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# SYNTHESIS OF SOME NEW ARYL THIADIAZOLES FROM M-CRESOL AND EVALUATION AS POSSIBLE ANTIMICROBIAL AGENTS

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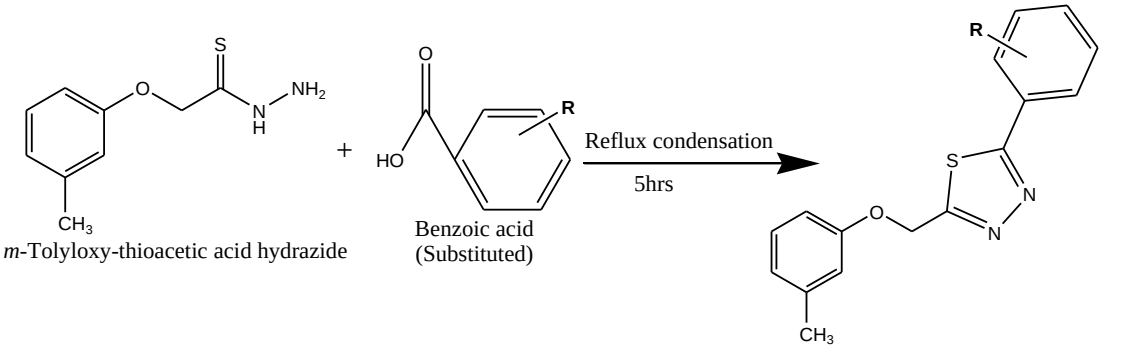
## ABSTRACT

*Thiadiazoles are well-known for their anticonvulsant [1], Anti-inflammatory [1], anti-diabetic [1] activities. In this present investigation Aryl derivatives of thiadiazoles were synthesized by various intermediate products which were synthesized from 2-(m-Tolyloxy)-thioacetohydrazide* ***($J_3$)*** *which is the derivative of Ethyl-2-(m-tolyloxy)-thioacetate* ***($J_2$)****, which undergoes cyclization with substituted Aromatic carboxylic acids resulted in the production of 2-(Aryl)-5-(m-tolyloxy methyl)-1,3,4-thiadiazole derivatives* ***($J_{a1}$ – $J_{a5}$)****.The synthesized compounds were identified and confirmed by the Spectral data obtained by $^1$H NMR, FT-IR and Mass Spectroscopy. The synthesized compounds were found to be novel and evaluated for their Antimicrobial activity and all derivatives were compared.*




| ***($J_3$)*** | ***($J_4$)*** | ***($J_{a1}$ - $J_{a5}$)*** |
|---|---|---|

## KEY WORDS

*Aromatic carboxylic acid, antimicrobial agents, Ethylchlorothioacetate and*

## Introduction:

As We all are depending directly/indirectly on others/other things for survival, microorganisms are also depending on others especially human beings may be directly/indirectly, these microorganisms may be harmful/harmless. But most of these are found to be harmful, causing various infections ranging from minor infections to fatal infections. As a nature we are counter-attack to the microbial attack for our survival. The population of the human beings is very negligible to that of the population of the microorganisms. As Human is ultimately the dominant over all the creatures, by technique he is using again the microorganism to protect himself from another microorganism, so need to be dependent on other microorganisms and also on their metabolic products (i.e., antibiotics). According to the literature phenol and it's derivatives are found to have profound disinfectant

activity, so used in many Food and pharmaceutical preparations and also the Hydrazide derivatives (i.e., Isoniazid) were found to have Anti-mycobacterial activity (Anti-tubercular). According to the literary reports Thiadiazoles were found to have Antiepileptic activity [1], Anti-inflammatory activity [1], anti-diabetic activity[1] etc. In most of the syntheses of Thiadiazoles and its derivatives resulted in maximum yields. Finally, it's stated that synthesis and evaluation of these compounds is convenient and interesting.

