# BANGLADESH UNIVERSITY OF ENGINEERING AND TECHNOLOGY, DHAKA, BANGLADESH

# SYNTHESIS AND PHARMACOLOGICAL STUDIES OF MONO AND DITHIAZOLIDINE DERIVATIVES

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BY

Examination Roll - 9603105P
Registration No. 961805

ORGANIC RESEARCH LABORATORY
DEPARTMENT OF CHEMISTRY
BANGLADESH UNIVERSITY OF ENGINEERING AND TECHNOLOGY
DHAKA-1000, BANGLADESH

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# BANGLADESH UNIVERSITY OF ENGINEERING AND TECHNOLOGY, DHAKA, BANGLADESH
## DEPARTMENT OF CHEMISTRY

## THESIS ACCEPTANCE LETTER

We hereby recommend thesis entitled **"Synthesis and Pharmacological studies of mono and dithiazolidine derivatives"** presented by SYED AHSAN HABIB (Roll No. 9603105P, Reg. No. 961805, Session: 1995-96-97) to accept as partial fulfilment of the requirements for the degree of Master of Philosophy (M. Phil) in Chemistry, on the 20th November, 2002.

### Board of Examiners

1. **DR. MD. ABDUR RASHID**
   Professor
   Department of Chemistry,
   BUET, Dhaka-1000, Bangladesh.

   ---------- 20.11.02
   Supervisor

2. **DR. MD. RAFIQUE ULLAH**
   Professor and Head
   Department of Chemistry,
   BUET, Dhaka-1000, Bangladesh.

   ---------- 20/11/02
   Member

3. **DR. ENAMUL HUQ**
   Professor
   Department of Chemistry,
   BUET, Dhaka-1000, Bangladesh.

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4. **DR. A. K. M. MATIOR RAHMAN**
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   Department of Chemistry,
   BUET, Dhaka-1000, Bangladesh.

   ---------- Member 20/11/02

5. **DR. NAZMUL QAIS**
   Professor
   Department of Pharmacy
   University of Dhaka
   Dhaka-1000, Bangladesh.

   ----------
   Member (External)

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Author

# DECLARATION

I hereby declare that the whole of the work of this thesis has been carried out by myself in the Organic Research Laboratory of Department of Chemistry, under the supervision of Dr. Md. Abdur Rashid, Professor in Chemistry, Bangladesh University of Engineering and technology (BUET), Dhaka, during the Period starting from December 6, 1998 to October 10, 2002. I, further, declare that this work has not been submitted in part or full any where else for a degree or diploma. Any source of information in connection with this has been duly acknowledged and all quotation has been marked by quotation marks.

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**Registration No. 961805**
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**DEDICATED**

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# CHAPTER - 1

# INTRODUCTION

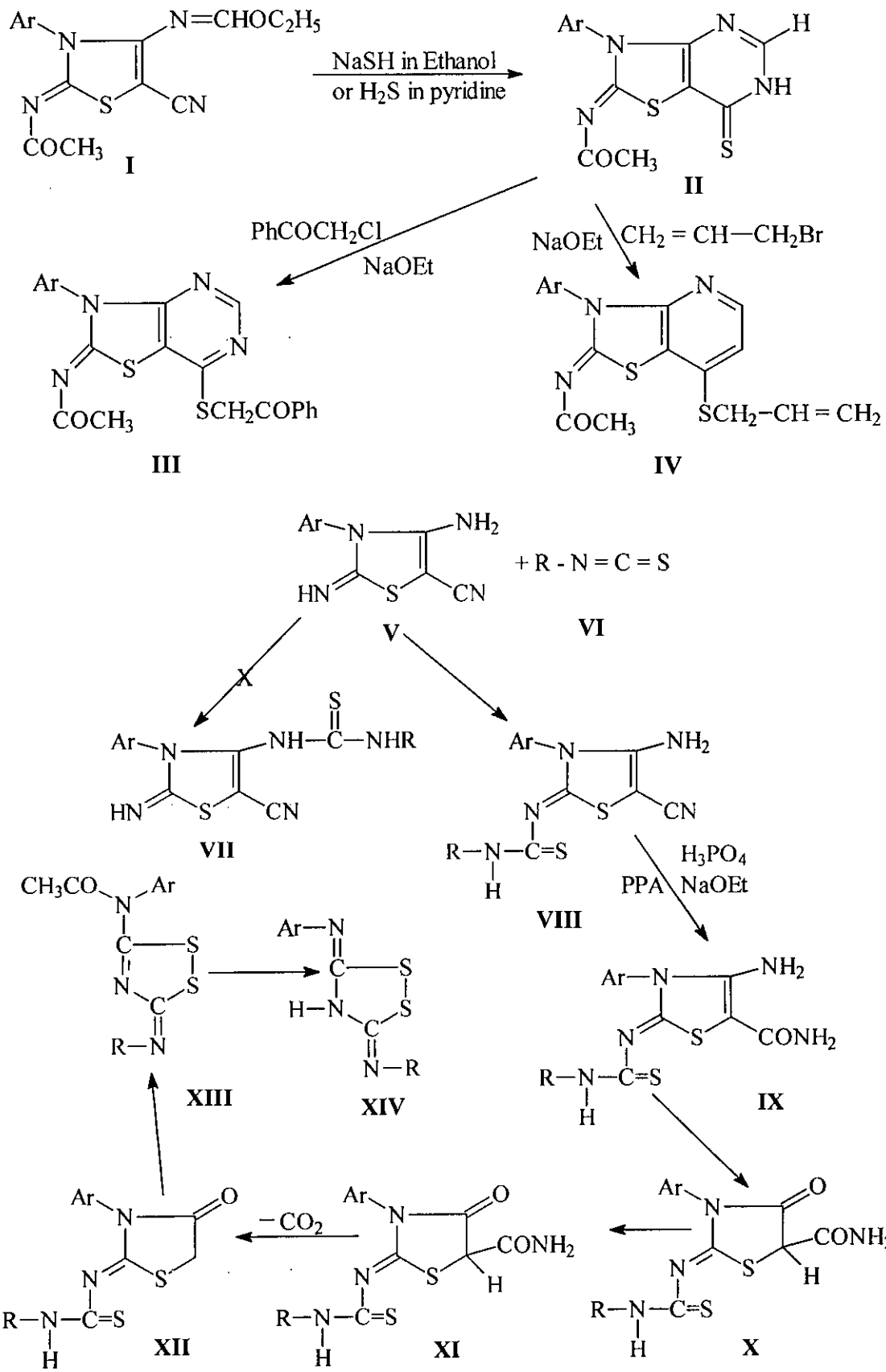
# INTRODUCTION

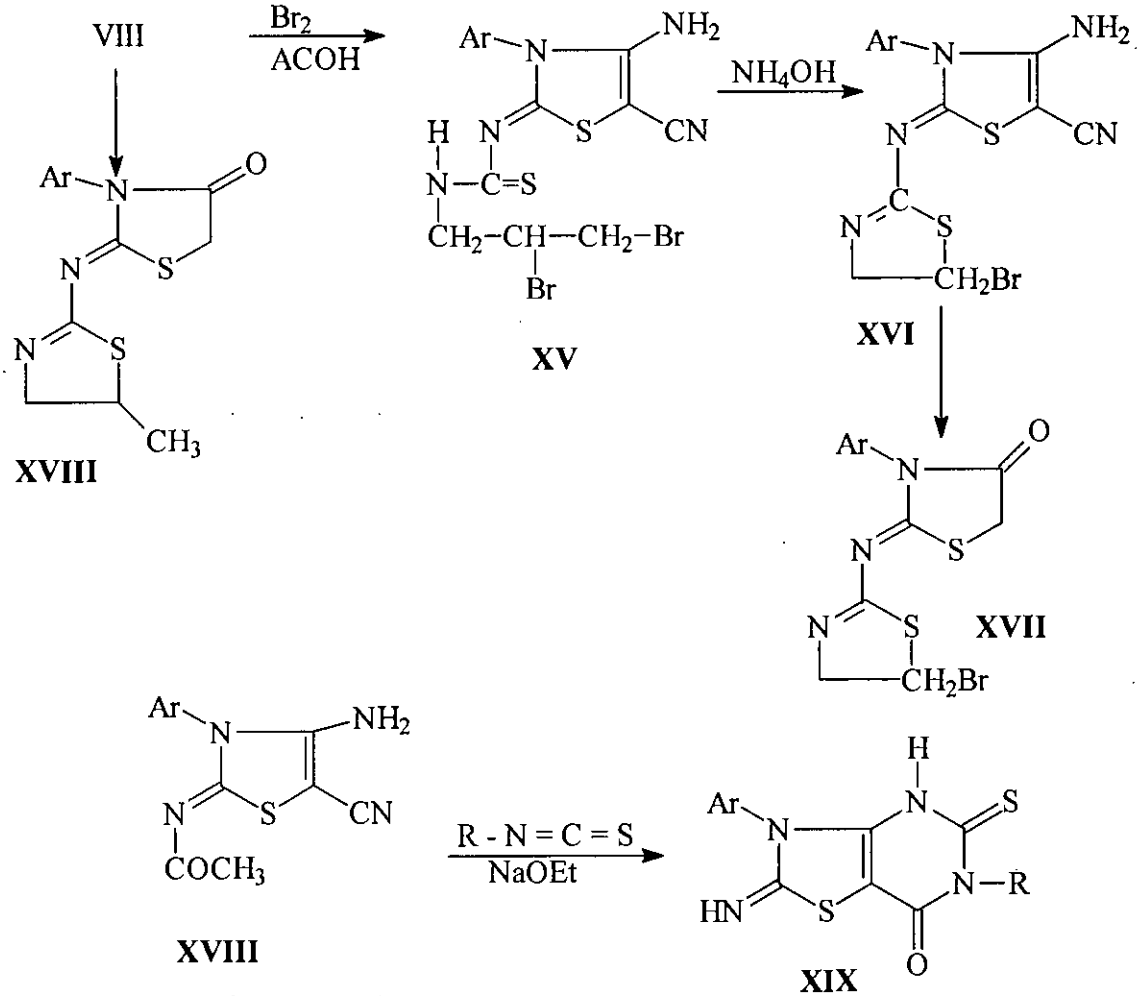
The chemical synthesis of carbon-containing molecules and carbon-hetero atom containing molecules have been a major field of scientific endeavor of over a century. Nonetheless, the subject is still far from fully developed. For example, of the almost infinite number and variety of carbon-hetero atomic structures which are capable of discrete existence, only a minute fraction have actually been prepared and studied. In addition, during the last century there has been a continuing and dramatic growth in the power of the science of constructing complex molecules which shows no sign of decreasing. The ability of chemists to synthesize compounds which were beyond reach in a preceding 10-20 year period is dramatically documented by the chemical literature of the last century.

The development of carbon-hetero atom chemistry has been strongly influenced by the need to affect such synthesis successfully and at the same time, it has been stimulated and sustained by advances in the field of synthesis. Carbon-hetero atom chemistry is an information rich field because of the multitude of known types of reactions as well as the number and diversity of possible compounds. This richness provides the chemical methodology, which makes possible the broad access to synthetic heterocyclic compounds.

Singh ***et al.***[1] reported the synthesis and pharmacological activities of 2-acetylimino-3-aryl-thiazolo [4, 5-d) pyrimidine-7-thiones, 3-aryl-2-imino-7(4H)-oxo-6-substituted-thiazolo [4, 5-d) pyrimidine-5-thiones and 1,2, 4-

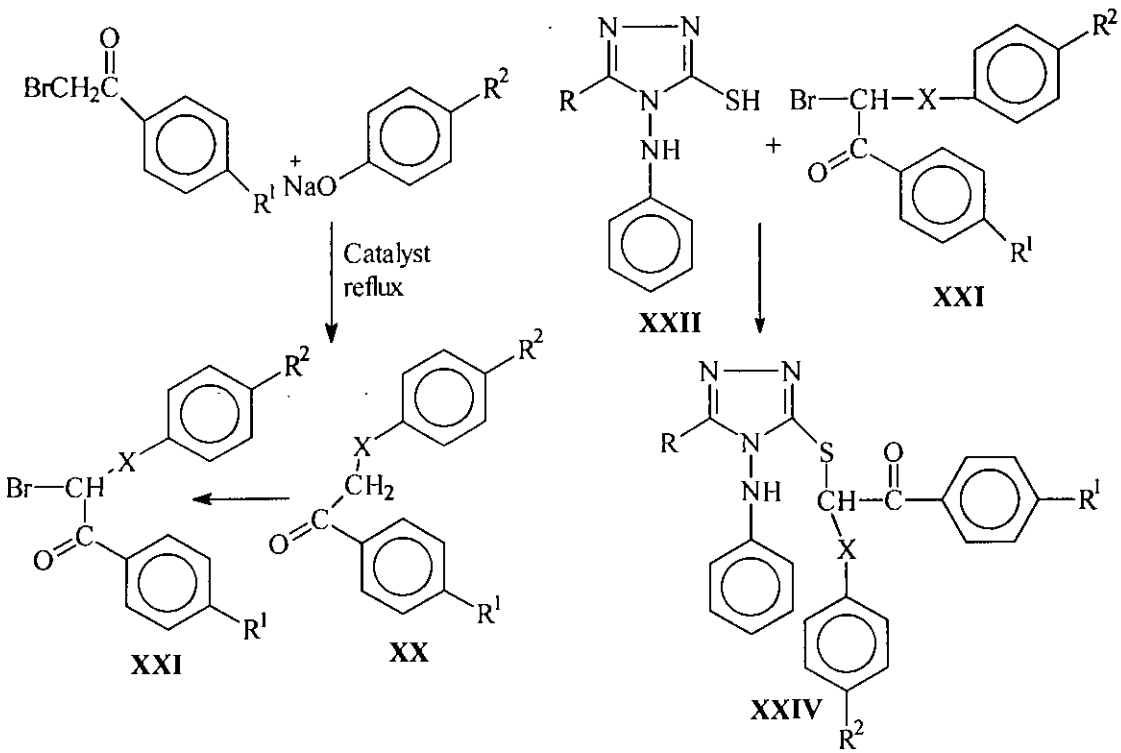
dithiazolidines. Their group synthesized 2-acetyl imino-3-aryl thiazolo [4,5-d] pyrimidine-7-thiones (**II**) from 2-acetylimino-3-aryl-5-cyano-4-ethoxylmethyleneamino-$\Delta^4$-thiazolines (**I**) on reaction with sodium hydro sulphide in ethanol. The compounds (**II**) are also obtained by the reaction of (**I**) with hydrogen sulfide in pyridine. Phenacyl chloride and allyl bromide reacts with (**II**) in the presence of sodium ethoxide in ethanol to give the corresponding S-phenacyl (**III**) and S-allyl (**IV**) derivatives in very good yields. On their synthetic path way they prepared 4-amino-3-aryl-5-cyano-2-substituted-thioureido-$\Delta^4$-thiazolines (**VIII**) from 4-amino-3-aryl-5-cyano-2-imino-$\Delta^4$-thiazolines (**V**) and isothiocyanates (**VI**) in ethanol on reflux condition but not any 3-aryl-5-cyano-2-imino-4-substituted thioureido-$\Delta^4$-thiazolines (**VII**) compounds. The thiourea (**VIII**) gives 3,5-di(substituted imino)-1,2,4-dithiazolidines (**XIV**) on heating with orthophosphoric acid or PPA on steam bath for one hour through a series of hydrolytic decarboxylation and intramolecular cyclization reactions. The 1, 2, 4-dithiazolidines (**XIV**) are also obtaind when thioureas (**VIII**) are heated in ethanol in the presence of sodium ethoxide or when anhydrous hydrogen chloride gas is passed through ethanolic solutions of (**VIII**). The thioureas (**VIII**, R =allyl) when heated with PPA at 150-160$^0$ for five minutes yields 3-aryl-2-(5′-methyl-$\Delta^2$-thiazoline-2′-ylimino) thiazolidine-4-one (**XVIII**).

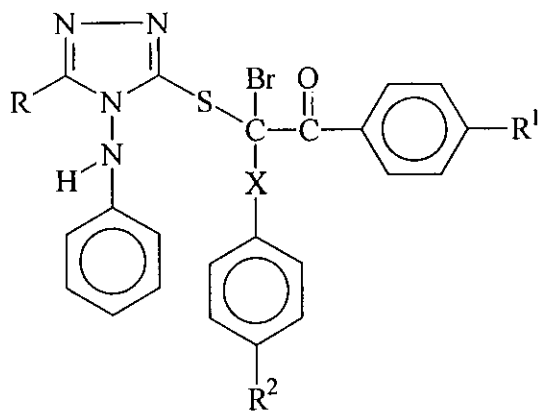

NaSH in Ethanol
or H2S in pyridine
PhCOCH2Cl
NaOEt
NaOEt
CH2 = CH—CH2Br
+ R - N = C = S
H3PO4
PPA
NaOEt
−CO2
I
II
III
IV
V
VI
VII
VIII
IX
X
XI
XII
XIII
XIV



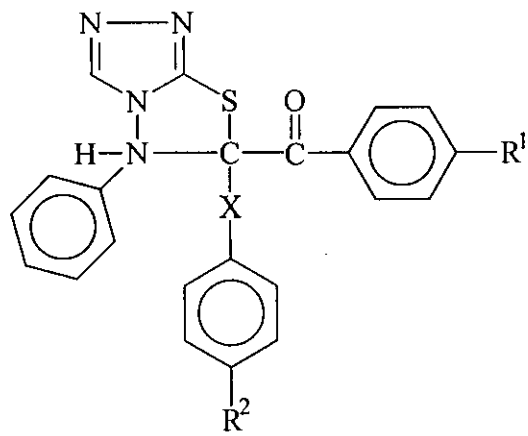

The thioureas (**VIII**, R = allyl) on reaction with bromine in acetic acid folowed by dehydrobromination with ammonia furnishes 4-amino-2-(5′-bromoethyl-$\Delta^2$-thiazoline-2′-yliminol)-3aryl-5-cyano-$\Delta^4$-thiazolines (**XVI**). One of the derivatives of (**XVI**) is obtained as 2-(5′-bromomethyl-$\Delta^4$-thiazoline-2′-ylimino-3-*p*-tolyl-thiazolidine-4-one (**XVII**). 2-Acetylimino-4-amino-3-aryl-5-cyano-$\Delta^4$-thiazolines (**XVIII**) on reaction with isothiocyanates in the presence of sodium ethoxide in ethanol yields 3-aryl-2-imino-7(4H)-oxo-6-substituted-thiazolo[4, 5-d) pyrimidine-5-thiones (**XIX**) in good yield.

Madhukar and his group[2] synthesized some 3-substituted-5-phenyl-6-substituted benzoyl-6-substituted-phenoxy / thiophenoxy-1,2,4-triazolo-[3, 4-b][1, 3, 4] thiadiazolines as potential antibacterial active compounds. They used very simple synthetic technique and prepared 4-anilino-5-(2′-substituted phenoxy / thiophenoxy) phenacylmercapto-3-substituted –1,2,4-triazole (**XXIV**, X = 0, S) by the interaction of 4-anilino-5-mercapto-3-substituted -1,2,4-triazole with 2-bromo-2-substituted phenoxy / thiophenoxy acetophenones (**XXI**, X = 0, S) which upon bromination followed by cyclization afforded 3-substituted-5-phenyl-6-substituted benzoyl-6-substituted phenoxy / thiophenoxy-1,2,4-triazolo[3,4-b][1,3,4] thiadiazolines (**XXVI**, X = 0, S).





**XXV**



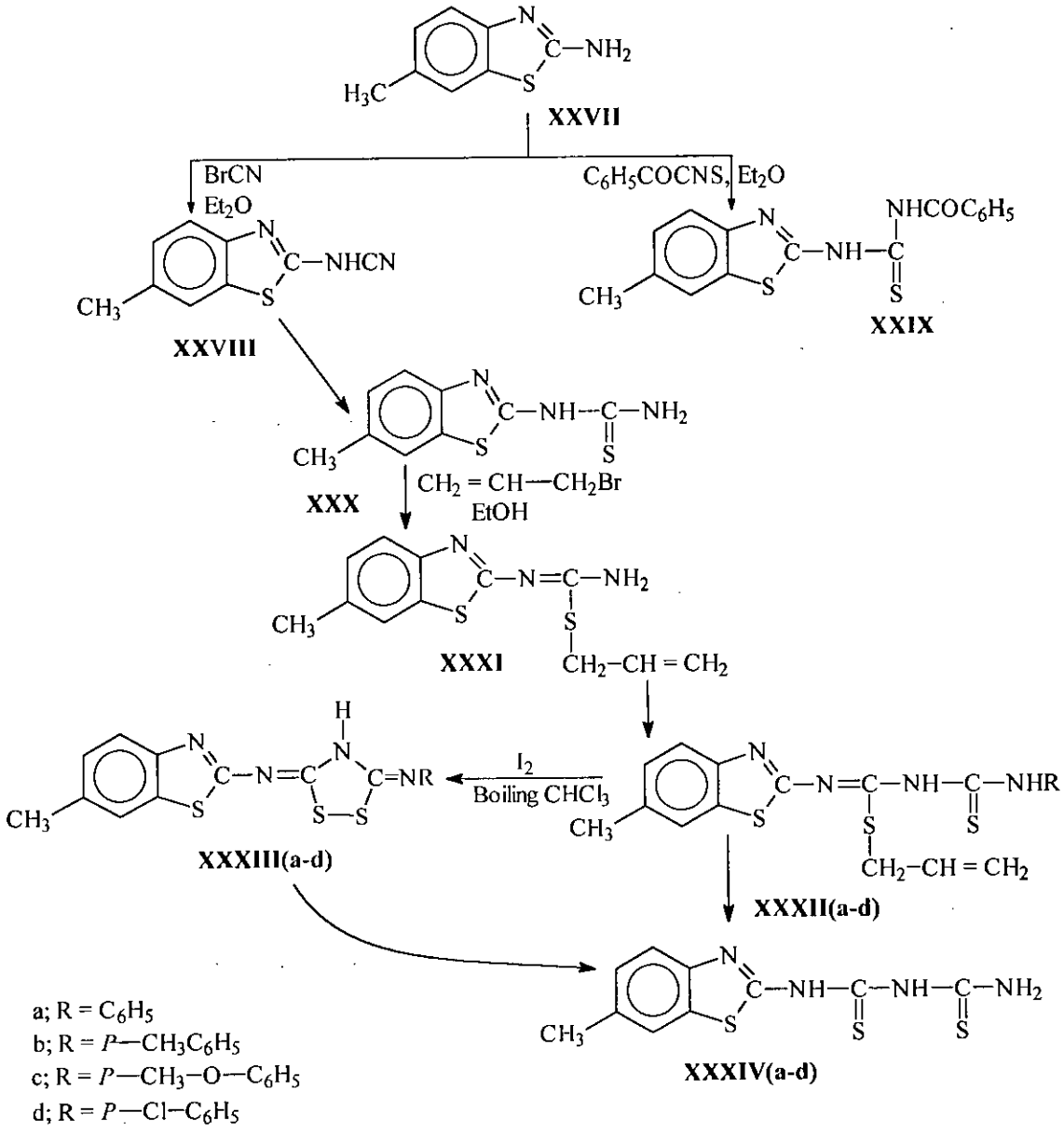
**XXVI**

$R^1$= H, Cl, $CH_3$
$R^2$= Cl, H
X = O, S

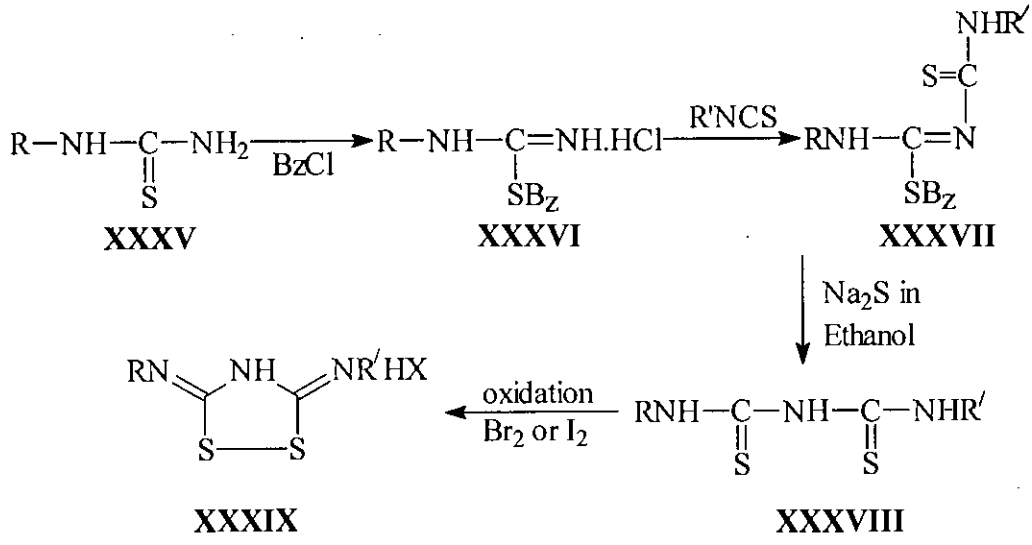
Verma and his co-workers[3] chemically examined widely reported biologically active compounds 5-substituted benzothiazolyl imino-3-arylimino-1,2,4-dithiazolidines. His group used a simple and convenient method for the synthesis of 5-[2-(6-methyl)benzothiazolyl]-imino-3-arylimino-1,2,4-dithiazolidines **XXXIII**(a-d) by the oxidation and cyclization of the corresponding 1-[2-(6-methyl)benzothiazolyl]-2-s-allyl isothiocarbamide (**XXXI**) with appropriate aryl isothiocyanate.

The reaction of 6-methyl-2-aminobenzothiazole (**XXVII**) with either cyanogenbromide followd by thiohydrolysis of the product (**XXVIII**)) or with benzoyl iso thiocyanate and alkaline hydrolysis of the product (**XXIX**) resulted in the formation of identical 1-[2-(6-methyl) bezothiazolyl] thiocarbamide (**XXX**). Compound (**XXX**) on alkylation with allyl bromide and interaction with appropriate aryl isothiocyanate afforded the related 1-[2-(6-methyl) benzothiazolyl]-5-aryl-2-s-allyl iso-2,4-dithiobiurets (**XXXII**). The product, on oxidation with iodine in boiling chloroform was dealkylated and cyclized to 5-[2-(6-methyl)-benzthiazolyl]imino-3-arylimino-1,2,4-diathiazolidines (**XXXIII**). Their group also prepared (**XXXIV**) by the

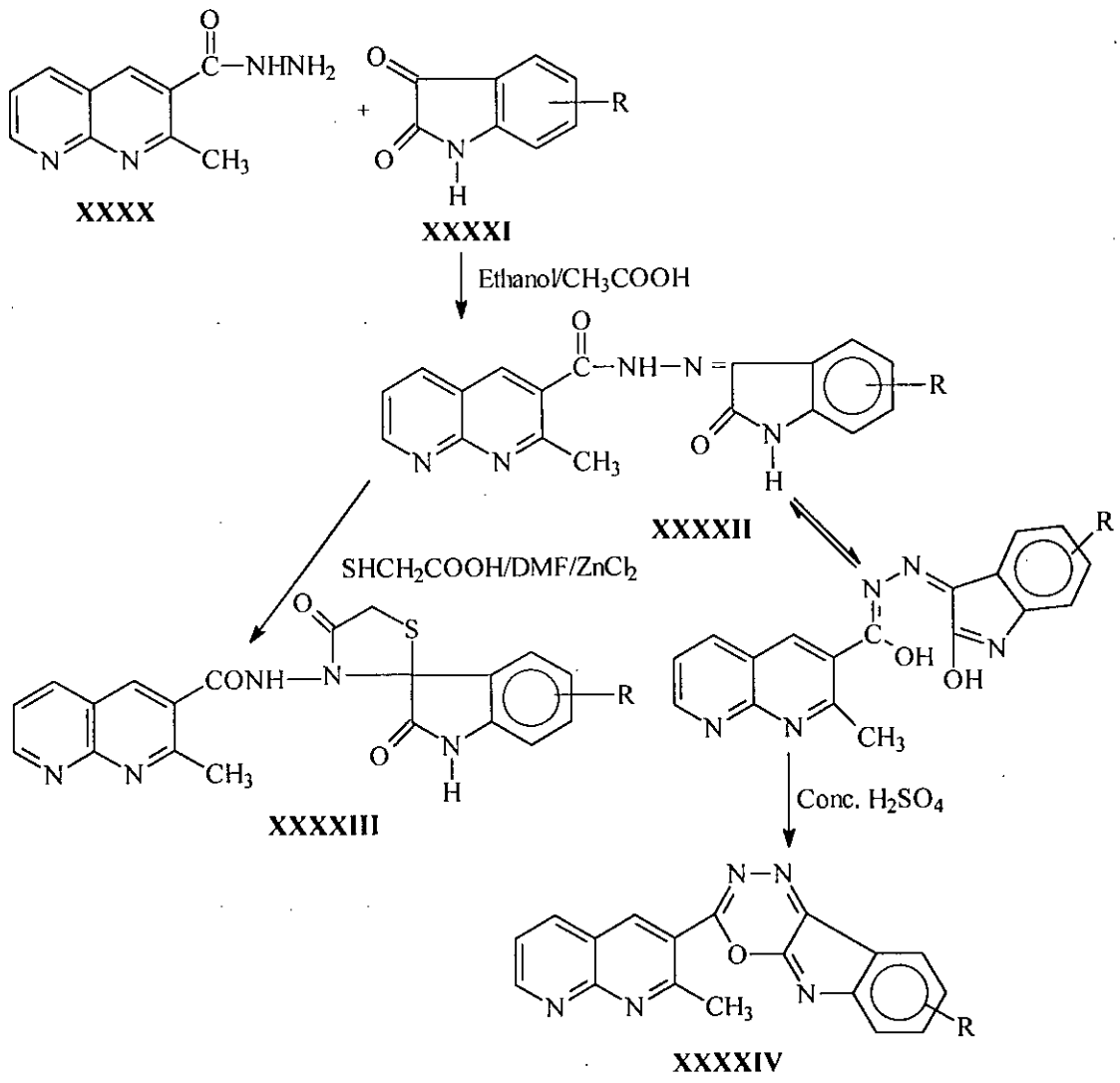
oxidation of the corresponding 2,4-dithiobiurets which in turn were obtianed by reductive dealkylation of the related isodithiobiurets with hydrogen sulphide in ethanolic ammoniacal sulphide solution and also by reduction of (**XXXIII**) under identical condition.



Dixit ***et al.***[4] synthesized some 1,5-disubstituted 2,4-dithiobiurets and their oxidation products 3,5-disubstituted imino-1,2,4-dithiazolidines by following a simple technique and from available materials.

