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SYNTHESIS, SPECTRAL CHARACTERIZATION AND IN VITRO ANTIMALARIAL EVALUATION OF NOVEL QUINOLINE-BASED THIAZOLIDIN-4-ONE DERIVATIVES

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ABSTRACT

A series of novel quinoline-based thiazolidin-4-one derivatives were synthesized through a three-step synthetic pathway involving nucleophilic substitution, Schiff base formation and cyclization reactions. Initially, 4-chloroquinoline was converted into 4-hydrazinylquinoline by reaction with hydrazine hydrochloride under reflux conditions. The obtained hydrazine derivative was condensed with various substituted aromatic aldehydes to afford Schiff base intermediates. Finally, cyclization of these intermediates with thioglycolic acid in the presence of anhydrous aluminium chloride produced the desired 2-substituted phenyl-3-(quinolin-4-ylamino)thiazolidin-4-one derivatives. The synthesized compounds were purified by recrystallization and characterized by suitable analytical techniques. The developed synthetic route was found to be simple, efficient and suitable for preparing structurally diverse quinoline-thiazolidinone hybrids.

KEYWORDS: Quinoline, Thiazolidin-4-one, Schiff base, Heterocyclic compounds and antimalarial.

1. INTRODUCTION

Malaria remains one of the most serious vector-borne infectious diseases worldwide and continues to impose a significant public health burden, particularly in tropical and subtropical regions. According to the World Health Organization (WHO), hundreds of millions of malaria cases are reported annually with the majority occurring in Africa and Southeast Asia. Despite substantial progress in malaria control programs, the emergence and spread of drug-resistant *Plasmodium falciparum* strains have considerably reduced the effectiveness of conventional antimalarial drugs. Consequently, the discovery and development of novel antimalarial agents possessing improved efficacy, safety and resistance profiles remain a major objective in medicinal chemistry and pharmaceutical research.[1,2]

Heterocyclic compounds constitute one of the most important classes of organic molecules because of their remarkable structural diversity and wide spectrum of biological activities. The incorporation of nitrogen, sulfur and oxygen atoms into cyclic systems often enhances biological activity by improving molecular recognition and interactions with biological macromolecules. Numerous heterocyclic compounds have demonstrated antibacterial, antifungal, antiviral, anti-inflammatory, antioxidant, antiparasitic, antitubercular and anticancer properties. As a result, heterocyclic chemistry has become a cornerstone of modern drug discovery and development.[3,4]

Among nitrogen-containing heterocyclic compounds, quinoline occupies a prominent position because of its broad range of pharmacological activities and its presence in several clinically important therapeutic agents. Quinoline is a fused bicyclic aromatic heterocycle consisting of a benzene ring condensed with a pyridine ring. Since the discovery of quinine from the bark of *Cinchona* species, quinoline derivatives have been extensively investigated for their medicinal applications. Numerous marketed drugs, including chloroquine, hydroxychloroquine, amodiaquine, primaquine and mefloquine contain the quinoline

nucleus and have played a crucial role in the treatment and prevention of malaria.[5,6]

In addition to their well-established antimalarial activity, quinoline derivatives have demonstrated significant antibacterial, antifungal, antiviral, antitubercular, anti-inflammatory, antioxidant, antiproliferative and anticancer properties. The biological versatility of the quinoline scaffold is attributed to its planar aromatic structure, favourable physicochemical properties and ability to interact with multiple biological targets through hydrogen bonding, π–π stacking and hydrophobic interactions. These characteristics make quinoline one of the most extensively explored privileged scaffolds in medicinal chemistry.[7–9]

Recent advances in synthetic organic chemistry have facilitated the preparation of structurally diverse quinoline derivatives with enhanced pharmacological profiles. Structural modification of the quinoline nucleus through the introduction of various electron-donating and electron-withdrawing substituents has been shown to influence biological activity, selectivity and pharmacokinetic behaviour. Consequently, quinoline-based molecular hybrids have attracted increasing attention as promising candidates for the development of next-generation antimicrobial and antimalarial agents.[10,11]

Another important class of biologically active heterocyclic compounds is thiazolidin-4-one, which has attracted considerable interest because of its broad spectrum of pharmacological activities. Structurally, thiazolidin-4-one is a five-membered heterocyclic ring containing one sulphur atom, one nitrogen atom and a carbonyl group. The presence of these heteroatoms imparts unique physicochemical and biological properties, making thiazolidin-4-one an important pharmacophore in medicinal chemistry. Numerous studies have demonstrated that thiazolidin-4-one derivatives exhibit antimicrobial, antifungal, antitubercular, anticonvulsant, antioxidant, anti-inflammatory, antiviral, anticancer, antidiabetic and antiparasitic activities. Because of their diverse biological profile, thiazolidin-4-one derivatives continue to receive considerable attention as potential therapeutic agents for the treatment of various infectious and non-infectious diseases.[12–15]

The synthesis of thiazolidin-4-one derivatives is commonly achieved through the cyclization of Schiff bases with thioglycolic acid under acidic catalysed conditions. This synthetic methodology is widely employed because of its simplicity, high efficiency and ability to accommodate a broad range of aromatic substituents. The resulting thiazolidinone derivatives often exhibit improved biological activity owing to the presence of both sulphur and nitrogen atoms within the heterocyclic framework. Consequently, incorporation of the thiazolidin-4-one nucleus into biologically active molecules has become an important strategy in medicinal chemistry research.[16,17]

Schiff bases are another important class of compounds extensively used as intermediates in organic synthesis. These compounds contain the characteristic azomethine(–CH=N–) functional group and are generally synthesized by condensation of primary amines or hydrazine with aldehydes or ketones. Apart from their synthetic utility, Schiff bases themselves possess a variety of biological activities including antimicrobial, antifungal, antiviral, antioxidant, anti-inflammatory, antitubercular and antimalarial activities. Furthermore, Schiff bases readily undergo cyclization reactions with thioglycolic acid to produce thiazolidin-4-one derivatives making them valuable intermediates in heterocyclic synthesis.[18–20]

