ABSTRACT
Thiadiazoles have proved their potential in the development of pharmaceutically important organic compounds both of natural and synthetic origin. Thiadiazole analogs deal with a variety of biological activities viz. antimicrobial, antitubercular, anti-inflammatory, anticancer, anticonvulsant and Antioxidant/Radio-protective agents. This review also discusses the chemistry and various methods for synthesis of thiadiazoles. It can act as an important tool for future researcher to develop newer thiadiazole derivatives that could be a better analog in relation to efficacy and safety.

Keywords: Chemistry, Synthesis, Antimicrobial, Antitubercular, Anticancer, Antiviral, Anticonvulsant.

INTRODUCTION
Resistance towards present drugs is majorly becoming a worldwide problem. Today’s maximum research is focusing on development of new molecules against these problems. Thiadiazoles exhibits a wide variety of biological activities. Thiadiazole moiety acts as “hydrogen binding domain” and “two-electron donor system”. Thiadiazoles are 5-membered ring system containing one sulphur and two nitrogen atoms. They occur in nature in four isomeric forms viz. 1,2,3-thiadiazole; 1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole. The 1,3,4-thiadiazole isomer of thiadiazole series and its dihydro-derivatives provide a bulk of review on thiadiazole. A detailed review and standard reference work shows that more work has been carried out on the 1,3,4-thiadiazole than all other isomers. Thiadiazoles has got many applications as pharmaceuticals, oxidation inhibitors, cyanine dyes, & metal complexing agents. The literature review showed that the thiadiazole nuclei have antimicrobial, antitubercular, analgesic and anti-inflammatory, anticancer, antiviral, anticonvulsant and Antioxidant/Radio-protective agents.

CHEMISTRY OF 1,3,4-THIADIAZOLES
The advent of Sulphur drugs and the later discovery of mesoionic compounds greatly accelerated the rate of progress in the field of thiadiazole. The thiadiazole system contains the following members, the 1,2,3-thiadiazoles (a) and their benzo derivatives (b), the 1,2,4-thiadiazoles (c), the 1,3,4-thiadiazoles (d) and 1,2,5-thiadiazoles (e) and their benzo derivatives (f), 1,3,4-thiadiazolines (g) and (h) and 1,3,4-thiadiazolidines (i).

Of the possible thiadiazoles, the chemistry of 1,3,4-thiadiazole (d) has attracted maximum attention since its discovery by Emil Fischer in 1882, in view of variety of its compounds finding applications in agriculture, drugs, dyes and photographic materials. 1,3,4-Thiadiazole can be looked upon 4-aza-thiazole or 3,4-diazathiophene so far.
as they are electronically isosteric. However, the replacement of -CH= by electronegative -N= atom in the 5-membered thiophene ring changes the chemical/physical behaviour considerably. The structure (d) represents π-excessive ring system as the two adjacent N atoms of the ring carry a lone pair of electrons each. Actually, 1,3,4-thiadiazole molecule does not display a true aromatic behaviour as do benzene, pyridine and thiophene.

Bak et al in 1966 have made analysis of microwave spectra of the molecule and calculated bond lengths, bond angles and bond orders. They concluded that the aromatic character as measured by the π-electron delocalization decreases in the order of 1,2,5-thiadiazole > thiophene > thiazole ≥ 1,3,4-thiadiazole. Koutecký and Paldus in 1961 made series of M.O. calculations by HMO method using the Longuet-Higgins model for the sulfur atom of thiadiazole isomers and showed that π-electron delocalization is more in (5) than in thiazole. Bak et al in 1962 observed the dipole moment value 3.25D for 1,3,4-thiadiazole and 1.61D for thiazole. These findings suggested that 1,3,4-thiadiazole is a polar symmetric molecule exhibiting pseudo aromatic character 6-20.

SYNTHESIS OF 1,3,4-THIADIAZOLES

The majority of 1, 3, 4-thiadiazole synthesis are based on cyclisation of thiosemicarbazide derivatives. Other methods involve ring closure of dithiocarbazates, acylhydrazines, bisthioureas or interconversions of oxadiazoles etc., into 1, 3, 4-thiadiazoles.

