

## Synthesis of some new 2,3-diaryl-1,3-thiazolidin-4-ones as antibacterial agents

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### Abstract

Some new 2,3-diaryl-1,3-thiazolidin-4-one derivatives having a 2,6-dichlorophenyl, antipyrine, or 1,2,4-triazole ring at N-3 and variously substituted 3-iodo- or 3-bromo-phenyl rings at C-2 have been synthesized and tested as antibacterial agents. The results of the *in vitro* tests showed that some of them have effective antibacterial activity.

**Keywords:** 4-Amino-antipyrine, 4-amino-1,2,4-triazole, 2,6-dichloroaniline, 3-iodo- and 3-bromobenzaldehyde, thiazolidin-4-ones

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### Introduction

Hetaryl- substituted 1,3-thiazolidin-4-ones containing imidazole,<sup>1</sup> thiazole,<sup>2,3</sup> benzimidazole,<sup>4</sup> acridine,<sup>5</sup> quinazolin-4(3H)-one,<sup>6</sup> *syn*-triazine,<sup>7</sup> pyridine, or diazine<sup>8,9</sup> fragments show high antibacterial, antimicrobial, antitumor, or anti-HIV activity, and also have effects on the CNS. 2,3-Diaryl-1,3-thiazolidin-4-one derivatives also possess anticonvulsant,<sup>10</sup> hypnotic,<sup>11</sup> or anticancer<sup>12</sup> properties and have been reported as novel inhibitors of the bacterial enzyme Mur B which is a precursor acting during the biosynthesis of peptidoglycan.<sup>13</sup>

In view of the above observations, the synthesis of novel 2,3-diaryl-1,3-thiazolidin-4-one derivatives has been developed starting from various substituted benzylidene-anilines with the aim of investigating their biological activities.

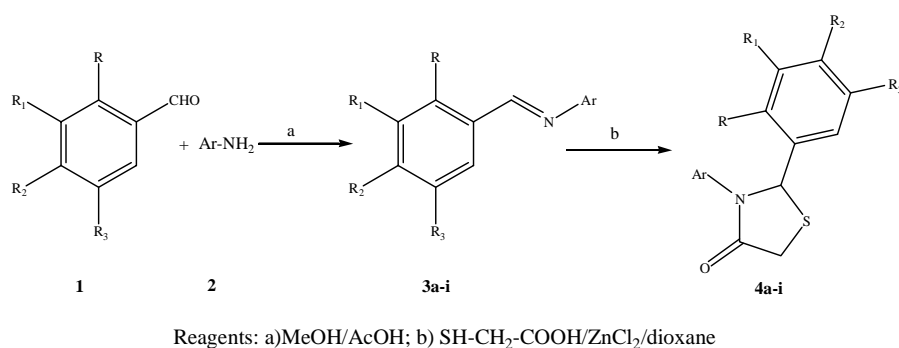
### Results and Discussion

The synthesis of the new 2,3-diaryl-1,3-thiazolidin-4-ones was carried out by reacting various substituted benzylidene-aniline derivatives with mercapto-acetic acid in the presence of zinc

chloride. In the preparation of these compounds the starting materials used were the products of the condensation of 4-hydroxy-3-iodo-5-methoxybenzaldehyde, 4-hydroxy-3-bromo-5-methoxybenzaldehyde, or 2-hydroxy-3,5-diiodobenzaldehyde with 2,6-dichloroaniline, 4-aminoantipyrine, or 4-amino-1,2,4-triazole, giving the benzylidene aniline derivatives (**3a-i**). These benzylidene anilines on reaction with mercapto-acetic acid give the corresponding 2,3-diaryl-1,3-thiazolidin-4-ones (**4a-i**). The best yield of the compounds is achieved by refluxing the reagents in dry dioxane for 8–10 hr., with a molar ratio of the substituted benzylidene-aniline derivatives and mercapto-acetic acid of 1:1 to 1:1.5, in the presence of 3–5 wt % of zinc chloride (Scheme 1). The products were obtained were isolated in satisfactory yields by conventional workup. Both analytical and spectroscopic data of all the synthesized compounds are in full agreement with the proposed structures.

We have shown that a high level of activity was associated with the presence of a 3-iodo- or 3-bromo- substituted phenyl ring at C-2. Moreover, we found that an increase in antibacterial activity was dependent on the presence of a 2,3-dichlorophenyl group at N-3.

