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# SYNTHESIS, CHARACTERIZATION AND ANTIMICROBIAL ACTIVITY OF THIAZOLIDINONE BASED PYRIMIDIN-2-ONE DERIVATIVES

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## ABSTRACT

Heterocyclic Compounds have so far been synthesized mainly due to the wide range of biological activities. Thiazolidinone plays an important role in biological field. From these reviews we synthesized a new series of 2-(4-hydroxyphenyl)-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-hydroxyphenyl)-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.

**KEYWORDS:** Thiazolidinone, IR, NMR, Cup Borer method.

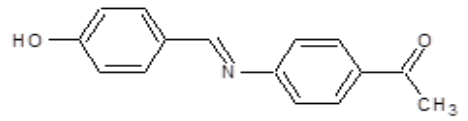
## INTRODUCTION

4-Thiazolidinones are associated with anticancer[1] and versatile pharmacological activities[2,3] like Anti-tubercular[4] Anti–inflammatory[5] antimicrobial,[6] Anti – HIV,[7] antioxidant,[8] etc. Some thiazolidinones are reported as analgesic and ulcerogenic.[6] Moreover, annals are reported to have significant anticancer[9] and antibacterial[10] activity. All these observations and important role of annals and 4-thiazolidinones in certain biological reactions prompted us to synthesize some 4-Thiazolidinones incorporating sterile moieties and to study their antibacterial activity.

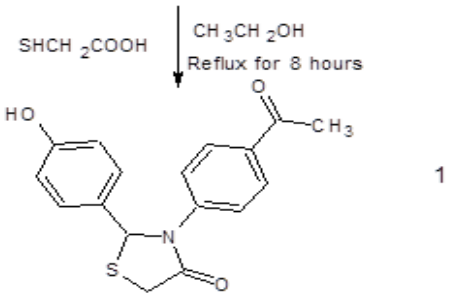
## Experimental

All reagents were of analytical reagent grade and were used without further purification, All the product were 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 Scheme**

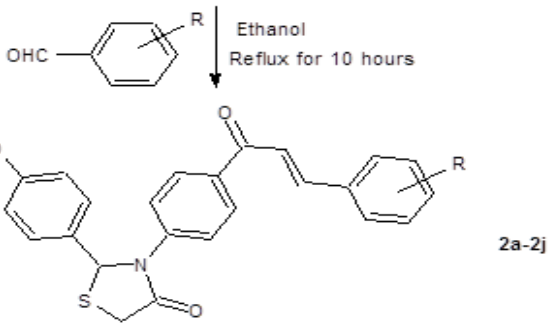


1-(4-{[(4-hydroxyphenyl)methylene]amino}phenyl)ethanone



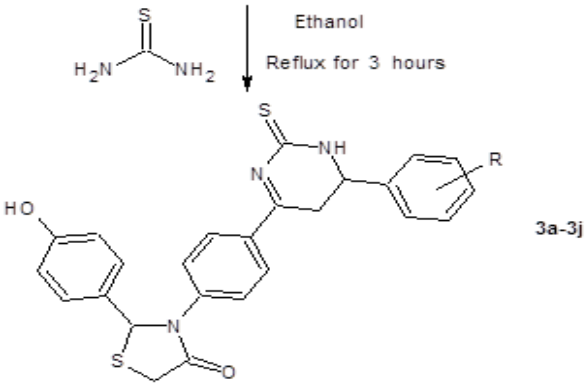

1

3-(4-acetylphenyl)-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one




**2a-2j**

3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one




**3a-3j**

2-(4-hydroxyphenyl)-3-{4-[6-(substitutedphenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl]phenyl}-1,3-thiazolidin-4-one

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

A solution of compound 1-(4-{[(4-hydroxyphenyl) methylene]amino}phenyl) ethenone (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. The yield of the product was 87% and the product melts at $197^0$C. **IR(1)**, $cm^{-1}$: 3280 (-OH), 3048 (=C-H ), 2948 (-C-H stretching), 1666 (>C=O stretching), 1509 (>C=C< Aromatic), 1450 ($-CH_2-$ bend), 1375 ($-CH_3$), 1315 (C-N), 700 (C-S-C) **$^1$H-NMR (1-DMSO, δ, ppm)**: 2.519 (3H, s, $-COCH_3$), 3.343 (2H, s, $-CH_2-$),5.875 (1H, S, >CH-) 6.612-7.896(8H, m, Ar-H),9.027 ( 1H, s,-OH).

