Chapter 1

Introduction
The title of the thesis suggests that the present work is connected with the hydrazones of 1,2,4-Triazole derivatives. Hence, it is suitable to review the derivatives of hydrazone, 1,2,4-Triazole derivatives, Brief review on Hydrazone derivatives containing Triazole moiety.

1.1 Hydrazone Derivatives:

Hydrazones have been demonstrated to possess, among other, antimicrobial, anticonvulsant, analgesic, antiinflammatory, antiplatelet, antitubercular and antitumoral activities.

A new series of antinociceptive compounds that belong to the N-acylarylhydrazone class were synthesized from natural safrole. [(4’-N,N-Dimethylaminobenzylidene-3-(3’,4’-methyleneoxyphenyl) Propionylhydrazine] was more potent than dipyrone and indomethacine, are used as standard antiinflammatory/antinociceptive drugs [1].

Duarte et al have described N’-(3,5-Di-tert-butyl-4-hydroxybenzylidene)-6-nitro-1,3- benzodioxole-5-carbohydrazine as a novel anti-inflammatory compound [2].
The aroylhydrazone chelator 2-hydroxy-1-naphthylaldehyde isonicotinoyl hydrazone showed greater antimalarial agent activity than desferrioxamine against chloroquine-resistant and sensitive parasites [3].

Nifuroxazide and six analogs were synthesized by varying the substituent at the p-position of the benzene ring and the heteroatom of the heterocyclic ring. These compounds were evaluated for their antimicrobial activity against *S. aureus* and found to be active [4].

4-Substituted benzoic acid [(5-nitro-thiophene-2-yl)methylene]hydrazides were synthesized as potential bacteriostatic activity and some of them indeed showed bactericidal activity [5].

Various 2,3,4-pentanetrione-3-[4-[[5-nitro-2-furyl/pyridyl/substituted-phenyl]- methylene]hydrazino]carbonyl]phenyl]hydrazones were synthesized for their antimycobacterial activity [6].
The reaction of 2-acetylimidazo [4,5-b] pyridine with isoniazide yielded the corresponding hydrazidehydrazones. This compound exhibited activity against *M. tuberculosis*. *M. tuberculosis*, isolated from patients and resistant against isoniazide, ethambutol, rifampicine at 3.13 µg/ml [7].

Novel coupling products were synthesized and evaluated for their antimycobacterial activity against *M. tuberculosis* and *M. avium*. Compound was found to be the most potent derivatives of these series with the MIC value of 6.25 µg/ml against *M. tuberculosis* [8].

Novel fluoroquinolones containing a hydrazone structure were synthesized and evaluated in vivo against *M. tuberculosis* in Swiss albino mice by Shindikar et al. Results of the study indicate the potent antitubercular activity of the test compounds [9].
In 2006 Nayyar et al found that the most active compounds of type, N-(2-fluorophenyl)-N'-quinoline-2-yl-methylenehydrazine, N-(2-adamantan-1-yl)-N'-quinoline-4-yl-methylene-N'-4-fluorophenyl) hydrazone and N-(2-cyclohexyl)-N'-quinoline-4-yl-methylene)-(2-fluorophenyl)hydrazine exhibited 99% inhibition at the lowest tested concentration of 3.125 μg/ml against drug-sensitive *M.tuberculosis* strain [10].

N'-(1-{1-[4-nitrophenyl-3-phenyl-1H-pyrazole-4-yl}methylene)-2-chlorobenzohydrazide was found to be the most active, with full panel median growth inhibition, total growth concentration and median lethal concentration mean graph mid-point of 3.79, 12.5 and 51.5 μm, respectively [11].
Some novel 2,6-dimethyl-N'-substituted-phenylmethyleneimidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazides were synthesized and showed the most favorable cytotoxicity [12].

![Chemical structure](image1.png)

R. M. Mohareb et al [13] synthesize new hydrazone derivatives from cyanoacetyl hydrazide and 3-acetyl pyridine and latter compound goes a series of heterocyclization to give new heterocyclic compounds.

