# *General methods for synthesis of compounds*

## 2-1 ***Synthesis of 10H Phenothiazine (1):-***

A mixture of diphenylamine (1.69 g, 0.01 mol), sulfur (0.64g, 0.02 mol) and trace amount of iodine was heated in sand bath maintained at 250-260 °C for 5 hours. The reaction mixture was cooled and dissolved in hot ethanol; the solution was added to water. The formed yellow precipitate was filtered and recrystallization from ethanol m.p. (185°C), yield 80%.

## 2-2 ***Synthesis of $N_{10}$- (chloro acetyl) phenothiazine (2):-***

To a solution of phenothiazine (1.99 g, 0.01 mol) in dry benzene (20 ml) chloroacetyl chloride (1.13 g, 0.01 mol) in dry benzene (10 ml) containing triethylamine (1ml) was added with continuous stirring .The mixture was refluxed on water bath for 9 hours. The solvent was distilled to give residue which was washed with 5% sodium bicarbonate to remove the acid impurities. The yellow crystal was crystallized from ethanol m.p. (109-110 °C), yield 75%.

## 2-3 **Synthesis of *N-[$N_{10}$-(acetyl phenothiazine)] hydrazine (3)*[(140)]*:-***

To a solution of [(chloroacetyl) phenothiazine], (2.76g, 0.01 mol) in absolute ethanol (25ml.), hydrazine hydrate (0.5 ml, 0.5 g, 0.01 mol) was added with continuous stirring and the resulting mixture was refluxed on a water-bath for 3 hours. After cooling the mixture, yellow precipitate was formed. The precipitate was filtered and recrystallized from ethanol m.p. (164-166°C) yield 94%.

## 2-4 ***Synthesis of potassium $N_{10}$-(acetyl phenothiazine) dithiocarbazate (4) [141]:-***

A solution of N-[$N_{10}$-(acetyl phenothiazine)] hydrazine (2.71g , 0.01 mol) and carbon disulphide (0.5 ml, 0.76 g, 0.01 mol) in absolute ethanol (25 ml) containing KOH (0.56 g, 0.01 mol) was refluxed on a water bath for 1 hour. The solvent was removed and the solid salt which had been formed, cooled and washed with cold ether, dried to give pale- yellow crystals m.p. (280-282 °C), yield 90%.

## 2-5 ***Synthesis of $N_{10}$-(4- amino-3 -mercapto-[1H]-1,2,4- triazin-5- yl) phenothiazine (5)[141]:-***

A mixture of the salt (4) (1.16 g 0.003 mol) dissolved in water (5 ml) and hydrazine hydrate was add (0.15 ml, 0.15g, 0.003 mol) was refluxed with stirring for 4 hours. The contents were cooled, diluted with water and acidified with HCl. The precipitate was collected by filteration, and washed with water m.p. (75-78°C), yield 87%.

## 2-6 ***Synthesis of $N_{10}$- (acetyl phenothiazine) thiosemicarbazide (6) [142]:-***

To a solution of [(chloro acetyl) phenothiazine] (1.38 g, 0.005 mol) in absolute ethanol (30 ml), thiosemicarbazide (0.455 g, 0.005 mol) was added. The mixture was refluxed for 3 hours after cooling the precipitate was filtered and pale brown precipitate was formed m.p. (302-305°C), yield 47 %.

## 2-7 ***Synthesis of $N_{10}$-(3-mercapto-[1H, 6H]-1, 2, 4-triazin-5-yl) phenothiazine (7)*** [143]***:-***

Compound (6) (3.30 g, 0.01 mol) was dissolved in NaOH (20 ml, 2N) and refluxed for 4hours. The reaction mixture was cooled and acidified with acetic acid. The solid precipitate was washed by 5% sodium bicarbonate, water and then filtered; m.p. (195-196°C), yield 53%.

## 2-8 ***Synthesis of $N_{10}$-(acetyl phenothiazine) thiourea (8)*** [142]***:-***

To a solution of [(chloroacetyl) phenothiazine] (1.38 g**,** 0.005 mol) in absolute ethanol (30 ml), thiourea (0.38 g, 0.005 mol) was added. The mixture was refluxed for 3 hours. After cooling the precipitate and filtering, white precipitate was obtained m.p. (188-190 °C), yield 45%.

## 2-9 ***Synthesis of $N_{10}$-(2-amino-1, 3-thiazol-5-yl) phenothiazine (9)*** [143]***:-***

Compound (8) (0.316 g, 0.001 mol) was dissolved in cold concentrated sulfuric acid (10 ml). The reaction mixture was refluxed for overnight, and then the mixture was cooled and poured onto ice-cold water, neutralized by 5% sodium bicarbonate to remove the acid impurities. The precipitate was filtered and washed with water and recrystllized from ethanol, blue precipitate was obtained, decomposed (120 °C), yield 64%

## 2-10 *Synthesis of $N_{10}$-(2-mercapto-[5H]-1, 3- imidazol-4-yl)] phenothiazine (10)* [143]:-

Compound (10) was prepared by the same method described for the preparation of compound (7). Brown precipitate was obtained m.p. (201-202°C), yield 49%.

## 2-11 *Synthesis of $N_{10}$-[(2-([5H]-1, 3-imidazol-4-yl) hydrazine] phenothiazine (11)* [144]:-

Compound (11) was prepared by the same method described by the preparation compound (3). Silver precipitate was obtained m.p. (172-173°C), yield 82%.

## 2-12 *Synthesis of Schiff's bases compounds {$N_{10}$-([5H]-1, 3-imidazol-4-yl) hydrazone] phenothiazine} [12-14]* [145]:-

To a solution of compound (11) (1.48 g, 0.005 mol) in absolute ethanol (25 ml), appropriate aldehyde (0.005 mol) was added. The mixture was refluxed for 4-5 hours and cooled. The precipitate was filtered and recrystallized from appropriate solvent .The physical properties of compounds (12-14) are listed in table (3-1).

## 2-13 *Synthesis of N [$N_{10}$-(acetyl phenothiazine)]-4-nitrophenyl hydrazine (15)* [146]:-

Compound (15) was prepared by the same method for the preparation of compound (3), using (1.46 g, 0.01 mol) 4-nitrophenyl hydrazine instead of hydrazine. Orange precipitate was formed, m.p. (141-142°C), yield 96%.

## 2-14 *Synthesis of 4N [$N_{10}$-(acetylphenothiazine)]-1-phenyl-3-p-nitro phenyl semicabazide (16)* [147]*:-*

To a solution of compound (15) (1.9 g ,0.005 mol) in absolute ethanol (20ml), phenyl isocyanate (0.59 g, 0.005 mol ) was added with continuous stirring and the mixture was refluxed for 5 hours .The reaction mixture was cooled and the formed solid was filtered off , washed with petroleum ether (80-100) °C . Dark yellow precipitate was formed m.p. (158-160°C), yield 93 %.

## 2-15 *Synthesis of $N_{10}$-(3-N-phenyl-4-pbromophenyl-2-hydroxy-4-oxazolin-2-yl)acetylphenothiazine-2N-nitrophenylhydrazine (17)* [148]*:-*

To a solution of compound (16) (1.02g, 0.002 mol) in (30 ml) ethanol, *p*-bromo phenancyl bromide (0.55 g, 0.002 mol) was added. The reaction mixture was refluxed for 8 hours, cooled and neutralized with ammonium hydroxide solution. The precipitate was filtered off, washed with water, and petroleum ether (80-100) was used for recrystallization, m.p. (135-137°C), yield 84%.

## 2-16 *Synthesis of Aryl Amino acetyl $N_{10}$-phenothiazine (18-23)* [149]*:-*

To a solution of $N_{10}$-(chloroacetyl) phenothiazine (1.38 g, 0.005 mol) in absolute ethanol (20 ml), appropriate amine (0.005 mol) was added gradually and the reaction mixture was refluxed for 24 hours. The excess of ethanol and amine were recovered by distillation. The solid product was filtered, washed with sodium bicarbonate 5% and water. The physical properties of compounds are listed in table (3-2).

## 2-17 *5-Amino-[3H]-1, 3, 4-thiadiazol-2-thione (24)* [150]*:-*

Potassium hydroxide (2.24 g, 0.04 mol) was dissolved in absolute ethanol (20 ml) and carbon disulfide (3.62 g, 4.57 g, 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 off to give (24). The crude product was washed with cold water and the pale yellow solid was recrystllized from ethanol, m.p. (230-231) °C, lit. [150] (230-232), yield 92%.

## 2-18 *Synthesis of $N_{10}$-(acetyl-5-amino-[3H]-1, 3, 4-thiadiazol-2-thione)phenothiazine (25)* [150]*:-*

To a solution of $N_{10}$-(chloroacetyl) phenothiazine (1.38 g, 0.005 mol) in absolute ethanol (25 mol), triethyl amine (2ml, 0.3 g, 0.005 mol) was added with stirring followed by the addition of compound (24) (0.66g, 0.005 mol) to the reaction mixture which was refluxed for 24 hours .Triethyl amine hydrochloride was filtered off, the solution was concentrated to one-third of its original volume and carefully treated with concentrated hydrochloride acid. The white precipitate was collected by filtration and recrystllized from 95% ethanol, m.p. (175-177°C), yield 97%.

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

# *Synthesis of Heterocyclic Derivatives of N- Substituted Phenothiazine*

*A thesis*
*Submitted to the College of Science*
*Al-Nahrain University*
*In partial fulfillment of Requirements*
*For the Degree of Master of Science in*
*Chemistry*

*By*
*Zahraa Sabah Saeed Al-Taie*
*B.Sc. (Al-Nahrain University 2002)*

*July 2005* *Jamadi Al-Aker 1426*

I certify that this thesis was prepared under my supervision at Al-Nahrain University, College of Science, as a partial fulfillment of the requirement for the degree of Master of Science in Chemistry.

**Signature:**

**Advisor: Dr. Sawsan H.Shawkat**

**Date:**

In view of the available recommendation, I forward this thesis for debate by the examining committee.

**Signature:**

**Name:**

**Head of Chemistry Department**

**College of Science**

**Al-Nahrain University**

**Date:**

We, the examining committee, certify that we have read this thesis and examined the student in its contents and that, in our opinion, it is adequate with “ ” standing as a thesis for the degree of Master of Science in Chemistry.

**Signature:**
**Name:**
**Date:**
**Member**

**Signature:**
**Name:**
**Date:**
**Chairman**

**Signature:**
**Name:**
**Date:**
**Member**

**Signature:**
**Name: Dr.Sawsan H.Shawkat**
**Date:**
**Supervisor**

Approved by the University Committee of Graduate Studies.

**Signature:**
**Name: Dr.Laith Abd Al-Aziz**
**Dean of College of Science**
**Al-Nahrain University**
**Date:**

## ACKNOWLEDGEMENTS

**I wish to express my sincere gratitude and great appreciation to my Supervisor Dr. Sawsan H. Shawkat for her guidance and her encouragement throughout this work.**

**Many thanks are due to the Department of Chemistry, College of Science, at Al- Nahrain University for providing the facility which helped in accomplishing this research.**

**Also I would like to express my gratitude to Mr.Yahya Kamaal Al-Baiati for his assistance.**

**My thanks are extended to all friends that helped me in my research.**

# Abstract


The aim of the present work is the synthesis of new derivatives of N-substituted 10H phenothiazine.

To obtain these derivatives, the diphenylamine was chosen as the starting material which was heated for 5hrs. with sulfur in presences of iodine, it gave the phenothiazine (1).

1- Reaction of phenothiazine with chloro acetyl chloride gave $N_{10}$- (chloro acetyl) phenothiazine (2), which was treated with hydrazine hydrate to give $N_{10}$- (acetyl phenothiazine) hydrazine (3) which is the desired product. The hydrazine derivative (3) was reacted with carbon disulfide in presence of KOH to give potassium $N_{10}$-(acetyl phenothiazine) dithiocarbazate (4) which was refluxed with hydrazine hydrate to give $N_{10}$-(4-amino-3-mercapto-[1H]-1,2,4- triazin-5-yl)] phenothiazine (5).

2- $N_{10}$-(3-mercapto-[1H,6H]-1, 2, 4-triazin-5-yl) phenothiazine (7) was obtained from the reaction of phenothiazine (1) with thiosemicarbazide to give $N_{10}$-(acetyl phenothiazine) thiosemicarbazide (6) which suffered intramolecular cyclization when refluxed with basic media ( 2N NaOH) for 3hrs. to give triazine derivative (7).

3- Treatment of phenothiazine (1) with thiourea gave $N_{10}$-(acetyl phenothiazine) thiourea (8), which was used for the preparation of two types of heterocyclic derivatives:

A- The compound $N_{10}$-(2-amino-[5H]-1, 3-thiazol-5-yl) phenothiazine (9) was synthesized by the intramolecular cyclization of thiourea derivative (8) which was refluxed with conc. $H_2SO_4$ for overnight.

B- $N_{10}$-(2-mercapto-[5H]-1,3-imidazol-4-yl) phenothiazine (10) was synthesized by the intramolecular cyclization of thiourea derivative (8) through its reflux with (2N NaOH) for 3hrs.

4- Synthesis of $N_{10}$-[2-([5H]-1, 3-imidazol-4-yl) hydrazine] phenothiazine (11) was obtained from the reaction of compound (10) with hydrazine hydrate.

5- Schiff's bases: compounds {$N_{10}$-[(2-[5H]-1, 3-imidazol-4-yl) hydrazone] phenothiazine [12-14]} have been synthesized from the reaction of compound (11), with different aromatic aldehydes.

6- N-[$N_{10}$-(acetyl phenothiazine)]-4-nitrophenyl hydrazine (15) was synthesized by the reaction of $N_{10}$-(chloro acetyl) phenothiazine (2) with 4-nitrophenyl hydrazine, which then was treated with phenylisocyanate to give 4N [$N_{10}$-(acetyl phenothiazine)]-1-phenyl-3-p-nitrophenyl semicarbazide (16).

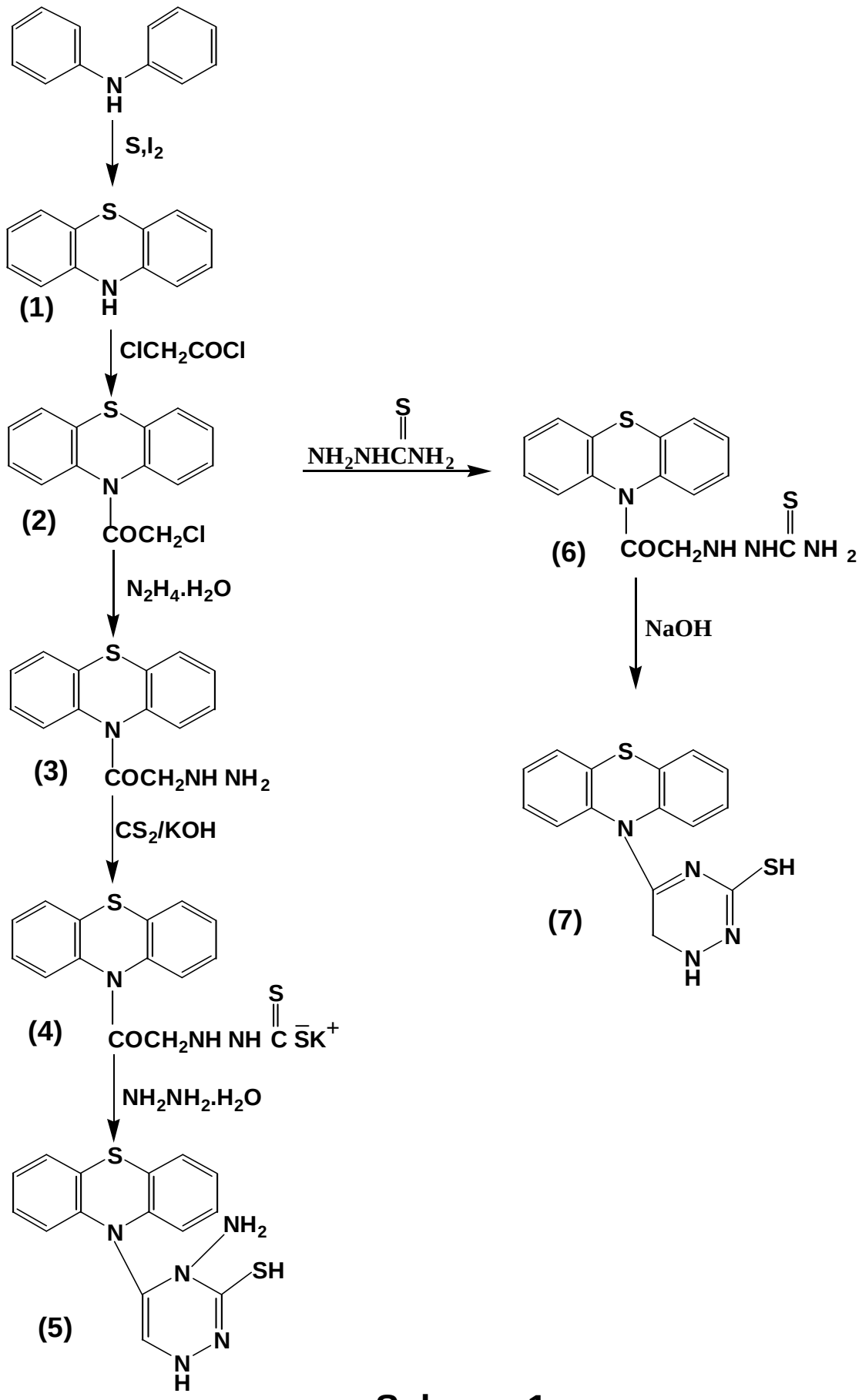
7-$N_{10}$- (3- N- phenyl-4- *p*- bromophenyl-2- hydroxy-4- oxazolin-2- yl) acetyl -2N-nitrophenyl hydrazine (17) was synthesized by the intermolecular cyclization of compound (16) with 4-bromophenancyl bromide.

8- Aryl amino acetyl $N_{10}$-phenothiazine (18-23) were obtained from the reaction $N_{10}$-(chloro acetyl) phenothiazine (2) with different aromatic amines under refluxing condition.

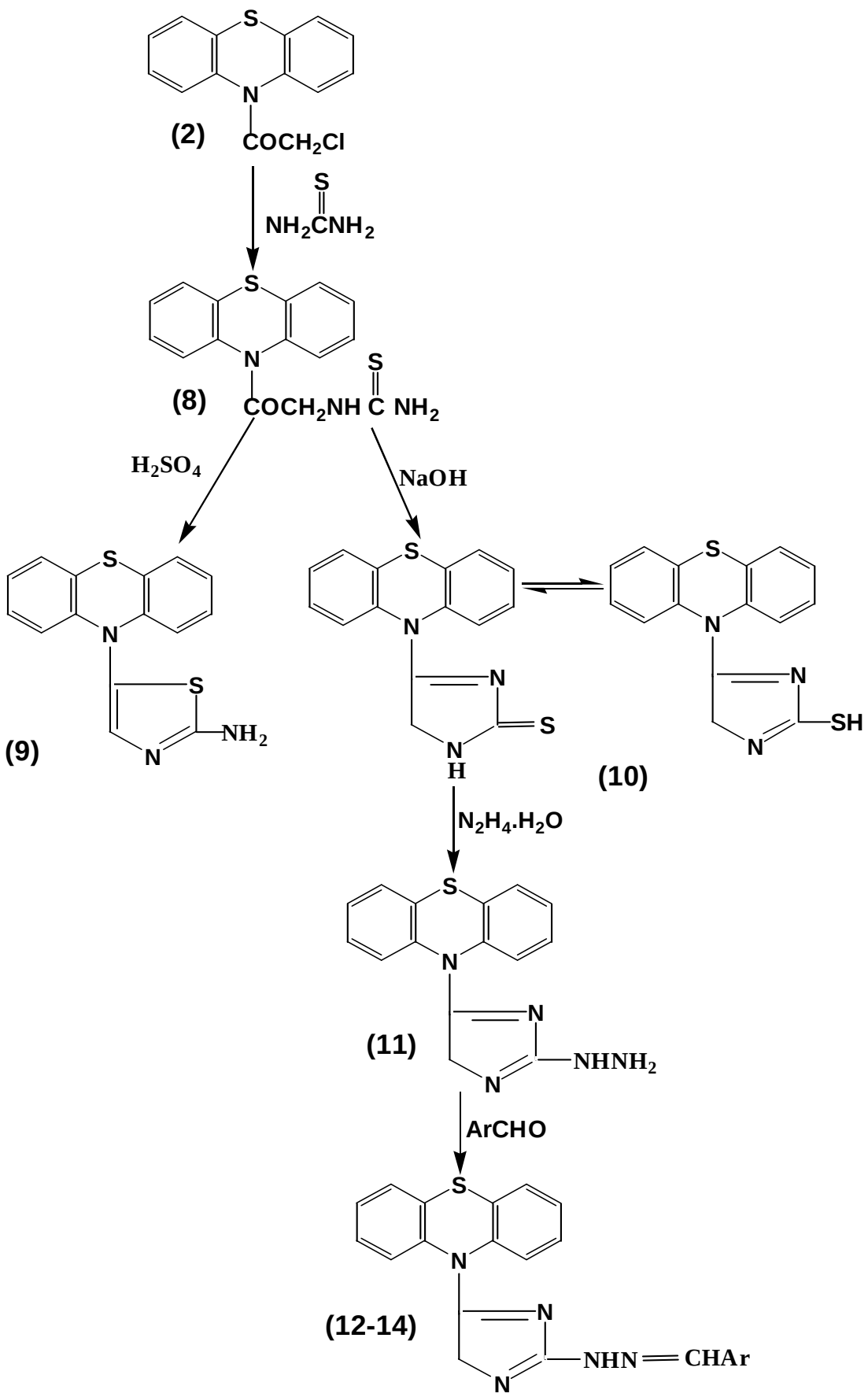
9- 5-Amino-[3H]-1, 3, 4-thiadiazole-2-thione (24) was obtained from the reflux of carbon disulfide with thiosemicarbazide in presence KOH/abs. EtOH for about 6hrs.

10- $N_{10}$-(acetyl-5-amino-[3H]-1, 3, 4-thiadiazole-2-thione) phenothiazine (25) was synthesized from the reaction of compound (2) with 5-Amino-[3H]-1, 3, 4-thiadiazole-2-thione (24) under refluxing condition for 24hrs.

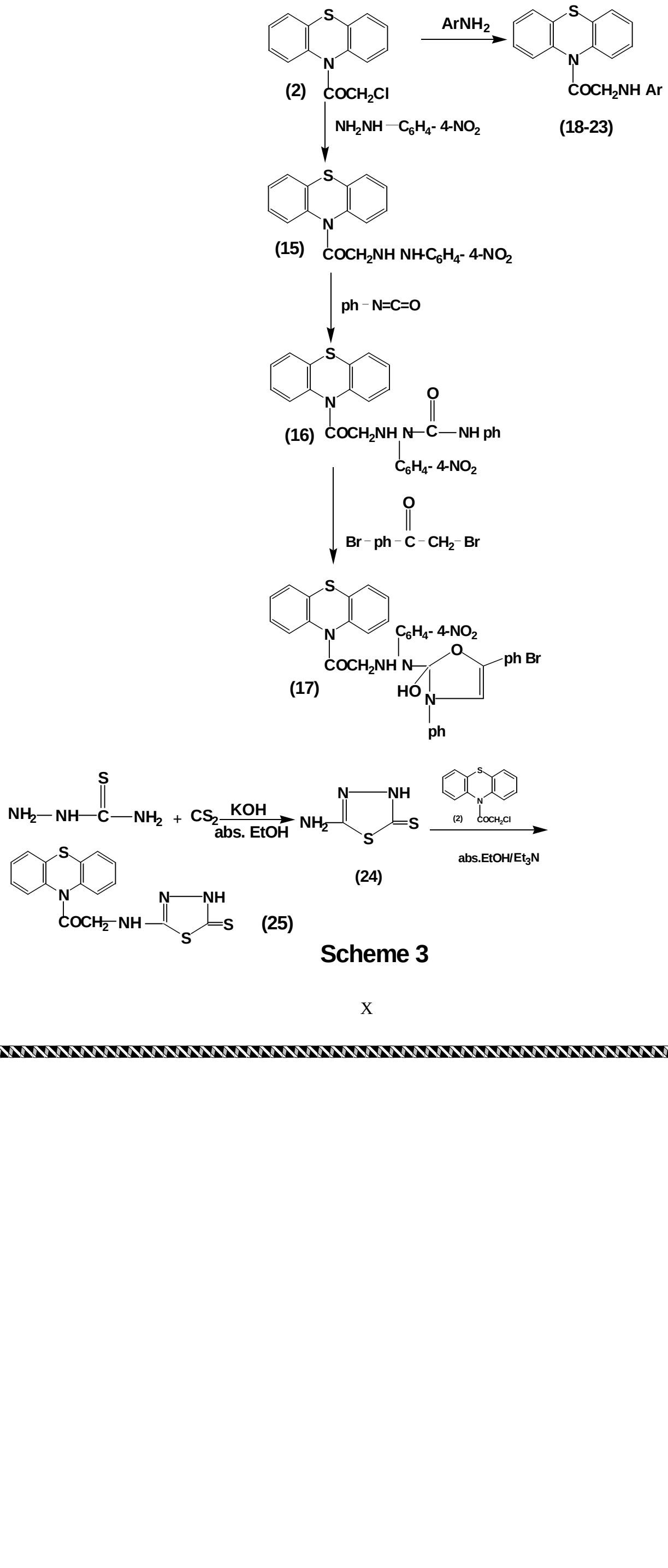
All prepared compounds were identified using FTIR technique, melting points and thin layer chromatography.


