STUDIES ON SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME SUBSTITUTED FLUOROQUINOLONES'

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Abstract
In the present study the synthesis of Fluoroquinolone nucleus, 7-chloro-6-fluoro-1, 4-dihydro-4-oxoquinoline-3-ethyl carboxylate has been reported by the microwave-assisted condensation of 3-chloro-4-fluoro aniline and diethyl (ethoxymethylene) malonate (EMME) under solvent free conditions. The microwave-assisted synthesis of Fluoroquinolone nucleus was successfully standardized and optimized making the method easy, more convenient & less time – consuming and eco-friendly requiring less chemicals and reagents and with better yield making the process more economic than other conventional methods. N₁-alkyl / aryl/arylsulphonyl substituted and C₇ piperazinyl derivatives of the title compounds have been synthesized to identify newer fluoroquinolones which have better efficacy, lesser side-effects and well tolerability than
the already available ones. The biological evaluation of the synthesized fluoroquinolone
derivatives was carried out using disc method and compounds V₂, VP₂, V₃, VP₃ₐ, V₅, VP₅
V₁₀, VP₁₀ were found to be active against both Gram-positive and Gram-negative bacteria
having activity comparable to that of standard drug i.e. Ciprofloxacin.(5 μg/disc)
Comparison of activity of the test compounds indicates that benzenesulphonamido
moiety at N₁ position and piperazine moiety at C₇ position possibly contributes to activity
either due to stronger binding with the receptor or better hydrophilic lipophilic balance
of the overall molecule. It is clear from the results that replacement of 7-chloro
substituent by piperazine improves the spectrum of activity of fluoroquinolones, showing
activity against *Pseudomonas* species as well as Gram-positive and Gram-negative
bacteria whereas the 7-chloroquinolones are active against Gram-positive and Gram-
negative bacteria.

**Key words:** Fluoroquinolone, microwave, Gram-positive bacteria, Gram-negative
bacteria.

1. Introduction

Fluoroquinolones as a class is now a days one of the frequently prescribed class of
antibacterial. Fluoroquinolones have gained stupendous importance during the last two
decades because of their potent anti-bacterial activity against wide varieties of gram-
positive and gram-negative pathogenic bacteria with minimum toxic side-effects and
some what different mechanism of action than other available antibacterial drugs.¹ To
date, many fluoroquinolone antibacterial agents have been introduced into clinical use
with significant improvement in antibacterial spectrum and activity. A vast array of
fluoroquinolones having excellent broad-spectrum activity forms an invaluable part of the
present anti-infective armory of the clinicians. A number of these compounds are today's
blockbusters of the antibacterial market due to their therapeutic efficacy and tolerable
side-effects even, challenging the predominance of well-established β-lactam antibiotics
which are becoming more prone to the resistant pathogenic bacteria. The fluoroquinolones
are the fastest growing antibacterial class in terms of global revenue, increasingly being used in both the hospital and community sectors to treat a broad range
of infection ². The boost in fluoroquinolone prescribing was attributable to the
introduction and use of newer, broader-spectrum fluoroquinolones with activity against *S.
Pneumoniae* (for example, levofloxacin, gatifloxacin, and moxifloxacin). However,
increased prescribing has led to the recent emergence of fluoroquinolone-resistant
bacteria which has necessitated the search or newer drugs with efficacy against resistant
strains and efforts are on worldwide in this direction.³,⁴ The present work is a part of
these worldwide efforts to develop better Fluoroquinolones than the available ones with
respect to activity or toxicity or resistance or all of these.
1.1 Structure-Activity Relationship (SAR): \(2,5,6\)

![Chemical Structure](image)

**Position 1:** \(2,5,6\)

Earlier study indicated that substitution at N-1 position is important for anti-bacterial activity. QSAR analysis of a set of N-1 allyl and alkyl derivatives suggested and optimum STERIMOL length of 0.42 nm, corresponding approximately to an ethyl group. STERIMOL is a program that calculates a set of five parameters characterizing size and shape of a substituent. STERIMOL length is defined as length of substituent along the axis of bond between the substituent and the parent molecule. Introduction of a t-butyl group at N-1 produced quinolones with enhanced activity against gram positive bacteria with minor reduction of activity against gram-negative bacteria.

