AL-TAHADY UNIVERSITY
FACULTY OF SCIENCE
CHEMISTRY DEPARTMENT

M. Sc. Thesis Entitled

SYNTHESIS OF SOME NEW PURINE-RELATED COMPOUNDS WITH EXPECTED BIOLOGICAL ACTIVITY

SUBMITTED BY
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UNDER SUPERVISION OF
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SIRTE - LIBYA

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بسم الله الرحمن الرحيم

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

صدق الله العظيم

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No words can ever express my sincere gratitude to ***Allah*** *who guide, aid, and bless me in every thing and everywhere in my life.*

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I owe great thanks and sincere love to my family who supported me during difficult and hard times.

Tajdida Bashir Al-Shibani

To my

Father, Mother, Brothers,

And Sisters

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CONTENTS

SUMMARY OF THE ORIGINAL WORK

1- Summary of the original work

Synthesis of some new purine-related compounds

1.1 Regioselective one-pot synthesis of novel tetrazolo[1,5-*a*]-pyrimidine derivatives:

Tetrazolopyrimidines play an essential role in several biological processes and have very important chemical and pharmacological importance. In this work, we described an easy and efficient route for the synthesis of tetrazolopyrimidines by the reaction of 5-aminotetrazole and the early-synthesized sodium salts of formyl ketones (**2**). Thus, treatment of 5-amino-1*H*-tetrazole hydrate (**4**) with the sodium formyl salts of cyclic ketones, namely sodium (2-oxocycloalkylidine)methenoates (**2**) in the presence of aqueous piperidine acetate and acetic acid as a one-step reaction, afforded in a good yield the cycloalkane ring-fused tetrazolo[1,5-*a*]pyrimidines (**6**) as outlined in chart (1).

The characterization of the reaction products was confirmed by using the available elemental analysis and spectral data (IR, Ms, ^{1}H NMR).

1.2 Synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives as purine analogues:

Pyrazolopyrimidine systems are reported in literatures as inhibitors for the synthesis of DNA and RNA in the cells of some kinds of cancers

and viruses and generally possess a potent biological and pharmaceutical effect.

In this part, an interesting series of pyrazolopyrimidines were prepared through the reaction of aminopyrazoles with the sodium formyl salts of cyclic and acyclic ketones. Thus, the reaction of 3,4-disubstitued 5-aminopyrazoles (**9**) with the formyl salts (**2**) afforded in an excellent yield the pyrazolo[1,5-*a*]pyrimidine derivatives (**10a-y**) under the same reaction condition and following the same reaction mechanism discussed in the preparation of tetrazolopyrimidines (**6**).

The structures of compounds (**10**) were confirmed using their elemental analysis and spectral data (IR, Ms, ^{1}H NMR).

The behavior of aminopyrazoles towards the sodium formyl salts of aliphatic and aromatic acyclic ketones was also investigated. Thus, some selected derivatives of the 5-aminopyrazoles (**9**) were condensed with sodium formylacetone (**11**) in piperidine acetate and acetic acid to afford the 2-anilino-7-methyl-*N*-arylpyrazolo[1,5-*a*]pyrimidine-3-carboxamides (**12**). Other derivatives of the aminopyrazoles (**9**) were allowed to react with sodium formyl acetophenone (**13**) as acyclic aromatic ketone to give the 2-anilino-7-phenyl-*N*-arylpyrazolo[1,5-*a*]-pyrimidine-3-carboxamides (**14**) as shown in chart (2).

The structures of the newly synthesized compounds were confirmed by using the elemental analysis and the spectral data (IR, Ms, ^{1}H NMR).

1.3 Novel synthesis of 3*H*-pyrimido[1,6-*a*]pyrimidine derivatives :

Pyrimidopyrimidines are an important class of annulated uracil and thiouracil of biological importance. Recently, pyrimidopyrimidines, analogues of folic acid (one of the B vitamins that are a key factor in the

synthesis of nucleic acids RNA and DNA) have been screened for anti-tumor activity. Thus, fusion of 6-aminothiouracil with the formyl salts of cyclic ketones (**2**) in piperidine acetate and acetic acid afforded in considerable yields the cyclocondensed pyrimido[1,6-*a*]pyrimidines (**16a-d**) as outlined in chart (3).

The identity of compounds (**16**) was proven on the basis of their elemental analysis and spectral data (IR, Ms, ^{1}H NMR).

A successful trying for establishment of the phenomenon has been carried out by the reaction of 6-aminothiouracil with the sodium salts of acyclic ketones (**11**) and (**13**) under the same reaction conditions to afford 4-methyl-6-thioxo-6,7-dihydro-8*H*-pyrimido[1,6-*a*]pyrimidin-8-one (**17**) and 4-phenyl-6-thioxo-6,7-dihydro-8*H*-pyrimido[1,6-*a*]pyrimidin-8-one (**18**) respectively. Chart (3).

The structures of the reaction products were confirmed using their elemental analysis and spectral data (IR, Ms. ^{1}H NMR).

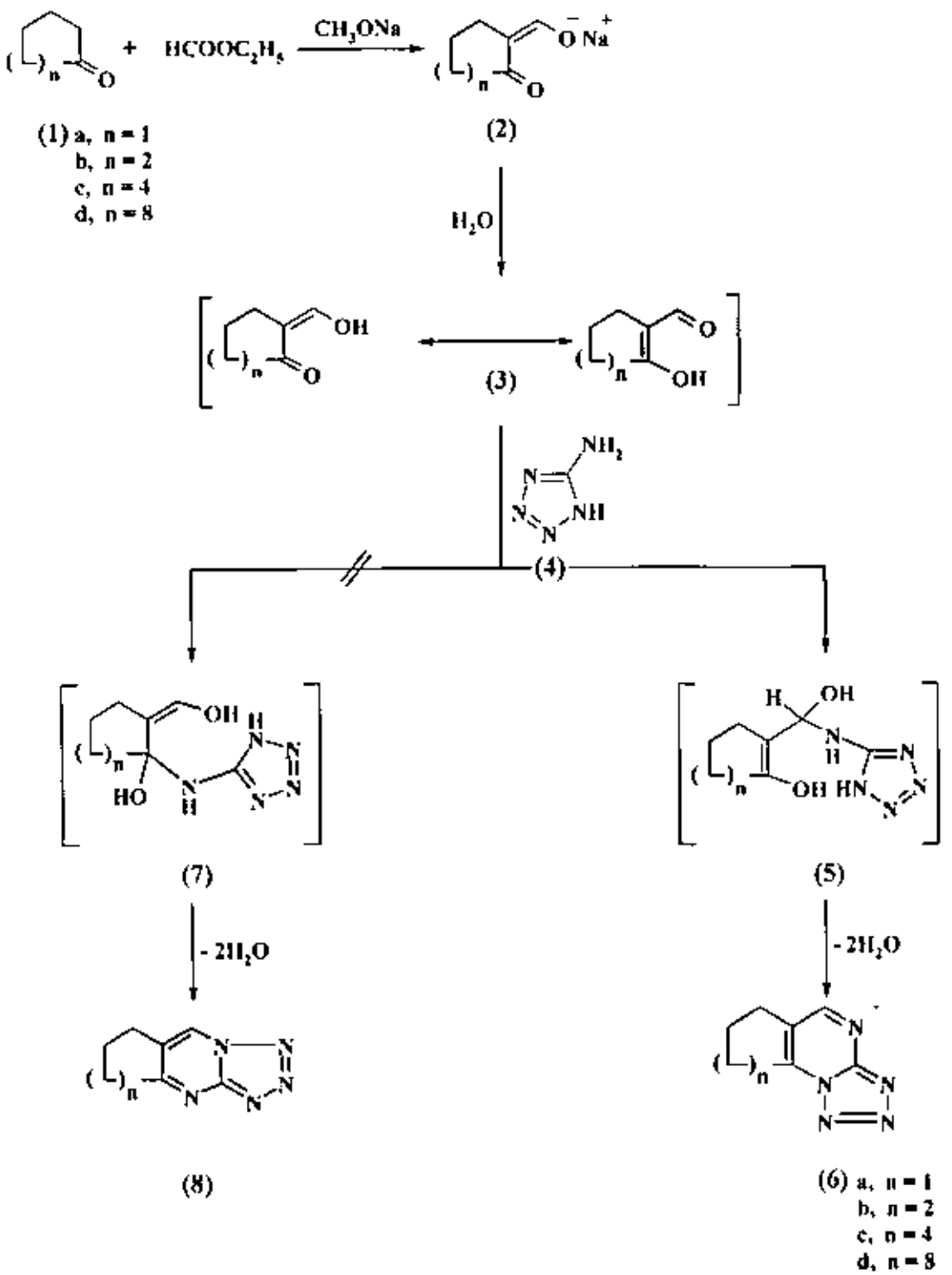
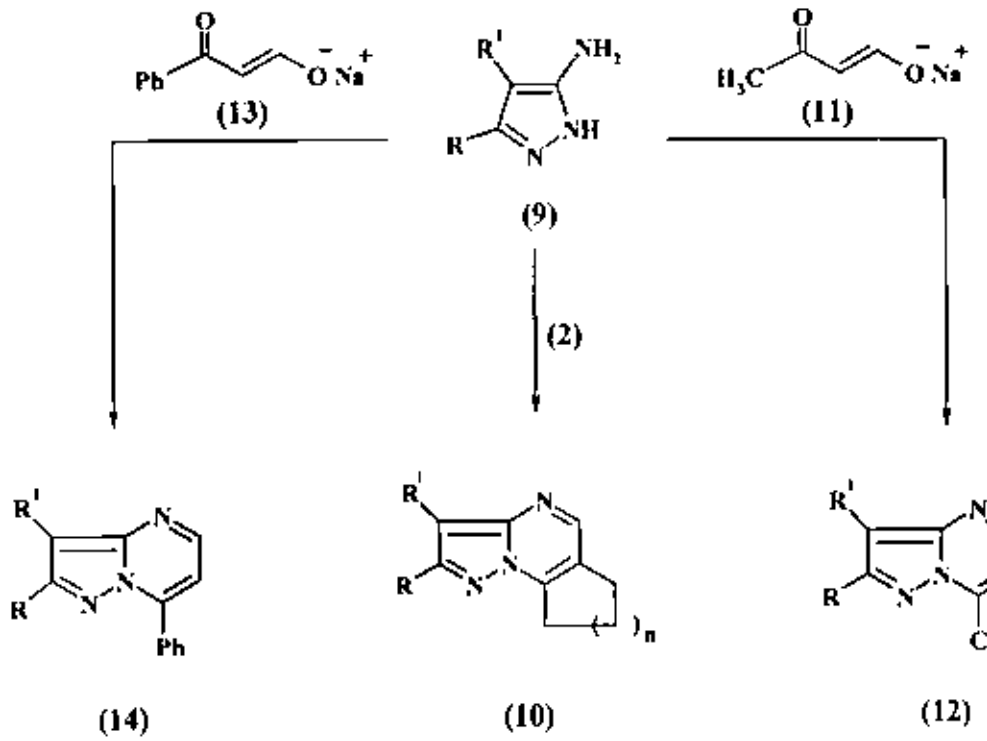

CH3ONa
HCOOC2H5
(1) a, n = 1
b, n = 2
c, n = 4
d, n = 8
(2)
H2O
(3)
(4)
(7)
(5)
- 2H2O
- 2H2O
(8)
(6) a, n = 1
b, n = 2
c, n = 4
d, n = 8

Chart (1)



(14)	R	R^1
a	NHPh	CONHPh
b	NHPh	CONHPhMe-p
c	NHPh	CONHPhCl-p
d	NHPh	CONHPhOMe-p
e	NHPh	CONHPhBr-p
f	NHPhCl-p	CONHPhMe-p
g	NHPhCl-p	CONHPhCl-p
h	NHCOPh	CONHPh

(12)	R	R^1
a	NHPh	CONHPh
b	NHPh	CONHPhMe-p
c	NHPh	CONHPhCl-p

Chart (2)

(10)	n	R	R^1	(10)	n	R	R^1
a	1	NHPh	CONHPh	q	4	NHPh	CONHPh
b	1	NHPh	CONHPhMe-p	r	4	NHPh	CONHPhMe-p
c	1	NHPh	CONHPhCl-p	s	4	NHPh	CONHPhCl-p
d	1	NHPh	CONHPhOMe-p	t	4	NHPhCl-p	CONHPhCl-p
e	1	NHPh	CONHPhBr-p	u	4	NHCOPh	CONHPh
f	1	NHPhCl-p	CONHPhMe-p	v	8	NHPh	CONHPh
g	1	NHPhCl-p	CONHPhCl-p	w	8	NHPh	CONHPhMe-p
h	1	NHCOPh	CONHPh	x	8	NHPh	CONHPhCl-p
i	2	NHPh	CONHPh	y	8	NHCOPh	CONHPh
j	2	NHPh	CONHPhMe-p				
k	2	NHPh	COPNHPhCl-p				
l	2	NHPh	CONHPhOMe-p				
m	2	NHPh	CONHPhBr-p				
n	2	NHPhCl-p	CONHPhMe-p				
o	2	NHPhCl-p	CONHPhCl-p				
p	2	NHCOPh	CONHPh				

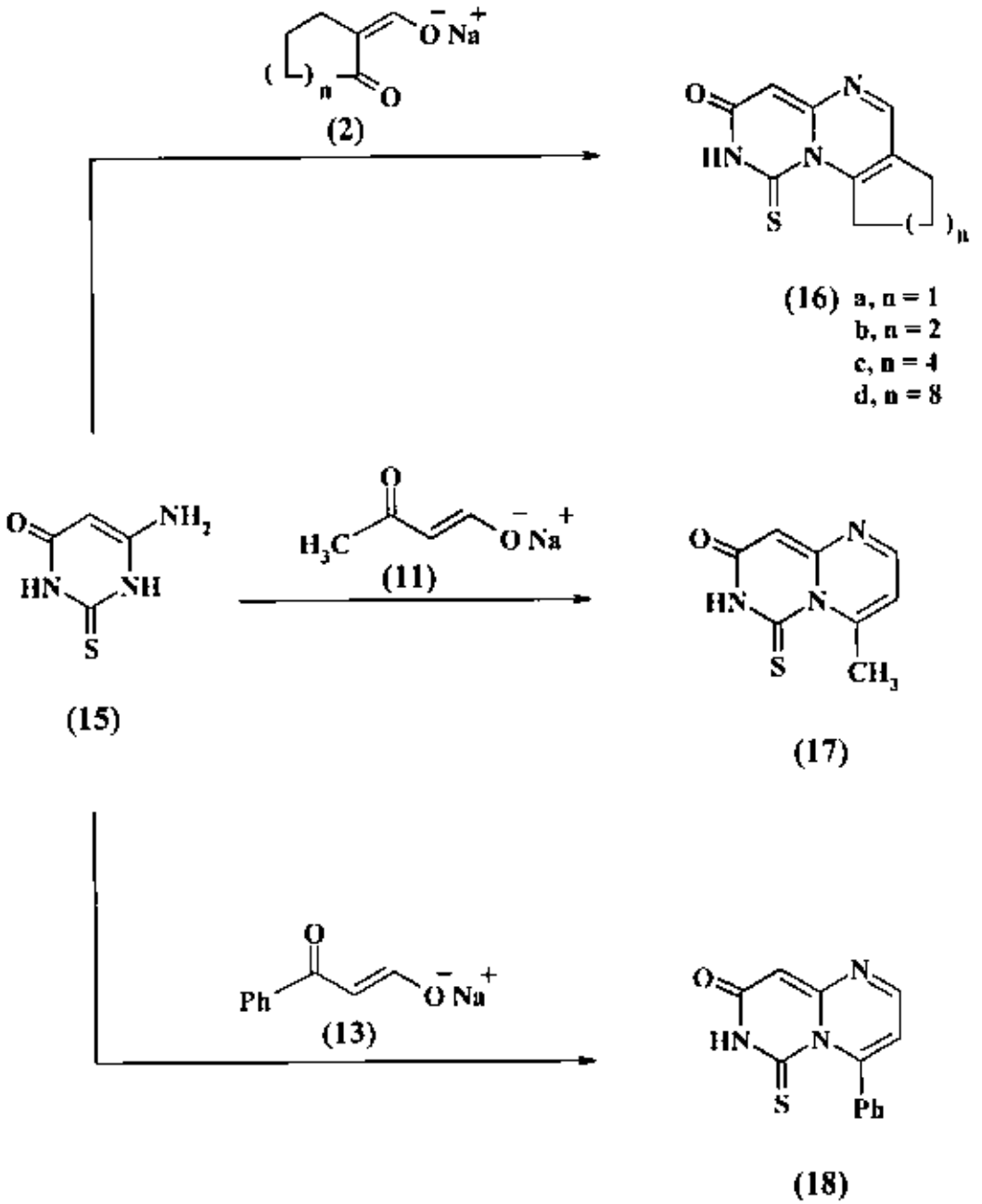


Chart (3)

INTRODUCTION

2. Introduction

2.1 Synthesis and chemistry of pyrazolopyrimidines and their biological activities

. Chemistry associated with genes has attracted a great public interest during the last two decades. Nucleotides are the backbone of the nucleic acid molecules. The common pyrimidine bases in nucleotides are cytosine, thymine and uracil.

The two common purine bases in nucleic acids are adenine and guanine. Pyrazolopyrimidine derivatives are very important in the fields of medicinal chemistry and chemotherapy as they have antimetabolic, (anticancer, antiviral and antitumor), microbiological and pharmacological effects[1-50]. Consequently, the search for new molecules which exhibit high therapeutic indexes is today of great interests for research.

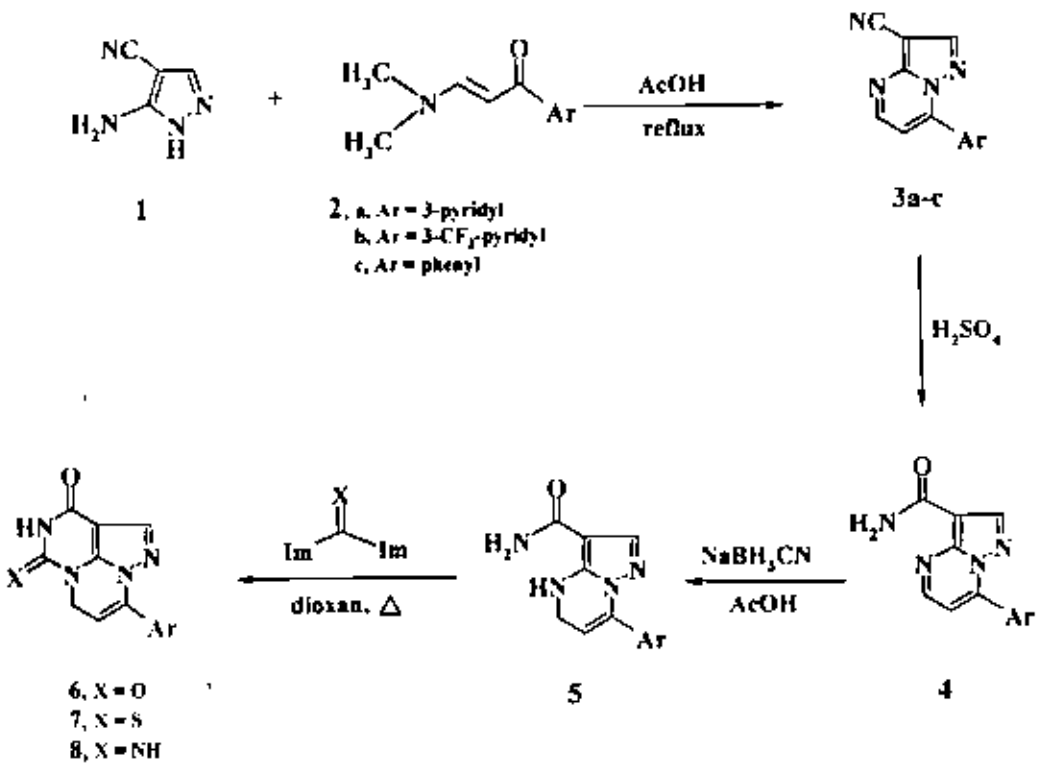
Pyrazolopyrimidines may be divided into:
pyrazolo[1,5-*a*], [1,5-*c*], [2,3-*d*], [3,4-*d*], [4,3-*d*] and [5,4-*d*] pyrimidines.

The following contains an up to date survey of most important preparations, chemical properties and biological activities of the different categories pyrazolopyrimidines.

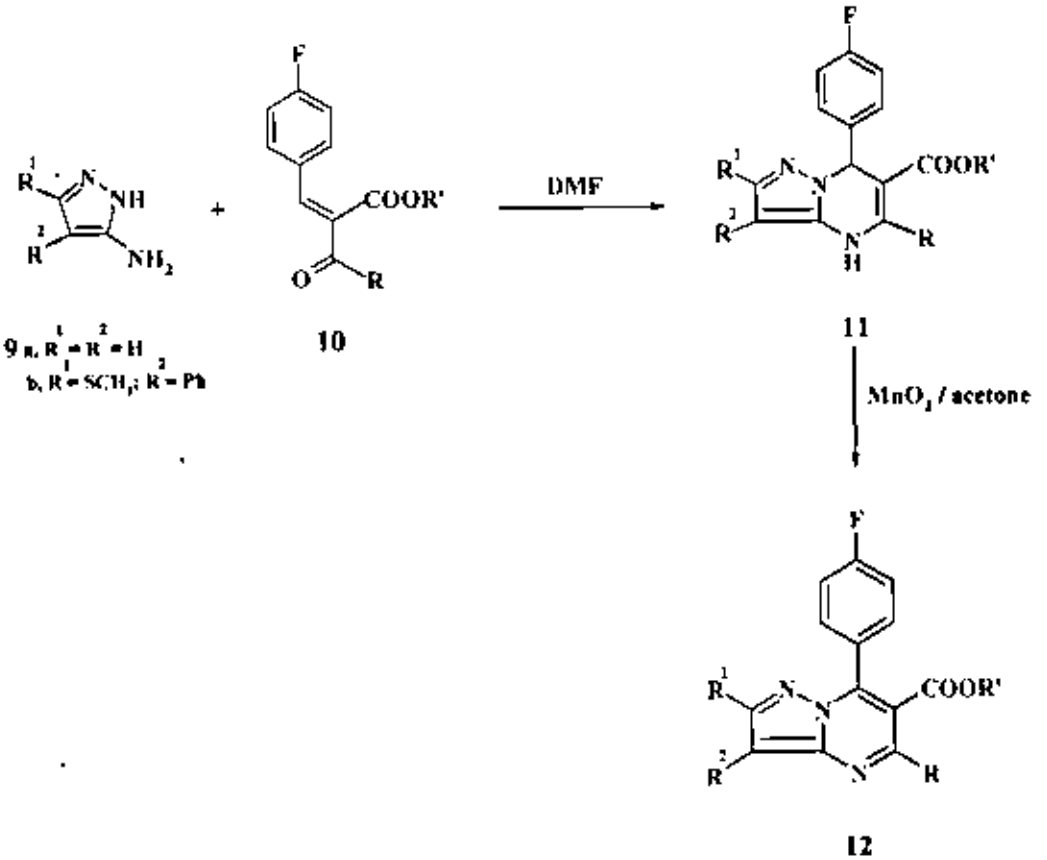
2.1.1 Pyrazolo[1,5-*a*] pyrimidine derivatives:

It has been reported that 7-arylpyrazolo[1,5-*a*]pyrimidines **3a-c** could be constructed through the reaction of 4-cyano-3-aminopyrazole **1** with aryl enaminones **2a-c** in refluxing acetic acid. The cyano compound **3a** could be hydrolyzed to the amide **4**. Sodium cyanoborohydride in acetic acid converted compounds **4** into 4,5-dihydropyrazolo[1,5-*a*]-

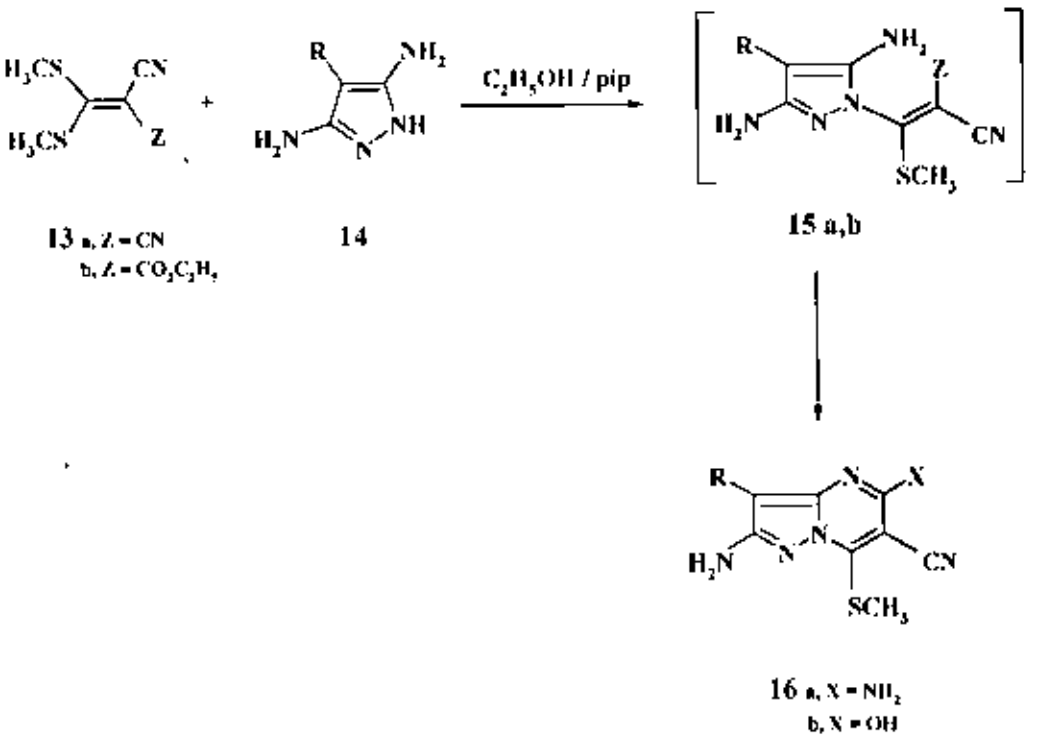
pyrimidines 5, which could be reacted with carbonyl diimidazole in refluxing dioxan to give the diones **6-8**.[51-53]



Cyclocondensation of the substituted aminopyrazoles **9** with benzylidene keto esters **10** followed by oxidation with manganese oxide resulted in the preparation of pyrazolopyrimidine derivatives **12**.[54]



Elgemeie et al.,[55-56] reported that the reaction of bis(methylthio)-methylene malononitrile **13a** and ethyl 2-cyano-3,3-bis(methylthio)-acrylate **13b** with pyrazole derivatives **14** afforded the 7-methylthio-pyrazolo[1,5-a]pyrimidines **16a,b** through the intermediates **15a,b**.



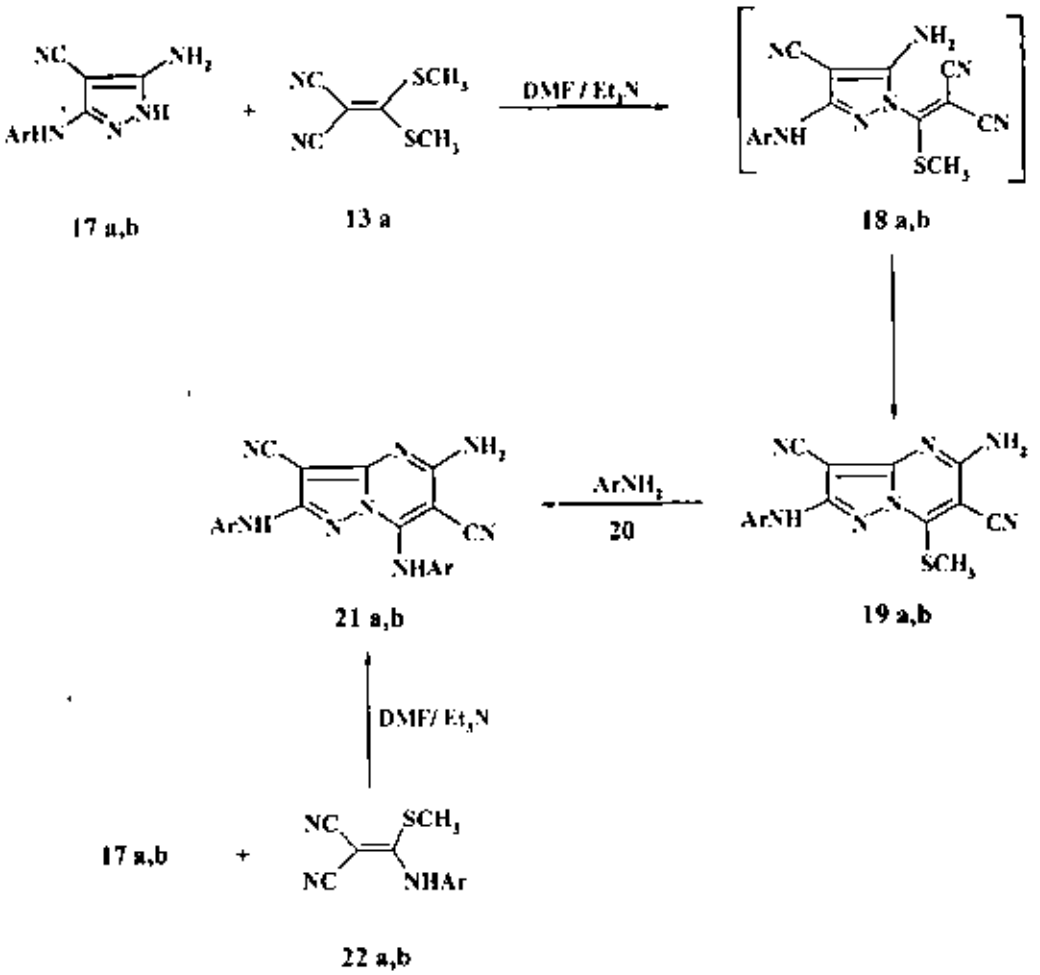
13 a, Z = CN
b, Z = $CO_2C_2H_5$

14

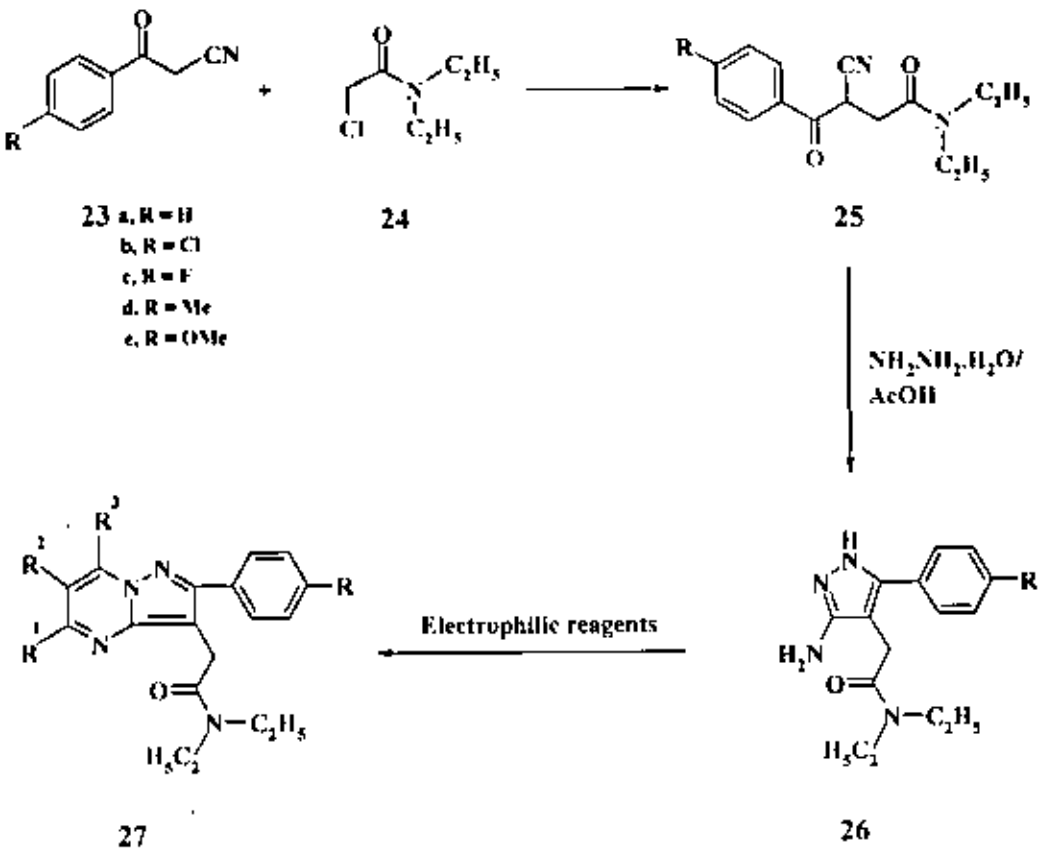
15 a,b

16 a, X = NH_2
b, X = OH

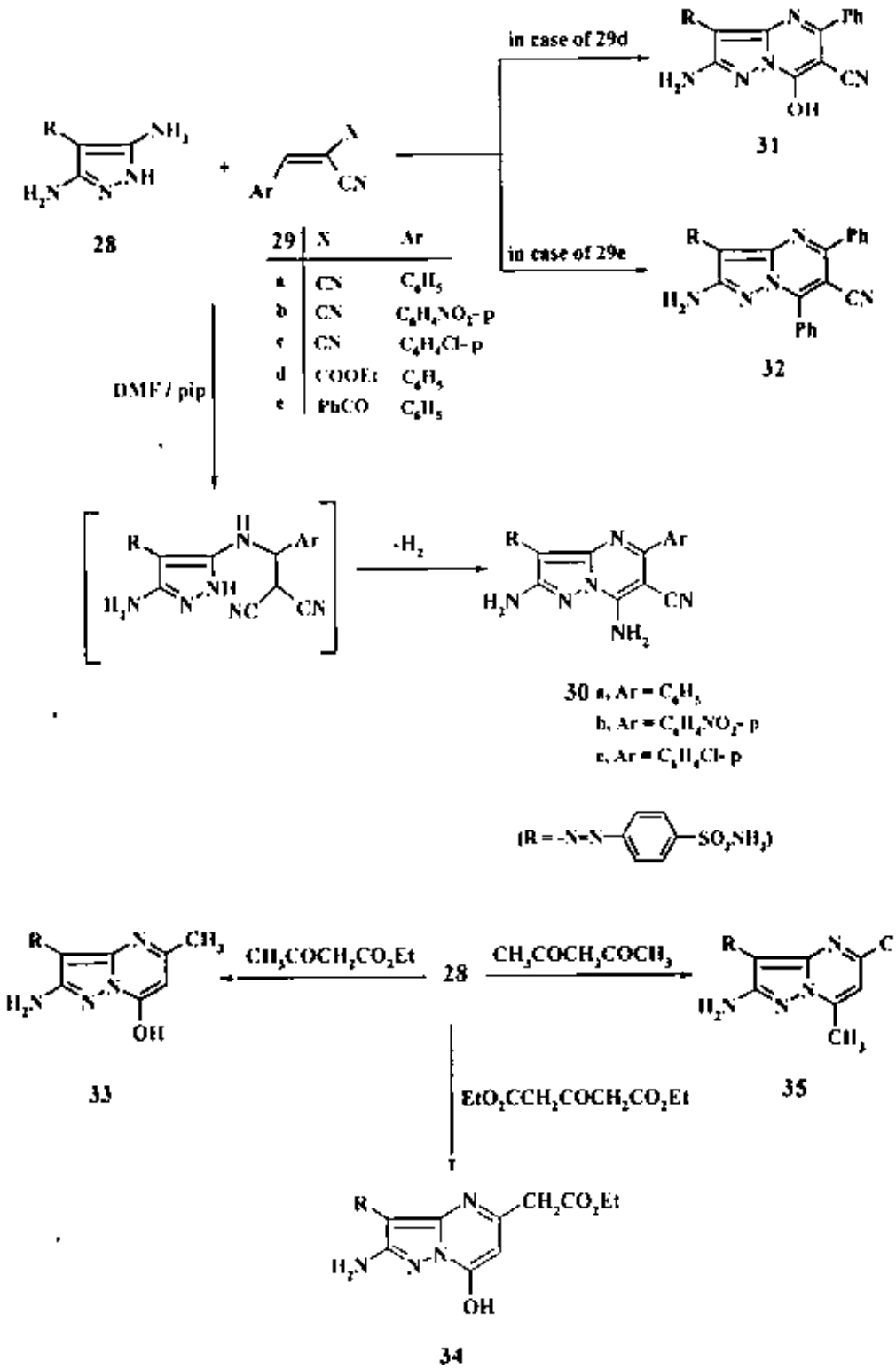
Similarly, Zaharan et al., has reported that the reaction of [bis(methylthio) methylene]malononitrile **13a** with aminopyrazoles **17a,b** afforded the corresponding pyrazolo[1,5-*a*]pyrimidines **19a,b** through the intermediacy of **18**. Fusion of **19** with aromatic amines **20** at 140°c furnished the corresponding anilino derivatives **21a,b**. Also, the reaction of aminopyrazoles**17a,b** with [(arylamino)(methylthio)methylene]-malononitriles **22a,b** gave the same pyrazolopyrimidines **21a,b**.[57-60]



The reaction of aroylacetonitriles **23** with *N,N*-diethylchloroacetamide **24** in alkaline medium produced *N,N*-diethyl-butanamides **25**, which were reacted with hydrazine hydrate to give the corresponding *N,N*-diethyl-(3-amino-5-arylpyrazol-4-yl)acetamides **26**. Condensation of **26** with the suitable electrophilic reagents (such as: *β*-diketones, *β*-ketoaldehydes or their acetals) led to the closure of the pyrimidine ring affording the pyrazolo[1,5-*a*]pyrimidine-3-yl-acetamides **27**.[61]

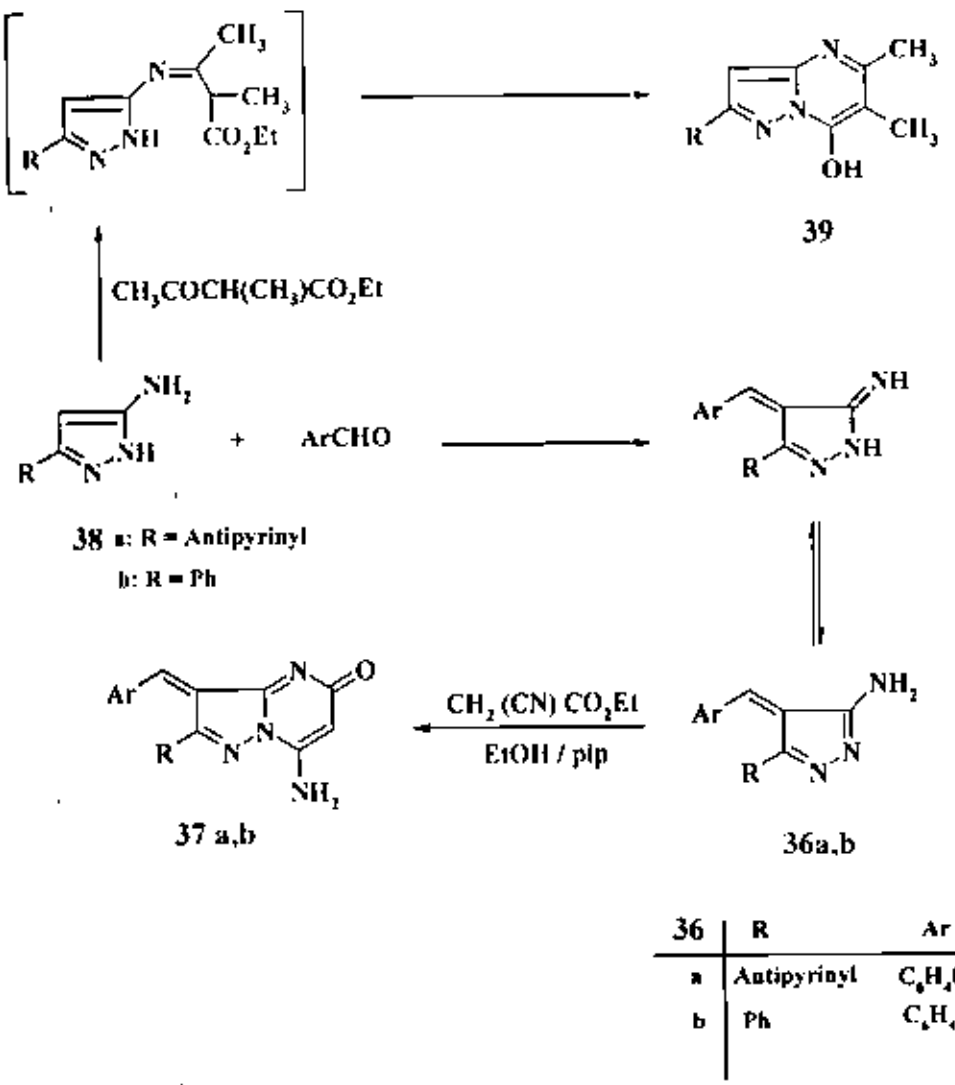


The reaction of pyrazole derivative **28** with an equimolar amount of α-substituted cinnamonitriles **29a-e** provided pyrazolopyrimidine derivatives **30a-c**, **31** and **32**. Also. compound **28** could be condensed with ethyl acetoacetate, diethyl acetonedicarboxylate and acetylacetone to yield different pyrazolo[1,5-*a*]pyrimidine derivatives **33**, **34** and **35** respectively.[62]



Condensation of 5-amino-4-arylidenepyrazoles **36a,b** with ethyl cyanoacetate afforded the pyrazolo[1,5-*a*]pyrimidine derivatives **37a,b.**

the reaction of 5-amino-2-antipyrinylpyrazole **38a** with ethyl α-methyl acetoacetate in glacial acetic acid to give the pyrazolo[1.5-*a*]pyrimidines **39** was also reported.[62]



38 a: R = Antipyrinyl
b: R = Ph

39

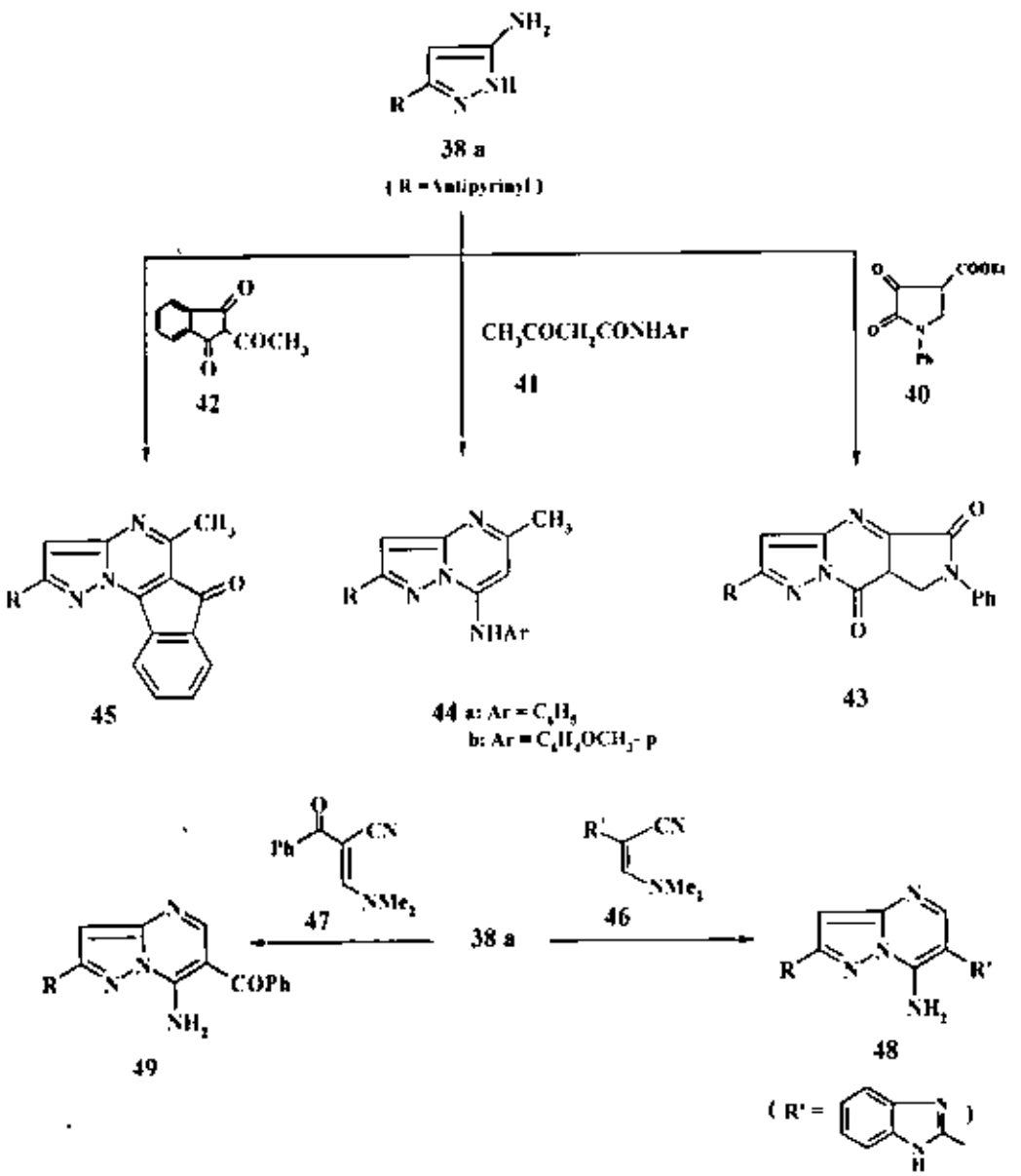
36a,b

37 a,b

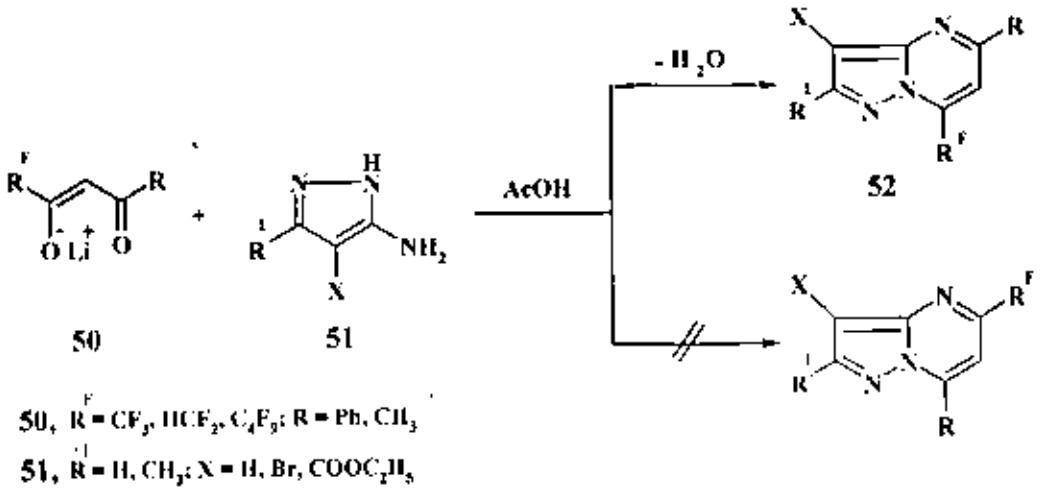
36	R	Ar
a	Antipyrinyl	C_6H_4OH-o
b	Ph	C_6H_4Br-p

Similarly, compound **38a** reacted with the cyclic β-ketoester **40**, acetoacetanilides **41** in glacial acetic acid and 2-acetyindan-1,3-dione **42** in ethanol catalyzed by acetic acid under reflux to afford pyrazolopyrimidine derivatives **43**, **44** and **45** respectively. Also, compound **38a** could be reacted with 3-dimethylamino-2-(benzimidazol-2-yl)propenenitrile **46** or 3-(dimethylamino)-2-benzoyl propenonitrile **47**

in refluxing ethanol catalyzed by acetic acid to give the pyrazolo[1,5-*a*]-pyrmidine derivatives **48** or **49** respectively.[63]



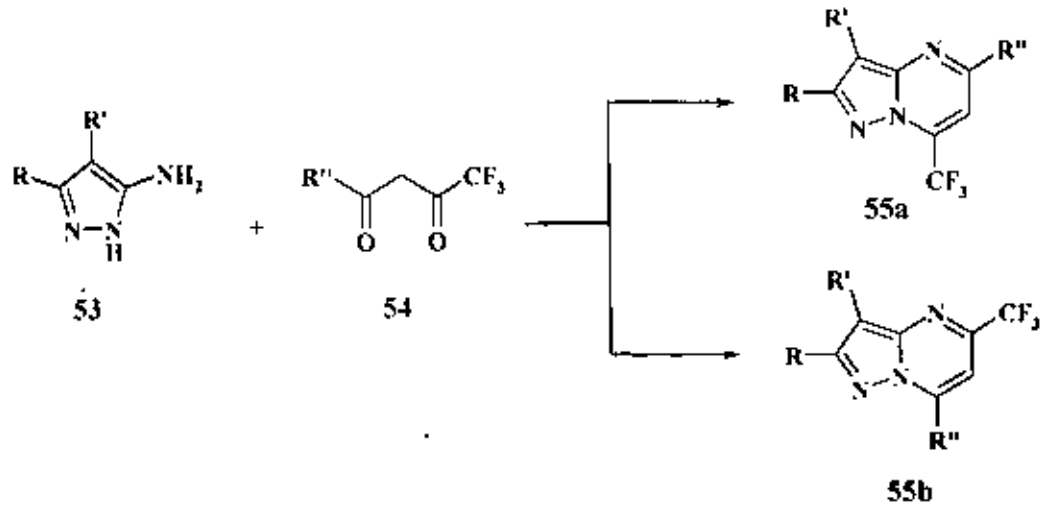
Filyakova et al.,[64] studied the reaction of lithium enolates of fluorine-containing *β*-diketones **50** with 3-aminopyrazoles **51** that afforded (7-polyfluoroalkyl)pyrazolo[1,5-*a*]pyrimidines **52**.



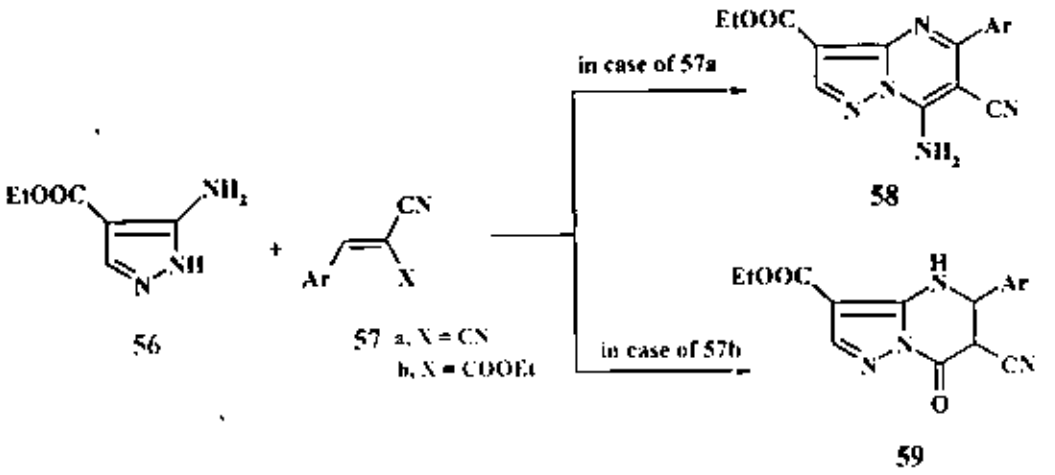
50, $R^F = CF_3, HCF_2, C_4F_9$; R = Ph, CH_3

51, $R^1 = H, CH_3$; X = H, Br, $COOC_2H_5$

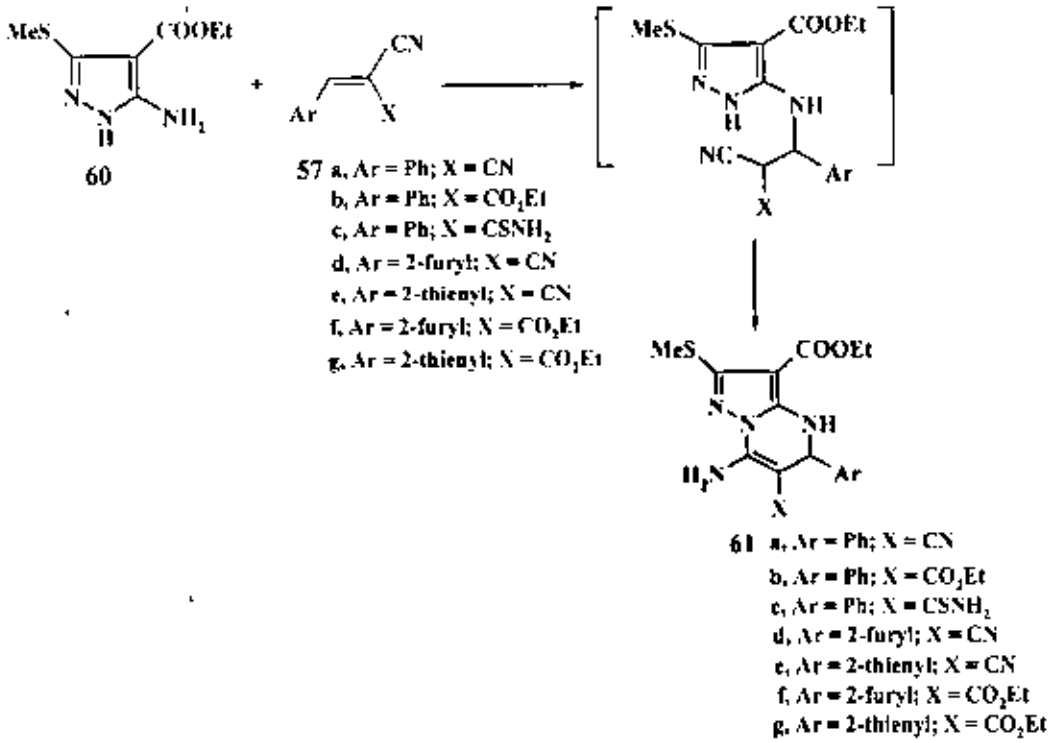
However, it was reported that the reaction of aminopyrazole derivatives **53** with trifluoromethyl diketones **54** resulted in the synthesis of a mixture of pyrazolo[1,5-*a*]pyrimidine derivatives **55a** and **55b**.[64]

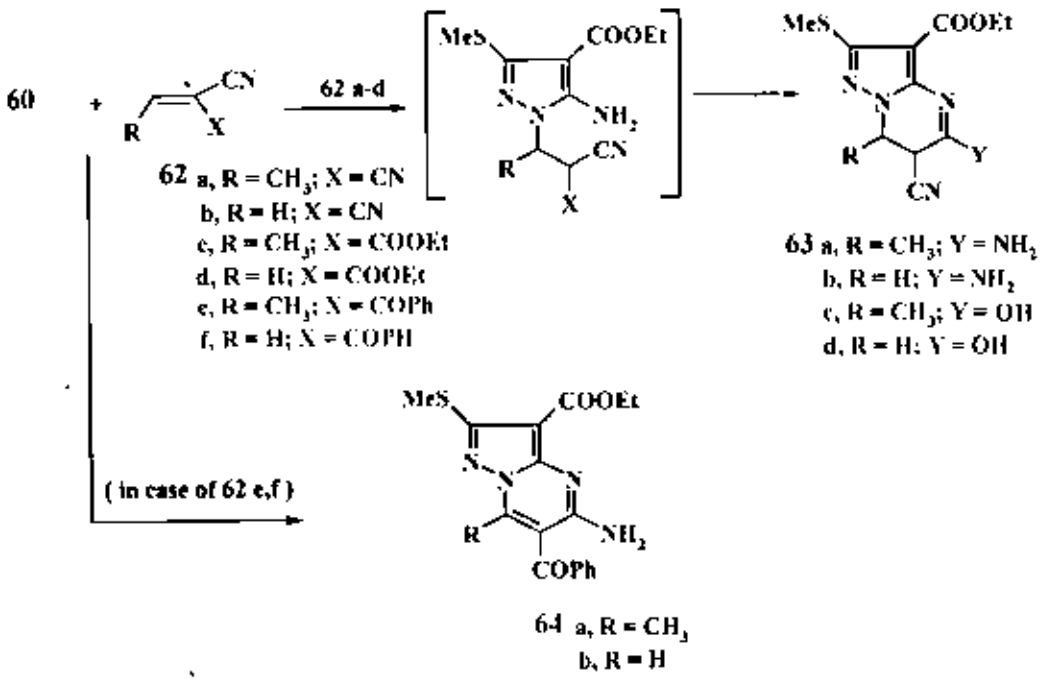


Refluxing of ethyl 5-amino-(*1H*)-pyrazole-4-carboxylate **56** with *α*-cyanocinnamonitriles **57a** or ethyl *α*-cyanocinnamates **57b** in pyridine led to the formation of ethyl 7-amino-5-aryl-6-cyanopyrazolo[1,5-*a*]pyrimidine-3-carboxylates **58** or ethyl 5-aryl-6-cyano-7-oxo-(*4H*),(*7H*)-pyrazolo[1,5-*a*]-pyrimidine-3-carboxylates **59** respectively.[65]

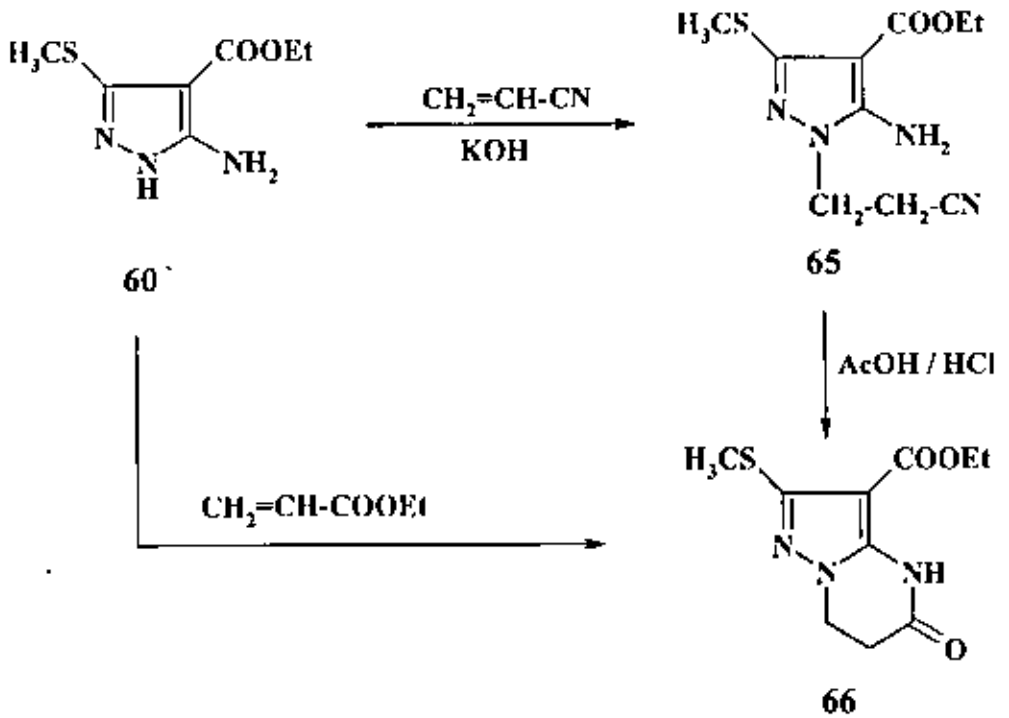


Raslan et al.,[66] reinvestigated some earlier works that discussed the reaction of 5- aminopyrazoles derivative **60** with cinnamonitriles **57** and has reported that the reaction of the aminopyrazole derivative **60** with **57a-g** afforded 7-amino pyrazolo[1,5-*a*]pyrimidine derivatives **61a-f**. Also, compound **60** was found to react with **62a-d** to yield the pyrazolo[1,5-*a*]pyrimidine derivatives **63a-d.** Whereas, the reaction of **60** with **62e,f** was reported to afford the 5-aminopyrazolo[1,5-*a*]pyrimidine derivatives **64a,b** [66-69]

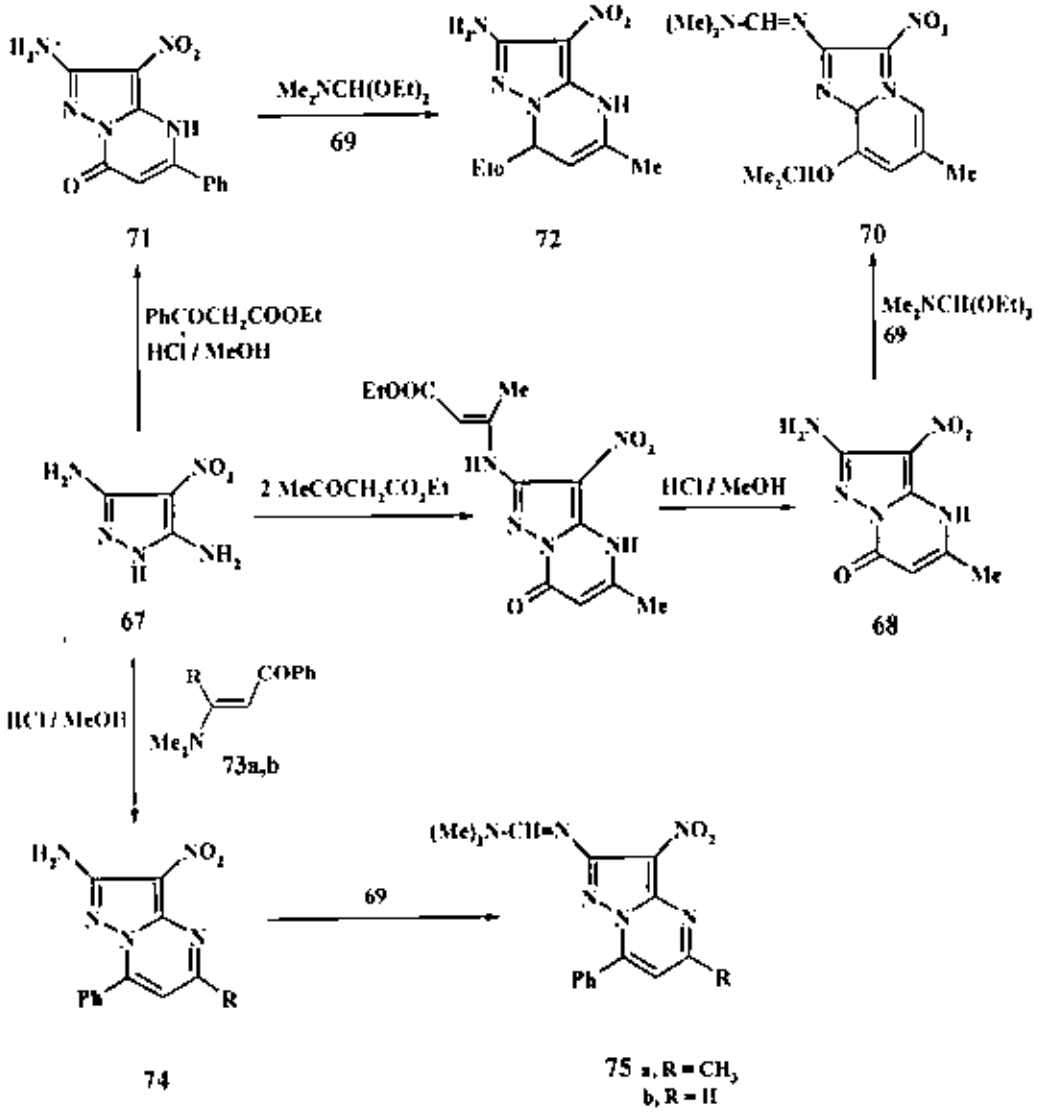




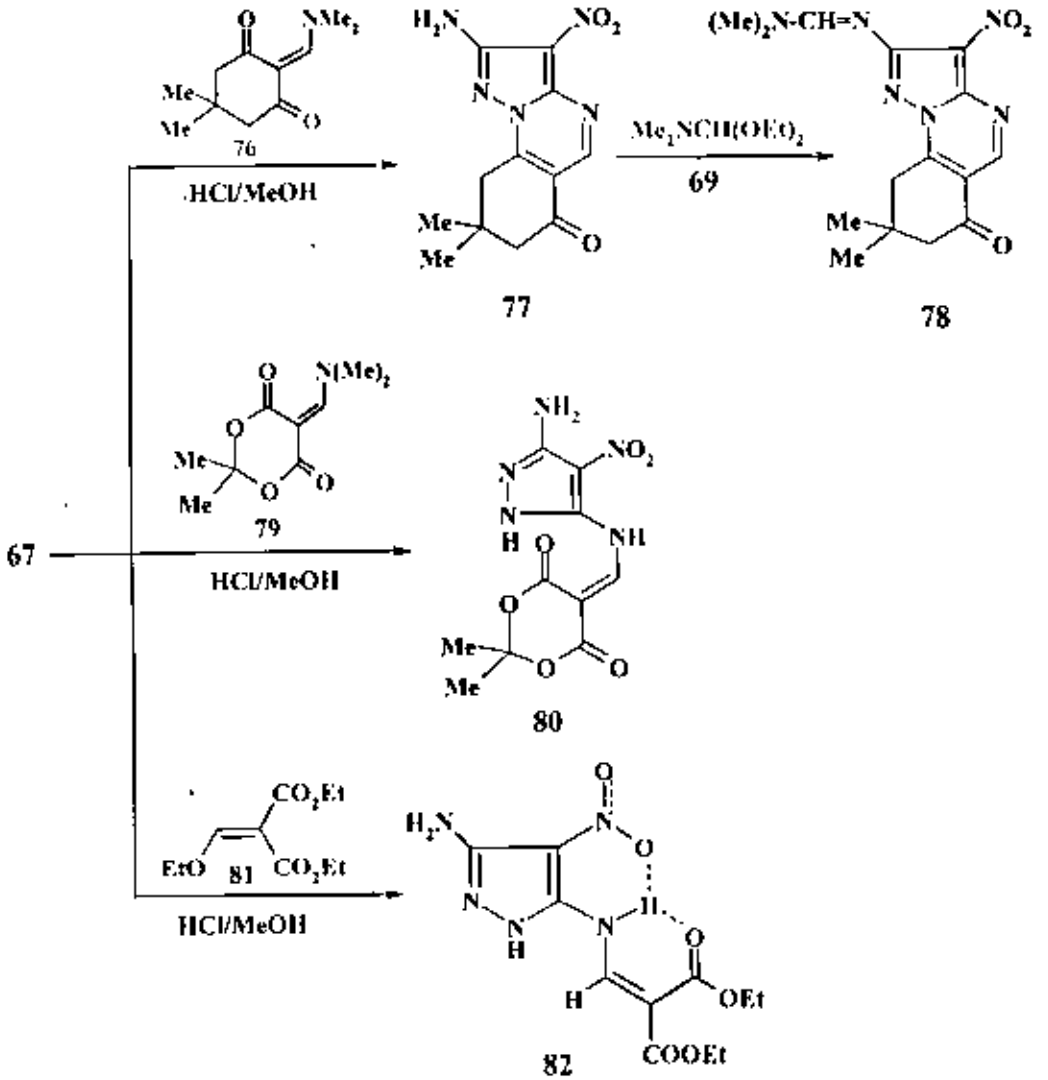
Moreover, compound **60** reacted with acrylonitrile in basic medium to yield the pyrazole-4-carboxylate derivative **65**. Cyclization of **65** in acidic medium afforded the pyrazolopyrimidine derivative **66** which could be obtained from the reaction of compound 60 with ethyl acrylate.[66-69]



It has been found that 3,5-diamino-4-nitropyrazole **67** [70] reacted with ethyl acetoacetate in the presence of methanolic hydrochloric acid to form pyrazolo[1,5-*a*]pyrimidine derivative **68.** Compound **68** was reacted with dimethylformamide diethylacetal **69** to yield pyrazolopyrimidine derivative **70**. In a similar manner, compound **67** reacted with benzoylacetic ester to yield compound **71**, which on reacting with acetal **69** transformed to compound **72**. Also, the reaction of compound **67** with *a*-dimethylaminoethylidene acetophenones **73a,b** yielded the bicyclic compounds **74**, which were converted into amidines **75** by the reaction with acetal 69.[71-76]

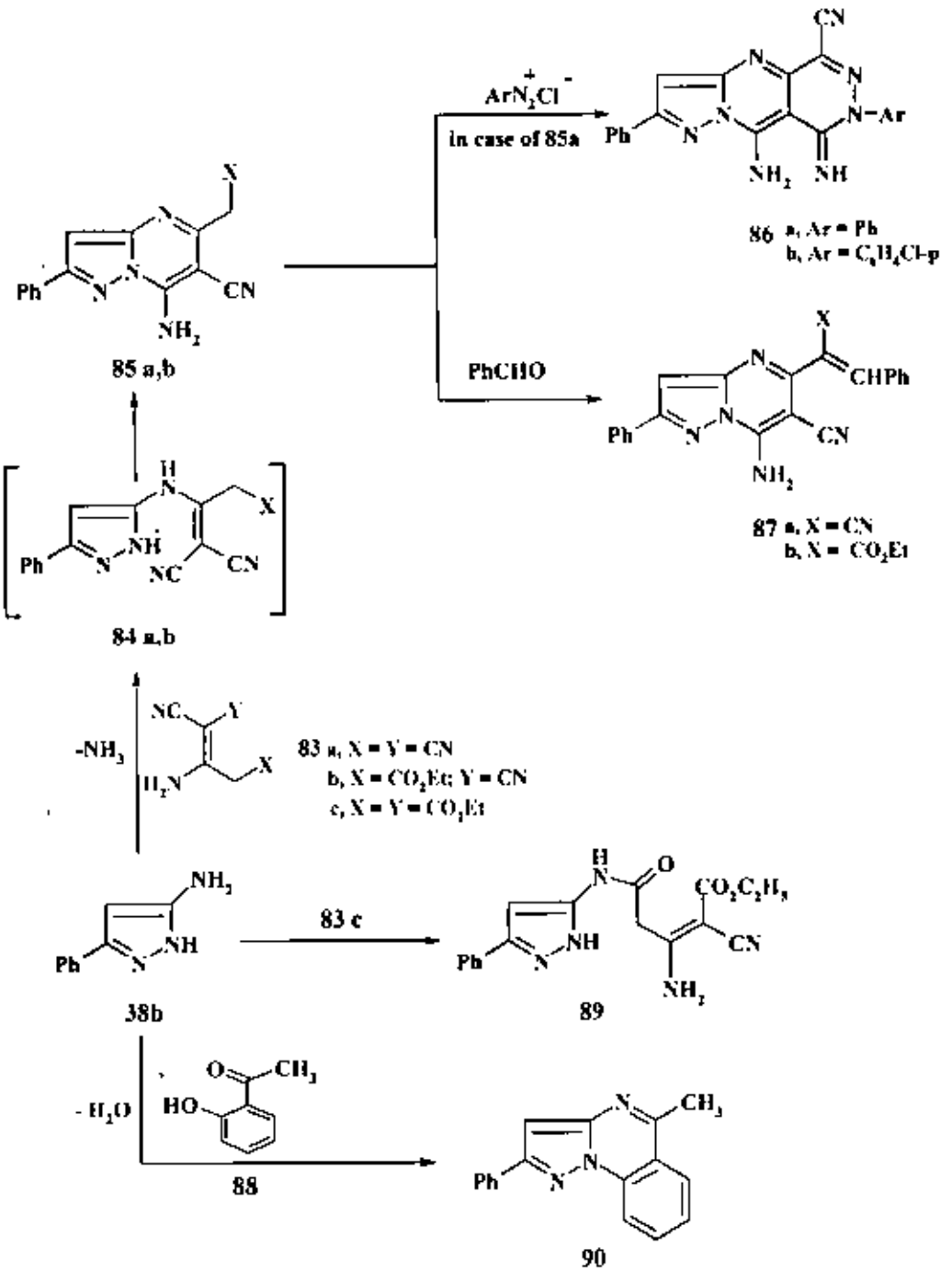


Similarly, aminopyrazole derivative **67** reacted with 2-dimethyl-aminomethylene dimedone **76** to afford the pyrazolopyrimidine derivative **77**. The latter on reaction with the acetal **69** afforded the amidine **78**. Also, compound **67** could be reacted with 5-dimethyl-aminomethylene-2,2-dimethyl-1,3-dioxane-4,6-dione **79** and ethoxy-methylenemalonic ester **81** to give compounds **80** and **82** respectively.[70,74-76]

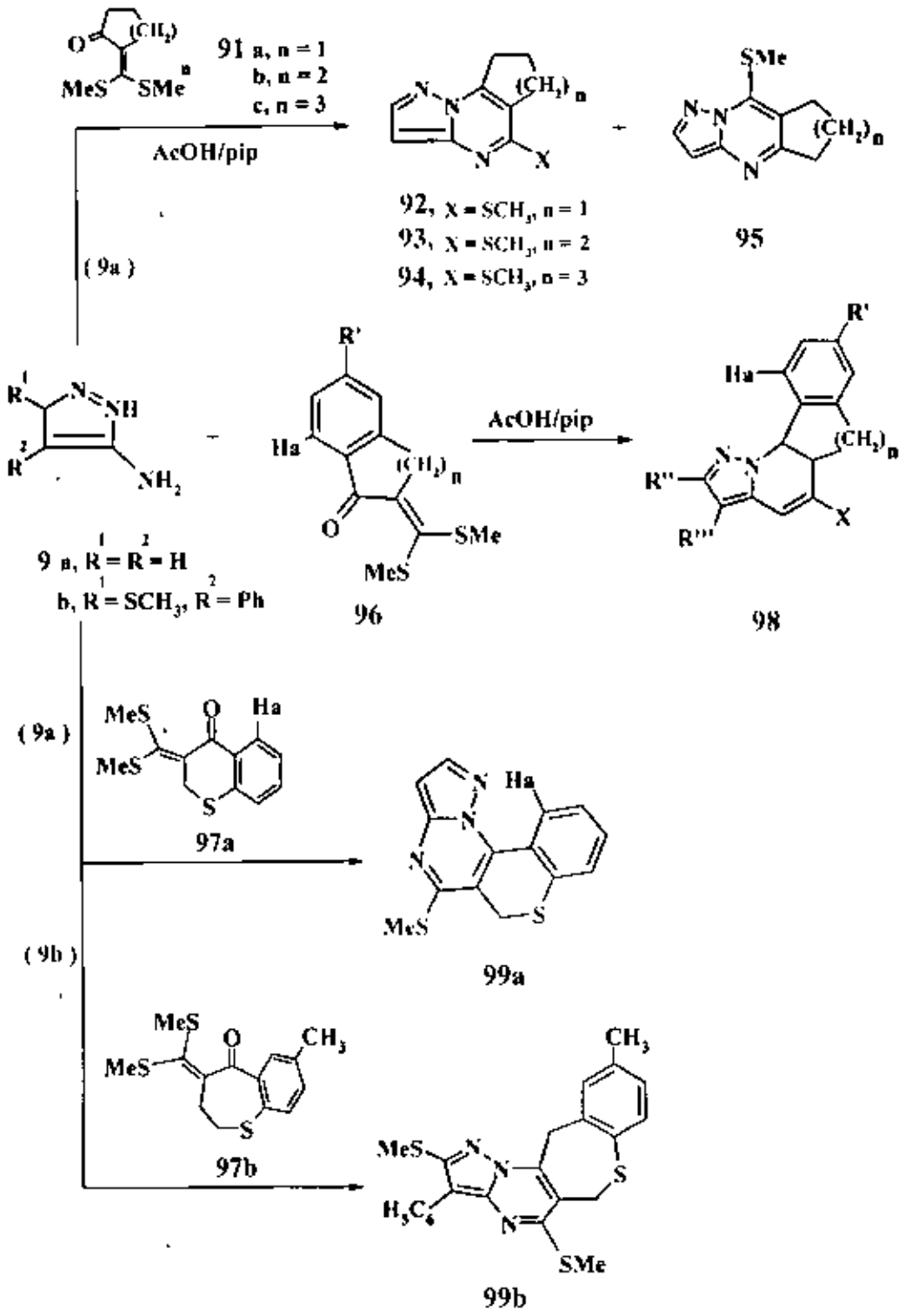


It has been found that the reaction of 5-amino-3-phenylpyrazole **38b** with malononitrile or ethyl cyanoacetate diamers **83a** or **83b** gave the intermediates **84a,b**, which were cyclized to the pyrazolo[1,5-*a*]-pyrimidine derivatives **85a** and **85b** respectively. The latters reacted with

aromatic diazonium chlorides or benzaldehydes to give compounds **86** or **87** respectively. When **38b** reacted with **83c** or 2-hydroxy-acetophenone **88**, compounds **89** or **90** were produced respectively.[77-79]

