Synthesis, Characterization and Biological evaluation of some newer 5-[6-chloro/fluoro/nitro-2-(p-chloro/fluoro/methyl phenyl)-quinolin-4-yl]-1,3,4-oxadiazole-2-thiols

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ABSTRACT
Recent study shows that quinolines represent one of the most active classes of compounds possess wide spectrum biodynamic activities and use as potent therapeutic agents. In present research work, 5-[6-chloro/fluoro/nitro-2-(p-chloro/fluoro/methyl phenyl)-quinolin-4-yl]-1,3,4-oxadiazole-2-thiols have been synthesized by condensation of substituted quinoline-4-carbohydrazides and mixture of carbon disulphide and potassium hydroxide. All of these compounds were screened for their in vitro anti microbial assay against gram (+ve), gram (-ve) bacteria and fungi activity compared with standard drugs viz., Ampicillin, Chloramphenicol, Ciprofloxacin, Norfloxacin, Griseofulvin and Nystatin at different concentrations.

Keywords: Quinolines; 1,3,4-oxadiazole-2-thiols; therapeutic agents; anti-microbial assay

1. INTRODUCTION

Tuberculosis (TB) is a global epidemic caused by various strains of mycobacterium, usually Mycobacterium tuberculosis (H37RV). Tuberculosis has been considered to be a disease of poverty for many years with quite rare occurrence in the developed countries. Unfortunately recently more people in the developed world are contracting tuberculosis because their immune systems are compromised by immunosuppressive drugs, substance abuse or AIDS. Several decades ago effective anti-TB drugs have been launched and one could hardly find a TB case to be demonstrated at the medicinal universities. But TB stroke back1. The return of tuberculosis was declared by World Health Organization (WHO) as a global emergency compared to a hypothetic third world war with 9 million new TB cases and two million deaths reported each year2,3, about one-third of the world’s population is already infected with M. tuberculosis.4

The quinoline was reported to exhibit various biological activity such as antiamoebic5, antimalarial6,7, antiviral8,9, as well as anti-inflammatory activity10,11. In addition, the discovery of nalidixic acid, a urinary tract antimicrobial drug12, prompted the synthesis of many quinoline derivatives and evaluation for their antimicrobial activity13-15 and antibacterial activity.
Norfloxacin, ofloxacin and ciprofloxacin (nalidixic acid analogs) were marketed as antibacterial agent\textsuperscript{16}. Besides, oxadiazone rings are important examples of the heteroazoles that by themselves or in combination with other ring systems possess antimicrobial\textsuperscript{17-19,21} as well as antibacterial activity. In view of this fact and as a continuation of a research program carried out in our laboratory series of substituted oxadiazolyquinoline have been synthesized to investigate their antimicrobial activity and antitubercular activity.

2. RESULT AND DISCUSSION

2.1. Chemistry

Preparation of 5-(2-(4-chloro/fluoro/methylphenyl)-6-fluoro/chloro/nitroquinoline-4-yl)-1,3,4-oxadiazone-2-thiol (4a-i) is summarized in Scheme 1. Various 2-(4-chloro/fluoro/methylphenyl)-6-(fluoro/chloro/nitroquinoline)-4-carbohydrazide (3a-i) were treated with potassium hydroxide and carbon disulphide in ethanol was heated under reflux until the evolution of H\textsubscript{2}S ceases. The reaction mixture was concentrated and dissolved in water and acidified with HCl. The resulting product was recrystallised from methanol. The yields of the products were obtained in the range of 65-80 %. Designed series of molecules scheme-1 were characterized by \textsuperscript{1}H NMR, IR and Mass spectrometry techniques before evaluating for antimicrobial and antitubercular activity.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {R$_1$ \(\text{SOCl}_2\) \text{H}_2\text{N}-\text{NH}_2\cdot\text{H}_2\text{O}};
\node at (1,1) {R$_1$ \text{KOH, CS}_2};
\node at (-1.5,0) {R=4-Cl-C$_6$H$_4$, 4-F-C$_6$H$_4$, 4-CH$_3$-C$_6$H$_4$};
\node at (1.5,0) {R$_1$=4-F, 4-Cl, 4-NO$_2$};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1}. Comparative antimicrobial activity of 5-[6-chloro/fluoro/nitro-2-(p-chloro/fluoro/methylphenyl)-quinolin-4-yl]-1,3,4-oxadiazone-2-thiols (4a-i). (Different Inhibition Concentration in \(\mu\text{g/ml}\)).