**Position - 7:** \(1,3,7,8\)

C-7 substituent is regarded as drug–enzyme interaction domain, it is also concluded that the cell permeability is dominantly controlled. It also affects the interaction with target site. The inhibition of DNA gyrase and cell permeability of quinolones is greatly influenced by the nature of C-7 substituent on the standard structure of 4-quinolone-3-carboxylic acid C-7 piperazinyl group in addition to C-6 fluorine substituent has anti-bacterial potency for superior to that of earlier classical quinolones against both gram-positive and gram-negative bacteria. The pipeprazine moiety of 7-piperazine quinolones possesses enough structural flexibility to allow product optimization. In general, the substitution of methyl at C-4 position of the piperazinyl group enhances gram-positive anti-bacterial activity with slight decrease in gram-negative activity.

2. Materials and Methods:
Melting points were taken in open glass capillary using Elico melting point apparatus and are uncorrected. The identification and purity of the synthesized compounds were checked by Thin layer chromatography using silica gel G as adsorbant. The spots were detected by exposure to iodine vapours. Infrared spectra of compounds were recorded on Schimadzu IR 408 spectrophotometer model using Nujol as medium. Proton (1H) NMR spectra of compounds were recorded on BROOT spectrophotometer (800 MHz) using DMSO-\(d_6\) as solvent, at Analytical Center, University of Pune. The elemental analysis (CHN) of compounds was carried out at SAIF IIT-Mumbai. All microwave reactions were carried on Raga’s Electromagnetic System with automatic power setting from P-1 to P-10. The reactions were started at power P-5 for initial 30 sec. and after every 30 sec. reaction mixtures were monitored for completion of the reaction with the help of TLC.
2.1 Procedure for Synthesis of 7-Chloro-6-Fluoro-1, 4-dihydro-4-Oxoquinoline-3-Carboxylic acid (4)\textsuperscript{4,9}

**Step 1:** (Scheme 1)

Equimolar amounts of 3-chloro-4-fluoro aniline (1) (1.45 gm, 0.01 mol) (white crystalline solid, m.p. 44 -47 °C) and diethyl (ethoxymethylene) malonate (EMME) (2) (2.16 gm, 0.01mol), (almost colourless liquid, b.p. 279-281 °C) were taken in a beaker under solvent-free condition, when clear solution was obtained by shaking which was irradiated under microwave for 1-1.5 min at high power (540-750 watts) by which time the whole reaction mixture was gradually converted into a semisolid mass having white to pale yellow appearance which was washed with acetone to get almost white solid and was recrystalized using N, N- dimethyl formamide (DMF) as solvent.

**Scheme 1:**

\[ \begin{align*}
\text{F} & \quad \text{Cl} \\
\text{NH}_2 & \quad \text{EtO} \\
\text{3-Chloro-4-Fluoro} & \quad \text{EMME} \\
\text{Aniline} & \quad \text{EtOOC} \\
\text{1} & \quad \text{COOEt} \\
& \quad \text{Microwave} \\
& \quad 1-1.5 \text{ min} \\
& \quad \text{3-Chloro-6-Fluoro-1,4-dihydro-} \\
& \quad \text{4-oxoquinoline-3-carboxylate} \\
\end{align*} \]

**Step 2** (Scheme 2)

The product of step-1 (an ethyl ester) (3) (2.7 gm, 0.01 mol) was dissolved in 50 ml of benzene and hydrolyzed to corresponding carboxylic acid using 50 ml of 5N aqueous hydrochloric acid. Then the reaction mixture was stirred and heated under reflux for 5-6 hours. The white solid was gradually precipitated at the bottom of aqueous layer. The solid thus obtained was filtered, washed with water till neutral, dried and recrystalized using acetone as solvent to give the product. (4)

**Scheme 2:**

\[ \begin{align*}
\text{F} & \quad \text{Cl} \\
\text{N} & \quad \text{H} \\
\text{3} & \quad \text{COOEt} \\
& \quad \text{Benzene / 5N aq. HCl} \\
& \quad \text{Reflux 6 hrs} \\
& \quad 7-\text{chloro-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid} \\
\end{align*} \]
2.2 General Method of Synthesis of \(n_1\)-alkyl / aryl/aryl Sulphonyl -7-Chloro-6-Fluoro-1,4-dihydro-4-Oxoquinoline-3- Carboxylic acid (5) (Scheme 3)\(^{10}\)

7-chloro-6-fluoro-1, 4-dihydro-4-oxoquinoline-3- carboxylic acid (4) (2.56 g, 0.01 mol) was added to 10 ml of N, N- dimethyl formamide (DMF), followed by addition of alkyl / aryl/aryl sulphonyl halide (0.01 mol). The reaction mixture was heated to dissolve the 3-acid which was partially soluble in cold condition. Then anhydrous potassium carbonate (3.40 g, 0.02mol) was added to the reaction mixture. The whole reaction mixture was heated to 120-140\(^0\)C and stirred for 5-8 hrs. Then the reaction mixture was poured onto crushed ice or ice cold water, washed with cold water to remove N, N- dimethyl formamide (DMF) and potassium carbonate if any. The solid (5) obtained was recrystallized from acetone to give the carboxylic acid.

