Chapter-4

Synthesis, characterization and biological activity of quinoline derivatives endowed with various substituted oxadiazoles
4.1. Introduction

The importance of quinoline and its derivatives is well recognized by synthetic and biological chemists\(^1\). Compounds possessing this ring system have wide applications as drugs and pharmaceuticals\(^2\). In synthetic medicinal chemistry, the quinoline motif is widely exploited revealing a spectrum of activity covering anticancer, antifungal, antibacterial and antiprotozoic effects\(^3\). The quinolines are historically among the most important antimalarial drugs ever used, for example, Chloroquine, Mefloquine, Quinacrine, Mepacrine, Amodiaquine, Piperaquine, Tafenoquine, Primaquine and Pyrimethamine\(^4\).

Oxadiazole nucleus is a fertile source of bioactivity in the area of drug discovery because of its varied biological activities viz. antimicrobial, antituberculosis, anticancer, etc. Moreover, It has long been known that compounds bearing 1,3,4-oxadiazole ring occupy a prominent place in medicinal chemistry due to its significant biological properties\(^5\). Moreover, it has been reported in the literature that compounds bearing 1,3,4-oxadiazole ring possessing quinazoline, coumarin and various heterocyclic nucleus showed potential bioactivities. Therefore, considerable efforts have been directed towards the preparation and synthetic manipulation of these molecules\(^6\).

Hence, in the research work of this chapter, a series of quinoline derivatives endowed with various aromatic or heterocyclic oxadiazoles have been synthesized in order to obtain potential biologically active compounds. 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 carbohydrazide derivatives, which were then cyclized to the corresponding 1,3,4-oxadiazole-2-thiol ring, followed by the condensation with 4,7-dichloroquinoline nucleus via sulphur linkage to obtain final analogues. The newly synthesized compounds were characterized and studied their biological activity against several bacterial strains (Staphylococcus aureus MTCC 96, Bacillus cereus MTCC 430, Pseudomonas aeruginosa MTCC 741, Klebsiella pneumoniae MTCC 109) and fungal strains (Aspergillus clavatus MTCC 1323 and Candida albicans MTCC 183).
4.1.1 Biological importance of quinoline derivatives

Quinoline derivatives are prevalent in a variety of pharmacologically active synthetic and natural compounds. Quinolines have antiseptic, antipyretic properties and are used as antimalarials and for preparing other antimalarial drugs. The discovery of chloroquine, the most famous drug containing this scaffold, resulted in control and treatment of malaria for decades. Quinoline and its derivatives are widely used as fungicides, biocides, antibiotics, alkaloids, dyes, rubber chemicals, and flavoring agents. Additional industrial applications include their use as corrosion inhibitors, preservatives, as solvents for resins and terpenes, and in transition-metal complex catalysis for uniform polymerization and luminescence chemistry. They are also used in manufacturing oil soluble dyes, food colorants, pharmaceuticals, pH indicators and other organic compounds. Quinoline is a catabolite of tryptophan, a fundamental structure in some antihypertensive agents such as the peripheral vasodilators prazosin and doxazosin.

3,5-Bis(alkyl-1,3,4-oxadiazole-2-yl) quinoline derivatives (I) were synthesized by a multi-step reaction sequence. The synthesized compounds were screened for their antimicrobial and in vitro antioxidant properties. The results of this investigation reveals that the newly synthesized compounds exhibit significant biological activity and certainly hold a greater promise for discovering potent biologically active molecules.

![Chemical Structure](image)

Where, 
\[ R = (\text{CH}_2)_6\text{CH}_3, (\text{CH}_2)_8\text{CH}_3, (\text{CH}_2)_{10}\text{CH}_3, (\text{CH}_2)_{10}\text{CH}_3, (\text{CH}_2)_{12}\text{CH}_3, (\text{CH}_2)_{14}\text{CH}_3 \]

A series of 5-(quinolin-2-yl)-1,3,4-oxadiazole-2(3H)-thione quinoline derivatives (II) have been synthesized by Juan Sun et al. and evaluated for their antitumor activities against HepG2, SGC-7901 and MCF-7 cell lines. Preliminary results showed that most of the compounds displayed enhanced inhibitory activities. Of all the studied compounds, compounds having fluoro substituent at ortho position and having chloro substituent at the para position of anilines
displayed the most potent anticancer activities. Considering the results, they concluded that the template quinoline with 1,3,4-oxadiazole moiety was suitable to reconstruct and design for development of more potential therapeutic drugs against cancer.