S,I2
ClCH2COCl
NH2NHCNH2
S
NaOH
N2H4.H2O
CS2/KOH
NH2NH2.H2O
(1)
(2)
(3)
(4)
(5)
(6)
(7)
COCH2Cl
COCH2NH NH2
COCH2NH NH C SK+
COCH2NH NHC NH 2
NH2
SH

**Scheme 1**


(2)
COCH2Cl
NH2CNH2
(8)
COCH2NH C NH2
H2SO4
NaOH
(9)
NH2
(10)
SH
N2H4.H2O
(11)
NHNH2
ArCHO
(12-14)
NHN CHAr

**Scheme 2**


ArNH2
(2)
COCH2Cl
COCH2NH Ar
(18-23)
NH2NH C6H4- 4-NO2
(15)
COCH2NH NH-C6H4- 4-NO2
ph N=C=O
(16)
COCH2NH N C NH ph
C6H4- 4-NO2
O
Br ph C CH2 Br
(17)
COCH2NH N
C6H4- 4-NO2
ph Br
HO
ph
NH2 NH C NH2
CS2
KOH
abs. EtOH
(24)
(2)
COCH2Cl
abs.EtOH/Et3N
(25)
COCH2 NH

**Scheme 3**

# Table of contents



## Chapter One – Introduction

## *Chapter three – Result & Discussion*

## *List of tables*

## *List of Figures*

# Chapter One

# Introduction

# Chapter Two

# Experimental

# Chapter three

# Results

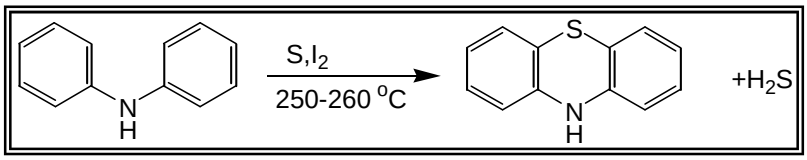
# And

# Discussion

# References

## 3-1 ***10H phenothiazine (1).***

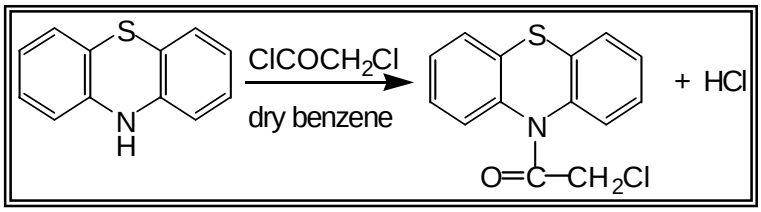
10H phenothiazine was obtained from diphenylamine which initially converted to phenothiazine (1) by its reaction with sulfur in presence of iodine as catalyst at (250-260) ºC.




The FTIR spectrum of phenothiazine showed strong stretching bands at 3338 $cm^{-1}$ for (NH), band at 3050 $cm^{-1}$ for (ν C-H) aromatic, at (1568.0 and 1596.9**)** $cm^{-1}$ assigned to the aromatic system (C=C) stretching and at 690 $cm^{-1}$ for (C-S-C) as shown in fig 1.

## 3-2 ***$N_{10}$-(chloro acetyl) phenothiazine (2).***

When chloro acetyl chloride was refluxed with 10H phenothiazine in dry benzene it gave the corresponding $N_{10}$-chloro acetyl phenothiazine (2).

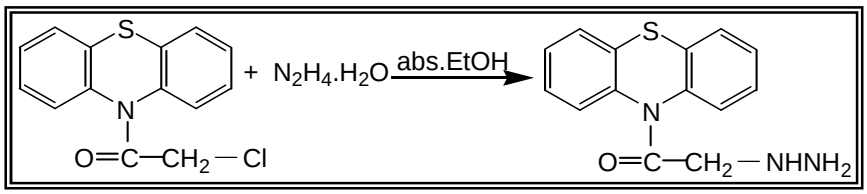



The FTIR spectrum showed the disappearance of NH band of phenothiazine and appearance of strong (C=O) stretching band at 1691.5$cm^{-1}$ in addition to(C-H) aliphatic stretching bands at (2960 and 2856.4) $cm^{-1}$.

Bands at (3090 and 1575.5) $cm^{-1}$ for (ν C-H) and (ν C=C) aromatic. Also bands at 651.9 $cm^{-1}$ represent (C-Cl) [151] and at 763.8 $cm^{-1}$ for (γ C-H) as shown in fig 2.

## 3-3 ***N-[$N_{10}$- (acetyl phenothiazine)] hydrazine (3).***

To synthesize the new heterocyclic $N_{10}$-substituted compound (triazine), the hydrazine (3) was seen a suitable route for this synthetic approach. So when $N_{10}$-chloro acetyl phenothiazine was refluxed with 98% $N_2H_4.H_2O$ it gave the expected hydrazine derivative (3).



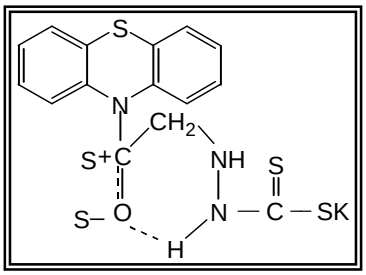

FTIR spectrum showed bands at 3336.6 $cm^{-1}$ and 3200 $cm^{-1}$ which were assigned to the asymmetric and symmetric stretching bands of ($NH_2$) and (NH) groups, and at 1666.4 $cm^{-1}$ for (C=O). Bands at (3053.1 and 1598.9)$cm^{-1}$ which were due to aromatic (C-H) and (C=C) stretching, respectively, and at 1471.6 $cm^{-1}$ for (N-H) bending as shown in fig 3.

## 3-4 ***Synthesis of Potassium $N_{10}$-(acetyl phenothiazine) dithiocarbazate (4).***

When $N_{10}$-acetyl phenothiazine hydrazine was refluxed with carbon disulfide in presence of KOH, it gave a salt of Potassium acetyl phenothiazine dithiocarbazate (4).

FTIR spectrum showed a broad stretching band at 3452.3 $cm^{-1}$ for (NH-NH). Bands for **(**C=S) appeared at 1330.8 $cm^{-1}$ [151] and at 1622 $cm^{-1}$ for **(**C=O).

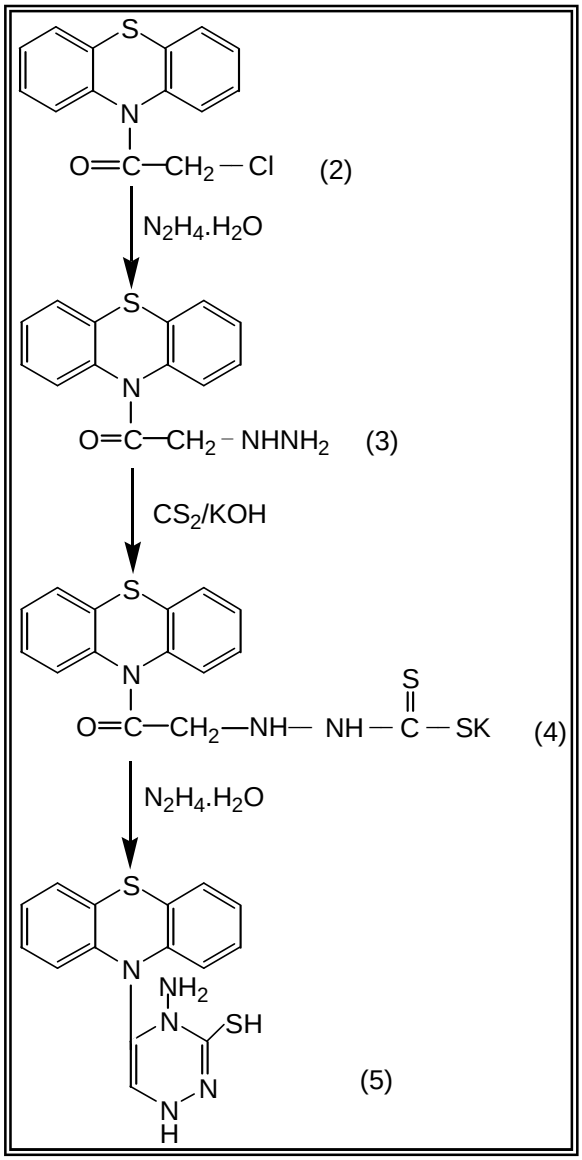
The cause of a broad band of (NH-NH), and a broad band of **(**C=O) is the formation of H-bonding between (NH) and (C=O) to from stable six memberd ring hydrogen bonding as shown in structure [3.1], all these bands are shown in fig 4.




Structure [3.1]

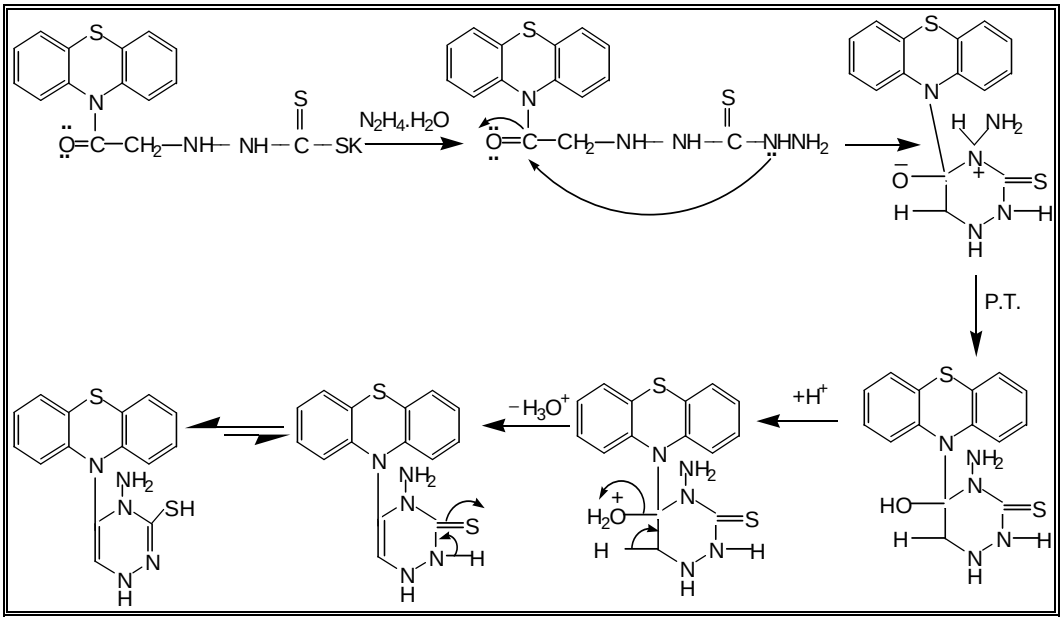
## 3-5 ***$N_{10}$-(4- amino-3 -mercapto-[1H]-1,2,4- triazin-5- yl)phenothiazine (5).***

The title compound (5) was synthesized according to reaction scheme (1).




Scheme (1)

The reaction of salt (4) with 98% $N_2H_4.H_2O$ under refluxing condition lead to intramolecular cyclization through the loss of $H_2O$ giving the desired amino-thio-triazine derivative (5), the formation of (5) may be visualized by the following mechanism: -




The structure of amino-thio-triazine derivative (5) was confirmed by FTIR. FTIR spectrum showed strong stretching bands at (3400 and 3278.8) $cm^{-1}$ for asymmetric and symmetric $NH_2$, weak band at 3150.0 $cm^{-1}$ for (ν N-H), 2580.0 $cm^{-1}$ (ν S-H), 1639.4 $cm^{-1}$ (ν C=N), 1328.9 $cm^{-1}$ (C=S). IR spectrum also showed characteristic of aromatic bands at 3091.7 $cm^{-1}$ and 1595$cm^{-1}$ for(C-H) aromatic and (C=C), respectively, as shown in fig 5.

