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Synthesis, Characterization and Antimicrobial Activity of Some Novel 4-Thiazolidinone Derivatives

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ABSTRACT

New series of (E)-methyl-2((E)-2-((Z)-(3-methyl-2,6-diarylpiperidin-4-ylidene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate have been synthesized from 2,6-diaryl-3-methyl-piperidin-4-one as a starting material by microwave method. Excellent yield was obtained in shorter reaction time as these reactions were carried out under microwave irradiation, it reduces the cost and time period of reaction. The synthesized compounds exhibited moderate to strong antibacterial activity and antifungal activity against some selected bacteria and fungi. The structures of all the synthesized compounds were confirmed by chemical and spectral analysis such as IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

Keywords: 3-methyl-2,6-diaryl-piperidin-4-thiosemicarbazone, Dimethylacetelenedicarboxylate (DMAD), thiazolidin-4-one, microwave, Montmorillonite K-10, antibacterial activity.

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INTRODUCTION

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The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures and for the physiological and industrial significance of heterocyclic compounds[1].

2,6-Disubstituted piperidin-4-ones are regarded as an important framework and served as a precursors for chiral biologically active natural alkaloids. Heterocyclic compounds carrying piperidine skeleton are attractive targets of organic synthesis owing to their pharmacological activity and their wide occurrence in nature[2-4]. Specifically, piperidine based chemical entities with aryl substituents at carbon 2 and carbon 6 of the piperidine ring have documented as potent antibacterial and antifungal activities[5–13].

The nucleus of 4-Thiazolidinone derivatives has occupied a unique place in the field of medicinal chemistry due to a wide range of biological activities[14]. They have interesting activity profiles mainly cox-1 inhibitors, inhibitors of bacterial enzyme, non-nucleoside inhibitors of HIV Type 1 Reverse Transcriptase (HIVRT) and antihistaminic agent. A literature search revealed that 4-thiazolidinone derivatives may exhibit various potential pharmaceutical applications. Recently, this framework containing compounds were effective against antimicrobial[15], antichistosomal activity[16], antifungal, anti-inflammatory, antimalarial[17], herbicidal[18], antiviral[19], antidiabetic[20] and antioxidant[21] activities. When one biologically active molecule is linked to another, the resultant molecule generally has increased potency. Hence in the present study the two pharmacopores, i.e., substituted piperidin-4-one and 4-thiazolidinone derivatives are fused to obtain highly potent, more specific and less toxic antimicrobial agent.

In view of above findings and continuation of our research programme to find effective new antibacterial and antifungal agents for the treatment of infectious diseases, the present study focused on the synthesis and biological evaluation of some 4-thiazolidinone derivatives by modified protocols.

MATERIALS AND METHODS

All the chemicals used were obtained from Sigma Aldrich, while the reagents and solvents were of analytical grade. Heating was done in microwave oven (LG, domestic oven, 900W). The melting points were determined in open capillary tube and were uncorrected. Completion of reaction and purity of synthesized compounds are checked on aluminium coated TLC plates 60 F_{245} (E. Merck) using Hexane: ethylacetate (6:4 V/V) as mobile phase and visualized under ultraviolet (UV) light. Elemental analysis (% C, H, N, S) is carried out by a VarioEL III analyser. IR spectra of compounds have been recorded on Thermo-Nicolet FT-IR-200 spectrophotometer

in KBr disc (cm^{-1}). ^{1}H NMR and ^{13}C NMR spectra are recorded on Bruker DRX (400 MHz) spectrometer using DMSO as a solvent and TMS as an internal standard. Chemical shifts are reported in parts per million (δ_{ppm}). Mass spectra of synthesized compounds were carried out using the Shimadzu LCMS 2010 spectrometer.

