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Synthesis and antimicrobial activities of thiadiazole containing quinoline derivatives

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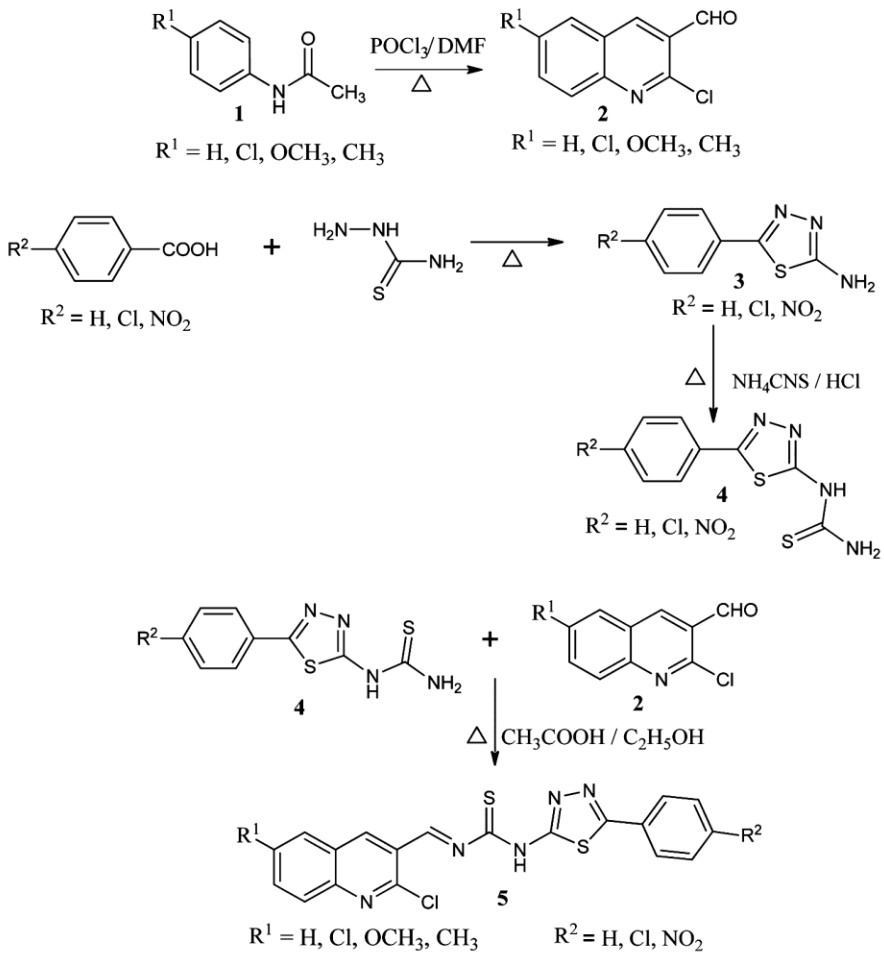
A novel series of 1-[(substituted 2-chloroquinolin-3-yl)methylidene]-3-[substituted-5-phenyl-1,3,4-thiadiazol-2-yl] thioureas have been synthesized by acid catalyzed reaction between the 1-(5-substitued phenyl-1,3,4-thiadiazol-2-yl) thioureas and 6-substituted-2-chloro-3-formyl quinolines. The structures of these compounds have been confirmed by spectral techniques like IR, ^{1}H NMR and mass spectroscopy. The new compounds have been screened for their antibacterial and antifungal activity studies. Most of the compounds show good activity comparable with that of the standard drugs.

