

THIAZOLIDIN-4-ONE DERIVATIVES: SYNTHESIS AND *IN VITRO* ANTIMALARIAL EVALUATION¹*Rakesh Kumar and ²Shailendra Patil¹Vaish Institute of Pharmaceutical Education and Research, Rohtak-124001.²SVN Institute of Pharmaceutical Sciences, Swami Vivekanand University, Sagar- 470003.***Corresponding Author: Rakesh Kumar**

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Article Received on 09/08/2017

Article Revised on 29/08/2017

Article Accepted on 19/09/2017

ABSTRACT

A series of thiazolidin-4-one derivatives (TH1-T9) was synthesized and evaluated for their antimalarial potential. Antimalarial activity was performed against the Plasmodium falciparum. Among the synthesized derivatives, compound 6 was found to be most active against Plasmodium falciparum. All the titled compounds (TH1-T9) were characterized by ¹H NMR and IR spectral data.

KEYWORDS: 4-Thiazolidinone, Hydrazone, Antimalarial activity.**INTRODUCTION**

Malaria is one of the most serious infectious diseases in tropical and subtropical regions. At least 300 million people are afflicted and 1–3 million people die from this disease annually.^[1]

Despite decades of fighting malaria, the disease is gaining ground as the parasite's resistance to drugs and the parasite-carrying mosquito's resistance to insecticides expands. The increasing spread of malaria together with the emergence of resistance against conventional drugs has put enormous pressure on public health systems to introduce new malaria treatments. Quinoline containing compounds are still attractive models for treatment of malaria. The success of the antimalarial aminoquinoline drug, chloroquine (CQ), has been based on its excellent clinical efficacy, limited host toxicity, ease to use and simple cost-effective synthesis. However, the use of this drug has been seriously eroded in recent years, mainly as a result of the development of parasite resistance to CQ. Amodiaquine (AQ), another drug based on 7-chloro-4-aminoquinoline nucleus, is effective against many CQ-resistant strains of Plasmodium falciparum.^[2]

4-Thiazolidinone scaffold and its derivatives have attracted considerable attention of medicinal chemists and have become an important class of heterocyclic compounds because of their diverse biological activities such as antimicrobial,^[3-5] anticancer,^[6-7] antimycobacterial,^[8-9] analgesic and anti-inflammatory,^[10-11] antioxidant activities.^[12] These works prompted us to synthesize the novel derivatives of 4-thiazolidinone and evaluation their antimalarial activity.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Sonar melting point apparatus and are uncorrected. ¹H nuclear magnetic resonance (¹H NMR) spectra were determined by Bruker Avance II 400 NMR spectrometer in appropriate deuterated solvents and are expressed in parts per million (δ , ppm) downfield from tetramethylsilane (internal standard). NMR data are given as multiplicity (s, singlet; d, doublet; t, triplet; m, multiplet) and number of protons. Infrared (IR) spectra were recorded on a Perkin Elmer FTIR spectrometer. Starting materials were obtained from commercial sources and were used without further purification. Reaction progress was observed by thin layer chromatography making use of commercial silica gel plates (Merck). All the synthesized titled derivatives have been evaluated for their antimalarial activity

Chemistry

A series of novel 4-thiazolidinone have been synthesized. The reaction between *p*-Nitro acetophenone, thiourea and iodine yielded the corresponding 4-(4-nitrophenyl)thiazol-2-amine (**2**) which on reaction with required aromatic aldehydes afforded the corresponding hydrazone of 4-(4-nitrophenyl)-thiazol-2-amine (**3**) in appreciable yield. Further the hydrazone were condensed with required amount of thioglycolic acid to yield 2-substituted 4thiazolidinones (**4**). In the next step 2-disubstituted-4-thiazolidinone was reacted with aromatic aldehydes (0.01 M) and anhydrous sodium acetate in glacial acetic acid yielded title compounds (TH1-TH9) (**5**).

General procedure of 4-thiazolidinone derivatives**Synthesis of 4-(4-nitrophenyl)thiazol-2-amine**

p-Nitro acetophenone, (0.01m), thiourea (0.02m) and iodine (0.01 m) were dissolved in appropriate amount of ethanol and refluxed for 8 hours on a heating mantle. The reaction mixture was then cooled and poured on to the crushed ice and NaOH solution (10%) was added. The solid thus acquired was filtered, washed with water, and the product was recrystallized from rectified spirit. The purity of the sample was tested by TLC using the solvent system petroleum ether and ethyl acetate 8:2.^[13]

Synthesis of hydrazone of 4-(4-nitrophenyl)-thiazol-2-amine

A mixture of (0.025 M) 4-(4-nitrophenyl)thiazol-2-amine was refluxed for about 2 hours with required amount of aldehydes (0.025 M) and methanol in the presence of a catalytic amount of glacial acetic acid. The solid thus acquired was filtered, washed with water, and the product was recrystallized from rectified spirit to give the corresponding hydrazones.

