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Synthesis and Characterization of Some New Thiazolo[3,2-b][1,2,4]triazoles

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A dissertation submitted to the Department of Chemistry, Quaid-i-Azam University, Islamabad, in partial fulfilment of the requirements for the degree of

Master of Philosophy

in

Organic Chemistry

By

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July, 2011

DECLARATION

This is to certify that this dissertation entitled ***"Synthesis and Characterization of Some New Thiazolo[3,2-b] [1,2,4]triazoles"*** submitted by ***Mr. Muhammad Waqas*** is accepted in its present form by the Department of Chemistry, Quaid-i-Azam University, Islamabad, as satisfying the dissertation requirements for the degree of ***Master of Philosophy in Organic Chemistry.***

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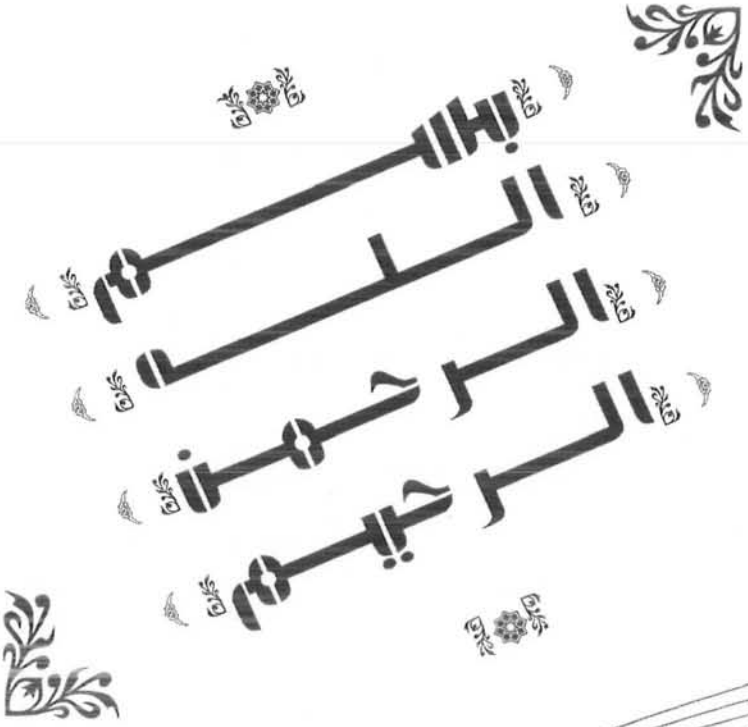

In the name of ALLAH, the most merciful, the most beneficient.

"He is Allah,
whom there is none worthy of worship except He,
the All-Knower of the unseen and the seen (open). He is
the Most Beneficent,
the Most Merciful.
He is Allah, whom there is none worthy of worship except He,
the King, the Holy,
the One Free from all imperfections, the Giver of security,
the Watcher over His creatures,
the All-Mighty,
the Compeller, the Supreme.
Exalted is He above all that they associate [in worship] with Him.
He is Allah,
the Creator, the Inventor of all things, the Bestower of forms. To Him belong the Best Names. All that is in the heavens and the earth glorify Him. And He is the All-Mighty, the All-Wise."

(Al-Hashr 59:22-24)

The Prophet (P.B.U.H) said,

" Acquire knowledge, it enables its professor to distinguish right from wrong; it lights the way to heaven. It is our friend in the desert, our company in solitude and companion when friendless. It guides us to happiness, it sustains us in misery, it is an ornament amongst friends and an armour against enemies"

This dissertation is dedicated to my family, my teachers and those who are serving the humanity.

ACKNOWLEDGMENTS

All praises be to the **Almighty Allah** who induced the man with intelligence, knowledge, sight to observe and mind to think. Peace and blessings of Allah be upon the **Holy Prophet Hazrat Muhammad (*P.B.U.H*)** who exhorted his followers to seek for knowledge from cradle to grave.

I am deeply indebted to my supervisor **Prof. Dr. Shahid Hameed**, Head of Organic Section, for his guidance and encouragement. His sympathetic attitude always encouraged me a lot to solve my problems.

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I am obliged to express my thanks to my class fellows, my lab fellows and my friends especially Mr. Imtiaz Bhatti, Mr. Muhammad Saleem, Mr. Muhammad Hanif, Mr. Tariq Mehmood, Mr. Sajid Ali, Mr. Shams ul Mehmood, Mr. Naeem Abbas, Mr. Ghulam Waris, Mr. Shahzad Nazir, Mr. Pervez Ali, Mr. Rizwan Maqsood, Mr. Tanvir Ahmed, Mr. Majid Hussain, Mr. Atta ur Rehman, Mr. Ismatullah, Mr. Mudassir Shahzad, Mr. Ehtisham ul Haq, Mr. Naeem Bhatti and Mr. Muhammad Jamil.

I would also like to pay bundle of thanks to Dr. Afzal Shah and Dr. Fida ul Mustafa for their moral support, encouragement and prayers.

From the core of my heart, special thanks are going to my parents, sisters and my brothers; Usman Mallhi & Umar Mallhi. Their praying hands always gave me enough courage to stand in all the circumstances and enabled me to accomplish my tasks.

I express my feelings to Mr. Shams Pervez, Mr. Matloob Ahmed, Mr. Tayyab, Mr. Sharif Chohan and all other members of non-teaching staff of department for their help.

May Almighty Allah shower His choicest blessings and prosperity on all those who assisted me in any way during the completion of my dissertation.

Allah bless you all.

Muhammad Waqas

ABSTRACT

A new series of thiazolo[3,2-*b*][1,2,4]triazoles was synthesized by intramolecular dehydrative cyclization of aryl-2-(4*H*-1,2,4-triazol-3-ylthio)ethanones by refluxing them in phosphorus oxychloride. The ethanones were prepared from 5-substituted 1,2,4-triazole-3-thiols and phenacylbromides by a nucleophilic substitution bimolecular reaction. The structures of newly synthesized thiazolo[3,2-*b*][1,2,4]triazoles were characterized by IR, ^{1}H NMR and ^{13}C NMR.

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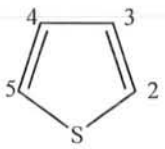
INTRODUCTION

Chapter-1

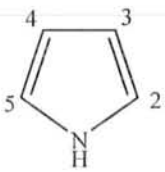
Of the millions of chemical compounds, about one-half contain heterocyclic systems. Heterocycles are important not only because of their abundance but also due to their chemical, biological and industrial applications. Heterocycles count among their numbers many natural products, such as vitamins, hormones, antibiotics, alkaloids, herbicides, dyes and some other products such as corrosion inhibitors, sensitizers, stabilizing agents, etc. Life, like ours, is totally dependent on the heterocyclic compounds; it takes birth with purine/pyrimidine bases, nourishes on carbohydrates and in case of disease, cures by medicines, many of which are heterocyclic in nature. Today, the heterocyclic chemistry delivers reagents and synthetic methods of its own traditional activity in synthesis of drugs, pesticides and detergents as well as in the related fields such as biochemistry, polymer and material sciences.

1.1 Heterocyclic compounds

Heterocyclic compounds are the type of cyclic compounds that contain one or more hetero atoms in the ring. Most common hetero atoms are nitrogen, oxygen and sulphur. More than half of the compounds produced by nature contain heterocyclic rings incorporated in their structures. Some common examples are: thiophene (**1**), pyrrole (**2**), pyridine (**3**), furan (**4**), thiazole (**5**), etc.



(1)



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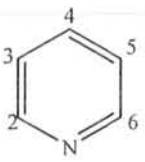

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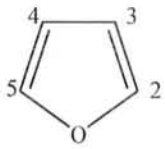

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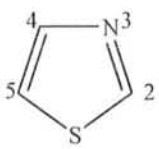
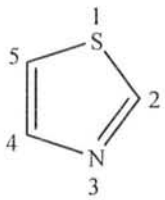


(5)

1.2 Thiazoles

The heterocyclic compounds having one nitrogen and one sulfur atom in a five-membered cyclic structure constitute an important class of compounds named as thiazoles or 1,3-thiazoles (**6**).



(6)

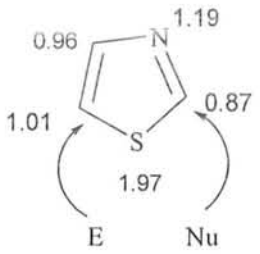
1.2.1 Chemistry of 1,3-thiazoles

Thiazole systems possess some important features which are being discussed briefly.

a) Aromaticity and stability

Thiazole rings are planar and aromatic. Four $2p_z$-orbitals and one $3p_z$-orbital form delocalized π-MOs to which three C-atoms and one N-atom each contributes one electron whereas S-atom contributes two electrons. Thus, thiazoles are characterized by larger *pi*-electron delocalization and have, therefore, greater aromaticity. This aromaticity is evidenced by the chemical shift values of the ring protons in proton NMR spectroscopy (between 7.27 and 8.77 ppm), clearly indicating a strong diamagnetic ring current.

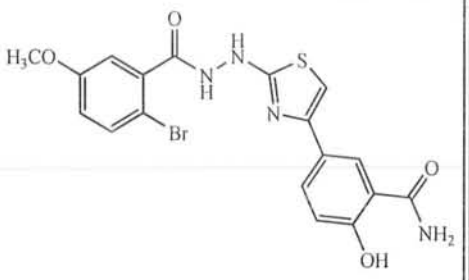
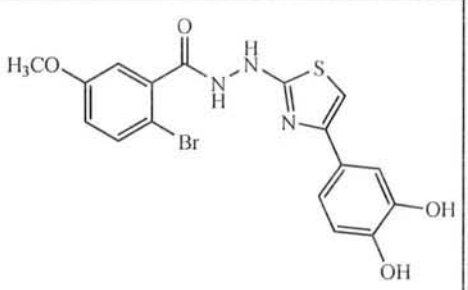
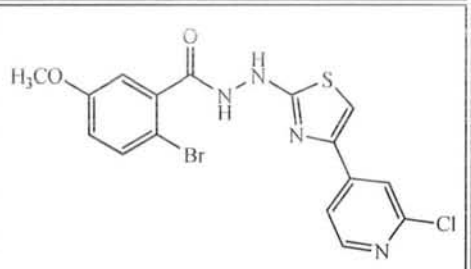
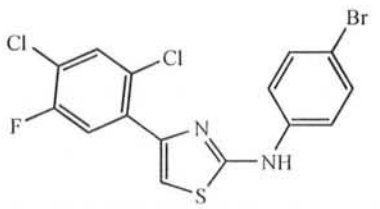
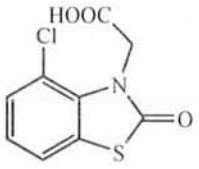
Thiazoles are π-excessive heterocycles but the excess is concentrated mainly on heteroatoms. The N-atom and S-atom of the ring attract π-electrons towards themselves, decreasing the π-electron density on C-atoms, more significantly on C-2 atom. The calculated π-electron density marks C-5 as the primary site for electrophilic substitution and C-2 as the site for nucleophilic substitution[1] as shown below:



1.2.2 Importance of thiazoles

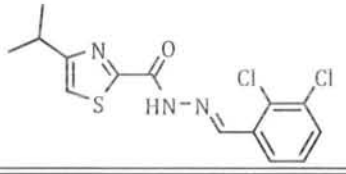
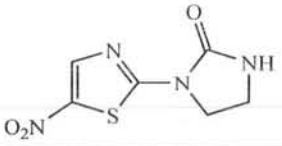
Thiazoles, being an integral part of many potent biologically-active molecules, are an important class of compounds in medicinal chemistry. Thiazole moiety, being a key pharmacophore, has low toxicity, excellent biological activity and ready access of diverse derivatives. The applications of thiazoles were found in drug development for the treatment of various diseases. Some important applications of thiazoles are given in the Table 1.1.

Table 1.1: Some important 1,3-thiazoles and their applications

S. No.	Structural Formula	Applications	Ref.
7		Anticancer activity	2
8		Antibacterial activity	2
9		Antifungal activity	2
10		Antiinflammato-ry activity	3
11		Herbicide	4

(Table 1.1 continued)

(Table 1.1 continued)

12		Antimicrobial activity	5
13		Applied in the treatment of bilharzia(schis-tosomiasis)	6

1.2.3 Synthetic strategies for 1,3-thiazoles

Various methods for the synthesis of thiazole ring have been described. These methods can be divided into following two categories:

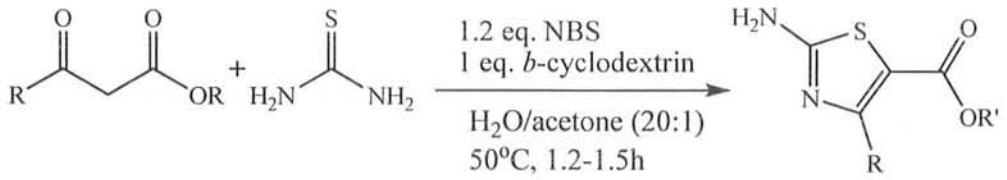
i) Intermolecualr cyclization reactions

ii) Intramolecular cyclization reactions

i) Intermolecular cyclization reactions

a) From β-keto esters and thiourea

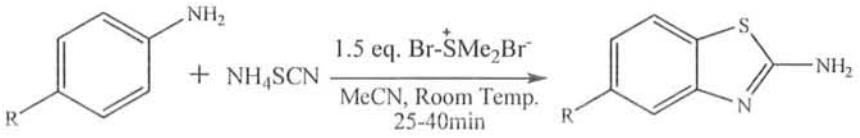
2-Amino-4-alkyl- and 2-amino-4-arylthiazole-5-carboxylates **(16)** were synthesized by α-halogenation of *β*-keto esters **(14)** with *N*-bromosuccinimide, followed by cyclization with thiourea[7] **(15)** in the presence of *β*-cyclodextrin in water at 50°C.



(14) **(15)** **(16)**

b) From anilines and ammonium thiocyanate

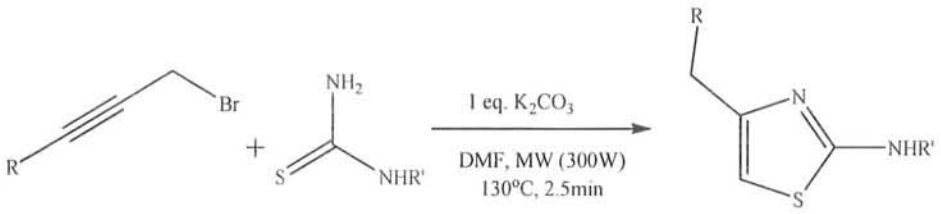
Various aromatic and heteroaromatic anilines have been efficiently thiocyanated using a combination of bromodimethylsulfonium bromide (BDMS) and ammonium thiocyanate to produce 2-aminobenzothiazoles[8] **(17)**.



(17)

c) From reaction of propargyl bromides with thioureas and thio-pyrimidinones

A domino alkylation-cyclization reaction of propargyl bromides **(18)** with thioureas allows the synthesis of 2-aminothiazoles[9] **(19)**. Domino reactions were performed under microwave irradiation leading to desired compounds in a few minutes with high yields.

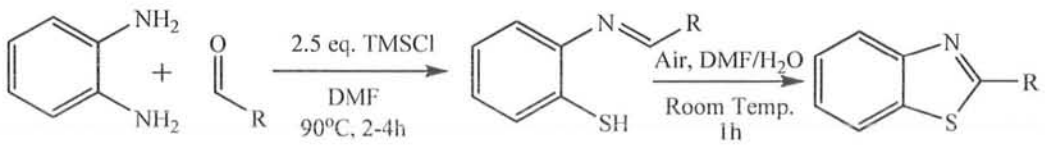


R = H, COPh R′ = alkyl, aryl

(18) **(19)**

d) From reaction of *ortho*-aminothiophenol and aldehydes

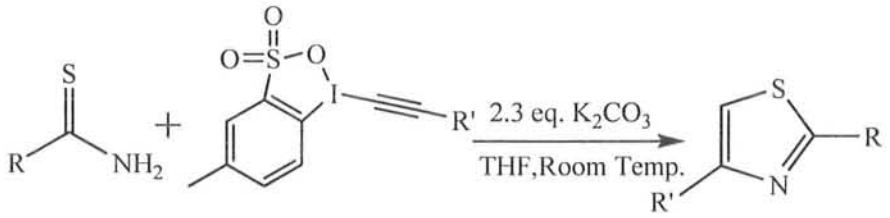
A set of benzothiazoles **(21)** was readily prepared from *ortho*-aminothiophenol **(20)** and aldehydes using chlorotrimethylsilane in DMF as a promoter and water-acceptor agent, followed by oxidation with oxygen from air[10].



(20) **(21)**

e) From 1*H*-1-(1′-alkynyl)-5-methyl-1,2,3-benziodoxathiole-3,3-dioxides

Thiazoles **(24)** were obtained in good yields by the reaction of 1*H*-1-(1′-alkynyl)-5-methyl-1,2,3-benziodoxathiole-3,3-dioxides **(22)** with thioamides **(23)**. The co-product, potassium 2-iodo-5-methylbenzenesulfonate, was recovered quantitatively by simple filtration of the reaction mixture, and was regenerated to 1*H*-1-(1′-alkynyl)-5-methyl-1,2,3-benziodoxathiole-3,3-dioxides to be reused[11].

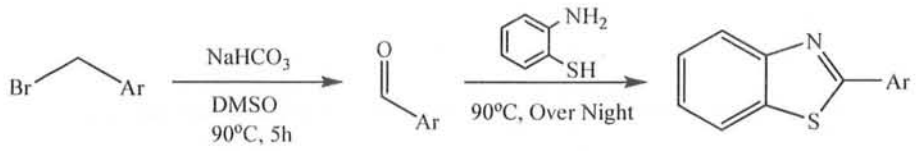


R = Ar, Me, NH_2 R′ = Ph, Bu, C_6H_{13}

(23) **(22)** **(24)**

f) From one-pot tandem reaction of benzyl halides

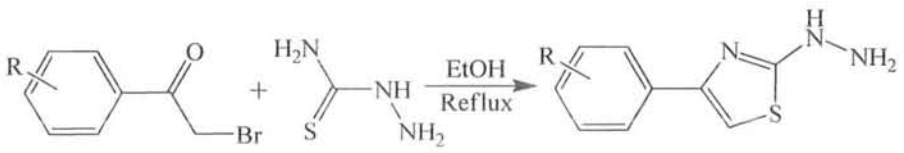
A one-pot tandem reaction of benzyl halides and *o*-aminobenzenethiol gives benzothiazoles **(25)** in high yields under mild conditions in DMSO in the absence of an additional oxidant[12]. Both benzyl chlorides and bromides bearing a range of substituents proved to be suitable substrates.



