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**Research Article**

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# Synthesis, characterization and antimicrobial activity of some novel 2,3-disubstituted thiazolidin-4-one derivatives

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**ABSTRACT**

*A series of new 3-(4-(p-toluidino)thiazol-2-yl)-2-phenylthiazolidin-4-one derivatives (**5a-g**) were synthesized from novel schiff base of 2-((4-(p-toluidino)thiazol-2-ylimino)methyl)phenol (**4a-g**) with thioglycolic acid in presence of anhydrous zinc chloride. The chemical structures of these compounds were confirmed by various physic-chemical methods viz, IR, $^1$H NMR, mass spectral data and elemental analysis. Newly synthesized compounds were screened in vitro for their antimicrobial activity against varieties of gram +ve and gram -ve bacterial strains such as Bacillus subtilis, Pseudomonas aeruginosa and fungi strain Candida albicans & Aspergillus nigar at 40 μg/mL. The chloro and bromo substituted 2,3-substituted thiazolidin-4-one derivatives are showing activity as compare to the other functional groups.*

**Keywords**: 2,3-substituted-Thiazolidine-4-one, Schiff base, Thiazole, Elemental analysis, Antimicrobial evaluation.

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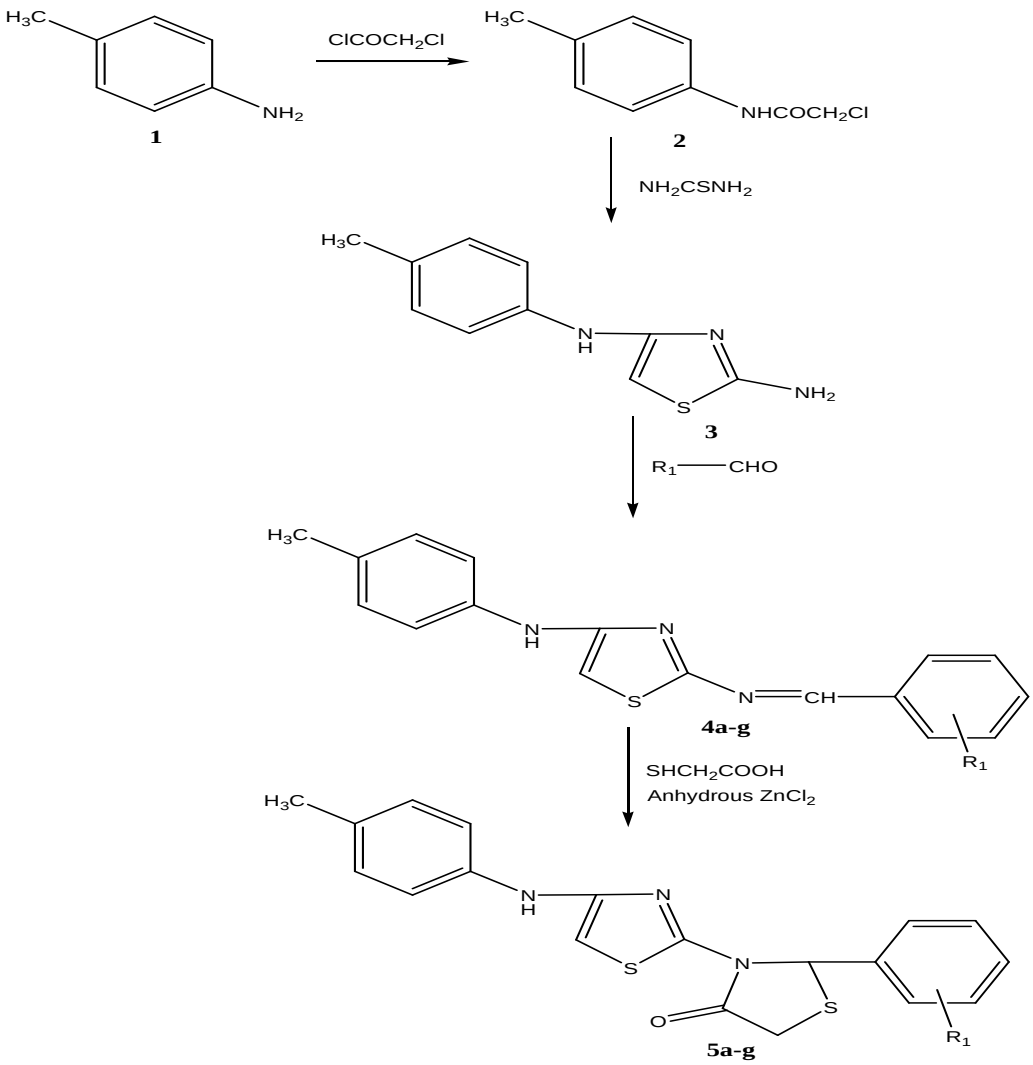
## INTRODUCTION