2.2. Antimicrobial and antitubercular activity

The products (4a-i) were assayed for their in vitro biological assay like antibacterial activity towards S. pyogens MTCC-442, S. aureus MTCC-96 (Gram positive) and E. coli MTCC-443, P. aeruginosa MTCC-424 (Gram negative) bacterial strain and antifungal activity towards A. niger MTCC-282 and A. clavatus MTCC-1323 at different concentrations: i.e. 0 (control), 5, 25, 50, 100, 250 (\(\mu\text{g/ml}\)) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds (Xa-i) were compared with standard drugs viz., Ampicilline, Chloramphenicol, Ciprofloxacin, Norfloxacin, Griseofulvin and Nystatin. The result of antimicrobial activity is presented Table in given below bold value presented that, these compounds are biological active near or above than the standard drugs.
Table 1

| Entry | R          | R₁         | Antibacterial activity (Zone of inhibition in m.m.) |  |
|-------|------------|------------|---------------------------------------------------|---|
|       |            |            | S.Pyogens MTCC-442 | S.aureus MTCC-96 |
|       |            |            | 5 25 50 100 250    | 5 25 50 100 250  |
| 4a    | 4-Cl-C₆H₄ | 4-F        | 09 14 17 **19**    | 13 14 15 19      |
| 4b    | 4-Cl-C₆H₄ | 4-Cl       | 10 13 15 17        | 10 12 **16** 18  |
| 4c    | 4-Cl-C₆H₄ | 4-NO₂      | 10 12 14 16        | 11 13 14 17      |
| 4d    | 4-F-C₆H₄  | 4-F        | 11 13 14 17        | 11 13 **16** 17  |
| 4e    | 4-F-C₆H₄  | 4-Cl       | 09 11 14 **19**    | 10 13 15 16      |
| 4f    | 4-F-C₆H₄  | 4-NO₂      | 10 13 14 18        | 12 13 **16** 17  |
| 4g    | 4-CH₃-C₆H₄| 4-F        | 11 13 15 18        | 09 11 **14** 19  |
| 4h    | 4-CH₃-C₆H₄| 4-Cl       | 10 14 17 **20**    | 10 13 14 **18**  |
| 4i    | 4-CH₃-C₆H₄| 4-NO₂      | 11 14 **18** 20    | 09 14 **17** 20  |

Comparative activity of 4(a-i) with known chosen standard drugs

| Standard drug       | Antibacterial activity |
|---------------------|------------------------|
| Ampicilline         | 11 14 19 18 19 10 13 14 16 18 |
| Chloramphenicol     | 10 13 19 20 20 12 14 19 20 21 |
| Ciprofloxacin       | 16 19 21 21 22 17 19 21 22 21 |
| Norfloxacin         | 18 19 20 21 21 19 22 25 26 28 |

Table 2

| Entry | R          | R₁         | Antibacterial activity (Zone of inhibition in m.m.) |  |
|-------|------------|------------|---------------------------------------------------|---|
|       |            |            | E.coli MTCC-443 | P.aeruginose MTCC-424 |
|       |            |            | 5 25 50 100 250 | 5 25 50 100 250  |
| 4a    | 4-Cl-C₆H₄ | 4-F        | **15** 17 20 21 | 12 13 14 15      |
| 4b    | 4-Cl-C₆H₄ | 4-Cl       | 12 13 17 19     | 13 **15** 18 19  |
| 4c    | 4-Cl-C₆H₄ | 4-NO₂      | 14 16 17 **21** | 10 12 13 15      |
| 4d    | 4-F-C₆H₄  | 4-F        | 11 12 15 **21** | 10 13 15 17      |
| 4e    | 4-F-C₆H₄  | 4-Cl       | 12 15 **19** 21 | 12 14 16 19      |
| 4f    | 4-F-C₆H₄  | 4-NO₂      | 14 16 17 18     | 11 **15** 16 18  |
| 4g    | 4-CH₃-C₆H₄| 4-F        | 12 13 15 17     | 12 14 16 18      |
| 4h    | 4-CH₃-C₆H₄| 4-Cl       | **15** 17 18 20 | 11 14 16 19      |
| 4i    | 4-CH₃-C₆H₄| 4-NO₂      | **15** 17 19 22 | 10 12 16 17      |

