Design, synthesis and antimicrobial evaluation of novel 2-aryl-thiazolidin-4-one derivatives

Davinder Prasad¹, Awanit Kumar², Praveen Kumar Shukla² and Mahendra Nath¹*

Abstract

Novel 2-arylthiazolidin-4-one derivatives (8a-q and 11) have been synthesized in good-to-excellent yields (70-96%) by one-pot three-component condensation-cyclization reaction of aromatic or aliphatic primary amines, aromatic aldehydes, and thioglycolic acid in polypropylene glycol at 110°C temperature. The in vitro antimicrobial activity of the synthesized 2-arylthiazolidin-4-ones was investigated against a panel of six pathogenic fungal strains, a Gram-positive and three Gram-negative bacteria. Results revealed that the compounds (8a-d) bearing 3-(4-((1H-imidazolyl)methyl)phenyl)-substituent displayed significant antibacterial efficacy specifically against *Klebsiella pneumoniae* (minimum inhibitory concentration 12.5 μg/mL). In addition, some of the synthesized compounds have also shown antimicotic activity against *Sporothrix schenckii*, *Trichophyton mentagrophytes*, and *Aspergillus fumigatus* at the concentration of 50 μg/mL.

Graphical abstract: A series of novel 2-arylthiazolidin-4-one analogues was prepared and assessed for their in vitro antimicrobial efficacy. Some of the synthesized compounds displayed significant antibacterial efficacy against *Klebsiella pneumoniae* and selective antimiocotic activity against *Trichophyton mentagrophytes*.

Keywords: 2-arylthiazolidinones, antimicrobial activity, 1,2,4-triazole, imidazole, morpholine

Introduction

The increasing cases of microbial resistance pose a major concern to the scientific community and have become a threat for human life worldwide. Moreover, invasive microbial infections caused by multi-drug-resistant Gram-positive bacteria and microbes are difficult to diagnose and treat [1]. They are the major cause of morbidity and mortality especially in immunosuppressed and hospital-acquired patients [2]. To overcome these problems, the development of new and safe antimicrobial agents with better effectiveness is urgently required. To this end, one of the best ways to design new antimicrobial agents is to generate hybrid molecules by combining two bioactive heterocyclic moieties in a single molecular scaffold.

Among pharmacologically important heterocyclic compounds, 4-thiazolidinone derivatives have been known to possess a wide range of biological properties such as anticonvulsant [3], anti-HIV [4], antifungal [5], antibacterial agents [6], and COX-1 inhibitors [7]. In addition, the five- and six-membered heterocycles, such as imidazole, triazole, and morpholine are of great interest due to their presence in many pharmaceutical agents [8-10]. Owing to the biological significance of these two classes of compounds and in continuation of our ongoing study on antimicrobial agents [11], we planned to synthesize a combined molecular framework that involves these two different chromophores. Thus, a series of 2-arylthiazolidin-4-ones bearing imidazole, triazole, or morpholine moiety has been synthesized using one-pot three-component methodology [12] to investigate their antibacterial and antimiocotic efficacy.