**Diagram 3:**

\[
\text{N-1 SUBSTITUTION}:
\]

\[
\begin{align*}
 &\text{F} &\text{O} &\text{COOH} \\
 &\text{Cl} &\text{N} &\text{H} \\
 &\text{4} &\xrightarrow{\text{anhydrous } K_2CO_3} &\text{F} &\text{O} &\text{COOH} \\
 &\text{Cl} &\text{N} &\text{1} &\text{SUTIST} &\text{1} &\text{O} \\
 &\text{dry DMF} / R_1-X &120-140^0C \\
 &\text{5} &\text{Where, } R_1= \text{various alkyl, aryl} &\text{aryl sulphonyl moieties}
\end{align*}
\]

2.3 General Procedure for the Synthesis of \(n_1\)-alkyl / aryl/aryl Sulphonyl -7-Piperazinyl -6-Fluoro-1,4-dihydro-4-Oxoquinoline-3- Carboxylic acid (6) (Scheme 4)\(^{10,11}\)

A mixture of the product i.e., \(N_1\) substituted 7-chloro-6-fluoro-1, 4-dihydro-4-oxoquinoline-3-carboxylic acid (5) (2.7 mmol) in dry dimethyl sulphoxide and piperazine (18 mmol, 1.6 gm) was heated at 140\(^0\)C with stirring for 2.5-8 hrs. Cooled to room temperature and then 10 ml of cold water was added to the mixture and acidified to pH 7 with dilute acetic acid. The resulting precipitate (6) washed with water, dried and recrystallized from ethanol and DMF.

**Diagram 4:**

\[
\text{C-7 SUBSTITUTION}:
\]

\[
\begin{align*}
 &\text{F} &\text{O} &\text{COOH} \\
 &\text{Cl} &\text{N} &\text{R_1} \\
 &\text{5} &\xrightarrow{\text{R_7-H, DMF, \text{140}^0C \text{8hrs}}} &\text{F} &\text{O} &\text{COOH} \\
 &\text{Cl} &\text{N} &\text{R_1} \\
 &\text{6}
\end{align*}
\]
2.4 Antimicrobial Screening test\textsuperscript{12,13}

The plates were prepared with Mueller Hinton Agar for the use in the Bauer-Kirby method for rapidly growing aerobic organisms. A sterile non-toxic cotton swab on a wooden applicator was dipped into the standardized inoculum (turbidity so adjusted, as to obtain confluent growth on the Petri plate) and the soaked swab was rotated firmly against the upper inside wall of the tube to express excess fluid. The entire agar surface was streaked off the plate with the swab three times, turning the plate at 60° angles between each streaking. The inoculum was allowed to dry for 5-15 minutes with the lid in place. The disc was applied using aseptic technique. The discs were deposited with centers at least 24 mm apart. The inoculated culture medium prepared as above was immediately incubated at 37°C and was examined after 14-19 hours or later if necessary. The zones showing complete inhibition were measured and the diameters of the zones to nearest millimeter were recorded.

3. Spectral analysis:

1) \(N_1(N^{-}-\text{phenyl carbamoyl methyl}) - 7\text{-chloro-6-fluoro-1, 4-dihydro-4-}
\text{oxoquinilone- 3-carboxylic acid. (V}_1\text{)}:\)

I.R. (KBr, cm\textsuperscript{-1}): 3190 (Secondary amide N-H), 1701 (Carboxylic acid C=O), 1600
(Pyridone C=O), 1473 (C-N stretch of quinoline having C=C-N), 1030 (C-F), 754 (C-Cl)

2) \(N_1(p\text{-ethylphenyl sulphonyl}) - 7\text{-chloro-6-fluoro-1, 4-dihydro-4-oxoquinoline-3-}
\text{carboxylic acid(V}_4\text{)}:\)

