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# SYNTHESIS AND EVALUTION OF ANTIMICROBIAL AND ANTIFUNGAL ACTIVITIES OF ANOVEL SERIES OF PYRANZINYL 2- AMINO 1, 3 THIAZOLIDIN – 4- ONES

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## ABSTRACT
In this study, Synthesis and pharmacological screening of various derivatives of pyranzinyl 2- amino 1,3 thiazolidin – 4- ones were reported. These compounds (4a-4l) were synthesized by cyclization of bezylidine arylidine acetohydrazidopyrazine derivatives (3a-3l) with thioglycolic acid in presence of anhydrous zinc chloride catalyst. The structure of newly synthesized supported by IR, 1H NMR and elemental analysis. These compounds were testedin vivo for their antimicrobial and antifungal activities. Some of newly synthesized compounds (4j & 4k) showed good antimicrobial activity against both gram + ve and gram –ve microorganism whereas rest of the compounds (4a,b,c,d,e,f.g.h,i & l) show moderate activity against all the organisms. On the other hand, in the study of antifungal activity, compounds (4h,4i & 4j) showed highest activity against both the organisms, while other compounds show moderate activity.

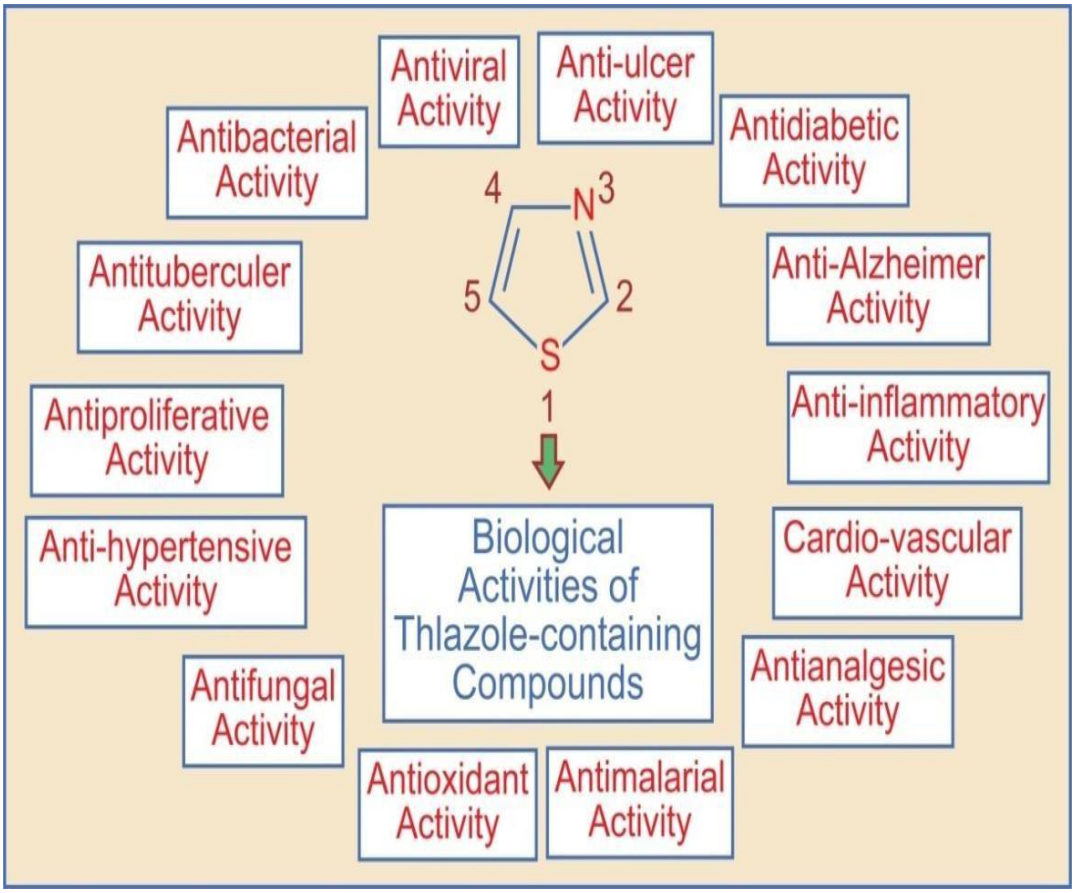
**KEYWORDS:** Thiazolidiones, Pyrazine, Antimicrobial activity, Antifungalactivity.

## INTRODUCTION
Thiazoles or 1, 3- thiazoles are one of the most intensively scrutinized classes of 5-membered aromatic heterocyclic compounds containg sulphur and nitrogen as hetero atoms.

