AL-TAHADY UNIVERSITY
FACULTY OF SCIENCE
CHEMISTRY DEPARTMENT

M. Sc. Thesis Entitled:

SYNTHESIS AND SOME REACTIONS OF SUBSTITUTED *PYRIDAZINONE* DERIVATIVES

SUBMITTED BY:
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SIRTE - LIBYA

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SYNTHESIS AND SOME REACTIONS OF SUBSTITUTED *PYRIDAZINONE* DERIVATIVES

بسم الله الرحمن الرحيم

﴿ وَأَنزَلَ اللَّهُ عَلَيْكَ الْكِتَابَ وَالْحِكْمَةَ وَعَلَّمَكَ مَا لَمْ تَكُن تَعْلَمُ
وَكَانَ فَضْلُ اللَّهِ عَلَيْكَ عَظِيمًا ﴾ النساء 113

صدق الله العظيم

ACKNOWLEDGEMENTS:

First and foremost, my deep gratefulness and indebtedness is to **ALLAH.**

I wish to express my sincere gratitude and deep indebtedness to Prof.Dr. **M. EL-MOBAYED,** professor of Organic Chemistry, Faculty of Science, Al-Tahady University, not only for suggesting the subject investigated, but also for continual help, guidance and valuable criticism.

I am grateful to the Al-Tahady University, Faculty of Science, and Chemistry Department; also all thanks and grateful to every one supported and adviced me.

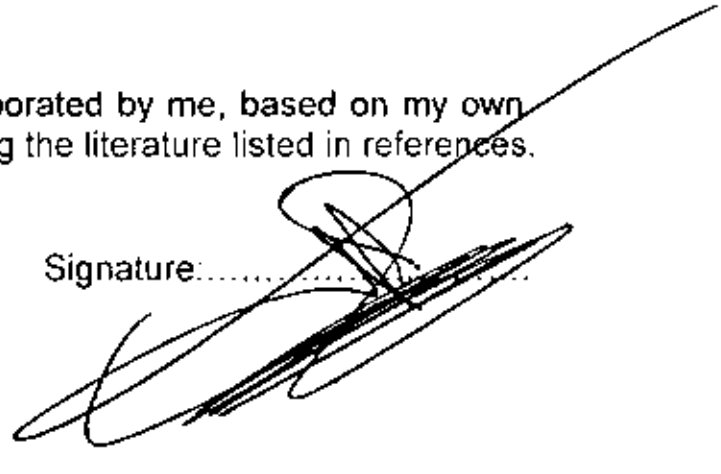
To my

father, mother, brothers

and sisters

I state that, the thesis has been elaborated by me, based on my own results, using the literature listed in references.

BSc. MOHAMED ERHAYEM OMER Signature:.....



CONTENTS

CONTENTS

SUMMARY OF THE ORIGINAL WORK

1. Summary of the original work: -

SYNTHESIS AND SOME REACTIONS OF SUBSTITUTED *PYRIDAZINONE* DERIVATIVES

The synthesis of 6-(p-bromophenyl)-4-(3-indolyl)-4,5-dihydropyridazin-3(2H)-one and some new derivatives which have highly biological activity was described.

It was found that the reaction of 4-(p-bromophenyl)-4-oxo-2-butenoic acid (I) with Indole in n-butanol yielded 4-(p-bromophenyl)-2-(3-indolyl)-4-oxo-butanoic acid (II) which was reacted with hydrazine hydrate or phenylhydrazine to give the corresponding 2-N-substituted pyridazinone derivatives (*III*) respectively.

On the other hand when compound (II) was reacted with hydroxylamine hydrochloride in pyridine afforded the oxazinone derivative (IV).

Also when the compound (II) was refluxed with acetic anhydride, the butenolide derivative (V) was obtained.

Treatment of the pyridazinone derivative (IIIa) with some alkylating agents such as dimethyl sulfate, ethyl Iodide, formaldehyde/methanol and/or ethyl chloroacetate gave the N-substituted products (VI a-d) respectively, but when (IIIa) reacted with aromatic aldehydes namely, benzaldehyde,

anisaldehyde and/or P-nitrobenzaldehyde in boiling ethanol afforded the disubstituted pyridazinone (VIIa-c) with the fission of 3-indolyl ring. Also this fission 3-indolyl ring was observed when 3-pyridazinone derivative (IIIa) was treated of $POCl_3$ with the formation of 3-chloropyridazine derivative (VIII).

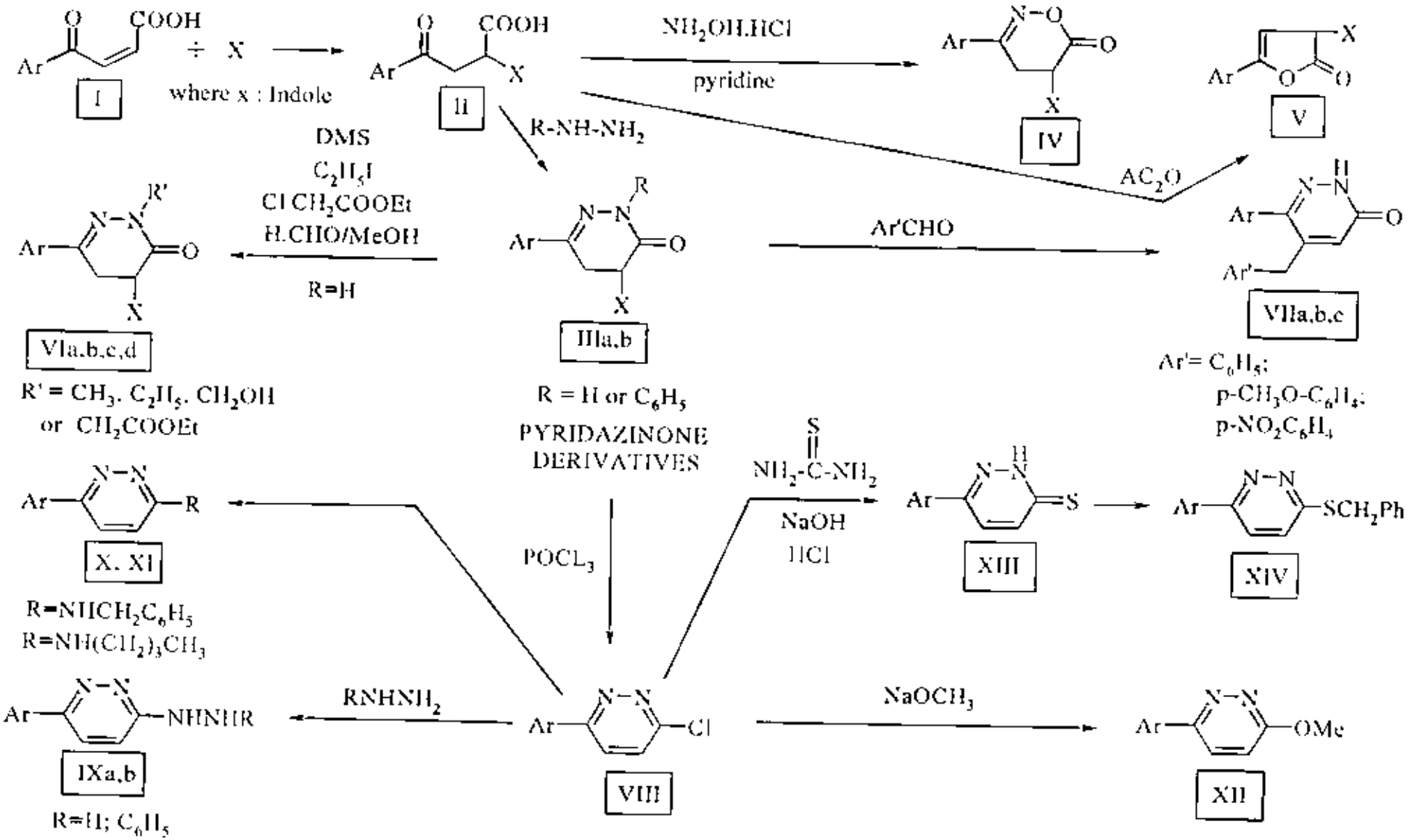
The latter compound (VIII) was subjected to many reactions as such the reaction with hydrazine hydrate and/or phenylhydrazine to form the hydrazino derivatives (IX a,b). Also the reaction with some amines as benzylamine and/or butylamine gave the (N-substituted) pyridazine (X) and (XI).

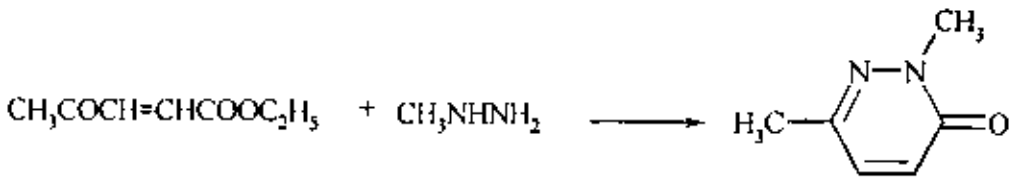
It has been found that the reaction of the 3-chloropyridazine (VIII) with thiourea afforded the pyridazin-3-thione derivative (XIII), which reacted with benzylchloride to give the S-benzyl derivative (XIV).

The mechanisms of the formation of the obtained compounds were illustrated and the structure were also proved by chemical and spectral data.

The biological activity of some prepared compounds (IV, VIa, VIIa, X and XII) against some species of Bacteria were studied.

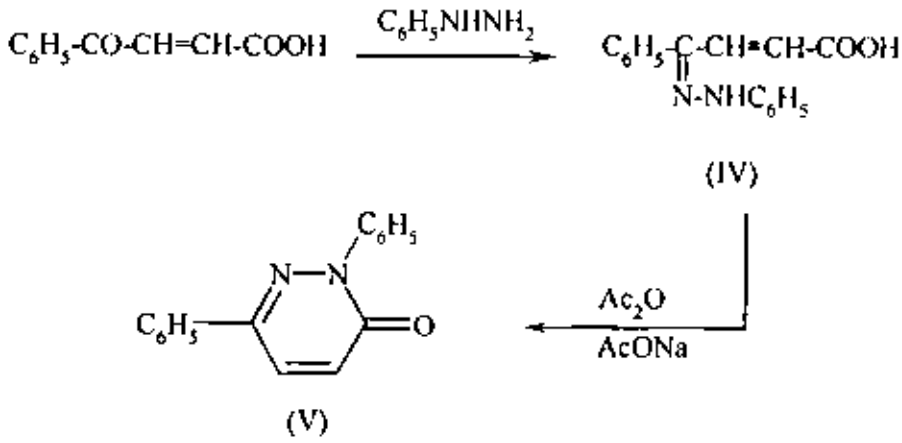
Introduction


I
where x : Indole
II
$NH_2OH.HCl$
pyridine
IV
V
AC_2O
DMS
C_2H_5I
$ClCH_2COOEt$
HCHO/MeOH
R=H
$R-NH-NH_2$
VIa,b,c,d
$R' = CH_3, C_2H_5, CH_2OH$
or CH_2COOEt
IIIa,b
$R = H$ or C_6H_5
PYRIDAZINONE
DERIVATIVES
Ar'CHO
VIIa,b,c
$Ar' = C_6H_5$;
$p\text{-}CH_3O\text{-}C_6H_4$;
$p\text{-}NO_2C_6H_4$
$POCl_3$
$NH_2\text{-}C(=S)\text{-}NH_2$
NaOH
HCl
XIII
XIV
X, XI
$R=NHCH_2C_6H_5$
$R=NH(CH_2)_3CH_3$
$RNHNH_2$
VIII
$NaOCH_3$
IXa,b
$R=H; C_6H_5$
XII



(III)

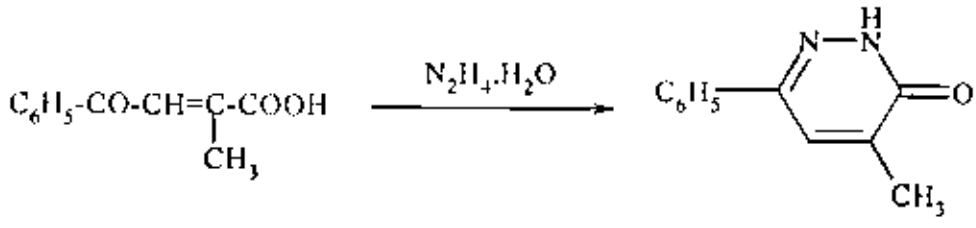
β-benzoylacrylic acid or its methyl ester reacts with phenylhydrazine to yield the corresponding phenylhydrazone (IV) which on heating with acetic anhydride and sodium acetate gives 2,6–diphenyl-3-oxo-pyridazine (V)[3].



(IV)

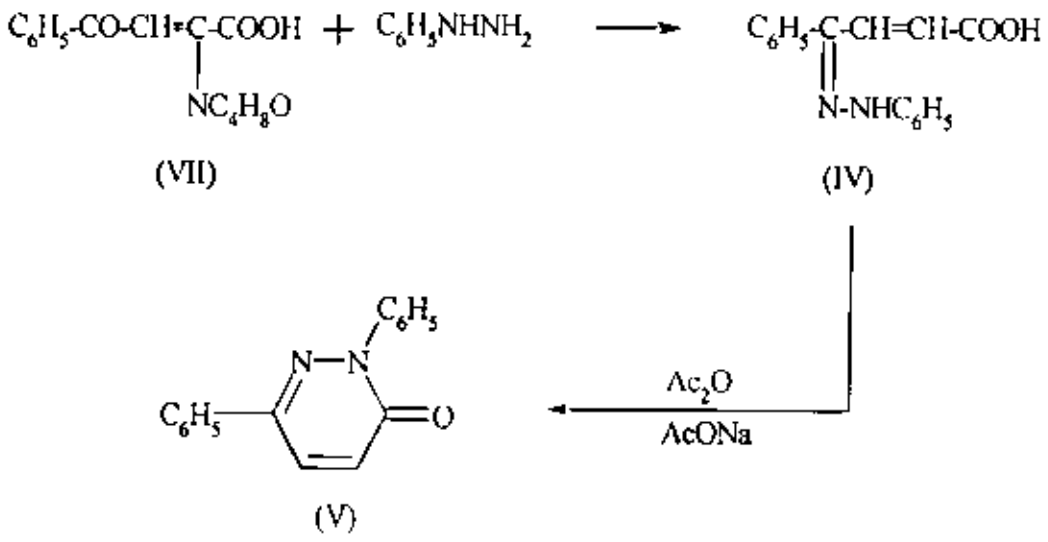
(V)

It was reported[4] that β-benzoyl-α-methylacrylic acid refluxed for two hours with hydrazine hydrate in sodium hydroxide gave 4-methyl-6-phenyl-pyridazin-3(2H)-one (VI).

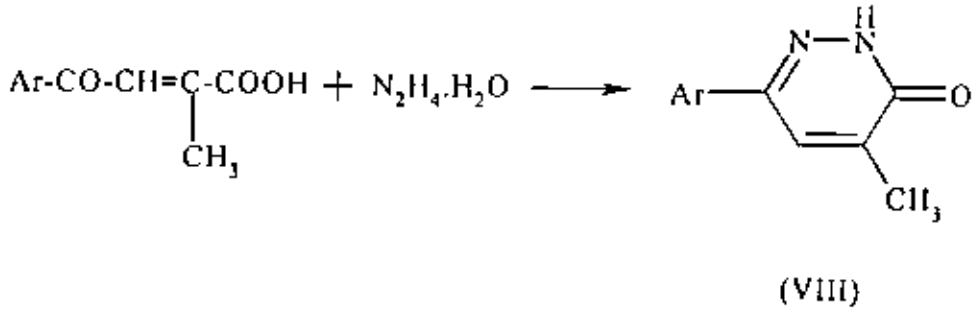


(VI)

Reaction of morpholine-β-benzoylacrylic acid (VII) with phenyl-hydrazine in glacial acetic acid, the phenylhydrazone (IV) was produced[3]. On heating the phenylhydrazone (IV) with acetic anhydride and sodium acetate gave the 2.6-diphenylpyridazin-3-one (V).

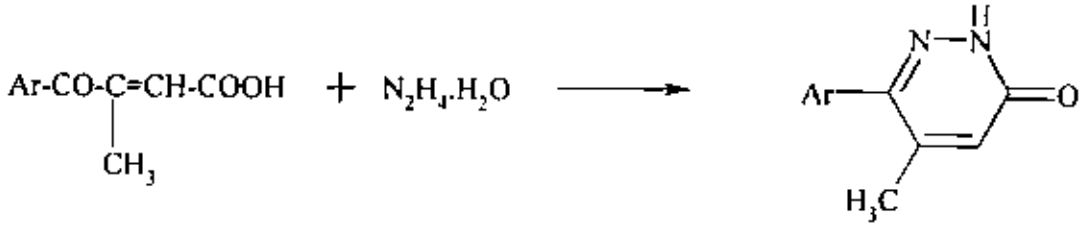


It has been found that[5], an excellent yield of 6-aryl-4-methyl-pyridazin-3(2H)-ones (VIII) was obtained when β-aroyl-2-methylacrylic acids were allowed to react with hydrazine hydrate in glacial acetic acid. However, in the presence of n-butanol as a solvent, the expected products were isolated in low yields.



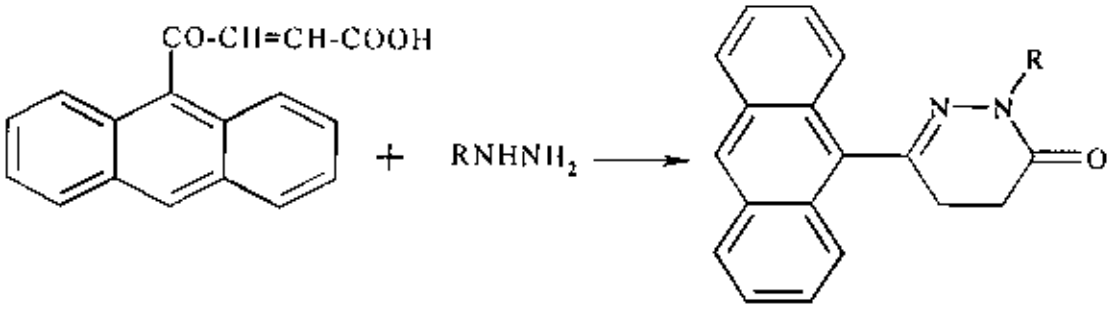
(VIII)

Similarly, when β-aroyl-β-methylacrylic acids were treated with hydrazine hydrate in glacial acetic acid, they gave 6-aryl-5-methylpyridazin-3(2H)-ones (IX)[6].



(IX)

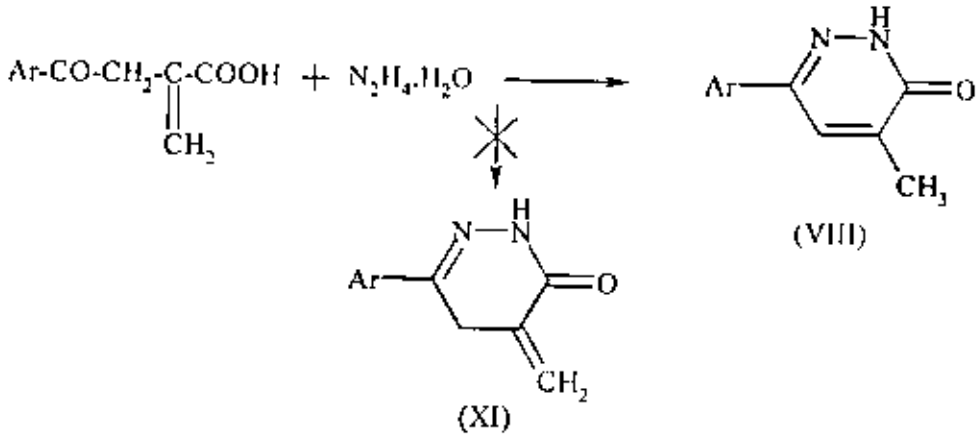
Condensation of β-(9-anthracenoyl) acrylic acid with hydrazine derivatives gave the pyridazin-3-one derivatives (X; R=H, Ph, $CONH_2$, $CSNH_2$, Ac)[7].



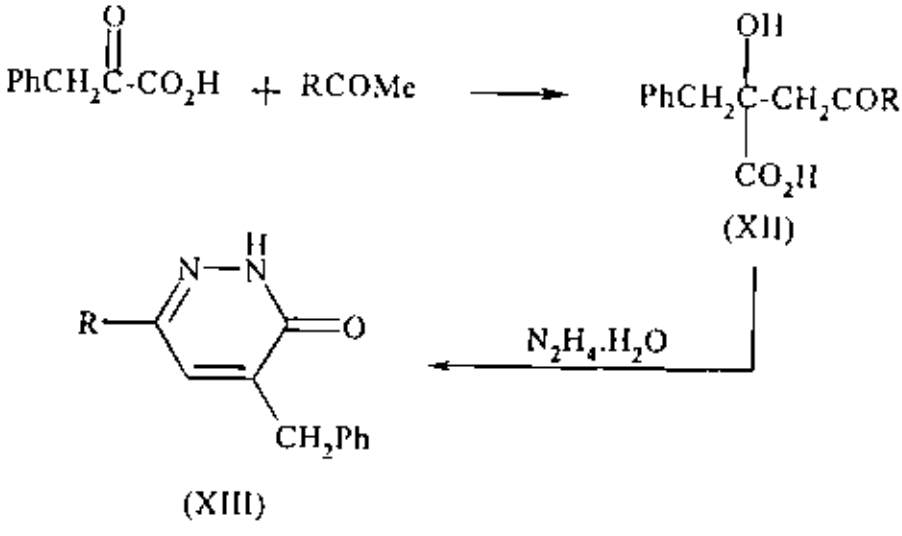
(X)

ii). <u>From α-substituted-β-aroyl propionic acids</u>: -

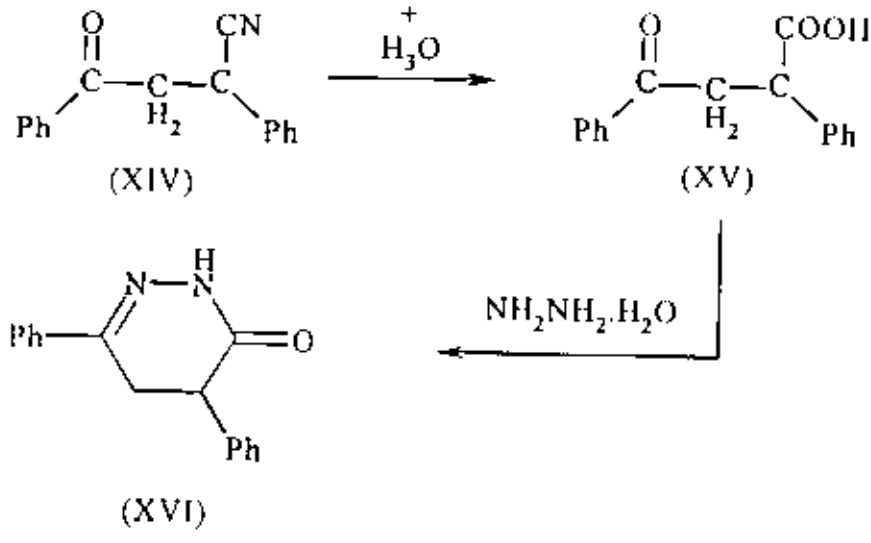
It has been found that[5], the condensation of β-aroyl-α-methylene propionic acids with hydrazine hydrate gave the 6-aryl-4-methylpyridazin-3(2H)-ones (VIII) and not the expected 6-aryl-4,5-dihydro-4-methylene-pyridazin-3(2H)-ones (XI).



Reaction of 2-oxo-3-phenylpropionic acid with RCOMe (R=Ph, 4-Me-C_6H_4, 4-MeO-C_6H_4) gave adduct (XII) which on cyclization with hydrazine hydrate afforded the corresponding pyridazin-3(2*H*)-one derivatives (XIII)[8].

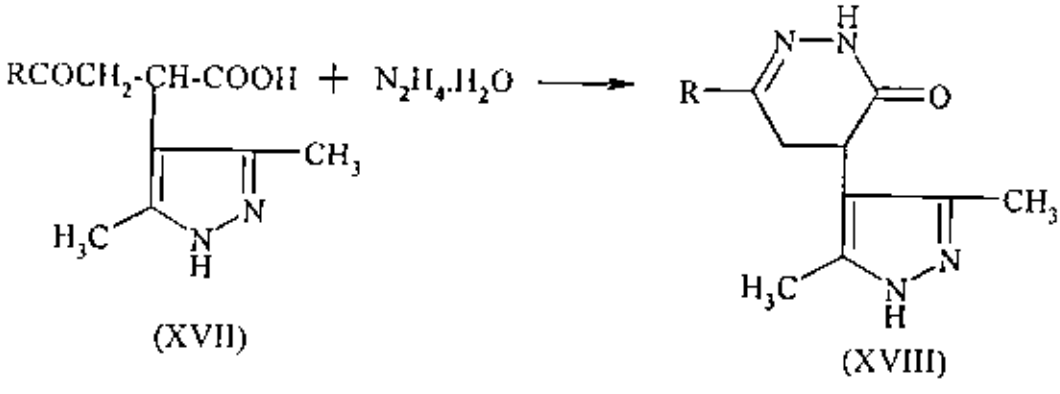


It has been found that[9], the γ-ketonitrile derivative (XIV) was hydrolyzed by 10 N hydrochloric acid to corresponding 2-phenyl-4-benzoylpropionic acid (XV). This acid was reacted with hydrazine hydrate to give 4,6-diphenyl-4,5-dihydropyridazin-3(2H)- one (XVI).



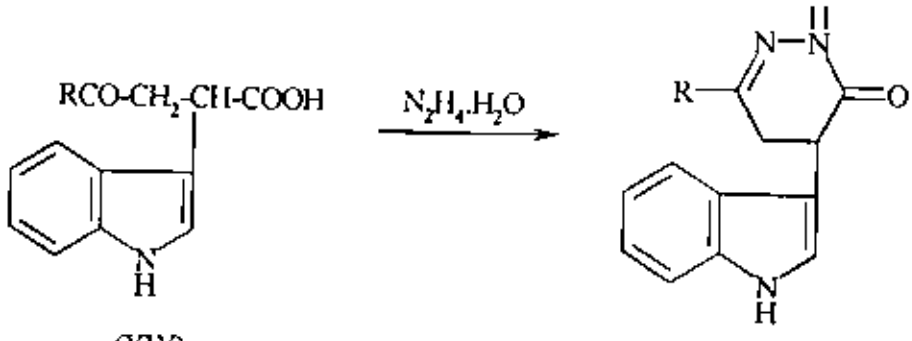
(XIV) (XV) (XVI)

Alkylation of R-CO-CH=CH-CO_2H (R= 4-dibenzothionyl, 4-dibenzo-pyrrol) with 3,5–dimethylpyrazole afforded α-(dimethylpyrazolyl) propionic acids (XVII). Reaction of (XVII) with hydrazine hydrate gave the 4,5-dihydro-pyridazin-3(2H)-one derivatives (XVIII)[10].



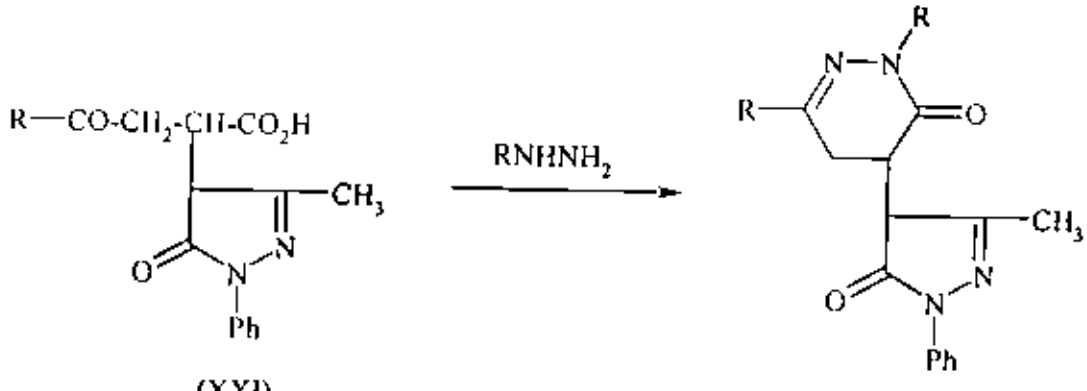
(XVII) (XVIII)

It has been found[11] that condensation of Indole with RCOCH:$CHCO_2H$ (R=4-ClC_6H_4; 2,5-$Me_2C_6H_3$; 2,4-$Me_2C_6H_3$) gave the indoleacetic acids (XIX) which cyclized with hydrazine hydrate to give pyridazine-3(2H)-ones (XX).



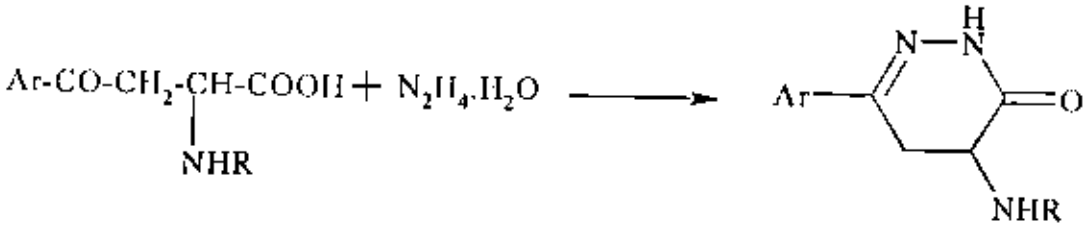
(XIX) (XX)

It has been found[12] that reaction propionic acid derivative (XXI) with hydrazine hydrate and/or phenylhydrazine afforded the corresponding 6-aryl-4-(1-phenyl-3-methyl-pyrazolin-5-one)Pyridazin-3-one derivatives (XXII, R=H, Ph).



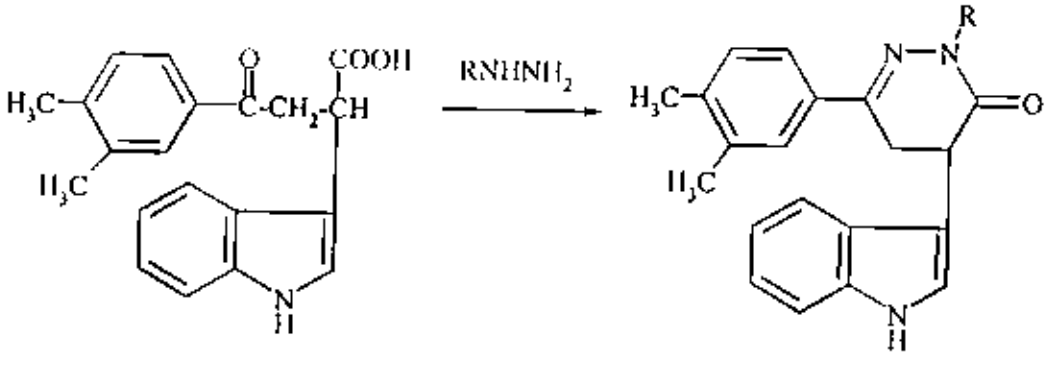
(XXI) (XXII)

It has been reported[13] that β-aroylacrylic acids ArCOCH= CHCOOH reacted with primary amines to give the corresponding α-amino substituted β-aroylpropionic acid (XXIII). Cyclocondensation of (XXIII) with hydrazine hydrate gave the pyridazine-3(2H)-one derivative (XXIV, R=H, Ph) respectively.



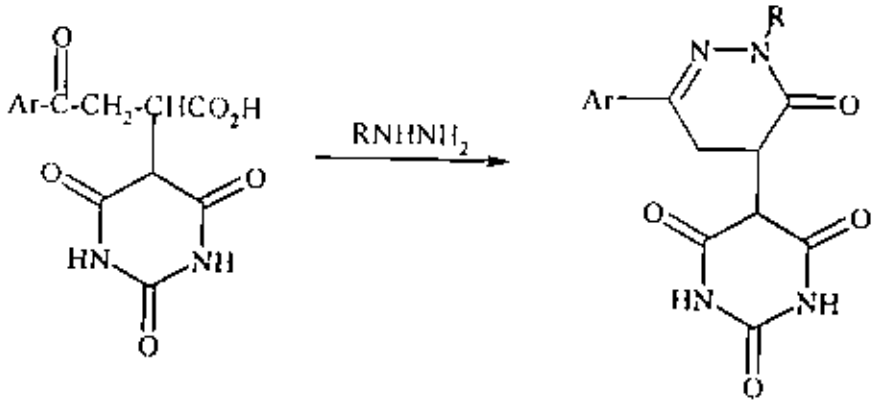
(XXIII) (XXIV)

It has been found that[14] β-(3,4-dimethylbenzoyl) α-(indol-3-yl) propionic acid (XXV) condensed with hydrazines, affording the corresponding pyridazine-3-one derivatives (XXVI, R=H, Ph).



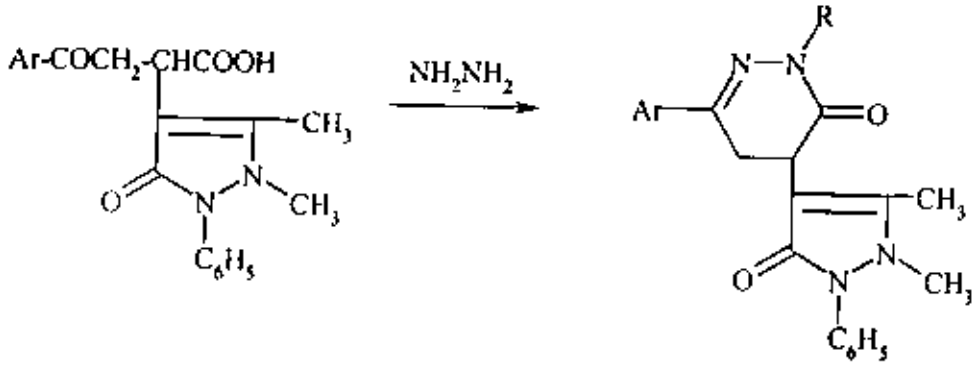
(XXV) (XXVI)

Some new pyridazine-3-one derivatives[15] (XXVII) containing the barbiturate moiety were synthesized through the reaction of β-aroyl (Ar = 4-chloro-3-methylbezoyl, 4-phenylbezoyl) α-(5-barbiturate) propionic acid with hydrazine derivatives (R=H, Ph, $CONH_2$, $CSNH_2$ and $COCH_3$)



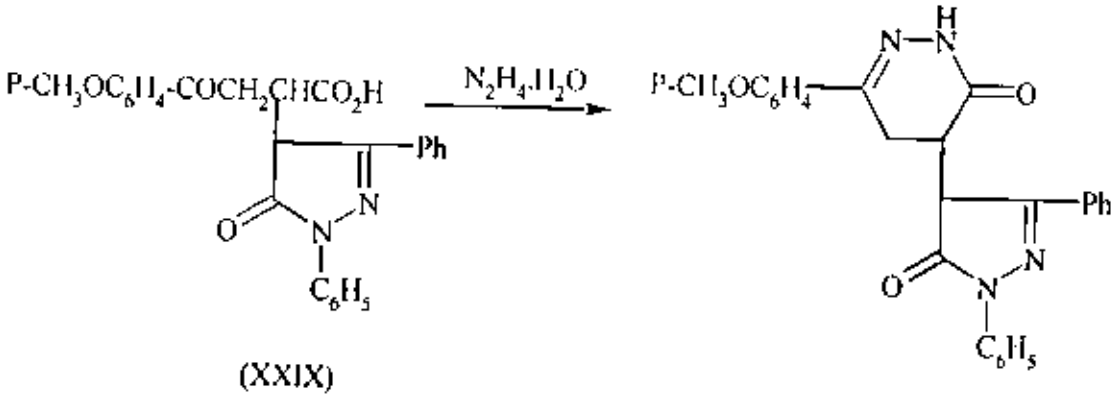
(XXVII)

It has been found that[16]. the reaction of substituted keto propionic acid with hydrazine hydrate gave the pyridazine-3-one derivative (XXVIII. R=H. Ph; Ar=3,4-dichlorophenyl).



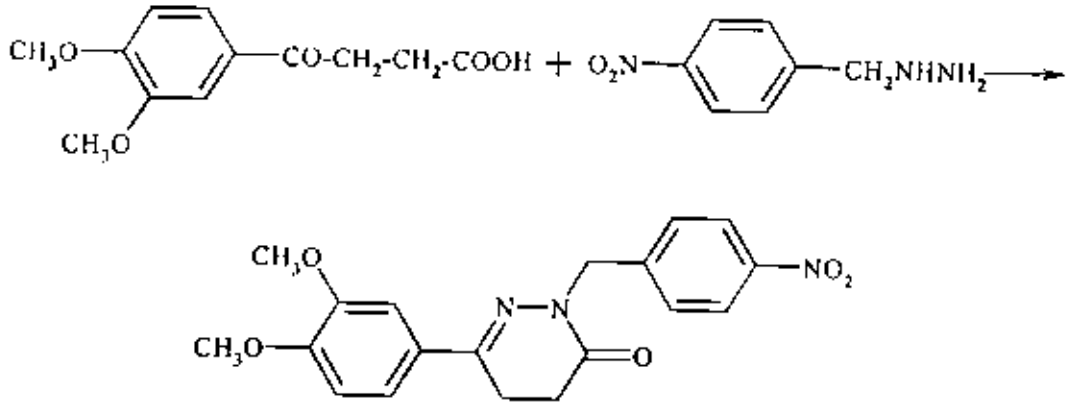
(XXVIII)

It has been reported that[17] condensation of β-(4-mthoxybenzoyl) α-(4,5-dihydro-5-oxo-1,3-diphenylpyrazol-4-yl)propionic acid (XXIX) with hydrazine hydrate afforded 4,5-dihydropyridazin-3(2H)-one derivative (XXX).



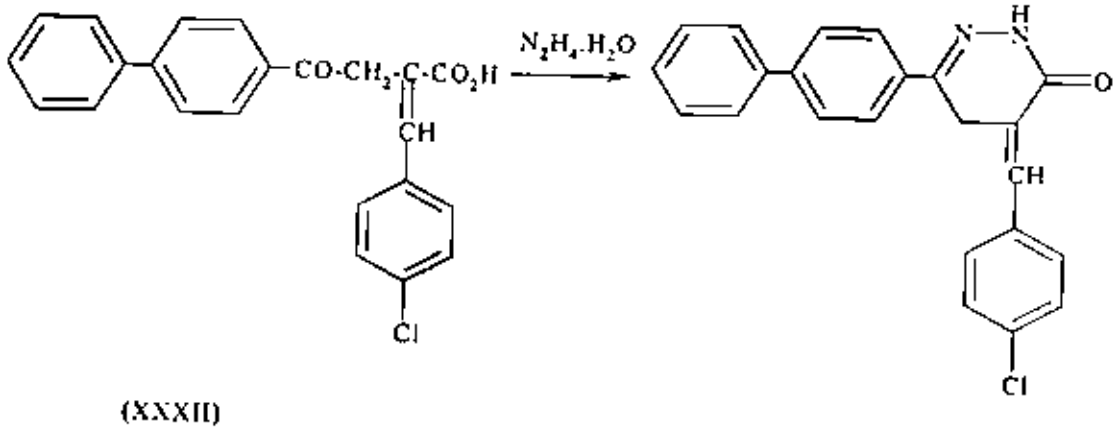
(XXIX) (XXX)

Cyclocondensation of β-(3,4-dimethoxybenzoy) propionic acid with 4-nitrobenzyl hydrazine gave the pyridazine-3-one derivative (XXXI)[18].



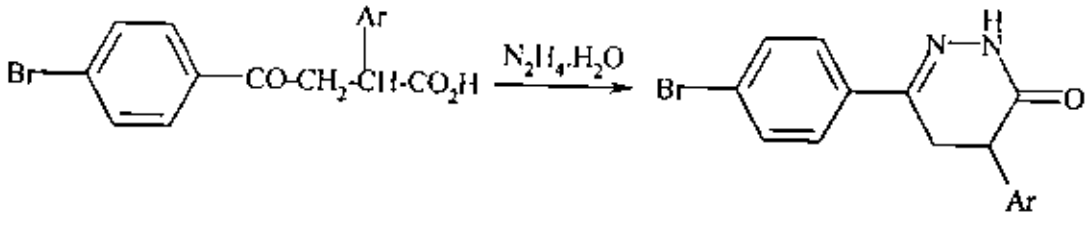
(XXXI)

It has been reported that [19], the condensation of phenylbenzoyl propionic acid derivative (XXXII) with hydrazine hydrate afforded the pyridazin-3(2H)-one derivative (XXXIII).



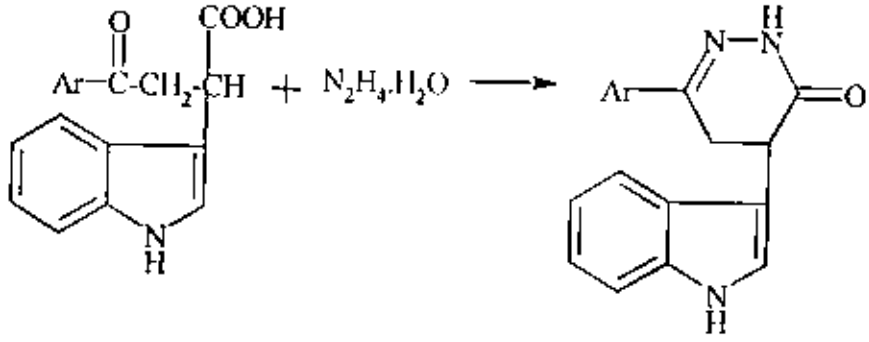
(XXXII) (XXXIII)

The reaction of α-aryl-β-(4-bromobezoyl) propionic acids with hydrazine hydrate yielded the corresponding 4-aryl-6-(4-bromophenyl)-4.5-dihydro-pyridazin-3(2H)-ones (XXXIV)[20].



(XXXIV)

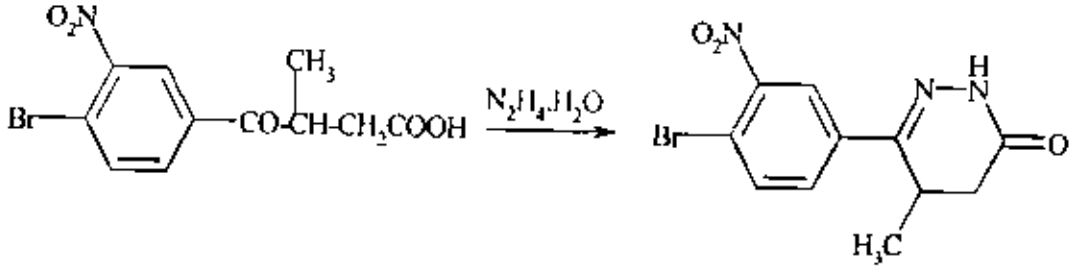
The β-aroyl-α-(3-indolyl) propionic acids reacted with hydrazine hydrate to yield the corresponding 4,6-disubstituted-4,5-dihydropyridazin-3(2H)-ones (XXXV)[21].



(XXXV)

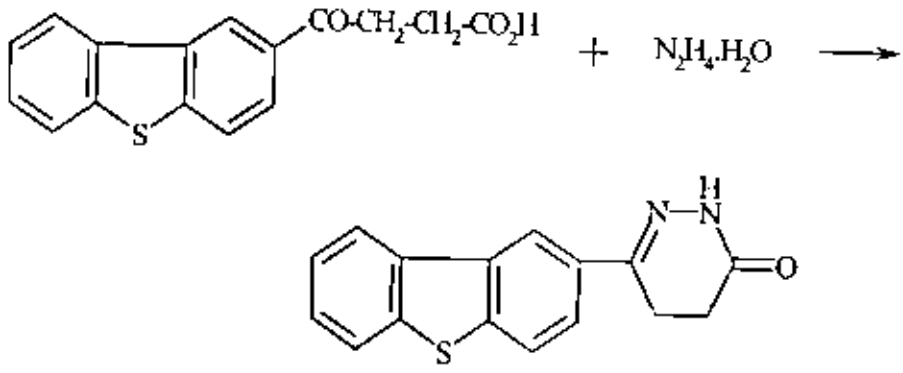
iii). **From butanoic acids derivative: -**

It has been reported[22] that, when 4-(4-bromo-3-nitrophenyl)-3-methyl-4-oxo-butanic acid was cyclocondensed with hydrazine hydrate in acetic acid, gave 6-(4-bromo-3-nitrophenyl)-4,5-dihydro-5-methylpyridazin-3(2H)-one (XXXVI).



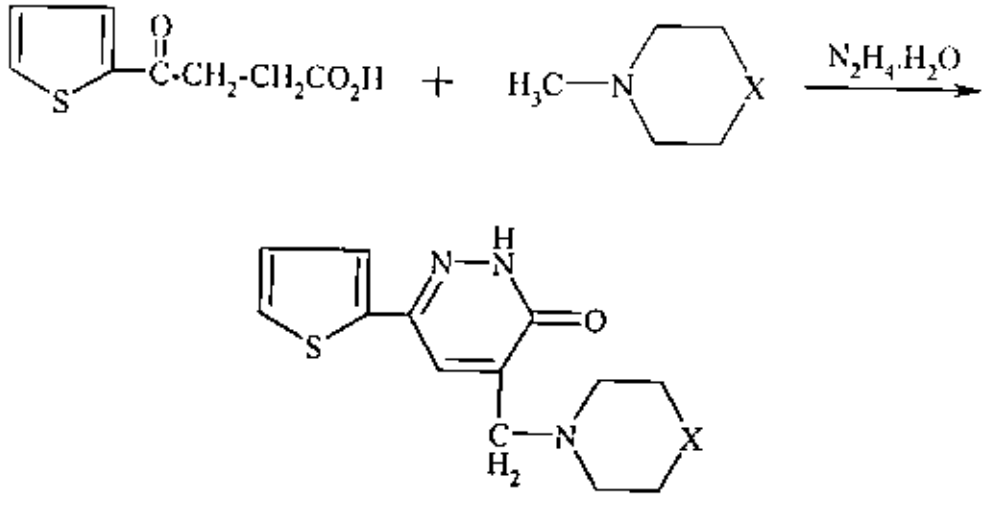
(XXXVI)

It has been found[23] that dihydrodibenzothienylpyridazin-3(2H)-one (XXXVII) was obtained as a main product in the reaction of dibenzothienyl-oxobutanoic acid with hydrazine hydrate.



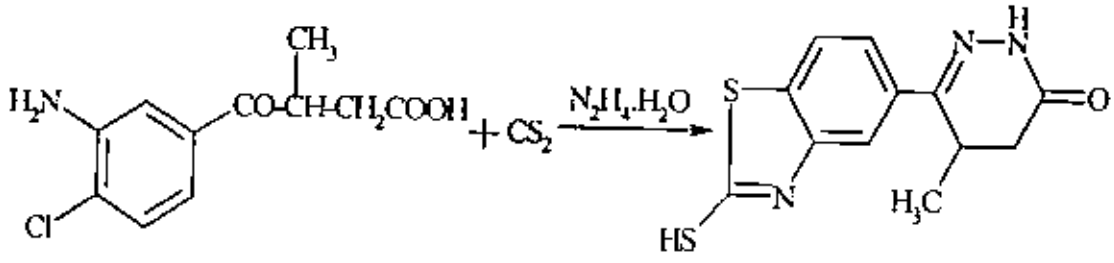
(XXXVII)

Pyridazin-3(2H)-one derivatives (XXXVIII, X= CHMe, NMe, O, NCH_2Ph)[24] were prepared by amino methylation of 4-oxo-4-thiophenobutanoic acid followed by cyclization with hydrazine hydrate.



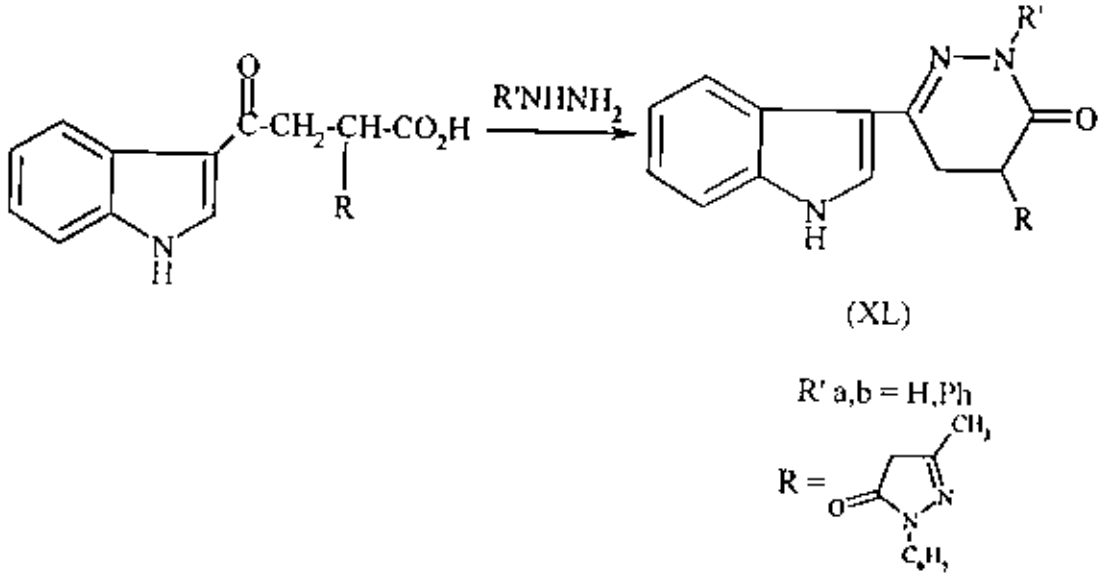
(XXXVIII)

4,5-Dihydro-3(2H)pyridazinone derivatives (XXXIX)[25] were prepared by cyclocondensation of 4-(3-amino-4-chlorophenyl)-3-methyl-4-oxo-butanoic acid with CS_2 and $N_2H_4.H_2O$.



(XXXIX)

It has been reported that[26,27] the synthesis of 4-(benzylamino)-6-(3-indolyl) and 4-(3-methylpyrazol-5-one)-6-(3-indolyl)-4,5-dihydropyridazin-3-ones (XLa and b) respectively were prepared through the condensation of the appropriate α-(substituted)-4-oxo-4-(3-indoyl) butanoic acid with hydrazines in refluxed butanol.

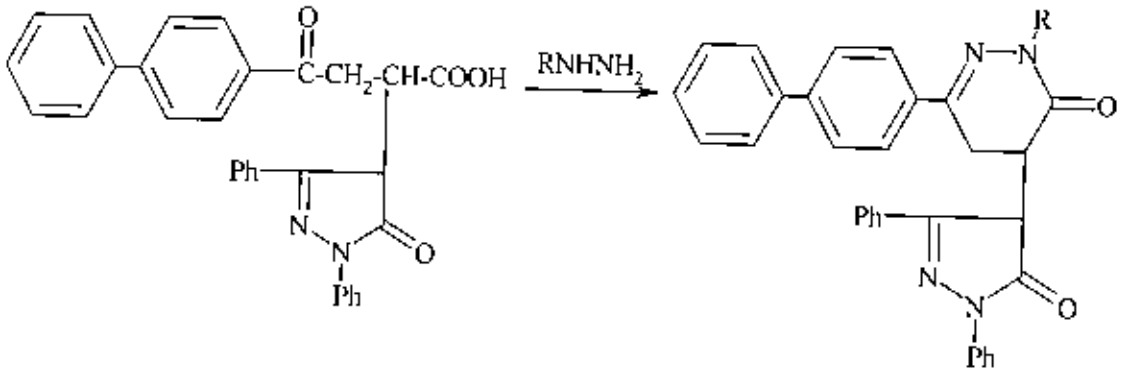


(XL)

R' a,b = H,Ph

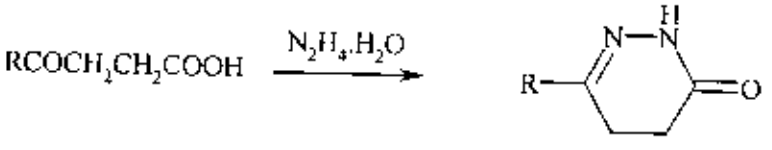
It was reported that[28,29] a new series of pyridazin-3-ones were prepared through the neucleophilic addition of 1,3-diphenyl-2-pyrazolin-5-one to 4-diphenyl-4-oxo-2-butanoic acid followed by cyclocondensation of the adduct

with hydrazine hydrate and/or phenylhydrazine to the corresponding dihydro-pyridazin-3-ones (XLI, R=H, Ph).



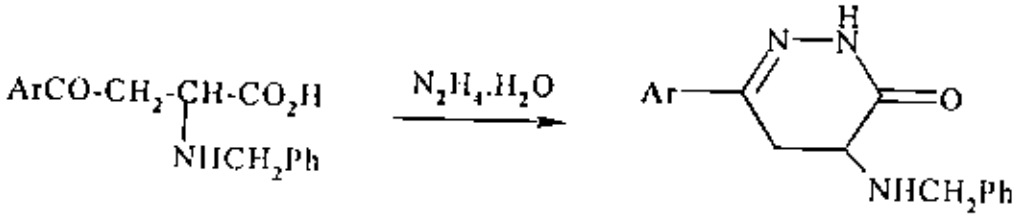
(XLI)

It has been reported[30] that 6-(P-methoxyphenyl)-4,5-dihydropyridazin-3(2H)-one (XLII) was prepared via reaction of butanoic acid derivatives with hydrazine hydrate.



(XLII)

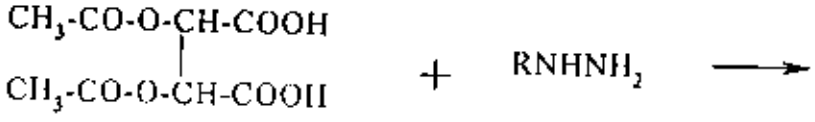
It has been reported that[31], the condensation of butanoic acid derivative with hydrazine hydrate in boiling ethanol furnished the corresponding 6-aryl-4-benzylamino-6-(5,5-dioxodibenzothiophen-2-yl)pyrida-zin-3(2H)-one (XLIII).

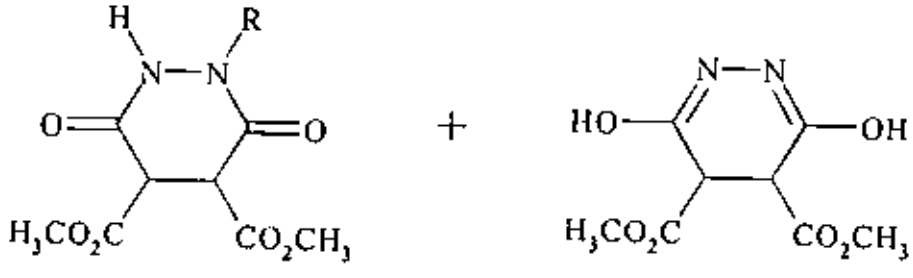


(XLIII)

iv). From tartaric acid derivative: -

Dihydropyridazinones (XLIV) and (XLV)[32] having antimicrobial activity were prepared by the reaction of diacetyl (L)-(+) tartaric acid anhydride with hydrazine.

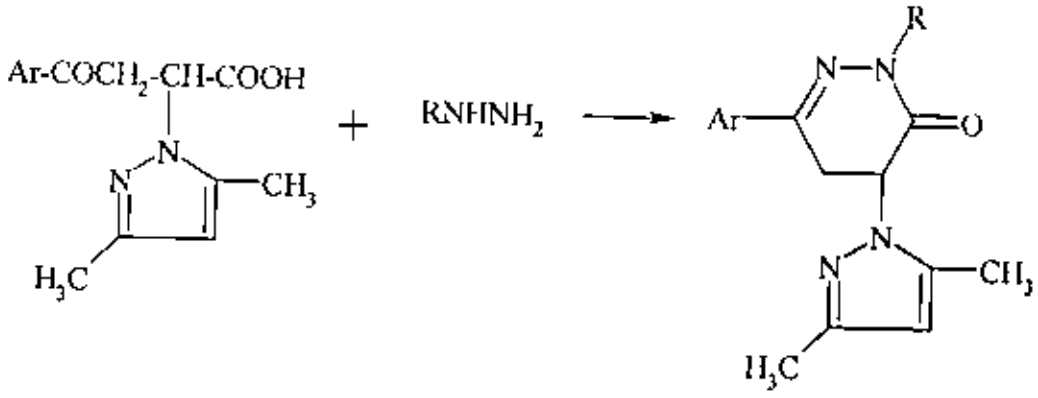




(XLIV) (XLV)

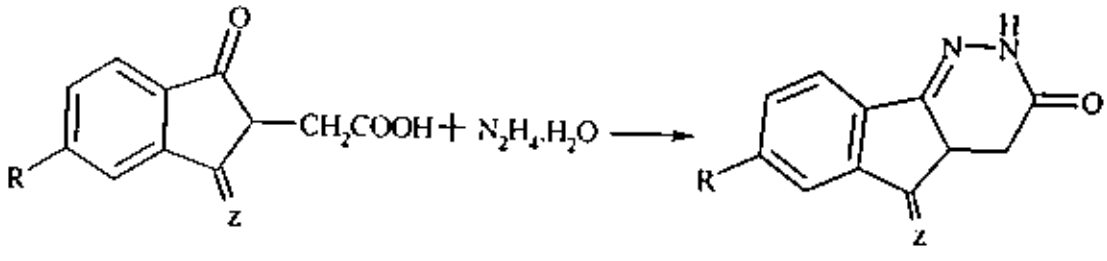
v). From acetic acid derivatives:-

It has been found[33] that phenacyldimethylpyrazolo acetic acids reacted with hydrazines, afforded the corresponding 6-aryl-4-(1-pyrazolyl)pyridazin-3-one (XLVI).



(XLVI)

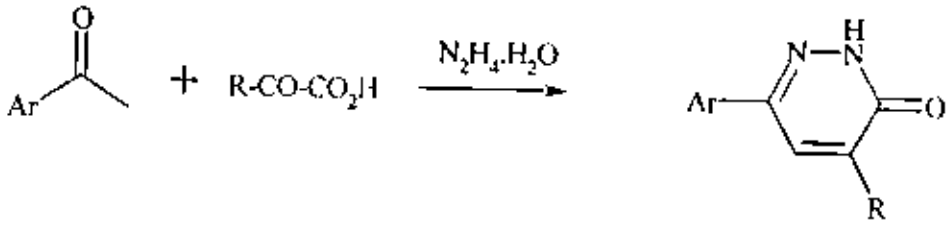
Indenepyridazin-3(2H)-one (XLVII. R= F, H; Z=H_2, O) were prepared and they exhibited antiinflammatory, analgesic and antipyretic activities[34].



(XLVII)

vi). **<u>From the reaction of arylmethylketones with α-keto acid derivatives in presence hydrazine hydrate</u>: -**

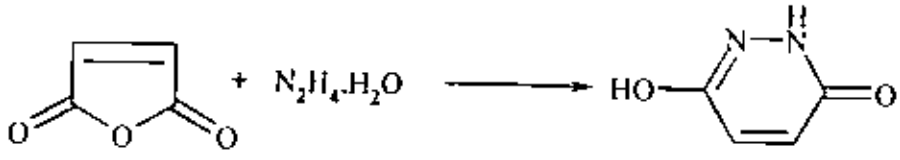
It has been reported that[35], the historical approach first involves a condensation of various arylmethylketones with commercially available α-ketoacids leading to the corresponding 6-aryl pyridazin-3(2H)-ones (XLVIII; R=H, Ph, Me; Ar=4MePh).



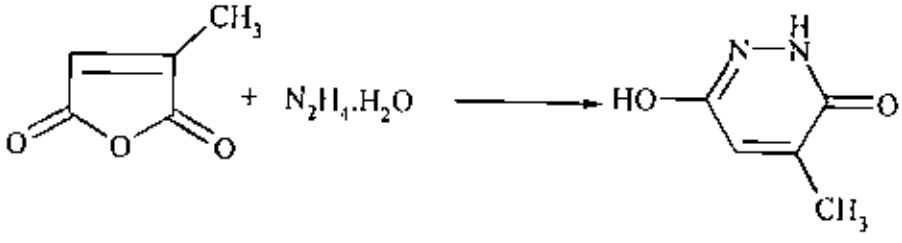
(XLVIII)

vii).<u>From dibasic acid anhydride</u>: -

Maleic and Citraconic anhydrides reacted with hydrazine hydrate to give 6-hydroxypyridazin-3(2H)-one (XLIX) and 6-hydroxy-4-methylpyridazin-3(2H)-one (L), respectively[36].