Keywords: Quinoline, thiadiazole, thiourea, antibacterial, antifungal

1,3,4-Thiadiazole moiety have been widely used by the medicinal chemist in the past to explore its biological activities. The first 1,3,4-thiadiazole was described by Fischer in 1882 but the true nature of the ring system was demonstrated first in 1890 by Freund and Kuh[1]. Members of this ring system have found their way in to such diverse applications as pharmaceuticals, oxidation inhibitors, cyanide dyes, metal complexing agents. During recent years there has been intense investigation of different classes of thiadiazole compounds, many of which known to possess interesting biological properties such as antimicrobial[2], antituberculosis[3], anti-inflammatory[4], anticonvulsants[5], antihypertensive[6], antioxidant[7], anticancer[8] and antifungal[9] activity. Jumat Saliman *et al*.[10] synthesized a series of 2-N-salicylidene-5-(substituted)-1,3,4-thiadiazole as potential antimicrobial agents. Hence, this field has ever growing importance resulting in the development scores of thiadiazoles. In heterocyclic chemistry quinoline derivatives are also very useful since they show diverse pharmacological properties. The derivatives of quinoline show a variety of medicinal properties such as antimalarial[11], antibacterial[12], antifungal[13], antiviral[14] and antituberculotic[15]. 5-Substituted-1,3,4-thiadiazole-based fluoroquinolone derivatives were synthesized as potential antibacterial and anticancer agents using a molecular hybridization approach[16]. New series of quinoline-based thiadiazole analogues were synthesized, characterized and subjected to their antileishmenial potential and molecular docking studies[17]. Synthesis and antibacterial, antimycobacterial activity of 7-[4-{5- (2-oxo-2-*p*-substituted-phenylethylthio)-1,3,4-thiadiazol-2yl}-3′-methylpiperazinyl] quinoline derivatives were reported by Kapil *et al*.[18] In the view of the varied biological and pharmacological applications of quinoline and 1,3,4-thiadiazole derivatives, we have planned to synthesize some 1,3,4-thadiazole containing quinoline derivatives and study their antibacterial and antifungal activities.

Results and Discussion

In the present study, twelve new 1-[(substituted 2-chloroquinolin-3-yl)methylidene]-3-[substitutued-5-phenyl-1,3,4-thiadiazol-2-yl] thioureas **5** were synthesized by the reaction of 1-(5-substitued phenyl-1,3,4-thiadiazole-2-yl) thioureas **4** and 6-substituted-2-chloro-3-formyl quinolines **2** using acetic acid as the catalyst (Scheme I). The intermediates, 1-(5-substitued phenyl-1,3,4-thiadiazole-2-yl) thioureas **4** were prepared by the reaction of 2-amino-5-substituted aryl-1,3,4- thiadiazoles **3** and ammonium thiocyante in presence of conc. HCl. 2-Amino-5-substituted aryl-1,3,4- thiadiazoles[19] **3** were prepared



Scheme I

by the reaction of thiosemicarbazides, substituted benzoic acids in the presence of conc. H_2SO_4 catalyst. 6-Substituted-2-chloro-3-formyl quinolines[20] **2** were prepared by the reaction of substituted acetanilide, dimethyl formamide and $POCl_3$ (Scheme I). The characterization data of the synthesized compounds **5a-l** was collected and presented in Table I.

Experimental Section

All the materials used were from Sigma Aldrich, Alfa, and Spectrochem Chemicals Pvt. Ltd. Melting points of all the synthesised compounds were recorded by melting point instrument and are uncorrected. The completion of the reaction process were checked by TLC. IR spectra were recorded on a Nicolet Avatar 330 FTIR spectrophotometer, ^{1}H NMR was recorded on Bruker 400 MHz spectrometer and mass of the compound was determined by LCMS on Shimadzu LCMS 2010A instrument.

