SYNTHESIS OF SOME NEW ANNELATED FUSED HETEROCYCLIC DERIVATIVES OF BIOLOGICAL IMPORTANCE

A DISSERTATION
SUBMITTED IN THE PARTIAL FULFILMENT OF THE REQUIREMENT
FOR THE DEGREE
OF
MASTER OF PHILOSOPHY(M. PHIL)
IN CHEMISTRY.

SUBMITTED BY

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December 21, 2006

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

THESIS ACCEPTANCE LETTER:

The thesis titled " **Synthesis of Some New Annelated Fused Heterocyclic Derivatives of Biological Importance**" Submitted by Mohammed Kabir Uddin, Student No. 100103111F, Registration No. 0110042, Session October, 2001 has been accepted as satisfactory in partial fulfilment of the requirement for the degree of Master of Philosophy (M. Phil) in Chemistry on December 21, 2006.

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It is hereby declared that this thesis or any part of it has not been submitted elsewhere for the award of any degree or diploma.

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Acknowledgement

All praise to the Almighty Allah for his infinite mercy bestowed on the human author in carrying out the research work presented in this dissertation.

I am extremely delighted to express my deepest sense of gratitude and indebtedness to my most honourable teacher and research supervisor Dr. Md. Wahab Khan, Professor of Chemistry, Bangladesh University of Engineering & Technology (BUET), Dhaka. I am really proud for his highly indispensable supervision, generous help, constructive criticism, invaluable suggestions, constant and untiring help through out the progress and successful completion of the research work.

I am especially indebted to my honorable teacher Dr. Nazrul Islam, Professor & Head, Department of Chemistry, BUET, Dhaka, for his valuable suggestion and constant co-operation through out the laboratory facilities.

I am highly grateful to all my respected teachers of this Department, particularly Dr. Enamul Huq, Dr. Md. Abdur Rashid, Dr. A. K. M. Matior Rahman, Dr. Md. Rafique Ullah, Dr. Md. Monimul Haque, Dr. Md. Manwarul Islam, Md. Nurul Islam, Dr. Shakila Rahman, Mrs. Tahera Saad and Dr. Al-Nakib Chowdhury, for their helpful suggestions at different stages of studies in Chemistry.

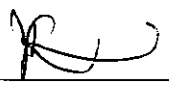
I desire to offer my pleasant thanks to Mr. Sarifur Rahman, Lecturer, Department of Pharmaceutical Chemistry, University of Dhaka, for his kind help to carry out biological test of various compounds. I am thankful to Mr. M. Shahidul Islam, Principal Scientific Officer (PSO), Analytical Res. Division, BCSIR, Dhaka, for performing ^{1}H NMR and ^{13}C NMR spectra.

I am grateful to Bangladesh University of Engineering & Technology (BUET) for giving me opportunity to do my M.Phil program in the Department of Chemistry, BUET, Dhaka and providing me financial support to carry out my research work.

I offer my special thanks to my Labmates and friends Ranjit, Morshed Masud, Tanvir, Zeba, Arifa, Raihan, Saiful, Selim and Bakkar for their generous help and co-operation.

I would like to convey my feeling of thanks to my elder brother M. Sala Uddin, M. Jashim Uddin and younger brother M. Nasir Uddin for their help and encouragement whenever needed.

I wish to thank Md. Shafiqul Islam, Department of Mathematics, BUET, Dhaka for their hard labour to compose this manuscript.



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Abbreviations

M.F.	Molecular Formula
NMR	Nuclear Magnetic Resonance
IR	Infra-red
M.P.	Melting Point
B.P.	Boiling Point
TLC	Thin Layer Chromatography
Toluyl	*p*-toluoylchloride
Ac	Acetyl
Ph	Phenyl
Bz	Benzoyl
^0C	Degree Celsius
Me	Methyl
Et	Ethyl
Et_3N	Triethylamine
Ph	Phenyl
DMF	*N,N*-dimethylformamide
THF	Tetrahydrofuran
DMSO	Dimethylsulfoxide
NBS	*N*-Bromosuccinimide
EMCA	Ethoxymethylene Cyanoacetate
Hrs.	Hours
Hz	Hertz
s	Singlet
d	Doublet
t	Triplet
q	Quartet
m	Multiplet

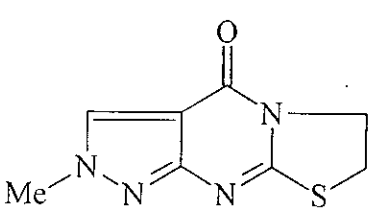
List of Figures

Abstract

"Synthesis of some new annelated fused heterocyclic derivatives of biological importance"

The synthesis of the annelated fused heterocyclic derivatives is divided into two headings: Such as; annelated substrate and annelating reagent. The annelating substrates *ortho*-amino ester such as 2-amino-4,5-diphenylfuran-3-carboxylate (**8**), ethyl-5-amino-2-methylpyrozolo-4-carboxylate (**2**) and ethyl-2-amino-4,5-dimethylthiophene-3-carboxylate (**14**) were prepared from bezoin (**7**), ethyl(ethoxy methylene)malonitrile (**1**) and butanone (**13**) respectively by using Gewald method and annelating reagents such as 2-methylthio-2-methyl thiozoline (**5**) and 2-methylthio-imidazoline (**11**) were synthesized from ethanol amine (**3**) and ethylene diamine (**9**) respectively by using Jenson and Hofmann procedure. The annelating substrates were used to synthesize 2,3-diphenyl-furano-6,7-dihydroimidazo[3,4-d]pyrimidin-4-one (**12**), 2-methyl-6,7-dihydropyrazoio [3,4-d]thiozolo[1,2-d] pyrimi-din-4-one (**6**) and 2,3-dihydro-6,7-dimethyl-5*H*-thiazolo [3,2-a]thieno[2,3-d]pyrimidin-5-one (**15**) by one step reaction in dry acetic acid. *In vitro* antimicrobial activity of fused heterocyclic derivatives were evaluated. All these synthesized products of the fused heterocyclic derivatives have been employed as test chemicals for determining their antibacterial and antifungal activities against a number of human and plant pathogens.

All the synthesized compounds demonstrated mild growth inhibition against antibiotic susceptible standard and clinically isolated strains of gram-positive and gram-negative bacteria as well as fungal pathogens.



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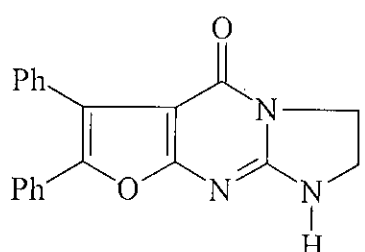

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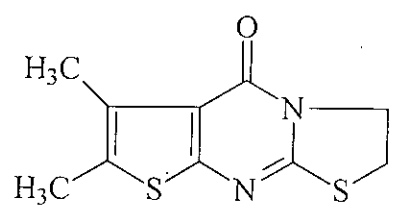

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Summary

Investigations incorporated in this dissertation entitled "*Synthesis of some new annelated fused heterocyclic derivatives of biological importance*" have been presented into two parts. Part-1 is divided into three sections and part-2 is divided into four sections. Each part has introductory section-1, in which the background, biological action and the important synthetic reactions involved in the synthesis are presented. Section-2 of each part deals with the detailed methodologies and experimental procedures for the synthesis of fused heterocyclic derivatives and its biological test. Section-2 of part-1 represent the results and discussion of the synthesis of fused heterocyclic derivatives.

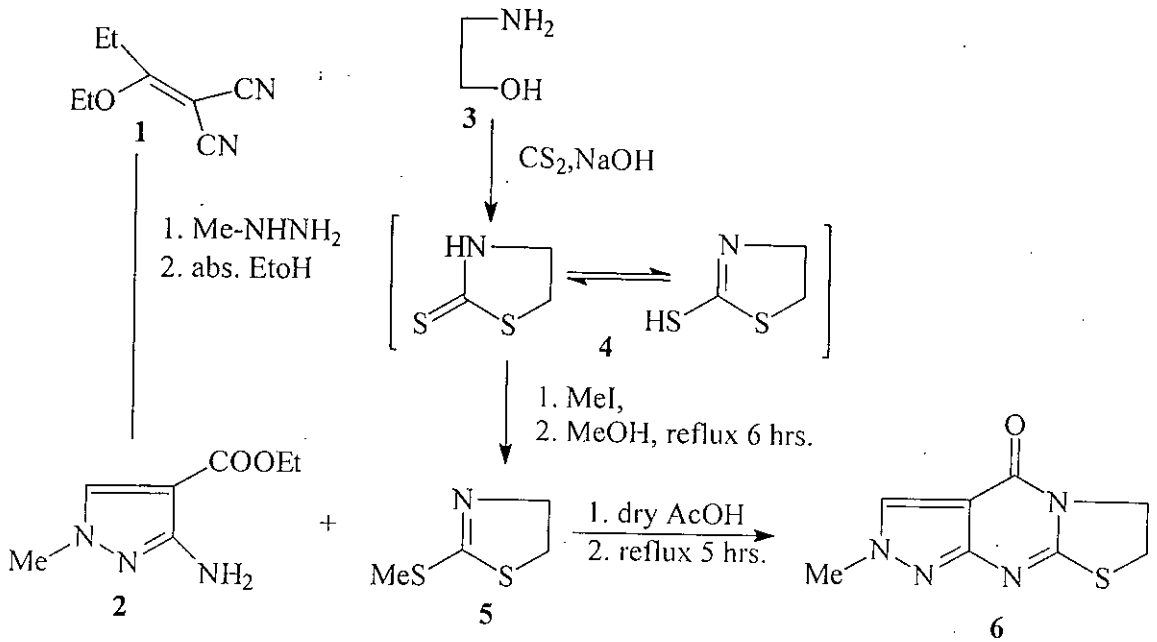
Part-1: Synthesis of fused heterocyclic derivatives.

Section-1 represents the importance of fused heterocyclic derivatives. In section-2, the work described in this dissertation concerns the preparation of new annelated fused heterocyclic derivatives by using the annelating reagent thiopseudourea and the *ortho*-aminoesters as a starting material due to pharmaceutical interest.

Annelating substrate as ethyl-5-amino-2-methylpyrozolo-4-carbonylate (**2**) was prepared from ethyl(ethoxymethylene)malonitrile (**1**) by using Gewald procedure in 70.45% yield. m.p.: 122 – 123°C. Another annelating reagent as 2-methylthio-2-thiazoline (**5**) was prepared from the ethanolamine by using Jenson method[68] in 85.50% yield; b.p.: 70–71°C (Lit.[68] b.p.: 70°C). When ethanolamine was treated with carbon disulfide in ethanol then the compound 2-Mercaptothiazoline (**4**) was afforded. This compound (**4**) was treated with methyl iodide to give 2-methylthio-2-thiozoline (**5**).

The annelating substrate (**2**) was used to synthesize of fused heterocyclic derivatives (**2**) and (**5**). 2-Methyl-6,7-dihydropyrozolo[3,4-d]thiazolo[1,2-a]pyrimidine-4-one (**6**) was prepared from annelating substrates as ethyl-5-amino-2-methylpyrazolo-4-carboxylate (**2**). When *ortho*-aminoester (**2**) was treated with annelating reagent(**5**) by one-step

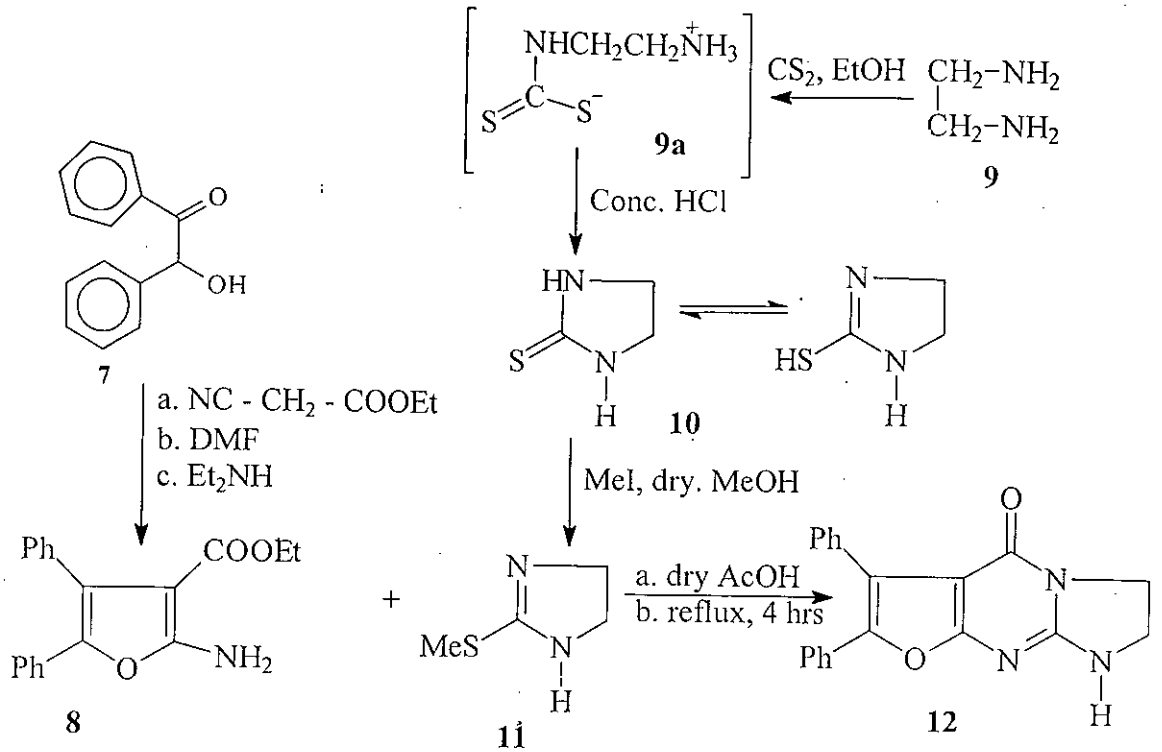
reaction in dry acetic acid then the compound(**6**) was furnished in 63.82% yield (Scheme-**1**), m.p.: >250°C.



Scheme-**1**

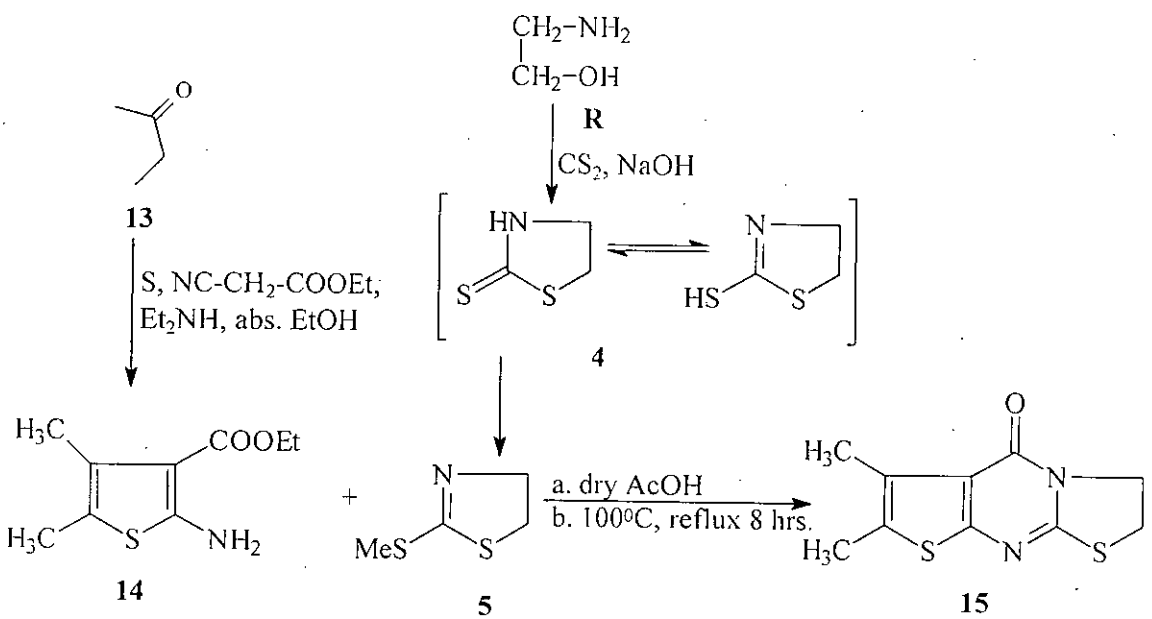
Annelating substrate, 2-amino-4,5-diphenylfuran-3-carboxylate (**8**) was prepared from benzoin (**7**) by using Gewald method[72] in 67.50% yield, m.p.: 163–165°C. Annelating reagent 2-methyltho-imidazoline (**11**) was prepared from the ethylene diamine by two-step method in 58.63% yield, m.p.: 119–121°C (Lit.[80] m.p.: 120–121°C). When ethylene diamine was reacted with carbon disulfide in ethanol then the compound 2-imidazoline-thione (**11**) was afforded. This compound (**10**) was treated with methyliodide in absolute methanol to give 2-methylthio-imidazoline (**11**).

2,3-Diphenylfurano-6,7-dihydroimidazo[3,4-d]pyrimidin-4-one (**12**) was prepared from *ortho*-aminoester (**8**) and annelating reagent (**11**). When the compound (**8**) was reacted with 2-methylthio-imidazoline(**11**) in dry acetic acid then the compound(**12**) was furnished (Scheme-**2**); m.p.: 201 – 203°C.



Scheme-2

2,3-Dihydro-6,7-dimethyl-5*H*-thiazolo[3,2-a]thieno[2,3-d]pyrimidin-5-one (**15**) was prepared from *ortho*-aminoester (**14**) and annelating reagent (**5**). When the compound (**14**) was heated with 2-methylthio-2-thiazoline (**5**) in dry acetic acid the compound (**15**) was obtained in 66.56% yield (Scheme-**3**); m.p.: 171°C – 172.



Scheme-3

Part-2: Biological activities of synthesis compounds.

In part-2, section-1 the introduction of the biological test is presented. In section-2 and section-3 the methodology and results and discussion of the biological importance of the synthesized fused heterocyclic derivatives are described.

Ten newly synthesized heterocyclic compounds have been tested for in antimicrobial activity angainst five gram-positive and seven gram-negative bacteria as well as four human fungal pathogens. Most of this compound demonstrated mild to nil rate of antimicrobial activity against most of the test organism. Twelve bacteriai strains and four fungi strains were used to study the antibacterial and antifungal activity of the compound at the higher concentration 200 μg/disc). From these structures we found that the fused heterocyclic ring causes relatively better microbial growth inhibition. Among tested compounds fused heterocyclic compounds(**6**),(**12**) and (**15**) exhibited relatively greater inhibition of growth of the microorganism.

Prefatory Note

Unless otherwise mentioned the following procedures were used throughout the research.

1. Purification of Solvents ant Reagents:

The purity of solvent is extremely important in chromatographic analysis as well as for other purposes like chemical reaction. The methods by which they were purified and dried are described below:

a) Dry methanol:

A dry 500 ml round bottom flask was fitted with a double surface condenser and a calcium chloride guard tube. In the flask 1.25 g of clear dry magnesium turnings and 0.125 g of iodine were placed followed by 20-25 ml of commercial grade methanol. The mixture were warmed until the iodine was disappeared. Heating was continued until all the magnesium was converted into methanolate then added 230 ml of commercial grade methanol and refluxed the mixture for one hour. Then the suspension was distilled and stored under nitrogen atmosphere, as the "super dry" methanol.

b) Ethyl alcohol:

These solvents were purified in exactly analogues manner as described with methyl alcohol.

c) Anhydrous acetone:

The acetone was heated under reflux with successive quantities of potassium permanganate until the violet color persists. It was then dried by the addition of anhydrous potassium carbonate, filtered and distilled. The distillate was collected at 55-56°C as pure solvent.

d) Dry acetic acid:

The commercial grade acetic acid was refluxed over phosphorus pentaoxide for 3 hours and then distilled. The destillate was collected at 116-117°C as dry acetic acid.

2. Melting Point (m.p):

Generally melting points are determined for solid and well dry compound. Melting points were recorded on Gallenkamp melting point apparatus (England) and paraffin oil bath were uncorrected.

3. Infra-red (IR) Spectra:

The infrared (IR) spectra were determined on KBr disc for films with a shimadzu FTIR spectrophotometer and the UV spectra were recorded in dry EtOH with a Shimadzu UV visible spectrophotometer at the Department of Chemistry, BUET, and Dhaka, Bangladesh.

4. Nuclear Magnetic Resonance (NMR) Spectra:

The NMR spectroscopy is very widely used for the detailed investigation of an unknown compound. With the help of this spectroscopy the structure or pattern of unknown can be set up. ^{1}H NMR (400 MHz) and ^{13}C-NMR (100 MHz) spectra were recorded in deuteriocholoroform ($CDCl_3$) & DMSO-d_5 with a Bruker DPX-400 spectrophotometer (400 MHz) using tetramethylsilane (TMS) as internal standard at the Bangladesh council of scientific and industrial research Laboratories (BCSIR), Dhaka, Bangladesh.

And also ^{1}H-NMR (500 MHz) and ^{13}C-NMR (125.65 MHz) were recorded in $CDCl_3$ & DMSO-d6 (TMS as internal standard) at Iwate University, Japan.

5) Evaporation:

All evaporations were conducted under reduced pressure using Buchi Rotatory Evaporator (W. Germany) with a bath temperature below 40^0C.

6. Drying:

All organic extracts were dried over anhydrous sodium sulfate (Na_2SO_4) or magnesium sulfate ($MgSO_4$) before concentration.

Part-1

Section-1

BACKGROUND OF THE PRESENT WORK

INTRODUTION

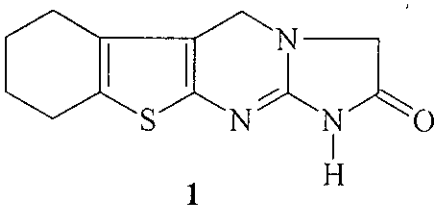
1.1. FUSED HETEROCYCLIC DERIVATIVES AND THEIR IMPORTANCES

Fused heterocyclic derivatives are the most important compounds in organic chemistry. The fused pyrimidines exhibit broad spectrum biological activities[1].

Fused heterocyclic compounds have become attractive targets for organic synthesis because of their structural diversity and biological importance. Recent development of physiologicaly highly potent fused pyrimidines with interesting sedative[2], antiviral[3,4], antibacterial[2,5], antimalarial[2,5,6], antialergic[3], antiparasitic[8], anti-inflammatory[7], anti-HIV[5], antihyper-tensive agents[9,10], blood platelet aggregation inhibitors[11] and specially anticancer agents[3,4,5,6] prompted a great interest in the preparation of annelated pyrimidines. Hetero aromatic carboamines and nitriles readily undergo cyclization, which allow convenient preparation of a variety of condensed pyrimidines[12].

With the development of isolation techniques and rapid structural elucidations by recent methods (UV, IR, NMR, Mass etc.) a large number of fused pyrimidine have been discovered from the various sources. Many pyrimidines and fused pyrimidine derivatives have important biological activity.

In view of the important of prophylactic agents for thrombosis and inhibitors of platelet aggregation are of considerable interest. Some potent cmpounds 1,2,3,5-tetrahydro-imidazo[1,2-a]thienopyrimidin-2-one(**1**), 6,7-dichloro-1,2,3,5-tetrahydroimidazo[2,1-b] quinazoline-2-one(**2**), 7-bromo-3,6-dimethyl-1,2,3,5-tetrahydroimidazo [2,1-b]quinazo-line-2-one (**3**) were prepared by F. Ishikawa *et al.*[11] also pointed out the essential contribution of the lactam structures and liophilic substitution in platelet aggregation inhibitory activity on the studies of imidazothieno-pyrimidines.



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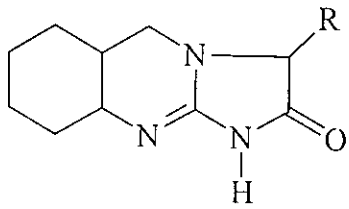
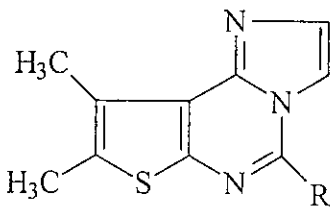


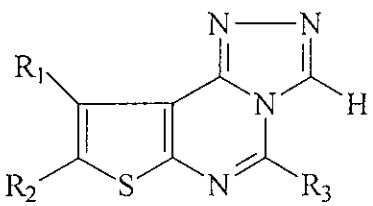
2. R = H, X = Y = Cl
3. R = X = Me, Y = Br

Rahman *et al.*[81] reported 8,9-Dimethylimidazo[1,2-c]thieno[3,2-e]pyrimidine (**3a**), 5,8,9-Trimethylimidazo[1, 2-c]thieno[3,2-e]pyrimindine (**3b**), 8,9-Dimethyl-5-phenylimidazo [1,2-c]thieno[3,2-e]pyriminine(**3c**) which showed antifungal and antibacterial activities.



3a: R = H
3b: R = CH_3
3c: R = Ph

Fumiyashi *et al.*[12] also pointed about the essential contribution of the lactum structure and lipophilic substitution molecules inhibit in platelet blood aggregation. Condensed triazoles posses a variety of pharmacological activities like mitotic (**3**) hypotensive (**4**) and analgesic activity[13](**4, 6**).



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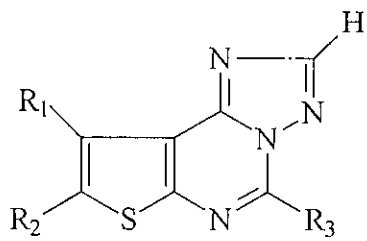

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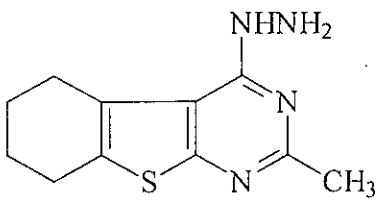

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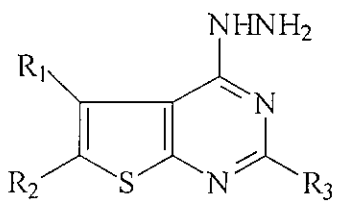

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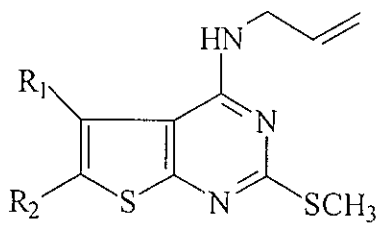
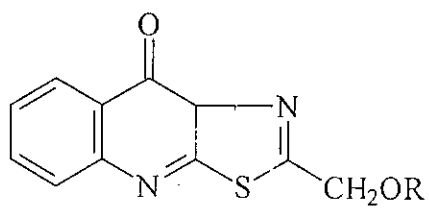
Rahman *et al.*[82] 4-Allylamino-5,6-dimethyl-2-methylthiothieno[2,3-d]pyrimidine(**7a**), 4-Allylamno-2-methylthio-5,6,7,8-tetrahydrobenzothieno[2,3-d]pyrimidine(**7b**) which showed antifungal and antibacterial activities.



7a: $R_1 = R_2 = CH_3$
7b: $R_1R_1 = -(CH_3)_4$

In 1991, Nirupama Tiwari *et al.*[14] reported that 2-aryloxymethyl-1,2,4-thiadiazolo[2,2-b] quinazoline-4-one (**9**) were evaluated for their fungicidal and herbicidal activities.



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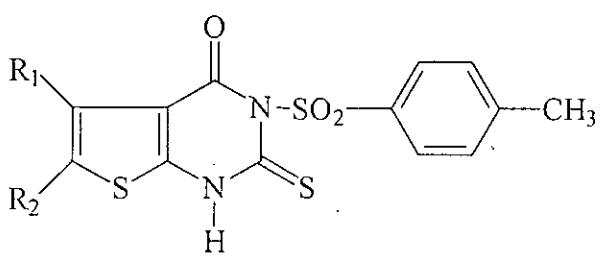
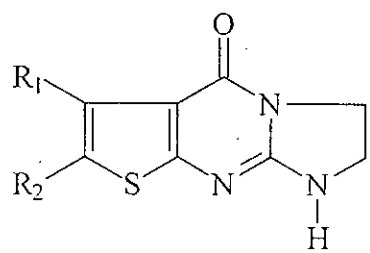
Shafifullah *et al.*[83] reported 4-Oxo-5,6-dimethylthieno[2,3-d]pyramidin-3-*p*-toluene sulfonate sester(**8a**), 2,3,6,7,8,9-Hexahydrobenzothieno[2,3-d]pyrimidin-5(4*H*)-one(**8b**), 2,3-Dihydro-6,7-dimethylthieno[2,3-d]imidazo[1,2-a]pyrimidine-5(4*H*)-one(**8c**) was synthesized which showed antifungal and antibacterial activities.



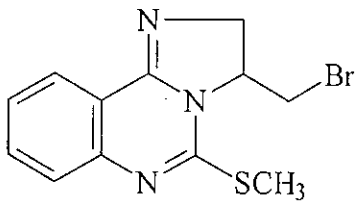
8a: $R_1R_2 = -(CH_2)_4$



8b: $R_1R_2 = -(CH_2)_4$
8c: $R_1{=}R_2 = CH_3$

The fused pyrimidine has been reported by Chern and his co-workers[15] 3-Bromomethyl-5-methylthio-2,3-dihydroimidazo[1,2-c]quinazoline(**9**) which was synthesized from anthranilonitrile. It showed antimalarial activity[15]. The compound imidazol[1,2-

c]quinazoline-2,5-(3*H*, 6*H*)dione(**10**) acted as hypertensive agent which was reported by papadopoulas *et al.*[16].



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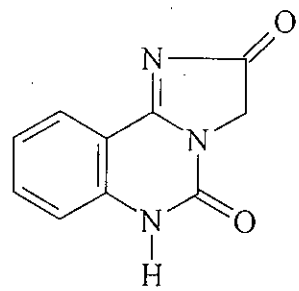

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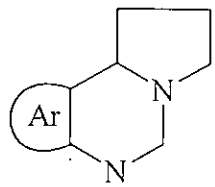
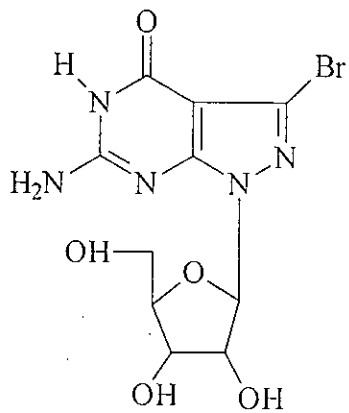
The above two compound(**9**),(**10**) are the analogous of our target products. The following system was chosen as target product which parent system showing below:



11

Ribo nucleosides compounds showed in vitro against certain viruses and tumor cells. The guanosins analogous(**12**) showed significant activity against muscle *in vitro* and to exhibit moderate antitumor activity *in vitro* against L_{R10} and P_{388} Leukemia[17].

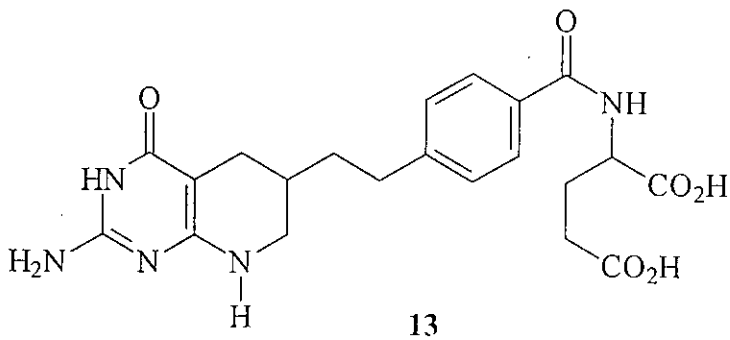


12

A detail description of the isolation, structural elucidation and synthesis of different types of fused pyrimidine and their biological activity will be given in the subsequent chapters.

1.2. NATURAL SOURCES OF FUSED PYRIMIDINES

Fused pyrimidines are found in a broad variety of natural products [e.g. purines, pyrolo-pyrimidines, pteridines], pharmaceuticals, agrochemcials and veterinary products(**13**)[18].

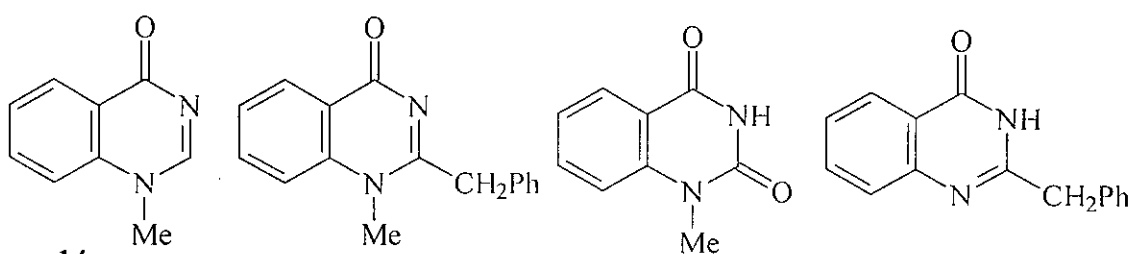


13

The fused pyrimidine rings or purine rings are present in the nucleic acids, co-enzymes etc. They were also isolated from the living cells[19].

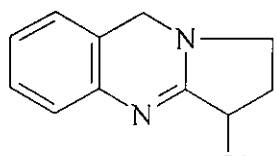
A variety of natural products such as purine alkaloids contain the pyrimidine ring systems. These include hypoxanthine and xanthine which occur in tea. Caffeine and theophylline are found in tea-leaves[19]. Theobromine is found in coca-beans which has a stimulating effect on the central nervous system[19].

The quinazoline alkaloids from a small but important group of naturally occurring bases which were isolated from a number of different families in the plant kingdom. Quinazolines were found in the botanical families. Glycorine(**14**), Aborine(**15**), Glycosmicine(**16**) and Glycosminine(**17**) were isolated from the leaves of *Glycosmis arborea.*



14 **15** **16** **17**

l-Vasicine(**18**) isolated from *Adhatoda vasica* and vasicinone(**19**) was isolated from *Pegnum harmala* and *Galega officinalis*. The vasicine group has bronchodilator activity[20].



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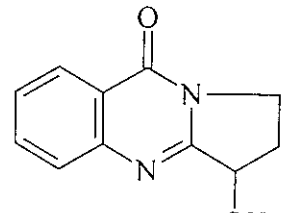
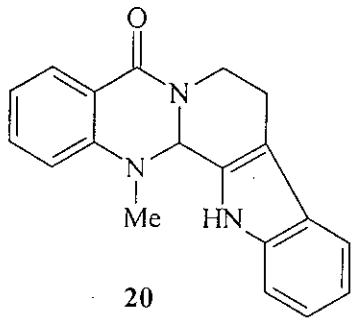


19

The evadomine(**20**) was isolated[20] from the dired fruits of *Evodia rutaecarapa* and it exhibits hypotensive action. The other alkaloids febrifugine(**21**) was isolated from *Dichora febrifuga* which was high antimalarial activity.



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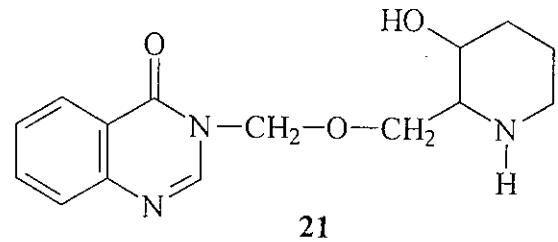
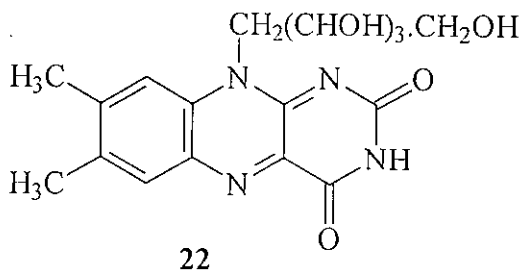


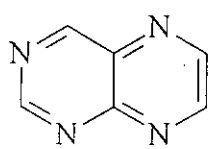
21

The fused pyrimidine rings are also present in vitamin riboflavin B_2(**22**). The best sources of vitamin B_2 are yeast, green vegetables, egg, milk, meat, fish etc.[21].



22

Folic acid contains a pteridine(**23**) nucleus which is a fused pyrimidine. The pterines are pigments of butterfly-wings, waps etc. They were first isolated from butterfly-wings. Some pterins are also found to be in man, e.g. Xanthopterin(**24**) and biopterin(**25**).



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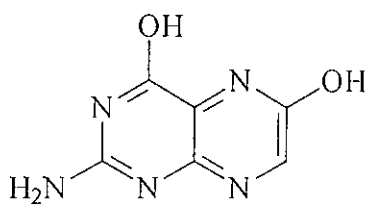

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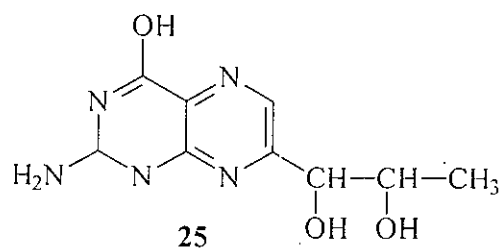
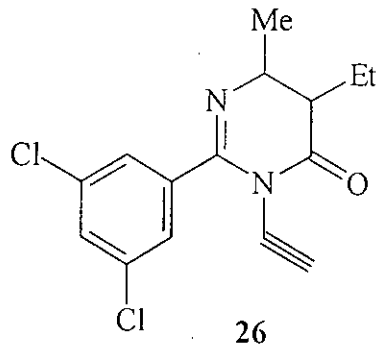


25

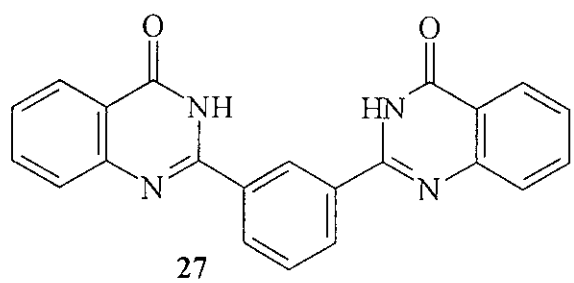
1.3. VARIOUS FUSED PYRIMIDINES

The synthesis and design of new herbicides is a continuing challenge in agricultural chemistry because of the persistent problem of resistance development and as a result of economic and environmental pressures to find compounds with different modes of action. Edward C. Taylor *et al.*[25] reported the novel synthesis of promising new herbicide 2-(2,6-dichloro-4-pyrilyl)-3-propargyl-5-ethyl-6-methyl-4-(3*H*)-pyrimidinone(**26**).



26

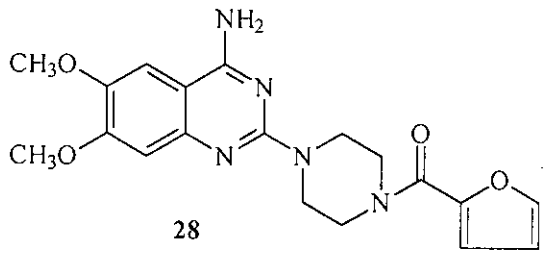
Bis[quinazoline-4-one-2-yl]-1,3-phenylene(**27**) and its 3-N-substiuted derivatives were prepared by S.A. Shiba *et al.*[23] from the corresponding bis[3,1-benzoxazine-4-one-2-yl]-1,3-phenyline as precursor. Quinazoline(**27**) was converted into several derivatives such as bis[quinazoline-4-thioxo-2-yl] etc. These types of compounds show activity against Gram-positive and Gram-negative bacterias.



27

Hypertension is serious risk factor for cerebrovascular disease and heart disease in developed countries. Although there are several antihypertensive drugs clinically available, due to the different origin and pathology of hypertension, it is difficult to control all types of hypertension through the use of only one drug. Varieties of antihypertensive agents contain pyrimidine and fused pyrimidine ring systems.

For example prazosin(**28**)[24] a 2-subsituted quinazoline derivative has been proven effective in the clinic, acting as a α-adrenoceptor antagonist[24]. Other 3-substitued quinazolines such as SGB-1534(**29**)[25] and ketanserin(**30**)[26] have been found to have anthypertensive activities medicated via-α-adrenoceptor and serotonic receptor antagonism respectively.



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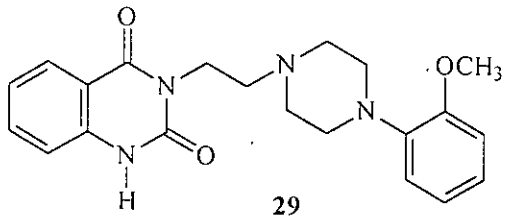

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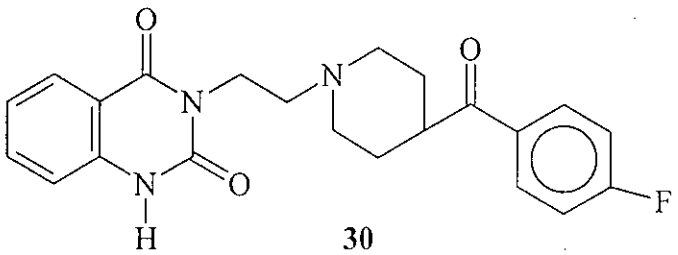
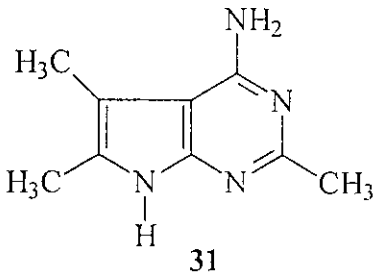


30

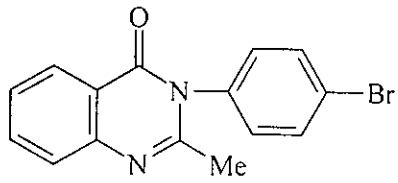
Compounds containing a fused pyrimidine ring represent a broad class of compound which have received considerable attention over the past years due to their wide range of biological activity with the development of clinically useful anticancer (5-fluorouracil) and antiviral drugs[27].

2-Substituted pyrolo[2,3-d]pyrimidin-4-amines(**31**) obtained with prove antiphlogisic and anticonvulsant properties[28].



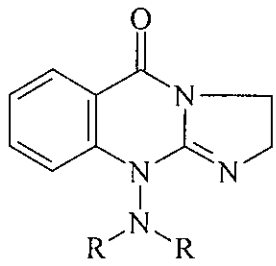
31

3-*p*-Bromophenyl-3,4-dihydro-2- methyl-4-oxoquinazoline(**32**) B. D. H. was one quarter as active as phenytoin against Leptazol and eight times more active than Troxidone against electroshocle induced convulsions[29].



32

Malecha and his co-workers reported[30] that imidazo[2,1-b]quinazolin-5(3*H*)-one(**33**) was synthesized from 1-(2-flurobenzyl)-2-methylthio-2-imidazoline(**34**)[30] which was used as potentially selective tracheal smooth muscle relaxants[30].



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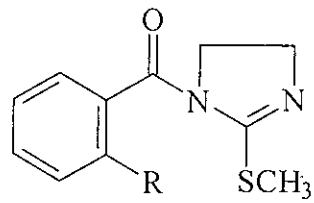
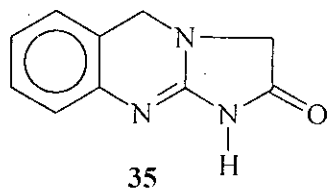


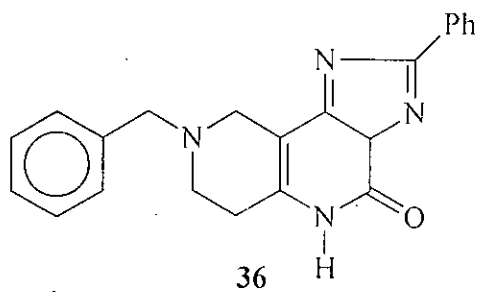
34

The best compound in view of chemical and biological evaluation, solubility in water, potency of the platelet aggregation inhibition, antithrombic drug with little effect on the cardiovascular system was 7-piperidino-1,2,3,4-tetrahydro-imidazo[2, 1-b]quinazolin-2-one (**35**) which was synthesized and reported by Fumiyoshi and his co-workers[31a].



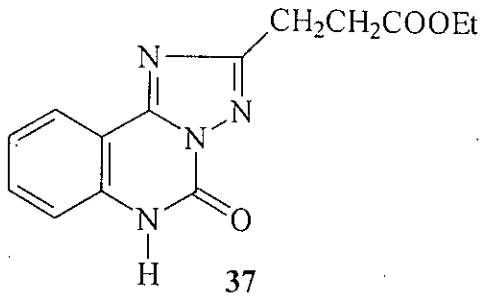
35

Antihypertensive and muscle relaxants type activity was showed by 7,8,9,10-tetrahydro-2-phenyl-9(phenylmethyl)pyrido[3,4-e][1,2,4]triazol[1,5-c]quinazo-line-5-(6*H*)-one(**36**) reported by John E. Francis and his co-workers[31b].



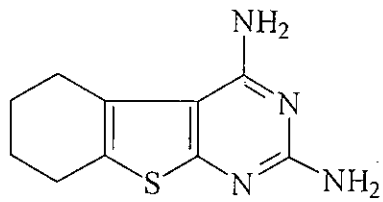
36

Schlecker and his co-workers[32] was reported that the triazoloquinazoline(**37**) acted as a nervous system agent and showed little effected on other bacteria, fungi and viruses.



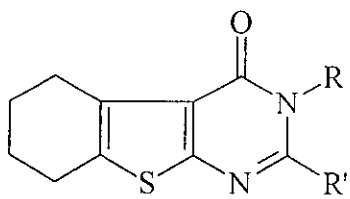
37

A. Rosowasky and his co-workers[33] reported the synthesis of 2,4-diamino-5,6,7,8-tetrahydrothianaptheno[2,3-d]pyrimidine(**38**) which acts as antifolates and antimalarial agent. It was obtained from the aminonitrile.



38

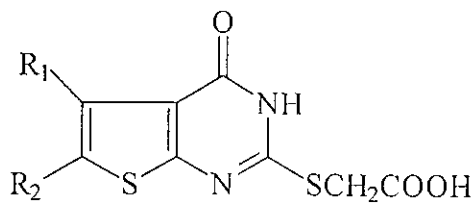
M. M. El-Enamy *et al.*[34] reported that substituted thieno[2,3-d]pyrimidones(**39**) have microbial activity.



R = $NHSO_2C_6H_5$
R' = Me

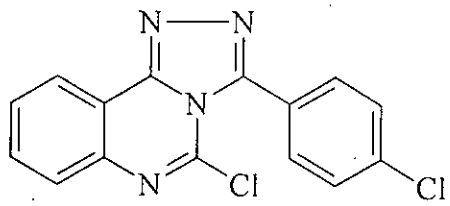
39

2-Marcapto-3,4-dihydrothieno[2,3-d]pyrimidine-4-one(**40**) showed hypocholest-erolemic and antitussive properties which was reported by P. Sukumaran and his co-workers[35].



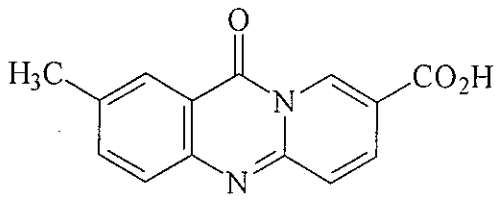
40

R. A. Glennon and his co-workers[36] revealed that triazoloquinazolines such as 3-aryl-1,2,4-triazolo[4,3-c]quinazolines(**41**) posses antiinflammatory activity.



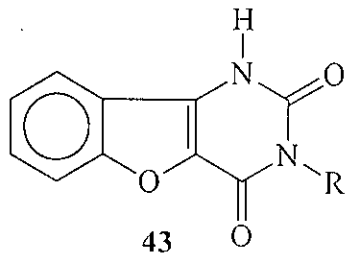
41

A great deal of synthetic work has been directed toward the discovery of more potent and orally active compounds. A series of 2-subsituted-pyrido[2,1-b]quinazolin-8-carboxylic acids(**42**) are used as orally active antiallergy agent which were reported by J. W. Tilley and his co-workers[37]. The compound(**42**) was synthesized from the reaction of the appropriate anthranilic acids with 6-chloronicotinic acid in 38% yields.



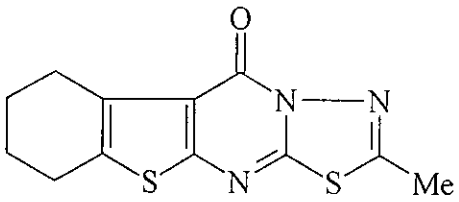
42

V. M. Patil and his co-workers[38] reported a new antialergic compound 3-amino-1,2,3,4-tetrahydro-2,4-dioxobenzofuro[3,2-d]pyrimidine(**43**).



43

The compound 6,7,8,9-tetrahydro-2-methyl-10*H*[1]benzothieno[2,3-d]thiadiazolo[3,2-a] pyrimidin-10-one(**44**)[7] and 2,3-dihydro-5*H*-[1,3,4]thiadiazolo[2,3-b]quinazolin-2,5-dione (**45**)[39] showed antiinflammatory and analgesic activities.



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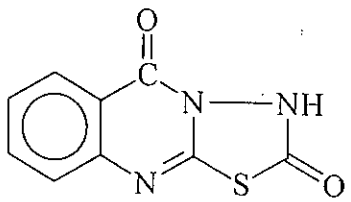
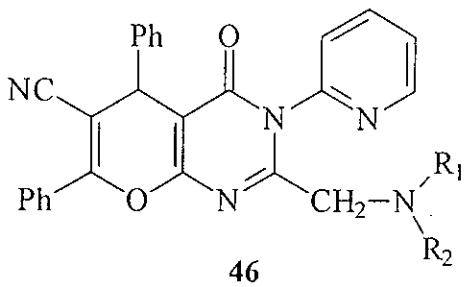


45

A. A. Fadda and his co-workers[39] reported the compound 2-(N,N-substituted amino-methyl)-6-cyano-4(3*H*)-oxo-5,7-diphenyl-3-(2-pyridal)-pyrazo-(3,2-b)pyrimidine(**46**), which is known to have diverse pharmacological properties including antibactrial, antiviral and antiallergic.

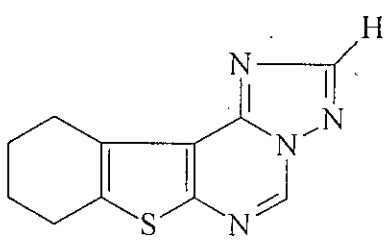


46

46(a): $R_1 = R_2 = CH_3$

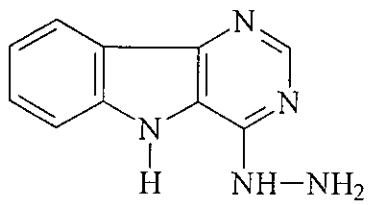
46(b): $R_1 = R_2 = C_2H_5$

C. J. Shishoo and his coworkers[13] reported the synthesis of triazolo-theino-pyrimidines (**47**) which was found to be potential antiinflammatory compounds.



47

A. Monge and his co-workers[40] reported the synthesis of 4-hydrazino-5*H*-pyrimido-[5,4-b]indole(**48**) and some related compounds(**49**) which are structural analogous of antihypertensive agent.