\[ \text{(II)} \]

Where, \( R = -\text{NH-C}_6\text{H}_5, -\text{NH-C}_6\text{H}_5(4-\text{CH}_3), -\text{NH-C}_6\text{H}_5(2-\text{OCH}_2\text{H}_5), -\text{NH-C}_6\text{H}_5(2-\text{F}), -\text{NH-C}_6\text{H}_5(4-\text{Cl}) \), etc

Dodiya et al.\(^9\) have reported a practical, efficient, and an inexpensive method for the synthesis of a new series of quinoline-oxadiazole-azetidinone derivatives (III). These Synthesized compounds were screened for their antimicrobial activity against different strains of bacteria (\( E. \text{coli}, P. \text{aeruginosa}, S. \text{aureus}, S. \text{pyogenes}, C. \text{albicans}, A. \text{niger}, \text{and} A. \text{clavatus} \)).

\[ \text{(III)} \]

Where, \( R = -\text{Cl}, -\text{NO}_2, -\text{OCH}_3, -\text{CH}_3, -\text{F}, \text{etc} \)

4.1.1 Biological importance of oxadiazole derivatives

Synthesis of 1,3,4-oxadiazole derivatives (V) had been described by D E A Rahman & coworkers\(^{10}\). All the synthesized derivatives were screened for anticancer activity against HT29 and MCF7 cancer cell lines using Sulfo-Rodamine B (SRB) standard method. Most of the tested compounds exploited potent antiproliferative activity against HT29 cancer cell line rather than MCF7 cancer cell line.
Where, 

\[ R = H, \ & \ R' = C_6H_5, C_6H_4CH_3, C_6H_4COCH_3, \text{ etc} \]

Hai-Bin Gong et al.\textsuperscript{11} have synthesized a series of 1,3,4-oxadiazole derivatives derived from 4-methoxysalicylic acid or 4-methylsalicylic acid and vanillic acid (VI) and evaluated their immunosuppressive activities against ConA (Concanavalin A) stimulated T cells. Preliminary results showed that most of the compounds displayed enhanced inhibitory activities and low toxicity.

Where, 

\[ R_1, R_2, R_3, R_4, R_5 = H, \text{ NO}_2, \text{ Cl, F, Br, Me} \]

Ravi L. Bakal et al.\textsuperscript{12} have described the synthesis, Identification and development of 2,5-disubstituted oxadiazole as potential candidate for treatment of XDR and MDR tuberculosis. They identified hit compound (VII) which has also been proved active against nearly 25 clinical isolates comparable with Isoniazid.
A series of new sulfone compounds containing the 1,3,4-oxadiazole moiety (VIII) were designed and synthesized by Bao-An Song et al.\textsuperscript{13} Antibacterial bioassays indicated that most compounds exhibited promising \textit{in vitro} antibacterial bioactivities against tobacco bacterial wilt at 200 \(\mu\)g/mL. The relationship between structure and antibacterial activity was also discussed.

\[ R = \text{CH}_3, \text{CH}_2\text{CH}_3 \]

(XVIII)

Where, \( R = \)

\begin{align*}
\text{O}_2\text{N} & \quad \text{H}_3\text{CO} \\
\text{Cl} & \quad \text{H}_3\text{CO} \\
\text{Cl} & \quad \text{Br}
\end{align*}

Xin-Ling Yang et al.\textsuperscript{14} have synthesized a novel series of 1,3,4-oxadiazole derivatives (IX) containing a 5-phenyl-2-furan moiety from the intermediates diacylhydrazine and acylhydrazone via an efficient approach under microwave irradiation in good yields. The antifungal tests indicated that the title compounds showed \textit{in vivo} fungicidal activity against \textit{Botrytis cinerea} and \textit{Rhizoctonia solani} at 500 \(\mu\)g/mL obviously. Some tested compounds even had a superiority effect over the commercial fungicides 40\% Pyrimethanil SC and 3\% Validamycin AS.

\[ R = \text{-Me, -Et, R}_1 \text{& R}_2 = \text{-H, -Me, -Br, -Cl, -OMe, -OEt} \]

(IX)

Where,

\[ R = \text{-Me, -Et, R}_1 \text{& R}_2 = \text{-H, -Me, -Br, -Cl, -OMe, -OEt} \]
4.2. Analogue synthesis

\[ R \overset{\text{(i)} SOCl_2}{\longrightarrow} R \overset{\text{(ii)} NH_2NH_2H_2O}{\longrightarrow} R \overset{\text{CS_2, KOH}}{\longrightarrow} R \overset{\text{EtOH}}{\longrightarrow} R \]