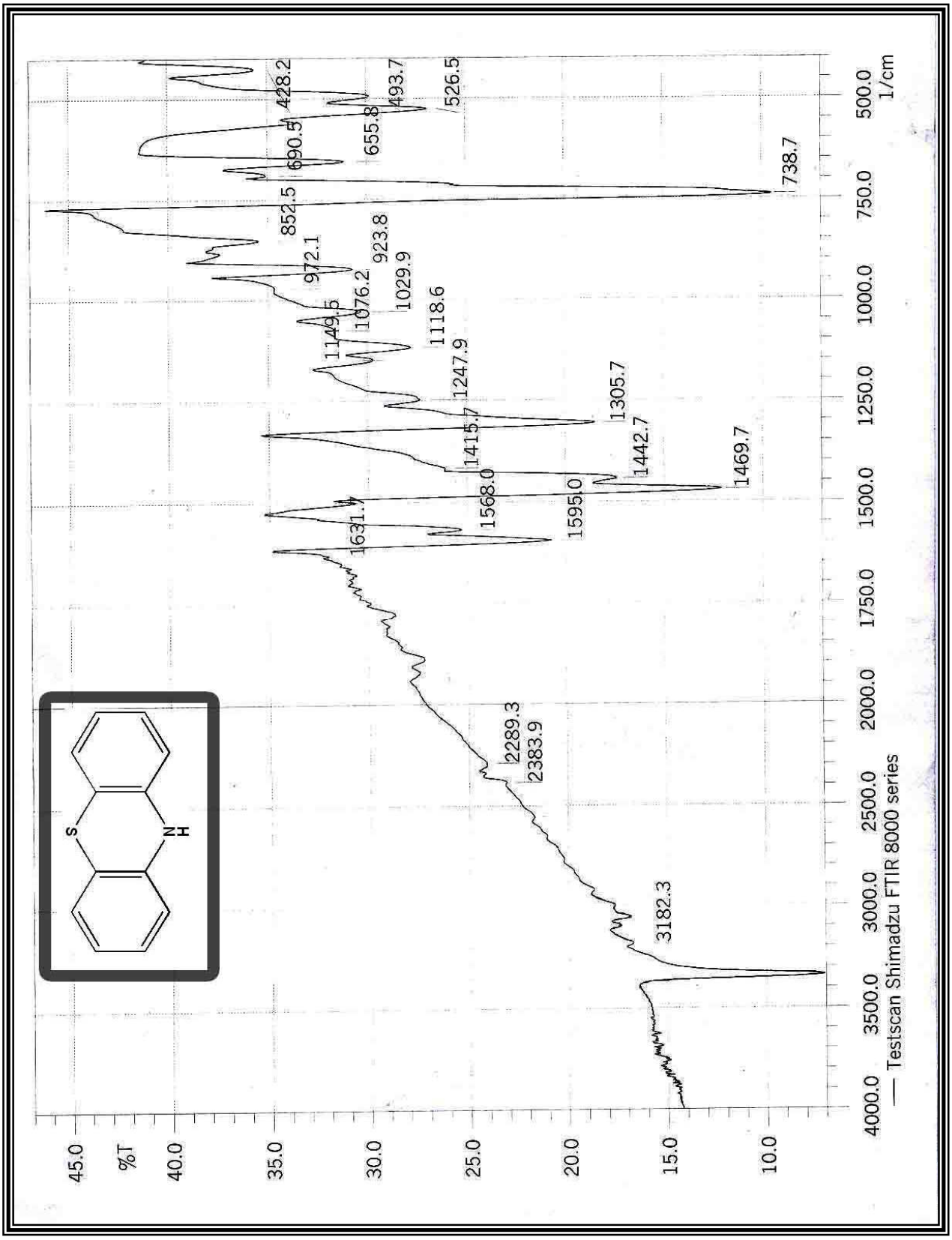



**Figure (1): infrared spectrum of compound (1).**

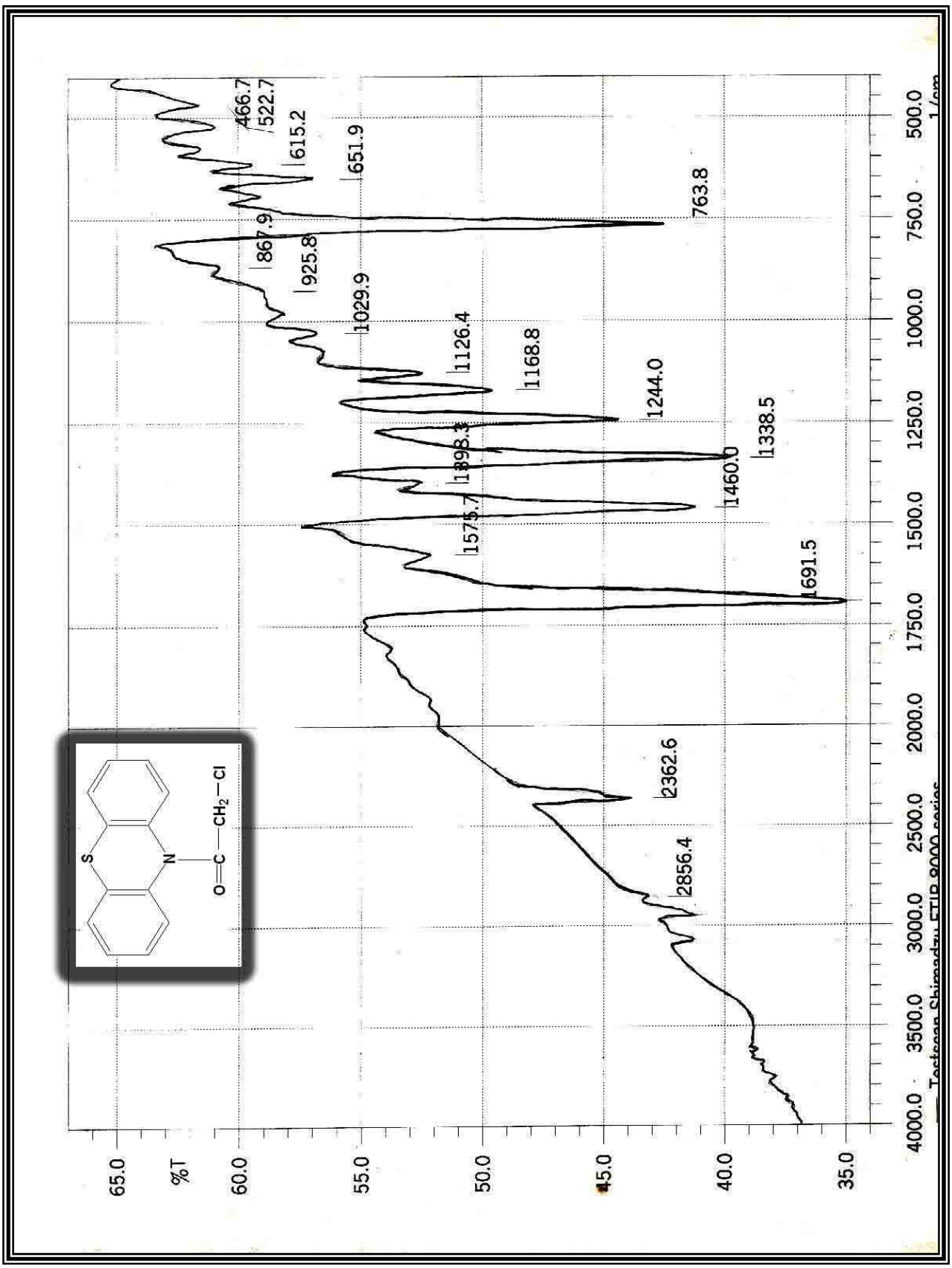



**Figure (2): infrared spectrum of compound (2).**

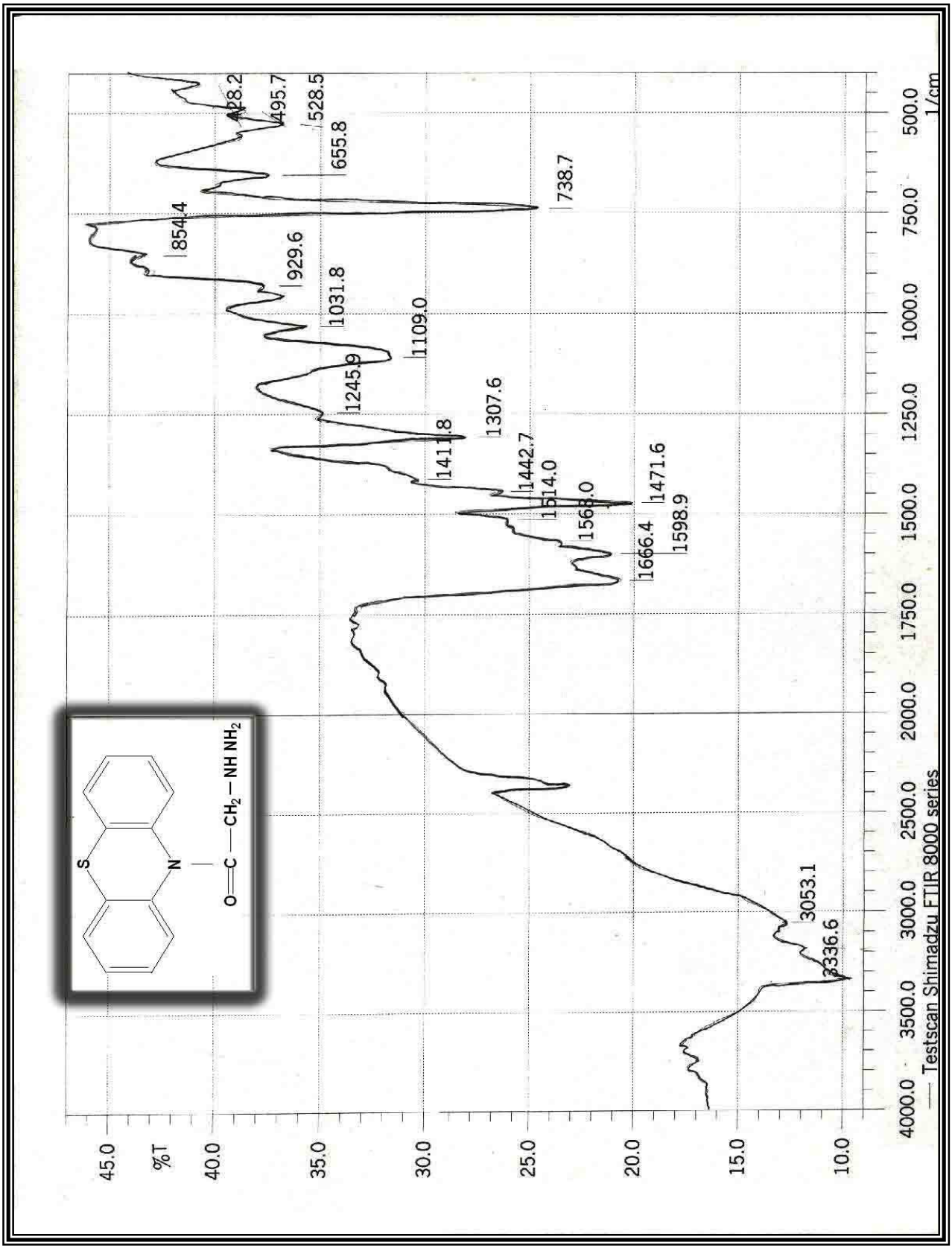



**Figure (3): infrared spectrum of compound (3).**

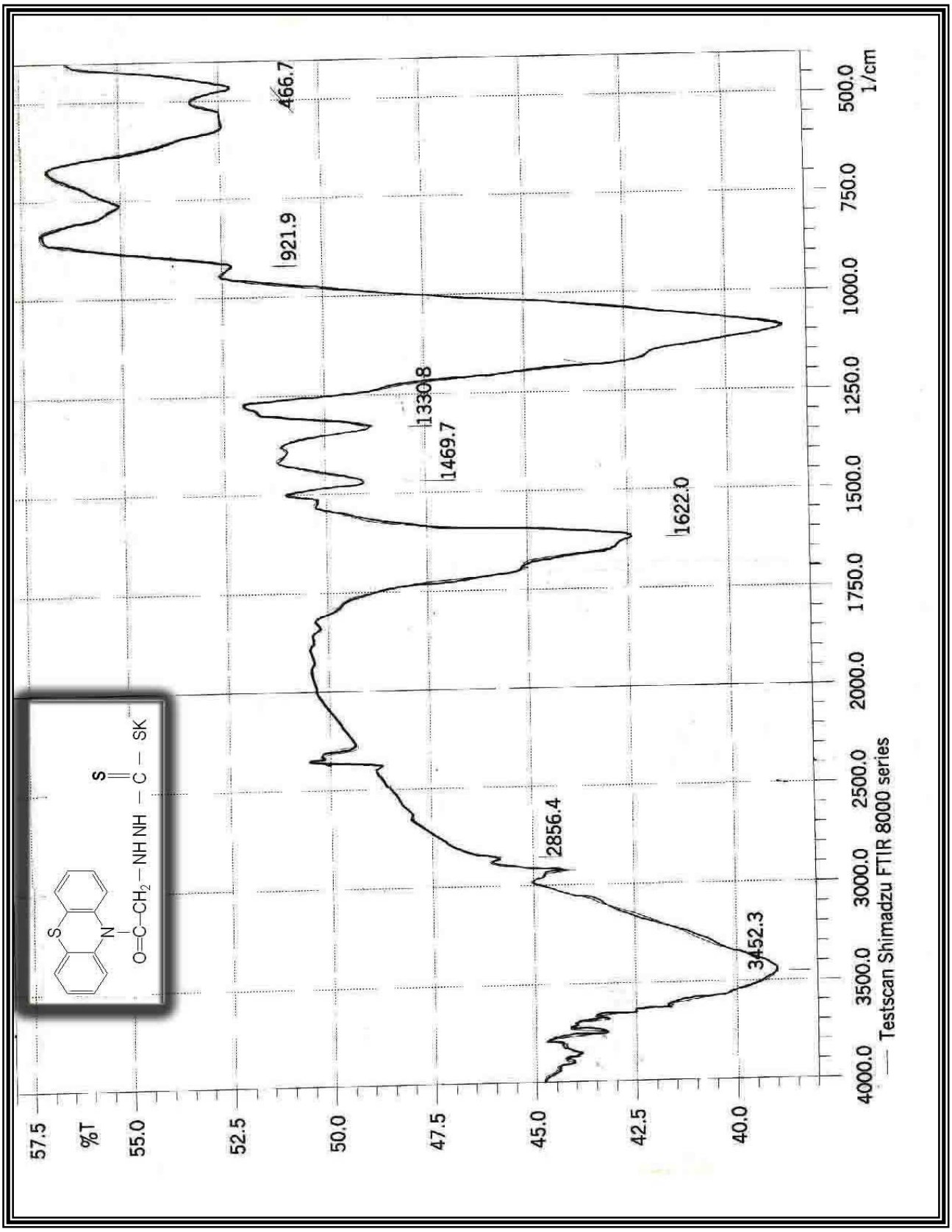



**Figure (4): infrared spectrum of compound (4).**

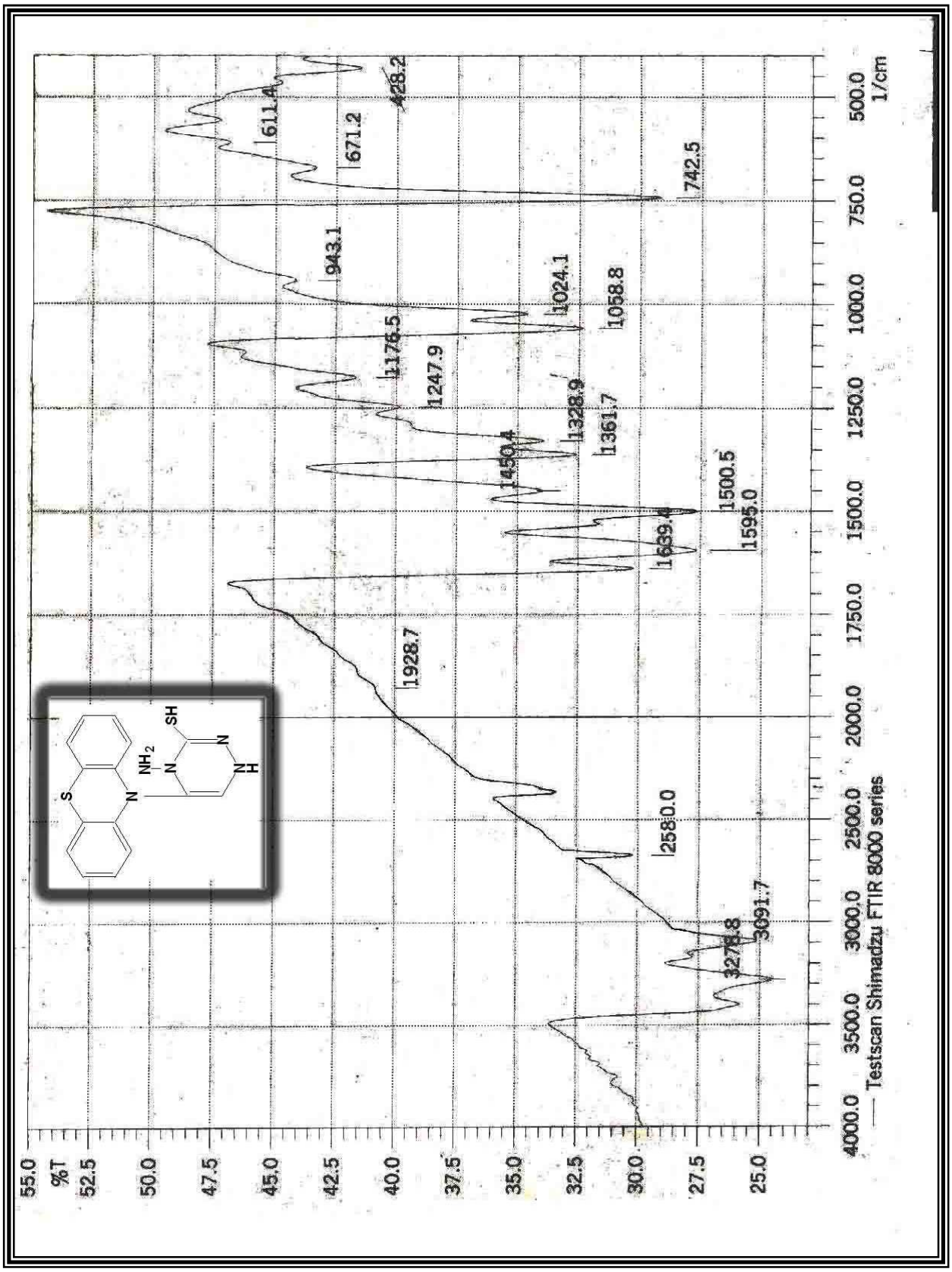
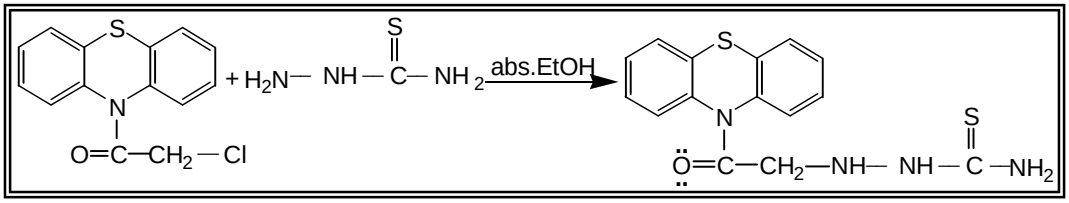



**Figure (5): infrared spectrum of compound (5).**

## 3-6 ***$N_{10}$- (acetyl phenothiazine)thiosemicarbazide (6).***

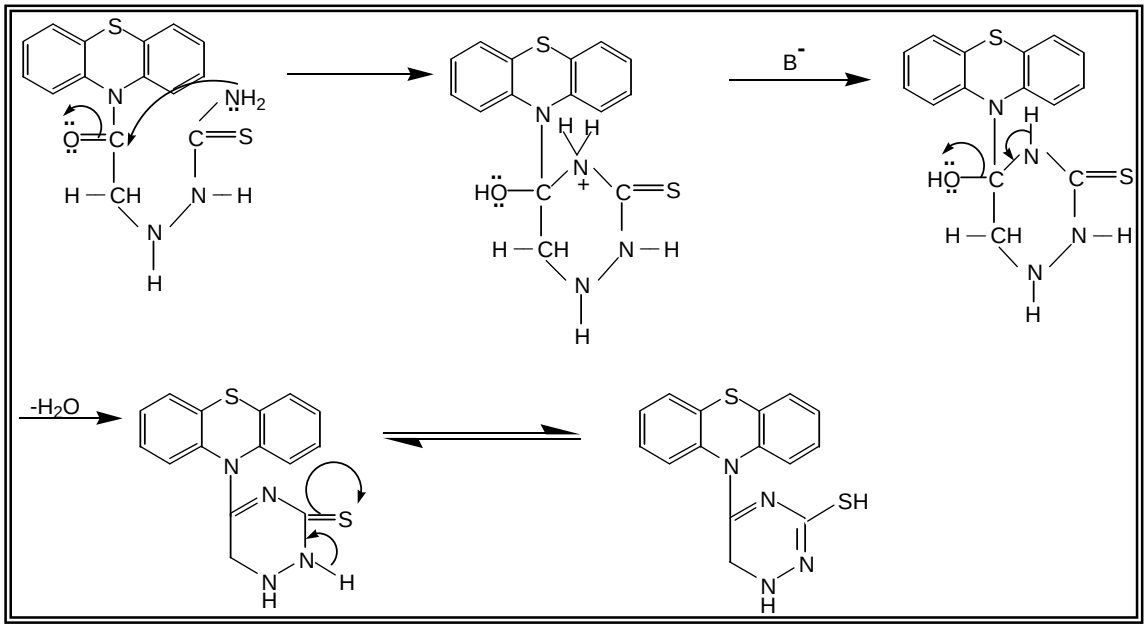
Reaction of thiosemicarbazide with $N_{10}$-chloroacetyl phenothiazine (2) under reflux condition, gave $N_{10}$-acetylphenothiazine thiosemicarbazide (6).




The structure of (6) was confirmed by FTIR. FTIR spectrum showed bands at (3370 -3130) $cm^{-1}$ for asymmetric and symmetric stretching ($NH_2$, NH); (ν C-H) aromatic is over laped with (ν N-H). Bands at (2985.6 and 2715.6**)** $cm^{-1}$ for aliphatic (C-H) stretching. Amide I band for (ν C=O) appeared at 1662.5 $cm^{-1}$ and at 1330.8 $cm^{-1}$ for (C=S) as shown in fig 6.

## 3-7 ***$N_{10}$-(3-marcapto-[1H,6H]-1,2,4-triazin-5-yl)phenothiazine (7).***

The reaction of thiosemicarbazide (6) with 10% NaOH under refluxing condition affected intramolecular cyclization through the loss of $H_2O$ giving the desired thio triazine derivative (7), the formation of (7) may be visualized by the following mechanism: -




The structure of thio-triazine derivative (7) was confirmed by FTIR. The FTIR spectrum showed bands at 3276.8 $cm^{-1}$ for (NH) stretching, 3085.9 $cm^{-1}$ (C-H aromatic), 2954.7 $cm^{-1}$ (C-H aliphatic), 1635.5 $cm^{-1}$ (C=N), 1500.5 $cm^{-1}$ (C=C), 2704 $cm^{-1}$ (S-H), and 1388.7 $cm^{-1}$ (C=S) as shown in fig (7).

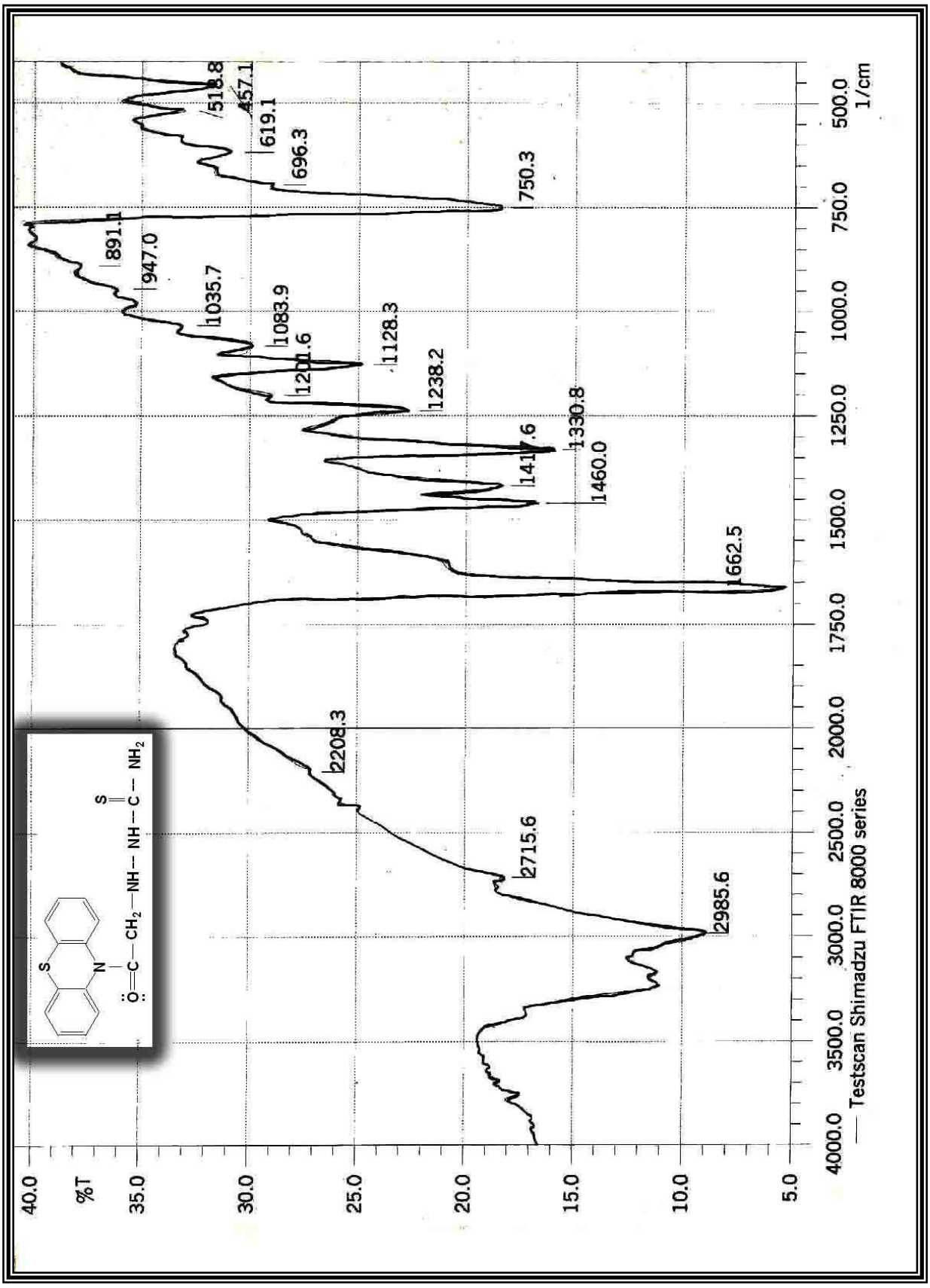



**Figure (6): infrared spectrum of compound (6).**

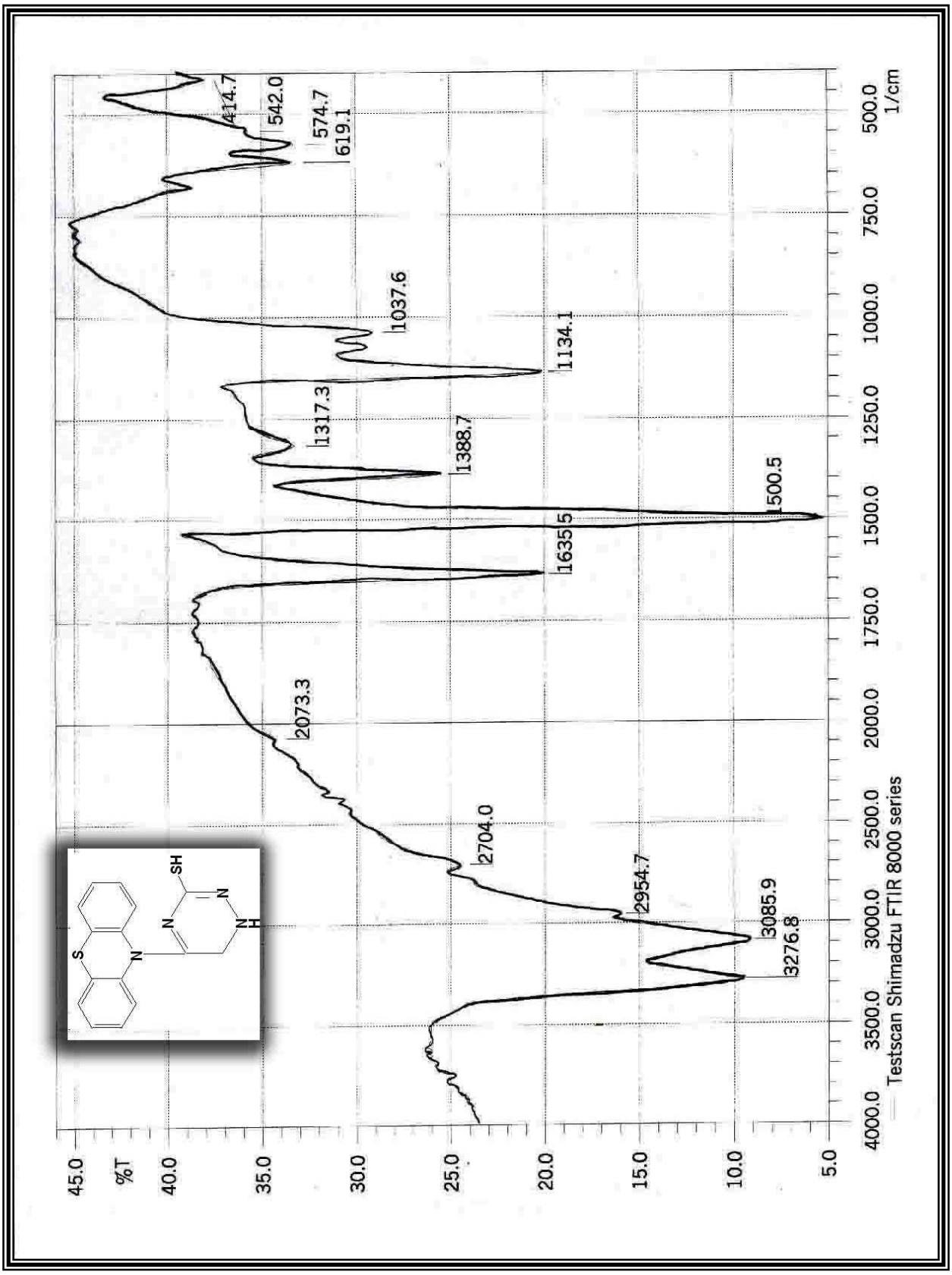
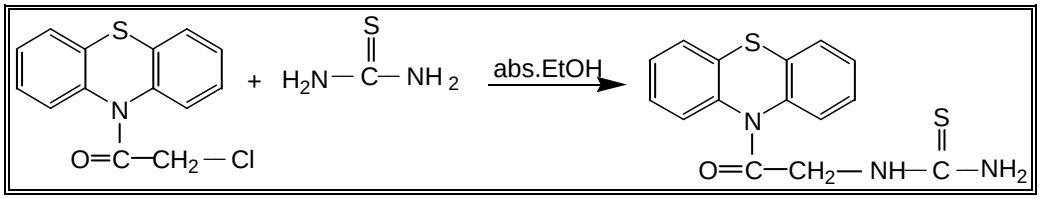



**Figure (7): infrared spectrum of compound (7).**

## 3-8 ***$N_{10}$-(acetyl phenothiazine) thiourea (8).***

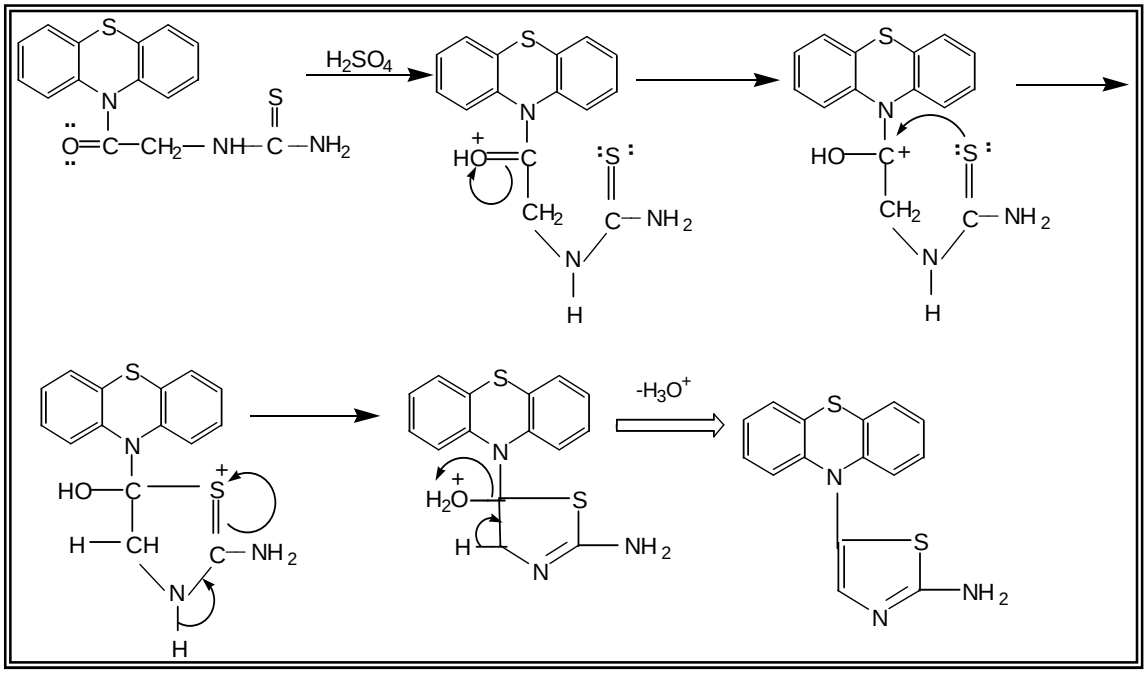
The refluxing of $N_{10}$-chloro acetyl phenothiazine with thiourea in absolute ethanol gave compound (8).




FTIR spectrum showed a split broad bands at (3300-3138)$cm^{-1}$ which was assigned to the asymmetric and symmetric stretching bands of ($NH_2$) and (NH) groups, at 1722.3 $cm^{-1}$ for (C=O), at 1330.8 $cm^{-1}$(C=S) and bands at (2997.0 and 1625.9) $cm^{-1}$ which were due to (C-H) and (C=C) stretching of aromatic system, respectively, and at 1471.6 $cm^{-1}$ for (N-H) bending as shown in fig 8.

## 3-9 ***$N_{10}$-(2-amino-1, 3-thiazol-5-yl) phenothiazine (9).***

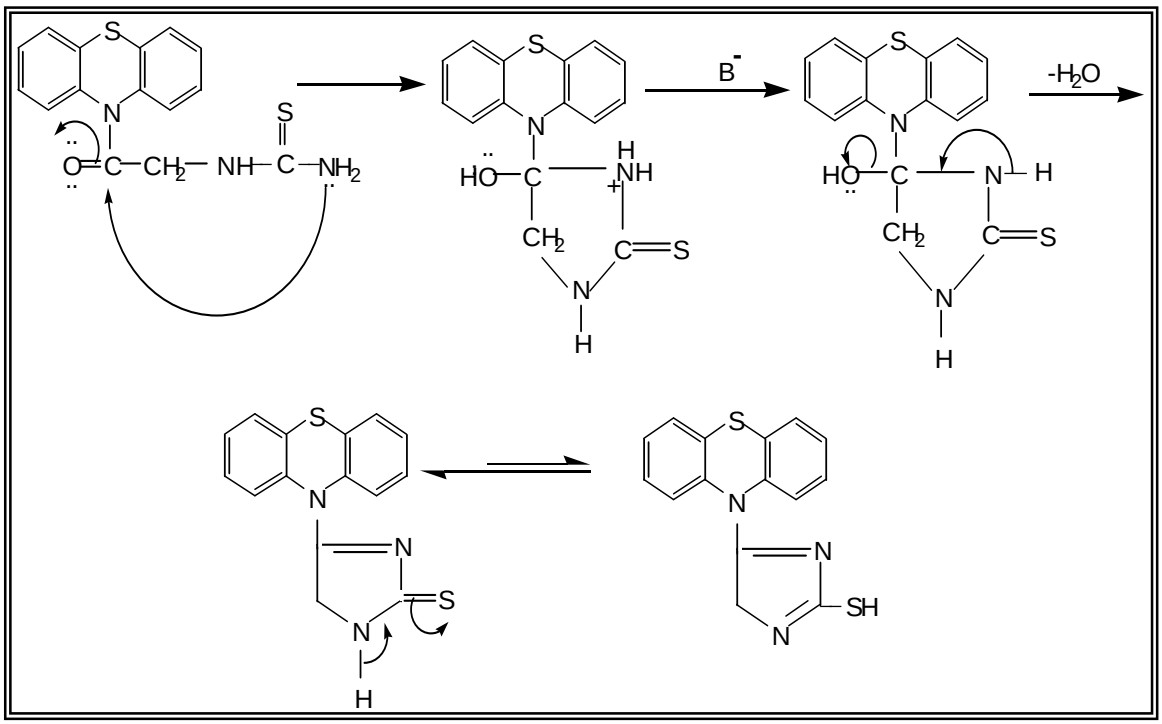
Treating $N_{10}$-acetyl phenothiazine thiourea with conc.$H_2SO_4$ under reflux condition affected intramolecular cyclization through the loss of $H_2O$ giving the amino-thiazole derivative (9), the formation of (9) may be described by the following mechanism:-




The FTIR spectrum of compound (9) showed the disappearance of the (C=O) band of compound (8) at 1722.3 $cm^{-1}$ and appearance of bands at (3280 and 3170.10) $cm^{-1}$ for asymmetric and symmetric stretching bands of ($NH_2$), the band at 1606.6 $cm^{-1}$ due to (ν C=N), also a band appeared at 752 $cm^{-1}$ for (C-S-C) [152], the characteristic aromatic bands at 3074.3 $cm^{-1}$ for (ν C-H) aromatic, and 1566.1 $cm^{-1}$ for (ν C=C) aromatic, and at 1488.9 $cm^{-1}$ for (N-H) bending as shown in fig (9).

## 3-10 ***$N_{10}$-(2-mercapto-[5H]-1,3-imidazol-4-yl)]phenothiazine (10).***

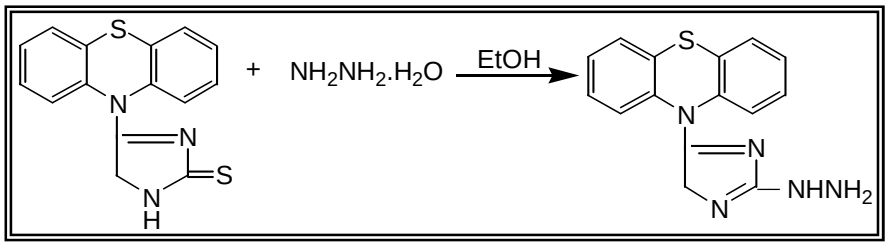
The reaction of thiourea derivative (8) with 10% NaOH under refluxing condition affected intramolecular cyclization through the loss of $H_2O$ giving the desired thio- imidazole derivative (10), the formation of (10) may be explained by the following mechanism:-




FTIR spectrum of compound (10) showed the disappearance of (C=O) band of the starting compound (8) at 1722.3 $cm^{-1}$ and appearance of bands at 3321.2 $cm^{-1}$ for (ν N-H), 1639.4 $cm^{-1}$ for (C=N), [2922.0 $cm^{-1}$, 2852.5 $cm^{-1}$ for asym. and sym. (CH) aliphatic], 1323.1 $cm^{-1}$ for (C=S), and also the characteristic aromatic bands at 3091.7 $cm^{-1}$ for (C-H) aromatic and 1581.5 $cm^{-1}$ for (C=C) as shown in fig (10).

## 3-11 ***$N_{10}$-[(2-([5H]-1, 3-imidazol-4-yl) hydrazine]phenothiazine (11).***

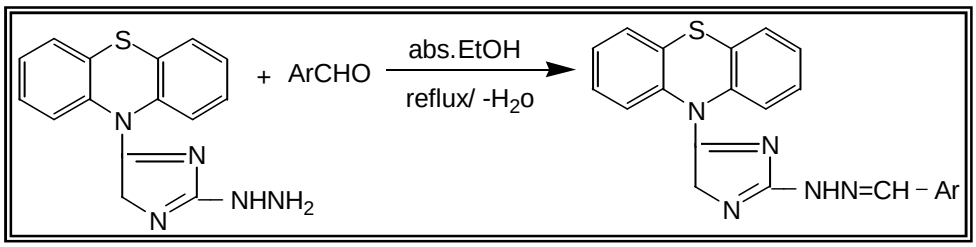
When imidazole compound (10) was refluxed with 98% hydrazine hydrate it gave the expected imidazole hydrazine (11).