Results and discussion

Chemistry

The starting materials, 4-((1H-imidazol-1-yl)methyl)aniline (4a), 4-((1H-1,2,4-triazol-1-yl)methyl)aniline (4b), and 4-(morpholinomethyl)aniline (4c) were prepared from 4-nitro-toluene in three steps. The bromination of...
4-nitrotoluene (1) with N-bromosuccinimide in the presence of catalytic amount of benzoyl peroxide was accomplished in carbon tetrachloride at reflux temperature. The resulting product, \( p \)-nitrobenzyl bromide (2), was then coupled with imidazole, 1,2,4-triazole, or morpholine according to the reported procedure [13], in the presence of DBU as a base in THF at ambient temperature to afford compounds (3a-c) which on subsequent reduction with SnCl\(_2\) in hydrochloric acid at 50-60°C yielded products (4a-c) (Scheme 1). The physical and spectral data of compounds (4a-c) are in agreement with the reported data [14-16]. 4-Morpholinobenzeneamine (5) and 3-morpholinopropan-1-amine (9) were purchased from Sigma-Aldrich and used without further purification. The synthetic routes to the target compounds are outlined in Schemes 2 and 3. For the synthesis of 2-arylthiazolidin-4-ones (8a-q and 11), the condensation-cyclization reactions of various amines (4a-c, 5, and 9), aromatic aldehydes, and thioglycolic acid were performed at 110°C using polypropylene glycol (PPG) as a solvent medium. Initially, we attempted the synthesis of 3-(4-((1H-imidazol-1-yl)methyl)phenyl)-2-phenylthiazolidin-4-one (8a) by reacting 4-((1H-imidazol-1-yl)methy)aniline (4a) with benzaldehyde and thioglycolic acid at 110°C in polyethylene glycol (PEG), as many organic transformations and multi-component reactions are reported in PEG, but surprisingly, no product formation was observed even after 24 h of the reaction. However, the reaction proceeds well in PPG under same reaction conditions and afforded the proffered product 8a in 83% yield. The success of the reaction in PPG is possibly due to its immiscibility with water, which helps in the removal of a water molecule from the reaction mixture during the formation of 2-thiazolidinone ring. In addition, PPG is an eco-friendly solvent and associated with many advantages, such as low cost, less toxicity, efficient recyclability, easy work-up, and miscibility with a wide range of organic solvents.

The newly synthesized compounds were characterized by IR, \(^1\)H NMR, \(^{13}\)C NMR, ESI-MS, and elemental analysis. The formation of 3-(4-((1H-imidazol-1-yl)methyl)phenyl)-2-phenylthiazolidin-4-one (8a) was first indicated by IR. In IR spectrum, the compound 8a exhibited a sharp band at 1686 cm\(^{-1}\) because of CO stretching. The structure of compound 8a was confirmed by NMR spectroscopy. In \(^1\)H NMR, the appearance of two doublets at \( \delta \) 3.99 and 3.86 ppm due to geminal coupling between two hydrogens of S-CH\(_2\)-CO and a sharp singlet at \( \delta \) 6.08 ppm corresponding to N-CH-S indicated the presence of thiazolidinone ring. Similarly, three carbon signals at \( \delta \) 33.30, 65.24, and 171.05 ppm in the \(^{13}\)C NMR of 8a were assigned to S-CH\(_2\), N-CH-S, and CO groups, respectively. The mass spectral analysis produced further evidence for the formation of 8a by showing [M]\(^+\) ion peak at \( m/z \) 335 for the molecular formula, C\(_{19}\)H\(_{17}\)N\(_3\)OS. The general synthetic method and characterization data of compounds (8a-q and 11) are described in the “Experimental section.”

**Biological evaluation**

The **in vitro** antibacterial activities of compounds (8a-q and 11) and standard drugs (gentamycin and ampicillin) were carried out against a Gram-positive bacterial strain viz. *Staphylococcus aureus* (Sa) and three Gram-negative bacteria viz. *Escherichia coli* (Ec), *Klebsiella pneumoniae* (Kp) and *Pseudomonas aeruginosa* (Pa). The results of preliminary **in vitro** antibacterial testing are shown in Table 1. Out of 18 newly synthesized compounds, only 7 compounds (8a-f and q) were found to be active against the tested bacterial strains. 4-Thiazolidinones (8a-f) bearing 4-(1H-imidazolylmethyl)phenyl)-substituent at position 3 were found significantly active (minimum inhibitory concentration—MIC 12.5-50 \( \mu \)g/mL) against Gram-negative strain Kp. In addition, compounds (8a-c) have also shown moderate activity against Sa. In contrast, thiazolidinone 8q with 3-(4-morpholinophenyl)-substituent exhibited activity (50 \( \mu \)g/mL) specifically against a Gram-negative bacterial strain Ec, which was found to be comparable with the standard drug ampicillin. Surprisingly, 4-thiazolidinone derivatives containing 4-(1,2,4-triazolylmethyl)phenyl- and 4-(morpholinomethyl)phenyl-functionalities at position 3 were found inactive against all the tested bacterial strains. These results imply that the nature of substituent at
position 3 of thiazolidinone ring is responsible for antibacterial activity.

