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Original Article

SYNTHESIS AND ANTIMALARIAL ACTIVITY OF SOME NEW 3-PHENYL-2-THIOXOTHIAZOLIDIN-4-ONE DERIVATIVES

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ABSTRACT

Objective: Current therapies to treat *P. falciparum* malaria are heavily reliant on artemisinin-based combinations. However, resistance to artemisinin has recently been identified, and resistance to key artemisinin partner drugs is already widespread. Therefore, there is an urgent need for new antimalarial drugs with improved attributes over older therapies. The objective of this research work is to synthesize new antimalarial agents more effective against clinically relevant malarial strains.

Methods: In present work, a series of ten 3-phenyl-2-thioxothiazolidin-4-one (MF_1-MF_{10}) derivatives, were synthesized by Knoevenagel condensation of N-phenyl rhodanine (I_1) with substituted aromatic or hetro aromatic aldehydes using microwave irradiation. N-phenyl rhodanine (I_1) was synthesized by a conventional reaction involving methyl-2-mercaptoacetate (1) and phenyl Isothiocyanates in presence of triethylamine. All the synthesized compounds were characterized by various spectroscopic techniques and evaluated for *in-vitro* antimalarial activity by microdilution technique against resistance strains of *Plasmodium falciparum*.

Results: The antimalarial activity data showed that six compounds (MF_1, MF_3, MF_4, MF_5, MF_7 and MF_8) exhibited IC_{50} values ranging from 1.0-1.30 µg/ml, three compounds (MF_2, MF_6 and MF_{10}) displayed IC_{50} values in the range of 0.9-1.0 µg/ml. Compound MF_9 showed most significant result with maximum activity (IC_{50} = 0.85µg/ml).

Conclusion: The antimalarial activity results revealed that compound MF_9 possess potent activity and could be identified as a promising lead for further investigation.

Keywords: *P. falciparum*, 3-phenyl-2-thioxothiazolidin-4-one, Antimalarial activity

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INTRODUCTION

Malaria remains one of the most important infectious disease problems in the world, accounting for an estimated 212 million cases and up to 429 000 deaths in 2015. Malaria is caused by five species of parasites belonging to the genus *Plasmodium*. Four of these, *P. falciparum, P. vivax, P. malariae and P. ovale*–are human malaria species that are spread from one person to another via the bite of female mosquitoes of the genus Anopheles. [1] *Plasmodium falciparum* is the most lethal protozoan parasite of the genus, which is responsible for malaria complications such as cerebral malaria or severe anaemia. [2, 3] At present, no effective vaccines are available due to the high mutability of the genome of *P. falciparum*,[4] meanwhile, resistance of malaria parasites has also quickly developed to a variety of quinoline analogs (e. g., chloroquine), antifolates (e. g., sulfadoxine-pyrimethamine) and inhibitors of electron transport (e. g.,atovaquone). What's worse, resistance to artemisinin has now emerged [5, 6]. Accordingly, the discovery of new effective drugs to counter the spread of malaria parasites that are resistant to existing agents, especially acting on multi-targets, is an urgent need. The development of drug resistance has become a major health concern and has stimulated the search for alternative antimalarial agents. In this perspective rhodanine nucleus offers an alternative due to presence of wide spectrum of activities such as antibacterial [7], anti-inflammatory [8], antiviral [9, 10], antidiabetic [11], anticancer [12], tyrosinase inhibitors [8] and antimalarial [13] and are frequently associated with low toxicity and they can be considered as a privileged scaffold and an ideal framework for the design of compounds that can interact with different targets as their inherent affinity for several biological targets [14]. In present work, a series of ten new 3-phenyl-2-thioxothiazolidin-4-one (MF_1-MF_{10}) derivatives were synthesized and evaluated for their *in-vitro* antimalarial activities against resistant strain of *Plasmodium falciparum*. Herein synthesis and antimalarial activity of some new 3-phenyl-2-thioxothiazolidin-4-one derivatives is reported.

