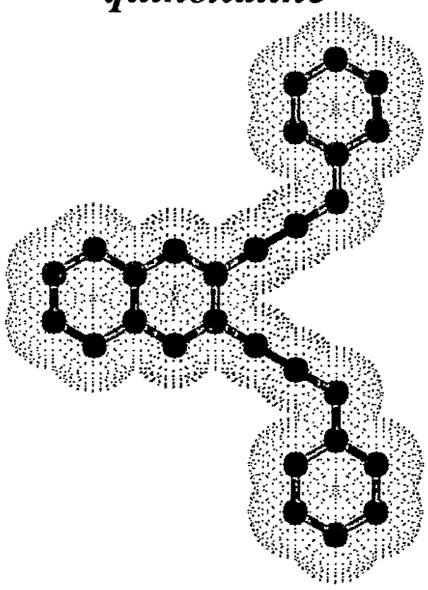
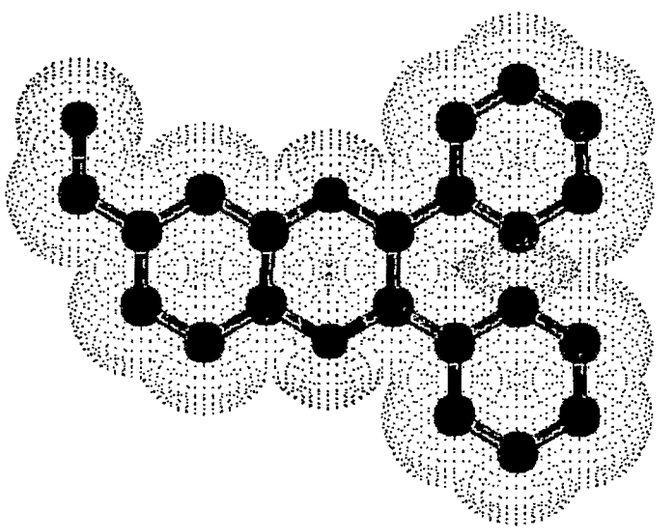
Chapter IV

Part-I Synthesis of Bis-amino benzylidene hydrazino quinoxaline



Part-II Synthesis of 2,3-diphenyl-7-(2-carbethoxy-2-cyano ethylene) quinoxaline



Part I

Solvent free synthesis of 2,3-bis (benzylidene hydrazino) quinoxalines under microwave irradiation

Introduction:

Hydrazones exhibit various biological activities.[1,2] Several diazo, hydrazine derivative are also found to be good CNS active oxidaze inhibitors[3,4] and antibacterial agents. On the other hand compounds having quinoxaline nuclei have been reported to exhibit a variety of biological activities[5]. With a view to assess the potential of hydrazine derivatives of type 3a-h, we report the microwave synthesis and anti-microbial effect of some new hydrazino-substituted quinoxaline

Previous work:

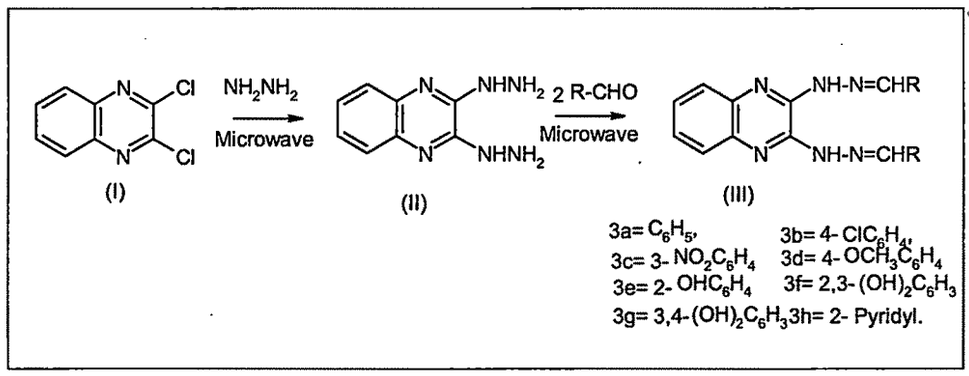
O. Hampel and et al reported synthesis of benzylidene hydrazine quinoxaline by conventional heating method using different aromatic aldehydes.[6]

Present work:

Recently, microwave assisted reactions have been highlighted due to their short reaction times compared to those of the conventionally heated reactions.[7]. Therefore, we have used the microwave as an energy source in our reaction. We found that quinoxalines could be obtained in high yields within one min under microwave irradiation without using a solvent. The method is found to be Eco-friendly for the synthesis of quinoxalines.