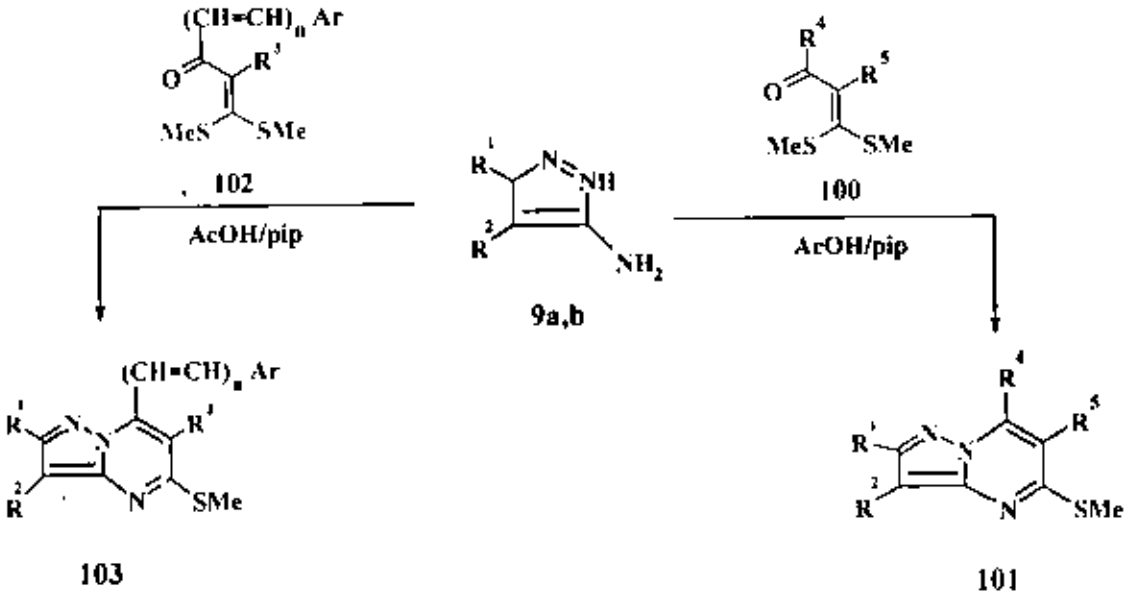


When **9a** reacted with cyclic ketene dithioacetals **91b** and **91c** the expected 5-methylthio-6,7,8,9-tetrahydropyrazolo[1,5-*a*]-quinazoline **93** and cyclohepta[e]pyrazolopyrimidine **94** were produced respectively. While, the dithioacetal **91a** derived from cyclopentanone yielded a mixture of angular and linearly fused pyrimidines **92** and **95** respectively. Similarly, the reactions of **9** with ketene dithioacetals **96** and **97a,b** derived from benzocyclic ketones were reported to give a series of benzocyclo and benzoheterocyclopyrazolopyrimidines **98**, **99a** and **99b** respectively.[80-83]

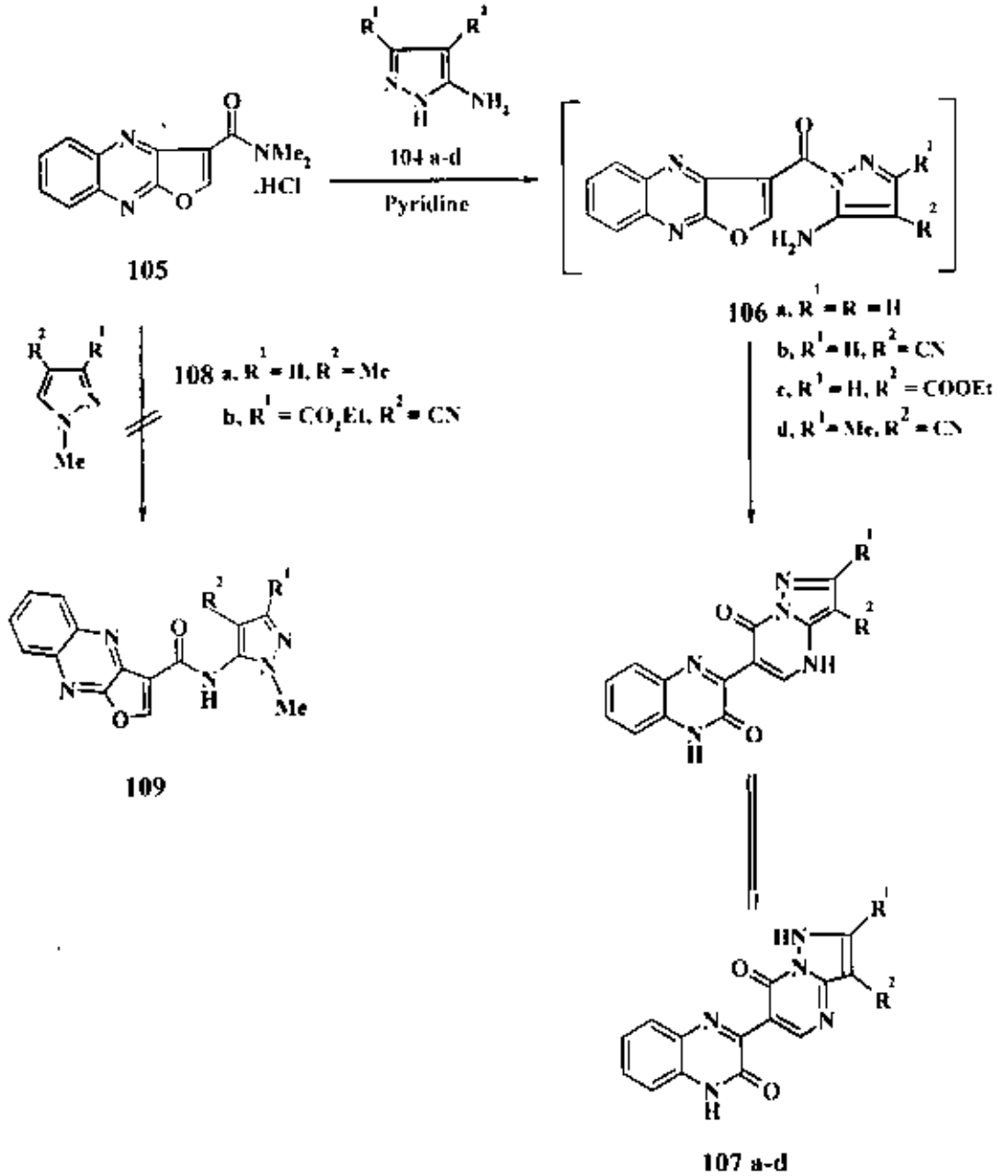


Moreover, cyclocondensation of 3-aminopyrazole derivatives **9a,b** with α-oxoketene dithioacetals **100**[81] afforded 5-methylthio-6,7-

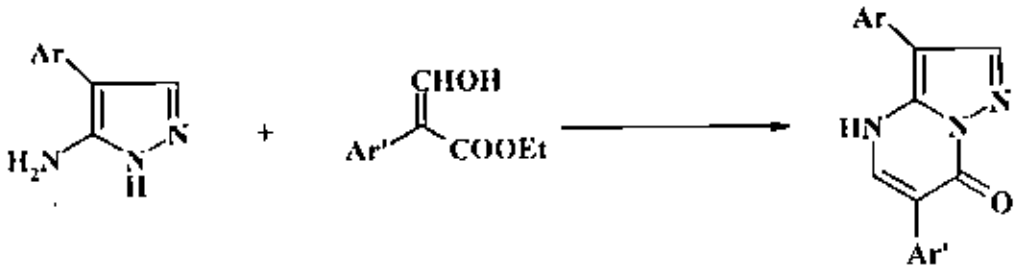
disubstituted pyrazolo[1,5-*a*]pyrimidines **101**. Also, the poly subsituted pyrazolo[1,5-*a*]pyrimidines **103** were performed by the reaction of the respective enoylketene dithioacetals **102a,b** with **9a,b**.[82,83]



Kurasawa et al., has reported the synthesis of novel 6-quinoxalinyldihydropyrazolo[1,5-*a*]pyrimidin-7-ones **107a-d** by the reaction of 3-(*N,N*-dimethylcarbamoyl)furo[2,3-*b*]quinoxaline hydrochloride **105** with 5-amino-(*1H*)-pyrazoles **104a-d**. Whereas, the reaction of **105** with 5-amino-1-methylpyrazoles **108a,b** in the presence of pyridine did not afford the expected 3-[*N*-(1-methyl-pyrazol-5-yl)carbamyol]furo[2,3-*b*]quinoxalines **109**, but also recovered the free base **107**.[84, 85]

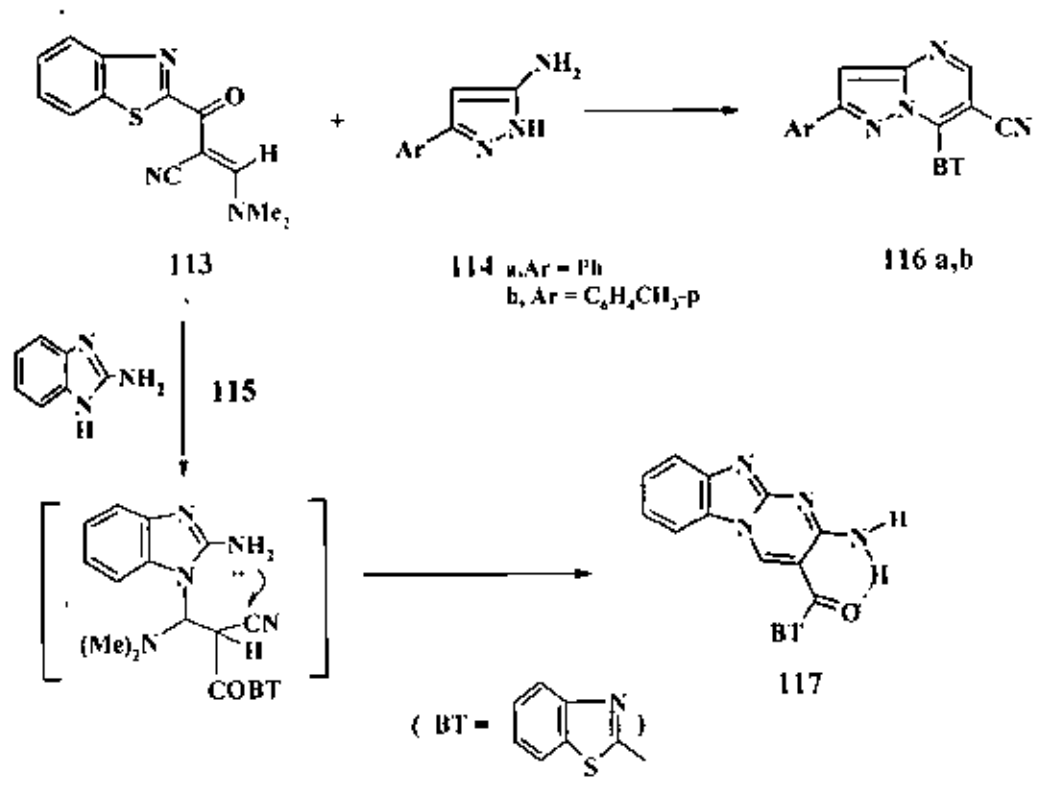


The synthesis of 4,7-dihydro-3,6-disubstituted pyrazolo[1,5-*a*]-pyrimidine-7-ones **112** were performed by a one-step reaction between 3(5)-amino-4-arylpyrazoles **110** and ethyl 2-aryl-3-hydroxypropenoates **111**.[86]



110 111 112

The reaction of 3-(benzothiazol-2-yl)-2-(*N,N*-dimethylamino)-methylene-3-oxopropanenitrile 113 with 5-amino-3-aryl-(*1H*)-pyrazoles **114a,b** or 2-aminobenzimidazole **115** afforded the pyrazolo[1,5-*a*]pyrimidine derivatives **116a,b** and the pyrimido [1,2-*a*]benzimidazole derivative **117** respectively.[87-89]



113 114 a, Ar = Ph b, Ar = $C_6H_4CH_3$-p 116 a,b

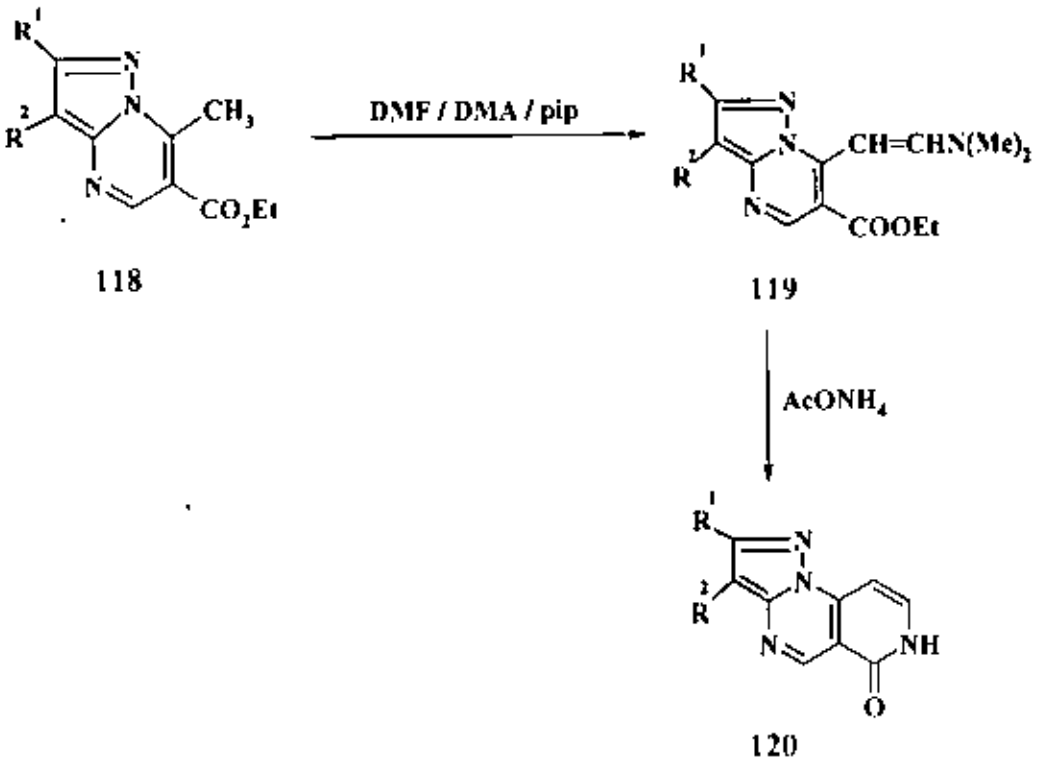
115

117

(BT =)

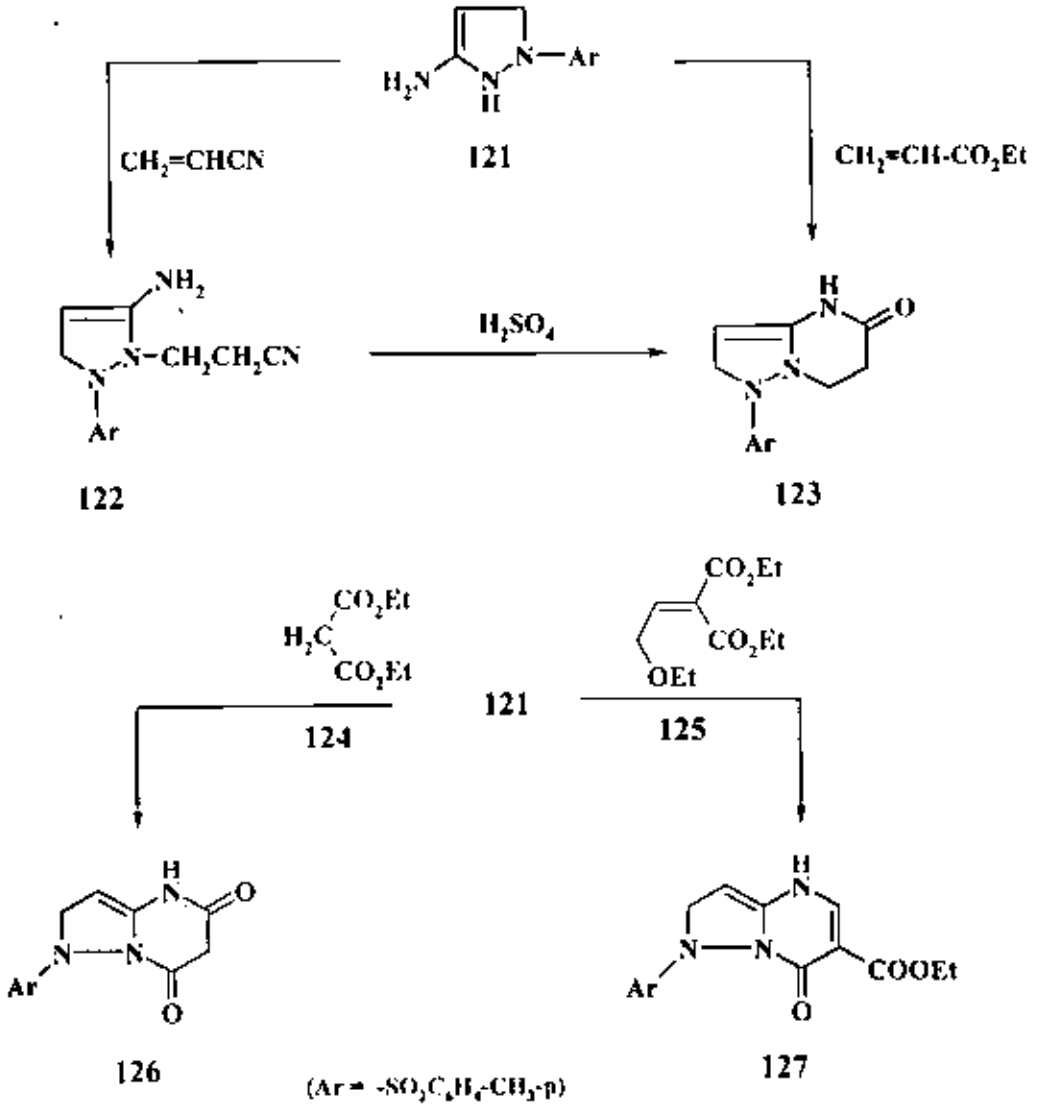
It has been found that pyrazolo[1,5-*a*]pyrimidine derivatives **118** reacted with DMF-DMA to give the corresponding 7-(2-dimethyl-

aminovinyl)pyrazolo[1,5-*a*]pyrimidines **119**, which reacted with excess ammonium acetate to give 2,3-disubstituted pyrazolo[1,5-*a*]-pyrido[3,4-*e*]pyrimidin-6-ones **120**.[90-94]

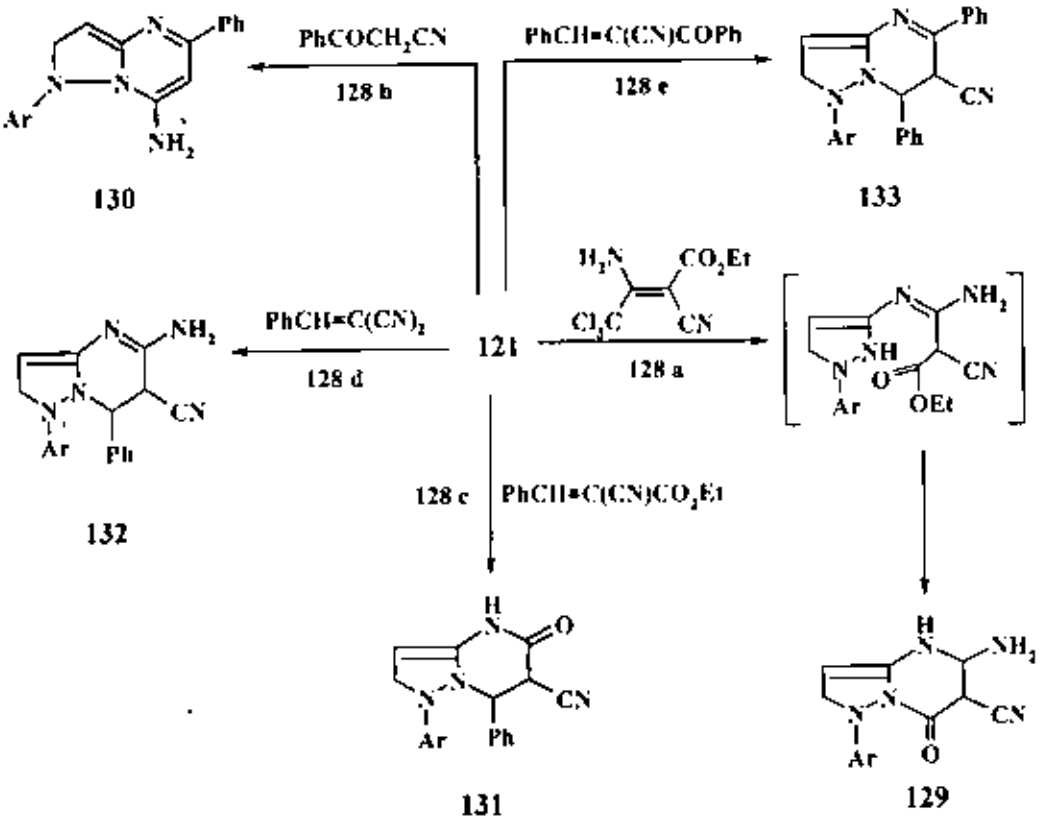


118 **119** **120**

When (*N*-tosyl)-3-aminopyrazoline derivative **121** treated with acrylonitrile, the corresponding 1-(*p*-tosyl)-3-amino-*β*-cyano-ethylpyrazole **122** was obtained, which was cyclized to pyrazolo[1,5-*a*]pyrimidine derivative **123** by the action of concentrated sulphuric acid. Also, compound **123** could be obtained directly upon treatment of **121** with ethyl acrylate. Compound **121** reacted with diethyl malonate **124** or its ethoxyethylene derivative **125** to yield the pyrazolo[1.5-*a*]pyrimidine derivatives **126** and **127** respectively.[95]

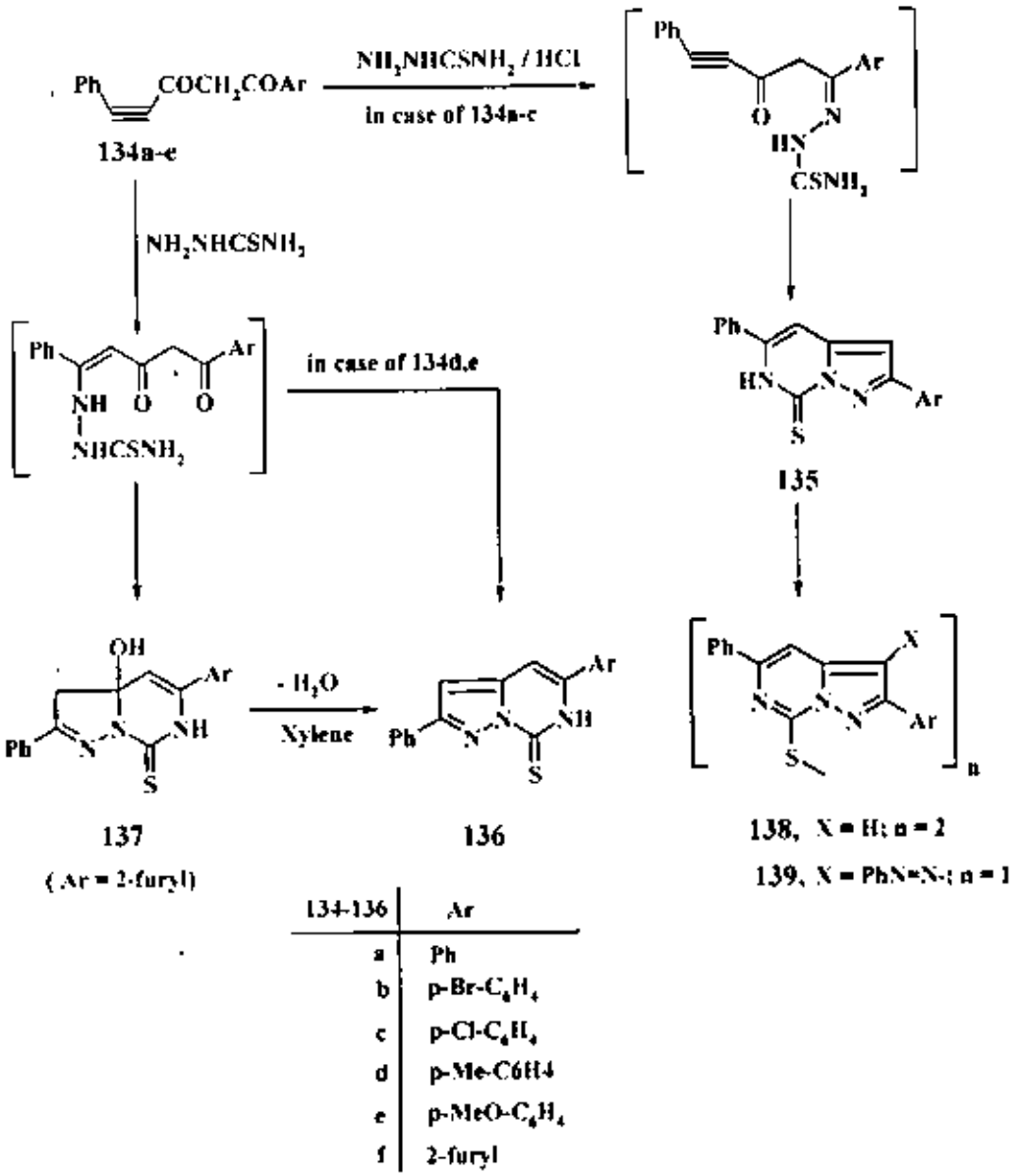


Moreover, condensation of compound **121** with ethyl 3-amino-3-trichloromethyl-2-cyanopropenoate **128a** in refluxing ethanol yielded the pyrazolo[1,5-*a*]pyrimidine **129**. In addition, the reaction of **121** with phenacyl cyanide **128b**, ethyl benzylidenecyanoacetate **128c**, benzylidenemalononitrile **128d** or *a*-cyanochalcone **128e** gave the pyrazolopyrimidine derivatives **130**, **131**, **132** or **133** respectively.[95]



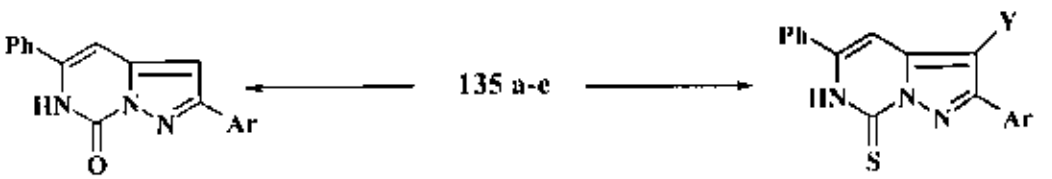
2.1.2 Pyrazolo[1,5-*c*] pyrimidine derivatives:

. The reaction of 1-phenyl-5-arylpent-1-yne-3,5-diones **134a-e** with thiosemicarbazide or with thiosemicarbazide hydrochloride afforded the respective 2-aryl-5-phenyl-(*6H*)-pyrazolo[1,5-*c*]pyrimidine-7-thiones **135a-c**. However, under identical conditions **134d,e** gave **135d,e** alongside with their isomers **136d,e** as minor products. On the other hand, 5-furyl-9-hydroxy-2-phenyl-(*3H*),(*6H*)-pyrazolo[1,5-*c*]pyrimidine-7-thione **137** was formed from **134f** under the same conditions. The latter could be converted into its thione **136f** on heating in xylene. Also, by oxidation of **135a-e** with sodium nitrite in glacial acetic acid or with benzene diazonium chloride gave the 7,7-bis-(2-aryl-5-phenyl pyrazolo[1,5-*c*]pyrimidinyl)disulfide **138a-e** or phenyl azodisulfide derivatives **139a-e** respectively.[96-101]



134-136	Ar
a	Ph
b	p-Br-C_6H_4
c	p-Cl-C_6H_4
d	p-Me-C6H4
e	p-MeO-C_6H_4
f	2-furyl

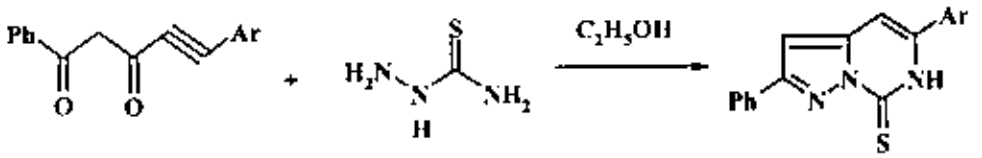
Also, bromination and iodination of **135a-e** afforded the corresponding 3-bromo **140a-e** and 3-iodo **141a-e** derivatives respectively. Morever, nitration of **135a-e** with nitric and sulfuric acids in glacial acetic acid led to the formation of the corresponding 3-nitro derivatives **142a-e**. While, on treatment of **135a-e** with alkaline hydrogen peroxide gave pyrazolo[1,5-*c*]pyrimidine-7-ones **143a-e**.[96]



143 a-e

140, Y = Br
141, Y = I
142, Y = NO_2

In a similar manner, the reaction of 1-aryl-5-phenylpent-1-yne-3,5-diones **144** with thiosemicarbazide gave 5-aryl-2-phenylpyrazolo[1,5-*c*]-pyrimidin-7-thiones **145**.[99-101]

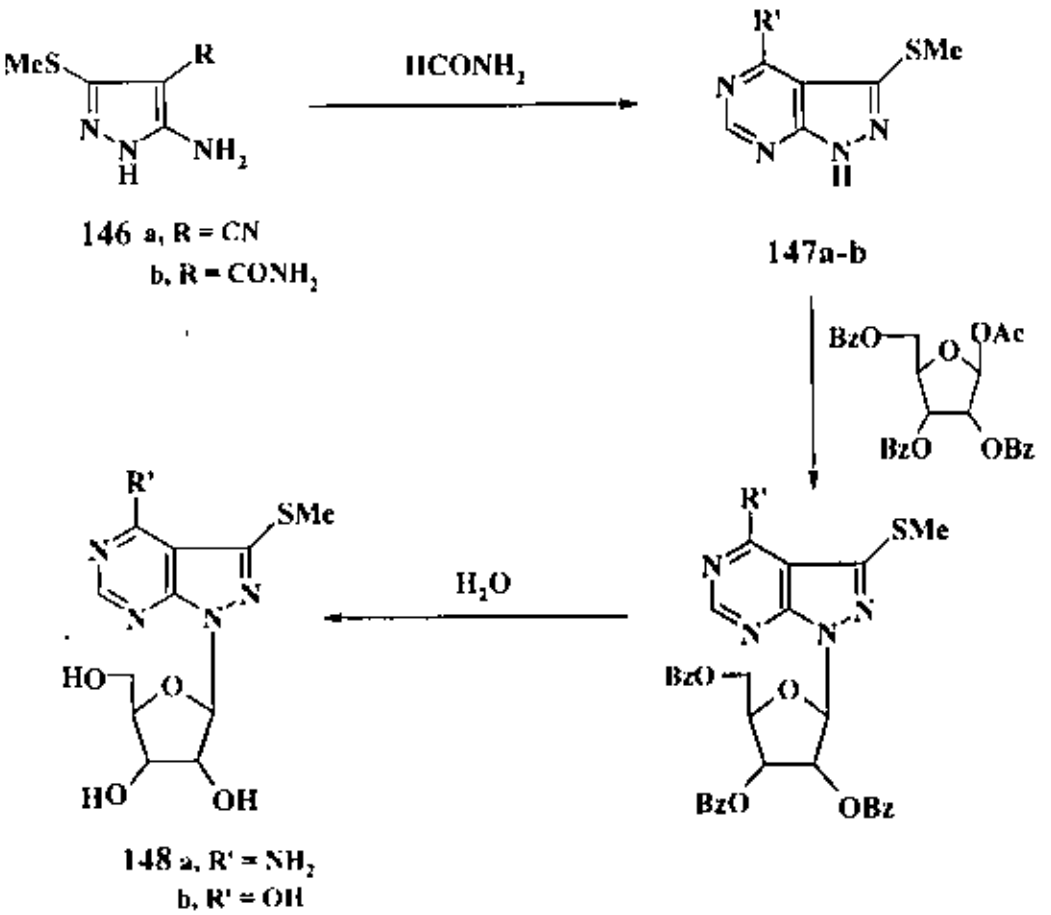


144

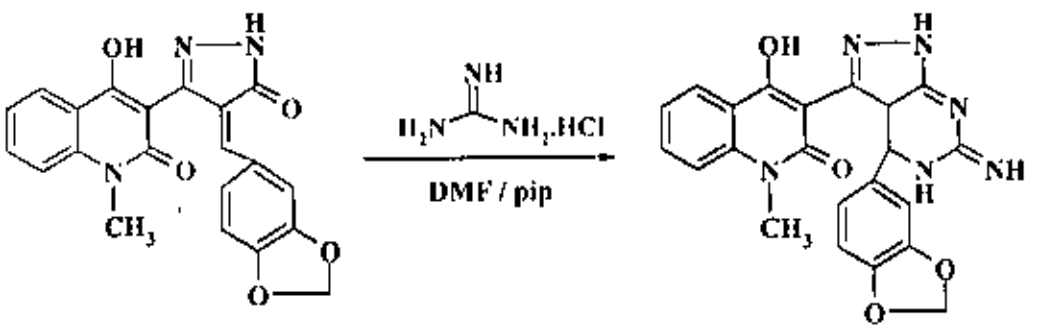
145 a, Ar = C_6H_5
b, Ar = C_6H_4-OCH$_3$-p
c, Ar = C_6H_4-CH_3-p

2.1.3 Pyrazolo[3,4-*d*] pyrimidine derivatives:

Cyclization of 5-amino-3-methylthiopyrazole derivatives **146a,b** with formamide afforded 4-amino- or 4-hydroxy-3-methylthio-pyrazolo[3,4-*d*]pyrimidines **147a,b**. The latters on glycosylation followed by hydrolysis afforded the nucleosides **148**.[102,103]

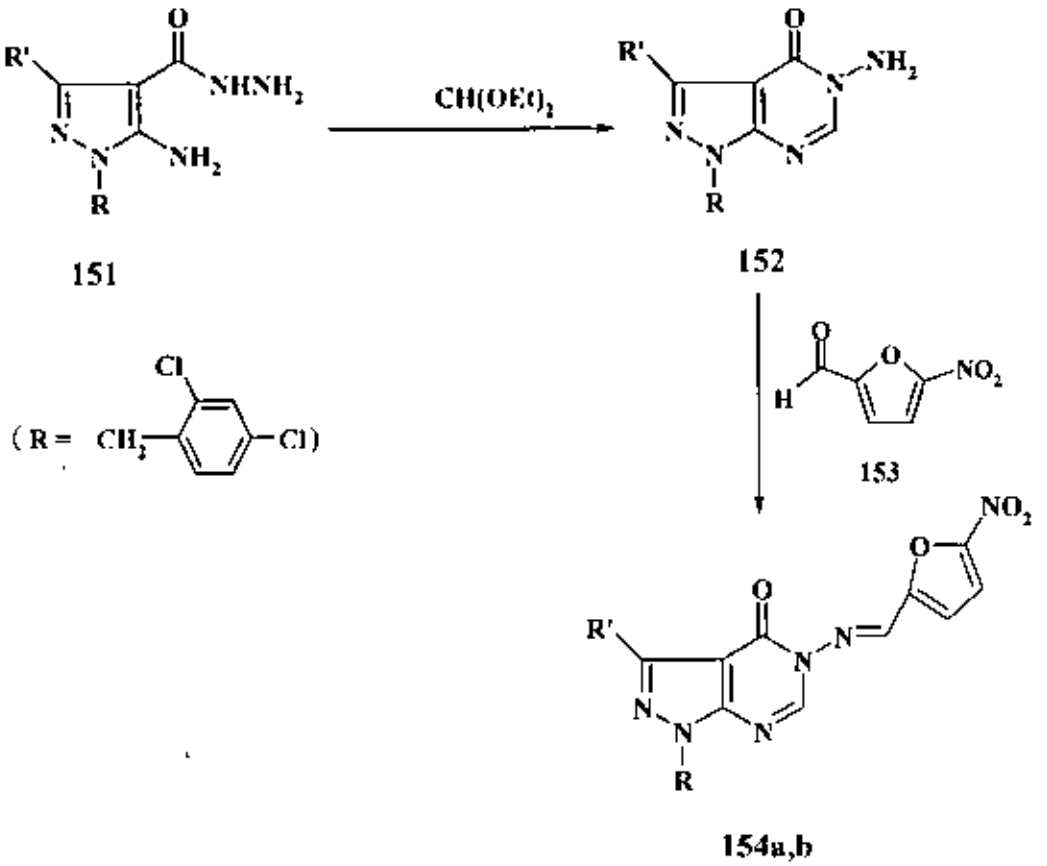


Recently, it has been reported that the cyclization of 3-[4-(benzo-1,3-dioxolylmethylene)-5-oxo-3-pyrazolyl]-4-hydroxy-1-methylquinolin-2(*1H*)-one **149** with guanidine hydrochloride led to the formation of the biologically interested fused pyrazolopyrimidine **150**.[104]

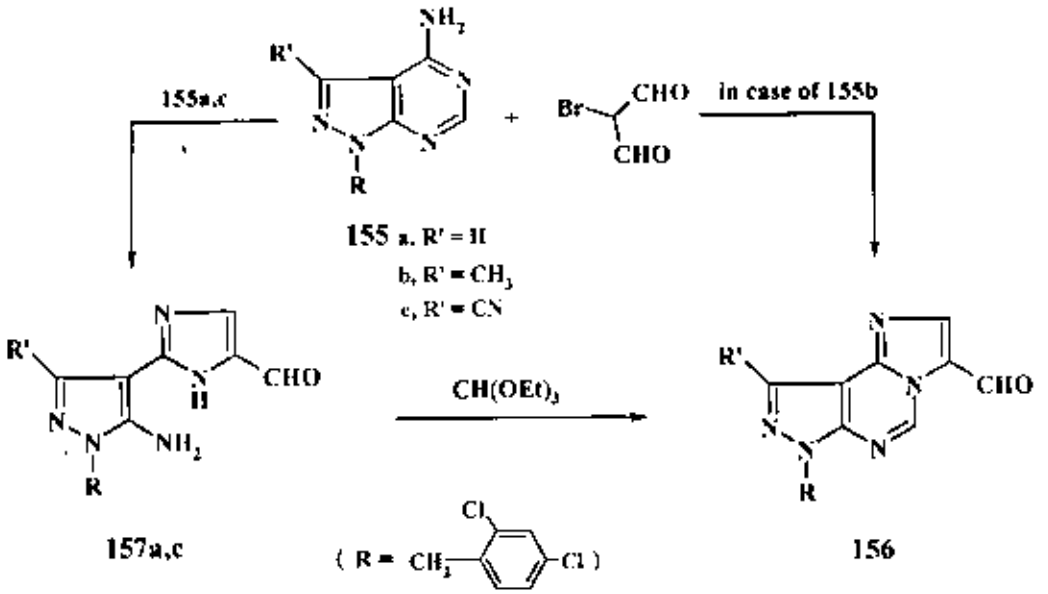


149 **150**

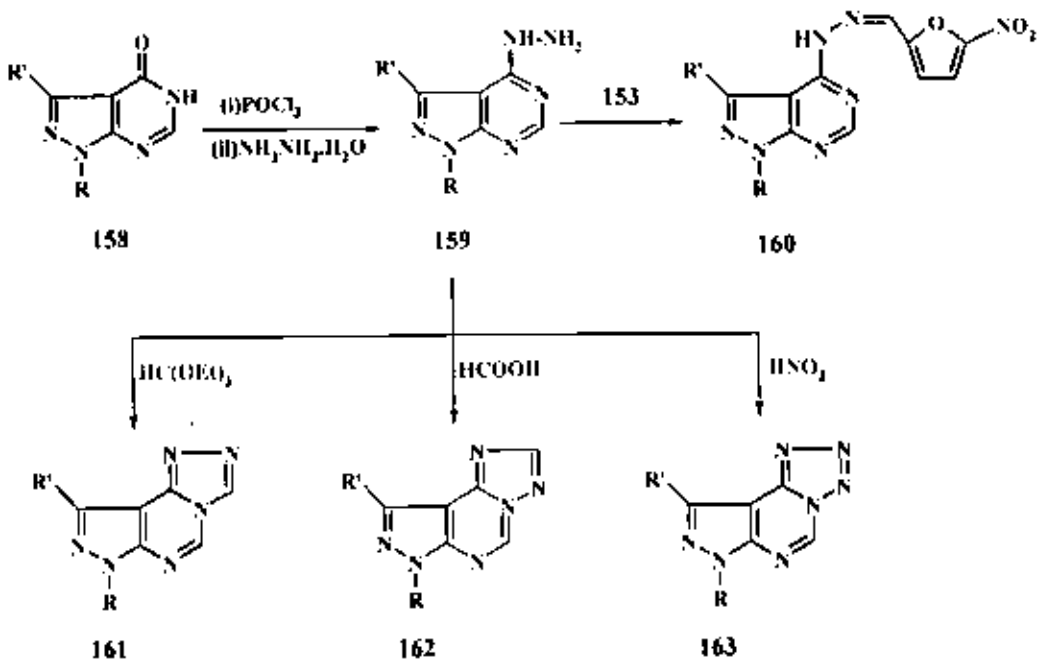
Gatta et al., described the synthesis of several pyrazolo-pyrimidines. Thus, the reaction of 5-amino-1-(2,4-dichlorobenzyl)-pyrazole-4-carboxylic acid hydrazides **151** with triethylorthoformate gave 5-amino-1-(2,4-dichlorobenzyl)-4,5-dihydropyrazolo[3,4-*d*]-pyrimidin-4-ones **152**. The latters were reacted with 5-nitrofurfural **153** to give the Schiff bases **154**.[105,106]



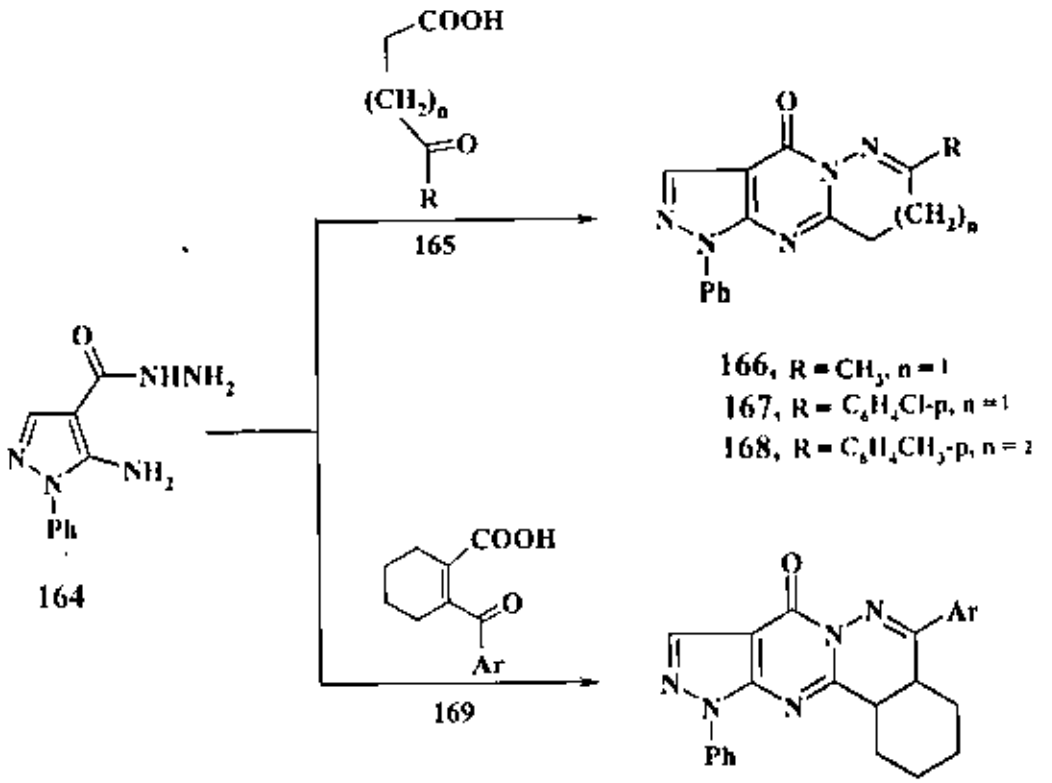
Also, the reaction of 4-aminopyrazolo[3,4-*d*]pyrimidine derivative **155b** with bromomalondialdehyde in aqueous dioxane gave the expected compound **156b**, while the reaction of **155a** and **155c** yielded only the corresponding imidazolylpyrazoles **157a,c**. Compounds **157a,c** could be cyclized with triethylorthoformate to give **156a,c**.[105,106]



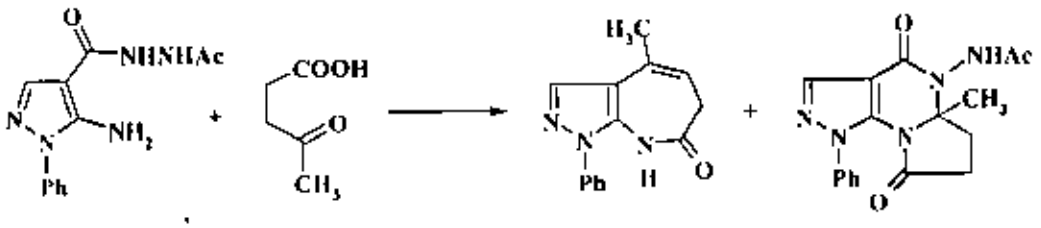
Moreover, refluxing 1-(2,4-dichlorobenzyl)-(*5H*)-pyrazolo[3,4-*d*]-pyrimidin-4-ones **158** with phosphorus oxychloride followed by the reaction with ethanolic hydrazine hydrate gave the 1-(2,4-dichlorobenzyl)-4-hydrazinopyrazolo[3,4-*d*]pyrimidines **159**, which were found to react with 5-nitrofurfural, triethylorthoformate or orthoacetate, with refluxing formic or acetic acid and with sodium nitrite in hydrochloric acid to give compounds **160**, **161**, **162**, and **163** respectively.[106]



Refluxing of 5-amino-1-phenyl-4-pyrazolecarbohydrazide **164** with levulinic acid **165** furnished 1-phenyl-7-methyl-8,9-dihydro-pyrazolo[3',4':4,5]pyrimido[5,6-*b*]pyridazin-4-one **166.** When 3-(*p*-chlorobenzoyl)propionic acid was applied, the reaction yielded the aryl-substituted analogue **167,** while with aroyl butyric acid the tricycle containing a seven-membered ring **168** was formed. On other hand, using of cis-2-toluoylcyclohexane carboxylic acid **169,** the reaction resulted in the cyclohexane cis-condensed tetracyclic compound **170.**[107]

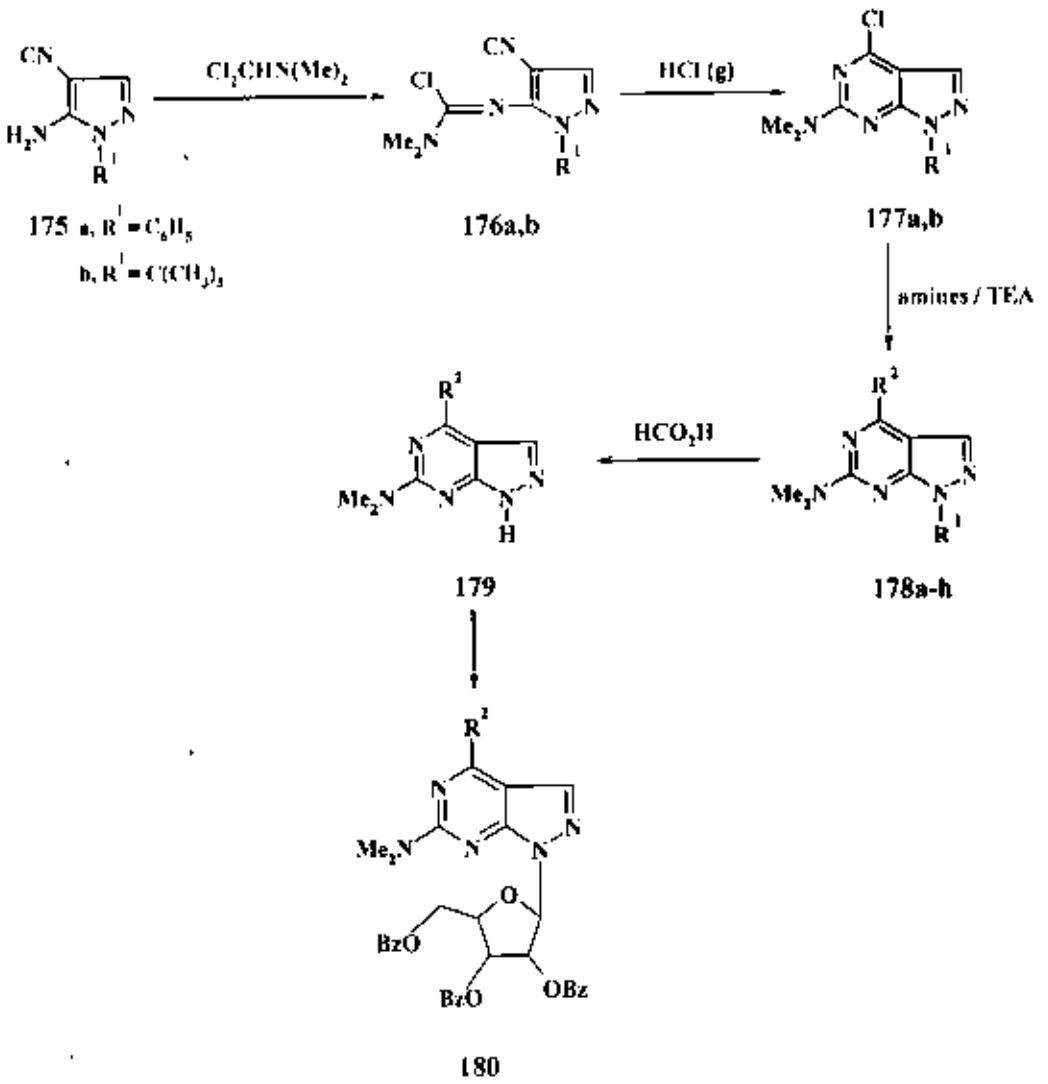


Similarly, the acetyl hydrazide derivative **171** reacted with levulinic acid **172** to yield a mixture of the pyrazoloazepinone derivative **173** and the pyrrolopyrazolopyrimidinone derivative **174**.[108-115]



Treatment of *N*-substituted 5-amino-4-cyanopyrazoles **175a,b** with phosgene iminium chloride afforded the corresponding chloroamidines **176a,b**, which on cyclization yielded the pyrazolo[3,4-*d*]pyrimidines

177a,b. The latters were converted into a variety of pyrazolo[3,4-*d*]pyrimidines **178a-h** by nucleophilic halide displacement with nucleophiles such as primary and secondary amines. Cleavage of the *t-Bu* group **178** with formic acid gave **179** that were subsequently glycosilated by the reaction with 1-*O*-acetyl-3,4,5-tri-*O*-benzoylribofuranose to give the nucleosides **180**.[116–118]



175 a, $R^1 = C_6H_5$
b, $R^1 = C(CH_3)_3$

176a,b

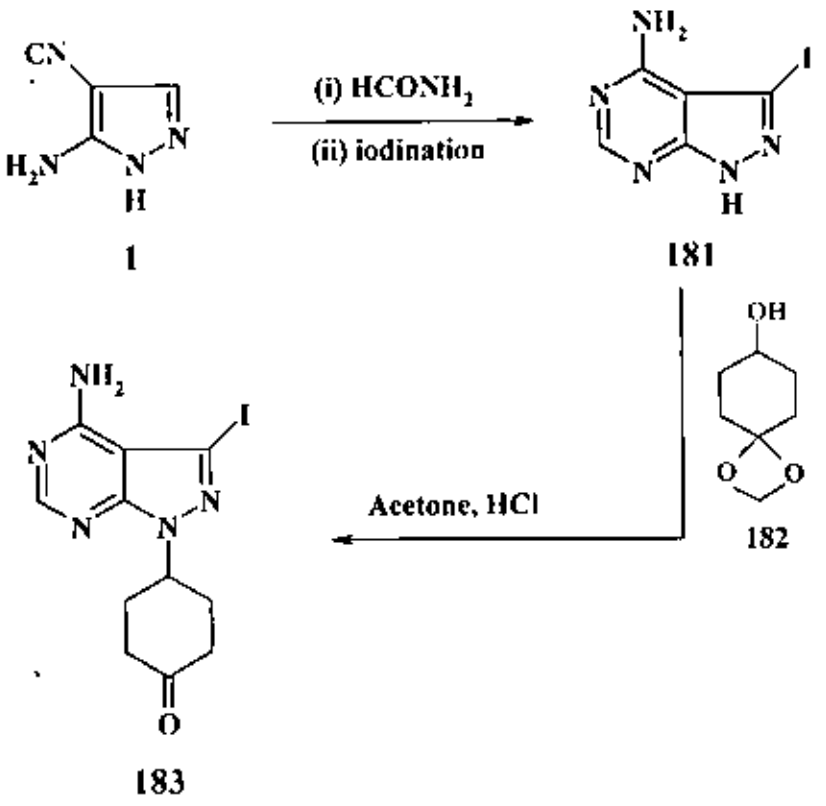
177a,b

178a-h

179

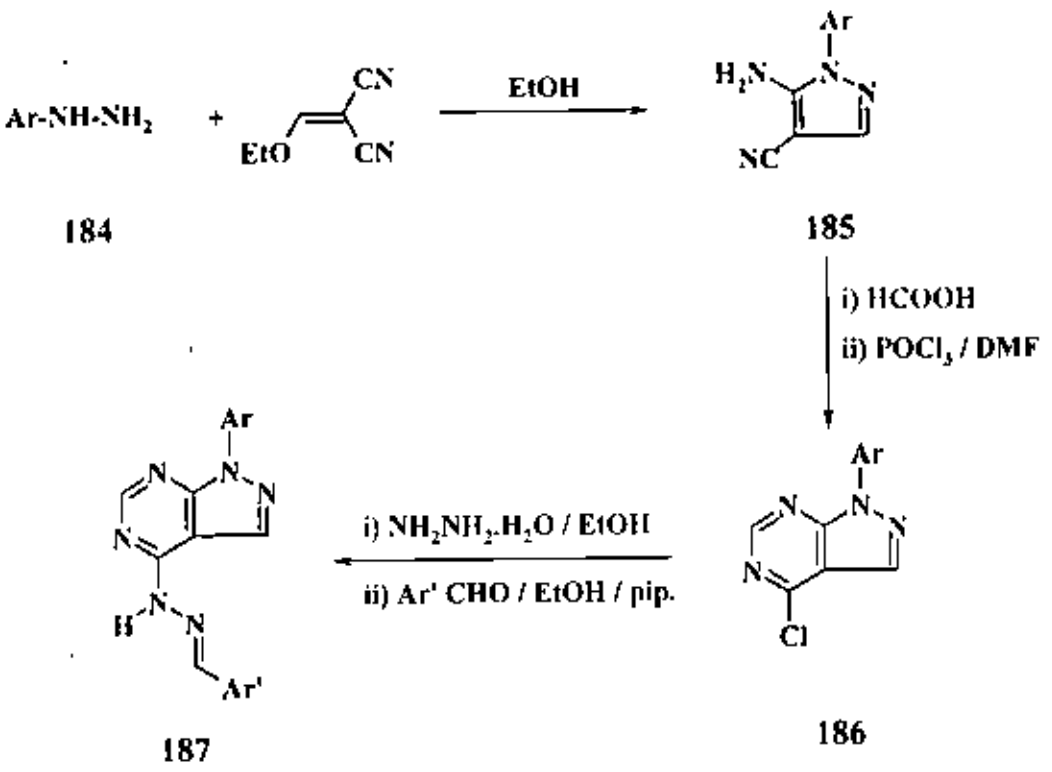
180

Cyclization of the aminopyrazole **1** with formamide followed by iodination at C3 gave the pyrazolopyrimidine derivative **181**, which under Mitsunobu coupling with the ketal-alcohol **182** followed by ketone unmasking gave compound **183**.[73,119,120]

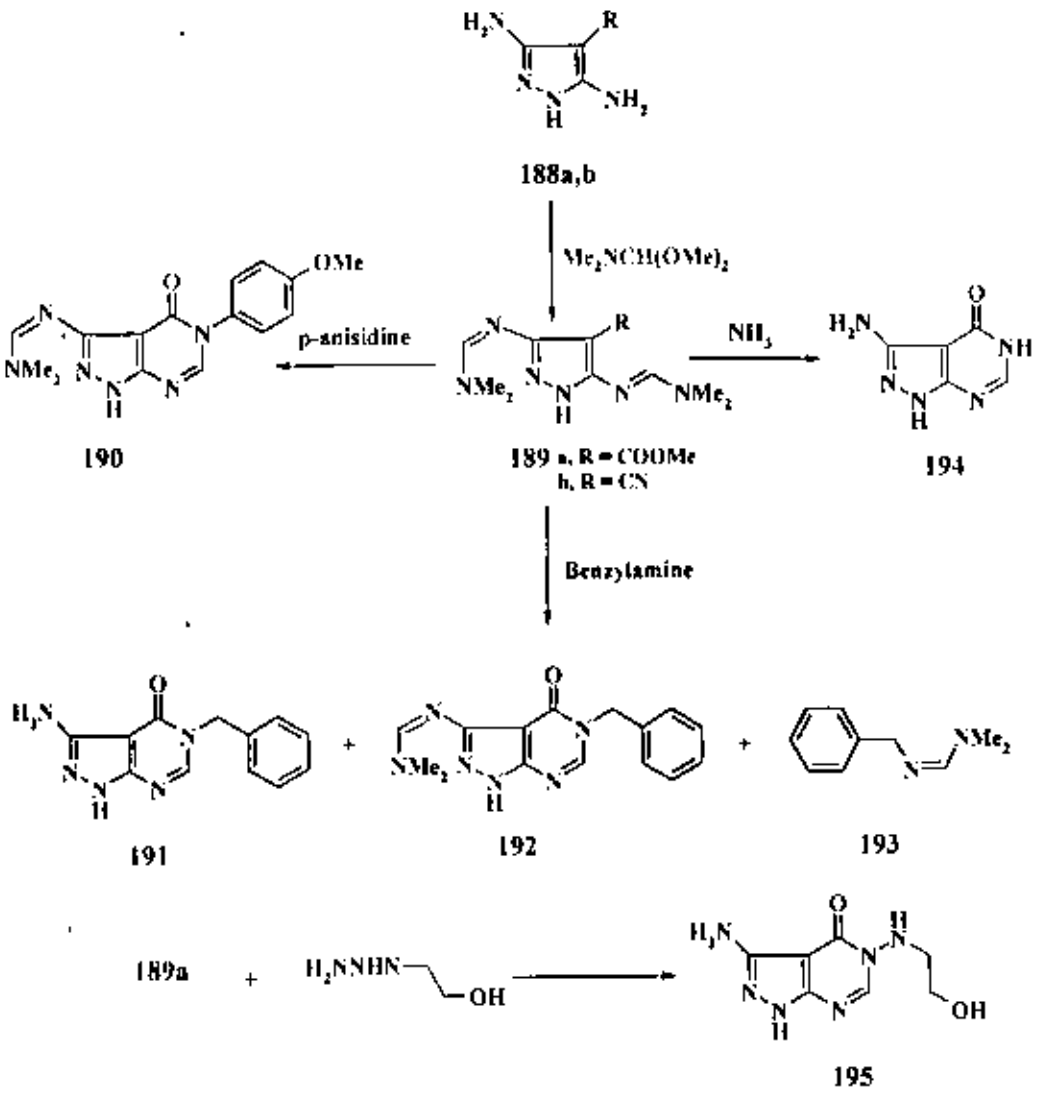


1 **181** **182** **183**

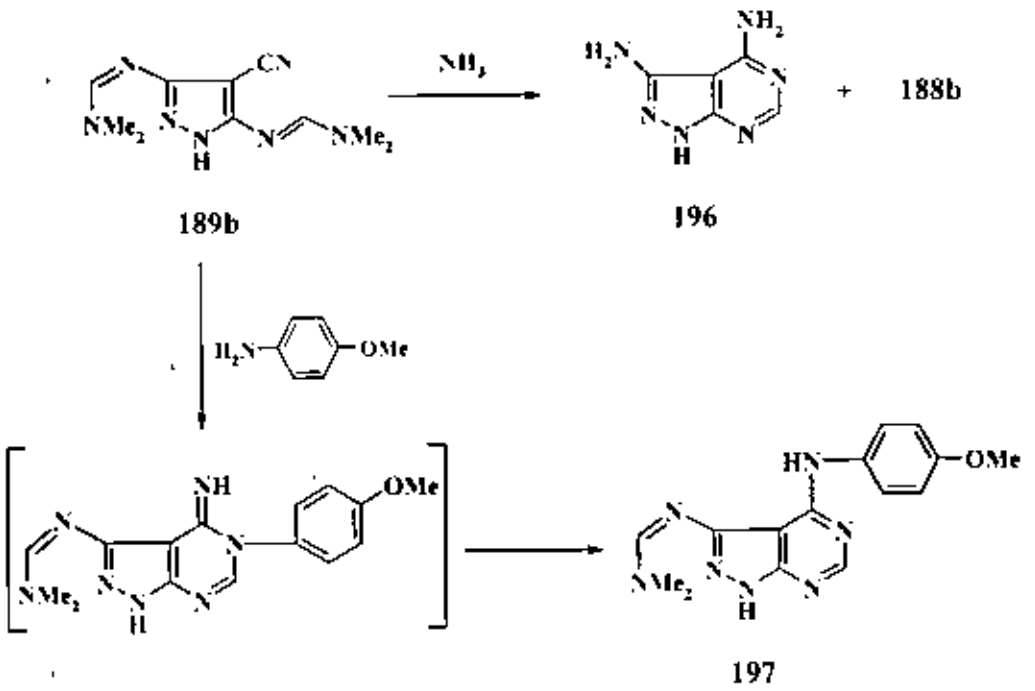
Condensation of 1-aryl-4-cyano-5-aminopyrazoles **185** with aqueous formic acid and subsequent treatment with phosphorous oxychloride gave the 4-chloropyrazolo[3,4-*d*]pyrimidines **186**. Displacement of the chloride with hydrazine and final condensation with aromatic aldehydes gave the GSK-3 inhibitors **187**.[121]



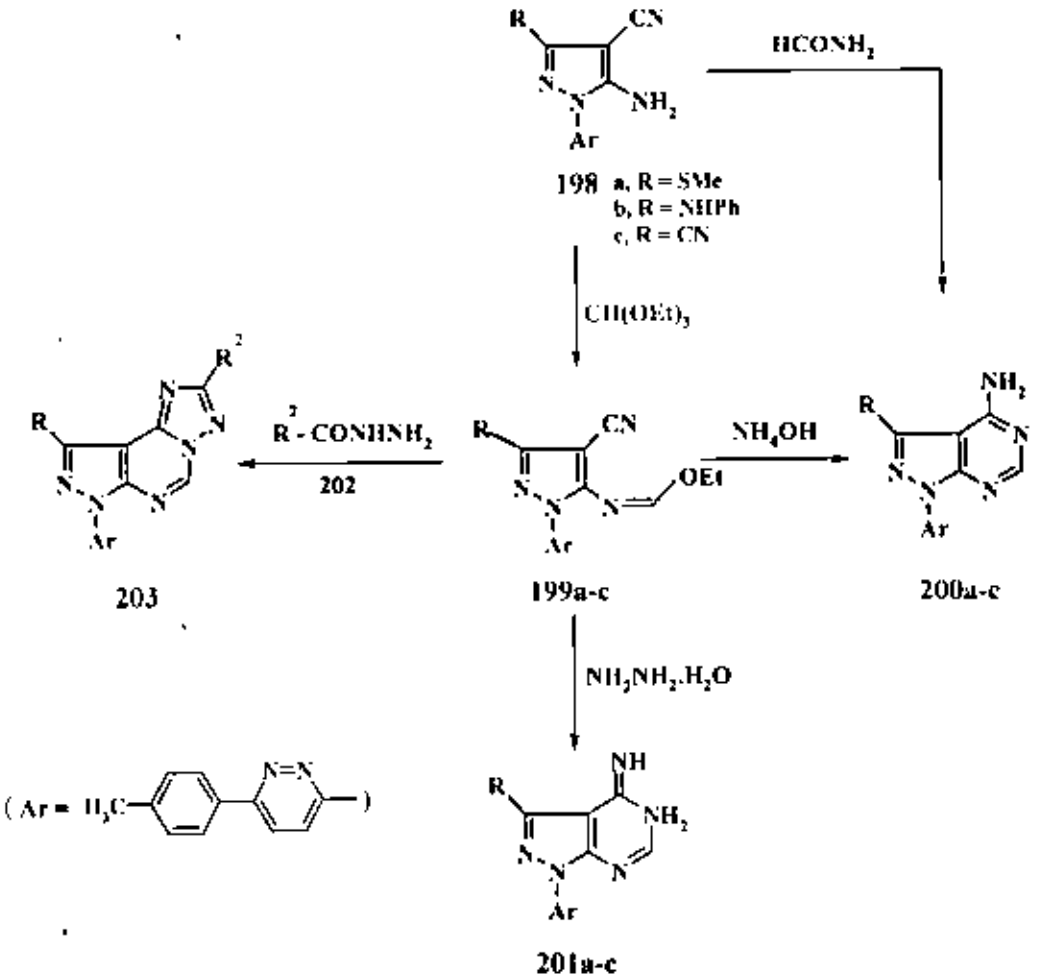
It has been reported that condensation of pyrazole derivatives **188a,b** with DMF and dimethyl acetal afforded 3,5-bis(dimethylamino-methylene)amino-4-methoxycarbonyl and 4-cyanopyrazoles **189a,b**.[78-81] Heating of diamidino-4-methoxycarbonyl pyrazole **189a** with *p*-anisidine gave 3-amidine derivative **190,** while with the more basic benzylamine a mixture of 3-amino, 3-amidine derivatives **191,192** and *N*-dimethylaminomethylenebenzylformamidine **193** were produced respectively. Also, the reaction of pyrazole **189a** with ammonia led to the formation of 3-aminopyrazolo[3,4-*d*]pyrimidine derivative **194**. Also, pyrazolopyrimidine **195** could by obtained by the reaction of **189a** with hydroxyethylhydrazide.[122-124]



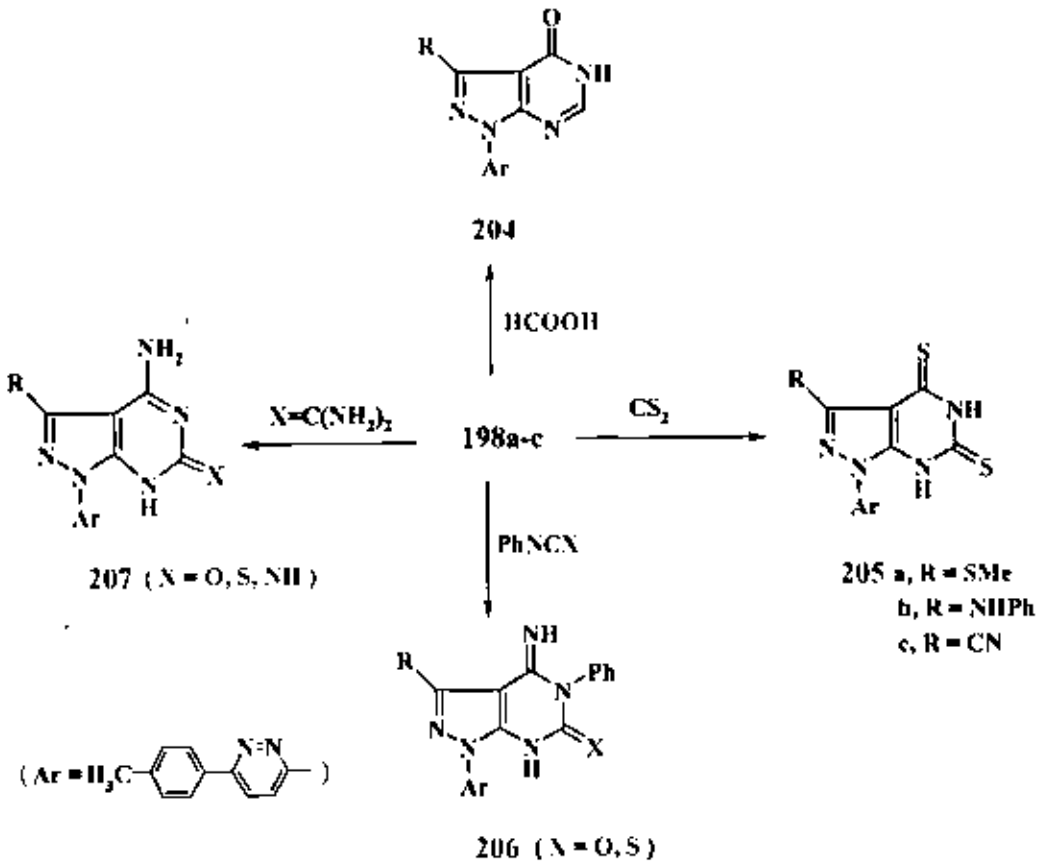
However, the reaction of the diamidine **189b** with ammonia and *p*-anisidine is different. Thus, heating of **189b** with methanolic ammonia gave a mixture of 3,4-diaminopyrazolo[3,4-*d*]pyrimidine **196** and the diamino derivative **188b**, while with *p*-anisidine 3-dimethylamino-methylencamino-4-*p*-anisidinopyrazolo[3,4-*d*]pyrimidine was formed **197**.[122]



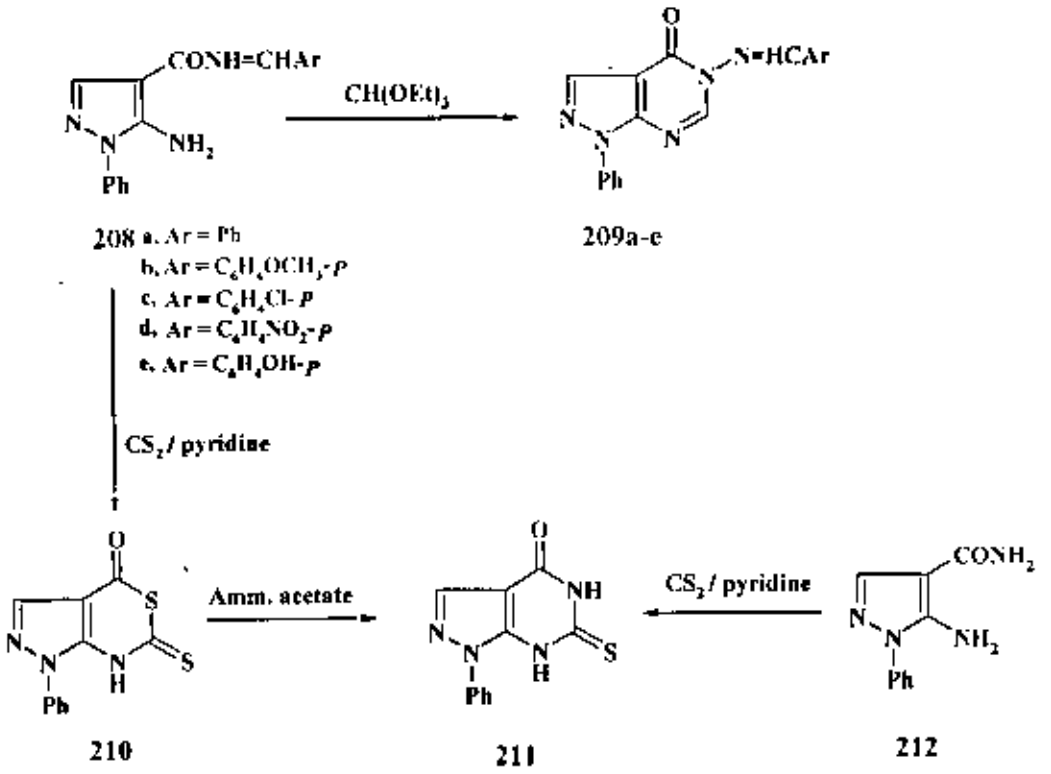
Condensation of 5-aminopyrazole nitriles **198a-c** with triethylorthoformate afforded the intermediate ethoxymethyleneamino derivatives **199a-c.** The latters on treatment with cold aqueous alcoholic ammonia yielded 4-aminopyrazolo[3,4-*d*]pyrimidines **200a-c**, which could be synthesized directly by treating the pyrazoles **198a-c** with formamide. When compounds **199a-c** were stirred with hydrazine hydrate, the 5-amino-4-iminopyrazolo[3,4-*d*]pyrimidines **201a-c** were produced in good yields. Compounds **199a-c** gave 2-arylpyrazolo[3,4-*d*]-1,2,4-triazolo[5,1-*f*]pyrimidine systems **203** when reacted with the acid hydrazides **202**.[125]



