Synthesis of quinoline based [1,2,4]-dithiazolidines through sulfur-sulfur bond formation and their evaluation as anti-inflammatory and antibacterial agents

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ABSTRACT

A series of [1,2,4]-dithiazolidines carrying the quinoline moiety has been synthesized. 2-Chloroquinolin-3-carbaldehyde reacted with various 4-arylthiosemicarbazides to form the corresponding 1-[(2-chloroquinolin-3-yl)methylene]-4-arylthiosemicarbazides. The synthesis of 3,5-(diarylimino)-4-[2-chloroquinolin-3-yl)methyleneamine]-[1,2,4]-dithiazolidines was achieved by the interaction of 1-[(2-chloroquinolin-3-yl)methylene]-4-arylthiosemicarbazides with N-aryl-S-chloroisothiocarbamoyl chlorides through S–S and C–N bond formations. The structures of newly synthesized compounds were confirmed on the basis of IR, 1H & 13C NMR and Mass spectral data. The title compounds were screened for their anti-inflammatory and antibacterial activities.

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INTRODUCTION

Quinoline is one of the most frequently encountered heterocycles in medicinal chemistry. The quinoline skeleton is often used for the design of many synthetic compounds with diverse pharmacological properties such as antibacterial, antifungal, antitumour, antimalarial, anti-inflammatory, and antidepressant. In search of more potential bioactive molecules with improved pharmacokinetic properties, potency and lower side effects, a large number of quinoline derivatives and related compounds have been prepared.

Small ring heterocycles containing nitrogen and sulfur have been under investigation for a long time because of their important properties. [1,2,4]-Dithiazolidines have shown varied biological and physiological activities due to the presence of disulfide (–S–S–) linkage. The literature survey revealed that the [1,2,4]-dithiazolidines have been found to possess potent anti-diabetic, anti-tuberculosis, antibacterial, antifungal anti-inflammatory, and anti-cancer properties. The synthesis of various dithiazolidines have been reported earlier involving methods like oxidative debenzylation, oxidative cyclization using bromine and iodine and by using the reagent N-aryl-S-chloroisothiocarbamoyl chloride.

N-Aryl-S-chloroisothiocarbamoyl chloride is very useful reagent in the synthesis of nitrogen and sulfur-containing heterocyclic compounds as it has ability to undergo cyclization. In addition, the precursor used i.e. 1-[(2-chloroquinolin-3-yl)methylene]-4-arylthiosemicarbazide (quinoline thiosemicarbazone) is associated with diverse biological activities. In view of these facts, we have synthesized [1,2,4]-dithiazolidines by the interaction of 1-[(2-chloroquinolin-3-yl)methylene]-4-arylthiosemicarbazides and N-aryl-S-chloroisothiocarbamoyl chlorides.

In view of utility of quinoline nucleus in different medicinally active compounds, we are reporting the synthesis of [1,2,4]-dithiazolidines incorporated with quinoline moiety through the successive S–S and C–N bond formations and their evaluation for anti-inflammatory and antibacterial activity.

RESULTS AND DISCUSSION

Vilsmeier approach is found to be most efficient for the synthesis of functionalized quinolines.
3-carbaldehyde 2 was prepared by a reported method. This quinoline derivative 2 reacted with various 4-arylthiosemicarbazides to form the corresponding Schiff bases viz. 1-[(2-chloroquinolin-3-yl)methylene]-4-arylthiosemicarbazides in refluxing ethanol. The Schiff bases were found to be desulphurizable with alkaline lead acetate solution indicating the presence of >C=S group. The compounds 4a-f were obtained by the controlled chlorination of aryl isothiocyanates.

The reaction conditions were optimized for the synthesis of [1,2,4]-dithiazolidine 5a with 1-[(2-chloroquinolin-3-yl)methylene]-4-arylthiosemicarbazide 3a and N-aryl-S-chloro isothiocarbamoyl chlorides 4a, as substrates (Table 1). Various solvents such as chloroform (CHCl₃), dichloromethane (DCM), tetrahydrofuran (THF), acetone, and dimethylformamide (DMF) were examined. The results (Table 1) indicated that the solvent had a significant effect on the product yield and completion of reaction time. It was noticed that the transformation occurred smoothly in THF with 76% yield. The product was obtained in moderate yields using CHCl₃, DCM, and acetone. However, no reaction occurred in DMF. Hence, from the aforesaid discussion, it is evident that THF is a better solvent for the reaction.

