Design, Synthesis and Antimicrobial Activity of 2-Aromatic Substituted-1,3-Thaizolidine Derivatives

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ABSTRACT
A series of N-[(2-(substituted methylidene)hydrazinyl)(methylsulfanyl)methyl]-2-substituted-1,3-thiazolidine-4-carboxamide derivative were synthesized. The synthesized compounds were characterized by IR, NMR, Mass spectral data. The synthesized compounds were screened for their antifungal and antibacterial activity against pathogenic fungus and bacteria. Compounds TS-2, TS-4 and TS-9 exhibited good antibacterial and antifungal activity against the tested microorganisms, and the rest of the molecules shows good to moderate activity.

Keywords: substitute thiazolidine, microwave assisted synthesis, minimum inhibitory concentration, antibacterial, antifungal.

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INTRODUCTION

Thiazolidine derivatives containing aromatic ring plays an important role in modern medicinal chemistry, showing a wide range of biological activities such as antimicrobial, analgesic, antitubercular, antidepressant, anticancer, anti-inflammatory, anticonvulsant, hypolipidemic, analgesic, immunotropic activities and NPY receptor ligands binding. The prevalence of aromatic substituted thiazolidine cores in biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic lead thiazolidine as an important class of compounds for new drug development attracting much attention. The inevitable consequence of the widespread use of antimicrobial agents has been the emergence of antibiotic-resistant pathogens, fuelling an ever increasing need for new drugs. Several aromatic substituted thiazolidine derivatives have been synthesized as target structures and evaluated for their biological activities. The cytotoxicity of the reported compounds in the review indicate good safety associated with many of the thiazolidine derivatives[1-5].

Literature Review

Pandey et al [6] derived a series of Schiff base and Mannich bases, prepared from isatin. The synthesized compounds were evaluated for Antimicrobial activity by agar diffusion method.

Ranjana et al [7] prepared a series of phthalimido [ 2-aryl-3-(5′-(4′-pyridyl)-1′,3′,4′-thiadiazol-2′-yl)-4-oxothiazolidin-5-yl] ethanoates. The synthesized compounds were analyzed for antimicrobial activity against Escherichia coli, Proteus vulgaris, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhi and Bacillus subtilis bacterial strains by cup or well method.
Meltem Ceylan et al \[8\] prepared 3-(substituted-benzyl)-5-(4-chloro-2-piperidin-1yl-thiazole-5-ylmethylene)-thiazolidine-2,4-dione derivatives and evaluated their antimicrobial activity against *Staphylococcus aureus* ATCC 250 and *Escherichia coli*.

![Chemical structure](image)

Bhoot D. P. et al \[4\] prepared a series of 2-arylimino-3-aryl-5-[5'-(3,4-dichlorophenyl)-2'furylidene]-4-thiazolidinones and analyzed their antimicrobial activity against *E. coli*, *P. vulgaris*.

![Chemical structure](image)

Sharma M. C. et al \[9\] prepared a series of N-(5-methyl-4-oxo-thiazolidin-3-yl)-nicotinamide and analyzed the antimicrobial activity against *B. subtilis*, *S. aureus*, *E. coli*, *A. niger* and *C. albicans*.

![Chemical structure](image)

**Aim and Objective**

The purpose of the present work was to explore and develop novel molecules with improved potential for treating microbial infections. In this paper we report the design, synthesis and evaluation of antimicrobial activity of 2-aromatic substituted-1,3-thiazolidine-4-carboxamide derivatives.
MATERIALS AND METHOD

Synthesis of methyl thiourea from thiourea (T1)\[10\]
Thiourea (10g, 131mmol, 1meq) was dissolved in 100ml of methanol. Methyl iodide (8.21ml, 131mmol, 1meq) was added to the reaction mixture and refluxed for 1h. After completion of the reaction, solvent was evaporated to yield crude product. This crude product was washed thrice with diethyl ether to yield the desired product as white solid.