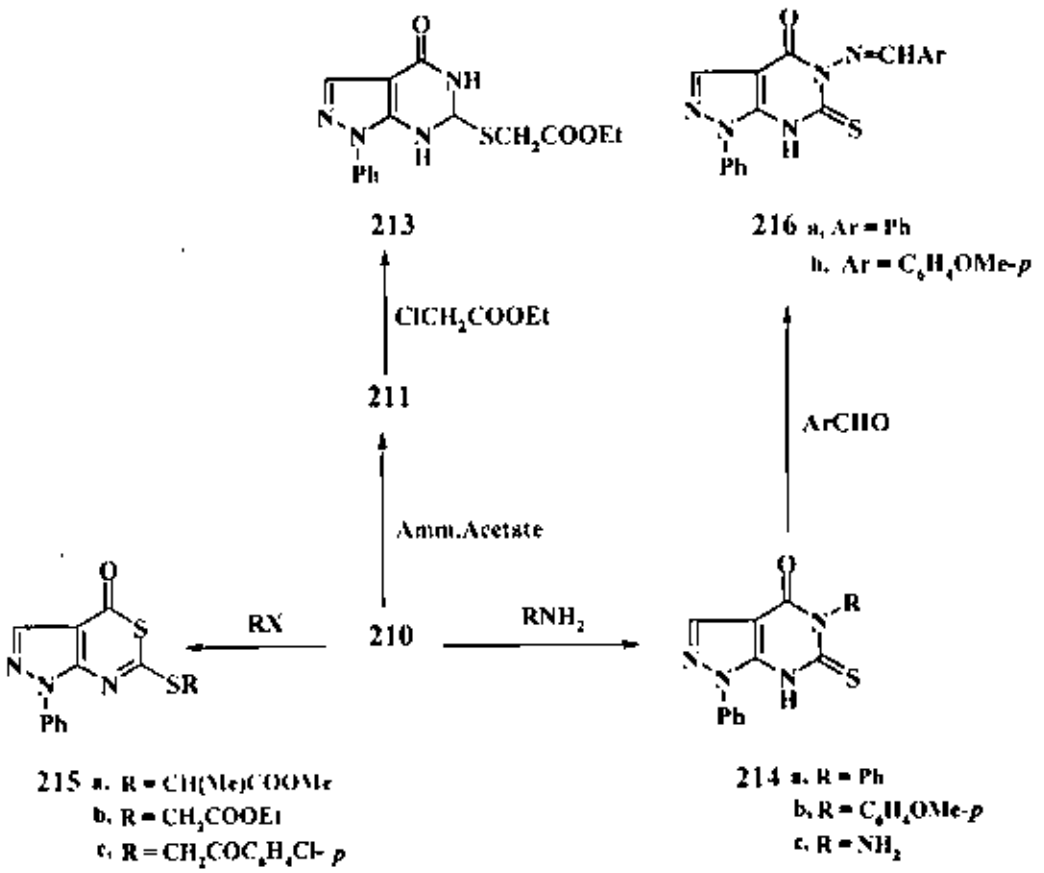
Also, the pyrazole derivatives **198a-c** undergo cyclization to afford several new pyrazolo[3,4-*d*]pyrimidines **204-207** when reacted with formic acid,. carbon disulfide, phenylisocyanate, phenylisothiocyanate, urea, thiourea and guanidine respectively.[125]



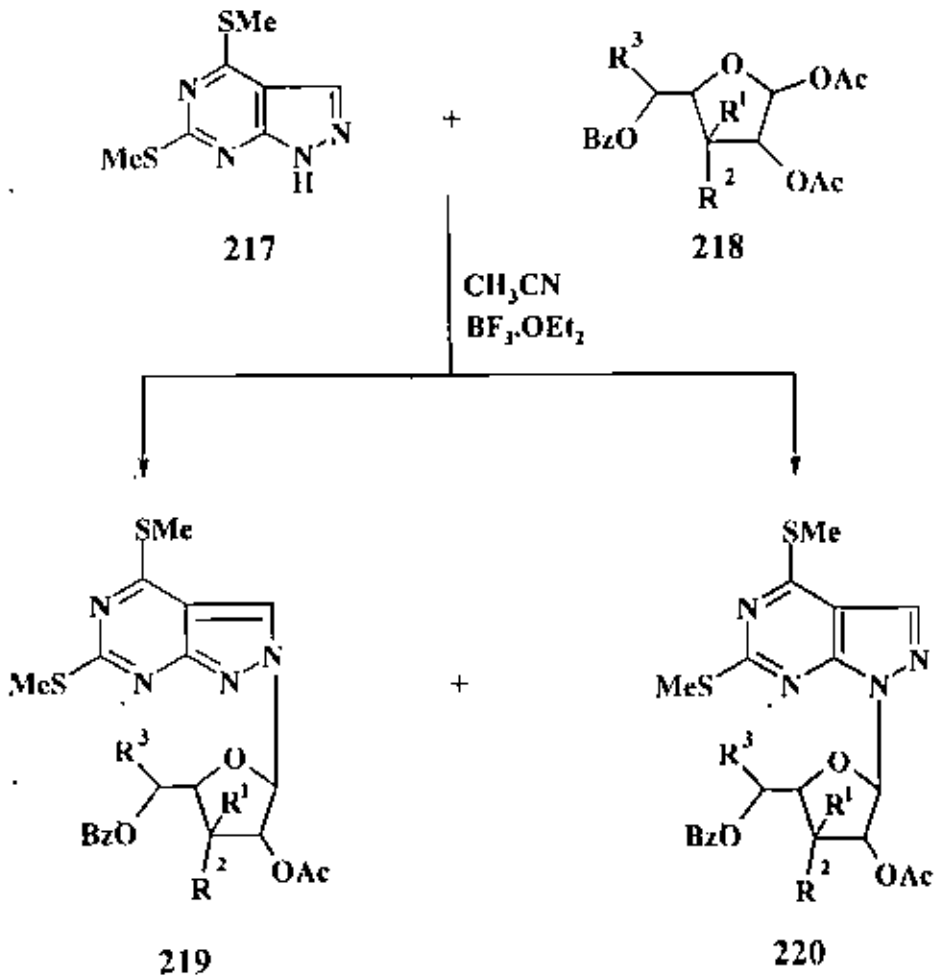
Treatment of arylmethylidenehydrazones **208a-e** with ethylortho-formate gave the pyrazolopyrimidines **209a-e**. Treatment of **208a** with carbon disulfide in pyridine gave pyrazolothiazinethione **210**. Pyrazolopyrimidinethione **211** could be obtained from the reaction of aminopyrazole **212** with carbon disulfide or by treatment of **210** with ammonium acetate.[126]



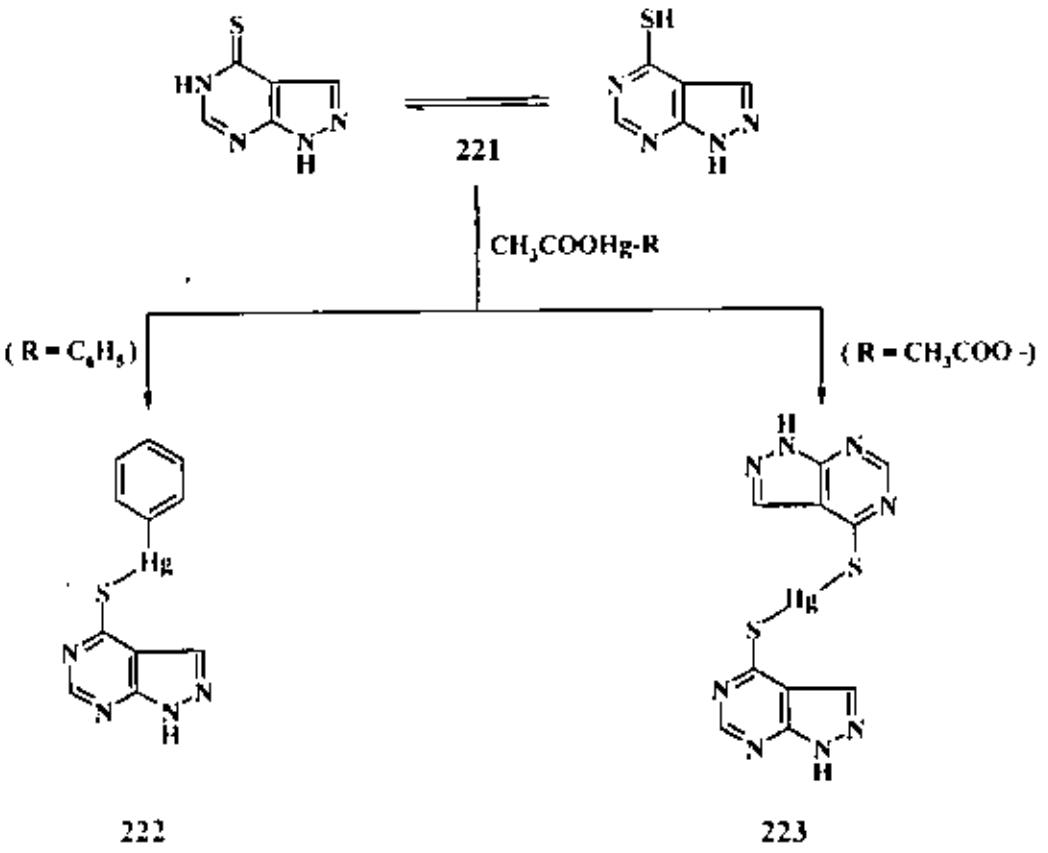
Moreover, the *S*-ester **213** could be obtained from the reaction of compound **211** with ethyl chloroacetate. Also, compound **210** reacted with aromatic amines or hydrazine hydrate to afford the pyrazolopyrimidine derivatives **214a-e**. The *S*-alkylated derivatives **215a-e** were produced through the reaction of **210** with α-haloesters.[126] Whereas, treatment of **214c** with aromatic aldehydes afforded the pyrazolopyrimidine derivatives **216**.[126,127]



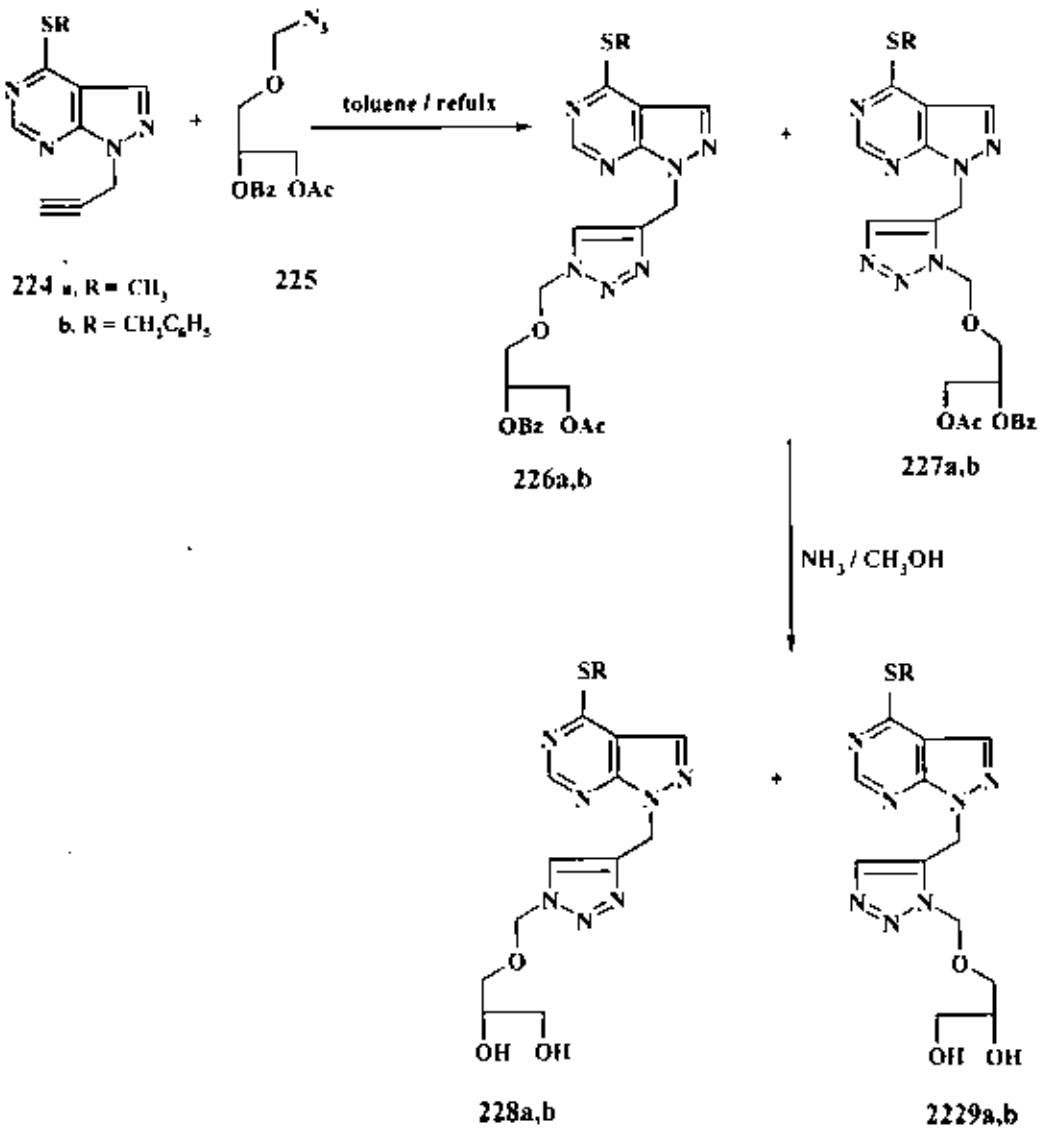
It was reported that glycosylation of 4,6-bis(methylthio)-(*1H*)-pyrazolo[3,4-*d*]pyrimidine **217** with 1,2-di-*O*-acetyl-3,5-di-*O*-benzoyl-*D*-xylofuranose **218** gave *N*-2-β-isomer **219** as the major product along with *N*-1-α-isomer **220**.[128–134]



The reaction of 4-mercaptopyrazolo[3,4-*d*]pyrimidine **221** with acetoxyhydrargyriobenzol afforded 4-(phenylhydrargyriothio)pyrazolo-[3,4-*d*]pyrimidine **222**. Also, compound **221** could be treated with mercuric acetate to afford bis-(4-pyrazolo[3,4-*d*]pyrimidylthio)-hydrargyrium **223**.[135,136]

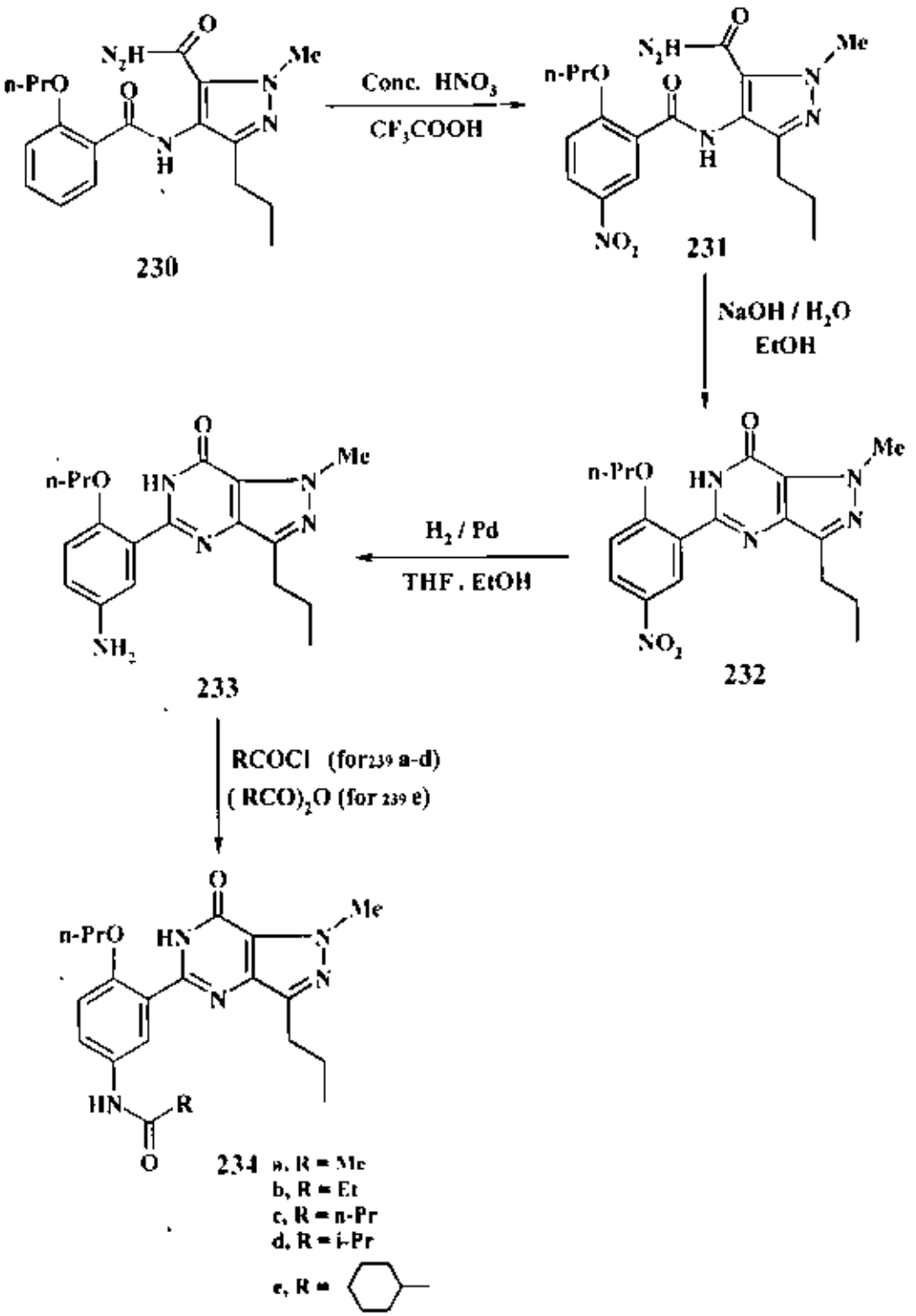


The reaction of 4-(methyl and benzyl)thio-1-propargyl-(*1H*)-pyrazolo[3,4-*d*]pyrimidines **224a,b** with azido-compound **225** afforded a mixture of two possible regioisomers (**226a,b** and **227a,b**) which by treatment with a solution of methanol saturated with ammonia affording the acyclic nucleosides **228a,b** and **229a,b**.[137,138]



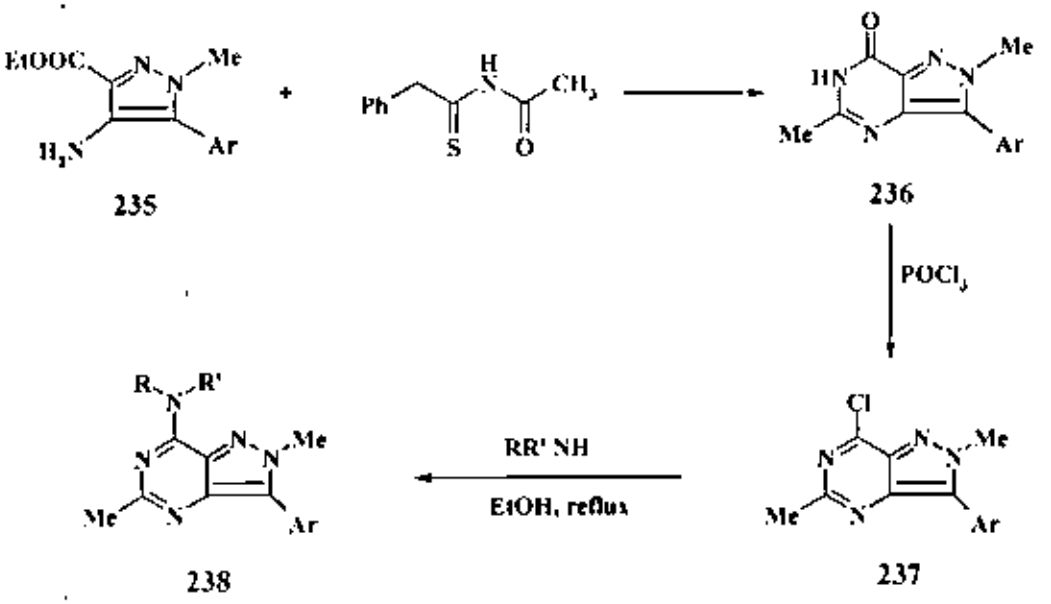
2.1.4 Pyrazolo[4,3-*d*] pyrimidine derivatives:

The synthetic reactions of pyrazolo[4,3-*d*]pyrimidine are very rare in letratures and few reactions are reported. Thus, nitration of 1-methyl-4-(2-*n*-propoxybenzamido)-3-*n*-propylpyrazole-5-carboxamide **230** afforded mono-nitroproduct **231**. Cyclization of **231** under basic condition afforded the corresponding pyrazolopyrimidinone **232**, which was reduced to the amino derivative **233.** The latter on acylation afforded the target phosphodiesterase 5 inhibitors **234a-e.**[139,140]



Treatment of aminopyrazoles **235** with benzyl thioacetimidate hydrobromide [95] in refluxing pyridine afforded the pyrazolopyrimidinone **236**, which on heating with phosphorus oxychloride in the presence of *N,N*-diethylaniline gave the corresponding chlorides **237**. Displacement

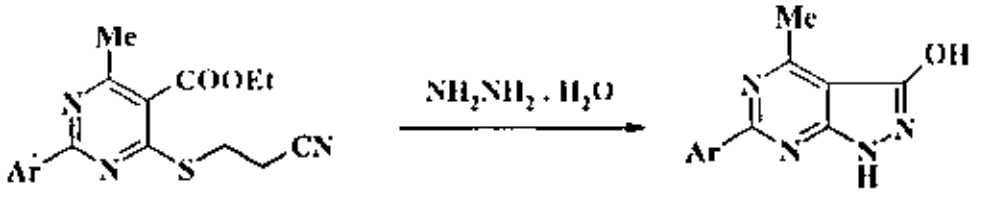
of **237** with the appropriate amine afforded the target 7-amino substituted pyrazolo[4,3-*d*]pyrimidines **238**.[141-144]



235 **236** **237** **238**

2.1.5 Pyrazolo[5,4-*d*]pyrimidine derivatives:-

It has been found that hydrazinolysis of 4-cyanoethylmercapto-pyrimidine **239** using hydrazine hydrate afforded the pyrazolo[5,4-*d*]-pyrimidine derivative **240**.[145]



239 **240**

(Ar = C_6H_4Cl-*p*)

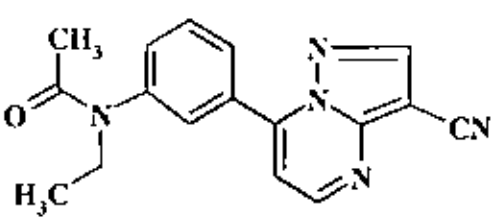
2.2 Biological activity of pyrazolopyrimidines:-

2.2.1 Pyrazolo[1,5-*a*] pyrimidine derivatives:

Suzki et al., studied that the five-member ring-fused nitrogen-containing pyrimidine compounds that can be used as a surrogate for the stucturally complex hexahydronaphthalene ring that present in the naturally occurring HMG-CoA reductase inhibitors which is the major rate limiting enzyme in cholesterol biosynthesis and hence, pyrazolo[1,5-*a*]pyrimidine ranked as hypocholesterolemics and so become important reagent for prevention of atherosclerotic diseases.[54]

It has been found that pyrazolo[1,5-*a*]pyrimidines are of considerable chemical and pharmacological importance as purine analogues. The purine analogue 4-hydroxypyrazolopyrimidine (allopurine), used in the treatment of hyperuricemia and gout, inhibits de novo purine biosynthesis and xanthine oxidase. Also, it was found that pyrazolo[1,5-*a*]pyrimidines possess various antimicrobial activities with minimal inhibitory concentration (MIC) values 100-125 $\mu g / ml$.[55]

Moore et al., noticed that zaleplon is pyrazolopyrimidine derivative hypnotic, whose chemical structure is unrelated to benzodiazepines or other known hypnotics. Zaleplon interacts with the GABA-BZ receptor complex which is thought to be responsible for the sedative, anxiolytic, muscle relaxant and anticonvulsive properties of the benzodiazepines so, it is used for insomnia (difficulty falling asleep) treatment.[146-160]



Zaleplon

Yasuda et al., suggested that Ot-7100 is a new type of analgesic compound named, 5-*n*-butyl-7-(3,4,5-trimethoxybenzoylaminopyrazolo-[1,5-*a*]pyrimidine) with the effect of normalizing the nociceptive threshold in peripheral neuropathic hyperalgesia.[161]

Elagamey et al.,[77] noticed the biological and medicinal activities of pyrazolopyrimidines as adenine analogues, antagonists and antitumor agents as these ring systems inhibit cAMP-phosphodiesterase. Robins found that pyrazolo[1,5-*a*]pyrimidines are potential drugs for schistosomiasis which is one of the most difficult diseases and is anational problem in many countries.[77,162-168]

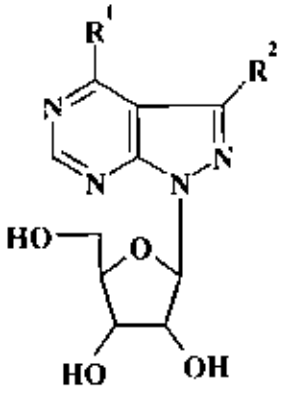
2.2.2 Pyrazolo[2,3-*d*] pyrimidine derivatives:

It was found that Src. tyrosine Kinase is a therapeutic target for bone diseases and Src has a positive regulatory role in Qsteoclasts and anegative regularty role in osteoblasts. The potential use of Src inhibitors for osteoporosis therapy has been shown by novel bone-targeted ligands of the Src SH_2 and non-bone-targeted, ATP-based inhibitors of Src kinase. Recently novel analogues of pyrazolopyrimidine template-based Src kinase inhibitors that incorporate bone-targeting group modifications designed to provide tissue (bone) selectivity and diminished side effects.[169,170]

2.2.3 Pyrazolo[3,4-*d*]pyrimidine derivatives:

Mercaptopyrazolopyrimidine derivatives **148** were tested *in vitro* against certain viruses, tumor cells and the parasite leishmania tropica and some of these compounds showed significant activity against para 3

viruses and were found to be potent inhibitors of growth of L1210 and P388 leukemia [102] as shown in table (1) :

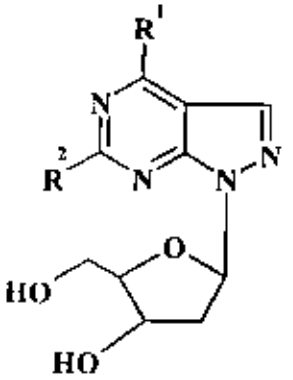


148

Table (1) Antiviral activity of mercaptopyrazolopyrimidines **148a-c:**

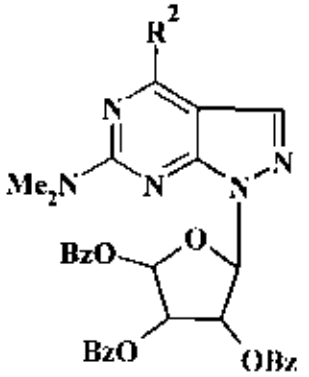
Compd.	R^1	R^2	Toxic Level	Virus rating			
				Para 3	VSV	VV	HSV 1
148a	OH	SMe	$5X10^{-3}$	0.11	Not tested	0	0.16
148b	SH	CN	Non toxic	1.10	0.56	1.24	1.00
148c	OH	$CSNH_2$	$5X10^{-3}$	1.15	0	0.40	0

Seela et al., noticed that a slight destabilization of the parallel-stranded (*P*s) DNA duplexes is observed when the 8-aza-7-deazaadenosine pyrazolo[3,4-*d*]pyrimidine derivative is introduced while the amino-8-aza-2,7-deazpurine nucleoside pyrazolo[3,4-*d*] pyrimidine derivative led to a strong decrease of the **Tm**-value, but incorporation of 8-aza-7-deaza-2,6-diaminopurine nucleoside increases the stability of the **Ps**-duplex while it did not alter the stability of a **Ps**-hybrid.[171]



a; $R^1 = NH_2$, $R^2 = H$
b; $R^1 = H$, $R^2 = NH_2$
c; $R^1 = R^2 = NH_2$

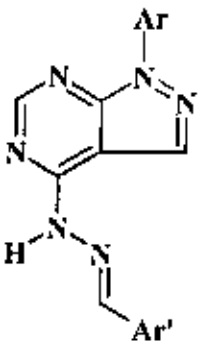
It was found that several pyrazolopyrimidine derivatives show an important effect in treatment of asthma, as they acted as new drugs useful as inhibitors of the release of histamine and other vasoactive mediators, such as leukotrienes and prostaglandins. It was found that pyrazolopyrimidine derivatives show inhibition similar to DSCG (disodium cromoglycate) which is one of the most extensively used drugs for this purpose.[116,172]



180

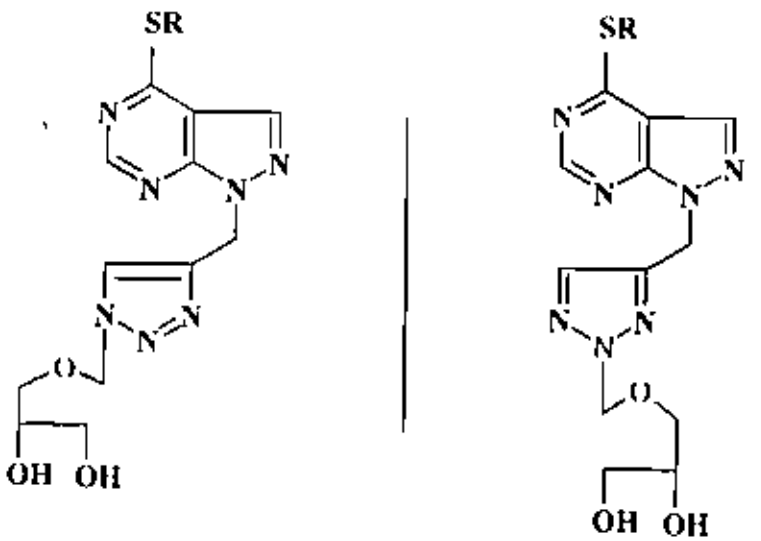
A series of 1-aryl-(*1H*)-pyrazolo[3,4-*d*]pyrimidin-4-arylhydrazones were discovered as novel inhibitors for glycogen synthase Kinase-3 (GSK-3) which is responsible for phosphorylation of glycogen synthase

(GS) (the rate-limiting step for glycogen synthesis). Also, it was found that GSK-3 activity and expression levels were significantly higher in the skeletal muscle from Type 2 diabetic humans than those in healthy subjects. So, this gave an evidence that GSK-3 activity may contribute to diabetes & Alzheimer's disease (AD).[121,173-175]



187

Chafiq et al.. has reported that some acyclic pyrazolo[3,4-*d*]-pyrimidine nucleosides were evaluated for their cytotoxicity and their inhibitory effects on HIV-1(IIIB) and HIV-2 (ROD) replication in MT-4 cells.[137]

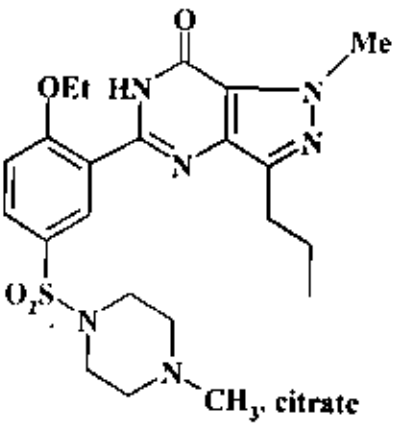


228, 229 a, R = Me
b, R = $CH_2C_6H_5$

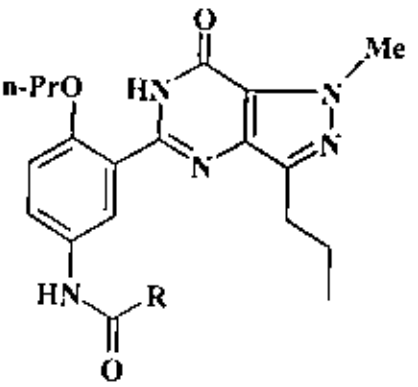
2.2.4 Pyrazolo[4,3-*d*] Pyrimidine derivatives:

It was found that 3-arylpyrazolo[4,3-*d*] pyrimidine derivatives act as functional antagonist at the corticotrophin-releasing factor (**CRF-1**) receptor. **CRF** is a modulator of the body's responses to stress and overstimulation of it causes several diverse neuropsychiatric diseases including depression, anxiety and stress-related disorders.[141,176,177]

Thus, 5-phenyl-1,6-dihydro-(7*H*)-pyrazolo[4,3-*d*]pyrimidine-7-one was found to act as potent agent in the treatment of male erectile dysfunction (**MED**) via its inhibition for phosphodiesterase type 5 (**PDE5**) activity so leading to enhanced relaxation of smooth muscle, increased arterial flow, venous congestion and so, resulting in improved penile erection in men with erectile dysfunction.[139,178,179]



Viagra



234a-e

ORIGINAL WORK

RESULTS AND DISCUSSION

3. Results and Discussion

Synthesis of Some New Purine-Related Compounds

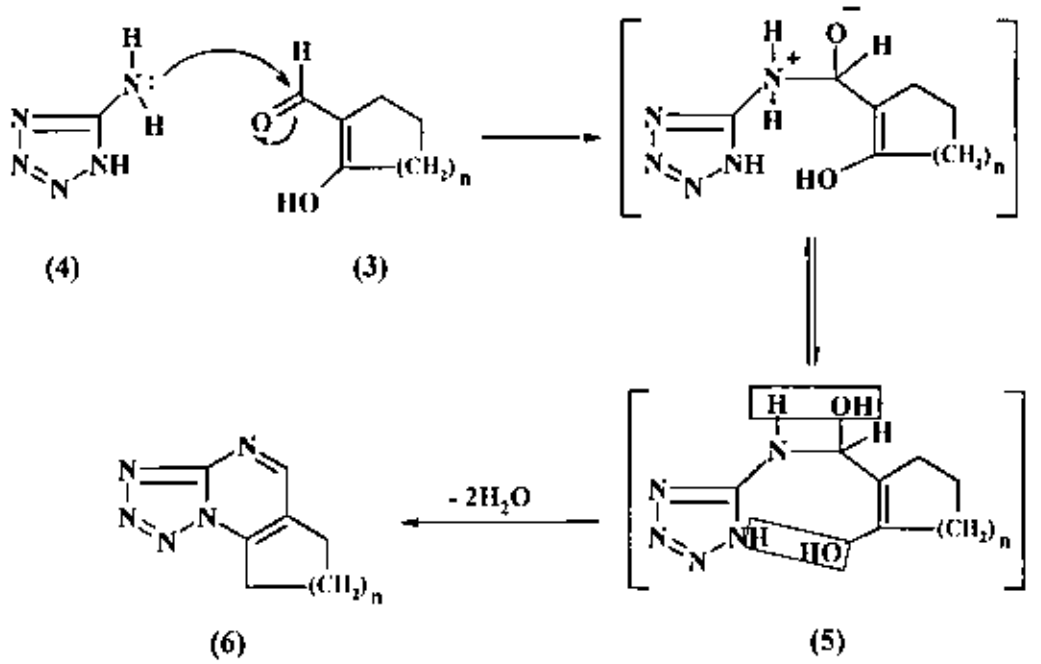
3.1 Regioselective one-pot synthesis of novel tetrazolo[1,5-*a*]-pyrimidine derivatives:

It has been declared from literature survey that articles for synthesis of tetrazolopyrimidines are rare,[180-184] but to some extent, a large number of patents were found in their vital biological activities in the last few years.[185-189] Tetrazole compounds, specially tetrazolopyrimidines play an essential role in several biological processes and have very important chemical and pharmacological importance. They are used in the treatment of obesity, diabetes, atherosclerosis, hypertension, coronary heart disease, hypercholesterolemia, hyperlipidemia, thyroid disease, thyroid cancer, hypothyroidism, depression, glaucoma, cardiac arrhythmias, and congestive heart failure.[190, 191]

Since the direct introduction of some specific substances for construction of tetrazolopyrimidines nucleus is not always easy, new methods for direct synthesis of these compounds from readily available starting materials have been of a great interest. In the present work, we described an easy and efficient route for the synthesis of tetrazolopyrimidines by the reaction of 5-aminotetrazole and the early-synthesized sodium salts of formyl ketones (**2**)[192]. Thus, treatment of 5-amino-1*H*-tetrazole hydrate (**4**) with the sodium formyl salts of cyclic ketones, namely sodium (2-oxocycloalkylidine)methenoates (**2**) in the presence of aqueous piperidine acetate and acetic acid as a one-step reaction, afforded in a good yield (69-73 %) the solid reaction products.

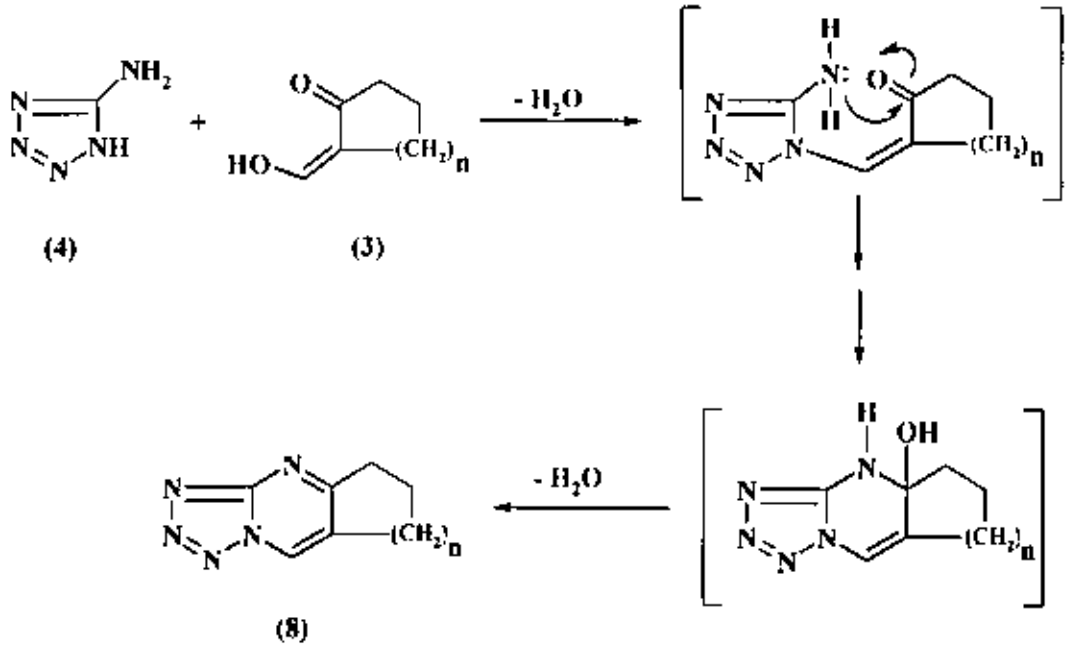
The reaction products were suggested to be cycloalkane ring-fused tetrazolo[1,5-*a*]pyrimidines (6) and not the isomeric tetrazolopyrimidines (8) as outlined in chart (1).

The reaction mode for the formation of the products is suggested to



proceed through the initial nucleophilic attack by the exocyclic amino group at the formyl group of compound (3), that formed *in situ* due to the reaction of the formyl salts (2) with water, followed by cyclization through the elimination of two water molecules leading to the formation of the reaction products (6).

The suggestion of the formation of the alternative isomeric planer products (8) is based on the probability of the initial attack of the indocyclic NH of the tetrazole ring, which is expected to be more nucleophlic at the formyl group in (3) followed by cyclization and climination of water. This suggestion is principally excluded due to the more streic hindrance around the endocyclic nitrogen atom than the exocyclic one that can easily attack the unhindered and the electronically favoured formyl group of compound (3).



(4) (3) (8)

The characterization of the reaction products was confirmed by using the available elemental analysis and spectral data (IR, Ms, ^{1}H NMR). Thus, the structure of compound (6b) was established according to the following data:

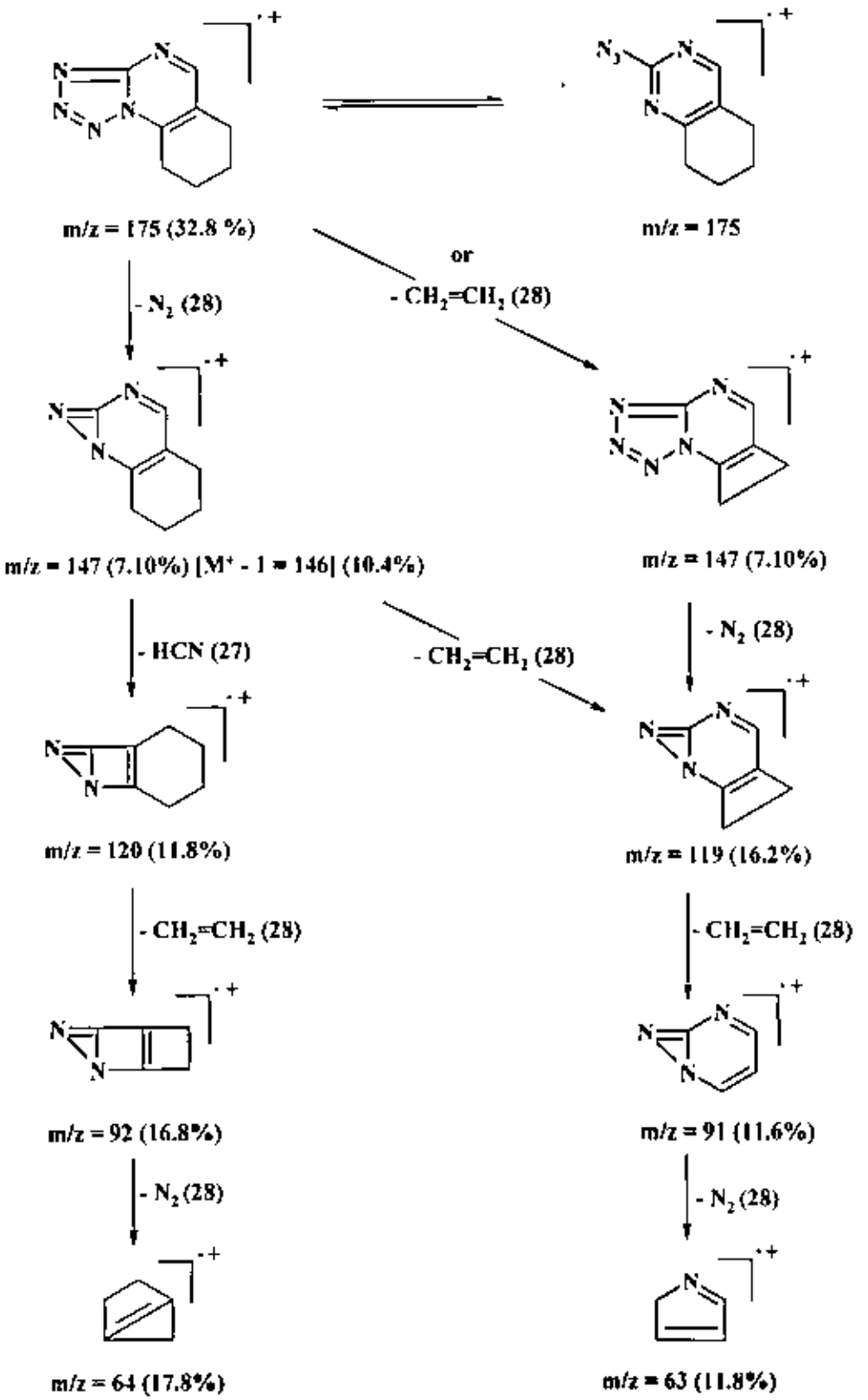
a) Correct elemental analysis that compatible with the compound's chemical formula $C_8H_9N_5$.

b) The IR (KBr) spectrum of compound (6b) showed the absence of the peaks related to NH or NH_2 of the start and revealed bands at ύ = 2948 Cm^{-1}, (paraffinic CH), 1655 Cm^{-1} (C=N), and at 1619 Cm^{-1} (C=C). (fig. 3).

c) The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) revealed the presence of signals at δ = 1.96-2.11 ppm (m, 4H, $2CH_2$); 2.91-3.33 (m, 4H, $2CH_2$), 8.70 (s, 1H, pyrimidine proton). (fig. 4).

d- The mass spectrum of this compound showed a molecular ion peak at m/z = 175 (32.8%) coincident with the molecular weigh of the compound (175.19) and revealed the base peak at 107 (100%). (fig. 5).

e- The fragmentation pattern of (6b) has been shown in scheme [1].



Fragmentation pattern of compound (6b)

Scheme [1]

3.2 Synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives as new purine analogues:

Pyrazolopyrimidine systems, as they are structurally related to purine, are considered typical examples for purine analogues that are reported in literatures as inhibitors for the synthesis of DNA and RNA in the cells of some kinds of cancers[171] and viruses[102, 137]. Also, purine analogues are widely used in the CNS stimulation *in vivo*[1139, 146-155], antagonists[116], antibacterial[172] and in the treatment of gout[55]. Many patents in the field of synthesis and biological activity of pyrazolopyrimidines have been reported[193, 194].

In this part, an interesting series of pyrazolopyrimidines were prepared through the reaction of aminopyrazoles with the sodium formyl salts of cycloalkanones. Thus, the reaction of 3,4-disubstitued 5-aminopyrazoles (**9**) with the formyl salts (**2**) afforded in an excellent yield (78-89 %) the products that were assumed to be the pyrazolo[1,5-*a*]pyrimidine derivatives (**10a-y**) under the same reaction condition and following the same reaction mechanism discussed in the preparation of tetrazolopyrimidines (**6**). Chart (2).

The structures of compounds (**10**) were confirmed using their elemental analysis and spectral data (IR, Ms, ^{1}H NMR). Thus, the structure of compound (**10b**) was established as follows:

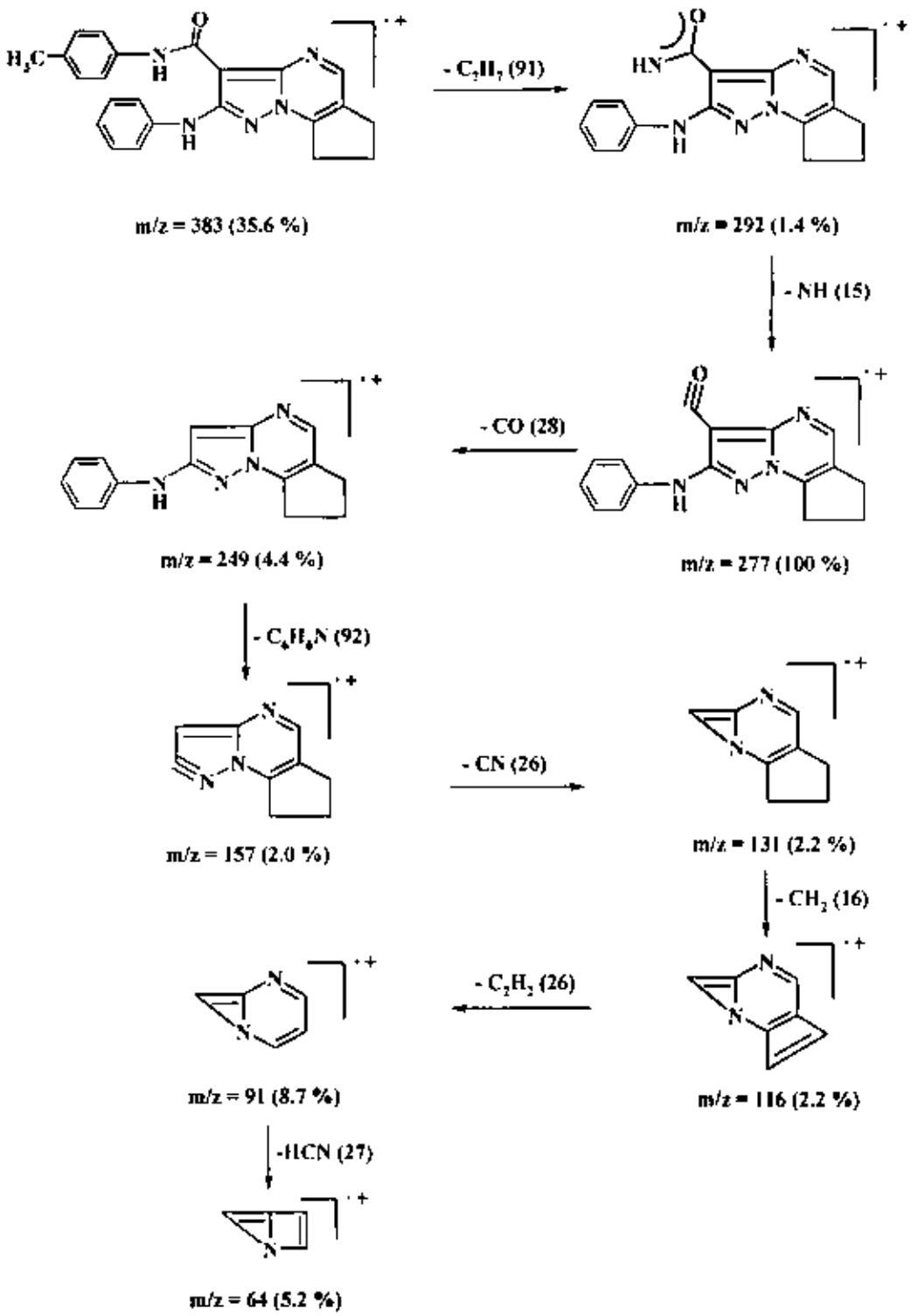
a) The compound has a correct elemental analysis compatible with its chemical formula $C_{23}H_{21}N_5O$.

b) The IR (KBr) spectrum of compound (**10b**) showed the absence of the peaks related to NH_2 of the starting pyrazole and revealed bands at ύ = 3307 Cm^{-1} (NH), 2920 Cm^{-1}, (paraffinic CH), and at 1650 Cm^{-1} (enolic C=O). (fig. 12).

c) The ^{1}H NMR spectrum (300 MHz, $CDCl_3$) revealed singlet peak at δ = 1.56 ppm. related to the p-CH_3 group; 2.31.2.38 ppm. (m, 2H, CH2); 3.08-3.13 (m, 2H, CH2); 3.77-3.3.43 (m, 2H, CH2); 6.96-7.76 (m, 9H, aromatic protons); 8.35 (s, 111, pyrimidine proton); 9.59 (s, 1H, NH); 9.87 (s, 1H, NH). (fig. 13).

d- The mass spectrum of compound (**10b**) showed the molecular ion peak at m/z = 383 (35.6%) coincident with the molecular weigh of the compound (383.46) with the base peak at m/z = 277 (100%). (fig. 14).

e- The fragmentation pattern of (**10b**) has been shown in scheme [2].



Fragmentation pattern of compound (10b)

Scheme [2]

The behavior of aminopyrazoles towards the sodium formyl salts of aliphatic and aromatic acyclic ketones was also investigated. Thus, some selected derivatives of the 5-aminopyrazoles (**9**) were condensed with sodium formylacetone (**11**) in piperidine acetate and acetic acid to afford the 2-anilino-7-methyl-*N*-arylpyrazolo[1,5-*a*]pyrimidine-3-carboxamides (**12**). Other derivatives of the aminopyrazoles (**9**) were allowed to react with sodium formyl acetophenone (**13**) as acyclic aromatic ketone to give the 2-anilino-7-phenyl-*N*-arylpyrazolo[1,5-*a*]pyrimidine-3-carboxamides (**14**) as shown in chart (2).

The structure of compound (**12a**) was confirmed through the following data:

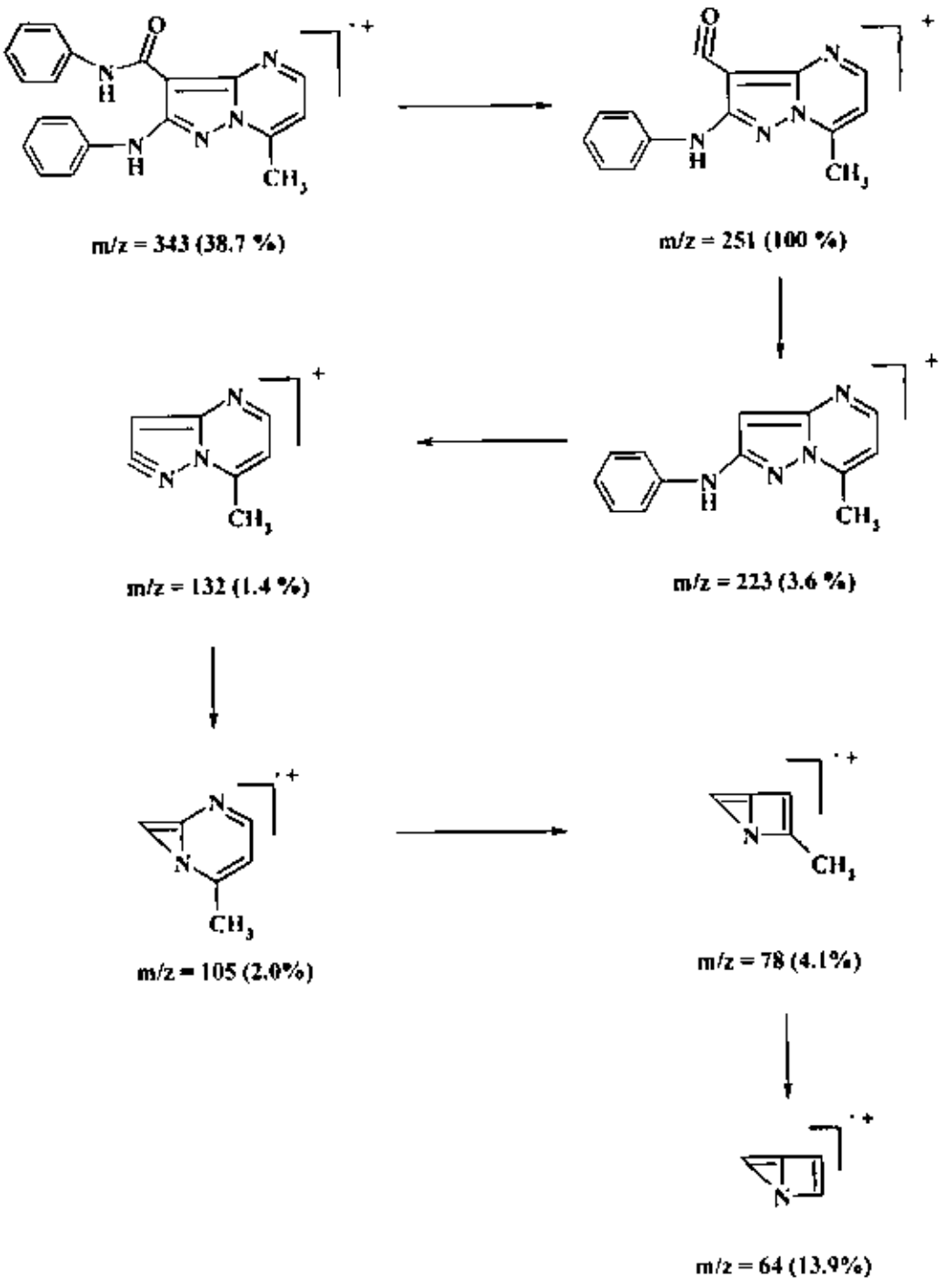
a) Correct elemental analysis for the molecular formula $C_{20}H_{17}N_5O$.

b) The IR (KBr) spectrum of (**12a**) showed the absence of the peaks related to NH_2 of the starting pyrazole and revealed bands at υ = 3304 Cm^{-1} (NH), 2923 Cm^{-1}, (paraffinic CH), and at 1653 Cm^{-1} (enolic C=O), 1597 Cm^{-1} (C=N. (fig. 47).

c) The ^1H NMR spectrum (300 MHz, $CDCl_3$) revealed a singlet at δ = 2.77 ppm. related to the CH_3 group and at δ = 6.68-7.76 ppm. (m, 10H, aromatic protons); 8.32 (s, 1H, pyrimidine C=CH); 8.34 (s, 1H, pyrimidine N=CH); 9.54 (s. 1H. NH); 9.88 (s, 1H, NH). (fig. 48).

d- The mass spectrum of this compound revealed a molecular ion peak at m/z = 343 (38.7%) coincident with the molecular weigh of the compound (343.39) and showed the base peak at m/z = 251 (100%). (fig. 49).

e- The fragmentation pattern of (12a) has been shown in scheme [3].



Fragmentation pattern of compound (12a)

Scheme [3]

Also, the structure of compound (**14a**) was confirmed as follows:

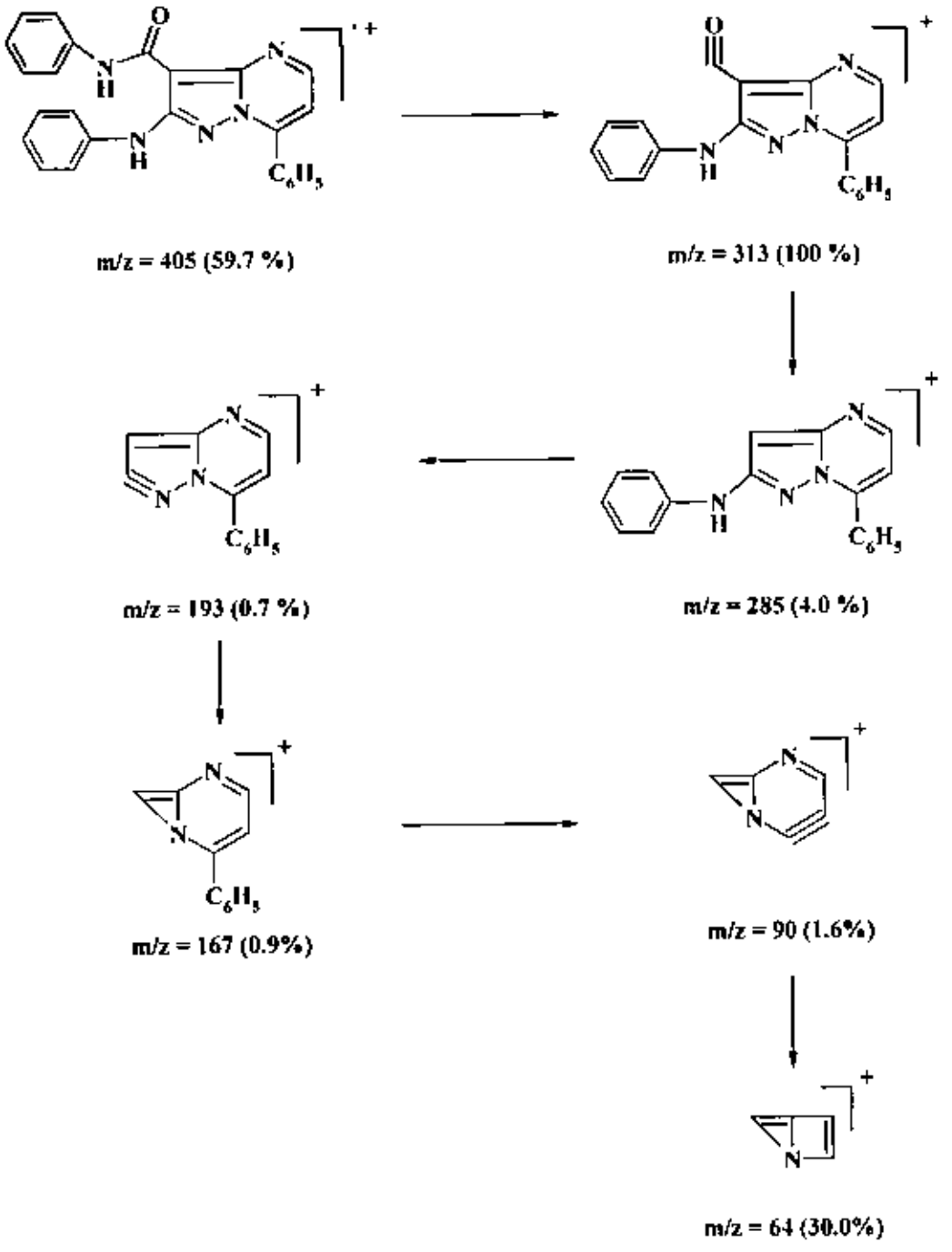
a) Correct elemental analysis for the molecular formula $C_{25}H_{19}N_5O$.

b) The IR (KBr) spectrum of (**14a**) showed bands at ύ = 3311 Cm^{-1} (NH); 1648 Cm^{-1} (enolic C=O), 1597 Cm^{-1} (C=N); 1555 Cm^{-1} (C=C). (fig.52).

c) The ^1H NMR spectrum of compound (**14a**) (300 MHz, $CDCl_3$) showed peaks at δ = 6.98-8.22 ppm. (m, 15H, aromatic protons); 8.53 (s, 1H, pyrimidine C=CH); 8.55 (d, 1H, pyrimidine N=CH); 9.65 (s, 1H, NH); 10.14 (s, 1H, NH). (fig. 53).

d- The mass spectrum of (**14a**) revealed a molecular ion peak at m/z = 405 (59.7%) coincident with the molecular weigh of the compound (405.46) and showed the base peak at m/z = 313 (100%). (fig. 54).

e- The fragmentation pattern of (**14a**) has been shown in scheme [4].



Fragmentation pattern of compound (14a)

Scheme [4]

3.3 Novel synthesis of 3*H*-pyrimido[1,6-*a*]pyrimidine derivatives :

Here, the construction of some new and interesting pyrimidopyrimidines, the ring systems that can be found in marine–derived natural products such as crambescidin[195] and batzelladine[196] alkaloids has been achieved. Pyrimidopyrimidines are an important class of annulated uracil and thiouracil of biological importance[197] because of their connection with purine pteridine systems.[198] Several patents have been reported for the preparation of these fused heterocycles, derivatives of which are useful as bronchodilators[199], Vasodilators[200], antiallergic[201], antihypertensive[202], and anticancer[199] agents.

Recently, pyrimidopyrimidines, analogues of folic acid (one of the B vitamins that is a key factor in the synthesis of nucleic acids RNA and DNA) have been screened for anti-tumor activity,[203] as they exhibit observable inhibition of the human Epidermal Growth Factor Receptors (EGFRs) that occurs frequently in human cancers and is associated with aggressive tumor behavior and poor patient prognosis.[204]

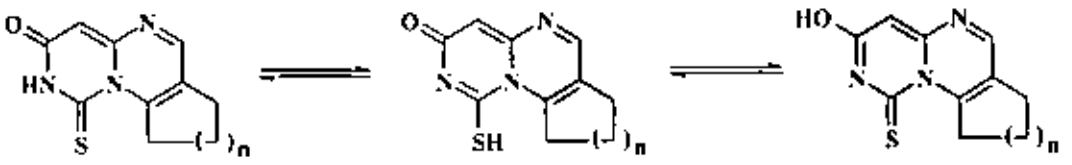
In fact, a great number of articles has been reported in literatures on the synthesis of different pyrimidopyrimidine ring systems, but a few of them has been found for the synthesis of pyrimido[1,6-*a*]pyrimidines, and the most promising methods for the synthesis of these systems are almostly multistep synthesis[205,206]. However, our synthetic strategy commences from the easily available compound, 6-aminothiouracil and the sodium salts of formyl ketones, which led to the construction of the requested pyrimido[1,6-*a*]pyrimidine nucleus.

Thus, fusion of 6-aminothiouracil with the formyl salts of cyclic ketones (**2**) in piperidine acetate and acetic acid afforded in considerable

yields the cyclocondensed pyrimido[1,6-*a*]pyrimidines **(16a-d)** as outlined in chart (3).

The identity of compounds (**16**) was proven on the basis of their elemental analysis and spectral data (IR, Ms, ^{1}H NMR).

However, the nucleus of pyrimido[1,6-*a*]pyrimidine has more than one resonating forms must be taken in consideration while we discuss their spectral data. This ring system may be found in the following resonating forms:



A B C

Considering these resonating forms, the structure of compound (**16c**) was supported by the following:

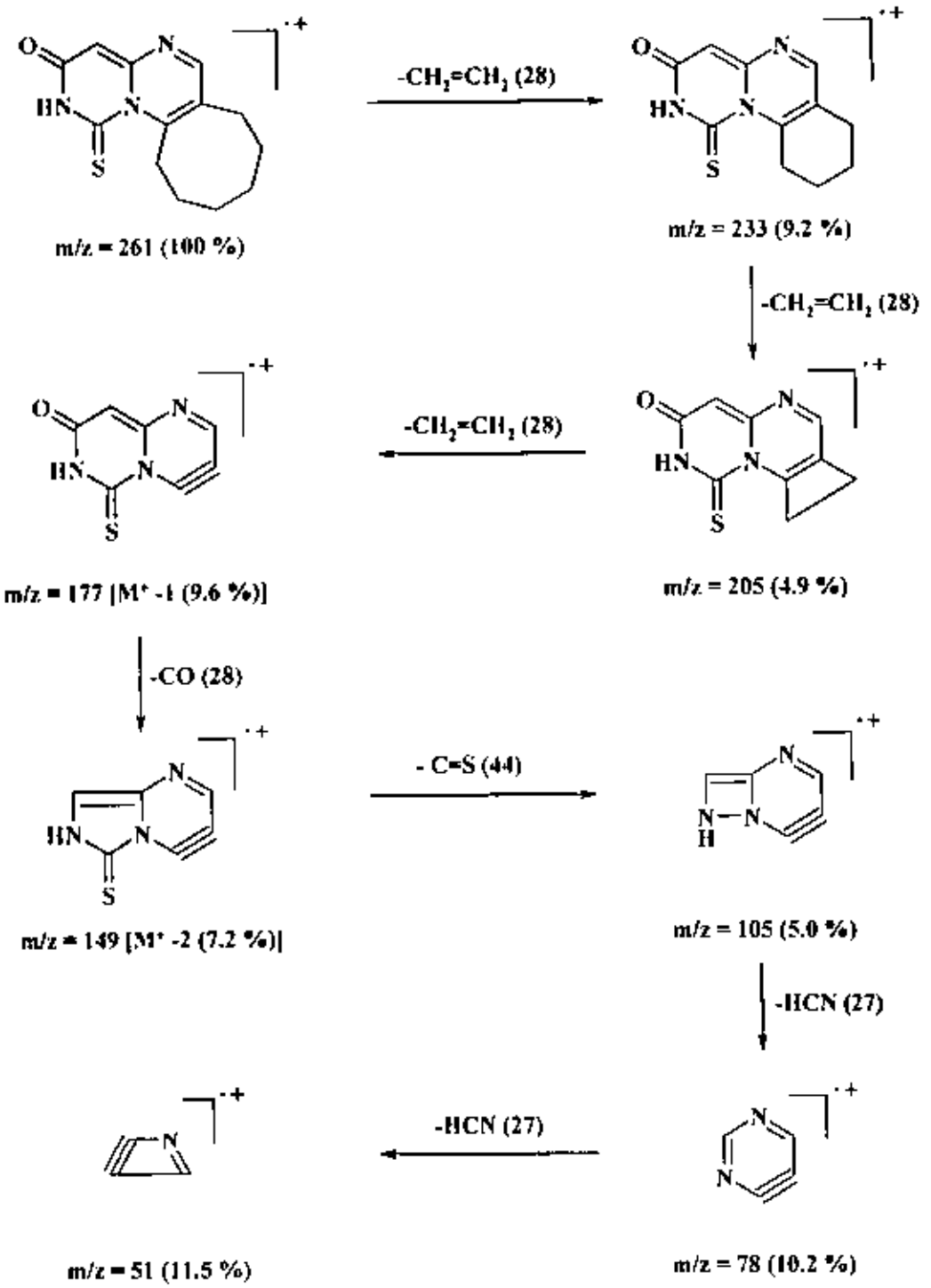
a) Correct elemental analysis that compatible with the chemical formula $C_{13}H_{15}N_3OS$.

b) The IR (KBr) spectrum revealed bands at υ = 3427 Cm^{-1} (NH); 2927 (paraffinic CH); 1680 (C=O); 1135 (C=S), 1541 (C=N). (fig. 67).

c) The ^{1}H NMR spectrum (300 MHz, DMSO) showed signals at δ = 1.29-1.67 ppm (m, 4H, $2CH_2$); 2.42-2.92 (m, 4H, $2CH_2$); 3.22-3.41 (m, 4H, $2CH_2$), 7.99 (s, 1H, pyrimidine N=C-H); 8.01 (s, 1H, pyrimidine C=CH); 12.39 (br s, 1H, OH); 12.91 (br s, 1H, SH). (fig. 68)

d- The mass spectrum of this compound showed a molecular ion peak at m/z = 261 (100%), the base peak, coincident with the molecular weigh of the compound (261.35). (fig. 69).

e) The mass fragmentation pattern of compound (**16c**) is shown in scheme [5].



Fragmentation pattern of compound (16c)

Scheme [5]

A successful trying for establishment of the phenomenon has been carried out by the reaction of 6-aminothioiuracil with the sodium salts of acyclic ketones (**11**) and (**13**) under the same reaction conditions to afford 4-methyl-6-thioxo-6,7-dihydro-8*H*-pyrimido[1,6-*a*]pyrimidin-8-one (**17**) and 4-phenyl-6-thioxo-6,7-dihydro-8*H*-pyrimido[1,6-*a*]pyrimidin-8-one (**18**) respectively.

The structures of the reaction products were confirmed using their elemental analysis and spectral data (IR, Ms, ^{1}H NMR). Thus, the structure compound (**17**) was established as follows:

a) Its elemental analysis is correct and compatible with its molecular formula $C_8H_7N_3OS$.

b) The IR (KBr) spectrum revealed bands at ύ = 3427 Cm-1 (enolic OH); 3325 (NH); 1627 (C=O); 1552 (C=S). (fig. 72)

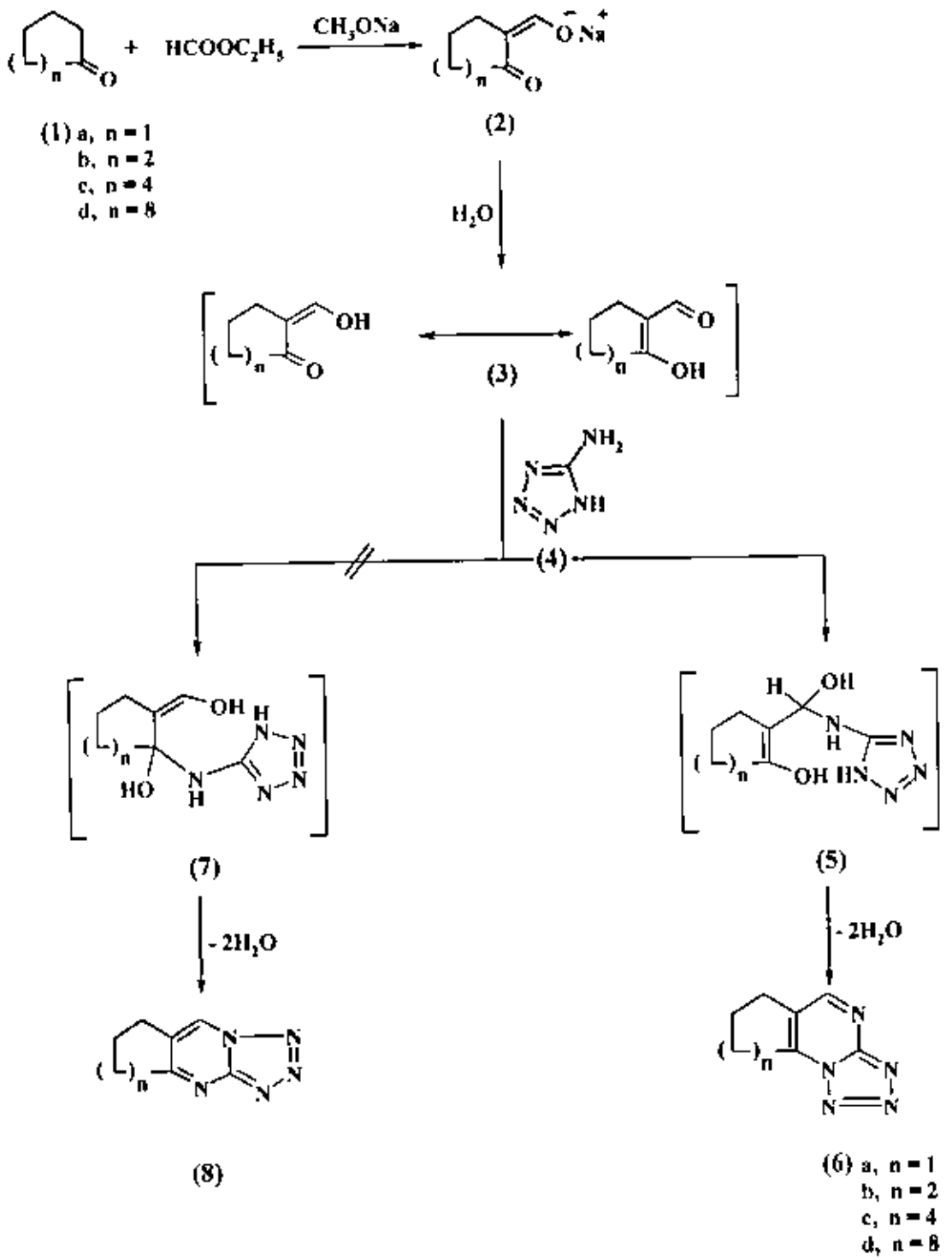
c) The mass spectrum of compound (**17**) showed a molecular ion peak at m/z = 193 (37.4%) coincident with its molecular weigh (193.23) and the base peak appeared at m/z = 186 (100 %). (fig. 73).

The structure compound (**18**) was confirmed by:

a) Its correct elemental analysis that compatible with its molecular formula $C_{13}H_9N_3OS$.

b) The IR (KBr) spectrum revealed bands at ύ = 3434 Cm-1 (enolic OH); 3325 (NH); 1630 (C=O); 1552 (C=S). (fig. 74).

c) The mass spectrum of compound (18) showed the molecular ion peak at m/z = 255 (0.7%) coincident with its molecular weigh (255.30). (fig. 75).