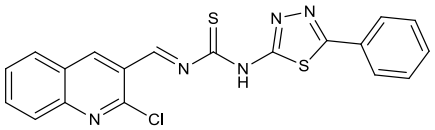
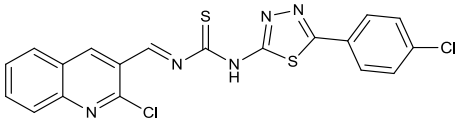
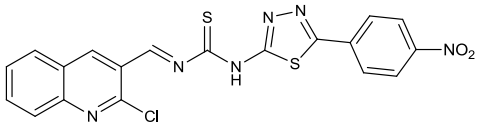
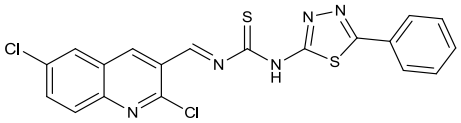
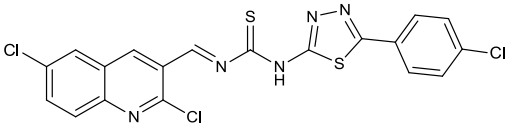
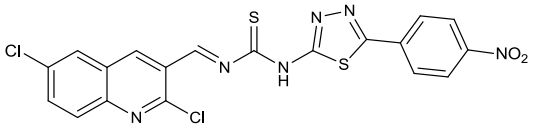
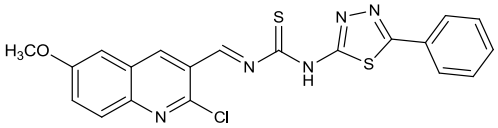
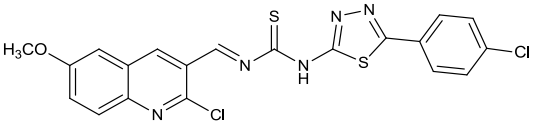
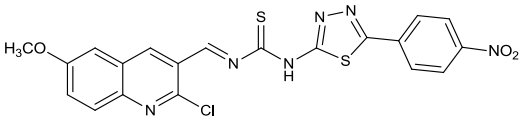
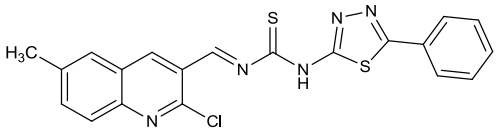
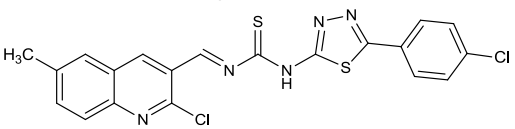
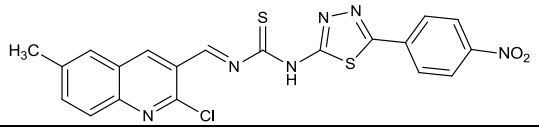
General procedure for the synthesis of 6-substituted-2-chloro-3-formyl quinolines, 2

To a solution of substituted acetanilide (5 mmol) in dry dimethyl formamide (15 mmol) at 0-5°C with stirring $POCl_3$ (60 mmol) was added drop-wise and the mixture stirred at 80-90°C for time ranging between 4-16 h. The product obtained was poured into crushed ice, stirred for 5 min and the resulting solid mass was filtered, washed well with water and dried. The compounds were recrystallized from ethyl acetate.

General procedure for synthesis of 2-amino -5-substituted aryl -1,3,4- thiadiazoles, 3

A mixture of thiosemicarbazide (0.01 mol), substituted benzoic acid (0.01 mol) and conc. H_2SO_4 were refluxed for 2 h and poured into crushed ice. The resulting solid was collected by filtration, washed with water, dried and recrystallized from ethanol.

Table I — Characteristic data of 1-[(substituted 2-chloroquinolin-3-yl)methylidene]-3-[substitutued -5-phenyl-1,3,4-thiadiazol-2-yl] thioureas **5a-l**

Compd	Structure	Colour	m.p. (°C)	Yield (%)	Crystallization solvent
5a		white	192	60	Ethanol
5b		yellow	230	65	Ethanol + DMF
5c		orange	172	65	Ethanol
5d		yellow	190	66	Ethanol
5e		yellow	256	66	Ethanol + DMF
5f		yellow	201	63	Ethanol
5g		white	291	75	Ethanol
5h		yellow	255	77	Ethanol + DMF
5i		orange	245	67	Ethanol
5j		white	267	66	Ethanol
5k		yellow	269	75	Ethanol + DMF
5l		orange	257	60	Ethanol

General procedure for synthesis of 1-(5-substitued phenyl-1,3,4-thiadiazole-2-yl) thioureas, 4

A mixture of 2-amino-5-substituted aryl-1,3,4-thiadiazoles (0.01 mol), ammonium thiocyante (0.02 mol), conc. HCl (1 mL) and water (20 mL) mixture refluxed for 3 h. After cooling, the resulting solid was collected by filtration, washed with water, dried and recrystallized from ethanol.