Furthermore, the in vitro antifungal activity of compounds (8a-q and 11) was investigated along with standard drugs Ketoconazole and Fluconazole against a panel of six fungal strains, viz., Candida albicans (Ca), Cryptococcus neoformans (Cn), Sporothrix schenckii (Ss), Trichophyton mentagrophytes (Tm), Aspergillus fumigatus (Af), and Candida parapsilosis (Cp) and the results are presented in Table 2. Although, none of the compounds showed better efficacy than the standard drugs Ketoconazole and Fluconazole against the tested fungi, 12 of the title compounds (8a, 8g-q) were found to be equipotent against Tm with MIC value of 50 μg/mL. The antifungal activity profile of these molecules seems to be dependent mainly on the substitution at position 3 of the thiazolidinone ring. Compounds 8g-i containing 4-(1,2,4-triazolylmethyl)phenyl-moiety were found to be equipotent against Tm with MIC value of 50 μg/mL.

In summary, various 2-arylthiazolidin-4-ones (8a-q) and 3-(3-morpholinopropyl)-2-(4-(trifluoromethyl)phenyl)thiazolidin-4-one (11) have been synthesized via one-pot three-component methodology using PPG as a solvent medium and screened for their in vitro antimicrobial efficacy. It was observed that, instead of thiazolidinone ring, the heteroaromatic moiety present at position 3 in the thiazolidinone ring seems to be responsible for the antimicrobial activity.
imidazolylmethylphenyl substituent at position 3 of thiazolidinone ring showed significant antibacterial efficacy (MIC 12.5-50 µg/mL) against Gram-negative strain Kp, while compounds with the corresponding 1,2,4-triazole and morpholine substituents displayed comparable antmycotic activity (MIC 50 µg/mL) against Tm. Furthermore, these results may be useful for the designing of potent new antimicrobial agents.

**Experimental**

**Chemistry**

All the chemicals were purchased from Sigma-Aldrich and used without any further purification. Thin-layer chromatography was performed on precoated Merck silica gel 60 F254 plates, and spots were developed under UV light (254 nm) or in iodine chamber. All the compounds were purified by column chromatography using silica gel (60-120 mesh). The 1H NMR spectra were recorded on Bruker 300 or Jeol 400 MHz spectrometer. The IR spectra were obtained on a Perkin Elmer IR spectrometer, and peaks are given in reciprocal centimeter (cm⁻¹). Mass spectra were determined on Elementar Analysensysteme GmbH VarioEL V3.00, and CHNS values were found within ± 0.4 of theoretical values for all the new compounds. The melting points were obtained by Perkin Elmer differential scanning calorimetry.

**General procedure for the synthesis of 8a-q and 11**

A mixture of amine (1 mmol), aldehyde (2 mmol), and thioglycolic acid (3 mmol) in PPG ~2000 (2 mL) was heated at 110°C for 4-11 h. After completion of the reaction as indicated by TLC, the reaction mixture was diluted with hexane, and the precipitated product was filtered. In the case of oily products, the hexane layer was decanted, with hexane, and the precipitated product was filtered. In addition, the hexane layer was decanted, and the oily product was triturated with hexane, and the precipitated product was filtered. In the case of oily products, the hexane layer was decanted, and the precipitated product was filtered.

