Experimental Parasitology 185 (2018) 107–114

Contents lists available at ScienceDirect

Experimental Parasitology

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

Novel arylidene derivatives of quinoline based thiazolidinones: Synthesis, *in vitro*, *in vivo* and *in silico* study as antimalarials

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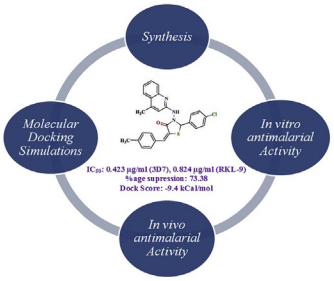
HIGHLIGHTS

- Synthesis and characterization of arylidene derivatives of quinoline based thiazolidinones.
- Evaluation for *in vitro* antimalarial potential against CQ-sensitive and CQ-resistant strains of *P. falciparum*.
- Top five potent compounds were further evaluated *in vivo* against *P. berghei*.
- Docking studies have been performed in the active site of *P. falciparum* lactate dehydrogenase.
- **5g** was found to be most promising candidate with 73.38% of suppression.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 19 April 2017
Received in revised form
3 January 2018
Accepted 14 January 2018

1. Introduction

Malaria is a common and life-threatening disease transmitted via the bites of infected female *Anopheles* mosquitoes and caused by protozoan parasites of the genus *Plasmodium*. The prevalent species responsible for it are *Plasmodium falciparum* and *Plasmodium vivax* and the most lethal parasite is former one. The parasitic multiplication begins in the liver, infecting erythrocytes where a cyclic asexual replication begins with the cycles of fever and chills as symptoms of malaria. This infected person with severe illness can result to death within hours to days; if untreated (Warhurst et al., 2003; Mishra et al., 2017). According to the World Health Organisation (WHO) report, 212 million new cases of malaria worldwide in 2015 were reported (range 148–304 million). The WHO African Region accounted for most global cases of malaria (90%), followed by the South-East Asia Region (7%) and the Eastern Mediterranean Region (2%) (WHO, World Malaria Report, 2016). The surge in resistance of malaria parasites particularly in *P. falciparum* is an important factor in the persistence of this disease as a major worldwide public health threat (Sinha et al., 2014). The existing chemotherapy lacks satisfaction and effectiveness due to the side effects associated to long-term treatments. The existing drugs come across shortcomings like drug resistance and strain sensitivity for the clinically accessible chemotherapy (Sahu et al., 2016; Manohar et al., 2014; Teixeira et al., 2014).

Quinoline derived drugs like chloroquine, amodiaquine, quinine, quinidine, mefloquine, primaquine, lumefantrine, and halofantrine have long been used against malaria and all these shows

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https://doi.org/10.1016/j.exppara.2018.01.015

potent activity against the erythrocytic stage of infection (Olson et al., 1999). Primaquine also kills intrahepatic forms and gametocytes. The drugs act by accumulating in the parasite food vacuole and forming a complex with heme that prevents crystallization in the *Plasmodium* food vacuole. Heme polymerase activity is restraint, resulting in accumulation of cytotoxic-free heme (Foley and Tilley, 1998; Bekhit et al., 2012). The appearance of drug-resistant strains of the malaria parasite was the distressing outcome of efforts for the development of insecticide-resistant mosquitos (Kumar et al., 2015).

Several biological activities are associated with a five-membered ring thiazolidine which is an important pharmacophore. 4-Thiazolidinones having wide range of biological activities are evolved from thiazolidine with a carbonyl group at the position 4. Substitution of group to the carbon atom present at position 2 shows marked difference in structure and physicochemical properties of 4-thiazolidones (Singh et al., 2010; Dorn et al., 1995). Rigid molecules present in the nitrogen containing heterocyclic skeleton (thiazolidine-4-one) show biologically active scaffold for the design of new antimalarial drugs active against *Plasmodium* malaria parasite (Rojas Ruiz et al., 2011; Kumar et al., 2014; Rosenthal et al., 2002). In the current study, novel thiazolidinone-quinoline hybrids and their corresponding arylidene derivatives were prepared in good yield. Structure-Activity relationship has also been established to get a deep insight into the effect of different substitutions on antimalarial potential of the series. This work also includes the docking simulation of the active agents among the series to get an idea about the ligand receptor interaction. We, herein present study, reported the synthesis, *in vitro*, *in vivo* and *in silico* screening of synthesized series for antimalarial potential.

2. Experimental

2.1. Synthetic strategy adopted

The synthetic protocol followed for the synthesis of compounds under study has been outlined in Scheme 1.

2.1.1. General experimental procedure for synthesis of hydrazone (3a-e)

The whole synthesis is outlined in Scheme 1. To a mixture of 2-hydrazino-4-methylquinoline, **compound 2** in EtOH (20 ml) was added in an equimolar amount of various aromatic aldehyde and refluxed in the presence of 1–2 drop of glacial acetic acid for 6 h. The resulting solution was poured on crushed ice to yield hydrazones in high yield (Unsal-Tan et al., 2012; Kumar et al., 2007).

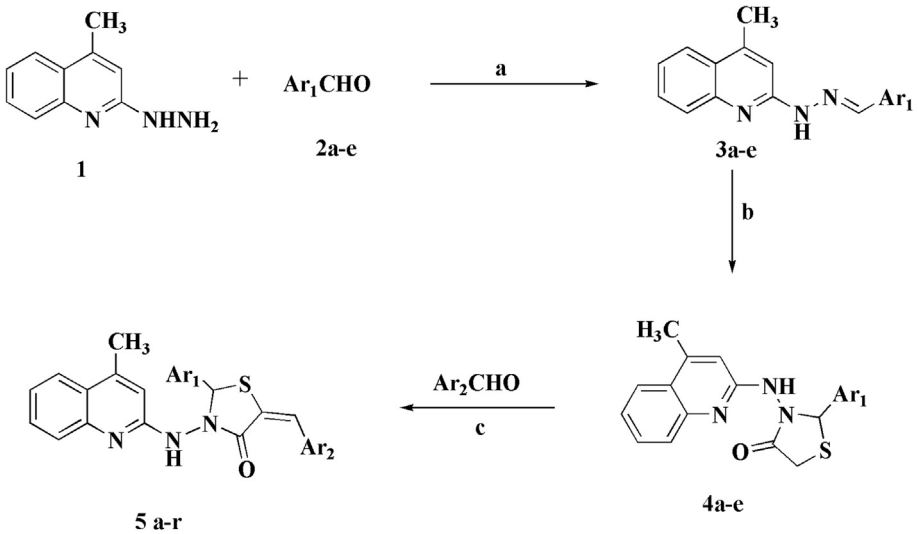
2.1.1.1. 1-Benzylidene-2-(4-methylquinolin-2-yl)hydrazine ***(3a)***. Yield 73%, mp 153–154 °C IR (υ, cm^{-1}): 3354.20 (N-H), 2919.50 (C-H), 1612.10 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.59 (s, br, 1H, NH), 8.23 (s, 1H, quinoline ring), 7.43–7.89 (m, 9H, aromatic), 7.28 (s, 1H, -N=CH), 2.74 (s, 3H, CH_3 of Qu-ring).