Synthesis of N-tert-butoxycarbonyl methyl thiourea (T2)\[10\]
A solution of BOC\(_2\)O (18.65g, 124mmol, 1meq) in 50ml DCM was slowly added to a solution of methyl thiourea (T1, 28.0g, 128.0mmol, 1meq) and Triethylamine (17.4ml, 124mmol, 1meq) in 200 ml DCM. After stirring for 20h at room temperature, the reaction mixture was washed with water and brine and the organic phase was dried over magnesium sulphate. The solvent was evaporated under reduced pressure and crude product was formed.

Synthesis of 2-Substituted-thiazolidine-4-carboxylic acid (T3)\[12\]
A mixture of L-cysteine (3.16g, 26.11mmol) and appropriate aldehydes (26.15mmol) in ethanol (300ml) and water (30ml) was stirred at room temperature for 6-15h, and the solid precipitated out was collected, washed with diethyl ether and dried to afford according (2RS, 4R)-2-aryl-thiazolidine-4-carboxylic acid.

Synthesis of N-(amino(methylthio)methyl)-2-substituted thiazolidine-4-carboxamide (T4)\[11\]
A mixture of 2-Substituted-thiazolidine-4-carboxylic acid (T3, 0.3-0.5g), DCC (1.2meq) and HOBT (1.05 meq) in DCM (200ml) was stirred at room temperature for 10min. To this solution, tert-butyl amino(methylthio)methyl carbamate (1.05meq) and Triethyl amine (1.2 meq) were added and stirring continued at room temperature for 12-16h. The reaction mixture was diluted with DCM (50ml) and sequentially washed with water, satd. Sodium bicarbonate, brine and dried over magnesium sulphate. The solvent was removed under reduced pressure to yield tert-butyl (2-substituted thiazolidine-4-carboxamido) (methylthio)methylcarbamate as crude product, which were stirred with TFA (0.6-1.0l) in 20ml DCM at room temperature for 1-8h to cleave the BOC group. The reaction mixture was concentrated, washed with satd. Sodium bicarbonate and the solvent was removed to yield crude solid.

Synthesis of 2-substituted-[hydrazinyl(methylsulfanyl)methyl]-1,3-thiazolidine-4-carboxamide (T5)\[13\]
Conventional Method:
Concentrated HCl was added dropwise with stirring to hydrazine hydrate which was previously maintained at a temperature of 5-25°C followed by ethylene glycol (25ml). To the above reaction mixture N-(amino(methylthio)methyl)-2-substituted thiazolidine-4-carboxamide (T4, 0.01mol) was added in small portions. The mixture was then refluxed for 2h and then poured into crushed ice. The separated solid was then filtered and recrystallized from ethanol.

**Microwave Method:**

Concentrated HCl was added dropwise with stirring to hydrazine hydrate which was previously maintained at a temperature of 5-25°C followed by ethylene glycol (22ml). To the above reaction mixture N-(amino(methylthio)methyl)-2-substituted thiazolidine-4-carboxamide (T4, 0.01mol) was added in small portions. The mixture was charged under microwave for 6 minutes and allowed to cool, poured into crushed ice. The separated solid was then filtered and recrystallized from ethanol.

**Synthesis of N-{[2-(substituted methylidene)hydrazinyl](methylsulfanyl)methyl}-2-substituted-1,3-thiazolidine-4-carboxamide (TS i-xxiv)**

**Conventional Method:**

To a solution of substituted aldehydes (0.01 mol) in methanol/ethanol (15ml), compound (T5, 0.01mol) was added along with few drops of acetic acid and the mixture was refluxed for 3h. The reaction mixture was cooled, then poured into ice-cold water and the separated solid was filtered, dried and recrystallized from ethanol.

**Microwave Method:**

To a solution of substituted aldehydes (0.01mol) in methanol/ethanol (15ml), compound (T5, 0.01mol) and a few drops of acetic acid were added and the mixture was charged under microwave for 6-7 minutes. The reaction mixture was cooled, poured into ice-cold water and the separated solid was filtered, dried and recrystallized from ethanol.