(23a-23g)  (24a-24g)

Scheme 4.1 Synthetic pathway of compounds (25a-25g)

Where, \( R = \)

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<thead>
<tr>
<th>25a</th>
<th>25d</th>
</tr>
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<tr>
<td><img src="image1" alt="25a" /></td>
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<th>25f</th>
<th>25g</th>
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<td><img src="image6" alt="25f" /></td>
<td><img src="image7" alt="25g" /></td>
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4.3. Experimental

4.3.1. Materials and methods

All the chemicals and reagents were of analytical grade of Sdine, Aldrich and Merck unless and otherwise specified. The starting material 4,7-dichloro quinoline was purchased from SigmaAldrich, India. All solvents were dried over an appropriate drying agent and purified by standard methods. Melting points were determined in open capillaries on a Veego electronic apparatus VMP-D (Veego Instrument Corporation, Mumbai, India) and are uncorrected. Analytical thin-layer chromatography was performed on Merck precoated aluminum plates 60 F_{254} 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 \(^1\text{H}\) resonant frequency of 400 MHz and \(^{13}\text{C}\) resonant frequency of 100 MHz. All \(^1\text{H}\) and \(^{13}\text{C}\) NMR chemical shifts are quoted in ppm and were calibrated on solvent signals and were conducted at Zydus Research Centre, Ahmedabad, India. Multiplicities are given as s (singlet), d (doublet), dd (doublet–doublet), q (quartet), t (triplet), and m (multiplet). Elemental analyses (C, H and N) were performed using a GmbH Vario Micro cube Elementar Analyzer (Germany).

**Preparation of 2-(7-chloroquinolin-4-yl-thio)-5-(substituted)-1,3,4-oxadiazole**

It was prepared in the following three steps

**Step-I**

4.3.2. General method for the preparation of carbohydrazide compounds (23a-23g)

A mixture of appropriate acid (0.10 mole) and thionyl chloride (17.8 gm, 0.15 mole) was refluxed for 1-2 hrs. Excess of thionyl chloride was distilled off and cooled in an ice bath. The resulting compound was taken in methanol immediately used for further processing. Hydrazine hydrate (4.8 gm, 0.1 mole) was added slowly with constant stirring, and the reaction mixture was refluxed for 4-5 hrs. Excess solvent was removed by distillation under reduced pressure, and the residue was poured into ice-cold water. The resultant solid was filtered, dried and recrystallized from ethanol to get the corresponding compound (23a-23g).

**Step-II**

4.3.3. General method for the preparation of various 1,3,4-oxadiazole-2-thiol (24a-24g)

A mixture of compound (23a-23g) (0.01 mole), carbon disulphide (0.01 mole) and potassium hydroxide (0.01 mole) in ethanol (50 mL) was refluxed until the evolution of \(\text{H}_2\text{S}\) gas ceased. After the completion of the reaction, excess solvents were evaporated under reduced pressure to get the residue which was dissolved in water and then acidified with dilute hydrochloric acid (10%) to pH 6. Progress of the reaction was monitored by TLC using solvent system hexane: ethyl acetate (8:2). The precipitate was filtered off, dried, and recrystallized from ethanol afforded the desired compounds (24a-24g).
Step-III

4.3.4. General method for the preparation of 2-(7-chloroquinolin-4-yl-thio)-5-(substituted)-1,3,4-oxadiazole (25a-25g)

A mixture of 4,7-dichloroquinoline (22) (0.5 gm, 2.5 mmole), appropriate 1,3,4-oxadiazole-2-thiol (24a-24g) (2.6 mmole) and potassium carbonate (0.38 gm, 2.75 mmole) in 10 mL of DMF was stirred for 5 hrs at room temperature and then heated for 10-12 hrs at 120 °C. After the completion of reaction, it was poured in ice-water, extracted with ethyl acetate. Progress of the reaction was monitored by TLC using hexane: ethyl acetate (7:3). The organic layer was separated, washed with brine and water, dried over anhydrous sodium sulfate and evaporated under reduced pressure gave a crude solid which was purified by crystallization in ethyl acetate: n-hexane solvent (25a-25g).