The several thiazole and thiazolidinone derivatives have been shown to exhibit excellent medicinal property. Thiazolidinones possessing antibacterial[1], anti-tubercular[2], antithyroid and amoebicidal[3]activity, as well as compounds exhibiting anti- inflammatory, analgesic, anticonvulsant[4] and antifungal[5-7]properties have been revealed. Thiazolidinone herbicides are the potent inhibitor of glucose incorporation into cell wall[8]. Apart from this some of them showed oxytocic, catatonic[9], antibiotic[10] and antiviral[11] activity, arthritis[12]. Beside this they are proved as calcium antagonists with both calcium overload inhibition and antioxidant activity[13]. We report in this paper the synthesis of some 2,3-substituted thiazolidine-4-one derivatives of thiazole and biological activity of the newly synthesized compounds.

## EXPERIMENTAL SECTION

Melting points were taken in open capillaries and are uncorrected. IR spectra were recorded on DR-8001, Shimadzu FT-IR spectrophotometer. $^1$H-NMR spectra were measured using WP 400-NMR spectrometer, deuterated solvents such as dimethyl-sulphoxide (DMSO-$d_6$), methanol ($CD_3OD$) and chloroform ($CDCl_3$) were used as solvents and the chemical shifts were quoted as δ-value relative to tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on LC-MS Schimadzu 2010A using dimethyl sulfoxide as solvent. C, H, N and S analysis were performed at Cochin university, Sophisticated Test & Instrumentation centre, Cochin, Kerala, India The purity of the compounds was monitored by thin layer chromatography on silica gel plates and iodine was used as a visualizing agent.

**Scheme**




**Synthesis of 2-chloro-N-p-tolylacetamide (2)**

p-Toluidene(0.05mole) were dissolved in glacial acetic acid(25ml) containing (25ml) saturated solution of sodium acetate, then mixture was warmed and then the solution was cooled in ice-bath with stirring. To this chloroacetyl chloride(0.06mole) was added drop wise to avoid the vigorous reaction. After half an hour a white colored product was separated and filtered. The product was washed with 50% aqueous acetic acid and finally with water. It was recrystallized from aqueous alcohol. IR (KBr, $\nu cm^{-1}$); 3406 (NH), 3108 (Ar-H), 1694 (C=O), 1530 (C=C), 780 (C-Cl).$^1$H NMR (400 MHz, $CDCl_3$, δ ppm);10.30(s,1H,NH), 8.20-7.44 (m, 4H, Ar-H),4.33(s, 2H, $CH_2$), 2.7(t,2H,$CH_2$), 1.24(s, 3H, $CH_3$). Mass(m/z): 184.63 (M+1).

