Synthesis, Characterization and Evaluation of Anti-tubercular Activity of Ofloxacin Chalcone Conjugates

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Authors’ contributions
This work was carried out in collaboration between both authors. Author RC analyzed the data and synthesis, characterization, author VSG analyzed anti-tubercular activity and managed literature searches. Both authors read and approved the final manuscript.

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ABSTRACT
Synthesis and characterization of Ofloxacin Chalcone derivatives were carried out and evaluated for their antitubercular activity. Synthesized Ofloxacin Chalcone derivatives (Compound A to F). These molecules are characterized by analytical methods (TLC), melting point, and Spectroscopic methods (FT-IR, Mass, NMR). The evaluated antitubercular activity of molecules of synthesized compounds and Ciprofloxacin Pyrazinamide, and Streptomycin as standard drugs. concentrations of synthesized derivatives were prepared (0.8, 1.6, 3.12, 6.25, 12.5, 25, 50, 100 µg/ml) by using sterile deionized water as a solvent. Antitubercular Assay was performed by Mycobacterium tuberculosis using the MABA method. Analyzed MIC values. Compound E showed the best results among 6 Compounds at a very low concentration at 3.12 µg/ml.

Keywords: Ofloxacin chalcone conjugate, anti-tubercular activity, blanc reaction.
ABBREVIATIONS

MIC : Minimum Inhibitory Concentration.
TLC : Thin layer chromatography.
FTIR : Fourier transform infrared.
NMR : nuclear magnetic resonance.
TB : tuberculosis.
MABA: microplate Alamar blue assay.

1. INTRODUCTION

The fluoroquinolones are very important antimicrobial agents. The present focus on Ofloxacin derivatives. The structure bears a fluorne group at the C-6 position and acid group at C-3 and ketone group at the C-4 position which is crucial for activity, these quinolones can be synthesized by laboratory synthesis method, research studies found that quinolones have appreciable concentration and their MIC (minimum inhibitory concentration) are good in biological tissues. The fluoroquinolones have been analyzed by various methods which have been described in different kinds of works of literature. This research becomes needful because of rapid progress and development in fluoroquinolones. [1,2].

The boost in fluoroquinolones prescribing was attributable to the introduction and use of newer, against S. Pneumoniae (for example, levofloxacin, Gemifloxacin, and moxifloxacin). Fluoroquinolones have a very useful role in many bacterial infections, Ofloxacin is a broad-spectrum antibiotic that belongs to the second-generation of fluoroquinolones. It inhibits DNA replication repair of bacterial DNA and RNA transcription of gram-negative and gram-positive cocci acting open DNA topoisomerase enzyme which eventually leads to blockage cell growth. Advances in the quinolone field are likely to provide better compounds capable of dealing with resistant strains. [3-5].

Chalcones are important biological compounds that form enone (aromatic ketones), which are collectively called chalcones. Which two aromatic rings are conjugated together through a reactive α-β unsaturated carbonyl system. Chalcones are considered as precursors in many flavonoids, a very large group of plant constituents, and have defense strategies such as anti-microbial. Antifungal, anti-oxidants potential healing of diverse diseases. It has anti-bacterial, anti-inflammatory, analgesic, and other activities [6].

A five or six-membered rings are employed as a substitution at the C-7 position example trovafloxacin having amino pyrrolidine substituent C-7. Fluoroquinolones with piperazinyl moiety at the C-7 position have been reported to possess potent antibacterial activity. Mechanism of action and structural activity relationship studies of quinolones reveals that the site near the C-7 substituent regards as the drug enzyme interaction domain. besides, it is also reported that the cell permeability is dominantly by C-7 substituents. These facts motivated our concerns to develop some C-7 substituted analogs of the quinolone. [7-10]

A wide range of drugs used as fluoroquinolones antibacterial agents, namely norfloxacin, ciprofloxacin. ofloxacin levofloxacin. Levofloxacin and ofloxacin are isomers and chiral versions of the drugs. The main targets identified for levofloxacin activity, topoisomerase II (DNA-gyrase inhibitor) in Gram-negative bacteria, and topoisomerase IV inhibitor in Gram-positive bacteria [11-13].

