Journal Pre-proof

Pyrazole and pyrazoline derivatives as antimalarial agents: A key review

Lekkala Ravindar , Siti Aishah Hasbullah , K.P. Rakesh , Nurul Izzaty Hassan

PII: S0928-0987(22)00250-0
DOI: https://doi.org/10.1016/j.ejps.2022.106365
Reference: PHASCI 106365

To appear in: *European Journal of Pharmaceutical Sciences*

Received date: 27 September 2022
Revised date: 28 November 2022
Accepted date: 20 December 2022

Please cite this article as: Lekkala Ravindar , Siti Aishah Hasbullah , K.P. Rakesh , Nurul Izzaty Hassan , Pyrazole and pyrazoline derivatives as antimalarial agents: A key review, *European Journal of Pharmaceutical Sciences* (2022), doi: https://doi.org/10.1016/j.ejps.2022.106365

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Published by Elsevier B.V.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Journal Pre-proof

Review Highlights

1. The development of drug resistance in malaria parasites is one of the most critical problems with malaria control.
2. Heterocycles play an essential role in designing and discovering novel malaria-active compounds.
3. Various N-containing heterocycles such as pyrazole and pyrazoline derivatives have been broadly studied for antimalarial potency in recent years.
4. Summary of the recent developments in antimalarial activities of pyrazole and pyrazoline derivatives bearing quinoline, pyran, pyrazoline, pyridine, pyrimidine, imidazopyridazine, diazepine, curcumin, thiazole, benzothiazole, thiazolidine, triazine, oxadiazole, chalcone, furan, and the aryl moiety were discussed.

Journal Pre-proof

Journal Pre-proof

Pyrazole and pyrazoline derivatives as antimalarial agents: A key review

Lekkala Ravindar [1], Siti Aishah Hasbullah[1], K. P. Rakesh[2], and Nurul Izzaty Hassan[1]*

[1]Department of Chemical Sciences, Faculty of Science and Technology, Universiti Kebangsaan Malaysia (UKM), Bangi 43600, Selangor, Malaysia

e-mail: drizz@ukm.edu.my

[2]Department of Chemistry, University of North Carolina, Chapel Hill, 27955, USA

Abstract

Malaria poses a severe public health risk and a significant economic burden in disease-endemic countries. One of the most severe issues in malaria control is the development of drug resistance in malaria parasites. The standard treatment for malaria is artemisinin-combination therapy (ACT). Nevertheless, the Plasmodium parasite's extensive resistance to prior drugs and reduced ACT efficiency necessitates novel drug discovery. The progress in discovering novel, affordable, and effective antimalarial agents is significant in combating drug resistance, and the hybrid drug concept can be used to covalently link two or more active pharmacophores that may act on multiple targets. Pyrazole and pyrazoline derivatives are considered pharmacologically necessary active heterocyclic scaffolds that possess almost all types of pharmacological activities. This review summarized recent progress in antimalarial activities of synthesized pyrazole and pyrazoline derivatives. The studies published since 2000 are included in this systematic review. This review is anticipated to be beneficial for future study and new ideas in searching for rational development strategies for more effective pyrazole and pyrazoline derivatives as antimalarial drugs.

Keywords: Pyrazoles, pyrazolines, malaria, antimalarial potency, parasite, *Plasmodium falciparum*

1. Introduction

Malaria is a dangerous disease that can endanger human life and is spread by mosquito bites (Anopheles). The disease is dangerous and can result in death due to Plasmodium protozoa (Birkholtz et al., 2012). The disease is prevalent in tropical and subtropical regions such as Malaysia, Brazil, West Africa, and Indonesia. The number of global deaths reported in 2017 was 435000, 61% of total malaria deaths are accounted for children under five years old (World malaria report 2018). Four species of the Plasmodium genus causing the disease are *Plasmodium malariae*, *Plasmodium ovale*, *Plasmodium vivax*, and *Plasmodium falciparum* (Manohar et al., 2010). It has been reported that *Plasmodium falciparum* is a significant and dangerous protozoan parasite in the Plasmodium genus (Hasan et al., 2015).

From the public health viewpoint, a cure for malarial diseases aims to decrease the spread of infection to others by decreasing the infectious population and transmitting resistance to antimalarial drugs. A broad range of drugs has been utilized to prevent the malarial disease like quinoline, an important heterocyclic moiety employed for the malarial treatment, based drugs (e.g., chloroquine, hydroxychloroquine, mefloquine, primaquine, amodiaquine, pamaquine, aablaquine, mepacrine, quinine, quinidine, and piperaquine), folate synthesizes inhibitors (e.g., sulfalene, dapsone, cycloguanil, pyrimethamine, sulfadoxine, proguanil, and chloroproguanil), artemisinin and related peroxide-based drugs (e.g., dihydroartemisinin, artesunate, and artemether), antibiotics (e.g., clindamycin, and doxycycline) and other antimalarial drugs (e.g., deferoxamine, halofantrine, and atovaquone) (**Figure 1**). Hence, progress in cost-effective, novel, and promising antimalarial agents is urgently needed (Tibon et al., 2020). The progress in multi-therapeutic methodologies (Alven and Aderibigbe, 2019) developed analogs, and the discovery of advanced routes was evaluated as viable alternatives since ACT is the only standard treatment recommended by WHO facing similar antimalarial resistance (Alonso and Tanner, 2013).

Among heterocycles (Kalaria et al., 2018), unique and highly valuable compounds, *N*-containing heterocyclic compounds are widely found as a core framework in a huge library of heterocyclic compounds. They are extensively observed in natural products from vitamins, alkaloids, antibiotics, hormones, and many others (Ju and Varma, 2006; Pai and Chattopadhyay, 2016; Srivastava et al., 2012; Zárate-Zárate et al., 2015). Pyrazoles, more potential doubly unsaturated five-membered heterocyclic compounds containing two nitrogen atoms, have gained significant attention of pharmacologists and chemists because of their wide range of biological activities (Faisal et al., 2019) including insecticidal (Heller and Natarajan, 2006), antianxiety (Jamwal et al., 2013), antimicrobial (Kumar et al., 2016), antihyperglycemic (Kees et al., 1996), antipyretic (Wiley and Wiley, 1964), anticancer (Alam et al., 2016; Ardiansah 2017; Shamsuzzaman et al., 2015), anticonvulsant (Michon et al., 1995), anti-AIDS (Sony and Ganguly, 2016), antidepressant (Bailey et al., 1985), antimalarial agents (Cunico et al., 2006; Ebenezer et al., 2022; Karrouchi et al., 2018; Khan et al., 2016; Küçükgüzel and Şenkardeş, 215; Nasution et al., 2016; Pinheiro et al. 2019; Queiroz et al., 2022; Sant'anna et al., 1996; Sharmabc and Prasher, 2020; Singhet al., 2021; Vaidya et al., 2014), cardiovascular (Raffa et al., 2015), antitubercular (Khunt et al., 2012; Pathak et al., 2012), anti-inflammatory [(Gokhan-Kelekci et al., 2007), analgesic (Vijesh et al., 2013) etc (**Figure 2**).

Journal Pre-proof

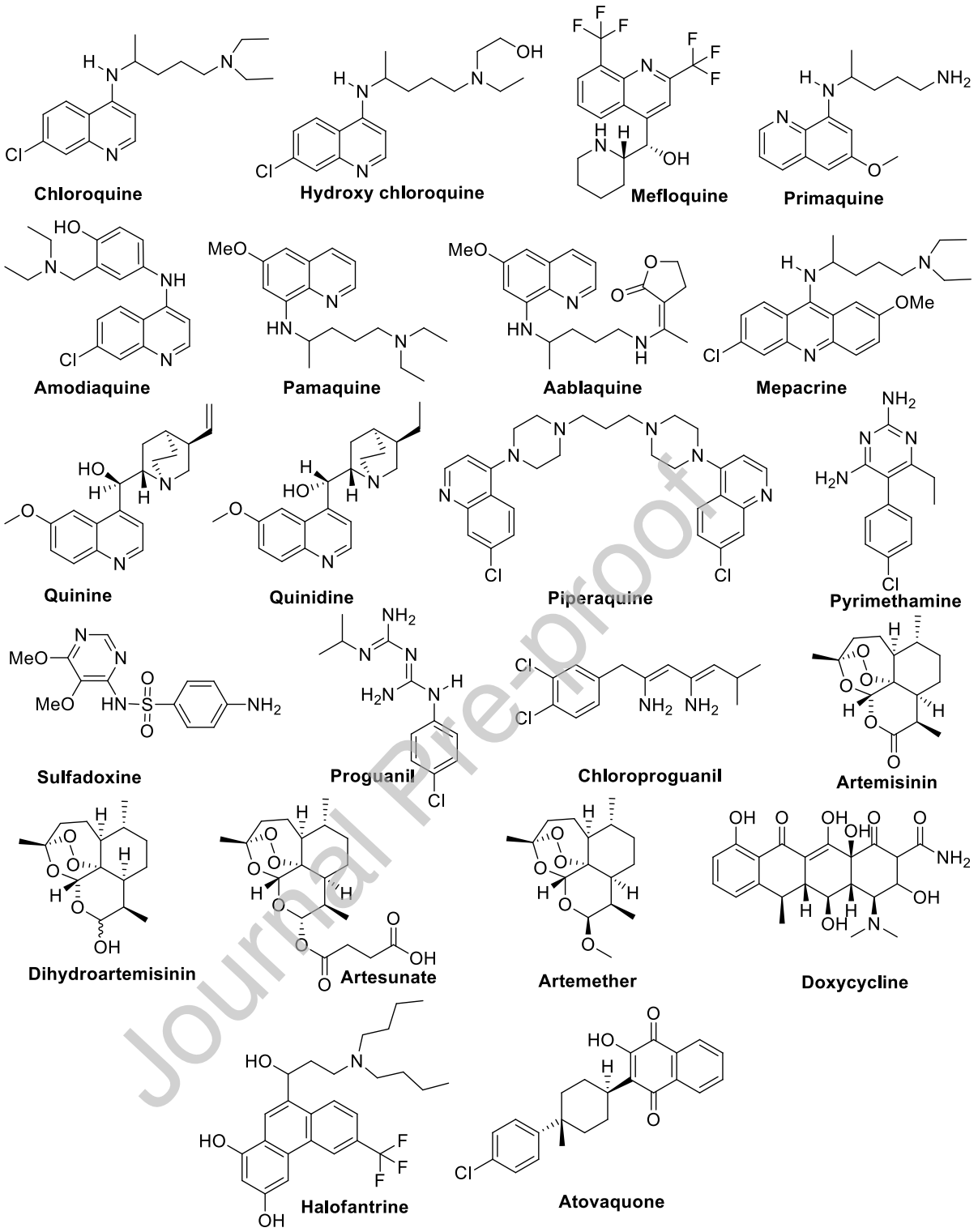


Figure 1. Antimalarial drugs in current clinical use and under development

Journal Pre-proof

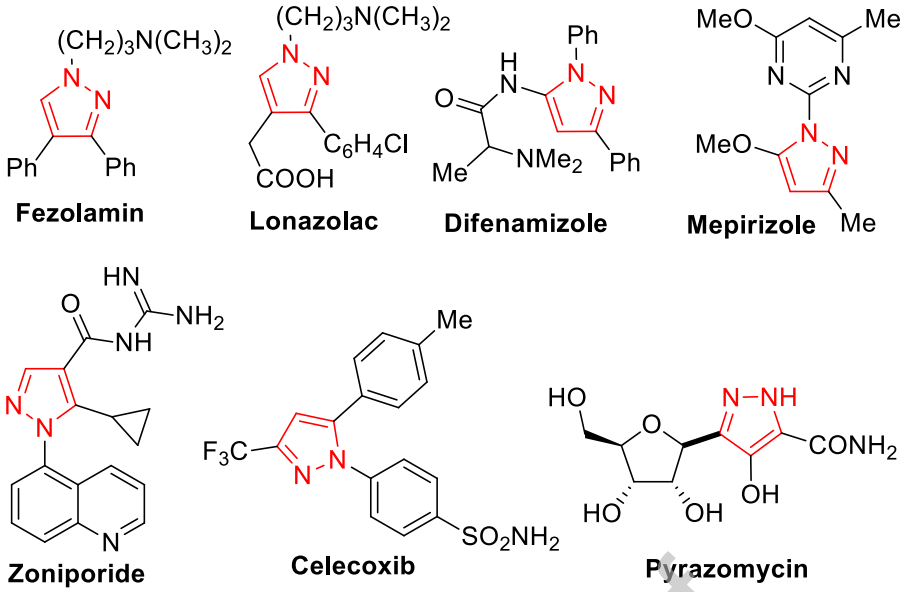


Figure 2. Commercially available drugs containing pyrazole nucleus

Functionalized pyrano[2,3-c]pyrazole derivatives are highly explored and broadly studied and have a significant role in pharmaceuticals. Because of extensive synthetic utilities and potential biological activities, pyrano[2,3-c]pyrazoles have gained significant attention as an important class of heterocycles in organic synthesis and pharmaceutical industries (Guo et al., 2013). It has many appealing biological activities varying from anticancer (Wang et al., 2009), anti-fungicidal (Ramiz et al., 2012), antimicrobial (Mistry et al., 2012), anti-inflammatory (Mandha et al., 2012), antimalarial (Biswas and Das, 2022; García-Cañaveras et al., 2021; Shamsuddin et al., 2020; Witschel et al., 2015), vasodilator (Ahluwalia et al., 1997), inhibitors of human Chkl kinase (Foloppe et al., 2006), analgesic (Kuo et al., 1984) as well as biodegradable agrochemical (Kiyani et al., 2013) (Figure 3).

Pyrazolines, another class of *N*-containing heterocycles (the reduced form of pyrazoles), also possess a broad range of biological activities, counting antitrypanosomal (Havrylyuk et al., 2014), antidepressant (Kaplancıklı et al. 2010), antifungal (Hassan 2013), anticancer (Patel et al., 2021), antinociceptive (Özkay et al., 2011), antitubercular (Joshi et al., 2016), antiamoebic (Bhat et al., 2009), anticonvulsant (Bhandari et al., 2013), antibacterial (Sivakumar et al., 2010), antimalarial (Acharya et al., 2010; Ardiansah 2017; Bhutani et al., 2015; Faheem et al., 2022; Jat et al., 2008; Nehra et al., 2020), anti-inflammatory (Kharbanda et al., 2014), and carbonic anhydrase (Çelik et al., 2020), monoamine oxidase (Sahoo et al., 2010), cholinesterase (Mishra and Sasmal, 2013), EGFR tyrosine kinase (Lv et al., 2011), aldose re-educates (Ovais et al., 2014) and cannabinoid CB1 (Lange et al., 2010) inhibitory activities (**Figure 4**).

Journal Pre-proof

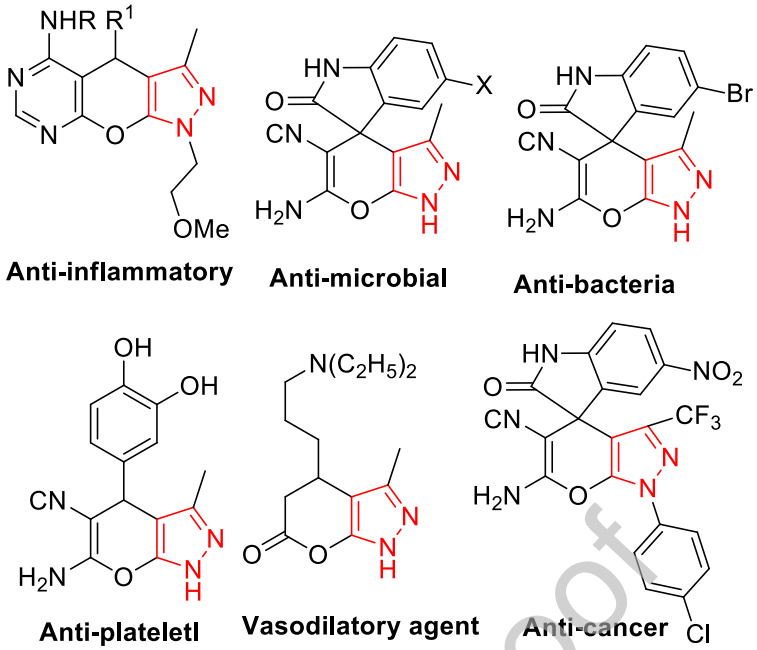


Figure 3. Biologically active pyrano[2,3-*c*]pyrazoles

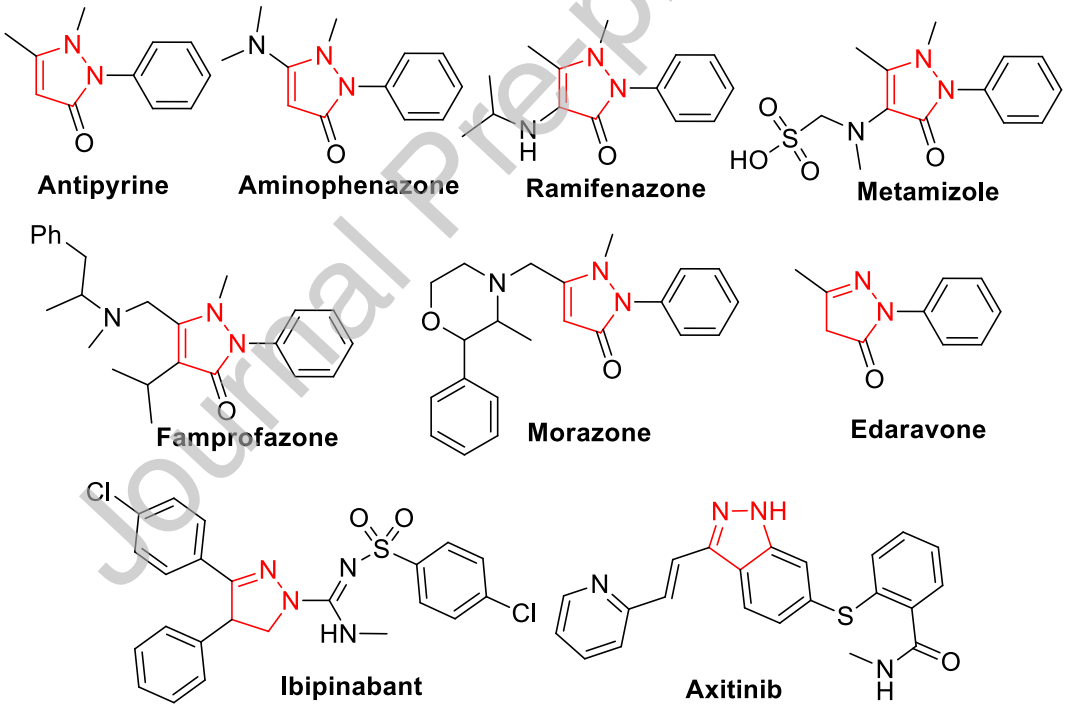


Figure 4. Various pyrazoline-based clinically used drugs

Considering the biological and pharmaceutical importance of pyrazoles and pyrazolines, a comprehensive report regarding the progress of pyrazole and pyrazoline derivatives as promising candidates for antimalarial drugs in the global research community is of great significance. Now a day's, various *N*-containing heterocyclic derivatives have been broadly studied for antimalarial potency. Some important *N*-heterocyclic scaffolds are depicted

Journal Pre-proof

in **Figure 5**. Here, we summarize recent antimalarial activities of furnished pyrazoles and pyrazolines.

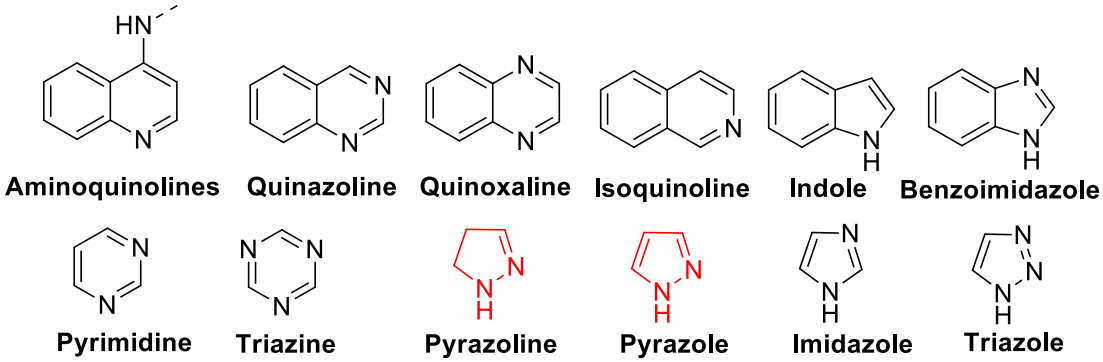


Figure 5. Various heterocyclic compounds embedded in antimalarial agents

The following section covered the two main heterocyclic skeletons embedded in various organic frameworks (**Figure 6**) that have demonstrated antimalarial activity against specific *P. falciparum* strains.

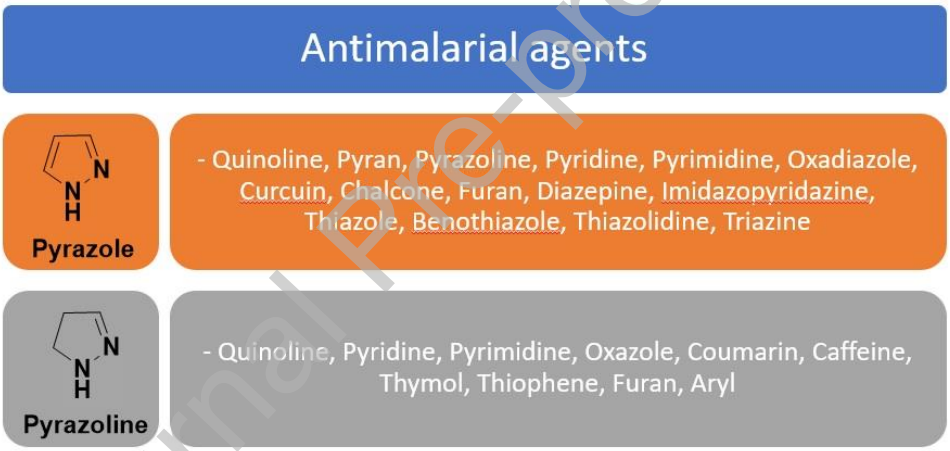


Figure 6. Antimalarial agents' pyrazole and pyrazoline derivatives listed in sections 2 and 3

2. Pyrazole derivatives with antimalarial activity:

Pyrazole derivatives bearing quinoline, pyran, pyrazoline, pyridine, pyrimidine, imidazopyridazine, diazepine, curcumin, thiazole, benzothiazole, thiazolidine, triazine, oxadiazole, chalcone, furan, and aryl moiety are significant scaffolds in the advancement of novel antimalarial drugs.

2.1.Quinoline containing pyrazoles:

Kalaria et al. (2014) identified the 5-imidazopyrazole-based polyhydroquinolines **1** as a novel class of antimalarial agents. They screened for *in vitro* antimalarial potency against *P. falciparum* clone utilizing CQ and quinine as the reference compounds. Compound **1a-r** exhibited potent activity counter to *P. falciparum* with an IC_{50} value range between 0.057 and 1.79 µg/mL. Among all, compounds **1s** and **1t** exhibited significant antimalarial potency

counter to *P. falciparum* with IC_{50} 0.033 and 0.034 µg/mL, respectively, aligned with CQ (**Figure 7**).

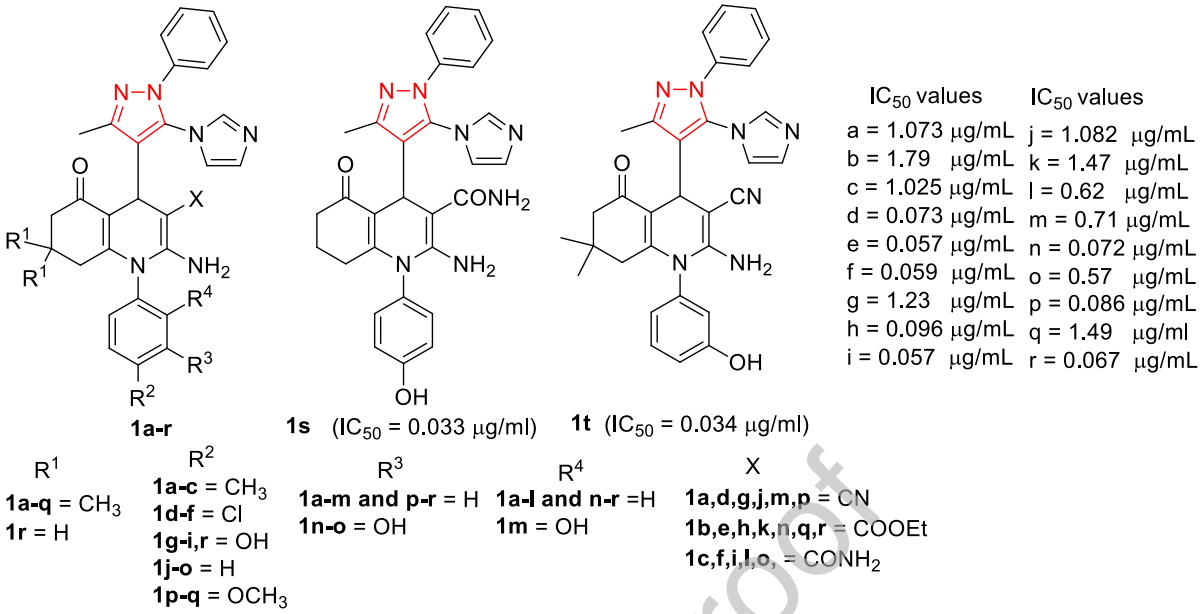


Figure 7. Antimalarial activity of 5-imidazopyrazole-based polyhydroquinolines against *P. falciparum* strain

Karad et al. (2015) evaluated *in vitro* antimalarial potency of a new series of fluorinated 5-aryloxypyrazole incorporated polyhydroquinolines **2** against *P. falciparum* clone employing CQ and quinine as standard drugs. Compounds **2a-k** showed poor to moderate antimalarial activity, whereas **2l-p** displayed potent antimalarial action against the *P. falciparum* clone. Among all, compound **2m** was more potent against the *P. falciparum* clone with 0.042 µg/mL IC_{50} value (**Figure 8**).

Journal Pre-proof

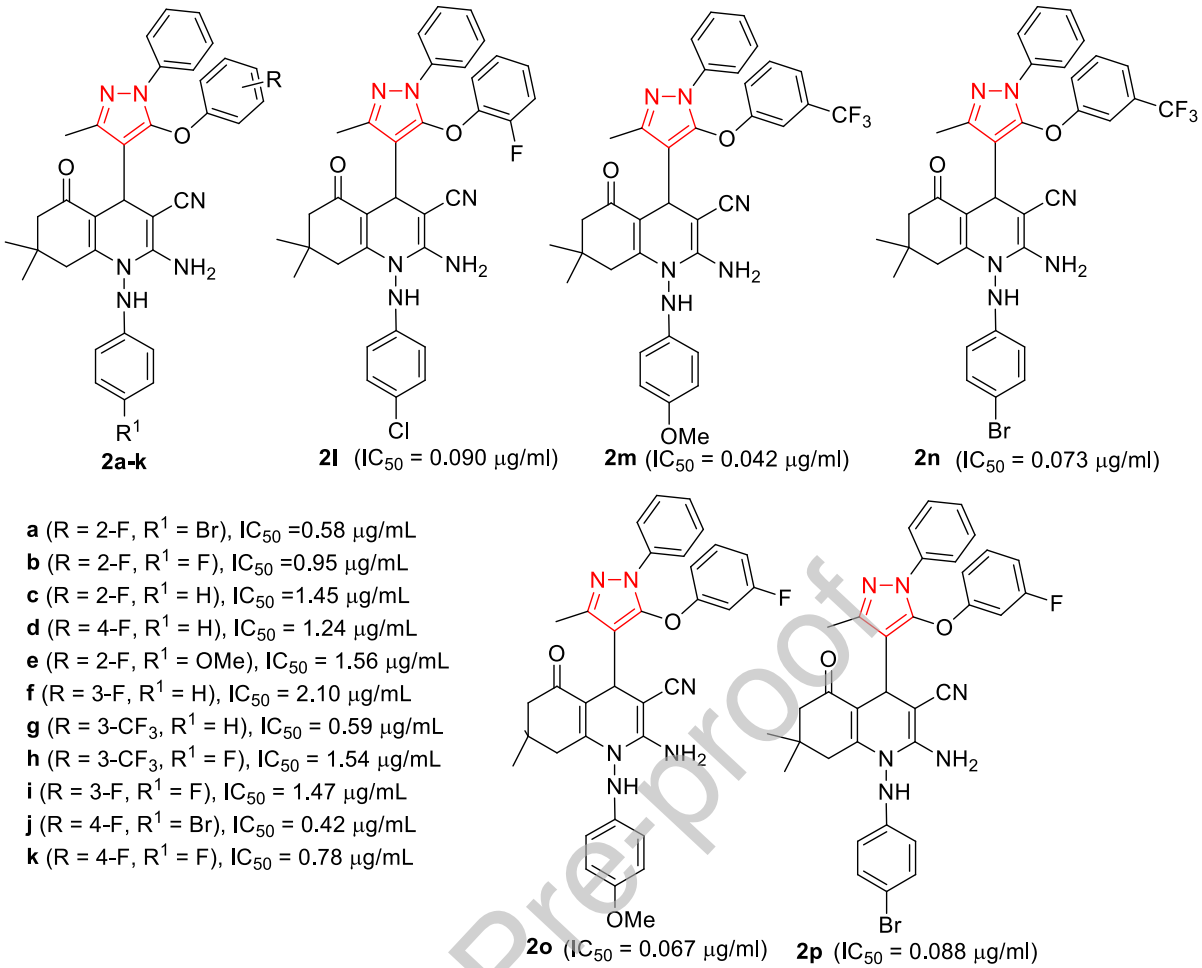


Figure 8. Antimalarial activity of 5-aryloxypyrazole incorporated polyhydroquinolines against *P. falciparum* strain

A broad range of quinoline carboxylic acids containing substituted pyrazole derivatives were furnished and examined *in vitro* antimalarial potency counter to *P. falciparum* clone employing quinine and CQ as reference drugs (Pandya et al., 2019). All the clubbed quinoine-pyrazoles **3**-**6** demonstrated excellent antimalarial potency against the *P. falciparum* clone with an IC_{50} value range between 0.036 and 1.55 µg/mL. Twenty-five of thirty-five synthesized were the most potent, with less than 1 µg mL^{-1} of IC_{50} values. Among them, compound **5g** emerged as more potent with IC_{50} 0.036 µg/ml, followed by **6f** and **5f** with 0.087 and 0.092 µg/mL of IC_{50}values, respectively, which were lower than that of standard agent quinine (IC_{50} = 0.268 µg/mL). All other hybrids were not as potent as quinine and CQ counter to the *P. falciparum* clone (**Figure 9**).