In conclusion, a new series of 2,3-diaryl-1,3-thiazolidin-4-ones was synthesized and characterized, and some of them proved to have potent antibacterial activity. The results confirm that the antibacterial activity is strongly dependent on the nature of the substituents at C-2 and N-3 of the thiazolidinone ring.



## Scheme 1

### Antibacterial activity

Most of the newly synthesized compounds were tested for their antibacterial activity *in vitro* against bacterial strains such as *E. coli*, *B. subtilis* and *S. typhi*, employing the nutrient agar disc diffusion method<sup>14</sup> at 50–100 µg/ml concentration. The results showed that all the compounds exhibited a marked degree of activity against bacteria at the minimum inhibitory concentration (MIC) of 50 µg/ml in comparison to tetracycline, which was taken as a standard drug. Also, the results showed the degree of inhibition varied with the tested compounds (Table 1).

**Table 1.** Diameter of the inhibition zone (mm)

Entry	Ar	R	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	<i>E. coli</i>	<i>B. subtilis</i>	<i>S. typhi</i>
3a	Antipyrine	H	OCH <sub>3</sub>	OH	I	20	17	21
3b	2,6-Dichlorophenyl	H	OCH <sub>3</sub>	OH	I	27	22	14
3c	1,2,4-Triazole	H	OCH <sub>3</sub>	OH	I	20	19	19
3d	Antipyrine	H	OCH <sub>3</sub>	OH	Br	15	20	18
3e	2,6-Dichlorophenyl	H	OCH <sub>3</sub>	OH	Br	23	22	16
3f	1,2,4-Triazole	H	OCH <sub>3</sub>	OH	Br	21	16	18
3g	Antipyrine	OH	I	H	I	14	18	17
3h	2,6-Dichlorophenyl	OH	I	H	I	19	16	22
3I	1,2,4-Triazole	OH	I	H	I	18	20	21
4a	Antipyrine	H	OCH <sub>3</sub>	OH	I	14	18	20
4b	2,6-Dichlorophenyl	H	OCH <sub>3</sub>	OH	I	21	19	14
4c	1,2,4-Triazole	H	OCH <sub>3</sub>	OH	I	20	18	19
4d	Antipyrine	H	OCH <sub>3</sub>	OH	Br	13	20	23
4e	2,6-Dichlorophenyl	H	OCH <sub>3</sub>	OH	Br	21	23	13
4f	1,2,4-Triazole	H	OCH <sub>3</sub>	OH	Br	15	17	24
4g	Antipyrine	OH	I	H	I	27	24	25
4h	2,6-Dichlorophenyl	OH	I	H	I	19	16	15
4i	1,2,4-Triazole	OH	I	H	I	25	23	21
	Tetracycline					30	25	28

## Experimental Section

**General Procedures.** Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer-1420 spectrophotometer. <sup>1</sup>H- NMR spectra (CDCl<sub>3</sub>) were recorded on a Gemini-200 MHz spectrophotometer with TMS as internal standard.

**General procedure for the preparation of benzylidene aniline derivatives (3a–i).** To a solution of 0.01 mol of the appropriate benzaldehyde (**1**) in 15 mL of methanol, 0.01 mol of the aromatic or heteroaromatic amine (**2**) and a few drops of acetic acid were added and reaction

mixture was refluxed for 3 h. The reaction mixture was cooled, poured into ice-cold water, and the separated solid was filtered, dried, and recrystallized from ethanol.

**4-[(4-Hydroxy-3-iodo-5-methoxy-benzylidene)-amino]-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one (3a).** Yield 93 %, mp 192-194 °C; IR (cm<sup>-1</sup>) 3155, 1622, 1590, 1465, 1430. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.45 (s, 3H, CH<sub>3</sub>), 3.17 (s, 3H, N-CH<sub>3</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 7.42-7.86 (m, 8H, Ar-H, OH), 9.42 (s, 1H, =CH). Anal. Calcd for C<sub>19</sub>H<sub>18</sub>N<sub>3</sub>O<sub>3</sub>I: C, 49.26; H, 3.92; N, 9.07. Found: C, 48.97; H, 3.77; N, 9.18.