2.1.1.2. 1-(4-chlorobenzylidene)-2-(4-methylquinolin-2-yl)hydrazine ***(3b)***. Yield 71%, mp 166–168 °C IR (υ, cm^{-1}): 3361.12 (N-H), 2921.17 (C-H), 1613.24 (C=N), 653.27 (C-Cl); ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.61 (s, br, 1H, NH), 8.26 (s, 1H, quinoline ring), 7.83 (d, 2H), 7.65–7.89 (m, 4H), 7.29 (s, 1H, -N=CH), 6.98 (d, 2H), 2.78 (s, 3H, CH_3).

2.1.1.3. 1-(4-methylbenzylidene)-2-(4-methylquinolin-2-yl)hydrazine ***(3c)***. Yield 79%, mp 172–174 °C IR (υ, cm^{-1}): 3349.11 (N-H), 2929.41 (C-H), 1609.81 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.61(s, br, 1H, NH), 8.23 (s, 1H, quinoline ring), 7.86 (d, 2H), 7.55–7.78 (m, 4H), 7.26 (s, 1H, -N=CH), 6.99 (d, 2H), 2.73 (s, 3H, CH_3 of Qu-ring), 2.31 (s, 3H, CH_3).

2.1.1.4. 1-(4-methoxybenzylidene)-2-(4-methylquinolin-2-yl)hydrazine ***(3d)***. Yield 81%, mp 151–153 °C IR (υ, cm^{-1}): 3327.33 (N-H), 2932.45 (C-H), 1615.11 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.64 (s, br, 1H, NH), 8.23 (s, 1H, quinoline ring), 7.81 (d, 2H), 7.68–7.90 (m, 4H), 7.28 (s, 1H, -N=CH), 6.98 (d, 2H), 3.89 (s, 3H, OCH_3), 2.79 (s, 3H, CH_3).

2.1.1.5. 1-(4-methylquinolin-2-yl)-2-(thiophen-2-ylmethylene)hydrazine ***(3e)***. Yield 69%, mp 140–142 °C IR (υ, cm^{-1}): 3341.29 (N-H), 2922.17 (C-H), 1613.62 (C=N); ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.59 (s, br, 1H, NH), 8.17 (s, 1H, quinoline ring), 7.21 (s, 1H, -N=CH), 6.83–7.56 (m, 7H), 2.70 (s, 3H, CH_3).



Scheme 1. Synthesis of arylidene derivatives **(5 a-r): a)** 1–2 drops Glacial acetic acid, Ethanol, reflux, 6 h. **b)** Thioglycolic acid, 1,4-Dioxane, $ZnCl_2$, reflux, 8–10 h. **c)** Glacial acetic acid, Sodium acetate, reflux, 12 h.

*2.1.2. General experimental procedure for synthesis of thiazolidinone **(4a-e)***

To a solution of compound (3) (0.01 mol) in 1,4 dioxane (50 ml) was added mercapto acetic acid (0.015 mol) with stirring and a little amount of anhydrous $ZnCl_2$ was added. The mixture was refluxed for 10–12 h, after the completion of reaction, it was cooled and the excess solvent distilled and poured into sodium bicarbonate solution to neutralize it. The solid product was filtered and washed with cold water. The resulting solid was recrystallized in ethanol (99%) (Desai and Dodiya, 2014; Nagalakshmi et al., 2013).

*2.1.2.1. 3-(4-methylquinolin-2-ylamino)-2-phenylthiazolidin-4-one **(4a)**.* Yield 51%, mp 202–204 °C IR (υ, cm^{-1}): 3406.34 (N-H), 1656.17 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.46 (s, 1H, NH), 8.16 (s, 1H, H_3 of quinoline), 7.33–7.90 (m, 9H), 6.77 (s, 1H, thiazolidinone, 2nd position), 5.29 (s, 2H, Thiazolidinone, 4th position), 2.63 (s, 3H, CH_3 of quinoline).

*2.1.2.2. 2-(4-chlorophenyl)-3-(4-methylquinolin-2-ylamino)thiazolidin-4-one **(4b)**.* Yield 54%, mp 230–232 °C IR (υ, cm^{-1}): 3409.46 (N-H), 1659.32 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.52 (s, 1H, NH), 8.14 (s, 1H, H_3 of quinoline), 7.20–7.85 (m, 8H), 6.65 (s, 1H, thiazolidinone, 2nd position), 5.33 (s, 2H, Thiazolidinone, 4th position), 2.68 (s, 3H, CH_3 of quinoline).

*2.1.2.3. 3-(4-methylquinolin-2-ylamino)-2-p-tolylthiazolidin-4-one **(4c)**.* Yield 49%, mp 236–238 °C IR (υ, cm^{-1}): 3411.43 (N-H), 1659.22 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ):8.41 (s, 1H, NH), 8.19 (s, 1H, H_3 of quinoline), 7.15–7.95 (m, 8H), 6.73 (s, 1H, thiazolidinone, 2nd position), 5.06 (s, 2H, Thiazolidinone, 4th position), 2.65 (s, 3H, CH_3 of quinoline), 2.35 (s, 3H, CH_3 of phenyl).

*2.1.2.4. 2-(4-methoxyphenyl)-3-(4-methylquinolin-2-ylamino)thiazolidin-4-one **(4d)**.* Yield 57%, mp 220–222 °C IR (υ, cm^{-1}): 3410.58 (N-H), 1654.63 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.42 (s, 1H, NH), 8.26 (s, 1H, H_3 of quinoline), 7.06–7.80 (m, 8H), 6.54 (s, 1H, thiazolidinone, 2nd position), 5.15 (s, 2H, Thiazolidinone, 4th position), 4.35 (s, 3H, OCH_3 of phenyl), 2.67 (s, 3H, CH_3 of quinoline).