MATERIALS AND METHODS

Melting points were determined by the open capillary method and are uncorrected. The progress of the reactions was monitored by thin layer chromatography (TLC) with ethyl acetate: hexane (1:1 v/v) as eluent. TLC was carried out on precoated plates (silica gel 60, F_{254}) and visualized with UV light. Column chromatography was performed on silica gel (100-200). Anton Paar, Monowave 300, Microwave Synthesis Reactor was used for microwave-assisted synthesis. Infrared spectra were determined as KBr pellets on a Shimadzu IR affinity-1 model 1400 spectrophotometer and are expressed in cm^{-1}. ^1H NMR spectra were recorded on a Bruker's Avance-III FT NMR spectrometers using $CDCl_3$ as a solvent; chemical shifts are expressed in δ (ppm). HRMS spectral data were obtained with a Bruker micro, TOF QII high-resolution mass spectrometer and both the above analysis were performed at Indian Institute of science and research technology (IISER, Bhopal); IR analyses were performed in Department of Pharmacy, S. G. S. I. T. S., Indore M. P.

General method for synthesis of N-phenyl Rhodanine [15]

A mixture of phenyl isothiocyanate (0.11 mmol), methyl-2-mercaptoacetate (0.1 mmol) and Et_3N (0.03 mmol) in CH_2Cl_2 was stirred for 1 hour. Excess isothiocyanate was removed by amino-methylated polystyrene resin (0.015 mmol). The solution was filtered and concentrated to give N-phenyl rhodanine (I_1).

General method for Synthesis of MF_1-MF_{10}

A mixture of N-phenyl rhodanine (I_1) (0.2 mmol,), substituted aromatic/heteroaromatic aldehydes (0.2 mmol), and three drops of piperidine in absolute ethanol (5 ml) were thoroughly mixed in a glass vial (G10/G30). The reaction mixture was then heated with microwave irradiation at 100 °C for 25 min (table 1). After cooling, the solid mass was placed in 50 ml of cold ethanol and crushed ice.

The slurry was filtered to give solid mass and dried under vaccum to give corresponding MF_1 to MF_{10} derivatives.

Table 1: Experiment setting and method for microwave assisted synthesis

Step	Program	Temperature	Time	Cooling	Stirrer Speed
		°C	mm: ss		Rpm
1.	Heat as fast as possible	100	-	Off	600
2.	Hold	-	25:00	Off	600
3.	Cool down	55	0	On	600

(Z)-5-benzylidene-3-phenyl-2-thioxothiazolidin-4-one (MF_1)

Yellow crystal; IR (KBr) cm^{-1}; 3064.06 (=C-H, stretch), 2926.14 (C-H, stretch, aromatic), 1673.32 (C=O), 1611.59 (C=S), 1370.48 (C=C, aromatic), 842.93 (C-H, bend, aromatic); ^{1}H NMR ($CDCl_3$): 7.98 (s, 1H, =CH), 7.53 (d, 2H, N-Phenyl), 7.49 (d, 2H, Phenyl), 7.46 (t, 2H, N-Phenyl), 7.43 (t, 2H, Phenyl), 7.34 (t, 1H, N-Phenyl), 7.25 (t, 1H, Phenyl); HRMS (ESI^+) (m/z): [M+1], 298.

(Z)-5-(4-chlorobenzylidene)-3-phenyl-2-thioxothiazolidin-4-one (MF_2)

Yellow crystal; IR (KBr) cm^{-1}; 3017.76 (=C-H, stretch), 2923.25 (C-H, stretch, aromatic), 1716.72 (C=O), 1599.06 (C=S), 1490.07 (C=C, aromatic), 838.11 (C-H, bend, aromatic), 747.45 (C-Cl); ^{1}H NMR ($CDCl_3$): 7.65 (s, 1H, =CH), 7.54 (d, 2H, Chloro phenyl), 7.49 (d, 2H, N-Phenyl), 7.43 (d, 2H, Chloro phenyl), 7.26 (t, 3H, N-Phenyl); HRMS (ESI^+) (m/z): [M+], 332.

(Z)-5-(4-bromobenzylidene)-3-phenyl-2-thioxothiazolidin-4-one (MF_3)

Yellow crystal; IR (KBr) cm^{-1}; 3030.3 (=C-H, stretch), 2938.68 (C-H, stretch, aromatic), 1714.79 (C=O), 1594.23 (C=S), 1509.36 (C=C, aromatic), 832.32 (C-H, bend, aromatic), 737.8 (C-Br); ^{1}H NMR ($CDCl_3$): 7.92 (s, 1H, =CH), 7.55 (d, 1H, N-Phenyl), 7.49 (d, 2H, bromo phenyl), 7.33 (d, 2H, bromo phenyl), 7.31 (d, 1H, N-Phenyl), 7.25 (t, 3H, N-Phenyl); HRMS (ESI^+) (m/z): [M+], 316.