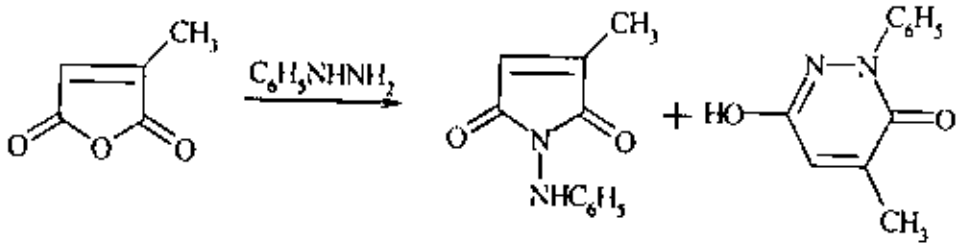


(XLIX)

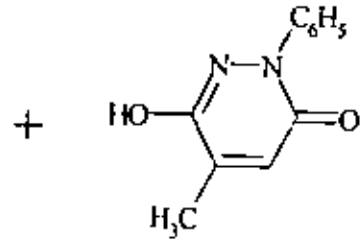


(L)

On the other hand, citraconic anhydride reacts with phenylhydrazine in boiling acetic acid to yield N-anilinocitraconimide (LI) with 6-hydroxy-4-methyl-2-phenylpyridazin-3-one (LII) and the corresponding 5-methyl isomer (LIII)[37].

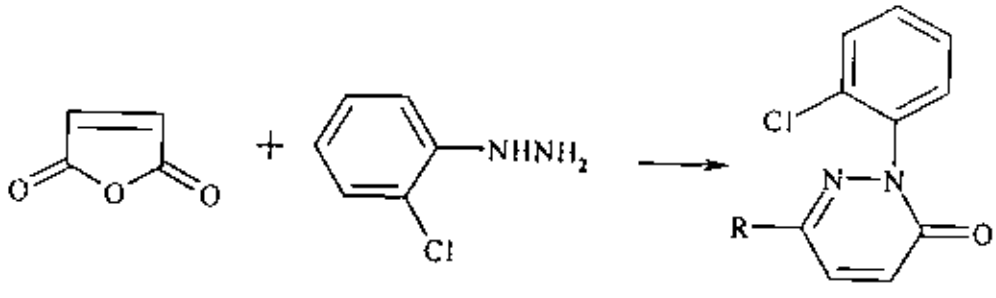


(LI) (LII)



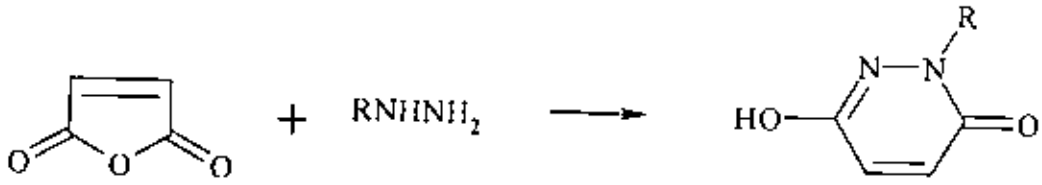
(LIII)

It has been found that[38], the reaction of maliec anhydride with o-chlorophenylhydrazine gave the pyridazin-3-one derivative (LIV).



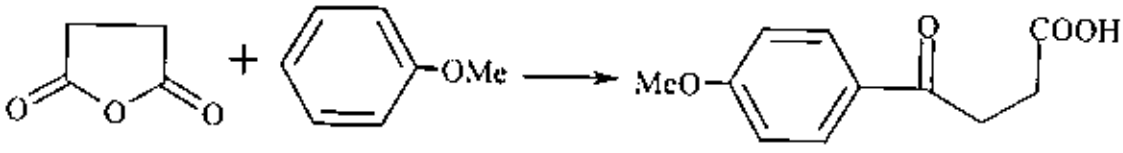
(LIV)

It is also reported that[39] 6-hydroxypyridazin-3-one (LV, R=1-$C_{10}H_7$; 2-$C_{10}H_7$) was prepared in 33.3% and 20.4% yields by cyclization of $RNHNH_2$ with maleic anhydride.

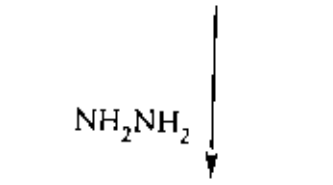


(LV)

It has been found that[40] treating of saturated acetic anhydride (LVI) with hydrazine hydrate gave the 4,5-dihydropyridazin-3(2H)-one derivative (LVII).



(LVI)



(LVII)

2.1.2 By the action of hydrazine hydrate on a mixture of o-dicarbonyl compound and carboxylic acid derivatives: -

In this method a mixture of three available starting materials are usually employed[41].

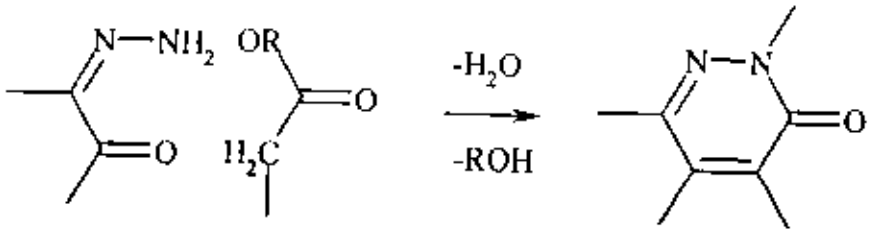
a) An o-dicarbonyl compound.

b) A carboxylic acid derivative containing a reactive methylene group.

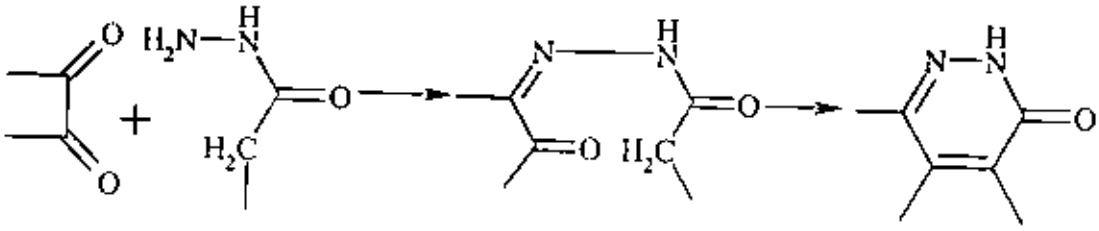
c) Hydrazine or monosubtituted hydrazine.

The reaction may takes place by the condensation of the monohydrazone of o-dicarbonyl compound with the ester of the carboxylic acid containing an active methylene group.

This method is recommended when using aromatic diketones and could be represented by general equation as follows:

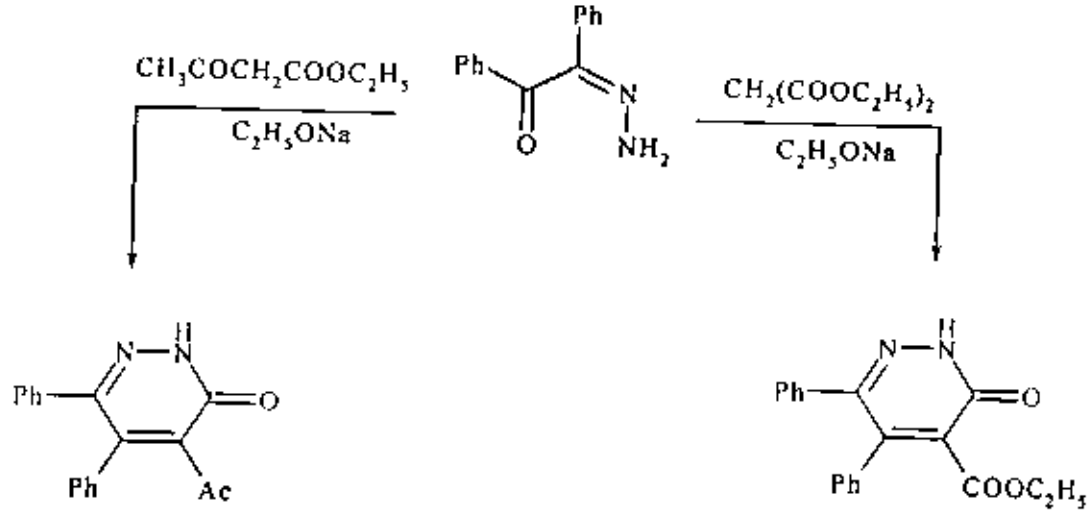


Alternatively, the hydrazide of the acid is allowed to condense with o-diketone followed by ring closure as follows:



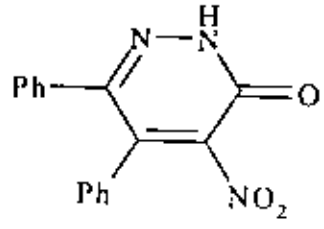
Among the dicarbonyl compound used in this synthesis are diacetyl, benzoylacetyl, benzil, cyclohexane dione, methyl glyoxal and phenanthraquinone.

The acid derivatives participating in the synthesis are diethyl malonate, ethyl cyanoacetate, ethyl phenyl acetate, ethyl hippurate and ethyl acetoacetate. For example, the condensation of benzyl monohydrazone with ethyl acetoacetate or diethyl malonate in the presence of sodium ethoxide gave 4-acetyl or 4-carboethoxy-5,6-diphenylpyridazin-3(2H)-one (LVIII) or (LIX).



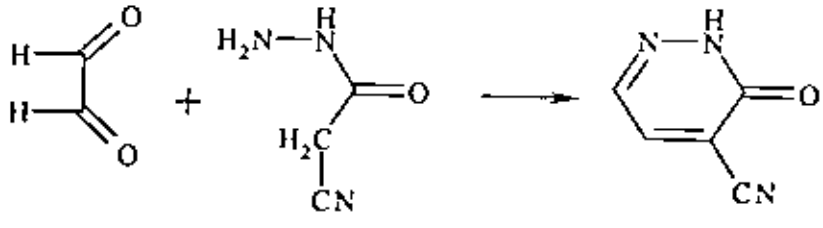
(LVIII) (LIX)

On the other hand[42], cyclocondensation of $PhCO-\overset{Ph}{\overset{|}{C}}=N-NH_2$ and $O_2NCH_2COOC_2H_5$ in piperidine at 105 °C gave 45% pyridazin-3(2H)-one (LX); this yield was obtained when piperidine was 1.4:1 excess.

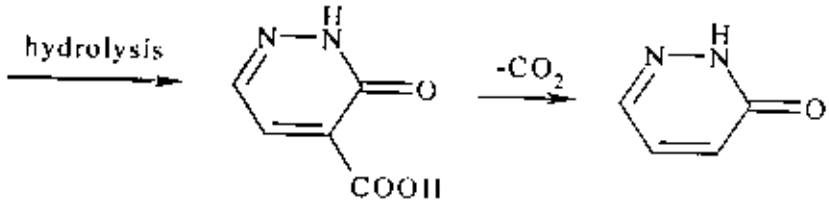


(LX)

The condensation of glyoxal with the hydrazide of cyanoacetic acid gave 4-cyanopyridazin-3(2H)-one (LXI), which on hydrolysis and decarboxylation of the formed acid gave the unsubstantiated Pyridazin-3(2H)-one (LXII)[43].



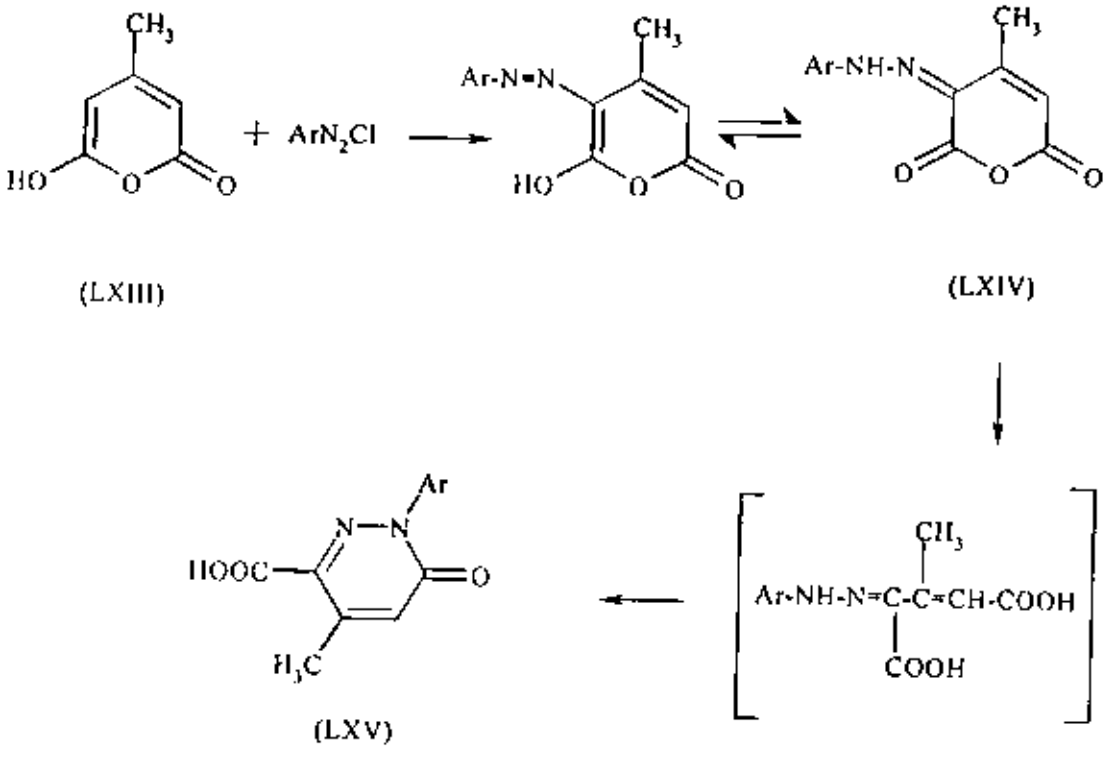
(LXI)



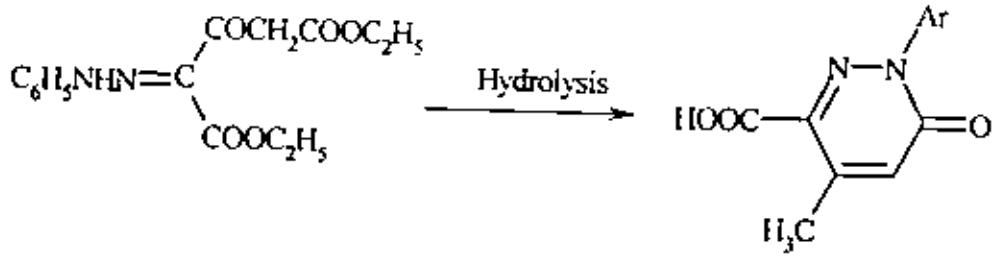
(LXII)

2.1.3 From diazonium salts: -

Aryl diazonium salts are coupled with β-methyl glutaconic anhydride (LXIII) to give α-keto-β-methyl glutaric anhydride arylhydrazones (LXIV), which on hydrolysis yield 2-aryl-6-carboxy-5-methylpyridazin-3-ones (LXV)[44].

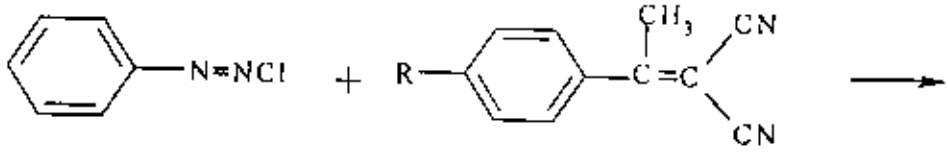


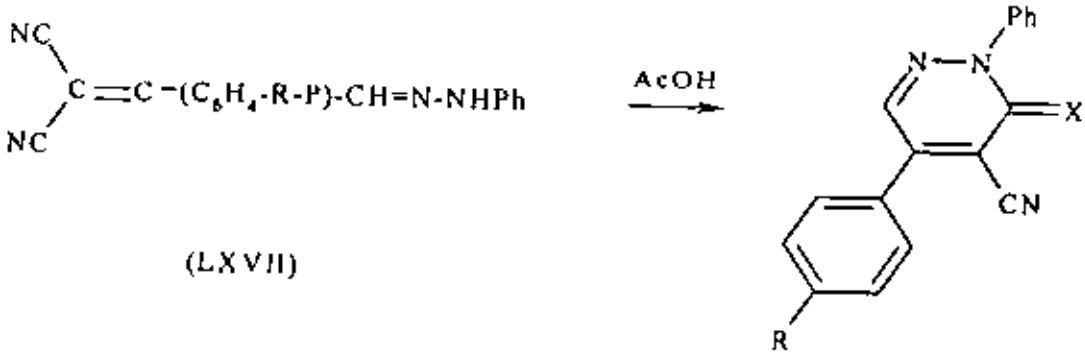
In similar manner acetone dicarboxylic ester reacts with benzene diazonium chloride to give a hydrazone derivative, which yields on hydrolysis 6-carboxy-5-hydroxy-2-phenylpyridazin-3-one (LXVI)[45].



(LXVI)

It has been reported that[46] pyridazin-3-ones (LXVIII) (, R=Me, Cl, OH, MeO) were obtained from 4-R-C_6H_3-(Me)-C=C-$(CN)_2$ when treated with benzene diazonium chloride and sodium acetate in ethanol to give (LXVII), which cyclized by refluxing in AcOH yielded (70%) (LXVIII).

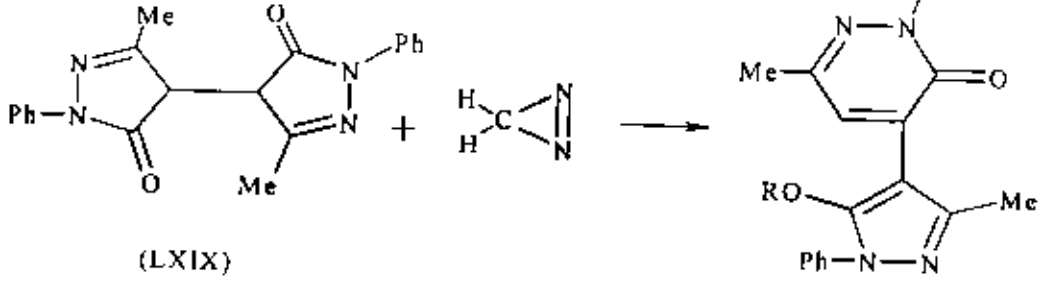




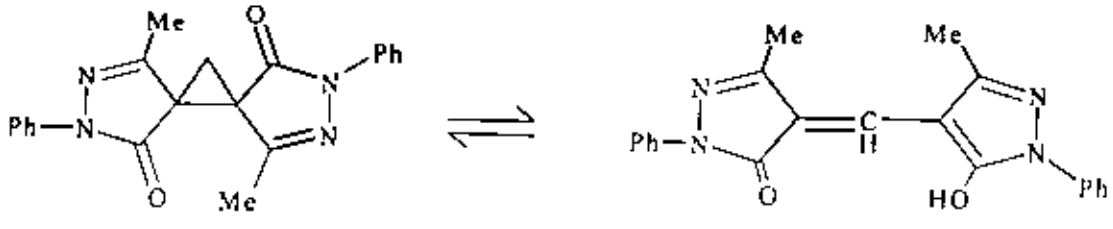
(LXVII)

(LXVIII)

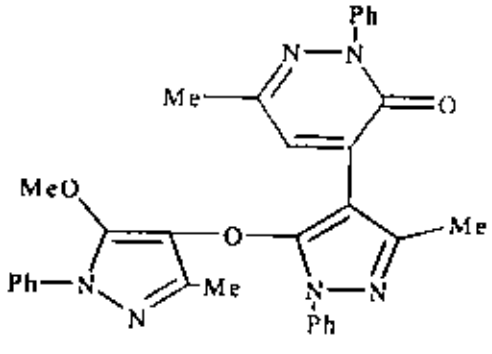
Reaction of diazomethane with pyrazolone blue (LXIX) gave a pyridazin-3-one (LXX, R=H) which was methylated by excess CH_2N_2 to give (LXX, R=CH_3); a dispiro compound (LXXI) which isomerized to (LXXII) and reaction of three moles from pyrazolone with two moles of diazomethane gave the pyridazin-3-one derivative (LXXIII)[47].



(LXIX) (LXX)



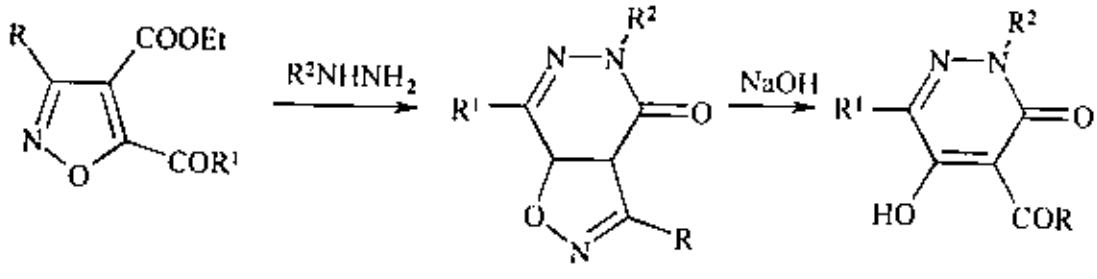
(LXXI) (LXXII)



(LXXIII)

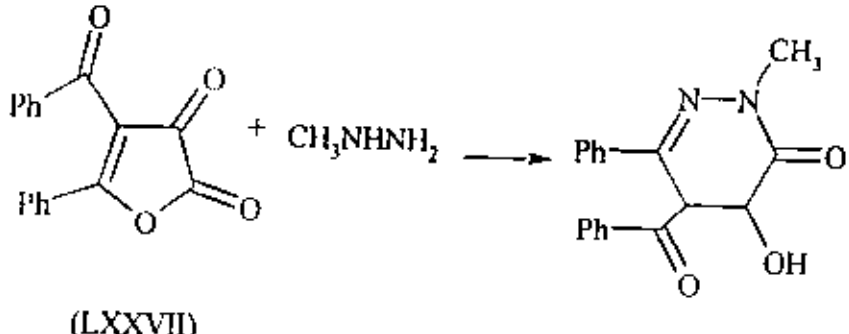
2.1.4 From heterocyclic compounds: -

Cyclocondensation of acylisoxazolecarboxylates (LXXIV, R=CH_3, R^1=H, CH_3-C_6H_4. R=C_6H_5; R^1= CH_3) with R^2NHNH_2 (R^2=H, CH_2-C_6H_4, C_6H_5) gave izoxazolopyridazin-3-ones (LXXV). Sequential reductive ring opening and hydrolysis with sodium hydroxide of (LXXV) gave acylhydroxypyridazin-3-ones (LXXVI)[48].



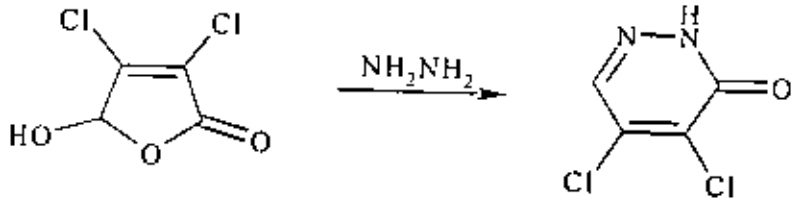
(LXXIV) (LXXV) (LXXVI)

It has been reported that[49] the reaction of furandione (LXXVII) with hydrazine hydrate the pyridazin-3-one was obtained (LXXVIII).



(LXXVII) (LXXVIII)

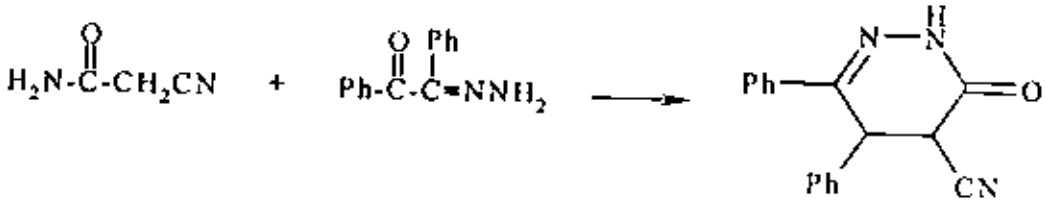
It was reported that[50] treatment of 3,4-dichloro-5-hydroxyfuran-2(5H)-one (LXXIX) with hydrazine sulfate in refluxing ethanol/water (v/v ¼ 1:1) in the presence of sodium acetate gave 4,5-dichloropyridazin-3(2H)-one (LXXX) in excellent yields.



(LXXIX) (LXXX)

2.1.5 From cyanoacetamide: -

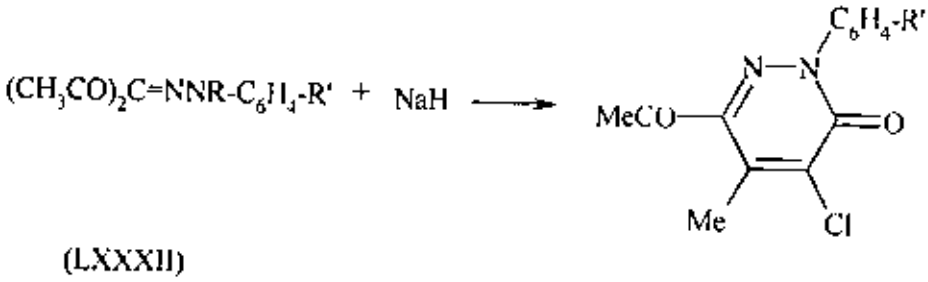
Cyclocondensation of cyanoacetamide and benzilmonohydrazone in dry pyridine gave 5,6-diphenyl-4-cyanopyridazin-3(2H)-one (LXXXI)[51].



(LXXXI)

2.1.6 From pentane-2,3,4-trione-3-arylhydrazone: -

It was found that deprotonation of pentane-2,3,4-trione-3-arylhydrazones ($(CH_3CO)_2C$=NNR$C_6H_4R^1$-4C, R=H, R^1=H,CH_3,OC_2H_5,NO_2) with equivalent NaH followed by addition of Cl-CH_2CO-Cl afforded the N-chloroacetyl derivatives (LXXXII) R=$COCH_2Cl$, along with cyclized (LXXXIII) were also prepared by treatment of (LXXXII, R=H) and Cl-CH_2CO-Cl with excess NaH, pyridazin-3-one (LXXXIII) were also obtained by treatment of (LXXXII, R=H) with Cl-CH_2CO-Cl in presence of either coc.H_2SO_4 or p-toluensulfonic acid[52].

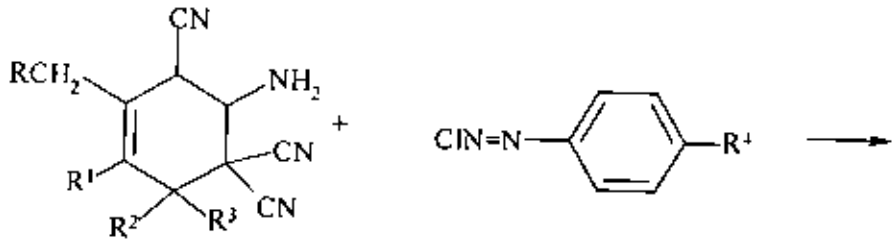


(LXXXII) (LXXXIII)

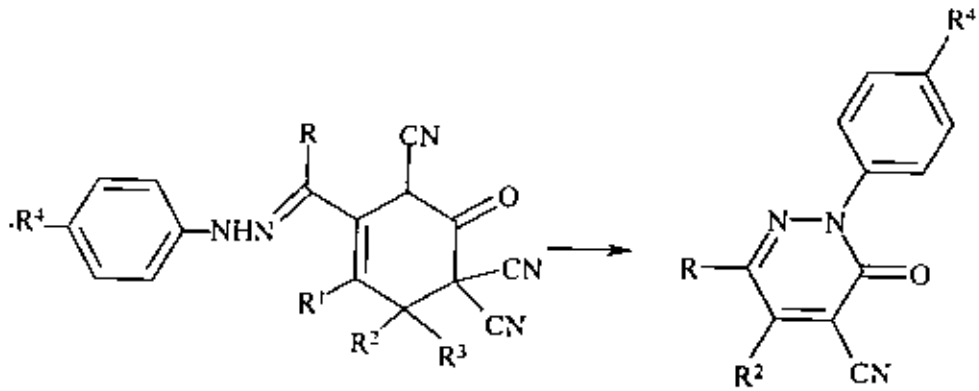
2.1.7 Form 1-amino-2,6,6-tricyanocyclohexadiene derivatives: -

The coupling of 1-amino-2, 6,6-tricyanocyclohexadiene derivatives (LXXXIV, R = R^1 = H; R^2 = R^3 = CH_3; R =R^2 =R^3 =CH_3, R^1 = H; R^2, R^1 = $(CH_2)_3$) with a variety of aryldiazonium salts produces the hydrazones

(LXXXV, R^4 = H, CH_3O, CH_3, Br, NO_2), which in the presence of an ethanolic weak base at elevated temperature, furnish 2-aryl-4-cyanopyridazin-3-ones (LXXXVI)[53].



(LXXXIV)



(LXXXV)

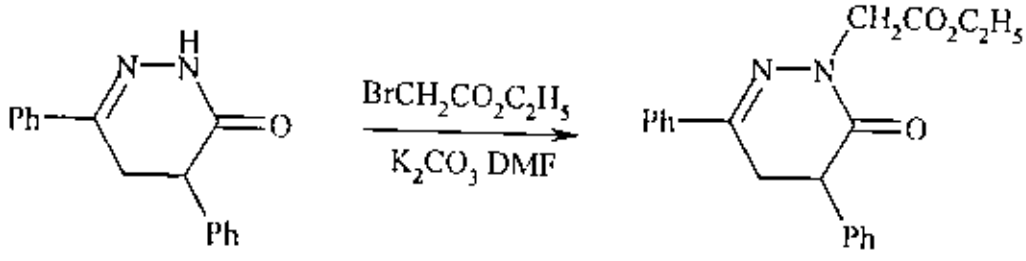
(LXXXVI)

2.2 Reaction of pyridazin-3(2H)-one: -

2.2.1 Alkylation of pyridazin-3(2H)-ones: -

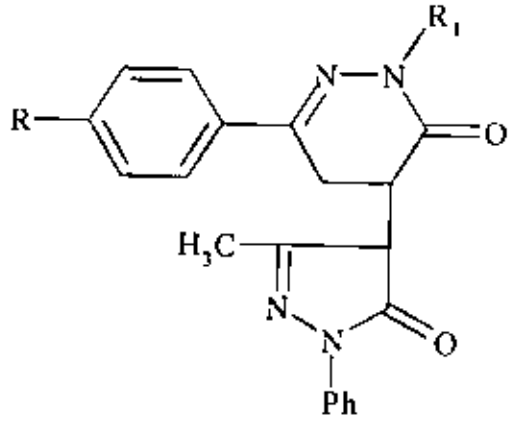
The reactivity of pyridazin-3(2H)-one towards some reagents which are known to attack the nitrogen atom at position 2 was studied.

It has been found that[9], the ester derivative of the reaction of pyridazin-3(2H)-ones (XVI) with bromoacetate in ethanol in the presence of 10% aqueous NaOH gave the N-substitutedpyridazin-3-one (LXXXVII).



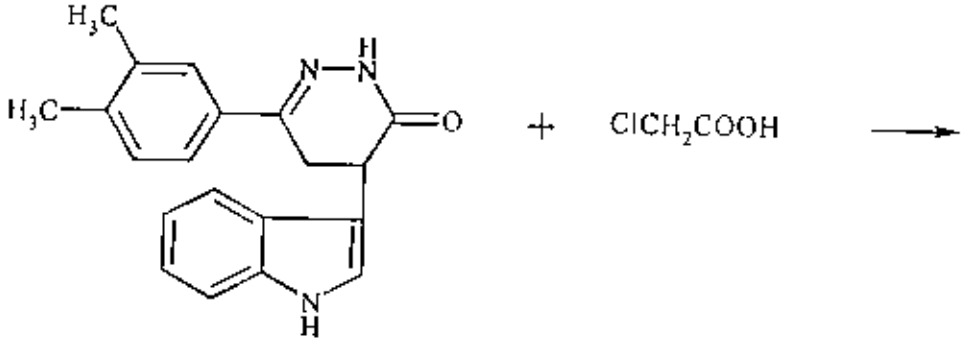
(XVI) (LXXXVII)

It was found that[12], alkylation of 4-pyrazolinonylpyridazin -3-ones with dimethylsulphate, diethylsulphate, ethyl bromoacetate and benzene- sulfonyl chloride, gave the corresponding N-substituted derivative (XXII, R^1= Me, Et, CH_2CO_2Et, $SO_2C_6H_5$).

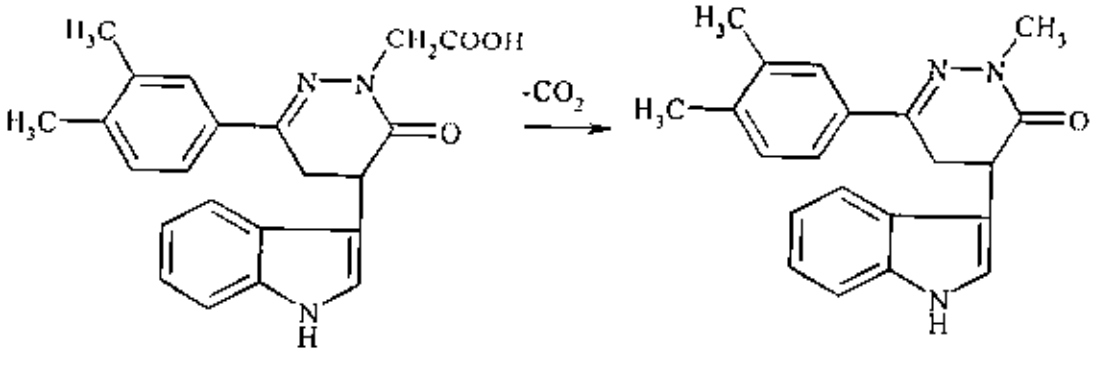


(XXII)

Surprisingly, the reaction of pyridazin-3(2H)-ones (XXVI) with chloroacetic acid in ethanol in the presence of 20% aqueous NaOH gave the N-methylpyridazin-3-one (LXXXVIII)[14].

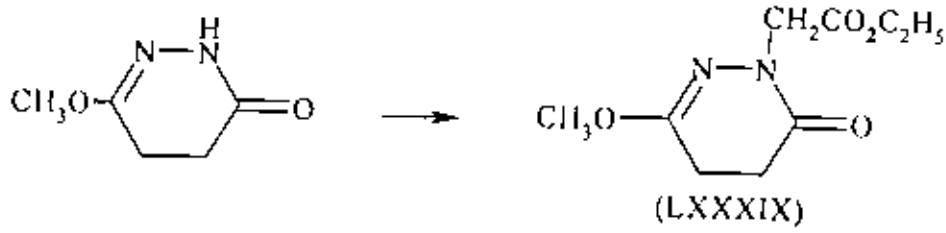


(XXVI)



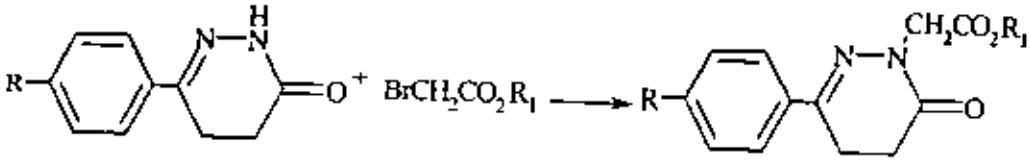
(LXXXVIII)

Recently, it was reported[40] that, the alkylation of 4,5-dihydropyridazin-3(2H)-one with bromoacetate gave the N-substituted (LXXXIX) and was hydrolyzed by 10 N HCl.

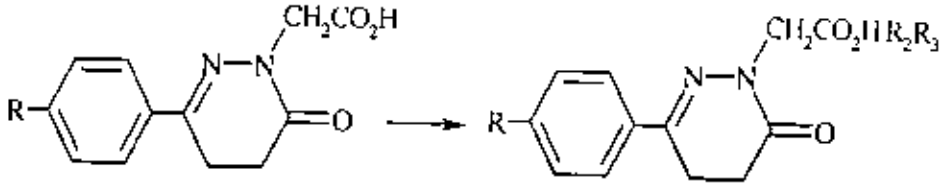


(LXXXIX)

It has been reported[54] that, when 6-aryldihydropyridazin-3(2H)-ones [XC. R=H, Cl, F, CH_3O] were treated with Br-CH_2-COOR^1 (R^1=CH_3-, -C_2H_5, $(CH_3)_3C$-) gave the corresponding esters (XCI) which hydrolyzed to the corresponding carboxylic acids. Coupling these carboxylic acids with various amines the corresponding oxopyridazine acetamides were obtained [XCII, R^2=H; R^3= $(CH_3)_2CH$, CH_3-, C_2H_5-, $(CH_3)_3C$-; R^2= R^3= CH_3-, R^3= -$(CH_2)_2N$-CH_3, $(CH_2)_2$-]. A number of these derivatives showed weak anticonvulsant and weak analgesic activities while nearly all displayed a sedative profile.

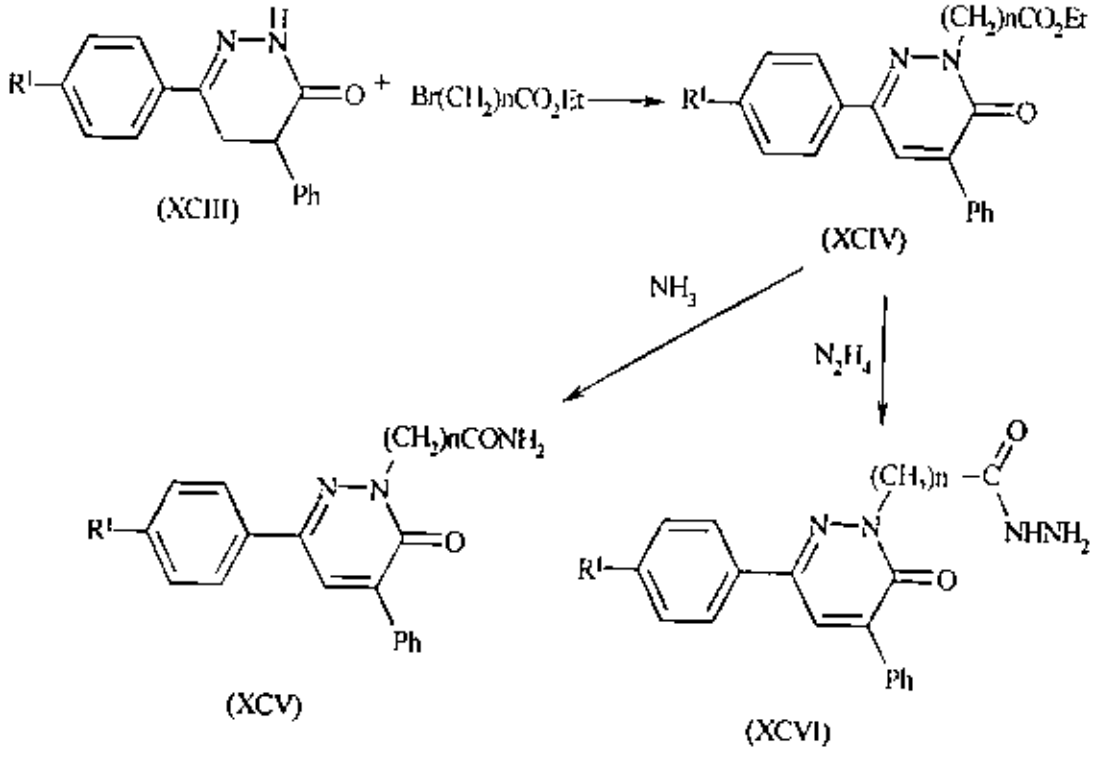


(XC) (XCI)

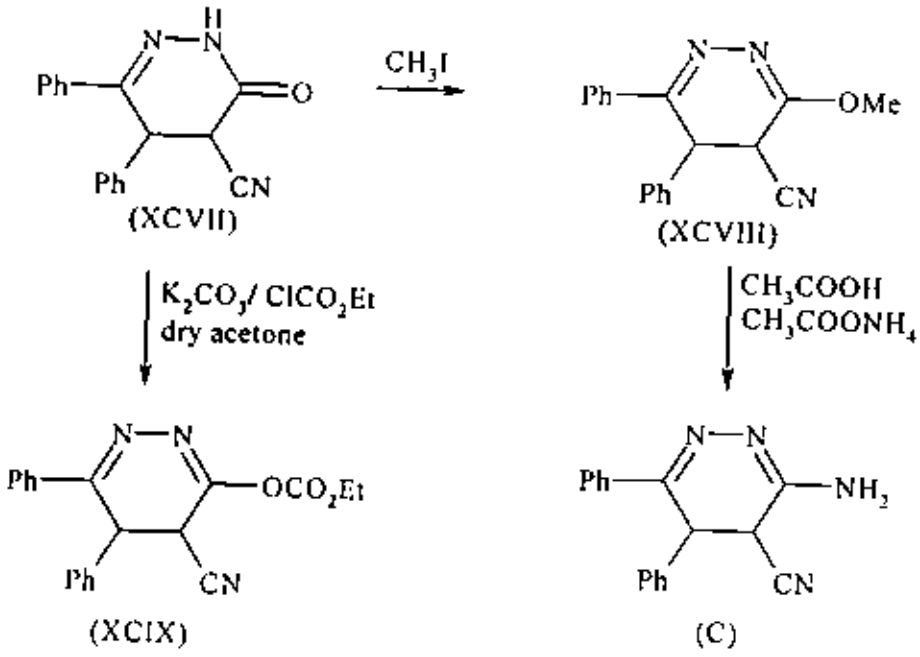


(XCII)

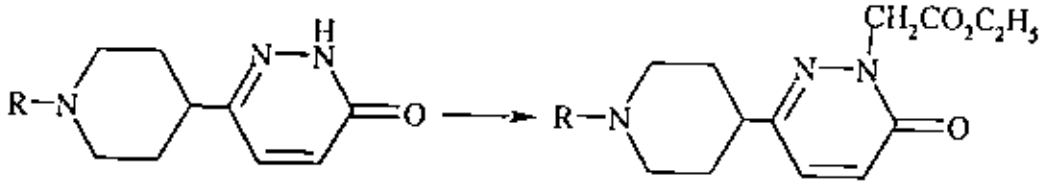
Treating diaryl pyridazin-3-ones (XCIII; R^1=H, Cl, F) with $Br\text{-}(CH_2)_n\text{-}COOC_2H_5$ (n=1,2,3) in the presence of NaOEt/EtOH gave (XCIV) which, when treated with NH_3 or N_2H_4 gave (XCV) and (XCVI)[55], the latter compound showed anticonvulsant activity as well as weak sedative.



Alkylation of pyridazin-3(2H)-one derivative (XCVII) with methyl iodide gave (XCVIII) which converted by $AcONH_4$/AcOH to aminopyridazine (XCIX)[56]. When pyridazin-3(2H)-ones (XCVII) was treated with ethylchloro-formate compound (C) was obtained.

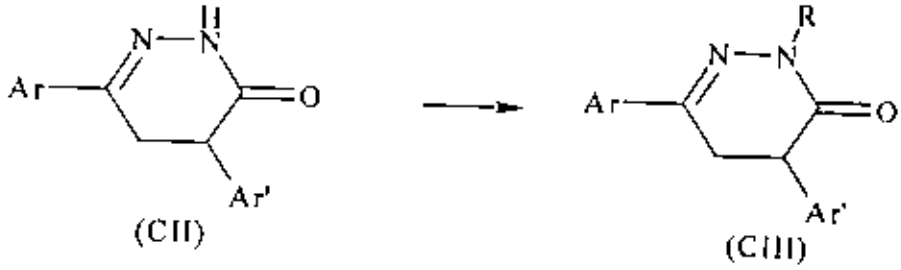


It has been reported that [57], the reaction of pyridazin-3(2H)-ones with bromoacetate in DMF in the presence of potassium carbonate gave the alkylation of pyridazin-3-ones (CI).



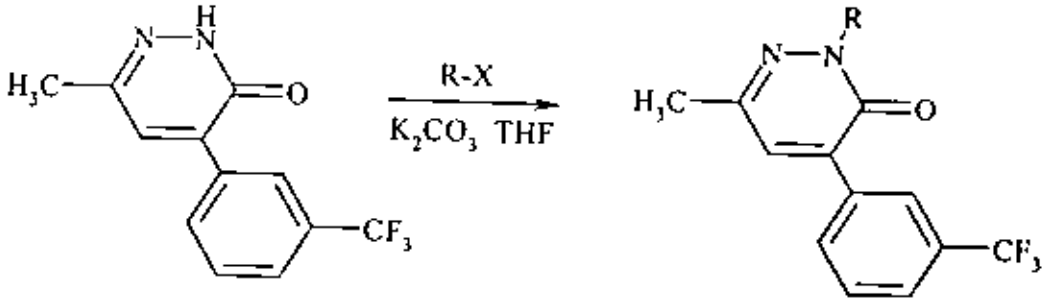
(CI)

It has been found that[58,59], when 4,6-diaryl-4,5-dihydropyridazin-3(2H)-ones (CII) were treated with dimethylsulfate, diethylsulfate and/or ethylbromoacetate in presence of potassium carbonate, the corresponding N-substituted derivatives (CIII, R= Me, Et, CH_2-$COOC_2H_5$) were obtained.



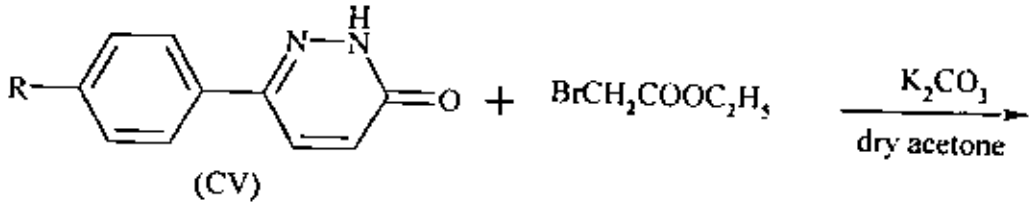
(CII) (CIII)

It has been found that[60], the reaction of pyridazin-3(2H)-one with R-X and K_2CO_3 in dry tetrahydrofuran N-substituted pyridazin-3-one (CIV) was obtianed.

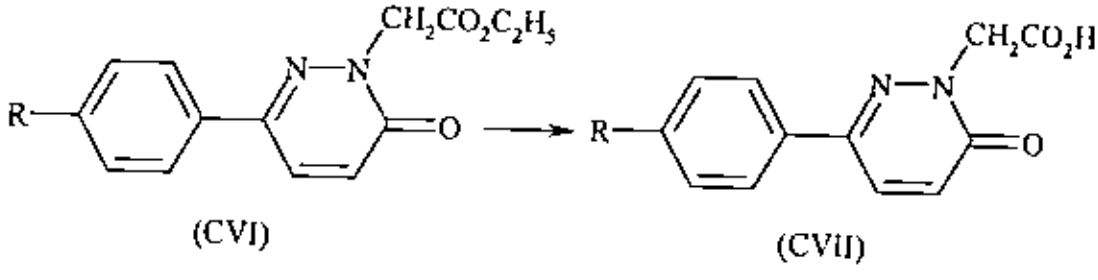


(CIV)

It has been found that [61], when pyridazin-3(2H)-one (CV) was treated with Br-$CH_2COOC_2H_5$ gave (CVI) which was hydrolyzed to (CVII).



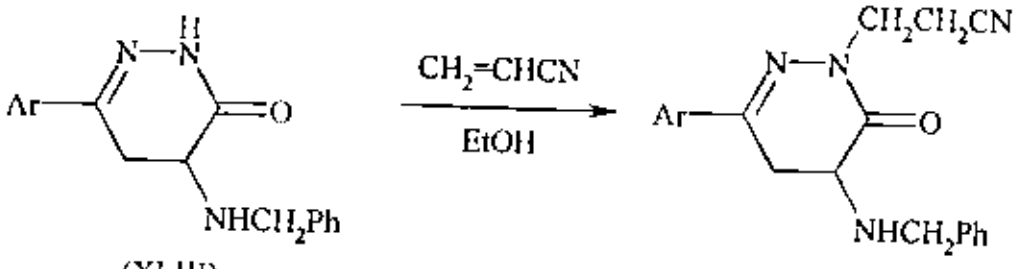
(CV)



(CVI) (CVII)

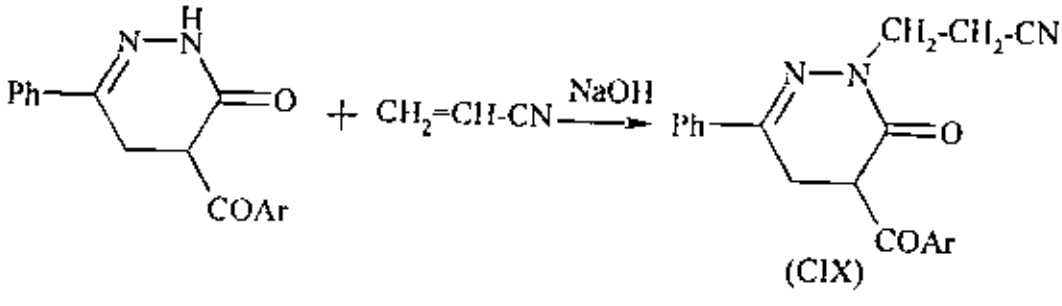
2.2.2 **Reaction with acrylonitrile**: -

On treatment of pyridazin-3(2H)-one (XLIII)[31] with acrylonitrile in boiling ethanol containing catalytic amounts of aqueous sodium hydroxide solution, a Michael-type addition occurred at the activated double bond and afforded the 4-benzylamino-2-cyanoethyl-6-(5.5-dioxodibenzothiophen-2-yl)-pyridazin-3-one (CVIII).



(XLIII) (CVIII)

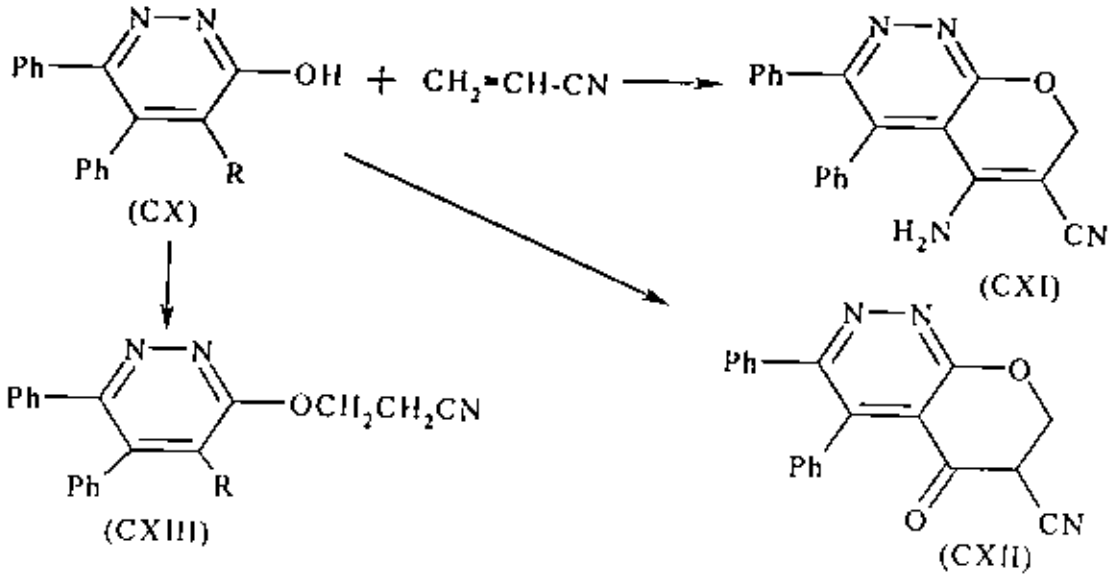
Reaction of 4-aroyl-6-phenylpyridazin-3(2H)-ones (Ar= Ph, 4-CH_3O-C_6H_4 and 4-Cl-C_6H_4) with acrylonitrile in ethanol in the presence of aqueous sodium hydroxide gave 4-aroyl-2-(2-cyanoethyl)-6-phenylpyridazin-3-ones (CIX)[62].



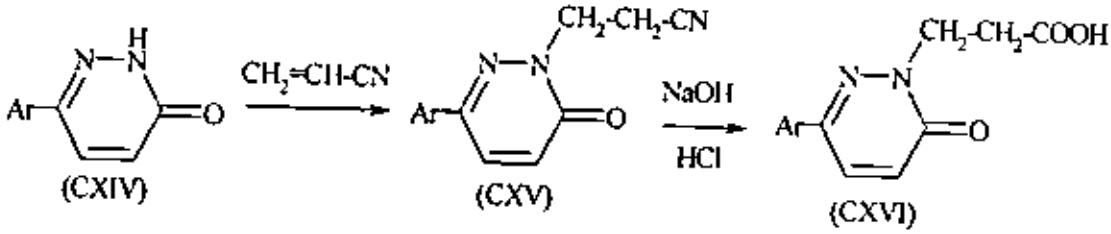
(CIX)

On the other hand, the reaction of hydroxypyridazine (CX, R=CN) with

acrylonitrile at high-temperature gave the corresponding pyranopyridazinone (CXI). When hydroxypyridazine (CX, R=$COOC_2H_5$) reacted with acrylonitrile gave the corresponding pyridazinone (CXII). However, when (CX, R=CN) reacted with acrylonitrile in ethanol and alkaline medium the addition product (CXIII) is obtained[63].

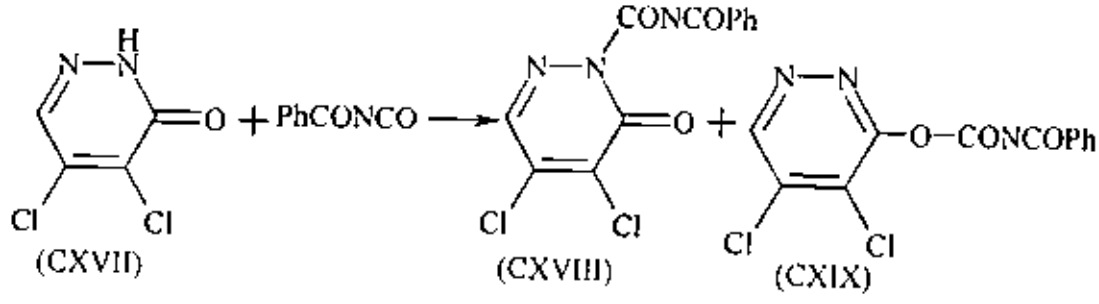


6-Arylpyridazin-3(2H)-ones (CXIV) reacted in the lactam form with acrylonitrile to give N-cyanoethyl derivatives (CXV)[64,65]. These nitriles were hydrolyzed easily to the corresponding carboxylic acids, (CXVI) when heated under reflux with sodium hydroxide, followed by acidification with hydrochloric acid.



2.2.3 Reaction with isocyanate: -

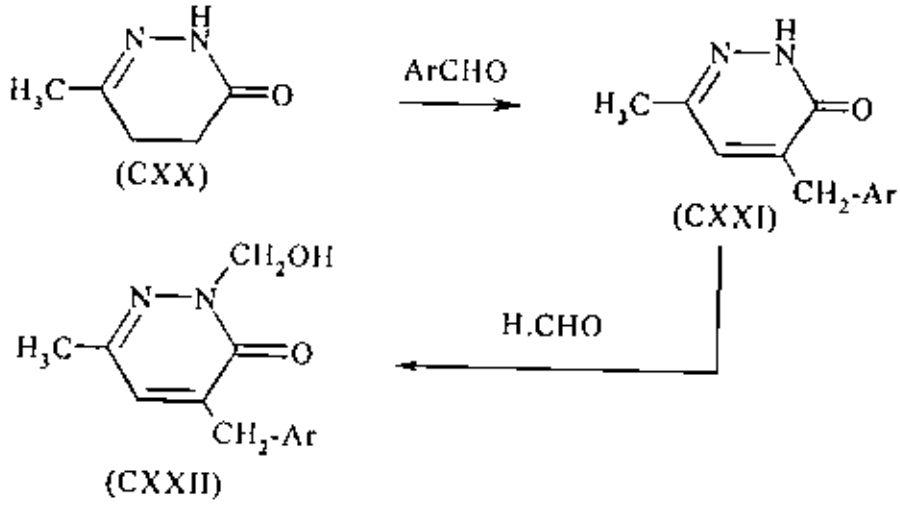
It was reported[66] that dichloropyridazin-3(2H)-ones (CXVII) reacted with benzoyl isocyanate gave a 5 % yield of N-adduct (CXVIII) and 60 % yield of O-adduct (CXIX).



(CXVII) (CXVIII) (CXIX)

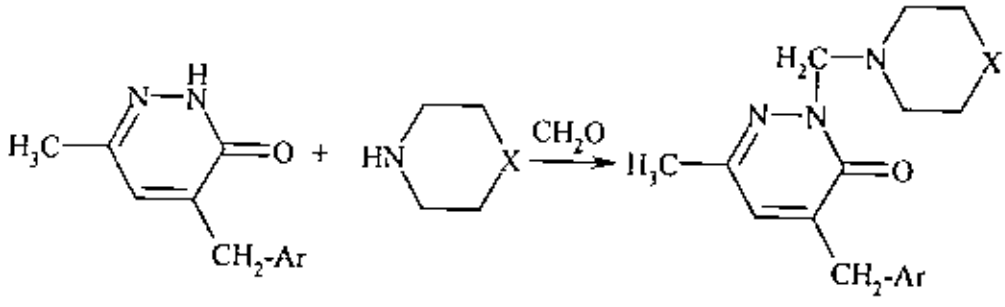
2.2.4 Reaction with aldehydes and Mannich reaction: -

It has been found[67] that reaction of methylpyridazin-3(2H)-ones (CXX) with ArCHO (Ar= 1.2-naphthyl, 2-$CH_3OC_6H_4$-) in 50 % ethanolic sodium hydroxide gave (CXXI). On the other hand the reaction of (CXXI) with formaldehyde gave the corresponding pyridazin-3-ones derivatives (CXXII).



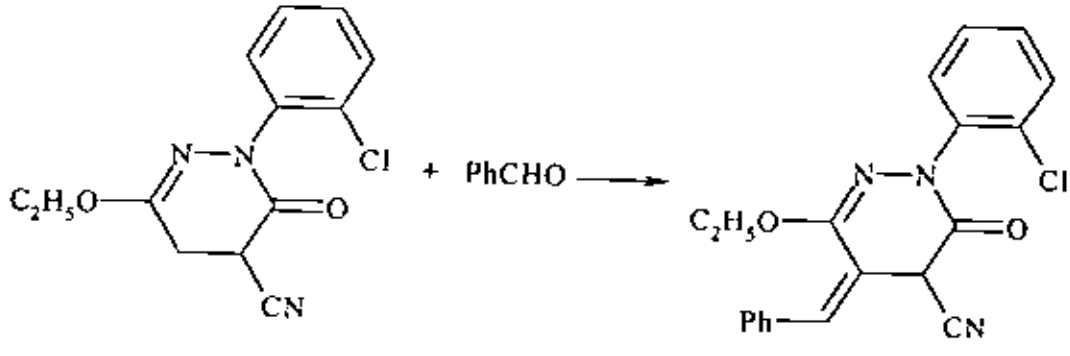
(CXX) (CXXI) (CXXII)

When the pyridazin-3(2H)-ones derivatives (CXXI) were allowed to react with secondary amines (piperidine and /or more morpholine) in the presence of aqueous formaldehyde in boiling methanol the corresponding Mannich bases (CXXIII)[67] were obtained.



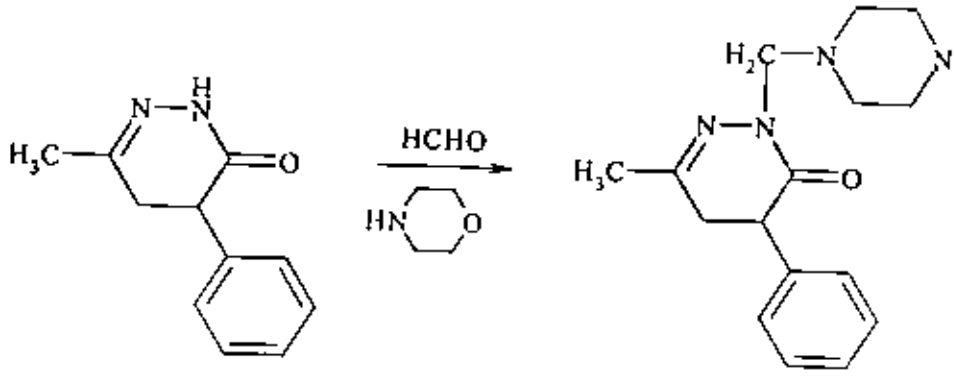
(CXXI) (CXXIII)

Condensation reaction of pyridazin-3-ones (CXXIV) with benzaldehyde in presence of piperidine in ethanol gave (CXXV)[68].