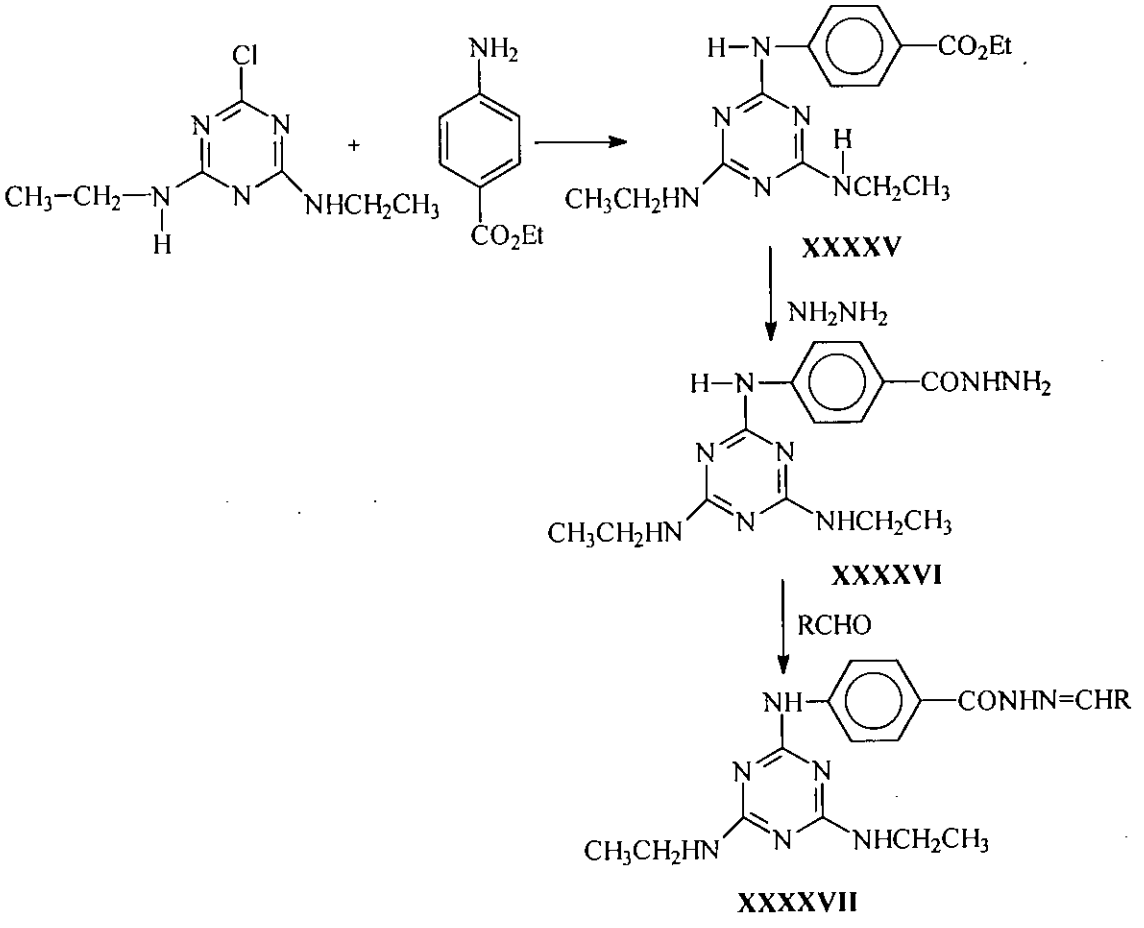



Rani and his group[5] carried out the synthesis of some 3′-(2-methyl-1,8-naphthyridine-3-carbonylamino) spiro[3H-indole-3, 2′-thiazolidine]-2,4′(1H)-diones and 2-(2-methyl-1,8-naphthyridine-3-yl)-[1,3,4] oxadiazino [5,6-b] indoles as an important bioactive compounds. Their group followed a simple synthetic technology such as the condensation of 2-methyl-1,8-naphthyridine-3-carbonylic acid hydrazide (**XXXX**) with different isatins (**XXXXI**) gives the corresponding isatin -β-(2-methyl-1,8-naphthyridine-3-carbonyl hydrazones (**XXXXII**), which on treatment with mercaptoacetic acid in DMF in the presence of anhydrous zinc chloride afforded the substituted 3′-(2-methyl-1, 8-naphthyridine-3-carbonylamino) spiro-[3H-indole –3,2′-thiazolidine]-2,4′(1H)-diones (**XXXXIII**). The hydrazones (**XXXXII**) on treatment with concentrated sulphuric acid undergoes cyclodehydration to yield the desired 2-(2-methyl)-1,8-naphthyridine-3-yl)-[1,3,4] oxadiazino [5, 6-b] indoles (**XXXXIV**).

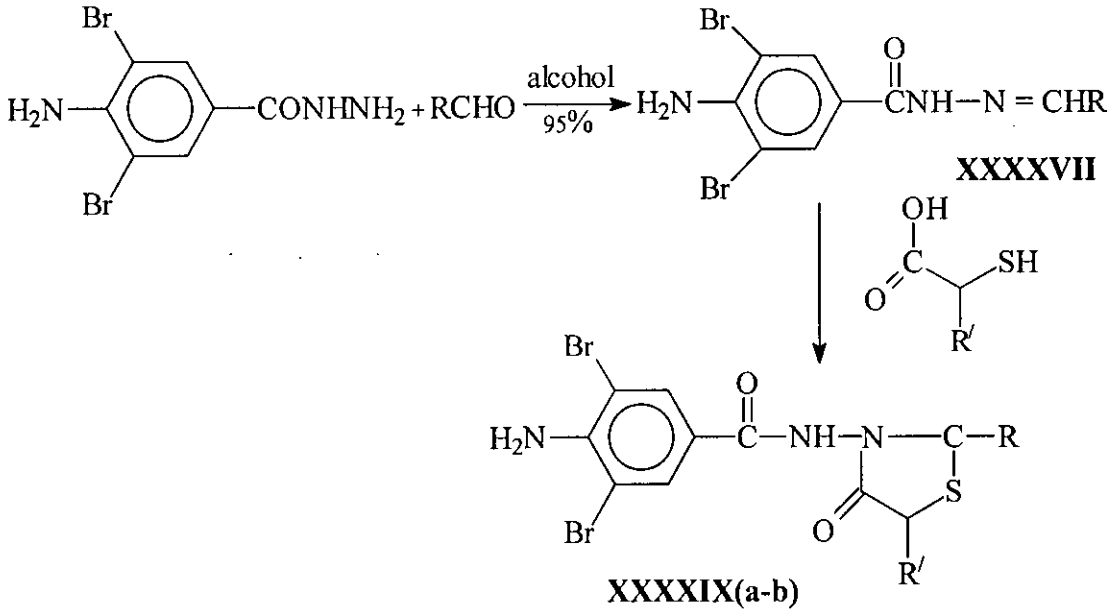



All the synthesized compounds were screened against the bacteria *Escherichia* Coli and *Bacillus Polymyxa* and the fungi *Fusarium oxysporum* and *curvularia lunata* using the filter paper disc technique and 400 µg/disc concentration Compounds **XXXXIIIa**, **XXXXIIIe**, **XXXXIIIf**, and **XXXXIVd** showed moderate antibacterial activity against both the bacteria. Other compounds exhibited very weak antibacterial activity. Regarding antifungal activity, compounds **XXXXIIIa**, **XXXXIIId**, **XXXXIVb**, **XXXXIVd**, and XXXXIVf showed moderate activity to against both the fungal species. The rest of the compunds displayed weak antifungal activity.

Patel *et al.*[6] studied on the synthesis and antimicrobial activity of 2-aryl-3-p-(2′,4′-diethylamino-s-triazine-6′-ylamino benzoylamino-5H/methyl-4-thiazolidinones. In their synthetic technique they prepared some new 4-thiazolidinones bearing s-triazin moiety by the condensation of the schiff bases from *p*-2,4-diethylamino-s-triazin-6-ylaminobenzoyl hydrazine with thioglycolic and thiolactic acid. The products (**XXXXV-VII**) have been screened for antimicrobial activity. Most of the compounds showed moderate activity.

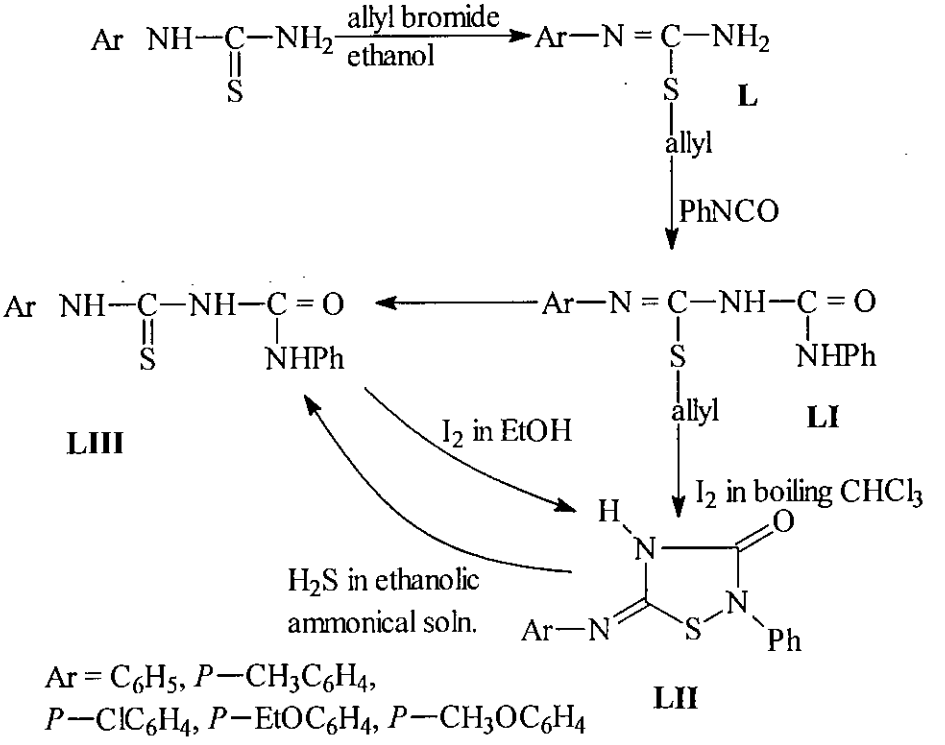



Thaker and his group[7] studied on the thiazolidinones as potential antitubercular compounds. Their group prepared 2-aryl-3-(4-amino-3,5-dibromobenzamido)-5-substituted-4-thiazolidinones [**(XXXXIX(a-b)]** by the condensation of mercaptoalkonic acids with azomethines (**XXXXVIII**).

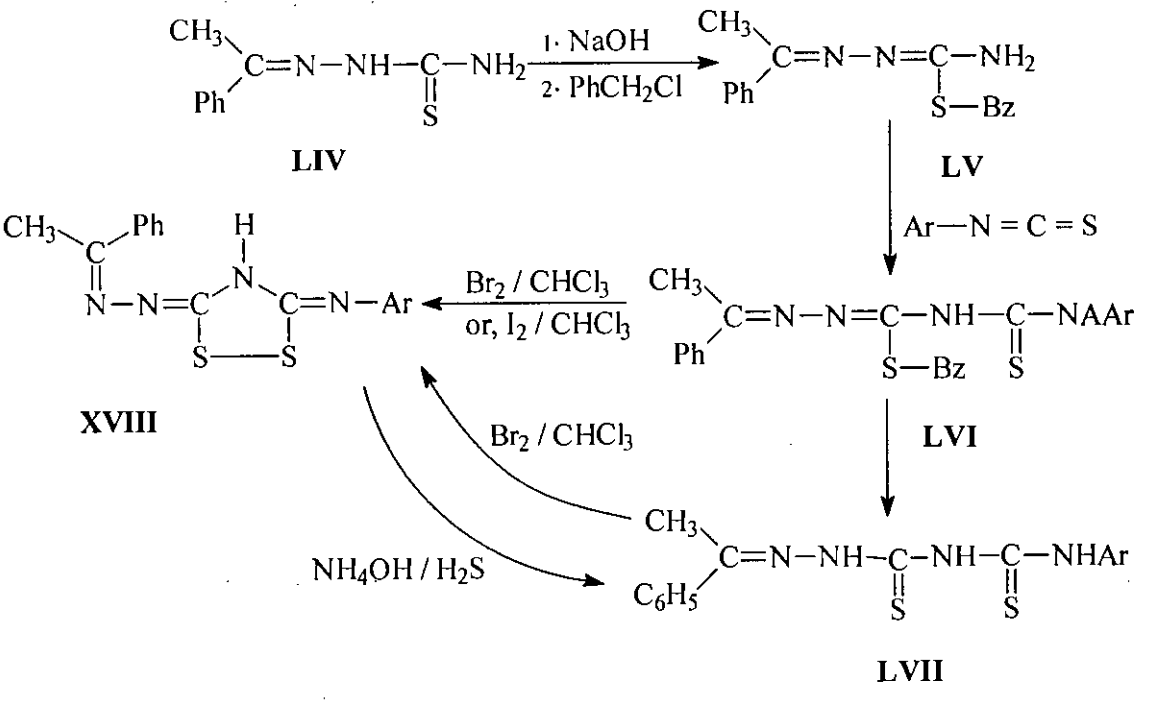



The *invitro* antimycobacterial activity of the compounds were studied at 0,5 and 30 μg $ml^{-1}$(solvent DMF) against $H_{37}$ $R_V$ strain of Mycobacterium tuberculosis using Lowenstein-Jensen egg medium. The retardation of growth rate was studied up to six weeks at $37^0$. The thiazolidinones **XXXXIX(a-b)** were tuberculostatic at 30 μg $ml^{-1}$.

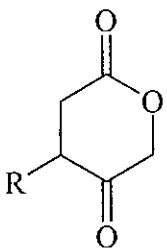
Verma *et al.*[8] studied on the oxidative deallylation and cyclization of 2-s-allyl-1-aryl-5-phenylisobiurets as an alternative route to the synthesis of 5-arylimino-3-oxo-2-phenyl-1,2,4-thiadiazolidine.




Rai and his co-workers[9] reported the synthesis of 3-Arylimino-5-(α-methyl-benzylidine hydrazido)-1,2,4-dithiazolidines as an antibacterial reagents. They followed a simple synthetic technique and synthesized their desired compounds (**LVIII**) by the oxidative debenzylation and cyclization of the corresponding 5-aryl-1-(α-methyl benzylidene amino)-2-s-benzyliso-4-thiobiurets (**LVI**).

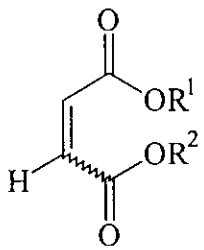



Balasubramaniyan ***et al.***[10] synthesized 5-substituted-2-imino-4-oxo-1, 3-thiazolidines by heterocyclization of maleic anhydride derivative with thiourea. In their synthetic technique they prepared 2-imino-2,3,4,5-tetrahydro-1, 3-thiazol-5-acetic acid (**LXVa**) from the reaction of thiourea with maleic anhydride, maleic acid, fumeric acid, methylhydrogen fumarate or sodium salt of methyl hydrogen fumarate; a mixture of (**LXVa**) and its methyl ester (**LXVg**) is obtained with methyl hydrogen maleate; a mixture of (**LXVb**) and (**LXVc**) with methyl maleic anhydride and a mixture of (**LXVd**) and (**LXVe**) with phenylmaleic anlydride

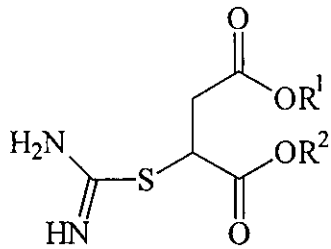


a, R = H
b, R = Me
c, R = Ph

**LIX**



**LX(Z), LXI(E)**



**LXVIII**

For LX LXI LXVIII

a, $R^1 = R^2 = H$

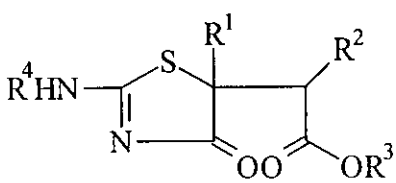
c, $R^1 = R^2 = Me$

d, $R^1 = Me$, $R^2 = H$

e, $COO\,R^1 = COO\overline{O}N\overset{+}{a}$, $R^2 = Me$

f, $R^1 = Me$, $COOR^2 = CO\overline{O}N\overset{+}{a}$

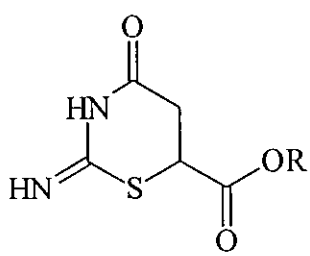
g, $COOR^1 = COOR^2 = CO\overline{O}N\overset{+}{a}$



**LXII**

a, $R^1 = R^2 = R^3 = R^4 = H$

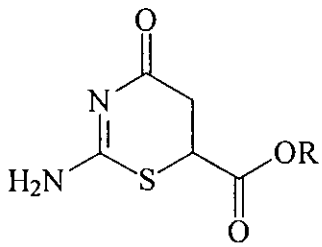
b, $R^1 = R^2 = R^4 = H$, $R^3 = Me$



**LXIV**

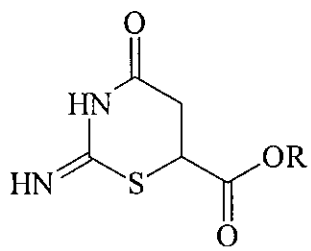
a, R = H

b, R = Me



**LXIII**

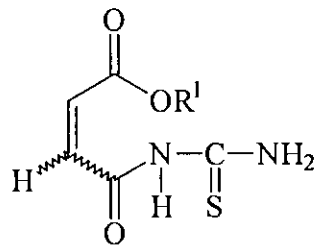
a, R = H
b, R = Me



**LXIV**

a, R = H
b, R = Me

**LXV**

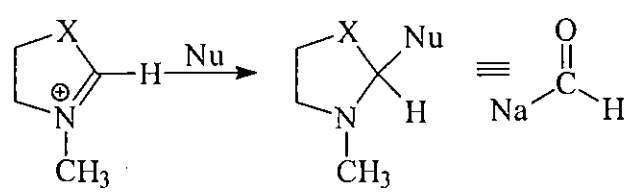


**LXVI(Z), LXVII(E)**

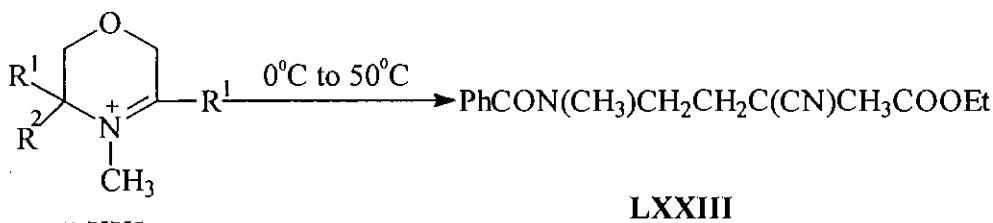
a, $R^1$ = H
b, $R^1$ = Me
c, $COOR^1 = CO\bar{O}N\overset{\oplus}{a}$

| | $R^1$ | $R^2$ | $R^3$ | | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|---|---|---|---|
| a, | H | H | H | f | H | H | Ph |
| b, | H | Me | H | g | H | H | H |
| c, | Me | H | H | h | Me | H | H |
| d, | H | Ph | H | i | H | Ph | H |
| e, | Ph | H | H | j | Ph | H | H |
| | | | | k | H | H | Ph |

Singh and his group[11] carried out the synthesis of functionalized oxazolidines and their novel open chain enamine tautomers. Homologated and functionalized oxazolidines existing mostly as stable and unprecedented aldehyde enamine tautomers are formed from the addition of bis and mono carbanions at C-2 of 3,4,4-trimethyl-$\Delta^2$-oxazolinium iodide at -78$^0$C.



**LXIX** **LXX**




**LXXI** **LXXIII**

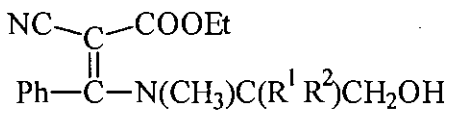
LXXI

a, $R^1 = Ph, R^2 = H$

b, $R^1 = H, R^2 = CH_3$

c, $R^1 = Ph, R^2 = CH_3$

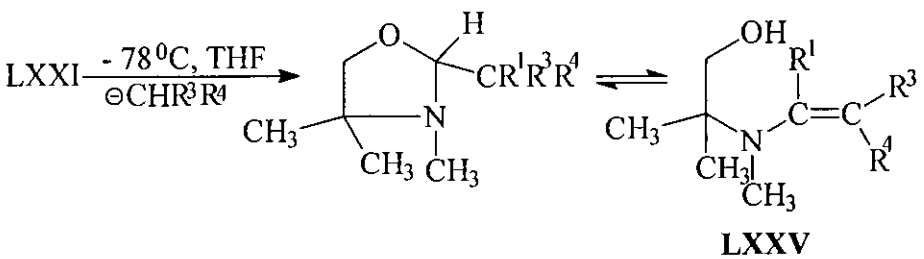
d, $R^1 = R^2 = CH_3$



**LXXII**

a, $R^1 = R^2 = H$

b, $R^1 = R^2 = CH_3$




**LXXV**

For LXXV

$R^1 = R^3 = H$; $R^4$ in

a, $R^4 = COCH_2COOEt$

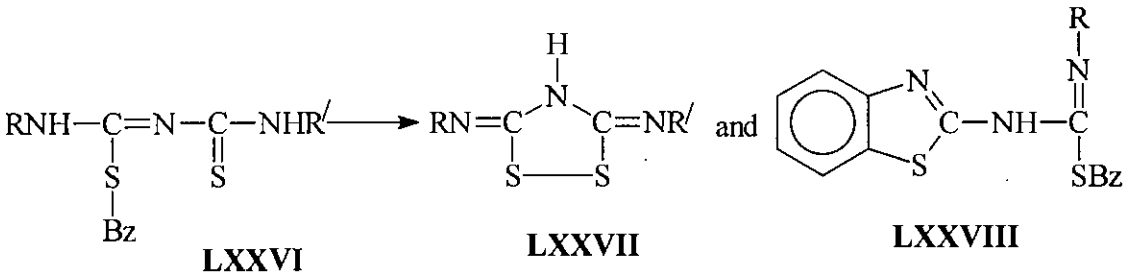
b, $R^4 = COCH_2 COOMe$

c, $R^4 = COCH_2COCH_3$

d, $R^4 = COPh$

Dixit ***et al.***[12] studied on the oxidative debenzylation and cyclization of 1,5-disubstituted 2-s-benzyliso-4-thiobiurets. They investigated the effect of debenzylation of 1,5-diaryl and 1-alkyl-5-aryl-2-*s*-benzyliso-4-thiobiurets by adding bromine and iodine in hot concenrated solution of chloroform or benzene. Depending on the reaction conditions, smaller or larger quantities of the related *N*-2-benzothiazolyl-*N'*-substituted-s-benzyliso thiocarbamides are produced simultaneously. When the substituents in positions 1,5 in the

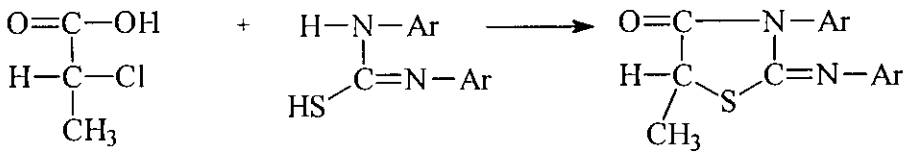
starting isodithiobiuret are an aryl and alkyl group respectively, the related 3.5-disubstituted imino-1,2,4-dithiazolidine is the sole product. Similarly when both 1,5-positions are substituted by alkyl groups, the related dithiazolidines or the 1,3,4-thiadiazolines are the main products.




**LXXVI** **LXXVII** **LXXVIII**

(Where R and R′ both are aryl groups or R is alkyl and R′ is aryl group)

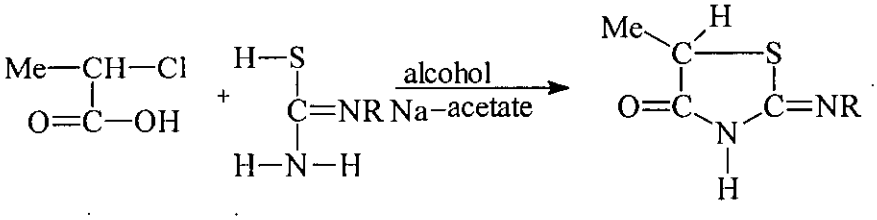
Raj Singh ***et al.***[13] reported the synthesis and fungicidal activity of 5-methyl-3-aryl-2-aryl imino-4-thiazolidinones and their acetoxy derivatives. Nine new 5-methyl-3-aryl-2-arylimino-4-thiazolidinones (**LXXXI**) have been synthesized by condensing various sym. diaryl thioureas (**LXXX**) with α chloropropionic acid (**LXXIX**) in presence of anhydrous sodium acetate in absolute ethanol. The acetoxymercuri derivatives of these 4-thiazolidinones have also been prepared by refluxing the solutions of the corresponding 4-thiazolidinones and mercuric acetate in presence of ethanol and acetic acid. The fungicidal activity of the 5-methyl-3-aryl-2-arylimino-4-thiazolidinones and their acetoxy mercuri derivatives showed moderate activities.




**LXXIX** **LXXX** **LXXXI**

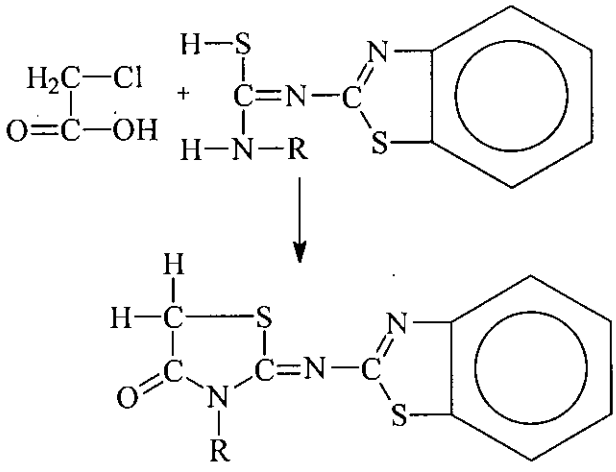
Rout ***et al.***[14] reported the synthesis of 2-*p*-aminophenyl imino-4-thiazolidone and some of its derivatives. They prepared 2-*p*-aminophenylimino-4-thiazolidone and its arylidine derivatives by reduction with iron and acetic acid of the corresponding 2-p-nitrophenylimino-4-thiazolidone and its arylidine derivatives. The compounds thus prepared have been mercurated and also brominated. The position of acetoximercuri group introduced on mercuration, has been determind. 2-*p*-aminopheylimino-4-thiazolidone does not undergo nuclear substitution on bromination. Both the mercurated and brominated compounds showed fungicidal activity.

Bhargava ***et al.***[15] studied on the 2-arylimino-5-methyl-4-thiazolidinones and 3-alkyl-2, 2′-benzothiazolylimino-4-thiazolidones. Several 2-aryl imino-5-methyl-4-thiazolidinones and 3-alkyl-2, 2′-benzothiazolylimino-4-thiazolidones have been synthesized and the fungicidal activity of hydrochlorides of 2-arylimino-5-methyl-4-thiazolidones have been studied.




**LXXXI**

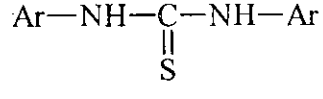
2-arylimino-5-methyl-4-thiazolidinones



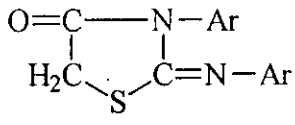
**LXXXIII**

3-alkyl-2, 2′-benzothiazolylimino-4-thiazolidones.

Ravindra ***et al.***[16] reported 3-aryl-2-arylimino-4-thiazolidinones derived from sym-diaryl thioureas. The workers prepared 3-aryl-2-arylimino-4-thiazolidinones by condensing thiourea with mono chloroacetic acid in presence of sodium acetate. By passing dry hydrogen chloride gas in dry benzene solution of the 3-aryl-2-arylimino-4-thiazolidinones, the corresponding hydrochlorides have been prepared. *Nematicidal*, *insecticidal*, *acaricidal* and fungicidal activities of some 3-aryl-2-arylimino-4-thiazolidinones have been reported. Some of the compounds showed considerable fungicidal activity.



Sym-diaryl thioureas



**LXXXIV**

3-aryl-2-arylimino-4-thiazolidinones

Recently a number of workers[17-28] reported biological activities of dithiazoline ring in conjugation with C=N and C–N–S moieties.

# AIM OF THE PROJECT

Heteocyclic compounds containing thiazolidinone moiety in the molecular framework plays an important role as common denominator for various biological activities such as antibacterial, fungicidal and herbicidal that discussed so far. On this point of view, the object of the research is to synthesize mono and di-thiazolidinone derivatives in the molecular framework and to characterize them by physical constant and spectral evidences, thus the aim of the project is as following

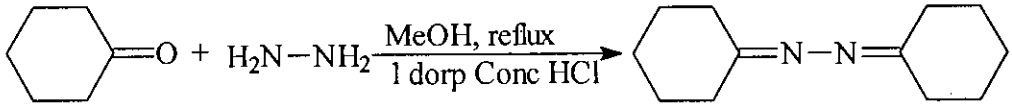
1. First step involves formation of imino compounds with hydrazine derivatives.
2. Second step involves thiazolidinone ring formation.
3. Purification by different techniques.
4. Characterization by physical constant and spectroscopic methods.
5. Biological test.

# CHAPTER - 2

# EXPERIMENTAL

## 2.1.A SYNTHESIS OF CYCLOHEXANONE BIS HYDRAZONE (H–1)

**Reaction involved**




**Procedure**

A mixture of cyclohexanone (0.786g, 8 m mol) and hydrazine (0.128g, 4 m mol) was refluxed in methanol (10 ml) in presence of hydrochloric acid (1 drop) for 6 hours. The progress of the reaction was monitored by TLC (ethylacetate – pet.ether, 1:1, $R_f$ = 0.70). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resulting crude liquid product was purified by preparative thin layer chromatography, yield 71%.

**IR Spectrum**

$\nu_{max}$ (KBr) $cm^{-1}$ : 2931 (C–H, aliphatic), 2856 (C–H, aliphatic), 1638 ( C=N), 1557 (C = N).

**$^1$H – NMR (300 MHz, $CDCl_3$)**

δ : 1.4–1.9 (m, 12H), 2.2–2.4 (m, 8H)

**$^{13}$C – NMR (300 MHz, $CDCl_3$)**

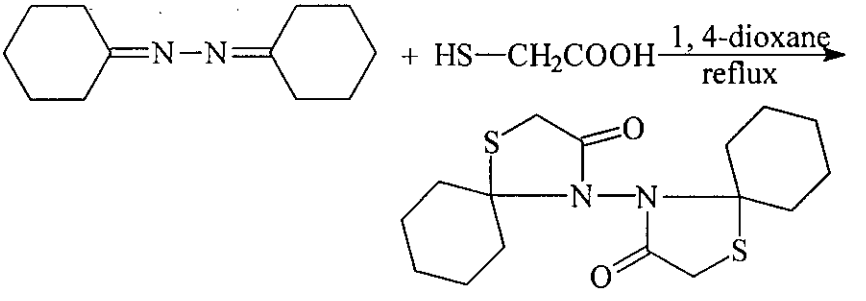
δ : 23.09, 24.94, 25.89, 26.33, 26.97, 27.52, 27.85, 35.60, 36.45, 41.9, 163.23, 165.48.

**Mass Spectrum**

m/z : 192($M^+$.), 163, 149, 136, 124, 110, 96, 82, 69, 55.

## 2.1.B SYNTHESIS OF BIS SPIRO-(CYCLOHEXANE- THIAZOLIDINONE) (H–2)

**Reaction involved**




**Procedure**

A mixture of cyclohexanone bis hydrazone (0.768g. 4 m mol) and mercaptoacetic acid (1.472g, 16 m mol) was refluxed in 1,4-dioxane (8 ml) for 8 hours. The progress of the reaction was monitored by TLC (pet.ether-ethylacetate, 1:1, $R_f$ = 0.67). The reaction mixture was then cooled to room temperature and 1, 4-dioxane was removed by rotary evaporator under reduced pressure. The crude product was purified by column chromatography. The desired compound was isolated as a yellow liquid yield 58%.