**1-(4-Hydroxy-3-iodo-5-methoxybenzylidene)-2,6-dichloroaniline (3b).** Yield 84%, mp 180-181 °C; IR (cm<sup>-1</sup>) 3159, 1621, 1585, 1463, 1435. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.76 (s, 3H, OCH<sub>3</sub>), 6.93-7.63 (m, 6H, Ar-H & OH), 9.36 (s, 1H, =CH). Anal. Calcd for C<sub>14</sub>H<sub>10</sub>NO<sub>2</sub>Cl<sub>2</sub>I: C, 39.84; H, 2.39; N, 3.32. Found: C, 39.65; H, 2.13; N, 3.12.

**4-[(4-Hydroxy-3-iodo-5-methoxy-benzylidene)amino]-1,2,4-triazole (3c).** Yield 78%, mp 184-186 °C; IR (cm<sup>-1</sup>) 3150, 1620, 1592, 1467, 1428. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.80 (s, 3H, OCH<sub>3</sub>), 7.70-8.44 (m, 5H, Ar-H, OH), 9.23 (s, 1H, =CH). Anal. Calcd for C<sub>10</sub>H<sub>9</sub>N<sub>4</sub>O<sub>2</sub>I: C, 34.90; H, 2.64; N, 16.28. Found: C, 34.68; H, 2.47; N, 16.08.

**4-[(4-Hydroxy-3-bromo-5-methoxy-benzylidene)amino]-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one (3d).** Yield 88%, mp 220-223 °C; IR (cm<sup>-1</sup>) 3162, 1621, 1592, 1466, 1432. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.44 (s, 3H, CH<sub>3</sub>), 3.20 (s, 3H, N-CH<sub>3</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 7.25-7.97 (m, 8H, Ar-H, OH), 9.35 (s, 1H, =CH). Anal. Calcd for C<sub>19</sub>H<sub>18</sub>N<sub>3</sub>O<sub>3</sub>Br: C, 54.82; H, 4.36; N, 10.09. Found: C, 54.62; H, 4.18; N, 10.21.

**1-(4-Hydroxy-3-bromo-5-methoxy-benzylidene)-2,6-dichloroaniline (3e).** Yield 91%, mp 189-192 °C; IR (cm<sup>-1</sup>) 3157, 1622, 1592, 1465, 1433. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.78 (s, 3H, OCH<sub>3</sub>), 7.58-7.92 (m, 6H, Ar-H, OH), 9.38 (s, 1H, =CH). Anal. Calcd for C<sub>14</sub>H<sub>10</sub>NO<sub>2</sub>BrCl<sub>2</sub>: C, 44.83; H, 2.69; N, 3.73. Found: C, 44.75; H, 2.59; N, 3.61.

**4-[(4-Hydroxy-3-bromo-5-methoxy-benzylidene)amino]-1,2,4-triazole (3f).** Yield 79 %, mp 260-262 °C; IR (cm<sup>-1</sup>) 3155, 1618, 1595, 1460, 1425. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.78 (s, 3H, OCH<sub>3</sub>), 7.47-8.14 (m, 5H, Ar-H, OH), 9.46 (s, 1H, =CH). Anal. Calcd for C<sub>10</sub>H<sub>9</sub>N<sub>4</sub>O<sub>2</sub>Br: C, 40.43; H, 3.05; N, 18.86. Found: C, 40.55; H, 2.87; N, 18.74.

**4-[(2-Hydroxy-3,5-diiodobenzylidene)-amino]-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one (3g).** Yield 85 %, mp 224-226 °C; IR (cm<sup>-1</sup>) 3155, 1621, 1592, 1466, 1432. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.44 (s, 3H, CH<sub>3</sub>), 3.18 (s, 3H, N-CH<sub>3</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 7.48-7.97 (m, 8H, Ar-H, OH), 9.39 (s, 1H, =CH). Anal. Calcd for C<sub>19</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>I<sub>2</sub>: C, 38.67; H, 2.70; N, 7.52. Found: C, 38.49; H, 2.87; N, 7.60.

**1-(2-Hydroxy-3,5-diiodobenzylidene)-2,6-dichloroaniline (3h).** Yield 86 %, mp 189-191 °C; IR (cm<sup>-1</sup>) 3154, 1620, 1592, 1465, 1431. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.78 (s, 3H, OCH<sub>3</sub>), 7.36-7.88 (m, 6H, Ar-H, OH), 9.44 (s, 1H, =CH). Anal. Calcd for C<sub>13</sub>H<sub>7</sub>NOCl<sub>2</sub>I<sub>2</sub>: C, 30.15; H, 1.36; N, 2.70. Found: C, 30.03; H, 1.11; N, 2.61.

