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Biological significance and synthetic approaches for 1,3,4-Thiadiazoles: A Review

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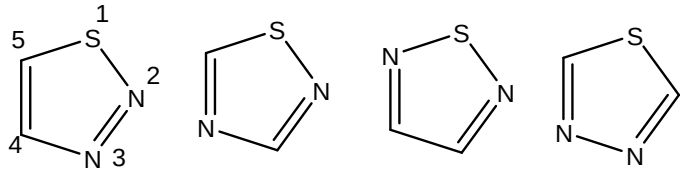
Abstract:

In this article the authors presented a short review of literature survey on the synthetic approaches for the synthesis of thiadiazoles and their derivatives. Further, various biological activities of these derivatives were also summarized.

Keywords: Thiadiazole, synthesis, pharmacological activity

1. Introduction

Thiadiazole is a prevalent biologically active scaffold in heterocyclic compounds having five membered ring consisting of 2 nitrogen atoms, 2 carbon atoms, 1 sulphur atom, and 2 double bonds. Thiadiazole moiety behaves as "hydrogen binding domain" and "two-electron donor system". As shown in Figure 1, 4 isomers of thiadiazoles (**Figure 1**) are possible based on the nitrogen atom position in the ring. Among these isomers, 1,3,4-thiadiazoles have been studied more than other isomers owing to possessing versatile biological activities.[1]



1,2,3- 1,2,4- 1,2,5- 1,3,4-

Figure 1

1,3,4-Thiadiazoles are more prone to nucleophilic attack due to the presence of 2 'N' in the ring allowing substitutions into 2' or 5' positions of the ring to afford wide range of analogues. When treated with aqueous base, ring cleavage can occur, whereas, in acid solutions, the ring has more stability. Thus possessing these properties, 1,3,4-dithiadiazoles derivatives are applied widely in pharmacological, agricultural and material chemistry.[2]

2. Biological significance of 1,3,4-thiadiazoles

Several 1,3,4-thiadiazoles are found to have characteristic drug activity in different biological evolution studies, makes the medicinal chemists to concentrate over the synthesis and biological evolution of novel 1,3,4-thiadiazole derivatives.

The following are a few examples of the 1,3,4-thiadiazole derivatives consists of biological significance.

2.1 Antimicrobial activity

Hussain *etal*[3] synthesized 4-amino phenol derived 1,3,4-thiadiazoles (Figure 2) which showed promising antimicrobial activity.

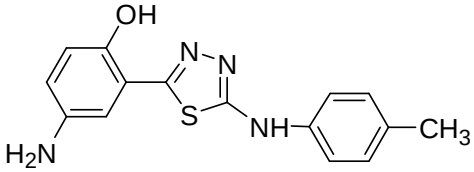
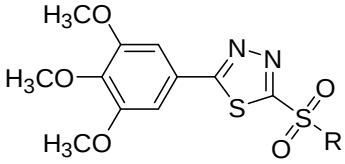


Figure 2

2.2 Anti-Fungal activity

Jun-Chen *et al*[4] prepared 3,4,5-trimethoxy derived 1,3,4-thiadiazoles (Fig. 3) and screened for antifungal activities, in vitro.



R=(a) = H2C = CH-CH2
(b) = O2N - C6 H 6 - C H 2 -
(c) = C6H6 -CH2
(d) = CH3 -

Figure 3

2.3 Anticonvulsant activity

Gupta *et al*[5] have synthesized wide range of 3-aryl amino/amino-4-aryl-5-imino-D2-1,2,4-thiadiazoline derivatives (Fig. 4) and evaluated successfully for their anti-convulsant properties,

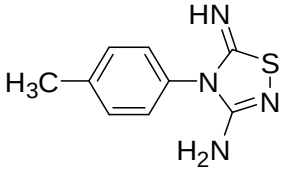


Figure 4

2.4 Anti-inflammatory activity

Sharma et al.[6] synthesized 2-amino-5-sulfanyl-1,3,4-thiadiazole derivatives which were exploited as selective inhibition of COX-2 enzyme (Fig. 5).

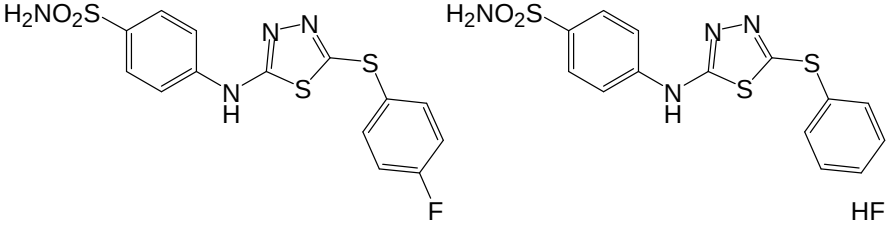


Figure 5

2.5 Antileishmanial activity

Ram *et al*[7] prepared several analogues of 2,4 disubstituted 1,3,4 thiadiazole (Fig. 6) and evaluated for antileishmanial activity, in vitro.

