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# "SYNTHESIS AND CHARACTERIZATION OF PYRIMIDINE CONTAINING THIAZOLIDINONE DERIVATIVES"

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**ABSTRACT**

Antibiotic resistance is considered one of the world's major public health concerns. The main cause of bacterial resistance is the improper and repeated use of antibiotics. To alleviate this problem, new chemical substances against microorganisms are being synthesized and tested. Thiazolidines are compounds having many pharmacological activities including antimicrobial activities. For this purpose some thiazolidine derivatives substituted at position 5 in the thiazolidine nucleus were synthesized and tested against several microorganisms. From these reviews we synthesized a new series of 2-(4-chlorophenyl)-3-{4-[6-(substitutedphenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl]phenyl}-1,3-thiazolidin-4-one derived from 3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-2-(4-chlorophenyl)-1,3-thiazolidin-4-one and thiourea. The title compounds were characterized by element analysis, IR, NMR and spectral data. All the compounds were tested for their antibacterial and antifungal activities by Cup Borer method.

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## INTRODUCTION

Thiazolidine is a class of compounds which merit special attention because it belongs to a group of substances with activity in medicinal chemistry. This nucleus is associated with antibacterial, antifungal, antiviral, antituberculosis, anticancer, and antiparasitic biological activities.[1–4] The use of new synthetic methods and structure-activity relationship studies has made possible a broad study of new drugs with different actions. Currently, Multiple antibiotic resistant bacteria represent a challenge in the treatment. It is imperative, therefore, that new substances with antimicrobial properties be found to fight these microorganisms.[5] Increasing bacterial resistance to antibiotics, attention has become focused on the development of new derivatives to be used as antimicrobial therapy in infection control.[6] Research groups are worried about the rise in recurrence of many infectious diseases and the lack of new drugs and development of new antimicrobial products in the face of increasing resistance to existing agents.[7] The literature reports on the results of a number of biological activities when the substituents and their positions on the thiazolidine ring are changed.[8] In this case, chemistry is an important aid in the discovery of new active molecules using small heterocyclic rings to increase the biological activity of certain nuclei.[9]

## EXPERIMENTAL

All reagents were of analytical reagent grade and were used without further purification, All the product was synthesized and characterized by their spectral analysis. Melting points were taken in open capillary tube. The IR spectra were recorded on Bruker Model; Alpha, Laser Class1, made in Germany and Brooker instrument used for NMR Spectroscopy was 500 MHz and tetramethyl silane used as internal standard. Solvent used were DMSO. Purity of the compounds was checked by TLC on silica- G plates. Anti-microbial activities were tested by Cup-Borer method.