General Procedure for the synthesis of 3-methyl-2,6-diarylpiperidin-4-ones under Microwave method

A green synthetic approach was reported for the facile synthesis of various 3-methyl-2,6-diaryl-piperidin-4-ones via Mannichenamine substitution reaction using Montmorillonite K-10 as catalyst. Dry ammonium acetate (0.1 mole) was mixed with Montmorillonite K-10 (100 mg) in a dry condition. Freshly distilled substituted benzaldehyde (0.2 mole) and ethylmethylketone (0.1 mole) was added and the reaction mixture was placed in a microwave oven, covered with a glass funnel. The reaction mixture was irradiated with microwaves at different microwave intensities until the solution turned yellow and left at room temperature overnight. To monitor the progress of reaction, a TLC was run using Hexane: Ethylacetate (6:4) solvent system. The reaction mixture was dissolved in ether (10ml), treated with aqueous HCl (20ml, 1:1 (V/V)). The hydrochloride salt of the piperidin-4-one was filtered and washed with ether. The base was liberated from an alcoholic solution of the hydrochloride by adding a slight excess of aqueous ammonia and diluted with water at $0^{o}C$. The piperidin-4-one were recrystallized from abs.ethanol.

General procedure for the synthesis of 3-methyl-2,6-diarylpiperidin-4-thiosemicarbazone

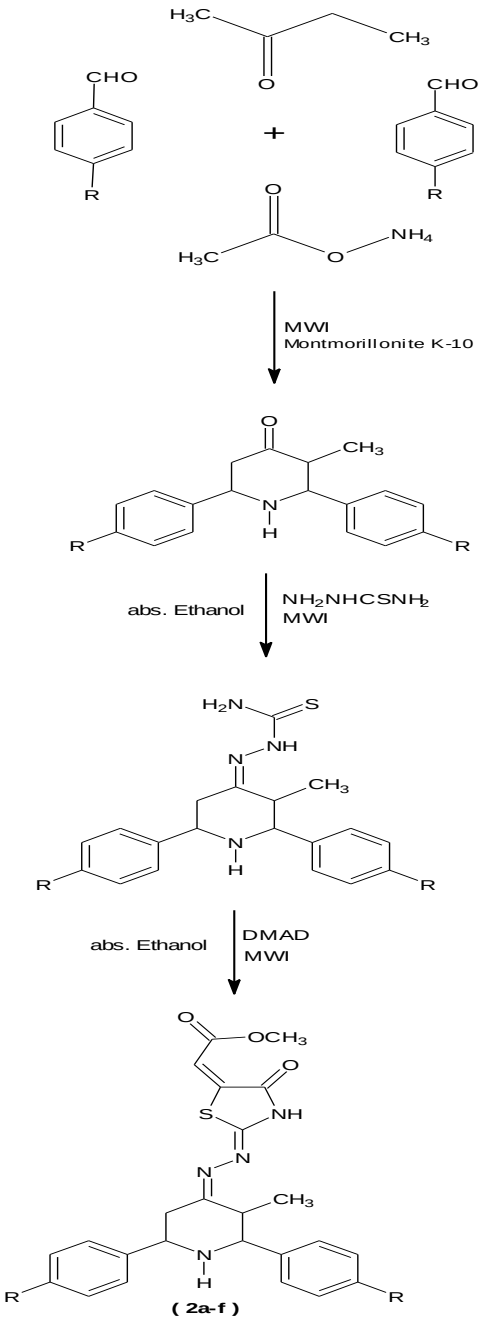
To the mixture of 3-alkyl-2,6-diaryl-piperidin-4-one (0.05 mole) in 10ml abs. ethanol, few drops of con.HCl were added. Thereafter thiosemicarbazide (previously dissolved in 10ml abs.ethanol) solution (0.05 mole) was added drop-wise with constant stirring. The mixture was subject to microwave irradiation under microwave at 160W for 5 minutes. A beaker containing water was also kept in the oven to serve as a heat sink. To monitor the progress of reaction, a TLC was run to confirm the completion of reaction. After completion of reaction, the solid product was filtered off and recrystallized from abs.ethanol.

General procedure for the synthesis of (E)-methyl-2((E)-2-((Z)-(3-methyl-2,6-diarylpiperidin-4-ylidene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate (2a-f)

To a mixture of 3-methyl-2,6-diarylpiperidin-4-thiosemicarbazone (0.01 mole) in abs.ethanol (20 ml), the solution of dimethylacetelenedicarboxylate (DMAD) (0.01 mole) is added in small portion. The mixture was subject to microwave irradiation under microwave at 80W for 3 min. To monitor the progress of reaction, a TLC was run to confirm the completion of reaction. After

cooling, the reaction mixture to ambient temperature. The resulting yellow precipitate was filtered, washed with abs.ethanol, a yellow solid was separated.