![Chemical structure](image2.png)

P. Mail Kumaran and his team [14] reported new synthesis and biological evaluation of hydrazone derivatives.

Minika Mishra, Karishma Tiwari and Ashish Kumar Singh [15] reported versatile coordination behavior of a multi dentate Schiff base with various ions and their corrosion behavior.

![Chemical structure](image3.png)

Muddassar Siddique, Ammar bin said and Naveed aslam Dogar [17] reported Biological potential of synthetic hydrazide based on Schiff bases.

Govindasami Thiyagarajan and his team [18] reported new synthesis, characterization and biological evaluation of biologically important vanillin related hydrazone derivatives.

Where, $R =$ various alkyl series

### 1.2 Review on 1,2,4-Triazole and its Derivatives:

1,2,4-triazoles are cyclic hydrazidines with hydrogen atom (or substituent) on either hydrazide nitrogen I or on amide nitrogen II. Parent 1,2,4-triazole (1$H$-form) is in tautomeric equilibrium with 1,3,4-triazole (4$H$-form).

![Diagram of 1H-1,2,4-triazole and 4H-1,2,4-triazole](image-url)
The interconversion of two tautomeric forms occurs rapidly and their separation is difficult, however, 1,2,4-triazole tautomer is preferred over 1,3,4-triazole tautomer (less symmetrical 1H-form is favoured over symmetrical 4H-form).

Triazole is a five-membered heterocycles containing three nitrogens in the ring and its derivatives have biological activities such as antiviral, antibacterial, antifungal and antituberculous.

**Pharmacological properties:**

The 1\(H\)-1,2,4-triazole compounds are considered interesting heterocycles since they possess important pharmacological activities such as antifungal and antiviral activities. Examples of antifungal drugs \([19,20]\) are fluconazole (1) \([21]\), itraconazole (2) \([22]\), ravuconazole (3) \([23]\), voriconazole (4) \([24,25]\), ICI 153066 (5) \([26]\), and posaconazole (6) \([27]\). The action of these compounds is based on the inhibition of biosynthesis of ergosterol, the major steroid in fungal membranes, by blocking 14-\(\alpha\)-demethylation, which occurs with accumulation of 14-\(\alpha\)-methylsteroids and disruption of the fungal membranes \([28,29]\). Fluconazole (1) causes second bronchialarch anomalies in mice \([30]\).
Some triazole derivatives are considered as angiotensin II receptor antagonists [31]. These compounds, such as (7) and (8), are used to increase the blood pressure. Furthermore, various 1,2,4-triazole derivatives have been reported as fungicidal [32], insecticidal [33], antimicrobial [34,35], and antiastmatic [36] agents, anticonvulsants [37], antidepressants [38], and plant growth regulators [39]. In addition, it was reported that compounds having triazole moieties, such as vorozole (9), letrozole (10), and anastrozole (11), appeared to be very effective aromatase inhibitors, which in turn prevented breast cancer [40,41]. It is known that 1,2,4-triazole moieties interact strongly with heme iron, and aromatic substituents on the triazoles are very effective for interacting with the active site of aromatase [42]. Other laboratories reported the same biological activity of the triazole family [43,44].
1.2.1 1,2,4-Triazole derivatives

Looking after the systematic literature survey reveals that there is extensive work was reported on 3,5-disubstituted-4-amino-1,2,4-triazole, especially on 3-mercapto derivatives.

Demirbas, N. and co-workers [45] reported that 5-alkyl-4-amino-2-[4-amino-4H-3-oxo-1,2,4-triazol-3-yl]-2,4-dihydro-3H-1,2,4-triazol-5-thiones was led to react with acetic acid to produce 5-alkyl-4-amino-2-[(6-methyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazol-3-yl)methyl]-2,4-dihydro-3H-1,2,4-triazol-3-ones (12), while its condensation with carbon disulphide or formic acid afforded the triazolothiadiazoles, respectively, compounds (13) and (14).

Holla, B. S. and co-workers [46,47] prepared Triazolothiadiazole derivatives (15) in a better yield by the cyclization of 4-amino-4H-1,2,4-triazol-3-thiones with arylfuroic acid.
Where, \( R = \text{Me, Et, Pr, C}_6\text{H}_5, 4-\text{ClC}_6\text{H}_4, 2-\text{OH-C}_6\text{H}_4 \)
\[ R^1 = \text{NO}_2, \text{Cl, Br} \]

Husain, M. I. and co-workers [48] reported new 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazole derivatives (16).