**RESULTS AND DISCUSSION:**

In the present study, various 2-aromatic substituted-1,3-thiazolidine derivatives were synthesized. The structure of the synthesized compounds were confirmed by IR, NMR, Mass spectral data. The IR spectrum of all the synthesized compounds show bands in the region of 3150-3302 cm\(^{-1}\) and 1450- 1750 cm\(^{-1}\) corresponding to NH and C=O. The IR spectrum in the region of 2950 to 3100 cm\(^{-1}\) shows the presence of C-H in aliphatic and aromatic ring respectively. All the synthesized compounds show bands in the region of 1100 to 1400 cm\(^{-1}\) showing the presence of C-CH\(_3\), Ar C=C and mono substituted phenyl ring. The NMR spectrum
of all the compounds shows characteristic peak of for CH$_2$ at 2.8 δ ppm, the NH$_2$ protons at 3.8 δ ppm, for aromatic protons multiplet appears at 1.3 to 7.6 δ ppm. The Mass spectra of the synthesized compounds were found to be corresponding with its m/z mass. The synthesized compounds were screened for their in-vitro antimicrobial activity against various bacteria species like *Salmonella paratyphi*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Bacillus subtilis*, *Micrococcus luteus*, *Staphylococcus aureus*, *Klebsiella pneumonia*, *Staphylococcus albus* and various fungal organisms like *Aspergillus niger*, *Aspergillus fumigatus*, *Candida albicans* and *Monascus purpureus*. Among the synthesized 2-substituted thiazolidine derivatives, compound **TS-2**, **TS-4** and **TS-9** shows good activity against both bacterial and fungal organisms with MIC value of 3.12 µg/ml.

**TS-i:** M.P.(°C): 178-180; IR spectral values (cm$^{-1}$): 3418.21 (NH$_2$ stretching), 2919.22 (CH$_3$ stretching Ali), 1686.93 (C=N stretching), 1489.7 (C=C stretching), 1462.7 (C=O stretching), 1380.78 (C-H bending in Ali), 1204.33 (C-N stretching), 1086.12 (N-N stretching), 756.38 (C-Cl in Ar), 824.3 (C-S stretching).

**TS-ii:** M.P.(°C): 182-184; IR spectral values (cm$^{-1}$): 3419.17 (NH$_2$ stretching), 2922.11 (CH$_3$ stretching Ali), 1489.7 (C=N stretching), 1382.23 (C-N stretching), 750.3 (C-Cl in Ar), 759.3 (monosub ring), 825.8 (C-S stretching); 1H NMR: 2.5 (s, H, NH), 6.9 (s, 1H, Ar group), 7.8-7.9 (m, 3H, ArH), 7.9 (m, 3H, thiazolidine); Mass (m/z): M-1=418.

**TS-iii:** M.P.(°C): 177-179; IR spectral values (cm$^{-1}$): 3419.17 (OH stretching), 2919.22 (CH$_3$ stretching Ali), 1685.96 (C=N stretching), 1489.7 (C=O stretching), 1382.71 (C-N stretching), 1204.33 (N-N stretching), 693.0 (C-Cl in Ar), 733.69 (disub ring), 870.36 (C-S stretching).

**TS-iv:** M.P.(°C): 184-186; IR spectral values (cm$^{-1}$): 3328.53 (NH$_2$ stretching), 2923.56 (CH$_3$ stretching Ali), 1685.96 (C=N stretching), 1627.63 (C=C stretching), 1576.52 (C=O stretching), 1380.3 (C-H bending in Ali), 1313.2 (C-N stretching), 1204.3 (N-N stretching), 668.69 (C-Cl in Ar), 894.7 (C-S stretching).

**TS-v:** M.P.(°C): 188-190; IR spectral values (cm$^{-1}$): 3446.17 (NH$_2$ stretching), 2925.0 (CH$_3$ stretching Ali), 1684.5 (C=N stretching), 1627.14 (C=C stretching), 1576.04 (C=O stretching), 668.69 (C-Cl in Ar).