**Synthesis of$N^4$-p-tolylthiazole-2, 4-diamine(3)**

A mixture of 2-chloro-N-p-tolylacetamide (0.02mole) and thiourea (0.01mole) in absolute acetone (90ml) was refluxed for 12hr. The excess of solvent was distilled off and the solid obtained was poured into ice-cold water, and then purified by recrystallization from methanol. Now, the solid was washed with 2% sodium carbonate and then with water to liberate the base completely, dried and purified by recrystallization from ethanol/water to furnish compound. .IR (KBr, $\nu cm^{-1}$);3406, 3230, 3200 ($NH_2$/NH), 2998 (Ar-CH), 1519 (C=C), 1099 (C-S),$^1$H NMR (400 MHz, $CDCl_3$, δ ppm);10.30(s,1H,NH), 8.20-7.24 (m, 4H, Ar-H and1H, s, CH of thiazole), 5.67(s, 2H, $NH_2$), 2.32(s, 3H, $CH_3$). Mass (m/z): 206.63 (M+1).

**General procedure for the synthesis of compound (4a-g)**

To a solution of compound **2**(0.01mole) in ethanol(60ml), substituted aromatic aldehydes(0.01mole) and a few drops of glacial acetic acid were added and the mixture refluxed for 10hr. It was then cooled, concentrated and poured into crushed ice and filtered. The product thus obtained was purified by recrystallization from methanol to obtain Schiff bases.

**$N^2$-benzylidene-$N^4$-p-tolylthiazole-2,4-diamine(4a)**
IR (KBr, ν $cm^{-1}$): 3395(NH), 3010(Ar-CH),1620(C=N ),1530( C=C)1099 (C-S),830 (Ar-H).$^1$H NMR (400 MHz, $CDCl_3$, δ ppm); 10.23(1H, s, NH), 9.17(1H, s, HC=N), 6.97-8.32(9H, m, Ar-H and 1H, s, CH of thiazole), 2.32 (3H, s, $CH_3$). Mass (m/z): 294.18 (M+1).

**$N^2$-(naphthalen-1-ylmethylene)-$N^4$-p-tolylthiazole-2,4-diamine (4b)**
IR (KBr, ν $cm^{-1}$): 3335(NH), 2978(Ar-CH), 1624(C=N ), 1525(C=C), 1122 (C-S), 830 (Ar-H). $^1$H NMR (400 MHz, $CDCl_3$, δ ppm); 11.10(1H, s, NH), 9.27(1H, s, HC=N), 6.55-8.32 (11H, m, Ar-H and 1H, s, CH of thiazole), 2.32 (3H, s, $CH_3$). Mass (m/z): 344.48 (M+1).

**$N^2$-(2,4-dichlorobenzylidene)-$N^4$-p-tolylthiazole-2,4-diamine(4c)**
IR (KBr, ν $cm^{-1}$): 3345(NH), 2982(Ar-CH), 1620(C=N ), 1498( C=C), 1102 (C-S), 830 (Ar-H), 780 (C-Cl). $^1$H NMR (400 MHz, $CDCl_3$, δ ppm); 10.27(1H, s, NH), 9.20(1H, s, HC=N), 6.85-8.15 (9H, m, Ar-H and 1H, s, CH of thiazole), 2.37 (3H, s, $CH_3$). Mass (m/z): 363.32 (M+1).

**2-((4-(p-toluidino)thiazol-2-ylimino)methyl)phenol (4d)**
IR (KBr, ν$cm^{-1}$): 3421(OH), 3204(NH), 2978(Ar-CH), 1610(C=N ), 1481( C=C), 1102 (C-S), 838 (Ar-H). $^1$H NMR (400 MHz, $CDCl_3$, δ ppm); 13.40(1H, s, OH), 11.10(1H, s, NH), 9.12(1H, s, HC=N), 6.85-8.52(8H, m, Ar-H and 1H, s, CH of thiazole), 2.33 (3H, s, $CH_3$). Mass (m/z): 310.44 (M+1).

**2-((4-(p-toluidino)thiazol-2-ylimino)methyl)-4-bromophenol(4e)**
IR (KBr, ν $cm^{-1}$): 3427(OH), 3214(NH), 2998(Ar-CH), 1618(C=N ), 1479( C=C), 1112 (C-S), 832 (Ar-H). $^1$H NMR (400 MHz, $CDCl_3$, δ ppm); 13.55(1H, s, OH), 11.10(1H, s, NH), 9.24(1H, s, HC=N), 6.75-7.77 (7H, m, Ar-H and 1H, s, CH of thiazole), 2.33 (3H, s, $CH_3$). Mass (m/z): 389.29 (M+1).

