CHAPTER ONE

INTRODUCTION

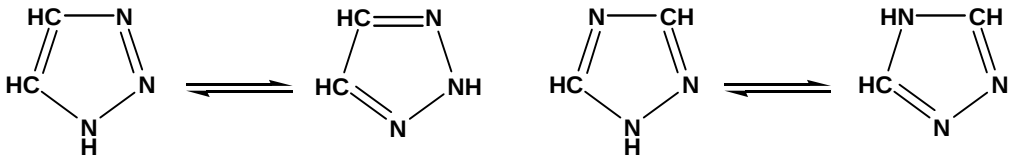
1.1 Heterocyclic Compounds:

Heterocyclic compounds are considered one of important types of organic compounds due to their applications in drug and industrial studies. Heterocyclic compounds are cyclic compounds in which one or more of the atoms of the ring are hetero atoms. The name comes from the Greek word heteros, which means "different". A variety of atoms such as (N, O, S, Se, P, Si, B and As) can be incorporated into the ring structure[1].

1.1.0 Triazoles:

The name of triazole was first given to the carbon-nitrogen ring system $C_2N_3H_3$ by ***Potts*** [2], who described its derivatives early as 1885. Triazole ring is planar with 6π-electron aromatic system with distortion of the π-system induced by the annular nitrogen atoms [3].

Triazoles are five membered heterocyclic compounds containing three nitrogen and two carbon atoms. There are two types of combination for the atoms, the 1,2,3-triazoles or vic-(vicinal) triazoles (I) and the 1,2,4-triazoles (II) known as sym-(symmetrical) [4] Triazoles.

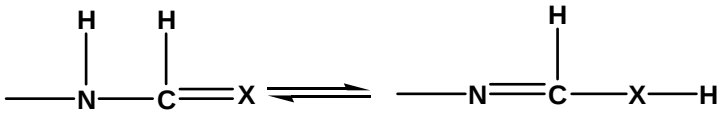


I **II**

As drugs, triazole compounds are highly efficient, low poisonous and inward-absorbent. The studies on triazole derivatives are mainly concentrated on compounds with the triazole as the only active group, the reports of triazole compounds than contain both triazole group and other active group in a single molecule has rarely been found[5].

Many triazole compounds possess good fungicidal and plant growth regulating activity [6]. The 1,2,4-triazole is an ubiquitous feature of many pharmaceutical and agrochemical products. The substituted 1,2,4-triazole nucleus is particularly common, and can be found in marketed drugs such as fluconozole, terconazole and rizatriptau alperazolam [7].

An important and versatile class of well established biologically active compounds are those containing the moiety (X = N, O, S) which can exist in two tautomeric forms [8].

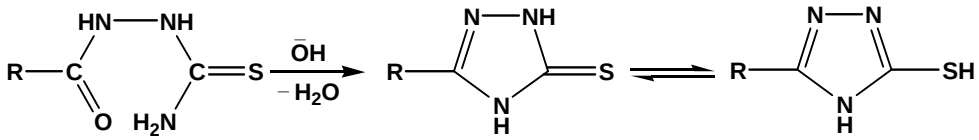


1.1.1 Synthesis of 1,2,4-triazoles:

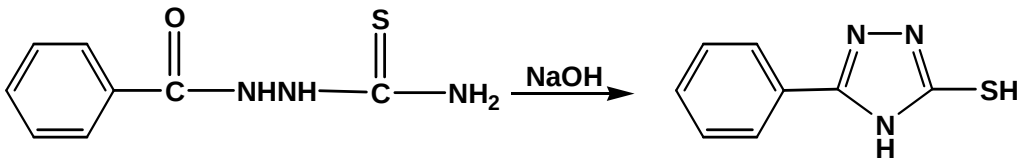
Several methods have been used to synthesize 1,2,4-triazoles that explore the possibility of obtaining biologically useful compounds containing the ring system, it was interesting for many scientists everywhere to synthesize numerous derivatives of these compounds.

1.1.1a Synthesis of 3,5-disubstituted-1,2,4-triazole derivatives:

Henichart et. al. [9], was prepared the 3,5-disubstituted triazole by interamolecular dehydration of thiosemicarbazide derivatives to triazole by using sodium hydroxide.

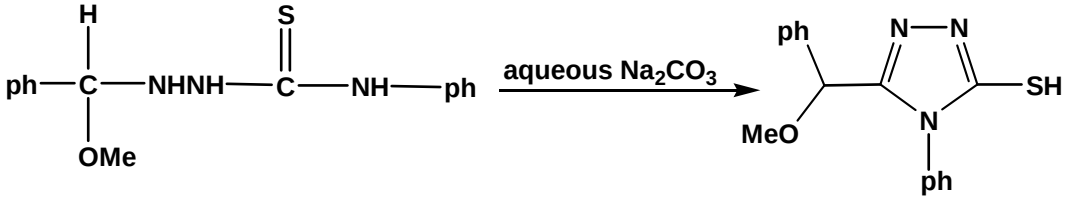


Goswambi et. al. [10], was prepared 3-(phenyl)-5-mercapto-4-H-1,2,4-triazole by cyclization of 1-(benzoyl) thiosemicarbazide with sodium hydroxide.

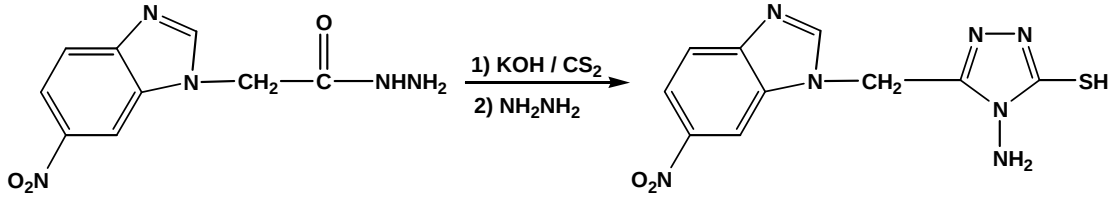


1.1.1b Synthesis of some 3,4,5-trisubstituted-1,2,4-triazole derivatives:

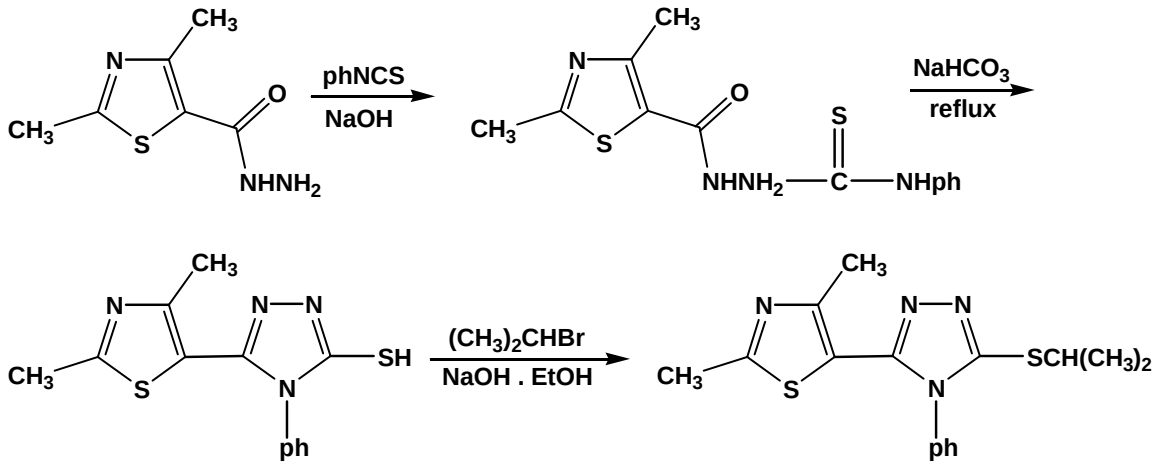
Al-Rubaiy [11] was prepared 3,4,5-trisubstituted-4-H-1,2,4-triazole from refluxing phenylthiosemicarbazide derivative in aqueous sodium carbonate solution.



Liu and ***Hui***[12] was synthesized the 6-nitrobenzimidazole-1-acetic acid hydrazide- 4-amino-5-mercapto-3-(6-nitrobenzimidazole-1methylen) -1,2,4-triazole was prepared by treating hydrazide with CS_2 and potassium hydroxide followed by addition of hydrazine hydrate.



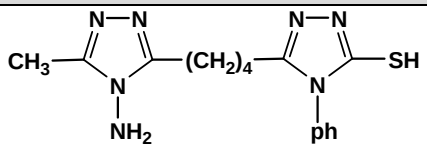
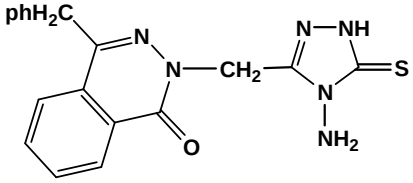
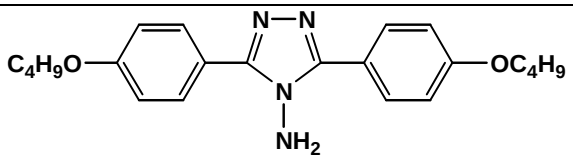
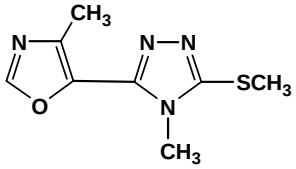
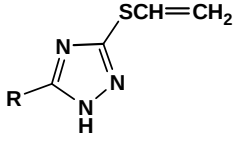
Shafiee et. al. [13], was prepared 3-(2,4-dimethyl-5-thiazolyl)-4-phenyl-5-isopropylthio-4-H-1,2,4-triazole as shown below, the newly prepared compound was tested for its anticonvulsant activity:



1.1.2 Biological activity of 1,2,4-triazole derivatives:

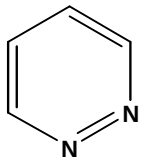
Among the five membered heterocyclic compounds, triazoles in general, and in particular 1,2,4-triazole derivatives have been found to exhibit wide spectrum of biological activities, they attracted attention owing to their antibacterial [14], fungicidal [15], pesticidal [16] or antianxiety[17] activities, so many attempts were carried out everywhere to incorporate structural modification in order to get compounds of potential activity. Table (1-1) summarizes structure and biological activity of some compounds of 1,2,4-triazole derivatives.

Table (1-1): Biological activity of some 1,2,4-triazole derivatives.

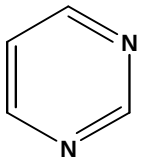
No.	Name	Structure	Biological activity	Ref
1	Bis-1,4-(4`-amino-5-mercapto-4H-1,2,4-triazol-3-yl)butane		Antibacterial activity	18
2	4-Benzyl-2-(1-amino-2`-thio-1,3,4-triazol-5-yl-methyl)pathaiazin-1-(2H)one		Antifungal activity	19
3	3,5-Di(*p*-butyloxyphenyl)-4`-amino-4H-1,2,4-triazole		Antibacterial	20
4	3(4-Methyl-5-oxazolyl)-4`-methyl-5`-methylthio-4H-1,2,4-triazole		Potential biological activity	21
5	3-Vinylthio-1,2,4-triazole	 R = H , Me , 2-furyl	Antimicrobial activity	22

1.2.0 Pyridazines:

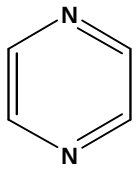
Pyridazine is a member of a diazine group. There are three possibly isomeric diazines with the nitrogen atoms in a 1,2-, 1,3- or 1,4-relationship:



pyridazine



pyrimidine

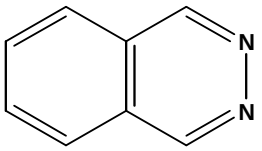


pyrazine

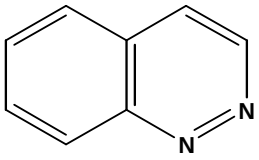
No naturally occurring pyridazines have been reported and indeed this comes as no surprise because of the paucity of chemical compounds containing two nitrogen atoms bonded to one another in nature.

Pyridazines is a colorless liquid, its boiling point is equal to (207.4 ^{o}C) and it is considered a weak base (pKa = 2.331).

Pyridazine ring can be fused on to a benzene ring in two ways giving phthalazine or cinnoline [23].



phthalazine

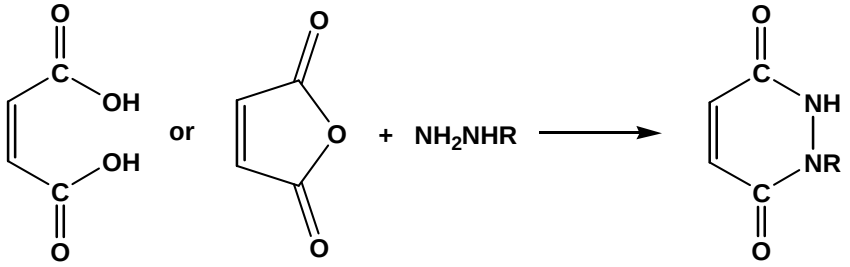


cinnoline

1.2.1 Synthesis of Pyridazine derivatives:

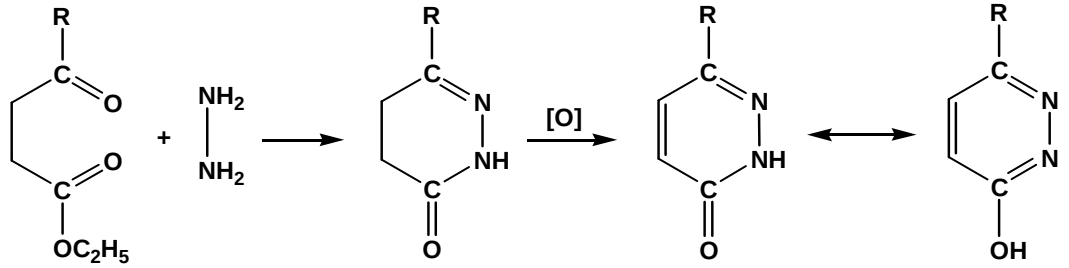
Pyridazine and number of its derivatives were prepared by different methods [23,24] such as.

From the reaction of maleic acid or maleic unhydride with hydrazine or substituted hydrazine.

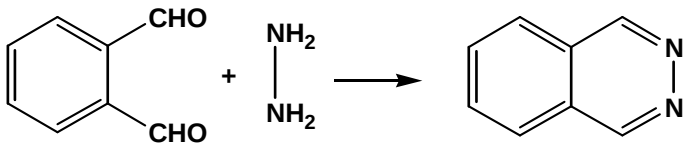


R = H , many different substituents

From the reaction of γ-keto carboxylic acid or their esters with hydrazine.

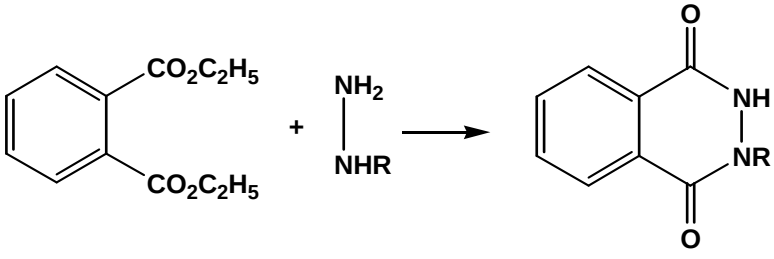


From the reaction of phthaldehyde with hydrazine.



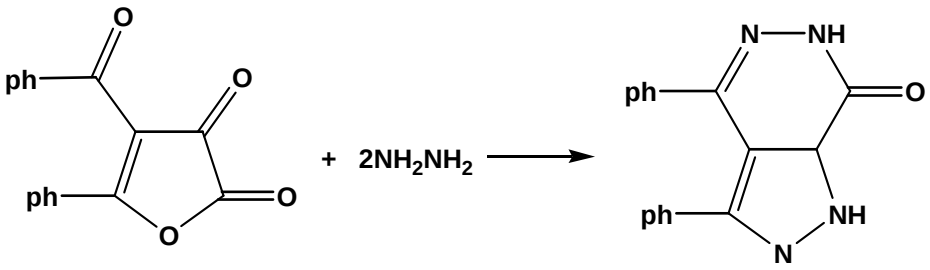
benzopyridazine (phthalazine)

From the reaction of phthalic acid or one of its derivatives (ester, anhydride and imide) with the hydrazine or substituted hydrazine.



R = many different substituents

Sener [25] found that 3,4-diphenyl-2H-pyrazol [3,4-d] pyridazin-7-one was obtained from the reaction of hydrazine with 4-benzoyl-5-phenyl-1,2,3-dihydro-2,4-furandione.



1.2.1 Biological activity of pyridazine:

Some imidazole [1,2-b] pyridazine derivatives are reported to possess antiasthmatic and analgesic activities [26]. It has been reported that a considerable number of 3(2H)-pyridazine derivatives bear analgesic activity as Emorfazone (4-ethoxy-2-methyl-5-morpholino-3(2H) pyridazinone [27].

Hydrazine-pyridazines continue to be an object of interest for improving medicinal drugs for blood pressure control such as hydralazine, which has been used for many years in the treatment of essential hypertension [28].

On the other hand, substituted pyridazine are often used in medicine field to their pronounced bactericidal and fungicidal effects[29] and consequently 4-phenylfuro [2,3-d] pyridazine-7-one is being used as intermediate for cardiovascular agents.

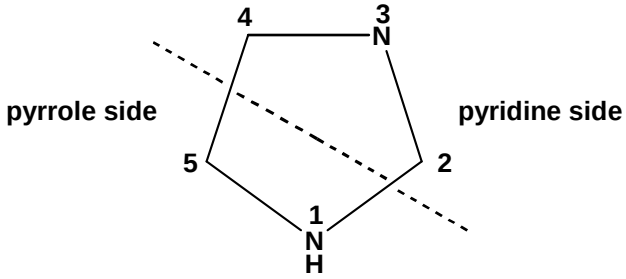
Pyridazine and condensed pyridazines are reported to have good biological activities. The discovery [30] of a natural antifungal antibiotic, containing this heteroarene system stimulated even broader interest in 1,2-diazine chemistry [31].

Therapeutic interest in this kind of drug has increased considerably due to their cytotoxic activity, notable decreasing blood flow in the tumors [32].

From their structure-activity relationship, it may be expected that hydrazinepyrazoleo [3,4-d] pyridazines, which are formed by replacement of the benzene ring in hydrazine with a pyrazole nucleus can exhibit interesting biological activity [29].

1.3.0 Imidazoles and Pyrazoles:

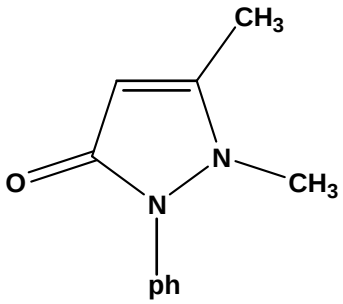
Imidazole is an aromatic compound because it is cyclic, planar and conjugated associated with 6π-electrons; one from each carbon one from the "pyridine" nitrogen and two from the "pyrrole" nitrogen:



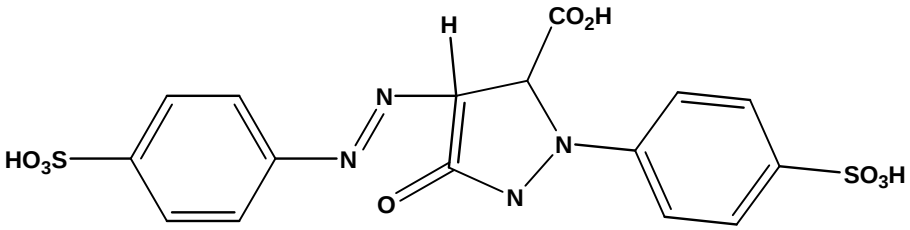
The emido hydrogen atom in imidazole is tautomeric and in practice the two nitrogen atoms are indistinguishable [33].

This is one of the reasons why histidine, the imidazole containing amino acid, is an important component of serine protease enzymes: these are family of closely related enzymes that contain uniquely reactive serine residue at the active site. They are called protease because they catalyze the hydrolysis of peptide bonds in polypeptides and proteins [34].

Antipyrine 2,3-dimethyl-1-phenyl-5-pyrazolone and its derivatives exhibit a wide variety of potentially useful applications including biological, clinical and pharmaceutical [35].



Tartrazine is a yellow dye for wool; this dye has been gaining commercial importance [35] because they are also used for the artificial coloring of foods:

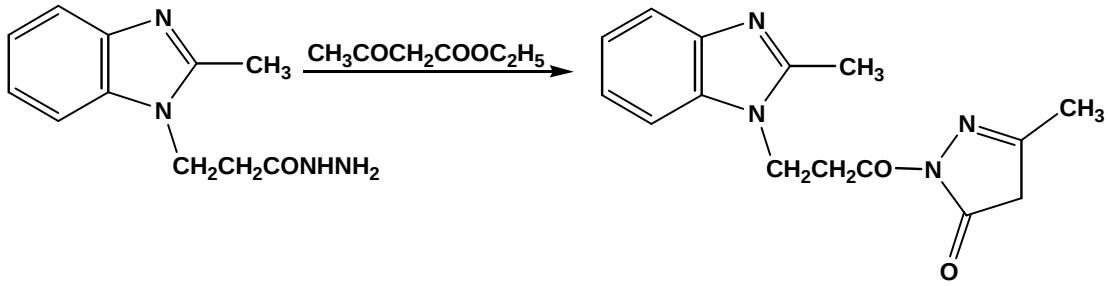


However very few pyrazole derivatives occur naturally, this may be due to the difficulty for living organisms to consider the N-N bond. The most important derivatives of pyrazole are in fact pyrazolones [36].

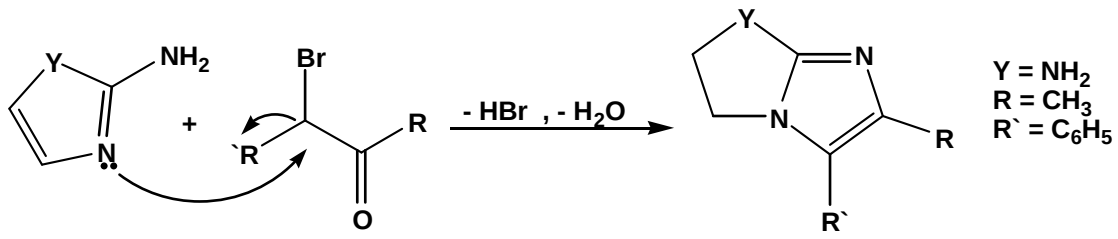
Pyrazole and imidazole are heterocyclic compounds of five membered diunsaturated ring structure composed of three carbon atom and two nitrogen atoms, if pyrazole is 1,2-diazole while imidazole is 1,3-diazole. Pyrazole derivatives play a vital role in many biological processes and synthetic drugs [37].

1.3.1 Synthesis of pyrazoles and imidazles:

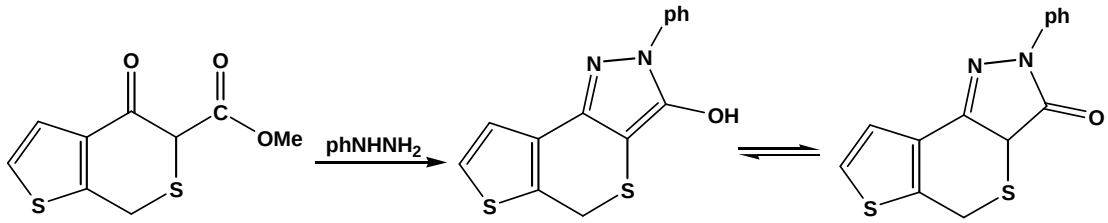
El-Massry et. al. [38], synthesized 1-[3-(2-methylbenzimidazol-1-yl) propanoyl]-4,5-dihydro-3-methylpyrazol-5-one from the reaction of 3-(2-methylbenzimidazol-1-yl) propanoic acid hydrazide with ethyl actoacetate.



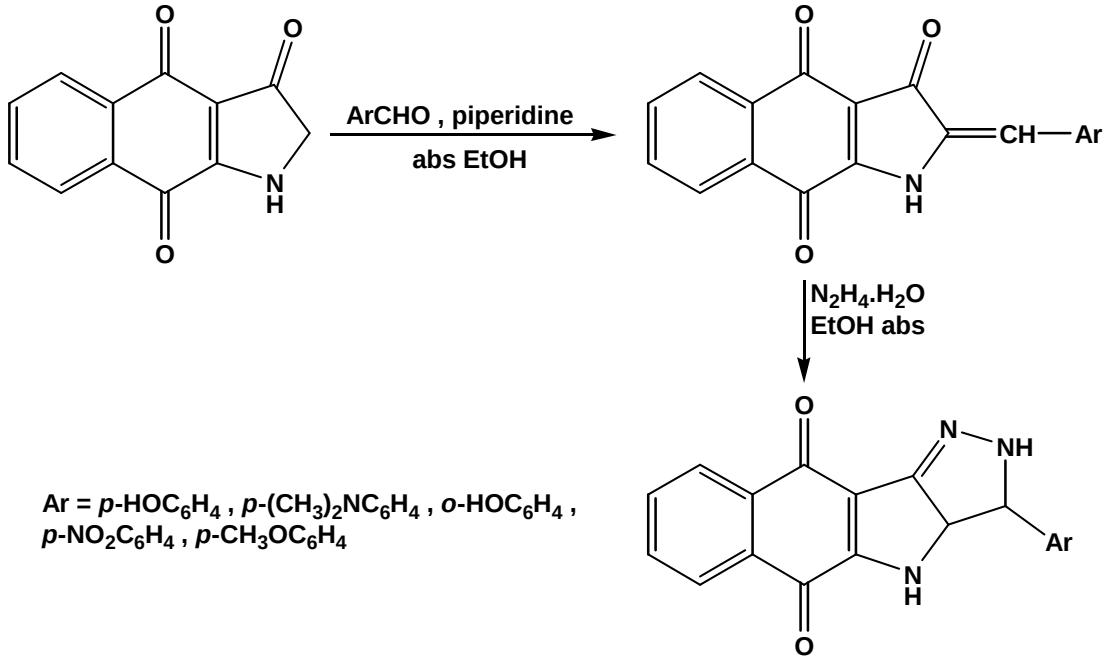
Various ring systems containing the –(NH_2)-N- moiety as a part of the ring have been found to condense with α-bromoketones to yield condensed imidazoheterocyclic systems; the ring nitrogen attacks the CH_2Br unit rather than the primary exocyclic amino group [39].



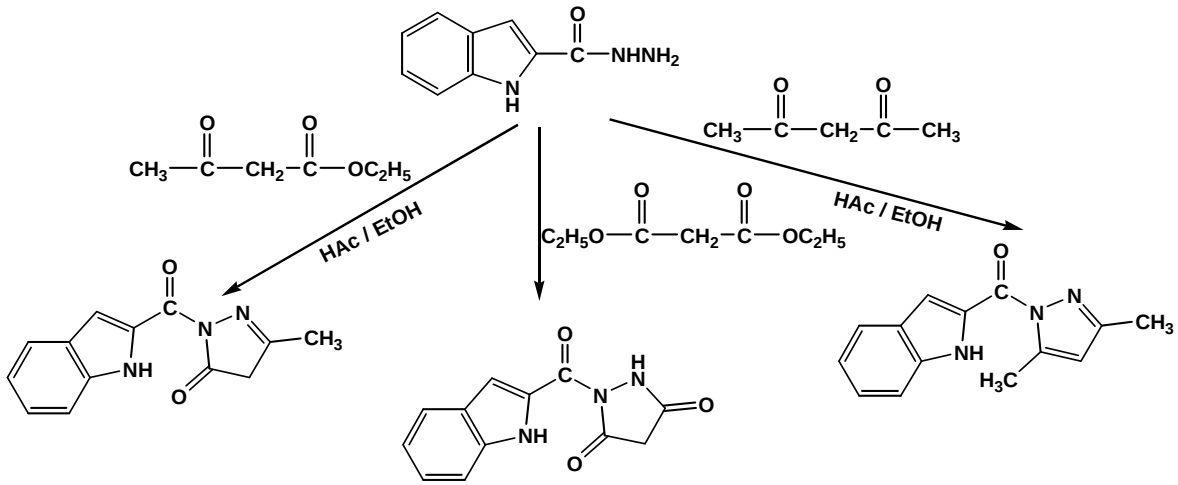
Soleiman et. al. [34], found that the β-oxoester reacted smoothly with phenylhydrazine in hot methanol to afford the tricyclic compounds. 3-hydroxy-2-phenyl-2,5-dihydrothienol [3`,4`,4,5] thionyranol [3,2-c] pyrazole 75% yield.



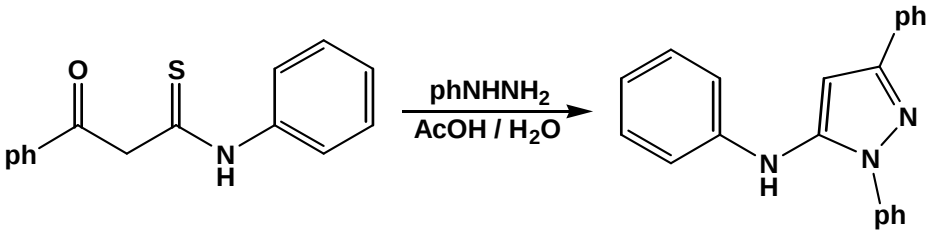
El-Massry et. al. [40], found that the compound below condensed with different aromatic aldehydes in the presence of piperidine as catalyst to give the corresponding styryl compound derivatives. Cyclocondensation addition reaction of hydrazine hydrate with the product gave pyrazoline [3,4-b] benz[g] indole derivatives.



Reaction of acid hydrazide and its derivatives reacted with ethylaceto acetate or acetyl acetone or diethyl malonate produced pyrazole derivatives [41].



Saleh et. al. [42], synthesized pyrazole derivatives by the reaction of β-ketothioanilide with phenyl hydrazine.



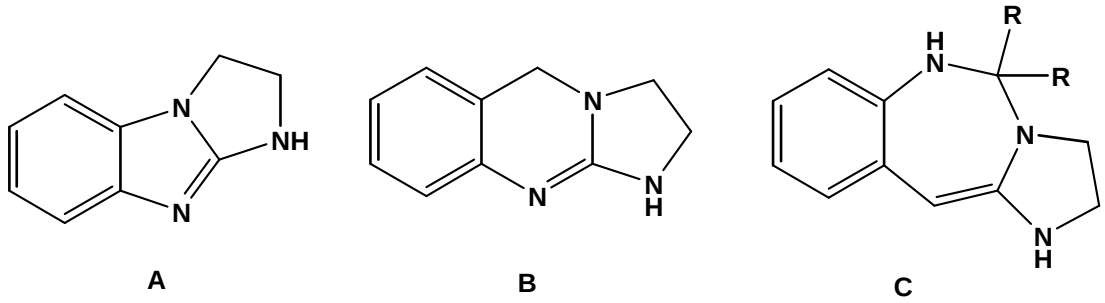
On the other hand, the reactions of α-bromoketones with urea derivatives give the corresponding imidazolone derivatives [43].

1.3.2 Biological activity of pyrazoles and imidazoles:

Imidazole drugs have been a broad spectrum in remedying various dispositions in clinical medicine[44].

It was found that interconnecting the imidazoline and phenyl ring, as was achieved in 2,3-dihydroimidazol [1,2-a] benzimidazole (A) or 1,2,3,5-tetrahydro-imidazo [2,1-b] quinazoline (B) afford agents capable of lowering the blood pressure of experimental animals.

On the other hand, it was recently found that certain 2,3,5,6-tetrahydro imidazo-[2,1-b][1,3,5] benzothiazepines of type (C) exhibit have been broad spectrum vasocontractile activity in isolated rabbit aortic [45].

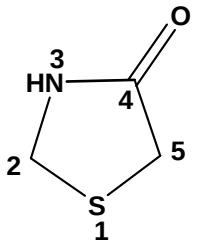


Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications. They have a broad antifungal spectrum as they inhibit the action of certain microorganisms[44,45].

The incorporation of the imidazole nuclei is an important synthetic strategy in drug discovery [46]. The high therapeutic properties of the related drugs have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents [47].

1.4.0 4-Thiazolidinones:

Thiazolidinones are derivatives of thiazolidines with carbonyl group in the 4-position.



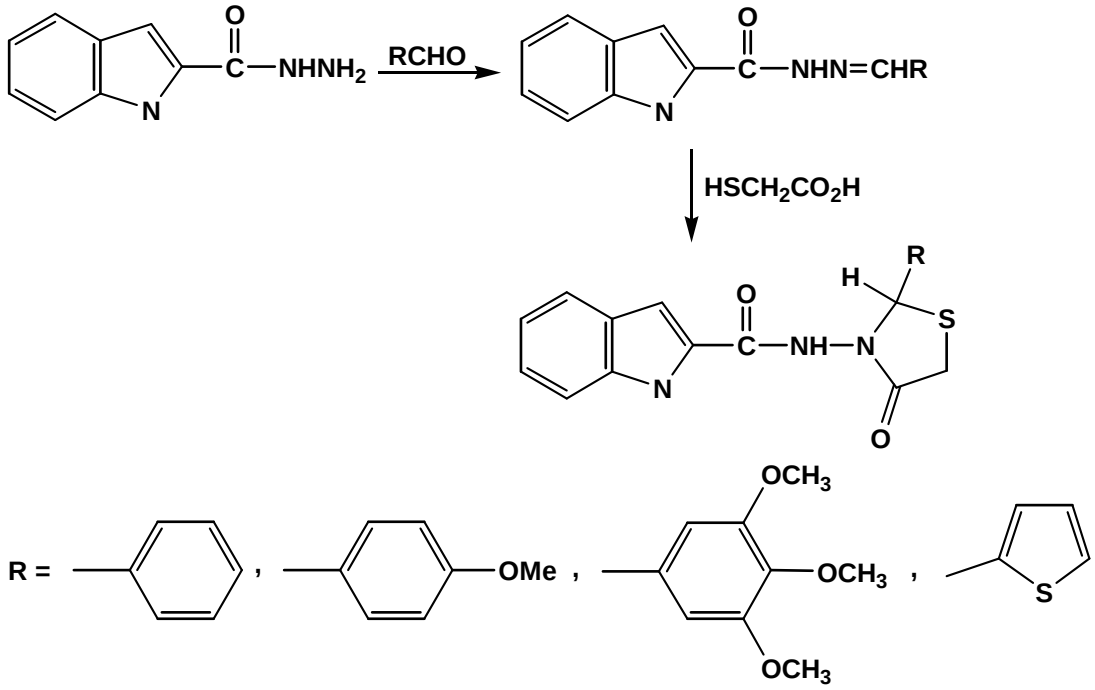
Sedative action is claimed for 3-methyl-5,5-diphenyl-2,4-thiazolidenediones, 5,5-dialkyl-2,4-thiazolidinediones and for 5,5-disubstituted-2-imino-4-thiazolinones. While the 3-alkoxyphenyl-2-(*p*-alkoxyphenylimino)-4-thiazolidinones have antituberculous activity [48,49].

Thiazolidin-4-ones are important compounds due to their broad range of biological activities. 2-aryl-4-thiazolidiones with an aminoalkyl group attached to nitrogen atom have local anesthetic properties [50].

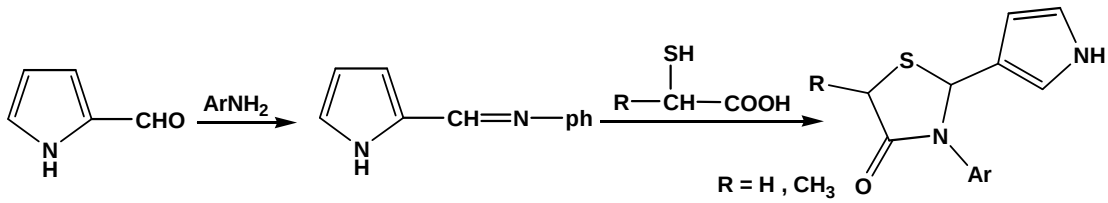
1.4.1 Synthesis of 4-thiazolidinones:

Several methods have been used to synthesize 4-thiazolidinones that explored the possibility of obtaining biologically useful compounds that contain the ring system.

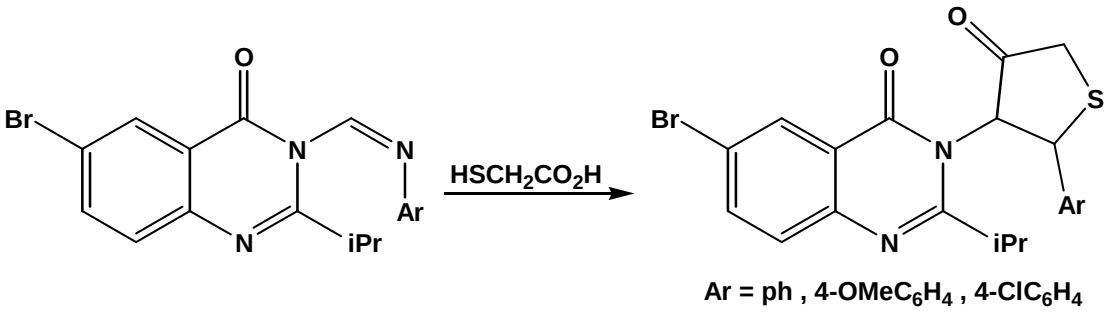
Fahmy et. al. [51], synthesized 2-aryl-3-(2-indolyamide) thiazolidin-4-ones from the reaction of 2-indolyl carbohydrazide with different aromatic or heterocyclic aldehydes to form 2-indolylarylidine hydrazones that cyclocondensed with thioacetic acid to give the compounds as shown is scheme.



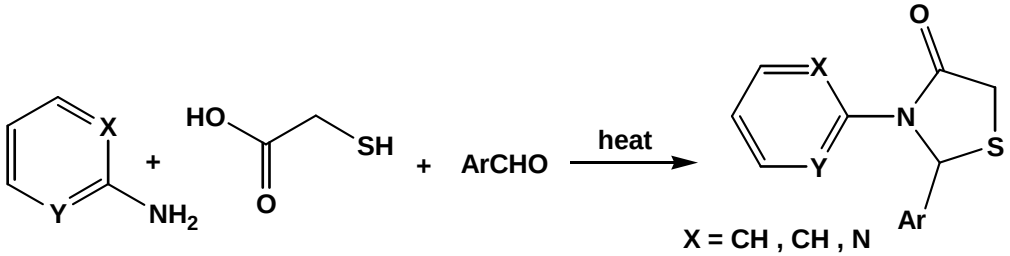
Aydogan et. al. [52], found that 4-thiazolidinones which are heterocyclic substituted at 2-position were prepared by the reaction of mercapto acids with aldimines which were prepared by the reaction of pyrrole-2-carboxyaldehyde with different aromatic amines:



Madkour [53] synthesized 6-bromo-3-[2-(4-chlorophenyl)-4-oxo-1,3-thiazol-3-yl]-2-isopropyl-4](3H)-quinazolinone from the reaction of 3-arylidenamino - 6- bromo- 2- isopropyl - 4 (3H) - quinazolines with thioglycolic acid in dry benzene.