(E)-5-((1H-pyrrol-2-yl)methylene)-3-phenyl-2-thioxothiazolidin -4-one (MF_4)

Yellow crystal; IR (KBr) cm^{-1}; 3337.96 (N-H, Pyrrole) 3027.41 (=C-H, stretch), 1689.72 (C=O), 1601.95 (C=S), 1495.86 (C=C, aromatic), 814 (C-H, bend, aromatic); ^{1}H NMR ($CDCl_3$): 8.90 (s, 1H, NH-pyrrole), 7.76 (s, 1H, =CH), 7.47 (t, 3H, N-Phenyl), 7.27 (d, 2H, N-Phenyl), 7.24 (d, 2H, Pyrrole), 6.45 (t, 1H, Pyrrole); HRMS (ESI^+) (m/z): [M+1]: 287.

(E)-5-((1H-indol-2-yl)methylene)-3-phenyl-2-thioxothiazolidin-4-one (MF_5)

Yellow crystal; IR (KBr) cm^{-1}; 3280.80 (N-H, Indole), 3057.30 (=C-H, stretch), 3014.87 (C-H, stretch, aromatic), 1678.14 (C=O), 1590.38 (C=S), 1515.15 (C=C, aromatic), 829.43 (C-H, bend, aromatic), 1235.46 (C-N);^{1}H NMR ($CDCl_3$): 8.83 (s, 1H, NH-Indole), 8.16 (s, 1H, =CH), 7.57 (d, 2H, N-phenyl), 7.51 (t, 3H, N-phenyl), 7.44 (d, 2H, Indole), 7.29 (t, 2H, Indole); HRMS (ESI^+) (m/z): [M+1], 337

(Z)-5-(3-nitrobenzylidene)-3-phenyl-2-thioxothiazolidin-4-one (MF_6)

Yellow crystal; IR (KBr) cm^{-1}; 3060.20 (=C-H, stretch), 3014.87 (C-H, stretch, aromatic), 1726.36 (C=O), 1604.84 (C=S), 1537.33 (C=C, aromatic), 823.64 (C-H, bend, aromatic), 1379.16 (-NO2); ^{1}H NMR ($CDCl_3$): 8.39 (s, 1H, NO_2-phenyl), 8.28 (d, 1H, NO_2-phenyl), 7.82 (d, 1H, NO_2-phenyl), 7.79 (s, 1H, =CH), 7.68 (t, 1H, NO_2-phenyl), 7.26-7.34 (d, 2H, N-Phenyl), 7.49-7.57 (t, 3H, N-Phenyl); HRMS (ESI^+) (m/z): [M+1], 343

(E)-3-phenyl-5-(thiophen-2-ylmethylene)-2-thioxothiazolidin-4-one (MF_7)

Orange crystal; IR (KBr) cm^{-1}; 3084.31 (=C-H, stretch), 3019.69 (C-H, stretch, aromatic), 1709.97 (C=O), 1590.38 (C=S), 1496.83 (C=C, aromatic), 842.93 (C-H, bend, aromatic); ^{1}H NMR ($CDCl_3$): 7.95 (s, 1H, =CH), 7.72 (d, 1H, Thiophen), 7.56 (t, 1H, Thiophen), 7.50 (t, 3H, N-Phenyl), 7.54 (t, 1H, N-Phenyl), 7.44 (d, 2H, N-Phenyl),; HRMS (ESI^+) (m/z): [M+1], 304

(Z)-3-phenyl-5-(pyridin-2-ylmethylene)-2-thioxothiazolidin-4-one (MF_8)

Yellow crystal; IR (KBr) cm^{-1}; 3044.77 (=C-H, stretch), 2932.54 (C-H, stretch, aromatic), 1710.93 (C=O), 1607.74 (C=S), 1495.86 (C=C, aromatic), 781.20 (C-H, bend, aromatic), 1675.21 (C=N); ^{1}H NMR ($CDCl_3$): 8.79 (d, 2H, Pyridine), 7.75 (d, 2H, N-Phenyl), 7.67 (s, 1H, =CH), 7.54 (t, 2H, Pyridine), 7.47 (t, 3H, N-Phenyl); HRMS (ESI^+) (m/z): [M+1], 299.

