A series of novel hybrid 2-(7-chloroquinolin-4-ylthio)-5-(substituted)-1,3,4-oxadiazole derivatives have been designed, synthesized which contains different pharmacophores like quinoline and 1,3,4-oxadiazole linked via sulfur atom. All the newly synthesized derivatives have been characterized by IR, $^1$H NMR, $^{13}$C NMR spectral and elemental analysis. Further, All the final synthesized scaffolds have been subjected to in vitro antimicrobial activity against several bacteria (E.coli, P.aeruginosa, S.aureus, S.pyogenus) and fungi (C.albicans, A.niger, A.clavatus) using broth dilution technique. Among the compounds tested, compounds 3f substituted with coumarin analogue and 3b with amine group at second position of phenyl to oxadiazole moiety are found to be most potent.

Keywords: Quinoline, 1,3,4-oxadiazole, antibacterial, antifungal

Many people died from bacterial infections than cancer due to the rise in antibiotic resistance in bacteria$^1$. The increased use of antibiotics in recent years has resulted in the development of resistance of pathogens against current marketed drugs. On the other hand, new antimicrobial agents stay in demand because of the expanding global spread of drug-resistant pathogens$^2$. Also multidrug resistance (MDR) of bacteria is until now an indecipherable serious problem threatening the health of people$^3$. For that reason, development of antibacterial molecules with novel structural characteristic, broad-spectrum of activity and activity against resistant pathogens is needed. In the recent years many research groups have been paying attention to the synthesis of nitrogen based heterocycles because of their pharmacological and medicinal significance. They are widely available in nature and are essential for life.

The advantage of hybrid compound through the array of different pharmacophores may provide compounds with good biological activities$^4$. Quinoline core is present as a basic structure in a wide variety of heterocyclic synthetic and natural bioactive compounds, most particularly within antimalarial agents$^5$. The quinolines are historically among the most important antimalarial drugs ever used, for example, Chloroquine, Mefloquine, Quinacrine, Mepacrine, Amodiaquine, Piperaquine, Tafenoquine, Primaquine and Pyrimethamine, etc$^5$. Quinoline derivatives also have been explored for the diverse pharmacological activity such as antimicrobial$^7$, antiinflammatory$^8$, antileishmanial$^9$, antituberculosis$^{10}$, cytotoxicity and HIV-1 Integrase Inhibitors$^{11}$, analgesics$^{12}$, antiamoebic$^{13}$, trypanocidal$^{14}$, anti-septic/anti-infective$^{15}$, antiserotonin$^{16}$, anti-neurodegenerative$^{17}$ and anticancer$^{18}$, etc. Attributable to such biological importance, quinoline derivatives have grown to be the synthetic goals of many organic and medicinal chemistry researcher$^5$.

Oxadiazole nucleus is a fertile source of bioactivity in the area of drug discovery because of its varied biological activities and It has performed to identify compounds bearing 1,3,4-oxadiazole ring occupy a important place in medicinal chemistry due to its significant biological properties as antimicrobial$^{19-22}$, antituberculosis$^{22-24}$ and anticancer$^{25}$. A numbers of pharmaceutical drugs such as HIV-integrase inhibitor Raltagravir, a nitrofuran antibacterial Furamizole, a potent PDF inhibitor BB-83698, antihypertensive agents Tiodazosin and Nesapidil are based on 1,3,4-oxadiazole moiety$^{26}$. Recently, it has also been reported in the literature that compounds bearing 1,3,4-oxadiazole ring possessing quinazoline, coumarin and various heterocycle nucleus showed potential bioactivities. Therefore, considerable efforts have been directed towards the preparation and synthetic manipulation of these molecules.
Attracted by different biological activity of these heterocycles, a hybrid system has been designed and synthesized by introducing an oxadiazole ring at the fourth position of the quinoline ring through sulfur linkage. In context to the above rationale and in continuation of our ongoing program focused on finding new leads with potent activities, we embarked on the synthesis of 2-(7-chloroquinolin-4-ylthio)-5-(substituted)-1,3,4-oxadiazole derivatives and evaluation of their experimental antimicrobial activity in vitro. The design concepts have been drawn in Figure 1, which elucidates the structural comparison of our novel derivatives with renowned drugs.