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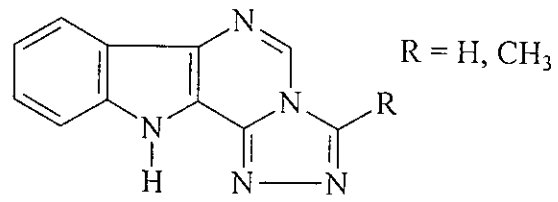
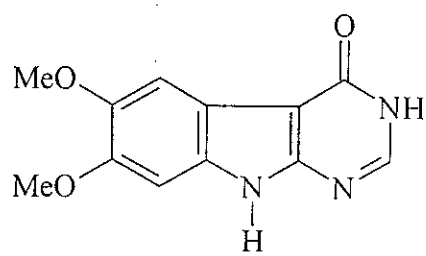


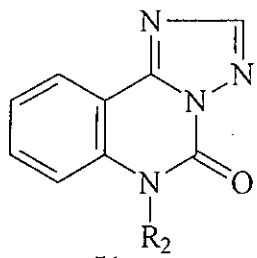
49

B. Venugopalon *et al.*[41] reported the synthesis of 4-oxo-pyrimido[4,5-b]indole(**50**) which as antihypertensive properties. *Ortho*-aminoesters serve as a good synthon for the construction of a pyrimidine ring.



50

The fused pyrimidine[1,2,4]triazolo[1,5-c]quinazoline(**51**) exhibited the anticonvulsant, muscle relaxant, anxilytic and sedative properties and benzofuro[2,3-e]imidazo[1,2-c] pyrimidine(**52**) showed antidepressant activity and antihypertensive agents[42].



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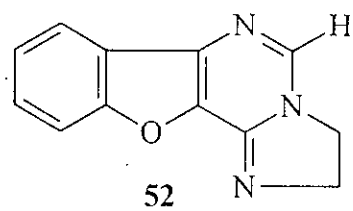


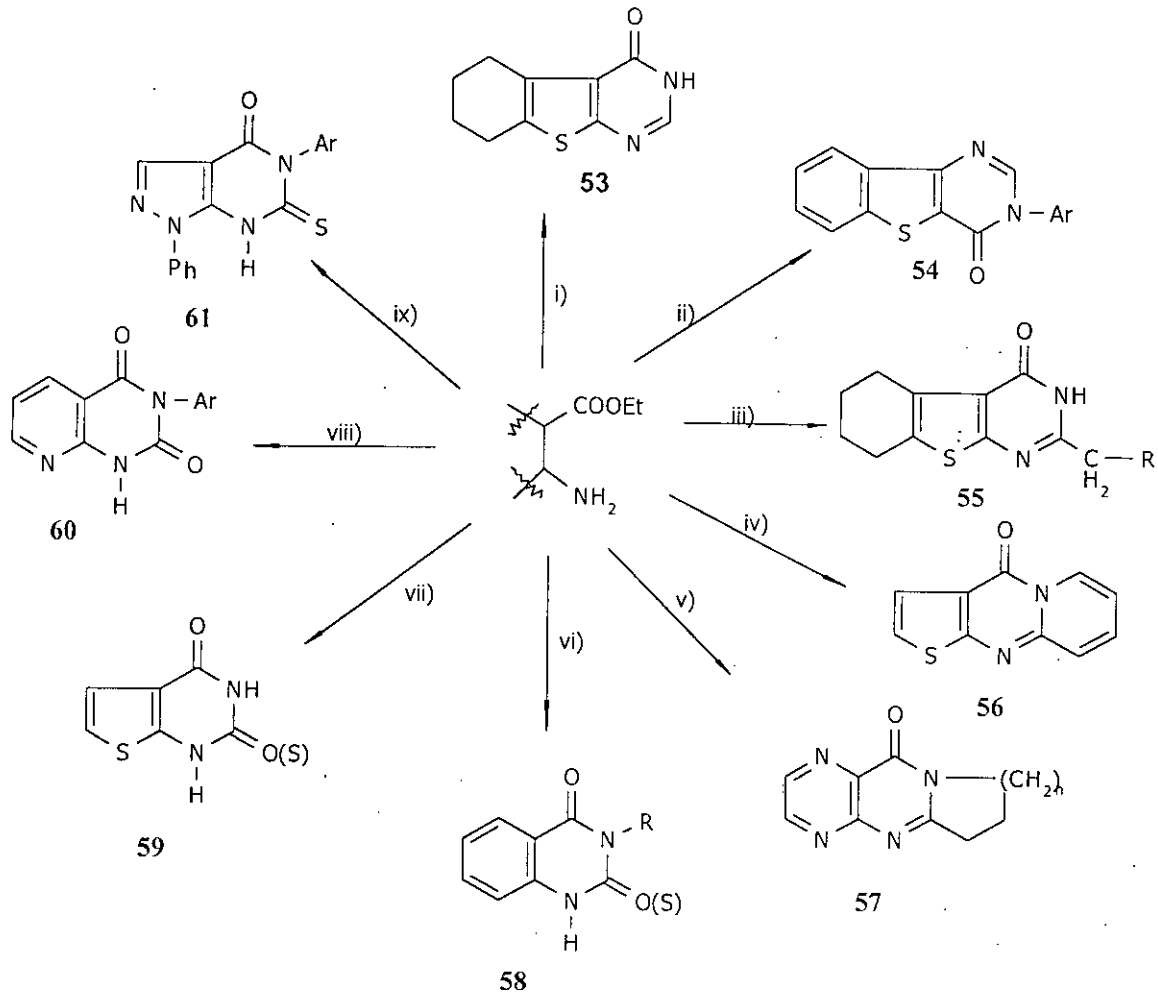
52

For more detail description pyrimidine and fused pyrimidine will be discussed in the next chapters.

1.4. METHODS OF SYNTHESIS OF FUSED PYRIMIDINES

For the synthesis of fused pyrimidines from *ortho*-aminoesters many procedures are published, some of them are outlined in below:

1.4(a). *SYNTHESIS OF FUSED PYRIMIDINES FROM ORTHO-AMINOESTERS*



Scheme - 1

Reagents:

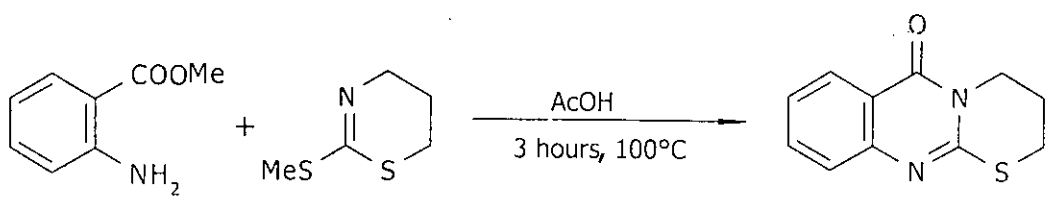
i) $HCONH_2$, Δ; ii) $ArNH_2$, $HC(OEt)_3$, decalin, Δ; iii) RCH_2CN, HCl-dioxane; iv) Iminodichloride or lactum, $POCl_3$; v) Lactim ether; vi) RNCO or RNCS, Pyridine, Δ; vii) $CO(NH_2)_2$ or $CS(NH_2)_2$, Δ; viii) $ArCON_3$, DMF; ix) ArNH-CSSMe, NaOH, DMF, Δ.

For cyclization of *ortho*-aminoesters the ring-closing reagents were usually formamide, urea, lactams, lactim, ethers, iminodichlorides, nitriles or isocyanates (Scheme-**1**).

Reaction of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate with formamide gave [1]benzothieno[2,3-d]pyrimidin-4(3*H*)-one(**53**)[2]. A mixture of a primary arylamine, an *ortho*-ester and an *ortho*-aminoester reacted on heating in declain to form a 3-N-arylpyrimidinone ring(**54**).[43] Nitriles (including cyana-mides) and amidines caused ring closure and relatively mild conditions, but only the lower alkyl amidines were effective. Chloroacetonitrile reacted with two moles of *ortho*-aminoester to benzothieno[2,3-d]pyrimidine-4-one(**55**).[12] Iminochlo-rides, a cyclic or acyclic chloroimine or a heterocycle containing a reactive halogen atom cyclize an *ortho*-aminoester to give a doubly fused pyrimidine type(**56**)[44a]. In the presence of phosphorus oxychloride, cyclic amides (lactams) also reacted and led to(**56**)[44b]. The reaction of 2-amino-3-methoxy carbonyl-pyrazine with lactim ethers led in one step to the polynuclear heterocyclic pteridines(**57**)[45]. The NH-CO(S) group appeared in ring(**58**)[46], when *ortho*-aminoesters reacted with isocyanates or isothiocyanates. A ureido or thioureido group, either formed *in situ* from an amine or present in the substrate, reacted with an ester group to give a pyrimidinedione or thioxo-one(**59**)[47]. A 3-substituted ureide(**60**)[48], can also be prepared by reaction of an amine and an azide. In alkaline solution an aminoester reacted with a dithiocarbamate to give a thioxo-pyrimidinone(**61**)[49] in good yield.

1.4(b). *SYNTHESIS OF FUSED PYRIMIDINES FROM SOME OTHER EDUCTS ANALOGOUS TO ORTHO-AMINOESTERS*

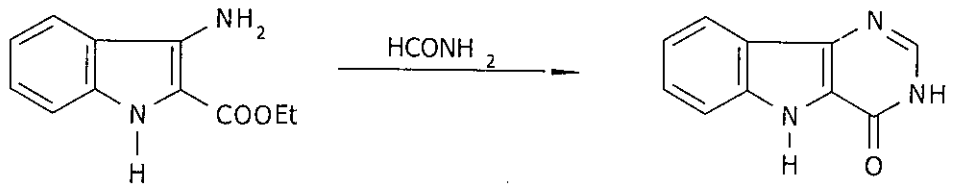
Methyl anthranilate(**62**) reacted with 5,6-dihydro-2-methylthio-4*H*-1,3-thiazine(**63**) in dry acetic acid to form 3,4-dihydro-2*H*,6*H*-[1,3]thiazino[2,3-b]quinazolin-6-one (**64**) published by F. Sauter *et al.*[50] in (Scheme-**2**).



62 **63** **64**

Scheme - **2**

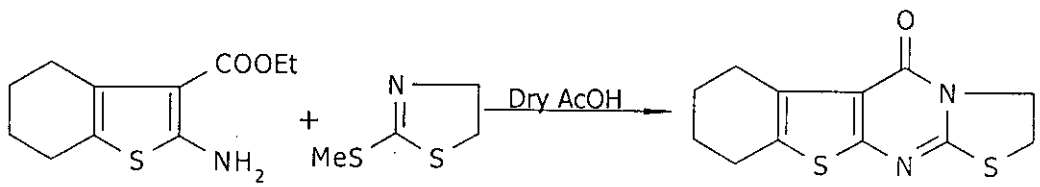
Ethyl-3-aminoindole-2-carboxylate(**65**) in formamide was warmed (Scheme-**3**) with stirring under nitrogen at about 220^{0}C for 2 hours, the product was collected 5*H*-pyrimido[5,4-b]indole-4-one(**66**) reported by Monge *et al.*[51]



65 **66**

Scheme - **3**

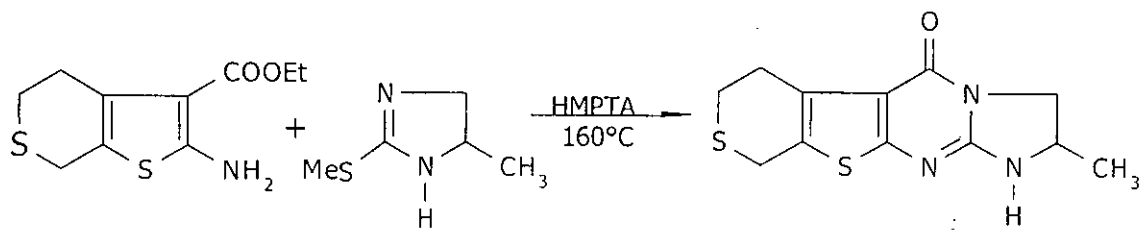
Shifullah and his co-workers[52] reported that ethyl 2-amino-4,5,6,7-tetrahydrobenzo-[b]thiophene-carboxylate(**67**) reacted with imino-thioether-2-methylthio-2-thiazoline(**68**) in dry acetic acid to give 2,3,6,7,8,9-hexahydro-5*H*-[1]benzo-thieno[2,3-d]thiazolo[3,2-a]pyrimidin-5-one(**69**) (Scheme-**4**).



67 **68** **69**

Scheme - **4**

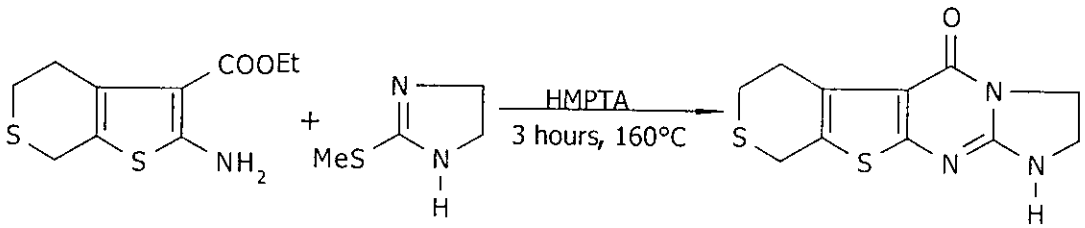
K.M.M. Rahman *et al.*[53] reported the synthesis of 1,2,3,6,7,9-hexahydro-5*H*-imidazo[1,2-a]thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimidin-5-one(**70**) from 2-ami-no-4,7-dihydro-5*H*-thieno[2,3-c]thiopyran-3-carboxylate(**71**) and 5-methyl-2-methylthio-imidazoline(**72**) in 64% yield shown in (Scheme-**5**).



70 **71** **72**

Scheme -**5**

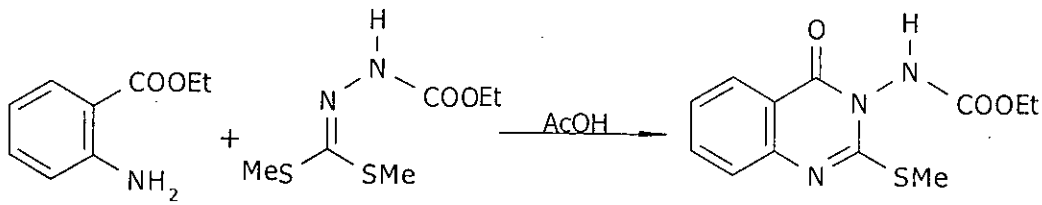
J. Fröhlich *et al.*[54] also reported ethyl 2-amino-4,7-dihydro-5*H*-thieno[2,3-c] thiopyran-3-carboxylale(**73**) reacted with 2-methylthio-2-imidazoline(**74**) in hexame-thylphosphoric triamide (HMPTA) at 160^{0}C for three hours afforded hexa-hydro-5*H*-imidazo[1,2-a]-thiopyrano-[4′,3′:4,5]thieno[2,3-d]pyrimidin-5-one(**75**) (Scheme-**6**).



73 **74** **75**

Scheme - **6**

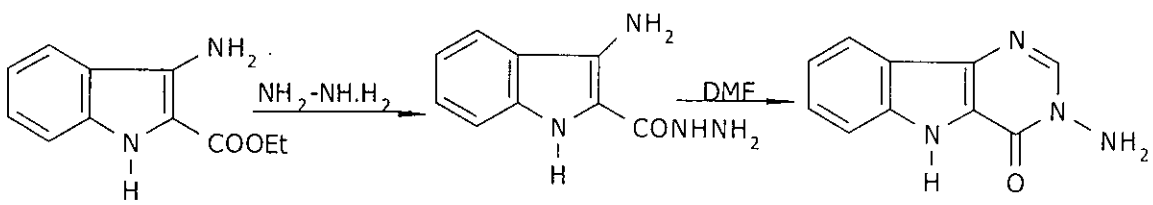
K. Blasl for the first time reported[55] that aza reagent N-[bis(methylthio) methyl-ene]hydrazine carboxylic acid ethylester(**77**) reacted with ethyl anthra-nilate(**76**) in acetic acid to afford the annelated pyrimidine product(**78**) in 70% yield, showing in (Scheme-**7**).



76 **77** **78**

Scheme - **7**

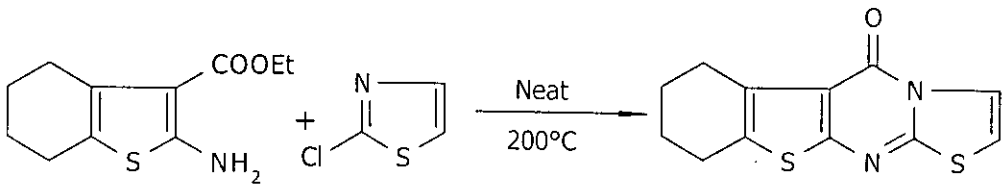
A. Monge and his co-workers[56a] reported that the ethyl 3-aminoindole-2-carboxylate(**79**) reacted with hydrazine hydrate afforded 3-aminoindole-2-carbohydrazide(**80**). Compound(**80**) boiling in N,N-dimethyl formamide for 10 hours to give 3-amino-5*H*-pyrimido[5,4-b]indol-4-one(**81**) (Scheme-**8**).



79 **80** **81**

Scheme - **8**

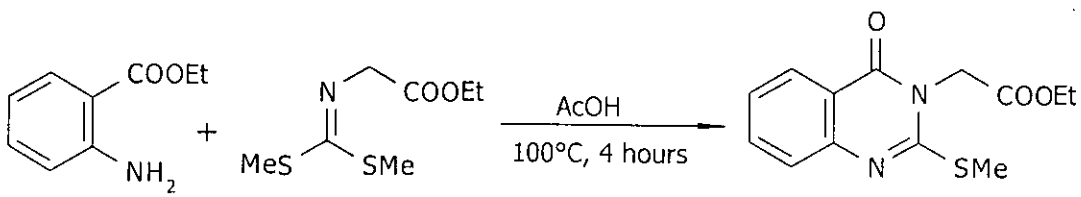
Mannhas *et al.* reported[56b] that ethyl-2-amino-4,5,6,7-tetrahydrobenzo[b]thioph-ene-carboxylate(**82**) reacted with iminochloride 2-chlorothiazole(**83**) afforded 2,3,6,9-tetrahydro-5*H*,7*H*-thiazolo[2,3-a]thiopyrano[4′,3′:4,5]thieno[2,3-d]pyrimi-din-5-one(**84**) as shown in (Scheme-**9**).



82 **83** **84**

Scheme - **9**

F. Sauter and his co-workers[57] reported that ethyl anthranilate(**85**) reacted with N-[bis(methylthio)-methylene]glycine-ethylester(**86**) formed 3,4-dihydro-2-met hylthio-4-oxo-quinazoline-3-acetic acid ethyl ester(**87**) (Scheme-**10**).



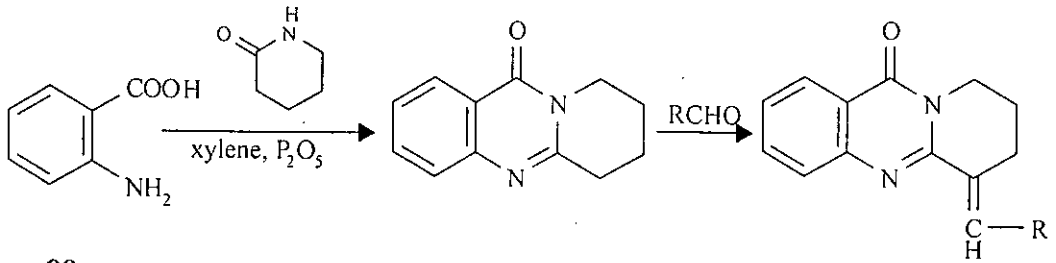
85 **86** **87**

Scheme - **10**

Synthesis of our target pyrimidine system will be discussed experimental, results and discussion part.

1.5. SYNTHESIS OF FUSED PYRIMIDINES BY VARIOUS METHOD

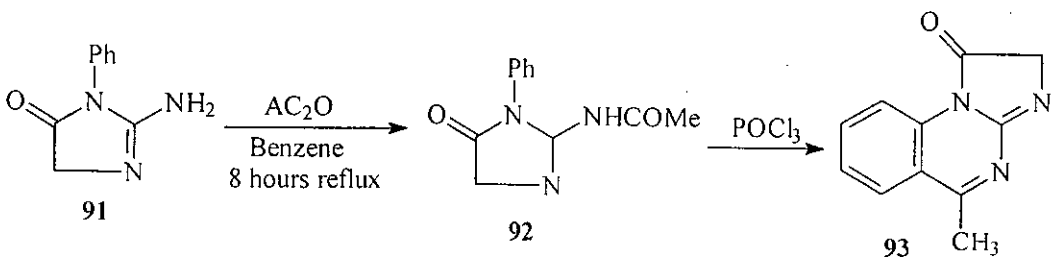
M.P. Jain *et al.*[58] reported the synthesis of tetrahydro[2,1-b]quinazolin-10(*H*)-one(**90**). The parent compound tetrahydropyridoquinazoline(**89**) was synthesized by the condensation of anthranilic acid(**88**) with 2-piperidone in xylene in the presence of phosphorus pentaoxide(**89**) on condensation with various aldehyde in xyline at 140^{0}C for 15-50 hours gave the(**90**). When R = C_6H_5 the product was obtained in 65% yield.



88 **89** **90**

Scheme-**11**

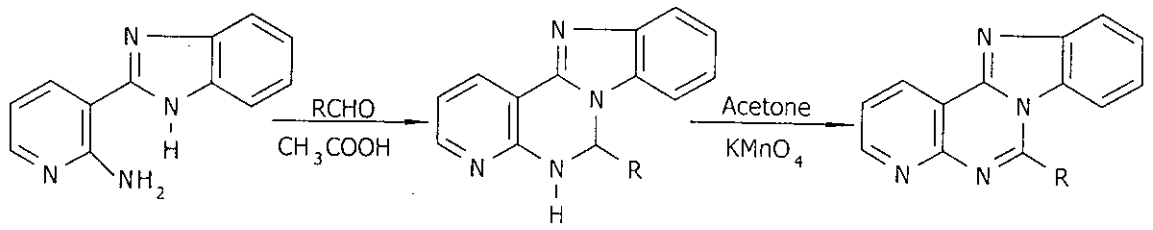
F. Shifullah *et al.*[52] reported that, amino-imidazole(**93**) was acylated by acetic anhydride in benzene the acylated product(**92**) was cyclized by $POCl_3$ afforded 5-methylimidazo[1,2-a]quinazoline-1(2*H*)-one(**93**) showing in (Scheme-**12**).



91 **92** **93**

Scheme-**12**

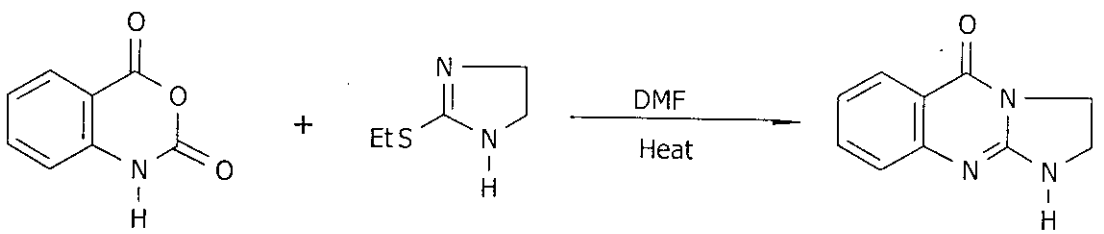
The starting compound 2-(2-amino-3-pyridyl)-benzimidazole(**94**) was obtained by the condensation of *O*-phenylenediamine with 2-amino-nicotinoaldehyde in the presence of ethanol and nitrobenzene. Condensation of (**94**) with aromatic alde-hyde in alcoholic acetic acid led to the formation of either 6-aryl-5,6-dihydro-pyrido[2′,3′:4,5]pyrimido[1,6-a]benzimidazole (**95**). The oxidation of (**95**) with $KMnO_4$ in acetone resulted in the formation of fully aromatic 6-arylpy-rido[2′,3′:4,5]pyrimido[1,6-a]benzimidazoles (**96**) reported by K. Vijayendar Reddy[59] showing in (Scheme-**13**).



94 95 96

Scheme - 13

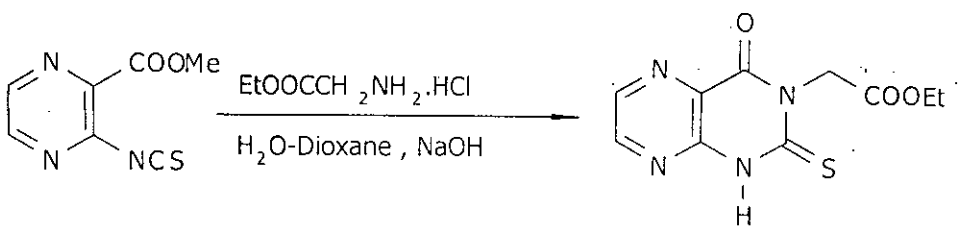
E. Zeigler and W. Steiger reported[60] isotoic anhydride(**97**) and 2-ethylmercapto-2-imidazoline(**98**) in DMF at high temperature to give 1,2,3,5-tetrahydro-imidazo[2,1-b]quinazolin-5-one(**99**) in good yield showing in (Scheme-**14**).



97 98 9

Scheme - 14

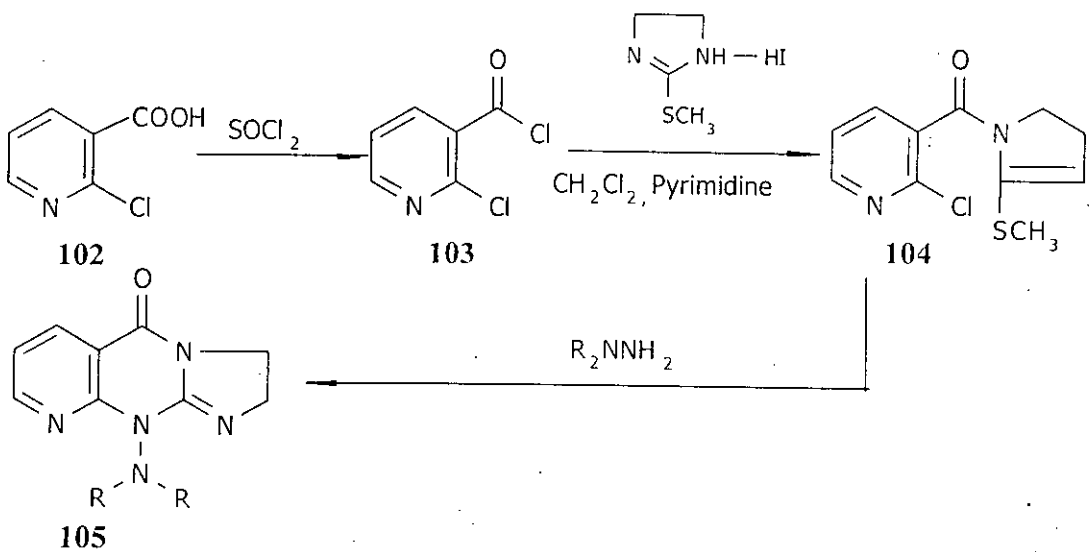
For the pteridine, a fused pyrimidine, synthesis Urleb described[61] the reaction of methyl-3-isothiocyanato-2-pyrazinecarboxylate(**100**) with ethyl glycinate-hydro-chloride in water-dioxane and sodium hydroxide leading to 3-(2-ethoxy-carbonyl-methyl)-2-thioxo-1,2-dihydro-4(3*H*)-pterdinone(**101**) as shown in (Scheme-**15**).



100 101

Scheme - 15

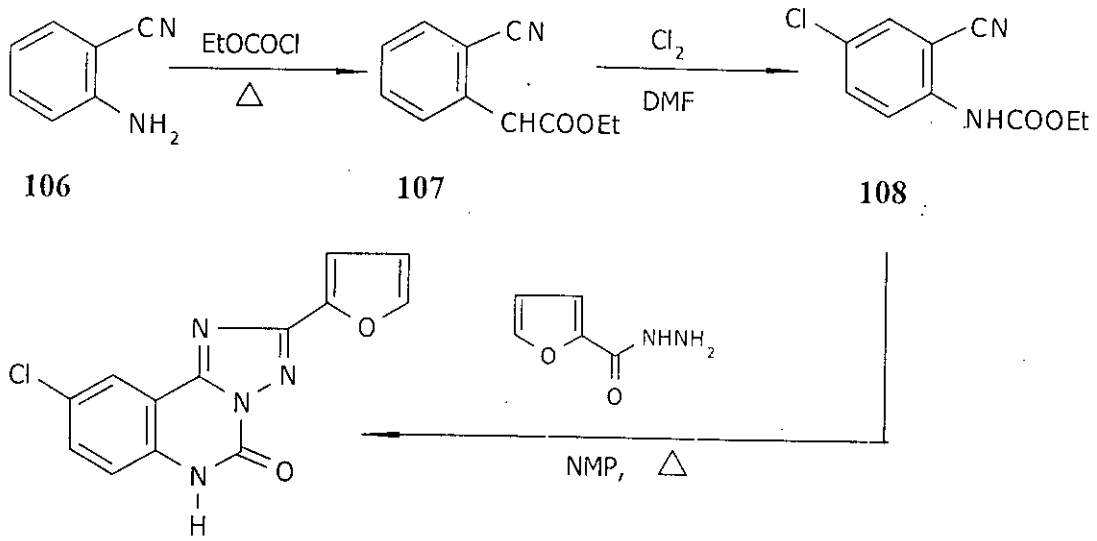
2-Chloropyridine-3-carboxylicacid(**102**) was concerted into 2,10-dihydro-10(4-morpho-linyl)imidazo[1,2-a]pyrido[2,3-d]pyrimidin-5(3*H*)-one(**105**) described by Norton P. Peet and his co-workers[62]. This reaction reported that the 2-chloropyridin-3-carboxylic acid(**102**) and thionyl chloride was reluxed for 3 hours and the resulting solution was concentrated to dryness. The resulting oil was twice diluted with methylene chloride and reflux to give of 2-chloropyridine-3-carbonyl chloride(**103**). The acid chloride was added to a mixture of 2-methylthio-2-imidazoline hydroiodide and triethylamine and new mixture was reflux for 16 hrs. to give the compound(**104**). Finally the compound(**104**) and N-amino-morpholine was heated in an oil bath at 160^{0}C for 1 hour afforded 2,10-dihydro-10-(4-morpho-linyl)imidazo[1,2-a]pyrido[2,3-d]pyrimidin-5(3*H*)-one(**105**) showing in (Scheme-**16**).



Scheme -**16**

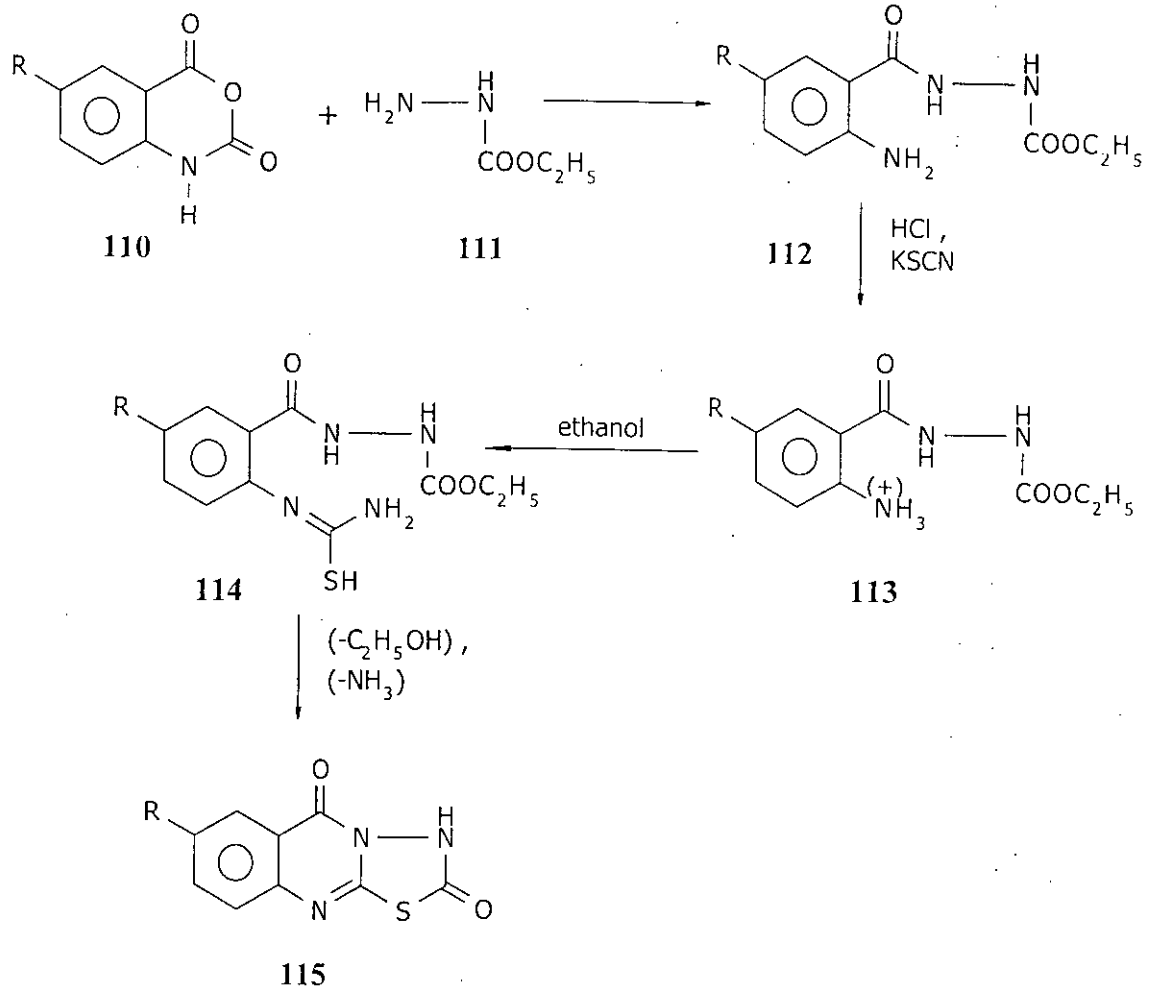
Anthranilonitrile(**106**) reacted with ethylchloroformate yielded ethyl N-(2-cyanophenyl) carbamate(**107**) which was then reacted with chlorine gas in N,N-dimethyl-formamide

afforded ethyl N-(4-chloro-2-cyano-phenyl)carbamate(**108**). Compound(**108**) and 2-furoic acid hydrazide reacted in 1-methyl-2-pyrolidinone (NMP) under nitrogen atmosphere to give 9-chloro-2-(2-furanyl)-5,6-dihdro[1,2, 4]triazo[1,5-c]quinazolin-5(6*H*)-one(**109**). This procedure by Karl O. Gelotte and his co-workers[63] showing in (Scheme-**17**).



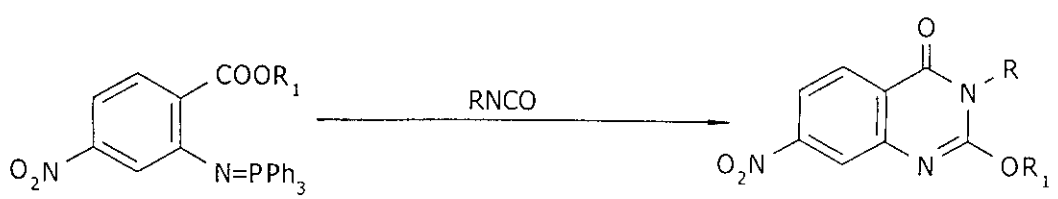
Scheme-**17**

This method descrived by H.K. Gakhar and his co-workers[64] that isotoic anhydride(**110**) was condensed with carbethoxy hydrazine(**111**) to obtain ethyl 2-(2-amino-benzyl)hydrazine carboxylate(**112**) which on treatment with KSCN in the pressure of HCl in cold gave the amino thiocyanate(**113**). The compound(**113**) on refluxing in ethanol for 30 minutes gave the compound(**114**) which was then refluxed and converted into 2,3-dihydro-5*H*-[1,3,4]thiadiazo[1,3-b]quinazolin-2,5-dione(**115**) in good yield (Scheme-**18**).



Scheme -18

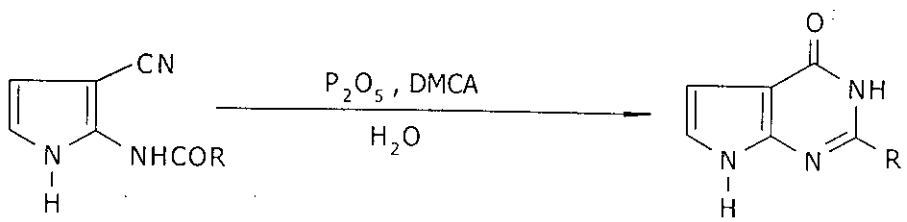
A sequence employed by Wamhoff and co-workers[65] (shown in Scheme-19) used the intermediate iminophosphorane(116), which was readily obtained from *ortho*-aminoesters by treatment with the triphenyl-phosphine, triethylamine and hexachloromethane in dry acetonitrile. Aza-wittig-type reaction of iminophos-phorane with several isocyanates in acetonitrile led to quinazoline derivatives(117).



116 117

Scheme - 19

The deazahypoxanthine(**119**) was obtained by a one step cyclization of the corresponding 2-acylamino-3-cyanopyrole derivatives(**118**). The reaction was carried out by heating 2-acylamino-3-cyanopyrroles(**118**) in a mixture phosphoruspen-taoxide, N,N-dimethylcyclohexanamine (DMCA) and water reported by Girgis *et al.*[79] (Scheme-**20**).



118 **119**

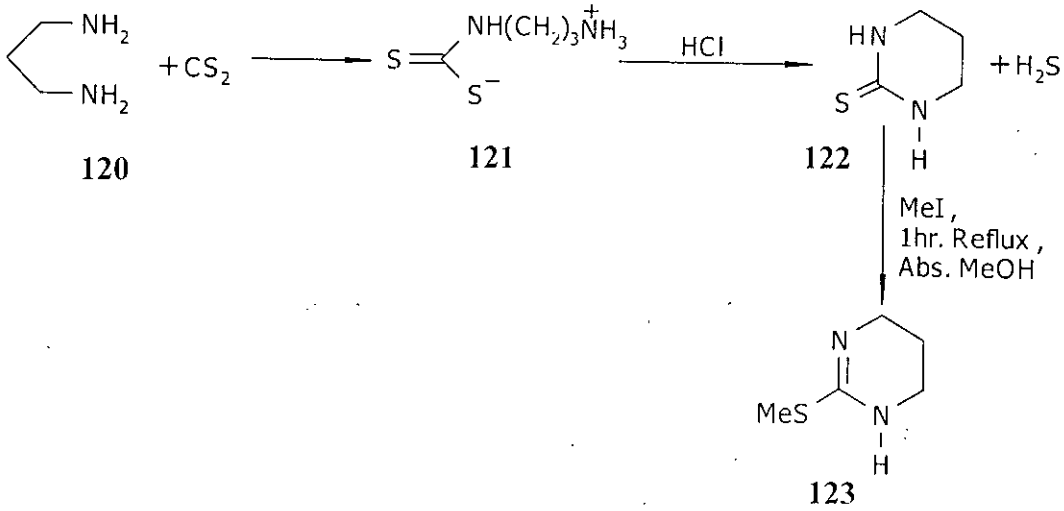
Scheme - **20**

1.6. SYNTHESIS OF ANNELATING REAGENTS

Synthesis of 2-methylthio-1,4,5,6-tetrahydropyrimidine (123):

2-methylthio-1,2,4,6-tetrahydropyrimidine(**123**) was prepared for the first time by Brown *et al.*[66] from 1,4,5,6-tetrahydro-pyrimidine by heating with sulfur. Exactly the same procedure[67] as for 2-imidazolidinethione was used for the preparation at 1,4,5,6-tetrahydropyrimidin-2-thione(**122**), in that case propylenediamine(**120**) has been used in place of ethylene diamine. The yield was 80% of colourless product, m.p.: 207-208^{0}C (after recrystalisation from water).

Methylation of thione(**122**) with MeI in dry methanol for one hour at reflux resulted in 2-methylthio-1,4,5,6-tetrahydropyrimidine hydroiodide salt(**120**). This was neutralized with 50% NaOH solution, extracted with $CHCl_3$, dried over Na_2SO_4 and the solvent evaporated to leave white crystals of iodide free 2-methylthio-1,2,4,6-tetrahydropyrimidine(**123**).

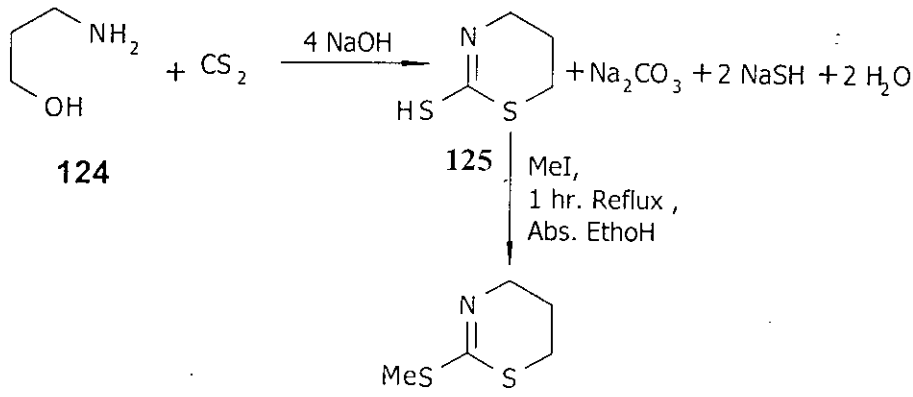


120 121 122 123

Synthesis of 5, 6-dihydro-2-methylthio-4H-1, 3-thiazine (126)

(126) was synthesized by following methods:

Jansens method[68] was used to prepare tetrahydro-1,3-thiazine-2-thione(**125**) in 62% yield. Thione(**125**) was methylated[69] with methyl iodide in dry methanol by heating under reflux for one hour. The solution was cooled and diluted with ether, the yellow crystalline hydroiodide salt was removed (86% yield, m.p.: 155-157^{0}C). The hydroiodide salt was neutralized with triethylamine, extracted with chloroform, dried and the solvent was evaporated to give the free base of(**126**) as a yellow oil.

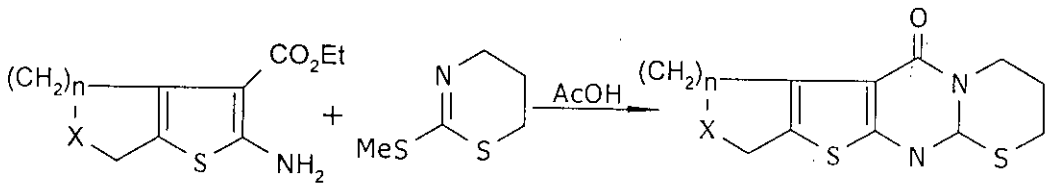


124 125 126

The iminothioether-5,6-dihydro-2-methylthio-4*H*-1,3-thiazine(**128**) is also a versatile reagent for the preparation of pyrimidine derivatives. The compound(**126**) reacted with *ortho*-aminoesters in a one-pot synthesis to give double annelated products of quinazolino-thiazine, thieno-pyrimido-thiazine and thiopyrano-thieno-pyrimido-thiazine derivatives.

Compound(**127**) is a derivative of new heterocylic system, it was smoothly prepared from *ortho*-aminoester and thiazine(**126**) in dry acetic acid. Compounds(**127a, 127b, 127c**) were synthesized in a similar manner.

Thus the following compounds were obtained 3,4-dihydro-2*H*,6*H*-[1,3]-thiazino[2,3-b]quinazolin-6-one(**127**), 3,4,7,8,9,10-hexahydro-2*H*,6*H*-9-methyl[1] benzothieno [2′,3′: 4,5]pyrimido[2,1-b][1,3]thiazin-6-one(**127a**),3,4,8,9,10,11-hexahydro-2*H*,6*H*,7*H*-cyclo-hepta[4,5]thieno[2′,3′:4,5]pyrimido[2,1-b][1,3]thiazin-6-one(**127b**) and 3,4,8,9-tetrahy-dro-2*H*,6*H*,7*H*-cyclopenta[4,5]thieno[2′,3′:4,5]pyri-mido[2,1-b][1,3]thiazin-6-one(**127c**).



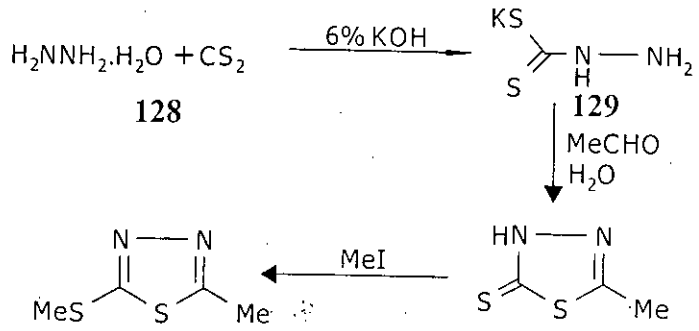
126 **127**

227a : X = MeCH ; n = 2
227b : X = CH_2 ; n = 3
227c : X = CH_2 ; n = 1

Thus the synthesis outlined in general scheme furnished a facile and efficient route for the synthesis of thiazino-pyrimidine derivatives.

Synthesis of 2-methylthio-5-methyl-1,3,4-thiadiazole (128)

2-Methylthio-5-methyl-1,3,4-thiadiazole(**131**) was synthesized from 2-thioxo-5-methyl-1,3,4-thiadiazole(**130**) by methylation, thiadiazole(**130**) was prepared from an aqueous solution of the potassium dithiocarbazate (**129**) with an acetaldehyde-water mixture in analogy to literature method[70]. Treatment of hydrazine hydrate with carbon disulfide and 6% potassium hydroxide gave the potassium dithiocarbazate (**129**).



128 **129** **130** **131**

As described in the introduction that various fused pyrimidines possess different biological and pharmaceutical activities. From the above discussion, it is conclusion that pyrimidine and fused pyrimidine derivatives have a great value for the medicinal chemistry as well as agrochemicals, veternary products and industrial purposes. Some of them are used to control the microbial pathogen of human body and other animals as medicine.

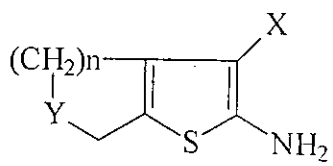
For more detail description of pyrimidine and fused pyrimidine will be discussed in the next chapters.

1.7. SYNTHESIS OF STARTING MATERIAL/SUBSTRATES: *ORTHO-AMINO-ESTERS*

Pyrimidine and fused pyrimidine compounds bearing *ortho*-aminoester moieties were useful substartes for the preparation of various condensed heterocyclic (pymimidine and fused pyrimidine) ring systems i.e. for synthesizing a group of new pyrimidine compounds and a variety of new heterocyclic condensed pyrimindine parent systems belonging to the class of annelated pyrimidine systems. Important starting materials of this type are *ortho*-aminoesters derived from furan, indole, thiophene, oxazole, pyrazole, isoxazole, thiazole and anthranilate fused to new heterocyclic pyrimidine derivatives or to new hetercyclic pyrimidine parent systems belonging to new heterocyclic condensed pyrimidine parent systems (e.g. some novel tri and tetracyclic systems obtained by annelation of imidazole, pyrimido, thiazolo and thiazino, moieties).

1.7(a). Synthesis of Gewald products: ortho-aminoesters of thiophene

The direct one-step base catalyzed condensation of ketones with malonitrile or ethylcyanoacetate and sulfur has been described by Gewald and co-workers[72] served as the basic for the synthesis of a homologous series of ethyl-2-amino-cycloalkano-thiophene-3-carboxylate(**132,133**) starting from cyclohexanone, cyclopentanone respectively. Similarly 4-methylcyclohexanone, its aza-analogue 1-methyl-4-piperidone and thiopyranone[73] were converted into the corresponding *ortho*-aminoesters(**132–134**) (Sceme-**21**).

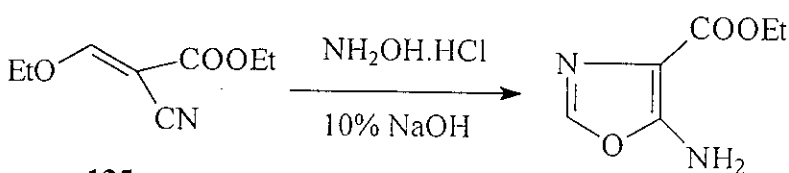


132. X = COOEt, Y = CH_2, n = 1
133. X = COOEt, Y = CH_2, n = 2
134. X = COOEt, Y = NMe, n = 2

Scheme-**21**

1.7(b). Synthesis of ethyl 1-methyl-5-aminopyrazole-4-carboxylate (136)

Ethyl-1-methyl-5-aminopyrazole-4-carboxylate(**136**) was prepared[74] from ethyl (ethoxy methylene)cyanoacetate(**135**) with hydroxylamine hydrochloride in 10% NaOH.

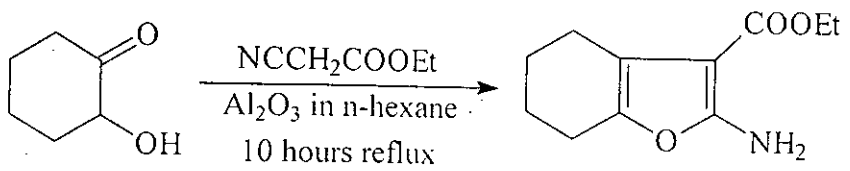


135 **136**

Scheme-**22**

1.7(c). Synthesis of ethyl-2-amino-4,5,6,7-tetrahydrobenzofuran-3-carboxylate (138)

Reaction of adipoin(**137**) with ethylcyanoacetate in n-hexane containing basic alumina (Al_2O_3) as catalyst reflux 10 hours formed ethyl 2-amino-4,5,6,7-tetrahy-drobenzofuran-3-carboxylate(**138**)[75] in yield 57%.

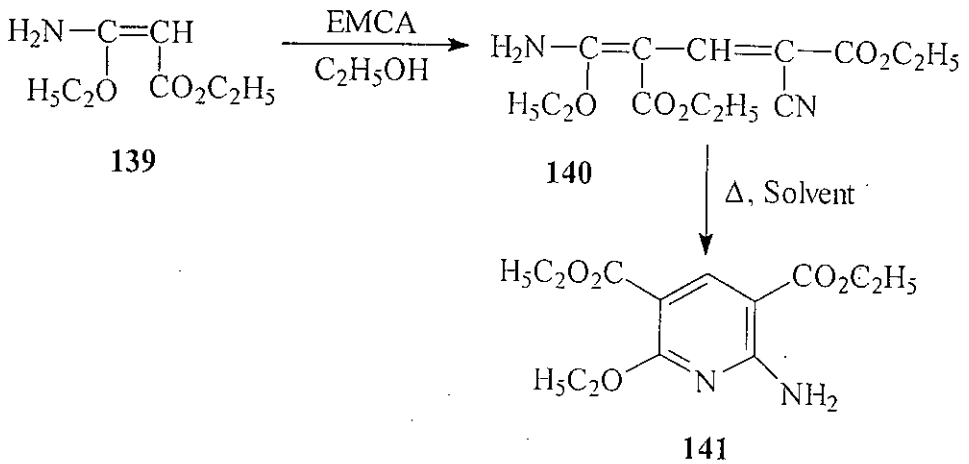


137 **138**

Scheme-**23**

1.7(d). Synthesis of ethyl-2-aminopyridine-3-carboxylate derivatives (141)

By reacting compounds of 3-ethoxy-3-iminopropoinate(**139**) or their correspon-ding amidines with an equivalent of ethoxy methylene cyanoacetate (EMCA) in alcohol solution at room temperature. M. J. Cocco *et al.*[77] obtained dienaminoesters(**140**) in good yields. The adducts undergo intramolecular condition easily when refluxed in dimethyl sulpoxide 2:1 solution or when treated with sodium ethoxide in ethanol at room temperature, to yield the ethyl 2-aminopyridine-3-carboxylate derivatives(**141**).

