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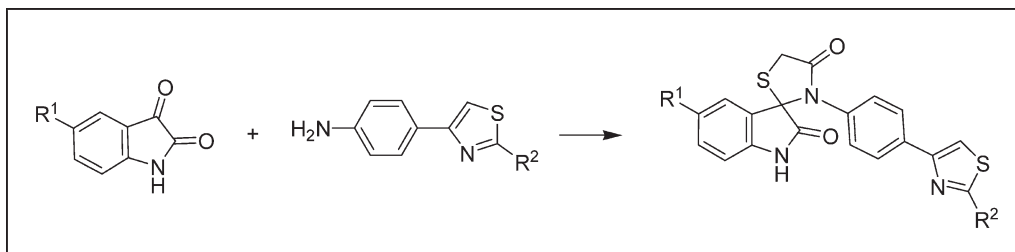
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A series of 3'-(4-(2-methyl/phenyl/benzylthiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-diones was synthesized. The structures of the synthesized compounds were evaluated by analytical and spectral (IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, LC-MS, and elemental analysis) methods. All the synthesized compounds were screened for qualitative (Zone of inhibition) and quantitative antimicrobial activities (MIC). Most of the derivatives showed good activity towards Gram-positive and Gram-negative bacteria.

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## INTRODUCTION

The chemistry of spiro derivatives of isatin continues to draw attention of synthetic organic chemists due to their varied biological activities [1–4]. Of these, spiro[indol-thiazolidenes] has attracted our attention because they show a broad spectrum of pharmacological properties [5,6]. On the basis of these observations it was thought that it would be worthwhile to design and synthesize some new isatin based spirothiazolidine derivatives derived by coupling spiro[indol-thiazolidenes] with biologically active thiazole nucleus. Hence, we have synthesized several 3'-(4-(2-substituted thiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-diones **13–32** and screened for their antimicrobial activity.

## RESULTS AND DISCUSSION

The synthesis of 3'-(4-(2-methyl/phenyl/benzylthiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-diones **13–32** is illustrated and outlined in Figure 1. The starting materials 2-methyl-4-(4-aminophenyl)thiazole **3**, 2-aryl-4-(4-aminophenyl)thiazole **4–6**, 2-benzyl-4-(4-aminophenyl)thiazole **7–12**, were prepared according to reported procedure [7]. The spiro compounds were synthesized by the reported procedure [8–13]. All the compounds were purified by column chromatography or

recrystallized from hexane: ethyl acetate (9:1). The structures of the compounds were established by IR, <sup>1</sup>H NMR, <sup>13</sup>C NMR, LCMS, and elemental analysis and the results are presented in the experimental section. The spectral data of compounds **13–32** were in accordance with the assumed structures. The mass spectra of all the compounds revealed the molecular ion peak M<sup>+</sup> and M+2 ion peak due to S, Br, and/or Cl. The IR spectra showed presence of characteristic absorption peaks at 3200–3400 cm<sup>-1</sup> (>NH), 1730 and 1695 cm<sup>-1</sup> (C=O) indicating that cyclocondensation has occurred which was confirmed by its <sup>1</sup>H NMR and <sup>13</sup>C NMR data. The <sup>1</sup>H NMR spectra revealed a double doublet integrating for two geminal protons of thiazolidine nucleus. <sup>13</sup>C NMR spectra showed all expected characteristic peaks in the aromatic and aliphatic region along with δ 110–111 (spiro carbon atom) [13]. As a representative case, the IR spectrum of compound **27** showed peaks at 3238 cm<sup>-1</sup>(>NH), 1735 and 1694 cm<sup>-1</sup> (C=O), 1619 cm<sup>-1</sup> (C=N) indicating that the cycloaddition has occurred. This was further confirmed by its <sup>1</sup>H NMR spectrum which revealed an AB quartet of thiazolidine methylene at δ 3.75 and 4.42 with *J* = 15 Hz. The benzylic methylene protons appeared at δ 4.18. All the aromatic protons appeared between δ 6.88 and 7.67. The lactam N–H appeared at δ 10.17. Further the <sup>13</sup>C NMR spectrum of **27** revealed two signals at δ 33.00 and 38.8 for