Journal Pre-proof

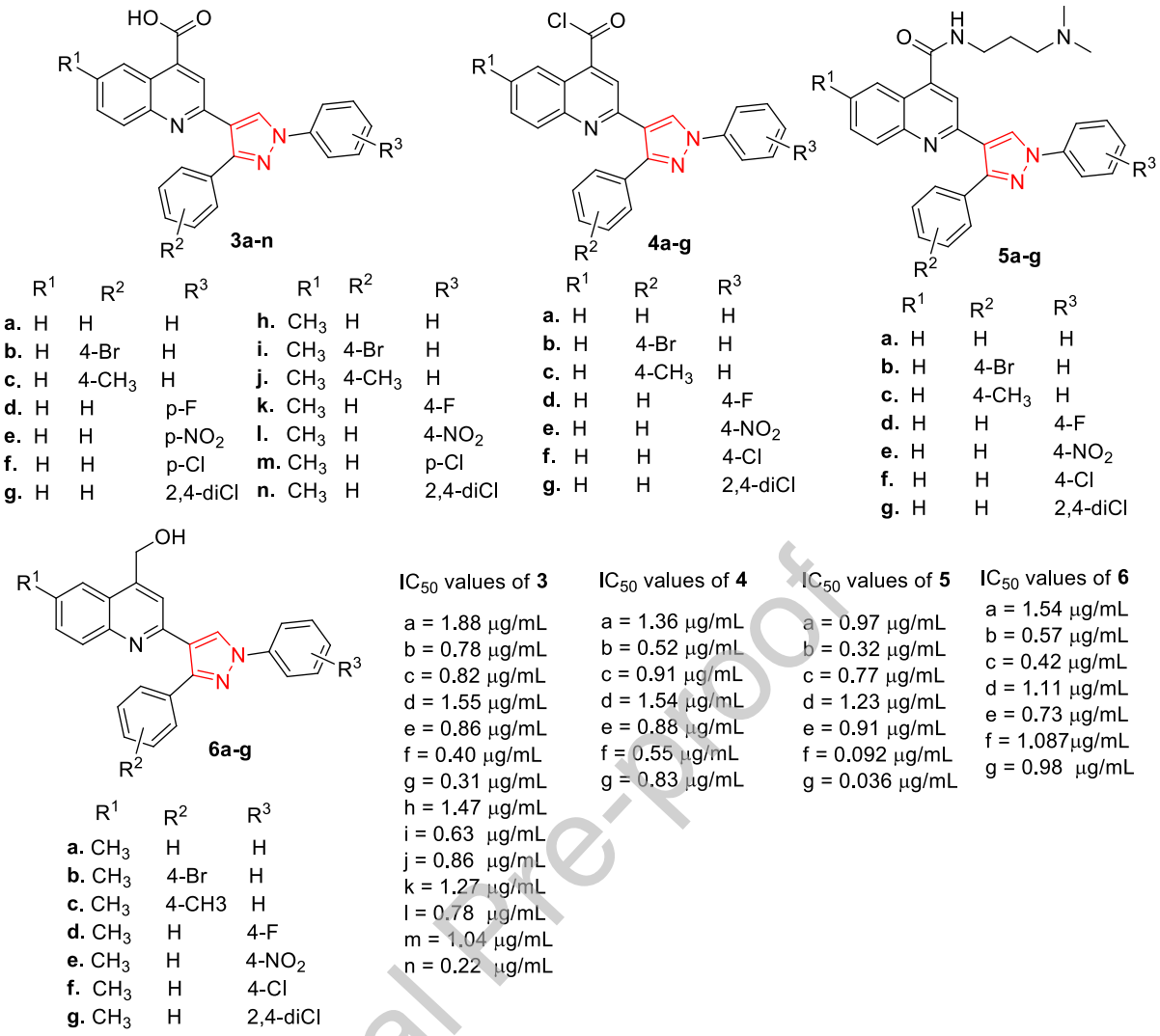


Figure 9. Antimalarial activity of quinoline in corporate pyrazoles against *P. falciparum* strain

The hybridization of 4-aminoquinoline with pyrano[2,3-c]pyrazoles will increase the antimalarial activity of pyrano[2,3c]pyrazole-aminoquinoline hybrids since pyranopyrazoles have a broad range of therapeutic applications. Very recently, a successful cascade process for conjugating 4-aminoquinolines and pyrano[2,3c]pyrazole derivatives as molecular hybrids **7** for antimalarial drugs was developed and displayed excellent *in vitro* antimalarial potency counter to CQ-resistant *P. falciparum* K1 (EC_{50} = 7.12 ± 3.72 µM) and CQ-sensitive *P. falciparum* 3D7 (EC_{50} = 3.39 ± 1.89 µM) strains (**Figure 10**) (Shamsuddin et al., 2021).

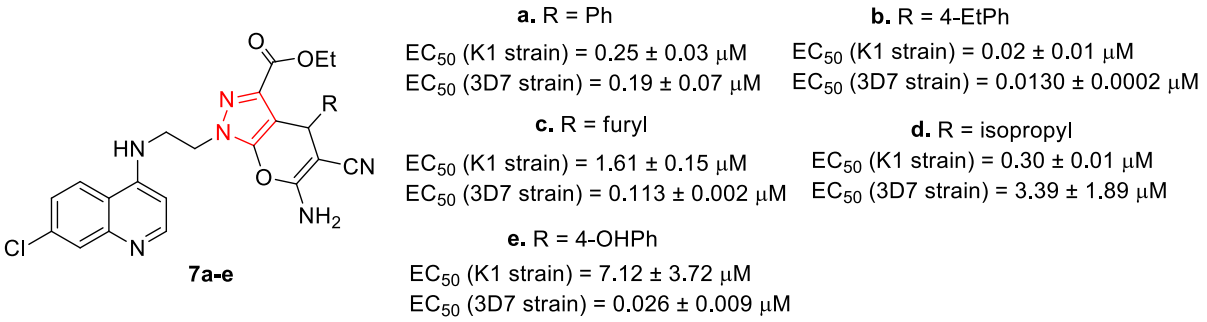


Figure 10. Antimalarial activity of 4-aminoquinoline corporated pyranopyrazoles against CQ-sensitive (3D7) and CQ- resistant (K1) strains of *P. falciparum*

2.2.Pyran containing pyrazoles:

Kalaria et al. (2014) also identified a new series of 5-imidazopyrazole incorporated fused pyran derivatives **8** as antimalarial targets and examined *in vitro* antimalarial efficacy counter to malaria parasite *P. falciparum* utilizing CQ and quinine as the standard drugs. All the screened hybrids exhibited potent antimalarial activity counter to *P. falciparum* with an IC_{50} value range between 0.034 and 1.88 μg mL^{-1}. Among them, compound **8x** showed higher antimalarial potency (IC_{50} = 0.034 μg mL^{-1}) (**Figure 11**).

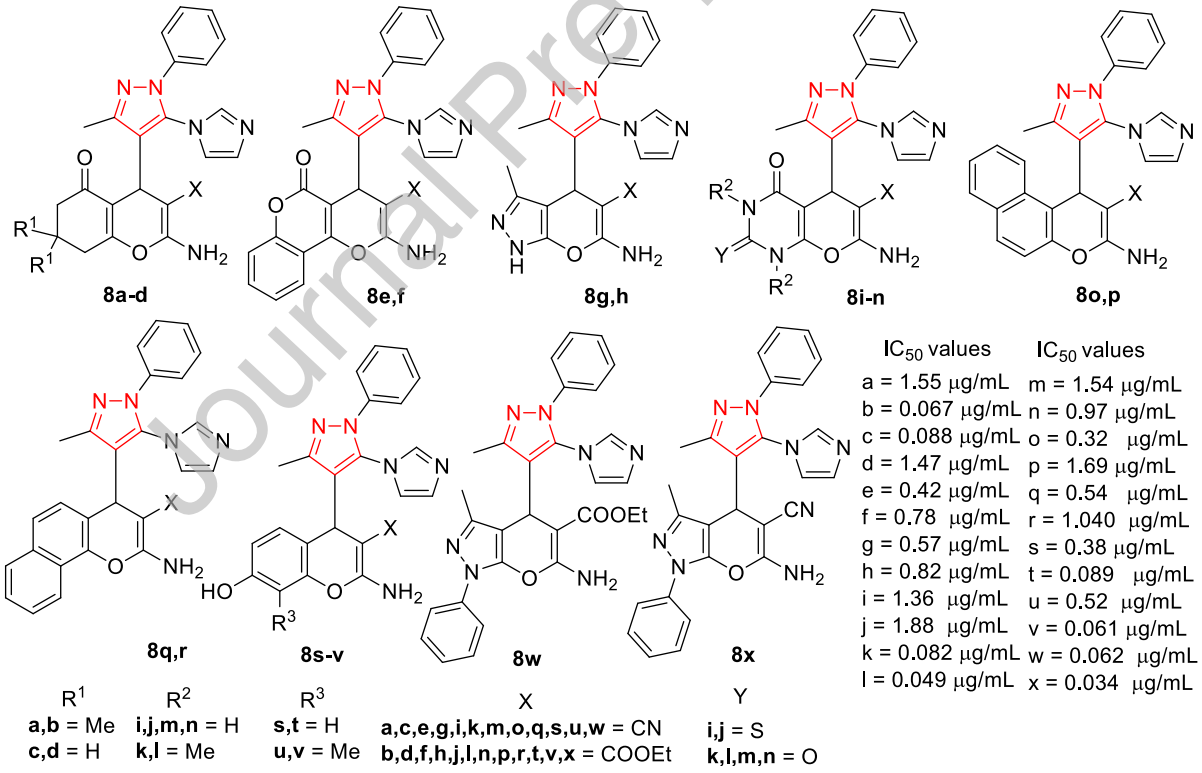
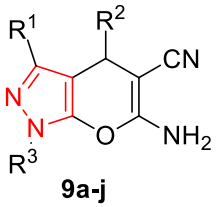


Figure 11. Antimalarial activity of 5-imidazopyrazole incorporated fused pyrans against *P. falciparum* strain

Journal Pre-proof

Very recently, a range of pyrano[2,3-*c*]-pyrazole-5-carbonitriles **9** were synthesized and identified as antimalarial drugs and screened for their antimalarial potency counter to the CQ-sensitive 3D7 clone of *P. falciparum* employing quinine (IC_{50} = 0.268 µg/mL) and CQ (IC_{50} = 0.020 µg/mL) as standard drugs (Parikh et al. 2022). All the ten constructed hybrids were found to be potent with a 0.027-2.09 µg/mL range of IC_{50} values, which is lower than the standard CQ. Compared to the standard quinine drug, compounds **9a-d** displayed higher antimalarial activity, whereas **9e-j** was lower in antimalarial potency than the 3D7 *P. falciparum* clone. Among all, compound **9d** (IC_{50} = 0.027 µg/mL), having a $–CF_3$ functional group, showed the highest activity, followed by **9c** (IC_{50} = 0.032 µg/mL) counter to the *P. falciparum* clone (**Figure 12**).



9a-j

	R^1	R^2	R^3	
a.	CF_3	Ph	Ph	(IC_{50} = 0.21 µg/mL)
b.	CF_3	4-BrPh	Ph	(IC_{50} = 0.26 µg/mL)
c.	CF_3	Ph	4-ClPh	(IC_{50} = 0.032 µg/mL)
d.	CF_3	4-OMePh	4-ClPh	(IC_{50} = 0.027 µg/mL)
e.	Me	Ph	3-NO_2Ph	(IC_{50} = 1.35 µg/mL)
f.	Me	3-Br-4-OMePh	3-NO_2Ph	(IC_{50} = 1.58 µg/mL)
g.	Me	4-NO_2Ph	3-NO_2Ph	(IC_{50} = 0.58 µg/mL)
h.	Me	4-OMePh	3-NO_2Ph	(IC_{50} = 1.24 µg/mL)
i.	Me	4-OHPh	3-NO_2Ph	(IC_{50} = 0.87 µg/mL)
j.	Me	5-Br-2-OHPh	3-NO_2Ph	(IC_{50} = 1.86 µg/mL)

Figure 12. Antimalarial activity of Pyran containing pyrazole derivatives against *P. falciparum* strain

2.3.Pyrazoline containing pyrazoles:

They continued their interest in forming diverse heterocyclic compounds with pyrazole as a unique moiety; Kalaria et al. (2014) constructed 5-imidazopyrazole incorporated pyrazoline derivatives **10** and screened the *in vitro* antimalarial efficacy counter to *P. falciparum* strain (IC_{50}value range between 0.012 and 1.25 µg mL^{-1}). Among all the tested analogs, compound **10l** exhibited excellent activity with 0.012µg mL^{-1} of IC_{50} value (**Figure 13**).

Journal Pre-proof

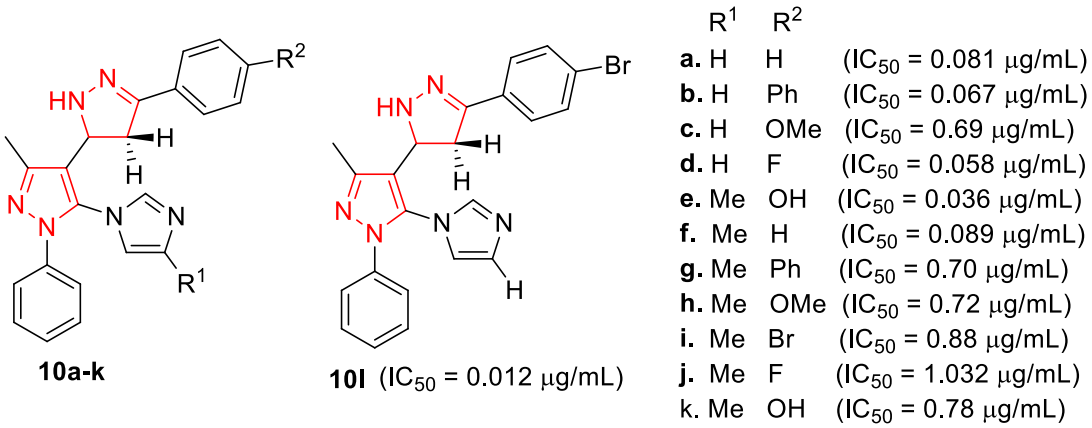


Figure 13. Antimalarial activity of 5-imidazopyrazole incorporated pyrazolines against *P. falciparum* strain

A new series of fluoro-substituted pyrazoles conjugated with pyrazoline moiety **11a-l** was constructed and examined for their antimalarial potency against *P. falciparum* clone employing quinine and chloroquine as reference compounds (Karad et al., 2014). All the tested compounds were found to possess IC_{50} values from 0.022 to 1.46 upon the *P. falciparum* strain. A significant antimalarial potency against the *P. falciparum* strain was displayed by compounds **11g-l** as compared to the standard quinine IC_{50}= 0.268 µM. Compound 11i (IC50 = 0.022 M) outperformed the other derivatives against the *P. falciparum* strain (**Figure 14**).

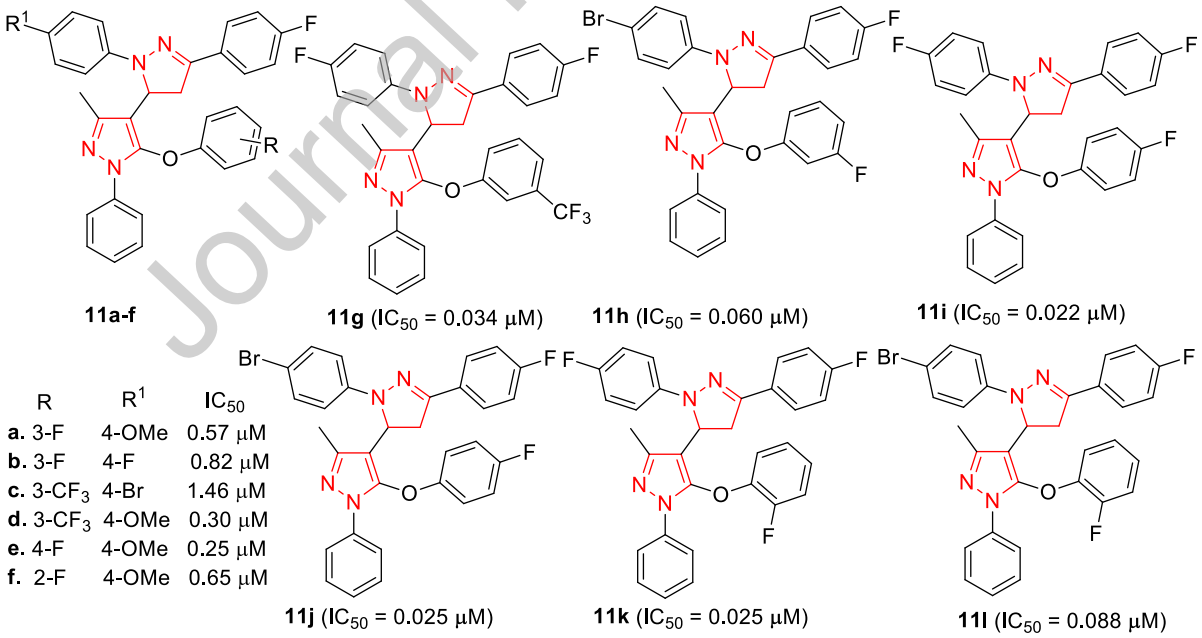


Figure 14. Antimalarial activity of fluorinated pyrazoles conjugated with pyrazoline against *P. falciparum* strain

Journal Pre-proof

Focussing their research interest on synthesizing and evaluating pyrazoles as antimalarial agents, Bekhit et al. (2014) developed a new series of 1*H*-pyrazoles **12-17**. They examined the *in vivo* antimalarial potency utilizing mice infected with *P. berghei* at a dose level of 48.4 µmol/kg. The length of the carbon chain of the acyl group (substitution of NH of pyrazoline ring) resulted inreduced antimalarial activity, compounds 12 (70.26%), 13 (33.6%), 14 (27.9%), and 15 (-15.1%) (Figure 15). Compound 12 exhibited superior antimalarial potency with suppression of 70.26%.

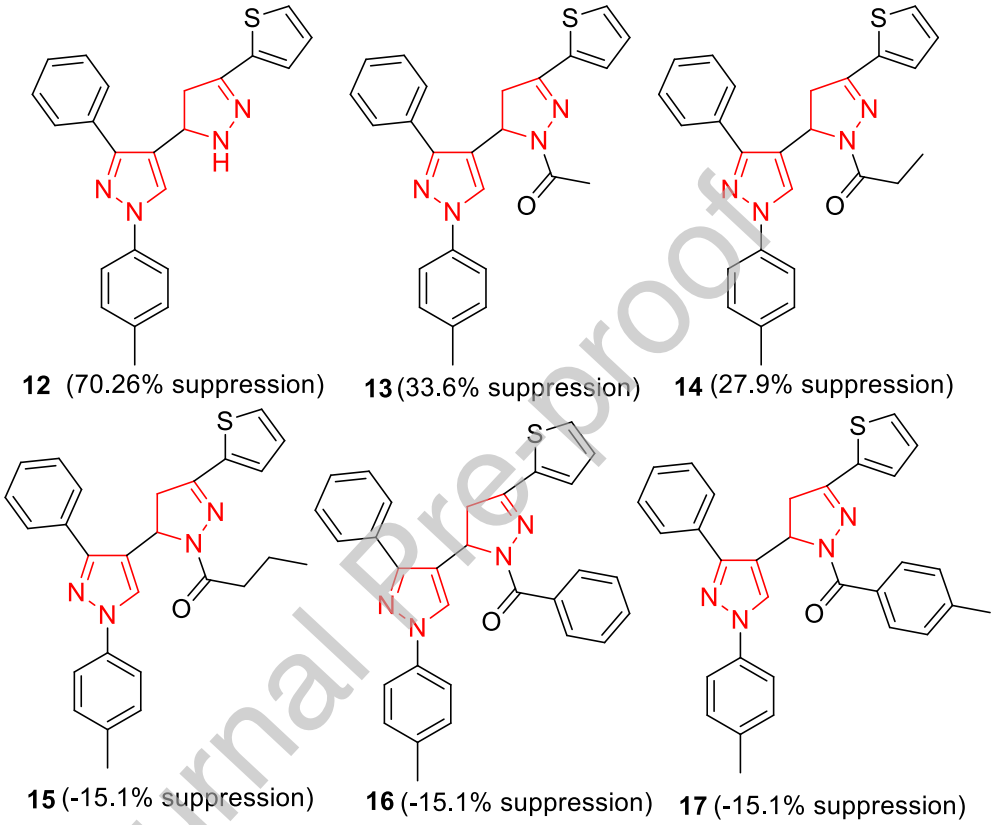
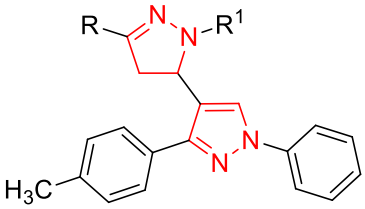


Figure 15. Antimalarial activity of 1*H*-pyrazole derivatives against *P. berghei*–infected mice

The same year, novel phenyl and thienyl clubbed pyrazole-pyrazoline hybrids **18** were developed and evaluated *in vivo* as antimalarial agents (Tuha et al., 2014). The furnished hybrids were screened for *in vivo* antimalarial potency counter to *P. berghei*-infected mouse models by implementing a four-day suppression test approach. The outcomes of *in vivo* antimalarial tests revealed that each hybrid displayed lower potency than the standard CQ phosphate at a dose of 48.46 µ mol/kg/day. With a percent suppression of 63.40% and 45.52%, respectively, the thienyl pyrazole-pyrazoline hybrid **18c** and the phenyl pyrazole-pyrazoline hybrid **18e** had the most potent antimalarial activity among all the tested hybrids. According to SAR analyses, molecules containing the phenyl pyrazolyl fragment had stronger antimalarial activity than those containing the thienyl pyrazole moiety (**Figure 16**).

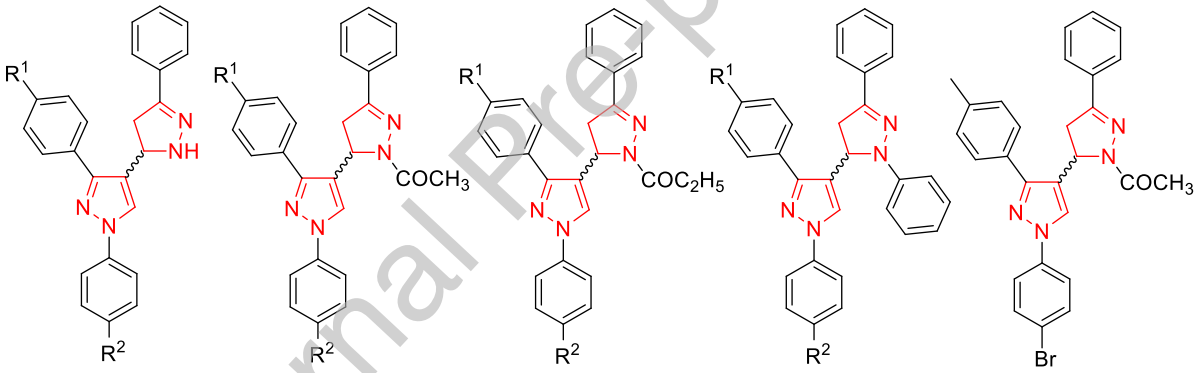


18a-e

	R	R^1	%Suppression
a.	2-thienyl	$COCH_3$	19.86
b.	2-thienyl	COC_2H_5	32.51
c.	2-thienyl	H	63.40
d.	Ph	$COCH_3$	40.21
e.	Ph	COC_2H_5	45.52

Figure 16. Antimalarial activity of phenyl and thienyl substituted pyrazole-pyrazolines against *P. berghei*-infected mice

The following year, Bekhit et al. (2015) furnished another class of pyrazoles **19-23** by hybridizing with pyrazolines and screened the *in vivo* antimalarial activity counter to *P. berghei*-infected mice. The hybrids **19c** and **23** showed >90% suppression of the parasitic potency compared to the reference CQ. Among the most active compounds further evaluated for their *in vitro* antimalarial potency counter to the CQ-resistant (RKL9) strain of *P. falciparum*, compound **23** (IC_{50} = 0.0368 ± 0.008 µM) was found to be the most active derivative, which was 5-fold higher than CQ (**Figure 17**).



	R^1	R^2	
a.	Me	Me	(65.12%)
b.	Me	Br	(67.44%)
c.	NO_2	Br	(95.35%)

c. IC_{50} = 0.0420 ± 0.006 µM

	R^1	R^2	
a.	Me	Me	(79.07%)
b.	NO_2	Br	(69.77%)

	R^1	R^2	
a.	Me	Me	(55.81%)
b.	Me	Br	(51.16%)
c.	NO_2	Br	(60.47%)

	R^1	R^2	
a.	Me	Me	(69.77%)
b.	Me	Br	(74.42%)
c.	NO_2	Br	(62.79%)

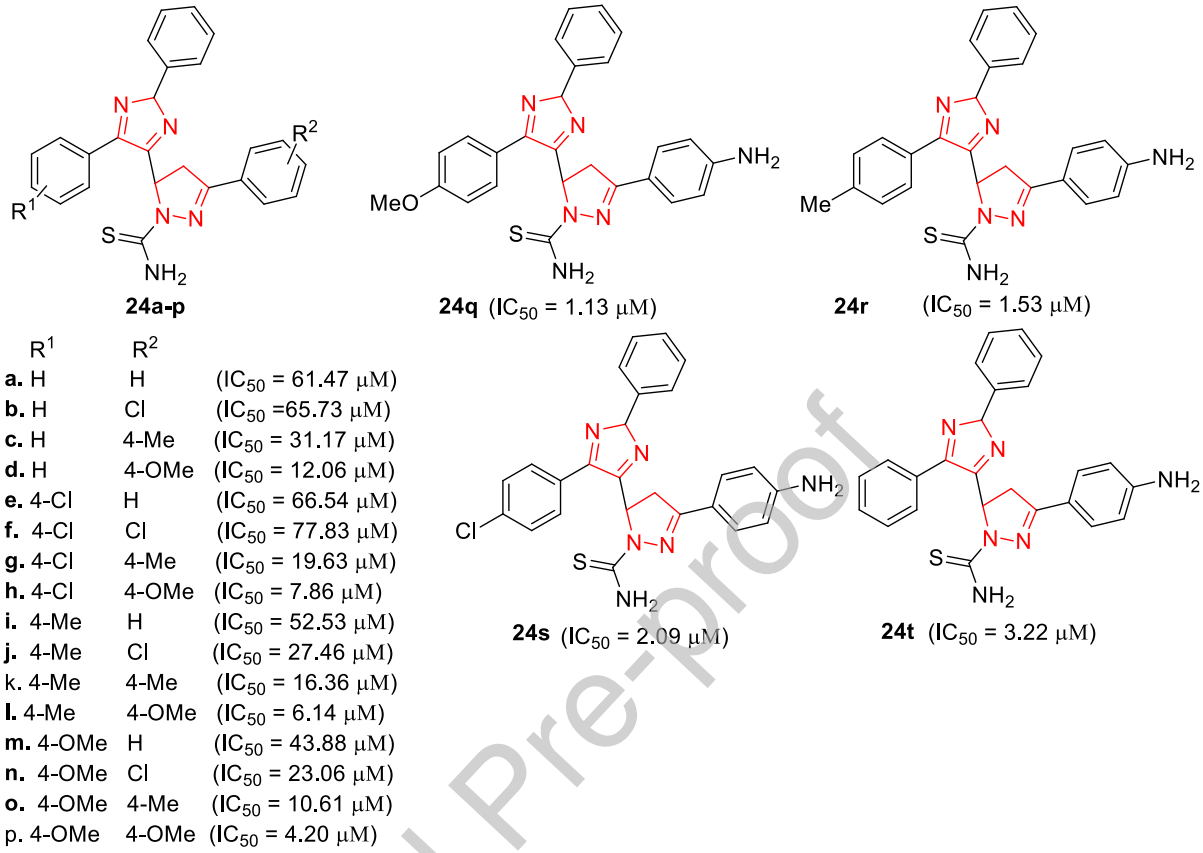
23
(IC_{50} = 0.0368 ± 0.008 µM)
(96.51% suppression)

Figure 17. Antimalarial activity of pyrazole-pyrazolines against *P. berghei*-infected mice and CQ-resistant (RKL9) strain of *P. falciparum*

A broad range of thioamide-substituted pyrazoline-pyrazole hybrids was developed and screened for the *in vitro* antimalarial potency counter to the CQ-sensitive 3D7 clone of *P. falciparum* (Marella et al., 2015). Compounds **24a-p** showed lower antimalarial efficacy counter to the 3D7 *P. falciparum* clone, with the IC_5

Journal Pre-proof

$_0$ value range between 4.2 and 77.83 µM. Compounds with NH_2 group on phenyl ring attached to pyrazoline ring **24q-t** exhibited the best antimalarial potency counter to the *P. falciparum* strain with 1.13, 1.53, 2.09, and 3.22 IC_{50} values, respectively (**Figure 18**).

