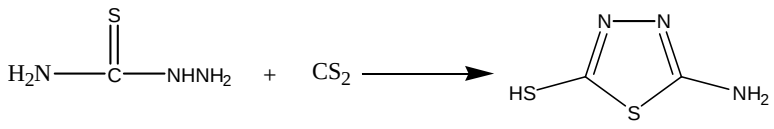
Chapter Three

Result and Discussion

3.1.0 Synthesis and characterization of 2-amino-5-mercapto-1,3,4-thiadiazole [1]

Various 1,3,4-thiadiazole derivatives are of interest for pharmaceuticals use as well as useful intermediates in the area of organic synthesis. Thiadiazole and its derivatives show particular activity as drugs for the treatment of thrombosis, as sedative and more recently as plant activators or inducers of systemic acquired resistance (SAR) in plants[(160)]. Because of the above mentioned various uses of 1,3,4-thiadiazole derivatives, it was considered desirable to synthesis the title compound with the hope that incorporation of another heterocyclic ring might enhance its biological activity.

Compound [1] was prepared through the reaction of thiosemicarbazide with CS_2 in the presence of anhydrous sodium carbonate in abs. ethanol:

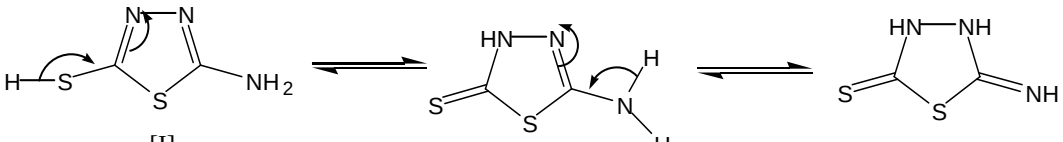


[1]

The structure of compound [1] was identified by its m.p. and FT-IR spectroscopy.

Infrared spectrum

The FT-IR spectrum of [1], fig. (3-1), shows the following characteristic bands: the two bands in the 3394cm^{-1} and 3274cm^{-1} were due to asymmetric and symmetric stretching vibrations of $-NH_2$ group, respectively, an absorption band at 3089cm^{-1} was due to the –NH stretching (tautomeric form). The bands at 2918cm^{-1} and 2771cm^{-1} were attributable to the intramolecularly hydrogen bonded of –NH group(161). The SH stretching band found as very weak shoulder at 2600cm^{-1}. A band at 1598cm^{-1} was due to (C=N) stretching of the thiadiazole ring moiety. The sharp bands at 1533cm^{-1} and 1494 cm^{-1} are due to the (N-H) bending and (C-N) stretching vibrations, respectively. Also, the absorption band at 1361cm^{-1} for the (C=S) group which evidence that compound [1] can exist in two tautomeric forms, thiol [I] and thion form [II](162). Beside this, the band at 669cm^{-1} due to (C-S) bond is good evidence for the structure given to the product.

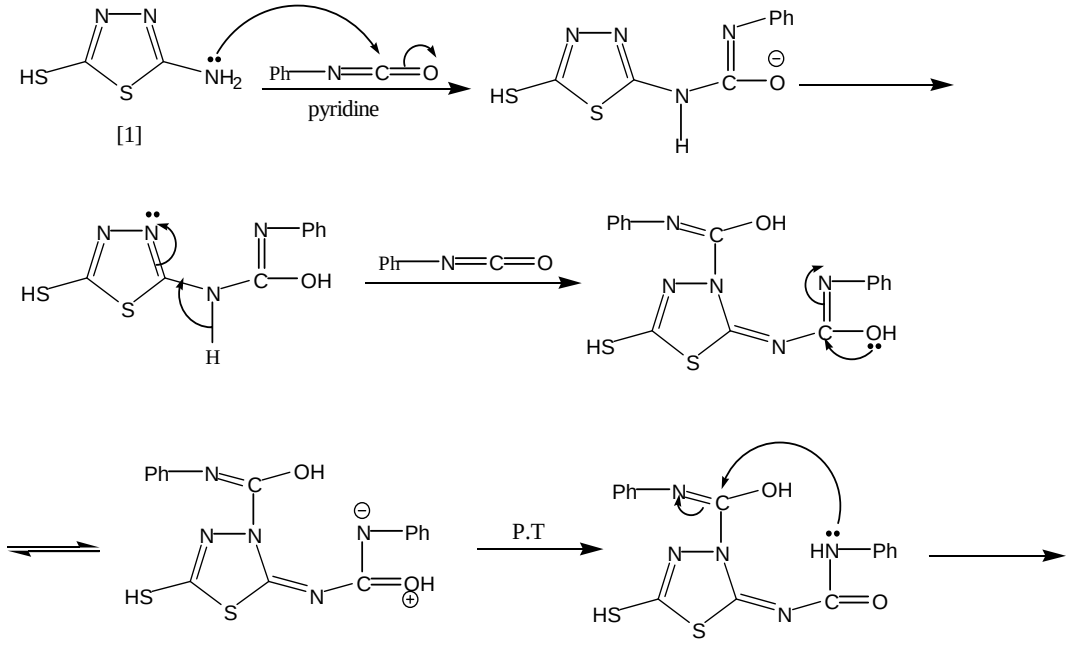


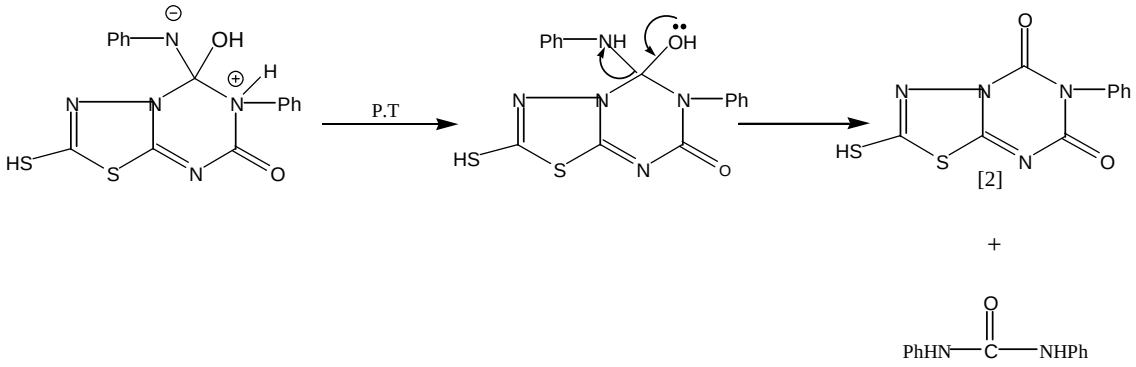
[I] [1I] [III]

3.2.0 Synthesis and characterization of 2-mercapto-5-phenyl -4,6-dione-1,3,5-triazino[6,5-b]-1,3,4-thiadiazole [2]

The formation of novel fused heterocyclic ring is an important task for heterocyclic chemist from various points of view. Furthermore many condensed heterocyclic systems, especially when linked to a triazine ring, play an important role as analgesic, antihypertensive, antipyretic, and antiinflammatory drugs, also in agriculture as pesticides, herbicides, and plant growth regulators[106]. These observations prompted us to synthesis compound [2] with expectation to produce an interesting biologically active compound.

For the synthesis of the target title heterocyclic compound, the following reaction mechanism may be outlined:





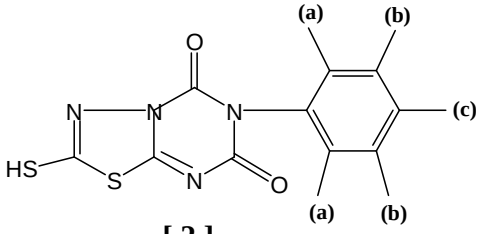
The structure of compound [2] was confirmed by its FT-IR, ^{1}H- and ^{13}C-NMR results.

Infrared spectrum

The FT-IR spectrum of compound [2], fig. (3-2), shows the following characteristic absorption bands: ν(N-H) (tautomeric proton) occur at 3282cm^{-1}, band at 3091cm^{-1} was due to ν(C-H) of aromatic ring, band at 1647cm^{-1} was assigned for the ν(C=O). The bands at 1596cm^{-1}, 1550cm^{-1} represented ν(C=N) and δ(N-H), respectively. The absorption band at 1305cm^{-1} was due to ν(C=S) bond. Furthermore, the bands at 752cm^{-1} and 694cm^{-1} represent the γ(C-H) of mono-substituted benzene ring.

[1]H-NMR

[1]H-NMR spectrum of compound [2], fig.(3-12), shows the following characteristic chemical shifts (DMSO-d_6, ppm).

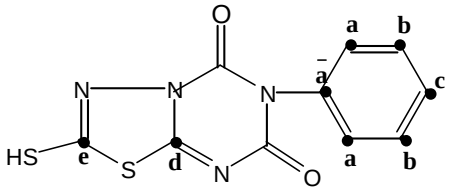


[2]

The five aromatic protons appear as: the signals at δ7.00, δ7.30 and δ7.50 were integrated for 1H(c proton), 2H(b protons) and 2H(a protons), respectively. Sulfhydryl proton (S-H) absorbed at δ8.45. Furthermore, the small peak at δ2.5 was due to DMSO. The above data agree with the proposed structure.

[13]C-NMR

[13]C-NMR spectrum of compound [2], fig.(3-13), shows the following characteristic chemical shifts (DMSO-d_6, ppm).



[2]

The chemical shifts at δ118.22, δ121.84 and δ128.80 were characteristic of aromatic carbon atoms c, b and a, respectively, for carbon atom, à, there is a possibility that it combined its signal with that of carbon atom, a. The two

signals at δ139.70 and δ152.56 are assigned to thiadiazole ring carbon e and d, respectively. Carbonyl signals are out of chart scale by the operator.

3.3.0 Synthesis and characterization of 5-(*p*-bromo-phenyl)-2-mercapto-imidazo[2,1-b]-1,3,4-thiadiazole [3]

In view of the diverse biological properties associated with the imidazole nucleus, it is desirable to obtain facile method for the synthesis of fused ring system derived from fusion of the imidazole ring with other heterocyclic ring because this have been less extensively studied as compared with monocyclic imidazole derivatives. A variety of imidazo[2,1-b][1,3,4]thiadiazoles have proved to be interesting from a commercial viewpoint for their diuretic, bactericide, antihypertensive properties. In addition, the imidazo[2,1-b] [1,3,4]thiadiazole framework has been incorporating into cyanine and azo dyestuffs to provide materials of value in color photography and for the dyeing of fibers[(163)].

The above mentioned finding promoted us to synthesis the title compound with the hope that incorporating of imidazole ring might enhance the biological activity of the originally synthesized compound. The structural assignment to the product was based on its FT-IR and ^{1}H-NMR data.

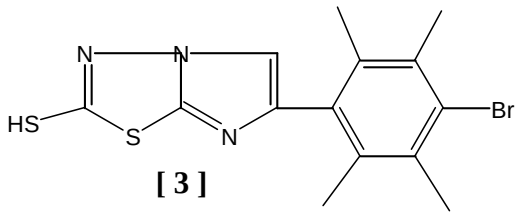
Infrared spectrum

The disappearance of bands at 3394cm^{-1} and 3274cm^{-1} attributed to –NH_2 stretching frequency together with appearance of band at 3100cm^{-1} assignable to (C-H) aromatic stretching frequency are good evidence for the structure given to the product, fig.(3-3). Furthermore, the band at 827cm^{-1} attributable

to the out of plane bending of *p*-disubstituted benzene ring and the band at 532cm^{-1} due to ν(C-Br) bond[(164)] agree with the proposed structure assigned to this compound.

^{1} H-NMR

^{1}H-NMR spectrum of compound [3], fig.(3-14), shows the following characteristic shifts (DMSO-d_6, ppm).



[3]

Signal at δ2.81 was attributed to N-H proton (tautomeric proton). The four aromatic ring protons of (AB) system appear as pair of doublet leaning towards each other which is typical for *p*-disubstituted rings, the two protons ortho to bromine atom resonate at δ(7.85-7.70) and the two other protons absorb at δ(7.72-7.56). Peaks at δ2.51 and δ3.27 were due to the DMSO and H_2O in DMSO, respectively[(164)]. Proton of imidazole ring appears within the aromatic region and the S-H proton is found at δ8.55. The ^{1}H-NMR spectrum is in agreement with the proposed structure.

Fig. (3-1) FT-IR spectrum of 2-amino-5-mercapto-1,3,4-thiadiazole [1]

Fig. (3-2) FT-IR spectrum of 2-mercapto-5-phenyl-4,6-dione-1,3,5-triazino[6,5-b]-1,3,4-thiadiazole [2]

Fig. (3-3) FT-IR spectrum of 5-(*p*-bromophenyl)-2-mercapto-imidazo [2,1-b]-1,3,4-thiadiazole [3]

3.4 Synthesis and characterization of tetrazolo- and thiazolidin-4-one-1,3,4-thiadiazole derivatives

3.4.0 Synthesis of 2-[substitutedbenzylidine]amino-5-mercapto-1,3,4-thiadiazole[4-8]

Compounds containing imine bond have been extensively synthesized for various reasons, one of which is their biological activity. Some of other reasons are the investigation of their ability to make a coordination complex with transition metals, their ready synthesis and myriad properties have been attributed greatly in their popularity[165]. The condensation reaction of equimolar quantity of primary amine with the appropriate aromatic aldehydes is the major method to prepare of Schiff bases. The synthesized compounds were characterized by their m.p. and FT-IR spectra.

Infrared spectra

The FT-IR spectra, figs.(3-4)-(3-7), show the disappearance of the two absorption bands due to the $-NH_2$ stretching of amino-thiadiazole [1]. On the other hand, the IR spectra showed all the suggested bands for olefinic (C-H), (C=C) aromatic, endocyclic (C=N) and exocyclic imine group[166] stretching vibrations in addition to out of plane bending of substituted benzene ring. Moreover, all compounds exhibit significant stretching band near the region (1260-1250)cm^{-1} , this indicated the presence of (═N—N═C—) cyclic[164] grouping. Other informative bands are listed in Table (3-1):

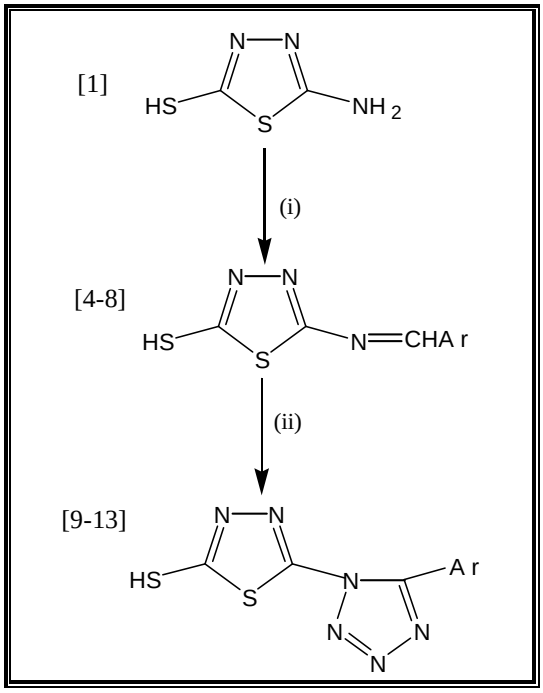
Table (3-1)
FT-IR data of compounds [4-8]

Comp No.	Fig. No.	ν N- H	ν C-H aromatic	ν C-H aliphatic	ν C=N exocyclic	ν C=N endocyclic	δ N-H	γ C- H
[4]	(3-4)	3300	3132	-	1608	1552	1477	752 730
[5]	(3-5)	3300	3091	2947	1614	1564	1500	835
[6]	(3-6)	3454	3100	2923 2868	1602	1568	1521	823
[7]	(3-7)	3327		-	1608	1564	1564	848
[8]	-	3276	3030	2964 2869	1608	1568	1488	736

3.4.1 Synthesis of 2-[5̀-substituted-tetrazolo-1̀-yl]amino-5-mercapto-1,3,4-thiadiazole [9-13]

The synthesis and interesting pharmacological properties of tetrazole compounds were recently described[167]. Exploratory research activity directed towards ascertaining new heterocycles capable of evoking antiparasitic or contragestational activity, keeping this in mind, it was considered desirable to synthesize the title compounds.

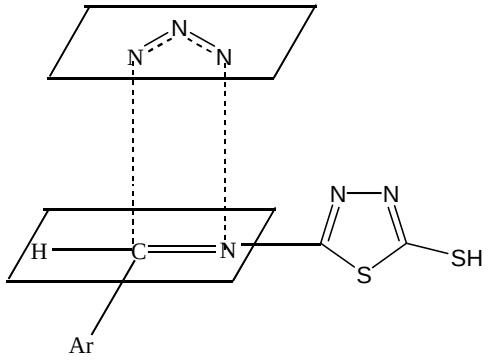
For synthesis of the target tetrazoles, the reaction sequence outlined in Scheme (3-1) was followed. The Schiff bases [4-8] were heated in a water bath at 55-60C°, keeping the temperature at this range, to give the desired product . The synthesized compounds are characterized by their m.p., FT- IR, and ^{1}H- NMR (compound [10]).



Scheme (3-1) Reagents and conditions: (i) aromatic aldehydes, abs. ethanol, reflux ; (ii) NaN_3 , THF ,water bath (50-60C°).

The mechanism of the reaction systematically investigated as [3+2] cycloadditions which christened as a 1,3-dipolar cycloadditions[85]. It is involved the addition of unsaturated systems, dipolarphiles, to 1,3-dipoles, a molecule possessing resonance contributors in which a positive and negative charge are located in 1,3-position relative to each other. The addition results in a five-member ring. Azides are a prominent class of 1,3-dipols and azide 1,3-dipolar cycloadditions are of great synthetic value and have been studied mechanistically in great detail[168].

The common features of this type of reactions is best accommodated by a T.S. geometry in which the dipolarphile and its ligands lies in one plane, and the azide lies in a parallel plane above or below, so that the orbitals perpendicular to the planes interact to form bonds, Scheme(3-2):



Scheme (3-2) Approximate transition state geometry for azide addition

Infrared spectra

The infrared absorption bands, fig. (3-8)-(3-11), were utilized to characterize the specific structure of the synthesized compounds. The disappearance of band at (1614-1600)cm^{-1}, attributed to C=N(imine group) stretching frequency is good evidence for the success of this step of reaction.

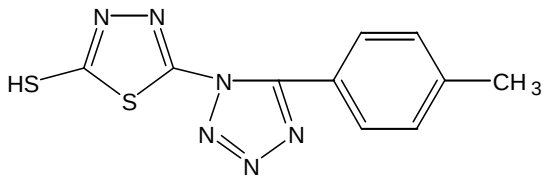
Beside this, the IR spectra of these compounds were devoid of a strong band at (2160-2120)cm^{-1} attributed to stretching frequency of azide group. A band at the range (1710-1700)cm^{-1} was due to the cyclic (C=N) stretching of tetrazole ring[169].The above data agree with the proposed structures assigned to these compounds. The characteristic data are reported in Table (3-2).

Table (3-2)
Characteristic data of tetrazole derivatives [9-13]

Comp. No.	Fig. No.	ν C-H aliphatic	ν C=N	δ N-H	ν C=S	ν C-N	γ C-H
[9]	(3-8)	-	1566	1510	1375	1313	767 705
[10]	(3-9)	2950 2875	1566	1510	1380	1319	829
[11]	(3-10)	2925	1566	1510	1380	1319	840
[12]	-	-	1570	1520	1378	1310	830
[13]	(3-11)	2923 2875	1566	1487	1371	1311	734

^{1}H-NMR

^{1}H-NMR spectrum of compound [10], fig.(3-15), shows the following characteristic chemical shifts (DMSO-d_6, ppm).



[10]

The methyl protons resonate at δ2.4 and its signal was coincide with that of DMSO, N-H proton (tautomeric proton) absorbed at δ2.5. Four aromatic ring protons of (AB) system appear as a pair of doublets, the protons ortho to methyl group absorb at δ(7.45-7.33) and the two other protons absorb at δ(7.95-7.84). Sulfhydryl group absorb at δ8.67. Furthermore, the signal at δ3.7 attributable to absorbed water in DMSO, respectively. Signal at δ1.85 was due to the impurities.

Fig. (3-4) FT-IR spectrum of 2-benzylidineamino-5-mercapto-1,3,4 thiadiazole [4]

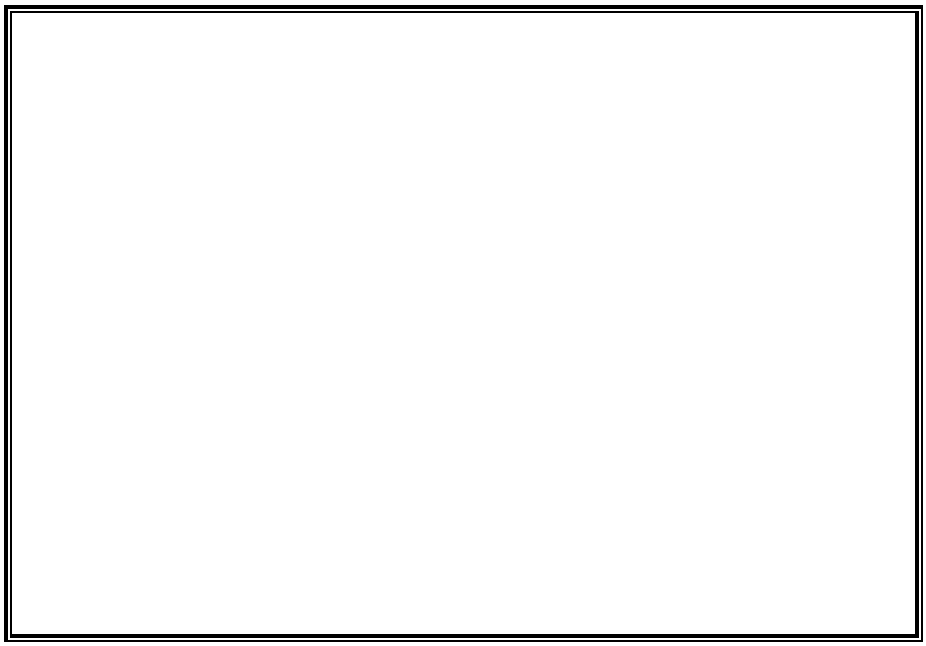


Fig. (3-5) FT-IR spectrum of 2-[*p*-methylbenzylidine]amino-5-mercapto -1,3,4-thiadiazole [5]

Fig. (3-6) FT-IR spectrum of 2-[*p*-methoxybenzylidine]amino-5- mercapto -1,3,4-thiadiazole [6]

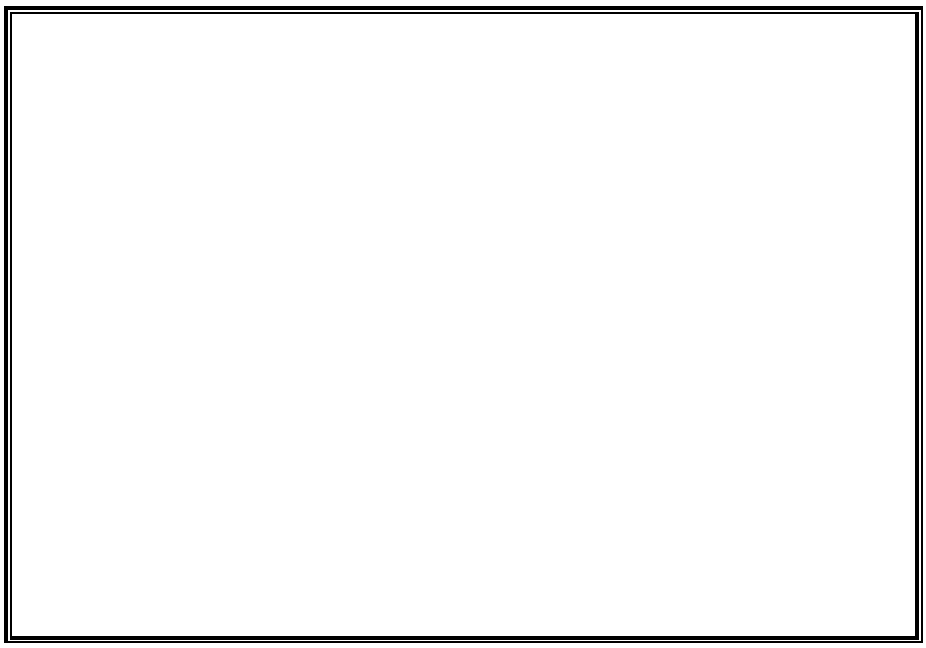


Fig. (3-7) FT-IR spectrum of 2-[*p*-nitrobenzylidine]amino-5-mercapto -1,3,4-thiadiazole [7]

Fig. (3-8) FT-IR spectrum of 2-[5̀-phenyl-tetrazolo-1̀-yl]-5-mercapto -1,3,4-thiadiazole [9]