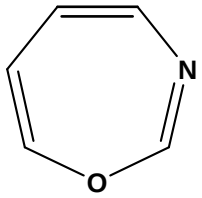
Rao et. al. [54], carried out the synthesis of 2,3-diaryl-1,3-thiazolidin-4-ones by reacting an aromatic aldehyde with an equimolar amount of (hetero) aromatic amine in the presence of mercaptoacetic acid:



X = CH , CH , N
Y = CH , N, N
Ar = ph

1.5.0 Oxazepines:

Oxazepine belongs taking non-homologous structure which has 7-membered that contains 2-non-homologous atoms (oxygen and nitrogen) and structure formula compounds:



1,3-oxazepine

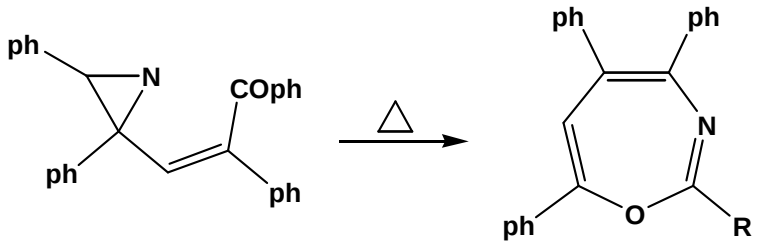
H. Abid et. al. [55,56] prepared new ways to build up this 7-membered heterocyclic ring system.

A. Hussein et. al.[57], discovery of the activity of 1,4-benzodiazepine on the central nervous system (CNS).

1.5.1 Synthesis of oxazepines:

Oxazepine and number of its derivatives were prepared by different methods such as:

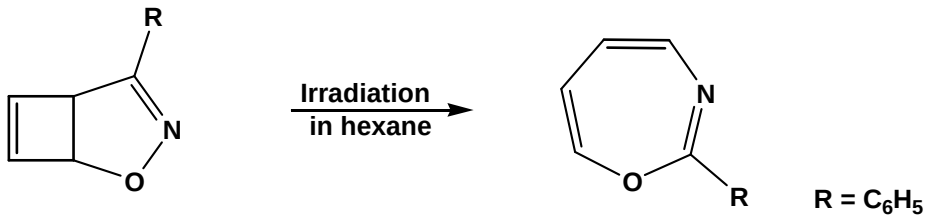
Le Roux et. al. [58], synthesized oxazepines in 90% [M_2] through heating of [M_1] in 100 ^{o}C.



[M_1] **[M_2]**

Tetraphenyl (Z) keto vinylazine **4,5,7-tetraphenyl-2-sub-1,3-oxazepine**

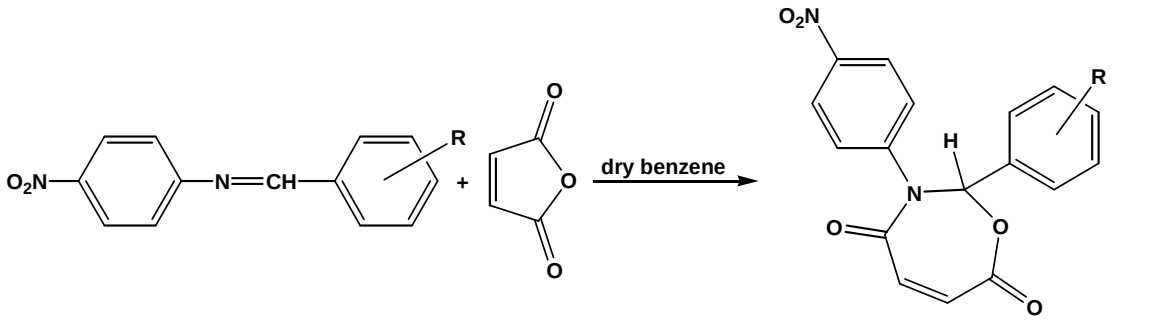
Kumagai et. al. [59], synthesized oxazepines through photochemical reaction of [M_1] as shown in the following equation:



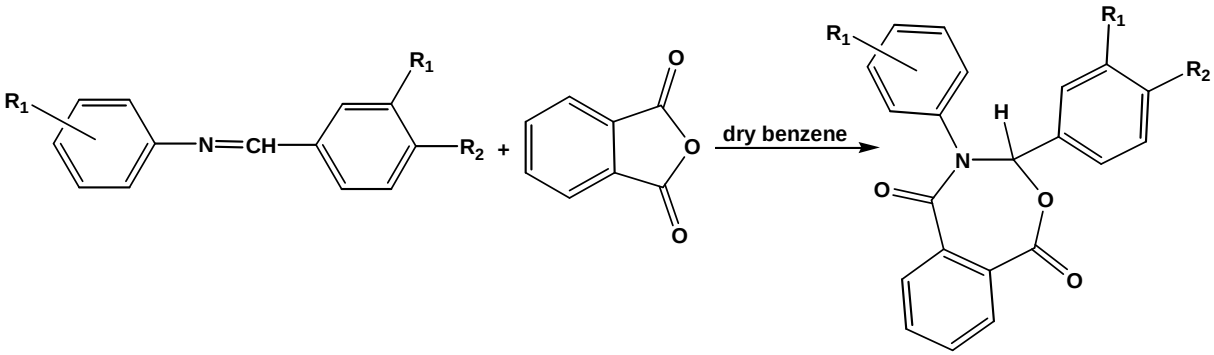
[M_3] **[M_4]**

2-oxa-3-azabicyclo [3.2.0] hepta-3,6-dione **2-Sub-1,3-oxazepine 80% yield**

Hussein and ***Obaid*** [55,56] prepared oxazepindione from the reaction of Schiff bases with maleic or phthalic anhydride in dry benzene.



Schiff bases **Maliec anhydride** **1,3-Oxazepine**



Schiff bases **Phthalic anhydride** **R_1 , R_2 , R_3 = Many different sub**

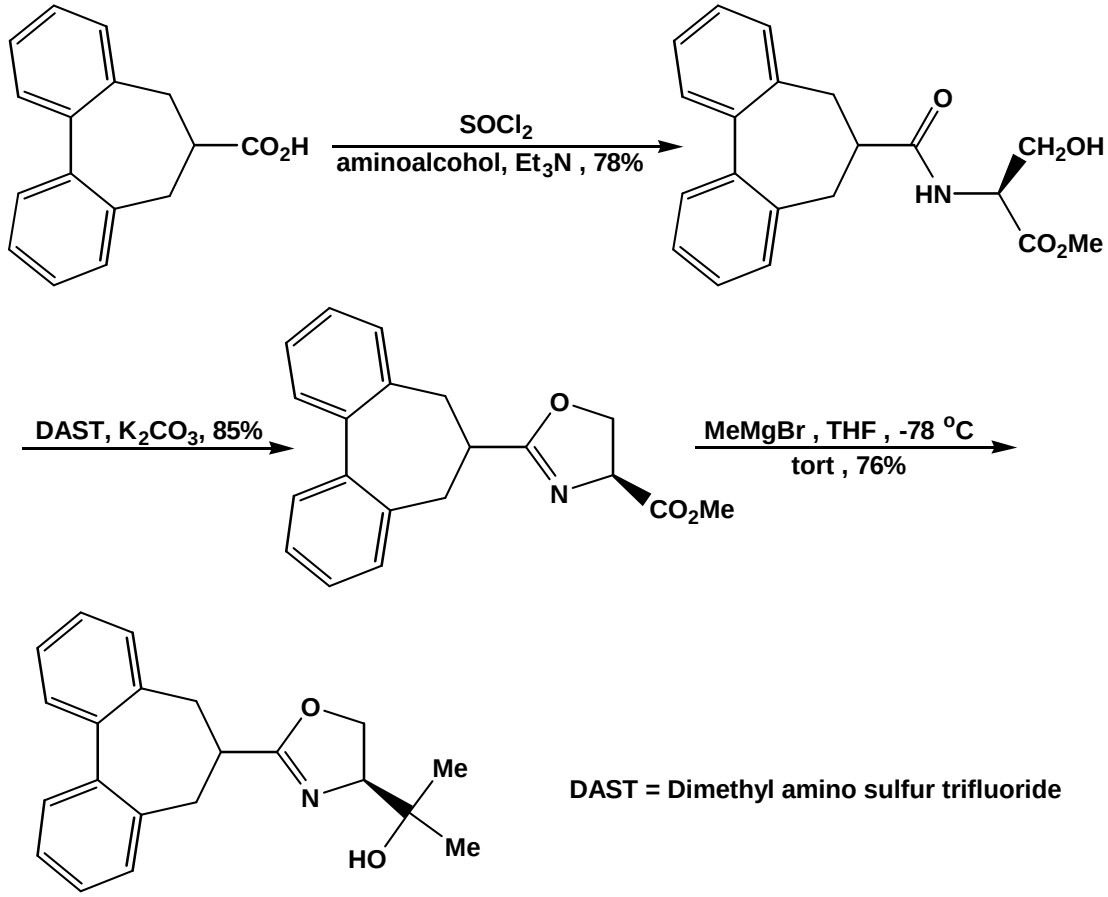
1.6.0 Oxazolines:

Oxazoline is one of a class of organic heterocyclic compounds containing a five member one unsaturated ring structure composed of one oxygen atom and one nitrogen atom, oxazoline can be represented by two forms [60].

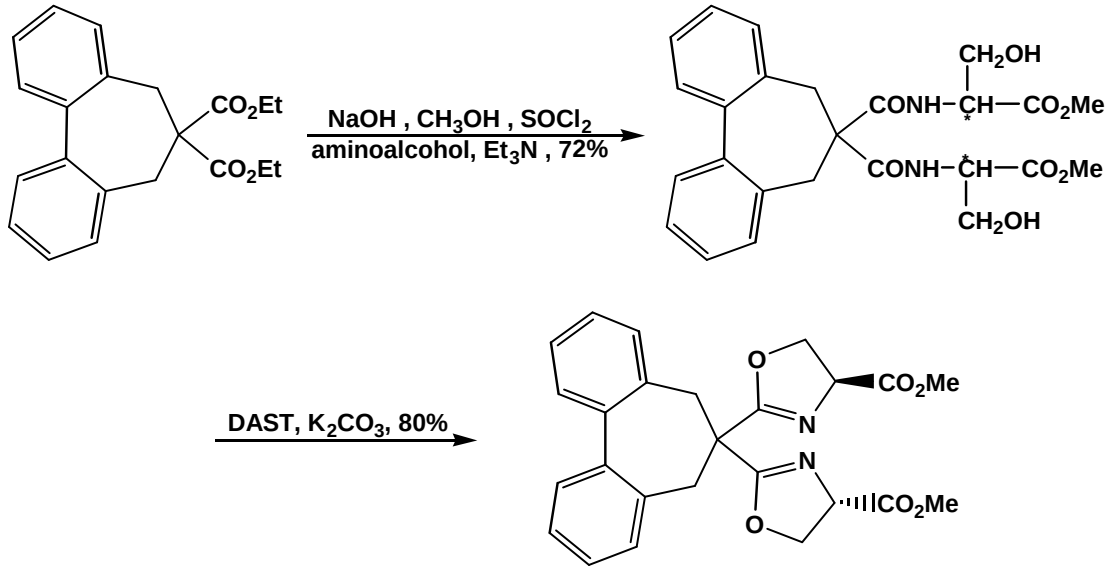
1,3-Oxazoline

1.6.1 Synthesis of oxazoline:

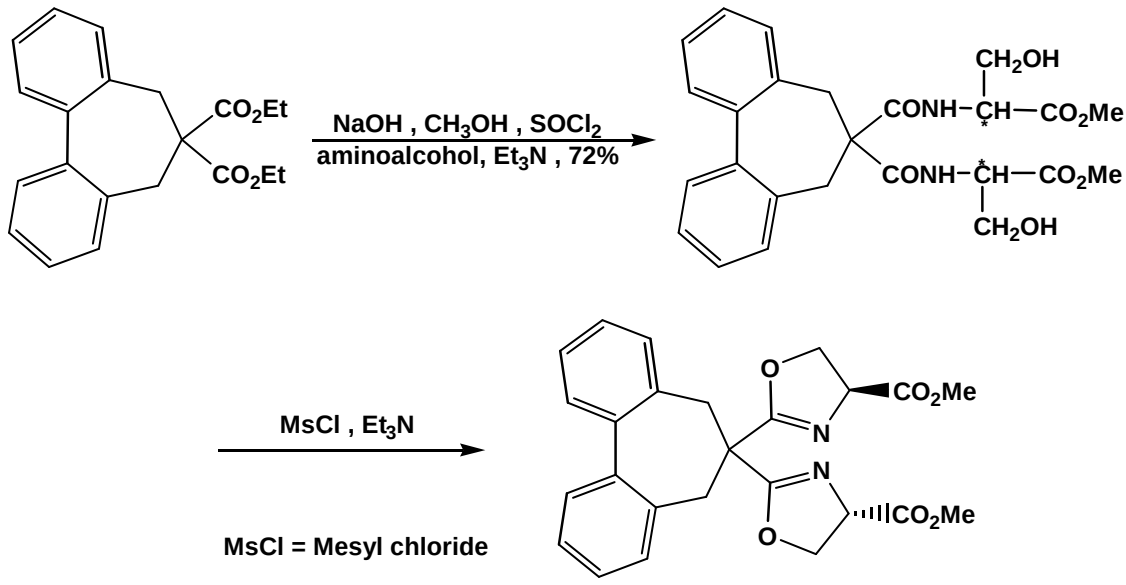
The mono-oxazoline ligands were obtained according to the above similar procedure from a mono acid [61,62].



Williams et. al. [63], synthesize bis (oxazoline) biscarboxylate in high yield from treatment of dihydroxy diamide with a slight excess of the dehydrating agent, dimethylaminosulfur trifluoride (DAST) at -78 ^{o}C in CH_2Cl_2 followed by addition of K_2CO_3 and warming to room temperature.



The compound below which bear tert-butyl on the oxazoline ring was also synthesized following the same procedure using MsCl, Et_3N instead.



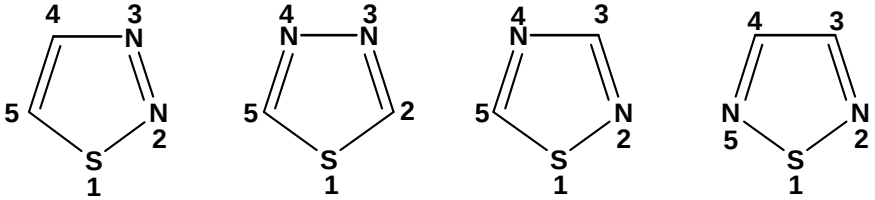
1.6.2 Oxazoline uses:

Chiral oxazolines especially chiral bis (oxazoline), have been widely applied in many catalytic asymmetric reaction as versatile ligands[64,65].

Oxazoline-base ligands were also found to be effective for the asymmetric addition of diethyl zinc to aldehydes [64,67]. In particular the ligand combining the oxazoline ring and hydroxyl group or an amino group have been reported to show excellent catalytic activity in the asymmetric addition of diethyl zinc to aldehydes [69-75].

1.7.0 Thiadiazoles:

Thiadiazole is the five-membered diunsaturated ring composed of two nitrogen atoms and one sulfur atom. There are four isomeric[76] types: 1,2,3-thiadiazole (I); 1,3,4-thiadiazole (II); 1,2,4-thiadiazole (III) and 1,2,5-thiadiazole (IV).



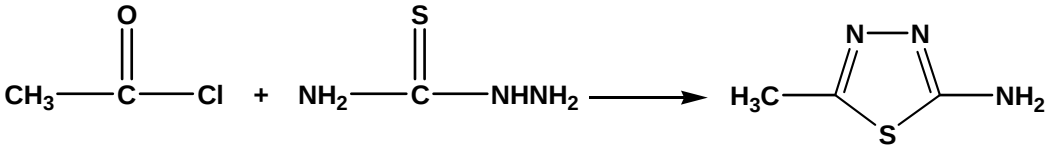
A glance at the standard references show that more studies have been carried out on the 1,3,4-thiadiazoles. Members of this ring system have found their ways into such diverse applications as pharmaceutical, oxidation inhibitors, cyanine dyes and metal complexing agents [77].

1.7.1 Synthesis of 1,3,4-thiadiazoles:

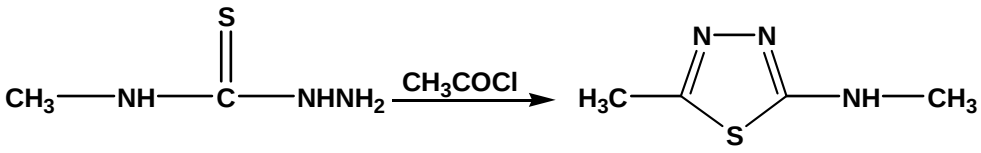
Synthesis of 2-amino-1,3,4-thiadiazole:

Many synthetic methods were used for preparing 2-amino-1,3,4-thiadiazole from thiosemicarbazide and substituted thiosemicarbazide.

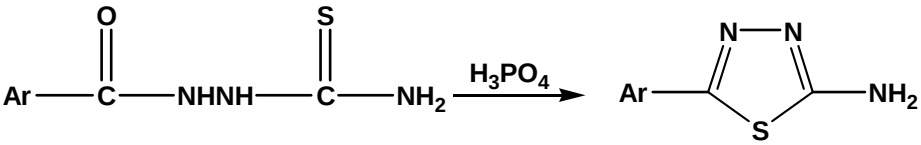
Freund and ***Meincke*** [78] cyclized thiosemicarbazide directly to 2-amino-5-methyl-1,3,4-thiadiazole through the reaction with acetyl chloride.



Pulvermacher [79] had earlier shown that acetyl chloride could bring about the cyclization of alkyl or aryl substituted thiosemicarbazide, for example the reaction of acetyl chloride with 4-methyl thiosemicarbazide produces 2-methyl amino-5-methyl-1,3,4-thiadiazole.

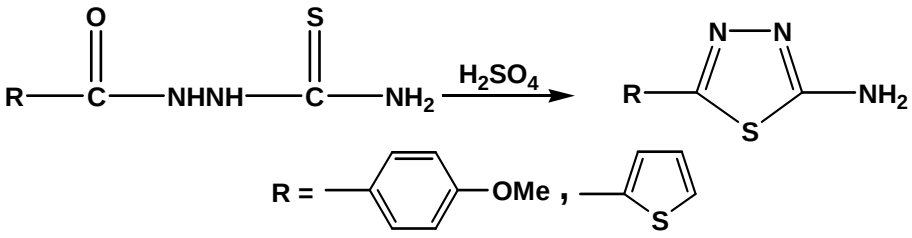


Hoggarth [80] prepared a number of 2-amino-5-arylthiadiazoles by cyclization of substituted thiosemicarbazide using phosphoric acid as dehydrating agent.

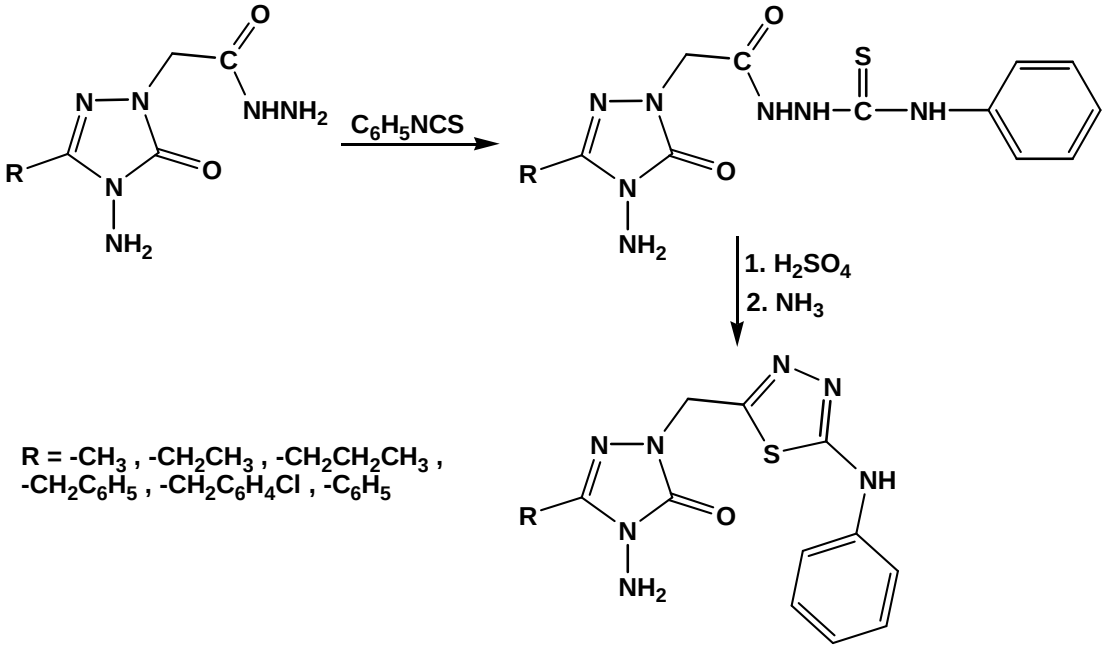


Ar =4-MeC$_6$H$_4$, 4-MeC$_6$h$_4$

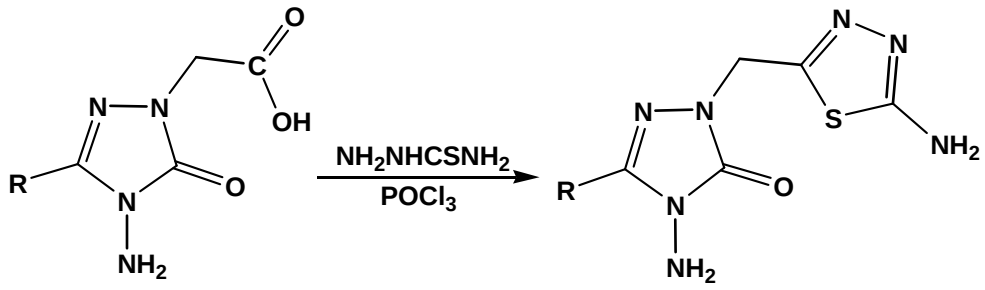
Cyclization of acyl thiosemicarbazide with hot sulfuric acid gave substituted 2-amino-1,3,4-thiadiazole [81].



Neslihan Demirbas [82] synthesized derivatives of 1,3,4-thiadiazole from the reaction of (4-amino-3-substituted-5-oxo-4,5-dihydro-1H-1,2,4-triazol-1-yl) acetic acid hydrazide with phenyl isothiocyanate and the resulting thiosemicarbazide derivatives were cyclized using sulfuric acid.



Neslihan Demirbas [83] also synthesized derivatives of 2-amino-1,3,4-thiadiazole from the reaction of (4-amino-3-substituted-5-oxo-4,5-dihydro-1H-1,2,4-triazole-1-yl) acetic acid with thiosemicarbazide in phosphorus oxychloride to give 1,3,4-thiadiazole ring.

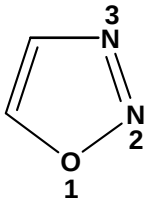


1.7.2 Biological activity of thiadiazoles:

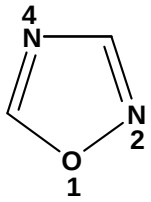
The growing patent literature from the sixties demonstrates that the 1,3,4-thiadiazoles are becoming of great interest, this is primarily due to the large number of uses of 1,3,4-thiadiazoles in the most diverse areas, for example in drug synthesis, scintillation materials, dye stuffs industry, photography and corrosion inhibitors. Numerous 1,3,4-thiadiazoles have been synthesized and reported to be biologically versatile compounds having bactericidal, fungicidal, muscle relaxant properties…etc., some 1,3,4-thiadiaozles derivatives possess central nervous system (CNS) depressant activity [80,84].

1.8.0 Oxadiazoles:

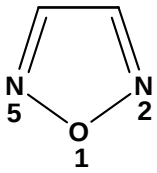
Oxadiazoles are five-membered ring compounds with three atoms one oxygen atom and two nitrogen atoms. The oxadiazole ring has four[85] isomers as shown below:



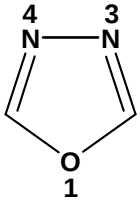
1,2,3-oxadiazole



1,2,4-oxadiazole



1,2,5-oxadiazole



1,3,4-oxadiazole

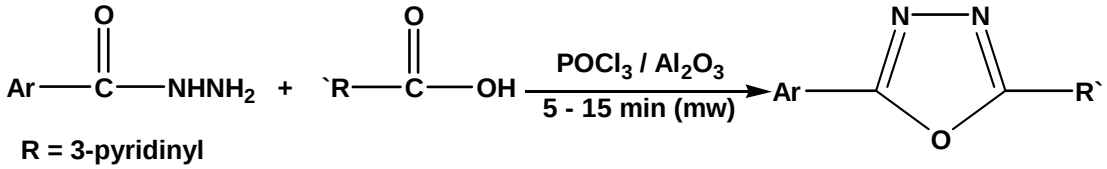
1,3,4-Oxadiazole is the most thermally stable isomer which has attracted special attention, this is primarily due to the large number of uses in many diverse areas, including drugs, scintillation materials, dyes[86] and surface active agents [87].

1.8.1 Synthesis of 2,5-disubstituted-1,3,4-oxadiazoles:

Several methods have been used to synthesize 1,3,4-oxadiazoles. Among these the following are most important methods:

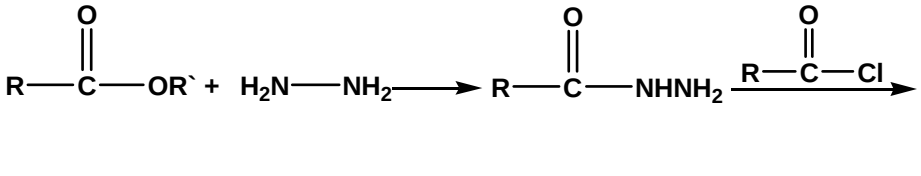
Dehydration of acid hydrazides:

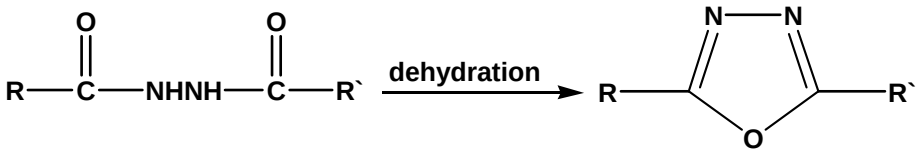
Carlson and ***Jorgensen*** [88] synthesized a number of 2,5-disubstituted-1,3,4-oxadiazole under microwave irradiation through the reaction of variable hydrazides with different carboxylic acids in the presence of phosphorous oxychloride. This method provides an excellent approach for the safe, rapid, inexpensive and simple synthesis medically important 2,5-disubstituted-1,3,4-oxadiazole.



R = 3-pyridinyl
R` = different groups

Acid hydrazides are usually prepared from the reaction of corresponding esters with hydrazine hydrate. These hydrazides are converted to di-acid hydrazides through their reaction with appropriate acid chlorides. The di-acid hydrazides are established to be the most convenient precursors for the synthesis of substituted 1,3,4-oxadiazole[89].

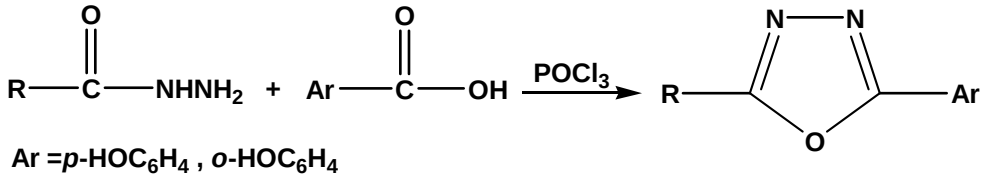




R = Many different substituents
R` = CH_3 , C_2H_5

Variant conditions influence the dehydration reaction, typically the reaction is promoted by heat and anhydrous agents including thionyl chloride or phosphorous oxychloride.

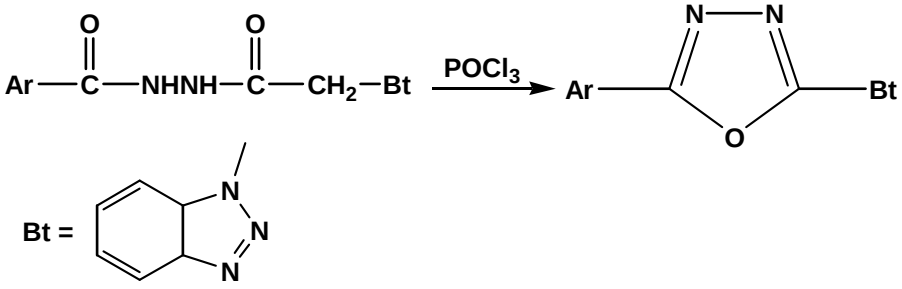
Recently 2,5-disubstituted-1,3,4-oxadiazoles have been synthesized by a route in which acid hydrazide was condensed with appropriate aromatic acid and phosphorous oxychloride.



Ar =*p*-HOC_6H_4 , *o*-HOC_6H_4

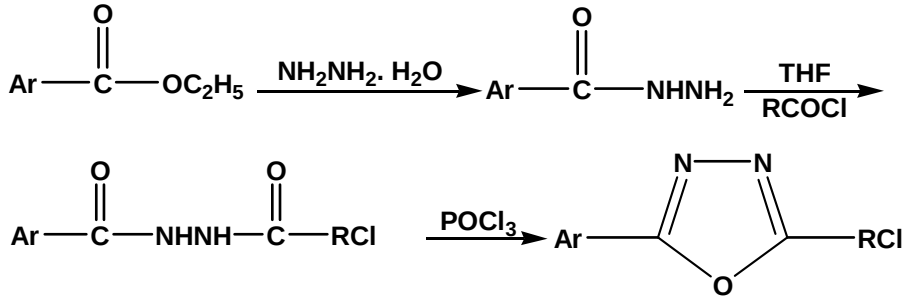
In the last few years, a great number of 1,3,4-oxadiazole derivatives were synthesized, the following examples include some of these compounds.

Katritzky [90] synthesized 1-[5-phenyl(1,3,4-oxadiazole-2-yl) methyl]-1H-benzotriazole by reaction of unsymmetrical diacylhydrazines with phosphorous oxychloride to form 1-[1,3,4-oxadiazole-2-yl) methyl]-1H-benzotriazole.



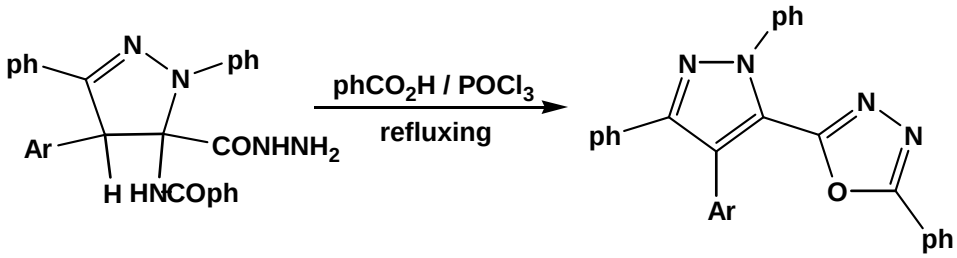
Ar = ph , 4-MeC_6H_4 , 4-$MeOC_6H_4$, 4-BrC_6H_4

Cao [91] synthesized 5-aryl-2-chloromethyl-1,3,4-oxadiaozles by cyclodehydration of N-chloroacetyl-N-aryl hydrazines in boiling $POCl_3$.



R = C_6H_5 , 4-$C_2H_5C_6H_4$, 4-ClC_6H_4 , 4-FC_6H_4 , 2-FC_6H_4 ,
2,4-Cl-2,4(Cl_2)-5-C_6H_2 , 4-$CH_3OC_6H_4$, 4-$NO_2C_6H_4$

Mansour [92] prepared 5-phenyl-2-(1,3,4-triphenyl pyrazole-5-yl)-1,3,4-oxadiazole by treatment of 4-aryl-5-benzoylamino-1,3-diphenyl-Δ^2-pyrazdine-5-carbohydrazides with benzoic acid and phosphorus oxychloride. The reaction was found to proceed via concurrent cyclocondensation and elimination of a benzamide molecule.

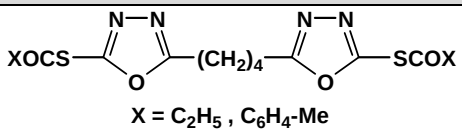
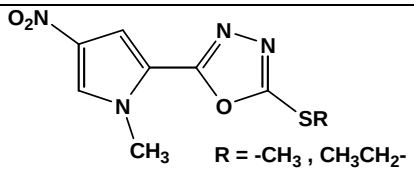
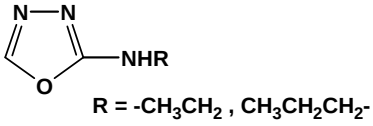
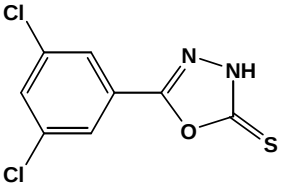
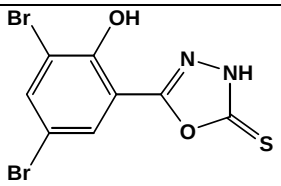


Ar = C_6H_5 , 2-$CH_3OC_6H_4$

1.8.2 Biological activity of 1,3,4-oxadiazoles:

The biological significance of oxadiazole ring is well documented in the literature. Thus, it has been shown that many substituted-1,3,4-oxadiazoles have biological and medical uses as antibacterial [93], antifungal [94], antimalarial [95,96] and anti-inflammatory [97] activities when probably substituted in (2) and (5) positions. Further, it was suggested that (-SH) group attached to a heterocyclic nucleus may include fungicidal activity [98]. Table (1-2) show the biological activity of some derivatives of 1,3,4-oxadiazoles.

Table (1-2): Biological activity of some oxadiazole derivatives.

No.	Name	Structure	Biological activity	Ref.
1	5,5`-(1,4`-Butene)bis-[1,3,4-oxadiazole-2-thiol substituent]		Antimicrobial activity	99
2	2-(1-Methyl-4`-nitro pyrrayl)-5-alkylthio-1,3,4-oxadiazole		Effective drugs against tropical diseases	100
3	N-Alkylated-2-amino-1,3,4-oxadiazole		Antimitotic activity	101
4	5`(2`,4-Dichlorophenyl)-1,3,4-oxadiazol-2-thione		Fungi toxic activity	102
5	5`(2`-Hydroxy-3`,5`-dibromophenyl)-1,3,4-oxadiazol-2-thione		Monomine oxidase and succinate dehydrogenase inhibitory	103

The aim of the Work:

Five, six and seven membered heterocyclic compounds have been of great interest on account of their variety of applications particularly in the field of chemotherapeutic, antimicrobial, pesticidal, agriculture and fungicide, therefore, the present work was directed toward the synthesis of new derivatives containing heterocyclic ring, starting from 2-mercapto benzothiazole.

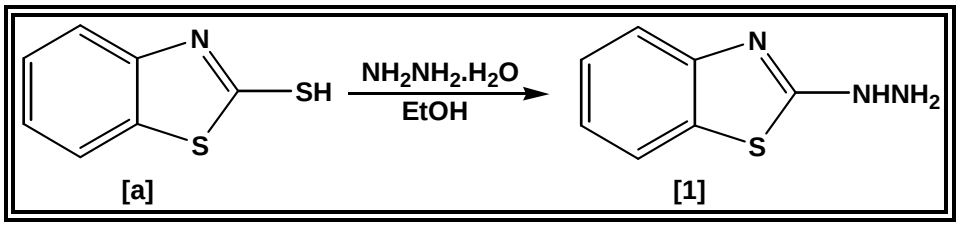
Such derivatives are expected to have high biological activity.

CHAPTER THREE

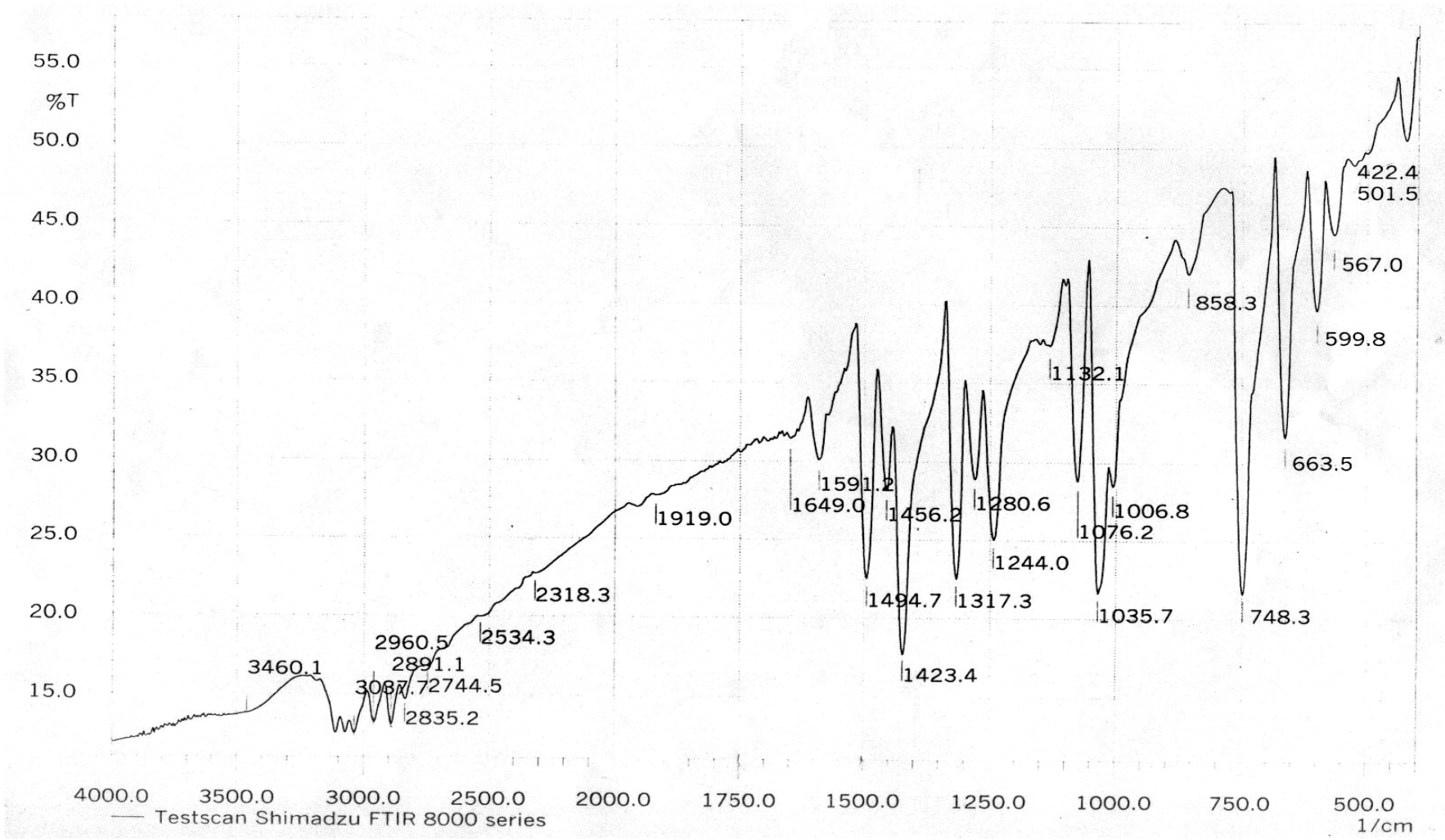
RESULTS AND DISCUSSION

3.1.1 Preparation of 2-hydrazino benzothiazole [1]:

2-Mercapto benzothiazole with hydrazine hydrate in ethanol was refluxed for 6 hours to afford the hydrazine benzothiazole [1]. The structure of the hydrazine benzothiazole [1] was confirmed from its melting point and F.T.IR spectrum.