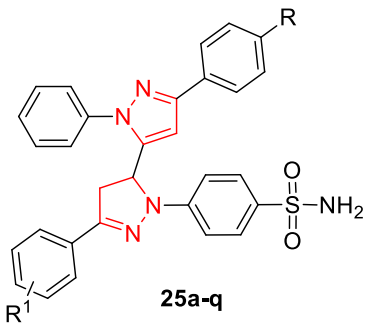


	R^1	R^2	
a.	H	H	(IC_{50} = 61.47 µM)
b.	H	Cl	(IC_{50} =65.73 µM)
c.	H	4-Me	(IC_{50} = 31.17 µM)
d.	H	4-OMe	(IC_{50} = 12.06 µM)
e.	4-Cl	H	(IC_{50} = 66.54 µM)
f.	4-Cl	Cl	(IC_{50} = 77.83 µM)
g.	4-Cl	4-Me	(IC_{50} = 19.63 µM)
h.	4-Cl	4-OMe	(IC_{50} = 7.86 µM)
i.	4-Me	H	(IC_{50} = 52.53 µM)
j.	4-Me	Cl	(IC_{50} = 27.46 µM)
k.	4-Me	4-Me	(IC_{50} = 16.36 µM)
l.	4-Me	4-OMe	(IC_{50} = 6.14 µM)
m.	4-OMe	H	(IC_{50} = 43.88 µM)
n.	4-OMe	Cl	(IC_{50} = 23.06 µM)
o.	4-OMe	4-Me	(IC_{50} = 10.61 µM)
p.	4-OMe	4-OMe	(IC_{50} = 4.20 µM)

Figure 18. Antimalarial activity of thioamide-substituted pyrazoline-pyrazole hybrids against CQ-sensitive (3D7) *P. falciparum* strain

Kumar et al. (2018) discovered a wide variety of pyrazoline-pyrazole hybrids endowed with benzenesulfonamide **25** and tested the *in vitro* antimalarial potency against both CQ-resistant (RKL9) and CQ-sensitive (3D7) *P. falciparum* strains using CQ as reference drug. All the tested compounds (**25a-q**) exhibited antimalarial potency against the 3D7 clone of *P. falciparum* with 1.38 to 6.67 µM range of EC_{50} values, whereas only selected compounds **25a-g** found to be potent counter to RKL-9 *P. falciparum* clone with the EC_{50} values range between 1.31 and 2.39 µM. Compared to their reference drug CQ, compounds **25a-g** exhibited higher potency against RKL-9 and 3D7 *P. falciparum* strains. *In vivo* antimalarial action of the most potent compound, **25f,** was tested against the *P. berghei* mouse model and demonstrated promising results with good mean survival days (**Figure 19**).

Journal Pre-proof

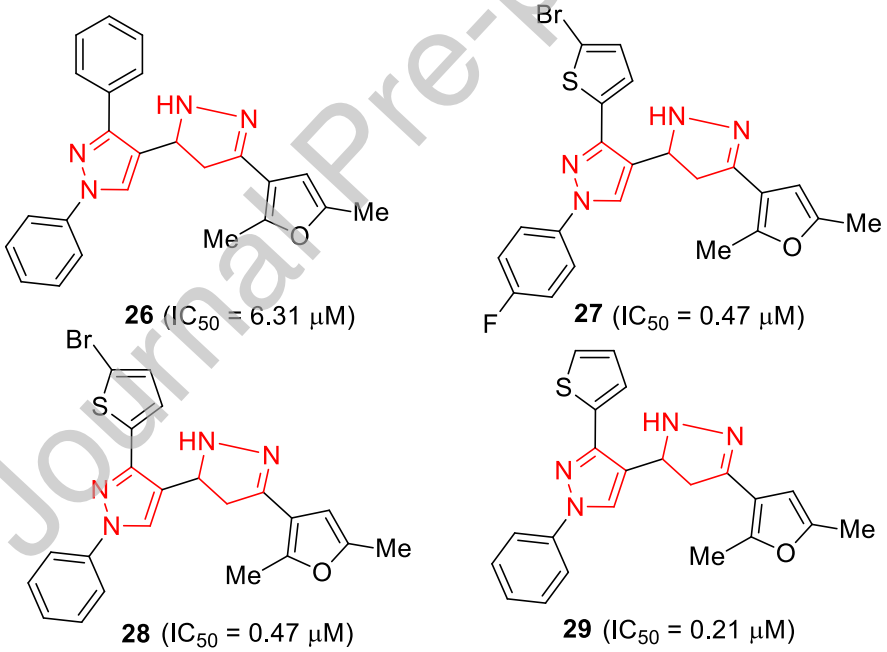


25a-q

	R	R^1	3D7 (EC_{50})	RLK-9 (EC_{50})		R	R^1	3D7 (EC_{50})
a.	H	4-OMe	1.42	1.78	**h.**	H	4-F	6.67
b.	4-F	4-OH	1.57	2.02	**i.**	H	4-Cl	3.35
c.	4-F	4-OMe	1.65	2.39	**j.**	H	4-OH	3.05
d.	4-Cl	4-OMe	1.61	2.12	**k.**	H	2,4-diCl	4.58
e.	4-Me	4-Me	1.43	1.64	**l.**	4-F	4-Br	3.08
f.	4-Me	4-OMe	1.38	1.31	**m.**	4-F	4-F	6.36
g.	4-Me	2,3-diOMe	1.61	1.55	**n.**	4-F	4-Me	2.23
					o.	4-Me	4-H	2.97
					p.	4-Cl	4-Cl	2.80
					q.	4-OMe	4-OMe	2.26

Figure 19. Antimalarial activity of pyrazoline-pyrazole hybrids against *P. berghei* and RKL9 and 3D7 strains of *P. falciparum*

Recently, Akolkar et al. (2020) have screened the antimalarial efficacy of pyrazoline containing pyrazole derivatives **26-29** counter to *P. falciparum* employing CQ and quinine as standard drugs. Molecular hybrids of the benzene, pyrazoline, and thiophene, ring increased the antimalarial activity (**Figure 20**). Hybrids **27** and **28** were equipotent with 0.47 µM of IC_{50} value, which is lower than the standard quinine (IC_{50} = 0.83 µM). The inhibition potency of **29** (IC_{50} = 0.21 µM) was 4-fold higher than the reference quinine.



26 (IC_{50} = 6.31 µM)

27 (IC_{50} = 0.47 µM)

28 (IC_{50} = 0.47 µM)

29 (IC_{50} = 0.21 µM)

Figure 20. Antimalarial activity of pyrazoline containing pyrazoles as against *P. falciparum*

2.4.Pyridine-containing pyrazoles:

Cabrera et al. (2011) identified pyridine-containing pyrazoles **30-32** as antimalarial agents and screened for their *in vitro* antiplasmodial activities counter to both CQ and multidrug-resistant (K1) and CQ-sensitive (NF54) clones of *P. falciparum*. For all the experiments, chloroquine IC_{50} 0.016 µM (NF54) and 0.194 µM (K1) and artesunate IC_{50} 0.004 µM (NF54) and 0.003 µM (K1) were used as the reference drugs. All the tested hybrids

Journal Pre-proof

demonstrated potency against *P. falciparum* stains. Among them, compound **30** exhibited better activity against K1 (with 6.45 µM of IC_{50} value) and NF54 (with 4.99 µM of IC_{50} value) strains of *P. falciparum* (**Figure 21**).

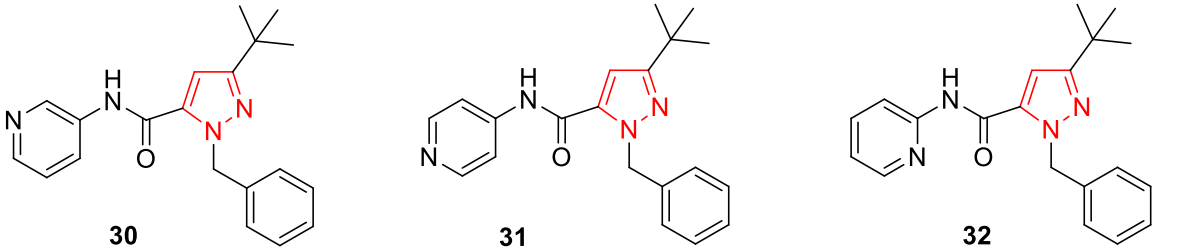


Figure 21. Antiplasmodial activity of pyridine-containing pyrazoles against CQ-resistant (K1) and CQ-sensitive (NF54) *P. falciparum* strains

A novel series of pyrazolopyridines **33-36** were identified as the antimalarial hybrid and examined for their *in vitro* antiplasmodial activity counter to multidrug-resistant (K1) and CQ-sensitive (NF54) *P. falciparum* clones using mefloquine, CQ, and artesunate as reference drugs (Manach et al., 2015). All the tested compounds demonstrated *in vitro* antiplasmodial potency counter to the CQ-sensitive strain (NF54), whereas only compound **35** exhibited potent antimalarial activity counter to the multidrug-resistant (K1) *P. falciparum* strain (**Figure 22**).

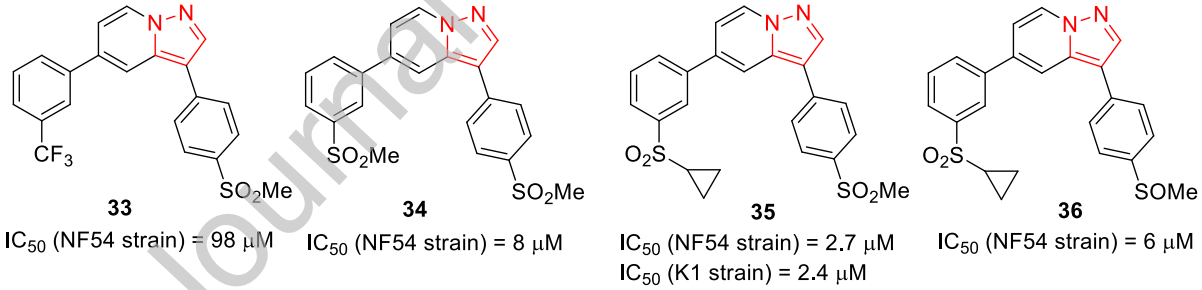


Figure 22. Antiplasmodial activity of pyrazolopyridines against CQ-resistant (K1) and CQ-sensitive (NF54) *P. falciparum* strains

In the following year, Silva et al. (2016) synthesized a wide variety of pyrazolopyridine derivatives conjugated with benzenesulfonamide moieties having diverse substituents at the *para*-position **37** and evaluated *in vitro* activity against CQ-resistant W2 *P. falciparum* clone employing CQ and sulfadoxine as reference compounds. All the compounds demonstrated lower activity than standard agent CQ (IC_{50} = 0.55 µM) and higher activity than standard agent sulfadoxine (IC_{50} = 15.0 µM) counter to the W2 *P. falciparum* clone with IC_{50} values ranging between 3.46 and 9.30 µM. Among all, hybrid **37b** (R^2 = Me) was found to be more active

with 3.46 µM of IC_{50}value, following hybrids **37d** (R^2 = Cl) and **37g** (R^2 = Me), both with 3.60 µM of IC_{50} value against *P. falciparum* (**Figure 23**).

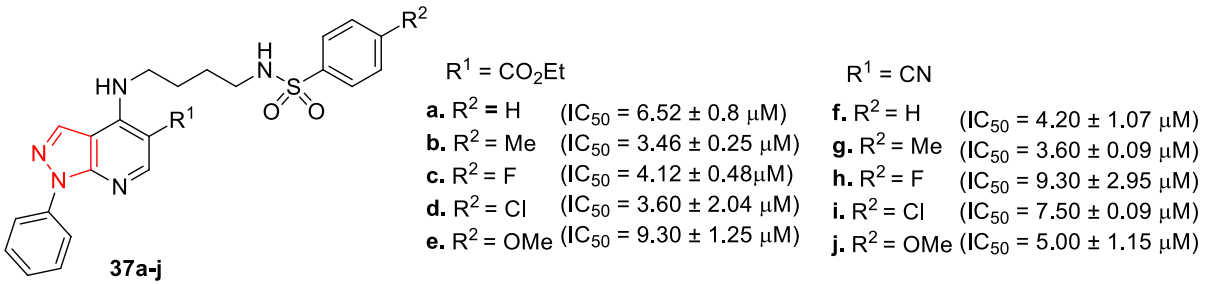


Figure 23. Antimalarial activity of pyrazolopyridine-benzenesulfonamide derivatives against CQ-resistant (W2) *P. falciparum* strain

A novel series of acyl hydrazone-based molecular hybrids of 1,4-dihydropyridine and pyrazole **38** was identified as an antimalarial hybrid and tested for their *in vitro* antimalarial potency counter to CQ-sensitive (3D7) *P. falciparum* strain employing chloroquine as reference compound (Kumar's et al., 2017). All the screened compounds exhibited higher antimalarial potency (IC_{50} values range between 4.40 and 16.87 µM) than commercial drugs artemisinin and chloroquine. Among all tested hybrids, compound **38g** was found to be more potent with 4.40 µM of IC_{50} value (**Figure 24**).

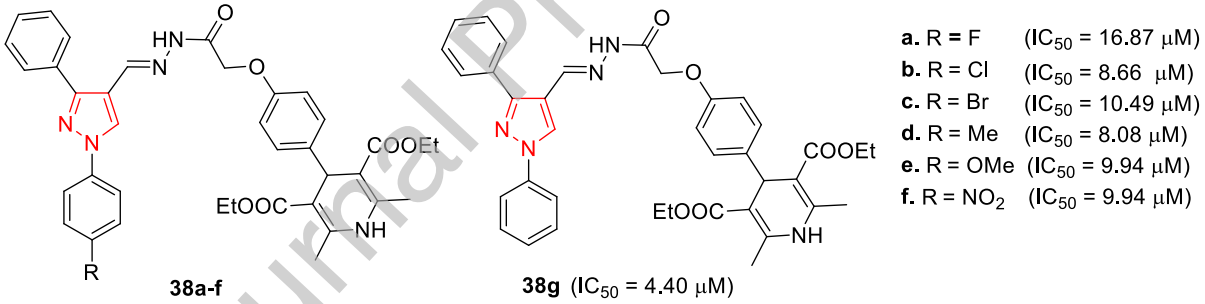


Figure 24. Antimalarial activity of acyl hydrazone substituted against CQ-sensitive (3D7) *P. falciparum* strain

2.5.Pyrimidine-containing pyrazoles:

A new series of pyrimidine-substituted pyrazole derivatives **39-41** were identified as antimalarial hybrids for targeting enoyl-ACP reductase of *P. falciparum* (Kumar et al., 2006). The hybrids showed good inhibitory potential counter to enoyl-ACP reductase enzyme with a 30-50 µM range of IC_{50}values. The molecular docking studies on the evaluated hybrids revealed widespread binding to the target enzyme's active site amino acid residues, predominantly through aromatic interaction and hydrogen bonding (**Figure 25**).

Journal Pre-proof

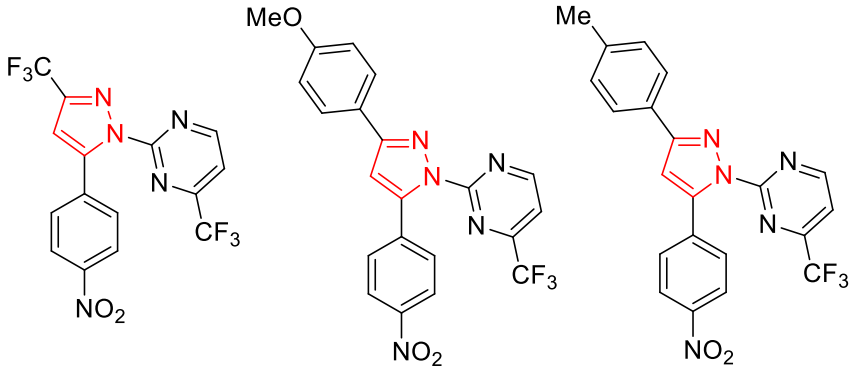
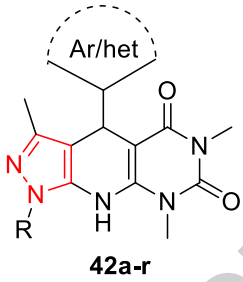


Figure 25. Antimalarial activity of pyrimidine-substituted pyrazoles against *P. falciparum* strain

The first examination of heterocyclic pyrazoles **42** for their *in vitro* antimalarial efficacy counter to the malaria parasite *P. falciparum* was reported by Satasia et al. (2014) based on pyrido[2,3-*d*]pyrimidine-diones. Quinine and CQ were used as standard compounds. All the evaluated hybrids showed potent antimalarial activity counter to the *P. falciparum* with an IC_{50} value range between 0.003 and 5.0 µg mL^{-1}. The hybrid **42p** was the highest antimalarial activity with 0.033 µg mL^{-1} of IC_{50} value, and the hybrid **42h** was the lowest with 5.0µg $mL^{-1}$of IC_{50} value (**Figure 26**).



Ar/het		Ar/het	
a = 4-$NO_2C_6H_4$	(IC_{50} = 1.18 µg/mL)	**l** = 4-BrC_6H_4	(IC_{50} = 0.072 µg/mL)
b = C_6H_5	(IC_{50} = 2.16 µg/mL)	**m** = C_6H_5	(IC_{50} = 1.45 µg/mL)
c = 4-OHC_6H_4	(IC_{50} = 0.068 µg/mL)	**n** = 4-$NO_2C_6H_4$	(IC_{50} = 3.10 µg/mL)
d = 4-ClC_6H_4	(IC_{50} = 0.85 µg/mL)	**o** = 4-MeC_6H_4	(IC_{50} = 2.75 µg/mL)
e = 4-$N(Me)_2C_6H_4$	(IC_{50} = 1.55 µg/mL)	**p** = 2- thienyl	(IC_{50} = 0.033 µg/mL)
f = 4-BrC_6H_4	(IC_{50} = 0.072 µg/mL)	**q** = 4-pyridyl	(IC_{50} = 2.73 µg/mL)
g = 3-$NO_2C_6H_4$	(IC_{50} = 1.44 µg/mL)	**r** = 4-FC_6H_4	(IC_{50} = 0.56 µg/mL)
h = 3-pyridyl	(IC_{50} = 5.00 µg/mL)		
i = 2, 4-ClC_6H_3	(IC_{50} = 2.16 µg/mL)		
j = cyclohexyl	(IC_{50} = 0.033 µg/mL)	R	
k = 3, 4, 5-$OMeC_6H_2$	(IC_{50} = 0.54 µg/mL)	**a-k** = H	
		l-r = Ph	

Figure 26. Antimalarial activity of pyrazole-based pyrido[2,3-*d*] pyrimidine-diones against *P. falciparum* strain

Manach et al. (2015) also identified a novel series of pyrazolopyrimidines **43-47** as a new class of antimalarial hybrid. They tested *in vitro* antiplasmodial activities counter to CQ-sensitive (NF54) and multidrug-resistant (K1) *P. falciparum* clones employing mefloquine, CQ, and artesunate as reference compounds. All the tested compounds demonstrated *in vitro* antiplasmodial potency counter to the CQ-sensitive strain (NF54), whereas only compound **46** displayed potent activity counter to the K1 *P. falciparum* clone (**Figure 27**).

Journal Pre-proof

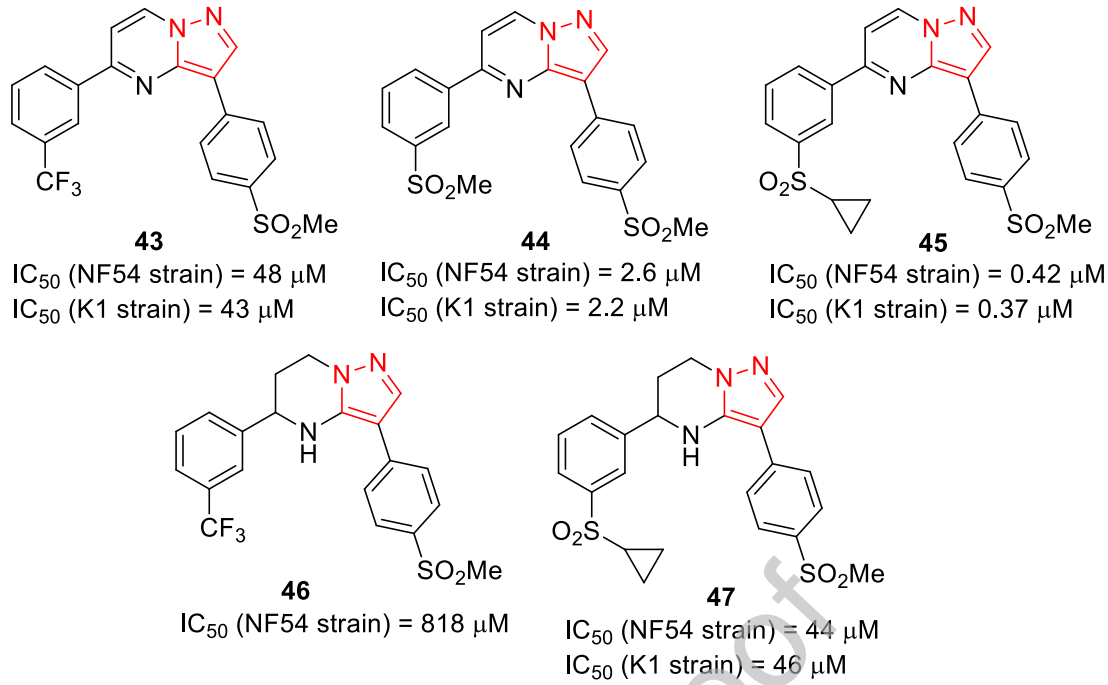


Figure 27. Antimalarial activity of pyrazolopyrimidines against CQ-sensitive (NF54) and multidrug-resistant (K1) *P. falciparum* clones

Azeredo et al. (2017) developed and synthesized the pyrazolopyrimidine derivatives incorporated with diverse arylamines at seventh position **48** and screened *in vitro* counter to CQ-resistant W2 *P. falciparum* clone *in vivo* counter to the *P. berghei*-infected mouse model, and *in vitro* as inhibitors of *Pf*-dihydroorotatede hydrogenase (*Pf*DHODH). Out of fifteen hybrids synthesized, thirteen were active counter to *P. falciparum*, with IC_{50} value range between 1.2 and 92.4 μM. The *Pf*DHODH inhibition revealed that compounds with β-naphthylamine at the seventh position (**48n-o**) were the more potent. Among them, hybrid **48o** exhibited higher and selective inhibitory activity (IC_{50} = 0.16μM), followed by **48n** and **48m**, with 4.0 and 6.0 μM of IC_{50} values, respectively. Hybrids **48n** and **48m** displayed low toxicity and higher SI (selectivity index) values of 79.6 and 467.8, respectively. Hence, these hybrids were screened *in vivo* in *P. berghei*-infected mouse mode. On day 5, upon treatment at 5 mg/kg, administered orally, both hybrids reduced parasitemia by 50% (**Figure 28**).

Journal Pre-proof

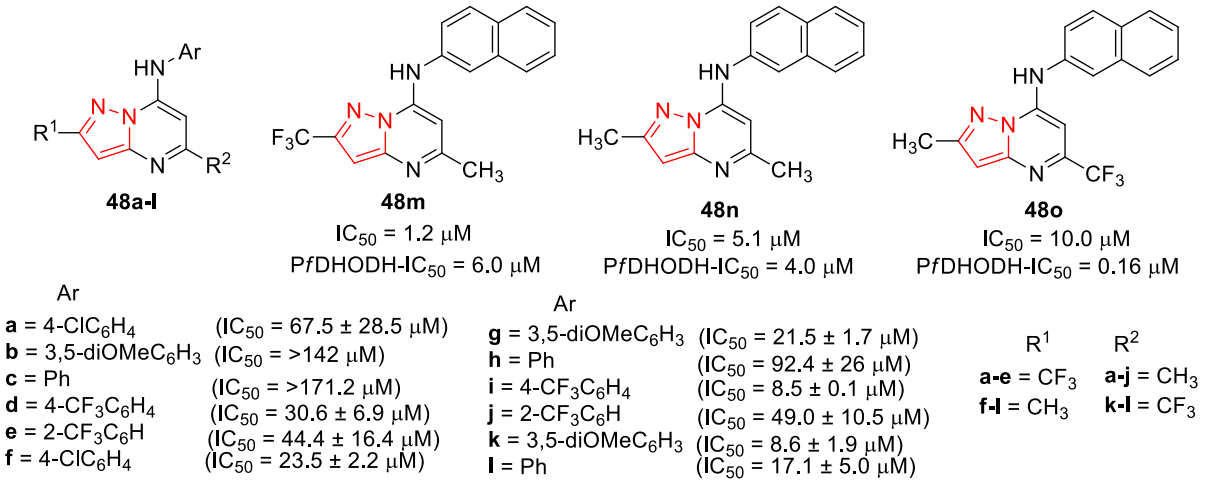
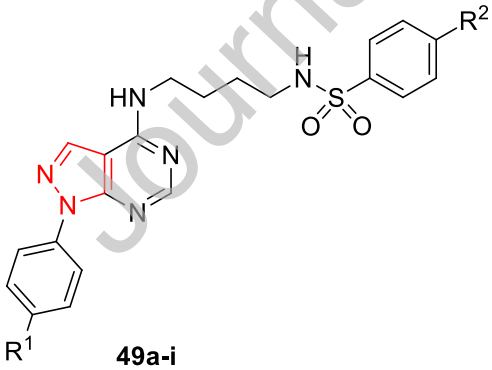


Figure 28. Antimalarial activity of 7-arylaminopyrazolo[1,5-*a*]pyrimidines against CQ-resistant (W2) *P. falciparum* clone and *P. berghei*

The following year, a broad range of pyrazolopyrimidine derivatives conjugated with phenyl and benzenesulfonamide moieties having various substituents at the *para*-position **49** were furnished and screened *in vitro* counter to CQ-resistant W2 *P. falciparum* clone (Silvira et al. 2018). Out of nine hybrids synthesized, six demonstrated *in vitro* potency against the W2 *P. falciparum* strain, with an IC_{50} value range between 5.13 and 43.40 μM. Among them, hybrid **49c** emerged as the most active one with an IC_{50} of 5.13 μM, which was higher than the reference compound CQ (IC_{50} = 0.55 μM) and lower compared to the sulfadoxine (IC_{50} = 15.0 μM). Most synthesized hybrids displayed higher SI values than sulfadoxine, the standard agent (**Figure 29**).



a. R^1 = F, R^2 = F (IC_{50} = 28.20 ± 9.20 μM)
b. R^1 = F, R^2 = Cl (IC_{50} = 21.15 ± 0.45 μM)
c. R^1 = F, R^2 = Me (IC_{50} = 5.13 ± 1.86 μM)
d. R^1 = Cl, R^2 = F (IC_{50} = 43.40 ± 3.80 μM)
e. R^1 = Cl, R^2 = Cl (IC_{50} = > 50 μM)
f. R^1 = Cl, R^2 = Me (IC_{50} = > 50 μM)
g. R^1 = Me, R^2 = F (IC_{50} = 42.12 ± 0.32 μM)
h. R^1 = Me, R^2 = Cl (IC_{50} = > 50 μM)
i. R^1 = Me, R^2 = Me (IC_{50} = 12.22 ± 0.02 μM)

Figure 29. Antimalarial activity of pyrazolopyrimidine-benzenesulfonamide derivatives against CQ-resistant (W2) *P. falciparum* strain

Further, imidazo[1,2-*a*]pyrimidine incorporated pyrazole derivatives **50-51** were designed and synthesized by Prasad et al. (2018) and screened antimalarial potency counter to *P. falciparum* employing chloroquine and quinine as reference drugs. All the tested hybrids exhibited superior potency with the IC_{50} value range between 0.030 and 1.45 μg/ml. SAR

studies showed that the hybrids having -F substituent at the *para* position of the phenyl ring (**50e** and **51e**) displayed excellent antimalarial activity with 0.030 and 0.041 µg mL^{-1}, respectively, whereas the hybrids with -Me group at the *para* position of the phenyl ring (**50b** and **51b**) demonstrated below average results with IC_{50} 1.84 and 1.50 µg mL^{-1}, respectively. Among the heterocyclic substituents at the sixth position of the pyrimidine ring, *N*-containing heterocycles demonstrated superior antimalarial activities than *S*-containing heterocycles (**Figure 30**).