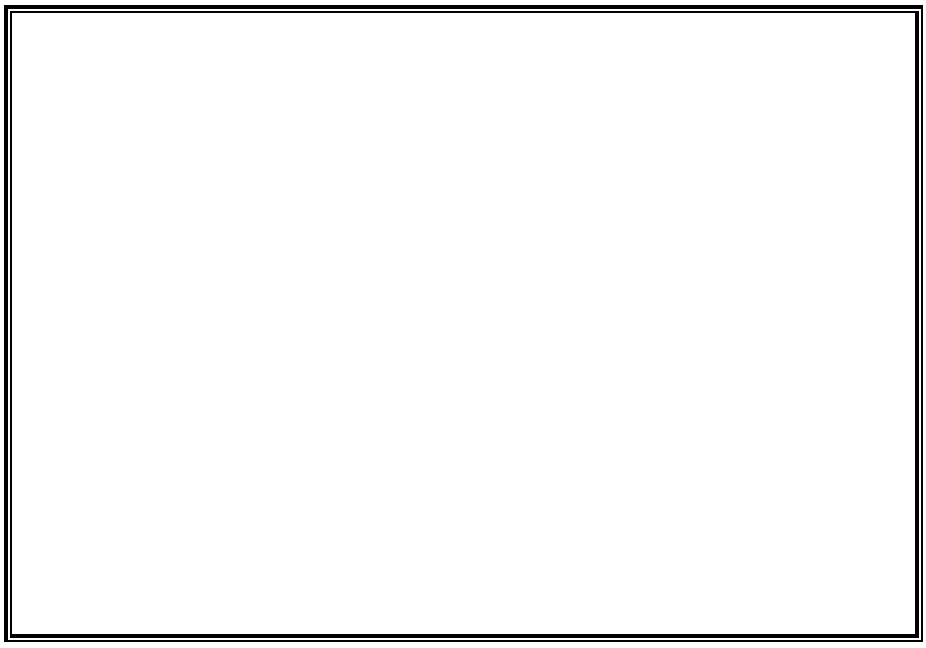


Fig. (3-9) FT-IR spectrum of 2-[5̀-*p*-methyl-tetrazolo-1̀-yl]-5-mercapto -1,3,4-thiadiazole[10]

Fig. (3-10) FT-IR spectrum of 2-[5̀-*p*-methoxy-tetrazolo-1̀- yl]-5-mercapto -1,3,4-thiadiazole [11]

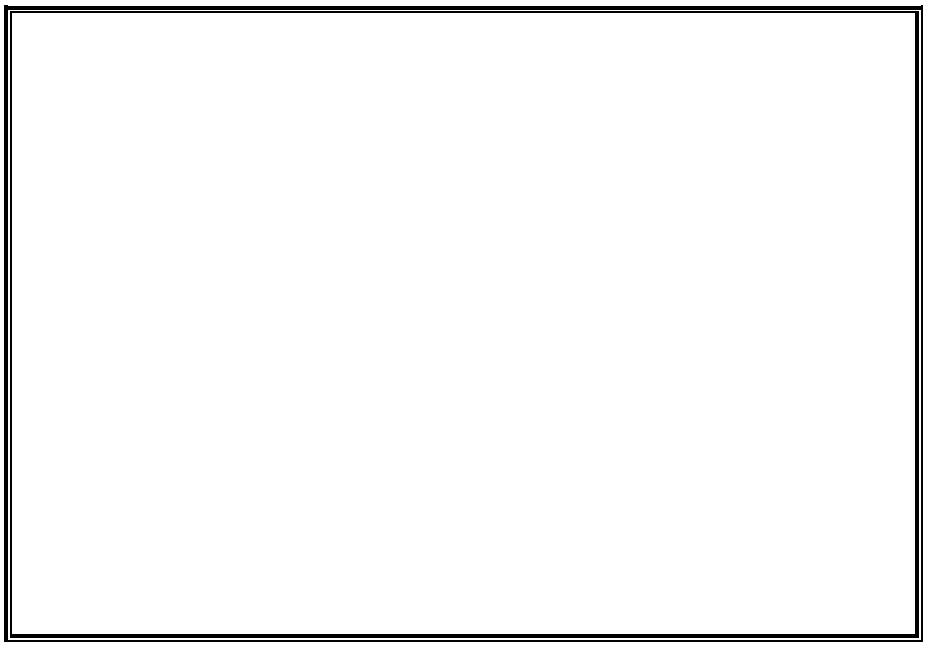


Fig. (3-11) FT-IR spectrum of 2-[5̀-*m*-methyl-tetrazolo-1̀-yl]-5-mercapto -1,3,4-thiadiazole [13]

Fig. (3-12) ^{1}H-NMR of 2-mercapto-5-phenyl-4,6-dione-1,3,5-triazino[6,5-b]-1,3,4-thiadiazole [2]

Fig. (3-13) ^{13}C-NMR of 2-mercapto-5-phenyl-4,6-dione-1,3,5-triazino[6,5-b]-1,3,4-thiadiazole [2]

Fig. (3-14) ^{1}H-NMR of 5-(*p*-bromophenyl)-2-mercapto-imidazo[2,1-b]-1,3,4-thiadiazole [3]

Fig. (3-15) ^{1}H-NMR of 2-[5̀-*p*-methyl-tetrazolo-1̀-yl]-5-mercapto -1,3,4-thiadiazole[10]

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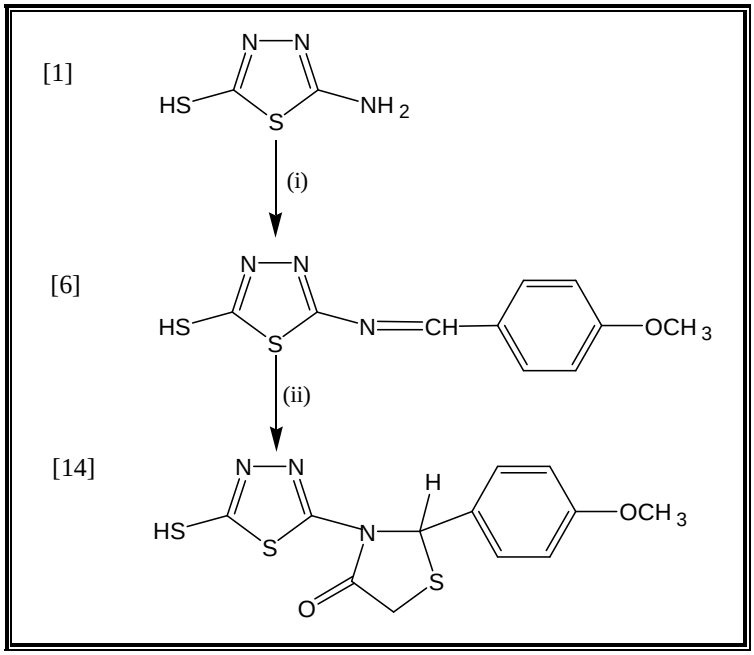
3.4.2 Synthesis of 2-[2̀-p-methoxyphenyl-4̀-oxo-1̀,3̀-thiazolidin-3̀-yl]-5-mercapto-1,3,4-thiadiazole [14]

4-Thiazolidinones play a vital role owing to their wide range of biological activity and industrial importance as stabilizers for polymeric materials[170]. The chemistry of the 4-thiazolidine ring system was reviewed in depth[100].

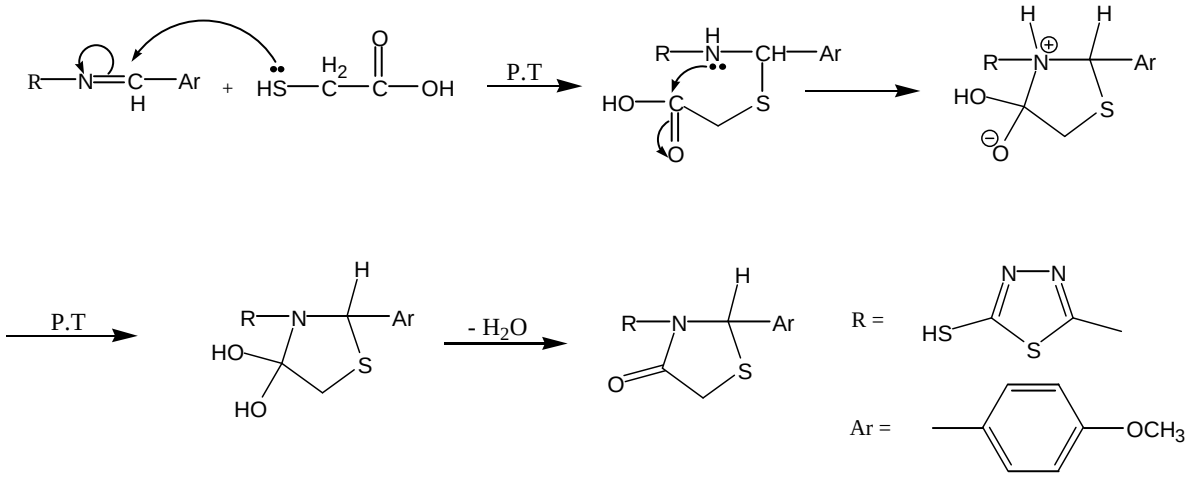
For a long time imines have been used successfully in the synthesis of nitrogen containing heterocycles. As part of ongoing project aimed to discover the bioactivity of 4-thiazolidinone, we employed the Schiff base toward its synthesis.

The 4-thiazolidinone derivative [14] was obtained by refluxing equimolar amounts from the imine [6] and thioglycolic acid in dry benzene, Scheme (3-3). The synthesized compound is characterized by its m.p. and FT-IR.



Scheme (3-3) Reagents and conditions: (i) *p*-$CH_3OC_6H_4CHO$, abs. EtOH, reflux; (ii) thioglycolic acid, dry benzene , reflux

The suggest mechanism to obtain the target product is outlined below:



Infrared spectrum

In the IR spectrum, the appearance of (C=O) stretching band at 1705cm^{-1} due to thiazolidinone ring[171] was the most characteristic evidence for the success of cyclization step. Fig. (3-16) also shows bands at 3100cm^{-1}, 2900cm^{-1} and 2846cm^{-1} attributable to ν(C-H) aromatic, asymmetric and symmetric stretching vibrations of (-OCH_3) group, respectively. Other characteristic bands of aromatic system is the appearance of ν(C=C) at about 1506cm^{-1} and γ(C-H) of *p*-disubstituted ring at 833cm^{-1}.

Fig. (3-16) FT-IR spectrum of 2[2̀-*p*-methoxyphenyl-4̀-oxo-thiazolidin-3̀-yl] -5-mercapto-1,3,4-thiadiazole [14]

3.5 Synthesis and characterization of 2,4-disubstituted oxazole derivatives

The demand for the scintillation chemicals is increasing with increase uses of radioactive isotopes. This necessitates prompted the development of new methods to improve upon the available procedures for the synthesis of scintillation chemicals. Some oxazoles are well known for their usefulness in fluorescent sensors, laser dyes and scintillates[(172)] for detecting nuclear radiations. Beside this, oxazole ring has been reported to be associated with diverse types of biological properties[(173)].

In view of the above mentioned and as a part of our ongoing research program aiming towards the synthesis of new biologically potent molecules, it was thought worthwhile to synthesis some new oxazole derivatives.

3.5.0 Synthesis of α-aminonitriles [15-22]

Aminonitriles are important intermediates in the synthesis of different organic compounds. Nitriles are found to undergo a variety of interesting reactions under the influence of various conditions. Hence it is worthwhile to investigate a good synthetic route for the preparation of these important compounds.

The infrared absorption bands were utilized to characterize the structure of the synthesized compounds. The FT-IR spectra of the title synthesized compounds, fig.(3-17)-(3-21), show the following characteristic features: significant bands in the region (3300-3200)cm^{-1} attributed to the stretching vibration of the (N-H) group present in the title compounds. The very weak shoulder at about 2300cm^{-1} was due to the stretching vibration of ($C\equiv N$) bond. This weak absorption is due to the presence of adjacent hetero atom nitrogen[174]. The cyano group was further characterized from its alkaline hydrolysis and evolution of ammonia. The above data agree with the proposed structures assigned of these compounds and other characteristic IR data are reported in Table (3-3).

Table (3-3)
Characteristic infrared absorption bands of compounds [15-22]

Comp. No.	Fig. No.	ν C-H aromatic	ν C-H aliphatic	ν C=N	ν C=C aromatic	γ C-H	Other bands
[15]	(3-17)	3050	2927	1562	1517	765 707	-
[16]	(3-18)	3087	2916	1595	1531	831	ν_{OH} 3400
[17]	(3-19)	3070	2949 2873	1600	1568	823	-
[18]	(3-20)	3089	2918	1598	1564	817	-
[19]	-	3030	2923 2856	1600	1593	740	-
[20]	(3-21)	3070	2871	1606	1568	758	ν_{OH} 3400
[21]	-	3075	2900	1600	1566	821	-
[22]	-	-	2930 , 2860 2830	1596	-	-	-

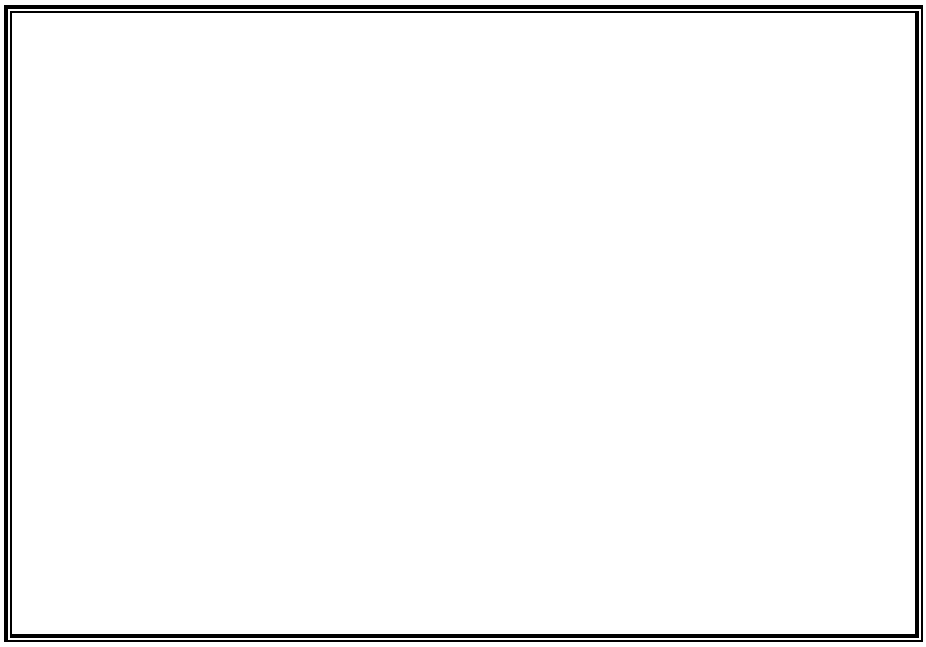


Fig. (3-17) FT-IR spectrum of 2-[N-cyanobenzyl]amino-5-mercapto -1,3,4-thiadiazole [15]

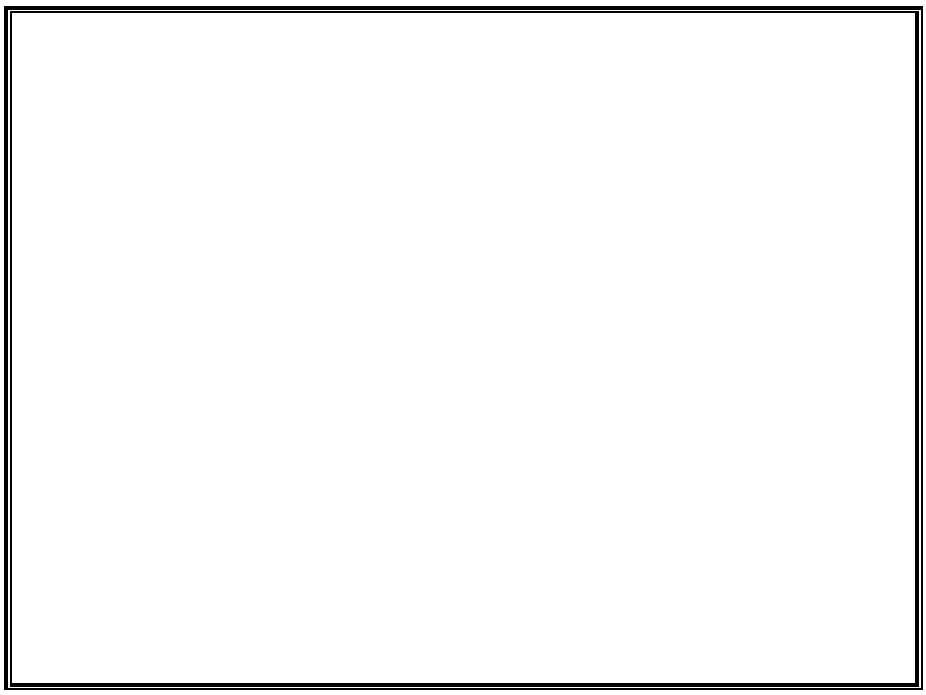


Fig. (3-18) FT-IR spectrum of 2-[N-(*p*-hydroxycyanobenzyl)]amino-5-mercapto-1,3,4-thiadiazole [16]

Fig. (3-19) FT-IR spectrum of 2-[N-(*p*-methoxycyanobenzyl)]amino-5-mercapto-1,3,4-thiadiazole [17]

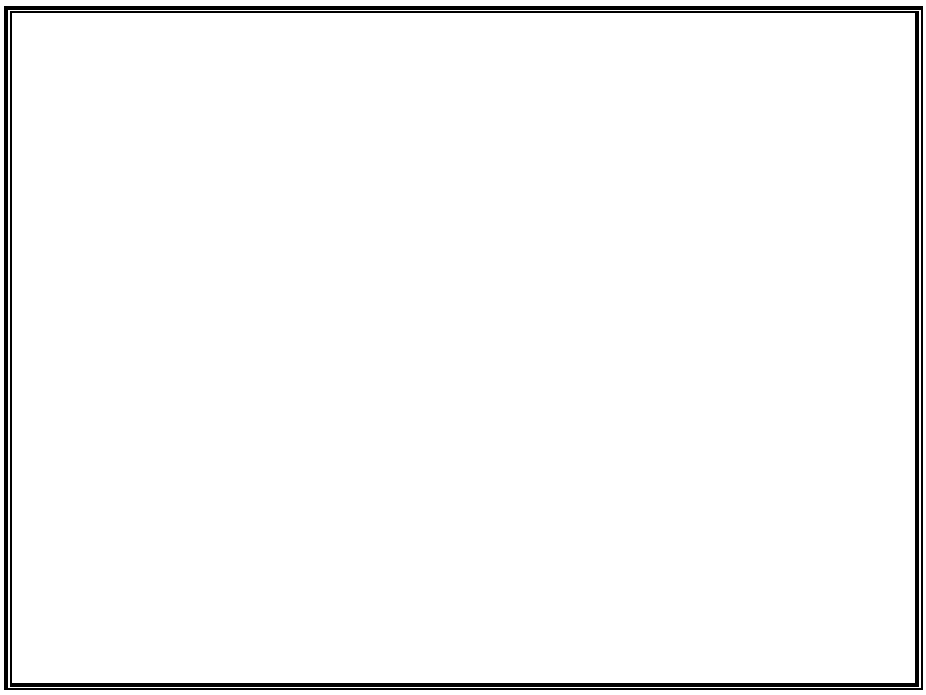


Fig. (3-20) FT-IR spectrum of 2-[N-(*p*-methylcyanobenzyl)]amino-5-mercapto-1,3,4-thiadiazole [18]

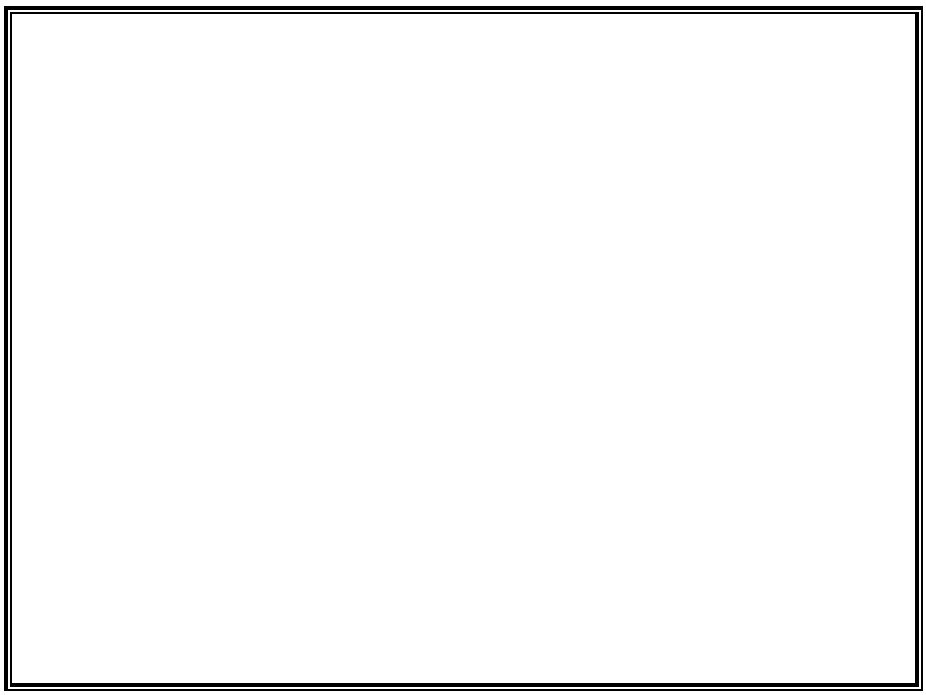


Fig. (3-21) FT-IR spectrum of 2-[N-(*o*-hydroxycyanobenzyl)]amino-5-mercapto-1,3,4-thiadiazole [20]

3.5.1 Synthesis of α-aminoamides [23-30]

α-Aminoamides were prepared directly from the hydrolysis of the previously prepared α-aminonitriles in acidic medium.

The FT-IR spectra of the title synthesized compounds, figs.(3.22)-(3-28), show the following characteristic features: a wide band at (3300-3250)cm^{-1} are attributed to NH_2 and NH stretching vibrations. The bands at (3100-3000) cm^{-1} and (1640-1625) cm^{-1} were assigned to ν(C-H) aromatic and ν(C=O) (Amide I), respectively. Beside this, the title compounds show a band at about 1590cm^{-1} due to δ(–NH_2) (Amide II). The strong to medium absorption bands appear at (900-650) cm^{-1} attributable to out of plane bending of substituted aromatic systems. Other bands were observed in FT-IR spectra of these compounds and listed in Table (3-4).