The structure of hydrazine derivative (11) was confirmed by FTIR spectroscopy. The FTIR spectrum showed bands of compound (11) at (3446.6 and 3334.7) $cm^{-1}$ which were assigned to the asymmetric and symmetric bands of $NH_2$ and NH group, a band at 1629.7 $cm^{-1}$ for (C=N).The FTIR spectrum also showed the characteristic aromatic bands at 3100 $cm^{-1}$ due to (CH aromatic), and 1583.4 $cm^{-1}$ (C=C) as shown in fig 11.

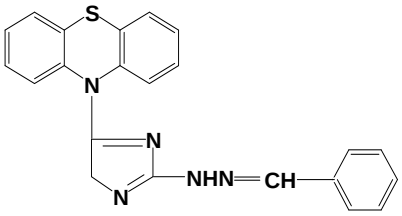
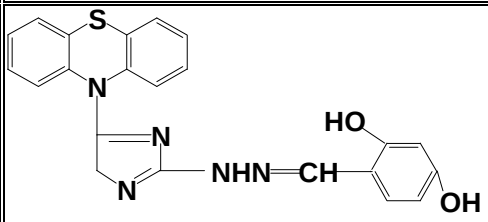
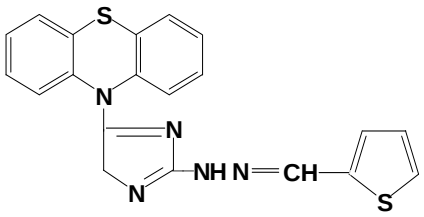
## 3-12 ***Schiff's base compounds: {N10-([5H]-1,3-imidazol-4-yl) hydrazone]phenothiazine [12-14]}.***

The last step of this series was the synthesis of Schiff base compounds [12-14] by the reaction of imidazole hydrazine derivative (11) with different aromatic aldehydes in absolute ethanol solution.



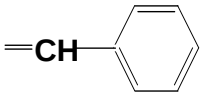
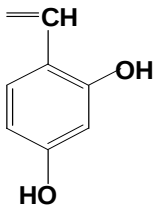
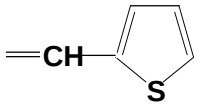

**Ar**=phenyl, 2, 4- dihydroxyphenyl, Thiophenyl.

The table (3.1) shows melting points, percent yields, colors and chemical formula of compounds [12-14].

| Compd. No. | Compd. structure | M.P. °C | Yield % | color | Chemical formula (Mol.wt) (g/mol) |
|---|---|---|---|---|---|
| **12** |  | 169-170 | 78 | Yellow | $C_{22}H_{17}N_5S$ (321) |
| **13** |  | 210 d. | 82 | orange | $C_{22}H_{19}N_5SO_2$ (355) |
| **14** |  | 140 | 63 | Pale green | $C_{20}H_{15}N_5S_2$ (347) |

The structures of Schiff's base compounds were confirmed by their FTIR spectra.

Table (3.2) shows FTIR absorption bands of compounds [12-14] as in figures [12-14].

| Compd. No. | Ar group | Fig No. | (ν N-H) $cm^{-1}$ | (ν C-H) $cm^{-1}$ aromatic | (ν C-H) $cm^{-1}$ aliphatic | (ν C=N) $cm^{-1}$ | Other bands $cm^{-1}$ |
|---|---|---|---|---|---|---|---|
| **12** |  | 12 | 3211.3 s | 3040.0 w | 2974.0-2883.4 w | 1598.9 s | (C=C) 1514.0s |
| **13** |  | 13 | 3224.8 s | Overlap with N-H | 2931.6 w | 1616.2 s | (O-H) 3520-3463.9 s.b. (C=C) 1515.9 m |
| **14** |  | 14 | 3377.1 s | 3064.7 w | 2920-2856.4 w | 1591.2 s | (C-S-C) 742.5 (C=C) 1510 |

