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ORIGINAL ARTICLE

Synthesis, characterization and antimicrobial evaluation of 2,5-disubstituted-4-thiazolidinone derivatives

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Abstract In the present study novel derivatives of 4-thiazolidinone were prepared from biphenyl-4-carboxylic acid and evaluated for their *in vitro* antimicrobial activity against two Gram negative strains (*Escherichia coli* and *Pseudomonas aeruginosa*) and two Gram positive strains (*Bacillus subtilis* and *Staphylococcus aureus*) and fungal strain *Candida albicans* and *Aspergillus niger*. The newly synthesized compounds were characterized by IR, ^{1}H NMR and C, H, N analyses. The results revealed that all synthesized compounds have a significant biological activity against the tested microorganisms. Among the synthesized derivatives **4g** (biphenyl-4-carboxylic acid [2-(3-bromophenyl)-5-(3-nitrobenzylidene)-4-oxo-thiazolidin-3-yl]-amide) and **4i** (biphenyl-4-carboxylic acid [5-(3-bromobenzylidene)-2-(3-bromophenyl)-4-oxo-thiazolidin-3-yl]-amide) were found to be most effective antimicrobial compounds.

1. Introduction

Microbial resistance to antimicrobial agents is of grave concern in the medical community. Hence, the development of novel, potent, and unique antimicrobial agents are the pre-eminent way to overcome microbial resistance and develop effective therapies. 4-Thiazolidinone and its derivatives have attracted considerable attention for the past few decades due to their chemotherapeutical values (Verma and Saraf, 2008).

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Table 1 Physical data of 2,5-disubstituted-4-thiazolidinones.

Compound	Ar	Ar′	Molecular formula	Molecular weight	Melting point (°C)	Yield (%)	R_f value
4a	C_6H_5–	C_6H_5–	$C_{29}H_{22}N_2O_2S$	462.56	214–216	71.32	0.63
4b	C_6H_5–	3-$NO_2C_6H_4$	$C_{29}H_{21}N_3O_4S$	507.56	217–219	78.14	0.71
4c	C_6H_5–	4-ClC_6H_4	$C_{29}H_{21}ClN_2O_2S$	497.01	223–224	82.26	0.59
4d	C_6H_5–	3-BrC_6H_4	$C_{29}H_{21}BrN_2O_2S$	541.46	216–217	79.40	0.62
4e	C_6H_5–	4-$OCH_3C_6H_4$	$C_{30}H_{24}N_2O_3S$	492.59	210–212	81.60	0.68
4f	3-BrC_6H_4	C_6H_5–	$C_{29}H_{21}BrN_2O_2S$	541.46	228–230	78.46	0.92
4g	3-BrC_6H_4	3-$NO_2C_6H_4$	$C_{29}H_{20}BrN_3O_4S$	586.46	238–239	78.40	0.88
4h	3-BrC_6H_4	4-ClC_6H_4	$C_{29}H_{20}BrClN_2O_2S$	575.90	225–227	81.20	0.79
4i	3-BrC_6H_4	3-BrC_6H_4	$C_{29}H_{20}Br_2N_2O_2S$	620.35	245–248	78.62	0.82
4j	3-BrC_6H_4	4-$OCH_3C_6H_4$	$C_{30}H_{23}BrN_2O_3S$	571.48	234–235	81.80	0.73
4k	4-FC_6H_4	C_6H_5–	$C_{29}H_{21}FN_2O_2S$	480.55	242–243	79.34	0.78
4l	4-FC_6H_4	3-$NO_2C_6H_4$	$C_{29}H_{20}FN_3O_4S$	525.55	235–237	78.86	0.84

For mobile phase: chloroform:benzene:glacial acetic acid (3:1:1, v/v/v).

These derivatives are known to possess several promising pharmacological actions such as antimicrobial (Bondock et al., 2007; Shah and Desai, 2007; Samir et al., 2007; Vicini et al., 2006; Sharma et al., 2006; Handan et al., 2005), analgesic (Knutsen et al., 2007), anti-inflammatory (Ottana et al., 2005; Goel et al., 1999), anti-HIV (Balzarini et al., 2007), cytotoxic (Mujeebur et al., 2005), and anticonvulsant (Gursoy and Terzioglu, 2005) activities. Also, 4-thiazolidinones have been found as novel inhibitors of bacterial enzyme MurB, a key enzyme responsible for the synthesis of peptidoglycon (Andres et al., 2000).