**Reaction schem**

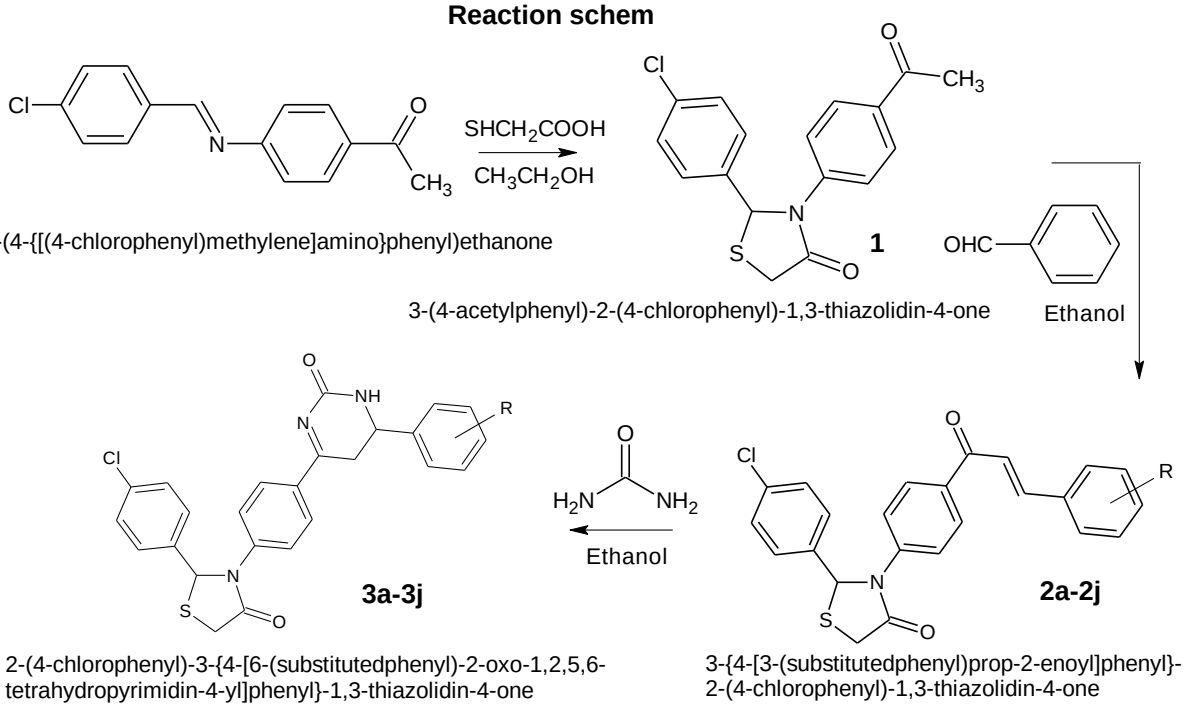

**Table: 1** ***Physical constant of 2a-2j.***

| Comp'd | R | M.F. | Yield % | M.P. °C | Elemental Analysis | | |
|---|---|---|---|---|---|---|---|
| | | | | | % C Found (Calcd) | % N Found (Calcd) | % H Found (Calcd) |
| 2a | -2-Cl | $C_{24}H_{18}ClNO_3S$ | 75 | 133 | 63.42 (63.44) | 3.05 (3.08) | 3.74 (3.77) |
| 2b | -4-Cl | $C_{24}H_{18}ClNO_3S$ | 78 | 126 | 63.41 (66.44) | 3.03 (3.08) | 3.73 (3.77) |
| 2c | -3,4- $(OCH_3)_2$ | $C_{26}H_{23}NO_5S$ | 80 | 134 | 65.04 (65.06) | 2.90 (2.92) | 4.59 (4.62) |
| 2d | -H | $C_{24}H_{19}NO_3S$ | 82 | 130 | 68.63 (68.65) | 3.32 (3.34) | 4.30 (4.32) |
| 2e | -2-OH | $C_{24}H_{19}NO_4S$ | 76 | 127 | 66.11 (66.13) | 3.18 (3.21) | 4.09 (4.16) |
| 2f | -4-OH-3-$OCH_3$ | $C_{25}H_{21}NO_5S$ | 78 | 139 | 64.43 (64.44) | 3.01 (3.01) | 4.30 (4.33) |
| 2g | -4-OH | $C_{24}H_{19}NO_4S$ | 74 | 123 | 66.09 (66.13) | 3.19 (3.21) | 4.12 (4.16) |
| 2h | -4-$N(CH_3)_2$ | $C_{26}H_{24}N_2O_3S$ | 80 | 140 | 67.43 (67.45) | 6.02 (6.05) | 5.00 (5.01) |
| 2i | -4-$OCH_3$ | $C_{25}H_{21}NO_4S$ | 77 | 138 | 66.71 (66.73) | 3.10 (3.11) | 4.47 (4.48) |
| 2j | -3-$NO_2$ | $C_{24}H_{18}N_2O_5S$ | 73 | 118 | 62.00 (62.00) | 6.01 (6.03) | 3.66 (3.69) |

**Preparation of 3-(4-acetylphenyl)-2-(4-chlorophenyl)-1,3-thiazolidin-4-one. (1)**

A solution of compound 1-(4-{[(4-chlorophenyl)methylene]amino}phenyl)ethanone(0.01M), thioglycolic acid (0.01M) and anhydrous zinc chloride(2g) in absolute ethanol (60 ml)was refluxed for 8 hours, concentrated, cooled overnight. The reaction mixture was poured into crushed ice, and then filtered. The product obtained was purified by recrystallization from acetone **IR (1)**, 3062 (=C-H), 2913 (-C-H stretching), 1690 (>C=O stretching), 1522 (>C=C< Aromatic), 1465 (-$CH_2$- bend), 1403 (-$CH_3$), 1465,1403 (-$CH_3$), 1318 (C-N), 819 (C-Cl), 675 (C-S-C). **$^1$H-NMR (1-DMSO, δ, ppm)**: 2.511 (2H, s, -$COCH_3$), 3.340 (2H, s, -$CH_2$-),5.815 (1H, s, >CH-) 6.696-7.940(8H, m, Ar-H),9.027 ( 1H, s,-OH).