Comparative activity of 4(a-i) with known chosen standard drugs

| Standard drug       | Antibacterial activity |
|---------------------|------------------------|
| Ampicilline         | 14 15 16 19 20        |
| Chloramphenicol     | 14 17 23 23 23        |
| Ciprofloxacin       | 20 23 28 28 28        |
| Norfloxacin         | 22 25 26 27 29        |
Table 3

| Entry | R               | R₁      | Antifungal activity (Zone of inhibition in m.m.) |
|-------|-----------------|---------|-----------------------------------------------|
|       |                 |         | A.nigar MTCC-282                              | A.clavatus MTCC-1323 |
|       |                 |         | 5     | 25   | 50   | 100  | 250  | 5    | 25   | 50   | 100  | 250  |
| 4a    | 4-Cl-C₆H₄       | 4-F     | -     | 19   | 21   | 24   | 25   | -    | 19   | 21   | 22   | 24   |
| 4b    | 4-Cl-C₆H₄       | 4-Cl    | -     | 18   | 20   | 23   | 24   | -    | 18   | 20   | 22   | 23   |
| 4c    | 4-Cl-C₆H₄       | 4-NO₂   | -     | 20   | 22   | 23   | 25   | -    | 18   | 19   | 22   | 24   |
| 4d    | 4-F-C₆H₄        | 4-F     | -     | 16   | 17   | 20   | 23   | -    | 10   | 20   | 21   | 24   |
| 4e    | 4-F-C₆H₄        | 4-Cl    | -     | 18   | 19   | 22   | 25   | -    | 18   | 20   | 22   | 24   |
| 4f    | 4-F-C₆H₄        | 4-NO₂   | -     | 17   | 19   | 22   | 24   | -    | 21   | 22   | 23   | 25   |
| 4g    | 4-CH₃-C₆H₄      | 4-F     | -     | 19   | 22   | 23   | 24   | -    | 21   | 22   | 23   | 25   |
| 4h    | 4-CH₃-C₆H₄      | 4-Cl    | -     | 18   | 21   | 22   | 24   | -    | 19   | 20   | 22   | 24   |
| 4i    | 4-CH₃-C₆H₄      | 4-NO₂   | -     | 19   | 20   | 21   | 23   | -    | 18   | 18   | 21   | 22   |

Comparative activity of 4(a-i) with known chosen standard drugs

| Standard drug | Antifungal activity |
|---------------|---------------------|
| Griseofulvin  | 19 23 25 28 18 21 22 22 24 |
| Nystain       | 18 19 24 29 18 21 24 25 26 |

All compounds were initially screened for their antitubercular activity at 6.25 μg/mL concentration against MTB H37Rv strain by the Tuberculosis Antimicrobial Acquisition & Coordinating Facility (TAACF) in BACTEC 12B medium using the Microplate Alamar Blue Assay. Unfortunately, in the preliminary screening all compounds (4a-i) were inactive against MABA assay and all compounds possess both IC₅₀ > 100 and IC₉₀ > 100.

3. EXPERIMENTAL SECTION

All research chemicals were purchased from Sigma–Aldrich and used as such for the reactions. Reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel GF254 plates from E-Merck Co and compounds visualized either by exposure to UV light or staining with reagents. Melting points were determined in open capillaries and are uncorrected. The IR spectra were recorded on SHIMADZU- FTIR-8400 spectrophotometer using KBr pellet method. ¹H NMR spectra were recorded on Bruker 300-MHz NMR spectrometer in CDCl₃ with TMS as internal standard. Mass spectrum was recorded on JOEL SX 102/DA-600-Mass spectrometer and elemental analysis was carried out using Heraus C, H, and N rapid analyzer.

General procedure for the synthesis of 2-(4-chloro/flouro/methylphenyl)-6-(fluoro/chloro/nitroquinoline)-4-carboxylic acid (1a-i)

A mixture of 4-chloro/flouro/methylbenzaldehyde (0.01 mole), freshly distilled pyruvic acid (0.01 mole; 0.88 g) and absolute ethyl alcohol (25 ml) was refluxed to the boiling point on a water bath and a solution of 4-flouro/chloro/nitroaniline (0.01 mole) in absolute ethyl alcohol (25 ml) was added slowly with frequent shaking. The content was refluxed for 3 hours and allowed to stand overnight. The product was filtered and recrystallised from ethanol. Yield: 70-80 %.
General procedure for the synthesis of 2-(4-chloro/flouro/methylphenyl)-6-(fluoro/chloro/nitroquinoline)-4-carboxyhydrazide (3a-i)

A mixture of 2-(4-chloro/flouro/methylphenyl)-6-(fluoro/chloro/nitroquinoline)-4-

General procedure for the synthesis of 5-(2-(4-chloro/flouro/methylphenyl)-6-fluoro/chloro/nitroquinoline-4-yl)-1,3,4-oxadiazole-2-thiol (4a-i)

A mixture of 2-(4-chloro/flouro/methylphenyl)-6-(fluoro/chloro/nitroquinoline)-4-

5-(6-chloro-2-(4-chlorophenyl)quinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4b)

5-(2-(4-chlorophenyl)-6-nitroquinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4c)

5-(6-fluoro-2-(4-fluorophenyl)quinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4d)

5-(6-chloro-2-(4-fluorophenyl)quinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4e)
(d, 2H, Ar-H), 8.03-8.05 (m, 1H, Ar-H); IR (KBr, cm⁻¹): 3010, 2936, 2902, 1674, 1458, 1344, 1305, 1117, 1027, 807, 644. ;Anal. Caled for C₁₁H₈ClN₅O₃S: C, 57.05; H, 2.52; N, 11.70; O, 4.47; S, 8.96. Found: C, 57.15; H, 2.57; N, 11.20; O, 4.76; S, 8.52.; MS: m/z 357.