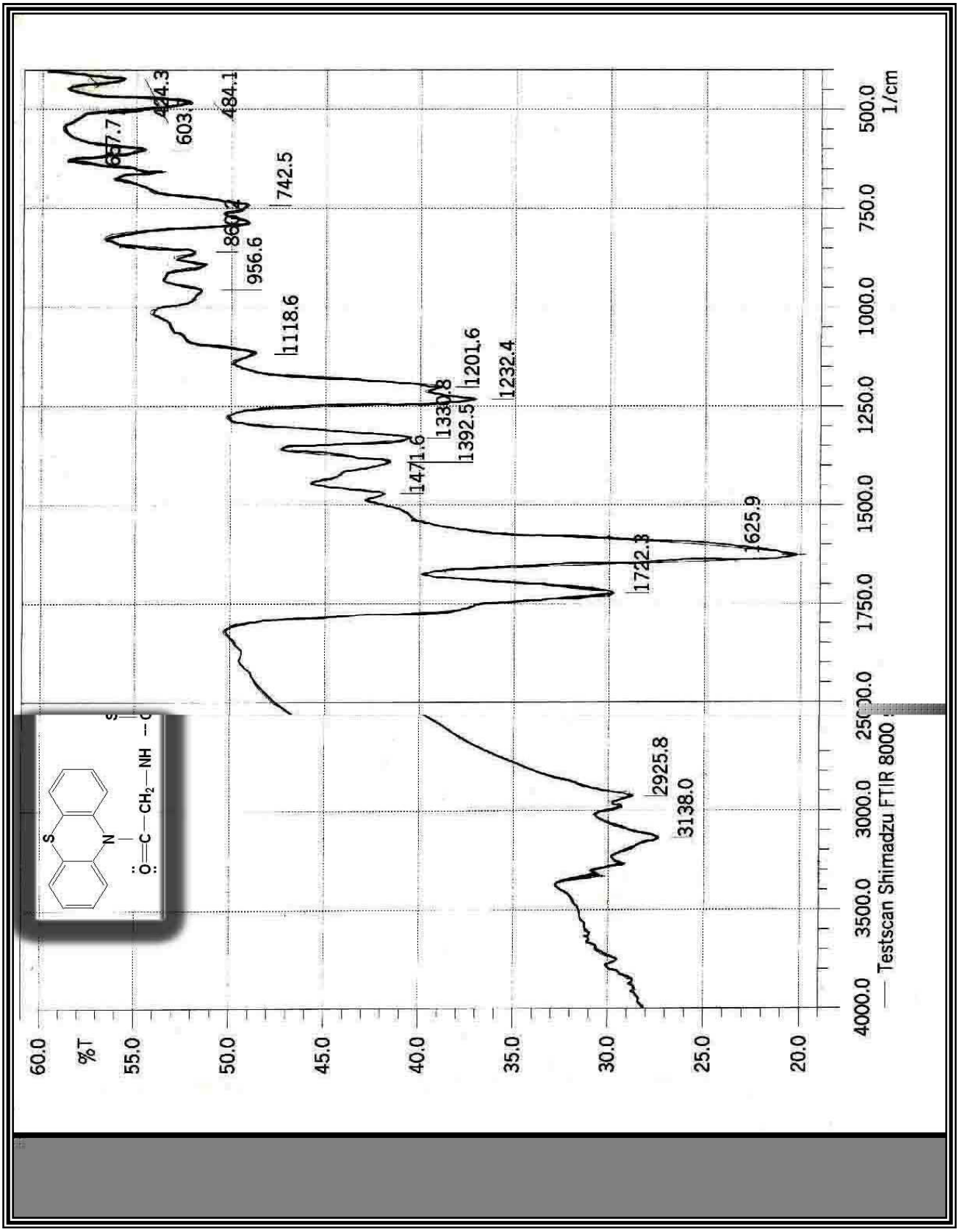



**Figure (8): infrared spectrum of compound (8).**

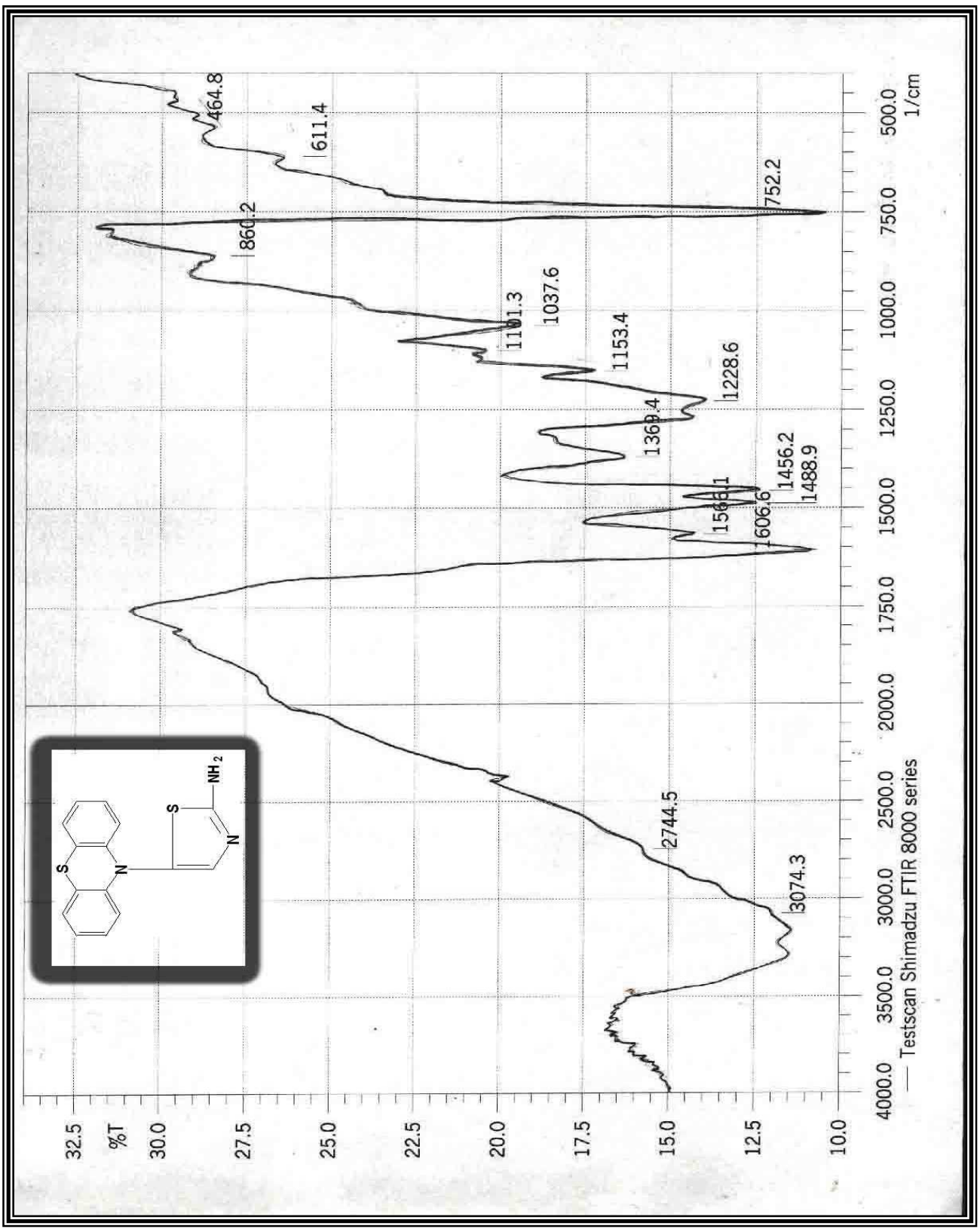



**Figure (9): infrared spectrum of compound (9).**

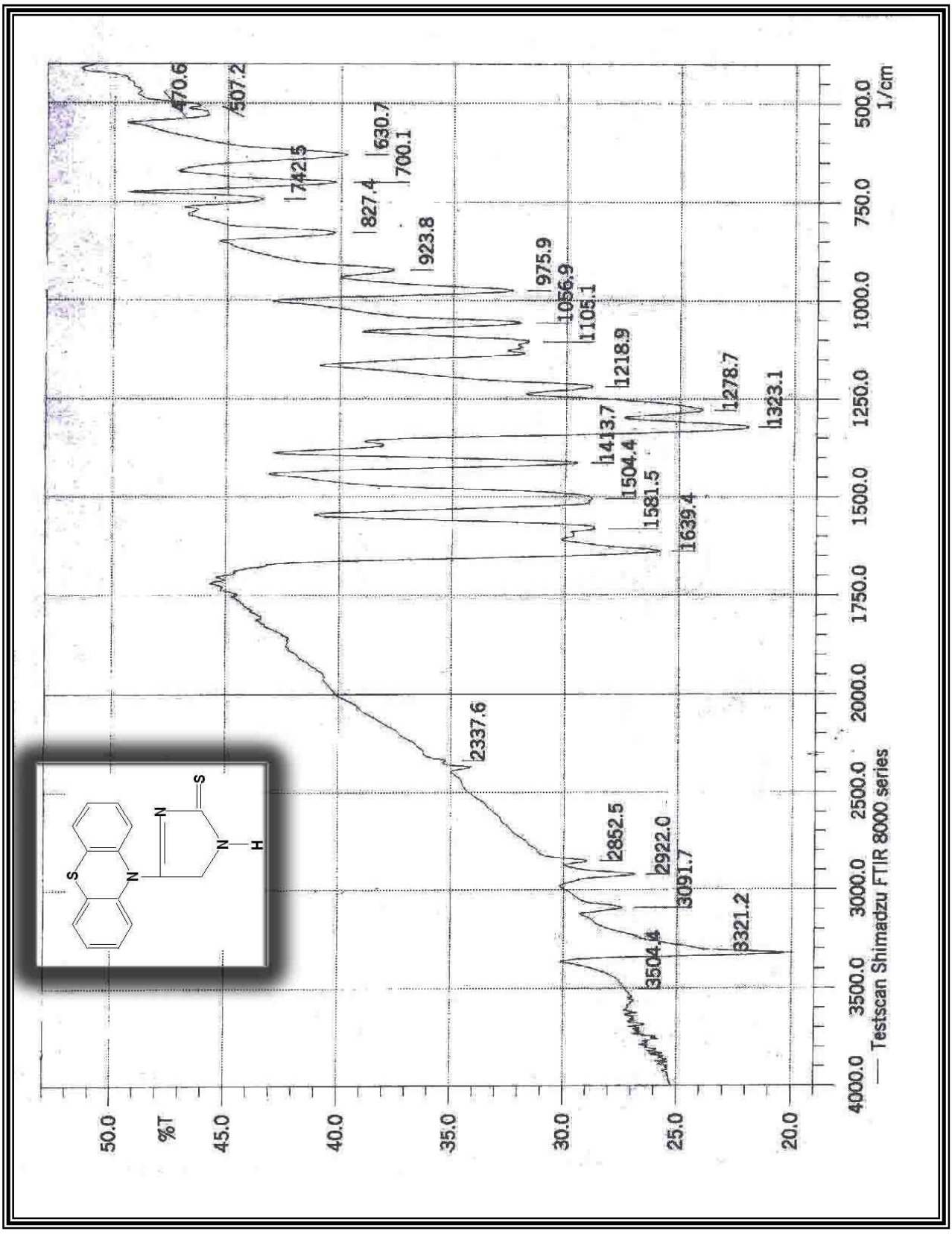



**Figure (10): infrared spectrum of compound (10).**

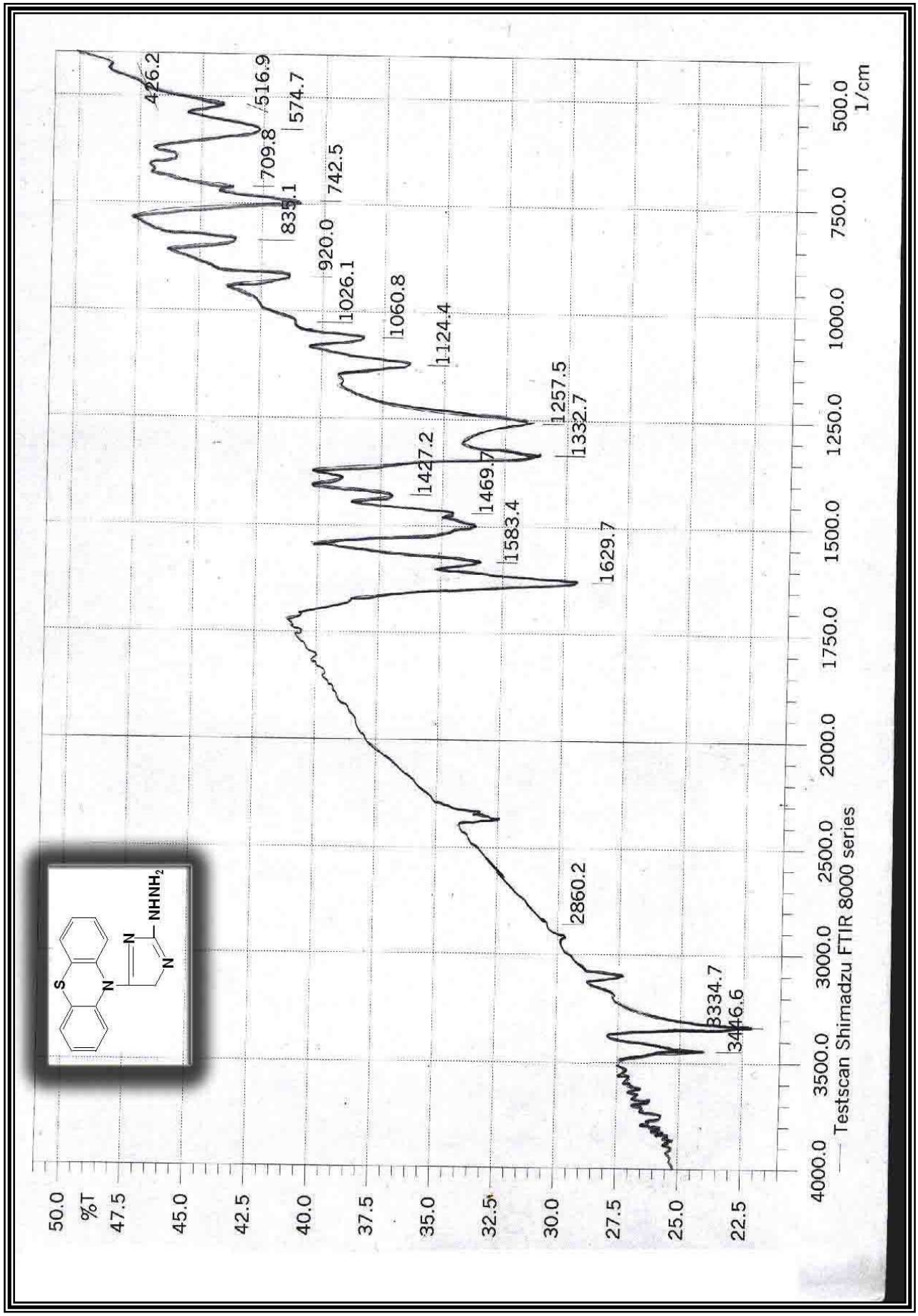



**Figure (11): infrared spectrum of compound (11).**

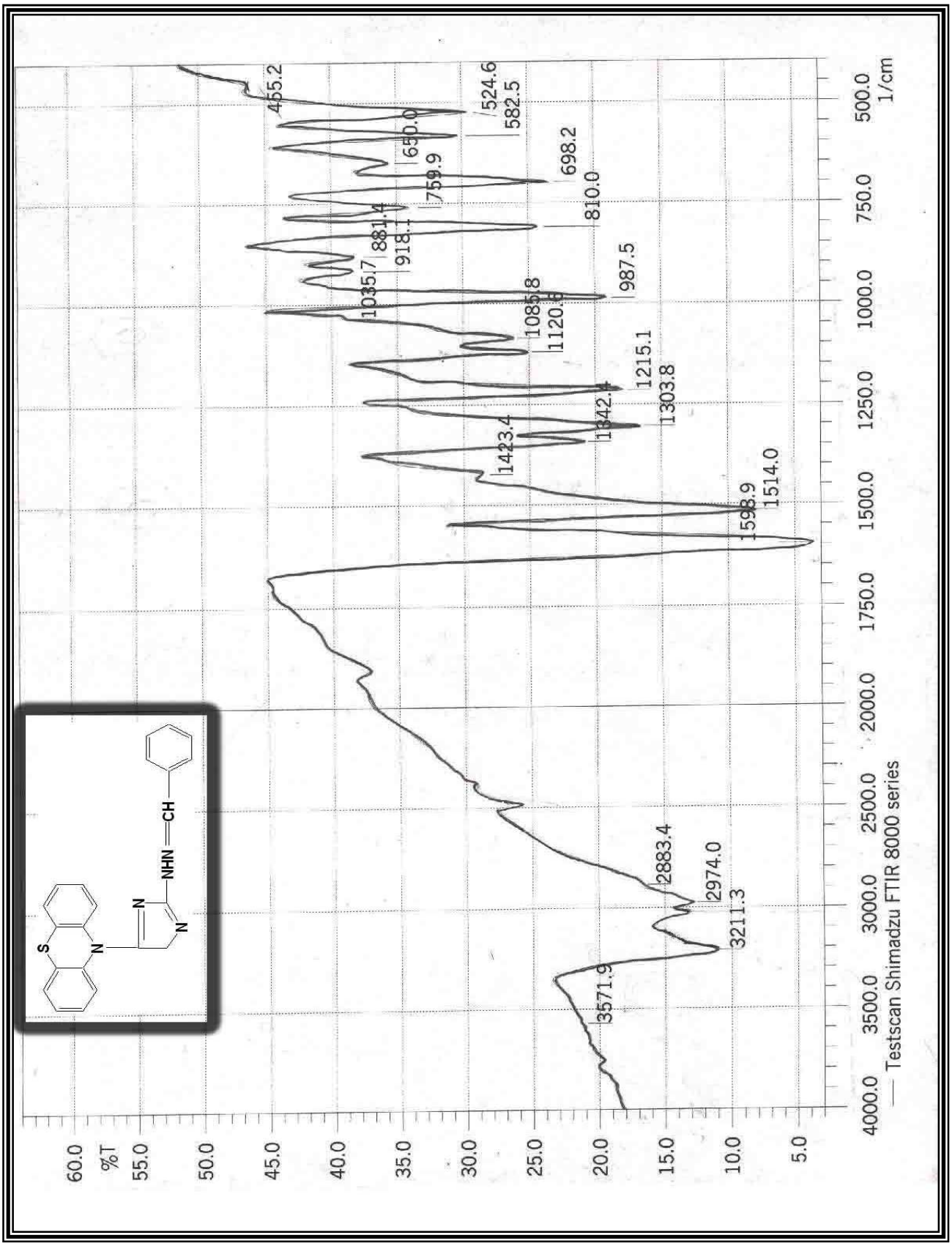



**Figure (12): infrared spectrum of compound (12).**

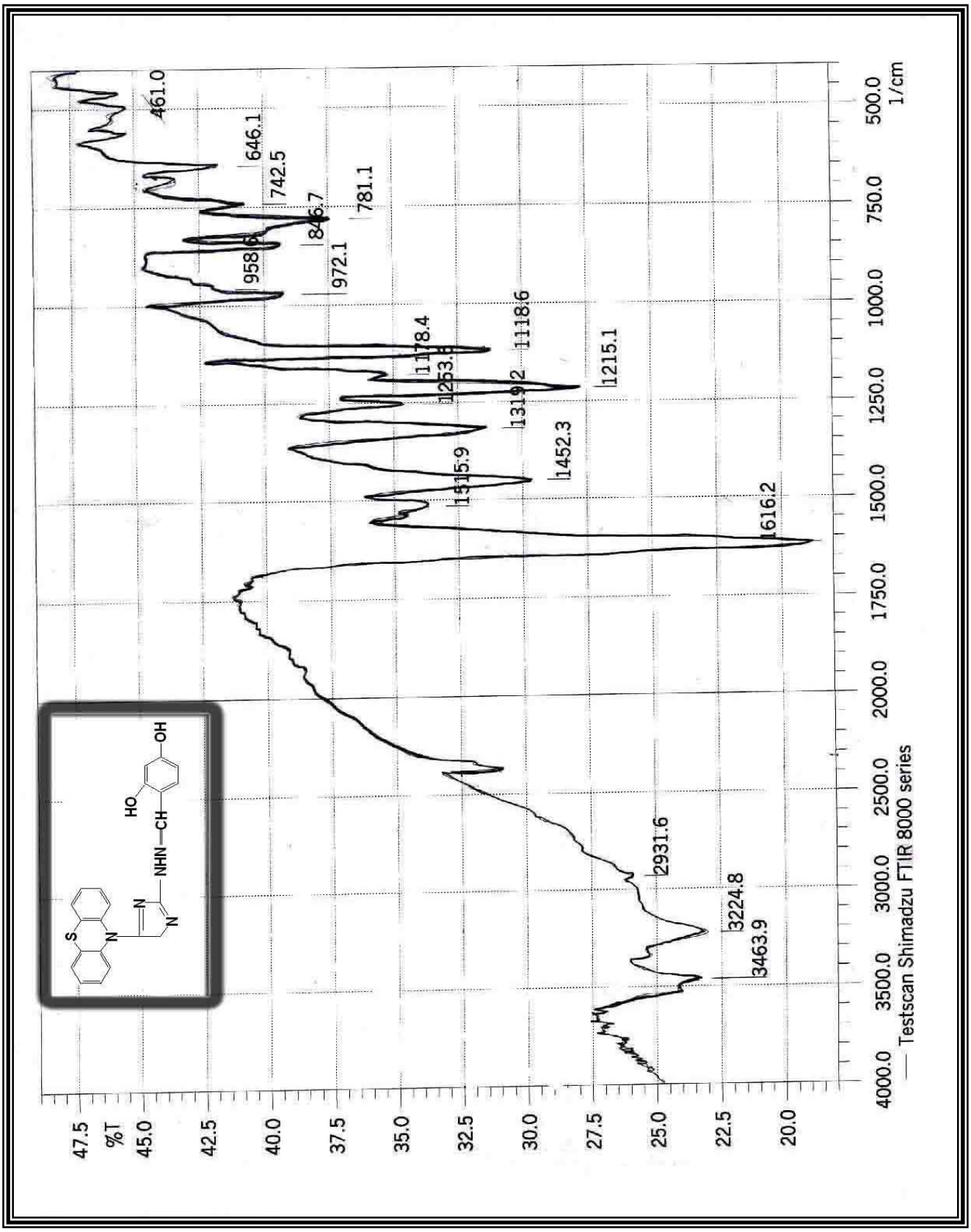



**Figure (13): infrared spectrum of compound (13).**

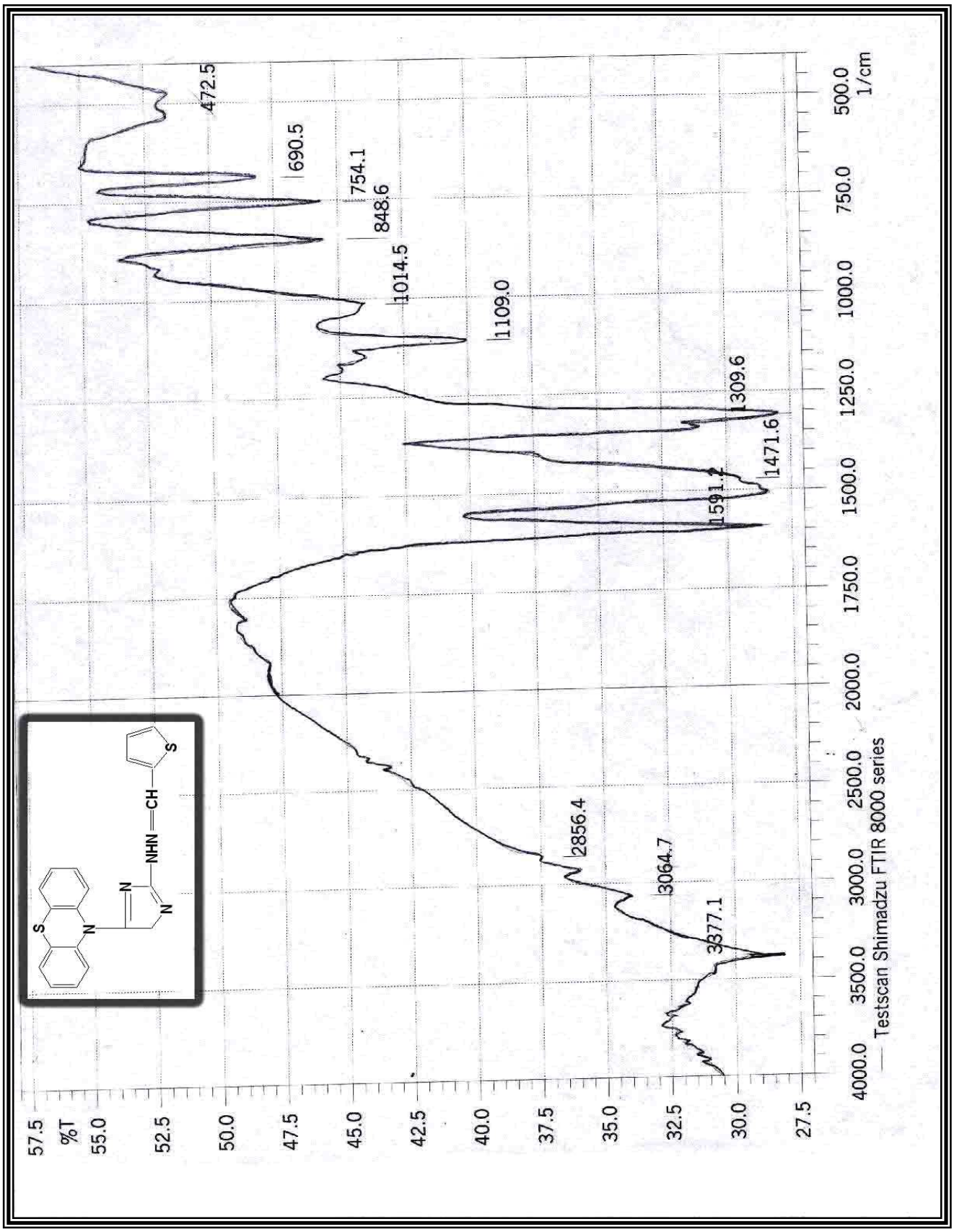
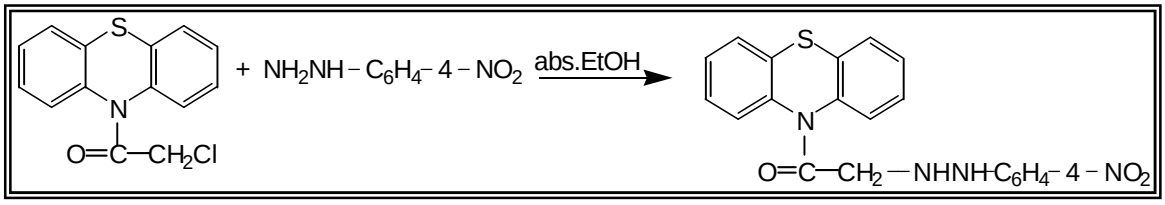



**Figure (14): infrared spectrum of compound (14).**

## 3-13 ***N [$N_{10}$-(acetyl phenothiazine)]-4-nitropheny hydrazine (15).***

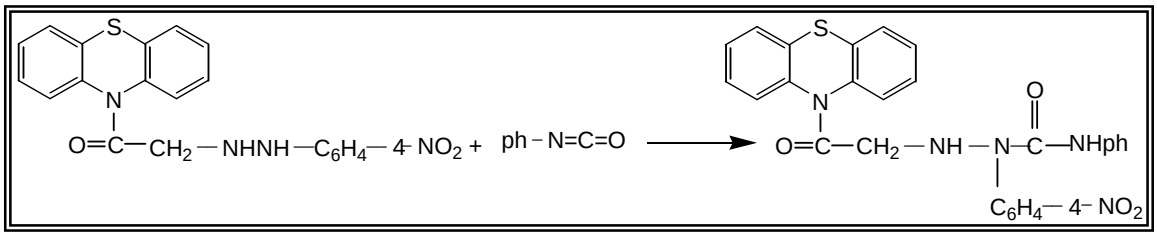
To synthesize new heterocyclic $N_{10}$-substitued compound (oxazoline), the hydrazine derivative (15) was a suitable root for this synthetic approach. So when $N_{10}$-(chloro acetyl) phenothiazine (2) was treated with 4-nitrophenyl hydrazine under refluxing condition, it gave the expected hydrazine derivative (15).




FTIR spectrum showed two bands at 3274.9 $cm^{-1}$ and 3217.0 $cm^{-1}$ which were assigned to (NH-NH) group, 1683.7 $cm^{-1}$ for (C=O), 2890 $cm^{-1}$ and 2821.7 $cm^{-1}$ for (ν C-H aliphatic). The FTIR spectrum also showed characteristic aromatic bands at 3091.7 $cm^{-1}$ for (C-H aromatic) and 1608.5 $cm^{-1}$ for (C=C). Other bands that were present in the FTIR spectrum are asymmetric and symmetric stretching bands of $NO_2$ at (1500.5 $cm^{-1}$ and 1342.4 $cm^{-1}$), respectively, all these bands of compound (15) are shown in fig 15.

## 3.14 ***4N [$N_{10}$-(acetyl phenothiazine)]-1-phenyl-3-p-nitro phenyl semicabazide (16).***

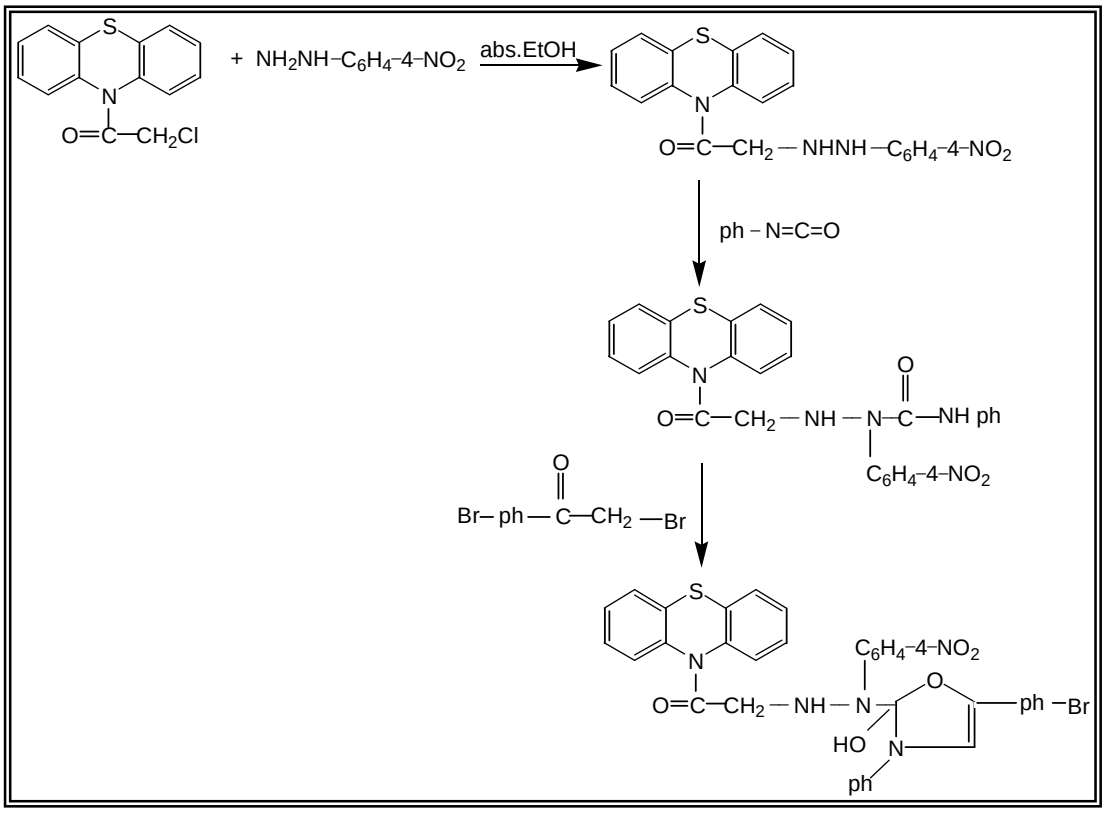
The reaction of phenyl isocyante with hydrazine derivative (15) under refluxing condition gave semicabazide derivative (16).




The structure of semicabazide derivative (16) was confirmed by FTIR spectroscopy. The FTIR spectrum showed two stretching bands for (NH, NH) group at (3315.0$cm^{-1}$ and 3282.6$cm^{-1}$). Two other bands at (1681.8 $cm^{-1}$ and 1640.0$cm^{-1}$) for the two carbonyl groups, asymmetric and symmetric starching band of $NO_2$ appeared at (1502.4$cm^{-1}$ and 1328.9$cm^{-1}$) all these bands are shown in fig (16).

## 3.15 ***$N_{10}$-(3-N-phenyl-4-pbromophenyl-2-hydroxy-4-oxazolin-2-yl) acetylphenothiazine-2N-nitrophenylhydrazide (17).***

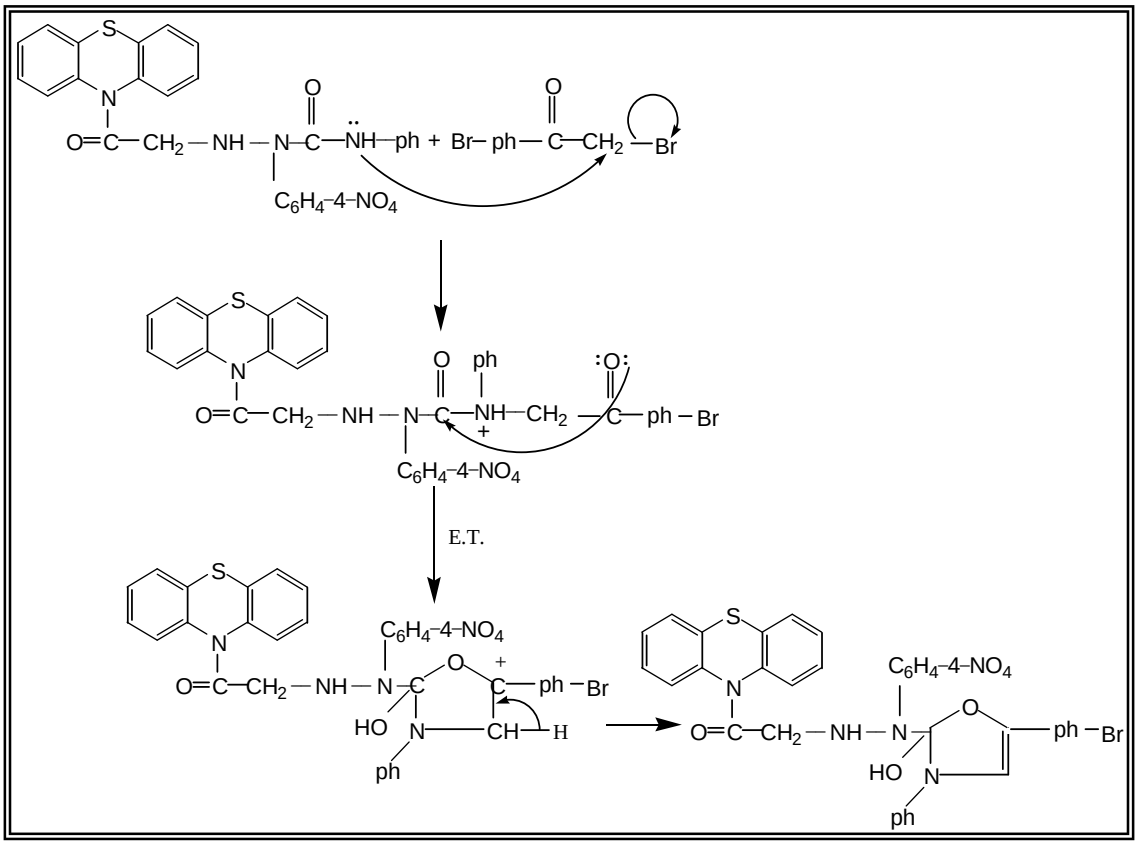
The title compound (17) was synthesized according to reaction scheme (2).




Scheme (2)

The reaction of compound (16) with *p*-bromophenancyl bromide under refluxing condition affected on intermolecular cyclization through $S_N2$ mechanism giving the desired 4-oxazoline derivatives (17).

The formation of (17) may be posses by the following mechanism:-




The structure of oxazoline derivative was confirmed by FTIR spectroscopy. FTIR spectrum showed a broad band of (O-H) group at 3470 $cm^{-1}$, strong sharp band of N-H at 3317.3 $cm^{-1}$, asymmetric and symmetric (C-H) aliphatic at (2910 $cm^{-1}$ and 2858.3 $cm^{-1}$), band of (C=O) at 1690 $cm^{-1}$, (C=C) for heterocyclic and aromatic system at 1641.3 $cm^{-1}$, 1593.1 $cm^{-1}$, (receptivity), stretching band of (C-O-C) at 1245 $cm^{-1}$ [151], band of C-Br at 550 $cm^{-1}$ [151], and asymmetric and symmetric ($NO_2$) (1454.2 $cm^{-1}$, 1336.6 $cm^{-1}$) as shown in fig 17.

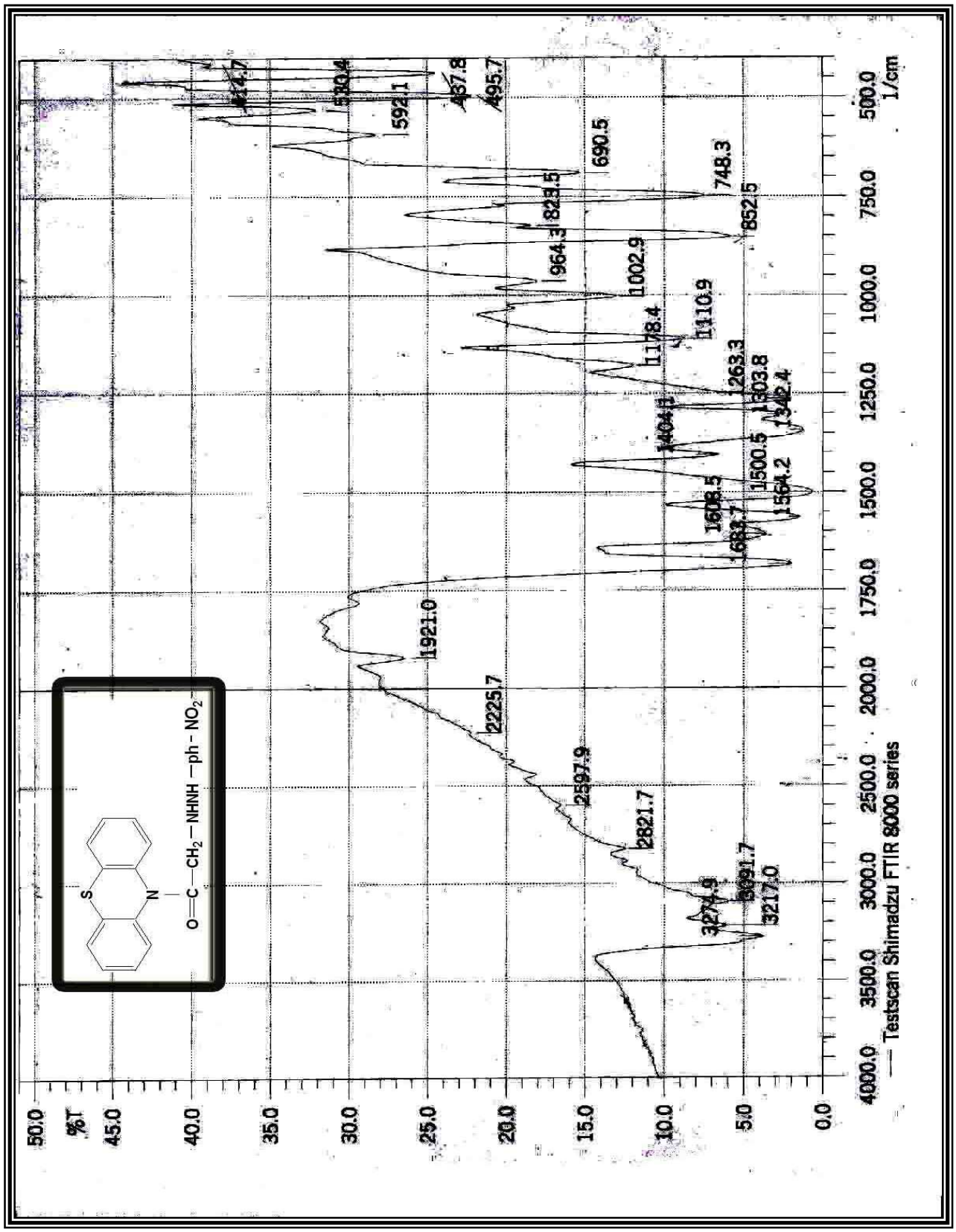



*Figure (15): infrared spectrum of compound (15).*

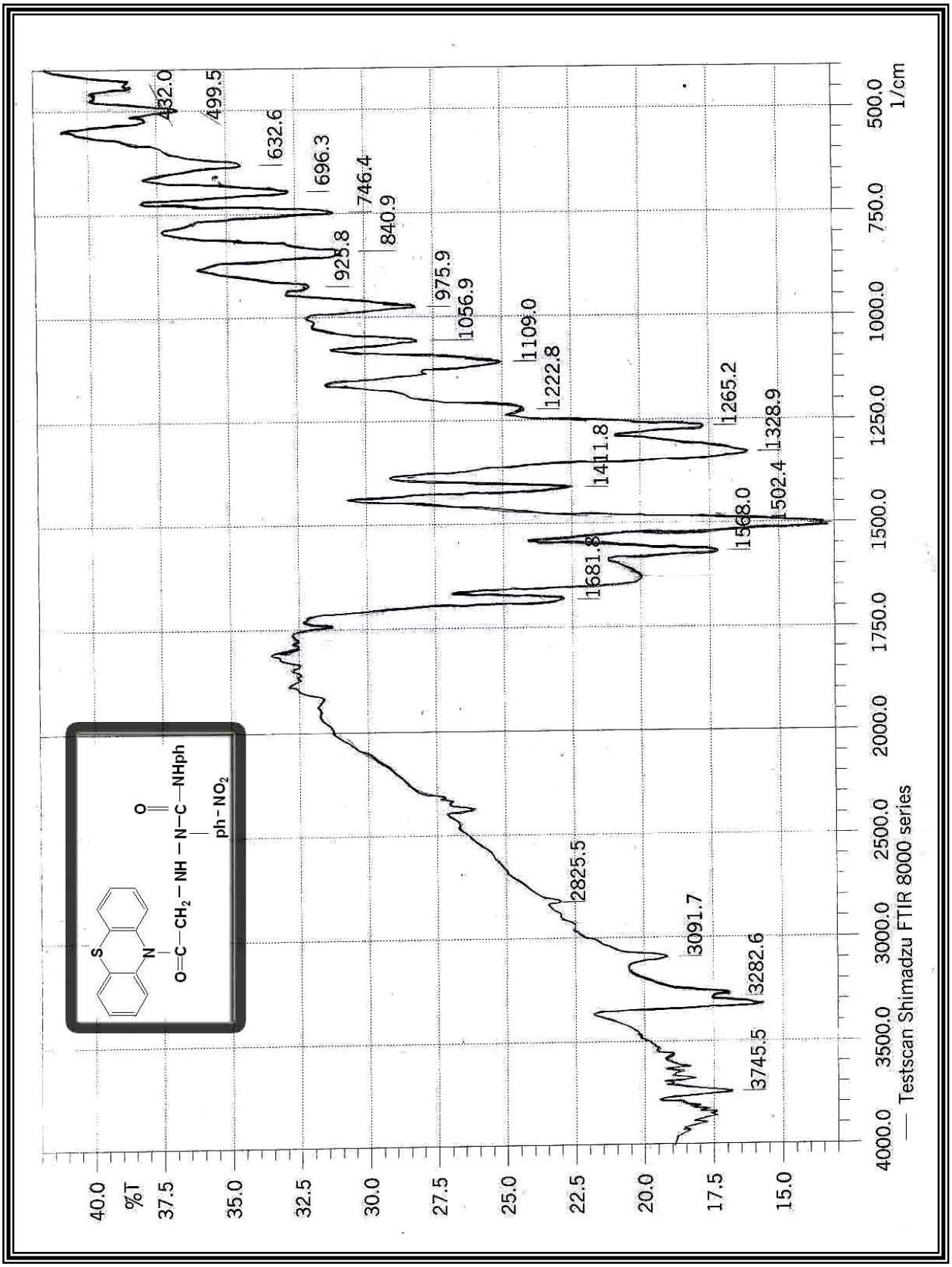



***Figure (16): infrared spectrum of compound (16).***

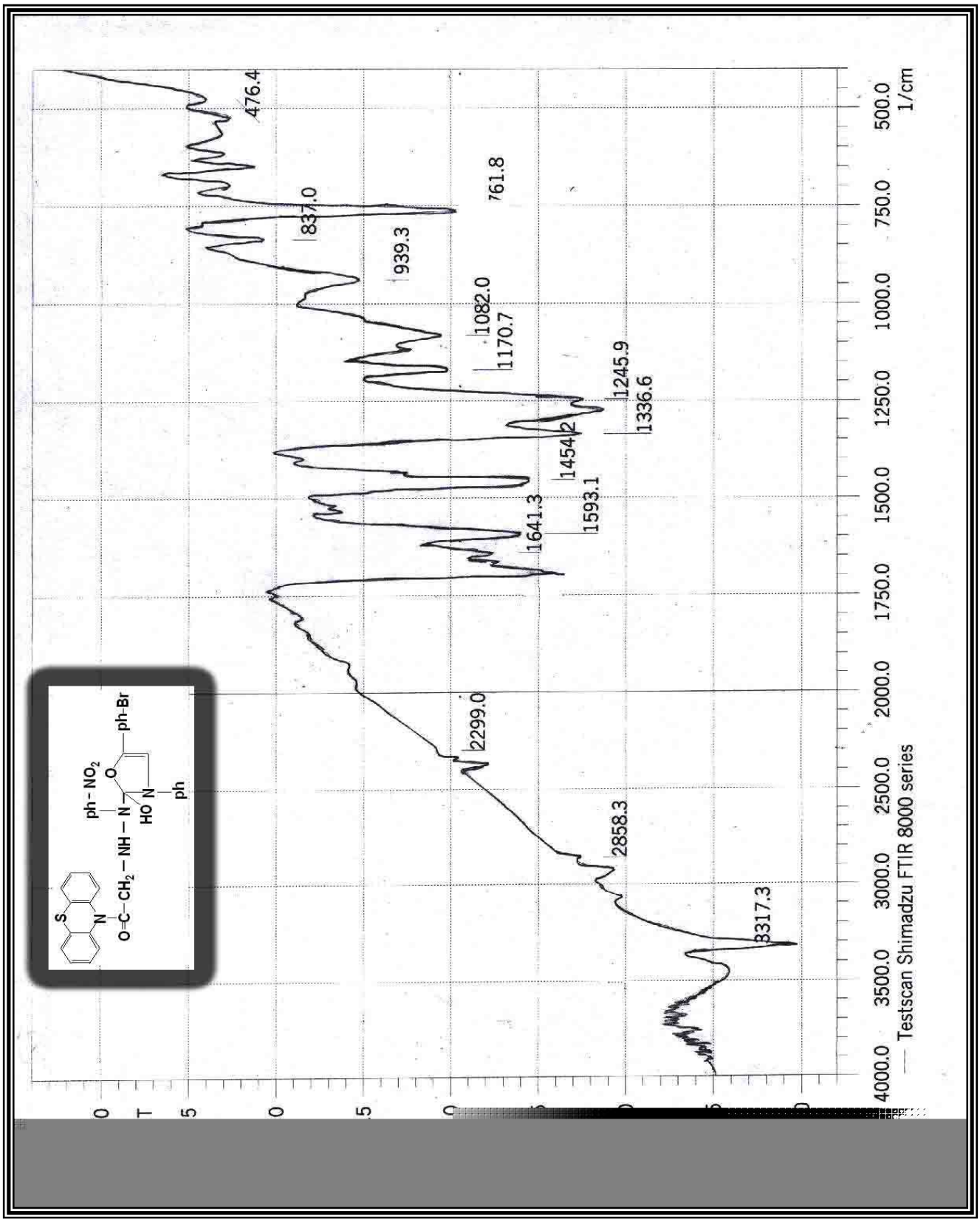
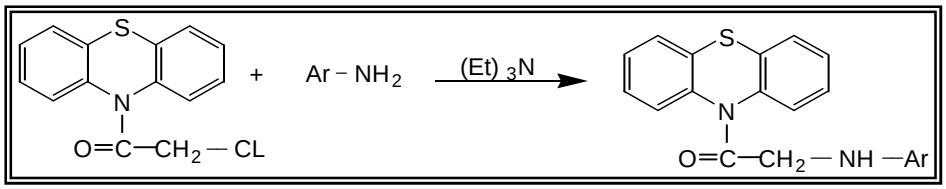