Where, \( \text{Ar} = \text{C}_6\text{H}_5, 4-\text{OHC}_6\text{H}_4, 3- \text{and} 4-\text{NO}_2\text{C}_6\text{H}_4, 2- \text{and} 4-\text{ClC}_6\text{H}_4, 2- \text{and} 4-\text{NH}_2\text{C}_6\text{H}_4 \)

Gakhar, H. K. and co-workers [49] synthesized Triazolothiadiazole (17) by reacting isatoic anhydride with 4-amino-3-methyl-1,2,4-triazol-5-thione and the subsequent cyclization of the intermediate (18) with phosphorous oxychloride and phosphorous trichloride.

Triazolo[3,4-b]-1,3,4-thiadiazine (19) were prepared by treating 4-amino-4\(H\)-1,2,4-triazole-thiones with substituted phenacyl bromide [50]. Raslan, M. A. and co-workers [51] reported 6-aryl-3-[2\(H\)-2-oxobenzo[b]pyran-3-yl]-7\(H\)-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines (20a,b) by treatment of 4-amino-5-[2\(H\)-2-oxobenzo[b]pyran-3-
yl]-1,2,4-triazole-3-thione with 4-substituted phenacyl chloride in absolute ethanol containing potassium carbonate.

\[
\begin{align*}
\text{(19)} & & \text{(20)} \\
\end{align*}
\]

Where, \(R = \text{H, Me, Et, Pr, Bu, CF}_3, \text{Ph, PhCH}_2, 4-\text{MeC}_6\text{H}_4, 4-\text{MeOCH}_3, 2-\text{ and 4-ClC}_6\text{H}_4, 2-, 3-\text{ and 4-BrC}_6\text{H}_4 \)  \\
\(\text{a, Ar}=\text{C}_6\text{H}_5 \)  \\
\(\text{b, Ar}=\text{4-CH}_3\text{C}_6\text{H}_4 \)  \\
\(\text{Ar} = \text{Ph, 4-MeC}_6\text{H}_4, 2,3-\text{Me}_2\text{C}_6\text{H}_3, 2-\text{ and 4-MeOC}_6\text{H}_4, 2-\text{EtC}_6\text{H}_4, 3-\text{CF}_3\text{C}_6\text{H}_4, 4-\text{ClC}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4, 3,4-\text{Cl}_2\text{C}_6\text{H}_3} \)

The cyclization of 4-amino-5-aryl-3-cyanomethylthio-1,2,4-triazoles (21) in the presence of conc. sulfuric acid gave 60–81\% of 7H-6-amino-s-triazolo[3,4-b]-1,3,4-thiadiazines (22) [52].

\[
\begin{align*}
\text{(21)} & & \text{(22)} \\
\end{align*}
\]

Where, \(R = \text{C}_6\text{H}_5\text{CH}_2, \text{C}_6\text{H}_5, 4-\text{CH}_3\text{C}_6\text{H}_4, 4-\text{BrC}_6\text{H}_4 \)

Yanchenko, V. A. and Heravi, M. M. and co-workers [53] said that heating (5-alkyl-4-amino-4H-1,2,4-triazol-3-ylsulfanyl)acetanilide (23) in boiling phosphorous oxychloride resulted in an intramolecular ring closure with the formation of 7H-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines (24). Similarly, several 7-carbethoxy-methyl-s-triazolo[3,4-b]thiadiazines (25) [54] have been synthesized by the reaction of appropriate ethyl \(\beta\)-aryl-\(\beta\)-bromopropionates with 4-amino-4H-1,2,4-triazole-3-thiones.
A series of 3-coumarinyl-s-triazolo-1,3,4-thiadiazines (26) was synthesized by the cyclocondensation of bromoacetylcoumarins with aminotriazolthiones [55].