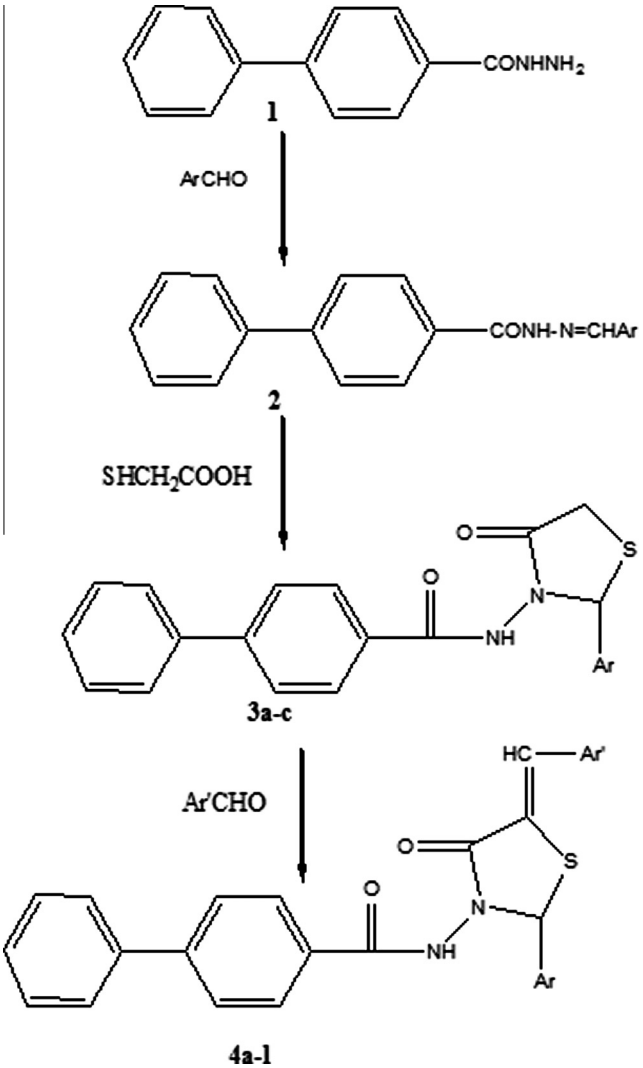
Inspired by the above facts and in continuation of our ongoing research program in the field of synthesis and antimicrobial activity of medicinally important compounds (Deep et al., 2010b; Madhukar et al., 2009; Kumar et al., 2010), we hereby report the synthesis and antimicrobial activity of 4-thiazolidinone derivatives. All these compounds have been reported with their anti-inflammatory activity elsewhere (Deep et al., 2010a). The structures of all compounds have been confirmed by elemental and spectral analysis (IR and ^{1}H NMR).

2. Experimental

The purity of the synthesized compounds were ascertained by thin layer chromatography on silica gel G in various solvent systems using iodine vapours as detecting agent. Melting points were determined by the melting point determination apparatus (TEMPO) in open capillary tubes and are uncorrected. Elemental analyses were done using Carlo Erba 1106 CHN Analyzer. Infra-red spectra were recorded on Perkin Elmer Spectrum RXI FTIR spectrophotomer in KBr phase. Proton NMR spectra were recorded on Bruker Avance II 400 NMR Ultra Shield Spectrometer using DMSO-d_6 as a solvent and tetramethyl silane as internal standard. Chemical shift value is expressed in delta parts per million (δ ppm). All the compounds have been screened *in vivo* for their anti-inflammatory activity.

2.1. Chemistry

A series of biphenyl-4-carboxylic acid-5-(arylidene)-2-(aryl)-4-oxothiazolidin-3-yl-amides has been synthesized. Reaction of acid hydrazide (**1**) with aromatic aldehydes yielded the corresponding hydrazones (**2a**–**c**) which on further reaction with thioglycolic acid in methanol afforded the corresponding 2-substituted-4-thiazolidinones (**3a**–**c**). The compounds (**3a**–**c**) were further reacted with aromatic aldehydes in presence of



Scheme 1 Preparation of biphenyl-4-carboxylic acid-5-(arylidene)-2-(aryl)-4-oxo-thiazolidin-3-yl-amides (**4a**–**l**).

few drops of glacial acetic acid to yield the 2,5-disubstituted-4-thiazolidinones (**4a**–**l**). The synthesized 2,5-disubstituted-4-thiazolidinones were characterized on the basis of the spectral and analytical studies.