3-(4-((1H-imidazol-1-yl)methyl)phenyl)-2-(4-bromophenyl)thiazolidin-4-one (8b)

Yellow solid; m.p. 166°C; yield 86%. IR (CHCl₃) ν: 1683 (C = O), 1515, 1380, 1326, 1232, 1166, 1027, 1017, 853, 753, 663 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ: 7.56 (d, J = 8.7 Hz, 2 H, ArH), 7.50 (s, 1 H, imidazole H), 7.40 (d, J = 8.2 Hz, 2 H, ArH), 7.18 (dd, J₁ = 7.7 Hz, J₂ = 1.83 Hz, 2 H, ArH), 7.07 (s, 1 H, imidazole H), 7.05 (d, J = 8.7 Hz, 2 H, ArH), 6.83 (s, 1 H, imidazole H), 6.14 (s, 1 H, CH), 5.04 (s, 2 H, CH₂Ph), 3.98 (dd, J₁ = 16.0 Hz, J₂ = 1.3 Hz, 1 H, CH₂), 3.87 (d, J = 15.5 Hz, 1 H, CH₃) ppm; 13C NMR (100 MHz, CDCl₃) δ: 170.91, 143.30, 137.04, 135.03, 129.52, 127.85, 127.06, 126.01, 125.97, 125.54, 64.39, 49.99, 33.21 ppm; MS (ESI): m/z 404 [M + H⁺]; Anal. calcd for C₂₀H₁₄BrN₃OS: C, 54.60; H, 4.26; N, 9.46; S, 7.59. Found: C, 56.63; H, 4.08; N, 9.55; S, 7.59.

3-(4-((1H-imidazol-1-yl)methyl)phenyl)-2-(4-bromophenyl)thiazolidin-4-one (8c)

Yellow solid; m.p. 166°C; yield 86%. IR (CHCl₃) ν: 1683 (C = O), 1515, 1380, 1326, 1232, 1166, 1027, 1017, 853, 753, 663 cm⁻¹; 1H NMR (400 MHz, CDCl₃) δ: 7.57 (d, J = 8.7 Hz, 2 H, ArH), 7.50 (s, 1 H, imidazole H), 7.40 (d, J = 8.2 Hz, 2 H, ArH), 7.18 (dd, J₁ = 7.7 Hz, J₂ = 1.83 Hz, 2 H, ArH), 7.07 (s, 1 H, imidazole H), 7.05 (d, J = 8.7 Hz, 2 H, ArH), 6.83 (s, 1 H, imidazole H), 6.14 (s, 1 H, CH), 5.04 (s, 2 H, CH₂Ph), 3.98 (dd, J₁ = 16.0 Hz, J₂ = 1.3 Hz, 1 H, CH₂), 3.87 (d, J = 15.5 Hz, 1 H, CH₃) ppm; 13C NMR (100 MHz, CDCl₃) δ: 170.91, 143.30, 137.04, 135.03, 129.52, 127.85, 127.06, 126.01, 125.97, 125.54, 64.39, 49.99, 33.21 ppm; MS (ESI): m/z 404 [M + H⁺]; Anal. calcd for C₂₀H₁₄BrN₃OS: C, 54.60; H, 4.26; N, 9.46; S, 7.59. Found: C, 56.63; H, 4.08; N, 9.55; S, 7.59.
3-(4-((1H-imidazol-1-yl)methyl)phenyl)-2-p-tolythiazolidin-4-one (8e)
Brown gummy matter; yield 87%. IR (CHCl₃) ν: 1708, 1387, 1138, 1116, 1035, 1014, 985, 906, 769, 679, 621 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.49 (s, 1 H, imidazole H), 7.17 (d, J = 6.4 Hz, 2 H, ArH), 7.15 (d, J = 5.5 Hz, 2 H, ArH), 7.09 (d, J = 8.2 Hz, 2 H, ArH), 7.05 (d, J = 9.1 Hz, 2 H, ArH), 7.02 (s, 1 H, imidazole H), 6.83 (s, 1 H, imidazole H), 6.05 (s, 1 H, CH), 5.03 (s, 2 H, CH₂Ph), 3.97 (d, J = 15.5 Hz, 1 H, CH₂), 3.84 (d, J = 15.5 Hz, 1 H, CH₂), 2.29 (s, 3H, CH₃) ppm; MS (ESI): m/z 350 [M + H⁺].