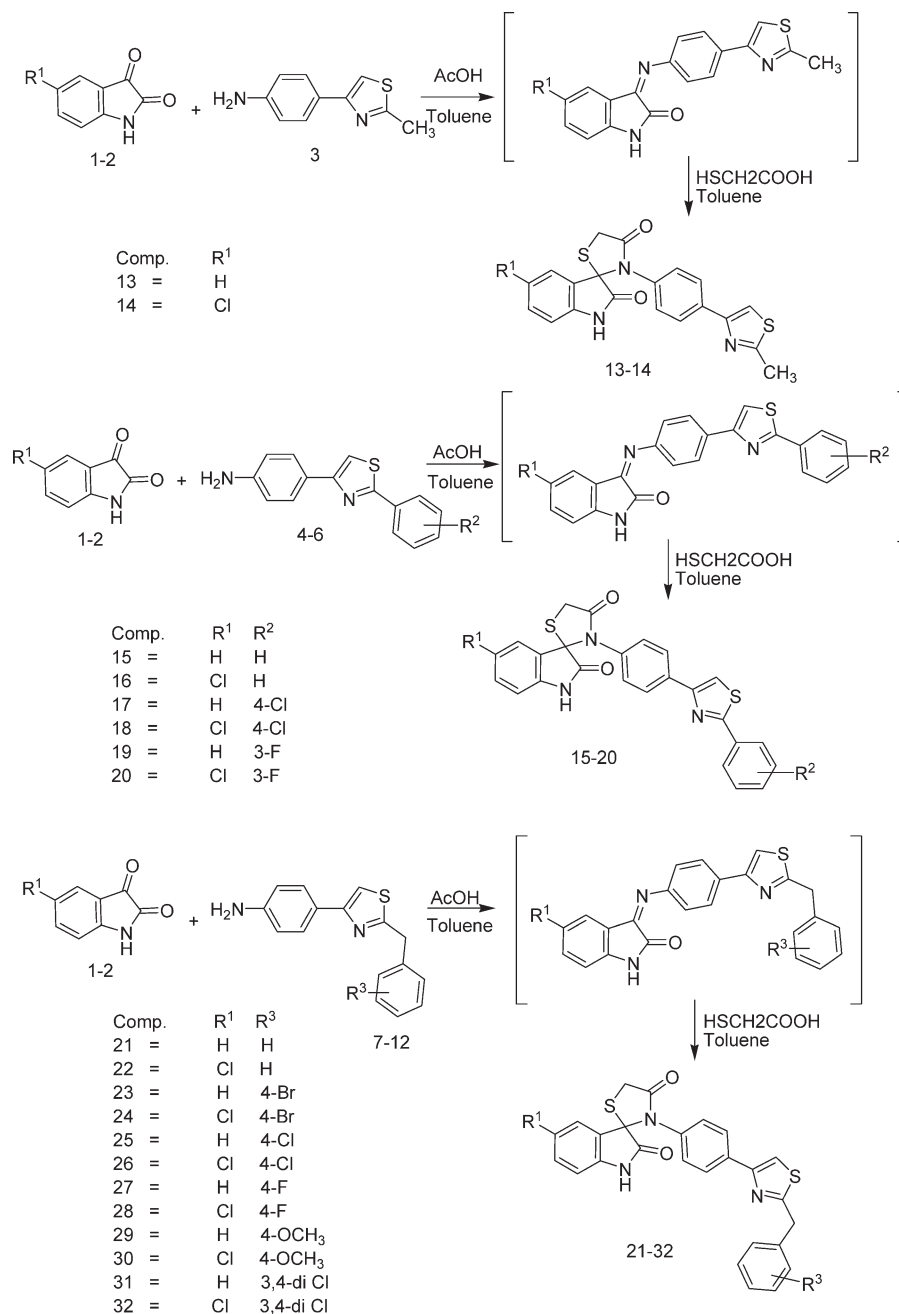


Figure 1. Synthetic pathway for the formation of the compounds 13–32.

benzylic and thiazolidine methylene carbons, in addition the spiro carbon appeared at  $\delta$  110.9. The aromatic ipso carbon attached to fluorine appeared as doublet with  $^1J = 246.8$  Hz (C–F). The ortho and the meta carbon atoms in the same ring also appeared as doublets with  $^2J = 21.5$  Hz and  $^3J = 8.3$  Hz. All other aromatic carbon atoms appeared between  $\delta$  113–119 and 163.8 and the two carbonyl carbons appeared downfield at  $\delta$  172.6 and 176.8. The mass spectrum showed a molecular ion

peak  $M^+$  at  $m/z$  427. The elemental analysis C (63.71), H (3.93), N (9.06), and S (12.87) was within  $\pm 0.4\%$  of the calculated.

**Antimicrobial evaluation.** The *in vitro* antibacterial activity was performed against Gram-positive bacteria including *Staphylococcus aureus* (NCIM 2079), *Bacillus subtilis* (NCIM 2250), and Gram-negative bacteria including *Escherichia coli* (NCIM 2109). The antifungal activity was against fungi including *Candida albicans*

**Table 1**  
Antimicrobial screening of synthesized compounds **13–32**.

Compounds <sup>a</sup>	Microorganisms				
	<i>B. subtilis</i>	<i>S. aureus</i>	<i>E. coli</i>	<i>C. albicans</i>	<i>A. niger</i>
13	15.64	12.52	–	–	–
14	–	16.00	14.97	–	–
15	11.95	10.11	–	–	–
16	13.78	9.00	–	–	–
17	12.88	12.13	11.80	–	–
18	9.76	8.00	–	–	–
19	–	11.65	10.12	–	–
20	11.50	10.28	–	–	–
21	15.06	11.23	–	10.12	9.80
22	–	12.88	–	–	–
23	–	10.47	–	–	–
24	10.97	–	11.74	–	–
25	12.79	11.90	8.34	–	–
26	10.38	10.04	–	–	–
27	–	12.71	–	–	–
28	–	9.52	9.36	–	–
29	10.20	12.94	11.98	–	–
30	9.88	11.04	10.34	–	–
31	–	10.02	–	–	–
32	–	8.60	–	–	–
Ciprofloxacin <sup>a</sup>	26	28	25	NA	NA
Nystatin <sup>a</sup>	NA	NA	NA	20.5	22.1

Zone diameter of growth inhibition in mm.

