cultured at 4–5% hematocrit in RPMI-1640 medium supplemented with 0.5% AlbuMAX II (complete RPMI) and incubated at 37 °C under the atmosphere of mixed gases (5% CO_2, 5% O_2, and 90% N_2). The heparinized human whole blood was collected from the Rotary Blood Bank (New Delhi, India). RBCs were separated under sterile conditions by centrifugation to remove plasma and peripheral blood mononuclear cells (PBMCs) using a Histopaque 1077 gradiant solution. The level of parasitemia was routinely monitored by thin blood smear and staining with 5% Giemsa solution.

3.3.2. Evaluation of in vitro antiplasmodial activity

In vitro antiplasmodial activity was determined based on the [^{3}H]-hypoxanthine incorporation inhibition assay. The level of radiolabelled precursor [^{3}H]-hypoxanthine incorporation in the nucleic acid of parasites was used as direct measurement for determining the inhibitory growth concentration of parasites. Stock solutions of test compounds (chalcones) and artemisinin were dissolved in 100% DMSO and chloroquine diphosphate in sterile distilled water. The final concentration of DMSO is 0.4% (vehicle control) was found to be non-toxic to parasites. Briefly, different concentrations of test compounds ranging from 50 µg/mL to 0.1 µg/mL were serially diluted (2-fold dilution) and added to *P. falciparum* infected asynchronous erythrocyte suspension (4% final hematocrit and 2% parasitemia) in a 96-well micro dilution plate along with untreated control. In another set, different concentration of standard antimalarial drugs chloroquine diphosphate (CQ) and artemisinin (ART) was added to infected erythrocyte suspension as positive control. After 30 h of incubation period at 37 °C, 20 µL of 0.2 µ-Ci/well of [^{3}H]-hypoxanthine (American Radiolabeled Chemicals, Inc., ST. Louis, MO, USA specific activity 25 µ-Ci/mmol) was added to each well and plate was further incubated for additional 18 h. At the end of incubation, the content of each well was harvested onto a glass-fiber filter mat (Whatman GF/A) using a semi-automated 96 well cell harvester (Skatron, Norway, MI, USA). The dried paper discs were placed in 5 mL toluene based scintillation cocktail and radioactive count was measured in a TriCarb 2900TR liquid scintillation analyzer beta-counter (PerkinElmer, Waltham, MA, USA). The 50% inhibitory concentration (IC50) values were determined by plotting the drug concentration versus the percent cell viability of the parasite after 48 h of incubation of growth assay period. All data points were collected in triplicate for each experiment conducted independently.

3.3.3. Assessment of in vitro cytotoxicity on HepG2 cells

The cytotoxic effect of most active molecules (**11**, **16**, **19** and **22**) was evaluated against HepG2 cells using MTT assay. In brief, exponentially growing HepG2 cells were seeded in 96 well plates at a cell density of 1×10^4 cells/well in 200 µL DMEM medium, 24 h prior to the experiment. Cells were incubated with different concentrations of compounds (100 µg/mL to 0.78 µg/mL) two-fold dilution and incubated further for 48 h at 37 °C, followed by incubating with 10 µL of 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide) MTT reagent (5 mg/mL) for additional 3 h at 37 °C. The presence of formazan crystals were solubilized using 100 µL DMSO and the absorbance of each well optical density was measured using a microplate reader (BioRad, CA, USA) at 570 nm. The 50% inhibitory concentration (IC_{50} value) was determined by plotting the drug concentration versus the percentage cell viability of 48 h of a growth assay period. The relative cell viability (%) compared with control cells were calculated as follows:

$$\text{Cell viability (\%)} = \frac{\text{Abs (sample)} - \text{Abs (blank)}}{\text{Abs (control)} - \text{Abs (blank)}} \times 100$$

4. Conclusions

To summarize, the palladium-catalyzed C—O cross-coupling of EAcHO with bromo-chalcones is described for the synthesis of novel chalcones. The ligand *t*BuXPhos (**L7**) and cataCXium®PIntB (**L16**), were found to be effective in the cross-coupling reaction. The catalyst system, $[(\pi\text{-allyl})PdCl]_2$/*t*BuXPhos (**L7**), effectively facilitated the coupling reaction only with 4-bromo-chalcones, whereas it failed to couple 3-bromo-chalcones which reveals that the ligand allows the C—O reductive elimination through electronic pathway only. *In vitro* antiplasmodial activity of the coupled products showed acceptable inhibitory effect on *P. falciparum*. Among the compounds, the chalcones **19** was found to be most active with an IC_{50} value of 6 µg/mL with a SI of greater than 16.7 against HepG2 cells showing non-toxic effects. Consequently, the novel functionalized chalcones may provide a new avenue in discovery of novel antimalarial agent against drug-resistant strains of *P. falciparum* in combating malaria infection.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2019.02.016.

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