From Acylhydrazines

The reaction of N, N′-diacylhydrazine with phosphorus pentasulfide was used by Stolle et al in 1889 and 1904 for the preparation of a large number of 2, 5-disubstituted 1, 3, 4-thiadiazole 21,22.

\[
\begin{align*}
\text{NHNH} & + \text{P}_2\text{S}_5 \rightarrow \text{S=S=S=S} \\
R' & \text{O} \quad \text{R} & \text{O} \\
\end{align*}
\]

From Thiosemicarbazides

Many synthesis of the 1, 3, 4 Thiadiazole proceed from thiosemicarbazide or substituted thiosemicarbazide. Hoggarth in 1949 was the first to reported cyclodehydration of acyl thiosemicarbazides in presence of acid catalyst like sulphuric acid, O-phosphoric acid etc., to get varieties of 2,5-substituted 1,3,4-thiadiazoles. The required acylthiosemicarbazides are obtained by treating an acid hydrazide with an isothiocyanate 23.

\[
\text{ArCOOH} + \text{NH}_2\text{CSNHNNH}_2 \rightarrow \text{NH}_2\text{CONHNHCSNHAr} \quad \text{80% H}_2\text{SO}_4
\]

They are also prepared by heating the carboxylic acid and thiosemicarbazide (NH$_2$CSNHNNH$_2$) in the acidic medium and are cyclized subsequently e.g.

\[
\text{R} \quad \text{NH} \quad \text{NH} \quad \text{O} \quad \text{Ar} \rightarrow \text{S=S=S=S} \quad \text{H}_2\text{O} \quad \text{80% H}_2\text{SO}_4
\]

Turner et al in 1988 were prepared 2-amino-5-aryl 1,3,4-thiadiazoles directly by heating a mixture of the acid and thiosemicarbazide with PPA, i.e. Polyphosphoric acid 24, e.g.,

Ram et al in 1990 synthesized the following types of thiadiazoles starting from the acid hydrazides 25.

\[
\text{ArCOOH} + \text{NHCSNHNNH}_2 \rightarrow \text{ArCONHNHCSNHAr} \quad \text{80% H}_2\text{SO}_4
\]

From Cyclization of aminoguanidines and diamino guanidines

Kurzer in 1970 prepared a number of 1,3,4-thiadiazoles by acid catalysed cyclization of acylthiosemicarbazides obtained from the reaction of aminoguanidine salts and arylisothiocyanates 26.

\[
\text{NHNH} \quad \text{NH} \quad \text{H} \quad \text{N} \quad \text{NH} \quad \text{PhCONCSNH}_2 \rightarrow \text{NHNH} \quad \text{NH} \quad \text{H} \quad \text{N} \quad \text{NH} \quad \text{PhCONCSNHAr} \quad \text{PhCONCSNHAr}
\]

He modified the method by heating a mixture of aryl isothiocyanate and 1,2-diamino-3-arylguanidine in DMF at 100°C, 2-arylamino-5-anilino-1,3,4-thiadiazole was obtained in good yield.

From Hydrazides and Aryl isothiocyanates

Kurzer in 1971 prepared a number of 2-hydroxy-5-acylamino-1,3,4-thiadiazole by heating carbonohydrazides with equimolecular quantity of an arylisothiocyanate 27 in DMF at 100°C, e.g.,

\[
\text{NH} \quad \text{N} \quad \text{NH} \rightarrow \text{N} \quad \text{N} \quad \text{NH} \quad \text{R} \quad \text{O} \quad \text{R} \quad \text{N} \quad \text{NH} \quad \text{PhCONCSNHAr}
\]

THERAPEUTIC POTENTIAL OF 1,3,4-THIADIAZOLES

A large number of 1,3,4-thiadiazole compounds has been synthesized since the discovery of potent sulfa drugs containing this nucleus after the second world war.

\[
\begin{align*}
\text{Thiadiazole} & \quad \text{NH} \quad \text{NH} \quad \text{O} \\
\text{N} & \quad \text{N} \quad \text{N} \quad \text{OH} \\
\text{N} & \quad \text{N} \quad \text{N} \quad \text{N} \\
\end{align*}
\]

Literature survey showed that most of the 1,3,4-thiadiazole compounds contain amino, hydrazine, oxo, thio or their substituted group at 2-position, and another amino, aryl, alkyl, or their substituted group or halogen at 5-position. Interestingly enough, 1,3,4-thiadiazole derivatives are generally found to possess various biological activities. A brief account of the information on biological activities of some 2,5-disubstituted, 1,3,4-thiadiazoles is given below with a view to appreciate their importance.

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Antimicrobial 1,3,4-thiadiazoles
Padmavathi et al in 2009 synthesized a few 2-(arylmethanesulfonylmethyl)-5-aryl-1,3,4-thiadiazoles and tested for in vitro antimicrobial activity against Gram positive bacteria S.aureus, B. subtilis; Gram negative bacteria Klebsiella pneumoniae, Proteus vulgaris and Fungi Fusarium solania, Aspergillus niger, etc. and found them to be active. The presence of benzylsulfonyl group and Chloro substituent enhances the activity of the compound.

A number of new 5-(1H-indol-3-yl methyl)-N-(substituted phenyl)-1,2,4-thiadiazol-2-amine derivatives were synthesized and evaluated for their antibacterial and antifungal activity by Siddiqui et al in 2009. Compounds (a) and (d) showed 80% and 72% inhibition respectively against S. aureus while compounds (b), (c) and (d) showed 76% inhibition against E. coli. Compounds (a), (d) and (h) showed 70%, 85% and 65% inhibition respectively against C. albicans.