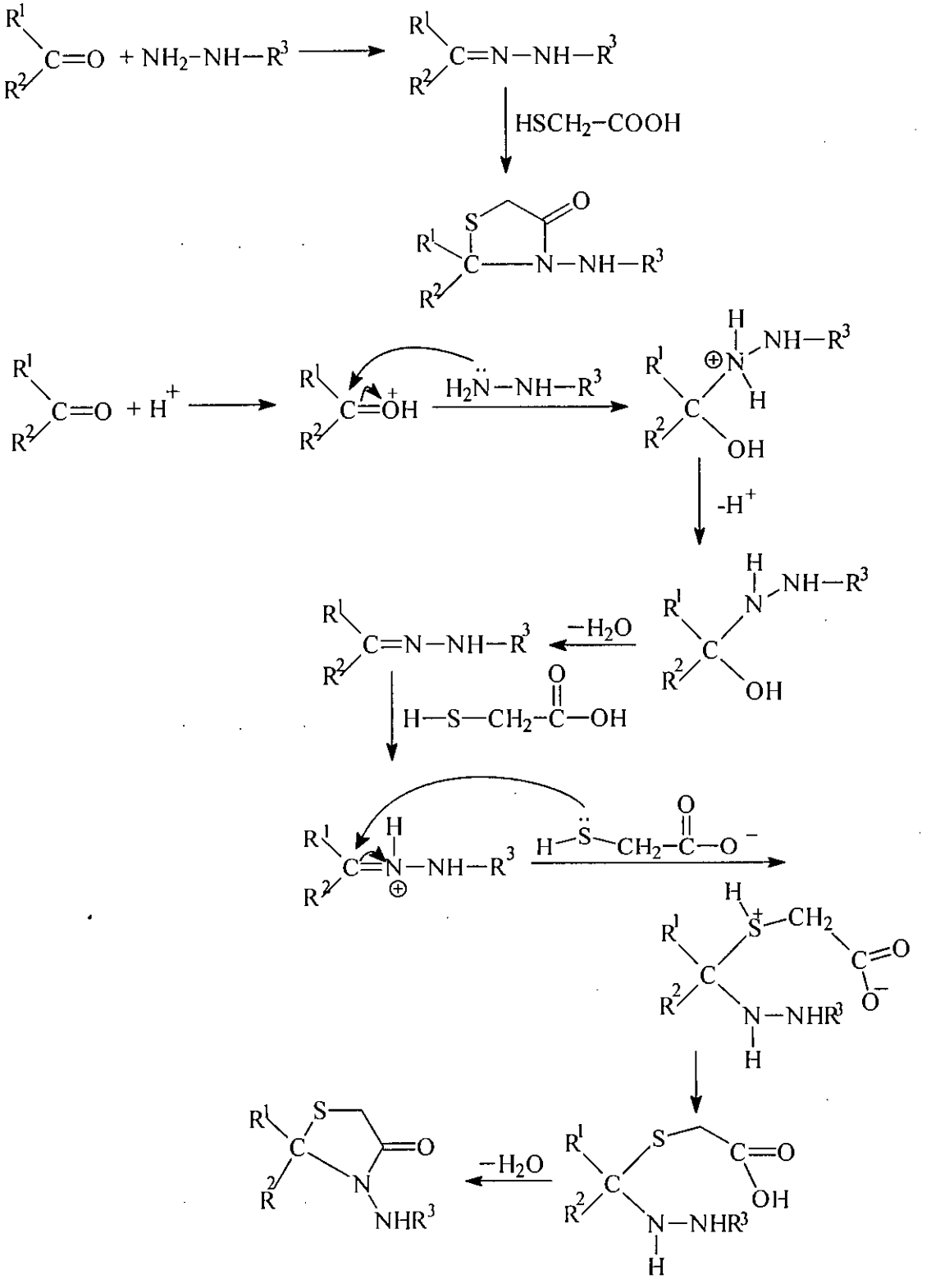
**IR Spectrum**

$\nu_{max}$ (KBr) $cm^{-1}$ : 2940 (C–H, aliphatic), 2858 (C–H, aliphatic), 1774 (b, C=O), 1223 (C–N), 1126 (C–S).

**$^1$H – NMR (300 MHz, $CDCl_3$)**

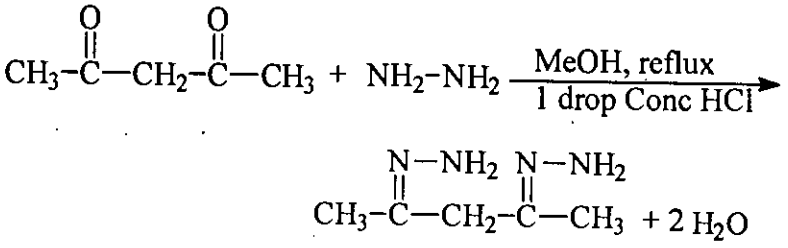
δ : 1.1–1.25 (m, 2H), 1.26–1.4 (m, 7H), 1.5–1.7 (m, 5H), 1.75–1.85 (m, 5H), 1.9–2.0 (m, 5H).

## General Mechanism



## 2.2.A SYNTHESIS OF ACETYLACETONE BIS HYDRAZONE (H–3)

**Reaction involved**

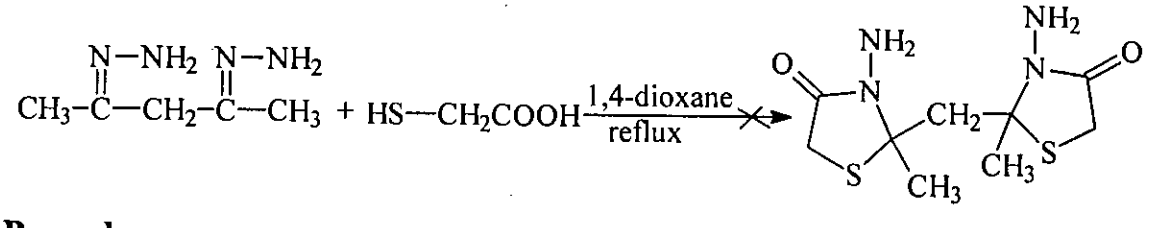


**Procedure**

A mixture of acetylacetone (0.60g, 6 m mol) and hydrazine (0.96g, 30 m mol) was refluxed in methanol (8 ml) in presence of hydrochloric acid (1 drop) for 16 hours. The progress of the reaction was monitored by TLC. The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The crude gummy mass was used for the second step.

## 2.2.B SYNTHESIS OF 2, 4-Di(1′–AMINO) THIAZOLIDINO PENTANE (H–4)

**Reaction involved**

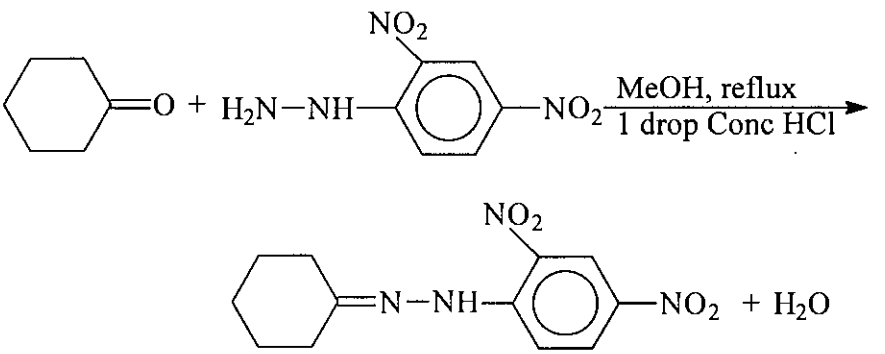


**Procedure**

The crude product (H–3) and mercaptoacetic acid (1.472g, 16 m mol) was refluxed in 1,4–dioxane (6 ml) for 18 hours. The reaction mixture was then cooled to room temperature and 1,4–dioxane was removed by rotary evaportor under reduced pressure. The crude mixture was not possible to isolate.

## 2.3.A SYNTHESIS OF CYCLOHEXANONE 2, 4-DINITROPHENYL HYDROZONE (H–5)

**Reaction involved**




**Procedure**

A mixture of cyclohexanone (0.294g, 3 m mol) and 2, 4-dinitrophenyl hydrazine (0.594g, 3 m mol) was refluxed in methanol (6 ml) in presence of hydrochloric acid (1 drop) for 6 hours. The progress of the reaction was monitored by TLC (pet.ether-ethylacetate, 7:3, $R_f$ =0.78). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resulting solid mass was recrystallized several times from ethylacetate. The desired compound was isolated as a yellow crystal, mp. 150–52$^0$C, yield 68%.

**IR Spectrum**

$\nu_{max}$ (KBr) $cm^{-1}$ : 3306 (N–H), 3109 (C–H, aromatic), 2942 (C–H, aliphatic), 1498 (C=C, aromatic), 1450 (C=C, aromatic), 1424 (C=C, aromatic), 1265 (N=O).

**$^1$H – NMR (300 MHz, $CDCl_3$)**

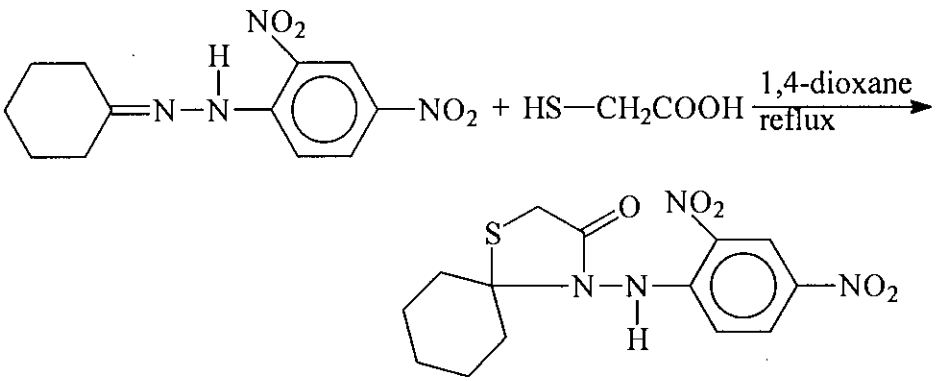
δ : 1.6–1.9 (m, 6H), 2.4–2.6 (m, 4H), 7.9 (d, 1H, aromatic), 8.2 (d, 1H, aromatic), 9.1 (S, 1H, aromatic), 11.2 (S, 1H, N–H).

**Mass Spectrum**

m/z: 278 ($M^+$.), 277, 260, 223, 207, 184, 168, 150, 141, 128, 115, 94, 77, 55.

## 2.3.B SYNTHESIS OF *N*(2, 4–DINITRO PHENYLAMINO) SPIRO–(CYCLOHEXANE–THIAZOLIDINONE) (H–6)

**Reaction involved**




**Procedure**

A mixture of cyclohexanone 2,4-dinitrophenyl hydrazone (0.278g, 1 m mol) and mercaptoacetic acid (0.184g, 2 m mol) was refluxed in 1,4-dioxane (6 ml) for 4 hours. The progress of the reaction was monitored by TLC (pet.ether-ethylactate, 6:4, $R_f = 0.53$). The reaction mixture was then cooled to room temperature and 1,4-dioxane was removed by rotary evaporator under reduced pressure. The resulting solid mass was recrystallized several times from 95% ethanol. The desired compound was isolated as redish yellow crystal, mp. 128–130$^0$C, yield 57%.

**IR Spectrum**

$\nu_{max}$ (KBr) $cm^{-1}$ : 3305 (N–H), 3109 (C–H, aromatic), 2942 (C–H, aliphatic), 1735 (C=O), 1550 (C=C, aromatic), 1510 (C=C, aromatic), 1495 (C=C, aromatic) 1260 (N=O).

**$^1$H – NMR (300 MHz, $CDCl_3$)**

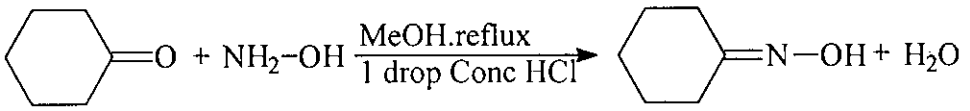
δ : 1.5–1.7 (m, 8H), 2.4–2.5 (m, 4H), 7.9 (d, 1H, aromatic), 8.2 (d, 1H, aromatic), 9.1 (S, 1H, aromatic), 11.1 (S, 1H, N–H).

**Mass Spectrum**

m/z : 352($M^+$.), 260, 223, 168, 141, 115, 77, 51.

## 2.4.A SYNTHESIS OF CYCLOHEXANONE OXIME (H–7)

**Reaction involved**




**Procedure**

A mixture of cyclohexanone (0.588g, 5 m mol) and hydroxylamine (0.417g, 6 m mol) was refluxed in methanol (10 ml) in presence of hydrochloric acid (1 drop) for 7 hours. The progress of the reaction was monitored by TLC (pet.ether-ethylacetate, 7:3, $R_f$=0.66). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The desired compound was purified by column chromatography as a colourless semi solid, yield 62%.

**IR Spectrum**

$\nu_{max}$ (KBr) $cm^{-1}$ : 3376–3490 (b, O–H), 2951– 2810 (b, C–H, aliphatic), 1605 (C=N).

**$^1$H – NMR (300 MHz, $CDCl_3$)**

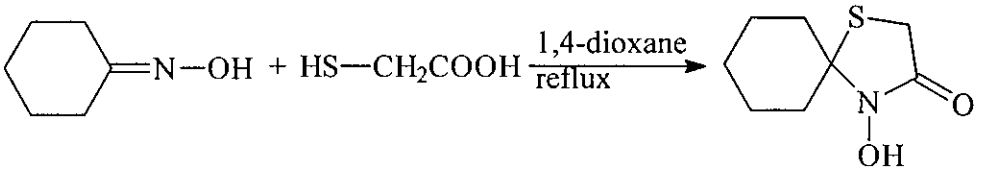
δ : 1.3–1.5 (m, 2H), 1.5–1.65 (m, 4H), 2.5–2.7 (m, 4H).

**Mass Spectrum**

m/z : 113($M^+$), 98, 85, 72, 55.

## 2.4.B SYNTHESIS OF *N*–HYDROXY SPIRO–(CYCLOHEXANE–THIAZOLIDINONE) (H – 8)

**Reaction involved**




**Procedure**

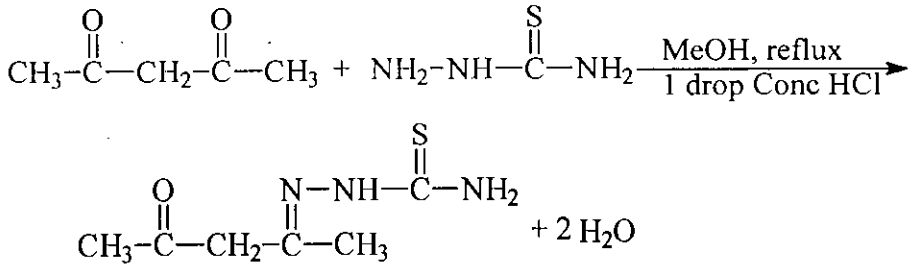
A mixture of cyclohexanone oxime (0.678g, 6 m mol) and mercaptoacetic acid (1.11g, 12 m mol) was refluxed in 1,4-dioxane (10 ml) for 3 hours. The progress of the reaction was monitored by TLC (pet.ether-ethylactate, 7:3, $R_f$ = 0.59). The reaction mixture was then cooled to room temperature and 1,4-dioxane was removed by rotary evaporator under reduced pressure. The crude solid mass was purified by column chromatography as white crystal, mp. 177–179$^0$C, yield 63%.

**IR Spectrum**

$\nu_{max}$ (KBr) cm$^{-1}$ : 3450 – 3260 (b, O–H), 2960–2850 (b, C–H, aliphatic), 1715 (b, C=0).

## 2.5.A SYNTHESIS OF ACETYLACETONE THIOSEMICARBAZONE (H–10)

**Reaction involved**




**Procedure**

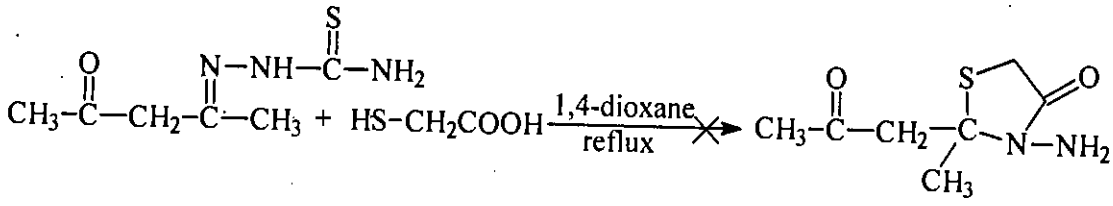
A mixture of acetylacetone (0.20g, 2 m mol) and thiosemicarbazide (0.364g, 4 m mol) was stirred in methanol (8 ml) in presence of hydrochloric acid (1 drop) for 4 hours at room temperature. The progress of the reaction was monitored by TLC (pet.ether-ethylacetate, 7:3, $R_f$ = 0.76). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resulting semi solid mass was recrystallized several times from ethylacetate. The desired compound was isolated as a white crystal, yield 65%.

**IR Spectrum**

$\nu_{max}$ (KBr) $cm^{-1}$ : 3100–3450 ($NH_2$, N–H), 2945 (C–H, aliphatic), 1710 (C=0) 1609 (C=N), 1501 (C=S).

## 2.5.B SYNTHESIS OF 2(*N*-AMINOTHIAZOLIDINONO)PENTANE-4-ONE (H–11)

**Reaction involved**

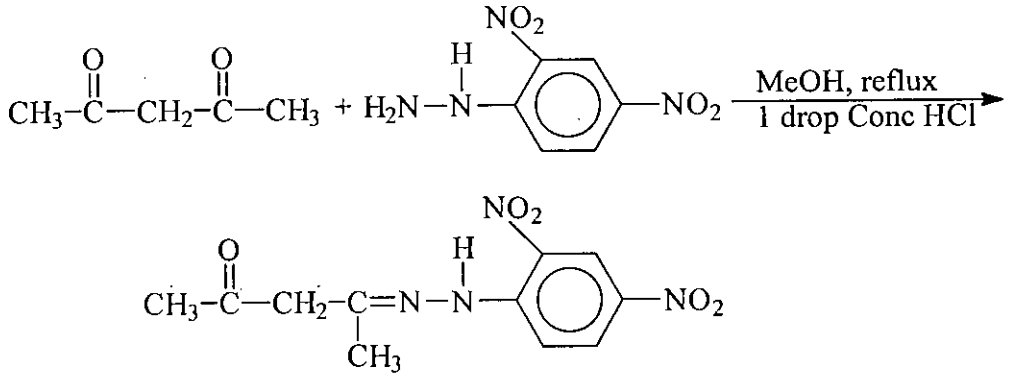



**Procedure**

A mixture of acetylacetone thiosemicarbazone (0.49g, 2 m mol) and mercaptoacetic acid (0.74g, 8 m mol) was refluxed in 1,4-dioxane (8 ml) for 6 hours. The reaction mixture was then cooled to room temperature and 1,4-dioxane was removed by rotary evaporator under reduced pressure. The crude gummy mass was not possible to purify.

## 2.6.A SYNTHESIS OF ACETYLACETONE 2,4-DINITROPHENYL HYDRAZONE (H –12)

**Reaction involved**




**Procedure**

A mixture of acetylacetone (0.30g, 3 m mol) and 2,4-dinitrophenyl hydrazine (1.188g, 6 m mol) was refluxed in methanol (8 ml) in presence of hydrochloric acid (1 drop) for 7 hours. The progress of the reaction was monitored by TLC (ethylacetate-pet.ether, 1:1, $R_f$=0.82). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resulting solid mass was recrystallized several times from ethylacetate. The desired compound was isolated as a redish yellow crystal, mp. 90–92$^0$C, yield 58%.

**IR Spectrum**

$\nu_{max}$ (KBr) cm$^{-1}$ : 3350–3460 (b, N–H), 3105 (C–H, aromatic), 3079 (C–H, aromatic) 2961 (C–H, aliphatic), 2928 (C–H, aliphatic) 1700 (C = 0), 1540 (C=N), 1501(C=C), 1490 (C=C), 1350 (C=C).

**$^1$H – NMR (300 MHz, $CDCl_3$)**

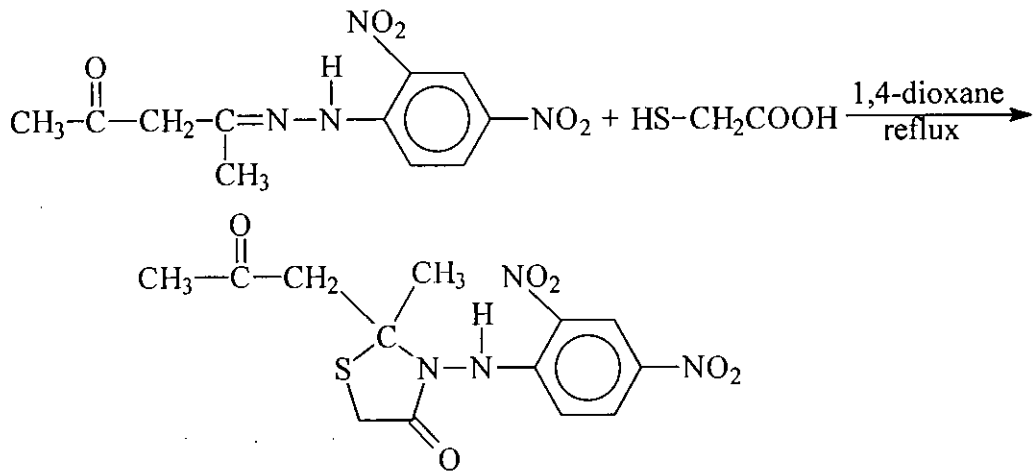
δ : 1.6 (b, 2H, $CH_2$), 2.2 (S, 6H, $CH_3$), 6.1 (S, 1H, N–H), 7.6 (d, 1H, aromatic), 8.5 (d, 1H, aromatic), 8.8 (S, 1H, aromatic).

**Mass Spectrun**

m/z : 278($M^+$.), 264, 222, 180, 110, 96, 83, 69, 55.

## 2.6.B SYNTHESIS OF 1-(2′,4′-DINITROPHENYLAMINO)-5,5-METHYL, ACETONYL THIAZOLIDINONE (H–13)

**Reaction involved**




**Procedure**

A mixture of acetylacetone 2,4-dinitrophenylhydrazone (0.28g, 1 m mol) and mercaptoa-cetic acid (0.184g, 2 m mol) was refluxed in 1,4-dioxane (10 ml) for 6 hours. The progress of the reaction was monitored by TLC (ethylacetate-pet.ether, 1:1, $R_f$ = 0.76). The reaction mixture was then cooled to room temperature and 1,4-dioxane was removed by rotary evaporator under reduced pressure. The resulting solid mass was recrystallized several times from ethylacetate. The desired compound was isolated as red crystal, mp. 109–111$^0$C, yield 53%.

**IR Spectrum**

$\nu_{max}$ (KBr) cm$^{-1}$ : 3377–3440 (b, N–H), 3079 (C–H, aromatic), 2977 (C–H, aliphatic), 1720 (C=O), 1550 (C=C, aromatic), 1511 (C=C, aromatic, 1495 (C=C, aromatic).

**$^1$H–NMR (300 MH$_z$, CDCl$_3$)**

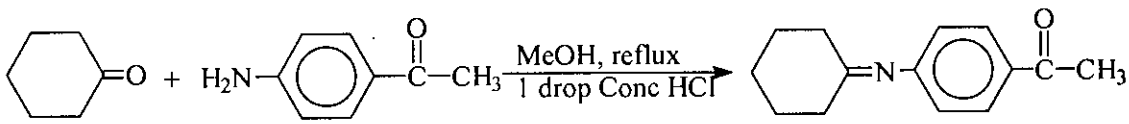
δ : 2.3 (S, 6H, $CH_3$), 3.6 (S, 2H, $CH_2$), 3.7 (S, 2H, $CH_2$), 6.7 (S, 1H, N–H), 7.7 (d, 1H, aromatic), 8.5 (d, 1H, aromatic), 8.7 (s, 1H, aromatic)

**Mass Spectrun**

m/z : 354($M^+$.), 311, 281, 255, 199, 143, 97, 74, 55.

## 2.7.A SYNTHESIS OF *P*-CYCLOHEXIMINOACETOPHENONE (H–14)

**Reaction involved**




**Procedure**

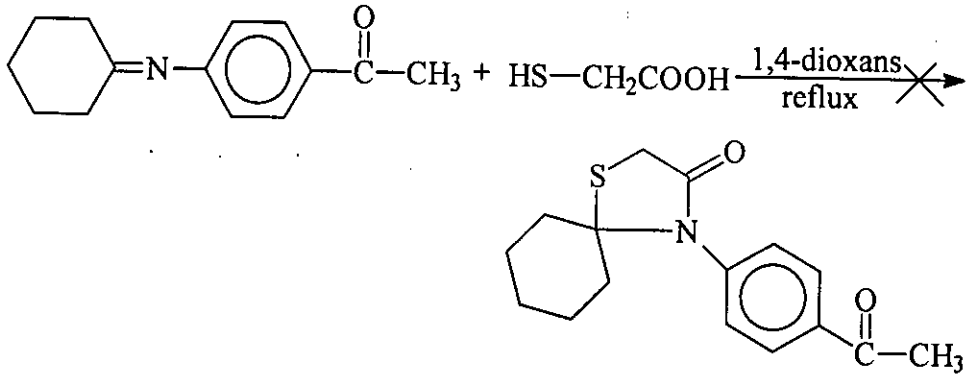
A mixture of cyclohexanone (0.294g, 3 m mol) and *p*-aminoacetophenone (0.405g, 3 m mol) was stirred in methanol (6 ml) for 3 hours at ice cool temperature. The progress of the reaction was monitored by TLC (pet.ether-ethylacetate, 1:1, $R_f = 0.65$). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resulting solid mass was recrystallized several times from ethylacetate. The desired compound was isolated as a yellow crystal, mp. 85–87$^0$C, yield 67%.

**Mass Spectrun**

m/z : 214($M^+$.), 183, 171, 157, 143, 129, 115, 101, 87, 74, 55.

## 2.7.B SYNTHESIS OF *N*(*p*-ACETOPHENYL)-SPIRO-(CYCLOHEXANE–THIAZOLIDINONE) (H–14a)

**Reaction involved**

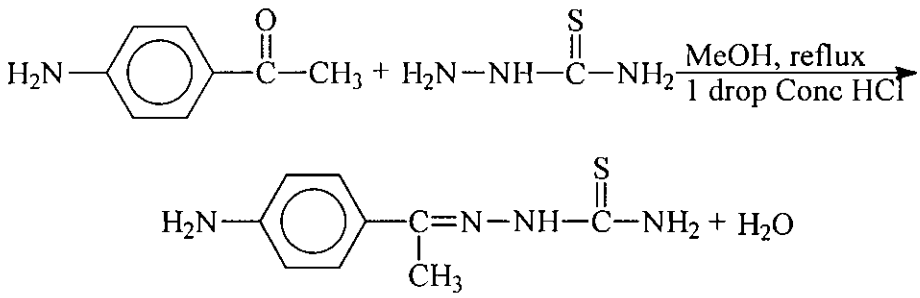



**Procedure**

A mixture of *p*-cyclohexaimino acetophenone (0.215g, 1 m mol) and mercaptoacetic acid (0.184g, 3 m mol) was refluxed in 1,4-dioxane (6 ml) 2 hours. The progress of the reaction was monitored by TLC (ethylacetate-pet.ether, 1:1). After two hours reflux many spots were observed on TLC which indicates many unstable products. The desired compound was not possible to isolate.

## 2.8.A SYNTHESIS OF *P*-AMINOACETOPHENONE THIOSEMICARBAZONE (H–15)

**Reaction involved**




**Procedure**

A mixture of *p*-aminoacetophenone (0.405g, 3 m, mol) and thiosemicarbazide (0.273g, 3 m mol) was refluxed in methanol (6 ml) for 7 hours. The progress of the reaction was monitored by TLC (ethylacetate-pet.ether, 7:3, $R_f$ = 0.57). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resulting solid mass was recrystallized several times from ethylacetate. The desired compound was isolated as a yellowish red crystal, mp. 155–157$^0$C, yield 66%.

**IR Spectrum**

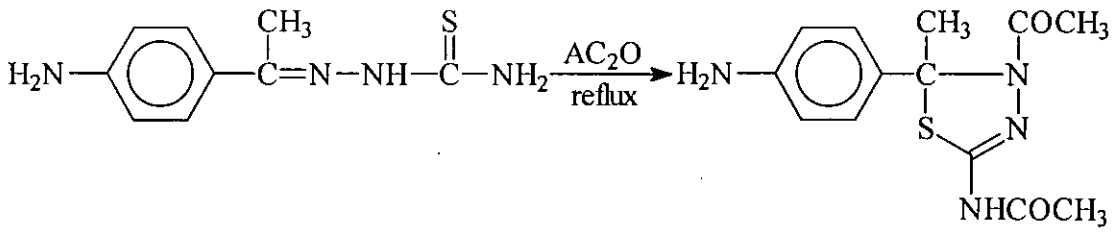
$\nu_{max}$ (KBr) cm$^{-1}$ : 3388–3444 (b, $NH_2$, NH), 3017 (C–H, aromatic), 2960 (C–H, aliphatic), 1620 (C=N), 1586 (C=C, aromatic), 1580 (C=C, aromatic), 1488 (C=S)

**Mass Spectrun**

m/z : 207($M^+$.), 147, 134, 118, 105, 92, 77, 65, 52.

## 2.8.B SYNTHESIS OF 5-METHYL-5-(*p*-AMINO PHENYL)-4-ACETYL-2-(ACETYLAMINO) $-\Delta^2-$THIADIAZOLINE (H–16)

**Reaction involved**




**Procedure**

A mixture of *p*-aminoacetophenone thiosemicarbazone (0.624g, 3 m mol) and distilled acetic anhydride (15 ml) was refluxed for 4 hours. The progress of the reaction was monitored by TLC (ethylacetate-pet.ether, 7:3, $R_f$ = 0.51). The reaction mixture was then cooled to room temperature and acetic anhydride was removed by rotary evaporator under reduced pressure. The resulting solid mass was purified by preparative thin layer chromatography as a yellow crystal, mp. 131–133$^0$C, yield 51%.

**IR Spectrum**

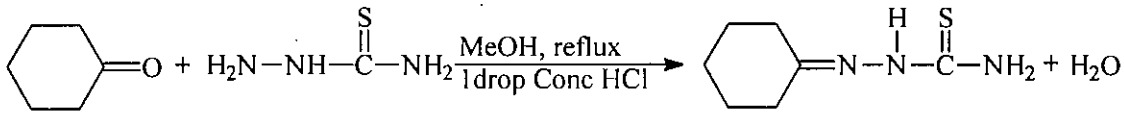
$\nu_{max}$ (KBr) $cm^{-1}$ : 3233–3437 ($NH_2$, NH), 3077 (C–H, aromatics, 2981 (C–H, aliphatic), 1671 (C=O), 1646 (C=0), 1612 (C=N), 1514 (C=C, aromatic), 1495 (C=C, aromatic), 1407 (C=C, aromatic).

**Mass Spectrum**

m/z : 292($M^+$.), 279, 250, 213, 165, 137, 123, 109, 95, 81, 69, 55.

## 2.9.A SYNTHESIS OF CYCLOHEXANONE THIOSEMICARBAZONE (H –19)

**Reaction involved**




**Procedure**

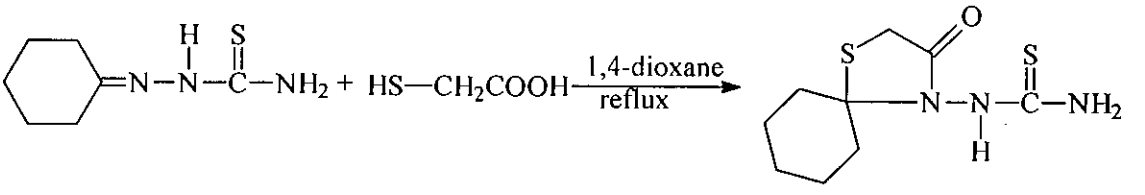
A mixture of cyclohexanone (0.588g, 6 m mol) and thiosemicarbazide (0.546g, 6 m mol) was refluxed in methanol (8 ml) in presence of hydrochloric acid (1 drop) for 6 hours. The progress of the reaction was monitored by TLC (ethylacetate-pet.ether, 1:1, $R_f$=0.51). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resulting solid mass was recrystallized several times from ethylacetate. The desired compound was isolated as a white crystal, mp. 156–158$^0$C, yield 72%.

**IR Spectrum**

$\nu_{max}$ (KBr) $cm^{-1}$ : 3143–3379 (b, $NH_2$, NH), 2972 (C–H), 2940 (C–H) 1641 (C=N), 1502 (C=S).

## 2.9.B SYNTHESIS OF *N*(THIOEURIDO)-SPIRO-(CYCLOHEXANE-THIAZOLIDINONE) (H –20)

**Reaction involved**




**Procedure**

A mixture of cyclohexanone thiosemicarbazone (0.513g, 3 m mol) and mercaptoacetic acid (0.552g, 6 m mol) was refluxed in 1,4-dioxane (10 ml) for 5 hours. The progress of the reaction was monitored by TLC (pet.ether-ethylacetate, 1:1, $R_f$=0.41). The reaction mixture was then cooled to room temperature and 1,4-dioxane was removed by rotary evaporator under reduced pressure. The crude solid mass was purified by column chromatography as a white crystal, mp. 177–179$^0$C, yield 51%.