The F.T.IR spectrum of compound [1] indicates the disappearance of the thiol bond at (2534.3 cm^{-1}) and appearance of doublet bands of NH_2 group asymmetric and symmetric at (3313.5, 3201.6 and ν NH stretching band at 3128.3 cm^{-1}). Figures (3-a) show the F.T.IR of 2-mercapto benzothiazole and (3-1) shows the F.T.IR spectrum of compound [1].



Melting point: 177-179^{o}C

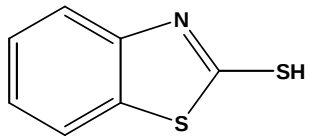
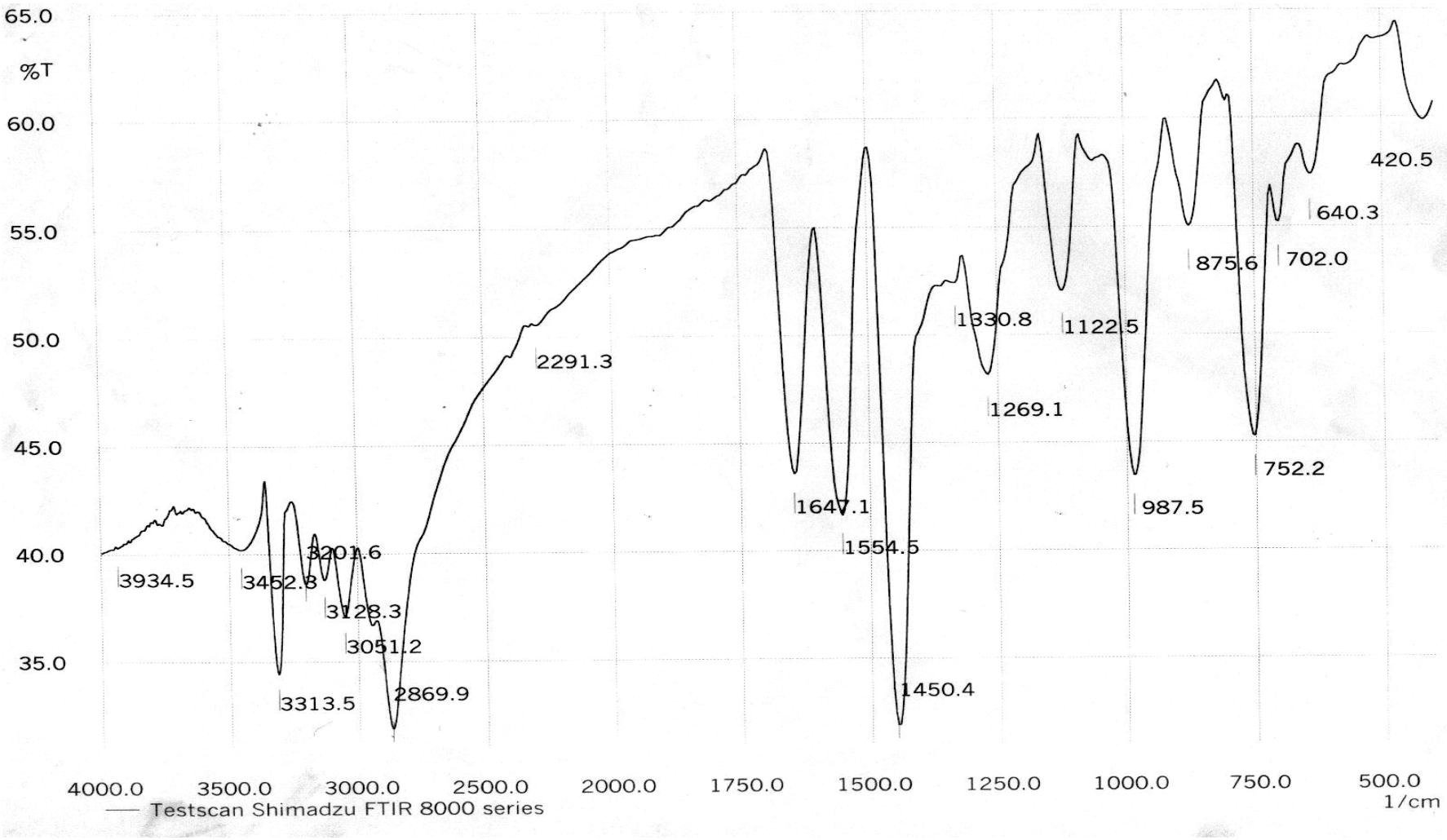


Figure (3-a): Structure, Physical Properties and F.T.IR spectrum of 2-mercapto benzothiazole.



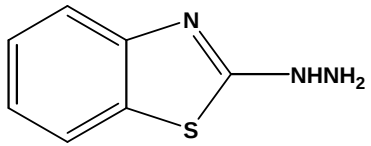
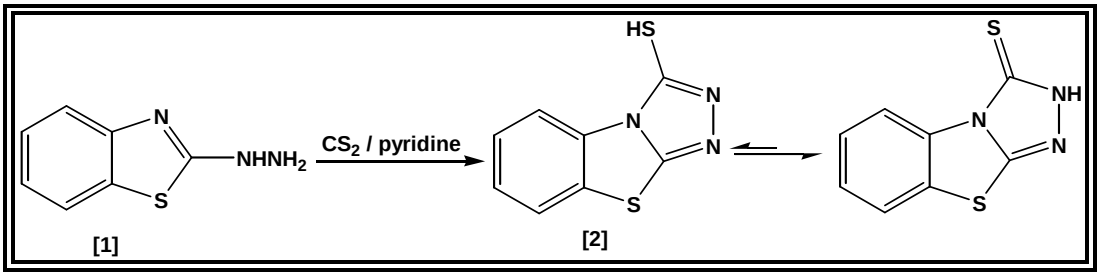
Melting point: 203-205 ^{o}C	
Yield: 80%	

Figure (3-1): Structure, Physical Properties and F.T.IR spectrum of 2-hydrazino benzothiazole [1].

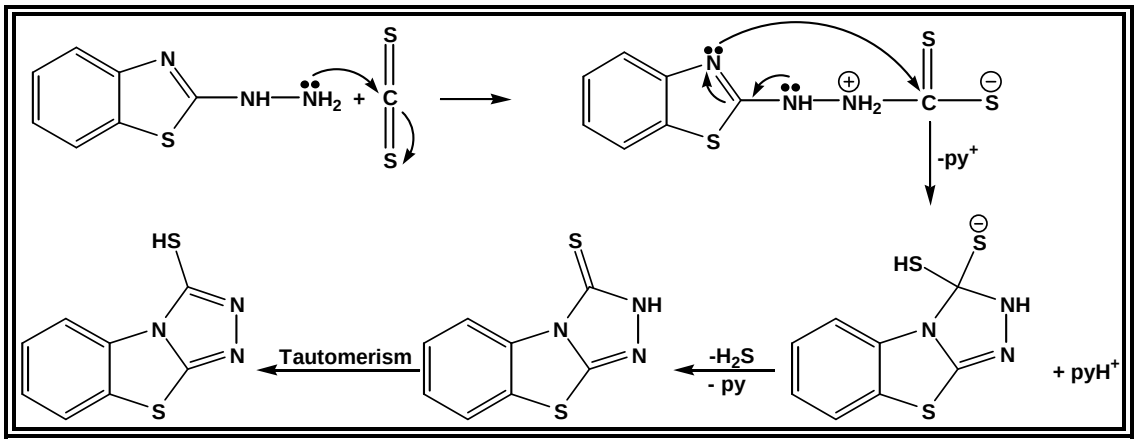
3.1.2 Preparation of 2-mercapto-1,3,4-triazole benzothiazole [2]:

Compound [2] was synthesized from the reaction of compound [1] with carbon disulfide and pyridine. The compound was characterized by F.T.IR spectrum.

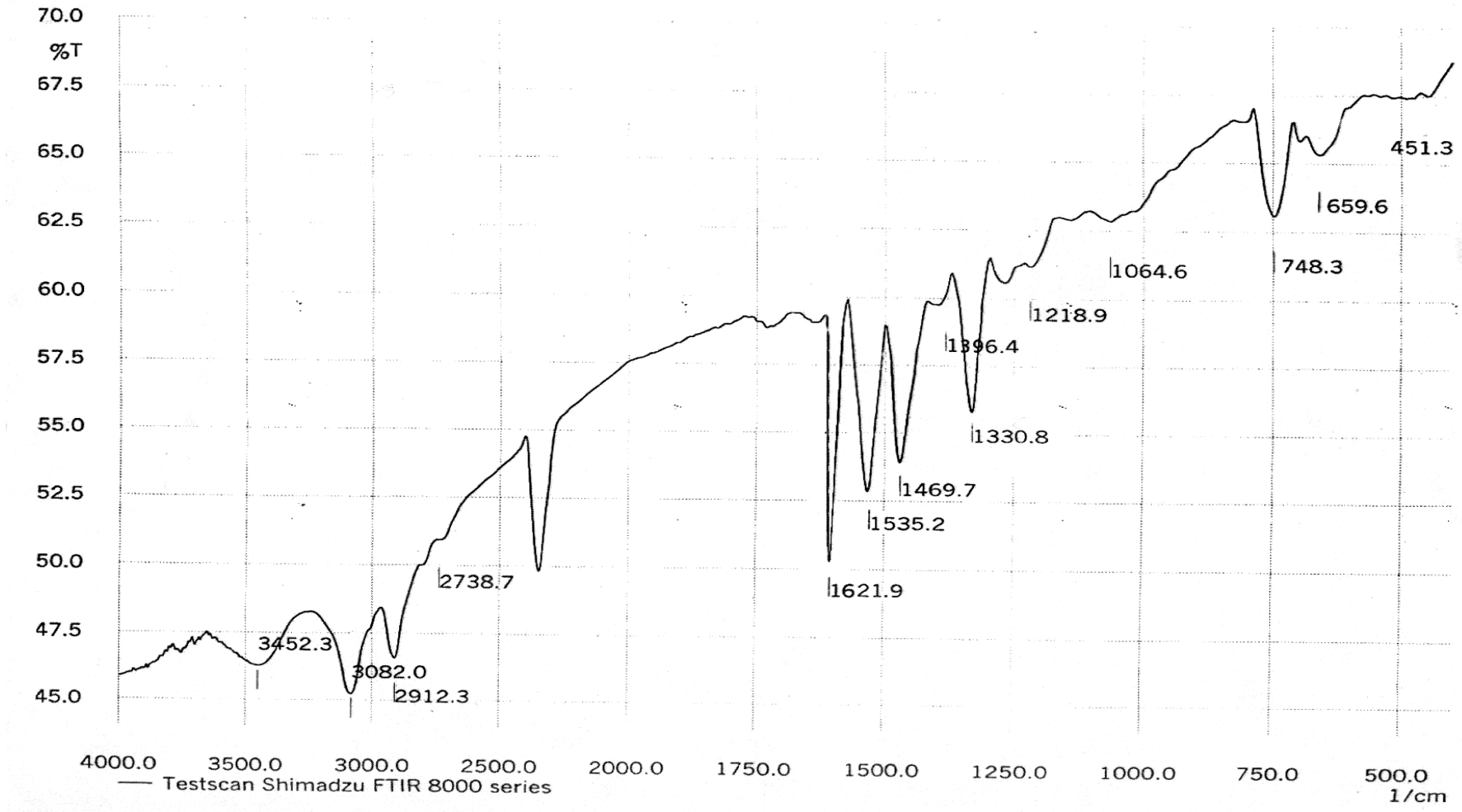


The F.T.IR spectrum of compound [2] indicated the disappearance of NH_2 band at (3313.5 and 3201.6 cm^{-1}) of the starting material of compound [1] and appearance of a thione band at (1330.8 cm^{-1}) and N-H of the tautomerizm appeared at (3082.0 cm^{-1}). Figure (3-2) shows the F.T.IR spectrum of compound [2].

The suggested mechanism of the reaction is shown in Scheme (3-1).



Scheme (3-1): Mechanism steps for the preparation of compound [2].



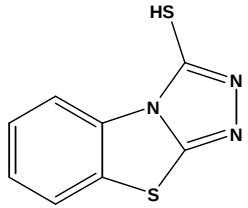
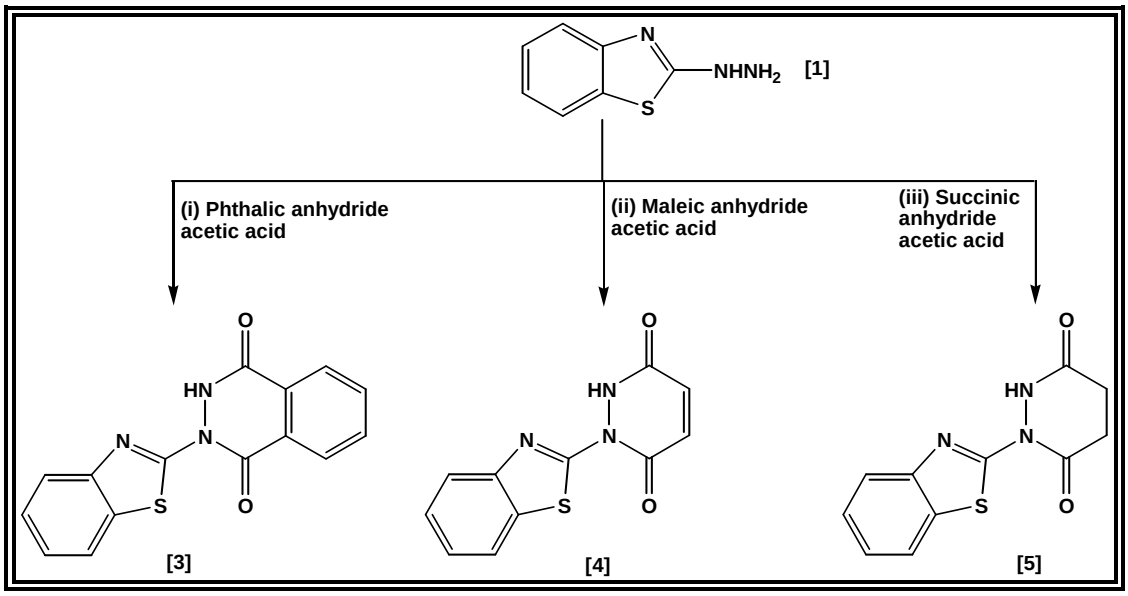
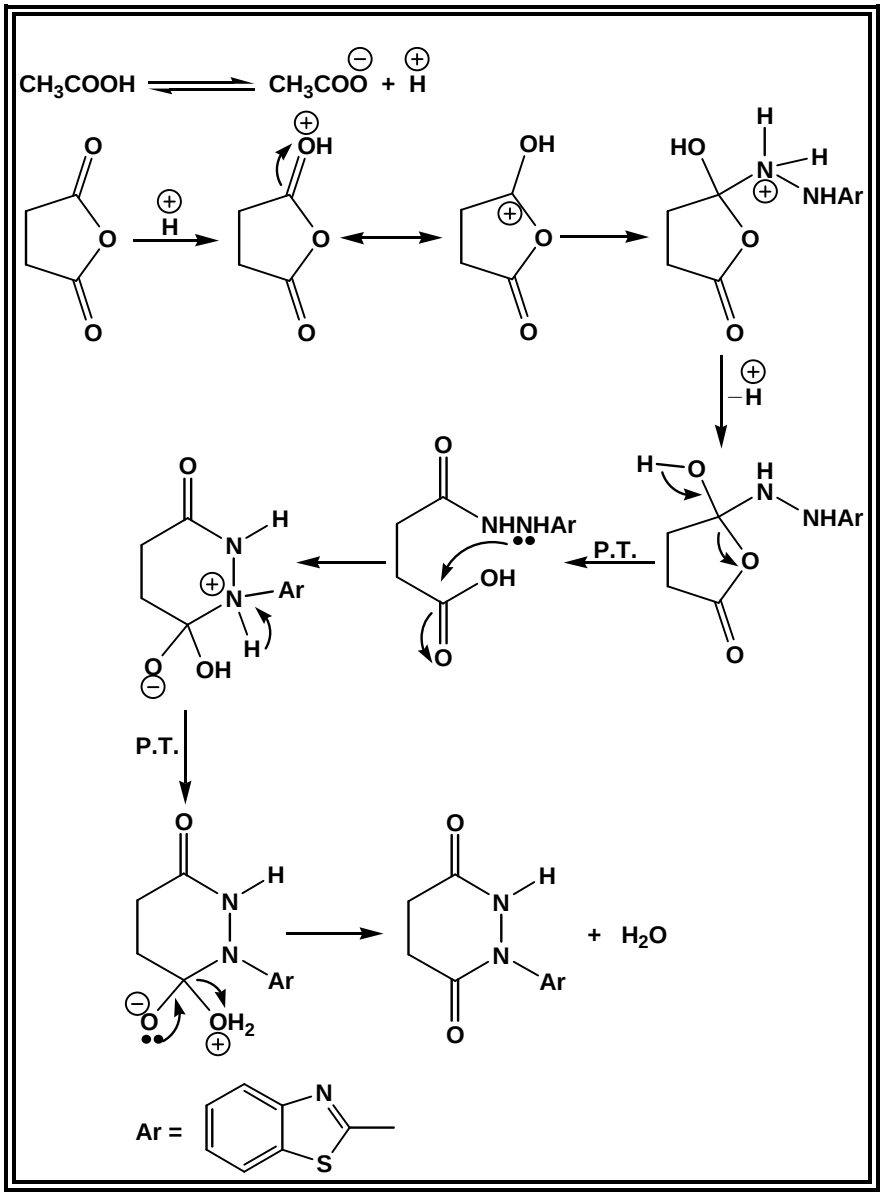
Melting point: 243-245 ^{o}C	
Yield: 85%	

Figure (3-2): Structure, Physical Properties and F.T.IR spectrum of 2-mercapto-1,3,4-triazole benzothiazole [2].

3.1.3 Preparation of phthalazine and pyridazin-dione derivatives [3], [4] and [5]:

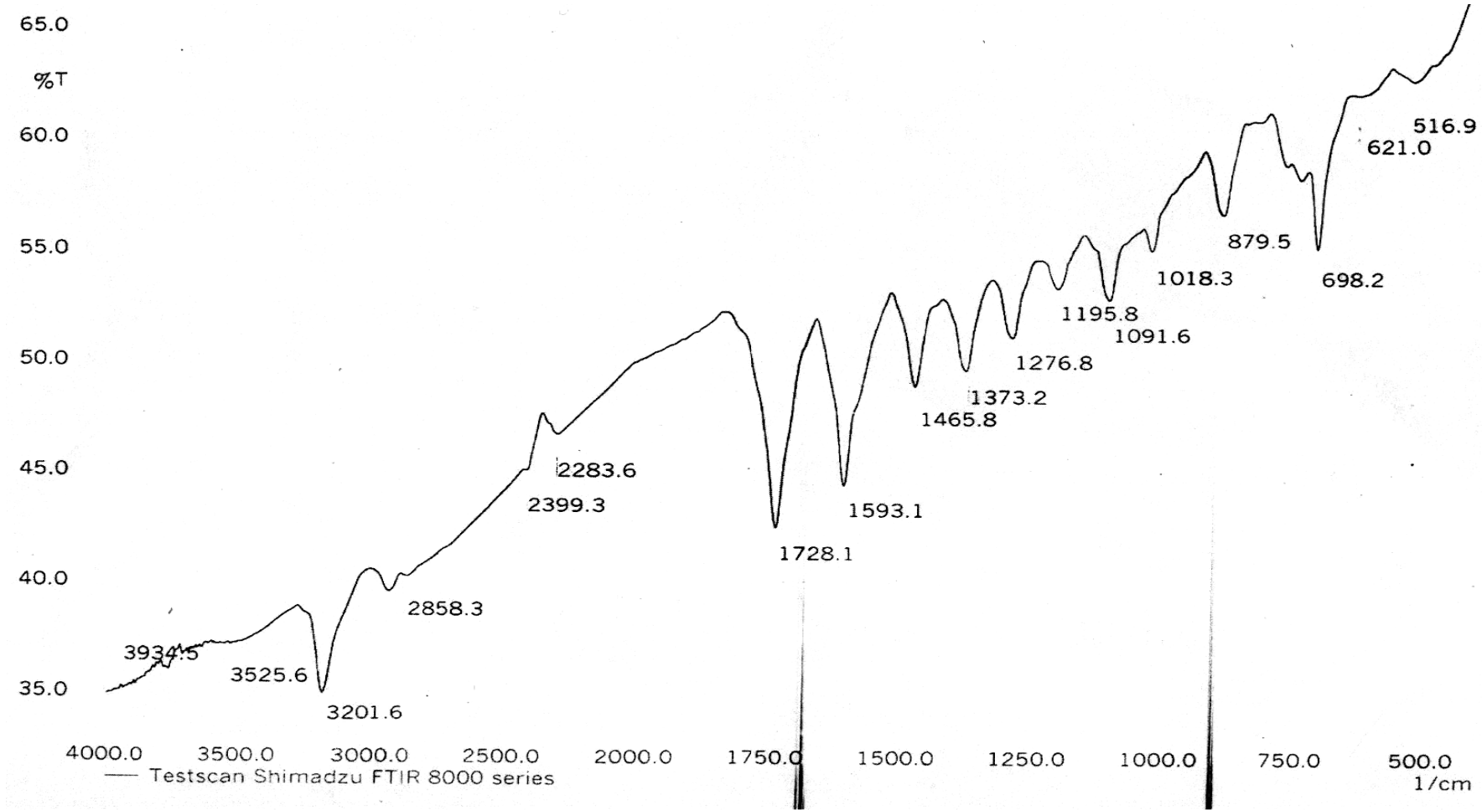


Compounds [3], [4] and [5] were synthesized from the reaction of compound [2] with phthalic anhydride, maleic anhydride and succinic anhydride respectively in the presence of acetic acid as solvent and catalyst. The suggested mechanism for the synthesis of the compound [5] derivatives can be explained as follows. In the first step of the reaction, a protonation process takes place by the acid, followed by a nucleophilic attack by the hydrazide on the carbon atom bearing the positive charge. Losing a proton and rearrangement lead to cyclization with losing a water molecule. The suggested mechanism of the reaction is shown in Scheme (3-2). Similarly the formation of compounds [3] and [4] were followed the same mechanism as in compound [5].



Scheme (3-2): Mechanism steps for the preparation of compounds [5].

The F.T.IR spectrum of compounds [3], [4] and [5] indicated the disappearance of NH_2 band (3313.5 and 3201.6 cm^{-1}) of the starting material [1] and appearance of N-H band at (3201.6 cm^{-1}) and carbonyl group band at (1728.1 cm^{-1}) in compound [3], N-H band at (3244.0 cm^{-1}) and carbonyl group at (1735.8 cm^{-1} in compound [4], and N-H band at (3205.0 cm^{-1} and carbonyl group at (1690.3 cm^{-1}) in compound [5]. Figures (3-3), (3-4) and (3-5) show the F.T.IR spectrum of compounds [3], [4] and [5].



Melting point: 212-214 ^{o}C

Yield: 72%

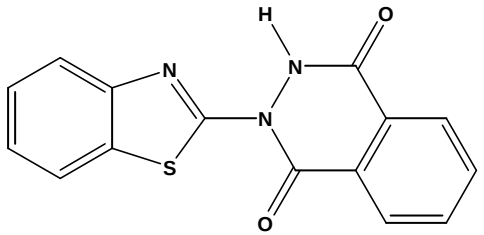
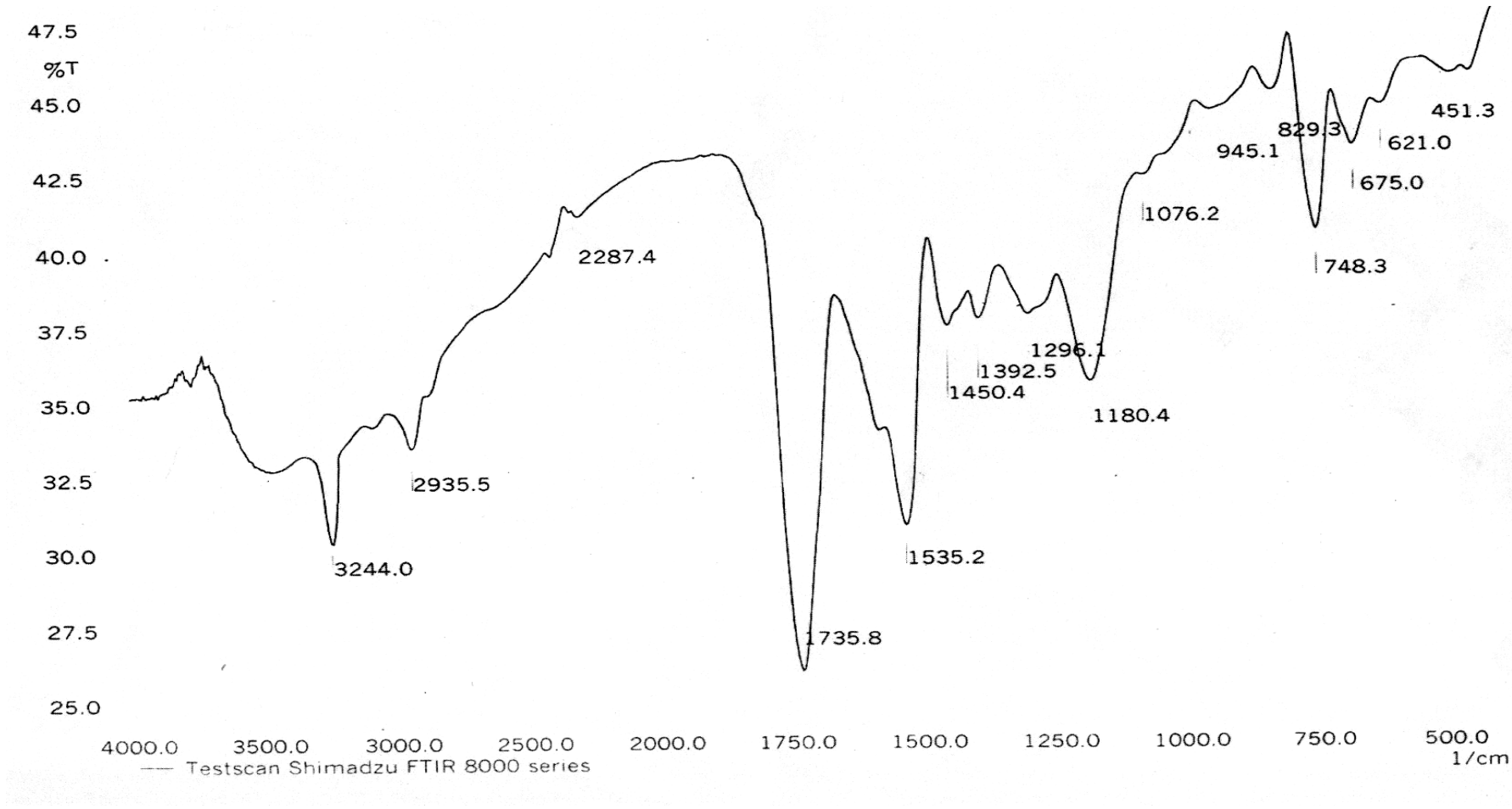


Figure (3-3): Structure, Physical Properties and F.T.IR spectrum of 1-benzothiazole-2-hydrophthalazin-3,4-dione [3].



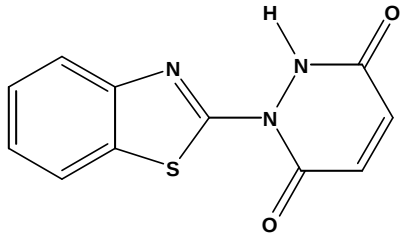
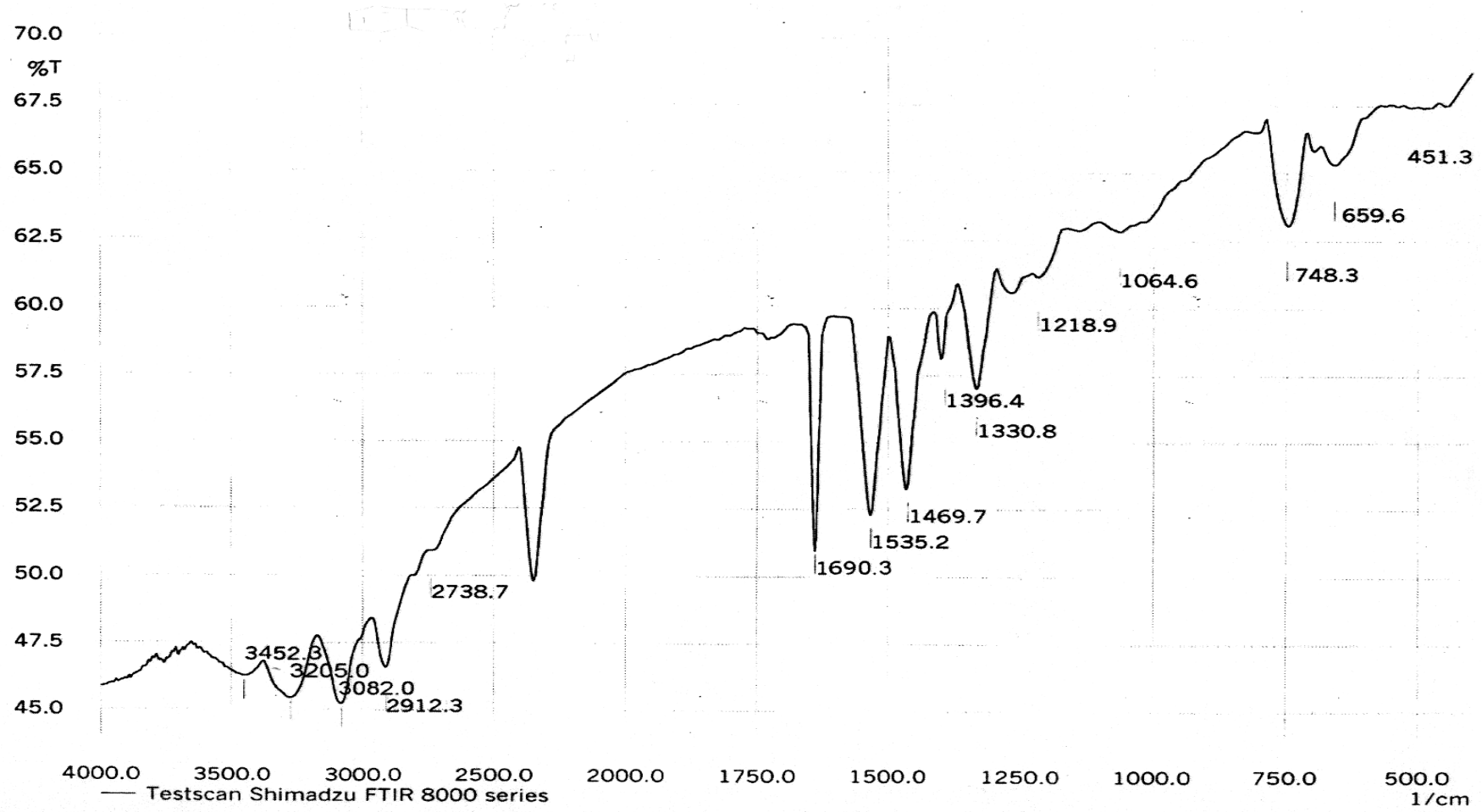
Melting point: 193-195 ^{o}C	
Yield: 70%	

Figure (3-4): Structure, Physical Properties and F.T.IR spectrum of 1-benzothiazole-2-hydro pyridazine-3,6-dione [4].



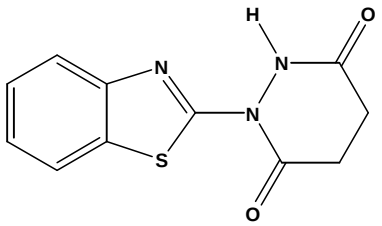
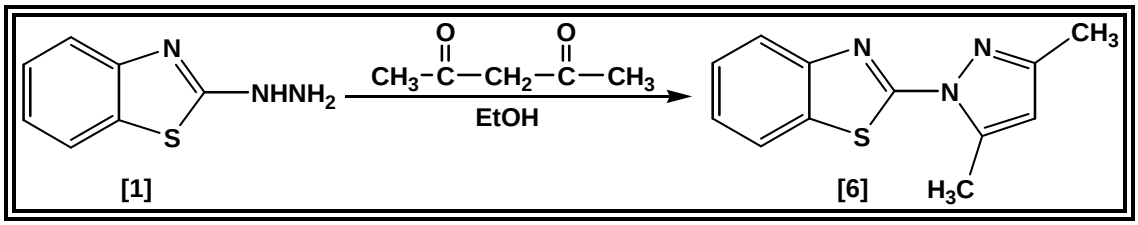
Melting point: 161-163 ^{o}C	
Yield: 65%	

Figure (3-5): Structure, Physical Properties and F.T.IR spectrum of 1-benzothiazole 2,4,5-trihydro pyridazine-3,6-dione [5].

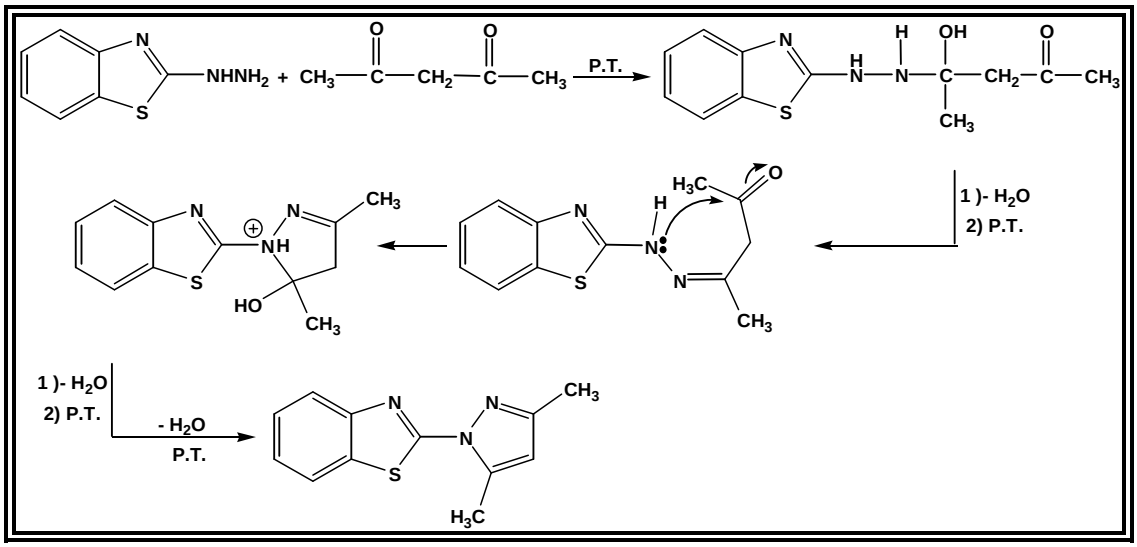
3.1.6 Preparation of 1-benzothiazol-3,5-dimethyl pyrazole [6]:

Compound [6] was synthesized from the reaction of compound [1] with acetyl acetone in the presence of acetic acid using absolute ethanol as solvent. The compound was characterized by its melting point and F.T.IR spectroscopy.

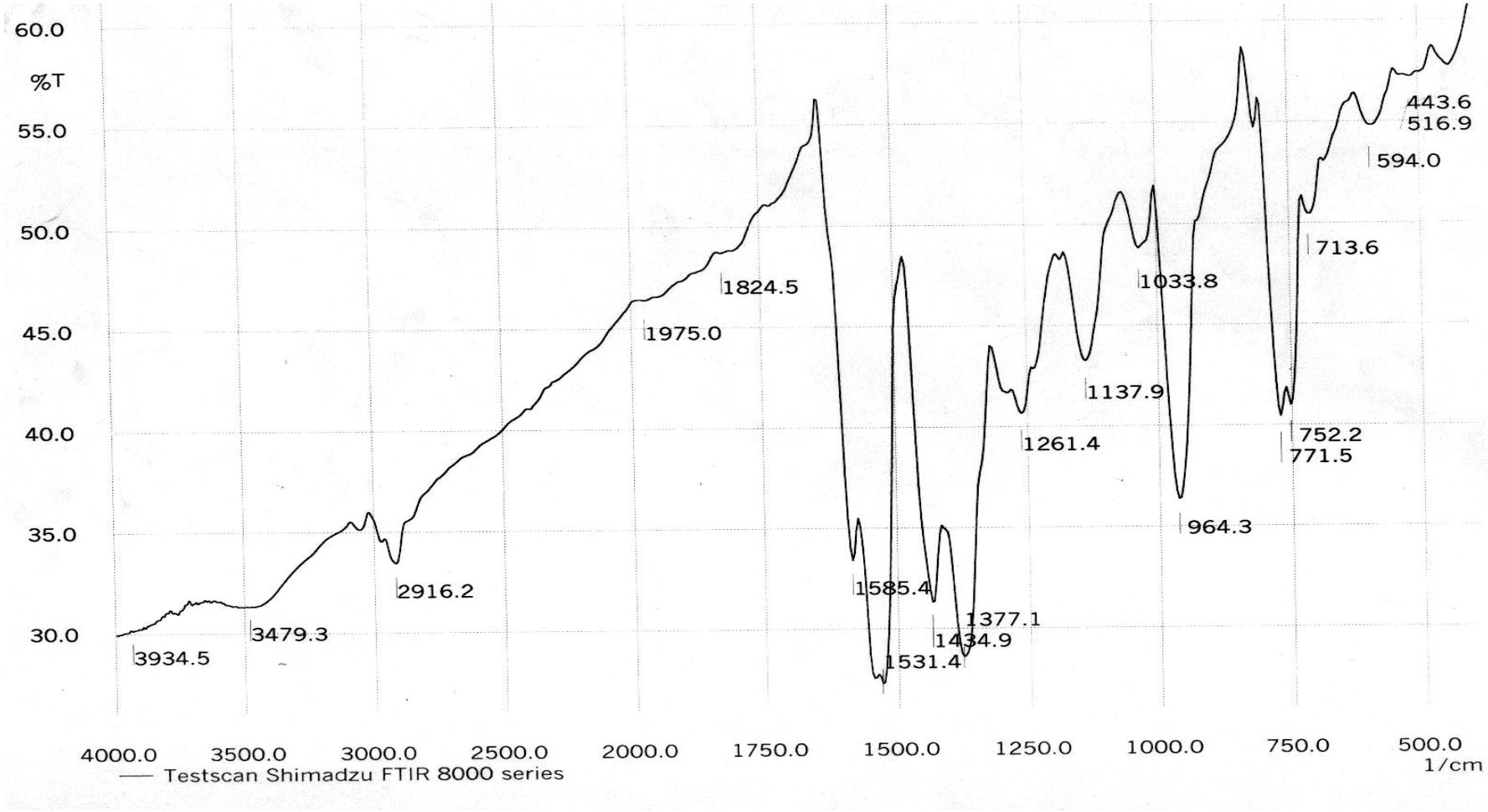


The F.T.IR spectrum of compound [6] indicated the disappearance of NH_2 bands (3313.5 and 3201.6 cm^{-1}) of the starting material and the appearance of the C=N band at (1585.4 cm^{-1}) and C=C at (1531.4 cm^{-1}) and C-H aliphatic (2916.2 cm^{-1}). Figure (3-6) shows the F.T.IR spectrum of compound [6].