Accordingly, the reaction of 1-[(2-chloroquinolin-3-yl)methylene]-4-arylthiosemicarbazides 3a-f was carried out with N-aryl-S-chloro isothiocarbamoyl chlorides 4a-f in refluxing tetrahydrofuran for 4 h. The evolution of hydrogen chloride gas was clearly noticed as tested with moist blue litmus paper. The solvent was distilled off to yield [1,2,4]-dithiazolidines 5a-f as a solid mass which were recrystallized from ethanol. The final compounds were found to be non-desulphurizable with alkaline lead acetate solution indicating the absence of >C=S group. The overall reaction is schematically represented in Scheme 1. The physical characterization data of compounds 5a–f are tabulated in Table 2. All the synthesized compounds 5a–f were characterized by IR, ¹H NMR, ¹³C NMR, mass, and elemental analysis. The IR spectra of final compounds showed characteristic band of functional group (–C=N–) at 1620–1637 cm⁻¹. The bands corresponding to S–S, C–S, and C–N stretching vibration were observed at 511–568 cm⁻¹, 644–696 cm⁻¹, and 1243–1338 cm⁻¹, respectively, which confirmed the presence of dithiazolidine ring. The absorption bands were also observed in the range of 751–777 cm⁻¹ due to the presence of C–Cl group in the moiety. In ¹H NMR spectra of compounds, a singlet was observed in the range of 8.74–8.84 ppm due to –CH=N proton.

**Table 1.** Optimization of reaction conditions for the synthesis of [1,2,4]-dithiazolidine (5a).

| Entry | Solvent | Time(h) | Yield of 5a(%) |
|-------|---------|---------|----------------|
| 1.    | CHCl₃   | 4       | 62             |
| 2.    | DCM     | 5       | 56             |
| 3.    | THF     | 4       | 76             |
| 4.    | Acetone | 7       | 39             |
| 5.    | DMF     | 7       | –              |

**Table 2.** Physical characterization data of 3,5-(diarylimino)-4((2-chloroquinolin-3-yl) methyleneamino) [1,2,4]-dithiazolidine 5a-f.

| Compound | R¹ | R² | Molecular Formula | % Yield | m.p. (°C) | Rf value* |
|----------|----|----|-------------------|---------|-----------|-----------|
| 5a       | C₆H₅ | C₆H₅ | C₆H₅ClN₂S₂      | 76       | 244       | 0.60      |
| 5b       | C₆H₅ | 4-MeC₆H₄ | C₆H₅ClN₂S₂ | 75       | 262       | 0.56      |
| 5c       | 4-ClC₆H₄ | 4-ClC₆H₄ | C₆H₅ClN₂S₂ | 71       | 240       | 0.50      |
| 5d       | 4-ClC₆H₄ | 4-OC₆H₄ | C₆H₅ClN₂S₂ | 76       | 260       | 0.64      |
| 5e       | 4-ClC₆H₄ | C₆H₅ | C₆H₅ClN₂S₂ | 73       | 248       | 0.52      |
| 5f       | 3-ClC₆H₇ | C₆H₅ | C₆H₅ClN₂S₂ | 70       | 258       | 0.62      |

*Solvent system- ethyl acetate: petroleum ether (1:9).

In 1, 3 & 5 a: R¹ = C₆H₅ b: R¹ = C₆H₅ c: R¹ = 4-ClC₆H₄ d: R¹ = 4-ClC₆H₄ e: R¹ = 4-ClC₆H₄ f: R¹ = 3-ClC₆H₄

In 4 & 5 a: R² = C₆H₅ b: R² = 4-ClC₆H₄ c: R² = 4-ClC₆H₄ d: R² = 4-MeC₆H₄ e: R² = C₆H₅ f: R² = C₆H₅
Aromatic protons and quinoline protons resonated in the range 6.80–7.60 ppm, and 7.54–8.73 ppm, respectively. $^{13}$C NMR spectra of compounds showed characteristic peaks around 155.2–165.9 for dithiazolidine ring carbons, –CH=N carbons resonated at 150.6–153.3, while remaining aromatic and quinoline carbons resonated in the range of 115.0–150.7. The mass spectra of final compounds showed $[M+H]^+$ peaks which were consistent with the assigned structure.