*2.1.2.5. 3-(4-methylquinolin-2-ylamino)-2-(thiophen-2-yl)thiazolidin-4-one **(4e)**.* Yield 42%, mp 200–202 °C IR (υ, cm^{-1}): 3399.18 (N-H), 1659.47 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.48 (s, 1H, NH), 8.21 (s, 1H, H_3 of quinoline), 7.16–7.85 (m, 7H), 5.23 (s, 2H, Thiazolidinone, 4th position), 6.67 (s, 1H, thiazolidinone, 2nd position), 2.56 (s, 3H, CH_3 of quinoline).

2.1.3. General experimental procedure for synthesis of arylidine derivatives

A well-stirred solution of 3-(4-methylquinolin-2-ylamino)-2-arylthiazolidin-4-ones **(4a-e)** in 20 ml glacial acetic acid was buffered with sodium acetate, 0.66 g (8 mmol) followed by addition of substituted arylaldehyde (6 mmol). The solution was refluxed for 12 h and then poured into ice-cold water to yield titled compounds, **5a-r**. The resulting product was purified by recrystallization from dioxane (Omar et al., 2010; Deep et al., 2014).

*2.1.3.1. 5-Benzylidene-3-(4-methylquinolin-2-ylamino)-2-phenylthiazolidin-4-one **(5a)**.* Yield 62%, mp 212–214 °C IR (υ, Cm^{-1}): 1527 (=C-H), 2974 (=C-H), 1565 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.25 (s, 1H, NH), 8.11 (s, 1H, H_3 of quinoline), 6.82 (s, 1H, thiazolidinone, 2nd position), 6.9–7.85 (m, 14H), 5.88 (s, 1H, =CH-Ar), 2.70 (s, 3H, CH_3 of quinoline); MS: m/z = 424.35 (M+1); Anal. Calcd for $C_{26}H_{21}N_3OS$: C, 73.73; H, 5.00; N, 9.92. Found: C, 73.81; H, 5.02; N, 9.89.

*2.1.3.2. 5-(4-chlorobenzylidene)-3-(4-methylquinolin-2-ylamino)-2-phenylthiazolidin-4-one **(5b)**.* Yield 56%, mp 219–221 °C IR (υ, cm^{-1}): 1525 (=C-H), 2975 (=C-H), 1569 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.24 (s, 1H, NH), 8.13 (s, 1H, H_3 of quinoline), 6.88 (s, 1H, thiazolidinone, 2nd position), 6.78–7.67 (m, 13H), 5.82 (s, 1H, =CH-Ar), 2.73 (s, 3H, CH_3 of quinoline); MS: m/z = 458.73 (M+1); Anal. Calcd for $C_{26}H_{20}ClN_3OS$: C, 68.19; H, 4.40; N, 9.18. Found: C, 68.21; H, 4.46; N, 9.25.

*2.1.3.3. 5-(4-methylbenzylidene)-3-(4-methylquinolin-2-ylamino)-2-phenylthiazolidin-4-one **(5c)**.* Yield 60%, mp 199–201 °C IR (υ, cm^{-1}): 1526 (=C-H), 2972 (=C-H), 1571 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, δ):8.23 (s, 1H, NH), 8.11 (s, 1H, H_3 of quinoline), 6.92–7.83 (m, 13H), 6.86 (s, 1H, thiazolidinone, 2nd position), 5.80 (s, 1H, =CH-Ar), 2.69 (s, 3H, CH_3 of quinoline), 2.45 (s, 3H, CH_3 of phenyl). MS: m/z = 438.47 (M+1); Anal. Calcd for $C_{27}H_{23}N_3OS$: C, 74.11; H, 5.30; N, 9.60. Found: C, 74.19; H, 5.37; N, 9.71.

*2.1.3.4. 5-(4-methoxybenzylidene)-3-(4-methylquinolin-2-ylamino)-2-phenylthiazolidin-4-one **(5d)**.* Yield 63%, mp 205–206 °C IR (υ, cm^{-1}): 1529 (=C-H), 2976 (=C-H), 1573 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.23 (s, 1H, NH), 8.17 (s, 1H, H_3 of quinoline), 6.83 (s, 1H, thiazolidinone, 2nd position), 6.77–7.69 (m, 13H), 5.83 (s, 1H, =CH-Ar), 4.03 (s, 3H, OCH_3 of phenyl), 2.67 (s, 3H, CH_3 of quinoline); MS: m/z = 454.35 (M+1); Anal. Calcd for $C_{27}H_{23}N_3O_2S$: C, 71.50; H, 5.11; N, 9.26. Found: C, 71.53; H, 5.16; N, 9.21.

*2.1.3.5. 5-Benzylidene-2-(4-chlorophenyl)-3-(4-methylquinolin-2-ylamino)thiazolidin-4-one **(5e)**.* Yield 63%, mp 205–206 °C IR (υ, cm^{-1}): 1531 (=C-H), 2972 (=C-H), 1571 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.27 (s, 1H, NH), 8.19 (s, 1H, H_3 of quinoline), 7.1–7.92 (m, 13H), 6.79 (s, 1H, thiazolidinone, 2nd position), 5.84 (s, 1H, =CH-Ar), 2.65 (s, 3H, CH_3 of quinoline); MS: m/z = 458.35 (M+1); Anal. Calcd for $C_{26}H_{20}ClN_3OS$: C, 68.19; H, 4.40; N, 9.18. Found: C, 68.21; H, 4.46; N, 9.25.

*2.1.3.6. 5-(4-chlorobenzylidene)-2-(4-chlorophenyl)-3-(4-methylquinolin-2-ylamino) thiazolidin -4-one **(5f)**.* Yield 61%, mp 217–218 °C IR (υ, cm^{-1}): 1527 (=C-H), 2971 (=C-H), 1573 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.29 (s, 1H, NH), 8.18 (s, 1H, H_3 of quinoline), 7.12–7.97 (m, 12H), 6.75 (s, 1H, thiazolidinone, 2nd position), 5.87 (s, 1H, =CH-Ar), 2.68 (s, 3H, CH_3 of quinoline). MS: m/z = 492.45 (M+1); Anal. Calcd for $C_{26}H_{19}Cl_2N_3OS$: C, 63.42; H, 3.89; N, 8.53. Found: C, 63.52; H, 3.93; N, 8.55.