The physical constant of the synthesized compounds are tabulated in the following Table 4.1.
4.4. Characterization

4.4.1. Characterization data of compounds (25a-25g)

![Chemical structure diagram]

Table 4.1 Physical and analytical data of compounds (25a-25g)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Mol. Formula</th>
<th>M.W.</th>
<th>% Yield</th>
<th>M.P. (°C)</th>
<th>Elemental Analysis</th>
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<td></td>
<td></td>
<td></td>
<td>Found</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>%C %H %N %C %H %N</td>
</tr>
<tr>
<td>25a</td>
<td></td>
<td>C_{16}H_{9}ClN_{4}OS</td>
<td>340.79</td>
<td>81</td>
<td>236</td>
<td>56.39 2.66 16.44 56.23 2.67 16.40</td>
</tr>
<tr>
<td>25b</td>
<td></td>
<td>C_{17}H_{11}ClN_{4}OS</td>
<td>354.81</td>
<td>66</td>
<td>207-208</td>
<td>57.55 3.12 15.79 57.64 3.11 15.75</td>
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<tr>
<td>25c</td>
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<td>C_{16}H_{9}ClN_{4}OS</td>
<td>340.79</td>
<td>76</td>
<td>225-228</td>
<td>56.39 2.66 16.44 56.26 2.67 16.42</td>
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<tr>
<td>25d</td>
<td></td>
<td>C_{19}H_{12}ClN_{3}OS</td>
<td>365.84</td>
<td>79</td>
<td>216</td>
<td>62.38 3.31 11.49 62.55 3.30 11.46</td>
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<tr>
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<td>C_{20}H_{10}ClN_{3}O_{3}S</td>
<td>407.83</td>
<td>57</td>
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<td>58.90 2.47 10.30 58.82 2.48 10.33</td>
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<td>25f</td>
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<td>C_{20}H_{11}ClN_{4}OS</td>
<td>390.85</td>
<td>68</td>
<td>222</td>
<td>61.46 2.84 14.33 61.59 2.83 14.30</td>
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<td>25g</td>
<td></td>
<td>C_{17}H_{10}ClN_{3}OS</td>
<td>339.80</td>
<td>83</td>
<td>173-175</td>
<td>60.09 2.97 12.37 59.92 2.97 12.34</td>
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4.4.2. Characterization data for 2-(7-chloroquinolin-4-ylthio)-5-(pyridin-4-yl)-1,3,4-oxadiazole (25a)

IR (KBr, cm\(^{-1}\)):
- 3041 (C-H str. in aromatic ring)
- 1778 (-C=N- str. in oxadiazole ring)
- 1570 (-C=C- str. in aromatic ring)
- 1329 (-C-N- str. in quinoline ring)
- 1203 (-N-N- in oxadiazole ring)
- 1076 (-C-O-C- str. in oxadiazole ring)
- 783 (-C-Cl str.)
- 752 (-C-S-C- str. in sulfone group)

\(^1\)H NMR (400 MHz, DMSO–d\(_6\)):
- δ 8.90 (d, 1H, ArH of g)
- δ 8.84 (d, 1H, ArH of f)
- δ 8.20 (d, 1H, ArH of e)
- δ 8.17 (d, 1H, ArH of d)
- δ 7.80 (d, 2H, ArH of a)
- δ 7.76 (d, 2H, ArH of b)

\(^13\)C NMR (100 MHz, DMSO–d\(_6\)):
- δ 151.92
- δ 150.98
- δ 148.81
- δ 141.30
- δ 140.92
- δ 135.37
- δ 135.06
- δ 128.45
- δ 128.14
- δ 126.15
- δ 125.84
- δ 125.20
- δ 124.27
- δ 124.25
- δ 122.07

ESI-MS (m/z):
- 341.1 (M\(^+\))
- 343.0 (M\(^+\)+3)

Figure 4.1 FT–IR spectrum of compound 25a
Figure 4.2 $^1$H NMR spectrum of compound 25a

Figure 4.3 $^{13}$C NMR spectrum of compound 25a
4.4.3. Characterization data for 2-(5-(7-chloroquinolin-4-ylthio)-1,3,4-oxadiazol-2-yl)aniline (25b)

