Research Article

Novel 4-Thiazolidinone Derivatives as Anti-Infective Agents: Synthesis, Characterization, and Antimicrobial Evaluation

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A series of new 4-thiazolidinone derivatives was synthesized, characterized by spectral techniques, and screened for antimicrobial activity. All the compounds were evaluated against five Gram-positive bacteria, two Gram-negative bacteria, and two fungi, at concentrations of 50, 100, 200, 400, 800, and 1600 \( \mu \)g/mL, respectively. Minimum inhibitory concentrations of all the compounds were also determined and were found to be in the range of 100–400 \( \mu \)g/mL. All the compounds showed moderate-to-good antimicrobial activity. Compounds 4a [2-(4-fluoro-phenyl)-3-(4-methyl-5,6,7,8-tetrahydro-quinazolin-2-yl)-thiazolidin-4-one] and 4e [3-(4,6-dimethyl-pyrimidin-2-yl)-2-(2-methoxy-phenyl)-thiazolidin-4-one] were the most potent compounds of the series, exhibiting marked antimicrobial activity against Pseudomonas fluorescens, Staphylococcus aureus, and the fungal strains. Thus, on the basis of results obtained, it may be concluded that synthesized compounds exhibit a broad spectrum of antimicrobial activity.

1. Introduction

Infections caused by microbes are among the leading causes of death worldwide. The availability of limited number of antibiotics for the treatment of infections, and continuous development of resistance to the recently used antimicrobial agents, pose a serious challenge [1]. Thus, the discovery of innovative and potent antimicrobial agents may be the only way to resolve the resistance problem and develop successful remedy for the treatment of infectious diseases. 4-Thiazolidinones have recently been reported to be novel inhibitors of the bacterial enzyme Mur B (a precursor during the biosynthesis of peptidoglycan) and also to block some pathogenic mechanisms of bacteria [2]. 4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group at the fourth position. This is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities such as antimycobacterial [3–5], antimicrobial [6–19], anticancer [20, 21], anticonvulsant [22–32], anti-inflammatory and analgesic [33–37], antiparasitic [38–43], antiviral and anti-HIV [44–49], antidiabetic [50–52], antihypertensive [53–55], antihyperlipidemic [56–58], and MAO inhibitors [59]. The substituted thiazolidine moiety has attracted considerable interest in the development of biologically active compounds. In the present study, novel arylidene substituted 4-thiazolidinones were synthesized and evaluated as antimicrobial agents from heterocyclic scaffold.

2. Materials and Methods

All the chemicals and solvents used in the study were procured from S. D. Fine-Chem. Ltd., Mumbai, and Sigma-Aldrich Chemie, Germany. Culture media for antimicrobial screening were procured from HiMedia Laboratories, Mumbai. The standard microbial strains were procured from Microbial Type Culture Collection (MTCC), Institute of Microbial Technology, Chandigarh, India. Spectral studies (IR, NMR, and mass spectrometry, Table 1) of the synthesized compounds were performed at Central Drug Research Institute, Lucknow.

2.1. Chemistry. 4-Thiazolidinones were synthesized in two steps. In the first step, 2-aminopyrimidine derivatives were synthesized by the reaction of 1,3-dicarbonyl compounds with guanidine. Final compounds (4a–4f) were synthesized...
2.2. Antimicrobial Screening

2.2.1. Test Microorganisms. Antimicrobial activity of the synthesized compounds was studied against nine microorganisms, including seven bacterial strains—Bacillus subtilis (MTCC 441), Staphylococcus aureus (MTCC 1430), Pseudomonas aeruginosa (MTCC 1573), Penicillium chrysogenum (MTCC 2546) and百日咳杆菌 (MTCC 1538)—and two fungal strains, Aspergillus niger (MTCC 2546) and Penicillium chrysogenum (MTCC 161).

2.2.2. Preparation of the Samples and Standard Solution. The compounds (4a–4f) were dissolved in 10% DMSO at the concentrations of 50, 100, 200, 400, 800, and 1600 μg/mL, respectively. Norfloxacin and fluconazole, used as the standard drugs for antibacterial and antifungal studies, respectively, were also dissolved in 10% DMSO at the concentrations of 10 μg/mL.