NA, not applicable; –, inactive.

<sup>a</sup>Ciprofloxacin (10 µg/disc) and Nystatin (100 U/disc) were used as reference; synthesized compounds (100 µg/disc).

(NCIM 3471) and *Aspergillus niger* (NCIM 545). To evaluate the activity of the synthesized compounds against bacteria, the zone of inhibition and minimum inhibitory concentrations (MICs) were determined. Known antibiotic Ciprofloxacin (the reference for antibacterial drugs) and Nystatin (the reference antifungal drug) were used for comparison. The zone of inhibition and MIC against micro organisms tested is reported in (Tables 1 and 2), respectively.

The results of the antibacterial activity showed that the tested compounds are effective against the Gram-positive bacteria *S. aureus* and *B. subtilis* and Gram-negative bacteria *E. coli*. The investigation showed moderate inhibitory effects, with the majority of the compounds with the MIC values between 50 and 100 µg/mL. As shown in Table 2, all the compounds were active against *S. aureus* except compound **24**. The 4-methoxy substituted compounds **29** and **30** were active against all the three species. In general, compound with methyl group and the benzyl ring at 2 position of thiazole moiety showed enhanced activity.

The results of antifungal activity showed that all the compounds were inactive except compound **21**, which showed moderate activity against *C. albicans* and *A. niger*.

**Table 2**  
Antibacterial activity of compounds **13–32**.

Compounds	Microorganisms		
	<i>B. subtilis</i>	<i>S. aureus</i>	<i>E. coli</i>
13	–	50	60
14	–	50	60
15	100	90	–
16	100	100	–
17	90	85	85
18	100	100	–
19	–	80	100
20	100	90	–
21	60	60	–
22	–	50	–
23	–	85	–
24	70	–	80
25	90	100	90
26	100	100	–
27	–	90	–
28	–	100	100
29	100	80	80
30	100	90	90
31	–	80	–
32	–	100	–
Ciprofloxacin	4	4	4

MIC in µg/mL.

## EXPERIMENTAL

Melting points were determined in an open capillary using Veego melting point apparatus and are uncorrected. The purity of the compounds was checked on silica gel-G plates. Infrared spectra ( $\text{cm}^{-1}$ ) were recorded in KBr on a Shimadzu Model FTIR-435 spectrophotometer.  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra were recorded in  $\text{CDCl}_3$  and  $\text{DMSO}-d_6$  solution on a Varian Mercury YH-300 spectrometer operating at 300 MHz or on BRUKER ADVANCE II 400 spectrometer operating at 400 MHz for  $^1\text{H}$  and 75 MHz for  $^{13}\text{C}$ . Chemical shifts are expressed relative to tetramethylsilane (TMS) and were reported as  $\delta$  (ppm). LCMS measurements were made on a Jeol-JMS-DX 303 mass spectrometer. The elemental analysis was performed on FLASH EA 1112 analyzer.

**General procedure for compounds (13–32).** To a solution of isatin **1** (0.37 g, 2.5 mmol) in glacial acetic acid (1 mL) and dry toluene (30 mL), 2-methyl-4-(4-aminophenyl)thiazole, **3** (0.48 g, 2.5 mmol) was added. The mixture was refluxed using a Dean-Stark apparatus for 5–8 h to obtain the Schiff's base. After the completion of the reaction as monitored on TLC, thioglycolic acid (3.0 mmol) was added and mixture was further refluxed for 7–10 h. The solvent was removed under reduced pressure and the residue was treated with saturated solution of  $\text{NaHCO}_3$  to remove the unreacted acid. The product was extracted with ethyl acetate, washed with water, brine and dried ( $\text{Na}_2\text{SO}_4$ ). The solvent was removed under vacuum, the thick liquid thus obtained was added dropwise to a stirred solution of hexane to obtain crystalline solid.

**3'-(4-(2-Methylthiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (13)** Yield: 67%; mp 200–202°C dec., recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $\text{cm}^{-1}$ ) 3221 (NH); 3118, 3020 (CH, Ar-H); 1730 (CO); 1695 (CO); 1609 (C=N);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.71 (s, 3H,  $-\text{CH}_3$ ); 3.87 (d, 1H,  $J = 15.6$  Hz, Thiazolidine); 4.37 (d, 1H,  $J = 15.6$  Hz, Thiazolidine); 6.67–7.74 (m, 8H, Ar-H); 7.39 (s, 1H, Thiazole) ppm; ms:  $m/z$  394.0 ( $\text{M}^+$ ) Anal. Calcd. for  $\text{C}_{20}\text{H}_{15}\text{N}_3\text{O}_2\text{S}_2$ : C, 60.05; H, 3.84; N, 10.86; S, 16.30. Found: C, 59.97; H, 3.78; N, 10.58; S, 15.95.