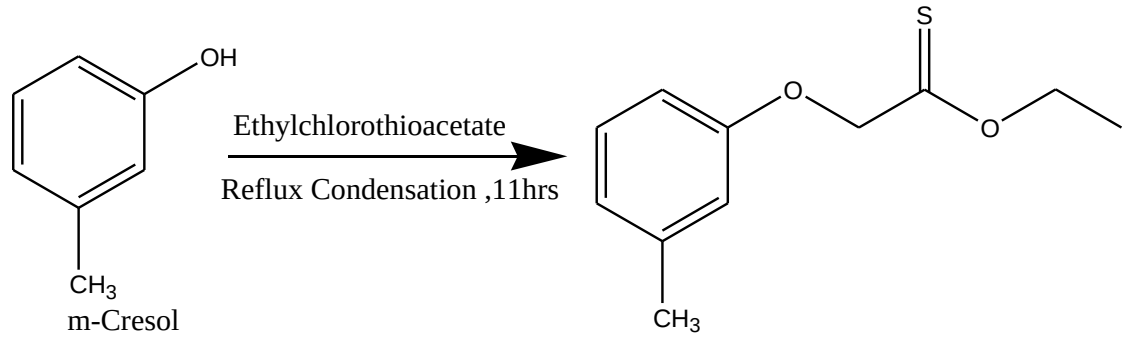
**Materials and Methods:**

All the chemicals used in the current syntheses were pure and of laboratory grade (LR Grade) which were from various industries like Sigma-Aldrich, Merck, Qualikem, Ranikem etc. The Melting Points of the synthesized compounds were determined by using a Glass capillary tube using a Stuart Melting Point Apparatus. The synthesized compounds were identified and confirmed by FT-IR [Shimatzu 8200], by KBr pellet method in between 400-4000cm$^{-1}$, $^1$H NMR [Bruker] using $CDCl_3$ as solvent, δ-values in ppm with Tetramethyl Silane as internal standard and Mass Spectrophotometer [Agilent 300],up to 70 e.V.

In the experimental method, Thiadiazole and it's derivatives were synthesized by a Scheme consisting of three steps. In the first step m-Cresol **($J_1$)** was converted to a Ethyl ester upon Esterification with Ethylchlorothioacetate **($J_2$)**. In the second step Ethylchlorothioacetate **($J_2$)** was made to react with Hydrazine which produced 2-(m-tolyloxy)-thioacetohydrazide **($J_3$)** by Nucleophilic substitution and in the third step 2-(m-tolyloxy)-thioacetohydrazide **($J_3$)** was made to react with substituted Aromatic carboxylic acids**($J_4$)** which produced 2-(Aryl)-5-(m-tolyloxymethyl)-1,3,4-thiadiazole derivatives **($J_{a1}$ - $J_{a5}$)** by cyclization. The reactions were monitored by using TLC plates with silica Gel 60 F254 (0.2mm) using Ethanol: Chloroform (8:2) as the solvent system.