*2.1.3.7. 5-(4-methylbenzylidene)-2-(4-chlorophenyl)-3-(4-methylquinolin-2-ylamino) thiazolidin-4-one **(5g)**.* Yield 59%, mp 221–223 °C IR (υ, cm^{-1}): 1528 (=C-H), 2968 (=C-H), 1571 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.33 (s, 1H, NH), 8.17 (s, 1H, H_3 of quinoline), 7.14–7.93 (m, 12H), 6.79 (s, 1H, thiazolidinone, 2nd position), 5.80 (s, 1H, =CH-Ar), 2.65 (s, 3H, CH_3 of quinoline), 2.47 (s, 3H, CH_3 of phenyl); MS: m/z = 492.45 (M+1); Anal. Calcd for $C_{27}H_{22}ClN_3OS$ C, 68.71; H, 4.70; N, 8.90. Found: C, 68.76; H, 4.73; N, 8.94.

*2.1.3.8. 5-(4-methoxybenzylidene)-2-(4-chlorophenyl)-3-(4-methylquinolin-2-ylamino) thiazolidin-4-one **(5h)**.* Yield 65%, mp 198–201 °C IR (υ, cm^{-1}): 1532 (=C-H), 2976 (=C-H), 1577 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6, δ): 8.31 (s, 1H, NH), 8.20 (s, 1H, H_3 of quinoline), 6.88–7.87 (m, 12H), 6.72 (s, 1H, thiazolidinone, 2nd position), 5.84 (s, 1H, =CH-Ar), 4.12 (s, 3H, OCH_3 of phenyl), 2.71 (s, 3H, CH_3 of quinoline); MS: m/z = 488.34 (M+1); Anal. Calcd for $C_{27}H_{22}ClN_3O_2S$; C, 66.45; H, 4.54; N, 8.61. Found: C, 66.47; H, 4.53; N, 8.64.

*2.1.3.9. 5-Benzylidene-3-(4-methylquinolin-2-ylamino)-2-p-tolylthiazolidin-4-one **(5i)**.* Yield 54%, mp 213–215 °C IR (*ν*, cm^{-1}): 1530 (=C-H), 2974 (=C-H), 1573 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.26 (s, 1H, NH), 8.15 (s, 1H, H_3 of quinoline), 7.1–7.92 (m, 13H), 6.71 (s, 1H, thiazolidinone, 2nd position), 5.87 (s, 1H, =CH-Ar), 2.66 (s, 3H, CH_3 of quinoline), 2.34 (s, 3H, CH_3 of phenyl). MS: *m/z* = 438.47 (M+1); Anal. Calcd for $C_{27}H_{23}N_3OS$: C, 74.11; H, 5.30; N, 9.60. Found: C, 74.19; H, 5.37; N, 9.71.

*2.1.3.10. 5-(4-chlorobenzylidene)-3-(4-methylquinolin-2-ylamino)-2-p-tolylthiazolidin-4-one **(5j)**.* Yield 61%, mp 219–220 °C IR (*ν*, cm^{-1}): 1529 (=C-H), 2967 (=C-H), 1569 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.28 (s, 1H, NH), 8.12 (s, 1H, H_3 of quinoline), 7.12–7.96 (m, 12H), 6.72 (s, 1H, thiazolidinone, 2nd position), 5.80 (s, 1H, =CH-Ar), 2.64 (s, 3H, CH_3 of quinoline), 2.32 (s, 3H, CH_3 of phenyl). MS: *m/z* = 492.45 (M+1); Anal. Calcd for $C_{27}H_{22}ClN_3OS$ C, 68.71; H, 4.70; N, 8.90. Found: C, 68.76; H, 4.73; N, 8.94.

*2.1.3.11. 5-(4-methylbenzylidene)-3-(4-methylquinolin-2-ylamino)-2-p-tolylthiazolidin-4-one **(5k)**.* Yield 49%, mp 209–211 °C IR (*ν*, cm^{-1}): 1525 (=C-H), 2965 (=C-H), 1567 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.36 (s, 1H, NH), 8.12 (s, 1H, H_3 of quinoline), 6.98–7.81 (m, 12H), 6.59 (s, 1H, thiazolidinone, 2nd position), 5.68 (s, 1H, =CH-Ar), 2.68 (s, 3H, CH_3 of quinoline), 2.41 (s, 3H, CH_3 of phenyl), 2.34 (s, 3H, CH_3 of phenyl). MS: *m/z* = 452.35 (M+1); Anal. Calcd for $C_{28}H_{25}N_3OS$; C, 74.47; H, 5.58; N, 9.31. Found: C, 74.56; H, 5.62; N, 9.36.

*2.1.3.12. 5-(4-methoxybenzylidene)-3-(4-methylquinolin-2-ylamino)-2-p-tolylthiazolidin-4-one **(5l)**.* Yield 54%, mp 206–207 °C IR (*ν*, cm^{-1}): 1526 (=C-H), 2969 (=C-H), 1572 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.29 (s, 1H, NH), 8.15 (s, 1H, H_3 of quinoline), 7.12–7.96 (m, 12H), 6.61 (s, 1H, thiazolidinone, 2nd position), 5.73 (s, 1H, =CH-Ar), 4.25 (s, 3H, OCH_3 of phenyl), 2.71 (s, 3H, CH_3 of quinoline), 2.38 (s, 3H, CH_3 of phenyl). MS: *m/z* = 468.53 (M+1); Anal. Calcd for $C_{28}H_{25}N_3O_2S$; C, 71.92; H, 5.39; N, 8.99. Found: C, 71.99; H, 5.45; N, 9.02.

*2.1.3.13. 5-Benzylidene-2-(4-methoxyphenyl)-3-(4-methylquinolin-2-ylamino)thiazolidin-4-one **(5m)**.* Yield 61%, mp 202–203 °C IR (*ν*, cm^{-1}): 1527 (=C-H), 2974 (=C-H), 1576 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.37 (s, 1H, NH), 8.20 (s, 1H, H_3 of quinoline), 7.1–7.92 (m, 13H), 6.71 (s, 1H, thiazolidinone, 2nd position), 5.74 (s, 1H, =CH-Ar), 4.27 (s, 3H, OCH_3 of phenyl), 2.68 (s, 3H, CH_3 of quinoline), MS: *m/z* = 454.35 (M+1); Anal. Calcd for $C_{27}H_{23}N_3O_2S$: C, 71.50; H, 5.11; N, 9.26. Found: C, 71.53; H, 5.16; N, 9.21.