**$N^2$-(4-methoxybenzylidene)-$N^4$-p-tolylthiazole-2,4-diamine (4f)**
IR (KBr, ν$cm^{-1}$): 3256(NH), 2947(Ar-CH), 1617(C=N ),1499( C=C), 1109 (C-S), 833 (Ar-H). $^1$H NMR (400 MHz, $CDCl_3$, δ ppm): 11.10(1H, s, NH), 9.12(1H, s, HC=N), 6.85-8.52 (8H, m, Ar-H and 1H, s, CH of thiazole), 3.85(1H, s, $OCH_3$) 2.33 (3H, s, $CH_3$). Mass (m/z): 324.28 (M+1).

**$N^2$-(4-nitrobenzylidene)-$N^4$-p-tolylthiazole-2,4-diamine(4g)**
IR (KBr, ν$cm^{-1}$): 3268(NH), 2957(Ar-CH), 1619(C=N), 1501( C=C), 1112 (C-S), 833 (Ar-H). $^1$H NMR (400 MHz, $CDCl_3$, δ ppm): 10.98(1H, s, NH), 9.17(1H, s, HC=N), 6.85-7.99 (8H, m, Ar-H and 1H, s, CH of thiazole), 3.85(1H, s, $OCH_3$) 2.33 (3H, s, $CH_3$). Mass (m/z): 339.41 (M+1).

**General procedure for the synthesis of compound (5a-g)**
A solution of Schiff bases (4a-g), thioglycolic acid (0.01 mole) and anhydrous zinc chloride (2g) in absolute ethanol (60ml) was refluxed for 8hr, concentrated, cooled and poured into crushed ice, and then filtered. The product obtained was purified by recrystallization from acetone to get substituted thiazolidinones.

**3-(4-(p-toluidino)thiazol-2-yl)-2-phenylthiazolidin-4-one (5a)**
IR (KBr, ν$cm^{-1}$): 3400(NH), 3015(Ar-CH), 1697(C=O),1537( C=C), 1100 (C-S), 838 (Ar-H). $^1$H NMR (400 MHz, $CDCl_3$, δ ppm); 10.23(1H, s, NH), 6.97-8.32 (9H, m, Ar-H and 1H, s, CH of thiazole), 5.84(2H, s, $CH_2$ of thiazolidinone), 5.42(1H, s, CH of thiazolidinone), 2.32 (3H, s, $CH_3$). Mass (m/z): 368.48(M+1).

**3-(4-(p-toluidino)thiazol-2-yl)-2-(naphthalen-1-yl)thiazolidin-4-one (5b)**
IR (KBr, ν$cm^{-1}$): 3338(NH), 2980(Ar-CH), 1683(C=O), 1525( C=C), 1122 (C-S), 830 (Ar-H). $^1$H NMR (400 MHz, $CDCl_3$, δ ppm); 11.10(1H, s, NH), 6.55-8.32 (11H, m, Ar-H and 1H, s, CH of thiazole), 6.12(2H, s, $CH_2$ of thiazolidinone), 5.38(1H, s, CH of thiazolidinone), 2.32 (3H, s, $CH_3$).Mass (m/z): 418.57(M+1).

**3-(4-(p-toluidino)thiazol-2-yl)-2-(2,4-dichlorophenyl)thiazolidin-4-one (5c)**
IR (KBr, ν$cm^{-1}$): 3340(NH), 2980(Ar-CH), 1690(C=O), 1496( C=C), 1100 (C-S), 832 (Ar-H), 783 (C-Cl). $^1$H NMR (400 MHz, $CDCl_3$, δ ppm); 10.27(1H, s, NH), 6.85-8.15 (9H, m, Ar-H and 1H, s, CH of thiazole), 5.92(2H, s, $CH_2$ of thiazolidinone), 5.63(1H, s, CH of thiazolidinone), 2.37 (3H, s, $CH_3$). Mass (m/z): 437.37(M+1).