The suggested mechanism of the reaction is shown in Scheme (3-3).



Scheme (3-3): Mechanism steps for the preparation of compound [6].



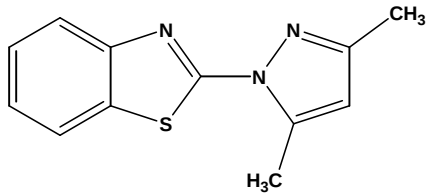
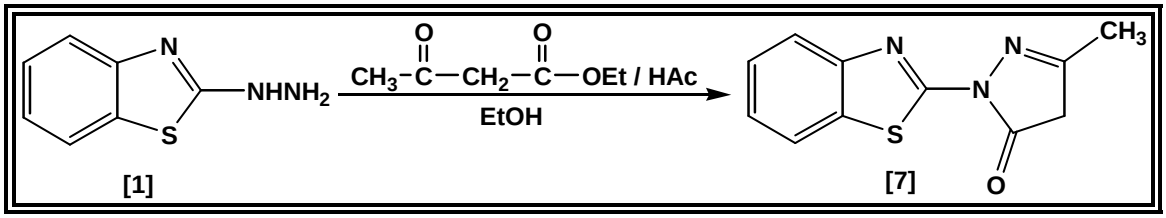
Melting point: 138-140 ^{o}C	
Yield: 86%	

Figure (3-6): Structure, Physical Properties and F.T.IR spectrum of 1-benzothiazol-3,5-dimethyl pyrazole [6].

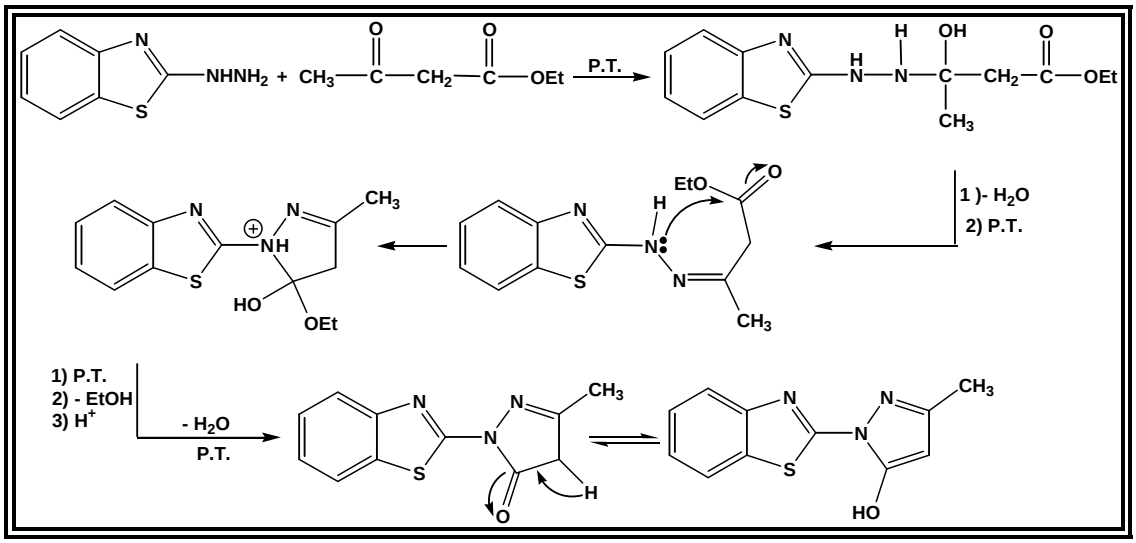
3.1.7 Preparation of 1-benzothiazole-3-methyl pyrazol-5-one [7]:

Compound [7] was synthesized from the reaction of compound [1] with ethyl acto acetate and acetic acid in absolute ethanol. The compound was characterized by its melting point and F.T.IR spectroscopy.

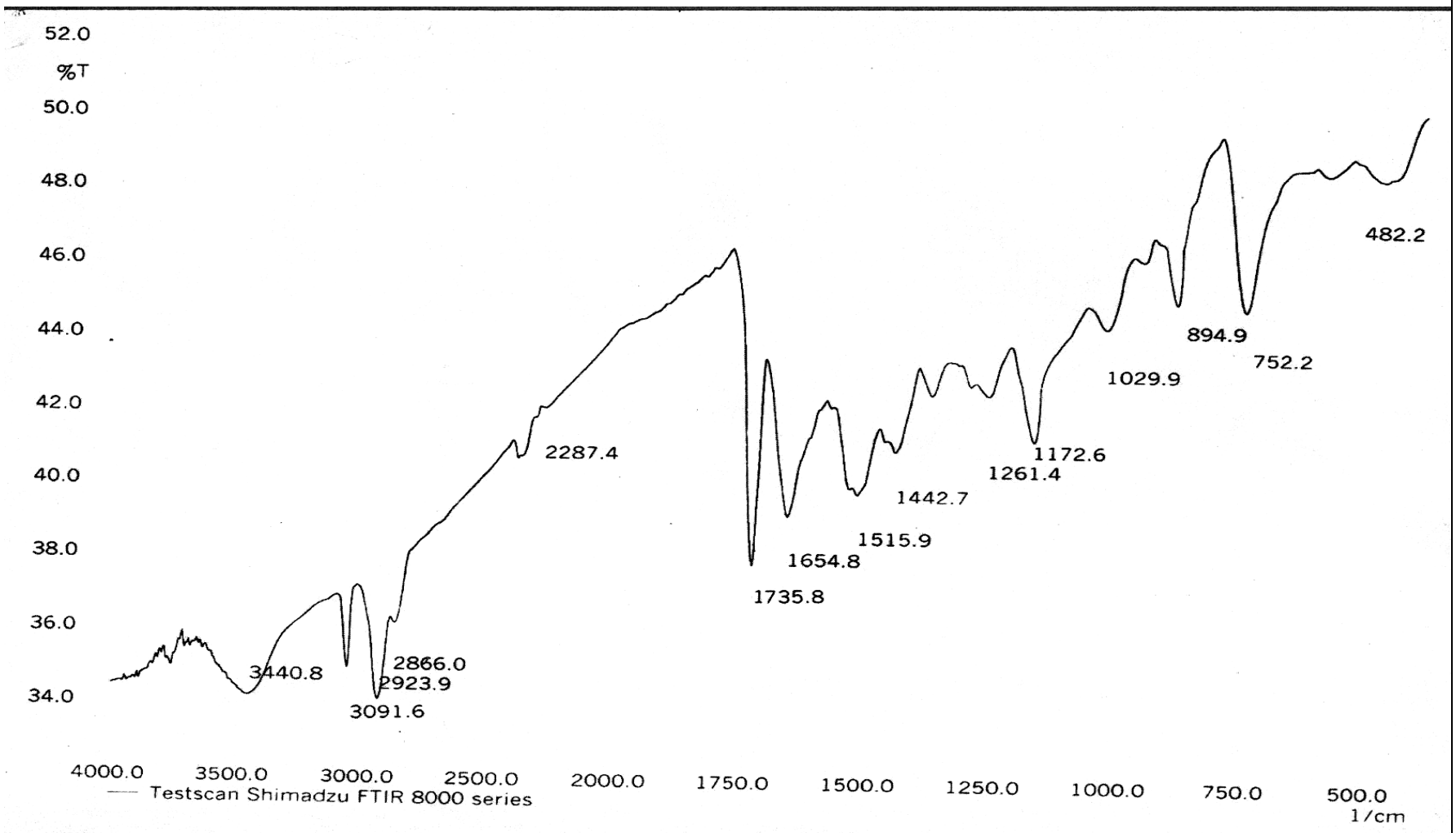


The F.T.IR spectrum of compound [7] indicated the disappearance of NH_2 bands (3313.5 and 3201.6 cm^{-1}) of the starting material and the appearance of carbonyl group band at (1735.8 and N-H band at (3100.0 cm^{-1}) and the C-H aliphatic band at (2923.9 cm^{-1}). Figure (3-7) shows the F.T.IR spectrum of compound [7].

The suggested mechanism of the reaction is shown in Scheme (3-4).



Scheme (3-4): Mechanism steps for the preparation of compound [7].



Melting point: 262-264 °C

Yield: 65%

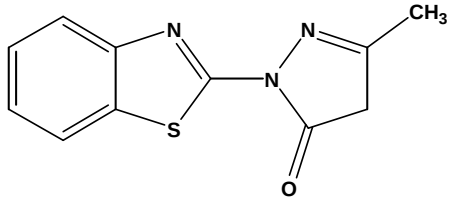
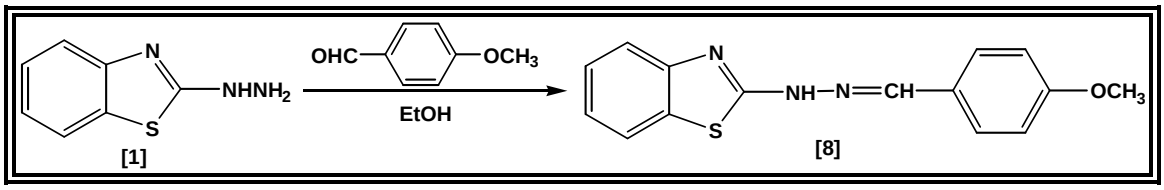


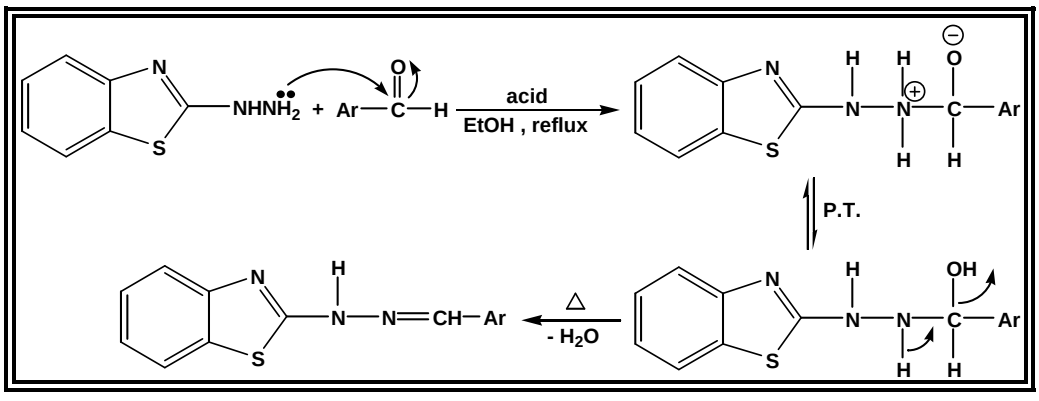
Figure (3-7): Structure, Physical Properties and F.T.IR spectrum of 1-benzothiazole-3-methyl pyrazol-5-one [7].

3.1.8 Preparation of 2-(4-methoxy benzylidine) hydrazine-2-benzothiazole [8]:

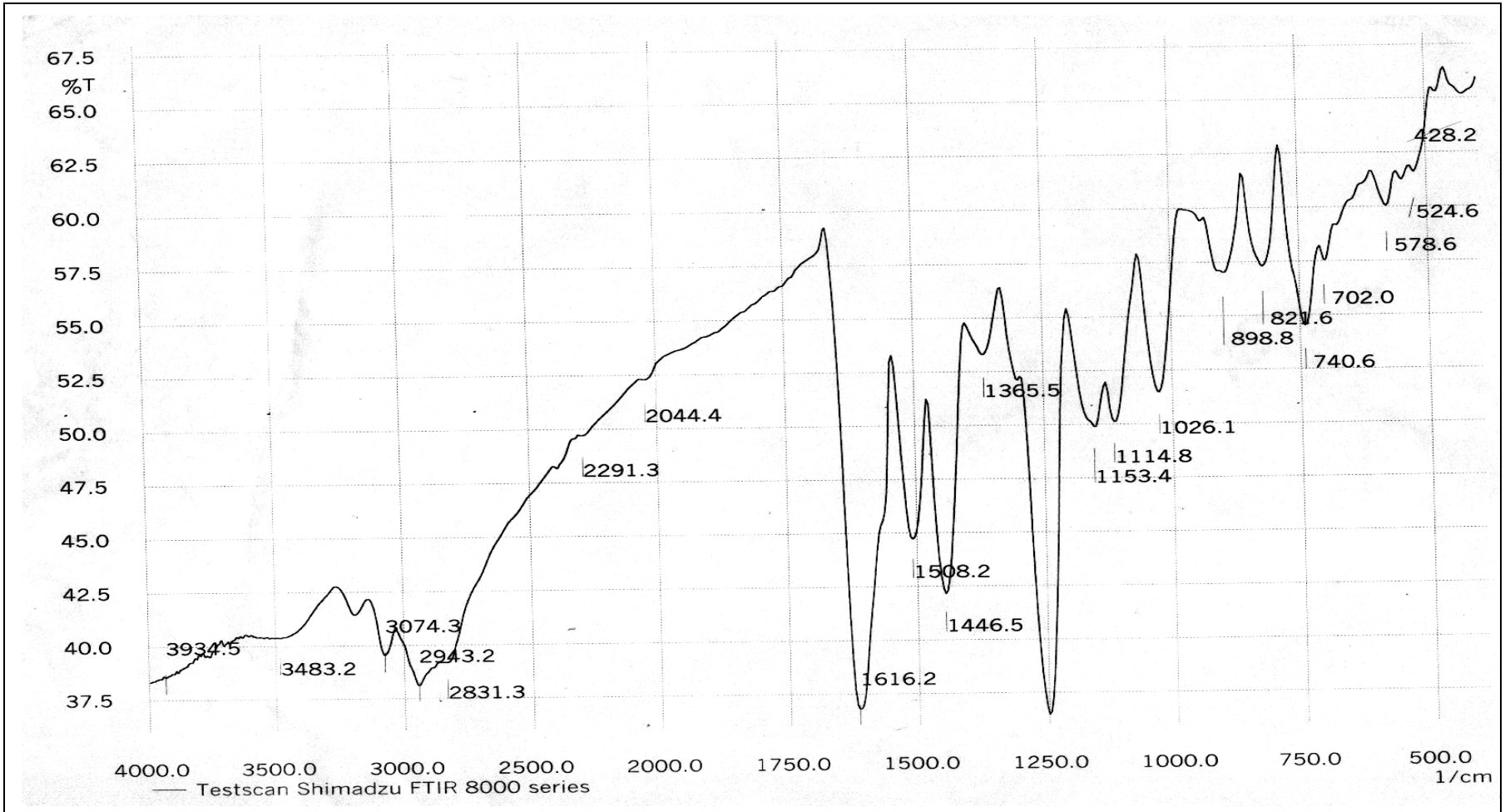
Compound [8] was synthesized from the reaction of compound [1] with 4-methoxy benzaldehyde in absolute ethanol afforded the imine. The compound was characterized by its melting point and F.T.IR spectroscopy.



The F.T.IR spectrum of compound [8] indicated the disappearance of NH_2 bands at (3313.5 and 3201.6 cm^{-1}) of the starting material and the appearance of N-H band at (3199.7 cm^{-1}) and the (*p*-OCH_3) substituted out of plane at (821.6 cm^{-1}) and the C=N band of the imine appeared at (1616.2 cm^{-1}) and the C-H aliphatic (2831.3 cm^{-1}). Figure (3-8) shows the F.T.IR spectrum of compound [8]. The proposed mechanism of the reaction [116] is shown in Scheme (3-5).



Scheme (3-5): Mechanism steps for the preparation of compound [8].



Melting point: 187-189 ^{o}C

Yield: 95%

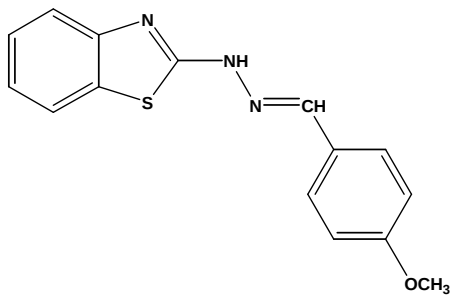
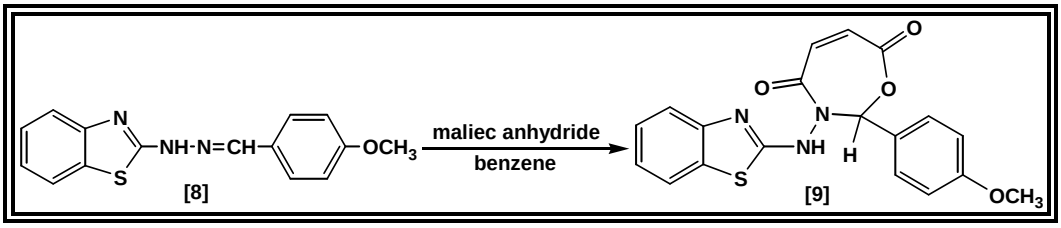


Figure (3-8): Structure, Physical Properties and F.T.IR spectrum of 2-(4-methoxy benzylidine) hydrazine-2- benzothiazole [8].

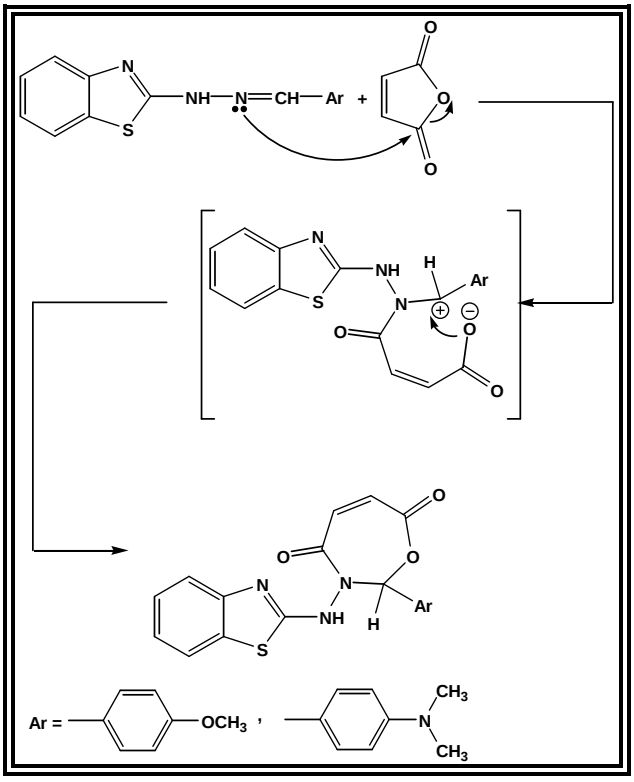
3.1.9 Preparation of 2-[2-(4-methoxyphenyl)-4,7-dione-2,2-dihydro-1,3-oxazepin-3(2H)-yl] benzothiazole hydrazine [9]:

Compound [9] was synthesized from the reaction of compound [8] with maliec anhydride in dry benzene. The compound was characterized by its melting point and F.T.IR spectroscopy.

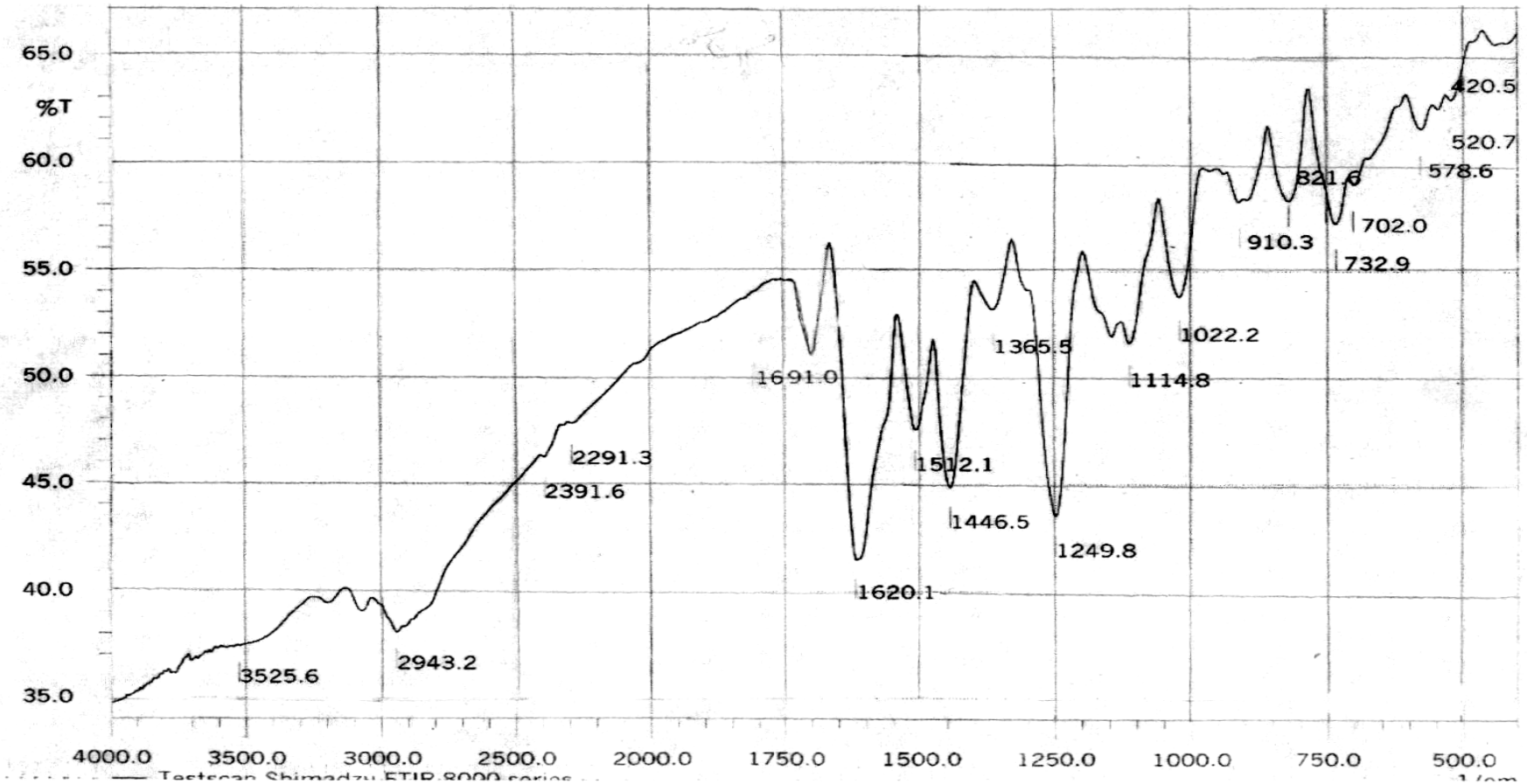


The F.T.IR spectrum of compound [9] was confirmed from the appearance of carbonyl group band at (1691.0 cm^{-1}) and N-H band at (3199.7 cm^{-1}) and C-H aliphatic band at (2943.2 cm^{-1}) and bands at (1249.8 and 1022.2 cm^{-1}) belong to the asymmetric and symmetric (C-O-C) band. Figure (3-9) shows the F.T.IR spectrum of compound [9].

The suggested mechanism of the reaction is shown in Scheme (3-6).



Scheme (3-6): Mechanism steps for the preparation of compound [9].



Melting point: 175-177 ^{o}C

Yield: 85%

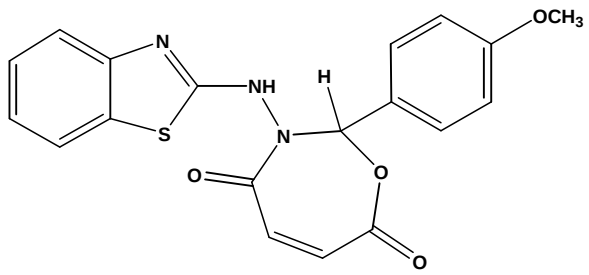
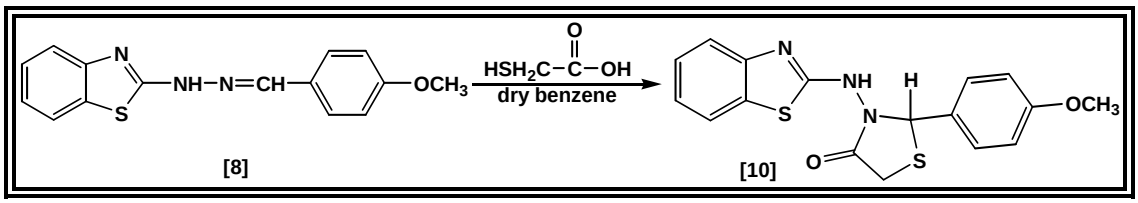


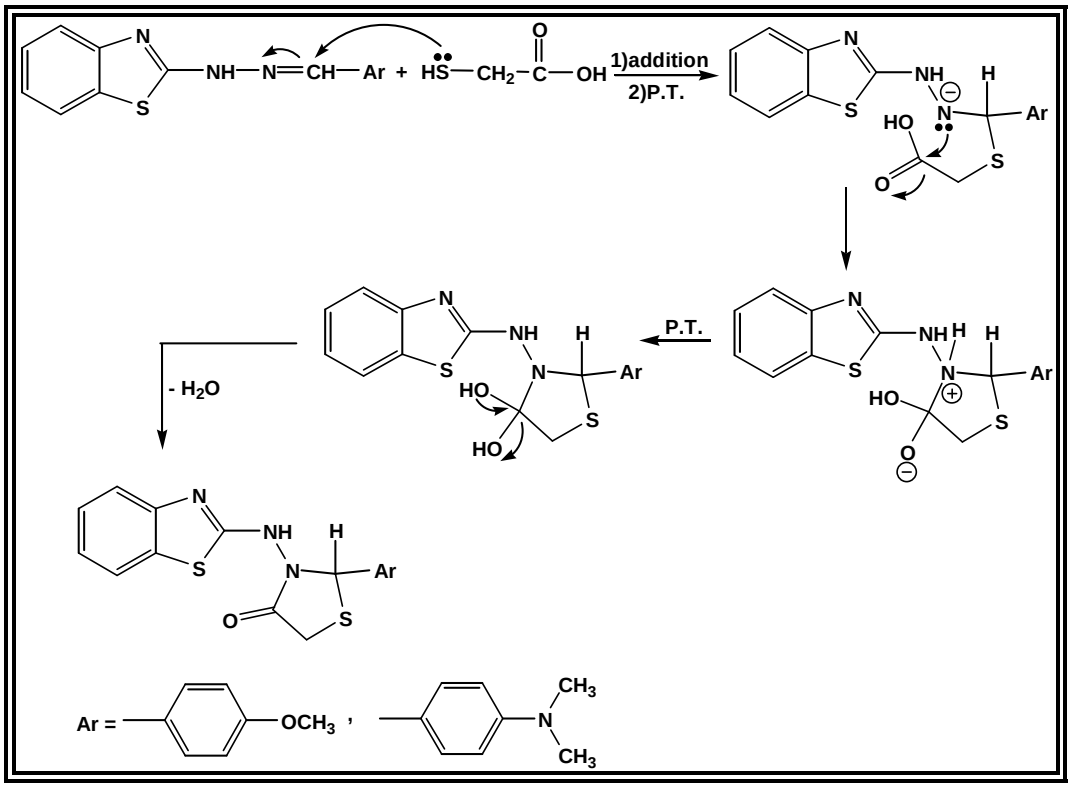
Figure (3-9): Structure, Physical Properties and F.T.IR spectrum of 2-[2-(4-methoxyphenyl)-4,7-dione-2,2-dihydro-1,3-oxazepin-3(2H)-yl] benzothiazole hydrazine [9].

3.1.10 Preparation of 2-[(2`-(4-methoxyphenyl)-4`-oxo-1`,3`-thiazolidin-3`- benzothiazole hydrazine [10]:

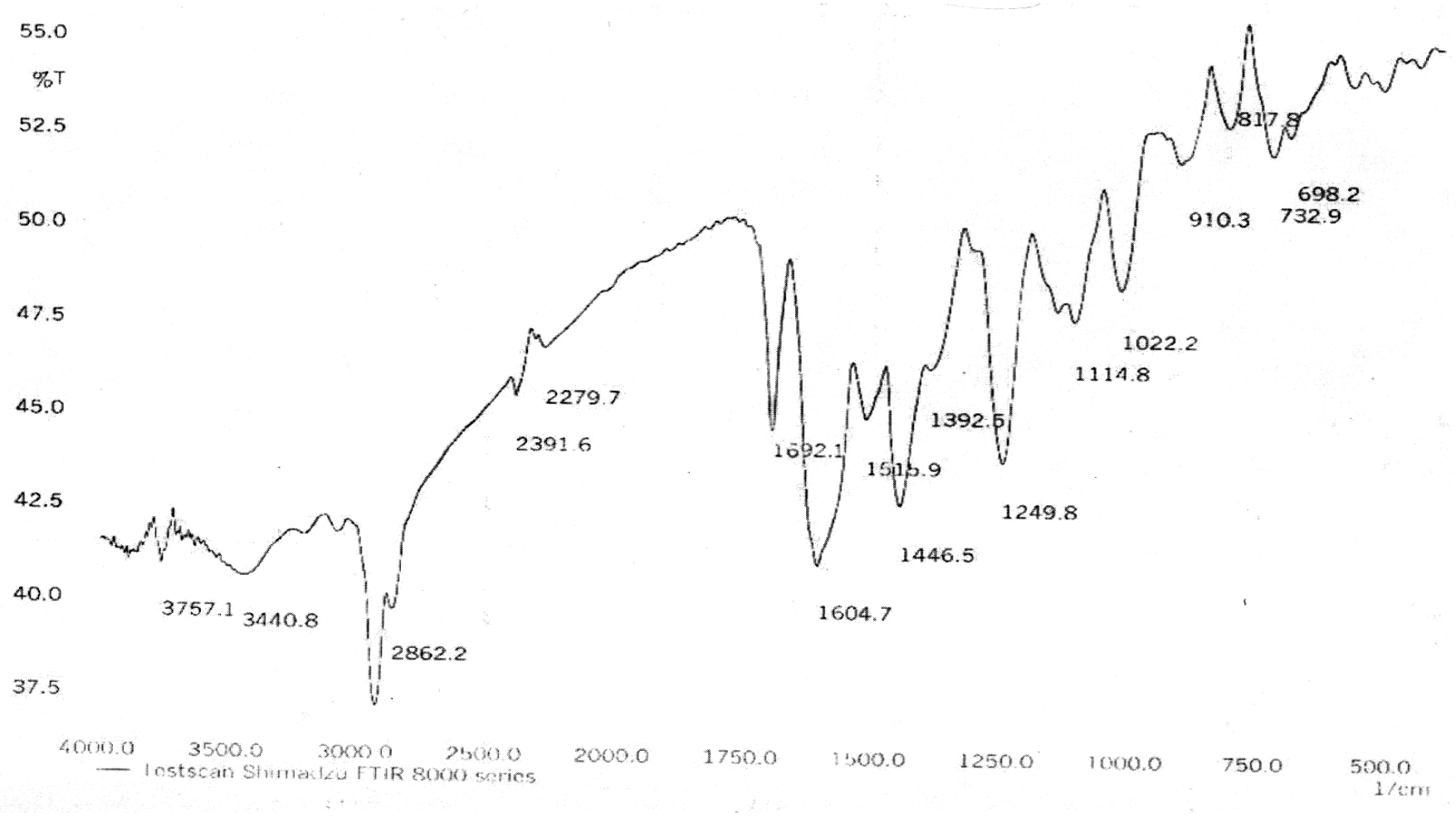
Compound [10] was synthesized from the reaction of compound [8] with mercapto acetic acid dissolved in dry benzene. The compound was characterized by its melting point and F.T.IR spectroscopy.



The F.T.IR spectrum of compound [10] was confirmed from the appearance of carbonyl group band of the oxo-thiazolidine ring at (1692.1 cm^{-1}) in addition O-H and N-H bands at (3440.8 cm^{-1}) and (3199.7 cm^{-1}) respectively. Figure (3-10) shows the F.T.IR spectrum of compound [10]. The suggested mechanism of the reaction is shown in Scheme (3-7).



Scheme (3-7): Mechanism steps for the preparation of compound [10].



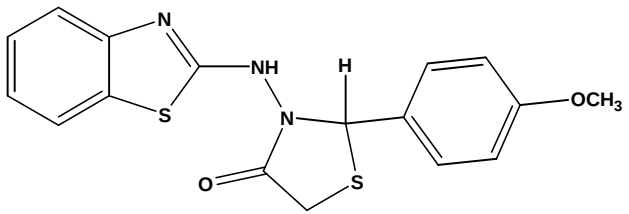
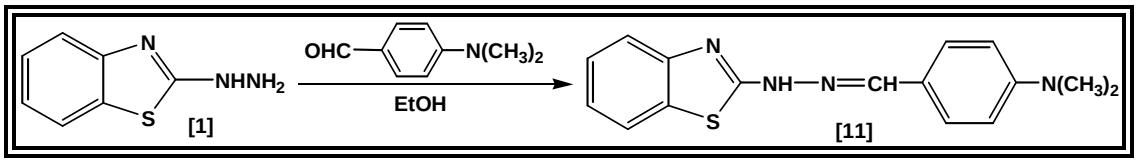
Melting point: 237-239 °C	
Yield: 80%	

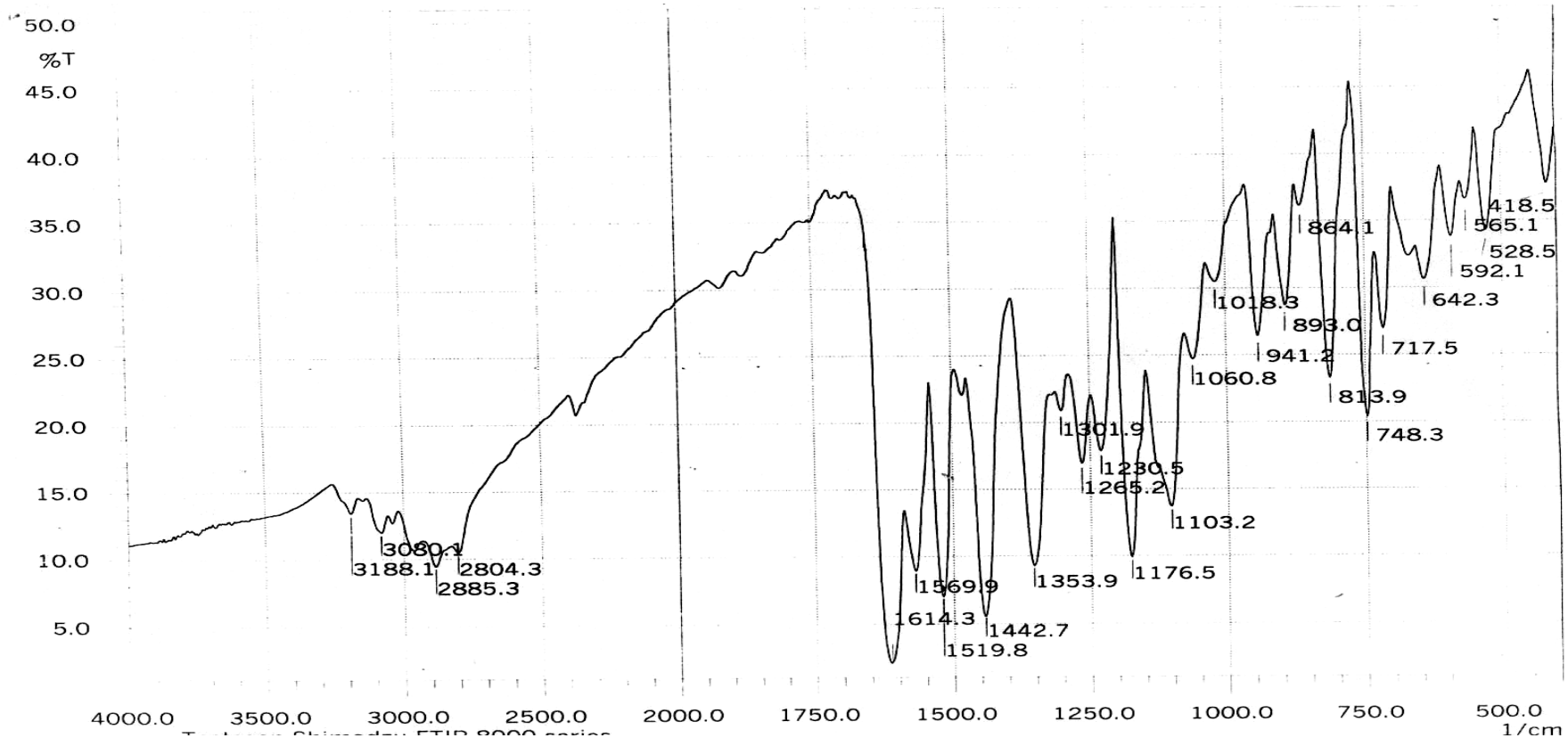
Figure (3-10): Structure, Physical Properties and F.T.IR spectrum of 2-[(2`-(4-methoxyphenyl)-4`-oxo-1`,3`-thiazolidin-3`- benzothiazole hydrazine [10].

3.1.11 Preparation of 2-(4-dimethyl amino)benzylidine) hydrazine] benzothiazole [11]:

Compound [11] was synthesized from the reaction of compound [1] with 4-dimethyl amino benzaldehyde in absolute ethanol afforded the imine. The compound was characterized by its melting point and F.T.IR spectroscopy.