(25)

g) From thiosemicarbazide and phenacyl bromides

Thiosemicarbazide on refluxing with phenacylbromides **(26)** in ethanol, produces 4-aryl-2-hydrazinothiazoles **(27)** under refluxing conditions on water bath for about half an hour[3].

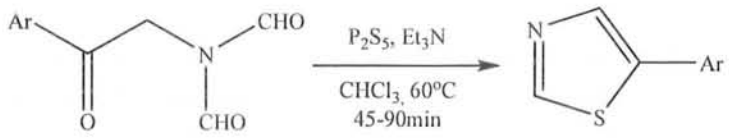


(26) (27)

ii) Intramolecular condensation reactions

a) From *N,N*-diformylaminomethylaryl ketones

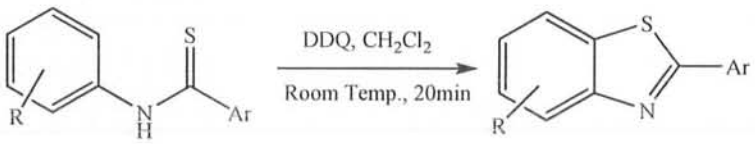
Treatment of *N,N*-diformylaminomethyl aryl ketones **(28)** with phosphorus pentasulfide and triethylamine in chloroform gives 5-arylthiazoles **(29)** in good yield[13]. The 5-aryl-1,3-thiazole core has been successfully functionalised at the 2-position to yield, over two steps, a large array of 5-aryl-2-arylsulfonyl-1,3-thiazoles.



(28) (29)

b) From cyclization of thioformanilides

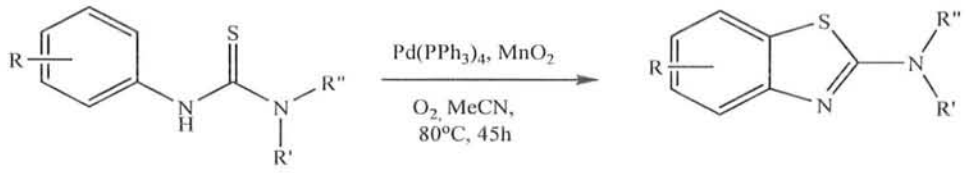
Various benzothiazoles **(31)** were synthesized by the intramolecular cyclization of thioformanilides **(30)** using 2,6-dichloro-3,5-dicyano-1,4-benzoquinone (DDQ) in dichloromethane at ambient temperature in high yields[14].



(30) (31)

c) From *N*-arylthioureas

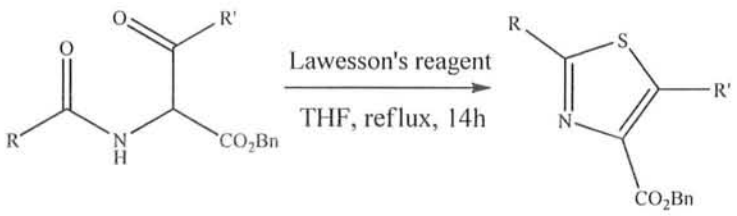
N-Arylthioureas **(32)** are converted to 2-aminobenzothiazoles **(33)** *via* intramolecular C-S bond formation/C-H functionalization in the presence of an unusual cocatalytic $Pd(PPh_3)_4/MnO_2$ system[15] under an oxygen atmosphere at 80°C. This method eliminates the need for an *ortho*-halo substituted precursor, instead achieving direct functionalization of the *ortho*-aryl C-H bond.



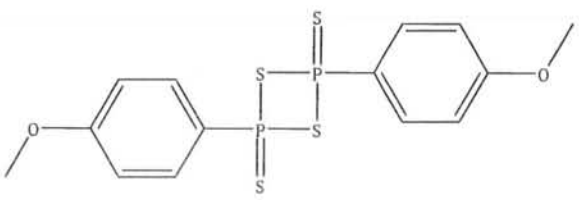
(32) **(33)**

d) From Lawesson's reagent

A small library of compounds with thiazole scaffolds and structural diversity in both positions 2 and 5 has been synthesized by this method. Double acylation of a protected glycine affords intermediate α-amido-β-ketoesters **(34)**, which in turn, can be reacted with Lawesson's reagent to furnish 1,3-thiazoles[16] **(35)**.



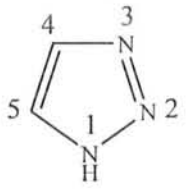
(34) **(35)**



Lawesson's reagent (LR)

1.3 Triazoles

Triazoles contain five-membered heterocyclic ring with two carbon atoms and three nitrogen atoms. The presence of three nitrogen atoms defines this interesting class of compounds. Triazoles may be of two structural types: 1,2,3-triazoles **(36)** and 1,2,4-triazoles **(37)**.



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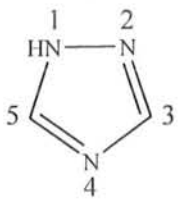


(37)

The name triazole was first given by Baldin to this carbon nitrogen ring system[17], $C_2N_3H_3$, who described its derivatives in early 1885, although the structures reported were slightly incorrect[18].

A little interest emerged in this field around 1925 to 1946. The successors of Andreocci carried out most intensive investigations of the chemistry of 1,2,4-triazoles[18]. The chemical industry get renewed attention in the synthesis of both simple and fused triazole systems after the discovery that certain triazoles are capable of inhibiting fog formation in photographic emulsion and some others being useful herbicide and convulsants[19].

All triazoles are of synthetic origin and there is no triazole ring system detected as yet in nature.

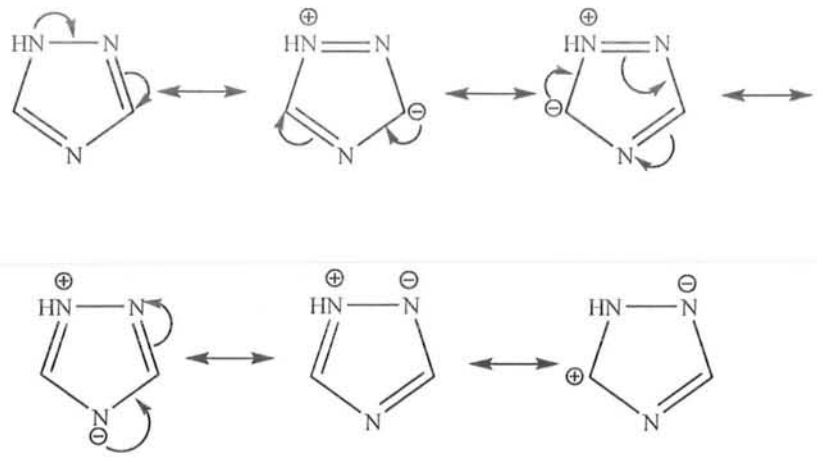
1.3.1 Chemistry of 1,2,4-triazoles

1,2,4-Triazole systems possess some important features:

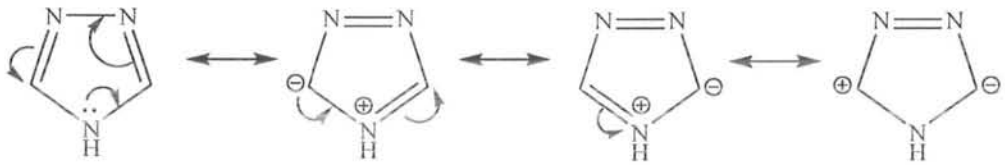
a) Aromaticity and stability

The stability of 1,2,4-triazole nucleus is an inherent property from its aromatic nature. An aromatic sextet is formed by contribution of one π-electron from each atom joined by double bonds and the remaining two electrons from nitrogen atom. Such a system is stabilized by resonance and thus the triazole nucleus may be represented by canonical forms, each being capable of extended

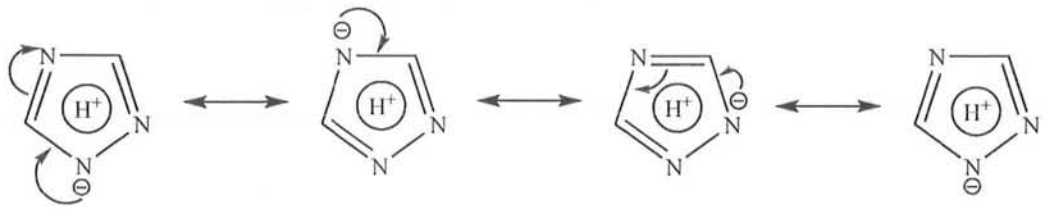
resonance and the structure may be represented more correctly as a hybrid to which the following forms contribute[20]:



It is also necessary to consider the canonical forms where the imino hydrogen atom is at 4-position. The canonical forms that contribute to this resonance hybrid are given below[20]:



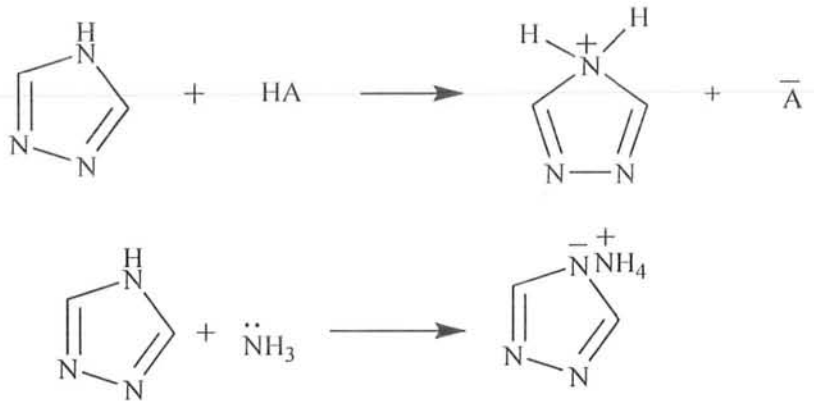
This representation makes the assumption that the triazole nucleus actually consists of two hybrid structures, each representing an individual tautomeric form. In modern theories such a view is incorrect. A more suitable expression is to regard 1,2,4-triazole as a true aromatic system, stabilized by resonance and represented as[20]:



It is not intended to represent the charges on a nitrogen atom and on the hydrogen atom as separate, complete charges but merely as a slight overall negative charge on the ring, balanced by a corresponding positive charge on the hydrogen atom.

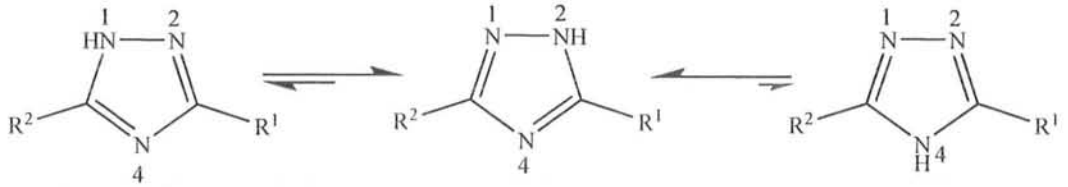
b) Acid-base reactions

1,2,4-Triazoles have amphoteric nature and form salts when treated with acids as well as bases. 1,2,4-Triazole is a weak base ($pK_a = 2.19$) and protonation occurs at position-4. 1,2,4-Triazoles unsubstituted at nitrogen atom are NH-acidic ($pK_a = 10.26$).



c) Tautomerism

1,2,4-Triazoles exhibit annular prototropic tautomerism with three possible structural types. The three possible tautomeric forms namely (1*H*)-1,2,4-triazoles **(38)**, (2*H*)-1,2,4-triazoles **(39)** and (4*H*)-1,2,4-triazoles (**40**) are shown below.



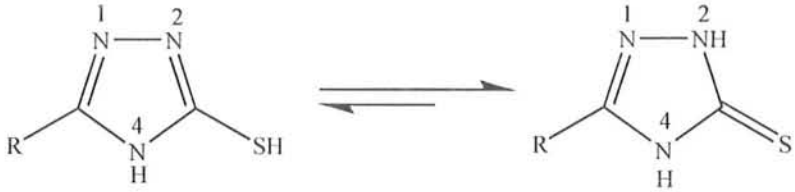
(38) **(39)** **(40)**

Tautomer **39** with hydrogen at nitrogen-2 is more favored as compared to other two tautomers **38** and **40** which contain hydrogen at nitrogen-1 and nitrogen-4, respectively. The study of 3-amino-1,2,4-triazole ($R_1 = NH_2$, $R_2 = H$) in aqueous solution using ^{15}N NMR spectroscopy concludes that tautomer **39** dominates over tautomer **38** with ratio being approximately 2:1 whereas tautomer **40** is not present to any measureable extent[21]. The tautomer **40** has higher dipole moment; this property partially shifts tautomeric equilibrium towards tautomer **40** in dipolar solvents. In ^{15}N NMR of 1,2,4-triazole ($R^1 = R^2 =$

NH_2), only 5% of tautomer **40** was observed in DMSO solution. Another evidence showed that tautomer **39** is the only form observed in ^{15}N MMR method in DMSO[22].

i. Tautomerism in substituted 1,2,4-triazoles

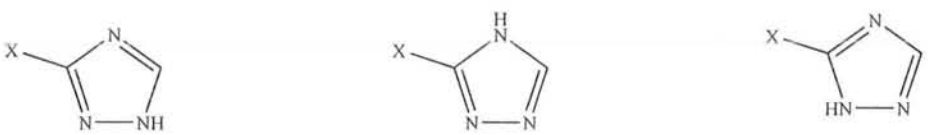
The substituted 1,2,4-triazoles like 3-mercapto-1,2,4-triazoles exist in two tautomeric forms, thiol form **(41)** and thione form **(42)**. It is because of the labile hydrogen which may be attached either to the nitrogen or the sulphur atom. It exhibits thione-thiol tautomeric forms as shown below. This compound exists predominantly in thione (**42**) form[23].



(41) **(42)**

Similarly, chloro-1,2,4-triazoles exist as 3-chloro-1*H*-1,2,4-triazole (**43a**), 3-chloro-4*H*-1,2,4-triazole (**43b**) and 5-chloro-1*H*-1,2,4-triazole (**43c**). These tautomers have the stability order: **43a** > **43c** > **43b** according to physical and theoretical calculations[24].

In bromo-1,2,4-triazoles, the possible corresponding tautomeric forms would be 3-bromo-1*H*-1,2,4-triazole (**44a**), 3-bromo-4*H*-1,2,4-triazole (**44b**) and 5-bromo-1*H*-1,2,4-triazole (**44c**). According to physical and theoretical calculations, the tautomers (**44a**) and (**44c**) are of similar energy and the most stable tautomer is (**44b**). These calculations agree with the results of Flammang *et al.*



(a) **(b)** **(c)**

43: X = Cl

44: X = Br

1.3.2 Applications of 1,2,4-triazoles

1,2,4-Triazoles and their derivatives are of great importance due to their biological, industrial and agricultural activities.

a) Biological applications

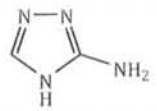
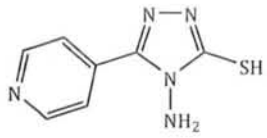
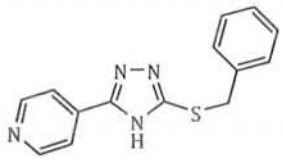
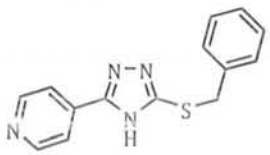
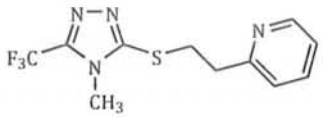
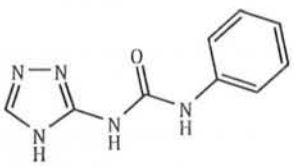
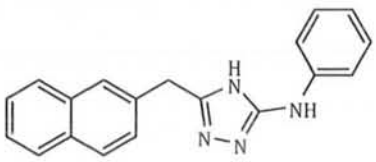
Triazole ring displays a broad spectrum of biocidal activities. A well-known example is that of fluconazole: an antifungal agent for the treatment of superficial and systemic infections[25]. Many other substituted 1,2,4-triazoles have diuretic[26], antibacterial[27], hypoglycemic[28] and antitubercular[29] activities. Some others have been reported as antifungal[30], plant growth accelerators/inhibitors[31] and herbicides[32].

Over the last few decades, the biological and pharmaceutical properties of 1,2,4-triazoles have created considerable interest in their synthesis and characterization[33]. 1,2,4-Triazole and its derivatives possess widely-differing activities, *e.g.*, bacteriostatic[34], bactericidal[35], antifungal[36], antiviral[37], muscle relaxant[38] and antihuman immunodeficiency virus (HIV)[39].

The pathogenic fungi cause life-threatening infections that have become increasingly common during the past two decades. Fungal infections are common in individuals with immuno-compromised hosts, such as patients undergoing anticancer chemotherapy or organ transplants and patients with AIDS.

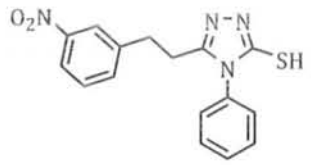
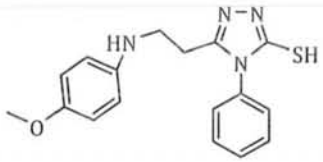
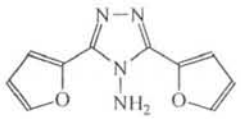
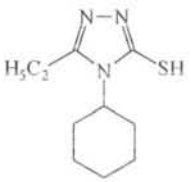
A variety of other triazoles have several activities, *e.g.*, antidepressant[40], CNS-depressant[41], antibiotic[42], antiinflammatory[43], antihypertensive[44], anticarcinogenic[45], sedative[46], dopamine-β-hydroxylase inhibitor[47], plant growth regulator[48] and insecticidal[49]. Some important 1,2,4-triazoles along with their applications are listed in Table 1.2.