Kaplancıklı, Z. A. and co-workers [56] reported in his work that reaction of 1H-indol-3-acetic acid with thiocarbohydrazide gave the 4-amino-3-mercapto-5-[(1H-indol-3-yl)methyl]-4H-1,2,4-triazole. The reaction of triazole with arylaldehydes in ethanol gave the 4-arylideneamino-3-mercapto-5-[(1H-indol-3-yl)methyl]-4H-1,2,4-triazoles (27). The 3-[(1H-indol-3-yl)methyl]-6-aryl-7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines (28) were obtained by condensing triazole with phenacyl bromides in absolute ethanol. Their antimicrobial activities against *Micrococcus luteus* (NRLL B-4375), *Bacillus cereus* (NRRL B-3711), *Proteus vulgaris* (NRRL B-123), *Salmonella typhimurium* (NRRL B-4420), *Staphylococcus aureus* (NRRL B-767), *Escherichia coli* (NRRL B-3704), *Candida albicans* and *Candida glabrata* (isolates obtained from Osmangazi University, Faculty of Medicine) were investigated and significant activity was obtained.
Kalluraya, B. and co-workers [57] reported new thiazadiazepine derivatives (29) were synthesized from the reaction of heterocyclic α-bromochalcone derivatives, i.e., 5-nitro-2-thienyl, with 4-amino-4H-1,2,4-triazole-3-thione using sodium acetate as a catalyst.

Where, R = Me, Et, (un)substituted Ph; R\(^1\) = (un)substituted Ph

Kidwai, K. and co-workers [58] reported the reaction of aminotriazolthiones and substituted chalcones supported by basic alumina or in a solution phase under microwave irradiation afforded 5-substituted-1,2,4-triazo[3,4-b]-1,3,4-thiadiazepines (30).

\[\text{Ar}^1 = 4-\text{CH}_3\text{COC}_6\text{H}_5, 3,4-\text{O}_2\text{H}_2\text{CC}_6\text{H}_3, \text{Ar}^2 = \text{C}_6\text{H}_5, 4-\text{BrC}_6\text{H}_4\]
The reaction of 6-substituted-2-chloro-3-formyl-quinoline and aminotriazolthiones afforded 1,2,4-triazolo[3,4-b]-1,3,4-quinolinothiadiazepines (155) rather than the expected Schiff bases. Compounds (31) could also be prepared by the reaction of 4-amino-4H-1,2,4-triazole-3-thiones with 6-substituted quinolines [177]. The synthesis of s-triazolothiadiazepinoquinolines (32) and the facile intramolecular rearrangement of (32) to s-triazolothiazinoquinolines (33) involving N, N-bond scission is reported [59].

Eser, I. and co-workers [60] reported new thiorea and azomethine derivatives of 4-amino-5-[hydroxyl(diphenyl)methyl]-2,4-dihydro-3H-1,2,4-triazol-3-thione (34,35,36) as a potential antimicrobial agent.
Labanauskas, L. and co-workers [61] reported synthesis of 7-methyl-3-methylthio-7,8-dihydro[1,2,4]triazolo[3,4-f][1,2,4]triazine (37) from 4-amino-5-methylthio-4H-1,2,4-triazol-3-ylmethanol (38).

\[
\begin{align*}
(37) & \quad \quad (38)
\end{align*}
\]

Zafer, A. K. and co-workers [62] reported synthesis and antituberculosis activity of new 3-alkylsulfanyl-1,2,4-triazole derivatives (39).

\[
\begin{align*}
(39)
\end{align*}
\]

Where, \( R = \text{H, F, Cl, Br, OH, NO}_2, \text{CH}_3, \text{OCH}_3 \)

El-Zemity, S. R. and co-workers [63] reported fungicidal and bactericidal Properties of chiral \( N-[(\text{S,S})\text{-3,5-bis(1-methoxyethyl)-1,2,4-triazol-4-yl}]]\)arylimines (40). Here (R)-configuration has shown better fungicidal activity against the tested fungi than (S)-configuration. The presence of chlorine atom as in compound also improved their fungicidal activity. Lengthen the carbon chain \( (n = 1 \text{ and/ or } 2) \) reduced the fungicidal activity.
Al-Amin, M. and Islam, M. R. [64] reported a series of bis–[4-N-amino-5-mercpto-1,2,4-triazol-3-yl] alkanes and their Schiff bases with 2-adamanta-none (41).