The F.T.IR spectrum of compound [11] indicated the disappearance of NH_2 band (3313.5 and 3201.6 cm^{-1}) of the starting material and appearance of N-H band at (3188.1 cm^{-1}) and C=N group band of the imine appeared at (1614.3 cm^{-1}) and C-H aliphatic at (2885.3 cm^{-1}) and *p*-N-CH_3 at (813.9 cm^{-1}). Figure (3-11) shows the F.T.IR spectrum of compound [11].



Melting point: 254-256 ^{o}C

Yield: 90%

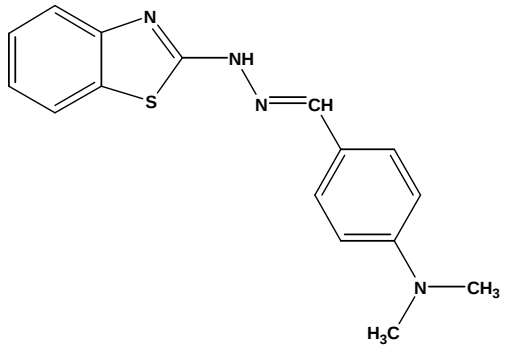
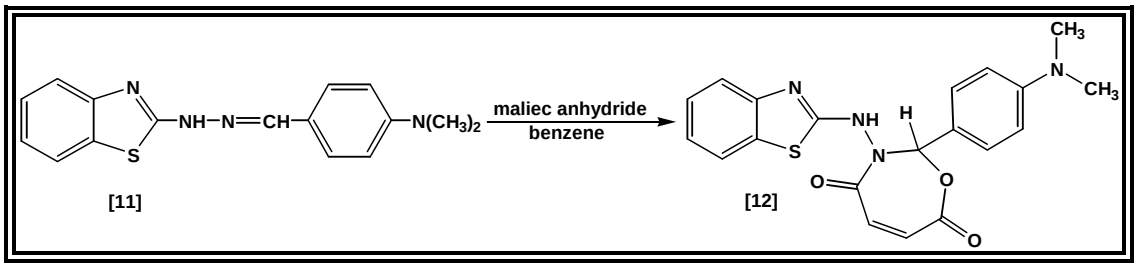


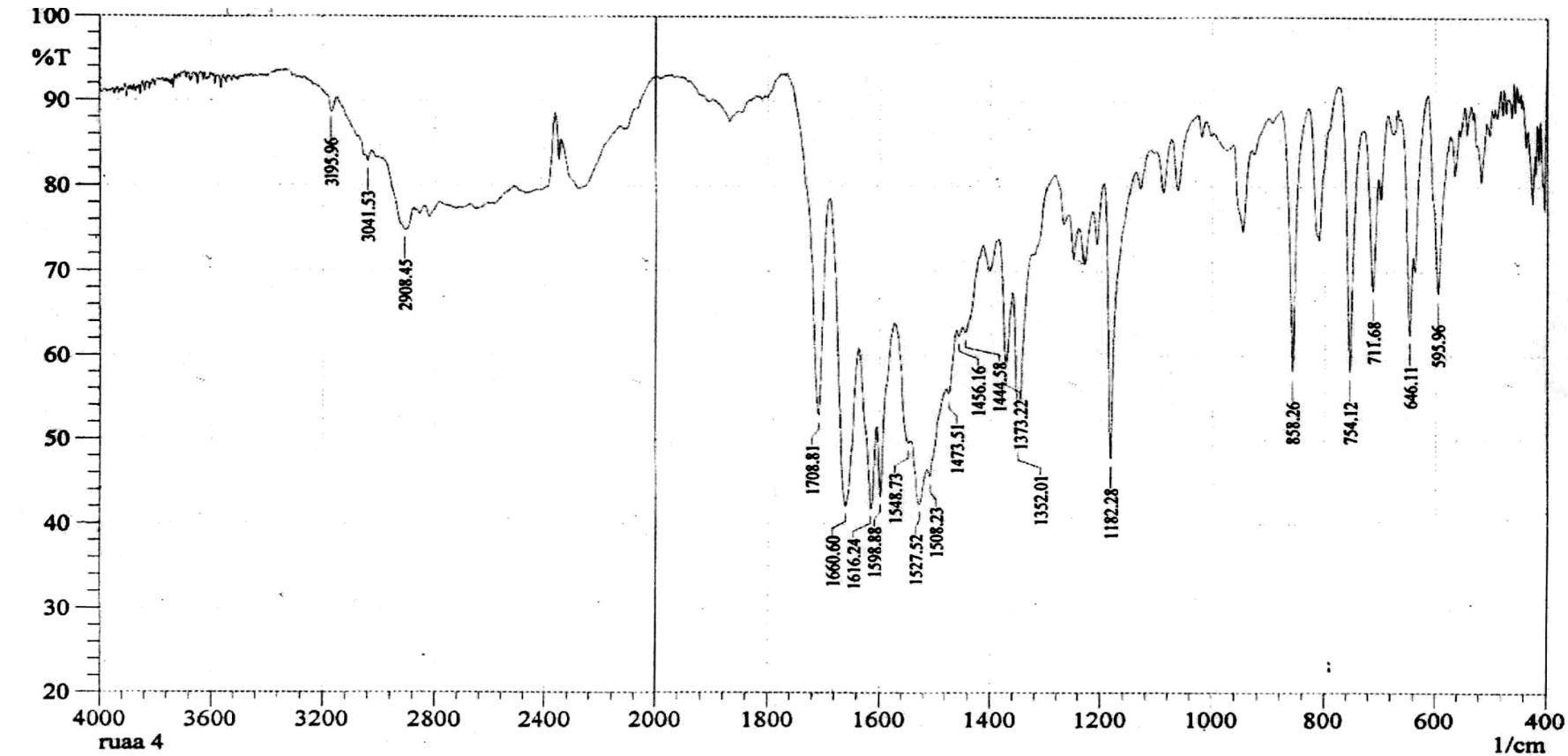
Figure (3-11): Structure, Physical Properties and F.T.IR spectrum of 2-(4-dimethyl amino)benzylidine) hydrazine] benzothiazole [11].

3.1.12 Preparation of 2-[(2-(4-(dimethylamino)phenyl)-4,7-dione-2,2-dihydro-1,3-oxazepin-3(2H)] benzothiazole hydrazine [12]:

Compound [12] was synthesized from the reaction of compound [11] with maliec anhydride in dry benzene. The compound was characterized by its melting point and F.T.IR spectroscopy.



The F.T.IR spectrum of compound [12] was confirmed from the appearance of carbonyl group band at (1708.8 cm^{-1}) and N-H band at (3195.9 cm^{1}) and C-H aliphatic band at (2908.4 cm^{-1}) and bands at (1250.0 cm^{-1}) and (1030.1 cm^{-1}) belong to the asymmetric and symmetric (C-O-C) band. Figure (3-12) shows the F.T.IR spectrum of compound [12].



Melting point: 149-150 °C

Yield: 66%

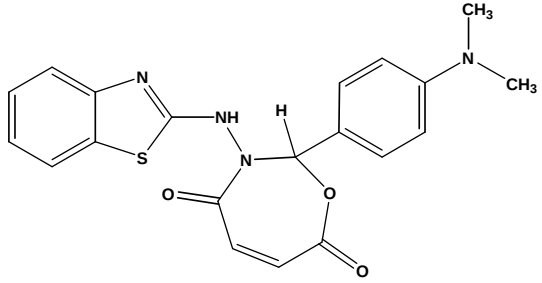
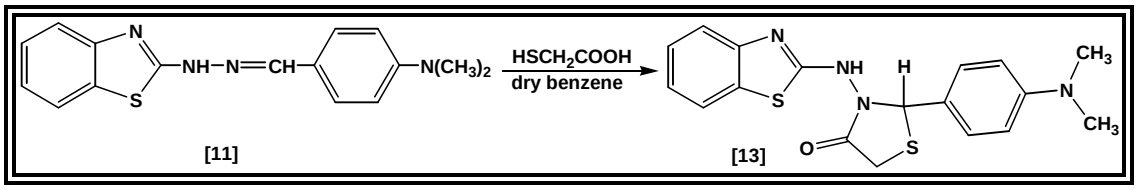


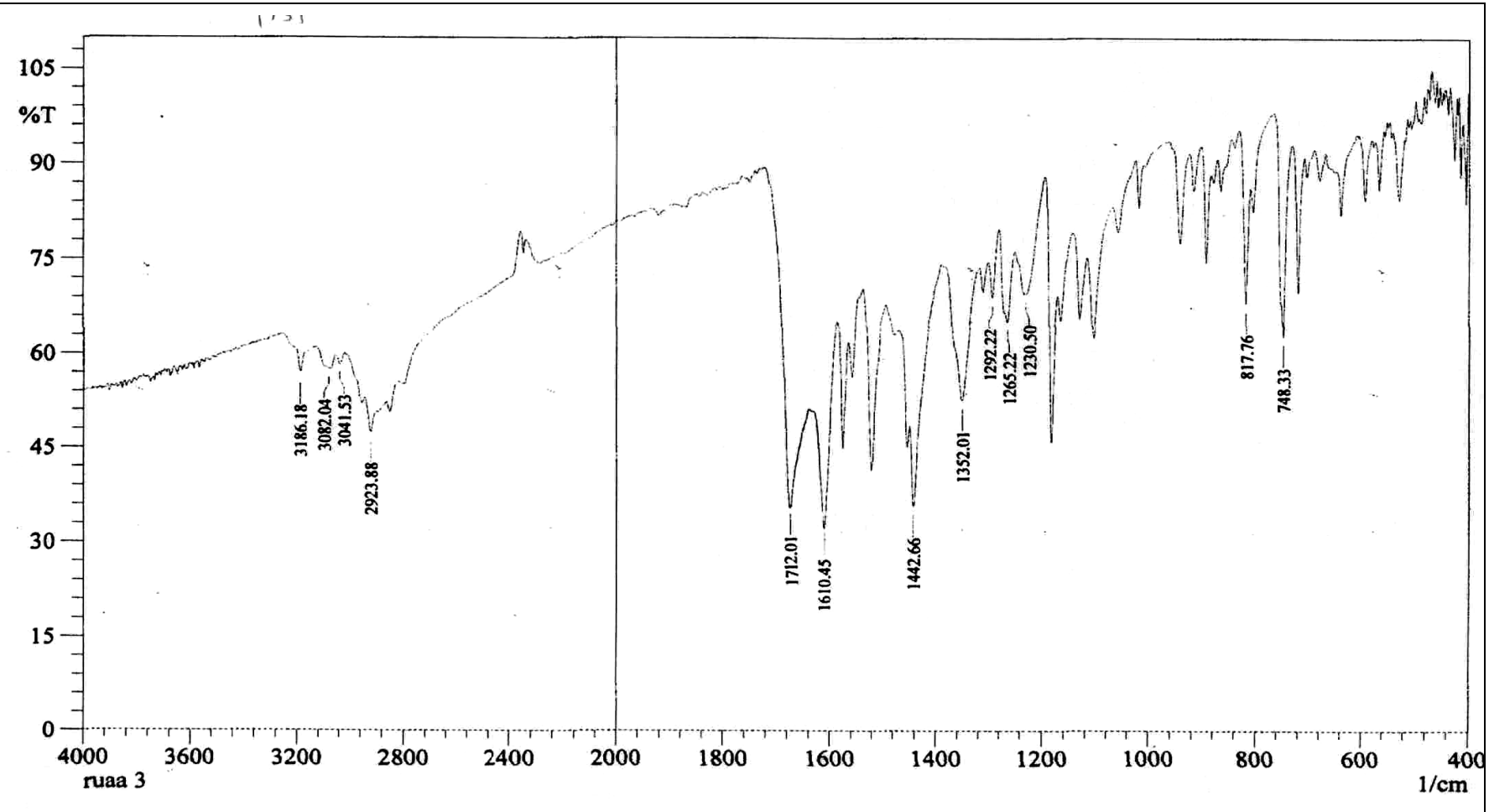
Figure (3-12): Structure, Physical Properties and F.T.IR spectrum of 2-[(2-(4-(dimethylamino)phenyl)-4,7-dione-2,2-dihydro-1,3-oxazepin-3(2H)] benzothiazole hydrazine [12].

3.1.13 Preparation of 2-[(2`-(4-(dimethylamino)phenyl)-4`-oxo-1`,3`-thiazolidin-3`-yl)] benzothiazole hydrazine [13]:

Compound [13] was synthesized from the reaction of compound [11] with mercapto acetic acid dissolved in dry benzene. The compound was characterized by its melting point and F.T.IR spectroscopy.



The F.T.IR spectrum of compound [13] was confirmed from the appearance of carbonyl group band of the oxo-thiazolidine ring at (1712.0 cm^{-1}) and N-H band at (3186.1 cm^{-1}). Figure (3-13) shows the F.T.IR spectrum of compound [13].



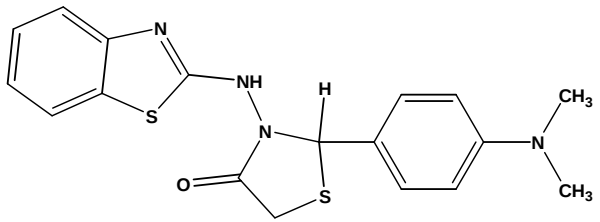
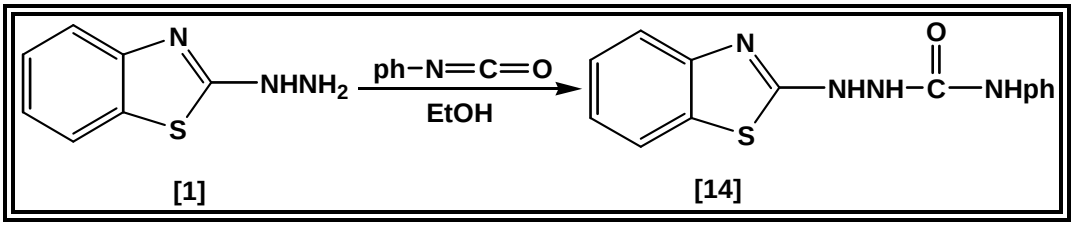
Melting point: 278-280 °C	
Yield: 91%	

Figure (3-13): Structure, Physical Properties and F.T.IR spectrum of 2-[(2`-(4-(dimethylamino)phenyl)-4`-oxo-1`,3`-thiazolidin-3`-yl)] benzothiazole hydrazine [13].

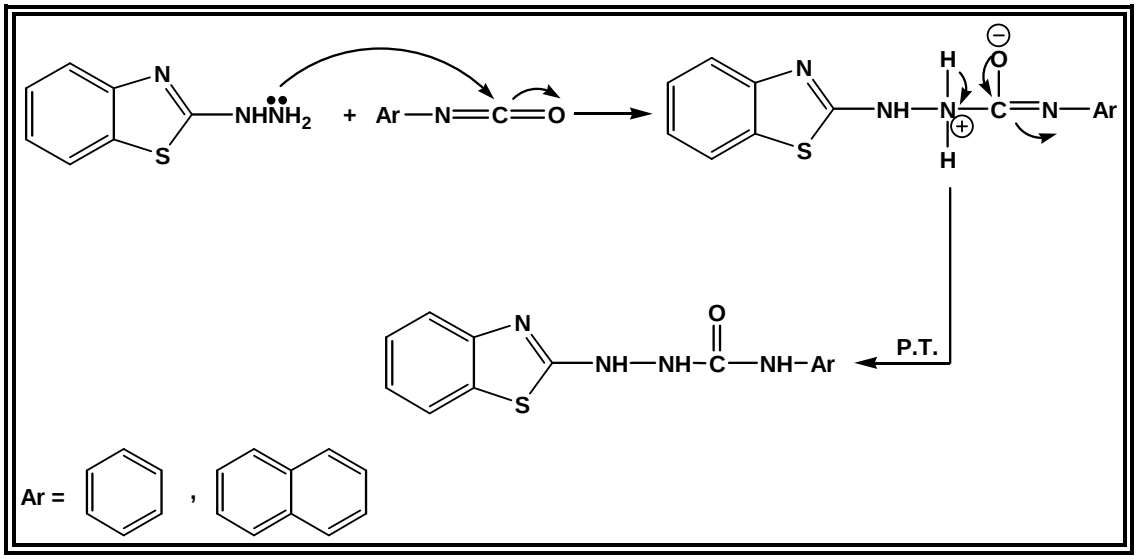
3.1.14 Preparation of 2-N-benzothiazole-N`-phenyl hydrazine carboxamide [14]:

Compound [14] was synthesized from the reaction of compound [1] with phenyl isocyanate. The compound was characterized by its melting point and F.T.IR spectroscopy.

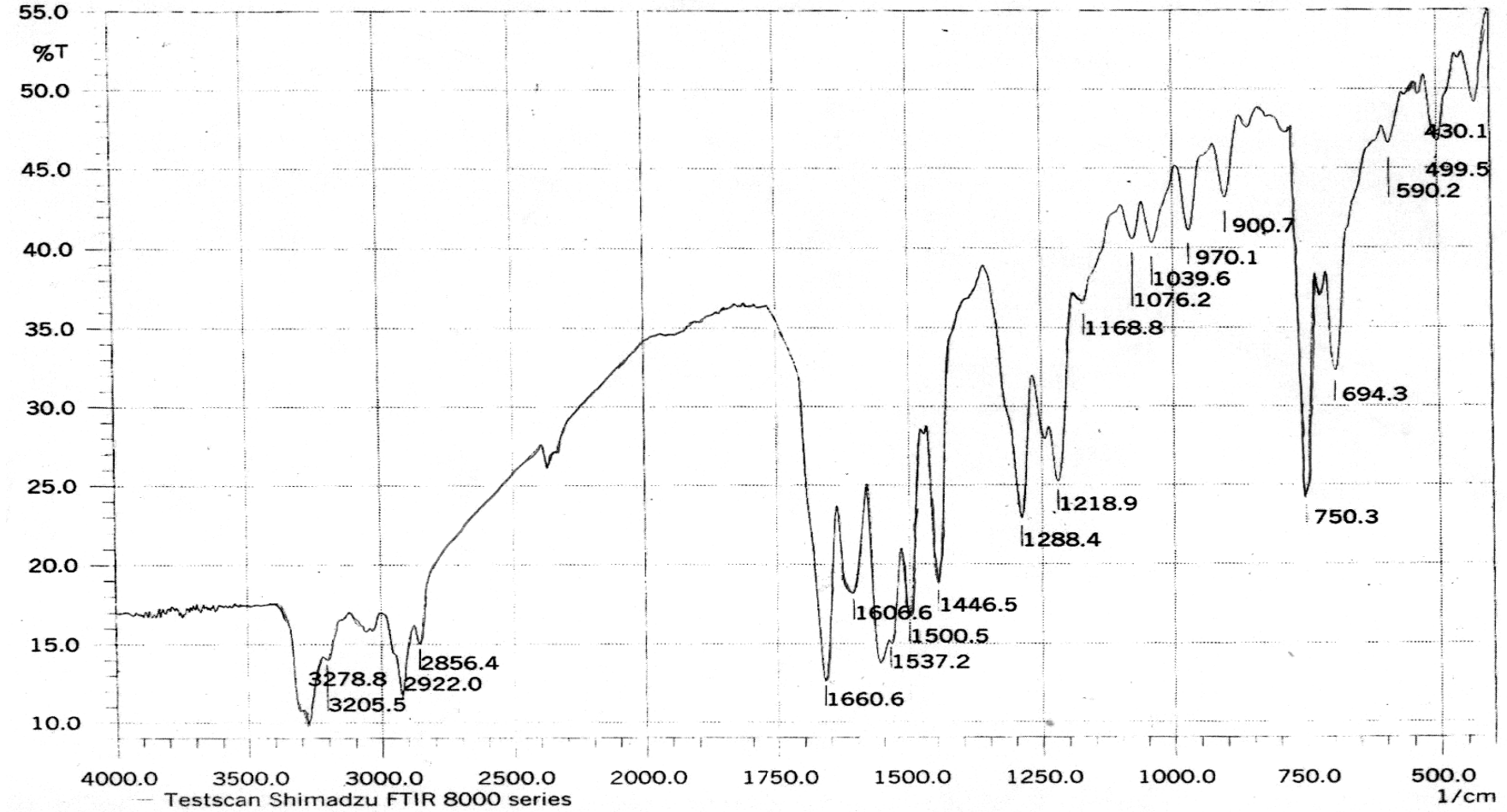


The F.T.IR spectrum of compound [14] indicated the disappearance of NH_2 band (3313.5 and (3201.6 cm^{-1}) of the starting material and the appearance of N-H band at (3278.8 cm^{-1}) and carbonyl group at (1660.6 cm^{-1}). Figure (3-14) shows the F.T.IR spectrum of compound [14].

The suggested mechanism [110] of the reaction is shown in Scheme (3-8).



Scheme (3-8): Mechanism steps for the preparation of compound [14].



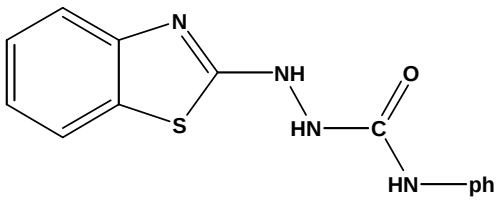
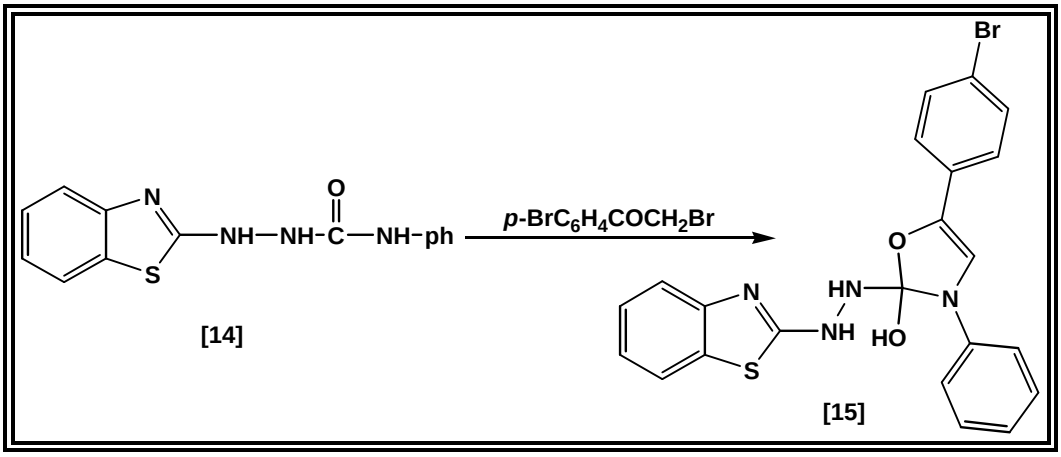
Melting point: 214-216 ^{o}C	
Yield: 81%	

Figure (3-14): Structure, Physical Properties and F.T.IR spectrum of 2-N-benzothiazole-N`-phenyl hydrazine carboxamide [14].

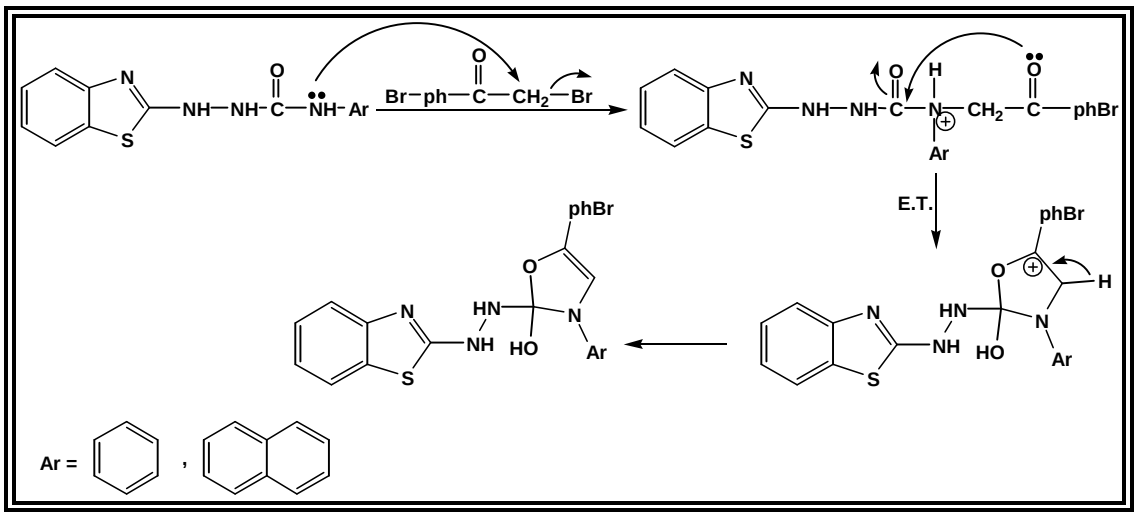
3.1.15 Preparation of 2-N-[(3)-N-phenyl-5-(p-bromophenyl)-2-hydroxy-1,3-oxazolin-2-yl] benzothiazol hydrazine [15]:

Compound [15] was synthesized from the reaction with compound [14] with *p*-bromo phenacyl bromide. The compound was characterized by its melting point and F.T.IR spectroscopy.

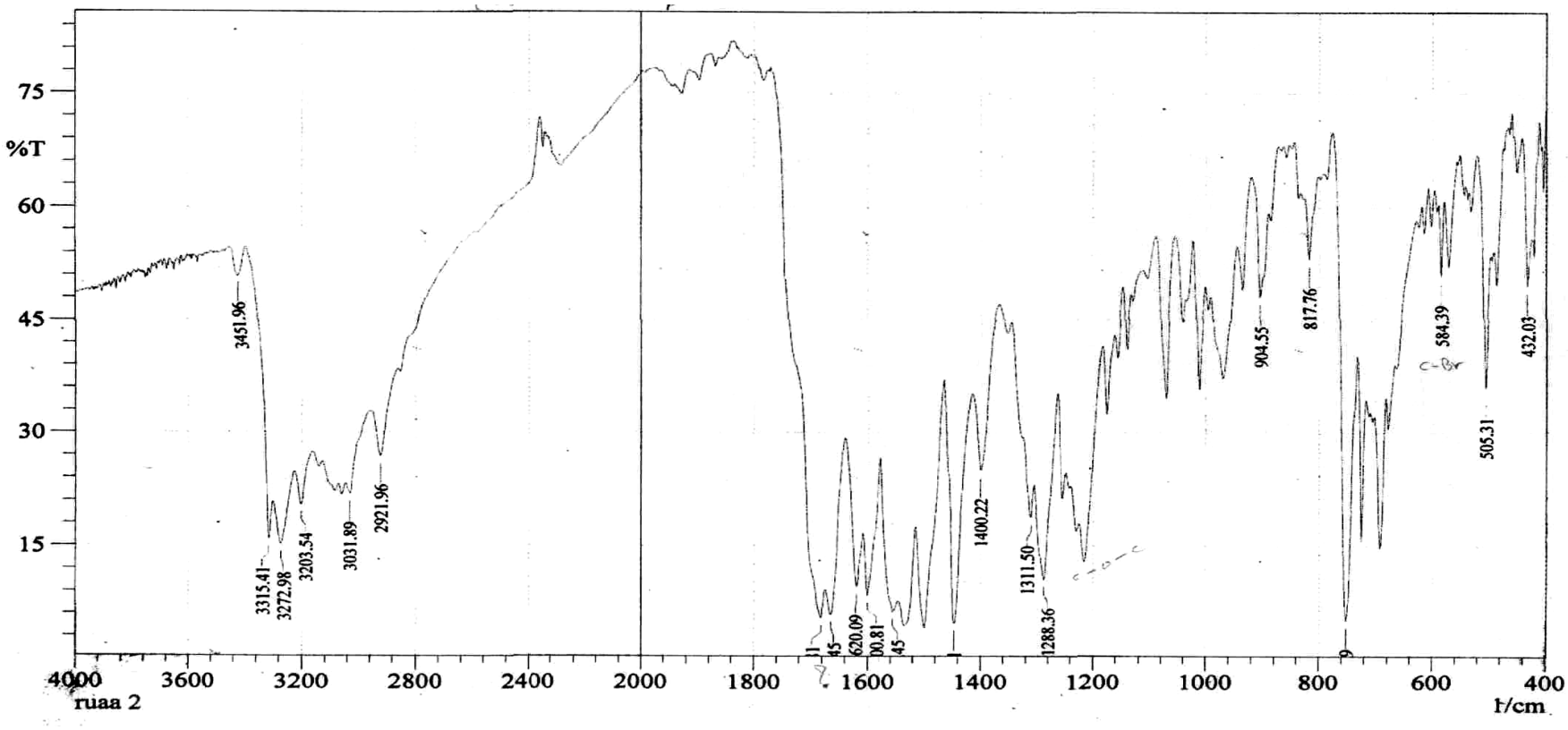


The F.T.IR spectrum of compound [15] indicated the disappearance of carbonyl group band at (1660.6 cm^{-1}) of the compound [14] and appearance of N-H band at (3272.9 cm^{-1}) and O-H band at (3451.9 cm^{-1}) and bands at (1250.0 cm^{-1}), (1016.4 cm^{-1}) belong to the asymmetric and symmetric (C-O-C) band. It is assume that the S_N2 mechanism. Figure (3-15) shows the F.T.IR spectrum of compound [15].

The mechanism [110] of the reaction is shown in Scheme (3-9).



Scheme (3-9): Mechanism steps for the preparation of compound [15].



Melting point: 178-180 ^{o}C

Yield: 74%

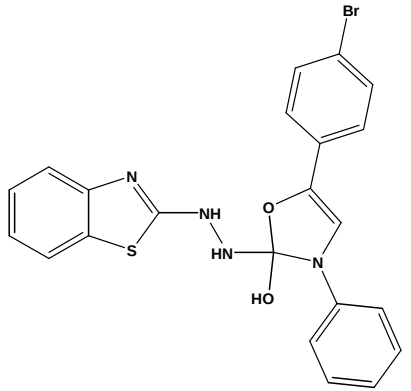
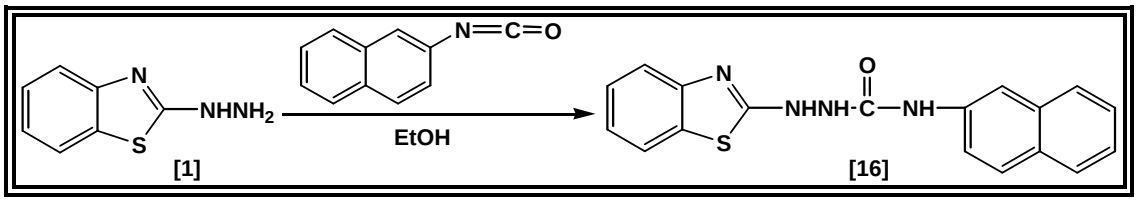


Figure (3-15): Structure, Physical Properties and F.T.IR spectrum of 2-N-[(3)-N-phenyl-5-(p-bromophenyl)-2-hydroxy-1,3-oxazolin-2-yl] benzothiazol hydrazine [15].

3.1.16 Preparation of 2-N-benzothiazole-N`-1-naphthyl hydrazine carboxamide [16]:

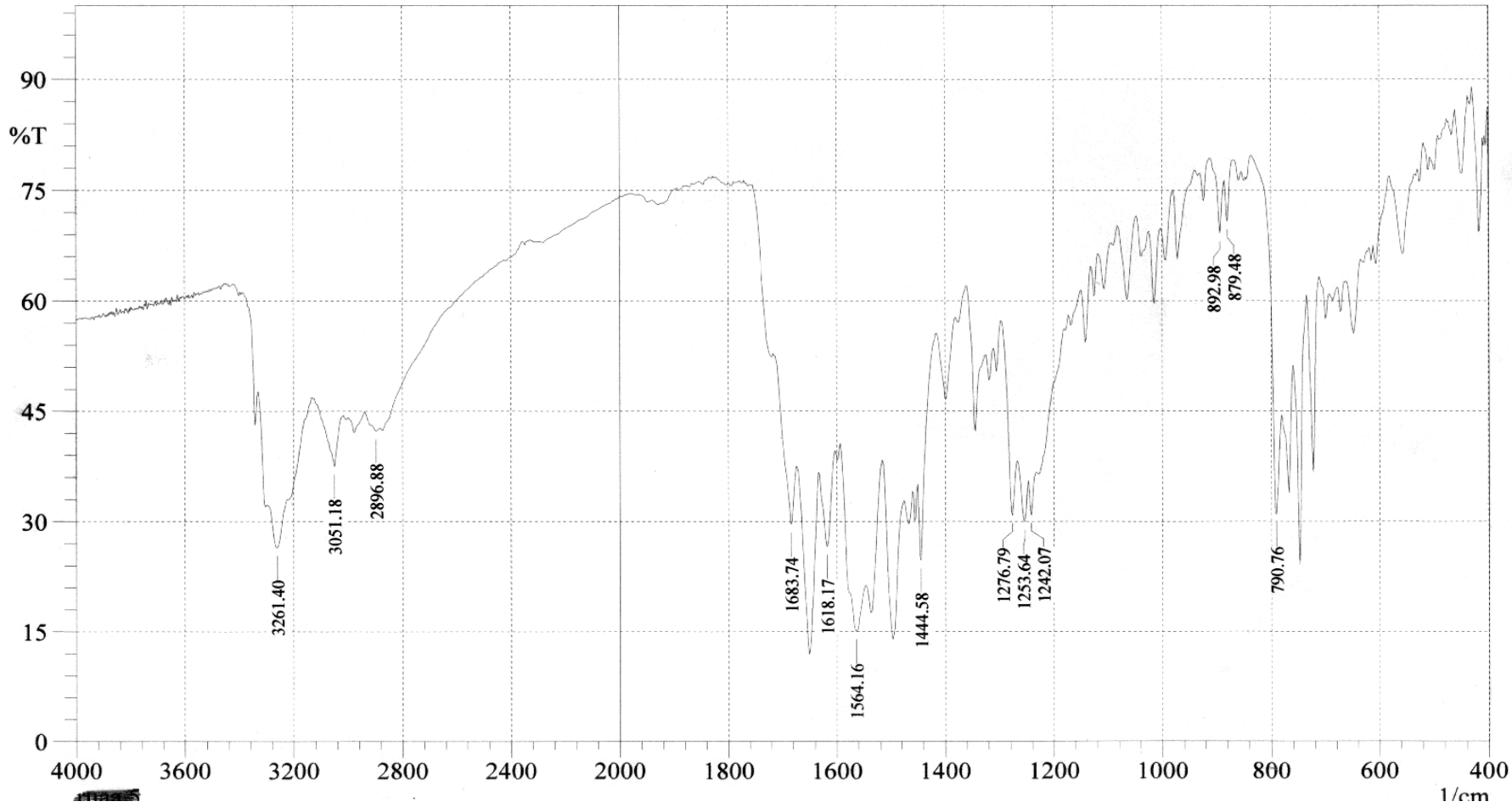
Compound [16] was synthesized from the reaction of compound [1] with 1-naphthyl isocyanate.

The compound was characterized by its melting point and F.T.IR spectroscopy.



The F.T.IR spectrum of compound [16] indicated the disappearance of NH_2 bands at (3313.5 and 3201.6 cm^{-1}) of the starting material and appearance of N-H band at (3261.4 cm^{-1}) and carbonyl group band at (1683.6 cm^{-1}).

Figure (3-16) shows the F.T.IR spectrum of compound [16].



Melting point: 223-225 ^{o}C

Yield: 96%

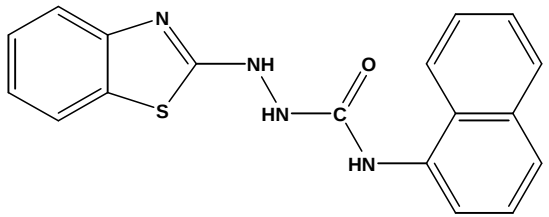
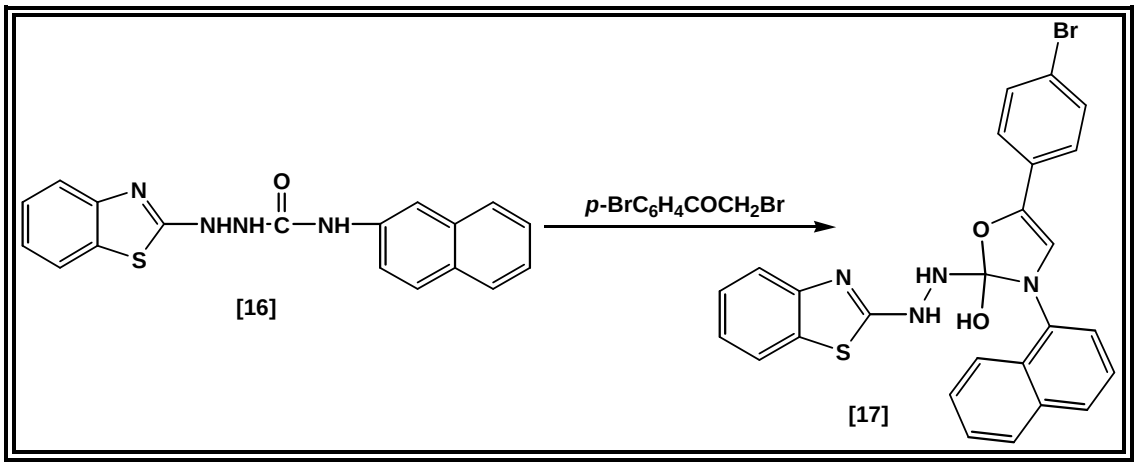


Figure (3-16): Structure, Physical Properties and F.T.IR spectrum of 2-N-benzothiazole-N`-1-naphthyl hydrazine carboxamide [16].