In recent years, molecular hybridization has emerged as an effective approach for the development of novel therapeutic agents. This strategy involves combining two or more biologically active pharmacophores into a single molecular framework with the aim of improving biological activity, selectivity and pharmacokinetic properties. The hybridization of quinoline and thiazolidin-4-one scaffolds is particularly attractive because both pharmacophores individually possess significant antimalarial activity. Their combination is expected to produce synergistic effects and generate compounds with enhanced potency against *Plasmodium* species while reducing the likelihood of drug resistance.[10,11,21]

Although a number of quinoline derivatives and thiazolidin-4-one analogues have been reported in the literature studies on quinoline–thiazolidin-4-one hybrid molecules containing different substituted phenyl rings remain comparatively limited, particularly with respect to their antimalarial evaluation against *Plasmodium falciparum*. Moreover, the influence of various electron-donating and electron-withdrawing substituents on the biological activity of these hybrid molecules has not been systematically investigated. Therefore, there is a continuing need to synthesize structurally diverse quinoline-based thiazolidin-4-one derivatives and evaluate their biological potential.[22–23]

Based on these observations, the present investigation was undertaken to synthesize a series of novel 2-substituted phenyl-3-(quinolin-4-ylamino)thiazolidin-4-one derivatives through a three-step synthetic route involving nucleophilic substitution, Schiff base formation and cyclization with thioglycolic acid. The synthesized compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry. Further the antimalarial activity of the synthesized derivatives was evaluated in vitro against the chloroquine-sensitive *Plasmodium falciparum* 3D7 strain using the SYBR Green I fluorescence assay with chloroquine as the reference standard. The findings of this study may

contribute to the development of new quinoline-based antimalarial agents with improved biological efficacy.

2. MATERIALS AND METHODS

2.1 Materials

All chemicals and reagents used in the present investigation were of analytical reagent grade and were used without further purification unless otherwise specified. 4-Chloroquinoline, hydrazine hydrochloride, substituted aromatic aldehydes, thioglycolic acid, anhydrous aluminium chloride, glacial acetic acid, absolute ethanol, 1,4-dioxane, ethyl acetate, n-hexane and dimethylformamide (DMF) were procured from standard commercial suppliers and used as received. The purity of the synthesized compounds was monitored by thin-layer chromatography (TLC) using silica gel 60 F254 precoated aluminium plates. The spots were visualized under ultraviolet light at 254 nm.

2.2 Instrumentation

Melting points of the synthesized compounds were determined by the open capillary method and are uncorrected. FT-IR spectra were recorded using the KBr pellet technique and are expressed in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 using tetramethylsilane (TMS) as the internal standard and the chemical shifts are reported in δ (ppm). Mass spectra were recorded using an electrospray ionization mass spectrometer (ESI-MS). The progress of all reactions and the purity of the synthesized compounds were monitored by TLC using suitable solvent systems.

2.3 Chemistry

2.3.1 Synthesis of 4-Hydrazinylquinoline

A mixture of 4-chloroquinoline (0.01 mol) and hydrazine hydrochloride (0.012 mol) was dissolved in 30 mL of absolute ethanol in a 100 mL round-bottom flask fitted with a reflux condenser. The reaction mixture was refluxed for 4 h with continuous stirring. The progress of the reaction was monitored by TLC using ethyl acetate:n-hexane (3:7). After completion, the reaction mixture was cooled to room temperature and poured onto crushed ice. The precipitated solid was filtered, washed with cold water, dried and recrystallized from ethanol to obtain 4-hydrazinylquinoline.

2.3.2 General Procedure for the Synthesis of 4-(2-Benzylidenehydrazinyl)quinoline Derivatives

Equimolar quantities of 4-hydrazinylquinoline (0.01 mol) and substituted aromatic aldehydes (0.01 mol) were dissolved in absolute ethanol. A few drops of glacial acetic acid were added as a catalyst. The reaction mixture was refluxed for 4 h with continuous stirring. The reaction progress was monitored by TLC using ethyl acetate:n-hexane (4:6). After completion, the reaction mixture was cooled and the precipitated Schiff bases were filtered, washed with cold ethanol, dried and recrystallized from ethanol.

2.3.3 General Procedure for the Synthesis of 2-Substituted Phenyl-3-(quinolin-4-ylamino)thiazolidin-4-one Derivatives

The appropriate Schiff base (0.01 mol) was dissolved in 30 mL of 1,4-dioxane. Thioglycolic acid (0.012 mol) and anhydrous aluminium chloride (0.5 g) were added to the reaction mixture, which was refluxed for 12 h. Reaction completion was monitored by TLC using ethyl acetate:n-hexane (5:5). After completion, the reaction mixture was cooled and poured into crushed ice. The precipitated product was filtered, washed thoroughly with water, dried and purified by recrystallization from ethanol.

2.4 Antimalarial Activity

The synthesized compounds were evaluated for their in vitro antimalarial activity against the chloroquine-sensitive *Plasmodium falciparum* 3D7 strain using the SYBR Green I fluorescence assay, following a reported protocol with minor modifications.[24,25]

Briefly, synchronized cultures of *P. falciparum* were maintained in human O^{+} erythrocytes suspended in RPMI-1640 medium supplemented with human serum under standard culture conditions. Stock solutions of the synthesized compounds were prepared in DMSO and serially diluted to obtain the desired test concentrations. Equal volumes of parasite suspension and test compound solutions were transferred to 96-well microplates and incubated at 37°C in a controlled gaseous atmosphere for 72 h.

Following incubation, SYBR Green I lysis buffer was added to each well and the plates were incubated in the dark for approximately 1 h. Fluorescence intensity was measured using a fluorescence microplate reader at appropriate excitation and emission wavelengths. The percentage inhibition of parasite growth was calculated by comparison with untreated controls, and the IC_{50} values were determined using nonlinear regression analysis. Chloroquine was used as the reference antimalarial drug in all experiments.

<Scheme-1>

3. RESULTS AND DISCUSSION

3.1 Chemistry

A series of novel 2-substituted phenyl-3-(quinolin-4-ylamino)thiazolidin-4-one derivatives (3a–3m) were synthesized through the synthetic route illustrated in Scheme 1. The synthesis was accomplished in three consecutive steps involving nucleophilic substitution, Schiff base formation and cyclization.