***Figure (17): infrared spectrum of compound (17).***

## 3-16 ***Synthesis of Aryl Amino acetyl 10-phenothiazine (18-23).***

Condensation of $N_{10}$-chloro acetyl phenothiazine (2) with different aromatic amines produced various Aryl Amino acetyl $H_{10}$-phenothiazine (18-23):-



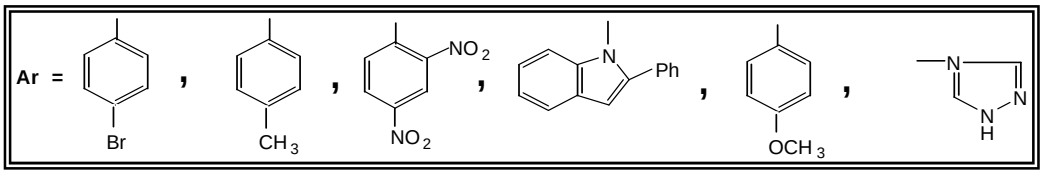
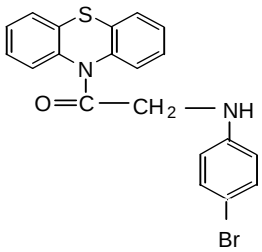




Table (3.3) shows the physical properties (melting points, percentage yields, colors) and molecular formula of Aryl Amino Acetyl 10-phenothiazine (18-23).

| Compd. No. | Compd. structure | M.P. °C | % | color | Molecular formula (M.wt)(g/mole) |
|---|---|---|---|---|---|
| **18** |  | 130-132 | 84 | Gray | $C_{20}H_{15}N_2SOBr$ (410) |

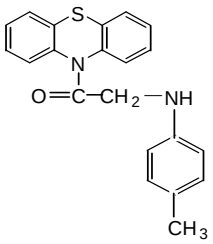
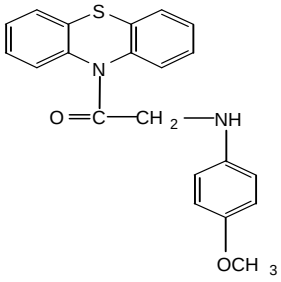
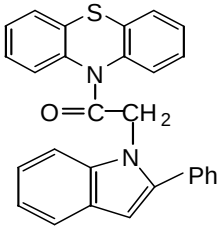
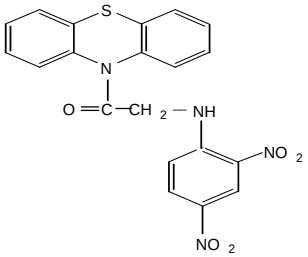
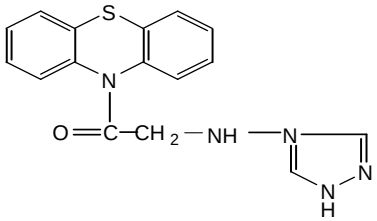
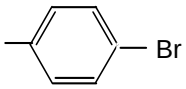
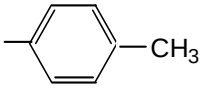
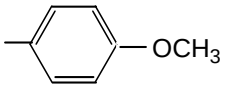
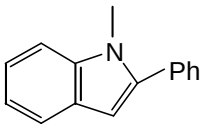
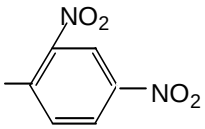
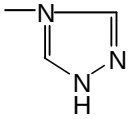
| | | | | | |
|---|---|---|---|---|---|
| **19** |  | 120-121 | 75 | Blue | $C_{21}H_{18}N_2SO$ (346) |
| **20** |  | 247-249 | 77 | Pale yellow | $C_{21}H_{18}N_2SO_2$ (362) |
| **21** |  | 78-80 | 65 | Reddish-brown | $C_{20}H_{15}N_4SO_5$ (423) |
| **22** |  | 150-152 | 86 | Light yellow | $C_{28}H_{20}N_2SO$ (396) |
| **23** |  | | 90 | white | $C_{16}H_{15}N_5SO$ (325) |

Table (3.4) shows FTIR absorption bands of compounds [18-23] as shown in figures [18-23].

| Compd. No. | Ar group | Fig No. | N-H $cm^{-1}$ | C-H $cm^{-1}$ aromatic | C-H $cm^{-1}$ aliphatic | C=O $cm^{-1}$ | C=C $cm^{-1}$ | Other Bands $cm^{-1}$ |
|---|---|---|---|---|---|---|---|---|
| **18** |  | 18 | 3370.5 | 3050 | 2922-2854.5 | 1680 | 1614.3 | p-disubstitution 810 |
| **19** |  | 19 | 3357.8 | 3045 | 2923.9-2852.5 | 1672.2 | 1589.2 | p-disubstitution 798.5 |
| **20** |  | 20 | 3440.8 | 3064 | 2933.5-2860.2 | 1700.4 | Overlap with C=O | m-disubstitution 746.4 |
| **21** |  | 21 | ___ | 3014 | 2929.7 | 1712.7 | 1580 | ___ |
| **22** |  | 22 | 3377.1 | 3010 | 2949-2860 | 1693.4 | 1587.3 | $NO_2$ 1500.5-1309.6 |
| **23** |  | 23 | 3220 3112.9 | 2990 | 2920-2854.4 | 1687 | 1550 | (C=N) 1649 |