IR (KBr, cm$^{-1}$): 3417 & 3255 (N-H, 1$^\circ$ Amine), 3025 (C-H str. in aromatic ring), 1795 (-C=N str. in oxadiazole ring), 1560 (-C=C str. in aromatic ring), 1370 (-C-N str. in quinoline ring), 1230 (-N-N in oxadiazole ring), 1040 (-C-O-C str. in oxadiazole ring), 785 (-C-Cl str.), 755 (-C-S-C str. in thioether linker); $^1$H NMR (400 MHz, DMSO-d$_6$): δ 8.11 (d, 1H, ArH of g), 7.95 (d, 1H, ArH of e), 7.82 (d, 1H, ArH of i), 7.80 (d, 1H, ArH of f), 7.76 (d, 1H, ArH of h), 7.71 (dd, 1H, ArH of d), 7.64 to 7.33 (m, 3H, ArH of b & c), 7.05 (s, 2H, NH of a); $^{13}$C NMR (100 MHz, DMSO-d$_6$): δ 151.94, 151.61, 149.34, 148.24, 145.71, 141.03, 133.40, 128.77, 128.53, 128.50, 127.30, 126.19, 125.88, 125.22, 124.20, 123.12, 122.09; ESI-MS (m/z): 355.03 (M$^+$), 356.9 (M+3).
Figure 4.5 FT–IR spectrum of compound 25b

Figure 4.6 $^1$H NMR spectrum of compound 25b
Figure 4.7 $^{13}$C NMR spectrum of compound 25b

Figure 4.8 Mass spectrum of compound 25b
4.5. Biological evaluation

4.5.1. Antimicrobial activity data of compounds (25a-25g)

**Table 4.2. In-vitro antibacterial and antifungal activity in MIC* (μg/ml) of compounds (25a-25g)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>LogP#</th>
<th>Gram +Ve</th>
<th>Gram -Ve</th>
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<tr>
<td></td>
<td></td>
<td>Staphylococcus aureus</td>
<td>Streptococcus pyogenes</td>
<td>Pseudomonas aeruginosa</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MTCC 96</td>
<td>MTCC 442</td>
<td>MTCC 741</td>
</tr>
<tr>
<td>25a</td>
<td>2.6868</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>25b</td>
<td>3.0286</td>
<td>3.125</td>
<td>6.25</td>
<td>12.5</td>
</tr>
<tr>
<td>25c</td>
<td>2.6868</td>
<td>50</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>25d</td>
<td>4.5796</td>
<td>12.5</td>
<td>12.5</td>
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<tr>
<td>25e</td>
<td>3.5728</td>
<td>25</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>25f</td>
<td>4.0708</td>
<td>3.125</td>
<td>6.25</td>
<td>50</td>
</tr>
<tr>
<td>25g</td>
<td>3.9856</td>
<td>25</td>
<td>25</td>
<td>12.5</td>
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<tr>
<td>Ciprofloxacin†</td>
<td>3.125</td>
<td>3.125</td>
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<td>3.125</td>
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<tr>
<td>Ketoconazole†</td>
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<td>---</td>
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</tr>
<tr>
<td>DMSO (Control)</td>
<td>---</td>
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</table>

*MIC=Minimum inhibitory concentration
† Standard
# CLogP value determined by ChemDraw Ultra 11.0 software
4.6. Results and discussion

4.6.1. Antimicrobial activity

The antimicrobial activity studied (Table 4.2) for quinoline-oxadiazole derivatives (25a-25g) against several strains demonstrated that some of the compounds revealed a good deal of activity against all the mentioned bacteria. Compound 25b with 2-amino phenyl and 25f 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 (25b and 25f) were also found to contribute highest inhibition of *Streptococcus pyogenes* at 6.25 μg/mL of MIC. Likewise, among the potent derivatives against *P. aeruginosa*, the most potent compounds possessed highest lipophilicity (25d, LogP = 4.5796) and higher lipophilicity of compounds 25b (LogP = 3.0286) and 25g (LogP = 3.9856) at 12.5 μg/mL of MIC. Final derivatives 25b (LogP = 3.0286) with 2-amino phenyl, 25e (LogP = 3.5728) with coumarin and 25g (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 25a (LogP = 2.6868) with 4-pyridinyl and 25c (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 seen that the compound (25d, 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. Compound 25f also showed good activity with MIC of 12.5 μg/mL to inhibit the *E. coli* growth. 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 reveal that, the synthesized compounds showed good potency against the mentioned fungi. Final compounds 25b with 2-amino phenyl (LogP = 3.0286), 25f with quinoline (LogP = 4.0708) and 25g 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 25c with lowest lipophilicity (LogP = 2.6868) exhibited lower activity at 100 μg/mL of MIC against the same fungal strain. In case of compound 25a exhibiting lower lipophilicity showed good activity (MIC 25 μg/mL) against the mentioned fungi, activity decreased with the increase in lipophilicity (LogP). The later compounds 25b, 25e, and 25f 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.
References