Many natural and synthesized thiazole and its derivatives showed significant biological and pharmacological activity.[1,2] Thiazole derivatives are actually a considerable group of heterocyclic compound that have therapeutic effects against several diseases.[3,4] The most pertinent and modern studies have manifested that these molecules display antifungal, antibacterial,[5] anti-inflammatory,[6] analgesic,[7] and anti-canceractivities. Many patents have been registered for thiazole compounds with antimicrobial activity.[8,9] Thus, many researchers have become interested in the synthesis of molecules containing more than one thiazole moiety.[10,11] Owing to their versatile chemotherapeutic[12,13] importance significant amounts of research effort has been focoused on this nuclei.

In this context, literature survey reveals that 4-Thiazolidinones and its derivatives are known to possess a variety of pharmacological properties like antituberculosis.[14] antifungal,[15] antimicrobial,[16] antitumor[17a-c] activities.

In view of the above discussion, it was thought worthwhile to explore some pyrazine derivaties bearing thiazolidinone moiety and screened for their promising biological activity i.e. antibacterial and antifungal activity.



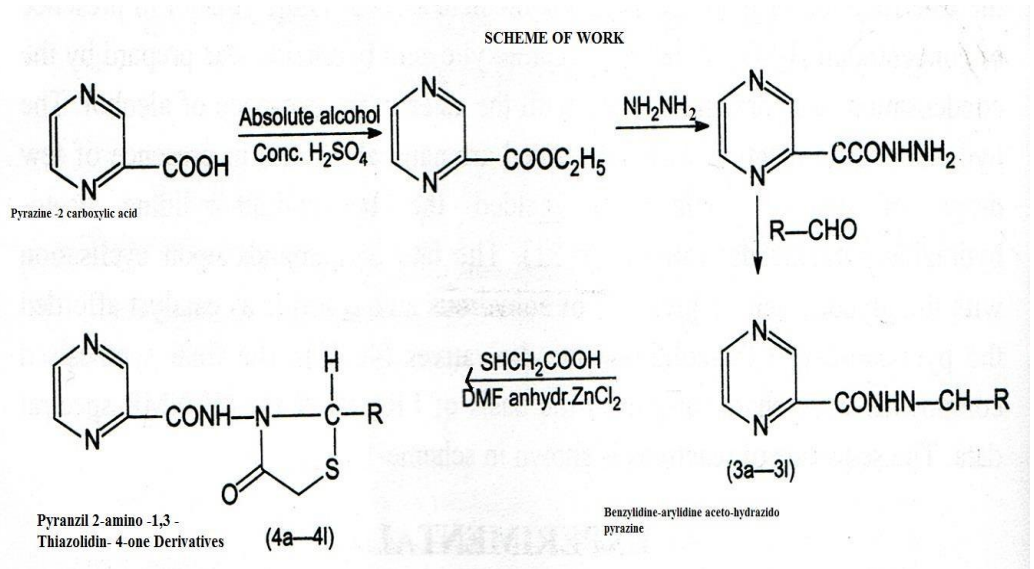

**Experimental section**

**Materials: -** Solvents are carried of S.D fine chem. and E. Merck grade, were purified and dried by conventional method.[18] All other chemicals of S.D. Fine Chem and E. Merck grade have checked for their purity before use.

The homogeneity and purity of the compounds were checked over thin layer chromatography coated with silica Gel – G (thickness 0.5 mm) developing solvent acetone /DMF (3:1) non saturated chamber at room temp ($20\pm 1^0$c).

The melting points of the synthesized compounds were determined by capillary method and were uncorrected. The IR spectra (in KBr) were recorded on JASCO FI-IR spectrophotometer. $^1$NMR spectra (DMSO/$CDCl_3$) were taken on VRO – 300 MHZ spectrophotometer and chemical shift expressed as ppm and TMS was used as internal standard.

SCHEME OF WORK



**Experimental method**

**A. Synthesis of pyrazine -2- carbohydrazide**

A mixture containing pyrazine -2- carboxylic acid ethyl ester (0.1 mol) hydrazine hydrate (99%) (0.1 mol), absolute alcohol was refluxed on water bath for 4 hours. Excess of solvent was removed through distillation and reacting contents was poured into ice cold water. The colourless solid mass is obtained, which is filtered, dried and washed with hot water. Recrystallise the product from ethanol.

Yield: 80%, M.P. $165^0$ C, IR (KBr) (in $Cm^{-1}$) 1615 (C=N), 1670 (C=N), 3050 (-CH of pyrazine)

**B. Synthesis of benzylidine – arylidine aceto-hydrazido pyrazine (3a-3l)**

Mixture of hydrazide (0.01 mol), substituted aldihyde (0.01 mol), 30 ml ethanol and few drops of acetic acid was refluxed for about 6 hours after completion of reaction, the reacting contents was poured into ice cold water resulting in the formation of solid mass, which was filtered, dried and washed with water. The product was recrystallised from ethanol.