3-(4-((1H-imidazol-1-yl)methyl)phenyl)-2-(4-fluorophenyl)thiazolidin-4-one (8f)
Yellow solid; m.p. 178°C; Yield 76%. IR (CHCl₃) ν: 1708, 1387, 1138, 1116, 1017, 958, 842, 751, 679 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 8.04 (s, 1 H, triazole H), 7.95 (s, 1 H, triazole H), 7.42 (d, J = 7.8 Hz, 2 H, ArH), 7.17 (m, 6H, ArH), 6.06 (s, 1 H, CH), 5.27 (s, 2 H, CH₂-Ph), 3.96 (d, J = 15.0 Hz, 1 H, CH₂), 3.85 (d, J = 15.9 Hz, 1 H, CH₂) ppm; MS (ESI): m/z 415 [M + H⁺]; Anal. calcd for C₁₉H₁₅F₃N₄OS 0.35H₂O: C, 51.28; H, 3.75; N, 13.29; S, 7.61. Found: C, 51.36; H, 3.96; N, 12.98; S, 7.69.

3-(4-((1H-1,2,4-triazol-1-yl)methyl)phenyl)-2-(4-fluorophenyl)thiazolidin-4-one (8g)
Yellow solid; m.p. 176°C; yield 88%. IR (CHCl₃) ν: 1682, 1609, 1510, 1537, 1376, 1273, 1225, 1158, 1138, 1016, 958, 848, 789, 755, 679 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 8.02 (s, 1 H, triazole H), 7.95 (s, 1 H, triazole H), 7.27-7.24 (m, 2 H, ArH), 7.16 (m, 4 H, ArH), 6.97 (t, J = 8.4 Hz, 2 H, ArH), 6.09 (s, 1 H, CH), 5.26 (s, 2 H, CH₂-Ph) ppm; MS (ESI): m/z 355 [M + H⁺]; Anal. calcd for C₁₉H₁₅F₃N₄OS 0.15H₂O: C, 60.54; H, 4.32; N, 15.69; S, 8.98. Found: C, 60.78; H, 4.02; N, 15.45; S, 8.85.

2-(4-Bromophenyl)-3-(4-(morpholinomethyl)phenyl)thiazolidin-4-one (8k)
Yellow solid; m.p. 110°C; yield 94%. IR (CHCl₃) ν: 1708, 1387, 1138, 1116, 1035, 1008, 914, 865, 838, 797, 754, 664, 644, 624 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.41 (dd, J₁ = 6.6 Hz, J₂ = 1.6 Hz, 2 H, ArH), 7.25 (d, J = 8.4 Hz, 2 H, ArH), 7.16 (dd, J₁ = 6.7 Hz, J₂ = 1.6 Hz, 2 H, ArH), 7.09 (d, J = 8.2 Hz, 2 H, ArH), 6.04 (s, 1 H, CH), 3.96 (dd, J₁ = 15.8 Hz, J₂ = 1.3 Hz, 1 H, CH₂), 3.86 (d, J = 15.8 Hz, 1 H, CH₂), 3.67 (t, J = 4.5 Hz, 4 H, morpholine H), 3.40 (s, 2 H, CH₂-Ph), 2.38 (t, J = 4.3 Hz, 4 H, morpholine H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ: 170.83, 138.52, 136.71, 136.06, 131.97, 129.76, 128.54, 125.28, 122.75, 66.76, 64.82, 62.53, 53.43, 33.30 ppm; MS (ESI): m/z 433 [M + H⁺]₂.