Bekircan, O. and Bektas, H. [65] synthesized Schiff and Mannich bases of Isatin derivatives with 4-amino-4,5-Dihydro-1H-1,2,4-triazole-5-ones (42).

Where, $n = 0, 1, 2$; $R' = \text{H, Cl, CH}_3$; $R'' = \text{H, CH}_3$

Where, $R = 2$-F, 4-F; and $X = \text{H, Cl}$
Foroughifar, N. and co-workers [66] synthesized a new series of new 1,2/1,(10,45),(991,987)3-bis[O-(N-methyld enamino-5-aryl-3-thiol-4H-1,2,4-triazole-4-yl)phenoxy] alkane derivatives were prepared by condensation of 4-amino-5-(aryl)-4H-1,2,4-triazole-3-thiols with bis-aldehydes. Further reaction of these compounds with dibromoalkanes afforded the new macrocycles (43). The cyclization does not require high dilution techniques and provides the expected azathia macrocycles in good yields, ranging from 55% to 68%.

![Diagram of macrocycle](image)

Xiang, J. and co-workers [67] synthesized a new series of d-glucopyranosyl-1,2,4-triazole-3-thione derivatives (45) were synthesized by the reaction of 1,2,4-triazole-3-thione Schiff bases (44) with 2,3,4,6-tetra-o-acetyl-σ-d-glucopyranosyl bromide. These analogues (44) and (45) have shown cytotoxic activity against human MCF-7 and Bel-7402 malignant cell lines.

![Diagram of Schiff base reaction](image)

Where, R = H, 4-Cl, 3-OCH3, 4-OH, 4-OH

Yuksek, H. and co-workers [68] prepared eight 3-alkyl(aryl)-4-(3,4-dihydroxybenzylideneamino)-4,5-dihydro-1H-1,2,4-triazol-5-ones (46) synthesized by the reactions of 3-alkyl(aryl)-4-amino-4,5-dihydro-1H-1,2,4-triazol-5-ones with
3,4-dihydroxy-benzaldehyde and their antioxidant activities are investigated. In addition, compounds are titrated potentiometrically with tetrabutylammonium hydroxide in non-aqueous solvents and the half-neutralization potential values and the corresponding pK_a values are determined.

\[ \text{HN} \begin{array}{c} N \end{array} \text{N} \begin{array}{c} CH \end{array} \text{OH} \]

Where, R = (a) CH_3  \hspace{1cm} (46)
(b) CH_2CH_3
(c) CH_2C_6H_5
(d) CH_2C_6H_5CH_3(4-)
(e) CH_2C_6H_5Cl(4-)
(f) CH_2C_6H_5OCH_3(4-)
(g) C_6H_5
(h) \[ \begin{array}{c} N \end{array} \begin{array}{c} CH \end{array} \]

El-Sayed, R. [69] reported Sodium 1-[4-(substituted benzylidene-amino)-5-mercaptop-4H-[1,2,4]triazol-3-yl] heptadecane-1-sulfonate (47) synthesize by facile condensation reaction of Sodium 1-[4-amino-5-mercaptop-4H-(1,2,4)triazol-3-yl] heptadecane-1-sulfonate with different substituted aromatic aldehydes. All these products have antimicrobial activity and they can be used as surface active agents.

\[ \text{HN} \begin{array}{c} N \end{array} \text{N} \begin{array}{c} CH \end{array} \text{Ar} \]

Where, R = CH_3(CH_2)_{15}CH(SO_3Na)-

Ar = (a) C_6H_5
(b) C_6H_4Cl(p)
(c) C_6H_4OCH_3(p)  \hspace{1cm} (47)
Kalluraya, B. and co-workers [70] said in his work that 4-amino-3-substituted-5-mercapto[1,2,4]-triazole condensed with substituted pyrazole containing formyl group to give 3-(substituted)-4-(1-phenyl-3-methyl-5-chloro-4-pyrazolidene)amino-1,2,4-triazole-5-thione (48). All these compounds were tested for their antifungal and antibacterial activity.

\[
\begin{align*}
\text{(b) Ethyl} \\
\text{(c) Phenyl} \\
\text{(d) } p\text{-Cresyloxymethyl} \\
\text{(e) } p\text{-Chlorophenoxy methyl}
\end{align*}
\]

Holla, B. S. And co-workers [71] synthesize a series of 3-substituted-4-(5-nitro-2-furfuralidene)amino-5-mercapto-1,2,4-triazoles (49) and their manich bases were prepared. These new synthesized compounds were evaluated for their antibacterial activities. The title compounds are highly active against Gram-positive bacteria at 5 μg/ml concentration.

