2. REVIEW OF LITERATURE

A brief review of the literature available on the correlation between the chemical structure and the pharmacological activity of Thiadiazoles, Azetidinones and Thiazolidinones is presented below. Thiadiazoles, Azetidinones and Thiazolidinones and related compounds are well known for their wide spectrum of antitubercular and antimicrobial activity.

2.1 CHEMISTRY OF 1,3,4-THIADIAZOLE

Thiadiazole nucleus contains two atoms of nitrogen, two atoms of carbon and one atom of sulfur.

The following are the possible combinations

\[
\begin{align*}
\text{HC} & \equiv \text{N}^3 \\
\text{HC} & \equiv \text{S}^2 \\
\text{HC} & \equiv \text{N}^1
\end{align*}
\]

1,2,3-thiadiazole

\[
\begin{align*}
\text{N} & \equiv \text{C} \\
\text{S} & \equiv \text{H}
\end{align*}
\]

1,2,4-thiadiazole

\[
\begin{align*}
\text{HC} & \equiv \text{H} \\
\text{N} & \equiv \text{S} \\
\text{N} & \equiv \text{N}
\end{align*}
\]

1,2,5-thiadiazole

\[
\begin{align*}
\text{N} & \equiv \text{N} \\
\text{S} & \equiv \text{CH}
\end{align*}
\]

1,3,4-thiadiazole

Out of the four, it is 1,3,4-isomer of the thiadiazole series that received much attention. Synthesis of 1,3,4-thiadiazoles are mainly by the cyclisation of thiosemicarbazide. The thiadiazole system contains the following members, the 1,2,3(thiadiazoles) (a) & their (b) benzo derivatives, the (c) 1,2,4(thiadiazoles), (d) 1,3,4(thiadiazoles) & (e) 1,2,5(thiadiazoles) & their (f) benzo derivatives, (g) 1,3,4(thiadiazolines) and (h) 1,3,4(thiazadizolidines).
Of the possible thiadiazoles, the 1,3,4-thiadiazole (d) has given 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. Koutecky and Paldus in 1961 made series of M.O. calculations by HMO method using the Longuet-Higgins model for the sulfur atom of thia diazole isomers and showed that π-electron delocalization is more than the thiazole. Bak et al in 1962 observed the dipole moment value 3.25 D for thia diazole and 1.61 D for thiazole. These findings suggested that thia diazole is a polar symmetric molecule exhibiting pseudo aromatic character.

The chemistry of 1,3,4-thiadiazole has given lot of attention since its discovery by Emil Fischer on account of its derivatives finding various uses in drugs, agriculture, dyes and photographic materials.

4-azathiazole or 3,4-diaza thiophene so far as they are electronically isosteric can be looked upon as 1,3,4-thiadiazole (I). However, the replacement of –CH= by electronegative –N= atom in the five membered thiophene ring changes its physical or chemical behavior considerably. The structure (I) represents π-excessive ring system as the two adjacent nitrogen atoms of the ring carry pair of electrons each. Actually 1,3,4-
thiadiazole molecule does not display a true aromatic behaviour as do benzene, pyridine and thiophene. Some researchers have made analysis of microwave spectra of this molecule and calculated bond lengths, bond orders and bond angle (Bak et al., 1966). They concluded that the aromatic character as measured by the electron delocalization decreases in the way of 1,2,5-thiadiazole > thiophene > thiazole > 1,3,4-thiadiazole. Zaharnik and Koutechy in 1961 made a series of calculation by method using the longuet Higgins model for the sulphur atom of thiadiazole isomer and showed that π electrons delocalization is more in 1,2,5-isomer than in thiazole. Bak et al., 1962 have reported the dipole movement valued of 3.25 D for 1,3,4-thiadiazole and 1.61 D for thiazole. These finding suggests that thiadiazole is a polar symmetric compound exhibiting pseudo aromatic character.

The majority of 1,3,4-thiadizaole synthesis are based on thiosemicarbazide derivatives cyclisation. Other methods involve ring closure of dithio carbazates, acyl hydrazines, bisthioureas or inter conversions of oxadiazoles etc., into 1,3,4-thiadiazoles.

2.1.1 CHARACTERISTIC REACTIONS OF THE 1,3,4-THIADIAZOLES

➢ Substitution reactions:

Though 1,3,4-thiadiazole is a weak base, it forms salts of hydrochloride. It will resist the electrophilic substitution reaction generally, e. g. Nitration, Bromination and Sulfonation etc., do not take place. But the presence of strong electron donating groups like NH₂ at second position activates the fifth position for attack. Bak et al., have obtained 2(amo) 5(bromo) 1,3,4(thiadiazole) by bromination and subjected to reaction of Sandmeyers to get the corresponding 2-substituted 5-bromo 1,3,4-thiadiazole. Nitration and Halogenation of 2-arylamino 5-methyl 1,3,4(thiadiazole) occur in aryl nucleus. The halogen at second or fifth position is reactive and undergoes a variety of displacement of nucleophilic reactions. In fact thiadiazole is susceptible to nucleophilic attack at second or fifth position as both are activated sites. The nucleophilic sensitivity attack e.g., the reaction of hydroxylamine in the presence of alkali leads to the synthesis of 2-aryl 5-amino thiadiazoles in about 45-70 percent yield. Also a substituent like amino, methyl, carboxy, halogen present at this position undergoes characteristic reactions. Though weak base, amino group of 2(amo) 1,3,4(thiadiazole) and its substituted
Compounds are readily acylated and diazotized. It undergoes reactions of Mannich with variety of reactive compounds of methylene. Alkylation takes place on ring nitrogen with halide in most of the cases suggesting the imino structure for alkylated product (Ohta, 1953).

Pentimalli et al., (1975), have synthesized different derivatives of thiadiazoles and reported the various types of reactions of electrophilic substitution of diaryl and 2(alkyl) 6(aryl) imidazo substituted 2,1-b 1,3,4-thiadiazoles taking place at fifth position.

Burmistrov et al., (1984), have given the important reactions of 2(aminio) 1,3,4(thiadiazoles) with secondary alcohols and tertiary alcohols in presence of 80-99 percentage of sulphuric acid giving the corresponding derivatives of 2-alkyl amino 1,3,4(thiadiazoles) in better yields.
Ring cleavage and rearrangement:

1,3,4-thiadiazole is susceptible to the attack by strong nucleophiles, at the carbon atoms which is explained by an account of the poor electron density created by electronegative nitrogen atoms e.g., 2-amino and 2-methyl amino thiadiazoles are rearranged to the isomeric triazole 3-thiones on heating with methylamine at 150\(^0\) C. 2-amino thiadiazole on heating with benzyl amine gave a mixture of 2-benzylamino 1,3,4-thiadiazole and 1-benzyl triazole 3-thione (Geordeler and Galinke, 1957).

Such arrangements are reported to take place via ring opening to an intermediate carbohydrazone derivative (amidrazone), which further recyclises to triazolo 3-thione in the basic medium.

Pyl et al., (1963), have done the research work on the ring cleavage reaction of thiadiazole compound (8) with ethanolic hydrazine hydrate. The reaction involves the ring cleavage reaction of thiadiazole by heating hydrazine hydrate.

Where, R= H, CH\(_3\); R\(^1\)= Me, Ph, p-bromo
Similar work is done by Barnish and their groups in 1980 and have given the report on the reaction of thiazole ring cleavage by heating with sodium hydroxide in the following derivative.

![Reaction 1](image1)

**Hough, (1983),** have studied regarding 2,6-di-t-butyl 5-nitroimidazo 2,1-b (1,3,4)thiazoles to reduction reaction with moiety of sodium dithionite. An unexpected reaction i.e. imidazole ring cleavage is reported as shown below which is quite unusual.

![Reaction 2](image2)

➢ **Nucleophilic displacement reactions:**

**Ingendoh el al., (1985),** have prepared thiazoles by nucleophilic displacement reaction. They have synthesized 2-alkyl amino imidazo substituted (2,1-b) 1,3,4(thiazoles) by the reaction with appropriate compound of alkyl amine.

![Reaction 3](image3)

**Hough, (1983),** obtained cyano derivatives by treating the bromo derivative with compound of cuprous cyanide in dimethyl formamide. By his research he reported that bromine derivative of 2,6(di-t-butyl) 5(bromo) imidazo substituted 2,1-b (1,3,4) thiazoles cannot be displaced by the action with alkylamine or ammonia.
The spectral studies involving UV, IR, \(^1\)HNMR, Mass, \(^{13}\)CNMR spectroscopic data of imidazo derivatives of 2,1-b 1,3,4(thiadiazole) have been reported by Torogova et al., in 1988 and the mass spectral fragmentation of some 2-arylamino 5-alkyl 1,3,4-thiadiazoles and 2(alkyl) 6(aryl) imidazo substituted 2,1-b (1,3,4)thiadiazoles was by Khazi et al., in 1994, wherein they observed the Mc Lafferty rearrangement of many of these molecules.

Kano et al., (1972), have prepared 5-thiocyanato derivatives of (17) by the reaction of the 5-bromoderivative with potassium thiocyanate.
➢ Tautomerism:
By the reaction of tautomerism 2-hydroxy 1,3,4(thiadiazole), 2(mercapto) 1,3,4 (thiadiazole) and 2(amo) 1,3,4(thiadiazole) have been reported to exist in the tautomeric forms as shown below.

\[
\begin{align*}
\text{N} \quad \equiv \quad \text{N} \\
\text{S} \quad \equiv \quad \text{S} \\
\text{X} \quad \equiv \quad \text{X}
\end{align*}
\]

\[\text{H} + \quad \text{N}_{2}\]

Where \(X = \text{O, S, NH}\)

Both hydroxyl and mercapto-1,3,4-thiadiazoles exist mostly in ketoform (20) in free state. But their hydroxyl or thiol function is often elicited during the chemical reactions (Katritzky and Logowski, 1963).

Mesoionic 1,3,4-thiadiazoles:

The interest in the mesoionic 1,3,4-thiadiazoles is reviewed to study the physico-chemical aspects of varieties of mesoionic compounds containing heteroaromatic rings. Kurzer et al., has given a concise account of mesoionic 1,3,4-thiadiazoles in a review article. Some of the mesoionic thidiazoles are given below.

\[
\begin{align*}
\text{Ph} & \quad \equiv \quad \text{Ph} \\
\text{Ph} & \quad \equiv \quad \text{Ph} \\
\text{S} & \quad \equiv \quad \text{S} \\
\text{Me} & \quad \equiv \quad \text{Me}
\end{align*}
\]

Mesoionic 4-phenyl-5-aryl-1,3,4-thiadiazole-2-thione

Mesoionic 5-phenyl-4-methyl-1,3,4-thiadiazole-2-amine

The mesoionic 1,3,4-thiadiazole-2-thiones are reported to display large dipole moment, which is confirmed by X-ray photoelectron spectroscopy. Their characteristic UV, IR, NMR spectra are reported (Talukdar and Sengupta, 1970).