Table 1.2: Some important 1,2,4-triazoles and their applications

Sr. No.	Structural Formula	Applications	Ref.
45		Inhibitive effect on the pitting corrosion of copper on mild steel and on copper wires	50
46		Bactericidal and fungicidal activity	51
47		Plant growth regulators	52
48		Inhibitive effect on blood platelets aggregation	53
49		Antiulcer activity	46
50		Antihypertensive	45
51		Anti-inflammatory	44

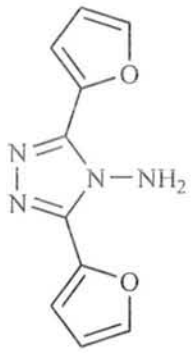
(Table 1.2 continued)

(Table 1.2 continued)

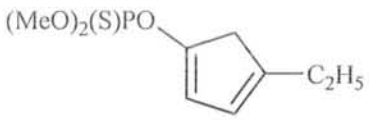
52		Antiamoebic	54
53		Antifungal	37
54		Herbicidal	33
55		Anticonvulsant	55

b) Agricultural applications

In the plant protection technology, the research has been promoted to discover more efficient pesticides to tackle new challenging problems. In order to selectively control the growth of weeds, a whole range of azole herbicides has been developed exhibiting high levels of activity, application flexibility, crop tolerance and low levels of toxicity to mammals. A series of 1,2,4-triazole derivatives has been patented and extensively employed. One example of a herbicidal[32] (**56**) and pesticidal[56]1,2,4-triazole (**57**) is given below:



(56)



(57)

c) Industrial applications

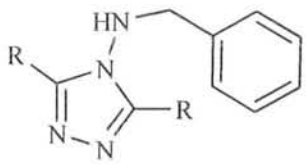
i) Chemical industry

Some selected triazoles have been used as light emitting diodes in electroluminescent devices[57]. Some triazole systems have extensive use in the separation of silver from other metal cations in liquid membrane systems[58].

In addition, these compounds are used as synthetic dyes and bleaching agents[59]. Moreover, the inks having smooth writing properties also contain triazole derivatives, *e.g.*, 3-amino-5-mercapto-1,2,4-triazole[60]. These compounds have also been reported as inhibitors of corrosion of copper, brass, aluminium and steel in marine environment[61] and inhibit fog formation in photographic emulsions[62].

ii) Textile industry

The triazole derivatives have many applications in textile industry, *e.g.*, sodium salt of a sulphonated triazole derivative possesses good detergent action and N-benzylated amino triazoles (**58**) show useful properties in inhibiting the acid-fading of dyestuff[63].



(58)

iii) Cotton industry

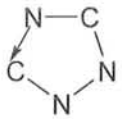
In the cotton industry, 3-amino-1,2,4-triazole (under its trade name *amizol)*, has been used as a commercial defoliant for a number of years[64].

1.3.3 Synthetic approaches towards 1,2,4-triazoles

The early methods for the preparation of 1,2,4-triazoles were simple and low yielding but they made the nucleus available for study within a year of the original discovery by Baldin. These have now been replaced by later modifications and by more efficient methods[65].

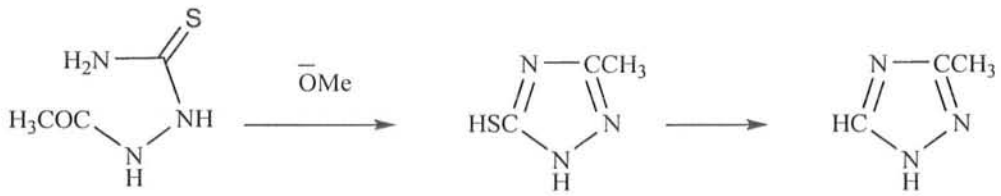
a) From thiosemicarbazides

Usually, 1,2,4-triazoles are formed by the cyclization of a preformed nucleus of the following type (**59**):



(59)

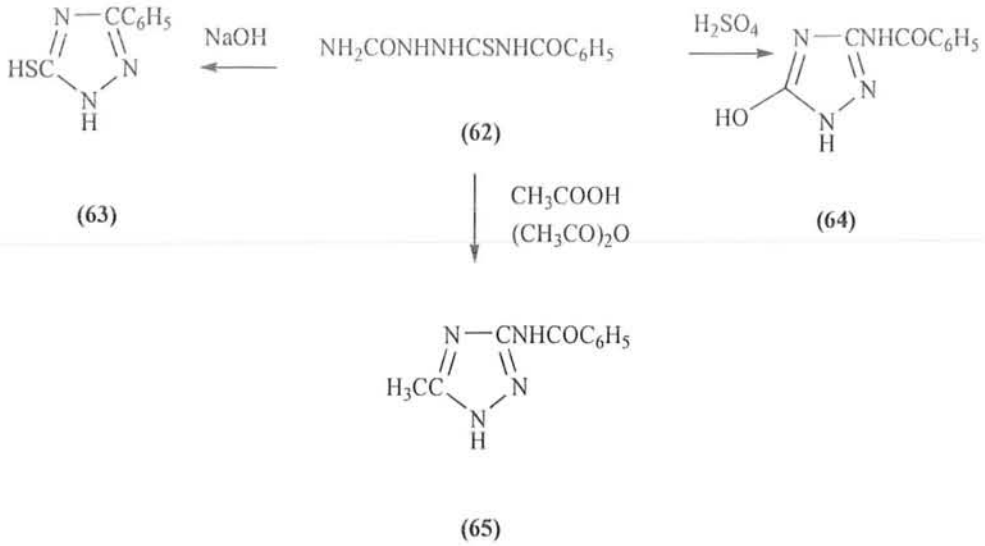
This is the most efficient method for the synthesis of C-monosubstituted triazoles. In this way, a triazole containing a mercapto or hydroxyl group is obtained which then may be removed by oxidation. Thus, the cyclization of 1-acetylthiosemicarbazide with sodium methoxide in methanol results in the formation of 5-mercapto-3-methyl-1,2,4-triazole **(60)** which readily loses the mercapto group on oxidation with nitric acid[66] to form 3-methyl-1,2,4-triazole **(61)**[67].



(60) **(61)**

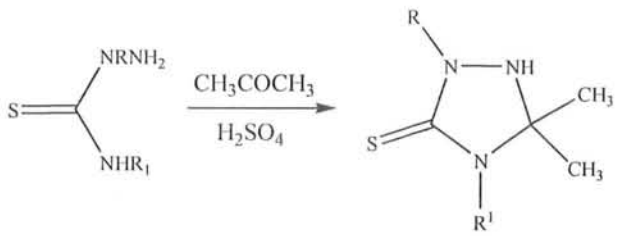
It is interesting that 4-benzoyl-1-carbamoyl-3-thiosemicarbazide **(62)**, under various reaction conditions, forms different products: with 20% sodium hydroxide, it yields 5-mercapto-3-phenyl-1,2,4-triazole **(63)** that is the normal cyclization product of 4-acylthiosemicarbazides with alkali; with concentrated sulfuric acid, at room temperature, it forms 3-benzamido-5-hydroxy-1,2,4-triazole **(64)** by the elimination of hydrogen sulfide and a hot acetic anhydride-

acetic acid mixture results in the formation of 3-benzamido-5-methyl-1,2,4-triazole **(65)**[68].



b) From thiosemicarbazides and carbonyl compounds

The cyclocondensation of 2,4-disubstituted thiosemicarbazides with carbonyl functions forms triazoles. Reaction of 4-(2-methylallyl)-2-phenylthiosemicarbazide (**66**) with ketones, in the presence of catalytic amount of sulfuric acid, afforded 3,3-dimethyl-4-(2-methylallyl)-1-phenyl-1,2,4-triazolidin-5-thione (**67**)[69].

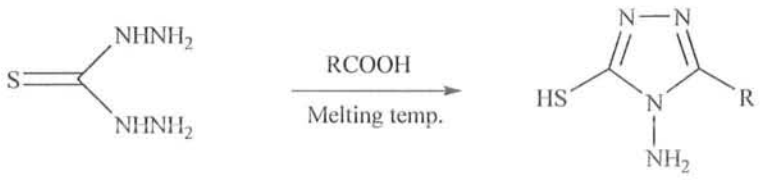


(66) **(67)**

R = phenyl R^1 = 2-methylallyl

c) From thiocarbohydrazides and carbohydrazides

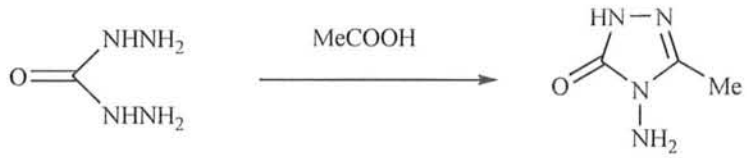
The condensation of thiocarbohydrazides (**68**) with aliphatic and aromatic carboxylic acids is the easiest method for the preparation of 3-alkyl/aryl-4-amino-5-mercapto-1,2,4-triazoles[70]. The reaction is improved by using carboxylic acids at their melting points, resulting in the preparation of 3-alkyl/aryl-4-amino-5-mercapto-1,2,4-triazoles (**69**)[71].



(68) **(69)**

R = alkyl, aryl

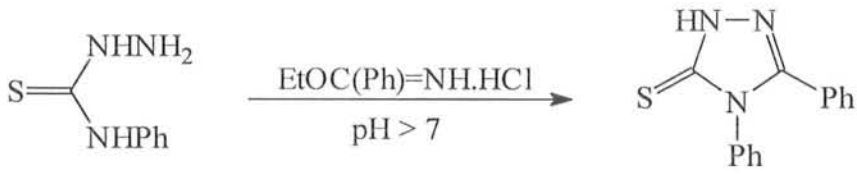
The carbohydrazide (**70**), on treatment with acid, forms 4-amino-3-methyl-1,2,4-triazolin-5-one (**71**).



(70) **(71)**

d) From phenylthiosemicarbazide with ethylphenylimidate hydrochloride

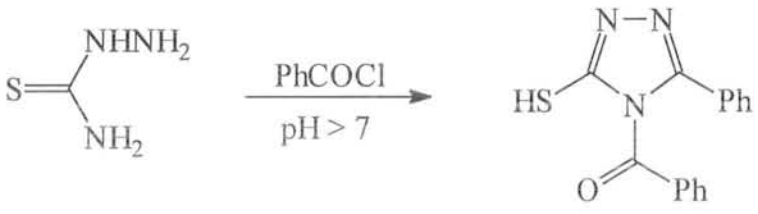
The reaction of 4-phenylthiosemicarbazide (**72**) with ethylphenylimidate hydrochloride illustrated the formation of 3,4-diphenyl-1,2,4-triazoline-5-thione (**73**)[72].



(72) **(73)**

e) From thiosemicarbazides with benzoyl chloride

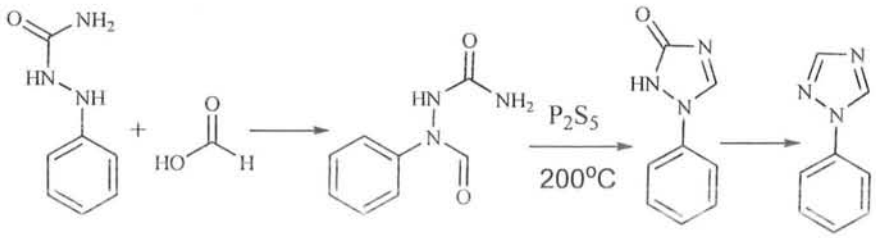
Thiosemicarbazide with benzoyl chloride in boiling pyridine or alkali undergoes benzoylation followed by cyclization resulting in the formation of 4-benzoyl-3-phenyl-5-mercapto-1,2,4-triazoline (**74**)[73].



(74)

f) From semicarbazides

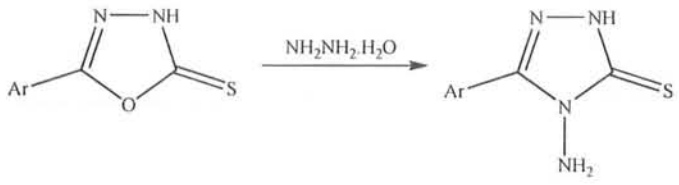
A method of practical importance involves synthesis of 1-phenyl-1*H*-1,2,4-triazole **(77)** from 1-phenylsemicarbazides **(75)**. This is illustrated by the formation of 1-phenyl-1*H*-1,2,4-triazol-3(2H)-one **(76)** from 1-phenylsemicarbazide **(75)** and boiling anhydrous formic acid. By heating **76** to over 200 °C with phosphorous pentasulfide[74], 1-phenyl-1*H*-1,2,4-triazole (**77**) is obtained in 80 % yield.



(75) (76) (77)

g) From 1,2,4-oxadiazol-5-thione

1,3,4-Oxadiazole-5-thiones are converted into 4-amino-1,2,4-triazol-5-thiones with hydrazine hydrate[75]. Thus, Reid and Heindel indicated that the 5-aryl-1,3,4-oxadiazol-2-thione (**78**) recyclized to form 4-amino-1,2,4-triazol-3-thione (**79**) with hydrazine hydrate.

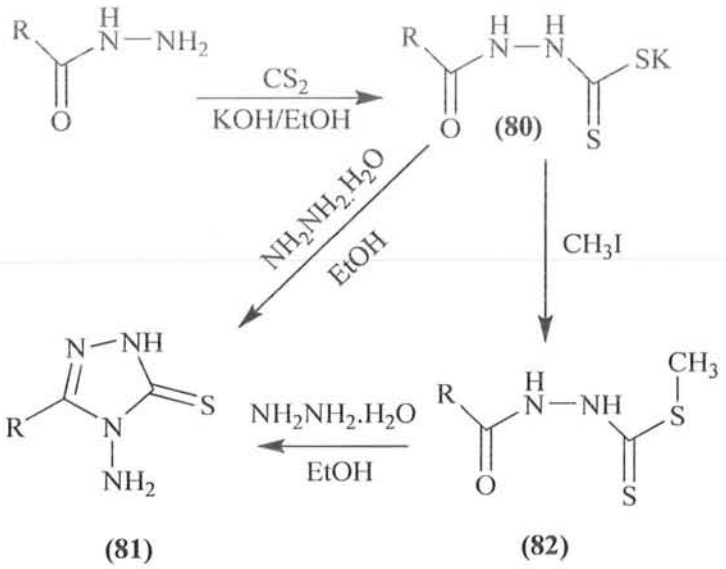


(78) (79)

h) From carboxylic acid hydrazides

The condensation of carboxylic acid hydrazide with carbon disulphide in ethanolic potassium hydroxide yields potassium 3-aroyldithiocarbazate (**80**) that is directly converted to 4-amino-4*H*-1,2,4-triazole-3-thione (**81**) with an

excess of hydrazine[76]. The methylation of **80** with methyl iodide provided the S-alkylated derivatives (**82**) that also cyclizes to (**81**) with hydrazine.

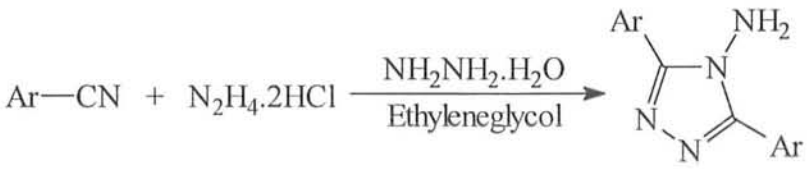


(81) **(82)**

R = C_6H_{11}, C_6H_5, 4F-C_6H_4

i) From aromatic nitriles and hydrazine hydrate

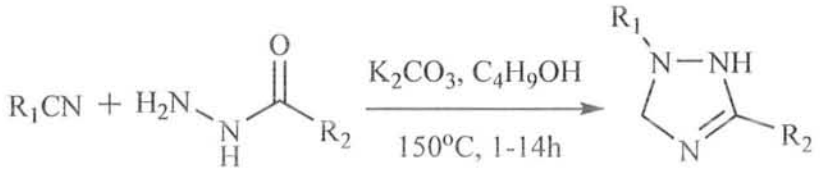
Aromatic nitriles (**83**) on reaction with hydrazine dihydrochloride, in the presence of hydrazine hydrate under microwave irradiation, give 3,5-disubstituted 4-amino-(4*H*)-1,2,4-triazoles[77] (**84**).



(83) **(84)**

j) From condensation of a nitrile and a hydrazide

3,5-Disubstituted 1,2,4-triazoles (**85**) are synthesized from the condensation of a nitrile and a hydrazide in a convenient and efficient one-step base-catalyzed synthesis described by Yeung and coworkers[78] from Bristol-Myers Squibb. Under the reaction conditions, a diverse range of functionality and heterocycles are tolerated.

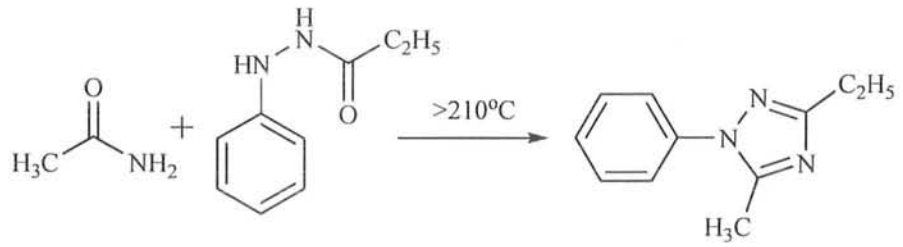


R_1, R_2 = aryl, heteroaryl

(85)

k) From Pellizari reaction

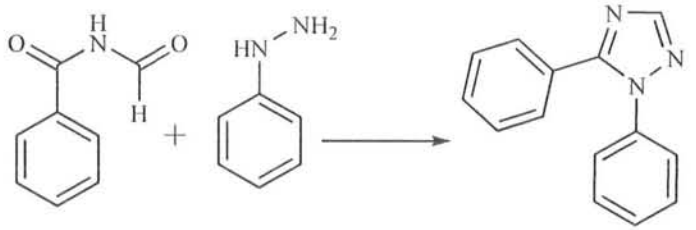
The Pellizari reaction of hydrazides and amides, at high temperatures in the absence of solvent, yields substituted 1,2,4-triazoles (**86**).