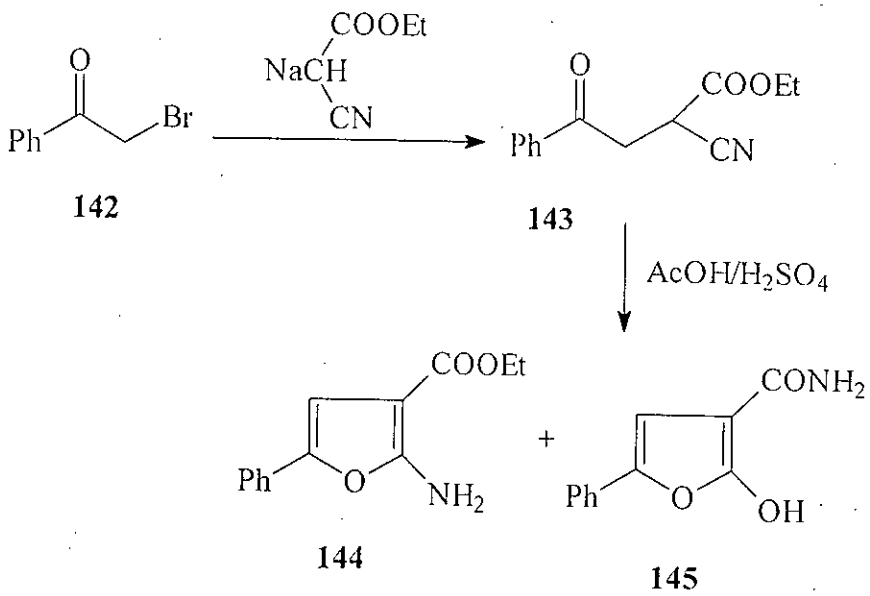


139 **140** **141**

Scheme-**24**

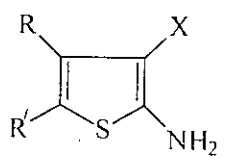
1.7(e). Synthesis of ethyl-2-phenyl-5-aminofuran-4-carboxylate (144)

ω-Bromo acetophenone(**142**) reacted with sodium salt of ethylcyanoacetate to form ethyl phenyl cyanoacetate(**143**) which as treated with acetic acid or sulphuric acid to form a mixture of ethyl 2-phenyl-5-aminofuran-4-carboxylate(**143**)[76] and compound(**144**) reported by Fathy *et al.*[76]



Scheme-25

Again, the direct one-step base catalyzed condensation of ketones with malonitrile or ethyl cyanoacetate and sulfur has been described by Gewald and co-workers[72] served as the basis for the synthesis of a homologous series of 2-amino-4,5-dimethylthiophene-3-carbonitrile(**146**) and ethyl 2-amino-4,5-dimethylthiopene-3-carboxylate(**147**), starting from butanone. Similarly, acetophenone, its aza-analogue ethyl 2-amino-5-phenylthiophene-3-carboxylate(**148**) and *ortho*-aminoamide(**149,150**) and *ortho*-aminoesters(**149–157**) (Scheme-**26**)



Scheme-**26**

146. X = CN, R = CH_3, R′ = CH_3

147. X = $CO_2C_2H_5$, R = CH_3, R′ = CH_3

148. X = $CO_2C_2H_5$, R = H, R′ = C_6H_5

149. X = $CONH_2$, R = H, R′ = C_6H_5

150. X = $CONH_2$, R = CH_3, R′ = C_6H_5

151. X = $CO_2C_2H_5$, R = C_2H_5, R′ = CH_3

152. X = $CO_2C_2H_5$, R = CH_3, R′ = C_2H_5

153. $X = CO_2C_2H_5$, $R = H$, $R' = CH_3$

154. $X = CO_2C_2H_5$, $R = H$, $R' = C_2H_5$

155. $X = CO_2C_2H_5$, $R = C_6H_5$, $R' = H$

156. $X = CO_2C_2H_5$, $R = C_6H_5$, $R' = CH_3$

157. $X = CO_2C_2H_5$, $R = CH_3$, $R' = C_6H_5$

Ortho-aminoester(**147**) is also a useful intermediate, the preparation and its application will be discussed in experimental , results and discussion chapters.

For the synthesis of fused pyrimidines from *ortho*-aminoesters and *ortho*-aminonitriles many procedures are published, some of them are describe in next chapters.

1.8. PRESENT WORK

Synthesis of some new annelated fused heterocyclic derivatives of biological importance.

Rationale:

Fused heterocyclic and their derivatives are the most important compounds in organic chemistry. Heterocyclic compounds containing the pyrimidine skeleton have generated considerable interest in recent years as reflected by recent articles dealing with their synthesis and emphasizing their biological and medicinal properties. The fused pyrimidines exhibited broad spectrum biological activites. Recent development of physiologically highly potent fused pyrimidines with interesting sedative, antiviral, antibacterial, anitmalarial, antiallergic, antihypertensive agents and specially anticancer agents prompted a great interest in this field and to find out facile routes for the synthesis of these molecules in useful yields.

Various methods for the synthesis of fused pyrimidine systems have been developed and employed successfully in heterocyclic chemistry as described in sec.-1. Pyrimidine and fused pyrimidine derivatives have a great value for the medicinal chemistry as well as agrochemicals, veterinary products and industrial purposes. Some of them are used to control the microbial pathogen of human body and other animals as medicine.

Fused pyrimidine compounds bearing aminoester moieties were useful substrates for the preparation of various condensed heterocyclic ring systems i. e. for synthesizing a variety of new heterocyclic condensed pyrimidine parent systems.

In view of the extensive natural occurrence and biological importance of fused heterocyclic derivatives a general and facile method for the synthesis of fused pyrimidines were planned. We were interested in developing methods for the synthesis of a novel series of linear or angular *tetra-*, *penta-* and *hexa-* hetercoclic ring system. In our present studies, for the synthesis of new fused heterocyclic compound were planned to use aminoester and annelating reagents as the starting materials. These would be reacted with suitable reagents to develop new synthetic routes.

It was also planned to test the syntehsized hetarocyclic derivatives for biological and physiological activities.

Section-2

PRESENT WORK:

"SYNTHESIS OF SOME NEW ANNELATED FUSED HETEROCYCLIC DERIVATIVES OF BIOLOGICAL IMPORTANCE"

Results and Discussion

As already mentioned in the introduction, various methods for the synthesis of fused pyrimidine systems have been developed and employed successfully in heterocyclic chemistry. In the present work some fused heterocyclic derivatives were synthesized which are described below.

4.1 SYNTHESIS OF 2-METHYL-6,7-DIHYDROPYROZOLO[3,4-d]THIZOLO [1,2-a]PYRIMIDIN-4-ONE(6)

The synthesis of the fused heterocyclic derivatives is divided into two headings.

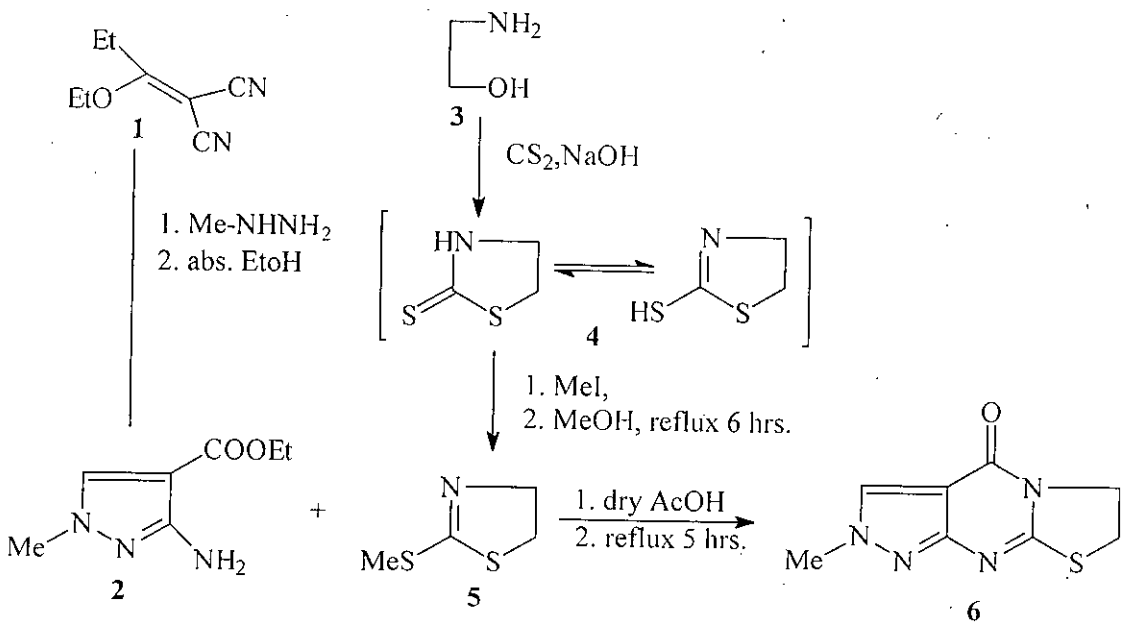
a) Synthesis of annelating substrate:

Ethyl-5-amino-2-methylpyrozolo-4-carboxylate(2)

b) Synthesis of annelating reagent:

2-Methylthia-2-thiazoline(5).

In this approach we used annelated substrate ethyl-5-amino-2-methylpyrazolo-4-carboxylate(**2**) and annelating reagent as 2-methylthio-2-thiazoline(**5**) for the synthesis of fused heterocyclic ring 2-methyl-6,7-dihydropyrazolo[3,4-d]thiazolo[1,2-a]pyrimidin-4-one(**6**) by one-step reaction in dry acetic acid medium (Scheme-**1**).



Scheme-**1**

a) Synthesis of annelating Substrate:

Ethyl-5-amino-2-methylpyrazolo-4-carboxylate(2).

The annelating substrate (**2**) was synthesized by using Gewald method[72] which is given below:

Methyl hydrazine was added dropwise to a solution of ethyl(ethoxymethylne)malonitrile (**1**) in absolute ethanol and the temperature of the mixture maintained below 60°C. After one hour stirring at room temperature of the mixture, the progress of the reaction was checked by TLC (n-hexane: ethylacetate; 5 : 1, v/v, $R_f = 0.81$) showed the completion of the reaction. The precipitate was collected by filtration with ether and recrystallized from ethanol to give yellowish needle shaped crystals in 70.45% yield, m.p.: 222 - 223°C.

Formation of this compound (**2**) was confirmed by analysis of its UV, IR, ^{1}H NMR and ^{13}C NMR spectra.

In the UV spectrum (Fig. No. **1**) the λ_{max} value was found in the range of 268 nm. The IR spectra (Fig. No. **2**) of this compound (**2**) showed absorption bands at 3433.1 and 3284.5 cm^{-1} for -NH_2 group, 3197.8 cm^{-1} for -CH stretching in –N(CH_3) molecule, 1691.5 cm^{-1} for C=O stretching, 1575.7 cm^{-1} indicated for C=C bonds and 1261.4 cm^{-1} and 1105.1 cm^{-1} stretching for the ester group.

The ^{1}H NMR spectrum (Fig. No. **3** & **4**) showed one-proton singlet at δ 7.52 for –CH group, two-proton singlet at δ 4.38 indicated the presence of -NH_2 proton, two-proton quartet at δ 4.25 (q, –CH_2, $J = 7.1$ Hz) for –CH_2 group, three-proton singlet at δ 3.66 for –NMe group and a three-proton triplet at δ 1.28 (t, –CH_3, $J = 7.1$ Hz) indicated the structure of amino-ester compound (**2**).

The structure was further confirmed by ^{13}C–NMR data (Fig. No. **5**). The signal exhibited at δ 164.09 for (C = O), 156.38, 133.24 (tertiary carbon), 99.10 (CH), 59.72 (CH_2), 38.90 (N-CH_3) and 14.46 (CH_3) respectively. Therefore, the ^{13}C spectrum of the compound was in agreement with the structure assignment of compound (**2**).

b) Synthesis of annelating reagent

2-methylthio-2-thiazoline(5)

For the synthesis of the above compound 2-methylthio-2-thiazoline(**5**) is as used as annelating reagent. The reagent was synthesis in two-step process from ethanolamine by using Jansen et al[68].

Synthesis of 2-mercaptothiazoline(4)

To a solution of ethanolamine, water and sodium hydroxide in carbon disulfide was added dropwise. The temperature of the reaction mixture was cooled to 35°C and the reaction mixture was warmed to keep it at 45°C. After refluxing for 7 hours the reaction mixture was heated up to 100°C. The progress of the reaction was checked by TLC (chloroform: methanol, 13:1, v/v). The precipitate was collected by filtration, washed with conc. HCl and recrystallized from water to afford the desired compound(**4**) light yellow crystals in 82.43% yield, m.p.: 102 - 104°C.

In the UV spectrum (Fig. No. **6**) the λ_{max} value was found in the range of 240 nm. The IR spectrum (Fig. no. **7**) of this compound showed following characteristic peaks: 3133 cm^{-1} (–NH str.) and 1296 cm^{-1} (C = S str.) respectively.

The ^1H NMR spectrum (Fig. No. **8** & **9**) showed two-proton triplet at δ 3.98 (t, CH_2, J = 7.9 Hz) and δ 3.55 (t, CH_2, J = 7.9 Hz). The one-proton singlet at δ 8.16 was observed due to –SH proton or –NH proton which is involved in *phototropic tautomerism* or shown (Scheme-**1**) in the molecule(**4**).

Synthesis of 2-methylthio-2-thiazoline(5)

Methylation of the compound 2-mercaptothiazoline(**4**) was carried out by standard procedure[68] using methyl iodide in methanol. The mixture was heated under reflux for one hour. The suspension was cooled and diluted with ether. The crystalline hydroiodide salts was recovered by filtration in 87.21% yield, m.p.: 112 – 114°C. The hydroiodide salts was decomposed with 15% NaOH solution and extracted with chloroform. The solvent was evaporated under *vacuo* and the compound 2-methylthio-2-thiazoline(**5**) was obtained as a yellow oil syrup in 56% yield, b.p.: 70°C.

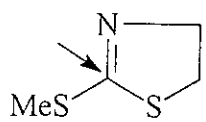
In the UV spectrum (Fig. No. **10**) the λ_{max} value was found in the range 253 nm. The IR-spectrum (Fig. NO. **11**) of this compound showed absorption bands at 2931.6 cm^{-1} (–CH str. in CH_3), 2852.4 cm^{-1} (–CH Str. in CH_2), 1564.2 cm^{-1} (C=C str.) and 1255 cm^{-1} (C=S str.) respectively.

The ^1H NMR spectrum (Fig. No. **12** & **13**) showed a three-proton singlet at δ 2.50 for –SMe group, a two-proton triplet at δ 4.20 (t, CH_2, J = 7.9 Hz) and δ 3.39 (t, CH_2, J = 7.9 Hz) were observed for two methylene (–CH_2) group which indicated the formation of compound(**5**).

The compound was further confirmed by ^{13}C NMR. In the ^{13}C NMR spectrum (Fig. No. **13a**) of compound 2-methylthio-2-thiazoline(**5**) showed the signals at δ 63.74 and 35.26 due to two methylene carbon atoms, C=N peak appeared at δ 165.47 and –SMe peak also observed at δ 14.83.

Behaviour of 2-methylthio-2-thiazoline(5)

The compound(**5**) was an extremely interesting reagent and was used as a carbon-nitrogen double bond fragment for the synthesis of heterocyclic compounds having a thiazolo moiety. Iminothioether(**5**) has good leaving groups (–SMe) and also shows nucleophilic are well as electrophilic character like N-[bis(methylthio)methylene]glycine ethylester(**86**).



5

Synthesis of 2-methyl-6,7-dihydropyrozolo[3,4-d]thiazolo[1,2-a]pyrimidin-4-one(6)

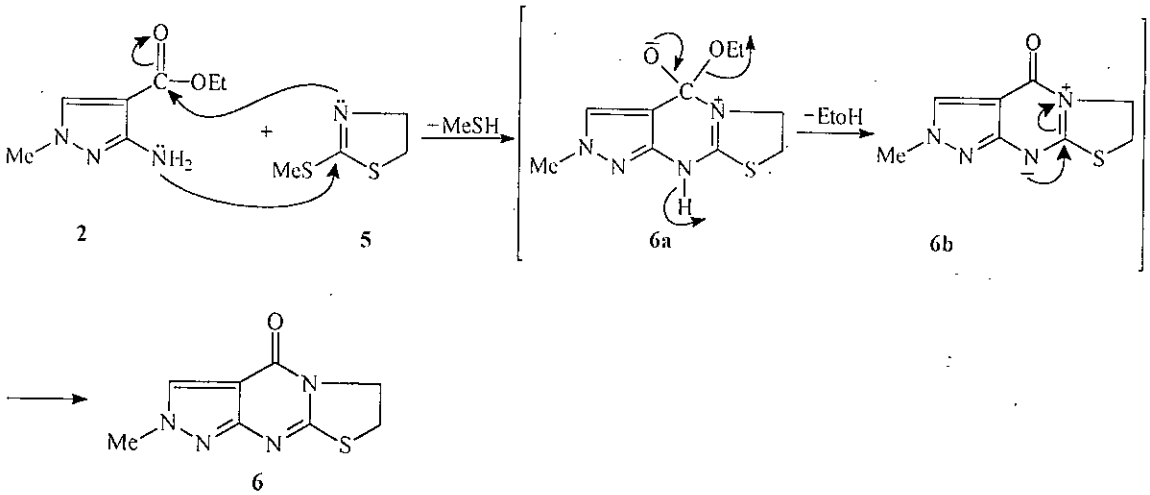
The title compound(6) was synthesized by following way:

Annelating reagent 2-methylthio-2-thiazoline(**5**) with *ortho*-aminoester, ethyl-5-amino-2-methylpyrozolo-4-carboxylate(**2**) in dry acetic acid was heated under reflux for 4 hrs. The progress of the reaction was checked by TLC (Chloroform: methanol, 11 : 1 v/v). The

reaction mixture was poured into ice-water and solid mass was filtered and dried and recrystallized from ethanol to give(**6**) as shining redish crystals in 63.82% yield, m.p: above 250°C.

Reaction Mechanism

The mechanism for the condensation of annelating substrate *ortho*-amino ester, ethyl-5-amino-2-methypyrozolo-4-carboxylate(**2**) and annelating reagent 2-methylthio-2-thiazoline(**5**) for the synthesis of fused pyrimidine 2-methyl-6,7-dihydropyrozole[3, 4-d] thiazolo[1,2-a]pyrimidin-4-one(**6**) may be shown in below:



Mechanism-**1**

The mechanism of this reaction probably involved in initial nucleophilic addition of the amino group of *ortho*-aminoester(**2**) to the electron deficient carbon of the thiazoline(**4**) to form the intermediate(**6a**) by elimination of methyl mercaptane (–MeSH). The intermediate(**6a**) subsequently carried out a nucleophilic attack of the nitrogen atom of the thiazole moiety to SP^2 carbon of the carboxylate followed by an elimination of ethanol to give(**6**) *via* an intramolecular cyclization. The reaction proceed smoothly. Thus *ortho*-aminoester(**2**) to give(**6**) directly in good yield.

In UV spectrum (Fig. no. **14**) the λ_{max} value was found in the range of 280 nm. The IR-spectrum (Fig. no. **15**) of this compound showed the 3096.5, 1675.1, 1598.9 and 1543.5 cm^{-1} indicated for –CH, C=0, C=N and C=C bonds. The absence of –NH peak indicated the formation of the product(**6**).

The ^{1}H NMR spectrum (Fig. No. **16** & **17**) exhibited a one proton singlet at δ 7.76 for –CH, a two-proton triplet at δ 4.15 (t, 2H, J = 7.2 Hz) and 3.26 (t, 2H, J = 7.5 Hz) for two methylene (–CH_2) groups and a three-proton singlet at δ 2.47 for –NCH_3 group in the molecule. Disappearance of –NH peak from the ^{1}H-NMR (Fig. No. **16**) indicated the formation of a new thiazoline ring.

The ^{13}C NMR spectrum (Fig. No. **17a**) showed peak at δ 164.48 for C=O, 149.23, 139.01 for CH carbon, 96.13 and 46.78 for tartiary carbon, 59.47 and 33.99 for CH_2, 14.43 for NCH_3 which was compatible with structure of the compound(**6**).

Thus it is efficient and facile method for the preparation of fused pyrimidine 2-methyl 6.7-dihydropyrozolo[3,4-d]thiazolo[1,2-a]pyrimidin-4-one(**6**).

4.2 SYNTHESIS OF 2,3-DIPHENYLFURANO-6,7-DIHYDROIMIDAZO[3,4-d] PYRIMIDIN-4-ONE(12)

The synthesis of the fused pyrimidine is divided into two headings.

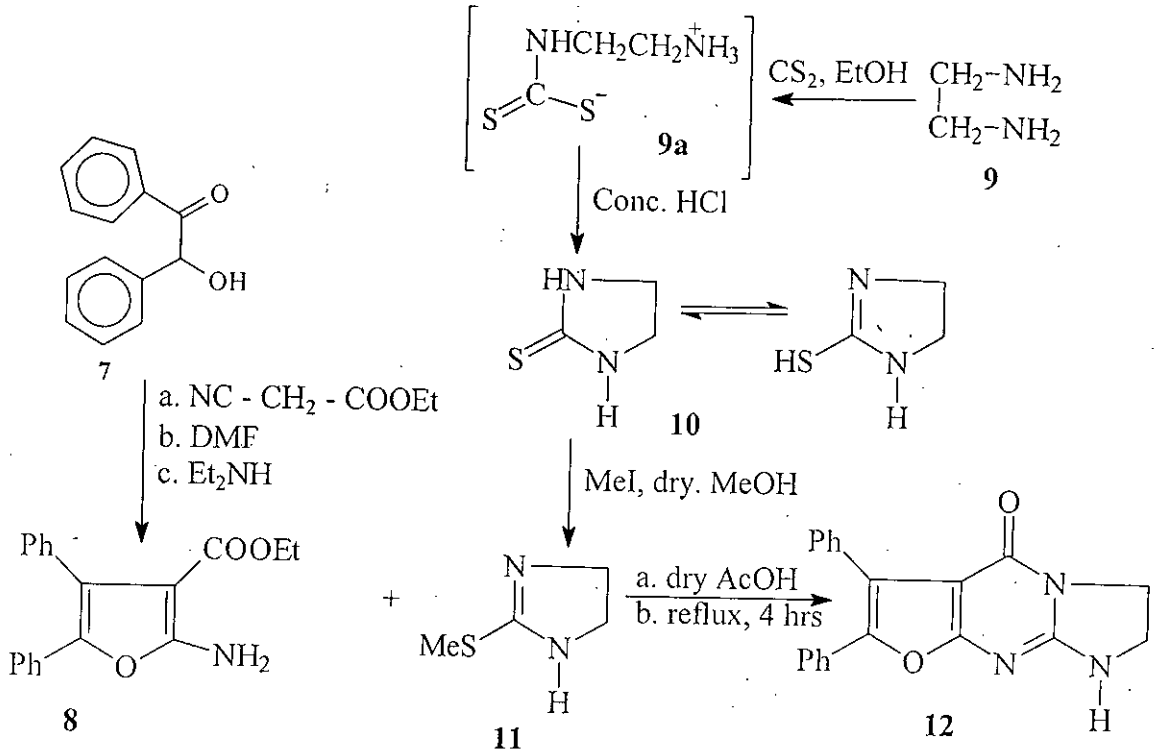
i) Synthesis of annelating substrate:

2-amino-4,5-diphenylfuran-3-carboxylate(**8**)

ii) Synthesis of annelating reagent:

2-methylthio-imidazole(**11**)

In this approach annelated substrate was used as 2-amino-4,5-diphenylfuran-3-carboxylate(**8**) and annelating reagent as 2-methylthio-imidazoline(**11**) for the synthesis of fused pyrimidine 2,3-diphenylfurano-6,7-dihydroimidazo[3, 4-d]pyrimidin-4-one(**12**) by one-step reaction in dry acetic acid medium.



Scheme-2

i) Synthesis of annelating substrate

2-amino-4,5-diphenylfuran-3-carboxylate (**8**).

The annelating substrate (**8**) was synthesized by using Gewald method[72] which is given below:

Diethylamine was added dropwise to a solution of benzoin, ethyl cyanoacetate and DMF. After 12 hours stirring the mixture was poured into H_2O, the coagulated solid was collected by filtration and recrystallized from ethanol. to give(**8**) as white needle shaped crystals in 67.50% yield, m.p.: 163–165°C. Formation of this compound(**8**) was confirmed by analysis of UV, IR, ^{1}H NMR and ^{13}C NMR spectra.

The UV-spectrum (Fig. No. **18**) of this compound(**8**) showed the λ_{max} value in the range of 253 nm. The IR Spectra (Fig. No. **19**) of this compound showed absorption bands at 3383.0 cm^{-1} for $-NH_2$ group, 3059.9 cm^{-1} –CH str., 2933.5 cm^{-1} –CH str. in $-CH_2$ group, 1677 cm^{-1} for C=O stretching, 1595 cm^{-1} for C = C str. for aromatic ring and 1206.4 cm^{-1} for stretching of the ester group.

The ^{1}H NMR spectrum (Fig. No. **20, 21, 22 & 23**) showed a two-proton broad singlet at δ 9.26 (brs, 2H, -NH_2), a two proton doublet at δ 7.85 (d, 2H, Ar–H), a proton multiplet at δ 7.63 (m, 2H, Ar–H), one-proton multiplet at δ 7.47 (m, 1H, Ar–H), a five-proton multiplet at δ 7.38 (m, 5H, Ar–H), a two proton quartet at δ 4.27 (q, CH2, J = 7.2 Hz) and a three-proton triplet at δ 1.04 (t, 3H, – CH_3, J = 7.2 Hz).

The ^{13}C NMR spectrum (Fig. No. **24**) displayed singlet at δ 164.87, 161.47, 136.05, 132.89, 132.56, 130.88, 128.97, 128.60, 128.50, 128.29, 117.32, 113.40, 100.72, 60.29, 42.24, 29.68 and 11.13 which indicated the formation of the compound (**8**).

ii) Synthesis of annelating reagent:

2-methylthio-imidazoline (**11**)

This compound (**11**) was synthesized from 2-imidazolinethione (**10**) by using Hofmann method[80].

Synthesis of 2-imidazolinethione (10)

The title compound (**10**) was synthesized by treating the mixture of carbon disulfide, ethylenediamine, rectified spirit and water with occasional shaking for two hours and refluxing on a water bath for one hrs. Concentrated HCl was then added to the reaction mixture and refluxed for 9-10 hrs. The resulting solid was filtered, washed with cold acetone and crystallized from ethanol to give the desired compound (**10**) as white crystals in 47% yield: m.p. 155–156°C.

In the UV spectrum (Fig. No. **25**) the λ_{max} value was found in the range of 245.60 nm. The IR spectrum (Fig. No. **26**) of this compound (**10**) showed absorption bands at 3244.9 cm^{-1} and 2879.5 cm^{-1} corresponding to –NH and –CH stretching respectively.

The ^{1}H NMR spectrum (Fig. No. **27**) showed a two proton singlet at δ 6.00 for two –NH group and four-proton multiplet at δ 3.76 for two methylene (–CH_2) groups indicated the formation of(**10**).

Synthesis of 2-methylthio-imidazoline (11)

The reaction was performed by stirring compound (**10**) and methyl iodide in absolute methanol for 2 hrs. Methanol was removed under reduced pressure and this was neutralized with 15% sodium hydroxide solution, extracted with chloroform, dried over sodium sulfate and the solvent evaporated to give the desired compound (**11**) as white crystals in 58.63% yield: m.p. 119 – 121°C.

In the UV spectrum (Fig. No. **28**) the λ_{max} value was found in the range of 251 nm. The IR spectrum (Fig. No. **29**) of this compound showed the following characteristic peaks: 3392 cm^{-1} (–NH str.), 3149.5 (–CH str.) and 1603.7 cm^{-1} (–CN) stretching absorption.

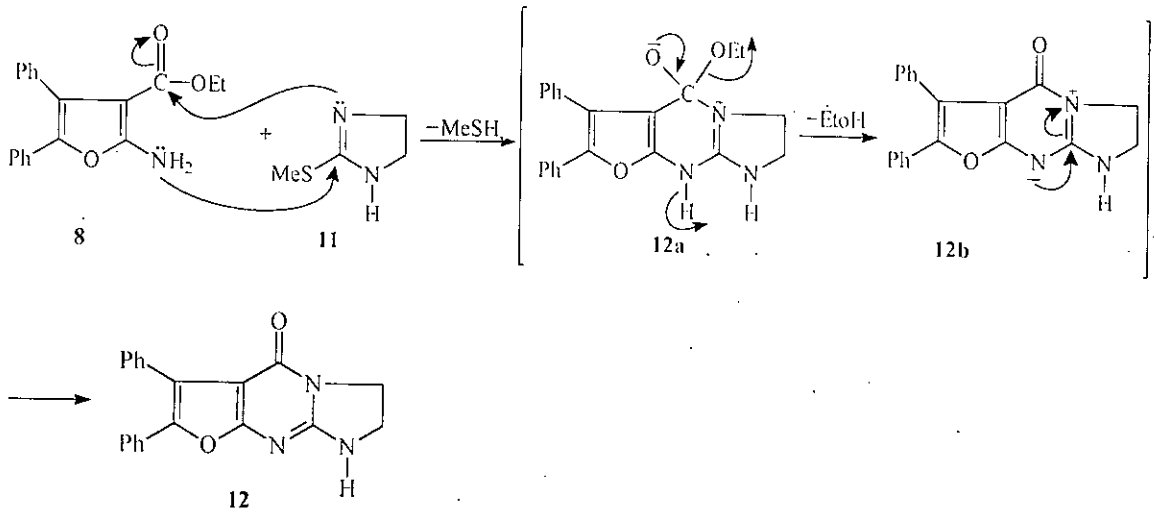
In the ^1H NMR spectrum (Fig. No. **30**) a one-proton singlet at δ 7.29 for –NH group, a three-proton singlet at δ 2.48 for –SMe group and a four-proton multiplet at δ 3.86 were observed for two methylene ($-CH_2$) group, which indicated the formation of the compound (**11**).

The structure of 2-methylthio-imidazoline (**11**) was also confirmed by ^{13}C NMR spectrum (Fig. No. **30a**). The spectrum exhibited the signal at δ 164.85 for C–2, δ 13.25 for –SMe, 50.15 for C-4 and C-5 respectively. The spectrum displayed the presence of four carbon atoms corresponding to its molecular formula ($C_4H_8N_2S$).

Synthesis of 2,3-diphenylfurano-6,7-dihydroimidazo[3,4-d]pyrimidine-4-one(12)

The title compound(**12**) was synthesized by treating annelating reagent 2-methylthio-imidazoline(**11**) and 2-amino-4,5-diphenylfuran-3-carboxylate(**8**) in presence of dry acetic acid under reflux for 4 hrs. The reaction mixture was filtered and the solid mass obtained was recrystallized from methanol to afford new tricyclic fused pyrimidine compound(**12**) in 63.82% yield, m.p.: 201 - 203°C.

Reaction Mechanism:



Mechanism-2

The mechanism of this reaction probably involved in the inital nucleophilic addition of the amino group of ortho-aminoester(**8**) to the electron deficient carbon of the imidazoline, 2-methylthio-imidazoline(**11**) to form the intermediate(**12a**) which eliminates the marcapto group (–SH) from the intermediate(**12b**). Ring closure occured by nucleophilic attack of imidazoline nitrogen atom to the sp^2 carbon of the carboxylate followed by an elimination of ethanol to give compound 2,3-diphenylfurano-6,7-dihydroimidazo[3,4-d]pyrimidin-4-one(**12**).

The structure of the compound(**12**) was established by spectral data. In the UV spectrum (Fig. No. **31**) the λ^{max} value was found in the range of 288 nm. The IR spectrum (Fig. No. **32**) of this compound (**12**) showed absorption bands at 3392.6 cm^{-1} for NH stretching absorption and 1661.6 cm^{-1} for C=O stretching absorption.

In the ^1H NMR spectrum (Fig. No. **33** & **34**) a one-proton singlet at δ 8.76 for –NH proton, a four proton multiplet at δ 7.88 (m, 4H, Ar–H) for Ar–H a two-proton triplet at δ 7.49 (t, 2H, Ar-H, J = 8.1), a two-proton triplet at δ 7.26 (t, 2H, Ar–H, J = 8.0), a two-proton triplet at δ 7.11 (t, 2H, N–H, J = 7.6) for Ar–H group, a two-proton triplet at δ 377 (t, 2H, CH_2, J = 7.8), a two-proton triplet at δ 2.21 (t, 2H, CH_2, J = 7.8) were observed.

The ^{13}C NMR spectrum (Fig. No. **34a**) showed chemical shift position at δ 172.47 (C=O), 171.38, 142.74, 137.88 and 129.50 and 124.10 (C-tartiary), 131.00, 128.89, 128.26, (Ar-CH), 123.93, 122.32, 118.68 (Ar-CH), 61.37, 59.33 (C-tartiary) 60.62 and 37.95 (CH_2) which was compatible with the structure of the compound (**12**).

4.3 SYNTHESIS OF 6,7-DIMETHYL-2,3-DIHYDRO-5*H*-THIAZOLO[3,2-a] THIENO[2,3-d]PYRIMIDIN-5-ONE (15).

The synthesis of the fused pyrimidine is divided into two headings

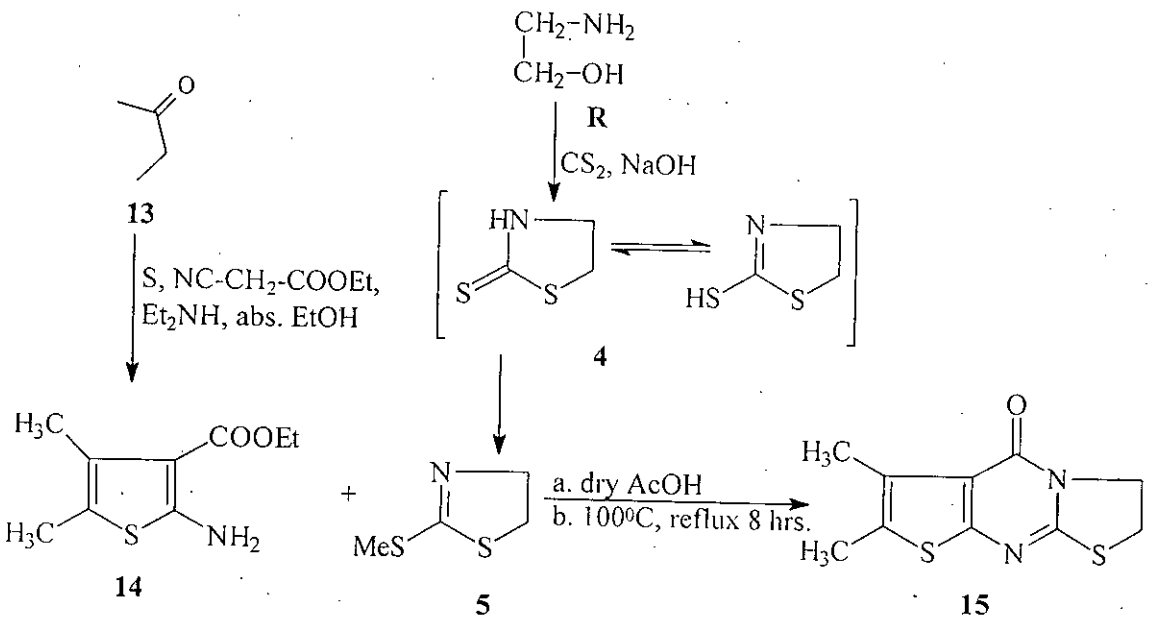
a) Synthesis of annelating substrate:

Ethyl-2-amino-4,5-dimethylthiophene-3-carboxylate (14)

b) Syntheisis of annelating reagent:

2-methylthio-2-thiazoline (5)

In this approach annelated substrate ortho-aminoester, Ethyl-2-amino-4,5-dimethylthiophene-3-carboxylate (**14**) and annelating reagent 2-methylthio-2-thiazoline (**5**) were used for the synthesis of fused pyrimidine 6,7-dimethyl-2,3-dihydro-5*H*-thiazolo[3,2-a]thieno [2,3-d]pyrimidine-5-one (**15**) by one-step reaction in dry acetic acid (scheme-3).



Scheme-3

a) Synthesis of annelating substrate:

Ethyl-2-amino-4,5-dimethuylthiophene-3-crboxylate (14)

The annelating substate (**14**) was synthesized by using Gewald method[72] which was reported in (Scheme-**3**).

A suspension of sulfur, ethylcyanoacetate in diethylamine and ethanol was stirred at 60°C for one hour. After one hour stirring at room temperature, TLC indicated (n-hexane: ethylacetate, 1:1 v/v) complete conversion to the product. The yellowish precipitate was collected by filtration and washed with water, and crystallized from ethanol to afford ethyl-2-amino-4,5-dimethylthiophene-3-carboxylate (**14**), 76.30% yield as yellowish crystals, m.p.: 89–91°C [Lit 72 m.p.: 91 – 92°C].

In the UV spectrum (Fig. No. **35**) the λ_{max} value was found in the range of 240 nm. The IR spectrum (Fig. No. **36**) of this compound (**14**) showed absorption bands at 34331.1 cm^{-1} which confirmed the presence at –NH group, at 3196.8 cm^{-1} for –CH str. for ethylene ($-CH_2$) group, 1692.4 cm^{-1} for (C=O) str. at 1314.4 cm^{-1} for (C = S) str. and at 1261.4 cm^{-1} for ester group.

The ^1H NMR spectrum (Fig. No. **37, 38** & **39**) showed chemical shift position as two-proton singlet at δ 5.28 for $-NH_2$ proton, two-proton tripilet at δ 4.23 (q, 2H, CH_2, J = 7.1 Hz) for $-CH_2$ group six-proton singlet at δ 3.60 indicated for two methyl groups, and three proton triplet at δ 1.32, (t, 3H, CH_3, J = 7. 1Hz) for methyl group in the molecule.

The ^{13}C NMR spectrum (Fig. No. **39a**) showed chemical shift signals at δ 164.31 for carbonyl (C=O), 138.86, 113.96, 95.76 (C-tartiary), 59.29 (CH_2), 46.69 (C-tartiary), 33.87, 25.04 and 14.26 (CH_3) respectively.

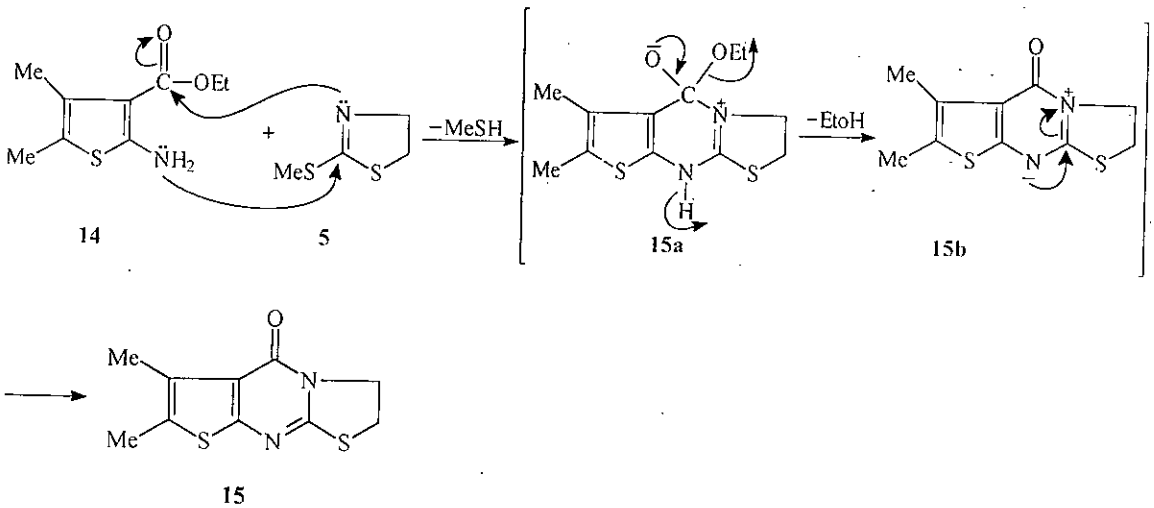
b) Synthesis of annelating reagent:

2-methylthio-2-thiazoline (5)

Synthesis of 2-methylthio-2-thiazoline (**5**) has already been discussed in the scheme-**1** (page-35).

Synthesis of 6,7-dimethyl-2,3-dihydro-5H-thiazolo[3,2-a]thiono[2,3-d] pyrimidine-5-one (15)

Annelating reagent 2-methylthio-2-thiazoline (**5**) with ortho-aminoester, Ethyl-2-amino-4,5-dimethylthiophene-3-carboxylate (**14**) in dry acetic acid was heated under reflux for 8 hrs. The reaction mixture was poured into ice-water and solid mass was filtered and dried and recrystallized from ethanol to give (**15**) shining yellowish crystals in 66.56% yield, m.p.: 171–172°C.

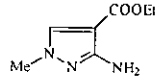
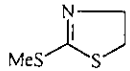
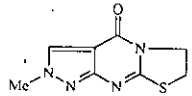
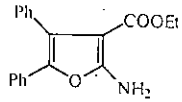


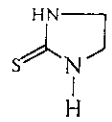
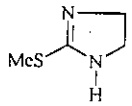
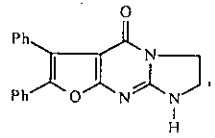
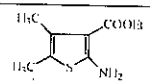
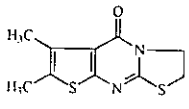
In the UV-spectrum (Fig. No. 41) of the compound (**15**) showed the λ_{max} value in the range of 265 nm. The IR spectrum (Fig. No. **42**) of this compound showed absorption band at 3095.5 cm^{-1} for –CH, str., 1675.1 cm^{-1} for carbonyl (C = O) str. and 1396.4 cm^{-1} for stretching of the ester group.

The ^{1}H NMR spectrum (Fig. No. **43** & **44**) of the product showed two proton tirplet at δ 4.22 (t, 2H, CH_2, J = 7.8) and δ 3.411 (t, 2H, CH_2, J = 7.8) for two methylene ($-CH_2$) groups at 2 and 3 position respectively. The six proton singlet at δ 2.52 indicated for the two methyl group at position 6 and 7 position of the ring. All these NMR data are in consisted with the structure of fused heterocyclic compound (**15**).

The ^{13}C NMR spectrum (Fig. No. **44a**) showed chemical shift position at δ 178.33 (C=O), 170.48, 138.87, 128.06, 61.49 and 60.43 (C-tartiary), 46.91 (CH_2), 37.75 (CH_2), 25.39 (CH_3) and 14.06 (CH_3) which was compatible with the structure of the compound (**15**).

1. Comparison of some spectral data of fused pyrimidine derivativs.

Comd. No.	Structure	Physical Properties	UV (nm)	IR (cm^{-1})	^1H NMR (δ_H)	^{13}C NMR (δ_C)
2		State: Crystals Color: Yellowish m.p: 222–223°C Yield: 70.45%	268	3433.1 (γ_{NH2}) 3197.8 (γ_{CH}) 1691.5 (γ_{CO})	δ_H 7.52 (s, 1H, CH), 4.38 (brS, 2H, NH_2), 4.25(q, 2H, CH_2, J = 7.1 Hz), 3.66 (s, 3H, NCH_3), 1.28 (t, 3H, CH_3, J = 7.1 Hz)	δ_C 164.09 (C=O), 156.38, 133.24, 99.10, 59.72, 38.90, 14.46.
4		State: Crystals Color: Light yellow m.p: 102–104°C Yield: 82.43%	253	3133.1(γ_{NH}) 1296.1 (γ_{CS})	δ_H 8.16(s, 1H, SH), 3.98 (t, 2H CH_2, J = 7.9 Hz), 3.55 (t, 2H, CH_2, J = 7.9 Hz).	
5		State: Syrup Color: Yellow b.p: 70°C Yield: 65.06%	253	2931.6 (γ_{CH}) 1255 (γ_{CS})	δ_H 4.2 (t, 2H, CH_2, J = 7.9 Hz), 3.39 (t, 2H, CH_2, J = 7.9 Hz), 2.50 (s, 3H, CH_3).	δ_C 165.47 (–CN), 63.74 (CH_2), 44.31, 35.26 (CH_2), 14.83 (q, SCH_3).
6		State: Crystals Color: redish m.p: above 250°C Yield: 63.82%	280	3147.6 (γ_{CH}) 1675.1 (γ_{CO}) -NH peak absence	δ_H 7.76 (s, 1H, CH), 4.15 (t, 2H, CH_2, J = 7.2 Hz), 3.26 (t, 2H, CH_2, J = 7.2 Hz), 2.47 (s, 3H, NCH_3)	δ_C 164.48 (C = O), 149.23, 139.01 (CH), 96.13 (C - tartiary), 59.14 (CH_2), 46.78 (C-tartiary), 33.99 (CH_2), 14.43 (N-CH_3)
8		State: Crystals Color: White m.p: 163–165°C Yield: 67.50%	253	3383.9 (γ_{NH2}) 2933.5 (γ_{CH}) 1677.0 (γ_{CO}) 1206.4 (γ_{COOET})	δ_H 9.26 (brs, 2H, NH_2), 7.45 (d, 2H, Ar–H), 7.63 (m, 2H, Ar – H), 7.47 (m, 1H, Ar–H), 7.38 (m, 5H, Ar–H), 4.27 (q, 2H, CH_2, J = 7.2 Hz), 1.04 (t, 3H, CH_3, J = 7.2 Hz)	δ_C164.87, 161.47, 136.05, 132.89, 132.56, 130.88, 128.97, 128.60, 128.50, 128.28, 117.32, 113.40, 100.73, 60.29, 42.24, 29.68, 11.13

10		State: Crystals Color: White m.p: 155–156°C Yield: 47%	245.60	3248.9 (γ_{NH}) 2879.5(γ_{CH2})	δ_H 6.00 (s, 2H, 2×NH), 3.76 (m, 4H, 2×CH_2)	
11		State: Crystals Color: White m.p: 119–121°C Yield: 65.75%	251.	3392 (γ_{NH}) 3149.5 (γ_{CH2}) 1603.7 (γ_{CN})	δ_H 7.29 (s, 1H, NH), 3.86 (m, 4H, 2×CH_2), 2.48 (s, 3H, SCH_3).	δ_C 164.85 (C–2), 50.13 (C–4 and C–5), 13.25 (–SMe)
12		State: Crystals Color: Light yellow m.p: 201–203°C Yield: 63.82%	288	3392.6 (γ_{NH}) 1661.6 (γ_{CO})	δ_H 8.76 (s, 1H, NH), 7.88 (m, 4H, Ar–H), 7.49 (t, 2H, Ar–H, J = 8.1), 7.26 (t, 2H, Ar–H, J = 8.0), 7.11 (t, 2H, Ar–H, J = 7.6), 3.77 (t, 2H, CH_2, J = 7.8), 2.21 (t, 2H, CH_2, J = 7.8).	δ_C 172.47 (C = O), 171.38, 142.74, 137.88 (C-tartiary), 131.00, 129.50 (Ar-CH), 128.89, 128.26, 124.10 (Ar C-tartiary), 123.93 (CH), 122.32, 118.68 (Ar-CH), 61.37, 60.62 (CH_2), 59.33 (C-tartiary), 37.95 (CH_2).
14		State: Crystals Color: Yellowish m.p: 89–91°C Yield: 76.30%	240	3433.1 (γ_{NH}) 3196.8 (γ_{CH2}) 1692.4 (γ_{CO}) 1314.4 (γ_{CS})	δ_H 5.27 (s, 2H, NH_2), 4.29 (q, 2H, CH_2, J = 7.2), 3.60 (s, 6H, 2×CH_3), 1.39 (t, 3H, CH_3, J = 7.2)	δ_C 164.31, 138.86, 113.96, 95.76, 59.29, 46.69, 33.87, 25.04, 14.26
15		State: Crystals Color: Yellowish m.p: 271–272°C Yield: 66.56%	265	3096.5 (γ_{CH}) 1675.1 (γ_{CO}) 1396.4 (γ_{COOET})	δ_H 4.22 (t, 2H, CH_2, J = 7.5), 3.41 (t, 2H, CH_2, J = 7.5), 2.53 (s, 6H, 2×CH_3)	δ_C 178.33 (C = O), 170.48, 138.87, 128.06, 61.49, and 60.43 (C-tartiary), 46.91 (CH_2), 37.75 (CH_2), 25.39 (CH_3) and 14.06 (CH_3)

4.4. CONCLUSION

A convenient, general and facile method for the synthesis of fused heterocyclic derivatives from the reaction of *ortho*-amino substrate with annelating regent was developed.

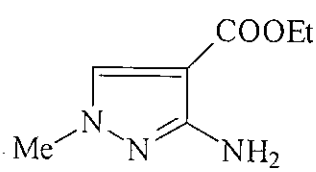
The most important features of the synthesis are that readily available, inexpensive staring materials were used at relatively mild reaction conditions and relatively good yields were obtained. Also, no toxic and hazardous compounds were produced by this procedure. A variety of fused heterocyclic ring could be introduced at the suitable positions by this procedure. Through this methodology biologically and medicinally important fused heterocyclic derivatives might be synthesized.

EXPERIMENTALS

5.1. SYNTHESIS OF 2-METHYL-6,7-DIHYDROPYROZOLO[3,4-d]THIAZOLO [1,2-a] PYRIMIDIN 4-ONE(6).

5.1.(i). Preparation of ethyl-5-amino-2-methylpyrozolo-4-carboxylate(2)

To a solution of ethyl(ethoxymethylene)malonitrile (10.85 g, 88.9 mmol) in absolute ethanol (35 ml) was added the solution of methyl hydrazine (3.6 g, 57.5 mmol) in absolute ethanol (30 ml). The resulting solution was refluxed with stirring for 1 hour. The progress of the reaction was cheeked by TLC (n-hexane: ethylacetate, 5:1, v/v, R_f=0.81). The reaction mixture was evaporated to dryness. The residue was washed with ether and recrystalized from ethanol to give(**2**) yellowish crystals. The yield was 7.6 g, (70.45%), m.p.: 222–223°C.



2

M. F.: $C_7H_{11}N_3O_2$ (169).

UV (EtOH): λ_{max} 268.

IR (KBr) : ν_{max} 3433.1, 3284.5, 3197.8, 1691.5, (C=O), 1575.7, 1261.4, 1105.1 cm^{-1}.

^{1}H NMR(400 MHz, $CDCl_3$): δ_H 7.52 (s, 1H, CH), 4.38 (brS, 2H, NH_2), 4.25(q, 2H, CH_2, J = 7.1 Hz), 3.66 (s, 3H, NCH_3), 1.28 (t, 3H, CH_3, J = 7.1 Hz)

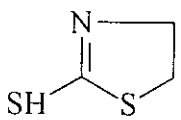
^{13}C NMR (100 MHz, $CDCl_3$): δ_C 164.09 (C=O), 156.38, 133.24, 99.10, 59.72, 38.90, 14.46.