**IR Spectrum**

$\nu_{max}$ (KBr) cm$^{-1}$ : 3177–3428 (b, $NH_2$, NH), 2936 (C–H), 2853 (C–H) , 1692 (C=0), 1501(C=S)

**Mass Spectrum**

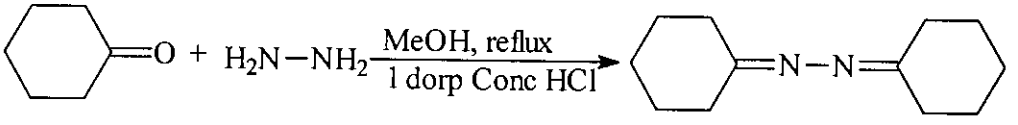
m/z : 245($M^+$.), 232, 215, 199, 186, 169, 157, 145, 128, 115, 95, 75, 63, 51.

# CHAPTER - 3

# RESULTS AND DISCUSSION

### 3.1.A Synthesis and characterization of cyclohexanone bis hydrazone (H–1)

A mixture of cyclohexanone (0.786g, 8 m mol) and hydrazine (0.128g, 4 m mol) was refluxed in methanol (10 ml) in presence of hydrochloric acid (1 drop) for 6 hours. The progress of the reaction was monitored by TLC (ethylacetate–pet.ether, 1:1, $R_f$ = 0.70). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resulting crude liquid product was purified by preparative thin layer chromatography, yield 71%.




**H–1**

Its IR spectrum (Fig: 1) showed a strong wide absorption bands at 2931 $cm^{-1}$ and 2856 $cm^{-1}$ for aliphatic C–H stretching of the cyclohexane ring. The two sharp bands at 1638 $cm^{-1}$ and 1557 $cm^{-1}$ were suggestive for two C=N bonds. A bunch of tiny bands at lower wave number were for C–H bending vibrations.

The $^1$H–NMR spectrum (300 MHz, $CDCl_3$, Fig: 2) showed a broad multiplet at δ 1.4–1.9 of twelve protons were indicating for cyclohexane protons far from nitrogen atom. A multiplet at δ 2.2–2.4 integrating eight protons were ascribable for cyclohexane ring protons nearby to the pyramidal nitrogen atoms. The spliting of the cyclohexane protons were due to the absence of coplanarity of the two cyclohexane ring.

The mass spectrum (Fig: 3a) showed m/z 192 ($M^+$) which was suggestive for the molecular weight (192). The fragmentation pattern (Fig: 3b) and other important peaks would be rationalized as fragments from m/z 192.

The $^{13}$C–NMR (300 MHz, CDCl3 Fig: 4) showed the signals for 12 carbons as δ 23.09, 24.94 (C–4, C–4′), 25.89, 26.33 (C–3, C–3′), 26.97, 27.52 (C–5, C–5′), 27.85, 35.60 (C–2, C – 2′), 36.45, 41.90 (C–6, C–6′), 163.23, 165.48 ( C–1, C–1′). The two signals at the lowest field were indicative for imino carbon.

Therefore, IR spectrum, $^{1}$H–NMR spectrum, Mass spectrum and $^{13}$C–NMR spectrum expressed harmony for the structure and it was named as cyclohexane bis hydrazone.

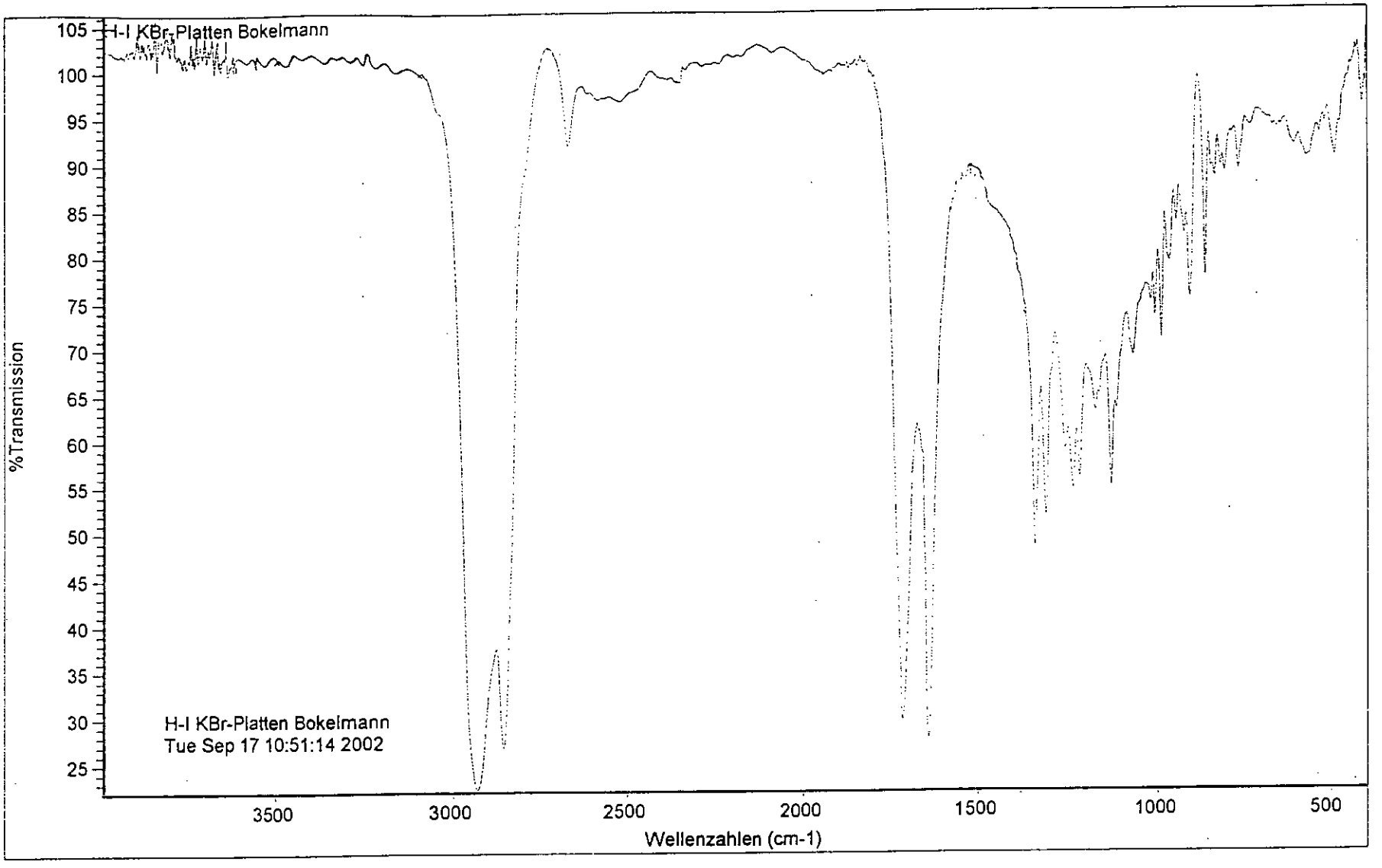



**Figure 1: IR spectrum of the compound (H–1)**

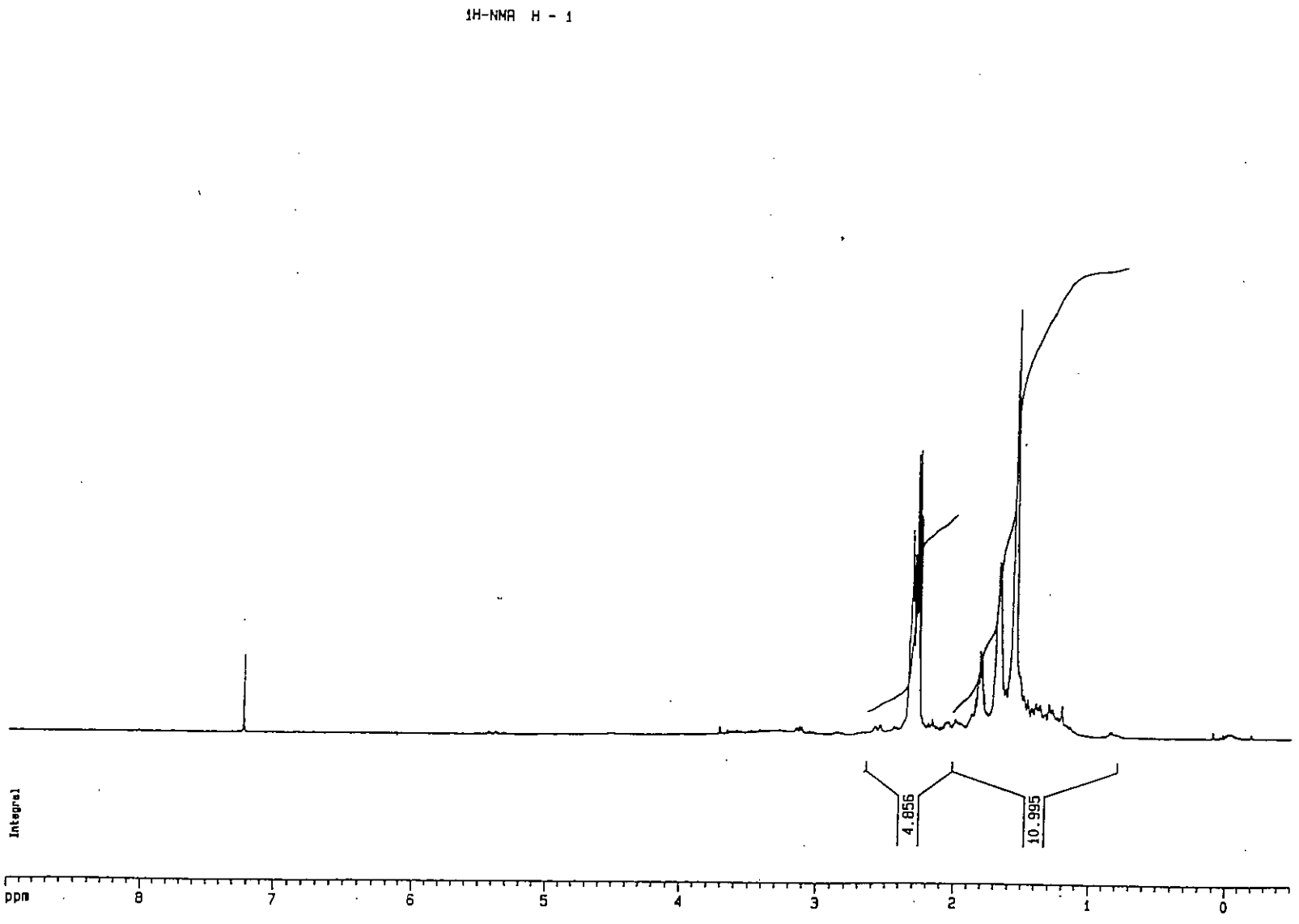



**Figure 2:** $^{1}$**H–NMR spectrum of the compound (H–1)**

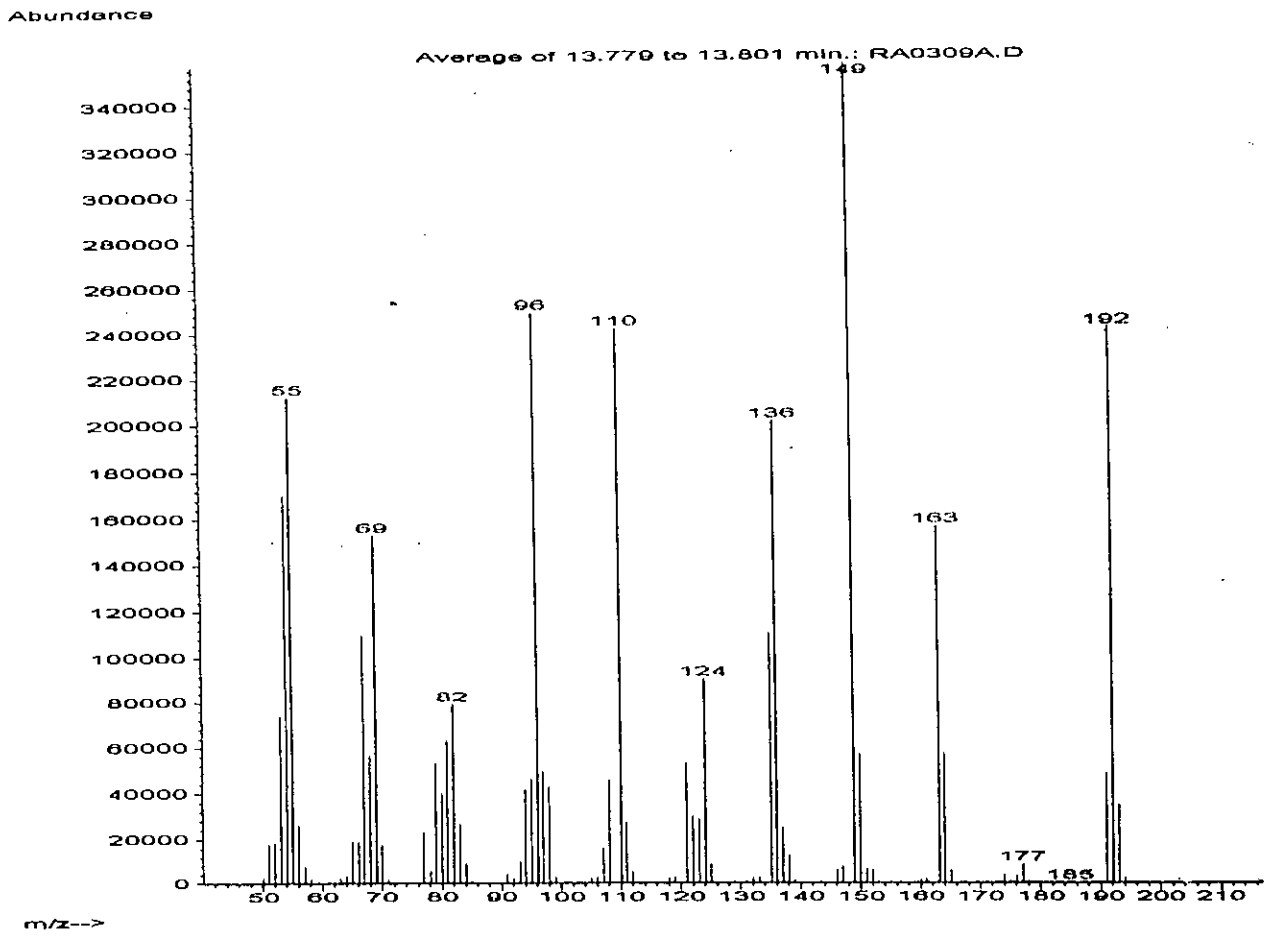



**Figure 3a: Mass spectrum of the compound (H–1)**

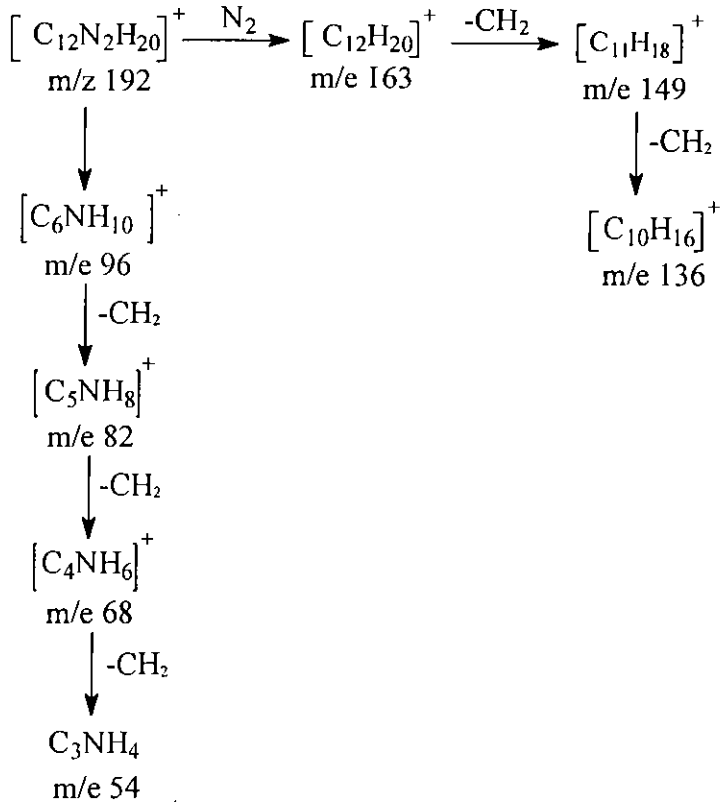



Fig: 3b Fragmentation pattern of the compound (H–1)

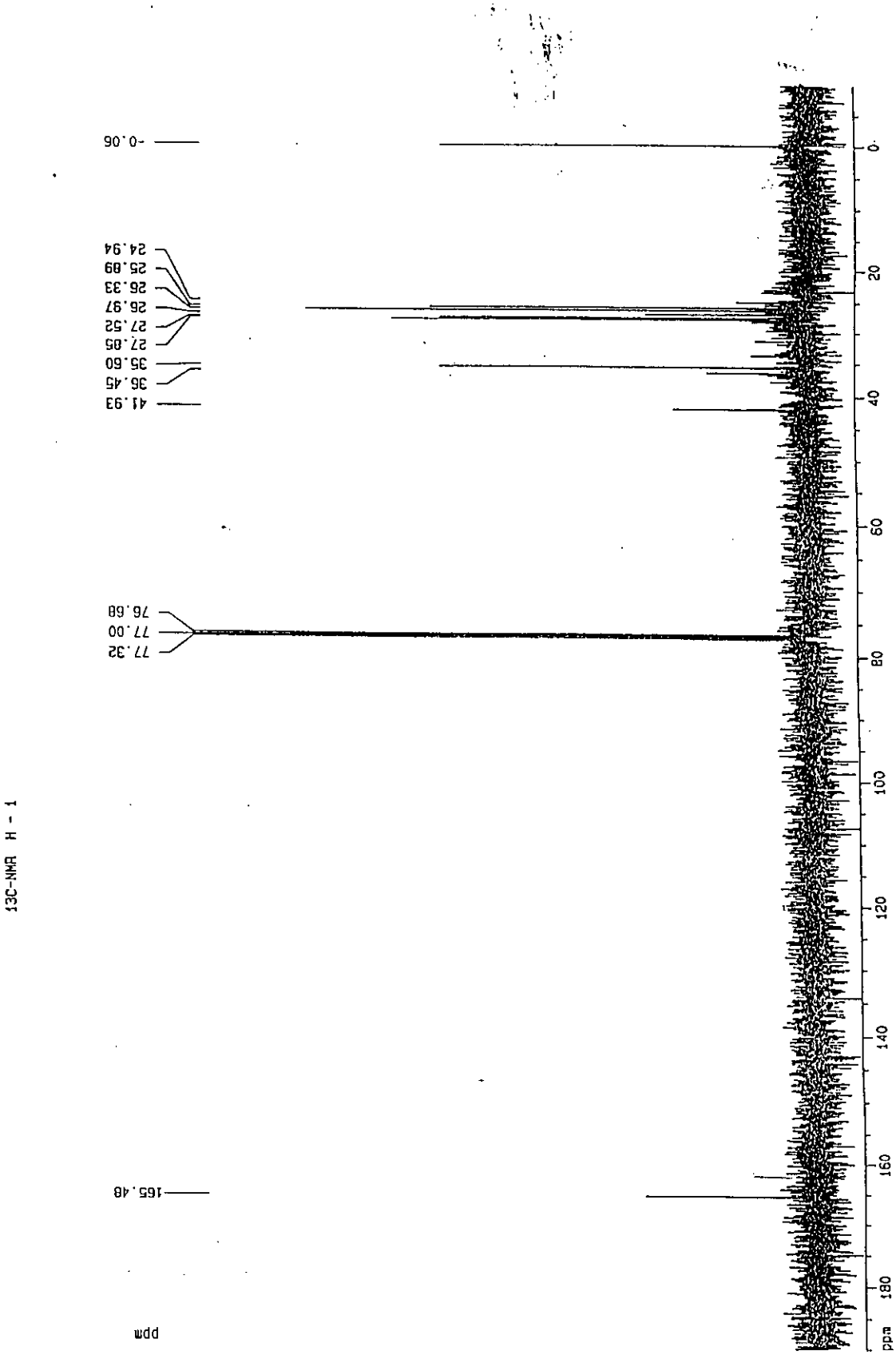
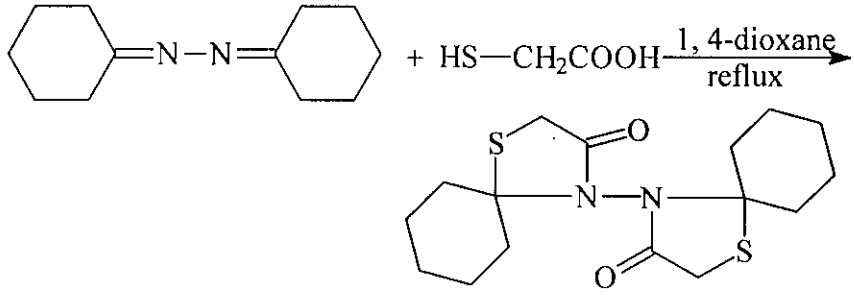



**Figure 4:** $^{13}C$–NMR spectrum of the compound (H–1)

### 3.1.B Synthesis and characterization of bis spiro-(cyclohexane-thiazolidinone) (H–2)

A mixture of cyclohexanone bis hydrazone (0.768g. 4 m mol) and mercaptoacetic acid (1.472g, 16 m mol) was refluxed in 1,4-dioxane (8 ml) for 8 hours. The progress of the reaction was monitored by TLC (pet.ether-ethylacetate, 1:1, $R_f$ = 0.67). The reaction mixture was then cooled to room temperature and 1, 4-dioxane was removed by rotary evaporator under reduced pressure. The crude product was purified by column chromatography. The desired compound was isolated as a yellow liquid yield 58%.




**H–2**

Its IR spectrum (Fig: 5) showed wide absorption bands at 2940 $cm^{-1}$ and sharp 2858 $cm^{-1}$ for aliphatic C–H stretching. The broad absorption band at 1774 $cm^{-1}$ was observed for two overlapping C=O group of five membered ring. The absorption band at 1223 $cm^{-1}$ was due to C–N stretching. The sharp band at 1126 $cm^{-1}$ was suggestive for C–S stretching absorption. All other intensified peaks were observed for C–H bending vibrations.

The $^1$H–NMR spectrum (300 MHz, $CDCl_3$ Fig: 6) showed multiplet at δ 1.1–1.25 integrating two protons. The multiplet at δ 1.26–1.4 integration seven protons, multiplet at δ 1.5–1.7 integrating for five profons, multiplet at 1.75–1.85 for five protons and multiplet at 1.9–2.0 for five protons. The total 24 protons were detected from integration but specific signal for specific protons were not assignable.

Therefore, based on the IR spectrum and $^1$H–NMR spectrum confirmed (H–2) as the desired compound named as bis spiro-(cyclohexane-thiazolidinone).

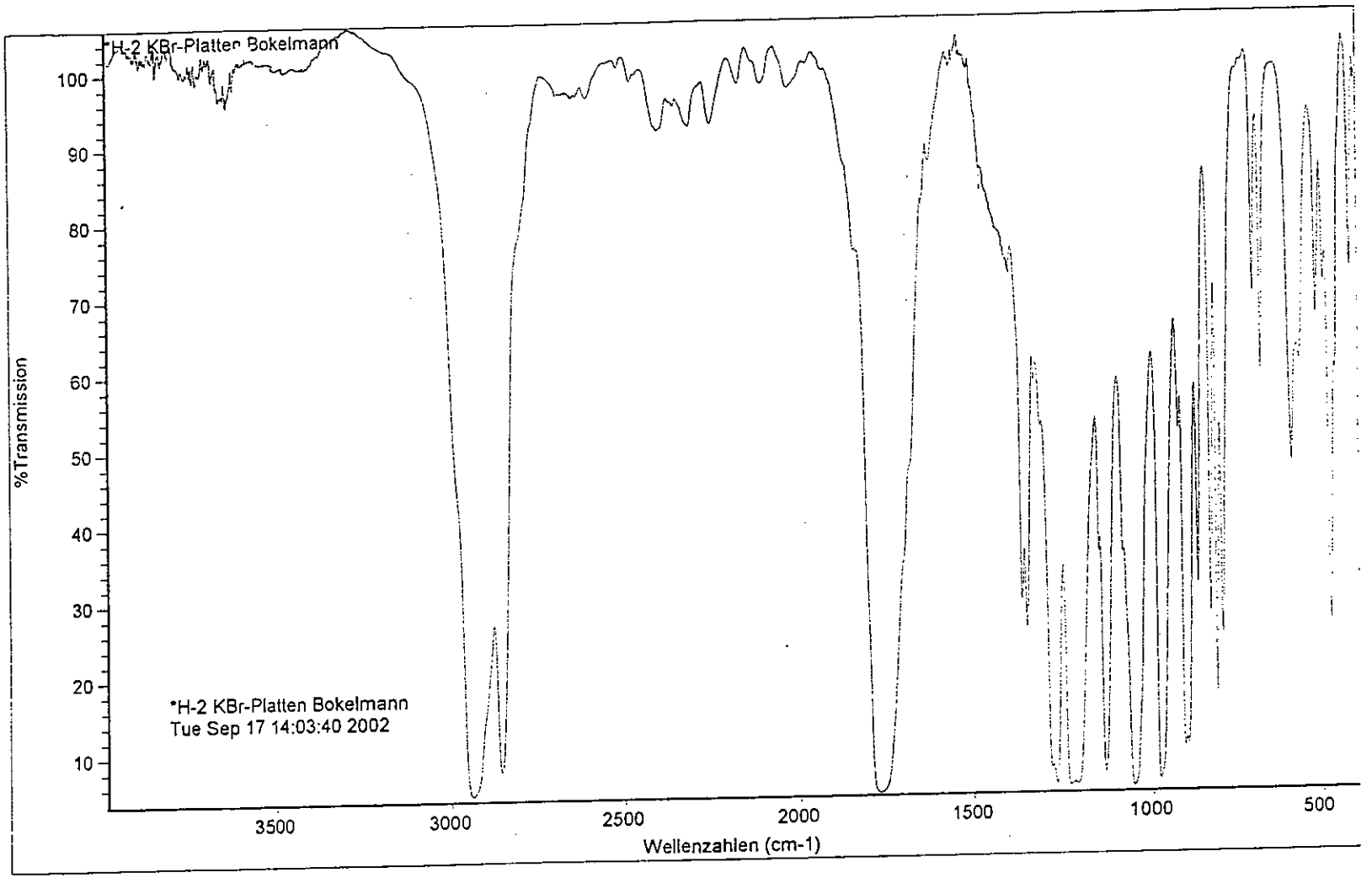



**Figure 5: IR spectrum of the compound (H–2)**

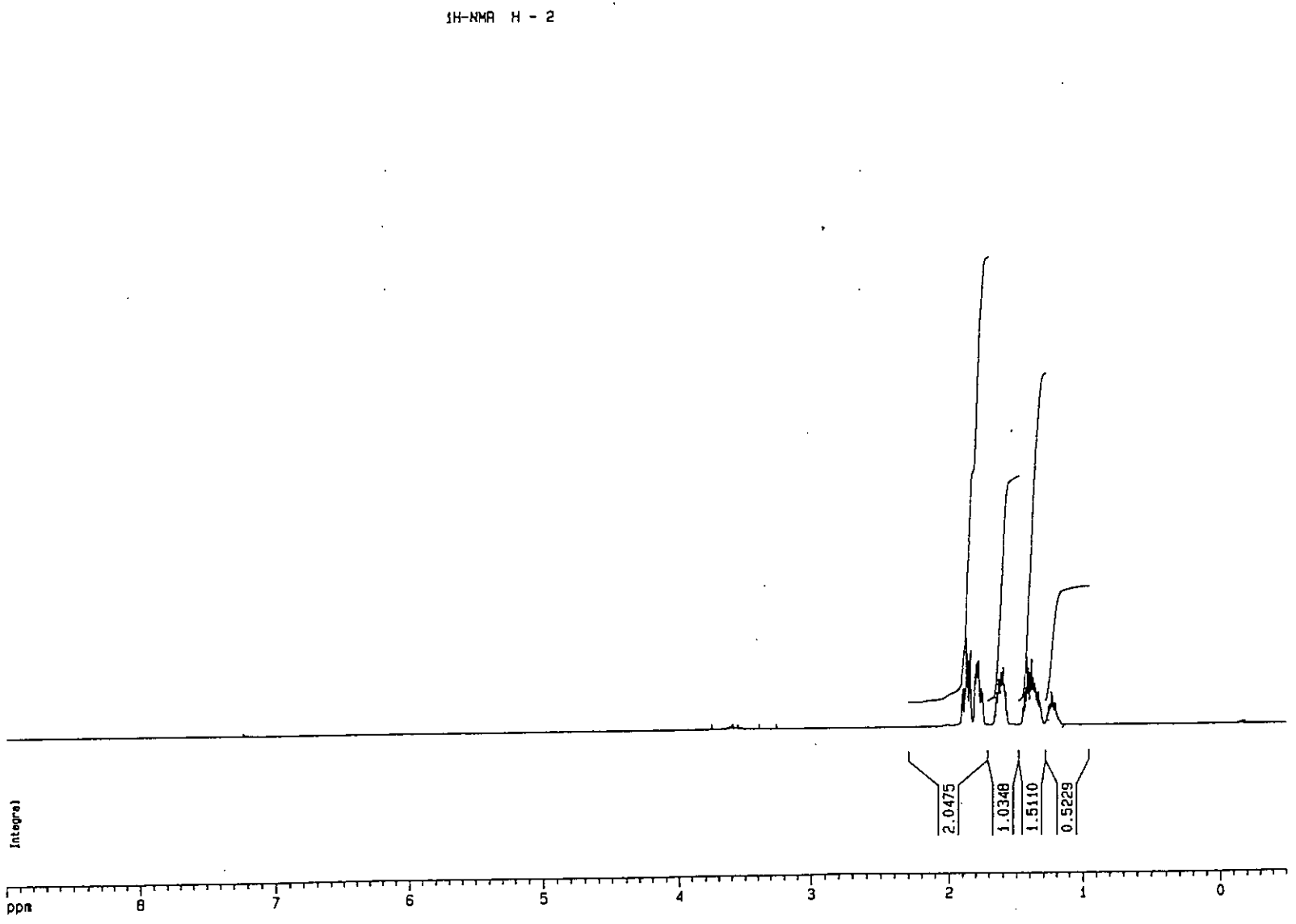
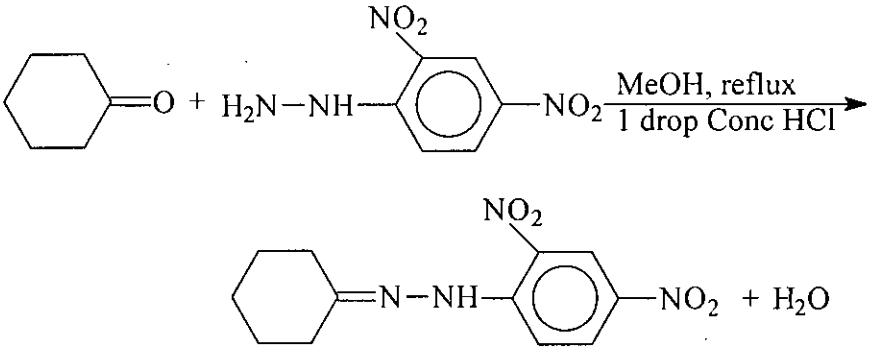



**Figure 6:** $^{1}$**H–NMR spectrum of the compound (H–2)**

### 3.3.A Synthesis and characterization of cyclohexanone 2,4-dinitrophenyl-hydrazone (H–5)

A mixture of cyclohexanone (0.294g, 3 m mol) and 2, 4-dinitrophenyl hydrazine (0.594g, 3 m mol) was refluxed in methanol (6 ml) in presence of hydrochloric acid (1 drop) for 6 hours. The progress of the reaction was monitored by TLC (pet.ether-ethylacetate, 7:3, $R_f$ =0.78). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resulting solid mass was recrystallized several times from ethylacetate. The desired compound was isolated as a yellow crystal, mp. 150–52$^0$C, yield 68%.




**H–5**

Its IR spectrum (Fig: 7) showed a sharp absorption band at 3306 $cm^{-1}$ was ascribable for NH group. A weak band showed at 3109 $cm^{-1}$ was suggestive for C–H stretching of aromatic moiety. Another weak band at 2942 $cm^{-1}$ were indicative for C–H stretching of aliphatic moiety. The aromatic C=C bonds were assigned from the band at 1498 $cm^{-1}$, 1450 $cm^{-1}$, 1424 $cm^{-1}$. The band at 1265 $cm^{-1}$ was observed for N=0 bond.