(86)

l) From Einhorn-Brunner reaction

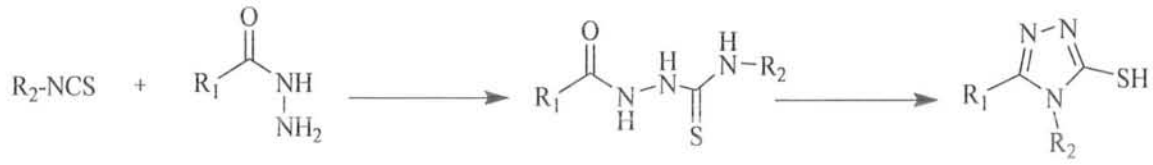
The Einhorn-Brunner[79] reaction of hydrazine with diacylamines, in mildly acidic conditions, yields 1,2,4-triazoles (**87**).



(87)

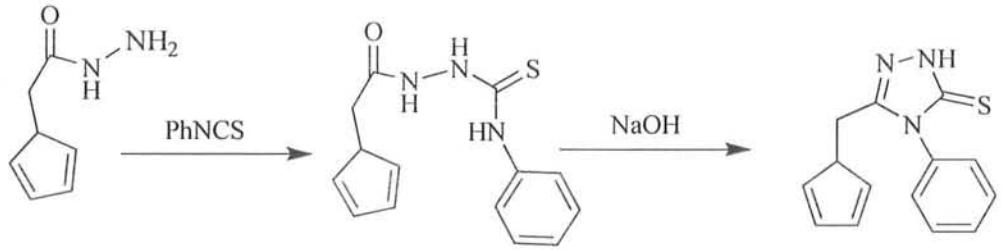
m) From isothiocyanates

Isothiocyanates on condensation with acylhydrazide affords hydrazine carbothioamides which are cyclized to 3-mercapto-1,2,4-triazoles **(88)** under basic conditions[80].



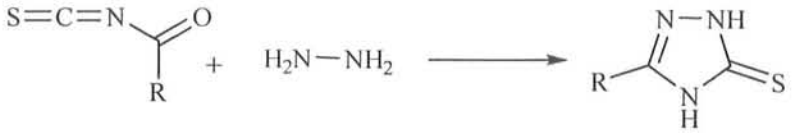
(88)

The phenylacetic acid hydrazide on refluxing with phenyl isothiocyanate in absolute ethanol yields 1-phenylacetyl-4-phenylthiosemicarbazide **(89)**, which is cyclized in the presence of NaOH to produce 5-(cyclopenta-1,3-dienylmethyl)-1-phenyl-1H-1,2,4-triazol-3(2H)-thione **(90)**.



(89) **(90)**

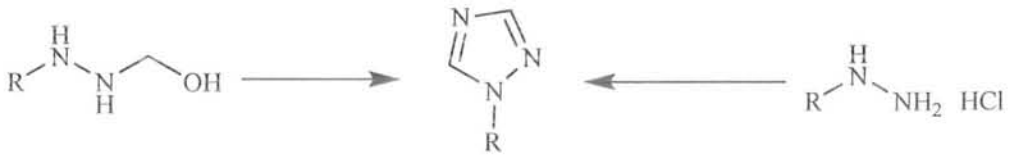
Similarly, the reactions of benzoylisothiocyanates with hydrazine give rise to 3-mercapto derivatives **91**.



(91)

n) From hydrazines with formamide

The fusion of *N*-formyl-*N'*-alkyl or aryl hydrazine with formamide gives 1-substituted triazoles **(92)** at 250-280 °C in poor yields[74]. The separation of by-products is tedious and the reaction is of more importance in the preparation of di- and tri-substituted triazoles. The reaction may be varied by heating formamide with a substituted hydrazine hydrochloride and this general type of reaction is known as Pellizari reaction.



(92)

R= CH_3, C_6H_5, *o*-$CH_3C_6H_4$, *p*-$CH_3C_6H_4$

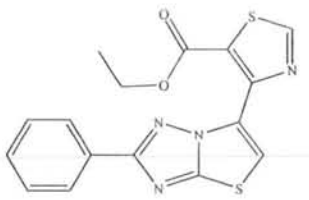
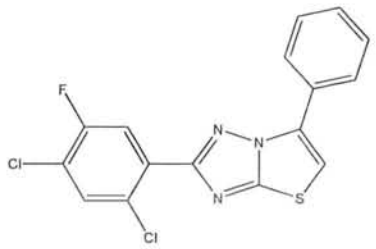
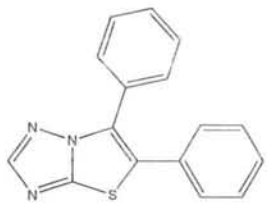
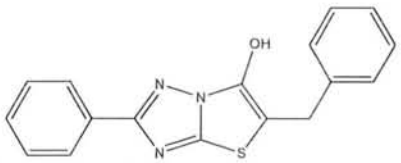
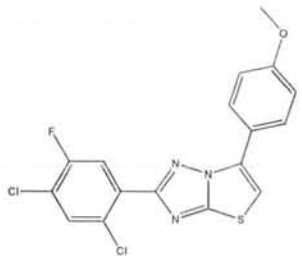
1.4 Thiazolo-1,2,4-triazoles

In recent years, the chemistry of fused-heterocyclic derivatives of thiazoles and triazoles have received considerable attention owing to their synthetic and effective biological importance. 1,3-Thiazole and 1,2,4-triazole are among the most biologically-active classes of compounds, possessing a wide spectrum of activities. Derivatives of 1,3-thiazole and 1,2,4-triazole condensed nucleus, *i.e.*, thiazolo-1,2,4-triazoles, were found to have diverse pharmacological activities such as fungicidal, bactericidal, anticancer, antiinflammatory and COX2-inhibitor.

1.4.1 Applications of thiazolo-1,2,4-triazoles

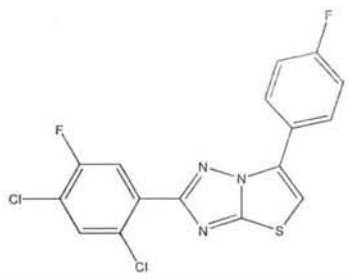
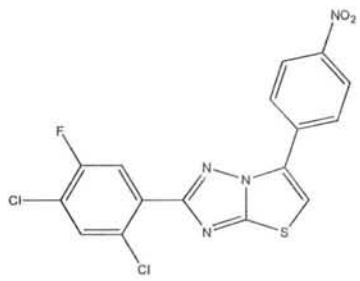
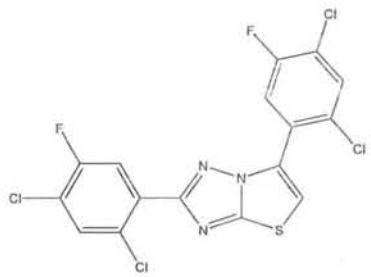
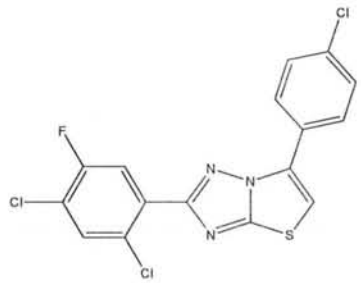
Various substituted thiazolo-1,2,4-triazoles are associated with diverse pharmacological activities. Some of the examples have been shown in the Table 1.3 along with their applications.

Table 1.3: Some important thiazolo-1,2,4-triazoles and their applications

S. No.	Structural formula	Application	Ref.
93		Anticancer activity	81
94		Analgesic activity	82
95		COX2-inhibitor	83
96		Antiinflammatory activity	84
97		Antibacterial activity	82

(Table 1.3 continued)

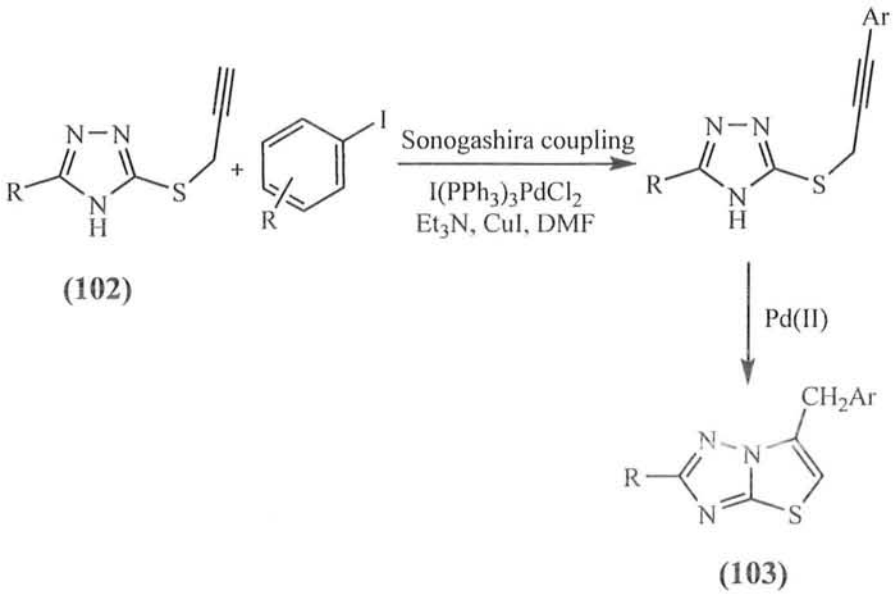
(Table 1.3 continued)

98		Antifungal activity	82
99		Analgesic activity	82
100		Antiinflammatory activity	82
101		Antiinfllammatory activity	82

1.4.2 Synthetic approaches towards thiazolo-1,2,4-triazoles

a) From 3-mercaptopropargyl-1,2,4-triazoles

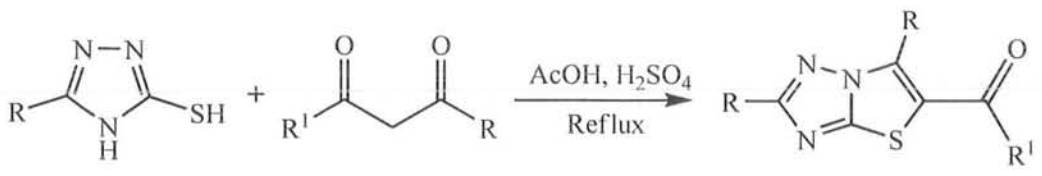
The reaction of 3-mercaptopropargyl-1,2,4-triazoles **(102)** with various iodobenzenes, catalyzed by Pd–Cu, leads to the regioselective formation of 6-benzylthiazolo[3,2-*b*]1,2,4-triazoles **(103)**. Probably a two-step process had occurred: a standard Sonogashira coupling followed by a Pd(II)-catalyzed intermolecular cyclization[85].



(102) **(103)**

b) From 1,2,4-triazole-3-thiols and 1,3-dicarbonyl compounds

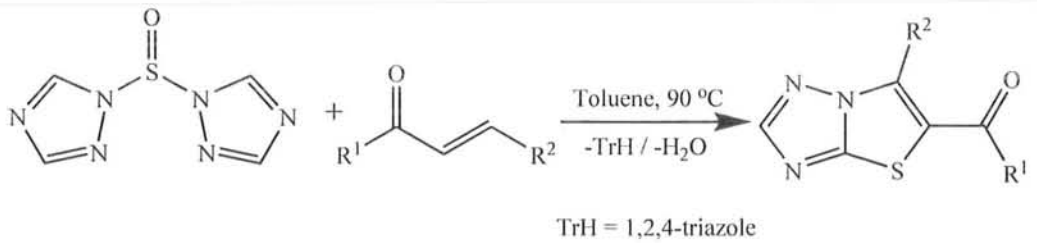
The substituted thiazolo-1,2,4-triazoles **(106)** can be synthesized by a one-pot reaction of 1,2,4-triazole-3-thiols **(104)** with 1,3-dicarbonyl compounds **(105)** in the presence of acid[86].



(104) **(105)** **(106)**

c) From bis(1*H*-1,2,4-triazolyl)sulfoxide and α,β-unsaturated carbonyl compounds

Thiazolo-1,2,4-triazoles **(109)** can be synthesized in a one-pot reaction of bis(1*H*-1,2,4-triazolyl)sulfoxide **(107)** and α,β-unsaturated carbonyl compounds[87] **(108)**. The highest yields are obtained by heating them in toluene at 90 °C.



TrH = 1,2,4-triazole

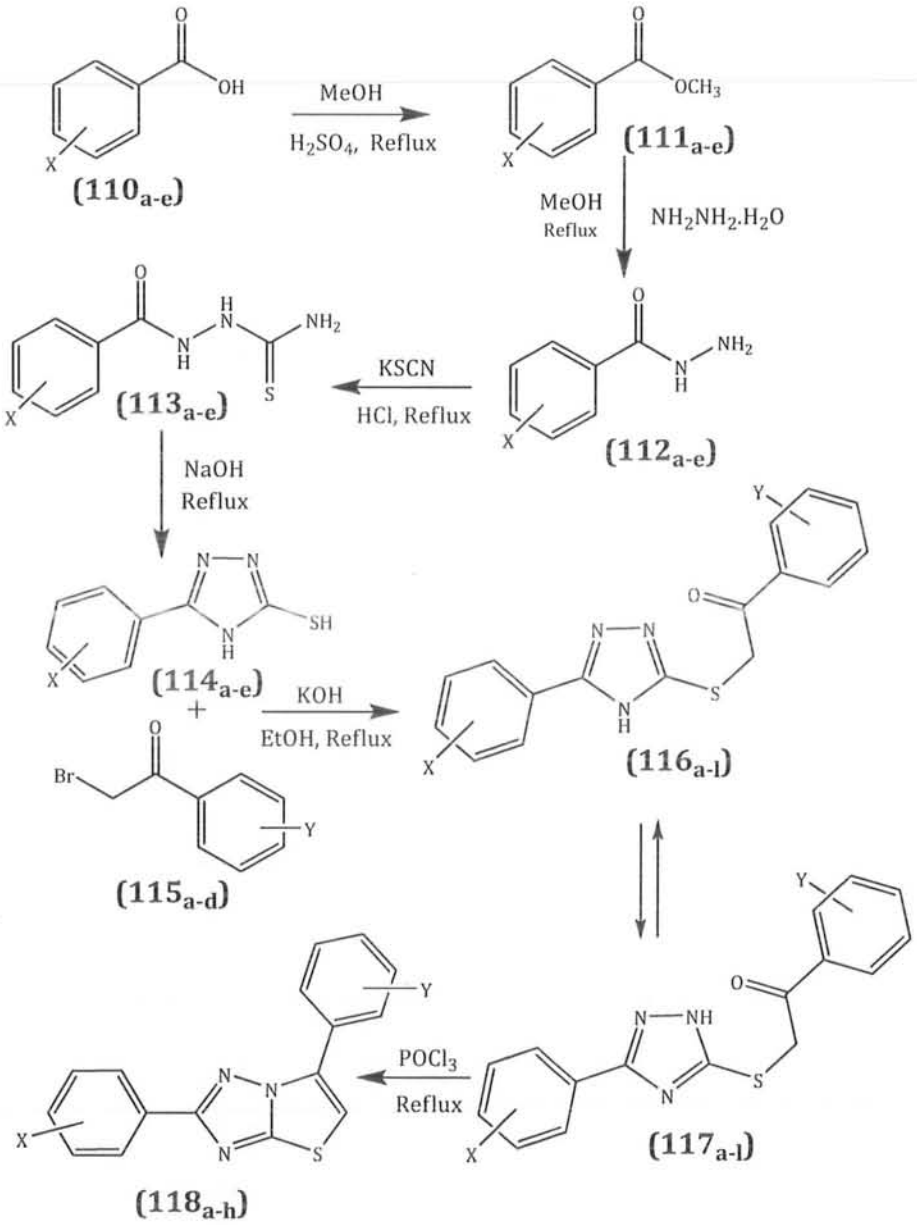
(107) **(108)** **(109)**

In above discussion, the various features are shown for heterocycles like thiazole, 1,2,4-triazole and the derivatives of their fused nucleus. Their applications in different fields and various methods of synthesis have been discussed briefly. In the light of this information a plan was worked out to synthesize the target nucleus.

1.5 Plan of work

It was noticed during literature review that 1,2,4-triazoles are important from medicinal, industrial and agricultural point of view. Similarly, thiazole derivatives also possess diverse pharmacological activities. It is, therefore, thought to combine these two potential biologically-active units to produce fused derivatives of thiazolo-1,2,4-triazoles. In view of all these facts, it was intended to utilize carboxylic acid hydrazides in the synthesis of thiazolo[3,2-*b*][1,2,4]triazoles.

In order to achieve the objectives of the present work, a synthetic plan was devised (Scheme 1).



Scheme 1.1

The plan, illustrated by scheme 1, was based on the following known principles:

1. Carboxylic acids undergo esterification in acidic medium in the presence of an alcohol.
2. Esters of carboxylic acid can converted to their respective hydrazides with hydrazine hydrate.
3. Condensation of carboxylic acid hydrazides with potassium thiocyanate in the presence of hydrochloric acid, yields carbothioamides.
4. Intramolecular dehydrative cyclization of substituted carbothioamides, in basic medium, affords corresponding substituted 3-mercapto-1,2,4-triazoles.
5. Coupling of substituted acetophenones in basic medium gives corresponding substituted ethanones.
6. Substituted ethanones on treating with phosphorus oxychloride produce corresponding substituted thiazolo-1,2,4-triazoles.