I.R. (KBr, cm\textsuperscript{-1}): 2972 (Ethyl C-H stretch), 1700 (Carboxylic acid C=O), 1600
(Pyridone C=O), 1473 (C-N stretch of quinoline having C=C-N), 1359, (SO\textsubscript{2} symmetric),1155 (SO\textsubscript{2} asymmetric), 1033 (C-F), 734(C-Cl)

3) \(N_1(p\text{-acetamidobenzenesulphonyl}) - 7\text{-chloro-6-fluoro-1, 4-dihydro – 4-}
\text{oxoquinoline-3-carboxylic acid (V}_6\text{)}:\)
I.R. (KBr, cm\(^{-1}\)): 3185 (Secondary amide N-H), 1700 (Carboxylic acid C=O), 1600 (Pyridone C=O), 1473 (C-N stretch of quinoline having C=C-N), 1359 (SO\(_2\) symmetric) 1172 (SO\(_2\) asymmetric) 1035 (C-F), 734 (C-Cl)

4) \(N_1\) (3-carboxyphenyl sulphonyl) -7-chloro-6-fluoro-1, 4-dihydro- 4-oxoquinoline-3-carboxylic acid(V\(_8\)):

I.R. (KBr, cm\(^{-1}\)): 1700 (Carboxylic acid C=O), 1618 (Pyridone C=O), 1473 (C-N stretch of quinoline having C=C-N), 1379 (Aryl C-O stretch) 1359 (SO\(_2\) symmetric), 1120 (SO\(_2\) asymmetric) 1035 (C-F), 655 (C-Cl)

5) \(N_1\) (2-hydroxyethyl) -7-chloro-6-fluoro-1, 4-dihydro-4-oxoquinoline- 3-carboxylic acid (V\(_{10}\)):

I.R. (KBr, cm\(^{-1}\):1720 (Carboxylic acid C=O), 1612 (Pyridone C=O), 1488 (C-N stretch of quinoline having C=C-N), 1047 (Primary alcohol O-H), 1029 (C-F), 739, (C-Cl)

\(^1\)H NMR (DMSO- d\(_6\), \(\delta\) ppm): 1.29 (t, 2H, ethyl C-1), 3.71(t, 2H, ethyl C-2), 4.23 (t, 1H, alcoholic OH), 8.03 (d, 1H, C8 proton), 8.21(d, 1H, C5 proton), 8.49 (s, 1H, C2 proton.) 8.58 (s, 1H, carboxylic-OH)

Elemental analysis (C\(_{12}\)H\(_9\)NO\(_4\)FCl), Found (Calcd) %: C, 49.88 (50.42), H, 4.23 (3.75), N, 5.45 (4.92).

6) \(N_1\) (p-tolyl sulphonyl)-7-(N'\(_4\)-(3-trifluromethylphenyl)-piperazino-6-fluoro- 1, 4-dihydro-4-oxoquinoline -3-carboxylic acid (VP\(_{3B}\))

I.R. (KBr, cm\(^{-1}\):2850 (Piperazine C-H), 1710 (Carboxylic acid C=O), 1618 (Pyridone C=O) 1310 (SO\(_2\) symmetric) 1172 (SO\(_2\) asymmetric) 1034 (C-F)

7) \(N_1\) (p-acetamidophenylsulphonyl)-7-piperazino-6-fluoro-1, 4-dihydro- 4-piperazino-6-fluoro-1, 4-dihydro- 4-oxoquinoline-3-carboxylic acid (VP\(_6\)):

I.R. (KBr, cm\(^{-1}\)): 3340 (Piperazine N-H), 2853 (Piperazine C-C), 1718 (Carboxylic acid C=O), 1616 (Pyridone C=O), 1484 (C-N stretch of quinoline having C=C-N), 1378 (Aromatic C-N), 1295 (SO\(_2\) symmetric), 1172 (SO\(_2\) asymmetric), 1037 (C-F)

8) \(N_1\) (3-carboxyphenyl)-7-piperazino-6-fluoro-1, 4-dihydro-4-oxoquinoline-3-carboxylic acid (VP\(_8\))

I.R. (KBr, cm\(^{-1}\)): 3422 (Piperazine N-H), 2863 (Piperazine C-H), 1707 (Carboxylic acid C=O) 1618 (Pyridone C=O) 1490 (C-N stretch of quinoline having C=C-N) 1378(SO\(_2\) symmetric), 1126 (SO\(_2\) asymmetric) 1032 (C-F)