The $^1$H–NMR spectrum (300 MHz, $CDCl_3$, Fig: 8) showed multiplet at δ 1.6–1.9 integrating six ($3CH_2$) cyclohexane ring proton away from nitrogen and δ 2.4–2.6 integrating four protons for $2CH_2$ of cyclohexane ring nearby C=N bond. The dublet at δ 7.9 and δ 8.2 were suggestive for aromatic proton. A singlet at δ 9.1 was suggestive for aromatic proton. One proton integration at δ 11.2 was assignable for NH group.

The Mass spectrum (Fig: 9) showed m/z 278 ($M^+$) which was suggestive for the molecular weight (278). The fragmentation pattern was not exactly correlated with the molecular ion peak (m/z 278).

Therefore, based on the IR spectrum, $^1$H–NHR spectrum and Mass spectrum confirmed (H–5) as the desired compound and it was named as cyclohexanone 2,4-dinitrophenyl hydrazone.

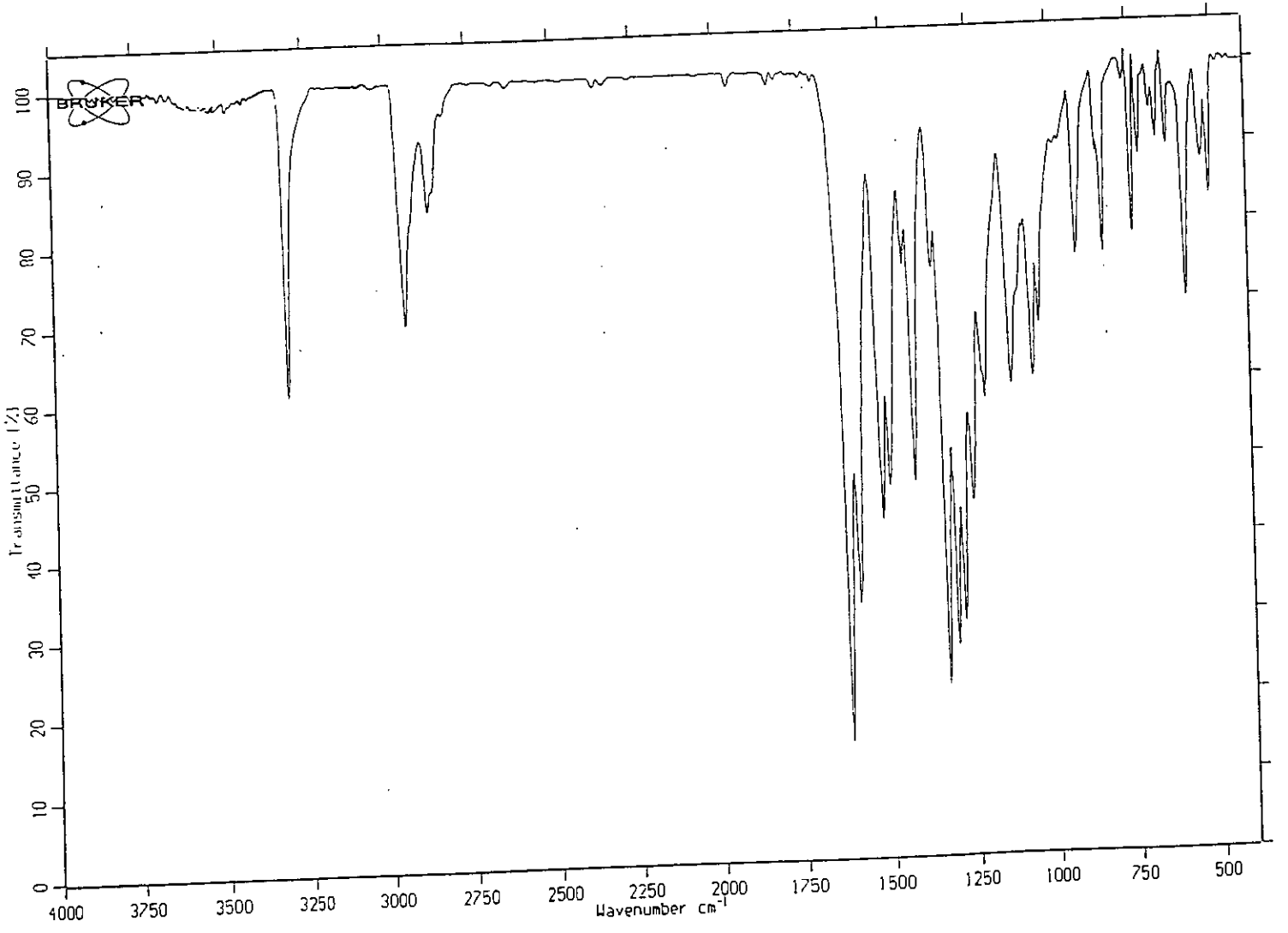



**Figure 7: IR spectrum of the compound (H–5)**

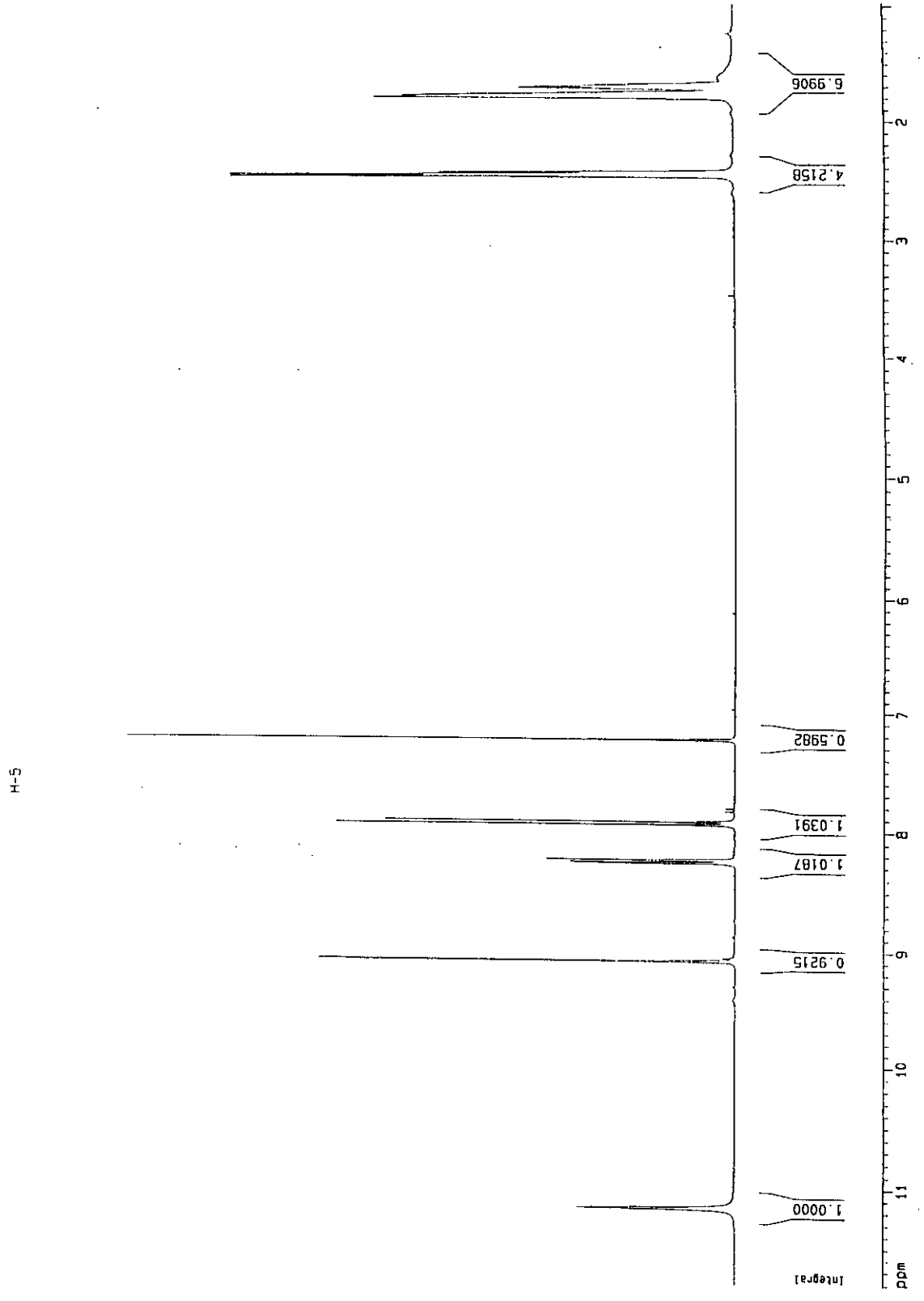



**Figure 8:** $^{1}$H–NMR spectrum of the compound (H–5)

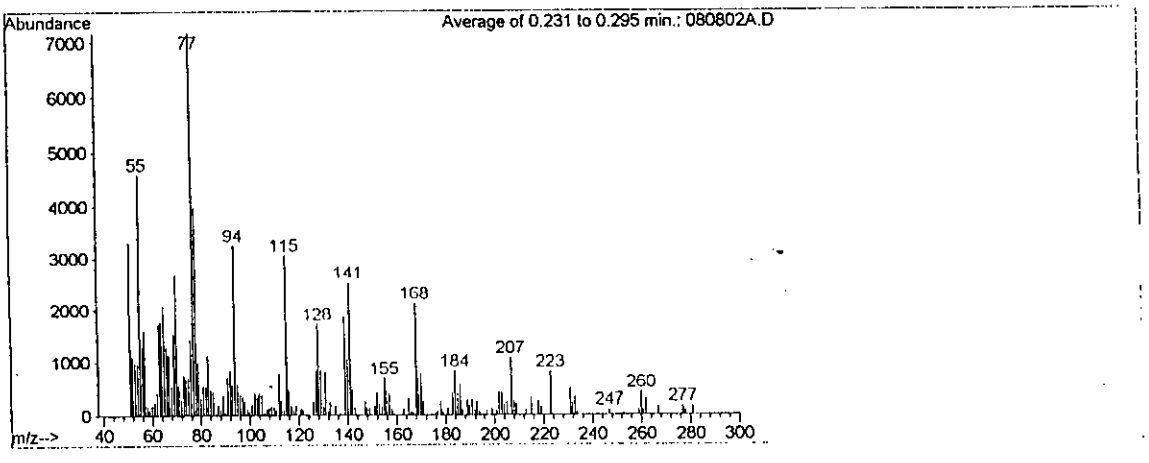
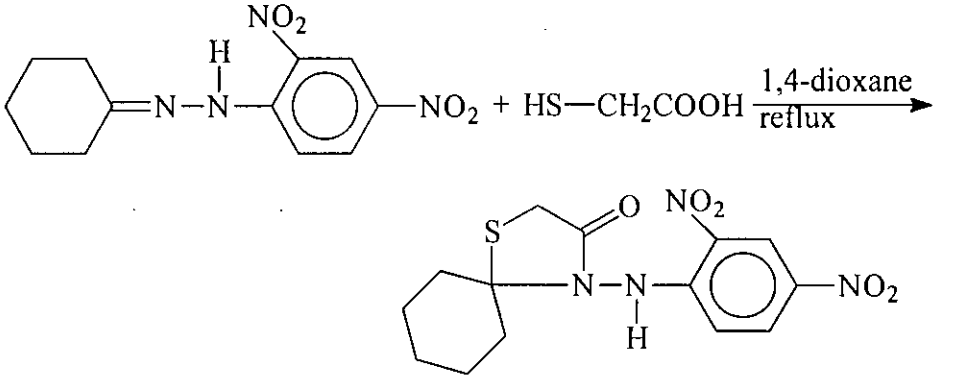



**Figure 9: Mass spectrum of the compound (H–5)**

### 3.3.B Synthesis and characterization of *N*–(2,4-dinitrophenylamino) spiro-(Cyclohexane-thiazolidinone) (H–6)

A mixture of cyclohexanone 2,4-dinitrophenyl hydrazone (0.278g, 1 m mol) and mercaptoacetic acid (0.184g, 2 m mol) was refluxed in 1,4-dioxane (6 ml) for 4 hours. The progress of the reaction was monitored by TLC (pet.ether-ethylactate, 6:4, $R_f$ = 0.53). The reaction mixture was then cooled to room temperature and 1,4-dioxane was removed by rotary evaporator under reduced pressure. The resulting solid mass was recrystallized several times from 95% ethanol. The desired compound was isolated as redish yellow crystal, mp. 128–130$^0$C, yield 57%.




**H–6**

Its IR spectrum (Fig: 10) showed a sharp absorption band at 3305 cm$^{-1}$ was ascribable for NH group. A weak band showed at 3109 cm$^{-1}$ was suggestive for C–H stretching of aromatic moiety. Another weak band at 2942 cm$^{-1}$ was indicative for C–H stretching of aliphatic moiety. The sharp absorption band at 1735 cm$^{-1}$ was observed for C=0. The aromatic C=C bonds were assigned from the band at 1550 cm$^{-1}$, 1510 cm$^{-1}$, 1495 cm$^{-1}$. The band at 1260 cm$^{-1}$ was indicative for N = 0 bond.

The $^1$H–NMR spectrum (300 MHz.$CDCl_3$, Fig:11) showed multiplet at δ 1.5–1.7 integrating eight protons for cyclohexane ring away from nitrogen atom and δ2.4–2.5 indicative four proton for two protons of $CH_2$ cyclohexane ring nearby nitrogen atom and two proton for $CH_2$–CO. The dublets at δ 7.9 and δ 8.2 were assignable for aromatic protons. A singlet at δ 9.1 integrating for one aromatic proton. One proton integration at δ 11.1 was assignable for NH group.

The mass spectrum (Fig: 12) showed m/z 352 ($M^+$) which was suggestive for the molecular ion peak. The fragmentation pattern was not exactly rationalized with the m/z 352. Only few fragmentations showed correlation with m/z 352.

Therefore IR spectrum, $^1$H–NMR spectrum and Mass spectrum confirmed (H – 6) as the desired structure and it was named as *N*-(2,4-dinitro-phenylamine) spiro-(cyclohexane-thiazolidinone).

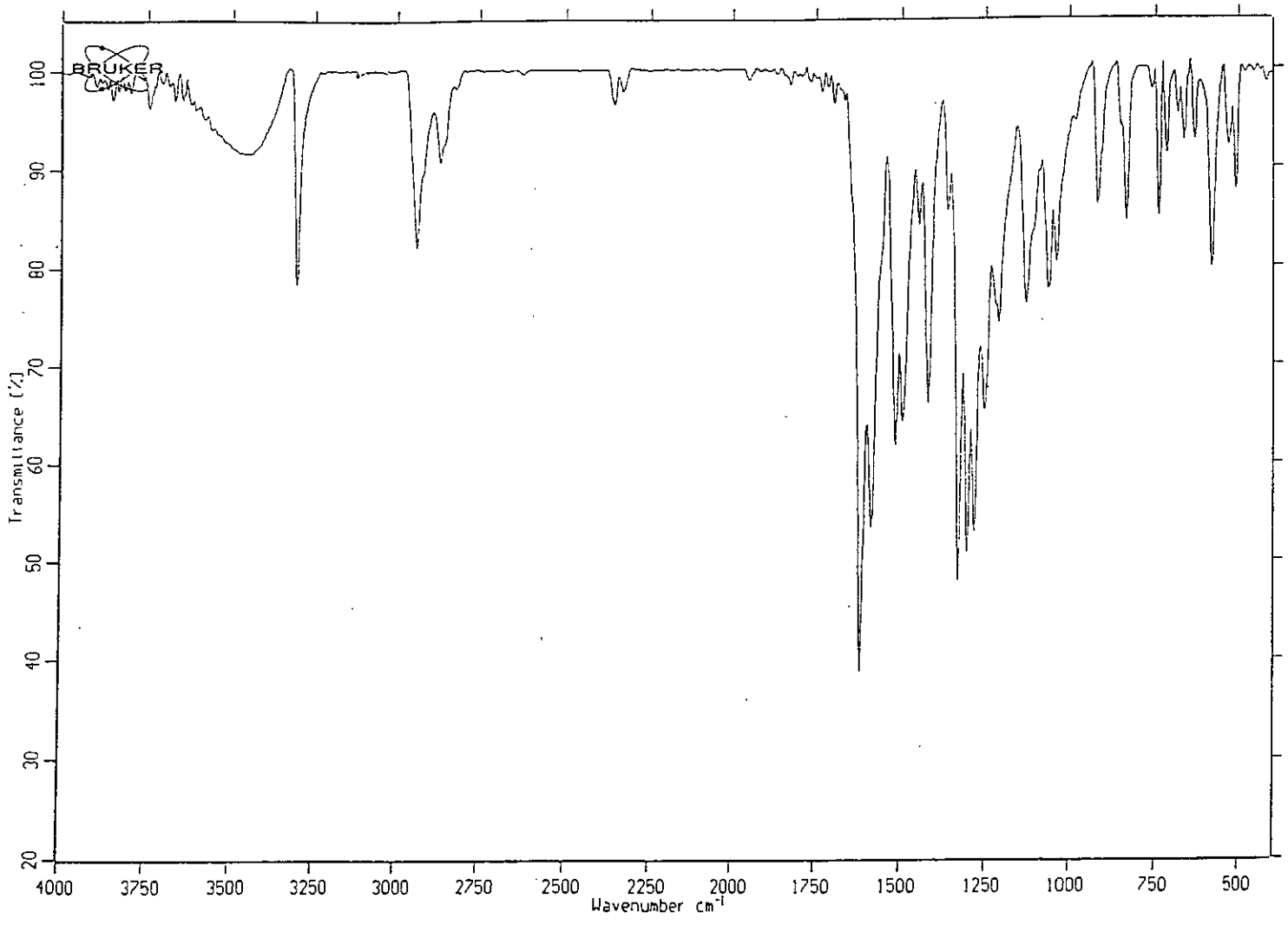



**Figure 10: IR spectrum of the compound (H–6)**

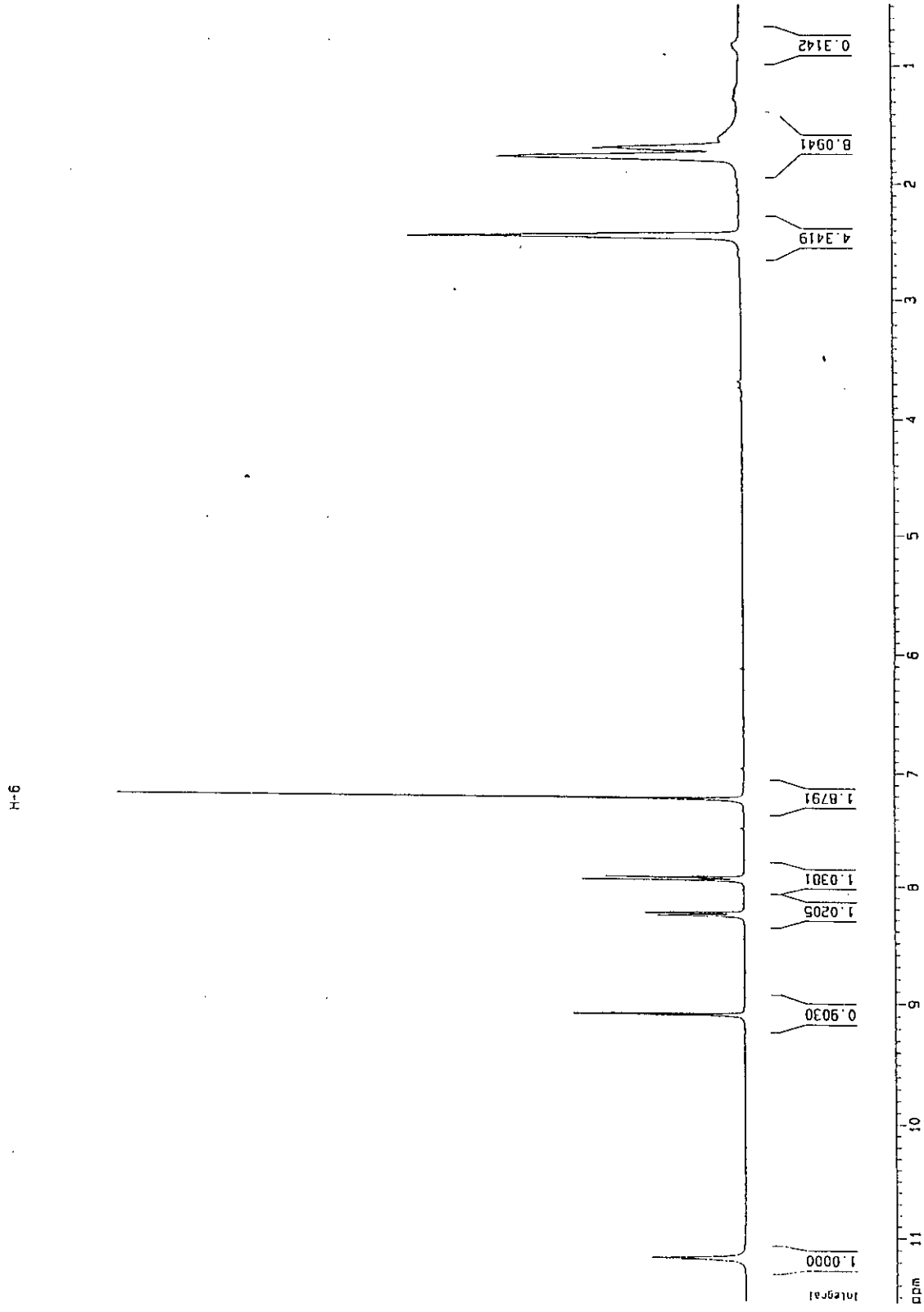



**Figure 11: $^{1}$H–NMR spectrum of the compound (H–6)**

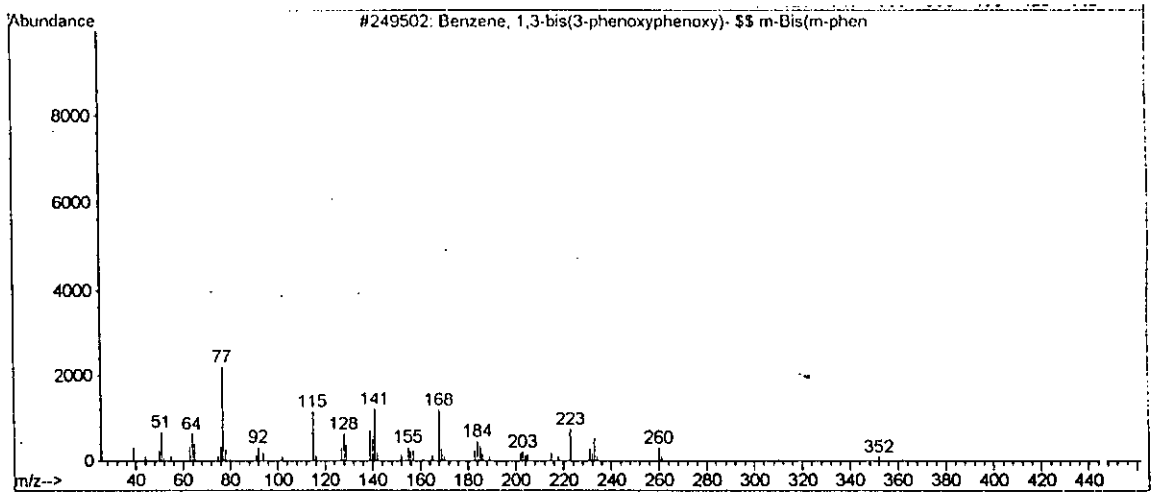
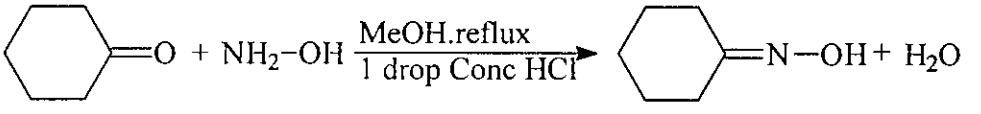



**Figure 12: Mass spectrum of the compound (H–6)**

### 3.4.A Synthesis and characterization of cyclohexanone oxime (H–7)

A mixture of cyclohexanone (0.588g, 5 m mol) and hydroxylamine (0.417g, 6 m mol) was refluxed in methanol (10 ml) in presence of hydrochloric acid (1 drop) for 7 hours. The progress of the reaction was monitored by TLC (pet.ether-ethylacetate, 7:3, $R_f$=0.66). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The desired compound was purified by column chromatography as a colourless semi solid, yield 62%.




**H–7**

Its IR spectrum (Fig: 13) showed a broad absorption band at 3376–3490 $cm^{-1}$ was indicative for O–H. The broad band at 2951–2810 $cm^{-1}$ was indicative for aliphatic C–H stretching. The sharp absorption band at 1605 $cm^{-1}$ was due to the C=N stretching.

The $^1$H-NMR spectrum (300 MHz, $CDCl_3$, Fig: 14) showed multiplet at δ 1.3–1.5, δ 1.5–1.65 and δ 2.5–2.7 were ascribed for aliphatic protons. The integrations were not assignable for specific protons but total ten cyclohexane proton were indicative. The O–H peak was merged with the cyclohexane ring absorption peak.

The mass spectrum (Fig: 15) showed m/z 113 ($M^+$), which was suggestive of the molecular ion peak. The fragmentation pattern was rationalized with the molecular ion peak.

Therefore, IR spectrum, $^1$H-NMR spectrum and Mass spectrum of the compound confirmed (H–7) to be the desired structure named as cyclohexanone oxime.