2.2.3. Method. Antimicrobial activity of the synthesized compounds was evaluated by cup-plate method. Nutrient broth suspension of test microorganism (10 mL) was added to 100 mL of sterile molten nutrient agar growth media (cooled to 45°C), mixed well, and poured on to sterile petri plates. The agar was allowed to solidify and was then punched to make six wells/cups, using a 6 mm sterile cork borer (separate borer for each organism), to ensure proper distribution of wells in the periphery and one well in the centre. Agar plugs were removed and 50 μL solution of test samples (each compound in six concentrations) was poured into the corresponding marked well using micropipette. Triplicate plates of each organism were prepared. The plates were left at room temperature for 2 h to allow diffusion of samples and then incubated face upward, at corresponding temperature for 48 h [61]. The diameters of zone of inhibition were measured to the nearest millimeter (the cup size also included) and are presented in Table 2.

2.2.4. Determination of Minimum Inhibitory Concentration (MIC). A series of glass tubes, containing different concentrations of the synthesized compounds (in 10% DMSO), with nutrient broth was inoculated with the required quantity of the inoculums to obtain a suspension of microorganisms which contained 10^5 colony forming units per milliliter. One growth control tube was prepared without the addition of the compounds or the microorganisms. The tubes were incubated at 37°C for 24 h. The turbidity produced in each
Figure 1: Synthetic pathway for the compounds (4a–4f).
| S. number | Compounds | Conc. (μg/mL) | Gram +ve strains | Gram –ve strains | Fungal strains |
|-----------|-----------|---------------|------------------|------------------|----------------|
|           |           |               | SA               | BS               | BP             | ML             | PA             | PF             | EC             | AN             | PC             |
| 1         | ![Chemical Structure](4a.png) | 50             | 8                | 10               | 8               | 10             | 8               | 14               | 8               | 9               | 8               | 8               | 9               |
|           |           | 100            | 9                | 11               | 9               | 10             | 10              | 14               | 10              | 10              | 10              | 10              | 10              |
|           |           | 200            | 10               | 11               | 12              | 12             | 13              | 16               | 12              | 11              | 11              | 11              | 11              |
|           |           | 400            | 10               | 12               | 16              | 13             | 14              | 17               | 13              | 12              | 12              | 12              | 13              |
|           |           | 800            | 11               | 13               | 18              | 14             | 16              | 18               | 13              | 13              | 13              | 13              | 15              |
|           |           | 1600           | 14               | 14               | 20              | 14             | 18              | 19               | 14              | 14              | 14              | 14              | 17              |
| 2         | ![Chemical Structure](4b.png) | 50             | 8                | 12               | 13              | 15             | 12              | 12               | 8               | 12              | 12              | 12              | 12              |
|           |           | 100            | 13               | 13               | 14              | 16             | 13              | 13               | 12              | 14              | 13              | 11              | 11              |
|           |           | 200            | 14               | 15               | 15              | 17             | 14              | 15               | 14              | 16              | 14              | 14              | 14              |
|           |           | 400            | 15               | 16               | 17              | 18             | 15              | 16               | 15              | 17              | 15              | 15              | 15              |
|           |           | 800            | 16               | 17               | 18              | 19             | 17              | 17               | 16              | 18              | 17              | 18              | 17              |
|           |           | 1600           | 18               | 19               | 20              | 21             | 19              | 19               | 18              | 19              | 18              | 18              | 18              |
| 3         | ![Chemical Structure](4c.png) | 50             | 8                | 8                | 8               | 8              | 9               | 10               | 10              | 8               | 10              | 8               | 10              |
|           |           | 100            | 8                | 8                | 10              | 8              | 12              | 12               | 10              | 8               | 11              | 8               | 11              |
|           |           | 200            | 8                | 12               | 14              | 10             | 13              | 14               | 13              | 10              | 13              | 10              | 13              |
|           |           | 400            | 8                | 14               | 16              | 13             | 14              | 15               | 14              | 12              | 15              | 15              | 15              |
|           |           | 800            | 10               | 15               | 18              | 14             | 15              | 16               | 14              | 13              | 16              | 13              | 16              |
|           |           | 1600           | 12               | 16               | 20              | 14             | 16              | 18               | 15              | 14              | 17              | 14              | 17              |
| 4         | ![Chemical Structure](4d.png) | 50             | 8                | 13               | 12              | 14             | 15              | 13               | 12              | 8               | 8               | 8               | 12              |
|           |           | 100            | 13               | 14               | 13              | 16             | 16              | 14               | 13              | 12              | 12              | 12              | 12              |
|           |           | 200            | 15               | 15               | 14              | 17             | 17              | 15               | 15              | 13              | 14              | 14              | 14              |
|           |           | 400            | 17               | 17               | 16              | 18             | 18              | 16               | 16              | 14              | 16              | 14              | 16              |
|           |           | 800            | 19               | 18               | 17              | 19             | 19              | 17               | 18              | 16              | 17              | 16              | 17              |
|           |           | 1600           | 21               | 19               | 18              | 20             | 20              | 19               | 20              | 18              | 19              | 18              | 19              |
| 5         | ![Chemical Structure](4e.png) | 50             | 12               | 14               | 12              | 13             | 8               | 8                | 8                | 8               | 12              | 8               | 8               |
|           |           | 100            | 13               | 15               | 13              | 15             | 13              | 13               | 13              | 13              | 13              | 13              | 13              |
|           |           | 200            | 14               | 16               | 15              | 16             | 14              | 14               | 14              | 14              | 14              | 14              | 14              |
|           |           | 400            | 15               | 20               | 16              | 17             | 15              | 16               | 15              | 15              | 15              | 15              | 16              |
|           |           | 800            | 16               | 21               | 18              | 19             | 17              | 17               | 17              | 17              | 17              | 17              | 17              |
|           |           | 1600           | 17               | 24               | 19              | 20             | 19              | 18               | 19              | 18              | 19              | 18              | 19              |
Table 2: Continued.