Macroheterocyclic product formation
An interesting reaction of condensation of 2,5-diamino-1,3,4-thiadiazole and phthalonitrile in ethylene glycol at 120° C, leads to the preparation of the following macro heterocyclic product (81%) has been reported (Borodkin and Kolesnikov, 1971).

![24]

Lot of information is given in the literature on spectral investigation of 1,3,4-thiadiazole and its compounds. Bak et al., have recorded the IR and NMR spectra of a number of thiadiazole derivatives. Reports on the mass spectra of some 2,5-di substituted 1,3,4-thiadiazole derivatives have provided data for fragmentation patterns in the system (Bottino et al., 1982).

By these studies on the chemical reactivities and the spectral features of 1,3,4-thiadiazoles we can summarize their properties as follows: 1,3,4-thiadiazole is a typical pseudo-aromatic molecule with dipole moment value of 3.25 D. It is stable to acid but affected by strong base leading to cleavage of ring. It resists electrophilic substitution reactions. Facile nucleophilic attack takes place at 2nd and 5th positions. Groups like methyl, halogen, NH2, COOH present in this position is reactive and exhibits its specific reactions. 2-hydroxy, mercapto and amino derivatives display behavior of tautomeric.

> **Free radical reactions:**

**Butler et al., (1973),** have reported the following reaction involving homolysis to C6H5OH and nitrogen by Gomberg-Bachman reaction.

![25](Ph)_2S_NHNO → Benzene (Ph)_2S_NHNO + N2
2.1.2 SOME ESTABLISHED METHODS FOR THE SYNTHESIS OF 1,3,4-
THIADIAZOLES

The process commonly employed for the preparation of 1,3,4-thiadiazole is the
cyclisation of thiosemicarbazide derivatives by incorporating the basic structural unit.
Other process involves the ring closure of acyl hydrazines, dithiocarbazates, bistioureas
or inter conversions of oxadiazoles into 1,3,4-thiadiazoles have also been reported.

- From cyclisation of acyl thiosemicarbazides

Hoggarth, (1949), for the first time reported the preparation of 2-amino-1,3,4-
thiadiazoles, by acylthiosemicarbasides cyclodehydration in presence of acid catalyst like
sulphuric acid, phosphoric acid etc. The required acylthiosemicarbazides are prepared by
treating and acid hydrazide with an isothiocyanate. They are also prepared by heating the
carbocyclic acid and thiosemicarbazides in the acid medium and are subsequently
cyclised.

\[
\begin{align*}
R & \quad \overset{\text{H}_2O}{\text{OH}} \quad 27 \\
\overset{\text{NH}_2}{\text{NH}} \quad \overset{\text{H}_2\text{SO}_4}{\text{S}} \quad 28 \\
\end{align*}
\]

\[ \overset{\text{R}}{\text{N}} \quad \overset{\text{N}}{\text{S}} \quad \overset{\text{NH}_2}{\text{R}} \quad 29 \]

Turner et al., (1988), have synthesized 2-amino 5-aryl thiadiazoles directly by treating
the mixture of the thiosemicarbazide with carboxylic acids PPA. Instead of PPA,
phosphorous oxy chloride can also be used.

Fulltop et al., (1990), have reported the cyclo dehydration reaction of thiosemicarbazide.
They used ethanolic hydrochloric acid for the reaction of cyclo dehydration of acyl
thiosemicarbazides.

Mahajanshetti and Udapudi, (1984), have prepared various derivatives of thiadiazoles.
They have synthesized these derivatives of thiadiazoles containing a long alkyl chain by
using phosphoric acid as dehydrating agent.
From 1,2-diacyl hydrazines and P$_2$S$_5$

Stolle, (1899), have prepared a number of 2,5-dialkyl thiadiazoles from 1,2-diacyl hydrazines and P$_2$S$_5$. Instead of using P$_2$S$_5$, thioacetylation of 1,2-diacyl hydrazine is effected by carboxy methyl dithioate which on heating yields 2,5-distubstituted thia diazoles.

![Chemical Structure](30-31)

From cyclisation of aminoguainidines and diaminoguainidines

Kurzer, (1970), prepared a number of 1,3,4-thia diazoles by acid catalyzed cyclisation of acyl thiosemi carbazides obtained from the reaction of aroyl isothiocyanates and aminoguanidine salts.

![Chemical Structure](32-33)

From the oxidation of thiosemi carbazides:

Young and Eyre, (1901), have synthesized various derivatives of thia diazoles. They prepared 2(amino) 5(phenyl) 1,3,4(thia diazoles) by the reaction of oxidative cyclisation of corresponding aldehyde thiosemi carbazone by ferric chloride.

![Chemical Structure](34)
• From carbohydrazide and acylisothiocyanate

Kurzer, (1977), synthesized a number of 2-hydroxy 5-acyl amino thiadiazoles by heating carbohydrazide with equimolar quantity of an acyl iso thiocyanate in dimethyl formamide at 100° C.

\[
\begin{align*}
\text{H}_2\text{NN}_2\text{NH} + \text{RCONCS} & \rightarrow \text{RCONCSNHNNH}_2 \\
\text{H}^+ & \rightarrow \text{RCONCSCO} \\
\text{RCONCSCO} \text{N-N-S-OH} & \equiv 35
\end{align*}
\]

• From hydrazine and hydrogen sulfide

Ruhlman, (1959), obtained 2,5-dialkyl-1,3,4-thiadiazoles in high yields via thia diazolidines prepared from the reaction of hydrazide, aliphatic aldehyde and hydrogen sulphide. The thia diazolidinones thus prepared were further dehydrogenated by sulphur in boiling pyridine.

\[
\begin{align*}
2\text{RCHO} + \text{H}_2\text{NNNH}_2 + \text{H}_2\text{S} & \rightarrow \text{RCONCSCO} \\
\text{S} & \rightarrow \text{RCONCSCO} - \text{H}_2 \\
\text{RCONCSCO} \text{N-N-S} & \equiv 36, 37
\end{align*}
\]

• From dithiocarbazates

Various dithiocarbazates readily undergo the desired cyclisation to form a 2(substituted) 5(mercapto) 1,3,4(thiadiazoles).
Guha, (1922), synthesized 2(amino) 5(mercapto) 1,3,4(thiadiazoles) by the reaction of carbon disulfide and thiosemicarbazide in presence of potassium hydroxide, followed by heating the intermediate potassium dithiocarbazate.

- From bisthioureas:
Formme, (1923), reported on bisthiourea and substituted bisthioureas when treated with 3% hydrogen peroxide are converted to 2,5-diamino 1,3,4-thiadiazole derivative.
• From 1,3-dipolar addition of diazomethane:

Kurzer, (1961), have reported an interesting method that involves the addition of diazomethane to an appropriate thiobenzyol chloride to yield 2(aryl) 1,3,4(thiadiazole).

Structure and reactivity of Imidazo substituted (2,1-b)1,3,4(thiadiazole):

Two types of bicyclic imidazo substituted (2,1-b)1,3,4(thiadiazole) ring system are possible.

Imidazo substituted (2,1-b)1,3,4(thiadiazole) and (5,1-b)1,3,4(thiadiazole)
Both types contain nitrogen atom as a bridgehead atom at 4\textsuperscript{th} place. Ban and their group have reported the preparation of some derivatives of imidazo substituted (2,1-b) 1,3,4(thiadiazole) in 1952 and since then many reports on this work have been published containing different aspects of this system of bicyclic. Systematic work was not carried out covering all chemical and physical characters of the bicyclic system. A brief work on the structure and chemical reactivity of the chemical reactivity and information of this system (I) is given below.

Important resonance structure of (I) are given below

These structures resonance indicates greater will be the \( \pi \)-electrons delocalization in the imidazole nucleus, while the thiadiazole nucleus containing double bond is almost localized. In this structure I will be the highest contributing structure.

Schenetti, (1980), have given important work on the protonation and the structure of the imidazo substituted (2,1-b)1,3,4(thiadiazole) by spectroscopic method of \(^1\text{HNMR},\) model of ring current performance, X-ray analysis and their calculations. Some of the most important points of the work are given below.

- Electron delocalization as given from experimental measurements, both NMR and calculations involves electrons moving from thiadiazole to imidazole ring. This causes the de shielding of H2 whereas H5 and H6 appear at low field with respect to the thiadiazole parent and imidazole system respectively.
- Out of the three atoms of nitrogen of structure, N7 will be the basic center. The order of basicity is N7 \( > \) N3 \( > \) N4. Because of this, protonation occurs initially or first at N7 and then at position of N3.
- Density of \( \pi \) electron charge measurements indicates that the nucleus of imidazole is rich in density of \( \pi \) electron having more at position of N7 and then at fifth position.
The system I is bioisosteric and electronically isosteric with imidazo (2,1-b) thiazole. However the presence of nitrogen at third position of I causes a lot of difference in electronic and chemical behaviour. Ex. H-2 of unsubstituted I appear at delta 8.56 where as that of thiazole analogue appears at delta 6.73. The bridgehead nitrogen in both systems is responsible for downfield shift of 5-H compared to 6-H. The bicyclic imidazo substituted (2,1-b)1,3,4(thiadiazole) can be constructed with an appropriately substituted 2-amino 1,3,4-thiadiazole moiety and building the imidazole ring or vice versa. The first method is commonly used.

➢ **From cyclisation of N-1,3,4-thiadiazol-2-yl) formamidelines:**

Fajgelj et al., (1987), have reported a method for the preparation of imidazo substituted (2,1-b)1,3,4(thiadiazole). Here the method involves the transformation of N-1,3,4-thiadiazol 2yl formamidinies to the corresponding bicyclic system by cyclisation with phenacyl bromides.

![Chemical diagram]

This route provides a useful method for the synthesis of imidazo substituted (2,1-b) 1,3,4(thiadiazoles) having a benzoyl group at fifth position without any substituent at sixth position.
From the condensation reaction of 2(amo)1,3,4(thiadiazoles) with α halo ketones:

A mixture of an appropriately substituted 2-amino 1,3,4-thiadiazole and halo ketones is heated in a suitable solvent medium for 6 to 10 hrs. Hydro halides are obtained in good yields. The respective free bases are obtained by neutralization of salts with sodium carbonate solution. The method provides required substituent at second, fifth, and sixth position by starting with appropriate substituted synthons (Matsukawa and Ban, 1952).

\[
\text{NH}_2 \quad + \quad R^1\text{COCHBrR}^2 \quad \xrightarrow{\text{Solvent}} \quad R^1\text{COCHNR}^2\]

The ring nitrogen of the thiadiazole is involved in the nucleophilic displacement of halogen of haloketone forming the intermediate as shown above. It undergoes further cyclo dehydration on heating in a suitable medium like dimethyl formamide, ethanol to afford imidazo substituted (2,1-b)1,3,4(thiadiazole) in good yield. The cyclo dehydration involves nucleophilic intermolecular addition of the 2-imino group to carbonyl function of the intermediate followed by the water elimination. Various reports are available in the literature which involve this method for the synthesis of imidazo substituted (2,1-b) 1,3,4(thiadiazole).