(1) a, n = 1
b, n = 2
c, n = 4
d, n = 8

(2)

(3)

(4)

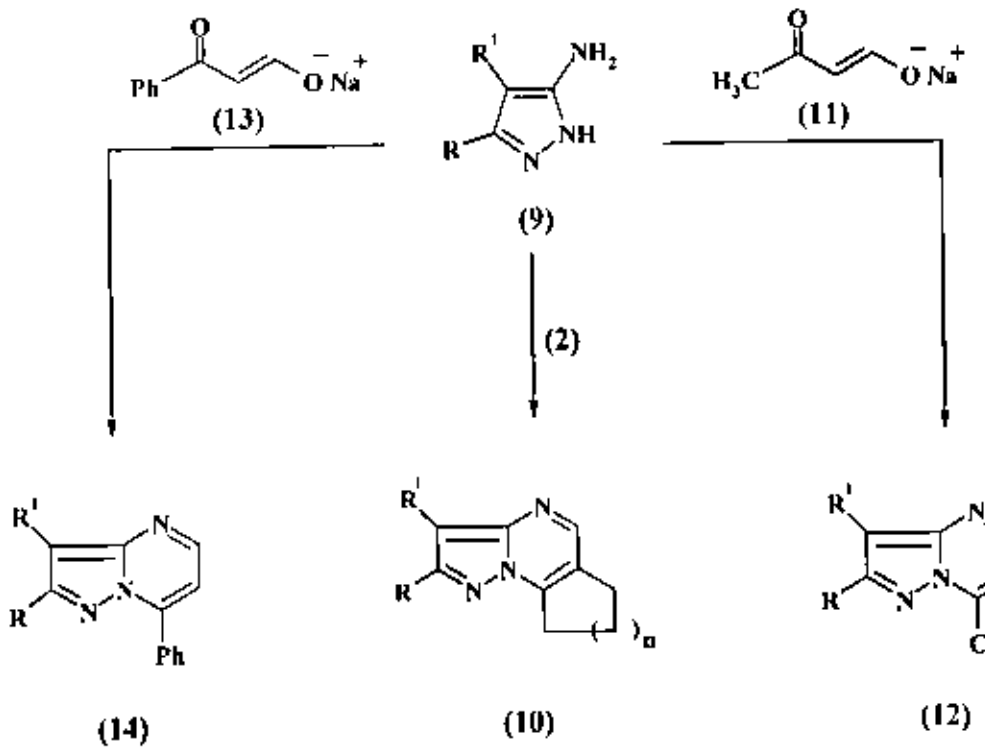
(5)

(6) a, n = 1
b, n = 2
c, n = 4
d, n = 8

(7)

(8)

Chart (1)



(14)	R	R'
a	NHPh	CONHPh
b	NHPh	CONHPhMe-p
c	NHPh	CONHPhCl-p
d	NHPh	CONHPhOMe-p
e	NHPh	CONHPhBr-p
f	NHPhCl-p	CONHPhMe-p
g	NHPhCl-p	CONHPhCl-p
h	NHCOPh	CONHPh

(12)	R	R'
a	NHPh	CONHPh
b	NHPh	CONHPhMe-p
c	NHPh	CONHPhCl-p

Chart (2)

(10)	n	R	R^1	(10)	n	R	R^1
a	1	NHPh	CONHPh	q	4	NHPh	CONHPh
b	1	NHPh	CONHPhMe-p	r	4	NHPh	CONHPhMe-p
c	1	NHPh	CONHPhCl-p	s	4	NHPh	CONHPhCl-p
d	1	NHPh	CONHPhOMe-p	t	4	NHPhCl-p	CONHPhCl-p
e	1	NHPh	CONHPhBr-p	u	4	NHCOPh	CONHPh
f	1	NHPhCl-p	CONHPhMe-p	v	8	NHPh	CONHPh
g	1	NHPhCl-p	CONHPhCl-p	w	8	NHPh	CONHPhMe-p
h	1	NHCOPh	CONHPh	x	8	NHPh	CONHPhCl-p
i	2	NHPh	CONHPh	y	8	NHCOPh	CONHPh
j	2	NHPh	CONHPhMe-p				
k	2	NHPh	COPNHPhCl-p				
l	2	NHPh	CONHPhOMe-p				
m	2	NHPh	CONHPhBr-p				
n	2	NHPhCl-p	CONHPhMe-p				
o	2	NHPhCl-p	CONHPhCl-p				
p	2	NHCOPh	CONHPh				

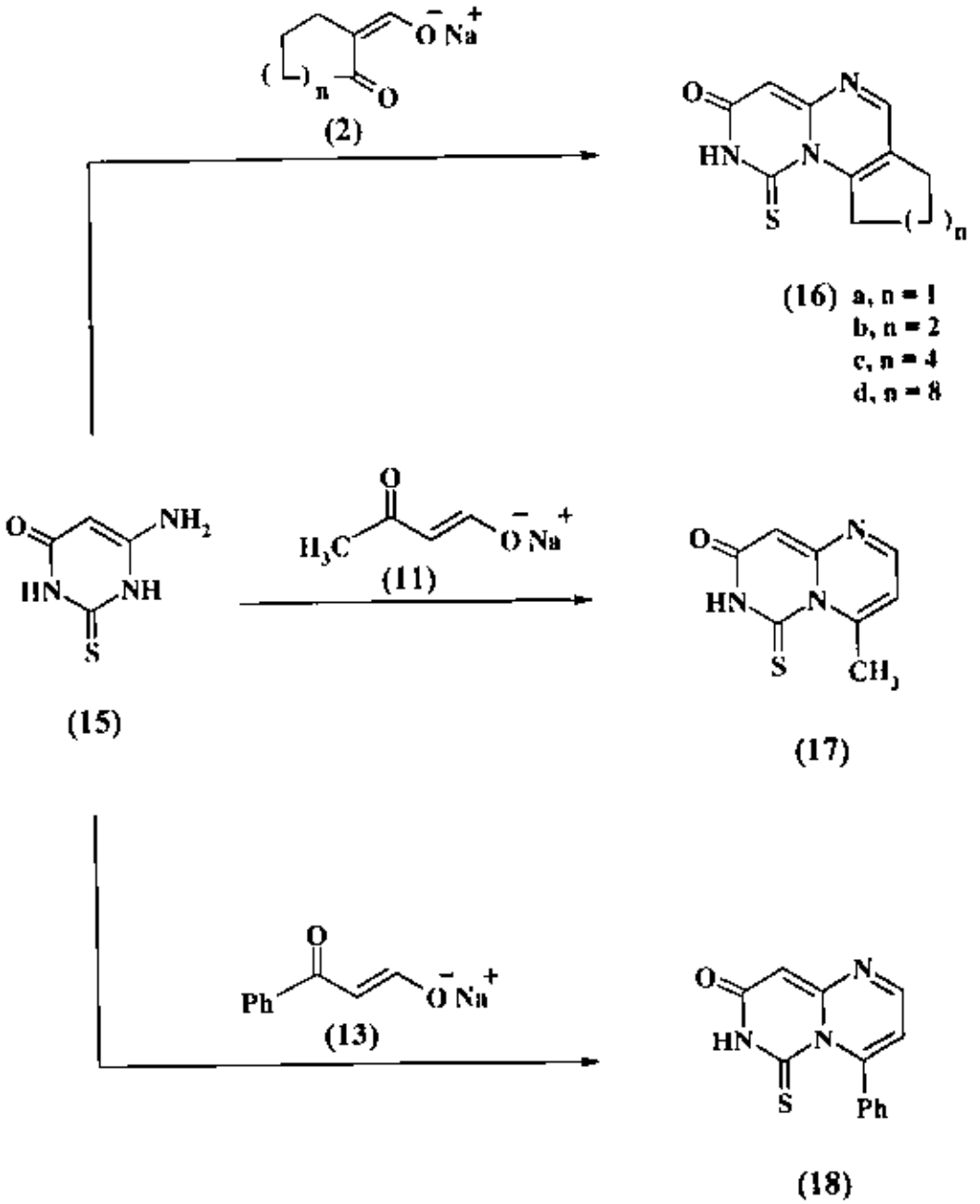


Chart (3)

BIOLOGICAL ACTIVITY

4. BIOLOGICAL ACTIVITIES

4.1 Preliminary Antimicrobial Screening

Test organisms:

Ten selected compounds were screened for their antimicrobial activity using five selected standard isolates which have been chosen as representative examples of different types of microorganisms as follows: Gram's positive both non sporulated bacteria as *Staphylococus aureus* and sporulated as *Bacillus subtilis*, Gram's negative as *Escherichia coli* and *Pseudomonas aeruginosa* and a fungus as *Candida albicans*.

Method: Agar Dilution Technique: [207]

The used Agar Dilution Method is a recent technique for testing the antimicrobial activities of drugs against Gram's positive and Gram's negative bacteria and also against fungi.

Procedure:

The appropriate volumes of membrane filtered stock solution of 0.05 gm/5ml of each compound were prepared by the two-fold dilution method to obtain the concentrations: 400, 200, 100, 50 and 25 (µg/ ml). The volumes were added to the molten LB agar (about 50°C). After mixing, the media were allowed to harden and dry by placing in an incubator at 37°C for 10 minutes.

Plates containing serial dilutions of each compound were inoculated with a sterile multiinculator onto the surface of the agar medium so that the final inoculum of each isolate on the agar surface was in order of 10^4 to 10^5 CFU/spot.

Ciprofloxacin and Triflucan were used as positive controls and the solvent, dimethylsulfoxide (DMSO) as negative control. Minimum inhibitory concentrations (MIC's) were read after 18 hours incubation at 37°C for bacteria and 25°C for fungus. The MIC is reported as the lowest concentration of the compound that prevents the growth of visible colonies.

Results and discussion:

The obtained MIC's of ten representative examples were presented in table (1).

Table (1):

Compd. no.	*S .aureus*	*B. subtilis*	*E. coli*	*Ps. aeruginosa*	*C. albiacns*
18	≥1600	≥800	≥800	≥800	≥800
10w	≥1600	≥800	≥800	≥800	≥800
16d	≥1600	≥800	≥800	≥800	≥800
6a	≥1600	≥800	≥800	≥800	≥800
12b	≥1600	≥800	≥800	≥800	400
16b	≥1600	≥800	≥800	≥800	≥800
12c	≥1600	≥800	≥800	≥800	≥800
16c	≥1600	≥800	≥800	≥800	≥800
16a	≥1600	≥800	≥800	≥800	≥800
10g	≥1600	≥800	≥800	≥800	≥800
DMSO	>1600	>800	>800	>800	>800
Ciprofloxacin	≤100	≤25	≤25	400	≥800
Triflucan	≥800	≥800	≥800	≥800	≤25

As shown from the table, there is variability in the susceptibilities of the different organisms to the different tested compounds. *Staphylococus aureus*

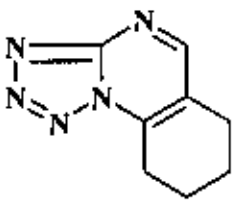
were the most resistant organism. Some compounds showed antibacterial activity, while others showed antifungal activity.

On conclusion. the tested compounds exhibited a moderate to low activity against the tested bacteria and fungus as shown in table (1).

4.2 Specific Biological Activities:

Two selected compounds are chosen for some important biological activities *in vivo* and *in vitro* treatments.

A) 6,7,8,9-Tetrahydrotetrazolo[1,5-*a*]quinazoline (6b):



(6b)

The following biological activities were carried out for this compound and afforded very interesting results summarized as follows:

i) Toxicity studies:

The doses was dissolved in 10% DMSO and injected orally to the animals and the results were found:-

200 mg/kg. body weight was injected orally into mice (6 weeks old) caused the death of one animal of the sample (16 animals).

1000 mg/kg. body weight was injected orally into mice caused death of all animals of the tested sample. From these results the LD_{50} for this substance was calculated and was found to be 520 mg/kg. body weight.

ii) Anti Carcinogenic effect *in vivo*:

a) The effect of the compound (**6b**) on Ehrilch Ascites volume in tumor-bearing mice:

The effect of the tetrazolopyrimidine derivative (**6b**) on Ehrilch Ascites volume in tumor-bearing mice was studied. The experiments showed a decrease in the average volume of the tumor-bearing mice cells from (5.3375 ± 0.449 ml) in the control mice sample (6 in number) to (2.25 ± 0.368 ml) after treating the animals 10 mg tetrazolopyrimidine / kg. body weight give orally for two weeks.

i.e.: The volume of the tumor cells has been decreased by 47.2 % after treating the tested animals by the reagent (**6b**) for 14 days.

In a parallel experiment the **% mortality** of animals (mice) in the control tumor-bearing mice was calculated and was found to be 33.33 %. While the **% mortality** of the treated mice (tumor-bearing mice tested) was found to be 16.66 %.

[% Mortality = (no. of dead animals / total no. of animals) x 100]

Also, the **survival rate** of the animals in the control (EAC) was calculated and was found to be 66.666. while the survival rate in the treated animals was found to be 83.333.

[Survival rate = (no. of survived animals / total no. of animals) x 100]

b) Ehrilch Ascites burden:

Here the number of the tumor cells were counted in the control tumor-bearing mice and in the tumor-bearing mice treated with the tetrazolopyrimidine (**6b**) and then the % of the dead cells (of the tumor) in each case was calculated. The experiments showed that the % of the dead cells has obviously increased in the treated mice than in the control mice.

i.e.: The tested compound was found to has potent effect on the tumor cell of the Ehrlich Ascites type.

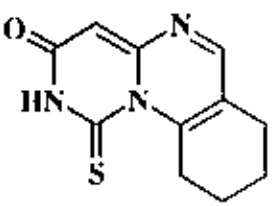
iii)Anti Carcinogenic effect *in vitro*:

The anti-tumor activity of the reagent (**6b**) using the EAC *in vitro* was also studied and the experiments afforded the following net results:

The % inhibition of cell viability against the concentration of the solution of the reagent in the treatment afforded the following results:

Concentration	25 µg/ml	50 µg/ml	100µg/ml
% Inhibition of cell viability	10	20	30

B) 1-Thioxo-1,2,7,8,9,10-hexahydro-(3*H*)-pyrimido[1,6-a]quinazolin-3-one (16b):



(16b)

The following biological activities were carried out for this substance and afforded very interesting results summarized as follows:

i) Toxicity studies:

200 mg/kg. body weight was injected orally into mice (6 weeks old) caused no death of any animal of the sample (16 animals).

1200 mg/kg. body weight was injected orally into mice caused death of all animals of the tested sample. From these results the LD_{50} for this substance was found to be 766 mg/kg. body weight.

ii) Hypoglycemic effect:

The tested agent (**16b**) at a dose level of 10 mg/kg. body weight injected orally into rats induced significant improvement in the oral glucose tolerance curve of the experimentally-induced streptozotonic diabetic rats.

i.e. the tested compound has a significant positive effect as a hypoglycemic agent.

iii) Hypolipidemic effect:

Compound (**16b**) produced significant decreases of the elevated serum total lipids, total cholesterol, LDL-cholesterol triglycerides in the previously described animal models at the same dose.

iv)Anti Carcinogenic effect:

The tested compound showed a positive effect against Ehrlich Ascites Carcinoma *in vitro*.

EXPERIMENTAL WORK

5. EXPERIMENTAL

All melting points were determined on an electrothermal apparatus and are uncorrected. IR spectra were recorded (KBr discs) on a BRUKER IFS-25 FT-IR spectrophotometer at the region 400-4000 cm^{-1}. 1H NMR spectra were recorded in $CDCl_3$ and $(CD_3)_2SO$ solutions on a Varian Gemini 300 MHz spectrometer and chemical shifts are expressed in δ units using TMS as an internal reference. Mass spectra were recorded on a GC-MS QP 1000 EX Shimadzu. Elemental analyses were carried out at the Microanalytical Center of the Cairo University, Giza, Egypt.

The preliminary antimicrobial screening was carried out at the Faculty of Pharmacy, Bani-Suef University. The other biological activities studies were performed at the Zoology Department, Faculty of Science, Bani-Suef University. Bani-Suef, Egypt.

Aminopyrazoles (9) were prepared according to the literature procedure.[208,209] Piperidine acetate was prepared by addition of 5 ml piperidine to a mixture of 4 ml acetic acid and 10 ml water[192].

5.1 Synthesis of tetrazolo[1,5-*a*]pyrimidine derivatives (6a-d):

General procedure:

A mixture of sodium salts (2) (0.012 mole) was refluxed with 5-aminotetrazole monohydrate (4) (0.01 mole) in a solution of piperidine acetate (1ml) for 3-5 minutes. 1.5 ml acetic acid was added to the reaction mixture while boiling, then the mixture was cooled and solid product was collected by filtration and recrystallized from ethanol.

The results are tabulated in table {1}.

Table {1}

Compd. No.	*M.P.°C Solvent*	*Color Yield%*	*Mol. Formula (M.Wt.)*	*Elemental analysis calc. / found%*		
				C	H	N
6a	182-183 EtoH	Pale brown 69.1	$C_7H_7N_5$ (161)	52.17 52.22	4.38 4.19	43.45 43.66
6b	119-121 EtoH	Orange 73.3	$C_8H_9N_5$ (175)	54.85 54.88	5.18 5.00	39.97 39.78
6c	103-106 EtoH	White 71	$C_{10}H_{13}N_5$ (203)	59.10 58.89	6.45 6.65	34.46 34.45
6d	110-112 EtoH	White 73.4	$C_{14}H_{19}N_5$ (257)	65.34 65.47	7.44 7.41	27.21 27.00

5.2 Synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives (10a-y) :

The same general procedure described for preparation of (6). The products were recrystallized from the appropriate solvent.

The results are listed in table {2}

Table {2}

Compd. No.	*M.P.^{0}C Solvent*	*Color Yield%*	*Mol. Formula (M.Wt.)*	*Elemental analysis calc. / found%*		
				C	**H**	**N**
10a	209-212 Dioxan	Yellow 79.7	$C_{22}H_{19}ON_5$ (369)	71.53 71.09	5.18 5.01	18.96 19.01
10b	224-226 Dioxan	Pale yellow 81.6	$C_{23}H_{21}ON_5$ (384)	72.04 72.11	5.52 5.36	18.26 18.41
10c	239-242 Dioxan	Pale yellow 81	$C_{22}H_{18}ON_5Cl$ (403.5)	65.43 -----	4.49 -----	17.34 -----
10d	225-227 EtOH	colourless 80	$C_{23}H_{21}O_2N_5$ (399)	69.16 ------	5.30 -----	17.53 -----
10e	244-245 Dioxan	Pale yellow 79.5	$C_{22}H_{18}ON_5Br$ (448)	58.94 -----	4.05 -----	15.62 -----
10f	230-232 Dioxan/ EtOH	white 80.5	$C_{23}H_{20}ON_5Cl$ (417.5)	66.11 -----	4.82 -----	16.76 -----

10g	241-244 Dioxan	Pale brown 80.9	$C_{22}H_{17}ON_5Cl_2$ (438)	60.29 -----	3.91 -----	15.98 -----
10h	276-278 Dioxan	Pale brown 81.8	$C_{23}H_{19}O_2N_5$ (397)	69.51 69.44	4.82 5.02	17.62 17.60
10i	240-241 EtOH	White 83	$C_{23}H_{21}ON_5$ (383)	72.04 72.11	5.52 5.59	18.26 18.21
10j	248-250 Dioxan	Pale yellow 82.2	$C_{24}H_{24}ON_5$ (398)	72.52 -----	5.83 -----	17.62 -----
10k	239-240 EtOH	Pale yellow 84.6	$C_{23}H_{20}ON_5Cl$ (417.5)	66.11 65.98	4.82 4.80	16.76 17.22
10l	240-241 Dioxan	Yellowish white 83.5	$C_{24}H_{23}O_2N_5$ (413)	69.72 -----	5.61 -----	16.94 -----
10m	243-245 Dioxan	White 85	$C_{23}H_{20}ON_5Br$ (462)	59.75 -----	4.36 -----	15.15 -----
10n	246-247 Dioxan	Pale yellow 84	$C_{24}H_{22}ON_5Cl$ (431.5)	66.74 -----	5.13 -----	16.21 -----
10o	249-251 Dioxan/ EtOH	White 82.5	$C_{23}H_{19}ON_5Cl_2$ (452)	61.07 -----	4.23 -----	15.48 -----
10p	284-286 Dioxan	Pale brown 85.4	$C_{24}H_{21}O_2N_5$ (411)	70.06 -----	5.14 -----	17.02 -----

10q	209-211 EtOH	White 91.1	$C_{25}H_{25}ON_5$ (411)	72.97 73.02	6.12 6.20	17.02 17.31
10r	212-215 Dioxan	Pale yellow 89.7	$C_{26}H_{27}ON_5$ (425)	73.39 -----	6.40 -----	16.46 -----
10s	208-210 Dioxan	Pale yellow 90	$C_{25}H_{24}ON_5Cl$ (445.5)	67.33 -----	5.42 -----	15.70 -----
10t	243-244 EtOH	White 90.4	$C_{25}H_{23}ON_5Cl_2$ (480)	62.51 63.00	4.83 4.66	14.58 14.57
10u	288-291 Dioxan	Pale brown 90.7	$C_{26}H_{25}O_2N_5$ (439)	71.05 -----	5.73 -----	15.93 -----
10v	221-222 Dioxan	Yellowish white 91.8	$C_{29}H_{33}ON_5$ (467)	74.81 -----	6.71 -----	15.04 -----
10w	229-232 Dioxan	Pale yellow 91.5	$C_{30}H_{35}ON_5$ (481)	75.13 -----	6.94 -----	14.60 -----
10x	227-229 Dioxan	White 92.3	$C_{29}H_{32}ON_5Cl$ (501.5)	69.66 -----	6.05 -----	14.01 -----
10y	278-280 Dioxan	Pale brown 92.8	$C_{30}H_{33}O_2N_5$ (495)	73.00 -----	6.33 -----	14.19 -----

5.3 Synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives (12a-c):

The same general procedure described above by using an equimolar amounts the suitable aminopyrazole (9) and the sodium formylacetone (11). The products were recrystallized from ethanol.

The results are listed in table {3}.

Table {3}

Compd. No.	*M.P.°C Solvent*	*Color Yield%*	*Mol. Formula (M.Wt.)*	*Elemental analysis calc. / found%*		
				C	**H**	**N**
12a	185-190 EtOH	Pale yellow 89	$C_{20}H_{17}ON_5$ (343)	69.96 69.84	4.99 4.49	20.39 20.64
12b	182-189 EtOH	Yellow 88.7	$C_{21}H_{19}ON_5$ (357)	70.57 70.52	5.36 5.29	19.59 19.50
12c	187-200 EtOH	orange 89.5	$C_{20}H_{16}ON_5Cl$ (377.5)	63.58 -----	4.27 -----	18.54 -----

5.4 Synthesis of pyrazolo[1,5-*a*]pyrimidine derivatives (14a-h):

The same general procedure described above by using an equimolar amounts the suitable aminopyrazole (9) and the sodium formylacetophenone (13). The products were recrystallized from the appropriate solvent.

The results are listed in table {4}.

Table (4)

Compd. No.	*M.P.°C Solvent*	*Color Yield%*	*Mol. Formula (M.Wt.)*	*Elemental analysis calc. / found%*		
				C	H	N
14a	190-207 Dioxan	Reddish yellow 88.2	$C_{25}H_{19}ON_5$ (405)	74.06 74.21	4.72 4.66	17.27 17.54
14b	250-256 Dioxan	Yellowish orange 86	$C_{26}H_{21}ON_5$ (419)	74.45 -----	5.05 -----	16.69 -----
14c	260-263 Dioxan	Pale yellow 87.8	$C_{25}H_{18}ON_5Cl$ (439.5)	68.26 -----	4.12 -----	15.92 -----
14d	225-234 Dioxan	Orange 87.3	$C_{26}H_{21}O_2N_5$ (435)	71.71 71.28	4.86 4.89	16.08 16.18
14e	238-244 Dioxan	Yellow 85.8	$C_{25}H_{18}ON_5Br$ (484)	62.00 -----	3.75 -----	14.46 -----
14f	Over265 Dioxan	Pale orange 86.7	$C_{26}H_{20}ON_5Cl$ (453.5)	68.80 -----	4.44 -----	15.43 -----
14g	252-261 Dioxan	Orange 87	$C_{25}H_{17}ON_5Cl_2$ (474)	63.30 63.00	3.61 3.11	14.76 14.54
14h	164-173 Dioxan	Orange 88.2	$C_{26}H_{19}O_2N_5$ (433)	72.04 72.22	4.42 4.32	16.16 16.27

5.5 Synthesis of pyrimido[1,6-*a*]pyrimidine derivatives (16a-d):

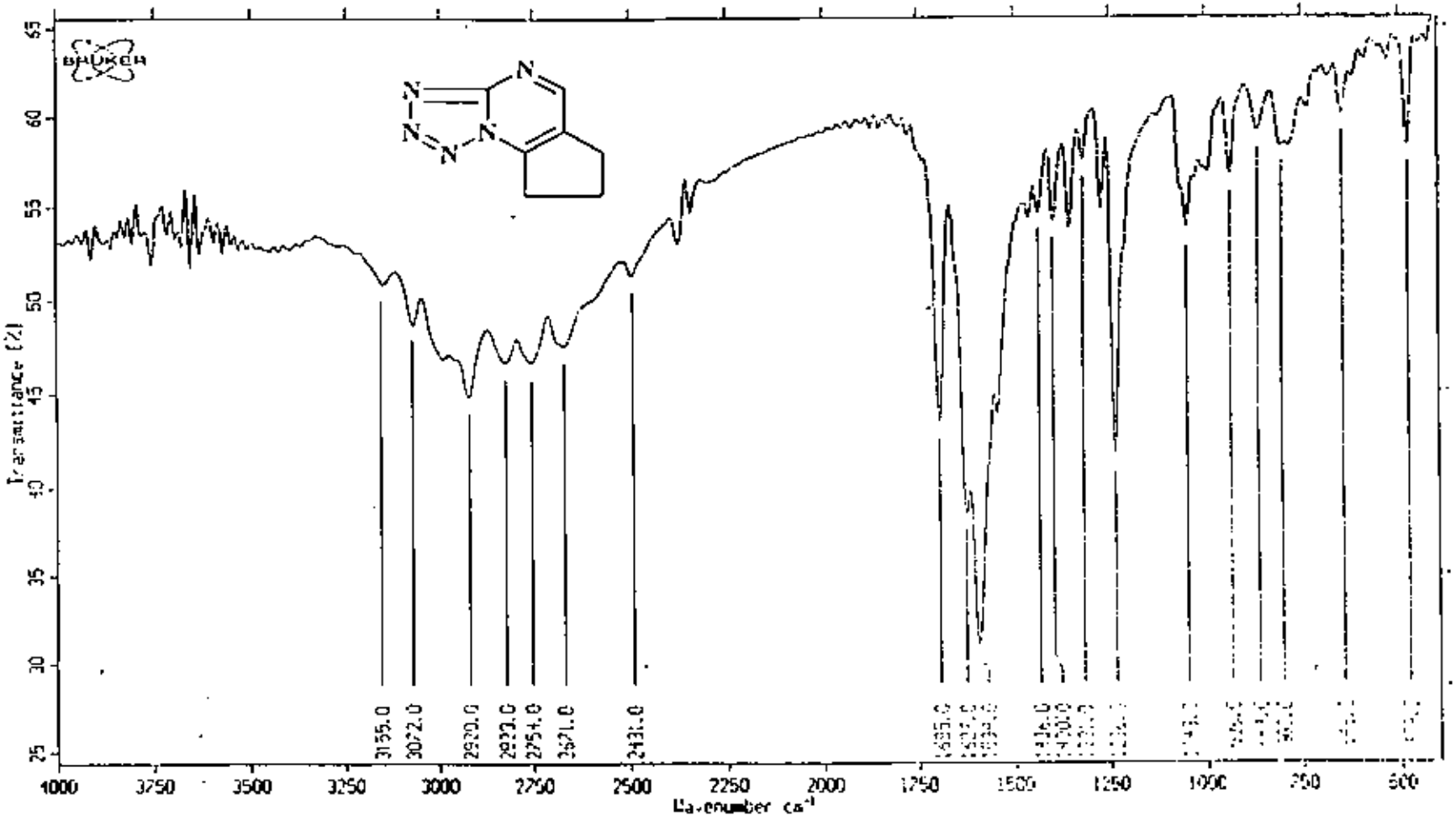
A mixture of equivalent amounts of sodium salts (**2**), (**11**) or (**13**) (0.012 mole) and 6-aminothiouracil was refluxed with a solution of piperidine acetate (1.5 ml) for 15-20 minutes. The reaction mixture is then diluted with 20 ml ethanol and refluxed for another 1 hr. the reaction was quenched by the addition of 1.5 ml acetic acid, then the mixture was cooled and solid product was collected by filtration and recrystallized from the appropriate solvent to afford the reaction product (**16**), (**17**), (**18**) respectively. The results are listed in table {5}.

Table {5}

Compd No.	*M.P.^{0}C Solvent*	*Color Yield%*	*Mol. Formula (M.Wt.)*	*Elemental analysis calc. / found%*			
				C	H	N	S
16a	275-277 EtoH	Pale brown 80.6	$C_{10}H_9ON_3S$ (219)	54.78 54.88	4.14 4.22	19.16 19.00	14.61 14.60
16b	225-232 EtoH	Yellow 89.2	$C_{11}H_{11}ON_3S$ (233)	56.63 ------	4.75 -----	18.01 ------	13.73 ------
16c	245-251 EtoH	Yellow 81	$C_{13}H_{15}ON_3S$ (261)	59.75 59.55	5.79 5.89	16.08 15.99	12.27 12.26
16d	210-231 EtoH	Yellow 83.3	$C_{17}H_{21}ON_3S$ (315)	64.73 ------	6.71 -----	13.32 ------	10.16 ------

17	266-268 EtoH	Pale yellow 79.1	$C_8H_7ON_3S$ (193)	49.73 49.58	3.65 3.61	21.75 21.65	16.58 16.65
18	287-289 EtoH	Yellowish green 70.5	$C_{13}H_9ON_3S$ (255)	61.16 61.44	3.55 3.42	16.46 16.45	12.55 12.34

SPECTRAL DATA


BRUKER
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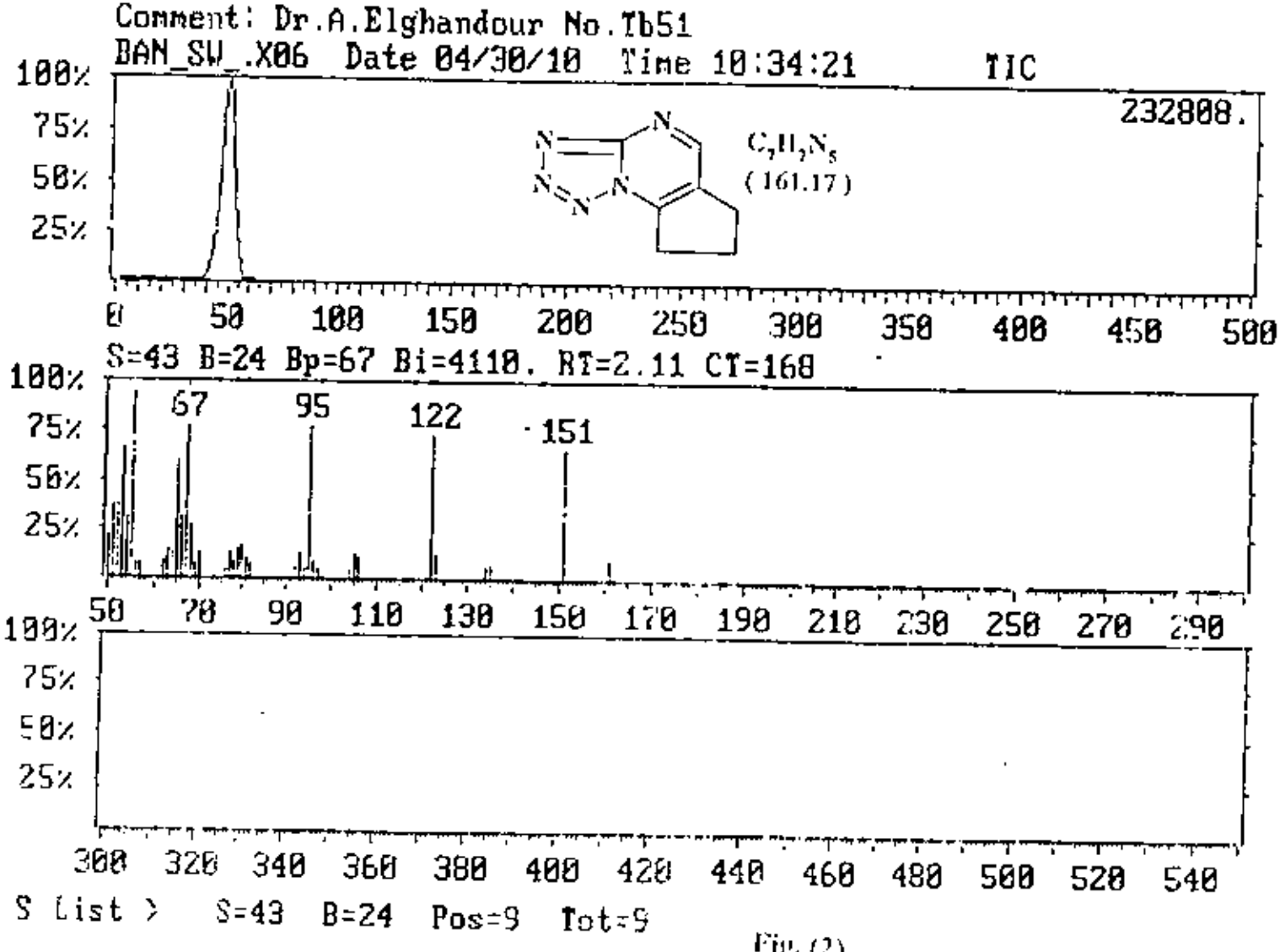
ZENIB
ELF81H.328

Fig. (1)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(161.17)
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67
95
122
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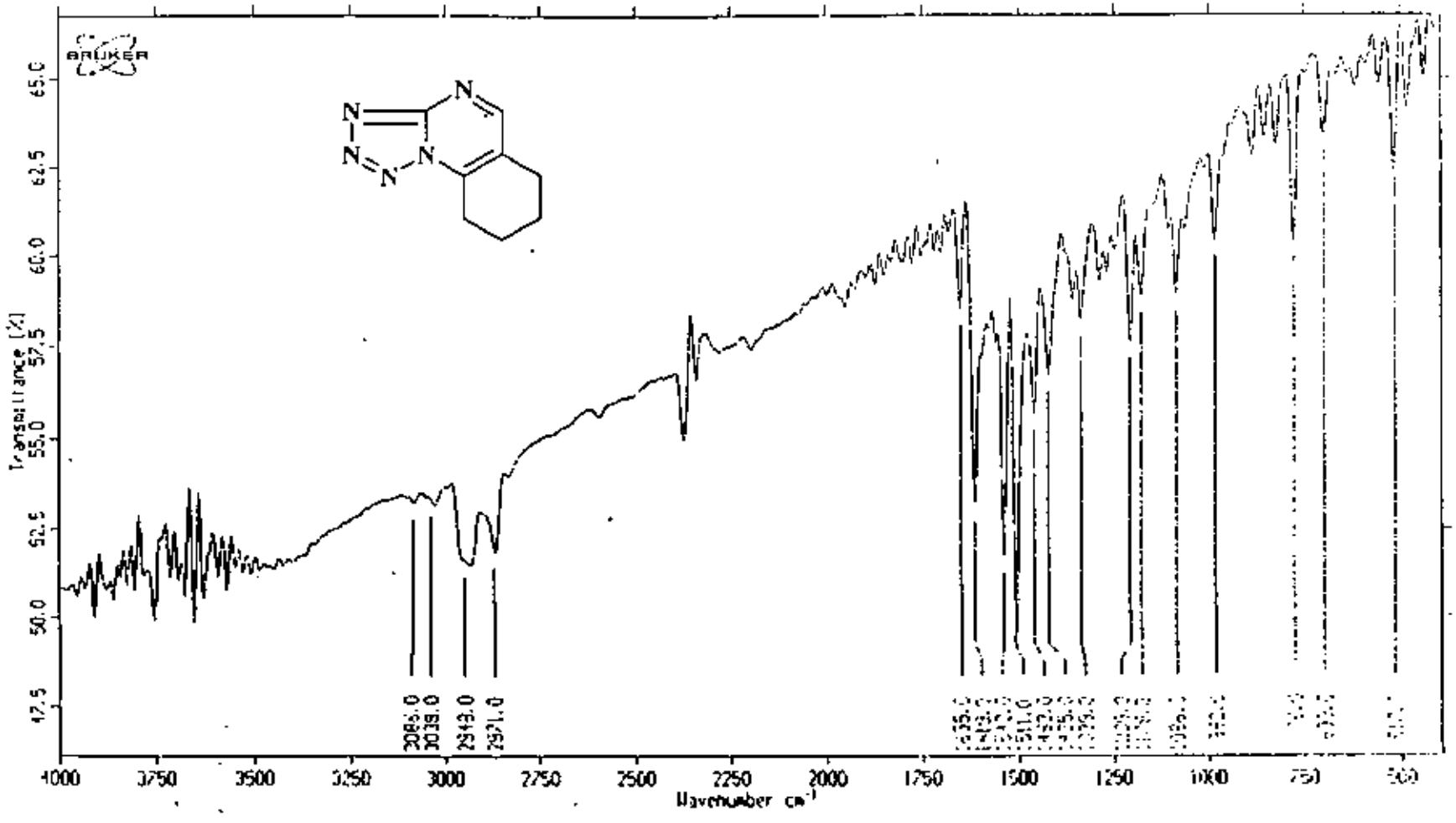
Fig. (2)


BRUKER
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3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Tajdida (Tb49) 2/5/2007 KBr. Disk
ZENIB
MLTANNOL.9

Fig. (3)

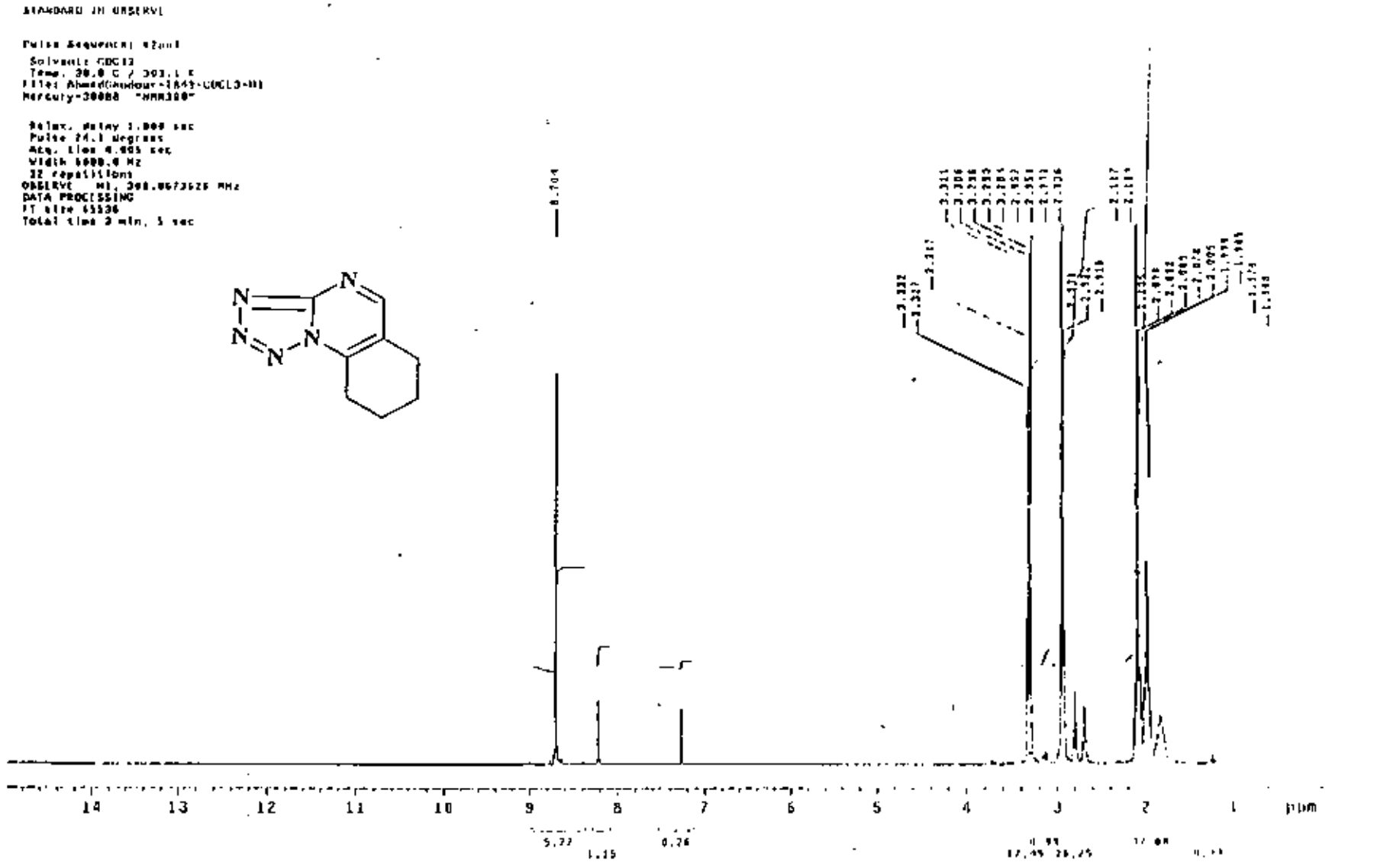

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 30.0 C / 303.1 K
File: AhmedGhadour-1843-CDCL3-1H
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 24.1 degrees
Acq. time 4.005 sec
Width 5000.0 Hz
32 repetitions
OBSERVE H1, 300.0673525 MHz
DATA PROCESSING
FT size 65536
Total time 3 min, 5 sec
8.704
7.336
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
5.22
1.15
0.26
0.93
17.45
28.25

Fig. (4)

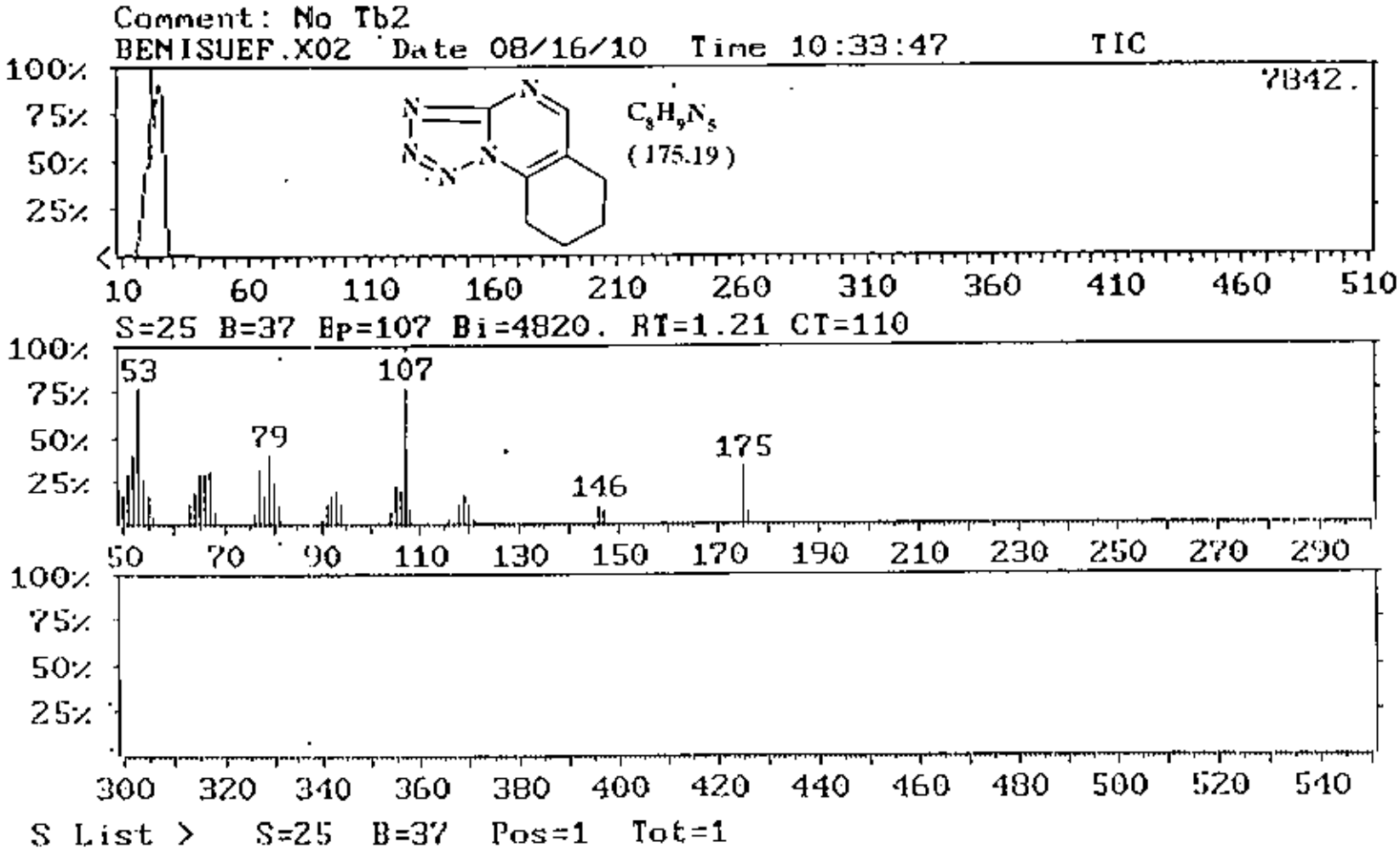

Comment: No Tb2
BENISUEF.X02 Date 08/16/10 Time 10:33:47 TIC
7842.
100%
75%
50%
25%
$C_8H_9N_5$
(175.19)
10 60 110 160 210 260 310 360 410 460 510
S=25 B=37 Bp=107 Bi=4820. RT=1.21 CT=110
53
107
79
175
146
50 70 90 110 130 150 170 190 210 230 250 270 290
300 320 340 360 380 400 420 440 460 480 500 520 540
S List > S=25 B=37 Pos=1 Tot=1

Fig. (5)

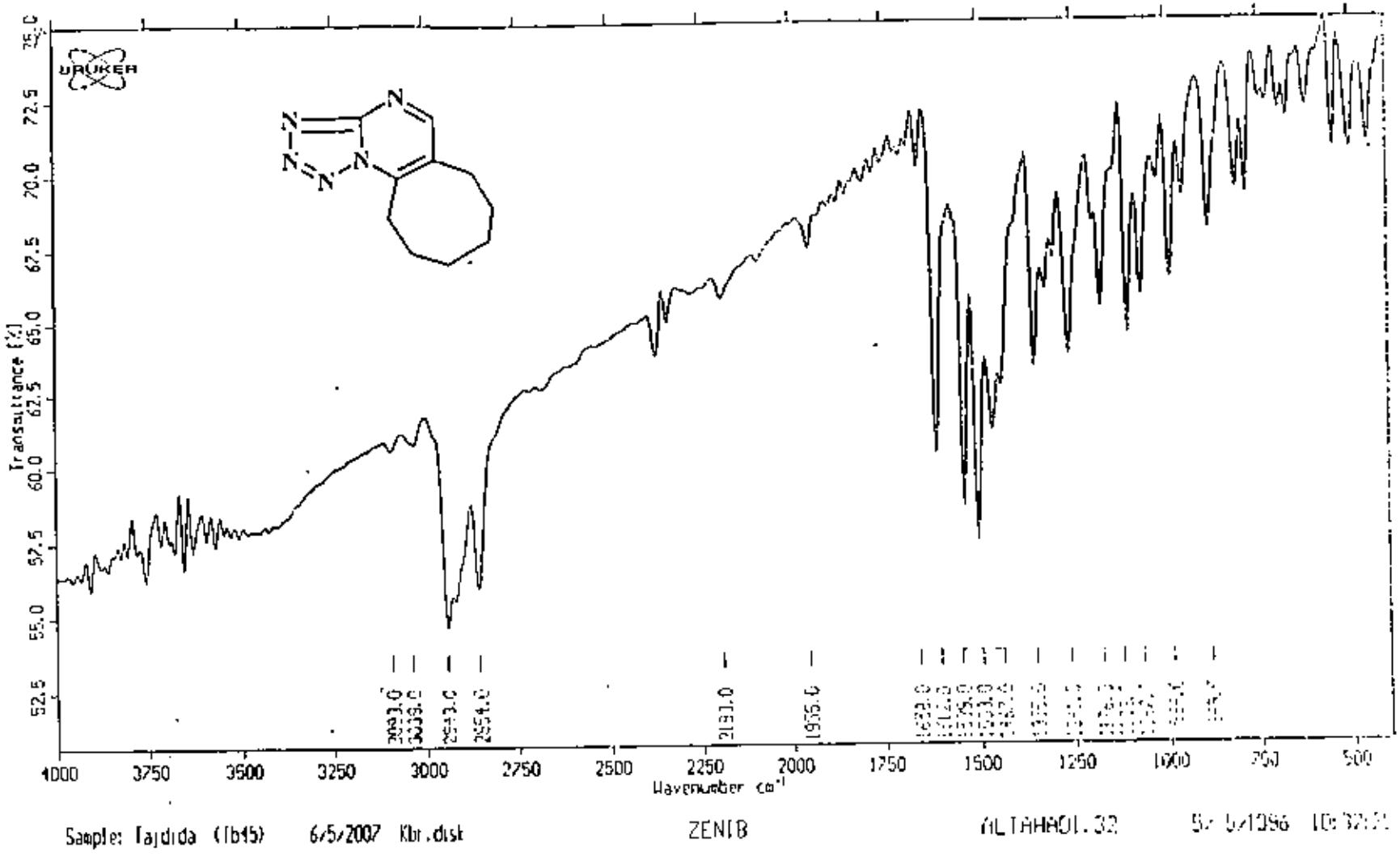

BRUKER
Transmittance [%]
Wavenumber cm-1
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
500
Sample: Tajdida (Tb15) 6/5/2007 Kbr.dsk
ZENIB
ALTAHHAOI.32

Fig. (6)

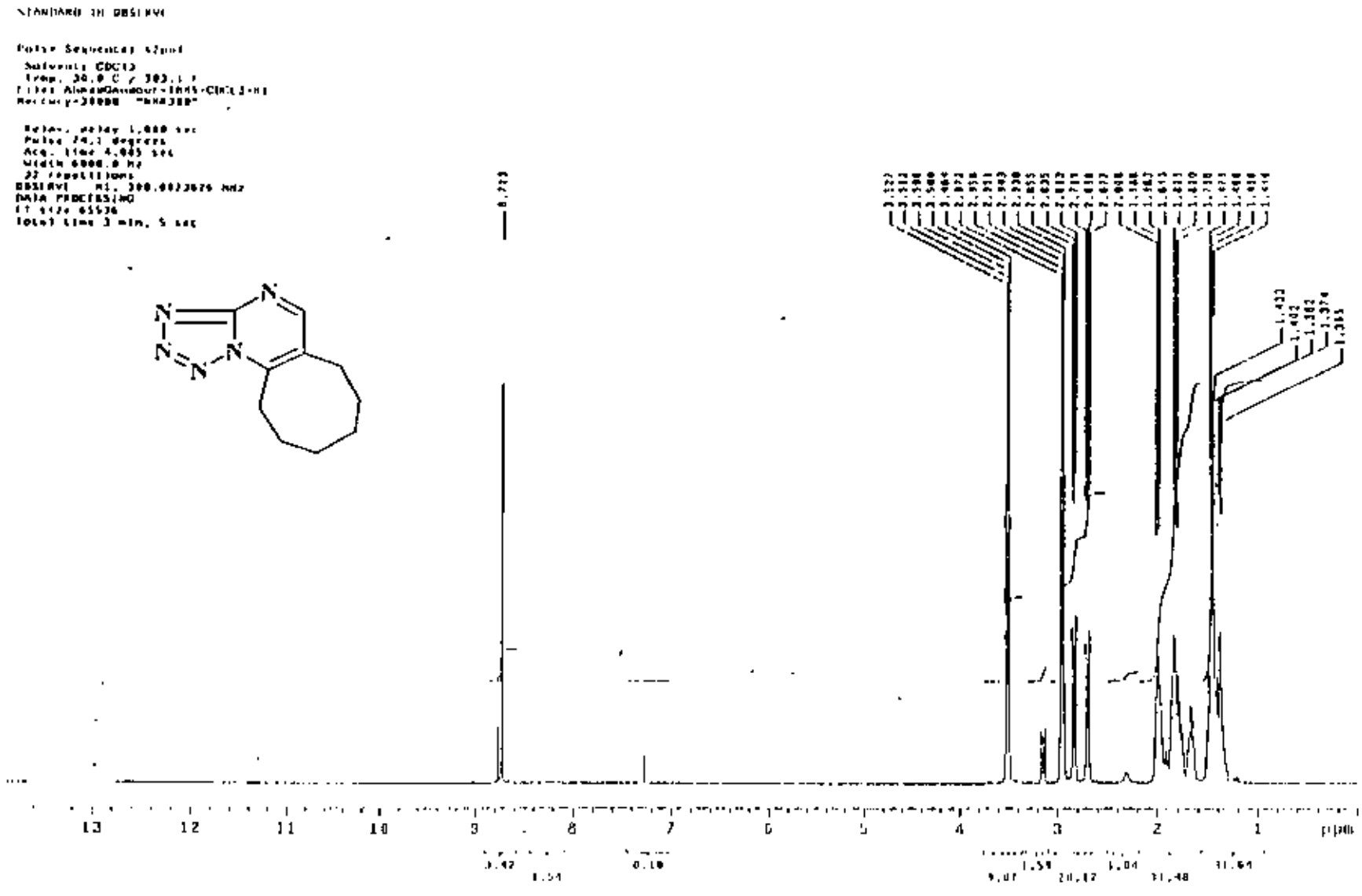


Fig. (7)

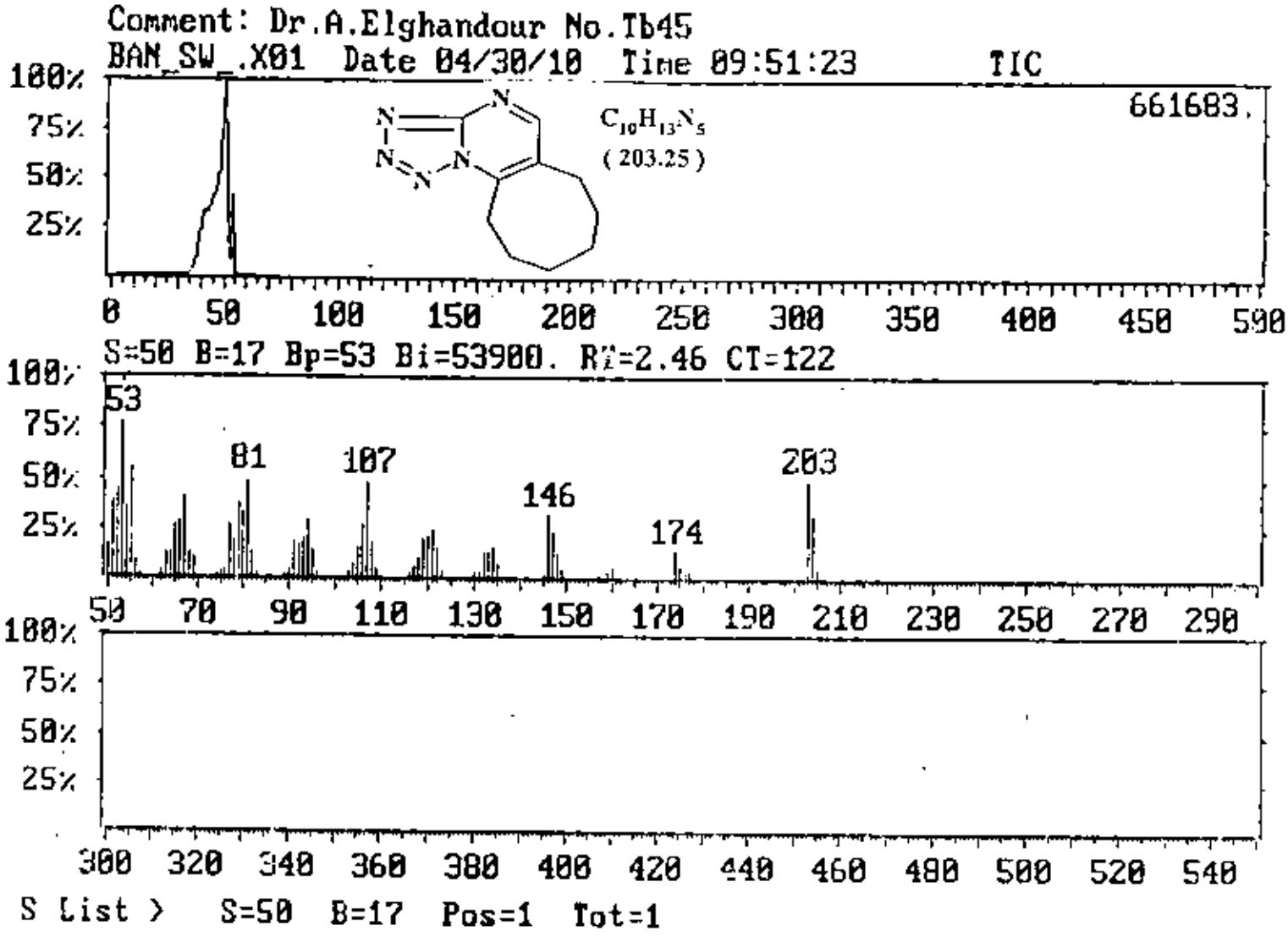

Comment: Dr.A.Elghandour No.Tb45
BAN_SW_.X01 Date 04/30/10 Time 09:51:23 TIC
100%
75%
50%
25%
661683.
$C_{10}H_{13}N_5$
(203.25)
0 50 100 150 200 250 300 350 400 450 500
S=50 B=17 Bp=53 Bi=53900. RT=2.46 CT=122
53
81
107
146
174
203
50 70 90 110 130 150 170 190 210 230 250 270 290
300 320 340 360 380 400 420 440 460 480 500 520 540
S List > S=50 B=17 Pos=1 Tot=1

Fig. (8)

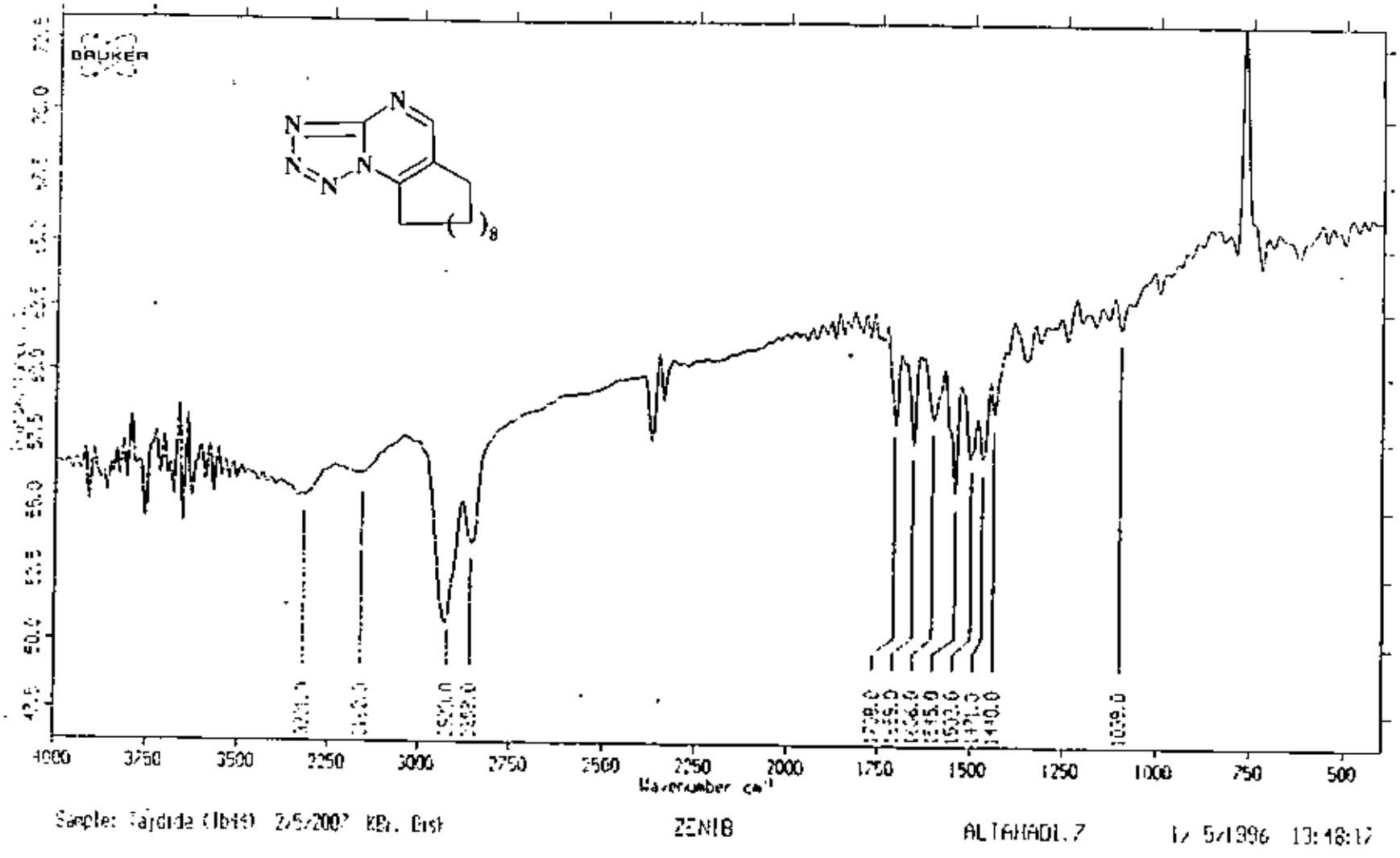

BRUKER
N
N
N
N
N
)8
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
ZENIB
ALTAHADI.7

Fig. (9)

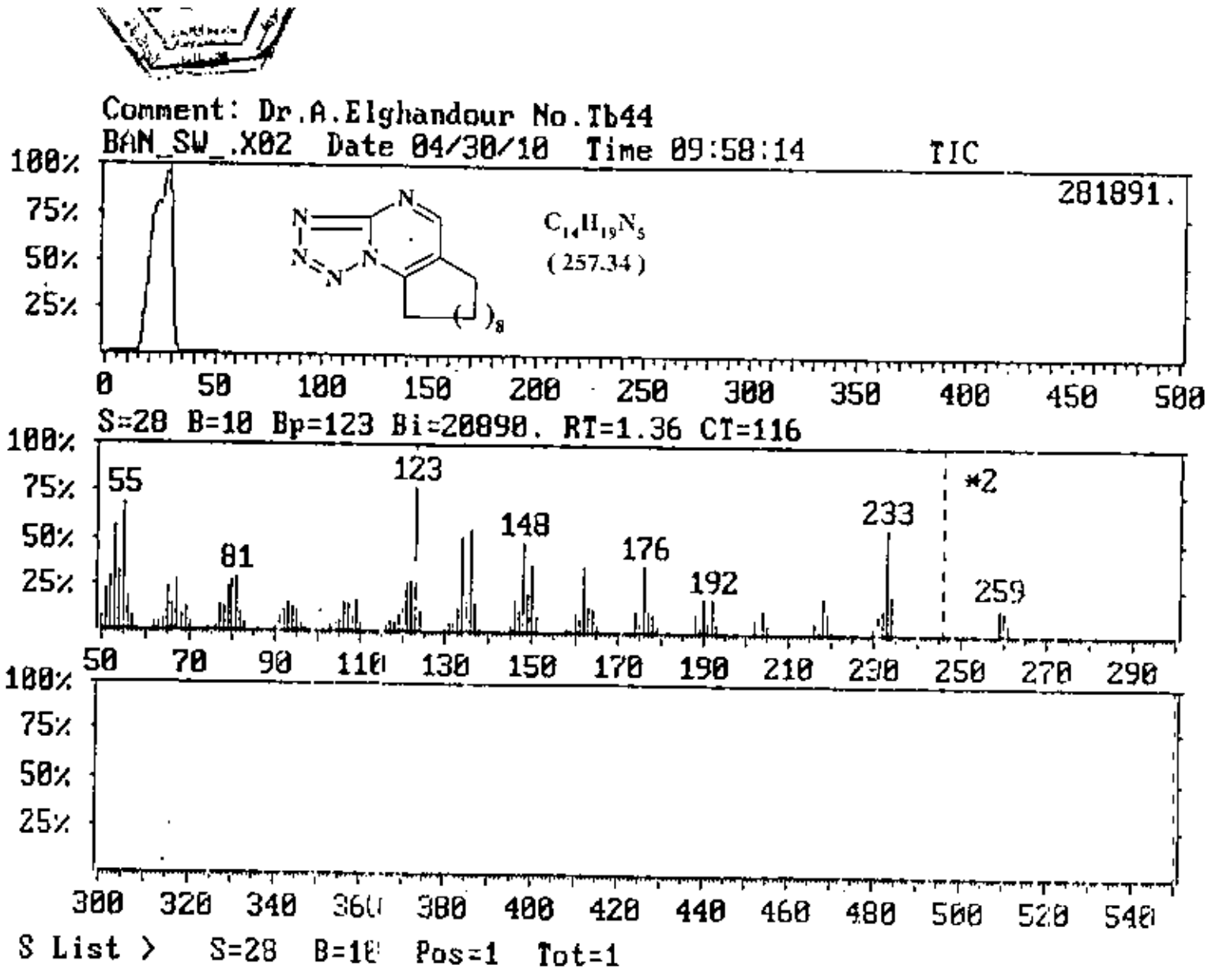

Comment: Dr.A.Elghandour No.Tb44
BAN_SW_.X02 Date 04/30/10 Time 09:58:14 TIC
281891.
100%
75%
50%
25%
$C_{14}H_{19}N_5$
(257.34)
0 50 100 150 200 250 300 350 400 450 500
S=28 B=10 Bp=123 Bi=20890. RT=1.36 CT=116
55
81
123
148
176
192
233
*2
259
50 70 90 110 130 150 170 190 210 230 250 270 290
300 320 340 360 380 400 420 440 460 480 500 520 540
S List > S=28 B=10 Pos=1 Tot=1

Fig. (10)

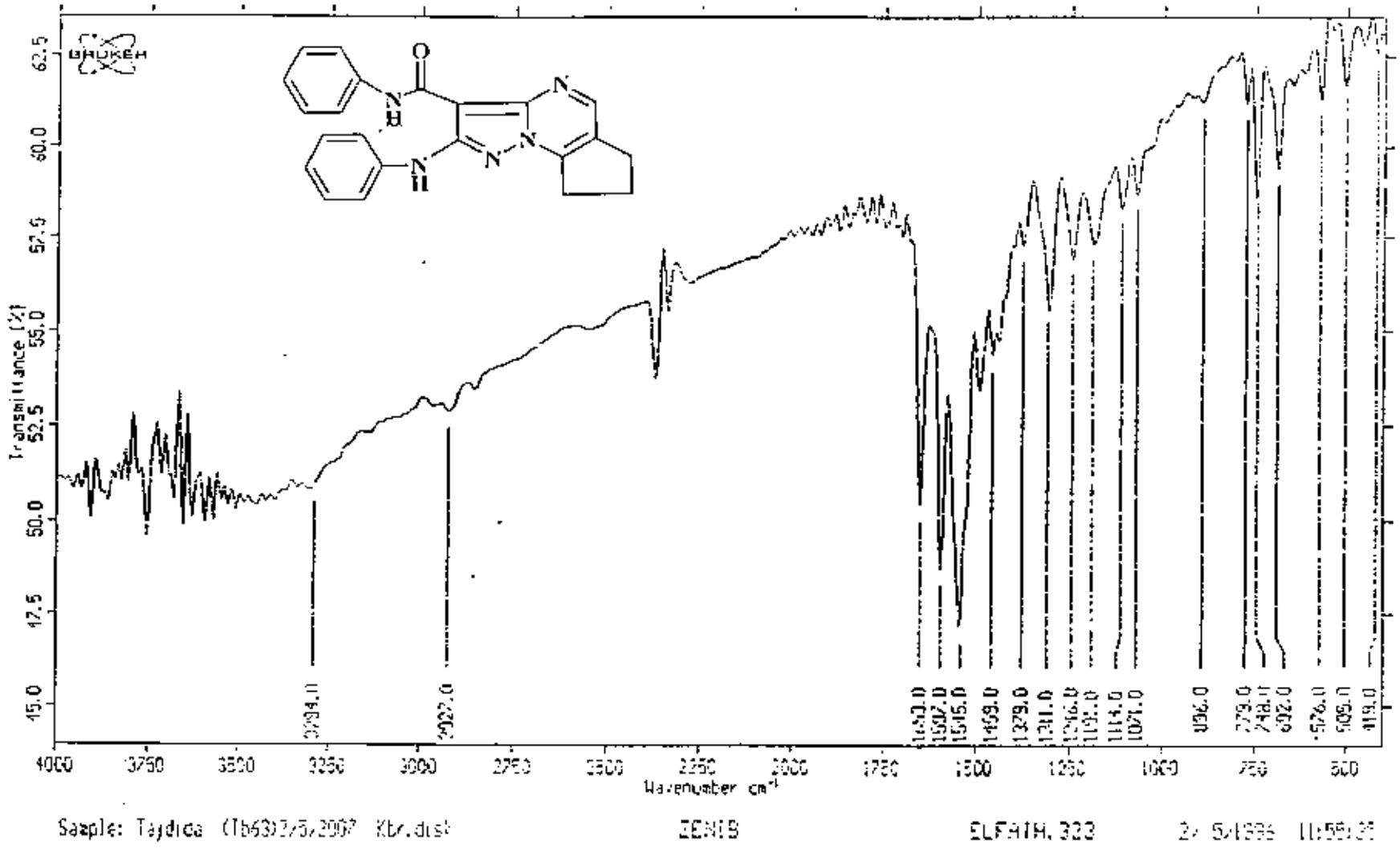

BRUKER
O
N
H
N
N
N
N
Transmittance [%]
62.5
60.0
57.5
55.0
52.5
50.0
47.5
45.0
2994.0
2922.0
1593.0
1567.0
1545.0
1468.0
1329.0
1281.0
1236.0
1193.0
1114.0
1071.0
936.0
775.0
748.0
692.0
576.0
505.0
419.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Tajdica (Tb63)2/5/2007 Kbr.disk
ZENIB
ELFATIH, 323

Fig. (11)

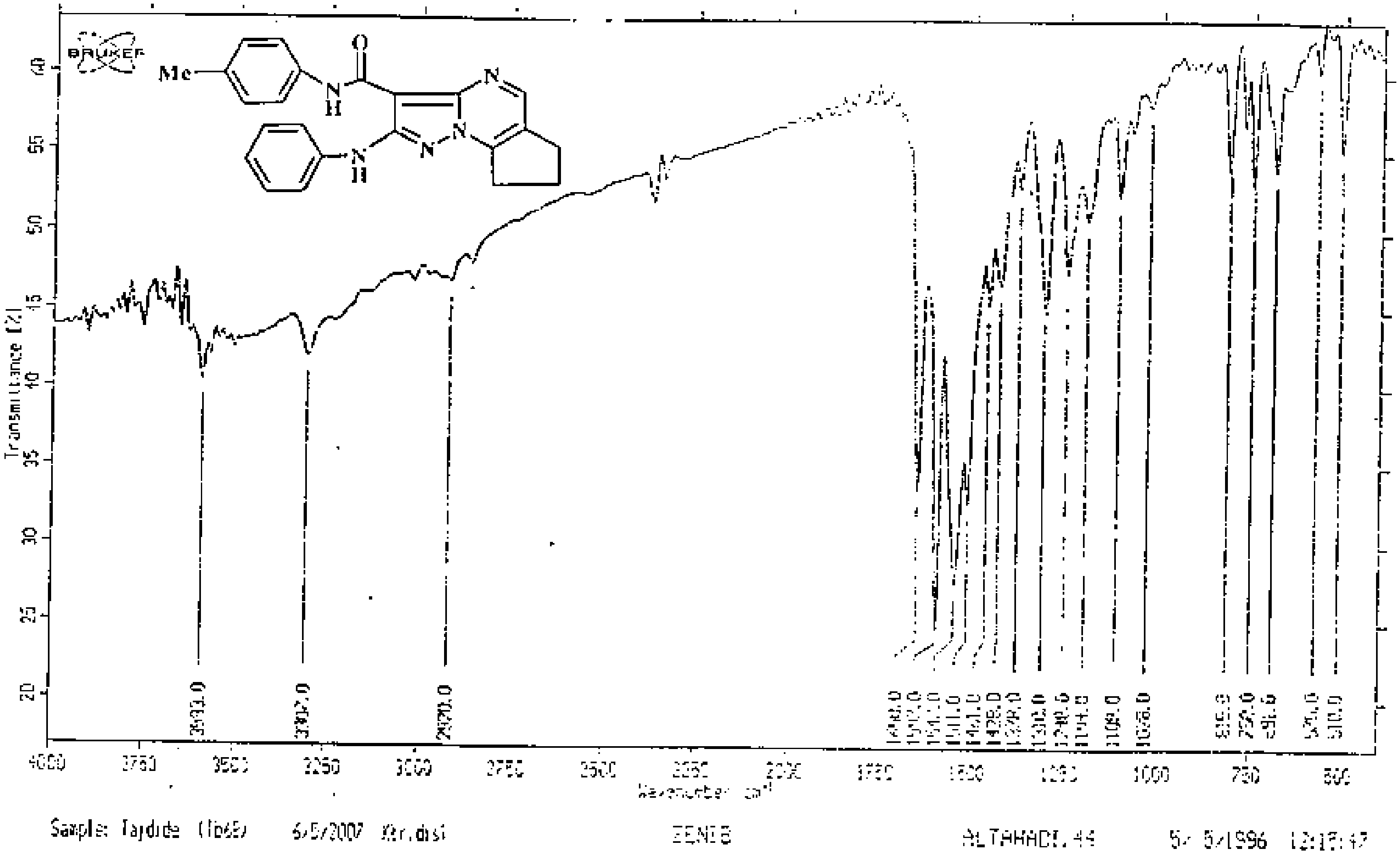


Fig. (12)