5.1.(ii). Preparation of 2-mercaptothiazoline(4)

A mixture of ethanolamine(**3**) (3.66 g) and sodium hydroxide (9.61 g) in water (26 ml) was cooled to 30°C. Then carbondisulfide (12 g) was added to the reaction mixture with constant stirring under cooling condition. The reaction mixture was warmed to keep it at 45°C. After refluxing for seven hours the reaction mixture was heated more strongly

(100°C) for three hours. The progress of the reaction was checked by TLC (chloroform: methanol, 13:1, v/v, $R_f = 0.62$), which indicated formation of faster moving compound.

Upon cooling to room temperature the 2-mercaptothiazoline was deposited as a solid, the remainder being precipitated by the addition of 200 ml of concentrated hydrochloric acid. The product was filtered off, washed with water and dried. The yield was 5.90 g (82.43%), m.p.: 102–104°C.



4

M. F.: $C_3H_5NS_2$(119)

UV (EtOH): λ_{max} 240 nm.

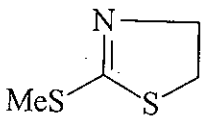
IR (KBr): ν_{max} 3133.1, 1507.3, 1296.1 and 1050.2 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.16(s, 1H, SH), 3.98 (t, 2H CH_2, J = 7.9 Hz), 3.55 (t, 2H, CH_2, J = 7.9 Hz).

5.1.(iii). Preparation of 2-methylthio-2-thiazoline(5)

The solution of 2-mercaptothiazoline(**4**) (6 g, 50.4 mmol) and methyl iodide (7.15 gm, 50.4 mmol) in absolute methanol (30.25 ml) was heated under reflux for 1.5 hours. The solvent was removed to give the product hydroiodide as a white crystalline mass. The progress of the reaction was monitored by TLC (chloroform: methanol 13:1, v/v, R_f = 0.54), which showed conversion of the starting material into one faster moving product with complete disappearance of starting materials.

The solid white hydroiodide salt was dissolved in water (35 ml) and neutralized with 15% NaOH (4.10 ml). Then the reaction mixture was stirred for one hour, extracted with chloroform (30 ml × 4). The combined organic layer was dried over sodium sulfate and chloroform was evaporated to dryness under reduced pressure in vacuum evaporator to give syrup. The syrup was distilled to give yellow 2-methylthio-2-thiazoline (**5**) as a syrup. The yield was 6 g (65.06%); b. p. : 70°C.



5

M. F.: $C_4H_7NS_2$ (133)

UV (EtOH): λ_{max} 253 nm.

IR (KBr): ν_{max} 2931.6, 2452.5, 1564.2, 1303.8, 1001.0, 920.0 and 727.1 cm^{-1}.

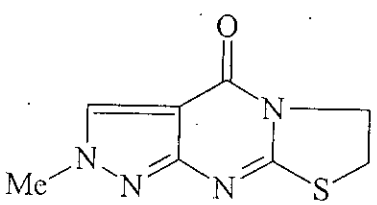
^{1}H NMR (400 MHz, $CDCl_3$) : δ_H 4.2 (t, 2H, CH_2, J = 7.9 Hz), 3.39 (t, 2H, CH_2, J = 7.9 Hz), 2.50 (s, 3H, SCH_3).

^{13}C NMR (100 MHz, $CDCl_3$) : δ_C 165.47 (–CN), 63.74 (CH_2), 44.31, 35.26 (CH_2), 14.83 (q, SCH_3).

5.1.(iv). Preparation of 2-methyl-6,7-dihydropyrozolo[3,4-d]thiazolo[1,2-a]pyrimidin-4-one(6)

A soluton of *ortho*-aminoester (**2**) (1 g, 5.92 mmol) and 2-methylthio-2-thiazoline (**4**) (0.79 g 5.92 mmol) in dry acetic acid (AcOH) was added in a 100 ml round bottom flask. The mixture was heated under reflux for 5 hrs. The progress of the reaction was monitored by TLC (chloroform: methanol, 11 : 1, v/v, R_f = 63.82), which showed the conversion of the starting material into product.

After cooling to room temperature crushed ice (25 g) was added and the mixture stirred for one hour. The precipitated was collected and crystallised from methanol to give (**6**) as redish crystals. The yield was 0.63 g (63.82%); m.p.: above 250°C.



6

M. F.: $C_8H_8N_4OS$ (208)

UV (EtOH): λ_{max} 280 nm.

IR (KBr): ν_{max} 3147.6, 3096.5, 3017.4, 2896.9, 2861.2, 1675.1, 1598.9, 1396.4, 927.7, 785.0 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.76 (s, 1H, CH), 4.15 (t, 2H, CH_2, J = 7.2 Hz), 3.26 (t, 2H, CH_2, J = 7.2 Hz), 2.47 (s, 3H, NCH_3)

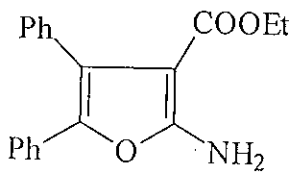
^{13}C NMR (100 MHz, $CDCl_3$) : δ_C 164.48 (C = O), 149.23 (C-tartiary), 139.01 (CH), 96.13 (C - tartiary), 59.14 (CH_2), 46.78 (C-tartiary), 33.99 (CH_2), 14.43 (N-CH_3)

DEPT ^{13}C NMR (100 MHz, $CDCl_3$) : δ_C 139.01 (CH), 59.14 (CH_2), 33.99 (CH_2), 14.43 (N-CH_3)

5.2. SYNTHESIS OF 2,3-DIPHENYLFURANO-6,7-DIHYDROIMIDAZO[3,4-d] PYRIMIDIN-4-ONE (12).

5.2.(i). Preparation of 2-amino-4,5-diphenylfuran-3-carboxylate (8)

A solution of ethylcyanoacetate (2.125 g, 33.2 mmol) and benzoin(**14**) (5.25 g, 25 mmol) in 7.5 ml DMF was treated with 4 ml diethylamine. After 12 hours stirring at room temperature the mixture was poured into 60 ml water, the separated solid was collected by filtration and recrystallized from ethanol. The reaction was checked by TLC (n-hexane: ethylacetate, 4:1, v/v, R_f = 0.55) showed complete conversion into product. The yield was 3.52 g (67.50%); m.p.: 163–165°C.



8

M. F.: $C_{19}H_{17}NO_3$ (307)

UV (EtOH) : λ_{max} 253 nm.

IR (KBr) : ν_{max} 3383.9, 3059.5, 2933.5, 1677.0 (C=O), 1595.0, 1388.7 (CN), 1206.4 (C=S), 976.9, 928.7, 755.1 cm^{-1}.

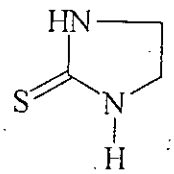
^{1}H NMR : δ_H 9.26 (brs, 2H, NH_2), 7.45 (d, 2H, Ar–H), 7.63 (m, 2H, Ar – H), 7.47 (m, 1H, Ar–H), 7.38 (m, 5H, Ar–H), 4.27 (q, 2H, CH_2, J = 7.2 Hz), 1.04 (t, 3H, CH_3, J = 7.2 Hz)

^{13}C NMR : δ_C164.87, 161.47, 136.05, 132.89, 132.56, 130.88, 128.97, 128.60, 128.50, 128.28, 117.32, 113.40, 100.73, 60.29, 42.24, 29.68, 11.13.

DEPT ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 132.89,130.89, 128.97, 128.60, 128.50, 128.28 (CH), 42.25 (CH_2), 11.14 (CH_3).

5.2.(ii). Preparation of 2-imidazolinethione(10)

To a mixture of ethylene diamine(**9**) (5 g, 83.33 mmol), rectified spirit (100 ml) and water (100 ml), carbon disulfide (3.95 ml, 83.33 mmol) was added dropwise with occasional shaking for 2 hrs. and refluxed on a water-bath for 1 hour. Concentrated HCl (15 ml) was then added and further refluxed for 9-10 hours. The progress of the reaction was checked by the TLC (acetone: chloroform, 1:2, v/v). The resulting solid on cooling was filtered, washed with cold acetone (80 ml) and recrystallized from ethanol to give(**10**) as white crystal. The yield was 4 g (47%); m. p.: 155–156°C.



M. F.: $C_3H_6N_2S$ (102)

UV (EtOH) : λ_{max} 245.60 nm. **10**

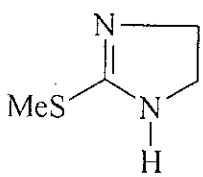
IR (KBr) : ν_{max} 3248.9, 2879.5, 2570.9, 1498.6, 1491.6, 1274.9, 1195.8 and 920.0 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) : δ_H 6.00 (s, 2H, 2×NH), 3.76 (m, 4H, 2×CH_2)

5.2.(iii). Preparation of 2-methylthio-imidazoline(11)

The solution of 2-imidazolinethione(**10**) 3 g, 29.41 mmol), methyliodide (1.85 ml, 29.41 mmol) in absolute methanol (18 ml) was refluxed for 2 hrs. with stirring. The progress of the reaction was checked by TLC (acetone: chloroform, 1:1, v/v).

Methanol was removed under reduced pressure and the solid white hydroiodide salt was neutralized with 50% NaOH (2.4 ml). Then it was stirred for 1/2-2 hrs., extracted with chloroform (30 ml × 4), dried over sodium sulfate and the solvent was evaporated to dryness under reduced pressure in vacuum evaporator to give(**11**) as white crystals (1.5g, 65.75%); m. p.: 119 – 121°C.



M. F.: $C_4H_8N_2S$ (116)

UV (EtOH) : λ_{max} 251 nm. **11**

IR (KBr) : ν_{max} 3392.6, 3149.5, 1603.7, 1582 and 1107.1 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) : δ_H 7.29 (s, 1H, NH), 3.86 (m, 4H, 2×CH_2),
2.48 (s, 3H, SCH_3).

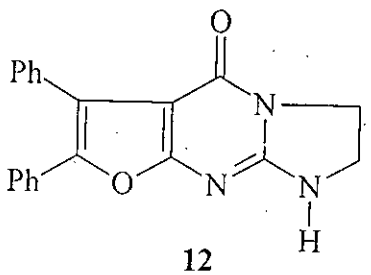
^{13}C NMR (100 MHz, $CDCl_3$) : δ_C 164.85 (C–2), 50.13 (C–4 and C–5), 13.25 (–SMe).

5.2.(iv). Preparation of 2,3-diphenylfurano-6,7-dihydropyrozolo[6,7-d]imidazo[3,4-a] pyrimidin-4-one(12).

A solution of *orth*-aminoester(**8**) (0.78 g, 3 mmol) and 2-methylthio-imidazoline(**11**) (0.522 g, 4.5 mmol) in dry acetic acid (6 ml) was heated under reflux for 6 hours. The

progress of the reaction was monitored by TLC (chloroform: methanol, 13:1, v/v) which showed the conversion of the starting material into product.

The R_f value is 0.45. After cooling the reaction mixture to room temperature, crushed ice was added and the mixture was stirred for one hour. The precipitated was collected and crystallised from methanol to give(**12**) light yellow crystals. The yield was (0.50 g, 63.82%); m. p.: 201 – 203°C.



12

M. F.: $C_{20}H_{15}N_2O_2$ (315)

UV (EtOH) : λ_{max} 288 nm.

IR (KBr) : ν_{max} 3392.6, 3334.7, 3148.6, 2207.4, 1661.6 (C=O), 1579.6, 1452.3, 1198.7 and 972.1 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$) : δ_H 8.76 (s, 1H, NH), 7.88 (m, 4H, Ar–H), 7.49 (t, 2H, Ar–H, J = 8.1), 7.26 (t, 2H, Ar–H, J = 8.0), 7.11 (t, 2H, Ar–H, J = 7.6), 3.77 (t, 2H, CH_2, J = 7.8), 2.21 (t, 2H, CH_2, J = 7.8).

^{13}C NMR (100 MHz, $CDCl_3$) : δ_C 172.47 (C = O), 171.38, 142.74, 137.88 (C-tartiary), 131.00 (Ar-CH), 129.50 (C-tartiary), 128.89, 128.26 (Ar-CH), 124.10 (C-tartiary), 123.93 (Ar-CH), 122.32, 118.68 (Ar-CH), 61.37 (C-tartiary), 60.62 (CH_2), 59.33 (C-tartiary), 37.95 (CH_2).

DEPT ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 130.81,128.69, 128.06, 123.90, 122.12, 118.49 (Ar-CH), 60.42 (CH_2), 37.75 (CH_2).

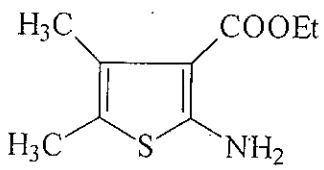
5.3. SYNTHESIS OF 6,7-DIMETHYL-2,3-DIHYDRO-5*H*-THIAZOLO[3,2-a] THIENO[2,3-d]PYRIMIDIN-5-ONE(15).

5.3.(i). Preparation of ethyl-2-amino-4,5-dimethylthiophene-3-carboxylate(14):

A solution of butanone(**13**) (8.9 ml, 100 mmol), ethylcyanoacetate (11.303 g, 100 mmol) and sulfer (3.20 g, 100 mmol) in 95% ethanol (30 ml) was treated with diethylamine (4

ml) slowly. The internal temperature being maintained below 60°C by means of an ice-bath. When addition was completed the mixture was stirred for 2 hours at room temperature. The progress of the reaction was checked by TLC on silica gel (n-hexane: ethylacetate, 1:1, v/v, R_f = 0.57) which showed conversion of the starting material into one faster moving product.

Then the mixture was poured into ice-water. The precipitate was filtered, washed with water and recrystallized from ethanol to give *ortho*-aminoester(**14**) as yellowish crystals. Yield: 15.2 g (76.38%), m.p.: 89–91°C.



14

M. F.: $C_9H_{13}NO_2S$ (199).

UV (EtOH) : λ_{max} 240 nm.

IR (KBr) : ν_{max} 3433.1, 3284.5, 3196.8, 1648.1, 1501.5, 1452.3, 1314.4, 1261.4 and 1026.1 cm^{-1}.

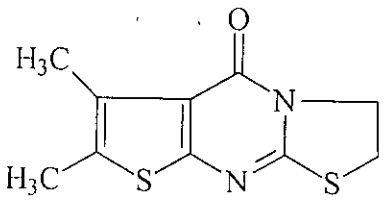
^{1}H NMR (400 MHz, $CDCl_3$) : δ_H 5.27 (s, 2H, NH_2), 4.29 (q, 2H, CH_2, J = 7.2) 3.60 (s, 6H, 2×CH_3), 1.39 (t, 3H, CH_3, J = 7.2).

^{13}C NMR (100 MHz, $DMSl_3$) : δ_C 164.31, 138.86, 113.96, 95.76, 59.29, 46.69, 33.87, 25.04, 14.26.

5.3.(ii). Preparation of 2,3-dihydro-6,7-dimethyl-5H-thiazolo[3,2-a]thieno[2,3-d] pyrimidin-5-one(15).

The solution of ethyl-2-amino-4,5-dimethylthiophene-3-carboxylate(**14**) (1.00 g, 5.025 mmol) and 2-methylthio-2-thiazoline(**5**) (0.668 g, 5.025 mmol) in dry acetic acid (6 ml) was heated under reflux for 8 hours. TLC (n-hexane: ethylacetate, 9:1, v/v, R_f = 0.51) examination showed complete disappearance of starting material with the formation of product.

Then the mixture was poured into ice-water. The resulting precipitate was filtered off and washed with water. Recrystallisation from ethanol afforded product(**6**) as yellowish crystals. The yield was 0.66 g, (66.56%), m.p.: 171 – 172°C.



15

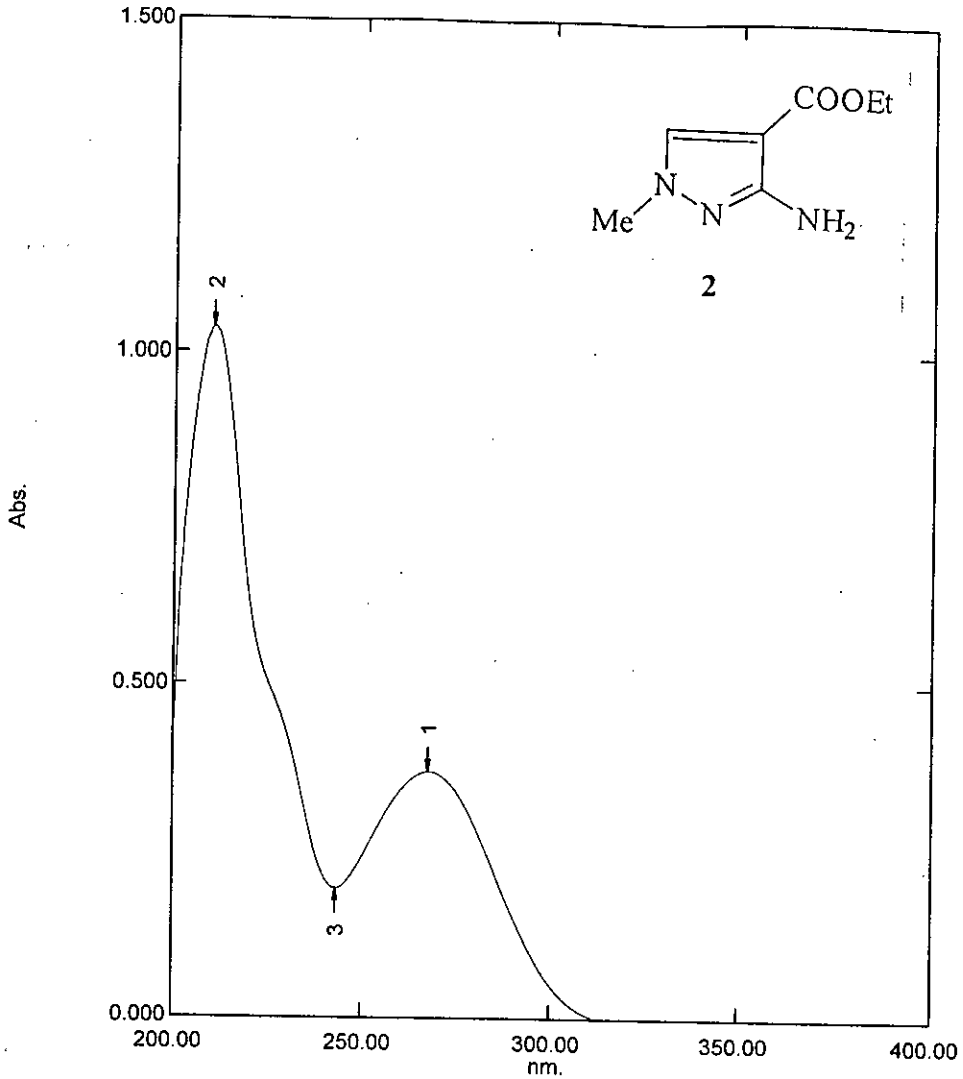
M. F.: $C_{10}H_{10}N_2OS_2$ (238).

UV (EtOH) : λ_{max} 265 nm.

IR (KBr) : ν_{max} 3096.5, 3018.4, 2970.2, 1675.1, 1534.3, 1396.4 and 927.7 cm^{-1}.

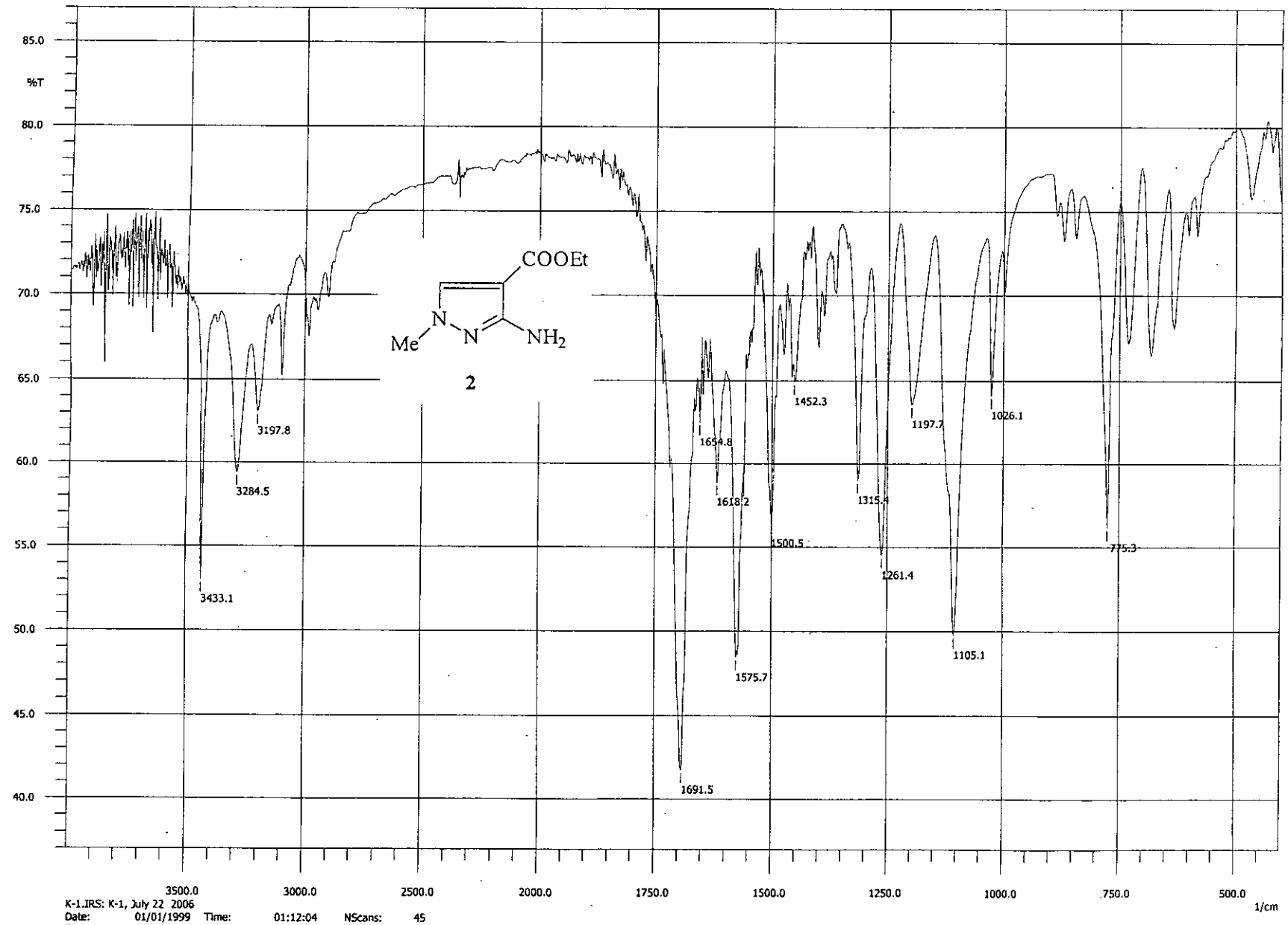
^{1}H NMR (400 MHz, $CDCl_3$) : δ_H 4.22 (t, 2H, CH_2, J = 7.5), 3.41 (t, 2H, CH_2, J = 7.5) 2.53 (s, 6H, 2×CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) : δ_C 178.33 (C = O), 170.48, 138.87, 128.06, 61.49, and 60.43 (C-tartiary), 46.91 (CH_2), 37.75 (CH_2), 25.39 (CH_3) and 14.06 (CH_3)



Wavelength	Abs.
268	0.369
210	1.036

Fig. 1: UV Spectrum of Compound **2**

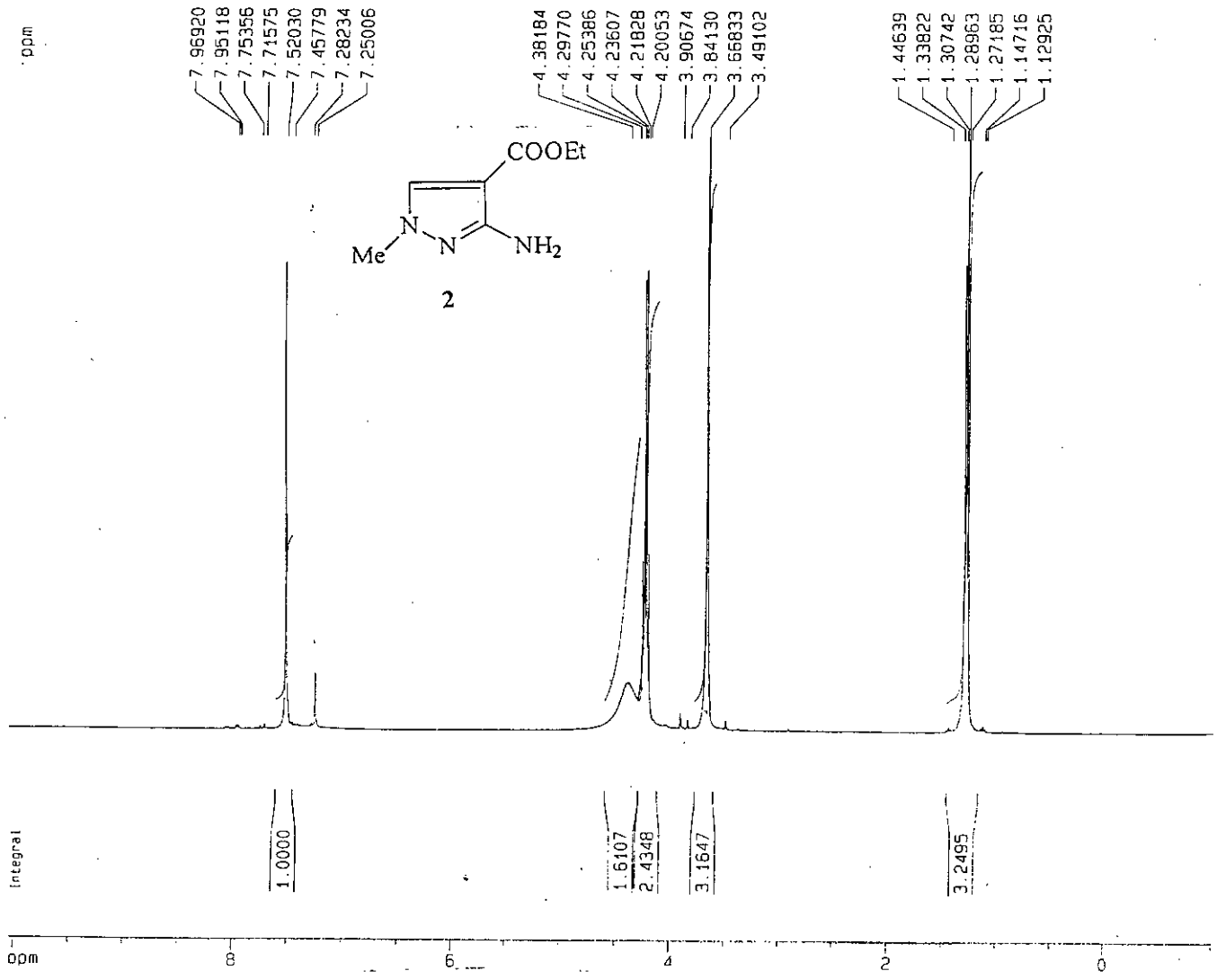


K-1.IRS: K-1, July 22 2006

Date:	01/01/1999	Time:	01:12:04	NScans:	45
Type:	HYPER IR	User:	user	Detector:	standard
Abscissa:	1/cm	Ordinate:	%T	Apodization:	Happ
Min:	401.17	Max:	3998.16	Range:	1/cm
Ndp:	1866	Data Interval:	1.92868	Resolution:	4.0
Gain:	auto	Aperture:	auto	Mirror Speed:	2.8(low)

Fig. 2: IR Spectrum of Compound **2**

Analytical, BCSIR Lab. Dhaka, 1H Spectrum, S1-K in CDCl3. Kabir, BUET



Current Data Parameters

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EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	90.5
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428077 MHz

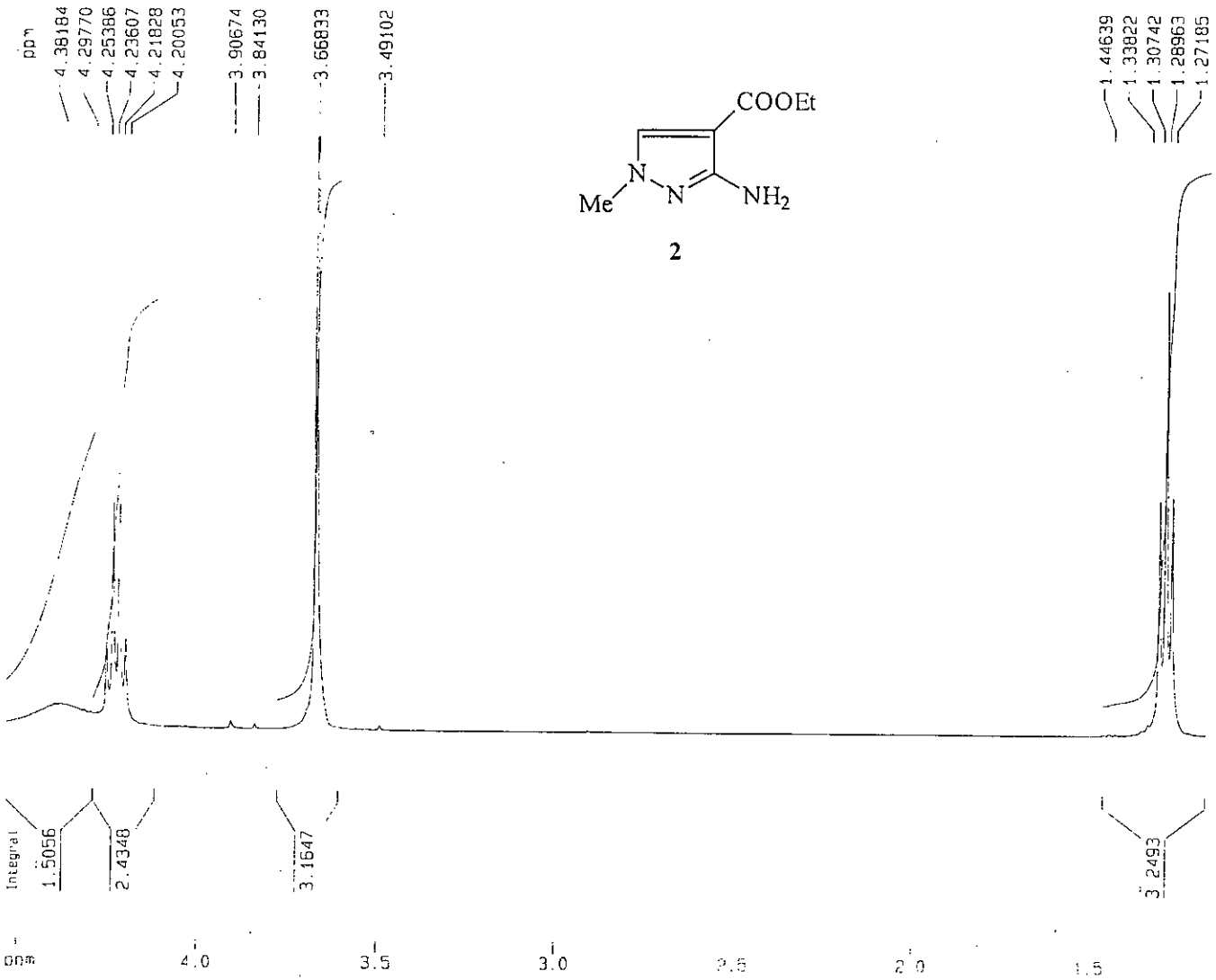
F2 - Processing parameters

SI	32768
SF	400.1400124 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	10.045 ppm
F1	4019.28 Hz
F2P	-1.007 ppm
F2	-402.99 Hz
PPMCM	0.55259 ppm/cm
HZCM	221.11327 Hz/cm

Analytical, BCSIR Lab. Dhaka, 1H Spectrum, S1-K in CDCL3. Kabir, BUET



2

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Current Data Parameters
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EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
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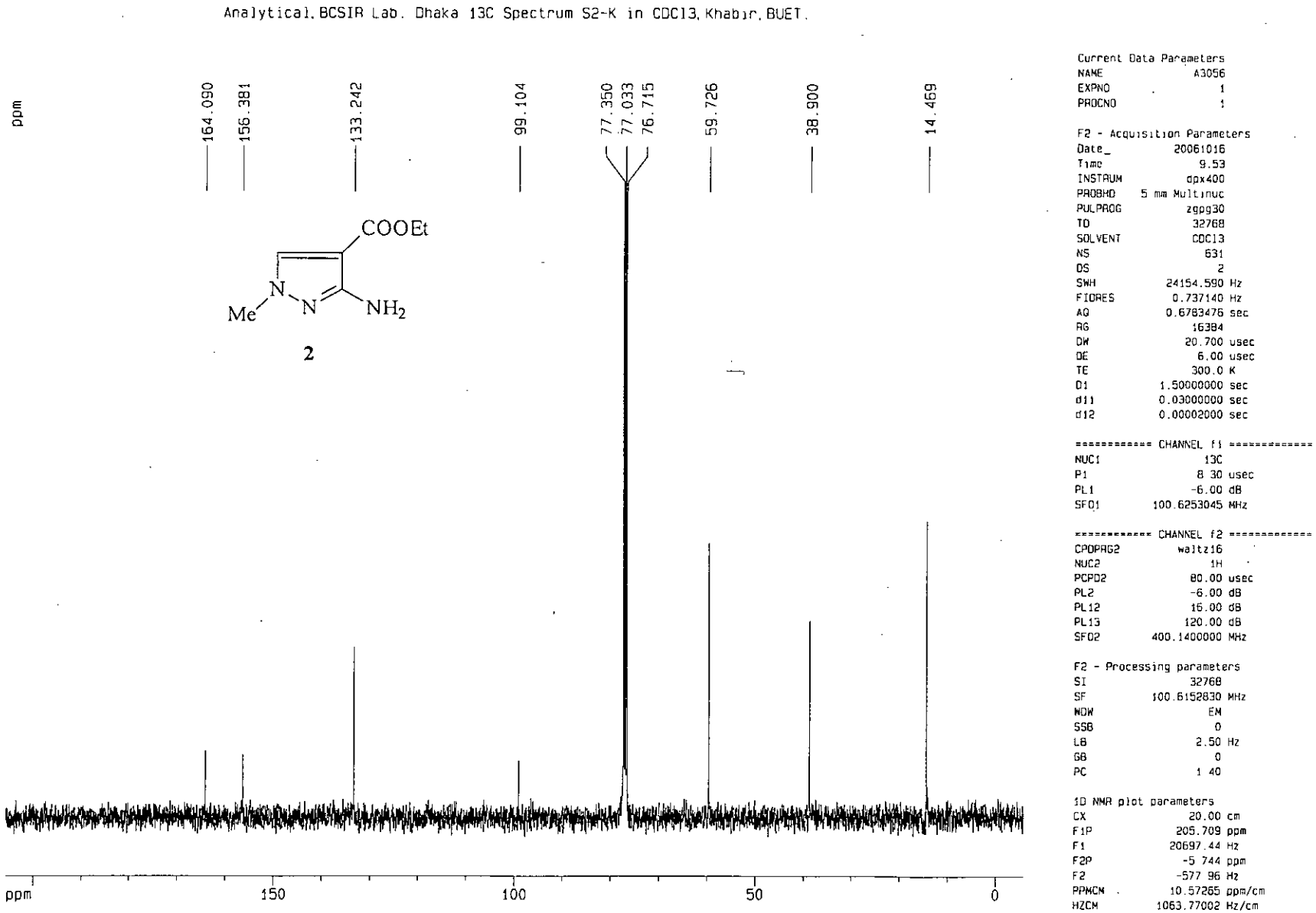
PULPROG               zg30
TD                   32768
SOLVENT              CDCl3
NS                     128
DS                       2
SWH           6410.256 Hz
FIDRES        0.195625 Hz
AQ            2.5559540 sec
RG                    90.5
DW              78.000 usec
DE               6.00 usec
TE                310.0 K
D1            1.00000000 sec

============ CHANNEL f1 ============
NUC1                  1H
P1                 8.30 usec
PL1               -6.00 dB
SFO1        400.1428077 MHz

F2 - Processing parameters
SI                   32768
SF          400.1400124 MHz
WDW                     EM
SSB                      0
LB                    0.30 Hz
GB                       0
PC                    1.40

1D NMR plot parameters
CX                   20.00 cm
F1P                 4.532 ppm
F1                1813.39 Hz
F2P                 1.175 ppm
F2                 470.11 Hz
PPMCM          0.16785 ppm/cm
HZCM           67.16402 Hz/cm
```



Current Data Parameters

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EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	631
DS	2
SWH	24154.590 Hz
FIDRES	0.737140 Hz
AQ	0.6783476 sec
RG	16384
DW	20.700 usec
DE	6.00 usec
TE	300.0 K
D1	1.50000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

========== CHANNEL f1 ==========

NUC1	13C
P1	8.30 usec
PL1	-6.00 dB
SFO1	100.6253045 MHz

========== CHANNEL f2 ==========

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-6.00 dB
PL12	16.00 dB
PL13	120.00 dB
SFO2	400.1400000 MHz

F2 - Processing parameters

SI	32768
SF	100.6152830 MHz
WDW	EM
SSB	0
LB	2.50 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	205.709 ppm
F1	20697.44 Hz
F2P	-5.744 ppm
F2	-577.96 Hz
PPMCM	10.57265 ppm/cm
HZCM	1063.77002 Hz/cm

Fig. 5: ^{13}C NMR Spectrum of Compound **2**

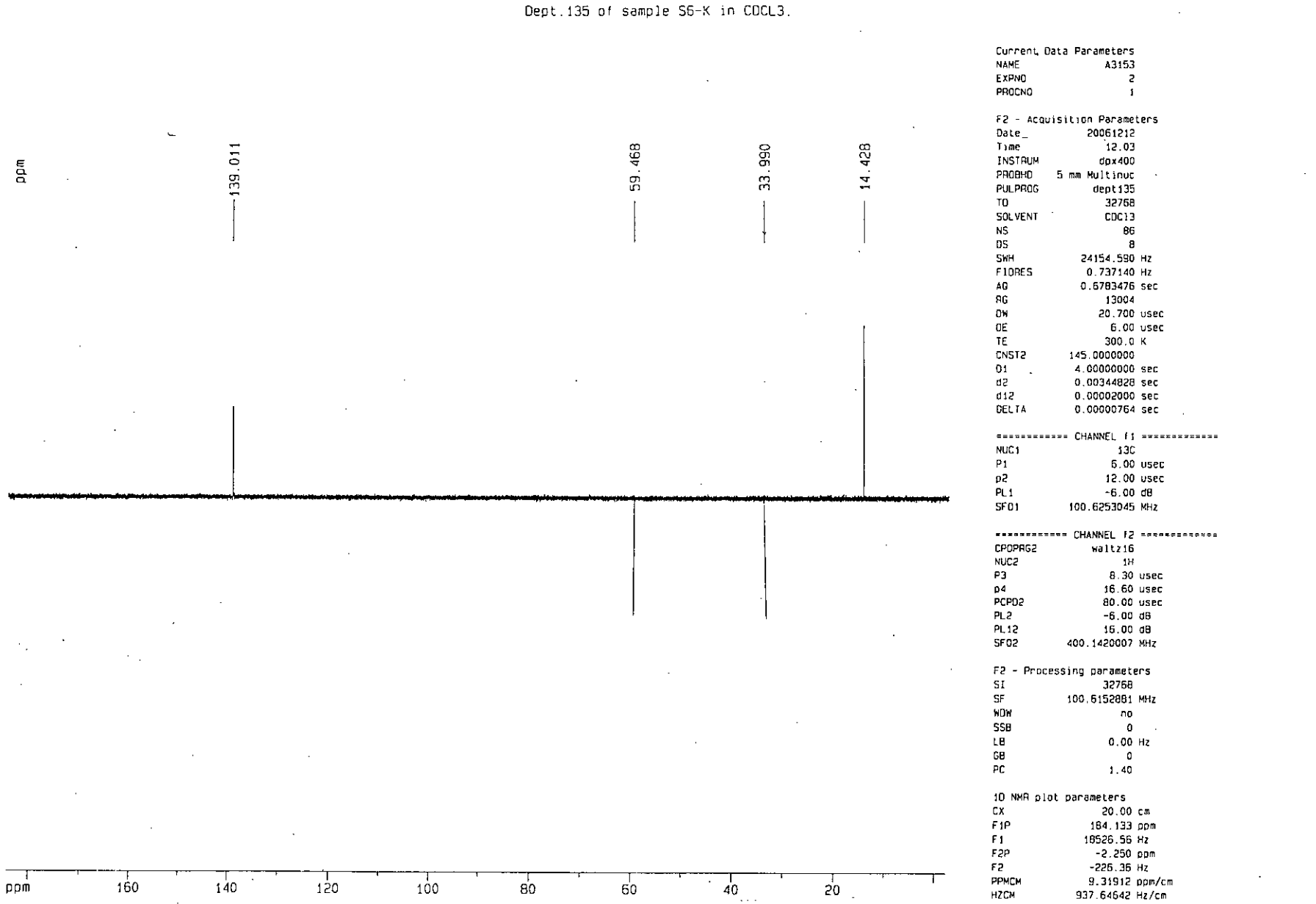
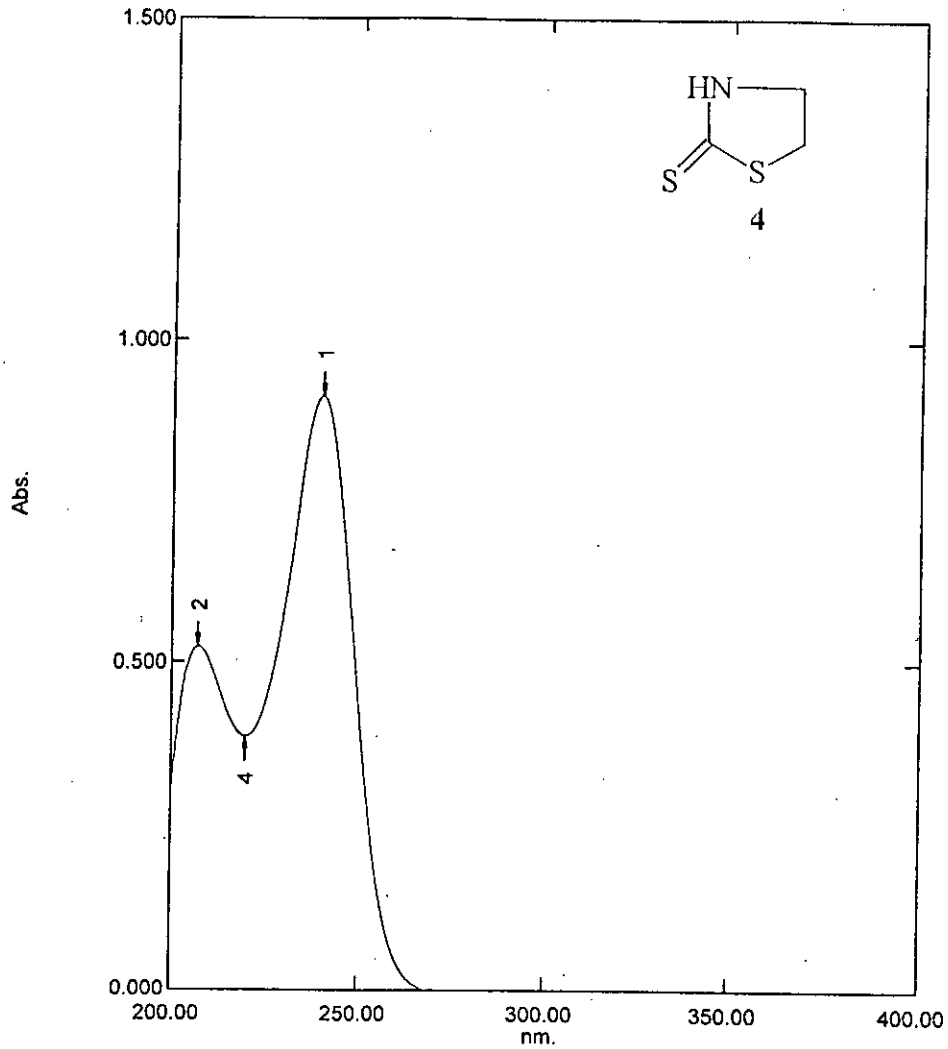


Fig.17b: DEPT ^{13}C NMR Spectrum of Compound 6

S4-K



Wavelength	Abs.
240	0.913
207	0.525

Fig. 6: UV Spectrum of Compound **4**

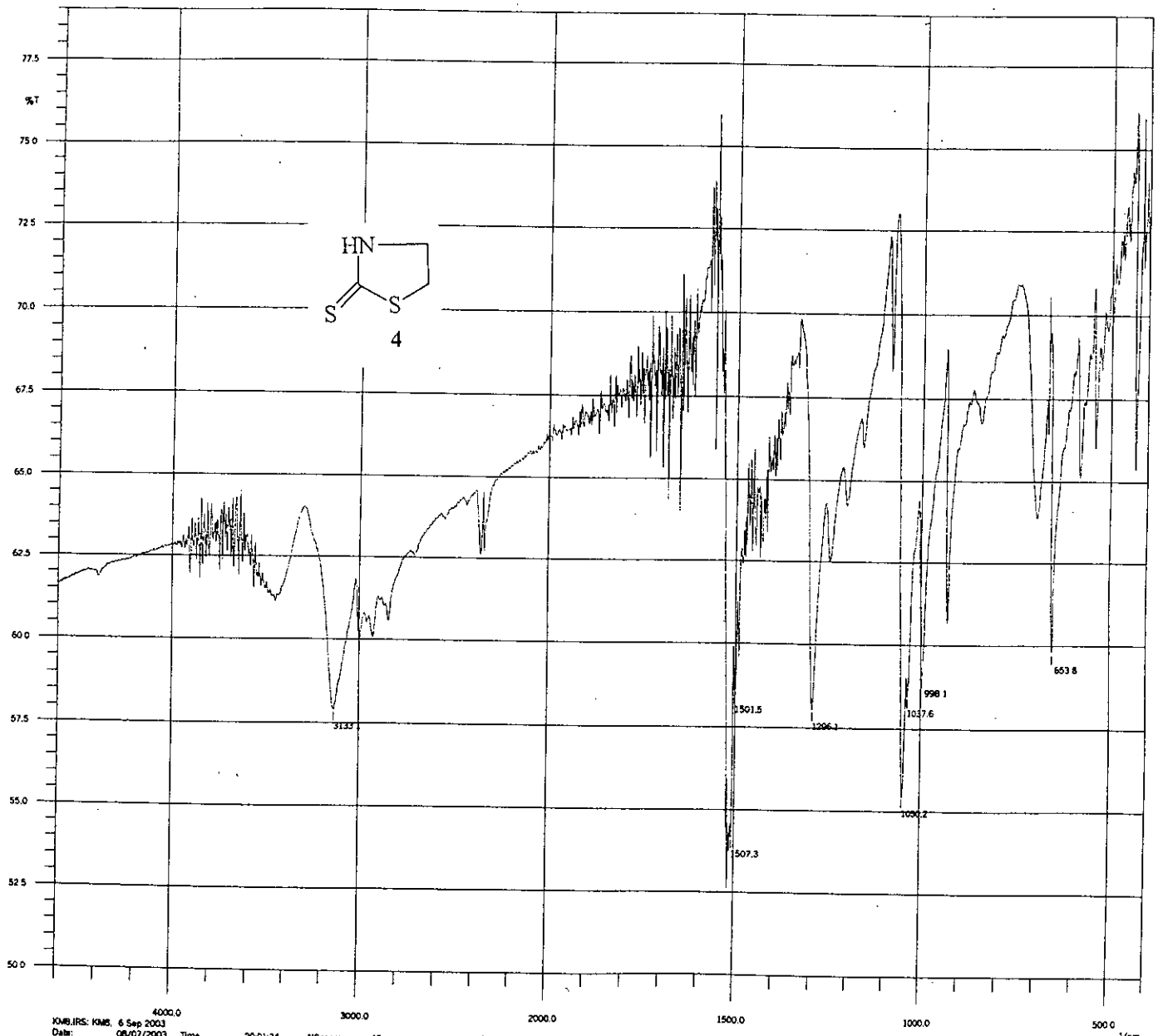


Fig. 7: IR Spectrum of Compound **4**/9010210

Peaktable of KM8.IRS, 8 Peaks
Threshhold: 60, Noise: 2, No Range Selection

No.	Pos. (1/cm)	Inten. (%T)
1	653.8	59.784
2	998.1	59.079
3	1037.6	58.465
4	1050.2	55.440
5	1296.1	58.043
6	1501.5	58.525
7	1507.3	54.154
8	3133.1	57.895

KM8, 6 Sep 2003

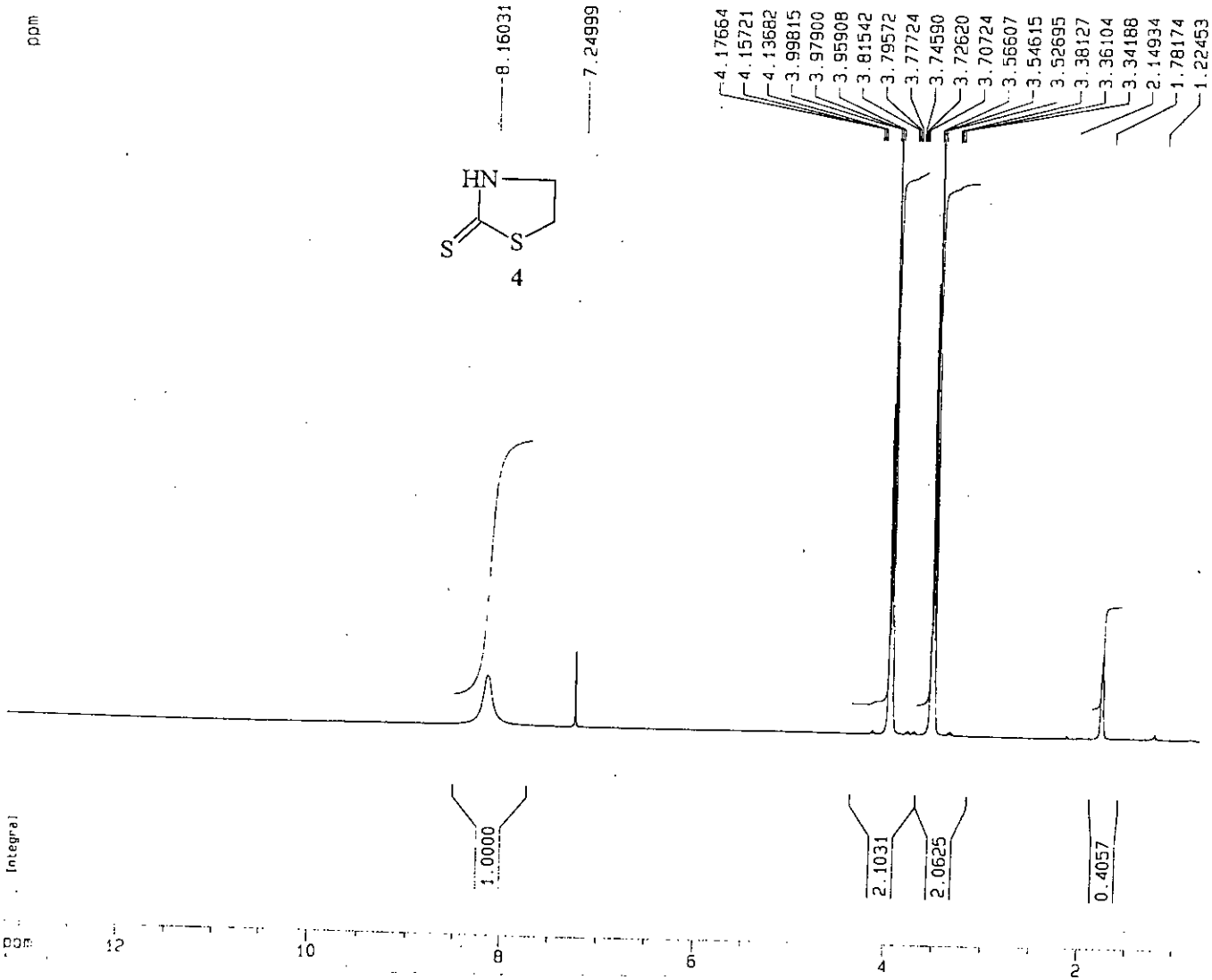


Fig. 8: ^{1}H NMR Spectrum of Compound 4