Initially, 4-chloroquinoline underwent nucleophilic substitution with hydrazine hydrochloride to afford 4-hydrazinylquinoline in good yield. The successful conversion was confirmed by TLC and further supported by spectroscopic analysis. Subsequently, condensation of the hydrazine intermediate with various substituted aromatic aldehydes in ethanol containing catalytic glacial

acetic acid furnished the corresponding Schiff base intermediates. The formation of Schiff bases was indicated by the disappearance of the aldehydic proton and the appearance of the characteristic azomethine (–CH=N–) functionality. Finally, cyclization of the Schiff bases with thioglycolic acid in the presence of anhydrous aluminium chloride in 1,4-dioxane yielded the desired quinoline-based thiazolidin-4-one derivatives.

The reactions proceeded smoothly under reflux conditions and afforded the target compounds in satisfactory yields. The progress of each reaction was monitored by TLC, and the final products were purified by recrystallization from ethanol or ethanol–DMF. The synthesized compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometry, confirming the proposed structures. Similar synthetic methodologies have been successfully employed for the preparation of biologically active thiazolidinone derivatives reported in the literature.[12,16,17,26]

3.2 Spectral Characterization

2-phenyl-3-(quinolin-4-ylamino)thiazolidin-4-one(3a)

Chemical Formula: C18H15N3OS ; Yellow Crystalline solid; Yield 82 %; M.P. 198-202 °C; IR ν cm-1: 3406.60(N-H str), 3021.86(aromatic C-H str), 1700.55(C=O str), 1579.44(C=N, quinoline); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 10.603(s, 1H, NH), 8.482-7.548 (m,6H, quinoline), 7.480-6.962 (m, 5H, Ar-H), 4.042 (s,1H, CH thiazolidinone), 3.739-3.680 (m, 2H, CH_2 thiazolidinone); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 171.36 (C=O), 149.69-117.56 (aromatic carbons); 63.91(CH); 42.08(CH_2); ESI–MS: m/z calculated 321.1, found $[M+H]^+$ 322.1

2-(2-nitrophenyl)-3-(quinolin-4-ylamino)thiazolidin-4-one (3b)

Chemical Formula: C18H14N4O3S ; Yellow Crystalline solid; Yield 80 %; M.P. 214-216 °C; IR ν cm-1: 3410.40(N-H str), 3028.26(aromatic C-H str), 1710.35(C=O str), 1585.65(C=N, quinoline); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 10.621(s, 1H, NH), 8.542-7.568 (m,6H, quinoline), 8.180-7.242 (m, 4H, Ar-H), 4.082 (s,1H, CH thiazolidinone), 3.759-3.681 (m, 2H, CH_2 thiazolidinone); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 171.42 (C=O), 149.82-118.16 (aromatic carbons); 64.18(CH); 42.15(CH_2); ESI–MS: m/z calculated 366.1, found $[M+H]^+$ 367.1

2-(3-nitrophenyl)-3-(quinolin-4-ylamino)thiazolidin-4-one (3c)

Chemical Formula: C18H14N4O3S ; Yellow Crystalline solid; Yield 82 %; M.P. 221-223 °C; IR ν cm-1: 3410.46(N-H str), 3028.47(aromatic C-H str), 1710.86(C=O str), 1585.14(C=N, quinoline); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 10.625(s, 1H, NH), 8.545-7.571 (m,6H, quinoline), 8.184-7.246 (m, 4H, Ar-H), 4.086 (s,1H, CH thiazolidinone), 3.763-3.685 (m, 2H, CH_2 thiazolidinone); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 171.45 (C=O), 149.89-118.22 (aromatic carbons); 64.24(CH); 42.23(CH_2); ESI–MS: m/z calculated 366.1, found $[M+H]^+$ 367.1

2-(4-nitrophenyl)-3-(quinolin-4-ylamino)thiazolidin-4-one (3d)

Chemical Formula: C18H14N4O3S ; Bright Yellow solid; Yield 84 %; M.P. 228-230 °C; IR ν cm-1: 3411.21(N-H str), 3028.77(aromatic C-H str), 1710.72(C=O str), 1585.90(C=N, quinoline); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 10.615(s, 1H, NH), 8.535-7.557 (m,6H, quinoline), 8.172-7.238 (m, 4H, Ar-H), 4.071 (s,1H, CH thiazolidinone), 3.762-3.687 (m, 2H, CH_2 thiazolidinone); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 171.51 (C=O), 149.92-118.27 (aromatic carbons); 64.29(CH); 42.27(CH_2); ESI–MS: m/z calculated 366.1, found $[M+H]^+$ 367.1

2-(2-chlorophenyl)-3-(quinolin-4-ylamino)thiazolidin-4-one (3e)

Chemical Formula: C18H14ClN3OS; Yellow Crystalline solid; Yield 80%; M.P. 194-196°C; IR ν cm-1: 3403.60(N-H str), 3053.03(aromatic C-H str), 2923.60(aliphatic C-H str), 1710.99(C=O str), 1574.75(C=N, quinoline); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 10.413(s, 1H, NH), 8.984-7.850 (m,6H, quinoline), 7.697-7.384 (m, 4H, Ar-H), 4.003 (s,1H, CH thiazolidinone), 3.813-3.617 (m, 2H, CH_2 thiazolidinone); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 169.64 (C=O), 135.15-117.97 (aromatic carbons); 62.61(CH); 42.69(CH_2); ESI–MS: m/z calculated 355.1, found $[M+H]^+$ 356.1(^{35}Cl), 357.6(^{37}Cl).