**TS-vi:** M.P.(°C): 168-170; IR spectral values (cm$^{-1}$): 3412.9 (NH$_2$ stretching), 3067.23 (CH stretching in Ar), 2927.0 (CH$_3$ stretching Ali), 1718.75 (C=N stretching), 1627.14 (C=C stretching), 1563.02 (C=O stretching), 1379.3 (C-H bending in Ali), 1233.74 (C-N stretching), 1092.96 (N-N stretching), 643.14 (C-Cl in Ar).
**TS-vii**: M.P.(°C): 192-194; IR spectral values (cm⁻¹): 3328.59 (NH₂ stretching), 2927.41 (CH₃ stretching Ali), 1627.6 (C=N stretching), 1574.5 (C=C stretching), 1486.2 (C=O stretching), 1312.1 (C-N stretching), 1088.62 (N-N stretching), 641.25 (C-Cl in Ar), 886.71 (C-S stretching).

**TS-viii**: M.P.(°C): 182-184; IR spectral values (cm⁻¹): 3328.53 (NH₂ stretching), 2927.41 (CH₃ stretching Ali), 1575.08 (C=N stretching), 1538.4 (C=C stretching), 1574 (C=O stretching), 1439.71 (C-N stretching), 892.39 (C-S stretching).

**TS-ix**: M.P.(°C): 192-194; IR spectral values (cm⁻¹): 3327.67 (NH₂ stretching), 2924.5 (CH₃ stretching Ali), 1718.26 (C=N stretching), 1627.6 (C=C stretching), 1239.04 (C-N stretching), 775.24 (C-F in Ar).

**TS-x**: M.P.(°C): 184-186; IR spectral values (cm⁻¹): 3379.6 (OH stretching), 3025.76 (CH stretching in Ar), 2927.86 (CH₃ stretching Ali), 1576.04 (C=N stretching), 1622.04 (C=C stretching), 1088.14 (N-N stretching), 641.25 (C-Cl in Ar), 842.74 (C-S stretching); 1H NMR (δ values): 12.8 (bs, 1H, NH); 8.5 (bs, 1H, CONH); 7.9 (s, 1H, CH=N); 7.0 - 7.6 (m, 10H, Ar-H); 3.3 (s, 2H, CH2); 1.8 (s, 2H, Thiazolidine-CH₂); Mass (m/z): M-2=450.

**TS-xi**: M.P.(°C): 192-194; IR spectral values (cm⁻¹): 3114.47 (Ar C-H stretching), 1608.34 (C=N in Ar), 1525.42 (C=C stretching), 1348.96 (NO₂ stretching), 1103.08 (S-H bending), 820.16 (di subs benzene), 718.35 (C-Cl stretching).

**TS-xii**: M.P.(°C): 188-190; IR spectral values (cm⁻¹): 3181.9 (NH₂ stretching), 2921.63 (CH₃ stretching Ali), 1599.6 (C=O stretching), 1396.14 (C-H bending in Ali), 1290.14 (C-N stretching), 1027.8 (N-N stretching), 744.3 (C-Cl in Ar), 854.3 (C-S stretching).

**TS-xiii**: M.P.(°C): 202-204; IR spectral values (cm⁻¹): 3414.55 (OH stretching), 3114.47 (NH₂ stretching), 3041.1 (CH stretching in Ar), 2927.89 (CH₃ stretching Ali), 1628.11 (C=N stretching), 1575.6 (C=C stretching), 1522.62 (C=O stretching), 1386.7 (C-N stretching), 1046.13 (N-N stretching), 848.04 (disub ring), 892.3 (C-S stretching).

**TS-xiv**: M.P.(°C): 198-200; IR spectral values (cm⁻¹): 3414.55 (OH stretching), 3337.5 (NH₂ stretching), 3056.6 (CH stretching in Ar), 2925.4 (CH₃ stretching Ali), 1718.2 (C=N stretching), 1627.8 (C=C stretching), 1582.31 (C=O stretching), 1379.82 (C-H bending in Ali), 1244.83 (C=N stretching), 1086.12 (N-N stretching), 1453.1 (N=O stretching), 759.6 (disub ring), 889.9 (C-S stretching).