```
Current Data Parameters
NAME                  A1428
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20040525
Time                 12.59
INSTRUM              dpx400
PROBHD     5 mm Multinuc
PULPROG              zg30
TD                  32768
SOLVENT             CDCl3
NS                    128
DS                      2
SWH              6410.256 Hz
FIORES           0.195625 Hz
AQ               2.5559540 sec
RG                  228.1
DW                78.000 usec
DE                 6.00 usec
TE                310.0 K
D1             1.00000000 sec

============ CHANNEL f1 =============
NUC1                   1H
P1                  8.30 usec
PL1                -6.00 dB
SFO1          400.1428077 MHz

F2 - Processing parameters
SI                  32768
SF            400.1400129 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                  20.00 cm
F1P                13.169 ppm
F1                 5269.64 Hz
F2P                 0.749 ppm
F2                 299.66 Hz
PPMCM             0.62103 ppm/cm
HZCM              248.49887 Hz/cm
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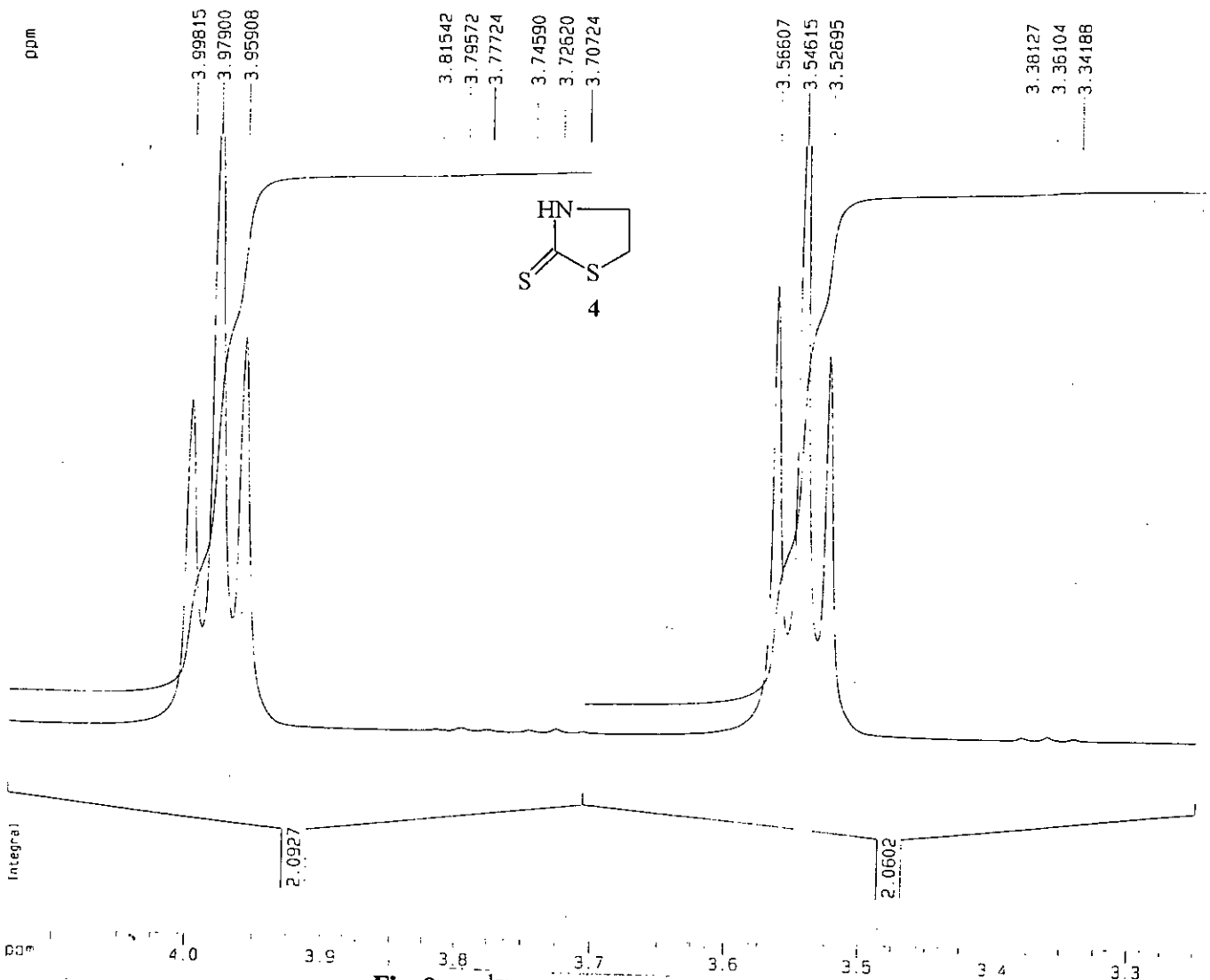

Current Data Parameters

NAME	A1428
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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Time	12.59
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PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	228.1
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428077 MHz

F2 - Processing parameters

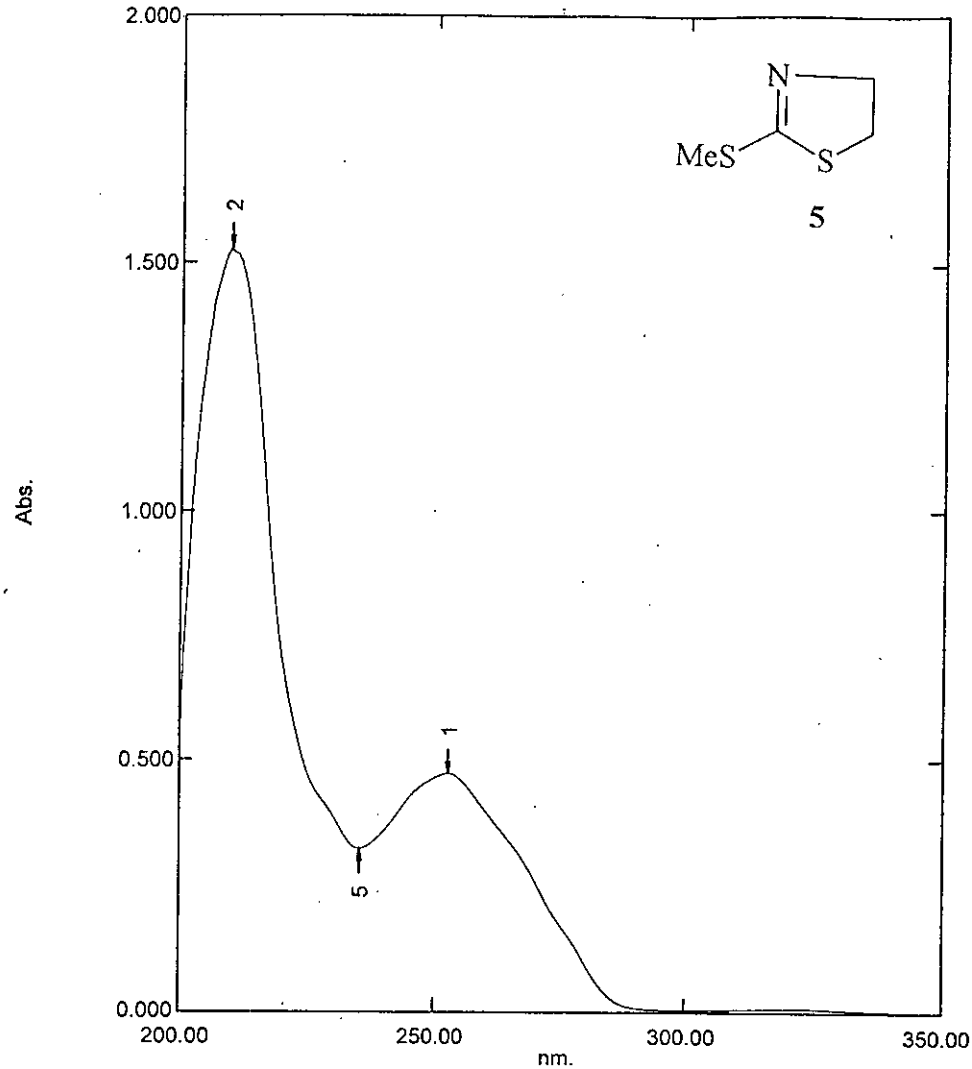
SI	32768
SF	400.1400129 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	4.134 ppm
F1	1654.27 Hz
F2P	3.250 ppm
F2	1300.26 Hz
PPMCM	0.04424 ppm/cm
HZCM	17.70039 Hz/cm

Fig. 9: ^{1}H NMR Spectrum of Compound **4** (Expansion)

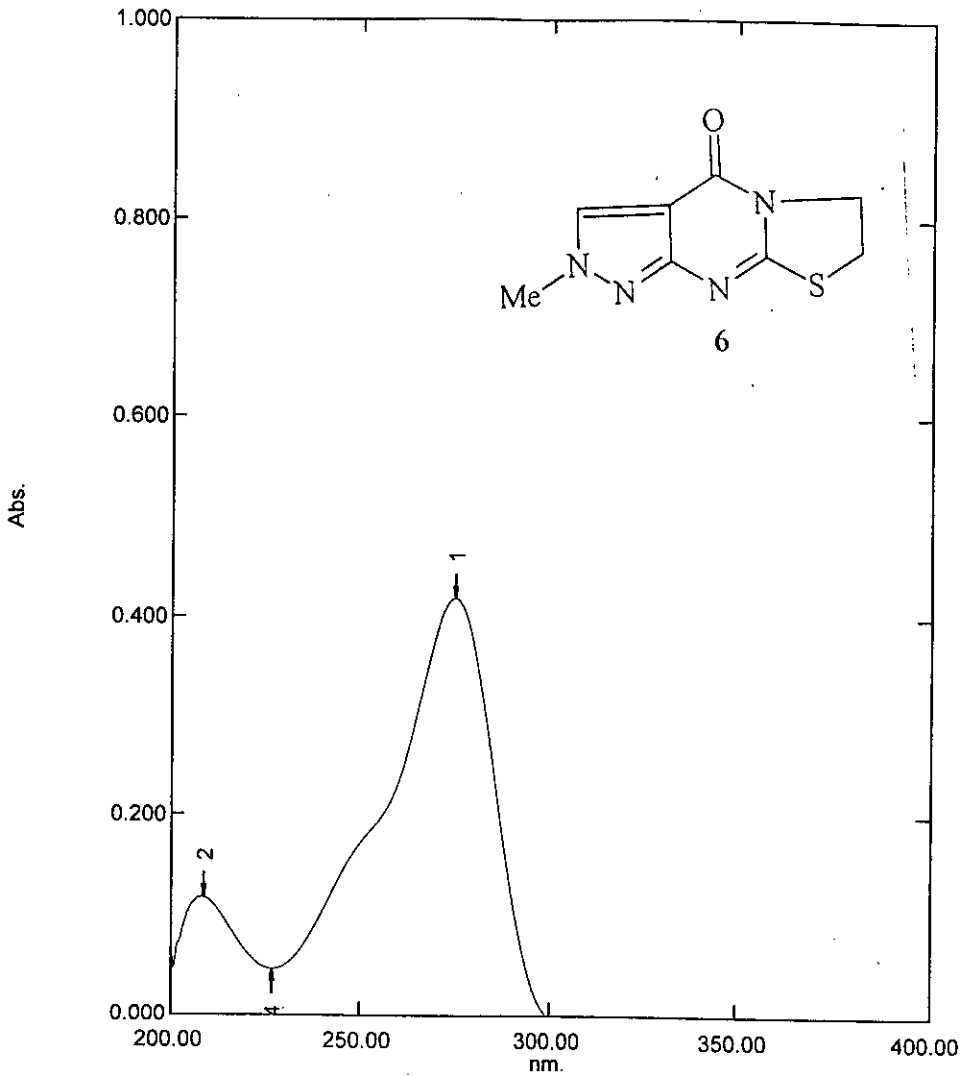
S5-K



Wavelength	Abs.
253	0.473
209	1.473

Fig. 10: UV Spectrum of Compound **5**

S6-K



Wavelength	Abs.
280.00	0.419
	0.118

Fig. 14: UV Spectrum of Compound **6**

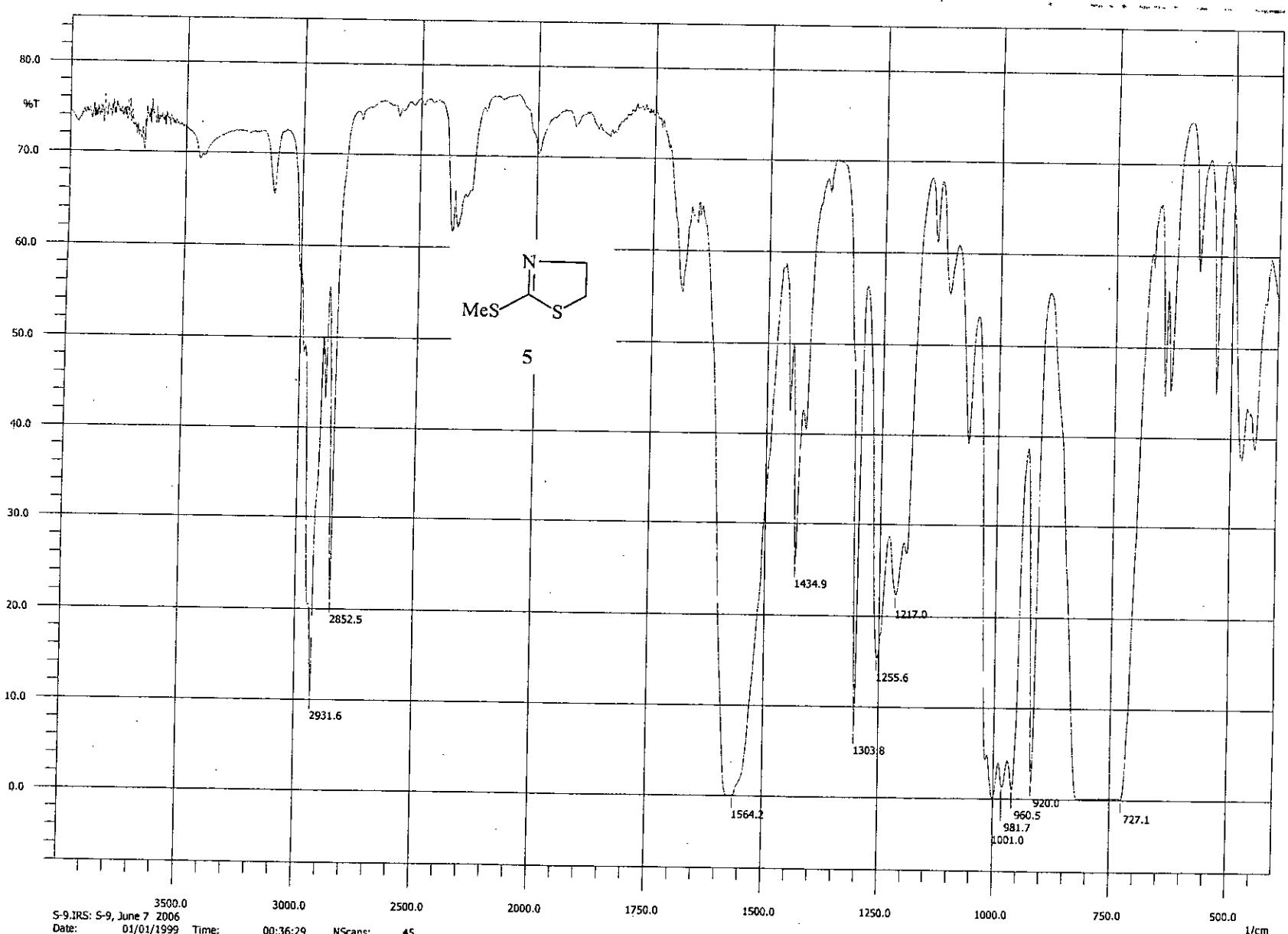


Fig. 11: IR Spectrum of Compound **5**

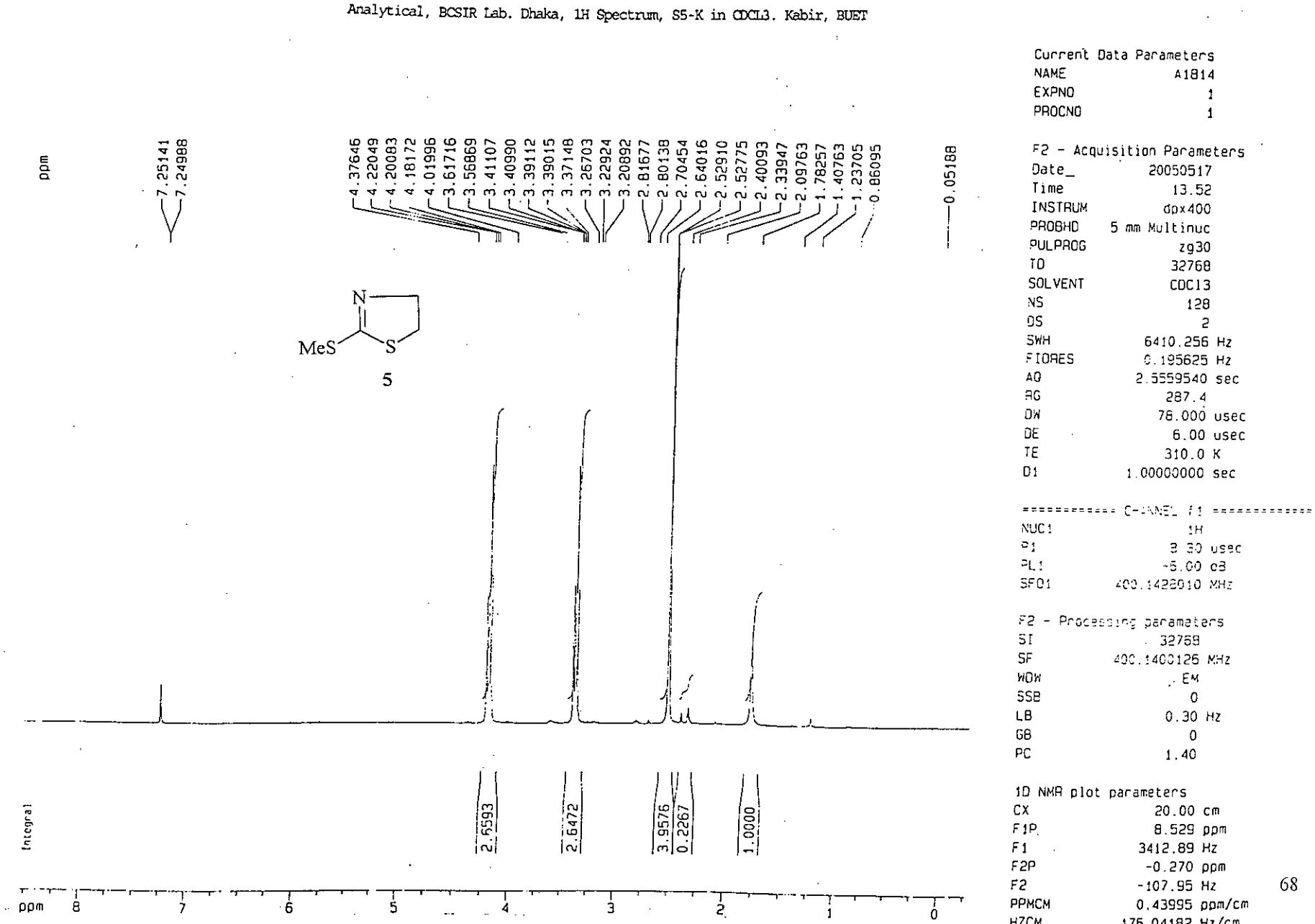


Fig. 12: ^{1}H NMR Spectrum of Compound **5**

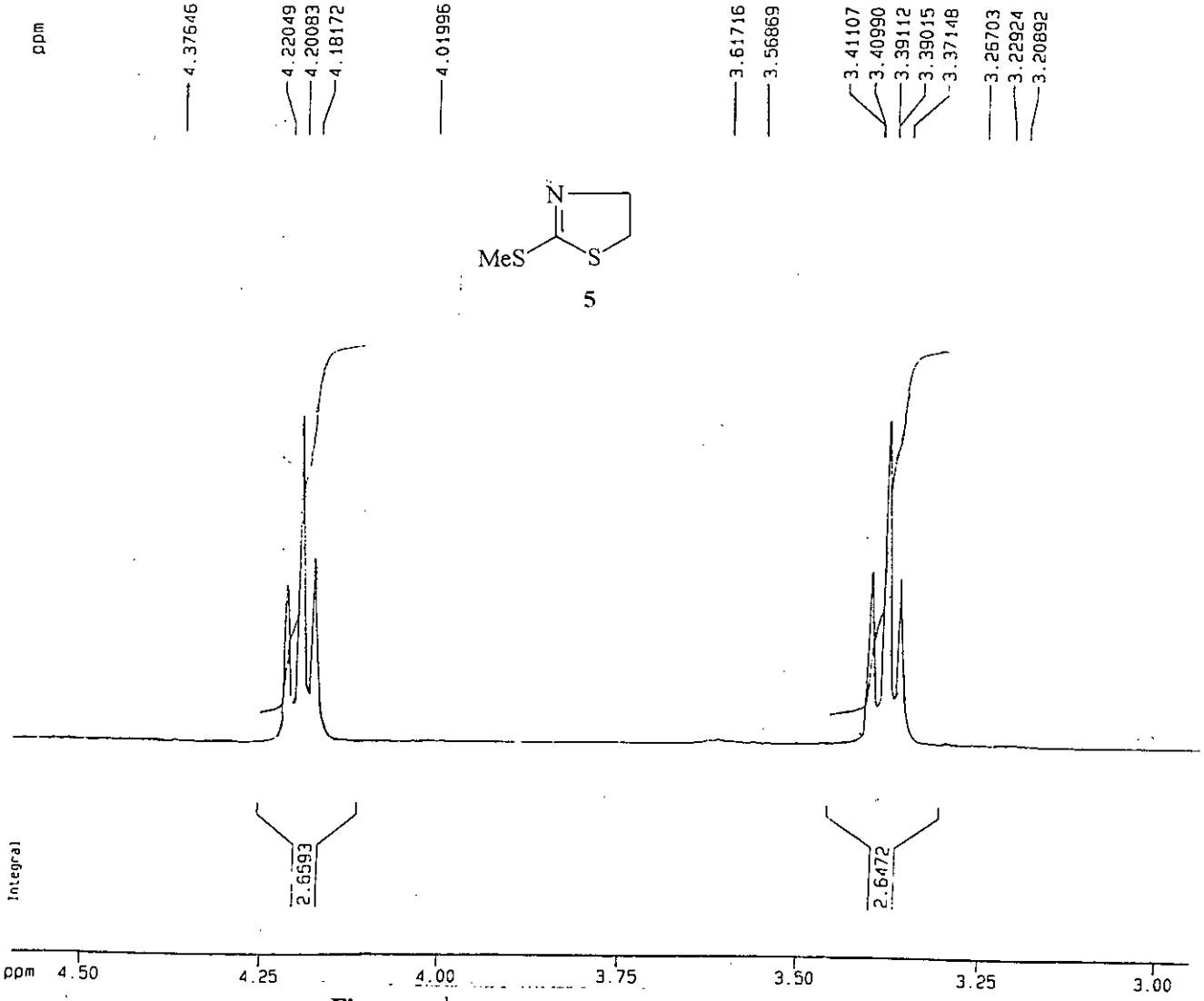


Fig. 13: ^{1}H NMR Spectrum of Compound **5** (Expansion)

```
Current Data Parameters
NAME                  A1814
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20050517
Time                 13.52
INSTRUM              dpx400
PROBHD     5 mm Multinuc
PULPROG              zg30
TD                  32768
SOLVENT              CDCl3
NS                     128
DS                       2
SWH              6410.256 Hz
FIDRES           0.195625 Hz
AQ               2.5559540 sec
RG                   287.4
DW                 78.000 usec
DE                  6.00 usec
TE                  310.0 K
D1               1.00000000 sec

============ CHANNEL f1 ============
NUC1                   1H
P1                  5.30 usec
PL1                -6.10 dB
SFO1          400.1428010 MHz

F2 - Processing parameters
SI                  32768
SF            400.1400166 MHz
WDW                    EM
SSB                     0
LB                   0.30 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                  20.00 cm
F1P                 4.601 ppm
F1                1840.95 Hz
F2P                 2.943 ppm
F2                1177.50 Hz
PPMCM          0.08290 ppm/cm
HZCM          33.17276 Hz/cm
```

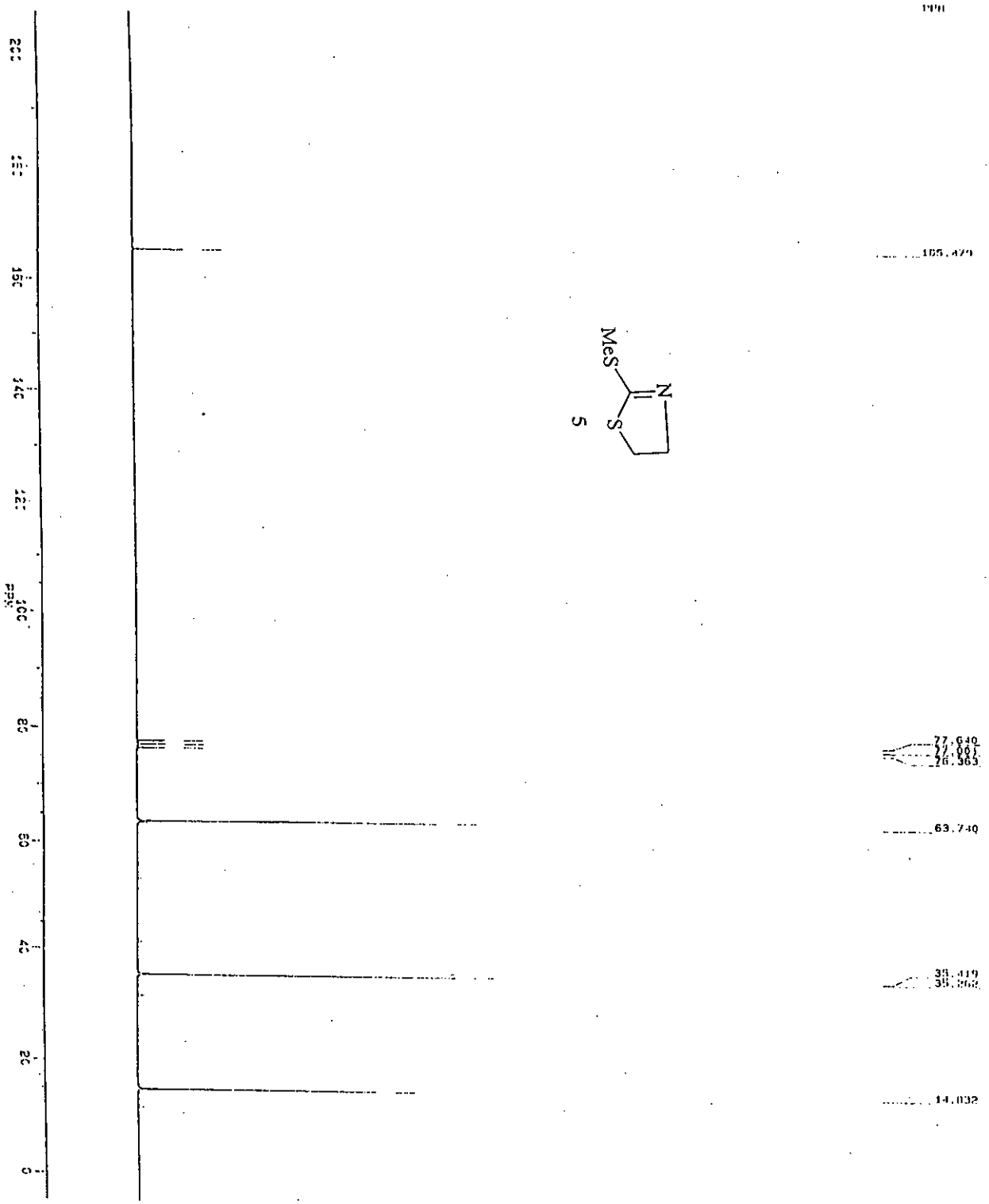


Fig. 13a: ^{13}C NMR Spectrum of Compound 5

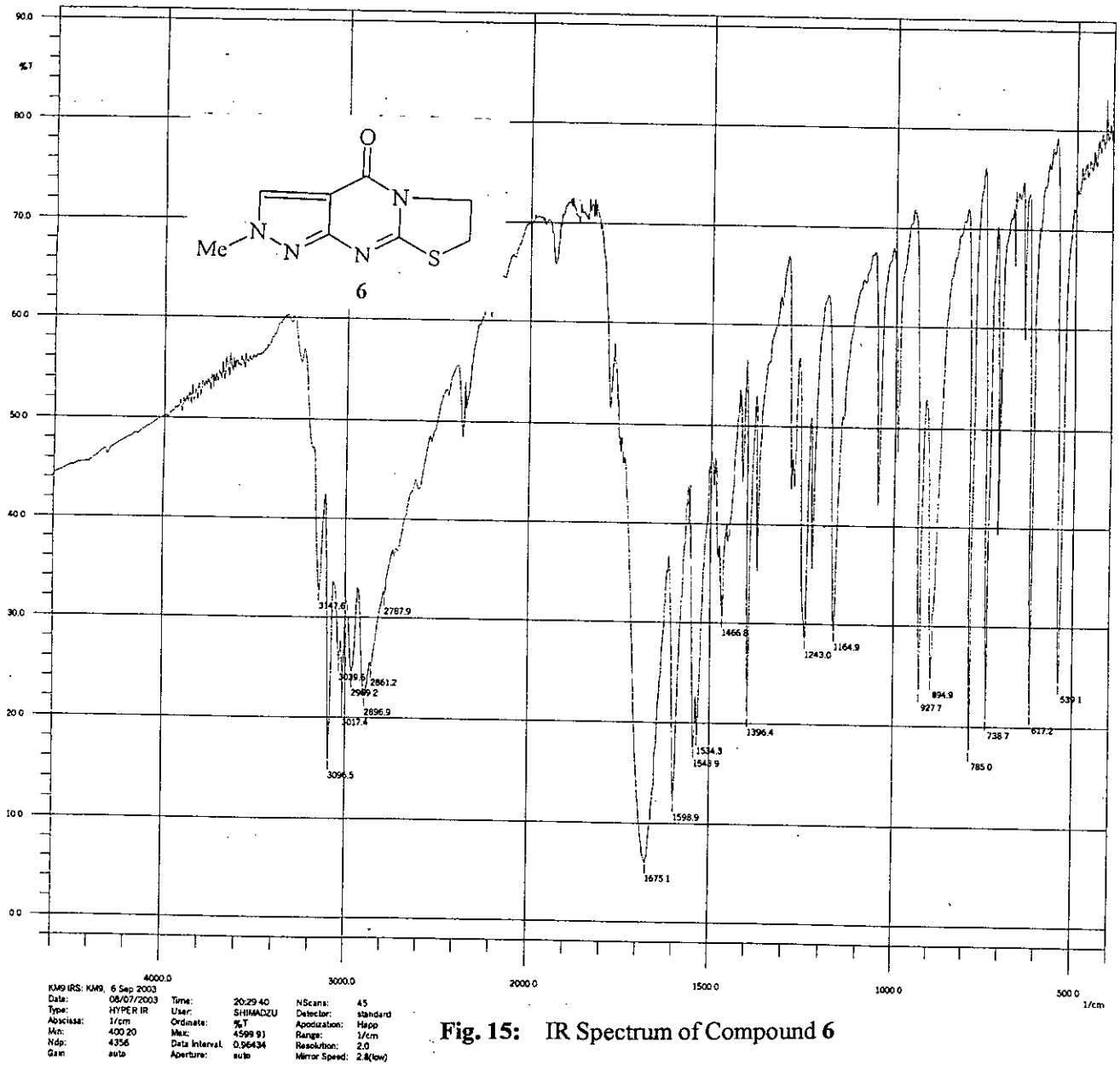


Fig. 15: IR Spectrum of Compound **6**

Peaktable of KM9.IRS, 22 Peaks
Threshhold: 35, Noise: 2, No Range Selection

No.	Pos. (1/cm)	Inten. (%T)
1	539.1	24.521
2	617.2	21.389
3	738.7	20.789
4	785.0	17.702
5	894.9	24.771
6	927.7	23.490
7	1164.9	29.396
8	1243.0	28.593
9	1396.4	20.754
10	1466.8	30.617
11	1534.3	18.810
12	1543.9	17.589
13	1598.9	12.215
14	1675.1	6.030
15	2787.9	32.202
16	2861.2	25.113
17	2896.9	22.153
18	2969.2	24.632
19	3017.4	24.450
20	3039.6	25.624
21	3096.5	15.844
22	3147.6	32.672

KM9, 6 Sep 2003

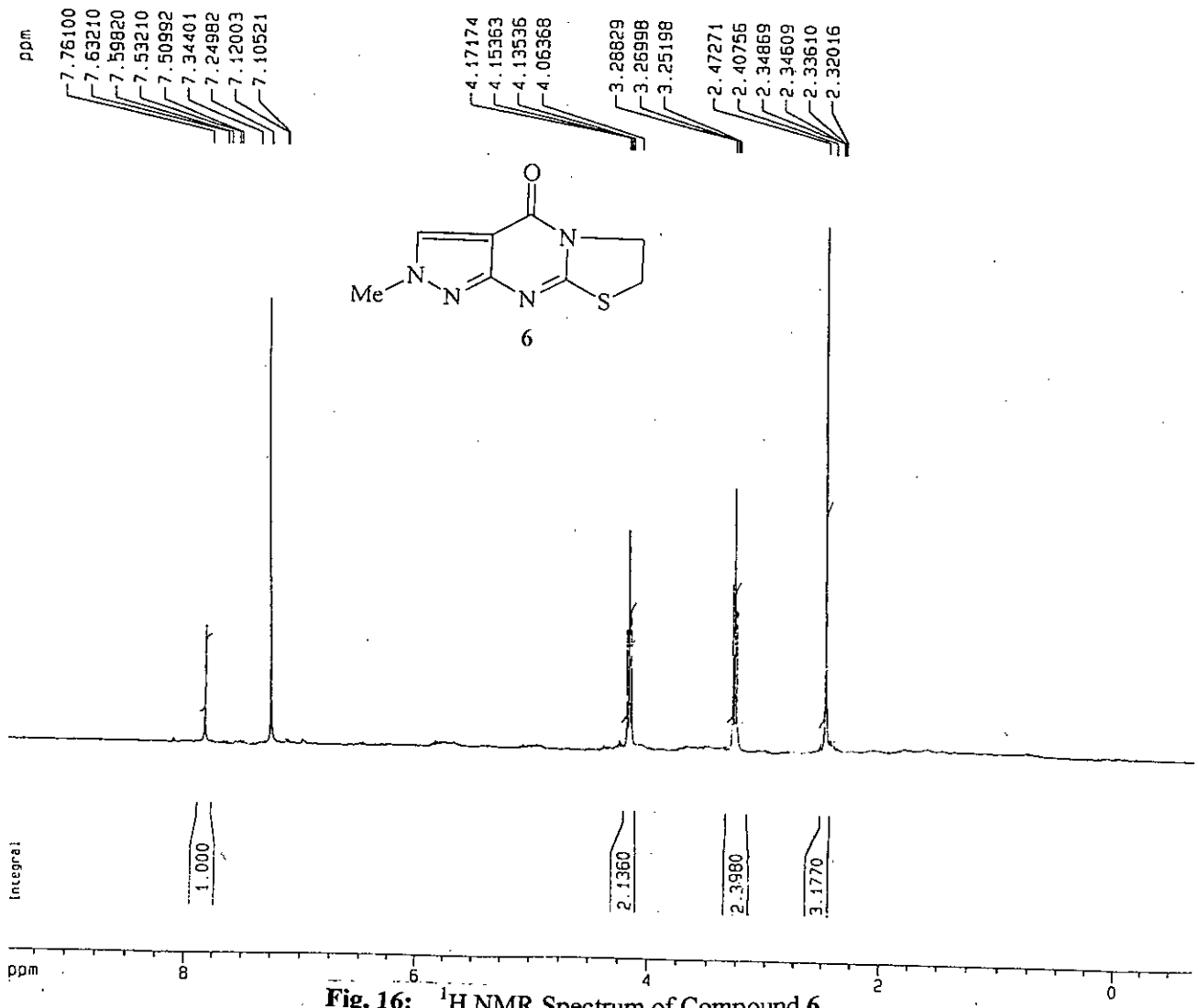


Fig. 16: ^{1}H NMR Spectrum of Compound **6**

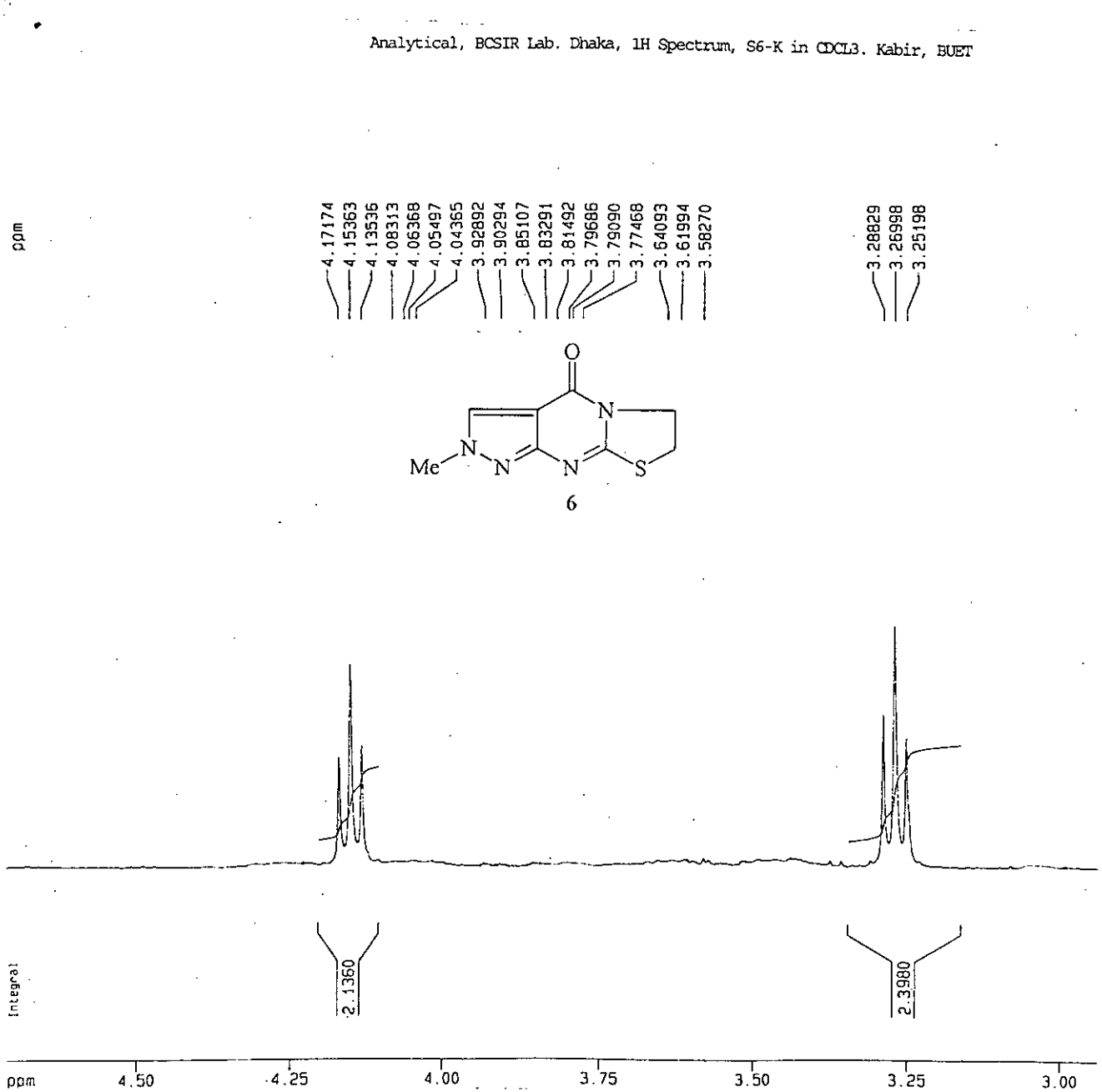
```
Current Data Parameters
NAME                  A1813
EXPNO                    1
PROCNO                   1

F2 - Acquisition Parameters
Date_              20050517
Time                 13.33
INSTRUM              dpx400
PROBHD     5 mm Multinuc
PULPROG              zg30
TD                  32768
SOLVENT             CDCl3
NS                    128
DS                      2
SWH              6410.256 Hz
FIDRES           0.195625 Hz
AQ               2.5559540 sec
RG                    362
DW                78.000 usec
DE                 6.00 usec
TE                310.0 K
D1               1.00000000 sec

========== CHANNEL f1 ============
NUC1                  1H
P1                 8.30 usec
PL1               -6.00 dB
SFO1          400.1428010 MHz

F2 - Processing parameters
SI                  32768
SF            400.1400126 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                  1.40

1D NMR plot parameters
CX                20.00 cm
F1P               9.473 ppm
F1              3790.37 Hz
F2P               -0.716 ppm
F2              -286.39 Hz
PPMCM          0.50942 ppm/cm
HZCM          203.83792 Hz/cm
```



Current Data Parameters

NAME	A1813
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20050517
Time	13.33
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	362
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428010 MHz

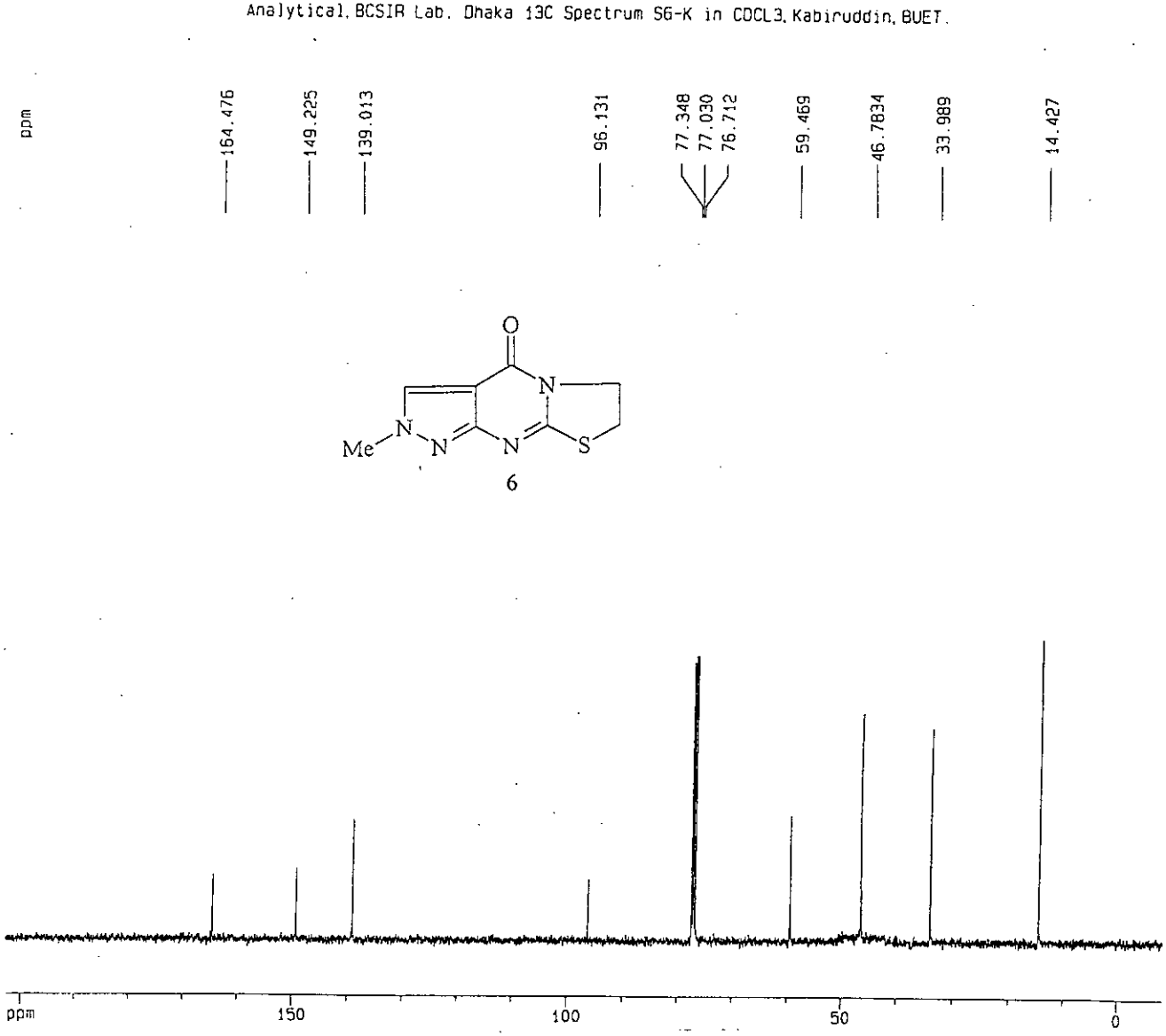
F2 - Processing parameters

SI	32768
SF	400.1400126 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	4.704 ppm
F1	1882.39 Hz
F2P	2.938 ppm
F2	1175.48 Hz
PPMCM	0.08833 ppm/cm
HZCM	35.34563 Hz/cm

Fig. 17: ^{1}H NMR Spectrum of Compound **6** (Expansion)



Current Data Parameters

NAME	A3153
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20061212
Time	11.54
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	309
DS	2
SWH	24154.590 Hz
FIDRES	0.737140 Hz
AQ	0.6783476 sec
RG	16384
DW	20.700 usec
DE	6.00 usec
TE	300.0 K
D1	1.50000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

========== CHANNEL f1 ==========

NUC1	13C
P1	8.30 usec
PL1	-6.00 dB
SFO1	100.6253045 MHz

========== CHANNEL f2 ==========

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-6.00 dB
PL12	16.00 dB
PL13	120.00 dB
SFO2	400.1400000 MHz

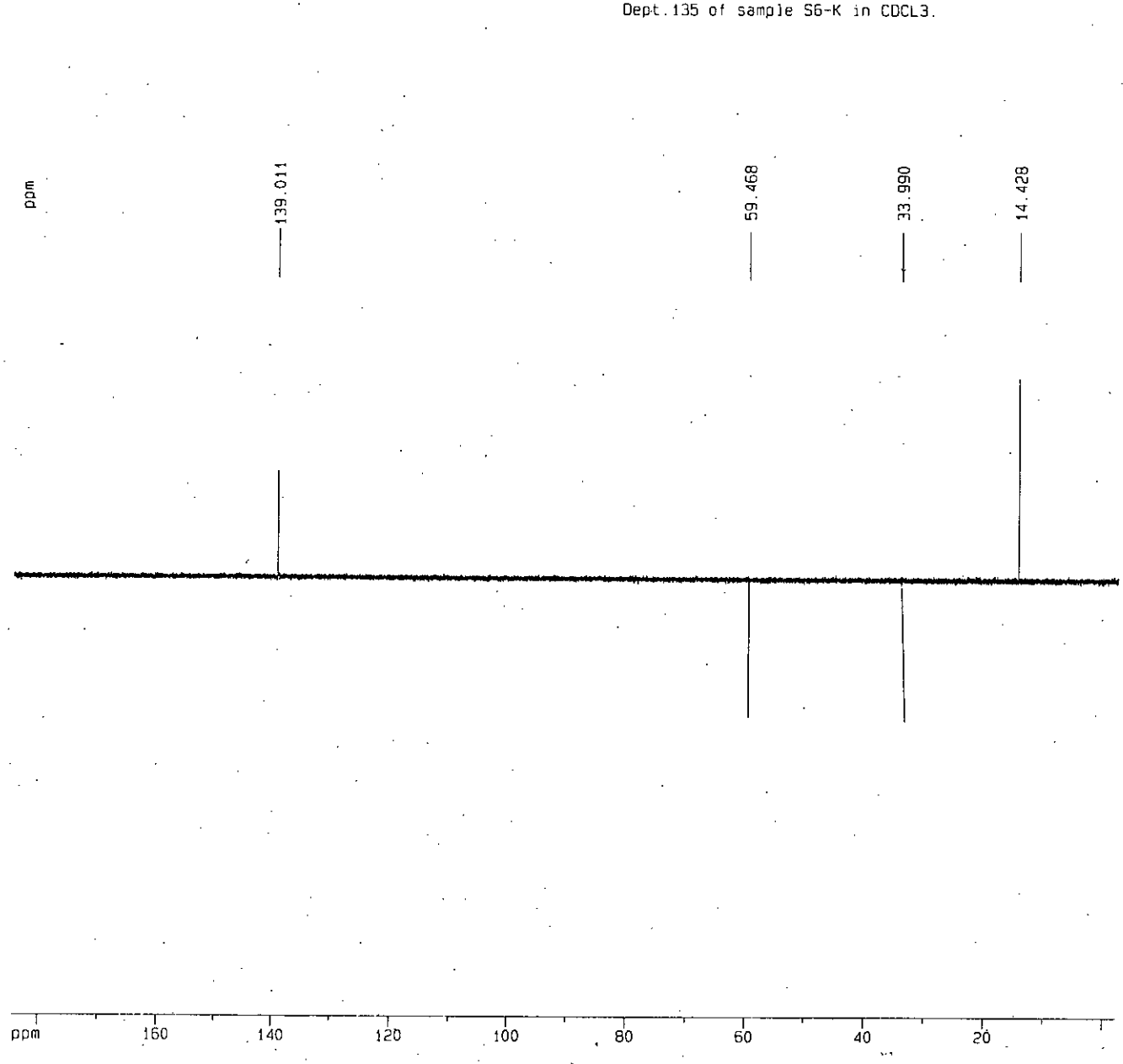
F2 - Processing parameters

SI	32768
SF	100.6152882 MHz
WDW	EM
SSB	0
LB	2.50 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	202.619 ppm
F1	20386.53 Hz
F2P	-8.328 ppm
F2	-837.91 Hz
PPMCM	10.54733 ppm/cm
HZCM	1061.22217 Hz/cm