2-(3-chlorophenyl)-3-(quinolin-4-ylamino)thiazolidin-4-one (3f)

Chemical Formula: C18H14ClN3OS ; White Crystalline solid; Yield 83 %; M.P. 201-203 °C; IR ν cm-1: 3403.25(N-H str), 3053.55(aromatic C-H str), 2923.85(aliphatic C-H str), 1710.75(C=O str), 1574.10(C=N, quinoline); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 10.417(s, 1H, NH), 8.988-7.854 (m,6H, quinoline), 7.690-7.389 (m, 4H, Ar-H), 4.010 (s,1H, CH thiazolidinone), 3.818-3.625 (m, 2H, CH_2 thiazolidinone); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 169.68 (C=O), 135.19-118.02 (aromatic carbons); 62.67(CH); 42.72(CH_2); ESI–MS: m/z calculated 355.1, found $[M+H]^+$ 356.1(^{35}Cl), 357.6(^{37}Cl).

2-(4-chlorophenyl)-3-(quinolin-4-ylamino)thiazolidin-4-one (3g)

Chemical Formula: C18H14ClN3OS; Yellow Crystalline solid; Yield 85 %; M.P. 206-208 °C; IR ν cm-1: 3403.82(N-H str), 3053.25(aromatic C-H str), 2923.72(aliphatic C-H str), 1710.47(C=O str), 1574.96(C=N, quinoline); ^{1}H NMR (400 MHz, DMSO-d6) δ (ppm): 10.415(s, 1H, NH), 8.985-7.852 (m,6H, quinoline), 7.698-7.385 (m, 4H, Ar-H), 4.004 (s,1H, CH thiazolidinone), 3.814-3.618 (m, 2H, CH_2 thiazolidinone); ^{13}C NMR (100 MHz, DMSO-d6) δ

(ppm): 169.72 (C=O), 135.24-118.10 (aromatic carbons); 62.71(CH); 42.76(CH_2); ESI–MS: m/z calculated 355.1, found $[M+H]^+$ 356.1(^{35}Cl), 357.6(^{37}Cl).

2-(2-hydroxyphenyl)-3-(quinolin-4-ylamino)thiazolidin-4-one (3h)

Chemical Formula: C18H15N3O2S ; Yellow Crystalline solid; Yield 81 %; M.P. 218-220°C; IR ν cm-1: 3402.60(N-H str, phenolic OH str), 3007.27(aromatic C-H str), 1716.67(C=O str), 1577.88(C=C/C=N, quinoline); ^1H NMR (400 MHz, DMSO-d6) δ (ppm): 12.487(br-s, 1H, phenolic OH), 11.131(s, 1H, NH), 8.482-7.390 (m,6H, quinoline), 7.283-6.905 (m, 4H, Ar-H), 3.714 (s,1H, CH thiazolidinone), 3.338 (m, 2H, CH_2 thiazolidinone); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 169.63 (C=O), 135.35-117.92 (aromatic carbons); 62.21(CH); 42.89(CH_2); ESI–MS: m/z calculated 337.1, found $[M+H]^+$ 338.1.

2-(3-hydroxyphenyl)-3-(quinolin-4-ylamino)thiazolidin-4-one (3i)

Chemical Formula: C18H15N3O2S; White Crystalline solid; Yield 85 %; M.P. 225-227 °C; IR ν cm-1: 3402.35(N-H str, phenolic OH str), 3007.02(aromatic C-H str), 1716.45(C=O str), 1577.63(C=C/C=N, quinoline); ^1H NMR (400 MHz, DMSO-d6) δ (ppm): 12.497(br-s, 1H, phenolic OH), 11.141(s, 1H, NH), 8.492-7.397 (m,6H, quinoline), 7.293-6.915 (m, 4H, Ar-H), 3.724 (s,1H, CH thiazolidinone), 3.348 (m, 2H, CH_2 thiazolidinone); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 169.66 (C=O), 135.38-117.95 (aromatic carbons); 62.24(CH); 42.92(CH_2); ESI–MS: m/z calculated 337.1, found $[M+H]^+$ 338.1

2-(4-hydroxyphenyl)-3-(quinolin-4-ylamino)thiazolidin-4-one (3j)

Chemical Formula: C18H15N3O2S; White Crystalline solid; Yield 86 %; M.P. 232-234 °C; IR ν cm-1: 3402.85(N-H str, phenolic OH str), 3007.52(aromatic C-H str), 1716.92(C=O str), 1577.99(C=C/C=N, quinoline); ^1H NMR (400 MHz, DMSO-d6) δ (ppm): 12.492(br-s, 1H, phenolic OH), 11.136(s, 1H, NH), 8.489-7.395 (m,6H, quinoline), 7.290-6.912 (m, 4H, Ar-H), 3.721 (s,1H, CH thiazolidinone), 3.345 (m, 2H, CH_2 thiazolidinone); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 169.69 (C=O), 135.41-117.98 (aromatic carbons); 62.27(CH); 42.95(CH_2); ESI–MS: m/z calculated 337.1, found $[M+H]^+$ 338.1

2-(2-methoxyphenyl)-3-(quinolin-4-ylamino)thiazolidin-4-one (3k)

Chemical Formula: C19H17N3O2S ; White Crystalline solid; Yield 80 %; M.P. 182-184 °C; IR ν cm-1: 3377.12(N-H str), 3025.62(aromatic C-H str), 2875.32(aliphatic C-H str, -OCH3), 1715.42(C=O str), 1585.25(C=C/C=N, quinoline); ^1H NMR (400 MHz, DMSO-d6) δ (ppm): 10.536(s, 1H, NH), 8.489-7.595 (m,6H, quinoline), 7.313-6.912 (m, 4H, Ar-H), 4.021 (s,1H, CH thiazolidinone),3.824(s, 3H, OCH_3) 3.747-3.632 (m, 2H, CH_2 thiazolidinone); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 169.75 (C=O), 139.35-117.95 (aromatic carbons); 62.31(CH), 55.71(OCH_3), 42.85(CH_2); ESI–MS: m/z calculated 351.1, found $[M+H]^+$ 352.1

2-(4-methoxyphenyl)-3-(quinolin-4-ylamino)thiazolidin-4-one (3l)