**3-(4-(p-toluidino)thiazol-2-yl)-2-(2-hydroxyphenyl)thiazolidin-4-one (5d)**
IR (KBr, ν$cm^{-1}$): 3419(OH), 3213(NH), 2976(Ar-CH), 1701(C=O), 1479( C=C), 1110 (C-S), 836 (Ar-H). $^1$H NMR (400 MHz, $CDCl_3$, δ ppm); 13.40(1H, s, OH), 11.10(1H, s, NH), 6.85-8.52 (8H, m, Ar-H and 1H, s, CH of thiazole), 5.65(2H, s, $CH_2$ of thiazolidinone), 5.25(1H, s, CH of thiazolidinone), 2.33 (3H, s, $CH_3$). Mass (m/z): 384.37 (M+1).

**3-(4-(p-toluidino)thiazol-2-yl)-2-(5-bromo-2-hydroxyphenyl)thiazolidin-4-one (5e)**
IR (KBr, νcm$^{-1}$): 3425(OH), 3212(NH), 2996(Ar-CH), 1681(C=O), 1477( C=C), 1110 (C-S), 830 (Ar-H). $^1$H NMR (400 MHz, $CDCl_3$, δ ppm); 13.55(1H, s, OH), 11.10(1H, s, NH), 6.75-7.77 (7H, m, Ar-H and 1H, s, CH of thiazole), 5.82(2H, s, $CH_2$ of thiazolidinone), 5.45(1H, s, CH of thiazolidinone), 2.33 (3H, s, $CH_3$). Mass (m/z): 463.37 (M+1).

**3-(4-(p-toluidino)thiazol-2-yl)-2-(4-methoxyphenyl)thiazolidin-4-one(5f)**
IR (KBr, νcm$^{-1}$): 3257(NH), 2947(Ar-CH), 1701(C=O), 1496( C=C), 1110 (C-S), 835 (Ar-H). $^1$H NMR (400 MHz, $CDCl_3$, δ ppm): 11.10(1H, s, NH), 6.85-8.52 (8H, m, Ar-H and 1H, s, CH of thiazole), 5.88(2H, s, $CH_2$ of thiazolidinone), 5.41(1H, s, CH of thiazolidinone), 3.85(1H, s, $OCH_3$), 2.33 (3H, s, $CH_3$). Mass (m/z): 398.54 (M+1).

**3-(4-(p-toluidino)thiazol-2-yl)-2-(4-nitrophenyl)thiazolidin-4-one (5g)**
IR (KBr, νcm$^{-1}$): 3269(NH), 2955(Ar-CH), 1697(C=O), 1503( C=C), 1109 (C-S), 832 (Ar-H). $^1$H NMR (400 MHz, $CDCl_3$, δ ppm): 10.98(1H, s, NH), 6.85-7.99 (8H, m, Ar-H and 1H, s, CH of thiazole), 5.86(2H, s, $CH_2$ of thiazolidinone), 5.48(1H, s, CH of thiazolidinone), 3.85(1H, s, $OCH_3$), 2.33 (3H, s, $CH_3$). Mass (m/z): 413.57 (M+1).