Table (3-4)
Characteristic infrared absorption bands of compounds [23-30]

Comp. No.	Fig. No.	ν NH_2	ν C-H aromatic	ν C-H aliphatic	ν C=O	δ N-H	γ C-H	Other bands
[23]	(3-22)	3271	3078	2900	1637	1560w	780 682	-
[24]	-	3274	3082	2878	1633	1570sh	875	ν_{OH} 3400
[25]	(3-23)	3274	3085	2954	1637	1602w	870	-
[26]	(3-24)	3274	3084	2918 2852	1633	1585w	830	-
[27]	(3-25)	3280	3101	2956	1631	1580sh	780	-
[28]	(3-26)	3300	3080	2954	1629	1580w	750	ν_{OH} 3400
[29]	(3-27)	3274	3082	2900	1633	1570w	820	-
[30]	(3-28)	3276	-	2954 2854	1637	1550w	-	-

* sh = shoulder, w = weak

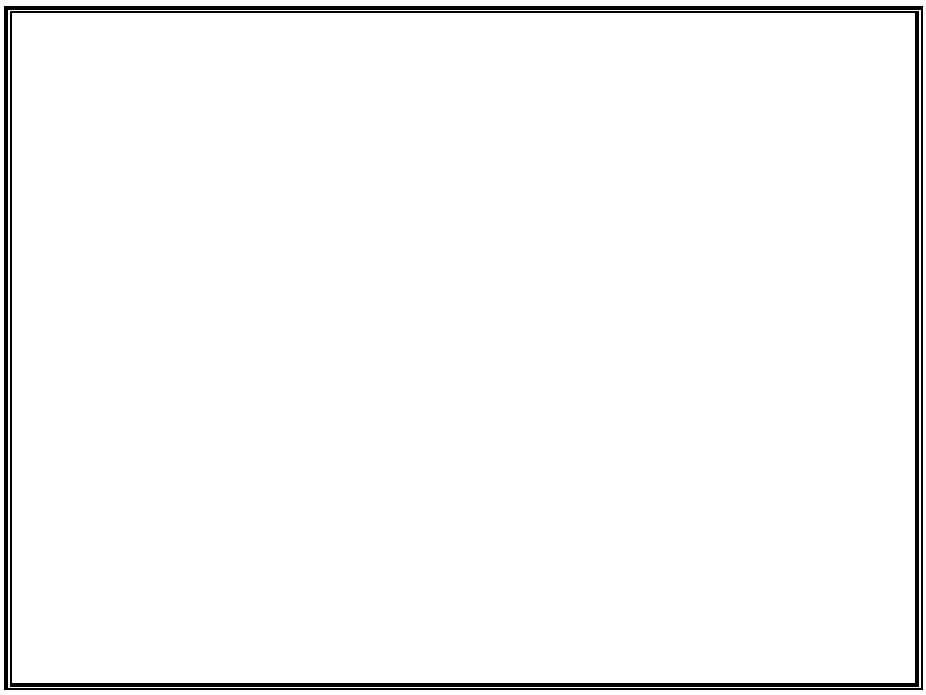


Fig. (3-22) FT-IR spectrum of 2-[N-(phenylacetamide)]amino-5-mercapto -1,3,4-thiadiazole [23]

Fig. (3-23) FT-IR spectrum of of 2-[N-(*p*-methoxyphenylacetamide)]amino-5-mercapto-1,3,4-thiadiazole [25]

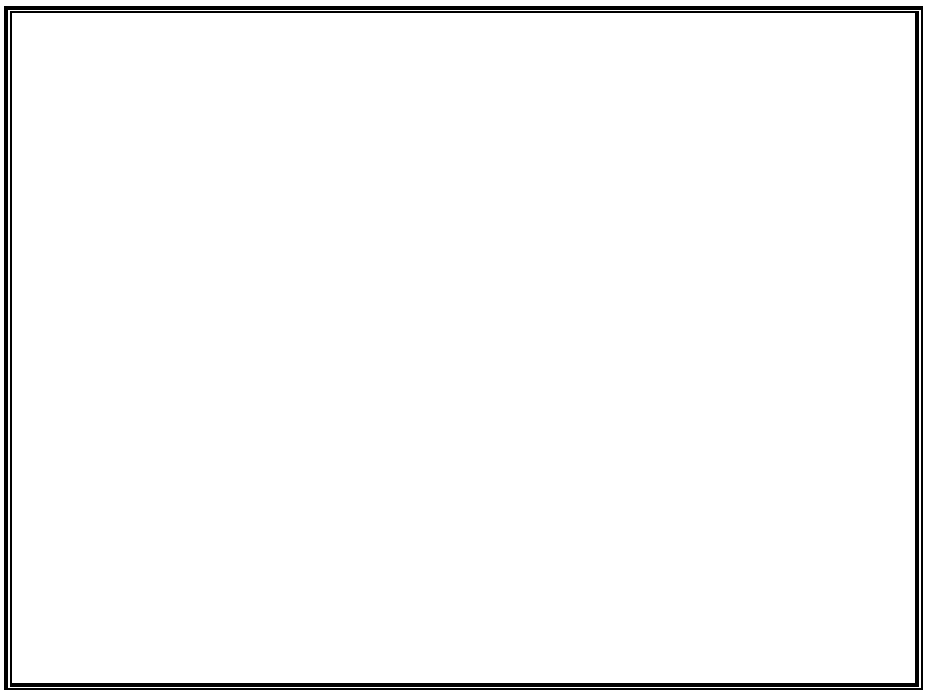


Fig. (3-24) FT-IR spectrum of 2-[N-(*p*-methylphenylacetamide)] amino-5-mercapto-1,3,4-thiadiazole [26]

Fig. (3-25) FT-IR spectrum of 2-[N-(*m*-methylphenylacetamide)] amino-5-mercapto-1,3,4-thiadiazole [27]

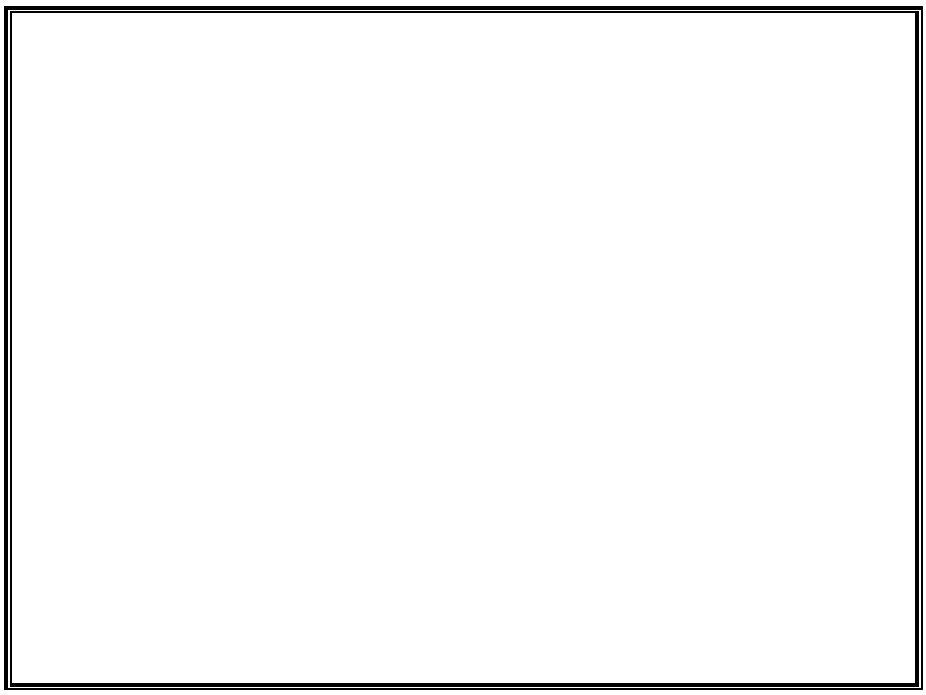


Fig. (3-26) FT-IR spectrum of 2-[N-(*o*-hydroxyphenylacetamide)]amino-5-mercapto-1,3,4-thiadiazole [28]

Fig. (3-27) FT-IR spectrum of 2-[N-(*p*-aminophenylmethylacetamide)]-5-mercapto-1,3,4-thiadiazole [29]

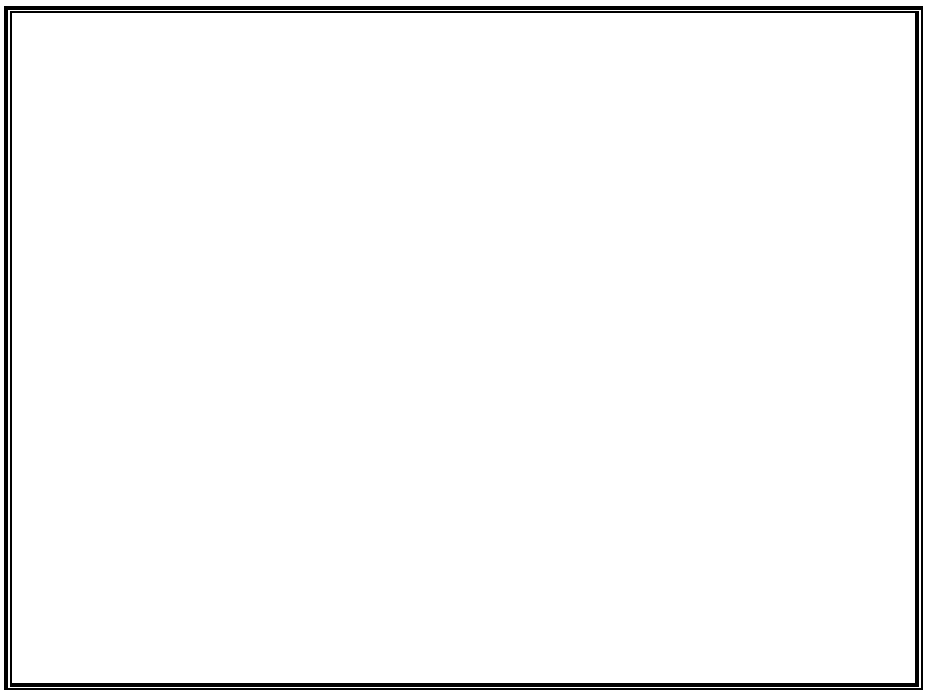
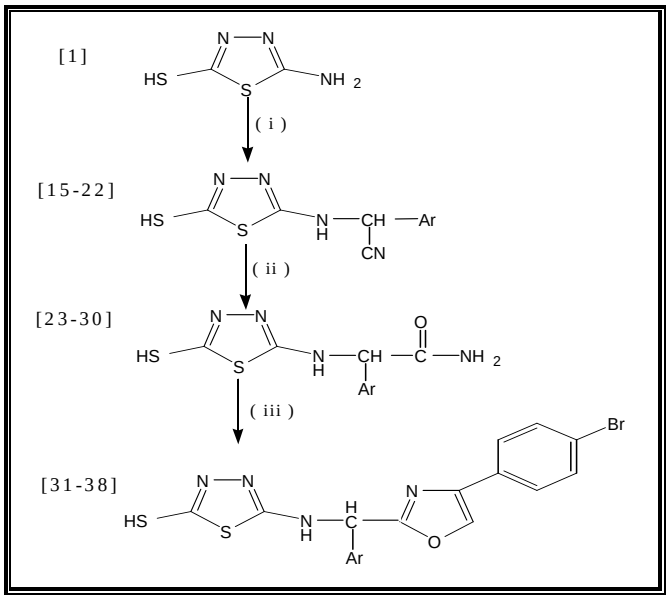


Fig. (3-28) FT-IR spectrum of 2-[N-(1-carbomylcyclohexyan-1-yl)]-5-mercapto-1,3,4-thiadiazole [30]

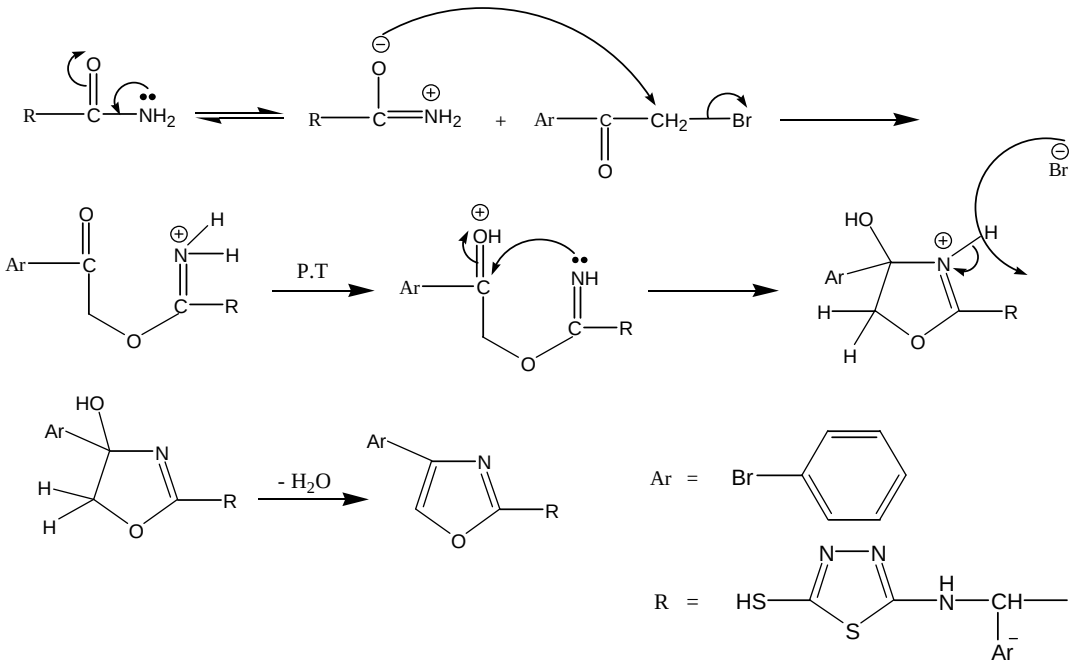
3.5.2 Synthesis of N(5-mercapto-1,3,4-thiadiazol-2-yl),α-(4̀-p-bromophenyl oxazol-2̀-yl)substituted-benzylamine [31-38]

Oxazole derivatives were obtained from the treatment of the previously prepared amides [23-30] with *p*-bromophenancyl bromide as shown in Scheme (3-4):



Scheme (3-4) Reagents and conditions: (i) HCl, ArCHO, KCN, stirring overnight ;(ii) 90-95% H_2SO_4, steam bath(10min);(iii) *p*-bromophenancyl bromide, abs. EtOH, reflux.

The mechanism for the formation of the title compounds is outlined:



The structure of the synthesized compounds was established on the basis of their m.p., FT-IR, ^{1}H-NMR (compound [35]).

Infrared spectra

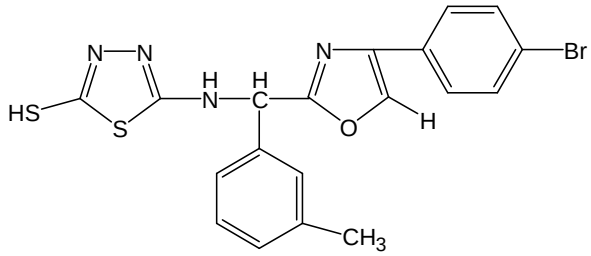
The FT-IR spectra, figs.(3-29)-(3-34), show the following common features: the disappearance of the bands in the region (3300-3250)cm^{-1} attributed to the $-NH_2$ stretching frequency of amide moiety together with the appearance of band at (1680-1630)cm^{-1} assignable to ν(C=N) of oxazole ring[175] and disappearance of amide (C=O) stretching band at about 1637cm^{-1}, are good evidence for the structure given to these compounds. Beside this, a strong band at (1070-1050) cm^{-1} attributed to ν(=C-O-C=) bond (ether linkage) is another good evidence for oxazole formulation[176]. Other bands were also observed in FT-IR spectra of these compounds and listed in Table (3-5).

Table (3-5)
Characteristic IR data of compounds [31-38]

Comp. No.	Fig. No.	ν N-H	ν C-H aromatic	ν C=N	ν =C-O-C=	γ C-H	Other bands
[31]	(3-29)	3400	3100	1681	1066	827	-
[32]	-	3300	3100	1681	1070	833	ν_{OH} 3400
[33]	(3-30)	3442	3120	1685	1024	823	-
[34]	-	3400	3050	1668	1050	820	-
[35]	(3-31)	3444	3100	1662	1070	823	-
[36]	(3-32)	3350	3100	1600	1070	827	ν_{OH} 3350
[37]	(3-33)	3150		1680	1053	815	ν_{NH2} 3400, 3300
[38]	(3-34)	3250	3120	1681	1022	821	-

^{1}H-NMR

^{1}H-NMR spectrum of compound [35], fig.(3-35), shows the following characteristic chemical shifts (DMSO-d_6, ppm).



[35]

The methyl group and N-H proton absorb at δ2.00 and δ4.64, respectively. Signal of (C-H) appeared at δ4.4. Protons of *p*-substituted, *m*-substituted aromatic rings and the proton of oxazole ring appear at the range δ(7.00-7.50) as a multiplet peaks. S-H Protons absorb at δ8.17.

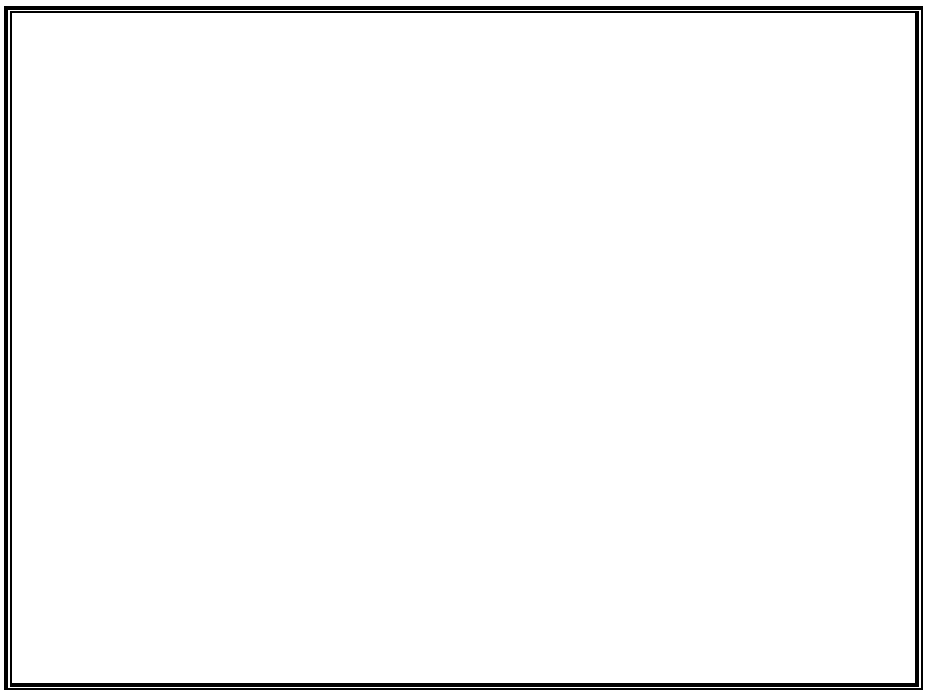


Fig. (3-29) FT-IR spectrum of N(5-mercapto-1,3,4-thiadiazol-2-yl),α-(4̀-*p*-bromophenyloxazol-2̀-yl) benzylamine [31]

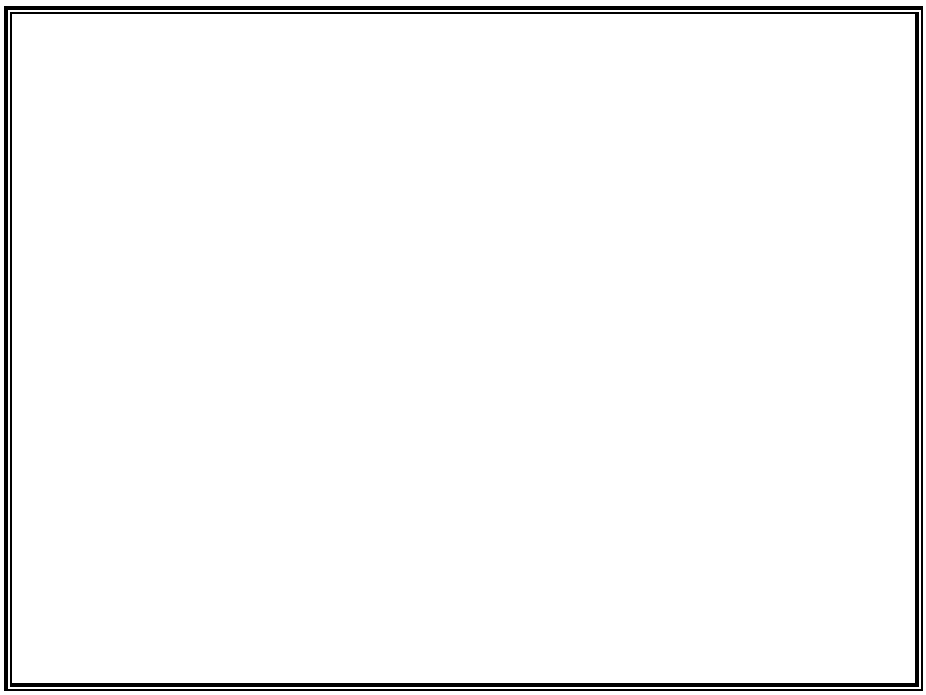


Fig. (3-30) FT-IR spectrum of N(5-mercapto-1,3,4-thiadiazol-2-yl),α-(4̀-*p*-bromophenyloxazol-2̀-yl)-*p*-methoxybenzylamine [33]

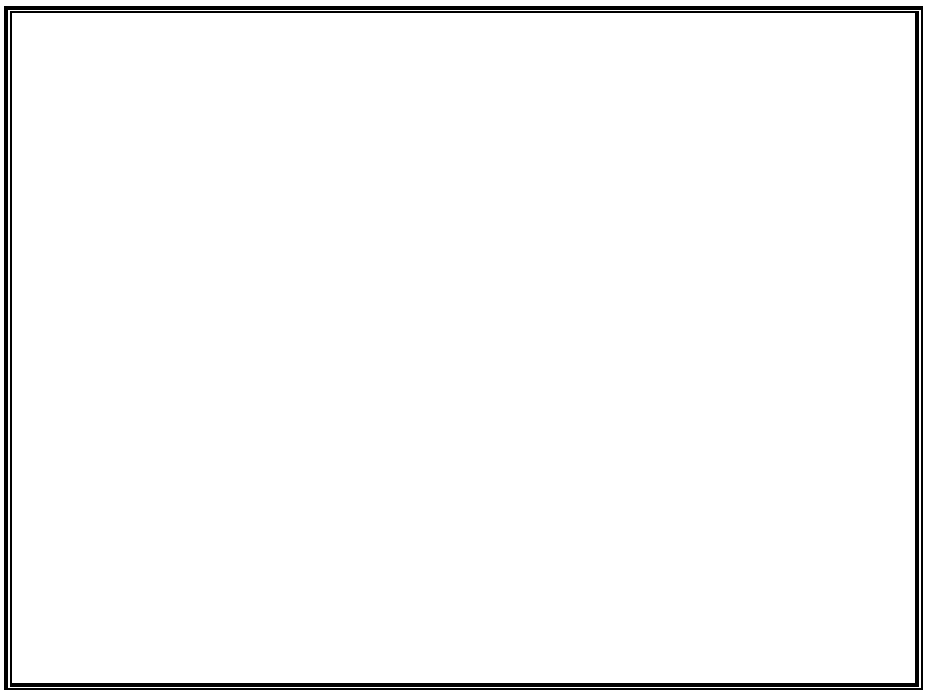


Fig. (3-31) FT-IR spectrum of N(5-mercapto-1,3,4-thiadiazol-2-yl),α(4̀-*p*-bromophenyloxazol-2̀-yl)-*m*-methylbenzylamine [35]

Fig. (3-32) FT-IR spectrum of N(5-mercapto-1,3,4-thiadiazol-2-yl),α(4̀-*p*-bromophenyloxazol-2̀-yl)-*o*-hydroxybenzylamine [36]

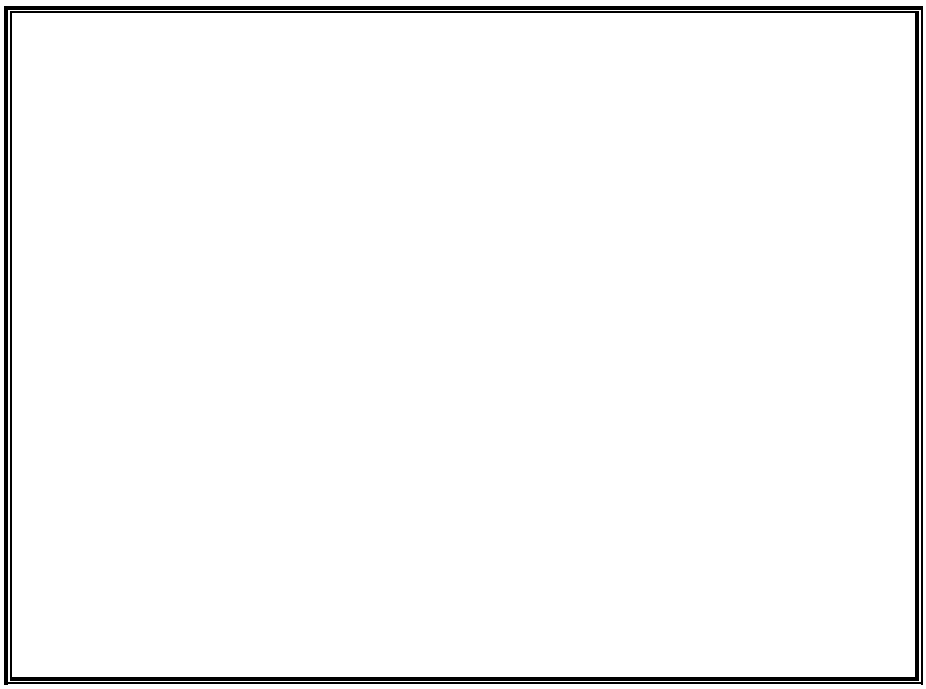


Fig. (3-33) FT-IR spectrum of N(5-mercapto-1,3,4-thiadiazol-2-yl),α(4̀-*p*-bromophenyloxazol-2̀-yl)-*p*-aminobenzylamine [37]

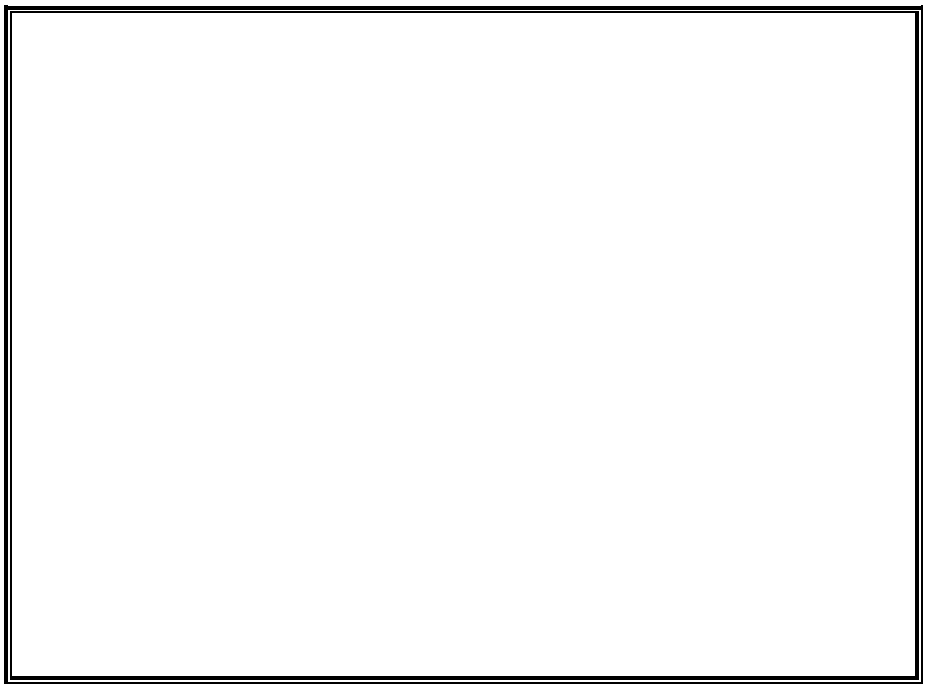


Fig. (3-34) FT-IR spectrum of N(5-mercapto-1,3,4-thiadiazol-2-yl),α(4̀-*p*-bromophenyloxazol-2̀-yl) cyclohexylamine [38]

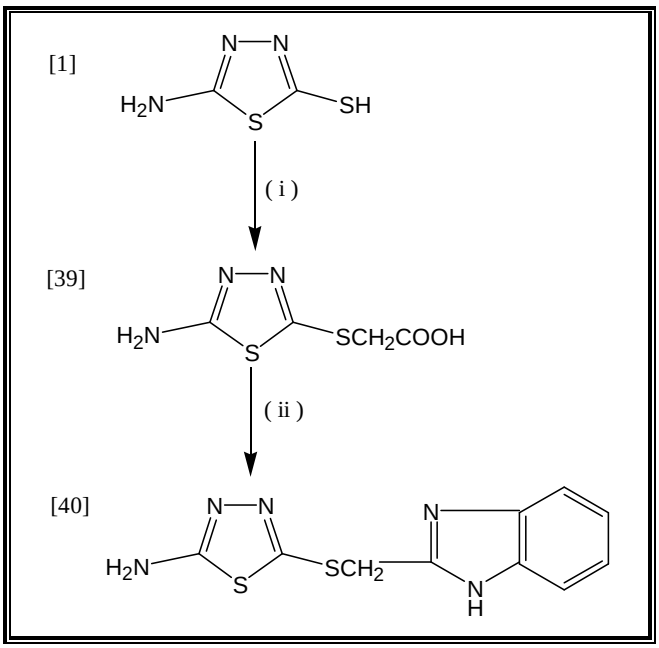
Fig. (3-35) ^{1}H-NMR spectrum of N(5-mercapto-1,3,4-thiadiazol-2-yl),α(4̀-*p*-bromophenyloxazol-2̀-yl)-*m*-methylbenzylamine [35]

3.6.0 Synthesis and characterization of 2-amino-5-[1̀H-benzimidazol-2̀-ylmethylthio]-1,3,4-thiadiazole [40]

Benzimidazole and its derivatives have attracted researcher's interest in the fields of bioorganic and medicinal chemistry, due to their significant antifungal, antibacterial and insecticidal properties[107]. Encouraged by these observations, it was considered worthwhile to synthesize compound [40] according to the reaction sequence outlined in Scheme (3-5).