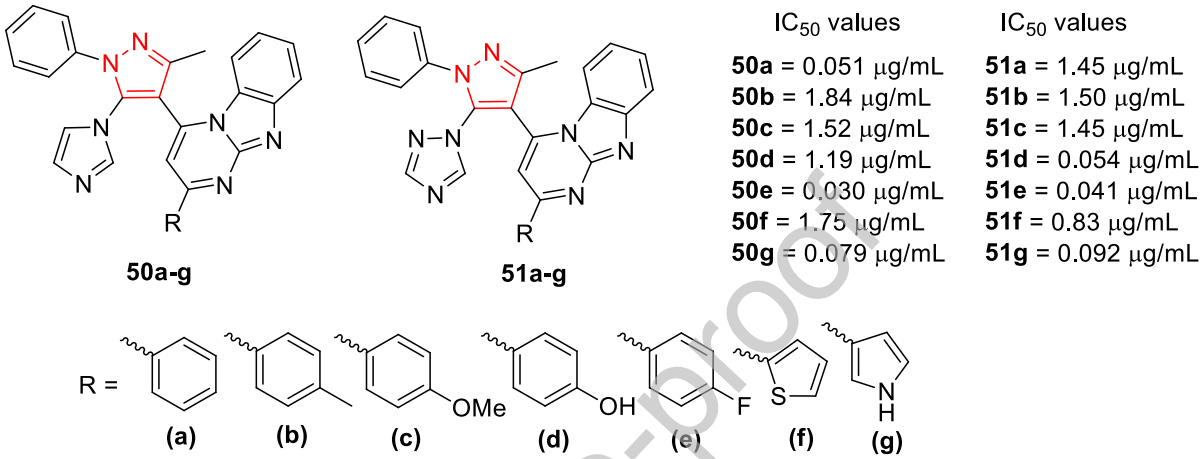


Figure 30. Antimalarial activity of imidazo[1,2-*a*]pyrimidine substituted pyrazoles against *P. falciparum*

2.6.Oxadiazole containing pyrazoles:

In continuation of their interest in the construction of fluorinated pyrazoles, Karad et al. (2016) developed a range of fluoro-substituted pyrazoles conjugated with 1,3,4-oxadiazole moiety **52** and tested the antimalarial efficacy against CQ and quinine sensitive *P. falciparum* clones. Compounds **52l-p** displayed higher antimalarial potency against the *P. falciparum* clone than the standard quinine IC_{50} = 0.826 µM. Among all, compound **52m** (IC_{50} = 0.506 µM) was found to be more potent against the *P. falciparum* clone (**Figure 31**).

Journal Pre-proof

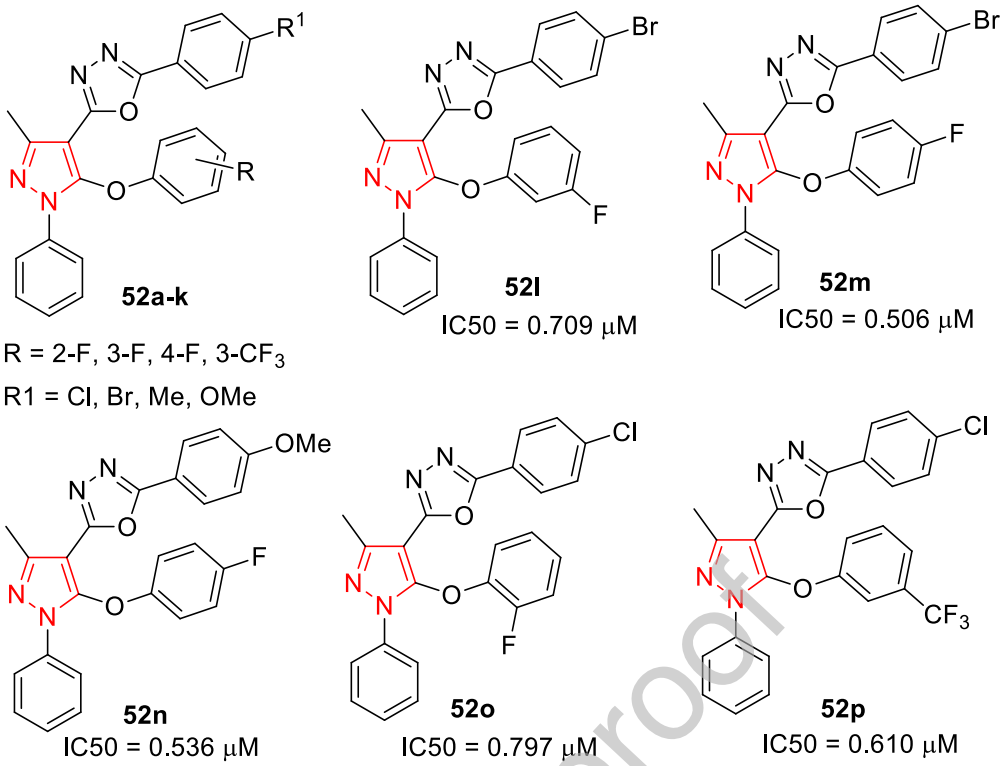
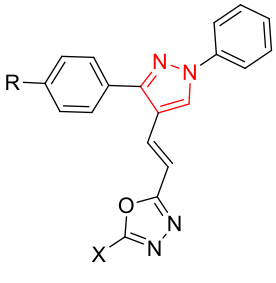


Figure 31. Antimalarial activity of fluorinated pyrazoles conjugated with 1,3,4-oxadiazole against *P. falciparum*

The *in vitro* antimalarial potency of pyrazole acrylic acid-based oxadiazoles **53** counters to CQ-sensitive 3D7 *P. falciparum* clone was tested by Verma et al. (2018) and displayed potent antimalarial activity with 0.245 to 3.507 µg/ml range of IC_{50} values. Four compounds, **53e, 53q, 53t, and 53v,** out of twenty-four synthesized, were the most potent, with less than 1 µg/ml of IC_{50} values (0.515, 0.489, 0.503, and 0.245 µg/ml, respectively). These four compounds were further examined for activity counter to CQ-resistant RKL9 *P. falciparum* clone and showed an IC_{50} value of 1.1571, 0.902, 1.571, and 0.724 µg/ml, respectively (**Figure 32**).



	R	X	IC_{50} 3D7 (µg/mL)
a.	H	Ph	3.208
b.	Me	Ph	2.461
c.	F	Ph	3.507
d.	H	4-ClPh	1.186
e.	Me	4-ClPh	0.515
f.	F	4-ClPh	3.331
g.	H	3-MePh	3.010
h.	Me	3-MePh	3.464
i.	F	3-MePh	1.161
j.	H	4-FPh	1.140
k.	Me	4-FPh	1.912
l.	F	4-FPh	1.135

	R	X	IC_{50} (3D7) (µg/mL)
m.	H	2-BrPh	2.659
n.	Me	2-BrPh	2.266
o.	F	2-BrPh	2.149
p.	H	2,4-diClPh	2.727
q.	Me	2,4-diClPh	0.489
r.	F	2,4-diClPh	2.236
s.	H	4-NO_2Ph	1.012
t.	Me	4-NO_2Ph	0.503
u.	F	4-NO_2Ph	2.813

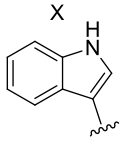
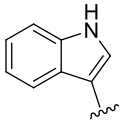
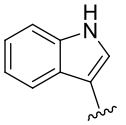
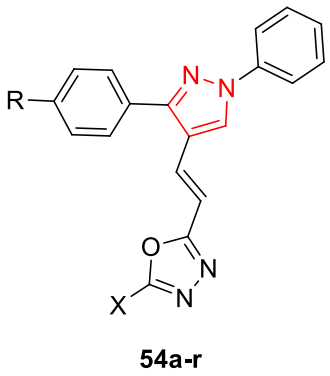
	R	X	IC_{50} (3D7) (µg/mL)
v.	H		0.245
w.	Me		1.417
x.	F		1.372

Figure 32. Antimalarial activity of pyrazole acrylic acid-based oxadiazole derivatives against CQ-sensitive (3D7) and CQ-resistant (RKL9) *P. falciparum* strains

Continuance of their interest in the antimalarial potency of pyrazole acrylic acid-based oxadiazole derivatives; an extension was carried out in the next year by Verma et al. (2019). All the furnished hybrids demonstrated potent antimalarial activity against the CQ-sensitive 3D7 *P. falciparum* clone with an IC_{50} value range between 0.248 and 4.316 µg ml^{-1}. Out of eighteen compounds synthesized, six (**54a, 54f, 54g, 54n, 54o, and 54r)** were found to be the most potent with less than 1 µg/ml of IC_{50} values (0.886, 0.248, 0.647, 0.322, 0.582 and 0.494 µg ml^{-1}, respectively). Among them, compound **54f** has emerged as the most active one with an IC_{50} of 0.248 µg ml^{-1} followed by **54n** with an IC_{50} of 0.322 µg ml^{-1}. Both were lower than standard agent CQ (IC_{50} = 0.405 µg ml^{-1}) (**Figure 33**).



54a-r

	R	X	IC_{50} 3D7 (µg/mL)
a.	H	3,4,5-triOMePh	0.886
b.	Me	3,4,5-triOMePh	1.708
c.	H	3,4,-diOMePh	1.180
d.	Me	3,4,-diOMePh	2.234
e.	F	3,4,-diOMePh	2.203
f.	H	furyl	0.248
g.	Me	furyl	0.647
h.	H	benzyle	2.302
i.	Me	benzyle	2.736
j.	H	4-MePh	1.650
k.	Me	4-MePh	2.769

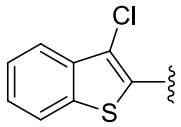
	R	X	IC_{50} 3D7 (µg/mL)
l.	H	2,6-diClPh	3.073
m.	Me	2,6-diClPh	4.316
n.	H	pyridine	0.322
o.	Me	pyridine	0.582
p.	H	4-OHPh	1.942
q.	Me	4-OHPh	3.382
r.	Me		0.494

Figure 33. Antimalarial activity of pyrazole acrylic acid-based oxadiazole derivatives against CQ-sensitive (3D7) *P. falciparum* strain

2.7.Curcumin analogues containing pyrazoles:

Curcumin compounds were promising candidates for synthesizing and designing novel antimalarial drugs and a class of highly selective *P. falciparum* inhibitors. Mishra et al. (2008) constructed a variety of curcumin analogs having pyrazole rings **55-60** and evaluated them for their ability to inhibit *P. falciparum* growth in culture. The more potent curcumin analogs **57** and **60** were inhibitory for CQ-resistant *P. falciparum* at IC_{50} of 0.89, 0.45 µM, and CQ-sensitive *P. falciparum* at IC_{50} of 0.87, 0.48 µM, respectively. The most efficient Pyrazole moiety of curcumin (**60**) displayed ninefold higher antimalarial activity against CQ-resistant and sevenfold higher antimalarial activity against CQ-sensitive (**Figure 34**).

Journal Pre-proof

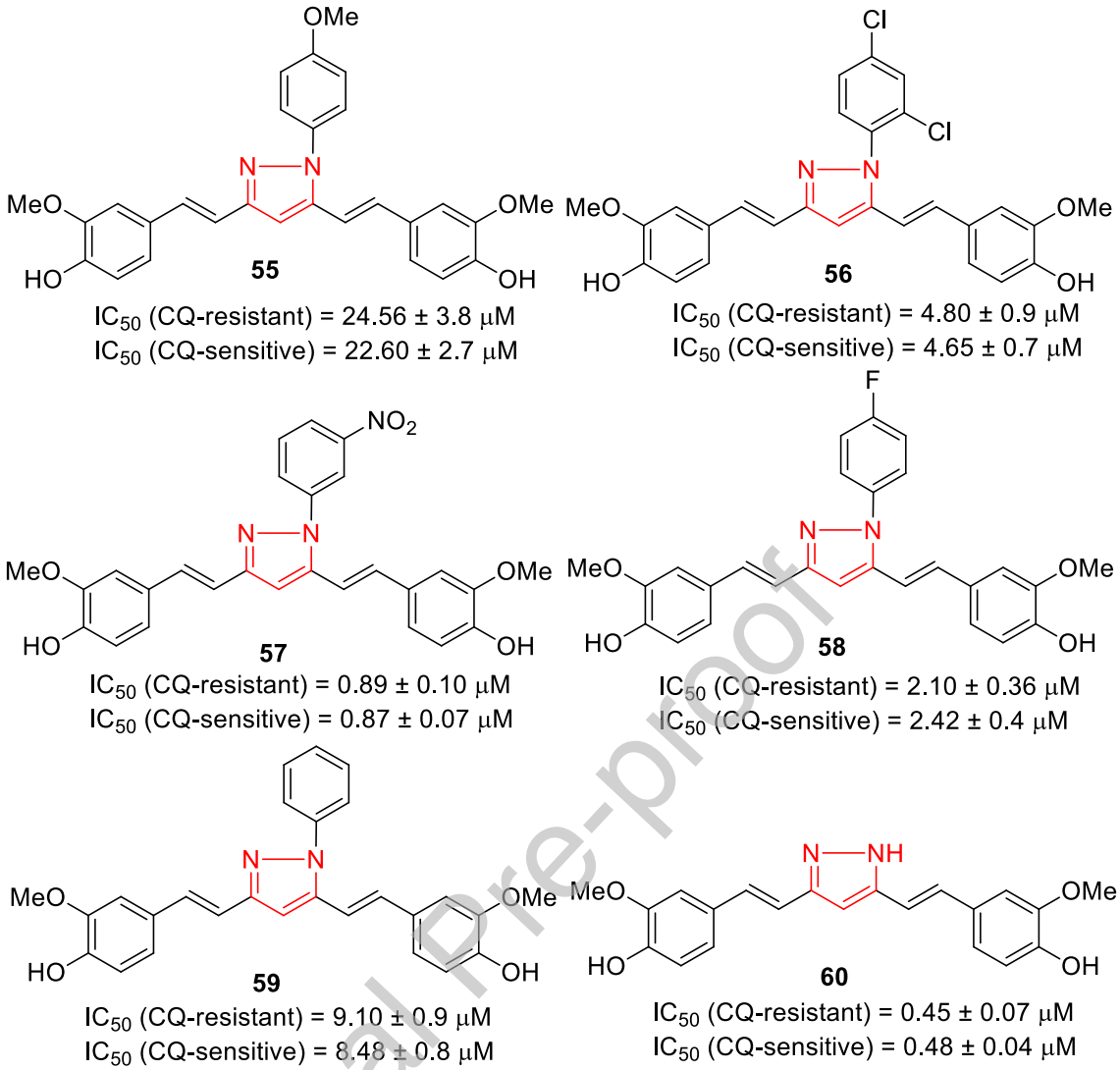


Figure 34. Antimalarial activity of curcumin analogs having pyrazole rings against CQ-sensitive and CQ-resistant *P. falciparum* strains

Balaji et al. (2015) also tested the *in vitro* antimalarial activity of several curcumin analogs having pyrazole ring **61**. All the examined compounds displayed schizonticidal potency with an IC_{50} value range between 4.21 and 23.09 μM and parasiticidal activity with minimum killing concentrations (MKCs) ranging from 4.18 to 25.35 μM. Among the tested carboxamide (**61a-e**) and methanone (**61f-o**) analogs, compounds **61e** (IC_{50}; 9.87 μM) and **61o** (IC_{50}; 4.21 μM) exhibited maximum schizonticidal activity, respectively. Compound **61q** was found to be a lesser schizonticidal activity with a 23.09 IC_{50} value among all the tested compounds (**Figure 35**).

Journal Pre-proof

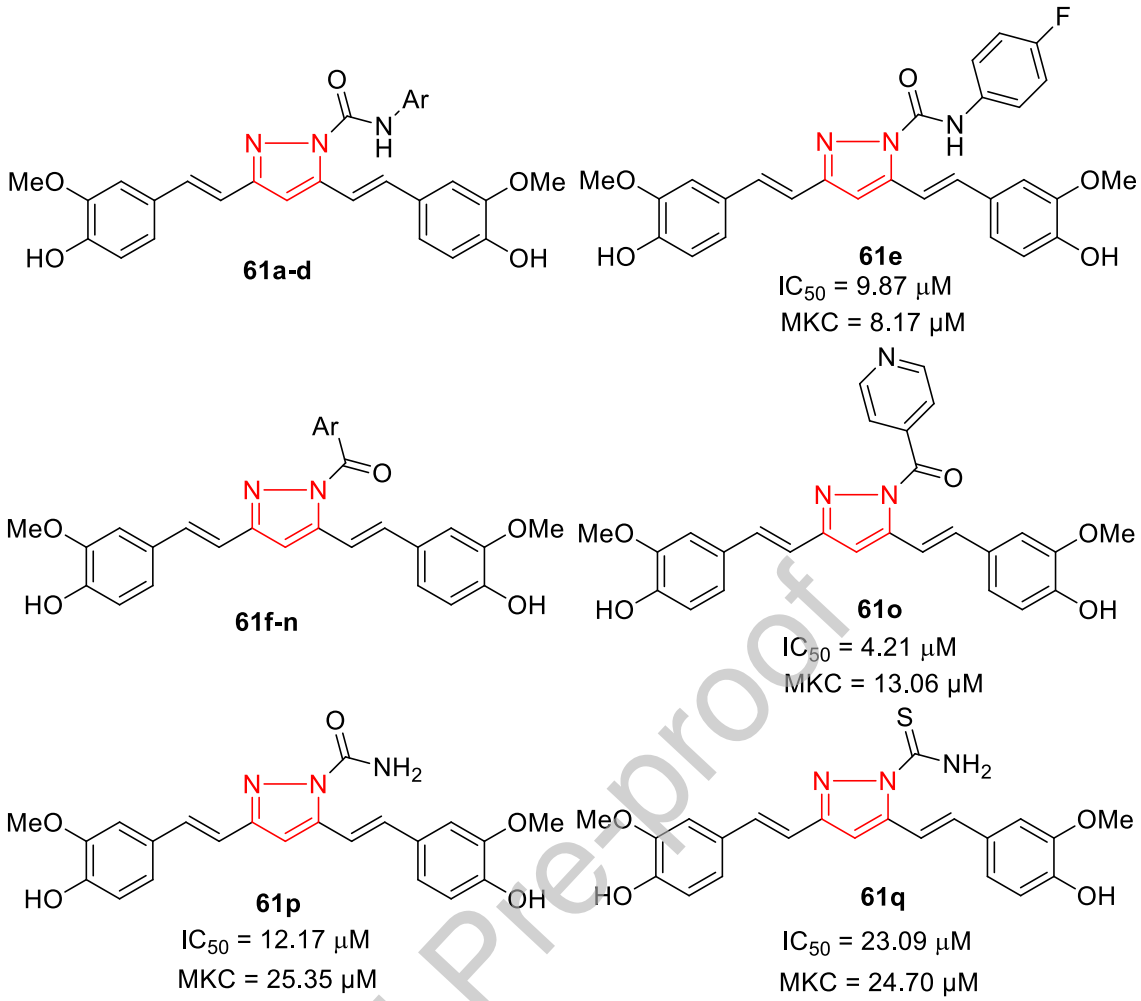


Figure 35. Antimalarial activity of curcumin analogs having pyrazole rings against *P. falciparum*

2.8.Chalcone containing pyrazoles:

Chalcone (1,3-diaryl-2-propen-1-one) derivatives are simple and well-known analogs that played an important role in the progress of highly active, less toxic antimalarials (Qin et al., 2020). In continuation of their interest in the antimalarial evaluation of pyrazoles, Bekhit et al. (2014) tested the *in vivo* antimalarial potency of chalcone containing pyrazole **62** utilizing mice infected with *P. berghei* at a dose level of 48.4 µmol/kg. It exhibited lower antimalarial activity with suppression of -55.9%. Recently, Akolkar et al. (2020) have examined the antimalarial potency of chalcone containing pyrazole derivatives **63-66** counter to *P. falciparum* employing CQ and quinine as standard drugs. All the tested hybrids displayed potency with an IC_{50} value range between 1.46 and 3.93 µM. The strongest potency was found in hybrid **63** with an IC_{50} 1.46 µM. (**Figure 36**).

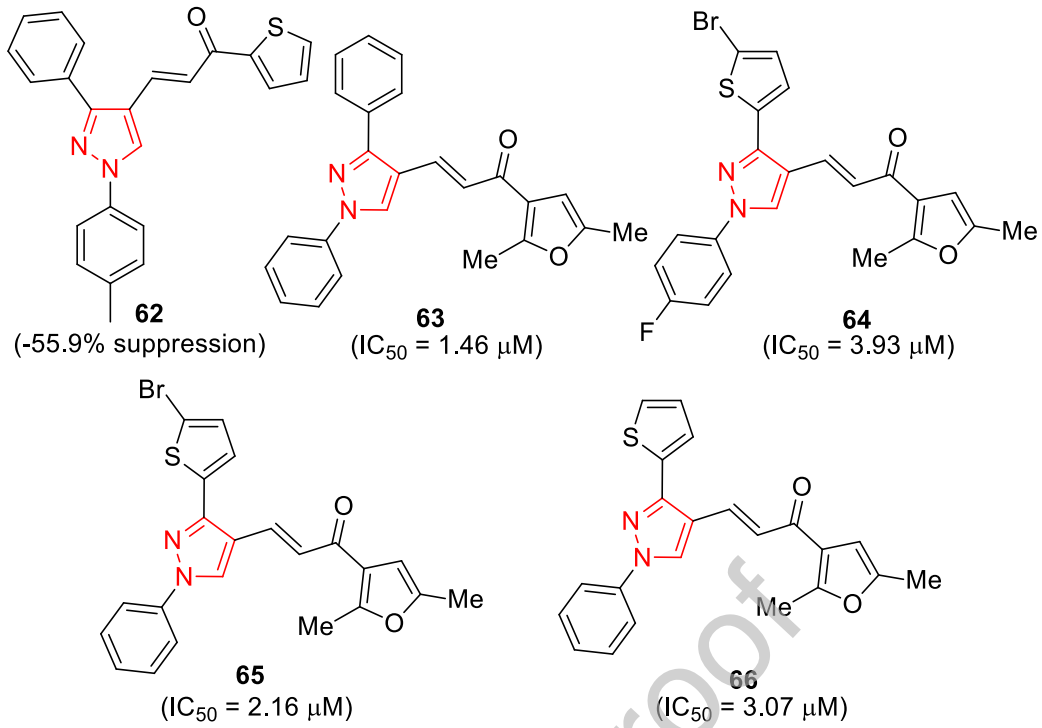
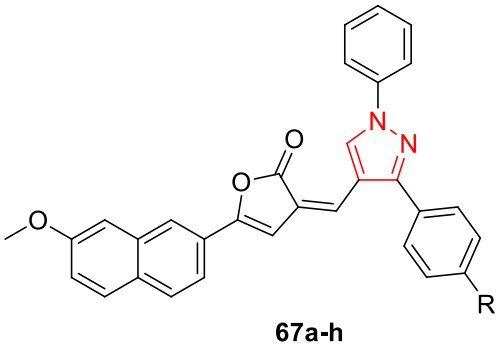


Figure 36. Antimalarial activity of compound **62** against *P. berghei* and compounds **63-65** against *P. falciparum*

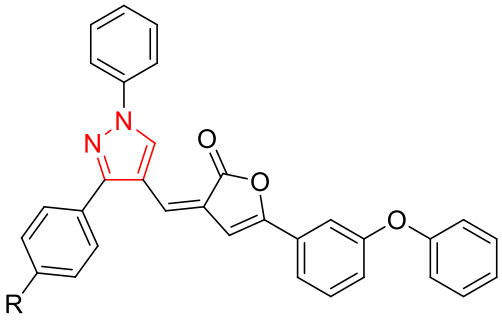
2.9.Furan containing pyrazoles:

Choudhary et al. (2022) furnished a wide variety of novel furan containing pyrazoles **67-69** and examined antiplasmodial potency based on *in vitro* antimalarial potency counter to the CQ-resistant K1 *P. falciparum* strain. All the twenty-four furnished compounds displayed potent anti-plasmodial activity counter to the CQ-resistant (K1) clone of *P. falciparum*. Among the series **67(a-h)**, hybrids **67a**, **67d**, **67e**, **67f**, and **67g** exhibited very good activity with IC_{50}value <5 µg/ml, followed by hybrid **67b** with IC_{50} value <10 µg/ml, whereas hybrids **67c** and **67h** displayed lower antimalarial activity with IC_{50} value greater than 10 µg/ml. Similarly, the hybrids **68d**, **68e**, **68f**, and **68g** displayed excellent antimalarial potency, while hybrids **68c** and **68h** were found with poor activity. In addition, hybrids **69e**, **69f**, and **69g** also exhibited higher antimalarial potency, although hybrids **69b** and **69h** demonstrated a much lesser activity. According to the SAR studies, halogen as R substituent resulted in enhanced activity, whereas electron-donating or electron-withdrawing groups as R substituent resulted in reduced activity. Among all the twenty-four furnished hybrids, **68d** and **68g** have emerged as excellent antimalarial agents with IC_{50} values of 1.968 and 1.983 µg/mL, respectively (**Figure 37**).

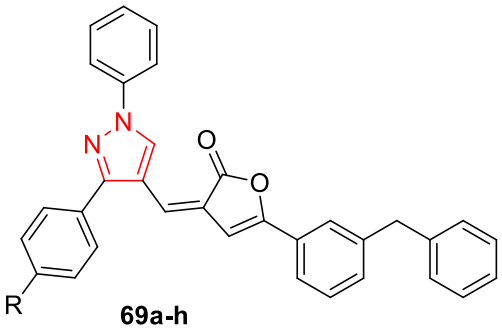
Journal Pre-proof



67a-h



68a-h



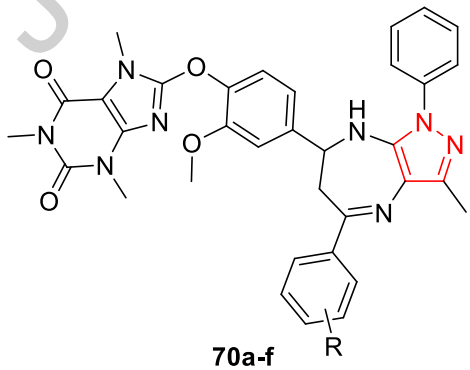
69a-h

R	IC50 K1 (μg/mL)	R	IC50 K1 (μg/mL)	R	IC50 K1 (μg/mL)
67a. H	2.241	**68a**. H	8.271	**69a**. H	5.157
67b. Me	7.451	**68b**. Me	5.243	**69b**. Me	11.028
67c. OH	12.006	**68c**. OH	16.062	**69c**. OH	14.149
67d. OMe	2.258	**68d**. OMe	1.968	**69d**. OMe	7.251
67e. Cl	3.960	**68e**. Cl	3.251	**69e**. Cl	2.069
67f. F	2.238	**68f**. F	2.025	**69f**. F	2.358
67g. Br	3.125	**68g**. Br	1.983	**69g**. Br	2.473
67h. NO_2	15.406	**68h**. NO_2	23.792	**69h**. NO_2	16.837

Figure 37. Antimalarial activity of furan containing pyrazole derivatives against CQ-resistant (K1) *P. falciparum* strain

2.10. Diazepine containing pyrazoles:

A broad range of Pyrazolo[3,4-*b*][1,4]diazepine derivatives **70** was identified as antimalarial agents and screened *in vitro* antimalarial potency counter to Plasmodium parasite using CQ as the reference compound (Insuasty et al., 2015). All the tested compounds **70a-f** exhibited moderate *in vitro* antimalarial potency against the Plasmodium parasite, with the IC_{50} value range between 11.3 ± 2.3 and 18.9 ± 1.7μg mL^{-1}. Hybrid **70f** displayed an efficient antimalarial potency against the Plasmodium parasite with 11.3 ± 2.3 μg $mL^{-1}$of IC_{50} value (**Figure 38**).