Chemical Formula: C19H17N3O2S; Yellow Crystalline solid; Yield 85 %; M.P. 188-190 °C; IR ν cm-1: 3377.24(N-H str), 3025.24(aromatic C-H str), 2875.18(aliphatic C-H str, -OCH3), 1715.33(C=O str), 1585.87(C=C/C=N, quinoline); ^1H NMR (400 MHz, DMSO-d6) δ (ppm): 10.522(s, 1H, NH), 8.476-7.545 (m,6H, quinoline), 7.341-6.953 (m, 4H, Ar-H), 4.0242(s,1H, CH thiazolidinone),3.872(s, 3H, OCH_3) 3.753-3.685(m, 2H, CH_2 thiazolidinone); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 169.79 (C=O), 139.39-117.99 (aromatic carbons); 62.35(CH), 55.75(OCH_3), 42.89(CH_2); ESI–MS: m/z calculated 351.1, found $[M+H]^+$ 352.1

2-(3-bromophenyl)-3-(quinolin-4-ylamino)thiazolidin-4-one (3m)

Chemical Formula: C18H14BrN3OS; White Crystalline solid; Yield 79 %; M.P. 209-211°C IR ν cm-1: 3423.60(N-H str), 3053.03(aromatic C-H str), 2923.60(aliphatic C-H str), 1700.99(C=O str), 1575.94(C=N, quinoline), 548.03(C-Br str); ^1H NMR (400 MHz, DMSO-d6) δ (ppm): 10.813(s, 1H, NH), 8.404-7.696 (m,6H, quinoline), 7.600-7.299 (m, 4H, Ar-H), 4.005 (s,1H, CH thiazolidinone), 3.781-3.614 (m, 2H, CH_2 thiazolidinone); ^{13}C NMR (100 MHz, DMSO-d6) δ (ppm): 169.61 (C=O), 132.51-118.02 (aromatic carbons); 64.86(CH); 45.99(CH_2); ESI–MS: m/z calculated 399.0, found $[M+H]^+$ 400.1(^{79}Br), 402.1(^{81}Br).

General Spectral Discussion

The structures of the synthesized quinoline-thiazolidin-4-one derivatives were established by FT-IR, ^1H NMR, ^{13}C NMR and mass spectrometry. FT-IR spectra of all compounds exhibited characteristic absorption bands corresponding to the carbonyl (C=O) group of the thiazolidin-4-one ring around 1700–1720 cm^{-1}, confirming successful cyclization. The broad absorption band observed around 3400 cm^{-1} was assigned to N–H stretching vibration, whereas aromatic C–H stretching vibrations appeared around 3020–3060 cm^{-1}. The characteristic C=N stretching vibration of the quinoline nucleus was observed between 1570 and 1625 cm^{-1}, while C–S stretching vibrations appeared in the fingerprint region.

In the ^1H NMR spectra, aromatic protons resonated within the expected region of δ 6.8–9.0 ppm, whereas the methylene protons of the thiazolidinone ring appeared as characteristic signals around δ 3.5–4.0 ppm. The NH proton appeared as a downfield singlet owing to

hydrogen bonding. Compounds containing hydroxyl and methoxy substituents exhibited additional characteristic resonances corresponding to OH and OCH_3 groups, respectively.

The ^{13}C NMR spectra displayed the carbonyl carbon signal around δ 169–171 ppm, while aromatic carbons resonated between δ 115 and 160 ppm. The methylene carbon of the thiazolidinone ring appeared around δ 40–45 ppm, confirming successful ring formation.

Mass spectrometry showed molecular ion peaks corresponding to the calculated molecular weights of the synthesized compounds, providing additional confirmation of the proposed molecular structures.[18,28]

3.3 In Vitro Antimalarial Activity

The synthesized quinoline-thiazolidin-4-one derivatives were evaluated in vitro against the chloroquine-sensitive *Plasmodium falciparum* 3D7 strain using the SYBR Green I fluorescence assay. Chloroquine served as the reference standard. The antimalarial activity results are summarized in Table 2.

All synthesized derivatives exhibited measurable inhibitory activity with IC_{50} values ranging from 0.66 to 1.18 µM, indicating that the quinoline-thiazolidinone framework possesses significant antimalarial potential.

Among the synthesized compounds, the unsubstituted derivative (3a) exhibited the highest activity with an IC_{50} value of 0.66 µM. The 3-bromo derivative (3m) also demonstrated excellent potency (0.68 µM), followed closely by the 4-hydroxy (3j, 0.69 µM) and 2-hydroxy (3h, 0.72 µM) analogues. The 4-methoxy derivative (3l) showed good inhibitory activity with an IC_{50} value of 0.74 µM, while the 4-chloro derivative (3g) exhibited an IC_{50} value of 0.76 µM.

Compounds containing 3-hydroxy, 4-nitro, 2-methoxy, and 3-chloro substituents showed moderate antimalarial activity. In contrast, the 2-nitro derivative (3b) displayed the lowest potency (IC_{50} = 1.18 µM), indicating that ortho nitro substitution is unfavorable for antimalarial activity within this series.

Overall, the synthesized quinoline-thiazolidinone derivatives exhibited encouraging antimalarial activity and provide a useful foundation for further structural optimization.

3.4 Structure–Activity Relationship (SAR)

The biological evaluation demonstrated that the antimalarial activity of the synthesized compounds was strongly influenced by the nature and position of substituents on the phenyl ring.

The unsubstituted derivative (3a) exhibited the greatest activity, indicating that the quinoline-thiazolidinone core itself is highly effective against *P. falciparum*. Introduction of a bromine atom at the meta position (3m) further maintained excellent activity, suggesting that this substitution pattern is favourable.

Hydroxyl-substituted derivatives, particularly 4-OH and 2-OH exhibited higher activity than the corresponding nitro-substituted analogues. This enhancement may be attributed to the ability of hydroxyl groups to participate in hydrogen-bonding interactions with biological targets thereby improving binding affinity.

Among the methoxy derivatives, 4-OCH_3 displayed greater potency than 2-OCH_3, indicating that para substitution is more favourable than ortho substitution. A similar trend was observed for chloro-substituted compounds, where the 4-Cl derivative showed better activity than the 2-Cl and 3-Cl analogues.