Antimicrobial Activity:



Compounds	R
2a	H
2b	OCH_3
2c	CH_3
2d	OH
2e	Cl
2f	NO_2

SCHEME - 1

Antimicrobial analysis was followed using standard agar well diffusion method[22] to study the antimicrobial activity of compounds. Each bacterial and fungal isolate was suspended in Brain Heart Infusion (BHI) broth and diluted to approximately 10^5 colony forming unit (CFU) per mL. Mac Farland standard number 5 was used to compare the growth pattern of the micro-organism. They were flood-inoculated onto the surface of BHI agar and then dried. Five-millimeter

diameter wells were cut from the agar using a sterile cork-borer and 30 µL (50 µg compound in 1 ml of solvent-DMSO) of the sample solution were poured into the wells. The plates were incubated for 18 h at 37°C for bacteria and at room temperature for fungi. Antimicrobial activity was evaluated by measuring the zone of inhibition in mm against the test microorganisms. DMSO was used as solvent control. Ciprofloxacin was used as reference antibacterial agent. Amphotericin B was used as reference antifungal agent. The tests were carried out in triplicates.

RESULTS AND DISCUSSION

The preliminary studies on spectral data and anti-microbial activity of the new series of (E)-methyl-2((E)-2-((Z)-(3-methyl-2,6-diarylpiperidin-4-ylidene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate have generated some interesting data.

Characterization data of (E)-methyl-2((E)-2-((Z)-(3-methyl-2,6-diphenylpiperidin-4-ylidene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate (2a)

Yield: 86% M.p., 195°C. IR(KBr): 1723 cm^{-1} (C=O stretching of ester), 1639 cm^{-1} (C=O stretching of thiazole ring), 1594 cm^{-1} (-C=N-), ^{1}H NMR (DMSO, 200 MHz): δ 2.11 (s, 1H, NH of piperidine ring), δ 3.79 (s, 3H, OCH_3 of ester), δ 6.28 (s, 1H, **H**C-CO-OCH_3)**,** δ 7.24-7.49 (m,10H, Ar-H of two phenyl ring), δ 8.32 (s, 1H, NH of thiazole ring). ^{13}C NMR (DMSO,200MHz): δ 50.59 ppm (OCH_3, 1C of ester), δ 125.13-128.87 ppm (Ar-C, 12C of two phenyl ring), δ 165.47ppm (-CO-OCH3, 1C of carbonyl carbon of ester), δ 168.74 ppm (-NH-C=O, 1C carbonyl carbon of thiazolidinone). LC-MS: m/z 449.1 (M+1), Anal. Calcd. (%) for $C_{24}H_{24}N_4O_3S$: C, 64.27; H, 5.39; N, 12.49; Found: C, 63.84; H, 5.40; N, 12.54.

Characterization data of (E)-methyl-2((E)-2-((Z)-(3-methyl-2,6-dianisylpiperidin-4-ylidene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate (2b)

Yield: 86% M.p., 213°C. IR(KBr): 1733 cm^{-1} (C=O stretching of ester), 1645 cm^{-1} (C=O stretching of thiazole ring), 1591 cm^{-1} (-C=N-), ^{1}H NMR (DMSO, 200 MHz): δ 2.18 (s, 1H, NH of piperidine ring), δ 3.68 (s, 3H, OCH3 of anisyl), δ 3.79 (s, 3H, OCH_3 of ester), δ 6.31 (s, 1H, **H**C-CO-OCH_3)**,** δ 6.78-7.05 (m, 8H, Ar-H of two phenyl ring), δ 8.29 (s, 1H, NH of thiazole ring). ^{13}C NMR (DMSO,200MHz): δ 50.64 ppm (OCH_3, 1C of ester), δ 57.14 ppm (OCH_3,1C of anisyl), δ 113.16-129.68 ppm (Ar-C, 10C of two phenyl ring), δ 159.28-160.36 ppm (Ar-C,2C of Ar-**C**-OCH3), δ 164.86 ppm (-**C**O-OCH_3, 1C of carbonyl carbon of ester), δ 168.13 ppm (-NH-C=O, 1C carbonyl carbon of thiazolidinone). LC-MS: m/z 510.2 (M+1), Anal. Calcd. (%) for $C_{26}H_{28}N_4O_5S$: C, 61.40; H, 5.55; N, 11.02; Found: C, 60.88; H, 5.46; N, 12.24.