From 1-amino 2-mercapto 4,5-disubstituted imidazoles:
Pyl et al., (1963), have reported that 2-benzyl mercapto 5,6-disbustituted imidazo substituted (2,1-b)1,3,4(thiadiazole) on heating with hydrazine hydrate is cleaved into the corresponding 1-amino 2-mercapt (4,5) di substituted imidazole. Further they built thiadiazole ring on this moiety by cyclisation of 1-acyl derivative in phosphphoryl oxy trichloride as shown below.

![Chemical Structure](image)

A number of 2(sulfamoyl) imidazo sibstotituted (2,1-b)1,3,4(thiadiazole) compounds were prepared by Barnish et al., in 1980. They have reported them as carbonic anhydrase inhibitors

![Chemical Structure](image)

R¹ = H, CH₃, C₂H₅, isopropyl, n-butyl, ph, t-butyl

R² = H, CH₃, Ph.

Many of these derivatives showed the same ionization as methazolamide and acetazolamide with higher character of lipophilic. They were tested for activity of anticonvulsant. Derivative (51) (R¹=t-butyl and R²=H) had an anticonvulsant when administered to mice orally. This derivative specifically increased cerebral blood flow in animals without forming a high level of metabolic acidosis.

Mazzone et al., (1984), have synthesized a number of imidazo substituted (2,1-b)1,3,4(thiadiazoles) and evaluated them for their analgesic, antiinflammatory antimicrobial and antipyretic activities.
**Abignentai et al., (1985)**, have done research work on the pharmacological activities of thiadiazoles. They have reported antipyretic, analgesic and ulcerogenic activities associated with imidazo substituted (2,1-b)1,3,4(thiadiazoles) of the following type.

![Chemical Structure 52](image)

\[R = \text{H, Me, Br, SCN, CHO}\]

Several new 1,3,4-thiadiazoles, imidazo substituted (2,1-b)1,3,4(thiadiazoles) and thiadiazole 3,2-pyrimidines derived from 1-ethyl or benzyl 2-(2-amino 1,3,4-thiadiazol 5yl) thio methyl benzimidazole were synthesized by Ashour et al., in 1990. They found them as very good activity of antimicrobial.

**Suzuki et al., (1992)**, have synthesized derivatives of thiadiazole. They have synthesized 1,2,3-triazolo 4,5-d pyrimidine derivatives as pharmacologically important molecules.

![Chemical Structure 54](image)

**Zhang et al., (2002)**, have prepared various 3,2(furanyl) 6(aryl) 1,2,4(triazolo)3,4b 1,3,4(thiadiazole) and reported that many of these derivatives are having significant promoting growth of effects on radicals of mug bean.
Andreani et al., (2002), have prepared new fused heterocyclic system with 2,7-di substituted di imidazo substituted (2,1b)1,3,4(thiadiazole) and di imidazo 1,2-pyrimidine and studied their activity of antitumor on cell lines of human tumor.

Nalan et al., (2003), have synthesized some newer 2,6(dimethyl) substitutedphenyl methylene imidazo substituted (2,1b)(1,3,4) thia diazole 5(carbohydrazides) (59) from 2,6(dimethyl) imidazo (2,1b)(1,3,4)thiadiazole 5(carbo-hydrazide) (58). The newly prepared derivatives were evaluated for the activity of anticancer. 2,6(dimethyl) N2 hydroxy phenyl methylene imidazo substituted (2,1b)1,3,4(thiadiazole) 5(carbo hydrazide) have shown the good cytotoxicity on cell line of ovarian cancer.
Gadad et al., (2004), have prepared derivatives of 2(sulfonamide) or (trifluro methyl) 6,4(substituted) aryl or hetero aryl imidazo (2,1b)1,3,4(thiadiazole) compounds and were evaluated for their preliminary invitro activity of antitubercular against strain of antimycobacterium tuberculosis using BACTEC radiometric and broth dilution methods. Further they have reported the preparation of 5-bromo, 5-thio and 5-guanyl hydrazone compounds for the study of biological activity.

\[
\begin{align*}
\text{aryl or heteroaryl} & \\
R^1 &= \text{SO}_2\text{NH}_2, \text{CF}_3 \\
R^2 &= \text{Br}, \text{SCN}
\end{align*}
\]

Andreani et al., (2005), have synthesized and evaluated for antitumor activity of new guanyl hydrazones from imidazo 2,1-b thiazoles (61) and the new heterocyclic system thiazolo imidazo (4,5-c) quinolone (62). The derivatives were tested for antitumor agents. They are found to be active on cell lines.

Preparation of various imidazo substituted (2,1b) 1,3,4(thiadiazole) derivatives has been explained here briefly.
1,3,4-thiadiazole derivatives have prepared by the action of amino thiadiazoles with substituted phenacyl bromides. The derivative further subjected to manich reaction with formaldehyde with secondary cyclic amines in methanol with glacial acetic acid to yield different compounds. The imidazo 1,3,4-thiadiazole 5-carbaldehydes which were used to synthesize thiazolidine 2,4-dione derivatives have been utilized here to prepare various imidazo derivatives of (2,1b)1,3,4(thiadazole). The functional group of aldehydes has been exploited to prepare corresponding derivatives of nitriles, alcohols and thiazolidinone. The aldehyde reduction in methanol at room temperature yielded the carbinols respectively. The condensation of aldehyde with hydroxylamine hydrochloride in solvent pyridine yielded corresponding oxime, which on dehydration with thionyl chloride produced the corresponding nitrile in good yields. The aldehydes treated with aniline to get corresponding schiff’s base, which on refluxing with thioglycolic acid in benzene underwent cyclisation to yield the derivative of thiazolidinone.
The reaction of aldehyde with 2-amino thiophenol in dimethylsulfoxide yielded the derivative of benzo thiazole in high yield. All the structures of newly prepared compounds have been identified by their spectral and analytical data. Some of these derivatives were evaluated for their antifungal, antitubercular, anthelmintic, antibacterial and antiinflammatory activities.

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

➢ **From Acylhydrazines**

**Stolle and Hillis, (1904),** have found out the following reaction. The reaction of phosphorus penta sulfide with diacyl hydrazine was used by them for the formation of 2,5-di substituted thiazole.

\[
\begin{align*}
\text{R} - \text{CONH} - \text{NH} - \text{R'} + P_2S_5 & \rightarrow \\
\text{68} & \rightarrow \\
\text{N} - \text{N} - \text{S} - \text{R} - \text{R'}
\end{align*}
\]

➢ **From Thio-semicarbazides**

**Hoggarth, (1949),** was the first person to report cyclo dehydration of acyl
thiosemicarbazides in presence of catalyst acid like phosphoric acid, sulphuric acid etc., to get different 2,5-substituted thiadiazoles. The required acyl thiosemicarbazides are obtained by treating an acid hydrazide with an isothiocyanate.

\[
\text{ArCOOH} + \text{NH}_2\text{CSNHNH}_2 \xrightarrow{\text{Sulphuric acid}} \text{70}
\]

\[
\text{71}
\]

They have also prepared by heating the carboxylic acid and thiosemicarbazide (NH\textsubscript{2}CSNH\textsubscript{2}) in the acidic medium and are cyclized subsequently.

\[
\begin{align*}
\text{R} & \quad \text{NH} \quad \text{Ar} \\
\text{NH} & \quad \text{NH} \\
\text{O} & \quad \text{S} \\
\end{align*}
\]

\[
\xrightarrow{80\% \text{ H}_2\text{SO}_4} \\
\begin{align*}
\text{R} & \quad \text{N} \quad \text{N} \quad \text{S} \\
\text{S} & \quad \text{NH} \quad \text{Ar} \\
\end{align*}
\]

\[
\text{72}
\]

They have prepared a number of derivatives of 1,3,4-thiadiazoles from the corresponding thiosemicarbazides by using phosphoric acid as the dehydrating agent. Further he reported that sulfuric acid was also effective in these reactions. Using this method Sherman et al., (1961), synthesized 2(substituted amino) 5-nitro 2-furyl thiadiazoles (**73**) from the corresponding thiosemicarbazides.

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{S} \quad \text{N} \\
\text{N} & \quad \text{N} \quad \text{N} \quad \text{S} \\
\text{N} & \quad \text{N} \quad \text{NH} \quad \text{R} \\
\end{align*}
\]

\[
\text{73}
\]
From 1,2-diacyl hydrazines and P₂S₂

Stolle et al., (1904), prepared a number of 2,5-dialkyl-1,3,4-thiadiazoles from 1,2-diacyl hydrazines and P₂S₂. The method is known after stole. Instead of using P₂S₂, thioacylation of 1,2-diacyl hydrazine is effected by carboxy methyl dithiate which on heating gives 2,5-disubstituted thiadiazoles.

Hoggarth, (1949), was the first to effect cyclodehydration of acyl thiosemicarbazides in presence of catalyst like phosphoric acid, sulphuric acid etc., resulting into varieties of 1,3,4-thiadiazoles. The required acyl thiosemicarbazides are obtained by treating an acid hydrazide with an isothiocynate. They have also prepared by heating the carboxylic acid and thiosemicarbazide in the medium and are subsequently cyclized.

\[
\text{RCOOH} + \text{NH}_2\text{CSNHNH}_2 + 80\% \text{H}_2\text{SO}_4 \rightarrow \text{74}
\]
From Carbonohydrazide and aroylisothiocynate

Kurzer et al., (1970), prepared a number of 2-hydroxy 5-acyl amino thiadiazoles by heating carbon hydrazide with equimolar quantity of an aroyl isothiocynate in dimethyl formamide at 100°C.