Fig.17a: ^{13}C NMR Spectrum of Compound **6**



Current Data Parameters

NAME	A3153
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20061212
Time	12.03
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	dept135
TD	32768
SOLVENT	CDCl3
NS	86
DS	8
SWH	24154.590 Hz
FIDRES	0.737140 Hz
AQ	0.6783476 sec
RG	13004
DW	20.700 usec
DE	6.00 usec
TE	300.0 K
CNST2	145.0000000
D1	4.00000000 sec
d2	0.00344828 sec
d12	0.00002000 sec
DELTA	0.00000764 sec

========== CHANNEL f1 ==========

NUC1	13C
P1	6.00 usec
p2	12.00 usec
PL1	-6.00 dB
SFO1	100.6253045 MHz

========== CHANNEL f2 ==========

CPDPRG2	waltz16
NUC2	1H
P3	8.30 usec
p4	16.60 usec
PCPD2	80.00 usec
PL2	-6.00 dB
PL12	16.00 dB
SFO2	400.1420007 MHz

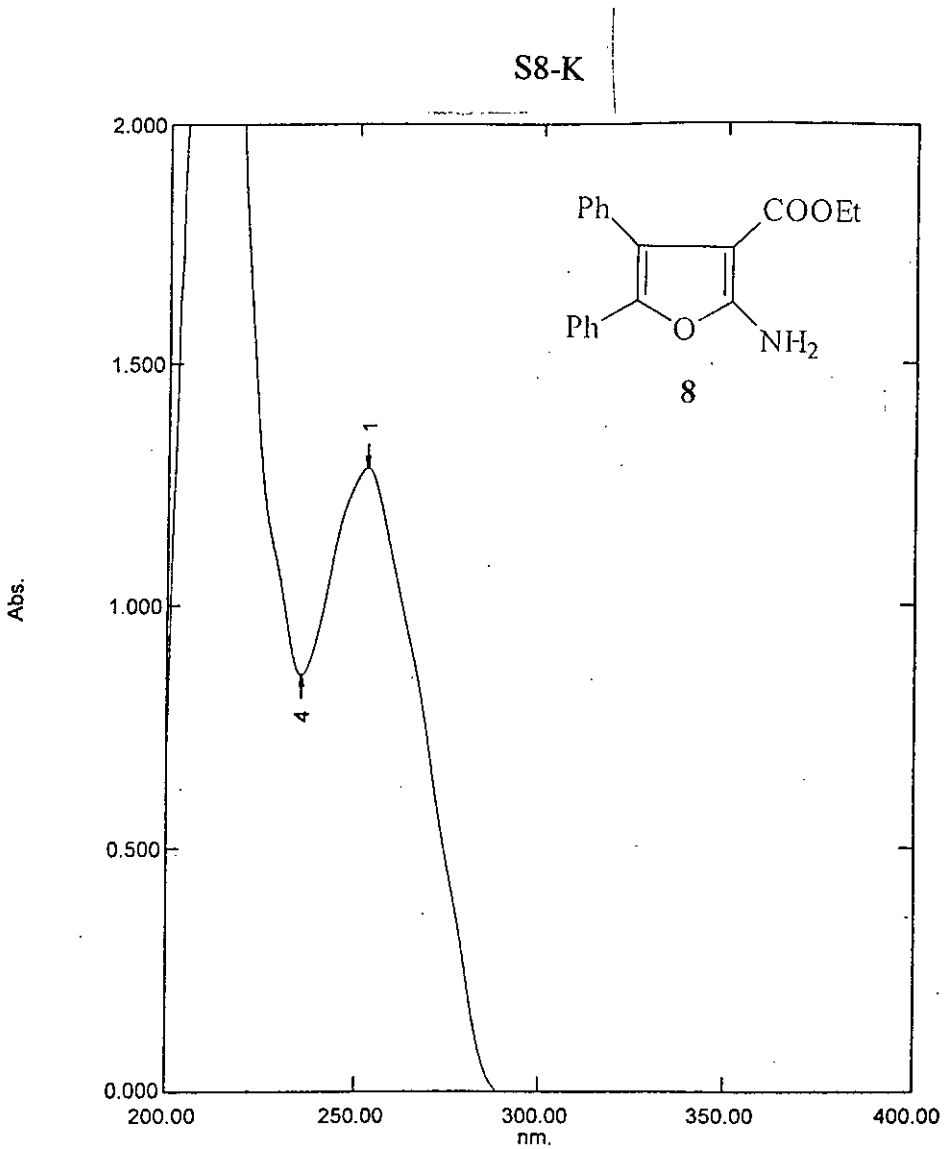
F2 - Processing parameters

SI	32768
SF	100.6152881 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	184.133 ppm
F1	18526.56 Hz
F2P	-2.250 ppm
F2	-226.36 Hz
PPMCM	9.31912 ppm/cm
HZCM	937.64642 Hz/cm

Fig.17b: DEPT ^{13}C NMR Spectrum of Compound **6**



Wavelength	Abs.
253	1.285
215	2.824

Fig. 18: UV Spectrum of Compound **8**

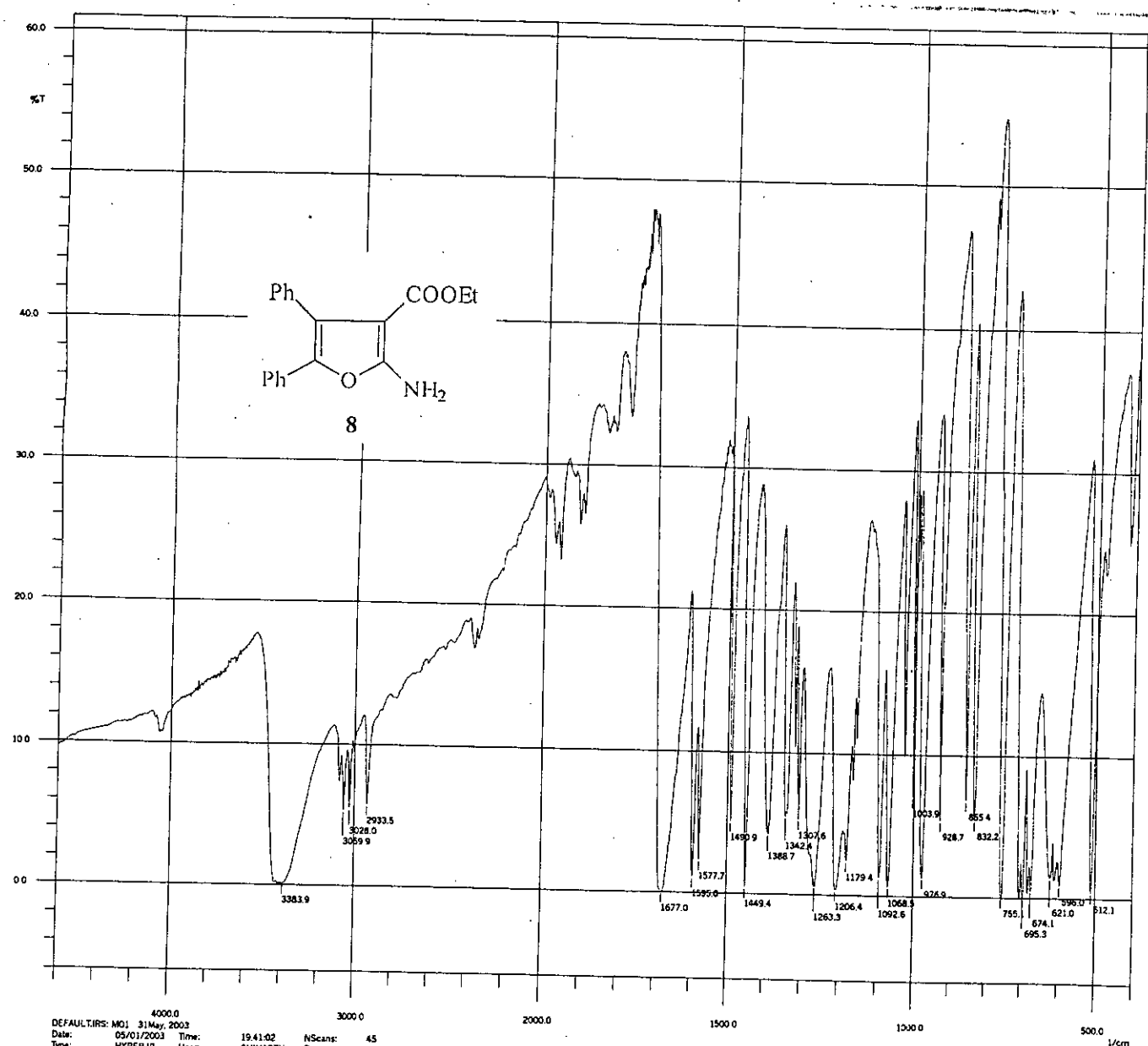
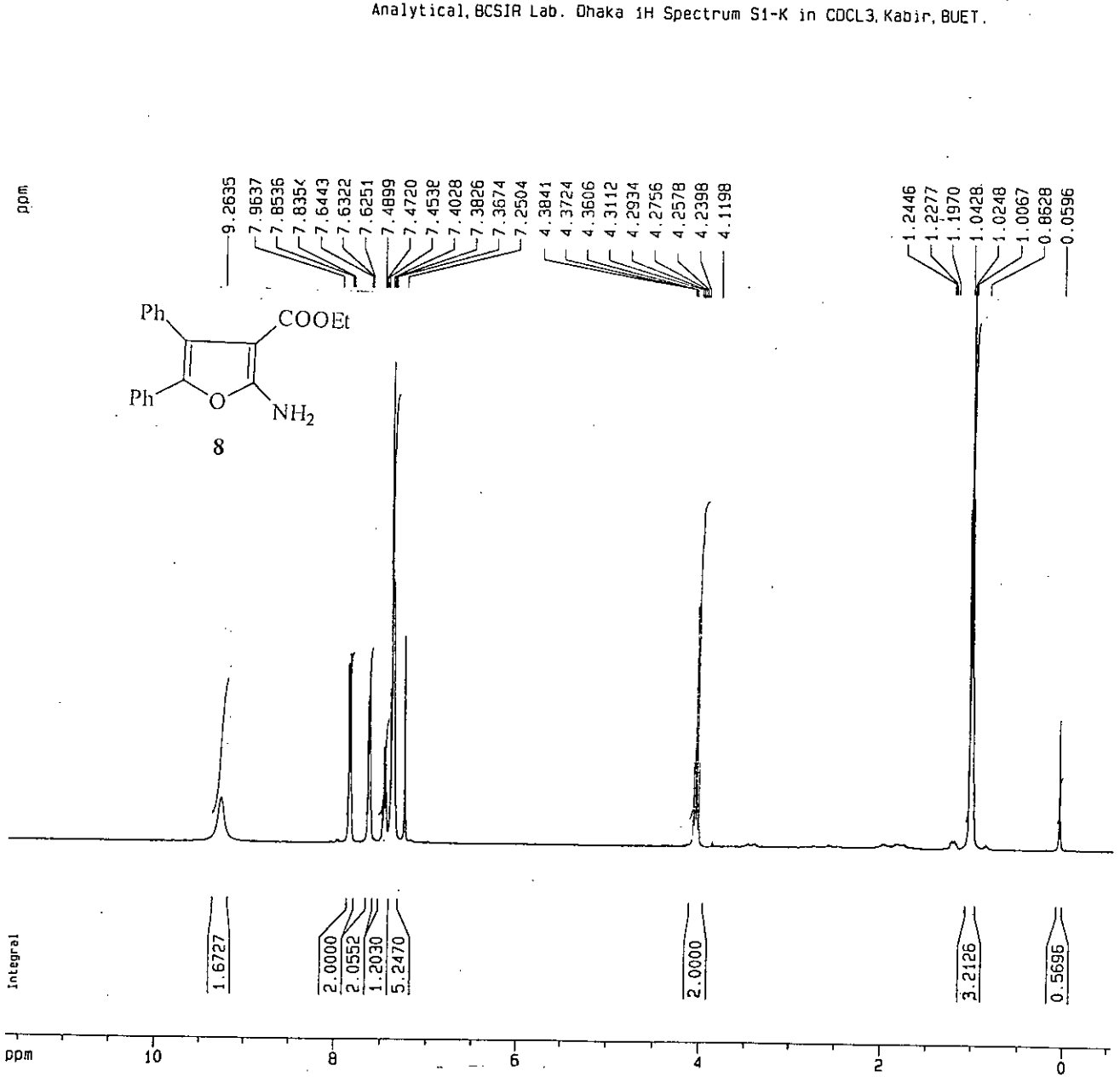


Fig. 19: IR Spectrum of Compound **8**

Peaktable of DEFAULT.IRS, 28 Peaks
Threshhold: 8, Noise: 2, No Range Selection

No.	Pos. (1/cm)	Inten. (%T)
1	512.1	0.4404
2	596.0	0.9408
3	621.0	1.4568
4	674.1	0.5382
5	695.3	0.0713
6	755.1	0.0799
7	832.2	5.4466
8	855.4	6.8190
9	928.7	5.3832
10	976.9	1.3088
11	1003.9	7.0450
12	1068.5	0.6782
13	1092.6	1.3263
14	1179.4	2.4240
15	1206.4	0.3616
16	1263.3	0.5952
17	1307.6	5.3205
18	1342.4	5.4990
19	1388.7	4.2404
20	1449.4	0.4828
21	1490.9	5.0910
22	1577.7	2.3416
23	1595.0	1.0965
24	1677.0	0.0356
25	2933.5	5.7905
26	3028.0	5.4451
27	3059.9	5.3563
28	3383.9	0.1041

MO1 31May, 2003



Current Data Parameters

NAME	A2614
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060523
Time	16.32
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	512
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428010 MHz

F2 - Processing parameters

SI	32768
SF	400.1400126 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	11.632 ppm
F1	4654.61 Hz
F2P	-0.552 ppm
F2	-220.70 Hz
PPMCM	0.60920 ppm/cm
HZCM	243.76555 Hz/cm

Fig. 20: ^{1}H NMR Spectrum of Compound **8**

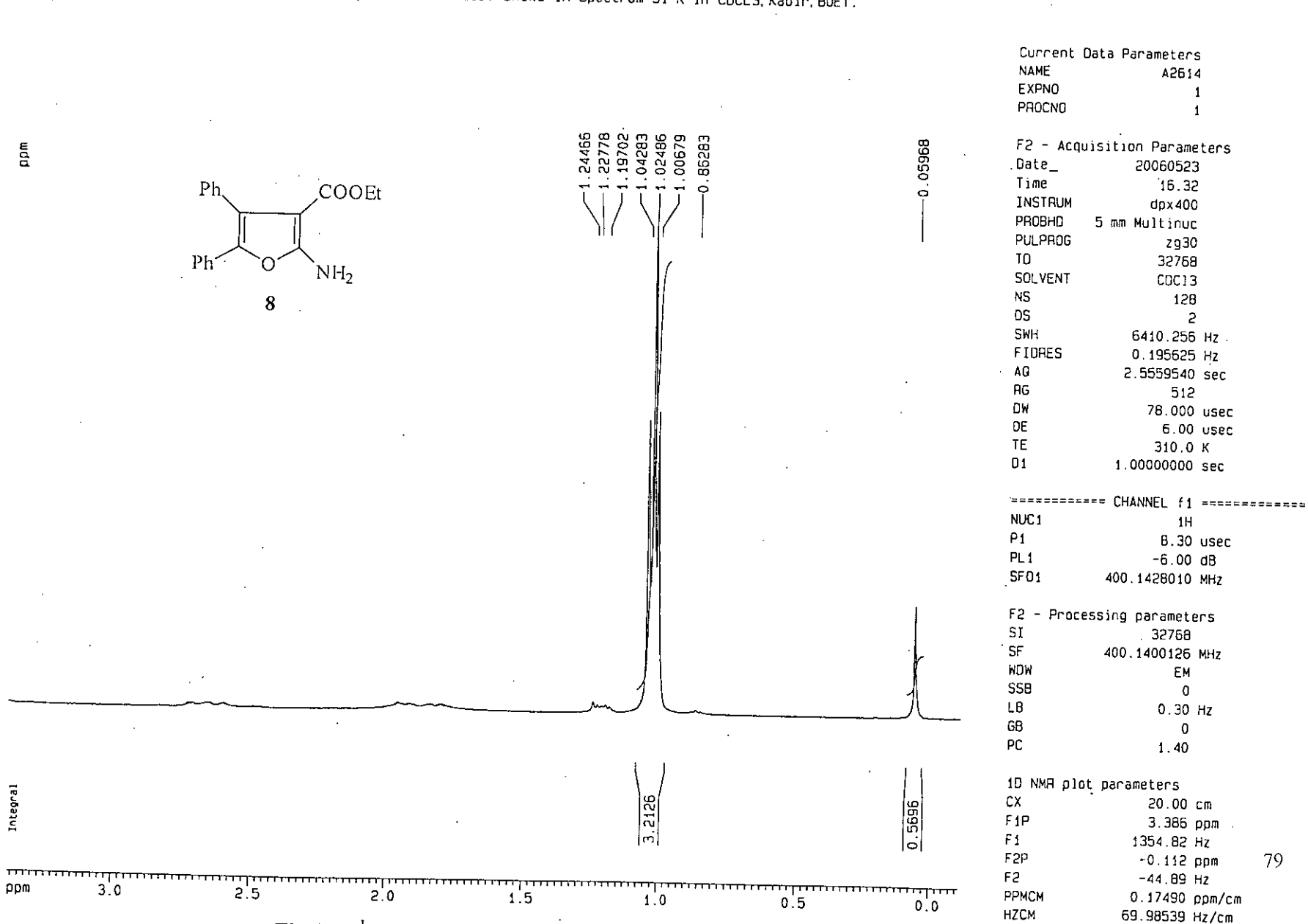
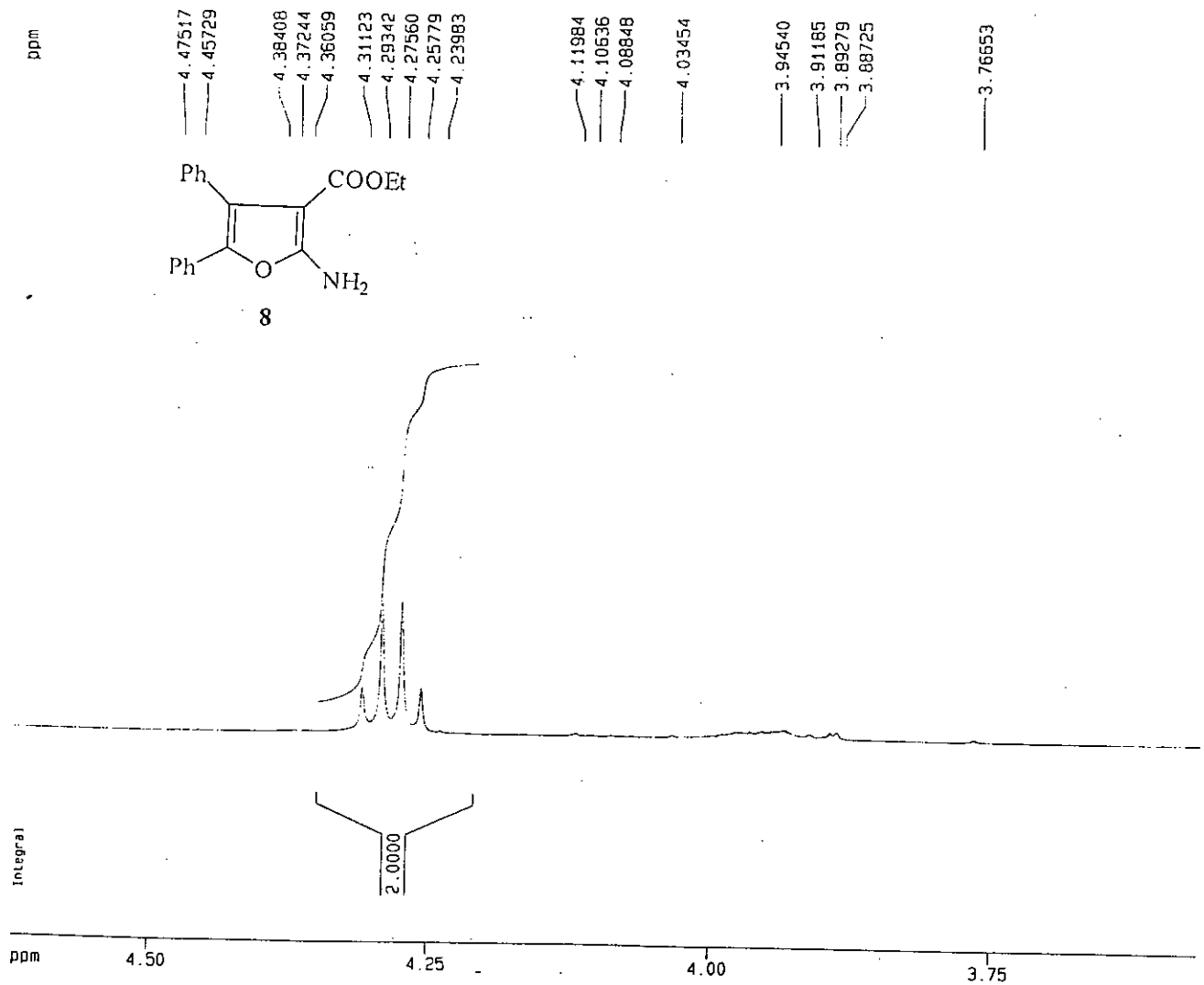


Fig. 21: ^{1}H NMR Spectrum of Compound **8** (Expansion)



8

Fig. 22: ^{1}H NMR Spectrum of Compound **8** (Expansion)

Current Data Parameters

NAME	A2614
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060523
Time	16.32
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	512
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428010 MHz

F2 - Processing parameters

SI	32768
SF	400.1400126 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	8.037 ppm
F1	3215.84 Hz
F2P	7.124 ppm
F2	2850.42 Hz
PPMCM	0.04566 ppm/cm
HZCM	18.27080 Hz/cm

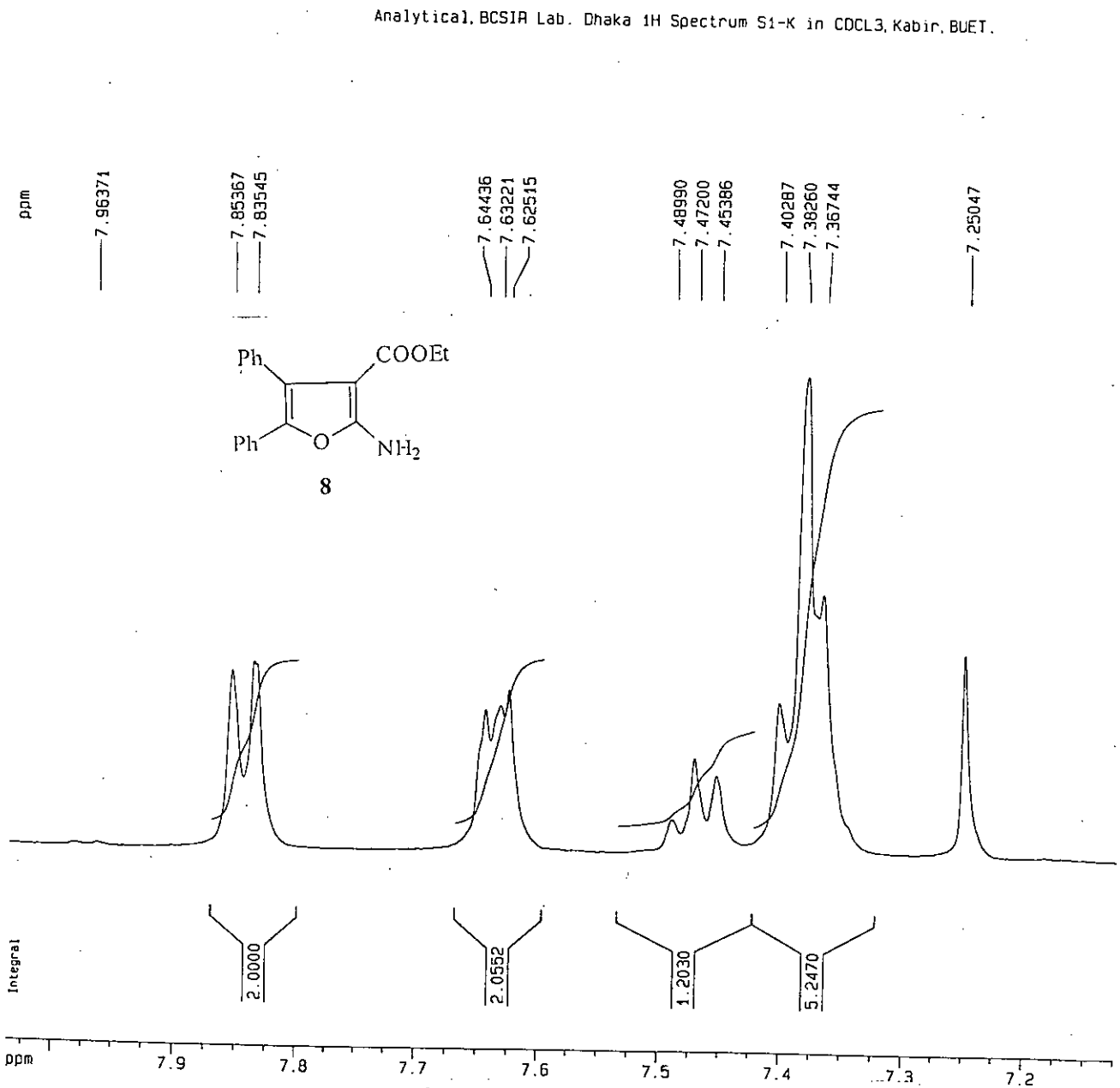


Fig. 23: ^{1}H NMR Spectrum of Compound **8** (Expansion)

Current Data Parameters

NAME	A2614
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060523
Time	16.32
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	512
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

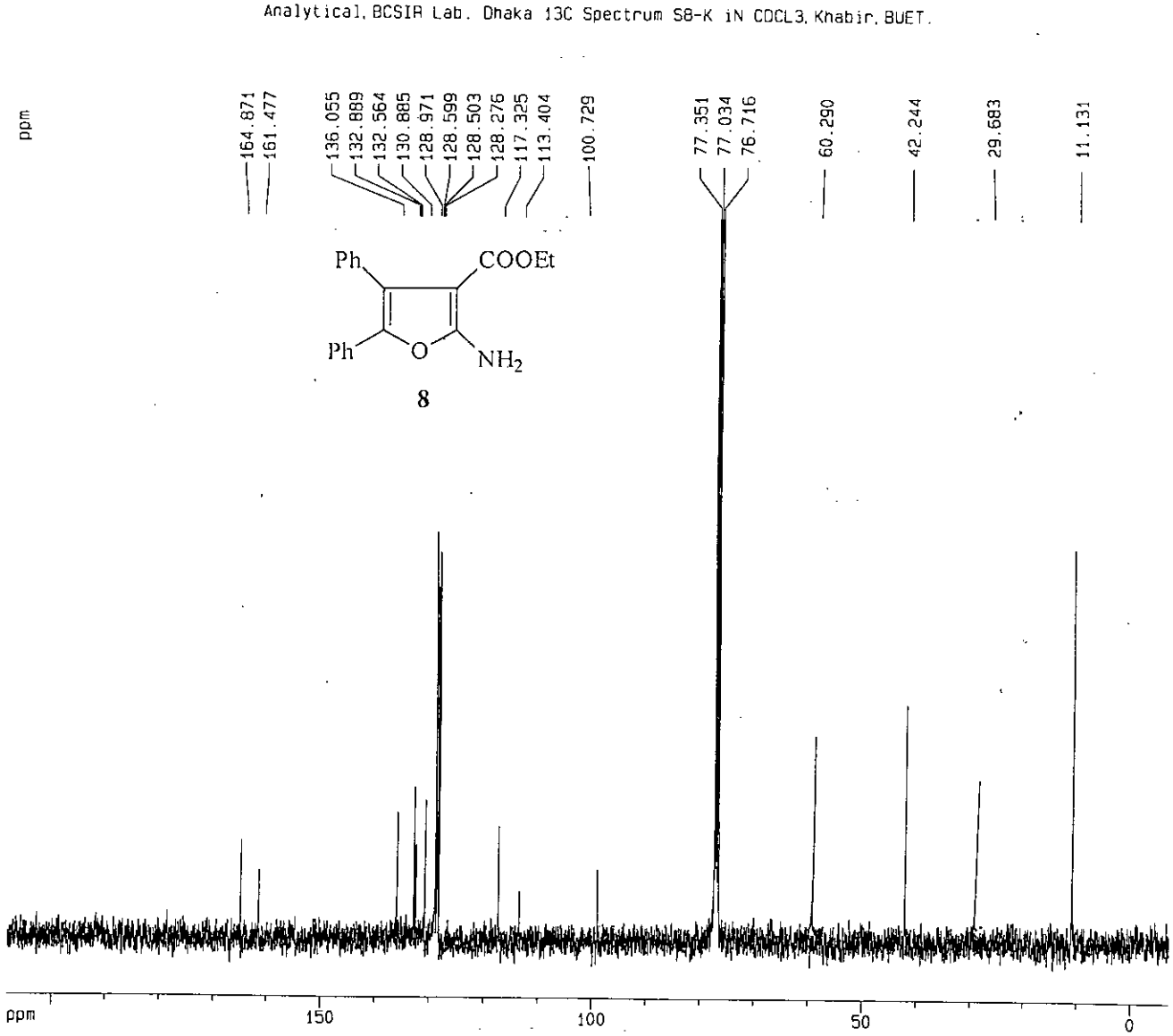
NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428010 MHz

F2 - Processing parameters

SI	32768
SF	400.1400126 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	8.037 ppm
F1	3215.84 Hz
F2P	7.124 ppm
F2	2850.42 Hz
PPMCM	0.04566 ppm/cm
HZCM	18.27080 Hz/cm



Current Data Parameters

NAME	A3057
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20061016
Time	10.41
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	795
DS	2
SWH	24154.590 Hz
FIDRES	0.737140 Hz
AQ	0.6783476 sec
RG	16384
DW	20.700 usec
DE	6.00 usec
TE	300.0 K
D1	1.50000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

========== CHANNEL f1 ==========

NUC1	13C
P1	8.30 usec
PL1	-6.00 dB
SFO1	100.6253045 MHz

========== CHANNEL f2 ==========

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-6.00 dB
PL12	16.00 dB
PL13	120.00 dB
SFO2	400.1400000 MHz

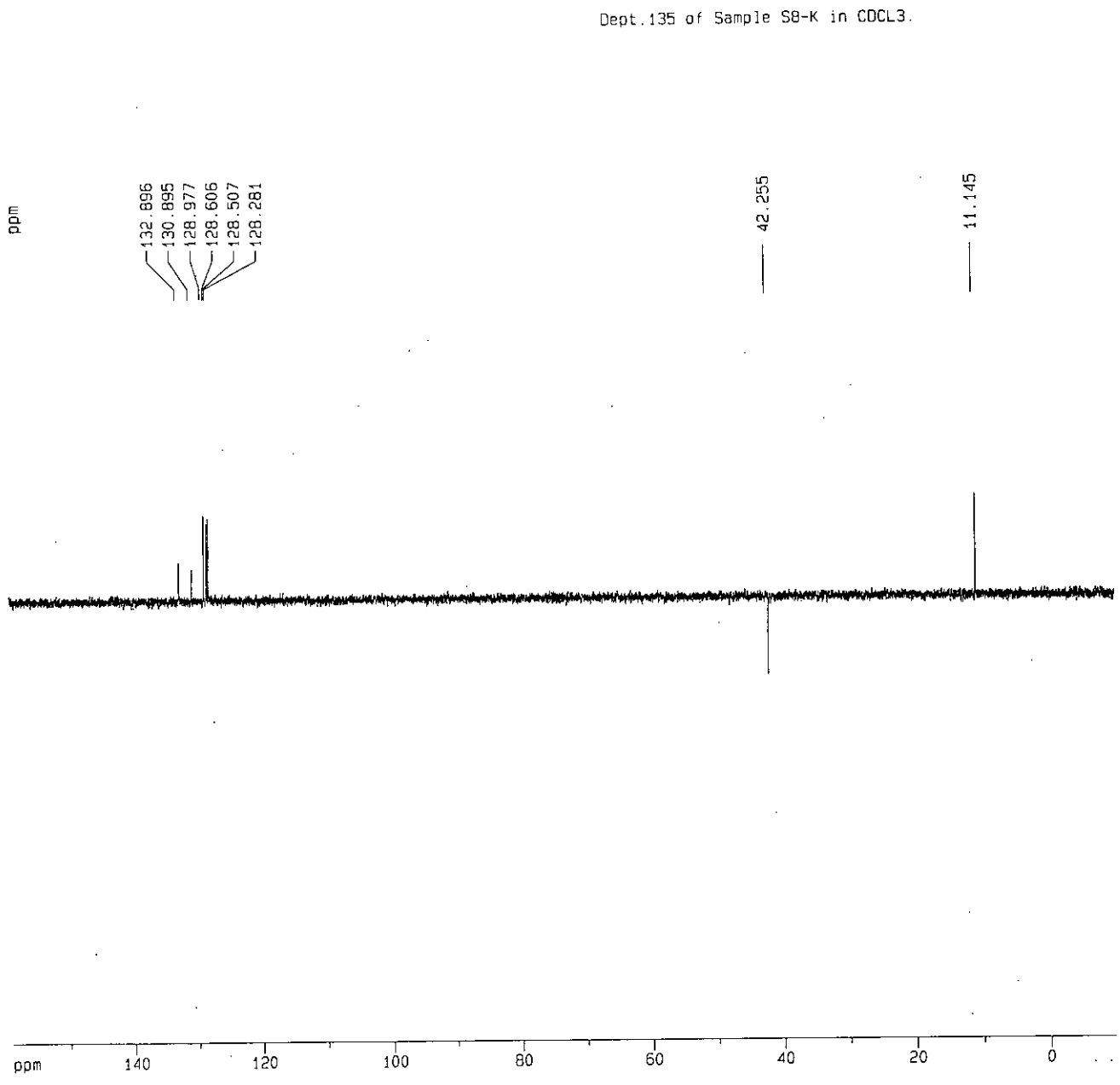
F2 - Processing parameters

SI	32768
SF	100.6152823 MHz
WDW	EM
SSB	0
LB	2.50 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	208.248 ppm
F1	20952.97 Hz
F2P	-7.003 ppm
F2	-704.62 Hz
PPMCM	10.76258 ppm/cm
HZCM	1082.87976 Hz/cm

Fig. 24: ^{13}C NMR Spectrum of Compound **8**



Current Data Parameters

NAME	A3057
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

Date_	20061016
Time	10 51
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	dept135
TD	32768
SOLVENT	CDCl3
NS	67
DS	8
SWH	24154.590 Hz
FIDRES	0.737140 Hz
AQ	0.6783476 sec
RG	13004
DW	20.700 usec
DE	6.00 usec
TE	300.0 K
CNST2	145.0000000
D1	4.00000000 sec
d2	0.00344828 sec
d12	0.00002000 sec
DELTA	0.00000764 sec

========== CHANNEL f1 ==========

NUC1	13C
P1	6.00 usec
p2	12.00 usec
PL1	-6.00 dB
SFO1	100.6253045 MHz

========== CHANNEL f2 ==========

CPDPRG2	waltz16
NUC2	1H
P3	8.30 usec
p4	16.60 usec
PCPD2	80.00 usec
PL2	-6.00 dB
PL12	16.00 dB
SFO2	400.1420007 MHz

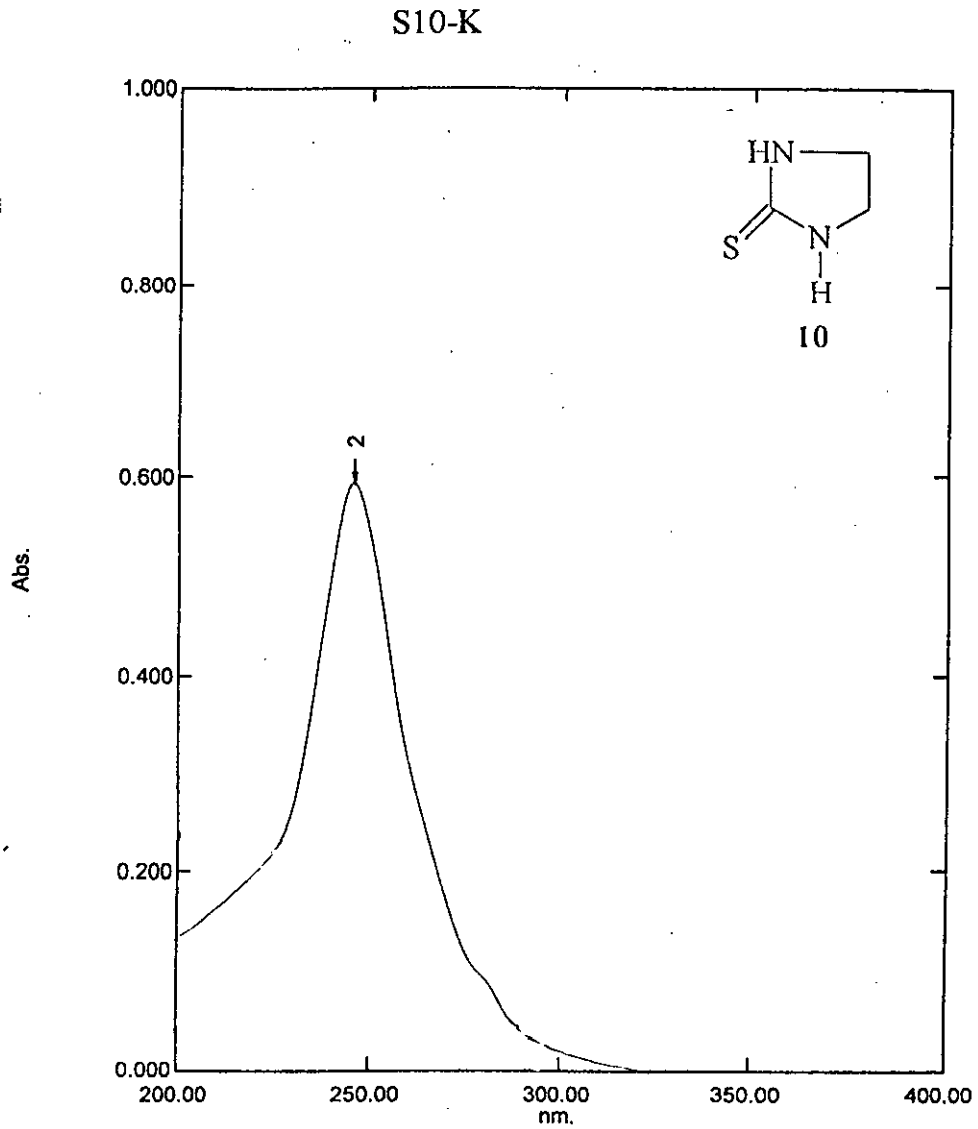
F2 - Processing parameters

SI	32768
SF	100.6152814 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	159.129 ppm
F1	16010.84 Hz
F2P	-9.780 ppm
F2	-984.00 Hz
PPMCM	8.44546 ppm/cm
HZCM	849.74207 Hz/cm

Fig.24a: DEPT ^{13}C NMR Spectrum of Compound **8**



Wavelength	Abs.
245.60	0.593

Fig. 25: UV Spectrum of Compound **10**

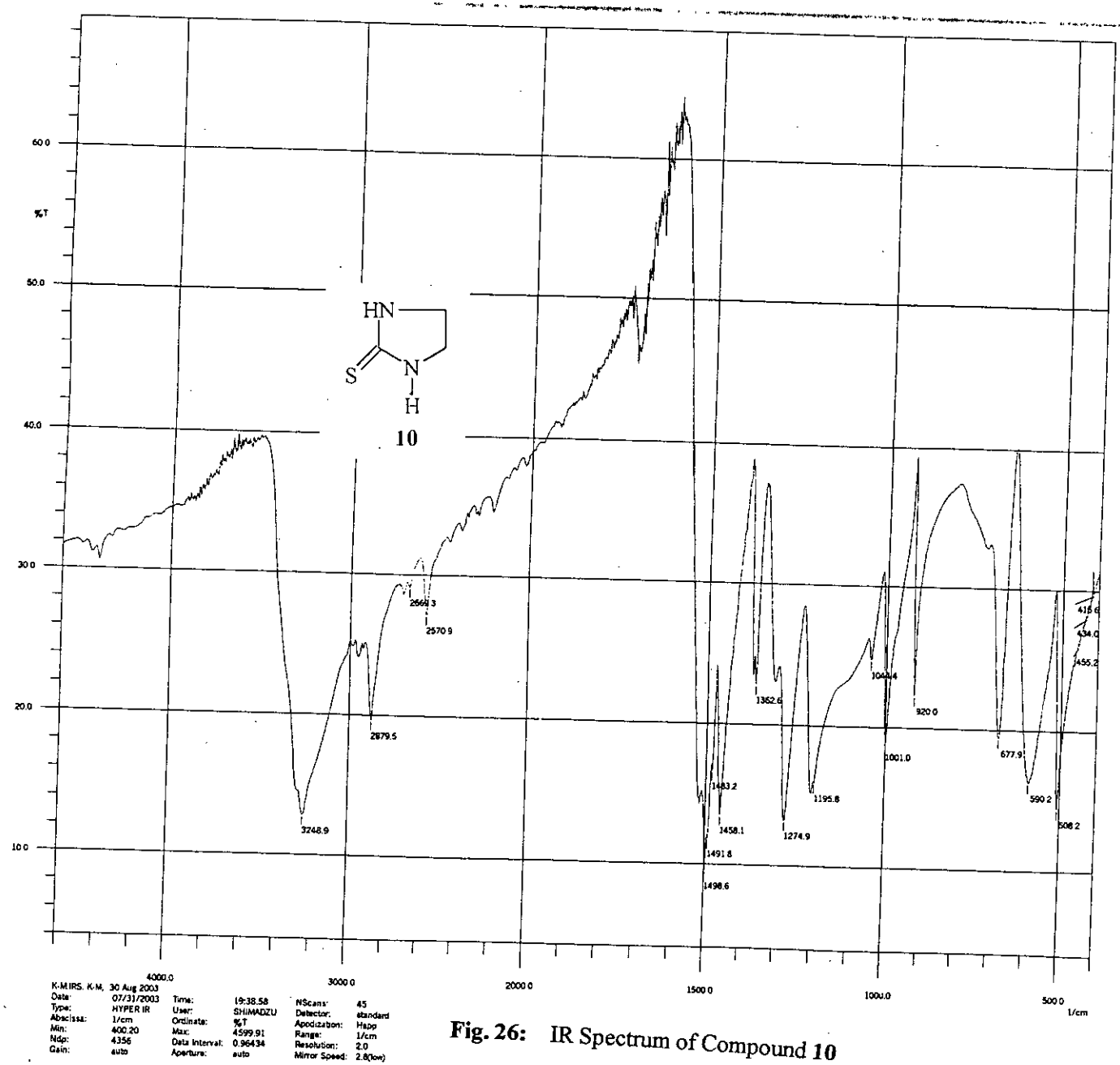


Fig. 26: IR Spectrum of Compound ***10***

Peaktable of K-M.IRS, 20 Peaks
Threshhold: 30, Noise: 2, No Range Selection

No.	Pos. (1/cm)	Inten. (%T)
1	415.6	29.784
2	434.0	28.111
3	455.2	26.075
4	508.2	14.483
5	590.2	16.313
6	677.9	19.460
7	920.0	22.307
8	1001.0	18.987
9	1044.4	24.766
10	1195.8	15.976
11	1274.9	13.234
12	1362.6	22.815
13	1458.1	13.523
14	1483.2	16.660
15	1491.8	11.834
16	1498.6	9.542
17	2570.9	27.149
18	2669.3	29.085
19	2879.5	19.629
20	3248.9	12.819

K-M, 30 Aug 2003

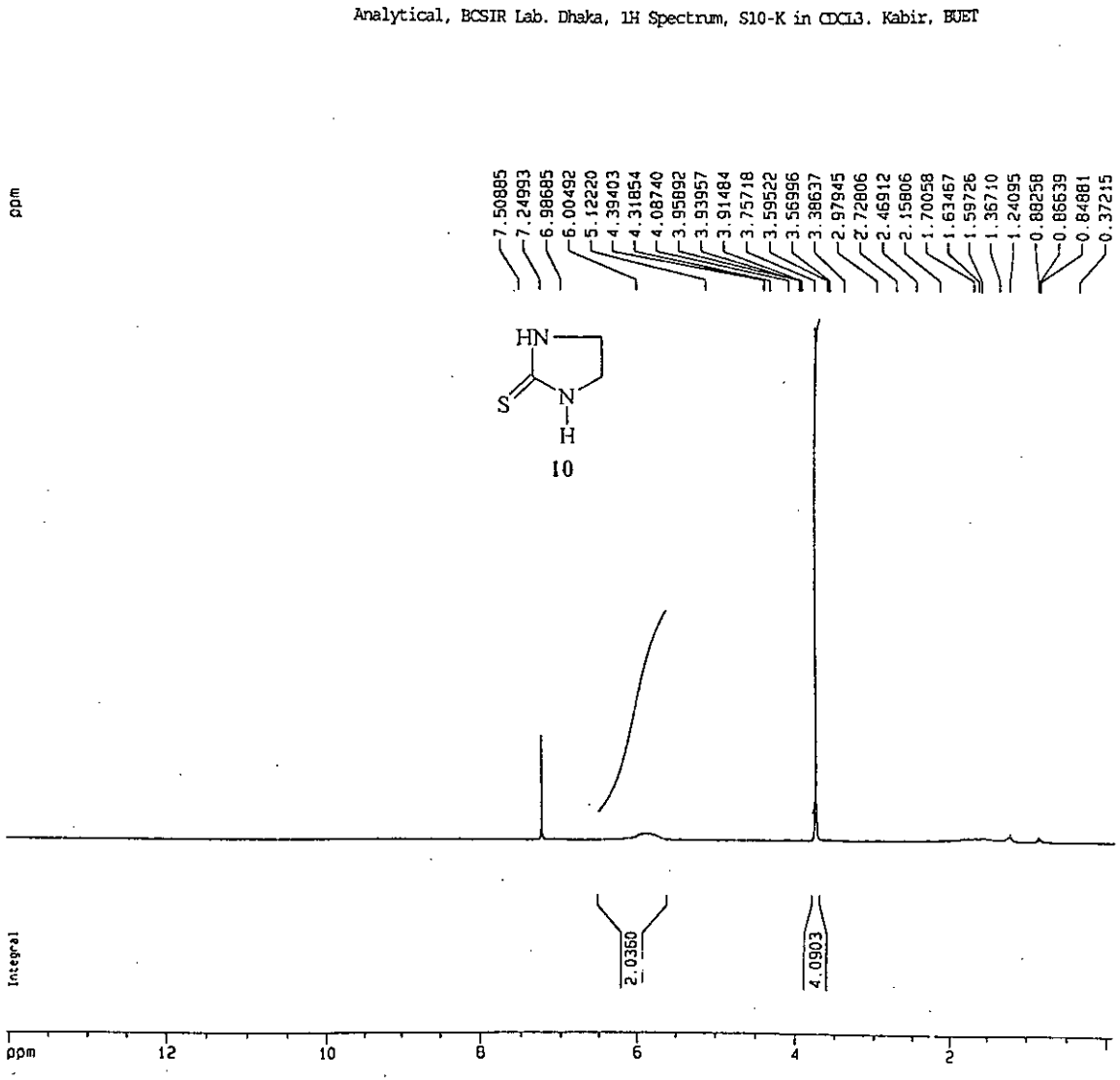
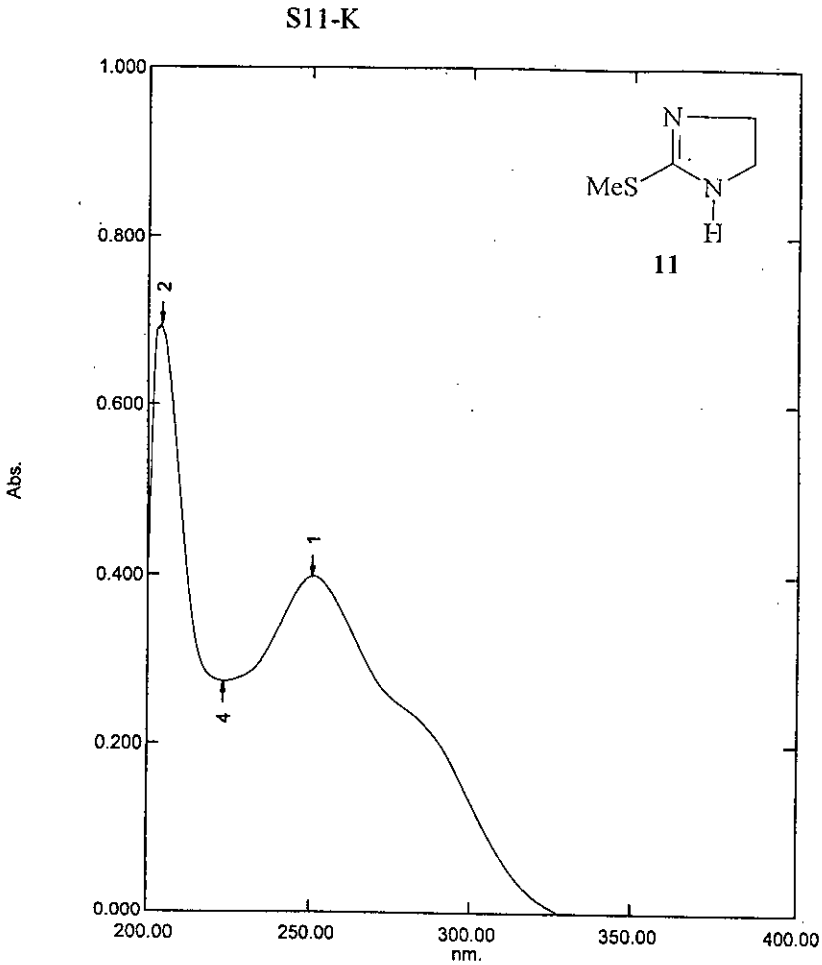