70a-f

R	IC_{50} (μg/mL)
a. H	13.3 ± 1.9
b. 4-Cl	14.1 ± 2.1
C. 4-F	12.5 ± 2.4
d. 4-CH_3	12.3 ± 2.1
e. 4-OCH_3	13.1 ± 2.4
f. 3,4,5-triOCH_3	11.3 ± 2.3

Figure 38. Antimalarial activity of pyrazolo[3,4-*b*][1,4]diazepine derivatives against Plasmodium parasite

2.11. Imidazopyridazine containing pyrazoles:

Large et al. (2013) explored and extended a novel pyrazole class containing imidazopyridazine inhibitors of *P. falciparum* calcium-dependent protein kinase 1 (P*f*CDPK1). Among all the tested compounds, diaminocyclohexane substituted compound **72** exhibited a good metabolic stability profile and *in vitro* potency against *P. falciparum* (Pf anti-parasite EC_{50} = 0.262 µM, P*f*CDPK1 enzyme IC_{50} = 0.056 µM) (**Figure 39**).

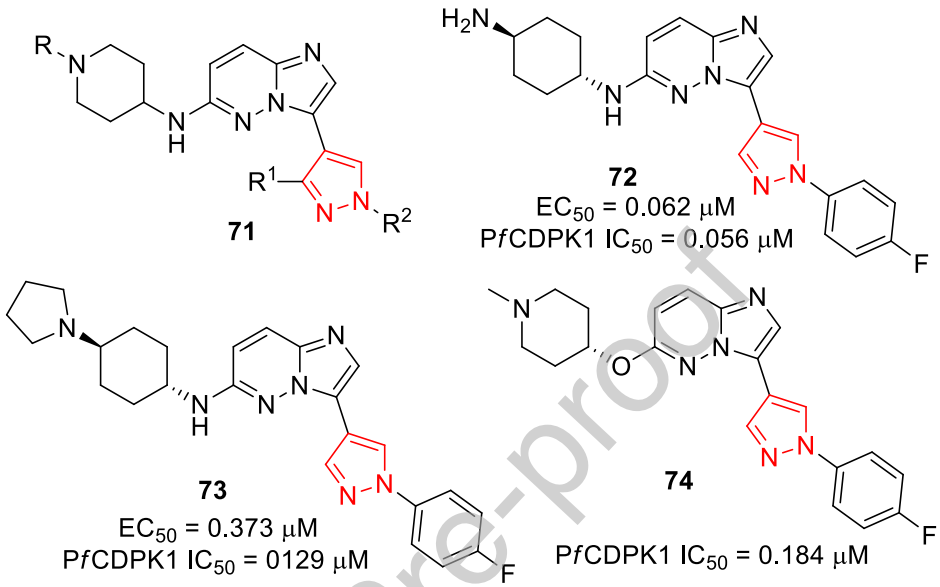


Figure 39. Antimalarial activity of imidazopyridazine substituted pyrazoles against P*f*CDPK1

2.12. Thiazole containing pyrazoles:

Aminomethylthiazole pyrazole carboxamide **75** and its derivatives **76-83** were identified as antimalarial hybrids by Cabrera et al. (2011) and evaluated for their *in vitro* antiplasmodial activities against chloroquine and multidrug-resistant (K1) and CQ-sensitive (NF54) clones of *P. falciparum*. For all the experiments, chloroquine IC_{50} 0.016 µM (NF54) and 0.194 µM (K1) and artesunate IC_{50} 0.004 µM (NF54) and 0.003 µM (K1) were employed as the reference compounds. Most of the evaluated analogs were less active with IC_{50} >1 µM. Among all, analog **75** emerged as the more potent one against K1 (with 0.08 µM of IC_{50} value) and NF54 (with IC_{50} 0.07 µM) strains of *P. falciparum* (**Figure 40**).

Journal Pre-proof

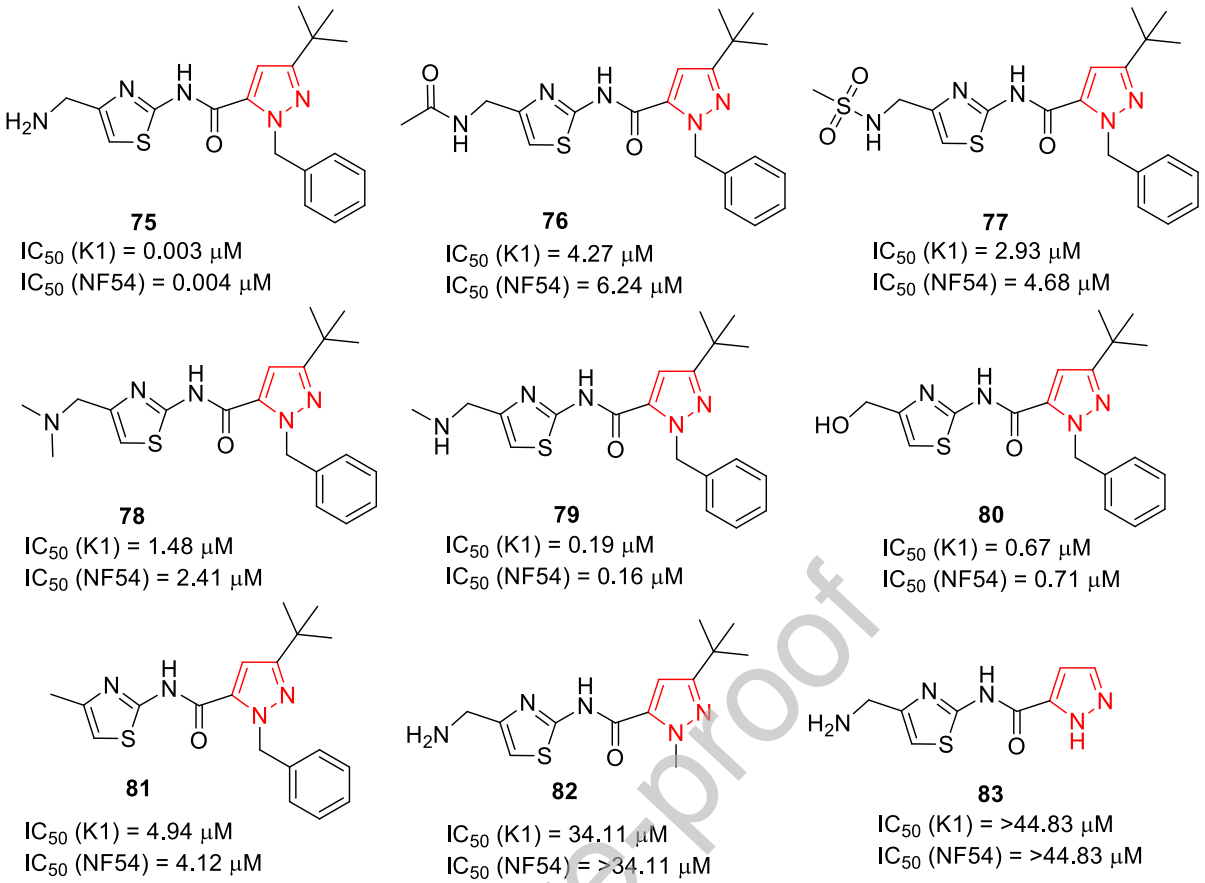


Figure 40. Antimalarial activity of aminomethylthiazole pyrazole carboxamide and its derivatives against CQ-resistant (K1) and CQ-sensitive (NF54) clones of *P. falciparum*

The significant *in vitro* antiplasmodial activity of lead compound **75** has motivated Cheuka et al. (2014) to extend the construction of uncovered aminomethylthiazole pyrazole carboxamide derivatives **84-93** by replacing the pyrazole and thiazole cores. Among all the tested analogs, compound **87** exhibited better activity with a 1.84 µM IC_{50} value (**Figure 41**). However, all the synthesized compounds were shown lower *in vitro* antiplasmodial activity against CQ-sensitive malaria parasite *P. falciparum* (NF54) with an IC_{50} value range between 1.84 and 67.5 µM.

Journal Pre-proof

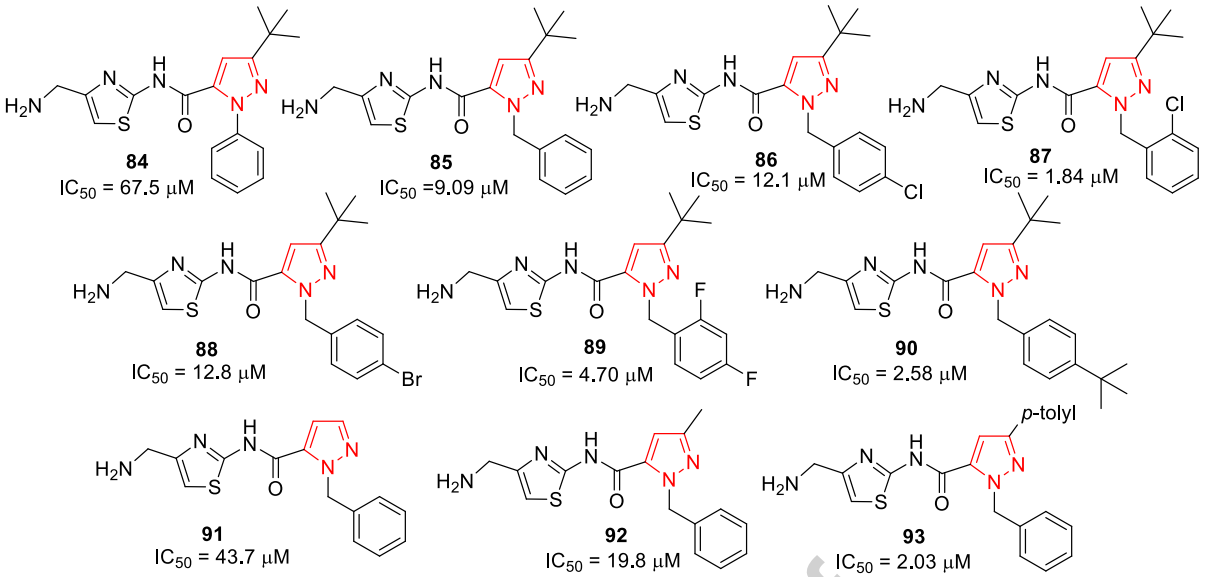
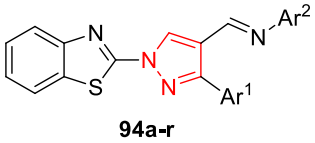


Figure 41. Antimalarial activity of aminomethylthiazole pyrazole carboxamide derivatives against CQ-sensitive (NF54) strain of *P. falciparum*

2.13. Benzothiazole containing pyrazoles:

A wide variety of pyrazoles having benzenethiazole and iminium groups **94** were identified as antimalarial hybrids and tested *in vitro* antimalarial potency counter to CQ-sensitive 3D7 *P. falciparum* clone (Aggarwal et al., 2018). Hybrids **94g-l** with Ar^1 = 4-MePh exhibited higher antimalarial potency with EC_{50} values ranging from 1.953 to 3.518 µg/mL, whereas hybrids **94m-r** with Ar^1 = 4-FPh and **94a-f** with Ar^1 = Ph exhibited moderate (EC_{50}= 2.59-5.9 µg/mL) and lower (EC_{50}= 2.7-8.3 µg/mL) antimalarial activity, respectively. Among all the tested compounds, hybrid **94l** (Ar^2 = 3-ClPh) was found to be the most active one with 1.953 µg/mL of EC_{50}value, followed by hybrid **94j** (Ar^2 = 4-ClPh) with the EC_{50} of 1.98 µg/mL while hybrid **94a** (Ar^2 = Ph) was found to be the least active one with 8.34 µg/mL of EC_{50} value (**Figure 42**).



94a-r

Ar^1 = Ph	EC_{50} (µg/mL)	Ar^1 = 4-MePh	EC_{50} (µg/mL)	Ar^1 = 4-FPh	EC_{50} (µg/mL)
a. Ar^2 = Ph	8.342	**g**. Ar^2 = Ph	3.518	**m**. Ar^2 = Ph	5.920
b. Ar^2 = 4-MePh	2.760	**h**. Ar^2 = 4-MePh	2.241	**n**. Ar^2 = 4-MePh	2.726
c. Ar^2 = 4-OMePh	4.126	**i**. Ar^2 = 4-OMePh	3.923	**o**. Ar^2 = 4-OMePh	5.009
d. Ar^2 = 4-ClPh	2.769	**j**. Ar^2 = 4-ClPh	1.983	**p**. Ar^2 = 4-ClPh	5.009
e. Ar^2 = 2-ClPH	4.038	**k**. Ar^2 = 2-ClPH	2.621	**q**. Ar^2 = 2-ClPH	3.753
f. Ar^2 = 3-ClPh	2.702	**l**. Ar^2 = 3-ClPh	1.953	**r**. Ar^2 = 3-ClPh	2.621

Figure 42. Antimalarial activity of benzenethiazole incorporated pyrazoles against CQ-sensitive (3D7) strain of *P. falciparum*

Journal Pre-proof

2.14. Thiazolidine containing pyrazoles:

Bekhit et al. (2015) synthesized another class of pyrazoles **95, 96** by hybridizing with thiazolidinones examined for their *in vivo* antimalarial potent counter to *P. berghei*-infected mice. These hybrids showed >90% suppression of the parasitic potency compared to the reference CQ. Among the most potent analogs further evaluated for their *in vitro* antimalarial activity counter to CQ-resistant (RKL9) strains of *P. falciparum*, analog **96** (IC_{50} = 0.0364 ± 0.004 µM) was found to be the most active derivative, which was 5-fold higher than CQ (**Figure 43**).

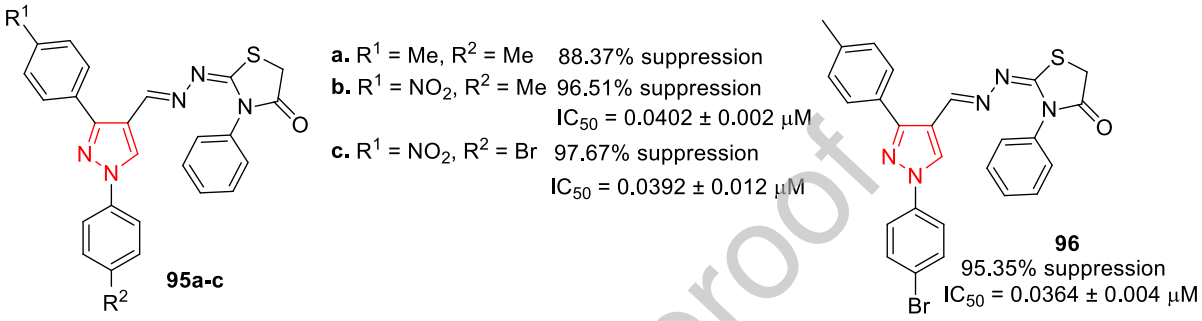


Figure 43. Antimalarial activity of thiazolidine-incorporated pyrazoles against *P. berghei*-infected mice and CQ-resistant (RKL9) strain of *P. falciparum*

Very recently, various pyrazole derivatives linked to thiazolidine moiety were developed and examined for their *in vivo* antimalarial potency counter to the *P. falciparum* clone (Bekhit et al., 2022). All the examined hybrids displayed considerable antimalarial potency with a minimum of 59.3% suppression and the lowest mean survival time of 8.71 days reported with hybrid **97a**. Among the studied compounds, **98a** and **98b** emerged as the most promising antimalarial agents with a maximum suppression of 95.35% and 96.51% and the highest mean survival time of 17.6 and 16.22 days, respectively (**Figure 44**).

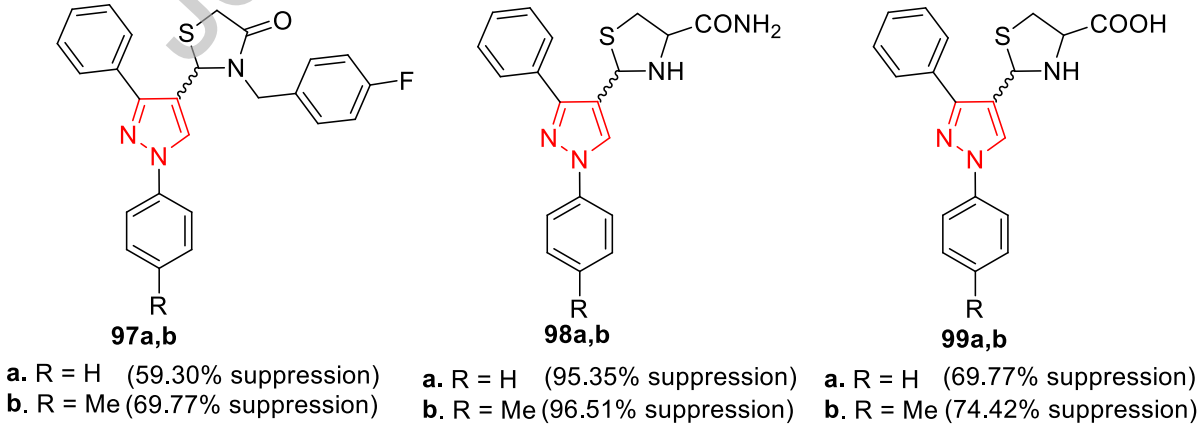


Figure 44. Antimalarial activity of thiazolidine incorporated pyrazoles against *P. falciparum*

2.15. Triazine containing pyrazoles:

Gogoi et al. (2020) examined the *in vitro* antimalarial potency of 1,3,5-triazine-incorporated pyrazole derivatives **100** counter to the CQ-sensitive 3D7 *P. falciparum* clone employing CQ as the standard agent. Out of ten hybrids synthesized, three hybrids, **100e** (*p*-chlorophenyl amino-functionalized), **100g** (*p*-bromophenyl amino-functionalized), and **100h** (*m*-chlorophenyl amino-functionalized), displayed considerable *in vitro* antimalarial potency counter to CQ-sensitive 3D7 *P. falciparum* clone with 53.85, 62.50, and 100 µg/mL of IC_{50} values, respectively. In contrast, other hybrids displayed no antimalarial potency (**Figure 45**).

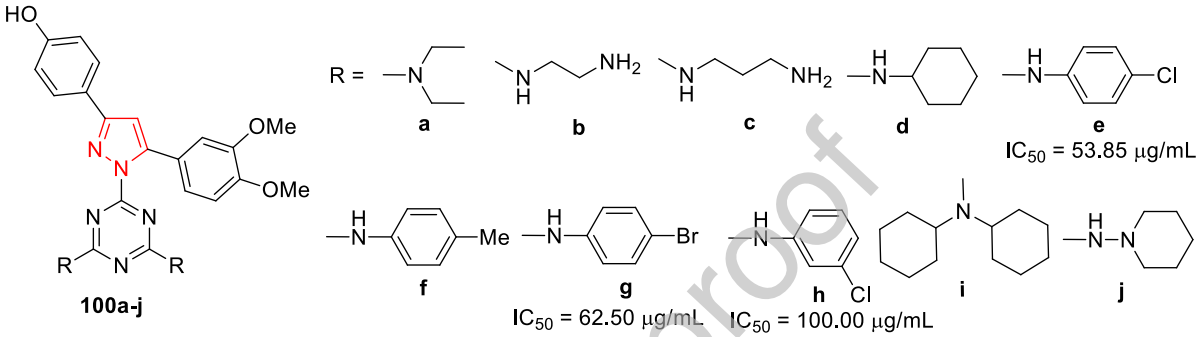
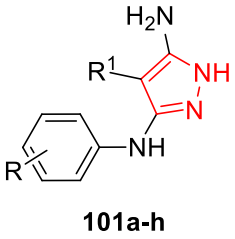


Figure 45. Antimalarial activity of 1,3,5-Triazine incorporated pyrazoles against CQ-sensitive (3D7) *P. falciparum* clone

2.16. Aryl containing pyrazoles:

The progress of novel antimalarial drug synthesis is urgently needed, considering the rising prevalence of drug-resistant *P. falciparum* parasites. Domínguez et al. (2002) studied aryl-substituted pyrazoles **101** and examined their antimalarial potency counter to *P. falciparum*. Compounds containing ester group on pyrazole ring exhibited commendable potency. However, the replacement of the ester group by the nitrile group resulted in reduced antimalarial activity due to the lack of hydrogen-bond formation. Among all the tested compounds, methyl 5-amino-3-anisidinepyrazole-4-carboxylic acid was identified as the most active against *P. falciparum* with an IC_{50} 0.149 µM. This work used ciprofloxacin as a standard drug (IC_{50}= 39.80 µM) (**Figure 46**).



a. R = H, R^1 = COOMe (IC_{50} = 0.149 µM)
b. R = 2-OMe, R^1 = COOMe (IC_{50} = >100 µM)
c. R = 3-OMe, R^1 = COOMe (IC_{50} = 0.150 µM)
d. R = 4-OMe, R^1 = COOMe (IC_{50} = >100 µM)
e. R = H, R^1 = CN (IC_{50} = 2.97µM)
f. R = 2-OMe, R^1 = CN (IC_{50} = 4.69 µM)
g. R = 3-OMe, R^1 = CN (IC_{50} = 1.15 µM)
h. R = 4-OMe, R^1 = CN (IC_{50} = 4.04 µM)

Figure 46. Antimalarial activity of aryl substituted pyrazoles against *P. falciparum*

Bekhit et al. (2012) synthesized a range of pyrazoles and evaluated *in vivo* antimalarial potency utilizing mice infected with CQ-sensitive *P. berghei* at a 50 µmol/kg dose level. From the analogs tested, compound **103** showed the most potent antimalarial potency counter to the CQ-resistant (RKL9) *P. falciparum* clone with an IC_{50} value of 0.033 µM (**Figure 47**). In addition, the more potent analogs **102-105** were evaluated counter to the CQ-resistant (RKL9) *P. falciparum* clone and displayed superior potency (with IC_{50} value range between 0.033 and 0.076 µM) than chloroquine diphosphate (IC_{50} = 0.188 µM).

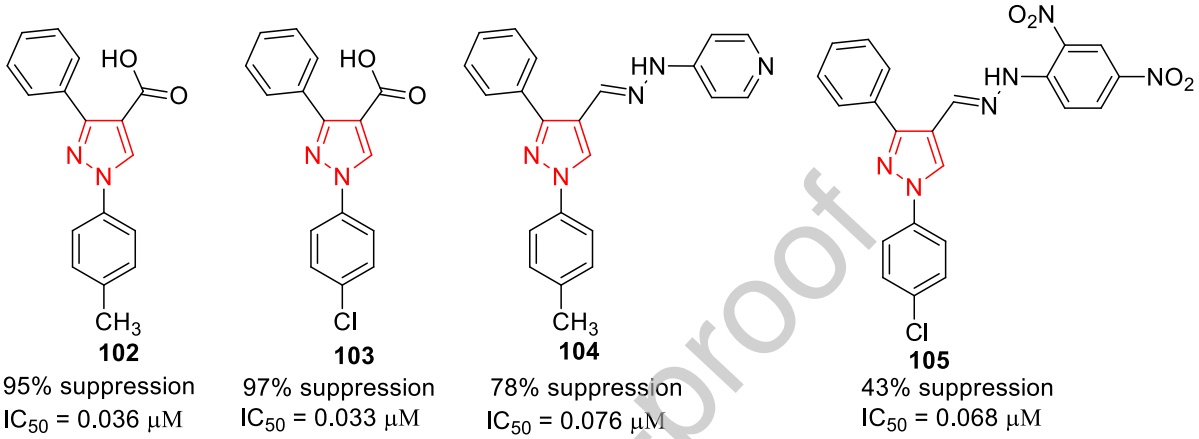
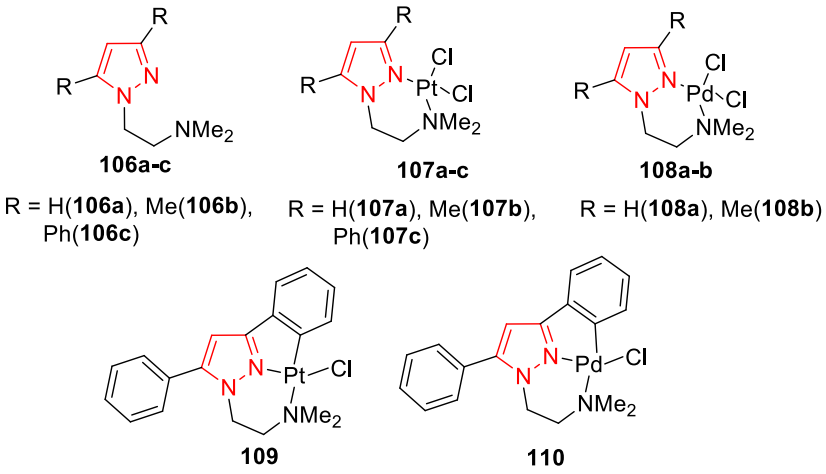


Figure 47. Antimalarial activity of pyrazole derivatives against CQ-sensitive *P. berghei* and CQ-resistant (RKL9) *P. falciparum* clone

2.17. The metal complex containing pyrazoles:

Quirante's et al. (2011) evaluated the antimalarial activities of pyrazoles containing ligands **106** and platinum(II) or palladium(II) based complexes **107-110** against the chloroquine-sensitive (W2) and chloroquine susceptible (3D7) *P. falciparum* clones. The cyclopalladated analog **110** was 10 times more potent than its platinum(II) complex 109 against *P. falciparum* W2 and 3D7 strains (**Figure 48**). Platinum(II) complexes **107a-c** exhibited higher in vitro antimalarial potency against W2 and 3D7 strains of *P. falciparum* than that of their corresponding parent ligands **106a-c**. The toxicity of complexes 108a and **108b** was low on two *P. falciparum* parasites.

Journal Pre-proof



	IC_{50} 3D7 (μM)	IC_{50} W2 (μM)
106a.	182.3±19.6	196.3±13.8
106b.	248.0±15.5	183.3±16.6
106c.	38.4±4.2	20.2±4.3
107a.	18.9±1.2	22.5±0.8
107b.	18.3±0.7	24.9±2.4
107c.	13.8±4.5	16.1±1.1
108a.	133.3±11.6	111.0±10.6
108b.	132.0±10.1	85.8±3.1
109.	111.7±18.0	138.0±6.2
110.	10.3±5.5	19.2±0.8

Figure 48. Antimalarial activity of pyrazoles containing ligands and Pt(II) or Pd(II) based complexes against the CQ-sensitive (W2) and CQ-susceptible (3D7) *P. falciparum* clones

2.18. Miscellaneous pyrazoles:

A new class of 1,3,4-trisubstituted pyrazole derivatives was developed and studied *in vitro* antimalarial potency counter to CQ-resistant (RKL9) *P. falciparum* strain and antiplasmodial activity counter to *P. berghei* (Bekhit et al., 2018). Hybrids **113b**, **113c**, **116a**, and **116d** were the most active antiplasmodial agents counter to *P. berghei*, with a higher percent of inhibition range between 90-100%. The hybrid **113c** demonstrated superior antimalarial potency (IC_{50} = 0.0142 μ M), 13-folder higher than standard CQ phosphate. The *in silico* studies of the most potent analogs counter to the quadruple and wild type mutant *pf* DHFR-TS structures confirmed the antimalarial activity. Moreover, the hybrids demonstrated significant *in silico* drug-likeness and pharmacokinetics. RBC hemolysis assay and acute toxicity analysis showed satisfactory physiological tolerability of the most potent hybrids up to 150 mg kg^{-1} through the oral route and 75 mg kg^{-1} through the parenteral route (**Figure 49**).