Padmavathi et al., (2009), prepared derivatives of 1,3,4-thiadiazole by using following method. 1-Benzoyl-4-phenyl thiosemicarbazide on treatment with acetyl chloride yielded aniline 5-phenyl substituted 1,3,4-thiadiazole (78), but gave 3,4-diphenyl 5-mercapto triazole (79) when acted upon by access of benzoyl chloride or treated above its melting point.
Vogel, (1978), synthesized many compounds of 2-mercapto 5-alkyl or arylamino thiadiazoles (80). These were synthesized by using 4-substituted thiosemicarbazides (81) with carbon disulphide in dimethyl formamide.

\[
\begin{align*}
\text{R} &= \text{alkyl; R} = \text{aryl} \\
\text{In our present investigation we adopted the reaction sequence as applied by Jain and Mishra, (2004), for the synthesis of reported compounds.}
\end{align*}
\]
Turner et al., (1988), were prepared 2-amino 5-aryl thiazole directly by heating the thiosemicarbazide and acid mixture with PPA, i.e. Polyphosphoric acid. Synthesized derivatives were characterized by elemental analysis and spectroscopic data.

\[
\text{R} - \text{COOH} + \text{H}_2\text{NCSNHNH}_2 \xrightarrow{\text{PPA}} \text{82}
\]

Where R = 2SCH₃, R = 2SOCH₃, R = 2,6(OCH₃)₂

Ram et al., (1990), have synthesized the various derivatives of thiazole starting from the acid hydrazides. Synthesized derivatives were characterized or identified by elemental analysis and spectral data. Final derivatives were synthesized by using phosphoric acid with acid hydrazides.

\[
\text{ArHN} - \text{NHAr} \xrightarrow{(\text{CH}_2)_5} \text{83}
\]
From Cyclization of aminoguanidines and diaminoguanidines

Kurzer, (1970), prepared a number of 1,3,4-thiadiazoles by acid catalyzed acyl-thiosemicarbazide cyclization which is obtained from the reaction of aminoguanidine salts and arylisothiocyanates. Synthesized compounds were identified by elemental analysis and spectral data.
They have 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-thiadiazole was obtained in good quantity. Aminoguanidine and its derivatives are important compounds for the 1,3,4 thiadiazole synthesis.
From Hydrazides and Aryl isothiocyanates

Kurzer, (1971), synthesized a number of 2-hydroxy-5-acylamo-1,3,4-thiadiazoles by heating carbonohydrades with equimolecular quantity of an aroylisothiocyanate in DMF at 100°C.
Poll, (1984), have synthesized various derivatives of 1,3,4-thiadiazoles by using starting material aminoguanidine. They showed that thiobenzoylthioacetic acid and aminoguanidine or 1-amino-3-phenylguanidine reacts in aqueous sodium hydroxide solution to yield N-(thiobenzamido) guanidine or 1-phenyl-3-thiobenzamido guanidine. Compound undergo cyclisation with boiling hydrochloric acid, with loss of ammonia to yield 1,3,4-thiadiazoles compounds.

Servi et al., (2005), have synthesised novel derivatives of arylthio (methyl) carbamates, arylidythio (dimethyl) carbonimidates and 2aryl-amino 2-imidazoline and reported for antimicrobial activity.
Synthesised newer compounds of aryl-thio (methyl) carbamates, arylidithio (dimethyl) carbonimidates and 2aryl-amino 2-imidazoline have shown very good activity of antimicrobial.
Aromatic amine + S=C=S + H₃C—I

\[
\begin{align*}
\text{NaOH} & \quad \text{DMF} \\
& \downarrow \\
\text{Ar} & \quad \text{N} \\
& \quad \text{S} \\
& \quad \text{S} \\
& \quad \text{R} \\
& \quad \text{CH}_3 \\
\end{align*}
\]

+ 

\[
\begin{align*}
\text{H}_2\text{N} \\
\text{H}_2\text{N} \\
\end{align*}
\]

\[
\begin{align*}
\text{DMF} & \quad 120 \\
& \downarrow \\
\text{N} & \quad \text{N} \\
& \quad \text{Ar} \\
\end{align*}
\]

\[
\begin{align*}
\text{R}^2 & \quad \text{N} \\
& \quad \text{S} \\
& \quad \text{N} \\
& \quad \text{NH} \\
& \quad \text{N} \\
\end{align*}
\]

89

These derivatives of carbamates, carbonimidates and imidazoline are characterized by the data of elemental analysis and spectroscopy.
Wang et al., (2010), prepared the newer compounds of thiazole. Thiazole derivatives of 2(amino)substituted 1,3,4(thiazole) has given important process for the synthesis of newer derivatives of thiazoles.

\[
\text{R = C}_6\text{H}_5\text{OCH}_2; \text{R= 2-ClC}_6\text{H}_4\text{OCH}_2; \text{R = 2-CH}_3\text{C}_6\text{H}_4\text{OCH}_2; \text{R = 4-CH}_3\text{OC}_6\text{H}_4}
\]

In their research work they have prepared various N-formyl compounds.
2.1.3 Therapeutic potential of 1,3,4-thiadiazoles

A brief account of the information on biological activities of some 1,3,4-thiadiazoles is given below with a view to appreciate their importance. Number of Thiadiazole compounds (92) has been synthesized since the discovery of potent sulfa drugs containing this nucleus after the second world war.

\[
\begin{array}{c}
\text{N} \\
\text{S} \\
\text{1} \\
\text{2} \\
\text{3} \\
\text{4} \\
\text{5}
\end{array}
\]

1,3,4-thiadiazole chemistry development started since the interesting reports on the antibacterial activity of 2-sulfonamido-5-substituted-1,3,4-thiadiazoles.

\[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{H}_3\text{C} \\
\text{N} \\
\text{S} \\
\text{N} \\
\text{O} \\
\text{NH} \\
\text{OMe} \\
\text{SO}_2
\end{array}
\quad
\begin{array}{c}
\text{N} \\
\text{S} \\
\text{R} \\
\text{NH}_2 \\
\text{NH}_2 \\
\text{SO}_2 \\
\text{NH}
\end{array}
\]

93

94

Sherman and their co-workers have prepared a number of 2(amo) 5(5-nitro 2-furyl) 1,3,4(thiadiazole) as antibacterial and tested them orally and by intramuscular route in the infected animals. He found that the free amino group conferred maximum activity compared to the 2-substituted amino derivatives. This view was further strengthened by the observation of an active drug against the infection of gastrointestinal tract. Prepared derivatives were characterized by the spectral and elemental analysis data.

\[
\begin{array}{c}
\text{O}_2\text{N} \\
\text{S} \\
\text{N} \\
\text{N} \\
\text{NH}_2 \\
\text{N}
\end{array}
\]

95
Bonía et al., (1970), prepared a number of 2(amo) 5(2-sulfomoyl phenyl) 1,3,4(thiadiazole) 96 (R = H, Me, CH₂CH=CH₂ and C₂H₅) and tested them against DNA and RNA virus. (R=Me) was most active against virus of RNA while rest of them were not shown good activity.

![Chemical Structure](image)

Brookes et al., (1950), have reported the sulphonamides antitubercular activity of a number of 2-amino 5-alkyl 1,3,4-thiadiazoles, where alkyl group ranged from sixth carbon to seventeen carbon. Lower alkyl substituted compounds showed better *invivo* tests activity.

Miyahara et al., (1982), have tested twenty compounds of the thiadiazole derivatives and reported that compound (R=NH N (NO) Me and R1=H, Me, SH or SCH₂Ph) were most effective against both mouse lymphoid leukemia and rat as ascites hepatoma.

![Chemical Structure](image)

Where R=NHCONHMe, NHCONHEt, NHCON(NO)Me  
R’= H, Me, SH or SCH₂Ph

A review article on the pharmacology of 2(amo) 1,3,4(thiadiazole) compounds in the study of cancer chemotherapy is given by Hill in 1980.

Ermili and Cortese, (1968), have synthesized a number of 5-hetero aryl methyl thio 1,3,4-thiadiazole derivatives of possible antiulcer agents. Many of the synthesized derivatives have shown very good antiulcer activity as compared to standard drugs.
1,3-bis 5-alkyl 1,3,4-thiadiazole 2yl ureas were tested for hypoglycemic activity by Ermili and Cortese in 1968. The compounds were found to be good hypoglycemic agents. 

Hokfelt, (1962), prepared the following derivatives of sulphonamides and reported them as potent agents of hypoglycemic. R=C₃-₅ alkyl group.

Neal et al., (1962), have reported oral potent hypoglycemic activity in dogs and rats for 2-para toluene sulfonamide 5-cyclohexyl 1,3,4-oxadiazole and thiadiazole derivative. The latter compound showed very good potent activity.
Grant et al., (1972), have prepared the derivatives of the following type and reported their activity of hypotensive after administering orally as a suspension in 2% gelatin to conscious male rats. Some of them $R^2 = \text{NHCONHC}_6\text{H}_5$, \text{NHCOCH}_3 caused significant blood pressure reduction.

![Chemical Structure 101](image1.png)

Where $R_1 = \text{H and C}_2\text{H}_5$

$R_2 = \text{NHCOCH}_3, \text{NHCOOCH}_3, \text{NHCOOC}_2\text{H}_5$

Turner et al., (1988), prepared 2(aryl) 5(hydrazine) and 2(aryl) 5(guanidine) 1,3,4(thiadiazole) having activity of vasodilator and evaluated them for antihypertensive activity. They have shown that 2-substituted phenyl ring increased the activity in both the cases, particularly in 2-ethylphenyl and 2-tolyl substituted derivatives were most potent derivatives amongst the series. They further concluded that lowering the blood pressure by these derivatives was due to a direct relaxant effect on smooth muscles of vascular.

Stillings et al., (1986), have studied a set of amino alkyl thiadiazoles and screened them for their activity of anticonvulsant. A derivative of alkyl 5(nitrothienyl) substituted 1,3,4(thiadiazole) 2yl thio acetic acid esters were synthesized by Foroumadi et al., in 2003. They have evaluated the derivatives for invitro antitubercular activity against \textit{M. tuberculosis} strain using the radiometric BACTEC system and medium of BACTEC 12B. The derivatives are found to be very good antitubercular agents. Many of the compounds have shown good activity as compared to reference drugs.

![Chemical Structure 102](image2.png)

$R = \text{methyl, ethyl, n-propyl, n-butyl, benzyl}$
Some 2-aryl 5-hydrazino 1,3,4(thiadiazole) have been prepared and tested for the biological activity of antihypertensive by Turner et al., in 1988. The 2-methyl phenyl and 2-ethyl phenyl derivatives (103) and (104) were the most potent members of the series. Preliminary studies indicated that the action of hypotensive of these compounds was due to a direct relaxant effect on smooth vascular muscles.

Elcin et al., (2004), have reported a series of thiadiazoles i.e. 2,5(di-substituted) 1,3,4(thiadiazole) were prepared and evaluated for the biological activity of antituberculosis by using the radiometric BACTEC 460 system. In this among the evaluated compounds, 2-phenyl amino 5(4-fluoro phenyl) 1,3,4(thiadiazole) have shown the good activity. The relationships between the structures of derivatives and their activity of antitubercular were investigated by method of Electronic Topological and neural forward networks trained with the back propagation algorithm. As a result of the approach, a system of pharmacophores and anti pharmacophores has been list out. They have separated effectively derivatives under examination into groups of active and inactive derivatives. They concluded that 1,3,4-thiadiazole system can be applied to the evaluation and design of new active compounds.