**Scheme** [3]**:**

**Step:1**



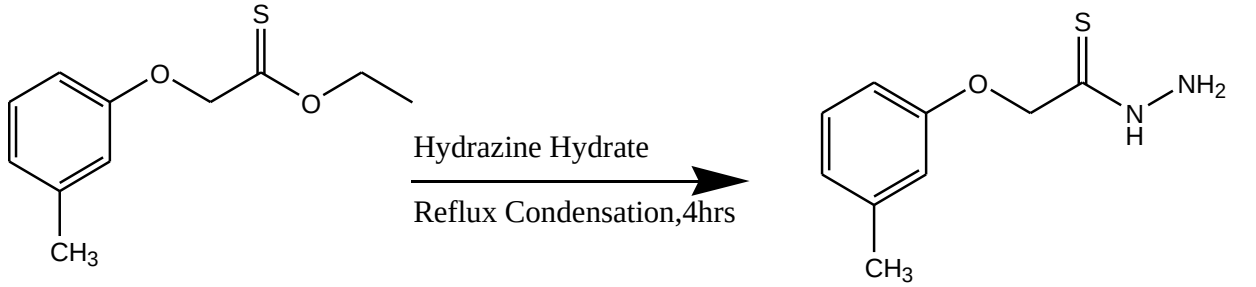

m-Cresol

**($J_1$)**

*m*-Tolyloxy-thioacetic acid *O*-ethyl ester

**($J_2$)**

**Step:2**



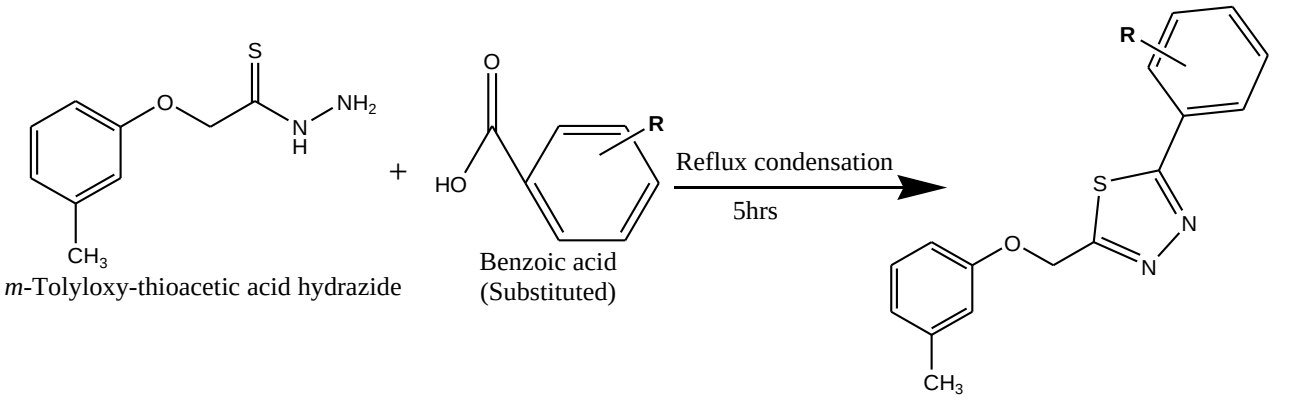

*m*-Tolyloxy-thioacetic acid *O*-ethyl ester

**($J_2$)**

*m*-Tolyloxy-thioacetic acid hydrazide

**($J_3$)**

**Step:3**




*m*-Tolyloxy-thioacetic acid hydrazide

Benzoic acid (Substituted)

**2-Phenyl-5-*m*-tolyloxymethyl-[1,3,4]thiadiazole** (Substituted)

**($J_3$)** **($J_4$)** **($J_{a1}$ - $J_{a5}$)**

**Table:1**

| S.No. | R | Derivative |
|---|---|---|
| 1. | -NHCH$_3$ | $J_{a1}$ |
| 2. | -Cl | $J_{a2}$ |
| 3. | -F | $J_{a3}$ |
| 4. | -OC$_2$H$_5$ | $J_{a4}$ |
| 5. | -OH | $J_{a5}$ |

**Table: 2 Antimicrobial activity of synthesized compounds**

| S.No. | Compound | Diameter of zone of inhibition`(mm) | | | | |
|---|---|---|---|---|---|---|
| | | S.Aureus | Pro.Vulgaris | E.Coli | C.albicans | A.flavus |
| 1. | $J_2$ | 7 | 6 | 9 | --- | --- |
| 2. | $J_3$ | 10 | 8 | 11 | --- | --- |
| 3. | $J_{a1}$ | 18 | 19 | 18 | 7 | 6 |
| 4. | $J_{a2}$ | 26 | 25 | 26 | 16 | 15 |
| 5. | $J_{a3}$ | 27 | 26 | 27 | 17 | 16 |
| 6. | $J_{a4}$ | 18 | 18 | 19 | 11 | 10 |
| 7. | $J_{a5}$ | 17 | 17 | 18 | 10 | 9 |
| 8. | Ciprofloxacin | 29 | 28 | 28 | --- | --- |
| 9. | Fluconazole | --- | --- | --- | 19 | 18 |