*2.1.3.14. 5-(4-chlorobenzylidene)-2-(4-methoxyphenyl)-3-(4-methylquinolin-2-ylamino) thiazolidin-4-one **(5n)**.* Yield 56%, mp 199–201 °C IR (*ν*, cm^{-1}): 1526 (=C-H), 2972 (=C-H), 1575 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.33 (s, 1H, NH), 8.21 (s, 1H, H_3 of quinoline), 6.92–7.94 (m, 12H), 6.74 (s, 1H, thiazolidinone, 2nd position), 5.79 (s, 1H, =CH-Ar), 4.27 (s, 3H, OCH_3 of phenyl), 2.67 (s, 3H, CH_3 of quinoline). MS: *m/z* = 488.34 (M+1); Anal. Calcd for $C_{27}H_{22}ClN_3O_2S$; C, 66.45; H, 4.54; N, 8.61. Found: C, 66.47; H, 4.53; N, 8.64.

*2.1.3.15. 5-(4-methylbenzylidene)-2-(4-methoxyphenyl)-3-(4-methylquinolin-2-ylamino)thiazolidin-4-one **(5o)**.* Yield 53%, mp 210–211 °C IR (*ν*, cm^{-1}): 1522 (=C-H), 2976 (=C-H), 1577 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.38 (s, 1H, NH), 8.16 (s, 1H, H_3 of quinoline), 6.98–7.90 (m, 12H), 6.72 (s, 1H, thiazolidinone, 2nd position), 5.72 (s, 1H, =CH-Ar), 4.18 (s, 3H, OCH_3 of phenyl), 2.62 (s, 3H, CH_3 of quinoline), 2.38 (s, 3H, CH_3 of phenyl). MS: *m/z* = 468.53 (M+1); Anal. Calcd for $C_{28}H_{25}N_3O_2S$; C, 71.92; H, 5.39; N, 8.99. Found: C, 71.99; H, 5.45; N, 9.02.

*2.1.3.16. 5-(4-methoxybenzylidene)-2-(4-methoxyphenyl)-3-(4-methylquinolin-2-ylamino)thiazolidin-4-one **(5p)**.* Yield 52%, mp 229–231 °C IR (*ν*, cm^{-1}): 1527 (=C-H), 2976 (=C-H), 1573 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ):8.26 (s, 1H, NH), 8.12 (s, 1H, H_3 of quinoline), 6.98–7.88 (m, 12H), 6.69 (s, 1H, thiazolidinone, 2nd position), 5.68 (s, 1H, =CH-Ar), 4.26 (s, 3H, OCH_3 of phenyl), 4.17 (s, 3H, OCH_3 of phenyl), 2.72 (s, 3H, CH_3 of quinoline). MS: *m/z* = 484.25 (M+1); Anal. Calcd for $C_{28}H_{25}N_3O_3S$; C, 69.54; H, 5.21; N, 8.69. Found: C, 69.58; H, 5.28; N, 8.73.

*2.1.3.17. 5-Benzylidene-3-(4-methylquinolin-2-ylamino)-2-(thiophen-2-yl)thiazolidin-4-one **(5q)**.* Yield 67%, mp 189–191 °C IR (*ν*, cm^{-1}): 1526 (=C-H), 2979 (=C-H), 1569 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.34 (s, 1H, NH), 8.13 (s, 1H, H_3 of quinoline), 6.93–7.75 (m, 12H), 6.72 (s, 1H, thiazolidinone, 2nd position), 5.81 (s, 1H, =CH-Ar), 2.76 (s, 3H, CH_3 of quinoline). MS: *m/z* = 430.19 (M+1); Anal. Calcd for $C_{24}H_{19}N_3OS_2$; C, 67.11; H, 4.46; N, 9.78. Found: C, 67.18; H, 4.51; N, 9.83.

*2.1.3.18. 5-(4-methylbenzylidene)-3-(4-methylquinolin-2-ylamino)-2-(thiophen-2-yl)thiazolidin-4-one **(5r)**.* Yield 54%, mp 182–183 °C IR (*ν*, cm^{-1}): 1531 (=C-H), 2971 (=C-H), 1573 (C=N); ^1H NMR (400 MHz, DMSO-d_6, δ): 8.36 (s, 1H, NH), 8.17 (s, 1H, H_3 of quinoline), 6.98–7.96 (m, 12H), 6.92 (s, 1H, thiazolidinone, 2nd position), 5.84 (s, 1H, =CH-Ar), 2.78 (s, 3H, CH_3 of quinoline), 2.36 (s, 3H, CH_3 of phenyl). MS: *m/z* = 444.61 (M+1); Anal. Calcd for $C_{25}H_{21}N_3OS_2$; C, 67.69; H, 4.77; N, 9.47. Found: C, 67.68; H, 4.77; N, 9.51.

2.2. In vitro antimalarial activity

Schizont Maturation Inhibition (SMI) assay was performed against Chloroquine sensitive strain, 3D7 and Chloroquine resistant strain, RKL9 of *Plasmodium falciparum* in RPMI medium (Rieckmann et al., 1978). The cultures of both strains were synchronized using 5% aqueous sorbitol solution. All stages except trophozoites (ring form) of parasite were degenerated and removed by centrifugation at 1500 rpm for 5 min. The test solutions were prepared in 0.1 ml DMSO and further diluted to produce concentration of 1.98–500 μg/ml with RPMI 1640 medium. 96 well plates were used for both cultures and inoculated with synchronized parasites. The plates were kept for 24–30 h in 5% CO_2 incubator at 37 °C. Thick smear was prepared for each well, stained with Giemsa stain and examined microscopically. EC_{50} was calculated for evaluation of antimalarial potential (Saini et al., 2016).

2.3. In vivo antimalarial screening

Acute toxicity study was performed by following OECD guidelines 423. Overnight fasted 4–6 week old using Swiss Albino Mice were used. The mice was observed for any symptom of toxicity such as change in colour of eyes, fur, urination, defecation, posture alteration, aggressiveness or any lethal response for first 4 h and examined for 24 h. If no lethal response was found, then second animal was administered with higher dose and observed as earlier. The animal were given dose for 14 days and kept under observation for the calculation of LD_{50} (Ecobichon, 1977).