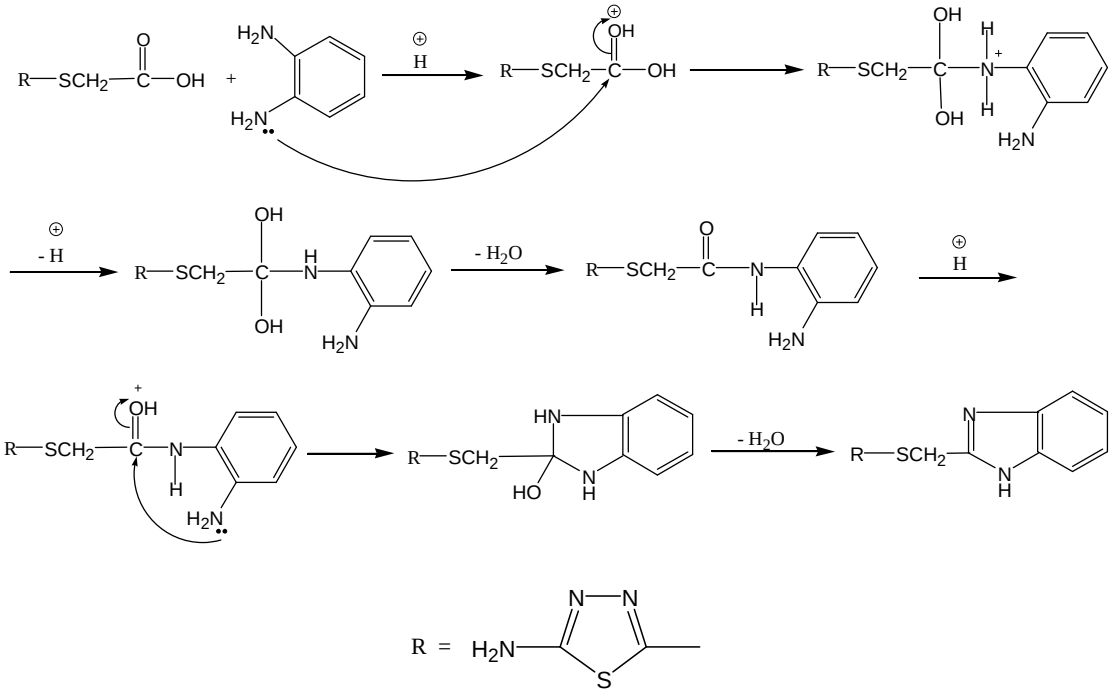
In order to synthesize the title compound, 2-amino-5-mercapto-1,3,4-thiadiazole [1] was reacted with monochloroacetic acid to produce 2-amino-5-mercaptoacetic acid-1,3,4-thiadiazole [39].

Condensing compound [39] with *o*-phenylenediamine yielded the benzimidazole derivative:



Scheme (3-5) Reagents and conditions: (i) KOH, $ClCH_2COOH$, abs. EtOH, reflux; (ii) *o*-phenylenediamine, HCl, reflux.

The mechanism of the reaction may be as follow:



The structure of compound [40] was confirmed by FT-IR spectral data which shows the disappearance of bands at 3400cm^{-1} and 1706cm^{-1} attributed to ν(-OH) and ν(C=O) of carboxylic acid [39]. The characteristic IR bands of compound [39] and [40] were shown in Table (3-6) and figs. (3-36) and (3-37).

Table (3-6)
FT-IR data of compounds [39] and [40]

Comp. No.	ν OH	ν C-H aromatic	ν C-H aliphatic	ν C=O	ν C=N	δ N-H	γ C-H
[39]	3400	-	2975 2800	1706	1630	1515	-
[40]	-	3041	2860	-	1612	1500	750

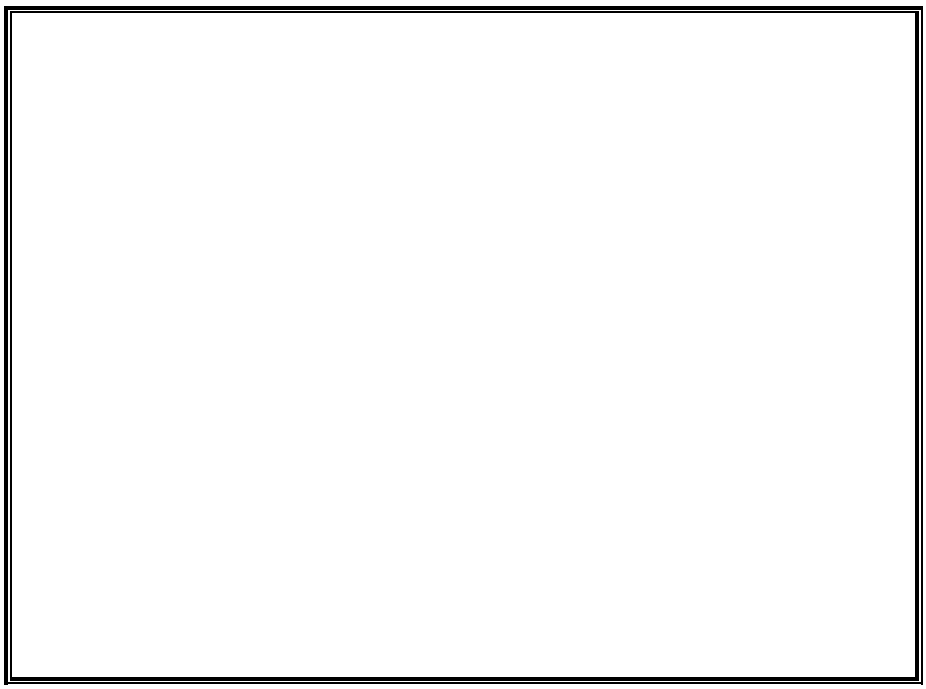


Fig. (3-36) FT-IR spectrum of 2-amino-5-thioacetic acid-1,3,4-thiadiazole [39]

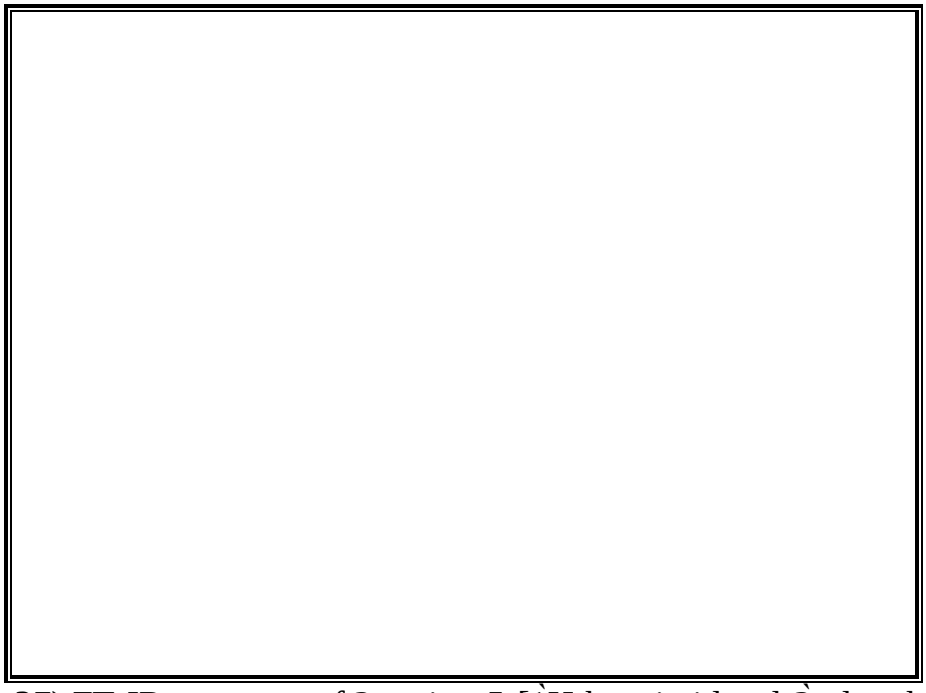


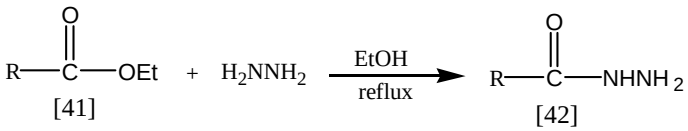
Fig. (3-37) FT-IR spectrum of 2-amino-5-[1̀H-benzimidazol-2̀-ylmethylthio] -1,3,4-thiadiazole [40]

3.7 Synthesis and characterization of 1-substituted-3-methylpyrazol-5-one

Interest in the chemistry of pyrazolone derivatives which mainly arises from the large variety of industrial and biological activities observed. Pyrazolone compounds were recommended in the synthesis of cyanine dyes which have been used as photo sensitizers. Also, it is of interest to note that 5-thiopyrazolone possess antifungal activity against the rice blast pathogen P. oryza[177]. Moreover, pyrazolones have played a crucial part in the development of theory in heterocyclic chemistry and also used extensively as useful synthons in organic synthesis[178]. Thus, owing to the wide application of pyrazole and its derivatives, we aimed to synthesize the title compound with hope to get improved biological activities.

3.7.0 Synthesis of acid hydrazide [42]

For the synthesis of acid hydrazide [42], the following reaction was followed:



The 2-amino-5-thioethylacetate-1,3,4-thiadiazole [41] was allowed to react with hydrazine hydrate in refluxing ethanol to give the desired product. The structure of this compound was confirmed by its m.p., and FT-IR spectral data.

Infrared spectrum

The infrared spectrum of the hydrazide, fig. (3-39), shows two stretching bands at (3300-3200) cm^{-1} which were assigned to the NH_2 stretching frequency. Beside this, the disappearance of (C=O) stretching band attributable to ester group at 1728cm^{-1}, fig. (3-38), with the appearance of bands at 1645 cm^{-1} (Amide I) and at 1595 cm^{-1} (Amide II) proved the formation of compound [42].

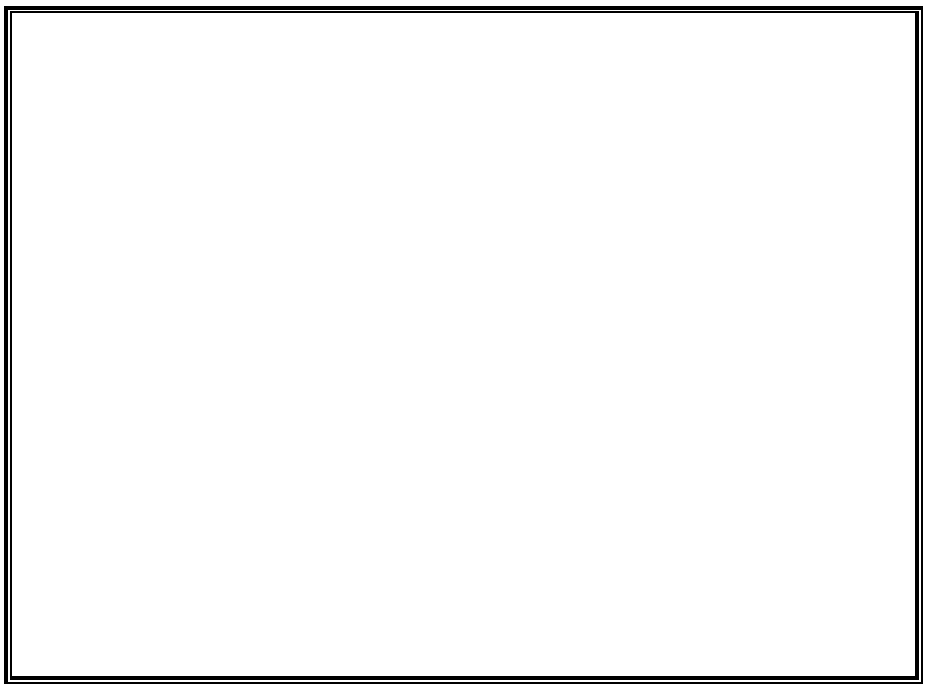


Fig. (3-38) FT-IR spectrum of 2-amino-5-thioethylacetate-1,3,4-thiadiazole [41]

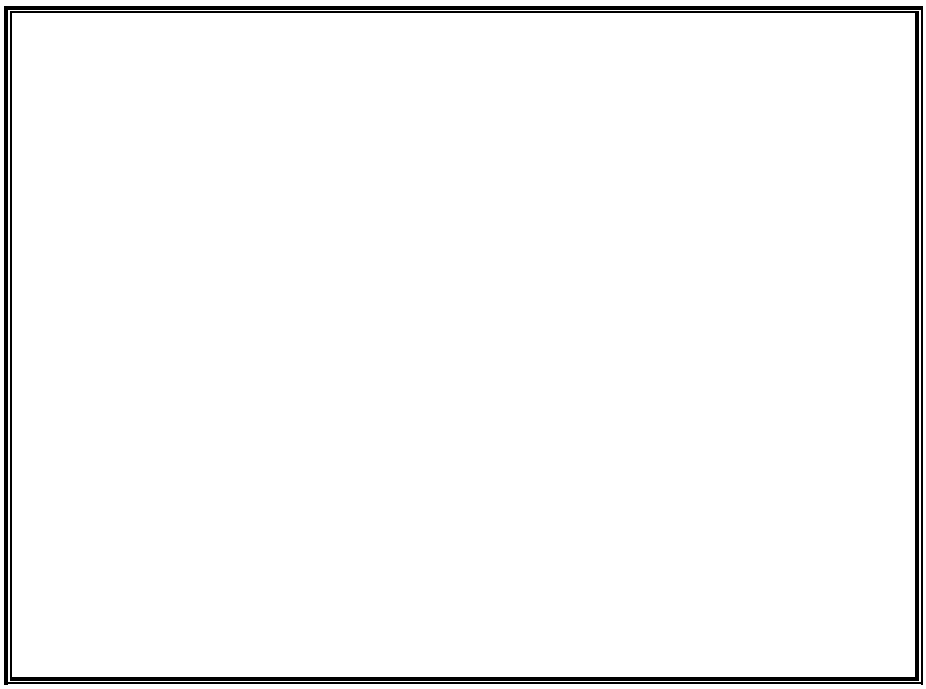
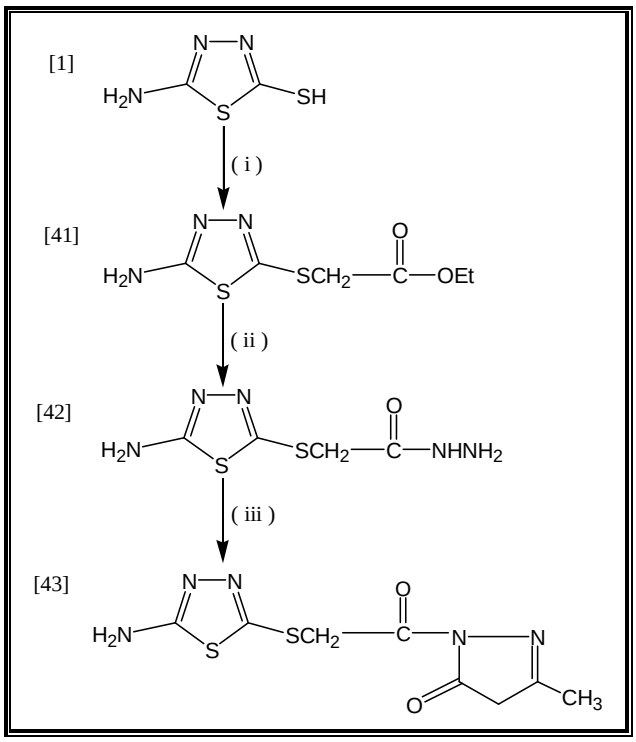


Fig. (3-39) FT-IR spectrum of 2-amino-5-thioacetic acid hydrazide-1,3,4-thiadiazole [42]

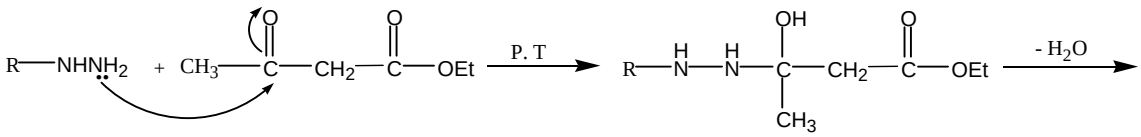
3.7.1 Synthesis of 1̀-[2̀-(2-amino-1,3,4-thiadiazol-5-ylthio)acetyl]-3̀-methyl-pyrazol-5̀-one [43]

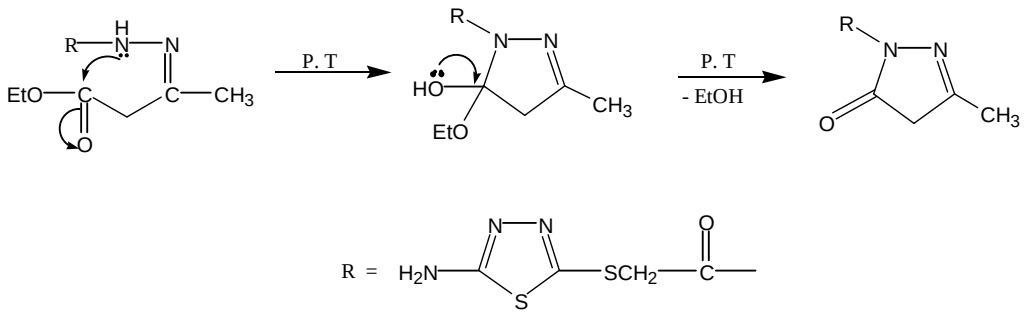
The route for the preparation of title compound involves the reaction of acid hydrazide with ethyl acetoacetate, Scheme (3-6):



Scheme (3-6) Reagents and conditions: (i) KOH, $ClCH_2COOEt$, reflux 8h; (ii) N_2H_4, abs. EtOH, reflux; (iii) CH_3COCH_2COOEt, abs. EtOH, reflux 7h.

The suggested mechanism for this reaction involve the nucleophilic attack of nitrogen atom of the hydrazide on the ketonic carbonyl of ethyl acetoacetate followed by the formation of Schiff base as intermediate compound, then another nucleophilic attack occur between the other nitrogen atom of hydrazide and the esteric carbonyl of ethyl acetoacetate as shown:

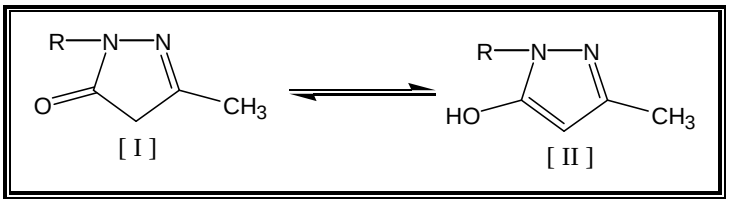




The structure of the target synthesized compound was confirmed by its m.p., FT-IR, ^{1}H- and ^{13}C-NMR.

Infrared spectrum

The most characteristic IR features, fig. (3-40), for the formation of compound [43] are the presence of bands at 3550cm^{-1} and 1718cm^{-1} which were due to the ν(O-H) and ν(C=O) moieties of pyrazole ring, respectively, while the (C=O) stretching band of amide occur at 1651cm^{-1}. From the above mentioned facts, we can say that compound [43] can exist in equilibrium between keto [I] and enol [II] forms.



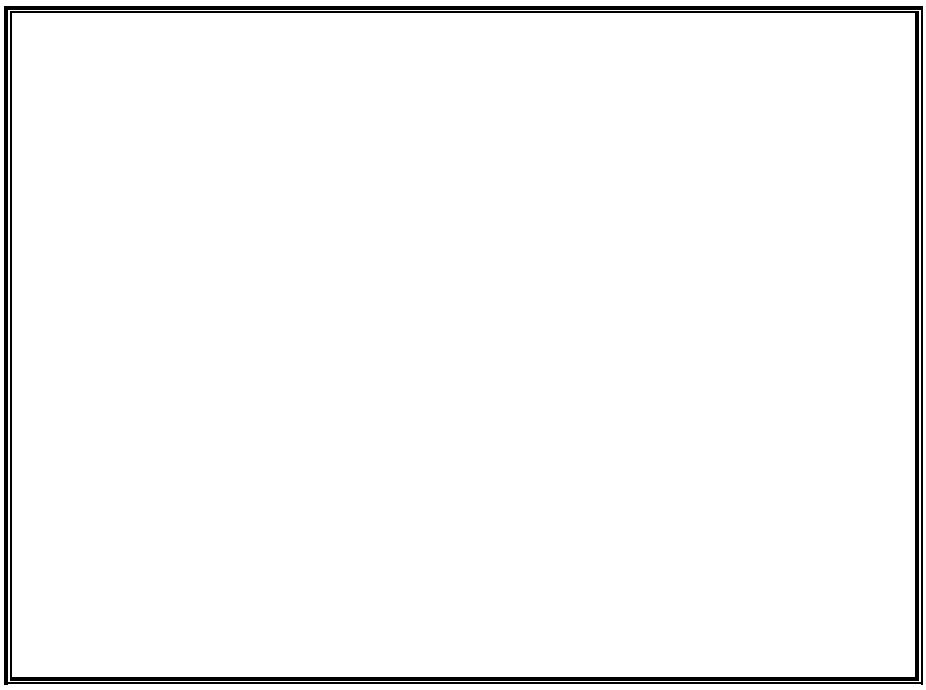
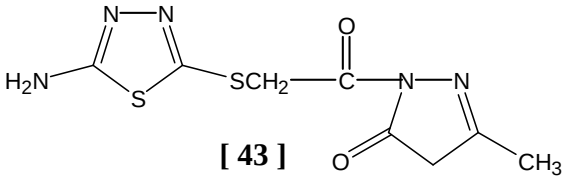


Fig. (3-40) FT-IR spectrum of 1̀-[2̀-(2-amino-1,3,4-thiadiazol-5-ylthio)acetyl]-3̀-methylpyrazol-5̀-one [43]

^{1}H-NMR

^{1}H-NMR spectra of compound [43], fig.(3-41) and (3-42), show the following characteristic chemical shifts (DMSO-d_6, ppm).