General procedure for the synthesis of 1-[(substituted 2-chloroquinolin-3-yl)methylidene]-3-[substituted -5-phenyl-1,3,4-thiadiazol-2-yl] thioureas, 5

The solution of 1-(5-substitued phenyl-1,3, 4-thiadiazole-2-yl) thioureas **4** (0.01 mol) and 6-substituted-2-chloro-3-formyl quinolines (0.01mol) in ethanol (100-200 mL) and glacial acetic acid (2 mL) was added and refluxed for 16 h. The crude product obtained was purified by recrystallization from a mixture of ethanol and dimethyl formamide to obtain pure crystalline compounds.

The structures of newly synthesized compounds **5** have been characterised by FT-IR, ^{1}H NMR and LC-MS.

FT-IR spectrum (KBr) of compound **5b** showed absorption band at 1687 cm^{-1} due to (-CH=N stretching), 3268.89 cm^{-1} due to the (N-H stretching) and other bands are 2941.54 cm^{-1} (C-H aromatic stretching), 1619.93 cm^{-1} (C=C stretching), 1017.65 cm^{-1}(N-N stretching), 647.27 cm^{-1} (C-S-C stretching), 764.98 cm^{-1} (C-Cl stretching), 1432cm^{-1} (C-N stretching) and 700.6 cm^{-1} (C-S stretching). ^{1}H NMR spectrum of compound **5b** showed signals at δ 10.45 (s) belongs to -CH=N proton, 8.5 (s) belongs to NH, 8.77 (s) belongs to quinoline H-4 proton, 7.7 to 8.3 (m) belongs quinoline H-5, H-6, H-8 protons and 7.25 to 7.67 (m) belongs to phenyl ring protons. The mass spectrum of the compound **5b** showed the molecular ion peak at *m/z* 443, consistent with the molecular formula $C_{19}H_{11}Cl_2N_5S_2$.

Similarly FTIR, ^{1}H NMR and mass spectra of novel compounds **5c, 5h** and **5i** were recorded and the peaks observed are assigned as follows.

5c: FT-IR (KBr): 1687.25 (-CH=N- stretching), 1617 (C- H stretching), 2868.28 (N-H stretching), 1617.62 (C=C stretching), 1012.27 (N-N stretching), 643.77 (C-S-C stretching), 1425.32 (C-N stretching) and 1044 cm^{-1} (C-S stretching); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.5 (s, 1H, CH=N), 8.5 (s, 1H, NH), 8.62 (s, 1H, quinoline H-4) and 7.17 – 7.95 (m, 8H, quinoline, phenyl protons); LC-MS: M^+ at *m/z* 454.5 (Mol. Formula: $C_{19}H_{11}ClN_6O_2S_2$).

5h: FT-IR (KBr): 1687.96 (–CH=N stretching), 2866.15 (N-H stretching) 1619.93 (C=C stretching) 1017.65 (N-N stretching) 764.98 (C-Cl stretching) 1619.93 (C=C aromatic stretching), 1488.64 (C-N stretching) and 647.27 cm^{-1} (C-S-C stretching); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.5 (s, 1H, CH=N), 7.98 - 8.05 (m, 3H, quinoline protons), 7.20-7.51 (m, 4H, phenyl protons), 8.6 (s, 1H, quinoline H-4) and 3.95 (s, 3H, OCH_3 protons); MS: M^+ at at *m/z* 473 (Mol. Formula: $C_{20}H_{13}Cl_2N_5OS_2$).

5i: FT-IR (KBr): 1693.46 (CH=N stretching), 2841.22 (N-H strectching), 1604.11 (C=C stretching), 715.48 (C-S-C stretching) 799.14 (C-Cl stretching) 1012.02 (N-N stretching) 1428.03 (C-N stretching) and 715.48 cm^{-1} (C-S stretching); ^{1}H NMR (DMSO-d_6, 400 MHz): δ 10.5 (s, 1H, CH=N), 7.17-7.95 (m, 8H, quinoline, N-H and aromatic protons), 8.6 (s, 1H, quinoline H-4)) and 3.9 (s, 3H, OCH_3 protons); MS: M^+ at *m/z* 484 (Mol. Formula: $C_{20}H_{13}ClN_6O_3S_2$).