**TS-xv**: M.P.(°C): 184-186; IR spectral values (cm⁻¹): 3435.56 (OH stretching), 3114.47 (NH₂ stretching), 1532.12 (C=N stretching), 1482.2 (C=C stretching), 1340.2 (C-N stretching), 1039.4 (N-N stretching), 773.31 (C-Cl in Ar), 846.59 (disub ring), 911.2 (C-S stretching).
TS-xvi: M.P.(°C): 188-190; IR spectral values (cm⁻¹): 3181.9(NH₂ stretching), 2921.63(CH₃ stretching Ali), 1599.6(C=O stretching), 1396.14(C-H bending in Ali), 1290.14(C-N stretching), 1027.8(N-N stretching), 744.3(C-Cl in Ar), 854.3(C-S stretching).

TS-xvii: M.P.(°C): 192-194; IR spectral values (cm⁻¹): 3326.12 (NH₂ stretching), 3025.7 (CH stretching in Ar), 2926.9 (CH₃ stretching Ali), 1744.3 (C=N stretching), 1628.1 (C=C stretching), 1576.04 (C=O stretching), 1312.8 (C-N stretching), 1092.9 (C-O-C stretching), 641.2 (disub ing), 894.8 (C-S stretching).

TS-xviii: M.P.(°C): 184-186; IR spectral values (cm⁻¹): 3416.46 (OH stretching), 3213.79 (NH₂ stretching), 3035.4 (CH stretching in Ar), 1650 (C=N stretching), 1517.7 (C=C stretching), 1340.28 (C=S stretching), 1399.1 (C-N stretching), 1108.8 (C-O-C stretching), 852.38 (C-S stretching).

TS-xix: M.P.(°C): 168-170; IR spectral values (cm⁻¹): 3327.57 (NH₂ stretching), 2927.41 (CH₃ stretching Ali), 1723.09 (C=N stretching), 1628.5 (C=C stretching), 1572.8 (C=O stretching), 1327.7 (C=S stretching), 1259.2 (C-N stretching), 1040.8 (C-O-C stretching), 756.64 (disub ing), 889.0 (C-S stretching).

TS-xx: M.P.(°C): 192-194; IR spectral values (cm⁻¹): 3420.14 (NH₂ stretching), 3100.0 (CH stretching in Ar), 1629.55 (C=N stretching), 1541.8 (C=O stretching), 1422.8 (C=S stretching), 1346.05 (C-N stretching), 1107.0 (C-O-C stretching), 722.21 (C-Cl in Ar), 851.4 (disub ring), 927 (C-S stretching).

TS-xxi: M.P.(°C): 196-198; IR spectral values (cm⁻¹): 3413.3 (OH stretching), 3327.5 (NH₂ stretching), 3067.23 (CH stretching in Ar), 2927.41 (CH₃ stretching Ali), 1718.2 (C=N stretching), 1626.8 (C=C stretching), 1573.6 (C=O stretching), 1371.03 (C-N stretching), 1191.7 (C-O-C stretching), 775.3 (disub ring).

TS-xxii: M.P.(°C): 188-190; IR spectral values (cm⁻¹): 3244.6 (NH₂ stretching), 2926.4 (CH₃ stretching Ali), 1712.4 (C=N stretching), 1624.7 (C=C stretching), 1563.02 (C=O stretching), 1343.86 (C-N stretching), 1113.69 (C-O-C stretching), 769.45 (disub ring).

TS-xxiii: M.P.(°C): 184-186; IR spectral values (cm⁻¹): 3413.3 (NH₂ stretching), 3062.4 (CH stretching in Ar), 2926.45 (CH₃ stretching Ali), 1718.2 (C=N stretching), 1627.1 (C=C stretching), 1562.05 (C=O stretching), 1374.03 (C-H bending in Ali), 1238.5 (C-N stretching), 1046.1 (C-O-C stretching), 889.5 (C-S stretching).