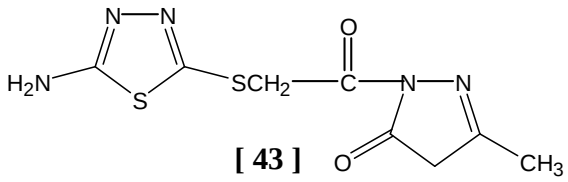
[43]

Methyl protons appear at δ1.24. The methylene protons of pyrazolone ring together with –CH- (enol form) absorb at δ1.99 and δ2.03, respectively.

DMSO peak occur at δ2.5. The two single peaks at δ3.34 and δ3.52 were due to the absorption of $–NH_2$ and –NH, respectively, which were further characterized by their disappearance due to the D_2O exchange, fig.(3-43). The signal of $–SCH_2$- protons was split into quartet and appeared in the region δ(4.11-4.20), this resembles (AB) system .The single peak at δ8.51 was attributed to O-H group of the tautomeric form, which was further assigned by D_2O exchange, this gives a good support for the results obtained from IR analysis.

^{13}C-NMR

^{13}C-NMR spectrum of compound [43], fig.(3-44), show the following characteristic chemical shifts (DMSO-d_6, ppm).



[43]

A signal at δ14.53 is characteristic of methyl group carbon. Signal at δ16.41 is assignable to (CH_2) group of the pyrazolone ring. The ($–C-CH_3$) carbon of pyrazole ring appears at δ44.14. The $–SCH_2$- absorption occurs at δ60.95. Thiadiazole ring carbon atoms absorption appears at δ149.93 and δ150.47. The signals at δ164.75 and δ170.12 are due to the absorption of the two carbonyl carbon atoms.

Fig.(3-41) ^{1}H-NMR spectrum of 1̀-[2̀-(2-amino-1,3,4-thiadiazol-5-ylthio)acetyl]- 3̀-methylpyrazol-5̀-one [43]

Fig.(3-42) Expansion ^{1}H-NMR spectrum of 1̀-[2̀-(2-amino-1,3,4-thiadiazol-5-ylthio)acetyl]- 3̀-methylpyrazol-5̀-one [43]

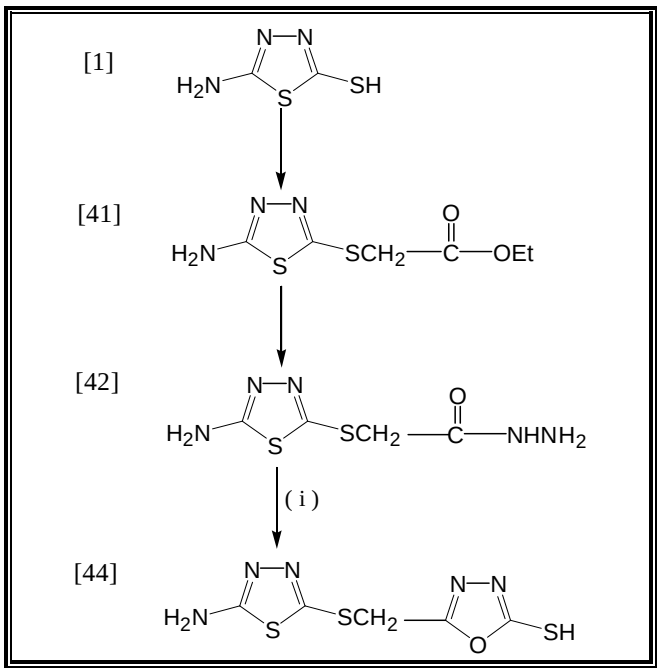
Fig.(3-43) ^{1}H-NMR spectrum of 1̀-[2̀-(2-amino-1,3,4-thiadiazol-5-ylthio) acetyl]- 3̀-methylpyrazol-5̀-one after the addition of D_2O [43]

Fig. (3-44) ^{13}C-NMR spectrum of 1̀-[2̀-(2-amino-1,3,4-thiadiazol-5-ylthio) acetyl]- 3̀-methylpyrazol-5̀-one [43]

3.8.0 Synthesis and characterization of 2̀-(2-amino-1,3,4-thiadiazol-5-ylmethylthio)-1̀,3̀,4̀-oxadiazole-5̀-thiol [44]

1,3,4-Oxadiazoles represent an important class of heterocyclic compounds that have many applications in the daily life. Numerous reports have highlighted their chemistry and uses[179]. Diverse biological activities such as antituberculostatic, anti-inflammatory, analgesic, antipyretic and anticonvulsant, have been found to be associated with oxadiazole derivatives[180]. These finding prompted us to synthesis the title compound with the hope that incorporating of 1,3,4-oxadiazole ring might enhance the biological activity.

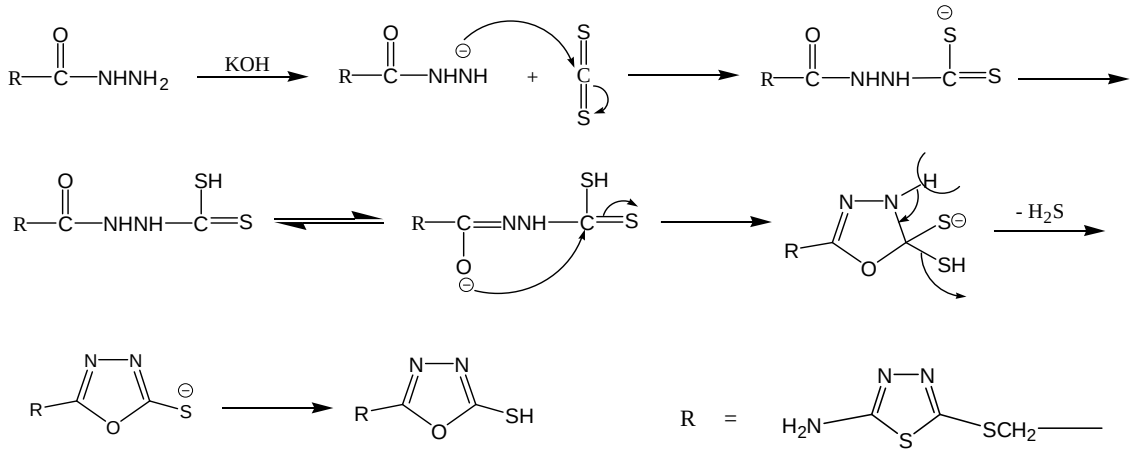
The 2-substituted-5-thiol-1,3,4-oxadiazole [44] was obtained due to the reaction sequence shown in Scheme (3-7):



Scheme (3-7) Reagents and conditions: (i) KOH, CS_2, EtOH, reflux 7h, HCl.

The target synthesized compound was characterized on the basis of its m.p. and FT-IR data.

The mechanism of the reaction may be outlined as follow:



Infrared spectrum

The disappearance of the band at 1645cm^{-1} due to ν(C=O) moiety of compound [42] with the appearance of a bands at 1620 cm^{-1} assignable to ν(C=N) of oxadiazole ring and at 1276cm^{-1} due to ν(C-O-C) (cyclic) group in oxadiazole are good evidences for the structure assigned to this compound. Strong bands at 1515cm^{-1} and 1371cm^{-1} were due to δ(N-H) and ν(C=S), respectively. FT-IR spectrum of compound [44], fig. (3-45), displayed other characteristic bands.

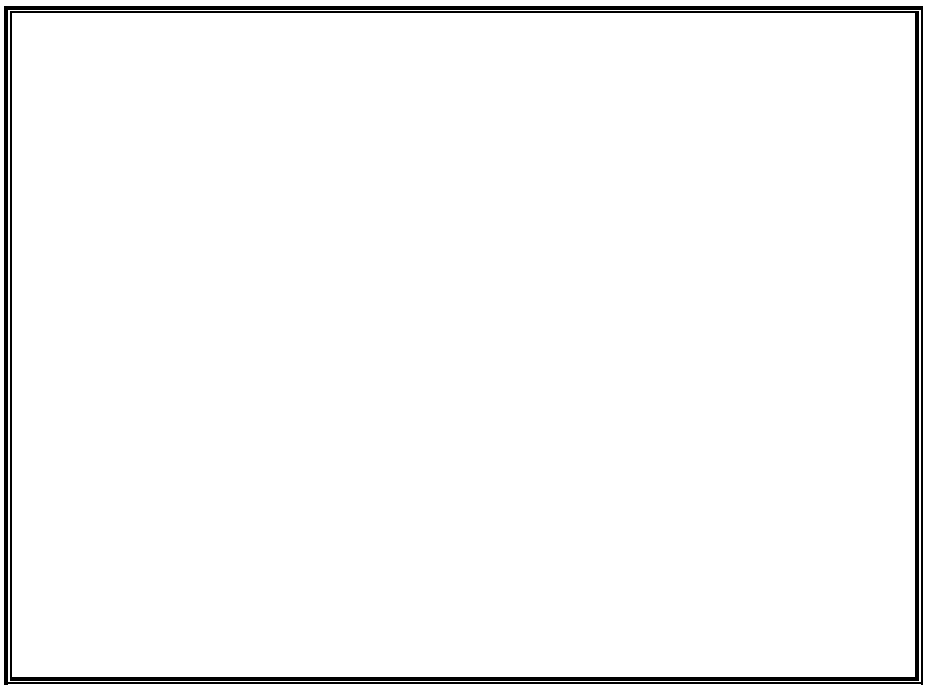
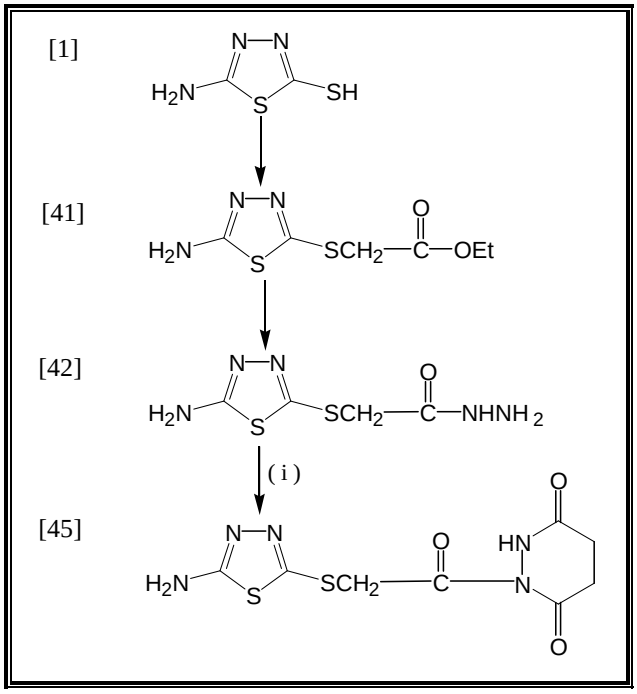


Fig. (3-45) FT-IR spectrum of 2̀-(2-amino-1,3,4-thiadiazol-5-ylmethylthio) -1̀,3̀,4̀-oxadiazole-5̀-thiol [44]

3.9.0 Synthesis and characterization of 1̀-[2̀-(2-amino -1,3,4-thiadiazol-5-ylthio)acetyl]-2̀,4̀,5̀-trihydropyridazin-3̀,6̀-dione [45]

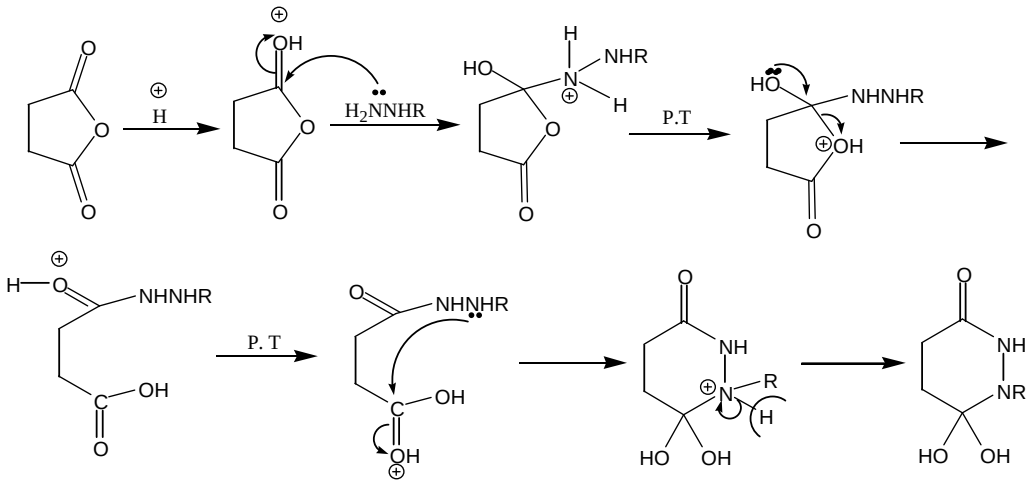
Synthetic pyridazinone derivatives are important scaffolds in drug discovery, with many of their analogs being used in the treatment of various human pathological states. They were described as nonsteroidal anti-inflammatory agents for treatment intervention of renal-urologic, cardiovascular, respiratory and dermatologic diseases[181]. On the basis of the above mentioned important applications, we aimed to synthesize the title compound with hope to obtain biologically active compound.

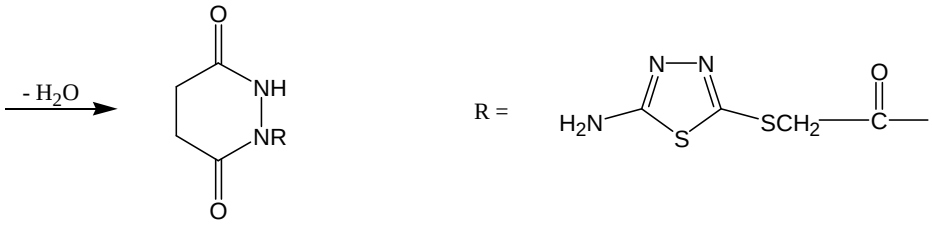
Compound [45] was obtained from the reaction of acid hydrazide with succinic anhydride and the reaction sequence is outline in Scheme (3-8):



Scheme (3-8) Reagents and conditions: (i) succinic anhydride, CH_3COOH, reflux 7h.

The mechanism of the reaction can be as the following:

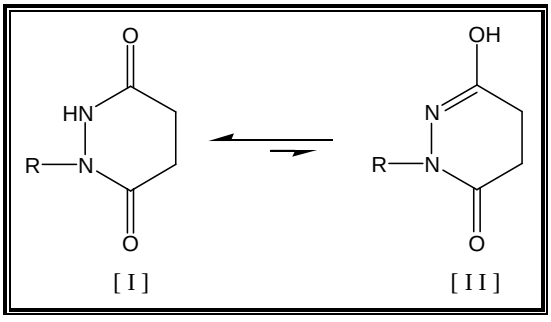




The synthesized compound was characterized on the basis of its m.p., FT-IR, ^{1}H- and ^{13}C-NMR.

Infrared spectrum

The FT-IR spectrum, fig. (3-46), shows two broad bands at 3460cm^{-1} and 3203cm^{-1} which where assignable to (O-H), (-NH_2) and (N-H) stretching vibrations. The band at 1726cm^{-1} was due to ν(C=O) moiety of pyridazine ring. Band at 1625cm^{-1} was due to the ν(C=O) of amide, this value appear to be lower than expected due to the hydrogen bond between it and (N-H) group of pyridazine ring. From the above mentioned results we can say that the compound [45] can be exist in two tautomeric forms; keto [I] and enol [II] forms:



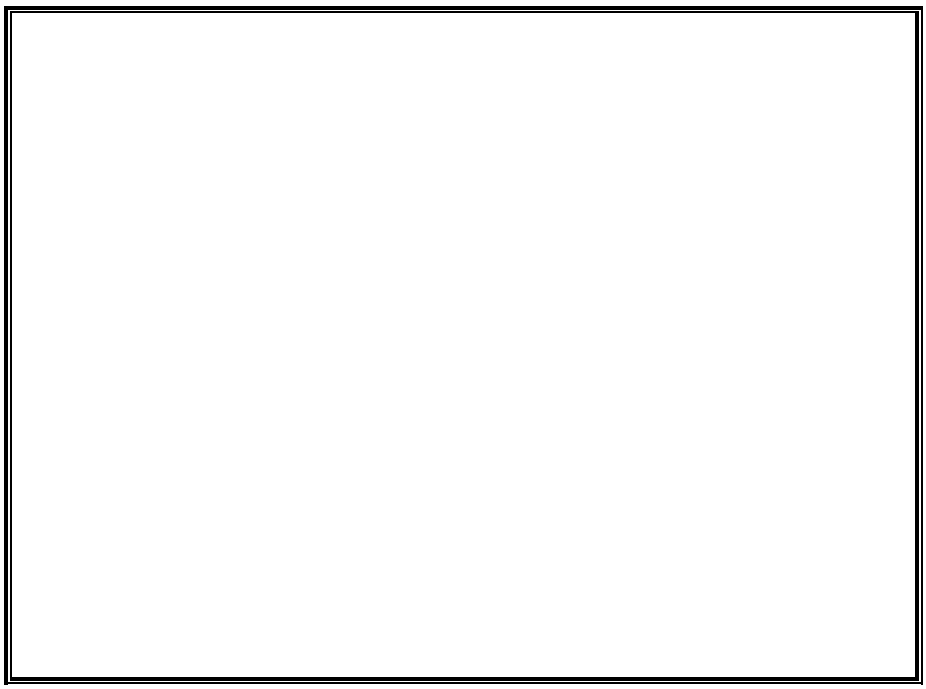
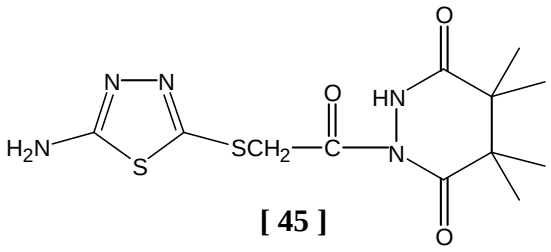


Fig. (3-46) FT-IR spectrum of 1̀-[2̀-(2-amino-1,3,4-thiadiazol-5-ylthio)acetyl] -2̀,4̀,5̀-trihydropyridazin-3̀,6̀-dione [45]

^{1}H-NMR

^{1}H-NMR spectrum of compound [45], fig.(3-47), shows the following characteristic absorption bands (DMSO-d_6, ppm).



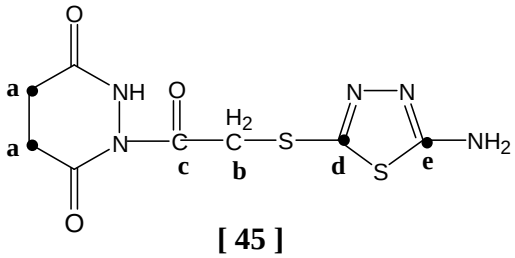
[45]

The two methylene groups of pyridazine ring appear in the region δ(1.87-2.03). Signal at δ2.5 was due to DMSO. The $–SCH_2$- absorption occurs at δ2.78 (s, 2H). Two single peaks at δ5.27 and δ5.39 are due to $–NH_2$ and -NH (tautomeric proton), respectively. The pyridazine (N-H) absorption occurs at

δ(9.45-9.67). The latter two absorption was further proved by D_2O exchange, fig.(3-48). The above data agree with the proposed structure.

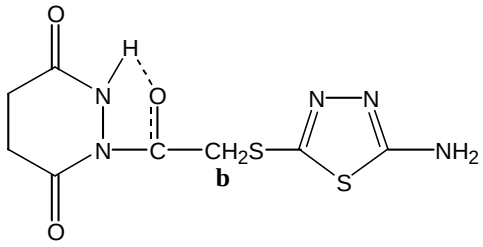
^{13}C-NMR

^{13}C-NMR spectrum of compound [45], fig.(3-49), shows the following characteristic absorption bands (DMSO-d_6, ppm).



[45]

The two methylene carbon atom, a, of pyridazine ring absorb at δ21.10. The $-SCH_2-$ carbon, b, appear upfield than expected, at δ28.96, this is due to the hydrogen bonding between –NH of pyridazine ring and the exocyclic (C=O) group:



Thiadiazole ring carbon, d and e, absorb at δ151.18 and δ152.62. The signals at δ168.49 and δ168.84 are assigned to the two carbonyl atoms of pyridazine ring. The carbonyl, c, absorb at δ174.27.

Fig.(3-47) ^{1}HNMR spectrum of 1̀-[2̀-(2-amino-1,3,4-thiadiazol-5-ylthio) acetyl]-2̀,4̀,5̀-trihydropyridazin-3̀,6̀-dione [45]

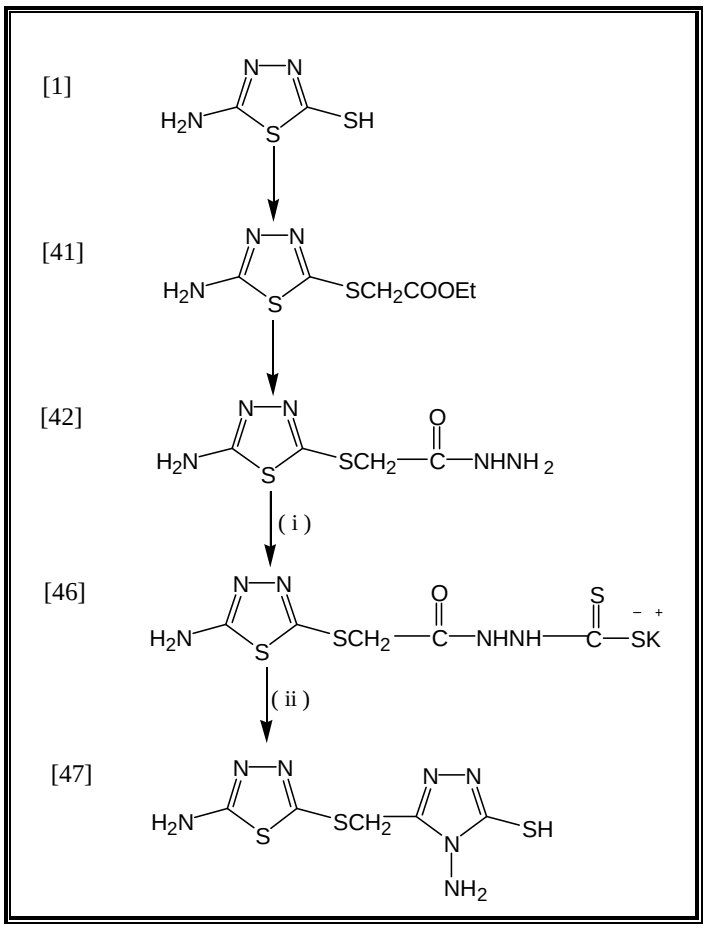
Fig.(3-48) ^{1}H-NMR spectrum of 1̀-[2̀-(2-amino-1,3,4-thiadiazol-5-ylthio) acetyl]-2̀,4̀,5̀-trihydropyridazin-3̀,6̀-dione [45] after the addition of D_2O

Fig. (3-49) ^{13}C-NMR spectrum of 1̀-[2̀-(2-amino-1,3,4-thiadiazol-5-ylthio) acetyl]-2̀,4̀,5̀-trihydropyridazin-3̀,6̀-dione [45]

3.10.0 Synthesis and characterization of 4̀-amino-5̀-[2-amino-1,3,4-thiadiazol-5-ylmethylthio]-1̀,2̀,4̀- triazole-3̀-thiol [47]

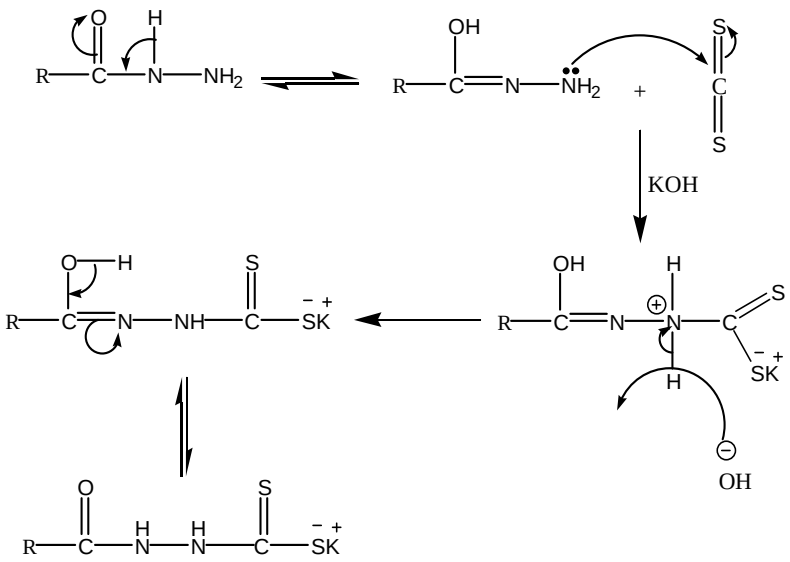
The therapeutic effects of 1,2,4-triazole containg compounds have been well studied for a pathological conditions including inflammation, cancer, tuberculosis and hypertension. Moreover, the new changing problems in plant protection technology have promoted research to discover more efficient pesticides, in particular the development of herbicides, now an unavoidable means to selectively control the growth of weeds, resulted in a whole range of azoles exhibiting high levels of activity, application flexibility, crop tolerance and low levels of toxicity to mammals[182]. Triazoles play an important role among this glass of heterocycles. Keeping this in view, it was considered desirable to synthesis the title compound with the hope that the incorporation of 1,2,4-triazole ring might enhance the biological activity of the originally synthesized compound.