Conversely, nitro substitution generally reduced biological activity, with the 2-NO_2 derivative being the least active compound of the series. This observation suggests that strongly electron-withdrawing groups at the ortho position may negatively influence molecular target interactions.

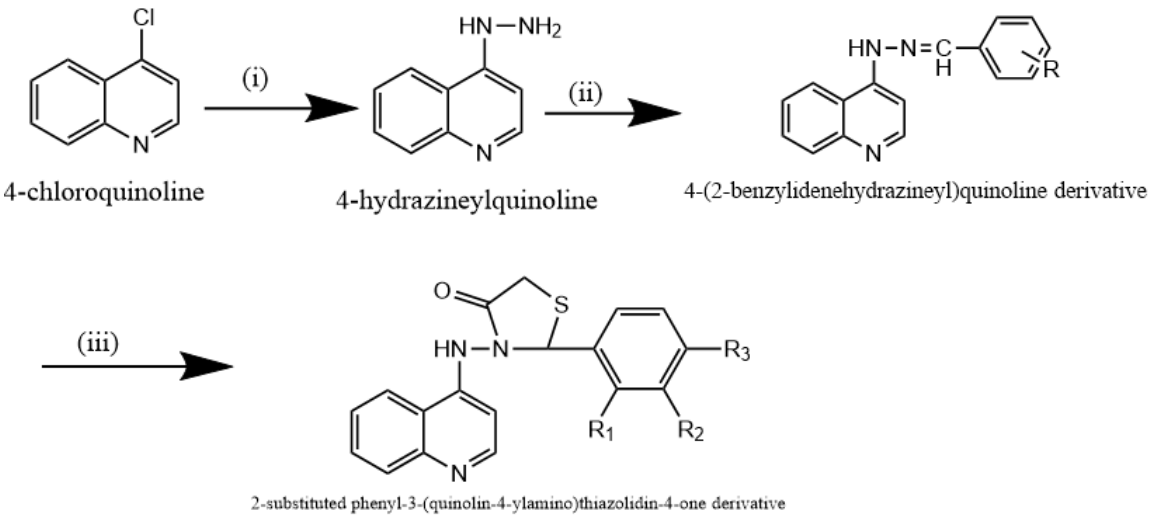
These findings demonstrate that subtle structural modifications significantly influence antimalarial activity and provide useful guidance for the design of more potent quinoline-thiazolidinone hybrids.

3.5 Comparison with Reported Literature

Previous studies have established that both quinoline derivatives and thiazolidin-4-one analogues possess promising antimalarial properties.[5,14,22,29] The present study further supports these observations by demonstrating that hybridization of these two pharmacologically important scaffolds results in compounds with encouraging activity against the chloroquine-sensitive *P. falciparum* 3D7 strain.

The observed activity of hydroxyl, methoxy and bromine-substituted derivatives highlights the importance of substituent selection in optimizing biological activity. These findings are consistent with reports indicating that appropriate aromatic substitution can significantly influence the physicochemical properties and biological efficacy of quinoline-based antimalarial agents.[6,11,23]

Scheme-1



(i) N_2H_4/H_2O, Ethanol, 4h Reflux
(ii) substituted Benzaldehyde, gla.HAc, Ethanol, 4h Reflux
(iii) $HSCH_2COOH$, Anhy $AlCl_3$ in 1,4 Dioxane, 12h Reflux

Scheme 1: Synthetic route for the preparation of quinoline-based thiazolidin-4-one derivatives.

Table-1

Compound	R	Molecular Formula	Mol. Wt. (g/mol)	Yield (%)†	M.P. (°C)
3a	H	C18H15N3OS	321.40	82	198-202
3b	2-NO_2	C18H14N4O3S	366.40	80	214-216
3c	3-NO_2	C18H14N4O3S	366.40	82	221-223
3d	4-NO_2	C18H14N4O3S	366.40	84	228-230
3e	2-Cl	C18H14ClN3OS	355.84	80	164-196
3f	3-Cl	C18H14ClN3OS	355.84	83	201-203
3g	4-Cl	C18H14ClN3OS	355.84	85	206-208
3h	2-OH	C18H15N3O2S	337.40	81	218-220
3i	3-OH	C18H15N3O2S	337.40	85	225-227
3j	4-OH	C18H15N3O2S	337.40	86	232-234
3k	2-OCH_3	C19H17N3O2S	351.42	80	182-184
3l	4-OCH_3	C19H17N3O2S	351.42	85	188-190
3m	3-Br	C18H14BrN3OS	400.29	79	209-211

Table-2

DERIVATIVE	Compound	Mean IC50 (µg/mL) Anti malarial P. falciparum
H	3a	0.66
2 NO2	3b	1.18
3 NO2	3c	0.98
4 NO2	3d	0.84
2 Cl	3e	1.05
3 Cl	3f	0.91
4 Cl	3g	0.76
2 OH	3h	0.72
3 OH	3i	0.81
4 OH	3j	0.69
2 OCH3	3k	0.87
4 OCH3	3l	0.74
3 Br	3m	0.68

Table 2. In vitro antimalarial activity of synthesized compounds against *Plasmodium falciparum* 3D7.

ABBREVIATIONS

FT-IR	Fourier Transform Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
ESI-MS	Electrospray Ionization Mass Spectrometry
TLC	Thin Layer Chromatography
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
RPMI	Roswell Park Memorial Institute Medium
IC_{50}	Half Maximal Inhibitory Concentration
SAR	Structure–Activity Relationship