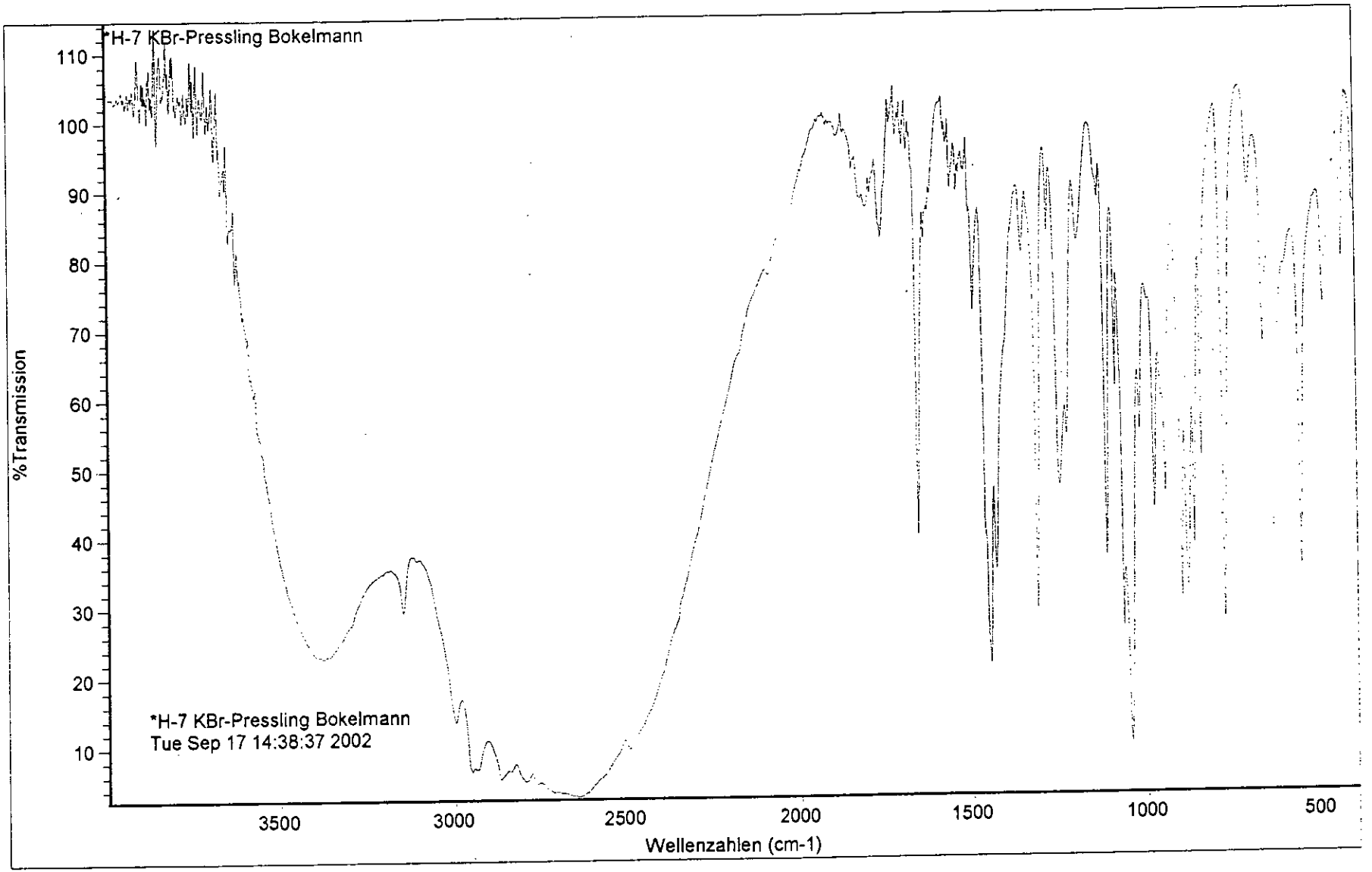



**Figure 13: IR spectrum of the compound (H–7)**

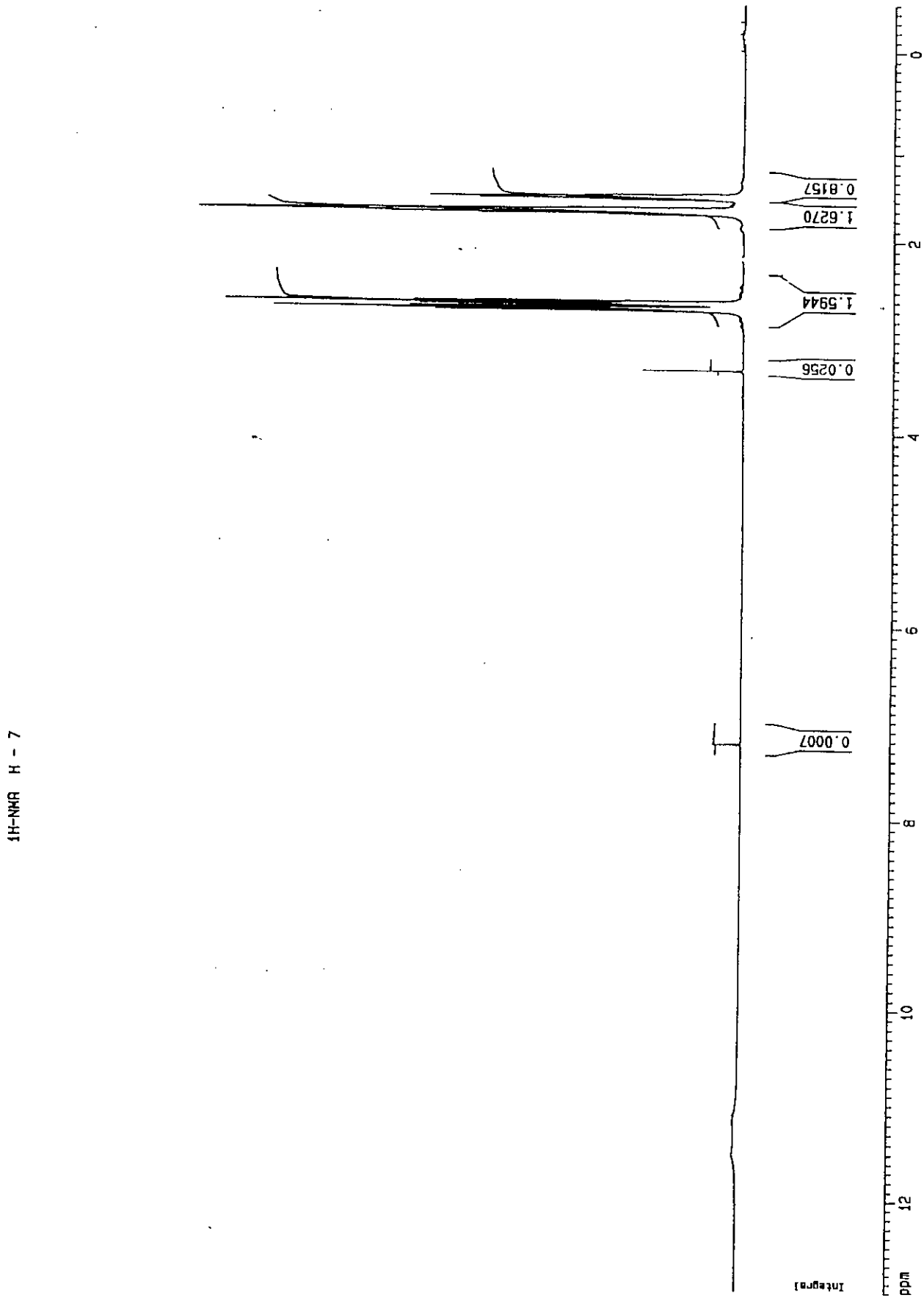



**Figure 14: $^{1}$H–NMR spectrum of the compound (H–7)**

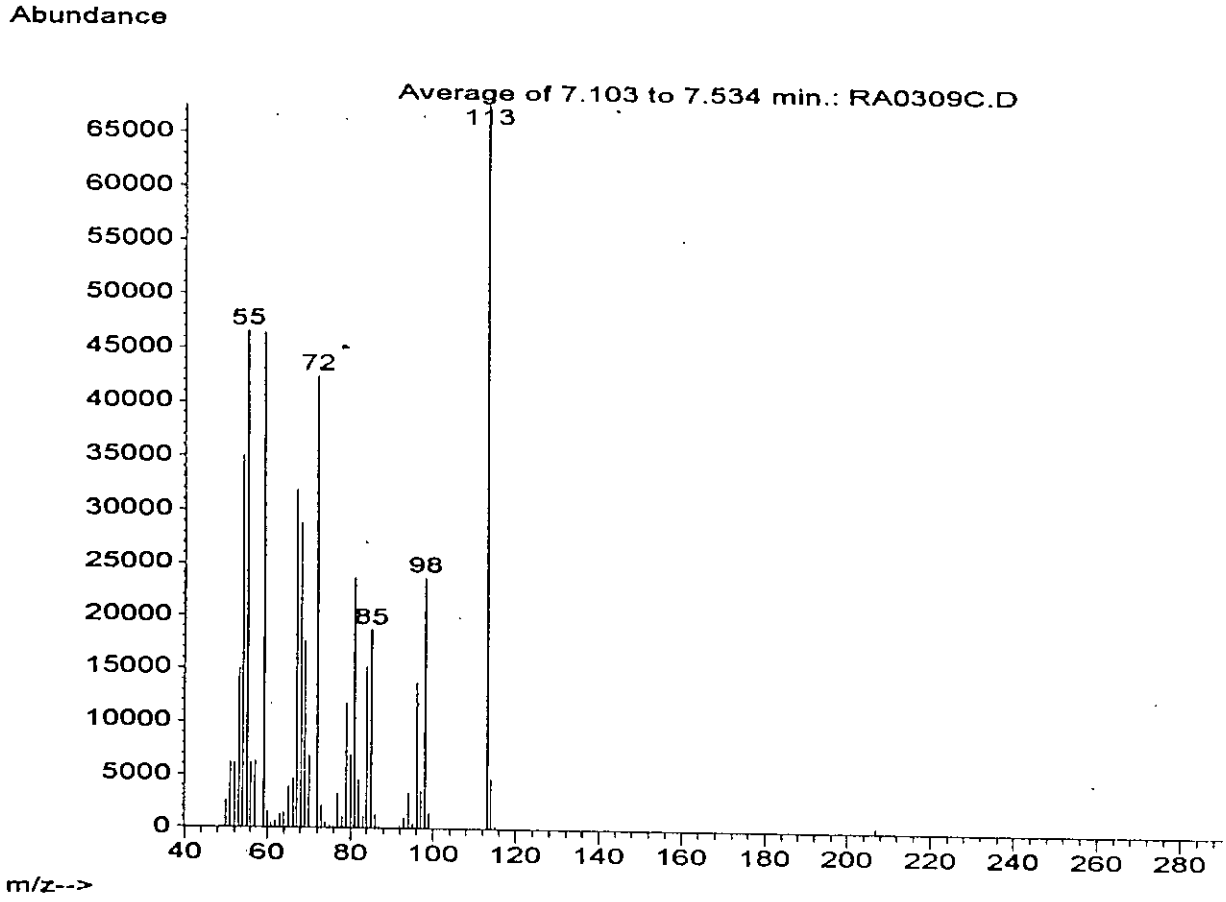
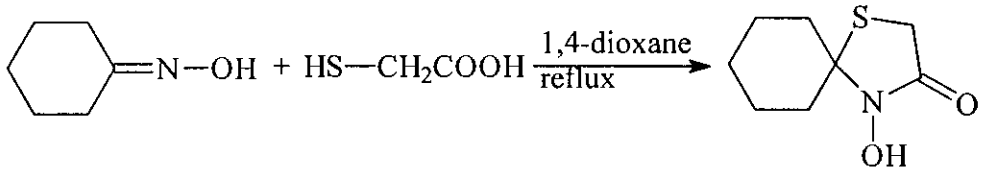



**Figure 15: Mass spectrum of the compound (H–7)**

### 3.4.B Synthesis and characterization of *N*-hydroxy spiro-(cyclohexane-thiazolidinone) (H–8)

A mixture of cyclohexanone oxime (0.678g, 6 m mol) and mercaptoacetic acid (1.11g, 12 m mol) was refluxed in 1,4-dioxane (10 ml) for 3 hours. The progress of the reaction was monitored by TLC (pet.ether-ethylactate, 7:3, $R_f$= 0.59). The reaction mixture was then cooled to room temperature and 1,4-dioxane was removed by rotary evaporator under reduced pressure. The crude solid mass was purified by column chromatography as white crystal, mp. 177–179$^0$C, yield 63%.




**H–8**

Its IR spectrum (Fig: 16) showed a broad absorption band at 3450 – 3260 $cm^{-1}$ was indicative for O–H stretching which showed intermolecular hydrogen bonding. The broad band at 2960 – 2850 $cm^{-1}$ was indicative for aliptatic C–H stretching. The broad absorpton band at 1715 $cm^{-1}$ was due to the C=O stretching.

Other spectral evidences were not available but the distinct absorption of OH, C–H and C=O group in IR proved the desired structure.

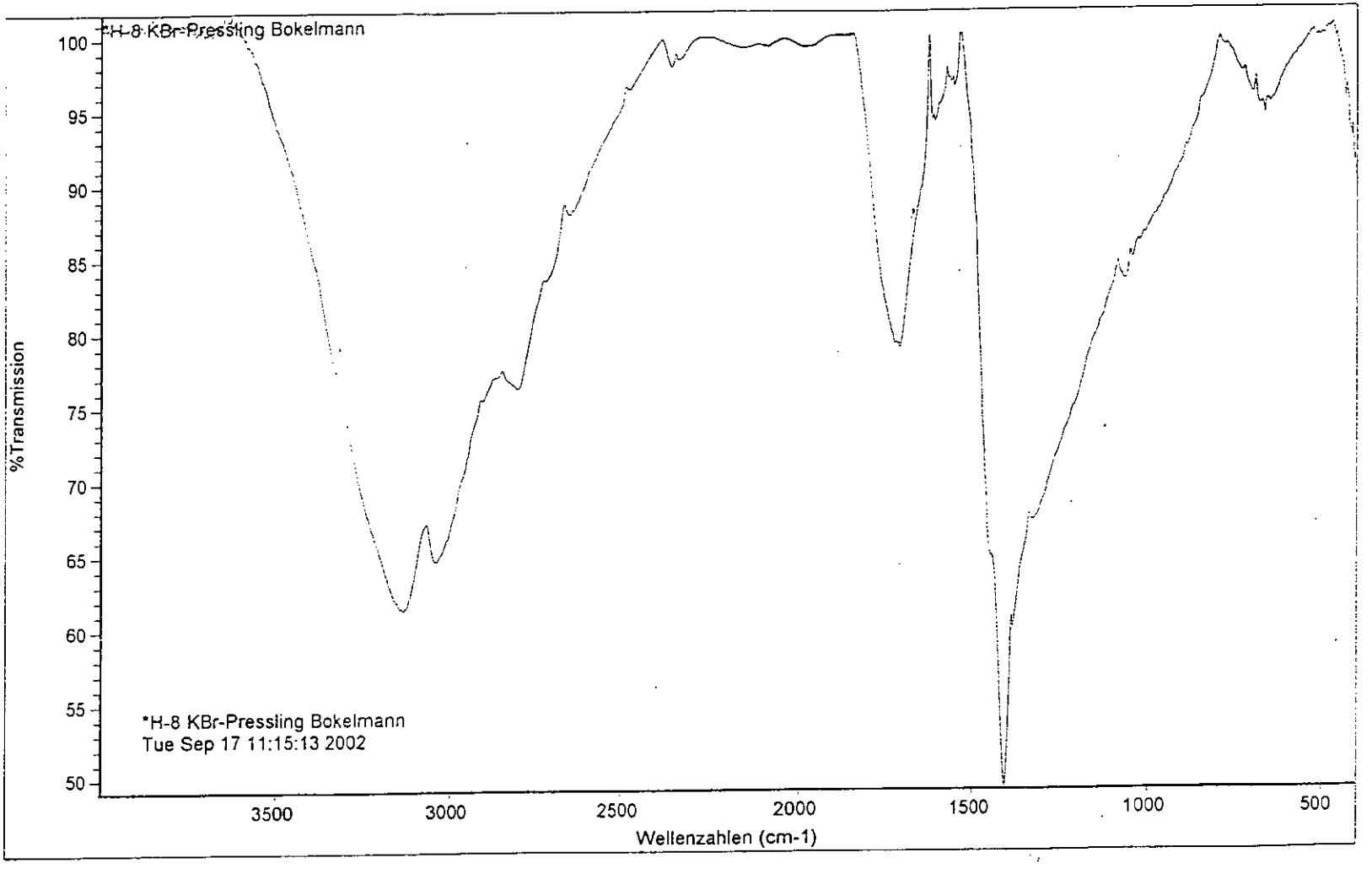
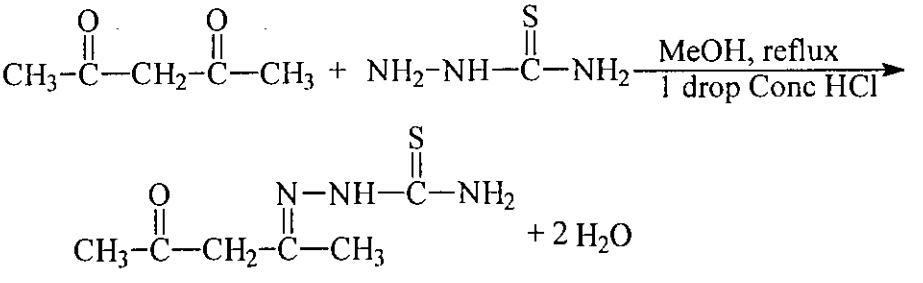



**Figure 16: IR spectrum of the compound (H–8)**

### 3.5.A Synthesis and characterization of acetylacetone thiosemicarbazone (H–10)

A mixture of acetylacetone (0.20g, 2 m mol) and thiosemicarbazide (0.364g, 4 m mol) was stirred in methanol (8 ml) in presence of hydrochloric acid (1 drop) for 4 hours at room temperature. The progress of the reaction was monitored by TLC (pet.ether-ethylacetate, 7:3, $R_f$ = 0.76). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resulting semi solid mass was recrystallized several times from ethylacetate. The desired compound was isolated as a white crystal, yield 65%.




**H–10**

Its IR spectrum (Fig: 17) showed a broad absorption band at ranging from 3100–3450 $cm^{-1}$ was indicative for $NH_2$ or NH groups. The absorption band at 2945 $cm^{-1}$ for aliphatic C–H stretching. The band at 1710 $cm^{-1}$ was due to the C=O moiety. The band at 1609 $cm^{-1}$ was suggestive for C=N moiety. The band at 1501 $cm^{-1}$ was indicative for C=S bond. The shorter wave length absorption of C=S moiety was due to the presence of two nearby electronegative nitrogen atom. The distinctive absorption in IR was suggestive for the desired structure.

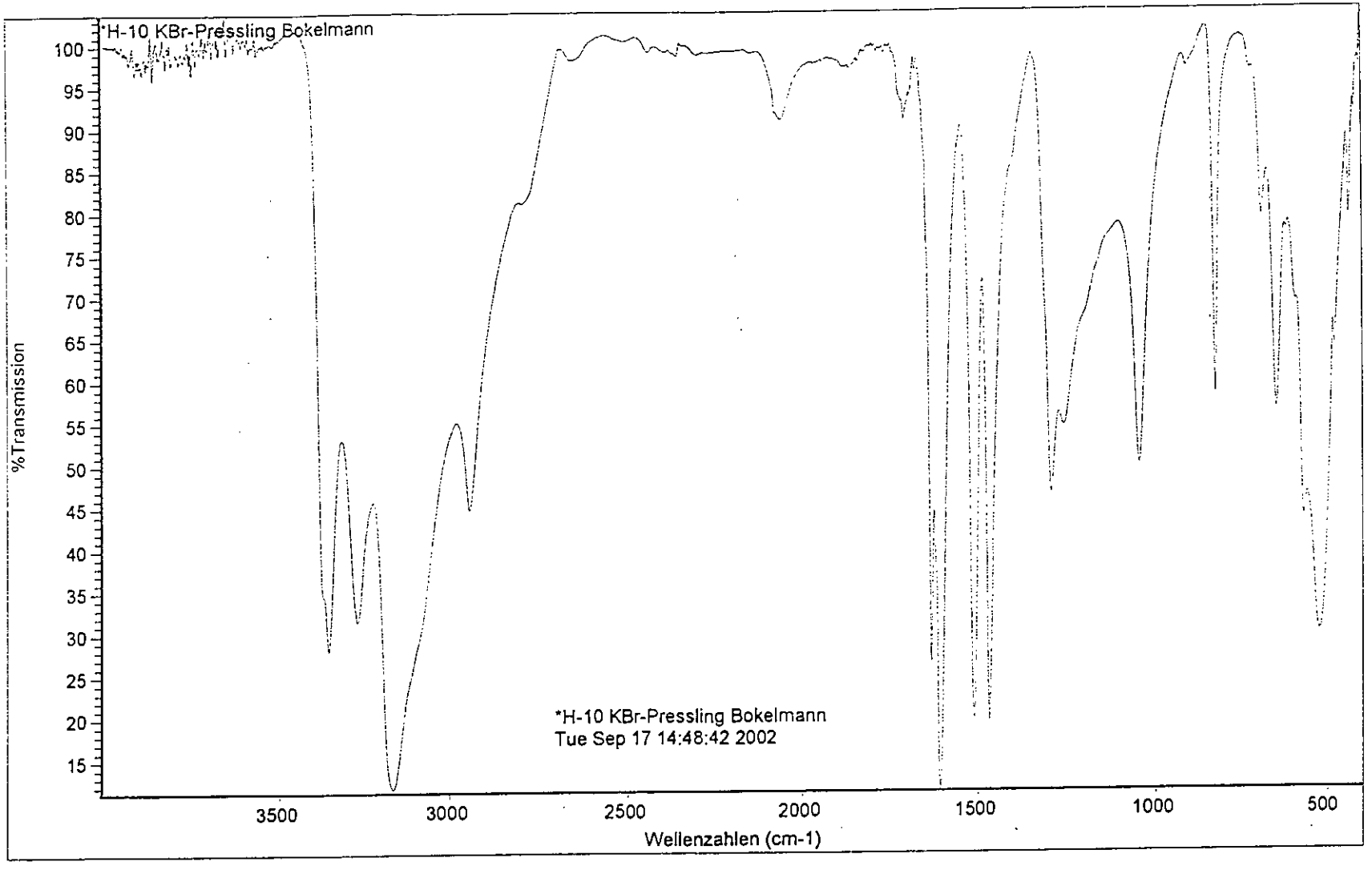
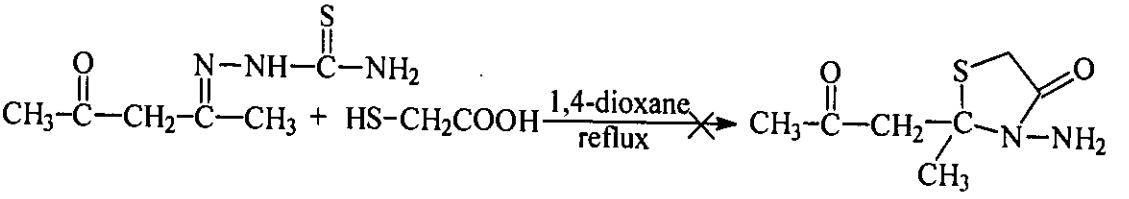



**Figure 17: IR spectrum of the compound (H–10)**

### 3.5.B Synthesis and characterization of 2(*N*-aminothiazolidinono) pentane-4-one) (H–11)

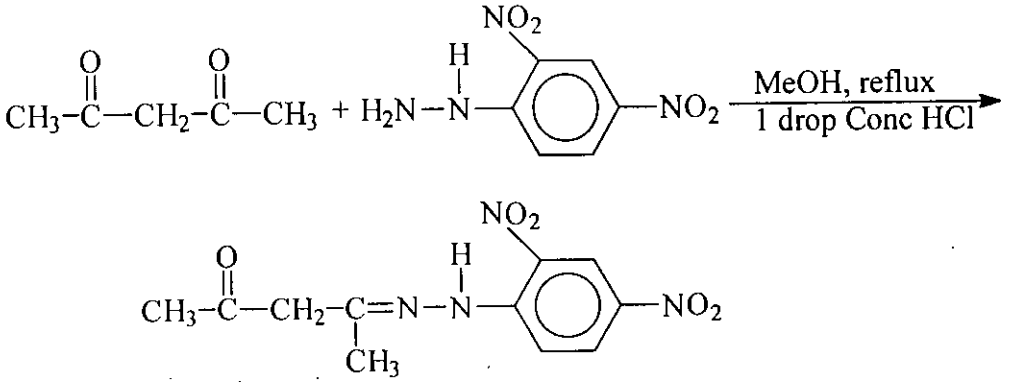
A mixture of acetylacetone thiosemicarbazone (0.49g, 2 m mol) and mercaptoacetic acid (0.74g, 8 m mol) was refluxed in 1,4-dioxane (8 ml) for 6 hours. The reaction mixture was then cooled to room temperature and 1,4-dioxane was removed by rotary evaporator under reduced pressure. The crude gummy mass was not possible to purify.




**H–11**

### 3.6.A Synthesis and characterization of acetylacetone 2,4-dinitrophenyl hydrazone (H–12)

A mixture of acetylacetone (0.30g, 3 m mol) and 2,4-dinitrophenyl hydrazine (1.188g, 6 m mol) was refluxed in methanol (8 ml) in presence of hydrochloric acid (1 drop) for 7 hours. The progress of the reaction was monitored by TLC (ethylacetate-pet.ether, 1:1, $R_f$=0.82). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resulting solid mass was recrystallized several times from ethylacetate. The desired compound was isolated as a redish yellow crystal, mp. 90–92$^0$C, yield 58%.




**H–12**

Its IR spectrum (Fig: 18) showed a broad absorption band ranging from 3350–3460 $cm^{-1}$ was indicative for NH group. The absorption band at 3105 $cm^{-1}$ and 3079 $cm^{-1}$ were C–H stretching for aromatic C–H, very weak absorption band were observed at 2961 $cm^{-1}$ and 2928 $cm^{-1}$ for aliphatic C–H stretching. The band at 1700 $cm^{-1}$ was indicative for C=O bond. The bands at 1540 $cm^{-1}$ was ascribable for C=N moiety. The band at 1501, 1490 and 1350 $cm^{-1}$ were ascribable for the C=C bond of aromatic ring.

The $^1$H–NMR spectrum (300 MHz, $CDCl_3$, Fig: 19) showed broad singlet at δ 1.6 integrating two protons were suggestive for methylene group. A singlet at δ 2.2 integrating six protons were attributable for methyl group. A peak at δ 6.1 integrating one proton was ascriable for NH proton. Two doublets at δ 7.6 and δ 8.5 were assignable for aromatic protons. A singlet at δ 8.8 integrating one proton was assignable for aromatic proton.

The Mass spectrum (Fig: 20) showed m/z ($278^+$) which was suggestive for the molecular ion peak. The unusual fragmentation pattern in the mass spectrum was not possible to establish correlation to the molecular ion peak. Therefore, IR spectrum, $^1$H-NMR spectrum and Mass spectrum expressed harmony for the structure named as acetylacetone 2,4-dinitrophenyl hydrazone.

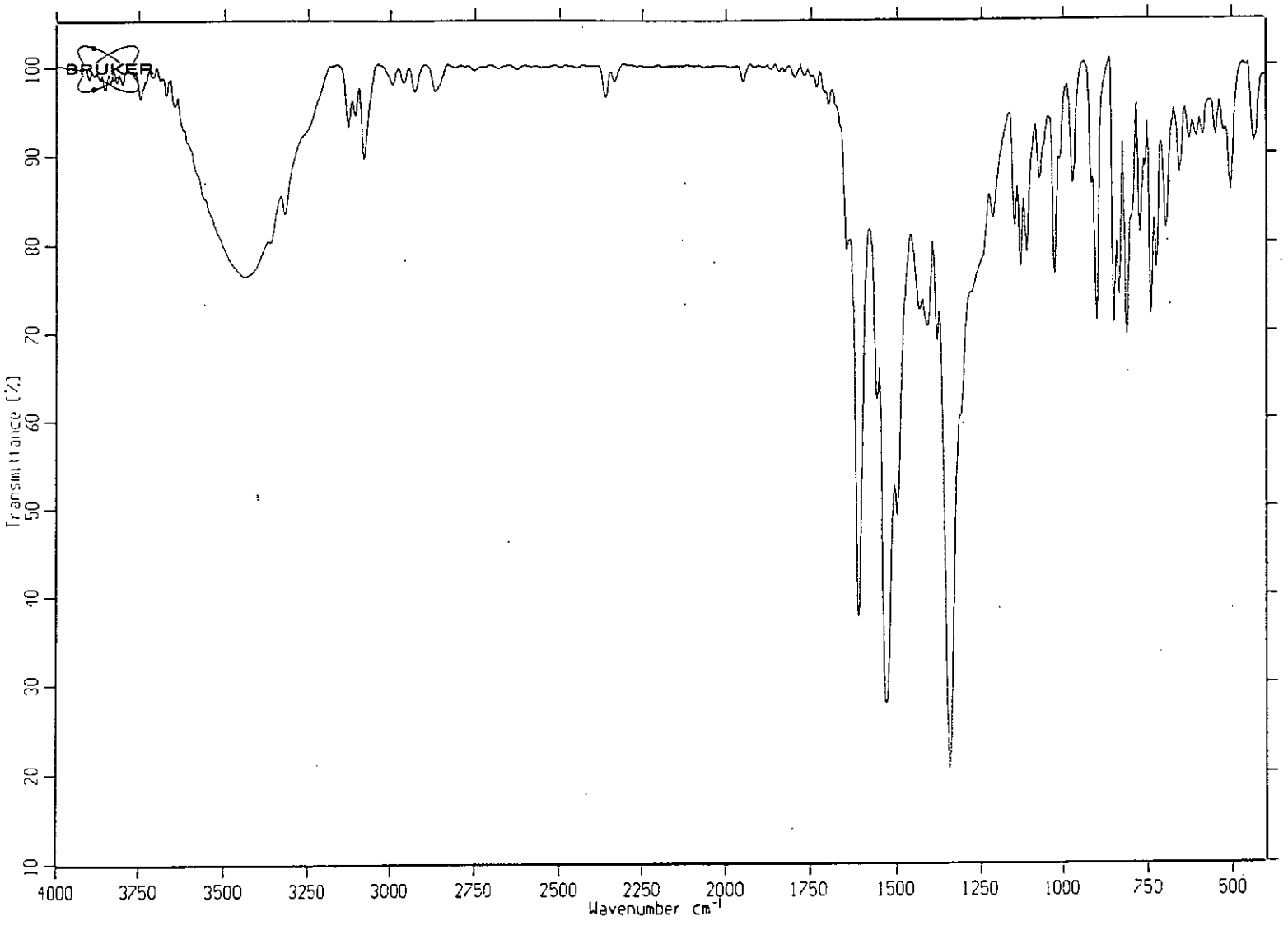



**Figure 18: IR spectrum of the compound (H–12)**

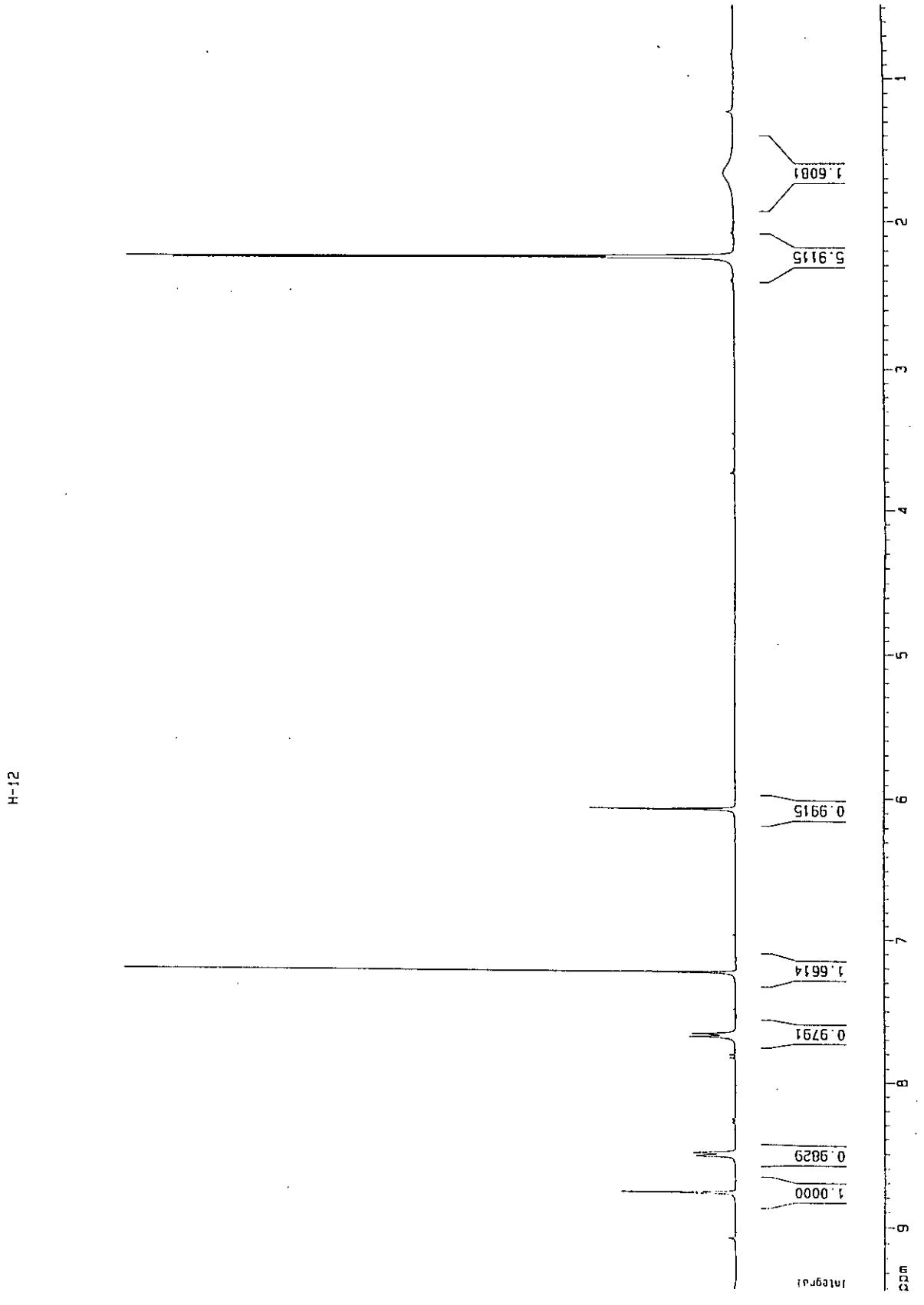



**Figure 19: $^1$H–NMR spectrum of the compound (H–12)**

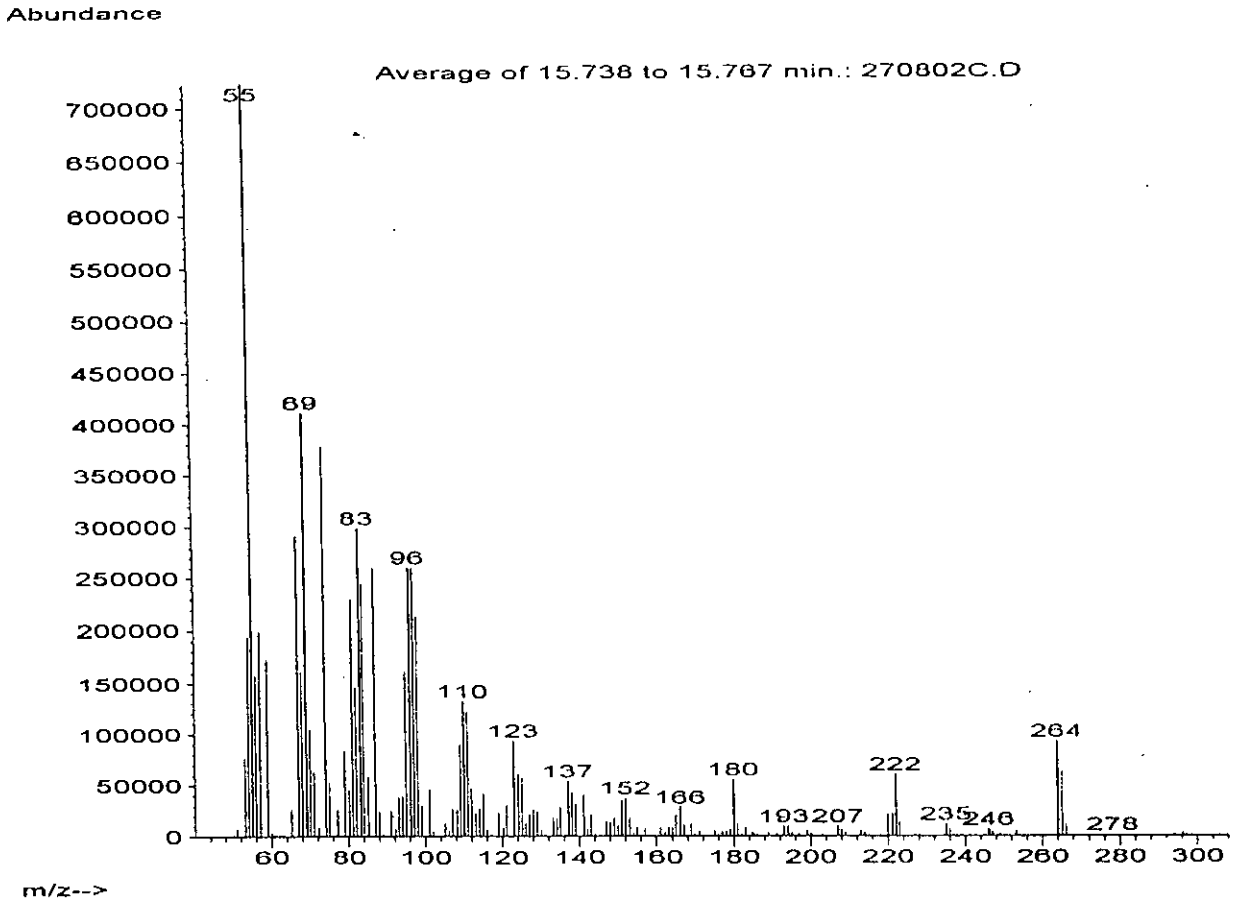
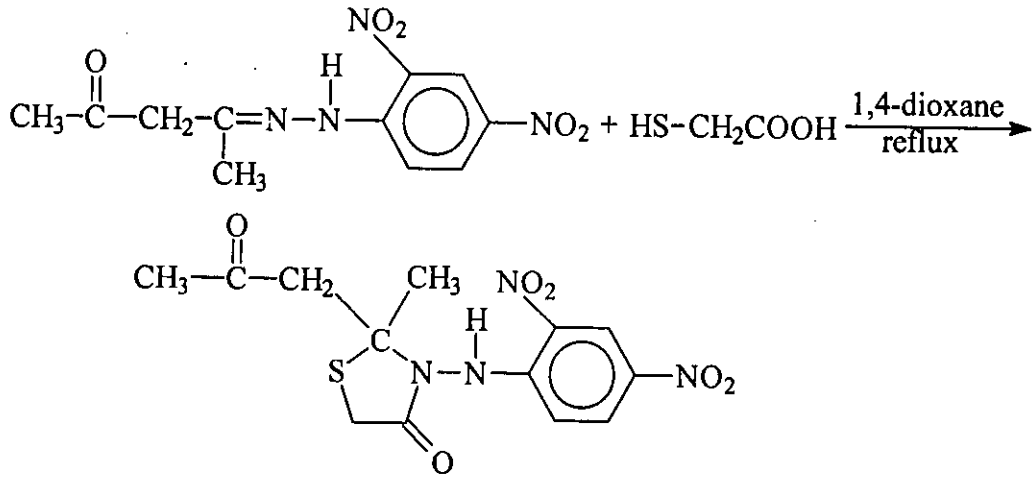



**Figure 20: Mass spectrum of the compound (H–12)**

### 3.6.B Synthesis and characterization of 1-(2′,4′-dinitrophenylamino)-5, 5-methyl acetonyl thiazolidinone (H–13).

A mixture of acetylacetone 2,4-dinitrophenylhydrazone (0.28g, 1 m mol) and mercaptoa-cetic acid (0.184g, 2 m mol) was refluxed in 1,4-dioxane (10 ml) for 6 hours. The progress of the reaction was monitored by TLC (ethylacetate-pet.ether, 1:1, $R_f = 0.76$). The reaction mixture was then cooled to room temperature and 1,4-dioxane was removed by rotary evaporator under reduced pressure. The resulting solid mass was recrystallized several times from ethylacetate. The desired compound was isolated as red crystal, mp. 109–111$^0$C, yield 53%.