Characterization data of (E)-methyl-2((E)-2-((Z)-(3-methyl-2,6-ditoluylpiperidin-4-ylidene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate (2c)

Yield: 78% M.p., 211°C. IR(KBr): 1731 cm^{-1} (C=O stretching of ester), 1653 cm^{-1} (C=O stretching of thiazole ring), 1613 cm^{-1} (-C=N-), ^{1}H NMR (DMSO, 200 MHz): δ 2.07 (s, 1H, NH of piperidine ring), δ 2.47 (s, 3H, CH_3 of toluyl), δ 3.76 (s, 3H, OCH_3 of ester), δ 6.23 (s, 1H, **H**C-CO-OCH_3)**,** δ 6.98-7.07 (m,8H, Ar-H of two phenyl ring), δ 8.13 (s, 1H, NH of thiazole ring). ^{13}C NMR (DMSO,200MHz): δ 50.53 ppm (OCH_3, 1C of ester), δ 21.09 ppm (CH_3,1C of toluyl), δ 128.14-137.38 ppm (Ar-C, 12C of two phenyl ring), δ 167.23 ppm (-**C**O-OCH3, 1C of carbonyl carbon of ester), δ 167.58 ppm (-NH-C=O, 1C carbonyl carbon of thiazolidinone). LC-MS: m/z 477.8 (M+1), Anal. Calcd. (%) for $C_{26}H_{28}N_4O_3S$: C, 65.52; H, 5.92; N, 11.76; Found: C, 66.03; H, 5.98; N, 11.84.

Characterization data of (E)-methyl-2((E)-2-((Z)-(3-methyl-2,6-(4-hydroxy)diphenylpiperidin-4-ylidene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate (2d)

Yield : 71% M.p., 193°C. IR(KBr): 1743 cm^{-1} (C=O stretching of ester), 1638 cm^{-1} (C=O stretching of thiazole ring), 1609 cm^{-1} (-C=N-), ^{1}H NMR (DMSO, 200 MHz): δ 2.11 (s, 1H, NH of piperidine ring), δ 3.72 (s, 3H, OCH_3 of ester), δ 5.08 (s, 1H, OH of hydroxyl), δ 6.19 (s, 1H, **H**C-CO-OCH_3)**,** δ 6.67-6.93 (m,8H, Ar-H of two phenyl ring), δ 8.19 (s, 1H, NH of thiazole ring). ^{13}C NMR (DMSO,200MHz): δ 50.58 ppm (OCH_3, 1C of ester), δ 114.58-153.78 ppm (Ar-C, 12C of two phenyl ring), δ 164.75 ppm (-**C**O-OCH3, 1C of carbonyl carbon of ester), δ 167.97 ppm (-NH-C=O, 1C carbonyl carbon of thiazolidinone). LC-MS: m/z 490.72 (M+1), Anal. Calcd. (%) for $C_{24}H_{24}N_4O_5S$: C, 59.99; H, 5.03; N, 11.66; Found: C, 58.78; H, 5.09; N, 11.83

Characterization data of (E)-methyl-2((E)-2-((Z)-(3-methyl-2,6-(4-chloro)diphenylpiperidin-4-ylidene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate (2e)

Yield: 71% M.p., 179°C. IR(KBr): 1731 cm^{-1} (C=O stretching of ester), 1647 cm^{-1} (C=O stretching of thiazole ring), 1617 cm^{-1} (-C=N-), ^{1}H NMR (DMSO, 200 MHz): δ 2.06 (s, 1H, NH of piperidine ring), δ 3.83 (s, 3H, OCH_3 of ester), δ 6.36 (s, 1H, **H**C-CO-OCH_3)**,** δ 7.09-7.28 (m,8H, Ar-H of two phenyl ring), δ 8.14 (s, 1H, NH of thiazole ring). ^{13}C NMR (DMSO,200MHz): δ 50.37 ppm (OCH_3, 1C of ester), δ 128.73-136.87 ppm (Ar-C, 12C of two phenyl ring), δ 165.07 ppm (-**C**O-OCH3, 1C of carbonyl carbon of ester), δ 168.57 ppm (-NH-C=O, 1C carbonyl carbon of thiazolidinone). LC-MS: m/z 518.23 (M+1), Anal. Calcd. (%) for $C_{24}H_{22}Cl_2N_4O_3S$: C, 55.71; H, 4.29; N, 10.83; Found: C, 55.16; H, 4.37; N, 10.68