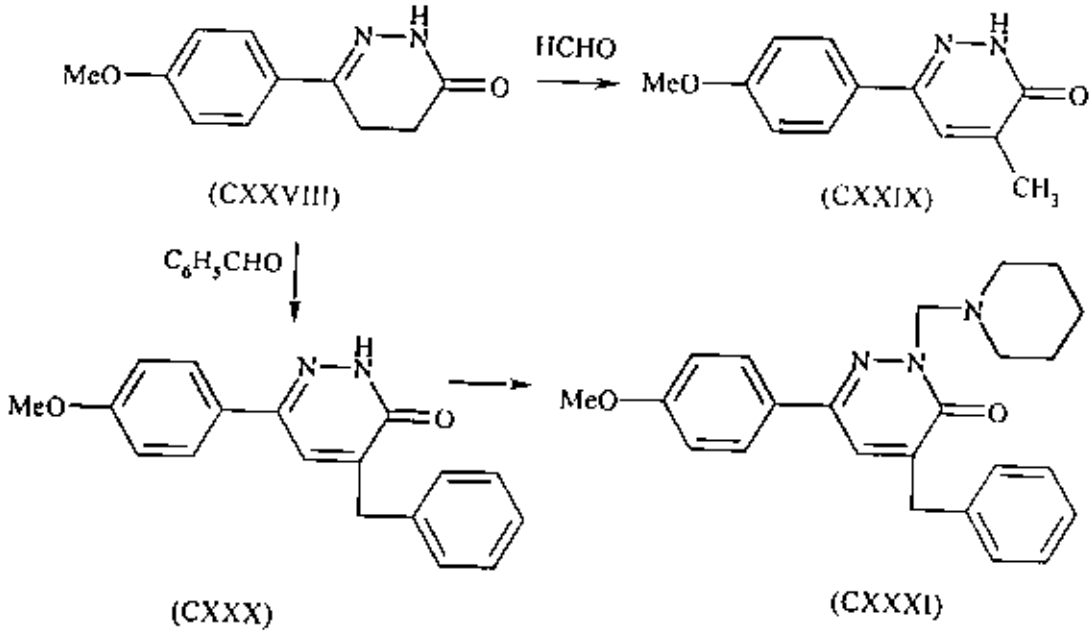
(CXXIV) (CXXV)

It was found also that pyridazin-3(2H)-ones (CXXVI) react with formaldehyde and morpholine to give (CXXVII)[69].



(CXXVI) (CXXVII)

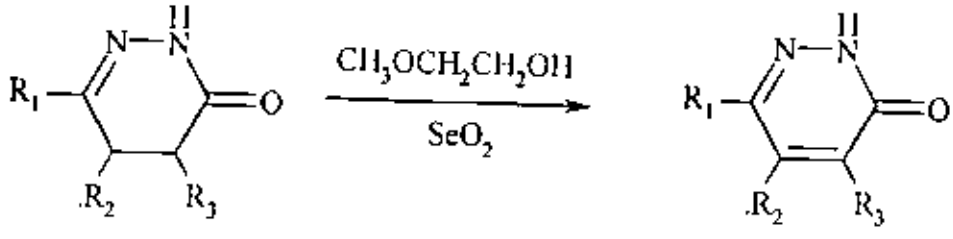
It was reported[70] that pyridazin-3(2H)-one (CXXVIII) condensed with formaldehyde or benzaldehyde to give (CXXIX) and (CXXX) respectively. Treatment of (CXXIX) with piperidine and formaldehyde gave the corresponding 2-(piperdinomethyl) pyridazin-3-one derivative (CXXXI).



(CXXVIII) (CXXIX) (CXXX) (CXXXI)

2.2.5 Oxidation of pyridazinone: -

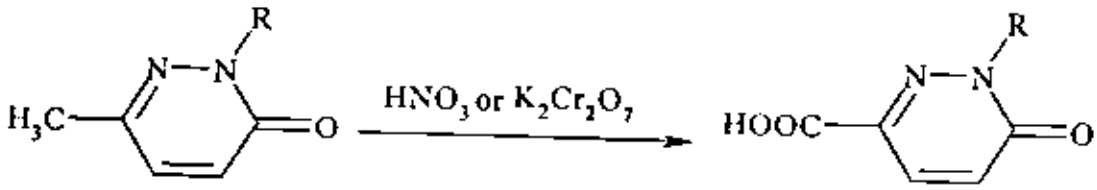
Some of resulting thieny substituted 4,5-dihydropyridazin-3-ones were converted into the corresponding pyridazin-3-ones. The standard reagent for oxidizing 4,5-dihydropyridazin-3-ones is bromine in ethanoic acid. It has been reported that[61] oxidation of thiophene ring by bromination occurs more readily than oxidation of the 4,5-dihydropyridazin-3-ones. Oxidation of 4,5-dihydro-pyridazin-3(2H)-one derivatives (CXXXII) with selenium dioxide on heating under reflux with 2-methyloxy ethanol for 4-6 hrs gave good yield of substituted pyridazin-3(2H)-ones (CXXXIII).



(CXXXII) (CXXXIII)

(R_1=2-thienyl, 3-thienyl, 2-pyridyl, CH3, Ph; R_2=H; R_3= H, Ph)

The stability of the hetero ring in pyridazin-3-ones toward oxidizing agents is illustrated by the oxidation of 6-methyl and 2,6-dimethylpyridazin-3-ones (CXXXIV) with nitric acid or potassium dichromate and sulphuric acid to 6-carboxypyridazin-3-ones (CXXXVa) and methyl derivative (CXXXVb)[71,72].



(CXXXIV)

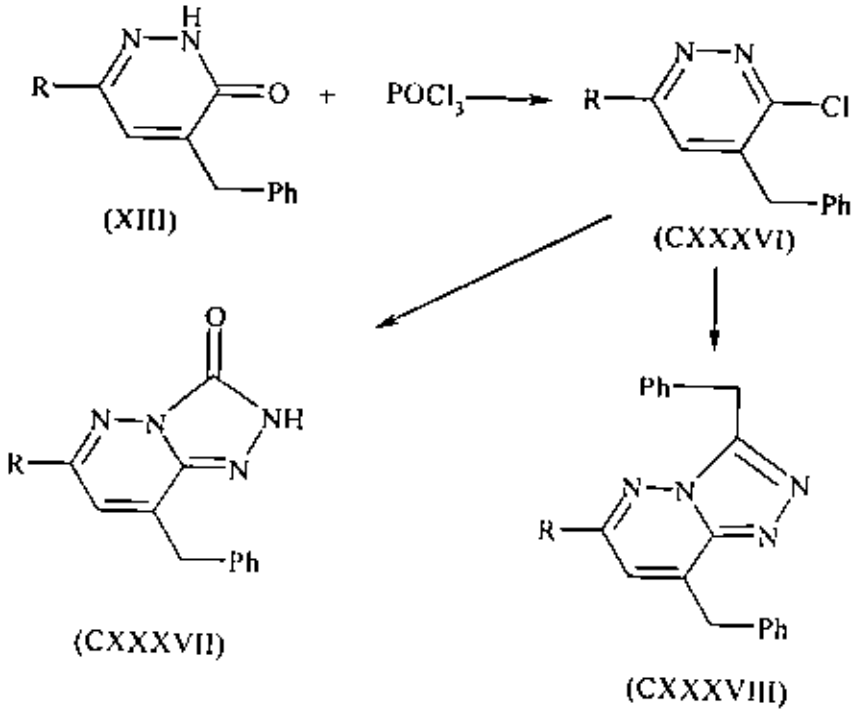
(CXXXVa) R=H

(CXXXVb) R=CH_3

2.2.6 Chlorination of pyridazinone: -

It was used as starting material to prepare new heterocyclic compounds:

Chlorination of (XIII)[8] with $POCl_3$ gave 3-chloropyridazines (CXXXVI, R=Ph, 4-$CH_3C_6H_4$, 4-$CH_3OC_6H_4$) which on cyclization with $H_2NCONHNH_2$ or $PhCH_2CONHNH_2$ gave (CXXXVII) and (CXXXVIII) respectively.

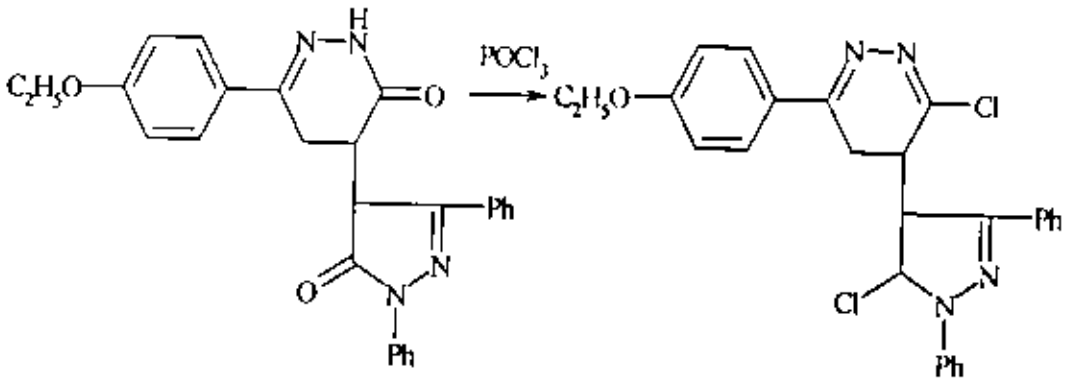


(XIII)

(CXXXVI)

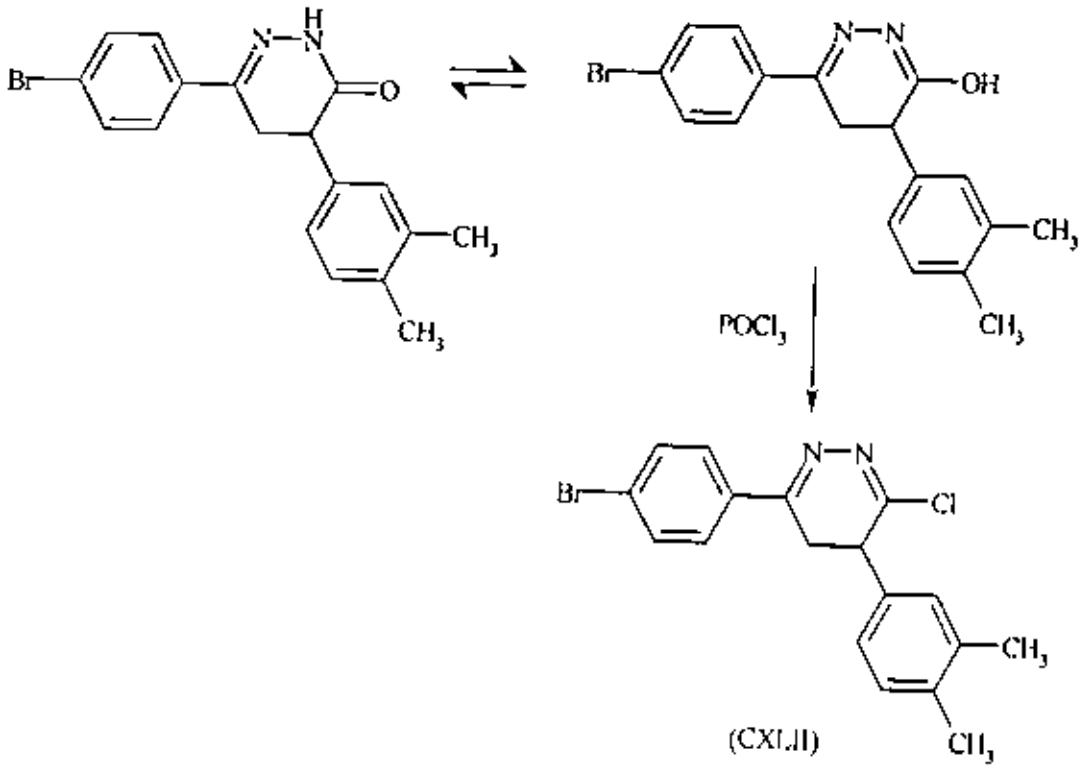
(CXXXVII)

(CXXXVIII)



(XXX) (CXLI)

It was reported that[20] when the pyridazin-3(2H)-one derivatives were allowed to react with phosphorus oxychloride yielded the chloropyridazine derivative (CXLII).



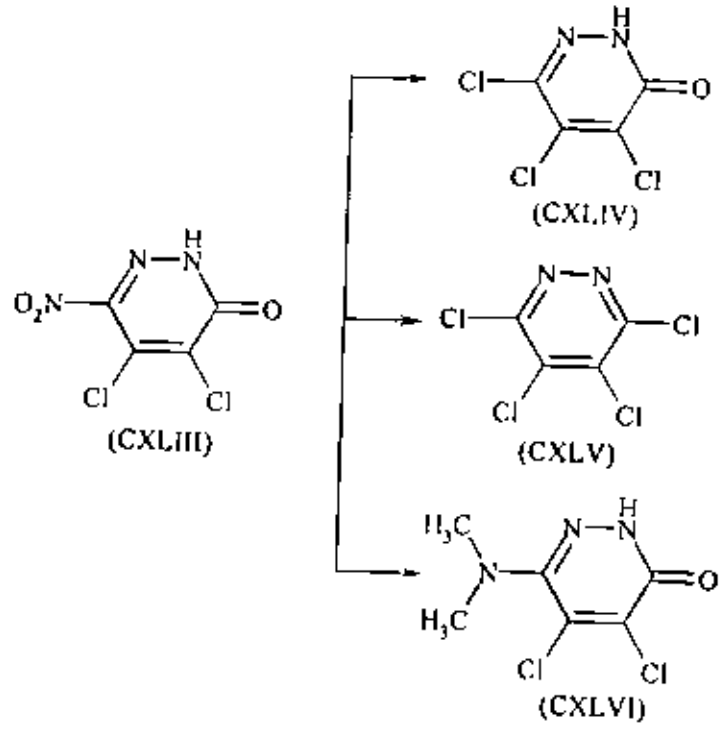
(CXLII)

It was reported[73] that refluxing a mixture of compound (CXLIII) and one equivalent of dimethyl chloromethylencammonium chloride $[(CH_3)_2\text{-}N^+\text{=}CHCl]\text{-}Cl$ in SO_2Cl_2 yielded (CXLIV) as the major and (CXLV) as minor products. Whereas refluxing (CXLIII) with two equivalent $[(CH_3)_2N^+\text{=}CHCl]\text{-}Cl$ in SO_2Cl_2 gave (CXLV) as the major and (CXLIV) as minor products.

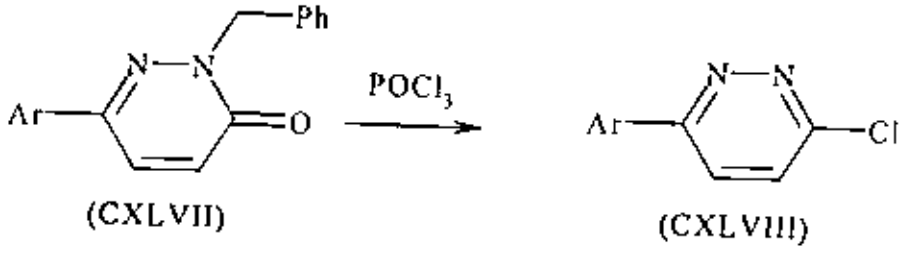
Reaction of (CXLIII) with excess $[(CH_3)_2\text{-}N^+\text{=}CHCl]\text{-}Cl$ in SO_2Cl_2 six equivalent under the same conditions afforded only (CXLV). The reaction of (CXLIII) with one or two equivalent $[(CH_3)_2\text{-}N^+\text{=}CHCl]\text{-}Cl$ in dry benzene gave only (CXLIV).

The reaction of (CXLIII) with $[(CH_3)_2\text{-}N^+\text{=}CHCl]\text{-}Cl$ one equivalent in dry toluene afforded (CXLV) as main product but this reaction with two equivalent $[(CH_3)_2\text{-}N^+\text{=}CHCl]\text{-}Cl$ in dry toluene gave (CXLV) as main and (CXLIV) as minor products.

In addition, chlorination of (CXLIII) with $POCl_3$ yielded (CXLV) as the major product (37%) and bipyridazin-3-one as minor[74] products, whereas treatment of (CXLIII) with two equivalent $[(CH_3)_2\text{-}N^+\text{=}CHCl]\text{-}Cl$ in dimethyl formamide yielded compound (CXLVI).

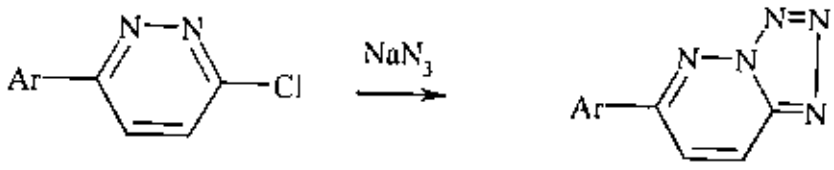


It has been reported[75] that 6-Arylpyridazin-3(2H)-ones (CXLVII) were chlorinated by chlorine in the presence phosphorus oxychloride to give 3-chloropyridazine (CXLVIII).



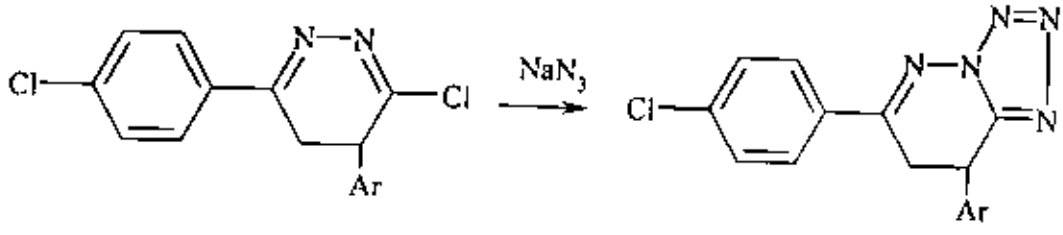
a. Reaction of chloropyridazine with sodium azide and anthranilic acid: -

The chloropyridazine derivative[16] reacted with sodium azide in dimethyl formamide to give new heterocyclic compound (CXLIX).



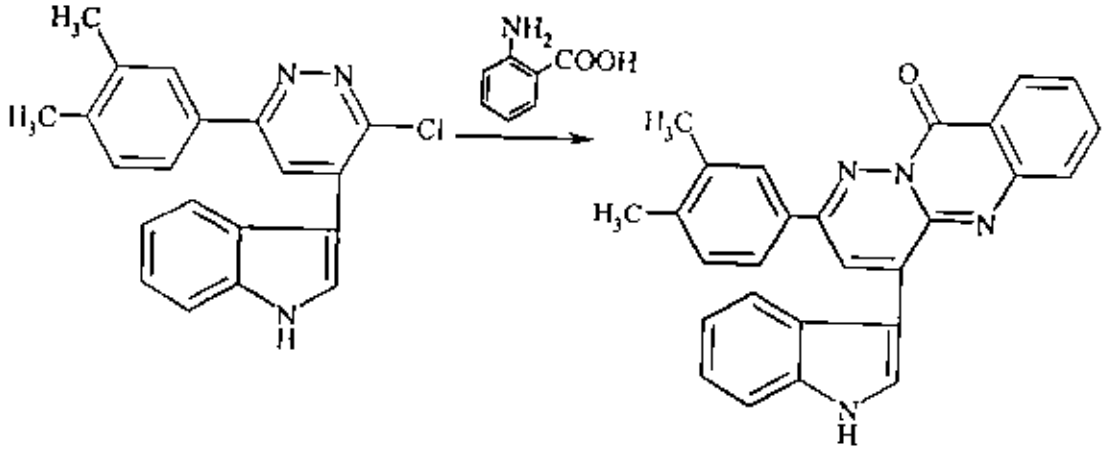
(CXLIX)

It was reported[59] that the chloropyridazine derivative reacted with sodium azide in dimethyl formamide to give the tetrazolopyridazine derivative (CL).



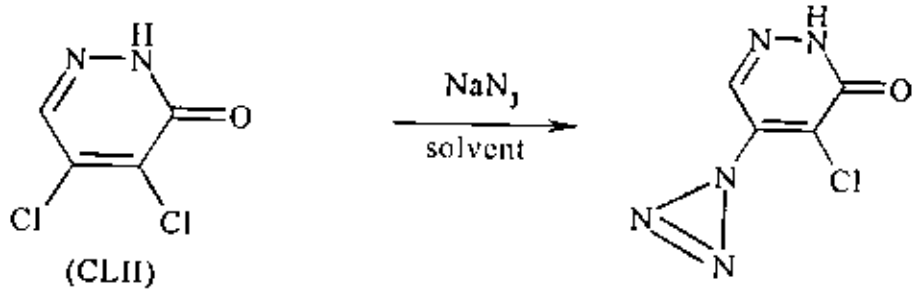
(CL)

It was reported[14] also that the reaction of chloropyridazine with anthranilic gave quinazolinone derivatives (CLI), respectively.



(CLI)

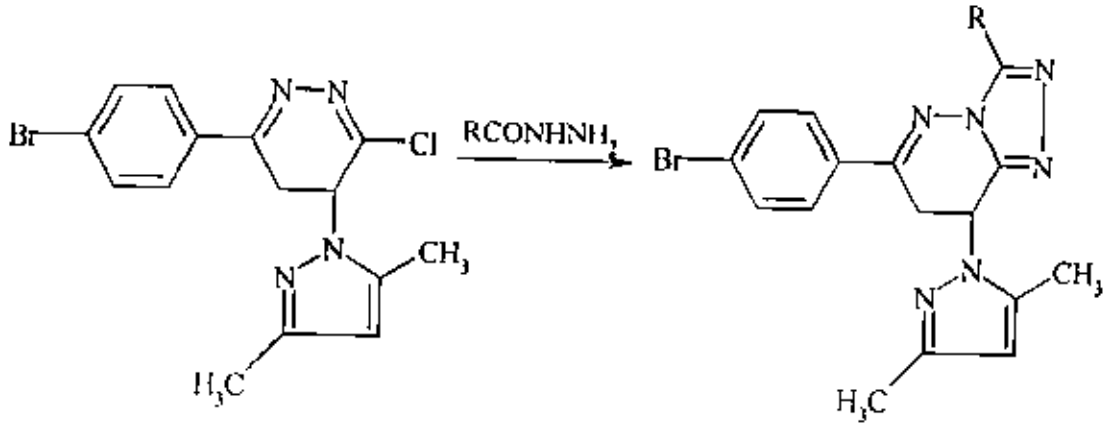
Recently in 1999 it was found[76] that reaction of 4,5-dichoro-pyridazin-3(2H)-one (CLII).with sodium azide in seven solvents gave regioselectively 5-azido-4-chloropyridazin-3(2H)-one (CLIII).



(CLII) (CLIII)

b. Reaction of chloropyridazine with acylhydrazines: -

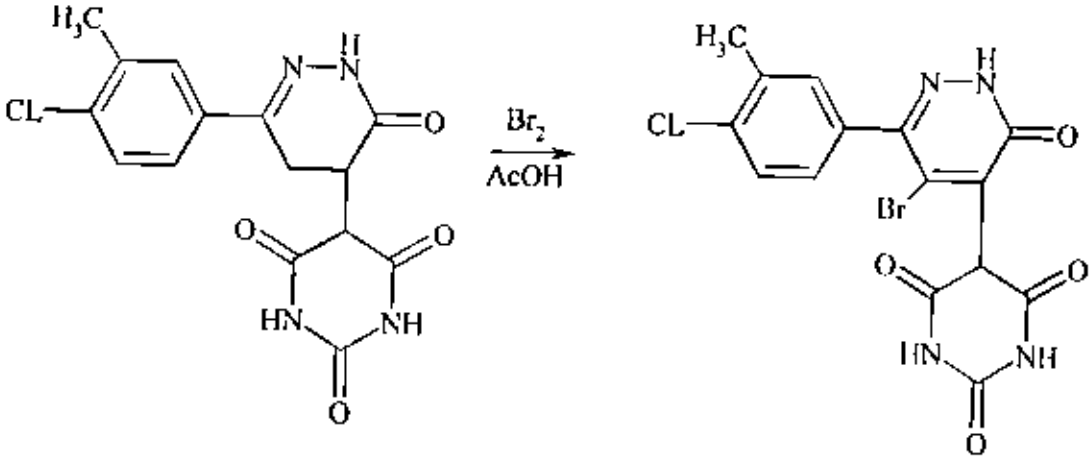
Chloropyridazine (CLIV) reacted with bezoylhydrazine and/or acetyl-hydrazine in refluxing 1-butanol to gave the triazolopyridazine (CLV, R=Ph, CH_3)[76].



(CLIV) (CLV)

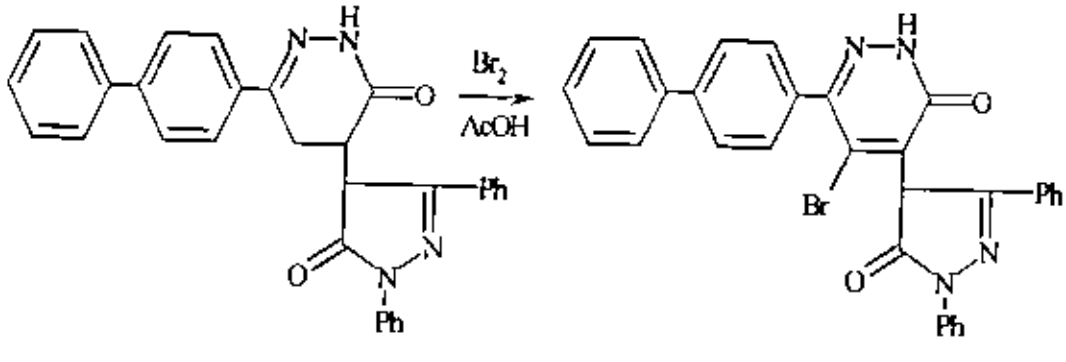
2.2.7 Bromination of pyridazinones: -

It was found that[15], treatment of (XXVII) with bromine-acetic acid mixture afforded compound (CLVI). The formation of this compound can be explained on the basis that. the first step is dehydrogenation followed by addition of bromine on the formed double bond and the elimination of HBr.



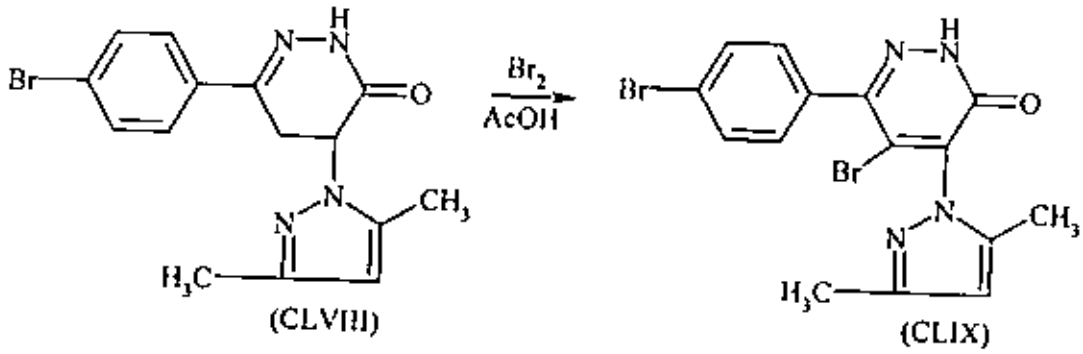
(XXVII) (CLVI)

Recently, it was found[28] that treatment of pyridazin-3(2H)-one (XLI) with bromine-acetic acid mixture afforded the 5-bromoderivative (CLVII).



(XLI) (CLVII)

Similarly, treatment of the pyridazin-3(2H)-one (CLVIII) with bromine-acetic acid mixture gave the bromoderivative (CLIX)[77].

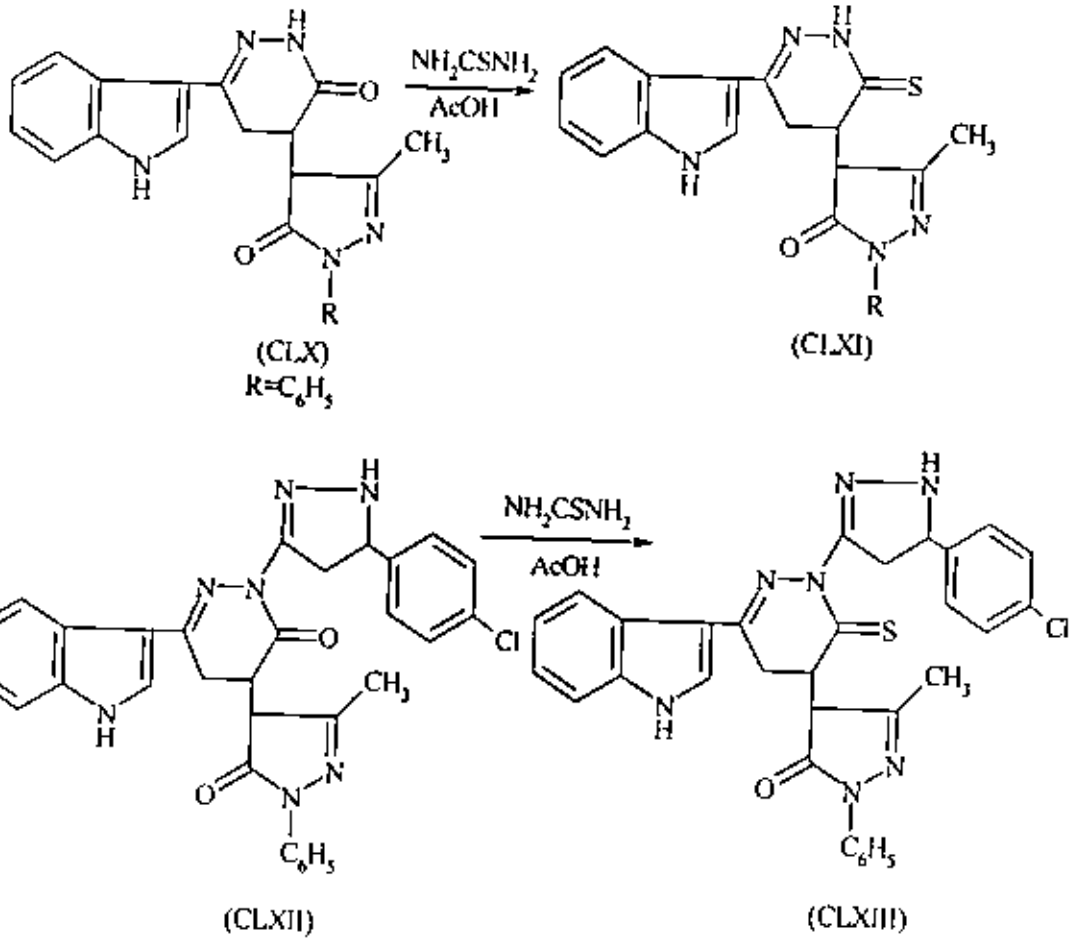


(CLVIII) (CLIX)

2.2.8 Reaction with phosphorus pentasulphide: -

The pyridazin-3(2H)-one derivative (CLX) was readily thionated upon treatment with thiourea in boiling acetic acid and gave the corresponding 4,6-diarylpyridazin-3(2H)-one thione derivative (CLXI) in which thionation together with dehydrogenation took place [27].

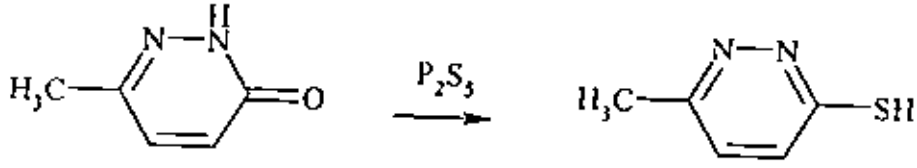
It was also reported that[27] reaction of pyridazinone derivative (CLXII) with thiourea in boiling acetic acid yielded the corresponding 2-N-pyridazinyl-(pyrazolin)-3-thione derivative (CLXIII).



(CLX) $R=C_6H_5$ (CLXI)

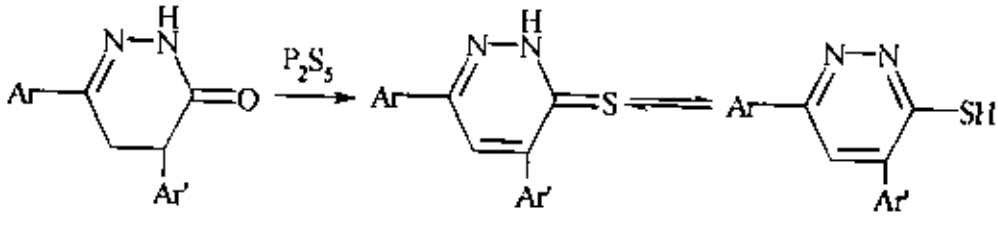
(CLXII) (CLXIII)

Pyridazinones bearing no substituents in the 2-postion reacted with phosphorus pentasulphide in boiling xylene to give 3-mercaptopyridazines[78,79]. Thus, It has been found that[79] 6-methylpyridazin-3(2H)-one (CLXIV) reacted readily with phosphorus pentasulphide in xylene gave 3-mercapto-6-pyridazine (CLXV).



(CLXIV) (CLXV)

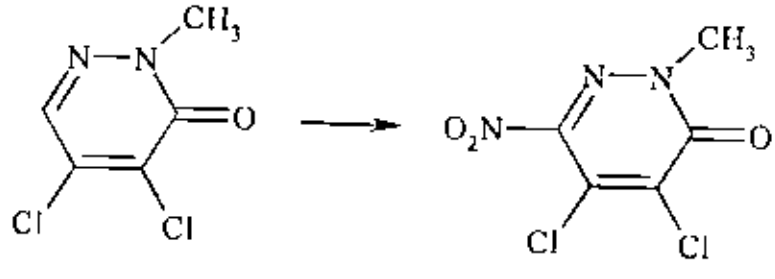
Similarly, It has been found that[80] when the pyridazin-3(2H)-one derivatives (CLXVI) were allowed to react with phosphorus pentasulphide in boiling xylene yielded the corresponding pyridazinethione derivatives (CLXVII).



(CLXVI) (CLXVII)

2.2.9 Nitration of pyridazinone derivatives:-

It was found that[74], reaction of pyridazinone (CLXVI) with KNO_3 and concentrated sulphuric acid gave the nitro derivative (CLXVII).

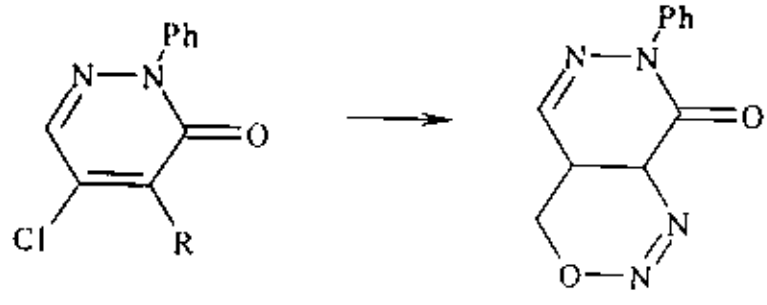


(CLXVIII) (CLXVIX)

2.2.10 Reaction of pyridazinone with nitrous acid: -

The dichloropyridazin-3-one (CLXX, R=Cl) was prepared by diazotizing (CLXX, $R=NH_2$) to give 87% of the oxadiazole (CLXXI), which was chlorinated with thionyl chloride to give 92.4% yield (CLXX, R=Cl)[81].

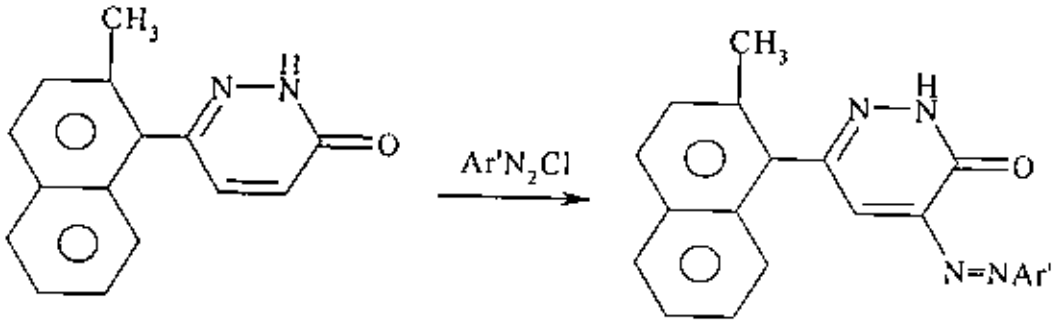
On the other hand, compound (CLXX, R=Cl) was prepared by diazotizing (CLXX, R=NH_2) with $NaNO_2$/HCl gave oxadiazine.



(CLXX) (CLXXI)

2.2.11 Reaction of pyridazinone with aryldiazonium chloride: -

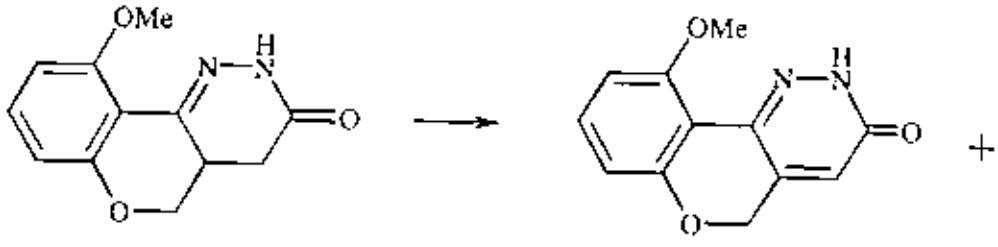
When the pyridazin-3-one (CLXXII) was allowed to react with aryldiazonium chloride gave the coupling products (CLXXIII)[82].



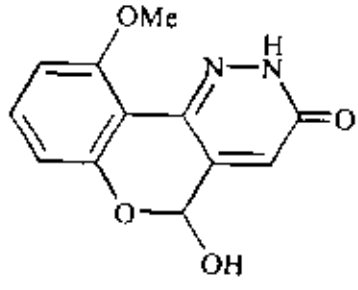
(CLXXII) (CLXXIII)

2.2.12 Reaction of pyridazinone with m-nitrobezesulphonate: -

Sodium-m-nitrobezesulphonate, widely used in dehydrogenation of 4,5-dihydro-3(2H)-pyridazinone, to their corresponding aromatic derivatives, behaves in unexpected way when 4,4a-dihydro-5H-bezopyrano-[4,3-C]-pyridazin-3(2H)-ones are employed as substrate. The reaction of sodium-m-nitrobezesulphonate with (CLXXIV) gave (CLXXV) in traces. the main product being (CLXXVI)[83].



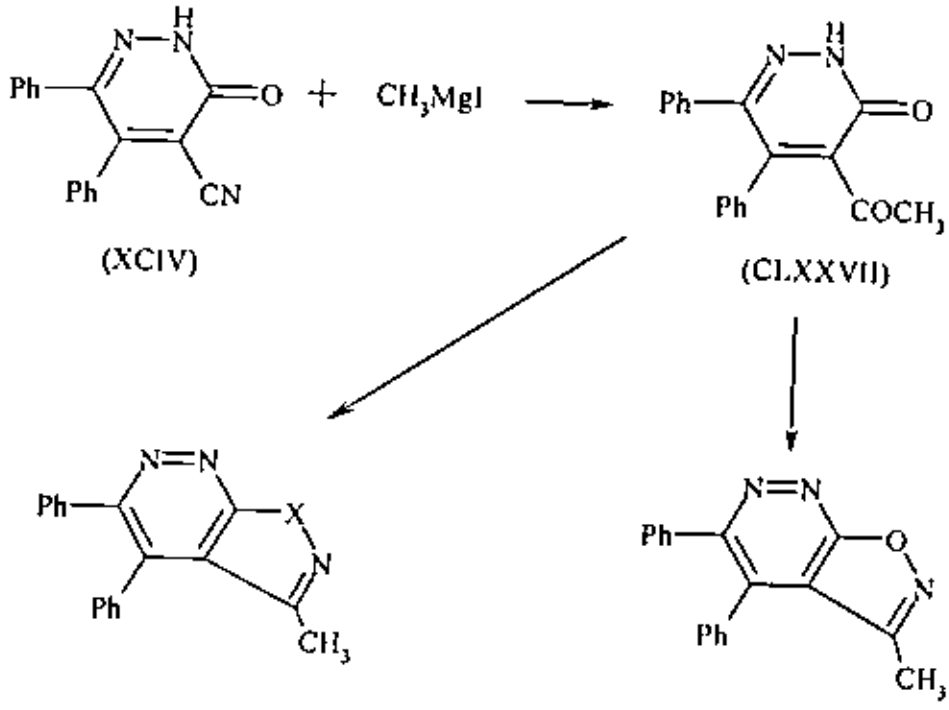
(CLXXIV) (CLXXV)



(CLXXVI)

2.2.13 Action of Grignard reagent: -

When pyridazin-3(2H)-one (XCIV) was treated with CH_3MgI gave acetyl derivative (CLXXVII), which reacted with $N_2H_4.H_2O$, $PhNHNH_2$, and/or NH_2OH to give pyrazolo-[3,4-C]-pyridazine (CLXXVIII, X=NH, NPh) and isoxazolopyridazinone derivative (CLXXIX)[56], respectively.



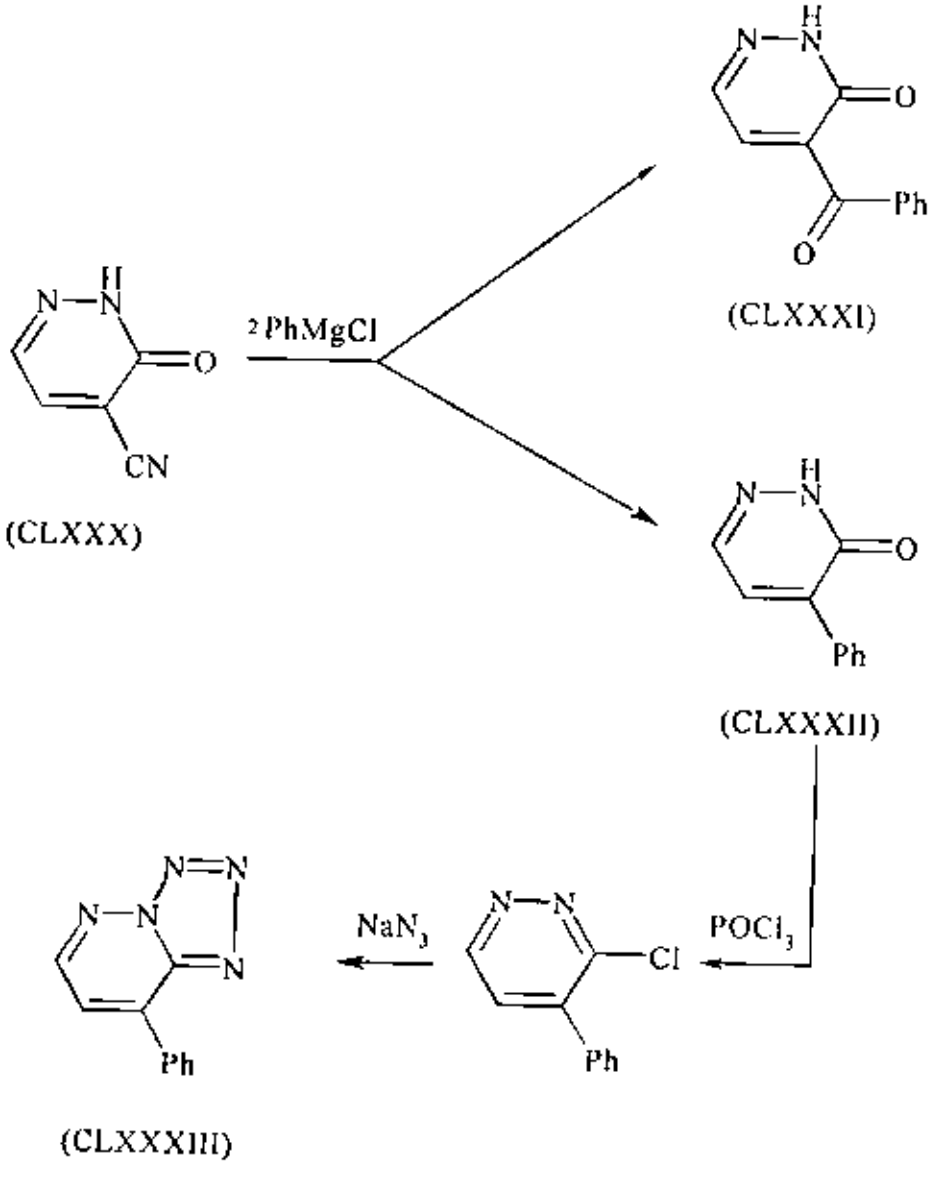
(XCIV) (CLXXVII)

(CLXXVIII) (CLXXIX)

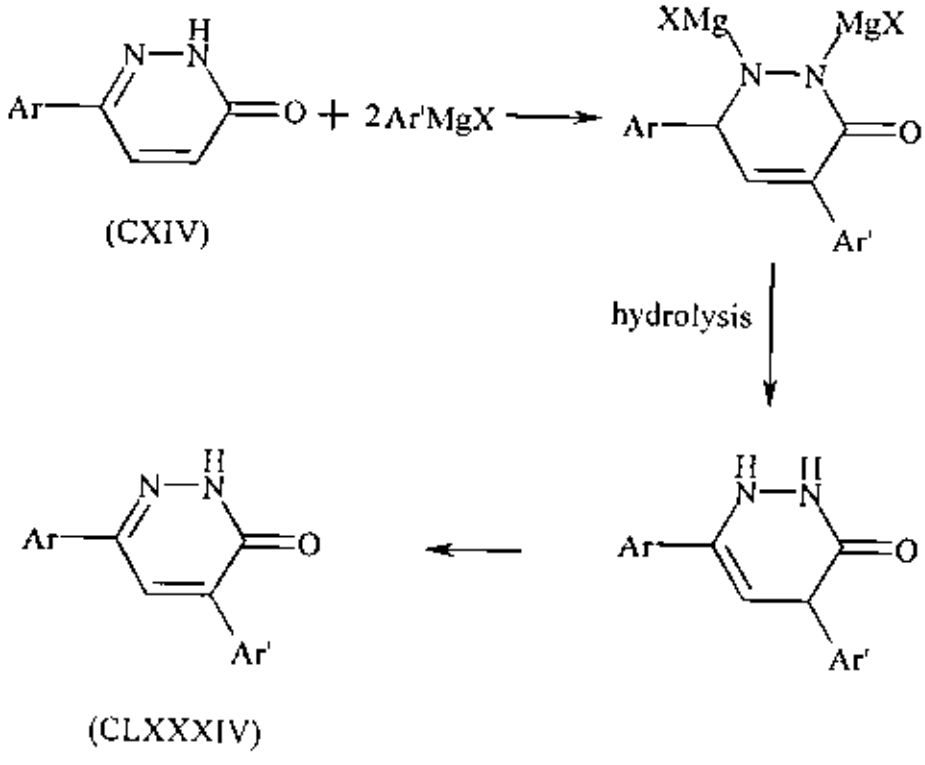
Similar results were reported for the reaction of 4,6-diarylpyridazin-3(2H)-ones with Grignard reagents[59].

When 4-cyano-3(2H)-pyridazinone (CLXXX) was treated with Grignard reagent (PhMgX) in tetrahydrofuran solution at 0°C, only minor amounts (20%) of the expected ketone (CLXXXI) were formed, whereas the main

product (70%) was phenylpyridazin-3(2H)-one (CLXXXII)[84]. In this case the ring position attacked by the Grignard reagent was found not be the carbon atom bearing the nitrile group this could be proved by on unequivocal synthesis of 8-phenyltetra-zolo-[1,5-b]-pyridazine (CLXXXIII) from compound (CLXXXII) via chloropyridazin-3(2H)-one derivative.



It has been found that[85] when 6-arylpyridazin-3(2H)-ones (CXIV) were treated with different arylmagnesium bromides, they gave the corresponding 4,6-diarylpyridazin-3(2H)-ones (CLXXXIV). The authors claimed that the reaction took place by 1,4-addition to the –C=C-C=N- group followed by dehydrogenation.

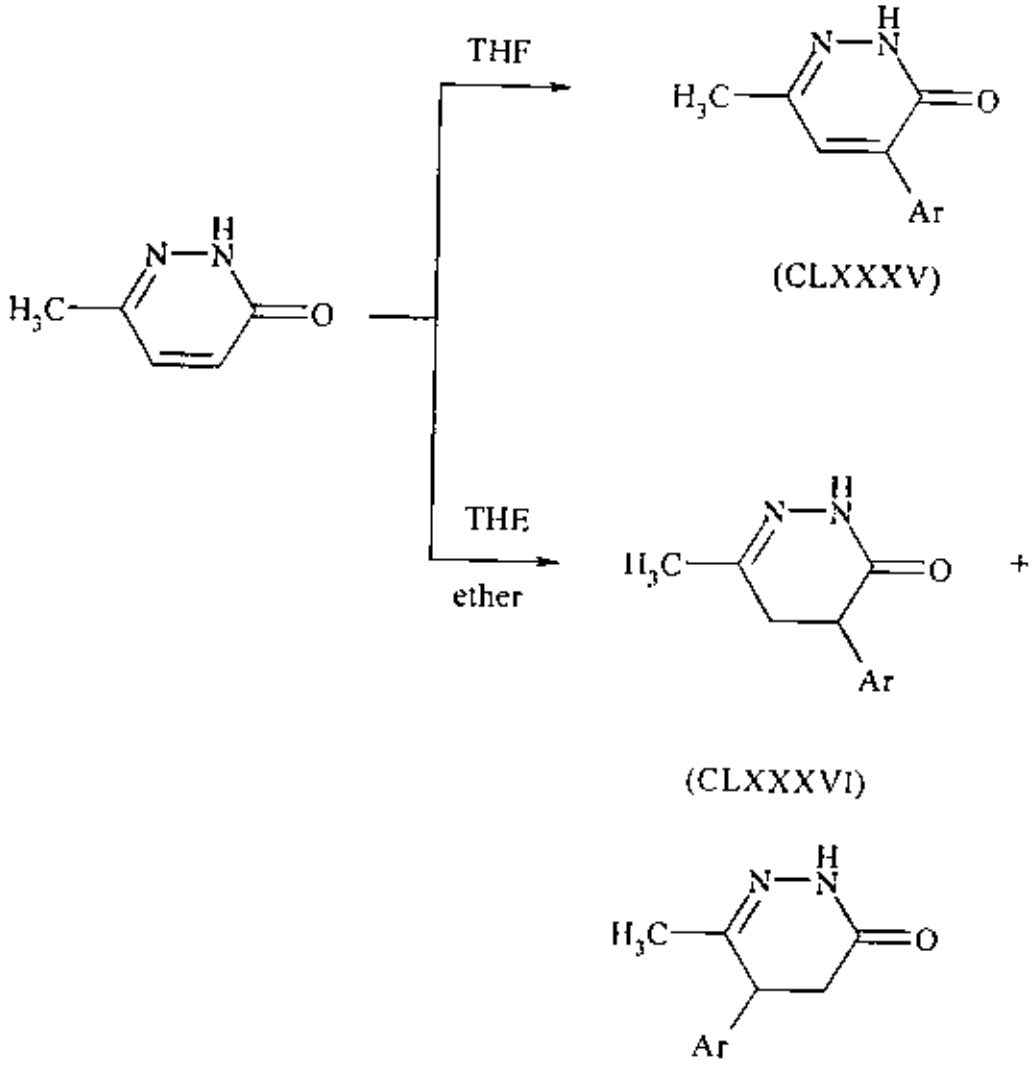


(CXIV)

(CLXXXIV)

It has been found that[86] the action of Grignard reagent on 6-methylpyridazin-3(2H)-ones and indicated that the addition was dependent mainly on the solvent used. Thus, in tetrahydrofuran, the reaction took place by 1,4-addition to –C=C-C=N- system followed by dehydrogenation to give the corresponding 4-aryl-6-methylpyridazin-3(2H)-ones (CLXXXV).On the other hand, when the reaction was carried out in a mixture of ether-tetrahydrofuran

(50:50) as solvent a mixture of two compounds was obtained. The predominant product was found to be 4-aryl-4,5-dihydro-6-methylpyridazin-3(2H)-ones (CLXXXVI) formed by 1,4-addition to the –C=C-C=N- system. The second product was proved to be 5-aryl-4,5-dihydro-6-methylpyridazin-3(2H)-ones (CLXXXVII) resulting from 1,4-addition to the –C=C-C=O group.



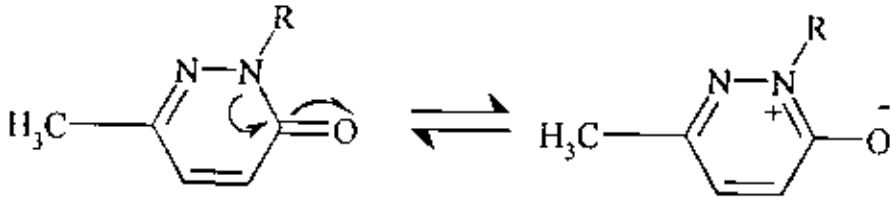
(CLXXXV)

(CLXXXVI)

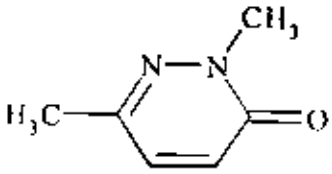
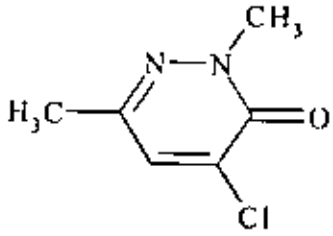
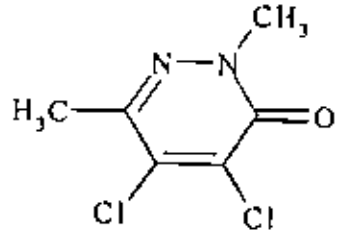
(CLXXXVII)

2.3 Electronic and infrared spectra: -

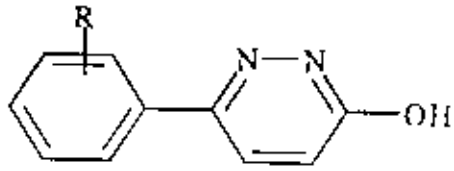
Overend, Turton and Wiggins[2] concluded from the absorption spectra of pyridazin-3(2H)-ones, that these compounds exist normally to a large extent in the lactam form, on addition of sodium hydroxide to their solution, the position of maximum absorption moves from 285 nm (ε_{max} 2200) to 300 nm (ε_{max} 3000), i.e. it is still nearer to that 2-substituted-pyridazinone derivatives. On addition of hydrochloric acid to the solution of the sodium derivatives of 6-methylpyridazin-3(2H)-one, maximum absorption reverts to its original position (λ_{max} 285 nm, ε_{max} 2000). Consequently, it seems likely that 6-methylpyridazin-3-one under the influence of sodium hydroxide reacts in its lactam form to give N-sodium derivatives and not in its lactim form to give the salt of an enol. 2,6-Dimethyl and 6-methyl-2-phenyl-pyridazin-3-ones have very similar absorption to the above absorption at about 300 nm (ε_{max} 2500-3000) can be considered as characteristic of the pyridazin-3-ones. The fact that the similarity of spectra of 2-substutited-6-methylpyridazin-3-ones to that of 6-methylpyridazin-3-one indicates that the resonance indicated below is responsible for the mentioned spectra.



Similarly, it was found that both 4-chloro- and 2,6-dimethylpyridazin-3-ones respectively absorb at 294 nm. This shows that these compounds essentially the same type of structure [86]

The electronic spectra of 6-arylpyridazin-3(2H)-ones are very similar to that of diphenyl (λ_{max} 250 nm, ε_{max} 18000) [41]. These spectra may be due to the existence of these compounds in the lactim form, which confers on the molecule an aromatic character like benzene.



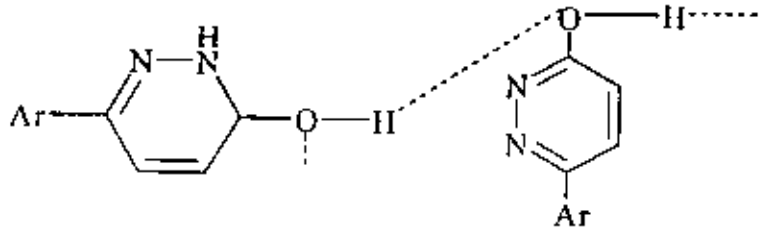
(CLXXXVIII)

However, the electronic spectra of 2,6-diarylpyridazin-3-ones (CLXXXVIII) show three maximum and absorb at a longer wavelength than the corresponding 6-arylpyridazin-3(2H)-ones, which show only one maximum. This indicated that these compounds exist normally in the lactam form, although they can react sometimes in the lactim form.

The infrared spectra of pyridazin-3(2H)-ones (CLXXXIX) generally show strong bands in the regions characteristic of the carbonyl stretching frequencies. The absorption due to the carbonyl group (-O=C-N-) appears at about 1680 cm^{-1} for the lactam structure, but the lactim structure an absorption resulting from (-O-C=N-) appears at about 1610 cm^{-1}. The broad peak around 3400 cm^{-1} suggests that pyridazinone with OH or NH groups[87].

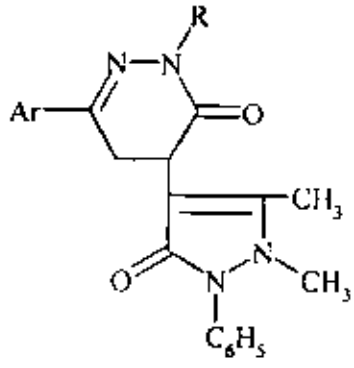
(CLXXXIX)

It has been found that [2] 6-methylpyridazin-3(2H)-one exists in a dimeric form via strong hydrogen bonding as indicated by the frequency shift in their spectra. Pyridazin-3(2H)-ones show, in addition, a very broad bond in the 3 μ region when the spectra are run in the condensed phase (KBr), when the spectra are run in chloroform, the broad band is replaced by two bands, one of them is weak and the other is strong. The strong absorption observed in three μ regions may indicate the partial existence of these compounds in the lactim form in polymeric association.



2.4 Studies on application and biological activity of Pyridazinone derivatives: -

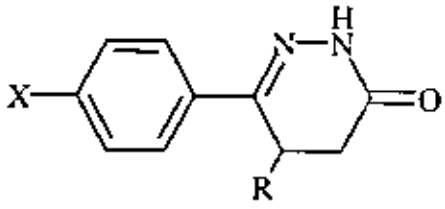
It has been found that[18], the Pyridazin-3-one (XXVIII, R=H, Ph) were prepared as a antimicrobial and antifungal activities.



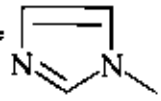
(XXVIII)

It has been found that[88], the 6-substituted-phenyl-4,5-dihydro-3(2H)pyridazinones exhibited considerable and long lasting activity as hypotensive agents. In recent reports [89], antiagregatory and antiulcer activity coupled with hypotensive action for 4,5-dihydro-3(2H)pyridazinones analogues have also been described.

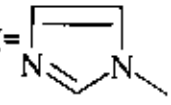
It has been found that[90], the new class of potent positive inotropic agents, incorporating the 4,5-dihydro-3(2H)pyridazinones (CXC), (CXCI). The pyridazinones (CXCII)[91] as intropic and chronotropic analogues of (CXC), (CXCI).

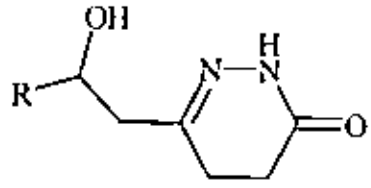


(CXC) R=H, X=



(CXCI) R=CH_3, X=

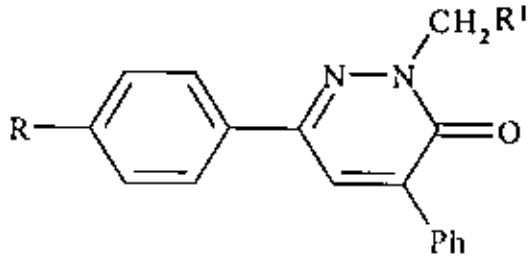




(CXCII)

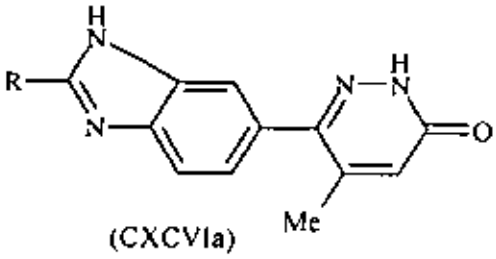
R= n-C_3H_7, n-C_4H_9; n-C_6H_{13}

It has been found that[92], the all compounds (CXCIII) were screened for analgesic, antipyretic activities.