2.2. General method

The title compounds were prepared in following steps:

2.2.1. Synthesis of hydrazone (**2**)

A mixture of biphenyl-4-carboxylic acid hydrazide (0.025 mol, 5.3 g) and required aromatic aldehydes (0.025 mol) was refluxed in methanol (50 ml) in the presence of a catalytic amount of glacial acetic acid for about 2 h. The mixture was cooled and the solid obtained was separated by filtration and recrystallized from methanol to give the corresponding hydrazones.

2.2.2. Synthesis of 2-substituted-4-thiazolidinone (**3a**–**c**)

A mixture of appropriate Schiff's base (0.015 mol) (**2**) and required amount of thioglycolic acid (0.015 mol, 1.40 ml) in *N*,*N*-dimethylformamide (DMF) (50 ml), containing a pinch of anhydrous $ZnCl_2$ was refluxed for about 6 h. The reaction mixture was cooled and poured on to crushed ice. The solid thus obtained was filtered, washed with water and the product was recrystallized from rectified spirit.

2.2.3. Synthesis of 2,5-disubstituted-4-thiazolidinone (**4a**–**l**)

A suspension of 2-substituted-4-thiazolidinone (0.01 mol), required aromatic aldehydes (0.01 mol) and anhydrous sodium acetate was prepared in glacial acetic acid and refluxed for 5–7 h. After cooling, the solution was poured on crushed ice to precipitate the product. The product was recrystallized from ethanol.

By adopting similar type of procedures, and employing equimolar quantities of reactants, 12 compounds were synthesized. Physical and analytical data of synthesized compounds is given in Table 1. Synthetic pathway for preparation of title compounds is shown in Scheme 1.

2.3. Spectral data

2.3.1. Biphenyl-4-carboxylic acid (5-benzylidene-4-oxo-2-phenylthiazolidin-3yl)-amide (**4a**)

IR (KBr, cm^{-1}): 3198 (N–H), 3028–2923 (C–H), 1634–1657 (C═O), 1605–1483 (C═C), 1446–1402 (C–N). *^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):* 8.43–7.38 (m, 9H, Ar H), 8.06 (s, 1H, –NH), 7.68–7.50 (m, 5H, Ar′ H), 7.48–7.40 (m, 4H, Ar H), 7.32 (s, 1H, C═CH), 4.62 (s, 1H, –NCHS). Anal. Calcd. for $C_{29}H_{22}N_2O_2S$: C, 75.30; H, 4.79; N, 6.06. Found C, 75.26; H, 4.81; N, 6.01.

2.3.2. Biphenyl-4-carboxylic acid [5-(3-nitrobenzylidene)-4-oxo-2-phenylthiazolidin-3-yl]-amide (**4b**)

IR (KBr, cm^{-1}): 3253 (N–H), 3052 (C–H), 1657 (C═O), 1608–1485 (C═C), 1448–1435 (C–N), 1529–1581 (N–O). *^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):* 8.60–7.79 (m, 4H, Ar′ H), 8.05 (s, 1H, –NH), 7.78–7.47 (m 9H, Ar, H), 7.51–7.42 (m, 5H, Ar H), 7.40 (s, 1H, C═CH), 3.34 (s, 1H, –NCHS). Anal. Calcd. for $C_{29}H_{21}N_3O_4S$: C, 68.62; H, 4.17; N, 8.28. Found C, 68.66; H, 4.21; N, 8.22.

2.3.3. Biphenyl-4-carboxylic acid [5-(4-chlorobenzylidene)-4-oxo-2-phenylthiazolidin-3-yl]-amide (**4c**)

IR (KBr, cm^{-1}): 3403 (N–H), 2933 (C–H), 1716–1681 (C═O), 1606–1485 (C═C), 1436–1422 (C–N), 749–698 (C–Cl). *^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):* 8.49–7.77 (m, 9H, Ar H), 8.04 (s, 1H, –NH), 7.47–7.40 (m, 5H, Ar H), 7.67–7.50 (m, 4H, Ar H), 7.41 (s, 1H, C═CH), 3.92 (s, 1H, –NCHS). Anal. Calcd. for $C_{29}H_{21}ClN_2O_2S$: C, 70.08; H, 4.26; N, 5.64. Found C, 70.02; H, 4.30; N, 5.66.