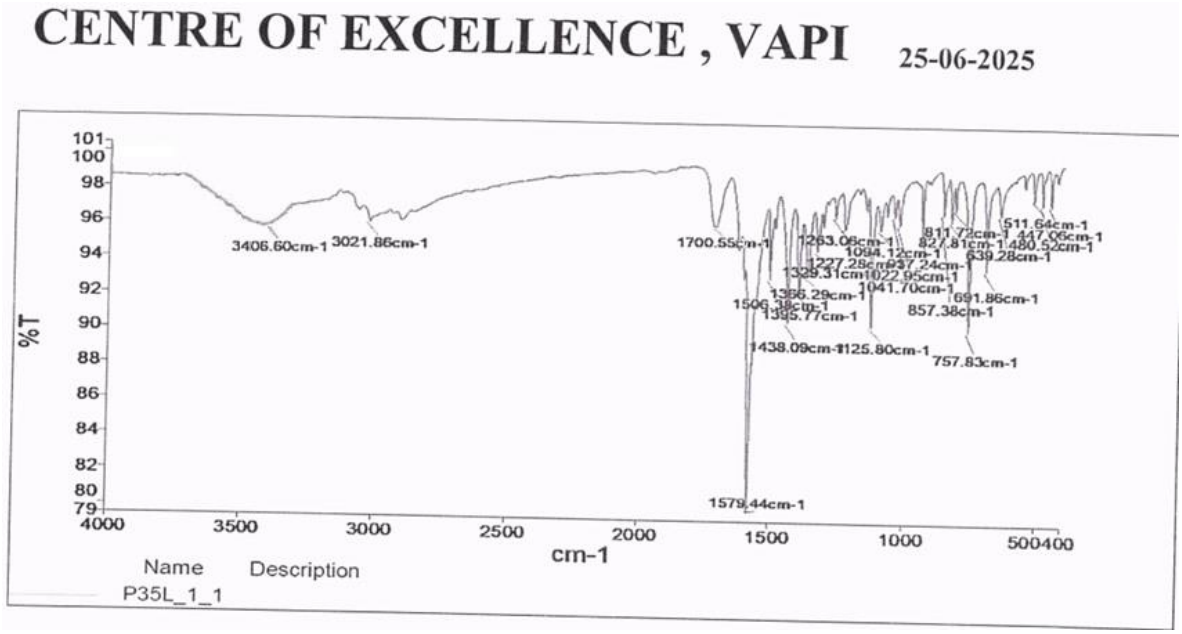


Figure 1: FT-IR spectrum of representative synthesized compound.

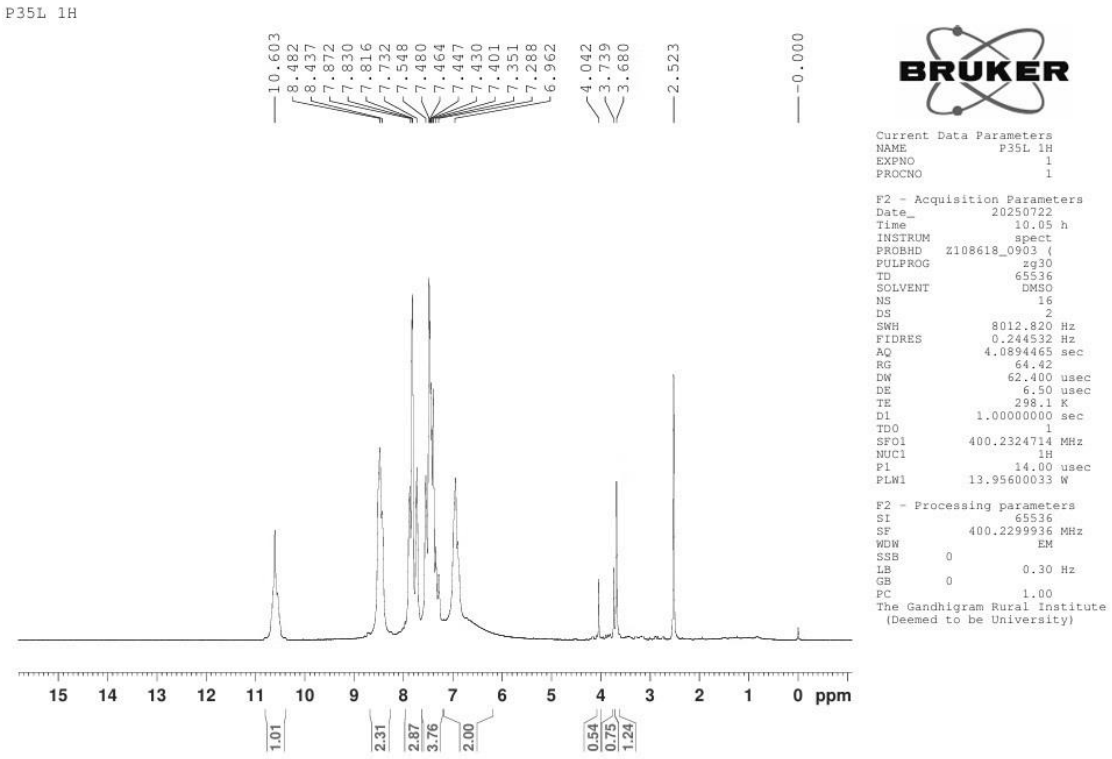


Figure 2: ^{1}H NMR spectrum of representative synthesized compound.