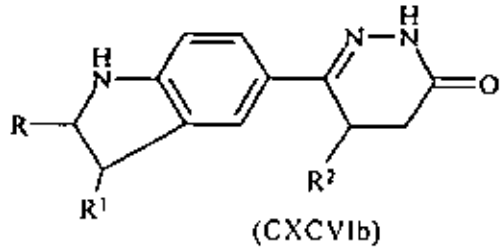


(CXCIII)

It has been found that[93,94], the compounds (CXCVIa,b) as a positive in trop in rats and cats.

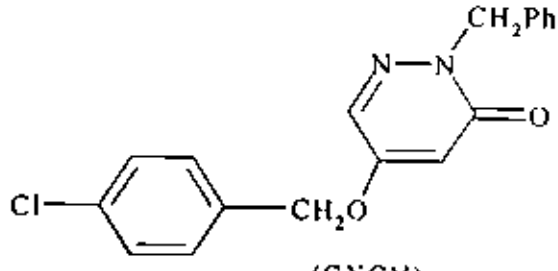


(CXCVIa)



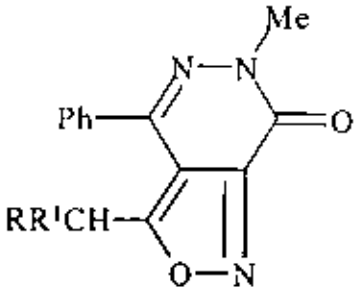
(CXCVIb)

It has been found that[95], the 3-Pyridazinone (CXCV) as insecticides control of Nephotettix cincticeps nympha on rice.

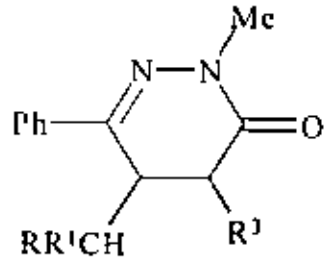


(CXCV)

It has been found that[96], isoxazolopyridazin-3-one derivatives showed antitumor activity against human tumor cell lines (CXCVI. CXCVII).

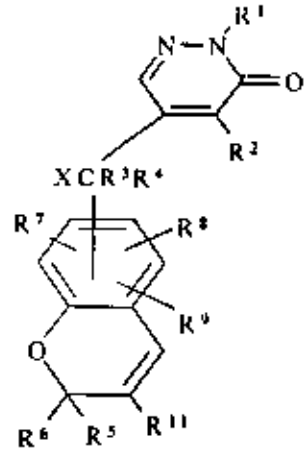


(CXCVI)

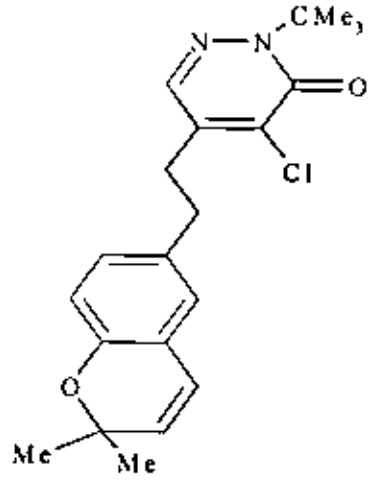


(CXCVII)

It has been found that[97], the pyridazin-3-one derivative (CXCIX) is said to give superior control of phaedon, cochlearia larvae on cabage leaves



(CXCVIII)

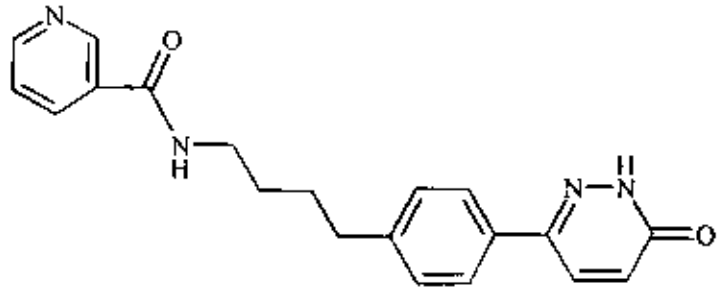


(CXCIX)

It has been found that[98], the statistically significant antiulcer properties and also displayed significant antisecretory activity and proved to be able to reduce the acidity of the gastric secretions

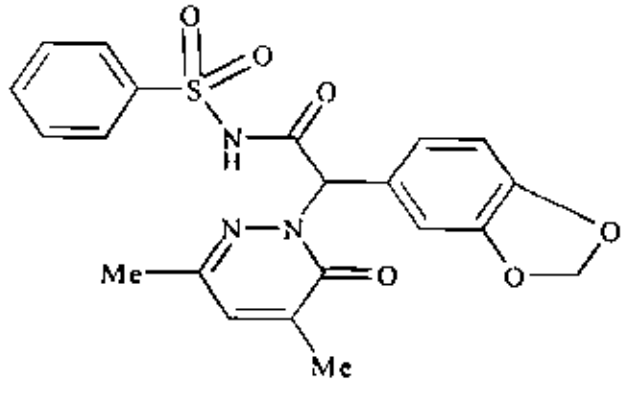
It has been found that[99], the antihypertensive 5,6-diarylpyridazin-3-one.

It has been found that[100], the showed 82.5% inhibition of protein excretion in rabbits.



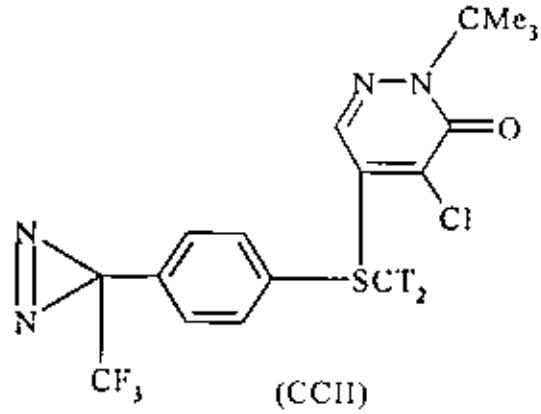
(CC)

It has been found that[101], as endothelin receptor antagonists .



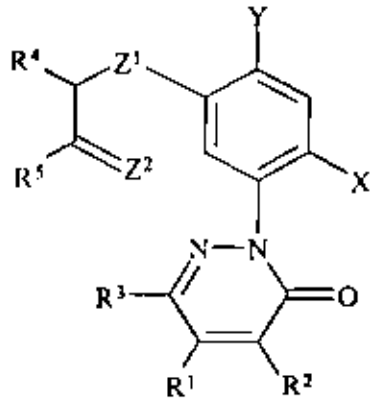
(CCI)

It has been found that[102], the Pyridazin-3-one (CCII) derivatives was an improved photo affinity radioligand combining outstanding potency for inhibiting NADH: ubiquinone oxidoreductase activity, high specific activity close to the theoretical.



(CCII)

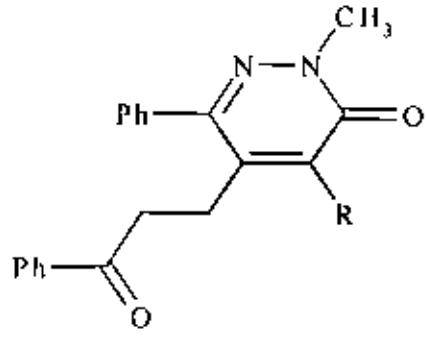
It was reported that[103], useful as herbicides .



(CCIII)

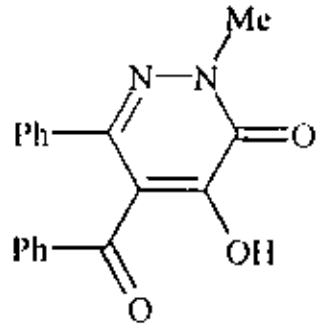
It has been found that[104], as anti-aggregating properties have been described.

It has been found that[105], as antithrombotic agents and platelet aggregation inhibitors.



(CCIV)

It has been found that[106], as weak activity against fungi and bacteria.



(CCV)

ORIGINAL WORK

3. SYNTHESIS AND SOME REACTIONS OF SUBSTITUTED *PYRIDAZINONE* DERIVATIVES: -

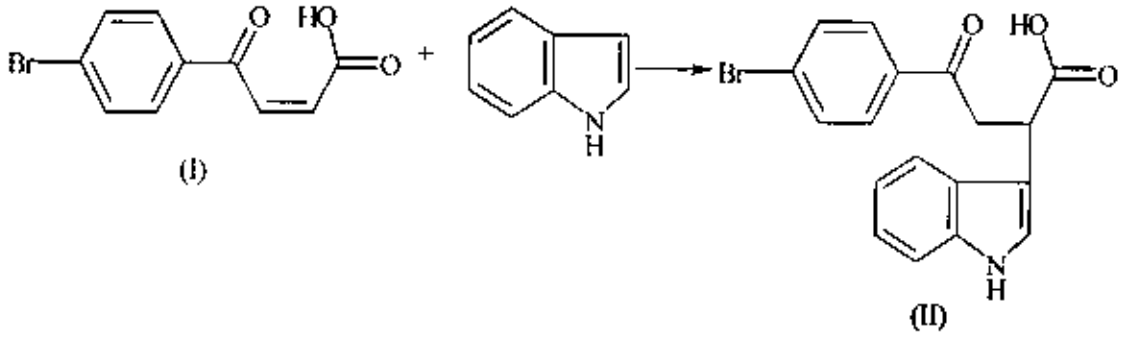
A large number of pyridazinones occupy a unique by significant position in medicinal chemistry as insecticidal[107], herbicidal[18,108], antiallergenic[109,110], antihypertensive[18,,97,111,112,113], analgesic[54,105,106,114,116], anti-inflammatory [114,115], bacterial activities[49,115,117] and blood platelet aggregation[18,93,94,115].

The combination of both active indole and pyridazinone nuclei is the aim of the present investigation by studied their reactivity towards different nucleophiles and electrophiles, this prompted us to synthesize a new series of pyridazinones containing the Indole moiety.

Through the addition of indole to 4-(p-bromophenyl)-4-oxo-2-butenoic acid followed by cyclocondensation of the adduct with hydrazines to the corresponding dihydropyridazinones derivative and study the behavior of the latter towards different reagents.

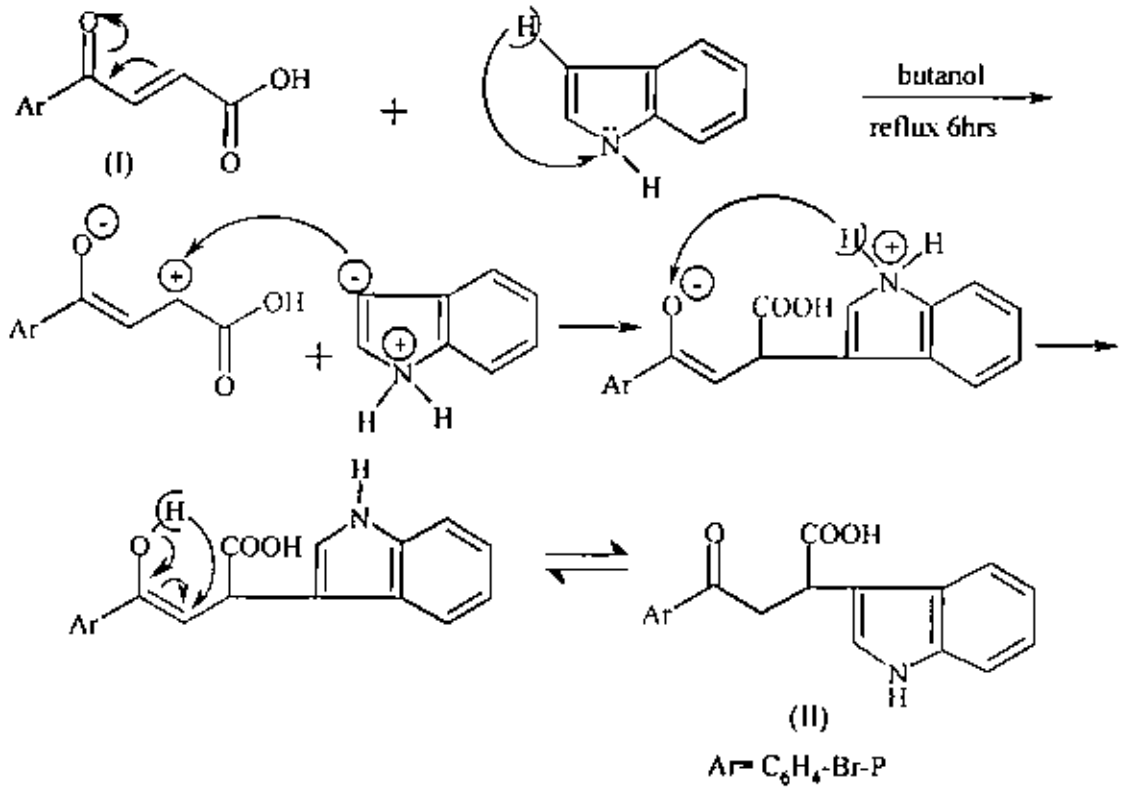
3.1. Nucleophilic addition of Indole to 4-(P-bromophenyl)-4-oxo-2-butenoic acid: -

The reaction of 4-(p-bromophenyl)-4-oxo-2-butenoic acid (I)[119,120] in boiling butanol gave 4-(p-bromophenyl)-2-(3-indolyl)-4-oxobutanoic acid (II).



(I) (II)

The reaction possibility took place via the following mechanism:



(II)

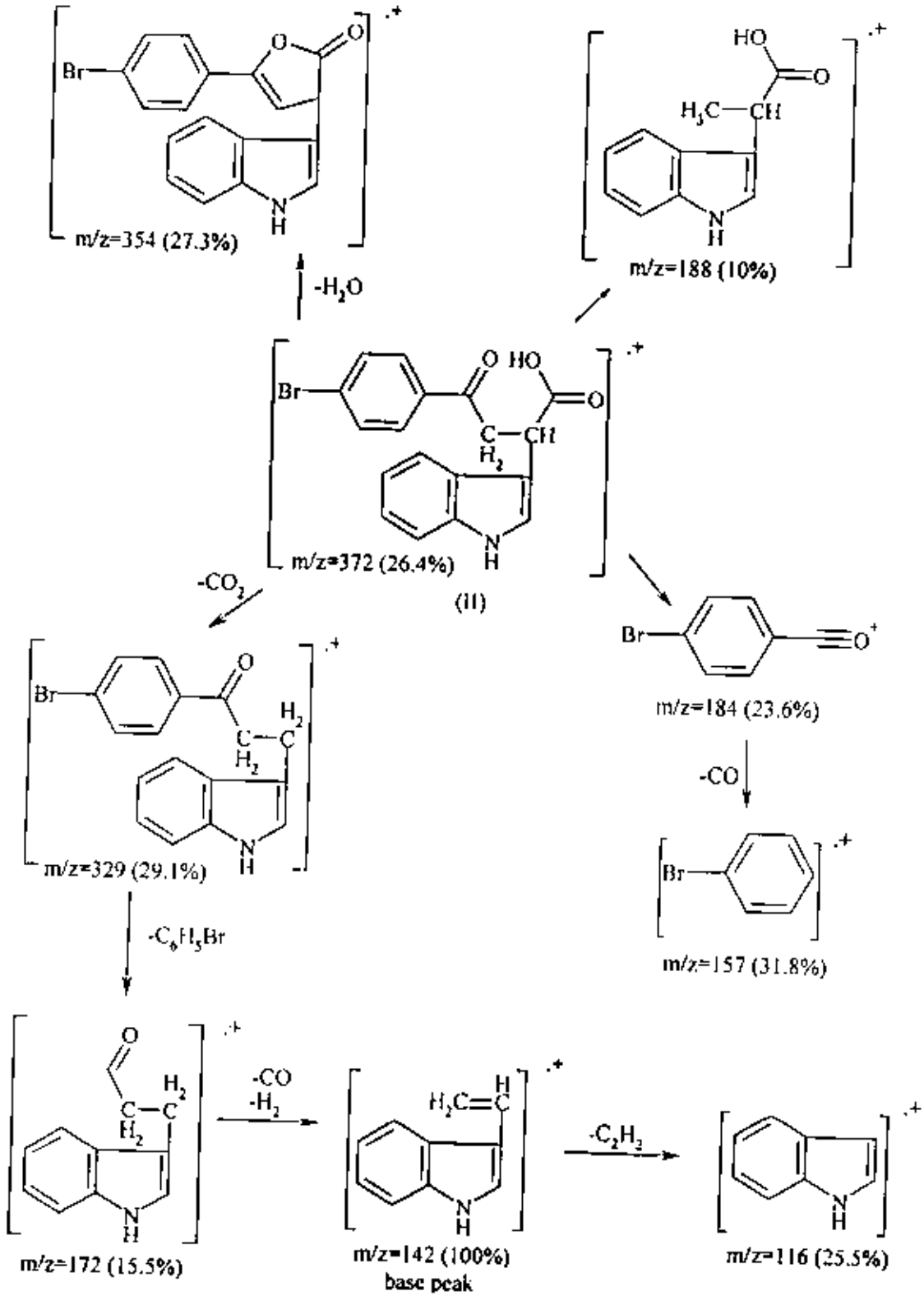
Ar= C_6H_4-Br-P

The structure of the acid (II) was established from the following:

a. Correct elemental analysis.

b. The infrared spectrum of (II) which exhibited absorption bands at 3474-3231cm^{-1} (γ_{O-H}, γ_{N-H}); 2920cm^{-1} (γ_{C-H}); 1735cm^{-1} ($\gamma_{C=O}$ acid) and at 1670cm^{-1} ($\gamma_{C=O}$) (cf. fig 1).

c. The mass spectrum of (II) showed molecular ion peak at m/z=372(26.4%), which underwent further fragmental ion processes to afford m/z=354(27.3%); m/z=329(29.1%); m/z=172(15.5%); m/z=142(100%) and at m/z=116 (25.5%) (cf. scheme 1; fig.2).



(Scheme 1)

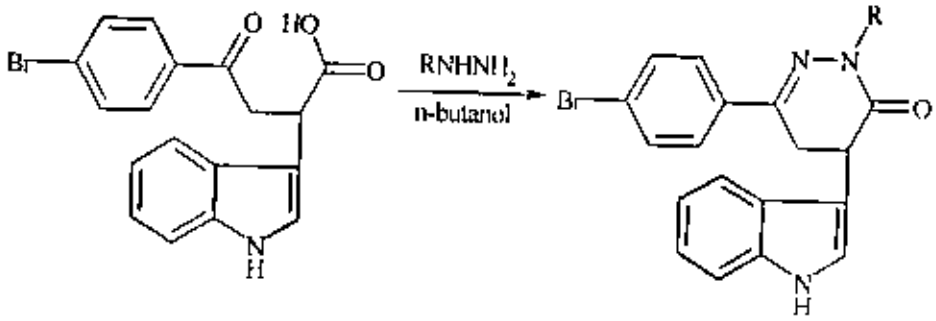
(Fragmentation pattern of compound II)

3.2. Reaction of 4-(P-bromophenyl)-4-oxo-2-indolylbutanoic acid (II) with hydrazines: -

It was reported[121,122], that butanoic acid derivatives (II) reacted readily with hydrazines to form of the corresponding substituted Pyridazinones.

In the present investigation, this reaction has been applied with the aim of obtaining some new Pyridazinones derivatives and studied the behaviors of the nucleus towards nucleophilies and electrophilies.

Thus refluxing compound (II) with hydrazine hydrate and/or phenylhydrazine in n-butanol yielded the corresponding 6-(P-bromophenyl)-4,5-dihydro-4-(3-indolyl)Pyridazin-3(2H)-one (IIIa) and 2-N-phenylPyridazin-3-one (IIIb) respectively.



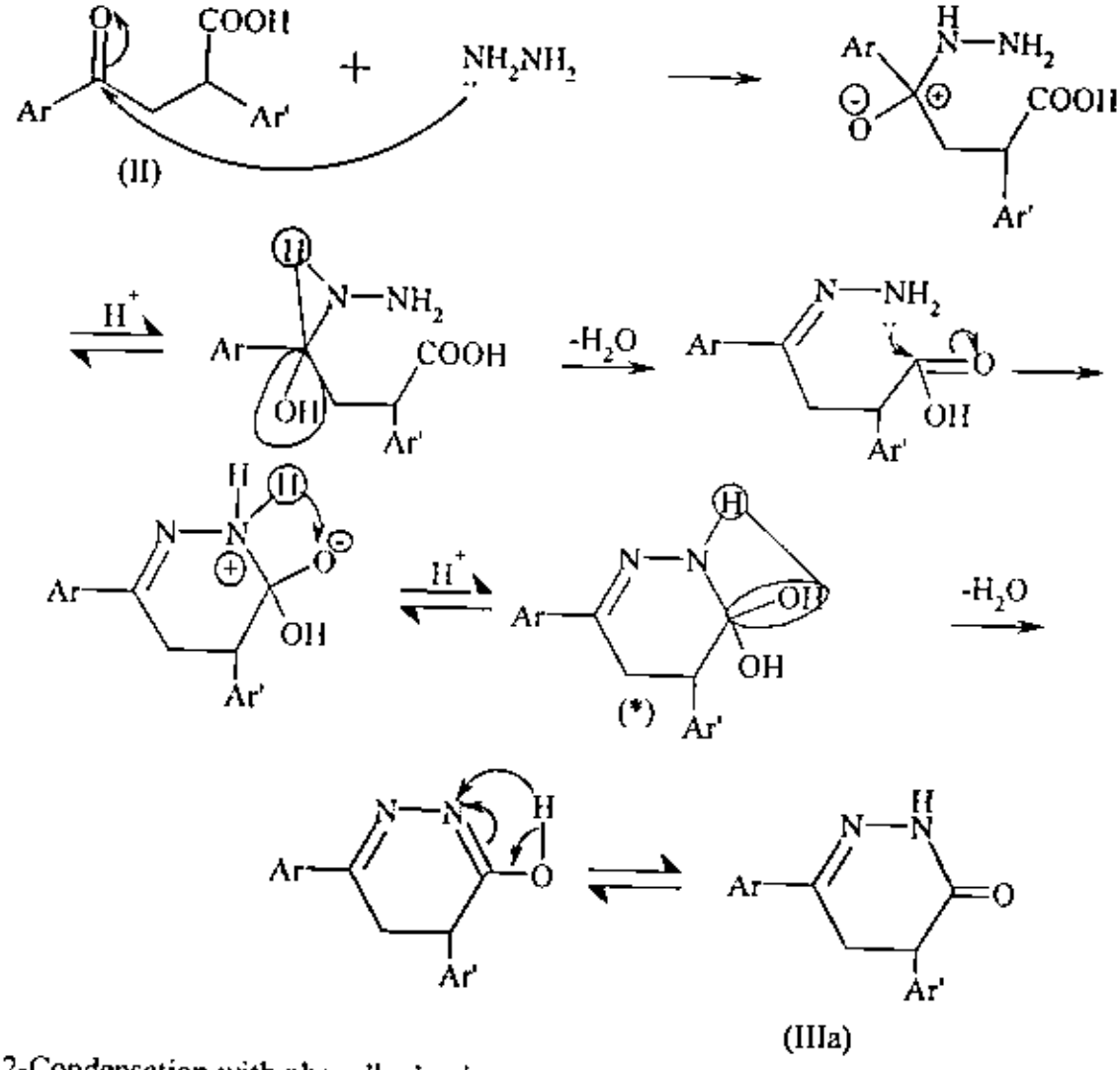
(II)

(III a,b)

a, R=H
b, R=Ph

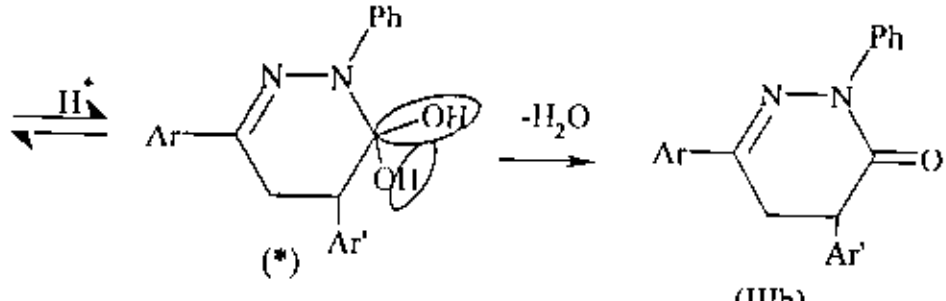
The reaction possibly takes place according to the following mechanism:

1-Condensation with hydrazine hydrate:



(IIIa)

2-Condensation with phenylhydrazine:



(IIIb)

Ar =C_6H_4-Br-P

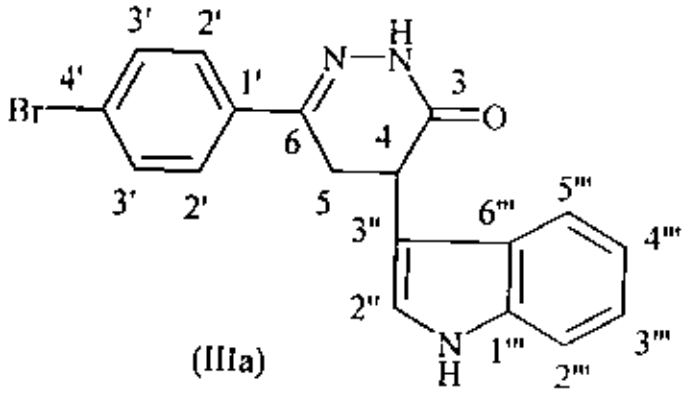
Ar'= 3-indolyl

The structure of Pyridazin-3(2H)-one (IIIa,b) was supported by the following facts: -

a. Correct elemental analysis.

b. Infrared spectrum showed the absorption bands of $\gamma_{C=O}$ at 1680cm^{-1}: $\gamma_{C=N}$ at 1646cm^{-1} and γ_{N-H} at 3225cm^{-1} (cf. fig 3,4).

c. The proton NMR (DMSO-d_6) spectrum of compound (IIIa) showed signals at δ 3.35-3.42(d, 2H, $\underline{CH_2}$-CH); δ 4.0-4.10(t, 1H, CH_2-$\underline{CH}$); δ 7.36(s, 1H, NH of pyridazinone ring); δ 6.98-7.78(m, 9H, 5 protons of Indole ring and 4 protons of P-bromophenyl) and at δ 10.95(s, 1H, NH of Indole ring) (cf. fig. 5).



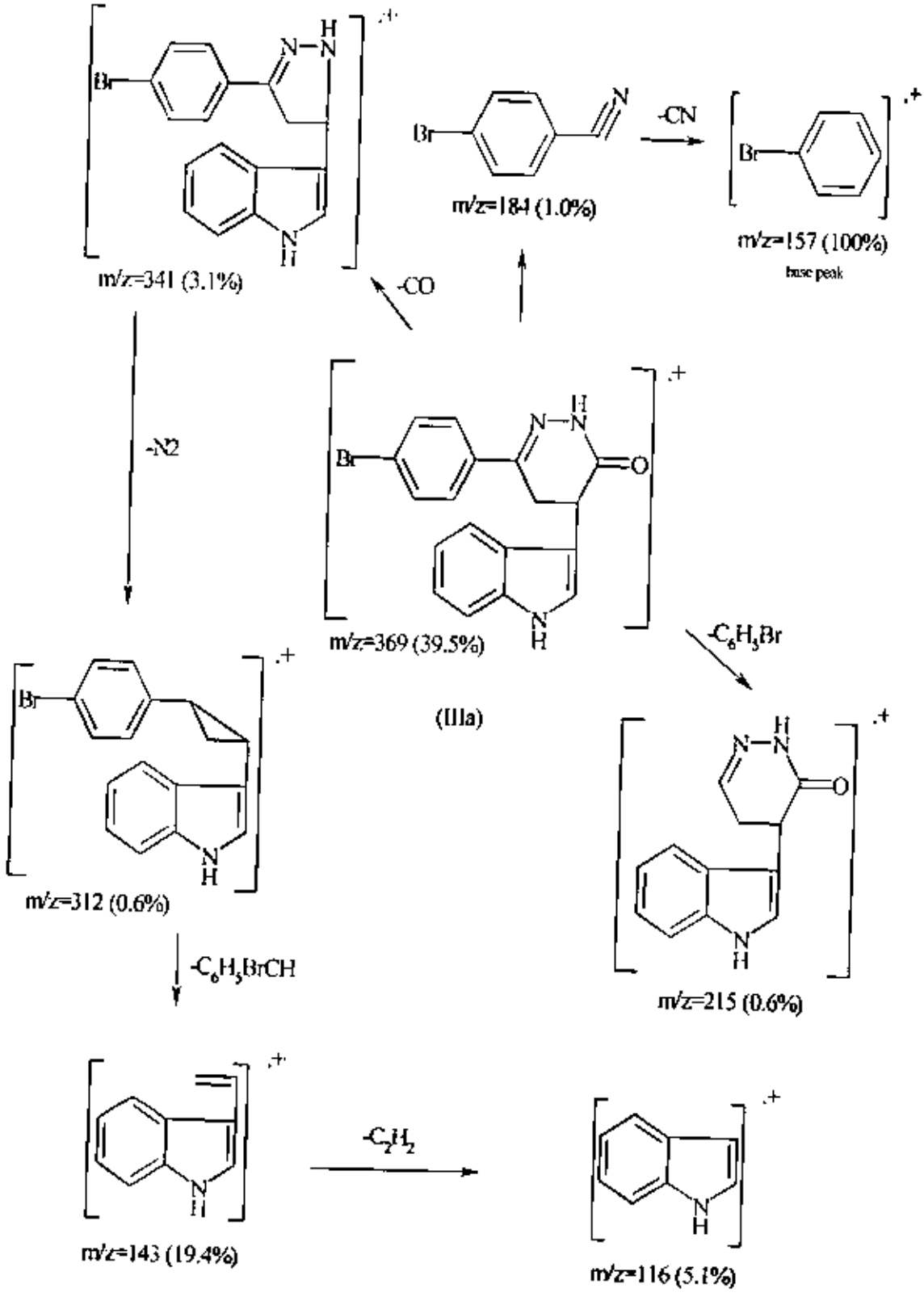
(IIIa)

d. The ^{13}C NMR (DMSO, 50 MHz) of compound (IIIa) has 16 peaks due to the symmetry found in the two carbon atoms in P-bromophenyl, these peaks showed at δ 135.248(C-1'); δ 127.679(C-2'); δ 131.562(C-3'); δ 122.784(C-4'); δ 122.285(C-2"); δ 110.932(C-3"); δ 136.250(C-1'"); δ 111.495(C-2'"); δ 119.317(C-3'"); δ 121.306(C-4'"); δ 118.619(C-5'");

δ 126.353(C-6'''); δ 167.691(C-3); δ 33.808(C-4); δ 28.619(C-5) and at δ 148.552(C-6) (cf. fig. 6).

e. The DEPT NMR of compound (IIIa) has 9 peaks these peaks showed at δ 127.679(C-2'); δ 131.564(C-3'); δ 122.248(C-2''); δ 111.495(C-2'''); δ 119.318(C-3'''); δ 121.309(C-4'''); δ 118.622(C-5'''); δ 33.803(C-4) and at δ 28.609(C-5) (cf. fig. 7).

f. The mass spectrum of (IIIa) revealed the molecular ion peak at m/z=369(39.5%) with important fragments at m/z=341(3.1%); m/z=312(0.1%); m/z=215(0.6%); m/z=184(1.0%); m/z=157(100%); m/z=143(19.4%) and at m/z=116(5.1%) (cf. scheme 2; fig.8).

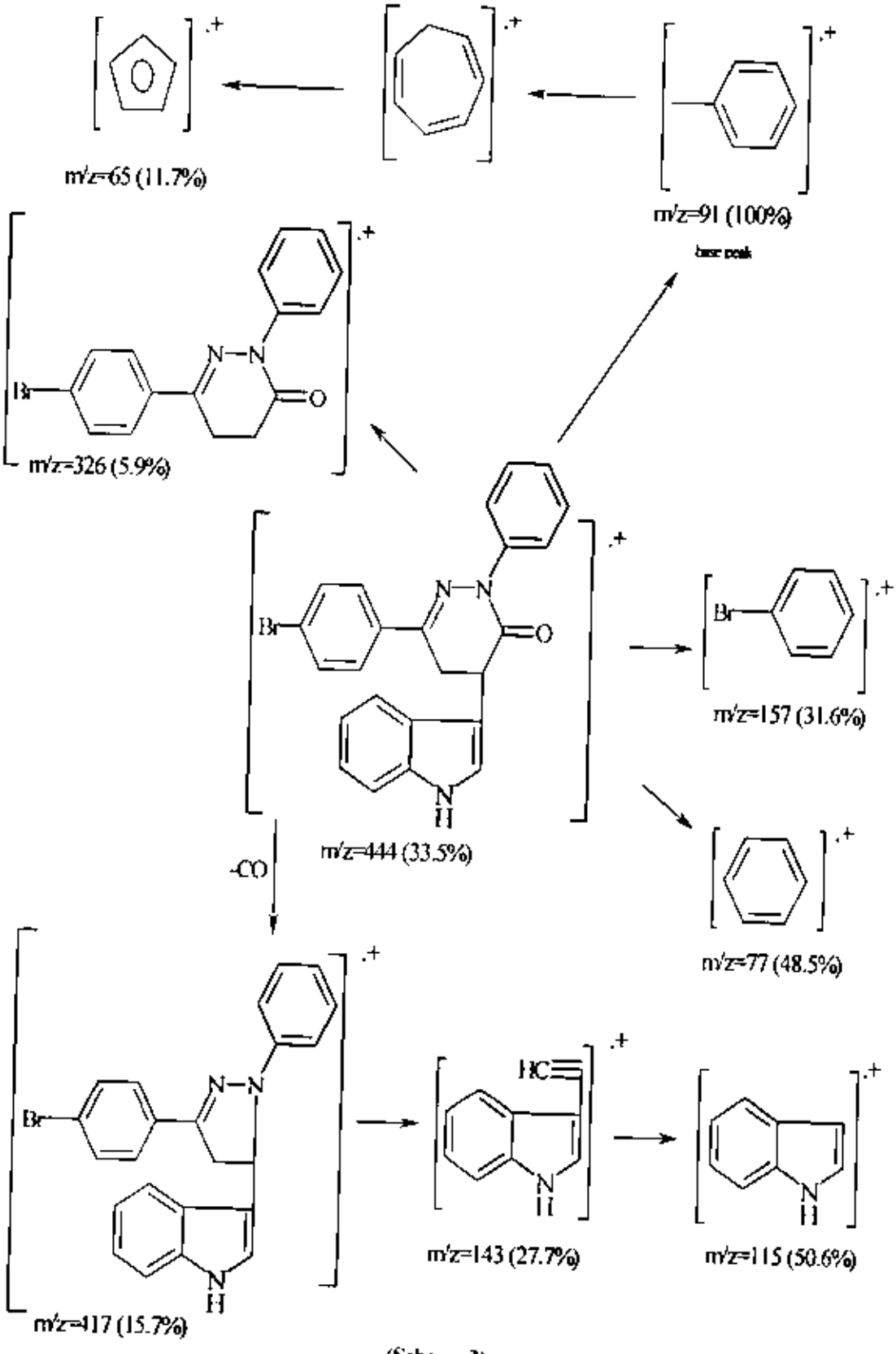


(Scheme 2)

(Fragmentation pattern of compound III a)

g. The ^{1}H NMR (DMSO-d_6) spectrum of compound (IIIb) showed signals at δ 3.30-3.14(d, 2H, $\underline{C}H_2$-CH); δ 4.0-4.10(t, 1H, CH_2-$\underline{C}H$); δ 7.72(s, 1H, NH of pyridazinone ring); δ 7.15-7.78(m, 14H, 5 protons of Indole ring, 4 protons of P-bromophenyl and 5 protons of phenyl ring) and at δ 10.94(1H, s, NH of Indole ring) (cf. fig. 9).

h. The mass spectrum of compound (IIIb) showed the molecular ion peak at m/z=444(33.5%) with important fragments at m/z=417(15.7%); m/z=157(31.6%); m/z=144(0.1%); m/z=115(50.6%) and m/z=91(100%) (cf. scheme 3; fig. 10).

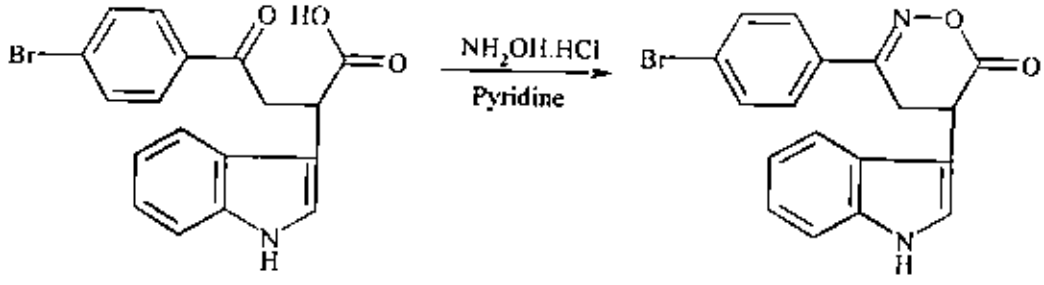


(Scheme 3)

(Fragmentation pattern of compound III b)

3.3. Reaction of (II) with hydroxylamine. Hydrochloride in pyridine: -

When the reaction of (II) with $NH_2OH.HCl$ was carried in boiling pyridine; 4-(P-bromophenyl)-4,5-dihydro-5-(3-indolyl)-1,2-oxazin-6-one (IV) was obtained.



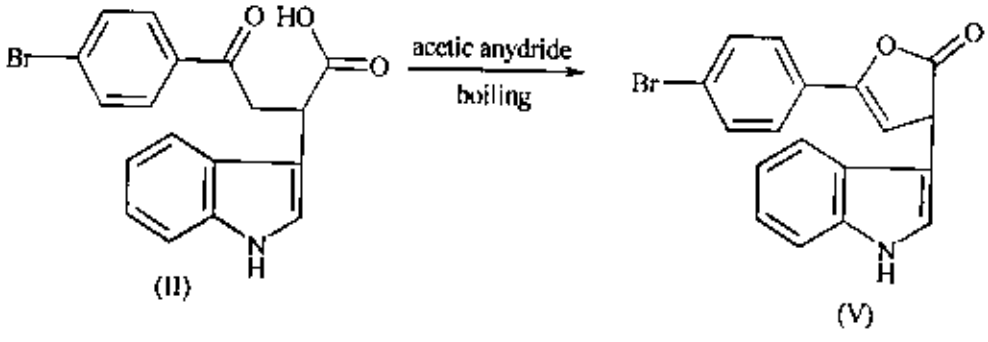
(II)

(IV)

The infrared spectrum showed lack of $\gamma_{C=O}$ (acid) and retained $\gamma_{C=O}$ at 1702cm^{-1}; $\gamma_{C=N}$ at 1625cm^{-1} (cf. fig 11).

3.4. Dehydration of the acid (II): -

The acid (II) was easily dehydrated by boiling with acetic anhydride or heated at its melting point to yield 4-(3-indolyl)-γ-P-bromophenyl butenolide (V).



(II) (V)

The infrared spectrum of (V) showed strong absorption at 1742cm^{-1} characteristic of five membered lactones and the band at 1636cm^{-1} due to $\gamma_{C=N}$ (cf. fig 12).

The structure of (V) was further established by the following:

a. It readily hydrolyzed by hot alkali giving the corresponding acid (II).

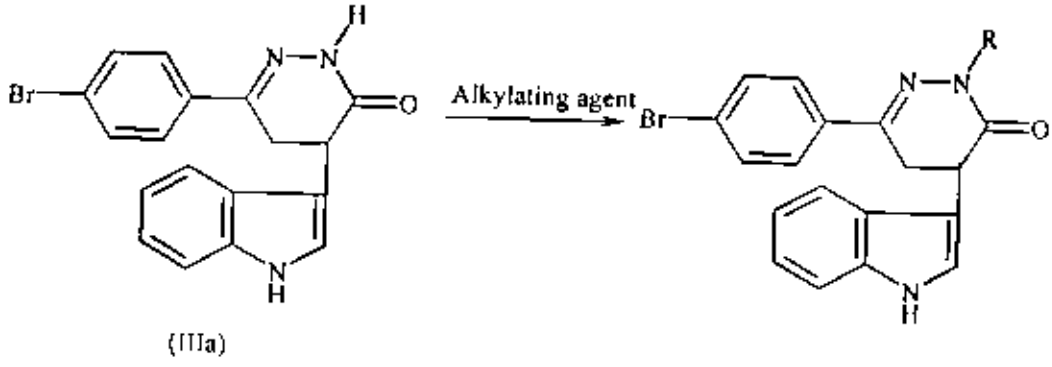
b. The compound (V) reacted with hydrazine hydrate in boiling ethanol to give Pyridazinone derivative (IIIa), which was identified by m.p. and mixed m.p. determination.

Pyridazinone derivative (IIIa) was subjected to further studies: -

A. <u>Alkylation of (IIIa) with electrophilic reagents</u>: -

The Pyridazinone could be alkylated with a variety of electrophilic reagents. The alkylation was conveniently carried out in acetone using potassium carbonate as catalyst.

Thus treatment of (IIIa) with dimethyl sulfate, ethyl Iodide, formaldehyde/Methanol and ethyl chloro acetate gave the N-substituted products (VI a-d) respectively.



(IIIa)

(VI a-d)

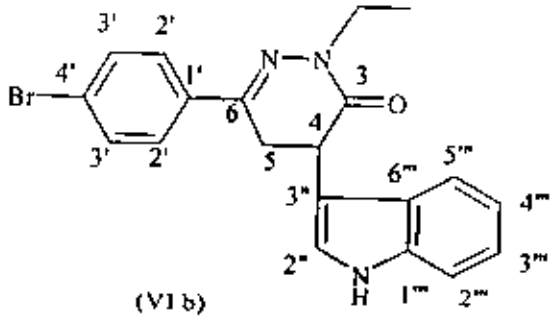
a, R= CH_3
b, R= CH_2-CH_3
c, R= CH_2OH
d, R= $CH_2COOC_2H_5$

The structure of (VI a-d) was supported by the following: -

a. Correct elemental analysis.

b. The Infrared spectra of (VI a-d) showed γ_{N-H} at 3277-3230 cm^{-1}; γ_{C-H} at 3058-2920cm^{-1}; $\gamma_{C=O}$ at 1680-1652cm^{-1}; $\gamma_{C=N}$ at 1649-1600cm^{-1} in addition to a strong band and 1740 cm^{-1} characteristic of $\gamma_{C=O}$ of ester for compound (VId) and at 1388cm^{-1} corresponding to γ_{CH3} for compound (VIa) (cf. fig 13 a-d).

c. The ^1H NMR (DMSO-d_6) spectrum of compound (VId) showed signals at δ 1.14-1.21(t, 3H, CH_2-C<u>H</u>$_3$); δ 4.47-4.50(t, 2H, C<u>H</u>$_2$-CH_3); δ 3.31(s, 2H, C<u>H</u>$_2$-COO); δ 3.44-3.46(d, 2H, CH-C<u>H</u>$_2$); δ 4.07-4.13(t, 1H, C<u>H</u>-CH_2), δ 7.37(s, 1H, NH of pyridazinone ring) and δ 7.03-7.93(m, 9H, 5 proton of Indole ring and 4H, 4 protons of P-bromophenyl) (cf. fig. 14).



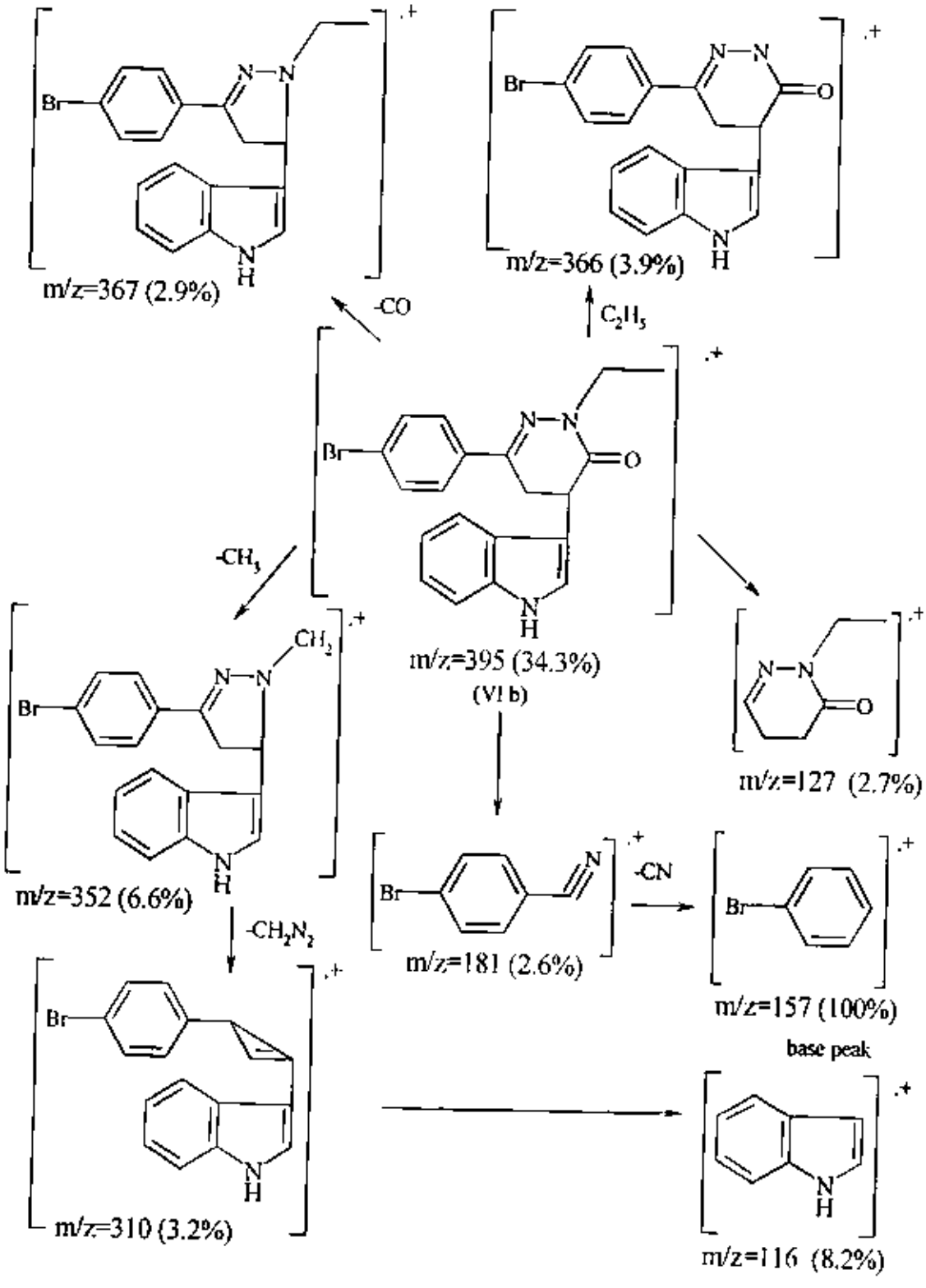
(VI b)

d. The ^{13}C NMR (DMSO, 50 MHz) of compound (VIb) has 16 peaks due to the symmetry found in the two carbon atoms in P-bromophenyl, that peaks showed signals at δ 134.920(C-1'); δ 127.827(C-2'); δ 131.585(C-3'); δ 123.046(C-4'); δ 122.104(C-2''); δ 110.910(C-3''); δ 136.182(C-1''');

δ 111.492(C-2'''); δ 119.171(C-3'''); δ 121.303(C-4'''); δ 118.627(C-5'''); δ 126.226(C-6'''); δ 165.569(C-3); δ 34.198(C-4); δ 28.933(C-5); δ 149.357(C-6); δ 13.322(CH_3) and at δ 43.167(CH_2) (cf. fig. 15).

e. The DEPT NMR of compound (VIb) has 11 peaks these peaks showed at δ 127.830(C-2'); δ 131.592(C-3'); δ 122.111(C-2''); δ 111.501(C-2'''); δ 119.175(C-3'''): δ 121.302(C-4'''); δ 118.638(C-5'''); δ 34.200(C-4); δ 28.919(C-5); δ 13.329(CH_3) and at δ 43.164(CH_2) (cf. fig. 16).

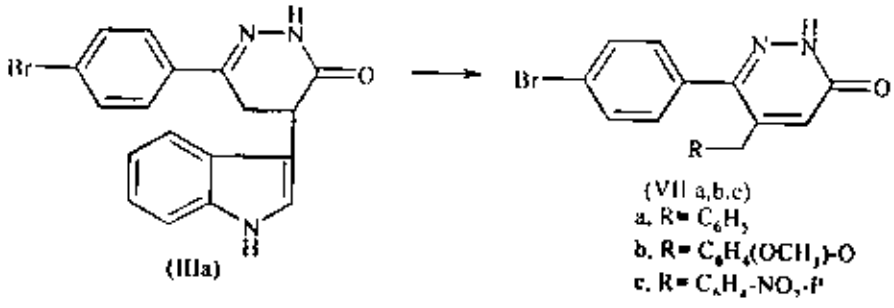
f. The mass spectrum of (VIb) showed the molecular ion peak at m/z=395(P-1)(34.3%) with important fragments at m/z=367(2.9%); m/z=352(6.6%); m/z=310(3.2%); m/z=184(4.5%); m/z=157(100%); m/z=127(2.7%) and m/z=116 (8.2%) (cf. scheme 4; fig. 17).



(Scheme 4)
(Fragmentation pattern of compound VI b)

B. <u>Reaction of (IIIa) with aromatic aldehydes</u>: -

Interaction of pyridazin-3(2H)-one derivatives (IIIa) with aromatic aldehydes namely benzaldehyde, o-methoxybenzaldehyde and/or p-nitrobenzaldehyde in presence of ethanolic sodium hydroxide afforded the disubstituted pyridazin-3(2H)-one derivatives (VIIa,b,c).



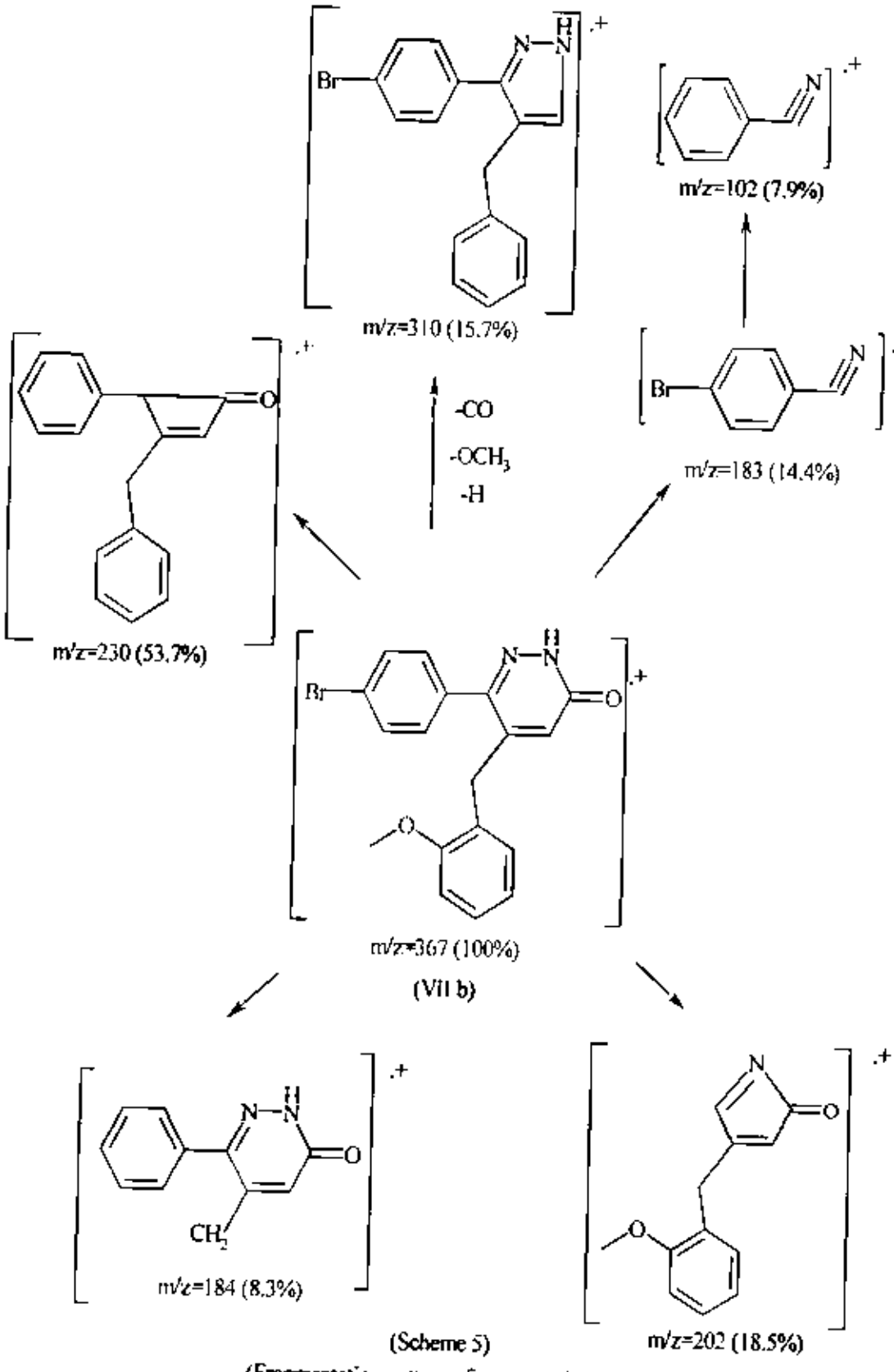
The fission of the Indole ring was observed which may be due to the presence of two bulky groups ortho to each other on the pyridazinone ring. This was observed in other cases [123,124].

The structures of (VIIa,b,c) were established from the following:

a. Correct elemental analysis.

b. The infrared spectra of (VII a,b,c) showed γ_{N-H} at 3481-3404 cm^{-1}; γ_{C-H} at 3197-2920cm^{-1} and $\gamma_{C=O}$ at 1720-1680cm^{-1} (cf. fig 18 a-c).

c. The mass spectrum of (VIIb) showed the molecular ion peak at m/z=367(100%), which underwent further fragmentation to afford the Ion peaks at m/z=310(15.7%); m/z=114(25%) and at m/z=77(22.7%) (cf. scheme 5; fig. 19).



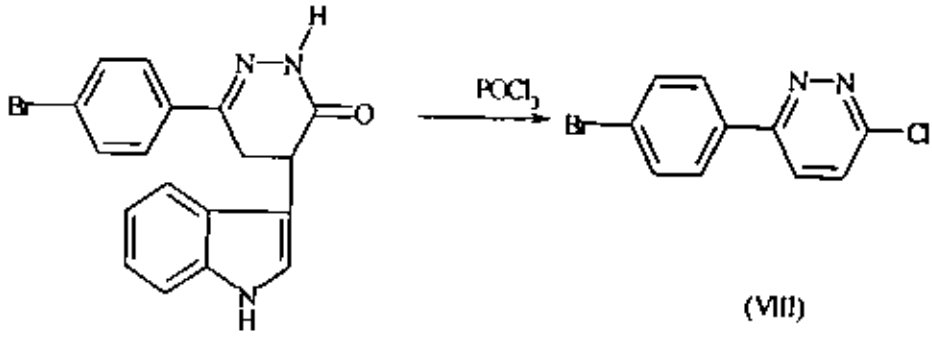
(Scheme 5)

(Fragmentation pattern of compound VII b)

C. Reaction of (IIIa) with phosphorus oxytrichloride: -

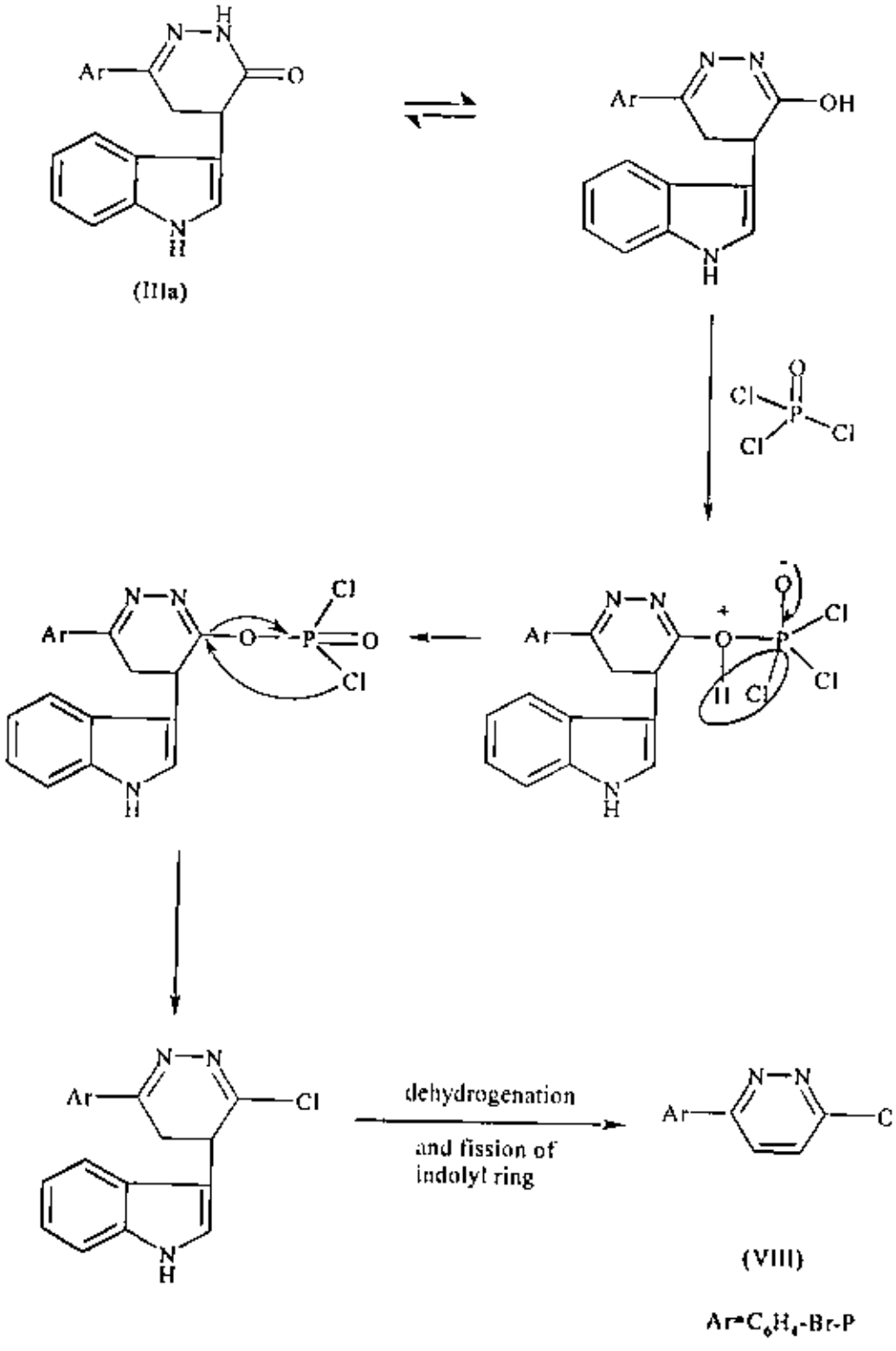
Pyridazinone (IIIa) reacted with nucleophilic reagents like phosphorus oxytrichloride to give 3-chloropyridazine derivative (VIII) by substitution of hydroxyl group of the enol form of Pyridazinone with chlorine and dehydrogenation and fission of indolyl ring.

The phenomeno of dehydrogenation is not strange since it is observed in the reaction of Pyridazinone with P_2S_5 and Grignard reactions. This is also in accordance with previous results [16,125,126].



(IIIa) (VIII)

The reaction presumably takes place according to the following mechanism: -



(IIIa)

(VIII)

Ar=C_6H_4-Br-P

The structure of the 3-chloropyridazine (VIII) was established from the following: -

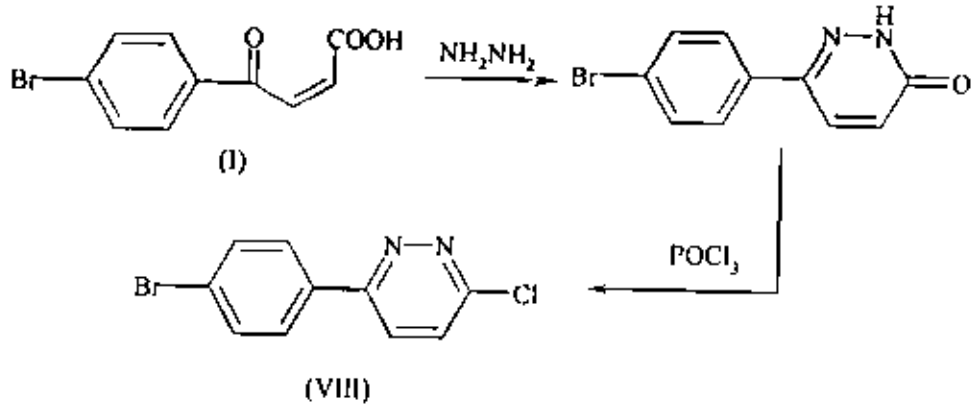
a. Correct elemental analysis.

b. The Infrared spectra of (VIII) which showed absorption bands at 2927cm^{-1} (γ_{C-H}): 1652cm^{-1} ($\gamma_{C=N}$) and at 489cm^{-1} (γ_{C-Cl}) (cf. fig. 20).

c. Chemically.