3.1.17 Preparation of 2-N-[(3`)-N-(1-naphthyl)-5`-(p-bromo phenyl)-2-hydroxy-1,3-oxazolin-2-yl)] benzothiazol hydrazine [17]:

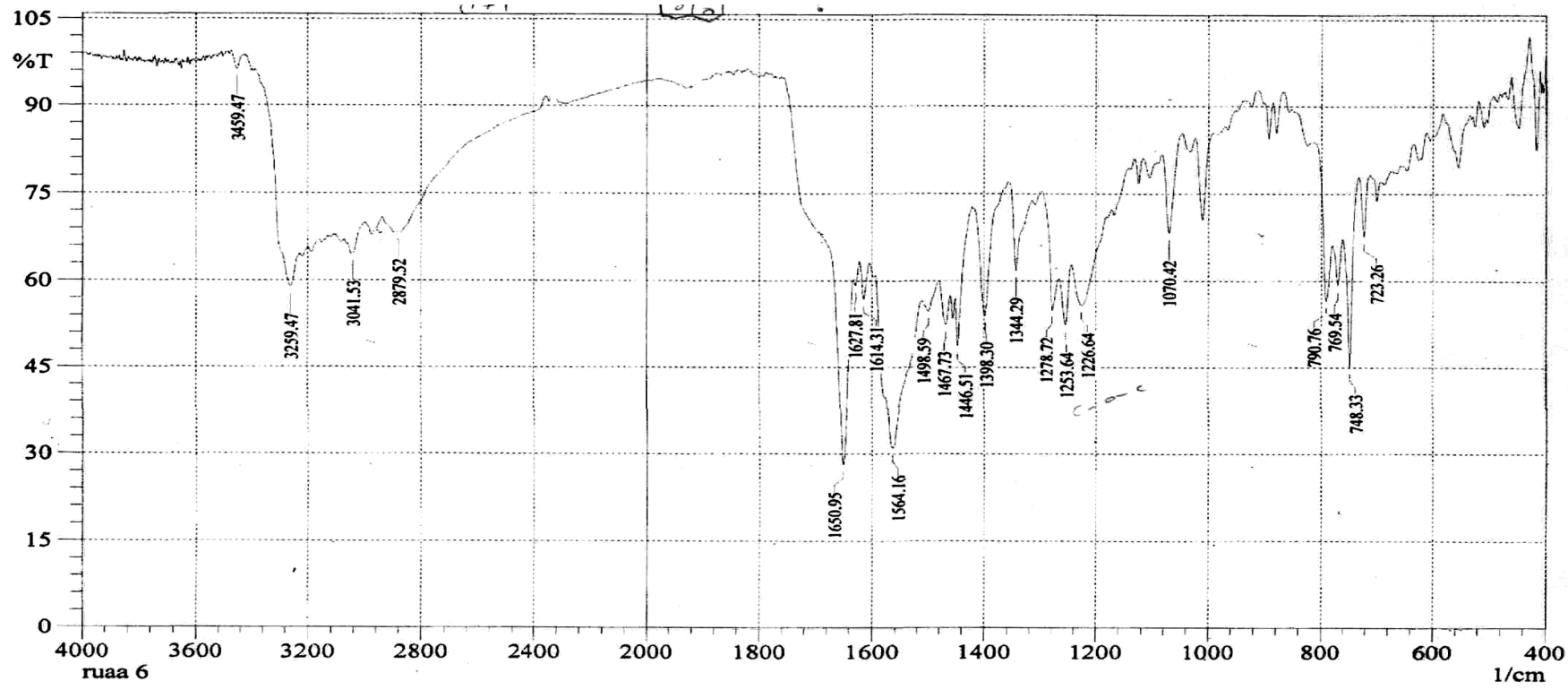
Compound [17] was synthesized from the reaction of compound [16] with *p*-bromo phenacyl bromide.

The compound was characterized by its melting point and F.T.IR spectroscopy.



The F.T.IR spectrum of compound [17] indicated the disappearance of carbonyl group band at (1683.0 cm^{-1}) of the compound [16] and appearance of N-H band at (3259.4 cm^{-1}) and O-H band at (3459.4 cm^{-1}) and appearance of the C=C band at (1564.1 cm^{-1}), bands at (1253.6 and 1010.0 cm^{-1}) belong to the asymmetric and symmetric (C-O-C).

Figure (3-17) shows the F.T.IR spectrum of compound [17].



Melting point: 179-181 ^{o}C

Yield: 62%

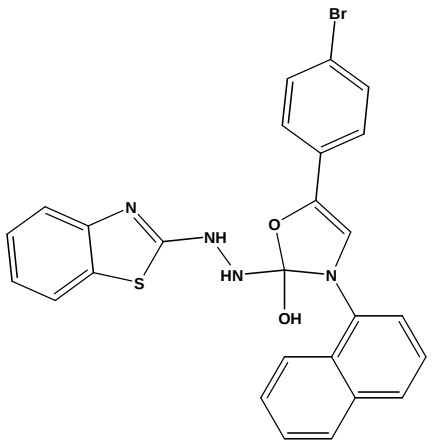
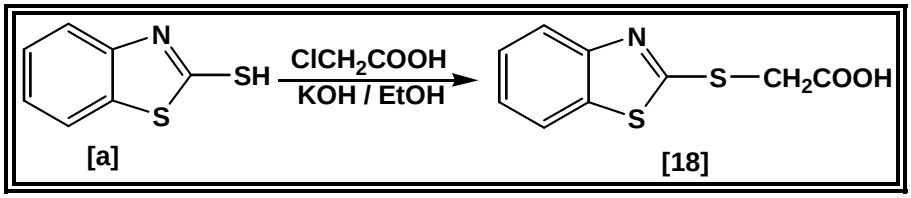


Figure (3-17): Structure, Physical Properties and F.T.IR spectrum of 2-N-[(3`)-N-(1-naphthyl)-5`-(p-bromo phenyl)-2-hydroxy-1,3-oxazolin-2-yl)] benzothiazol hydrazine [17].

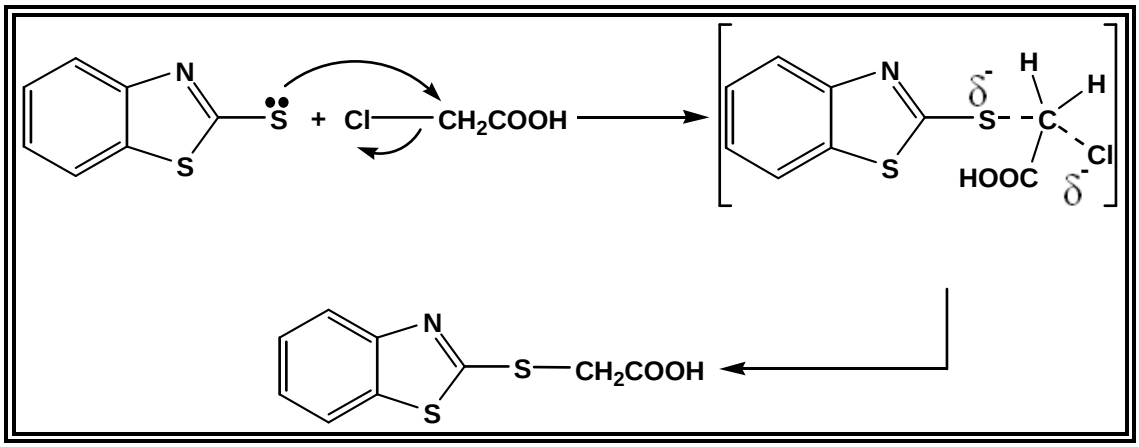
3.1.18 Preparation of 2-thiaacetic acid benzothiazole [18]:

Compound [18] was synthesized from the reaction of 2-mercapto benzothiazole with chloro acetic acid. The compound was characterized by its melting point and F.T.IR spectroscopy.

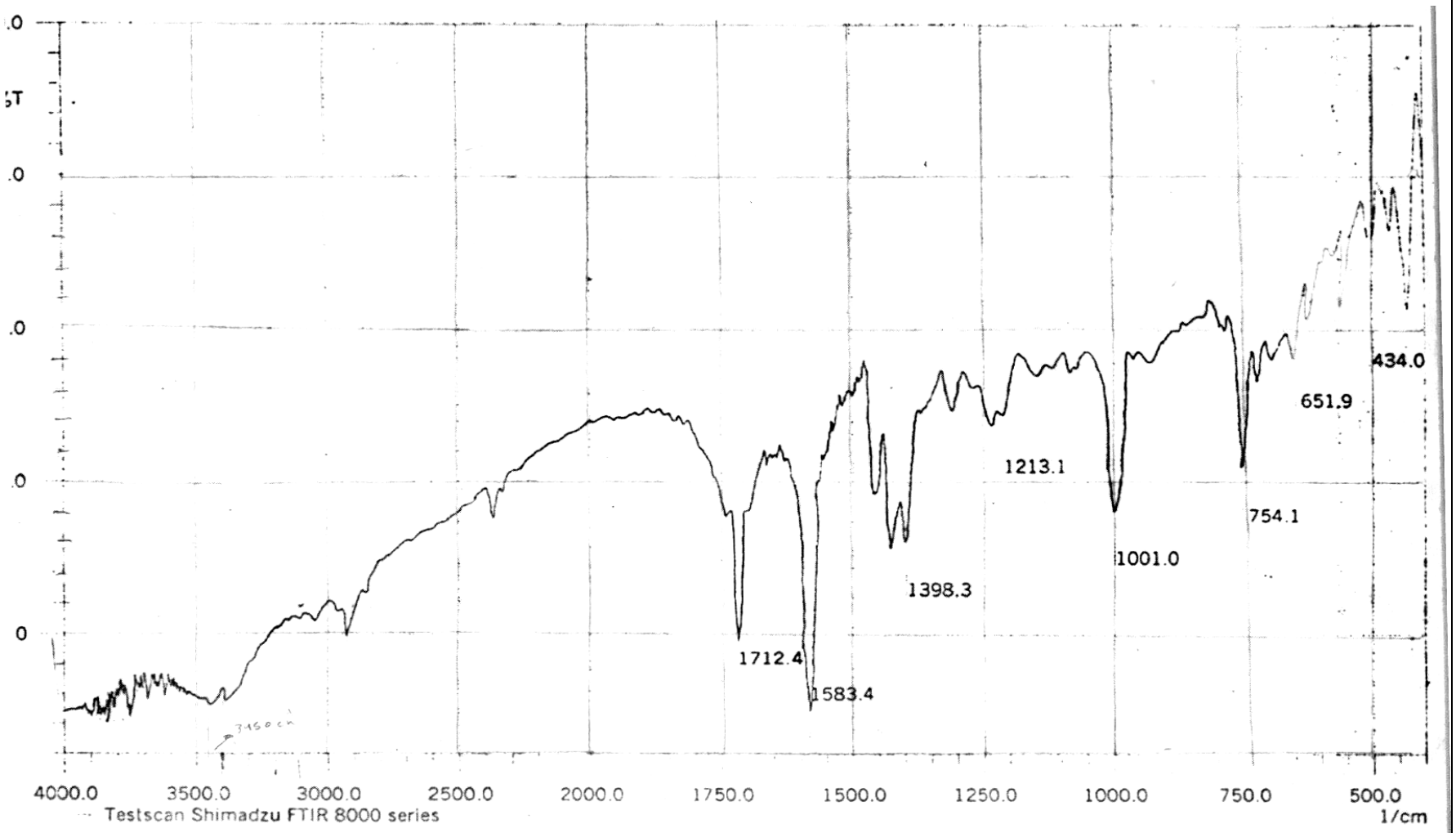


The F.T.IR spectrum of compound [18] indicated the disappearance of S-H band at (2754.2 cm^{-1}) and appearance of the carbonyl group band at (1712.4 cm^{-1}) of the acid and appearance of O-H group band at (3450 cm^{-1}) and C-H aliphatic at (2900 cm^{-1}), which displayed broad band in the region (3450.0 cm^{-1}), and the mechanism of the reaction may be considered as S_N2 mode reaction through the nucleophilic attack of the sulfide anion at the saturated carbon Cl-CH_2-CO_2H carrying the leaving group. Figure (3-18) shows the F.T.IR spectrum of compound [18].

The suggested mechanism of the reaction is shown in Scheme (3-10).



Scheme (3-10): Mechanism steps for the preparation of compound [18].



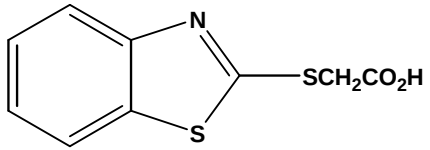
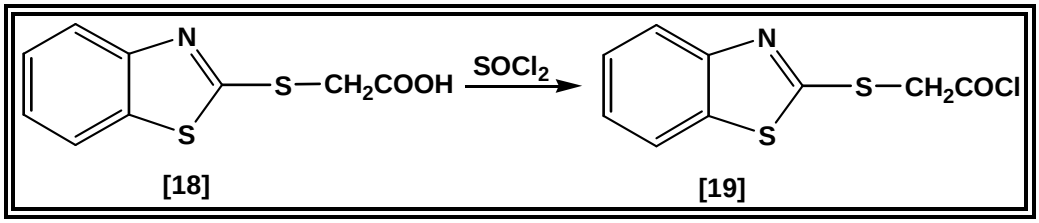
Melting point: 228-230 ^{o}C	
Yield: 62%	

Figure (3-18): Structure, Physical Properties and F.T.IR spectrum of 2-thiaacetic acid benzothiazole [18].

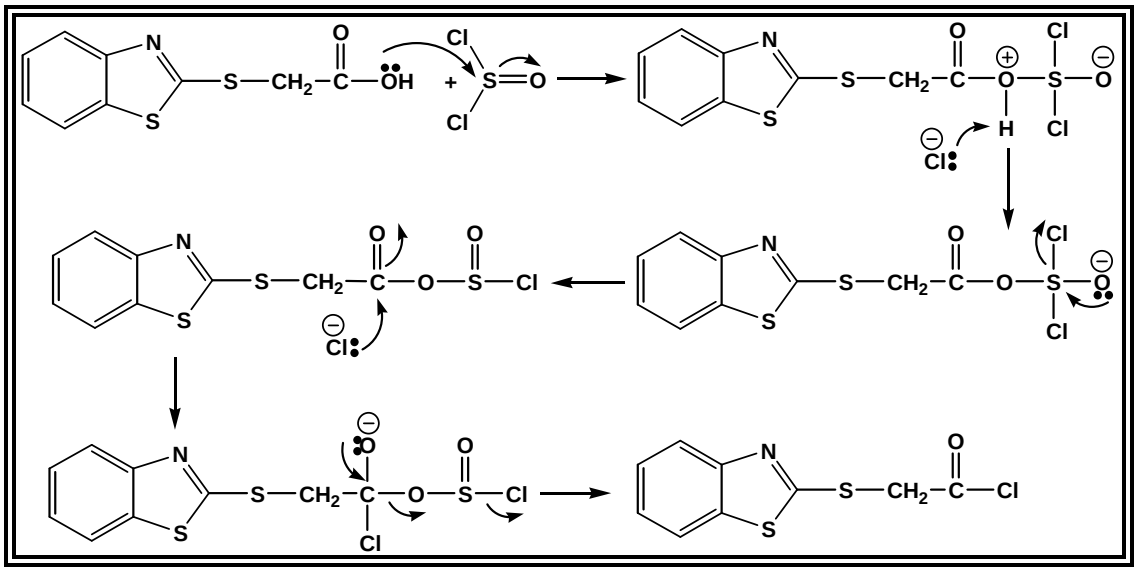
3.1.19 Preparation of 2-thiacetyl chloride benzothiazole [19]:

Compound [19] was synthesized from the reaction of 2-thiacetic acid benzothiazole with thionyl chloride. The compound was characterized by its melting point and F.T.IR spectroscopy.

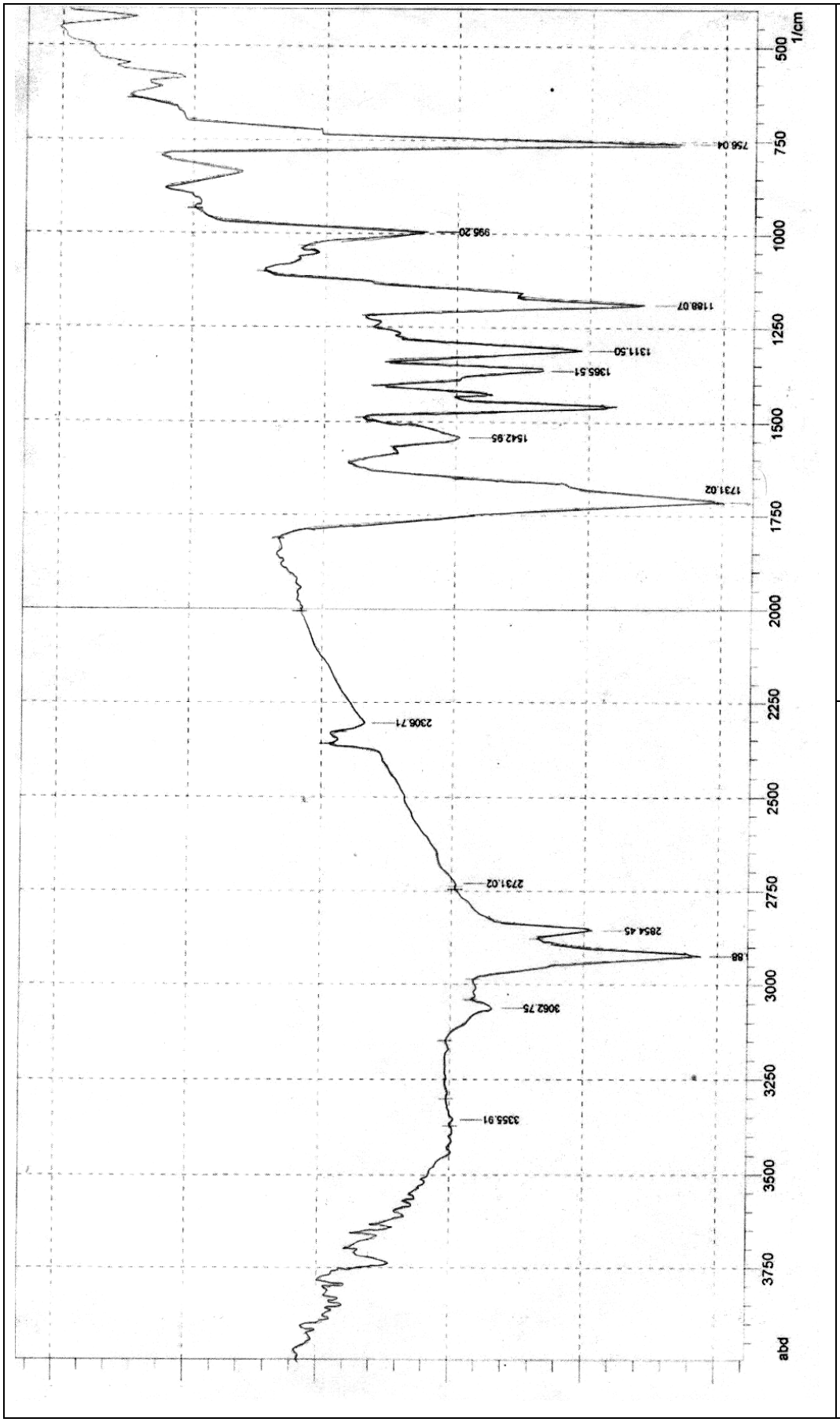


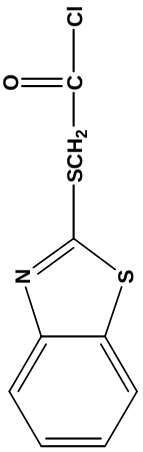
The F.T.IR spectrum of compound [19] indicated the disappearance of broad band of O-H at (3450.0 cm^{-1}) and appearance of the carbonyl group of the acid chloride at (1730.2 cm^{-1}) and C-H aliphatic (2854.4 cm^{-1}) and (C-Cl) at (758.0 cm^{-1}). Figure (3-19) shows the F.T.IR spectrum of compound [19].

The suggested mechanism [117] is shown in Scheme (3-11).



Scheme (3-11): Mechanism steps for the preparation of compound [19].





Melting point: 307-309 °C

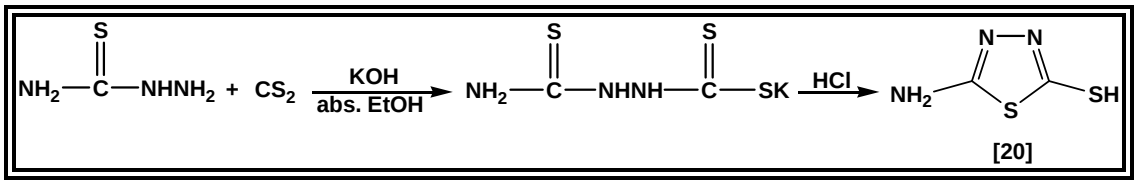
Yield: 90%

Figure (3-19): Structure, Physical Properties and F.T.IR spectrum of 2-thiaacetyl chloride benzothiazole [19].

3.1.20 Preparation of 5-amino-2-mercapto-1,3,4-thiadiazole [20]:

Compound [20] was synthesized from the reaction of carbon disulfide with thiosemicarbazide in ethanol.

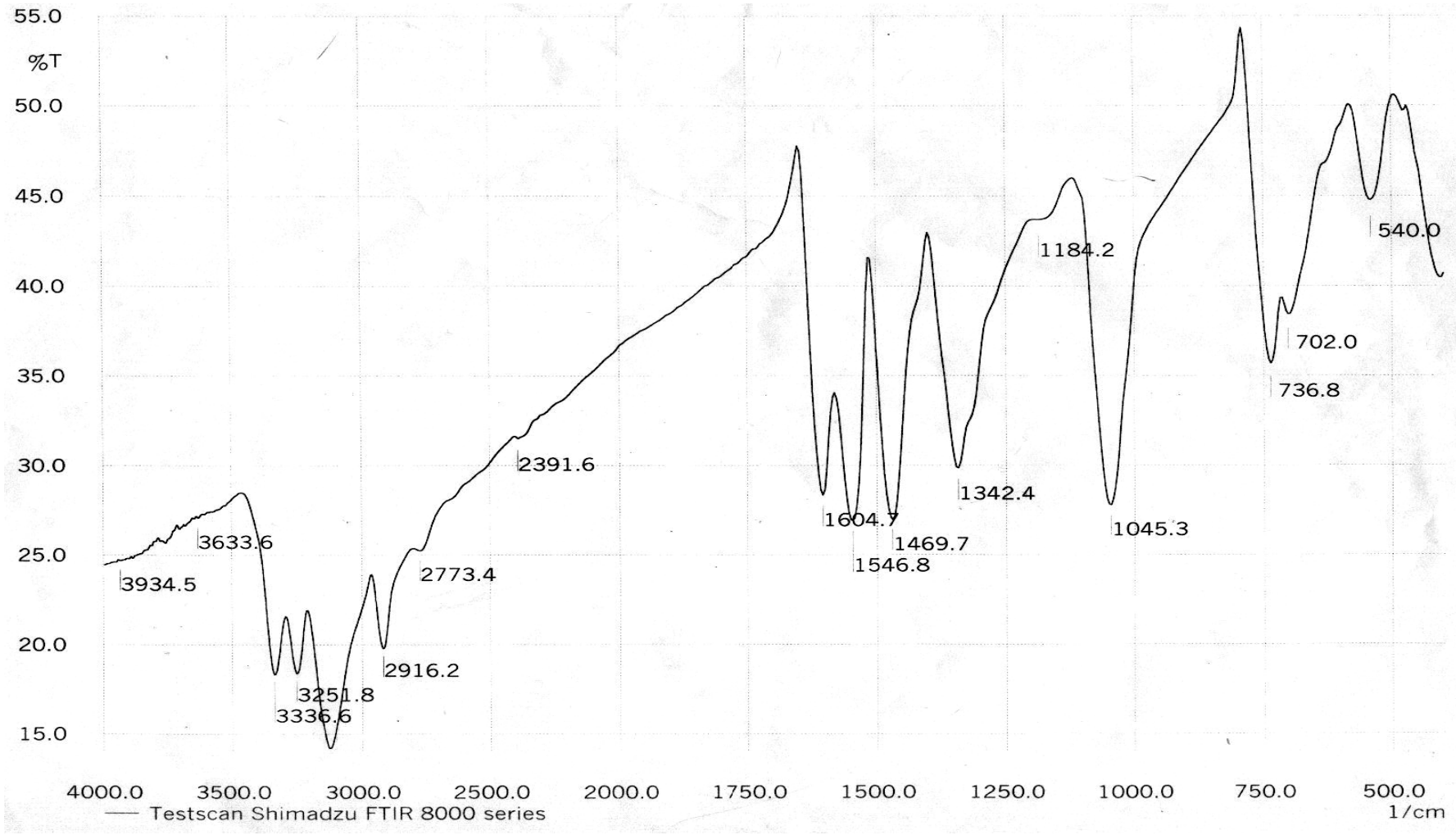
The compound was characterized by its melting point and F.T.IR spectroscopy.



[20]

The F.T.IR spectrum of compound [20] indicated the appearance of S-H band at (2773.4 cm^{-1}) and NH_2 band asymmetric and symmetric at (3336.6-3251.8 cm^{-1}) and appearance of thione band at (1342.4 cm^{-1}) and N-H band of the tautomerism appeared at (3130.0 cm^{-1}).

Figure (3-20) shows the F.T.IR spectrum of compound [20].



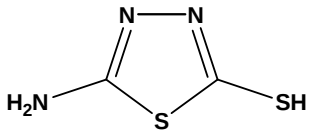
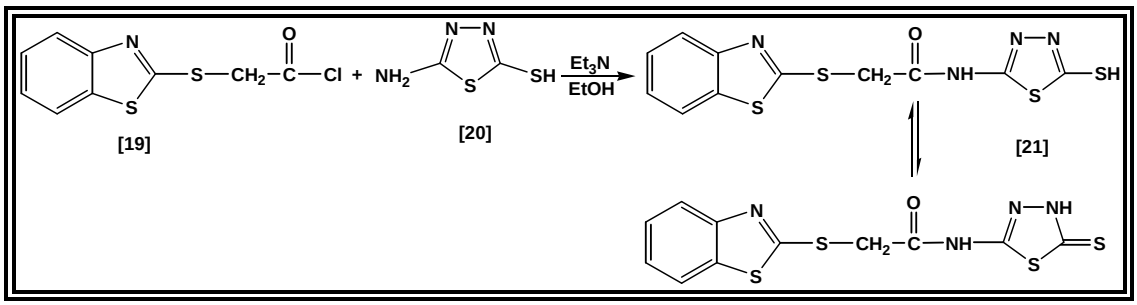
Melting point: 229-231 ^{o}C	
Yield: 92%	

Figure (3-20): Structure, Physical Properties and F.T.IR spectrum of 5-amino-2-mercapto-1,3,4-thiadiazole [20].

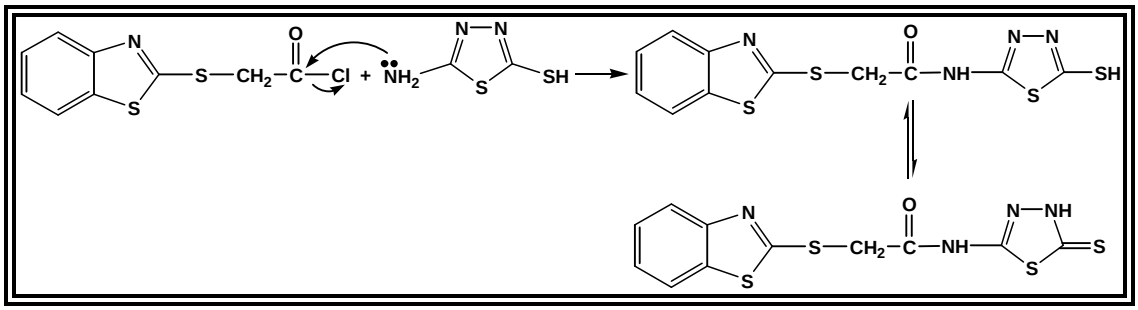
3.1.21 preparation of 2-mercapto-[5- acetamid thiamethyl benzothiazol]-1,3,4-thiadiazole [21]:

Compound [21] was synthesized from the reaction of [19] with compound [20]. The compound was characterized by its melting point and F.T.IR spectroscopy.

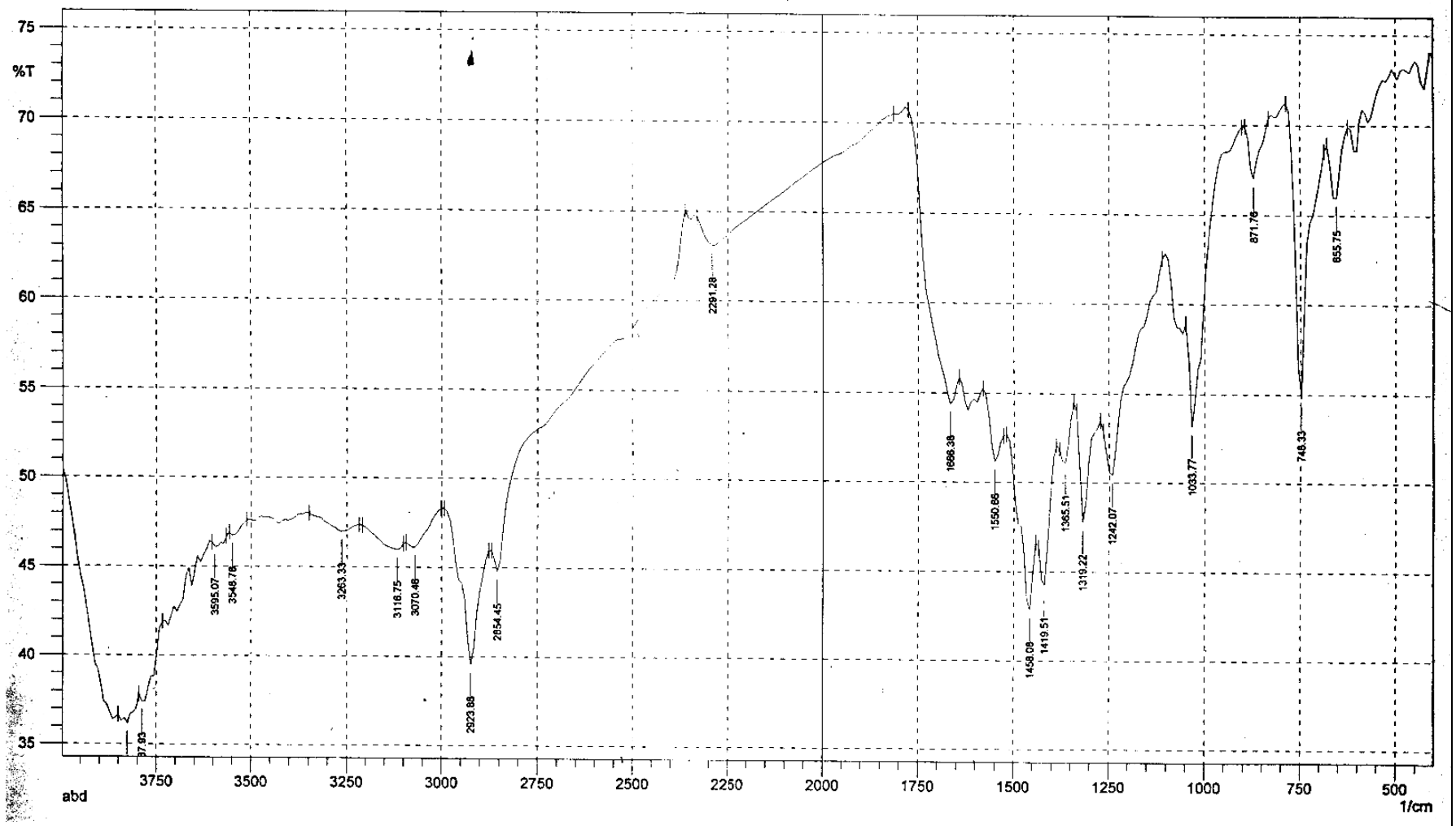


The F.T.IR spectrum of compound [21] indicated the appearance of N-H band at (3263.3 cm^{-1}) and the carbonyl band at (1666.3 cm^{-1}) and aromatic (C-H) at (3116.7 cm^{-1}) and C-H aliphatic at (2854.4 cm^{-1}) and appearance of S-H band at (2525.0 cm^{-1}) and appearance of thione band at (1365.5 cm^{-1}) and N-H band tautomerism and (N-N) band at (1242.0 cm^{-1}) and assume that alkylation step involves S_N2 mechanism. Figure (3-21) shows the F.T.IR spectrum of compound [21].

The mechanism of the reaction is shown in Scheme (3-12).



Scheme (3-12): Mechanism steps for the preparation of compound [21].



Melting point: 120-122 ^{o}C

Yield: 57%

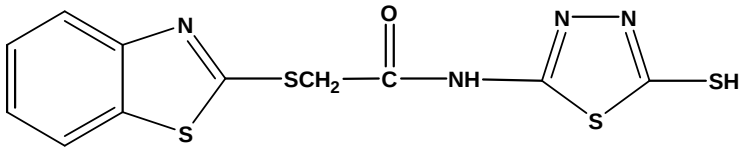
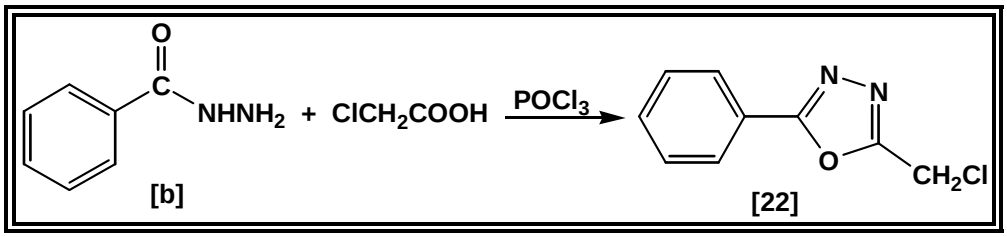


Figure (3-21): Structure, Physical Properties and F.T.IR spectrum of 2-mercapto-[5- acetamid thiamethyl benzothiazol]-1,3,4-thiadiazole [21].

3.1.22 Preparation of 2-phenyl-5-chloroethyl-1,3,4-oxadiazole [22]:

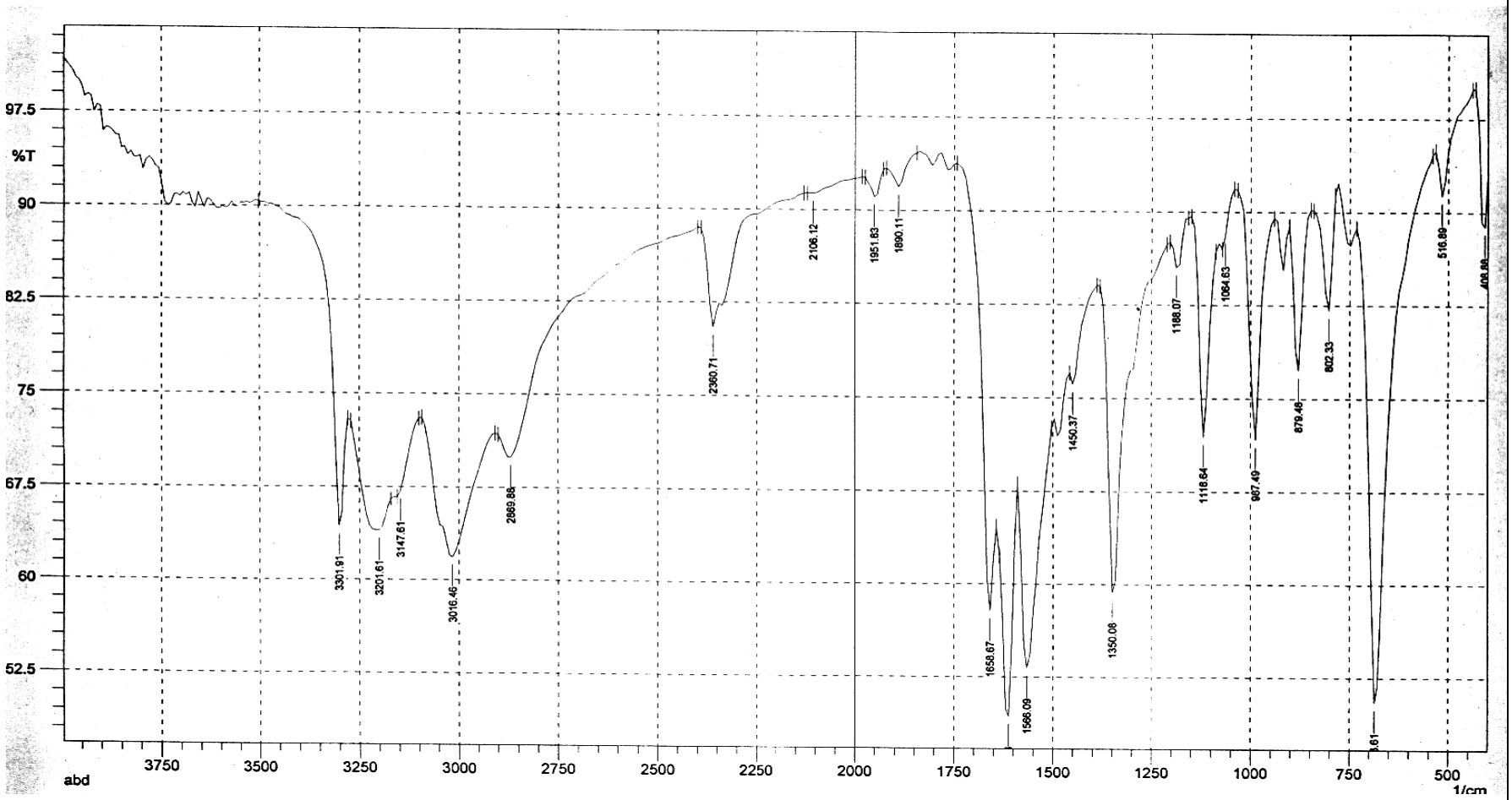
Compound [22] was synthesized form the reaction of benzohydrazine with phosphorous oxychloride mono chloroacetic acid.

The compound was characterized by its melting point and F.T.IR spectroscopy.



The F.T.IR spectrum of compound [22] indicated the disappearance of NH_2 bands in benzohydrazine at (3301.9 cm^{-1}) and (3201.6 cm^{-1}) N-H band at (3147.6 cm^{-1}) and disappearance of carbonyl group at (1658.6 cm^{-1}) and appearance of C=N band at (1550.6 cm^{-1}) and (C-O-C) asymmetric, symmetric at (1242.0 cm^{-1}) and (1018.3 cm^{-1}) and C-H aliphatic at (2854.4 cm^{-1}), C-Cl at (856.3 cm^{-1}) and (540.0 cm^{-1}).

Figure (3-b) shows the F.T.IR spectrum of benzoic acid hydrazide and figure (3-22) shows the F.T.IR spectrum of compound [22].