3-(4-((1H-1,2,4-triazol-1-yl)methyl)phenyl)-2-(4-fluorophenyl)thiazolidin-4-one (8l)
Dark brown gummy solid; m.p. 110°C; yield 94%. IR (CHCl₃) ν: 1682 (C = O), 1609, 1516, 1450, 1421, 1379, 1325, 1263, 1165, 1120, 1067, 1017, 930, 851, 825, 803, 752, 659 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.55 (d, J = 8.2 Hz, 2 H, ArH), 7.41 (d, J = 8.2 Hz, 2 H, ArH), 7.02 (dd, J₁ = 6.8 Hz, J₂ = 2.0 Hz, 2 H, ArH), 6.78 (dd, J₁ = 6.8 Hz, J₂ = 2.0 Hz, 2 H, ArH), 6.04 (s, 1 H, CH), 3.99 (dd, J₁ = 15.8 Hz, J₂ = 1.6 Hz, 1 H, CH₂), 3.88 (d, J = 15.8 Hz, 1 H, CH₂), 3.79 (t, J = 4.8 Hz, 4 H, morpholine H), 3.09 (t, J = 5.0 Hz, 4 H, morpholine H) ppm; MS (ESI): m/z 409 [M + H⁺]₂.
2-(4-(Bromophenyl))-3-(4-morpholinophenyl)thiazolidin-4-one (8m)

Bright yellow solid; m.p. 144°C; yield 85%. IR (CHCl₃) ν: 1685 (C = O), 1619, 1447, 1410, 1325, 1273, 1209, 1165, 1117, 1067, 1017, 1034, 955, 917, 862, 813, 775, 750, 667 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.49-7.36 (m, 1 H, ArH), 7.36 (s, 1 H, ArH), 7.22-7.14 (m, 2 H, ArH), 7.01 (dd, J = 6.7 Hz, J₂ = 2.0 Hz, 2 H, ArH), 6.79 (dd, J = 6.8 Hz, J₂ = 2.3 Hz, 2 H, ArH), 5.92 (d, J = 1.6 Hz, 1 H, CH₃), 3.98 (dd, J₁ = 15.7 Hz, J₂ = 1.8 Hz, 1 H, CH₂), 3.86 (d, J = 15.8 Hz, 1 H, CH₂), 3.80 (t, J = 4.8 Hz, 4 H, morpholine H), 3.10 (t, J = 5.0 Hz, 4 H, morpholine H) ppm; MS (ESI): m/z 375 [M + H]^+; Anal. calcd for C₁₉H₁₉BrN₂O₂S: C, 61.82; H, 5.19; N, 7.25; S, 8.32.

2-(4-Chlorophenyl)-3-(4-morpholinophenyl)thiazolidin-4-one (8n)

Brown gummy solid; yield 96%. IR (CHCl₃) ν: 1685 (C = O), 1619, 1593, 1516, 1488, 1450, 1379, 1333, 1305, 1263, 1234, 1177, 1143, 1121, 1072, 1052, 931, 902, 873, 826, 803, 754, 686, 665, 619 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.26-7.22 (m, 2 H, ArH), 7.09 (d, J = 1.4 Hz, 1 H, CH), 3.98 (dd, J₁ = 15.7 Hz, J₂ = 1.8 Hz, 1 H, CH₂), 3.86 (dd, J₁ = 15.8 Hz, J₂ = 1.8 Hz, 1 H, CH₂), 3.80 (t, J = 4.8 Hz, 4 H, morpholine H), 3.09 (t, J = 3.4 Hz, 4 H, morpholine H) ppm; ¹³C NMR (100 MHz, CDCl₃) δ: 170.83, 150.00, 130.36, 130.27, 128.71, 126.75, 122.64, 115.92, 115.64, 114.08, 113.85, 66.62, 65.00, 48.33, 32.12 ppm; MS (ESI): m/z 359 [M + H]^+; Anal. calcd for C₁₉H₁₉F₃N₂O₂S: C, 63.67; H, 5.34; N, 7.82; S, 8.95. Found: C, 63.45; H, 5.45; N, 7.47; S, 8.74.