In vivo antimalarial potential was investigated by 4-day suppressive test using Swiss Albino Mice of 4–6 week (22±5 g, 5 animal/group) against *P. berghei*. Each mice was inoculated with 0.2 ml of 1×10^6 parasitized RBC (from donor mice) intraperitoneally on day 0. Two hour post-infection, all the test groups were

administered with test drug at 200 mg/kg and standard at 5 mg/kg for 4 consecutive days. On day 4, thin smears were prepared from tail vein and were stained using Giemsa stain for evaluation of parasitemia microscopically. The mortality was observed for 7 days to check the survival rate. Percentage of parasitemia inhibition was calculated by (A-B)/A × 100, where A is the parasitemia of negative control (without any treatment) and B is the parasitemia of each test group (Devi et al., 2001; Manohar et al., 2012).

2.4. Docking study

In an effort to get insight the factors determining the bioactivity of novel arylidene derivatives of thiazolidinone-quinoline hybrids, docking simulations were performed in the active sight of *Plasmodium falciparum* lactate dehydrogenase (Singh et al., 2016; Prathiban et al., 2015). The molecular docking study was done by AutodockVina and autodock tools using Lamarckian Genetic Algorithm (Trott and Olson, 2010). The crystal structure of protein (PDB ID: 1CET) was obtained from Protein Data Bank (www.rcsb.org) (Kaushik et al., 2015). The structures of five ligands were prepared using ChemDrawUltra 8.0.3. Then the structures were converted into required. pdbqt format using ADT 1.5.6. During protein preparation, all the water molecules were removed; polar hydrogen and partial charges were added and saved as. pdbqt. The active grid was generated for docking with size 40 × 40 × 40 along x, y & z centres, 25.8, 26.829 & 9.405 respectively with 0.375 Å grid spacing. Further, ADT and Python were used for visualisation and identification of residues involved in binding.

3. Result and discussion

3.1. Chemistry

The synthetic protocol was successfully followed for the synthesis of thiazolidinone and their respective arylidene derivatives. The first step, compounds **(3a-e)** were prepared in good yield by condensation of 2-hydrazino-4-methylquinoline with different aromatic aldehyde in acidic conditions. In next step, hydrazone intermediates were converted into thiazolidinone **(4a-e)** by reacting with thioglycolic acid in dioxane. Finally the target compounds, 5-Arylidene-3-(4-methylquinolin-2-ylamino)-2-arylthiazolidin-4-one, were obtained by reacting equimolar amount of **(4a-e)** and aryl aldehyde in Glacial acetic acid.

Characteristic data from FTIR and ^{1}H NMR was studied for the progression of reaction. A strong band in range of 3200–3400 cm^{-1} is attributed to secondary amine present in all the intermediates and final compounds. Similarly, ^{1}H NMR of all the derivatives were supported by the presence of one broad singlet corresponding to NH nearly at δ 8.3–8.6 and a sharp singlet for proton at 3rd position in quinoline ring around δ 8.2. Characteristic peak in FTIR of compounds **(4a-e)** was observed in range of 1650–1660 cm^{-1} due to the presence of carbonyl group. In ^{1}H NMR, two distinct singlets corresponding to C-CH$_2$-S and N-CH-S at δ 5.29 and 6.77 ppm respectively, confirmed the synthesis of thiazolidinone ring. Further, disappearance of singlet at δ 5.29 for two protons with emergence of new singlet in δ 5.88 for single proton authenticated the progression of reaction from thiazolidinone to target arylidene derivatives. Eventually, all the structures of synthesized compounds were found in accordance with mass and elemental analysis.

3.2. In vitro antimalarial evaluation and structure-activity relationship

The antimalarial potential of entire set of synthesized analogues was assessed by *in vitro* antimalarial assay against Chloroquine-sensitive, 3D7 and Chloroquine-resistant, RKL9 strains of *Plasmodium falciparum*. The activity results of the target molecules have been displayed in Table 1. All compounds exhibited good antimalarial potency with EC_{50} range 0.432–2.672 μg/ml against 3D7 while against RKL-9 EC_{50} varies from 0.824 to 11.451 μg/ml. EC_{50} value for all the synthesized derivatives against both Chloroquine sensitive and Chloroquine resistant strain has also been represented graphically in Fig. 1. Compound **5g** was found to be most potent among the series with EC_{50} of 0.423 μg/ml and 0.824 μg/ml against 3D7 and RKL-9 respectively. Compound **5r** displayed maximum EC_{50} against both the strains and hence considered as least active compound of the series. Compounds **5b, 5e, 5g, 5j** and **5n** were found to be five most potent analogues among the series with EC_{50} (3D7/RKL-9) values of 0.731/1.617, 0.734/2.011, 0.423/0.824, 0.562/0.992 and 0.632/1.211 μg/ml respectively. From *in vitro* study, we have concluded the results in structure-activity relationship.

3.2.1. Structure-activity relationship

It has been revealed that the presence of chloro group at *p*-position of either ring led to the development of best candidate for malaria as compounds **5b, 5e, 5g, 5h, 5j** and **5n** were found to have EC_{50} less than 1 μg/ml. Unfortunately, 5f, substitution of both rings with chloro group didn't meet the expectation of enhanced potency and was found to be less active than above given (substitution with chloro group at one ring only) derivatives. Incorporation of methyl group along with chloro group was proven to be best match and hence **5g** was the most potent derivative among the series. Furthermore, it was also indicated that the presence of methyl group was more preferred as compared to methoxy group at *p*-position of phenyl rings. The effect of ring size was also established by replacing phenyl ring with five membered sulphur containing thienyl ring, the activity was reduced by many folds, even compound **5r**, least active among the series, belongs to this category. The complete Structure-activity relationship study regarding various substitution around arylidene derivatives suggested that *p*-position of rings should be occupied by chloro group at one ring while methyl ring at another to get remarkable antimalarial activity. The SAR study of series is depicted in Fig. 2.