**Chemistry**

In view of the high pharmacological activity profile of quinoline compounds, quinoline-oxadiazole derivatives have been designed and synthesized. As per the synthetic strategy depicted in Scheme I, the synthetic approach to quinoline viz. the Skraup quinoline synthesis involves the formation of the intermediate 4,7-dichloroquinoline (derived from m-chloro aniline) was prepared in which m-chloro aniline and diethyl 2-(ethoxymethylene)malonate were reacted, cyclized at elevated temperature followed by chlorination with POCl3. The mentioned aromatic and heterocycle acid derivatives were chlorinated with thionyl chloride and then treated with hydrazine hydrate at reflux temperature in dioxane to get corresponding carbo-hydrazide derivatives 1a-g, which were then cyclized to the corresponding 1,3,4-oxadiazole-2-thiol ring 2a-g, followed by the condensation with previously prepared 4,7-dichloro quinoline nucleus via sulphur linkage obtained 2-(7-chloroquinolin-4-ylthio)-5-(substituted)-1,3,4-oxadiazole (3a-g) as the desired target compound.

**Results and Discussion**

**Antimicrobial activity**

The antibacterial activity studied (Table I) for quinoline-oxadiazole derivatives 3a-g against several strains demonstrated that some of the compounds revealed a good deal of activity against all the mentioned bacteria. Compound 3b with 2-amino phenyl and 3f with quinoline to oxadiazole ring appeared with potential inhibitory efficacy against Staphylococcus aureus at 3.12 µg/mL of MIC. In addition, the above mentioned two derivatives (3b and 3f) were also found to contribute highest inhibition of Salmonella typhi at 6.25 µg/mL of MIC. Likewise, among the potent derivatives against P. aeruginosa, the most potent compounds possessed highest lipophilicity (3d, LogP = 4.5796) and higher lipophilicity of compounds 3b (LogP = 3.0286) and 3g (LogP = 3.9856) at 12.5 µg/mL of MIC. Final derivatives 3b (LogP = 3.0286) with 2-amino phenyl, 3e (LogP = 3.5728) with coumarin and 3g (LogP = 3.9856) with phenyl ring to the oxadiazole nucleus were found to contribute excellent potency towards Escherichia coli at 25 µg/mL of MIC, while the lowest lipophilicity of 3a (LogP = 2.6868) with 4-pyridinyl and 3c (LogP = 2.6868) 3-pyridinyl functionality to the oxadiazole ring indicated diminished activity at 100 µg/mL of MIC against E. coli. Among the active compounds it can be clearly

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**Figure 1** — The design of 2-(quinolin-4-ylthio)-1,3,4-oxadiazole derivatives hybrid derivatives
seen that the compound (3d, LogP = 4.5796) of cinnamic analogue with higher lipophilicity displayed excellent activity against all bacterial strain (i.e. S. aureus, S. pyogenes, P. aeruginosa, E. coli) at 12.5 µg/mL of MIC. From the bioassay it can be stated that all the final quinoline derivatives in which more lipophilic compound were found more active then the remaining final analogues against both the Gram positive and Gram negative strains. All the remaining final quinoline-oxadiazole derivatives exerted good to moderate activity profiles.

The antifungal activity results summarized in Table 1 revealed that, the synthesized compounds showed good potency against the mentioned fungi. Final compounds 3b with 2-amino phenyl (LogP = 3.0286), 3f with quinoline (LogP = 4.0708) and 3g with phenyl group (LogP = 3.9856) to the oxadiazole ring showed promising activity against Aspergillus clavatus at 12.5 µg/mL of MIC. While compound 3c with lowest liphophilicity (LogP = 2.6868) exhibited lower activity at 100 µg/mL of MIC against the same fungal strain. In case of compound 3a exhibiting lower lipophilicity showed good activity (MIC 25 µg/mL) against the mentioned fungi, activity decreased with the increase in lipophilicy (LogP). The later compounds 3b, 3d, 3e, and 3f were also appeared with potential inhibitory effects towards Candida albicans at 25 µg/mL of MIC. Therefore, a converse trend of activity versus lipophilic character was observed in case of active analogues towards A. clavatus compared to active analogues against the other fungal strain as the compound with higher lipophilicity showed higher activity.