TS-xxiv: M.P.(°C): 192-194; IR spectral values (cm⁻¹): 3416.28 (OH stretching), 3208.7 (NH₂ stretching), 3073.01 (CH stretching in Ar), 2958.27 (CH₃ stretching Ali), 1728.87 (C=N
stretching), 1640.16 (C=C stretching), 1561.09 (C=O stretching), 1388.0 (C=S stretching), 1251.54 (C-N stretching), 1088.27 (C-O-C stretching), 884.20 (C-S stretching).

Scheme:

\[
\text{thiourea} \xrightarrow{\text{CH}_2\text{I}} \text{(methylthio)methanediamine} \xrightarrow{\text{CH}_3\text{OH, Reflux H}_2\text{N}} \text{di-tert-butyl dicarbonate} \\
\text{T1} \xrightarrow{\text{BOC2O, Et}_3\text{N, DCM, stirring}} \text{tert-butyl amino(methylthio)methylcarbamate} \xrightarrow{\text{T2}} \text{R-CHO, ethanol, H}_2\text{O, stirring 7-15hrs} \xrightarrow{\text{substituted thiazolidine-4-carboxylic acid}} \text{T3} \\
\text{L-Cysteine} \xrightarrow{\text{H}_3\text{C}} \text{N-(amino(methylthio)methyl)-2-substituted thiazolidine-4-carboxamide} \xrightarrow{\text{T4}} \text{tert-butyl (2-substituted thiazolidine-4-carboxamido)(methylthio)methylcarbamate}
\]

EDC.HCl, HOBT, Et3N, DCM stirring 8-12hrs.
\[ N-(\text{amino(methylthio)methyl})-2\text{-substituted thiazolidine-4-carboxamide} \]

\[ \text{NH}_2\text{NH}_2\cdot\text{HCl, ethylene glycol, MVI-5-8 min.} \]

\[ 2\text{-substituted-[hydrazinyl(methylsulfonyl)methyl]-1,3-thiazolidine-4-carboxamide} \]

\[ \text{R}_1\cdot\text{CHO, ethanol, glacial.CH}_3\text{COOH, MVI-5-8 min, 180W.} \]

\[ N\{[2-(substituted methylidene)hydrazinyl(methylsulfonyl)methyl]-2-substituted -1,3-thiazolidine-4-carboxamide} \]
Table 1: General structure and physical data of synthesized compounds.