Ofloxacin is pale yellow or bright yellow crystalline powder, and with a bitter taste forms colourless needles with spirit or ethanol. Ofloxacin should be stored at 4°C in the dark to minimize photolytically induced. Mycobacterium tuberculosis is the cause of TB infection, it affects the lungs and other body parts, which is spread through inhalation, of aerosolized droplets. Tuberculosis is highly transmissible during the active stage of the disease and can contaminate an individual through a breath of few as mycobacterium tuberculosis (MTB). After a breath, these bacteria are mainly taken by the alveolar macrophages, but they can escape the host resistant system for a long time at which point they can re-energize to an infectious form under immune-compromised situations of the host. [14-17].

Tuberculosis can be treated efficiently by using the first-line drug (FLD) Rifampicin (RIF), Pyrazinamide (PZA), Isoniazid (INH), and Streptomycin (SM), Ethambutol (EMB) The first-line therapy often fails to cure TB for several reasons. Replacement and the spread of the disease contribute to the emergence of drug-resistant bacteria. The emergence of multidrug-resistant TB (MDR-TB), requires the use of second-line drugs that are difficult to procure and are much more toxic and expensive than FLDs. [18-20].
Our present focus is to synthesize ofloxacin chalcone derivatives. Both have an anti-microbial, anti-bacterial activity which might be useful for the treatment of MDR-TB.

2. METHODS

The Blanc chloromethylation also called blanc reaction is the chemical reaction of aromatic rings with HCHO and HCl to form chloromethyl arenes. In 1923 Gustave Louis Blanc discovered the reaction. When the concentration is high, the formation of side products due to the second addition is observed.

3. PROCEDURE

A compound of Ofloxacin 0.01 M and 0.01 M of compounds (1-Naphthol, 4-Amino Phenol) were transferred to separate beakers in 5ml of Ethanol and 5% Sodium Hydroxide respectively, and both were mixed stirred on a magnetic stirrer at 70°C. To the above solution, 35 parts formaldehyde solution and 35% concentrated HCl was added dropwise. The reaction mixture was stirred for 4 hours at 70°C using a magnetic stirrer. The resultant mixture was cooled and basified with the addition of NH₃ solution. The solid was separated by filtration and dried. The above Blanc product was treated with equimolar quantities of 0.01 M of Pyridine and Acetyl Chloride to produce an Acetylated product. The acetylated product was collected and dried. The acetylated product was treated with an equimolar quantity of 0.01 M Benzaldehyde and it was stirred in an ice bath for 1 hour. After 1 hour 10% Sodium Hydroxide was added as a catalyst and stirring was further continued for 3 hours. Then the Ofloxacin Chalcone product was collected by filtration, dried, recrystallized by using ethanol.

3.1 Experimental Investigation

All the compounds were determined by melting point apparatus and Infrared spectra of the compounds were recorded on FT-IR Spectrophotometer, Thin layer chromatography using silica gel plates (Merck) monitored the progress of each reaction in the present examination. The chemicals used are obtained from Sd fine chemicals limited- Mumbai and are of Analytical reagent grade.

3.2 Spectral Data of Synthesized Compounds

3.2.1 9-fluoro-8-((4-hydroxynaphthalen-1-yl)methyl)-3-methyl-10-(4-methyl piprazin-1-yl)-7-oxo-3,7-dihydro-2H-(1,4)oxazino(2,3,4-ij)quinolone-6-carboxylic (compound A)

IR 1713,1660 cm⁻¹ (C=O), 3819 cm⁻¹ (OH), 1157 cm⁻¹ (C-N), 3166 cm⁻¹ (C-H) Aromatic, 1403 cm⁻¹ (C-H) Aliphatic, 827 cm⁻¹ (C-F), 1H-NMR 1.45 (3H, d, methyl), 2.50 (3H, s, N-CH₃), 2.72 (4H, t, piperazine), 3.17 (1H, m) 3.34 (4H, m, piperazine), 4.95 (1H,s,OH), 6.3-8.15 (6H, m, Aromatic naphthol), 4.28 (2H, d), 4.25(2H, s), 7.96 (1H, s), 11.0 (1H, s, OH) Carboxylic acid, MASS m/z 517.2
Fig. 2. Synthetic Scheme 1