(Z)-3-phenyl-5-(pyridin-4-ylmethylene)-2-thioxothiazolidin-4-one (MF_9)

Orange crystal; IR (KBr) cm^{-1}; 3070.81 (=C-H, stretch), 3016.8 (C-H, stretch, aromatic), 1718.85 (C=O), 1592.31 (C=S), 1543.12 (C=C, aromatic), 807.24 (C-H, bend, aromatic), 1693.57 (C=N); ^{1}H NMR ($CDCl_3$): 8.76 (d, 2H, Pyridine), 7.66 (s, 1H, =CH), 7.36 (d, 2H, Pyridine), 7.51 (t, 3H, N-Phenyl), 7.27 (d, 2H, N-Phenyl); HRMS (ESI^+) (m/z): [M+1], 299.

(Z)-5-(4-(dimethylamino)benzylidene)-3-phenyl-2-thioxothiazolidin-4-one (MF_{10})

Orange crystal; IR (KBr) cm^{-1}; 3083.34 (=C-H, stretch), 2924.21 (C-H, stretch, aromatic), 1735.04 (C=O), 1684.89 (C=S), 1583.63 (C=C, aromatic), 841 (C-H, bend, aromatic); ^{1}H NMR ($CDCl_3$): 7.89 (s, 1H, =CH), 7.47 (d, 2H, N-Phenyl), 7.43 (t, 3H, N-Phenyl), 7.32 (d, 2H, Phenyl), 7.24 (d, 2H, Phenyl), 3.06 (s, 6H CH_3); HRMS (ESI^+) (m/z): [M+1] 341.

***Invitro* antimalarial evaluation**

Assay protocol

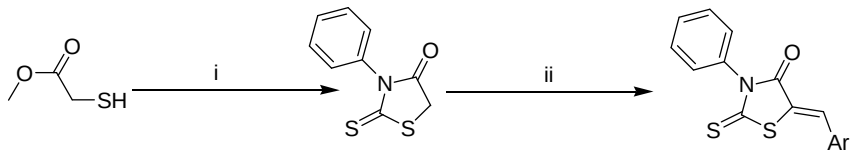
All the synthesized compounds were screened for *in vitro* antimalarial activity at Microcare laboratory and TRC, Surat, Gujarat. The *in vitro* antimalarial assay was carried out in 96 well microtiter plates according to the microassay protocol of Rieckmann and co-workers with minor modifications. All the cultures of *P. falciparum* strains were maintained in medium RPMI1640 supplemented with 25m MHEPES, 1% D-glucose, 0.23% sodium bicarbonate and 10% heat-inactivated human serum. The asynchronous parasites of *P. falciparum* were synchronized after 5% D-sorbitol treatment to obtain only the ring stage parasitized cells. For carrying out the assay, an initial ring stage parasitaemia of 0.8 to 1.5% at 3% haematocrit in a total volume of 200 µl of medium RPMI-1640 was determined by samples, prepared in DMSO and their subsequent dilutions were prepared with culture Jaswant Singh Bhattacharya (JSB) staining to assess the percent parasitaemia (rings) and maintained with 50 % RBCs (O+). A stock solution of 5 mg/ml of each of the test samples was prepared in DMSO and subsequent dilutions were prepared with culture medium, then diluted samples were added to the test wells so as to obtain final concentrations ranging between 0.4µg/ml-100µg/ml in duplicate well-containing parasite cell preparation. The culture plates were incubated at 37 °C in a candle jar, after 36-40 h of incubation; thin blood smear slides were prepared from each well and stained with JSB stain. The slides were observed under a microscope to record maturation of ring stage parasites into trophozoites and schizonts in presence of different concentrations of the test agents. The test concentration which inhibited the complete maturation into schizonts was recorded as the IC_{50} value of test compounds.

RESULTS AND DISCUSSION

Chemistry

The 3-phenyl-2-thioxothiazolidin-4-one (MF_1-MF_{10}) derivatives describe in present research work are shown in table 2. N-Phenyl Rhodanine (1) was synthesized by reacting methyl thioglycolate with phenyl isothiocyanate at room temperature as outlined in scheme 1.

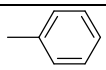
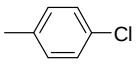
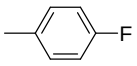
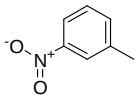
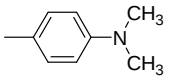
The intermediates 1 upon Knoevenagel condensation with suitably substituted aromatic/hetro aromatic aldehydes under microwave heating condition in presence of piperidine produced 3-phenyl-2-thioxothiazolidin-4-one (MF_1-MF_{10}) derivatives. This reaction generated a double bond that produced E and Z isomers. Similar analogs are reported to exist predominantly as Z-isomers. [8, 16] it is presumed that the derivatives synthesised here are mainly Z-isomers.