Reaction of (I) with hydrazine hydrate; Formation of 6-(P-bromophenyl) pyridazin-3-one: -

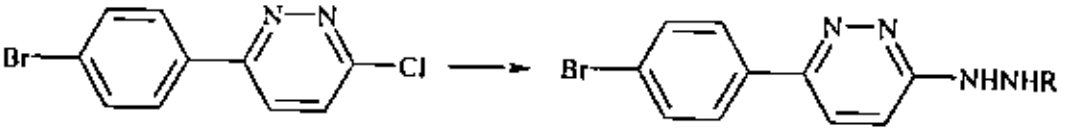
It must be noted that the compound 3-chloropyridazine derivative (VIII) can be obtained also by treatment of the compound 4-(P-bromophenyl)-4-oxo-2-butenoic acid (I) with hydrazine hydrate in butanol followed by treatment of the pyridazinone derivative obtained with phosphorus oxytrichloride to yield the compound 3-chloropyridazine derivative (VIII) which identified by mixed m.p and IR. Spectrum.



(VIII)

3.5. Reaction of (VIII) with hydrazines: -

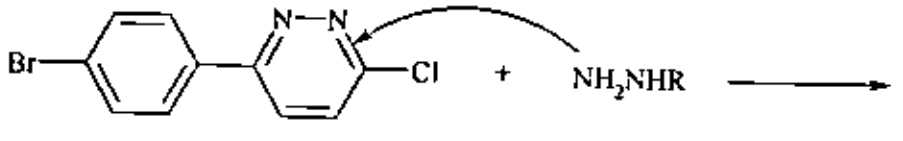
It was found that when pyridazin-3-chloro derivative (VIII) was submitted to react with hydrazine hydrate and/or phenylhydrazine in boiling n-butanol afforded the corresponding hydazino derivative (IXa,b).



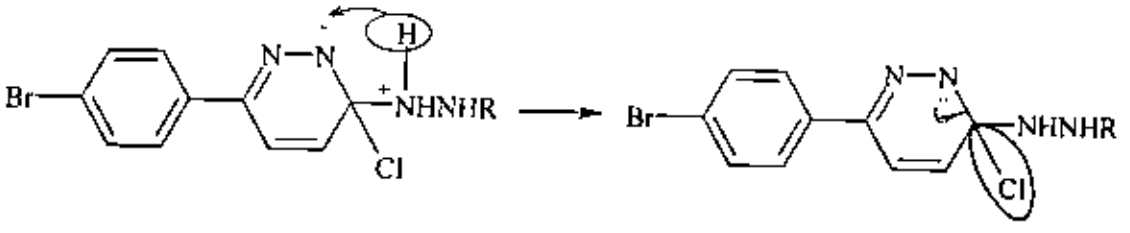
(VIII)

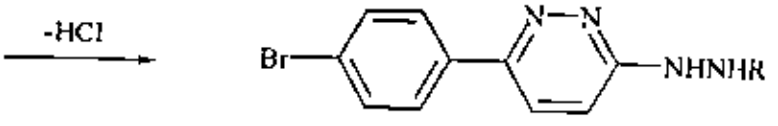
(IX a,b)
a, R=H
b, R= C_6H_5

The reaction possibly proceeded via the following route:



(VIII)





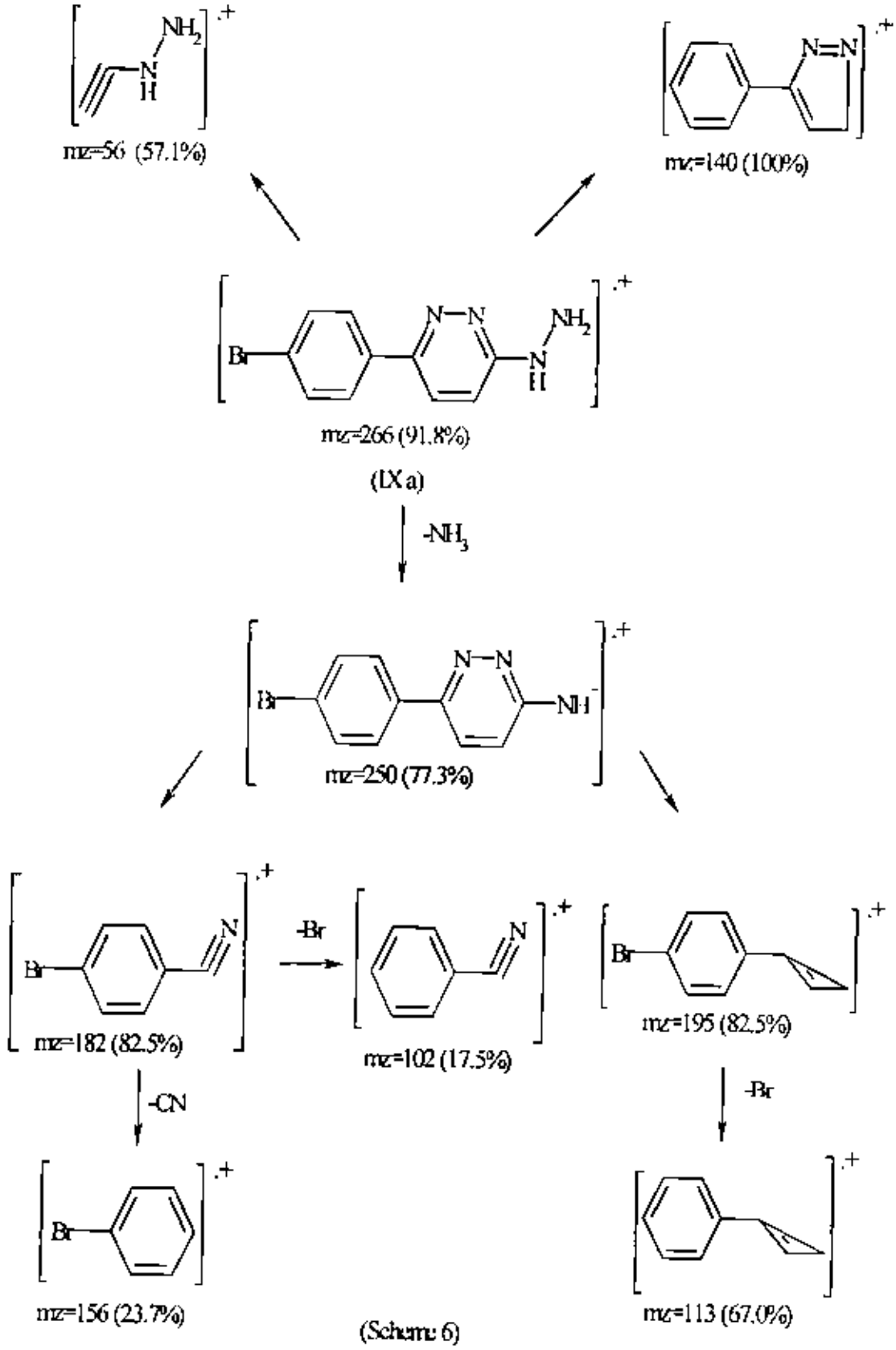
(IX a,b)
a, R=H
b, R= C_6H_5

The structure of (IXa,b) were established from the following: -

a. Correct elemental analysis.

b. The Infrared spectra of (IXa,b) revealed the presence of $\gamma_{N\text{-}H2}$ at 3287-3467cm^{-1}; $\gamma_{N\text{-}H}$ at 3287-3230cm^{-1} and $\gamma_{C=N}$ at 1609-1591cm^{-1} (cf. fig. 21 a,b).

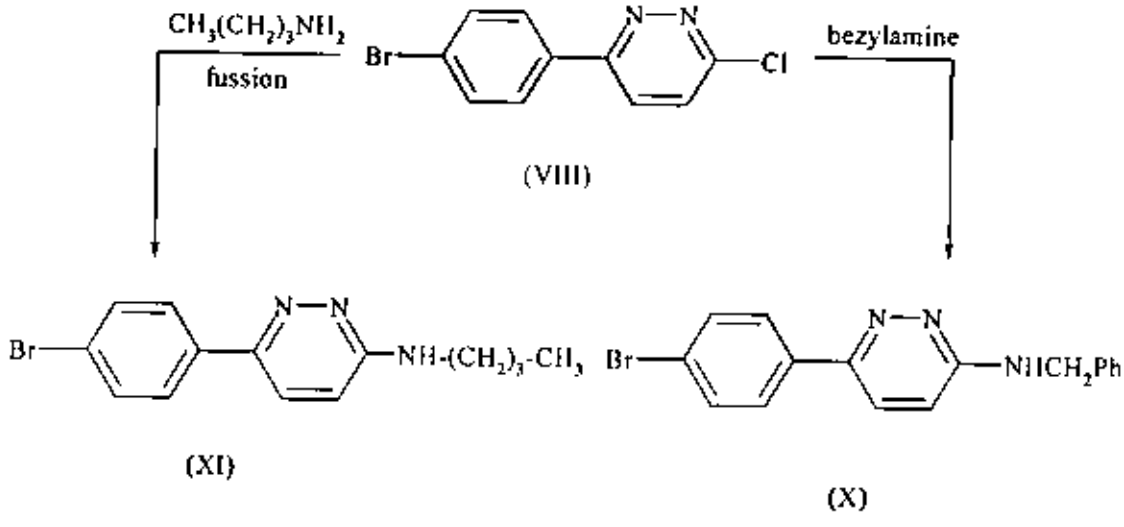
c. The mass spectrum of (IXa) showed the following ion peak at m/z=266(91.8%); m/z=250(77.3%); m/z=195(82.5%); m/z=182(35.1%); m/z=140(100%); m/z=114(44.3%); m/z=102(17.5%) and at m/z=56(83.5%) (cf. scheme 6; fig. 22).



(Scheme 6)
(Fragmentation pattern of compound IX a)

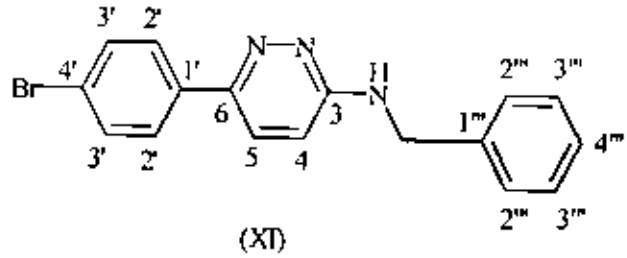
3.6. Reaction of 3-chloropyridazine derivative (VIII) with amines: -

Similarly, the interaction of 3-chloropyridazine derivative (VIII) with aliphatic amines namely benzylamine and/or n-butylamine was also carried out, the products were identified as 6-(p-bromophenyl)-3-(N-methylphenyl) pyridazine (X) and 6-(p-bromophenyl)-3-(N-butyl) pyridazine (XI).



The Infrared spectrum of (X and XI) agreed well with the proposed structures. It revealed the presence of γ_{N-H} at 3280-3209cm^{-1}; $\gamma_{C=N}$ at 1600-1566cm^{-1} and $\gamma_{C=C}$ at 1655-1591cm^{-1} (cf. fig. 23 a-b).

Also the ^{1}H NMR (DMSO-d_6) spectrum of compound (X) showed signals at δ 4.63-4.66(d, 2H, C$\underline{H_2}$-NH); δ 7.25-7.38(m, 5H, 5 protons of phenyl ring); δ 7.68-7.82(s, 1H, NH) and δ 6.94-7.82(m, 2H, pyridazinone ring) (cf.fig.24).

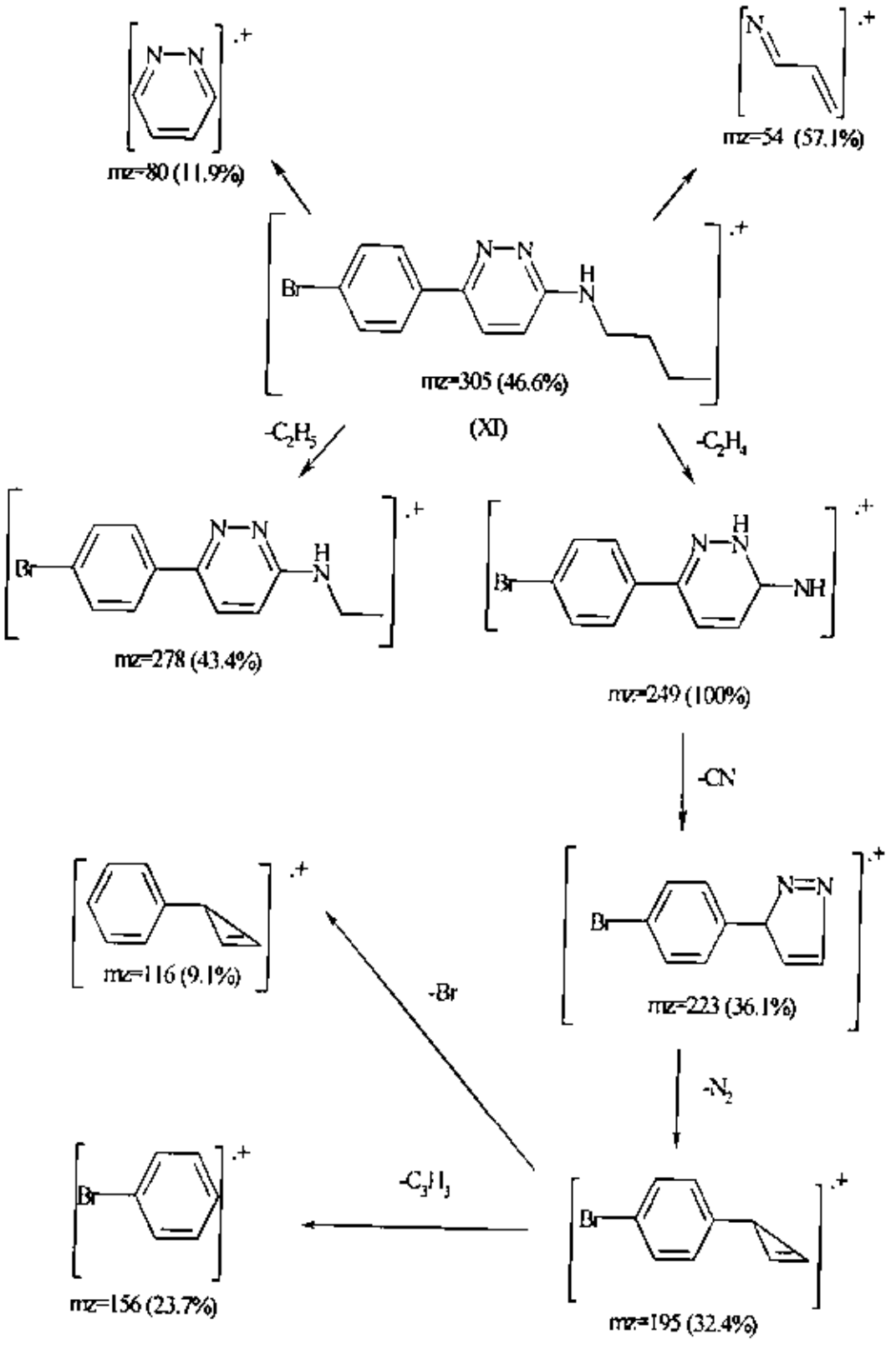


(XI)

The ^{13}C NMR (DMSO, 50 MHz) of compound (X) has 13 peaks due to the symmetry found in the two carbon atoms in P-bromophenyl, that's peaks showed at δ 136.194(C-1'); δ 127.394(C-2'); δ 131.650(C-3'); δ 121.738(C-4'); δ 126.760(C-4'''); δ 127.321(C-2'''); δ 128.303(C-3'''); δ 139.749(C-1'''); δ 44.302 (CH_2); δ 158.044(C-3); δ 114.784(C-4); δ 124.893(C-5) and at δ 148.934(C-6) (cf. fig. 25).

And the DEPT NMR of compound (X) has 8 peaks that's peaks showed at δ 127.390(C-2'); δ 131.649(C-3'); δ 126.761(C-4'''); δ 127.321(C-2'''); δ 128.303(C-3'''); δ 44.293(CH_2); δ 114.787(C-4) and at δ 124.894(C-5) (cf. fig. 26).

The mass spectrum of (XI) showed the molecular ion peak at m/z=305 (P-1)(46.6%), which followed by the following important fragmentation peak's m/z=276(59.8%); m/z=249(100%); m/z=220(36.1%); m/z=195(32.4%); m/z=156(23.7%); m/z=116(9.1%); m/z=78(26%) and at m/z=54(57.1%) (cf. scheme 7; fig. 27).



(Scheme 7)
(Fragmentation pattern of compound XI)

3.7. Reaction of 3-chloropyridazine derivative (VIII) with sodium methoxide (XII): -

The reaction of 3-chloropyridazine derivative (VIII) with sodium methoxide in ethanol afforded the 3-methoxypyridazine derivative (XII).

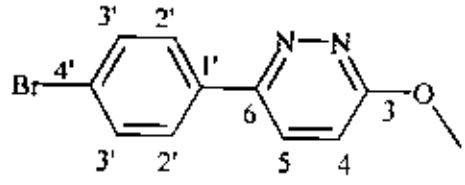
(VIII) (XII)

The structure of (XII) was supported by the following: -

a. Correct elemental analysis.

b. The Infrared spectra of (XII) showed $\gamma_{C=N}$ at 1597cm^{-1} and disappearance of the γ_{C-Cl} (cf. fig. 28).

c. The ^{1}H NMR (DMSO-d_6) spectrum of compound (XII) showed signals at δ 4.10(s, 3P, O-C$\underline{H_3}$) and δ 7.30-8.22(m, 6P, 4 protons of P-bromophenyl and 2 protons of pyridazinone ring) (cf. fig. 29).



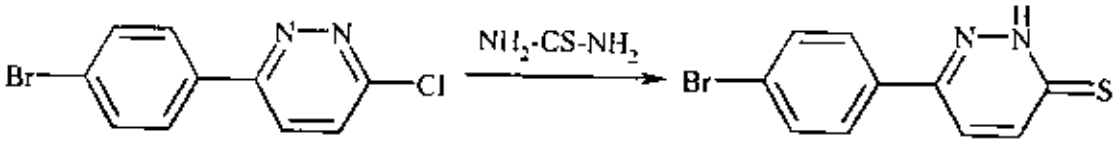
(XII)

d. The ^{13}C NMR (DMSO, 50 MHz) of compound (XII) has 9 peaks due to the presence of A_2B_2 system in P-bromophenyl. these peaks showed at δ 135.099(C-1'); δ 127.639(C-2'); δ 131.824(C-3'); δ 123.029(C-4'); δ 164.231(C-3); δ 117.611(C-4); δ 128.295(C-5); δ 153.701(C-6) and at δ=54.505 (OCH_3) (cf. fig. 30).

e. The DEPT NMR of compound (XII) has 9 peaks, these peaks appeared at δ 127.650(C-2'); δ 131.832(C-3'); δ 117.626(C-4); δ 128.295(C-5) and at δ=54.515(OCH_3) (cf.fig. 31).

3.8. Reaction of 3-chloropyridazine derivative (VIII) with thiourea (XIII): -

It was found that the interaction of 3-chloropyridazine derivative (VIII) with thiourea in boiling ethanol gave the corresponding pyridazin-3-thione derivative (XIII).

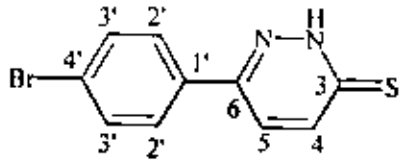


(VIII) (XIII)

The structure of (XIII) was supported by the following: -

a. Correct elemental analysis.

b. The Infrared spectra of (XIII) showed γ_{N-H} at 3270 cm^{-1}; $\gamma_{C=N}$ at 1655cm^{-1} and $\gamma_{N-C=S}$ at 1467cm^{-1} (cf. fig. 32).

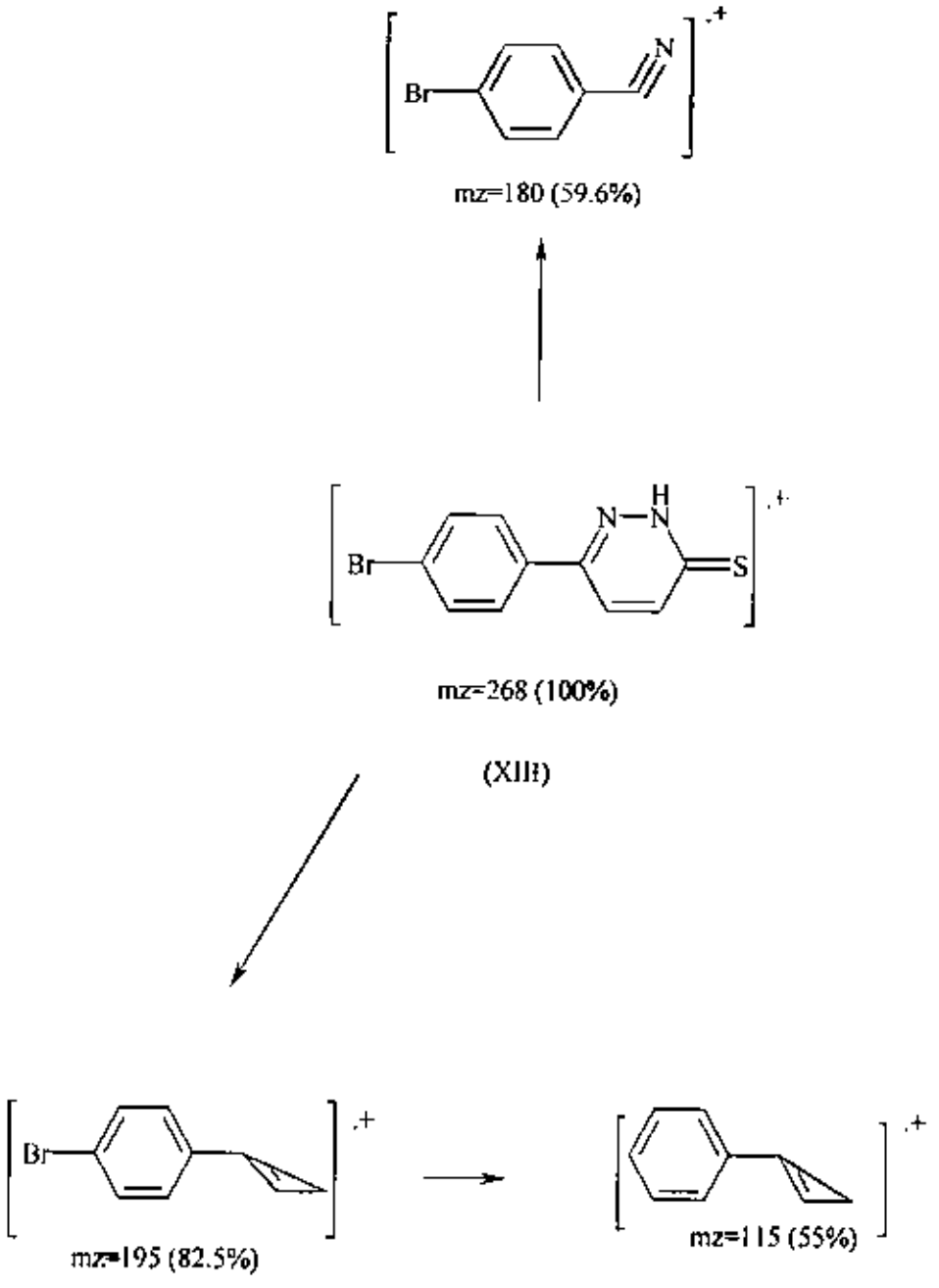


(XIII)

c. The ^{13}C NMR (DMSO, 50 MHz) of compound (XIII) has 8 peaks due to the symmetry found in the two carbon atoms in P-bromophenyl, these peaks showed at δ=132.880(C-1'); 127.933(C-2'); 131.944(C-3'); δ 123.688(C-4'); δ 178.977(C-3); δ 124.679(C-4); δ 141.418(C-5) and at δ 148.422(C-6) (cf. fig. 33).

d. The DEPT NMR of compound XIII has 4 peaks that peaks showed at δ 127.936(C-2'); δ 131.951(C-3'); δ 124.689(C-4) and at δ 141.417(C-5) (cf. fig. 34).

e. The mass spectrum of *XIII* showed the following ion peak at m/z=268(100%); m/z=195(82.5%) and at m/z=115(55%) (cf. scheme 8; fig. 35).

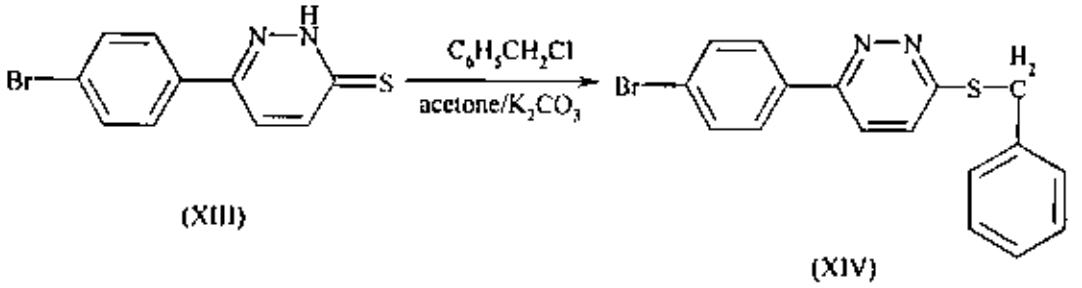


(Scheme 8)

(Fragmentation pattern of compound IX f)

3.9. Reaction of thiopyridazine derivative (XIII) with benzyl chloride (XIV): -

Treatment of the thiopyridazine derivative (XIII) with benzylchloride in dry acetone in presence of anhydrous potassium carbonate afforded the S-benzyl derivative (XIV).



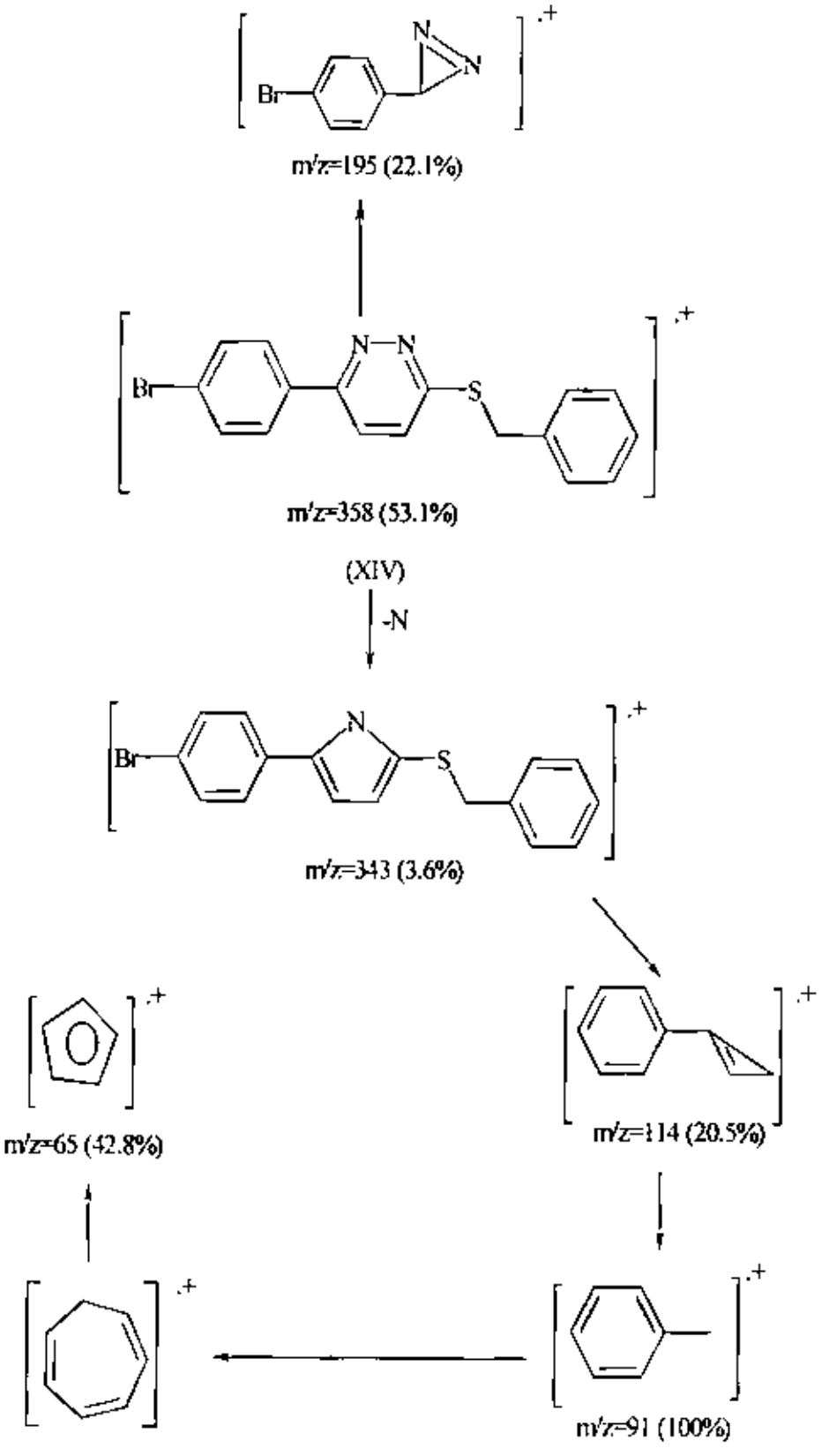
(XIII) (XIV)

The structure of (XIV) was supported by the following: -

a. Correct elemental analysis.

b. The Infrared spectra of (XIV) showed the band of $\gamma_{C=N}$ at 1579cm^{-1} and disappearance of γ_{NH} group (cf. fig. 36).

c. The mass spectrum of the S-benzyl derivative (XIV) afford the molecular ion peak at m/z=358 (53.1%) and the following important fragments at m/z=195(22.1%); m/z=114(20.5%); m/z=91(100%) and at m/z=65(42.8%) (cf. scheme 9; fig 37).



(Scheme 9)
(Fragmentation pattern of compound X)

BIOLOGICAL ACTIVITY

4. Biological Screening: -

The chemical compounds were tested for antibacterial activity against human pathogenic Gram-negative (*Escherichia. coli* ATCC 25922), Gram-positive bacteria (*Staphylococcus aureus* ATCC 29213. *Bacillus cereus*) and *Candida albicaus* bacteria[18, 33].

The antibiotic, Tetracycline and Metranidazol were used as control antibacterial agent.

According to the solubility of the tested compounds, different polar and nonpolar solvents were used, and a good solubility was shown in 10% acetone (v/v) for all test compounds.

Solutions of the test compounds and Ampicillin were dissolved in acetone at concentration (A=0.00125, B=0.0025, C=0.005 g/ml) were selected. The impregnated disks were placed on the medium suitably spaced apart and the plates were incubated at 5°C for 1 hr to permit good diffusion and then transferred to an incubator at 28°C for 24 hrs.

Statistically, the measurements of the inhibitor zone were recorded and compared with obtained results of control.

The results are summarized in Table {1}.

Table {1}

Compound	S.aurues			Bacillus			Candida			E.coli		
	A	B	C	A	B	C	A	B	C	A	B	C
IV	+	++	+++	++	+++	+++	-	-	-	+	+	+
VIa	+	+	-	-	-	-	-	-	-	-	-	-
VIIa	-	-	-	-	-	-	++	+++	+++	-	-	-
X	+	+	+	-	-	-	-	-	-	-	-	-
XII	+	++	++	-	+	+	-	-	-	-	-	-

Where the Solvent: acetone; (+) = weak activity (diameter 6-10 mm), (++) = moderate activity (diameter 11.7-14.3 mm), (+++) = high activity (diameter 17.3-20.7 mm), (-) = nil activity (diameter less than 6 mm); Reference substances: *Ampicillin* for *Candida*, *Bacillus*, *E.coli* and *S.aurues* bacteria.

Results: -

The compound IV and VIIa were found to have high activity against *S.aurues*, *Bacillus* and *Candida*, while the compound XII was found to have moderate activity against *S.aurues* and the compounds IV, X and XII were found to have weak activity against *E.coli*, S.aurues and *Bacillus* in highest concentration.

Also in moderate concentration the compounds IV and VIIa were found to have high activity against *Bacillus* and *Candida*, while the compounds IV and XII possess moderate activity against *S.aurues* and weak activity showed the compounds IV, X and XII against *E.coli*, *S.aurues* and *Bacillus*.

As well as, in low concentration the compounds IV and VIIa were showed moderate activity against *Bacillus* and *Candida* and the compounds IV, VIa, X and XII found to weak activity against *S.aurues* and *E.coli*.

LDS for S.aurues = 0.736693; Bacillus = 0.600544; Candida = 1.99585 and E.coli = 1.76914.

EXPERIMENTAL WORK

5. Experimental: -

The Infrared spectra were recorded on a BRUKER IFS-25 FT-IR spectrophotometer using KBr at the region 400-4000 cm^{-1}, ^{1}H, ^{13}C and DEPT NMR spectra on a BRUKER AVANCE/200 ULTRASHLIELD™ (temp. 22°C; humidity 46-53%) transform instrument using TMS as internal standard, Mass spectra were obtained with an Shimad 24 GCMS-QP 1000EX., Elemental analyses were determined on FISONS instruments DP200 series 2 and Euro EA3000 series Euro Vector Elemental Analyzers for CHNS-O) and are indicated only by the elemental symbols within (0.4%) of the theoretical values unless otherwise noted. All melting points were uncorrected.

5.1 Preparation of 4-(p-bromophenyl)-4-oxo-2-butenoic acid (I): -

This compound (I) was synthesized according to the literature procedure[119,120]. The solid product was crystallized from methanol to give (I) as pale yellow needles. The results are listed in table {1}.

5.2 Reaction of (I) with 3-indole; Formation of 4-(p-bromophenyl)-2-(3-indolyl)-4-oxo-butanoic acid (II): -

The compound (I) (0.01 mmol, 2.55 g) was refluxed with Indole (0.01 mmol, 0.17 g) for 6 hrs in 30 ml of n-butanol, the reaction mixture was cooled, left at room temperature over night and filtered off to give (II) as pale brown needles. The results are listed in table {1}.

5.3 Reaction of (II) with hydrazines; Formation of 6-(p-bromophenyl)-4,5-dihydro-4-(3-indolyl)Pyridazin-3(2H)-one (IIIa) and 6-(p-bromophenyl)-4,5-dihydro-4-(3-indolyl)-2-phenylpyridazinone (IIIb): -

Compound (II) (0.01 mmol, 3.72 g) reacted with (0.01 mmol) hydrazine hydrate and/or phenyl hydrazine in 50 ml n-butanol, the reaction mixture was refluxed for 10 hrs, concentrated, cooled, the separated solid were filtered off to give white crystals of 6-(P-bromophenyl)-4,5-dihydro-4-(3-indolyl)Pyridazin-3(2H)-one (IIIa) as pale yellow crystals and 6-(P-bromophenyl)-4,5-dihydro-4-(3-indolyl)-2-phenylpyridazinone (IIIb). The results are listed in table {1}.

5.4 Reaction of (II) with hydroxylamine hydrochloride in pyridine; Formation of 3-(P-bromophenyl)-4,5-dihydro-5- (3-indolyl)-1,2-oxazin- 6-one (IV): -

A mixture of (II) (0.01 mmol, 3.72 g), hydroxylamine hydrochloride (0.01 mmol, 0.695 g) in 20 ml pyridine, was heated in water bath for 6 hrs. The reaction mixture was cooled, poured onto ice/HCl mixture.

The obtained solid washed well with water and crystallized from suitable solvent to give (IV) as faint yellow crystals. The results are listed in table {1}.

5.5 Reaction of (II) with acetic anhydride; Formation of 4-(3-indolyl)-γ-P-bromophenyl butenolide (V): -

Compound (II) (0.01 mmol, 3.72 g) was refluxed for 8 hrs in 50 ml acetic anhydride.

The product was concentrated and the solid product was crystallized from a suitable solvent to give (V) as pale brown needles. The results are listed in table {1}.

Table {1}

Compound	M.P °C	Solvent of crystallization	Yield g %	Formula (M.Wt)	Analysis		
						Found	Required
I	158	MeOH	11 69	$C_{10}H_7BrO_3$ (255.07)	C H	47.31 2.95	47.09 2.77
II	203	MeOH	2.74 74	$C_{18}H_{14}BrNO_3$ (372.22)	C H N	57.71 3.89 3.83	58.08 3.79 3.76
IIIa	239	MeOH	3.5 95	$C_{18}H_{14}BrN_3O$ (368.24)	C H N	58.76 3.97 11.28	58.71 3.83 11.41
IIIb	189	EtOH	1.8 41	$C_{24}H_{18}BrN_3O$ (444.33)	C H N	65.04 3.87 7.70	64.88 4.08 7.46
IV	249	$CHCl_3$	3.5 95	$C_{18}H_{13}BrN_2O_2$ (369.21)	C H N	58.22 3.33 7.60	58.56 3.55 7.59
V	191	Pet.ether 120-160	2.1 59	$C_{18}H_{12}BrNO_2$ (354.20)	C H N	61.01 3.60 4.60	61.04 3.41 3.95

5.6 Reaction of (IIIa) with dimethyl sulfate, ethyl iodide and/or ethyl chloroacetate; Formation of (VI a,b,d): -

A mixture of (IIIa) (0.01 mmol, 3.68 g), anhydrous potassium carbonate (0.04 mmol, 5.5 g), (0.03 mmol) of dimethyl sulfate, ethyl iodide or ethyl chloroacetate and dry acetone (100 ml) was refluxed for 40 hrs. After filtration while hot, removing excess solvent under reduced pressure, the residue was dissolved in water and extracted with ether (4×30 ml). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed in vacuum, to give (VI a,b,d) as yellow needles. The results are listed in table {2}.

5.7 Reaction of (IIIa) with formaldehyde; Formation of (VI c): -

A solution of (IIIa) (0.01 mmol, 3.68 g) in 50ml methanol was treated with formaldehyde (0.01 mmol) and refluxed for 6 hrs. The ppt after cooling, filtered off and the solid obtained was crystallized from methanol to give 6-(p-bromophenyl)-4,5-dihydro-2-(hydroxymethyl)-4-(3-indolyl)pyridazin-3(2H)-one (VI c) as pale yellow needles. The results are listed in table {2}.

Table (2)

Compound	M.P ^0C	Solvent of crystallization	Yield g %	Formula (M.Wt)	Analysis		
						Found	Required
VIa	247	MeOH	1.2 31	$C_{19}H_{16}BrN_3O$ (382.25)	C H N	59.61 4.42 10.81	59.70 4.22 10.99
VIb	192	EtOH	1.2 30	$C_{20}H_{18}BrN_3O$ (396.28)	C H N	60.03 4.81 10.27	60.62 4.58 10.60
VIc	242	MeOH	2.3 58	$C_{19}H_{16}BrN_3O_2$ (398.25)	C H N	58.29 3.98 10.44	57.30 4.05 10.55
VId	208	EtOH	1.6 35	$C_{22}H_{20}BrN_3O_3$ (454.32)	C H N	58.00 4.36 9.99	58.16 4.44 9.25

5.8 Reaction of (IIIa) with benzalaldehyde; O-methoxybenzaldehyde and/or P-nitrobenzalaldehyde. Formation of (VIIa,b,c): -

A mixture of (IIIa) (0.01 mmol, 3.68 g) with benzalaldehyde, o-Methoxybenzalaldehyde or P-nitrobenzalaldehyde (0.01 mmol) in 20ml ethanol, was treated with 4% ethanolic sodium hydroxide solution (20 ml) and the whole mixture was refluxed for 3 hrs.

The formed solid product was cooled then filtered off and the solid product was crystallized from suitable solvent to give (VIIa,b,c) as pale brown needles. The results are listed in table {3}.

5.9 Reaction of (IIIa) with phosphorus oxychloride; Formation of 3-(4-bromophenyl)-6-chloropyridazine (VIII): -

A mixture of the pyridazinone (IIIa) (0.01 mmol, 3.68 g) and $POCl_3$ (10 ml) was heated at 100°C for 4 hrs. After cooling, the residue was poured into a mixture of ice/water (50 g).

The precipitate was collected by filtration and the solid product was crystallized from suitable solvent to give (VIII) as brown needles. The results are listed in table {3}.

5.10 Reaction of VIII with hydrazines; Formation of (IXa,b): -

A mixture of the chloro compound (VIII) (0.01 mmol, 2.70 g) and hydrazine hydrate or phenylhydrazine (0.03 mmol) in butanol (50 ml) was refluxed 6 hrs and the solid obtained was crystallized from suitable solvent to give:

1-(6-(P-bromophenyl)-3-pyridazinyl)hydrazine (IXa) as pale brown crystals and 1-(6-(P-bromophenyl)-3-pyridazinyl)-2-phenylhydrazine (IXb) as pale brown crystals. The results are listed in table {3}.

Table {3}

Compound	M.P ^0C	Solvent of crystallization	Yield g %	Formula (M.Wt)		Analysis Found	Analysis Required
VIIa	233	Benzene	1.8 47	$C_{17}H_{13}BrN_2O$ (341.20)	C H N	60.18 3.84 8.89	59.84 3.84 8.21
VIIb	216	$CHCl_3$	2.1 57	$C_{18}H_{15}BrN_2O_2$ (371.23)	C H N	58.12 4.39 7.93	58.24 4.07 7.55
VIIc	221	CH_3COOH	1.9 36	$C_{17}H_{12}BrN_3O_3$ (386.20)	C H N	52.53 3.39 10.54	52.87 3.13 10.88
VIII	199	MeOH	1.6 59	$C_{10}H_6BrN_2Cl$ (269.53)	C H N	44.88 2.46 10.28	44.56 2.24 10.39
IXa	184	MeOH	2 75	$C_{10}H_9BrN_4$ (265.11)	C H N	45.38 3.88 20.92	45.30 3.42 21.13.
IXb	225	MeOH	2 59	$C_{16}H_{13}BrN_4$ (341.21)	C H N	56.73 3.52 16.32	56.32 3.84 16.42

5.11 Reaction of (VIII) with aliphatic amines; Formation of (X) and (XI):

A mixture of chloro pyridazinone (VIII) (0.01 mmol, 2.70 g) and N-benzyl or butylamie (0.01 mmol) was heated on oil bath at 200°C for 2 hrs. After cooling, the residue was triturated with benzene. The precipitate was collected by filtration and crystallized from suitable solvent to give:

3-N-substitutedamino-6-(p-bromophenyl)pyridazine (X) and (XI), as yellow crystals; The results are listed in table {4}.

5.12 Reaction of (VIII) with sodium methoxide; Formation of 3-(P-bromophenyl)-6-methoxypyridazine (XII): -

A dry sodium methoxide solution was prepared by dissolving sodium (0.01 mmol, 2.3 g) in freshly dried and resonated methanol (50 ml), and compound (VIII) (0.01 mmol, 2.70 g), left for half an hour, then the solvent removed under vacuum.

The residue was suspended in 30 ml water and crystallized from suitable solvent to give (XII), as white crystals. The results are listed in table {4}.

5.13 Reaction of (VIII) with thiourea; Formation of 6-(P-bromophenyl) pyridazine-3(2H)-thione (XIII): -

A solution of the chloro compound (VIII) (0.01 mmol, 2.70 g) and thiourea (0.03 mmol, 2.2836 g) in ethanol (15 ml) was refluxed until the starting material was consumed (ca. 15 hrs; TLC). The solvent was removed under reduced pressure and the residue was refluxed in a mixture of 10% NaOH (3 ml) and ethanol (10 ml) for 1 hrs. The solvent was evaporated and the solid residue was dissolved in water.

The solution was acidified with 2 *N* HCl, and then the precipitate formed was collected by filtration and crystallized from suitable solvent to give (XIII), as yellow needles. The results are listed in table {4}.

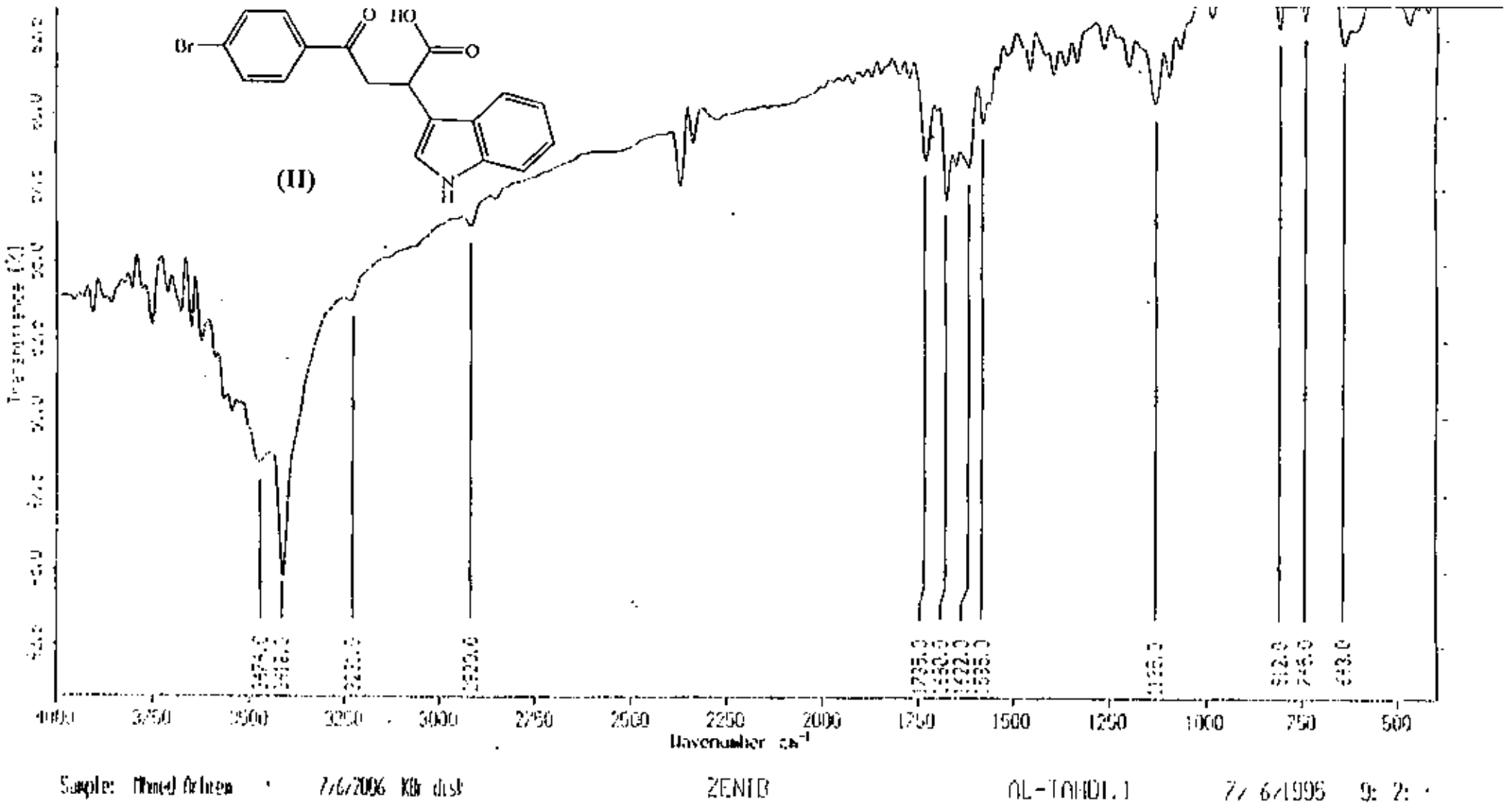
5.14 Reaction of (XIII) with benzyl chloride; Formation of 3-(benzylthio)-6-(p-bromophenyl)pyridazine (XIV): -

A mixture of (XIII) (0.01 mmol, 2.67 g), anhydrous potassium carbonate (0.03 mmol, 4.2 g), benzyl chloride (0.01 mol, 3.8 g) and dry acetone (100 ml) were refluxed for 40 hrs. After filtration while hot and removing excess solvent under reduced pressure, the residue was crystallized from suitable solvent to give (XIV), as yellow crystals. The results are listed in table {4}.

Table (4)

Compound	M.P °C	Solvent of crystallization	Yield g %	Formula (M.Wt)	Analysis		
						Found	Required
X	200	MeOH	1.5 46	$C_{17}H_{14}BrN_3$ (340.22)	C H N	59.70 4.40 12.32	60.02 4.15 12.35.
XI	183	MeOH	1.1 36	$C_{14}H_{16}BrN_3$ (306.21)	C H N	54.72 5.45 13.21	54.91 5.27 13.72
XII	179	EtOH	2.1 80	$C_{11}H_9BrN_2O$ (265.11)	C H N	49.97 3.57 10.32	49.84 3.42 10.57
XIII	223	EtOH	1.9 71	$C_{10}H_7BrN_2S$ (267.14)	C H N S	45.30 2.77 10.10 11.90	44.96 2.64 10.49 12.00
XIV	167	MeOH	2.2 62	$C_{17}H_{13}BrN_2S$ (357.27)	C H N S	57.10 3.60 7.80 8.76	57.15 3.67 7.84 8.98

SPECTRAL DATA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O
HO
O
N
H
(II)
Transmittance [%]
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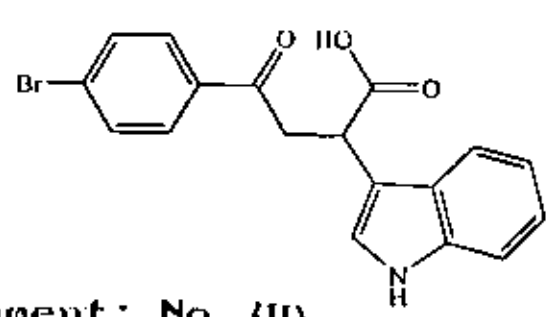
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
ZENIT
7/6/1995

fig. 1



$C_{18}H_{14}BrNO_3$

Mol. Wt.: 372.21

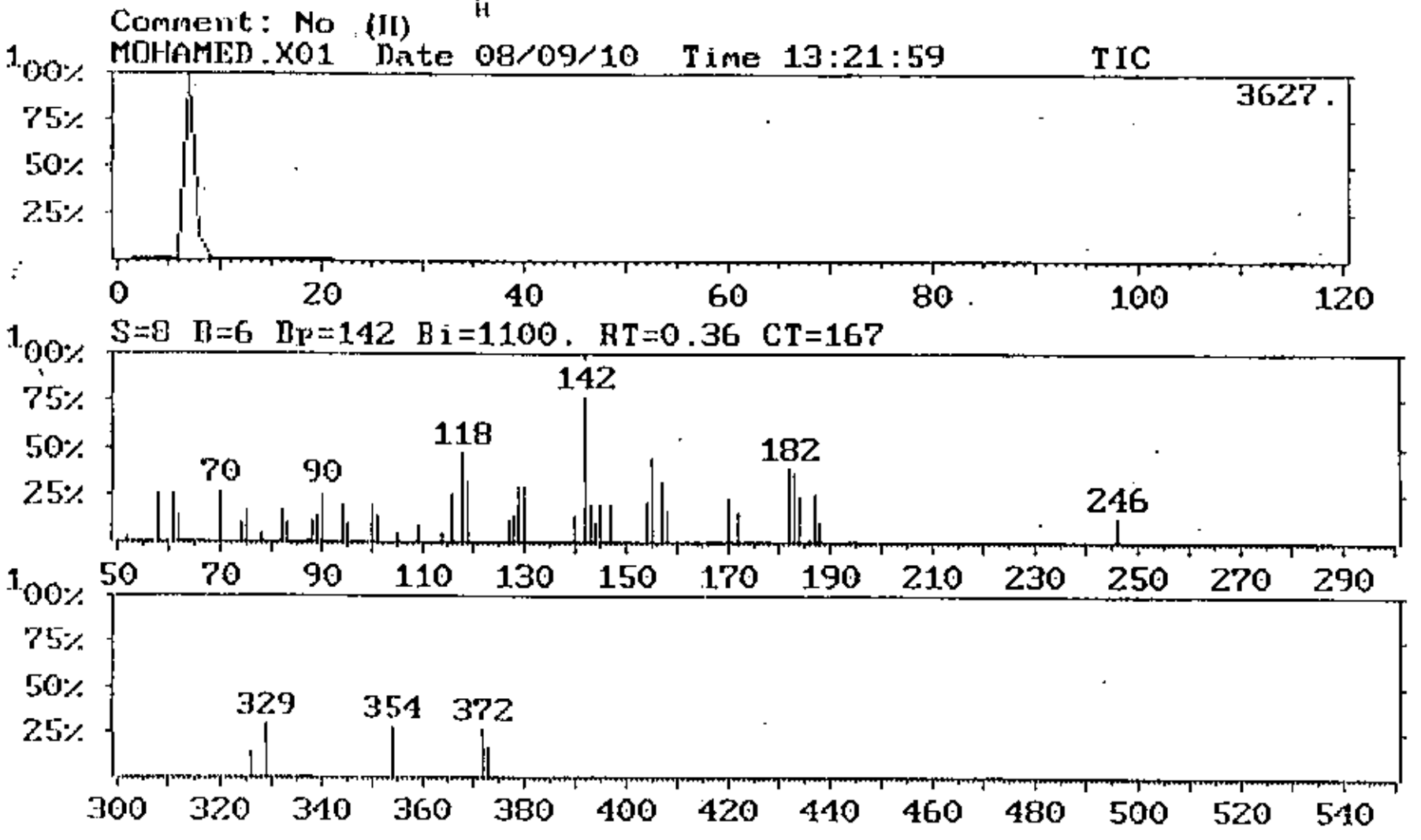
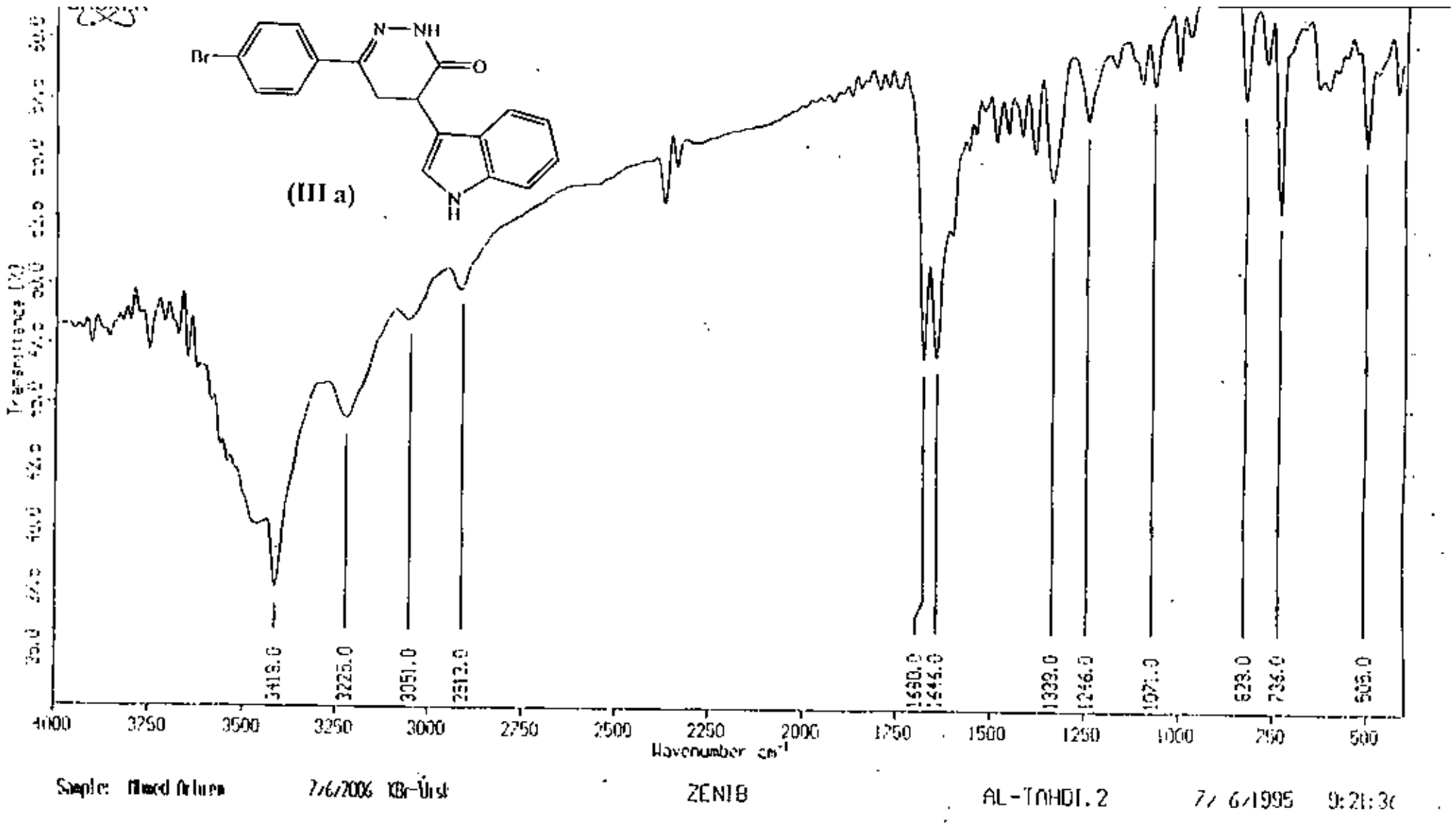


fig. 2

File : MOHAMED.XO1 Date 08/09/10 Time 13:21:59
S=8 B=6 Bp=142 Bi=1100. RT=0.36 CT=167