5-(2-(4-fluorophenyl)-6-nitroquinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4f)

Yield: 68 %; mp 126 °C; ¹H NMR (DMSO-d₆) δ ppm: 3.10 (s, 1H, -SH), 6.80-6.82 (d, 2H, Ar-H), 7.40-7.42 (m, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.90-7.92 (d, 1H, Ar-H), 8.18-8.20 (d, 1H, Ar-H), 8.60-8.62 (m, 1H, Ar-H); IR (KBr, cm⁻¹): 3300, 3010, 2856, 1734, 1300, 1110, 1022, 860. ;Anal. Caled for C₁₁H₈ClFN₅O₃S: C, 55.43; H, 2.46; N, 15.21; O, 13.03; S, 8.71. Found: C, 55.40; H, 2.50; N, 15.30; O, 13.10; S, 8.80.; MS: m/z 368.

5-(6-fluoro-2-p-tolyquinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4g)

Yield: 77 %; mp 138 °C; ¹H NMR (DMSO-d₆) δ ppm: 1.10 (s, 3H, -CH₃), 3.10 (s, 1H, -SH), 6.80-6.82 (d, 2H, Ar-H), 7.40-7.42 (m, 1H, Ar-H), 7.80 (s, 1H, Ar-H), 7.90-7.92 (d, 1H, Ar-H), 8.18-8.20 (d, 2H, Ar-H), 8.60-8.62 (m, 1H, Ar-H); IR (KBr, cm⁻¹): 3300, 3010, 2856, 1734, 1300, 1110, 1022, 860. ;Anal. Caled for C₁₁H₈FClN₅O₃S: C, 55.43; H, 2.46; N, 15.21; O, 13.03; S, 8.71. Found: C, 55.40; H, 2.50; N, 15.30; O, 13.10; S, 8.80.; MS: m/z 337.

5-(6-chloro-2-p-tolyquinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4h)

Yield: 69 %; mp 149 °C; ¹H NMR (DMSO-d₆) δ ppm: 1.12 (s, 3H, -CH₃), 3.04 (s, 1H, -SH), 6.98-7.00 (d, 2H, Ar-H), 7.10-7.12 (m, 1H, Ar-H), 7.39-7.42 (m, 1H, Ar-H), 7.80-7.82 (d, 2H, Ar-H), 7.98 (s, 1H, Ar-H), 8.04-8.06 (m, 1H, Ar-H); IR (KBr, cm⁻¹): 3300, 3240, 2900, 2535, 1850, 1670, 1110, 980, 830, 650. ;Anal. Caled for C₁₈H₁₂ClN₅O₃S: C, 61.10; H, 3.40; N, 11.86; O, 4.63; S, 9.00. Found: C, 61.05; H, 3.42; N, 11.80; O, 4.50; S, 9.05.; MS: m/z 354.

5-(6-nitro-2-p-tolyquinolin-4-yl)-1,3,4-oxadiazole-2-thiol (4i)

Yield: 77 %; mp 152 °C; ¹H NMR (DMSO-d₆) δ ppm: 1.11 (s, 3H, -CH₃), 3.10 (s, 1H, -SH), 7.10-7.13 (d, 2H, Ar-H), 7.60-7.62 (d, 2H, Ar-H), 8.10-8.13 (s, 1H, Ar-H), 8.40-8.44 (m, 1H, Ar-H), 8.50-8.52 (m, 1H, Ar-H), 8.80-8.83 (m, 1H, Ar-H); IR (KBr, cm⁻¹): 3325, 3240, 2939, 2900, 1850, 1670, 1116, 970, 820. ;Anal. Caled for C₁₈H₁₂N₄O₃S: C, 59.33; H, 3.30; N, 15.40; O, 13.17; S, 8.88. Found: C, 59.20; H, 3.15; N,15.45; O, 13.20. S, 8.80.; MS: m/z 364.

4. CONCLUSIONS

In the present paper, we report the synthesis, spectral studies and its Antimicrobial and antimycobacterial activity of various quinoline derivatives. The high bioactivity of these compounds makes them suitable hits for additional in vitro and in vivo evaluations, in order to develop new class of Antimicrobial and antimycobacterial drugs or prodrugs with potential use in the antibacterial, antifungal and tuberculosis treatment. Further studies in this area are in progress in our laboratory.

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