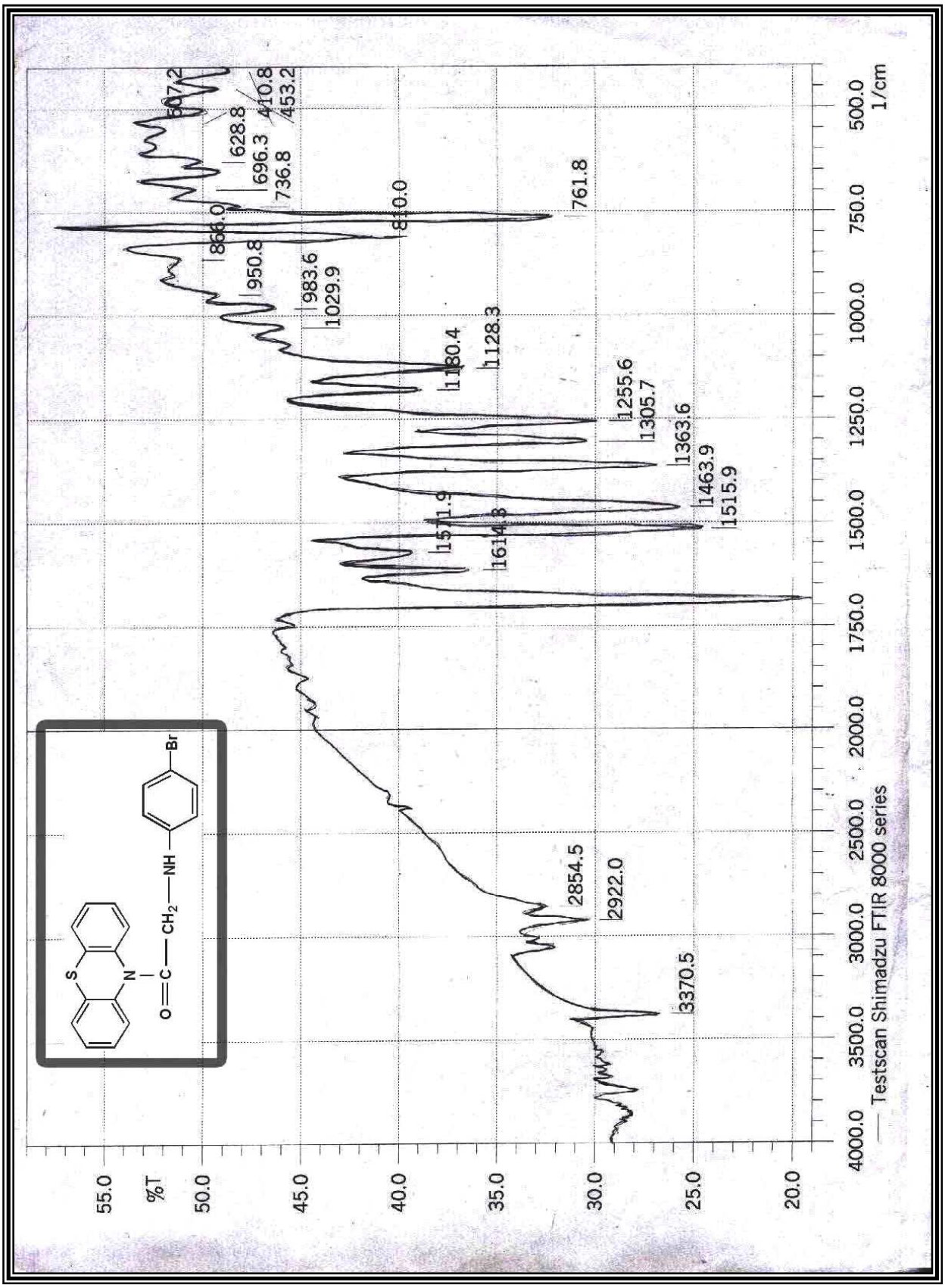



**Figure (18): infrared spectrum of compound (18).**

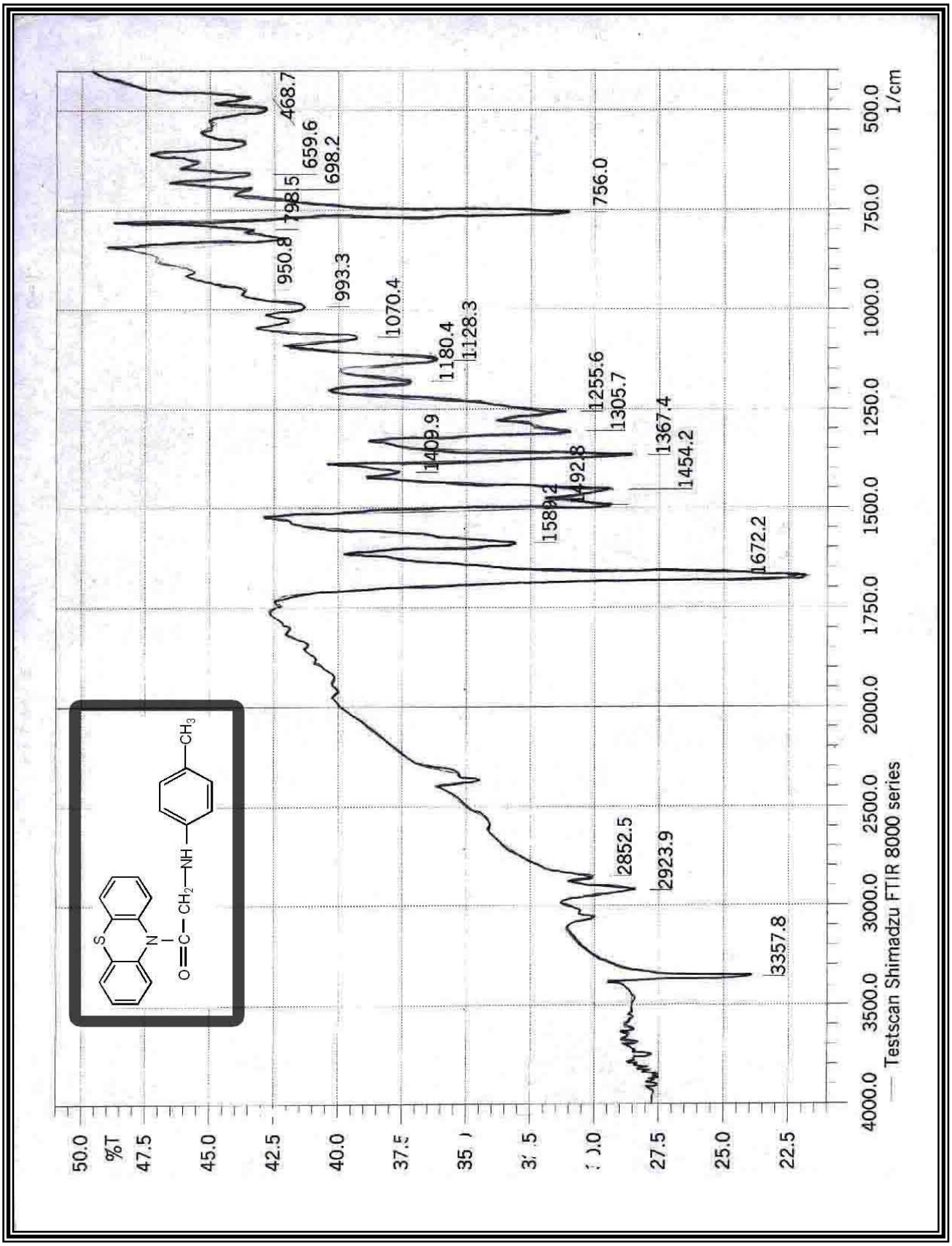



**Figure (19): infrared spectrum of compound (19).**

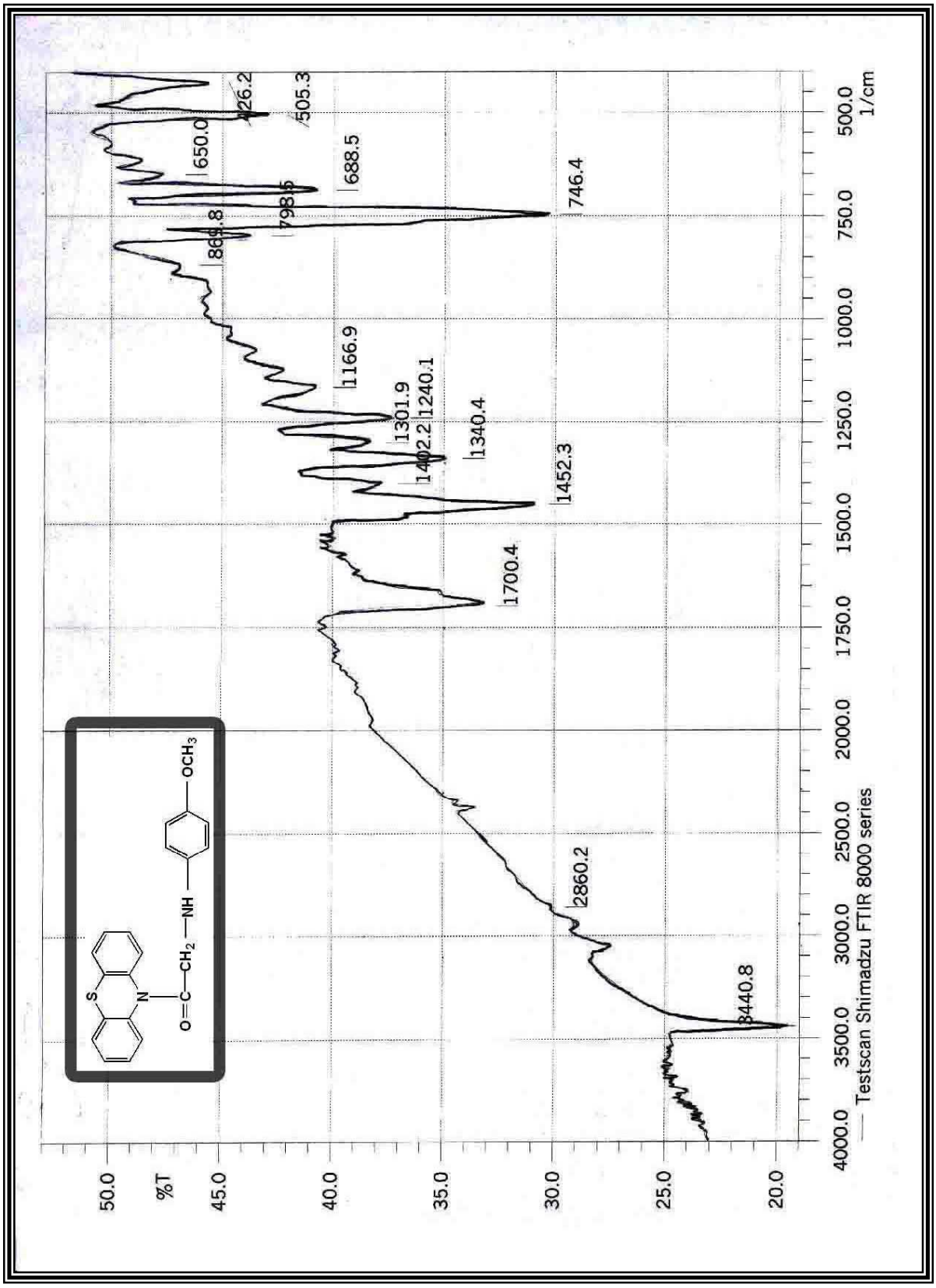



**Figure (20): infrared spectrum of compound (20).**

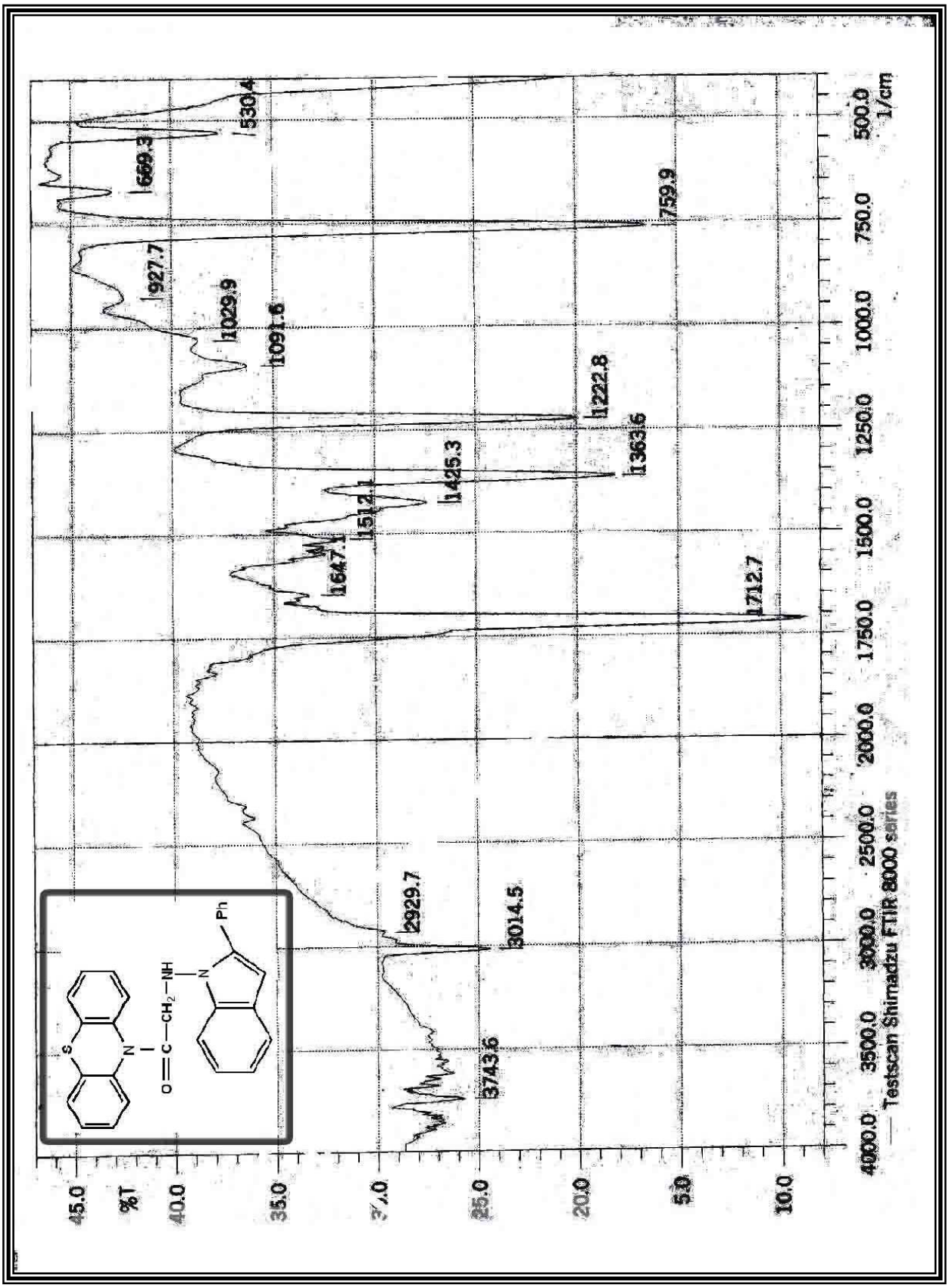



**Figure (21): infrared spectrum of compound (21).**

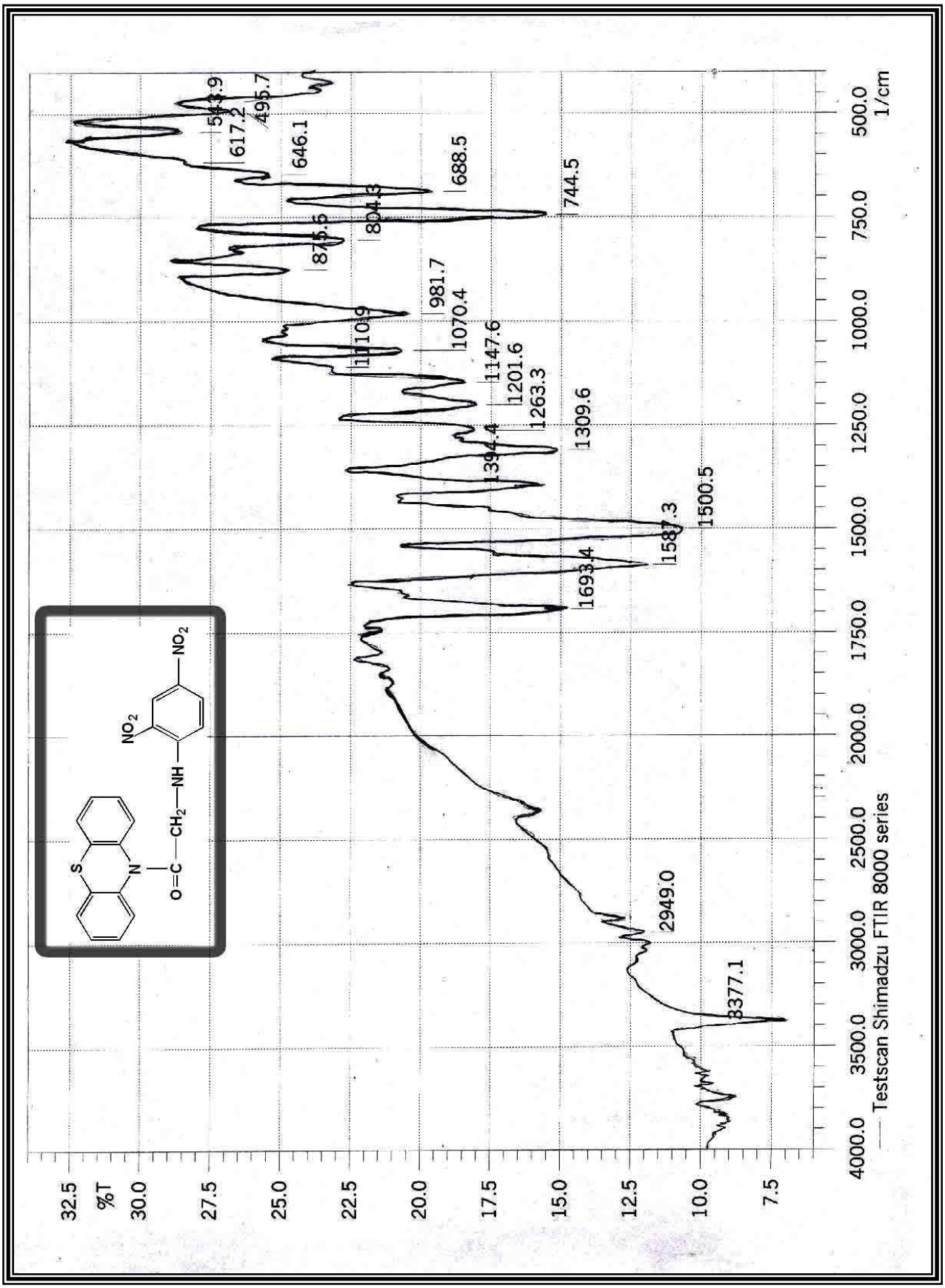



**Figure (22): infrared spectrum of compound (22).**

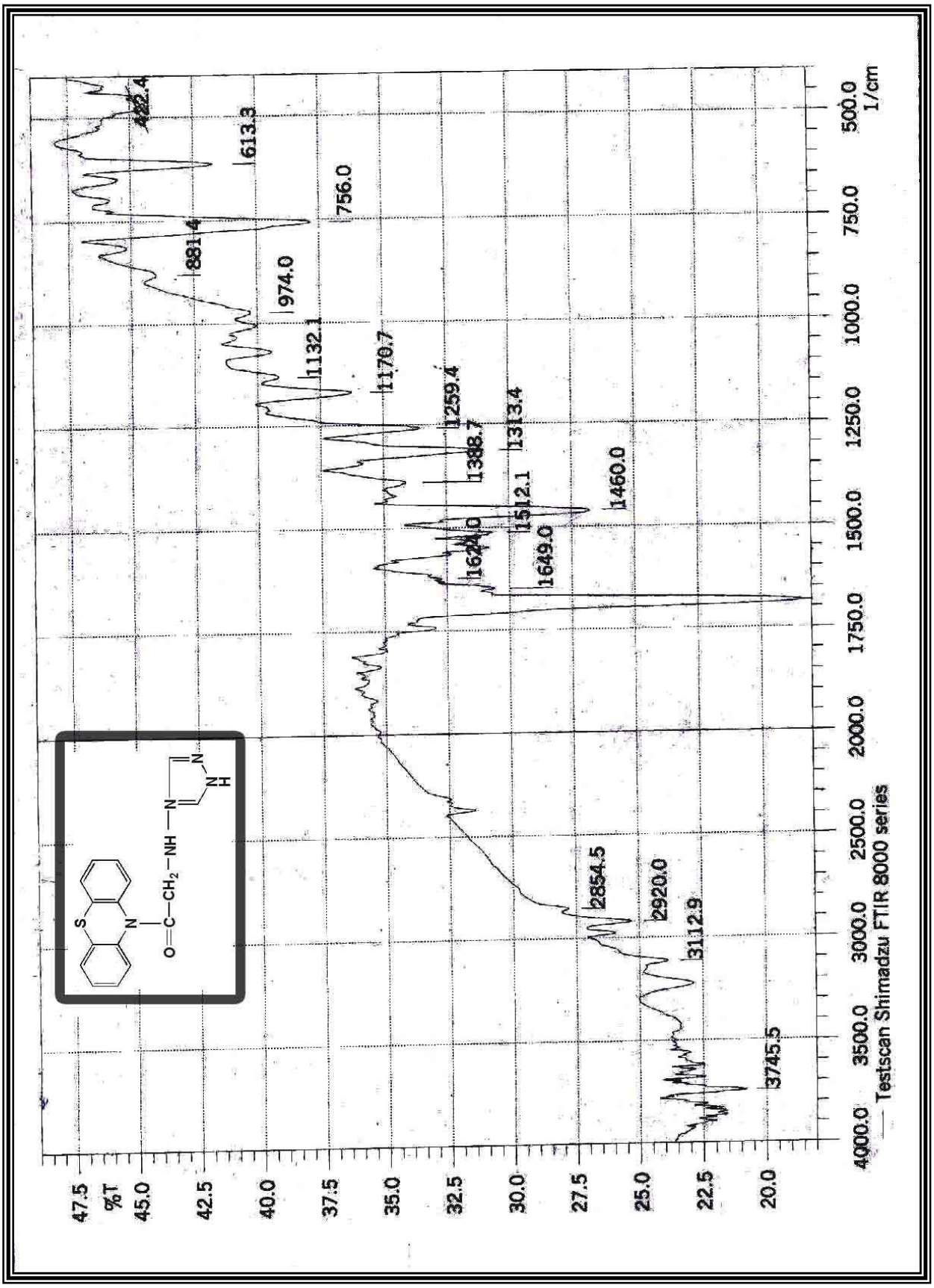
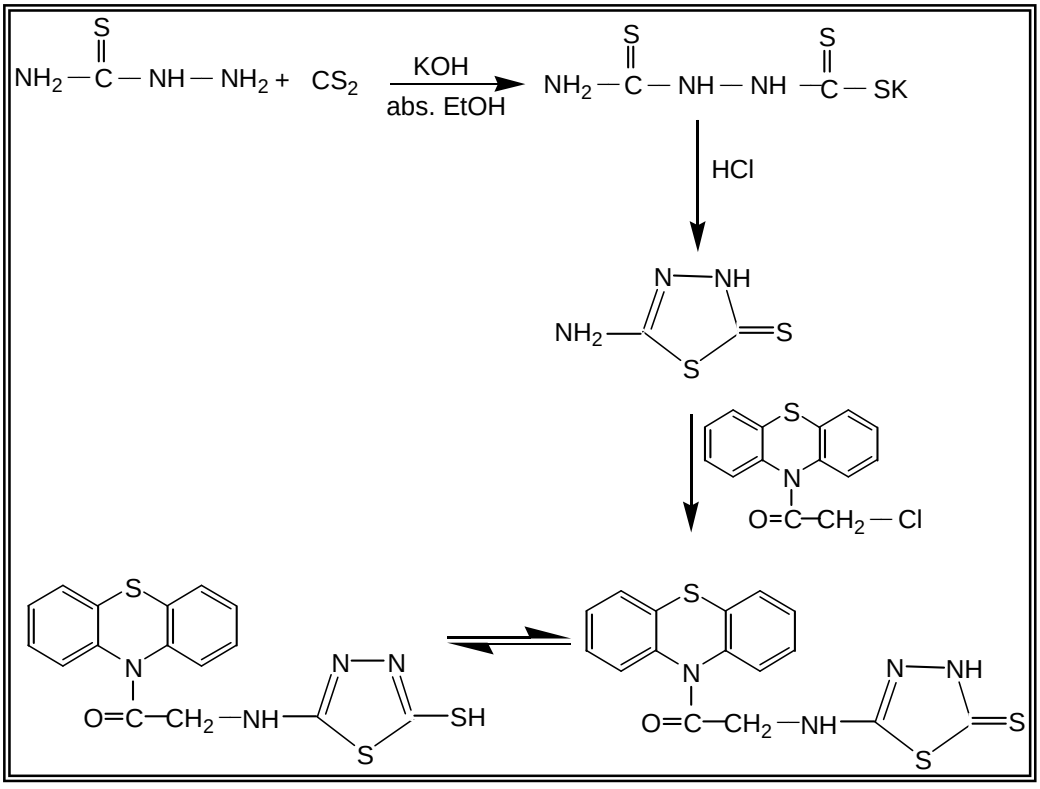



**Figure (23): infrared spectrum of compound (23).**

## 3-17 ***$N_{10}$-(acetyl-5-amino-[3H]-1, 3, 4-thiadiazol-2-thione) phenothiazine (24-25).***

Compounds (24 and 25) were synthesized according to reaction scheme (2).

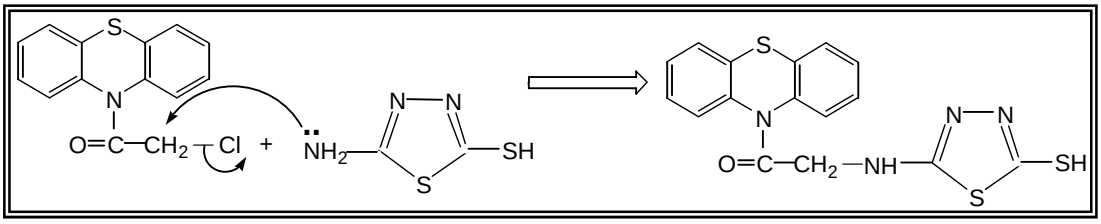



Scheme (2)

The reaction of thiosemicarbazide with carbon disulfide in presence potassium hydroxide under refluxing condition then neutralization by HCl gives [5-amino-[3H]-1, 2, 3- thiadiazole-2-thione] (24). The purity and structure of thiadiazole derivative (24) was confirmed by FTIR. The FTIR spectrum showed bands of compound (24) at 3394.5 $cm^{-1}$ and 3274.9 $cm^{-1}$ which assigned to asymmetric and symmetric stretching bands of $NH_2$ and

NH groups, 1596.9 $cm^{-1}$ for (C=N), 1326.9 $cm^{-1}$ for (C=S), and 742.5$cm^{-1}$ for (C-S-C) as shown in fig 24.

When compound (15) was refluxed with $N_{10}$-(chloro acetyl) phenothiazine (2), $N_{10}$-(acetyl-5-amino-[3H]-1, 2, 3 - thiadiazole - 2- thione) phenothiazine (25) was formed. It is logical to assume that the alkylation step involves $S_N2$ mechanism as outline below:-




The FTIR spectrum showed the purity and the bands of compound (25), at the region 3296.1 $cm^{-1}$ which assigned to (N-H), 3107 $cm^{-1}$ for (C-H) aromatic, at 1664.4 $cm^{-1}$ for (C=O) at 1629.7 $cm^{-1}$ for (C=N) , and at 1579.6 $cm^{-1}$ for (C=C) as shown in fig 25.

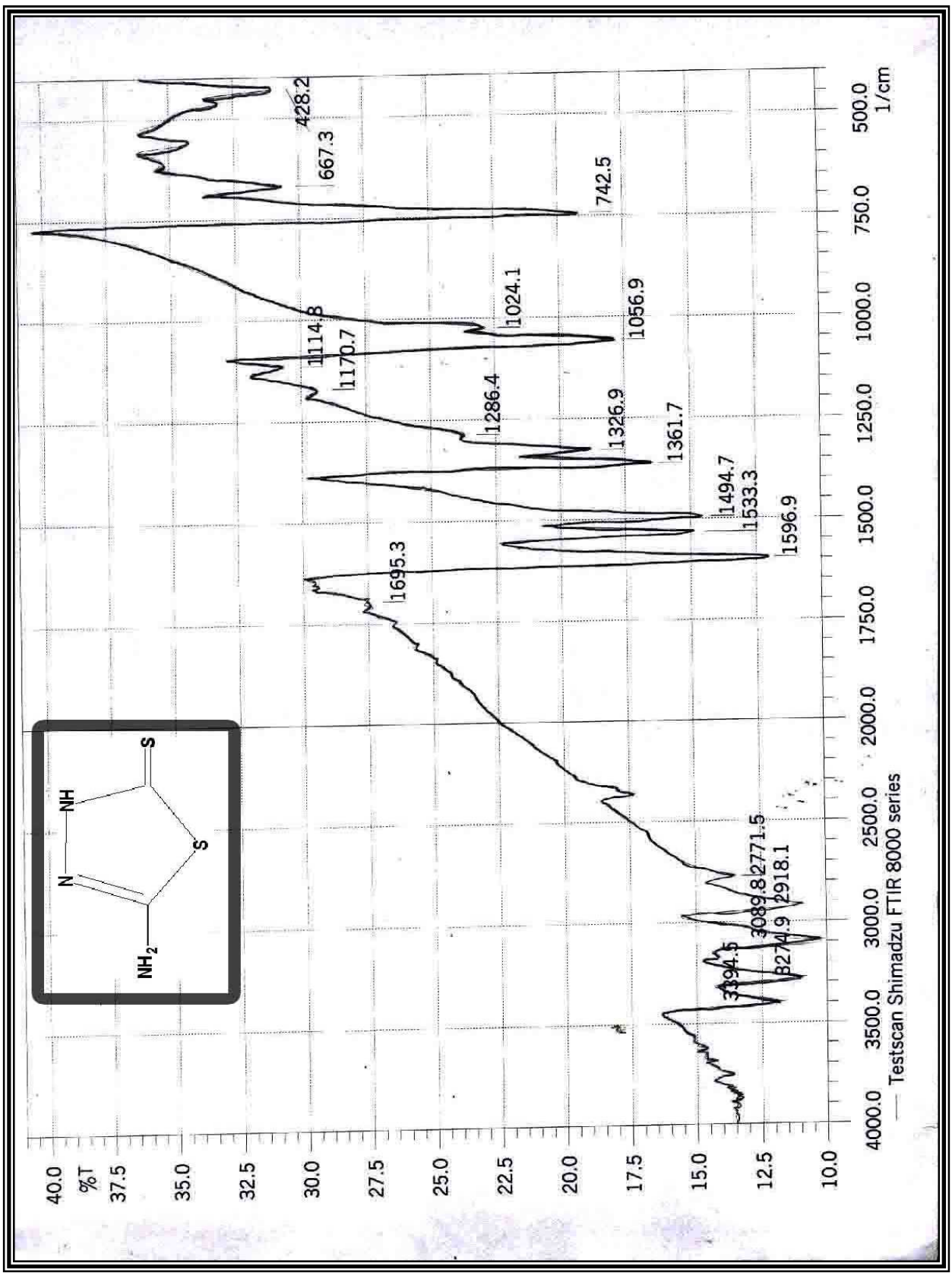



***Figure (24): infrared spectrum of compound (24).***

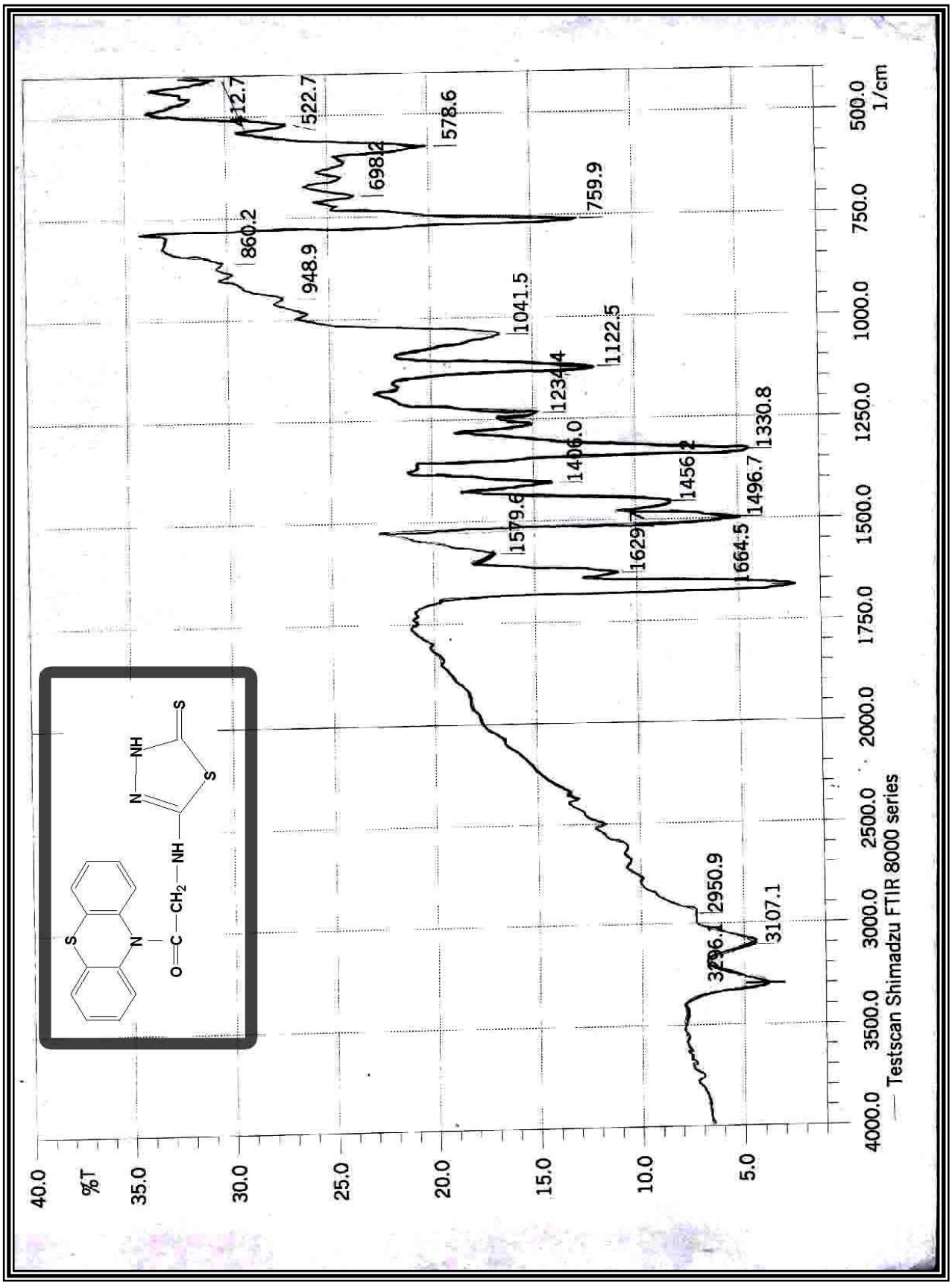



***Figure (25): infrared spectrum of compound (25).***

# Apparatuses

**1-** Melting points were recorded using a Gallen Kamp melting point apparatus and are uncorrected.

**2-** The FTIR spectra in the range (4000-400) $cm^{-1}$ were recorded using KBr disc on FTIR 8300 ***Shimadzu*** spectrophotometer (Japan).

**3-** Thin layer chromatography (T.L.C.) was performed on aluminum sheets precoated with silica-gel F254. Spots were detected with iodine vapour. TLC was used for checking the purity of compounds.

# REFERENCES


1- A. Bernthsen, *Burn- Chem. Ges*, **16**, 2896(1883).

2- R. B. Miller & C. F. Steven, *J. Analytical Sciences*, **19**, 653- 657 (2003).

3- B. Kanakapara & J. Manjunathswmy, *Turk. J. Chem.*, **26**, 551-558 (2002).

4- N. Padmarajaiah, D. Nandipura & M. Netkal, *J. analytical sciences*, **16**, 1127-1131 (2002).

5- H.M. Jones & L.S. Pilowsky, *British Journal of Psychiatry*, **181**, 271-275 (2002).

6- D.G. Friend & J.F. Cumins,J. Am. Med. Assoc., **153,** 481(1953).

7- The Columbic Encyclopidia, *Sixth Ed*. (2001).

8- Wen Fatal, *Aeta pharmacol sin*., **24**, 1001-1005(2003).
http: // www. China phar. com.

9- M.I. Andres, G.Repotto, P. Sanz, & M. Repotto, *Vet. Hum. Toxicol.*, **41**,273(1999).

10- G. Erenberg, *Adv. Neurol*., **58**, 241(1992).

11- F. Lechin, B. Vander Dijs, F. Gomez, E. Costa, & L. Arocha, *Biol. Psychiatry*, **17**, 103 (1982).

12- K. Singer & M. Wong, *Postgrad. Med. J*. **46**, 633 (1990).

13- C.M.Wisch, P.C. Edward, R .Y. Lai, M .Roth & C.R. Harrington, *Proc. Natl. Acad. Sci*., **93**, 11213(1996).

14- C.M. Korth, B.C. May, F.E, Cohen & S.B. Prusiner, *Pro. Nati*, *Acad. Sci*., **98**, 9836 (2001).

15- L. Amaral & J.E. kristiansen, *Int. J. Antimicrob. Agents*, 18,411(2001).

16- S.B. Prusiner, *N. Engl. J. Med*, **344**, 1516(2001).

17- http:// en. Wikipedia. Org / wike/ Phonothiazine.

18- K. Venkataraman, *The Chemistry of Synthetic Dyes*, **2**, 791. Academic Press, Inc., New York (1952).

# REFERENCES


19- R.M. Achson, *An Introduction to the Chemistry Heterocyclic Compounds*, **Third addition** (1976).

20- A.M. Pallerson & L.T. Capell: *The ring Index. Am. Chem. Soc.*, **89**, 252(1940).

21- V. Meyer & P.Jacobsen: *Lehrbuch der Organischen chemi*, **vol.2**, Part 3, P. 1490. Veit and Co., Leipzig (1920).

22- IUPAC Rule of Organic Nomenclature, *Bull. Sco. Chemistry France*, 1258(1958).

23- J. P. Malriece & B. Pullman, *Therot. Chemi. Acta*, **2**,293(1964).

24- E. Knoevenagel: *J. Parkt. Chem.*, **89**, 2(1944).

25- N. Sewald, *Organization*, **28**, 337-345(1998).

26- F. Kehrmann & J.H. Dardel, *Ber*., **55B**,2346(1922).

27- H. Gilman, & D. Shirley, *J. Am. Soc.*, **66**, 888(1944).

28- N.L. Smith, *J.Org. Chem.*, **15**, 1125 (1950).

29- R.R.Gupta, G. S. kalwania & M. kumar, *J. Heterocyclic Chem.*, **21**,893 (1984).

30- VC Okoro, *Indian Journal of Chemistry*, **29B**, 117 -120(1990).

31- H. kano & M. Fajimoto, *pharm. Bull (Tokyo)*, **5**, 393(1957).

32- M. Farjimoto, *Bull Chem. Soc. Japan*, **32**, 296 (1959).

33- J.B. Wright, E.H. Lwcoln, R.V. Heinzlman, & J.H.Hunter, *J. Am. Chem. Soc.*, **72**, 3536 (1950).

34- J.G. Michels, & E.D.Amstutz, *J. Am. Chem. Soc.*, **72**, 888(1950).

35- G. Pappalardo & G. Seapini, *Bol. Sci. Fae. Chemi. Ind. Bologa*, **21**, 143 (1963), Chem. Abst., 59, 13972e (1963).

36- E. Anodiff & M. Hausman. , *J.Organic Chem.*, **29**, 2453 (1964).

37- B.F. Hutford & J. F. Bunnett, *J. Am. Chem. Soc.*, **28**, 2021 (1958).

38- J.I. Cadogan., R.K. Moskie & M.J.Todel, *Chem. Common*, 491 (1966).

# REFERENCES


39- Al. Spasov & M. Zhchev, *Ball. Inst. Chemi. Acod.* Bulogave sci., **2**, 67 (1953), Chem. Abst., **49**, 54492e (1955).

40- M.L. Tomlinson, *J. Chem. Soc.*, **11**, 1107 (1946).

41- **[a],** C. Culvenor, W.Daries & N.S.Heath, *J. Chem. Soc.*, **27**, 278 (1949).

41- **[b],** K. Yahya Al-Baiati, *M.Sc. Thesis*, University Of Baghadad, College of Science (2002).

42- G. Cauqnil & A. Gasserd, *Compt. Tend.* , **225**, 578 (1947).

43- Y. Yang, Y. Peng, F. Zhao & B. Zeug, *Sensors*, **3**, 594-533 (2003).

44- A.R. Katritzky , H. Hai- ying , Q. Long , C. Xilin , L. Julian & A. L. Wilcox, *Arkivoc* , V**ol. 1**, part 3 (2000).

45- P. Charpentier, *Compt. Tend.*, **255**, 306 (1947).

46- P.J. khatari, V. kishore, V.I. Stenberg, & S.S. Parmer, *J. Heterocyclic Chem.*, **15**, 1101 (1978).

47- R. Dahlbom: P. Swedish **192**, 843; *Chem. Abstracts*, **45**,5143 (1951).

48- A. Bernthsen, *Ann.*, **230**, 73-210 (1885).

49- A.M. Dave, K.N. Bhatt, N.k. Undvia & P.B. Trivedi, *J.Indian Chem. Soc.*, Vol. LXV, PP. 365-366 (1988).

50- R. DahlBom, & T. Eestrand, *Acta Chem. Scand.*, **5**, 102 (1951).

51- T. Eestrand: Swedish Palent **127**, 566; *Chem. Abstract* **45**, 1886(1951).

52- G.S. Gadaginamath, S.A. Patil, & A.S. Shydligeri, *Ind. J.*, **35(B)**, 681-684 (1996).

53- P.S. Fernandes, A.M. Raiji, K. Rane & A.G. Yoshi, *J. Ind .Chem. Soc.*, **LIII**, 676-679 (1976).

54- K.S. Varma, & P.S. Fernandos, *J. Ind. Chem. Soc.*, **LXI,** 234- 236 (1989).

55- G. Kazimierz, M. Wieslaw, S. Piotr, & J. Agata, *Cellular& Molecular Biology Letters*, **vo1. 8**, 927- 942 (2003).

56- H.K. Shukla, N.A. Langalla, N.C. Desai & K.A. Thaker, *J. Indian Chem. Soc.*, **59**,1101 (1982).

57- H.K. Shukla, N.A. Langalla, & K.A. Thaker, *J. Inst. Chemists (Indian)*, **54**, 130(1982).

58- G. Gardner, J. R. Sanborn, and J. R. Goss, *Weed Science*, **35**, 763-769 (1987).

59- J.S. Thomas, S. Willem, P. G. John & B. Martin, *Toxicological Sciences*, 54**,** 121-127 (2000).

60- R. Lakan & B. Ternai, "*Advances in Heterocyclic Chemistry*", **vo1. 17**, A.R. katritsky & A.J. Boulton, eds, Academic press, New York, p182 (1974).

61- T.V. Saraswathi & V.R. Srnivasan, *Tetrahedron*, **33**, 1043 (1977).

62- A.W. Hofmann, *Ber.*, **12** , 1126 (1879); **13,** 8(1880).

63- A.R. Hantzsch & J.H. Weber, Ber., **20** , 3118 (1887); C.A.12, 938 (1888).

64- J. Green, *J. Soc. Chem. Ind.*, **7**, 179 (1888).

65- M.T. Bogert & M. Chertcoff, *J. Am. Chem. Soc.*, **44**, 826 (1922).

66- W.H. Mills & J.L. Smith, *J. Chem. Soc.*, **455**(1922); C.A. 17, 1024.

67- O. Uchikawa & T. Aono, *J. Het. Chem.*, **31**, 1545(1994).

68- A.R. katritzky, J. Chen. & Z.J. Yang, *J. Org. Chem.*, **60**, 5638 (1995).

69- J.V. Metzger, "*Thiazole and its Derivatives*", John Wiley and Sons, New York, pp. 395-399(1979).

70- R.R. Williams, *J. Am. Chem. Soc.*, **57**, 224, 53 (1935).

71- R. Breslow, *J. Am. Chem. Soc.*, **80**, 3719 (1958).

72- R.J. Fosbinder & L.W. Walter, *J. Am. Chem. Soc.*, **61**, 2032(1939).

73- M.F. Ahmad, M.D. Kamal & O.A. abdou, *Tetrahedron*, **53**, 17461-17468 (1997).

74- A. Dondoni & M.C. Scherrmann, *J. Org. Chem.*, **59**, 6404(1994).

75- C.K. Lau, C. Dufresne & A.W. Fodhutchinson, *Bio organic and Medical chem.Letters*, **5**, 1615 (1995).

76- Sulphur, Selenium and Tellurium,( *Specialist Periodical Reports*), The chemical Society, Landon (a) **Vol. l**, 1970; (b) **Vol. 2**; 1973; (c)**Vol. 3**, 1975.