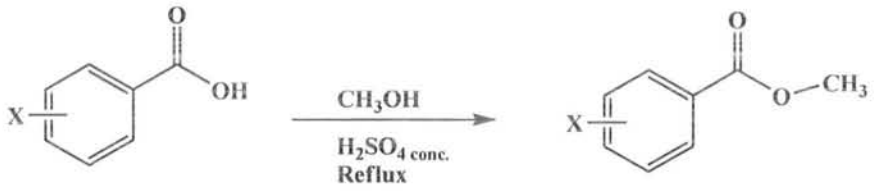
The characterization of the synthesized compounds will be effected through spectroscopic techniques, like IR, ^{1}H NMR and ^{13}C NMR.

RESULTS AND DISCUSSION

Chapter-2

2.1 Synthesis of aromatic esters (122_{a-e})

The methyl esters (111_{a-e}) were synthesized by the reaction of corresponding substituted aromatic acids (110_{a-e}) with methanol in the presence of a catalytic amount of sulfuric acid [88]. The physical constant data of synthesized esters (111_{a-e}) are given in the **Table 2.1.**



110_{a-e} 111_{a-e}

111_a: X = 3-Br **111_b:** X = 3-CH_3 **111_c:** X = 4-Cl

111_d: X = 3-NO_2 **111_e:** X = 3,4,5-tri-OCH_3

Scheme 2.1: Synthesis of aromatic esters

Table 2.1: Physical constant data of aromatic esters (111_{a-e})

Comp.	R_f* value	Yield (%)
111_a	0.83	91
111_b	0.82	83
111_c	0.78	89
111_d	0.79	86
111_e	0.83	89

*_n_-hexane : ethyl acetate (8 : 2) on silica gel 60 F_{254}

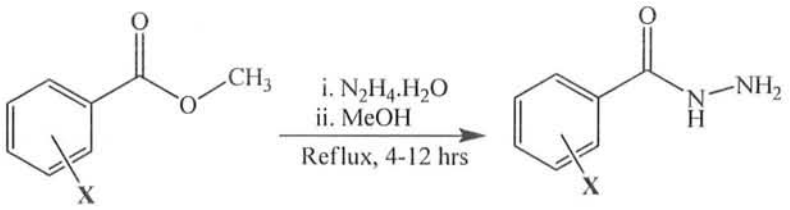
The synthesis of esters (**111_{a-e}**) was indicated in the IR spectra by the disappearance of broad peak for hydroxyl group of the acid in the range of 2400-3200 cm^{-1}. IR spectral data of these esters (**111_{a-e}**) are given in the **Table 2.2**.

Table 2.2: IR spectral data of aromatic esters (111_{a-e})

Comp.	υ (cm^{-1})				
	C_{sp2}–H	C_{sp3}–H	C=O	C–O	C=C
111_a	3064	2952, 2842	1733	1286	1611, 1458
111_b	3061	2954, 2839	1735	1267	1584, 1465
111_c	3045	2972, 2842	1715	1249	1594, 1479
111_d	3039	2967, 2846	1732	1276	1564, 1468
111_e	3063	2954, 2845	1728	1264	1585, 1487

2.2 Synthesis of aromatic acid hydrazides (112_{a-e})

The acid hydrazides (**112_{a-e}**) were synthesized by refluxing esters (**111_{a-e}**) with hydrazine hydrate (80%) in methanol[89]. The synthesized hydrazides (**112_{a-e}**) were recrystallized from ethanol. The physical constant data of hydrazides (**112_{a-e}**) are given in **Table 2.3**.



111_{a-e} **112_{a-e}**

112_a: X = 3-Br **112_b:** X = 3-CH_3 **112_c:** X = 4-Cl

112_d: X = 3-NO_2 **112_e:** X = 3,4,5-tri-OCH_3

Scheme 2.2: Synthesis of aromatic hydrazides

Table 2.3: Physical constant data of aromatic acid hydrazides (112_{a-e})

Comp.	Melting point °C	R_f* value	Yield (%)
112_a	115-117	0.14	90
112_b	127-126	0.23	84
112_c	110-111	0.10	85
112_d	151-152	0.15	71
112_e	124-125	0.22	85

****n*-hexane : ethyl acetate (8 : 2) on silica gel 60 F_{254}**

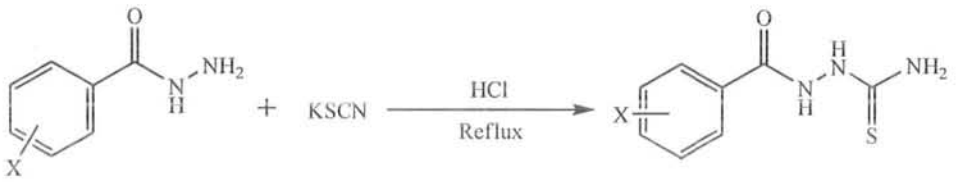
The IR spectra of hydrazides **(112_{a-e})** exhibited a characteristic absorption band for primary NH_2, along with a shoulder, in the region 3303-3347 cm^{-1} while absorption band for the secondary NH was observed in the range 3193-3254 cm^{-1}. A strong absorption in the region 1626-1659 cm^{-1} was assigned to the carbonyl group of amide linkage. The IR spectral data of hydrazides **(112_{a-e})** are given in **Table 2.4**.

Table 2.4: IR spectral data of substituted aromatic acid hydrazides (112_{a-e})

Comp.	υ (cm^{-1})			
	NH_2	NH	C=O	C=C
112_a	3303, 3243	3195	1659	1558, 1505
112_b	3314, 3223	3193	1626	1545, 1484
112_c	3319, 3198	3196	1634	1569, 1491
112_d	3347, 3241	3254	1651	1546, 1485
112_e	3324, 3219	3194	1654	1561, 1486

2.3 Synthesis of thiosemicarbazides (113_{a-e})

The thiosemicarbazides **(113_{a-e})** were synthesized by the condensation of corresponding carboxylic acid hydrazides **(112_{a-e})** and potassium thiocyanate in hydrochloric acid[90]. The synthesized thiosemicarbazides **(113_{a-e})** were recrystallized using ethanol. Physical constant data of thiosemicarbazides **(113_{a-e})** are given in **Table 2.5**.



(112_{a-e}) (113_{a-e})

113_a: X = 3-Br **113_b:** X = 3-CH_3 **113_c:** X = 4-Cl

113_d: X = 3-NO_2 **113_e:** X = 3,4,5-tri-OCH_3

Scheme 2.3: Synthesis of thiosemicarbazides

Table 2.5: Physical constant data of thiosemicarbazides (113_{a-e})

Comp.	Melting point °C	R*f** value	Yield (%)
113_a	148-149	0.15	57
113_b	150-151	0.17	53
113_c	155-156	0.19	73
113_d	175-176	0.13	71
113_e	165-166	0.14	75

******n*-hexane : ethyl acetate (8 : 2) on silica gel 60 F_{254}

The formation of thiosemicarbazides **(113_{a-e})** was indicated in the IR spectra where C=O absorption appeared in the range of 1665-1683 cm^{-1} and C=S absorption in 1235-1268 cm^{-1}. The characteristic absorption bands for two secondary and one primary N–H groups were observed in the region of 3123-3396 cm^{-1}. The IR spectral data of the synthesized thiosemicarbazides **(113_{a-e})** are presented in **Table 2.6**.

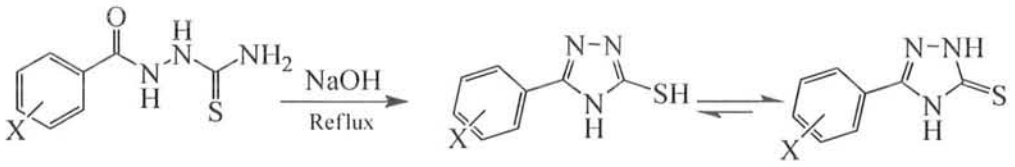
Table 2.6: IR spectral data of thiosemicarbazides (113_{a-e})

Comp.	υ (cm^{-1})			
	N-H*	C=O	C=S	C=C
113_a	3341-3123	1677	1245	1515, 1498
113_b	3350-3154	1665	1237	1555, 1496
113_c	3356-3281	1683	1235	1593, 1469
113_d	3385-3143	1674	1236	1522, 1497
113_e	3396-3163	1673	1268	1596, 1512

***three to four bands were observed in this region**

2.4 Synthesis of 5-substituted 1,2,4-triazole-3-thiols/thiones (114_{a-e})

The respective 5-substituted 1,2,4-triazole-3-thiols/thiones (**114_{a-e}**) were synthesized by refluxing thiosemicarbazides (**113_{a-e}**) in aqueous sodium hydroxide (5%)[91]. The products were purified by recrystallization from ethanol. The physical constant data of synthesized triazoles (**114_{a-e}**) are given in **Table 2.7**.



(113_{a-e}) (114_{a-e})

114_a: X = 3-Br **114_b:** X = 3-CH_3

114_c: X = 4-Cl **114_d:** X = 3-NO_2

114_e: X = 3,4,5-tri-OCH_3

Scheme 2.4: Synthesis of 1,2,4-triazoles

Table 2.7: Physical constant data of 1,2,4-triazoles (114_{a-e})

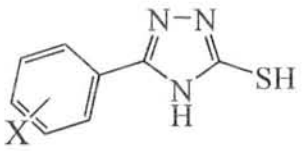
Comp.	Melting point °C	R_f* value	Yield (%)
114_a	206-208	0.12	79
114_b	196-197	0.13	67
114_c	185-187	0.14	73
114_d	215-217	0.11	76
114_e	175-177	0.15	71

****n*-hexane : ethyl acetate (8 : 2) on silica gel 60 F_{254}**

The formation of 1,2,4-triazoles (**114_{a-e}**) from thiosemicarbazides (**113_{a-e}**) was indicated in the IR spectra by the appearance of C=N absorption in the range 1410-1464 cm^{-1}. The appearance of (S-H) absorption in the range of 2542-2551 cm^{-1} indicated the thiol form of triazoles in solid state but in solution

form it exists predominately in thione form as explained in introduction part. The disappearance of peak due to C=O group in thiosemicarbazides also indicated the conversion of thiosemicarbazides into 1,2,4-triazoles. IR spectral data of the 1,2,4-triazoles (**114$_{a-e}$**) (as thiols) are shown in **Table 2.8**.

Table 2.8: IR spectral data of triazoles (114$_{a-e}$)

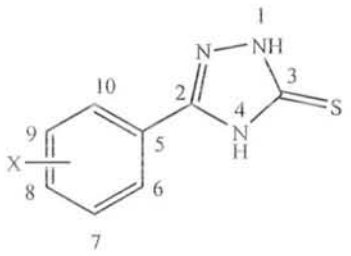


(114$_{a-e}$)

Comp.	υ (cm^{-1})			
	N-H	S-H	C=N	C=C
114$_a$	3345	2544	1410	1542, 1475
114$_b$	3341	2542	1424	1533, 1485
114$_c$	3324	2549	1415	1532, 1481
114$_d$	3331	2551	1445	1556, 1496
114$_e$	3348	2548	1464	1542, 1492

The formation of triazoles (**114$_{a-e}$**) was confirmed by ^{1}H NMR spectra. In ^{1}H NMR, signal for N-H proton (H-1) of triazoles appeared in the range of 11.65-13.71 ppm. The 2nd N-H proton (H-4) of triazole ring did not appear in ordinary NMR technique. ^{1}H NMR data of the triazoles **114$_{a-c}$** are given in **Table 2.9** and that of **114$_{d,e}$** in **Table 2.11**.

The formation of triazoles (**114$_{a-e}$**) was also confirmed by ^{13}C NMR spectroscopy on the basis of the absence of peaks due to C=O and C=S groups in ^{13}C NMR spectra of triazoles and the appearance of peak due to C=N group in the range of 135.20-148.30 ppm. The ^{13}C NMR data of the triazoles **114$_{a-c}$** is given in the **Table 2.10** and that of **114$_{d,e}$** in **Table 2.12**.



(114_{a-e})

Table 2.9: ^{1}H NMR data of the triazoles (114_{a-c})

H #	114_a (ppm)	114_b (ppm)	114_c (ppm)
1 (N-H)	13.33 (s)	13.10 (s)	13.42 (s)
6	8.03-8.04 (m)	7.91-7.93 (m)	7.88 (d, J = 8.1Hz)
7	-	-	8.08-8.11 (m)
8	7.92-7.95 (m)	7.40-7.42 (m)	-
9	7.45-7.50 (m)	7.26-7.28 (m)	8.08-8.11 (m)
10	7.81-7.85 m)	7.35-7.36 (m)	7.88 (d, J = 8.1Hz)
CH_3	-	2.63 (s)	-

Table 2.10: ^{13}C NMR data of the triazoles (114_{a-c})

C #	114_a (ppm)	114_b (ppm)	114_c (ppm)
2	136.06	135.20	139.56
3	166.43	167.00	166.20
5	132.20	133.34	132.65
6	131.37	132.14	133.80
7	133.53	131.02	131.48
8	129.33	128.96	129.19
9	122.18	123.77	124.54
10	128.74	128.96	129.35
CH_3	-	134.61	-

Table 2.11: ^{1}H NMR data of the triazoles ($114_{d,e}$)

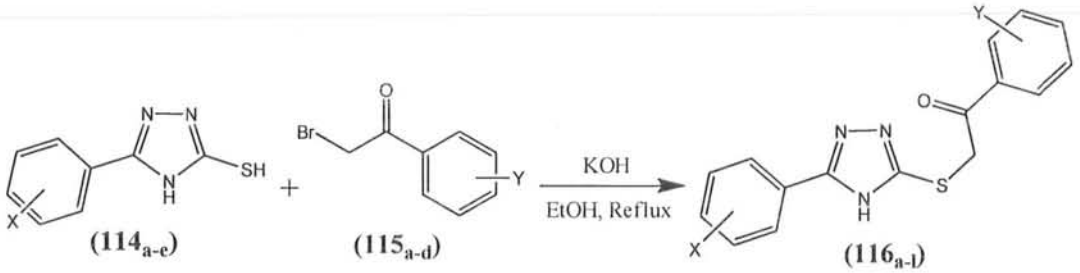
H #	114_d (ppm)	114_e (ppm)
1 (N-H)	13.71 (s)	11.65 (s)
6	8.59-8.60 (m)	7.39 (s)
8	8.43-8.47 (m)	-
9	7.77-7.82 (m)	-
10	8.33 (m)	7.39 (s)
-OCH_3	-	3.95 (s)
-OCH_3	-	3.95 (s)
-OCH_3	-	3.95 (s)

Table 2.12: ^{13}C NMR data of the triazoles ($114_{d,e}$)

Carbon	114_d (ppm)	114_e (ppm)
2	148.30	142.84
3	165.97	172.00
5	132.92	133.34
6	130.98	127.28
7	135.82	152.95
8	127.26	132.01
9	124.13	152.95
10	127.18	127.28
p-OCH_3	-	61.02
m-OCH_3	-	56.25
m-OCH_3	-	56.25

2.5 Synthesis of aryl-2-(4*H*-1,2,4-triazol-3-ylthio)ethanones (116_{a-l})

The substituted aryl-2-(4*H*-1,2,4-triazol-3-ylthio)ethanones (**116_{a-l}**) were synthesized by refluxing corresponding 1,2,4-triazoles (**114_{a-e}**) with phenacylbromides (acetophenones) (**115_{a-d}**) in alcoholic potassium hydroxide solution[82]. The products were purified by recrystallization from ethanol. The physical constant data of synthesized ethanones (**116_{a-l}**) are given in **Table 2.13**.



116_a: X = 3-Br, Y = 4-CH_3 **116_b:** X = 3-Br, Y = 4-F

116_c: X = 3-Br, Y = 4-Cl **116_d:** X = 3-Br, Y = 4-NO_2

116_e: X = 3- CH_3, Y = 4-F **116_f:** X = 3- CH_3, Y = 4-NO_2

116_g: X = 4-Cl, Y = 4-CH_3 **116_h:** X = 4-Cl, Y = 4-NO_2

116_i: X = 3-NO_2, Y = 4-CH_3 **116_j:** X = 3,4,5-tri-OCH_3, Y = 4-CH_3

116_k: X = 3,4,5-tri-OCH_3, Y = 4-F **116_l:** X = 3,4,5-tri-OCH_3, Y = 4-Cl

Scheme 2.5: Synthesis of aryl-2-(4*H*-1,2,4-triazol-3-ylthio)ethanones

Table 2.13: Physical constant data of ethanones (116_{a-l})

Comp.	Melting point °C	R_f* value	Yield(%)
116_a	104-105	0.66	69
116_b	90-92	0.63	57
116_c	101-103	0.64	63
116_d	103-104	0.51	66
116_e	112-114	0.57	47
116_f	105-106	0.59	53

(Table 2.13 continued)

(Table 2.13 continued)

116$_g$	118-119	0.62	72
116$_h$	124-126	0.64	57
116$_i$	96-98	0.65	63
116$_j$	113-115	0.56	53
116$_k$	135-137	0.63	75
116$_l$	121-123	0.62	72

****n*-hexane : ethyl acetate (8 : 2) on silica gel 60 F_{254}**

The formation of ethanones **(116$_{a-l}$)** was indicated in the IR spectra where C=O absorption appeared in the range of 1684-1701 cm^{-1} and (C_{sp3}-H) absorption in 2824-2949 cm^{-1}. The characteristic absorption band for N–H was observed in the region of 3363-3394 cm^{-1}. The IR spectral data of the synthesized ethanones **(116$_{a-l}$)** are presented in **Table 2.14**.