Fig. 27: ^{1}H NMR Spectrum of Compound **10**



Wavelength	Abs.
251	0.398
204	0.695

Fig. 28: UV Spectrum of Compound **11**

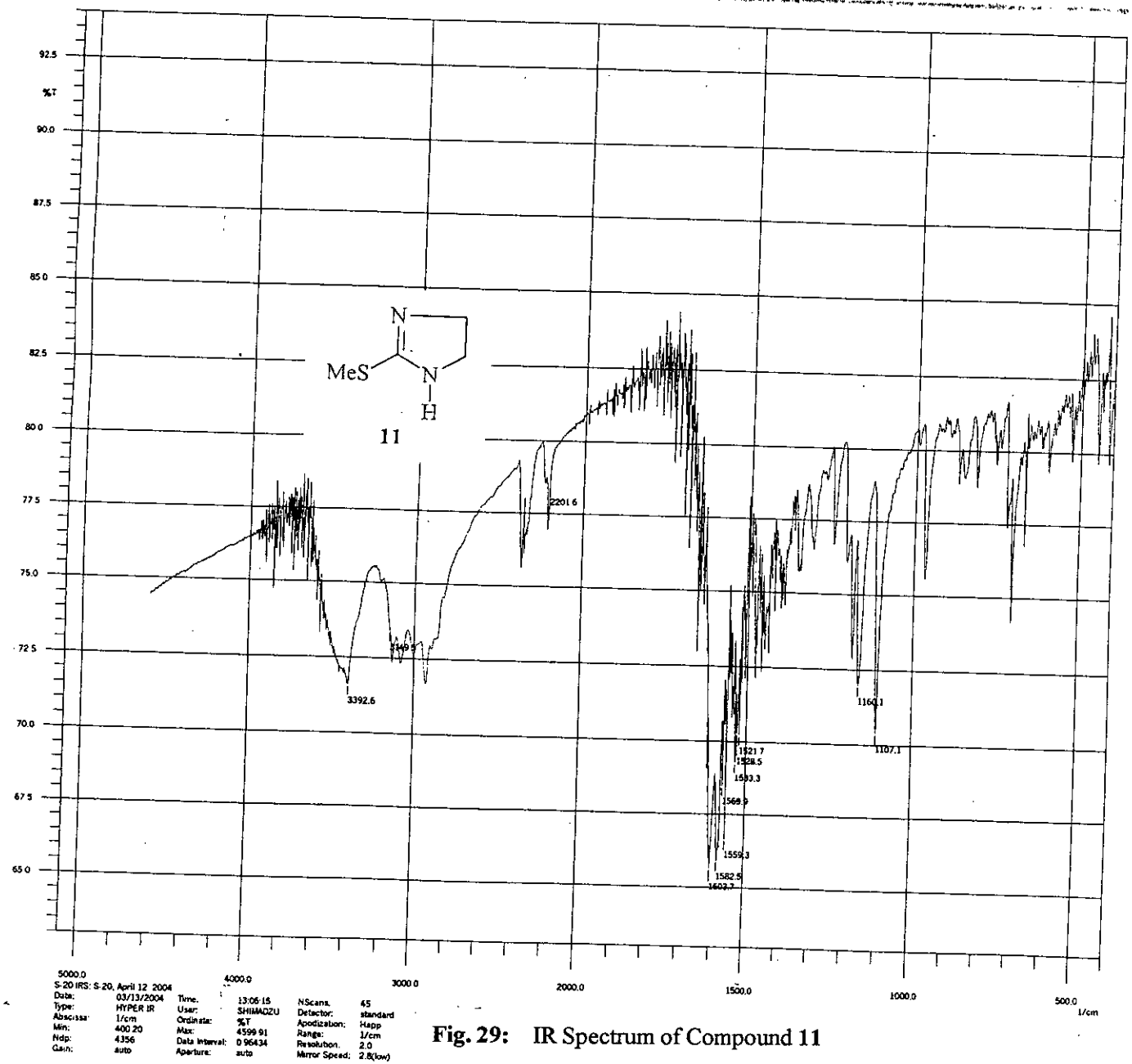
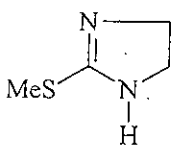


Fig. 29: IR Spectrum of Compound **11**

Peaktable of S-20.IRS, 12 Peaks
Threshhold: 72, Noise: 2, No Range Selection

No.	Pos. (1/cm)	Inten. (%T)
1	1107.1	70.393
2	1160.1	71.969
3	1521.7	70.236
4	1528.5	70.297
5	1533.3	69.310
6	1559.3	66.648
7	1569.9	68.477
8	1582.5	65.918
9	1603.7	65.661
10	2201.6	78.432
11	3149.5	73.382
12	3392.6	71.599

S-20, April 12, 2004



11

^{1}H NMR Spectrum of Compound **11**

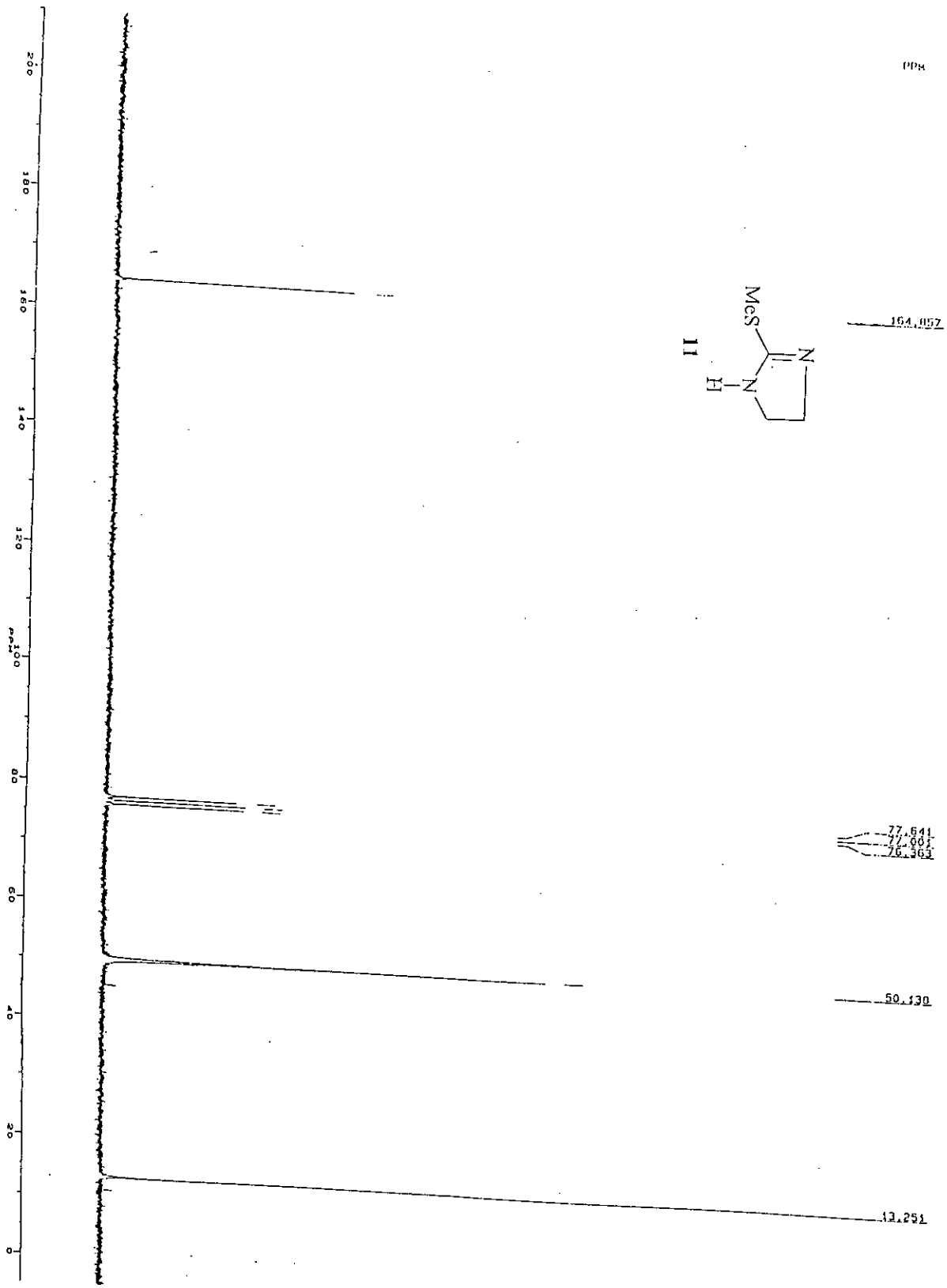
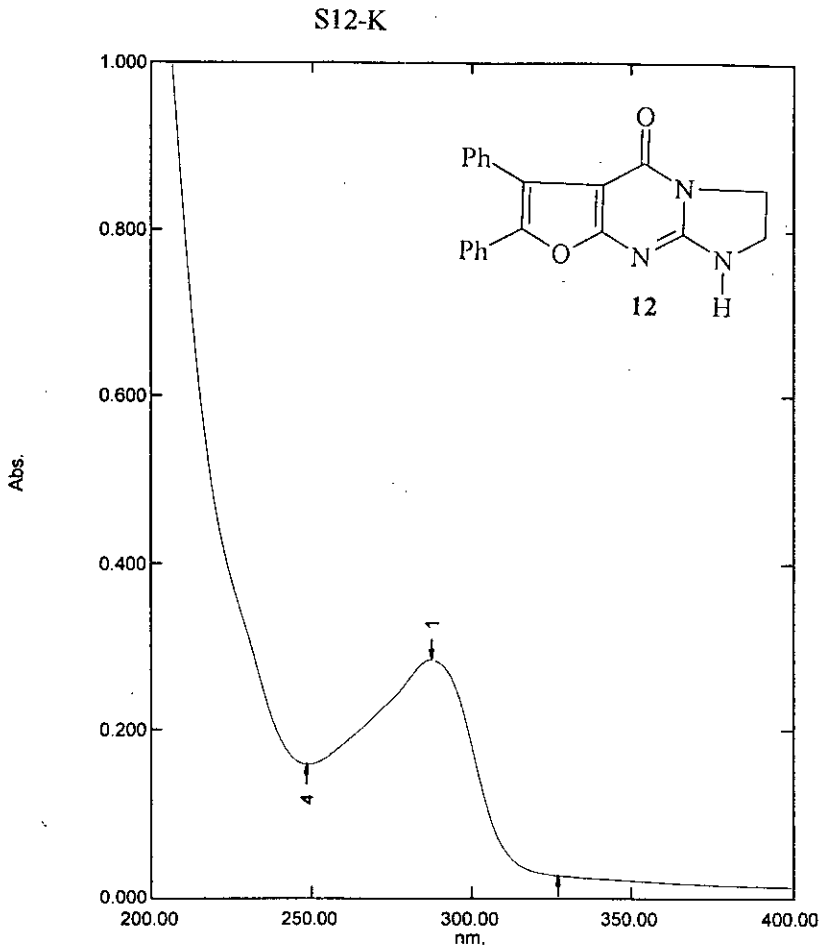
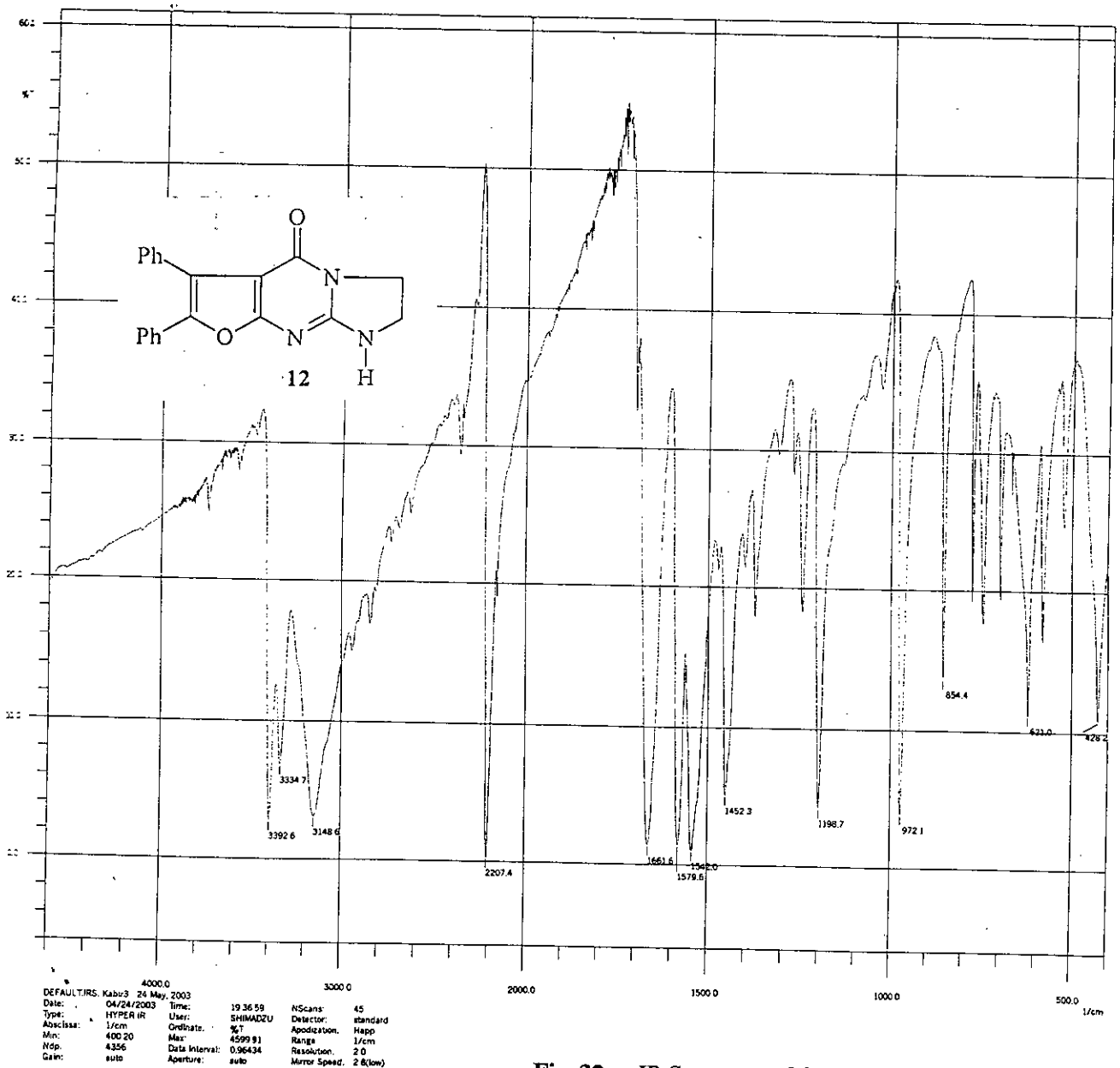


Fig. 30a : ^{13}C NMR Spectrum of Compound **11**



Wavelength	Abs.
288.00	0.285

Fig. 31: UV Spectrum of Compound **12**



Peaktable of DEFAULT.IRS, 13 Peaks
Threshhold: 15, Noise: 2, No Range Selection

No.	Pos. (1/cm)	Inten. (%T)
1	428.2	10.891
2	621.0	11.231
3	854.4	13.750
4	972.1	3.912
5	1198.7	4.272
6	1452.3	5.080
7	1542.0	1.057
8	1579.6	1.461
9	1661.6	1.405
10	2207.4	0.327
11	3148.6	3.107
12	3334.7	6.851
13	3392.6	2.783

Kabir3 24 May, 2003

Fig. 32: IR Spectrum of Compound **12**

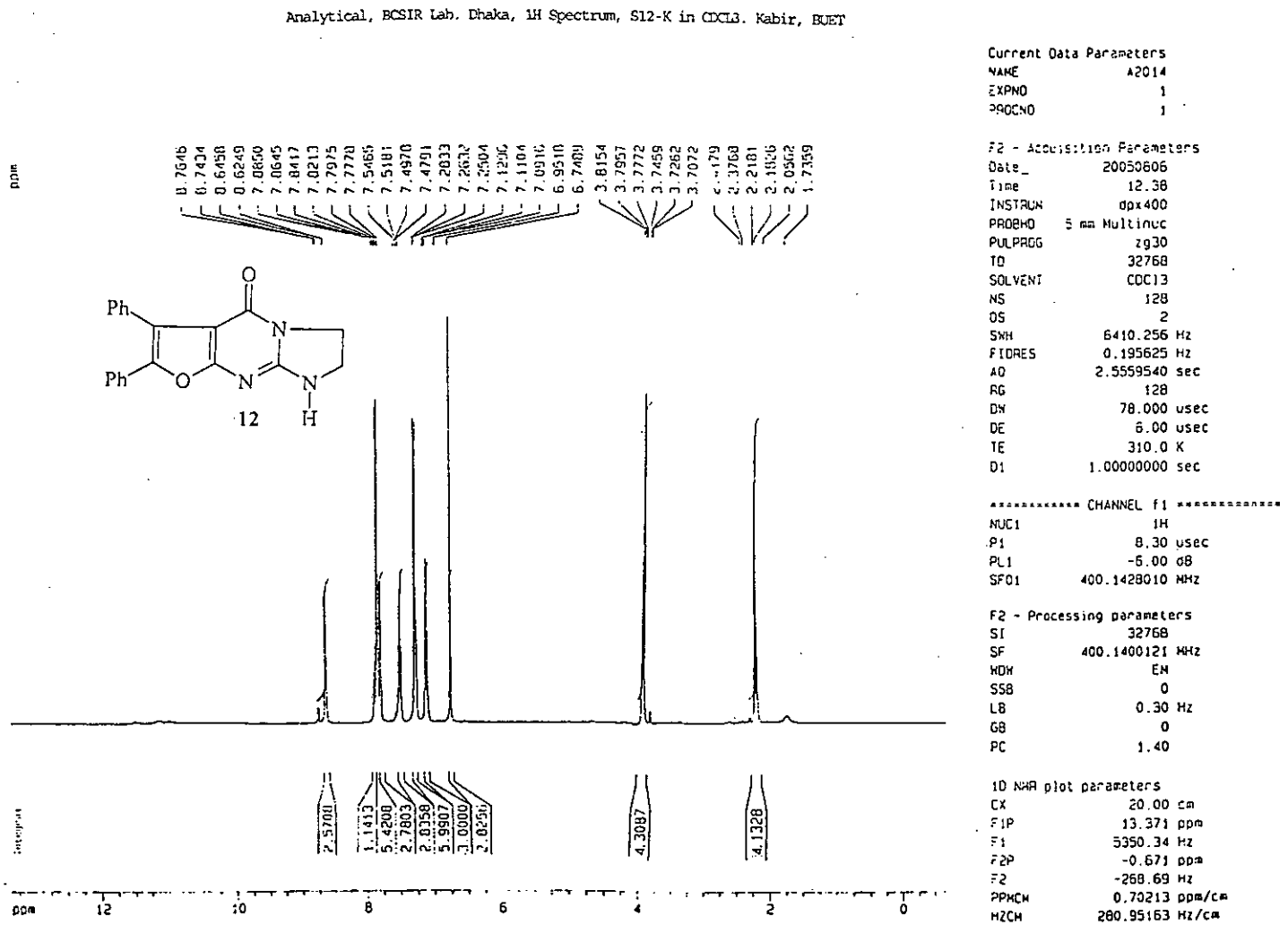
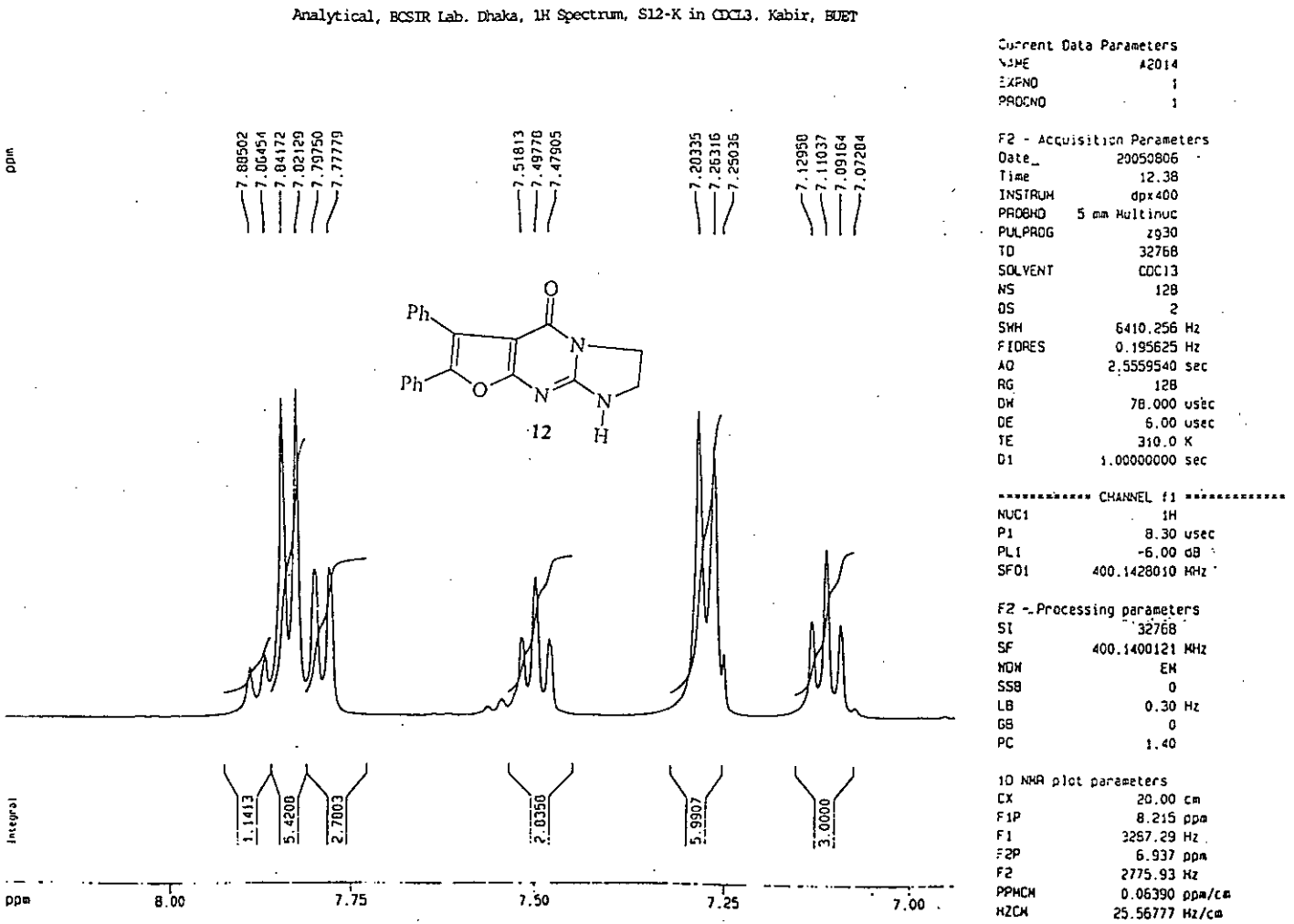


Fig. 33: ^{1}H NMR Spectrum of Compound **12**



Current Data Parameters

NAME	A2014
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20050806
Time	12.38
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	128
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428010 MHz

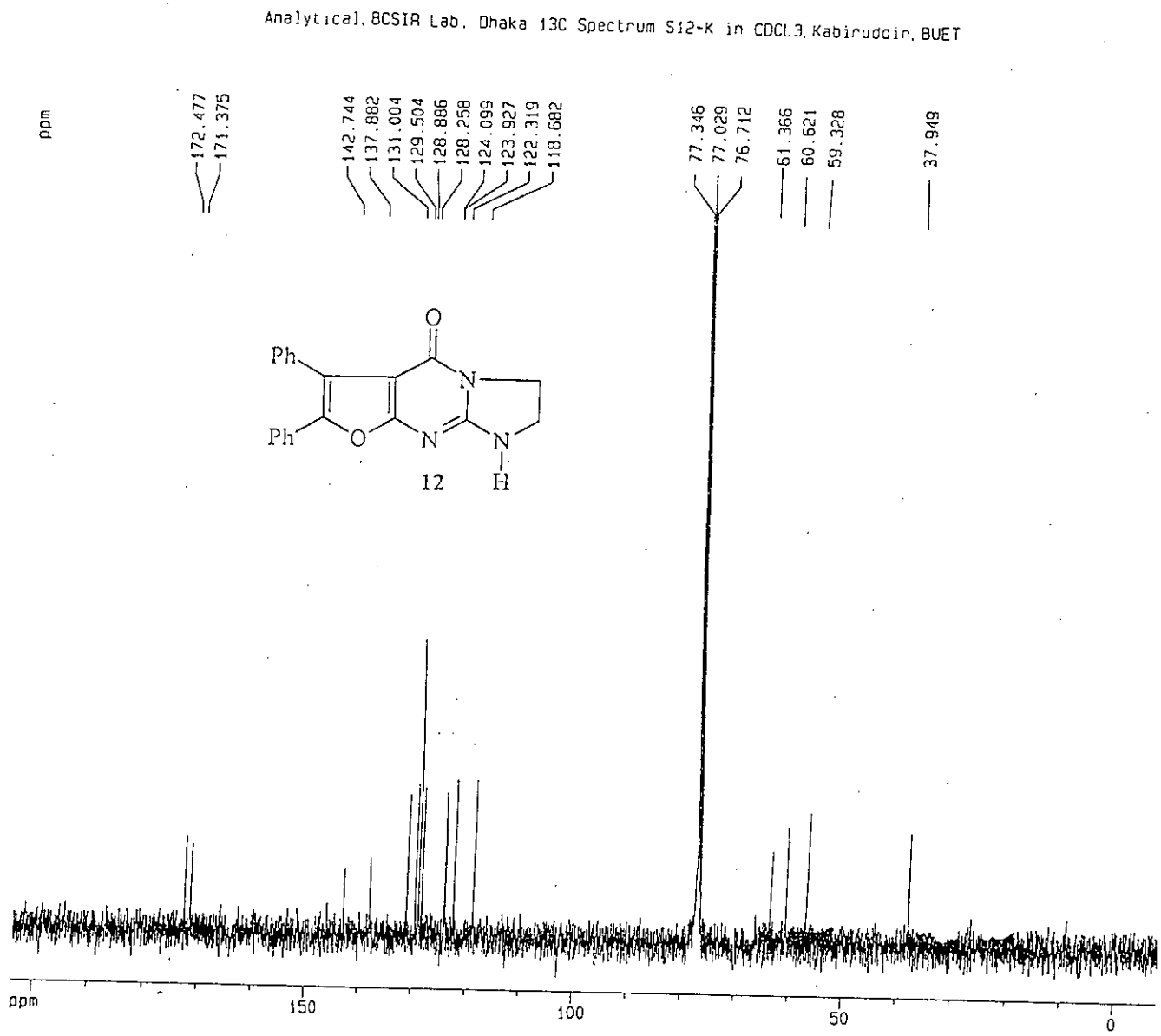
F2 - Processing parameters

SI	32768
SF	400.1400121 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	8.215 ppm
F1	3287.29 Hz
F2P	6.937 ppm
F2	2775.93 Hz
PPMCM	0.06390 ppm/cm
HZCM	25.56777 Hz/cm

Fig. 34: ^{1}H NMR Spectrum of Compound **12** (Expansion)



Current Data Parameters

NAME	A3155
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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Time	12.34
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	369
DS	2
SWH	24154.590 Hz
FIDRES	0.737140 Hz
AQ	0.6783476 sec
RG	16384
DW	20.700 usec
DE	6.00 usec
TE	300.0 K
D1	1.50000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

========== CHANNEL f1 ==========

NUC1	13C
P1	8.30 usec
PL1	-6.00 dB
SFO1	100.6253045 MHz

========== CHANNEL f2 ==========

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-6.00 dB
PL12	16.00 dB
PL13	120.00 dB
SFO2	400.1400000 MHz

F2 - Processing parameters

SI	32768
SF	100.6152823 MHz
WDW	EM
SSB	0
LB	2.50 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	203.943 ppm
F1	20519.82 Hz
F2P	-8.016 ppm
F2	-806.54 Hz
PPMCM	10.59797 ppm/cm
HZCM	1066.31799 Hz/cm

Fig.34a: ^{13}C NMR Spectrum of Compound 12

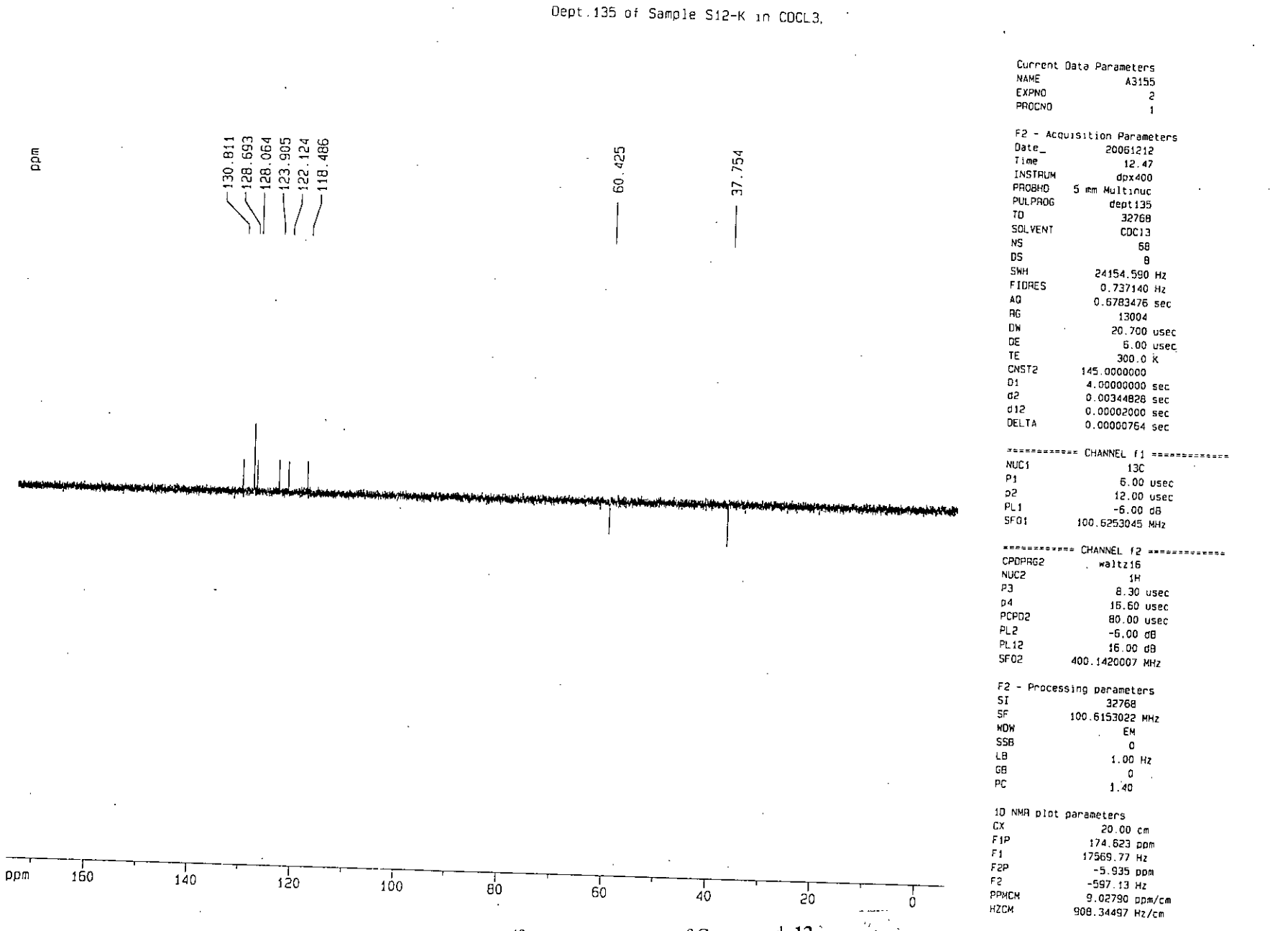
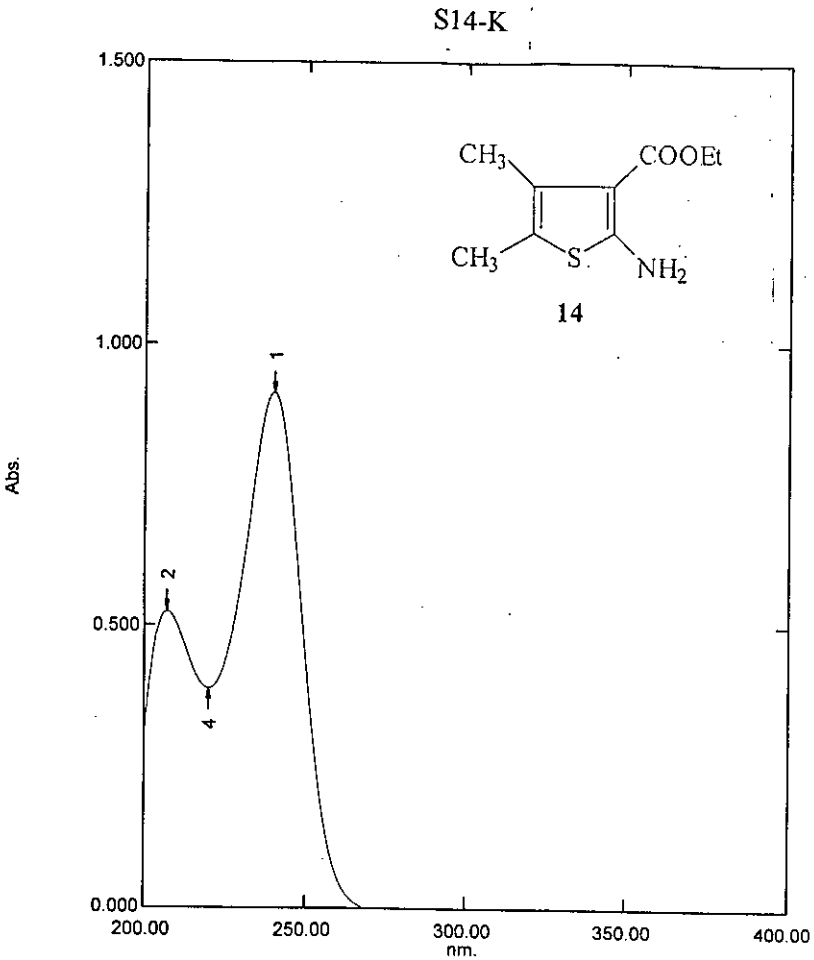


Fig.34a: DEPT ^{13}C NMR Spectrum of Compound **12**



Wavelength	Abs.
240	0.913
207	0.525

Fig. 35: UV Spectrum of Compound **14**

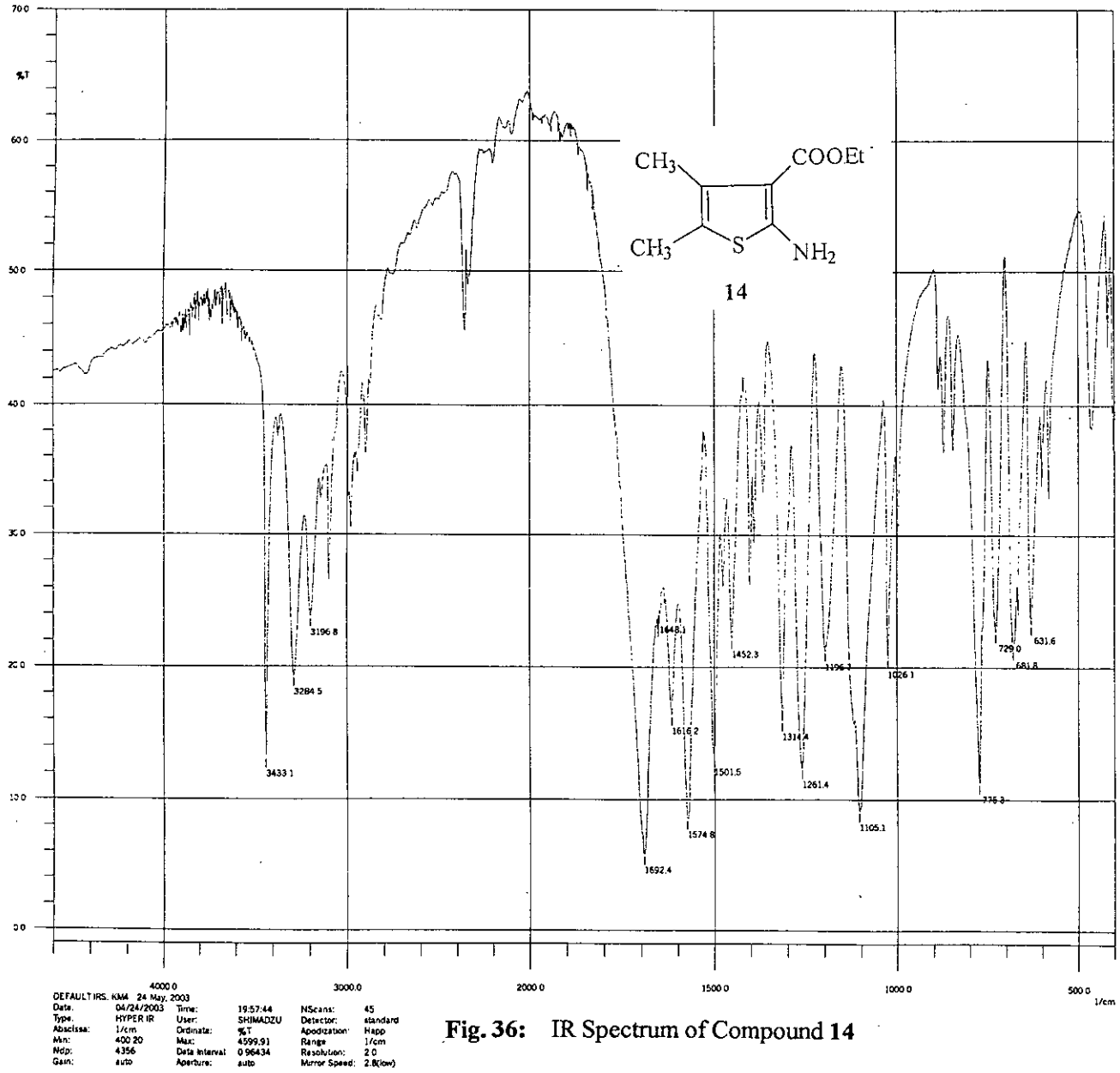
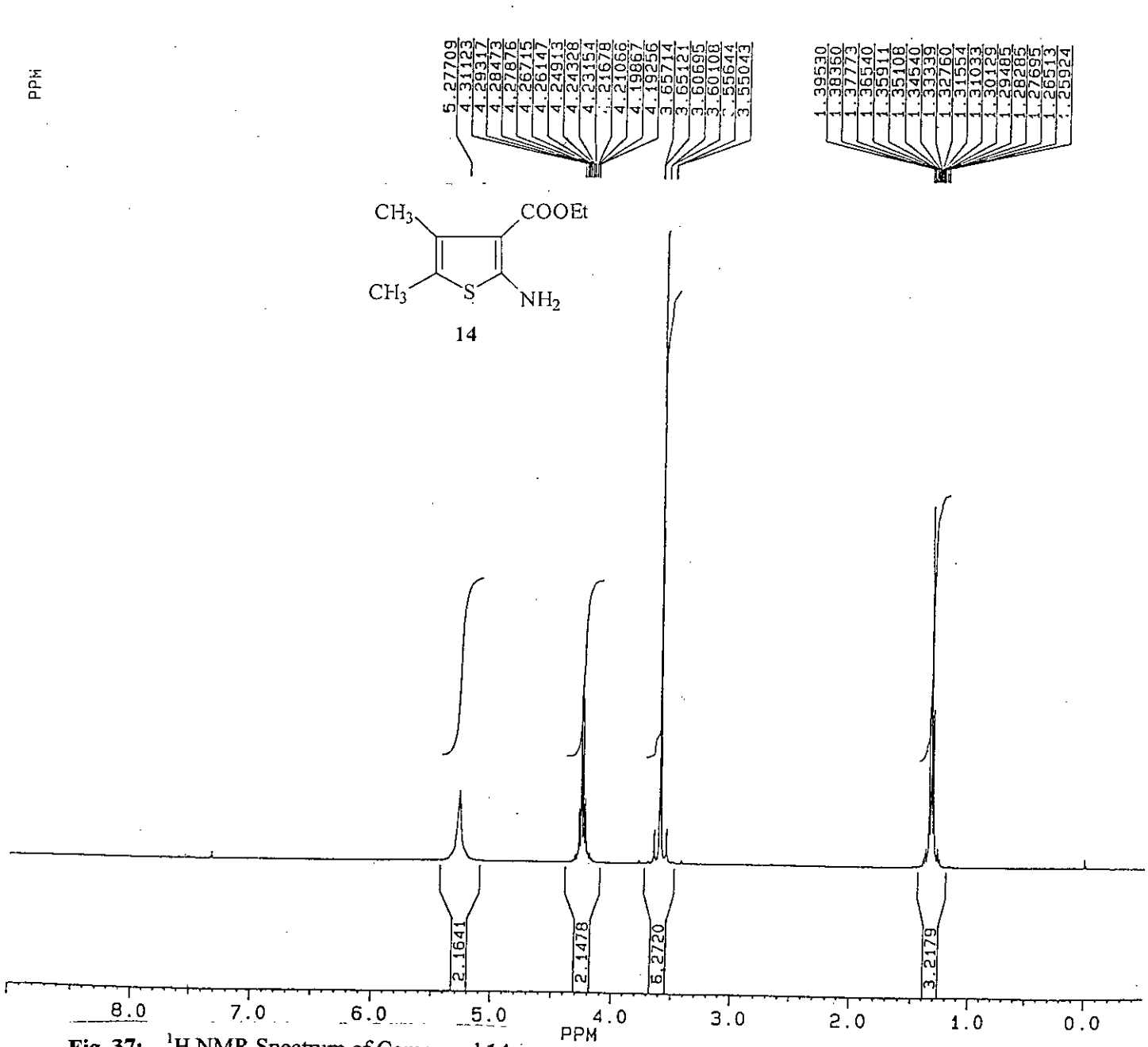


Fig. 36: IR Spectrum of Compound **14**

Peaktable of DEFAULT.IRS, 18 Peaks
Threshhold: 25, Noise: 2, No Range Selection

No.	Pos. (1/cm)	Inten. (%T)
1	631.6	23.332
2	681.8	21.427
3	729.0	22.739
4	775.3	11.247
5	1026.1	20.694
6	1105.1	9.134
7	1196.7	21.260
8	1261.4	12.371
9	1314.4	15.944
10	1452.3	22.190
11	1501.5	13.284
12	1574.8	8.576
13	1616.2	16.387
14	1648.1	24.081
15	1692.4	5.843
16	3196.8	23.794
17	3284.5	19.298
18	3433.1	13.132

KM4 24 May, 2003



KSMDKHAN.001
DATE 14-1-4

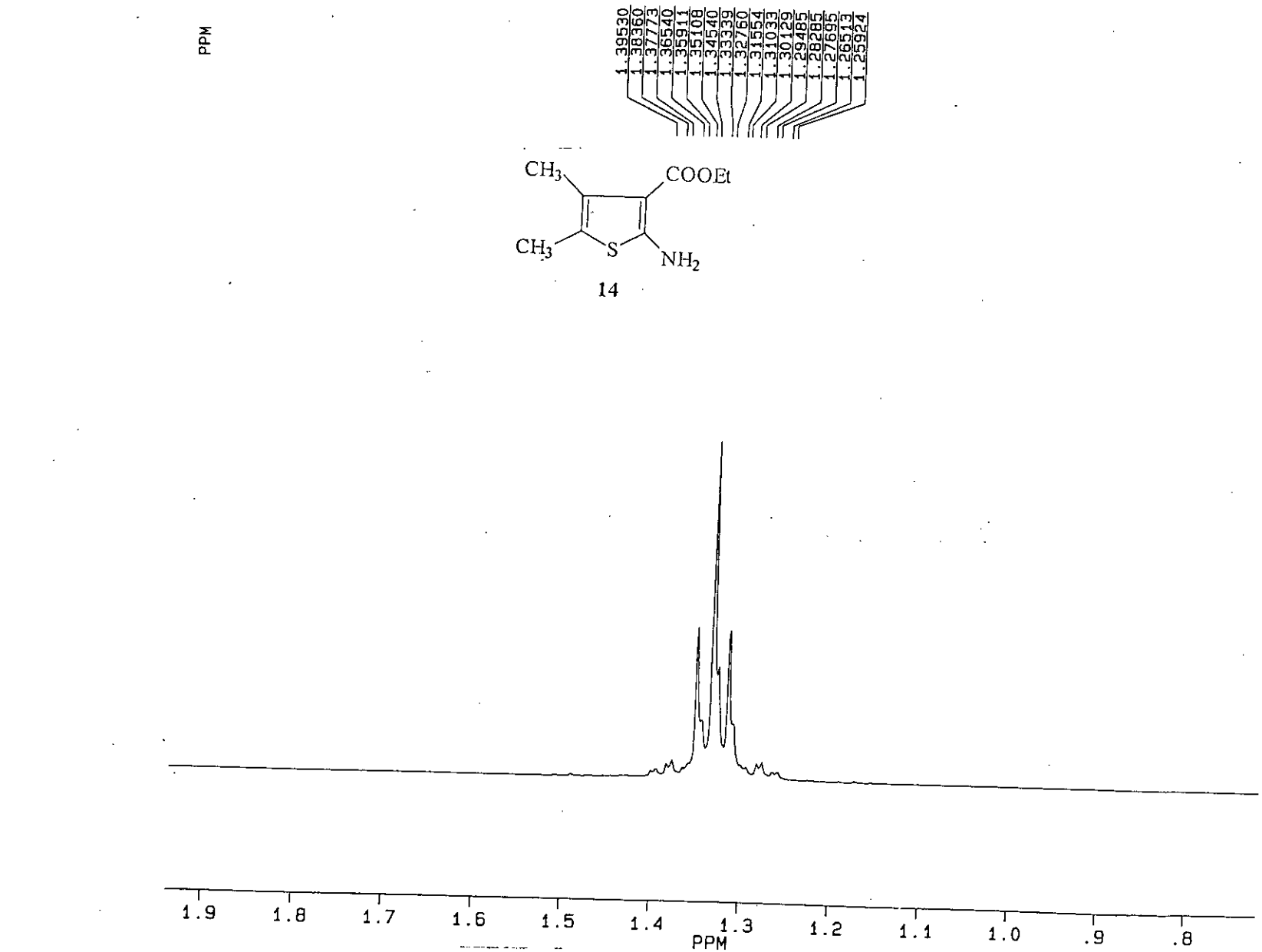
SF 400.134
SY 230.0
O1 6395.963
SI 32768
TD 32768
SW 8064.516
HZ/PT .492

PW 6.2
RD 2.000
AQ 2.032
RG 2
NS 8
TE 297

FW 10100
O2 20.000
DP 63L PO

LB .200
GB 0.0
CX 22.00
CY 12.00
F1 9.001P
F2 -.498P
HZ/CM 172.769
PPM/CM .432
SR 4363.59

Fig. 37: ^{1}H NMR Spectrum of Compound **14**



14

Fig. 38: ^{1}H NMR Spectrum of Compound **14** (Expansion)

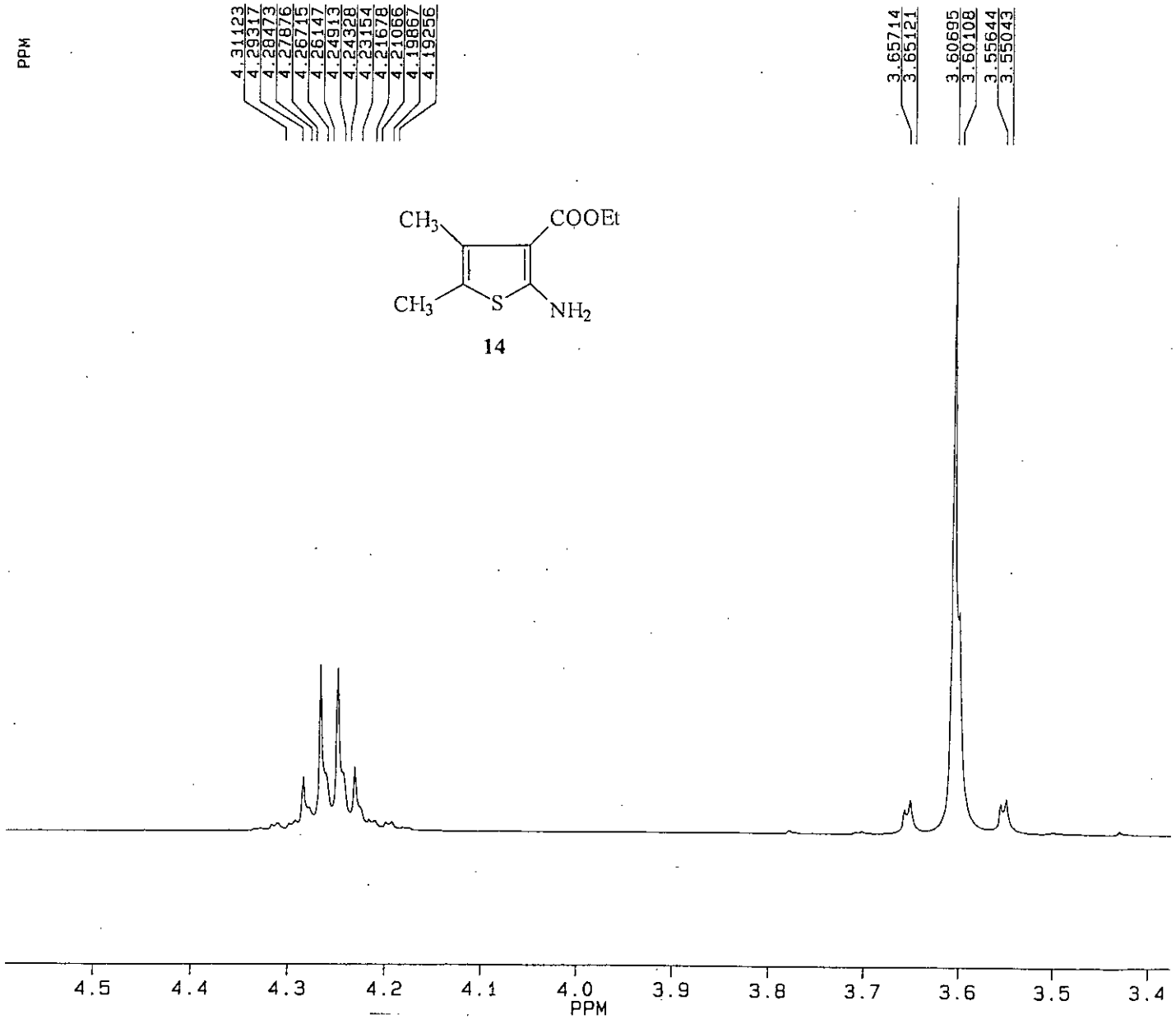
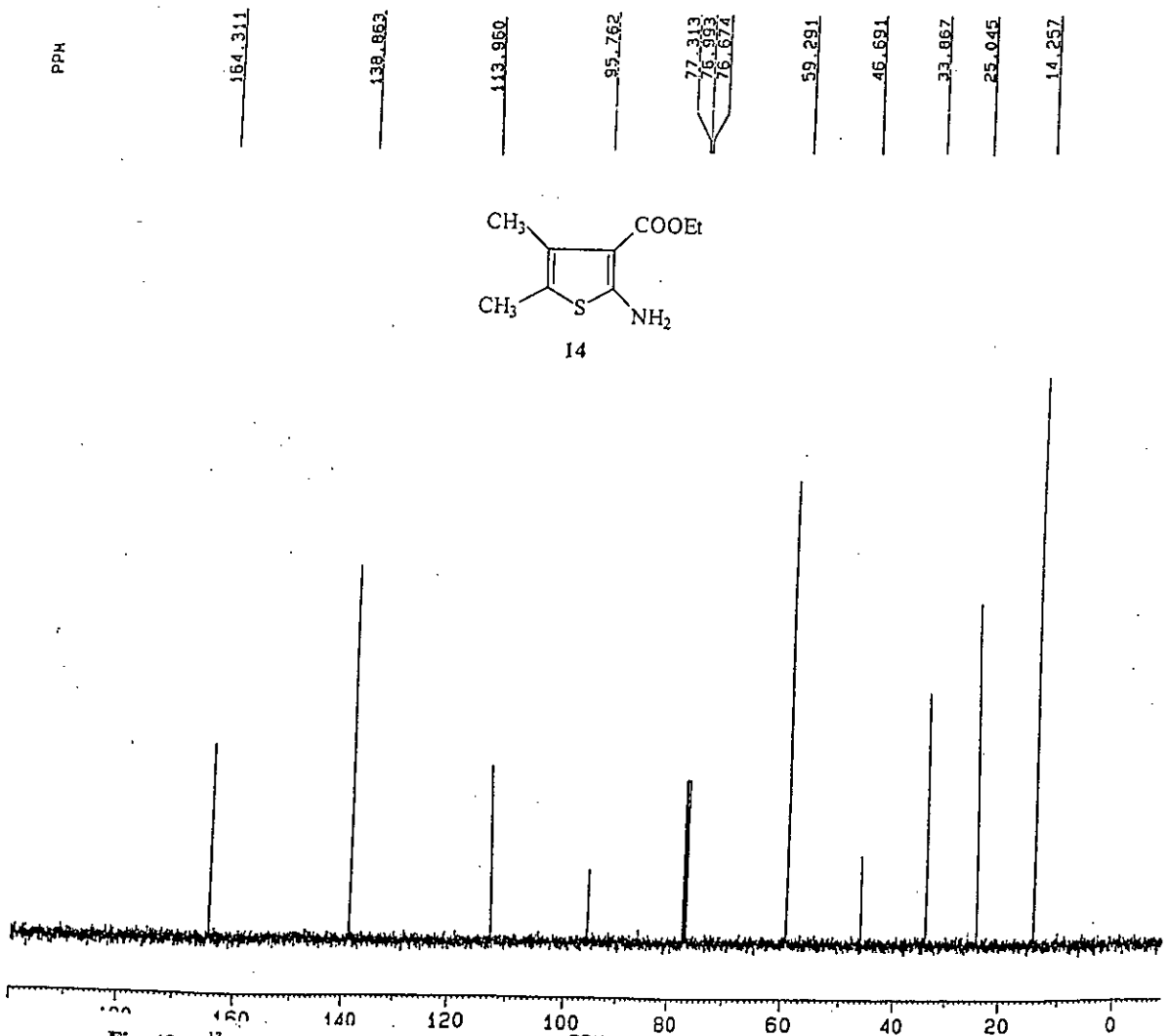