3-(3-Morpholinopropyl)-2-(4-(trifluoromethyl)phenyl)thiazolidin-4-one (11)

Brown solid; m.p. 106°C; yield 91%. IR (CHCl₃) ν: 1685 (C = O), 1608, 1593, 1573, 1516, 1449, 1419, 1378, 1330, 1262, 1234, 1179, 1121, 1070, 1052, 930, 902, 826, 796, 756, 686, 666 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.45-7.36 (m, 1 H, ArH), 7.36 (s, 1 H, ArH), 7.22-7.14 (m, 2 H, ArH), 7.01 (dd, J₁ = 6.7 Hz, J₂ = 2.0 Hz, 2 H, ArH), 6.79 (dd, J₁ = 6.8 Hz, J₂ = 2.3 Hz, 2 H, ArH), 5.92 (d, J = 1.6 Hz, 1 H, CH₃), 3.98 (dd, J₁ = 15.7 Hz, J₂ = 1.8 Hz, 1 H, CH₂), 3.86 (d, J = 15.8 Hz, 1 H, CH₂), 3.80 (t, J = 4.8 Hz, 4 H, morpholine H), 3.10 (t, J = 5.0 Hz, 4 H, morpholine H) ppm; MS (ESI): m/z 419 [M + H]^+; Anal. calcd for C₁₉H₁₉F₃N₂O₂S: C, 54.42; H, 4.57; N, 6.68; S, 7.65. Found: C, 54.78; H, 4.33; N, 6.45; S, 7.85.
bacterial cells were suspended in normal saline containing TWEEN 20 at 0.05% concentration of approximately 1.0-2.0 × 10^7 cells/mL by matching with McFarland standards. Proper growth control, drug control, and the negative control were adjusted on to the plate. Compounds were dissolved in dimethyl sulfoxide at a concentration of 1 mg/mL, and 20 mL of this solution was added to each well of 96-well tissue culture plate having 180 mL of Mueller Hinton broth. The solution was then serially diluted to afford twofold serial dilutions of the test compounds in the subsequent wells. Then, McFarland-matched bacterial suspension (100 mL) was diluted with 10 mL of media. The diluted bacterial suspension (100 mL) was added to each well and then kept for incubation. The maximum concentration of compounds tested was 50 mg/mL. Microtitre plates were incubated at 35°C in a moist, dark chamber. MICs were recorded spectrophotometrically after 24 h incubation. Gentamycin and ampicillin were used as reference anti-bacterial agents.

**In vitro antifungal assay**

The *in vitro* antifungal activity of 4-thiazolidinone derivatives (8a-q and 11) was investigated against six pathogenic fungi, viz., *Ca*, *Cn*, *Ss*, *Tm*, *Af*, and *Cp* by broth microdilu-

ventions. The starting propanesulphonic acid in microtitre plates. The solution was then serially diluted to afford twofold serial dilutions of the test compounds in the subsequent wells. Then, McFarland-matched bacterial suspension (100 mL) was diluted with 10 mL of media. The diluted bacterial suspension (100 mL) was added to each well and then kept for incubation. The maximum concentration of compounds tested was 50 mg/mL. Microtitre plates were incubated at 35°C in a moist, dark chamber. MICs were recorded spectrophotometrically after 24 h incubation. Gentamycin and ampicillin were used as reference anti-bacterial agents.

**In vitro antifungal assay**

The *in vitro* antifungal activity of 4-thiazolidinone derivatives (8a-q and 11) was investigated against six pathogenic fungi, viz., *Ca*, *Cn*, *Ss*, *Tm*, *Af*, and *Cp* by broth microdilution technique as per guidelines of the National Committee for Clinical Laboratory Standards [17] using RPMI Medium 1640 buffered with MOPS [3-(N-morpholino) propanesulfonic acid] in microtitre plates. The starting inoculums of test culture were 1.5 × 10^3 cfu/mL. Microtitre plates were incubated at 35°C. Minimal inhibitory concentrations were determined by spectrophotometric method at 492 nm after 24-48 h (yeasts) and 72-96 h (mycelial fungi) incubations. Ketoconazole and fluconazole were used as reference fungicides.

**Abbreviations**

MIC: minimum inhibitory concentration, PEG: polyethylene glycol, PPG: polypropylene glycol.

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**Author details**

1Department of Chemistry, University of Delhi, Delhi 110 007, India
2Fermentation Technology Division, Central Drug Research Institute, Lucknow 226 001, India

**Competing interests**

The authors declare that they have no competing interests.

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