| S. number | Compounds | Conc. (µg/mL) | Gram +ve strains | Gram -ve strains | Fungal strains |
|-----------|------------|---------------|------------------|------------------|---------------|
|           |            |               | SA  | BS  | BP  | ML  | PA  | PF  | EC  | AN  | PC  |
| 6         |            |               | 50  | 8   | 9   | 8   | 8   | 10  | 10  | 8   | 8   |
|           |            |               | 100 | 9   | 10  | 8   | 8   | 12  | 14  | 10  | 8   |
|           |            |               | 200 | 10  | 12  | 10  | 8   | 16  | 16  | 12  | 10  |
|           |            |               | 400 | 12  | 14  | 12  | 10  | 18  | 17  | 14  | 12  |
|           |            |               | 800 | 13  | 16  | 18  | 12  | 20  | 18  | 14  | 14  |
|           |            |               | 1600| 15  | 18  | 21  | 14  | 21  | 19  | 16  | 17  |
| 7         | Norfloxacine| 10          | 25  | 22  | 30  | 24  | 26  | 25  | 27  | —   | —   |
| 8         | Fluconazole | 10          | —   | —   | —   | —   | —   | —   | —   | —   | —   |
| 9         | Control (10% DMSO) | — | —   | —   | —   | —   | —   | —   | —   | —   | —   |

BS: B. subtilis, SA: S. aureus, BP: B. pumilus, ML: M. luteus, PA: P. aeruginosa, EC: E. coli, PF: P. fluorescens, AN: A. niger, PC: P. chrysogenum, control = 10% v/v DMSO, and (—) = no activity.

Table 3: Values of the minimum inhibitory concentration of the synthesized compounds and reference standards.