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

To the solution of 3-(4-acetylphenyl)-2-(4-hydroxyphenyl)-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(2a)**, $cm^{-1}$: 3276 (-OH), 3056 (=C-H), 2925 (-C-H stretching), 1725 (>C=O stretching), 1590 (>C=C< Aromatic),1440($-CH_3-$ bend), 1305 (C-N), 800 (C-Cl), 725 (C-S-C). **$^1$H-NMR (2b-DMSO, δ, ppm)**: 3.358 (2H, s, $-CH_2-$), 5.843 (1H, s, >CH-), 6.643-7.639(12H, m, Ar-H), 7.955 (2H, d, -CH=CH-), 9.016 ( 1H, s,-OH).

**Preparation of 2-(4-hydroxyphenyl)-3-{4-[6-(substitutedphenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl]phenyl}-1,3-thiazolidin-4-one (3a-3j)**

A mixture of 3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one (0.01M),thiourea (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(2c), $cm^{-1}$**: 3325 (>NH-),3251(-OH), 3077 ( =C-H), 2969 (-C-H stretching), 1733 (>C=O stretching), 1602 (>C=N- stretching), 1512 (>C=C< Aromatic), 1458 ($-CH_2-$ bend), 1398 ($-CH_3$), 1336 (C-N), 1202 (>C=S), 1259 (C-O-C), 720 (C-S-C). **$^1$H-NMR (3i-DMSO, δ, ppm)**: 1.928 (2H, d, $-CH_2-$), 2.061 (1H, s, -NH-),3.355 (2H, s, $-CH_2-$),3.755 (3H, s, $-OCH_3$), 3.783 (1H, t, -CH<),5.890(1H, s, >CH-), 6.634-7.903 (12H, m, Ar-H),9.006 ( 1H, s, -OH).

**Table 1:** ***Physical constant of 3-{4-[3-(substitutedphenyl)prop-2-enoyl]phenyl}-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one.***

| Comp'd | R | M.F. | Yield % | M.P. °C | Elemental Analysis | | |
|---|---|---|---|---|---|---|---|
| | | | | | % C Found (Calcd) | % N Found (Calcd) | % H Found (Calcd) |
| 2a | -2-Cl | $C_{24}H_{18}ClNO_3S$ | 85 | 122 | 66.10 (66.13) | 3.16 (3.21) | 4.12 (4.16) |
| 2b | -4-Cl | $C_{24}H_{18}ClNO_3S$ | 81 | 128 | 66.11 (66.13) | 3.18 (3.21) | 4.14 (4.16) |
| 2c | -3,4- $(OCH_3)_2$ | $C_{26}H_{23}NO_5S$ | 77 | 140 | 67.63 (67.66) | 3.01 (3.03) | 5.00 (5.02) |
| 2d | -H | $C_{24}H_{19}NO_3S$ | 67 | 125 | 71.76 (71.80) | 3.44 (3.49) | 4.74 (4.77) |
| 2e | -2-OH | $C_{24}H_{19}NO_4S$ | 73 | 142 | 69.01 (69.05) | 3.33 (3.36) | 4.53 (4.59) |
| 2f | -4-OH- 3-$OCH_3$ | $C_{25}H_{21}NO_5S$ | 70 | 148 | 67.08 (67.10) | 3.09 (3.13) | 4.69 (4.73) |
| 2g | -4-OH | $C_{24}H_{19}NO_4S$ | 65 | 127 | 69.03 (69.05) | 3.33 (3.36) | 4.57 (4.59) |
| 2h | -4-$N(CH_3)_2$ | $C_{26}H_{24}N_2O_3S$ | 80 | 138 | 70.24 (70.25) | 6.27 (6.30) | 5.42 (5.44) |
| 2i | -4-$OCH_3$ | $C_{25}H_{21}NO_4S$ | 75 | 134 | 69.56 (69.59) | 3.23 (3.25) | 4.88 (4.91) |
| 2j | -3-$NO_2$ | $C_{24}H_{18}N_2O_5S$ | 73 | 130 | 64.53 (64.56) | 6.22 (6.27) | 4.02 (4.06) |