Table 2.14: IR spectral data of ethanones (116$_{a-l}$)

Comp.	υ (cm^{-1})				
	NH	C_{sp2}-H	C_{sp3}-H	C=O	C=C
116$_a$	3394	3065	2926,2832	1701	1588,1505
116$_b$	3363	3071	2932,2824	1694	1586,1511
116$_c$	3376	3066	2938,2830	1696	1572,1498
116$_d$	3390	3072	2940,2834	1698	1586,1506
116$_e$	3386	3076	2946,2834	1695	1569,1499
116$_f$	3389	3068	2939,2846	1684	1591,1501
116$_g$	3391	3064	2941,2836	1697	1579,1497
116$_h$	3373	3081	2942,2834	1693	1576,1497

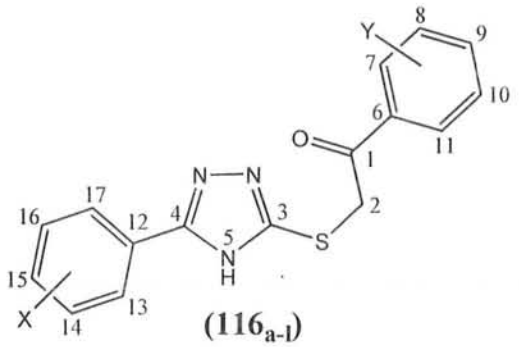
(Table 2.14 continued)

(Table 2.14 continued)

116$_i$	3378	3063	2935,2826	1698	1562,1502
116$_j$	3394	3038	2949,2842	1686	1581,1501
116$_k$	3389	3065	2938,2838	1687	1582,1502
116$_l$	3391	3064	2941,2836	1697	1579,1497

The formation of ethanones **(116$_{a-l}$)** was confirmed by ^{1}H NMR spectra. In ^{1}H NMR, the signal for CH_2 protons of ethanones **(116$_{a-l}$)** appeared in the range of 5.53-5.84 ppm. The disappearance of the signal due to N-H proton (H-1) confirmed the formation of ethanones from triazoles and acetophenones. ^{1}H NMR data of the ethanones **116$_{a-d}$** are given in **Table 2.15**, **116$_{e-h}$** in **Table 2.17** and **116$_{i-l}$** in **Table 2.19**.

The formation of the ethanones **(116$_{a-l}$)** was also confirmed by ^{13}C NMR spectra. The appearance of signals due to C=O and CH_2 groups, in the range of 190.24-192.40 ppm and 66.11-67.98 ppm, respectively, proved the formation of C-S bond. The ^{13}C NMR data of the ethanones **116$_{a-d}$** are given in **Table 2.16**, **116$_{e-h}$** in **Table 2.18** and **116$_{i-l}$** in **Table 2.20.**



(116$_{a-l}$)

Table 2.15: ^{1}H NMR data of ethanones (116_{a-d})

H #	116_a (ppm)	116_b (ppm)	116_c (ppm)	116_d (ppm)
2 (-CH_2-)	5.59 (s)	5.77 (s)	5.56 (s)	5.60 (s)
7	8.01-8.09 (m)	8.08-8.13 (m)	7.92 (d, *J* = 8.4Hz)	8.38 (d, *J* = 8.1Hz)
8	7.39-7.41(m)	7.42 (m)	7.51 (d, *J* = 8.4Hz)	8.24 (d, *J* = 8.1Hz)
10	7.39-7.41 (m)	7.42 (m)	7.51 (d, *J* = 8.4Hz)	8.24 (d, *J* = 8.1Hz)
11	8.01-8.09 (m)	8.08-8.13 (m)	7.92 (d, *J* = 8.4Hz)	8.38 (d, *J* = 8.1Hz)
13	8.19 (s)	8.13 (m)	8.29 (s)	8.27 (s)
15	7.82 (m)	7.93 (m)	7.75 (m)	7.76 (m)
16	7.42 (m)	7.56 (m)	7.37 (m)	7.38 (m)
17	7.89 (m)	8.03 (m)	8.07 (m)	8.06 (m)
-CH_3 (Y)	2.64 (s)	-	-	-

Table 2.16: ^{13}C NMR data of of ethanones (116_{a-d})

C #	116_a (ppm)	116_b (ppm)	116_c (ppm)	116_d (ppm)
1	191.21	191.62	190.65	190.67
2	67.26	67.89	66.53	66.73
3	164.48	164.46	164.72	164.65
4	136.52	136.92	136.43	138.53
6	131.98	132.46	132.42	132.96
7	131.23	131.51	129.35	129.00
8	128.13	116.71	129.24	128.57
9	138.24	136.54	140.59	150.81
10	128.64	116.42	129.24	128.57
11	130.54	131.39	129.35	129.00
12	132.06	132.21	132.96	136.62
13	130.44	131.70	130.09	130.17
14	122.24	122.42	122.59	122.65
15	128.15	128.86	128.57	126.20
16	127.87	128.76	128.68	124.20
17	129.65	128.97	129.37	129.45
-CH_3 (Y)	21.56	-	-	-

Table 2.17: ^{1}H NMR data of ethanones (116_{e-h})

H #	116_e (ppm)	116_f (ppm)	116_g (ppm)	116_h (ppm)
2 (-CH_2-)	5.63 (s)	5.53 (s)	5.57 (s)	5.84 (s)
7	7.64 (m)	7.94 (d, *J* = 8.1Hz)	8.08-8.11 (m)	8.25 (d, *J* = 8.4Hz)
8	7.43 (m)	7.51 (d, *J* = 8.4Hz)	7.45-7.47 (m)	8.39 (d, *J* = 8.4Hz)
10	7.43 (m)	7.51 (d, *J* = 8.4Hz)	7.45-7.47 (m)	8.39 (d, *J* = 8.4Hz)
11	7.64 (m)	7.94 (d, *J* = 8.1Hz)	8.08-8.11 (m)	8.25 (d, *J* = 8.4Hz)
13	7.31 (m)	7.28 (m)	7.88 (d, *J* = 8.1Hz)	8.04 (d, *J* = 8.1Hz)
14	-	-	7.31 (d, *J* = 8.1Hz)	7.66 (d, *J* = 8.1Hz)
15	7.49 (m)	7.44 (m)	-	-
16	7.61 (m)	7.30 (m)	7.31 (d, *J* = 8.1Hz)	7.66 (d, *J* = 8.1Hz)
17	8.06 (m)	8.08 (m)	7.88 (d, *J* = 8.1Hz)	8.04 (d, *J* = 8.1Hz)
-CH_3 (X)	2.63 (s)	2.65 (s)	-	-
-CH_3 (Y)	-	-	2.45 (s)	-

Table 2.18: ^{13}C NMR data of ethanones (116_{e-h})

C #	116_e (ppm)	116_f (ppm)	116_g (ppm)	116_h (ppm)
1	190.24	191.26	191.44	191.68
2	66.12	66.11	66.54	66.45
3	166.97	166.84	165.25	165.36
4	138.46	140.41	139.83	139.65
6	131.54	132.49	130.28	130.28
7	129.34	129.28	127.92	129.70
8	128.46	129.26	128.82	128.49
9	139.67	140.76	145.01	149.46
10	129.19	129.26	128.82	128.49
11	129.11	129.28	127.92	129.70
12	131.68	132.63	131.06	130.06
13	130.76	130.98	129.61	129.31
14	125.94	125.83	131.38	131.47
15	128.90	128.62	131.69	128.15
16	126.81	128.95	131.38	131.47
17	129.26	129.10	129.61	130.31
$-CH_3$ (X)	21.35	21.72	-	-
$-CH_3$ (Y)	-	-	21.80	-

Table 2.19: ^{1}H NMR data of ethanones (116_{i-l})

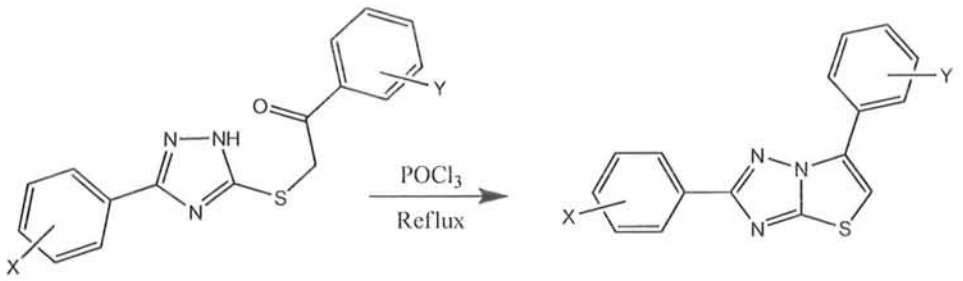
H #	116_i (ppm)	116_j (ppm)	116_k (ppm)	116_l (ppm)
2 (-CH_2-)	5.65 (s)	5.59 (s)	5.55 (s)	5.73 (s)
7	7.88 (d, J = 8.1Hz)	7.76 (d, J = 8.1Hz)	8.01-8.05 (m)	8.03 (d, J = 8.4Hz)
8	7.33 (d, J = 8.1Hz)	7.27 (d, J = 8.1Hz)	7.18-7.29 (m)	7.67 (d, J = 8.4Hz)
10	7.33 (d, J = 8.1Hz)	7.27 (d, J = 8.1Hz)	7.18-7.29 (m)	7.67 (d, J = 8.4Hz)
11	7.88 (d, J = 8.1Hz)	7.76 (d, J = 8.1Hz)	8.01-8.05 (m)	8.03 (d, J = 8.4Hz)
13	8.99 (s)	7.45 (s)	7.41 (s)	7.31 (s)
15	8.48 (m)	-	-	-
16	7.61 (m)	-	-	-
17	8.48 (m)	7.45 (s)	7.41 (s)	7.31 (s)
-CH_3 (Y)	2.46 (s)	2.38 (s)	-	-
p-OCH_3	-	3.91 (s)	3.93 (s)	3.76 (s)
m-OCH_3	-	3.91 (s)	3.93 (s)	3.85 (s)
m-OCH_3	-	3.91 (s)	3.93 (s)	3.85 (s)

Table 2.20: ^{13}C NMR data of ethanones (116_{i-l})

C #	116_i (ppm)	116_j (ppm)	116_k (ppm)	116_l (ppm)
1	190.85	191.28	190.64	192.40
2	66.98	67.24	66.33	67.65
3	164.06	165.94	165.69	165.28
4	145.23	136.21	136.43	133.01
6	131.47	130.87	130.28	131.54
7	129.68	129.45	130.63	130.26
8	127.92	148.16	116.35	129.58
9	148.31	167.46	167.89	139.40
10	127.92	148.57	116.05	129.58
11	129.68	130.67	130.51	130.26
12	135.65	109.46	124.20	124.58
13	129.75	126.12	107.17	107.04
14	132.75	153.46	153.01	153.15
15	127.77	141.26	142.61	142.45
16	127.67	153.46	153.01	153.15
17	130.21	126.12	107.17	107.04
-CH_3 (Y)	21.83	21.29	-	`-
p-OCH_3	-	-	60.98	60.66
m-OCH_3	-	-	56.26	56.47
m-OCH_3	-	-	56.26	56.47

2.6 Synthesis of thiazolo[3,2-*b*][1,2,4]triazoles (118_{a-h})

The thiazolo[3,2-*b*][1,2,4]triazoles **(118_{a-h})** were synthesized by refluxing the ethanones **(116_{a-l})** in phosphorus oxychloride[92]. The products were purified by recrystallization from ethanol, column chromatography or preparative thin layer chromatography. The physical constant data of synthesized thiazolo[3,2-*b*][1,2,4]triazoles **(118_{a-h})** are given in **Table 2.21**.



(118_{a-h})

118_a: X = 3-Br, Y = 4-CH_3 **118_b:** X = 3-Br, Y = 4-F

118_c: X = 3-Br, Y = 4-Cl **118_d:** X = 3- CH_3, Y = 4-F

118_e: X = 3- CH_3, Y = 4-Cl **118_f:** X = 3-NO_2, Y = 4-CH_3

118_g: X = 3,4,5-tri-OCH_3, Y = 4-F **118_h:** X = 3,4,5-tri-OCH_3, Y = 4-Cl

Scheme 2.6: Synthesis of thiazolo[3,2-*b*][1,2,4]triazoles

Table 2.21: Physical data of thiazolo[3,2-*b*][1,2,4]triazoles (118_{a-h})

Comp.	Melting point °C	R*f** value	Yield (%)
118_a	224-226	0.69	59
118_b	237-239	0.67	57
118_c	214-216	0.68	63
118_d	248-250	0.56	66
118_e	232-234	0.60	51
118_f	218-220	0.64	61
118_g	251-252	0.54	55
118_h	224-226	0.68	52

***n-hexane : ethyl acetate (8 : 2) on silica gel 60 F_{254}**

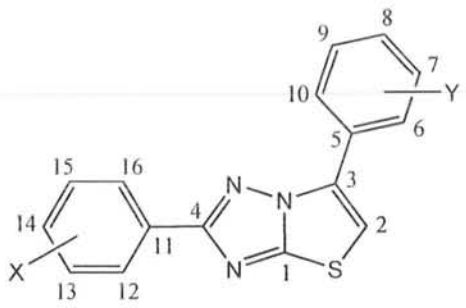
The formation of thiazolo[3,2-*b*][1,2,4]triazoles **(118$_{a-h}$)** was indicated by the IR spectra where C=O peak and C_{sp3}-H peak did not appear. The characteristic absorption band for N–H in thiazolo[3,2-*b*][1,2,4]triazoles **(118$_{a-h}$)** was also not observed in the spectrum further confirming their formation. The only signal observed in the main functional group region was that of C_{sp2}-H in range of 3074-3094 cm^{-1}. The IR spectral data of the synthesized thiazolo[3,2-*b*][1,2,4]triazoles **(118$_{a-h}$)** are presented in **Table 2.22**.

Table 2.22: IR spectral data of thiazolo[3,2-*b*][1,2,4]triazoles (118$_{a-h}$)

Comp.	υ (cm^{-1})		
	C_{Sp2}-H	C=N	C=C
118$_a$	3094	1425	1578, 1501
118$_b$	3078	1454	1594, 1502
118$_c$	3074	1435	1567, 1507
118$_d$	3085	1467	1579, 1498
118$_e$	3078	1399	1589, 1489
118$_f$	3089	1432	1588, 1506
118$_g$	3074	1416	1576, 1503
118$_h$	3088	1419	1581, 1499

The formation of the thiazolo[3,2-*b*][1,2,4]triazoles **(118$_{a-h}$)** was confirmed by ^{1}H NMR spectra. In ^{1}H NMR, signal for CH_2 protons of thiazolo[3,2-*b*][1,2,4]triazoles **(118$_{a-h}$)** did not appear in the range of 5.53-5.84 ppm. The appearance of signal for C-H proton attached to thiazole ring in aromatic region (in the range of 8.13-8.26 ppm) confirmed the ring closer and, thus, formation of thiazolo[3,2-*b*][1,2,4]triazoles **(118$_{a-h}$)**. ^{1}H NMR data of thiazolo[3,2-*b*][1,2,4]triazoles **118$_{a-d}$** are given in **Table 2.23** and that of **118$_{e-h}$** in **Table 2.25**.

The formation of thiazolo[3,2-*b*][1,2,4]triazoles **(118_{a-h})** was also confirmed by the disappearance of signals due to C=O and CH_2 groups and appearance of the signal for C-2 in the range of 119.35-121.45 ppm. The ^{13}C NMR spectral data of thiazolo[3,2-*b*][1,2,4]triazoles **118_{a-d}** are given in **Table 2.24** and that of **118_{e-h}** in **Table 2.26**.



(118_{a-h})

Table 2.23: ^1H NMR data of thiazolo[3,2-*b*][1,2,4]triazoles (118_{a-d})

H #	118_a (ppm)	118_b (ppm)	118_c (ppm)	118_d (ppm)
2	8.19 (s)	8.23 (s)	8.13 (s)	8.26 (s)
6	7.56-7.63 (m)	7.71-7.76 (m)	7.55-7.58 (m)	7.63-7.67 (m)
7	7.26-7.34 (m)	7.28-7.33 (m)	7.37-7.40 (m)	7.19-7.24 (m)
9	7.26-7.34 (m)	7.28-7.33 (m)	7.37-7.40 (m)	7.19-7.24 (m)
10	7.56-7.63 (m)	7.71-7.76 (m)	7.55-7.58 (m)	7.63-7.67 (m)
12	8.00-8.04 (m)	8.18-8.19 (m)	8.33-8.34 (m)	8.11-8.12 (m)
14	7.93-7.96 (m)	7.98-8.0 (m)	7.78-7.81 (m)	7.76-7.78 (m)
15	7.56-7.63 (m)	7.58-7.64 (m)	7.41-7.47 (m)	7.43-7.48 (m)
16	8.10-8.12 (m)	8.10-8.13 (m)	8.14-8.17 (m)	8.02-8.04 (m)
-CH_3 (X)	-	-	-	2.65 (s)
-CH_3 (Y)	2.34 (s)	-	-	-

Table 2.24: ^{13}C NMR data of thiazolo[3,2-*b*][1,2,4]triazoles (118_{a-d})

C #	118_a (ppm)	118_b (ppm)	118_c (ppm)	118_d (ppm)
1	161.57	161.25	161.39	161.46
2	120.96	119.35	121.45	119.54
3	129.34	129.01	129.98	129.46
4	139.52	137.71	136.43	137.24
5	132.46	131.84	133.27	132.51
6	129.33	129.29	129.45	129.41
7	126.34	116.42	124.13	116.37
8	136.97	133.11	134.54	128.57
9	126.34	116.42	124.13	116.37
10	129.33	129.29	129.45	129.41
11	133.16	132.53	129.35	132.44
12	131.64	131.91	130.14	131.92
13	122.76	122.60	122.67	122.24
14	129.42	129.01	122.59	129.65
15	128.84	128.90	128.51	128.63
16	131.28	130.35	131.16	130.97
-CH_3(X)	-	-	-	21.72
-CH_3(Y)	21.22	-	-	-

Table 2.25: ^{1}H NMR data of thiazolo[3,2-*b*][1,2,4]triazoles (118_{e-h})