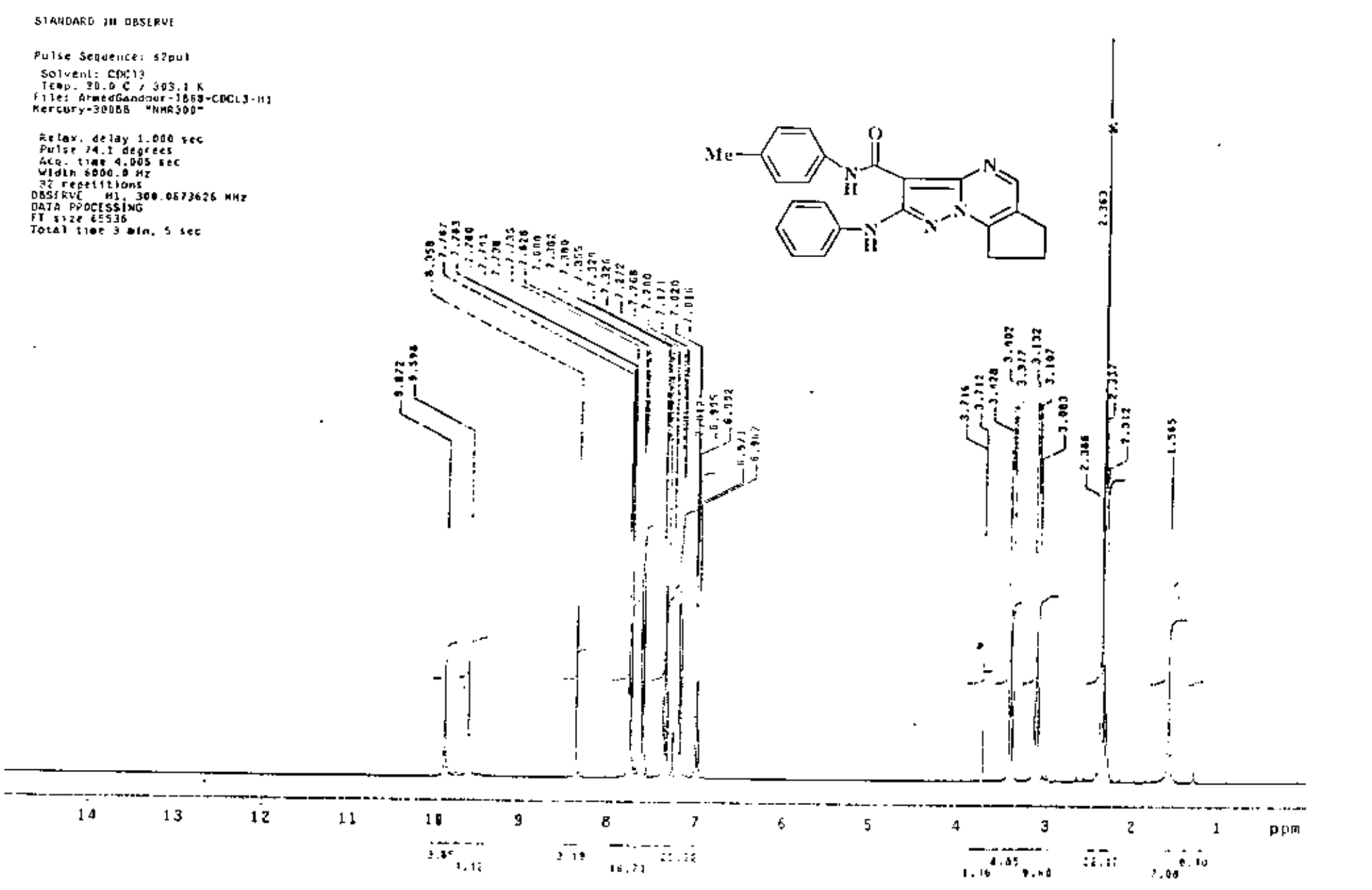

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 30.0 C / 303.1 K
File: AhmedGandour-1668-CDCL3-H1
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 74.1 degrees
Acq. time 4.005 sec
Width 6000.0 Hz
32 repetitions
OBSERVE H1, 300.0673626 MHz
DATA PROCESSING
FT size 65536
Total time 3 min, 5 sec
Me
O
N
H
N
N
N
N
H
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

Fig. (13)

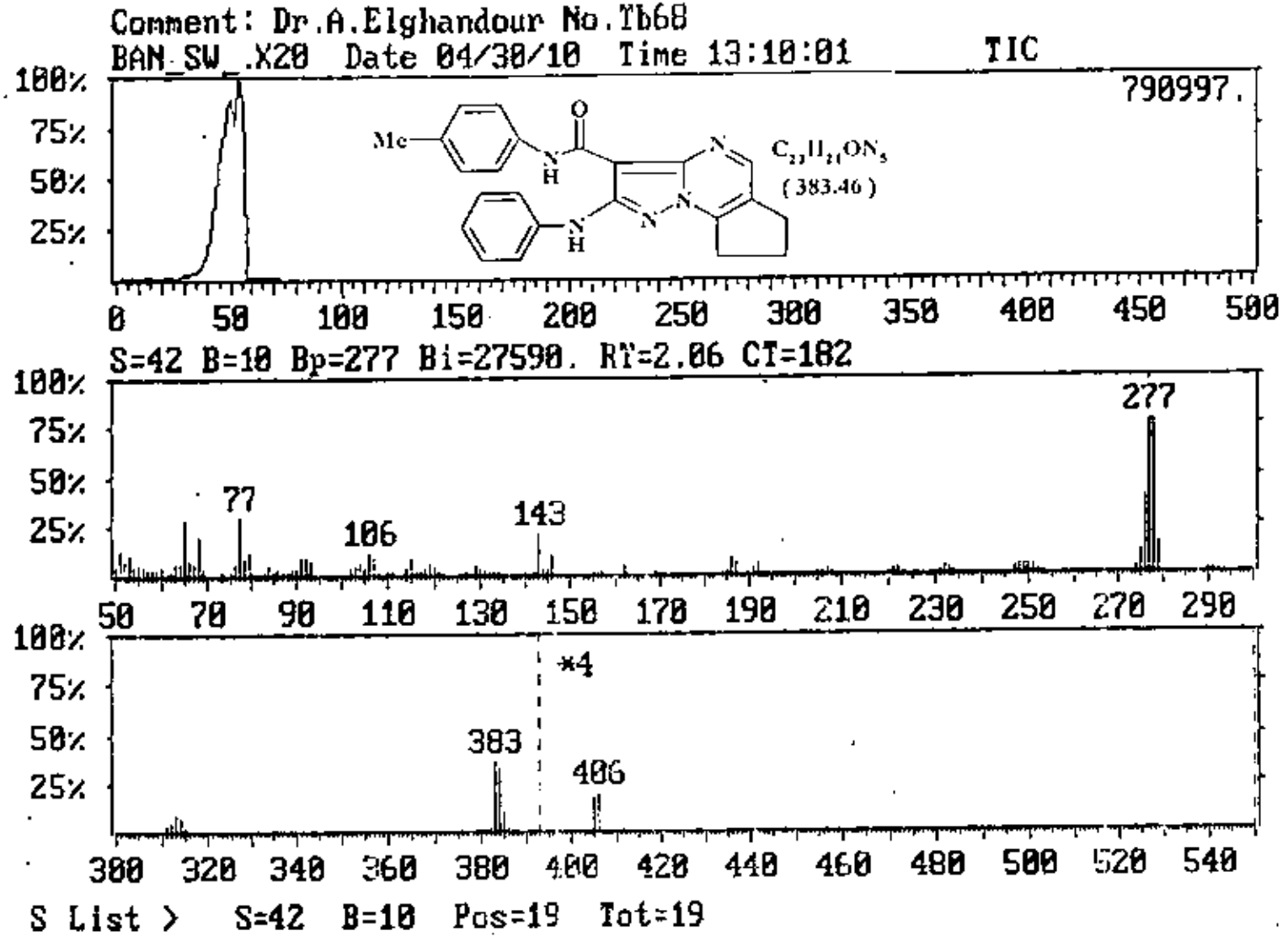

Comment: Dr.A.Elghandour No.Tb68
BAN_SW_.X20 Date 04/30/10 Time 13:10:01 TIC
790997.
Me
O
N
H
N
N
N
N
H
C21H21ON5
(383.46)
100%
75%
50%
25%
0 50 100 150 200 250 300 350 400 450 500
S=42 B=10 Bp=277 Bi=27590. RT=2.06 CT=182
277
77
106
143
50 70 90 110 130 150 170 190 210 230 250 270 290
*4
383
406
300 320 340 360 380 400 420 440 460 480 500 520 540
S List > S=42 B=10 Pos=19 Tot=19

Fig. (14)

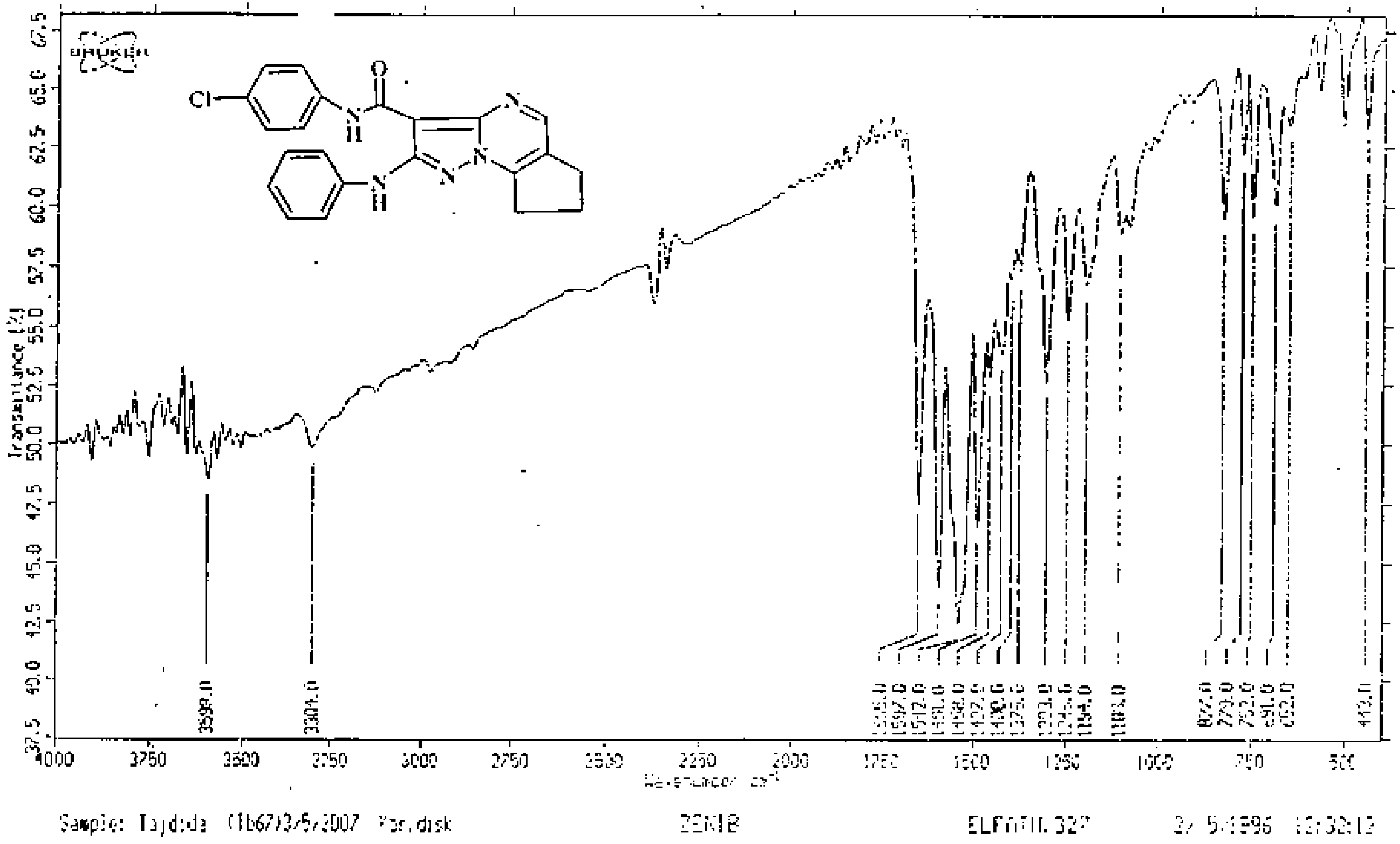

BRUKER
Transmittance [%]
Wavenumber cm-1
3599.0
3304.0
1458.0
1432.0
1400.0
1375.0
1293.0
1245.0
1194.0
1103.0
822.0
770.0
752.0
691.0
652.0
442.0
Sample: Tajdida (1b67)3/5/2007 Kbr.disk

Fig. (15)

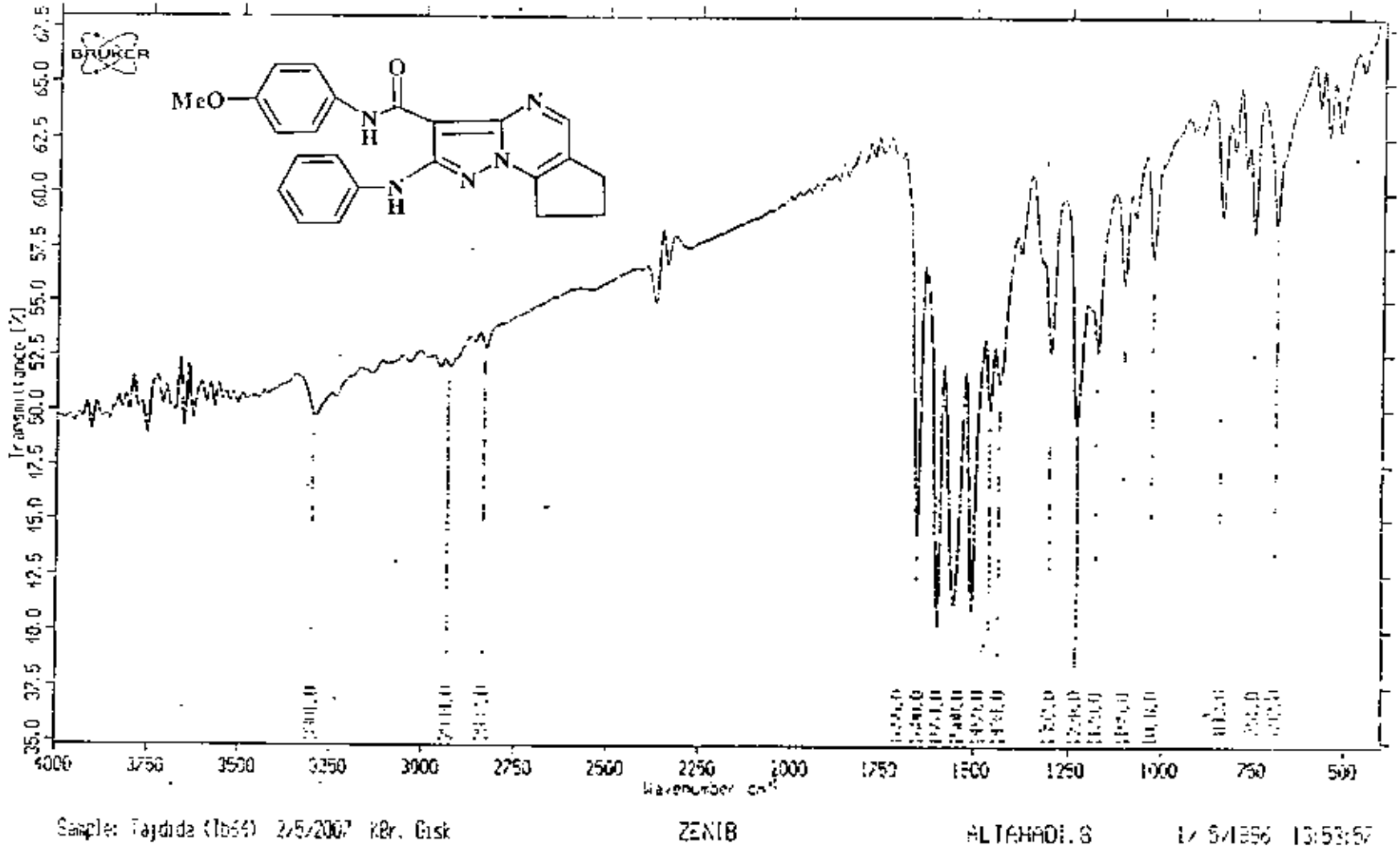

BRUKER
MeO
O
N
H
N
N
N
N
H
Transmittance [%]
67.5
65.0
62.5
60.0
57.5
55.0
52.5
50.0
47.5
45.0
42.5
40.0
37.5
35.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Tajdida (Ib64) 2/5/2007 KBr, Disk
ZENIB
ALTAHADI.S
2/5/1856 13:53:57

Fig. (16)

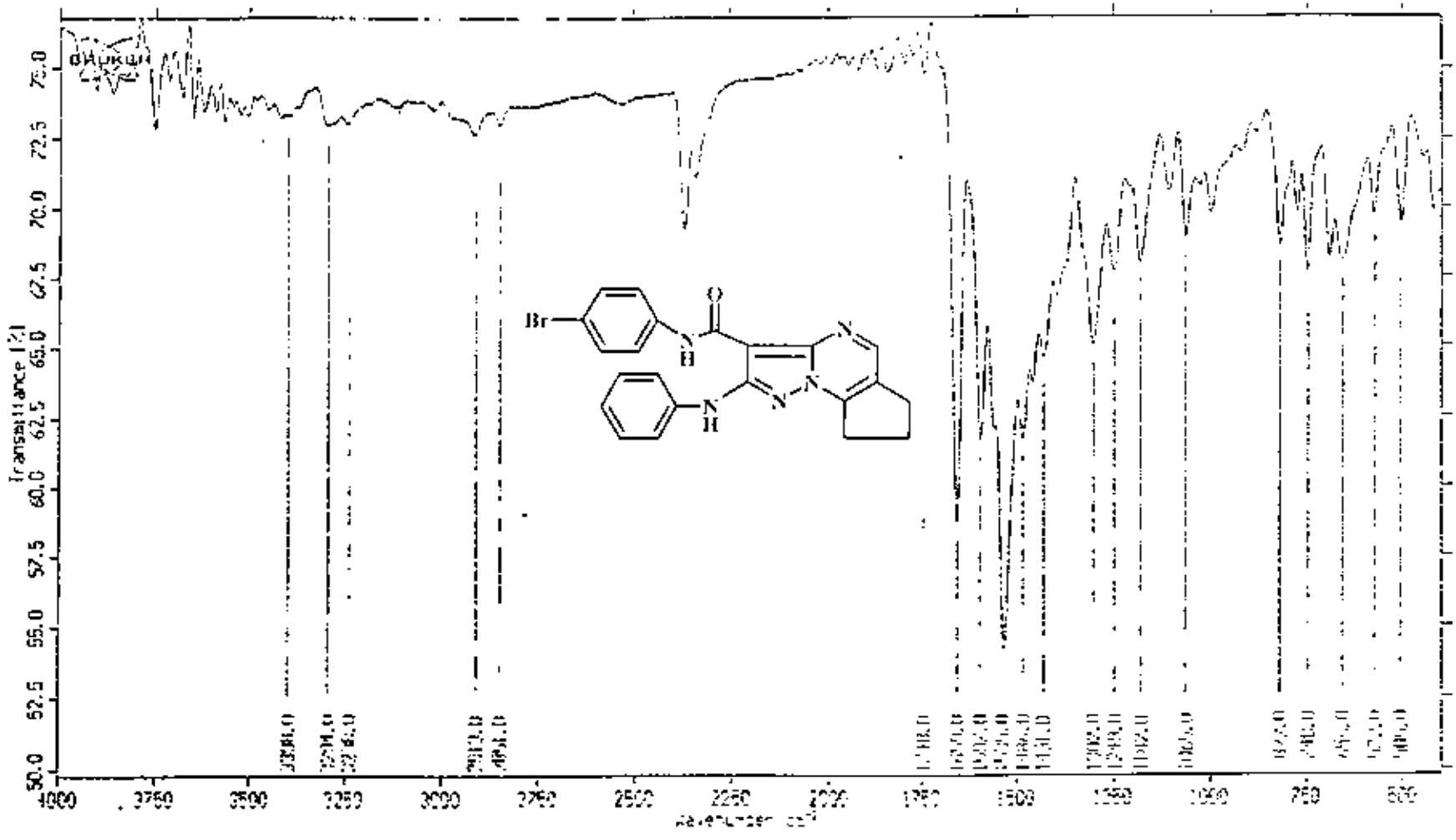

Transmittance [%]
75.0
72.5
70.0
67.5
65.0
62.5
60.0
57.5
55.0
52.5
50.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Br
O
N
H
N
H
N
N

Fig. (17)

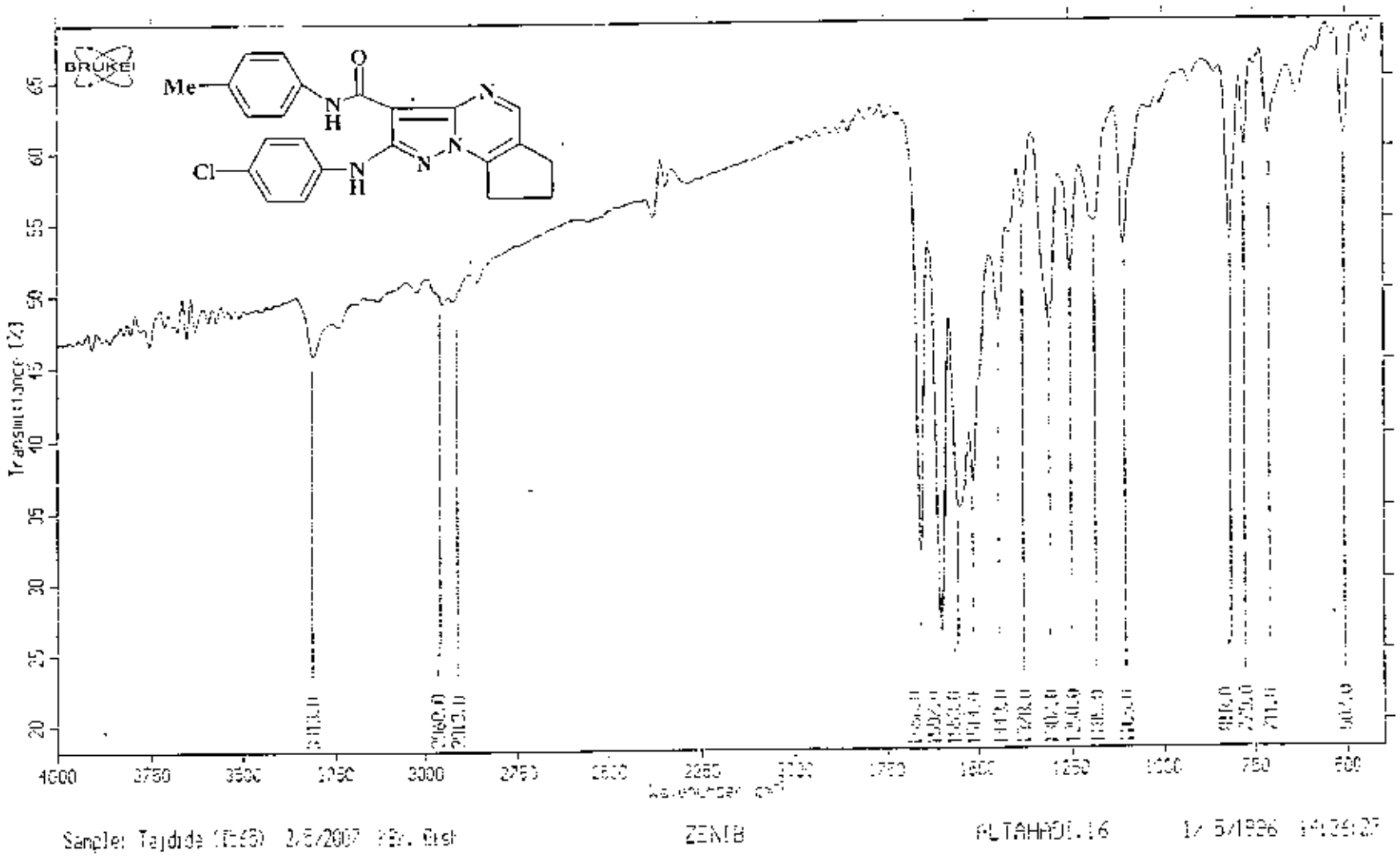

BRUKER
Me
O
N
H
N
N
N
Cl
N
H
Transmittance [%]
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Tajdida (E68) 2/6/2007 KBr, Disk
ZENIB
ALTAHADI.16
1/ 5/1996 14:26:27

Fig. (18)

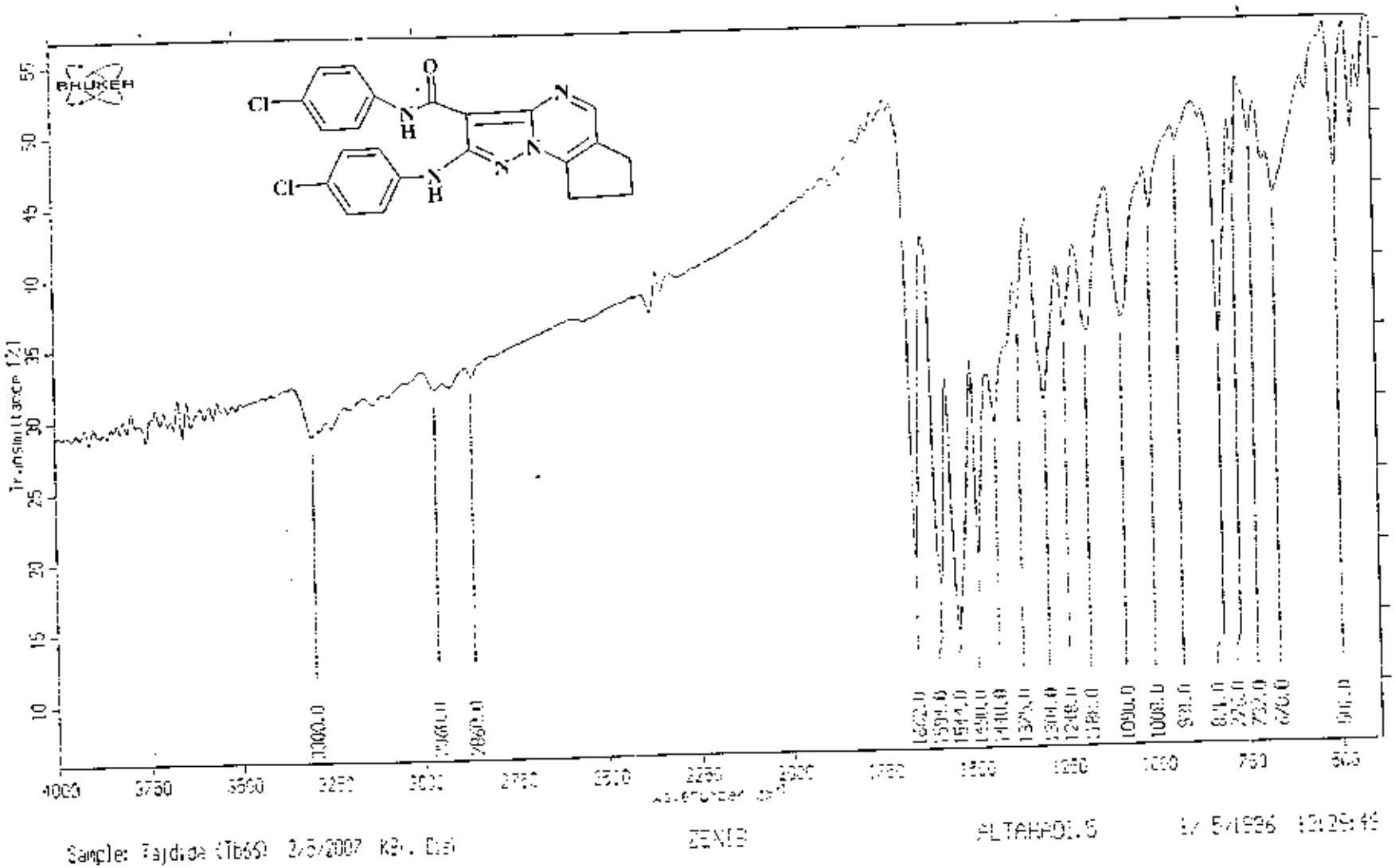

BRUKER
Cl
Cl
O
N
H
N
N
N
H
Transmittance [%]
55
50
45
40
35
30
25
20
15
10
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
1000.0
2960.0
2869.0
1662.0
1591.0
1544.0
1490.0
1410.0
1375.0
1304.0
1248.0
1158.0
1090.0
1008.0
938.0
814.0
758.0
732.0
676.0
566.0
Sample: Tajdida (Tb66) 2/5/2007 KBr. Dia
ZENIT
ALTAHPOL.S
1/ 5/1996 12:25:46

Fig. (19)

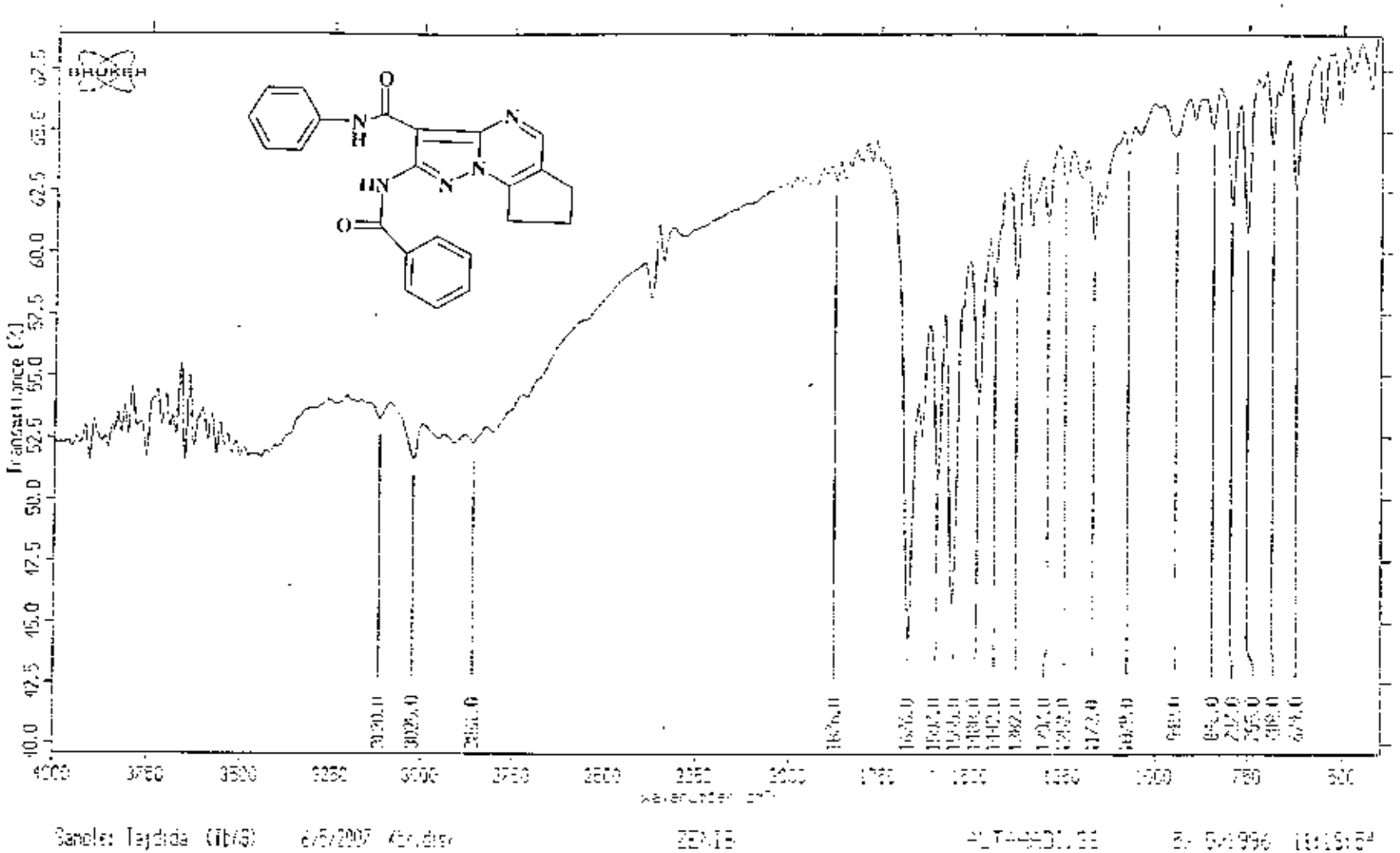

BRUKER
Transmittance (%)
Wavenumber cm-1
Sandra Tajdida (Tb48) 6/6/2007

Fig. (20)

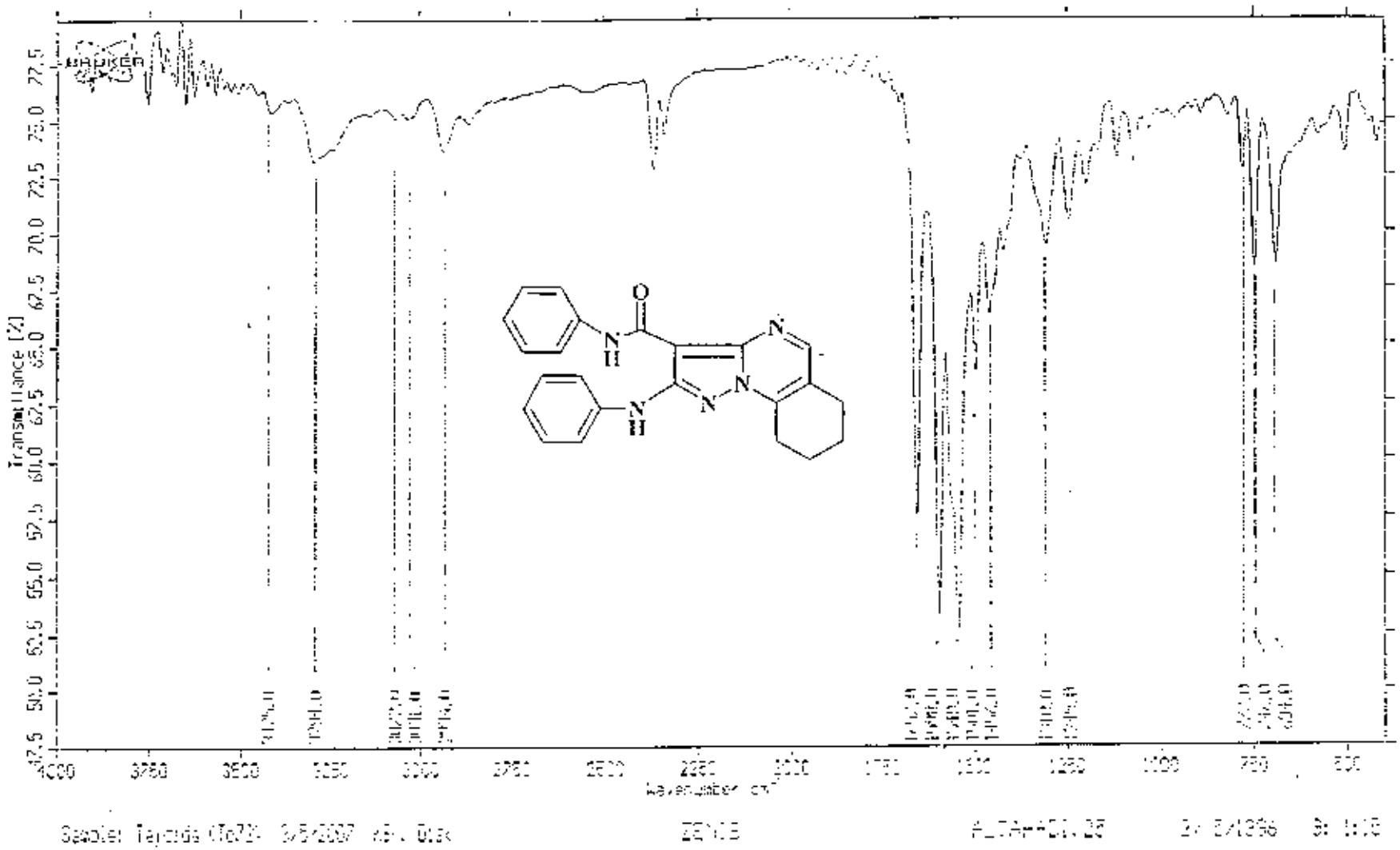


Fig. (21)

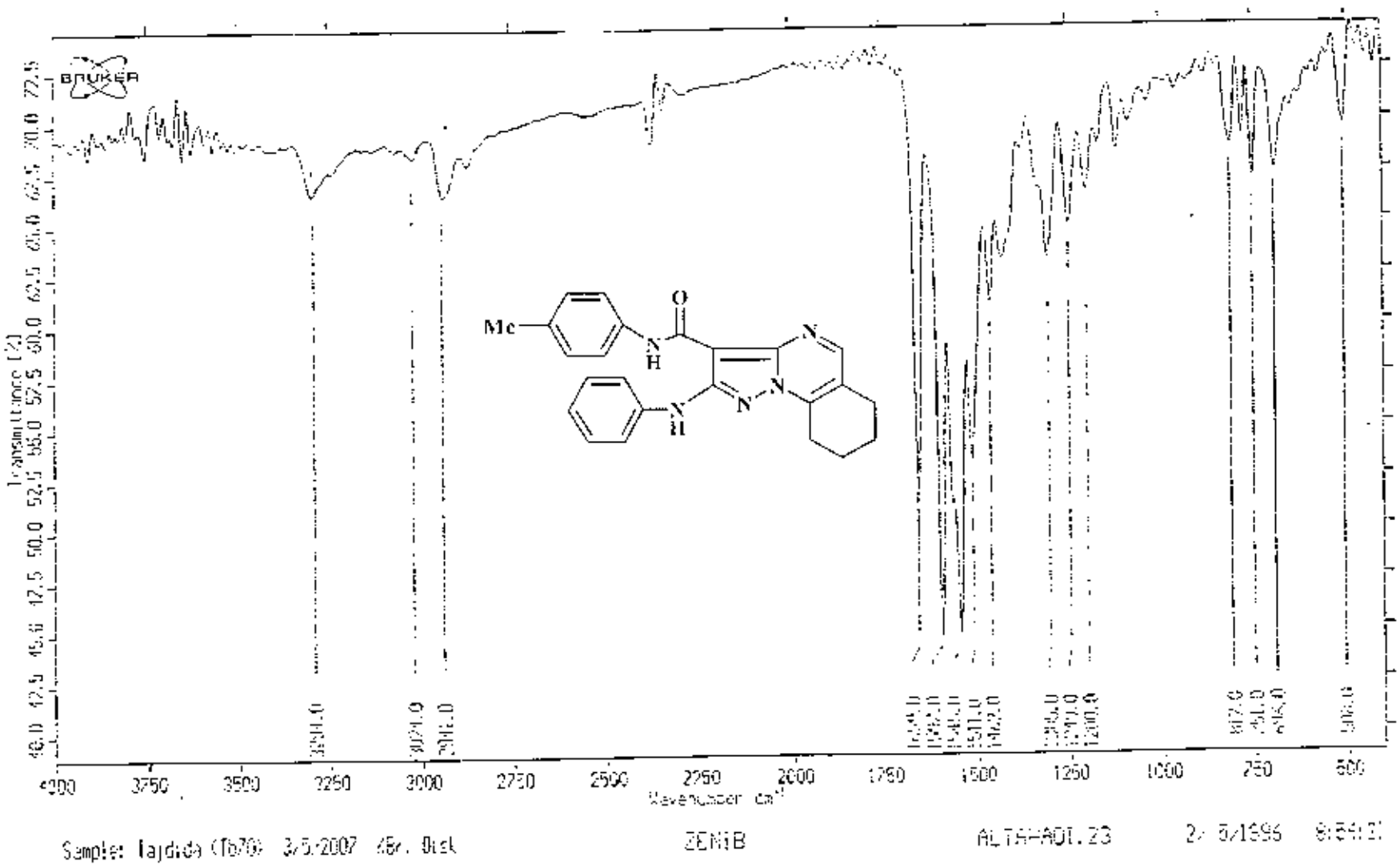

BRUKER
Transmittance [%]
Wavenumber cm-1
Me
O
N
H
N
N
N
N
H
3304.0
3071.0
2946.0
1604.0
1586.0
1548.0
1511.0
1462.0
1396.0
1291.0
1260.0
817.0
751.0
696.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Sample: Tajdida (To70) 3/5/2007 KBr Disk
ZENIB
ALTAHADI.23
2/ 3/1996

Fig. (22)

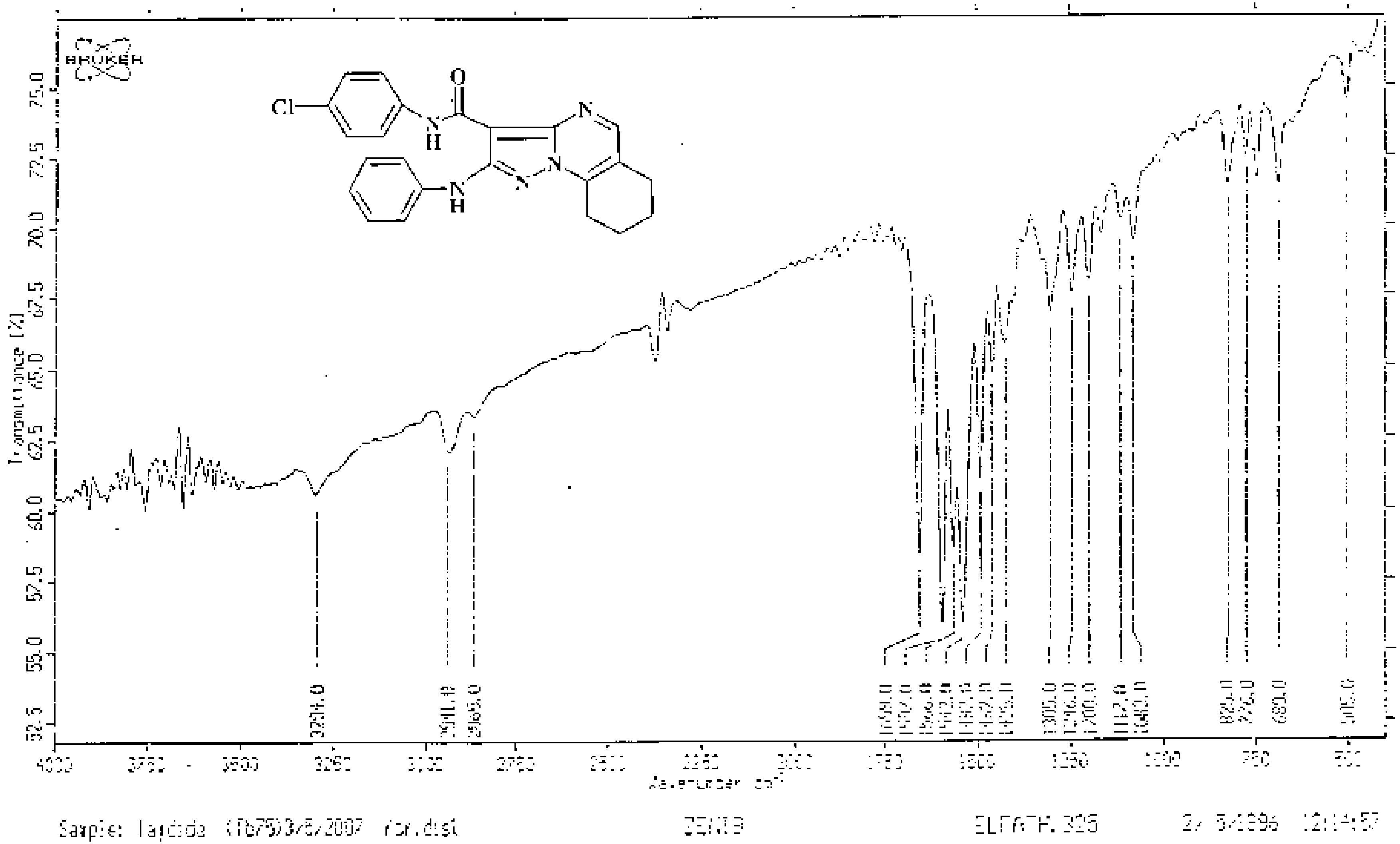

BRUKER
Cl
N
H
O
Transmittance [%]
75.0
72.5
70.0
67.5
65.0
62.5
60.0
57.5
55.0
52.5
3294.0
2865.0
1305.0
1200.0
689.0
505.0

Fig. (23)

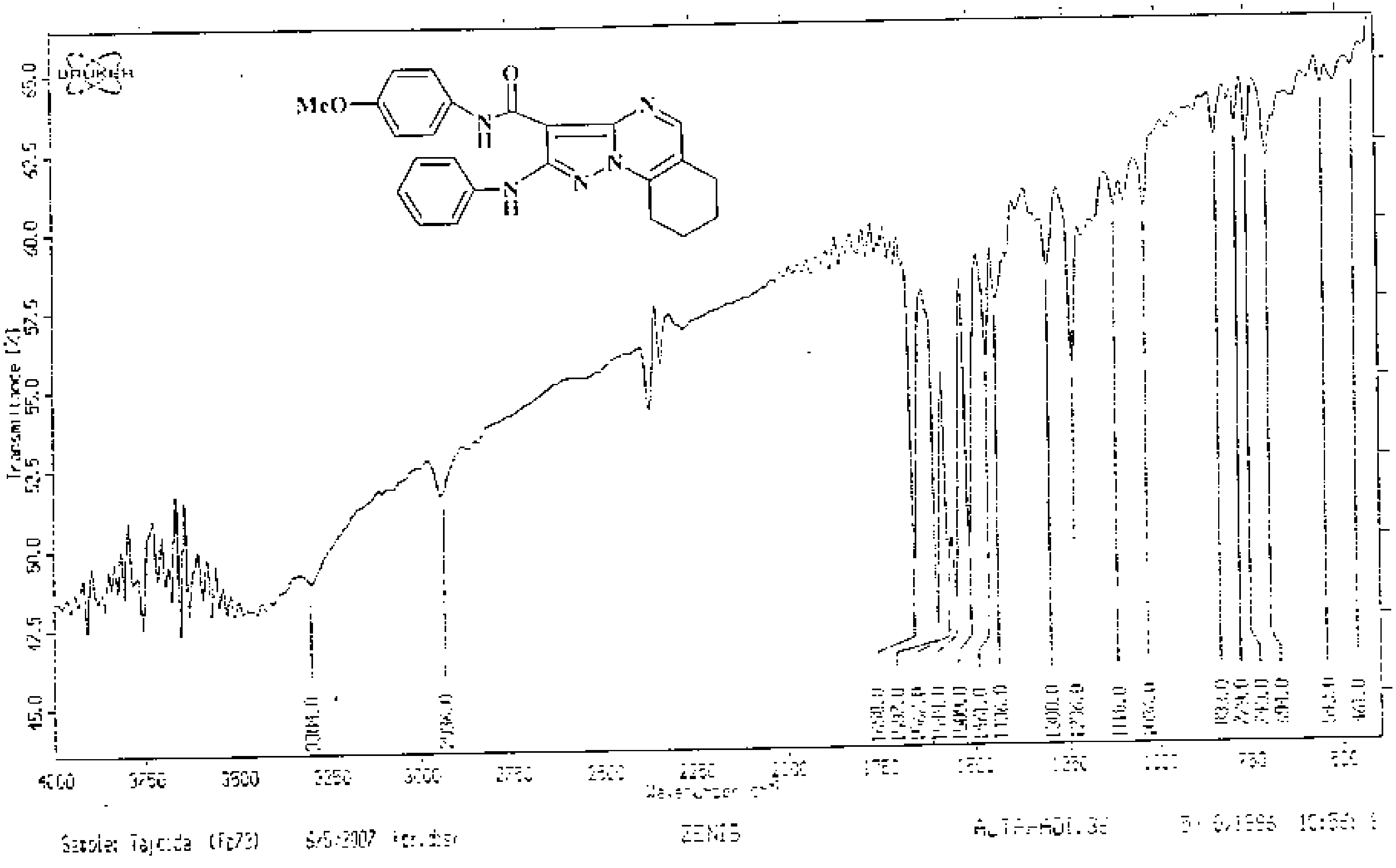


Fig. (24)

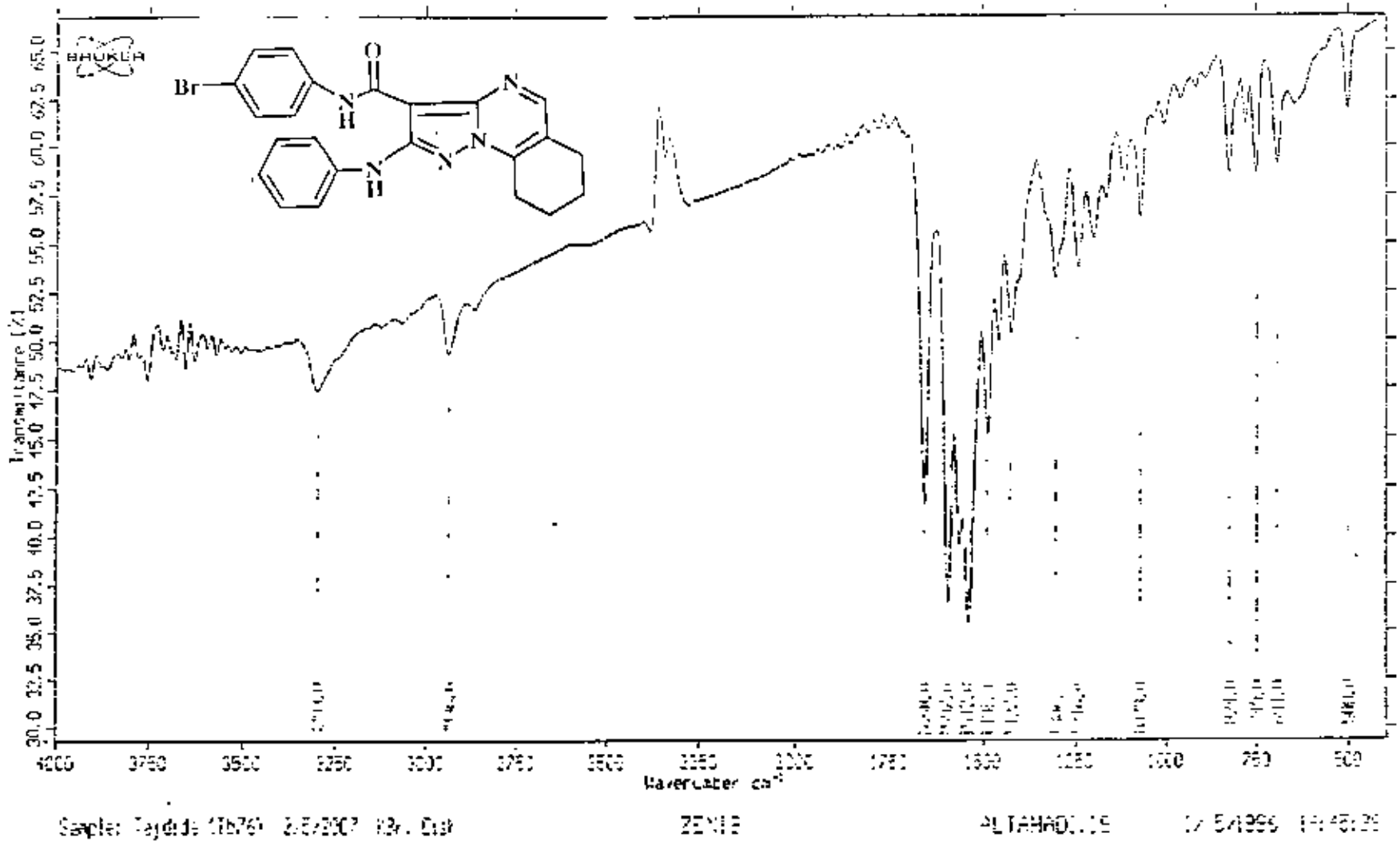


Fig. (25)

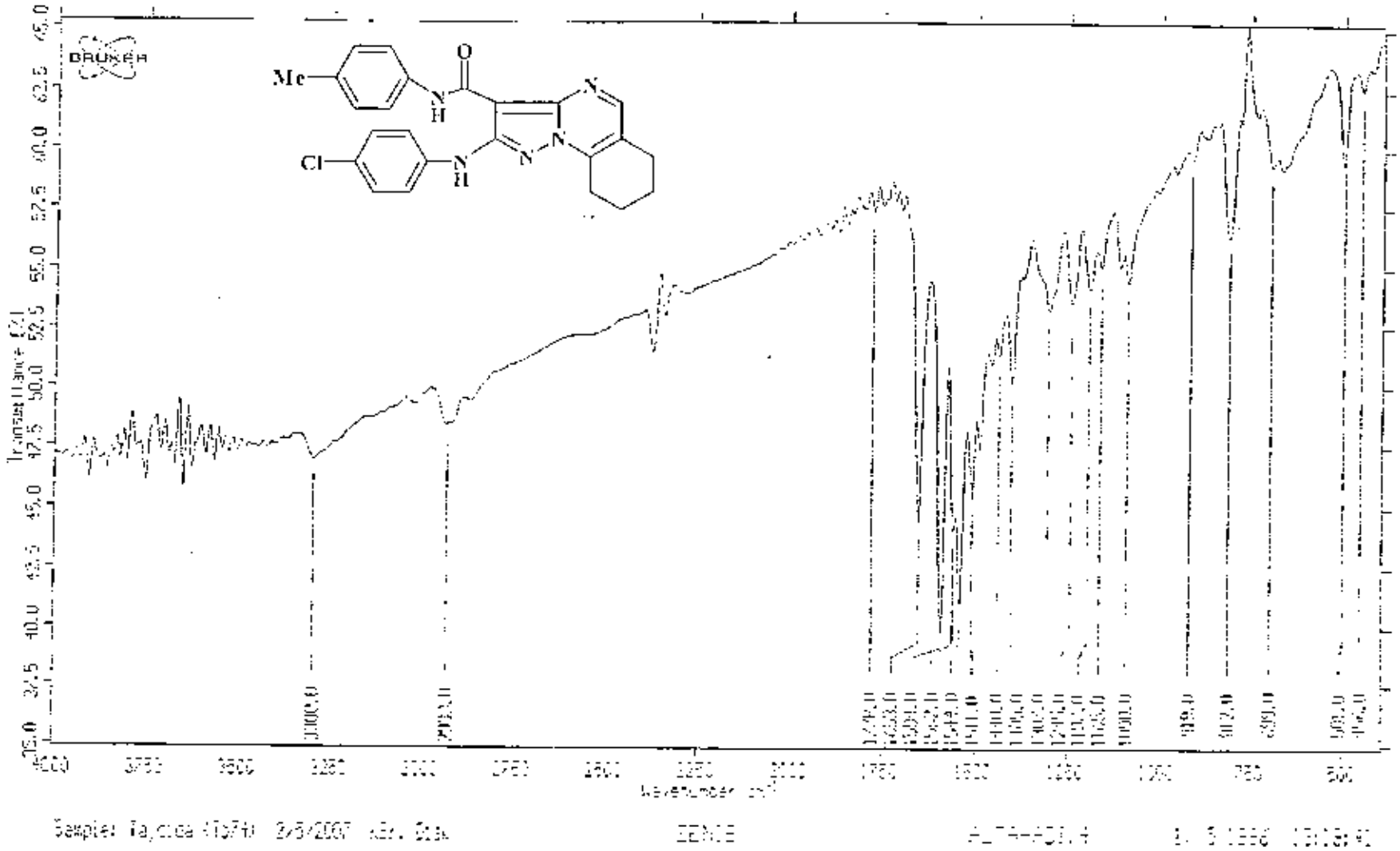


Fig. (26)

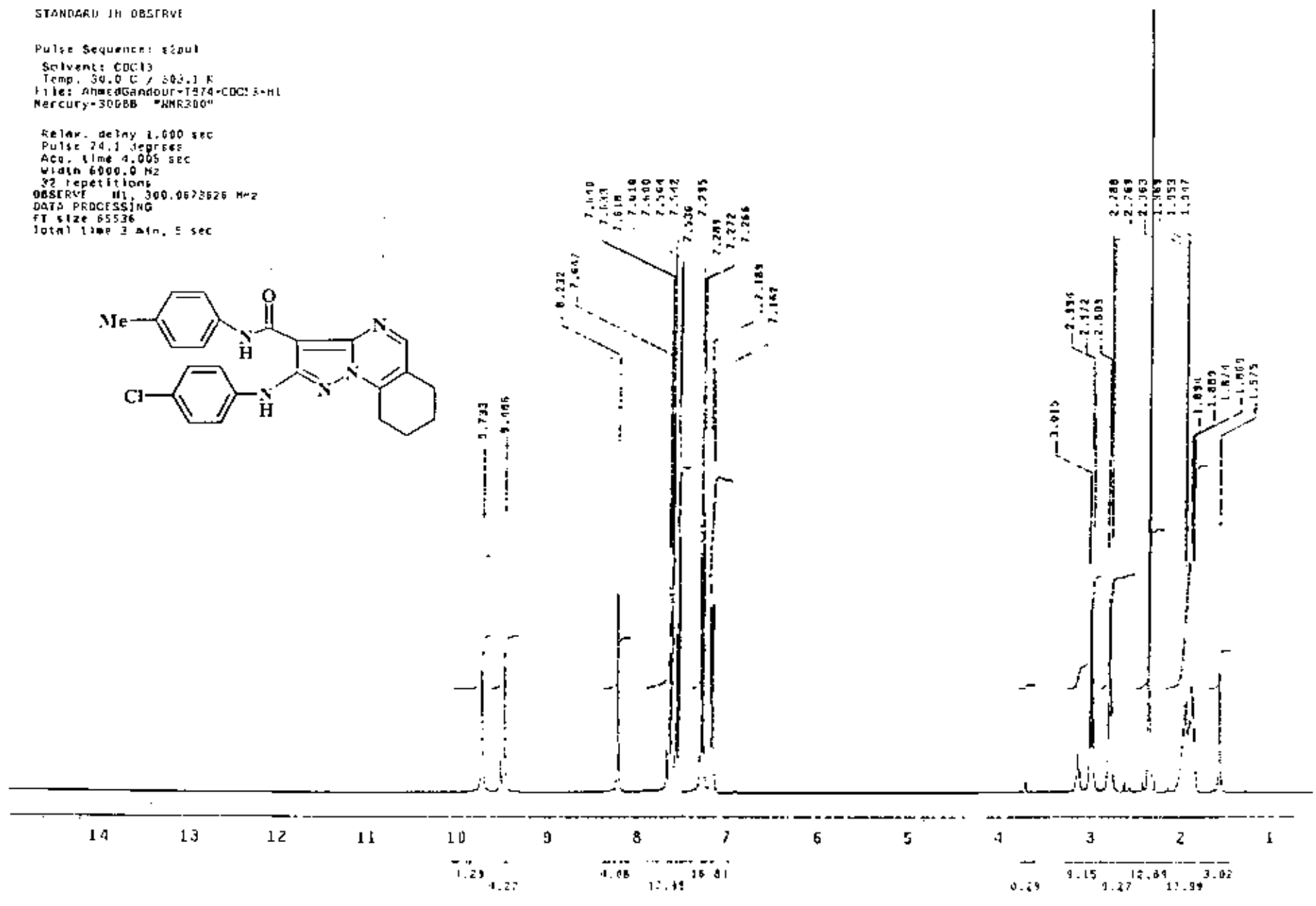

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 30.0 C / 303.1 K
File: AhmedGaadour-T874-CDCl3-H1
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 24.1 degrees
Acq. time 4.005 sec
Width 6000.0 Hz
32 repetitions
OBSERVE H1, 300.0673626 MHz
DATA PROCESSING
FT size 65536
Total time 2 min, 5 sec
Me
O
N
H
N
N
N
Cl
H
14
13
12
11
10
9
8
7
6
5
4
3
2
1

Fig. (27)

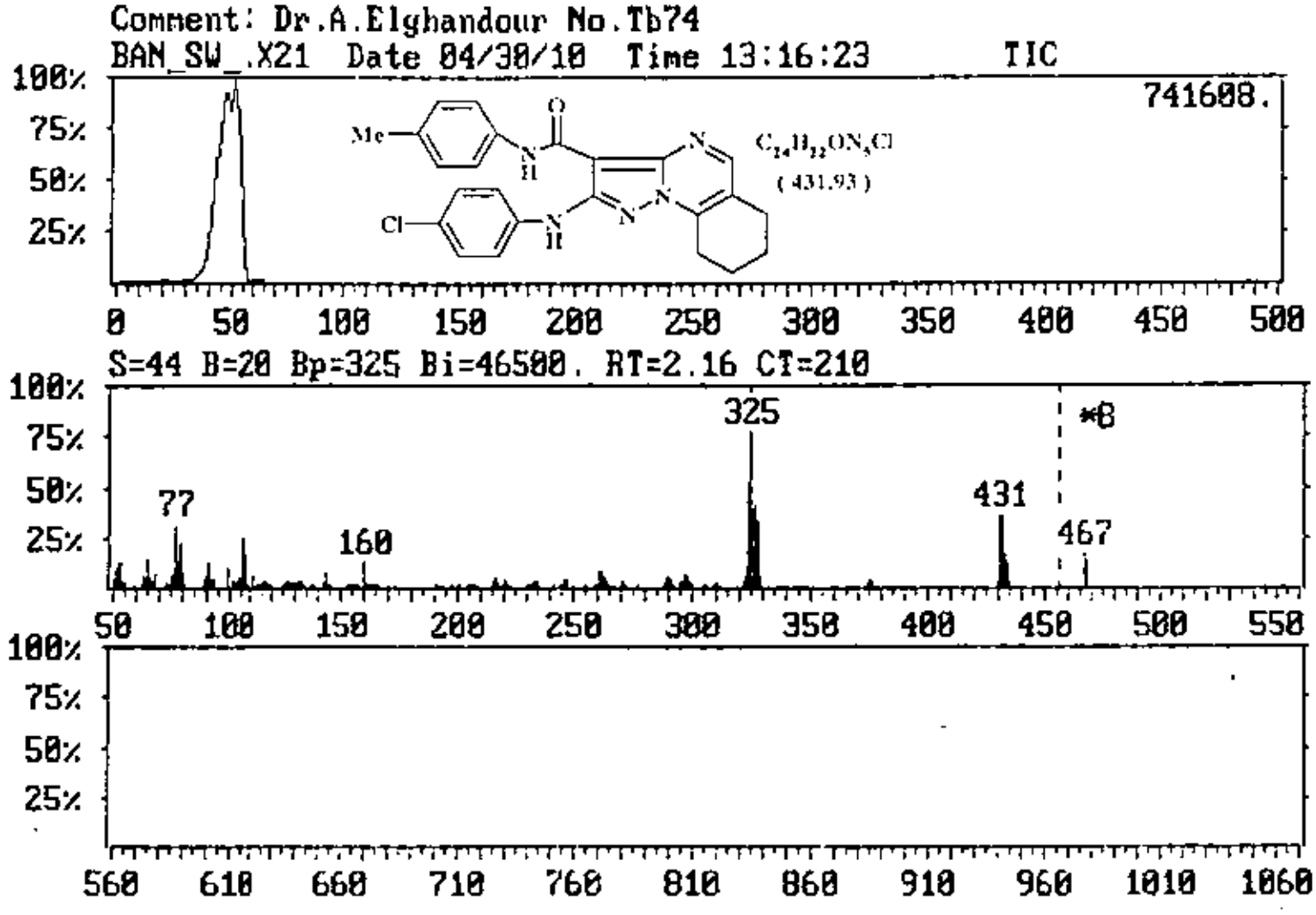

Comment: Dr.A.Elghandour No.Tb74
BAN_SW_.X21 Date 04/30/10 Time 13:16:23 TIC
741608.
100%
75%
50%
25%
Me
Cl
$C_{24}H_{22}ON_5Cl$
(431.93)
0 50 100 150 200 250 300 350 400 450 500
S=44 B=20 Bp=325 Bi=46500. RT=2.16 CT=210
325
*B
77
160
431
467
50 100 150 200 250 300 350 400 450 500 550
560 610 660 710 760 810 860 910 960 1010 1060
S List > S=44 B=20 Pos=5 Tot=5

Fig. (28)

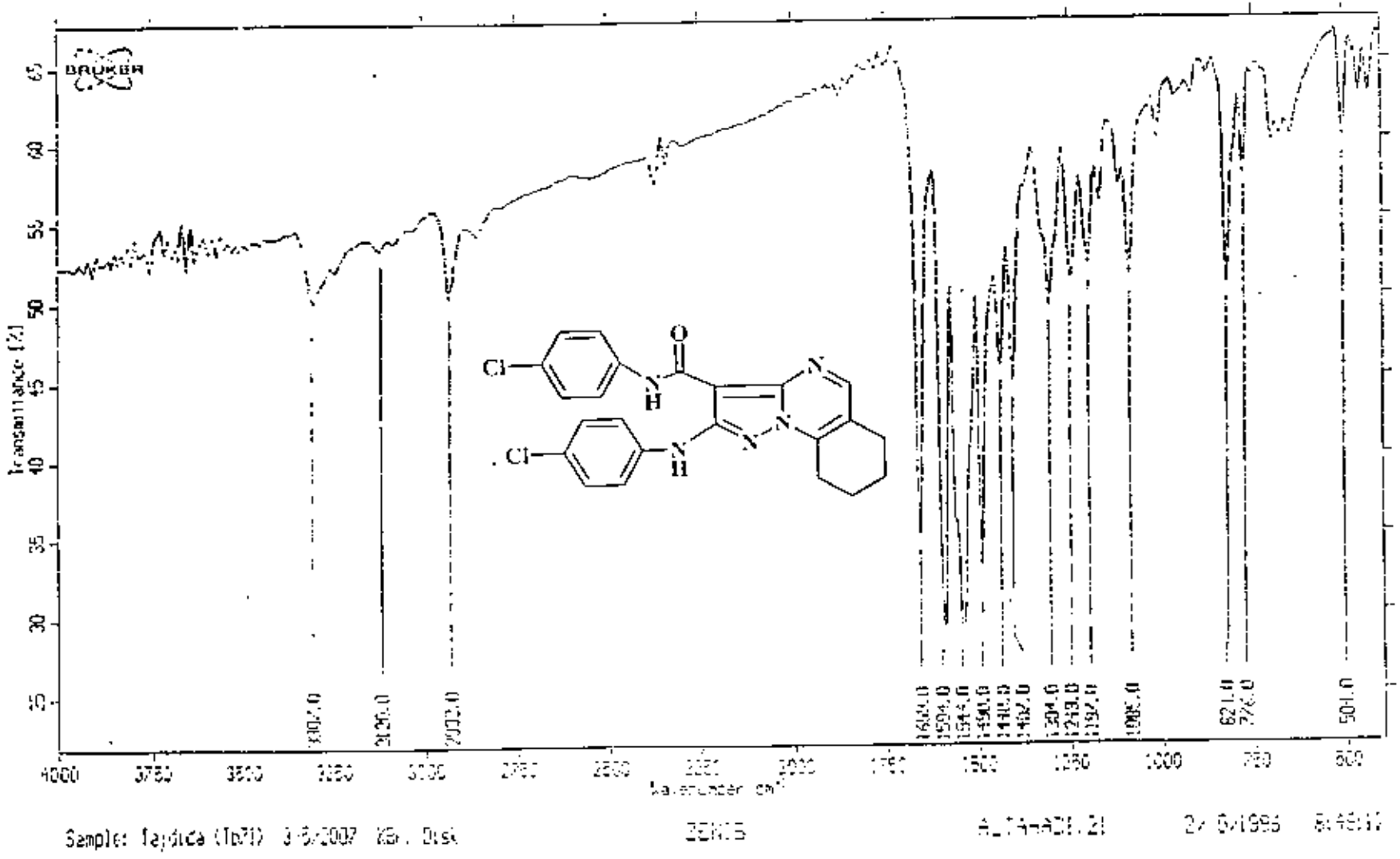

BRUKER
Transmittance [%]
Wavenumber cm-1
Cl
O
N
H
N
N
N
Cl
1600.0
1584.0
1544.0
1490.0
1462.0
1294.0
1243.0
1192.0
1085.0
821.0
756.0
501.0

Fig. (29)

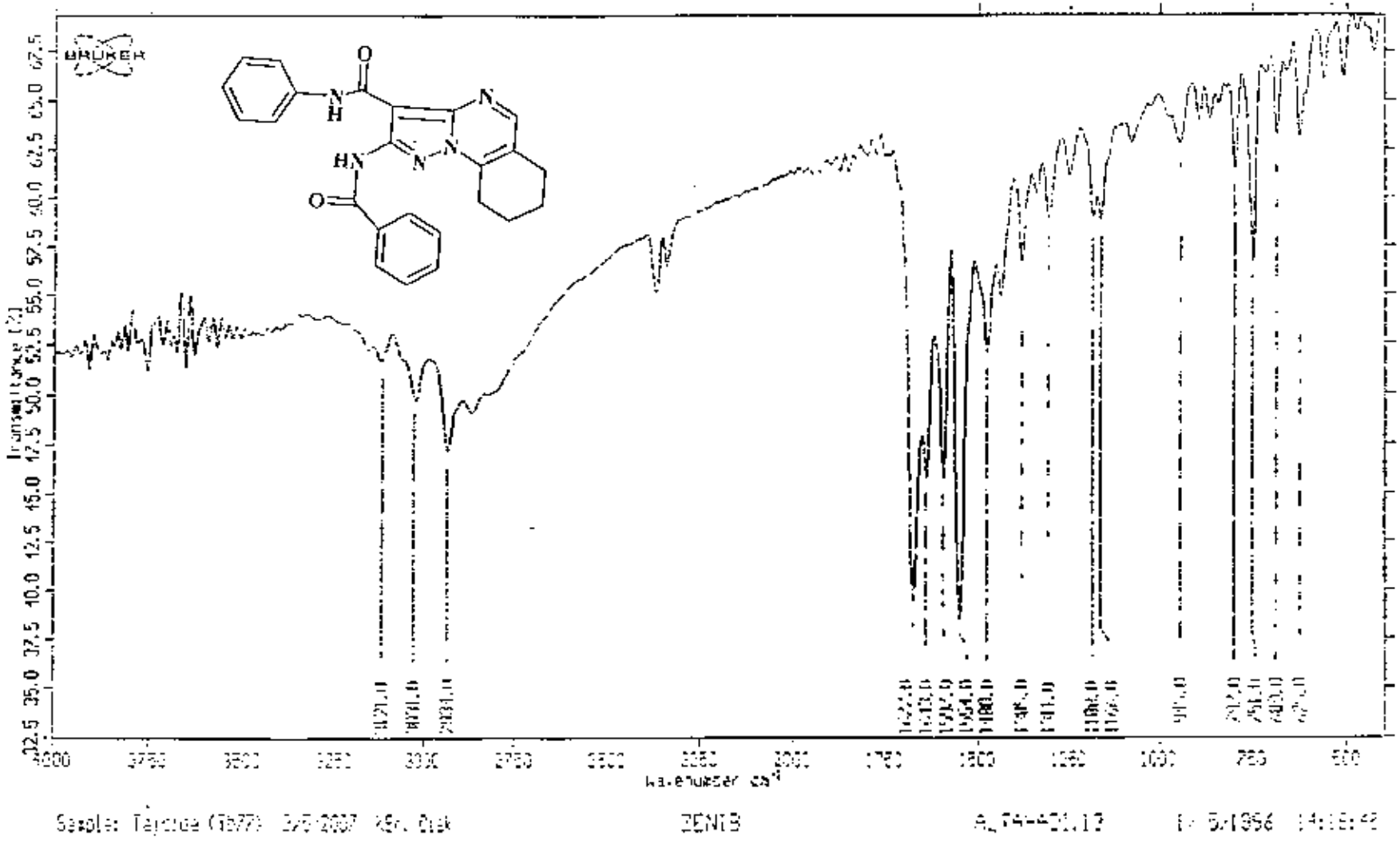

BRUKER
O
N
H
HN
N
N
O
Transmittance [%]
wavenumber cm-1
Sample: Tejinder (1577) 2/5/2007 Kbr. Disk
ZENIT

Fig. (30)

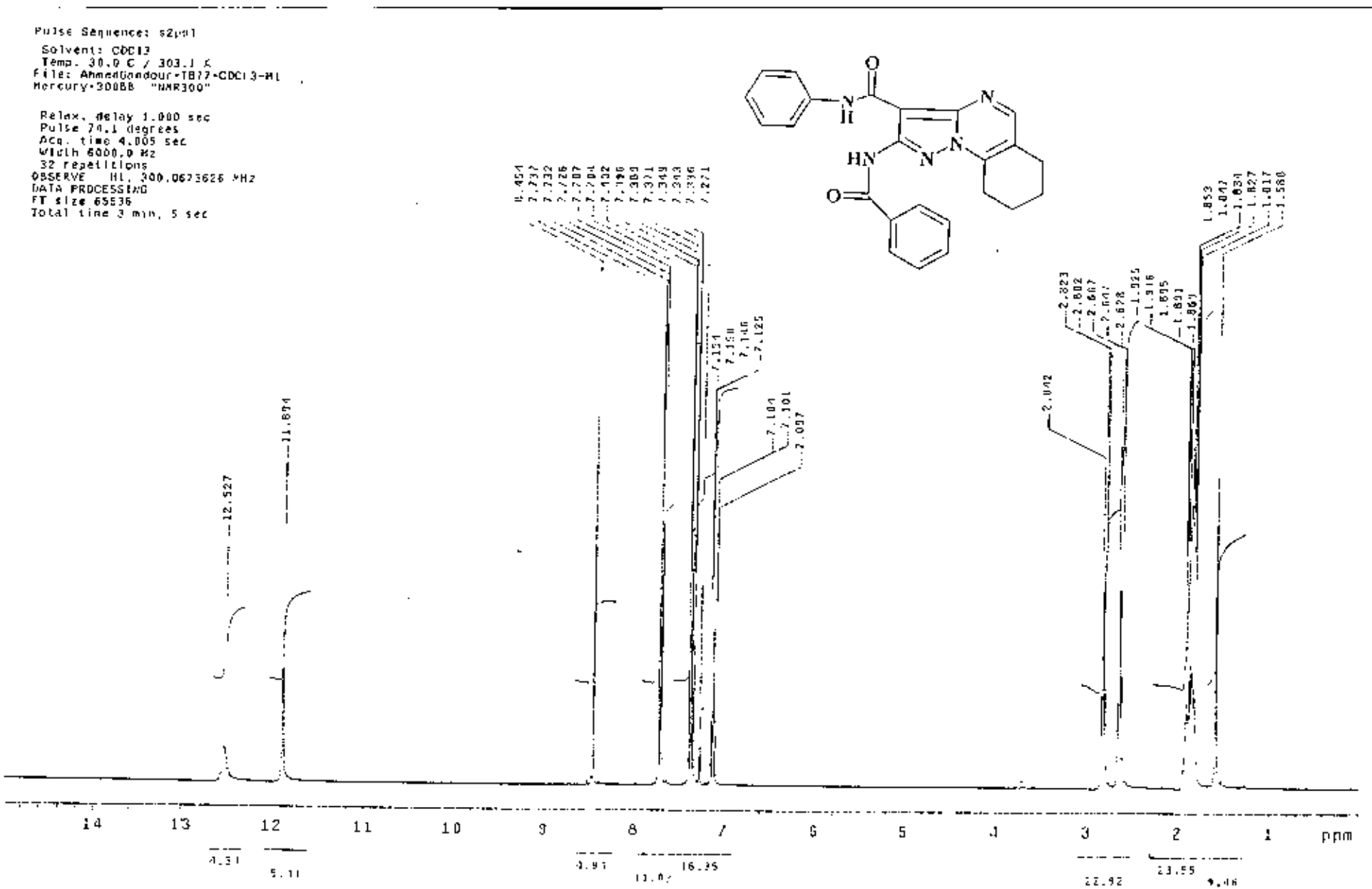

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 30.0 C / 303.1 K
File: AhmedGandour-TB77-CDCl3-H1
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 70.1 degrees
Acq. time 4.005 sec
Width 6000.0 Hz
32 repetitions
OBSERVE H1, 300.0673626 MHz
DATA PROCESSING
FT size 65536
Total time 3 min, 5 sec
12.527
11.804
2.042
ppm