Melting point: 112-114°C

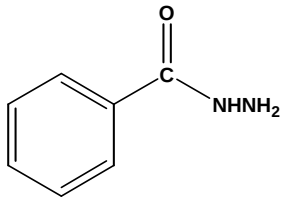
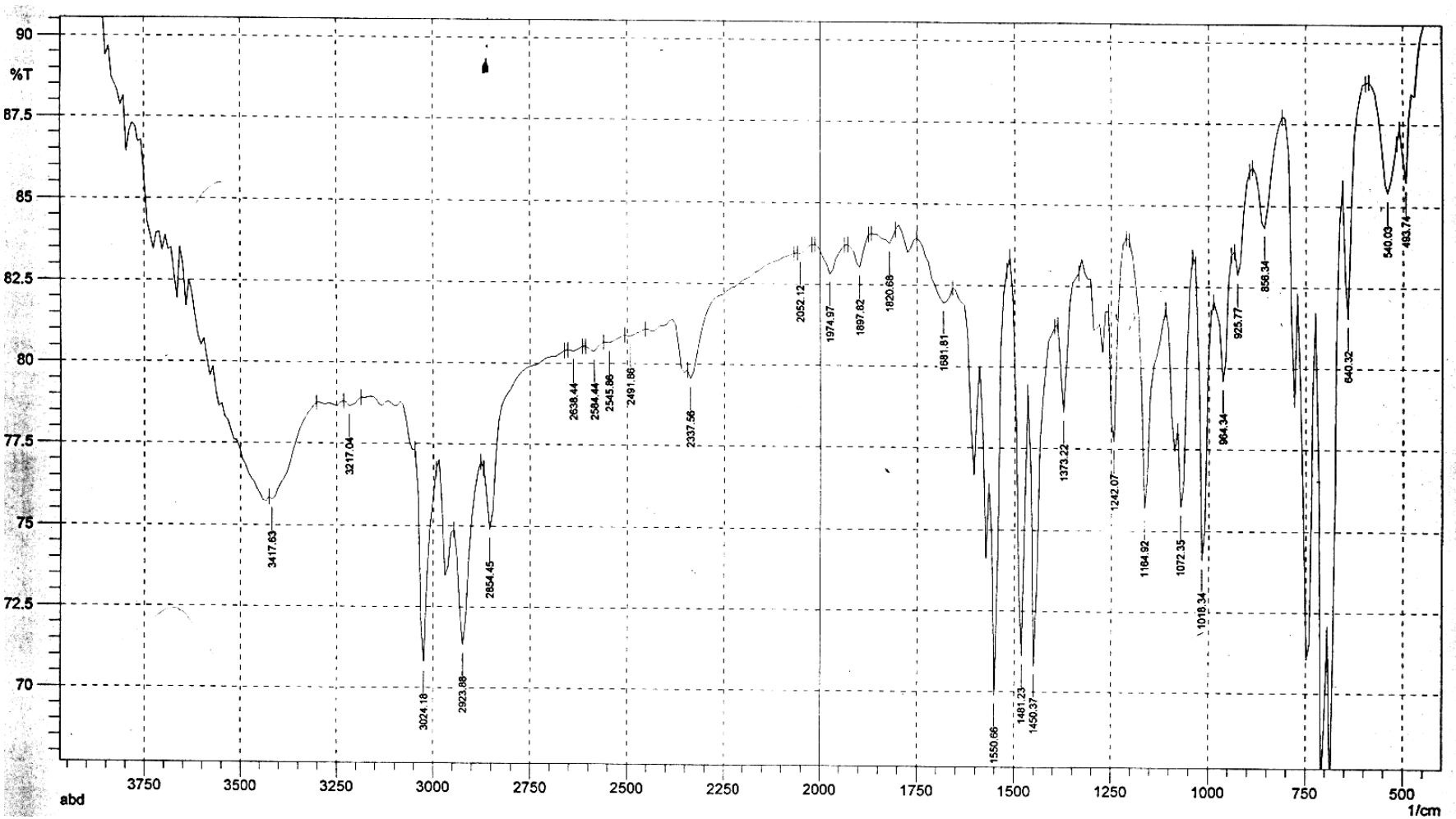


Figure (3-b): Structure, Physical Properties and F.T.IR spectrum of benzoic acid hydrazide.



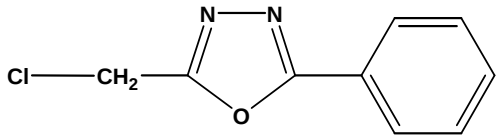
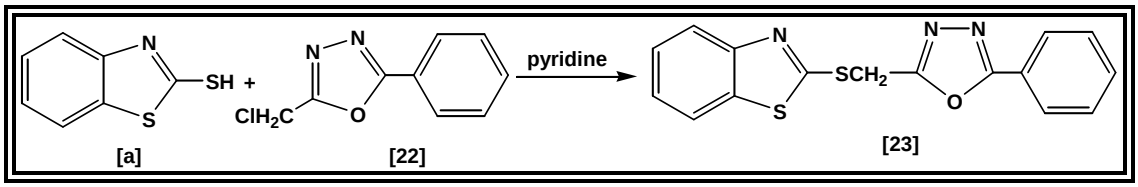
Melting point: 107-109 ^{o}C	
Yield: 70%	

Figure (3-22): Structure, Physical Properties and F.T.IR spectrum of 2-phenyl-5-chloromethyl-1,3,4-oxadiazole [22].

3.1.23 Preparation of 2-[5-phenyl-1,3,4-oxadiazol-2-thiomethyl] benzothiazole [23]:

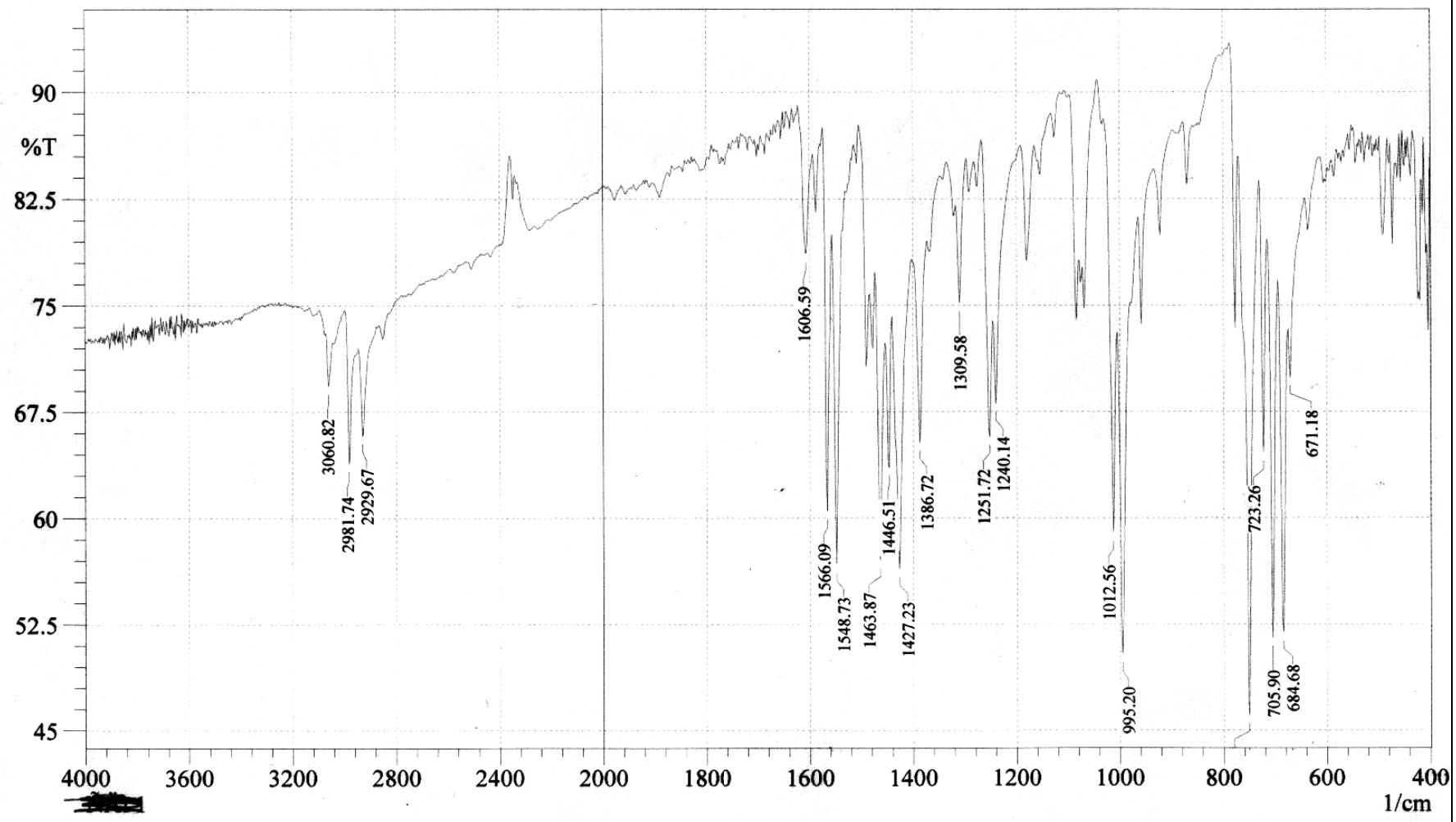
Compound [23] was synthesized from the reaction of 2-MBt with 2-phenyl-5-chloromethyl-1,3,4-oxadiazole in pyridine.

The compound was characterized by its melting point and F.T.IR spectroscopy.



The F.T.IR spectrum of compound [23] indicated the disappearance of S-H band of 2-MBt and the appearance of C-S-C band at (750.0 cm^{-1}), and the C-H band at (2981.7 cm^{-1}).

Figure (3-23) shows the F.T.IR spectrum of compound [23].



Melting point: 121-123 °C

Yield: 65%

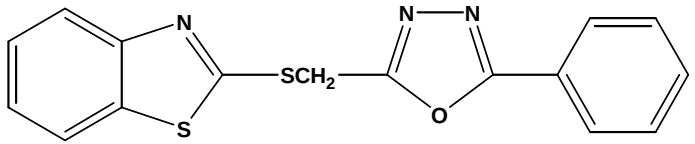
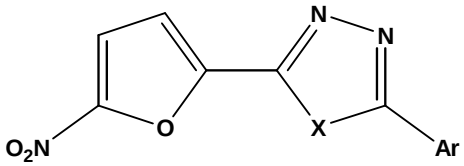


Figure (3-23): Structure, Physical Properties and F.T.IR spectrum of 2-[5-phenyl-1,3,4-oxadiazol-2-thiomethyl] benzothiazole [23].

3.2 Biological activity:

Scheman [118] found that the (–C=N–N=C–) system described by ***Dodd*** et. al. [119] may be incorporated in heterocyclic systems such compound is described in general terms by structure:



(X = NH , O and S)

Biologically significant of heterocyclic derivatives are well documented in the literature [120]. Five membered heterocyclic like 1,3,4-thiadiazoles possess a broad spectrum of biological activity [121], including antimicrobial, sedative, anticonvulsant and anti-inflammatory.

Furthermore, some substituted 5-amino-3H-1,3,4-thiadiazole-2-thiones are of interest in photography as potential anticancer agents [122], and antibacterial agents [123]. With a view to explore the possibility of obtaining biologically useful compounds that contain oxadiazole, thiadiazole and triazole ring system, such biological activity prompt us to prepare some new series containing the above mentioned units. The antimicrobial activity of some prepared compounds was determined by the agar diffusion method [123].

3-3Microbiological Method

In this work the antimicrobial test was performed according to agar well diffusion method [124], and selected three concentration for ten derivative compounds as in table(3-1) The prepared compound were tested against two pathogenic microorganism, ***Staphylococcus Aureus (G+)*** and ***Proteus vulgaris (G-)***. In the solidified media (Nutrient agar) ,suitable spaced apart holes were made (6 mm in diameter)these holes were filled with (0.1 ml) of prepared compound concentration that dissolve in DMSO(Di Methyl Sulfoxid) after spread the bacteria on agar . These plate were incubated at 37 ^{o}C for 24 hour ,the zone of inhibition of

bacteria growth around the hole was absorbed and measured in mm and are represented by (+), (++) and (+++) depending upon the diameter and clarity[125] as in table (3-2) and figure (3-24) .

Table (3-1): Concentrations used within the test.

Compound concentration	Prepare stock		Concentration
Stock	0.01 gram	2 ml DMSO	5 mg/ml
	Prepare concentrations		
	Stock	DMSO	
Concentration (a)	0.4 ml	0.6 ml	2 mg/ml
Concentration (b)	0.5 ml	0.5 ml	2. 5 mg/ml
Concentration (c)	0.6 ml	0.4 ml	3 mg/ml

Table (3-2): Antibacterial activities of some of the prepared compounds.

Strains	*Proteus vulgaris* (G-)			*Staphylococcus aureus* (G+)		
Compound No.	Concentrations			Concentrations		
	a	b	c	a	b	c
1	+++	+++	+++	++	++	+++
2	++	+++	+++	-	-	-
4	++	+++	+++	-	-	-
6	-	+	+	+	+	+
9	-	+	+	+	+	+
10	++	++	++	-	-	-
14	-	-	-	+	+	++
15	-	-	-	-	+	-
18	-	-	+	-	++	++
20	++	++	++	+	++	++

Key to symbols:

Highly active = +++ (inhibition zone > 20 mm).

Moderately active = ++ (inhibition zone 11-20 mm).

Slightly active = + (inhibition zone 5-10 mm).

Inactive = - (inhibition zone <5 mm).

The preliminary screening results reveal that the compounds contained (pyrazole, 4-thiazolidenin, oxazepine, oxazoline, thiadiazole, oxadiazole, triazole, pyridazine moiety, triazole moiety imino and thiol groups in their structures [1,2 and 4] exhibit the highest antibacterial activity against ***Proteus vulgaris (G-)*** while the substituted thiadiazole and triazole compounds showed either low or no activity against both organisms.

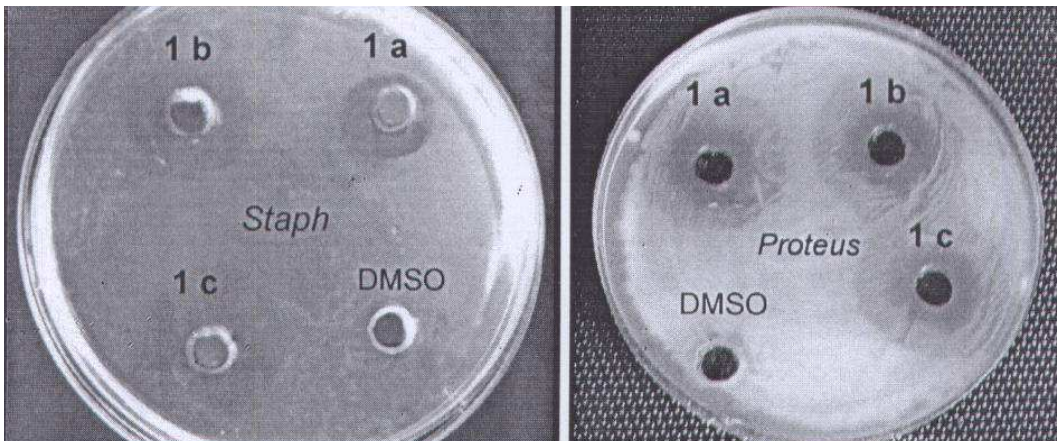


Figure (3-24): the biological activity zone of compound [1].

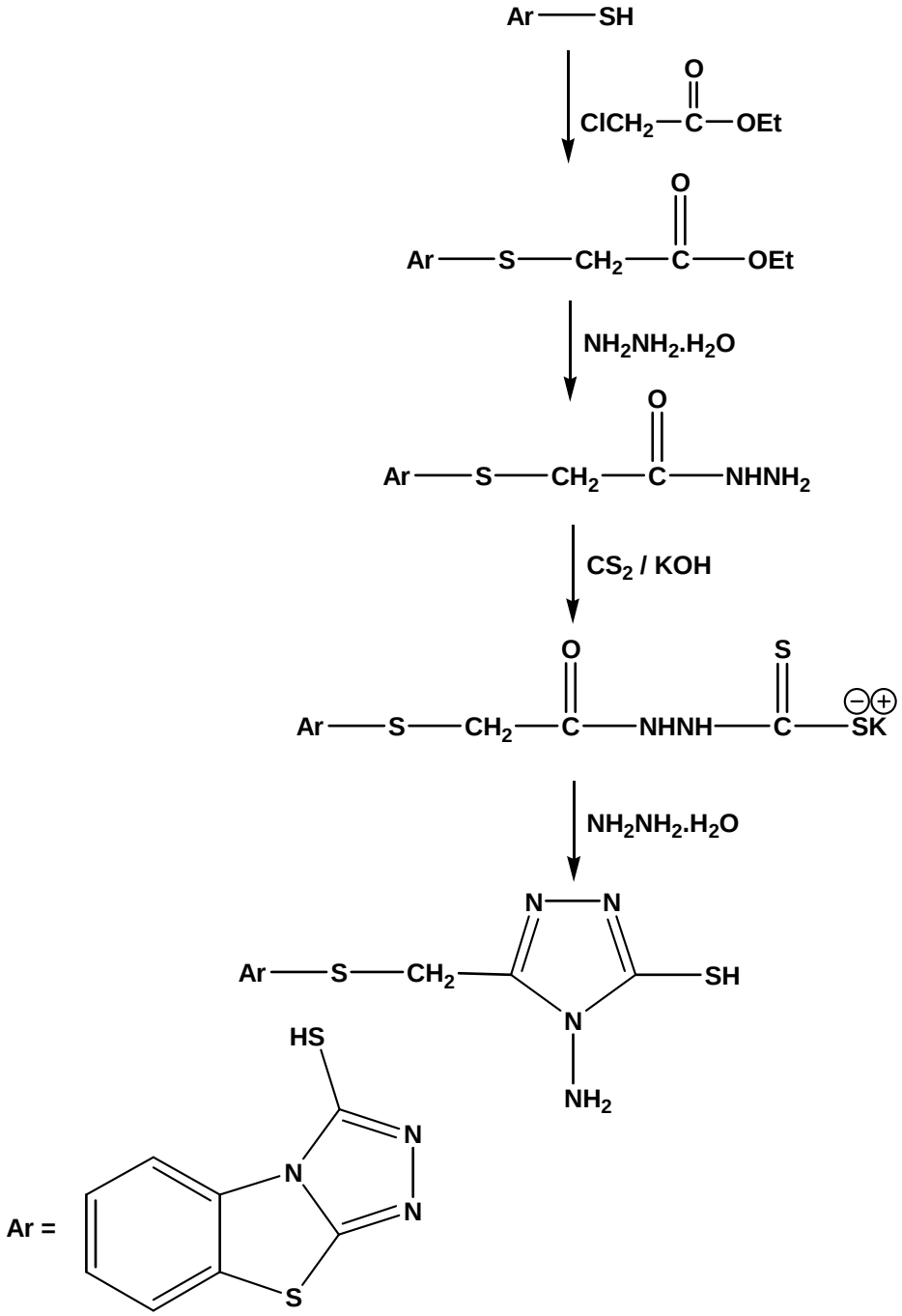
3.3 Conclusion:

In the present work synthesis and study the effect of some heterocyclic compounds on two type of bacteria ***Staphylococcus Aureus (G+)*** and ***Proteus Vulgaris (G-)*** have been described. Some of these derivatives (1,2 and 4) have shown high activity at (2, 2.5 and 3.0mg/ml).

Moreover, the compounds have been found to be the most active in the same concentration. These results confirm the fact that compounds with NH, SH and OH with heterocyclic have great potential as antibacterial agents. Thus concluded (1,2) deserve further investigation for the development of more potent agent for therapcuticuse.

stion for further work:

Formation of triazole derivatives by acylation of compound [126] [a]:



CHAPTER TWO

EXPERIMENTAL PART

2.1 Materials:

The chemicals used and the manufactures are listed in table (2-1).

Table (2-1): The chemicals and manufactures used through the project.

Compound	Supplied from
Acetic acid	BDH
Acetyl acetone	BDH
p-Bromo phenacyl bromide	Fluka
Carbon disulfide	Fluka
Chloroform	Hopkin and Williams
Dry benzene	BDH
4-Dimethyl amino benzaldehyde	BDH
Ethanol (96%)	BDH
Ethanol (abs)	BDH
Ethyl actoacetate	BDH
Hydrazine hydrate (99%)	BDH
Hydrochloric acid	BDH
Maliec acid	Fluka
Mercapto acetic acid	BDH
2-Mercapto benzothiazole	BDH
4-Mercapto benzaldehyde	BDH
4-Methoxy benzaldehyde	BDH
1-Naphthyl isocyanate	Fluka
Phenyl isocyanate	Fluka
Phosphorus oxychloride	Fluka
Phthalic anhydride	BDH
Potassium hydroxide	BDH
Pyridine	Fluka
Sodium bicarbonate	BDH
Succinic anhydride	Hopkin and Williams
Thiosemicarbazide	Fluka

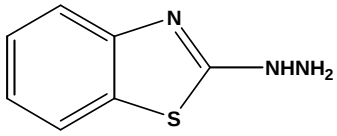
2.2 Instruments:

1) Melting points were measured using hot stage ***Gallen Kamp*** melting point apparatus and were uncorrected.

2) The F.T.IR spectra in the range (4000-600) cm^{-1} were recorded using KBr disk on a ***SHIMADZU*** F.T.IR 8300 spectrophotometer Japan.

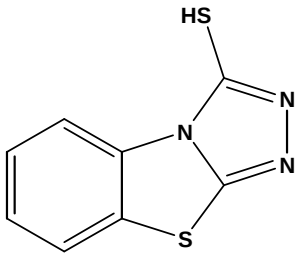
3) Thin Layer Chromatography (TLC) was carried out using Fertigfollen precoated sheets type PolyGram silg, and the plates were developed with iodine vapor.

2.3.1 Preparation of 2-hydrazino benzothiazole [1]:



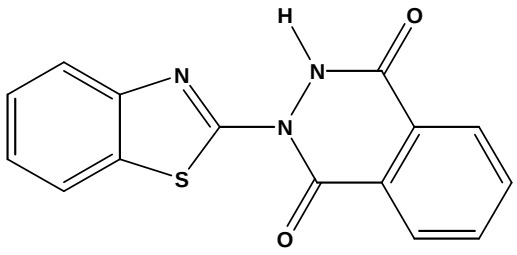
To 2-mercapto benzothiazole (1.67 g, 0.01 mol) dissolved in ethanol, was added hydrazine hydrate (99%) (0.32 g, 0.317 ml, 0.01 mol) and the mixture was then refluxed for 6 hours, excess solvent was distilled off. The resulting solid then was separated out on cooling filtered and recrystallized from ethanol [104], m.p. (203-205 ^{o}C), yield (80%).

2.3.2 Preparation of 2-mercapto-1,3,4-triazole benzothiazole [2]:



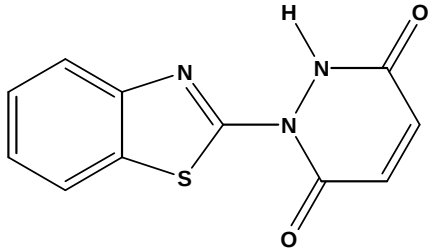
A mixture of 2-hydrazido benzothiazole [2] (0.5 g, 0.003 mol) with carbon disulfide (1.4 ml) and (1.3 ml) pyridine was refluxed on a water bath for 7 hours. Then the mixture was allowed to cool and the solid product was collected by filtration and recrystallized from ethanol [105], m.p. (243-245 ^{o}C), and yield (85%).

2.3.3 Preparation of 1-benzothiazole-2-hydrophthalazin-3,6-dione [3]:



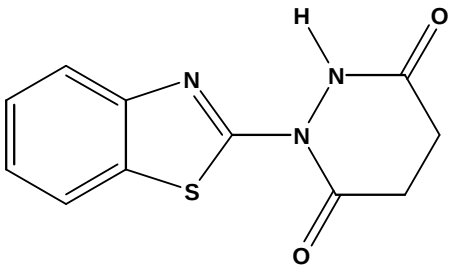
A mixture of 2-hydrazido benzothiazole [1] (0.5 g, 0.003 mol) was mixed with phthalic anhydride (0.3 g, 0.003 mol) in acetic acid (30 ml), the mixture was refluxed for 7 hours ,and then cooled and added to crushed ice. The precipitate was filtered off, washed with water and recrystallized from ethanol to the final product [106] m.p. (212-214 ^{o}C), yield (72%).

2.3.4 Preparation of 1-benzothiazole-2-hydro pyridazine-3,6-dione [4]:



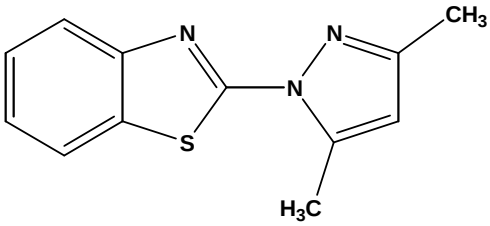
A mixture of 2-hydrazido benzothiazole [1] (0.5 g, 0.003 mol) was mixed with maleic anhydride (0.29 g, 0.003 mol) in acetic acid (30 ml) the mixture was refluxed for 7 hours, then cooled and poured on crushed ice, the precipitate was filtered off, washed with water, recrystallized from ethanol to give the final product [106], m.p. (193-195 ^{o}C), yield (70%).

2.3.5 Preparation of 1-benzothiazole 2,4,5-trihydro pyridazine-3,6-dione [5]:



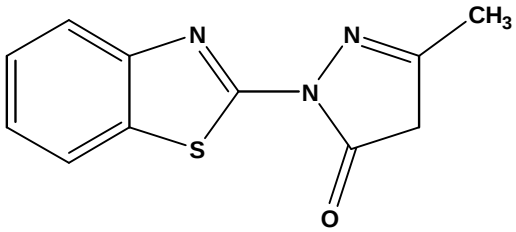
A mixture of 2-hydrazido benzothiazole [1] (0.5 g, 0.003 mol) was mixed with succinic anhydride (0.3 g, 0.003 mol) in acetic acid (30 ml), the mixture was refluxed for 7 hours, then cooled and added onto crushed ice, the precipitate was filtered off, washed with water, and recrystallized from ethanol to give the final product [106] m.p. (161-163 ^{o}C), yield (65%).

2.3.6 Preparation of 1-benzothiazol-3,5-dimethyl pyrazole [6]:



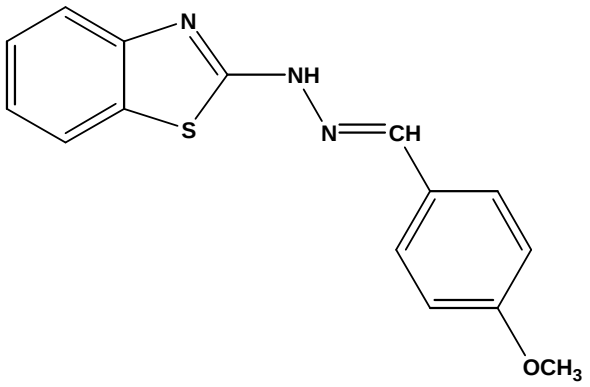
A mixture of 2-hydrazido benzothiazole [1] (0.5 g, 0.003 mol) and acetyl acetone (0.3 g, 0.003 mol) and (0.1 ml) of acetic acid in absolute ethanol (30 ml) was refluxed for 7 hours. The solution was concentrated and the solid product [107] that was formed filtered off and recrystallized from ethanol m.p. (138-140 ^{o}C), yield (86%).

2.3.7 Preparation of 1-benzothiazole-3-methyl pyrazol-5-one [7]:



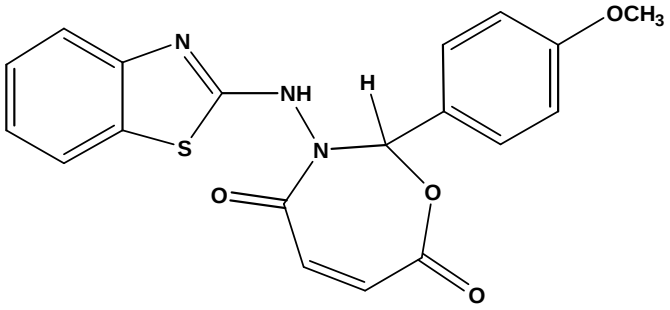
Compound [7] was prepared by the same method described by the preparation of compound [6]. The precipitate was obtained [107] m.p. (262-264 ^{o}C), yield (65%).

2.3.8 Preparation of 2-(4-methoxy benzylidine) hydrazine-2-benzothiazole [8]:



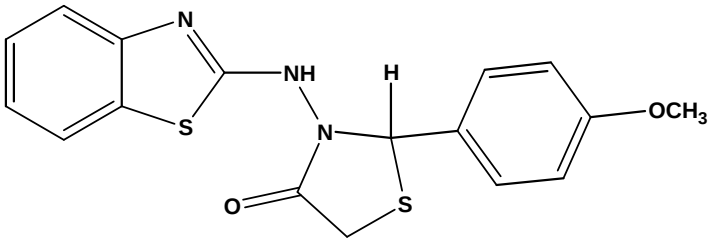
A mixture of 2-hydrazido benzothiazole [1] (0.5 g, 0.003 mol) with 4-methoxy benzaldehyde (0.41 g, 0.003 mol) in absolute ethanol (15 ml) and drops of glacial acetic acid was refluxed for 8 hours, the mixture was cooled and the solid then recrystallized from ethanol and collected by filtration [108] m.p. (187-189 ^{o}C), yield (95%).

2.3.9 Preparation of 2-[2`-(4`-methoxyphenyl)-4,7-dione-2,2`-dihydro-1,3-oxazepin-3`(2H)-yl] benzothiazole hydrazine [9]:



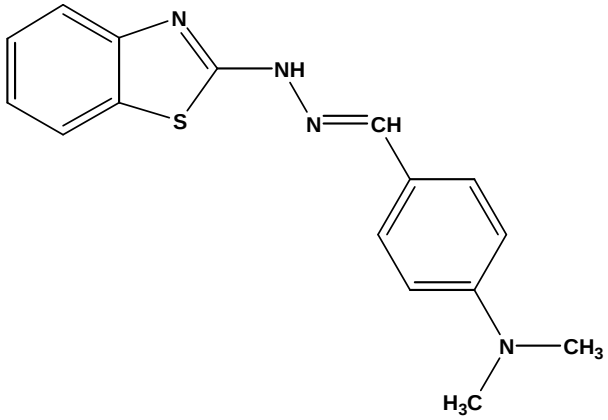
A mixture of [8] Schiff base (0.4 g, 0.001 mol) with maleic anhydride (0.98 g, 0.001 mol) dissolved in (20 ml) dry benzene and then the mixture was refluxed for 5 hours in water bath at (70 ^{o}C). Excess solvent was distilled, filtered off and recrystallized from ethanol [(109)], m.p. (175-177 ^{o}C), yield (85%).

2.3.10 Preparation of 2-[(2`-(4-methoxyphenyl)-4`-oxo-1`,3`-thiazolidin-3`- benzothiazole hydrazine [10]:



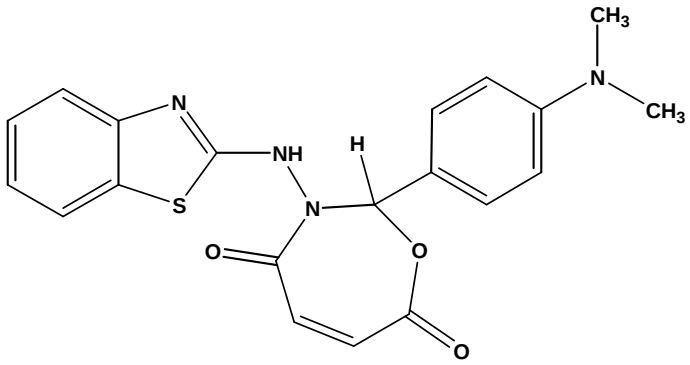
To mercapto acetic acid (0.1 g, 0.001 mol) dissolved in dry benzene (7.5 ml) was added slowly to (0.4 g, 0.001 mol) of compound [8] dissolved in dry benzene. The addition continued about 10 seconds with stirring then the mixture was refluxed for 10 hours. Excess solvent was evaporated and the residue was treated with sodium bicarbonate to produce compound [10] as solid precipitate and recrystallized from ethanol [(109)] m.p. (237-239 ^{o}C), yield (80%).

2.3.11 Preparation of 2-(4-dimethyl amino)benzylidine) hydrazine] benzothiazole [11]:



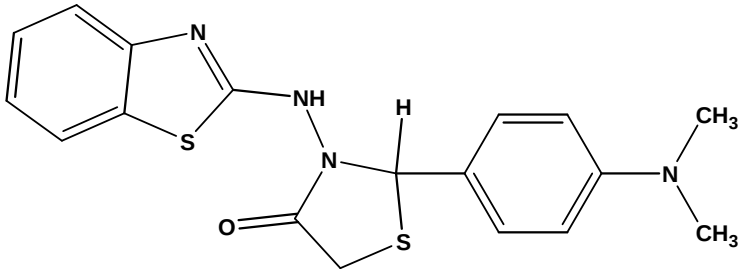
A mixture of 2-hydrazido benzothiazole [1] (0.5 g, 0.003 mol) with 4-dimethyl amino benzaldehyde (0.4 g, 0.003 mol) in absolute ethanol (15 ml) and drops of glacial acetic acid was refluxed for 8 hours. The mixture was cooled to form solid precipitate and recrystallized from ethanol [108] m.p. (254-256 ^{o}C), yield (90%).

2.3.12 Preparation of 2-[(2`-(4`-(dimethylamino)phenyl)-4,7-dione-2,2-dihydro-1,3-oxazepin-3`(2H)] benzothiazole hydrazine [12]:



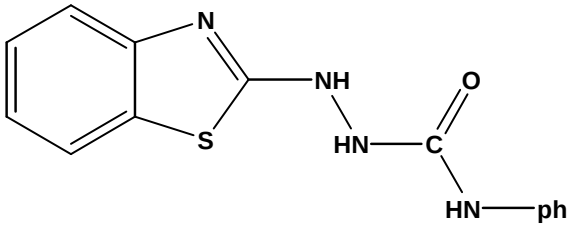
A mixture of [11] Schiff base (0.4 g, 0.001 mol) with maliec anhydride (0.98 g, 0.001 mol) dissolved in (20 ml) dry benzene. Then the mixture was refluxed for 5 hours in water bath at (70 ^{o}C). Excess solvent was distilled and filtered of the precipitate and recrystallized from ethanol[109] m.p. (149-150 ^{o}C), yield (66%).

2.3.13 Preparation of 2-[(2`-(4-(dimethylamino)phenyl)-4`-oxo-1`,3`-thiazolidin-3`-yl)] benzothiazole hydrazine [13]:



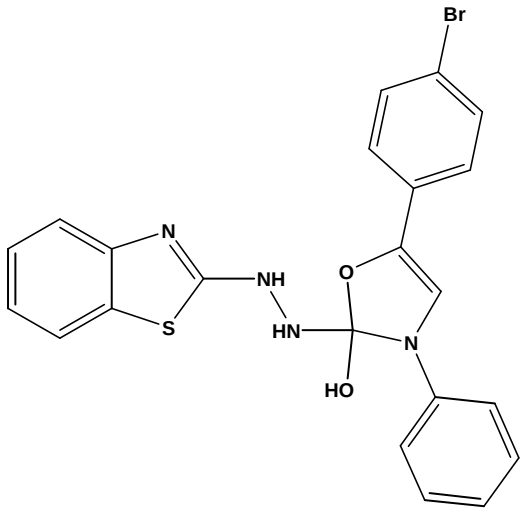
Mercapto acetic acid (0.1 g, 0.01 mol) dissolved in dry benzene (7.5 ml) was added slowly to (0.4 g, 0.001 mol) of compound [11] dissolved in dry benzene. The addition continued about 10 seconds with stirring then the mixture was refluxed for 10 hours. Excess solvent was evaporated and remains were treated with sodium bicarbonate to produce compound [13] as solid precipitate and recrystallized from ethanol [109] m.p. (278-280 ^{o}C), yield (91%).

2.3.14 Preparation of 2-N-benzothiazole-N`-phenyl hydrazine carboxamide [14]:



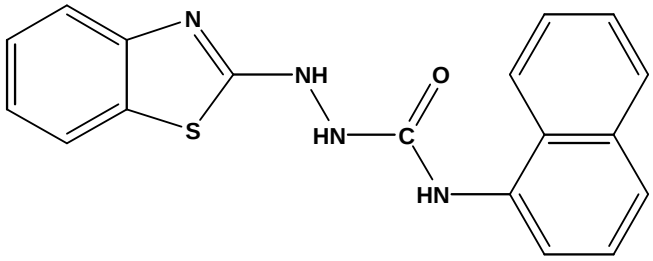
A mixture of 2-hydrazido benzothiazole [1] (1 g, 0.006 mol) and phenyl isocyanate (0.71 g, 0.006 mol) was refluxed in absolute ethanol (30 ml) for 6 hours, then cooled and filtered, the formed solid was recrystallized from benzene [110], m.p. (214-216 ^{o}C), yield (81%).

2.3.15 Preparation of 2-N-[(3)-N`-phenyl-5-(p-bromophenyl)-2`-hydroxy-1,3-oxazolin-2`-yl] benzothiazol hydrazine [15]:



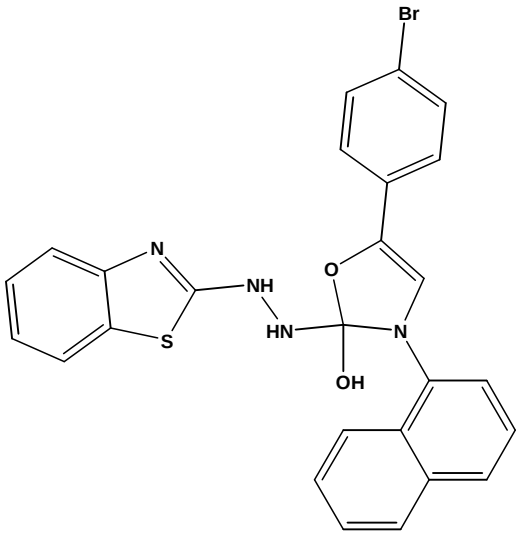
A mixture of compound [14] (0.85 g, 0.003 mol) and *p*-bromo phenacyl bromide (0.83 g, 0.003 mol) in absolute ethanol (30 ml) was refluxed for 8 hours, cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washed with water, dried and recrystallized from ethanol giving the final product [110] m.p. (178-180 ^{o}C), yield (74%).

2.3.16 Preparation of 2-N-benzothiazole-N`-1-naphthyl hydrazine carboxamide [16]:



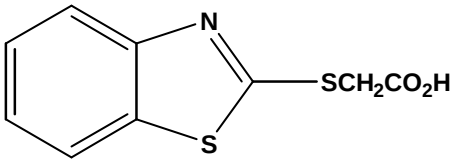
Compound [16] was synthesized by the same method described for the preparation of compound [14] using 1-naphthyl isocyanate (0.5 g, 0.003 mol) [110] m.p. (223-225 ^{o}C), yield (96%).

2.3.17 Preparation of 2-N-[(3`)-N`-(1-naphthyl)-5`-(p-bromo phenyl)-2`-hydroxy-1,3-oxazolin-2`-yl)] benzothiazol hydrazine [17]:



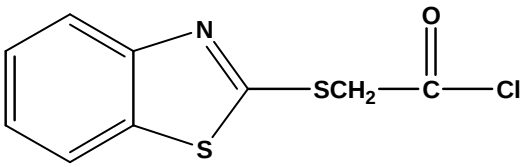
Compound [17] was synthesized by the same method described foe the preparation of compound [15] using compound [16] (0.68 g, 0.003 mol) instead [110] m.p. (179-181 ^{o}C), yield (62%).