Table 1: Physical data of Synthesized \(r_1\) Substituted 3-acid compounds

<table>
<thead>
<tr>
<th>Structure No.</th>
<th>Substituent (R_1)</th>
<th>Addendum ((R_1)-X)</th>
<th>Melting point (°C)</th>
<th>Yield (%)</th>
<th>Recrystalizing solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>(V_1).</td>
<td>Acetanilido-</td>
<td>Chloro acetanilide</td>
<td>180-182</td>
<td>65.00</td>
<td>Acetone</td>
</tr>
<tr>
<td>(V_4).</td>
<td>p-ethylphenyl sulphonyl-</td>
<td>p-ethylphenyl sulphonyl chloride</td>
<td>280-284</td>
<td>81.00</td>
<td>Methanol</td>
</tr>
<tr>
<td>(V_6).</td>
<td>p-acetamido phenyl sulphonyl-</td>
<td>p-acetamido phenyl sulphonyl-chloride</td>
<td>&gt; 300</td>
<td>77.98</td>
<td>DMF</td>
</tr>
<tr>
<td>(V_7).</td>
<td>p-acetyl phenyl-</td>
<td>p-chloro acetophenone</td>
<td>294-296</td>
<td>69.89</td>
<td>DMF</td>
</tr>
<tr>
<td>(V_8).</td>
<td>3-carboxy phenyl sulphonyl-</td>
<td>3-carboxy phenyl sulphonyl chloride</td>
<td>290-292</td>
<td>84.66</td>
<td>Acetone</td>
</tr>
<tr>
<td>(V_{10}).</td>
<td>Hydroxy ethyl-</td>
<td>Ethylene chlorhydrin</td>
<td>205-207</td>
<td>75.70</td>
<td>Methanol</td>
</tr>
<tr>
<td>(V_{11}).</td>
<td>p-methoxy phenyl sulphonyl-</td>
<td>p-methoxy phenyl sulphonyl-chloride</td>
<td>252-254</td>
<td>70.50</td>
<td>Acetone</td>
</tr>
</tbody>
</table>
### Table 2: Physical data of Synthesized r<sub>1</sub> with r<sub>7</sub> Substituted 3-acid compounds

<table>
<thead>
<tr>
<th>Structure No.</th>
<th>Substituent R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>Substituent R&lt;sub&gt;7&lt;/sub&gt;</th>
<th>Melting point (°C)</th>
<th>Yield (%)</th>
<th>Recrystalizing solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>VP&lt;sub&gt;3B&lt;/sub&gt;</td>
<td>p-tolyl-sulphonyl-3-trifluoromethylphenyl piperazino-</td>
<td>243-245</td>
<td>71.50</td>
<td>Acetone</td>
<td></td>
</tr>
<tr>
<td>VP&lt;sub&gt;4&lt;/sub&gt;</td>
<td>p-ethylphenyl sulphonyl-Piperazino-</td>
<td>268-270</td>
<td>74.76</td>
<td>Acetone-methanol</td>
<td></td>
</tr>
<tr>
<td>VP&lt;sub&gt;6&lt;/sub&gt;</td>
<td>p-acetamido phenyl sulphonyl-Piperazino-</td>
<td>270-272</td>
<td>68.48</td>
<td>DMF</td>
<td></td>
</tr>
<tr>
<td>VP&lt;sub&gt;8&lt;/sub&gt;</td>
<td>3-carboxy phenyl sulphonyl-Piperazino-</td>
<td>278-280</td>
<td>73.00</td>
<td>Acetone</td>
<td></td>
</tr>
<tr>
<td>VP&lt;sub&gt;10&lt;/sub&gt;</td>
<td>Hydroxy ethyl-Piperazino-</td>
<td>222-224</td>
<td>67.98</td>
<td>Methanol</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3: Activity of the compounds taken at higher concentration against following Standard strains