(a-h)

The successful synthesis and antimicrobial activity of new 1,2,4-triazolo thiadiazoles carrying 4-methyl/ethy1 thio and methyl sulfonylurea phenoxy moieties at position 3 were reported by Karabasanagouda et al in 2007. The antimicrobial activity study revealed that all the compounds tested showed moderate to good antibacterial and antifungal activities against pathogenic strains. SAR of title compounds showed that the presence of 4-thialkyl phenoxy groups at position 3 and biologically active groups like -CH₃, OCH₃, NH₂ and 2,3-dichloro groups at aryl moiety attached to position 6 of title compounds are responsible for increased antimicrobial activity.

Antitubercular 1,3,4-thiadiazoles
Karakus and Rollas in 2002 and 2004 have found that one of the thiadiazole derivative, namely 2-(4-chlorophenylamino)-5-(4-aminophenyl)-1, 3, 4-thiadiazole, showed 57% inhibition against Mycobacterium tuberculosis. Further they found that compound has exhibited the highest inhibitory activity (69% inhibition) against in vitro growing Mycobacterium tuberculosis.

This compound while not active enough to be considered as therapeutics, are definitely lead compounds in the search for novel agents to combat resistance. Alireza Foroumadi et al in 2006 have synthesized two series of 2- and 3-[5-(nitro aryl)-1,3,4-thiadiazol-2-ythio, sulfon1y1 and sulfonyl] propionic acid alkyl esters and screened for antituberculosis activity against Mycobacterium tuberculosis and found that the compound that is Propyl 3-[5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-ythio] propionate was the most active one. This compound while not active enough to be considered as therapeutics, are definitely lead compounds in the search for novel agents to combat resistance.
thiadiazol-2-ylthio, sulfinyl and sulfonyl] propionic acid alkyl esters and screened for antituberculosis activity against Mycobacterium tuberculosis and found that the compound 74 that is Propyl 3-[5-(5-nitrotio phen-2-yl)-1,3,4-thiadiazol-2-ylthio]propionate was the most active one.

Rao and Srinivasan in 1964, reported the structure activity relation of 4-arylthiosemicarbazones and their cyclised products like 2.arylamino.5.aryl.1,3,4.thiadiazoles against M.tuberculosis in vitro. No definite conclusions were drawn regarding the effect of substituents in benzene rings. Most of the compounds showed interesting activity even at low dosage.

Bhat and Shenoy in 2001, reported the synthesis of 7 nitro-2.methyl-3.{5'(aryl).1,3,4.thiadiazol.2.yl}aminomethyl quinazolin.4.one. The compounds were found to be active against Mycobacterium tuberculosis.

Anticancer 1,3,4-thiadiazoles
A number of N-substituted 2-amino-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazoles were synthesized and evaluated for their antiproliferative activity by Matysiak and Opolski in 2006. The panel substitution included alkyl, aryl and morphinoalkyl derivatives. The cytotoxicity in vitro against the four human cell lines: SW707 (rectal), HCV29T (bladder), A549 (lung) and T47D (breast) was determined. Alkyl and morphinoalkyl derivatives exhibited significantly lower effect than phenyl ones. The highest antiproliferative activity was found for 2-(2,4-dichlorophenylamino)-5-(2,4-dihydroxyphenyl)-1,3,4-thiadiazole, with ID50 two times lower (SW707, T47D) than for cisplatin studied comparatively as the control compound.

Antiviral 1,3,4-thiadiazoles
Giri et al in 1983, synthesized compound (a) and (b) and tested them against Alternaria brassicae and Helminthosporium oryzae for their antiviral and antifungal activity.

Anticonvulsant 1,3,4-thiadiazoles
A series of new substituted 1,2,4-thiadiazoles were synthesized and screened for anticonvulsant activity by Gupta et al in 2009. All the compounds showed protection against MES screen after 0.5 hr. It may be concluded that the synthesized compounds were potent against MES-induced seizures than scPTZ induced.

Antioxidant/Radio-protective 1,3,4-thiadiazoles
Some novel 5-[2-(substituted phenyl)-1H-benzimidazole-1-y]methyl]-N-methyl-1,3,4-thiadiazole-2-amines were synthesized and tested for antioxidant properties by Kus et al in 2008 using various in vitro systems. Compound, which is the most active derivative inhibited lipid peroxidation.
CONCLUSION

In conclusion the research subscribed in this review article represents a wide variety of synthesis and pharmacological activities of thiadiazoles. The biological profiles of these new generation of thiadiazoles would represent a fruitful matrix for further development of better and newer medicinal agents.

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