**Preparation of 3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-2-(4-chlorophenyl)-1,3-thiazolidin-4-one (2a-2j)**

To the solution of 3-(4-acetylphenyl)-2-(4-chlorophenyl)-1,3-thiazolidin-4-one (0.01M) in absolute ethanol (50 ml), substituted aldehyde (0.01M) and 2% NaOH (10 ml) were added and refluxed for 10 hours. After refluxing the reaction mixture was concentrated, cooled, filtered and neutralized with dil. HCl. The solid residue thus obtained was crystallized by absolute ethanol. **IR(2g)**, $cm^{-1}$: 3288 (-OH), 3045 ( =C-H ), 2948(-C-H stretching), 1739 (>C=O stretching), 1521 (>C=C< Aromatic), 1438 (-$CH_3$-bend), 1347 (C-N), 822(C-Cl), 651 (C-S-C). **$^1$H-NMR (2d-DMSO, δ, ppm)**: 3.339 (2H, s, -$CH_2$-), 5.810 (1H, s, >CH-), 6.15-7.923(13H, m, Ar-H), 7.945 (2H, d, -CH=CH-).

**Preparation of 2-(4-chlorophenyl)-3-{4-[6-(substitutedphenyl)-2-oxo-1,2,5,6-tetrahydro pyrimidin-4-yl]phenyl}-1,3-thiazolidin-4-one (3a-3j)**

A mixture of 3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-2-(4-chlorophenyl)-1,3-thiazolidin-4-one (0.01M),urea (0.01M) and 1gm. of potassium hydroxide (KOH) in 30 ml of ethanol was refluxed for 3 hours. After standing overnight the solid formed was collected and crystallized from acetone. **IR(3e), $cm^{-1}$**: 3380 (>NH-), 3248 (-OH), 3070 ( =C-H ), 2968 (-C-H stretching), 1712 (>C=O stretching), 1630 (>C=N- stretching), 1521 (>C=C< Aromatic), 1448 (-$CH_2$- bend), 1338 (C-N), 780 (C-Cl), 662 (C-S-C).**$^1$H-NMR (3c-DMSO, δ, ppm)**: 1.914 (2H, d, -$CH_2$-), 3.347 (2H, s, -$CH_2$- ),3.747 (6H, s, -$OCH_3$),3.850 (1H, t, -CH<), 5.915 (1H, s, >CH-), 7.944 ( 1H, s, -NH-),6.534-7.705 (12H, m, Ar-H).

**Table: 2*Physical constant of 3a-3j.***

| comp'd | R | M.F. | Yield % | M.P. °C | Elemental Analysis % C Found (Calcd) | % N Found (Calcd) | % H Found (Calcd) |
|---|---|---|---|---|---|---|---|
| 3a | -2-Cl | $C_{25}H_{20}ClN_3O_3S$ | 75 | 172 | 60.47 (60.49) | 8.43 (8.46) | 3.84 (3.86) |
| 3b | -4-Cl | $C_{25}H_{20}ClN_3O_3S$ | 80 | 163 | 60.46 (60.49) | 8.44 (8.46) | 3.84 (3.86) |
| 3c | -3,4- $(OCH_3)_2$ | $C_{27}H_{25}N_3O_5S$ | 81 | 168 | 62.10 (62.12) | 8.01 (8.05) | 4.62 (4.63) |
| 3d | -H | $C_{25}H_{21}N_3O_3S$ | 80 | 183 | 65.00 (65.00) | 9.08 (9.10) | 4.33 (4.36) |
| 3e | -2-OH | $C_{25}H_{21}N_3O_4S$ | 79 | 176 | 62.80 (62.82 | 4.20 (4.22) | 8.76 (8.79) |
| 3f | -4-OH- 3-$OCH_3$ | $C_{26}H_{23}N_3O_5S$ | 75 | 170 | 61.45 (61.47) | 8.26 (8.27) | 4.34 (4.37) |
| 3g | -4-OH | $C_{25}H_{21}N_3O_4S$ | 77 | 155 | 62.80 (62.82) | 8.77 (8.79) | 4.19 (4.22) |
| 3h | -4-$N(CH_3)_2$ | $C_{27}H_{26}N_4O_3S$ | 78 | 182 | 64.18 (64.21) | 11.08 (11.09) | 4.94 (4.99) |
| 3i | -4-$OCH_3$ | $C_{26}H_{23}N_3O_4S$ | 76 | 175 | 63.44 (63.47) | 8.52 (8.54) | 4.50 (4.51) |
| 3j | -3-$NO_2$ | $C_{25}H_{20}N_4O_5S$ | 82 | 165 | 59.21 (59.23) | 11.03 (11.05) | 3.77 (3.78) |