Bambas et al., (1945), have prepared 2-amino 5-amino benzene sulfonyl thiazole which was found to be activity of antitubercular as well as anti-thyroid with less toxicity. Synthesized derivatives have shown good activity of antituberculosis as compared to reference drugs.
Dahlbom et al., (1947), have reported that hydroxyl promisole is as active as sulfathiazole in vitro towards haemolytic *streptococci*, Type I *pneumococci* and *E. coli*. It is twenty to forty times more active than Promisole but found to be toxic.

![Chemical structure](image1)

**106**

Blank et al., (1977), have prepared ethyl 5-methoxy benzyl thiazole 4-carboxylate (107), its corresponding carboxylic acid (108) and tested them for the activity of hypoglycaemic.

![Chemical structure](image2)

**107**

**108**

Garin et al., (1987), have prepared a series of 2-(2-thiazolyl amino) 1,3-heterocycles II using dimethyl dithio carbonimidates I, with various bi nucleophiles, in better yields.

![Chemical structure](image3)

**109**

R = H, 4-Cl, 6-NO₂, 6-OMe

**110**

X = O, S
In the light of the various applications of various 1,3,4-thiadiazoles derivatives, it was considered of interest to synthesize various derivatives bearing pharmacologically important moieties.

2.1.3.1 1,3,4-thiadiazoles as antimicrobial

Literature survey showed that most of the 1,3,4-thiadiazole compounds contain amino, hydrazine, oxo, thio or their substituted group at second position, and another amino, aryl, alkyl, or their substituted group or halogen at fifth position.

Padmaavathi et al., (2009), prepared a few 2-(aryl methane sulfonyl methyl)-5aryl 1,3,4-thiadiazoles and evaluated for the activity of antimicrobial (111).

![Chemical Structure](image)

R₁ = 4-Cl & R₂ = 2-Cl

111

Siddiqui et al., (2009), were synthesized a series of newer 5(Indol) 3yl methyl substituted phenyl 1,2,4(thiadiazol) amine compounds and tested for the activity of anti-fungal and anti-bacterial. Derivatives (112a) and (112d) showed more than 70% of inhibition respectively against S. aureus and compounds (112b), (112c) & (112d) shown 76% against E. coli. Compounds (112a) shown 70%, (112d) shown 85% and (112h) have shown 65% of inhibition against C. albicans.

![Chemical Structure](image)

2Cl, 3Cl, 2CH₃, 3CH₃

112 (a-h)
Karabasanagouda et al., (2007), have synthesized 1,2,4(triazolo) fused thiadiazoles containing 4-CH₃ or C₂H₅ thio and CH₃ sulfonyl urea phenoxy nucleus at 3ⁿᵈ position and tested for the activity of antimicrobial. They showed that all the derivatives (113) tested showed good antifungal and antibacterial activities against different strains.

![Chemical structure](image)

R=SCH₃, SC₂H₅ Ar = C₆H₅, 4 CH₃C₆H₄, 4 OCH₃C₆H₄

113

Suman and Bahel, (1979), established the activity of antifungal for certain aryl oxy substituted 1,3,4(thiadiazole) derivatives. During their study on correlation between structure and activity of the prepared compounds they observed that the compound (114) with 3, 4-Me (Cl) C₆H₅O group had the highest activity. However, the thiadiazole derivatives (115) were shown to be more active than oxadiazoles (115).

![Chemical structure](image)

114 and 115

R=3-MeC₆H₄, 4-MeC₆H₄, 4-Et C₆H₄; R₁=Ph, 3,4-Me (Cl) C₆H₅O; X=O, S

Arunkumar et al., (1999), have reported numerous 2-anilino/ally amino/alkyl amino 5nitro 2-furyl 1,3,4-thiadiazoles (116) were found to inhibit the growth of *staphylococcus aureus*, *Salmonella shigella* and other bacteria.

![Chemical structure](image)

116

R = alkyl, aryl, allyl.
Karabasanagouda et al., (2007), reported antifungal activity of some derivatives of thiadiazoles. In this research work, certain aryl oxy thiadiazoles (117) have shown to be potent activity of antifungal. It was reported that the compound where $R = 4$-Cl, $R = 4$-MeO, $X = S$ inhibited the growth of A. flavus 90% at 1:1000 concentration, 66.4% at 1:10,000 concentration and 47.2% at 1:100,000 concentrations.

$$\begin{align*}
R &= H, 2 \text{ and } 4\text{-chloro}, 2\text{-Me}, 3\text{-Me}, 4\text{-Me} \\
R_1 &= 4\text{-Cl}, 4\text{-MeO}. \quad X = S, O.
\end{align*}$$

Sharma et al., (2002), have reported the preparation of some novel indolyl substituted thioadiazolyl pyridilines and indolyl substituted oxadiazolyl pyrazolines which have shown potential anti-inflammatory activity.

$$\begin{align*}
\text{118} \\
R &= C_6H_5, C_6H_5OCH_3
\end{align*}$$

Zamani et al., (2004), have reported the synthesis of some newer naphthyl and pyridil substituted thaidazole and triazole derivatives. The antibacterial studies of some of the synthesized derivatives are done against different strains by using MIC method.

$$\begin{align*}
\text{119} \\
\text{120}
\end{align*}$$
2.1.3.2 1,3,4-thiadiazoles as anticonvulsant

**Pradeep et al., (2006),** have synthesized of 2-methyl 1,3,4-thiadiazoyl 4,3 (quinazolinones) (122) compounds and tested for the activity of anticonvulsant and the activity of CNS depressant. Synthesized derivatives are identified by elemental and spectral analysis data.

![Diagram](image)

**122**

R = CH₃, C₃H₇, C₆H₅.

**Varsha et al., (2008),** have prepared newer compounds of 3-5-substituted 1,3,4(thiadiazole) quinazoline-(3H)-ones and are tested for sedative, CNS depressant and anticonvulsant activities. Out of 18 compounds only 4 a, d, e, j and k showed good activity of anticonvulsant. It is also observed that some of the compounds have shown good activity of CNS depressant.

![Diagram](image)

**123**

R = C₆H₅, p-OCH₃C₆H₄, p-CH₃C₆H₄,
Ar = C₆H₅, p-OCH₃C₆H₄.
2.1.3.3 1,3,4-thiadiazoles as antitubercular

Karakus and Rollas, (2002), have reported that thiadiazole derivative, namely 2(4-chloro phenyl amino) 5(4-amino substituted phenyl) 1,3,4(thiadiazole) showed fifty seven percentage of inhibition against *M. tuberculosis*.

\[
\text{F} - \text{C} = \text{N} - \text{S} \quad \text{NH} - \text{C} - \text{F} \\
\text{124}
\]

Rao and Srinivasan, (1964), reported the structure activity relation of 4-arylthiosemicarbazones and their cyclised products like 2aryl-amino 1,3,4-thiadiazoles (54) against *M. tuberculosis* invitro. No definite conclusions were drawn regarding the effect of substituents in benzene rings. Most of the compounds showed interesting activity even at low dosage.

\[
\text{C} = \text{H}_2 \text{NHC} = \text{SNH} = \text{CHAr} \\
\text{[O]} \\
\text{\text{125}} \\
\text{Ar=p-tolyl, p-hydroxy phenyl and m-hydroxy phenyl}
\]

Bhat and Shenoy, (2001), reported the synthesis of 7-nitro-2-methyl-5aryl 1,3,4-thiadiazol 2yl amino methyl quinazolinone (126). The compounds were found to be active against *Mycobacterium tuberculosis*. 
Ramachander and Srinivasan, (1962), studied the structure activity relationship of 4-aryl-thiosemicarbazones and their cyclized products (127) against Mycobacterium tuberculosis. It was observed that most of the derivatives have shown good activity of antituberculosis.

\[
\text{Ar} = 2-\text{Cl-Ph}; 4-\text{NO}-\text{Ph}
\]

126

Nilufer and Sevim, (2006), synthesized the 4amino phenyl thia diazoles and their schiff’s bases. A schiff’s base series were synthesized by the reaction of 1,3,4-thiadiazoles containing aromatic amine and hydroxyl benzaldehyde, salicylaldehyde, nitro furfuraldehyde or nitro benzaldehydes.

Choudhary et al., (1995), have prepared the 2,3(methyl) 7(substituted) 1,4(benzo thiazine) 2yl 5(un)substituted analino 1,3,4(thiadiazole) (128) and evaluated for antitubercular activity. Many of the derivatives synthesized have shown very good activity of antituberculosis.

\[
\text{R} = \text{alkyl}, \text{R}_1 = (\text{un}) \text{substituted aniline}
\]

128
Alireza et al., (2003), have reported the synthesis of some newer antitubercular agents. They have synthesized various derivatives of alkyl nitro 2thienyl substituted 1,3,4-thiadiazole 2yl thio acetates (129).

\[
\text{O}_2\text{N} - \text{S} - \text{N} - \text{S} - \text{SCH}_2 - \text{O} - \text{OR}
\]

129

\[ R = \text{Methyl, Ethyl, n-Propyl.} \]

2.1.3.4 1,3,4-thiadiazoles as analgesic and anti-inflammatory

Kumar et al., (2007), have reported the preparation of heterocyclic fused triazolo-1,3,4-thiadiazole compounds of naproxen moiety. These derivatives are having antiinflammatory and analgesic activities similar to derivatives of naproxen, but with lesser damage to gastric. Final derivatives (130) and (131) are tested for the activity of antiinflammatory.

\[
\begin{align*}
\text{MeO} & - \text{N} - \text{N} - \text{N} - \text{N} - \text{N} - \text{S} - \text{R} \\
& \quad \quad \quad \quad \quad \quad \quad \\
130 & \quad \quad \quad \quad \quad \quad \quad \\
\text{R} & = \text{C}_6\text{H}_5, 4-\text{Cl}-\text{C}_6\text{H}_4, 2,4-(\text{Cl})_2-\text{C}_6\text{H}_3, 2-\text{NH}_2-\text{C}_6\text{H}_4.
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & - \text{N} - \text{N} - \text{N} - \text{N} - \text{N} - \text{S} - \text{N} - \text{H} - \text{R}^1 \\
& \quad \quad \quad \quad \quad \quad \quad \\
131 & \quad \quad \quad \quad \quad \quad \quad \\
\text{R}^1 & = \text{n-C}_4\text{H}_9, \text{C}_6\text{H}_5, 2,4-(\text{CH}_3)_2-\text{C}_6\text{H}_3
\end{align*}
\]

Amir et al., (2007), reported the preparation and pharmacological activity of triazolo fused 1,3,4(thiadiazole) compounds of bi-phenyl 4yl oxy acetic acid and ibuprofen. The tested derivatives (132) and (133) showed very good anti-inflammatory activity.
Arvind et al., (2009), synthesized and evaluated some new derivatives of thiadiazoles. The preparation of thiadiazoles from thiosemicarbazide is done by benzoyl chloride and thiosemicarbazide condensation by using calcium chloride guard tube. All the new compounds have been identified by $^1$HNMR and MASS spectroscopy and all newly derivatives are studies for their analgesic activity.