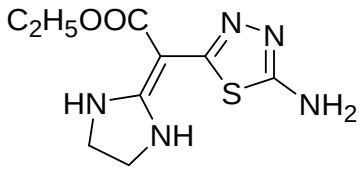
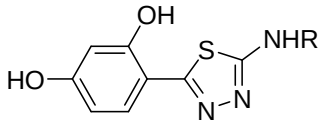


Figure 6

2.6 Cytotoxic activity

Matysiak *et* al[8] synthesized a new series of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles which showed excellent antiproliferative activities against human cancer cell lines (Fig. 7).

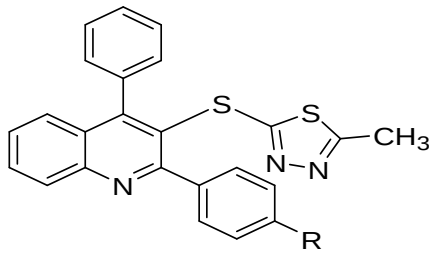


R = aryl,alkyl.

Figure 7

2.7 Antitubercular activity

Chitra *et al*[9] synthesized 3-heteroarylthioquinoline derivatives of 1,3,4-thiadiazole and screened their *in vitro* antimycobacterial activity (Fig. 8).

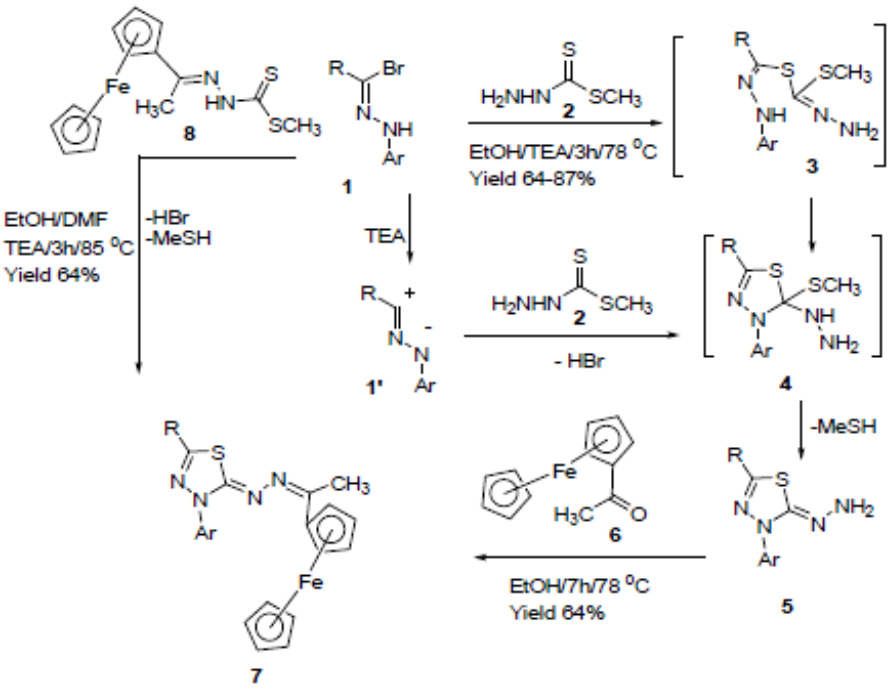


R =Cl, Br

Figure 8

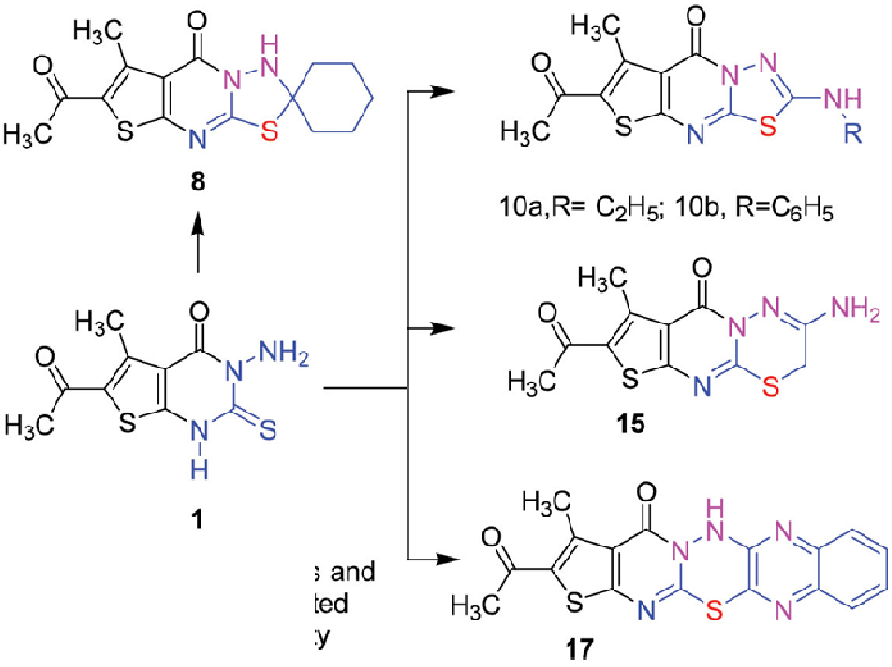
3. Existing Synthetic Approaches