Journal Pre-proof

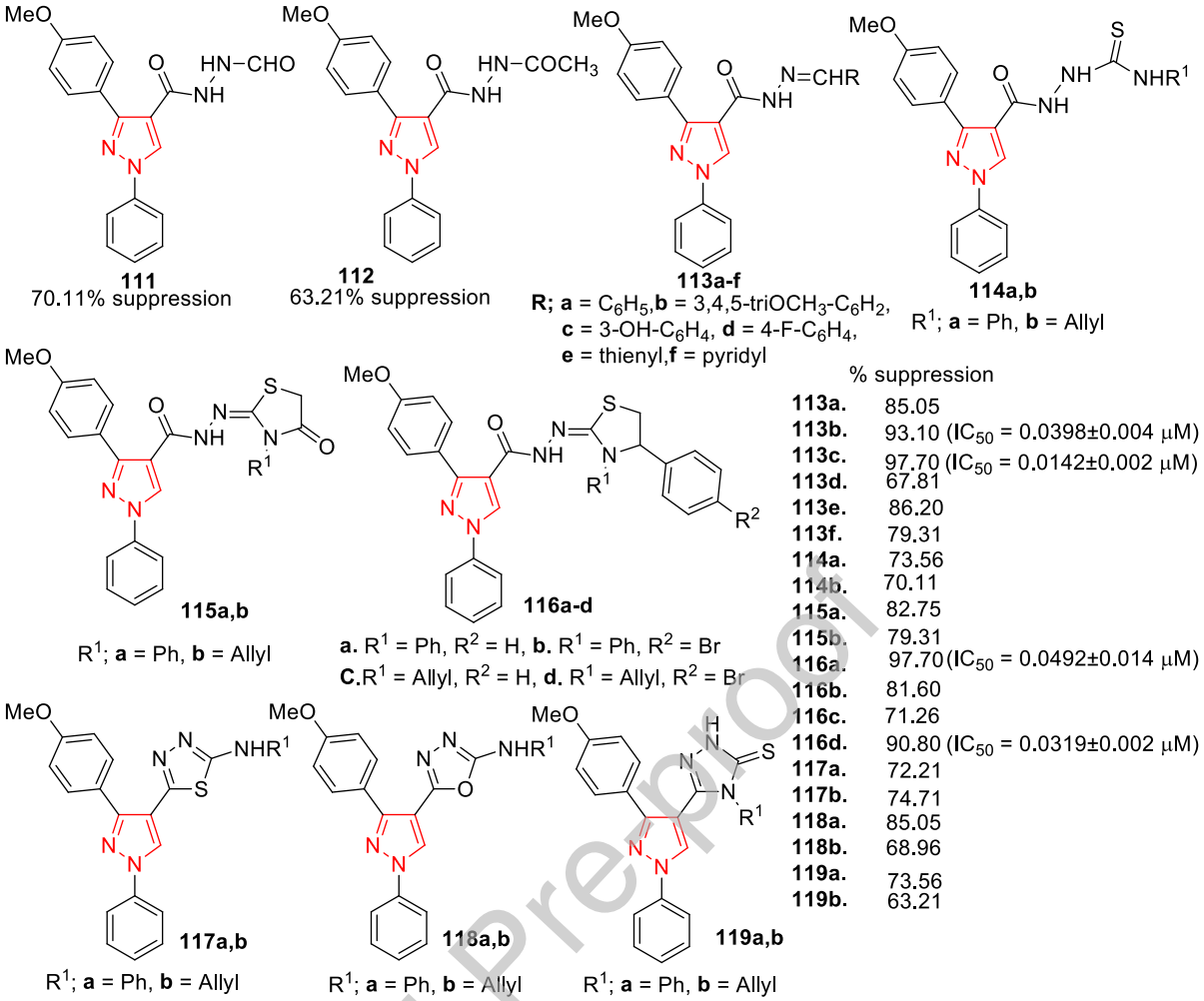
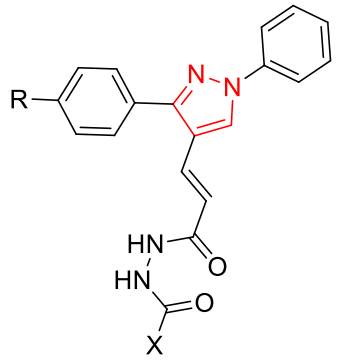


Figure 49. Antimalarial activity of 1,3,4-trisubstituted pyrazoles against *P. berghei* and CQ-resistant (RKL9) *P. falciparum* clone

In the same year, the *in vitro* antimalarial potency of pyrazole acrylic acid-based amide derivatives **120** counter to CQ-sensitive 3D7 *P. falciparum* clone was tested and displayed potent antimalarial activity with 0.985 to 4.412 µg/mL range of IC_{50} values (Verma et al., 2018). Compound **120g** was further screened for activity counter to CQ-resistant RKL9 *P. falciparum* clone and showed an IC_{50} value of 4.234 µg/mL (**Figure 50**). One compound, **120g** out of eight synthesized, was the most potent, with IC_{50} less than 1 µg/mL of IC_{50} value (0.985µg/mL).

Journal Pre-proof



120a-h

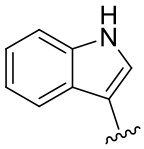
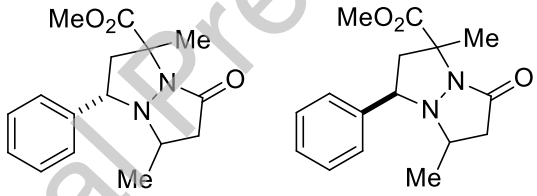
	R	X	IC_{50} 3D7	
a.	H	4-NO_2Ph	2.711 μg/mL	
b.	Me	4-NO_2Ph	2.776 μg/mL	
c.	H	3-MePh	3.633 μg/mL	
d.	Me	3-MePh	3.633 μg/mL	
e.	H	2,4-diClPh	2.536 μg/mL	
f.	Me	2,4-diClPh	4.059 μg/mL	
g.	F	2,4-diClPh	0.985 μg/mL	(IC_{50} (RKL9) = 4.234 μg/mL)
h.	H		4.412 μg/mL	

Figure 50. Antimalarial activity of pyrazole acrylic acid-based amide derivatives against CQ-sensitive (3D7) and CQ-resistant (RKL9) *P. falciparum* clones

The synthetic method for the construction of tetrahydro-1*H*,5*H*-pyrazolo[1,2-*a*]pyrazole-1-carboxylate derivatives **121** and **122** were reported by Strašek et al. (2019), and an assessment inhibition of dihydroorotate dehydrogenase of *Pf*DHODH was demonstrated. All the tested hybrids developed selectivity for P*f*DHODH more than HsDHODH (**Figure 51**). Compound **122** was found to be the more active with an IC_{50} 2.9 μM.



121 IC_{50} = 221 μM

122 IC_{50} = 2.9 μM

Figure 51. Antimalarial activity of tetrahydropyrazolo[1,2-*a*]pyrazole-1-carboxylates

3. Pyrazoline derivatives with antimalarial activity:

Pyrazoline has become an interesting subclass of *N*-containing heterocycles with pharmacological significance, including antimalarial activity (Arwansyah et al., 2021; Kryshchyshyn-Dylevych et al., 2020; Lohidashan et al., 2018; Mehta et al., 2015).

3.1.Quinoline containing pyrazolines:

A new class of quinoline containing *N*-formyl and *N*-acetyl-pyrazoline hybrids **123-125** for the possible antimalarial candidate was investigated by Insuasty et al. (2013). Upon *in vitro* antimalarial evaluation against *P. falciparum* (NF54 strain), compound **125** demonstrated remarkable potency with a growth inhibition percentage of 50.8%, a hemolytic capacity of 3.2%, and an IC_{50} value of 14.1 μg/mL (**Figure 52**).

Journal Pre-proof

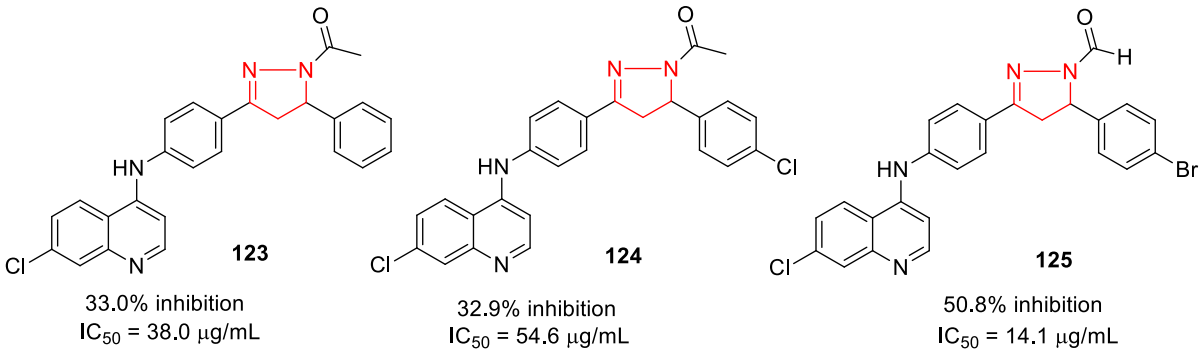


Figure 52. Antimalarial activity of quinoline-containing pyrazolines against NF54 *P. falciparum* strain

A facile synthesis of morpholinoquinoline nucleus clubbed with pyrazoline derivatives **126-129** as antimalarial agents were reported by Karad et al. (2016). All the furnished hybrids were evaluated for their *in vitro* antimalarial potency counter to the *P. falciparum* clone employing quinine and CQ as the reference compounds. Upon evaluation, the best antimalarial response was observed for hybrids **126a** (IC_{50}= 0.034 μM), **126b** (IC_{50}= 0.018 μM), **127b** (IC_{50} = 0.044 μM), **128a** (IC_{50} = 0.051 μM), **128b** (IC_{50}= 0.015 μM), **129b** (IC_{50} = 0.040 μM), and **129d** (IC_{50} = 0.028 μM), superior activity than that of standard Quinine (IC_{50} = 0.826 μM) and CQ (IC_{50} = 0.062 μM). All other hybrids were found to be less potent against the CQ-sensitive *P. falciparum* clone (**Figure 53**).

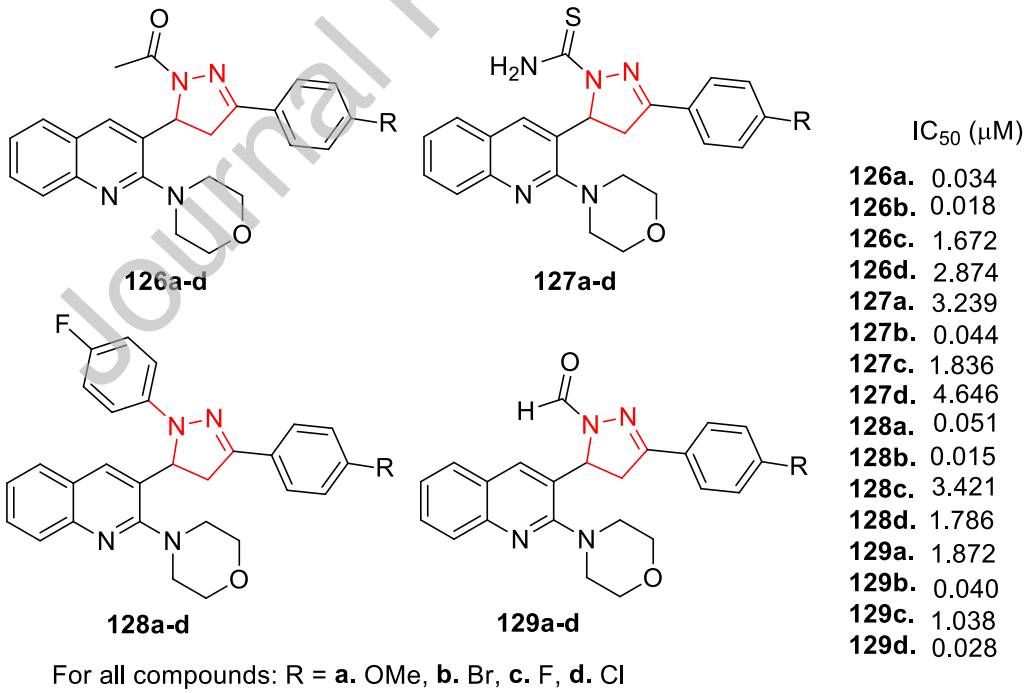


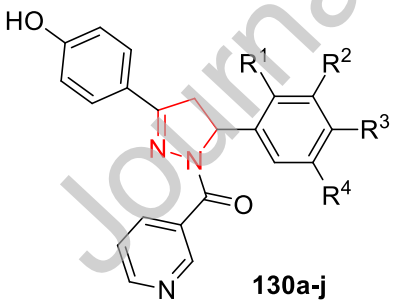
Figure 53. Antimalarial activity of quinoline-containing pyrazolines against *P. falciparum*

Journal Pre-proof

3.2.Pyridine-containing pyrazolines:

Acharya et al. (2010) developed a variety of 1,3,5-trisubstituted pyrazoline derivatives **130**. They tested them for their *in vitro* effectiveness of antimalarials counter to both CQ-resistant (RKL9) and CQ-sensitive (MRC-02) clones of *P. falciparum* employing chloroquine diphosphate as the standard drug. Compared to the standard drug (IC_{50} = 0.177 µM), hybrids **130a**, **130c**, **130d**, **130f**, and **130g** of this series have demonstrated superior activity against the RKL9 clone of the parasite. Compounds **130a-b** and **130f-h** were equivalent in vitro antimalarial potency to the standard drug (IC_{50} = 0.021 µM) against the MRC-02 *P. falciparum* clone.

Both RKL9 (IC_{50} = 0.0425 µM) and MRC-02 (IC_{50} = 0.0265 µM) strains of *P. falciparum* was most susceptible to compound **130g**. Intriguingly, compound **130b** also demonstrated antimalarial potency counter to the MRC-02 clone (IC_{50} = 0.0304 µM) in a range similar to **130g**. However, against the CQ-resistant clone, hybrid **130b** (IC_{50}= 0.1305 µM) was threefold less active than **130g** (IC_{50} = 0.0425 µM). Halogen-containing compounds **130a**, **130f,** and **130i** also demonstrated very good potency counter to both CQ-sensitive and CQ-resistant clones of *P. falciparum*. The three most potent hybrids (**130a**, **130f**, and **130g**) identified in the *in vitro* antimalarial experiments were examined in mice orally infected with *P. berghei*. Comparatively to CQ's 100% suppression at 8 mg/kg/day, compound **130a** demonstrated a 69% average suppression at 50 mg/kg/day (**Figure 54**).



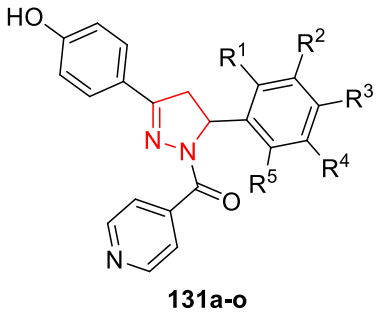
130a-j

	R^1	R^2	R^3	R^4	IC_{50} MRC-02 (µM)	IC_{50} RKL9 (µM)
a.	Cl	H	Cl	H	0.0375	0.0680
b.	H	H	H	H	0.0304	0.1305
c.	Me	H	H	H	0.0625	0.1019
d.	H	H	Me	H	0.0555	0.0887
e.	H	OEt	OMe	H	0.0755	0.2140
f.	Br	H	H	H	0.0272	0.0640
g.	H	OMe	OMe	OMe	0.0265	0.0425
h.	OMe	H	H	Br	0.0495	0.2420
i.	H	Br	H	H	0.0260	0.0786
j.	H	NO_2	H	H	0.1065	0.4235

Figure 54. Antimalarial activity of pyridine-containing pyrazolines against CQ-resistant (RKL9) and CQ-sensitive (MRC-02) clones of *P. falciparum*

Mishra et al. (2017) synthesized a broad range of 1,3,5-trisubstituted pyrazolines **131** and studied *in vitro* on CQ-resistant (RKL-9) and CQ-sensitive (MRC-2) strains of *P. falciparum* malaria parasite. Compared to the standard CQ (IC_{50} = 0.050 µM), hybrids **131d** (0.040 µM), **131e** (0.030 µM), **131m** (0.034 µM), **131n** (0.022 µM), and **131o** (0.038 µM) of

this series have displayed better activity counter to the MRC-2 clone of the parasite. Against the RKL-9 *P. falciparum* clone, compounds **131d** (0.330 µM), **131e** (0.251 µM), **131n** (0.0192 µM), and **131o** (0.337 µM) have demonstrated superior potency than CQ (IC_{50} = 0.401µM). Among all tested, compound **131n** emerged as the most active agent against both MRC-2 (IC_{50} = 0.022 µM) and RKL-9 (IC_{50} = 0.192 µM) *P. falciparum* clones (**Figure 55**).



131a-o

	R^1	R^2	R^3	R^4	R^5	IC_{50} MRC-02 (µM)	IC_{50} RKL9 (µM)
a.	C_2H_5	H	H	H	H	0.081	0.471
b.	i-C_3H_7	H	H	H	H	0.110	1.650
c.	Me	H	Me	H	OMe	0.094	0.544
d.	OMe	H	H	OMe	H	0.040	0.330
e.	H	OMe	OMe	H	H	0.030	0.251
f.	H	H	$OCH_2C_6H_5$	H	H	0.214	2.550
g.	H	Me	OMe	H	H	0.063	0.779
h.	H	H	Br	H	H	0.141	0.970
i.	H	H	F	H	H	2.500	2.902
j.	H	H	NO_2	H	H	2.902	2.441
k.	H	H	OMe	H	H	0.059	0.556
l.	H	Cl	H	H	H	0.240	2.332
m.	H	H	i-C_3H_7	H	H	0.034	0.465
n.	H	H	C_3H_7	H	H	0.022	0.192
o.	H	H	Oi-C_3H_7	H	H	0.038	0.337

Figure 55. Antimalarial activity of pyridine-containing pyrazolines against CQ-resistant (RKL9) and CQ-sensitive (MRC-02) clones of *P. falciparum*

3.3.Pyrimidine-containing pyrazolines:

Design, construction, antimalarial screening, docking study, and 3D-QSAR analysis of novel pyrimidine containing nitrile-pyrazoline derivatives **132** were carried out by Marella et al. (2014) based on the pharmacophore hybridization technique. All the furnished hybrids were found to be potent against the CQ-sensitive 3D7 *P. falciparum* clone with an IC_{50} value range between 0.9 and 32.02 µg mL^{-1}. Among the series, four hybrids **132aa-132ad** demonstrated good antimalarial activity with IC_{50} value less than 2 µg mL^{-1} (**Figure 56**).

Journal Pre-proof

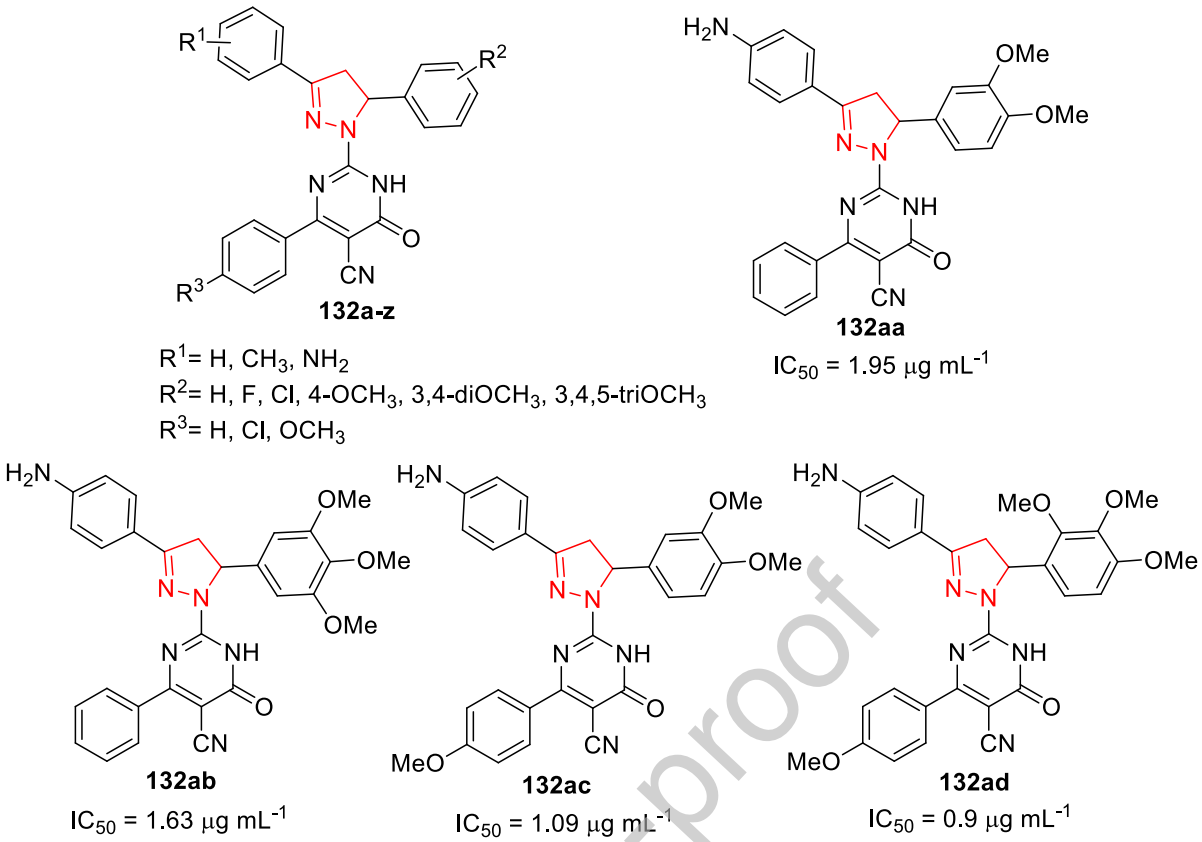
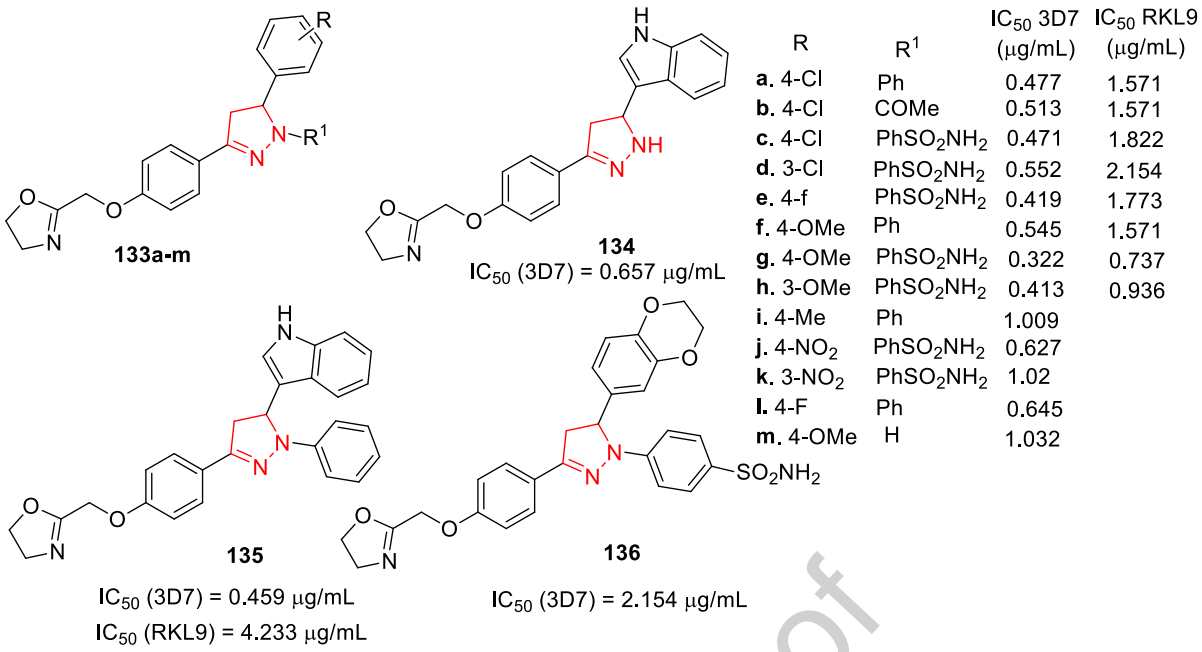


Figure 56. Antimalarial activity of pyrimidine-containing nitrile-pyrazolines against CQ-sensitive (3D7) *P. falciparum* clone

3.4.Oxazole containing pyrazolines:

Pandey et al. (2016) synthesized a class of 4,5-dihydrooxazole-pyrazoline hybrids and examined them for their *in vitro* effectiveness of antimalarials counter to both CQ-resistant (RKL9) and CQ-sensitive (3D7) *P. falciparum* clones. All the tested compounds **133-136** displayed excellent antimalarial potency against the CQ-sensitive (3D7) *P. falciparum* clone with an IC_{50} value range between 0.413 and 2.154 µg mL^{-1}. In contrast, only nine (**133a-h** and **135**) out of sixteen compounds exhibited antimalarial potency (IC_{50} value range between 0.737 and 4.233 µg mL^{-1}) against the RKL9 *P. falciparum* clone. After examination of *in vivo* antimalarial potency against the *P. berghei* mouse model, hybrid **133g** was denoted as the most active hybrid with IC_{50} of 0.322 µg mL^{-1} (**Figure 57**).

Journal Pre-proof

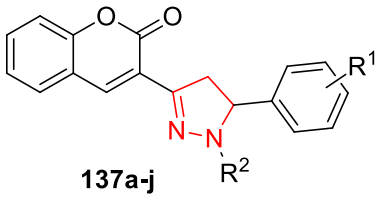


R	R^1	IC_{50} 3D7 (μg/mL)	IC_{50} RKL9 (μg/mL)
a. 4-Cl	Ph	0.477	1.571
b. 4-Cl	COMe	0.513	1.571
c. 4-Cl	$PhSO_2NH_2$	0.471	1.822
d. 3-Cl	$PhSO_2NH_2$	0.552	2.154
e. 4-f	$PhSO_2NH_2$	0.419	1.773
f. 4-OMe	Ph	0.545	1.571
g. 4-OMe	$PhSO_2NH_2$	0.322	0.737
h. 3-OMe	$PhSO_2NH_2$	0.413	0.936
i. 4-Me	Ph	1.009	
j. 4-NO_2	$PhSO_2NH_2$	0.627	
k. 3-NO_2	$PhSO_2NH_2$	1.02	
l. 4-F	Ph	0.645	
m. 4-OMe	H	1.032	

Figure 57. Antimalarial activity of oxazole-containing pyrazolines against CQ-resistant (RKL9) and CQ-sensitive (3D7) *P. falciparum* clones

3.5.Coumarin containing pyrazolines:

The construction of coumarin-pyrazoline hybrids **137** was reported by Akhtar et al. (2015). They also tested *in vitro* antimalarial potency of the ten furnished hybrids against the CQ-sensitive 3D7 *P. falciparum* clone employing CQ as the standard drug by Schizont maturation inhibition assay. According to the results of an *in vitro* testing, hybrid **137h** exhibited higher inhibitory activity with an IC_{50} 9.648 μg mL^{-1}. SAR studies showed that substituting the bulky group at the R^2 position favored the antimalarial potency, whereas substitution with acylpyridine at position R^2 was found to be most effective compared to the benzene ring (**Figure 58**).

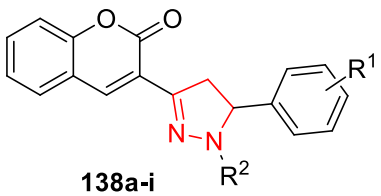


	R^1	R^2	IC_{50} (μg/mL)
a.	H	COMe	25.008
b.	4-OMe	COMe	23.109
c.	H	Ph	14.710
d.	4-OMe	Ph	13.360
e.	H	COC_6H_4N	10.610
f.	4-OMe	COC_6H_4N	10.577
g.	3,4-diOMe	COC_6H_4N	9.735
h.	3,4,5-triOMe	COC_6H_4N	9.684
i.	4-Me	COC_6H_4N	10.936
j.	4-Cl	COC_6H_4N	11.523

Figure 58. Antimalarial activity of coumarin-containing pyrazolines against CQ-sensitive (3D7) *P. falciparum* clone

Journal Pre-proof

Continuing their interest in the construction and *in vitro* antimalarial examination of coumarin-containing pyrazolines, Akhtar et al. (2017) synthesized another nine hybrids and examined *in vitro* antimalarial efficacy against the CQ-sensitive 3D7 *P. falciparum* clone employing CQ as the standard drug by Schizont maturation inhibition assay. Hybrid **138g** was denoted as the most active one with an IC_{50} 11.63 μg mL^{-1}. According to SAR analyses, the bulky group replacement at the pyrazoline moiety's ring nitrogen favored the antimalarial activity. Similarly, antimalarial activity declines as the number of methoxy groups bonded to the phenyl ring increases (**Figure 59**).



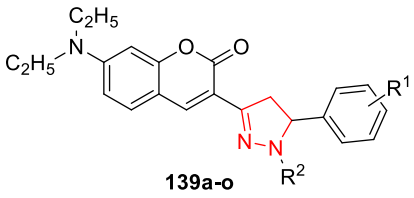
138a-i

	R^1	R^2	IC_{50} (μg/mL)
a.	3,4-diOMe	COMe	23.080
b.	3,4,5-triOMe	COMe	22.314
c.	4-Me	COMe	24.589
d.	4-Cl	COMe	31.344
e.	4-OMe	Ph	15.230
f.	3,4-diOMe	Ph	12.417
g.	3,4,5-triOMe	Ph	11.633
h.	4-Me	Ph	14.388
i.	4-Cl	Ph	16.003

Figure 59. Antimalarial activity of coumarin-containing pyrazolines against CQ-sensitive (3D7) *P. falciparum* clone

The following year, Himangini et al. (2018) developed a range of novel coumarin-containing pyrazolines **139** and tested them for their *in vitro* antimalarial potency counter to CQ-resistant RKL9 and CQ-sensitive MRC-02 clones of *P. falciparum*. According to the *in vitro* examination results, some furnished compounds exhibited significant potency counter to the MRC-02 clone, while three hybrids (**139h**, **139n**, and **139o**) demonstrated superior potency counter to the RKL-9 clone of *P. falciparum* with IC_{50} values less than 10 μM. The most potent analogs in the series were found to be compounds **139n** (IC_{50} RKL9 = 1.9 μM; IC_{50} MRC-02 = 4.2 μM) and **139o** (IC_{50} RKL9 = 2.1 μM; IC_{50} MRC-02 = 3.3 μM), despite that their activity was more than the reference drug CQ (IC_{50} = 0.02 μM). Compounds **139h**, **139n**, and **139o** were next evaluated for *in vivo* antimalarial potency counter to *P. berghei* at 25 mg/kg/day dose. According to the results, compound **139n** offered 100% protection at the tested dose level, and all the rodents survived for four weeks (**Figure 60**).