The synthesis of this compound involved the direct hydrazinolysis of the potassium salt [46]. Scheme (3-9) illustrates the reaction steps for the formation of title compound:



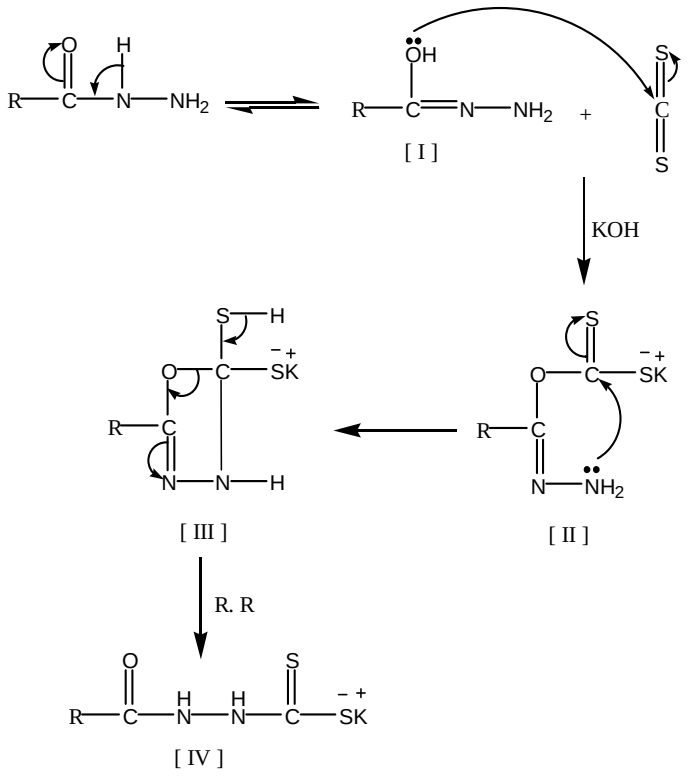
Scheme (3-9) Reagents and conditions: (i) KOH, CS_2, EtOH, stirred (8-10)h at R. T. ; (ii) $N_2H_4.H_2O$, reflux, HCl

Hoggarth's[183] method for the preparation of 5-substituted-4-amino-3-mercapto-4H-1,2,4-triazole has been widely utilized as the method of choice for the preparation of this useful class of heterocyclic compounds. Practically, stirring the acid hydrazide [42] with carbon disulfide in ethanolic potassium hydroxide gave the salt [46] in good yield which was then cyclized by refluxing with hydrazine hydrate to give a moderate yield of the desired triazole [47]. The formation steps of the potassium salt may be visualized as shown in Scheme (3-10):



Scheme (3-10)

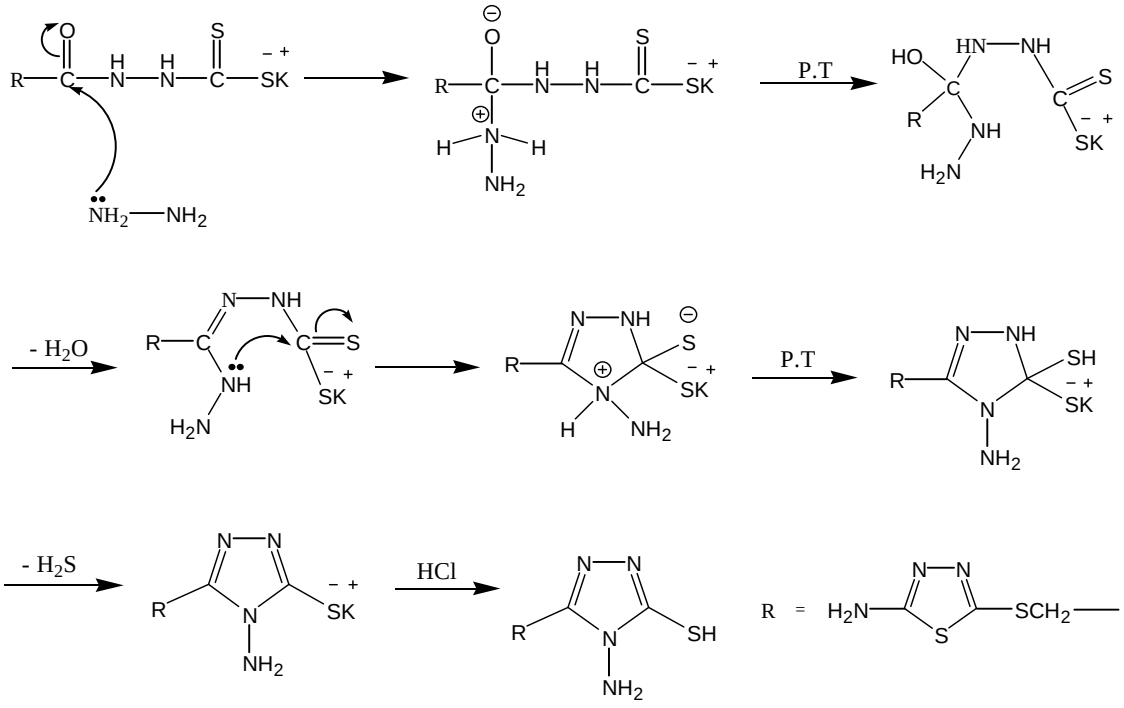
Young and Wood[158] suggested an alternative mechanism, Scheme (3-11). This involves a nucleophilic attack first by the enol ion of hydrazide [I] on the thione group of the carbon disulfide forming the xanthate salt [II] which undergoes intramolecular addition to form the intermediate oxadiazoline [III], which might rearrange to produce the salt [IV]:



Scheme (3-11)

The salt [46] was characterized on the basis of its FT-IR spectrum, fig.(3-50); the characteristic IR spectral features showed (NH_2), (N-H) stretching bands at 3381cm^{-1}, 3269cm^{-1} and 3132cm^{-1}. Beside this, the intense bands at 1728cm^{-1} and 1624cm^{-1} were due to the ν(C=O) and δ(N-H), respectively. The spectrum also shows absorption band at 1363cm^{-1} due to ν(C=S).

The suggested mechanism for the cyclization of potassium salt [46] is illustrated in Scheme (3-12):



Scheme (3-12)

The structure of triazole derivative [47] was characterized by its m.p. and FT-IR spectrum.

Infrared spectrum

In the IR spectrum, fig.(3-51), the disappearance of carbonyl stretching band attributable to dithiocarbazate salt [46] at 1728cm^{-1} was the most characteristic evidence for the formation of the title compound. Furthermore bands in the range (3350-3000)cm^{-1} can be attributed to (NH_2) and (N-H) stretching vibrations. The spectrum also shows bands at 1600cm^{-1}(C=N), 1284cm^{-1}(N-N) and 673cm^{-1}(C-S) stretching vibrations.

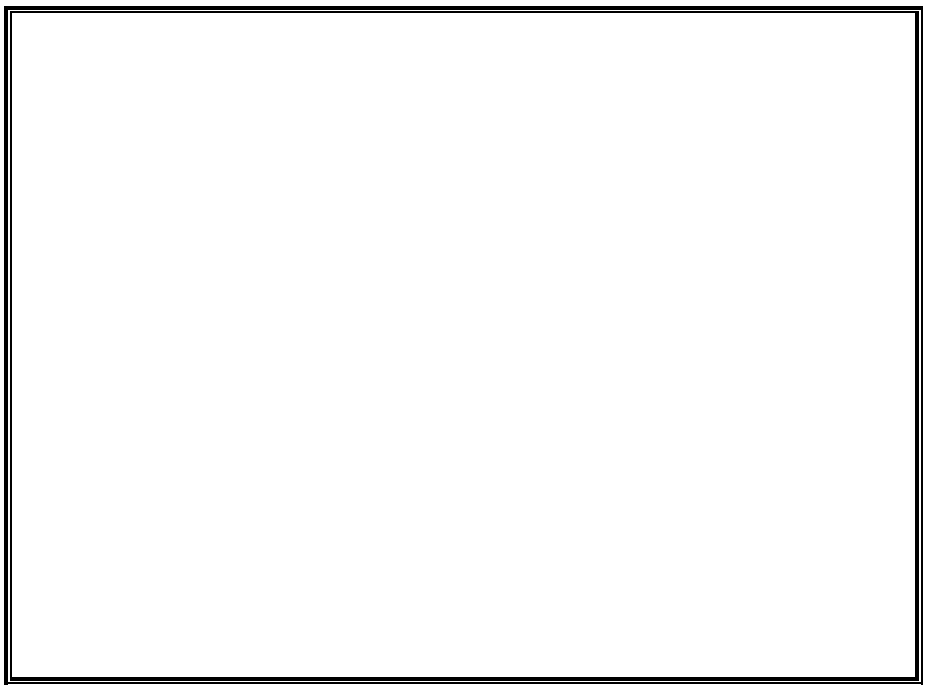


Fig. (3-50) FT-IR spectrum of potassium [2-(2-amino-1,3,4-thiadiazol-5-ylthio)acetyl]dithiocarbazate [46]

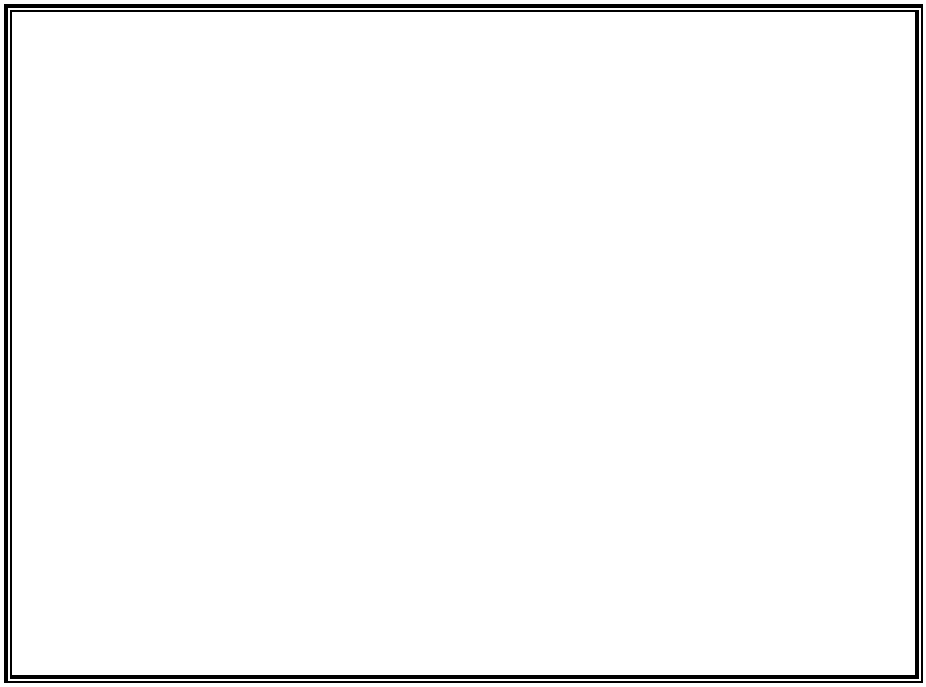


Fig. (3-51) FT-IR spectrum of 4̀-amino-5̀-[2-amino-1,3,4-thiadiazol-5-ylmethylthio]-1̀,2̀,4̀-triazole-3̀-thiol [47]

3.11 Biological activity

Microorganism causes different kind of diseases to humans and animals. Discovery of chemotherapeutic agents played a very important role in controlling and preventing such diseases.

Chemotherapeutic agents are isolated either from living organism known as antibiotics like penicillin and tetracycline etc., or they are chemical compounds prepared by chemist such as the sulfa drugs etc.[82].

Multiple drug resistant organisms, such as methicillin-resistant *Staphyloccus auresus*, vancomycin-resistant *Enterococci*, etc., are becoming common causes of infections in the acute and long term care units in hospitals. The emergence of these resistant bacteria has created a major concern and an urgent need to agents in structural classes distinct from known chemotherapeutic agents.

The most essential feature of good chemotherapeutic agent is that, it must show a high degree of selective toxicity towards a microorganism, so that, it can be given in sufficient doses to inhibit or kill the microorganism through out the body without harming the body cell. Heterocyclic rings constitute an important class of compounds having a wide spectrum of biological activity[184].

3.11.0 Microbiological tests

In this work, the antibacterial and antifungal test was performed according to the disc diffusion method. Compounds ([1], [2], [14], [43], [45]) were assayed for their antimicrobial activity in vitro against 3 strains of Gram-negative bacteria (*Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*)

and 2 strains of fungi: Yeast-like fungi (*Candida albicans*) and moulds (*Aspergillus niger*). Prepared agar and petridishes were sterilized by autoclaving for 15min at 121C°. The agar plates were surface inoculated uniformly from the broth culture of the tested microorganisms. In the solidified medium suitably spaced apart holes were made all 6mm in diameter. These holes were filled with 100µl of the prepared compounds (1mg of the compound dissolved in 1ml of DMSO solvent), DMSO was used as a solvent. These plates were incubated at 37C° for 24h for both bacteria and fungi, except the Aspergillus niger plate was incubated at 28Cº for 72h. The inhibition zones caused by the various compounds were examined. The results of the preliminary screening tests are listed in Table (3-7).

From the data obtained, it is found clearly that compounds [2], [14] and [45] have the highest activity against *E.coli*, *Klebsiella* and *Proteus* than others. In case of fungi, compounds [1], [2], [14], [43] and [45] show no activity against *Aspergillus niger* while in case of *Candida*, compound [1] show the higher activity than others. Figures (3-52)-(3-56) show the inhibition zones of the synthesized compounds against bacteria and fungi.

Table (3-7)
Antibacterial and antifungal activities of the synthesized compounds

Comp. No.	Escherichia coli	Klebsiella pneumoniae	Proteus vulgaris	Candida albicans	Aspergillus niger
[1]	-	+	++	++	-
[2]	++	++	++	+	-
[14]	+++	+++	+++	+	-
[43]	-	+	-	+	-
[45]	++	++	+++	-	-

Note :

- = No inhibition = inactive
\+ = (5-10) mm = slightly active
++ = (11-20) mm = moderately active
+++ = more than 20mm = highly active

Fig. (3-52) Effect of compounds [1], [2], [14], [43], [45] on *Escherichia coli*

Fig. (3-53) Effect of compounds [1], [2], [14], [43], [45] on *Klebsiella pneumoniae*

Fig. (3-54) Effect of compounds [1], [2], [14], [43], [45] on *Proteus vulgaris*

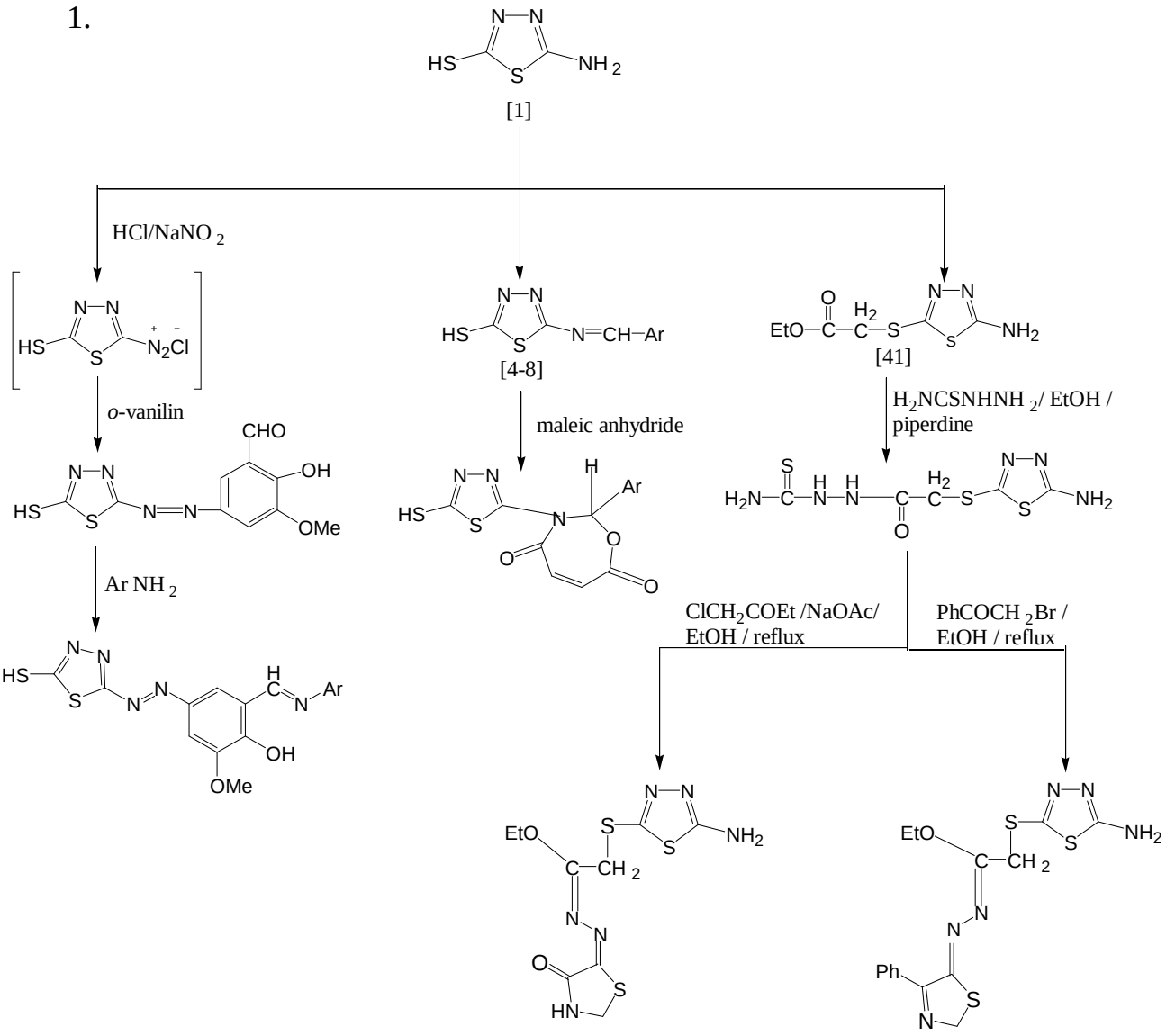
Fig. (3-55) Effect of compounds [1], [2], [14], [43], [45] on *Candida albicans*

Fig. (3-56) Effect of compounds [1], [2], [14], [43], [45] on *Aspergillus niger*

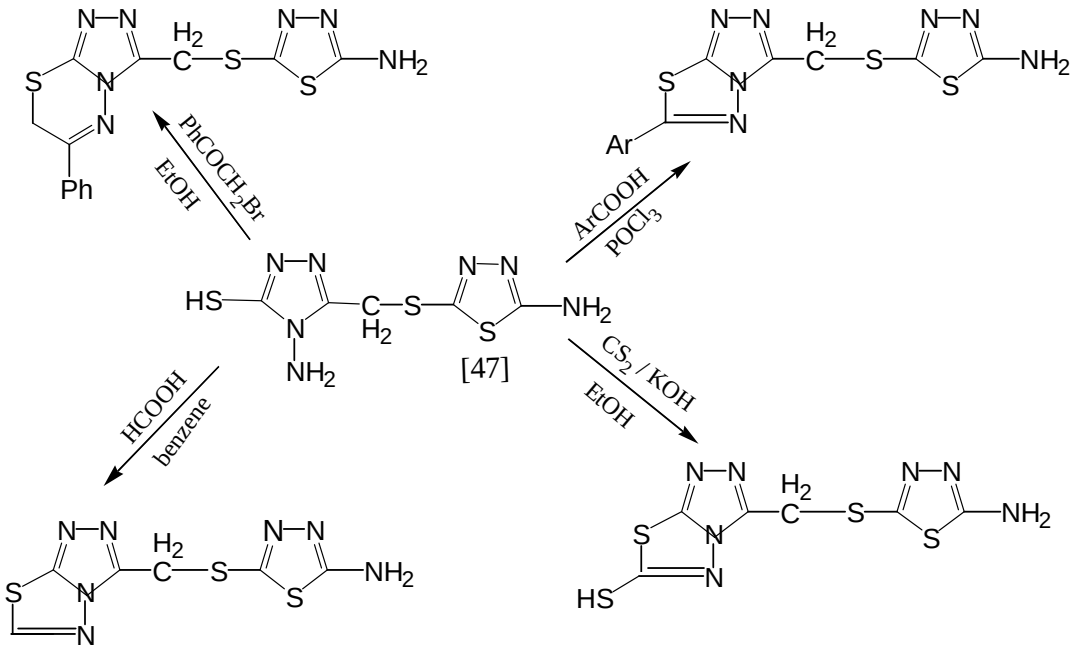
Suggestions for further work

On the bases of the experience gained during this work, one can suggest the following as future work:

1.



2.



3. More detailed investigations are required to reveal the biological activity of the synthesized compounds against other microorganism, their toxicity, absorption, excretion and the side effects which may produce before they can be used clinically.

Chapter Two

Experimental

2.1 Chemicals

Table (2-1) shows all the utilized chemicals in the experimental course of the thesis.

Table (2-1) Chemicals and their manufacturers

Chemicals	Supplied from
p-Aminoacetophenone	Fluka
Anisaldehyde	BDH
Benzaldehyde	BDH
p-Bromophenacyl bromide	Fluka
Carbon disulfide	Fluka
Chloroacetic acid	Hopkin and William
Cyclohexanone	Fluka
Ethanol(abs.)	BDH
Ethylacetoacetate	BDH
Ethylchloroacetate	BDH
Hydrazine hydrate	Merck
p-Hydroxybenzaldehyde	Merck
Hydrochloric acid	Merck
p-Methylbenzaldehyde	BDH
m-Methylbenzaldehyde	BDH
p-Nitrobenzaldehyde	Merck
o-Phenylenediamine	Fluka
Phenyl isocyanate	Fluka
Potassium cyanide	Fluka
Potassium hydroxide	Merck
Sodium azide	Merck

Continue:-

Chemicals	Supplied from
Sodium carbonate(anhydrous)	BDH
Sulfuric acid	Fluka
Succinic anhydride	Hopkin and William
Thiosemicarbazide	Fluka
Tetrahydrofuran	BDH
Thioglycolic acid	BDH

2.2 Techniques

1. Melting points were recorded on a hot stage Gallen Kamp melting point apparatus and were uncorrected.

2. Infrared spectra were recorded on Shimadzu FTIR-8300 spectrometer as potassium bromide disc.

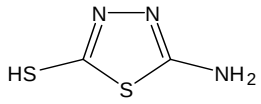
3. ^{1}H-NMR spectra were recorded on a Fourier transform Varian spectrometer operating at 300 MHz with tetramethylsilane as internal standard in DMSO-d^6. Measurements were made at the Chemistry Department, Georgia State University (Georgia, USA).

4. ^{13}C-NMR spectra were recorded on a Fourier transform Bruker spectrometer operating at 75MHz in DMSO-d^6. Measurements were made at the Organic Chemical Technology Department, Technical University of Budapest (Budapest, Hungary).

5. Thin layer chromatography (tlc) was carried out using Fertigfollen precoated sheets type Polygram SilG, and the plates were developed with iodine vapour.

2.3 Synthesis of compounds

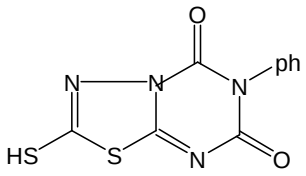
2.3.1 Synthesis of 2-amino-5-mercapto-1, 3, 4-thiadiazole [1]



[1]

A mixture of (13.5g, 0.1mol) of thiosemicarbazide and (9g, 0.1mol) of anhydrous sodium carbonate was dissolved in 70ml abs. ethanol, to this solution (18.3g, 0.24mol) of carbon disulfide was added. The resulting mixture was heated under reflux for 7 hours. The reaction mixture was then allowed to cool down to room temperature. Most of the solvent was removed under reduced pressure and the residue was dissolved in distilled water 60ml, and carefully acidified with conc. hydrochloric acid to give pale yellow precipitate. The crude product was filtered and washed with cold water, recrystallized from ethanol to give the desired product as yellow needles, yield 70%, m.p. 230-231C˚, reported 227C˚[149,150].