Fig. 3 Synthetic Scheme 2
3.2.2 8-((4-acetoxynaphthalen-1-yl)methyl)-9-fluoro-3-methyl-10-(4-methyl piperazin-1-yl)-7-oxo-3,7-dihydroxy-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (Compound B):

IR 3657 cm\(^{-1}\) (OH) 3406 cm\(^{-1}\) (C=O), 1623 cm\(^{-1}\) (C=O), 1258 cm\(^{-1}\) (C-N), 1050 cm\(^{-1}\) (C-F), 1401 cm\(^{-1}\) (C-N) \(\delta\), H-NMR 1.45 (3H, d, methyl), 2.08 (3H, s, ester) 2.50 (3H, s, N-CH\(_3\)), 2.72 (4H, t, piperazine), 3.17 (1H, m) 3.34 (4H, m, piperazine), 7.04-8.15 (6H, m, Aromatic naphthol), 4.28 (2H, d), 4.25(2H, s), 7.96 (1H, s), 11.0 (1H, s, OH) Carboxylic acid Mass m/z 559.21

3.2.3 9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-8-((3-phenylacryloyloxy)naphthalen-1-yl)methyl)-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (Compound C):

IR 3882 cm\(^{-1}\) (OH), 3405 cm\(^{-1}\) (C-H), 1757 cm\(^{-1}\) (C=O), 2826 cm\(^{-1}\) (CO-H), 1600 cm\(^{-1}\) (C=C), 1372 cm\(^{-1}\) (C-F), 1040.8 cm\(^{-1}\) (C-N), \(\delta\), H-NMR 1.45 (3H, d, methyl), 2.50 (3H, s, N-CH\(_3\)), 2.72 (4H, t, piperazine), 3.17 (1H, m) 3.34 (4H, m, piperazine), 6.5-8.15 (6H, m, Aromatic naphthol), 4.28 (2H, d), 4.25(2H, s), 5.96(1H,d), 7.14-7.30 (5H,m, chalcone), 7.09 (1H,d), 7.96 (1H, s), 11.0 (1H, s, OH) Carboxylic acid, Mass m/z 647.69

3.2.4 8-(5-amino-2-hydroxybenzyl)-9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (Compound D):

IR 3421 cm\(^{-1}\) (O-H), 3201 cm\(^{-1}\) (C-H), 1511 cm\(^{-1}\) (C=O), 1287 cm\(^{-1}\) (C-O), 1680 cm\(^{-1}\) (C=O), 1018 cm\(^{-1}\) (C-N).1403 cm\(^{-1}\) (C-F), \(\delta\), H-NMR 1.45 (3H, d, methyl), 2.50 (3H, s, N-CH\(_3\)), 2.72 (4H, t, piperazine), 3.17 (1H, m) 3.34 (4H, m, piperazine), 3.81(2H,d), 4.0 (2H,m, amine) 4.28 (2H, d), 4.95 (1H,OH), 6.09-6.40 (3H, m, benzene), 7.96 (1H, s), 11.0 (1H, s, OH) Carboxylic acid, Mass m/z 482.2

3.2.5 8-(2-acetoxy-5-aminobenzyl)-9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (compound E):

IR 3819 cm\(^{-1}\) (ester), 3188 cm\(^{-1}\) (N-H), 3166 cm\(^{-1}\) (C-H), 2720 cm\(^{-1}\) (COOH), 1660 cm\(^{-1}\) (C=O), 1600 cm\(^{-1}\) (C=O), 1403 cm\(^{-1}\) (CH\(_3\)), 827 cm\(^{-1}\) (C-F). \(\delta\), H-NMR 1.45 (3H, d, methyl), 2.08 (3H, s, ester), 2.50 (3H, s, N-CH\(_3\)), 2.72 (4H, t, piperazine), 3.17 (1H, m) 3.34 (4H, m, piperazine), 3.81(2H,d), 4.0 (2H,m, amine) 4.28 (2H, d), 6.09-6.40 (3H, m, benzene), 7.96 (1H, s), 11.0 (1H, s, OH) Carboxylic acid Mass m/z 524.21