2.3.4. Biphenyl-4-carboxylic acid [5-(3-bromobenzylidene)-4-oxo-2-phenylthiazolidin-3-yl]-amide (**4d**)

IR (KBr, cm^{-1}): 2993–2944 (C–H), 1717–1682 (C═O), 1605–1485 (C═C), 1436–1422 (C–N), 545 (C–Br). *^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):* 8.47–7.73 (m, 9H, Ar H), 8.07 (s, 1H, –NH), 7.46–7.42 (m, 5H, Ar H), 7.69–7.48 (m, 4H, Ar H), 7.38 (s, 1H, C═CH), 4.24 (s, 1H, –NCHS). Anal. Calcd. for $C_{29}H_{21}BrN_2O_2S$: C, 64.33; H, 3.91; N, 5.71. Found C, 64.29; H, 3.96; N, 5.70.

2.3.5. Biphenyl-4-carboxylic acid [5-(4-methoxybenzylidene)-4-oxo-2-phenylthiazolidin-3-yl]-amide (**4e**)

IR (KBr, cm^{-1}): 3269 (N–H), 3030–2927 (C–H), 1650 (C═O), 1607–1485 (C═C), 1447–1419 (C–N), 1253 (C–O–C). *^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):* 8.41–7.46 (m, 9H, Ar H), 8.03 (s, 1H, –NH), 7.40–7.22 (m, 4H, Ar′ H), 7.42 (s, 1H, C═CH), 7.38–7.26 (m, 5H, Ar′ H), 5.18 (s, 1H, –NCHS), 3.52 (s, 1H, –OCH). Anal. Calcd. for $C_{30}H_{24}N_2O_3S$: C, 73.13; H, 4.91; N, 5.69. Found C, 73.11; H, 4.95; N, 5.72.

2.3.6. Biphenyl-4-carboxylic acid [5-benzylidene-2-(3-bromophenyl)-4-oxothiazolidin-3-yl]-amide (**4f**)

IR (KBr, cm^{-1}): 3209 (N–H), 3030 (C–H), 1649 (C═O), 1606–1484 (C═C), 1447–1403 (C–N), 554–506 (C–Br). *^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):* 8.48–7.40 (m, 9H, Ar H), 8.04 (s, 1H, –NH), 7.68–7.38 (m, 5H, Ar′ H), 7.48–7.28 (m, 4H, Ar H), 7.46 (s, 1H, C═CH), 3.09 (s, 1H, –NCHS). Anal. Calcd. for $C_{29}H_{21}BrN_2O_2S$: C, 64.33; H, 3.91; N, 5.17. Found C, 64.31; H, 3.96; N, 5.14.

2.3.7. Biphenyl-4-carboxylic acid [2-(3-bromophenyl)-5-(3-nitrobenzylidene)-4-oxo-thiazolidin-3-yl]-amide (**4g**)

IR (KBr, cm^{-1}): 3261 (N–H), 3034 (C–H), 1655 (C═O), 1528 (N–O), 1608–1483 (C═C), 1445–1402 (C–N), 509 (C–Br). *^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):* 8.84–7.45 (m, 4H, Ar′ H), 8.06–7.37 (m, 9H, Ar H), 8.00 (s, 1H, –NH), 7.54–7.32 (m, 4H, Ar H), 7.50 (s, 1H, C═CH), 4.59 (s, 1H, –NCHS). Anal. Calcd. for $C_{29}H_{20}BrN_3O_4S$: C, 59.39; H, 3.44; N, 7.17. Found C, 59.43; H, 3.47; N, 7.21.

2.3.8. Biphenyl-4-carboxylic acid [2-(3-bromophenyl)-5-(4-chlorobenzylidene)-4-oxo-thiazolidin-3-yl]-amide (**4h**)

IR (KBr, cm^{-1}): 3282 (N–H), 3036 (C–H), 1651 (C═O), 1607–1447 (C═C), 1447 (C–N), 780–603 (C–Cl), 513 (C–Br). *^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):* 8.45–7.48 (m, 9H, Ar H), 8.00 (s, 1H, –NH), 7.58 (s, 1H, C═CH), 7.52–7.46 (m 4H, Ar′ H), 7.50–7.28 (m, 4H, Ar H), 3.02 (s, 1H, –NCHS).

Table 2 *In vitro* antibacterial activity of the title compounds (**4a–l**).