**Biological activity**

**Antibacterial activity**

Antibacterial activity was carried out by broth dilution method. The newly synthesized compounds (5a-f) were screened for their antibacterial activity against *Escherichia coli*, *Salmonella typhi*, *Bacillus subtilis*, and *Staphylococcus aureus* at concentrations 1000, 500, 250, 125, 62.5 $\mu$g/mL. The disc assay with the assigned structure. The target compounds with electron donating methyl group showed good activity, while compounds 5a and 5d exhibited moderate activity against *E. coli*. Compounds 5b, 5c, 5e showed good activity, while compound 5a and 5d showed moderate activity against *B. subtilis*. Compounds 5a-e exhibited moderate activity against *S. aureus*. Compound 5f was found to possess insignificant activity against all the tested bacteria. All the compounds were considered to be inactive against *S. typhi*. The target compounds with electron donating methyl or methoxy substituents exhibited significantly higher activity than the other compounds.

**In vitro anti-Inflammatory activity**

The assay was performed according to Ling et al. and Sigma Protocol. Compounds 5b, 5c, and 5d were screened for anti-inflammatory activity and the results are depicted in Table S2. The results of anti-inflammatory activity revealed that compound 5b possesses better activity while compounds 5c and 5d possess mild activity with reference to the standard drug Indomethacin. (See Supplemental Materials.)

**Experimental**

**Materials and methods**

All melting points were uncorrected and measured using an electro-thermal apparatus. FT-IR spectra were recorded using KBr disk on Perkin-Elmer FT-IR KBr spectrophotometer as thin films with $v_{max}$ in inverse centimeter. $^1$H and $^{13}$C NMR spectra were taken on Brucker Avance II 400 NMR spectrometer using CDCl$_3$ and DMSO-$d_6$ as solvent and tetramethylsilane (TMS) as internal standard and chemical shifts being reported in parts per million ($\delta$) relative to TMS. Mass spectra were obtained using electron impact (EI) at an ionizing potential of 70eV. Purity of the compounds was checked by thin layer chromatography which was performed on aluminium sheet Silica Gel 60 F$_{254}$ (Merck). The spots were visualized by exposure to UV light and iodine vapours. The Supplemental Materials contains sample characterization spectra (IR, $^1$H, $^{13}$C NMR, and mass) for the products (Figures S3–S19).

**General procedure for the synthesis of 1-[(2-chloroquinolin-3-yl)methylene]-4-aryltiosemicarbazides, 3a-f**

A mixture of 4-aryltiosemicarbazides 1a-f (5 mmol) and 2-chloroquinolin-3-carbaldehyde 2 (5 mmol) was dissolved in ethanol (20 mL) with catalytic amount of glacial acetic acid (0.5 mL) and refluxed for 2h. After cooling, the crystals formed were filtered off and recrystallized from acetone to give compounds 3a-f. Compounds 3a-f were identified by their literature melting points.

**Synthesis of 3,5-(diphenylimino)-4[(2-chloroquinolin-3-yl)methyleneamino]-[1,2,4]-dithiazolidine, 5a**

The compound 1-[(2-chloroquinolin-3-yl)methylene]-4-aryltiosemicarbazide 3a (2 mmol) was suspended in tetrahydrofuran (15 mL). To this a solution of N-aryl-S-chloro isothiocarbamoyl chloride 4a (2 mmol) in tetrahydrofuran was added. The reaction mixture was refluxed for 4 h. The evolution of hydrogen chloride gas was noticed as tested with moist blue litmus paper. Progress of the reaction was monitored with TLC. After completion of the reaction, the solvent was evaporated under reduced pressure, a sticky mass was obtained. It was repeatedly washed with petroleum ether (60–80°C). A solid product was obtained which was recrystallized from ethanol and identified as 3,5-(diarylimino)-4[(2-chloroquinolin-3-yl)methyleneamino]-[1,2,4]-dithiazolidine 5a. The same procedure was applied for the synthesis of compounds 5b-f.