Mass	Int(%)	Mass	Int(%)	Mass	Int(%)	Mass	Int(%)
52	2.7	53	0.9	58	25.5	61	24.5
62	14.5	70	26.4	74	10.0	75	16.4
78	4.5	82	16.4	83	10.0	87	1.8
88	10.9	89	14.5	90	25.5	94	19.1
95	10.0	100	19.1	101	14.5	102	0.9
105	3.6	109	8.2	114	3.6	116	25.5
118	46.4	119	31.8	127	10.9	128	14.5
129	29.1	130	29.1	140	13.6	142	100.0
143	19.1	144	10.0	145	20.0	147	19.1
154	20.9	155	43.6	157	31.8	158	17.3
170	22.7	172	15.5	182	38.2	183	36.4
184	23.6	186	1.8	187	24.5	188	10.0
246	12.7	326	13.6	329	29.1	354	27.3
372	26.4	373	16.4				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O
N
H
(III a)
Transmittance [%]
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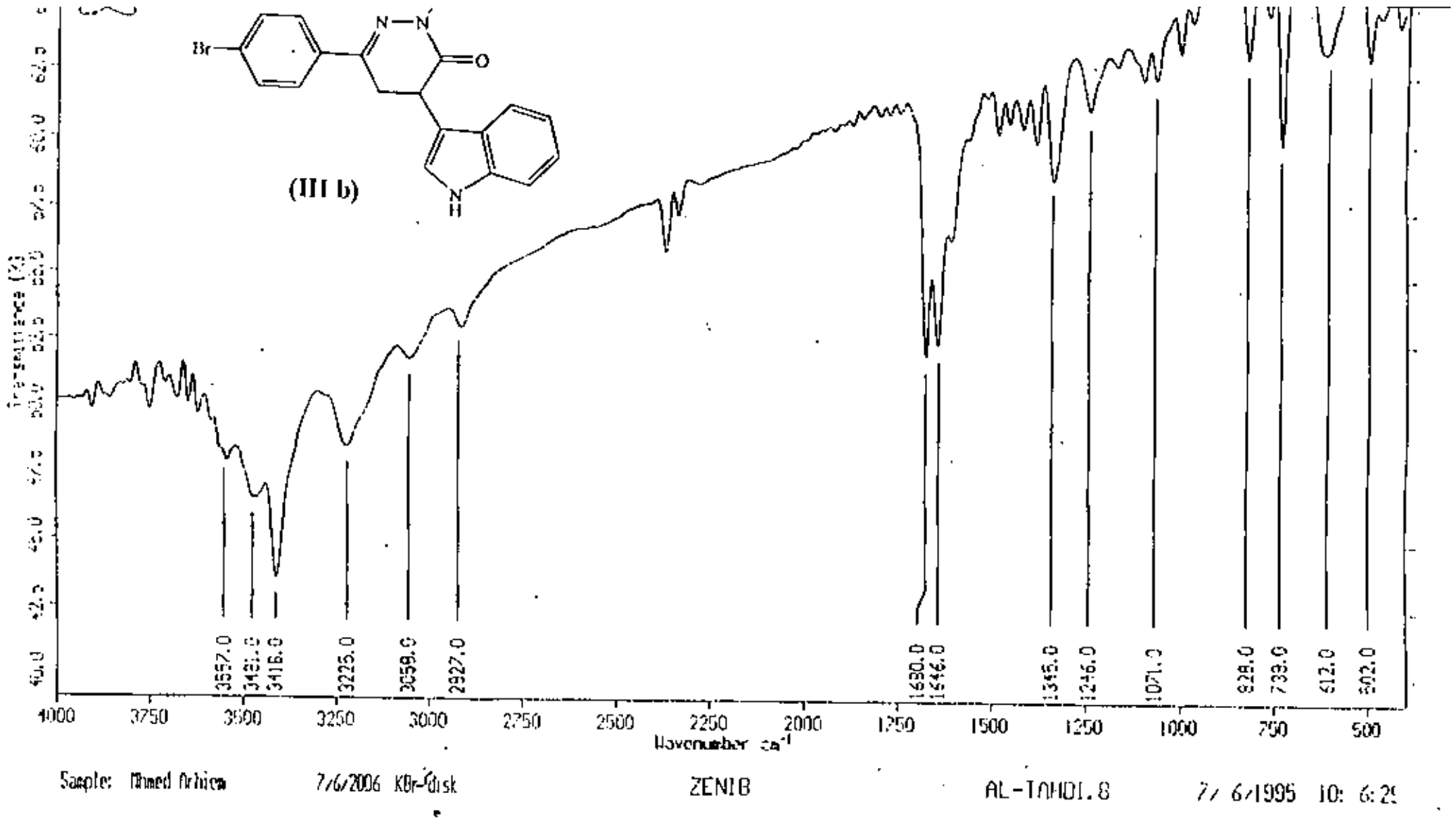
3051.0
2912.0
1660.0
1444.0
1339.0
1246.0
1072.0
823.0
736.0
505.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Mixed Isomers
7/6/2006 KBr-Disk
ZENIB
AL-TOHDI.2
7/ 6/1995

fig. 3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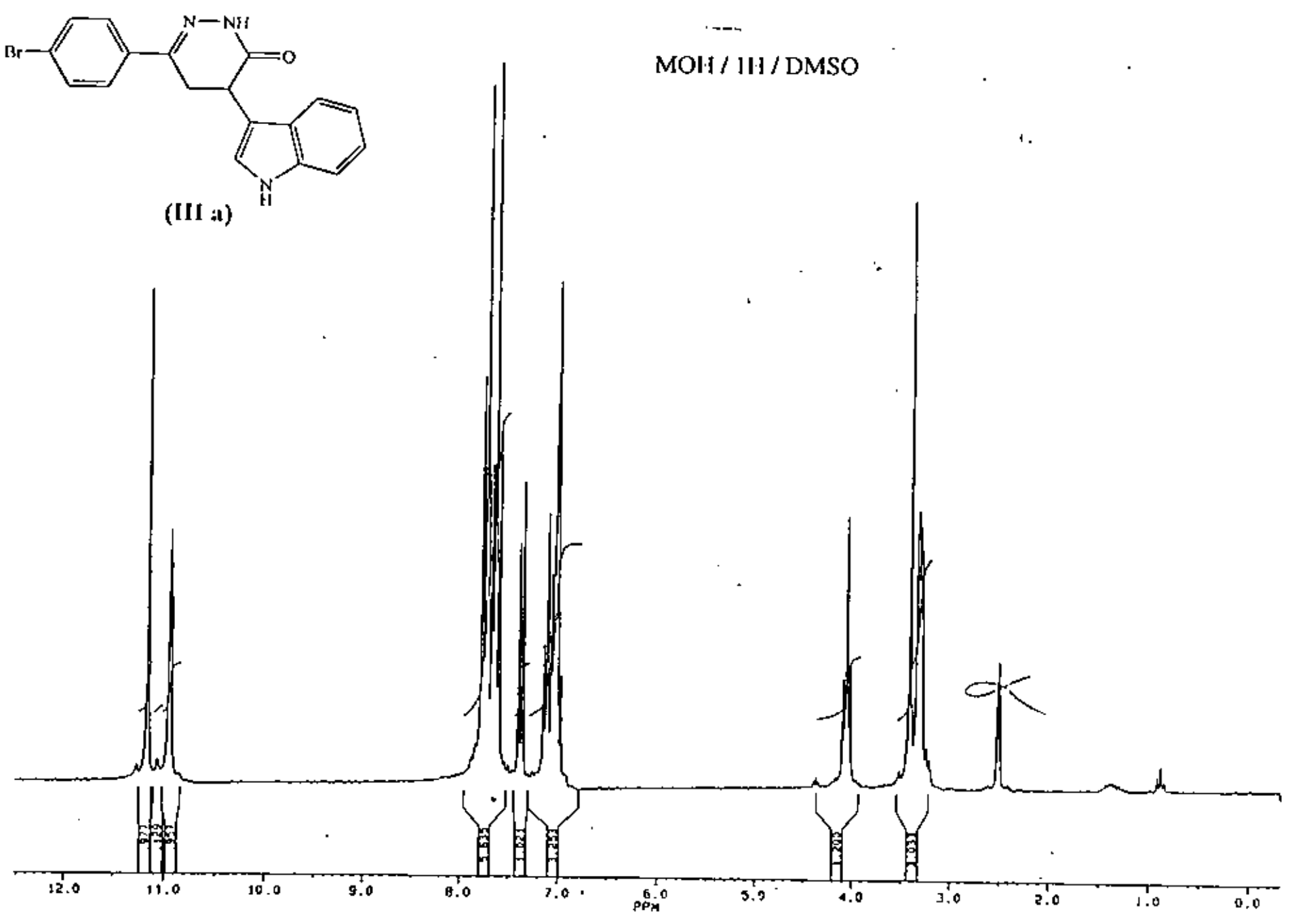
N
N
O
H
N
(III b)
3557.0
3416.0
3225.0
3059.0
2927.0
1630.0
1546.0
1345.0
1246.0
1071.0
828.0
739.0
612.0
502.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Ahmed Arbica
7/6/2006 KBr-Disk
ZENIB
AL-TAHDI.8
7/ 6/1995 10: 6:29

fig.4


Br
N
NH
O
N
H
(III a)
MOH / IH / DMSO
BRUKER
DATE 4-10-0
TIME 19:28
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SY 200.0
O1 4500.000
SI 32768
TD 32768
SW 4032.258
HZ/PT .246
PW 3.5
RD 1.000
AQ 4.063
RG 10
NS 16
TE 297
FW 5100
O2 2228.997
DP 63L PO
LB .300
GB 0.0
CX 35.00
CY 20.00
F1 12.505P
F2 -.322P
HZ/CM 73.348
PPM/CM .366
SR 3285.94
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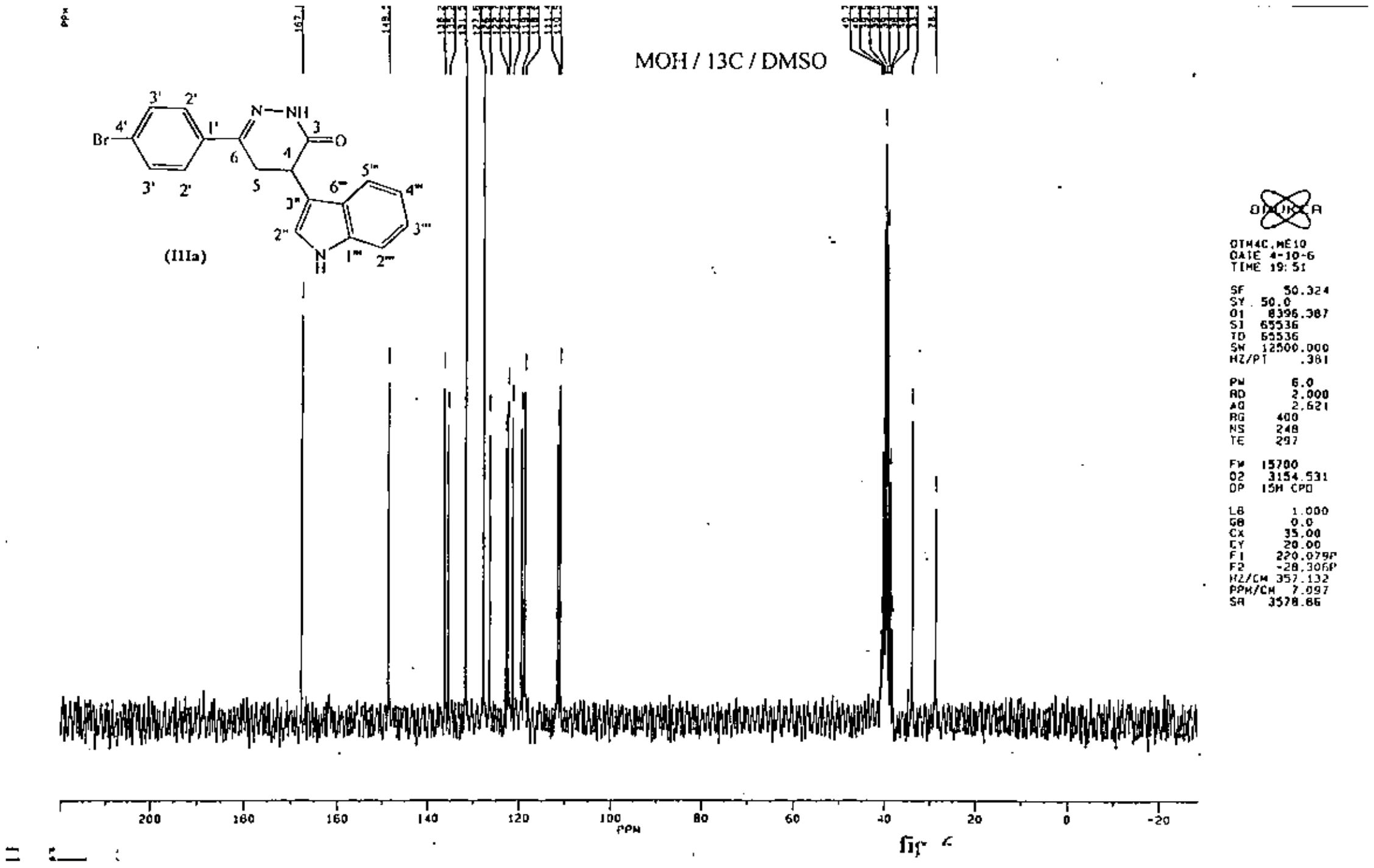
11.0
10.0
9.0
8.0
7.0
6.0
PPM
5.0
4.0
3.0
2.0
1.0
0.0

fig. 5

#	CURSOR	FREQUENCY	PPM	INTENSITY
1	4044	2234.887	11.1670	13.737
2	4218	2192.001	10.9527	7.144
3	6798	1557.237	7.7810	11.527
4	6833	1548.635	7.7380	19.709
5	6844	1545.719	7.7234	8.821
6	6879	1537.139	7.6806	9.036
7	6907	1530.405	7.6469	20.338
8	6939	1522.402	7.6069	10.219
9	7106	1481.439	7.4023	6.910
10	7136	1473.848	7.3643	8.604
11	7139	1473.192	7.3611	8.517
12	7311	1430.995	7.1502	4.073
13	7339	1424.037	7.1154	7.709
14	7371	1416.152	7.0760	6.064
15	7390	1411.514	7.0529	7.675
16	7395	1410.298	7.0468	6.645
17	7406	1407.449	7.0326	11.498
18	7416	1405.034	7.0205	14.121
19	7449	1396.807	6.9794	3.227
20	9788	821.169	4.1031	3.171
21	9817	814.168	4.0681	7.688
22	9845	807.255	4.0336	3.635
23	10344	684.464	3.4200	16.537
24	10400	670.561	3.3506	7.866
25	10409	668.360	3.3396	7.870
26	10427	664.052	3.3181	7.427
27	10438	661.337	3.3045	6.775
28	11077	503.914	2.5179	3.529
29	11083	502.625	2.5115	3.692

fig. 5


MOH / 13C / DMSO
(IIIa)
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DATE 4-10-6
TIME 19:51
SF 50.324
SY 50.0
O1 8396.387
SI 65536
TD 65536
SW 12500.000
HZ/PT .381
PW 6.0
RD 2.000
AQ 2.621
RG 400
NS 248
TE 297
FW 15700
O2 3154.531
DP 15H CPD
LB 1.000
GB 0.0
CX 35.00
CY 20.00
F1 220.079P
F2 -28.306P
HZ/CM 357.132
PPM/CM 7.097
SR 3578.86
200
180
160
140
120
100
80
60
40
20
0
-20
PPM

Fig. 6

CY= 20.000 CX= 35.000 MI= 2.421

OTM4C.ME10
MIN. INTENSITY = 2.421 MAXY = 20.00000 PP CONSTANT = 1.00000
INTENS. LEVEL = 2.421 NOISE = .32169 SENS. LEVEL = 1.28675
F1 = 11075.15 HZ = 220.0788 PPM F2 = -1424.47 HZ = -28.3061 PPM

#	CURSOR	FREQUENCY	PPM	INTENSITY
1	6891	8438.818	167.6911	12.586
2	9416	7475.681	148.5523	10.551
3	11039	6856.575	136.2497	10.394
4	11171	6806.179	135.2483	9.181
5	11657	6620.692	131.5624	20.333
6	12169	6425.258	127.6789	20.254
7	12344	6358.510	126.3525	9.084
8	12815	6178.945	122.7843	8.479
9	12881	6153.796	122.2846	9.910
10	13010	6104.547	121.3059	9.401
11	13273	6004.466	119.3172	9.157
12	13365	5969.354	118.6194	10.355
13	14304	5610.817	111.4948	8.641
14	14379	5582.490	110.9319	10.553
15	23634	2051.875	40.7736	2.773
16	23689	2030.717	40.3532	8.373
17	23745	2009.711	39.9358	15.382
18	23799	1988.789	39.5200	17.924
19	23854	1967.791	39.1028	14.871
20	23910	1946.589	38.6814	7.439
21	23964	1926.082	38.2739	2.801
22	24553	1701.351	33.8082	9.293
23	25237	1440.222	28.6192	6.606

fig. 6

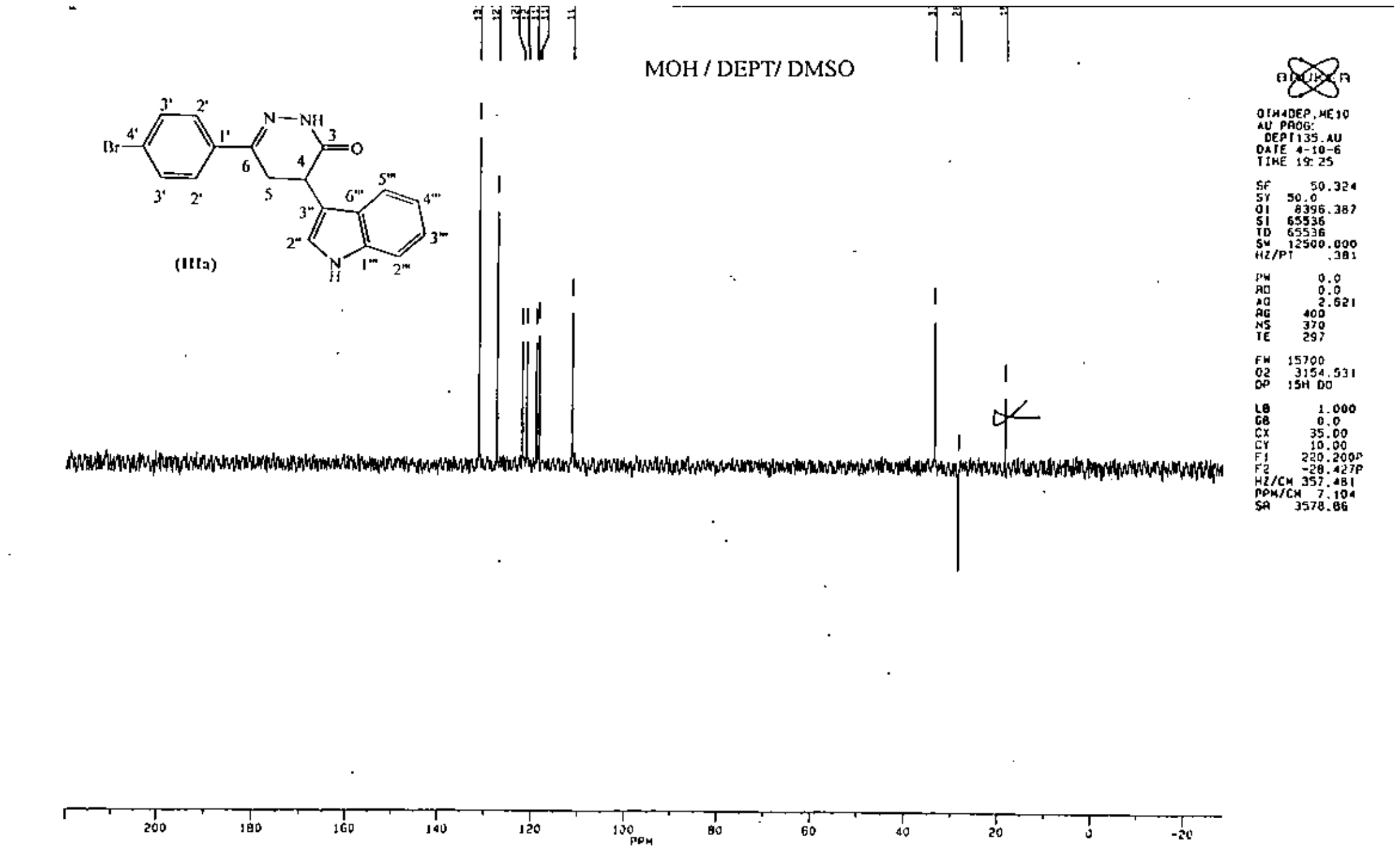

MOH / DEPT/ DMSO
(IIIa)
Br
N—NH
O
N
H
200
180
160
140
120
100
80
60
40
20
0
-20
PPM
BRUKER
OTH4DEP,ME10
AU PROG:
DEPT135.AU
DATE 4-10-6
TIME 19:25
SF 50.324
SY 50.0
OI 8396.387
SI 65536
TD 65536
SW 12500.000
HZ/PT .381
PW 0.0
RD 0.0
AQ 2.621
RG 400
NS 370
TE 297
FW 15700
D2 3154.531
DP 15H DO
LB 1.000
GB 0.0
CX 35.00
CY 10.00
F1 220.200P
F2 -28.427P
HZ/CM 357.481
PPM/CM 7.104
SR 3578.86

fig 7

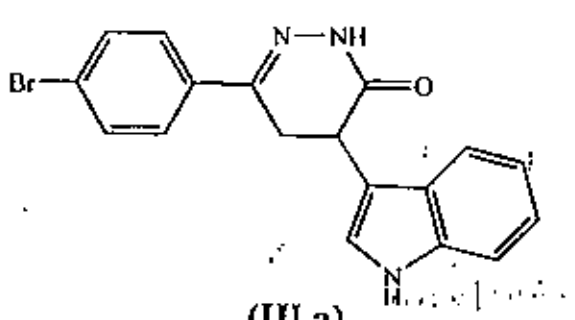
CY= 10.000 CX= 35.000 MI= 1.483

OTM4DEP.ME10

MIN. INTENSITY = 1.483 MAXY = 20.00000 PP CONSTANT = 1.00000
INTENS. LEVEL = 1.483 NOISE = .11294 SENS. LEVEL = .45177
F1 = 11081.26 HZ = 220.2001 PPM F2 = -1430.57 HZ = -28.4274 PPM

#	CURSOR	FREQUENCY	PPM	INTENSITY
1	11657	6620.785	131.5643	10.018
2	12169	6425.277	127.6792	7.849
3	12801	6153.783	122.2843	3.728
4	13010	6104.737	121.3097	3.755
5	13272	6004.523	119.3183	3.731
6	13364	5969.494	118.6222	3.917
7	14304	5610.878	111.4960	4.633
8	24554	1701.104	33.8033	4.433
9	25239	1439.688	28.6086	-3.114
10	26563	934.593	18.5717	2.091

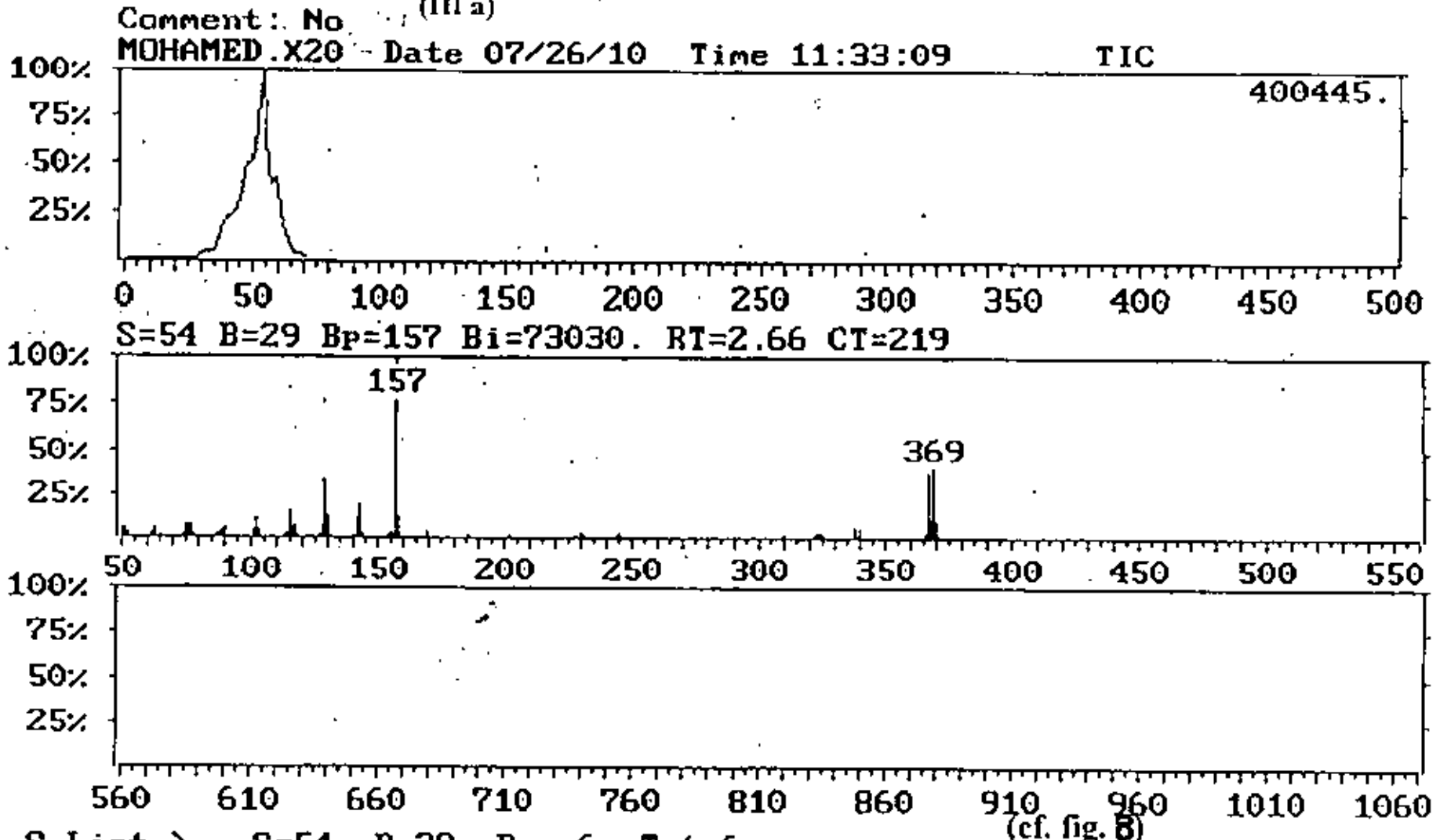
fig. 7



$C_{18}H_{14}BrN_3O$

Mol. Wt.: 368.23

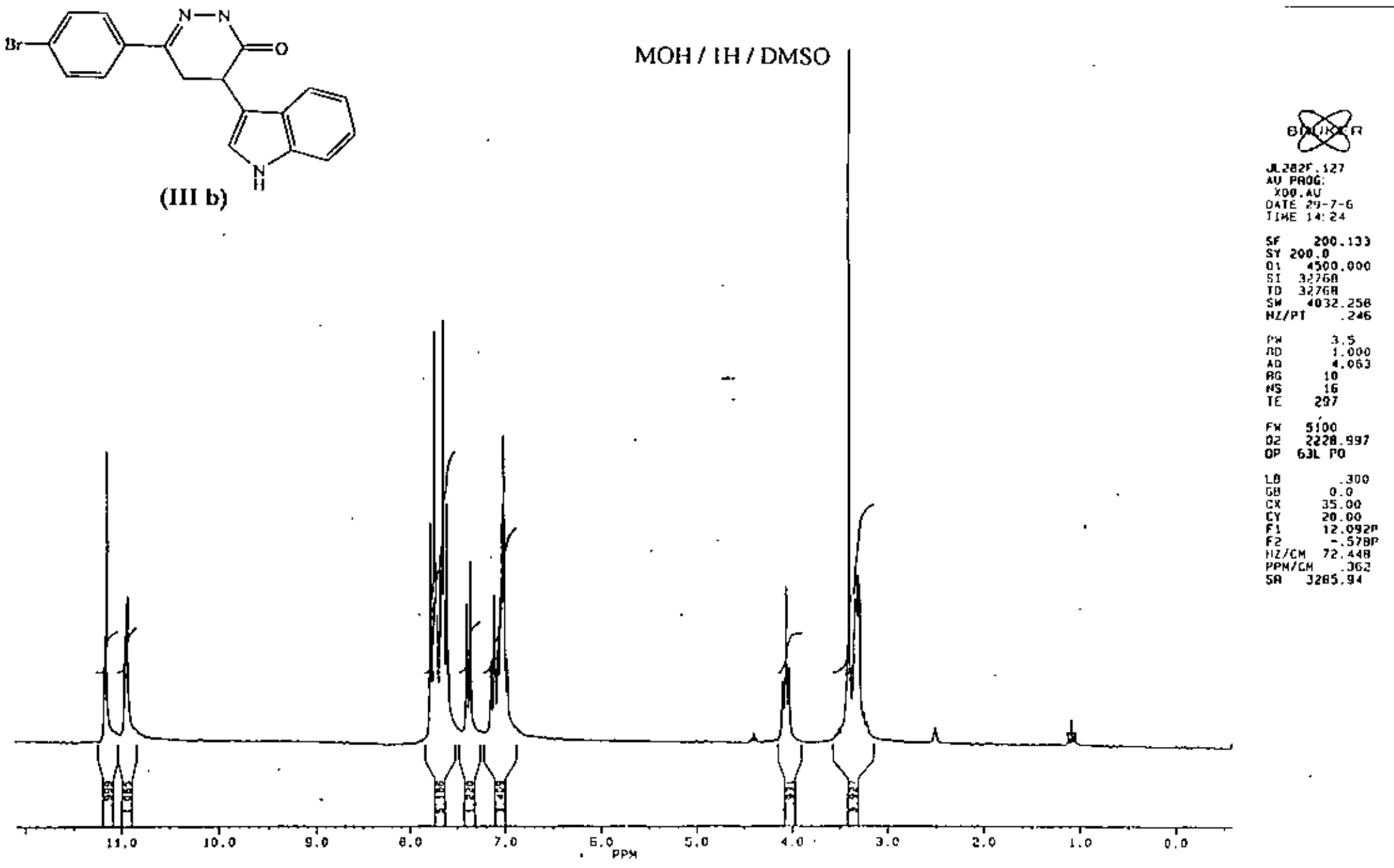
(III a)



(cf. fig. 6)

File : MOHAMED.X20 Date 07/26/10 Time 11:33:09
S=54 B=29 Bp=157 Bi=73030. RT=2.66 CT=219

Mass	Int(%)	Mass	Int(%)	Mass	Int(%)	Mass	Int(%)
50	5.4	51	5.9	52	2.6	53	0.6
54	0.4	55	0.2	58	0.4	59	0.5
61	0.5	62	2.4	63	5.4	64	1.3
65	1.7	66	0.4	67	0.2	71	0.3
73	0.4	74	2.2	75	6.8	76	7.3
77	6.4	78	1.6	79	0.4	80	0.2
81	0.4	82	0.5	86	0.7	87	1.4
88	3.1	89	4.6	90	5.4	91	0.8
92	0.4	95	0.2	96	0.4	98	0.3
99	0.5	100	1.1	101	4.2	102	11.4
103	4.2	104	1.0	105	0.2	108	0.5
109	0.5	113	1.6	114	3.5	115	15.7
116	5.1	117	7.4	118	1.6	119	0.3
121	0.4	122	0.7	123	0.3	124	0.1
126	0.8	127	1.5	128	6.4	129	33.0
130	12.4	131	1.6	132	0.5	138	0.3
139	0.5	140	1.5	141	2.1	142	10.5
143	19.4	144	3.1	145	0.2	150	0.5
151	0.5	152	0.6	153	0.5	154	1.5
155	2.7	156	3.0	157	100.0	158	13.2
159	1.0	163	0.5	164	0.1	167	0.5
168	1.0	169	3.8	170	1.1	171	0.8
175	0.4	176	0.5	178	0.3	180	0.3
181	1.1	182	0.8	183	1.1	184	1.0
185	0.9	186	1.8	188	0.3	189	0.5
190	0.1	193	0.3	194	0.2	195	0.5
197	0.8	198	0.5	199	0.6	200	1.2
201	1.1	202	2.0	203	0.9	204	1.1
205	0.5	215	0.6	216	0.7	217	1.0
218	0.5	219	0.3	226	0.4	227	0.8
228	1.9	229	1.3	230	3.3	231	1.6
232	0.9	242	1.1	243	1.4	244	1.7
245	2.3	253	0.4	258	1.1	259	1.1
260	1.2	261	0.1	288	0.8	289	0.3
308	0.9	310	1.4	312	0.6	322	1.5
323	2.4	324	2.3	325	2.2	326	0.6
337	0.7	338	5.3	339	2.2	340	5.5
341	1.3	342	0.3	365	0.7	366	2.8
367	37.4	368	11.1	369	39.5	370	9.6
371	1.5	372	0.7				


Br
N
N
O
N
H
(III b)
MOH / 1H / DMSO
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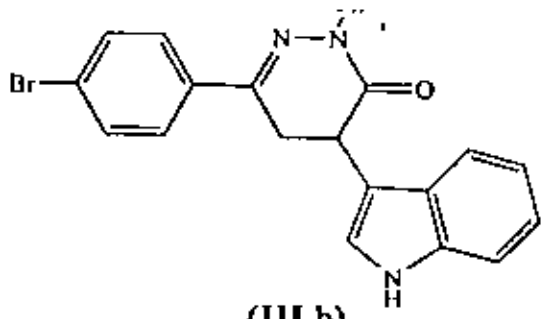
DATE 29-7-6
TIME 14:24
SF 200.133
SY 200.0
01 4500.000
SI 32768
TD 32768
SW 4032.258
HZ/PT .246
PW 3.5
D0 1.000
AQ 4.063
RG 10
NS 16
TE 297
FW 5100
02 2228.997
OP 63L PO
LB .300
GB 0.0
CX 35.00
CY 20.00
F1 12.092P
F2 -.578P
HZ/CM 72.448
PPM/CM .362
SR 3285.94
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

fig. 9

#	CURSOR	FREQUENCY	PPM	INTENSITY
1	4056	2231.993	11.1525	8.345
2	4232	2188.656	10.9360	43.219
3	6800	1556.657	7.7781	6.669
4	6835	1548.097	7.7353	11.045
5	6851	1543.995	7.7148	5.169
6	6884	1536.018	7.6756	5.235
7	6908	1529.981	7.6448	12.182
8	6942	1521.587	7.6029	6.926
9	7110	1480.272	7.3964	4.611
10	7143	1472.255	7.3564	5.219
11	7314	1430.080	7.1456	2.185
12	7342	1423.217	7.1113	4.258
13	7374	1415.389	7.0722	3.347
14	7393	1410.604	7.0483	4.419
15	7409	1406.766	7.0291	6.829
16	7420	1404.139	7.0160	8.830
17	7453	1396.006	6.9754	2.641
18	9792	820.388	4.0993	1.761
19	9820	813.459	4.0646	4.322
20	9848	806.516	4.0299	2.169
21	10352	682.572	3.4106	20.252
22	10403	670.006	3.3478	5.052
23	10412	667.812	3.3368	5.136
24	10430	663.379	3.3147	4.811
25	10441	660.675	3.3012	4.586

fig. 9



(III b)

$C_{24}H_{18}BrN_3O$

Mol. Wt.: 444.32

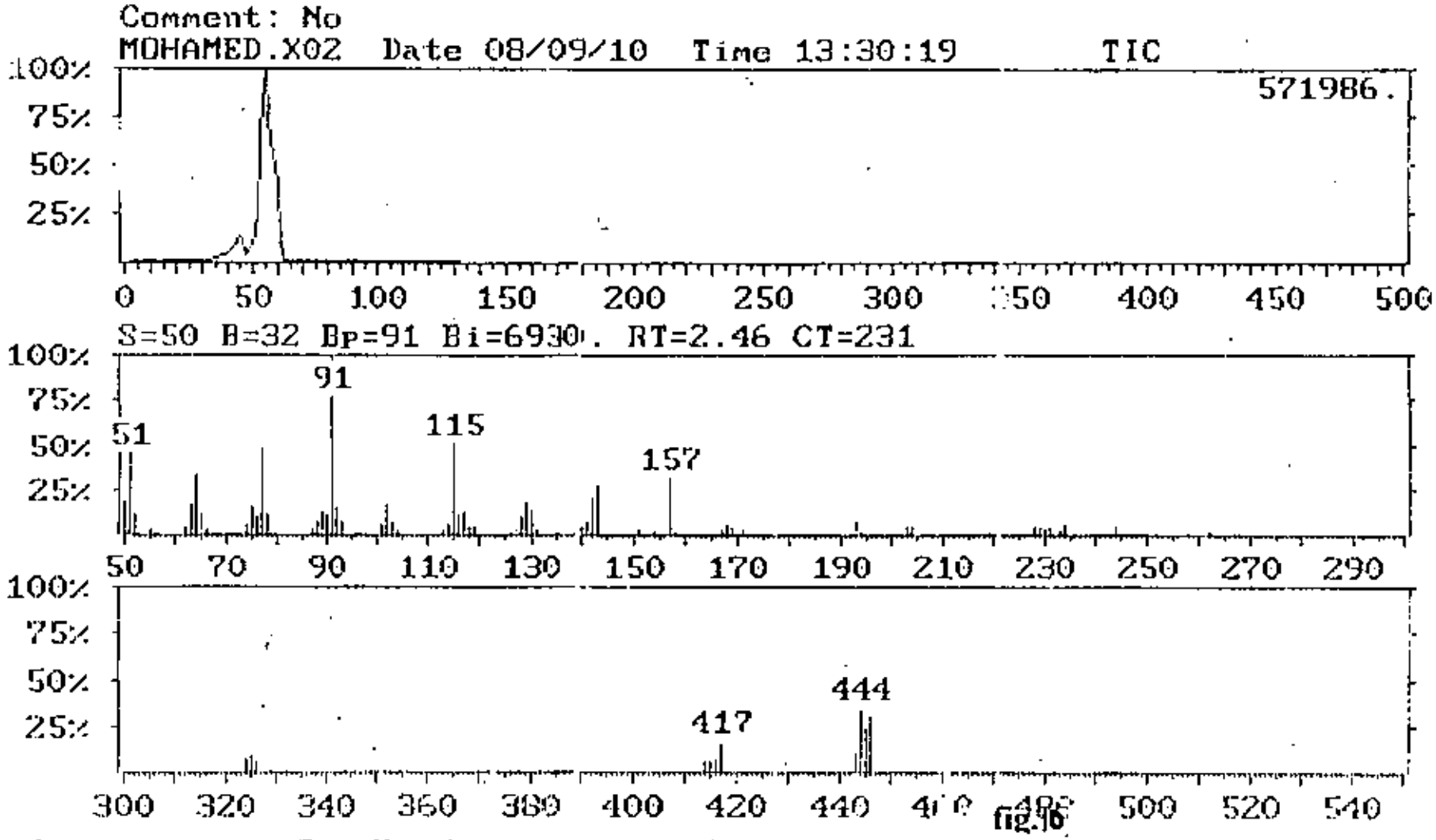


fig.16

File : MOHAMED.XOS Date 08/09/10 Time 13:36:19
S=50 B=32 Bp=91 Bi=6930. RT=2.46 CT=231

Mass	Int(%)	Mass	Int(%)	Mass	Int(%)	Mass	Int(%)
50	18.0	51	45.3	62	10.6	[illegible]	[illegible]
62	3.9	63	16.7	64	33.6	65	11.7
66	2.3	74	5.6	75	15.2	76	9.7
77	48.5	78	11.3	87	2.9	88	7.6
89	12.1	90	10.8	91	100.0	92	15.3
93	6.5	101	5.3	102	16.6	103	7.1
104	2.5	113	3.0	114	5.8	115	50.6
116	11.5	117	12.7	118	4.9	119	4.5
126	2.0	127	3.5	128	10.2	129	18.0
130	14.4	131	2.6	140	4.5	141	6.9
142	20.6	143	27.7	144	0.1	151	3.7
154	1.7	155	1.0	157	31.6	158	2.3
167	2.3	168	5.1	169	3.8	170	1.0
171	3.0	193	6.9	194	1.6	202	0.6
203	4.0	204	3.9	219	1.9	228	4.3
229	4.5	230	2.5	231	4.8	233	2.9
234	5.6	243	0.1	244	4.2	262	1.9
323	0.6	324	7.2	325	8.8	326	5.9
414	6.2	415	5.2	416	7.4	417	15.7
443	9.7	444	33.5	445	22.9	446	30.6

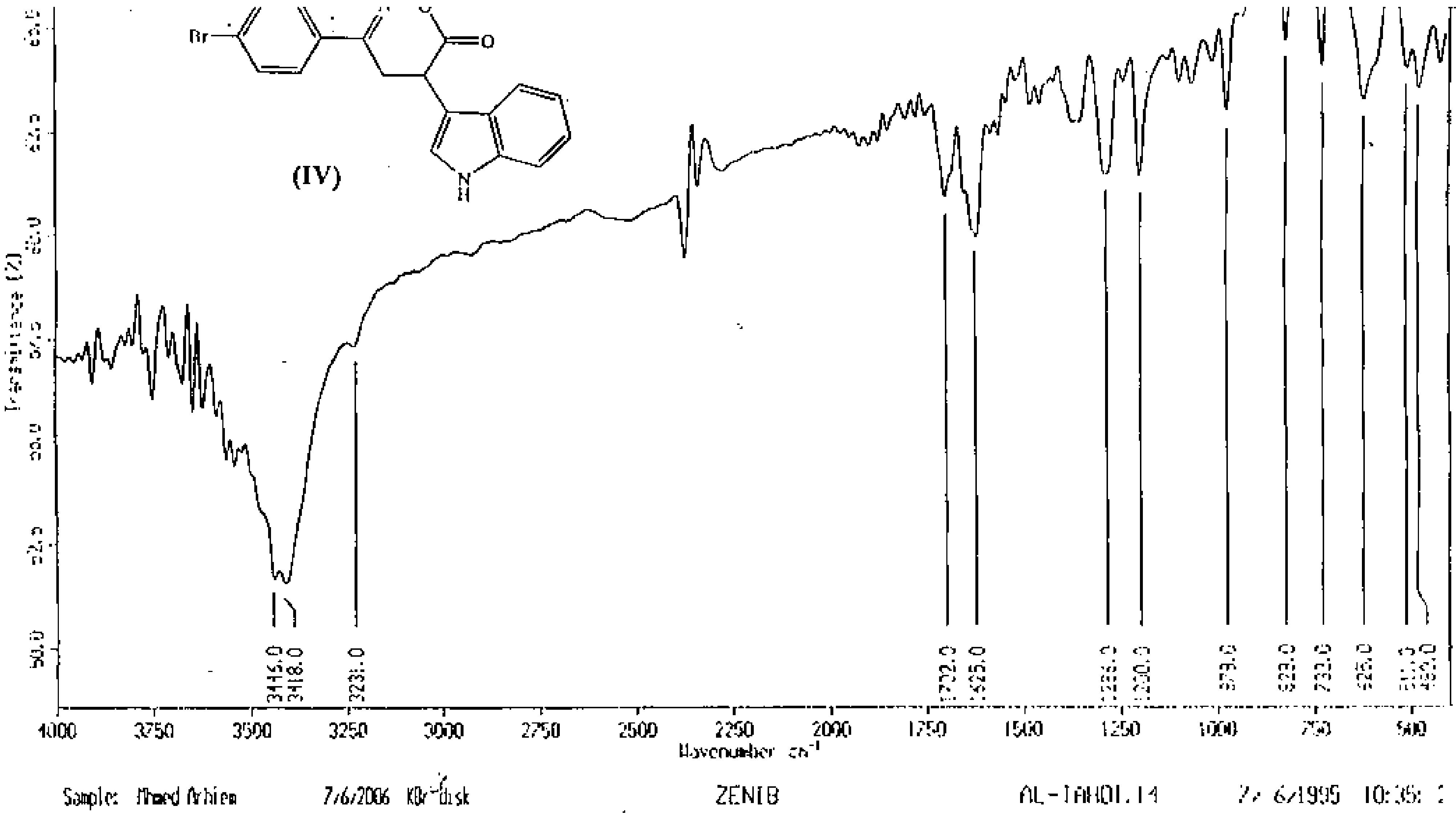

Br
O
(IV)
N
H
Transmittance (%)
50.0
3418.0
3231.0
1702.0
1625.0
1200.0
823.0
732.0
625.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Mhed Arhiem
7/6/2006 KBr-Disk
ZENIB
AL-TAHOL.14

fig. 11

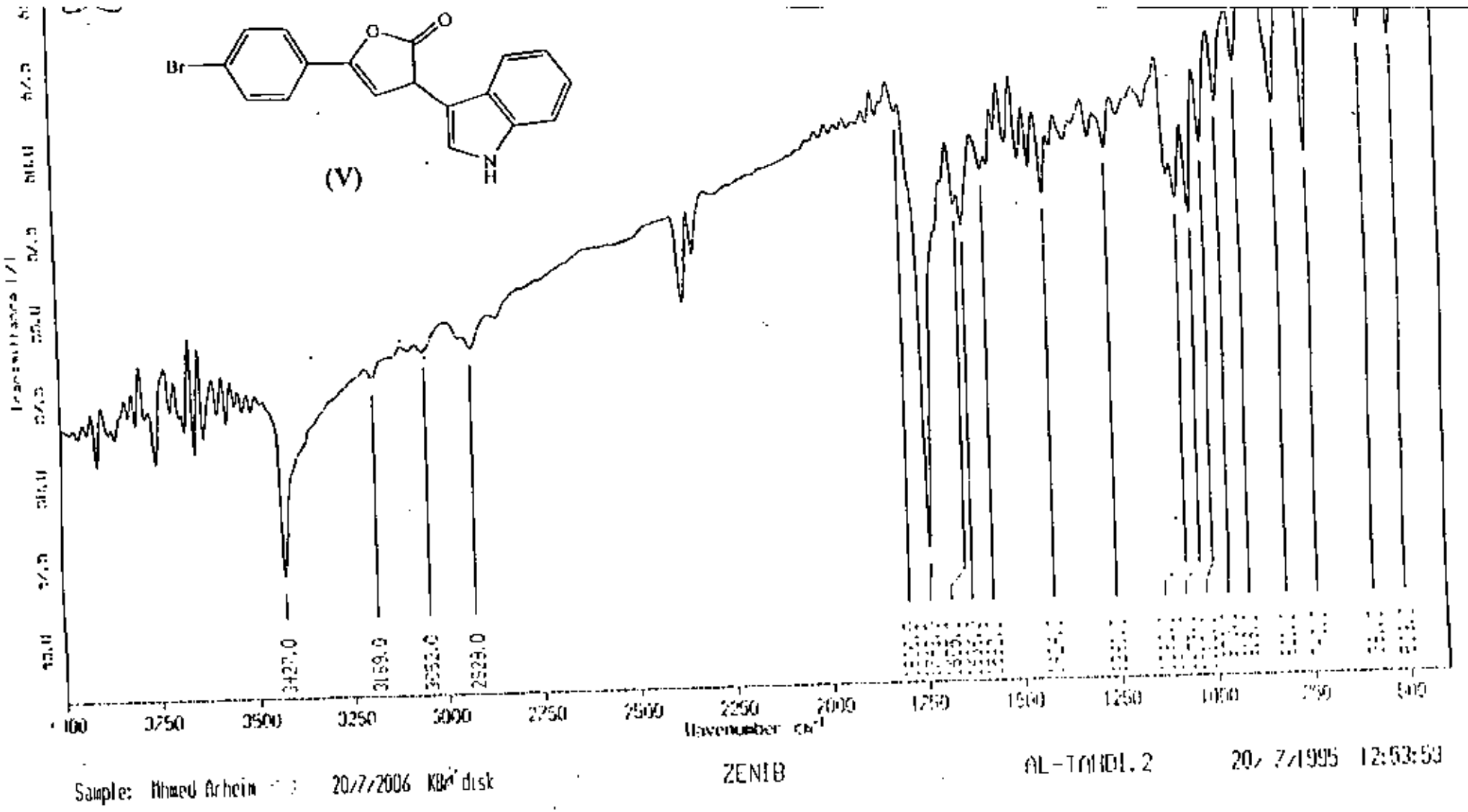

Br
O
O
N
H
(V)
3427.0
3159.0
3052.0
2929.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Ahmed Arhein
20/7/2006 KBr disk
ZENIB
AL-TOMOL.2
20/ 7/1995 12:53:58

fig. 12

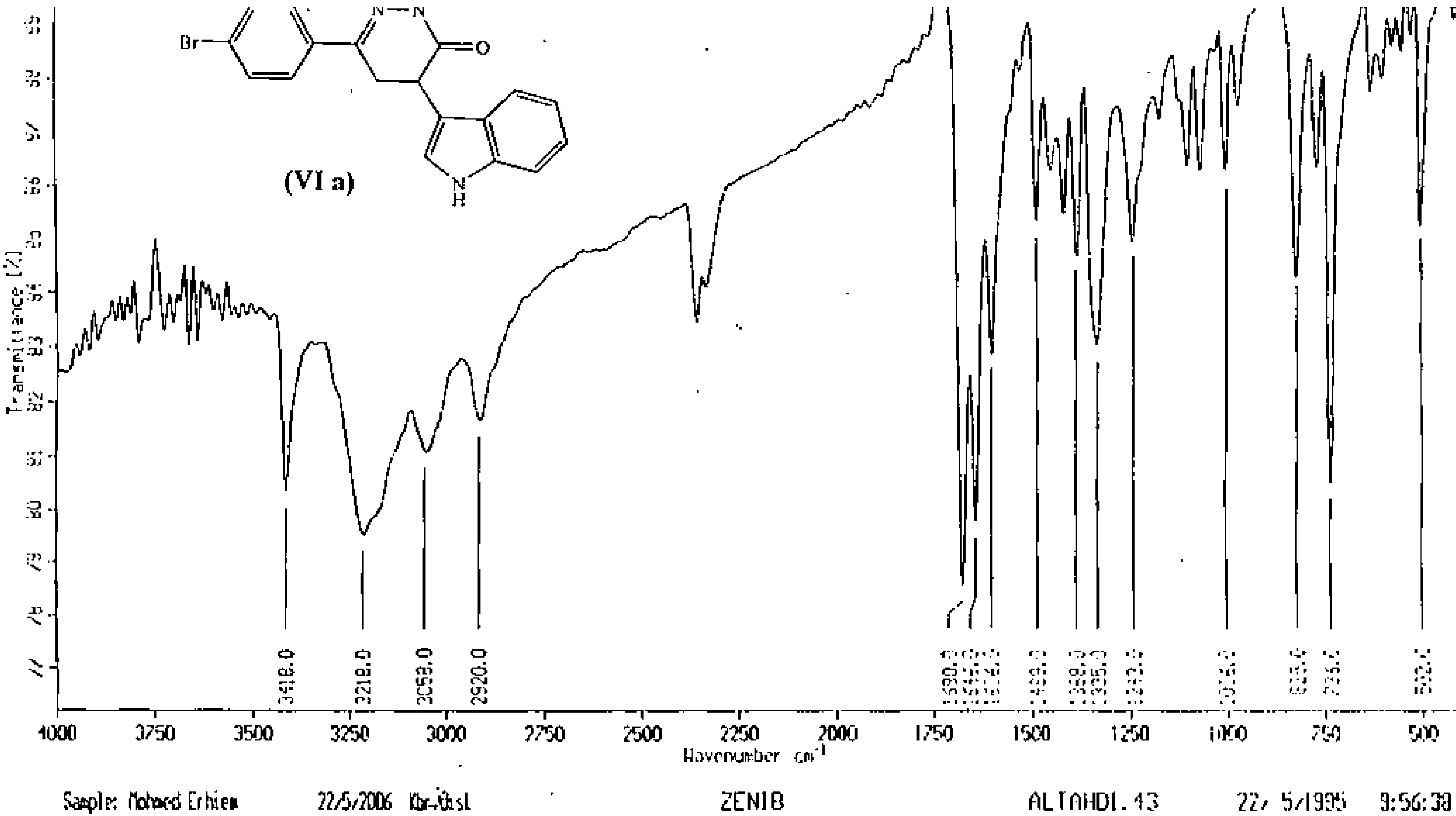

(VI a)
Transmittance [%]
3418.0
3218.0
3058.0
2920.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Mohmed Erhiem
22/5/2006 Kbr-Disk
ZENIB
ALTAHDI.43
22/ 5/1995 9:56:38

fig. 13a

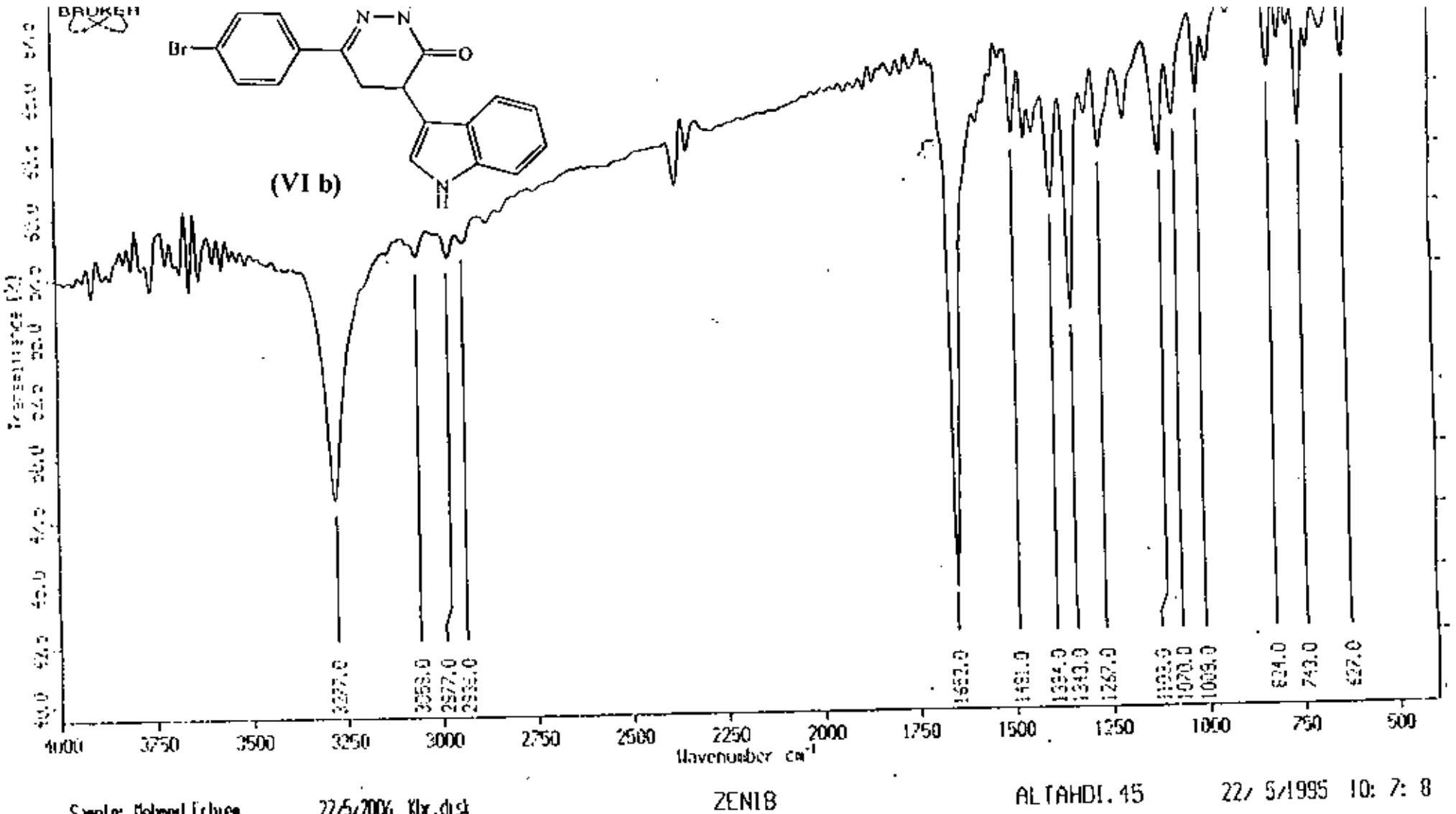

BRUKER
Br
N
N
O
N
H
(VI b)
Transmittance [%]
3337.0
3058.0
2977.0
2933.0
1652.0
1481.0
1334.0
1343.0
1267.0
1133.0
1070.0
1009.0
834.0
743.0
627.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Mohamed Erhuen
22/5/2006 Kbr.disk
ZENIB
ALTAHDI.45
22/ 5/1995 10: 7: 8

fig. 13b

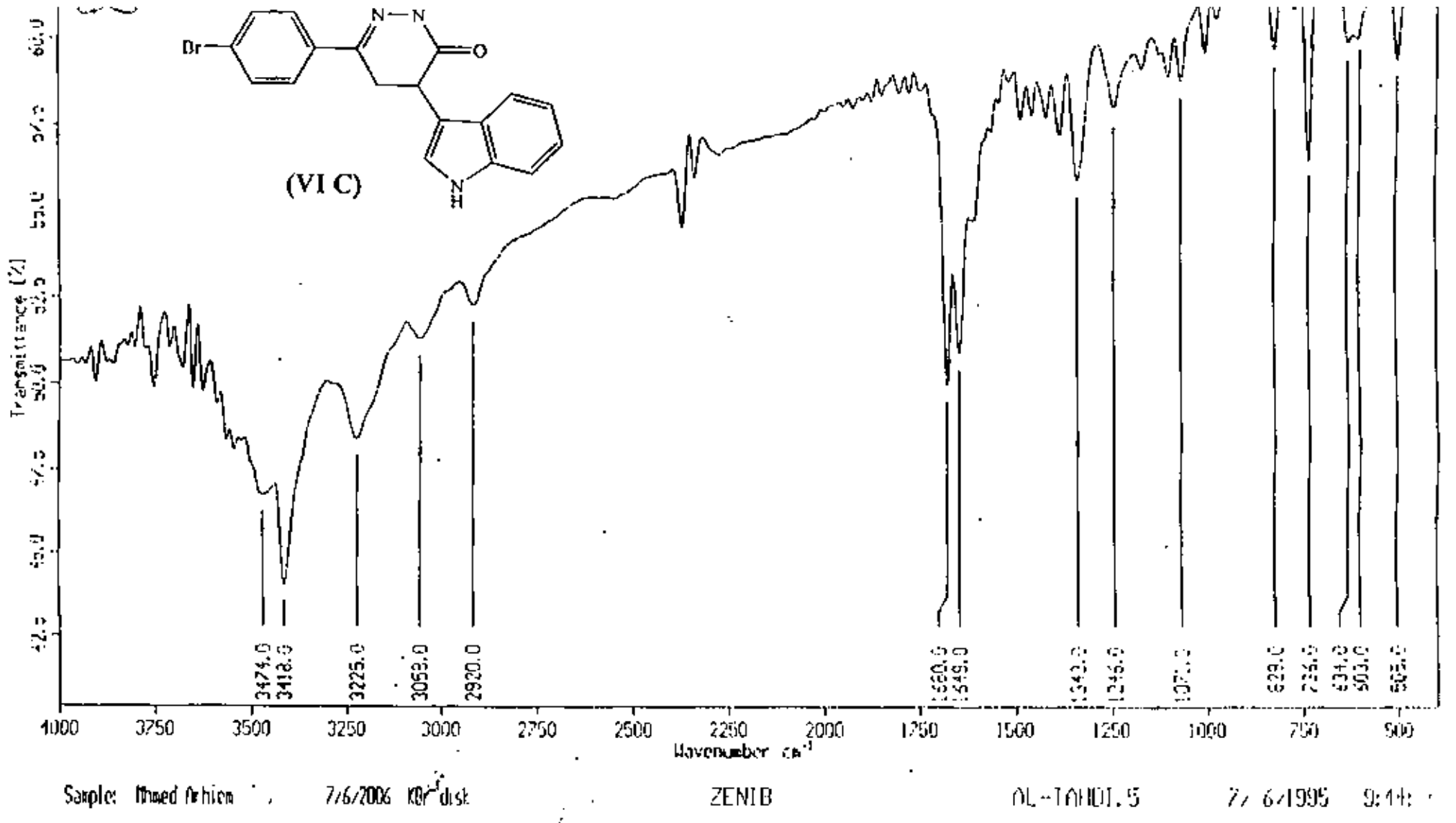

Br
N
N
O
N
H
(VI C)
Transmittance [%]
3474.0
3418.0
3225.0
3059.0
2920.0
1649.0
1343.0
1246.0
1071.0
829.0
735.0
634.0
603.0
582.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Mixed Archive
7/6/2006 KBr disk
ZENIB
DL-TARTRIC
7/ 6/1995

fig. 13c

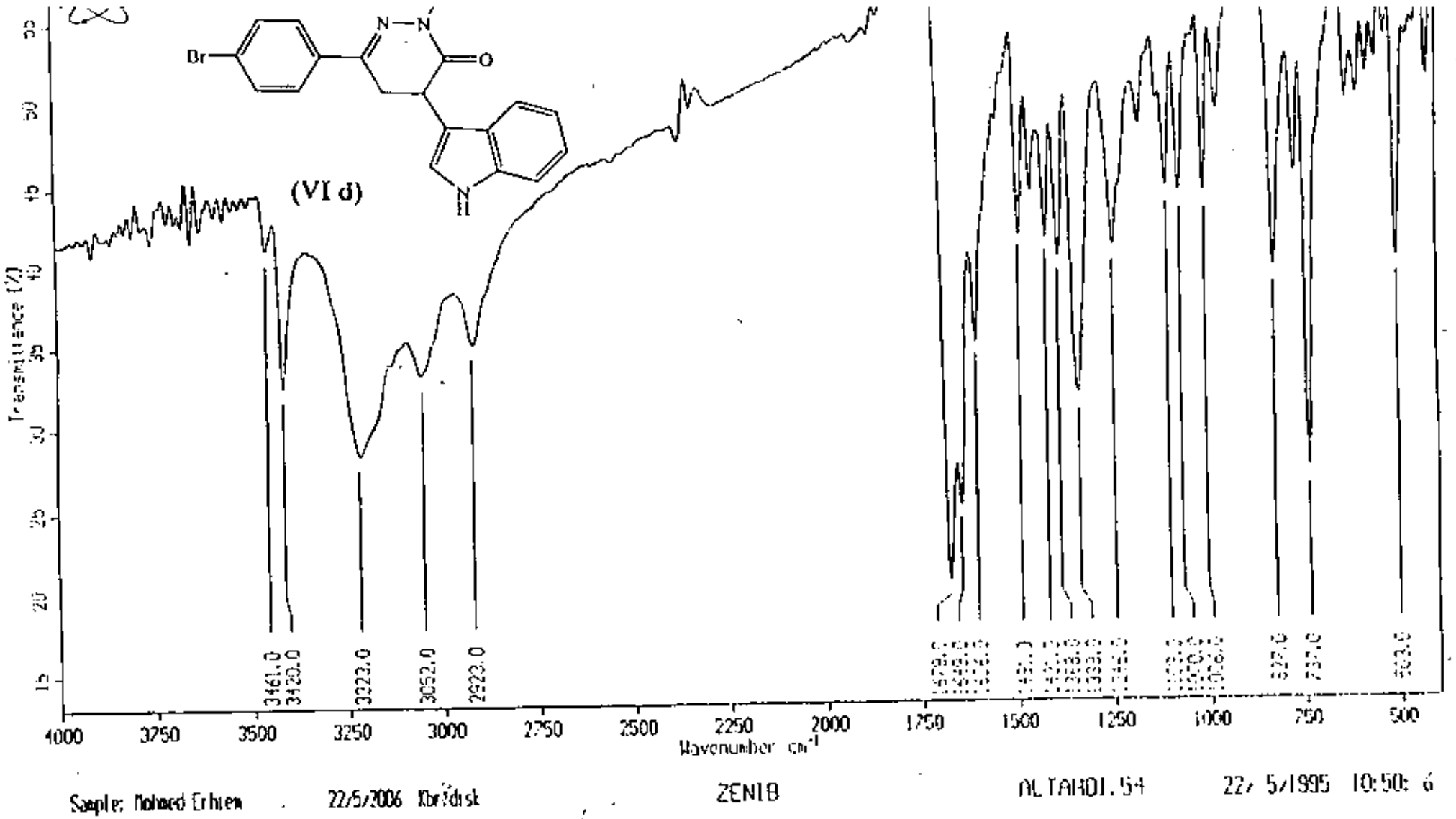
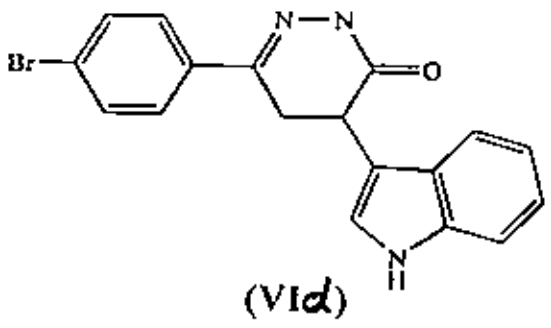