Compound	Minimum inhibitory concentration (μg ml^{-1})			
	E. coli (MTCC 40)	*P. aeruginosa* (MTCC 2453)	*S. aureus* (MTCC 121)	*B. subtilis* (MTCC 96)
4a	6.25	6.25	6.25	3.12
4b	6.25	3.12	3.12	1.56
4c	3.12	12.5	3.12	6.25
4d	12.5	6.25	3.12	6.25
4e	6.25	6.25	6.25	1.56
4f	6.25	3.12	3.12	3.12
4g	3.12	1.56	1.56	1.56
4h	12.5	6.25	6.25	6.25
4i	6.25	6.25	3.12	3.12
4j	1.56	12.5	3.12	1.56
4k	6.25	12.5	6.25	3.12
4l	12.5	3.12	6.25	6.25
Ciprofloxacin (standard drug)	0.01	0.25	0.15	0.12

Anal. Calcd. for $C_{29}H_{20}BrClN_2O_2S$: C, 60.48; H, 3.50; N, 4.86. Found C, 60.43; H, 3.54; N, 4.83.

*2.3.9. Biphenyl-4-carboxylic acid [5-(3-bromobenzylidene)-2-(3-bromophenyl)-4-oxo-thiazolidin-3-yl]-amide (**4i**)*

IR (KBr, cm^{-1}): 3428 (N–H), 3044 (C–H), 1650 (C═O), 1607–1484 (C═C), 1447–1406 (C–N), 554–503 (C–Br). *^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):* 8.41–7.42 (m, 9H, Ar H), 8.03 (s, 1H, –NH), 7.62–7.30 (m, 4H, Ar′ H), 7.51 (s, 1H, C═CH), 7.46–7.26 (m, 4H, Ar′ H). Anal. Calcd. for $C_{29}H_{20}Br_2N_2O_2S$: C, 56.15; H, 3.25; N, 4.52. Found C, 56.20; H, 3.23; N, 4.57.

*2.3.10. Biphenyl-4-carboxylic acid [2-(3-bromophenyl)-5-(4-methoxybenzylidene)-4-oxo-thiazolidin-3-yl]-amide (**4j**)*

IR (KBr, cm^{-1}): 3428 (N–H), 3034 (C–H), 1650 (C═O), 1606–1473 (C═C), 1447–1403 (C–N), 1280–1253 (C–O–C), 553–531 (C–Br). *^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):* 8.05–7.44 (m, 9H, Ar H), 8.02 (s, 1H, –NH), 7.46–7.26 (m, 4H, Ar H), 7.41 (s, 1H, C═CH), 7.39–6.93 (m, 4H, Ar′ H), 4.60 (s, 1H, –NCHS), 3.48 (s, 1H, –OCH). Anal. Calcd. for $C_{30}H_{23}BrN_2O_3S$: C, 63.05; H, 4.06; N, 4.90. Found C, 63.01; H, 4.08; N, 4.86.

*2.3.11. Biphenyl-4-carboxylic acid [5-benzylidene-2-(4-fluorophenyl)-4-oxothiazolidin-3-yl]-amide (**4k**)*

IR (KBr, cm^{-1}): 3211 (N–H), 3038 (C–H), 1657 (C═O), 1606–1475 (C═C), 1445–1401 (C–N), 1233 (C–F). *^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):* 8.22–7.47 (m, 9H, Ar H), 8.03 (s, 1H, –NH), 7.56–7.37 (m, 5H, Ar′ H), 7.34–7.12 (m, 4H, Ar H), 7.52 (s, 1H, C═CH), 3.58 (s, 1H, –NCHS). Anal. Calcd. for $C_{29}H_{21}FN_2O_2S$: C, 72.48; H, 4.40; N, 5.83. Found C, 72.45; H, 4.37; N, 5.85.

*2.3.12. Biphenyl-4-carboxylic acid [2-(4-fluorophenyl)-5-(3-nitrobenzylidene)-4-oxo-thiazolidin-3-yl]-amide (**4l**)*

IR (KBr, cm^{-1}): 3245 (N–H), 3033 (C–H), 1651 (C═O), 1522 (N–O), 1605–1483 (C═C), 1445–1402 (C–N), 1226 (C–F). *^{1}H NMR (300 MHz, DMSO-d_6, δ ppm):* 8.77–7.48 (m, 4H, Ar′ H), 8.11–7.35 (m, 9H, Ar H), 8.01 (s, 1H, –NH), 7.57–7.35 (4H, Ar H), 7.49 (s, 1H, C═CH), 4.31 (s, 1H, –NCHS). Anal. Calcd. for $C_{29}H_{20}FN_3O_4S$: C, 66.28; H, 3.84; N, 8.00. Found C, 66.25; H, 3.80; N, 6.03.