Fig. (31)

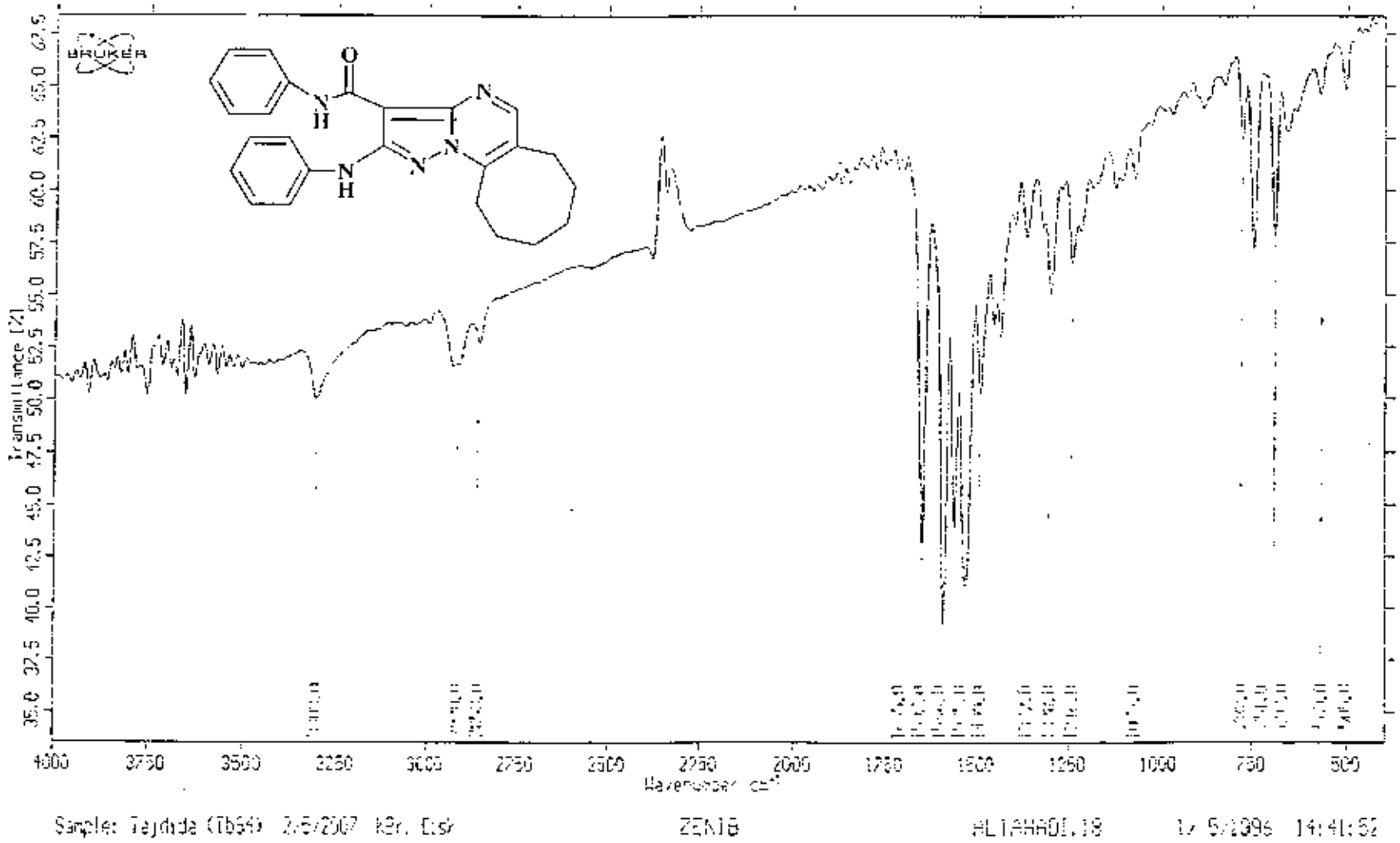

BRUKER
O
N
H
N
N
N
N
H
Transmittance [%]
100.0
97.5
95.0
92.5
90.0
87.5
85.0
82.5
80.0
77.5
75.0
72.5
70.0
67.5
65.0
62.5
60.0
57.5
55.0
52.5
50.0
47.5
45.0
42.5
40.0
37.5
35.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Tejada (Tb64) 2/5/2007 KBr, Est
ZEN18
ATR-HR01.18
1/ 5/1996 14:41:52

Fig. (32)

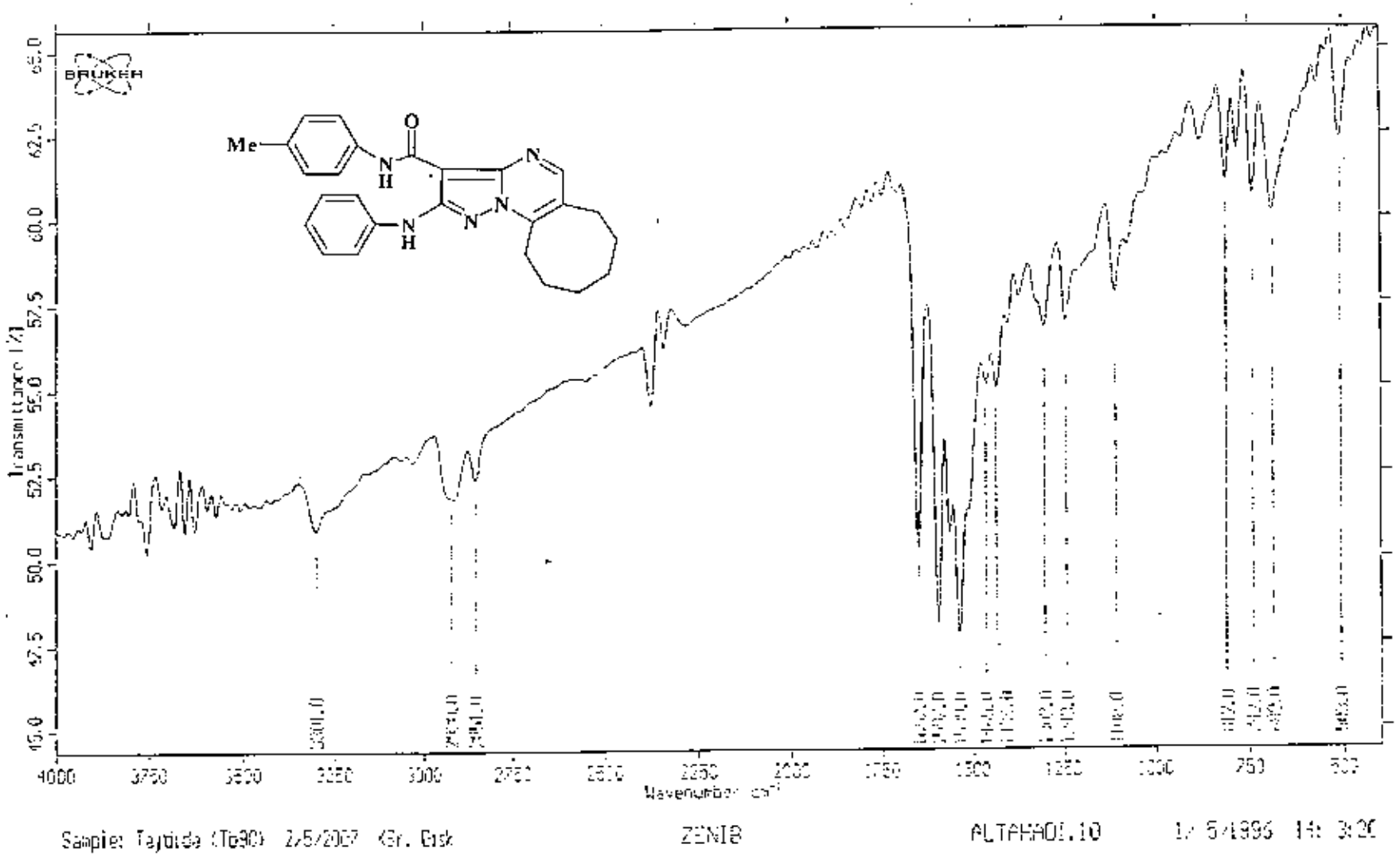

BRUKER
Me
O
N
H
N
N
N
N
H
Transmittance [%]
65.0
62.5
60.0
57.5
55.0
52.5
50.0
47.5
45.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Tajbida (Tb80) 2/5/2007 KBr. Disk
ZENIB
ALTAHADI.10
1/ 5/1996 14: 3:20

Fig. (33)

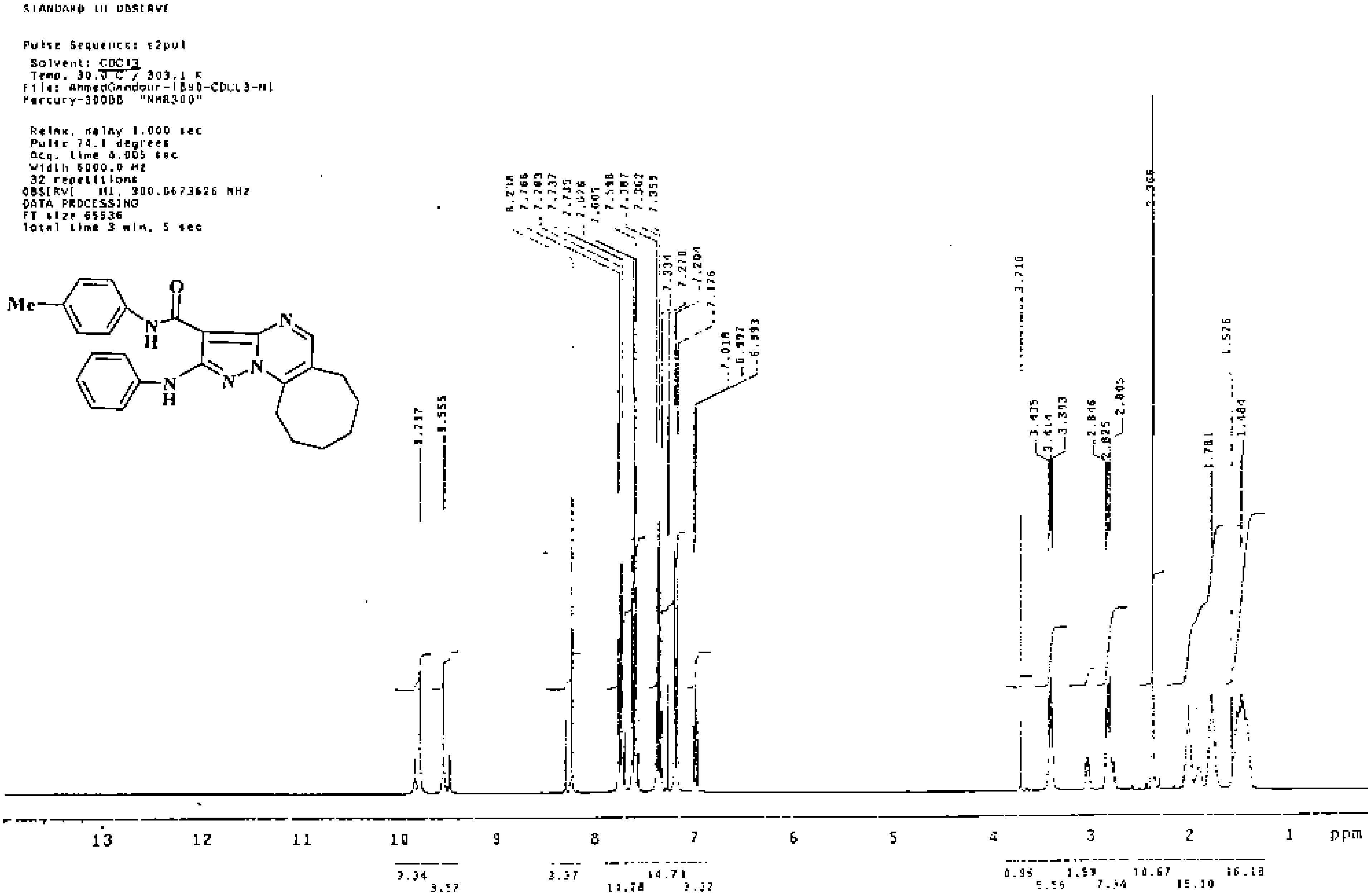

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 30.0 C / 303.1 K
File: AhmedGandour-IB90-CDCL3-H1
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 74.1 degrees
Acq. time 4.005 sec
Width 6000.0 Hz
32 repetitions
OBSERVE H1, 300.0673626 MHz
DATA PROCESSING
FT size 65536
Total time 3 min, 5 sec
Me
O
N
H
N
N
N
N
H
9.737
9.555
8.218
7.766
7.283
7.737
7.715
7.626
7.605
7.598
7.387
7.362
7.359
7.331
7.270
7.204
7.176
7.018
6.997
6.993
3.710
3.435
3.414
3.393
2.846
2.825
2.805
2.366
1.781
1.526
1.484
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
3.34
3.57
3.37
14.78
14.71
3.32
0.96
5.56
1.59
7.34
10.67
15.10
16.18

Fig. (34)

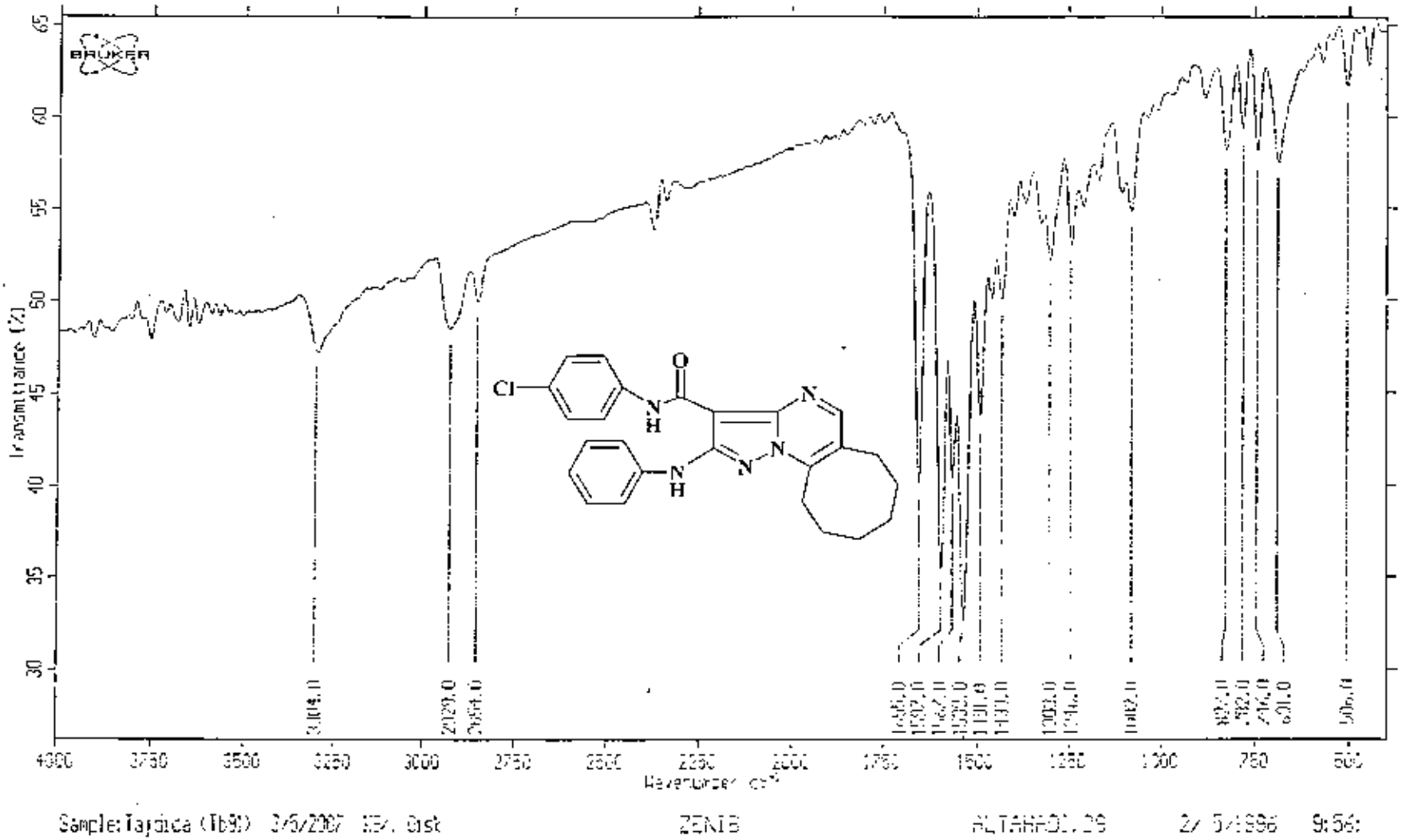

BRUKER
Transmittance (%)
Wavenumber cm-1
Cl
O
N
H
N
N
N
H
Sample: Tajadica (Tb9) 3/5/2007 KBr, Disk
ZENIT
ALTAHA01.25
2/ 5/1996 9:56:

Fig. (35)

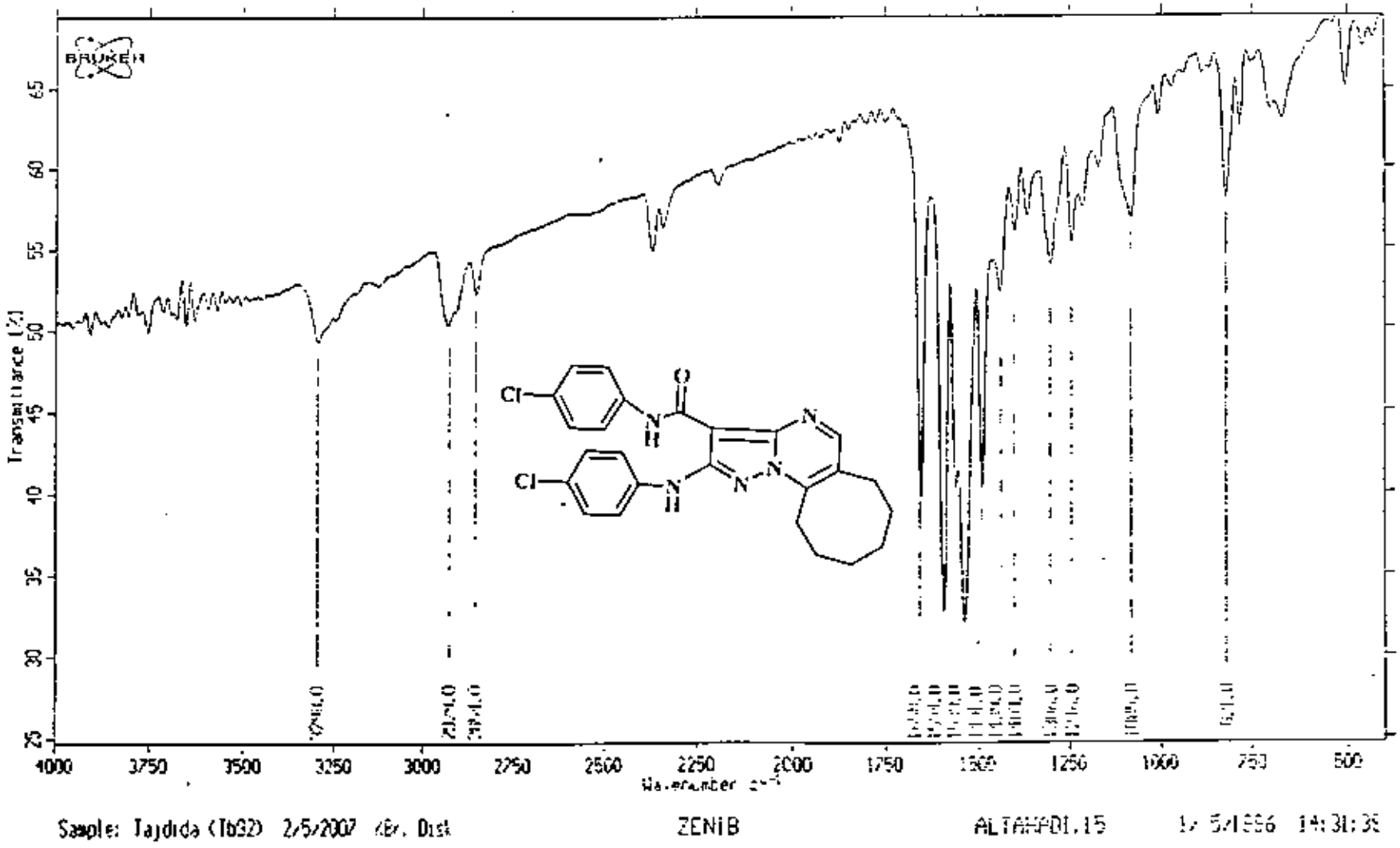

BRUKER
Transmittance [%]
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Cl
O
N
H
Cl
N
H
N
N
N
Sample: Tajdida (Tb32) 2/5/2007
ZENiB
ALTAHADI.15

Fig. (36)

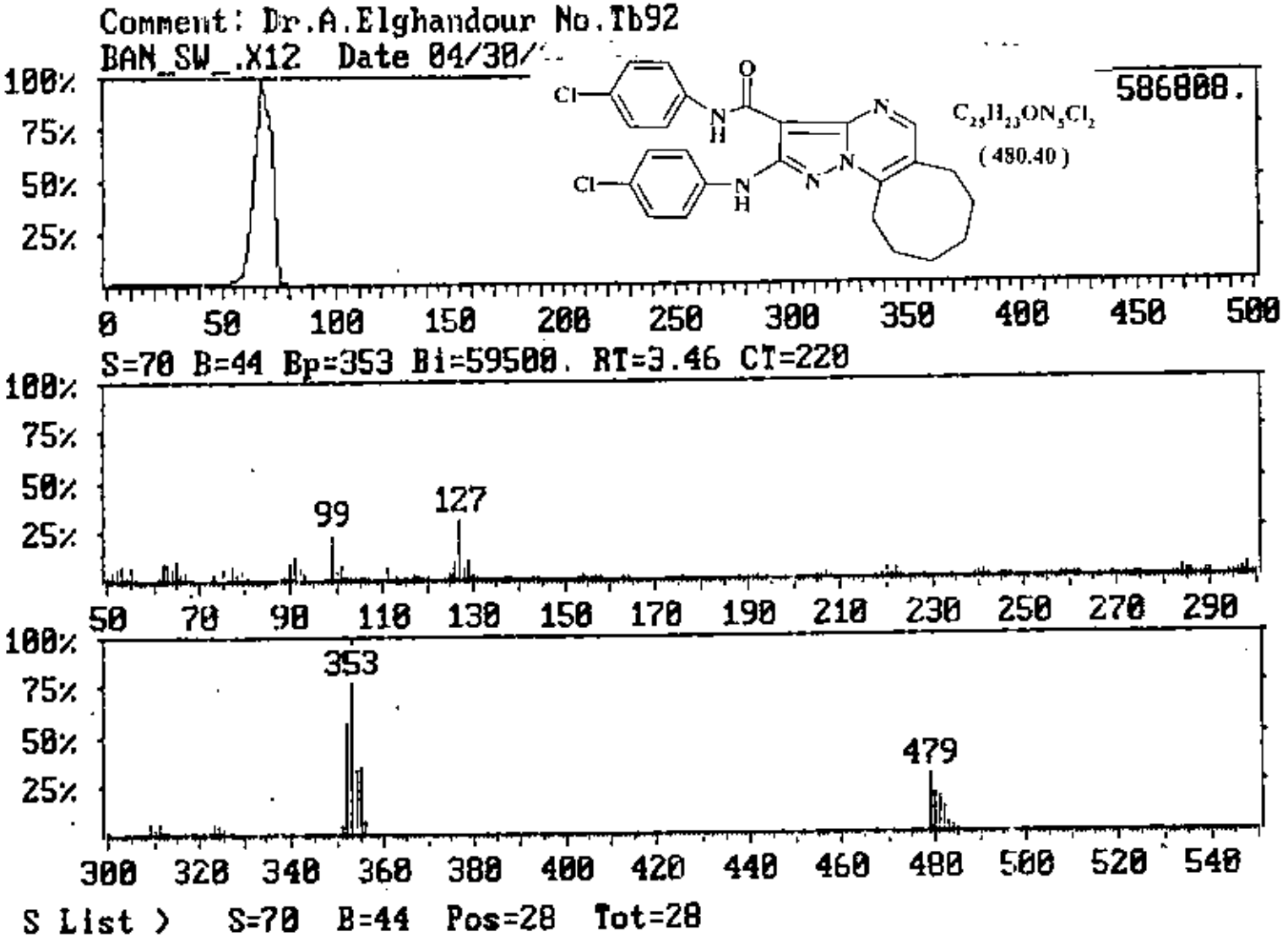

Comment: Dr.A.Elghandour No.Tb92
BAN_SW_.X12 Date 04/30/
586888.
$C_{25}H_{23}ON_5Cl_2$
(480.40)
S=70 B=44 Bp=353 Bi=59500. RT=3.46 CT=220
99
127
353
479
S List > S=70 B=44 Pos=28 Tot=28

Fig. (37)

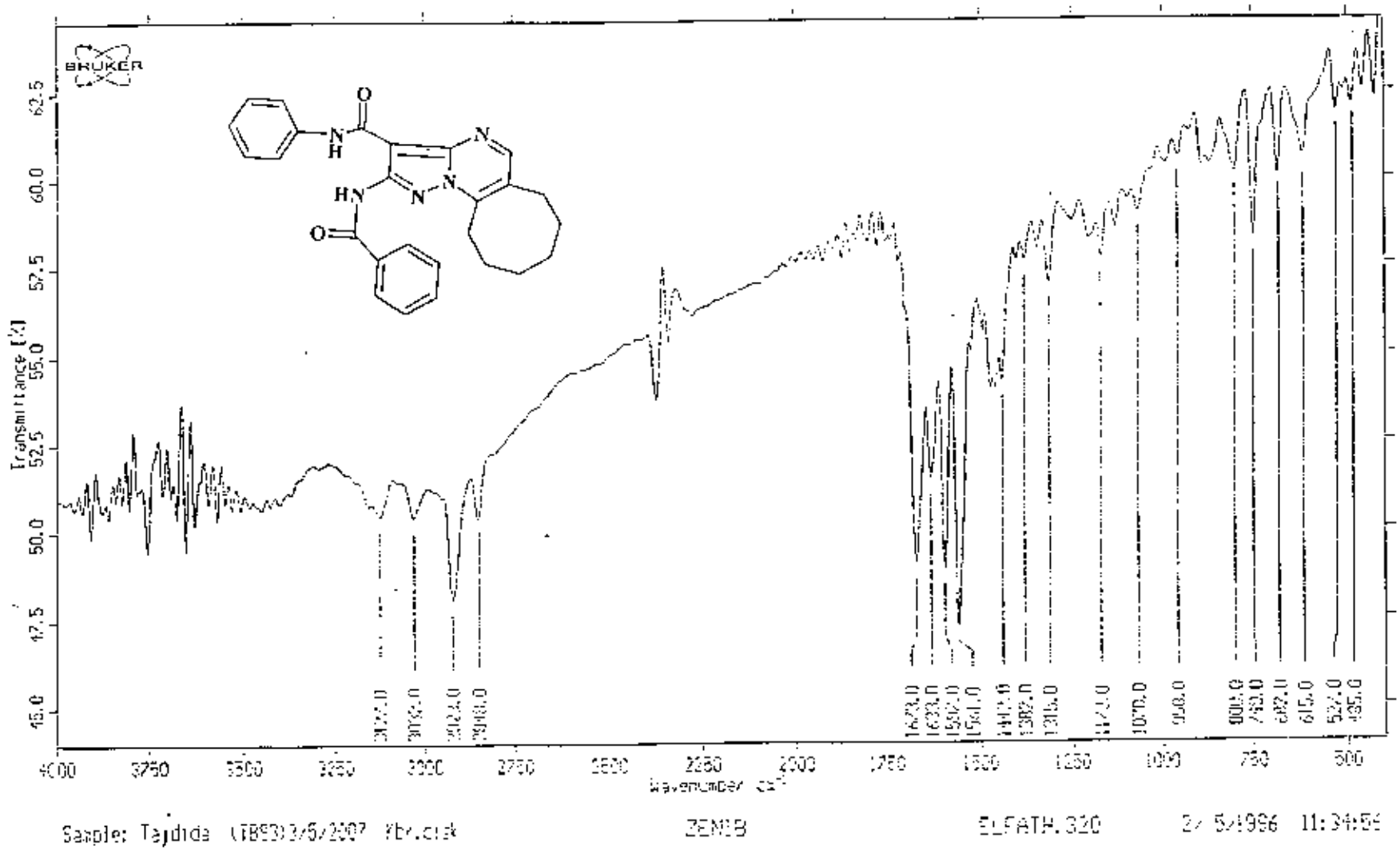

BRUKER
Transmittance [%]
Wavenumber cm-1
Sample: Tajdida (TB93)3/6/2007 Kbr.clk
ZEMIB
ELPATH.320
2/ 5/1996 11:34:59

Fig. (38)

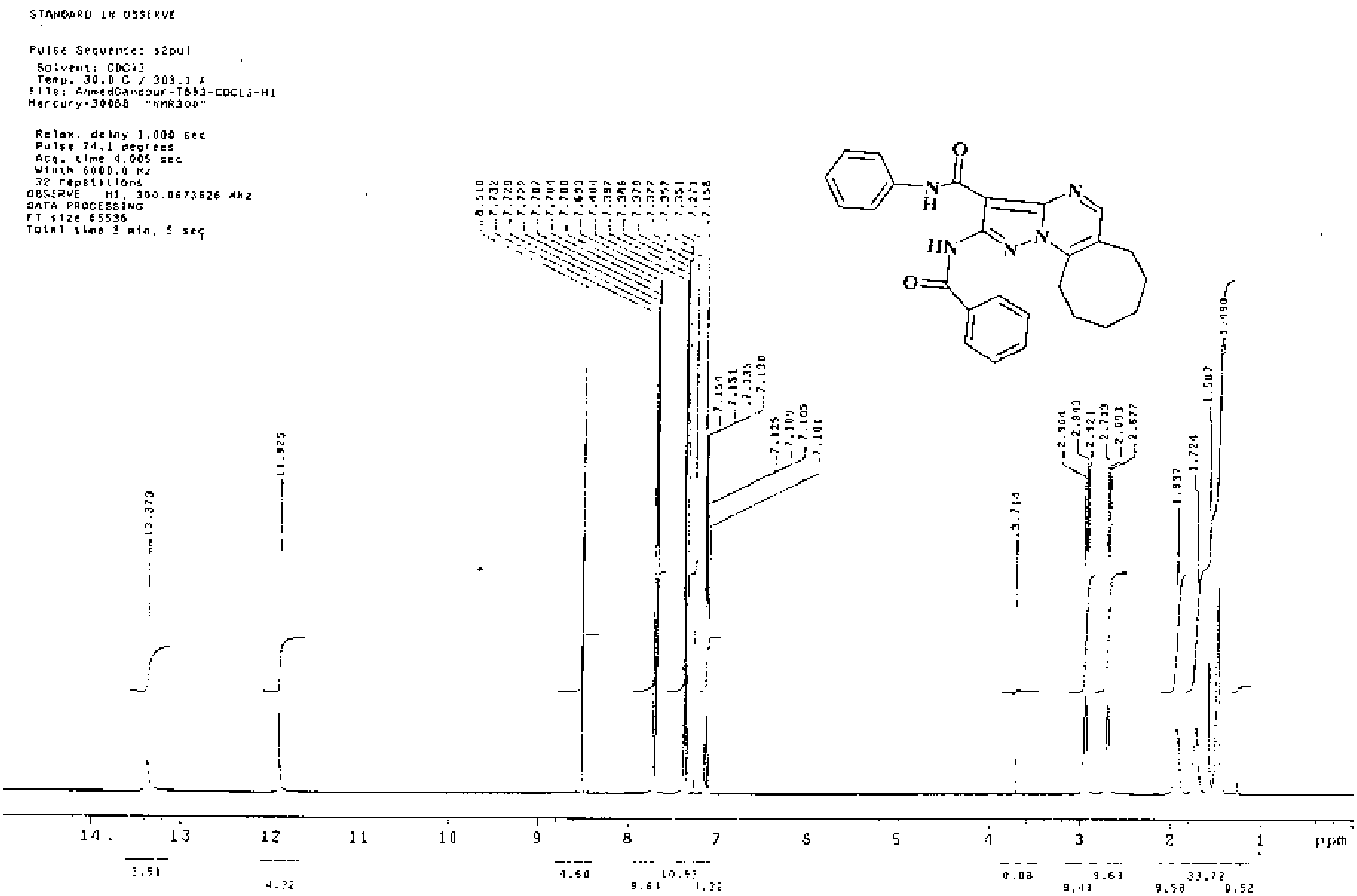

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 30.0 C / 303.1 K
File: AhmedDandour-T653-CDCL3-H1
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 74.1 degrees
Acq. time 4.005 sec
Width 6000.0 Hz
32 repetitions
OBSERVE H1, 300.0673626 MHz
DATA PROCESSING
FT size 65536
Total time 3 min, 5 sec
13.373
11.923
ppm
HN
O
N
H

Fig. (39)

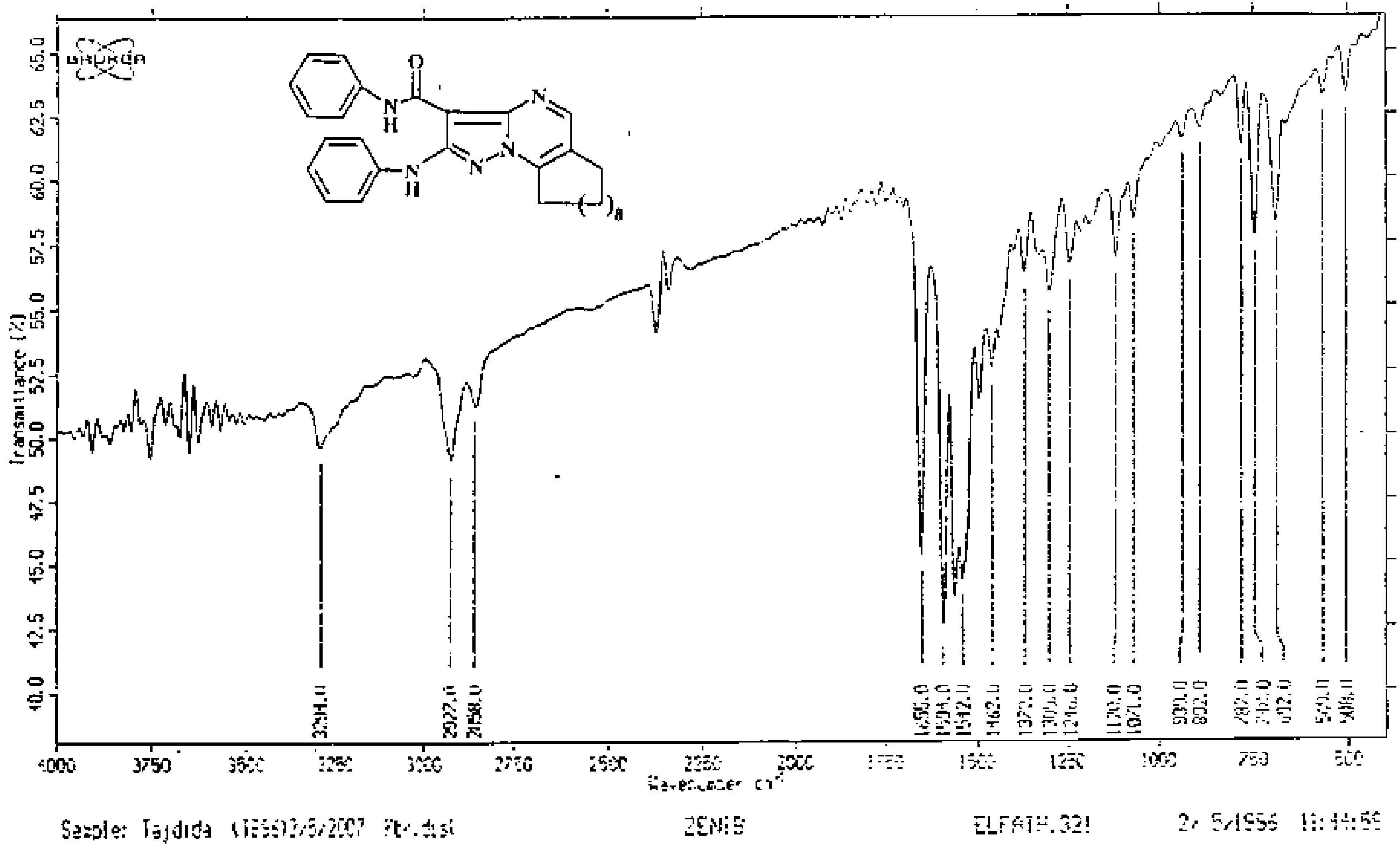

Transmittance (%)
65.0
62.5
60.0
57.5
55.0
52.5
50.0
47.5
45.0
42.5
40.0
3294.0
2922.0
2858.0
1656.0
1594.0
1542.0
1462.0
1372.0
1300.0
1246.0
1120.0
1071.0
900.0
802.0
782.0
712.0
612.0
520.0
508.0
4000
3750
3000
2750
2500
2000
1250
1000
750
500
Wavenumber cm-1
Sample: Tajdida
ZENIB
ELFATH.321

Fig. (40)

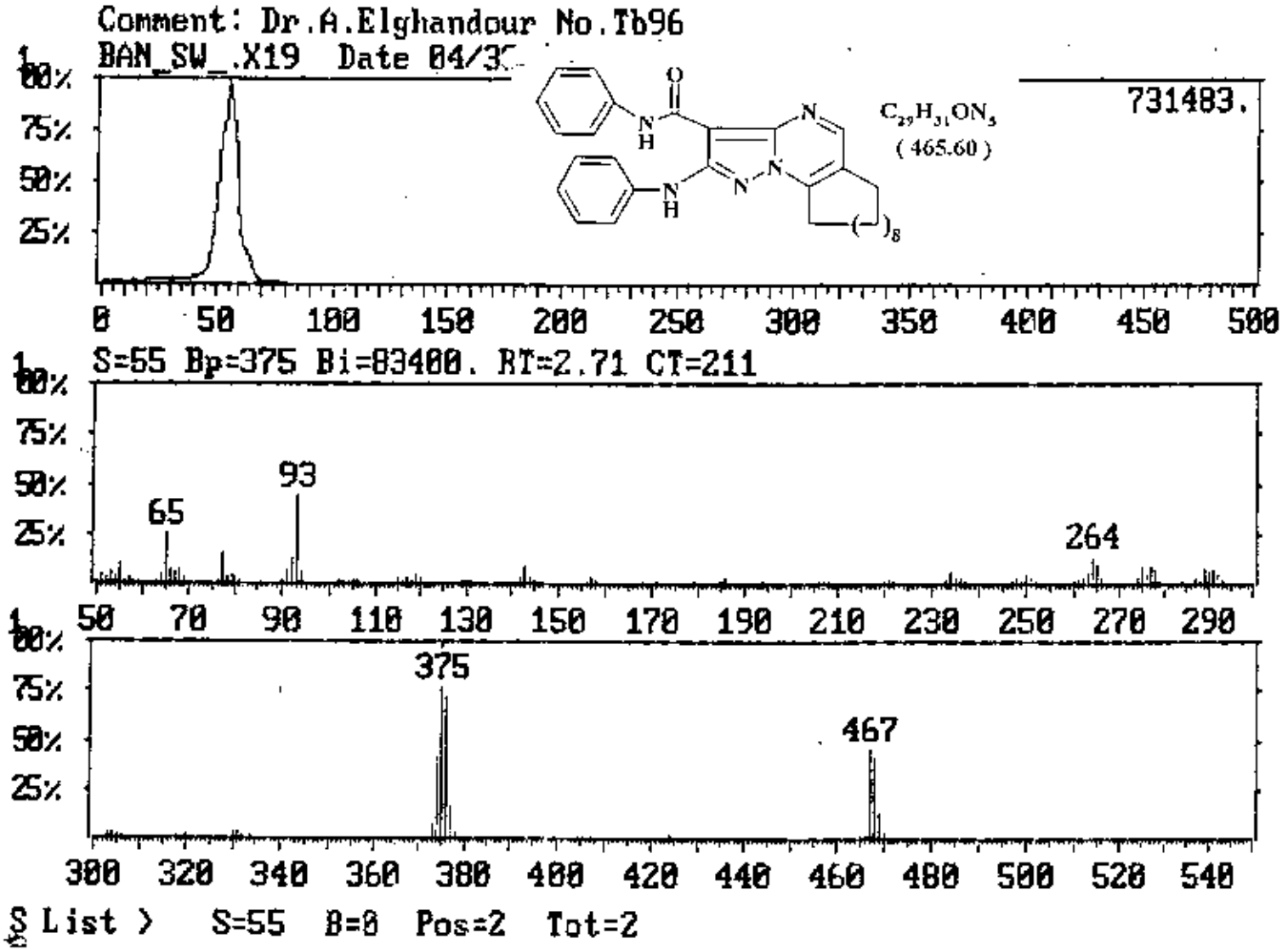

Comment: Dr.A.Elghandour No.Tb96
BAN_SW_.X19 Date 04/3
100%
75%
50%
25%
731483.
$C_{29}H_{31}ON_5$
(465.60)
0 50 100 150 200 250 300 350 400 450 500
S=55 Bp=375 Bi=83400. RT=2.71 CT=211
65
93
264
50 70 90 110 130 150 170 190 210 230 250 270 290
375
467
300 320 340 360 380 400 420 440 460 480 500 520 540
$ List > S=55 B=0 Pos=2 Tot=2

Fig. (41)

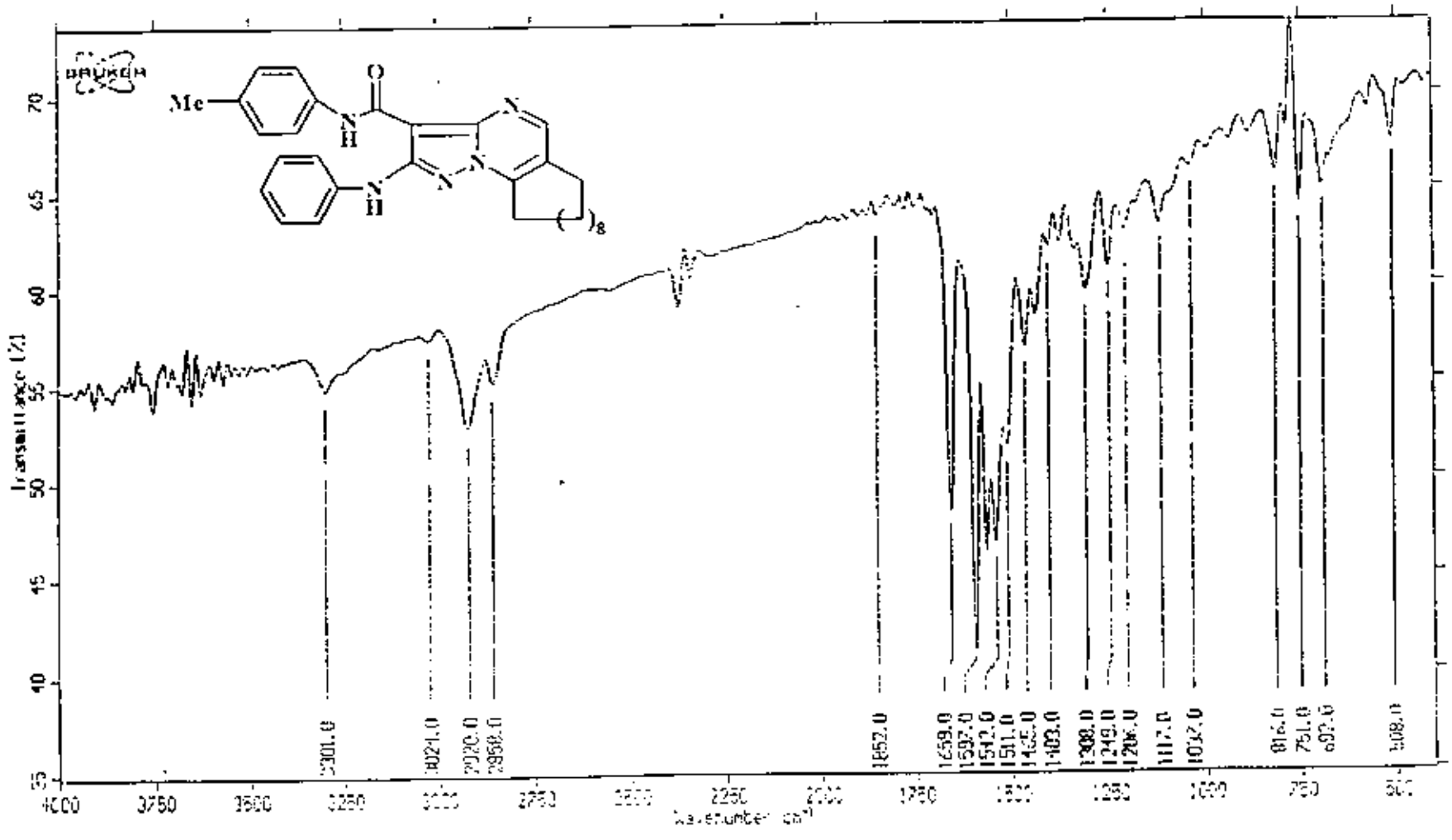

Me
O
N
H
N
N
N
H
N
)8
Transmittance [%]
70
65
60
55
50
45
40
35
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
3301.8
3021.0
2920.0
2850.0
1652.0
1559.0
1507.0
1542.0
1511.0
1465.0
1403.0
1308.0
1249.0
1206.0
1117.0
1042.0
816.0
751.0
692.0
508.0
Sample: Tajdida (1b65) 2/5/2007 KBr Disk
ZENIS
ALTAHADI.2
5/1996 13:

Fig. (42)

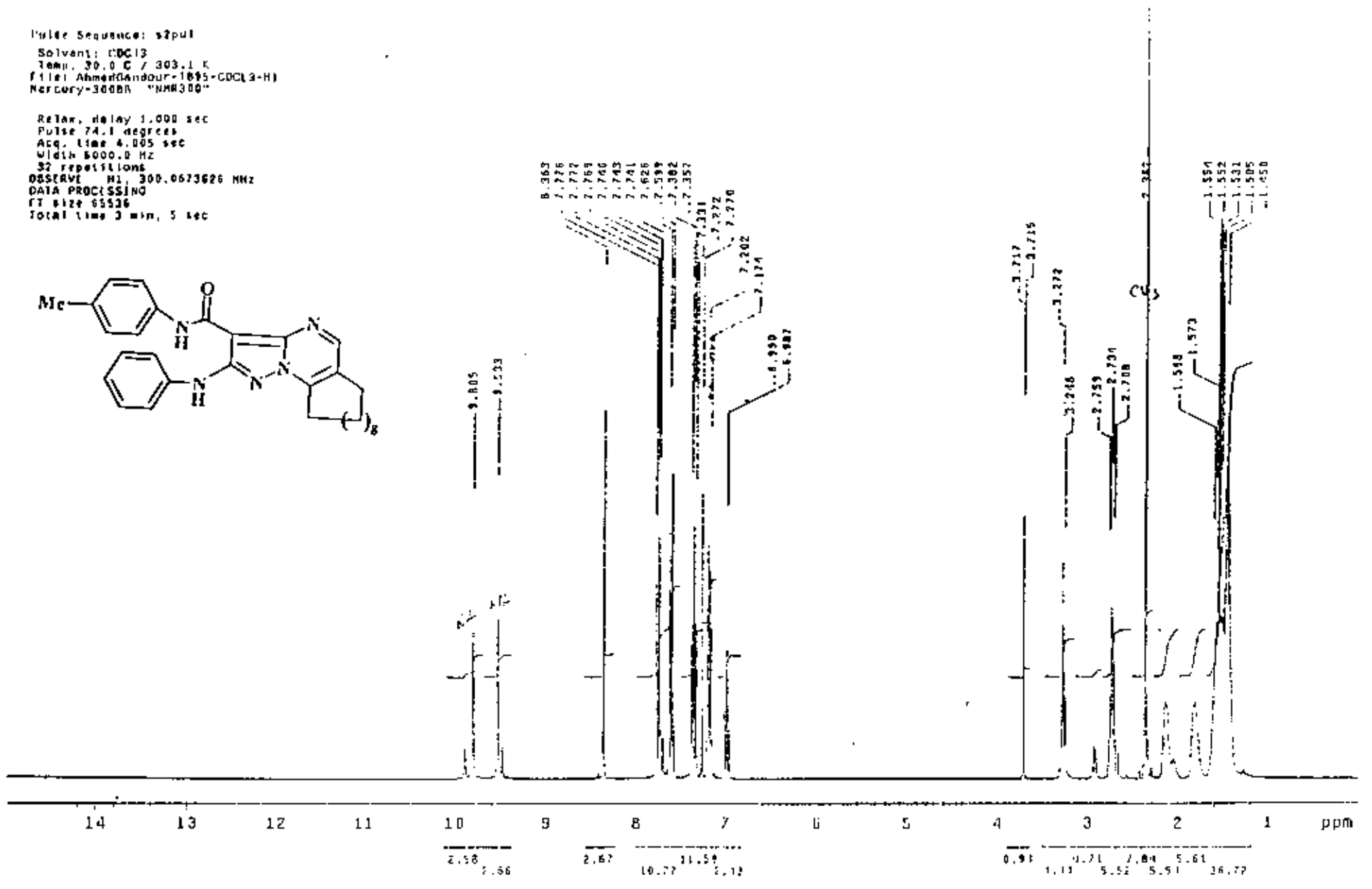

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 30.0 C / 303.1 K
File: AhmedGandour-1695-CDCl3-H1
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 74.1 degrees
Acq. time 4.005 sec
Width 6000.0 Hz
32 repetitions
OBSERVE H1, 300.0673626 MHz
DATA PROCESSING
FT size 65536
Total time 3 min, 5 sec
Me
O
N
H
N
H
N
N
N
( )g
9.805
9.533
8.363
7.776
7.769
7.746
7.743
7.741
7.626
7.599
7.382
7.357
7.331
7.272
7.270
7.202
7.174
6.959
6.957
3.717
3.715
3.272
3.248
2.759
2.756
2.708
1.573
1.518
1.554
1.552
1.531
1.505
1.450
CH3
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
2.58
2.66
2.67
11.59
10.77
2.12
0.91
1.11
0.71
5.52
7.84
5.51
5.61
26.77

Fig. (43)

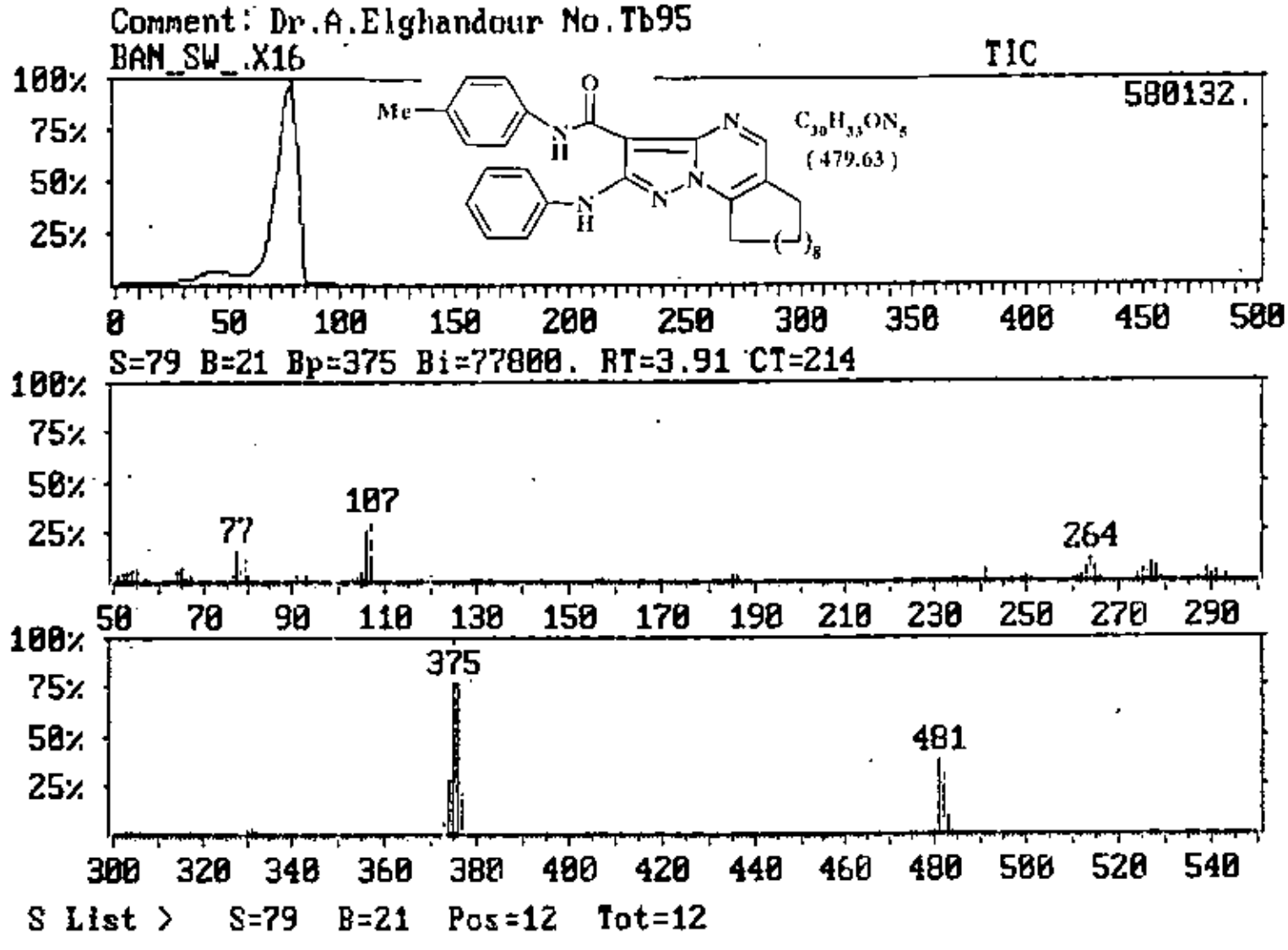

Comment: Dr.A.Elghandour No.Tb95
BAN_SW_.X16
TIC
580132.
100%
75%
50%
25%
Me
O
N
H
N
N
N
$C_{30}H_{33}ON_5$
(479.63)
0 50 100 150 200 250 300 350 400 450 500
S=79 B=21 Bp=375 Bi=77800. RT=3.91 CT=214
77
107
264
50 70 90 110 130 150 170 190 210 230 250 270 290
375
481
300 320 340 360 380 400 420 440 460 480 500 520 540
S List > S=79 B=21 Pos=12 Tot=12

Fig. (44)

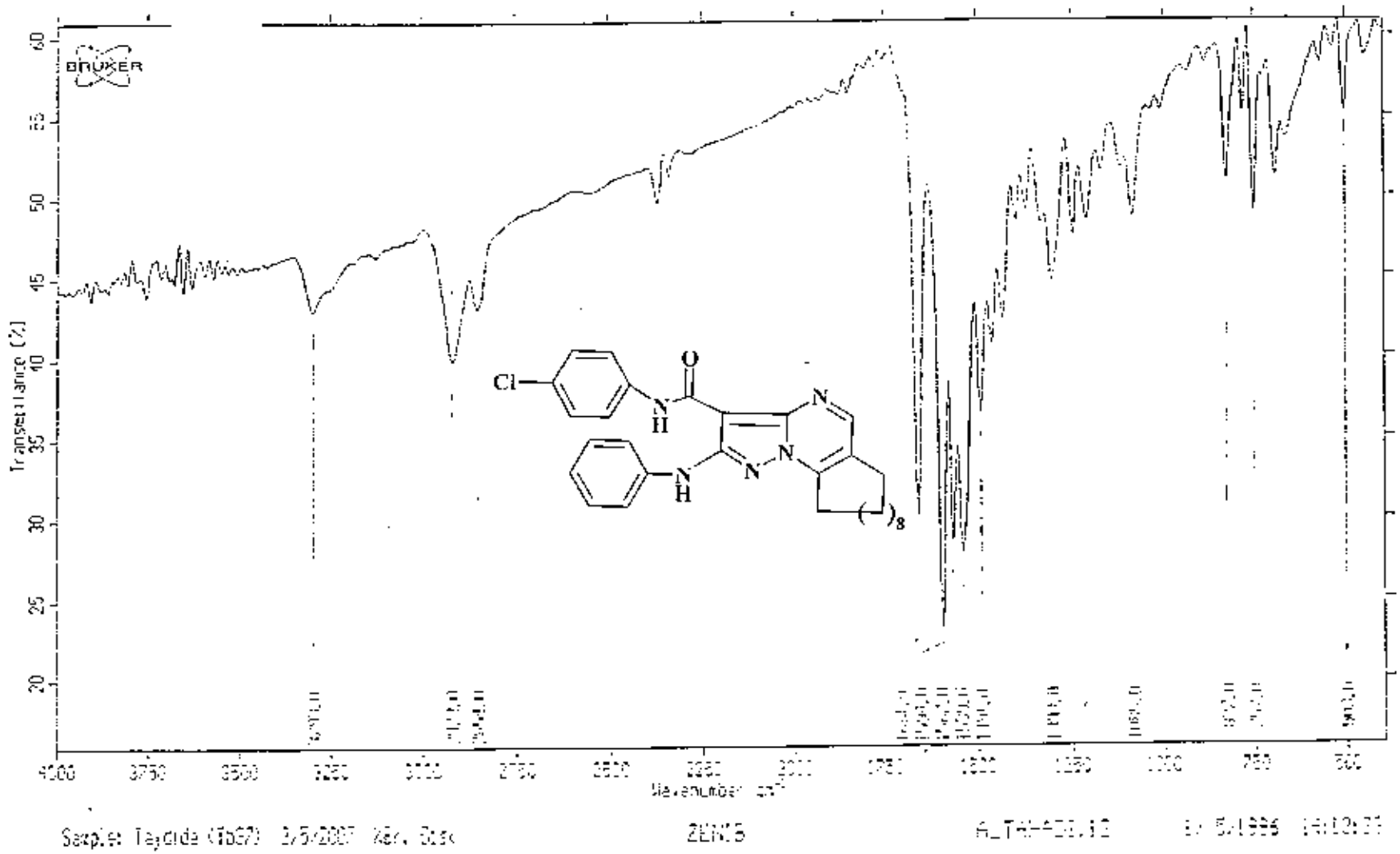
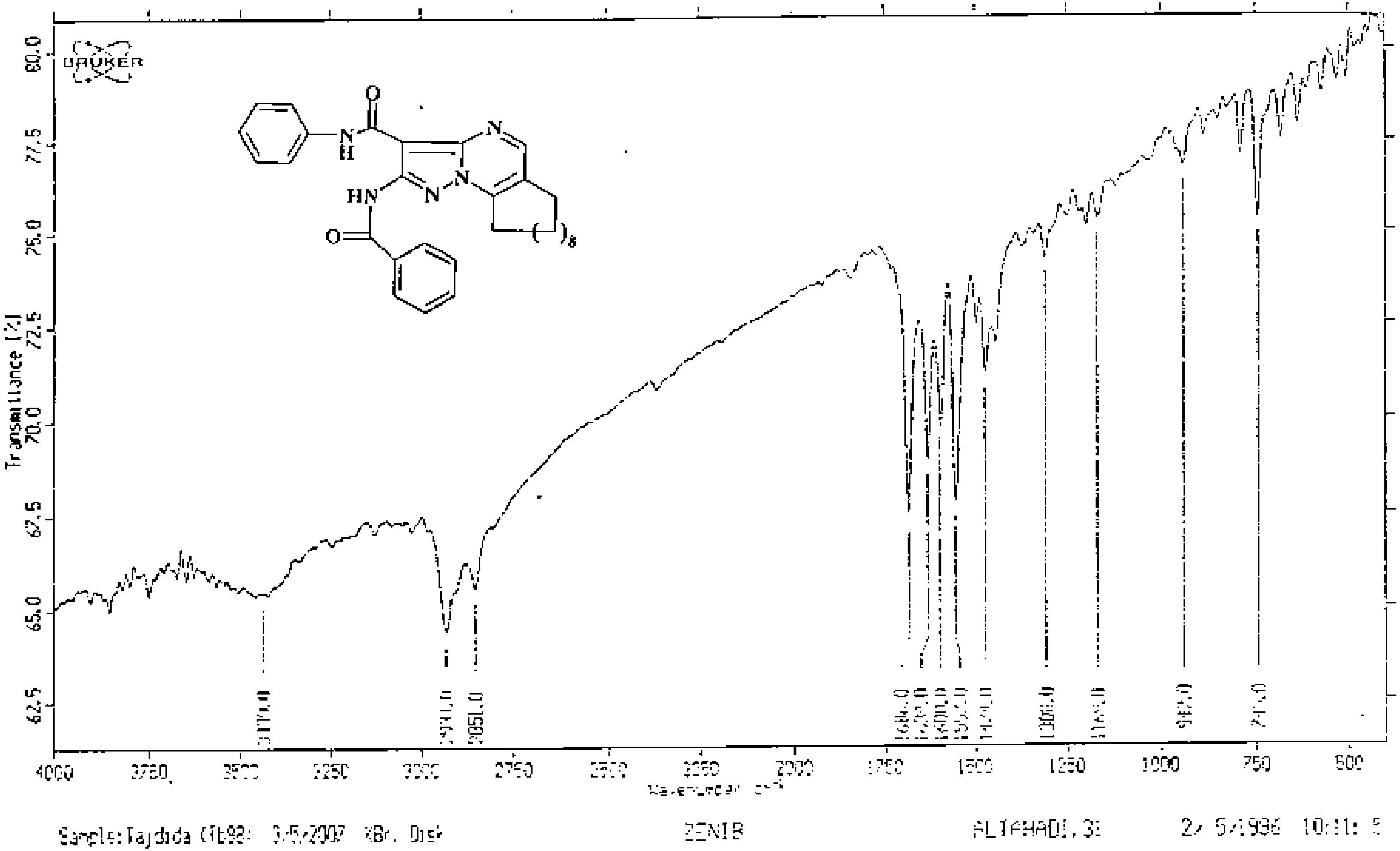


Fig. (45)



Transmittance [%]
80.0
77.5
75.0
72.5
70.0
67.5
65.0
62.5
4000
3500
3250
2750
2000
1750
1500
1250
1000
750
500
ZENIB

Fig. (46)

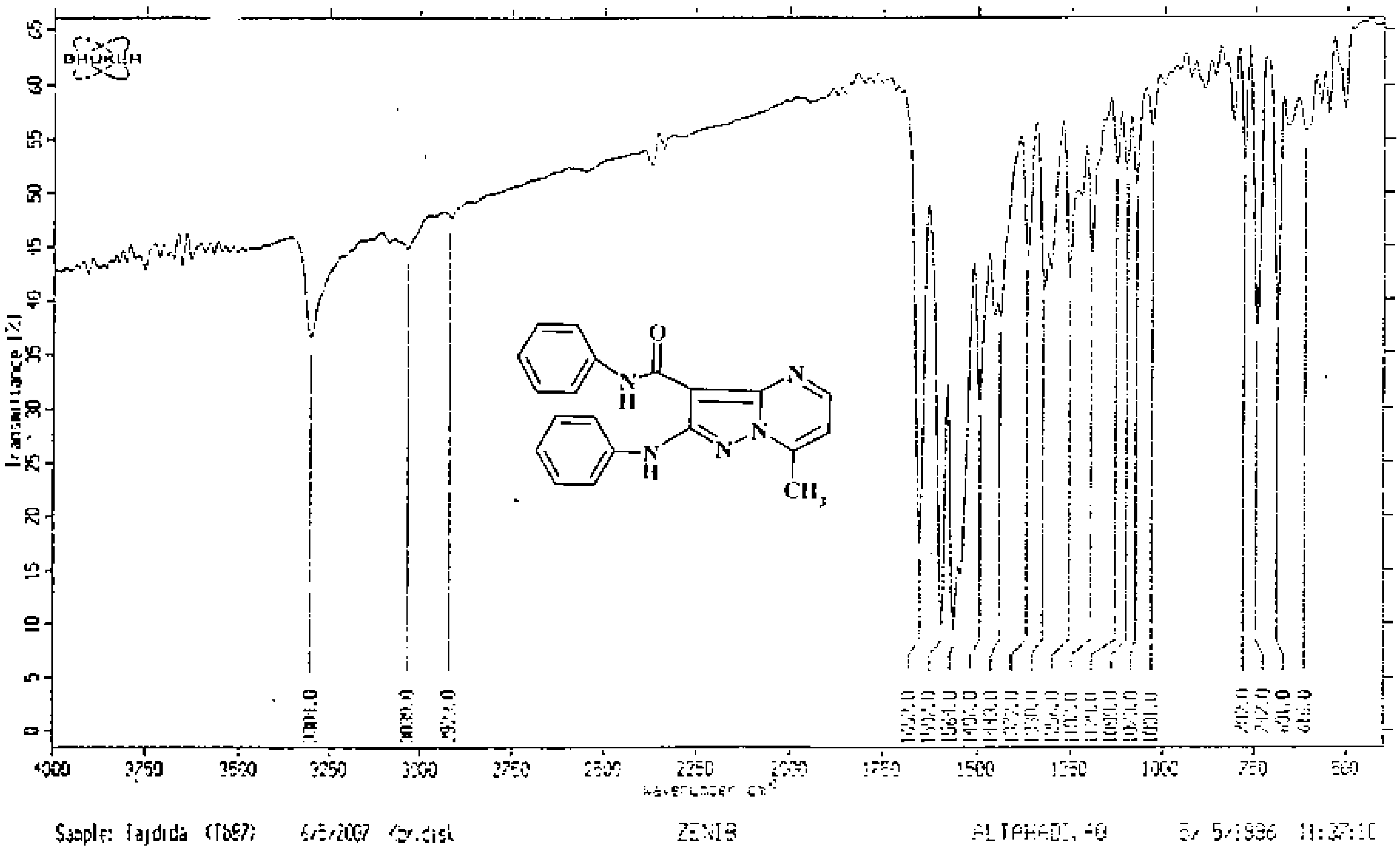

Transmittance [%]
Wavenumber cm-1
Sample: Tajdida (T687) 6/5/2007 Kbr.disk
ZENIB
ALTAHADI, 40 5/ 5/1996 11:37:10

Fig. (47)

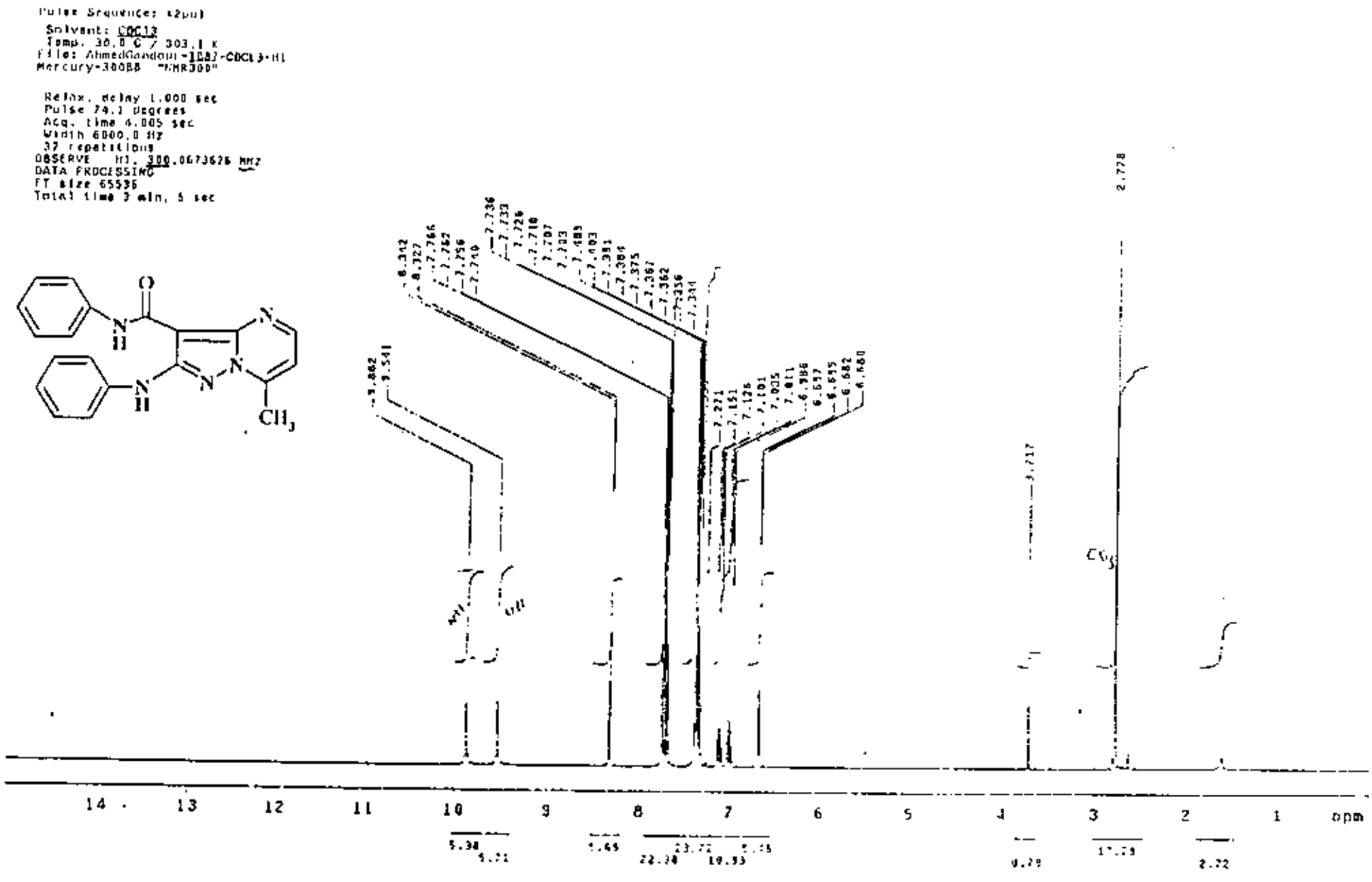

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 30.0 C / 303.1 K
File: AhmedGandopi-1087-CDCl3-H1
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 74.1 degrees
Acq. time 4.005 sec
Width 6000.0 Hz
32 repetitions
OBSERVE H1, 300.0673626 MHz
DATA PROCESSING
FT size 65536
Total time 3 min, 5 sec
O
N
H
N
N
N
N
H
CH3
NH
OH
CH3
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

Fig. (48)

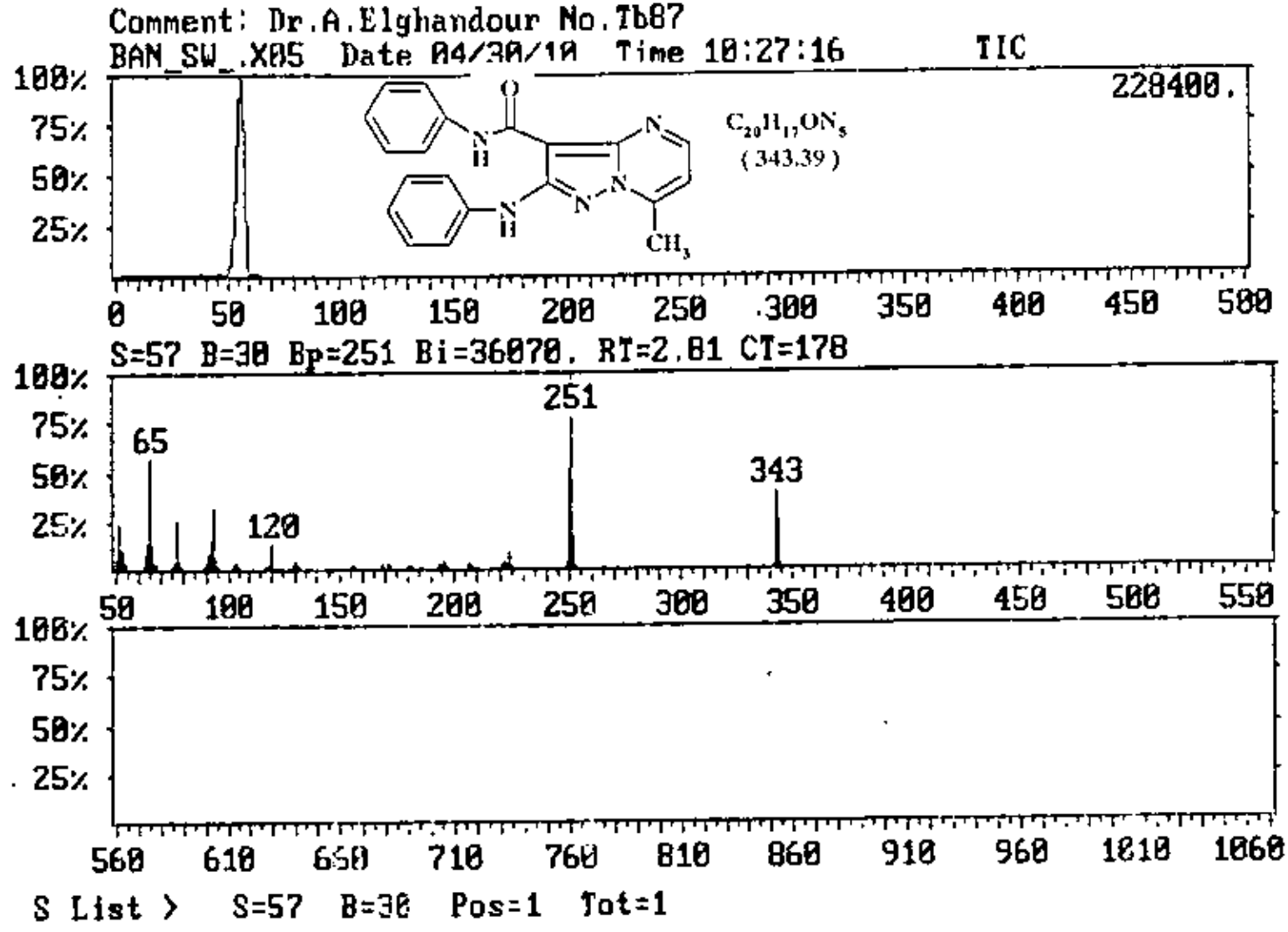

Comment: Dr.A.Elghandour No.Tb87
BAN_SW_.X05 Date 04/30/10 Time 10:27:16 TIC
228400.
100%
75%
50%
25%
$C_{20}H_{17}ON_5$
(343.39)
0 50 100 150 200 250 300 350 400 450 500
S=57 B=30 Bp=251 Bi=36070. RT=2.81 CT=178
65
120
251
343
50 100 150 200 250 300 350 400 450 500 550
560 610 660 710 760 810 860 910 960 1010 1060
S List > S=57 B=30 Pos=1 Tot=1