3.2.6 8-(5-amino-2-(3-phenylacryloyloxy)benzyl)-9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-3,7-dihydro-2H-[1,4]oxazino[2,3,4-ij]quinoline-6-carboxylic acid (compound F):

IR 3073 cm\(^{-1}\) (ester), 3073 cm\(^{-1}\) (N-H), 1727 cm\(^{-1}\) (C=O), 2885 cm\(^{-1}\) (COOH), 1452 cm\(^{-1}\) (C-H\(_2\)), 1285 cm\(^{-1}\) (C-N), 1172 cm\(^{-1}\) (C-F), \(\delta\), H-NMR 1.45 (3H, d, methyl), 2.50 (3H, s, N-CH\(_3\)), 2.72 (4H, t, piperazine), 3.17 (1H, m) 3.34 (4H, m, piperazine), 3.81(2H,d, methylene bridge), 4.0 (2H,m, amine) 4.28 (2H, d), 5.96(1H,d), 6.09-6.40 (3H, m, benzene), 7.09 (1H,d), 7.1-7.30 (5H,m, chalcone) 7.96 (1H, s), 11.0 (1H, s, OH) Carboxylic acid Mass m/z 612.65

4. RESULTS

The necessary Ofloxacin Chalcone derivatives are synthesized from commercially available reagents and are mentioned in the scheme. The title compounds of ofloxacin chalcone were formed via Blanc reaction then acetylation with acetyl chloride and chalcone formation in presence of benzaldehyde, the structures of all compounds confirmed by IR, NMR, Mass spectral data. The procedure is promising to yield good title derivatives, the IR spectrum is recorded gives the presence of various functional groups. \(\delta\)H NMR shows multiple signals to the resonance of ofloxacin chalcone derivatives, Mass spectrum is characterized by M+1 peak. All synthesized compounds characterized by Physicochemical properties like molecular weight, melting point, Rf values then solubility tested using different solvents, all compounds dissolved in DMSO, Insoluble in chloroform and water, mixed solubility result with ethyl acetate and spirit.

4.1 Evaluation of Anti-Tubercular Activity

Anti-TB activity using Alamar Blue Dye

4.2 Procedure

The anti - Mycobacterial activity of compounds
was evaluated using the microplate Alamar Blue assay (MABA method). It is a non-toxic methodology, uses a thermally stable reagent, and shows good correlation with a comparative and radiometric method. Sterile deionized water was added to all outer border wells of sterile 96 wells plate to lessen the evaporation of medium in the test wells during the incubation process. The 96 wells plate received 100 µl of the broth (Middlebrook 7H9) and sequential dilution of compounds were made directly on a plate. The ultimate drug concentrations tested were 100 to 0.2 µg/ml. Plates covered, sealed with parafilm at 37ºC five days incubated. 25 µl of freshly arranged 1:1 mixture of Alamar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs. the well was interpreted as no bacterial growth with blue color, and the well shows growth with red color. The MIC was well-defined as the lowest drug concentration which prevented the color change from blue to pink. [21,22]

4.3 Standard Strain used: *Mycobacteria tuberculosis* (H37 RV strain, Vaccine strain): ATCC No-27294. Standards for the Anti-Tubercular test were done. Pyrazinamide- 3.125µg/ml, Ciprofloxacin- 3.125µg/ml, Streptomycin- 6.25µg/ml

Table 1. Physicochemical characteristic of a compounds

| S.No. | Compound code | Molecular Formula | Molecular Weight | Melting point (°C) | Rf value |
|-------|---------------|-------------------|------------------|-------------------|----------|
| 1     | Compound A    | C_{29}H_{28}FN_{3}O_{5} | 517.55 | 220 | 0.783 |
| 2     | Compound B    | C_{31}H_{30}FN_{3}O_{6} | 559.58 | 235 | 0.81 |
| 3     | Compound C    | C_{35}H_{34}FN_{3}O_{6} | 647.69 | 230 | 0.911 |
| 4     | Compound D    | C_{29}H_{29}FN_{3}O_{6} | 482.50 | 225 | 0.852 |
| 5     | Compound E    | C_{27}H_{28}FN_{3}O_{6} | 524.54 | 210 | 0.875 |
| 6     | Compound F    | C_{34}H_{33}FN_{4}O_{6} | 612.65 | 230 | 0.906 |