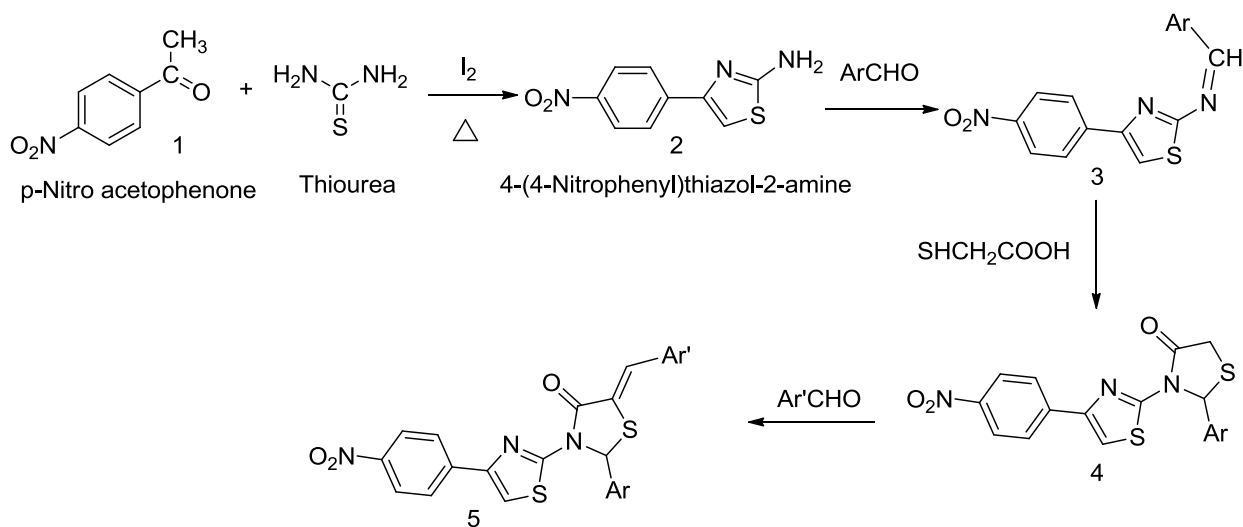
Synthesis of 2-disubstituted-4-thiazolidinone

A mixture of (0.015 M) hydrazone of 4-(4-nitrophenyl)-thiazol-2-amine and required amount of thioglycolic acid (0.015 M) in DMF was refluxed for about 6 h, containing a pinch of anhydrous ZnCl₂. The reaction mixture was cooled and poured on to crushed ice. The solid thus acquired was filtered, washed with water, and the product was recrystallized from rectified spirit to obtain the titled derivatives.^[4]

Synthesis of 2,5-disubstituted-4-thiazolidinone

A mixture of (0.01 M) 2-substituted-4-thiazolidinone required aromatic aldehydes (0.01 M) and anhydrous sodium acetate in glacial acetic acid (20 ml) and refluxed for 5–7 h. After cooling, the solution was poured on crushed ice to precipitate the product. The product was recrystallized from rectified spirit.^[4]

Synthetic pathway for preparation of title 4-thiazolidinone derivatives is shown in Scheme 1. Physical and analytical data of synthesized derivatives are presented in Table 1.



2,5-Disubstituted-4-thiazolidinone (TH1-TH9)

Scheme 1

Table 1: Physical data of title compounds (TH1-TH9).