**5-Chloro-3'-(4-(2-methylthiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (14)** Yield: 62%; mp 193–195°C dec., recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $\text{cm}^{-1}$ ) 3437, 3224 (NH); 3123, 3022 (CH, Ar-H); 1730 (CO); 1694 (CO); 1607 (C=N);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  2.77 (s, 3H,  $\text{CH}_3$ ); 3.88 (d, 1H,  $J = 15$  Hz, Thiazolidine); 4.36 (d, 1H,  $J = 15.6$  Hz, Thiazolidine); 6.71–7.82 (m, 7H, Ar-H); 7.48 (s, 1H, Thiazole) ppm; ms:  $m/z$  429.0 ( $\text{M}^+$ ), 431 ( $\text{M}+2$ ). Anal. Calcd. for  $\text{C}_{20}\text{H}_{14}\text{ClN}_3\text{O}_2\text{S}_2$ : C, 56.13; H, 3.30; N, 9.82; S, 14.99. Found: C, 56.30; H, 3.38; N, 9.93; S, 15.12.

**3'-(4-(2-Phenylthiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (15)** Yield: 67%; mp 66°C dec., recrystallized from hexane–ethyl acetate (9.5:0.5); IR (KBr,  $\text{cm}^{-1}$ ) 3435, 3224 (NH); 3115, 3024 (CH, Ar-H); 1730 (CO); 1694 (CO); 1607 (C=N);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  3.88 (d, 1H,  $J = 16$  Hz, Thiazolidine); 4.38 (d, 1H,  $J = 16$  Hz, Thiazolidine); 6.71–7.98 (m, 13H, Ar-H); 7.40 (s, 1H, Thiazole); ms:  $m/z$  456.1 ( $\text{M}^+$ ). Anal. Calcd. For  $\text{C}_{25}\text{H}_{17}\text{N}_3\text{O}_2\text{S}_2$ : C, 65.91; H, 3.76; N, 9.22; S, 14.08. Found: C, 65.58; H, 3.55; N, 9.46; S, 14.31.

**5-Chloro-3'-(4-(2-phenylthiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (16)** Yield: 72%; mp 84°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $\text{cm}^{-1}$ )

3440, 3221 (NH); 3118, 3021 (CH, Ar-H); 1731 (CO); 1695 (CO); 1612 (C=N);  $^1\text{H}$  NMR ( $\text{DMSO}$ ):  $\delta$  4.05 (d, 1H,  $J = 15.4$  Hz, Thiazolidine); 4.17 (d, 1H,  $J = 15.4$  Hz, Thiazolidine); 6.76–8.00 (m, 12H, Ar-H); 8.15 (s, 1H, Thiazole); 10.94 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable); ms:  $m/z$  490.0 ( $\text{M}^+$ ), 492.0 ( $\text{M}+2$ ). Anal. Calcd. for  $\text{C}_{25}\text{H}_{16}\text{ClN}_3\text{O}_2\text{S}_2$ : C, 61.28; H, 3.29; N, 8.58; S, 13.09. Found: C, 60.80; H, 3.55; N, 8.41; S, 12.81.

**3'-(4-(2-(4-Chlorophenyl)thiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (17)** Yield: 74%; mp 222°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $\text{cm}^{-1}$ ) 3436, 3216 (NH); 3118, 3011 (CH, Ar-H); 1730 (CO); 1694 (CO); 1605 (C=N);  $^1\text{H}$  NMR ( $\text{DMSO}$ ):  $\delta$  4.02 (d, 1H,  $J = 15.2$  Hz, Thiazolidine); 4.18 (d, 1H,  $J = 15.2$  Hz, Thiazolidine); 6.75–8.01 (m, 12H, Ar-H); 8.16 (s, 1H, Thiazole); 10.80 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable); ms:  $m/z$  490.0 ( $\text{M}^+$ ), 492.0 ( $\text{M}+2$ ). Anal. Calcd. for  $\text{C}_{25}\text{H}_{16}\text{ClN}_3\text{O}_2\text{S}_2$ : C, 61.28; H, 3.29; N, 8.58; S, 13.09. Found: C, 61.40; H, 3.45; N, 8.50; S, 13.21.