Characterization data of (E)-methyl-2((E)-2-((Z)-(3-methyl-2,6-(4-nitro)diphenylpiperidin-4-ylidene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate (2f)

Yield : 76% M.p., 197°C. IR(KBr): 1707 cm^{-1} (C=O stretching of ester), 1633 cm^{-1} (C=O stretching of thiazole ring), 1629 cm^{-1} (-C=N-), ^{1}H NMR (DMSO, 200 MHz): δ 2.09 (s, 1H, NH of piperidine ring), δ 3.71 (s, 3H, OCH_3 of ester), δ 6.23 (s, 1H, **H**C-CO-OCH_3)**,** δ 7.39-8.11 (m,8H, Ar-H of two phenyl ring), δ 7.96 (s, 1H, NH of thiazole ring). ^{13}C NMR (DMSO,200MHz): δ 50.46 ppm (OCH_3, 1C of ester), δ 123.47-147.71 ppm (Ar-C, 12C of two phenyl ring), δ 164.82 ppm (-**C**O-OCH3, 1C of carbonyl carbon of ester), δ 167.73 ppm (-NH-C=O, 1C carbonyl carbon of thiazolidinone). LC-MS: m/z 548.32 (M+1), Anal. Calcd. (%) for $C_{24}H_{22}N_6O_7S$: C, 53.53; H, 4.12; N, 15.61; Found: C, 54.05; H, 4.23; N, 15.79.

Table 1 Antibacterial activities of the newly synthesized compounds (Zone of inhibition in mm).

Antibacterial Activity						
Compd	***Staphylococcus aureus***	***Streptococcus faecalis***	***Pseudomonas aeruginosa***	***Escherichia coli***	***Klebsiellapneumoniae***	***Bac cer***
2a	6 mm	5 mm	-	4 mm	4 mm	5 m
2b	8 mm	6 mm	-	7 mm	7 mm	6 m
2c	10 mm	6 mm	-	4 mm	7 mm	5 m
2d	4 mm	5 mm	5 mm	10 mm	7 mm	7 m
2e	5 mm	6 mm	-	5 mm	4 mm	5 m
2f	5 mm	6 mm	6 mm	7 mm	8 mm	6 m
Ciprofloxacin	20 mm	15 mm	15 mm	15 mm	15 mm	13
Control DMSO	-	-	-	-	-	-

Antibacterial activity of 4-thiazolidinone derivatives

The newly synthesized 4-thiazolidinone derivatives were investigated for their antibacterial activity against *Staphylococcus aureus*, *Streptococcus faecalis*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiellapneumoniae* and *Bacillus cereus* bacterial strains by disc diffusion method.

Results of antibacterial activity of above synthesized compounds are given in Table 1. The synthesized compounds compared with the standard Ciprofloxacin and DMSO used as a control. The compounds tested against six strains by the disc diffusion method. Among the synthesized compounds, Compound **2c** showed high inhibition, compound **2a** and **2b** showed moderate activity in *Staphylococcus aureus.* Compounds **2c** and **2f** showed moderate activity against *Streptococcus faecalis* and other compounds with minimum inhibition. Compound **2b**, **2d** and **2f** also showed moderate activity against *Escherichia coli*. In *Klebsiellapneumoniae*, compound **2b**, **2c**, **2d**, **2e** and **2f** showed moderate inhibition.