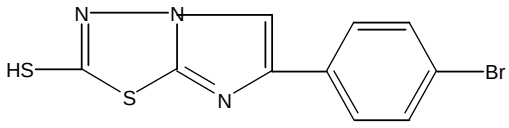
2.3.2 Synthesis of 2-mercapto-5-phenyl-4,6-dione-1,3,5-triazino[6,5-b][1,3,4]thiadiazole [2][(76)]



[2]

2-Amino-5-mercapto-1,3,4-thiadiazole [1](1.33g,0.01mol) and phenyl iso-cyanate (3.26ml,0.03mol) were heated under reflux in pyridine 15ml for 10 hours. Evaporation in vacuo gave the desired product. The crude product was recrystallized from chloroform. Yield 87%, m.p. 193-195C˚.

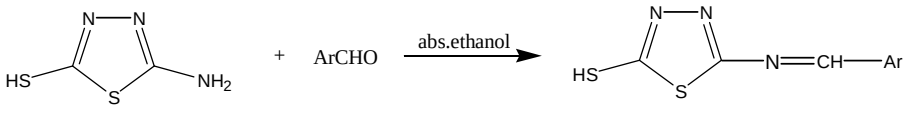
2.3.3 Synthesis of 5-(*p*-bromophenyl)-2-mercapto-imidazo[2,1-b]-1,3,4-thiadiazole [3][(151)]



[3]

A mixture of 2-amino-5-mercapto-1,3,4-thiadiazole [1] (1.33g,0.01mol) and *p*-bromophenacylbromide(2.78g,0.01mol) in abs. ethanol(20ml) was refluxed for 8 hours. The precipitate thus obtained was filtered and recrystallized from (ethanol-chloroform). Yield 70%, m.p. 159-160C˚.

2.3.4 Synthesis of 2-[substituted-benzylidine]amino-5-mercapto-1,3,4-thiadiazole [4-8]



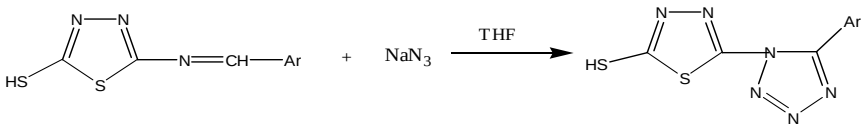
Ar = C_6H_5, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-$NO_2C_6H_4$, m-$CH_3C_6H_4$
[4] [5] [6] [7] [8]

A mixture of 2-amino-5-mercapto-1,3,4-thiadiazole [1](1.33g,0.01mol), abs. ethanol (20ml) and appropriate aromatic aldehydes(0.01mol) were refluxed for (4-5) hours. After cooling to room temperature the precipitate was filtered and dried. The products were recrystallized from ethanol. The physical properties for the synthesized compounds are given in, Table (2-2).

Table (2-2)
Physical data of compounds [4-8]

Comp. No.	Ar	Molecular formula	Molecular weight	M.P/˚C	% Yield
[4]	C_6H_5	$C_9H_7N_3S_2$	221	220-221	68
[5]	*p*-$CH_3C_6H_4$	$C_{10}H_9N_3S_2$	235	189-191	71
[6]	*p*-$CH_3OC_6H_4$	$C_{10}H_9N_3OS_2$	251	205-207	75
[7]	*p*-$NO_2C_6H_4$	$C_9H_6N_4O_2S_2$	266	225-227	52
[8]	*m*-$CH_3C_6H_4$	$C_{10}H_9N_3S_2$	235	178-180	60

2.3.5 Synthesis of 2-[5̀-substituted-tetrazolo-1̀-yl]-5-mercapto-1,3,4-thiadiazole [9-13]



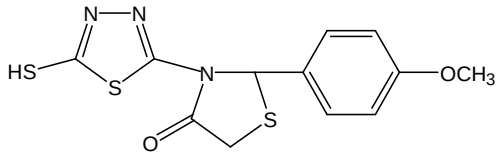
Ar = C_6H_5, *p*-$CH_3C_6H_4$, *p*-$CH_3OC_6H_4$, *p*-$NO_2C_6H_4$, *m*-$CH_3C_6H_4$
[9] [10] [11] [12] [13]

A mixture of (0.01mol) of appropriate Schiff bases [4-8],tetrahydrofuran (15ml) and sodium azide (0.01mol) was heated on a water bath, the temperature of the water bath was controlled between 50-55C˚.The end of the reaction was checked by TLC which showed the disappearance of the starting material, Table (2-3) lists the physical properties of the synthesized compounds.

Table (2-3)
Physical data of compounds [9-13]

Comp. No.	Ar	Molecular formula	Molecular weight	M.P/C˚	% Yield
[9]	C_6H_5	$C_9H_6N_6S_2$	262	215-217dec.	50
[10]	*p*-$CH_3C_6H_4$	$C_{10}H_8N_6S_2$	276	133-135	60
[11]	*p*-$CH_3OC_6H_4$	$C_{10}H_8N_6OS_2$	292	180-182	65
[12]	*p*-$NO_2C_6H_4$	$C_9H_5N_7O_2S_2$	307	200-202	48
[13]	*m*-$CH_3C_6H_4$	$C_{10}H_8N_6S_2$	276	176-178	55

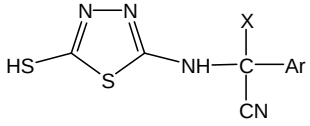
2.3.6 Synthesis of 2[2̀-*p*-methoxyphenyl-4̀-oxo-1̀,3̀-thiazolidin-3̀-yl]-5-mercapto-1,3,4-thiadiazole(152) [14]



[14]

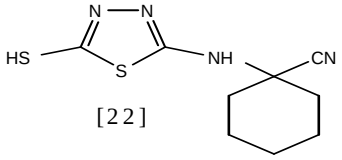
Thioglycolic acid (0.69ml, 0.01mol) was added dropwise to (2.51g, 0.01 mol) of 2-[*p*-methoxybenzylidine]amino-5-mercapto-1,3,4-thiadiazole [6] in 15ml dry benzene with stirring. The reaction mixture was refluxed for 10 hours. Then the solvent was distilled off and the residue neutralized with sodium bicarbonate solution. The precipitate was filtered off and recrystallized from ethanol. Yield 70%, m.p. 212-214C˚.

2.3.7 Synthesis of 2-[N-substituted-cyanobenzyl]amino -5-mercapto-1,3,4-thiadiazoles(153) [15-22]



X = H Ar = C_6H_5, *p*-HOC_6H_4, *p*-$CH_3OC_6H_4$, *p*-$CH_3C_6H_4$, *m*-$CH_3C_6H_4$, *o*-HOC_6H_4
[15] [16] [17] [18] [19] [20]

X = CH_3 Ar = *p*-$H_2NC_6H_4$; [21]



[22]

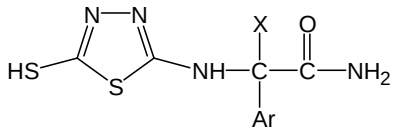
Molecular formula $C_9H_{12}N_4S_2$
Molecular wt. 240
m.p. 156-158 C
%Yield 36

The 2-amino-5-mercapto-1,3,4-thiadiazole [1](1.33g,0.015mol) was mixed with 2.5 ml conc. HCl and 10g of ice-water. To this solution (0.015 mol)of the appropriate aldehyde(ketone) was added, followed by (0.975g,0.015mol) of KCN in 4ml water, the reaction mixture was stirred overnight at room temperature. The solid that precipitated was collected by filtration, washed with water and dried. The physical properties for the synthesized compounds are given in Table (2-4).

Table (2-4)
Physical properties of compounds [15-21]

Comp No.	X	Ar	Molecular formula	Molecular weight	M.P/C°	% Yield
[15]	H	C_6H_5	$C_{10}H_8N_4S_2$	248	208-210	70
[16]	H	*p*-HOC_6H_4	$C_{10}H_8N_4OS_2$	264	220-222	70
[17]	H	*p*-$CH_3OC_6H_4$	$C_{11}H_{10}N_4OS_2$	278	198-200	62
[18]	H	*p*-$CH_3C_6H_4$	$C_{11}H_{10}N_4S_2$	262	202-204	50
[19]	H	*m*- $CH_3C_6H_4$	$C_{11}H_{10}N_4S_2$	262	178-180	48
[20]	H	*o*-HOC_6H_4	$C_{10}H_8N_4OS_2$	264	214-216	62
[21]	CH_3	*p*-$H_2NC_6H_4$	$C_{11}H_{11}N_5S_2$	277	225-227	73

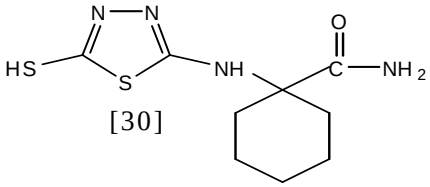
2.3.8 Synthesis of 2-[N-substituted-acetamide]amino -5-mercapto-1,3,4-thiadiazole [23-30]



X = H Ar = C_6H_5 , *p*-HOC_6H_4 , *p*-$CH_3OC_6H_4$, *p*-$CH_3C_6H_4$, *m*-$CH_3C_6H_4$, *o*- HOC_6H_4
[23] [24] [25] [26] [27] [28]

X = CH_3 Ar = *p*-$H_2NC_6H_4$;

[29]



[30]

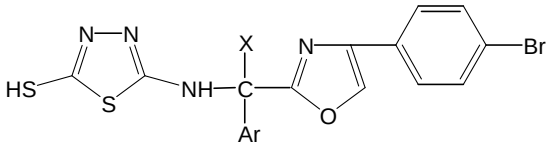
Molecular formula $C_{10}H_{15}N_4OS_2$
Molecular wt. 271
m.p. 183-185 C
%Yield 50

A mixture of (0.01mol) of the desired α-aminonitrile [15-22] and 10ml of 90-95% sulphuric acid was heated on steam bath for 10 min. The mixture was allowed to cool to room temperature and poured onto crushed ice. The solution was made alkaline with ammonia. The crude product was recrystallized either from acetone or petroleum ether .Table (2-5) summarizes the physical properties of the title synthesized compounds.

Table (2-5)
Characteristic physical data of compounds [23-29]

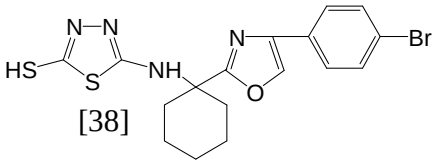
Comp. No.	X	Ar	Molecular formula	Molecular weight	M.P/C°	% Yield
[23]	H	C_6H_5	$C_{10}H_{10}N_4S_2$	266	218-220	60
[24]	H	*p*-HOC_6H_4	$C_{10}H_{10}N_4O_2S_2$	282	228-230	70
[25]	H	*p*-$CH_3OC_6H_4$	$C_{11}H_{12}N_4O_2S_2$	296	212-214	73
[26]	H	*p*-$CH_3C_6H_4$	$C_{11}H_{12}N_4OS_2$	280	201-202	60
[27]	H	*m*-$CH_3C_6H_4$	$C_{11}H_{12}N_4OS_2$	280	178-180	55
[28]	H	*o*-HOC_6H_4	$C_{10}H_{10}N_4O_2S_2$	282	207-208dec.	60
[29]	CH_3	*p*-$H_2NC_6H_4$	$C_{10}H_{11}N_5OS_2$	281	225-227	70

2.3.9 Synthesis of N(5-mercapto-1,3,4-thiadiazol-2-yl),α-(4̀-*p*-bromophenyloxazol-2̀-yl)substituted-benzylamine [31-38]



X = H Ar = C_6H_5, *p*-HOC_6H_4, *p*-$CH_3OC_6H_4$, *p*-$CH_3C_6H_4$, *m*-$CH_3C_6H_4$, *o*- HOC_6H_4
[31] [32] [33] [34] [35] [36]

X = CH_3 Ar = *p*-$H_2NC_6H_4$; [37]



[38]

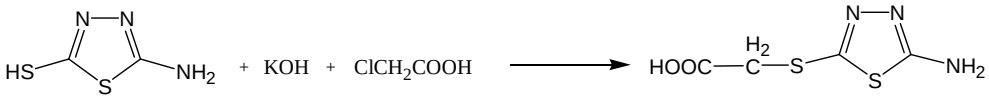
Molecular formula $C_{18}H_{16}N_4OS_2Br$
Molecular wt. 448
m.p. 180-182 C
%Yield 36

A mixture of *p*-bromophenacyl bromide (2.78g, 0.01mol) and the desired α-aminoamide [23-30] (0.01mol) in absolute ethanol was refluxed for about (10-12) hours then the reaction mixture was stirred overnight at room temperature. The end of the reaction was determined by TLC which showed the disappearance of the reacting amide. The physical properties for the synthesized compounds are given in Table (2-6).

Table (2-6)
Physical properties of compounds [31-37]

Comp. No.	X	Ar	Molecular formula	Molecular weight	M.P./C°	% Yield
[31]	H	C_6H_5	$C_{18}H_{12}N_4OS_2Br$	444	110-112	50
[32]	H	*p*-HOC_6H_4	$C_{18}H_{12}N_4O_2S_2Br$	460	159-161	68
[33]	H	*p*-$CH_3OC_6H_4$	$C_{19}H_{14}N_4O_2S_2Br$	474	190-192	73
[34]	H	*p*-$CH_3C_6H_4$	$C_{19}H_{14}N_4OS_2Br$	458	167-169	62
[35]	H	*m*-$CH_3C_6H_4$	$C_{19}H_{14}N_4OS_2Br$	458	117-119	53
[36]	H	*o*-HOC_6H_4	$C_{18}H_{12}N_4O_2S_2Br$	460	183-185dec.	58
[37]	CH_3	*p*-$H_2NC_6H_4$	$C_{19}H_{15}N_5OS_2Br$	473	176-178dec.	70

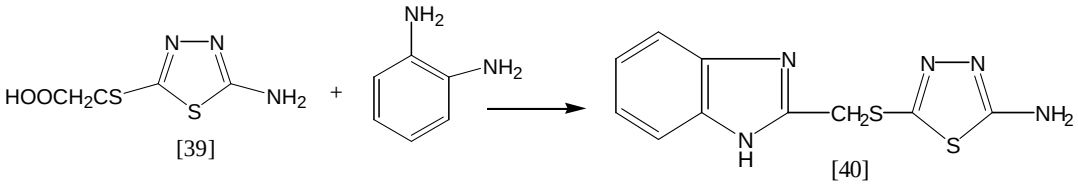
2.3.10 Synthesis of 2-amino-5-thioacetic acid-1,3,4-thiadiazole(154)[39]



[39]

To (1.33g, 0.01mol) of 2-amino-5-mercapto-1,3,4-thiadiazole [1] in (20ml) of ethanol, (0.56g,0.01mol) of KOH was added followed by (0.955g,0.01mol) of monochloroacetic acid. The reaction mixture was heated under reflux for 8 hours. The hot solution was filtered to separate any insoluble materials and the ethanolic solution was evaporated under reduced pressure. The reaction mixture was cooled, acidified with 10% HCl to precipitate the acid [39]. The obtained compound was filtered, washed with cold distilled water and dried, m.p. 187-190C°, Yield 70%.

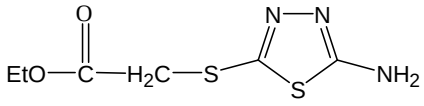
2.3.11 Synthesis of 2-amino-5-[1̀H-benzimidazol-2̀-yl-methylthio]-1,3,4-thiadiazole(155)[40]



[39] [40]

Compound [39] (1.19g,0.01mol) was refluxed for 12 hours with *o*-phenylene-diamine (1.08g,0.01mol) in 4N hydrochloric acid (20ml). The reaction mixture was cooled and then neutralized with ammonia to precipitate benzimidazole. The crude product was recrystallized from ethanol, m.p. 167-170C˚dec., Yield 73%.

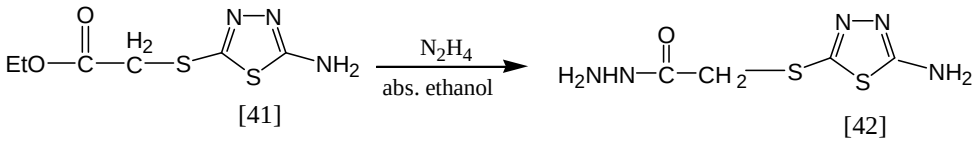
2.3.12 Synthesis of 2-amino-5-thioethylacetate-1,3,4-thiadiazole(156) [41]



[41]

Ethylchloroacetate (1.06ml, 0.01mol) was added dropwise to a stirred solution of 2-amino-5-mercapto-1,3,4-thiadiazole[1] (1.33g,0.01mol), KOH(0.56g,0.01 mol) in 20ml abs. ethanol. The reaction mixture was refluxed for 8 hours, after that the mixture was filtered and the filtrate poured on crushed ice. The resulting product was recrystallized from chloroform, m.p. 78-80C˚, Yield 80%.

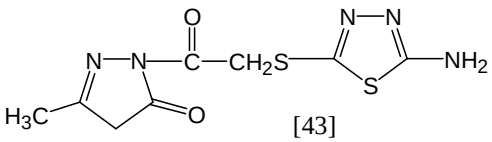
2.3.13 Synthesis of 2-amino-5-thioacetic acid hydrazid -1,3,4-thiadiazole [42]



[41] [42]

A mixture of ester [41] (2g, 0.01mol) and hydrazine hydrate (0.015mol) was refluxed for 4 hours, ethanol (15ml) was added and refluxed for 8 hours. The separated precipitate was filtered and washed with cold water. M.P. 212-215C˚, Yield 75%.

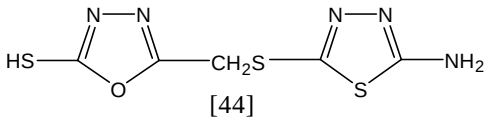
2.3.14 Synthesis of 1̀-[2̀-(2-amino-1,3,4-thiadiazol-5-ylthio)acetyl]-3̀-methylpyrazol-5̀-one[157] [43]



[43]

A mixture of (2.05g, 0.01mol) of the carbohdrazide [42] and ethyl acetoacetate (1.27ml, 0.01mol) in abs. ethanol (20ml) was heated under reflux for 7 hours. After concentration and cooling, the solid product that forms was filtered off and recrystallized from ethanol, m.p. 102-104C˚, Yield 80%.

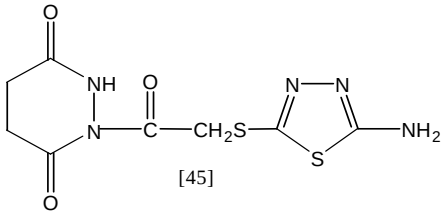
2.3.15 Synthesis of 2̀-(2-amino-1,3,4-thiadiazol-5-ylmethylthio)-1̀,3̀,4̀-oxadiazole-5̀-thiol[158] [44]



[44]

To a solution of carbohdrazide [42] (4.1g,0.02mol) in ethanol (50ml) at 0C, potassium hydroxide (1.12g,0.02mol) and carbon disulfide (2.4ml,0.04mol) were added respectively. The mixture was held at reflux for 7 hours or until most of the hydrogen sulfide has been evolved. The solvent was evaporated in vacuo, the residue dissolved in ice-water and acidified with conc. hydrochloric acid. The precipitate was filtered and recrystallized from (ethanol-water) to give the desired product, m.p. 189-190C˚, Yield 75%.

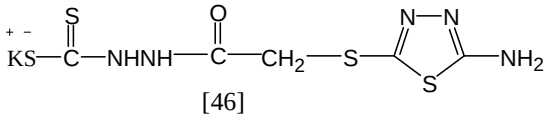
2.3.16 Synthesis of 1̀-[2̀-(2-amino-1,3,4-thiadiazol-5-ylthio)acetyl]-2̀,4̀,5̀-trihydropyridazin-3̀,6̀-dione[159][45]



[45]

Succinic anhydride (1.5g, 0.015mol) dissolved in 30ml acetic acid was added to carbohdrazide [42] (3.07g, 0.015mol) and the reaction mixture was refluxed for 7 hours. Then the mixture was poured on crushed ice, the formed solid product was filtered off and recrystallized from pet. ether (40-60)C˚. M.P. 76-78C˚, Yield 65%.

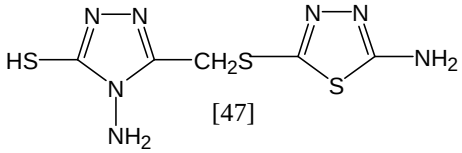
2.3.17 Synthesis of potassium [2̀-(2-amino-1,3,4-thiadiazol-5-ylthio)acetyl] dithiocarbazate [46]



[46]

To a solution of (0.56g,0.01mol) of potassium hydroxide, 15ml of abs. ethanol, and (2.05g,0.01mol) of carbohdrazide [42], carbon disulfide (1.8ml, 0.03mol) was added slowly. The reaction mixture was diluted with ethanol (15ml) and stirred for (8-10) hours, dry ether (20ml) was added and the yellow precipitate was filtered, washed with ether and vacuum dried. The salt was obtained in almost quantitative yield and was employed in the next step without further purification, m.p. 196- 198C˚.

2.3.18 Synthesis of 4̀-amino-5̀-(2-amino-1,3,4-thiadiazol-5-ylmethylthio)-1̀,2̀,4̀-triazole-3̀-thiol [47]



[47]

A suspension of potassium salt [46] (4.59g, 0.01mol) in excess hydrazine hydrate (5ml) was refluxed with stirring until the evolution of hydrogen sulfide was ceased (lead acetate paper); during reflux the color of the reaction mixture changed to green and a homogenous solution resulted. After cooling, the reaction mixture was filtered, acidified with 10% HCl to yield a white

precipitate, which was recrystallized from ethanol to give compound [47], Yield 50%, m.p. 205-207C˚.

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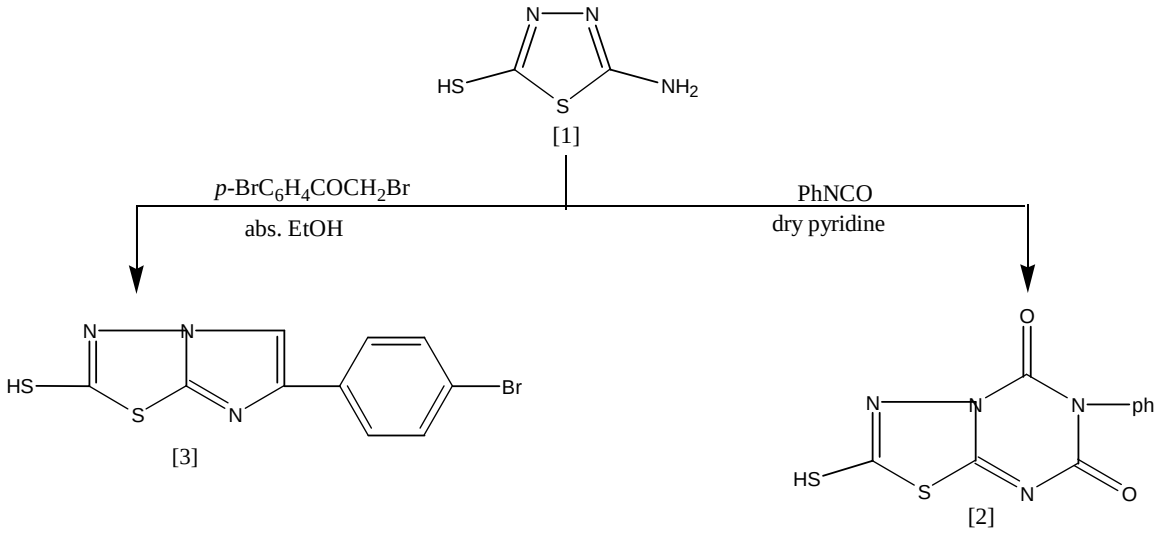
Summary

The scheme of this work involves synthesis of different heterocyclic rings utilizing the two different reactive sites of 2-amino-5-mercapto-1,3,4-thiadiazole.