Table 2. Solubility of synthesized compounds

| S. No. | Compound code | Solvents | Water | Spirit | Chloroform | Ethyl acetoacetate | DMSO |
|--------|---------------|----------|-------|--------|------------|-------------------|------|
| 1      | Compound A    | Insoluble | Insoluble | Insoluble | Insoluble | Soluble          |
| 2      | Compound B    | insoluble | Soluble | Insoluble | Soluble     | Soluble          |
| 3      | Compound C    | Insoluble | Insoluble | Insoluble | Insoluble  | Soluble          |
| 4      | Compound D    | Insoluble | Soluble | Insoluble | Insoluble  | Soluble          |
| 5      | Compound E    | Insoluble | Soluble | Insoluble | Soluble    | Soluble          |
| 6      | Compound F    | Insoluble | Insoluble | Insoluble | Insoluble  | Soluble          |

Fig. 4. Standard drug photograph
Table 3. Results of anti-tubercular activity

| Sl. No. | Sample | 100 µg/ml | 50 µg/ml | 25 µg/ml | 12.5 µg/ml | 6.25 µg/ml | 3.12 µg/ml | 1.6 µg/ml | 0.8 µg/ml |
|---------|--------|-----------|----------|----------|------------|------------|------------|----------|----------|
| 01      | A      | S         | S        | S        | S          | R          | R          | R        | R        |
| 02      | B      | S         | S        | S        | S          | R          | R          | R        | R        |
| 03      | C      | S         | S        | S        | R          | R          | R          | R        | R        |
| 04      | D      | S         | S        | S        | S          | R          | R          | R        | R        |
| 05      | E      | S         | S        | S        | S          | S          | R          | R        | R        |
| 06      | F      | S         | S        | R        | R          | R          | R          | R        | R        |

NOTE: S - Sensitive R - Resistant

Fig. 5. Results photograph

5. DISCUSSION

Due to the MDR-TB resistance, it requires the use of new drugs that are much less toxic, fewer side effects drugs are needed, in that view, we selected Fluoroquinolones especially Ofloxacin derivatives are prepared for the treatment of resistant TB. Results are summarized in tables and schemes and showed the details of the synthetic strategy adopted for these compounds. The ofloxacin is a versatile starting material for several compounds synthesized. ofloxacin and aromatic phenol compounds (1-Naphthol and 4-Amino Phenol) are linked with the Methylene bridge via blanc reaction. The Methylene bridge is linked between the two moieties. Then these compounds are acetylated and the acetylated compounds are treated with the aldehyde to give Ofloxacin Chalcones which are final products. Physicochemical characteristics and solubility, Analytical methods like TLC, Melting point were determined, spectroscopic methods like IR, NMR, mass spectra are confirmed. The prepared compounds were assessed for antitubercular activity using the MABA method, Pyrazinamide, Streptomycin, and Ciprofloxacin drugs used as standard drugs. Results photograph of prepared compounds and standard compounds were mentioned. The blue colour indicates no growth of bacteria and the red colour indicates the growth of bacteria. The synthesized compound showed promising activity as that of standard drugs at the concentration of 3.12, 6.25, 12.5, 25, 50, 100 µg/ml (Compound E), 6.25,12.5,25,50,100µg/ml (Compound A, Compound B, Compound D) and 25,50,100µg/ml (Compound C, Compound F). among six compounds Compound E is showing the best results at very low concentration i.e., at 3.12 µg/ml [23].

6. CONCLUSION

Ofloxacin Chalcone derivatives were synthesized and investigated for their antitubercular activity by the MABA method. comparing the antitubercular activity of Ofloxacin Chalcone derivatives their MIC values were significant. The beneficial effects of these drugs reveal that the results thus hold a great promise for the use of ofloxacin derivatives as potential future antitubercular drugs. Further synthetic work is extended on semi-synthetic derivatives of ofloxacin.
CONSENT AND ETHICAL APPROVAL

It is Not applicable.

AVAILABILITY OF DATA AND MATERIALS

All data and material are available upon request.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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