2.3.18 Preparation of 2-thiaacetic acid benzothiazole [18]:



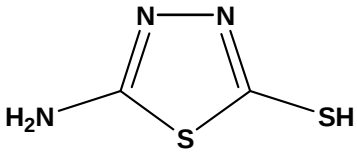
To a stirred solution of (2-MBT) (1.67 g, 0.01 mol) in (25 ml) of ethanol and excess of KOH was added slowly. Chloro acetic acid (0.94 g, 0.01 mol) was added gradually with stirring, the mixture was refluxed for 2 hours after that the mixture was cooled and filtered, the filtrate was poured into ice-water, the crude product was recrystallized from ethanol [111] m.p (228-230 ^{o}C), yield (62%).

2.3.19 Preparation of 2-thiaacetyl chloride benzothiazole [19]:



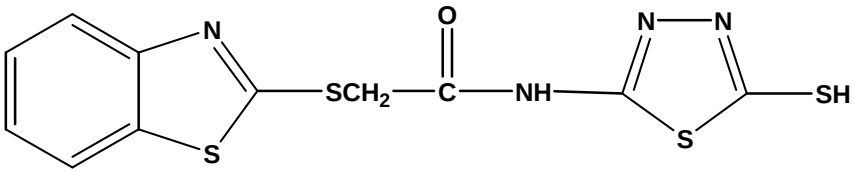
To a solution of 2-thiaacetic acid benzothiazole (0.4 g, 0.002 mol) and thionyl chloride (10 ml) was refluxed for 7 hours. Excess thionyl chloride was evaporated, the formed solid was recrystallized from benzene[112] m.p. (307-309 ^{o}C), yield (90%).

2.3.20 Preparation of 5-amino-2-mercapto-1,3,4-thiadiazole [20]:



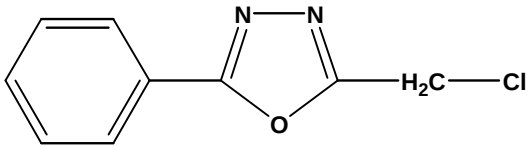
Potassium hydroxide (2.24 g, 0.04 mol) was dissolved in absolute ethanol (20 ml) and carbon disulfide (4.57 g, 3.62 ml, 0.06 mol) was added to the solution. After the addition of carbon disulfide thiosemicarbazide (3.38 g, 0.04 mol) in absolute ethanol (20 ml) was added and the mixture was stirred and refluxed for 6 hours most of the residue was dissolved in water (15 ml) and carefully acidified with concentrated hydrochloric acid (3.5 ml) the precipitate was filtered and washed with cold water and recrystallized from ethanol [112] m.p. (229-231 ^{o}C), yield (92%).

2.3.21 Preparation of 2-mercapto-[5-acetamid thiamethyl benzothiazol]-1,3,4-thiadiazole [21]:



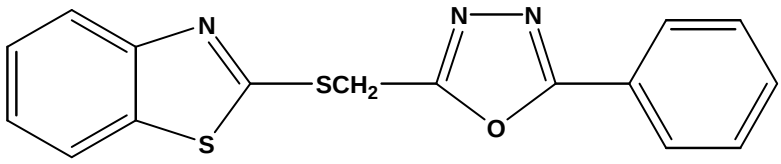
To a solution of [19] (0.4 g, 0.0016 mol) in absolute ethanol (25 ml), triethyl amine (0.23 ml, 0.0016 mol) was added with stirring followed by the addition of compound [20] (0.22 g, 0.0016 mol) to the reaction mixture which was refluxed for 4 hours. Triethyl amine hydrochloride was filtered off, the solution was concentrated to one-third of its original volume and carefully treated with concentrated hydrochloric acid, and the precipitate was collected by filtration and recrystallized from ethanol [112] m.p. (120-122 ^{o}C), yield (57%).

2.3.22 Preparation of 2-phenyl-5-chloromethyl-1,3,4-oxadiazole [22]:



A mixture of benzohydrazine (1.36 g,0.01 mol), chloro acetic acid (0.92 g, 0.01 mol) and phosphorous oxychloride (5 ml) was refluxed for 5 hours, the mixture was cooled, poured on ice-water and made alkaline by adding sodium bicarbonate solution. The resulting solid filtered, dried and recrystallized from (a mixture of acetone and ethanol) to give the titled compound [113] m.p. (107-109 ^{o}C), yield (70%).

2.3.23 Preparation of 2-[5-phenyl-1,3,4-oxadiazol-2`-thiomethyl] benzothiazole [23]:



A mixture of (2-MBT) (0.42 g, 0.0025 mol) and 5-phenyl-2-chloromethyl-1,3,4-oxadiazole (0.5g, 0.0025mol) was refluxed in pyridine (15 ml) for 4 hours. The mixture was then poured into ice-water the resulting solid was then washed and recrystallized from ethanol[114,115] m.p. (121-123 ^{o}C), yield (65%).

Table (3-): F.T.IR spectral data of the prepared compounds.

No	ν N-H (cm^{-1})	ν C-H arm (cm^{-1})	ν C-H aleph (cm^{-1})	ν C=N (cm^{-1})	ν C=C (cm^{-1})	ν C=O ester (cm^{-1})
1	3128.3	3051.2	-	1647.1	1554.5	-
2	3082.0	3000.0	-	1621.9	1535.2	-
3	3201.6	3000.0	-	1593.1	1465.8	-
4	3244.0	3020.0	-	1535.1	1450.8	-
5	3205.0	3082.0	-	1535.2	1450.4	-
6	-	3060.0	2916.2	1585.4	1531.4	-
7	3100.0	3091.6	2923.9	1585.4	1531.4	-
8	3199.7	3074.3	2831.3	1616.2	1508.2	-
9	3199.7	3080.0	2943.2	1512.1	1446.5	1691.0
10	3199.7	3020.0	2862.2	1604.7	1515.9	-
11	3188.1	3080.1	2885.3	1614.3	1569.9	-
12	3195.9	3041.53	2908.4	1616.2	1598.8	1708.81
13	3186.1	3082.0	2923.8	1610.4	1550.0	-

14	**3278.8**	**3080.0**	**-**	**1606.6**	**1537.2**	**-**
15	**3272.9**	**3031.8**	**-**	**1620.09**	**1500.0**	**-**
16	**3261.4**	**3051.18**	**-**	**1618.17**	**1564.16**	**-**
17	**3259.4**	**3041.53**	**-**	**1614.31**	**1564.1**	**-**
18	**-**	**3070.0**	**2900.0**	**1583.4**	**1500.0**	**1712.4**
19	**-**	**3062.7**	**2854.4**	**1542.9**	**1400.0**	**1731.02**
20	**-**	**-**	**-**	**1604.7**	**1546.8**	**-**
21	**3263.3**	**3116.7**	**2854.4**	**1550.6**	**1458.0**	**-**
22	**-**	**3024.1**	**2854.4**	**1550.6**	**1481.2**	**-**
23	**-**	**3060.8**	**2981.7**	**1606.5**	**1548.7**	**-**

No	**ν NH_2 (cm^{-1})**	**ν C=O amide (cm^{-1})**	**Others**
1	**3313.5-3201.6**	**-**	**C-S 752.2**
2	**-**	**-**	**C=S 1330.8**
3	**-**	**-**	**S-H 2560.0**
4	**-**	**1728.1**	**-**
5	**-**	**735.8**	**-**
6	**-**	**1690.3**	**-**
7	**-**	**-**	**-**
8	**-**	**1735.8**	**O-H 3440.8**
9	**-**	**-**	***p*-CH_3 821.6**
10	**-**	**1620.1**	**C-O-C 1249.8-1022.2**
11	**-**	**1692.1**	**O-H 3440.8, C-S 732.9**
12	**-**	**-**	***p*-NCH_3 813.9**
13	**-**	**1660.60**	**C-O-C 1250.0-1030.1**
14	**-**	**1712.01**	**C-S 748.33**
15	**-**	**1660.6**	**-**
16	**-**	**-**	**O-H 3451, C-O-C 1250-1016, C-Br 550**
17	**-**	**1683.74**	**-**
18	**-**	**-**	**O-H 3459, C-O-C 1253-1010, C-Br 550**

19	**-**	**-**	**O-H 3450, C-Cl 758.0**
20	**336.6-3151.8**	**-**	**S-H 2773.4, C=S 1342.4, C-S 736.8**
21	**-**	**1666.3**	**S-H 2525, C=S 1365, N-N 1242, C-S 746**
22	**-**	**-**	**C-O-C 1242-1-18, C-Cl 856, 540**
23	**-**	**-**	**C-S-C 750, C-O-C 1251-1030**

References:

1. H. l. Yalc and k. Losee, *J.* Med. Chem., **9**, 478 (1966).

2. K. Potts, Chem. Rev., **61**, 87 (1961).

3. P. y. Bruice, "Organic Chemistry", 2nd ed. Viacom Company (1998).

4. D. Barton and W.D. Oills, "Comprehensive Organic Chemistry", ed. P.G. Sammes. Vol. **4**, 357 (1979).

5. L. Z. Xu, k. Jioo, S.S. Zhang and s. P. Kuang, *Bull- Korean chem. Soc.*, **23**, 12 (2002).

6. Liang-Zhangxw Shu-Sheng Zhang, shu-Yon Nia, Xong-Qi Qin, xuemei Li and Kui Jiao, *Molecules*, **9**, 913 (2004).

7. Khosrow ZAMANI, Khalil FAGHIHI, Taraeh TOFIGHI, Mohammad rezas HARIATZADEH, *Turk. J. chem.*, **28**, 95 (2004).

8. W. T. Al-Rubayee, M. Sc. Thesis College of Science Al-Nahrain University (2004).

9. J. P. Henichart, H. Rymond and L. Brigitte, *Heterocyclic Chem. Soc.*, **14**(4) 615 (1977).

10. B. N. Goswami, J. C. S. Kataky and J. N. Baruah, *J. Indian Chem. Soc.*, Lxi, 530 (1984).

11. Z. M. Al-Rubaiy, M. Sc. Thesis Baghdad University Iraq (1998).

12. S.y. Liu and X. P. Hui, *Chemical Journal of Chinese University*, **21**, **9**, 1386 (2000).

13. A. shafiee, A. Reza and M. Sharifaoleh, *Daru*, **11**(2), 15 (2003).

14. J. Lang and H. Tondy, *Pol. Pharmacol. Pherm.*, **27**, 211 (1975).

15. A. Hazzaa and R. M. Shafik, *J. Pharm. Sci.*, **19**, 201 (1980).

16. D. M. Shapiro and M. E. Shils, *Chem. Pharm. Bull.*, **22**, 2773 (1974).

17. H. Shailaja, K. Mogilaiah, J. Sudhakar and B. Sreenirasuls, *Indian J. Chem.*, **3512**, 745 (1996).

18. H. X. Allawy, M. Sc. Thesis, Baghdad University Iraq (2000).

19. Mohye Abdel-Fatah and Ibrahimm El-Deen, *Indian J. Chem.*, **35B**, 1067 (1996).

20. N. A. Al-Naim, M. Sc. Thesis College of Science, Al-Nahrain University (2001).

21. A. Shafiee, E. Naimi, A. Foroumdi and M. Shekaria, *J. Heterocyclic Chem.*, **32**, 1235 (1995).

22. Chem. Abstract, Heterocyclic Vol:98 (143347) p. 573 (1983).

23. E. R. Alexander, "Principles of Ionic Organic Reactions", U.S.A. & U.K., **6** (1960).

24. K. Schogield, MTP, Inter. Review of Science, London, **4** (1973).

25. A. Sener, *Turk. J. Chem.*, **28**, 39 (2004).

26. P. Coudert, E. Albusson, J. Y. Boire and P. Bastide, *Eur. J. Med. Chem.*, **29**, 471 (1994).

27. O. B. Ostby, L. L. gunderson, F. Rise and A. Bast, *Arch. Pharm. Med. Chem.*, **29**, 471 (1994).

28. A. Önal, Y. Akcamur and B. Altural, *Turk. J. Chem.*, **20**, 159 (1996).

29. J. Contreras, y. Rival, S. Chayer and C. Wermuth, *J. Med. Chem.*, **42**, 730 (1999).

30. A. M. Ameer and I. A. G. Attia, m. el-Mobayad and S. Asker, *Polish J. Chem.*, **74**, 681 (2000).

31. A. K. Tewari and A. Mishra, *Bioorg & Med. Chem.*, **9**, 715 (2001).

32. H. Chen, Z. Li and Y. Han, *J. Agric. Food Chem.*, **48**, 5312 (2002).

33. G. M. Badger, "The Chemistry of Heterocyclic compounds", Academic Press, Inc., London (1961).

34. H. a. Soleiman, A. K. Khalafollah and H. M. Abdel Zahar, *J. Chin. Chem. Soc.*, **47**(61), 12670 (2000).

35. J. L. Wang, F. Ding, J. Z. Huo and Y. H. Qiang, *Polish J. Chem.*, **78**, 303 (2004).

36. F. A. L-Saied, M. I. Ayad, R. M. Issa and S. A. Aly, *Polish J. Chem.*, **75**, 941 (2004).

37. Al. Levai, AR KRKIVOC IX, 344 (2005).

38. I. L. Finer, "Organic Chemistry", 5th ed., U.K. (1975).

39. L. B. Twnsend, Chem. Rev. **67**, 533 (1976).

40. A. H. El-Massry, H. H. Fahmy and S. H. Abdel-Wahed, *Molecules*, **5**, 1429 (2000).

41. A. Danel, K. Chaczatuian and P. Tomasik, ARKIVOC, **1**(1), 51 (2001).

42. M. A. Saleh, M. F. Abdel-Magged, M. A. Abdo and A. M. Shokre, *Molecules*, **8**, 363 (2003).

43. M. Mclanghlin, R. M. Mohareb and H. Rapoport, *J. Org. Chem.*, **68**, 50 (2003).

44. C. Kus and N. Altaular, *Turk. J. Chem.*, **27**, 35 (2003).

45. Z. Kang, C. dykstra and D. Boykin, *Molecules*, **9**, 35 (2003).

46. A. K. Nezhad, M. N. Soltani, H. Mohabathkar and Z. Asrari, *Bioorg. & Med. Chem.*, **13**, 1931 (2005).

47. m. R. Grimmet, "Comprehensive Heterocyclic Chemistry, Five membered rinf with two or more nitrogen atom",ed. By K. T. Potts, Vol. 5, Part UA, Pergaman Press, LFd., Oxford.

48. J. A. Mohan, G. S. Anjaneyulu and R. Kiran, *Indian J. Chem.*, **27B**, 128 (1988).

49. F. C. Brown, Chem. Rev. **61**, 463 (1961).

50. F. Al-Omran, A. M. Mohareb and A. Abou El-Khair, *J. Heterocyclic Chem.*, **39**, 877 (2002).

51. H. Fahmay, E. M. M. Kassem, W. A. M. Abdou and S. A. Mohmoud, *Egypt J. Pharm.*, **38**(3), 13 (1997).

52. F. Aydogan, N. Öcal, Z. Turgut and C. Yolacan, *Bull. Korean Chem. Soc.*, **22**(5), 476 (2001).

53. H. M. F. Madkour, arkivocl, **36** (2004).

54. A. Rao, A. Chimirri, S. Ferro and P. Monofort, Arkivic, V, 147 (2004).

55. Obaid H. Abid, *Irq. J. Chem.*, **3**, 480-492 (2001).

56. F. A. Hussein and Obaid H. Abid, *Irq. J. Chem.*, **27**, 751-763 (2001).

57. F. A. Hussein and Sabah. T. Najim, *Irq. J. Chem.*, **28**, 13-25 (2002).

58. J. Ple Roux, J. C. Cherton and P. L. Dosbene, C. R. A. Cadsci, **37**, 280 (1975).

59. Kumaqai, Tsutmou, Facsci, Tohoku University Semdai, Nippon Kagaku Katshi, **64**, 158 (1984).

60. J. Wang and D. Ming, *J.Tetrahedron Asymmetry*, **15**, 119 (2004).

61. J. Kenner, *J. Chem. Soc.*, **15**, 613 (1913).

62. L. V. Dvorkeu, R. B. Symth and K. Mislow, *J. Am. Chem. Soc.*, **80**, 486 (1958).

63. A. J. Phillips, Y. Uto, P. Wife, M. J. Reno and D. R. Williams, *Org. Lett.*, **2**, 1165 (2000).

64. T. H. Chan and G. Z. Zhang, Can, *J. Chem.*, **75**, 629 (1997).

65. A. K. Chosh, P. Mathivanan, Cappiello, *J. Tetrahedron Asymmetry*, **9**, 1 (1998).

66. J. S. Johnson and D. A. Evans, *Acc. Chem.. Res.*, **33**, 325 (2000).

67. H. J. Zhu, B. T. Zhao, W. M. Dai, J. Zhau and X. J. Hao, *J. Tetrahedron Asymmetry*, **9**, 2879 (1998).

68. R. Shintani and G. C. fu, *Org. Lett.*, **4**, 3699 (2002).

69. J. V. Allen, C. G. Frost and J. M. Williams, *J. Tetrahedron Asymmetry*, **4**, 649 (1993).

70. W. p. Deng, X. L. Hau and L. X. Dai, *J. Tetrahedron Asymmetry*, **10**, 4689 (1999).

71. W. b. Zhang, H. Yoshnaga, Y. Imai, T. Kidu and Y. Nakatsuji, *I. Synlett*, **10**, 1512 (2000).

72. Y. Imai, S. Mastio, W. B. Zhang, Y. Nakatsuji and Ikeda, *I. Synlett*, **2**, 239 (2000).

73. C. Bolm, K. Miniz-Fernandez, A. Seger, G. Raabe and J. Gunther, *J. Org. Chem.*, **63**, 7860 (1998).

74. C. Blom, K. Muniz-Fernandez and J. P. Hildebrand, *Org. Lett.*, **1**, 491 (1998).

75. I. M. Pastor and H. Adolfsson, *Tetrahedron Lett.*, **43**, 1743 (2002).

76. J. Sand Storm, "Advanced in Heterocyclic Chemistry", CA. R. Katrizky and A. B. Bouttan, ed J. Vol. 9, Academic Press, Inc. New York, p.165 (1966).

77. J./ 1,3,4-thiadiazole)-3-amino-1,3,4-thiadiazol) F. htm.

78. A. Freund and R. meineck, *Ber.*, **29**, 2511 (1896).

79. H. Pulvermacher, *Ber.*, **27**, 613 (1894).

80. E. Hoggarth, *J. Chem. Soc.*, 1163 (1949).

81. E. V. Tao and C. F. Christie, *Org. Prep. Proced. Int.*, **7**, 179 (1975).

82. Neslihan Demirbas, *European Journal of Medicinal-Chemistry*, **39**, 793 (2004).

83. Neslihan Demirbas, *Turk. J. Chem.*, **29**, 125-133 (2005).

84. J:/ 1,3,4-thiadiazole/ 2-amino-1,3,4-thiadiazole-tm.

85. Desmet and Van Doemael, *Bull. Soc. Chim. Belgers*, **58**, 472 (1949). [C. A. 45, 607 (1951)].

86. Bottcher and Bauer, *Ann.*, **568**, 218 (1950).

87. Elderfield and Short, *J. Org. Chem.*, **17**, 758 (1952).

88. H. J. Carlson, K. B. J. Jorgensen, *J. Heterocyclic Chem.*, **31**, 805 (1994).

89. A. S. Hameed, Ph. D. Thesis, College of Science, Al-Nahrain University (1999).

90. A. R. Katritzky, D. O. Tymoshenko, D. Monteux, V. Vredensky, G. Nikonor, C. b. Cooper and M. J. Deshpande, *J. Org. Chem.*, **65**, 8059 (2000).

91. S. Cao, *Journal of Fluorine Chem.*, **117**, 63-66 (2002).

92. A. K. Mansour, *Molecules*, **8**, 744-755 (2003).

93. German Patent, **221**, 310 (1908).

94. J. L. Bolland and G. Gee, *Trans. Faraday Soc.*, **42**, 236 (1964).

95. L. Bateman and G. Gee, *Proc. Roy. Soc.*, **9**, 376 (1948).

96. A. M. Trozzolo, "Stabilization Against Oxidative Photodegradation", (W. Hawkins), Wiley Interscience Publisher, p. 159 (1971).

97. W. Schnabel, "Polymer Degradation: Principle and Practical Applications", Hanser Int. München. Chapter 14 (1981).

98. A. Torkai, T. Kobatake and F. Okisaki, *J. Appl. Sci.*, **67**, 1293 (1998).

99. I. k. Jassim, M. Sc. Thesis, College of Science, Baghdad University Iraq (1995).

100. F. Firoozi, K. Javidnia and A. Shafiee, *J. Heterocyclic Chem.*, **32**, 123 (1995).

101. D. H. Jones Slack; Squiress and Wolldringe, K. R. H. Medicine, 676 (1965).

102. I. L. Finar, "Organic Chemistry, Stereochemistry", Fifth Eddtion, London (1976).

103. N. Soni, J. P. Barthwal and P. Bhargava, *J. Heterocyclic Chem.*, **19**, 29 (1982).

104. Y. Watabe, H. Yoshiwara and M. Kahao, *J. Heterocyclic Chem.*, **30**, 195 (1993).

105. T. T. Abdel Rahman, Ph. D. Thesis, Baghdad university (2004).

106. G. E. Wieg and V. J. Bauer, *J. Med. Chem.*, **12**, 943 (1069).

107. I. M. Abdon, A. M. Salah and H. F. Zohdi, *Molecules*, **9**, 109 (2004).

108. S. A. Nassar, M. A. El-Hashsash, *Egypt J. Chem.*, **40**, 239 (1997).

109. Afaf H. Al-Masry, H. H. Fahmy and S. H. Ali Abdel Wahed, *Molecules*, **5**, 1429 (2000).

110. E. S. El-Tamaty, M. E. Abdel-Fattah and I. M. El-Deen, *Indian J. Chem.*, **35B**, 1067 (1997).

111. I. V. G. Nargund, G. R. N. Reddy and Hariprased, *Indian J. Chem.*, **35**, 499 (1996).

112. B. Miller, "Advanced Organic Chemistry", First Eddition, Viacom Company (1998).

113. J. Agre, Food Chem., No. 1, 51 (2003).

114. Basci. Biotech. Biochem., **57**(6), 989-991 (1993).

115. Synth. Rect. Inorg. Met. Org. Chem., **24**(1), 95-115 (1994).

116. P.W. Hichomott, *J. Tetrahedron*, **38**, 1975 (1982).

117. R. F. Daley and S. J. Daley, "Organic Chemistry", p. 359 (1996).

118. W. R. Sherman, *J. Org. Chem.*, **26**, 88 (1961).

119. I. Mir, M. T. Siddiqni**,** *J. chem. Soc. (C)*, 2798 (1971).

120. A. Fujinami, T. Ozaki, K. Nodera and K. Tanaka, *Agric. Biol. Chem.*, **36**, 318 (1972).

121. E. O. Lima, E. F. Queroz and V. C. Filho, *Bol. Soc. Chil. Quim*, **44**, 210 (1999).

122. M. Suiko, S. Hayashida and S. Nakatsu, *Agric. Biol. Chem.*, **46**, 2691 (1982).

123. Z. Li and B. Hu, *Ying Young Huazues*, **5**, 54 (1988); [C. A. 110, 723489 (1989)].

124. Rahman, M.U. and S. Gul. (2002) Antibacterial activity of hydrodistilled essential oil of *Psammogeton canescens* N.O. Umbelliferae. Biotechnol. 1(1): 55-60.

125. Harrigan, W.F. and McCance,M.E. (1976) Laboratory Methods in food and Dairy Microbiology pp.451. Academic press INC. (London)LTD.

126. E. H. El-Tmany, E. M. Salem, R. N. Matwaily and A. H. Soghier, *Egypt J. Chem.*, **40**(5), 339 (1997).

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SYNTHESIS AND BIOLOGICAL ACTIVITY OF FIVE, SIX AND SEVEN MEMBERED HETEROCYCLIC DERIVATIVESE

A THESIS
SUBMITTED TO THE COLLEGE OF SCIENCE AL-NAHRAIN UNIVERSITY IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCE IN CHEMISTRY

By
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(B.Sc 2004)

December 2006 *Thi-Alhjaa1427*

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة النهرين
كلية العلوم
قسم الكيمياء

تحضير ودراسة الفعالية البايولوجية لنوعين من البكتريا لمشتقات الحلقات الخماسية والسداسية والسباعية الغير متجانسة

رسالة
مقدمة إلى كلية العلوم- جامعة النهرين
وهي جزء من متطلبات نيل درجة الماجستير في الكيمياء

من قبل
رؤى محمد ضيدان الجبوري
بكالوريوس ٢٠٠٤ (جامعة النهرين)

ذي الحجة ١٤٢٧ كانون الاول ٢٠٠٦

Supervisor certification

I certify that this thesis was prepared under our supervision at the Department of Chemistry, College of Science, Al-Nahrain University as a partial requirements for the Degree of Master of Science in Chemistry.

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Date:

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Date:

In view of the available recommendation, I forward this thesis for debate by the Examining Committee.

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Head of the Department of Chemistry College of Science Al-Nahrain University

Examining Committee's Certification

We, the Examining Committee, certify that we read this thesis and have examined the student ***Ruua Muhammad Dhedan***, in its contents and that, in our opinion; it is adequate as a thesis for the Degree of Master of Science, in Chemistry.

Signature:

Name:
(Chairman).

Signature:

Name:
(Member)

Signature:

Name:
(Member)

Signature:

Name:
(Member\advisor)

Signature:

Name:
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بِسْمِ اللهِ الرحْمن الرحِيم

﴿اللهُ نُورُ السَمَوَاتِ والأَرْض مَثَلُ نُورِهِ كَمِشْكَوةٍ فِيهَا مِصْبَاحٌ الْمِصْبَاحُ فِي زُجَاجَةٍ الزُجَاجَة كَأَنَهَا كَوْكَبٌ دُرِيٌ يُوقدُ مِن شَجَرَةٍ مُبَارَكَةٍ زَيْتُونِةٍ لا شَرْقِيَةٍ ولا غَرْبِيَةٍ يَكَادُ زَيْتُهَا يُضِيءُ وَلوْ لَمْ تَمْسسهُ نَارٌ نُورٌ عَلى نُورٍ يَهْدِي اللهُ لِنُورهِ مَن يَشَاء وَيَضْربُ اللهُ الأَمْثالَ لِلنَاسِ واللهُ بِكُلِ شَيْءٍ عَلِيمٌ﴾

﴿صَدَقَ اللهُ العَظِيمْ﴾

سورة النور الآية (٣٥)

الإهداء

إلى من جاءنا نوراً وهدى من الجهل والضلال
إلى العلم ونور الأيمان
نبينا محمد (صلى الله عليه وسلم)
إلى من ضحى لأجل أن أكون

والدي العزيز
إلى من أفنت عمرها وترعرعت في أحضانها الدافئة

والدتي العزيزة
إلى مقلة عيني الشاب الشهيد السعيد

أخي أحمد
إلى الذين أرفدوني بالحب والحنان

أخي وأخواتي الغالين
إلى كل من مد يد العون والمساعدة لي

زملائي

أهدي ثمرة جهدي المتواضع

رؤى

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"O Allah to you belongs all praise, you are the light of the heavens and the earth and all that is within them. To you belongs all praise, you are the lord of the heavens and the earth and all that is within them. To you belongs all praise, and the kingdom of the heavens and the earth and all that is within them, and the prayer and peace upon the master of the mankind our beloved messenger of Allah "Muhammad" and his pure progeny: companions and all those who follow his way in charity to Judgment Day".

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Finally to all my friends, I present my thanks.

Ruua 2006

SUMMARY

This work involves synthesis of different five, six and seven membered heterocyclic rings starting from 2-hydrazino benzothiazole which was synthesized from the corresponding 2-mercapto benzothiazole on its reaction with hydrazine hydrate.

This work is divided into four different parts:

First part: This part involved the synthesis of oxadiazole, oxazoline, triazole, thiadiazole and diazole from compounds [a], [1] and [19] with different organic materials as shown in Schemes (1) and (2).

Second part: This part involved the synthesis of phthalazin and pyridazin-3,6-dione derivatives from the reaction of compound [1] with succinic, maleic and phthalic anhydrides as shown in Scheme (1).

Third part: This part involved the synthesis of two new Schiff bases derived from the reaction of compound [1] with two aromatic aldehydes and cyclization by the treatment with mercapto acetic acid and maleic anhydride resulted oxazepines [9, 12] and thiazolidins [10, 13] respectively as shown in Scheme (1).

Fourth part: This part deals with the study of antibacterial activities of some of the synthesized compounds and comparing these activities with that of the starting materials. These activities were determined ***in vitro*** using well diffusion method against two types pathogenic strains of bacteria ***Staphylococcus Aureus*** (G^+) and ***Proteus Vulgaris*** (G^-).

The results revealed that some of these compounds showed measurable activity as shown in Table (3-2).

الخلاصة

يتضمن موضوع البحث في هذه الرسالة تحضير مركبات حلقية غير متجانسة خماسية وسداسية وسباعية متنوعة أبتداءً من ٢-هايدرازينو بنزوثايازول والذي حُضِرَ باستعمال ٢-مركبتو بنزوثايازول المقابل بتفاعلها مع الهيدرازين المائي وقد تم تقسيم هذا العمل إلى أربعة أقسام:

القسم الأول:

يتضمن هذا القسم تحضير مركبات أوكسادايازول، أوكسازولين، ترايازول، ثايادايازول ودايازول ةالتي أُشتقت من تفاعل المركبات [a]، [١] و[١٩] مع مواد عضوية مختلفة وخطوات التفاعل موضحة في المخططين رقم (١)، (٢).

القسم الثاني:

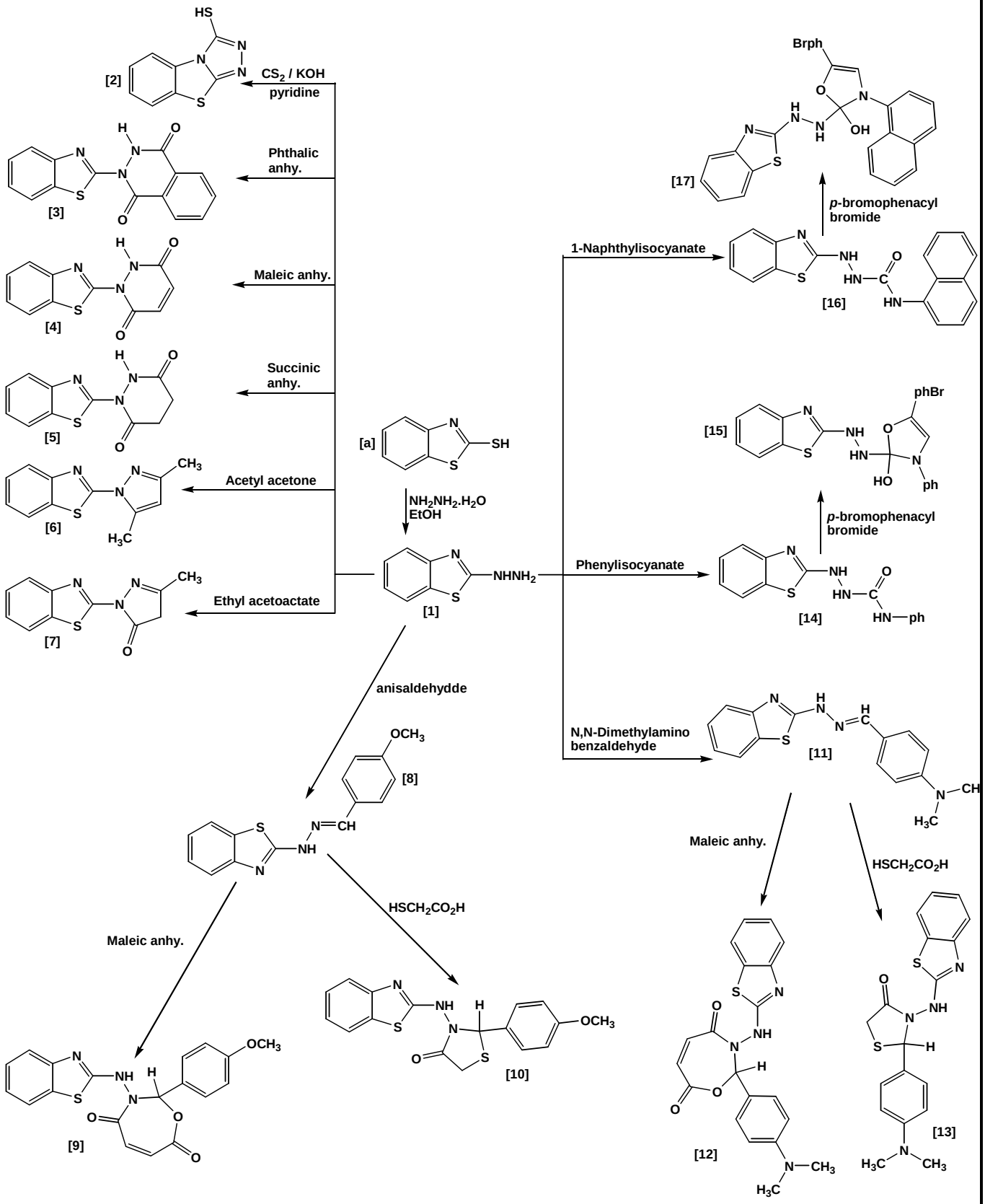
يتضمن هذا القسم تحضير مركبات الفثالازين والبريدازين-6,3 دايون المشتقة من تفاعل المركب [1] مع مواد عضوية مختلفة (أنهيدريدات) وخطوات التفاعل موضحة في المخطط رقم (١).

القسم الثالث:

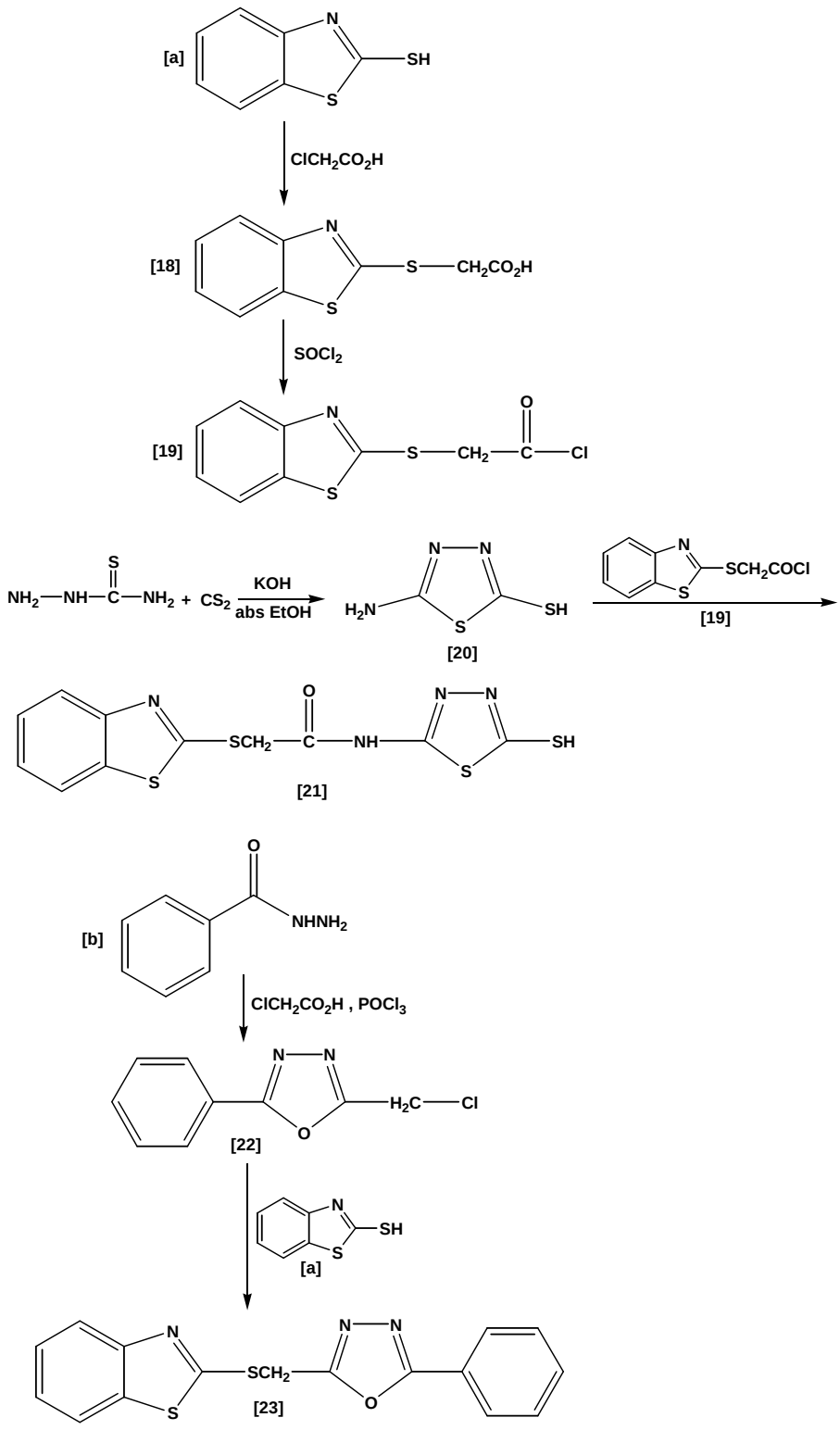
يتضمن هذا القسم تحضير مركبين جديدين من قواعد شف مشتقة من تفاعل المادة [1] مع أثنان من الألديهايد الأروماتية، حيث تمت عملية الغلق الحلقي باستعمال مركبتو أسيتك أسيد لتحضير الثايوزولدين والماليك أنهدريد لتحضيرأوكسازيبين وخطوات التفاعل موضحة في المخطط رقم (١).

القسم الرابع:

يتضمن هذا القسم أختبار الفعالية البايلوجية لبعض المركبات المحضرة ضد البكتريا (G^+) ، (G^-) وقد دلت النتائج المستحصلة بأن بعض المركبات أظهرت فعالية بايلوجية كما موضح في جدول (٣-٢).


[2]
CS_2 / KOH
pyridine
Phthalic anhy.
[3]
Maleic anhy.
[4]
Succinic anhy.
[5]
Acetyl acetone
[6]
Ethyl acetoactate
[7]
[a]
$NH_2NH_2.H_2O$
EtOH
[1]
1-Naphthylisocyanate
[16]
p-bromophenacyl bromide
[17]
Phenylisocyanate
[14]
p-bromophenacyl bromide
[15]
N,N-Dimethylamino benzaldehyde
[11]
anisaldehydde
[8]
Maleic anhy.
[9]
$HSCH_2CO_2H$
[10]
Maleic anhy.
[12]
$HSCH_2CO_2H$
[13]

Scheme (1)



Scheme (2)

CHAPTER ONE- INTRODUCTION

CHAPTER TWO- EXPERIMENTAL PART

CHAPTER THREE- RESULTS AND DISCUSSION

LIST OF FIGURES

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تاريخ المناقشة:٢٠٠٧/٣/٥