Comp. no.	Ar	Ar'	Molecular Formula	Molecular Weight	Melting Points(°C)	%Yields	R _f
TH1	C ₆ H ₅	2-NO ₂ C ₆ H ₄	C ₂₅ H ₁₆ N ₄ O ₅ S ₂	516.55	198-200	78.21	0.67
TH2	C ₆ H ₅	4-ClC ₆ H ₄	C ₂₅ H ₁₆ ClN ₃ O ₃ S ₂	506.00	207-209	75.33	0.62
TH3	C ₆ H ₅	2-ClC ₆ H ₄	C ₂₅ H ₁₆ ClN ₃ O ₃ S ₂	506.00	188–190	84.11	0.62
TH4	C ₆ H ₅	3-NO ₂ C ₆ H ₄	C ₂₅ H ₁₆ N ₄ O ₅ S ₂	516.55	203-205	79.11	0.60
TH5	2-NO ₂ C ₆ H ₄	2-NO ₂ C ₆ H ₄	C ₂₅ H ₁₅ N ₅ O ₇ S ₂	561.55	271-272	68.25	0.68
TH6	2-NO ₂ C ₆ H ₄	3-OCH ₃ C ₆ H ₄	C ₂₆ H ₁₈ N ₄ O ₆ S ₂	546.57	235–237	67.28	0.45
TH7	2-ClC ₆ H ₄	C ₆ H ₅	C ₂₅ H ₁₆ ClN ₃ O ₃ S ₂	506.00	173-175	67.01	0.61
TH8	2-ClC ₆ H ₄	3-BrC ₆ H ₄	C ₂₅ H ₁₅ BrClN ₃ O ₃ S ₂	584.89	222-224	71.14	0.75
TH9	2-ClC ₆ H ₄	4-OCH ₃ C ₆ H ₄	C ₂₆ H ₁₈ ClN ₃ O ₄ S ₂	536.02	225-227	73.12	0.56

Solvent system chloroform: benzene: glacial acetic acid (3:1:1).

Spectral Data

(Z)-5-(2-nitrobenzylidene)-3-(4-(4-nitrophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (1): IR (KBr, cm^{-1}): 3146 (C-H Ar), 1742 (C=O), 1649(C=C Ar), 1622 (C=N), 1519 (NO₂), 1421 (C-N), 670(C-S); ¹H NMR (DMSO-*d*₆, 400 MHz): 8.99-7.11 (m, 13H, ArH), 7.70 (s, 1H, CH), 6.81 (s, 1H, CH, thiazole), 6.79 (s, 1H, CH, thiazolidinone).

(Z)-5-(4-chlorobenzylidene)-3-(4-(4-nitrophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (2): IR (KBr, cm^{-1}): 3119 (C-H Ar), 1715 (C=O), 1649(C=C Ar), 1622 (C=N), 1519 (NO₂), 1419 (C-N), 736(Cl), 667(C-S); ¹H NMR (DMSO-*d*₆, 400 MHz): 8.45-7.56 (m, 13H, ArH), 7.59 (s, 1H, CH), 6.72 (s, 1H, CH, thiazole), 6.69 (s, 1H, CH, thiazolidinone).

(Z)-5-(2-chlorobenzylidene)-3-(4-(4-nitrophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (3): IR (KBr, cm^{-1}): 3007 (C-H Ar), 1749 (C=O), 1697(C=C Ar), 1639 (C=N), 1575 (NO₂), 1458 (C-N), 724(Cl), 629(C-S); ¹H NMR (DMSO-*d*₆, 400 MHz): 7.89-7.13 (m, 13H, ArH), 7.39 (s, 1H, CH), 7.12 (s, 1H, CH, thiazole), 6.84 (s, 1H, CH, thiazolidinone).

(Z)-5-(3-nitrobenzylidene)-3-(4-(4-nitrophenyl)thiazol-2-yl)-2-phenylthiazolidin-4-one (4): IR (KBr, cm^{-1}): 3010 (C-H Ar), 1723 (C=O), 1629(C=C Ar), 1602 (C=N), 1577 (NO₂), 1470 (C-N), 676(C-S); ¹H NMR (DMSO-*d*₆, 400 MHz): 8.55-7.19 (m, 13H, ArH), 7.37 (s, 1H, CH), 7.84 (s, 1H, CH, thiazole), 6.77 (s, 1H, CH, thiazolidinone).

(Z)-5-(2-nitrobenzylidene)-2-(2-nitrophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (5): IR (KBr, cm^{-1}): 3002 (C-H Ar), 1670(C=C Ar), 1588 (C=N), 1566 (NO₂), 1425 (C-N), 685(C-S); ¹H NMR (DMSO-*d*₆, 400 MHz): 7.84-7.21 (m, 12H, ArH), 7.36 (s, 1H, CH), 6.90 (s, 1H, CH, thiazole), 6.76 (s, 1H, CH, thiazolidinone).

(Z)-5-(3-methoxybenzylidene)-2-(2-nitrophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (6): IR (KBr, cm^{-1}): 3077 (C-H Ar), 1688 (C=O), 1636(C=C Ar), 1602 (C=N), 1549(NO₂), 1411 (C-N), 1281 (C-O-C str), 693(C-S); ¹H NMR (DMSO-*d*₆, 400 MHz): 8.69-7.00 (m, 12H, ArH), 7.23 (s, 1H, CH), 6.55 (s, 1H, CH, thiazole), 6.50 (s, 1H, CH, thiazolidinone), 3.81 (s, 3H, -OCH₃).