Sawhney et al., (1993), have studied the preparation and the pharmacological activity of antiinflammatory of some newer 3,5(alkyl amine) or 4(unsubstituted) aniline 1,3,4 (thiadiazolyle) 1,2(benzo isothiazoles) (134). From this work some of the derivatives have shown very good pharmacological activity as compared to reference drug Ibuprofen in rats.

![Chemical structure](image)

134

$R =$ alkyl, (un) substituted phenyl.

2.1.3.5 1,3,4-thiadiazoles as anticancer

Matysiak and Opolski, (2006), synthesized a number of 2(amino) 2,4(dihydroxy) phenyl 1,3,4(thiadiazole) and tested for the activity of anti-proliferative by aryl, alkyl and morphino alkyl compounds. The anticancer activity against four cell lines of human was determined.
2.1.3.6 1,3,4-thiadiazoles as antioxidant / radio-protective

Kus et al., (2008), prepared some newer substituted benzimidazole phenyl 1,3,4(thiadiazole) 2-amine and tested for the activity of antioxidant. Compound (136) exhibited most active compound that inhibits lipid peroxidation.

\[
\begin{align*}
\text{H}_3\text{C} & \text{NH} \quad \text{X}=5,6\text{-dichloro; Y}=3,4\text{-dimethyl} \\
\text{X} \quad \text{Y} 
\end{align*}
\]

2.1.3.7 1,3,4-thiadiazoles as antiviral

Giri and Srivastava, (1983), synthesized compound (137) and (138) and tested them against *Alternaria brassicae F* and *Helminthosporium oryzae* for its antiviral activity. They have shown that the synthesized derivatives have shown good activity of antiviral as compared to standard drugs used.

\[
\begin{align*}
\text{R} \quad \text{N=NH}_2 \\
\text{R} \quad \text{N=NNHCNCSNH}_2 \\
\end{align*}
\]
2.2 CHEMISTRY OF SCHIFF’S BASES

A German chemist Hugo (Ugo) Schiff has identified the Schiff’s bases and he was responsible for research study into different aldehydes and name is given as Schiff test after his discovery in this part. He also done work in the field of biuret reagents and amino acids and derivatives having (-CH=N-) groups and are now known as Schiff bases. They are prepared by the condensation of a carbonyl compounds with primary amine according to the following scheme by Karthikeyan in 2006.

\[ \text{R-CHO} + \text{H}_2\text{NR}^1 \rightarrow \text{RCH=NR} + \text{H}_2\text{O} \]
\[ \text{R} = \text{Aromatic or Aliphatic group.} \]

Derivatives of aliphatic aldehydes containing Schiff’s bases are unstable relatively and are polymerizable readily. In case of aromatic aldehydes which are having system of conjugation are more stable effectively. Reaction of condensation of aldehydes with amines and ketones has number of uses which includes detection, preparative use, determination and identification of ketones or aldehydes, purification of amino or carbonyl derivatives or protecting these groups during sensitive reaction or complex action by Walsh and their coworkers in 1996.

2.2.1 Therapeutic potential of Schiff’s bases (Lehlinger, 1975)

A brief account of the information of pharmacological activities of some Schiff’s bases is given below with a view to appreciate their importance. Schiff’s bases are the important intermediates in a number of various enzymatic reactions involving interaction of carbonyl group with enzyme or the substrate containing amino group.

They have also carried out research work on stereo chemical with the aim of Schiff’s bases molecular models formed between the lysine side chain containing amino group of proteins and methyl glyoxal towards the nitrogen of peptide that a transfer charge can occur between the oxygen atoms of the Schiff bases. By this respect, amino acids derived pyridoxal Schiff’s bases are considered as important ligand from the pharmacological point of view.
Desai et al., (1999), have done work on the preparation of some new sulphonamides, 1,3,4-oxadiazoles, 5-imidazolinones, azomethanes, 2-azetidinones, 4-thiazolidinones, formazans and terazolium chlorides which have shown good activity of antimicrobial against different strains of organisms. Derivatives also exhibited the activity of antifungal against A. awamori at 50 mg/ml concentration. They have prepared the final derivatives by coupling reaction of solution of sulphonamides with azomethine in pyridine at temperature 0-5\(^\circ\) C.

Desai KG and Desai KR, (2005), have prepared active schiff’s bases using microwave method and their compounds which have shown activity of antimicrobial against different strains of bacteria. The synthesized derivatives also exhibited the antifungal activity against C. albicans by filter paper disc technique. Final compounds were synthesized by condensation of p-nitro benzoyl hydride with aromatic substituted aldehydes under microwave irradiation and also by method of conventional to produce schiff’s bases. These schiff’s bases on condensation with diazonium salt of 6-methoxy 2-amino benzo thiazole yielded formazons.

Archana et al., (2003), have reported on the synthesis newer indolyl thia diazoles and their thiazolidinones which have shown potent activity of anticonvulsant. A derivatives of 2-substituted aryl imino 5(3-indol methylene) 1,3,4-thiadiazoles have been synthesized via condensation of 2(amino) 5(indo methylene) 1,3,4(thiadiazole) with various compounds of aromatic aldehydes. Cyclo addition reaction of thioglycolic acid gives 4-thiazolidinone compounds.

Khalil et al., (2009), have reported various acid base indicators by using schiff’s bases and it was found that in solutions schiff’s bases are unstable and undergo reaction of
hydrolysis. He also shown that chemical structure and type of the substitute of amine should reacts with different aldehydes to yield the schiff’s base derivatives.

Shreenivas et al., (2009), have reported many schiff’s bases and they were prepared by the condensation reaction of nitro compound containing biphenyl ether amines with ketones or aromatic aldehyde derivatives and thiazolidines were prepared by the reaction of thioglycolic acid with schiff’s bases. The prepared compounds were evaluated for the receptor of angiotensin antagonist activity. The compound nitro containing biphenyl ether schiff’s bases and thiazolidines shows better activity compared with losartan.

Wadher et al., (2009), have reported a schiff’s base series and azetidinones of diphenyl diamino sulphone synthesis. 4,4-diamino diphenyl sulphone was condensed with various aromatic or heterocyclic aldehydes in ethanol in presence of concentrated sulphuric acid as a catalyst to yield the schiff’s bases. All these derivatives were screened for their invitro activity against several microbes. Some of the derivatives exhibited potent antibacterial activity with the reference standard fluconazole and ciprofloxacin.

Mohamed et al., (1999), have reported many schiff’s base derivatives which were synthesized by the reaction of condensation of certain aromatic aldehydes with derivatives of aromatic amine and then the fluorescence properties of these schiff’s bases were examined in basic and acidic media. It shows that these derivatives can be used for spectro fluorimetric monitoring of small pH changes.
1.4 CHEMISTRY OF AZETIDINONES

Azetidin (a), azetin (b), 2-azetin (c) and azete (d) are the analogues of nitrogen of cyclobutene, cyclobutane and cyclobutadiene. Azetidinones (β-lactams) have got lot of attention, because of the properties of antibacterial of cephalosporins and penicillin and in mid-1960, chemistry of both 1 and 2 azetidins has been developed considerably.

![Diagram of azetidinones](image)

Azetidin-2-ones are the derivatives which are mostly studied, because of the antibacterial properties of penicillin, cephalosporin and cephamycin. Recently, there is lot of interest in other β-lactams fused derivatives, such as thienamycin, clavulanic acid and the related olivanic acid derivative and the penems. Non fused β-lactam containing natural products include the nocardicins (142) by Chiba et al in 1985 and the monobactams (143) by Cimarusti and Floyd and their coworkers in 1982 as well as the alkaloids by Kikuchi and Yveo in 1965, wild-fire toxin by Stewart and their group in 1971 and the bleomycins by Muraoka and their group in 1977.

![Diagram of nocardicin](image)

Amide linkage incorporation into a beta lactam ring results in angle strain chain. This ability is illustrated by the 4-alkoxyazetidinones epimerization (144) and (145).
2.3.1 Some established methods for the synthesis of Azetidinones

Freddy and Sushil, (2004), synthesized some novel azetidinone derivatives. The 0.01 mole of benzal hydrazine is dissolved in 40 ml of dimethyl formamide and 2.80 ml of 0.02 mole of triethyl amine was added to it. 1.60 ml of 0.02 mole of Chloroacetyl chloride is added for 30min with constant stirring. The reaction mixture is then refluxed for 5hr and filtered to separate the salt formed. The collected filtrate was concentrated half of its volume and the compound (146) was filtered, washed and recrystallised. Derivatives synthesized were evaluated for various pharmacological activities as compared with reference drugs. The solid recrystallized derivatives synthesized were characterized by using elemental analysis data and spectroscopic data.
Shanmugapandiyan et al. (2010), synthesized and evaluated some newer 2(4-[azetidinone] 3-chloro 4-phenyl) phenyl benzimidazoles. They have synthesized the novel series of 2 (4-[azetidinone] 3-chloro 4-phenyl) phenyl benzimidazoles by the action of schiff bases with CICNH₂COCl. The prepared derivatives were studied for analgesic, antibacterial, anti-inflammatory activity. Many of the derivatives have shown very good activity of analgesic, antiinflammatory activity as compared with standard drugs. The synthesized compounds were characterized by elemental analysis and spectroscopic data.
Himaja et al., (2012), have synthesized different derivatives of azetidinones and evaluated for the activity of antitubercular. They have synthesized the final derivative by dissolving substituted thiadiazole in ethanol which is then condensed with aldehyde to give schiff bases. These compounds were then identified by spectroscopy and elemental analysis. These on cyclo-condensation with chloroacetyl chloride afford 2-azetidinones (149). The structures of both these derivatives and were identified by spectroscopy and elemental analysis data.
Final derivatives of azetidinones have prepared by dissolving substituted thiadiazole in ethanol. Intermediate compounds i.e., schiff’s bases are yielded by the condensation with aldehyde. Cyclocondensation of schiff bases with chloroacetyl chloride yields 2-azetidinones. Many of the compounds synthesized have shown very good pharmacological activities as compared with standard drugs. Derivatives of these structures of both these derivatives identified by spectroscopic and data of elemental analysis.
Reaction sequence for the synthesis of Schiff’s bases and 2-azetidinones

**Bansal et al., (2000)**, synthesized some analogs of azetidinones. All the novel derivatives prepared were tested for their percentage inhibition of edema. Most active compounds were studied for ulcerogenic activity and acute toxicity also. Structures of novel synthesized derivatives were identified on the basis of analytical and spectral data.
**Kagthara et al., (2000),** synthesized derivatives of schiff’s bases. These schiff bases on treatment with chloroacetyl chloride in presence of TEA (Triethyl Amine) as basic catalyst afforded 2-azetidinones. The prepared derivatives were tested *in vitro* for the activity of antitubercular against *M. tuberculosis*. Some of these compounds exhibited highest antitubercular activity.