**General Method of preparation of synthesis of 2-Aryl-5-(m-tolyoxymethyl)-1,3,4-Thiadiazole derivatives ($J_{a1}$-$J_{a5}$)** [2]**:**

The mixture of the compound **$J_2$** (0.007 mol) and the aromatic carboxylic acid (0.003 mol) in the presence of Phosphorous Oxychloride was undergone Reflux condensation for 5hrs, then reactions contents were cooled and then the contents were poured into a containing crushed ice and then this was neutralized by adding sodium carbonate solution (2.5M), which precipitates a solid compound. The compound was filtered to collect the residue and it was recrystallized from alcohol (Eg: Ethanol) to get the pure compound.

**Results and Discussion:**

All the synthesized derivatives were obtained in a good to better yields, were identified and confirmed basing on the TLC spots and further by the Spectral data which was interpreted from IR, $^1$H NMR and Mass Spectra. In IR spectra a characteristic band was observed in between 1523-1527(-C=N) and characteristic peak for (-C=S) between 1025-1225cm$^{-1}$ and a characteristic band

for (N-C=S) due to mixed vibrations between 1395-1570,1260-1420,940-1140 $cm^{-1}$ were found to be absent which confirms the cyclization; $^1H$ NMR peaks for the protons of –NH and $–NH_2$ groups were found to be absent which confirms the cyclization, peaks obtained in between 6.71-7.42 represent the aromatic protons. The fragmentation pattern in the Mass Spectra of the compound **$J_{a1}$** is with m/z value at 311[$M^+$] ($C_{16}H_{14}N_2OS^+$), 161($C_8H_5N_2S^+$), 121($C_8H_9O^+$), 107($C_7H_7O^+$), 92($C_7H_8^+$), 77($C_7H_7^+$), 51($C_4H_3^+$), 91($C_7H_7^+$; base peak), 65($C_5H_5^+$) by which the fragmentation of all the synthesized compounds were characterized from **$J_{a2}$-$J_{a5}$**.

The synthesized compounds were evaluated for their anti-bacterial and anti-fungal activities, the results obtained confer that the compounds $J_{a2}$ and $J_{a3}$ were found to have higher anti-bacterial activity against *Staphylococcus aureus, Proteus Vulgaris* and *Escherichia coli* as well as anti-fungal activity against *Aspergillus flavus* and *Candida Albicans*. From these results (**Table:2**) it was clearly observed that the compounds containing the more electronegative atoms which act as the ring deactivators and thus increasing the potency of the compounds **$J_{a2}$** and **$J_{a3}$** (which have **–Cl** and **–F** respectively).