**5-Chloro-3'-(4-(2-(4-chlorophenyl)thiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (18)** Yield: 74%; mp 230°C dec., recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $\text{cm}^{-1}$ ) 3442, 3227 (NH); 3115, 3016 (CH, Ar-H); 1731 (CO); 1694 (CO); 1615 (C=N);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  4.04 (d, 1H,  $J = 15.6$  Hz, Thiazolidine); 4.17 (d, 1H,  $J = 15.6$  Hz, Thiazolidine); 6.76–8.02 (m, 11H, Ar-H); 8.18 (s, 1H, Thiazole); 10.94 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable); ms:  $m/z$  524.0 ( $\text{M}^+$ ), 525.9 ( $\text{M}+2$ ). Anal. Calcd. for  $\text{C}_{25}\text{H}_{15}\text{Cl}_2\text{N}_3\text{O}_2\text{S}_2$ : C, 57.25; H, 2.88; N, 8.01; S, 12.23. Found: C, 57.39; H, 2.98; N, 9.19; S, 12.44.

**3'-(4-(2-(3-Fluorophenyl)thiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (19)** Yield: 64%; mp 86–87°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $\text{cm}^{-1}$ ) 3440, 3222 (NH); 3121, 3008 (CH, Ar-H); 1731 (CO); 1696 (CO); 1609 (C=N);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  3.89 (d, 1H,  $J = 15.3$  Hz, Thiazolidine); 4.10 (d, 1H,  $J = 15.3$  Hz, Thiazolidine); 6.75–7.75 (m, 12H, Ar-H); 8.67 (s, 1H, Thiazole);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  33.2 ( $\text{CH}_2$ , Thiazolidine); 111.12 (Spiro C); 113.14–164.57 (21C-Ar-C, Thiazole-C); 172.7 (CONH); 177.1 (CONH); ms:  $m/z$  473.6 ( $\text{M}^+$ ). Anal. Calcd. for  $\text{C}_{25}\text{H}_{16}\text{FN}_3\text{O}_2\text{S}_2$ : C, 63.41; H, 3.41; N, 8.87; S, 13.54. Found: C, 63.35; H, 3.82; N, 8.27; S, 11.35.

**5-Chloro-3'-(4-(2-(3-fluorophenyl)thiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (20)** Yield: 62%; mp 140°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $\text{cm}^{-1}$ ) 3442, 3219 (NH); 3122, 3021 (CH, Ar-H); 1731 (CO); 1697 (CO); 1611 (C=N);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  3.92 (d, 1H,  $J = 15.3$  Hz, Thiazolidine); 4.30 (d, 1H,  $J = 15.3$  Hz, Thiazolidine); 6.77–7.82 (m, 11H, Ar-H); 8.65 (s, 1H, Thiazole); ms:  $m/z$  508.6 ( $\text{M}^+$ ), 510.2 ( $\text{M}+2$ ). Anal. Calcd. for  $\text{C}_{25}\text{H}_{15}\text{ClFN}_3\text{O}_2\text{S}_2$ : C, 59.11; H, 2.98; N, 8.27; S, 12.62. Found: C, 59.41; H, 3.17; N, 8.12; S, 13.01.

**3'-(4-(2-Benzylthiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (21)** Yield: 72%; mp 194°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $\text{cm}^{-1}$ ) 3443, 3200 (NH); 3109, 3026 (CH, Ar-H); 1736 (CO); 1697 (CO); 1617 (C=N);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  3.88 (d, 1H,  $J = 15.4$  Hz, Thiazolidine); 4.31 (s, 2H,  $\text{CH}_2$ ); 4.37 (d, 1H,  $J = 15.4$  Hz, Thiazolidine); 6.71–7.75 (m, 13H, Ar-H); 8.05 (s, 1H, Thiazole);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ):  $\delta$  33 ( $\text{CH}_2$ , Thiazolidine); 39.7 ( $\text{CH}_2$ , Benzyl); 110.82 (Spiro C); 113.85–154 (21C, Ar-C Thiazole-C); 170.7 (CONH); 172.5 (CONH); ms:  $m/z$  469.0 ( $\text{M}^+$ ).

Anal. Calcd. for  $C_{26}H_{19}N_3O_2S_2$ : C, 66.50; H, 4.08; N, 8.95; S, 13.66. Found: C, 66.20; H, 4.01; N, 9.11; S, 13.78.

**3'-(4-(2-Benzylthiazol-4-yl)phenyl)-5-chlorospiro[indoline-3,2'-thiazolidine]-2,4'-dione (22)** Yield: 72%; mp 112°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $cm^{-1}$ ) 3411, 3248 (NH); 3108, 3030 (CH, Ar-H); 1737 (CO); 1697 (CO); 1618 (C=N);  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  3.88 (d, 1H,  $J = 15.3$  Hz, Thiazolidine); 4.30 (s, 2H,  $CH_2$ ); 4.35 (d, 1H,  $J = 15.3$  Hz, Thiazolidine); 6.65–7.79 (m, 12H, Ar-H); 7.92 (s, 1H, Thiazole); 9.5 (s, 1H, NH,  $D_2O$  exchangeable); ms:  $m/z$  503.0 ( $M^+$ ), 505.0 ( $M+2$ ). Anal. Calcd. for  $C_{26}H_{18}ClN_3O_2S_2$ : C, 61.96; H, 3.60; N, 8.34; S, 12.72. Found: C, 62.06; H, 3.79; N, 8.86; S, 11.56.