Fig. (49)

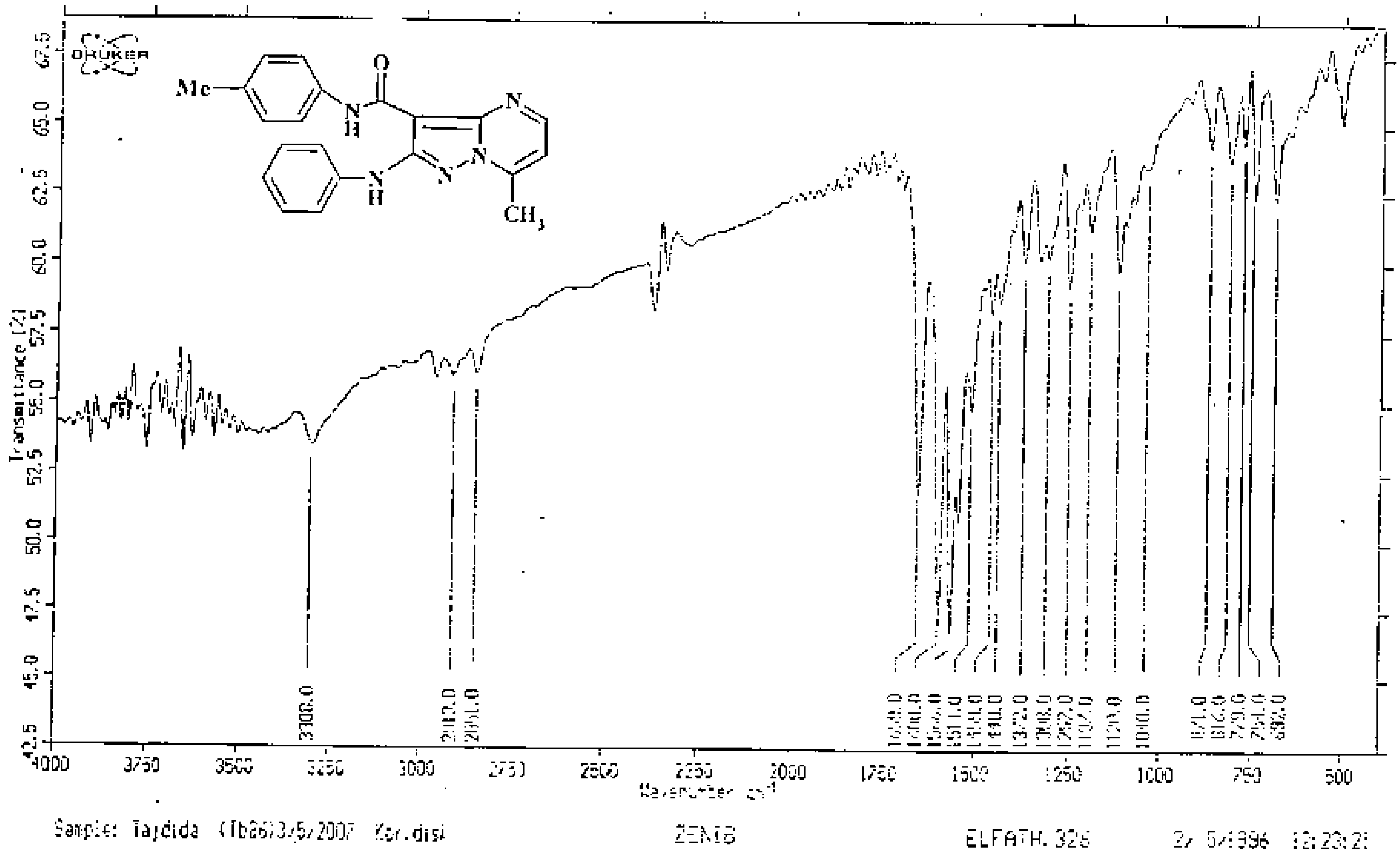
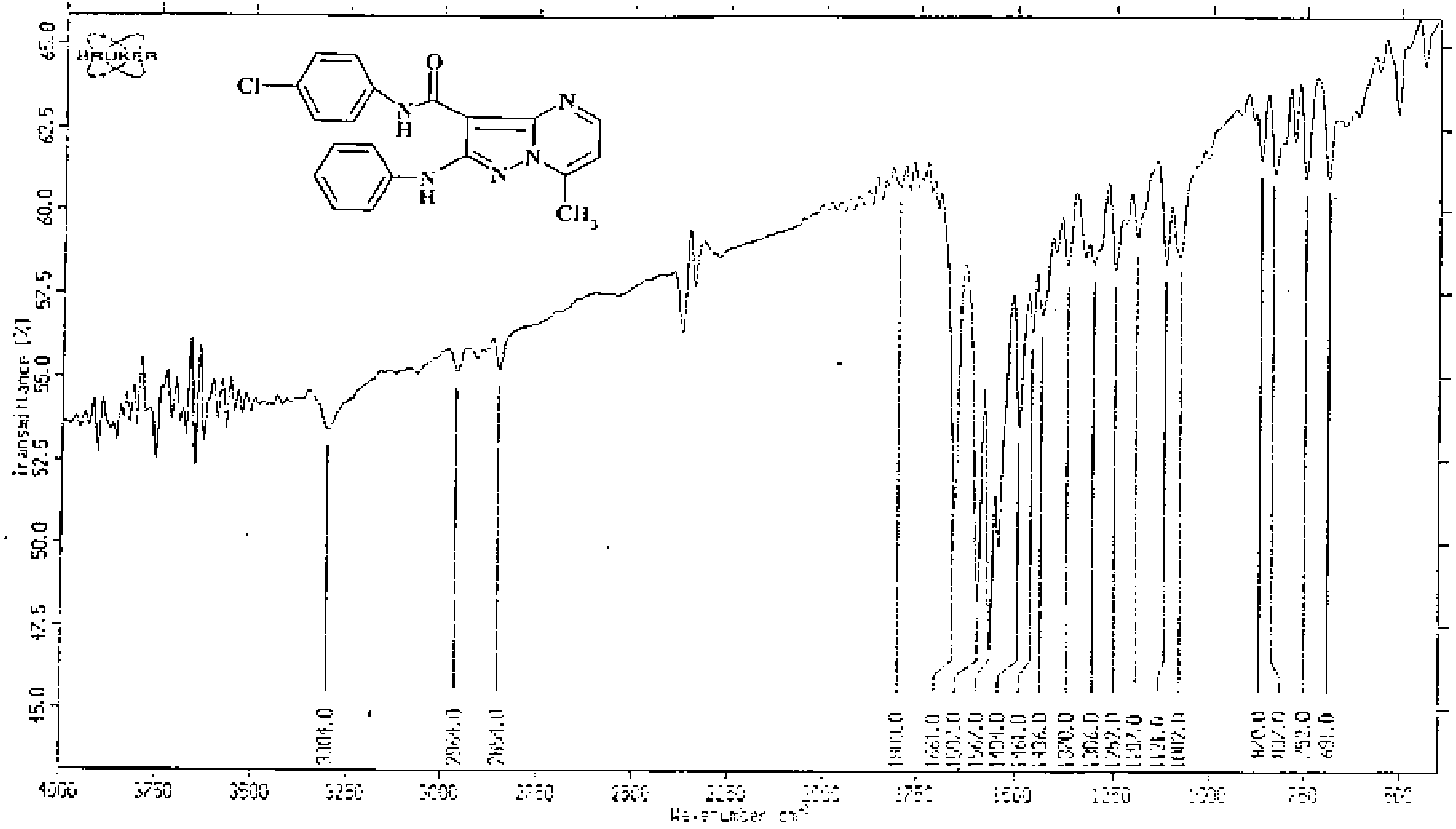
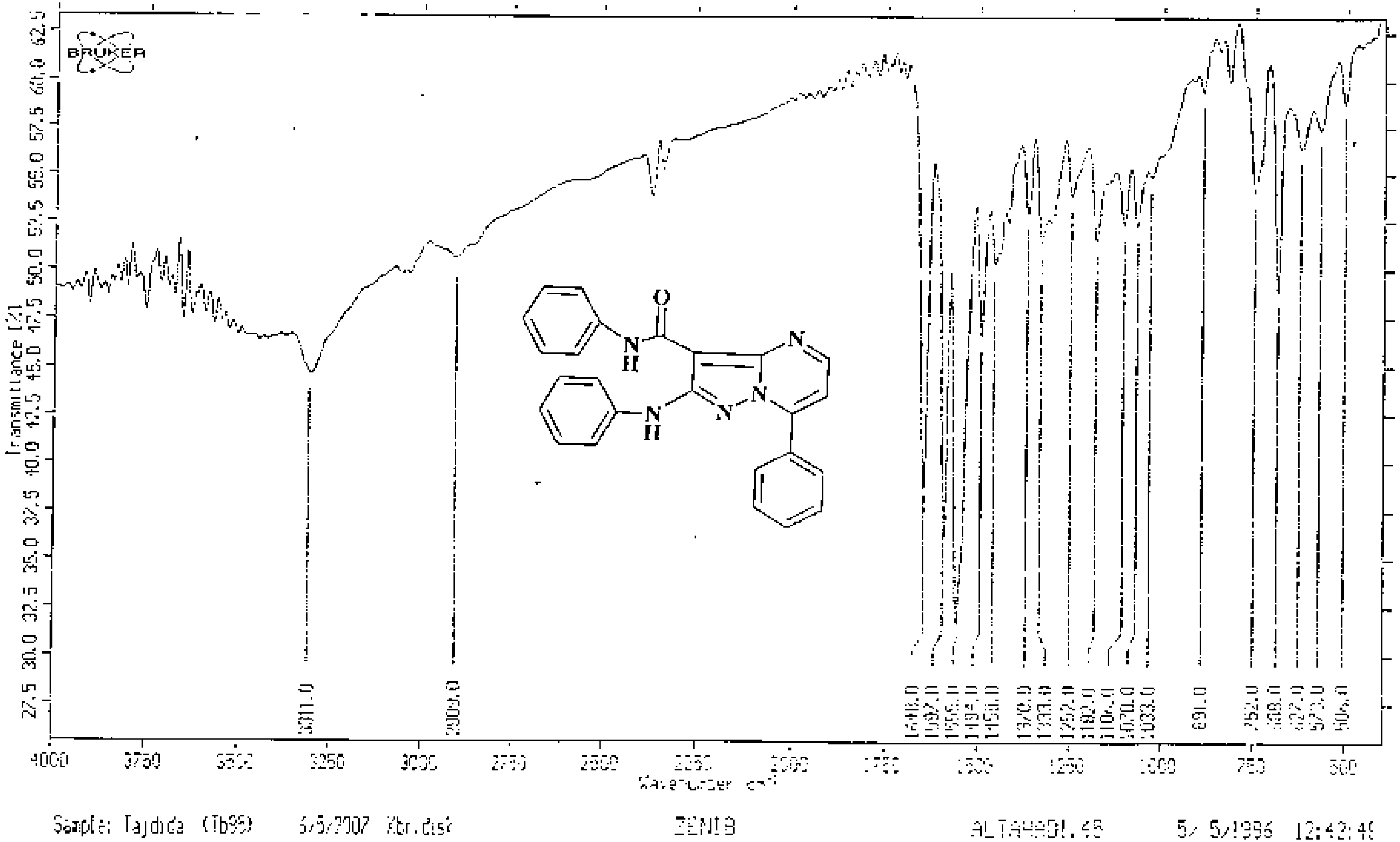

Transmittance [%]
Wavenumber cm-1
3308.0
2912.0
2851.0
1040.0
Sample: Tajdida (Ib26)3/5/2007 Kor.disi
ZEMB
ELFATH.326
2/ 5/1996 12:23:21

Fig. (50)



Sample: Tajdida (Ib58)3/5/2007 for.dis ZENIB ELFATH.330 2/ 5/1996 13:20:34

Fig. (51)



BRUKER
Transmittance [%]
62.5
60.0
57.5
55.0
52.5
50.0
47.5
45.0
42.5
40.0
37.5
35.0
32.5
30.0
27.5
3311.0
2909.0
1648.0
1592.0
1556.0
1494.0
1450.0
1370.0
1333.0
1252.0
1182.0
1104.0
1070.0
1033.0
891.0
752.0
688.0
622.0
573.0
504.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Tajdida (Tb95)
5/5/2007 Kbr.disk
ZENIB
ALTAHADI.45
5/ 5/1996 12:42:49

Fig. (52)

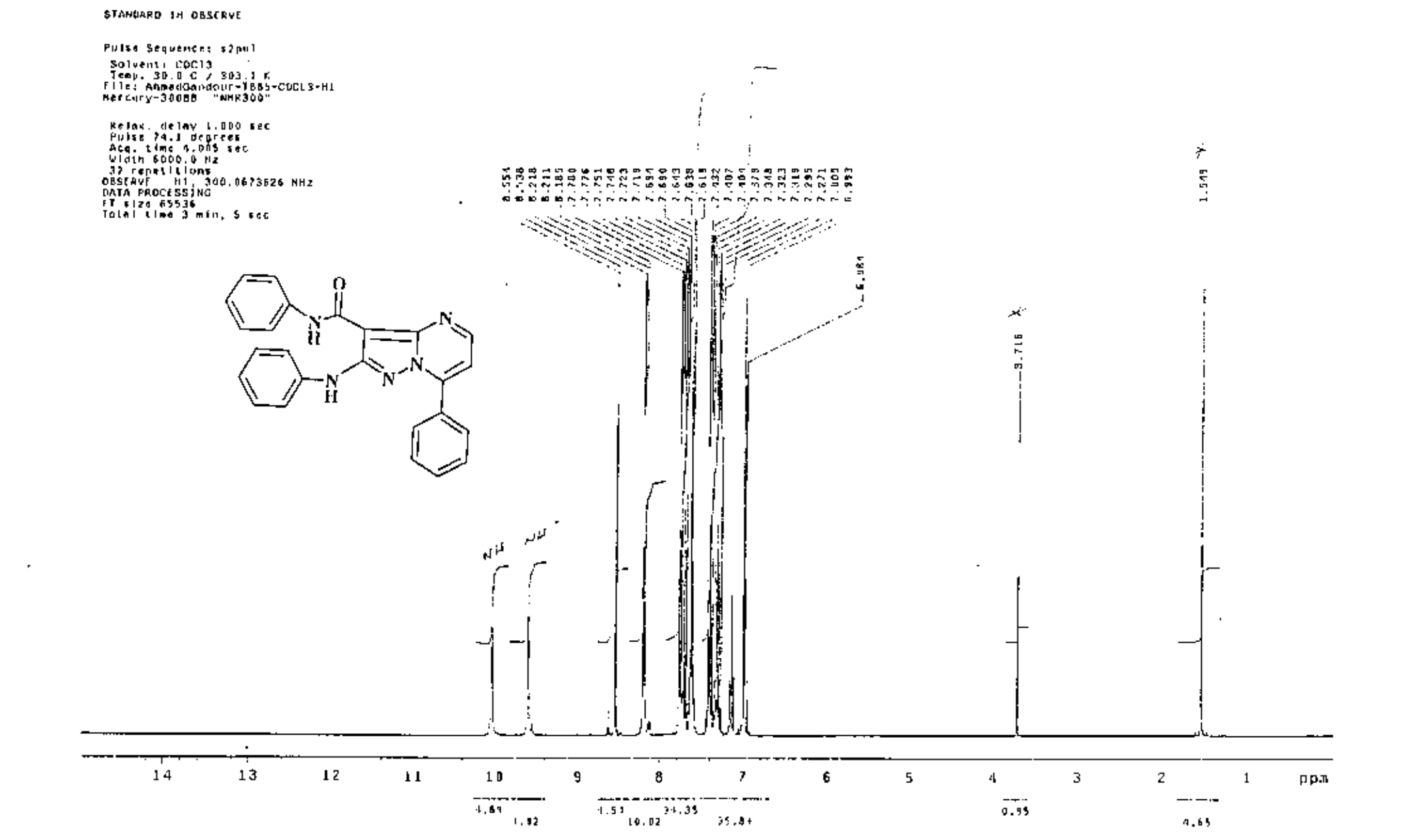

STANDARD 1H OBSERVE
Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 30.0 C / 303.1 K
File: AhmedGandour-1B85-CDCL3-H1
Mercury-300BB "NMR300"
Relax. delay 1.000 sec
Pulse 74.1 degrees
Acq. time 4.005 sec
Width 6000.0 Hz
32 repetitions
OBSERVE H1, 300.0673826 MHz
DATA PROCESSING
FT size 65536
Total time 3 min, 5 sec
8.554
8.538
8.218
8.211
8.185
7.780
7.776
7.751
7.746
7.723
7.719
7.694
7.690
7.643
7.638
7.618
7.432
7.407
7.401
7.379
7.348
7.323
7.319
7.295
7.271
7.105
6.983
6.984
8.716
1.549
NH
NH
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
4.89
1.92
1.53
34.35
10.02
35.84
0.95
4.65

Fig. (53)

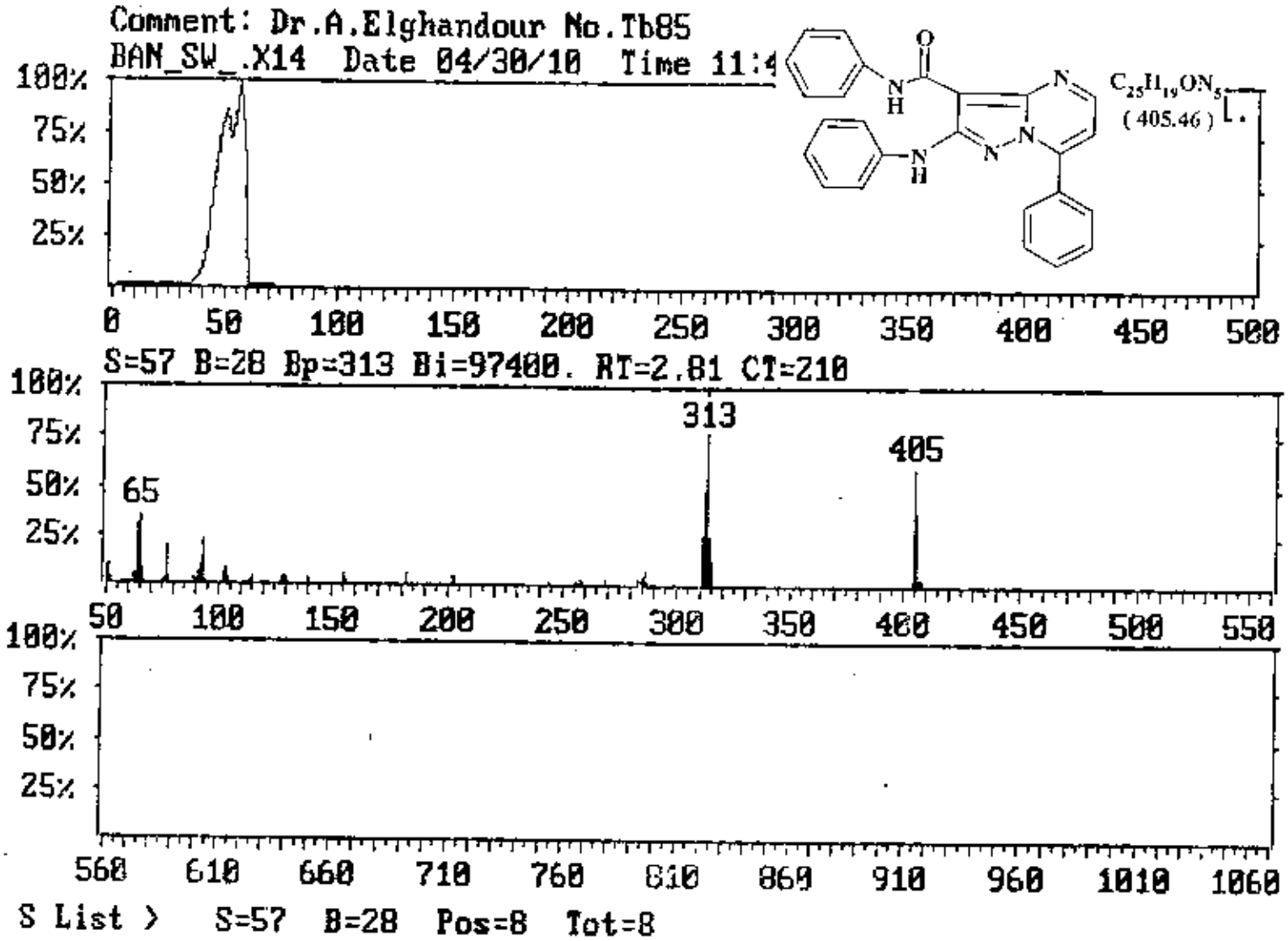

Comment: Dr.A.Elghandour No.Tb85
BAN_SW_.X14 Date 04/30/10 Time 11:4
100%
75%
50%
25%
0 50 100 150 200 250 300 350 400 450 500
$C_{25}H_{19}ON_5$
(405.46)
S=57 B=28 Bp=313 Bi=97400. RT=2.81 CT=210
313
405
65
50 100 150 200 250 300 350 400 450 500 550
560 610 660 710 760 810 860 910 960 1010 1060
S List > S=57 B=28 Pos=8 Tot=8

Fig. (54)

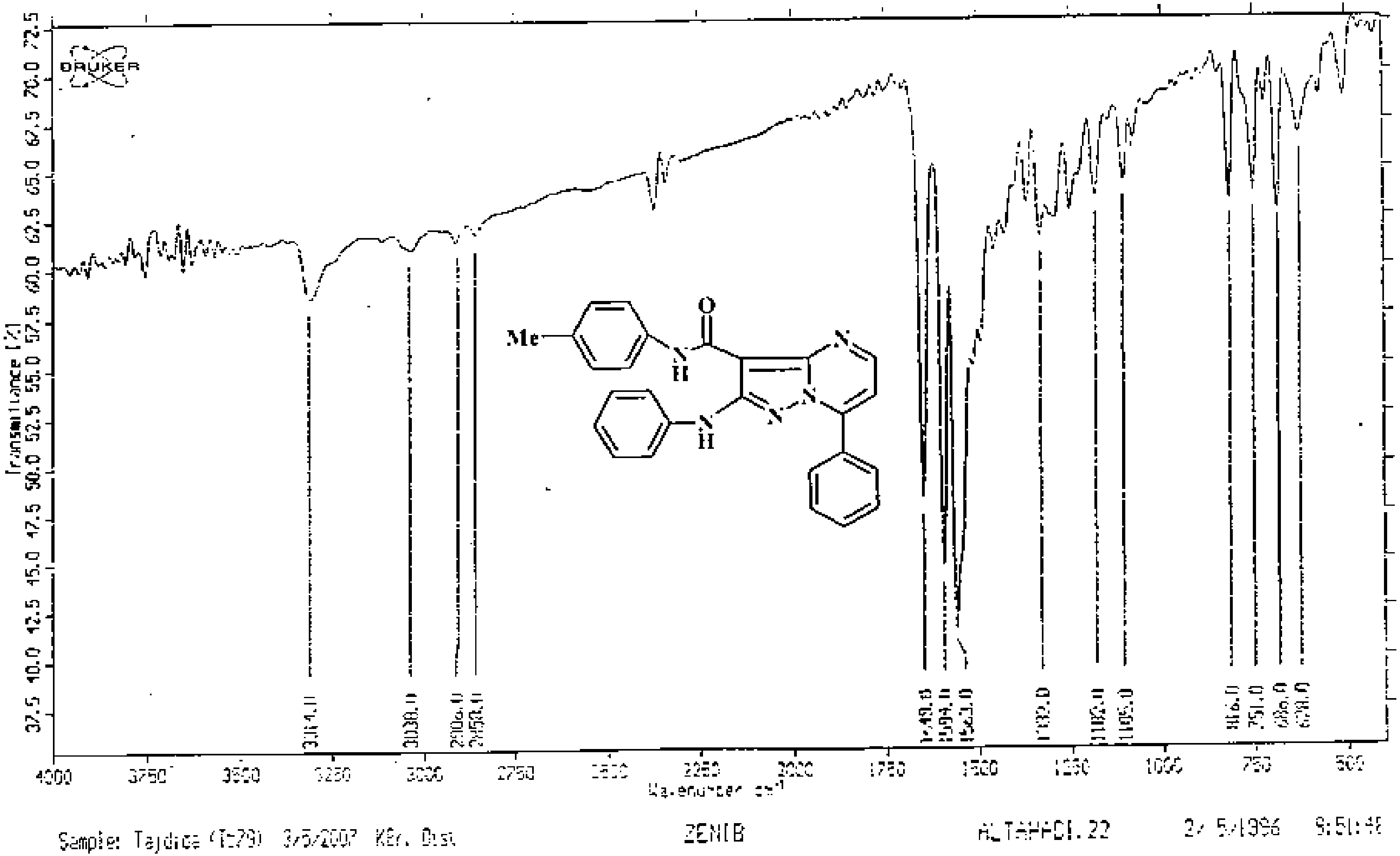


Fig. (55)

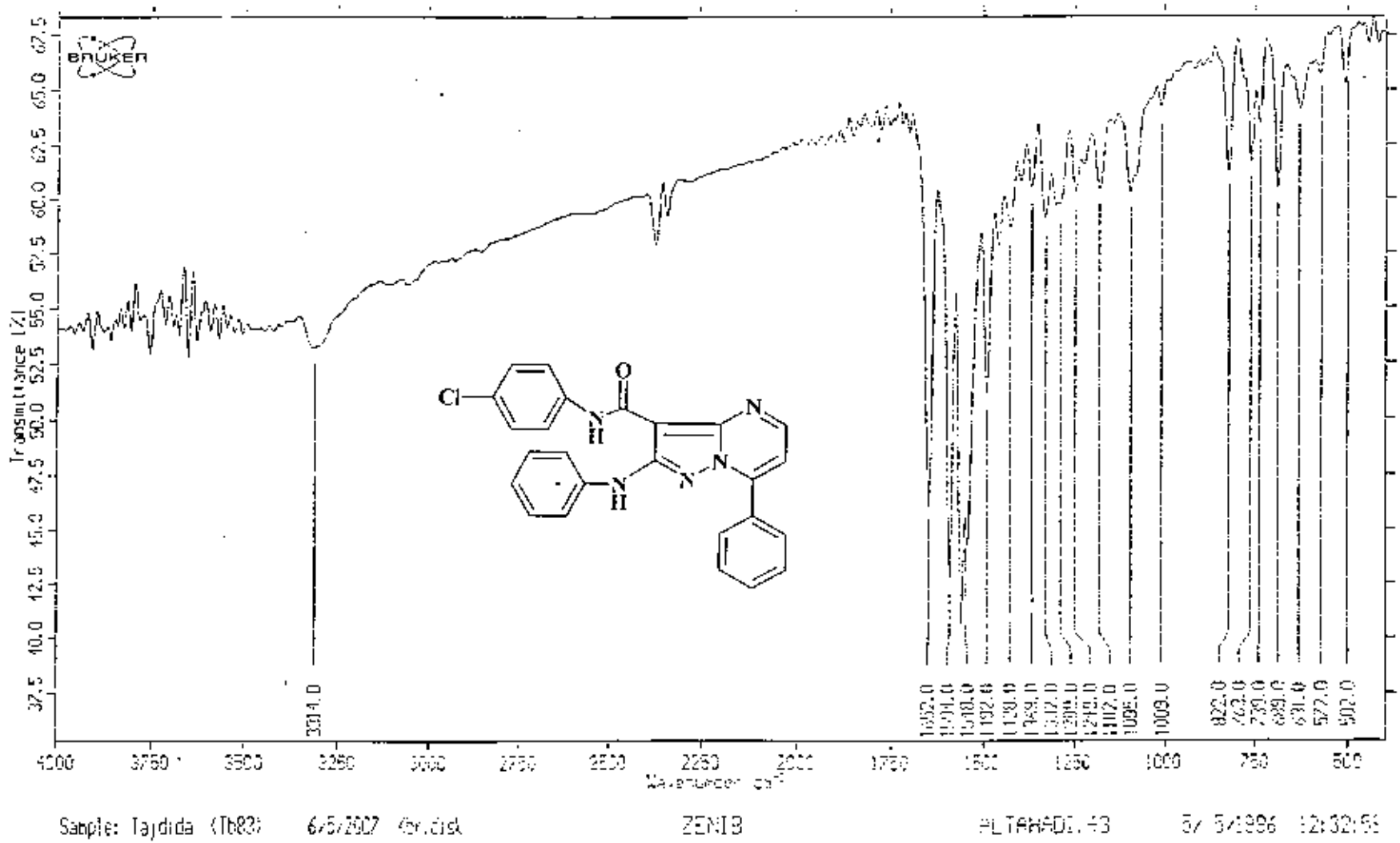

BRUKER
Transmittance [%]
3314.0
1652.0
1009.0
822.0
763.0
739.0
689.0
631.0
572.0
502.0
Cl
O
N
H
N
H
N
N
Sample: Tajdida (Tb83) 6/5/2007 Gr.disk
ZENIB
PLTANADI.43
5/ 5/1996 12:32:55

Fig. (56)

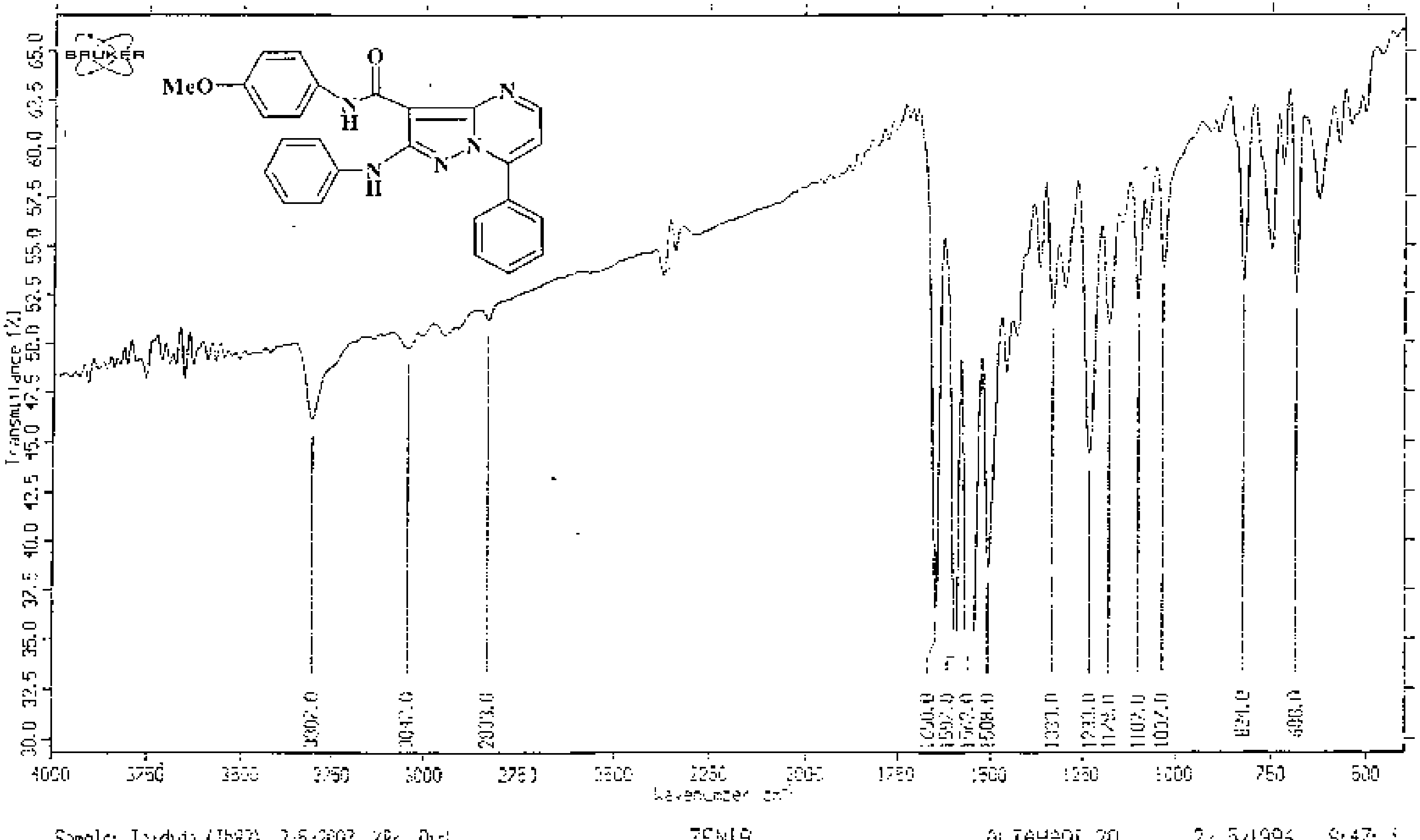
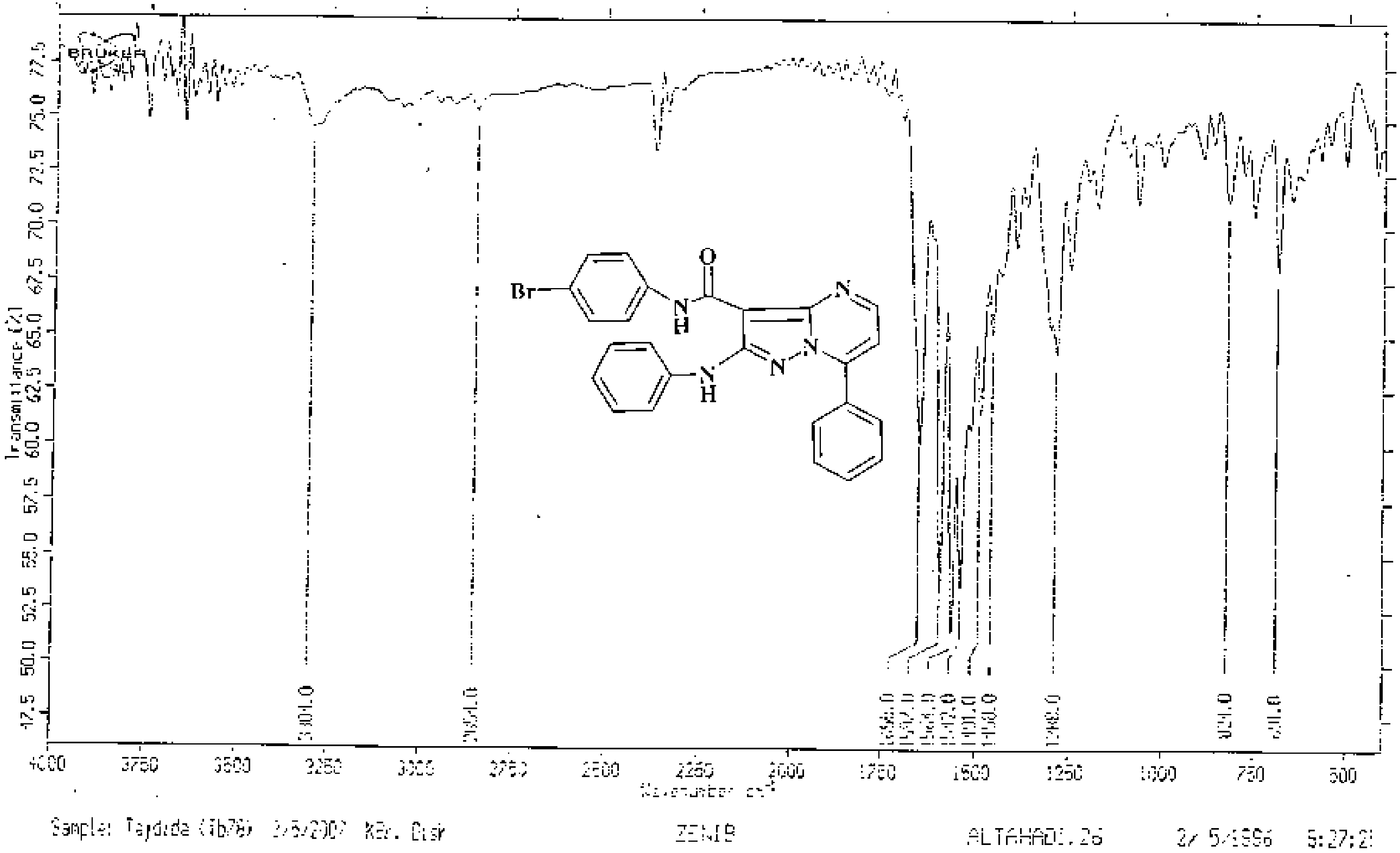

Transmittance [%]
Wavenumber cm-1
3302.0
3047.0
2003.0
1650.0
1597.0
1562.0
1508.0
1331.0
1231.0
1178.0
1107.0
1002.0
824.0
698.0
MeO
O
N
H
N
H
N
N
N
Sample: Tajdida (1682) 3/5/2007 KBr. Disk
ZENIB
ALTAHADI.20
2/ 5/1996 8:47:

Fig. (57)



Transmittance [%]
Wavenumber cm-1
3301.0
1248.0
824.0
701.0
Br
O
N
H
N
N
N
N
H
ZENIB
ALTAHADI.26

Fig. (58)

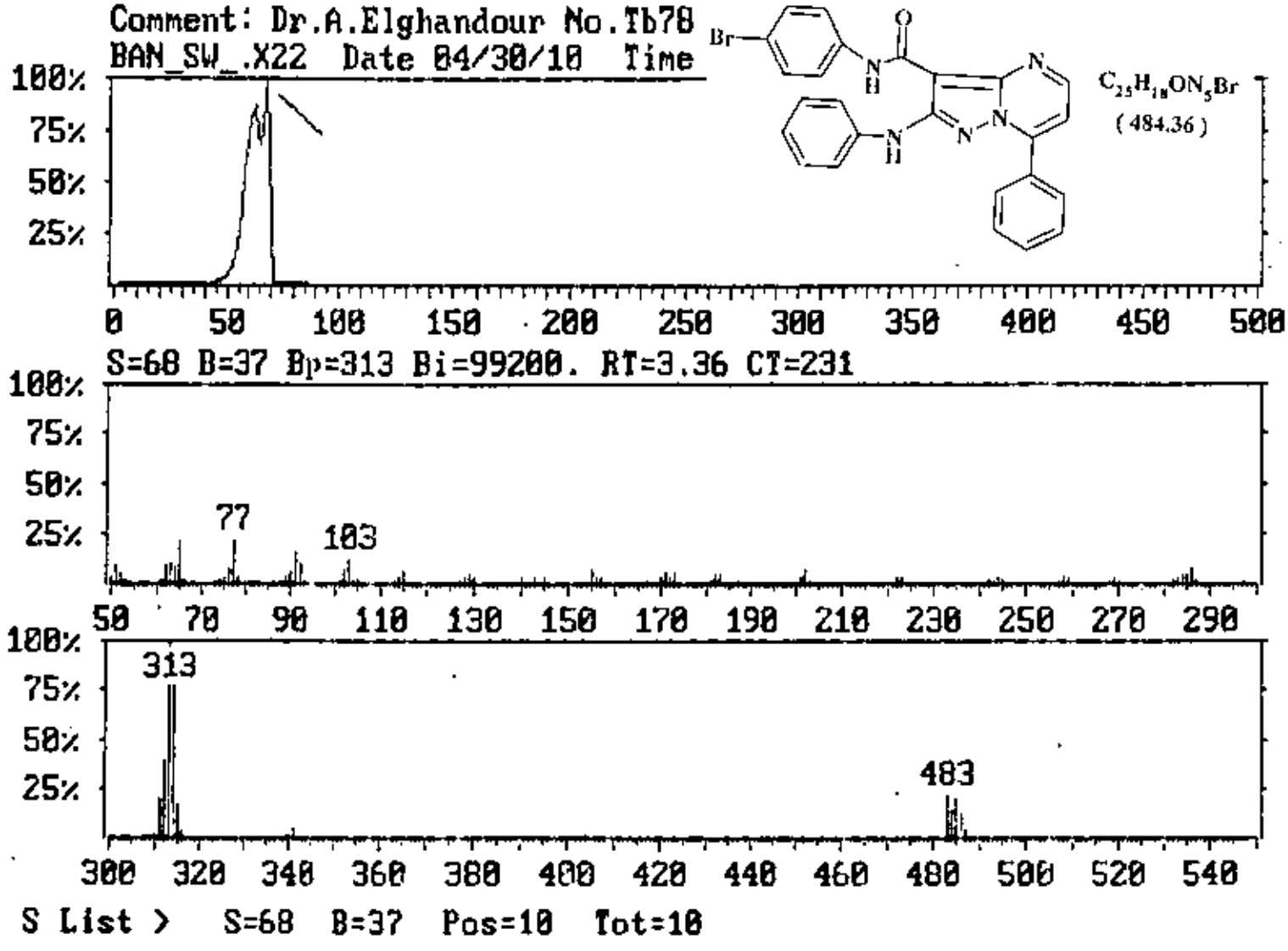
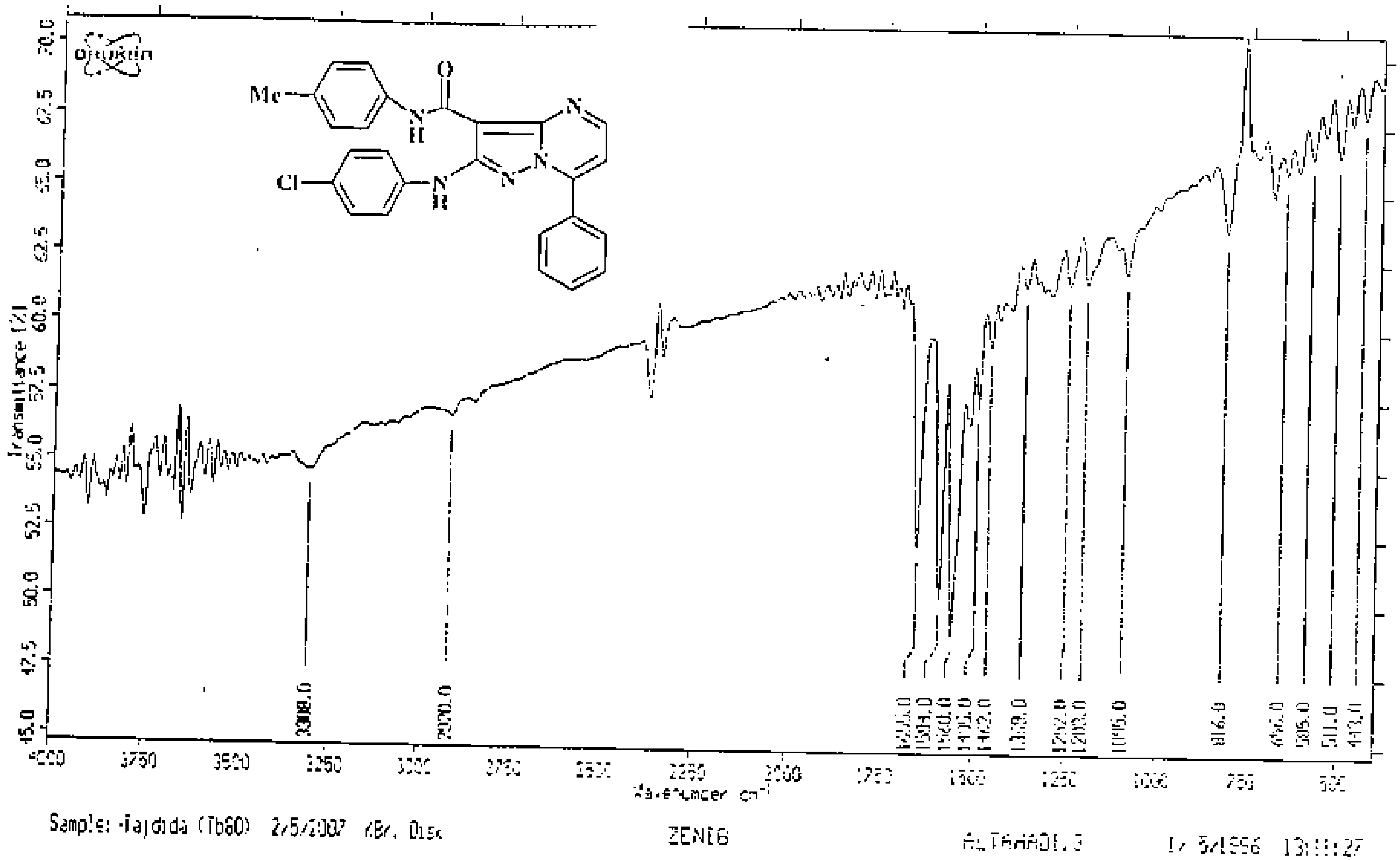

Comment: Dr.A.Elghandour No.Tb78
BAN_SW_.X22 Date 04/30/10 Time
100%
75%
50%
25%
0 50 100 150 200 250 300 350 400 450 500
S=68 B=37 Bp=313 Bi=99200. RT=3.36 CT=231
77
103
50 70 90 110 130 150 170 190 210 230 250 270 290
313
483
300 320 340 360 380 400 420 440 460 480 500 520 540
S List > S=68 B=37 Pos=10 Tot=10
Br
O
N
H
N
N
N
N
H
C25H18ON5Br
(484.36)

Fig. (59)



Transmittance [%]
Wavenumber cm-1
3308.0
2920.0
1620.0
1584.0
1540.0
1490.0
1442.0
1339.0
1242.0
1203.0
1095.0
816.0
696.0
585.0
511.0
443.0
Sample: Tajdida (Tb60) 2/5/2007 KBr Disk
ZENEB
ALTAHADE.3

Fig. (60)

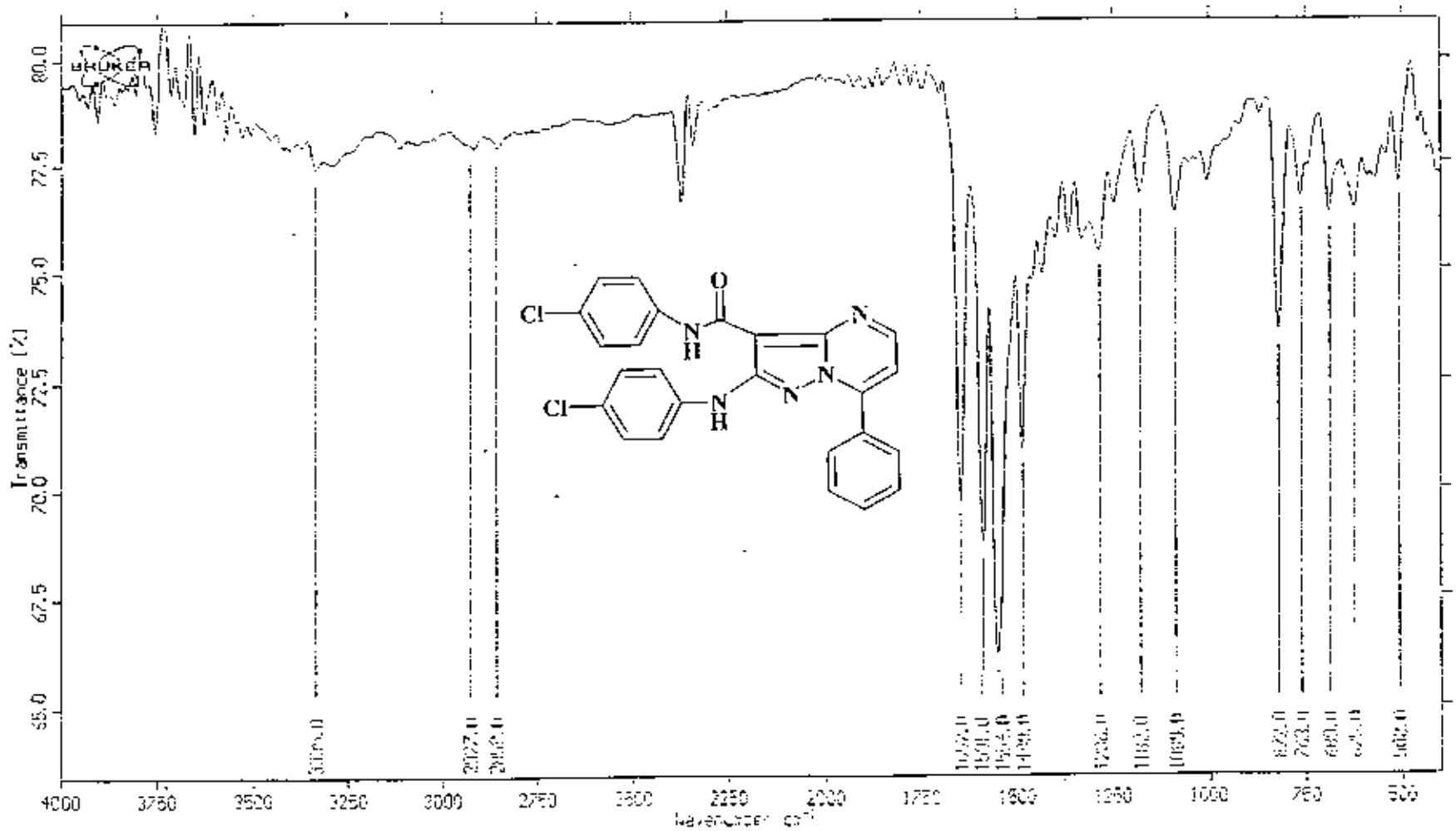

Transmittance [%]
80.0
77.5
75.0
72.5
70.0
67.5
65.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Cl
O
N
H
N
N
N
Cl
N
H
Sample: Tayside (1b8l) 3/5/2007 Gr. Desk
ZENIB
ALTAHFDS.24
2/ 5/1955 9:58:31

Fig. (61)

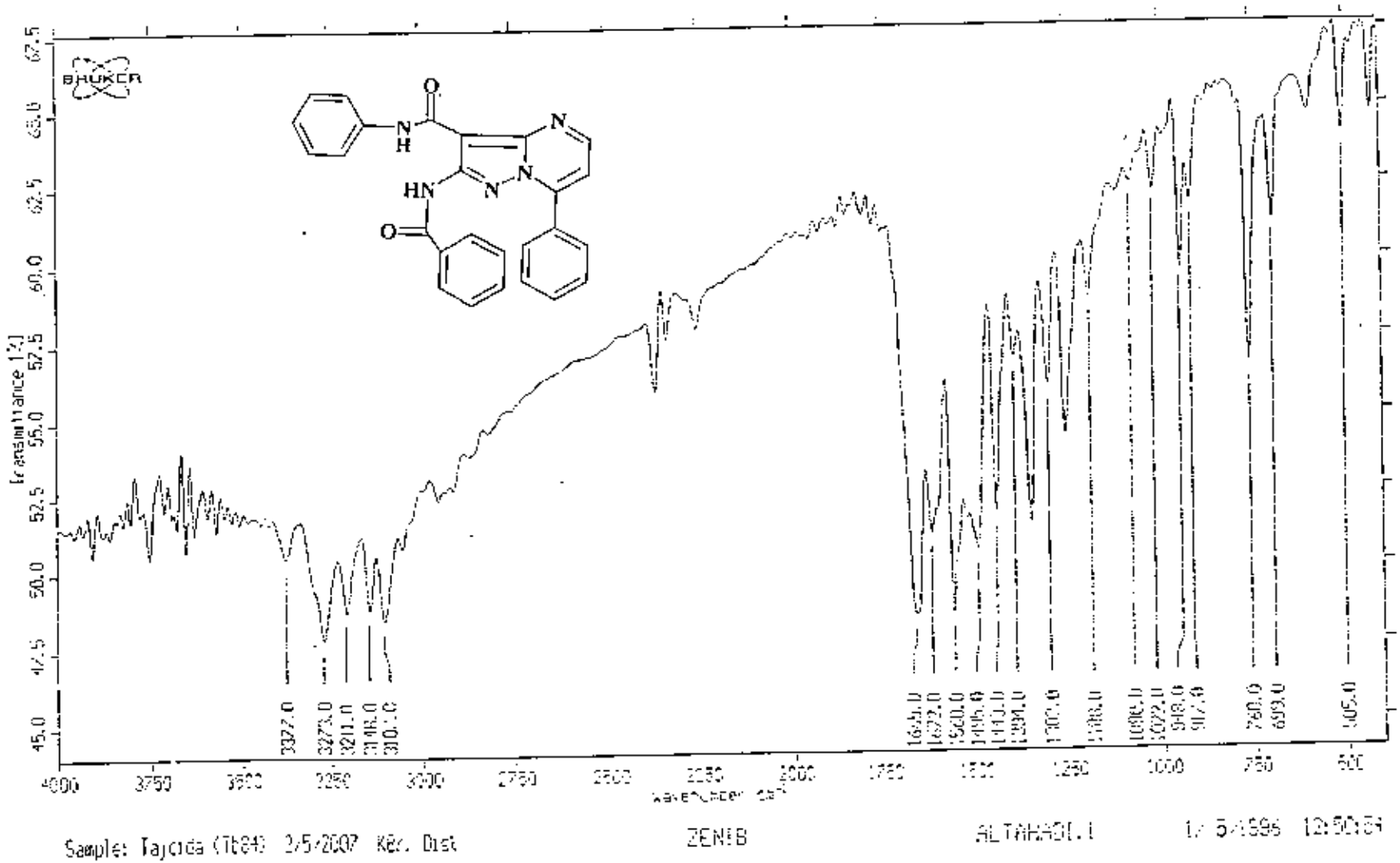
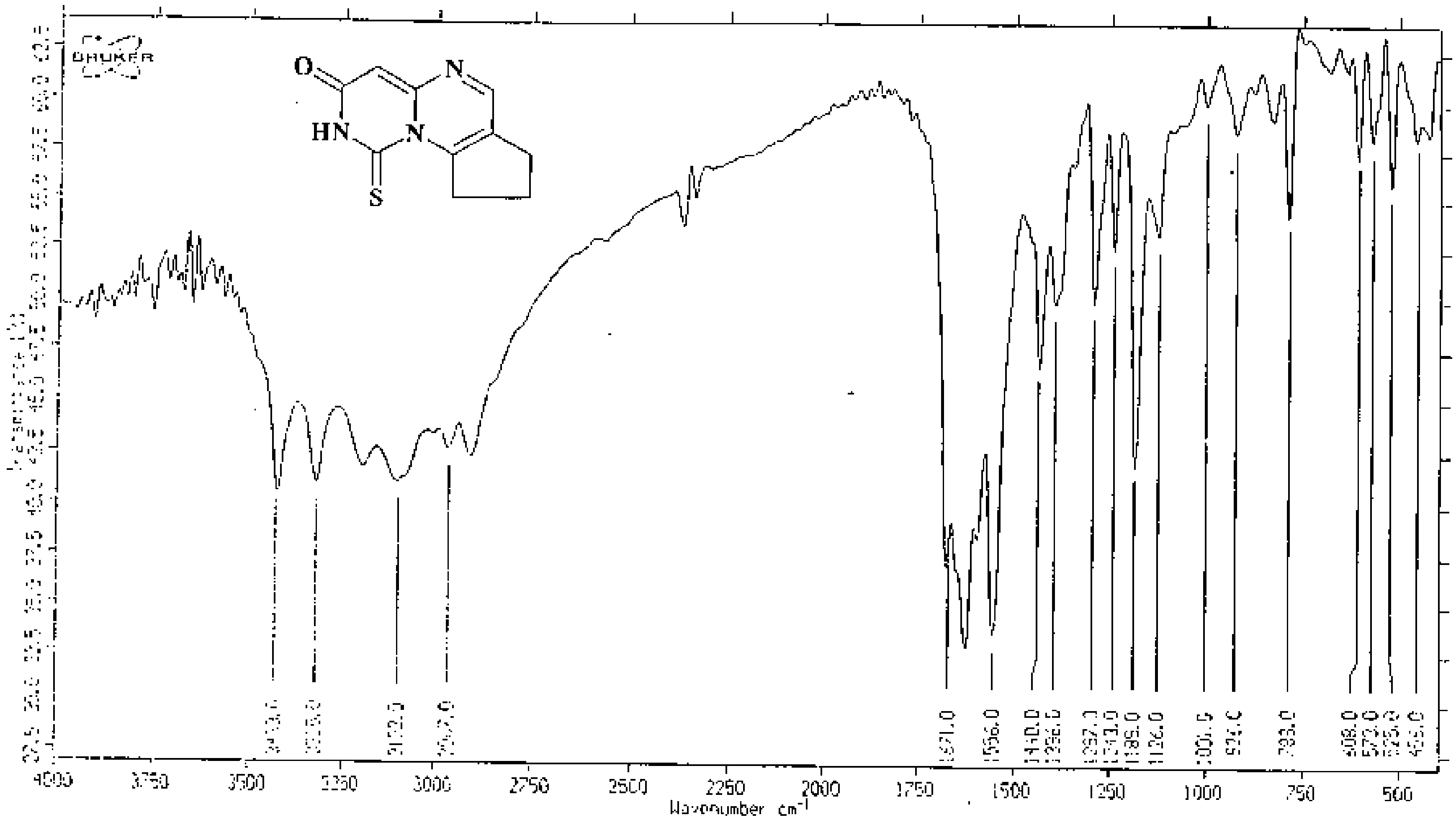

BRUKER
O
N
H
HN
N
N
N
O
Transmittance [%]
67.5
65.0
62.5
60.0
57.5
55.0
52.5
50.0
47.5
45.0
3327.0
3273.0
3211.0
3148.0
3101.0
1635.0
1572.0
1520.0
1496.0
1440.0
1394.0
1307.0
1288.0
1080.0
1022.0
948.0
917.0
760.0
699.0
505.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber [cm-1]
Sample: Tajrida (Tb84) 2/5/2007 Kbr. Dist
ZENIB
ALTAHASI.1
1/ 5/1996 12:50:04

Fig. (62)



Wavenumber cm-1
1671.0
1556.0
1440.0
1396.0
1297.0
1243.0
1185.0
1126.0
1001.0
924.0
783.0
608.0
572.0
525.0
465.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Sample: Hajdida (IM7) 2/5/2007 KBr. Disk
ZENIB
ALTAHADI.0
1/ 5/1996 12:39:57

Fig. (63)

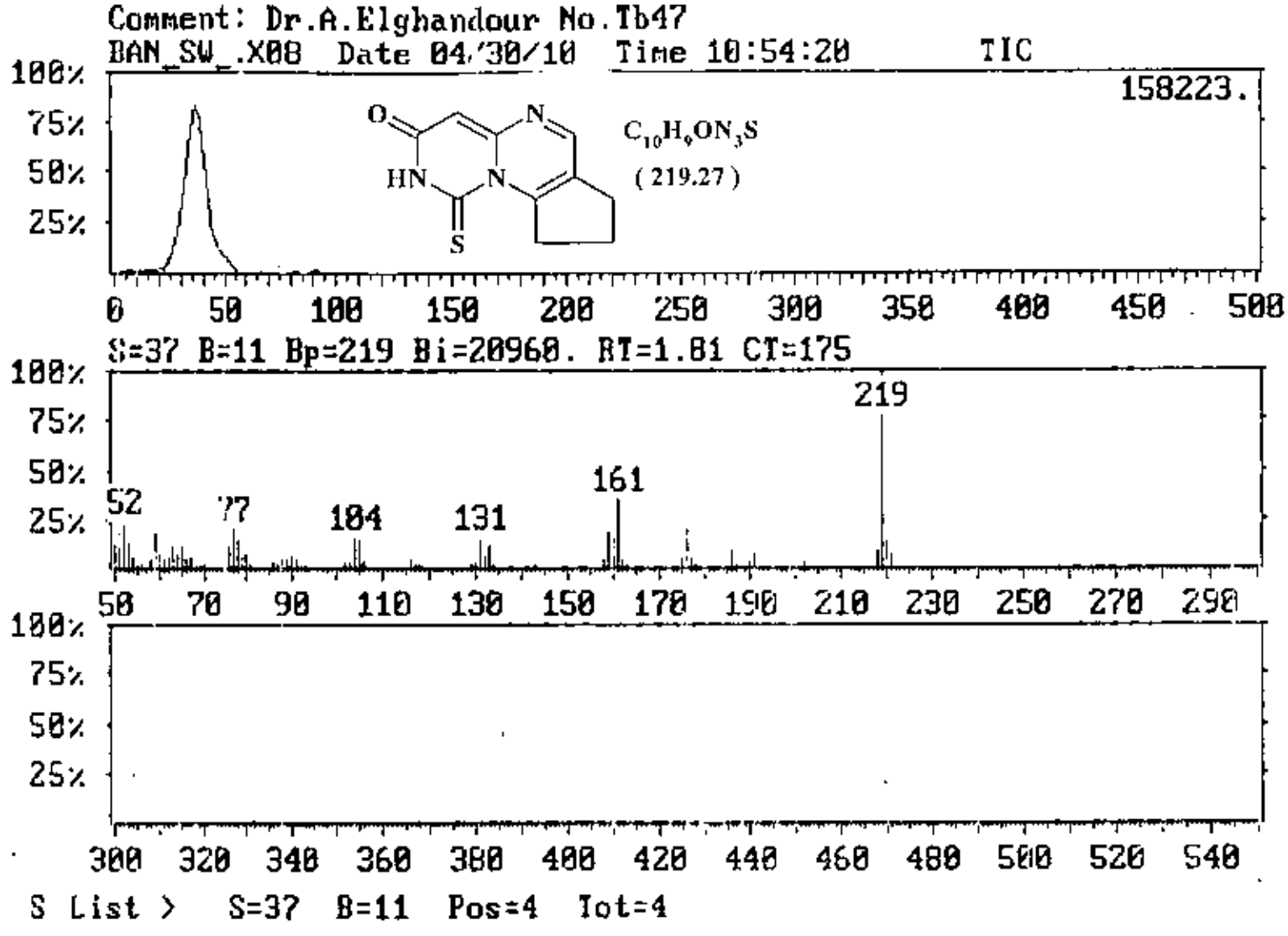

Comment: Dr.A.Elghandour No.Tb47
BAN_SW_.X08 Date 04/30/10 Time 10:54:20 TIC
158223.
100%
75%
50%
25%
O
N
HN
N
S
$C_{10}H_9ON_3S$
(219.27)
0 50 100 150 200 250 300 350 400 450 500
S=37 B=11 Bp=219 Bi=20960. RT=1.81 CT=175
219
161
52
77
104
131
50 70 90 110 130 150 170 190 210 230 250 270 290
300 320 340 360 380 400 420 440 460 480 500 520 540
S List > S=37 B=11 Pos=4 Tot=4

Fig. (64)

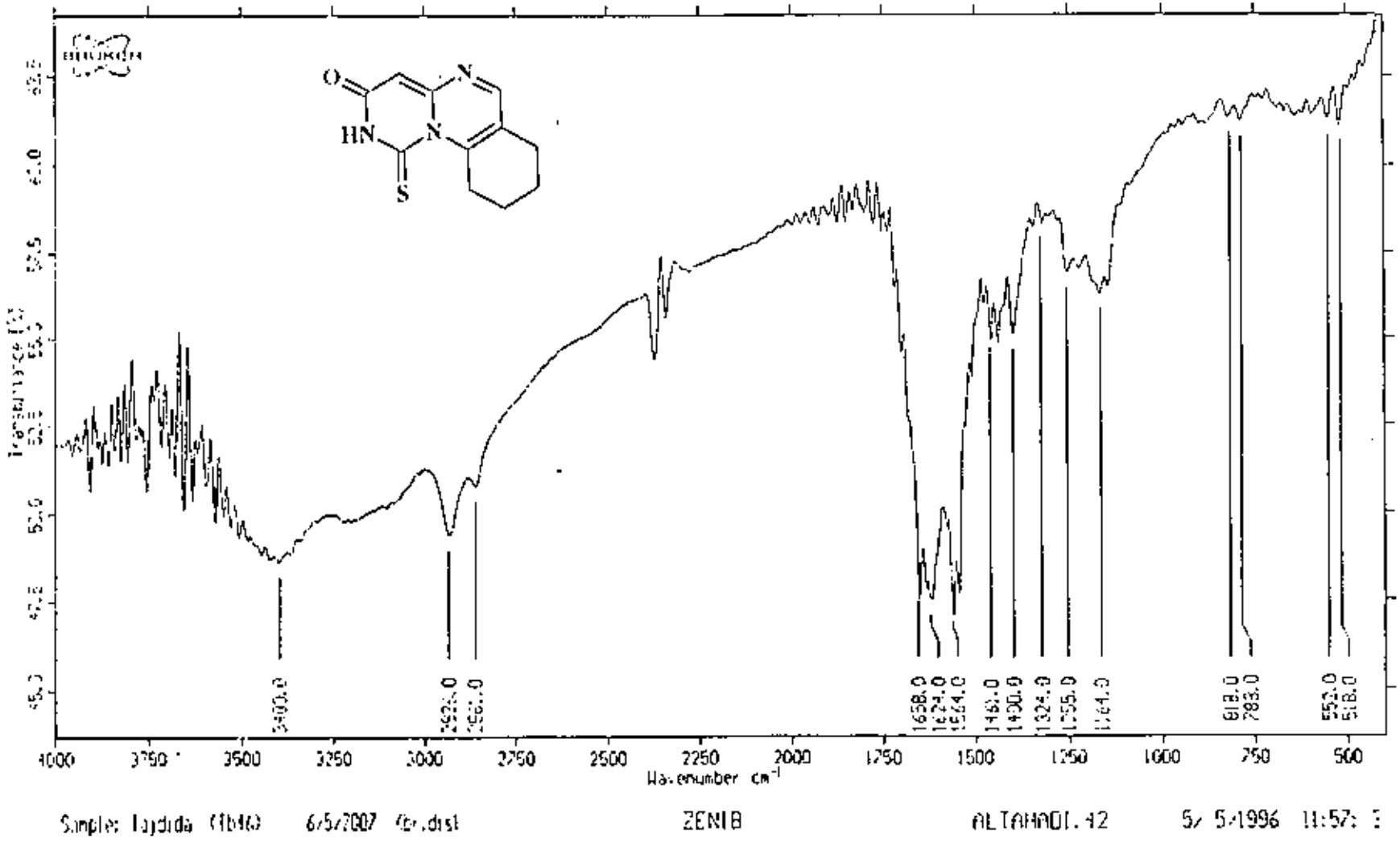

O
N
HN
N
S
1658.0
1624.0
1564.0
1460.0
1430.0
1324.0
1255.0
1164.0
818.0
783.0
552.0
518.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
ZENIB
ALTAHADI.42

Fig. (65)

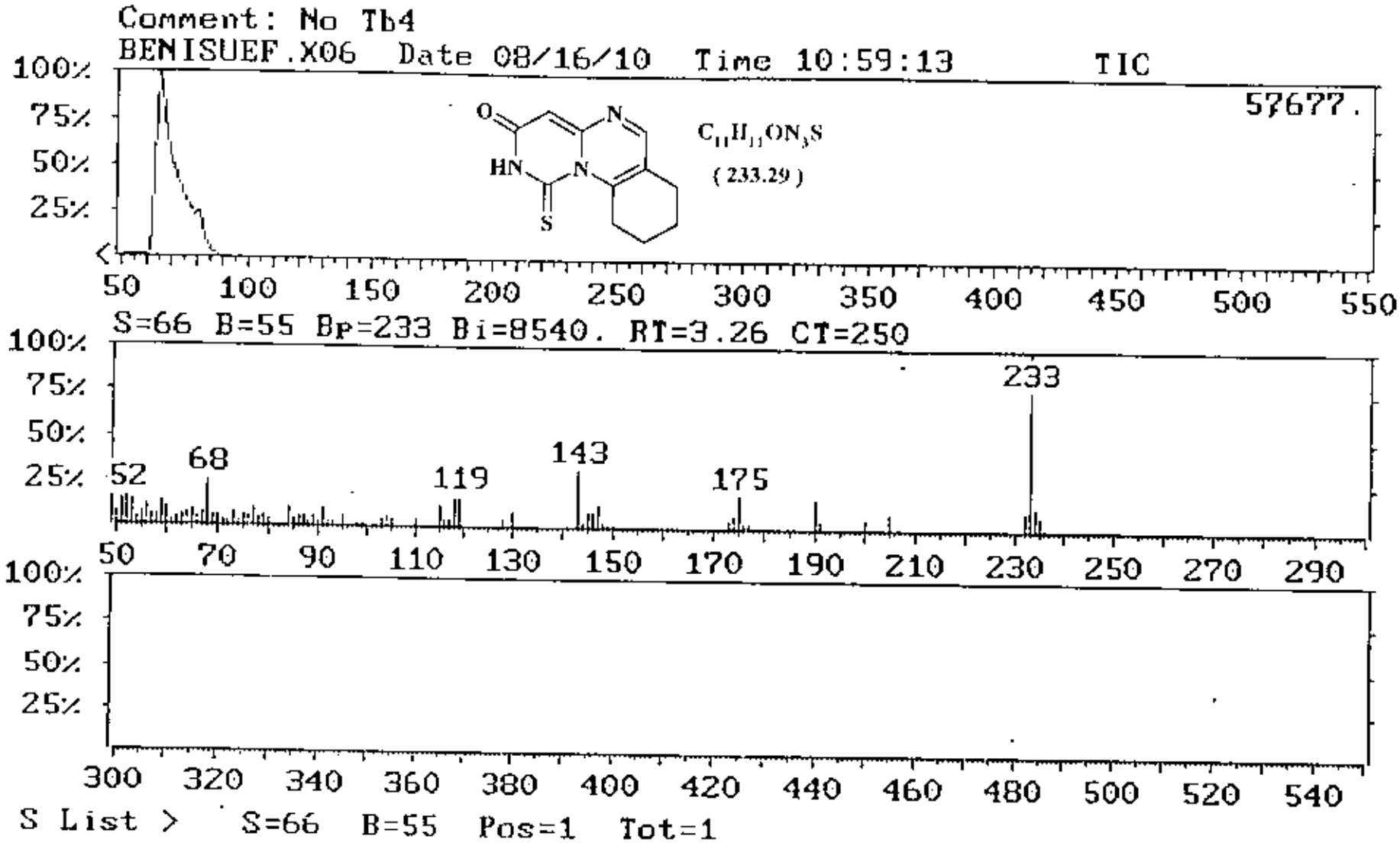

Comment: No Tb4
BENISUEF.X06 Date 08/16/10 Time 10:59:13 TIC
57677.
100%
75%
50%
25%
O
N
HN
N
S
$C_{11}H_{11}ON_3S$
(233.29)
50 100 150 200 250 300 350 400 450 500 550
S=66 B=55 Bp=233 Bi=8540. RT=3.26 CT=250
233
68
143
119
175
52
50 70 90 110 130 150 170 190 210 230 250 270 290
300 320 340 360 380 400 420 440 460 480 500 520 540
S List > S=66 B=55 Pos=1 Tot=1

Fig. (66)

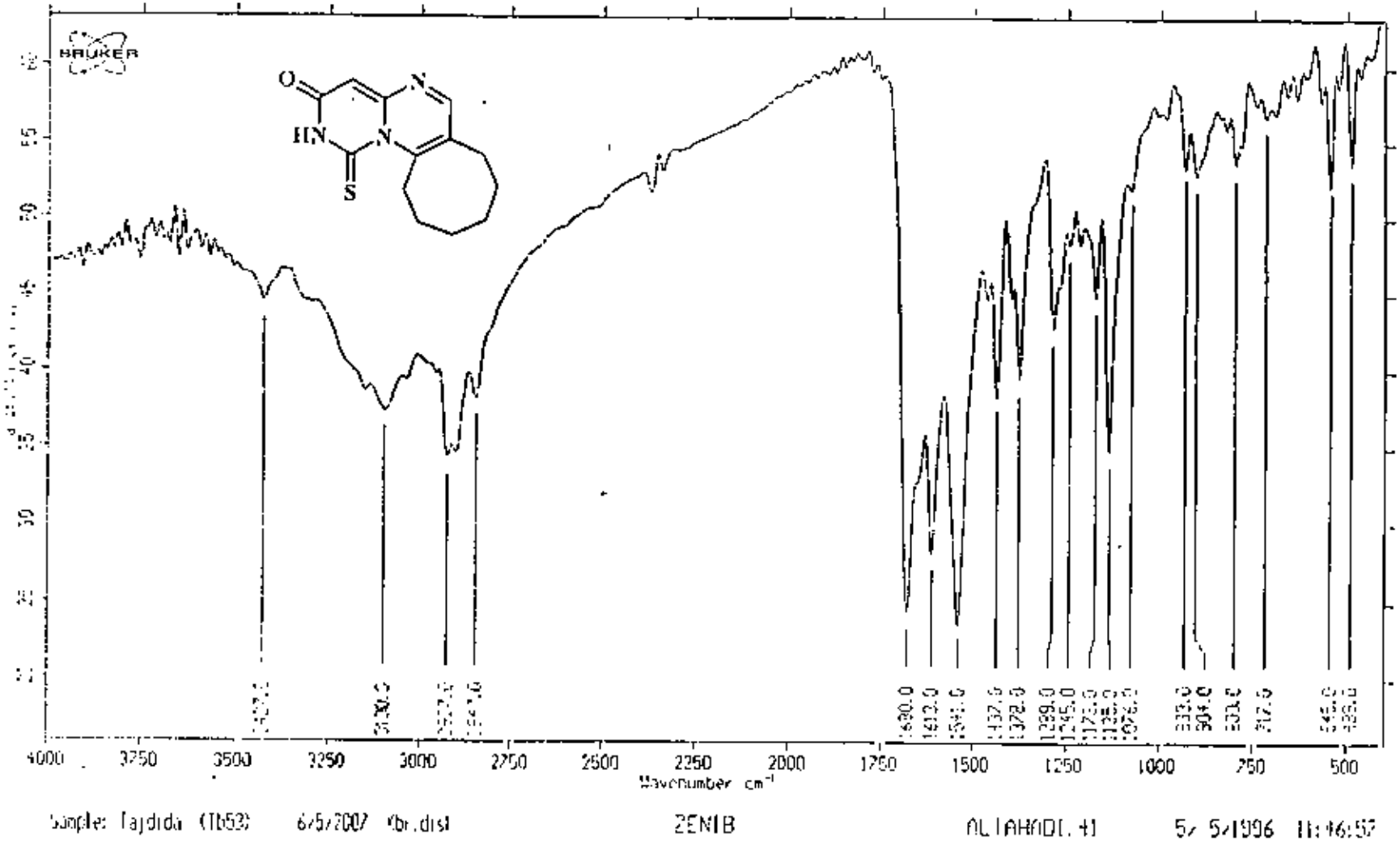

BRUKER
O
HN
N
N
S
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Tajdida (TB53) 6/5/2007 KBr.dsl
2ENIB
ALTAHRID[.4]
5/ 5/1996 11:46:57