Abdelwahed *et al*[10] has reported synthesis of thiadiazoles derivatives (Scheme 13) by treatment of hydrazonoyl halides **1** with methyl 2-(1-ferrocenylethylidene)hydrazine carbodithioate **8** in boiling ethanol/ dimethylformamide in the presence of triethylamine under reflux afforded compound **7** as shown in below Scheme 1.



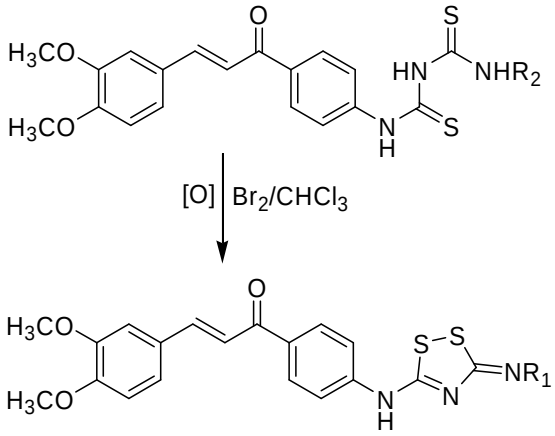
Scheme 1

Ameen Ali Abu-Hashem *et al*[11] prepared wide range of 1,3,4-thiadiazoles, 1,3,4-thiadiazines derivatives and exhibited higher antimicrobial activity as shown in Scheme 2.



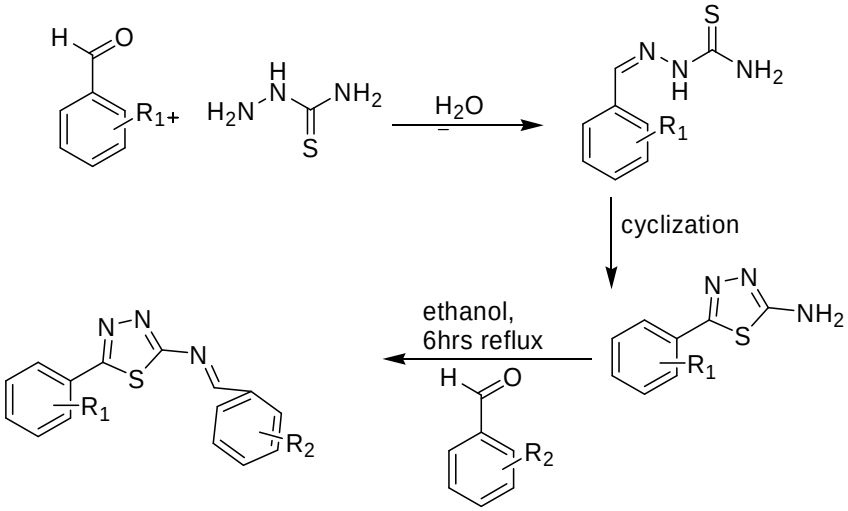
Scheme 2

Tayade and Waghmare *et al*[12] developed one-step preparation of of (2E)-1-[4-(3-substitutedimino-1,2,4-dithiazolo) aminophenyl] -3- (3,4- dimethoxyphenyl) prop-2-en-1-one in the presence of $Br_2/CHCl_3$ (Scheme 3).