<table>
<thead>
<tr>
<th>Comp. Code</th>
<th>Strength (µg / disc)</th>
<th>Zone of inhibition (in mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>E.coli ATCC 25922</td>
</tr>
<tr>
<td>V&lt;sub&gt;2&lt;/sub&gt;</td>
<td>100</td>
<td>33</td>
</tr>
<tr>
<td>VP&lt;sub&gt;2&lt;/sub&gt;</td>
<td>100</td>
<td>37</td>
</tr>
<tr>
<td>V&lt;sub&gt;3&lt;/sub&gt;</td>
<td>100</td>
<td>37</td>
</tr>
<tr>
<td>VP&lt;sub&gt;3A&lt;/sub&gt;</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>VP&lt;sub&gt;3B&lt;/sub&gt;</td>
<td>100</td>
<td>NSA</td>
</tr>
<tr>
<td>V&lt;sub&gt;5&lt;/sub&gt;</td>
<td>100</td>
<td>34</td>
</tr>
<tr>
<td>VP&lt;sub&gt;5&lt;/sub&gt;</td>
<td>100</td>
<td>37</td>
</tr>
<tr>
<td>V&lt;sub&gt;7&lt;/sub&gt;</td>
<td>100</td>
<td>NA</td>
</tr>
<tr>
<td>V&lt;sub&gt;10&lt;/sub&gt;</td>
<td>100</td>
<td>34</td>
</tr>
<tr>
<td>VP&lt;sub&gt;10&lt;/sub&gt;</td>
<td>100</td>
<td>39</td>
</tr>
<tr>
<td>Cipro</td>
<td>5</td>
<td>32</td>
</tr>
</tbody>
</table>

NSA: No significant activity, which signifies that the zone of inhibition is less than 10 mm, NA: No activity
Table 4: Activity of the compounds taken at lower concentration against following Standard strains

<table>
<thead>
<tr>
<th>Comp. Code</th>
<th>Strength (µg / disc)</th>
<th>Zone of inhibition (in mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E.coli ATCC 25922</td>
<td>Pseudomonas aeruginosa ATCC 27853</td>
</tr>
<tr>
<td><code>V₂</code></td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>VP₂</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>V₃</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>VP₃A</td>
<td>5</td>
<td>27</td>
</tr>
<tr>
<td>V₅</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td>VP₅</td>
<td>5</td>
<td>28</td>
</tr>
<tr>
<td>V₁₀</td>
<td>5</td>
<td>24</td>
</tr>
<tr>
<td>VP₁₀</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>Cipro.(V)</td>
<td>5</td>
<td>32</td>
</tr>
</tbody>
</table>

NA: No activity

Results and discussion
In the present work, the microwave method was used to synthesize ethyl- 7-chloro-6-fluoro-1, 4-dihydro-4-oxoquinoline-3-carboxylate from the corresponding 3-chloro-4 fluoroaniline. It was observed that while the yields were almost similar as that using the conventional methods, the time of reaction was very less (only a few minutes) in microwave method compared to the time required for the conventional methods (6-8 hrs). Further, microwave-assisted synthesis of quinolone nucleus could be carried out using the reactants only, without any solvent or any solid support which was an added advantage over the conventional methods requiring solvents. These observations prompted to optimize the reaction condition with respect to power and time, and after several experiments with various combinations of power and time of the reaction, the method was finally optimized to get very high yield of the product having very good quality which required minimum efforts, solvents and chemicals to purify the products. Physical data of synthesized R₁ substituted 3-acid compounds and R₁ with R₇ substituted 3-acid compounds is reported in Table 1 and Table 2 respectively. All 3- carboxyl fluoroquinolones synthesized were initially tested for their antibacterial activity using standard literature method using doses of 100 µgm/disc for test compounds, and the usual dose of 5 µgm/disc for the standard drug, Ciprofloxacin. This was done to identify even the weakly active compounds compared to Ciprofloxacin. The results
(Table 3) show a few compounds to be comparably active as Ciprofloxacin. Then the selected more potent compounds were further screened using the same method as before, but using all test compounds and Ciprofloxacin at doses of 5μg/disc.

It is interesting to note that compounds (VP$_2$, VP$_{3A}$, VP$_5$, VP$_{10}$) having piperazine substituent at C$_7$ position of quinolone ring showed broader spectrum of activity than their analogues (V$_2$, V$_3$, V$_5$, V$_{10}$) with chloro substituent at C$_7$ position, and this finding corroborates the similar findings reported in the literature.

The results of secondary screening (Table 4) is highly encouraging considering the fact that selected compounds (V$_2$, VP$_2$, V$_3$, VP$_{3A}$, V$_5$, VP$_5$, V$_{10}$,VP$_{10}$) were found to be comparably active against Gram-positive (Staphylococcus spp) and Gram-negative (Escherichia spp) pathogenic bacteria at the same dose 5μg/disc comparable as that of standard drug, Ciprofloxacin. Further, the compounds (VP$_2$, VP$_{3A}$, VP$_5$, VP$_{10}$) bearing substituent of piperazine at C$_7$ position of quinolone ring were found to be almost nearly active against Pseudomonas spp at the same dose of 5 μg/disc as the standard drug, Ciprofloxacin.

References


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