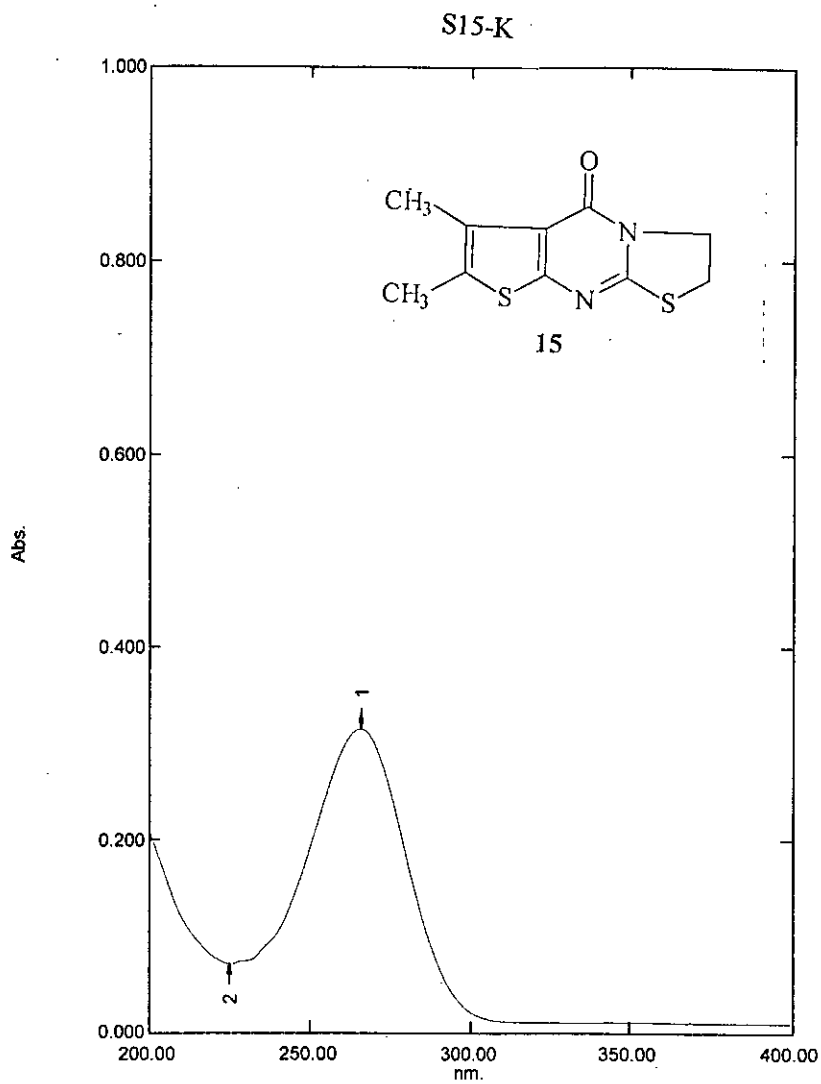
Fig. 39: ^{1}H NMR Spectrum of Compound **14** (Expansion)



KSMDKHAN.001.
DATE 14-1-4

SF	100.614
SY	100.0
O1	8938.338
SI	32768
TD	32768
SW	23809.524
HZ/PT	1.453
PW	2.0
RD	1.000
AQ	.688
RG	320
NS	132
TE	297
FW	29800
O2	6400.000
DP	19H CPD
LB	.200
GB	0.0
CX	22.00
CY	12.00
F1	200.015P
F2	-9.979P
HZ/CM	960.379
PPM/CM	9.545
SR	-109.56

Fig. 40: ^{13}C NMR Spectrum of Compound **14**



Wavelength	Abs.
265	0.315

Fig. 41: UV Spectrum of Compound **15**

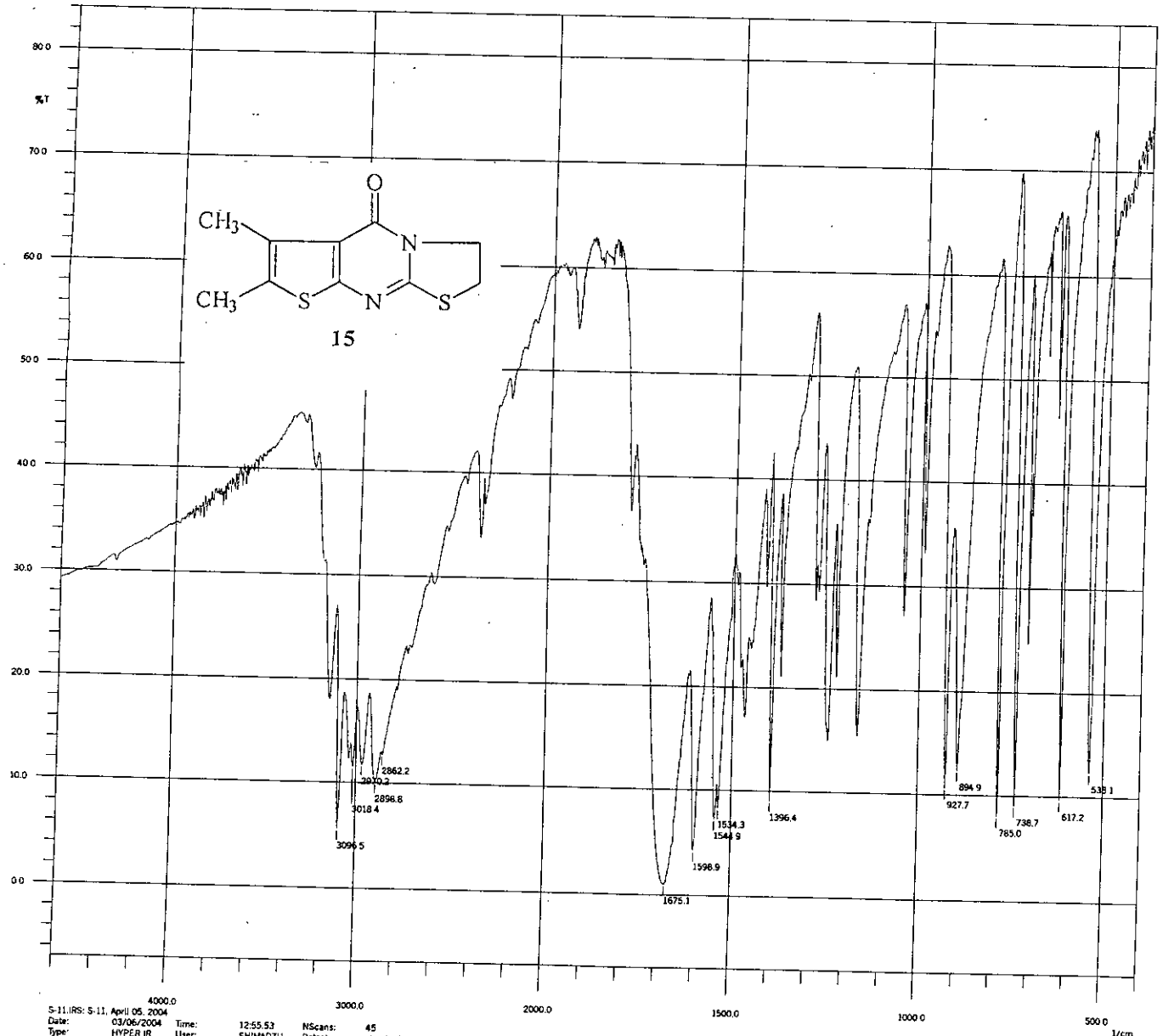


Fig. 42: IR Spectrum of Compound **15**

Peaktable of S-11.IRS, 16 Peaks
Threshhold: 15, Noise: 2, No Range Selection

No.	Pos. (1/cm)	Inten. (%T)
1	538.1	12.326
2	617.2	9.616
3	738.7	9.059
4	785.0	8.015
5	894.9	12.296
6	927.7	10.590
7	1396.4	9.065
8	1534.3	8.301
9	1544.9	7.237
10	1598.9	4.262
11	1675.1	1.020
12	2862.2	12.688
13	2898.8	10.043
14	2970.2	11.731
15	3018.4	11.502
16	3096.5	5.578

S-11, April 05. 2004

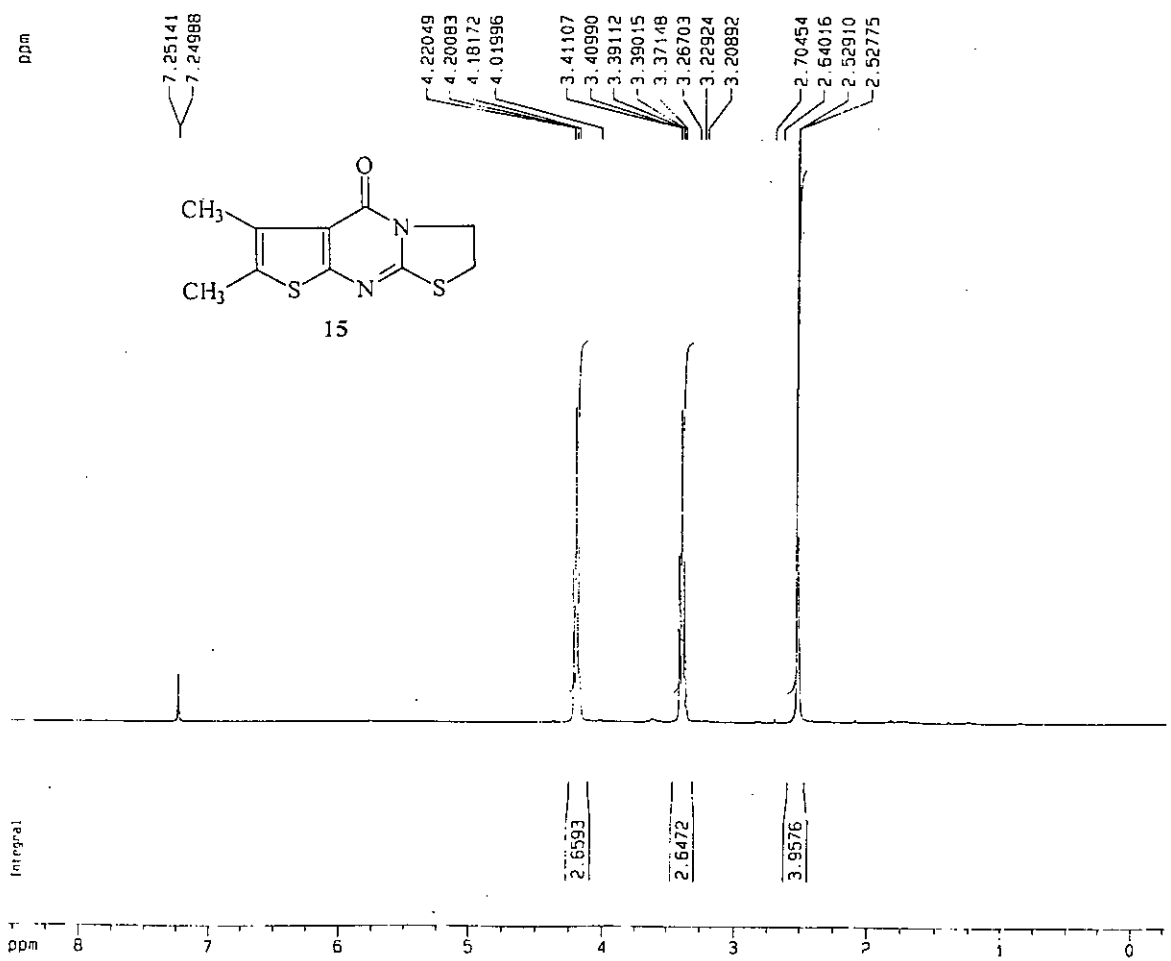


Fig. 43: ^{1}H NMR Spectrum of Compound **15**

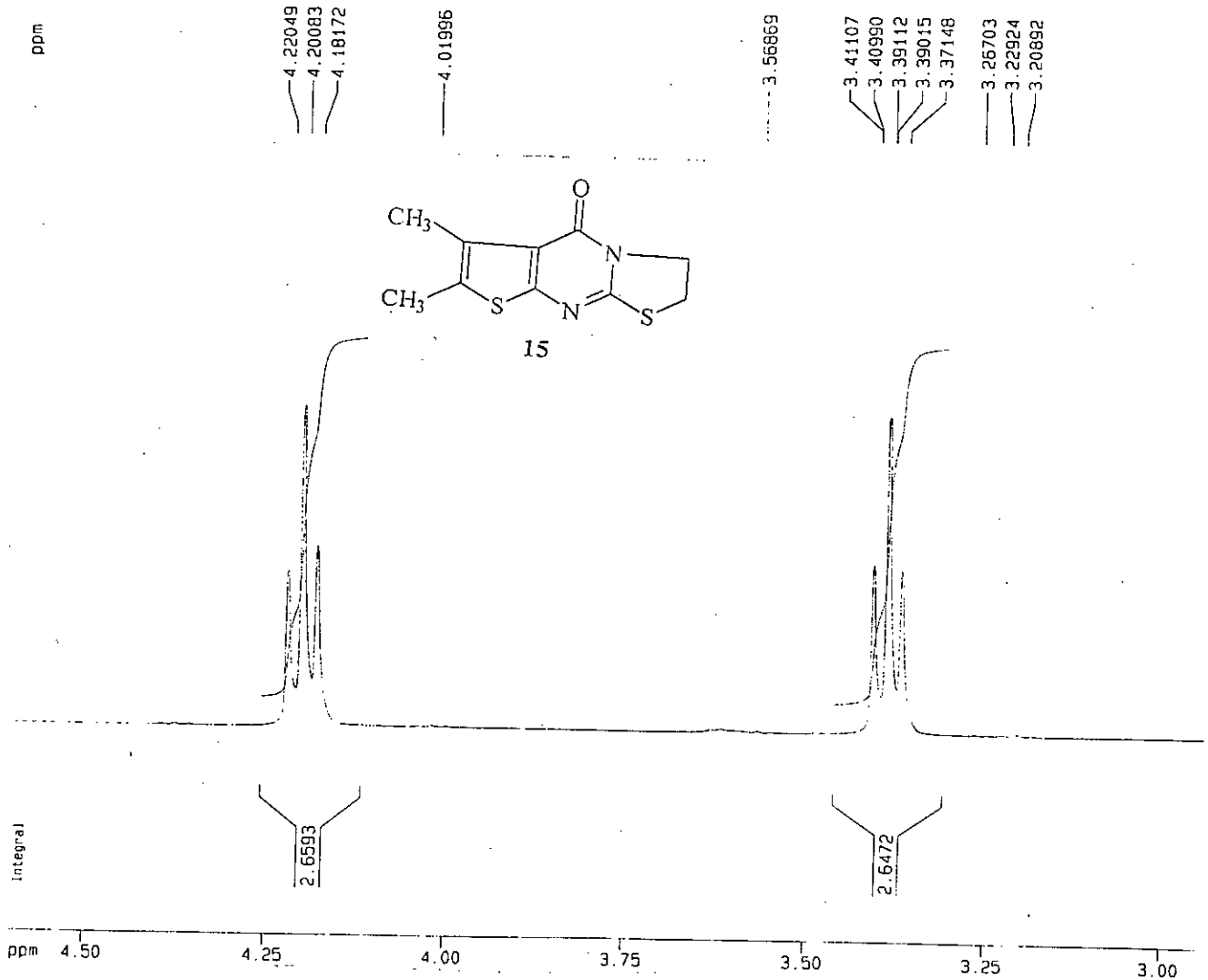
```
Current Data Parameters
NAME                  A1814
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20050517
Time                  13.52
INSTRUM               dpx400
PROBHD     5 mm Multinuc
PULPROG                zg30
TD                    32768
SOLVENT               CDCl3
NS                      128
DS                        2
SWH                6410.256 Hz
FIDRES             0.195625 Hz
AQ                 2.5559540 sec
RG                     287.4
DW                    78.000 usec
DE                     6.00 usec
TE                    310.0 K
D1                 1.00000000 sec

========== CHANNEL f1 ==========
NUC1                      1H
P1                     8.30 usec
PL1                   -6.00 dB
SFO1             400.1428010 MHz

F2 - Processing parameters
SI                    32768
SF               400.1400126 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.40

1D NMR plot parameters
CX                    20.00 cm
F1P                   8.529 ppm
F1                 3412.89 Hz
F2P                  -0.270 ppm
F2                 -107.95 Hz
PPMCM              0.43995 ppm/cm
HZCM             176.04182 Hz/cm
```



Current Data Parameters

NAME	A1814
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20050517
Time	13.52
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	128
DS	2
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	287.4
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428010 MHz

F2 - Processing parameters

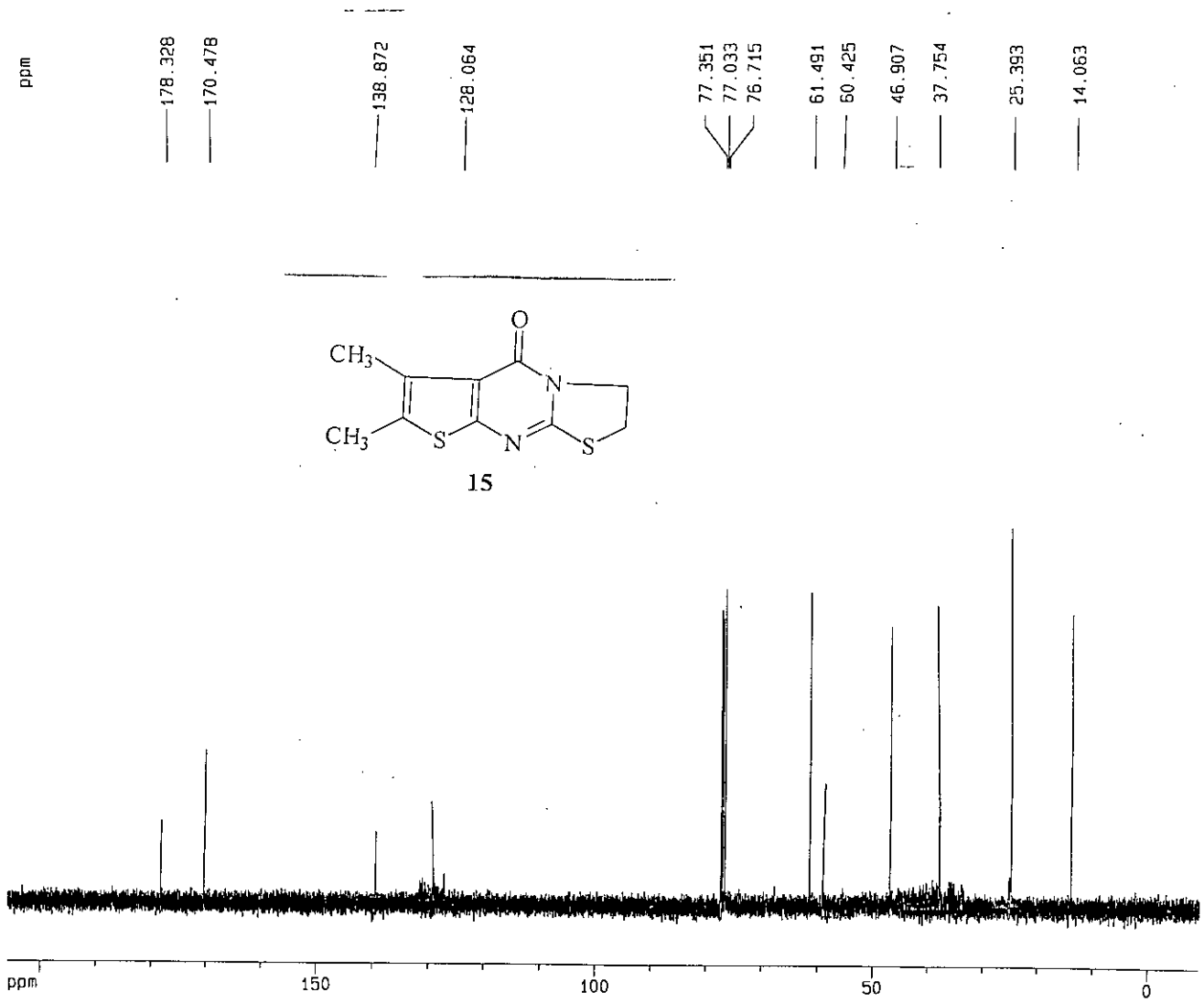
SI	32768
SF	400.1400186 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	4.601 ppm
F1	1840.95 Hz
F2P	2.943 ppm
F2	1177.50 Hz
PPMCM	0.08290 ppm/cm
HZCM	33.17276 Hz/cm

Fig. 44: ^{1}H NMR Spectrum of Compound **15** (Expansion)

Analytical, BCSIR Lab. Dhaka 13C Spwctrum S15-K in CCL3, Kabiruddin, BUET.



Current Data Parameters

NAME	A3154
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20061212
Time	12.17
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zgpg30
TD	32768
SOLVENT	CDCl3
NS	185
DS	2
SWH	24154.590 Hz
FIDRES	0.737140 Hz
AQ	0.6783476 sec
RG	16384
DW	20.700 usec
DE	6.00 usec
TE	300.0 K
D1	1.50000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

========== CHANNEL f1 ==========

NUC1	13C
P1	8.30 usec
PL1	-6.00 dB
SFO1	100.6253045 MHz

========== CHANNEL f2 ==========

CPDPRG2	waltz16
NUC2	1H
PCPD2	80.00 usec
PL2	-6.00 dB
PL12	16.00 dB
PL13	120.00 dB
SFO2	400.1400000 MHz

F2 - Processing parameters

SI	32768
SF	100.6152896 MHz
WDW	no
SSB	0
LB	0.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	205.896 ppm
F1	20716.29 Hz
F2P	-9.355 ppm
F2	-941.30 Hz
PPMCM	10.76258 ppm/cm
HZCM	1082.87976 Hz/cm

Section-3

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Part-2

Section-1

SYNTHESIS OF SOME NEW ANNELATED FUSED HETEROCYCLIC DERIVATIVES OF BIOLOGICAL IMPORTANCE

Introduction

Human struggle against the affliction disease, decay and death in eternal. The deterioration of human population due to an enhanced prevalence of infections diseases is becoming a global problem.[1] The contemporary treatment of infection disease involves administration of a multi drug resistant strains plus a high level of patient noncompliance.[1] From the time immemorial when the men needed medicine, most probably when the men realized about the cause of disease, they have been tried to discover any preventive agent against disease, from that time. It is universal truth that disease, decay and death have always co-existed with human life. The study of disease and their treatment must also have been come together with human intellect, when the man, occupied sufficient knowledge of chemistry to able to synthesize compounds.

Bangladesh is predominantly an agricultural country, depending mainly on crop plants, agricultural and forest products for its economic development. Although crops play a vital role in the economy of the country and agricultural conditions are favourable for the production of various crops, the yield of crops is often poor. Among the various factors responsible for poor yield of crops, plant diseases caused by various micro-organisms play a significant role. Gradually men occupied sufficient knowledge of chemistry to inhibit or to kill the micro-organisms i.e. only inhibit the microbial growth are called 'statis'. But the chemicals, which have the ability to kill the micro-organisms, are called 'cidal'. But some chemicals are called "pesticides" on the basis of kinds of pathogenic microorganisms. Pesticides may be different types, e.g. fungicides, bactericides, viricides etc.

The word bactericide and fungicide have originated from latin words: bacteria, fungus and caedo. The word caedo means "to kill". Thus literally speaking a bactericide and fungicide would be any agency, which have the ability to kill a bacteria or fungus. By common usage, the word is restricted to chemicals. Hence the words bactericide and fungicide would mean a chemical capable of killing bacteria and fungus respectively.

It is not enough that a chemical has high bacterial and antifungal activity. Such as, chemicals may have no utility unless it stands out in the tests and gives proof of significant control of diseases under varied field conditions. There are several factors, which influence the performance of a bactericide and fungicide under different field conditions. They may be either physical or chemical in nature.

A good pesticide should be toxic to the parasite or inhibit the germination of its spores without causing phytotoxicity. A number of chemicals are used to control the microbial pathogen of human and other animals as medicine. The number of chemicals available for plant disease control runs into hundreds, although all are not equally safe, effective and popular. Also different types of organic, aromatic, inorganic and heterocyclic compounds are employed as antibacterial agents. Salts of toxic metals and organic acids, organic compounds of mercury and sulfur, quinones and heterocyclic nitrogen compounds are the major fungicides in used today.

The organic compounds of sulfur are highly effective and popular fungicides in used today. All these compounds are derivatives of dithiocarbamic acid, thiram, ziram ferban, nabam, zineb and maneb are well known examples of sulfur fungicides. Many aromatic compounds have significant antimicrobial activity and have been developed into fungicides. Some of these are in commercial use. Example of these type of fungicides are Dexon (dimethylamino benzenediazo sodium sulphonate), Diconil (tetrachloro isohpthaloutrile) etc. Heterocyclic nitrogen compound used as fungicides included glyodin (2-hepto-decay-2-imidazolin acetate), oxine (8-hydroxy quinoline) etc.

It was found from the literature that nitrogen and sulfur containing heterocyclic compounds showed marked microbial activities.[2-6] When heterocyclic part like imidazoles, nitroimidazole etc. become attached to carbohydrates,[7] their efficiency to inhibit bacteria or fungus sharply increased. It was also found that a large number of biologically active compounds possess aromatic and heteroaromatic nucleus. If an active nucleus is linked to another nucleus, the resulting molecule may possess greater potential for biological activity.[8] The benzene and substituted benzene nuclei play an important role as common denominator for various biological activities. It was observed that many

a time the combination of two or more nuclei enhances the biological profile many fold than its parent nuclei.

In vitro antimicrobial activities of fused pyrimidines were successfully evaluated in our laboratory.[9] it was found that the fused pyrimidine derivative showed maximum average inhibition against four Gram-positive and four Gram-negative bacteria and four phytopathogenic fungi.

M. Shehab[10] a post graduate student of our laboratory carried out *in vitro* antimicrobial activities of fused pyrimidine derivatives. He used eleven bacteria such as *Bacillus subtilis, Bacillus megaterium, Bacillus cereus, Staphylococcus aureus, Shigella dysenteriae, Shigella sonnei, Salmonella typhi, Escherichia coli, Pseudomonas (sp.), Sarcina species* and INABA-ET (*Vibrio)* and four phytopathogenic fungi such as, *Macrophomina phaseolina, Fusarium equiseti, Alternaria alternata* and *Drechslera oryzae* were also used for this screening.

M. S. Rahman[11] showed that antimicrobial activities of the alkaloids of three plant leaves. The alkaloid fractions were screened against eight pathogenic bacteria, *viz., Shigella dysenteriae, Shigella sonnei, Salmonella typhi, Bacillus subtilis, B. megaterium, B. cereus, Staphylococcus aureu, and Pseudomonas mutabilis.* The highest zone of inhibition (38 mm) was recorded with the fraction No. 4 against *Salmonella typhi.*

S.M. Shahed[12,13] a former research student of organic laboratory carried out antifungal activities of a series of acylated D-mannose derivatives. He used four phytopathogenic fungi, such as *Macrophomina phaseolina, Fusarium equiseti, Alternaria alternata and Curvularia lunata.* Most of the tested chemicals showed good inhibition (more than 50% growth against the above organism).

M. Fakruddin[14] also a former resarch student of our laboratory carried out antifungal activities of fused pyrimidine. He used five human pathogenic bacteria, *viz. Bacillus subtilis, Bacillus megaterium, Staphylococcus aureus, Salmonella typhi, Escherichia coli* and four phytopathogenic fungi, *viz. Verticillum sp., Fusarium solanae, Aspergillus sp.,*

penicillum sp. He found that some of the tested chemicals showed very effective antibacterial and antifungal activity.

S.M. Abe Kawsar[15,16] also a former post graduate student of the same laboratory carried out *in vitro* antibacterial activities of a series of acylated uridine derivatives. He used ten bacteria such as, *Staphylococcus aureus, Bacillus megaterium, Bacillus cereus, Bacillus subtilis, Escherichia coli, Salmonella typhi, Shigella dysenteriae, Shigella sonnei, INABA-ET* (*Vibrio*) and *Sarcina species*. It was observed that most of the acylated compounds exhibit moderate to good antibacterial activity. Amongst the acylated compounds exhibit moderate to good antibacterial activity.

Recently, our groups synthesized 2-substituted benzofurans[17], isoindolinone and isoquinolinone[18] and tested their antibacterial and antifungal activities. The synthesized compounds demonstrated mild to significant growth inhibitors against antibiotic-susceptible standard and clinically isolated strains of gram-positive and gram-negative bacteria as well as human fungal pathogens.

In the present study, fused pyrimidine derivatives were used (which are shown **Table 1**) against eight human pathogenic bacteria and five phytopathogenic fungi. Among the bacterial strains five were Gram-positive; *viz. Bacillus cereus, Bacillus megaterium, Staphylococcus aureus, Bacillus subtilies, Sarcina lutea* and six were Gram-negative, *viz. Escherichia coli, pseudomonas aeruginosa, Salmonella paratyphi, Shigella boydii, Shigella dysenteriae, Vibrio mimicus and Vibrio parahemolyticus.* Antifungal activities of same compounds were also studied against four phytopathogenic fungi; *viz. Aspergillus niger, Candida albicans, Rhizopus oryzae and Saccharo myces cerevisiae.*

The present work was under taken to select the chemicals (fused pyrimidine) that have not been studied before phathogenic microorganisms of animals and plants.

Section-2

METHODOLOGY OF THE BIOLOGICAL WORK

Materials and Methods

The antibacterial activities of fused pyrimidine and 5-alkynyl pyrazol derivatives were studied against twelve bacteria and antifungal activities of the same compounds were also studied against five fungi. For the detection of antibacterial activities the disc diffusion method[19] was followed. The antifungal activities was assessed by poisoned food technique.[20,21]

Nutrient Agar (NA) and potato Dextrose Agar (PDA) were used as basal medium for test bacteria and fungi respectively. Methanol (MeOH)/Dimethylsulfoxide (DMSO) were used as a solvent to prepare 1% solution of the compound initially. Proper control was maintained with MeOH/DMSO. The materials and methods of the present work described detail in below:

2.1. Materials and Methods

Bacteria and fungi are responsible for many infections diseases. The increasing clinical importance of drug resistant microbial pathogens has lent additional urgency to antimicrobial research. The antimicrobial screening which is the first stage of antimicrobial research is performed to ascertain the susceptibility of various microbes to any agent. This test measures the ability of each antimicrobial agent to inhibit the in *vitro* microbial growth. This ability may be estimated by any of the following three methods.

I). Disc diffusion method
II). Serial dilution method
III). Bioautographic method.

The disc diffusion technique (Bauer et al[19], 1966) is a widely accepted in *vitro* investigation for preliminary screening of agents which may possess any antibacterial activity. It is essentially a quantitative or qualitative test indicating the sensitivity or resistance of the microorganisms to the test materials. However, no distinction between baceriostatic or bactericidal activity can be made by this method. (Roland[22], R, 1982).

2.2. Principle of Disc Diffusion method

Solutions of known concentration (μg/ml) of the test samples are made by dissolving measured amount of the samples in definite volume of solvents. Dried and sterilized filter paper discs (6 mm diameter) are then impregnated with known amounts of the test substances using micropipette. Discs containing the test material are placed on nutrient agar medium uniformly seeded with the test microorganisms. Standard antibiotic discs and blank discs (impregnated with solvents) are used as positive and negative control. These plates are then kept at low temperature (4°C) for 2h h to allow maximum diffusion. During this time dried discs absorb water from the surrounding media and then the test materials are dissolved and diffused out of the media. The diffusion according to the physical law that controls the diffusion of molecules through agar gel. As a result there is a gradual change of test materials concentration in the media surrounding the discs. The plates are then incubated at 37°C for 24 hrs. to allow maximum growth of the organisms. If the test materials have any antibacterial activity, it will inhibit the growth of the microorganisms giving a clear, distinct zone called "Zone of Inhibition". The antibacterial activity of the test agent is determined by measuring the diameter of zone of inhibition expressed in millimeter.

The experiment is carried out more than once and the mean of the readings is required (Bauer *et al*[19], 1966). In the present study some pure compounds were tested for antibacterial activity by disc diffusion method.

2.3. Experimental

2.3.(i). Apparatus and Reagents:

Filter Paper Discs
Sterile Cotton
Micropipette
Laminar Air Flow Hood
Refrigerator
Chloroform
Petridishes
Sterile Forceps
Screw Cap Test Tubes
Autoclave
Nutrient Agar Medium
Inoculating Loop
Spirit Burner
Nose Mask and Hand Gloves
Incubator
Ethanol

2.3.(ii). Test of Organisms:

The bacterial strains used for the experiment were collected as pure cultures from the Institute of Nutrition and Food Science (INFS), University of Dhaka. Both gram-positive and gram-negative organisms and fungi were taken for the test and they are listed in the table-1 and table-2.

Name of the organizom

Table-1: List of Test Bacteria

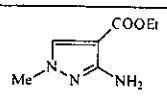
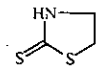
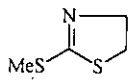
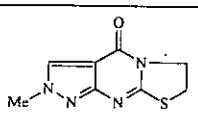
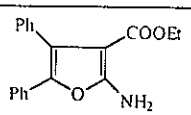
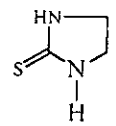
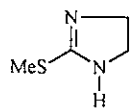
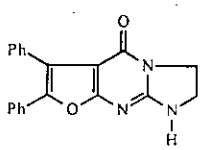
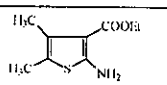
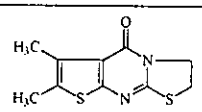
Gram positive	Gram negative
Bacillus cereus	*Esherichia coli*
Bacillus megaterium	*Pscudomonas aeruginosa*
Bacillus subtilis	*Salmonella paratyphi*
Staphylococcus aureus	*Sheigella boydii*
Sarcina lutea	*Shigella dysenteriae*
	Vibrio mimicus
	Vibrio parahemolyticus

Table-2: List of test fungi

Fugi
Aspergillus niger
Candida albicans
Rhizopus oryzae
Saccharo myces cerevisiae

2.3.(iii). Test of Materials:

Table-3: List of Test chemicals used for antimicrobial activities

Comd. No.	Structure	Name of the test chemicals	Molecular Formula
2		Ethyl-5-amino-2-methylpyrozolo-4-carboxylate.	$C_7H_{11}N_3O_2$
4		2-mercaptothiazoline	$C_3H_5NS_2$
5		2-methylthio-2-thiazoline	$C_4H_7NS_2$
6		2-methyl-6,7-dihydropyrozolo[3,4-*d*] thiazolo[1,2-*a*]pyrimidin 4-one.	$C_8H_8N_4OS$
8		2-amino-4,5-diphenylfuran-3-carboxylate	$C_{17}H_{12}N_2O$
10		2-imidazolinethione	$C_3H_6N_2S$
11		2-methylthio-imidazoline	$C_4H_8N_2S$
12		2,3-diphenylfurano-6,7-dihydropyrozolo [6,7-d]imidazo[3,4-a] pyrimidin-4-one	$C_{20}H_{15}N_2O_2$
14		Ethyl-2-amino-4,5-dimethylthiophene-3-carboxylate	$C_9H_{13}NO_2S$
15		2,3-dihydro-6,7-dimethyl-5H-thiazolo [3,2-a]thieno[2,3-d]pyrimidin-5-one	$C_{10}H_{10}N_2OS_2$

2.4. Culture Medium

Mueller-Hinton (MH) medium and Potato Dextrose Agar (PDA) were used for making plates on which antibacterial and antifungal sensitivity tests were carried out respectively. The antibacterial activities of the materials were detected by disc diffusion method [Bauer *et al*[19], 1966] and antifungal activity of the materials were assessed by food poison technique [Miah *et al*[20], 1990 and Grover *et al*[21], 1962]. This media were also used to prepare fresh cultures.

2.5. Medium Used

Nutrient Agar (NA) and potato Dextrose Agar (PDA) were used through out the work. The composition and preparation procedure of NA and PDA are described below:

Composition of Nutrient Agar Medium (for bacteria):

Ingredients	Amounts (gm/lit)
Peptone	5.0
Sodium chloride	5.0
Beef extract	1.5
Yeast extract	1.5
Agar	14.0
P^H (at 25°C)	7.2 – 7.6

Procedure:

To prepare required volume of this medium, calculated amount of each of the constituents was taken in a conical flask and distilled water was added to it to make the required volume. The contents were heated in a water bath to make a clear solution. The pH (at 25°C) was adjusted at 7.2–7.6 using NaOH or HCl. 10ml and 5 ml of the medium was then transferred in screw cap test tubes to prepare plates and slants respectively. The test tubes were then capped and sterilized by auto calving at 15-1bs/sq, pressure at 121°C for 20 minutes. The slants were used for making fresh culture of bacteria that were in turn used for sensitivity study.

Composition of Potato Dextrose Agar (for fungi):

Ingredients	Amounts (gm/lit)
Potato	200.0
Dextrose	20.0
Agar	15.0 g

Procedure:

200g of sliced potato was boiled in 500 ml distilled water and extract was decanted after proper boiling. The extract was taken in a 1000 ml beaker and the solution was made up to the mark with distilled water. This solution was taken in suspense and 20g dextrose was added slowly in the solution. Then 15g of agar powder was added in the solution and they were mixed throughly with a glass rod. After 10 minutes of boiling the medium was transferred in 250 ml conical flash. Before autoclaving the conical flask was closed with the cotton plug and rapping with aluminium foil. The medium was autoclaved for 15 minutes at 121°C and 15–1bs/sq pressure. After autoclaving the medium was used for culture of different microorganisms.

2.6. Sterilization Procedures

In order to avoid any type of contamination by the test organisms the antibacterial screening was done in Laminar Hood and all types of precautions were highly maintained. UV light was switched on an hour before working in the laminar hood. Petridishes and other glassware were sterilized by autoclaving at a temperature of 121°C and pressure of 15–1 bs/sq. inch for 20 minutes. Micropipette tips, cotton, forceps discs etc. were also sterilized.

2.7. Preparation of Subculture

In an aseptic condition under laminar air cabinet, the test organisms were transferred from the pure cultures to the agar slants with help of a transfer loop to have fresh pure cultures. The inoculated strains were then incubated for 24hrs. at 37°C for their optimum growth. These fresh cultures were used for the sensitivity test.

2.8. Preparation of the Test Plates

The test organisms were transferred from the subculture to the test tubes containing about 10 ml of sterilized agar medium with the help of a sterilized transfer loop in an aseptic area. The test tubes were shaken by rotation to get a uniform suspension of the

organisms. The bacterial suspension was immediately transferred to the sterilized petridishes. The petridishes were rotated several times clockwise and anticlockwise to assure homogenous distribution of the best organisms in the media.

2.9. Preparation of Discs

Three types of discs were used for antibacterial screening. They were:

(a) Standard Discs

(b) Blank Discs and

(c) Sample Discs

The descriptions of these discs were given below:

2.9.(a). Standard Discs

These were used as positive control to ensure the activity of standard antibiotic against the test organisms as well as for comparison of the response produced by the known antibacterial agent with that of produced by the test sample. In this investigation, kanamycin (30 μg / disc) standard disc was used as the reference.

2.9.(b). Blank Discs

These were used as negative control which ensures that the residual solvents (left over the discs even after air-drying) and the filter paper were not active themselves.

2.9.(c). Preparation of Sample Discs with Test Sample

Measured amount of each test sample was dissolved in specific volume of solvent to obtain the desired concentrations in an aseptic condition. Then discs were soaked with solutions of test samples and dried.

2.10. Antifungal activities test

The antifungal activities of fused pyrimidines were assessed by *food poison technique* [Miah *et al.*[20], 1990 and Grover *et al.*[21], 1962].

Food Poison Technique:

The test chemicals (1%) were mixed with sterilized Potato Dextrose Agar (PDA) medium (45°C) at the rate of 100 µg/ml PDA. The medium was poured in sterilized Petriplate and after solidification the equal diameter of fungal inoculums block (10 mm mycelial block) was placed on the center of the Petri plates.

Radial growth of fungal colony was measured in mm, after 3-5 days of incubation at $(25\pm2)^0$C, a control set was maintained in each experimental using only PDA with MeOH/DMSO of 1% as growth medium. Each experiment repeated thrice. The percentage inhibition of mycelial growth of the test fungi was calculated as follow:

$$I = \frac{(C-T)}{C} \times 100 .$$

Where,

I = percentage inhibition.

C = diameter of the fungal colony in control (DMF).

T = diameter of the fungal colony in treatment.

In control, Nystatin (for fungus) was used as standard antibiotic.

2.11. Diffusion and Incubation

The sample discs, the standard antibiotic discs and the control discs were placed gently on the previously marked zones in the agar plates pre-inoculated with test bacteria. The plates were then kept in a refrigerator at 4°C for about 24h to allow sufficient diffusion of the materials from the discs to the surrounding agar medium. The plates were then inverted and kept in an incubator at 37°C for 24hrs.

2.12. Determination of Antibacterial Activity by Measuring the Zone of Inhibition

After incubation, the antibacterial actives of the test materials were determined by measuring the diameter of the zones of inhibition in millimeter with transparent scale.

Results and Discussion

In the present study, fused pyrimidines and their derivatives **(Table 3)** were selected and screened for their antibacterial activity against twelve human pathogenic bacteria, *viz. Bacillus cereus, Bacillus megaterium, Staphylococcus aureus, Bacillus subtilies, Sarcina lutea, Escherichia coli, pseudomonas aeruginosa, Salmonella paratyphi, Shigella boydii, Shigella dysenteriae, Vibrio mimicus, Vibrio parahemolyticus, Shigella flexneri and Shigella sonnei.*

For antifungal activities of same chemicals were also studied against four phytopathogenic fungi, *viz. Aspergillus niger, Candida albicans, Rhizopus oryzae and Saccharo myces cerevisiae.*

The results of the diameter of inhibition zone and % inhibition of mycelial growth due to the effect of chemicals are presented in **Table-4** and **Table-5.**

A total of fourteen compounds (four starting materials, four fused pyrimidine and 5-alkynyl pyrazol derivatives) have been tested for in *vitro* antimicrobial activity against five Gram-positive and nine Gram-negative bacteria as well as four human fungal pathogens. The selected microbes were collected as fresh cultures from the Institute of Nutrition and Food Science (INFS), University of Dhaka, Dhaka-1000. No clinically isolated resistant strains were used for the present study. The antimicrobial activities were measured in terms of diameters of zone of inhibition (mm). All the experiments were performed thrice to minimize the experimental plus individual errors. The mean values of the diameters of zone of inhibition (M.DIZ) were taken as in disc for determining antimicrobial spectra. Sensitivity test results are interpreted in (**Table-4** and **Table-5**) and were compared with a standard antibiotic kanamycin (30 μg/dise).

The Gram positive as well as Gram-negative bacteria used in the present investigation, were found to be completely resistant against eight synthesized compounds (**2, 5, 6, 8, 11, 12, 14** and **15**), at a dose level of 200 μg/disc (**Table-4** and **Table-5**), compounds **2, 5, 8,**

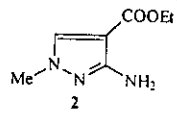
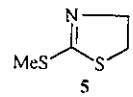
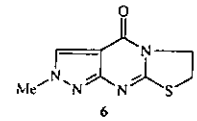
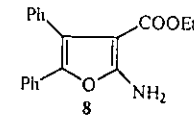
11 and **15** showed mild in *Vitro* antimicrobial activity, especially against the fungi, *Candida albicans* **2** (M.DIZ 9.8), **5** (M.DIZ 12), **8** (M.DIZ 9.5), **11** (M.DIZ 9.4), **15** (M.DIZ 105) and *Saccharomyces cerevaceae* **6** (M.DIZ 9.5), **11** (M.DIZ 7.8), **12** (M.DIZ 8.1), **14** (M.DIZ 7.8). *Aspergillus niger* **12** (M.DIZ 9.8), **14** (M.DIZ 9.5), **15** (M.DIZ 8.1) and *Rhizobus oryzae* were, however, resistant to the compound (**Table-4** and **Table-5**).

The compounds **2, 5, 6, 8, 11, 12, 14** and **15** showed mild in vitro antimicrobial activity especially against the Gram positive *Bacillus cereus* **6** (M.DIZ 7.6), **12** (M. DIZ 8.5), **14** (M.DIZ 8.1), **15** (M.DIZ 7.6), *Bacillus megaterium* **6** (M. DIZ 10.1), **12** (M.DIZ 9.8), **14** (M.DIZ 7.5), **15** (M.DIZ 10.1), *Staphylococcus aureus* **15** (M.DIZ 8.6), *Bacillus subtilies* **6** (M.DIZ 8.6), **8** (M.DIZ 6.5), **12** (M.DIZ 8.6). And also compounds **6, 12, 14** and **15** exhibited in *vitro* antimicrobial activity, especially against the Gram negative *Escherichia coli* **6** (M.DIZ 6.5), **12** (M.DIZ 7.9), **14** (M.DIZ 8.2), **15** (M.DIZ 6.5), *Shigella dysenteriae* **6** (M.DIZ 7.8), **12** (M.DIZ 8.2) and **15** (M.DIZ 9.1). This study can therefore, confer that formation of fused pyrimidine increases antimicrobial activity.

2.3.2. Conclusion:

Eight new synthesized heterocyclic compounds have been tested for in antimicrobial activity against five Gram-positive and nine Gram-negative bacteria as well as four human fungal pathogens. Most of this compound demonstrated mild to moderate antimicrobial activity against most of the test organism. From these structures we found that the fused pyrimidine ring causes relatively better microbial growth inhibition.

Table-4: In *Vitro* Antimicrobial activity of new synthesized compound 2,5,6 & 8.

Diameter of Zone of Inhibition (mm)					
Done	200µg/disc	200µg/disc	200µg/disc	200µg/disc	**Std. 30**
Name of the Microorganism	 2	 5	 6	 8	Kan
Gram (+) bacteria					
Bacillus cereus	-	-	7.6	-	31.9
Bacillus megaterium	-	-	10.1	-	34.2
Staphylococcus aureus	-	-	-	-	31.6
Bacillus subtilies	-	-	8.6	6.5	30.1
Sarcina lutea	-	-	-	-	26.9
Gram (-) bacteria					
Escherichia coli	-	-	6.5	-	34.2
Pseudomonas aepuginosa	-	-	-	-	34.8
Salmonella paratyphi	-	-	-	-	26.9
Shigella boydii	-	-	-	-	30.2
Shigella dysenteriae	-	-	7.8	-	36.9
Vibrio mimicus	-	-	-	-	29.8
Vibrio parahemolyticus	-	-	-	-	31.9
Shigella flexneri	NT	NT	NT	NT	33.2
Shigella sonnei	NT	NT	NT	NT	31.5
Fungi					
Aspergillus niger	-	-	-	-	35.0
Candida albicans	9.8	12	-	9.5	32.5
Rhizopus oryzae	-	-	-	-	27.6
Saccharo myces cerevaceae	-	-	9.5	-	32.1

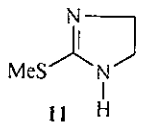
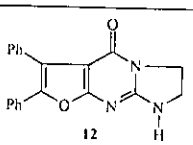
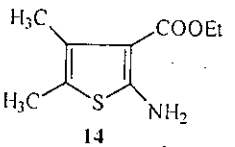
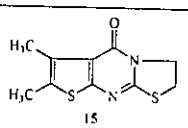
Interpretation of sensitivity test results:

Gram (+) bacteria:
> 18 mm (M.DIZ) = sensitive
14-18 mm (M.DIZ) = intermediate
< 14 mm (M.DIZ) = resistant

Gram (-) bacteria:
> 16 mm (M.DIZ) = sensitive
13 – 16 mm (M.DIZ) = intermediate
> 13 mm (M.DIZ) = resistant.

"-" indicates no sensitivity or zone of inhibition lower than 6 mm and NT refers to "Not Tested"

Table-5: In *Vitro* Antimicrobial activity of new synthesized compound 11, 12, 14 & 15.

Diameter of Zone of Inhibition (mm)					
Done	200µg/disc	200µg/disc	200µg/disc	200µg/disc	Std.30
Name of the Microorganism	 11	 12	 14	 15	Kan
Gram (+) bacteria					
Bacillus cereus	-	8.5	8.1	7.6	31.9
Bacillus megaterium	-	9.8	7.5	10.1	34.2
Staphylococcus aureus	-	-	-	8.6	31.6
Bacillus subtilies	-	8.6	-	-	30.1
Sarcina lutea	-	-	-	-	26.9
Gram (-) bacteria					
Escherichia coli	-	7.9	8.2	6.5	34.2
Pseudomonas aepuginosa	-	-	-	-	34.8
Salmonella paratyphi	-	-	-	-	26.9
Shigella boydii	-	-	-	-	30.2
Shigella dysenteriae	-	8.2	-	9.1	36.9
Vibrio mimicus	-	-	-	-	29.8
Vibrio parahemolyticus	-	-	-	-	31.9
Shigella flexneri	NT	NT	NT	NT	33.2
Shigella sonnei	NT	NT	NT	NT	31.5
Fungi					
Aspergillus niger	-	9.8	9.5	8.1	35.0
Candida albicans	9.4	-	-	10.5	32.5
Rhizopus oryzae	-	-	-	-	27.6
Saccharo myces cerevaceae	7.8	8.1	7.8	-	32.1

Interpretation of sensitivity test results:

Gram (+) bacteria:
> 18 mm (M.DIZ) = sensitive
14-18 mm (M.DIZ) = intermediate
< 14 mm (M.DIZ) = resistant

Gram (-) bacteria:
> 16 mm (M.DIZ) = sensitive
13 – 16 mm (M.DIZ) = intermediate
> 13mm (M.DIZ) = resistant.

"-" indicates no sensitivity or zone of inhibition lower than 6 mm and NT refers to "Not Tested"

Section-3

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