**Physical data of compound (3a-3l)**

| Compound | Substituted (R) Benzaldehyde | % yield | M.P. ( $^oC$ ) | Colour |
|---|---|---|---|---|
| 3a | H | 65 | 151 | White |
| 3b | 4-$OCH_3$ | 68 | 110 | White shining |
| 3c | 3,4,5-$OCH_3$ | 70 | 190 | Dull white |
| 3d | 4-$(CH_3)_2N$ | 65 | 140 | Light yellow |
| 3e | Furfural | 62 | 158 | White |
| 3f | 3-OH, 4-$OCH_3$ | 70 | 116 | Brownish white |
| 3g | 4-Cl | 65 | 168 | White |
| 3h | 4-$NO_2$ | 70 | 177 | Pale yellow |
| 3i | 3,4 – $OCH_3$ | 68 | 134 | White |
| 3j | 2,4 -Cl | 72 | 146 | White powdered |
| 3k | 2-OH | 65 | 118 | White |
| 3l | 4-$CH_3$ | 68 | 100 | White shining |

**Spectral data**

**3k: IR (KBr) (in $Cm^{-1}$)**: 3060 (CH-Ar), 2905 (C-H), 1658 (C=O), 1600 (C=C),

**$^1$H NMR ($CDCl_3$) (δ in ppm):** 6.8-9.2 (m, 8H, Ar-H, Ar-CH), 2.2-5.5 (s, 1H, OH), 12.0 (s, 1H,CONH), MS : m/z 241

**3i: IR (KBr) (in $Cm^{-1}$)**: 3220 (CH-Ar), 3060 (C-H0, 1675 (C=O), 1595 (C=C)

**$^1$H NMR ($CDCl_3$) (δ in ppm): 3**.80 (m, 3H, $OCH_3$), 3.84 (s,CH,$OCH_3$),6.87-9.2 (m, 8H, Ar-H, Ar-CH), 11.90 (s, 1H, CONH**)**

MS: m/z 285 [$M^+$](65);196(100)

**C. Synthesis of Pyranzinyl – 2-Amino-1, 3 Thiazolidin-4-one Derivatives (4a-4l)**

A mixture containing Schiff base (0.01 mol), DMF (20 ml) and pinch of anhydrous zinc chloride was refluxed on water bath for 12 hours. After completion of reaction, the mixture was cooled and poured into ice cooled water resulting the formation of solid mass. The product was filtered, dried and washed with water. So obtained producted was recrystallised from ethanol.

**Physical data of compound (3a-3l)**

| Compound | Substituted (R) Benzaldehyde | % yield | M.P. ( $^oC$ ) | Colour |
|---|---|---|---|---|
| 4a | H | 60 | 168 | Colourless |
| 4b | 4-$OCH_3$ | 62 | 190 | White |
| 4c | 3,4,5-$OCH_3$ | 65 | 175 | White amorphous |
| 4d | 4-$(CH_3)_2N$ | 55 | 186 | Pale yellow |
| 4e | Furfural | 54 | 148 | Light white |
| 4f | 3-OH, 4-$OCH_3$ | 65 | 212 | White |
| 4g | 4-Cl | 55 | 265 | White |
| 4h | 4-$NO_2$ | 60 | 215 | Yellow |
| 4i | 3,4 – $OCH_3$ | 58 | 197 | White |
| 4j | 2,4 -Cl | 68 | 234 | White powdered |
| 4k | 2-OH | 60 | 218 | Brown |
| 4l | 4-$CH_3$ | 70 | 235 | Brownish yellow |

**4h: IR (KBr) (in $Cm^{-1}$)**: 3090 (CH-Ar), 2990 (C-H), 1716 (C=O), 1575 (C=N),
**$^1$H NMR (CDCl3) (δ in ppm):** 3.5 (s, 1H, CH), 4.9(s, 2H, S-$CH_2$), 7.9-8.5 (m, 8H, Ar-H), 9.4( s, 1H, CONH) MS : m/z 344 [$M^+$] (75): 260(100), 214(54)
**4i: IR (KBr) (in $Cm^{-1}$)**: 3110 (CH-Ar), 2970 (C-H), 1710 (C=O), 1595 (C=N), 1520 &
1340 ($NO_2$)