3.3. In vivo antimalarial activity

No mortality was observed during acute toxicity study. At the end of study, the dose calculated for all the synthetic derivatives was 200 mg/kg. Among the synthesized analogues **5 a-r**, five most potent compounds, **5b, 5e, 5g, 5j** and **5n**, were further selected for *in vivo* antimalarial evaluation. Compounds were screened against *P. berghei* in swiss albino mice using 4-day suppressive test. Compound **5g**, bearing *p*-chloro group in one ring and *p*-methyl group in another, showed best activity with 73.38% of parasitemia inhibition. Four mice out of five were found to be alive on 7th day. Antimalarial potential displayed by 5 selected compounds has been presented in Table 2. Microscopic examination of thin smears of control group, standard (Chloroquine), **5g** (most active) and **5e** (least active) from *in vivo* study has been displayed in Fig. 3. Further the plausible route for antimalarial activity of compounds was studied through *in-silico* approach.

Table 1
In vitro antimalarial activity of synthetic derivatives **5(a-r)** against CQ-sensitive (3d7) and CQ-resistant (RKL-9) strain of *P. falciparum*.

S. No.	Compounds	Ar_1	Ar_2	EC_{50} (3D7, μg/ml)	EC_{50} (RKL-9, μg/ml)
1.	5a	C_6H_5-	C_6H_5-	1.012	3.121
2.	5b	C_6H_5-	*p*-Cl C_6H_4-	0.731	1.617
3.	5c	C_6H_5-	*p*-$CH_3C_6H_4$-	1.212	4.723
4.	5d	C_6H_5-	*p*-$OCH_3C_6H_4$-	1.230	5.123
5.	5e	*p*-Cl C_6H_4-	C_6H_5-	0.734	2.011
6.	5f	*p*-Cl C_6H_4-	*p*-Cl C_6H_4-	0.783	2.026
7.	5g	*p*-Cl C_6H_4-	*p*-$CH_3C_6H_4$-	0.423	0.824
8.	5h	*p*-Cl C_6H_4-	*p*-$OCH_3C_6H_4$-	0.791	2.114
9.	5i	*p*-$CH_3C_6H_4$-	C_6H_5-	1.501	6.726
10.	5j	*p*-$CH_3C_6H_4$-	*p*-Cl C_6H_4-	0.562	0.992
11.	5k	*p*-$CH_3C_6H_4$-	*p*-$CH_3C_6H_4$-	1.732	9.001
12.	5l	*p*-$CH_3C_6H_4$-	*p*-$OCH_3C_6H_4$-	1.621	7.992
13.	5m	*p*-$OCH_3C_6H_4$-	C_6H_5-	1.414	6.023
14.	5n	*p*-$OCH_3C_6H_4$-	*p*-Cl C_6H_4-	0.632	1.211
15.	5°	*p*-$OCH_3C_6H_4$-	*p*-$CH_3C_6H_4$-	1.536	7.231
16.	5p	*p*-$OCH_3C_6H_4$-	*p*-$OCH_3C_6H_4$-	1.801	9.373
17.	5q	2-thienyl	C_6H_5-	1.931	9.921
18.	5r	2-thienyl	*p*-$CH_3C_6H_4$-	2.672	11.451
19.	CQ	–	–	0.375	0.80

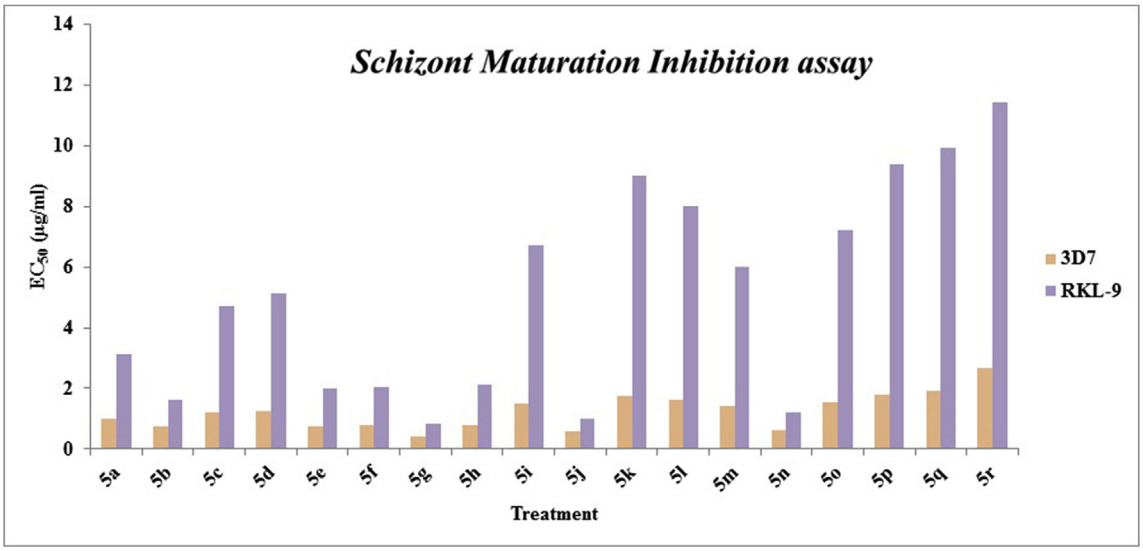


Fig. 1. EC_{50} of synthesized derivatives, **5a-r**, against 3D7 and RKL-9 of *Plasmodium falciparum*.

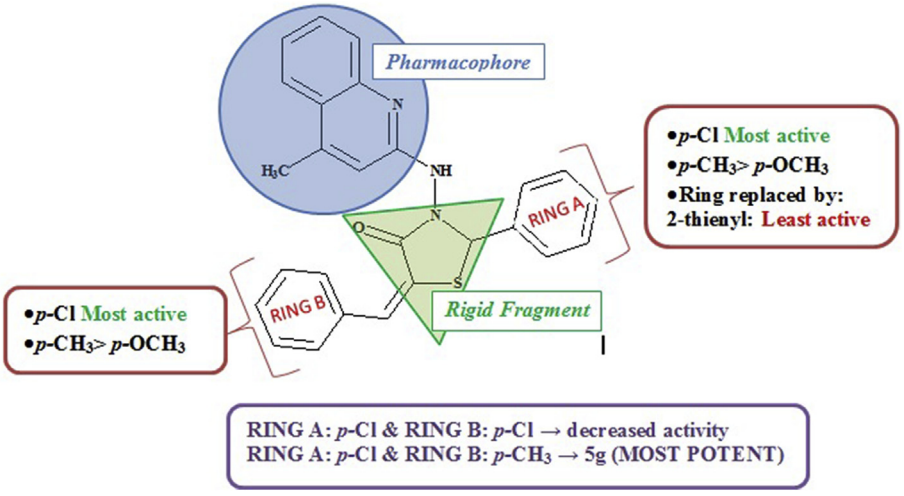


Fig. 2. Structure-Activity Relationship of Arylidene derivatives of Thiazolidinone-quinoline hybrids.

