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 (MF1-MF10) derivatives, were synthesized by Knoevenagel condensation of  N-phenyl rhodanine (I) with substituted aromatic or hetero aromatic aldehydes using microwave irradiation. N-phenyl rhodamine (I) was synthesized by a conventional reaction involving methyl-2-mercaptoacetate (I) and phenyl isothiocyanate 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 strains of Plasmodium falciparum.

Results: The antimalarial activity data showed that six compounds (MF1, MF2, MF3, MF4, MF9, and MF10) exhibited IC50 values ranging from 1.0-1.30 µg/ml, three compounds (MF2, MF3, and MF9) displayed IC50 values in the range of 0.9-1.0 µg/ml. Compound MF10 showed most significant result with maximum activity (IC50 = 0.85 µg/ml).

Conclusion: The antimalarial activity results revealed that compound MF10 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

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 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.

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, F254) 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). H NMR spectra were recorded on a Bruker’s Advance-III FT NMR spectrometers using CDCl3 as a solvent; chemical shifts are expressed in (δ ppm). HRMS spectral data were obtained with a Bruker micro, TOP 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,N (0.03 mmol) in CH2Cl2 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 rhodamine (I).

General method for Synthesis of MF1-MF10

A mixture of N-phenyl rhodanine (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,

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

**Table 1: Experiment setting and method for microwave assisted synthesis**

(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=C), 1611.59 (C=S), 1270.48 (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-Pheny), 7.43 (t, 2H, Phenyl), 7.34 (t, 1H, N-Phenyl), 7.25 (t, 1H, Phenyl); HRMS (ESI$^+$) (m/z): [M+1$^+$], 304.

(Z)-3-phenyl-5-(pyridin-2-ylmethylene)-2-thioxothiazolidin-4-one (MF$_3$)

Yellow crystal; IR (KBr) cm$^{-1}$: 3044.77 (=C-H, stretch), 2932.54 (C-H, stretch, aromatic), 1710.93 (C=C), 1495.86 (C=C, aromatic), 1781.20 (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$_4$)

Orange crystal; IR (KBr) cm$^{-1}$: 3070.81 (=C-H, stretch), 3016.83 (C-H, stretch, aromatic), 1718.85 (C=C), 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 (t, 2H, N-Phenyl); HRMS (ESI$^+$) (m/z): [M+1$^+$], 299.

(Z)-5-(4-(dimethylamino)benzylidene)-3-phenyl-2-thioxothiazolidin-4-one (MF$_5$)

Orange crystal; IR (KBr) cm$^{-1}$: 3083.34 (=C-H, stretch), 2924.21 (C-H, stretch, aromatic), 1735.94 (C=C), 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, 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.

**In vitro 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 Rickmann 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% FBS. The synchronous parasites of *P. falciparum* were prepared from each well and stained with JSB’s stain. The slides were air-dried and mounted under coverslips in VWR antifade. 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 IC$_{50}$ value of test compounds.
RESULTS AND DISCUSSION

Chemistry

The 3-phenyl-2-thioxothiazolidin-4-one (MF₁-MF₁₀) 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/hetero aromatic aldehydes under microwave heating condition in presence of piperidine produced 3-phenyl-2-thioxothiazolidin-4-one (MF₁-MF₁₀) 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 synthesized here are mainly Z-isomers.

![Scheme 1: Reagents and Conditions](image)

Table 2: Structure, molecular formula, molecular weight, % yield, melting point and antimalarial activity (IC₅₀µg/ml) of MF₁-MF₁₀ derivatives

| Comp. code | Substituent Ar | Molecular Formula | Molecular Weight | Melting Point °C | % Yield | IC₅₀ µg/ml |
|------------|----------------|-------------------|------------------|-----------------|---------|------------|
| MF₁ |  | C₁₀H₁₇NOS₂ | 297.39 | 200-202 | 78 | 1.16 |
| MF₂ | Cl | C₁₀H₁₆ONOS₂ | 331.94 | 160-162 | 80 | 0.90 |
| MF₃ | F | C₁₄H₁₃FNOS₂ | 315.39 | 180-182 | 80 | 1.28 |
| MF₄ | | C₁₄H₁₃N₂OS₂ | 286.37 | 240-242 | 76 | 1.14 |
| MF₅ | | C₁₀H₁₇N₂O₂S₂ | 336.43 | 220-222 | 82 | 1.22 |
| MF₆ | O | C₁₀H₁₇N₂O₂S₂ | 342.39 | 206-208 | 75 | 0.98 |
| MF₇ | | C₁₀H₁₇NOS₂ | 303.42 | 226-228 | 78 | 1.06 |
| MF₈ | | C₁₀H₁₇N₂O₂S₂ | 298.38 | 224-226 | 80 | 1.15 |
| MF₉ | | C₁₀H₁₇N₂O₂S₂ | 298.38 | 194-196 | 80 | 0.85 |
| MF₁₀ | CH₃ | C₁₀H₁₇N₂O₂S₂ | 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 IC₅₀ values ranging from 1.0-1.30 (MF₁, MF₉, MF₁₀, MF₁₀, MF₁₀). three compounds displayed IC₅₀ values in the range of 0.5-1.0 (MF₁, MF₂, MF₁₀). The compound MF₁₀ showed the most significant result with maximum activity (IC₅₀ = 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 MF₁ (IC₅₀: 1.16 µg/ml) substitution with chloro (compound MF₂, IC₅₀: 0.9 µg/ml) or N, N dimethyl (compound MF₁₀, IC₅₀: 0.94µg/ml) at para position of phenyl ring appeared to potentiate antimalarial activity while fluoro (compound MF₁₀, IC₅₀: 1.28 µg/ml) appeared to marginal reduction in activity. Compounds with 3-nitro (compound MF₁₀, IC₅₀: 0.76 µg/ml) substitutions on phenyl ring leads to a marginal increase in potency compared to unsubstituted compound MF₁. Substitution phenyl ring in Compound MF₁, by 2-pyridine/4-pyridine appeared to potentiate antimalarial activity and by Indole (compound MF₁₀, IC₅₀: 1.22 µg/ml) leads to a slight reduction in potency. Replacement of phenyl ring with a heterocyclic ring like Pyrrole (compound MF₁₀, IC₅₀: 1.14µg/ml) shows a moderate increase in an activity whereas in the case of Thiophen (compound MF₁₀, IC₅₀: 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\textsubscript{1}-MF\textsubscript{10}) derivatives, by Knoevenagel condensation of N-phenyl rhodanine (I\textsubscript{1}) with substituted aromatic or heteroaromatic 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\textsubscript{9} showed most significant result with maximum activity (IC\textsubscript{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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