Synthesis and *in vitro* Antitubercular Activity of 7-Substituted Fluoroquinolones

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Three novel fluoroquinolones with general structure 1-t-butyl-7-[4-substituted (piperazin-1-yl/piperidin-1-yl)]-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acids were synthesized and evaluated for antitubercular activity in vitro against *M. tuberculosis* H$_{37}$Rv in Middlebrook 7H9 broth using sparfloxacin, ciprofloxacin and isoniazid as standards. Test compounds were found to be less potent than sparfloxacin; however, one of the compounds was more potent than ciprofloxacin.

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Tuberculosis (TB) is a chronic respiratory disease resulting in 2-3 million deaths every year around the world. The currently available medications show serious side effects like hepatotoxicity (isoniazid), damage to auditory nerve (streptomycin), thrombocytopenic purpura (rifampicin). The emergence of multidrug resistant TB has further complicated the therapy. Fluoroquinolones, which have broad spectrum antibacterial activity coupled with better pharmacokinetic properties, have been found to have good antimycobacterial activity. E.g.: sparfloxacin, levofloxacin and moxifloxacin. Substituted piperazines and pyrrolidines at C-7 of fluoroquinolone nucleus are known to influence the spectrum of antibacterial activity. Hence it is proposed to retain the basic structural features of quinolones essential for exhibiting antibacterial activity and modify the substituents at C-7 position. The present work involves introduction of novel substituents on the piperazine ring present at the 7 position to study their contribution to activity. We also wanted to explore the contribution of substituted piperidine at the 7 position on the fluoroquinolone nucleus.

Title compounds I, II and III were synthesized from 1-t-buty1-7-chloro-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (1) (Scheme 1). Compound (1) was synthesized as per literature procedure. Condensation of equimolar quantities (0.0026 mol) of (1) with 3-(1-piperazinyl) benzisothiazole (2) / 4-(2,4-difluorobenzoyl)piperidine (3) in presence of anhydrous potassium carbonate in 15 ml of N, N-dimethylformamide (DMF) at 120º for 1.5 h followed by removal of DMF, washing with water and recrystallization from ethanol/DMF gave compounds I and II, respectively. Similarly condensation of equimolar amounts (0.0026 mol) of (1) and (1-t-butoxycarbonyl-3-t-butyl amino carbonyl)piperazine (4), in presence of anhydrous potassium carbonate in 15 ml of DMF at 130° for 2.0 h followed by removal of DMF, washing with water and recrystallization from ethanol-DMF (80:20) gave compound III.

All the reactions were monitored by thin layer chromatography. Melting points were taken on Thermonik melting point apparatus. Infrared spectra were recorded on Jasco FT-IR instrument and H-NMR spectra were recorded on Varian NMR spectrophotometer (300 MHz). Melting points, % yield and spectral data are given in Table 1.

Test compounds I-III were evaluated in vitro against M. tuberculosi H_37Rv using tube dilution method with Middlebrook 7H9 broth as the nutrient medium containing ADC growth supplement. Test compounds were evaluated in vitro against M. tuberculosis H_37Rv using tube dilution method with Middlebrook 7H9 broth as the nutrient medium containing ADC growth supplement.

### Table 1: Characterization Data of Test Compounds

<table>
<thead>
<tr>
<th>Compd.</th>
<th>M.P. “C”</th>
<th>% Yield</th>
<th>Spectral analysis values expressed: FT-IR in cm(^{-1}) and H(_{1})-NMR in δ ppm</th>
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<tr>
<td>I</td>
<td>178-180</td>
<td>78</td>
<td>FT-IR (Kbr): 3439 (O-H), 2924 (C-H, aromatic), 2854 (aliphatic), 1691 (C=O, acids), 1358 (C-N), 1253 (C-H, t-butyl)</td>
</tr>
<tr>
<td>II</td>
<td>220-222</td>
<td>72</td>
<td>FT-IR (Kbr): 3418 (O-H), 2924 (C-H, aromatic), 1666 (C=O, acids), 1358 (C-N), 1226 (C-H, t-butyl)</td>
</tr>
<tr>
<td>III</td>
<td>280-283</td>
<td>65</td>
<td>FT-IR (Kbr): 3454 (O-H), 2924 (C-H, aromatic), 1720 (C=O, acids), 1672 (CONH, amides), 1379 (C-N), 1232 (C-H, t-butyl)</td>
</tr>
</tbody>
</table>
A simple new spectrophotometric method has been developed for determination of rabeprazole in pharmaceutical bulk dosage form. The method was based on the formation of ion-pair complexes of the drug with four dyes, viz. bromothymol blue, bromocresol green, bromophenol blue and bromocresol purple in acidic buffer solutions followed by their extraction in chloroform. The absorbance of the organic layer was measured at its respective wavelength of maximum absorbance against the corresponding reagent blank. The method has been statistically evaluated and was found to be precise and accurate.

Phosphate buffer of pH 2 and bromocresol green dye gave maximum absorbance of rabeprazole at 454 nm.

<table>
<thead>
<tr>
<th>Compound</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>Sparfloxacin</th>
<th>Ciprofloxacin</th>
<th>Isoniazid</th>
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</thead>
<tbody>
<tr>
<td>MIC (µg/ml)</td>
<td>6.25</td>
<td>25</td>
<td>25</td>
<td>0.5</td>
<td>16.0</td>
<td>0.05</td>
</tr>
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</table>

*Values= mean±standard deviation, P ≤ 0.01 compared to control by T-test.

The results of antitubercular activity are given in Table 2. Test compounds I-III were found to be potent antitubercular agents when evaluated in vitro against M. tuberculosis H37Rv. They were found to be less potent as compared to sparflloxacin. Compound I was more active (MIC 6.25 µg/ml) as compared to ciprofloxacin (MIC 16.0 µg/ml).

ACKNOWLEDGEMENTS

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REFERENCES