**Table-I: Characterization data of Synthesized compounds**

| Code | $R_1$ | Molecular formula | M.W | M.P ($^0$C) | % Yield | Element % calculated (found) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | C | H | N | S |
| 2 | ----- | $C_9H_{10}ClNO$ | 183.63 | 85-87 | 88 | 58.88 | 5.45 | 7.66 | ----- |
| | | | | | | (58.86) | (5.43) | (7.65) | ----- |
| 3 | ----- | $C_{10}H_{11}N_3S$ | 205.27 | 95-97 | 72 | 58.45 | 5.35 | 20.46 | 15.58 |
| | | | | | | (58.43) | (5.32) | (20.46) | (15.56) |
| 4a | -Phenyl | $C_{17}H_{15}N_3S$ | 293.28 | 115-117 | 70 | 69.55 | 5.11 | 14.32 | 10.91 |
| | | | | | | (69.54) | (5.10) | (14.30) | (10.90) |
| 4b | -Naphthyl | $C_{21}H_{17}N_3S$ | 343.44 | 213-215 | 76 | 73.37 | 4.94 | 12.22 | 9.31 |
| | | | | | | (73.35) | (4.93) | (12.21) | (9.29) |
| 4c | -2,4-Cl | $C_{17}H_{13}Cl_2N_3S$ | 362.27 | 150-154 | 80 | 56.31 | 3.58 | 11.59 | 8.83 |
| | | | | | | (56.28) | (3.56) | (11.57) | (8.81) |
| 4d | -2-OH | $C_{17}H_{15}N_3OS$ | 309.38 | 118-121 | 72 | 77.02 | 4.84 | 13.57 | 10.34 |
| | | | | | | (77.00) | (4.83) | (13.55) | (10.32) |
| 4e | -5-Br,2- OH | $C_{17}H_{14}BrN_3OS$ | 388.28 | 174-176 | 78 | 52.53 | 3.60 | 10.81 | 8.24 |
| | | | | | | (52.51) | (3.59) | (10.80) | (8.23) |
| 4f | -4-$OCH_3$ | $C_{18}H_{17}N_3OS$ | 323.41 | 112-114 | 74 | 66.78 | 5.25 | 12.98 | 9.89 |
| | | | | | | (66.77) | (5.23) | (12.97) | (9.88) |
| 4g | -4-$NO_2$ | $C_{17}H_{14}N_4O_2S$ | 338.38 | 202-207 | 79 | 60.28 | 4.13 | 16.54 | 9.45 |
| | | | | | | (60.26) | (4.11) | (16.53) | (9.44) |
| 5a | -Phenyl | $C_{19}H_{17}N_3OS_2$ | 367.48 | 118-120 | 71 | 62.04 | 4.62 | 11.42 | 17.41 |
| | | | | | | (62.03) | (4.61) | (11.40) | (17.40) |
| 5b | -Naphthyl | $C_{23}H_{19}N_3OS_2$ | 417.54 | 218-220 | 82 | 66.10 | 4.55 | 10.05 | 15.32 |
| | | | | | | (66.09) | (4.53) | (10.04) | (15.30) |
| 5c | -2,4-Cl | $C_{19}H_{15}Cl_2N_3OS_2$ | 436.37 | 158-160 | 83 | 52.24 | 3.43 | 9.62 | 14.66 |
| | | | | | | (52.22) | (3.42) | (9.62) | (14.65) |
| 5d | -2-OH | $C_{19}H_{17}N_3O_2S_2$ | 383.48 | 125-127 | 80 | 59.45 | 4.43 | 10.95 | 16.68 |
| | | | | | | (59.44) | (4.41) | (10.93) | (16.66) |
| 5e | -5-Br,2-OH | $C_{19}H_{16}BrN_3O_2S_2$ | 462.38 | 217-218 | 84 | 49.31 | 3.46 | 9.08 | 13.84 |
| | | | | | | (49.30) | (3.45) | (9.07) | (13.83) |
| 5f | -4-$OCH_3$ | $C_{20}H_{19}N_3O_2S_2$ | 397.51 | 120-121 | 73 | 60.37 | 4.77 | 10.56 | 16.10 |
| | | | | | | (60.36) | (4.76) | (10.55) | (16.09) |
| 5g | -4-$NO_2$ | $C_{19}H_{16}N_4O_3S_2$ | 412.48 | 210-212 | 76 | 55.27 | 3.87 | 13.57 | 15.51 |
| | | | | | | (55.26) | (3.86) | (13.56) | (15.51) |

**Biological Activity**
**In vitro antibacterial screening**
All the newly synthesized compounds **(4a-g & 5a-g)** were screened in vitro for their antibacterial activity against *Bacillus subtilis, Staphylococcus aureus*, *Escherichia coli, Pseudomonas aeruginosa* by disc diffusion method[14] was performed using Mueller. Hinton agar(Hi-Media) medium. Each compound was tested at a concentration at 40µg/mL in DMSO. The diameter of zone of inhibition was measured in mm after 24h incubation at 37$^o$C. The known compound ciplofloxacin was used as standard drug for comparison study.