**Characterization of the synthesized compounds:**

- **Methyl-[4-(5-m-tolyloxymethyl-[1,3,4]-thiadiazol-2-yl)-phenyl]-amine ($J_{a1}$)**
  White crystalline solid (yield 69%, M.P. 221-223°C), IR (KBr) $cm^{-1}$: 3042 (Ar-C-H), 2921(-CH),1535(-C=N) ; $^1H$ NMR ($CDCl_3$) δ ppm, 2.43(3H,s, for Ar-$CH_3$), 4.34 (2H,s,for $CH_2$), 6.92-7.27 (8H,m, for Ar-H); Mass: 311[$M^+$],145,121,92,77, 91(base peak), 65, 51.
- **2-(4-Chloro-phenyl)-5-m-tolyloxymethyl-[1,3,4]thiadiazole ($J_{a2}$)**
  White crystalline solid (yield 73%, M.P. 198-201°C), IR (KBr) $cm^{-1}$: 3043 (Ar-C-H), 2923(-CH),1538(-C=N) ; $^1H$ NMR ($CDCl_3$) δ ppm, 2.44(3H,s,for Ar-$CH_3$), 4.36(2H,s, for $CH_2$), 6.94-7.29(8H,m, for Ar-H); Mass: 317[$M^+$],145,121,92,91(base peak), 77,65,51.
- **2-(4-Fluoro-phenyl)-5-m-tolyloxymethyl-[1,3,4]thiadiazole ($J_{a3}$)**
  Pale greenish crystalline solid (yield 75%, M.P. 202-204°C), IR (KBr) $cm^{-1}$: 3041 (Ar-C-H), 2924(-CH),1540(-C=N) ; $^1H$ NMR ($CDCl_3$) δ ppm, 2.46(3H,s,for Ar-$CH_3$), 4.38(2H,s, for $CH_2$), 6.97-7.31(8H,m, for Ar-H); Mass: 300[$M^+$],145,121,92,91(base peak), 77,65,51.
- **2-(4-Ethoxy-phenyl)-5-m-tolyloxymethyl-[1,3,4]thiadiazole ($Ja_4$)**
  White crystalline solid (yield 61%, M.P. 205-207°C), IR (KBr) $cm^{-1}$: 3045 (Ar-C-H), 2926(-CH),1536(-C=N) ; $^1H$ NMR ($CDCl_3$) δ ppm, 2.41(3H,s,for Ar-$CH_3$), 4.39(2H,s, for $CH_2$), 6.99-7.26(8H,m, for Ar-H); Mass: 326[$M^+$],145,121,92,91(base peak), 77,65,51.
- **4-(5-m-Tolyloxymethyl-[1,3,4]thiadiazol-2-yl)-phenol ($J_{a5}$)**
  Pale yellowish crystalline solid (yield 65%, M.P. 203-206°C), IR (KBr) $cm^{-1}$: 3040 (Ar-C-H), 2929(-CH),1537(-C=N) ; $^1H$ NMR ($CDCl_3$) δ ppm, 2.45(3H,s,for Ar-$CH_3$), 4.41(2H,s, for $CH_2$), 6.92-7.31(8H,m, for Ar-H); Mass: 298[$M^+$],145,121,92,91(base peak), 77,65,51.

**Biological Evaluation**

**(a). Anti-bacterial activity**

All the synthesized compounds were evaluated for their anti-bacterial activity against various bacterial species such as *Staphylococcus aureus, Proteus vulgaris* and *Escherichia coli* by performing in vitro bioassay by the agar well diffusion method. All the synthesized compounds were dissolved in acetone (in about 1mL), the fresh cultures were used for the bioassay by streaking the bacterial cultures onto the agar plates, wells were formed in the agar plate using a borer. Now the solutions were loaded using a micropipette accordingly as 0.1mg/mL (test compounds in acetone), 0.5mg/mL of Ciprofloxacin (Standard) and acetone (control). Then the agar plates were kept in an incubator for about 24 hrs at incubation temperature (38°C) and zones of inhibition values were observed and recorded after replicate experiments only.

**(b). Antifungal activity:**

The synthesized compounds were also evaluated for their anti-fungal activity, for this the compounds were used in solution form by dissolving them in acetone (about 1mL), the fresh cultures were used for the bioassay by streaking the fungal cultures onto the agar plates, wells were formed in the agar plate using a borer. Now the solutions were loaded using a micropipette accordingly as 0.1mg/mL (test compounds in acetone), 0.5mg/mL of Fluconazole (Standard) and acetone (control). Then the agar plates were kept in an incubator for about 24 hrs at incubation temperature (38°C) and zones of inhibition values were observed and recorded after replicate experiments only.

## Conclusion:

From the investigations and observations of the current research, it's concluded that the derivatives of thiadiazoles were found to possess high anti-microbial activity, specifically **$Ja_2$** & **$Ja_3$**. High activity is based on the type of substituents i.e., derivatives with electronegative substituents are highly potent, still need to explore furthermore to produce more potent thiadiazoles for other activities.

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