## RESULTS AND DISCUSSION

### Antibacterial activity

### Against Escherichia Coli:

From screening results, substituted derivatives 2a, 2h, 3e and 3a possesses very good activity against Penicillin and Kanamycin. The compounds 2f and 3h was shown minimum antibacterial activity.3b was found to be inactive against Escherichia Coli. Rest of all compounds were found to show good to moderate activity against Saccharomyces as compared to the standard drug Kanamycin.

### Against Staphylococcus aureus:

Biological evaluation of present investigation revealed the maximum antibacterial activity was shown by the compound 2i, 3a, 3d and 3j. The minimum antibacterial activity was shown by the compound 2e, 2h, and 3g. The remaining compounds were found to show good to moderate activity against Staphylococcus aureus as compared to the standard drug Kanamycin.

### Antifungal activity

### Against Candida albicans:

Biological evaluation of present investigation revealed the maximum antifungal activity was shown by the compound 2d, 3b, 3h and 3j. The minimum antifungal activity was shown by the compound 2a, 3e and 3a. 2b was found to be inactive against Escherichia Coli. Rest of all compounds were found to show good to moderate activity against Saccharomyces as compared to the standard drug Amphotericin.

**Table: 3 *Antimicrobial activities of 2a-2j.***

| Sr. No. | Comp. No. | R | Zone of Inhibitions in mm Antibacterial activity E. coli | Antibacterial activity E. coli | Antibacterial activity C. Albicans |
|---|---|---|---|---|---|
| 1 | 2a | -2-Cl | 18 | 19 | 11 |
| 2 | 2b | -4-Cl | 16 | 15 | NA |
| 3 | 2c | -3,4- $(OCH_3)_2$ | NA | 18 | 15 |
| 4 | 2d | -H | 14 | 16 | 18 |
| 5 | 2e | -2-OH | 15 | 14 | 17 |
| 6 | 2f | -4-OH- 3-$OCH_3$ | 12 | 15 | 14 |
| 7 | 2g | -4-OH | 14 | 17 | 15 |
| 8 | 2h | -4-$N(CH_3)_2$ | 17 | 13 | 13 |
| 9 | 2i | -4-$OCH_3$ | 16 | 18 | 14 |
| 10 | 2j | -3-$NO_2$ | 14 | 16 | 16 |

**Table: 4** ***Antimicrobial activities of 3a-3j.***

| Sr. No. | Comp. No. | R | Zone of Inhibitions in mm | | |
|---|---|---|---|---|---|
| | | | Antibacterial activity | Antibacterial activity | |
| | | | E. coli | E. coli | C. Albicans |
| 1 | 3a | -2-Cl | 18 | 18 | NA |
| 2 | 3b | -4-Cl | 14 | 15 | 18 |
| 3 | 3c | -3,4- $(OCH_3)_2$ | 15 | 16 | 15 |
| 4 | 3d | -H | 18 | 13 | 14 |
| 5 | 3e | -2-OH | 16 | 14 | 13 |
| 6 | 3f | -4-OH- 3-$OCH_3$ | 14 | 17 | 18 |
| 7 | 3g | -4-OH | 13 | 15 | 14 |
| 8 | 3h | -4-$N(CH_3)_2$ | 17 | 14 | 17 |
| 9 | 3i | -4-$OCH_3$ | 18 | 17 | 16 |
| 10 | 3j | -3-$NO_2$ | 15 | NA | 17 |

**Table: 5** ***Antibacterial Activity: Minimal Inhibition Concentration (The Standard Drugs).***

| Zone of inhibition of standard drugs and solvent | | | | | |
|---|---|---|---|---|---|
| Sr. No. | Comp. No. | Standard Drugs | Zone of inhibition (mm) | | |
| | | | *E. Coli* | *S. aureus* | *C. albicans* |
| 1 | SD - 1 | Penicillin | 15 | 17 | - |
| 2 | SD - 2 | Kanamycin | 17 | 19 | - |
| 3 | SD - 3 | Baycor 25 w.p. | - | - | 18 |
| 4 | SD - 4 | Amphotericin | - | - | 20 |
| 5 | Solvent | DMF | 11 | 12 | 12 |

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