The antibacterial screening data are recorded in **Table II.**

**In vitro antifungal screening**

The compounds **(4a-g & 5a-g)** were evaluated for their in vitro antifungal activity against *Candida albicans* using disc diffusion method [15] with sabouraud's dextrose agar (Hi-Media). Each compound was tested at a concentration of 40µg/mL in DMSO. The zone of inhibition (mm) was measured. The known compound Amphotericin B was used as standard drug for comparison study. The antifungal screening data are recorded in **Table II.**

**Table II: Antimicrobial activity data of synthesized compounds 5(a-g)**

| Compound | Antibacterial activity Zone of inhibition (in mm) | | Antifungal activity Zone of inhibition (in mm) | |
|---|---|---|---|---|
| | *Bacillus subtilis* | *Pseudomonas aeruginosa* | *Candida albicans* | *Aspergillusnigar* |
| 5a | 15 | -ve | 12 | 15 |
| 5b | -ve | 25 | 13 | 10 |
| 5c | 28 | 27 | 25 | 27 |
| 5d | 18 | 15 | 13 | 15 |
| 5e | 29 | 10 | 29 | 32 |
| 5f | 15 | -ve | 16 | 16 |
| 5g | 10 | 12 | -ve | -ve |
| Ciplofloxacin | 35 | 32 | -ve | -ve |
| Amphotericin B | -ve | -ve | 33 | 27 |

*Control (DMSO), (– ve) – No activity*

## RESULTS AND DISCUSSION

The $N^4$-(4-methylphenyl)-1,3-thiazole-2,4-diamine**(3)** was obtained by the cyclization reaction shown by the mixture of 2-chloro-N-(4-methylphenyl)acetamide and thiourea with high yield. In turn, the $N^2$-(substituted)-$N^4$-(4-methylphenyl)-1,3-thiazole-2,4-diamine**4(a-g)** were resulted by the condensation of compound (**3)** with different aromatic aldehydes with 70-80% yield which on cyclization with thioglycolic acid in presence of anhydrous zinc chloride as catalyst afforded 3-(4-(p-toluidino)thiazol-2-yl)-2-(2-substituted)thiazolidin-4-one **(5a-g) .** The newly synthesized compounds 4**(a-g)** and **5(a-g)** were established on the basis of IR, $^1$HNMR and MASS spectroscopy method. $^1$H NMR spectrum of compound **4(a-g)** shows a singlet at 9.17-9.27 ppm for -CH=N- proton is characteristic value of –CH- proton of the imine group. The strong absorption bands at 1681-1701cm$^{-1}$**5(a-g)** and at 1610-1619 cm$^{-1}$**4(a-g)** confirms the presence of C=O and C=N functional groups respectively.

The result of studies are summarized in Table II and from the result it is clear that all the compounds showing moderate to good antibacterial & antifungal activity. Among the tested compounds **5c &5e** carrying 2,4-chloro and 5-bromo-2-hydroxy phenyl group respectively have shown significant antibacterial & antifungal activity and is having zone of inhibition very similar to the standard drug used. Compound **5b** is also showing good antibacterial activity against gram -ve bacteria.

## CONCLUSION

In summary, the synthesized novel 2,3-Disubstituted Thiazolidin-4-onecontaining 2,4-disubstituted thiazole derivatives with very good yield. Further these compounds were evaluated for their antimicrobial activity. Most of the compounds showed moderate to significant activity against gram +ve and gram -ve bacterial strains and fungi. Compound **5c & 5e** were most active among all the synthesized compounds due to the presence of halogens.

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