H #	118_e (ppm)	118_f (ppm)	118_g (ppm)	118_h (ppm)
2	8.19 (s)	8.17 (s)	8.14 (s)	8.13 (s)
6	7.52-7.56 (m)	7.49-7.52 (m)	7.50 (d, *J* = 8.4Hz)	7.45-7.47 (m)
7	7.21-7.26 (m)	7.22-7.24 (m)	7.18 (d, *J* = 8.4Hz)	7.19-7.21(m)
9	7.21-7.26 (m)	7.22-7.24 (m)	7.18 (d, *J* = 8.4Hz)	7.19-7.21(m)
10	7.52-7.56 (m)	7.49-7.52 (m)	7.50 (d, *J* = 8.4Hz)	7.45-7.47 (m)
12	8.16-8.10 (m)	8.93-8.97 (m)	7.29 (s)	7.28 (s)
14	7.67-7.71 (m)	8.46-8.51 (m)	-	-
15	7.38-7.40 (m)	7.62-7.69 (m)	-	-
16	7.79-7.81 (m)	8.46-8.51 (m)	7.29 (s)	7.28 (s)
-CH_3 (X)	2.63 (s)	-	-	-
-CH_3 (Y)	-	2.31 (s)	-	-
p-OCH_3	-	-	3.83 (s)	3.82 (s)
m-OCH_3	-	-	3.83 (s)	3.82 (s)
m-OCH_3	-	-	3.83 (s)	3.82 (s)

Table 2.26: ^{13}C NMR data of thiazolo[3,2-*b*][1,2,4]triazoles (118_{e-h})

C #	118_e (ppm)	118_f (ppm)	118_f (ppm)	118_h (ppm)
1	160.95	161.24	161.61	160.92
2	121.33	119.45	121.42	121.30
3	129.67	130.47	130.31	129.71
4	136.64	134.64	134.71	135.14
5	132.25	132.58	131.92	131.21
6	129.16	130.46	130.24	129.15
7	127.48	128.16	128.21	128.30
8	133.14	133.21	134.32	133.83
9	126.64	127.01	127.71	127.52
10	129.55	129.42	129.68	129.59
11	133.37	134.44	134.11	134.24
12	131.68	130.37	130.74	130.81
13	124.91	122.16	122.31	122.29
14	128.28	129.11	128.34	129.07
15	128.47	127.34	127.68	127.23
16	130.94	130.61	130.57	130.92
-CH_3 (X)	21.71	-	-	-
-CH_3 (Y)	-	21.86	-	-
p-OCH_3	-	-	60.62	61.01
m-OCH_3	-	-	56.31	56.45
m-OCH_3	-	-	56.31	56.45

EXPERIMENTAL

Chapter-3

3.1 Substrates and reagents

Substituted benzoic acids, acetophenones, anhydrous sodium sulfate and sodium hydroxide were supplied by Sigma Aldrich. Hydrazine hydrate (80 %), sulphuric acid, hydrochloric acid, acetone and sodium bicarbonate were purchased from E. Merck. Chloroform and methanol were supplied by Lab Scan. Diethyl ether and dimethyl sulfoxide were products of Riedel de Haën. Magnesium sulphate was obtained from Fluka and lead nitrate was purchased from Fisher Scientific, while ethanol and ethyl acetate were obtained from commercial sources and dry-distilled. Aluminum pre-coated silica gel TLC plates 60 F_{254} were purchased from Merck (Germany).

3.2 Purification of solvents

All the solvents were used after necessary purification and drying according to the standard procedures. The dried solvents were stored over molecular sieves (4 Å). A brief account of purification procedures employed is as follow:

3.2.1 Methanol

Calcium oxide (250g), freshly activated in a muffle furnace at 300-400 °C, was introduced into a round bottom flask containing one liter of methanol. It was refluxed for 6 hours and distilled at 64 °C.

3.2.2 Ethanol

Calcium oxide (250g), freshly activated in a muffle furnace at 300-400 °C, was introduced into a round bottom flask containing one liter of ethanol. It was refluxed for 6 hours and distilled at 77-78 °C.

3.2.4 Ethyl acetate

In one liter of ethyl acetate, 50 mL of acetic anhydride and 10~15 drops of conc. H_2SO_4 were added and refluxed for 5 hours. It was fractionated and treated with 25g of potassium carbonate, filtered and distilled over 40g of calcium hydride at 77 °C.

3.2.5 Diethyl ether

Diethyl ether was first distilled over anhydrous calcium chloride. The distillate was refluxed on sodium wire, using benzophenone as an indicator. When the color of the mixture turned dark green, it was distilled and stored over molecular sieves (4 Å).

3.3 Instrumentation

The R_f values were determined using aluminum pre-coated silica gel plates 60 F_{254}, Merck (Germany). Melting points of the compounds were measured in open capillaries using Stuart melting point apparatus (SMP3) and are uncorrected. The IR spectra were recorded on FT-IR NICOLET 6700, Thermo Scientific spectrophotometer. The NMR spectra were run on a Bruker Avance 300 MHz NMR spectrometer as DMSO or $CDCl_3$ solutions using solvent residual signal as reference.

3.4 General procedure for the synthesis of aromatic esters[88] (111_{a-e})

Aromatic acid (0.2 mol) was dissolved in methanol (50 mL) in a round bottom flask equipped with a reflux condenser and an anhydrous calcium chloride guard tube. Concentrated sulfuric acid (0.002 mol) was added and the reaction mixture subjected to reflux for 8-10 hours and monitored by thin layer chromatography. After completion of the reaction, the excess alcohol was removed under reduced pressure and resulting oil was poured into water. The oily layer was separated and the aqueous portion was extracted with diethyl ether thrice (3 x 50 mL). The combined organic layers were washed with a dilute solution of sodium carbonate (100 mL) to remove unreacted acid. The organic layer was dried over anhydrous sodium sulphate. The solvent was removed on a rotary evaporator after filtration to give the product as an oily liquid.

Methyl 3-bromobenzoate (111_a):

Liquid; yield: 91 %; R_f: 0.83 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3064 (C_{sp2}-H), 2952, 2842 (C_{sp3}-H), 1733 (C=O), 1286 (C-O), 1611 (C=C), 1458 (C=C).

Methyl 3-methylbenzoate (111_b):

Liquid; yield: 83 %; R_f: 0.82 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3061 (C_{sp2}-H), 2954, 2839 (C_{sp3}-H), 1735 (C=O), 1267 (C-O), 1584 (C=C), 1465 (C=C).

Methyl 4-chlorobenzoate (111_c):

Liquid; yield: 89 %; R_f: 0.78 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3045 (C_{sp2}-H), 2972, 2842 (C_{sp3}-H), 1715 (C=O), 1249 (C-O), 1594 (C=C), 1479 (C=C).

Methyl 3-nitrobenzoate (111_d):

Yellow oily liquid; yield: 86 %; R_f: 0.79 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3039 (C_{sp2}-H), 2967, 2846 (C_{sp3}-H), 1732 (C=O), 1276 (C-O), 1564 (C=C), 1468 (C=C).

Methyl 3,4,5-trimethoxybenzoate (111_e):

Liquid; yield: 89 %; R_f: 0.83 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3063 (C_{sp2}-H), 2954, 2845 (C_{sp3}-H), 1728 (C=O), 1264 (C-O), 1585 (C=C), 1487 (C=C).

3.5 General procedure for the synthesis of aromatic acid hydrazides[89] (112_{a-e})

The aromatic ester (0.02 mol) was dissolved in methanol (100 mL) in a round bottom flask fitted with a reflux condenser and an anhydrous calcium chloride drying tube. Hydrazine hydrate (80 %, 0.04 mol) was added slowly and the reaction was monitored by thin layer chromatography. After completion of the reaction, the reaction mixture was concentrated under reduced pressure. The resulting crude solid was filtered, washed with water and recrystallized from aqueous ethanol.

3-Bromobenzohydrazide (112_a):

White solid; yield: 90 %; m.p.: 115-117 °C; R_f: 0.14 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3303, 3243 (NH_2), 3195 (N-H), 1659 (C=O), 1558 (C=C), 1505 (C=C).

3-Methylbenzohydrazide (112_b):

White solid; yield: 84 %; m.p.: 126-127 °C; R_f: 0.23 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3314, 3223 (NH_2), 3193 (N-H), 1626 (C=O), 1545 (C=C), 1484 (C=C).

4-Chlorobenzohydrazide (112_c):

White solid; yield: 85 %; m.p.: 110-111 °C; R_f: 0.10 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3319, 3198 (NH_2), 3196 (N-H), 1634 (C=O), 1569 (C=C), 1491 (C=C).

3-Nitrobenzohydrazide (112_d):

Yellow solid; yield: 71 %; m.p.: 151-152 °C; R_f: 0.15 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3374, 3241 (NH_2), 3254 (N-H), 1651 (C=O), 1546 (C=C), 1485 (C=C).

3,4,5-Trimethoxybenzohydrazide (112_e):

White solid; yield: 85 %; m.p.: 124-125 °C; R_f: 0.22 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3324, 3219 (NH_2), 3194 (N-H), 1654 (C=O), 1561 (C=C), 1486 (C=C).

3.6 General procedure for the synthesis of thiosemicarbazides[90] (113_{a-e}):

A mixture of 0.01 mol of aromatic acid hydrazides (**123_{a-e}**), and 0.02 mol of potassium thiocyanate was added to 10 mL of water containing 2 mL of conc. HCl. The mixture was warmed on water bath for 2 hours. The reaction mixture was cooled and poured onto crushed ice. The resulting solid was filtered, dried and recrystallized from ethanol.

2-(3-Bromobenzoyl)hydrazinecarbothioamide (113_a):

White crystalline solid; yield: 57 %; m.p.: 148-149 °C; R_f: 0.15 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3341-3123 (N-H), 1677 (C=O), 1245 (C=S), 1515 (C=C), 1498 (C=C).

2-(3-Methylbenzoyl)hydrazinecarbothioamide (113_b):

White crystalline solid; yield: 53 %; m.p.: 150-151 °C; R_f: 0.17 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3350-3154 (N-H), 1665 (C=O), 1237 (C=S), 1555 (C=C), 1496 (C=C).

2-(4-Chlorobenzoyl)hydrazinecarbothioamide (113_c):

White crystalline solid; yield: 73 %; m.p.: 155-156 °C; R_f: 0.19 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3356-3281 (N-H), 1683 (C=O), 1235 (C=S), 1593 (C=C), 1469 (C=C).

2-(3-Nitrobenzoyl)hydrazinecarbothioamide (113_d):

White crystalline solid; yield: 71 %; m.p.: 175-176 °C; R_f: 0.13 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3385-3143 (N-H), 1674 (C=O), 1236 (C=S), 1522 (C=C), 1497 (C=C).

2-(3,4,5-Trimethoxybenzoyl)hydrazinecarbothioamide (113_e):

White crystalline solid; yield: 75 %; m.p.: 165-166 °C; R_f: 0.14 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3396-3163 (N-H), 1673 (C=O), 1268 (C=S), 1596 (C=C), 1512 (C=C).

3.7 General procedure for the synthesis of 1,2,4-triazoles[91] (114_{a-e}):

The corresponding thiosemicarbazide, 0.01 mol, was refluxed for 3 hours in 100 mL of 5 % aqueous sodium hydroxide solution. The reaction mixture was cooled and then poured onto crushed ice. The mixture was acidified with concentrated HCl. The resulting solid was filtered, dried and recrystallized from ethanol.

3-(3-Bromophenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (114_a):

White crystalline solid; yield: 79 %; m.p.: 206-208 °C; R_f: 0.12 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3345 (N-H), 2544 (S-H), 1410 (C=N), 1542 (C=C), 1475 (C=C); **^{1}H NMR** (300MHz, DMSO): δ 13.33 (s, 1H, N-H), 8.03-8.04 (m, 1H, Ar-H), 7.92-7.95 (m, 1H, Ar-H), 7.81-7.85 (m, 1H, Ar-H), 7.45-7.50 (m, 1H, Ar-H); **^{13}C NMR**; 166.43, 136.06, 133.53, 133.34, 132. 20, 131.37, 129.33, 128.74, 122.18.

3-m-Tolyl-1*H*-1,2,4-triazole-5(4*H*)-thione (114_b):

White crystalline solid; yield: 67 %; m.p.: 196-197 °C; R_f: 0.13 (*n*-hexane : ethyl acetate, 8:2); **IR** (pure, cm^{-1}): 3341 (N-H), 2542 (S-H), 1424 (C=N), 1533 (C=C), 1485 (C=C); **^{1}H NMR** (300MHz, $CDCl_3$): δ 13.01 (s, 1H, N-H), 7.91-7.93 (m, 1H, Ar-H), 7.40-7.42 (m, 1H, Ar-H), 7.35-7.36 (m, 1H, Ar-H), 7.26-7.28 (m, 1H, Ar-H), 2.63 (s, 3H, CH_3); **^{13}C NMR**; 167.00, 135.20, 134.61, 133.34, 132.14, 131.02, 128.96, 123.77.

3-(3-Chlorophenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (114_c):

White crystalline solid; yield: 73 %; m.p.: 185-187 °C; R_f: 0.14 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3324 (N-H), 2549 (S-H), 1415 (C=N), 1532 (C=C), 1481 (C=C); **^{1}H NMR** (300MHz, DMSO): δ 13.42 (s, 1H, N-H), 8.08-8.11 (m, 2H, Ar-H), 7.88 (d, *J* = 8.1Hz); **^{13}C NMR**; 166.20, 139.56, 134.42, 133.80, 132.65, 131.48, 129.35, 129.19, 124.54.

3-(3-Nitrophenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (114_d):

Yellow crystalline solid; yield: 76 %: m.p.: 215-217 °C; R_f: 0.11 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3331 (N-H), 2551 (S-H), 1445 (C=N), 1556 (C=C), 1496 (C=C); **^{1}H NMR** (300MHz, DMSO): δ 13.71 (s, 1H, N-H), 8.59-8.60 (m, 1H, Ar-H), 8.43-8.47 (m, 1H, Ar-H), 8.33 (m, 1H, Ar-H), 7.77-7.82 (m, 1H, Ar-H), 2.58 (s, 3H, CH_3); **^{13}C NMR**; 165.97, 148.30, 135.82, 132.92, 130.98, 127.26, 127.18, 124.13.

3-(3,4,5-Trimethoxyphenyl)-1*H*-1,2,4-triazole-5(4*H*)-thione (114_e):

White crystalline solid; yield: 71 %; m.p.: 175-177 °C; R_f: 0.15 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3348 (N-H), 2548 (S-H), 1464 (C=N), 1542 (C=C), 1492 (C=C); **^{1}H NMR** (300MHz, $CDCl_3$): δ 11.65 (s, 1H, N-H), 7.39 (2, 2H, Ar-H); **^{13}C NMR**; 172.00, 152.95, 142.48, 133.34, 132.01, 127.28, 61.00, 56.25.

3.8 General procedure for the synthesis of aryl-2-(*4H*-1,2,4-triazol-3-ylthio)ethanones[81] (116_{a-l}):

To 0.01 mol of 1,2,4-triazole-3-thiol, 0.01 mol of substituted phenacyl bromide (acetophenone) **(116_{a-d})** was added in the presence of 0.015 mol of KOH in absolute ethanol and refluxed for 5 hours. The reaction mixture was cooled and poured onto crushed ice. The resulting solid was filtered, dried and recrystallized from ethanol.

2-(5-(3-Bromophenyl)-4*H*-1,2,4-triazol-3-ylthio)-1-p-tolylethanone (116_a):

White crystalline solid; yield: 69 %; m.p.: 104-105 °C; R_f: 0.66 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3394 (N-H), 3065 (C_{sp2}-H), 2926, 2832 (C_{sp3}-H), 1701 (C=O), 1588 (C=C), 1505 (C=C); **^{1}H NMR** (300MHz, $CDCl_3$): δ 8.19 (m, 1H, Ar-*H*), 8.01-8.09 (m, 2H, Ar-*H*), 7.89 (m, 1H, Ar-*H*), 7.82 (m, 1H, Ar-*H*), 7.42 (m, 1H, Ar-*H*), 7.39-7.41 (m, 2H, Ar-*H*), 5.59 (s, 2H, CH_2), 2.64 (s, 3H, CH_3); **^{13}C NMR** (75MHz, $CDCl_3$): δ 191.21, 164.48, 138.24, 136.52, 132.06, 131.98, 131.23, 130.54, 130.44, 129.65, 128.64, 128.15, 128.13, 127.87, 122.24, 67.26, 21.56.

2-(5-(3-Bromophenyl)-4*H*-1,2,4-triazol-3-ylthio)-1-(4-fluorophenyl)ethanone (116_b):

White crystalline solid; yield: 57 %; m.p: 90-92 °C; R_f: 0.63 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3363 (N-H), 3071 (C_{sp2}-H), 2932, 2824 (C_{sp3}-H), 1694 (C=O), 1586 (C=C), 1511 (C=C); **^{1}H NMR** (300MHz, $CDCl_3$): δ 8.13 (m, 1H, Ar-*H*), 8.08-8.13 (m, 2H, Ar-*H*), 8.03 (m, 1H, Ar-*H*), 7.93 (m, 1H, Ar-*H*), 7.56 (m, 1H, Ar-*H*),

7.42 (m, 2H, Ar-*H*), 5.77 (s, 2H, CH_2); **^{13}C NMR** (75MHz, $CDCl_3$): δ 191.62, 164.46, 136.92, 136.54, 132.46, 132.21, 131.70, 130.51, 131.39, 128.97, 128.86, 128.76, 122.42, 116.71, 116.42, 67.89.

2-(5-(3-Bromophenyl)-4*H*-1,2,4-triazol-3-ylthio)-1-(4-chlorophenyl)ethanone (116_c):

White crystalline solid; yield: 63 %; m.p.: 101-103 °C; R_f: 0.64 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3366 (N-H), 3071 (C_{sp2}-H), 2938, 2830 (C_{sp3}-H), 1696 (C=O), 1572 (C=C), 1498 (C=C); **^{1}H NMR** (300MHz, $CDCl_3$): δ 8.29 (m, 1H, Ar-*H*), 8.07 (m, 1H, Ar-*H*), 7.92 (d, 2H, *J* = 8.4Hz, Ar-*H*), 7.75(m, 1H, Ar-*H*), 7.51(d, 1H, *J* = 8.4Hz, Ar-*H*), 7.37 (m, 1H, Ar-*H*), 5.56 (s, 2H, CH_2); **^{13}C NMR** (75MHz, $CDCl_3$): δ 190.65, 164.72, 140.59, 136.43, 132.96, 132.42, 130.09, 129.37, 129.35, 129.24, 128.68, 128.57, 122.59, 66.53.