| Compd | R    | R1        | R2 | Mol. Formula       | Mol. Weight | cLog P |
|--------|------|-----------|----|--------------------|-------------|--------|
| TS-1   | 4-Cl-C₆H₄- | 4-Cl-C₆H₄- | -H | C₁₉H₂₀N₁O₂S₂Cl₂   | 454.02      | 3.879  |
| TS-2   | 4-Cl-C₆H₄- | C₆H₅-     | -H | C₁₉H₂₁N₁O₂S₂Cl   | 420.08      | 3.05   |
| TS-3   | 4-Cl-C₆H₄- | 2-OH-C₆H₄- | -H | C₁₉H₂₁N₁O₂S₂Cl   | 436.08      | 1.47   |
| TS-4   | 4-Cl-C₆H₄- | 4-OCH₃-C₆H₄- | -H | C₂₀H₂₃N₁O₂S₂Cl₂  | 450.10      | 3.49   |
| TS-5   | 4-Cl-C₆H₄- | 3,4-di-OCH₃-C₆H₅- | -H | C₂₁H₂₅N₁O₂S₂Cl   | 480.11      | 3.17   |
| TS-6   | 4-Cl-C₆H₄- | 4-CH₃-C₆H₄- | -H | C₂₀H₂₃N₁O₂S₂Cl₂  | 434.10      | 3.55   |
| TS-7   | 4-Cl-C₆H₄- | -H         | -CH₃ | C₂₀H₂₃N₁O₂S₂Cl₂ | 434.10      | 3.17   |
| TS-8   | 4-Cl-C₆H₄- | 4-OCH₃-C₆H₄- | -CH₃ | C₂₁H₂₅N₁O₂S₂Cl₂ | 464.11      | 3.94   |
| TS-9   | 4-Cl-C₆H₄- | 4-F-C₆H₄-  | -CH₃ | C₂₀H₂₂N₁O₂ClF    | 452.09      | 4.06   |
| TS-10  | 4-Cl-C₆H₄- | 2-OH-C₆H₄- | -CH₃ | C₂₀H₂₃N₁O₂S₂Cl₂  | 450.10      | 2.34   |
| TS-11  | 4-Cl-C₆H₄- | 4-NO₂-C₆H₄- | -CH₃ | C₂₀H₂₂N₁O₂S₂Cl₂  | 479.09      | 3.66   |
| TS-12  | C₆H₅-   | 4-Cl-C₆H₄- | -H | C₁₉H₂₁N₁O₂S₂Cl   | 420.98      | 3.16   |
| TS-13  | 2-OH-C₆H₄- | 2-OH-C₆H₄- | -CH₃ | C₂₀H₂₄N₁O₂S₂       | 432.13      | 0.91   |
| TS-14  | 2-OH-C₆H₄- | 4-NO₂-C₆H₄- | -CH₃ | C₂₀H₂₃N₁O₂S₂       | 461.12      | 2.23   |
| TS-15  | 2-OH-C₆H₄- | 4-Cl-C₆H₄- | -CH₃ | C₂₀H₂₃N₁O₂S₂Cl₂   | 450.10      | 3.20   |
| TS-16  | 4-OCH₃-C₆H₄- | 4-Cl-C₆H₄- | -H | C₂₀H₂₃N₁O₂S₂Cl₂   | 451.0       | 3.7    |
| TS-17  | 4-OCH₃-C₆H₄- | C₆H₅-     | -H | C₂₀H₂₄N₁O₂S₂       | 416.56      | 2.87   |
| TS-18  | C₆H₅-   | 4-OCH₃-C₆H₄- | -CH₃ | C₂₁H₂₆N₁O₂S₂       | 430.15      | 3.22   |
| TS-19  | - C₆H₅- | 2-OH-C₆H₄- | -CH₃ | C₂₀H₂₄N₁O₂S₂       | 416.13      | 1.63   |
| TS-20  | C₆H₅-   | 4-F-C₆H₄-  | -CH₃ | C₂₀H₂₃N₁OF₂S₂      | 418.13      | 3.35   |
| TS-21  | 4-OCH₃-C₆H₄- | 2-OH-C₆H₄- | -H | C₂₀H₂₄N₁O₂S₂       | 432.55      | 1.29   |
| TS-22  | 4-OCH₃-C₆H₄- | 4-OCH₃-C₆H₄- | -H | C₂₁H₂₆N₁O₂S₂       | 446.58      | 2.84   |
| TS-23  | 4-OCH₃-C₆H₄- | 3,4-di-OCH₃-C₆H₅- | -H | C₂₇H₂₈N₁O₂S₂       | 476.61      | 2.70   |
| TS-24  | C₆H₅-   | 4-Cl-C₆H₄- | -CH₃ | C₂₀H₂₃N₁O₂S₂Cl₂   | 434.10      | 3.92   |
Table 2: Minimum Inhibitory Concentration of Compounds