Antimicrobial activity

The newly synthesized compounds **5** were tested for antibacterial and antifungal activities using minimum inhibitory concentration (MIC)[21] by the serial dilution method[22]. The MIC of the antibiotic for the organism is determined first. For this, the antibiotic is serially diluted in broth. Then a standard drop of the culture prepared for the assay is added to each of the antibiotic dilutions and incubated for 16–18 h at 37°C. The MIC is the highest dilution of the antibiotic, which shows clear fluid with no development of turbidity. The test compound was dissolved in dimethylformamide (5 mL) to prepare a stock solution of concentration 1000 μg/mL. One loop full of an 18 h broth culture was inoculated into 5 mL of nutrient broth and this was incubated at 37°C for 4 h. An assay was prepared by diluting with labelled test tubes 1–11. An aliquot having 0.5 mL of stock solution test compound was added to the first tube. The solution was mixed well and 0.5 mL of this solution was transferred into second tube. This process was repeated serially to obtain the quantities indicated in each of the test tubes. The eleventh test tube was taken as growth control. A drop of diluted broth culture of the test organism (approximately 0.5 mL) was added into all the tubes using a sterilized Pasteur pipette. The solutions were mixed gently and

Table II — Antibacterial and antifungal activities of 1-[(substituted 2-chloroquinolin-3-yl)methylidene]-3-[substituted -5-phenyl-1,3, 4-thiadiazol-2-yl] thioureas **5a-l**

Compd	Antibacterial activity (MIC in μg/mL)		Antifungal activity (MIC in μg/mL)	
	Staphylococcus aureus	*Escherichia coli*	*Candida albicans*	*Aspergillus flavus*
5a	12.5	12.5	12.5	12.5
5b	6.25	6.25	6.25	6.25
5c	6.25	6.25	6.25	6.25
5d	6.25	6.25	6.25	6.25
5e	3.125	3.125	3.125	3.125
5f	3.125	3.125	3.125	3.125
5g	6.25	6.25	6.25	6.25
5h	3.125	3.125	3.125	3.125
5i	3.125	3.125	6.25	6.25
5j	12.5	12.5	12.5	12.5
5k	6.25	6.25	6.25	6.25
5l	3.125	3.125	6.25	6.25
Nitrofurazone	6.25	6.25	–	–
Fluconazole	–	–	6.25	6.25

Disc size = 5.5 mm; Duration = 24 h; DMF (Control)

the incubation was carried out at 37°C for 16–18 h. Nitrofurazone dissolved in dimethylformamide was used as standard drug. The concentration at which there was no turbidity was taken as minimum inhibitory concentration (MIC) and the results are tabulated in Table II. The antibacterial activity study of the newly synthesized compounds were carried out against two different pathogenic bacteria such as *Staphylococcus aureus* (gram positive*)* and *Escherichia coli* (gram negative). The majority of the compounds displayed moderate to good antibacterial activity comparable with that of standard drug Nitrofurazone. Among the compounds tested, **5e**, **5f**, **5h**, **5i** and **5l** showed significant antibacterial activity comparable with that of standard drug. The better efficacy of compounds **5e**, **5f**, **5h**, **5i** and **5l** could be due to the presence of the electron-withdrawing groups such as $–NO_2$ and –Cl.

Similarly the antifungal activity study of compounds **5** was carried out against the two fungi namely *Aspergillus flavus* and *Candida albicans* using the same procedure. Fluconazole was engaged as the standard. The results of antifungal activity data are also given in Table II. Among the compounds tested, the compounds **5e**, **5f** and **5h** exhibited the highest antifungal activity and all other compounds displayed potent activities comparable with that of standard drug Fluconazole.

Conclusion

1-[(Substituted-2-chloroquinolin-3-yl)methylidene]-3-[substitutued-5-phenyl-1,3,4-thiadiazol-2-yl] thioureas **5** were prepared by the condensation of 6/8-substituted -2-chloro-3-formyl quinoline with 1-(5-substituted phenyl-1,3,4-thiadiazol-2-yl) thioureas in the presence of glacial acetic acid. The products were characterized on the basis of their melting point, IR, ^{1}H NMR and mass spectroscopy. Synthesized compounds were screened for their antibacterial and antifungal activity. Among the twelve derivative compounds tested, most of compounds have shown good antibacterial and antifungal activities.

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