**$^1$H NMR (CDCl3) (δ in ppm):** 3.8 (m, 3H, OCH3), 3.5 (s, 1H, CH), 4.8 (s, 2H, S-$CH_2$), 7.4-8.0 (m, 7H, Ar-N), 9.0 (s, 1H, CONH) MS: m/z 329[$M^+$](60) : 243(100), 195(78)
**4k: IR (KBr) (in $Cm^{-1}$)**: 3085 (CH-Ar), 2990 (C-H), 1725 (C=O), 1585 (C=N),
**$^1$H NMR ( DCl3)(δ in ppm) :** 3.6 (m, 1H,CH ), 4.8(s, 2H, S-$CH_2$), 7.6-8.3( m, 8H, Ar-N), 8.7(s, 1H, CONH) MS: m/z 299[$M^+$](45) : 220(32), 177(100)

**Biological activity**

The in vitro antimicrobial activity of the synthesized derivatives was evaluated against *E. coli, P. aeruinosa* (Gram-negative bacteria); *Bacillus subtilis*, *S. aureus*, *B.subtils*, (Gram- positive bacteria) by using disc diffusion method [19-22]. Serial dilutions of the testing compounds and reference drugs were prepared in Muller –Hinton Agar. The stock solutions of standard drugs (10 ml) were prepared in dimethyl sulfoxide (DMSO) (1ml) and progressive dilution with melted Mullet-Hinton Agar were performed to obtain the required concentration of 1,2,4,8,16,31,62.5,125,250 and 500µg/ml. The tubes were inoculated with 105 cfu/Ml (colony forming unit/mL),. The bacterial cultures were incubated for a period of 24 h at 37 ± 2 °C. The lowest concentration (higest dilution) required to arrest the growth of bacteria was regarded as minimum inhibitory concentration (MIC). The results of antimicrobial activity were stated in terms of minimum inhibitory concentration (MIC).Ciprofloxacin and Grisesofulvin were used as standard drugs for antimicrobial and antifungal activity respectively.

**RESULT AND DISCUSSION**

A novel series of 4- Thiazolidinone derivatives were prepared by the cyclization of bezylidine arylidine aceto hydrazide pyrine derivatives with thioglycolic acid in presence of anhydrous $ZnCl_2$, while Schiff bases (3a-3l) were derived from pyrazine-2-carboxylic acid hydrazide which is subsequently condensed with substituted in presence of few drops of glacial acetic acid. The newly synthesised compounds were characterised by elematal analysis, I.R. and N.M.R. spectroscopy.

The newly synthesised compounds were screenrd for their promising antimicrobial and antifungal activity which is expressed as minimum inhibitory concentration(MIC) (table -3).

Antimicrobial and anti fungal activity of newly synthesised compoundswere evaluated, which showed antimicrobial activity at MIC – values 8.500 µg/mL, copound 4i was found to be more active than other compounds at an MIC – 8 µg/mL. The synthesised compounds showed antimicrobial activity with MIC values between 33.25 -500 µg/mL. Copond 4j and 4k showed good antibacterial activity against both gram +ve and gram –ve micro organisms, whereas rest of synthesised compounds showed moderate activity against all the given organisms. In the study of antifungal activity of synthesised compounds, it was found that compounds 4h,4i and 4j highest activity against both the fungal organisms while other compounds showed moderate activity.

**Antimicrobial and Antifungal activity of newly synthesised compounds (4a-4l)**

| Compounds | MIC of synthsised Thiazolidinone Derivaties | | | | | |
|---|---|---|---|---|---|---|
| | ***S.aureus*** | ***B.subtills*** | ***E.coli*** | ***P.aerugionosa*** | ***C.albisans*** | ***A.niger*** |
| 4a | 63.6 | 125 | 65 | 125 | 250 | 33.25 |
| 4b | 124 | 254 | 33.25 | 125 | 255 | 65 |
| 4c | 257 | 11 | 125 | 287 | 125 | 65 |
| 4d | 30.25 | 65 | 125 | 247 | 500 | 125 |
| 4e | 254 | 127 | 255 | 33.25 | 500 | 125 |
| 4f | 121 | 252 | 255 | 65 | 255 | 250 |
| 4g | 497 | 121 | 125 | 125 | 125 | 250 |
| 4h | 501 | 252 | 33.25 | 250 | 33.25 | 33.25 |
| 4i | 36.25 | 33.45 | 125 | 64.5 | 64.5 | 64.5 |
| 4j | 33.5 | 33.45 | 125 | 65 | 65 | 64.5 |
| 4k | 75.5 | 33.45 | 64.5 | 125 | 33.25 | 125 |
| 4l | 127 | 251 | 255 | 125 | 33.25 | 125 |
| Ciprofloxacin | 33.25 | 33.25 | 64.5 | 64.5 | ..... | .... |
| Griseofulvin | .... | ..... | ..... | ..... | 33.25 | 64.5 |
| Control (DMSO) | ..... | ..... | .... | ..... | ..... | ..... |

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