Br
N
N
O
H
N
(VI d)
Transmittance (%)
3461.0
3420.0
3223.0
3052.0
2923.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Mahsed Erhien
22/5/2006 KBr Disk
ZENIB
ALTAHDI.SH
22/ 5/1995 10:50: 6

fig. 13d



(VId)

MOH / 1H / CD_3OD

fig. 14

INTENS. LEVEL = 1.000 NOISE = 0.000

F1 = 2010.26 HZ = 10.0447 PPM F2 = -5.62 HZ -0.031 PPM

#	CURSOR	FREQUENCY	PPM	INTENSITY
1	3035	1590.591	7.9477	3.721
2	3070	1581.929	7.9044	5.264
3	3247	1538.370	7.6868	5.779
4	3283	1529.729	7.6436	4.119
5	3508	1474.272	7.3665	1.445
6	3538	1466.840	7.3294	2.787
7	3633	1443.476	7.2126	4.854
8	3715	1423.263	7.1116	1.741
9	3750	1414.571	7.0682	2.161
10	3783	1406.576	7.0282	1.606
11	5544	973.098	4.8623	72.612
12	5838	900.880	4.5014	1.143
13	5866	894.002	4.4671	1.371
14	5880	890.349	4.4488	1.342
15	6132	828.325	4.1389	2.346
16	6143	825.657	4.1256	1.818
17	6161	821.228	4.1034	2.615
18	6187	815.025	4.0724	3.191
19	6217	807.627	4.0355	2.365
20	6260	796.876	3.9817	1.537
21	6688	691.661	3.4560	1.860
22	6704	687.756	3.4365	1.917
23	6761	673.538	3.3655	1.710
24	6794	665.515	3.3254	9.877
25	6800	663.959	3.3175	16.787
26	6807	662.334	3.3095	22.103
27	6814	660.713	3.3014	15.967
28	6820	659.145	3.2935	8.657
29	8517	241.394	1.2062	5.100
30	8546	234.274	1.1706	10.141
31	8575	227.158	1.1350	4.772

1.PX 1.

fig. 14

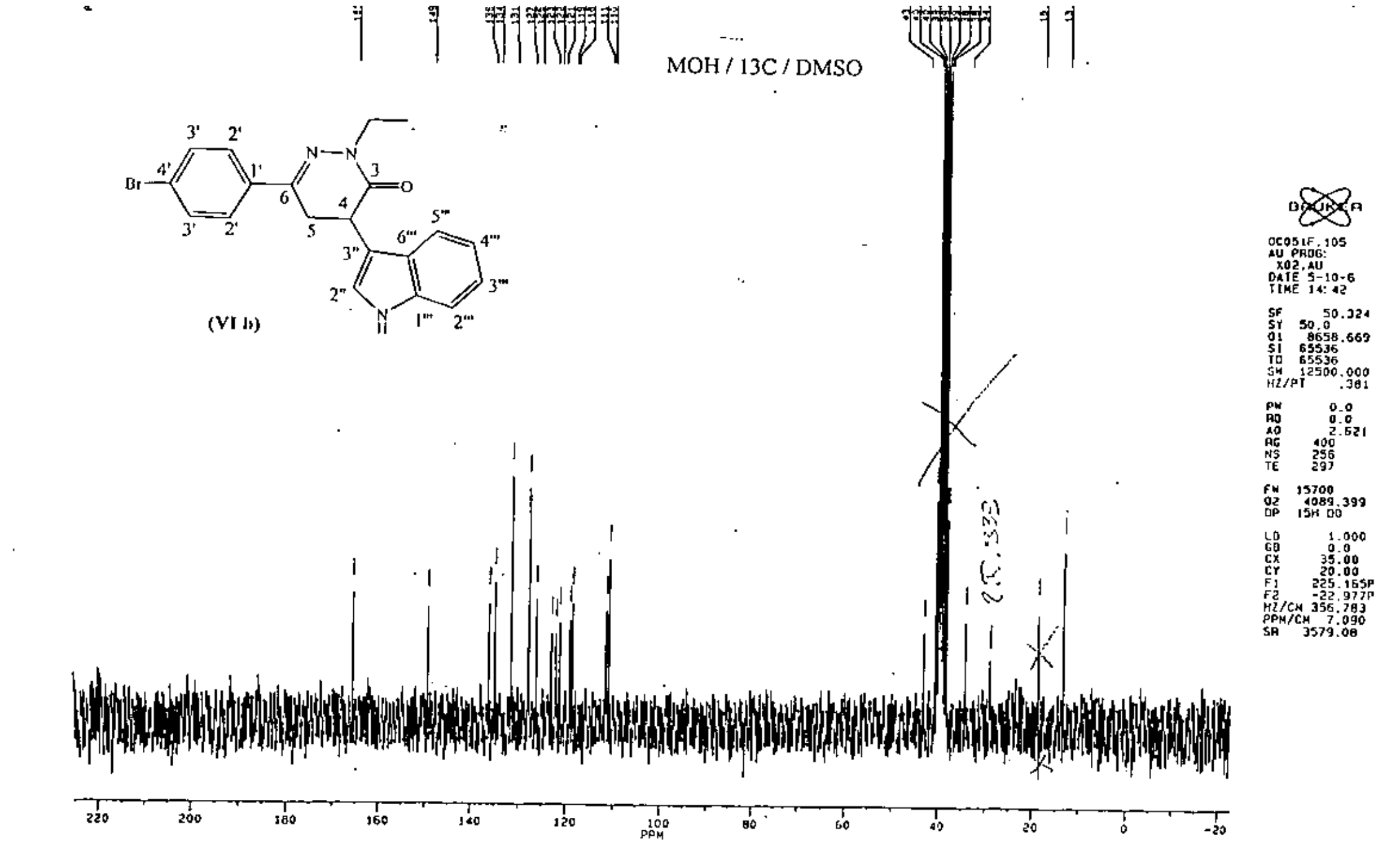
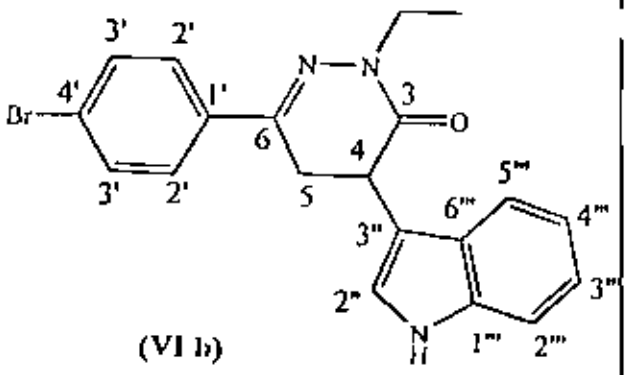

MOH / 13C / DMSO
(VI b)
OC051F.105
AU PROG:
X02.AU
DATE 5-10-6
TIME 14:42
SF 50.324
SY 50.0
O1 8658.669
SI 65536
TD 65536
SW 12500.000
HZ/PT .381
PW 0.0
RD 0.0
AQ 2.621
RG 400
NS 256
TE 297
FW 15700
GZ 4089.399
DP 15H 00
LB 1.000
GB 0.0
CX 35.00
CY 20.00
F1 225.165P
F2 -22.977P
HZ/CM 356.783
PPM/CM 7.090
SR 3579.08
220
200
180
160
140
120
100
PPM
80
60
40
20
0
-20

fig 15

#	CURSOR	FREQUENCY	PPM	INTENSITY
1	7858	8332.005	165.5686	3.828
2	9997	7516.172	149.3569	3.518
3	11735	6853.161	136.1819	3.590
4	11901	6789.668	134.9202	4.188
5	12341	6621.809	131.5846	7.467
6	12837	6432.706	127.8269	7.083
7	13048	6352.140	126.2259	3.684
8	13468	6192.108	123.0459	2.731
9	13592	6144.728	122.1044	2.664
10	13698	6104.403	121.3030	3.019
11	13979	5997.104	119.1709	3.085
12	14051	5969.735	118.6270	3.625
13	14992	5610.659	111.4916	3.365
14	15069	5581.367	110.9096	4.968
15	24005	2172.334	43.1673	2.745
16	24321	2051.757	40.7713	6.811
17	24377	2030.537	40.3496	20.004
18	24432	2009.560	39.9328	39.699
19	24487	1988.536	39.5150	46.513
20	24542	1967.606	39.0991	39.936
21	24597	1946.679	38.6832	19.920
22	24652	1925.699	38.2663	6.193
23	25188	1720.949	34.1977	3.132
24	27239	938.600	18.6513	3.429
25	27942	670.432	13.3224	5.302

fig. 15

MOH / DEPT/ DMSO



(VI b)

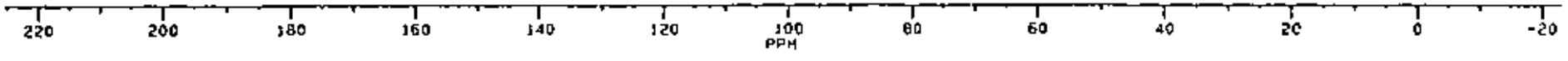


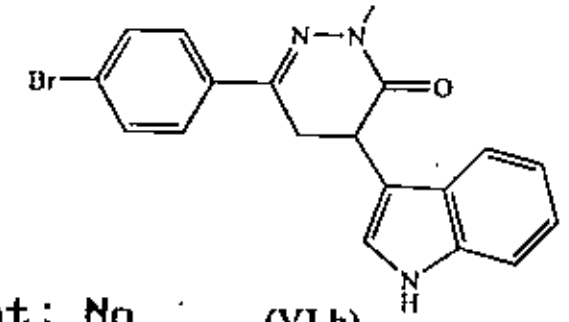
fig 15

CY= 10.000 CX= 35.000 MI= 2.211
MI= -3.513

OCO52F.105
MIN. INTENSITY = 3.513 MAXY = 20.00000 PP CONSTANT = 1.00000
INTENS. LEVEL = 3.513 NOISE = .35193 SENS. LEVEL = 1.40771
F1 = 11337.22 HZ = 225.2865 PPM F2 = -1162.40 HZ = -23.0984 PPM

#	CURSOR	FREQUENCY	PPM	INTENSITY
1	12340	6622.198	131.5923	10.025
2	12837	6432.850	127.8297	9.507
3	13591	6145.071	122.1112	3.836
4	13698	6104.367	121.3023	3.759
5	13978	5997.305	119.1749	4.462
6	14049	5970.266	118.6375	4.570
7	14991	5611.128	111.5010	4.155
8	24006	2172.158	43.1638	-4.531
9	25188	1721.069	34.2000	5.285
10	25885	1455.318	28.9192	-3.933
11	27941	670.758	13.3289	8.303

fig. 16



$C_{20}H_{18}BrN_3O$

Mol. Wt.: 396.28

Comment: No (VIb)
MOHAMED.X13 Date 07/26/10 Time 10:41:18 TIC
85498.
100%
75%
50%
25%
20 70 120 170 220 270 320 370 420 470 520
S=46 B=30 Bp=157 Bi=13250. RT=2.26 CT=178
157
395
50 100 150 200 250 300 350 400 450 500 550
560 610 660 710 760 810 860 910 960 1010 1060
S List > S=46 B=30 Pos=4 Tot=4

(of fig '7)

ile : MOHAMED.X13 Date 07/26/10 Time 10:41:18
=46 B=30 Bp=157 Bi=13250. RT=2.26 CT=178

Mass	Int(%)	Mass	Int(%)	Mass	Int(%)	Mass	Int(%)
50	6.1	51	6.6	52	3.5	56	2.6
62	2.8	63	4.9	64	1.9	65	3.2
74	2.4	75	9.7	76	10.3	77	8.5
78	3.2	87	2.0	88	2.9	89	6.0
90	4.5	100	2.1	101	6.3	102	16.3
103	7.1	113	3.3	114	7.9	115	23.1
116	8.2	117	9.7	118	2.3	119	0.4
127	2.7	128	8.5	129	28.1	130	21.8
131	2.4	136	4.3	137	4.8	140	2.6
141	4.0	142	14.6	143	24.2	144	7.8
154	4.1	155	5.9	156	8.5	157	100.0
158	11.8	168	3.6	169	5.7	171	4.6
181	2.6	182	5.1	183	4.7	184	4.5
202	4.3	203	3.2	204	3.2	205	0.7
209	2.6	216	1.4	228	3.8	229	2.4
230	8.3	231	4.6	310	3.2	323	5.2
325	6.0	326	1.9	352	6.6	366	3.9
367	2.9	368	5.9	395	34.3	396	13.5
397	33.9	398	8.1				

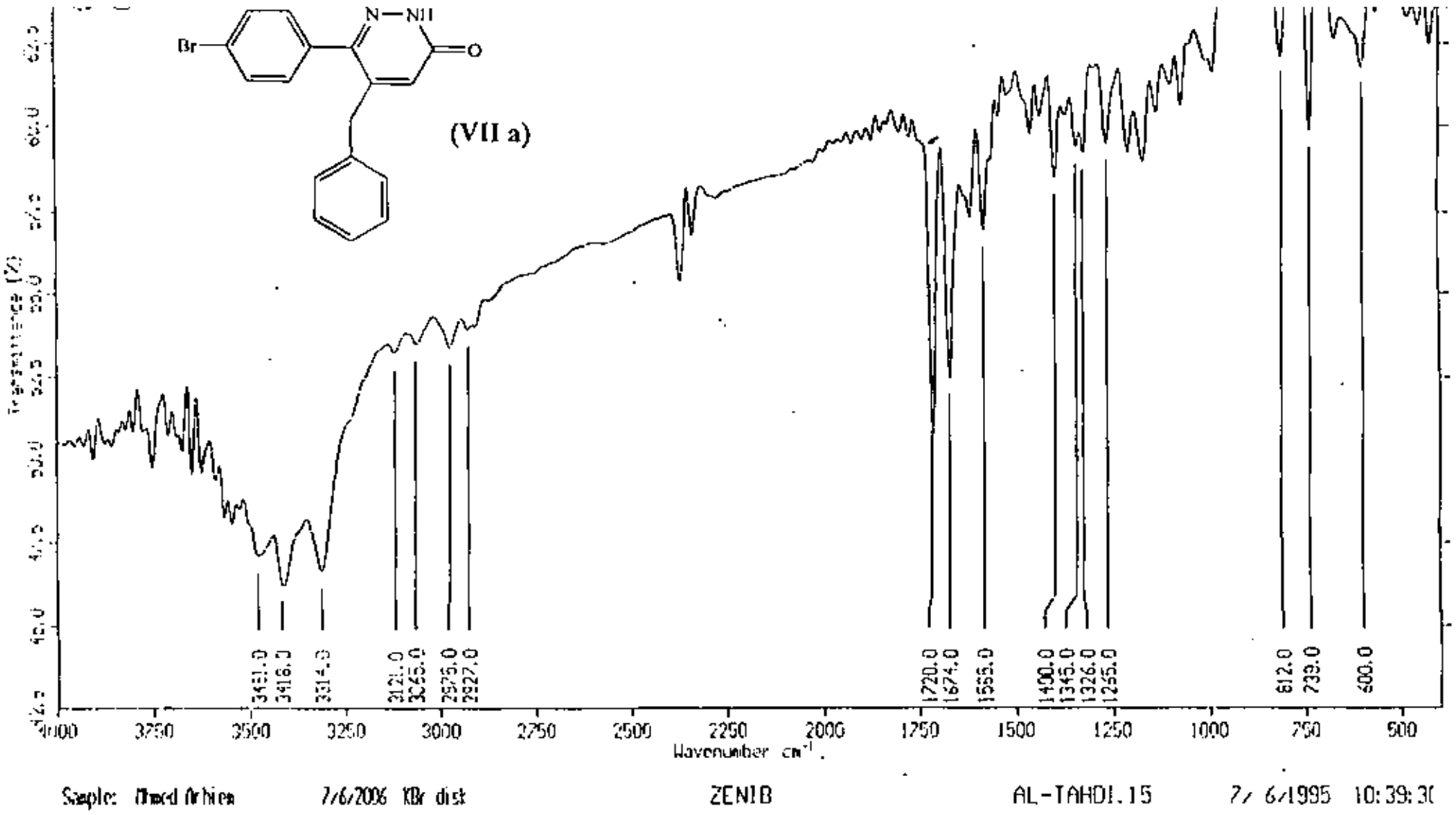

Br
N—NH
O
(VII a)
Transmittance (%)
3461.0
3416.0
3314.0
3121.0
3065.0
2975.0
2927.0
1720.0
1674.0
1555.0
1490.0
1345.0
1326.0
1255.0
812.0
739.0
600.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Thiad Arbien
7/6/2006 KBr disk
ZENIB
AL-TAHDI.15
7/ 6/1995 10:39:30

fig. 18a

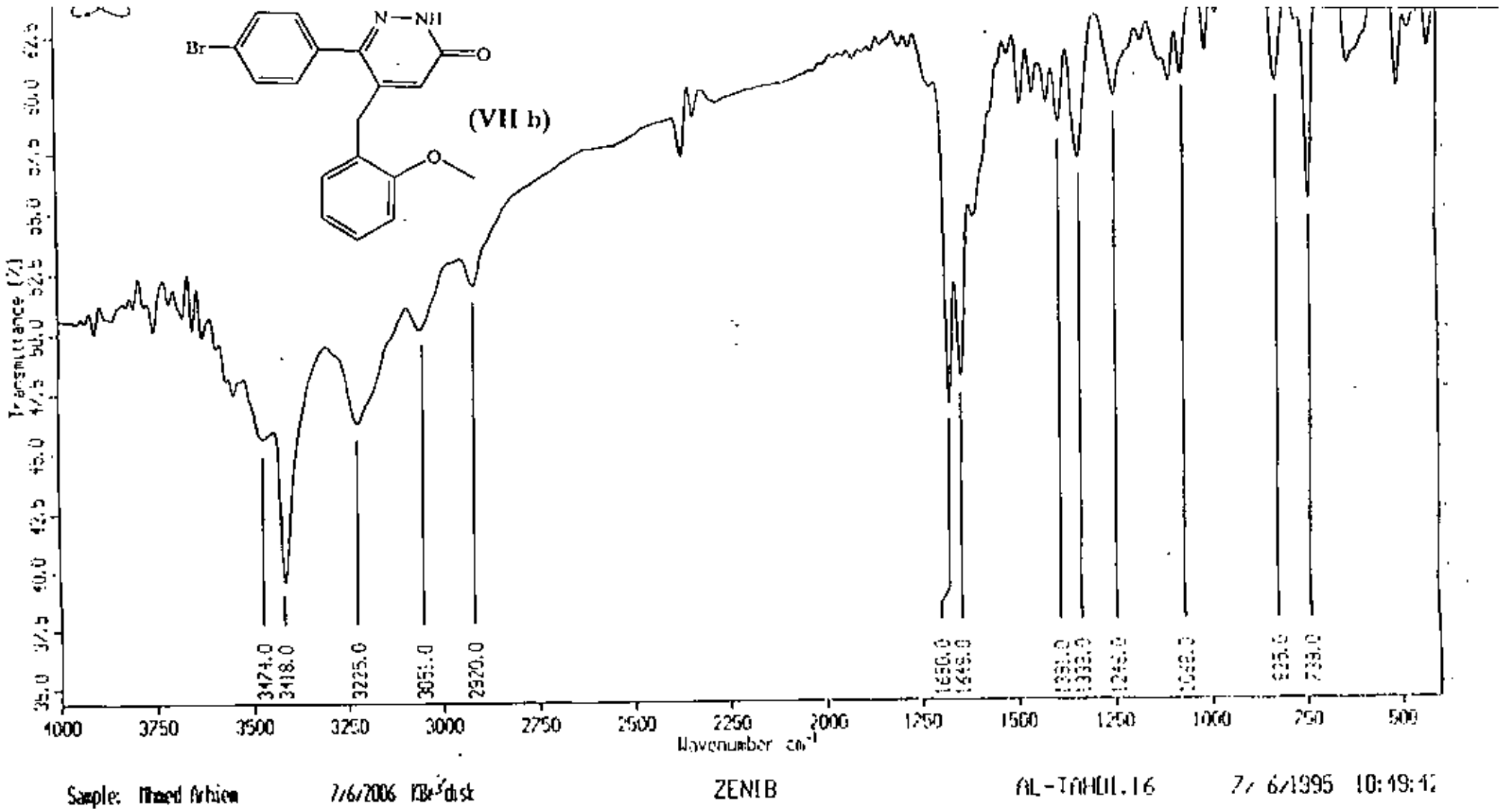

Br
N—NH
O
O
(VII b)
Transmittance (%)
3474.0
3418.0
3225.0
3051.0
2920.0
1650.0
1446.0
1331.0
1333.0
1246.0
1032.0
835.0
739.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Mixed fusion
7/6/2006 KBr disk
ZENIB
AL-TAHUL.16
7/ 6/1995 10:19:47

fig. 18b

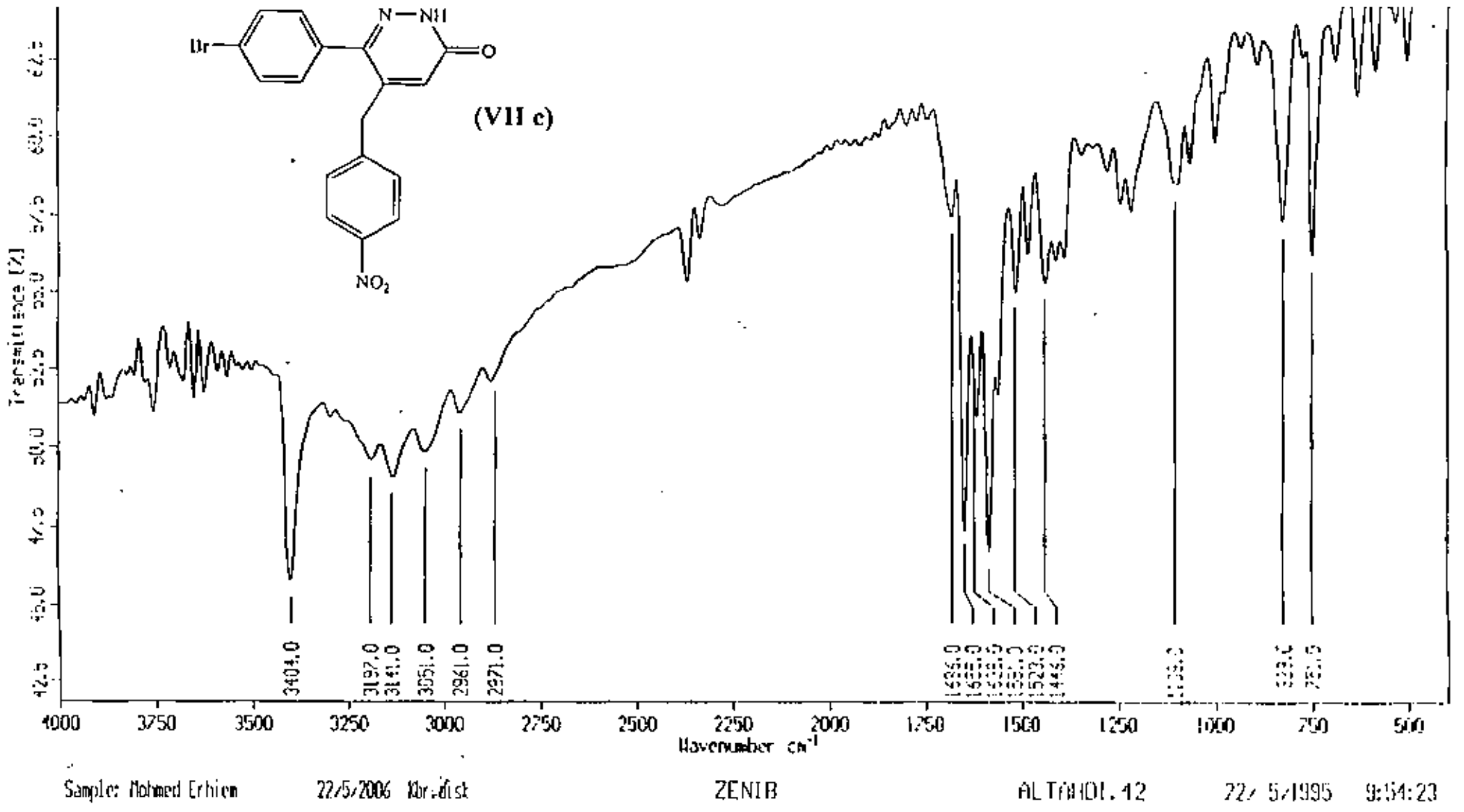
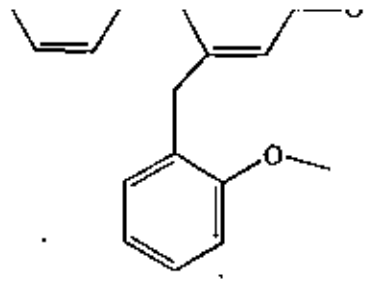

Br
N—NH
O
NO2
(VII c)
Transmittance [%]
3404.0
3197.0
3141.0
3051.0
2961.0
2871.0
1656.0
1523.0
1446.0
1133.3
833.3
755.5
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Mohmed Erhiem
22/5/2006
ZENIB
ALTAHOL.42
22/ 5/1995
9:54:23

fig. 18c



$C_{18}H_{15}BrN_2O_2$

Mol. Wt.: 371.23

(VII h)

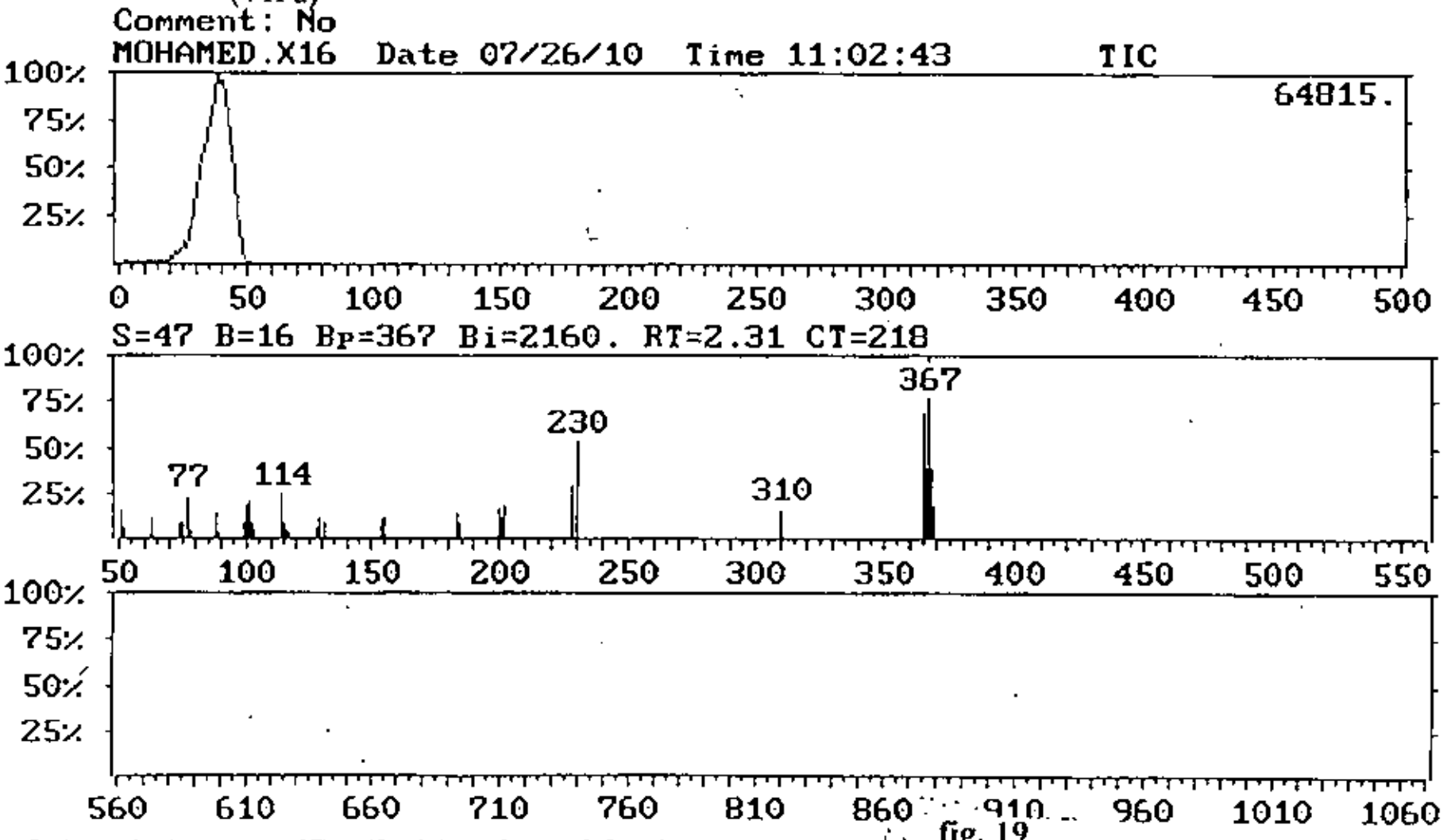
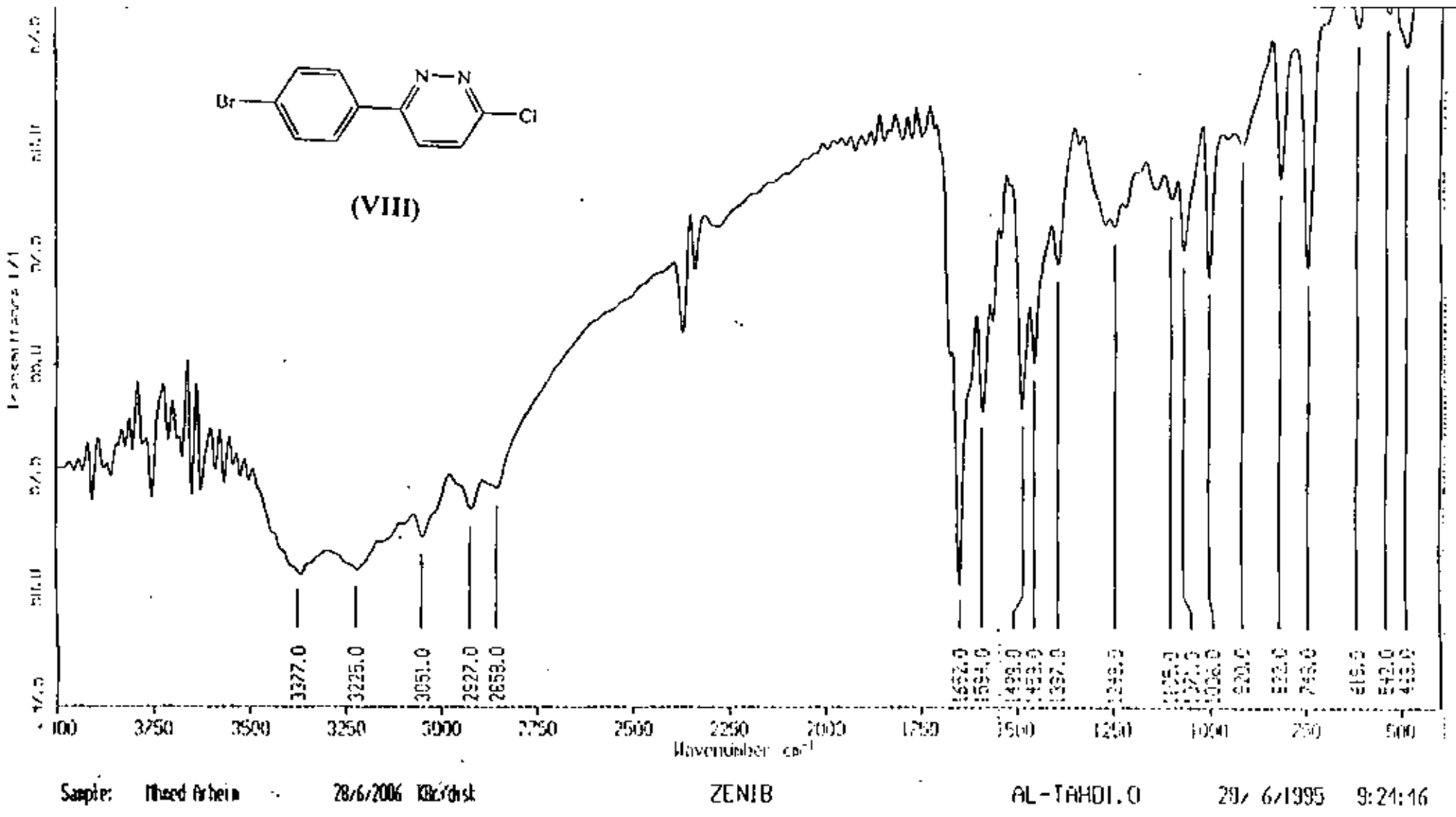


fig. 19

File : MOHAMED.X16 Date 07/26/10 Time 11:02:43
S=47 B=16 Bp=367 Bi=2160. RT=2.31 CT=218

Mass	Int(%)	Mass	Int(%)	Mass	Int(%)	Mass	Int(%)
51	14.8	52	6.0	63	11.6	74	8.8
75	8.3	77	22.7	78	4.6	88	14.4
89	2.3	99	8.8	100	18.1	101	20.4
102	7.9	103	3.7	114	25.0	115	8.3
116	4.6	117	3.2	128	5.6	129	11.6
131	7.9	154	9.7	155	11.6	183	14.4
184	8.3	200	17.1	201	11.1	202	18.5
228	29.2	230	53.7	310	15.7	365	68.5
366	38.0	367	100.0	368	38.0	369	17.6


Br
N
N
Cl
3327.0
3225.0
3051.0
2922.0
2858.0
1652.0
1584.0
1499.0
1453.0
1397.0
1249.0
1125.0
1093.0
1026.0
820.0
822.0
745.0
616.0
542.0
473.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Mixed Arbein
28/6/2006 KBr/disk
ZENIB
AL-TAHDI.O
29/ 6/1995 9:24:16

(VIII)

fig. 20

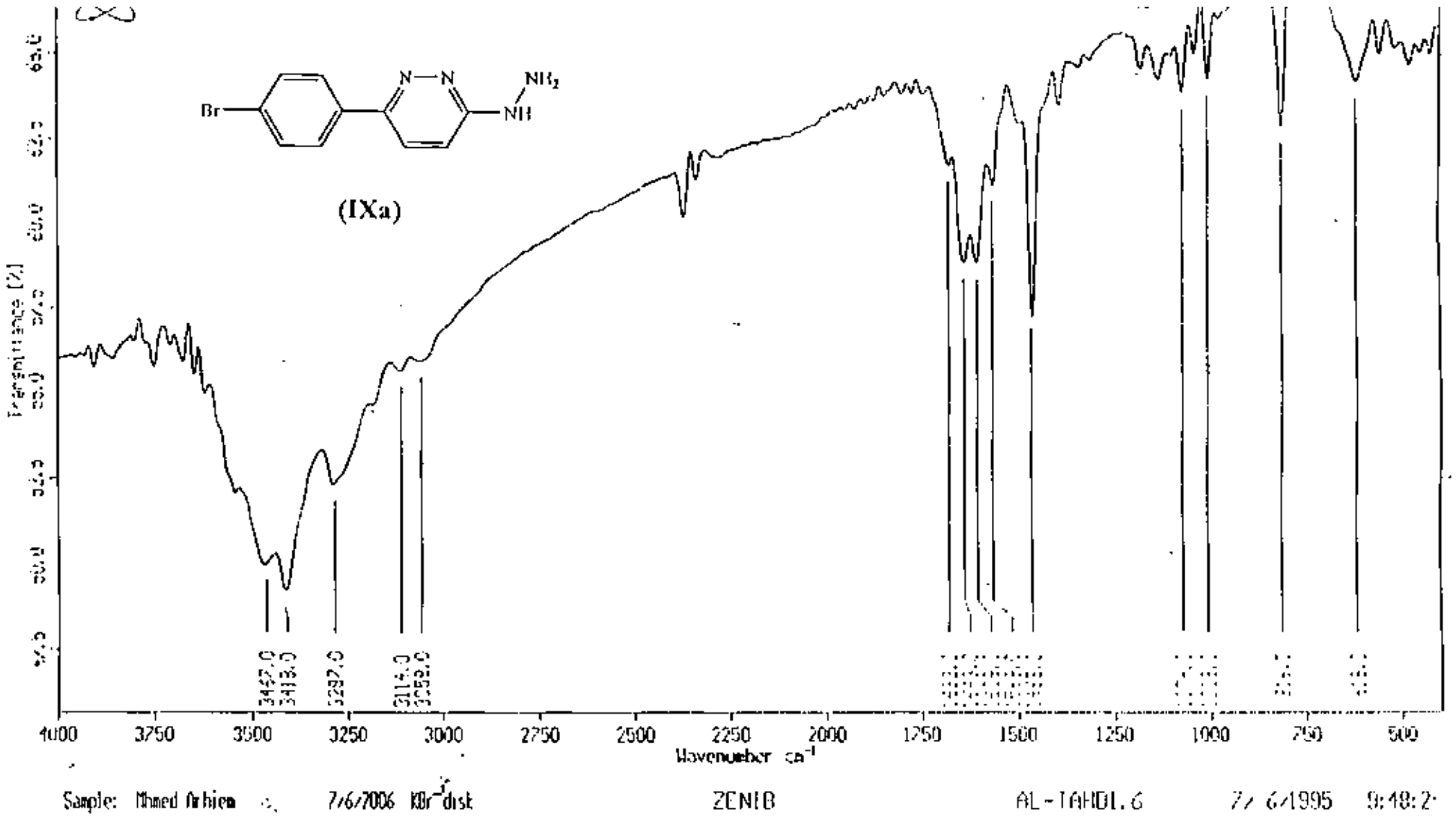
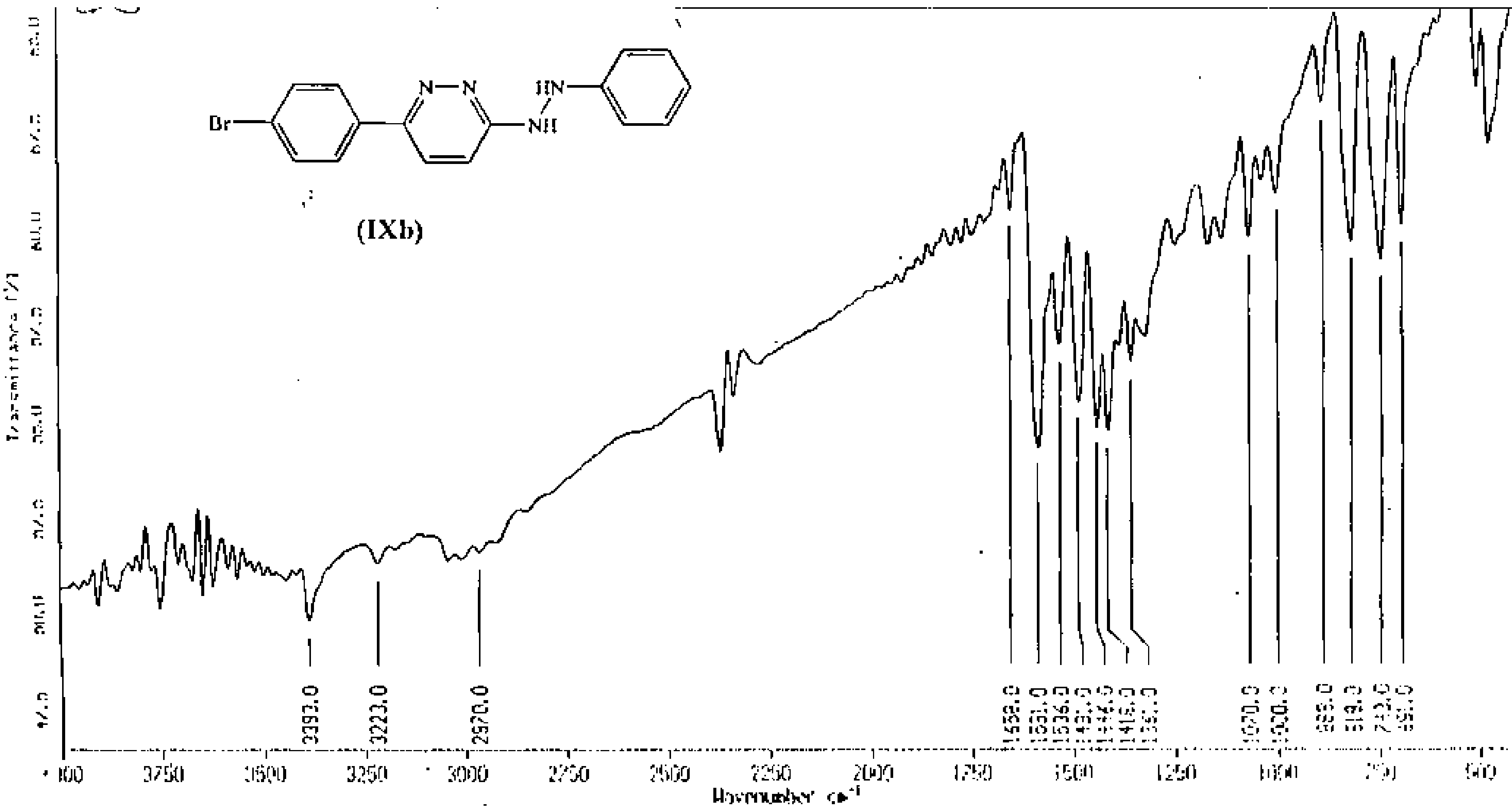
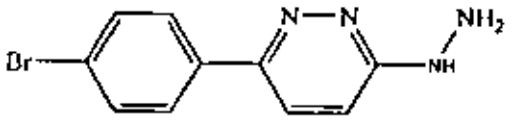

Br
N—N
NH2
NH
(IXa)
Transmittance [%]
3457.0
3418.0
3287.0
3114.0
3058.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Ahmed Arbiem
7/6/2006 KBr disk
ZENIB
AL-TAHDI.6
7/ 6/1995 9:48:2

fig. 21a



Sample: Ahmed Arhem 20/6/2006 KBr disk ZENIB AL-TAHDI.3 28/ 6/1995 9:50:52

fig. 21b



$C_{10}H_9BrN_4$

Mol. Wt.: 265.11

(IXa)

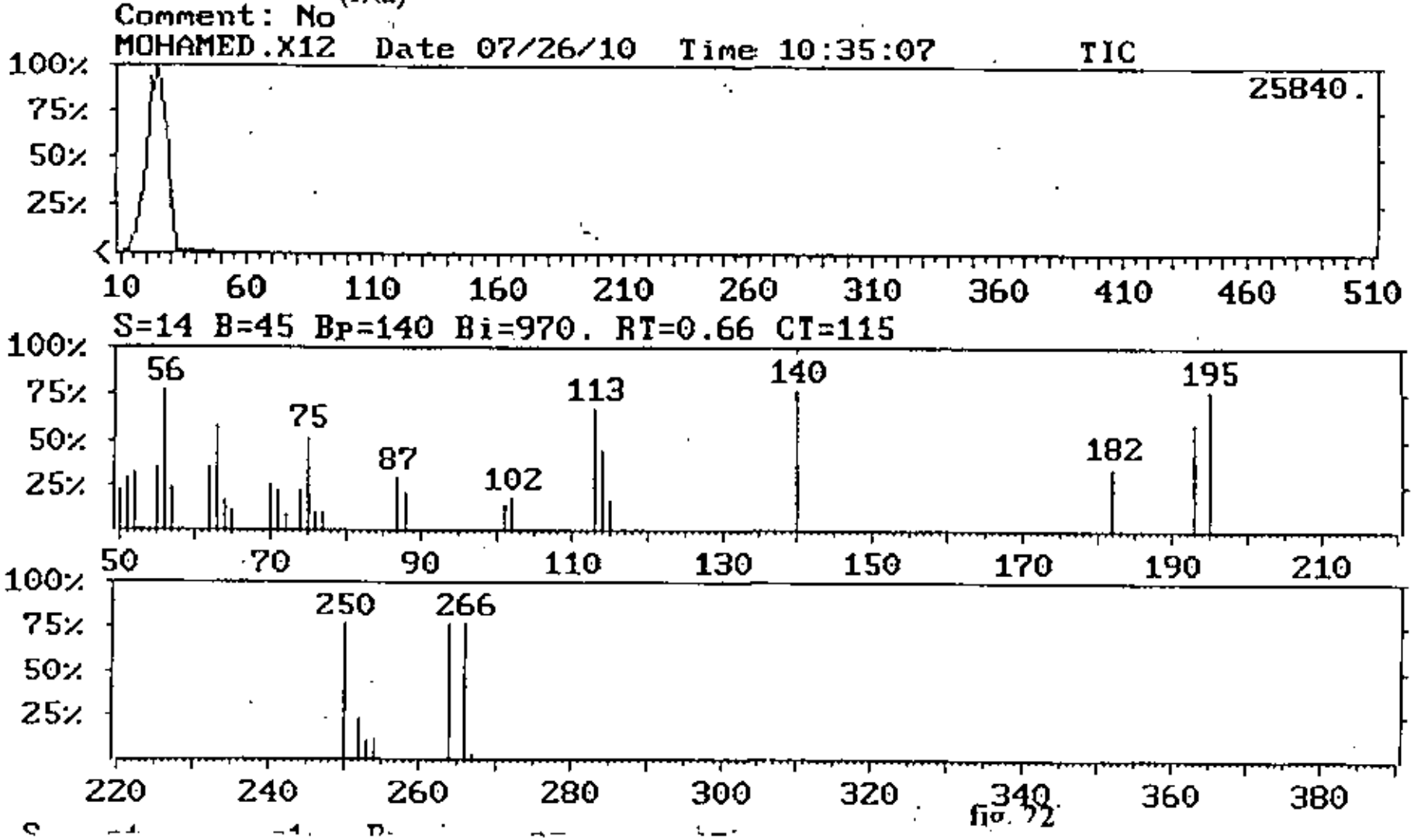


fig. 72

File : MOHAMED.X12 Date 07/26/10 Time 10:35:07
S=14 B=45 Bp=140 Bi=970. RT=0.66 CT=115

Mass	Int(%)	Mass	Int(%)	Mass	Int(%)	Mass	Int(%)
50	21.6	51	28.9	52	32.0	55	35.1
56	83.5	57	23.7	62	35.1	63	57.7
64	16.5	65	11.3	70	24.7	71	21.6
72	8.2	74	22.7	75	51.5	76	9.3
77	9.3	87	28.9	88	20.6	101	14.4
102	17.5	113	67.0	114	44.3	115	16.5
140	100.0	182	35.1	193	58.8	195	82.5
250	77.3	252	21.6	253	9.3	254	11.3
264	87.6	266	91.8	267	3.1		

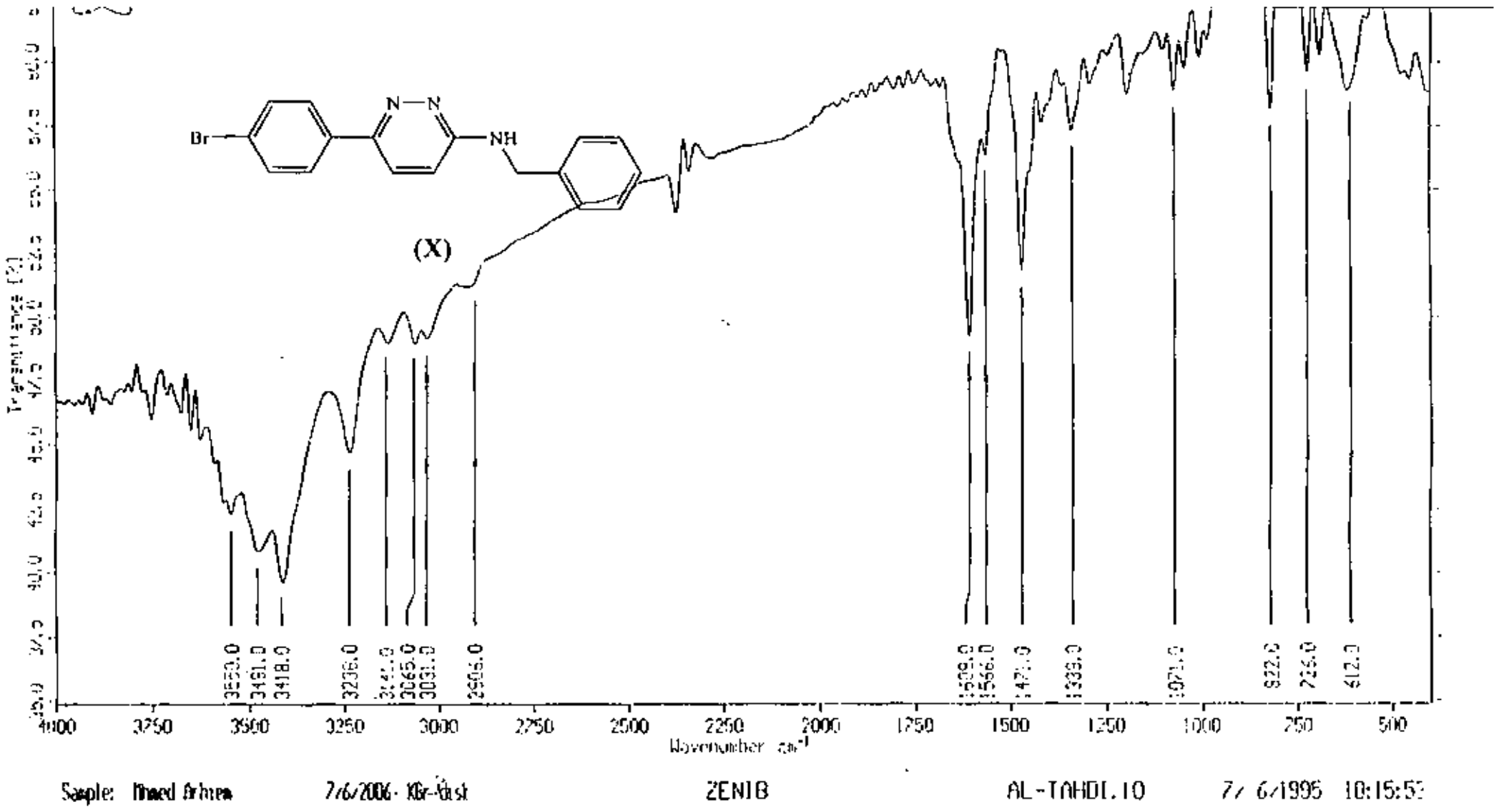
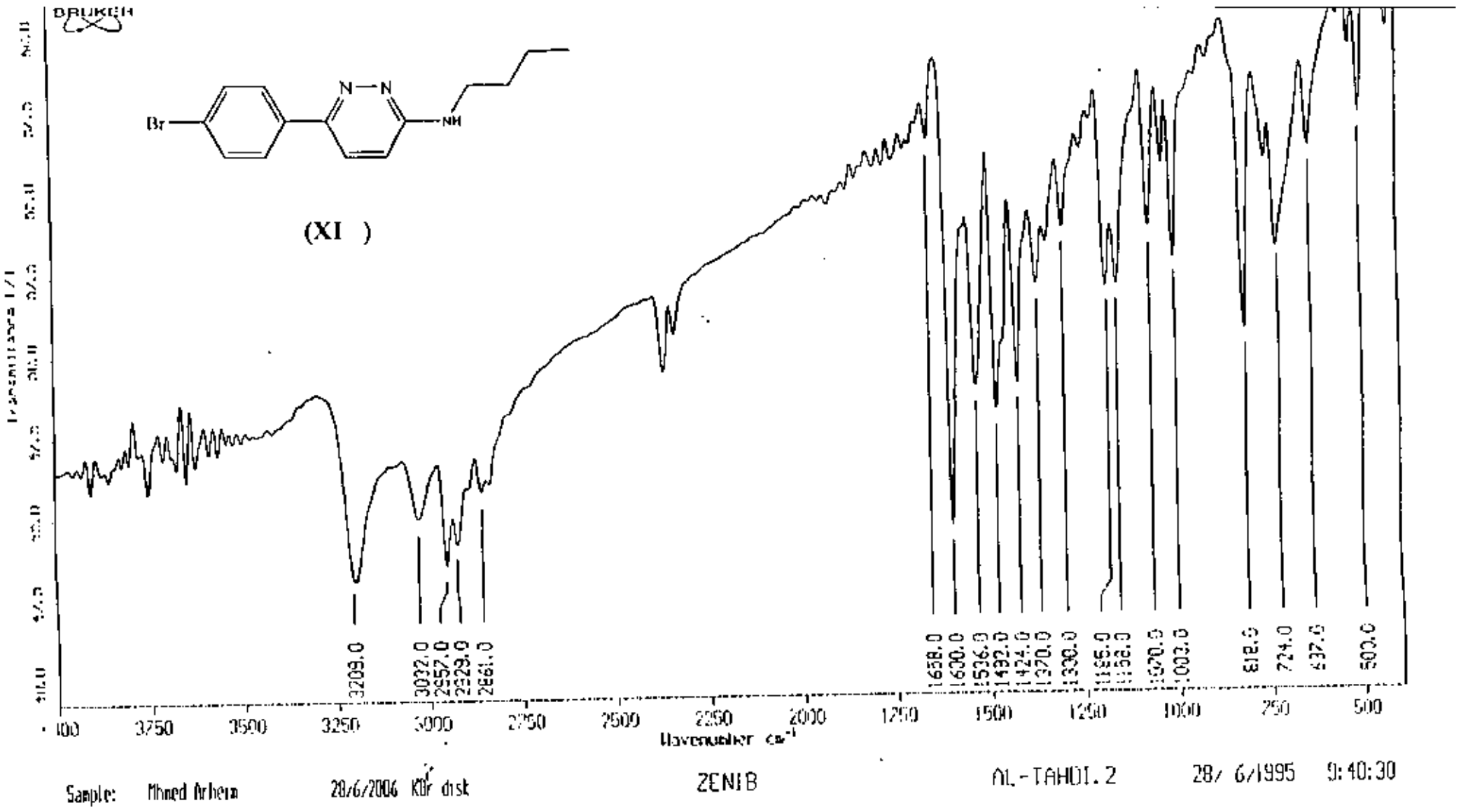
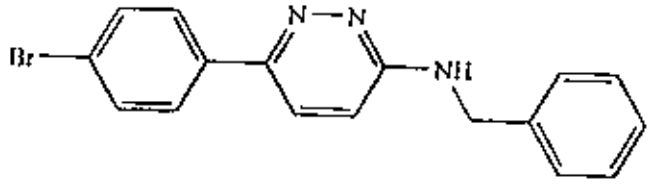

Br
N—N
NH
(X)
3418.0
3236.0
3065.0
3031.0
2905.0
1556.0
1338.0
822.0
726.0
612.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Phased Arbren
7/6/2006- KBr-Gast
ZENIB
AL-TAHDI.10
7/ 6/1995 10:15:53

fig. 23a


BRUKER
Br
N
N
NH
3209.0
3032.0
2957.0
2929.0
2861.0
1658.0
1600.0
1536.0
1492.0
1424.0
1370.0
1330.0
1195.0
1158.0
1070.0
1002.0
818.0
774.0
697.0
500.0
400
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Mhmed Arhem
28/6/2006 KBr disk
ZENIB
AL-TAHDI.2
28/ 6/1995 9:40:30

(XI)

fig. 23b


Br
N
N
NH

(X)

MOH / 1H / DMSO
0C050F.106
AU PROG:
XQQ.AU
DATE 5-10-6
TIME 15: 11
SF 200.133
SY 200.0
OI 4500.000
SI 32768
TD 32768
SW 4032.258
HZ/PT .246
PW 3.5
AD 1.000
AQ 4.063
RG 32
NS 16
TE 297
FW 5100
O2 2228.997
OP 63L P0
LB .300
GB 0.0
CX 35.00
CY 20.00
F1 12.0030
F2 -.6550
HZ/CM 72.841
PPM/CM .364
SR 3285.94
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

fig. 24

#	CURSOR	FREQUENCY	PPM	INTENSITY
1	6651	1593.206	7.9607	4.203
2	6686	1584.624	7.9178	5.233
3	6726	1574.853	7.8690	3.803
4	6764	1565.509	7.8223	3.227
5	6882	1536.538	7.6776	5.483
6	6916	1527.974	7.6348	4.643
7	6943	1521.381	7.6018	2.070
8	6966	1515.861	7.5743	1.163
9	7097	1483.629	7.4132	1.562
10	7125	1476.612	7.3781	7.808
11	7153	1469.751	7.3439	4.441
12	7157	1468.888	7.3395	3.948
13	7180	1463.049	7.3104	1.746
14	7185	1461.889	7.3046	1.884
15	7207	1456.584	7.2781	1.794
16	7231	1450.614	7.2482	1.488
17	7445	1397.899	6.9848	2.907
18	7483	1388.556	6.9382	2.696
19	9333	933.257	4.6632	4.401
20	9357	927.436	4.6341	4.264
21	10373	677.316	3.3843	20.011
22	11077	504.002	2.5183	2.177
23	11083	502.553	2.5111	2.298

fig. 24

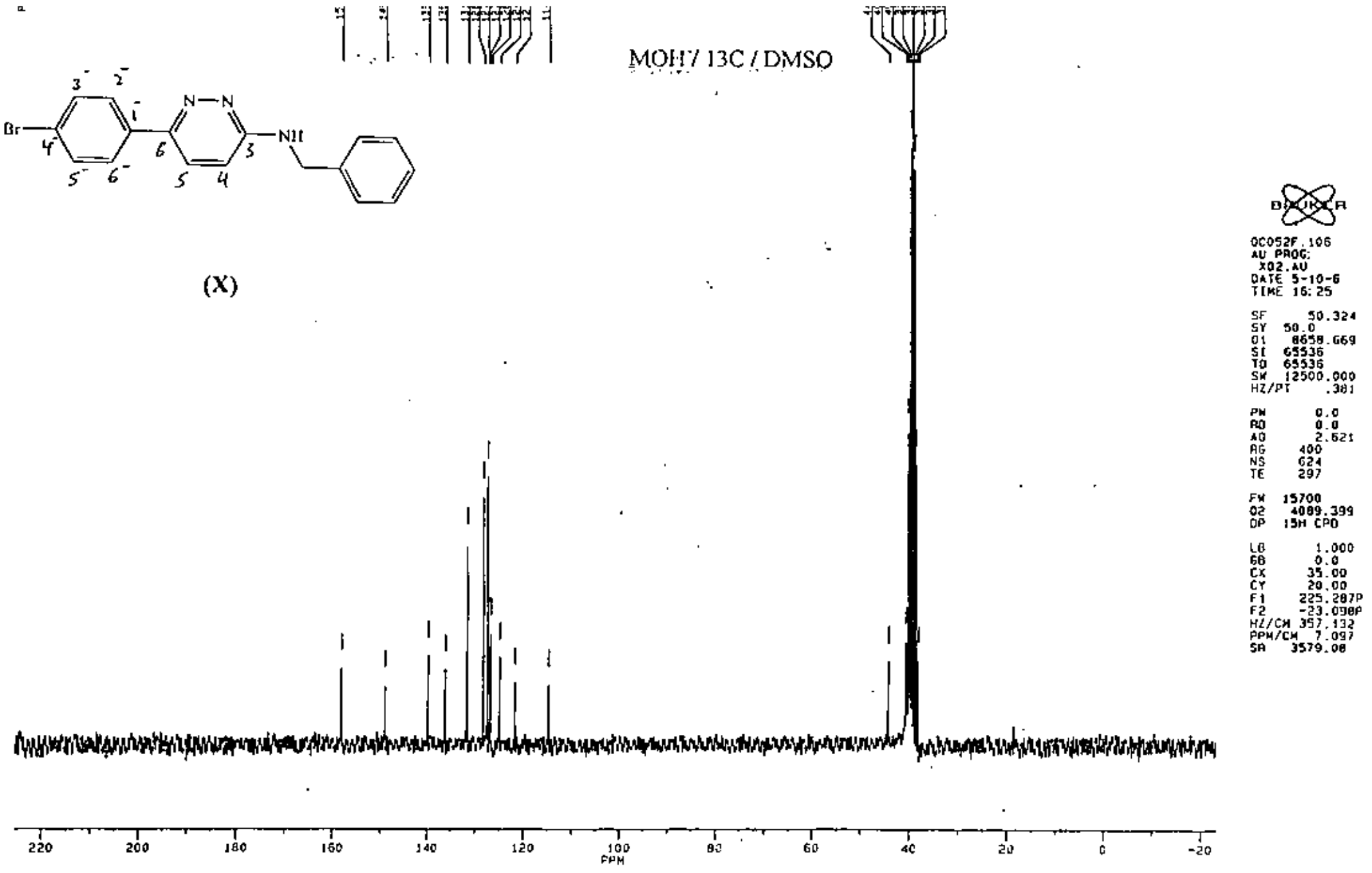

MOH7 13C / DMSO
Br
NH
N
N
1
2
3
4
5
6
1'
2'
3'
4'
5'
6'
(X)
0C052F.106
AU PROG:
X02.AU
DATE 5-10-6
TIME 16:25
SF 50.324
SY 50.0
01 8658.669
SI 65536
TD 65536
SW 12500.000
HZ/PT .381
PW 0.0
RD 0.0
AQ 2.621
RG 400
NS 624
TE 297
FW 15700
02 4089.399
DP 15H CPD
LB 1.000
GB 0.0
CX 35.00
CY 20.00
F1 225.287P
F2 -23.098P
HZ/CM 357.132
PPM/CM 7.097
SR 3579.08
220
200
180
160
140
120
100
80
60
40
20
0
-20
PPM

fig. 25

CY= 10.000 20 CX= 35.000 MI= 1.301

OC052F.106
MIN. INTENSITY = 1.301 MAXY = 20.00000 PP CONSTANT = 1.000000
INTENS. LEVEL = 1.301 NOISE = .15692 SENS. LEVEL = .62767
F1 = 11337.22 HZ = 225.2867 PPM F2 = -1162.40 HZ = -23.0995 PPM