| Microorganism | Minimum Inhibitory Concentration (µg/mL) |
|---------------|------------------------------------------|
|               | Compound | TS-i | TS-ii | TS-iii | TS-iv | TS-v | TS-vi | TS-vii | TS-viii | TS-ix | TS-x | TS-xi | TS-xii |
| S. albus      |          | 6.25 | 3.17  | 12.5   | 6.25  | 12.5 | 6.25  | 12.5   | 6.25   | 12.5  | 12.5 | 6.25 |
| B. subtilis   |          | 6.25 | 3.17  | 12.5   | 6.25  | 12.5 | 6.25  | 12.5   | 6.25   | 12.5  | 12.5 | 6.25 |
| S. aureus     |          | 6.25 | 3.17  | 25     | 6.25  | 12.5 | 6.25  | 25     | 6.25   | 12.5  | 12.5 | 6.25 |
| M. luteus     |          | 6.25 | 6.25  | 25     | 12.5  | 6.25 | 25    | 12.5   | 6.25   | 12.5  | 12.5 | 12.5 |
| E. coli       |          | 12.5 | 3.17  | 25     | 6.25  | 25   | 12.5  | 25     | 3.17   | 25    | 12.5 | 12.5 |
| S. paratyphi  |          | 12.5 | 6.25  | 25     | 6.25  | 25   | 12.5  | 25     | 6.25   | 25    | 25   | 6.25 |
| P. auroginosa |          | 6.25 | 3.17  | 6.25   | 6.25  | 6.25 | 12.5  | 6.25   | 6.25   | 25    | 12.5 | 12.5 |
| K. pneumonia  |          | 6.25 | 6.25  | 6.25   | 3.17  | 12.5 | 6.25  | 3.17   | 6.25   | 12.5  | 12.5 | 12.5 |
| C. albicans   |          | 12.5 | 3.17  | 6.25   | 6.25  | 12.5 | 6.25  | 25     | 12.5   | 6.25  | 12.5 | 12.5 |
| A. niger      |          | 12.5 | 6.25  | 12.5   | 3.17  | 25   | 3.17  | 12.5   | 6.25   | 25    | 12.5 | 12.5 |

Solvent: DMSO; Media: Muller Hinton Broth,

Table 3: Minimum Inhibitory Concentration of Compounds

| Micro-organism | Minimum Inhibitory Concentration (µg/mL) |
|---------------|------------------------------------------|
|               | Compound | TS-xiii | TS-xix | TS-xv | TS-xvi | TS-xvii | TS-xviii | TS-xix | TS-x | TS-xi | TS-xii | TS-xiii | TS-xxiv |
| S. albus      |          | 3.17    | 6.25   | 12.5  | 6.25   | 6.25    | 6.25     | 25     | 6.25 | 25    | 6.25   | 3.17    |
| B. subtilis   |          | 6.25    | 12.5   | 12.5  | 6.25   | 6.25    | 6.25     | 25     | 6.25 | 12.5  | 12.5   | 3.17    |
| S. aureus     |          | 6.25    | 12.5   | 25    | 6.25   | 6.25    | 6.25     | 3.17   | 50   | 12.5  | 12.5   | 6.25    |
| M. luteus     |          | 3.17    | 12.5   | 25    | 6.25   | 6.25    | 6.25     | 12.5   | 12.5 | 12.5  | 3.17   | 6.25    |
| E. coli       |          | 6.25    | 12.5   | 25    | 3.17   | 6.25    | 6.25     | 6.25   | 12.5 | 12.5  | 6.25   | 3.17    |
| S. paratyphi  |          | 3.17    | 6.25   | 12.5  | 6.25   | 6.25    | 6.25     | 12.5   | 25   | 12.5  | 6.25   | 3.17    |
| P. auroginosa |          | 6.25    | 6.25   | 12.5  | 6.25   | 6.25    | 6.25     | 3.17   | 12.5 | 50    | 25     | 3.17    |
| K. pneumonia  |          | 6.25    | 6.25   | 25    | 6.25   | 6.25    | 6.25     | 3.17   | 12.5 | 25    | 6.25   | 3.17    |
| C. albicans   |          | 12.5    | 12.5   | 25    | 3.17   | 3.17    | 12.5     | 6.25   | 25   | 25    | 12.5   | 6.25    |
| A. niger      |          | 12.5    | 12.5   | 25    | 6.25   | 6.25    | 6.25     | 6.25   | 25   | 25    | 3.17   | 6.25    |
|        |       |     |     |     |     |     |     |     |     |
|--------|-------|-----|-----|-----|-----|-----|-----|-----|-----|
| A. fumigates | 12.5  | 12.5| 25  | 3.17| 3.17| 12.5| 6.25| 25  | 50  |
| M. purpureus  | 12.5  | 12.5| 25  | 3.17| 6.25| 12.5| 3.17| 12.5| 50  |
|         | 12.5  | 12.5| 25  | 3.17| 12.5| 50  | 12.5| 6.25| 3.17|
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