3. Antimicrobial evaluation

The synthesized compounds were evaluated for their *in vitro* antimicrobial activity against Gram positive bacteria: *Staphylococcus aureus* (MTCC 121), *Bacillus subtilis* (MTCC 96), Gram negative *Escherichia coli* (MTCC 40), *Pseudomonas aeruginosa* (MTCC 2453) and fungal strain: *Candida albicans* (MTCC 8184) and *Aspergillus niger* (MTCC 8189). Antimicrobial activity was assessed by serial two-fold dilution technique. Ciprofloxacin was used as a standard drug for antibacterial activity and clotrimazole was used as a standard drug for antifungal activity. All the compounds were dissolved in dimethyl sulfoxide to give a concentration of 10 μg ml^{-1}. Twofold dilutions of test and standard compounds were prepared in double strength nutrient broth I.P. (bacteria) or Sabouraud dextrose broth I.P. (Pharmacopoeia, 1996) (fungi). The stock solution was serially diluted to give concentrations of 25–0.78 μg ml^{-1} in nutrient broth. The inoculum size was approximately

Table 3 *In vitro* antifungal activity of the title compounds (**4a–l**).

Compound	Minimum inhibitory concentration (μg ml^{-1})	
	C. albicans (MTCC 8184)	*A. niger* (MTCC 8189)
4a	3.12	6.25
4b	3.12	1.56
4c	1.56	3.12
4d	3.12	6.25
4e	3.12	1.56
4f	3.12	6.25
4g	1.56	3.12
4h	6.25	3.12
4i	1.56	1.56
4j	6.25	3.12
4k	6.25	12.5
4l	6.25	6.25
Clotrimazole (standard drug)	0.10	0.30

10^6 colony forming units (CFU/ml). The tubes were incubated at 37 ± 1 °C for 24 h (bacteria) and 25 °C for 7 days (*A. niger*). After that, the inoculated culture tubes were macroscopically examined for turbidity. The culture tube showing turbidity (lower concentration) and the culture tube showing no turbidity (higher concentration) gave the minimum inhibitory concentration (MIC) for the compound. The MIC for antibacterial is given in Table 2 and MIC for antifungal is given in Table 3.

4. Results and discussion

In this study 12 novel compounds incorporating the scaffold of thiazolidinone have been synthesized and evaluated for antimicrobial activity. We described here a convenient approach to the preparation of biphenyl-4-carboxylic acid-5-(arylidene)-2-(aryl)-4-thiazolidinone. All compounds were synthesized according to Scheme 1. At the first stage, Schiff's bases of biphenyl-4-carboxylic acid hydrazide and aromatic aldehydes were prepared. Further, reaction of these Schiff's bases with thioglycollic acid in DMF and in presence of a small amount of $ZnCl_2$ yield the 2-substituted-4-thiazolidinone. 2-Substituted-4-thiazolidinone was reacted with aromatic aldehydes in the presence of sodium acetate and glacial acetic acid to yield the 2,5-disubstituted-4-thiazolidinone. Data obtained were found to be in good agreement with the calculated values of the proposed structure. All the synthesized compounds (**4a**–**l**) showed significant antimicrobial activity, against bacterial strain, *E. coli* (MIC 12.5–1.56 μg ml^{-1}), *P. aeruginosa* (MIC 12.5–1.56 μg ml^{-1}), *S. aureus* (MIC 6.25–1.56 μg ml^{-1}) and *B. subtilis* (MIC 6.25–1.56 μg ml^{-1}) as compared to the standard drug ciprofloxacin and against fungal strain, *C. albicans* (MIC 6.25–1.56 μg ml^{-1}) and *A. niger* (12.5–1.56 μg ml^{-1}) as compared to the standard drug clotrimazole. Compound **4g** with its electron withdrawing group substitutions (bromo and nitro group) on aromatic rings was the most active compound against the bacterial strain. Compound **4i** with their bromo substitution on both the aromatic rings was the most active compound against the fungal strain. More extensive study is also warranted to determine additional physicochemical and biological parameters to have a deeper insight into structure–activity relationship and to optimize the effectiveness of this series of molecules.

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