**3'-(4-(2-(4-Bromobenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (23)** Yield: 72%; mp 204–207°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $cm^{-1}$ ) 3411, 3205 (NH); 3111, 3052 (CH, Ar-H); 1731 (CO); 1694 (CO); 1606 (C=N);  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  3.87 (d, 1H,  $J = 15.3$  Hz, Thiazolidine); 4.25 (s, 2H,  $CH_2$ ); 4.36 (d, 1H,  $J = 15.3$  Hz, Thiazolidine); 6.70–7.75 (m, 12H, Ar-H); 7.98 (s, 1H, Thiazole);  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta$  33 ( $CH_2$ , Thiazolidine); 39.05 ( $CH_2$ , Benzyl); 110.76 (Spiro C); 113.9–164.1 (21C, Ar-C, Thiazole-C); 171 (CONH); 173.2 (CONH); ms:  $m/z$  547.5 ( $M^+$ ), 549.6 ( $M+2$ ). Anal. Calcd. for  $C_{26}H_{18}BrN_3O_2S_2$ : C, 56.94; H, 3.31; N, 7.66; S, 11.69. Found: C, 57.06; H, 3.36; N, 8.07; S, 11.85.

**3'-(4-(2-(4-Bromobenzyl)thiazol-4-yl)phenyl)-5-chlorospiro[indoline-3,2'-thiazolidine]-2,4'-dione (24)** Yield: 65%; mp 190–192°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $cm^{-1}$ ) 3411, 3236 (NH); 3110, 3039 (CH, Ar-H); 1731 (CO); 1695 (CO); 1614 (C=N);  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  3.88 (d, 1H,  $J = 15.4$  Hz, Thiazolidine); 4.27 (s, 2H,  $CH_2$ ); 4.36 (d, 1H,  $J = 15.4$  Hz, Thiazolidine); 6.64–7.78 (m, 11H, Ar-H); 7.68 (s, 1H, Thiazole); ms:  $m/z$  581.9 ( $M^+$ ), 583.9 ( $M+2$ ), 585.9 ( $M+4$ ). Anal. Calcd. for  $C_{26}H_{17}BrClN_3O_2S_2$ : C, 53.48; H, 3.11; N, 7.20; S, 10.98. Found: C, 53.78; H, 3.33; N, 7.51; S, 11.17.

**3'-(4-(2-(4-Chlorobenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (25)** Yield: 70%; mp 56°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $cm^{-1}$ ) 3414, 3240 (NH); 3118, 3022 (CH, Ar-H); 1731 (CO); 1694 (CO); 1612 (C=N);  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  3.87 (d, 1H,  $J = 15.2$  Hz, Thiazolidine); 4.28 (s, 2H,  $CH_2$ ); 4.37 (d, 1H,  $J = 15.2$  Hz, Thiazolidine); 6.70–7.75 (m, 12H, Ar-H); 7.45 (s, 1H, Thiazole); ms:  $m/z$  504.0 ( $M^+$ ), 506.0 ( $M+2$ ). Anal. Calcd. for  $C_{26}H_{18}ClN_3O_2S_2$ : C, 61.96; H, 3.60; N, 8.34; S, 12.72. Found: C, 61.99; H, 3.82; N, 8.46; S, 11.28.

**5-Chloro-3'-(4-(2-(4-chlorobenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (26)** Yield: 65%; mp 99°C dec., recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $cm^{-1}$ ) 3418, 3239 (NH); 3120, 3014 (CH, Ar-H); 1732 (CO); 1695 (CO); 1612 (C=N);  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  3.76 (d, 1H,  $J = 15.4$  Hz, Thiazolidine); 4.28 (s, 2H,  $CH_2$ ); 4.34 (d, 1H,  $J = 15.4$  Hz, Thiazolidine); 6.70–7.75 (m, 11H, Ar-H); 7.68 (s, 1H, Thiazole);  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta$  33 ( $CH_2$ , Thiazolidine); 39.04 ( $CH_2$ , Benzyl); 111 (Spiro C); 113.4–165.6 (21C, Ar-C, Thiazole-C); 172.7 (CONH); 175.4 (CONH); ms:  $m/z$  538.0 ( $M^+$ ), 540.0 ( $M+2$ ), 542.1 ( $M+4$ ). Anal. Calcd. for  $C_{26}H_{17}Cl_2N_3O_2S_2$ : C, 56.99; H, 3.18; N, 7.8; S, 11.91. Found: C, 57.23; H, 3.26; N, 7.96; S, 12.13.