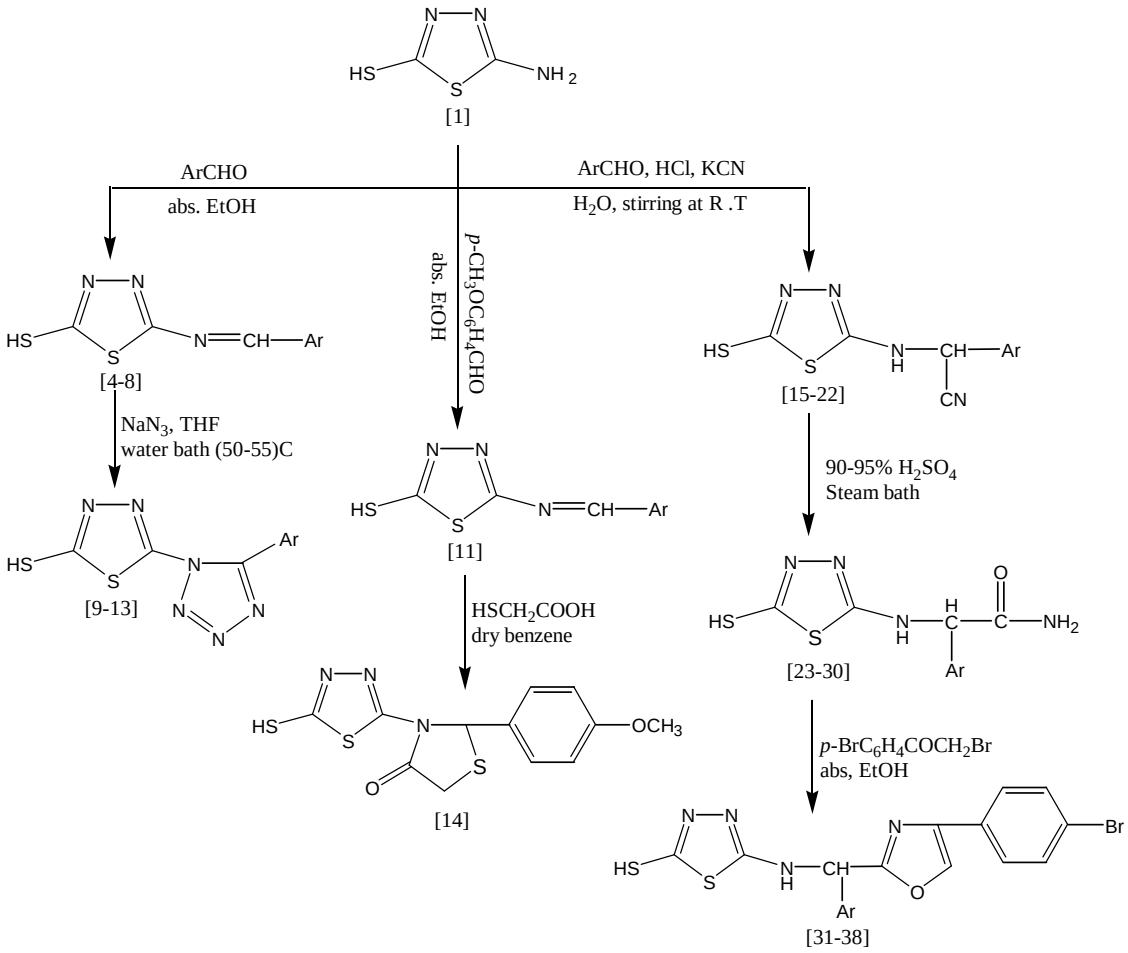
This work is divided into four different parts:

First Part: Involved synthesizing two new fused rings derived from the reaction of $-NH_2$ group of the starting material with different organic reagents. The following reaction steps shown in scheme [I] are of a feasible strategy:



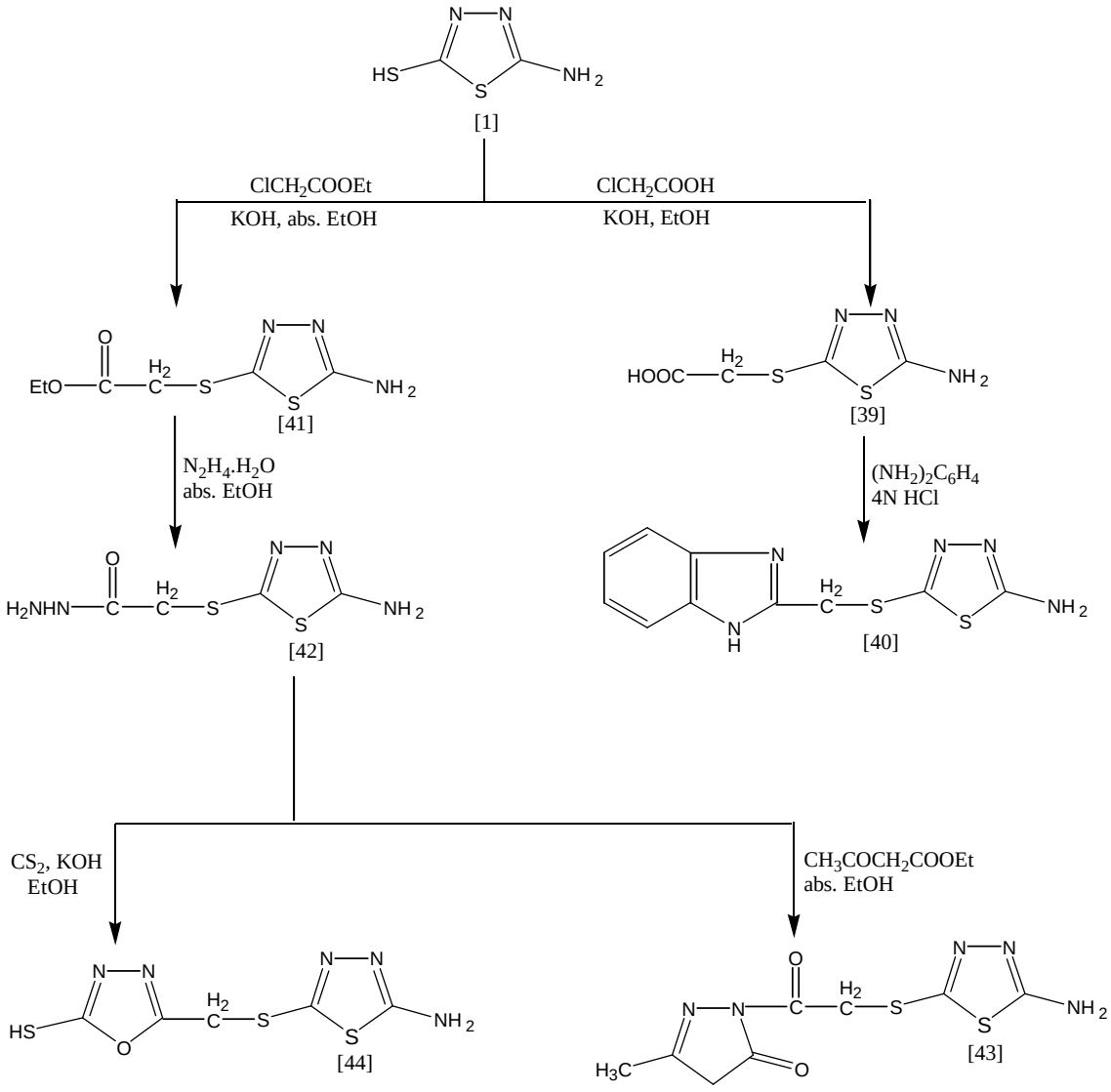
Scheme [I]

Second Part: Involved synthesizing oxazole, tetrazole and thiazolidinone derivatives from the reaction of $-NH_2$ group of the starting material with different organic reagents. Scheme [II] shows steps of the reactions:



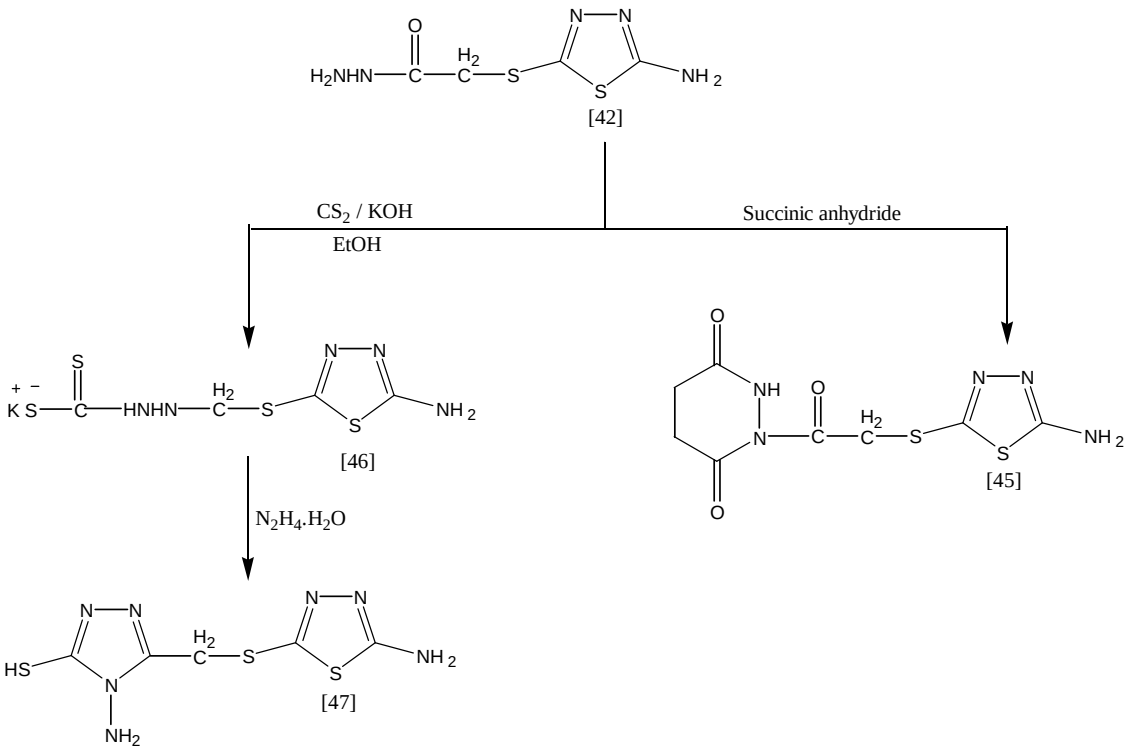
Scheme [II]

Third Part: Involved synthesizing of benzimidazole, pyrazolone, 1,3,4-oxadiazole, dihydro-pyridazin-3,6-dione and 1,2,4-triazole derivatives from the reaction of –SH group of the starting material with different organic reagents, the following reaction steps are shown in scheme [III] :


[1]
ClCH2COOEt
KOH, abs. EtOH
ClCH2COOH
KOH, EtOH
[41]
[39]
N2H4.H2O
abs. EtOH
(NH2)2C6H4
4N HCl
[42]
[40]
CS2, KOH
EtOH
CH3COCH2COOEt
abs. EtOH
[44]
[43]

Scheme [III]

Continued:



Scheme [III]

Fourth Part: This part deals with the study of antibacterial and antifungal activity of some of the synthesized compounds and comparing these activities with that of the starting material.

These activities were determined in **vitro** using disc diffusion method against three pathogenic strains of bacteria (Escherichia coli, Klebsiella pneumoniae, and Proteus vulgaris), and two pathogenic strains of fungus (Candida albicans and Aspergillus niger). The results revealed that some of these compounds showed measurable activity as shown in Table (3-7).

Republic of Iraq
The Ministry of Higher Education
And Scientific Research
Al-Nahrain University
College of Science
Department of Chemistry

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A Thesis
Submitted to the College of Science of Al-Nahrain University in Partial Fulfillment of the Requirements for the Degree of
Doctor of Philosophy in Chemistry

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2005 1426

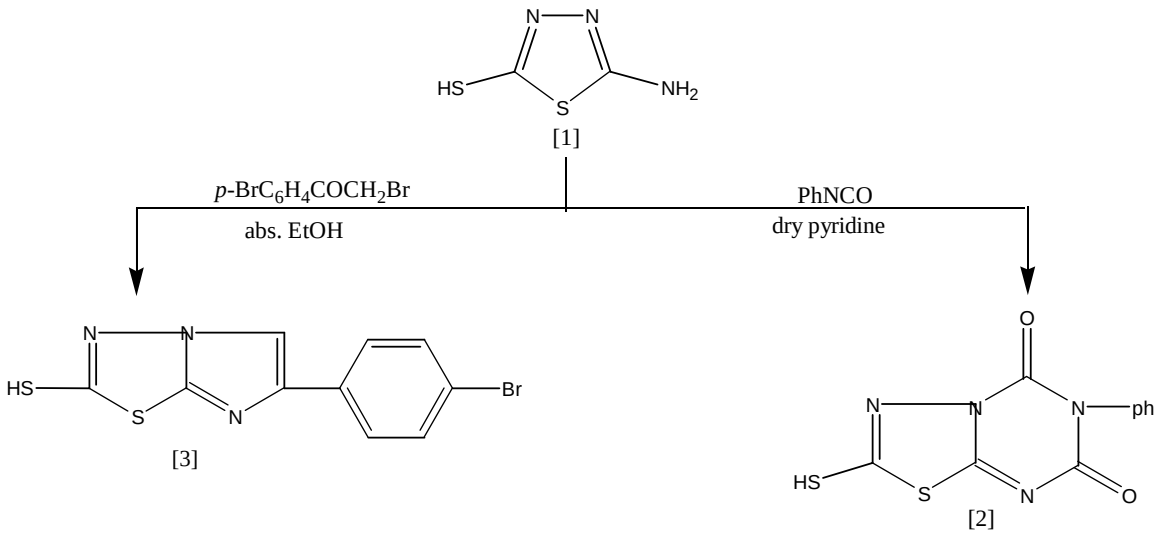
خلاصة الرسالة

يتضمن موضوع البحث في هذة الرسالة البدء من الـ ٢- أمينو -٥- مركابتو -١،٣،٤- ثاياديازول والحاوي على مجموعتين فعالتين وهما مجموعة الثايول (SH -) بالأضافه الى مجموعة الأمينو ($-NH_2$) لتحضير عدد من المركبات الحلقيه الغير متجانسة الجديده .

لقد تم تقسيم هذا العمل الى أربعة أجزاء :

الجزء الأول :

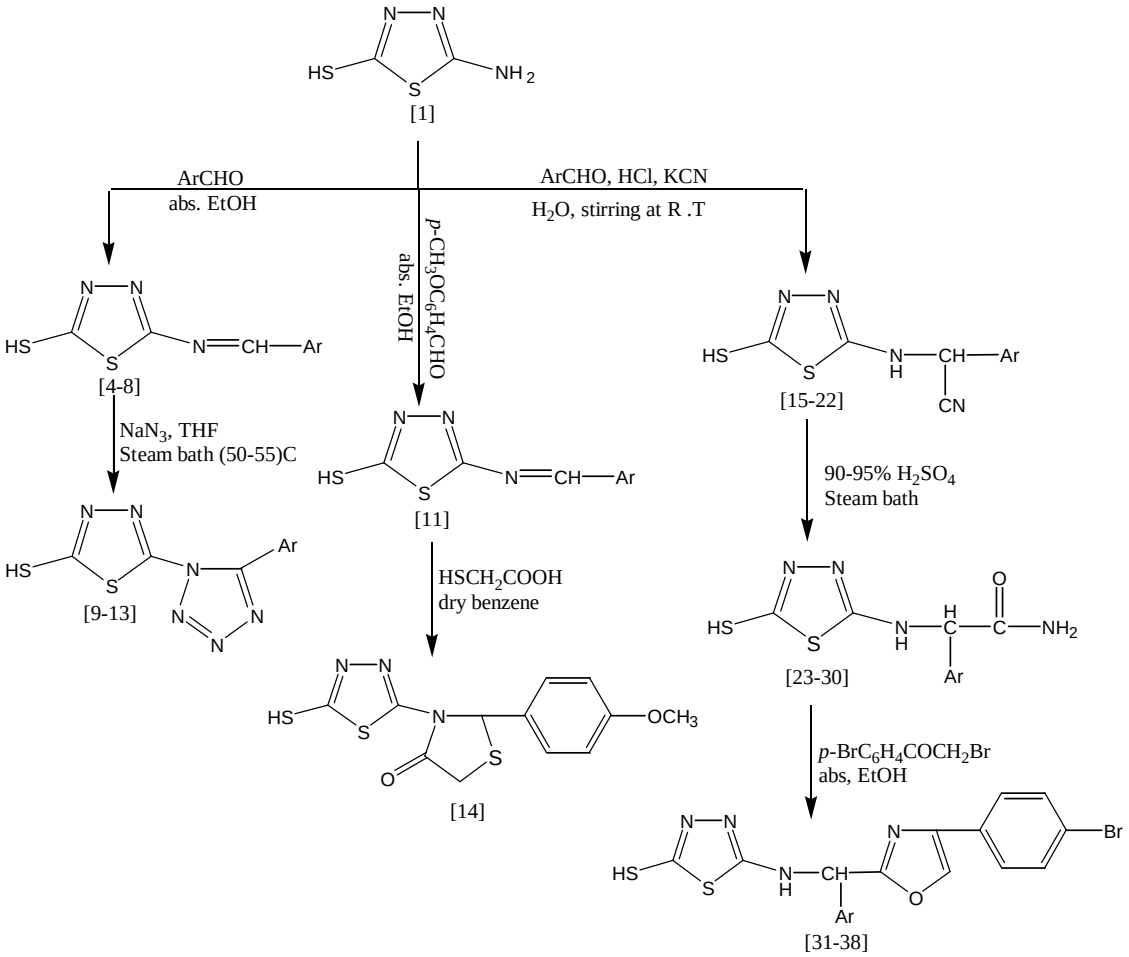
يحتوي هذا الجزء تحضير مركبان حلقيان ملتحمان جديدان وهما الـ إيمدازول و الـ ١،٣،٥-ترايزين كلاهما مشتق من تفاعل مجموعة الـ ($-NH_2$) الخاصة بالماده الأساس مع عدد من الكواشف العضوية المختلفة . للحصول على هذه المشتقات ، أتبعت الخطوا ت الموضحة في المخطط [I] .



Scheme [I]

الجزء الثاني :

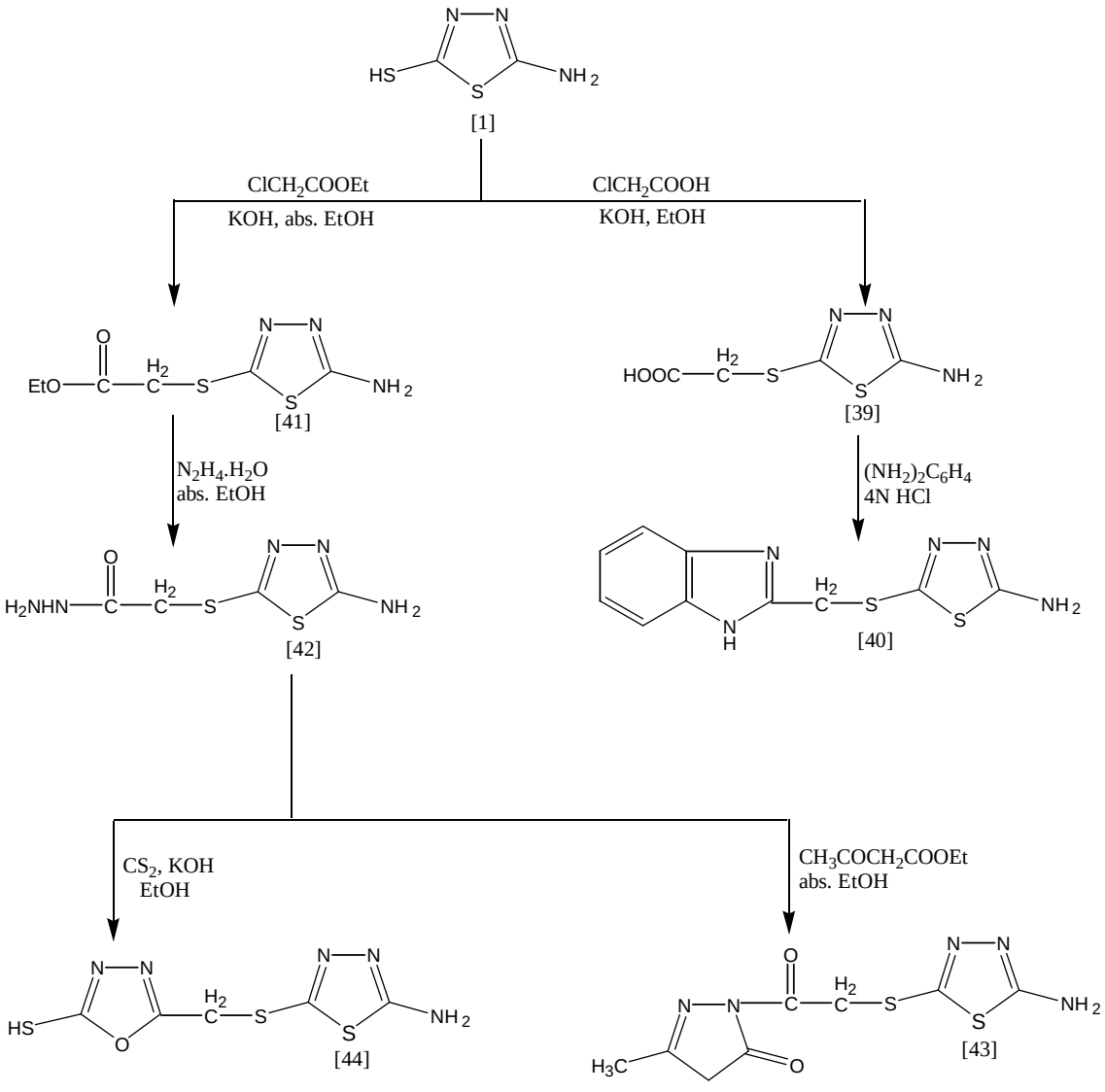
يحتوي هذا الجزء تحضير المركبات الحلقية الغير متجانسة الآتية : أوكسازول ، تترازول والثايازوليدين . جميع هذه المركبات حضرت من تفاعل مجموعة ($-NH_2$) الخاصه بالماده الأساس مع عدد من الكواشف العضوية المختلفة. للحصول على هذه المشتقات ، اتبعت الخطوات الموضحه في المخطط [II] :



Scheme [II]

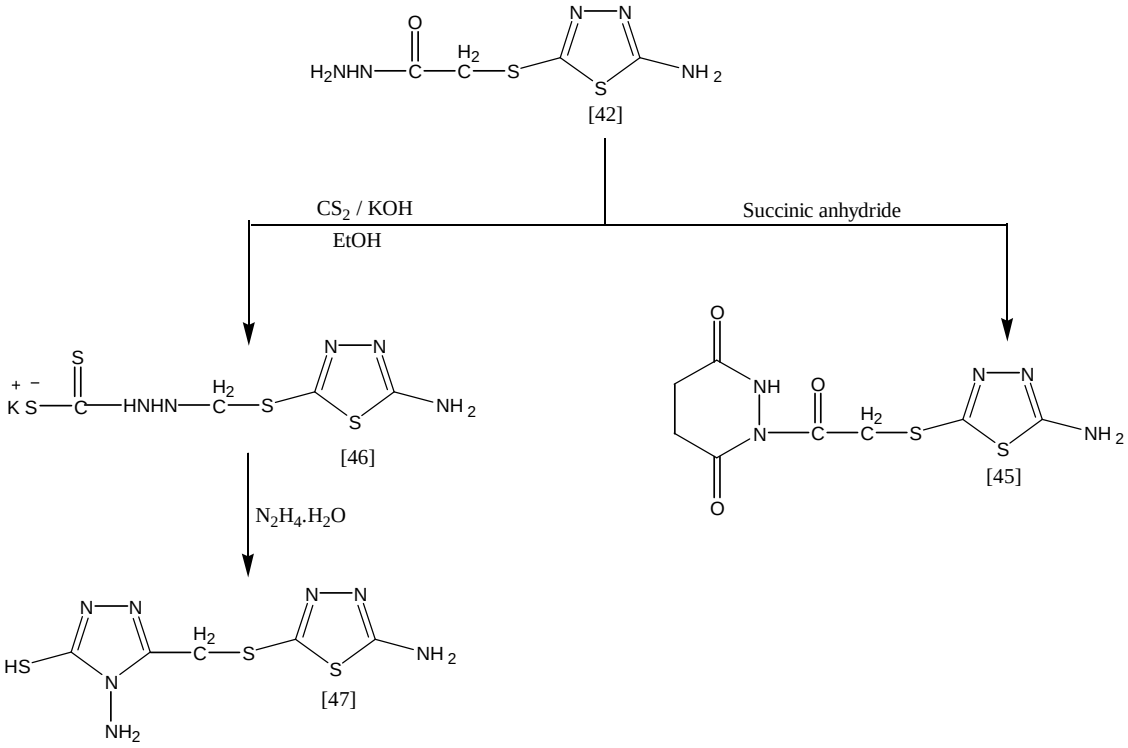
الجزء الثالث :

يحوي هذا الجزء تحضير المركبات الحلقية الغير متجانسة الآتية : البنزإيمدازول ، بايرازولون ، ٤،٣،١– أوكسادايازول ، دايهايدرو - ٦،٣ – دايون وأخيراً ٤،٢،١ ترايازول . جميع هذه المركبات أشتقت من مفاعلة مجموعة (SH -) الخاصة بالماده الأساس مع عدد من الكواشف العضوية المختلفة . للحصول على هذه المشتقات أتبعت الخطوات الموضحة في المخطط [III] :



Scheme [III]

التكملة



Scheme [III]

الجزء الرابع :

يتضمن قياس الفعالية البايولوجية لبعض المركبات المحضرة ضد ثلاث أنواع من البكتريا ونوعان من الفطريات ومقارنة هذه النتائج مع الماده الأساس .

دلت النتائج المستحصلة بأن بعض المركبات أظهرت فعالية عالية وكما موضح في الجدول (7-٣) .

جمهورية العراق
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تحضير مركبات حلقية غيرمتجانسة جديدة مشتقة من ٢-أمينو-٥-مركبتو-١،٣،٤-ثاياديازول

رسالة

مقدمة إلى كلية العلوم جامعة النهرين

وهي جزء من متطلبات نيل درجة دكتوراه فلسفة في الكيمياء

من قبل

نادية عادل صالح

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