Fig. (67)

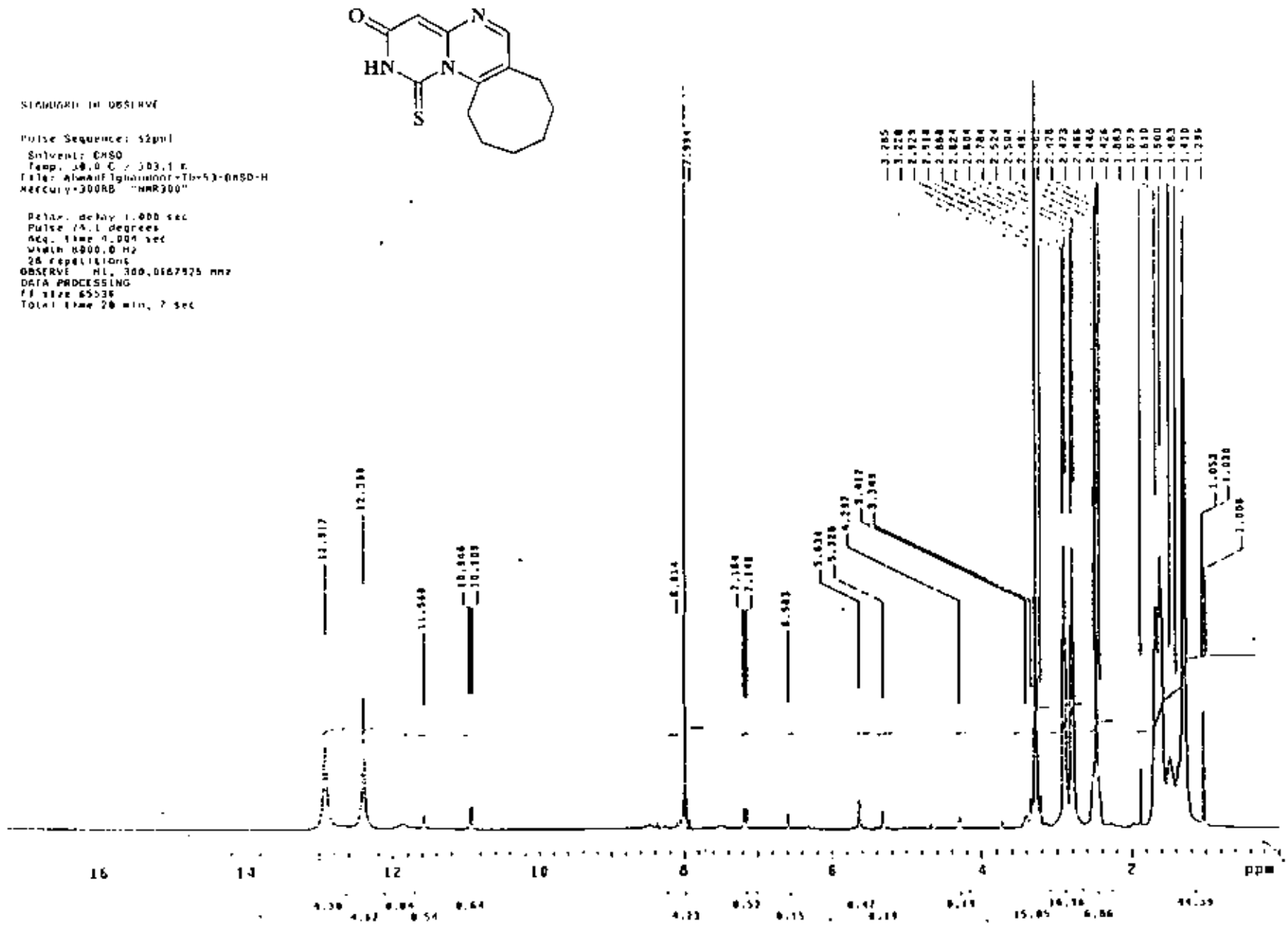

O
N
HN
N
S
Pulse Sequence: s2pul
Solvent: DMSO
Pulse 45.1 degrees
Width 8000.0 Hz
26 repetitions
DATA PROCESSING
FT size 65536
16
14
12
10
8
6
4
2
ppm

Fig. (68)

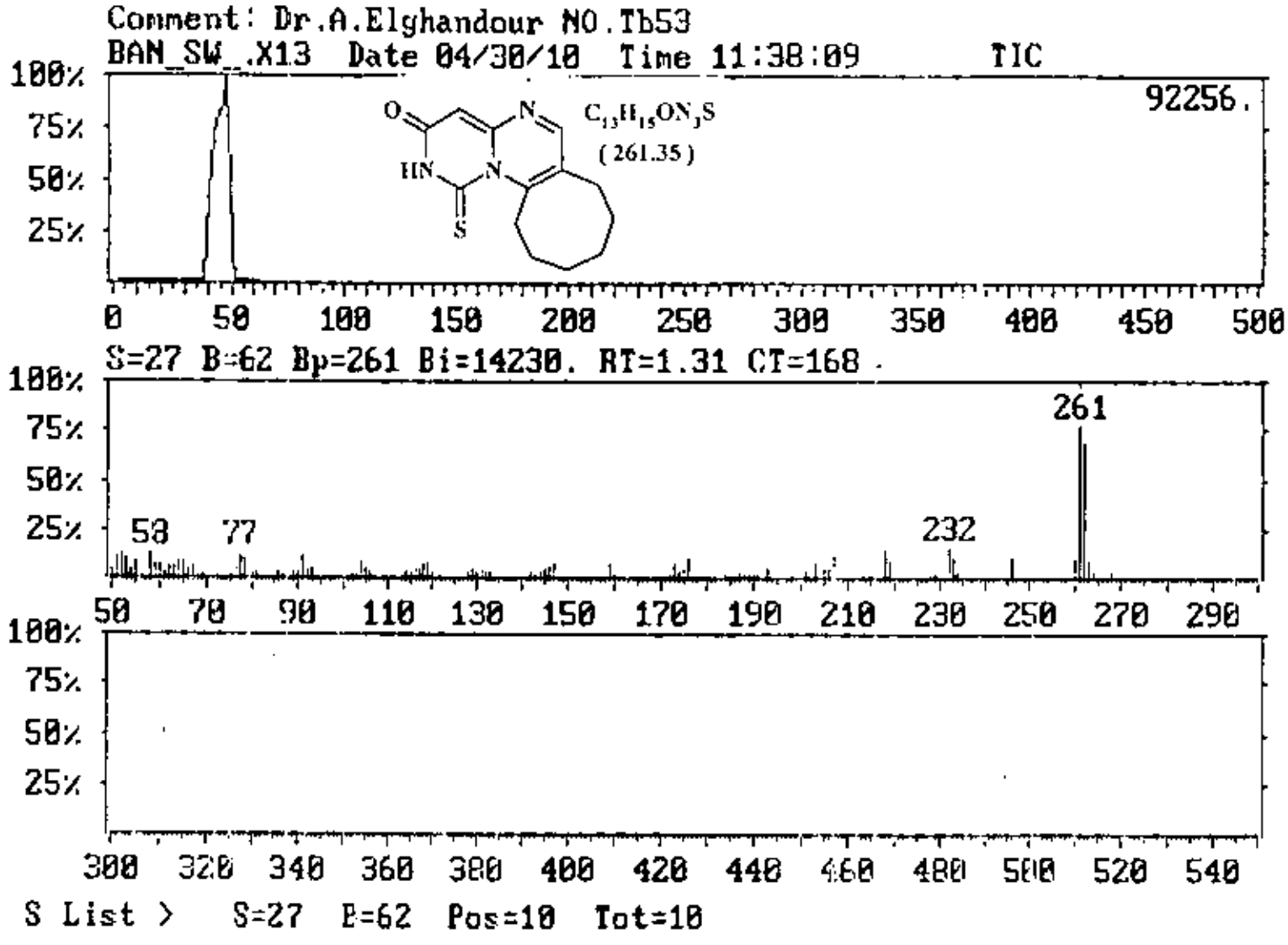

Comment: Dr.A.Elghandour NO.Tb53
BAN_SW_.X13 Date 04/30/10 Time 11:38:09 TIC
92256.
C13H15ON3S
(261.35)
S=27 B=62 Bp=261 Bi=14230. RT=1.31 CT=168
261
232
77
58
S List > S=27 B=62 Pos=10 Tot=10

Fig. (69)

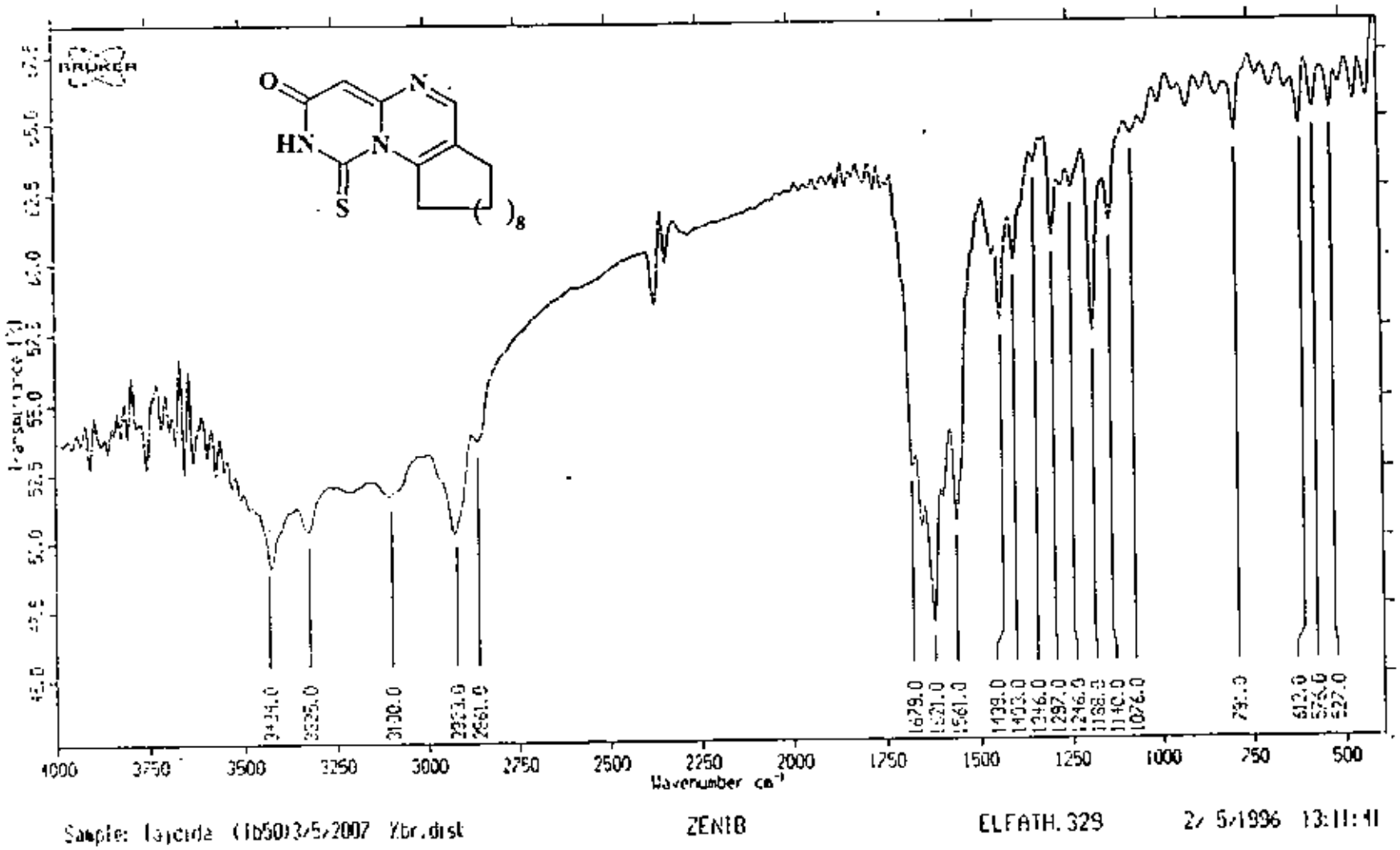

BRUKER
O
HN
N
N
S
)8
3434.0
3335.0
3130.0
2923.0
2861.0
1679.0
1621.0
1561.0
1439.0
1403.0
1346.0
1297.0
1246.0
1188.0
1140.0
1076.0
791.0
612.0
575.0
527.0
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
Sample: Tayeida (10503/5/2007 Ybr.dist
ZENIB
ELEATH.329
2/ 5/1996 13:11:41

Fig. (70)

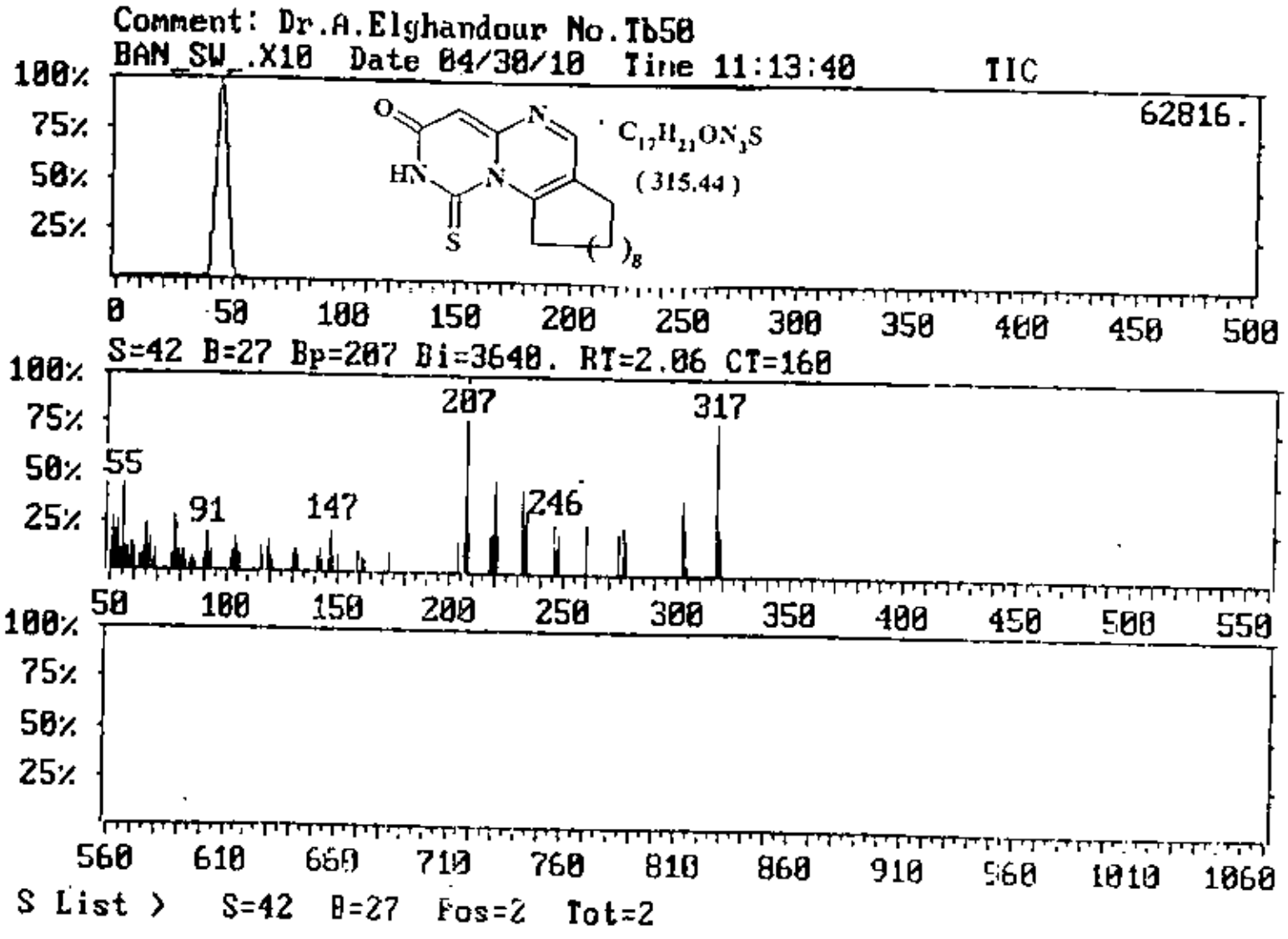

Comment: Dr.A.Elghandour No.Tb50
BAN_SW_.X10 Date 04/30/10 Time 11:13:40 TIC
100%
75%
50%
25%
62816.
O
N
HN
N
S
$C_{17}H_{21}ON_3S$
(315.44)
0 50 100 150 200 250 300 350 400 450 500
S=42 B=27 Bp=207 Bi=3640. RT=2.06 CT=160
207
317
55
91
147
246
50 100 150 200 250 300 350 400 450 500 550
560 610 660 710 760 810 860 910 960 1010 1060
S List > S=42 B=27 Pos=2 Tot=2

Fig. (71)

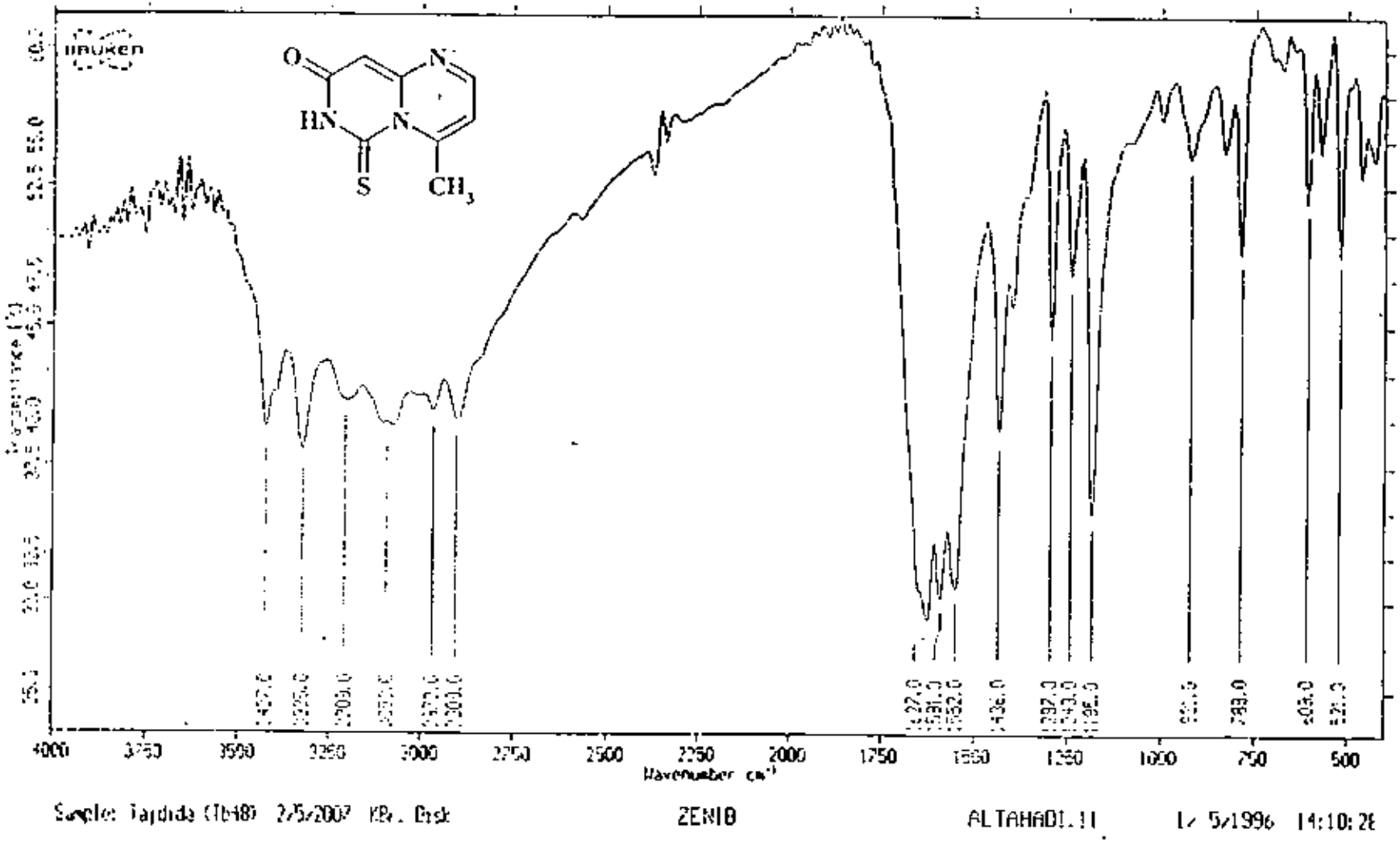

Bruker
O
HN
N
N
S
CH3
4000
3750
3500
3250
3000
2750
2500
2250
2000
1750
1500
1250
1000
750
500
Wavenumber cm-1
ZENIB
ALTAHADI.11

Fig. (72)

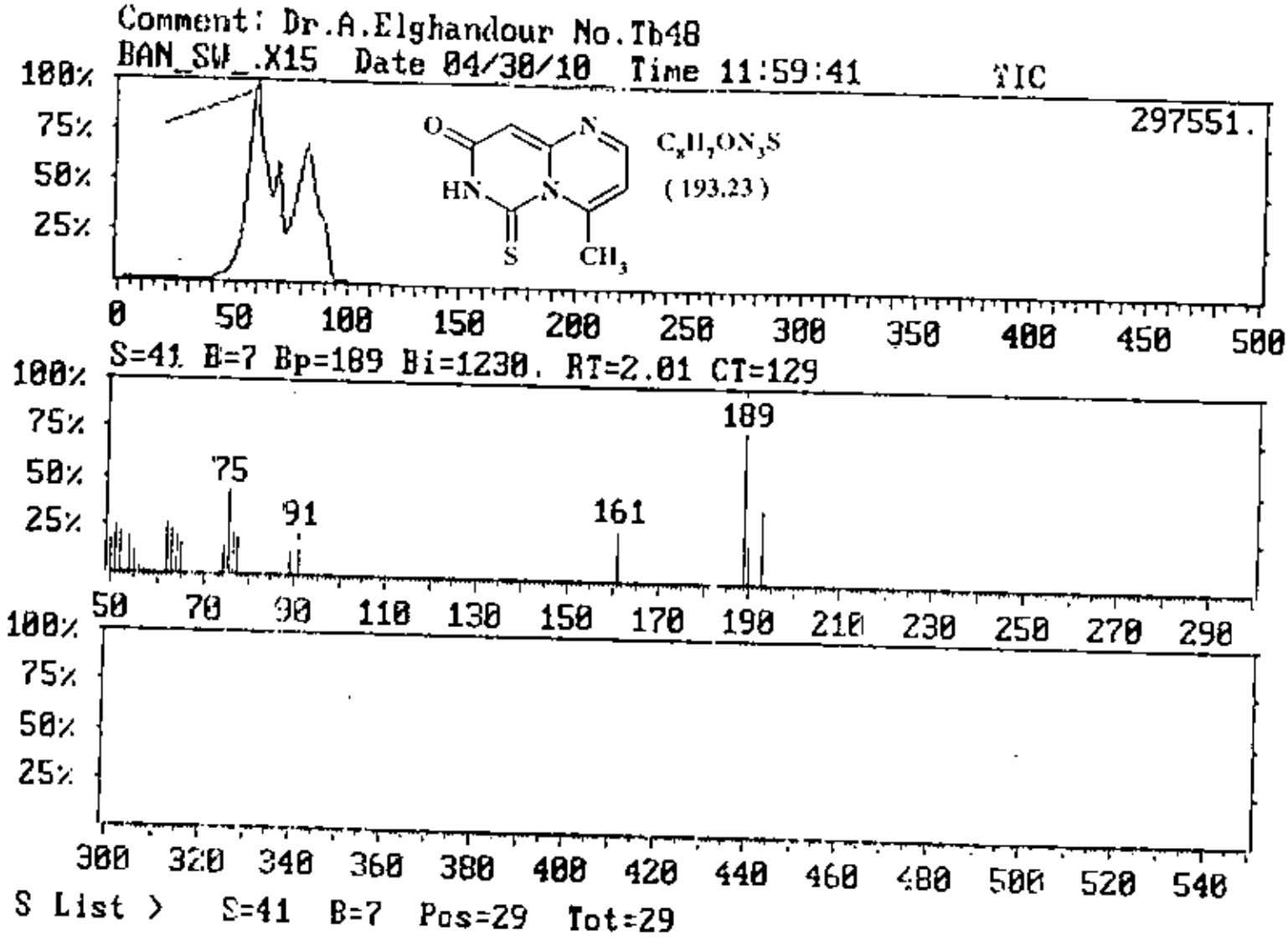

Comment: Dr.A.Elghandour No.Tb48
BAN_SW_.X15 Date 04/30/10 Time 11:59:41 TIC
297551.
100%
75%
50%
25%
O
N
HN
N
S
CH3
C7H7ON3S
(193.23)
0 50 100 150 200 250 300 350 400 450 500
S=41 B=7 Bp=189 Bi=1230. RT=2.01 CT=129
189
75
91
161
50 70 90 110 130 150 170 190 210 230 250 270 290
300 320 340 360 380 400 420 440 460 480 500 520 540
S List > S=41 B=7 Pos=29 Tot=29

Fig. (73)

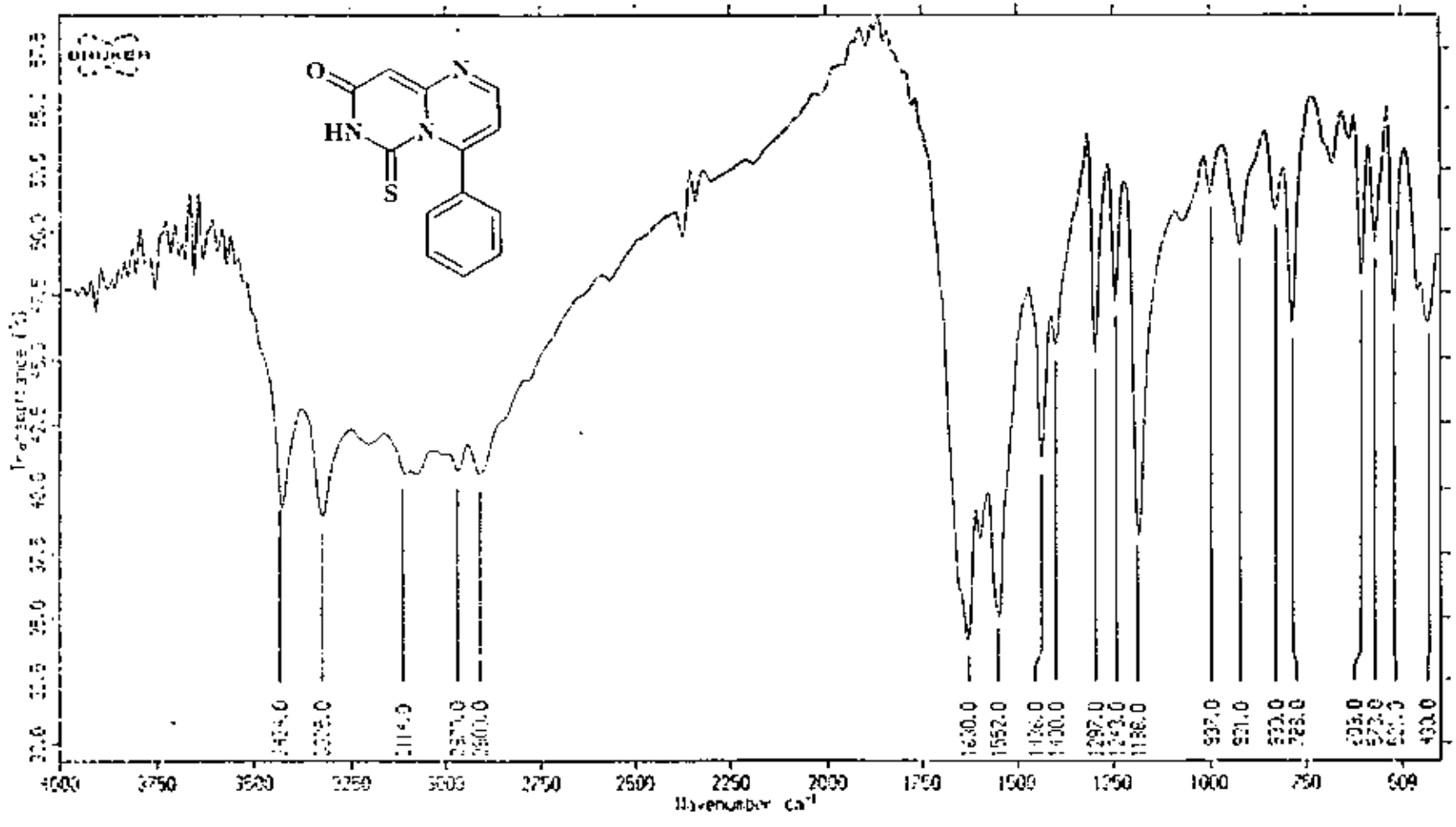

O
HN
N
N
S
1630.0
1552.0
1486.0
1400.0
1297.0
1243.0
1138.0
937.0
891.0
833.0
788.0
735.0
672.0
630.3
490.0
Wavenumber cm-1
ZENIB
ALTAHADI.39

Fig. (74)

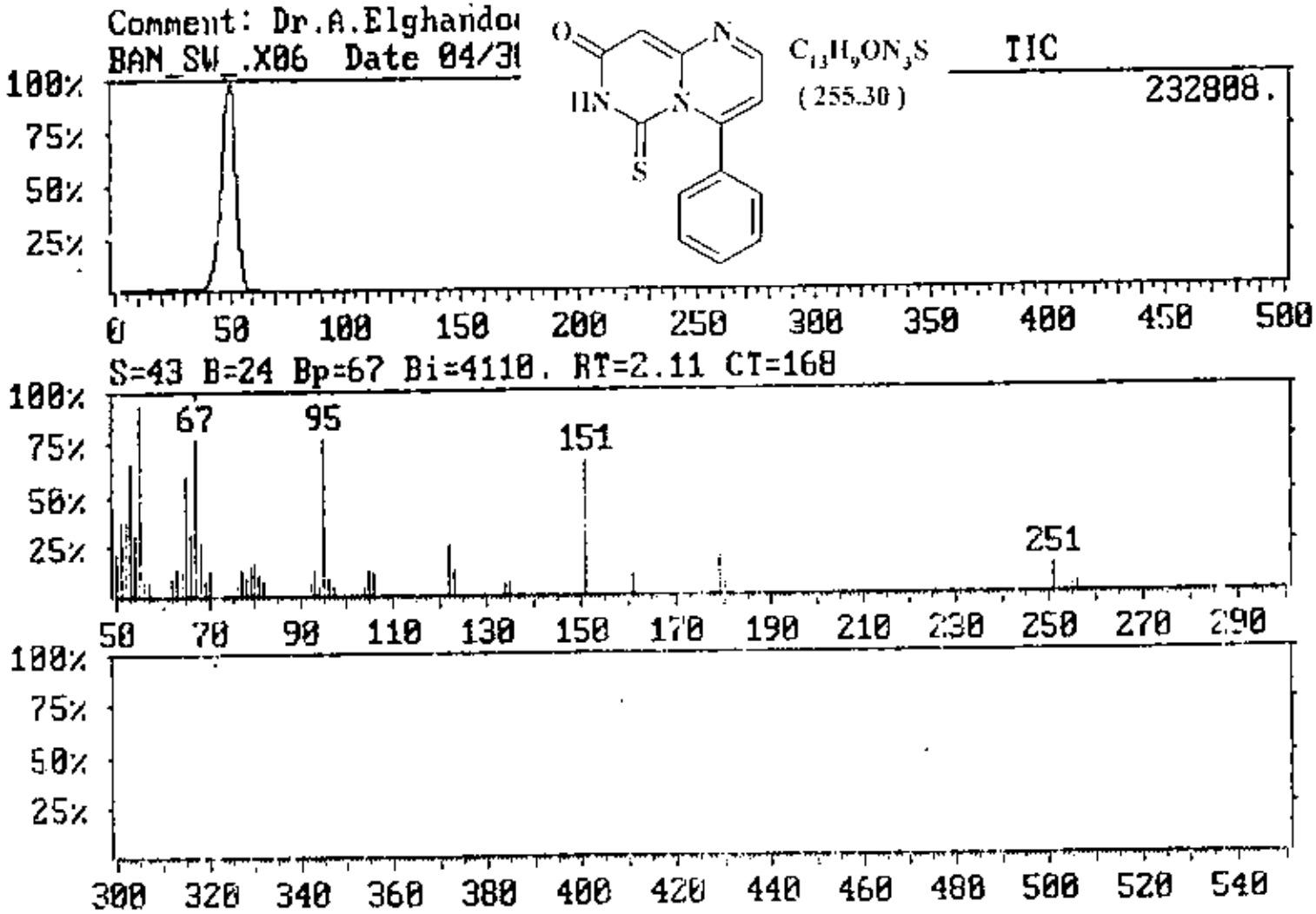

Comment: Dr.A.Elghandou
BAN_SW_.X06 Date 04/31
O
N
HN
N
S
$C_{13}H_9ON_3S$
(255.30)
TIC
232808.
100%
75%
50%
25%
0 50 100 150 200 250 300 350 400 450 500
S=43 B=24 Bp=67 Bi=4110. RT=2.11 CT=168
67
95
151
251
50 70 90 110 130 150 170 190 210 230 250 270 290
300 320 340 360 380 400 420 440 460 480 500 520 540
S List > S=43 B=24 Pos=9 Tot=9

Fig. (75)

REFERENCES

7. REFERENCES

1- F. Free man, *Sythesis*, 925 (1981).

2- S. Tripathi, S. Ahmed, Y. P. Borthwal, K. K. Tangri, K.Kishore and K. P. Bhorgava, *Indian Y. Exptl. Doil.*, **19,** 630 (1981).

3- U. Hanefeld, C. W. Ress, A. J. P. White and D. G. Williams. *J. Chem. Soc., Perkin Trans I*, 1545 (1996).

4- M. H. Elnagdi, N. S. Ibraheim, K. U. Sadek and M. H. Mohamed *Leibigs, Ann. Chem.*, 1005 (1988).

5- T. Novinson, J. P. Miller, M. Scholten, R. K. Robins, L. N. Simon, D. E. O'Brien and R. B. Meyer, *J. Med. Chem.*, **18,** 460 (1975).

6- K. U. Sadek, A. F. E. Mourad, A. E. Abdelhafeez and M. H. Elnagdi, *Synthesis*, 739 (1983).

7- R. K. Robins. *J. Am. Chem. Soc.*, **78,** 784 (1956).

8- T. Novinson. R. Hason. M. K. Dimmitt, L. N. Simon, R. K. Robins and D. E. O'Brien, *J. Med. Chem.*, **17,** 645 (1974).

9- T. J. Novinson, P. Miller, M. Scholten, R. K. Robins, L. N. Simon, D. E. O'Brien and R. B. Meyer, *J. Med. Chem.*, **18,** 460 (1975).

10- M. Culty, H. Li, N. Boujrad, H. Amri, B. Vidic, J. M. Bernassau, J. L. Revers and V. Papadopoulos, *J. Steroid Biochem. Mol. Biol.*, **69,** 123 (1999).

11- M. Mestre, T. Carriot, C. Belin, A. Uzan, C. Renault, M. C. Dubroeucq, C. Gueremy, A. Doble and G. Le Fur, *Life Sci.*, **36,** 391 (1985).

12- L. Miccoli, F. Poirson-Bichat, F. Sureau, R. Bras Goncalves, Y. B. Dutrillaux, M. F. Poupon and S. Oudard, *J. Natl. Cancer Inst.*, **90,** 1400 (1998).

13- S. R. R. Torres, G. M. Nardi, P. Ferrara, R. M. Ribeiro-dovalle and R. C. Farges, *Eur. J. Pharmacol.*, **385,** R1 (1999).

14- D. B. Zorov, B. F. Krasnikov, A. E. Kuzminova, M. Y. Vysokikb and L. D. Zorova, *Biosci. Rep.*, **17,** 507 (1997).

15- R. Moreno-Sanchez, B. A. Houge, C. Bravo, A. H. Newman, A. S. Basile and P. K. Chang, *Biochem. Pharmacol.*, **41,** 1479 (1991).

16- T. Curran and J. I. Morgan, *Science.*, **229,** 1265 (1985).

17- V. L. R. Rao, A. Dogan, K. K. Bowen and R. Dempsey, *J. Exp. Neurol.*, **161,** 102 (2000).

18- R. Springer, M. Scholten, D. O'Brien, T. Novinson, J. P. Miller and R. K. Robins, *J. Med. Chem.*, **25,** 235 (1982).

19- J. Cooper, F. Bloom and R. Roth,"*The Biochemical Basis of Neuropharmacology*", *5th Ed.; Oxfor. Univ. Press: New York.* (1986).

20- M. M. Ghorab, *Acta Pharm.*, **50,** 93 (2000).

21- D. C. Kim, Y. R. Lee, B. S. Yang, K. J. Shin, D. J. Kim and B. Y. Chung, *Eur. J. Med. Chem.*, **38,** (5) 525 (2003).

22- C. R. Petrie, H. B. Cottam, P. A. Mekernan, R. K. Robins and G. R. Revankar, *J. Med. Chem.*, **28,** 1010 (1985).

23- G. A. Bhat, J. G. Montero, R. P. Panzica, L. L. Worting and L. B. Towsend, *J. Med. Chem.*, **24,** 1165 (1981).

24- B. Zacharie, T. P. Connolly, R. Rej, G. Attardo and C. L. Penney, *Tetrahedron*, **52,** 2271 (1996).

25- J. D. Anderson, H. B. Cottam, S. B. Larson, L. D. Nord, G. R. Revankar and R. K. Robins, *J. Heterocyclic Chem.*, **27,** 439 (1990).

26- J. L. Avila, M. A. Polegre, A. R. Avila and K. Robins, *Comp. Biochem. Physiol.*, **83c,** 285 (1986).

27- G. Biagi, A. Costantini, L. Costantino, I. Giorgi, O. Livi, P. Pecorari, M. Rinaldi and V. Scartoni, *J. Med. Chem.*, **39,** 2529 (1996).

28- J. Dowden, and S. G. Ward, *Expert Opin. Ther. Pat.*, **11,** 295 (2001).

29- (a) K. J. Ryan, A. Arzoumanian, E. M. Acton and L. Goodman, *J. Am. Chem. Soc.*, **86,** 2506 (1964), (b) P. Kohn, R. H. Samaritano and L. M. Lerner, *J. Org. Chem.*, **31,** 1503 (1966), (c) A. J. Grant and L. M. Lerner, *J. Med. Chem.*, **22,** 1016 (1979).

30 - F. Seela and H. Steker, *Helv. Chim. Acta.*, **68,** 563 (1985).

31- C. Doria, C. Paassaroti, G. Arcori and A. Buttinoni, *Belg. Pat.* **893,** 835 (1983j). C. A. **99,** 70749 (1983).

32- F. Secla and M. Zulauf, *J. Chem. Soc., Perkin Trans. I,* 3233 (1998).

33- C. Matini, T. Rigacci, and A. Lucacchini, *J. Neurochem.*, **41,** 1183 (1983).

34- G. Palazzino, L. Cecchi, F. Melani, V. Colotta, G. Filacchioni, C. Martini and A. Lucacchini, *J. Med. Chem.*, **30,** 1737 (1987).

35- A. M. Gilbert, S. Caltabiano, F. E. Koehn, Zh. F. Chem, D. Gerardo, J. W. Ellingboe, Y. Kharode, Ma. AnnaMarie, R. Francis, M. Trailsmith, D. Grolnick, *J. Med. Chem.*, **45,** (11), 2342 (2002).

36- K. W. Weitzel, D. Pharm, J. M. Wickman, S. G. ugustin, and J. G. Strom, *Clinical Therapeutics*, **22,** (M), 1254 (2000).

37- M. Otsuka, Y. Matsuda, J. L. Fox and W. I. Pharm. *Pharmacal. Lett.* **5,** 18 (1995).

38- A. E. Eakin, R. Nieves-Alicea, R. Tosado-Acevedo, M. S. Chin, Wang, C. C. Craig and P. Sydney, *Antimicrob. Agents chemother*, **39,** 620 (1995).

39- K. A. Jacobson and J. W. Daly, *Nucleosides Nucleotides*, **10,** 1029 (1991).

40- S. Griffin, P. Branch, Y-z. Xu and P. Karran, *Biochemistry*, **33,** 4787 (1994).

41- S. Herber, L. Lennard, J. S. Lilleyman and J. Maddocks, *Br. J. Cancer*, **46**, 138 (1982).

42- R. A. Finch, K. M. Vasquez, N. B. Hanna, G. R. Revankar, R. K. Robins and T. L. Avery, *Cancer Lett.* **50**, 63 (1990).

43- R. P. Gale and A. Butturini, *Lancet*, **338**, 1315 (1991).

44- R. Gueroiolini, C. Szumlanski and R. M. Weinshilboum, *Clin. Pharmacol. Ther.* **50**, 663 (1991).

45- C. L. Szumlanski, R. Honchel, M. C. Scott and R. M. Weinshilboum, *Pharmacogenetics*, **2**, 148 (1992).

46- L. Lennard, J. Welch and J. S. Lilleyman, *Br. J. Cancer*, **72**, 1004 (1995).

47- P. C. Adamson, F. M. Balis, M. E. Hawkins, R. F. Murphy and D. G. Poplack, *Biochem. Pharmacol.* **46**, 1627 (1993).

48- C. Szumlanski, D. Otterness and C. Her, *DNA and cell Biology*, **15**, 17 (1996).

49- S. Piomelli and C. Seaman, *Am. J. Hematol.* **42**, 46 (1993).

50- R. T. Dorr and D. H. Von Hoff, *Cancer Chemotherapy Handbook*, 680 (1994).

51- J. I. Levin, J. W. Epstein, B. Beer, W. D. Dean, J. P. Dusza, S. S. Tseng, H. J. Schweitzer, W. T. Cain, R. T. Bartus and R. L. Dean, *Bioorg. Med. Chem. Lett.*, **1**, (9), 435 (1991).

52- W. Pfleiderer, R. Baur, M. Bartke and H. Lutz, *Gruyter &Co.*, 94 (1983)

53- C. A. Maryanoff, R. C. Stanziove, J. N. Plampin and J. E. Mills, *J. Org. Chem.*, **51**, 1986 (1882).

54- M. Suzuki, H. Iwasaki, Y. Fujikawa, M. Sakashita, M. Kitahara and R. Sakoda, *Bioorg. Med. Chem. Lett.*, **11**, 1285 (2001).

55- G. H. Elgemeie, S. E. Elezaby, H. A. Ali and A. Mansour, *Bull. Chem. Soc. Jpn.*, **67**, 738 (1994).

56- G. H. Elgemeie, H. A. Ali and A. K. Mansour, *Phosphorus, Sulfur and Silicon*. **90,** 143 (1994).

57- Medhat A. Zahran, Ahmed M. Sh. El-Sharief. Mohamed S. A. El-Gaby, Yousry A. Ammar and Usama H. El-Said, *IL Farmaco*., **56,** 277 (2001).

58- M. A. Elnagdi, M. R. H. Elmoghayer and G. H. Elgemeie, *Adv. Heterocyclic Chem.* **44,** 320 (1987).

59- Y. A. Ammar, A. M. Sh. El-Sharief, M. A. Zahran, M. Z. El-Said and U. H. El-Said, *J. Chem. Res.*(S), 324 (1995).

60- A. K. El-Shafei, A. M. Soliman, A. A. Sultan and A. M. M. El-Saghier, *Gazz. Chim. Ital*., **125,** 115 (1995).

61- S. Selleri, F. Bruni, C. Costagli, A.Costanzo, G. Guerrini, G. Ciciani, B. Costa and C. Martini, *Bioorg & Med. Chem*., **9,** 2661 (2001).

62- A. A. Hassanien, A. E. Amr and S. A. S. Ghozlan, *J. Chin. Chem. Soc*., **47,** 1273 (2000).

63- T. M. Abu-Elmaati and F. M. A. El-Taweel, *J. Chin.Chem. Soc*., **50,** 413 (2003).

64- V. I. Filyakova, O. A. Kuznetsova, E. N. Ulomskii, T. V. Rybalova, Yu. V. Gatilov, M. I. Kodess, V. L. Rusinov and I. Pashkevich, *Org. Chem*., (2) (2002).

65- A. M. S. Youssef, R. A. M. Faty and M. M. Youssef, *J. Korean. Chem. Soc*., **45,** (5) (2001).

66- M. A. Raslan, R. M. Abd El-Aal, M. E. Hassan, N. A. Ahamed and K. U. Sadek, *J. Chin. Chem. Soc*., **48,** 91 (2001).

67- J. J. Vapeuro, L. Ruentes, J. C. D. Castillo, M. Perez, J. L. Garcia and J. L. Soto, *Synthesis*., 33 (1987).

68- M. H. Elnagdi, N. H. Taha, F. A. Abdel-Al, R. M. Abdel-Motaleb and F. F. Mahmoud, *Collect. Czech. Chem. Commun*., **54,** 89 (1989).

69- K. U. Sadek, M. A. Selim, and M. H. Elnagdi, *Otto. Chem. Soc. Jpn.*, **66,** 2930 (1993).

70- N. P. Solov'eva,V. A. Makarov and V. G. Granik. *Khim, Gterotsikl. Soedin*, **89,** (1) (1997).

71- V. A. Makarov, N. P. Solov'eva, and V. G. Granik, *Chem. Heterocyclic Comp.*, **33,** 535 (1997).

72- V. A. Makarov, O. S. Anisimova, and V. G. Granik, *Khim. Geterosikl. Soedin*, **329,** (31) (1997).

73- V. G. Granik, *Usp. Khim.*, **53,** (4), 651 (1984).

74- V. G. Granik, A. M. Zhidkova and R. G. Glushkov, *Usp. Khim.*, **46,** (4), 685 (1977).

75- A. Holy, S. Chladek and J. Zemlitka, *Coll. Czech. Chem. Commum.*, **34,** 253 (1969).

76- N. Takeuchi, N. Okada and S. Tabinaga, *Chem. Pharm. Bull.*, **31,** 4355 (1983).

77- A. A. Elagamey and F. M. A. El-Taweel, *J. Prakt. Chemie.*, **333,** 333 (1991).

78- I. Ito, Japanese patent 7030101 (1970); Chem. Abst. 74. 22827 (1971).

79- B. C. Hinshaw, O. Leonoudakis and L. B. Townsend; Abst. 112d *National meeting of Am. Chem. Soci-Washington, D. C.*, Sept. (1971).

80- A. Thomas, M. Chakraborty, H. Ila and H. Junjappa, *Tetrahedron*, **46,** (2), 577 (1990).

81- A. Thomas, G. Singh, H. Ila and H. Junjappa, *Tetrahedron Lett.*, **30,** 3093 (1989).

82- S. M. S. Chauhan and H. Junjappa, *Tetrahedron*, **32,** 1179 (1976).

83- A. Kumar, H. Ila and H. Junjappa, *J. Chem.Res. (S)*, 268 (1979).

84- Y. Kurasawa, Ho Sik Kim, Rika Futatsukawa, Chisako Watanabe and Atsushi Takada, *J. Heterocyclic Chem.* **26,** 1159 (1989).

85- Y. Kurasawa and A. Takada, *Heterocyclic.* **14,** 281 (1980).

86- S. Selleri, F. Bruni, C. Costagli, A. Costanzo, G. Guerrini, G. Ciciani, B. Costa and C. Martini. *Bioorg. Med. Chem.* **7,** 2705 (1999).

87- K. M. Dawood, A. M. Farag and Z. E. Kandeel, *J.Chem. Research (S),* 88 (1999).

88- M. H. Elnagdi, F. A. Abdel All and G. E. H. Elgemeie, *Heterocycles,* **23,** 3121 (1985).

89- S. M. Sherief and A. M. Hussien, *Monatsh. Chem.*, **128,** 687 (1997).

90- F. Bruni, S. Selleri, A. Costanzo, G. Guerrini and M. L. Casilli, *J. Heterocyclic Chem.*, **32,** 291 (1995).

91- F. Bruni, S. Selleri, A. Costanzo, G. Guerrini and M. L. Casilli, *J. Heterocyclic Chem.*, **31,** 1193 (1994).

92- S. Selleri, F. Bruni, A. Costanzo, G. Guerrini, P. Malmberg Aiello and C. Martini, *Eur. J. Med. Chem.*, **27,** 985 (1992).

93- G. Auzzi, L. Cecchi, A. Costanzo, L. Pecori Vettori, F. Bruni, R. Pirisino and G. B. Ciottoli, *Farmaco, Ed. Sci.*, **43,** 478 (1979).

94- G. Auzzi, L. Cecchi, A.Costanzo, L. Pecori Vettori and F. Bruni, *Farmaco, Ed. Sci.*, **34,** 898 (1979).

95- H. H. Abdel-Razik and A. A. Fadda, *Synthetic Communications®*, **31,** (22), 3547 (2001).

96- M. G. Marei and M. El-ghanam, *J. Islamic Academy of Sciences.* **5,** (2), 86 (1992).

97- I. E. El-kholy, M. G. Marei and M. M. Mishrikey, *J. Heterocyclic Chem.*, **16,** 737 (1979).

98- I. E. El-kholy, M. M. Mishrikey and M. G. Marei, *Ibid.* **19,** 1421 (1982).

99- M. G. Marei, D. M. Aly and M. M. Mishrikey, *Afinided*, **49,** 319 (1992).

100- M. G. Marei, D. M. Aly and M. M. Mishrikey, *Bull. Chem. Soc. Jpn.*, **65,** 3419 (1992).

101- E. A. Zvezdina, M. P. Zhdanoa, I. I. Nechayuk, I. A. Barchan, Yu. N. Simkina and T. A. Buchnaya, *khim. Farm. Zh.*, **20,** 1328 (1986).

102- Y. Tominage, Y. Honkawa, M. Hara and A. Hosomi, *J. Heterocyclic Chem.*, **27,** 775 (1990).

103- H. B. Cottam et al., *J. Med. Chem.*, **27,** 1119 (1984).

104- E. S. Othman, *Acta Chim. Solv.*, **50,** 15 (2003).

105- F. Gatta and M. Luciani, *J. Heterocyclic Chem.*, **26,** 613 (1989).

106- V. Nair, R. J. Offeman and G. A. Turner, *J. Org. Chem.*, **49,** 4021 (1984).

107- F. Miklos, I. Kanizsai, P. Sohar and G. Stajer, *Journal of Molecular Structure*, **610,** 41 (2002).

108- P. Schmidt and I. Druey, *Helv. Chim. Acta.*, **39,** 986 (1956).

109- A. Dorrow and E. Hinz, *Chem. Ber.*, **91,** 1839 (1958).

110- F. Gatta, M. Luciani and G. Palazzo, *J. Heterocycl. Chem.*, **26,** 613 (1989).

111- F. Secla and G. Becher, *Helv. Chim. Acta*, **83,** 928 (2000).

112- E. R. El-Bendary and F. A. Badria, *Arch. Pharm. Med. Chem.*, **333,** 99 (2000).

113- N. P. Peet and S. Sunder, *Indian J. Chem.*, Sect. B., **27,** 298 (1989).

114- N. P. Peet, *Synthesis*, 1065 (1984).

115- P. Scheiner, S. Arwin, M. Eliacin and J. Tu., *J. Heterocycl. Chem.*, **22,** 1435 (1985).

116- J. M. Quintela, C. Peinador, M. J. Moreira, A. Alfonso, L. M. Botana and R. Riguera, *Eur. J. Med. Chem.*, **36,** 321 (2001).

117- J. M. Quintela, C. Peinador, M. J. Moreira and R. Alvarez-Sarandes, *Recent Res. Dev. Org. Chem.*, **2**, 409 (1998).

118- P. G. Barald, B. Cacciari, G. Spalluto, Pineda de las Infantas, M. J. Villatoro, C. Zocchi, S. Dionisotti and E. Ongini, *J. Med. Chem.*, **39**, 1164 (1996).

119- A. F. Burchat, D. J. Calderwood, M. M. Friedman, G. C. Hirst, B. Li, P. Rafferty, K. Ritter and B. S. Skinner, *Bioorg. Med. Chem. Lett.*, **12**, 1687 (2002).

120- D. J. Calderwood, D. J. Johnston, R. Munschaner and P. Rafferty, *Bioorg. Med. Chem. Lett.*, **12**, 1683 (2002).

121- A. J. Peat, J. A. Boucheron, S. H. Dickerson, D. Garrido, W. Mills, J. Peckham, F. Preugschat, T. Smalley, S. L. Schweiker, J. R. Wilson, T. Y. Wang, H. Q. Zhou and S. A. Thomson., *Bioorg. Med. Chem. Lett.*, **14**, 2121 (2004).

122- V. A. Makarov, O. B. Ryabova, L. M. Alekseeva, A. S. Shashkov and V. G. Granik., *Chemistry of Heterocyclic Compounds*, **39**, 238 (2003).

123- V. A. Makarov, O. B. Ryabova, L. M. Alekseeva, V. V. Chernyshev and V. G. Granik, *Khim. Geterotsikl. Soedin.*, 1087 (2002).

124- V. A. Makarov, O. S. Anisimova and V. G. Granik, Khim. *Geterotsikl. Soedin.*, 329 (1997).

125- E. I. Al-Afaleq and S. A. Abubshait, *Molecules*, **6**, 621 (2001).

126- A. M. Kamal El-Dean and A. A. Geies., *J. Chem. Research* (S), 352 (1997).

127- J. Carin, M. P. Loscertales, E. Melendez, F. L. Merchan, R. Rodrigues and T. Tejro, *Heterocycles*, **26**, 1304 (1987).

128- K. Avasthi, K. Deo, Neeraj Garg and D. S. Bhakuni, *Bioorg. Med. Chem. Lett.*, **5**, 249 (1991).

129- S. Phadtare and J. Zemlica, *J. Am. Chem. Soc.*, **111**, 5925 (1989).

130- N. Garg, K. Avasthi, Ram Pratap, D. S. Bhakuni and P. Y. Guru, *Ind. J. Chem.*, **29B**, 859 (1990).

131- I. A. Korbukh, N. G. Yakunia and M. N. Preobrazhenskaya, *Bioorg. Khim.*, 6, 1632 (1980) ; *Chem. Abst.*, **94**, 103745s (1981).

132- (a) J. Montgomery, S. Clayton and W. Fitzgibbon, *J. Heterocycl. Chem.*, **1**, 215 (1964); (b) J. D. Anderson, N. K. Dalley, G. R. Revenkar and R. K. Robins, *J. Heterocycl. Chem.*, **23**, 1869 (1986).

133- S. Misra, S. Jain, K. Avasthi and D. S. Bhakuni, *Nucleosides & Nucleotides*, **9**, 837 (1990).

134- A. Hasan, R. P. Tripathi, Ram Pratap, D. S. Bhakuni, R. Pal, A. Mishra, P. Y. Guru and J. C. Katiyar, *Ind. J. Chem.*, **28B**, 403 (1989).

135- J. Slouka, I. Wiedermannova, J. Frebortova, M. Hajduch and M. Strand, *Acta Chemica*, **38**, 65 (1999).

136- R. K. Robins, *J. Am. Chem. Soc.*, **78**, 784 (1956).

137- O. Moukha-chafiq, M. L. Taha, H. B. Lazrek, J. J. Vasseur, C. Pannecouque, M. Witvrouw and E. De Clercq., *Il Farmaco*, **57**, 27 (2002).

138- O. Moukha-chafiq, M. L. Taha, H. B. Lazrek, C. Pannecouque, M. Witvrouw, E. De Clercq, J. L. Barascut and J. L. Imbach, *Nucleosides Nuclotides.*, **20** (2001).

139- Dae-Kee Kim, Do Hyun Ryu, Namkyu Lee, Ju Young Lee, Jae-sun Kim, Sukho Lee, Jin-young Choi, Je-Ho Ryu, Nam-Ho Kim, Guang-Jin Im, Won-Son Choi and Tae-Kon Kim., *Bioorg. Med. Chem.*, **9**, 1895 (2001).

140- US Patent 5, 346, 901.

141- J. Yuan, M. Gulianello, S. De Lombaert, R. Brodbeck, A. Kieltyka and K. J. Hodgetts, *Bioorg. Med. Chem. Lett.*, **12**, 2133 (2002).

142- T. Takido and K. Itabashi, *Synthesis*, 817 (1987).

143- A. C. Butterworth, F. J. Medrano, A. E. Eakin and S. P. Craig, *Biochimica et Biophysica Acta*, **1699**, 87 (2004).

144- B. Canyuk, F. J. Medrano, M. A. Wenck, P. J. Focia, A. E. Eakin and S. P. Craig. *Journal of Moleculor Biology*, **335**, 905 (2004).

145- H. A. Saad, H. Y. Moustafa, M. G. Assay, and M. A. Sayed, *Bull. Korean Chem. Soc.* **22**, 311 (2001).

146- E. C. Moore and D. Pharm., *Journal of the pharmacy Society of Wisconsin* (2000).

147- E. Sanna, F. Busonero, G. Talani, M. Carta, F. Massa, M. Peis, E. Maciocco and G. Biggio, *Eur.J. Pharmacol.*, **451**, 103 (2002).

148- M. E. Erman, M. D. Insomnia, *Consult-Rakel: Conn's current Therapy. 52nd Ed., Saunder Co.* (2000).

149- M. D. Insomnia. *Consult-Goetz: Textbook of Clinical Neurology-1st Ed. Saunders Co.* (1999).

150- W.A. Kehoe., New Drug; Zaleplon (Sonata ®). *The pharmacist's Letter* (1999).

151- Sonata® (Zaleplon). Philadelphia, PA: Wyeth-Ayerst laboratories, 1999 Product Information.

152- Cr. Gelman, M. B. Moore, T. Hutchison, et al,. (Eds): Zaleplon (Sonata®). Drugdex System. Micromedex, Inc., Englewood. Colorado (Edition Expires 09/2000).

153- M. Hurst and S. Noble, Zaleplon. *CNS Drugs*, **11**, 387 (1999).

154- Zaleplon (Sonata®), New Drug Overiew, *AHFS Drug Information*, **28**: 24, 92 (1999).

155- M. H. Lader, *J. clin. Psychiatry.*, **4**, (Suppl. 1), 33 (2002).

156- M. Scharf, *Eur Neuropsychopharmacol.*, **9**, (Suppl. 5), 5360 (1999).

157- H. J. Mangano, *Eur Neuropsychopharmacol.*, **9,** (Suppl. 5), 5362 (1999).

158- K. A. Moore, T. L. Zemrus, V. Ramcharitar, B. Levine and D. R. Fowler, *Forensic Science International*, **134,** 120 (2003).

159- C. F. P George, *Lancet.*, **357,** 1623 (2001).

160- JK. Walsh and CI. Engelhart, "*The direct Economic Costs of Insomnia in The United States for 1995*", **22,** (Suppl 2), S186 (1999).

161- T. Yasuda, T. Iwamoto, M. Ohara, S. Sato, H. Kohpi, K. Noguchi and E. Senba., *J. Pharmacol.*, **79,** (1), 65 (1999).

162- G. B. Elion, S. M. Callahan, H. C. Nathan, R. S. Bieber, R. W. Rwndles and G. H. Hitchings, *Biochem. Pharmacol.*, **12,** 85 (1963).

163- J. A. Alexander, G. F. Wheeler, D. D. Hill and H. P. Morris, *Biochem. Pharmacol.*, **15,** 881 (1966).

164- R. A. Long, J. F. Gerster and L. B. Townsend, *J. Heterocycl. Chem.*, **3,** 863 (1970).

165- T. Novinson, R. Hanson, M. K. Dimitt, L. N. simon, R. K. Robins and D. E. O'Brien, *J. Med. Chem.*, **17,** 645 (1974).

166- H. E. Skipper, R. K. Robins, J. R. Thomson, C. C. Ching, R. Brockman and F. M. Schabel, *Cancer Res.*, **17,** 579 (1957).

167- H. E. Skipper, R. K. Robins and J. R. Thomson, *Proc. Soc. Exptl. Biol. Med.* **89,** 594 (1955).

168- B. Bear, M. Chasin, D. E. Clody, J. R. Vogel and Z. P. Horovitz, *Science*, **428,** 176 (1972).

169- R. Sundaramoorthi, W. C. Shakespeare, T. P. Keenan, C. A. Metcalf, III, Y. Wang, U. Mani, M. Taylor, S. Liu, R. S. Bohacek, S. S. Narula, D. C. Dalgarno, M. R. V. Schravandijk, S. M. Violette, S.

Liou, S. Adams, M. K. Ram, J. A. Keats, M. Weigele and T. K. Sawyer, *Bioorg. Med. Chem. Lett.* **13,** 3063 (2003)

170- J. H. Hanke, J. P. Gardner, R. L. Dow, P. S. Changehan, W. H. Brissette, E. J. Weringer, B. A. Pollack and P. A. Connelly, *J. Biol Chem.*, **271,** 695 (1996).

171- F. Secla, C. Wei, G. Becher, M. Zulauf and P. Leonard., *Bioorg. Med. Chem. Lett.*, **10,** 289 (2000).

172- J. Foreman and I. Garland, *Br. Med. J.*, **1,** 820 (1976).

173- J. R. Woodgett and P. Cohen, *Biochim. Biophys. Acta.*, **788,** 339 (1984).

174- S. E. Nikoulina, T. P. Ciaraldi, S. Mudailar, P. Mohideen, L. Carter and R. R. Henry, *Diabetes*, **49,** 263 (2000).

175- S. Lovestone, C. H. Reynolds, D. Latimer, D. R. Davis, B. H. Anderton, J. M. Gallo, D. Hanger, S. Mulot, and B. Marquardt, *Curr. Biol.*, **4,** 1077 (1994).

176- W. Vale, J. Spiess, C. Rivier and J. Rivier, *Science,* **213,** 1394 (1981).

177- (a) P. J. Gilligan, D. W. Robertson and R. Zaczek, *J. Med. Chem.*, **43,** 1641 (2000). (b) P. J. Gilligan, P. R. Hartig, D. W. Roertson and R. Zaczek, *Annual Rep. Med. Chem.*, **32,** 41 (1997). (c) E. B. De Souza, T. W. Lovenberg, D. T. Chalmers, D. E. Grigoriadis, C. W. liaw, D. P. Behan and J. R. McCarthy, *Annual Rep. Med. Chem.*, **30,** 21 (1995).

178- (a) I. Eardley, *Exp. Opin. Invert. Drugs*, **6,** 1803 (1997). (b) L. Garcia-Reboll, J. P. Mulhall and I. Goldstein, *Drugs Aging*, **11,** 140 (1997). (c) M. C. Truss and C. G. Stief, *Drugs Today*, **34,** 805 (1998).

179- B. Dumaitre and N. Dodic, *J. Med. Chem.*, **39,** 1635 (1996).

180- M. A. Metwally, E. I. Desoky, R. Fawzy, and H. A. Etman, *Chemistry of Heterocyclic Compounds*, **43** (3) (2007).

181- Nirmal D. Desai, and Rina D. Shah, *Synthesis*, 3275 (2006).

182- M. V. Pryadeina, Ya. V. Burgart, V. I. Saloutin, M. I. Kodess, E. N. Ulomskii, and V. L. Rusinov, *Russian Journal of Organic Chemistry*, **40** (6), 902 (2004).

183- Chaitanya G. Dave and Rina D. Shah, *Molecules*, **7**, 554 (2002).

184- Arcady L. Krasovsky, Andrew M. Moiseev, Valentine G. Nenajdenko and Elizabeth S. Balenkova, *Synthesis*, 901 (2002).

185- Y. Takayama, Y. Yoshida and M. Uehata, *US Patent No. 7109208; Appl. No.* (2006).

186- A. Fujii, H. Tanaka, M. Otsuki, T. Kawaguchi and K. Oshita, *US Patent No. 6930115*; Appl. No. (2005).

187- T. Takaya, M. Murata and K. Ito, *US Patent No. 4725600; Appl. No.* (1988).

188- T. Utsunomiya, T. Niki, T. Kikuchi, J. Watanabe, K. Yamagishi, M. Nishioka, H. Suzuki, T. Furusato, and T. Miyake, WO/1999/006380, PCT/JP1998/003397, (1999).

189- M. R. Dick, WO/1996/008968, (1996).

190- Gary E. Aspnes, Yuan-Ching P. Chiang, *US Patent No. 6441015;* (2002).

191- M. Uehata, T. Ono, H. Satoh, K. Yamagami, T. Kawahara, *US Patent No. 6218410; Appl. No.* (2001).

192- (a) Johnson, Woroch, and Mathews; *J. Am. Chem. Soc.*, **69**, 570 (1947).

(b) Raymond P. Mariella, *Organic synthesis*, **CV4**, 210 (1947).

193- Dunbar, Joseph E. (Midland, MI, US) Begin, Louis E. (Midland, MI, US); "Novel aminoalkyl purine and pyrazolopyrimidine compounds

useful in the inhibition of blood platelet aggregation in animals" *US patent no. 4169948; Application No. 962526* (1979).

194- Gross, Raymond S. (Poway, CA, US) Wilcoxen, Keith M. (San Diego, CA, US) Oglesby, Richard Christopher (Schodack Landing, NY, US): "Synthesis of substituted pyrazolopyrimidines" *US patent No. 7034154; Application No. 107534* (2006).

195- B. B. Suider and Z. Shi, *J. Org. Chem.*, **58,** 3828 (1993).

196- A. D. Patil, N. V. Kumar, W. C. Kokke, M. F. Bean, *J. Org. Chem.*, **60,** 1182 (1995).

197- S. K. Srivastava, W. Haq. and P. M. S. Chauhan, *Bioorg. Med. Chem. Lit.*, **9,** 965 (1999).

198- E. D. Clercq and R. J. Beraaerts, *Biol. Chem.*, **262,** 14905 (1987).

199- W. J. Coates, *European Patent* 351058, (1990).

200- (a) E. C. Taylor, R. J. Knopf, R. F. Meyer, A. Holmes and M. L. Hoefle, *J. Am. Chem. Soc.*, **82,** 5711(1960). (b) J. D. Figueroa Villar, C. L. Carneiro and E. R. Cruz, *Heterocycles* , **34,** 891 (1992).

201- N. Kitamura, A. Onishi, *European Patent* 163599, (1984); Chem. Abstr., **104,** 186439 (1984).

202- P. Raddatz, and R. Bergmann, *German Patent* 360731, (1988); Chem. Abstr., **109,** 54786 (1988).

203- T. J. Delia, M. Baumann, and A. Bunker, *Heterocycles,* **35,** 1397 (1993).

204- Flavio F. Solca. Anke Baum, Elke lang kopt. Georg Dahmann, Karl-Hein Z Heider, Frank Himmelsbach, and C. A. Jacques, *J. of pharmacology and Exp. The rapeutics* 502 (2004).

205- (a) K. Hirota, Y. Kitade, M. Sajika and Y. Maki, Synthesis, 589 (1984); (b) K. Hirota, Y. Kitade, M. Sajika and Y. Maki, *J. Chem. Soc., Perkin Trans I,* 123 (1990).

206- S. W. Srvastava, W. Haq and P. M. S. Chauhan, *Bioorg. Med Chem.*

Lett., **9**, 965 (1999).

207- A. A. El-helby; *J. Pharm. Sci.* **27**, 375 (2001).

208- G. H. Elgemeie, A. H. Elghandour, A. M. Elzanate and S. A. Ahmed, *J. Chem. Soc. Perkin Trans., I*, 3285 (1997).

209- G. H. Elgemeie, A. H. Elghandour, A. M. Elzanate and S. A. Ahmed, *J. Chem. Research (S)*, 162 (1998).

الملخص العربي

ملخص الأبحاث المبتكرة

تخليق بعض المركبات الجديدة ذات الصلة بالبيورين

(1) تخليق مشتقات تترازولو(*a*- 1,5) بيرميدين الجديدة في تفاعل انتقائي من خطوة واحدة:

تلعب مركبات التترازولوبيرميدين دور هام وأساسي في كثير من العمليات البيولوجية ، كما أن لها أهمية كبيرة من الناحية الكيميائية والعلاجية.

في هذا العمل قمنا بوصف طريقة سهلة وفعالة لتحضير مشتقات التترازولوبيرميدين عن طريق تفاعل مركب 5-أمينو تترازول مع أملاح الصوديوم لمركبات فورميل الكيتونات الحلقية ، فبمعالجة مركب 5- أمينو- 1H- تترازول المائي بأملاح الصوديوم لمركبات فورميل الكيتونات الحلقية المسماة: صوديوم (2- أوكزوسليكلوالكيليدين) ميثانوويت (2) في وجود أسيتات البريدين وحمض الأسيتك في تفاعل من خطوة واحدة أعطت وبنتائج تفاعل جيدة مركبات التترازولو(*a*-1,5) بيرميدين الملتحمة الحلقة مع السايكلوألكانات. كما هو موضح في المخطط [1].

تم إثبات التراكيب البنائية للمركبات المحضرة عن طريق نواتج تحاليلها العنصرية وكذلك التحاليل الطيفية المختلفة (طيف الأشعة تحت الحمراء ، طيف الكتلة ، طيف الرنين النووي المغنطيسي لذرة الهيدروجين).

(2) تخليق مشتقات البيرازولو(*a*- 1,5) بيرميدين كمشابهات للبيورين:

وجد أن أنظمة البيرازولوبيرميدين تعمل كمثبطات لتخليق الـ RNA و DNA في خلايا بعض أنواع السرطانات والفيروسات. وبصفة عامة ، وجد أنها تمتلك تأثير بيولوجي وعلاجي فعال.

في هذا الجزء تم تحضير سلسلة هامة من مركبات البيرازولوبيرميدين من خلال تفاعل الأمينو بيرازولات مع أملاح الصوديوم فورميل للكيتونات الحلقية والمفتوحة. لذا تتفاعل

مركبات 5-أمينو بيرازول المستبدلة في الموقعين 3 و 4 (9) مع أملاح الصوديوم فورميل (2) لتعطى مشتقات البيرازولو(1,5-*a*) بيرميدين (**10 a-y**) بنواتج تفاعل ممتازة تحت نفس ظروف التفاعل الموصوف لتحضير مركبات التترازولوبيرميدين (6) وبنفس ميكانيكية التفاعل كما هو موضح بالمخطط [2].

تم أيضا دراسة سلوك مركبات الأمينو بيرازول تجاه أملاح الصوديوم فورميل للكيتونات الأليفاتية والأروماتية المفتوحة ، فقد تكاثفت بعض المشتقات المختارة لمركبات 5-أمينو بيرازول (9) مع ملح الصوديوم فورميل أسيتون (11) في وجود أسيتات البيريدين وحمض الأستيك لتعطى مركبات 2- أنيلينو-7- ميثل-*N*- أريل بيرازولو(1,5-*a*) بيرميدين-3- كربوكساميد (12).

تفاعلت أيضا بعض المشتقات الأخرى لمركبات الأمينوبيرازول مع ملح الصوديوم فورميل أسيتوفينون (13) كمثال للكيتونات الأروماتية المفتوحة لتعطى مركبات 2-أنيلينو-7- فنيل-*N*- أريل بيرازولو (1,5-*a*) بيرميدين- 3- كربوكساميد (14) ، كما هو موضح بالمخطط [2].

تم إثبات التراكيب البنائية للمركبات الجديدة المحضرة باستخدام نواتج تحاليلها العنصرية وكذلك التحاليل الطيفية لها (طيف الأشعة تحت الحمراء ، طيف الكتلة ، طيف الرنين النووي المغناطيسي لذرة الهيدروجين).

(3) <u>تخليق مبتكر لمشتقات 3 *H*- بيرميدو(*a*- 1,6) بيرميدين :</u>

إن مركبات البيرميدوبيرميدين هي نوع من المركبات المشتقة من اليوراسيل أو الثيويوراسيل ذات أهمية بيولوجية كبيرة. وحديثا ، وجد أن مركبات البيرميدوبيرميدين – مشابهات حمض الفوليك (أحد أنواع فيتامين B والتي تعتبر المفتاح في تخليق الأحماض النووية DNA، RNA) تستخدم كمضادات للأورام. لذا ، فإن صهر مركب 6-أمينو ثيويوراسيل مع أملاح الصوديوم فورميل للكيتونات الحلقية (2) في وجود أسيتات البيريدين وحمض الأستيك أعطت وبنواتج تفاعل معقولة مركبات البيرميدو(*a*- 1.6) بيرميدين الملتحمة (**16 a-d**) كما هو موضح في المخطط [3].

تم إثبات وجود المركبات (16) بناءاً على نواتج التحاليل العنصرية والطيفية لها.

ولتأكيد وإثبات هذه الظاهرة تم عمل محاولة ناجحة لتفاعل مركب 6-أمينو ثيويوراسيل مع أملاح الصوديوم فورميل للكيتونات المفتوحة (11) ، (13) تحت نفس ظروف التفاعل لتعطى

مركبات 4- ميثل- 6- ثيواكزو- 7،6- داي هيدرو- *H*8- بيرميدو(*a*- 1,6) بيرميدين-8-أون (17) و 4- فنيل-6- ثيواكزو- 6 ،7- داي هيدرو- *H*8- بيرميدو(*a*- 1,6) بيرميدين-8- أون (18) كل على حده.

تم إثبات التراكيب البنائية للمركبات المحضرة عن طريق نواتج تحاليلها العنصرية وكذلك التحاليل الطيفية لها (طيف الأشعة تحت الحمراء ، طيف الكتلة ، طيف الرنين النووي المغناطيسي لذرة الهيدروجين).

بسم الله الرحمن الرحيم

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

صدق الله العظيم

الجماهيرية العربية الليبية الشعبية الاشتراكية العظمى

جامعة التحدي

سرت

إن الجامعة ليست غاية في حد ذاتها وإنما الغاية هي خلق الإنسان الثوري الجديد

التاريخ : 2008/7/18

الموافق : ....

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كلية العلوم

قسم الكيمياء

عنوان البحث

تخليق مركبات جديدة ذات صلة بالبيورين والمتوقع لها نشاط بيولوجي

مقدمة من الطالبة

نجديدة بشير الشيباني

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للطالبة

تجديدة بشـــير الشيباني عمـــر

تحت إشراف

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