| S. number | Microbial strains       | 4a | 4b | 4c | 4d | 4e | 4f | N  | F  |
|-----------|-------------------------|----|----|----|----|----|----|----|----|
| 1         | Staphylococcus aureus   | 300| 500| 300| 400| 400| 300| 2.5| —  |
| 2         | Bacillus subtilis       | 300| 200| 400| 300| 300| 100| 5  | —  |
| 3         | Bacillus pumilus        | 300| 100| 300| 100| 200| 500| 1.25| —  |
| 4         | Micrococcus luteus      | 300| 500| 500| 300| 300| 300| —  | —  |
| 5         | Pseudomonas aeruginosa  | 200| 300| 300| 300| 400| 400| 2.5| —  |
| 6         | Pseudomonas fluorescens | 100| 100| 300| 100| 200| 300| 2.5| —  |
| 7         | Escherichia coli        | 300| 100| 300| 400| 400| 200| 2.5| —  |
| 8         | Aspergillus niger       | 300| 100| 100| 100| 300| 300| —  | 2.5|
| 9         | Penicillium chrysogenum | 400| 100| 100| 100| 300| 300| —  | 1.25|

N: norfloxacine and F: fluconazole.

Tube was recorded on a UV-visible spectrometer [62, 63]. The observed MICs (µg/mL) are presented in Table 3.

3. Results and Discussion

4-Thiazolidinones were synthesized in two steps. In the first step, 2-aminopyrimidine derivatives were synthesized by the reaction of 1,3-dicarbonyl compounds with guanidine. Finally, the compounds (4a–4f) were synthesized by reaction of the compounds of step 1 with substituted aromatic aldehydes and mercaptoacetic acids, using DCC as intramolecular cyclizing agent.

Characteristic peaks were observed for N-H stretching, C=O stretching, and C-N stretching. The IR spectra of the 4-thiazolidinone derivatives exhibited C=O lactam amide stretching vibration in the range of 1637–1728 cm\(^{-1}\).\([M]^{+}/[M+1]^{+}\) peaks were observed for the synthesized compounds.\(^1\)H-NMR spectra of the compounds indicated the presence of two diastereotopic protons at C-5 position and one single proton at C-2 position; doublets were obtained in the region of 3.07–3.47 ppm. A doublet integrated for one proton appeared at the δ value of 2.37–2.74 ppm. This can be attributed to the C-2 proton of the 4-thiazolidinone ring.

The antimicrobial activity was observed at 50, 100, 200, 400, 800, and 1600 µg/mL, respectively (Table 2). Minimum inhibitory concentrations of the synthesized compounds were also determined, in nutrient broth by tube dilution method. MICs were in the range of 100–500 µg/mL, which were recorded as the optical density, at 530 nm.

The antimicrobial screening revealed that all the synthesized compounds possessed a wide spectrum of antimicrobial profile against the tested microbial strains. The compounds, which were active against bacterial and fungal strains, were effective at a much higher concentration than the standard drugs norfloxacine and fluconazole. All the compounds exhibited good-to-moderate antimicrobial activity against all the strains. Compounds 4b, 4c, and 4d were found to be more effective against the fungal strains than the bacterial strains.

On the basis of MIC values of the synthesized compounds, the order of antimicrobial spectrum was 4b > 4a > 4d > 4c > 4f > 4e. Compound 2-(4-fluoro-phenyl)-3-(4-methyl-5,6,7,8-tetrahydro-quinazolin-2-yl)-thiazolidin-4-one (4a) and
compound 3-(4,6-dimethyl-pyrimidin-2-yl)-2-(2-methoxy-phenyl)-thiazolidin-4-one were the most potent compounds of the series, exhibiting marked antibacterial activity against *Pseudomonas fluorescens* and *Staphylococcus aureus*.

4. Conclusion

In the present study, six new 4-thiazolidinone derivatives were synthesized, characterized, and evaluated for their antimicrobial potential. The compounds exhibited antimicrobial activity against the selected Gram-positive and Gram-negative bacterial strains and the fungal strains. Overall, 2-(4-fluoro-phenyl)-3-(4-methyl-5,6,7,8-tetrahydro-quinazolin-2-yl)-thiazolidin-4-one and 3-(4,6-dimethyl-pyrimidin-2-yl)-2-(2-methoxy-phenyl)-thiazolidin-4-one were found to be the most potent members of the series. On the basis of the antimicrobial activity studies, it may be concluded that all the compounds have a broad spectrum of antimicrobial activity.

Thus, the study provides a lead for the syntheses and evaluation of more 4-thiazolidinone derivatives for antimicrobial activity, as the same could lead to the discovery of some promising agents.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of the paper.

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