#	CURSOR	FREQUENCY	PPM	INTENSITY
1	8851	7953.308	158.0435	2.287
2	10052	7494.903	148.9344	1.772
3	11264	7032.679	139.7493	2.666
4	11733	6853.782	136.1944	2.253
5	12333	6625.073	131.6496	5.950
6	12774	6456.642	128.3026	7.277
7	12894	6410.936	127.3944	7.876
8	12904	6407.249	127.3211	5.680
9	12978	6378.993	126.7596	3.338
10	13224	6285.075	124.8933	2.617
11	13640	6126.262	121.7375	1.877
12	14558	5776.324	114.7837	1.810
13	23856	2229.413	44.3016	2.529
14	24321	2051.835	40.7729	3.088
15	24376	2030.801	40.3549	9.170
16	24431	2009.810	39.9378	17.617
17	24486	1988.831	39.5209	20.357
18	24541	1967.865	39.1043	16.941
19	24596	1946.832	38.6863	8.251
20	24652	1925.762	38.2676	2.514

fig. 25

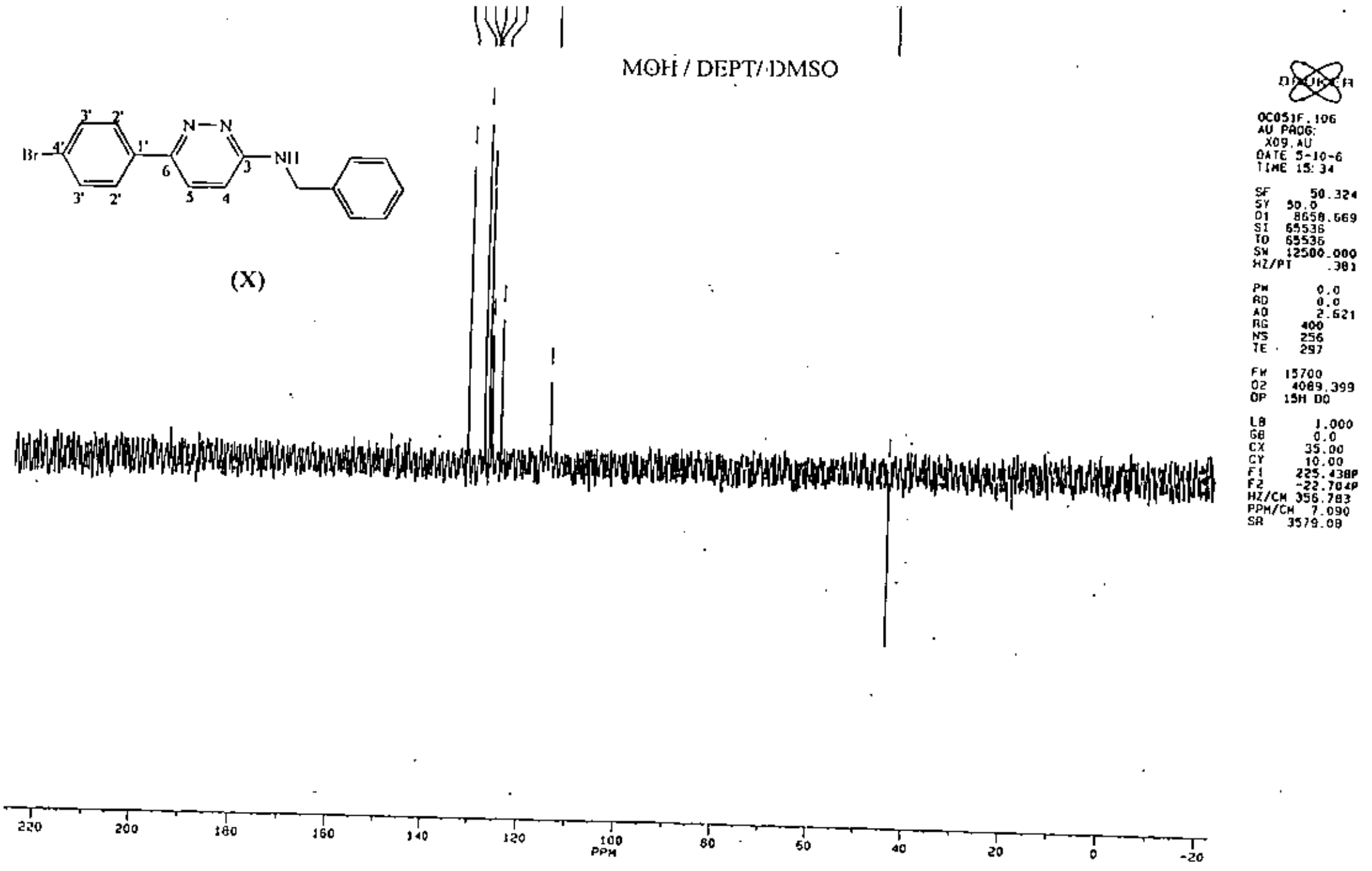

MOH / DEPT/DMSO
Br
NH
(X)
OC051F.106
AU PROG:
X09.AU
DATE 5-10-6
TIME 15:34
SF 50.324
SY 50.0
D1 8658.669
SI 65536
TD 65536
SW 12500.000
HZ/PT .381
PW 0.0
RD 0.0
AQ 2.621
RG 400
NS 256
TE 297
FW 15700
O2 4089.399
DP 15H D0
LB 1.000
GB 0.0
CX 35.00
CY 10.00
F1 225.438P
F2 -22.704P
HZ/CM 356.783
PPM/CM 7.090
SR 3579.09
220
200
180
160
140
120
100
PPM
80
60
40
20
0
-20

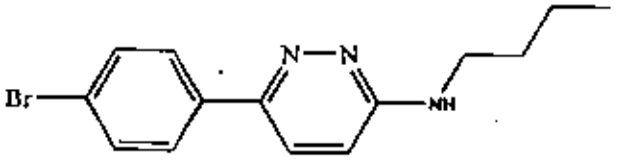
fig. 26

AUTO RG FINISHED
CY= 10.000 CX= 35.000 MI= 1.984

OC051F.106
MIN. INTENSITY = 1.984 MAXY = 20.00000 PP CONSTANT = 1.00000
INTENS. LEVEL = 1.984 NOISE = .20019 SENS. LEVEL = .380074
F1 = 11344.85 HZ = 225.4383 PPM F2 = -1142.56 HZ = -22.7043 PPM

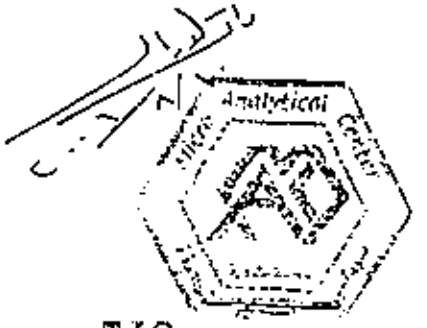
#	CURSOR	FREQUENCY	PPM	INTENSITY
1	12333	6625.047	131.6491	8.927
2	12774	6456.639	128.3026	10.051
3	12895	6410.730	127.3903	7.745
4	12905	6406.823	127.3127	8.256
5	12978	6379.047	126.7607	3.854
6	13224	6285.099	124.8938	4.245
7	14557	5776.492	114.7871	2.424
8	23857	2228.996	44.2933	-5.130

fig. 26



$C_{14}H_{16}BrN_3$

Mol. Wt.: 306.2



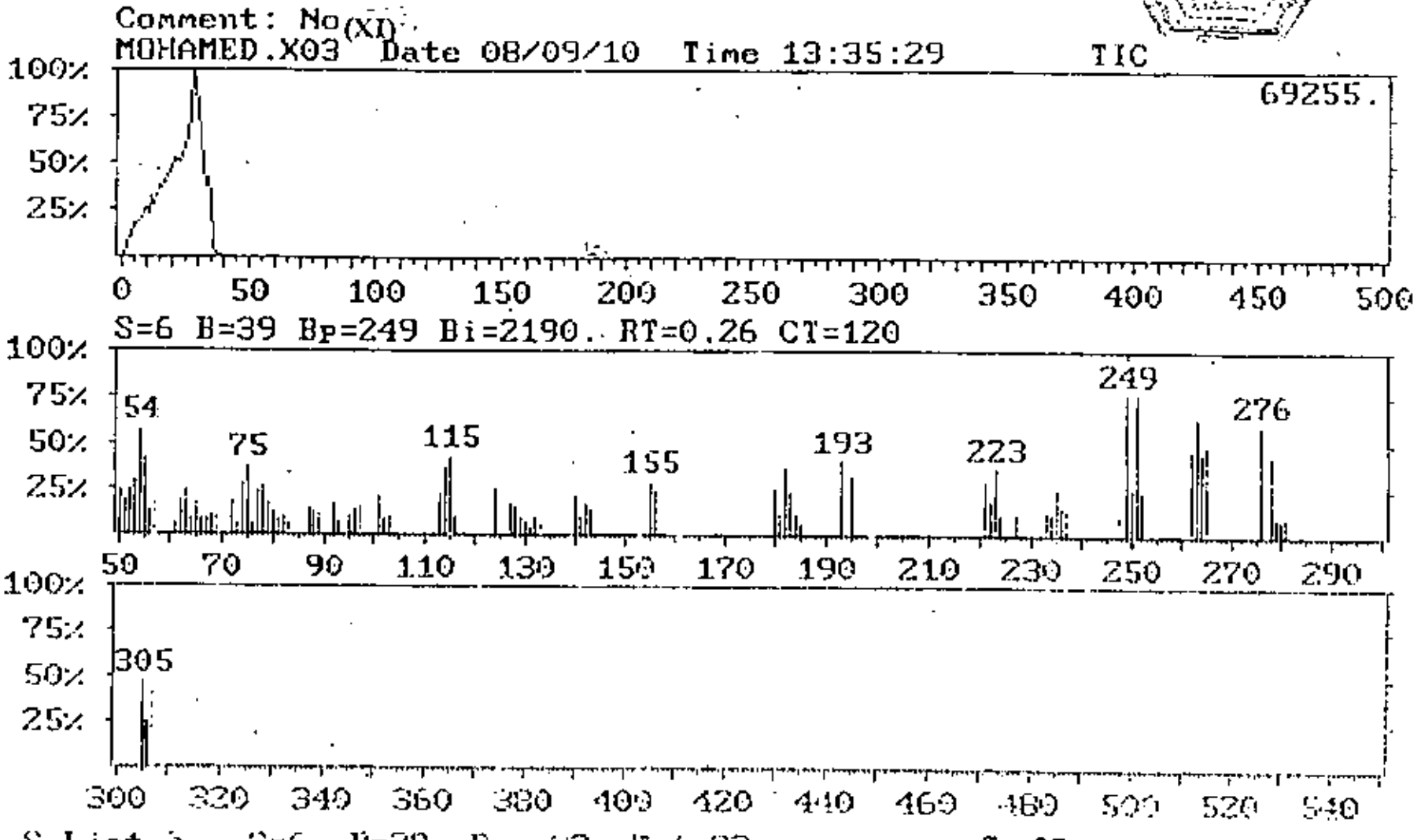


fig. 27

File : MOHAMED.X03 Date 08/09/10 Time 13:35:29
S=6 B=39 Bp=249 Bi=2190. RT=0.26 CT=120

Mass	Int(%)	Mass	Int(%)	Mass	Int(%)	Mass	Int(%
50	23.3	51	17.4	52	23.7	53	28.6
54	57.1	55	41.6	56	12.8	57	16.0
61	5.9	62	18.7	63	24.2	64	8.7
65	16.4	66	7.8	67	8.2	68	10.0
69	10.0	72	17.4	73	5.0	74	27.9
75	37.0	76	5.9	77	23.3	78	26.0
79	16.4	80	11.9	81	6.2	82	9.6
83	5.9	87	13.7	88	12.3	89	11.4
92	16.9	93	7.3	95	9.1	96	13.2
97	14.6	101	21.5	102	8.7	103	3.4
113	21.9	114	36.5	115	42.0	116	9.1
124	24.7	127	16.0	128	15.5	129	10.0
130	6.4	131	4.1	132	9.6	133	5.9
140	21.5	141	11.4	142	16.9	143	13.7
155	28.3	156	23.7	180	25.1	181	11.0
182	35.6	183	23.3	184	11.4	185	5.9
193	40.2	195	32.4	221	29.2	222	17.4
223	36.1	224	11.0	227	11.4	233	12.3
234	10.5	235	24.7	236	14.6	237	14.6
249	100.0	250	25.1	251	89.5	252	23.3
262	45.7	263	63.9	264	44.7	265	48.4
276	59.8	278	43.4	279	10.0	280	8.7
281	9.1	305	46.6	306	24.7	307	42.5

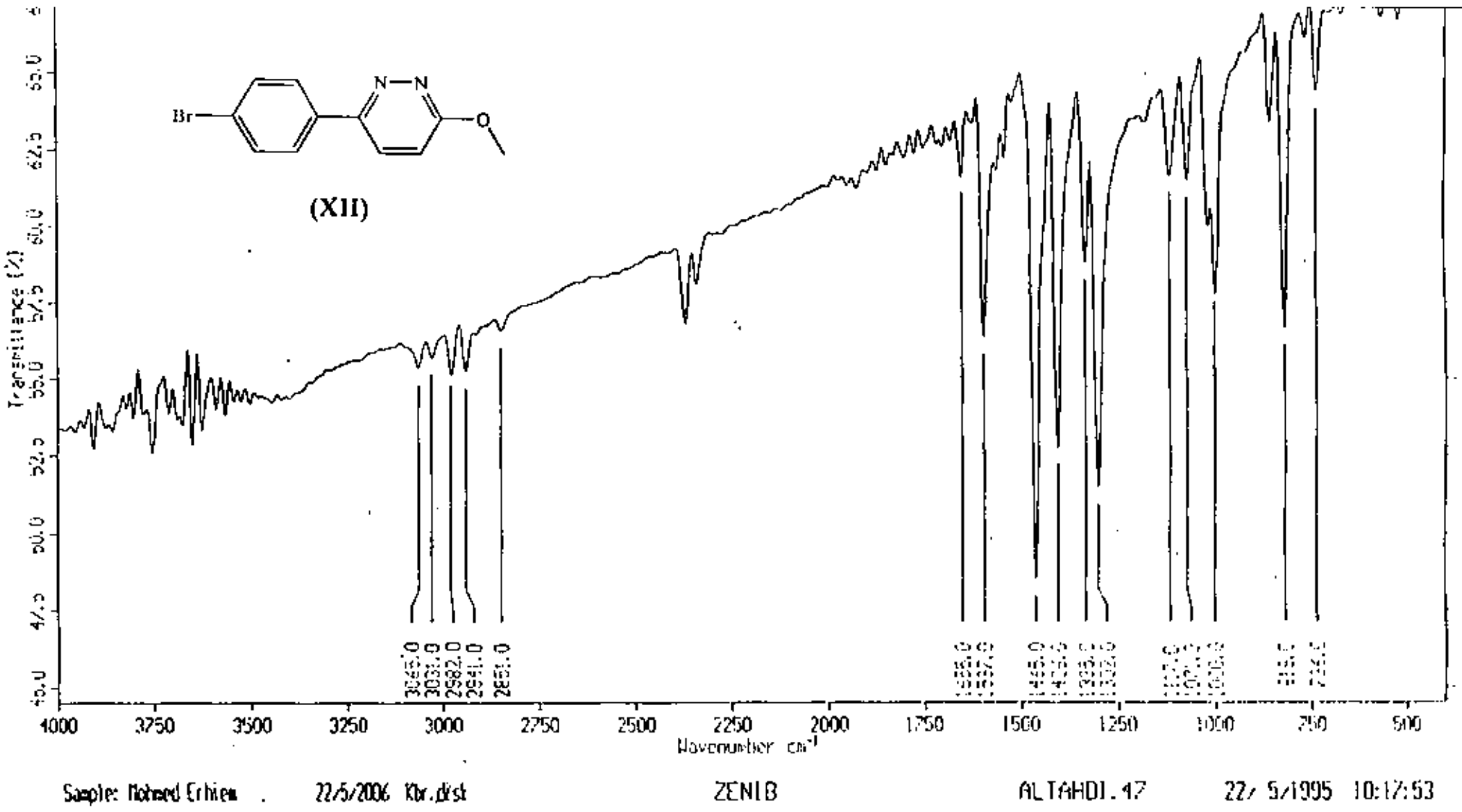

Br
N
N
O
(XII)
Transmittance (%)
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Mohamed Erhiem
22/5/2006 Kbr.dfst
ZENIB
ALTAHDI.47
22/ 5/1995 10:17:53

fig. 28

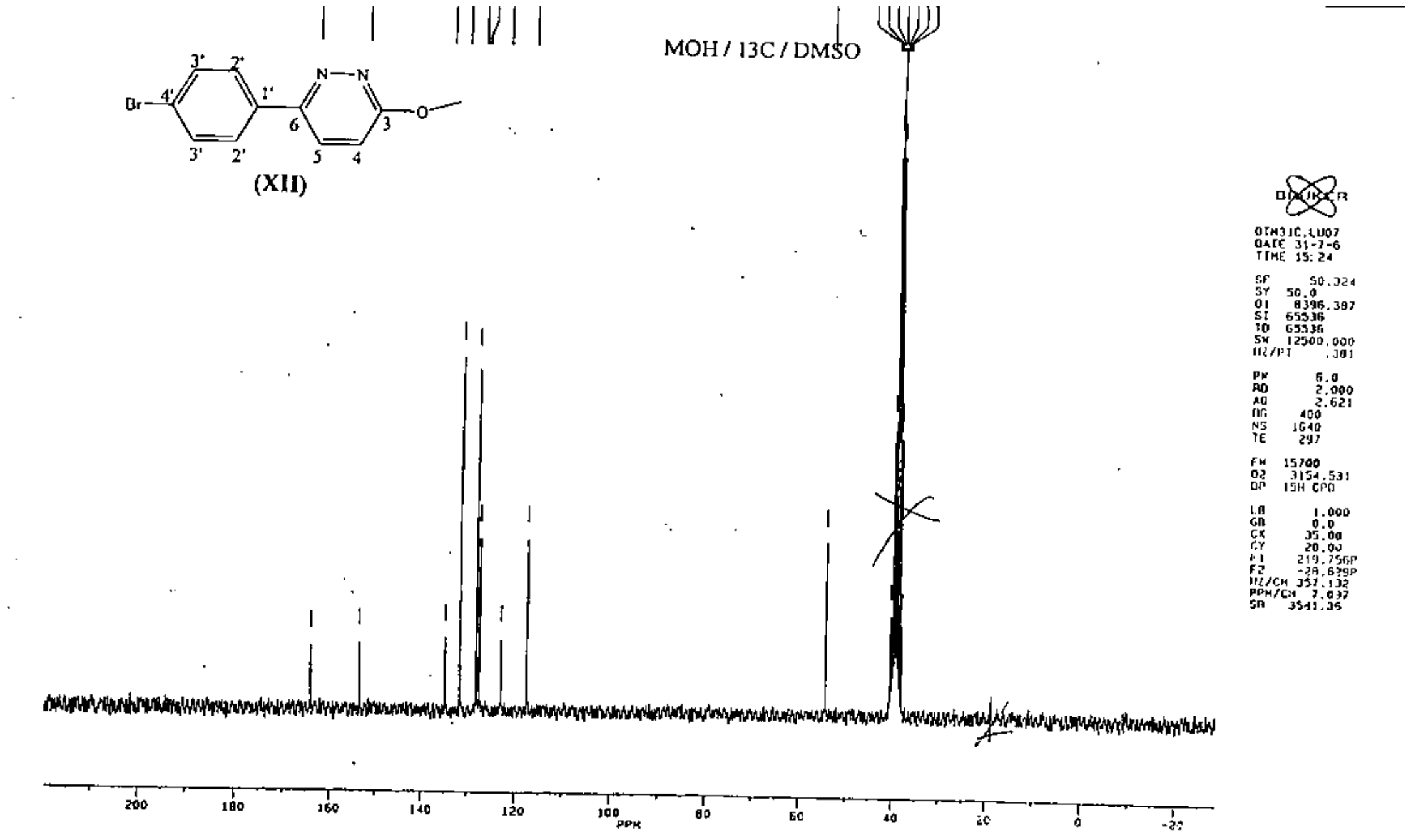

MOH / 13C / DMSO
Br
O
N
N
1'
2'
3'
4'
5
6
3
4
(XII)
OTN31C.LU07
DATE 31-7-6
TIME 15:24
SF 50.324
SY 50.0
OI 8396.387
SI 65536
TD 65536
SW 12500.000
HZ/PT .381
PW 6.0
AD 2.000
AQ 2.621
DG 400
NS 1640
TE 297
FM 15700
O2 3154.531
DP 15H CPD
LB 1.000
GB 0.0
GX 35.00
GY 20.00
F1 219.756P
F2 -28.699P
HZ/CM 357.132
PPM/CM 7.097
SR 3541.36
200
180
160
140
120
100
PPM
80
60
40
20
0
-20

fig. 30

#	CURSOR	FREQUENCY	PPM	INTENSITY
1	7341	8264.669	164.2305	1.381
2	8730	7734.784	153.7010	1.782
3	11184	6798.644	135.0986	7.180
4	11616	6633.842	131.8237	10.636
5	12082	6456.245	128.2946	10.453
6	12168	6423.273	127.6394	5.247
7	12776	6191.242	123.0286	2.171
8	13491	5918.587	117.6106	5.256
9	21816	2742.893	54.5051	5.265
10	23632	2049.949	40.7354	3.019
11	23687	2029.074	40.3205	8.695
12	23742	2008.156	39.9049	17.089
13	23797	1987.149	39.4874	20.001
14	23852	1966.161	39.0704	16.817
15	23907	1945.161	38.6531	8.426
16	23962	1924.108	38.2347	2.731

fig. 30

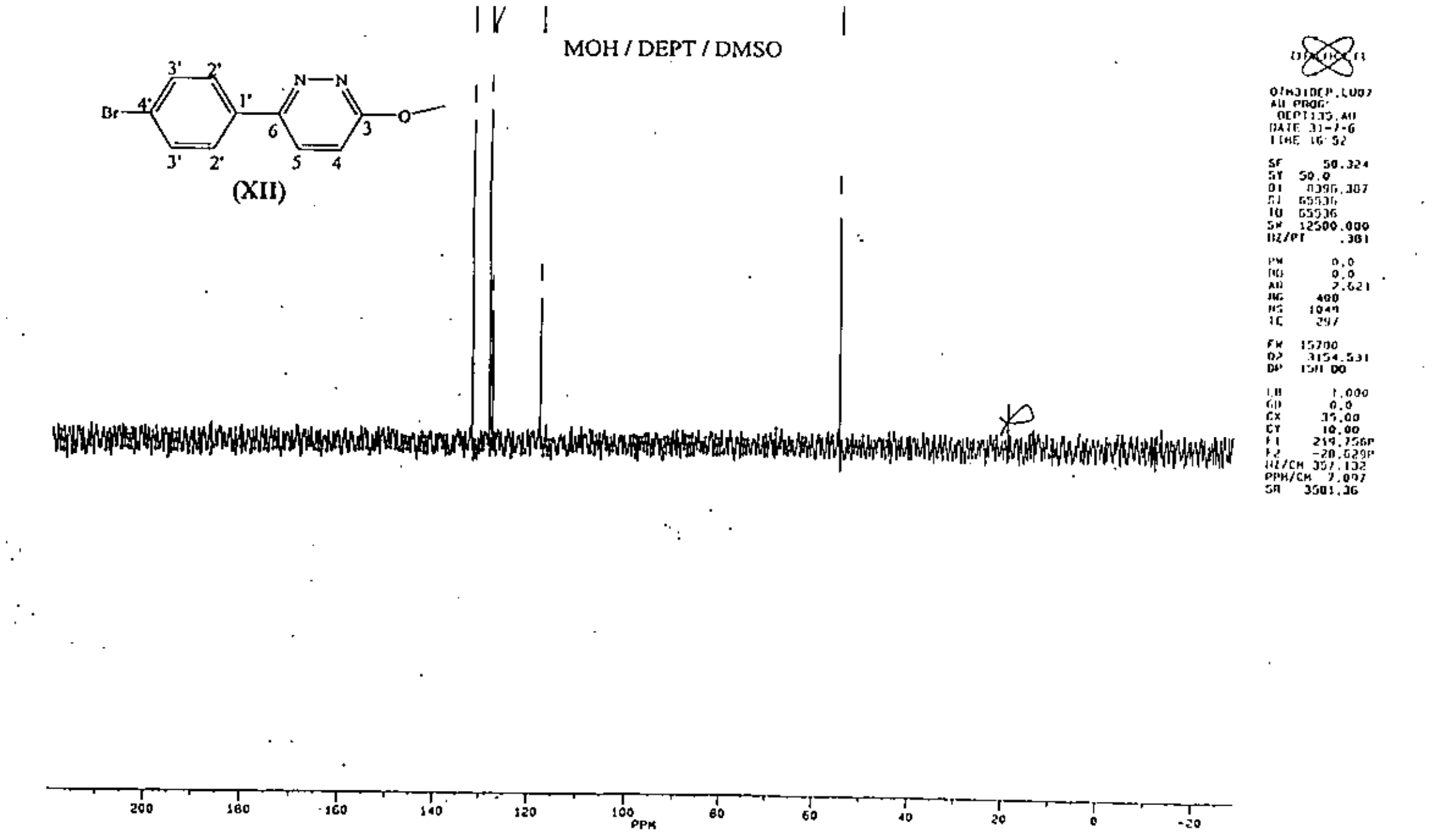

MOH / DEPT / DMSO
Br
4'
3'
2'
1'
6
N
N
3
O
3'
2'
5
4
(XII)
200
180
160
140
120
100
PPM
80
60
40
20
0
-20

fig. 31

```
PPM/CM=      7.097          F1[PPM]=    220.029 225
F2[PPM]=    -23.385 :       PPM/CM=      7.097          F1[PPM]=    335.002 219.7
F2[PPM]=    -28.629
CY=     10.000      CX=     35.000      MI=       4.017
MI=       3.659

 DTM31DEP.LU07
MIN. INTENSITY =     3.659      MAXY  =  20.00000     PP CONSTANT =    1.00000
INTENS. LEVEL  =     3.659      NOISE =    .16824     SENS. LEVEL =     .67297
F1 =   11058.92 HZ =  219.7563 PPM      F2 =   -1440.70 HZ =   -28.62936 PPM

      #  CURSOR     FREQUENCY       PPM    INTENSITY

      1   11615      6634.230   131.8316      9.705
      2   12081      6456.433   128.2984     10.035
      3   12167      6423.786   127.6496      4.071
      4   13489      5919.371   117.6262      4.392
      5   21815      2743.393    54.5151      7.091
```

fig. 31

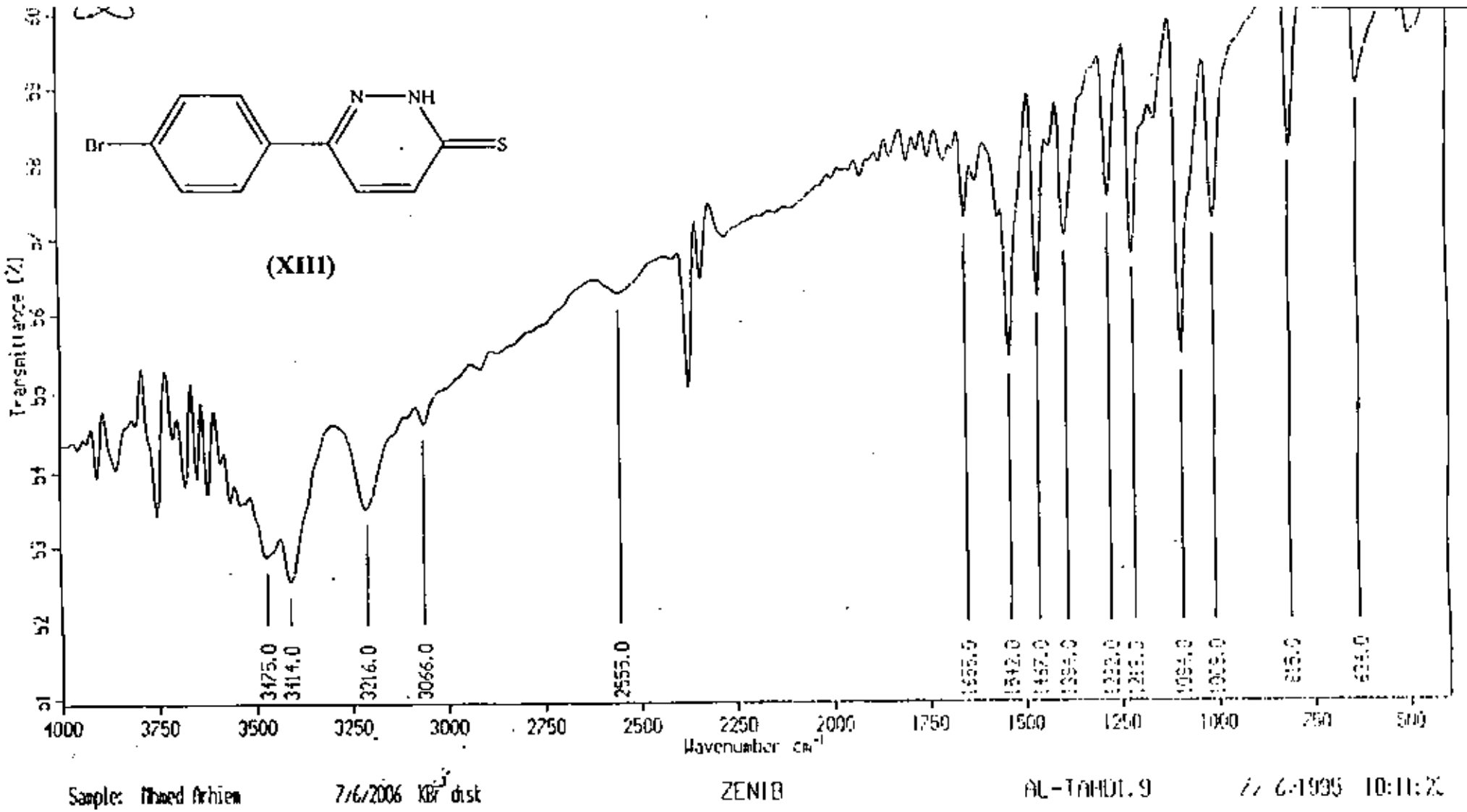

Br
N
NH
S
(XIII)
Transmittance [%]
3475.0
3414.0
3216.0
3066.0
2555.0
1655.9
1542.0
1467.0
1384.3
1322.0
1283.3
1084.9
1043.0
835.3
634.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Ahmed Arhiem
7/6/2006 KBr disk
ZENIB
AL-TAHDI.9
7-6-1995 10:11:2

fig. 32

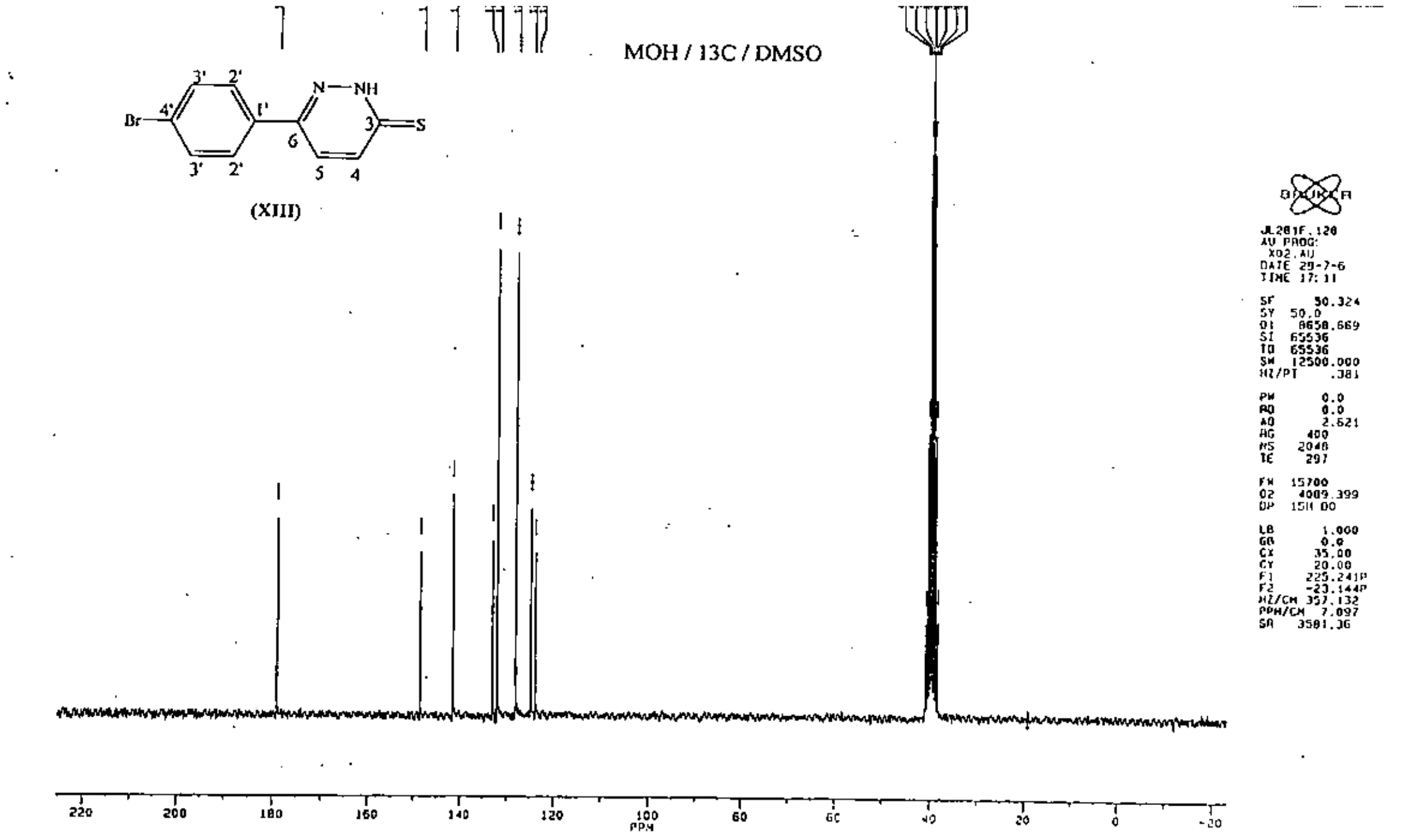

MOH / 13C / DMSO
Br
4'
3'
2'
1'
6
N
NH
3
S
5
4
(XIII)
JL281F.120
AU PROG:
XD2.AU
DATE 29-7-6
TIME 17:11
SF 50.324
SY 50.0
OI 8658.669
SI 65536
TD 65536
SW 12500.000
HZ/PT .381
PW 0.0
RD 0.0
AQ 2.621
RG 400
NS 2048
TE 297
FW 15700
D2 4009.399
DP 15H DO
LB 1.000
GB 0.0
CX 35.00
CY 20.00
F1 225.241P
F2 -20.144P
HZ/CM 357.132
PPM/CM 7.097
SR 3581.36
220
200
180
160
140
120
100
PPM
80
60
40
20
0
-20

fig. 33

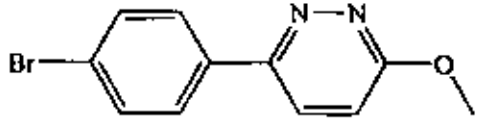
CY= 10.000 20 CX=

JL281F.128

MIN. INTENSITY = 1.736 MAXY = 20.00000 PP CONSTANT = 1.00000
INTENS. LEVEL = 1.736 NOISE = .06252 SCNS. LEVEL = .25007
F1 = 11334.94 HZ = 225.2413 PPM F2 = -1164.68 HZ = -23.1430 PPM

#	CURSOR	FREQUENCY	PPM	INTENSITY
1	6083	9006.759	178.9771	5.969
2	10114	7469.095	148.4215	4.939
3	11038	7116.644	141.4178	6.684
4	12164	6687.015	132.8805	5.359
5	12288	6639.884	131.9439	14.140
6	12817	6438.050	127.9332	13.976
7	13246	6274.282	124.6789	6.298
8	13377	6224.436	123.6884	4.929
9	24319	2050.384	40.7440	2.800
10	24374	2029.388	40.3268	8.564
11	24429	2008.401	39.9098	17.018
12	24484	1987.403	39.4925	20.000
13	24539	1966.412	39.0754	17.014
14	24594	1945.398	38.6578	8.548
15	24649	1924.429	38.2411	2.846

fig. 33


Br
N
N
O

(XII)

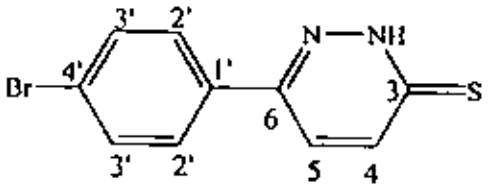
MOH / 1H / DMSO
DTK01H.LU07
DATE 31-7-6
TIME 15:27
SF 200.133
SY 200.0
O1 4500.000
SI 32768
TD 32768
SW 4032.258
HZ/PT .246
PW 3.5
RD 1.000
AQ 4.063
DG 40
NS 16
TE 297
FW 5100
O2 2228.997
DP 63L PD
LB .300
GB 0.0
CX 35.00
CY 20.00
F1 12.092P
F2 -.578P
HZ/CM 72.446
PPM/CM .362
SR 3285.94
5.98
2.000
2.032
3.551
2.935
5.381
3.161
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

fig. 29

MIN. INTENSITY = .735 MAXY = 23.50000 PP CONSTANT = [illegible]
INTENS. LEVEL = .735 NOISE = .00571 SLNG. LEVEL = [illegible]
F1 = 2419.99 HZ = 12.0919 PPM F2 = -115.67 HZ = -.5780 PPM

#	CURSOR	FREQUENCY	PPM	INTENSITY
1	6450	1642.861	8.2088	1.794
2	6407	1633.556	8.1623	2.001
3	6574	1612.347	8.0564	2.542
4	6581	1610.622	8.0477	1.083
5	6601	1605.581	8.0226	1.297
6	6608	1603.787	8.0136	3.264
7	6823	1550.979	7.7497	3.276
8	6851	1544.080	7.7153	1.124
9	6858	1542.427	7.7070	2.471
10	7148	1471.107	7.3506	2.020
11	7185	1461.826	7.3043	1.806
12	9800	818.410	4.0893	11.780
13	10402	670.251	3.3490	20.423
14	11075	504.482	2.5207	.786
15	11082	502.747	2.5121	.984

fig. 29



(XIII)

MOH / DEPT / DMSO

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AU PROG:
X09.AU
DATE 29-7-6
TIME 19:52

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O1 0658.669
SI 65536
TD 65536
SW 12500.000
HZ/PT .381

PW 0.0
D0 0.0
AQ 2.621
RG 400
NS 2048
TE 297

FW 15700
O2 4089.399
DP 15H D0

LB 1.000
GB 0.0
CX 35.00
CY 10.00
F1 225.241P
F2 -23.144P
HZ/CM 357.132
PPM/CM 7.097
SR 3581.36

fig. 34

CY= 20.3000 IO" CX= 33.000

MI= 2.718

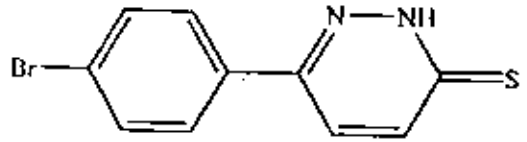
fig. 34

JL2D2F.128

MIN. INTENSITY =	2.718	MAXY = 20.00000	PP CONSTANT = 1.00000
INTENS. LEVEL =	2.718	NOISE = .03633	SENS. LEVEL = .14533
F1 = 7286.40 HZ =	144.7910 PPM	F2 = 4847.66 HZ =	96.3299 PPM

B	CURSOR	FREQUENCY	PPM	INTENSITY
1	11063	7116.614	141.4171	5.086
2	12292	6640.247	131.9510	8.075
3	12916	6438.203	127.9361	10.298
4	13243	6274.300	124.6891	4.084

F1(PPM)= 14.048 12.092



$C_{10}H_7BrN_2S$

Mol. Wt.: 267.14

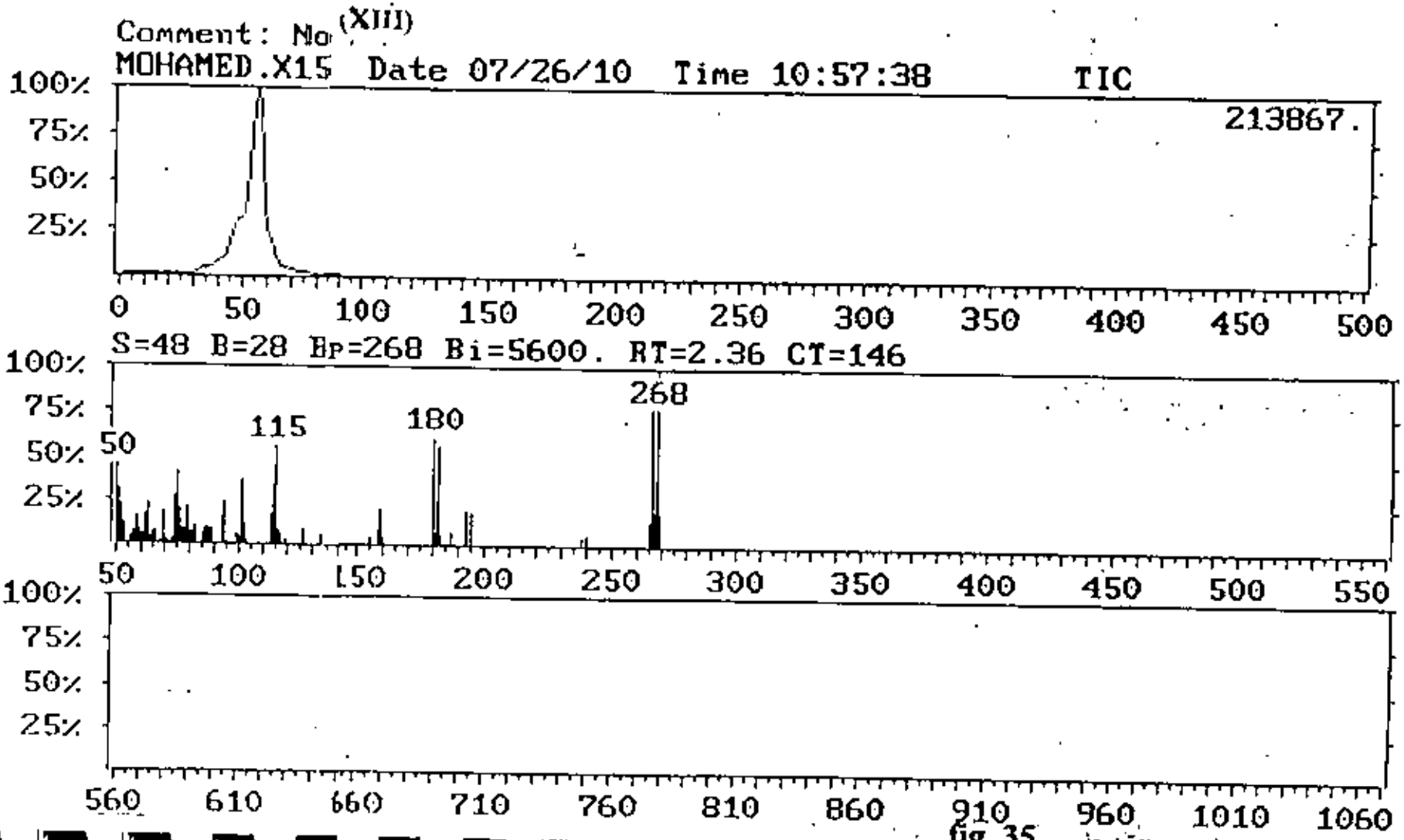


fig. 35

File : MOHAMED.X15 Date 07/26/10 Time 10:57:38
S=48 B=28 Bp=268 Bi=5600. RT=2.36 CT=146

Mass	Int(%)	Mass	Int(%)	Mass	Int(%)	Mass	Int(%)
50	44.1	51	30.7	52	22.0	53	10.7
56	3.8	57	6.4	58	15.0	59	9.1
60	5.5	61	9.5	62	16.1	63	21.6
64	4.8	65	6.8	66	6.8	68	2.1
69	17.5	70	4.8	71	1.4	73	3.0
74	26.4	75	39.6	76	19.1	77	7.9
78	7.9	79	21.4	80	7.1	81	6.4
82	10.2	85	5.2	86	7.9	87	10.2
88	7.9	89	8.8	93	15.4	94	23.8
95	2.1	99	5.7	100	3.8	101	36.3
102	11.6	103	2.7	113	16.4	114	33.0
115	55.0	116	7.9	117	5.9	119	2.7
126	8.4	133	5.4	155	4.6	158	8.6
159	19.1	160	4.6	180	59.6	181	7.1
182	54.5	183	5.9	187	7.0	193	18.8
195	18.4	238	4.3	240	5.7	265	13.4
266	93.0	267	19.3	268	100.0	269	17.7

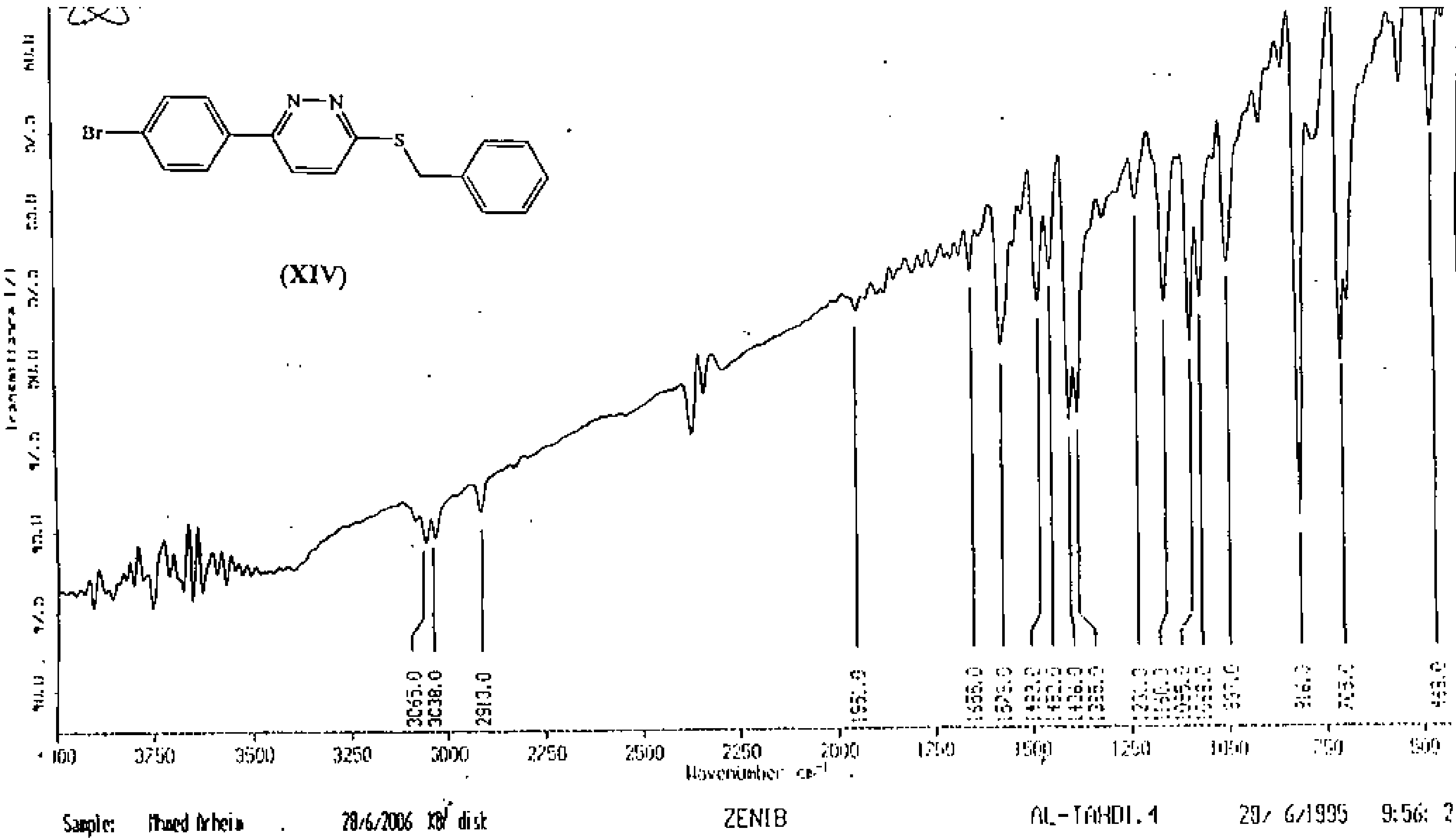
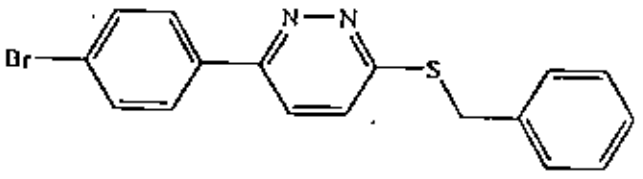

Br
N—N
S
(XIV)
Transmittance [%]
3065.0
3038.0
2913.0
1951.0
1555.0
1526.0
916.0
765.0
449.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample:
28/6/2006 KBr disk
ZENIB
AL-TARDI.4
29/ 6/1995 9:56: 2

fig. 36



$C_{17}H_{13}BrN_2S$

Mol. Wt.: 357.27

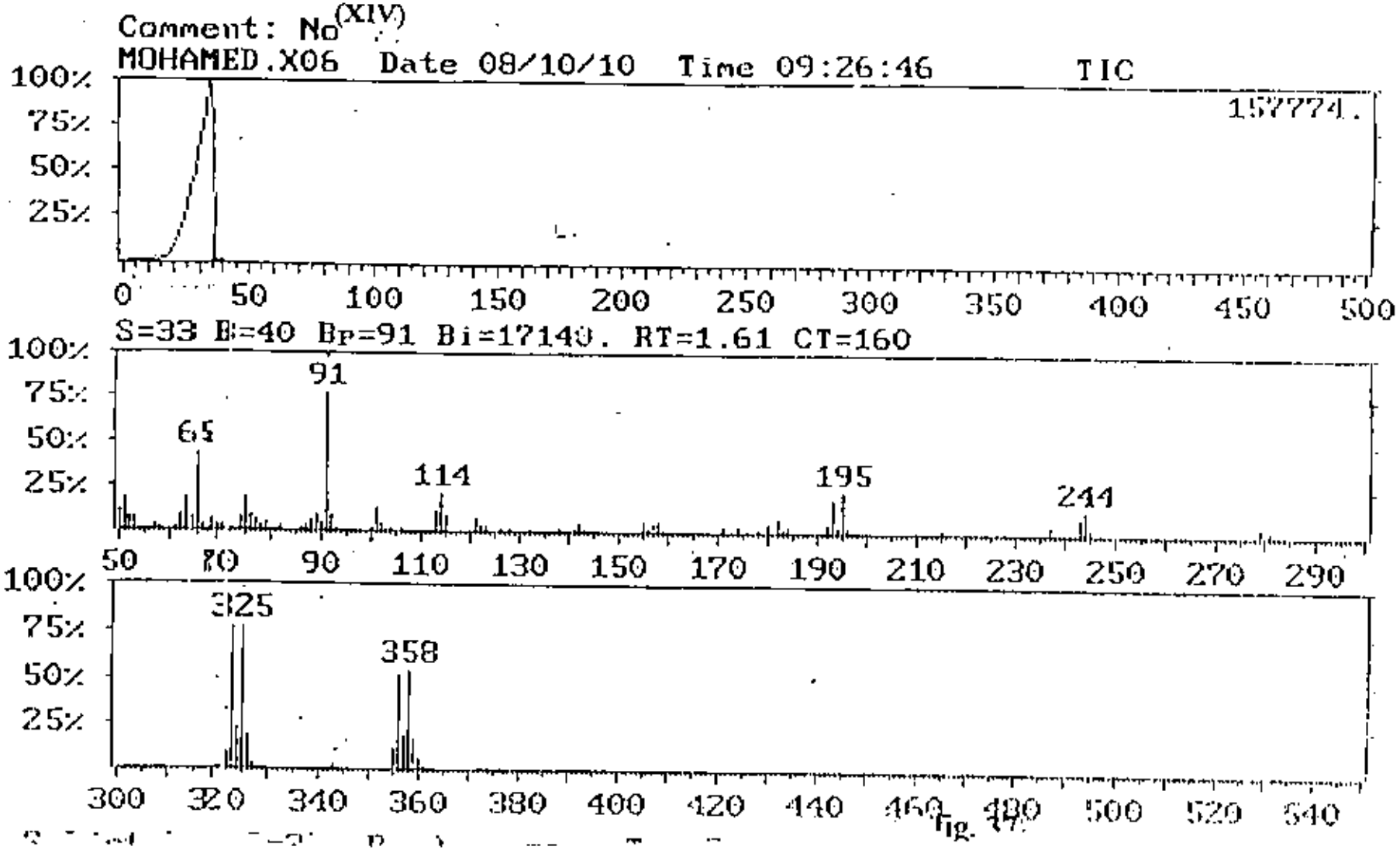


Fig. 47

File : MOHAMED X06 Date 08/10/10 Time 09:26:46
=33 B=40 Bp=91 Bi=17140. RT=1.61 CT=160

Mass	Int(%)	Mass	Int(%)	Mass	Int(%)	Mass	Int(%)
50	11.1	51	17.5	52	6.9	53	6.3
57	2.6	58	2.0	59	0.6	61	1.9
62	7.8	63	18.2	64	7.0	65	42.6
66	3.6	67	0.4	69	5.3	70	2.3
71	3.0	74	6.6	75	18.0	76	8.2
77	6.1	78	3.0	79	4.0	81	1.2
82	2.9	85	1.1	86	2.1	87	3.0
88	6.4	89	8.1	90	3.9	91	100.0
92	8.2	93	2.1	95	1.1	98	0.8
99	0.9	100	1.8	101	12.0	102	4.1
103	2.0	104	1.4	105	0.7	106	1.6
113	11.8	114	20.5	115	8.7	117	1.2
121	7.5	122	2.6	123	3.3	126	1.5
128	1.6	132	1.9	133	0.5	138	1.6
140	0.9	141	2.0	142	4.0	143	1.4
147	1.3	155	5.4	156	2.1	157	3.9
158	6.0	159	1.5	160	0.9	171	2.3
174	2.6	175	1.3	176	2.0	179	1.3
180	3.9	181	1.2	182	7.1	183	1.9
184	3.6	192	4.0	193	18.3	194	3.2
195	22.1	196	2.6	215	2.0	237	3.7
238	1.1	243	8.5	244	12.3	245	3.0
279	3.9	281	3.5	322	8.0	323	87.6
324	22.4	325	98.0	326	18.6	327	2.6
343	3.6	355	11.2	356	51.2	357	16.4
358	53.1	359	16.8	360	6.1	361	1.6
362	1.2						

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ARABIC SUMMARY

ملخص البحوث المبتكرة

لقد وجد بالبحث والدراسة أن تفاعل حمض البارابرومو-4-اوكسو-2-بيتانويك مع الانذول أعطى ناتج الإضافة (II) الذي يتفاعل مع هيدرات الهيدرازين أو الفينيل هيدرازين ليعطي مشتق البيرادازينون(IIIa,b).

كما يتفاعل المركب (II) مع الهيدروكسيل أمين هيدروكلوريد في وجود البيريدين ليعطي مشتق الاوكسازينون (IV) وأيضا يمكن حولقه المركب (II) إلى مشتق البيوتونليد (V).

وقد وجد أن الكلة مشتق البيرادازينون (IIIa) بكبريتات ثنائي الميثيل ، يوديد الايثيل ، الفورمالدهيد و الميثانول او كلورو خلات الايثيل أعطت مشتق N-الإحلال للبيرادازينون (VIa-d). كما تم تفاعله مع الالدهيدات الاروماتية مثل البنزالدهيد ، البارميتوكسي بنزالدهيد و البارانيترو بنزالدهيد مكونا المركبات (VIIa-c).

وعند تفاعل مشتق البيرادازينون (IIIa) مع أو كسي كلوريد الفوسفور لمدة ثلاث ساعات أعطى المركب غير متوقع 3-كلوروبيرادازين (VIII) وذلك من خلال كسر حلقه الانذول و إحلال مجوعة الهيدوكسيل بالكلور وقد وضعت الميكانيكية المناسبة لهذا التفاعل.

وقد تم دراسة تفاعل المركب السابق (VIII) مع هيدرات الهيدرازين و الفينيل هيدرازين ليعطي مشتقات الهيدرازينو (IXa,b) و كذلك تفاعل مع البنزيل أمين ، البيوتيل أمين ليعطي المشتقات (X) ، (XI).

أيضا تفاعل مشتق الكلوروبيرادازين مع الثيويوريا ليكون مشتق البيرادازين-3-ثيون(XIII) الذي يتفاعل مع كلوريد البنزيل ليعطي مشتق ال S- بنزيل-بيرادازين (XIV).

وهذا وتم وضع ميكانيكية لشرح المركبات الناتجة وتم إثبات تراكيب النواتج المختلفة بالطرق الكيميائية و الوسائل الطيفية المختلفة . وتم إجراء دراسة مختصرة للتأثير البيولوجي لبعض المركبات الناتجة.

بسم الله الرحمن الرحيم

﴿ دَعْوَاهُمْ فِيهَا سُبْحَانَكَ اللَّهُمَّ وَتَحِيَّتُهُمْ فِيهَا سَلَامٌ وَآخِرُ دَعْوَاهُمْ
أَنِ الْحَمْدُ لِلَّهِ رَبِّ الْعَالَمِينَ ﴾ يونس 10

صدق الله العظيم

كلية العلوم

قسم الكيمياء

عنوان البحث

((تحضير و بعض تفاعلات لمستبدل مشتقات البيرادازينيون))

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