Methyl-2-mercaptoacetate (1) N-Phenyl Rhodanine (I_1) MF_1-MF_{10}

Scheme 1: Reagents and Conditions (i) Phenyl Isothiocynates, TEA, CH_2Cl_2, rt, 1h; (ii) Piperidine, ethanol, MW,100 °C, 25 Min

Table 2: Structure, molecular formula, molecular weight, % yield, melting point and antimalarial activity (IC_{50}µg/ml) of MF_1-F_{10} derivatives

Comp. code	Substituent Ar	Molecular Formula	Molecular Weight	Melting Point °C	% yield	IC_{50} µg/ml
MF_1		$C_{16}H_{11}NOS_2$	297.39	200-202	78	1.16
MF_2		$C_{16}H_{10}ClNOS_2$	331.84	160-162	80	0.90
MF_3		$C_{16}H_{10}FNOS_2$	315.39	180-182	80	1.28
MF_4		$C_{14}H_{10}N_2OS_2$	286.37	240-242	76	1.14
MF_5		$C_{18}H_{12}N_2OS_2$	336.43	220-222	82	1.22
MF_6		$C_{16}H_{10}N2O_3S_2$	342.39	206-208	75	0.98
MF_7		$C_{14}H_9NOS_3$	303.42	226-228	78	1.06
MF_8		$C_{15}H_{10}N_2OS_2$	298.38	224-226	80	1.15
MF_9		$C_{15}H_{10}N_2OS_2$	298.38	194-196	80	0.85
MF_{10}		$C_{18}H_{16}N_2OS_2$	340.46	234-236	82	0.94
CQ	-	-	-	-	-	0.020
Quinine	-	-	-	-	-	0.268

Antimalarial activity

All the compounds were screened for intra-erythrocytic *in vitro* antimalarial activity against resistance strains of *Plasmodium falciparum* by using chloroquine and quinine as reference drugs. The results of antimalarial activity are summarised in table 2. Among the ten evaluated compounds, six compounds exhibited IC_{50} values ranging from 1.0-1.30 (MF_1, MF_3, MF_4, MF_5, MF_7, MF_8), three compounds displayed IC_{50} values in the range of 0.9-1.0 (MF_1, MF_6, MF_{10}). The compound MF_9 showed the most significant result with maximum activity (IC_{50} = 0.85µg/ml). Variations of the different substituent on the aromatic ring and replacement of aromatic ring with heterocyclic ring have been explored to ascertain the structure-activity relationship among the synthesised compounds. With reference to the compound MF_1 (IC_{50}: 1.16 µg/ml) substitution with chloro (compound MF_2, IC_{50}: 0.9 µg/ml) or N, N, dimethyl (compound MF_{10}, IC_{50}: 0.94µg/ml) at para position of phenyl ring appeared to potentiate antimalarial activity while fluoro (compound MF_3, IC_{50}: 1.28 µg/ml) appeared to marginal reduction in activity. Compounds with 3-nitro (compound MF_6, IC_{50}: 0.76 µg/ml) substitutions on phenyl ring leads to a marginal increase in potency compared to unsubstituted compound MF_1. Substitution phenyl ring in Compound MF_1 by 2-pyridine/4-pyridine appeared to potentiate antimalarial activity and by Indole (compound MF_5, IC_{50}: 1.22 µg/ml) leads to a slight reduction in potency. Replacement of phenyl ring with a heterocyclic ring like Pyrrole (compound MF_4, IC_{50}: 1.14µg/ml) shows a moderate increase in an activity whereas in the case of Thiophen (compound MF_7, IC_{50}: 1.06 µg/ml) leads to significant increase in antimalarial activity.

CONCLUSION

There is an urgent need for discovery of new and effective antimalarial agents after widespread development of resistance to currently available antimalarial drugs. As part of our research, we have synthesized a series of ten 3-phenyl-2-thioxothiazolidin-4-one (MF_1-MF_{10}) derivatives, by Knoevenagel condensation of N-phenyl rhodanine (I_1) with substituted aromatic or hetro aromatic aldehydes using microwave irradiation. After spectral confirmation, all the compounds were screened for invitro antimalarial activity against resistant strain of *plasmodium falciparum*. One compound MF_9 showed most significant result with maximum activity (IC_{50} = 0.85µg/ml), thus it could be useful as a structural lead for future development of novel antimalarial molecules.

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CONFLICTS OF INTERESTS

Authors have none to declare

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