**Experimental Section**

All the chemicals and reagents of analytical grade were purchased from of SD Fine (India), Aldrich and Merck unless and otherwise specified. All solvents were dried over a correct drying agent and purified as per standard methods. Melting points of all final derivatives were determined in open capillaries on a Veego electronic apparatus VMP-D (Veego Instrument Corporation, India) and are uncorrected. IR spectra were recorded on JASCO FT-IR 4100, Japan using KBr discs. Analytical TLC was performed on Merck precoated aluminum plates 60 F254 with a 0.2 mm layer of silica gel-G and spots were visualized under UV irradiation. NMR spectra
were recorded on a 400 MHz spectrometer (Bruker DRX 400) using DMSO as a solvent and TMS as an internal standard, with $^1$H resonant frequency of 400 MHz and $^{13}$C resonant frequency of 100 MHz. All $^1$H and $^{13}$C NMR chemical shifts are quoted in ppm and were calibrated on solvent signals and were conducted at Zydus Research Centre, Ahmedabad, India. Multiplicities are shown as the abbreviations: s (singlet), d (doublet), dd (doublet–doublet), t (triplet), and m (multiplet). Elemental analysis was performed using a GmbH Vario Micro cube Elementar Analyzer (Germany).

**General synthetic procedure for various 1,3,4-oxadiazole-2-thiol, 2a-g**

Major precursors of the reaction, i.e. 5-(Pyridin-4-yl)-1,3,4-oxadiazole-2-thiol 2a, 5-(2-aminophenyl)-1,3,4-oxadiazole-2-thiol 2b, 5-(pyridin-3-yl)-1,3,4-oxadiazole-2-thiol 2c, (E)-5-styryl-1,3,4-oxadiazole-2-thiol 2d, 3-(5-mercapto-1,3,4-oxadiazol-2-yl)-6,7-dihydro-2H-chromene-2-one 2e, 5-(quinolin-3-yl)-1,3,4-oxadiazole-2-thiol 2f, and 5-phenyl-1,3,4-oxadiazole-2-thiol 2g were synthesized according to a reported method$^{32-34}$.

**Table 1 — In-vitro antibacterial and antifungal activity in MIC*(µg/mL) of compounds 3a-g**

<table>
<thead>
<tr>
<th>Compd</th>
<th>R</th>
<th>LogP</th>
<th>Gram +ve</th>
<th>Gram -ve</th>
<th>Fungal strains</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Staphylococcus aureus MTCC 96</td>
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<td>Pseudomonas aeruginosa MTCC 741</td>
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<tr>
<td>3a</td>
<td></td>
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<td>2.6868</td>
<td>100</td>
<td>100</td>
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<tr>
<td>3b</td>
<td></td>
<td></td>
<td>3.0286</td>
<td>3.125</td>
<td>6.25</td>
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<tr>
<td>3c</td>
<td></td>
<td></td>
<td>2.6868</td>
<td>50</td>
<td>100</td>
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<tr>
<td>3d</td>
<td></td>
<td></td>
<td>4.5796</td>
<td>12.5</td>
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<tr>
<td>3e</td>
<td></td>
<td></td>
<td>3.5728</td>
<td>25</td>
<td>100</td>
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<tr>
<td>3f</td>
<td></td>
<td></td>
<td>4.0708</td>
<td>3.125</td>
<td>6.25</td>
</tr>
<tr>
<td>3g</td>
<td></td>
<td></td>
<td>3.9856</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

Ciprofloxacin | 1.56 | 3.125 | 3.125 | 3.125 | --- | --- |

Ketoconazole | --- | --- | --- | --- | 3.125 | 3.125 |

DMSO (Control) | --- | --- | --- | --- | --- | --- |

*MIC=Minimum inhibitory concentration

*CLogP value determined by ChemDraw Ultra 11.0 software

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General procedure for the synthesis of compounds, 1a-g

Isonicotinohydrazide 1a, 2-Aminobenzohydrazide 1b, Nicotinohydrazide 1c, Cinnamohydrazide 1d, 2-Oxo-6,7-dihydro-2H-chromene-3-carbohydrazide 1e, Quinoline-3-carbohydrazide 1f, and Benzohydrazide 1g were synthesized according to a reported method$^{32-34}$. 

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<td>3f</td>
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<td>4.0708</td>
<td>3.125</td>
<td>6.25</td>
</tr>
<tr>
<td>3g</td>
<td></td>
<td></td>
<td>3.9856</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

Ciprofloxacin | 1.56 | 3.125 | 3.125 | 3.125 | --- | --- |

Ketoconazole | --- | --- | --- | --- | 3.125 | 3.125 |

DMSO (Control) | --- | --- | --- | --- | --- | --- |

*MIC=Minimum inhibitory concentration

*CLogP value determined by ChemDraw Ultra 11.0 software
General procedure for synthesis of a novel series of differently substituted 2-(quinolin-4-ythio)-1,3,4-oxadiazole derivatives, 3a-g