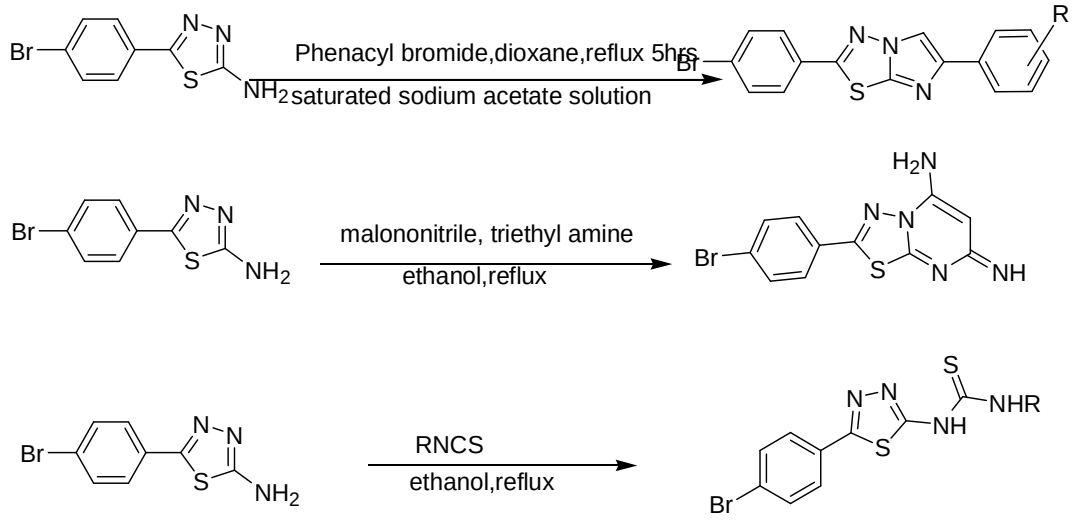
Scheme 3

Naskar *et al*[13] synthesized 2-amino-5-aryl-1,3,4-thiadiazoles by oxidative cyclization of thiosemicarbazones using $FeCl_3$ catalyst (Scheme 4).



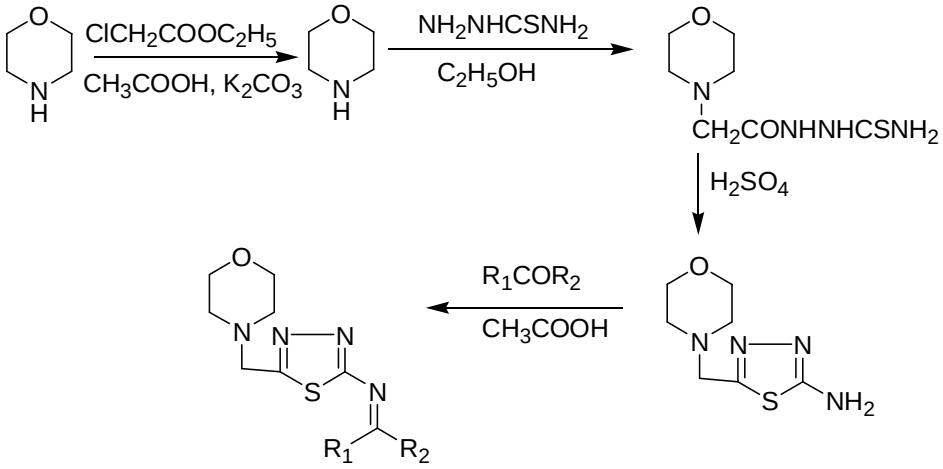
Scheme 4

Abdel Rahman *et al*[14] synthesized varying range of substituted imidazo [2,1-b]-1,3,4– thiadiazoles, substituted 1,3,4-thiadiazolo[3,2-a] pyrimidines and substituted thioureas. Most of the tested compounds exhibited potent cytotoxicity.



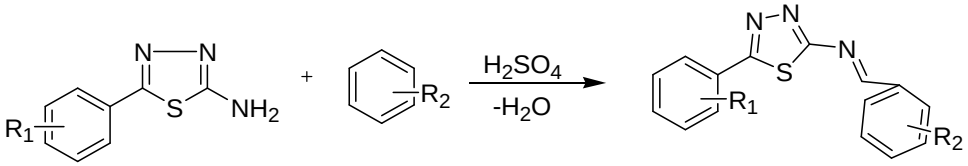
Scheme 5

Mahendra Singh *et al*[15] has reported the synthesis of thiadiazole derivative from morpholine and ethyl acetoacetate (Scheme 6).



Scheme 6

Khedr *et al*[16] has synthesized thiadiazole derived Schiff base ligands as shown in Scheme 7.



Scheme 7

Conclusion:

In conclusion, brief compilation on synthetic approaches and biological relevance of thiadiazole and its derivatives was performed and we do strongly hope that, this short report will be a valuable addition in the said field as well interest to the synthetic and medicinal chemists.

Acknowledgements

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Conflict of interest statement

The authors declare no conflict of interest.

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