**H–13**

Its IR spectrum (Fig: 21) showed a broad absorption band ranging from 3377–3440 cm$^{-1}$. This was indicative of the presence of a NH group. The absorption band at 3079 cm$^{-1}$ was for aromatic C–H stretching. The absorption band at 2977 cm$^{-1}$ was for aliphatic C–H stretching. The broad band at 1720 cm$^{-1}$ was indicative of C=O and C=N moieties. The aromatic C=C bonds were assigned from the band at 1550 cm$^{-1}$, 1511 cm$^{-1}$ and 1495 cm$^{-1}$.

The $^1$H–NMR spectrum (300 MHz, $CDCl_3$, Fig: 22) showed a singlet at δ 2.3 integrating six protons were suggestive for methyl group. A singlet at δ 3.6 and δ 3.7 were assignable for two methylene proton. A sharp peak at δ 6.7 integrating one proton was ascribable for NH. Two doublets at δ7.7 and δ 8.5 were assignable for aromatic protons. A singlet at δ 8.7 integrating one proton was assignable for aromatic proton.

The Mass spectrum (Fig: 23) showed m/z 354 ($M^+$) which was suggestive for the molecular weight 354. The fragmentation pattern showed the correlation to the molecular ion peak.

Therefore, based on the IR, $^1$H–NMR and Mass spectral data, it was confirmed that the compound (H–13) was 1–(2′,4′–dinitrophenylamino)–5,5–methyl acetonyl thiazolidinone.

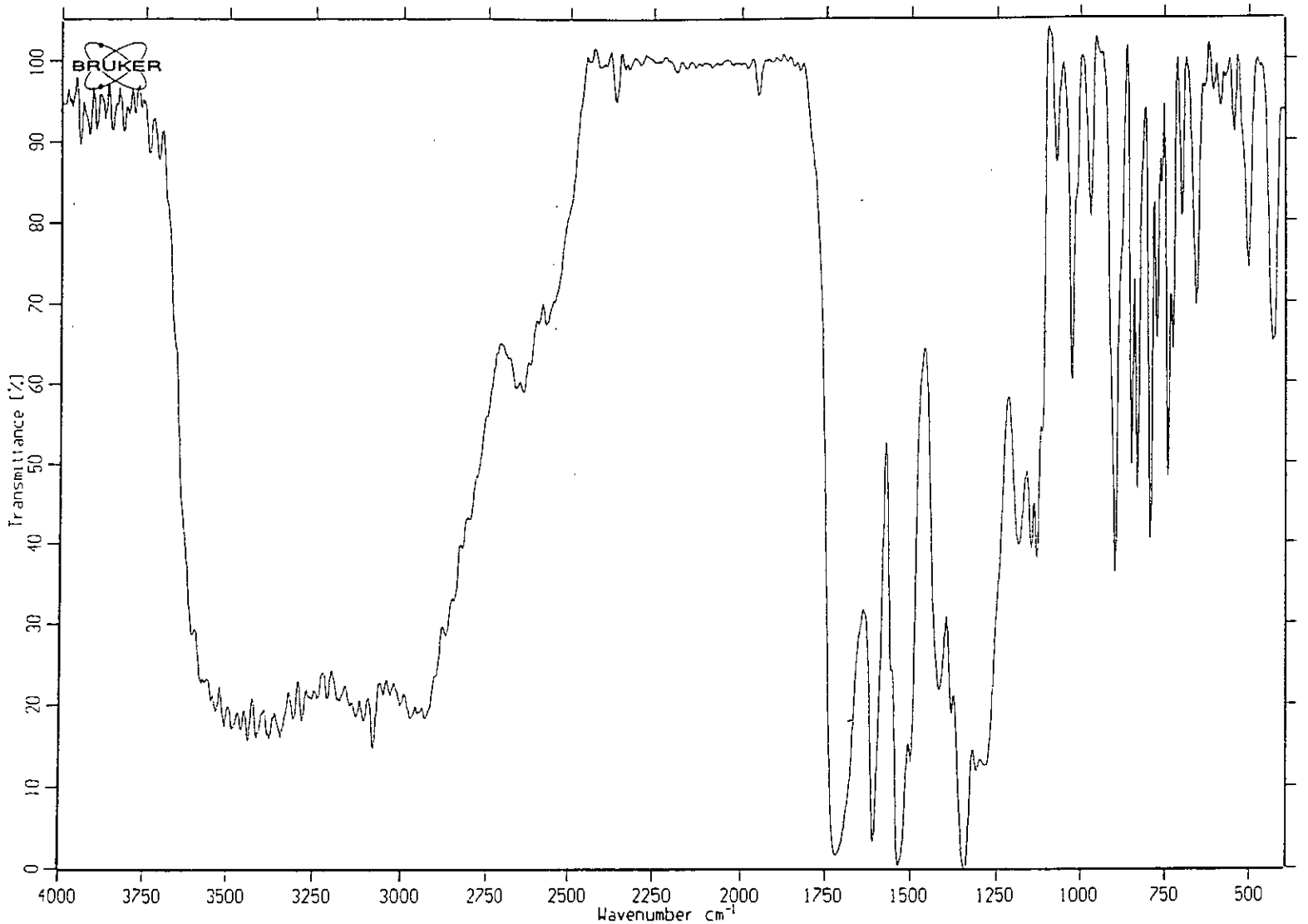



**Figure 21: IR spectrum of the compound (H–13)**

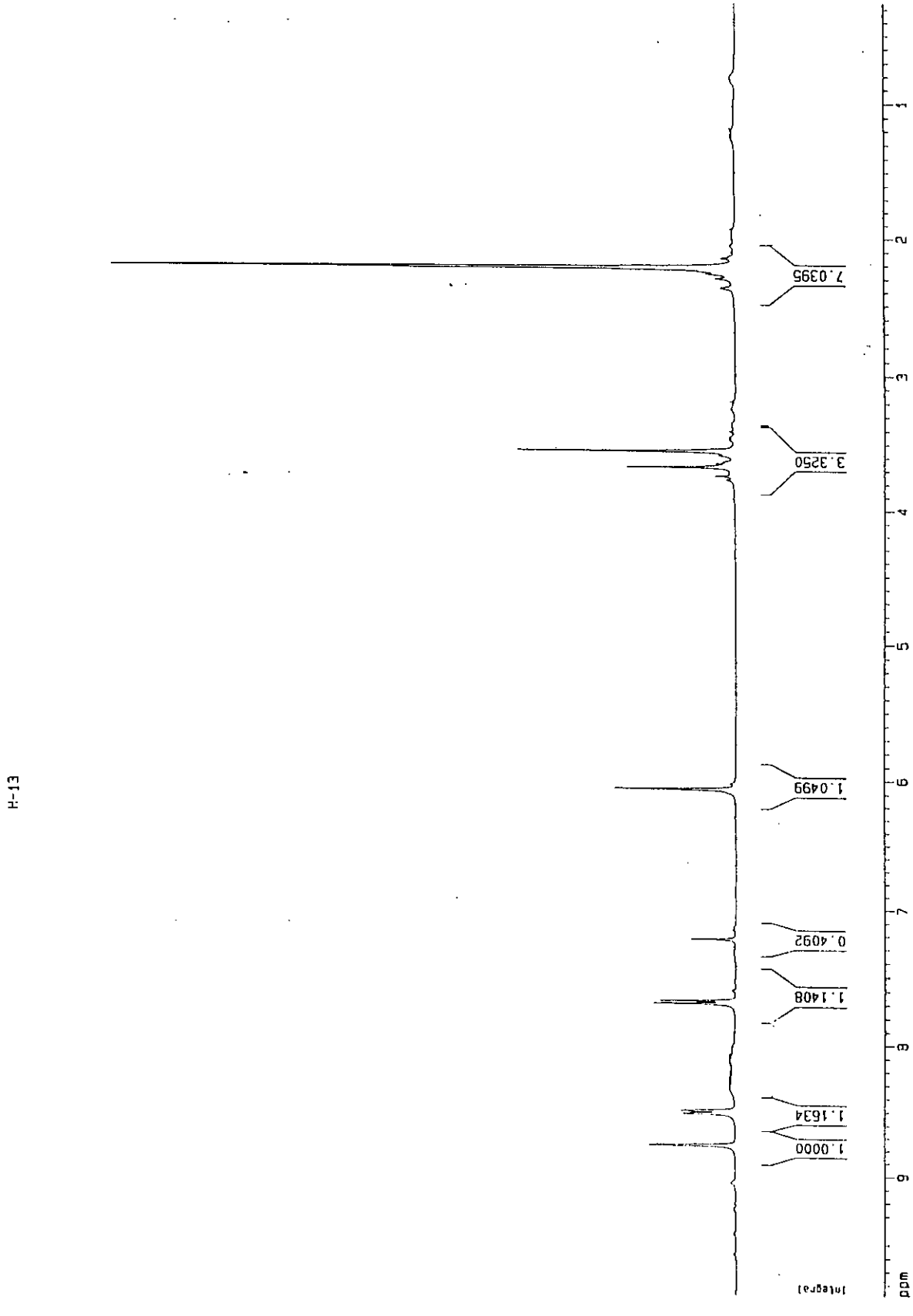



**Figure 22: $^{1}$H–NMR spectrum of the compound (H–13)**

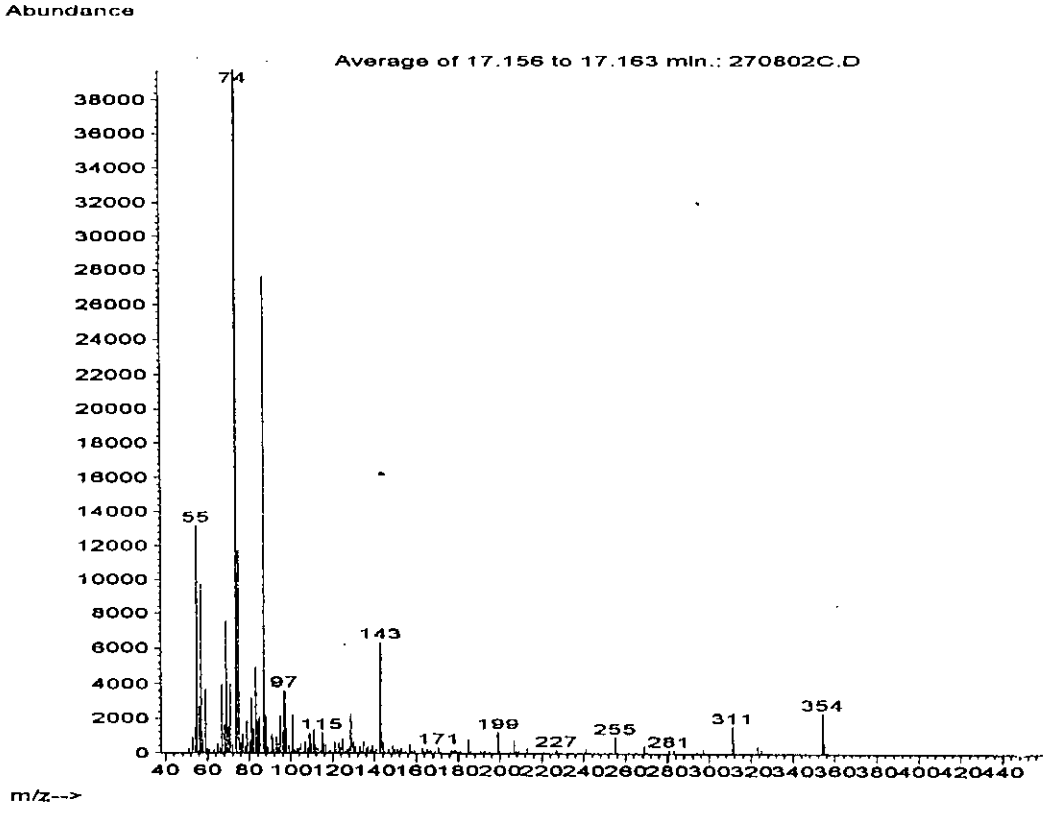
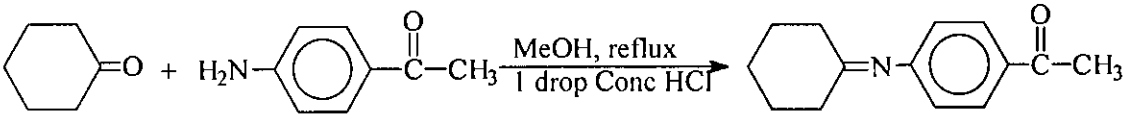



**Figure 23: Mass spectrum of the compound (H–13)**

### 3.7.A Synthesis and characterization of *p*-cycloheximino acetophenone (H–14).

A mixture of cyclohexanone (0.294g, 3 m mol) and *p*-aminoacetophenone (0.405g, 3 m mol) was stirred in methanol (6 ml) for 3 hours at ice cool temperature. The progress of the reaction was monitored by TLC (pet.ether-ethylacetate, 1:1, $R_f = 0.65$). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resulting solid mass was recrystallized several times from ethylacetate. The desired compound was isolated as a yellow crystal, mp. 85–87$^0$C, yield 67%.




**H–14**

The mass spectrum (Fig: 24) showed m/z 214 ($M^+$) which was suggestive for molecular weight 214. The fragmentation pattern was rationalized to the molecular ion peak. The molecular ion peak only was the suggestive tool for the desired structure.

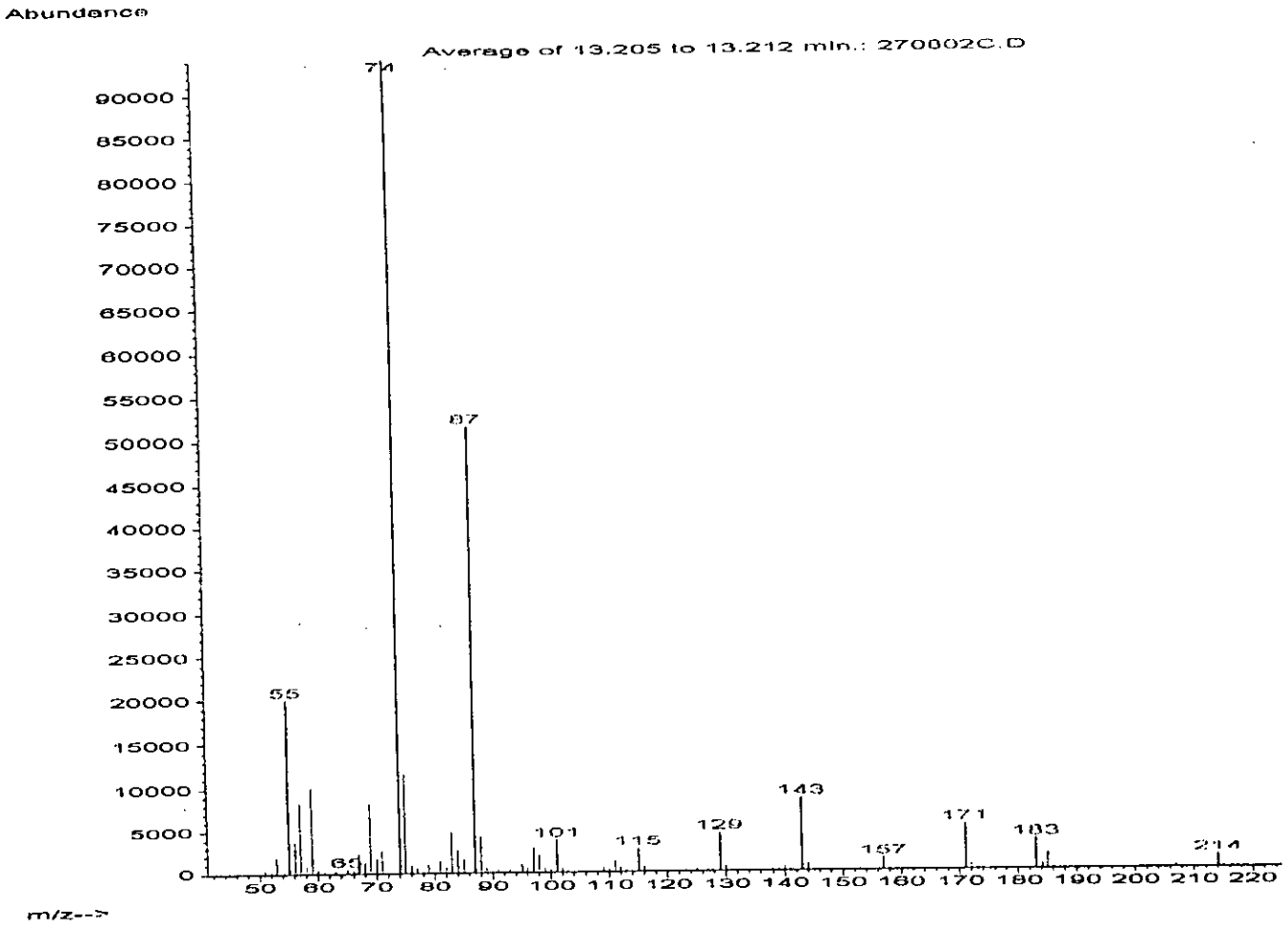
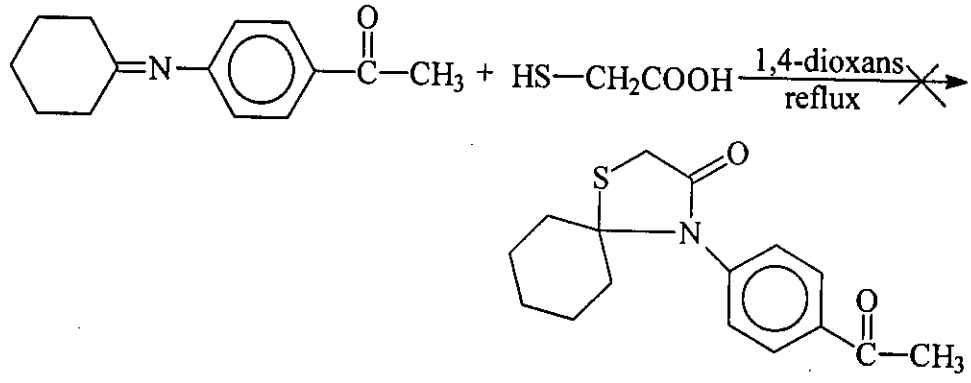



**Figure 24: Mass spectrum of the compound (H–14)**

### 3.7.B Synthesis and characterization of *N*(*p*-acetophenyl)-spiro-(cyclohexane-thiazolidinone) [H–14a)

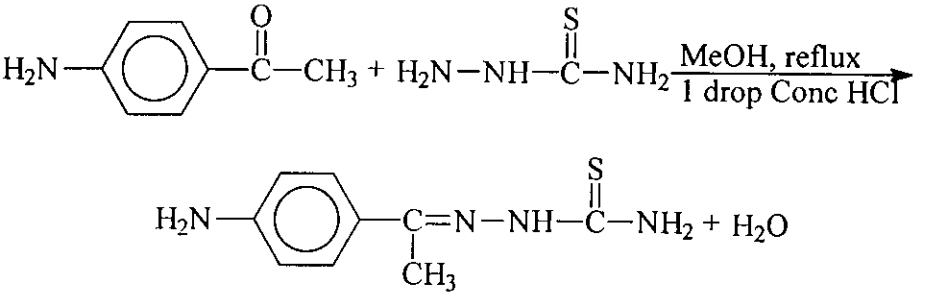
A mixture of *p*-cyclohexaimino acetophenone (0.215g, 1 m mol) and mercaptoacetic acid (0.184g, 3 m mol) was refluxed in 1,4-dioxane (6 ml) 2 hours. The progress of the reaction was monitored by TLC (ethylacetate-pet.ether, 1:1). After two hours reflux many spots were observed on TLC which indicates many unstable products. The desired compound was not possible to isolate.




**H–14a**

### 3.8.A Synthesis and characterization of *p*-aminoacetophenone thiosemicarbazone (H–15)

A mixture of *p*-aminoacetophenone (0.405g, 3 m mol) and thiosemicarbazide (0.273g, 3 m mol) was refluxed in methanol (6 ml) for 7 hours. The progress of the reaction was monitored by TLC (ethylacetate-pet.ether, 7:3, $R_f$ = 0.57). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resulting solid mass was recrystallized several times from ethylacetate. The desired compound was isolated as a yellowish red crystal, mp. 155–157$^0$C, yield 66%.




**H–15**

Its IR spectrum (Fig: 25) showed absorption band ranging from 3388–3444 $cm^{-1}$ was indicative for $NH_2$ or NH group. The absorption band at 3017 $cm^{-1}$ was for aromatic C–H stretching. Very weak absorption band was observed at 2960 $cm^{-1}$ for aliphatic C–H stretching. The band at 1620 $cm^{-1}$ was suggestive of C = N moiety. The sharp bands at 1586, 1580 and 1490 $cm^{-1}$ were ascribable for the C=C bond of aromatic ring. The band at 1488 $cm^{-1}$ was observed for C=S bond.

The Mass spectrum (Fig: 26) showed m/z, 207($M^+$) which was suggestive for the molecular weight (207). The fragmentation pattern showed the correlation to the molecular ion peak.

Therefore, IR spectrum and Mass spectrum confirmed (H–15) to be the desired structure named as *p*-aminoacetophenoe thiosemicarbazone.

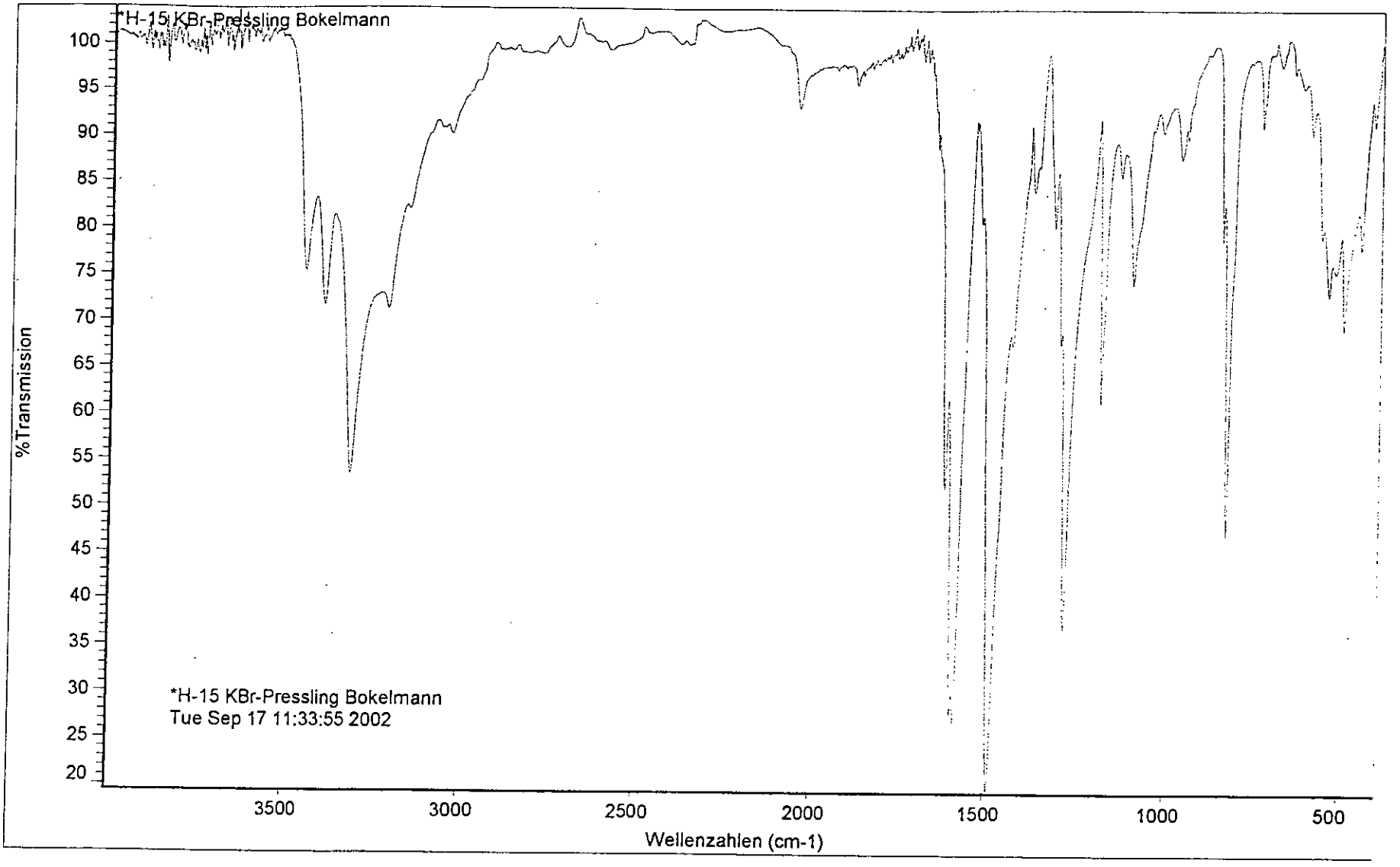



**Figure 25: IR spectrum of the compound (H–15)**

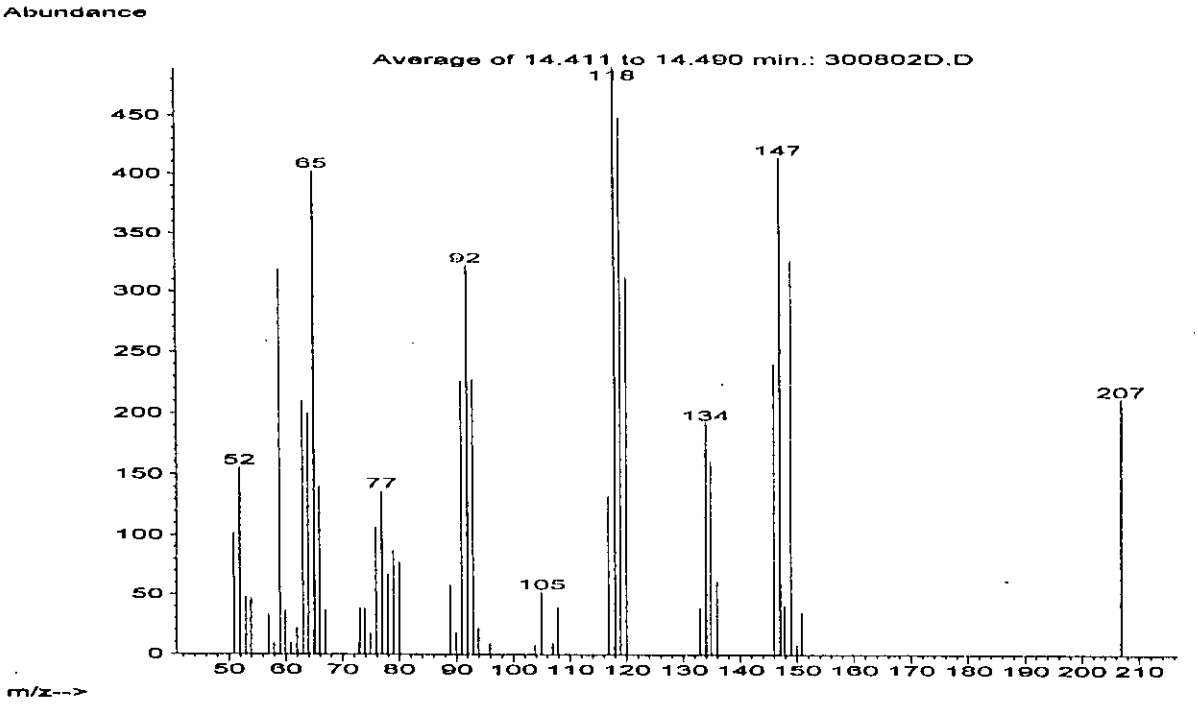
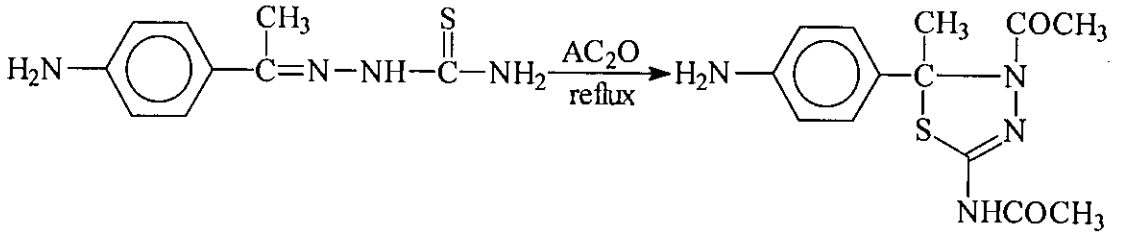



**Figure 26: Mass spectrum of the compound (H–15)**

### 3.8.B Synthesis and characterization of 5-methyl-5-(*p*-aminophenyl)-4-acetyl-2-(acetylamino)-$\Delta^2$-thiadiazoline (H–16)

A mixture of *p*-aminoacetophenone thiosemicarbazone (0.624g, 3 m mol) and distilled acetic anhydride (15 ml) was refluxed for 4 hours. The progress of the reaction was monitored by TLC (ethylacetate-pet.ether, 7:3, $R_f$=0.51). The reaction mixture was then cooled to room temperature and acetic anhydride was removed by rotary evaporator under reduced pressure. The resulting solid mass was purified by preparative thin layer chromatography as a yellow crystal, mp. 131–133$^0$C, yield 51%.




**H–16**

Its IR spectrum (Fig: 27) showed absorption band ranging from 3233–3437 $cm^{-1}$ was indicative for $NH_2$ or NH group. The absorption band at 3077 $cm^{-1}$ was C–H stretching for aromatic C–H. Very weak absorption band at 2981 $cm^{-1}$ for aliphatic C–H stretching. The absorption bands at 1671 $cm^{-1}$ and 1646 $cm^{-1}$ were ascribable for C = O bond. The aromatic C=C bonds were assigned from the band at 1514 $cm^{-1}$ and 1495 $cm^{-1}$ and 1407 $cm^{-1}$. The bands at 1612 $cm^{-1}$ was suggestive of C=N moiety.

The Mass spectrum (Fig: 28) showed m/z, 292($M^+$) which was suggestive molecular weight (292) but the fragmentation pattern was unusual.

Therefore, IR spectrum and Mass spectrum confirmed (H–16) to be the desired structure named as 5–methyl-5-(*p*-aminophenyl)-4-acetyl-2(acetylamino)-$\Delta^2$-thiadiazoline.