**Table 2:** ***Physical constant of 2-(4-hydroxyphenyl)-3-{4-[6-(substitutedphenyl)-2-thioxo-1,2,5,6-tetrahydropyrimidin-4-yl]phenyl}-1,3-thiazolidin-4-one.***

| Comp'd | R | M.F. | Yield % | M.P. °C | Elemental Analysis | | |
|---|---|---|---|---|---|---|---|
| | | | | | % C Found (Calcd) | % N Found (Calcd) | % H Found (Calcd) |
| 3a | -2-Cl | $C_{25}H_{20}ClN_3O_2S_2$ | 81 | 162 | 60.77 (60.78) | 8.49 (8.51) | 4.04 (4.08) |
| 3b | -4-Cl | $C_{25}H_{20}ClN_3O_2S_2$ | 85 | 132 | 60.77 (60.78) | 8.48 (8.51) | 4.06 (4.08) |
| 3c | -3,4-$(OCH_3)_2$ | $C_{27}H_{25}N_3O_4S_2$ | 78 | 145 | 62.41 (62.41) | 8.08 (8.09) | 4.81 (4.85) |
| 3d | -H | $C_{25}H_{21}N_3O_2S_2$ | 76 | 161 | 65.30 (65.33) | 9.12 (9.14) | 4.59 (4.61) |
| 3e | -2-OH | $C_{25}H_{21}N_3O_3S_2$ | 75 | 165 | 63.11 (63.14) | 8.83 (8.84) | 4.44 (4.45) |
| 3f | -4-OH- 3-$OCH_3$ | $C_{26}H_{23}N_3O_4S_2$ | 80 | 135 | 61.74 (61.76) | 8.29 (8.31) | 4.56 (4.59) |
| 3g | -4-OH | $C_{25}H_{21}N_3O_3S_2$ | 82 | 128 | 63.12 (63.14) | 8.83 (8.84) | 4.43 (4.45) |
| 3h | -4-$N(CH_3)_2$ | $C_{27}H_{26}N_4O_2S_2$ | 79 | 152 | 64.51 (64.25) | 11.13 (11.15) | 5.19 (5.21) |
| 3i | -4-$OCH_3$ | $C_{25}H_{20}ClN_3O_2S_2$ | 77 | 144 | 60.78 (60.77) | 8.49 (8.51) | 4.06 (4.08) |
| 3j | -3-$NO_2$ | $C_{26}H_{23}N_3O_3S_2$ | 80 | 142 | 63.72 (63.78) | 8.54 (8.58) | 4.71 (4.73) |

## RESULTS AND DISCUSSION

### Antibacterial activity

### Against escherichia coli

From screening results, substituted derivatives 2j, 3d and 3e possesses very good activity against Penicillin and Kanamycin. The compounds 2e, 3b and 3h was shown minimum antibacterial activity. 2j and 3j 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 2a, 3c and 3j. The minimum antibacterial activity was shown by the compound 2g, 2h, 3a and 3g. 3h was found to be inactive against aures. 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 2j, 3a, 3e and 3j. The minimum antifungal activity was shown by the compound 2h and 3g. 2e was found to be inactive against Eschirichia 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 3-{4-[3-(substitutedphenyl) prop-2-enoyl]phenyl}-2-(4-hydroxyphenyl)-1, 3-thiazolidin-4-one.***

| Sr. No. | Comp. No. | R | Zone of Inhibitions in mm | | |
|---|---|---|---|---|---|
| | | | Antibacterial activity | | Antifungal activity |
| | | | E. coli | S. aureus | C. albicans |
| 1 | 2a | -2-Cl | 16 | 20 | 18 |
| 2 | 2b | -4-Cl | 15 | 15 | 18 |
| 3 | 2c | -3,4- $(OCH_3)_2$ | 12 | 12 | 15 |
| 4 | 2d | -H | 11 | 13 | 12 |
| 5 | 2e | -2-OH | 10 | 12 | NA |
| 6 | 2f | -4-OH- 3-$OCH_3$ | 14 | 12 | 13 |
| 7 | 2g | -4-OH | 13 | 11 | 13 |
| 8 | 2h | -4-$N(CH_3)_2$ | 12 | 11 | 11 |
| 9 | 2i | -4-$OCH_3$ | NA | 14 | 13 |
| 10 | 2j | -3-$NO_2$ | 17 | 16 | 20 |

**Table 4:** ***Antimicrobial activities of 2-(4-hydroxyphenyl)-3-{4-[6-(substitutedphenyl)-2-thioxo-1, 2, 5, 6-tetrahydropyrimidin-4-yl]phenyl}-1, 3-thiazolidin-4-one.***

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

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

| Zone of inhibition of standard drugs and solvent | | | | | |
|---|---|---|---|---|---|
| **Sr. no.** | **Comp. no** | **Standrad 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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