2-(5-(3-Bromophenyl)-4*H*-1,2,4-triazol-3-ylthio)-1-(4-nitrophenyl)ethanone (116_d):

Yellow crystalline solid; yield: 66 %; m.p.: 103-104 °C; R_f: 0.51 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3390 (N-H), 3072 (C_{sp2}-H), 2940, 2834 (C_{sp3}-H), 1698 (C=O), 1586 (C=C), 1506(C=C); **^{1}H NMR** (300MHz, $CDCl_3$): δ 8.38 (d, 2H, *J* = 8.1Hz, Ar-*H*), 8.27 (s, 1H, Ar-*H*), 8.24 (d, 2H, *J* = 8.1Hz, Ar-*H*), 8.06 (m, 1H, Ar-*H*), 7.76 (m, 1H, *J* = 8.1Hz, Ar-*H*), 7.38 (m, 1H, Ar-*H*), 5.60 (s, 2H, CH_2); **^{13}C NMR** (75MHz, $CDCl_3$): δ 190.67, 164.65, 150.81, 138.53, 136.62, 132.96, 130.17, 129.45, 129.00, 129.24, 128.57, 126.20, 124.20, 122.65, 66.73.

1-(4-Fluorophenyl)-2-(5-m-tolyl-4*H*-1,2,4-triazol-3-ylthio)ethanone (116_e):

White crystalline solid; yield: 47 %; m.p.: 112-114 °C; R_f: 0.57 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3386 (N-H), 3076 (C_{sp2}-H), 2946, 2834 (C_{sp3}-H), 1695 (C=O), 1569 (C=C),1499 (C=C); **^{1}H NMR** (300MHz, $CDCl_3$): δ 8.06 (m, 1H, Ar-*H*), 7.64 (m, 2H, Ar-*H*), 7.61 (m, 1H, Ar-*H*), 7.49 (m, 1H, Ar-*H*), 7.43 (m, 2H, Ar-*H*), 7.31 (m, 1H, Ar-*H*), 5.63 (s, 2H, CH_2); **^{13}C NMR**; 190.24, 166.97, 139.67, 138.46,

131.68, 131.54, 130.76, 126.81, 129.34, 129.26, 129.19, 129.11, 128.90, 128.46, 125.94, 66.12, 21.35.

1-(4-Chlorophenyl)-2-(5-m-tolyl-4*H*-1,2,4-triazol-3-ylthio)ethanone (116_f):

White crystalline solid; yield: 53 %; m.p.: 105-106 °C; R_f: 0.59 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3389 (N-H), 3068 (C_{sp2}-H), 2939, 2846 (C_{sp2}-H), 1684 (C=O), 1591 (C=C), 1501 (C=C); **^{1}H NMR** (300MHz, $CDCl_3$): δ 8.08 (m, 1H, Ar-*H*), 7.94 (d, 2H, *J* = 8.1Hz, Ar-*H*), 7.51 (d, 2H, *J* = 8.1Hz, Ar-*H*), 7.44 (m, 1H, Ar-*H*), 7.30 (m, 1H, Ar-*H*), 7.28 (m, 1H, Ar-*H*), 5.53 (s, 2H, CH_2); **^{13}C NMR**; 191.26, 166.84, 140.76, 140.41, 132.63, 132.49, 130.98, 129.28, 129.26, 129.10, 128.95, 128.62, 125.83, 66.11, 21.72.

2-(5-(4-Chlorophenyl)-4*H*-1,2,4-triazol-3-ylthio)-1-p-tolylethanone (116_g):

White crystalline solid; yield: 72 %; m.p.: 118-119 °C; R_f: 0.62 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3379 (N-H), 3067 (C_{sp2}-H), 2928, 2830 (C_{sp3}-H), 1682 (C=O), 1586, 1504 (C=C); **^{1}H NMR** (300MHz, $CDCl_3$): δ 8.08-8.11 (m, 2H, Ar-*H*), 7.88 (d, *J*=8.1Hz, 2H, Ar-*H*), 7.45-7.47 (m, 2H, Ar-*H*), 7.31 (d, 2H, J=8.1Hz, Ar-*H*), 5.57 (s, 2H, CH_2), 2.45 (s, 3H, CH_3); **^{13}C NMR**; 191.44, 165.25, 145.01, 139.83, 131.69, 131.38, 131.06, 130.28, 129.61, 128.82, 127.92, 66.54, 21.80.

2-(5-(4-Chlorophenyl)-4*H*-1,2,4-triazol-3-ylthio)-1-(4-nitrophenyl)ethanone (116_h):

Deep yellow crystalline solid; yield: 57 %; m.p.: 124-126 °C; R_f: 0.64 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3373 (N-H), 3081 (C_{sp2}-H), 2942, 2834 (C_{sp3}-H), 1693 (C=O), 1576, 1497 (C=C); **^{1}H NMR** (300MHz, $CDCl_3$): δ 8.39 (d, 2H, *J*=8.4Hz, Ar-*H*), 8.25 (d, 2H, *J*=8.4Hz, Ar-*H*), 8.04 (d, 2H, *J*=8.1Hz, Ar-*H*), 7.66 (d, 2H, *J*=8.1Hz, Ar-*H*), 5.84 (s, 2H, CH_2); **^{13}C NMR**; 191.68, 165.36, 149.46, 139.65, 131.47, 130.31, 130.28, 130.06, 129.70, 129.31, 128.49, 128.15, 66.45.

2-(5-(4-Nitrophenyl)-4*H*-1,2,4-triazol-3-ylthio)-1-p-tolylethanone (116$_i$):

White crystalline solid; yield: 63 %; m.p.: 96-98 °C; R_f: 0.65 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3379 (N-H), 3067 (C_{sp2}-H), 2928, 2830 (C_{sp3}-H), 1682 (C=O), 1586 (C=C), 1504 (C=C); **^{1}H NMR** (300MHz, $CDCl_3$): δ 8.99 (s, 1H, Ar-*H*), 8.48 (m, 2H, Ar-*H*), 7.88 (d, 2H, *J*=8.1Hz, Ar-*H*), 7.61 (m, 1H, Ar-*H*), 7.33 (d, 2H, *J*=8.1Hz, Ar-*H*), 5.65 (s, 2H, CH_2), 2.46 (s, 3H, CH_3); **^{13}C NMR**; 190.85, 164.06, 148.31, 145.23, 135.65, 132.75, 131.47, 130.21, 129.75, 129.68, 127.92, 127.77, 127.67, 66.98, 21.83.

1-p-Tolyl-2-(5-(3,4,5-trimethoxyphenyl)-4*H*-1,2,4-triazol-3-ylthio)ethanone (116$_j$):

White crystalline solid; yield: 53 %; m.p.: 113-115 °C; R_f: 0.56 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3394 (N-H), 3038 (C_{sp2}-H), 2949, 2842 (C_{sp3}-H), 1686 (C=O), 1581 (C=C),1501 (C=C); **^{1}H NMR** (300MHz, $CDCl_3$): δ 7.76 (d, 2H, *J* = 8.1Hz, Ar-*H*), 7.45 (s, 2H, Ar-*H*), 7.27 (d, 2H, *J* = 8.1Hz, Ar-*H*), 5.59 (s, 2H, CH_2), 3.91 (s, 9H, CH_3), 2.38 (s, 3H, CH_3); **^{13}C NMR**; 191.28, 167.46, 165.94, 153.46, 148.57, 148.16, 141.26, 136.21, 130.87, 130.54, 130.67, 129.45, 126.12, 109.46, 67.24.

1-(4-Fluorophenyl)-2-(5-(3,4,5-trimethoxyphenyl)-4H-1,2,4-triazol-3-ylthio)ethanone (116$_k$):

White crystalline solid; yield: 75 %; m.p.: 135-137 °C; R_f: 0.63 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3389 (N-H), 3065 (C_{sp2}-H), 2938, 2838 (C_{sp3}-H), 1687 (C=O), 1582 (C=C), 1502 (C=C); **^{1}H NMR** (300MHz, $CDCl_3$): δ 8.01-8.05 (m, 2H, Ar-*H*), 7.41 (s, 2H, Ar-*H*), 7.18-7.29 (m, 2H, Ar-*H*), 5.55 (s, 2H, CH_2), 3.93 (s, 9H, CH_3); **^{13}C NMR**; 190.64, 167.89, 165.69, 153.01, 142.61, 136.43, 130.63, 130.51, 130.28, 124.20, 116.35, 107.17, 116.05, 66.33, 60.98, 56.26.

1-(4-Chlorophenyl)-2-(5-(3,4,5-trimethoxyphenyl)-4*H*-1,2,4-triazol-3-ylthio)ethanone (116$_i$):

White crystalline solid; yield: 72 %; m.p.: 121-123 °C; R_f: 0.62 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3391 (N-H), 3064 (C_{sp2}-H), 2941, 2836 (C_{sp3}-H), 1697 (C=O), 1579 (C=C), 1497 (C=C); **^{1}H NMR** (300MHz, $CDCl_3$): δ 8.03 (d, 2H, *J* = 8.4Hz, Ar-*H*), 7.67 (d, 2H, *J* = 8.4Hz, Ar-*H*), 7.31 (m, 2H, Ar-*H*), 5.73 (s, 2H, CH_2), 3.85 (s, 6H, CH_3), 3.76 (s, 3H, CH_3); **^{13}C NMR**; 192.40, 165.28, 153.15, 142.45, 139.40, 133.01, 131.54, 130.26, 129.58, 124.58, 107.04, 67.65, 60.66, 56.47..

3.9 General procedure for the synthesis of thiazolo[3,2-*b*][1,2,4]triazoles[92] (118$_{a-h}$):

The arylthiazolo[3,2-*b*][1,2,4]triazoles **(118$_{a-h}$)** were synthesized by refluxing 0.001 moles of the respective ethanone in 4 mL of phosphorus oxychloride. The products were purified by recrystallization from ethanol, column chromatography or thin layer chromatography.

2-(3-Bromophenyl)-6-*p*-tolylthiazolo[3,2-*b*][1,2,4]triazole (118$_a$):

White crystalline solid; yield: 59 %; m.p.: 224-226 °C; R_f: 0.69 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3094 (C_{sp2}-H), 1425 (C=N), 1578 (C=C), 1501 (C=C); **^{1}H NMR** (300MHz, DMSO): δ 8.19 (s, 1H, SCH), 8.10-8.12 (m, 1H, Ar-H), 8.00-8.04 (m, 1H, Ar-H), 7.93-7.96 (m, 1H, Ar-H), 7.56-7.63 (m, 3H, Ar-H), 7.26-7.34 (m, 2H, Ar-H), 2.34 (s, 3H, CH_3); **^{13}C NMR** (75MHz, DMSO): δ 161.57, 139.52, 136.97, 133.16, 131.64, 131.28, 129.42, 129.34, 129.33, 128.84, 126.34, 122.76, 120.96, 21.22.

2-(3-Bromophenyl)-6-(4-fluorophenyl)thiazolo[3,2-*b*][1,2,4]triazole (118$_b$):

Yellow crystalline solid; yield: 57 %; m.p.: 237-239 °C; R_f: 0.67 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3078 (C_{sp2}-H), 1454 (C=N), 1594 (C=C), 1502 (C=C); **^{1}H NMR** (300MHz, DMSO): δ 8.23 (s, 1H, SCH), 8.18-8.19 (m, 1H, Ar-H), 8.10-8.13 (m, 1H, Ar-H), 7.98-8.01 (m, 1H, Ar-H), 7.71-7.76 (m, 2H, Ar-H), 7.58-7.64 (m,

1H, Ar-H), 7.28-7.33 (m, 2H, Ar-H); **^{13}C NMR** (75MHz, DMSO): δ 161.25, 137.71, 133.11, 132.53, 131.91, 130.35, 129.29, 129.01, 128.90, 122.60, 119.35, 116.42.

2-(3-Bromophenyl)-6-(4-chlorophenyl)thiazolo[3,2-*b*][1,2,4]triazole (118_c):

Yellowish crystalline solid; yield: 63 %; m.p.: 214-216 °C; R_f: 0.68 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3074 (C_{sp2}-H), 1435 (C=N), 1567 (C=C), 1507 (C=C); **^{1}H NMR** (300MHz, DMSO): δ 8.33-8.34 (m, 1H, Ar-H), 8.14-8.17 (m, 1H, Ar-H), 8.13 (s, 1H, SCH), 7.78-7.81 (m, 1H, Ar-H), 7.55-7.58 (m, 2H, Ar-H), 7.41-7.47 (m, 1H, Ar-H), 7.37-7.40 (m, 2H, Ar-H); **^{13}C NMR** (75MHz, DMSO): δ 161.39, 136.43, 134.54, 131.16, 130.14, 129.98, 129.45, 129.35, 128.51, 124.13, 122.67, 122.59, 121.45.

6-(4-Fluorophenyl)-2-*m*-tolylthiazolo[3,2-*b*][1,2,4]triazole (118_d):

White crystalline solid; yield: 66 %; m.p.: 248-250 °C; R_f: 0.56 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3085 (C_{sp2}-H), 1467 (C=N), 1579 (C=C), 1498 (C=C); **^{1}H NMR** (300MHz, DMSO): δ 8.26 (s, 1H, SCH), 8.11-8.12 (m, 1H, Ar-H), 8.02-8.04 (m, 1H, Ar-H), 7.76-7.78 (m, 1H, Ar-H), 7.63-7.67 (m, 2H, Ar-H), 7.43-7.48 (m, 1H, Ar-H), 7.19-7.24 (m, 2H, Ar-H), 2.65 (s, 3H, CH_3); **^{13}C NMR** (75MHz, DMSO): δ 161.46, 137.24, 132.44, 131.92, 130.97, 129.65, 129.46, 129.41, 128.63, 128.57, 122.24, 116.37, 21.72.

6-(4-Chlorophenyl)-2-*m*-tolylthiazolo[3,2-*b*][1,2,4]triazole (118_e):

White crystalline solid; yield: 51 %; m.p.: 232-234 °C; R_f: 0.60 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3078 (C_{sp2}-H), 1399 (C=N), 1589 (C=C), 1489 (C=C); **^{1}H NMR** (300MHz, DMSO): δ 8.19 (s, 1H, SCH), 8.16-8.13 (m, 1H, Ar-H), 7.79-7.81 (m, 1H, Ar-H), 7.67-7.71 (m, 1H, Ar-H), 7.52-7.56 (m, 2H, Ar-H), 7.38-7.40 (m, 1H, Ar-H), 7.21-7.26 (m, 2H, Ar-H), 2.63 (s, 3H, CH_3); **^{13}C NMR** (75MHz, DMSO): δ 160.95, 136.64, 133.37, 133.14, 131.68, 130.94, 129.67, 129.55, 129.16, 128.47, 128.28, 127.48, 126.64, 124.91, 121.33, 21.71.

2-(3-Nitrophenyl)-6-*p*-tolylthiazolo[3,2-*b*][1,2,4]triazole (118_f):

Brownish crystalline solid; yield: 61 %: m.p.: 218-220 °C; R_f: 0.64 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3089 (C_{sp2}-H), 1432 (C=N), 1588 (C=C), 1506 (C=C); **^{1}H NMR** (300MHz, DMSO): δ 8.46-8.51 (m, 2H, Ar-H), 8.17 (s, 1H, SCH), 8.03-8.06 (m, 1H, Ar-H), 7.62-7.69 (m, 1H, Ar-H), 7.49-7.52 (m, 2H, Ar-H), 7.22-7.24 (m, 2H, Ar-H), 2.31 (s, 3H, CH_3); **^{13}C NMR** (75MHz, DMSO): δ 161.24, 134.64, 134.44, 133.21, 130.61, 130.47, 130.46, 130.37, 129.42, 129.11, 128.16, 127.34, 127.01, 122.16, 119.45.

6-(4-Fluorophenyl)-2-(3,4,5-trimethoxyphenyl)thiazolo[3,2-*b*][1,2,4]triazole (118_g):

Orange crystalline solid; yield: 55 %; m.p.: 251-252 °C; R_f: 0.54 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3074 (C_{sp2}-H), 1416 (C=N), 1576 (C=C), 1503 (C=C); **^{1}H NMR** (300MHz, DMSO): δ 8.14 (s, 1H, SCH), 7.50 (d, 2H, *J* = 8.4Hz, Ar-H), 7.29 (s, 2H, Ar-H), 7.18 (d, 2H, *J* = 8.4Hz, Ar-H), 3.83 (s, 9H, OCH_3); **^{13}C NMR** (75MHz, DMSO): δ 161.61, 134.71, 134.32, 134.11, 130.71, 130.57, 130.31, 130.24, 129.68, 128.34, 128.21, 127.71, 127.68, 121.42, 60.62, 56.31.

6-(4-Chlorophenyl)-2-(3,4,5-trimethoxyphenyl)thiazolo[3,2-*b*][1,2,4]triazole (118_h):

White crystalline solid; yield: 52 %: m.p.: 224-226 °C; R_f: 0.68 (*n*-hexane : ethyl acetate, 8:2); **IR** (neat, cm^{-1}): 3088 (C_{sp2}-H), 1419 (C=N), 1581 (C=C), 1499 (C=C); **^{1}H NMR** (300MHz, DMSO): δ 8.13 (s, 1H, SCH), 7.45-7.47 (m, 2H, Ar-H), 7.28 (s, 2H, Ar-H), 7.19-7.21 (m, 2H, Ar-H), 3.82 (s, 9H, OCH_3); **^{13}C NMR** (75MHz, DMSO): δ 160.92, 135.14, 134.24, 133.83, 131.21, 130.92, 130.81, 129.15, 129.07, 128.30, 127.52, 127.23, 122.29, 121.30, 60.01, 56.45.

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