77- S.D. Dimball, J.T. Hunt, F.Y. Lee, & K.R. Webster, *J. Med. Chem.*,**45**, 3905-3927 (2002).

78- S.C. Debnath & D.K. Basu, *Journal of Applied Polymer science*, **52**, 597 (1994).

79- A.H. Blalt, A.C, Cope & C. Niemann in "*Organic Reaction*", John Wiley and Sons, New York, **6**, 367 (1951).

80- A. Hantzsch, Ann., **1**, 249 (1888).

81- R.P. kurkjy & E.V. Brown, *J. Am. Chem. Soc.*, **74**, 5778(1952).

82- R.M. Dodson, *J. Am. Soc.*, **67**, 2242 (1945).

83- G.Y. Sarkis & S. Al-Azawe, *J. Chem. Eng. Data*, **18**, 99 (1979).

84- A.H. Cook, I. Heiborn & A.L. Levy, *J. Chem. Soc.*, **5**, 1594 (1947).

85- G. Asato, *J. Org. Chem.*, **33**, 2544 (1998).

86- S. Gabriel, *Ber.*, **43**, 134, 1283 (1910).

87- R. Hantzsch & D. Arlt, *Synthesis*, 675, (1975).

88- V.S. Sundara & R.B. Mitra, *Journal of Cleaner Production*, **9**, 65-67 (2001).

89- G. Vernin & J. Metzger, *Bull. Soc. Chim. France.*, 2498 (1968).

90- J.T. Gregory & R.A. Mathes, *J. Am. Chem. Soc.*, **47**, 1917, 3868(1952).

91- J. Tcherniac, *J. Chem. Soc.*, **115**, 1071, (1991).

92- A. Bonzom & J. Metzger, *Bull. Soc. Chim. France*, **11**, 2582 (1963).

93- T.G. Levi, *Gazz. Chim. Ital.*, **61**, 719 (1931).

94- S.D. Barton & W.D. Ollis, "*Comprehensive Organic Chemistry*", **vo1. 4**, (1979).

95- P.N. Preston, "*Condensed imidazoles"*, **vo1. 46**, (1986).

96- B. Radzisewski, *Ber*., **15**, 1493 (1882).

97- M.R. Grmmett, *Adv. Heterocycl. Chem.*, **12**, 104(1970).

98- G. Bredereck, R. Gampper, H.G. Schuh, & G. Theilig, *Angew. Chem.*, **71**, 753 (1959); and in "*Newer Methods of Preparative Organic Chemistry*", ed. W. Forest, Academic press, New York, **vol. 3**, P.241 (1964).

99- B. Steiner & J. Gajdos, *J. org .Chem. Soc.*, **1**, 30 (1997).

100- R.C. Elder field, "*Heterocyclic compounds*", John Wiley and Sons, New York (1957).

101- H.T. Clark, J.R. Johnson & Sir R. Robinson, "Chemistry of penicillin", Princeton University Press, Princeton, N.G. (1949).

102- P.C. Unagst, D.T. Connor, W.A. Cetenko, R.J. Sorenson , C.R.kostlan, J.C. Sircar, C.D. Wright, D.J. Schrier & R.D. Dyer, *J. Med. Chem.*, **77**, 322(1994).

103- R. Maeda, Y. Takehare & Y. Yoshida, *Japanese Pat*, **71**, 34, 422 (1971); *Chem. Abstr.*, **76**, 3838(1972).

104- k. Brown, JF. Cavella, D. Green & AH. Wilson, Nature *(London)*, **219**, 164 (1968).

105- E. Marehetti, G. Mattalia & V.Rosnati, *J. Med. Chem.*, **11**, 1092 (1968).

106- I.J. Turchi & M.S. Sewar, *Chem. Rev.*, **75**, 389 (1975).

107- L.K. Kuibcova, K. Waisser, J. Kunes &Z. Svbada, *Molecules*, **5,** 714-726 (2000).

108- C.O. Wilson, O. Gisvoid, & R.F. Doerge, "Text book of Medicinal and pharmaceutical Chemistry", Pitman, London, (1966).

109- M. Lora-Tamayo, R. Madrorero & H. Leipprand, *Chem. Ber.*, **77**, 2230 (1964).

110- M.P. Doyle, G.D. Spoelhof & M.A. Zaleta, *J. Heterocyclic Chem.*, **12**, 263 (1975).

111- I.J. Turchi, *lnd. Eng. Chem.*, **20**, 32 (1981).

112- K.S. Kim, S.D. Kim ball, R.N. Misra& D.B. Vawlins, *J. Med. Chem.*, 45(18), 3905-3927 (2002).

113- R.H. Good & G. Jones, *J. Chem. Soc.*, 1938 (1970).

114- H. Et-Tamaty, M. Abdel-Fattah &M. Ibrahim, *Indian Journal of Chemistry*, **35B**, 1067- 1072 (1996).

115- T. Dyole, *J. Org. Chem.*, **45**, 3657 (1980).

116- T. lbata and R. Sato, *Bull. Chem. Soc. Japan*, 52, 3597 (1979).

117- S.H. Mashraqui & P.M. Keehn, *J. Am. Chem. Soc.*, **104**, 4461 (1982).

118- H.H. Wasserman & T.J.Lu, *Tetrahedron Lett.*, **23**, 3831 (1982).

119- E.A. Bakhite, O.S. Mohamed & S.M. Radwan, *Bull. Korean Chem. Soc.*, **23(12),** 1715(2002).

120- M.Y. Chu-Moyer & R.Berger, *J. Org. Chem.*, **60**, 5721 (1995).

121- J. Sandstr, *Ann.*, **326**,147(1886).

122- H. Emilsom & A. Markovic, *J. Hetero. Chem.*, **26**, 81-107 (1989).

123- R.C. Elderfield, "*Heterocyclic Compounds*", Academic Press, London, **Ch.7**, PP. 587(1962).

124- A. Freund & R. Meinecke, *Ber.*, **29**,2511(1896).

125- H. Pulvermacher, *Ber.*, **27**,613(1894).

126- E.V. Tao & C.F. Christie, *Org. Prep. Proced. Int.*, **7**, 179 (1975).

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

128- J. Guha, *J. Am. Soc.*, **44**, 1510 (1922).

129- D.W. Rangnekar, V.R. Kareker & G.S. Shankarling, *J. Hetero. Chem.*, **36**, 95 (1999).

# REFERENCES


130- A. R. Katritzky, "*Hand Book of Heterocyclic Chemistry*", (1985).

131- B.S. Vashi, D.S. Metha & V.H. Shah, *Ind. J. Chem.*, **35B.**, 15(1989).

132- V.N. Sonar, K.R. Sekhar & M.G. Purohit, *Ind. J. Chem.*, **28B**., 626-630 (1996).

133- F. Luciano, L. Andera & R. Carla, *J. Hetero. Chem.*, 37, 63-70 (2000).

134- T. Saucius, Z.Cojocaru & U. Zvoristean, *Rev. Med. Chem.*, **86**, 313 (1982).

135- H. Hugen & H. Fleig, *Ger Offen.*, **2**, 329 (653, C.A. 86, 189963F (1977).

136- H. Zengoji & H. Hitokot, *Nippon Kagaku, Ryohgakukai Zasshi*, **19**, 192 (1972).

137- F. Russo & M. Santagati, *Farmaco. Educ. Sci.*, **41**, 3(1) (1976).

138- P. Thimo & C.F. Frieder, *Ger Offen.*, **2**, 818-830 (1979).

139- A. Abu Eltiman, *M.Sc. Thesis*, University Of Baghadad, College of Pharmacy (1987).

140- O.R. Gantum & P.J. Carlson, *Molecules*, **6**, 969078 (2001).

141- M.E. Theocliton & G.J. Delact, *J. Chin. Chem.*, **47**, 535-539 (2000).

142- J.J. Hamdi, Ph.D. Thesis, *Al-Mustansiria University* (1999).

143- G.R. Rama & K.R. Jahan, *J. Ind. Chem.*, **B (35)**, 205-210 (2003).

144- A.M. Dave, K.N. Bhatt & N.K. Undaria, *J. Ind. Chem. Soc.*, **66**, 246-247 (1989).

145- Y.K. Vaghasiya, R. Nari, M. Soni, S. Baluja & S. Chanda, *J. Serb. Chem. Soc.*, **62(12)**, 991-998 (2004).

146- H. Chen & Y. Han, *J. Chin. Chem. Soc.*, **49**, 363-369 (2002).

147- A. Alexander, A. Bush & V. Babaev, *Molecules*, **8**, 460-466 (2003).

148- H. Wahe, P.F. Asobo, R.A. Cherkasov & D. Doepp, *Arkivoc*, **1**, 130-137 (2004).

149- A.Kh. Al-Abodi, Ms. C. Thesis, *Al-Mustansiria University* (2000).

# REFERENCES


150- B. Miller, *"Advanced Organic Chemistry"*, **first Edition**, Viacom Company (1998).

151- M. Sliverstien & X. Webster, *"Spectrometric Identification of Organic Compounds*", **Sixth Edition**, (1999).

152- H. Williams & I. Fleming, *"Spectroscopic Method In Organic Chemistry"*, **Second Edition**, 1973.

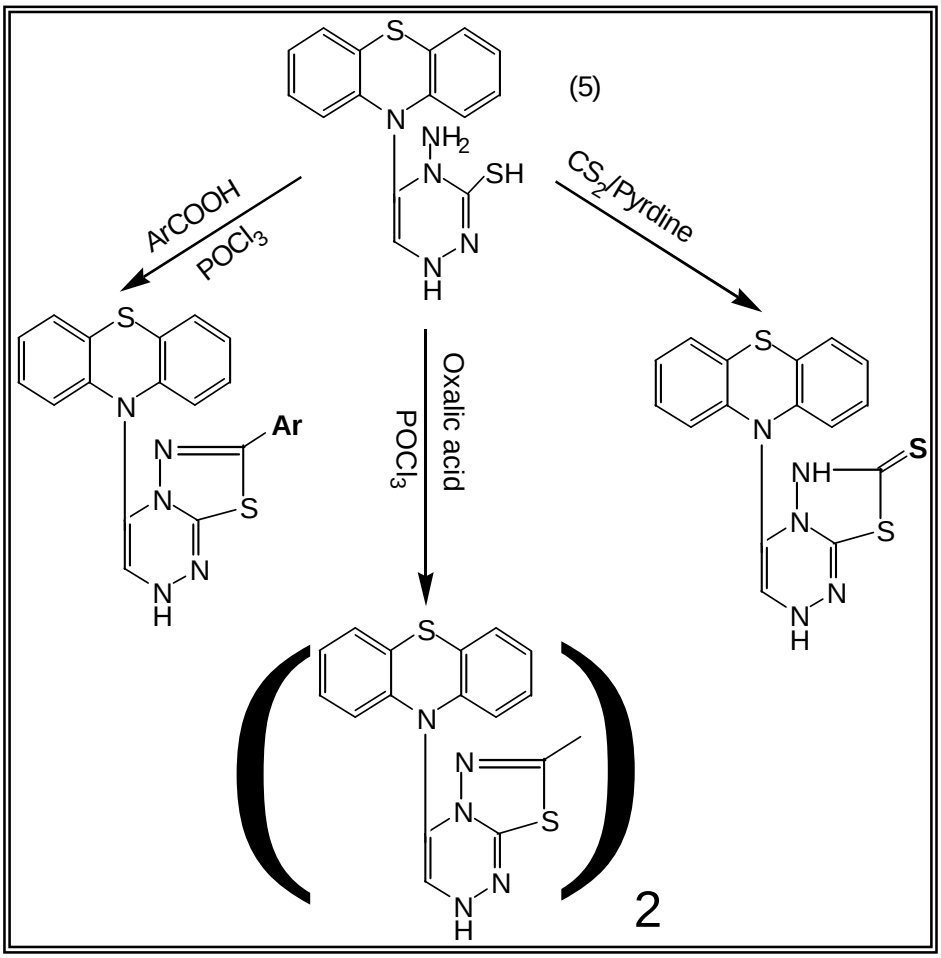
153- E.H. El-Tamany, E.M.Salem, R.N. Metwaily & A.H. Soghier, *Egypt J.Chem.*, **40(5)**, 339-351 (1997).

154- H.L.Lui, Z. Lui & T. Anthosen, *Molecules*, **5**, 1055-1061 (2000).

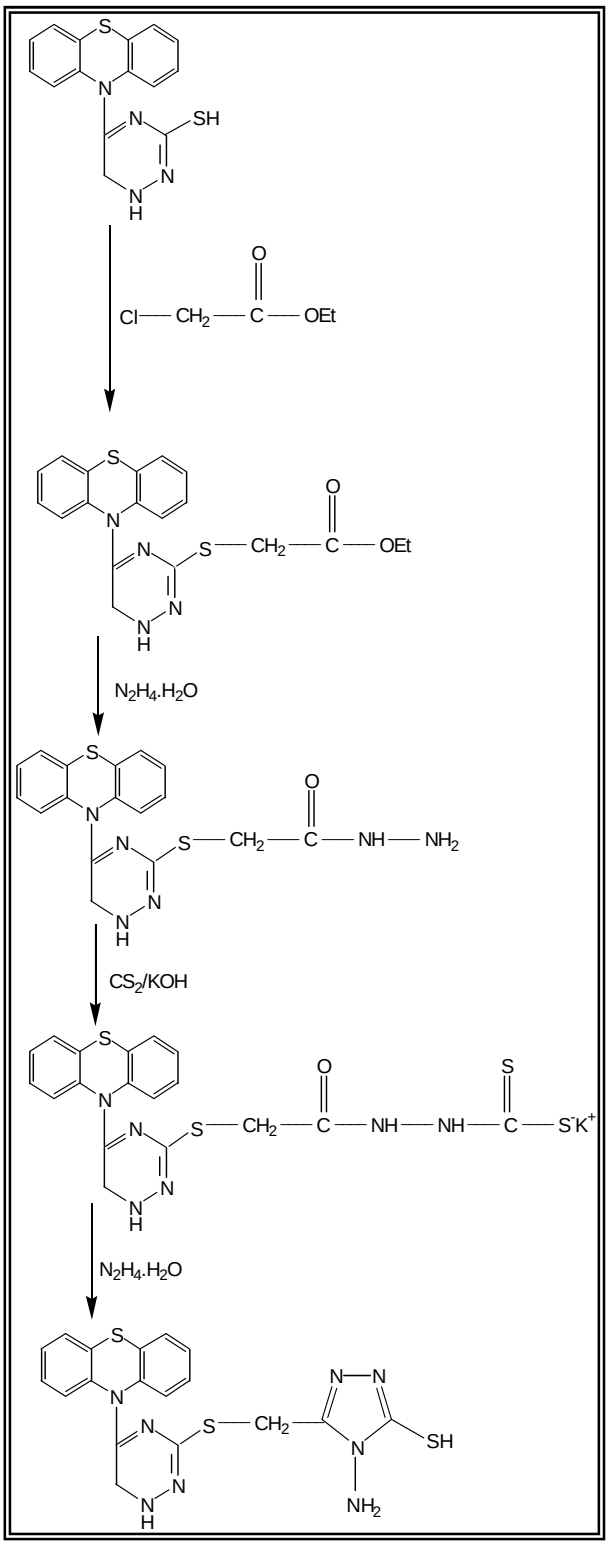
155- H.R. Maradiya, *J. Serb. Chem. Soc.*, **67(11)**, 709-718 (2002).

# Suggestion for further work

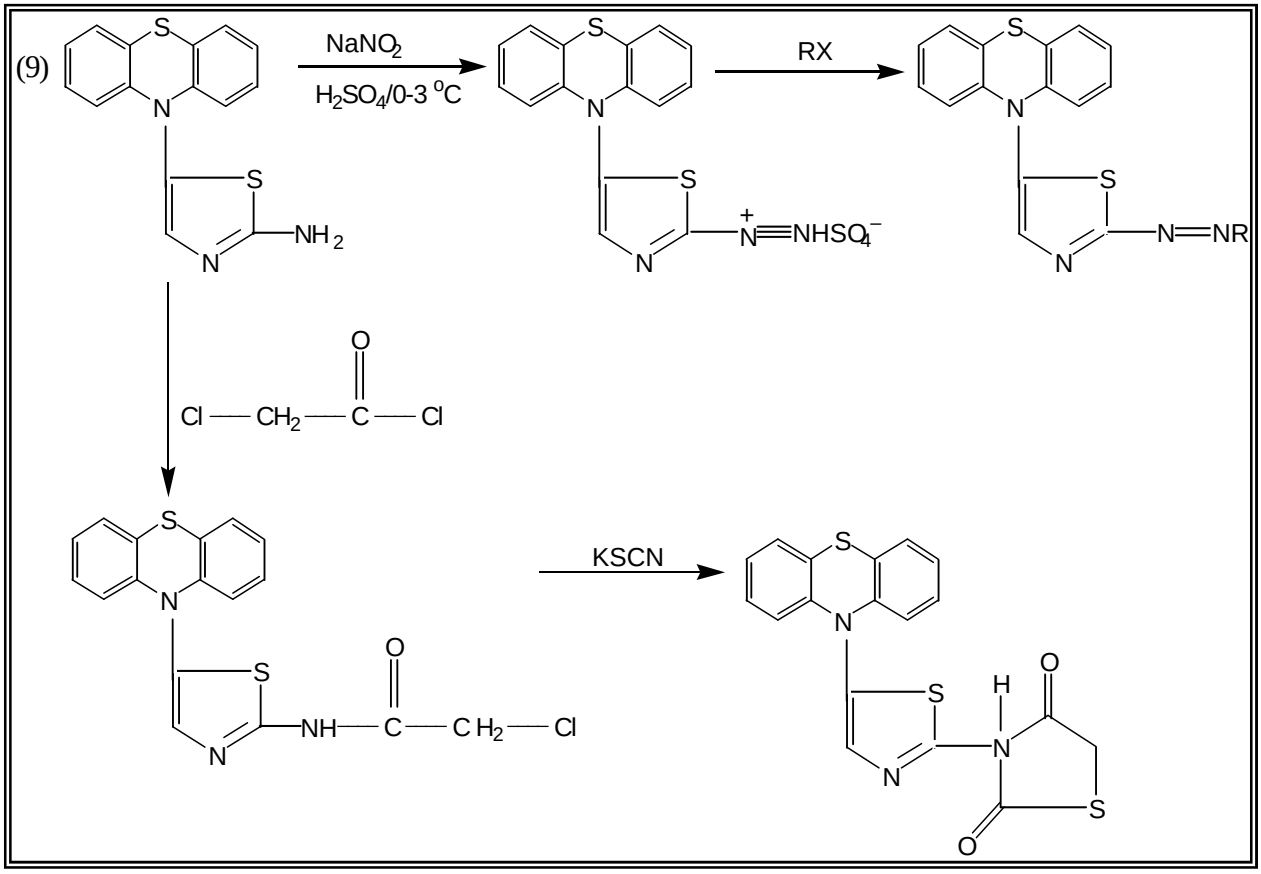
**1-** Cyclization between the two functional groups (SH and $NH_2$) of compound (5) by using different cyclization reagents to form new heterocyclic ring.



**2-** Formation of triazole derivative by acylation of compound (7) [153].



**3-** Alkylation [154] of compound (9) and formation new heterocyclic ring [155].



# *Aim of the work*

Phenothiazine is known to possess many pharmacological properties, so the aim of the present work was to synthesize heterocyclic rings known to possess pharmacological properties, such as 1,2,4-Triazine, Thiazole, Imidazole, Oxazoline, and 1,3,4-Thiadiazole ,rings attached to $N_{10}$-phenothiazine, hoping they may increase the biological activity of phenothiazine.

Schiff bases also known to contribute in pharmacological activities, so there different types of Schiff bases were synthesized.

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

# تحضير مشتقات حلقية غير متجانسة معوضة

# على ذرة النتروجين للفينوثايزين

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

**من قبل**
**زهراء صباح سعيد الطائي**
**بكالوريوس ٢٠٠٢ (جامعة النهرين)**

**تموز ٢٠٠٥** **جمادى الآخر ١٤٢٦**

بسم الله الرحمن الرحيم

# ويسئلونك عن الروح قل الروح من امر ربي * وما أوتيتم من العلم الأ قليلا

صدق الله العلي العظيم

سورة الأسراء (الآية٨٥)

# الأهداء

اهدي ثمرة جهدي المتواضع هذا

الى سيد المرسلين محمد وآل بيته الطاهرين

الى الروح التي ساندتني في مسيرة العلم

والدي

الى الشمعة التي انارت دربي

والدتي

الى رياحين حياتي

اخي و اخواتي

الى كل من ساندي وساعدني

زميلاتي

زهراء

# الخلاصة

الهدف من هذا البحث هو تحضير مركبات جديدة مشتقة معوضة بذرة نيتروجين الفينوثايازين، حيث تم تحضير الفينوثايازين(١) عن طريق انصهارثنائي فنيل امين مع الكبريت بوجود الايودين كعامل مساعد ولمدة خمس ساعات.

١- تفاعل الفينوثازين مع كلورواسيتايل كلورايد يعطي $N_{10}$-(كلورو اسيتايل) فينوثايازين، والذي عند معاملته مع الهايدرازين المائي يعطي $N_{10}$-(اسيتايل فينوثايازين) هايدرازين (٣). وبتفاعل مشتقات الهايدرازين(٣) مع ثنائي الكبريت كاربون تم تحضير بوتاسيوم $N_{10}$– (اسيتايل فينوثايازين) ثنائي ثايوكابازيت (٤)، ومن ثم يتفاعل مع الهايدرازين المائي بطريقة التصعيد العكسي ليعطي $N_{10}$- (امينو-٣-ميركبتو -[1H] -٤،٢،١ –ترايزين-٥-ايل) فينوثايازين (٥).

٢- يحضر $N_{10}$– (٣-ميركبتو-[6H,1H]-4,2,1- ترايزين-٥-ايل) فينوثايازين (7) ,من تفاعل الفينوثايازين مع الثايوسميكاربازايد ليعطي $N_{10}$-(اسيتايل فينوثايازين) الثايوسميكاربازايد (٦)، حيث يعاني المركب (٦) من تداخل حلقي ضمني عند تصعيده مع محيط قاعدي (2N NaOH ) لمدة ثلاث ساعات ليعطي مشتقات الترايزين (٧).

٣- معاملة الفينوثايازين مع الثايو يوريا يعطي $N_{10}$-(اسيتايل فينوثايازين) ثايو يوريا (8) , والذي يستعمل لتحضير نوعين من المشتقات الحلقية متجانسة:

أ- $N_{10}$-(٢-امينو-[5H] -٣،١- ثايول-٥- ايل) فينوثايازين (٩) يحضر من التداخل الحلقي الضمني للمركب (٨) عند تصعيده مع محيط حامضي ( $H_2SO_4$) لمدة يوم كامل.

ب- $N_{10}$-(٢- ميركبتو-[5H] -٣،١- اميدازول-٤-ايل) فينوثايازين (١٠) يحضر من التداخل الحلقي الداخلي للمركب (٨) عند تصعيده مع محيط قاعدي (NaOH ) لمدة ثلاث ساعات.

٤- للحصول على $N_{10}$- [(٢- ميركبتو-[5H]-٣،١- اميدازول-٤-ايل) هايدرازين] فينوثايازين (١١) بتفاعل المركب (١٠) مع الهايدرازين المائي .

٥- قواعد شيف:{ $N_{10}$-[(٢- ميركبتو-[5H]-٣،١-اميدازول-٤-ايل)هايدرازون] فينوثايازين (١٢-١٤) تحضر من تفاعل المركب (١١) مع ألديهايداد اروماتية مختلفة.

٦- N[ $N_{10}$-(اسيتايل فينوثايازين) ] - ٤ - نايتروفينل هايدرازين (١٥) يحضرمن تفاعل $N_{10}$ -(كلورو اسيتايل) فينوثايازين مع ٤- نايتروفينل هايدرازين، والذي بعد ذلك يعامل مع فينل ايزو سيانيت ليعطي 4N[ $N_{10}$-(اسيتايل فينوثايازين) ] -1- فينل- بارا- نايترفينل سميكاربازايد (١٦).

٧- $N_{10}$-(٣-N- فنيل-p- برومو فينل -٢-هايدروكسي- ٤ – اوكزولين-٢-ايل) استيل فينوثايازين -٢N- نايترفينل هايدرازين (١٧) يحضر من التداخل الحلقي الخارجي للمركب (١٦) مع بارا- برومو فيناسيل برومايد.

٨- يحضر اريل امينو اسيتايل $N_{10}$ - فينوثايازين (١٨-٢٣) من تفاعل المركب (٣) مع امينات اروماتية مختلفة.

٩- المركب ٥-امينو-٢ -[5H] - ٤،٣،١- ثايازول-٢- ثايول (٢٤) قد حضر من تفاعل ثنائي الكبريت كاربون مع الثايوسيمكارباز ايد بوجود بوتاسيوم هايدروكساي د المذاب في الايثانول اللامائي لمدة ستة ساعات.

١٠- $N_{10}$-( اسيتايل-٥- امينو-٢ -[5H] -1، ٤،٣ - ثايازول-٢-ثايول) فينوثايازين (٢٥) يحضر من تفاعل المركب (٢) مع٥- امينو-٢ -[5H] - ٤،٣،١- ثايازول-٢- ثايول (٢٤) تحت ضروف التصعيد ولمدة يوم كامل.

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


# *Synthesis of Heterocyclic Derivatives of N- Substituted Phenothiazine*

*A thesis*
*Submitted to the College of Science*
*Al-Nahrain University*
*In partial fulfillment of Requirements*
*For the Degree of Master of Science in Chemistry*

***By***
***Zahara Sabah Al-Taie***
***B.Sc. (Al-Nahrain University 2002)***

***July 2005*** ***Jamadi Al-Aker 1426***

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

# تحضير مشتقات حلقية غير متجانسة معوضة

# على ذرة النتروجين للفينوثايزين

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

**من قبل**
**زهراء صباح سعيد الطائي**
**بكالوريوس ٢٠٠٢ (جامعة النهرين)**

**تموز ٢٠٠٥** **جمادى الآخر ١٤٢٦**