![Chemical structure](image1.png)

**Desai et al., (2001),** synthesized several azetidinone analogs and tested against various strains of bacteria. Prepared derivatives were evaluated and calculated by MIC. Structures of the prepared derivatives were identified by elemental analysis and spectroscopic data.

![Chemical structure](image2.png)

**Mistry and Desai, (2005),** established method for the synthesis of azetidinones. Here the mixture of (0.01mol) in benzene was taken in a 50ml round bottom flask. To it chloroacetyl chloride (0.01mol) and triethyl amine (0.01mol) in benzene were added slowly. It was refluxed for 15-16 hr. The triethylamine hydrochloride formed during the reaction was removed and the benzene was distilling off to get the compound. The compound (153) was recrystallized from ethanol.
To a mixture of benzene add chloroacetyl chloride and triethyl amine in presence of benzene slowly. Reflux is done 15-16 hr. Triethyl amine hydrochloride formed during the reaction was removed and the benzene was distilled off to get the final derivatives of azetidinone derivatives. Final derivatives were recrystallized by using absolute ethanol. Many of the derivatives synthesized were characterized by using elemental analysis and spectroscopic data.
2.3.2 Therapeutic potential of azetidinones
A brief account of the information on biological activities of some azetidin-2-one is given below with a view to appreciate their importance.

2.3.2.1 Azetidin-2-one as antimicrobials
Ashok Kumar et al., (2003), synthesized some 2-azetidinone derivatives and their structures were established on the basis of their elemental, NMR and IR data. All the prepared derivatives were evaluated for the \textit{in vitro} growth of inhibitory activity against microbes. The synthesized compounds were subjected to acute toxicity studies to find out LD\textsubscript{50} values.
Priyadarshini and Vijayaraj, (2004), have synthesized different derivatives of azetidinones (156) and screened for antimicrobial activity. Synthesized derivatives were characterized by spectral and analytical data.

![Chemical Structure](image)

2-Cl-C₆H₄, 3-OCH₃-C₆H₄

156

Vasoya et al., (2005), have prepared some new compounds of azetidinones having thiophene benzo moiety as a potent pharmacological active compound. 2-hydradino carbonyl 3-chloro 5-phenoxy benzo thiophene have been synthesized by the condensation of hydrazine hydrae with 3-chloro-5-phenoxy benzo thiophenyl chloride. 2-hydradino carbonyl 3-chloro 5-phenoxy benzo thiophenyl chloride with hydrazine hydrate. 2-hydradino carbonyl 3-chloro 5-phenoxy benzo thiophene on condensation with aromatic aldehyde gives 2-substituted benzal hydrazine carbonyl 3-chloro 5-phenoxy benzo thiophene, which on condensation with CH₃COCl in presence of TEA i.e. triethyl amine afford 4(aryl) 3(chloro) 1(3-chloro) 5(phenoxy) 2(benzo) thiophenoyl amino azetidinones. The structures of the derivatives were characterized by spectroscopic and elemental analysis data. All the compounds were screened for their biological activity of antitubercular towards M. tuberculosis and antimicrobial activity against different microbes.

![Chemical Structure](image)

157

R = Aryl
Rawat and Srivastava, (1998), synthesized some new phenothiazino thia diazoles and their azetidinones (158). The prepared derivatives were studied for their antimicrobial activity.

\[
\begin{align*}
\text{158}
\end{align*}
\]

Sharma et al., (2002), have synthesized some new azetidinone compounds. The hydroxyl group of the N-3 hydroxy propyl imines was protected as tri methyl silyl ether followed by reaction with acetic acid phenoxy in presence of triethyl amine and benzene sulphonyl chloride to yield the beta lactams.

\[
\begin{align*}
\text{159}
\end{align*}
\]

Desai et al., (1999), synthesized some newer 1,3,4-oxadiazoles, sulphonamides, 5- imidazolinones, azomethines, 4-thiazolidinones, 2-azetidinones formazons and their tetrazolium chlorides (160). The products synthesized were characterized by spectroscopy and evaluated for the activity of antimicrobial.

\[
\begin{align*}
\text{160}
\end{align*}
\]
Mehta and Shah, (2001), synthesized some new analogs of azetidinones and tested for the activity of antimicrobial. Derivatives of these were characterized by the data of spectroscopy and elemental analysis.

![Chemical structure](image)

2.3.2.2 Azetidin-2-one as antitubercular

Modha et al., (2002), synthesized some new azetidinones (162). The prepared derivatives were characterized by the data of elemental analysis and spectroscopy. The products were evaluated for antibacterial, antifungal and anti-tubercular activities.

![Chemical structure](image)

Rajasekaran et al., (2010), synthesized some novel azetidinones and are evaluated for antitubercular activity. These derivatives of azetidinones were synthesized by cyclo condensation reaction of schiff’s bases of phenothiazine with chloroacetyl chloride. The derivatives were characterized by spectroscopy. The titled derivatives were evaluated for anti-tubercular, antibacterial, anti-fungal and anti-inflammatory activity by Lowenstein-Jensen medium method, cup plate method, disc diffusion method and carrageenan induced paw edema method respectively. All the derivatives at a rate of 100, 10 and 1 mg/l showed inhibition against the tuberculosis strain.
**Priyadarshini et al., (2004),** synthesized 3-(41-pyridyl) 4-[3-chloro-4-substituted 21-oxo azetidin] 5mercapto 1,2,4-triazoles (163) by treating the schiff’s bases of triazole with monochloro acetylchloride and triethylamine in dry dioxane. The prepared derivatives have been confirmed by chemical, spectral and analytical data and also tested for antitubercular, antifungal and antibacterial activities.

![Chemical Structure 163](image)

**Kagthara et al., (2000),** synthesized schiff’s bases which on treatment with ClCH₂COCl in presence of TEA afforded 2-azetidinones (164). The derivatives have been tested for *invitro* activity of antitubercular. Some of the prepared derivatives have shown very good activity of antituberculosis.

![Chemical Structure 164](image)

**2.3.2.3 Azetidin-2-one as antiviral**

**Thaker et al., (2003),** have prepared 2-azetidinones by the reaction of 2-substituted benzal hydrazine carbonyl 3,5-dichloro benzo thiophene with chloro acetyl chloride in the presence of triethyl amine. The structures of the derivatives synthesized are characterized on the basis of spectroscopic and elemental analysis data.

**Pandey et al., (2005),** have synthesized some derivatives of azetidinones. They have reported the synthesis of 1,3,4-substituted 2-azetidinones (165) and evaluation of anti-
viral & antimicrobial activities.

\[ \text{165} \]

### 2.3.2.4 Azetidin-2-one as anticonvulsant

Srivastava et al., (1999), have synthesized carbazolyl methyl-1,3,4-thiadiazole 2yl 4,3-chloro-2oxo-azetidines (166). Evaluation is done for final derivatives for the activity of anticonvulsant and antiinflammatory.

\[ \text{166} \]

### 2.3.2.5 Azetidin-2-one as antiinflammatory and analgesic

Srivastava et al., (2000), synthesized 1-[5-(N-2-chloropheno thiazinomethyl)-11, 31, 41-thiadiazole-21-yl] 4-(substituted phenyl)-3chloro-2-oxo-azetidines (167) and tested for their antibacterial, antifungal and anti-inflammatory activities. Derivatives of these have identified by the data of spectroscopy and elemental analysis.

\[ \text{167} \]
Udupi and Jeeson, (1996), reported the synthesis of azetidin-2-one derivatives (168). These were obtained by reacting p-nitroanthranilic acid and substituted aldehydes to get schiff bases, which on treatment with chloroacetic acid obtained different derivatives of azetidinones.

![Chemical structure of 168](Image)

2.4 CHEMISTRY OF THIAZOLIDINONES

Compound containing a simple thiazole nucleuses were first reported by Hantzch in 1881. After this pioneering work, knowledge of the thiazole system developed shortly. Many thiazole derivatives were found to have biological and commercial interest. In 1938, Robert Williams demonstrated the existence of a simple thiazole moiety in the structure of Vitamin B₁ (169). The historical importance of thiazole derivatives was further emphasized during the period 1941-45, when work on the structure of penicillin’s (170) showed the thiazolidine ring in it. The occurrence of thiazole derivative in nature was reported in nature was reported 1952 when actithiazic acid (171), an antibiotic was found to be a 4-thiazolidinone derivatives (Eisenberg and Hsiung in 1982).

![Chemical structure of 169 and 170](Images)
2.4.1 Some established methods for synthesis of Thiazolidinones

Freddy and Sushil, (2004), have established procedure for the preparation of thiazolidinones. In this process the benzal hydrazine (0.01mol) was refluxed with thioglycollic acid (1.40ml, 0.02mol) in presence of anhydrous aluminum chloride (0.05gm) at 120° c for 10-12hr. The mixture is cooled and triturate with NaHCO₃ solution. The compound (172) obtained was recrystallized from ethanol.

Amir and Faizul, (2004), established method for the preparation of thiazolidinones. In this process, reflux of a mixture of 173 (0.005mol) and thioglycollic acid (0.005mol) in DMF
(15ml) containing a pinch of anhydrous ZnCl$_2$ was done for 6hr., and the product obtained was recrystallised from acetic acid.

Malipeddi et al., (2012), have done research work on the preparation and activity of antituberculosis of newer thiazolidinone compounds. They have synthesized the final derivatives as follows. The substituted 1,3,4-thiadiazole was dissolved in ethanol and reacts with aldehydes to afford derivatives of schiff bases (174). These bases derivatives were then confirmed by spectroscopy and elemental analysis data. These on cyclo-condensation with thioglycolic acid to yield 4-thiazolidinones (175). Derivatives of these were synthesized by using thioglycollic acid and dimethyl formamide chemicals. Synthesized derivatives have shown comparable activity of antituberculosis as compared with reference drugs. The derivatives are then characterized by spectral and elemental analysis data.
The thiazolidine nucleus in a compound was introduced by the reaction of cycloaddition (174) with thioglycollic acid to give different derivatives of thiazolidinones (175). Derivatives of these were synthesized by using thioglycollic acid and dimethyl formamide.