Number of scientists [72,73] synthesized or reported azomethine of mercapto derivatives (50) and mercapto furan derivatives of amino triazole (51).
Where, $R = \text{C}_6\text{H}_5$, 4-$\text{CH}_3\text{C}_6\text{H}_4$, 4-$\text{Cl}\text{-C}_6\text{H}_4$, 3-$\text{NO}_2\text{-C}_6\text{H}_4$,

2-Naphthyl

$R^1 = \text{H}, \text{Me}, \text{4-$\text{CH}_3\text{O}$-C}_6\text{H}_4$, 4-$\text{Cl}$-C$_6$H$_4$, 4-$\text{Br}$-C$_6$H$_4$,

2-Furanyl

(50)

Where, $R = \text{C}_6\text{H}_5$, 4-$\text{CH}_3\text{C}_6\text{H}_4$, 4-$\text{Cl}$-C$_6$H$_4$, 3,4-$\text{(CH}_3\text{O)}_2$C$_6$H$_3$,

2-nitrofuryl

(51)

Ammar, Y. A., Ghorab, M. M., Sh. El-Sharief, A. M., and Mohamed S. I. [74] reported reaction of 4-amino mercapto triazole bearing naphthalene ring with 4-anisaldehyde in acetic acid afforded the Schiff base (52).

Turan-Zitouni, G. and co-workers [75] reacted 3-[(5,6,7,8-tetrahydro-naphthalen-2-yl)-oxymethyl]-4-amino-1,2,4-triazol-5-thione with different aromatic
aldehydes in the presence of conc. sulfuric acid using dioxane as a reaction solvent gave the corresponding Schiff bases (53).

![Schiff base 53](image)

Where, $R = \text{C}_6\text{H}_5$, 4-Cl-C\text{H}_4, 4-NO\text{}_2-\text{C}_6\text{H}_4$, 4-(CH\text{\textsubscript{3}})\text{\textsubscript{2}}\text{N}-\text{C}_6\text{H}_3$, 4-OCH\text{\textsubscript{3}}-\text{C}_6\text{H}_4$

Similarly El-Masry, A. H. [76] reported Schiff bases of 1,2,4-triazole having benzimidazole moiety (54) synthesized by similar procedure as in [76].

![Schiff base 54](image)

Where, $R = \text{2-Cl-C}_6\text{H}_4$, 4-CH\text{\textsubscript{3}}-\text{C}_6\text{H}_4$

Holla, B. S. and co-workers [77] as well as Wu, T. X. and co-workers reported Schiff bases of 4-amino-5-alkyl/aryl-2,4-dihydro-3H-1,2,4-triazole-3-thiones (55) were prepared via a facile method in glacial acetic acid as a solvent and catalyst.

![Schiff base 55](image)
Zhang, Y. and co-workers [78] synthesize a Schiff base of 3-mercapto-1,2,4-triazole bearing 1,2,3-triazole ring (56).

![Chemical structure](image)

Where, \( R = \text{H, CH}_3 \), \( R^1 = \text{H, CH}_3 \), \( R^2 = \text{CH}_3, \text{C}_6\text{H}_5 \) (56)

Holla, B. S. [79] described in his work that on reacting aminotriazolthione with 2,4-dichlorophenylfurfural in the presence of a few drops of conc. sulfuric acid as a catalyst produced Schiff bases (57) in good yields. These Schiff bases were then treated with a primary/secondary amine in the presence of formaldehyde to produce Mannich bases.