To a 4,7-dichloroquinoline (0.5 g, 2.5 mmol) in 10 mL of dimethylformamide, appropriate 1,3,4-oxadiazole-2-thiol 2a-g (2.6 mmol) and potassium carbonate was (0.38 g, 2.75 mmol) added and the reaction mixture was stirred for 5 hr at RT, then heated for 10 to 12 hr at 120°C. After cooling to RT, it was slowly poured into mixture of water and ethyl acetate. The organic layer was separated, washed successively with brine and water, and dried over anhydrous sodium sulphate. Evaporation under reduced pressure gave a crude solid or residue product which was purified by silica gel column chromatography [ethyl acetate: n-hexane solvent system as an eluent] to afford pure compounds (3a-n).

2-(7-Chloroquinolin-4-ythio)-5-(pyridin-3-yl)-1,3,4-oxadiazole, 3c

Yield 76%; m.p. 227.7°C; IR (KBr): 1682 (C≡N, aromatic), 1508 (C≡C aromatic), 1037 (C-O-C), 663 cm⁻¹ (C-S-C); ¹H NMR (400 MHz, chloroform-d): δ 8.82 (d, J = 1.5 Hz, 1H, pyridine ring), 8.74 (d, J = 7.5 Hz, 1H, quinoline), 8.65 (dd, J = 7.4, 1.5 Hz, 1H, pyridine ring), 8.19 (d, J = 7.5 Hz, 1H, quinoline), 8.00 (d, J = 1.6 Hz, 1H, quinoline), 7.98-7.92 (m, 1H, pyridine ring), 7.70 (dd, J = 7.4, 1.5 Hz, 1H, quinoline ring), 7.51 (dd, J = 7.6 Hz, 1H, pyridine ring), 7.34 (d, J = 7.5 Hz, 1H, quinoline); ¹³C NMR (100 MHz, DMSO): δ 163.53 (1C, oxadiazole), 161.90 (1C, oxadiazole), 151.16 (1C, C-S, quinoline), 150.44 (1C, C≡N, quinoline), 149.16 (1C, C≡N, pyridine), 149.12 (1C, C≡N, quinoline), 146.63 (1C, C≡N, pyridine), 135.23 (1C, C=Cl, quinoline), 131.52, 127.93, 126.93, 124.88, 123.84, 123.21, 121.45, 120.62 (8C, Ar-C). Anal. Calcd. for C₁⁵H₁₇ClN₂O₃S (340.79): C, 56.39; H, 2.66; S, 9.41. Found: C, 56.48; H, 2.65; N, 16.39; S, 9.40%.

(E)-2-(7-Chloroquinolin-4-ythio)-5-styryl-1,3,4-oxadiazole, 3d

Yield 79%; m.p. 216.2°C; IR (KBr): 1672 (C=C aliphatic), 1629 (C≡N), 1544 (C≡C aromatic), 1061 (C-O-C), 672 cm⁻¹ (C-S-C); ¹H NMR (400 MHz, Chloroform-d): δ 8.76 (d, J = 7.5 Hz, 1H, quinoline), 8.20 (d, J = 7.5 Hz, 1H, quinoline), 8.01 (d, J = 1.5 Hz, 1H, quinoline), 7.71 (dd, J = 11.9, 7.6, 2H, ArH), 7.66 (dd, J = 7.4, 1.5 Hz, 1H, quinoline ring), 7.47-7.37 (m, 2H, ArH), 7.34 (d, J = 7.5 Hz, 1H, quinoline), 7.25-7.16 (m, 1H, ArH), 6.98 (d, J = 15.1 Hz, 1H, -CH-), 6.74 (d, J = 15.1 Hz, 1H, -CH-); ¹³C NMR (100 MHz, DMSO): δ 160.69 (1C, oxadiazole), 154.03 (1C, oxadiazole), 151.62 (1C, C≡N, quinoline), 150.44 (1C, C≡N, quinoline), 149.12 (1C, C≡N, quinoline), 138.14 (1C, -CH=CH=CH-Ar), 135.23 (1C, C=Cl, quinoline), 135.18, 130.75, 128.96, 128.32, 127.93, 126.93, 124.88, 121.45, 120.62 (11C, Ar-C), 112.08 (1C, -CH=CH=CH-Ar). Anal. Calcd. for
C_{19}H_{14}ClN_{3}OS (365.84): C, 62.38; H, 3.31; N, 11.49; S, 8.76. Found: C, 62.23; H, 3.30; N, 11.46; S, 8.74%.