**3,5-(diphenylimino)-4-[(2-chloroquinolin-3-yl)methyleneamino]-[1,2,4]-dithiazolidine, 5a**

Pale yellow solid, IR (KBr): 1628 (C=O Quinoline), 7.60–7.50 (m, 5H, H$_7$ Ph), 6.91 (d, J = 7.6, 2H, H$_4$ Ph). $^{13}$C NMR (CDCl$_3$): $\delta$ 160.5, 159.4 (Dithiazolidine C) 150.6 (–N–N), 755 (C–Cl), 690 (C–S), 511 (S–S). A solid product was obtained which was recrystallized from ethanol and identified as 3,5-(diarylimino)-4[(2-chloroquinolin-3-yl)methyleneamino]-[1,2,4]-dithiazolidine 5a. The same procedure was applied for the synthesis of compounds 5b-f.

**3-(phenylimino)-4-[(2-chloroquinolin-3-yl)methyleneamino]-5-(4-methylphenylimino)-[1,2,4]-dithiazolidine, 5b**

Orange yellow solid, IR (KBr): 1637 (C=O Quinoline), 146.2–115.5 (Ar-C). MS: m/z = 354 $\left[2\text{M}+\text{H}\right]^+$. A solid product was obtained which was recrystallized from ethanol and identified as 3,5-(diarylimino)-4[(2-chloroquinolin-3-yl)methyleneamino]-[1,2,4]-dithiazolidine 5a. The same procedure was applied for the synthesis of compounds 5b-f.
(s, 3H, –CH₃). ¹³C NMR (CDCl₃): δ 163.2, 162.5 (Dithiazolidine C) 151.6 (–N=CH), 148.2 (C–Cl Quinoline), 145.4–116.0 (Ar–C), 23.0 (Ar–CH₃). MS: m/z = 488 [M+H]+ (Cl²⁵), 490 [M+H]+ (Cl²⁷). Anal. Calcd. for C₂₃H₁₈ClN₂S₂: C, 61.53; H, 3.72; N, 14.35. Found: C, 60.98; H, 3.63; N, 14.22.

3-(4-methoxyphenylimino)-4-(2-chloroquinolin-3-yl)methyleneamino]-5-(phenylimino)[1,2,4]-dithiazolidine, 5e

Pale yellow solid, IR (KBr): 1620 (C=O), 777 (C–Cl), 694 (C–S), 568 (M+H)+ (Cl²⁵), 512 [M+H]+ (Cl²⁷). Anal. Calcd. for C₂₄H₁₇Cl₂N₂S₂: C, 55.98; H, 3.63; N, 14.22. Found: C, 55.89; H, 3.25; N, 13.29.

3-(3-chlorophenylimino)-4-[2-chloroquinolin-3-yl)methyleneamino]-5-(phenylimino)[1,2,4]-dithiazolidine, 5f

Yellow solid, IR (KBr): 1620 (C=O), 1338 (C–N), 1156 (N–N), 777 (C–Cl), 694 (C–S), 568 (S–S). ¹H NMR (400 MHz, CDCl₃): δ 8.79 (s, 1H, –N=CH), 8.74 (s, 1H, H₄ Quinoline), 8.57–7.58 (m, 4H, H₃–₈ Quinoline), 7.52–6.94 (m, 9H, Ph, and ArCl). ¹³C NMR (CDCl₃): δ 165.9, 165.2 (Dithiazolidine C) 153.0 (–N=CH), 149.1, 148.8 (C–Cl Quinoline), 142.4–118.2 (Ar–C). MS: m/z = 508 [M+H]+ (Cl²⁵), 512 [M+H]+ (Cl²⁷). Anal. Calcd. for C₂₄H₁₅Cl₂N₂S₂: C, 56.69; H, 2.97; N, 13.77. Found: C, 55.89; H, 2.94; N, 12.65.

Conclusion

We have synthesized 3,5-(diarylimino)-4-[2-chloroquinolin-3-yl)methyleneamino]-[1,2,4]-dithiazolidinones by a simple method which involved formation of S–S and C–N bonds via cyclocondensation reaction. This is an efficient method for sulfur-sulfur bond formation without using any special conditions. The newly synthesized compounds 5a–f were screened for antibacterial and anti-inflammatory activities. The results of antibacterial screening revealed that most of the synthesized compounds have shown moderate to good antibacterial activity against the tested bacteria. Compounds 5b, 5c, and 5d exhibited mild to moderate activity.

These heterocycles accommodating both subunits, i.e., quinoline and [1,2,4]-dithiazolidine are expected to prove their utility in medicinal chemistry and drug development. As the title compounds have an additional imine linkage, they can be further reacted with ketene to give β-lactam which is a pharmacophoric moiety in various drugs.

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