**4-[(2-Hydroxy-3,5-diiodo-benzylidene)-amino]-1,2,4-triazole (3i).** Yield 83 %, mp 223-226 °C; IR (cm<sup>-1</sup>) 3157, 1621, 1588, 1468, 1432. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.79 (s, 3H, OCH<sub>3</sub>), 7.76-

8.30 (m, 5H, Ar-H, OH), 9.40 (s, 1H, =CH). Anal. Calcd for C<sub>9</sub>H<sub>6</sub>N<sub>4</sub>OI<sub>2</sub>: C, 24.57; H, 1.37; N, 12.73. Found: C, 24.38; H, 1.42; N, 12.53.

**General procedure for the preparation of 2,3-diaryl-1,3-thiazolidin-4-ones (4a-i).** To a solution of 0.01 mol benzylideneaniline derivative (**3a-i**) in 15 mL of dry dioxane, 0.01 mol of freshly distilled mercaptoacetic acid and anhydrous ZnCl<sub>2</sub> (0.2 g) was added and the mixture heated at reflux for 8-10 h. The solvent was removed (reduced pressure) and the residue washed with 5% sodium bicarbonate (3x25 mL), water (2x25 mL), dried, and recrystallized (ethanol).

**3-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-(4-hydroxy-3-iodo-5-methoxyphenyl)-thiazolidin-4-one (4a).** Yield 79 %, mp 120-121 °C; IR (cm<sup>-1</sup>) 1676, 1630, 1592. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.23 (s, 3H, CH<sub>3</sub>), 2.89 (s, 3H, CH<sub>3</sub>), 3.82 (s, 3H, OCH<sub>3</sub>), 4.45 (s, 2H, CH<sub>2</sub>S), 6.72 (s, 1H, N-CH), 6.94-7.65 (m, 8H, Ar-H, OH). Anal. Calcd for C<sub>21</sub>H<sub>20</sub>N<sub>3</sub>O<sub>4</sub>IS: C, 46.94; H, 3.75; N, 7.82. Found: C, 46.89; H, 3.62; N, 7.63.

**3-(2,6-Dichlorophenyl)-2-(4-hydroxy-3-iodo-5-methoxyphenyl)-thiazolidin-4-one (4b).** Yield 83 %, mp 164-166 °C; IR (cm<sup>-1</sup>) 1680, 1635, 1590. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.78 (s, 3H, CH<sub>3</sub>), 4.42 (s, 2H, CH<sub>2</sub>S), 6.68 (s, 1H, CH), 7.24-7.80 (m, 6H, Ar-H, OH). Anal. Calcd for C<sub>16</sub>H<sub>12</sub>NO<sub>3</sub>Cl<sub>2</sub>I<sub>2</sub>S: C, 38.73; H, 2.44; N, 2.82. Found: C, 38.58; H, 2.29; N, 2.76.

**3-[1,2,4]-Triazol-1-yl-2-(4-hydroxy-3-iodo-5-methoxyphenyl)-thiazolidin-4-one (4c).** Yield 80%, mp 229-231 °C; IR (cm<sup>-1</sup>) 1676, 1628, 1592. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.80 (s, 3H, OCH<sub>3</sub>), 4.42 (s, 2H, CH<sub>2</sub>S), 6.66 (s, 1H, CH), 7.66-8.23 (m, 5H, Ar-H, OH). Anal. Calcd for C<sub>12</sub>H<sub>11</sub>N<sub>4</sub>O<sub>3</sub>IS: C, 34.46; H, 2.65; N, 13.40. Found: C, 34.35; H, 2.49; N, 13.31.

**3-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-(4-hydroxy-3-bromo-5-methoxyphenyl)-thiazolidin-4-one (4d).** Yield 87 %, mp 158-160 °C; IR (cm<sup>-1</sup>) 1682, 1633, 1585. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.24 (s, 3H, CH<sub>3</sub>), 2.82 (s, 3H, CH<sub>3</sub>), 3.79 (s, 3H, OCH<sub>3</sub>), 4.43 (s, 2H, CH<sub>2</sub>S), 6.69 (s, 1H, CH), 7.41-7.92 (m, 8H, Ar-H, OH). Anal. Calcd for C<sub>21</sub>H<sub>20</sub>N<sub>3</sub>O<sub>4</sub>BrS: C, 51.44; H, 4.11; N, 8.57. Found: C, 51.35; H, 3.95; N, 8.39.