Table 2
Effect of five selected compounds on parasitemia of *P. berghei* infected mice.

S. No.	Drug treatment	Dose\kg	No. Of animals	%parasitemia	Percentage inhibition	Survival on 7th day
1.	Control	–	5	49.62 ± 0.304	–	0/5
2.	Standard	5 mg/kg	5	–	100	5/5
3.	5b	200 mg/kg[a]	5	29.43 ± 0.312	40.68**	2/5
4.	5e	200 mg/kg[a]	5	35.72 ± 0.403	28.01	3/5
5.	5g	200 mg/kg[a]	5	13.21 ± 0.126	73.38**	4/5
6.	5j	200 mg/kg[a]	5	17.34 ± 0.301	65.05**	4/5
7.	5n	200 mg/kg[a]	5	21.21 ± 0.116	57.26**	3/5

N = 5, Values are expressed as Mean ± SEM and analyze by ANOVA. **p < .01(significant). Values are compared with control group.
[a] Dose calculated by acute toxicity method.

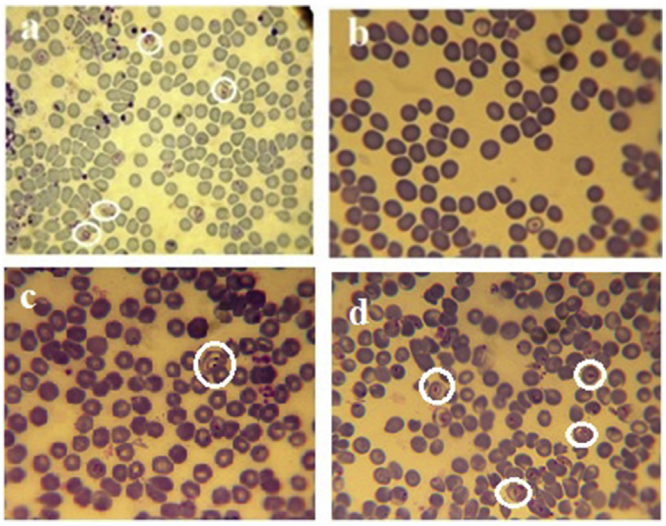


Fig. 3. Photomicrographs of blood smears of different groups showing parasitemia (encircled) (a) parasite infected RBCs in control group (b) parasitemia after treatment with standard drug, chloroquine c) parasitemia after treatment with **5g** (Most active) c) parasitemia after treatment with **5e** (Least active).

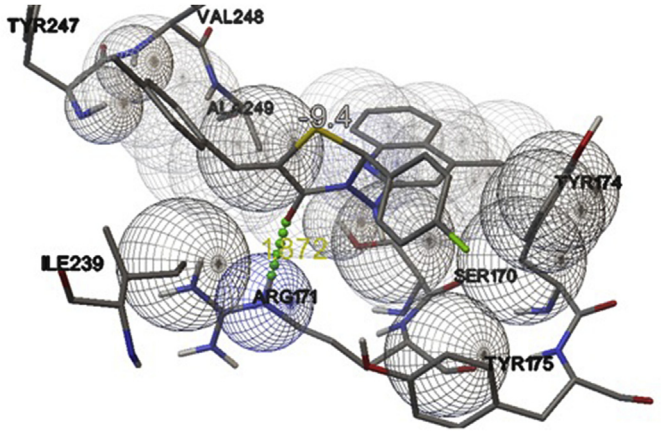


Fig. 4. Binding interaction of most potent synthesized ligand, **5g**, with active site of Lactate dehydrogenase (PDB ID: 1CET).

3.4. Docking study

Anaerobic life cycle of parasite *Plasmodium falciparum* is supported by *Plasmodium falciparum* Lactate Dehydrogenase (*Pf*LDH), being the terminal enzyme that leads the regeneration of NAD^+ from NADH for continual glycolysis. From the literature, it has been revealed that inhibition of *Pf*LDH may lead a pathway for designing of antimalarial agents and this has been illustrated in the present study by docking simulations using 1CET, *Pf* Lactate dehydrogenase enzyme complex as target protein. The docked confirmation and results of ligands in binding pocket is demonstrated in Table 3. The main amino acid residue that has played a vital role in interaction of ligands with target protein was ARG171. The biological evaluation was corroborated by *in silico* study as compound **5g** formed a stable interaction with *Pf*LDH enzyme having binding affinity −9.4 kCal/mol and hydrogen bond as well, depicted in Fig. 4. The results from docking study justified our preceding research of arylidene derivatives of quinoline-thiazolidinone hybrids as antimalarial agents.

4. Conclusion

In summary, we have synthesized novel series comprised of arylidene derivatives of quinoline-thiazolidinone hybrids, where compound **5g** exhibited promising *in vitro* antimalarial potency against both 3D7 and RKL-9 strains of *Plasmodium falciparum*. It also showed highest suppression of parasitemia against *P. berghei* during *in vivo* antimalarial screening. The present study also portrayed the utility of docking simulations to get a deep insight of interaction of synthesized scaffold with target proteins. From structure-activity relationship, **5g** may be utilised as a lead molecule for further investigation to improve their pharmacological potential. Thus, the current study serves as an encouragement for the development of new hybrids of thiazolidinone pharmacophore as antimalarial agent.

Conflicts of interest

The authors report no conflict of interest.

Table 3
Docking simulations of **5b**, **5e**, **5g**, **5j** and **5n** in active site of Lactate dehydrogenase receptor (PDB ID: 1CET).

S. No.	Compound	Dock Score (kCal/mol)	Number of hydrogen bonds	Amino Acid involved	Group of ligand involved
1.	5b	−9.0	1	ARG171	O of C=O (thiazolidinone)
2.	5e	−9.0	–	–	–
3.	5g	−9.4	1	ARG171	O of C=O (thiazolidinone)
4.	5j	−9.2	1	ARG171	O of C=O (thiazolidinone)
5.	5n	−9.2	–	–	–

Acknowledgement

The authors gratefully acknowledge financial assistance from Department of Science and Technology, New Delhi (Letter no. DST/INSPIRE Fellowship/2013/480).

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