![Chemical structures](image)

(57)

Kalluraya, B. and co-workers [80] reported reaction of 5-nitro-2-(diacetoxy methyl)-thiophene with aminotriazolthione to yield the Schiff bases (58). Treating the upper mentioned Schiff bases with formaldehyde and amines dialkyl amines gave the expected Mannich bases (59).
Where, $R = H, \text{Alkyl}, (\text{un})\text{substituted Ph, PhOCH}_2, \text{PhCH}_2$

$$R^1 = R^2R^3\text{NCH}_2 (R^2=R^3=\text{Ph, } R^2=4-\text{Cl-C}_6\text{H}_4, R^3=H, R^2R^3\text{NH}=\text{Morpholine, Piperidine})$$

Rahiman, M. A. and co-workers [81] reported Mannich reaction of 3-substituted-4-(3-aryl-4-sydnonylidene)-amino-1,2,4-triazol-5-thiones with formaldehyde and the appropriate amines resulted in the formation of 1-amino-methyl-3-substituted-4-(3-aryl-4-sydnonylidene)amino-1,2,4-triazole-5-thiones.

Holla, B. S. and co-workers [82] reported on the synthesis of 3-substituted-4-[5-(4-methoxy-2-nitrophenyl)-2-furfurylidene]amino-1,2,4-triazol-5-thiones (60). On the treatment of (60) with formaldehyde and various secondary amines, the reaction furnished the formation of the Mannich bases (61).

Where, $R = H, \text{Me, Et, Pr, 2-Cl-C}_6\text{H}_4\text{OCH}_2, 4-\text{Cl-C}_6\text{H}_4\text{OCH}_2, 2,4-\text{Cl}_2\text{-C}_6\text{H}_3\text{OCH}_2, 4-\text{Cl}-3-\text{MeC}_6\text{H}_4\text{OCH}_2; ; X = O, \text{NMe}$
Liu, X. Y. and co-workers [83] reported new 4-amino-5-furyl-2-yl-4H-1,2,4-triazole-3-thiol Derivatives (62) as a Novel Class of Endothelin (ET) Receptor Antagonists.

![Chemical Structure](image1)

(62)

Where, \( R^1 = \text{Ph, 3-OCH}_3\text{-Ph, 4-CN-Ph, C}_2\text{H}_5\text{OCO} \)
\( R^2 = 2\text{-NO}_2\text{Furyl, 3,4-(OCH}_3)_2\text{Ph} \)

Reddy, V., Patil, N., Reddy, T., and Angadi, S. D. co-workers [84] synthesized, characterized Cu(II), Co(II), Ni(II), Mn(II) and Fe(III) complexes (64) with Schiff bases derived from 3-(4-Chlorophenoxy)methyl)-4-amino-5-mercaptop-1,2,4-triazole (63). The antibacterial activities of ligand and its complexes were screened by cup plate method.

![Chemical Structures](image2)

(63)  (64)

Almajan, G. L. and co-workers [85] reported a series of Mannich bases of 4-substituted 5-[4-(4-X-phenylsulfonyl)phenyl]-2,4-dihydro-3H-1,2,4-triazole-3-thiones (65), \( X = \text{H, Cl, Br} \), were synthesized and characterized on the basis of IR, NMR and elemental analyses and potential antibacterial effects were investigated.
1.3 Hydrazone containing Triazole and Mercapto Triazole Derivatives:

Nitinchandra Balkrushna Kalluraya [86] reported synthesis, characterization and Pharmacological studies of novel hydrazones of 1,2,3-triazole as potent cytotoxic agents.

Keyume Abjajan and Wang Liju [87] reported some new hydrazone derivatives containing 1,2,3-triazole and thiazole derivatives.

Wagnat Wahba Wardakhan and co-workers [88] reported new approach for the synthesis of hydrazone derivatives and their Antitumor evaluation.

Kukasz Popiolek and Urszula Kosikowska [89] reported synthesis and antimicrobial activity of new Schiff bases hydrazones bearing 1,2,4-triazole moiety.
This review [90] provides detailed methods for the synthesis, structures and chemical properties of hydrazones bearing carboxamide, thioamide and amidine functions. The main accent was put on the cyclization reactions leading to pyrazoles, thiazoles, 1,2,3-triazoles, 1,2,3-thiadiazoles, 1,2,4-triazines and other heterocyclic compounds. In addition, we have reviewed methods for the synthesis of substrates for pericyclic reactions from the hydrazones.