**3'-(4-(2-(4-Fluorobenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (27)** Yield: 60%; mp 133–135°C,

recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $cm^{-1}$ ) 3439, 3228 (NH); 3101 (CH, Ar-H); 1735 (CO); 1694 (CO); 1619 (C=N);  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  3.75 (d, 1H,  $J = 15$  Hz, Thiazolidine); 4.18 (s, 2H,  $CH_2$ ); 4.22 (d, 1H,  $J = 15$  Hz, Thiazolidine); 6.56–7.67 (m, 12H, Ar-H); 7.21 (s, 1H, Thiazole); 10.17 (s, 1H, NH,  $D_2O$  exchangeable); ms:  $m/z$  487.6 ( $M^+$ ). Anal. Calcd. for  $C_{26}H_{18}FN_3O_2S_2$ : C, 64.05; H, 3.72; N, 8.62; S, 13.15. Found: C, 63.71; H, 3.93; N, 9.06; S, 12.87.

**5-Chloro-3'-(4-(2-(4-fluorobenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (28)** Yield: 66%; mp 139–140°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $cm^{-1}$ ) 3404, 3257 (NH); 3113, 3043 (CH, Ar-H); 1730 (CO); 1694 (CO); 1609 (C=N); 864 (Ar-Cl);  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  3.71 (d, 1H,  $J = 7.6$  Hz, Thiazolidine); 4.20 (s, 2H,  $CH_2$ ); 4.28 (d, 1H,  $J = 7.6$  Hz, Thiazolidine); 6.56–7.67 (m, 11H, Ar-H); 7.35 (s, 1H, Thiazole); 10.42 (s, 1H, NH,  $D_2O$  exchangeable);  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta$  33 ( $CH_2$ , Thiazolidine); 38 ( $CH_2$ , Benzyl); 111.7 (Spiro C); 113.9–160.2 (21C, Ar-C, Thiazole-C); 172.2 (CONH); 175.9 (CONH); ms:  $m/z$  521.2 ( $M^+$ ), 523.3 ( $M+2$ ). Anal. Calcd. for  $C_{26}H_{17}ClFN_3O_2S_2$ : C, 59.82; H, 3.28; N, 8.05; S, 12.29. Found: C, 60.05; H, 3.51; N, 8.26; S, 11.97.

**3'-(4-(2-(4-Methoxybenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (29)** Yield: 58%; mp 62°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $cm^{-1}$ ) 3440, 3230 (NH); 3118 (CH, Ar-H); 1732 (CO); 1696 (CO); 1609 (C=N);  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  3.80 (d, 1H,  $J = 15$  Hz, Thiazolidine); 4.18 (s, 2H,  $CH_2$ ); 4.27 (d, 1H,  $J = 15$  Hz, Thiazolidine); 4.33 (s, 3H,  $CH_3$ ); 6.66–7.74 (m, 12H, Ar-H); 7.68 (s, 1H, Thiazole); 10.17 (s, 1H, NH,  $D_2O$  exchangeable);  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta$  33.1 ( $CH_2$ , Thiazolidine); 38.4 ( $CH_2$ , Benzyl); 58.4 (O– $CH_3$ ); 111.4 (Spiro C); 113.4–164.4 (21C, Ar-C, Thiazole-C); 171.4 (CONH); 176.2 (CONH); ms:  $m/z$  499.6 ( $M^+$ ). Anal. Calcd. for  $C_{27}H_{21}N_3O_3S_2$ : C, 64.91; H, 4.24; N, 8.41; S, 12.84. Found: C, 65.11; H, 4.36; N, 8.52; S, 13.11.

**5-Chloro-3'-(4-(2-(4-methoxybenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (30)** Yield: 60%; mp 41°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $cm^{-1}$ ) 3412, 3252 (NH); 3121, 3033 (CH, Ar-H); 1734 (CO); 1696 (CO); 1612 (C=N); 864 (Ar-Cl);  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  3.82 (d, 1H,  $J = 15.3$  Hz, Thiazolidine); 4.20 (s, 2H,  $CH_2$ ); 4.28 (d, 1H,  $J = 15.3$  Hz, Thiazolidine); 4.36 (s, 3H,  $CH_3$ ); 6.68–7.88 (m, 11H, Ar-H); 7.76 (s, 1H, Thiazole); 10.42 (s, 1H, NH,  $D_2O$  exchangeable); ms:  $m/z$  533.2 ( $M^+$ ), 535.6 ( $M+2$ ). Anal. Calcd. for  $C_{27}H_{20}ClN_3O_3S_2$ : C, 60.72; H, 3.77; N, 7.87; S, 12.01. Found: C, 60.81; H, 3.89; N, 8.04; S, 12.23.