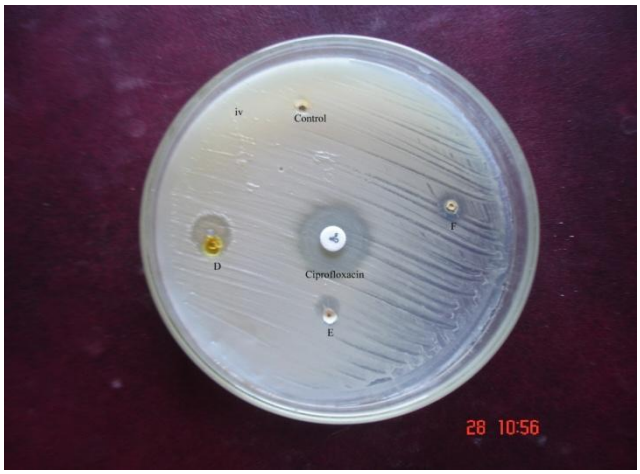
Table 2 Antifungal activities of the newly synthesized compounds (Zone of inhibition in mm).

Antifungal Activity						
Compd	***Aspergillus flavus***	***Candida albicans***	***Penicllium sps***	***Aspergillusniger***	***Mucor sps***	***Rhizopus sps***
2a	11 mm	5 mm	14 mm	10 mm	13 mm	11 mm
2b	6 mm	5 mm	7 mm	6 mm	11 mm	7 mm
2c	-	-	5 mm	-	6 mm	-
2d	9 mm	7 mm	9 mm	12 mm	7 mm	13 mm
2e	11 mm	8 mm	18 mm	11 mm	14 mm	14 mm
2f	12 mm	5 mm	10 mm	11 mm	10 mm	10 mm
Amphotericin-B	15 mm	12 mm	10 mm	10 mm	15 mm	11 mm
Control DMSO	-	-	-	-	-	-

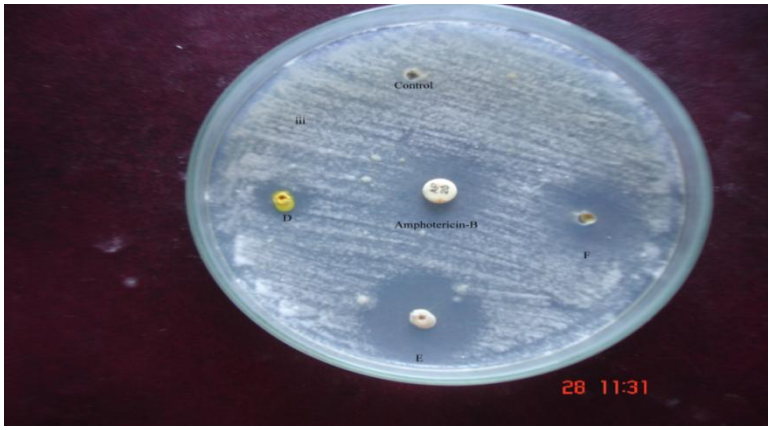
Antifungal activity of 4-thiazolidinone derivatives

The synthesized 4-thiazolidinone derivatives were investigated for their antifungal activity against *Aspergillusflavus*, *Candida albicans*, *Penicilliumsps*, *Aspergillusniger*, *Mucorsps* and *Rhizopussps* fungal strains by disc diffusion method. Results of antifungal activity of above synthesized compounds are given in Table 2. The synthesized compounds are compared with the standard Amphotericin-B and DMSO used as a control.

All the synthesized compounds showed good antifungal activity than antibacterial activity. Compound **2e** showed pronounced growth of inhibition against *Penicilliumsps* and *Mucorsps*. Compound **2a** also showed good inhibition against *Penicilliumsps*, *Mucorsps* and *Aspergillusniger*. Compound **2e** and **2a** showed good activity against *Aspergillusflavus* and compound **2e** and **2d** showed good inhibition against *Rhizopussps.*



Antibacterial Activity



Antifungal Activity

CONCLUSION

The main aim of the present study is to synthesis and investigates the antimicrobial activity of new heterocyclic derivatives containing piperidine and thiazolidin-4-one moieties with the hope of discovering new structures serving as potential broad spectrum antimicrobial agents. The antibacterial and antifungal data revealed that the compounds 2a, 2b, 2c, 2d, 2e and 2f showed good to moderate antimicrobial activity. Basically introduction of thiazolidin-4-one moiety in the piperidine ring has increased the antifungal activity.

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