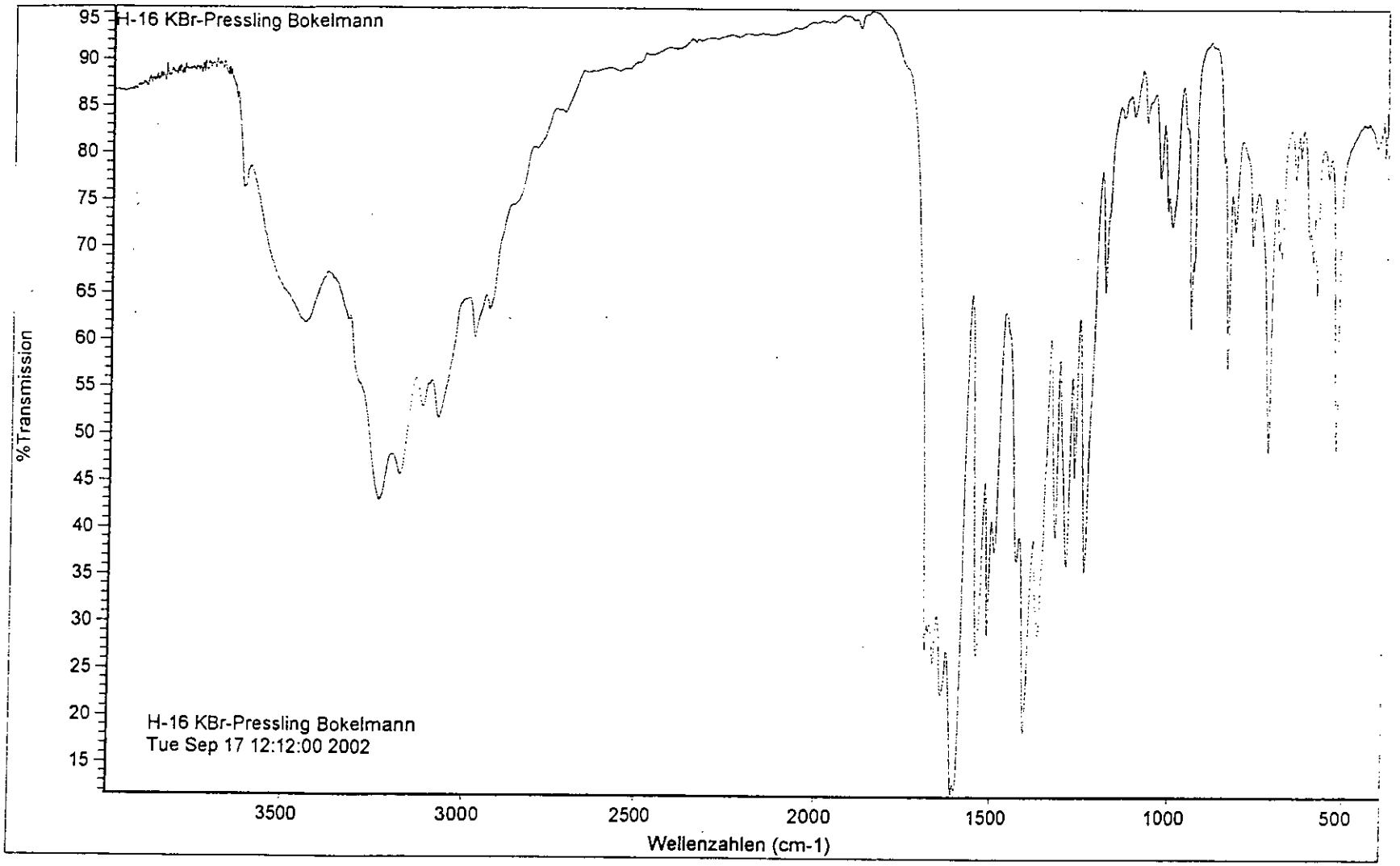



**Figure 27: IR spectrum of the compound (H–16)**

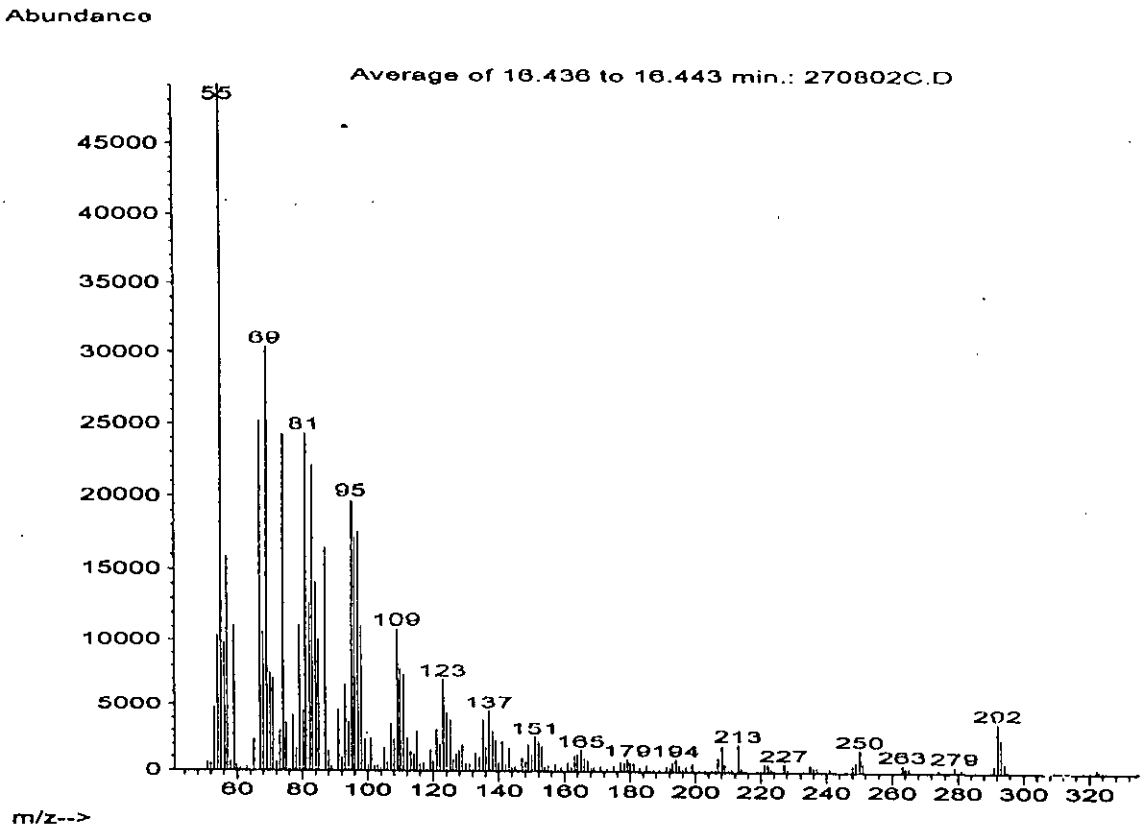
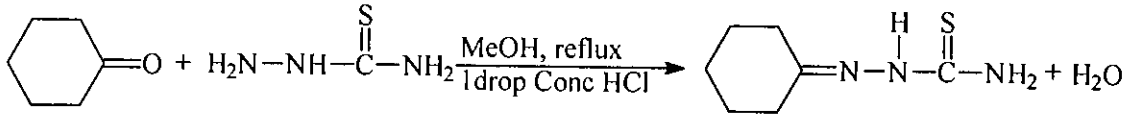



**Figure 28: Mass spectrum of the compound (H–16)**

### 3.9.A Synthesis and characterization of cyclohexanone thiosemicarbazone (H-19)

A mixture of cyclohexanone (0.588g, 6 m mol) and thiosemicarbazide (0.546g, 6 m mol) was refluxed in methanol (8 ml) in presence of hydrochloric acid (1 drop) for 6 hours. The progress of the reaction was monitored by TLC (ethylacetate-pet.ether, 1:1, $R_f$=0.51). The reaction mixture was then cooled to room temperature and methanol was removed by rotary evaporator. The resulting solid mass was recrystallized several times from ethylacetate. The desired compound was isolated as a white crystal, mp. 156–158$^0$C, yield 72%.




**H–19**

Its IR spectrum (Fig: 29) showed a broad absorption band ranging from 3143–3379 cm$^{-1}$ was indicative for $NH_2$ or NH group. The absorption band at 2972 and 2940 cm$^{-1}$ for aliphatic C–H stretching. The bands at 1641 cm$^{-1}$ was suggestive of C=N moiety. The band at 1502 cm$^{-1}$ was ascribable for C=S bond. The IR spectrum was suggestive for the desired structure named as cyclohexanone thiosemicarbazone.

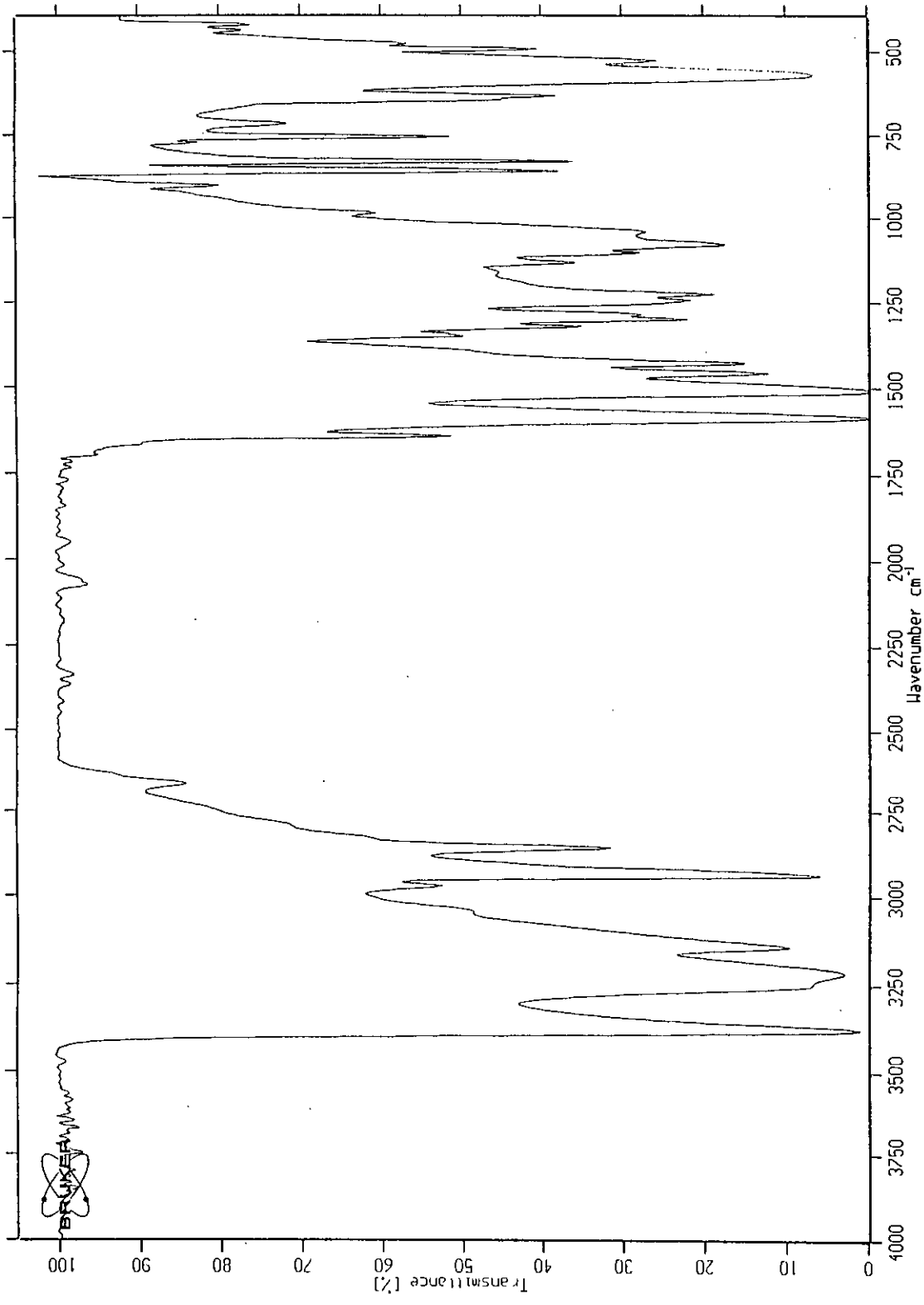
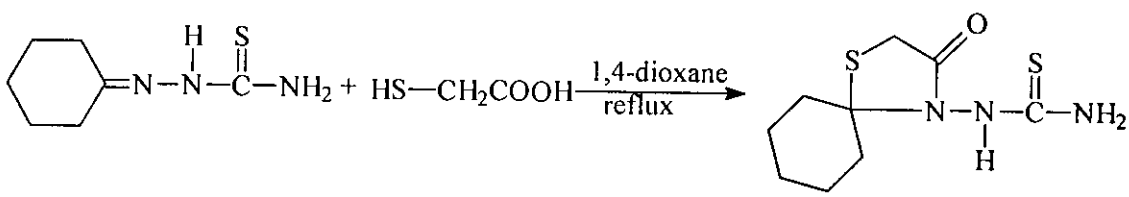



**Figure 29: IR spectrum of the compound (H–19)**

### 3.9.B Synthesis and characterization of *N*(thioeurido)-spiro-(cyclohexane-thiazolidinone) (H–20).

A mixture of cyclohexanone thiosemicarbazone (0.513g, 3 m mol) and mercaptoacetic acid (0.552g, 6 m mol) was refluxed in 1,4-dioxane (10 ml) for 5 hours. The progress of the reaction was monitored by TLC (pet.ether-ethylacetate, 1:1, $R_f$=0.41). The reaction mixture was then cooled to room temperature and 1,4-dioxane was removed by rotary evaporator under reduced pressure. The crude solid mass was purified by column chromatography as a white crystal, mp. 177–179$^0$C, yield 51%.




**H–20**

Its IR spectrum (Fig: 30) showed a broad absorption band ranging from 3177–3428 cm$^{-1}$ was indicative for $NH_2$ or NH groups. The absorption bands at 2936 and 2853 cm$^{-1}$ for aliphatic C–H stretching. The band at 1692 cm$^{-1}$ was suggestive C=O moiety. The band at 1501 cm$^{-1}$ was ascribable for C=S bond.

The Mass spectrum (Fig: 31) showed m/z, 245 ($M^+$) which was suggestive for the molecular weight 245. The fragmentation pattern was rationalized to the molecular ion peak.

Therefore, IR spectrum and Mass spectrum of the compound confirmed (H–20) to be the desired structure named as *N*(thioeurido)-spiro-(cyclohexane-thiazolidinone).

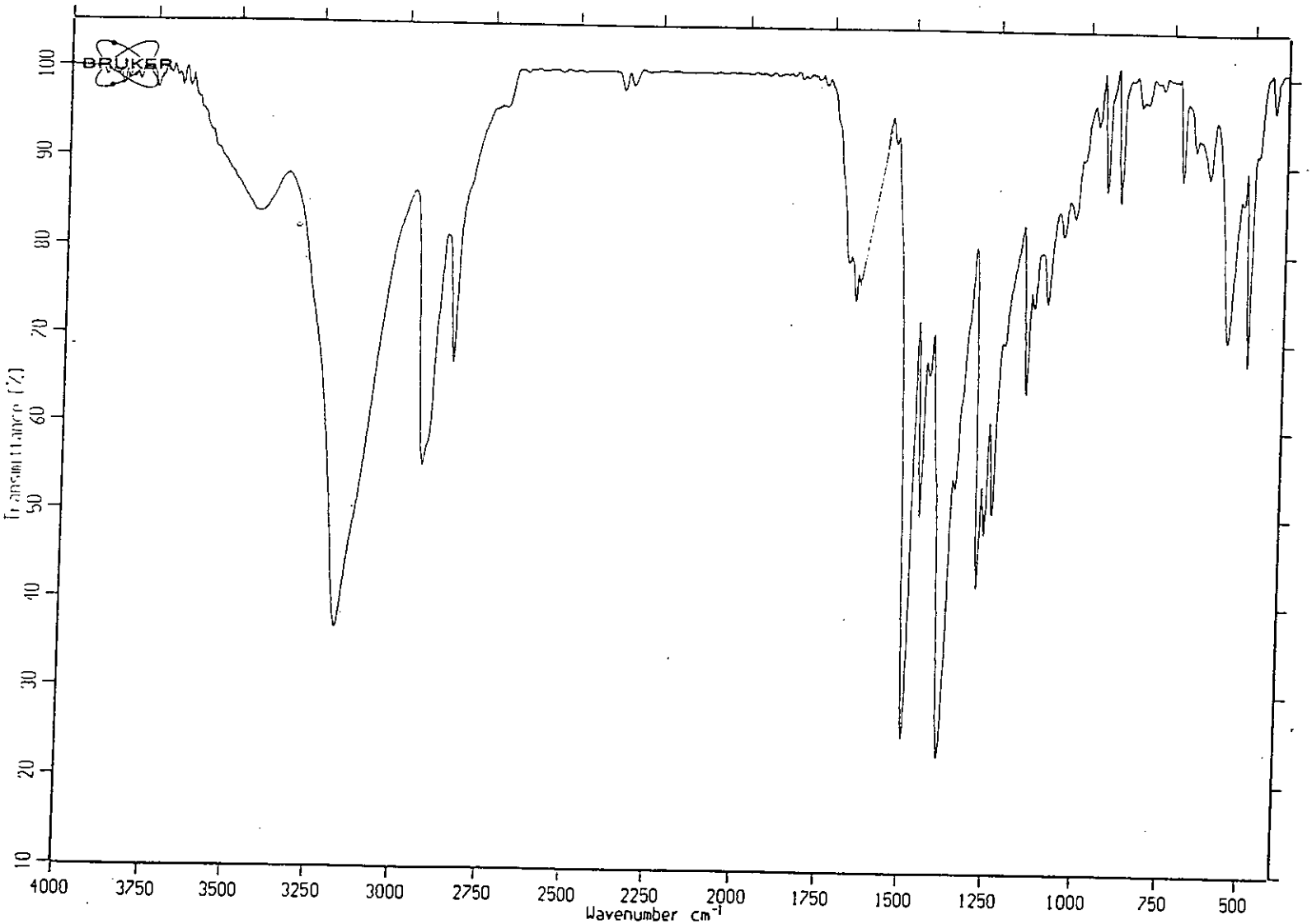



**Figure 30: IR spectrum of the compound (H–20)**

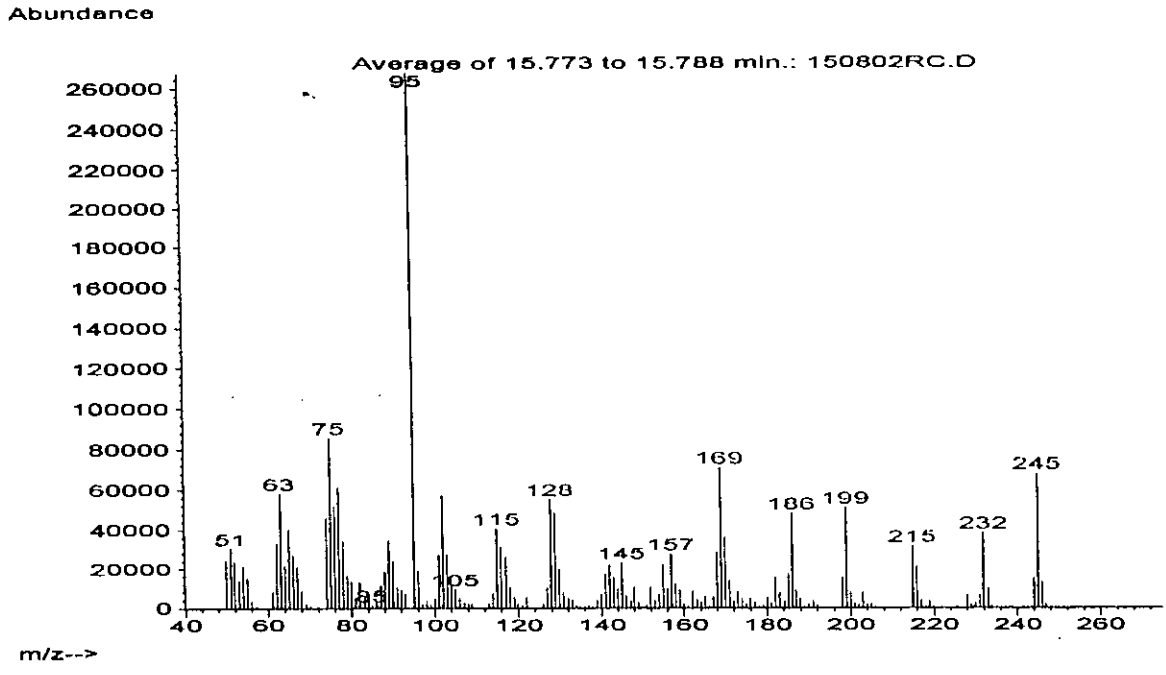



**Figure 31: Mass spectrum of the compound (H–20)**

# CHAPTER - 4

# PHARMACOLOGICAL STUDIES

# PHARMACOLOGICAL TEST

## 4.1. Introduction:

The susceptibility of micro-organisms to antibacterial agents can be measured invitro by a number of techniques among which the disc diffusion method, using different concentrations of the agents absorbed on sterile filter paper disc is widely acceptable for the preliminary evaluation of antibacterial activity.

## 4.2. The activity test:

Standard antibiotic discs were placed gently on the solidified agar plates, treshly seeded with the test organisms with the help of a sterile forceps to assure complete contact with media surface. The spatial arrangement of the discs were such that the disc were not closer than 15 mm to the edge of the plate and for enough apart to prevent overlapping in the zone of inhibition. The plates were then inverted and kept at $4^0$c for 24 hours. Finally, the plates were incubated at $37^0$C for 12 hours. After incubation the antibacterial activity of the test agent was determined by measuring the diameter of inhibition zone in term of mm with a transparent scale.

## 4.3. Result of antibacterial test:

The thiazolidinone derivatives showed no significant antibacterial activity against the two test organisms such as *shigella shigha, Bacillus substills.* Only bis spiro-(cyclohexane-thiazolidinone) showed partly sensitive against *Bacillus substills.*

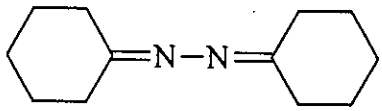
# CHAPTER - 5

# SUMMARY

The work done in this dissertation may be summarized as follows:

**H–1. Cyclohexanone bis hydrazone**

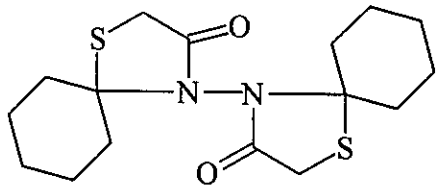
Cyclohexanone bis hydrazone was synthesized by simple acid catalyzed condensation of cyclohexanone (0.786g, 8 m mol) and hydrazine (0.128g, 4 m mol).



**71%**

**H–2. Bis spiro – (cyclohexane–thiazolidinone)**

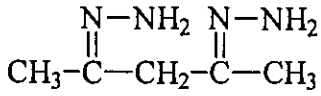
Refluxing a mixture of cyclohexanone bis hydrazone (0.768g, 4 m mol) and mercaptoacetic acid (1.472g, 16 m mol) in 1,4-dioxane produced bis spiro–(cyclohexane-thiazolidinone) in 58% yield.



**58%**

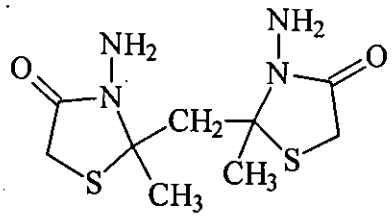
**H–3. Acetylacetone bis Hydrazone**

Acid catalyzed condensation of acetylacetone (0.60g, 6 m mol) and hydrazine (0.96g, 30 m mol) found a gummy mass, which was not possible to characterize as acetylacetone bis hydrazone.



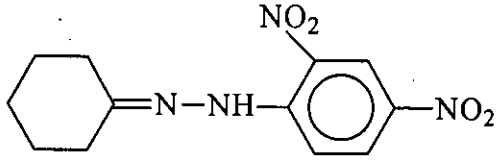
**H–4. 2,4–di(1′–amino) thiazolidino pentane**

The reaction of the crude acetylacetone bis hydrazone and mercaptoacetic acid was carried out in different conditions but 2,4-di(1′–amino) thiazolidinopentane was not possible to synthesize.



**H–5. Cyclohexanone 2,4–dinitrophenyl hydrazone**

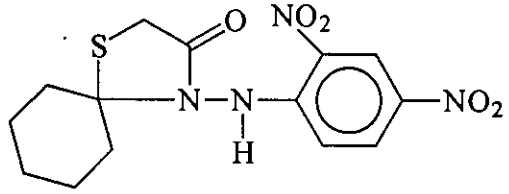
Condensation of equimolecular mixture of cyclohexanone and 2,4–dinitrophenyl hydrazine yielded cyclohexanone 2,4–dinitrophenyl hydrazone in 68% yield.



**68%**

**H–6. *N*(2,4–dinitrophenylamino)spiro–(cyclohexane–thiazolidinone)**

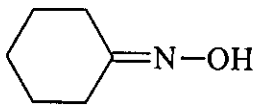
Refluxing a mixture of cyclohexanone 2,4–dinitrophenylhydrazone (0.278g, 1 m mol) and mercaptoacetic acid (0.184g, 2 m mol) yielded the desired compound as *N*-(2,4–dinitrophenylamino) spiro–(cyclohexane–thiazolidinone) in 57% yield.



**57%**

**H–7. Cyclohexanone oxime**

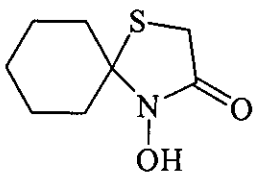
Cyclohexanone oxime was synthesized from the condensation of equimolar mixture of cyclohexanone and hydroxylamine.



**62%**

**H–8. *N*–Hydroxy spiro–(cyclohexane–thiazolidinone)**

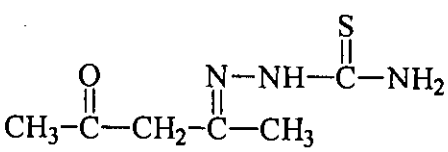
Refluxing a mixture of cyclohexanone oxime (0.678g, 6 m mol) and mercaptoacetic acid (1.104g, 12 m mol) produced *N*–Hydroxy spiro-(cyclohexane–thiazolidinone) in 63% yield.



**63%**

**H–10. Acetylacetone thiosemicarbazone**

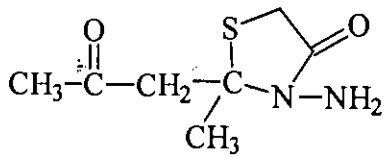
Acid catalyzed condensation of acetylacetone (0.20g, 2 m mol) and thiosemicarbazide (0.364g, 4 m mol) yielded acetylacetone thiosemicar-bazone in 65% yield.



**65%**

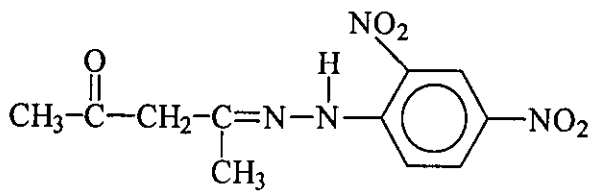
**H–11. 2(*N*-aminothiazolidinono) pentane-4-one**

The reaction of acetylacetone thiosemicarbazone and mercaptoacetic acid was carried out at different conditions but it was not possible to synthesize the desired product.



**H–12. Acetylacetone 2,4-dinitrophenylhydrazone**

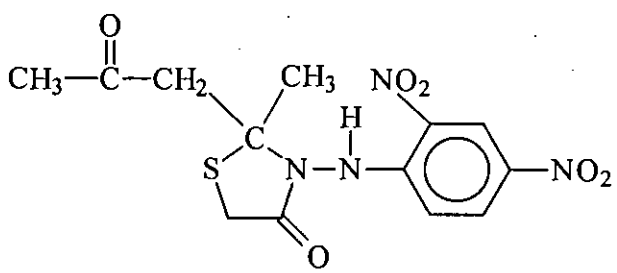
Condensation of a mixture of acetylacetone (0.30g, 3 m mol) and 2,4–dinitrophenyl-hydrazine (1.188g, 6 m mol) produced acetylacetone 2,4–dinitrophenyl hydrazone.



**58%**

**H–13. 1-(2′,4′–dinitrophenylamino)–5,5–methyl acetonyl thiazolidinone**

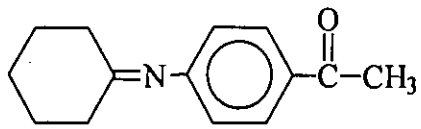
1-(2′,4′–dinitrophenylamino)–5,5–methyl acetonyl thiazolidinone was synthesized from the reaction of acetylacetone 2,4–dinitrophenyl hydrazone (0.28g, 1 m mol) and mercaptoacetic acid (0.184g, 2 m mol) in 53% yield.



**53%**

## H–14. *p*-cycloheximino acetophenone

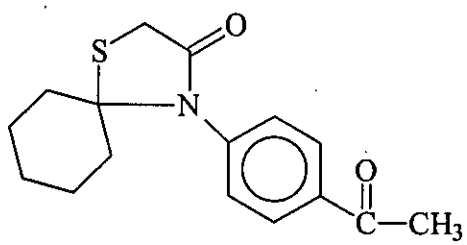
Condensation of equimolecular mixture of cyclohexanone and *p*-aminoacetophenone yielded *p*-cycloheximinoacetophenone in 67% yield.



**67%**

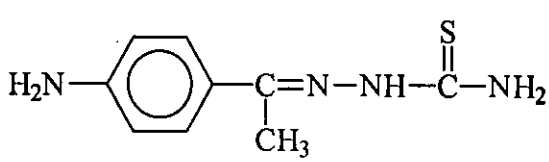
## H–14a. *N*(*p*-Acetophenyl)–spiro-(cyclohexane-thiazolidinone)

*N*-(*p*–Acetophenyl)–spiro–(cyclohexane–thiazolidinone) was not possible to synthesize.



## H–15. *p*-Aminoacetophenone thiosemicarbazone

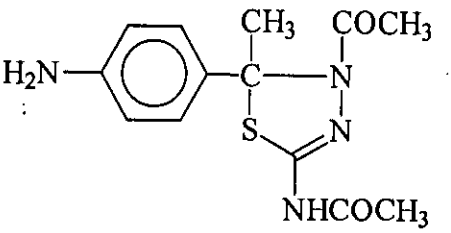
Condensation of equimolecular mixture of *p*-aminoacetophenone and thiosemicarbazide produced *p*-aminoacetophenone thiosemicarbazone in 66% yield.



**66%**

**H-16. 5–Methyl–5–(*p*-aminophenyl)–4–acetyl–2(acetylamino)–$\Delta^2$–thiadiazoline**

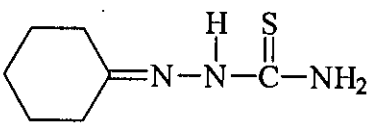
Refluxing of a mixture of *p*-aminoacetophenone thiosemicarbazone and acetic anhydride produced 5–methyl–5–(*p*–aminophenyl)–4–acetyl–2 (acetylamino)–$\Delta^2$–thiadiazoline in 51% yield.



**51%**

**H–19. Cyclohexanone thiosemicarbazone**

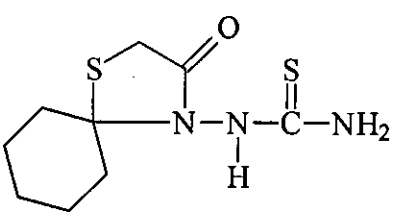
Cyclohexanone thiosemicarbazone was synthesized from the condensation of equimolar mixture of cyclohexanone and thiosemicarbazide.



**72%**

**H–20. *N*(Thioeurido)–spiro–(cyclohexane–thiazolidinone)**

Refluxing a mixture of cyclohexanone thiosemicarbazone (0.513g, 3 m mol) and mercaptoacetic acid (0.552g, 6 m mol) in 1,4–dioxane produced *N*(thioeurido) spiro–(cyclohexane–thiazolidinone) in 51% yield.



**51%**

Pharmacological investigations have been carried out on all the synthesized thiazolidinone derivatives which are described in the chapter 4.

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