Where R1 = H, 4-CH3, 4-OH
R2 = H, 2-Cl, 2-CH3, 4-CH3
Reaction sequence for the synthesis of 4-thiazolidinones

The thiazolidine nucleus in a compound was introduced by the reaction of cycloaddition with thioglycollic acid to give different derivatives of thiazolidinones. Derivatives of these were synthesized by using thioglycollic acid and dimethyl formamide. Synthesized derivatives have shown comparable activity of antituberculosis as compared with reference drugs. The derivatives are then characterized by spectral and elemental analysis data.
Reaction sequence for the preparation of Schiff bases and 4-thiazolidinones

Freddy and Sushil, (2004), have established procedure for the preparation of thiazolidinones. In this method thioglycollic acid (1.8gm / 0.02mol) was added to the solution of (0.01mol) in dry benzene (50ml) and mixture is refluxed for 15hr. The product obtained (176) was filtered and washed with NaHCO₃ solution.
Shanmugapandiyan et. al. (2010), have prepared thiazolidinone fused benzimidazoles and evaluated for its pharmacological activity. They have synthesized the new series of thiazolidinone fused benzimidazoles by the reaction of mercaptoacetic acid with schiff’s bases.

R = H/OH
R = NO/H/OH
2.4.2 Therapeutic potential uses of thiazolidinones

A brief account of the information on biological activities of some thiazolidinone is given below with a view to appreciate their importance.

2.4.2.1 Thiazolidinones as antimicrobials

Shukla and Kanchan, (1981), have synthesized thiazolidin-4-ones derivatives and are
evaluated for antibacterial activity. 2-Phenyl-2-methyl-3-aryl-thiazolidin-4-ones (178) have been prepared by addition of thioglycollic acid to substituted azomethines in benzene. The azomethines were prepared by KOH treatment of α-cyano-amines which were in turn obtained by reaction of aromatic amines, acetophenone and KCN.

Sattigeri et al., (2005), reported on novel synthesis of thiazolidine-2-one (179) and are evaluated for antifungal activity. Derivatives of thiazolidinones are described with the reaction of thio carbamation for the formation of heterocyclic ring. This new process is mainly applied for the preparation of thiazolidinones as analogs of bio isosteric of Linezolid.

Ingle et al., (2001), synthesized new derivatives of 4-thiazolidinones which are potentially active moieties. In his study 2-acyl-3-methyl-7-substituted-1,4-benzothiazines and 5-acyl-1-aryl-2-mercapto-4-methylimidazoles have been converted to their respective hydrazones and by refluxing them with hydrazine hydrate. The hydrazine derivative on condensation with aryl isothiocynates gives asymmetric thioureas and the thioureas when refluxed with monochloroacetic acid in glacial acetic acid using anhydrous sodium acetate as catalyst yield the products 2-[(3-methyl-4H-7-substituted-1,4-benzothiazin-2-yl) methyl ketoiminy] imino-3-aryl-4-thiazolidinones (180) and 2-[(1-substituted phenyl-2-mercapto-4-methylimidazo[5-yl) methyl ketoiminy] imino-3-substitue phenyl-4-thiazolidinones (181).
Abdel-Halim et al., (1994), synthesized 2-(pyrimidin-2-yl) iminothiazolidin-4-one (182) were evaluated for invitro antimicrobial activities. The synthesis of 2-primidin-2yl imino-
thiazolidin 4-one is affected by the action of monochloroacetic acid on the respective 
thiourea derivatives in the presence of anhydrous sodium acetate. 2-pyrimid-2yl imino-
thiazolidin-4-one on coupling with different diazotized sulphonamides yielded 
corresponding 5-N-substituted p-sulphmyl benzene-azo-2-pyrimidin-2yl imino-
thiazolidin 4-ones. Condensation of 2-pyrimidin 2-yl imino-thiazolidin 4-one with a 
number of aromatic aldehyde and ketones yielded the 5-arylidine derivatives. Mannich 
reaction on 2-pyrimidin-2yl imino thiazolidine 4-one using formaldehyde and different 
secondary amines yielded corresponding Mannich bases. Finally 1,3-bis pyrimidin 2-yl 
thiocarbamoyl formamidine was obtained almost quantitatively on heating N-pyrimidin 
2-yl thiourea and triethyl orthoformate in acetic anhydride. The assigned structures of the
novel prepared derivatives were evaluated for the activity of *invitro* antifungal and antibacterial.

![Chemical structure](image)

**Freddy et al., (2004),** synthesized some thiazolin-4-ones and azetidin-2-ones as potential antimicrobial agents. 3-bromo-4-methoxybenzoyl hydrazine on condensation with different aromatic aldehydes yielded the substituted benagal 3-bromo-4-methoxybenzoyl hydrazines which on cyclization with CICH₂COCl in presence of TEA i.e. triethylamine as catalyst furnished 3-chloro-4-substituted phenyl 1-(3-bromo-4-methoxybenzamido) azetidin-2-ones. The cyclization of benzal hydrazines with thioglycolic acid in presence of anhydrous aluminium chloride as catalyst afforded 2-substituted phenyl-3-(3-bromo-4-methoxy benzamido) thiazolidin-4-ones. The structures of the newly prepared compounds are identified by elemental analysis and spectroscopic data. These compounds were evaluated for the various biological activities.

![Chemical structure](image)

**Desai and Baxi, (1992),** have synthesized different derivatives of 5(2,4-dichloro phenoxy methyl) 2,4(aryl) 3(chloro) azetidinone 1yl 1,3,4(thiadiazole). All the derivatives have shown moderate activity of antibacteria against different microorganism. The compound (184) showed highest antibacterial activity.
Sharma et al., (2005), were reported the preparation and the activity of antimicrobial of phthalimido substituted 2(aryl) 3(iso nicotinamido) 4(oxo) 1,3(thiazolidine) 5yl ethanoic acid. 2-aryl 3-isonicotin amide 4-oxo 1,3-thiazolidnine 5yl ethanoic acid was synthesized via cycloaddition of r-arylidenehydrazido pyridine with mercaptosuccinic acid in THF containing a pinch of zinc chloride which on treatment with thionyl chloride gave corresponding ethanoyl chloride derivatives. These on treatment with N-hydroxyphthalimide afforded titled compounds. All the compounds synthesized were evaluated for antifungal and antibacterial activities. All compounds have shown very good activity against the strains of fungi and bacteria tested.

Manrao et al., (1995), synthesized 4-thiazolidinones (185) from ethylvanillin and reported for antifungal activity. Addition of thioacids to schiff’s bases of ethylvanillin resulted in the formation of 4-thiazolidinones. The derivatives were then identified by the data of elemental analysis and spectroscopy and compound were screened for antifungal activity against Curvularia lunata, Fusarium oxysporium, Alternaria alternate and Myrothecium roridum. Synthesized derivatives of thiazolidinones have shown very good activity of antifungal as compared with reference drugs. The derivatives synthesized were identified by using elemental analysis and spectroscopic data.
2.4.2.2 Thiazolidinones as antitubercular

Joshi et al. (2001), have synthesized some 4-thiazolidinone as potential antitubercular agents. The starting compound 5-nitro benzimidazole 2-yl benzoyl hydrazide, on treatment with aromatic aldehydes yielded the corresponding benzal (5-nitro benzaimidazole 2-yl benzoyl) hydrazines. The heterocyclisation of this with thioglycollic acid and thiolactic acid furnished the corresponding 2-aryl-2-(5-nitrobenzimidazol-2-yl-o-benzamido)-5-H-4-thiazolidinones (186) and 2-aryl-2-(5-nitrobenzimidazol-2-yl-o-benzamido)-5-methyl-4-thiazolidinones (187). The derivatives are evaluated for the activity of antituberculosis.
Bhatt et al., (1999), have been studied the preparation of some derivatives of thiazolidinones (188) from 4-amino benzophenone and found them to exhibit about 94% inhibition in the growth of mycobacterium tuberculosis.

\[
\begin{align*}
\text{188}
\end{align*}
\]

Shamsuzzaman and Nazish, (2004), were reported the preparation of thiazolidinone steroidal 3-diazo (4-thiazolidinone) cholest 4-ene with heterocyclic spiro system have been synthesized in quantitative yields by the treatment of cholest-4-en-3-one thiosemicarbazone with chloroacetic acid and anhydrous acetate sodium in acetic acid solvent at reflux temperature for 17 hour. Thiosemicarbazone is synthesized by the condensation reaction of thiosemicarbazide with cholest 5-en 3-one in presence of concentrated hydrochloric acid in alcohol. The products are characterized by spectral data.

\[
\begin{align*}
\text{189}
\end{align*}
\]

2.4.2.3 Thiazolidinones as antiviral

Barreca et al., (2010), have synthesized various derivatives of thiazolidinones. They have designed, synthesized and evaluated for the antiviral activity of derivatives of 2,3-diaryl 1,3(thiazolidinones) (190). Derivatives of these have shown comparable antiviral activity as compared with standard drugs. Synthesized derivatives were identified by elemental analysis and spectroscopic data.
Shukla and Kanchan, (1984), have reported the synthesis of a number of new 3-[substituted phenyl-5-(2-methyl 6 or 8-substituted quinolin 4-oxy-beta-ethylidenyl)-4-substituted phenoxy acetamido]-thiazolidinene 2-thione (191). They were screened for their cytocidal activity.

\[ R = p-\text{Cl} / o-\text{OMe} / p-\text{NO}_2 \quad R_1 = 6-\text{CH}_3 / 6-\text{Cl} / 6-\text{OMe} \]

2.4.2.4 Thiazolidinones as anticonvulsant

Mishra et al., (1997), have given the report on the synthesis of certain derivatives of thiazolidine-4-ones (192) and evaluated them for anti-inflammatory, anticonvulsant, analgesic and antimicrobial properties.

2.4.2.5 Thiazolidinones as antiinflammatory and analgesic

Srivastava et al., (2004), have synthesized a series of 1,3-thiazolidin 4-ones (193). All the derivatives have been evaluated for their antifungal activity, antibacterial activity, anti-inflammatory activity and anthelmintic activity, some of them showed moderate activity.
Amir et al., (2004), prepared a number of 2,3substituted 4-thiazolidinones derivative (194), showed significant anti-inflammatory, antibacterial and antifungal activity.

Venkatesan and Rameshwar, (2010), synthesized new series of fused morpholine and thiazolidinone derivatives. These derivatives were synthesized by using the starting material as thiazolidine-dione. All the derivatives were less toxic than the standard drug. The pharmacological evaluation showed that many of the derivatives have shown very good activity of anti-inflammatory as compared to reference drugs.