Journal Pre-proof

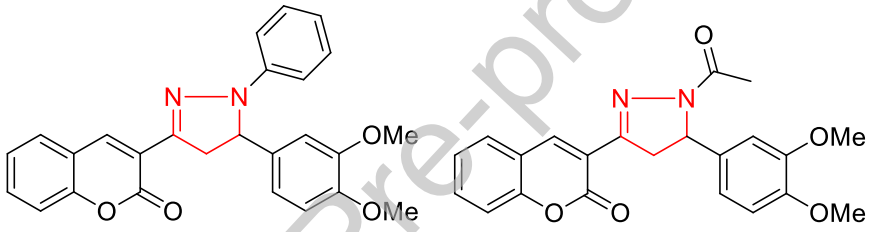


139a-o

	R^1	R^2	IC_{50} RKL9 (μM)	IC_{50} MRC-02 (μM)
a.	H	H	>100	>100
b.	4-OH	H	29.9	26.7
c.	4-Cl	H	27.1	18.6
d.	4-F	H	44.5	34.2
e.	4-NO_2	H	30.4	19.7
f.	H	Ph	>100	>100
g.	4-OH	Ph	25.3	17.5
h.	4-Cl	Ph	9.1	10.4
i.	4-F	Ph	33.8	26.9
j.	4-NO_2	Ph	41.6	20.9
k.	H	COPh	>100	>100
l.	4-OH	COPh	26.7	14.3
m.	4-Cl	COPh	>100	>100
n.	4-F	COPh	1.9	4.2
o.	4-NO_2	COPh	2.1	3.3

Figure 60. Antimalarial activity of coumarin-containing pyrazolines against CQ-resistant (RKL9) and CQ-sensitive (MRC-02) clones of *P. falciparum*

Wanare et al. (2010) furnished and screened the antimalarial potency of chromene-containing pyrazoline derivatives counter to CQ-resistant (RKL9) and CQ-sensitive (3D7) *P. falciparum* clones using artemisinin as standard drug. Hybrids **140** and **141** were equipotent against the CQ-sensitive (3D7) clone of *P. falciparum*, and hybrid **140** was more active than hybrid **141** against the CQ-sensitive (3D7) clone of *P. falciparum* (**Figure 61**).



140
IC_{50} 3D7 = 10 μg/mL
IC_{50} RKL9 = 7.6 μg/mL

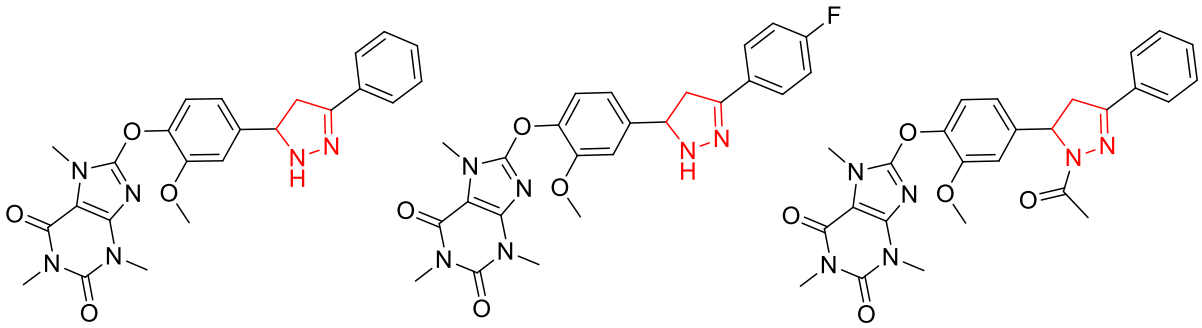
141
IC_{50} 3D7 = 10 μg/mL
IC_{50} RKL9 = 9 μg/mL

Figure 61. Antimalarial activity of chromene-containing pyrazolines against CQ-resistant (RKL9) and CQ-sensitive (3D7) clones of *P. falciparum*

3.6.Caffeine-containing pyrazolines:

Various caffeine based pyrazoline hybrids were furnished and examined for their *in vitro* effectiveness of antimalarials against the Plasmodium parasite employing CQ as the reference compound (Insuasty et al., 2015). All the tested compounds **142-144** exhibited moderate *in vitro* antimalarial potency against the Plasmodium parasite, with the IC_{50} value range between 13.7 and 20.8 μg mL^{-1}. Among all, hybrid **142** emerged as the more active one, followed by **144**, which was lower than standard CQ (18.9 μg mL^{-1}) (**Figure 62**).

Journal Pre-proof



142
IC_{50} = 13.7 μg/mL

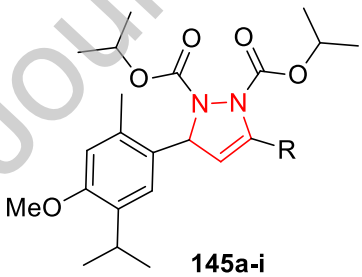
143
IC_{50} = 20.8 μg/mL

144
IC_{50} = 18.4 μg/mL

Figure 62. Antimalarial activity of caffeine-based pyrazoline against *P. falciparum*

3.7.Thymol-containing pyrazolines:

Raghuvanshi et al. (2019) identified a range of thymol-based pyrazolines **145** as antimalarial targets and examined them for their *in vitro* antimalarial efficacy against the malaria parasite *P. falciparum*. All the tested hybrids (**145a-i**) were found to be potent counter to the CQ-sensitive NF54 *P. falciparum* clone. Among them, hybrids **145c** and **145f** displayed significant antimalarial potency with IC_{50} <2 μM, while other pyrazoline derivatives also considerably inhibited the *P. falciparum* with IC_{50} <10 μM. The most active hybrid **145f** was further evaluated for *in vivo* antimalarial potency in mice infected with *P. berghei* and significantly inhibited the growth of *P. berghei* to the level of 8.03% and 4.62% on day six at a dose of 50 and 100 mg/kg body weight, respectively. It showed lower chemo-suppression in mice at 50 (25.29%) and 100 (55.60%) mg/kg body weight than that of standard chloroquine (100%) (**Figure 63**).



145a-i

R	IC_{50} (μM)
a. 4-MePh	2.32±0.22
b. naphthalene-2-yl	2.86±0.27
c. 3,4-diOMePh	1.75±0.18
d. benzo[*d*][1,3]dioxol-5-yl	9.84±0.42
e. 4-BrPh	3.61±0.26
f. 3,4,5-triOMePh	1.05±0.11
g. 4-OMePh	3.61±0.31
h. thiophen-2-yl	5.75±1.17
i. 3,5-diOMePh	3.11±0.16

Figure 63. Antimalarial activity of thymol-containing pyrazolines against CQ-resistant (RKL9) and clone of *P. falciparum*

3.8.Thiophene containing pyrazolines:

Very recently, a variety of thiophene containing pyrazoline derivatives **146-148** were identified as antimalarial drugs and examined for their *in vitro* antimalarial potency against CQ-resistant (RKL9) and CQ-sensitive (3D7) clones of *P. falciparum* employing CQ (IC_{50} =

Journal Pre-proof

20.63 µg/mL) and artemisinin (IC_{50} = 4.51 µg/mL) as reference compounds (Alidmat et al., 2021). Compared to standard drugs, almost all the tested compounds displayed better activity against both CQ-sensitive 3D7 (IC_{50} value range between 1.3 and 6.2 µg/mL) and CQ-resistant RKL9 (IC_{50} value range between 1.1 and 4.3 µg/mL) strains of *P. falciparum*. Among all, compound **148b** was more active against the CQ-sensitive 3D7 strain with an IC_{50} of 1.3 µg/mL, whereas compound **148a** emerged as the most potent agent against the CQ-resistant RKL9 strain with an IC_{50} of 1.1 µg/mL (**Figure 64**).

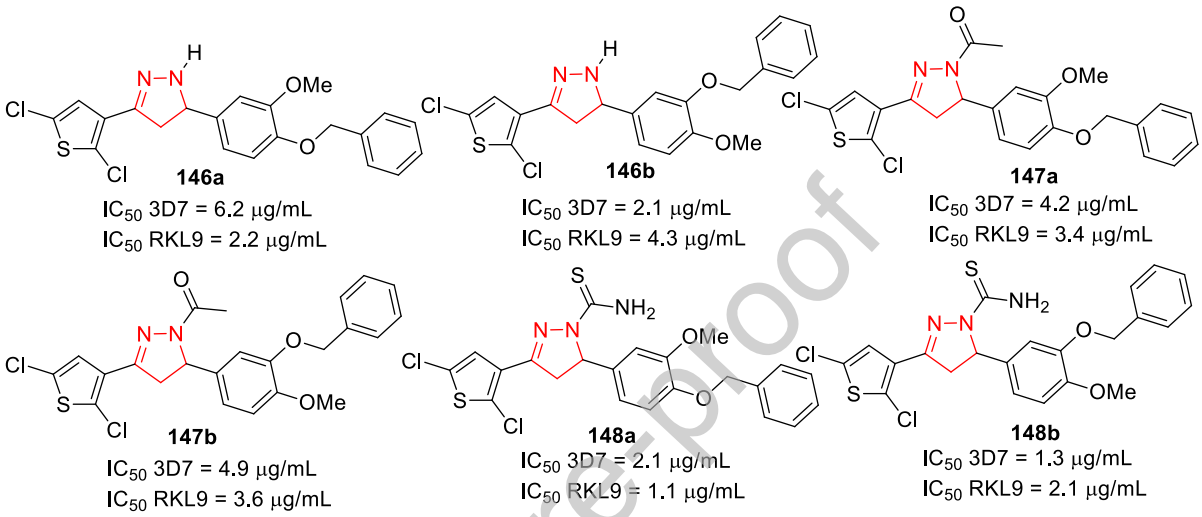


Figure 64. Antimalarial activity of thiophene-containing pyrazolines against CQ-resistant (RKL9) and CQ-sensitive (3D7) clones of *P. falciparum*

3.9.Furan containing pyrazolines:

Alidmat et al. (2021) also identified a variety of furan-containing pyrazolines **149-151** as antimalarial agents and screened for their *in vitro* antimalarial potency against CQ-sensitive 3D7 and CQ-resistant RKL9 *P. falciparum* clones using CQ (IC_{50} = 20.63 µg/mL) and artemisinin (IC_{50} = 4.51 µg/mL) as standard drugs. All the tested compounds were potent against CQ-sensitive 3D7 (IC_{50} values ranging from 2.2 to 18.2µg/mL) and CQ-resistant RKL9 (IC_{50} values ranging from 1.1 to 7.3 µg/mL) *P. falciparum* clones. Among them, compound **151b** exhibited a higher potency counter to CQ-sensitive 3D7 (IC_{50} = 2.2 µg/mL) and CQ-resistant RKL9 (IC_{50} = 1.1 µg/mL) clones of *P. falciparum*. Compared to the thiophene-containing pyrazoline derivatives, furan-containing pyrazolines displayed lower antimalarial potency against both 3D7 and RKL9 *P. falciparum* clones (**Figure 65**).

Journal Pre-proof

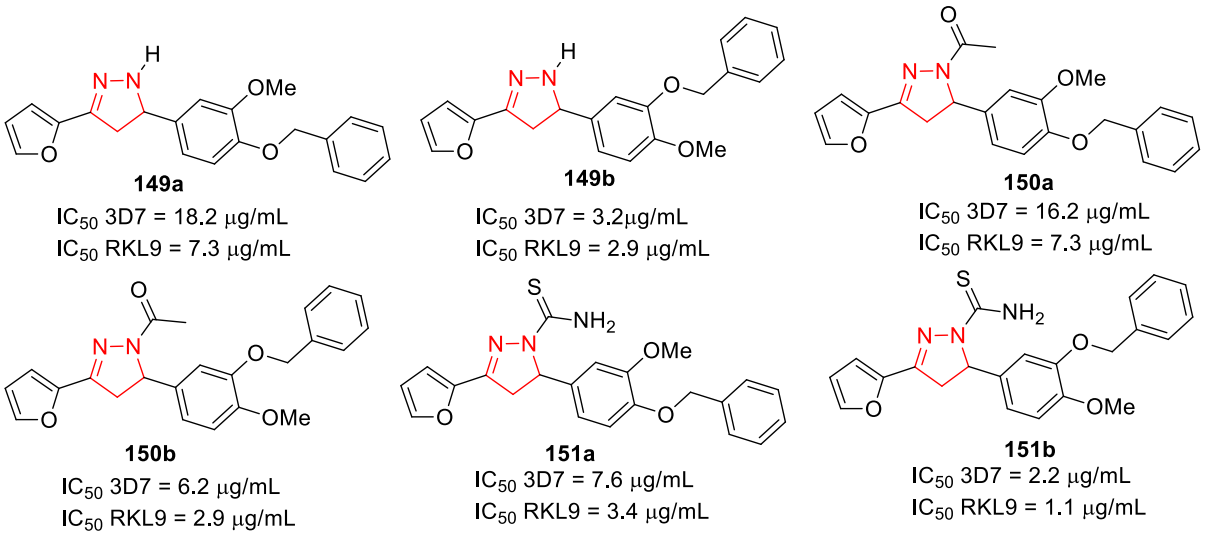


Figure 65. Antimalarial activity of furan containing pyrazolines against CQ-resistant (RKL9) and CQ-sensitive (3D7) clones of *P. falciparum*

3.10. Aryl containing pyrazolines:

Aher et al. (2011) synthesized several dibenzylideneacetones and some of their pyrazoline derivatives and tested them *in vitro* using the SYBR green-I fluorescence assay on *P. falciparum* culture for blood-stage antiplasmodial activities. Among the tested pyrazoline derivatives, compound **152b** exhibited better activity against CQ-sensitive (3D7) field isolate (IC_{50} = 9.10 µM) and CQ-resistant (RKL9) strain (IC_{50} = 11.09 µM) (**Figure 66**).

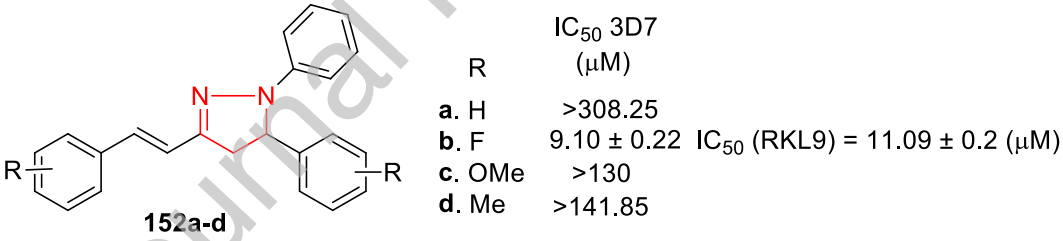


Figure 66. Antimalarial activity of pyrazoline derivatives against CQ-resistant (RKL9) and CQ-sensitive (3D7) clones of *P. falciparum*

4. Conclusion

In conclusion, we have presented an overview of recent development and applications of diverse pyrazole and pyrazoline derivatives as potential antimalarial agents to emphasize the route for the progress of novel antimalarial drugs. A broad range of pyrazole and pyrazoline derivatives engaged in developing diverse antimalarial agents were thoroughly discussed. Highlights on diverse pyrazoles and pyrazolines with their potency as antimalarials are discussed. The introduction of various pyrazole and pyrazoline moieties in the scaffolds has enabled pharmaceutical chemists to attain high levels of antimalarial potency.

Acknowledgments

We thank the Ministry of Higher Education (FRGS/1/2019/STG01/UKM/02/3) for its financial support and Universiti Kebangsaan Malaysia for awarding the UKM-Vice Chancellor Ph.D. scholarship for Ravindar Lekkala.

References

Acharya, B.N., Saraswat, D., Tiwari, M., Shrivastava, A.K., Ghorpade, R., Bapna, S., Kaushik, M.P., 2010. Synthesis and antimalarial evaluation of 1, 3, 5-trisubstituted pyrazolines. Eur. J. Med. Chem. 45, 430-438.

Aggarwal, S., Paliwal, D., Kaushik, D., Gupta, G.K., Kumar, A., 2018. Pyrazole Schiff base hybrids as antimalarial agents: Synthesis, in vitro screening and computational study. Comb. Chem. High Throughput Screen. 21, 194-203.

Aher, R.B., Wanare, G., Kawathekar, N., Kumar, R.R., Kaushik, N.K., Sahal, D., Chauhan, V.S., 2011. Dibenzylideneacetone analogues as novel *Plasmodium falciparum* inhibitors. Bioorg. Med. Chem. Lett. 21, 3034-3036.

Ahluwalia, V.K., Dahiya, A., Garg, V., 1997. Reaction of 5-amino-4-formyl-3-methyl(or phenyl)-1-phenyl-1H-pyrazoles with active methylene compounds: Synthesis of fused heterocyclic rings. Indian J. Chem., Sect. B 36, 88-90.

Akhtar, W., Khan, M.F., Verma, G., Shaquiquzzaman, M., Akhter, M., Marella, A., Parmar, S., Khatoon, R., Alam, M.M., 2017. Coumarin-pyrazoline derivatives: Their one-pot microwave assisted synthesis and antimalarial activity. J. Pharm. Med. Chem. 3, 6-9.

Akhter, W., Marella, A., Shaquiquzzaman, M., Akhter, M., Alam, M.M., 2015. Microwave assisted synthesis of pyrazoline-coumarin hybrids and their in-vitro antimalarial evaluation. J. Pharm. Res. 9, 318-322.

Akolkar, H.N., Dengale, S.G., Deshmukh, K.K., Karale, B.K., Darekar, N.R., Khedkar, V.M., Shaikh, M.H., 2020. Design, synthesis and biological evaluation of novel furan & thiophene containing pyrazolyl pyrazolines as antimalarial agents. Polycycl. Aromat. Compd. 11, 1-13.

Alam, R., Wahi, D., Singh, R., Sinha, D., Tandon, V., Grover, A., 2016. Rahisuddin. Design, synthesis, cytotoxicity, Hu Topollα inhibitory activity and molecular docking studies of pyrazole derivatives as anticancer agents. Bioorg. Chem. 69, 77.

Alidmat, M.M., Khairuddean, M., Norman, N.M., Asri, A.N.M., Suhaimi, M.H.M., Sharma, G., 2021. Synthesis, characterization, docking study and biological evaluation of new

Journal Pre-proof

chalcone, pyrazoline, and pyrimidine derivatives as potent antimalarial compounds. Arab. J. Chem. 14, 103304.

Alonso, P.L., Tanner, M., 2013. Public health challenges and prospects for malaria control and elimination. Nat. Med. 19, 150-155.

Alven, S., Aderibigbe, B., 2019. Combination Therapy Strategies for the Treatment of Malaria. Molecules. 24, 3601.

Ardiansah, B., 2017. Pharmaceutical importance of pyrazoline derivatives: a mini review. J. Pharm. Sci. & Res. 9, 1958-1960.

Ardiansah, B., 2017. Recent reports on pyrazole-based bioactive compounds as candidate for anticancer agents. Asian J. Pharm. Clin. Res. 12, 45.

Arwansyah, A., Arif, A.R., Syahputra, G., Sukarti, S., Kurniawan, I., 2021. Theoretical studies of Thiazolyl-Pyrazoline derivatives as promising drugs against malaria by QSAR modeling combined with molecular docking and molecular dynamics simulation. Mol. Simul. 47, 988-1001.

Azeredo, L.F.S.P., Coutinho, J.P., Jabor, V.A.P., Feliciano, P.R., Nonato, M.C., Kaiser, C.R., Menezes, C.M.S., Hammes, A.S.O., Caffarena, E.R., Hoelz, L.V.B., de Souza, N.B., Pereira, G.A.N., Ceravolo, I.P., Krettli, A.U., Boechat, N., 2017. Evaluation of 7-arylaminopyrazolo[1,5-a]pyrimidines as anti-*Plasmodium falciparum*, antimalarial, and Pf-dihydroorotate dehydrogenase inhibitors. Eur. J. Med. Chem. 126, 72-83.

Bailey, D.M., Hansen, P.E., Hlavac, A.G., Baizman, E.R., Pearl, J., Defelice, A.F., Feigenson, M.E., 1985. 3,4-Diphenyl-1H-pyrazole-1-propanamine antidepressants. J. Med. Chem. 28, 256.

Balaji, S.N., Ahsan, M.J., Jadav, S.S., Trivedi, V., 2015. Molecular modeling, synthesis, and antimalarial potentials of curcumin analogues containing heterocyclic ring. Arab. J. Chem. 12, 2492-2500.

Bekhit, A.A., Haimanot, T., Hymete, A., 2014. Evaluation of some 1H-pyrazole derivatives as a dual acting antimalarial and anti-leishmanial agents. Pak. J. Pharm. Sci. 27, 1767-1773.

Bekhit, A.A., Hassan, A.M.M., Abd El Razik, H.A., El-Miligy, M.M.M., El-Agroudy, E.J., Bekhit, A.E.A., 2015. New heterocyclic hybrids of pyrazole and its bioisosteres: Design, synthesis and biological evaluation as dual acting antimalarial-antileishmanial agents. Eur. J. Med. Chem. 94, 30-44.

Journal Pre-proof

Bekhit, A.A., Hymete, A., Asfaw, H., Bekhit, A.E.A., 2012. Synthesis and biological evaluation of some pyrazole derivatives as antimalarial agents. Arch. Pharm. Chem. Life Sci. 345, 147-154.

Bekhit, A.A., Nasralla, S.N., Bekhit, S.A., Bekhit, A.E.A., 2022. Novel dual acting antimalarial antileishmanial agents derived from pyrazole moiety. Biointerface Res. Appl. Chem.12, 6225-6233.

Bekhit, A.A., Saudi, M.N., Hassan, A.M.M., Fahmy, S.M., Ibrahim, T.M., Ghareeb, D., El-Seidy, A.M., Nasralla, S.N., Bekhit, A.E.A., 2018. Synthesis, in silico experiments and biological evaluation of 1,3,4-trisubstituted pyrazole derivatives as antimalarial agents. Eur. J. Med. Chem. 163, 353-366.

Bhandari, S., Tripathi, A.C., Saraf, S.K., 2013. Novel 2-pyrazoline derivatives as potential anticonvulsant agents. Med. Chem. Res. 22, 5290-5296.

Bhat, A.R., Athar, F., Azam, A., 2009. Bis-pyrazolines: Synthesis, characterization and anti amoebic activity as inhibitors of growth of Entamoeba histolytica. Eur. J. Med. Chem. 44, 426-431.

Bhutani, R., Pathak, D.P., Husain, A., Kapoor, G., Kant, R., 2015. A review on recent development of pyrazoline as a pharmacologically active molecule, Int. J. Pharm. Sci. Res, 6, 4113-4128.

Birkholtz, L.M., Bornman, R., Focke, W., Mutero, C., de Jager, C., 2012. Sustainable malaria control: Transdisciplinary approaches for translational applications. Malar. J. 11, 431.

Biswas, S.K., Das, D., 2022. One-pot synthesis of pyrano[2,3-c] pyrazole derivatives via multicomponent reactions (MCRs) and their applications in medicinal chemistry. Mini Rev. Org. Chem. 19, 552-568.

Cabrera, D.G., Douelle, F., Feng, T.-S., Nchinda, A.T., Younis, Y., White, K.L., Wu, Q., Ryan, E., Burrows, J.N., Waterson, D., Witty, M.J., Wittlin, S., Charman, S.A., Chibale, K., 2011. Novel orally active antimalarial thiazoles. J. Med. Chem. 54, 7713-7719.

Çelik, G., Arslan, T., Şentürk, M., Ekinci, D., 2020. Synthesis and characterization of some new pyrazolines and their inhibitory potencies against carbonic anhydrases. Archiv Der Pharmazie. 353, 1900292.

Cheuka, P.M., Cabrera, D.G., Paquet, T., Chibale, K., 2014. Structure-activity relationship studies of antiplasmodial aminomethylthiazoles. Bioorg. Med. Chem. Lett. 24, 5207-5211.

Choudhary, D., Rani, I., Monga, J., Goyal, R., Husain, A., Garg, P., Khokra, S.L., 2022. Pyrazole based furanone hybrids as novel antimalarial: A combined

experimental, pharmacological and computational study. Cent. Nerv. Syst. Agents Med. Chem. 22, 39-56.

Cunico, W., Cechinel, C.A., Bonacorso, H.G., Martins, M.A.P., Zanatta, N., de Souza, M.V.N., Freitas, I.O., Soares, R.P.P., Krettli, A.U., 2006. Antimalarial activity of 4-(5-trifluoromethyl-1H-pyrazol-1-yl)-chloroquine analogues. Bioorg. Med. Chem. Lett. 16, 649-653.

Dominguez, J.N., Charrisa, J.E., Caparellib, M., Riggione, F., 2002. Synthesis and antimalarial activity of substituted pyrazole derivatives. Arzneimittelforschung. 52, 482-488.

Ebenezer, O., Shapi, M., Tuszynski, J.A., 2022. A review of the recent development in the synthesis and biological evaluations of pyrazole derivatives. Biomedicines. 10, 1124.

Faheem, Dey, S., Johri, S., Abirami, M., Kumar, B.K., Taramelli, D., Basilico, N., Balana-Fouce, R., Sekhar, K.V.G.C., Murugesan, S., 2022. Search for structurally diverse heterocyclic analogs as dual-acting antimalarial and antileishmanial agents: An overview. Eur. J. Med. Chem. 4, 100031.

Faisal, M., Saeed, A., Hussain, S., Dar, P., Ali larik, F., 2019. Recent developments in synthetic chemistry and biological activities of pyrazole derivatives. J. Chem. Sci. 131, 70.

Foloppe, N., Fisher, L.M., Howes, R., Potter, A., Robertson, A.G.S., Surgenor, A.E., 2006. Identification of chemically diverse Chk1 inhibitors by receptor-based virtual screening. Bioorg. Med. Chem. 14, 4792-4802.

García-Cañaveras, J.C., Lancho, O., Ducker, G.S., Ghergurovich, J.M., Xu, X., da Silva-Diz, V., Minuzzo, S., Indraccolo, S., Kim, H., Herranz, D., Rabinowitz, J.D., 2021. SHMT inhibition is effective and synergizes with methotrexate in T-cell acute lymphoblastic leukemia. Leukemia. 35, 377-388.

Gogoi, P., Shakya, A., Ghosh, S.K., Gogoi, N., Gahtori, P., Singh, N., Bhattacharyya, D.R., Singh, U.P., Bhat, H.R., 2020. In silico study, synthesis, and evaluation of the antimalarial activity of hybrid dimethoxy pyrazole 1,3,5-triazine derivatives. J Biochem Mol Toxicol. 35, 22682.

Gokhan-Kelekci, N., Yabanoglu, S., Kupeli, E., Salgin, U., Ozgen, O., Ucar, G., Yesilada, E., Kendi, E., Yesilada, A., Bilgin, A.A., 2007. A new therapeutic approach in Alzheimer disease: some novel pyrazole derivatives as dual MAO-B inhibitors and anti-inflammatory analgesics. Bioorg. Med. Chem. 15, 5775-5786.

Journal Pre-proof

Guo, R.Y., An, Z.M., Mo, L.P., Yang, S.T., Liu, H.X., Wang, S.X., Zhang, Z.H., 2013. Meglumine promoted one-pot, four-component synthesis of pyranopyrazole derivatives. Tetrahedron 69, 9931-9938.

Hasan, A., Mazumder, H.H., Chowdhury, A.S., Datta, A., Khan, A., 2015. Moleculardocking study of malaria drug target enzyme transketolase in *Plasmodium falciparum* 3D7 portends the novel approach to its treatment. Biol. Med. 10, 1-14.

Hassan, S.Y., 2013. Synthesis, Antibacterial and Antifungal Activity of Some New Pyrazoline and Pyrazole Derivatives. Molecules. 18, 2683-2711.

Havrylyuk, D., Zimenkovsky, B., Karpenko, O., Grellier, P., Lesyk, R., 2014. Synthesis of pyrazoline-thiazolidinone hybrids with trypanocidal activity. Eur. J. Med. Chem. 85, 245-254.

Heller, S.T., Natarajan, S.R., 2006. 1,3-Diketones from Acid Chlorides and Ketones: A Rapid and General One Pot Synthesis of Pyrazoles. Org. Lett. 8, 2675.

Himangini, Pathak, D., Sharma, V., Kumar, S., 2018. Designing novel inhibitors against falcipain-2 of *Plasmodium falciparum*. Bioorg. Med. Chem. Lett. 28, 1566-1569.

Insuasty, B., Montoya, A., Becerra, D., Quiroga, J., Abonia, R., Robledo, S., Vélez, I.D., Upegui, Y., Nogueras, M., Cobo, J., 2013. Synthesis of novel analogs of 2-pyrazoline obtained from [(7-chloroquinolin-4-yl) amino]chalcones and hydrazine as potential antitumor and antimalarial agents. Eur. J. Med. Chem. 67, 252-262.