Hamid Khanmohammadi and his team [91] reported synthesis, biological and computational study of new Schiff base of hydrazones bearing 3-(4-pyridine)-5-mercapto-1,2,4-triazole moiety.

Hamid Khanmohammadi and his team [92] reported new acyclic 1,2,4-triazole based Schiff base hydrazone derivatives.

1.4 Research gaps about the heterocyclization of 4-(4H-[1,2,4]-triazol-3-yl sulfanyl)-butyric acid hydrazide (TSH).

The usage of most antimicrobial agents is limited, not only by the rapidly developing drug resistance, but also by the unsatisfactory status of present treatments of bacterial and fungal infections and drug side-effects [93]. Therefore, the development of new and different antimicrobial drugs is a very important objective and many research programs are directed the design of new antimicrobial agents.
As per the review about the derivatization of 1,2,4-triazole, It is a five-membered heterocycles containing three nitrogens in the ring and its derivatives have biological activities such as antibacterial, antifungal, antimycobacterial, anti-inflammatory, analgesic, anticancer, antihypertensive, antiviral, antidepressant, antiasthmatic, diuretic and hypoglycemic. All these facts were driving force to develop novel 1,2,4-triazole derivatives with wide structural variation. Thus 1,2,4-triazole derivatives plays pivotal role in medicinal chemistry.

As part of interest in heterocycles derived from Schiff bases that have been explored for developing pharmaceutically important molecules, 2-azetidinones [94,95], 4-thiazolidinones [95,96], 2-pyrrole and 2-pyrrolidinones [97,98], and tetrazole [99] have played a pivotal role in medicinal chemistry. Moreover they have been studied extensively because of their ready accessibility, diverse chemical reactivity and broad spectrum of biological activity. The area in which heterocyclization of 4-(4H-[1,2,4] triazol-3-yl sulfanyl)-butyric acid hydrazide (TSH) into above heterocycles has not been reported so far. Hence, it was thought to undertaken such study.

1.5 Objectives of the present work:

In view of above review, the prime objectives of the present thesis are,

- Derivatization of 4-(4H-[1,2,4] triazol-3-yl sulfanyl)-butyric acid hydrazide (TSH) into heterocycles like 2-azetidinone, 4-thiazolidinone, 2-pyrrole, 2-pyrrolidinone and tetrazole.
- Evaluation of antimicrobial activity of above prepared heterocycles.

1.6 The present work:

According to the above objectives, research work was carried and distributed into following chapters of the present thesis.
Chapter-2 of the thesis comprises into two sections.

**Part-A** comprises the details about techniques used for characterization.

**Part-B** deals with the formation and characterization of Schiff bases of 4-(4H-[1,2,4]triazol-3-yl sulfanyl)-butyric acid hydrazide (TSH).

The 2-azetidinone and 4-thiazolidinone derivatives were derived from 4-(4H-[1,2,4]triazol-3-yl sulfanyl)-butyric acid hydrazide (TSH). Their synthesis and characterization are included into Chapter-3.

The 2H-pyrrole-2-one and 2-pyrrolidinone derivatives were derived from 4-(4H-[1,2,4]triazol-3-yl sulfanyl)-butyric acid hydrazide (TSH). Their Synthesis and characterization of these compounds are included into Chapter-4 of the thesis.

The Tetrazole derivatives were derived from 4-(4H-[1,2,4]triazol-3-yl sulfanyl)-butyric acid hydrazide (TSH). Their synthesis and characterization are summarized into Chapter-5 of the thesis.

All the prepared compounds mentioned in chapters-2 to 6 were screened for their antimicrobial activity. The common biospecies have been selected. The results of such study are discussed in chapter-6.
The entire synthetic route is scanned in Scheme 1.1.

Where, Ar = (a) C₆H₅  (b) 2-CH₃C₆H₄
(C) 4-OH-C₆H₅  (d) 2-OCH₃C₆H₄
(e) 4-CH₃C₆H₄  (f) 4-OCH₃C₆H₄
References


Chapter 1


[47] Holla, B. S.; Shivananda, M. K.; Akberali, P. M.; Baliga, S.; Safeer, S.
Chapter-1