(Z)-5-benzylidene-2-(2-chlorophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (7): IR (KBr, cm^{-1}): 3079 (C-H Ar), 1701 (C=O), 1639(C=C Ar), 1602 (C=N), 1519 (NO₂), 1400 (C-N), 711(Cl), 668(C-S); ¹H NMR (DMSO-*d*₆, 400 MHz): 7.72-6.38 (m, 13H, ArH), 7.29 (s, 1H, CH), 6.17 (s, 1H, CH, thiazole), 5.58 (s, 1H, CH, thiazolidinone).

(Z)-5-(3-bromobenzylidene)-2-(2-chlorophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (8): IR (KBr, cm^{-1}): 3012 (C-H Ar), 1739 (C=O), 1692(C=C Ar),

1649 (C=N), 1539 (NO₂), 1416 (C-N), 723(Cl), 666(C-S) 631(Br); ¹H NMR (DMSO-*d*₆, 400 MHz): 7.62-7.35 (m, 12H, ArH), 7.50 (s, 1H, CH), 7.10 (s, 1H, CH, thiazole), 7.07 (s, 1H, CH, thiazolidinone).

(Z)-5-(4-methoxybenzylidene)-2-(2-chlorophenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)thiazolidin-4-one (9): IR (KBr, cm^{-1}): 3030 (C-H Ar), 1602 (C=N), 1506 (NO₂), 1457 (C-N), 744(Cl), 627(C-S); ¹H NMR (DMSO-*d*₆, 400 MHz): 9.36-7.20 (m, 12H, ArH), 7.16 (s, 1H, CH), 6.92 (s, 1H, CH, thiazole), 6.72 (s, 1H, CH, thiazolidinone), 3.47 (s, 3H, -OCH₃).

Biological Evaluations**Evaluation of Antimalarial activity****Determination of Minimum Inhibitory Concentration Screening of compounds using fluorescence based assay for antimalarial activity**

Cultivation of Plasmodium falciparum and plate setup: Prior to the experiment, the parasites were cultivated by the method of Trager and Jensen.^[14] Cultures were maintained in fresh group B-positive human erythrocytes suspended at 2% hematocrit in RPMI 1640 containing 10% human serum, 3 g of glucose per liter, 45 g of hypoxanthine per liter, and 50 g of gentamicin per liter. Flasks were incubated with 5% CO₂ at 37°C. Every 3 to 4 days, infected erythrocytes were transferred into fresh complete medium with uninfected erythrocytes (subculture). The stock culture was synchronized with 5% sorbitol and then after approximately 96 h, the level of parasitemia was determined by light microscopy by counting of a minimum of 500 erythrocytes on a Giemsa-stained thin blood smear. Parasites were noted to be late-ring and early trophozoites, with no evident schizonts. The stock culture was then diluted with complete medium and normal human erythrocytes to a starting 4% hematocrit and 0.5% parasitemia. For each test drug, plates for assay method were prepared in parallel with the same cells and medium. Stock solutions of the test drugs were prepared at a concentration of 10 mg/ml (DMSO), serially diluted in complete medium, and dispensed into triplicate test wells to yield final concentrations. Final well volume was 200µl for the fluorescence assay. The plates were then incubated. Antimalarial potential are shown in Table-2.

Table 2: Antimalarial potential of the Title Compounds (T1-T9).

Compounds	EC ₅₀ (µg)
1	16.23
2	8.39
3	15.05
4	6.06
5	6.57
6	5.01
7	9.94
8	14.68
9	10.56
Standard Drug(Primaquine)	33.09

RESULT AND DISCUSSION

All the synthesized thiazolidin-4-one derivatives were evaluated for their Antimalarial potential against *Plasmodium falciparum*. Primaquine was taken as standard drug for antimalarial activity. The newly synthesized compounds were characterized by IR and ¹H NMR analyses. The results revealed that all synthesized compounds have a significant biological activity against the *Plasmodium falciparum*. Among the synthesized derivatives, compound 6 was found to be most active against *Plasmodium falciparum*.

CONCLUSION

In conclusion, a series of thiazolidin-4-one derivatives (TH1-T9) was synthesized and evaluated for their antimalarial potential. Antimalarial potential against *Plasmodium falciparum*. Data obtained was found to be in good agreement with the calculated values of the proposed structure. Most of the synthesized compounds exhibited moderate to significant antimalarial activity.

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