**3'-(4-(2-(3,4-Dichlorobenzyl)thiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]-2,4'-dione (31)** Yield: 65%; mp 97°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $cm^{-1}$ ) 3414, 3246 (NH); 3103, 3048 (CH, Ar-H); 1729 (CO); 1695 (CO); 1613 (C=N); 864 (Ar-Cl);  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  3.88 (d, 1H,  $J = 15.3$  Hz, Thiazolidine); 4.35 (d, 1H,  $J = 15.3$  Hz, Thiazolidine); 4.37 (s, 2H,  $CH_2$ ); 6.70–7.73 (m, 11H, Ar-H); 7.40 (s, 1H, Thiazole); 8.6 (s, 1H, NH,  $D_2O$  exchangeable);  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta$  33 ( $CH_2$ , Thiazolidine); 36.5 ( $CH_2$ , Benzyl); 110.97 (Spiro C); 113.9–168.1 (21C, Ar-C, Thiazole-C); 172.6 (CONH); 176.9 (CONH); ms:  $m/z$  537.7 ( $M^+$ ), 539.7 ( $M+2$ ), 541.8 ( $M+4$ ). Anal. Calcd. for  $C_{26}H_{17}Cl_2N_3O_2S_2$ : C, 57.99; H, 3.18; N, 7.80; S, 11.91. Found: C, 58.23; H, 3.29; N, 8.02; S, 12.21.

**5-Chloro-3'-(4-(2-(3,4-dichlorobenzyl)thiazol-4-yl)phenyl)-spiro[indoline-3,2'-thiazolidine]-2,4'-dione (32)** Yield: 65%; mp 198–202°C, recrystallized from hexane–ethyl acetate (9:1); IR (KBr,  $\text{cm}^{-1}$ ) 3409, 3233 (NH); 3113, 3041 (CH, Ar-H); 1730 (CO); 1696 (CO); 1610 (C=N); 860 (Ar-Cl);  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  3.88 (d, 1H,  $J = 15$  Hz, Thiazolidine); 4.34 (d, 1H,  $J = 15$  Hz, Thiazolidine); 4.41 (s, 2H,  $\text{CH}_2$ ); 6.63–7.77 (m, 10H, Ar-H); 8.03 (s, 1H, Thiazole); 8.9 (s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable); ms:  $m/z$  571.9 ( $\text{M}^+$ ), 573.9 ( $\text{M}+2$ ), 575.9 ( $\text{M}+4$ ), 577.8 ( $\text{M}+6$ ). Anal. Calcd. for  $\text{C}_{26}\text{H}_{16}\text{Cl}_3\text{N}_3\text{O}_2\text{S}_2$ : C, 54.51; H, 2.81; N, 7.33; S, 11.19. Found: C, 54.65; H, 2.93; N, 7.46; S, 11.51.

**Antimicrobial activity.** Compounds **14–32** were screened for their *in vitro* antimicrobial activity against the standard strains *B. subtilis*, *S. aureus*, and *E. coli* by the disk diffusion method [14,15]. Disks measuring 6 mm in diameter were punched from Whatman no.1 filter paper. Batches of 100 disks were dispensed to each screw-capped bottle and sterilized by dry heat at 145°C for 1 h. The test compounds were prepared with 100  $\mu\text{g/mL}$  concentration in dimethyl sulfoxide. Disks of each concentration were placed in nutrient agar medium inoculated with fresh bacteria strains separately. The incubation was carried out at 37°C for 48 h. Ciprofloxacin was used as standard drugs at a concentration of 10  $\mu\text{g/mL}$ . Solvent and growth controls were kept and zones of inhibition were noted.

The two-fold dilution technique [16] was followed to determine the minimum inhibitory concentration (MIC) of the synthesized compounds. The test compounds were dissolved in dimethyl sulfoxide and then diluted with culture medium (Muelser-Hinton agar medium) at the required final concentration 150–155  $\mu\text{g/mL}$ . A plate containing only the culture medium and DMSO in the same dilution was used as negative control. The MIC values were recorded after incubation at 37°C for a period of 24 h. The lowest concentration of the test substance that completely inhibited the growth of the microorganism was reported as MIC expressed in terms of  $\mu\text{g/mL}$ .

The compounds were screened for their antifungal activity against *C. albicans* (MTCC 1637) and *A. niger* (AIIMS) in DMSO by disc diffusion method under standard conditions using Sabourad Dextrose Agar medium as described by NCCLS [17]. Sterile filter paper discs (6 mm diameter) containing specific amount of anti fungal agent (100  $\mu\text{g}$  for the synthesized compounds) were placed on the surface of an agar plate inoculated with the standardized suspension of microorganisms tested. The plates were incubated at 37°C for 7 days for evaluating antifungal activity. The diameters of inhibition zones (in mm) were measured. Nystatin was used as standard drug at a concentration of 10  $\mu\text{g/mL}$ .

## CONCLUSIONS

In conclusion, a series of new 3'-(4-(2-methyl/phenyl/benzylthiazol-4-yl)phenyl)spiro[indoline-3,2'-thiazolidine]

-2,4'-diones **13–32** was synthesized. The pharmacological studies were undertaken to evaluate the effects of substituents on the antimicrobial activities. Most of the synthesized compounds exhibited moderate activity towards Gram-positive and Gram-negative bacteria. These compounds, however, did not show any promising antifungal activity except compound **21**. Compounds with methyl group and benzyl ring at 2-position of thiazole nucleus showed enhanced antibacterial activity.

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