3-(5-(7-Chloroquinolin-4-ythio)-1,3,4-oxadiazol-2-yl)-6,7-dihydro-2H-chromen-2-one, 3e

Yield 57%; m.p. 240.1°C; IR (KBr): 1672 (C=O), 1658 (C=N), 1559 (C=C aromatic), 1048 (C-O-C), 671 cm^{-1} (C-S-C); \textsuperscript{1}H NMR (400 MHz, Chloroform-d): \( \delta \) 8.77 (d, \( J = 7.5 \) Hz, 1H, quinoline), 8.21 (d, \( J = 7.5 \) Hz, 1H, quinoline), 8.07 (d, \( J = 1.1 \) Hz, 1H, coumarin), 8.01 (d, \( J = 1.5 \) Hz, 1H, quinoline), 7.86 (m, 1H, coumarin), 7.69 (dd, \( J = 7.5, 1.5 \) Hz, 1H, quinoline), 7.55 (m, 1H, coumarin), 7.47–7.33 (m, 3H, ArH); \textsuperscript{13}C NMR (100 MHz, DMSO): \( \delta \) 164.52 (1C, oxadiazole), 162.91 (1C, C=C, coumarin), 159.96 (1C, oxadiazole), 152.43 (1C, C-O, coumarin), 151.62 (1C, C=S, quinoline), 150.44 (1C, C=N, quinoline), 149.12 (1C, C=N, quinoline), 135.23 (1C, C-Cl, quinoline), 129.32, 128.70, 128.01, 127.93, 126.93, 124.88, 124.63, 121.45, 120.62, 120.12, 116.47, 115.41 (12C, Ar-C). Anal. Calcd. for C_{10}H_{10}ClN_{3}OS (393.80): C, 60.09; H, 2.97; N, 12.37; S, 9.44. Found: C, 59.95; H, 2.96; N, 12.40; S, 9.43%.

**Biological assay**

*In vitro* evaluation of antibacterial and antifungal activity

The synthesized derivatives 3a-g were examined for antimicrobial activity against several bacteria (*Staphylococcus aureus* MTCC 96, *Streptococcus pyogenes* MTCC 442, *Pseudomonas aeruginosa* MTCC 741, *Escherichia coli* MTCC 119) and fungi (*Aspergillus clavatus* MTCC 1323, *Candida albicans* MTCC 183) species using agar streak dilution method\textsuperscript{38} for determination of the minimum inhibitory concentration of the compound. A stock solution of the tested compound (200 \( \mu \)g/mL) in dimethylsulfoxide was prepared and graded quantities of the test compounds were incorporated in a specified quantity of molten sterile agar, *i.e.* nutrient agar for evaluation of antibacterial and sabouraud dextrose agar for antifungal activity, respectively. The medium containing the test compound was poured into a petri dish at a depth of 4-5 mm and allowed to solidify under aseptic conditions. A suspension of the respective microorganism of approximately 10\(^5\) CFU/mL was prepared and applied to plates with serially diluted compounds with concentrations in the range of 3.125-200 \( \mu \)g/mL in dimethylsulfoxide and incubated at (37±1)°C for 24 hr (bacteria) or 48 hr (fungi). The lowest concentration of the compound that prevents the development of visible growth is considered to be the MIC value.

**Conclusion**

This research effort focused on the development of new potentially active antibacterial and antifungal agents based on quinoline-oxadiazole hybrid derivatives. In general, the results of the *in vitro* biological activities are encouraging, as compounds 3b, 3d, 3f, and 3g, which showed potent antibacterial as well as antifungal activities. Interestingly,
compounds 3f with coumarin analogue and 3h with amine group at second position of phenyl to oxadiazole moiety emerged as the class of compounds exhibiting the highest antimicrobial activity. In addition, the relationship between activity profiles and lipophilicity of the newer analogues was also discussed in which, in some cases higher lipophilic compounds showed higher biological activities, whereas, in some cases the opposite trend was observed. Higher inhibitory effects observed in this study appear to be dependent on the lipophilicity of molecules in most cases. As a result, the extent of activity, encouraging physicochemical parameters, demonstrated by a novel hybrid structural system of quinoline and oxadiazole rings creates such derivatives as advantaged structures to accomplish more active derivatives in ongoing studies. Further structural optimization as well as studies on the anti-HIV activities of these derivatives is also underway in our laboratories in order to obtain more information about their pharmacological applications.

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