**3-(2,6-Dichlorophenyl)-2-(4-hydroxy-3-bromo-5-methoxyphenyl)-thiazolidin-4-one (4e).** Yield 75 %, mp 180-182 °C; IR (cm<sup>-1</sup>) 1678, 1634, 1589. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.78 (s, 3H, OCH<sub>3</sub>), 4.42 (s, 2H, CH<sub>2</sub>S), 6.68 (s, 1H, CH), 7.24-7.80 (m, 6H, Ar-H, OH). Anal. Calcd for C<sub>16</sub>H<sub>12</sub>NO<sub>3</sub>BrCl<sub>2</sub>S: C, 42.79; H, 2.69; N, 3.12. Found: C, 42.58; H, 2.78; N, 3.04.

**3-[1,2,4]-Triazol-1-yl-2-(4-hydroxy-3-bromo-5-methoxyphenyl)-thiazolidin-4-one (4f).** Yield 86 %, mp 198-199 °C; IR (cm<sup>-1</sup>) 1678, 1629, 1595. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.82 (s, 3H, OCH<sub>3</sub>), 4.45 (s, 2H, CH<sub>2</sub>S), 6.68 (s, 1H, CH), 7.68-8.33 (m, 5H, Ar-H, OH). Anal. Calcd for C<sub>12</sub>H<sub>11</sub>N<sub>4</sub>O<sub>3</sub>BrS: C, 38.83; H, 2.99; N, 15.09. Found: C, 38.73; H, 3.12; N, 14.88.

**3-(1,5-Dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-2-(2-hydroxy-3,5-diiodo-phenyl)-thiazolidin-4-one (4g).** Yield 76 %, mp 201-203 °C; IR (cm<sup>-1</sup>) 1679, 1631, 1591. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.23 (s, 3H, CH<sub>3</sub>), 2.89 (s, 3H, CH<sub>3</sub>), 3.83 (s, 3H, OCH<sub>3</sub>), 4.41 (s, 2H, CH<sub>2</sub>S), 6.56 (s, 1H, CH), 7.24-7.80 (m, 8H, Ar-H, OH). Anal. Calcd for C<sub>20</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>I<sub>2</sub>S: C, 37.93; H, 2.71; N, 6.64. Found: C, 37.79; H, 2.56; N, 6.48.

**3-(2,6-dichloro phenyl)-2-(2-hydroxy-3,5-diiodo-phenyl)-thiazolidin-4-one (4h).** Yield 78 %, mp 145-147 °C; IR (cm<sup>-1</sup>) 1680, 1630, 1590. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.79 (s, 3H, OCH<sub>3</sub>), 4.45 (s,

2H, CH<sub>2</sub>S), 6.64 (s, 1H, CH), 7.42-7.73 (m, 6H, Ar-H, OH). Anal. Calcd for C<sub>15</sub>H<sub>9</sub>NO<sub>2</sub>Cl<sub>2</sub>I<sub>2</sub>S: C, 30.43; H, 1.53; N, 2.37. Found: C, 30.20; H, 1.36; N, 2.22.

**3-[1,2,4]-Triazol-1-yl-2-(2-hydroxy-3,5-diiodo-phenyl)-thiazolidin-4-one (4i).** Yield 85 %, mp 245-246 °C; IR (cm<sup>-1</sup>) 1678, 1632, 1589. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.78 (s, 3H, OCH<sub>3</sub>), 4.43 (s, 2H, CH<sub>2</sub>S), 6.70 (s, 1H, CH), 7.72-8.30 (m, 6H, Ar-H, OH). Anal. Calcd for C<sub>11</sub>H<sub>8</sub>N<sub>4</sub>O<sub>2</sub>SI: C, 25.70; H, 1.57; N, 10.90. Found: C, 25.49; H, 1.33; N, 10.78.

## Acknowledgements

The authors are grateful to the Principal, Yeshwant Mahavidyalaya, Nanded for providing laboratory facilities and the Department of Microbiology for the screening of antibacterial activity, and UGC New Delhi for sanctioning the major research grant.

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