Insuasty, B., Ramírez, J., Becerra, D., Echeverry, C., Quiroga, J., Abonia, R., Robledo, S.M., Vélez, I.D., Upegui, Y., Muñoz, J.A., Opsina, V., Nogueras, M., Cobo, J., 2015. An efficient synthesis of new caffeine-based chalcones, pyrazolines and pyrazolo[3,4-b][1,4]diazepines as potential antimalarial, antitrypanosomal and antileishmanial agents. Eur. J. Med. Chem. 93, 401-413.

Jamwal, A., Javed, A., Bhardwaj, V., 2013. A review on pyrazole derivatives of pharmacological potential. J. Pharm. BioSci. 3, 114.

Jat, J.L., Ojha, S., Bhambi, D., Dhakar, N., Talesara, G.L., 2008. Synthesis and characterization of biologically significant 5,5′-(1,4-phenylene)bis(1-Nalkoxyphthalimido-3-aryl-2-pyrazoline) derivatives. J. Enzyme Inhib. Med. Chem. 23, 882-887.

Joshi, S.D., Dixit, S.R., Kirankumar, M.N., Aminabhavi, T.M., Raju, K.V.S.N., Narayan, R., Lherbet, C., Yang, K.S., 2016. Synthesis, antimycobacterial screening and ligand-based molecular docking studies on novel pyrrole derivatives bearing pyrazoline, isoxazole and phenyl thiourea moieties. Eur. J. Med. Chem. 107, 133-152.

Ju, Y., Varma, R.S., 2006. Aqueous N-Heterocyclization of Primary Amines and Hydrazines with Dihalides: Microwave-Assisted Syntheses of N-Azacycloalkanes, Isoindole, Pyrazole, Pyrazolidine, and Phthalazine Derivatives. J. Org. Chem. 71, 135.

Kalaria, P.N., Karad, S.C., Raval, D.K., 2018. A review on diverse heterocyclic compounds as the privileged scaffolds in antimalarial drug discovery. Eur. J. Med. Chem. 2018 doi:10.1016/j.ejmech.2018.08.040.

Kalaria, P.N., Satasia, S.P., Raval, D.K., 2014. Synthesis, characterization and biological screening of novel 5-imidazopyrazole incorporated fused pyran motifs under microwave irradiation. New J. Chem. 38, 1512-1521.

Kalaria, P.N., Satasia, S.P., Raval, D.K., 2014. Synthesis, characterization and pharmacological screening of some novel 5-imidazopyrazole incorporated polyhydroquinoline derivatives. Eur. J. Med. Chem. 78, 207-216.

Kalaria, P.N., Satasia, S.P., Raval, D.K., 2014. Synthesis, identification and in vitro biological evaluation of some novel 5-imidazopyrazole incorporated pyrazoline and isoxazoline derivatives. New J. Chem. 38, 2902-2910.

Kaplancıklı, Z.A., Özdemir, A., Turan-Zitouni, G., Altıntop, M.D., Can, Ö.D., 2010. New pyrazoline derivatives and their antidepressant activity. Eur. J. Med. Chem. 45, 4383-4387.

Karad, S.C., Purohit, V.B., Avalani, J.R., Sapariya, N.H., Raval, D.K., 2016. Design, Synthesis and characterization of fluoro substituted novel pyrazole nucleus clubbed with 1,3,4-oxadiazole scaffolds and their biological applications. RSC Advances. 6, 41532-41541.

Karad, S.C., Purohit, V.B., Raval, D.K., 2014. Design, synthesis and characterization of fluoro substituted novel pyrazolylpyrazolines scaffold and their pharmacological screening. Eur. J. Med. Chem. 84, 51-58.

Karad, S.C., Purohit, V.B., Raval, D.K., Kalaria, P.N., Avalani, J. R., Thakor, P., Thakkar, V.R., 2015. Green synthesis and pharmacological screening of polyhydroquinoline derivatives bearing fluorinated 5-aryloxypyrazole nucleus. RSC Advances. 5, 16000-16009.

Karad, S.C., Purohit, V.B., Thakor, P., Thakkar, V.R., Raval, D.K., 2016. Novel morpholinoquinoline nucleus clubbed with pyrazoline scaffolds: Synthesis, antibacterial, antitubercular and antimalarial activities. Eur. J. Med. Chem. 112, 270-279.

Journal Pre-proof

Karrouchi, K., Radi, S., Ramli, Y., Taoufik, J., Mabkhot, Y.N., Al-aizari, F.A., Ansar, M., 2018. Synthesis and Pharmacological Activities of Pyrazole Derivatives: A Review. Molecules. 23, 134.

Kees, K.L., Fitzgerald, J.J., Steiner, K.E., Mattes, Mihan, B., Tosi, T., Mondoro, D., McCaleb, M.L., 1996. New potent antihyperglycemic agents in db/db mice: synthesis and structure-activity relationship studies of (4-substituted benzyl) (trifluoromethyl)pyrazoles and –pyrazolones. J. Med. Chem. 39, 3920.

Khan, M.F., Alam, M.M., Verma, G., Akhtar, W., Akhter, M., Shaquiquzzaman, M., 2016. The therapeutic voyage of pyrazole and its analogs: A review. Eur. J. Med. Chem. 120, 170-201.

Kharbanda, C., Alam, M.S., Hamid, H., Javed, K., Bano, S., Dhulap, A., Ali, Y., Nazreen, S., Haider, S., 2014. Synthesis and evaluation of pyrazolines bearing benzothiazole as antiinflammatory agents. Bioorg. Med. Chem. 22, 5804-5812.

Khunt, R.C., Khedkar, V.M., Chawda, R.S., Chauhan, N.A., Parikh, A.R., Coutinho, E.C., 2012. Synthesis, antitubercular evaluation and 3D-QSAR study of Nphenyl-3-(4-fluorophenyl)-4-substituted pyrazole derivatives. Bioorg. Med. Chem. Lett. 22, 666-678.

Kiyani, H., Samimi, H.A., Ghorbani, F., Esmaieli, S., 2013. One-pot, four-component synthesis of pyrano[2,3-c]pyrazoles catalyzed by sodium benzoate in aqueous medium. Curr. Chem. Lett. 2, 197-206.

Kryshchyshyn-Dylevych, A.P., Zelisko, N.I., Grellier, P., Lesyk, R.B., 2020. Preliminary evaluation of thiazolidinone- and pyrazoline-related heterocyclic derivatives as potential antimalarial agents. Biopolym. Cell. 36 48-60.

Küçükgüzel, Ş.G., Şenkardeş, S., 215. Recent advances in bioactive pyrazoles. Eur. J. Med. Chem. 97, 786-815.

Kumar, G., Tanwer, O., Kumar, J., Akhter, M., Sharma, S., Pillai, C.R., Alam, M.M., Zama, M.S., 2018. Pyrazole-pyrazoline as promising novel antimalarial agents: A mechanistic study. Eur. J. Med. Chem. 149, 139-147.

Kumar, P., Kadyan, K., Duhan, M., Sindhu, J., Singh, V., Saharan, B.S., 2017. Design, synthesis, conformational and molecular docking study of some novel acyl hydrazone based molecular hybrids as antimalarial and antimicrobial agents. Chem. Cent. J. 11, 115.

Kumar, R.S., Arif, I.A., Ahamed, A., Idhayadhulla, A., 2016. Antiinflammatory and antimicrobial activities of novel pyrazole analogues. Saudi J. Biol. Sci. 23, 614.

Kumar, S., Kumar, G., Kapoor, M., Surolia, A., Surolia, N., 2006. Synthesis and evaluation of substituted pyrazoles: potential antimalarials targeting the enoyl-ACP reductase of *Plasmodium falciparum*. Synth. Commun. 36 215-226.

Kuo, S.C., Huang, L.J., Nakamura, H., 1984. Studies on heterocyclic compounds. 6. Synthesis and analgesic and antiinflammatory activities of 3,4-dimethylpyrano[2,3-c]pyrazol-6-one derivatives. J. Med. Chem. 27, 539-544.

Lange, J.H.M., Attali, A., Van Der Neut, M.A.W., Wals, H.C., Mulder, A., Zilaout, H., Duursma, A., Van Aken, H.H.M., Van Vliet, B.J., 2010. Two distinct classes of novel pyrazolinecarboxamides as potent cannabinoid CB1 receptor agonists. Bioorg. Med. Chem. Lett. 20, 4992-4998.

Large, J.M., Osborne, S.A., Smiljanic-Hurley, E., Ansell, K.H., Jones, H.M., Taylor, D.L., Clough, B., Green, J.L., Holder, A.A., 2013. Imidazopyridazines as potent inhibitors of *Plasmodium falciparum* calcium-dependent protein kinase 1 (PfCDPK1): Preparation and evaluation of pyrazole linked analogues. Bioorg. Med. Chem. Lett. 23, 6019-6024.

Lohidashan, K., Rajan, M., Ganesh, A., Paul, M., Jerin, J., 2018. Pass and Swiss ADME collaborated in silico docking approach to the synthesis of certain pyrazoline spacer compounds for dihydrofolate reductase inhibition and antimalarial activity. Bangladesh J. Pharmacol. 13, 23-29.

Lv, P.C., Li, D.D., Li, Q.S., Lu, X., Xiao, Z.P., Zhu, H.L., 2011. Synthesis, molecular docking and evaluation of thiazolyl-pyrazoline derivatives as EGFR TK inhibitors and potential anticancer agents. Bioorg. Med. Chem. Lett. 21, 5374-5377.

Manach, C.L., Paquet, T., Brunschwig, C., Njoroge, M., Han, Z., Cabrera, D.G., Bashyam, S., Dhinakaran, R., Taylor, D., Reader, J., et al. 2015. A novel pyrazolopyridine with in vivo activity in *Plasmodium berghei*- and *Plasmodium falciparum*-infected mouse models from structure-activity relationship studies around the core of recently identified antimalarial imidazopyridazines. J. Med. Chem. 58, 8713-8722.

Mandha, S.R., Siliveri, S., Alla, M., Bommena, V.R., Bommineni, M.R., Balasubramanian, S., 2012. Eco-friendly synthesis and biological evaluation of substituted pyrano[2,3-c]pyrazoles. Bioorg. Med. Chem. Lett. 22, 5272-5278.

Manohar, S., Khan, S.I., Rawat, D.S., 2010. Synthesis, antimalarial activity, and cytotoxicity of 4-aminoquinoline-triazine conjugates. Bioorg. Med. Chem. Lett. 20, 322-325.

Marella, A., Akhter, M., Shaquiquzzaman, M., Tanwar, O., Verma, G., Alam, M.M., 2014. Synthesis, 3D-QSAR and docking studies of pyrimidine nitrile-pyrazoline: A novel class of hybrid antimalarial agents. Med. Chem. Res. 24, 1018-1037.

Marella, A., Shaquiquzzaman, M., Akhter, M., Verma, G., Alam, M.M., 2015. Novel pyrazole-pyrazoline hybrids endowed with thioamide as antimalarial agents: their synthesis and 3D-QSAR studies. J. Enzyme Inhib. Med. Chem, 30, 597-606.

Mehta, J.V., Gajera, S.B., Thakor, P., Thakkar, V.R., Patel, M.N., 2015. Synthesis of 1,3,5-trisubstituted pyrazoline derivatives and their applications. RSC Adv. 5, 85350.

Michon, V., Penhoat, C.H.D., Tombret, F., Gillardin, J.M., Lepage, F., Berthon, L., 1995. Preparation, structural analysis and anticonvulsant activity of 3- and 5-aminopyrazole N-benzoyl derivatives. Eur. J. Med. Chem. 30, 147.

Mishra, N., Sasmal, D., 2013. Additional acetyl cholinesterase inhibitory property of diaryl pyrazoline derivatives. Bioorg. Med. Chem. Lett. 23, 702-705.

Mishra, S., Karmodiy, K., Surolia, N., Surolia, A., 2008. Synthesis and exploration of novel curcumin analogues as antimalarial agents. Bioorg. Med. Chem. 16, 2894-2902.

Mishra, V.K., Mishra, M., Kashaw, V., Kashaw, S.K., 2017. Synthesis of 1,3,5-trisubstituted pyrazolines as potential antimalarial and antimicrobial agents. Bioorg. Med. Chem. 25, 1949-1962.

Mistry, P.T., Kamdar, N.R., Haveliwala, D.D., Patel, S.K., 2012. Synthesis, characterization, and in vitro biological studies of some novel pyran fused pyrimidone derivatives. J. Heterocycl. Chem. 49, 349-357.

Nasution, M.A.F., Ardiansah, B., Tambunan, U.S.F., 2016. Chalcone and its pyrazole derivatives as potential *Plasmodium falciparum* lactate dehydrogenase inhibitor: In silico approach for new antimalarial drug, 1st Asian Researchers Symposium. DOI:10.13140/RG.2.1.2887.3847.

Nehra, B., Rulhania, S., Jaiswal, S., Kumar, B., Singh, G., Monga, V., 2020. Recent Advancements in the development of bioactive pyrazoline derivatives. Eur. J. Med. Chem. 205, 112666-112699.

Ovais, S., Pushpalatha, H., Reddy, G.B., Rathore, P., Bashir, R., Yaseen, S., Dheyaa, A., Yaseen, R., Tanwar, O., Akthar, M., Samim, M., Javed, K., 2014. Synthesis and biological evaluation of some new pyrazoline substituted benzenesulfonylurea/thiourea derivatives as antihyperglycaemic agents and aldose reductase inhibitors. Eur. J. Med. Chem. 80, 209-217.

Özkay, Ü.D., Can, Ö.D., Kaplancikli, Z.A., 2011. Antinociceptive activities of some triazole and pyrazoline moieties-bearing compounds. Med. Chem. Res. 21, 1056-1061.

Pai, G., Chattopadhyay, A.P., 2016. N-arylation of nitrogen containing heterocycles with aryl halides using copper nanoparticle catalytic system. Tetrahedron Lett. 57, 3140.

Pandey, A.K., Sharma, S., Pandey, M., Alam, M.M., Shaquiquzzaman, M., Akhter, M., 2016. 4, 5-Dihydrooxazole-pyrazoline hybrids: Synthesis and their evaluation as potential antimalarial agents. Eur. J. Med. Chem. 123, 476-486.

Pandya, K.M., Patel, A.H., Desai, P.S., 2019. Development of antimicrobial, antimalarial and antitubercular compounds based on a quinoline-pyrazole clubbed scaffold derived via Doebner reaction. Chemistry Africa. 2019. doi.org/10.1007/s42250-019-00096-5.

Parikh, P.H., Timaniya, J.B., Patel, M.J., Patel, K.P., 2022. Microwave-assisted synthesis of pyrano[2,3-c]-pyrazole derivatives and their antimicrobial, antimalarial, antitubercular, and anticancer activities. J. Mol. Struct. 1249, 131605.

Patel, M., Pandey, N., Timaniya, J., Parikh, P., Chauhan, A., Jain, N., Patel, K., 2021. Coumarin-carbazole based functionalized pyrazolines: synthesis, characterization, anticancer investigation and molecular docking. RSC Adv. 11, 27627–27644.

Pathak, R.B., Chovatia, P.T., Parekh, H.H., 2012. Synthesis, antitubercular and antimicrobial evaluation of 3-(4-chlrophenyl)-4-substituted pyrazole derivatives. Bioorg. Med. Chem. Lett. 22, 5129-5133.

Pinheiro, L.C.S., Feitosa, L.M., Gandi, M.O., Silveira, F.F., Boechat, N., 2019. The Development of Novel Compounds Against Malaria: Quinolines, Triazolpyridines, Pyrazolopyridines and Pyrazolopyrimidines. Molecules. 24, 4095.

Prasad, P., Kalola, A.G., Patel, M.P., 2018. Microwave assisted one-pot synthetic route to imidazo[1,2-a]pyrimidine derivatives of imidazo/triazole clubbed pyrazole and their pharmacological screening. New J. Chem. 42, 12666-12676.

Qin, H.-L., Zhang, Z.-W., Lekkala, R., Alsulami, H., Rakesh, K.P., 2020. Chalcone hybrids as privileged scaffolds in antimalarial drug discovery: A key review. Eur. J. Med. Chem. 193, 112215.

Queiroz, J.E., Dias, L.D., Verde, G.M.V., Aquino, G.L.B., Camargo, A.J., 2022. An update on the synthesis and pharmacological properties of pyrazoles obtained from chalcone. Curr. Org. Chem. 26, 81-90.

Quirante, J., Ruiz, D., Gonzalez, A., López, C., Cascante, M., Cortés, R., Messeguer, R., Calvis, C., Baldomà, L., Pascual, A., Guérardel, Y., Pradines, B., Font-Bardía, M., Calvet, T., Biot, C., 2011. Platinum(II) and palladium(II) complexes with (N,N′) and (C,N,N′)- ligands derived from pyrazole as anticancer and antimalarial agents: Synthesis, characterization and in vitro activities. J. Inorg. Biochem. 105, 1720-1728.

Journal Pre-proof

Raffa, D., Maggio, B., Raimondi, M.V., Cascioferro, S., Plescia, F., Cancemi, G., Daidone, G., 2015. Recent advanced in bioactive systems containing pyrazole fused with a five membered heterocycle. Eur. J. Med. Chem. 97, 732-746.

Raghuvanshi, D.S., Verma, N., Singh, S.V., Khare, S., Pal, A., Negi, A.S., 2019. Synthesis of thymol-based pyrazolines: An effort to perceive novel potent-antimalarials. Bioorg. Chem. 88, 102933.

Ramiz, M.M.M., Hafiz, I.S.A., Rahim, M.A.M.A., Gaber, H.M., 2012. Pyrazolones as building blocks in heterocyclic synthesis: Synthesis of new pyrazolopyran, pyrazolopyridazine and pyrazole derivatives of expected antifungicidal activity. J. Chin. Chem. Soc. 59, 72-80.

Sahoo, A., Yabanoglu, S., Sinha, B.N., Ucar, G., Basu, A., Jayaprakash, V., 2010. Towards development of selective and reversible pyrazoline based MAO-inhibitors: Synthesis, biological evaluation and docking studies. Bioorg. Med. Chem. Lett. 20, 132-136.

Sant'anna, C.M.R., Alencastro, R.B., Rodrigues, C.R., Barreiro, G., Barreiro, E.J., Neto, J.D.M., Freitas, A.C.C., 1996. A semiempirical study of pyrazole acylhydrazones as potential antimalarial agents. Int. J. Quantum Chem. 60, 1835-1843.

Satasia, S.P., Kalaria, P.N., Raval, D.K., 2014. Catalytic regioselective Synthesis of pyrazole based pyrido[2,3-d]pyrimidine-diones and their biological evaluation. Bioorg. Med. Chem. 12, 1751-1758.

Shamsuddin, M.A., Ali, A.H., Zakaria, N.H., Mohammat, M.F., Hamzah, A.S., Shaameri, Z., Lam, K.W., Mark-Lee, W.F., Agustar, H.K., Razak, M.R.M.A., Latip, J., Hassan, N.I., 2021. Synthesis, Molecular Docking, and Antimalarial Activity of Hybrid 4-Aminoquinoline-pyrano[2,3-c]pyrazole Derivatives. pharmaceuticals. 14, 1174.

Shamsuddin, M.A., Zakaria1, N.H., Mohammat, M.F., Syahri, J., Latip, J., Hassan, N.I., 2020. Synthesis and Molecular Docking Studies of Pyrano[2,3-c] Pyrazole-3-Carboxylates as Potential Inhibitors of *Plasmodium falciparum*. Malays. J. Chem. 22, 52-61.

Shamsuzzaman, S., Siddiqui, T., Alam, M.G., Dar, A.M., 2015. Synthesis, characterization and anticancer studies of new steroidal oxadiazole, pyrrole and pyrazole derivatives. J. Saudi Chem. Soc. 19, 387.

Sharmabc, M., Prasher, P., 2020. An epigrammatic status of the 'azole'-based antimalarial drugs. RSC Med. Chem. 11, 184.

Journal Pre-proof

Silva, T.B., Bernardino, A.M.R., Ferreira, M.L.G., Rogerio, K.R., Carvalho, L.J.M., Boechat, N., Pinheiro, L.C.S., 2016. Design, synthesis and anti-*P.falciparum* activity of pyrazolopyridine-sulfonamide derivatives. Bioorg. Med. Chem. 24, 4492-4498.

Silveira, F.F., Feitosa, L.M., Mafra, J.C.M., Ferreira, M.L.G., Rogerio, K.R., Carvalho, L.J.M., Boechat, N., Pinheiro, L.C.S., 2018. Synthesis and anti-*Plasmodium falciparum* evaluation of novel pyrazolopyrimidine derivatives. Med. Chem. Res. 27, 1876-1884.

Singh, N., Gupta, S.K., Tiwari, L., 2021. Current study about pharmacological properties of pyrazole. Int. J. Pharm. Erud. 11, 1-21.

Sivakumar, P.M., Ganesan, S., Veluchamy, P., Doble, M., 2010. Novel chalcones and 1,3,5-triphenyl-2-pyrazoline derivatives as antibacterial agents. Chem. Biol. Drug Des. 76, 407-411.

Sony, J. K., Ganguly, S., 2016. A battle against AIDS: New pyrazole key to an older lock-reverse transcriptase. Int. J. Pham Pharm. Sci. 8, 75.

Srivastava, M., Singh, J., Singh, S.B., Tiwari, K., Pathak, K.V., Singh, J., 2012. Synthesis of novel fused heterocycleoxa-aza-phenanthrene and anthracene derivatives via sequential one-pot synthesis in aqueous micellar system. Green Chem. 14, 901.

Strasek, N., Lavrencic, L., Ostrek, A., Slapsak, D., Groselj, U., Klemencic, M., Zugelj, H.B., Wagger, J., Novinec, M., Svete, J., 2019. Tetrahydro-1H,5H-pyrazolo [1,2-a] pyrazole-1-carboxylates as inhibitors of *Plasmodium falciparum* dihydroorotate dehydrogenase. Bioorg. Chem. 89, 102982.

Tibon, N.S., Ng, C.H., Cheong, S.L., 2020. Current progress in antimalarial pharmacotherapy and multi-target drug discovery. Eur. J. Med. Chem. 188, 111983.

Tuha, A., Bekhit, A.A., Seid, Y., 2014. Synthesis and biological screening of some thienyl and phenyl pyrazoline derivatives as antimalarial agent. Thai. J. Pharm. Sci. 38, 121-129.

Vaidya, A.B., Morrisey, J.M., Zhang, Z., et al., 2014. Pyrazoleamide compounds are potent antimalarials that target Na+ homeostasis in intraerythrocytic *Plasmodium falciparum*. Nat. Commun, 5, 5521.

Verma, G., Chashoo, G., Ali, A., Khan, M.F., Akhtar, W., Ali, I., Akhtar, M., Alam, M.M., Shaquiquzzaman, M., 2018. Synthesis of pyrazole acrylic acid based oxadiazole and amide derivatives as antimalarial and anticancer agents. Bioorg. Chem. 77, 106-124.

Verma, G., Khan, M.F., Nainwal, L.M., Ishaq, M., Akhter, M., Bakht, A., Anwer, T., Afrin, F., Islamuddin, M., Husain, I., Alam, M.M., Shaquiquzzaman, M., 2019. Targeting malaria and leishmaniasis: Synthesis and pharmacological evaluation of novel pyrazole 1,3,4-oxadiazole hybrids. Part II, Bioorg. Chem. 89, 102986.

Vijesh, A.M., Isloor, A.M., Shetty, P., Sundershan, S., Fun, H.K., 2013. New pyrazole derivatives containing 1,2,4-triazoles and benzoxazoles as potent antimicrobial and analgesic agents. Eur. J. Med. Chem. 62, 410-415.

Wanare, G., Aher, R., Kawathekar, N., Ranjan, R., Kaushik, N.K., Sahal, D., 2010. Synthesis of novel α-pyranochalcones and pyrazoline derivatives as *Plasmodium falciparum* growth inhibitors. Bioorg. Med. Chem. Lett. 20, 4675-4678.

Wang, J.L., Liu, D., Zheng, Z.J., Shan, S., Han, X., Srinivasula, S.M., Croce, C.M., Alnemri, E.S., Huang, Z., 2009. Structure-based discovery of an organic compound that binds Bcl-2-protien and induces apoptosis of tumor cell. Proc. Natl. Acad. Sci. 97, 7124-7129.

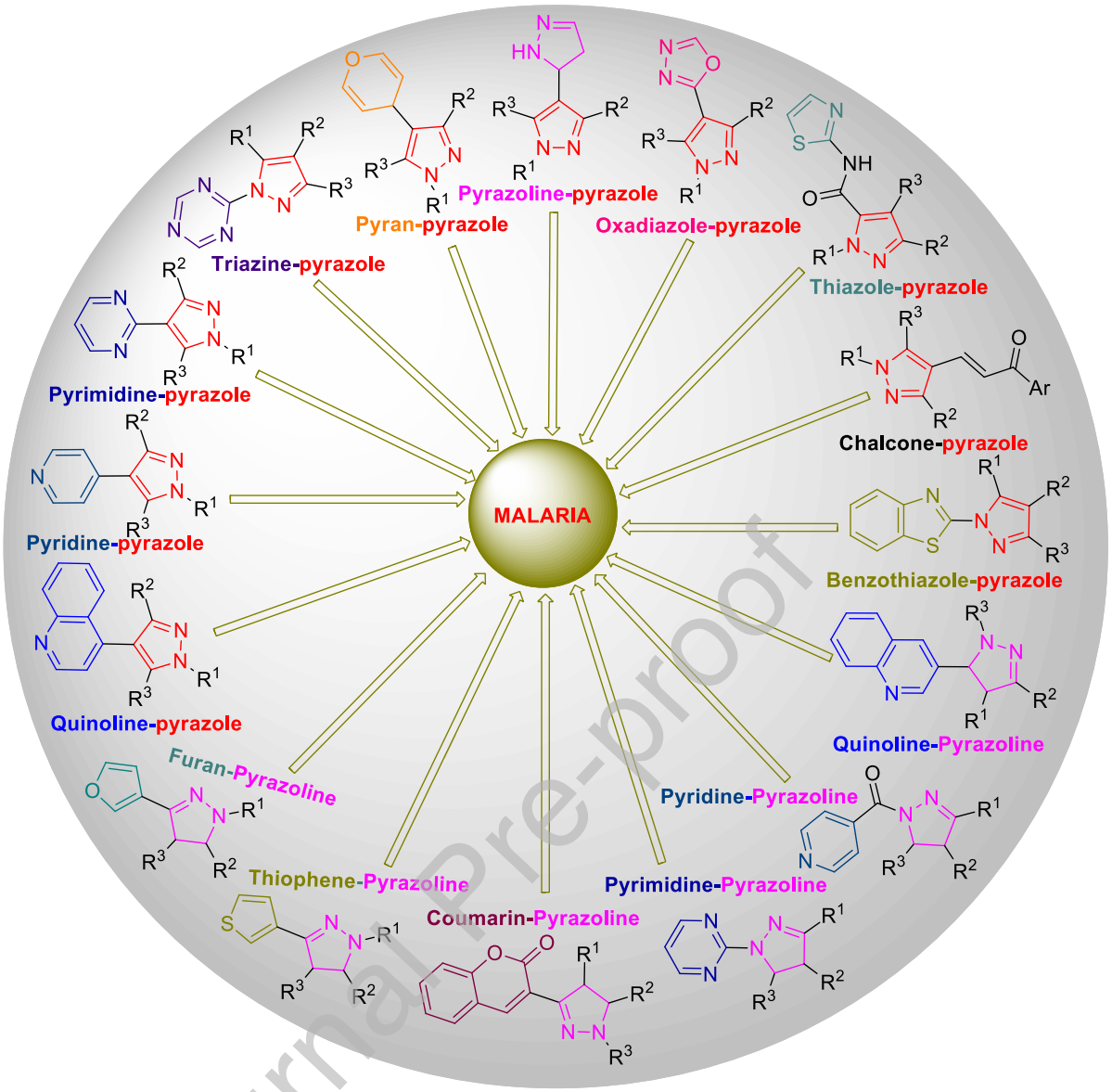
Wiley R H and Wiley P 1964 Pyrazolones, Pyrazolidones and Derivatives (New York: Wiley) p. 102.

Witschel, M.C., Rottmann, M., Schwab, A., Leartsakulpanich, U., Chitnumsub, P., Seet, M., Tonazzi, S., Schwertz, G., Stelzer, F., Mietzner, T., McNamara, C., Thater, F., Freymond, C., Jaruwat, A., Pinthong, C., Riangrungroj, P., Oufir, M., Hamburger, M., Mäser, P., Sanz-Alonso, L.M., Charman, S., Wittlin, S., Yuthavong, Y., Chaiyen, P., Diederich, F., 2015. Inhibitors of plasmodial serine hydroxymethyltransferase (SHMT): Cocrystal structures of pyrazolopyrans with potent blood- and liver-stage activities. J. Med. Chem. 58, 3117-3130.

World malaria report 2018, World Health Organization, Geneva, 2018, p. 166.

Zárate-Zárate, D., Aguilar, R., Hernández-Benitez, R.I., Labarrios, E.M., Delgado, F., Tamariz, J., 2015. Synthesis of α-ketols by functionalization of captodative alkenes and divergent preparation of heterocycles and natural products. Tetrahedron. 71, 6961.

Journal Pre-proof



graphical abstract

Journal Pre-proof