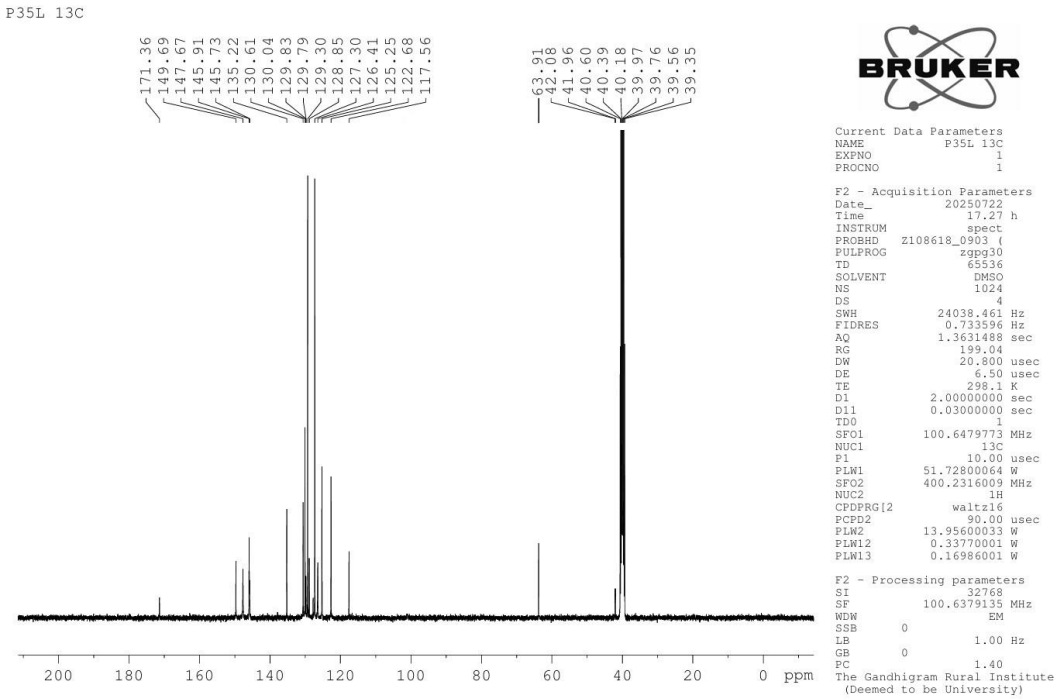
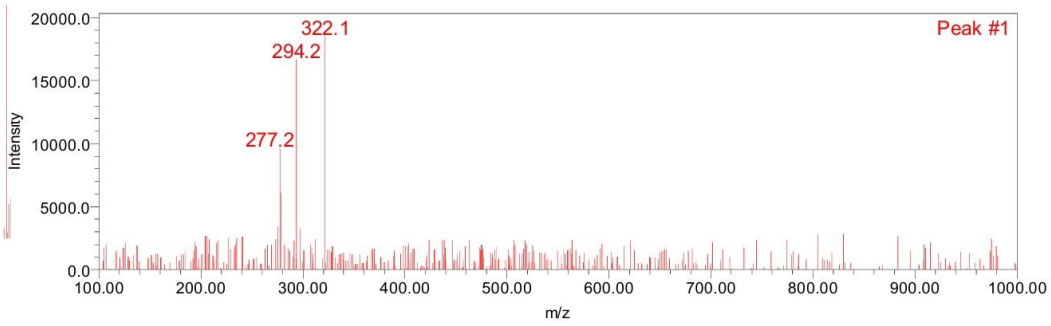


Figure 3: ^{13}C NMR spectrum of representative synthesized compound.



Name: SampleName: P35L Date Acquired: 01-07-2025 12:04:22 IST Channel Description 2: QDa Positive(+) Scan (100.00-1250.00)Da, Centroid, CV=10

Figure 4: Mass spectrum of representative synthesized compound.

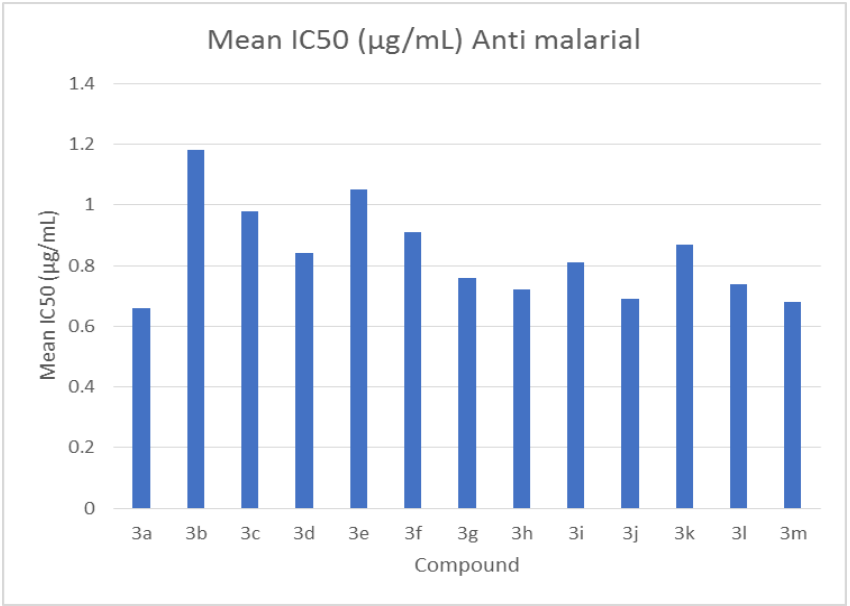


Figure 5: Comparative antimalarial activity (IC_{50} values) of synthesized compounds.

4. CONCLUSION

In the present investigation, a series of novel 2-substituted phenyl-3-(quinolin-4-ylamino)thiazolidin-4-one derivatives were successfully synthesized through a three-step synthetic strategy involving the synthesis of 4-hydrazinylquinoline, Schiff base formation and cyclization with thioglycolic acid. The synthesized compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectrometry which confirmed the proposed structures. The synthesized compounds were evaluated for their in vitro antimalarial activity against the chloroquine-sensitive *Plasmodium falciparum* 3D7 strain using the SYBR Green I fluorescence assay. All compounds exhibited appreciable antimalarial activity with IC_{50} values ranging from 0.66 to 1.18 µM. Among the synthesized series 3a (R = H) demonstrated the highest activity (IC_{50} = 0.66 µM), followed by 3m (3-Br), 3j (4-OH), 3h (2-OH), 3l (4-OCH_3) and 3g (4-Cl). The structure–activity relationship study indicated that both the nature and position of substituents on the phenyl ring significantly influenced antimalarial activity. The present findings suggest that the quinoline-thiazolidin-4-one framework represents a promising molecular scaffold for the development of new antimalarial agents. Further studies involving molecular docking, cytotoxicity evaluation, pharmacokinetic profiling and in vivo antimalarial investigations are warranted to optimize these compounds and explore their therapeutic potential.

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Author's Contribution

Piyushkumar D. Patel: Writing- Original draft preparation, Vatsal M Patel: Review, writing and editing draft, formal analysis, Tejas S. Gandhi: Supervision, Review, writing, editing draft and Conceptualization.

Conflict of Interest

The authors declare there is no conflict of interest.

Data availability statement

The datasets used and analyzed during the current study are available on request.

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