The target hydrazine derivatives of substituted quinoxalines was prepared by the treatment of chloro compound with hydrazine hydrate in ethanol, which on condensation with aromatic aldehehydes under microwave without using a solvent yielded 2,3-bis-(benzylidene hydrazino) quinoxaline 3a-h (scheme IV table I)

Scheme IV



Result and discussion:

2,3-Bis-(benzylidene hydrazino) quinoxalines obtained by conventional thermal heating using ethanol as a solvent resulted low yields[17]. Therefore, we have used the same reactions under microwave irradiation, and found that the yields were increased from 65% to 82 % (entry 3a-3h). In the proposed work, we have used different aromatic aldehydes for the synthesis of desired 2,3-bis-(benzylidenehydrazino) quinoxalines.

IR spectrum of compound (II) shows a sharp doublet at 3286 and 3190 cm^{-1} due to NH str. of NH_2 respectively. The compound (II) on condensation with aldehydes there are IR band disappear and another observed at 3299 cm^{-1} due to NH str. The ^1H NMR spectrum of compound (II) exhibited a broad signal at δ 4.22 due to NH_2 protons and another at δ 6.5 the characteristics of NH proton. The compound, on

condensation with aldehydes gave the hydrazones (III) which showed the disappearance of NH_2 proton signal, while that of NH signal shifted at δ 9.15-10.2 because of deshielding effect of HC=N- group in all compounds. The proton of azomethine (-N=CH-) exhibited a sharp singlet between δ 8.5-10.5 in all compounds.

Thus, we have developed an efficient, simple and eco-friendly method for the synthesis of 2,3-bis-(benzylidenehydrazino) quinoxalines from variety of different aromatic aldehydes with microwave technology. The synthetic route mainly emphasizes the MW reaction conditions, simple works up procedure resulting with clean products. As compared with conventional thermal heating, microwave irradiation decreased the reaction time from several hours to several minutes. To the best of our knowledge, this is one of the quickest, economical and simple alternatives towards the synthesis of 2,3-bis- (benzylidene hydrazino) quinoxalines.

Table I: Micro wave assisted reactions of 2,3- Bis hydrazino quinoxaline with aromatic aldehydes:

Entry	R	Temp.	M.P.(°C)	Yield
3a	C_6H_5	70	194	70
3b	4-ClC_6H_4	70	242	72
3c	3-$NO2C_6H_4$	70	213	68
3d	4-$MeOC_6H_4$	70	164	75
3e	2-OHC_6H_4	70	173	78
3f	2,3-$(OH)_2C_6H_3$	70	234	79
3g	3,4-$(OH)_2C_6H_3$	70	230	59
3h	2-Pyridyl	70	245	69

All reactions were carried in 1 mmol scale.

[c] Conventional thermal heating.

Table II- NMR spectral data of compound 3a-3h:

No	R	X	CH	NH	Ar-H
				δ (ppm)	
3a	C_6H_4	-	8.94(s,2H)	11.4(s,2H)	7.2-7.8(m,14H)
3b	$2NO_2C_6H_4$	-	8.4(s, 2H)	8.6(s,2H)	7.1-7.7(m,12H)
3c	4-Cl-C_6H_4	-	8.6(s, 2H)	9.78(s,2H)	6.9-7.9(m,12H)
3d	$4OMeC_6H_4$	3.85(s,6H)	8.7(s, 2H)	8.95(s,2H)	7.1-8.3(m,12H)
3e	2-OHC_6H_4	4.6(s,2H)	8.5(s, 2H)	9.8(s,2H)	6.9-8.1(m,12H)
3f	$2,3(OH)_2C_6H_3$	4.5(s,4H)	8.4(s, 2H)	9.1(s,2H)	6.7-8.7(m,10H)
3g	$3,4(OH)_2C_6H_3$	4.17(s,4H)	8.6(s, 2H)	8.51(s,2H)	7.0-7.5(m,10H)
3h	2-Pyridyl	-	8.6(s, 2H)	8.04(s,2H)	7.7-8.9(m,12H)

Experimental:

Specially fabricated mono-mode microwave reactors provide with homogeneous heating, temperature control and more importantly, improved safety features were used[8-11].

Synthesis of 2,3-bis (Benzylidenehydrazino) quinoxalines: (General procedure)

2,3-Bis- (hydrazino) quinoxaline 0.20 g (1mmol) and aldehyde 0.40 g (2 mmol) with 0.5 ml of hydrochloric acid were irradiated under microwave for one min. After completion of reaction (monitored by TLC), the reaction mixture was cooled to room temperature and the product obtained was filtered and recrystallized from methanol to afford desired compound.

Synthesis of 2,3-Bis-(benzylidenehydrazino) quinoxaline (3a):

^{1}H NMR (300 MHz DMSO-d_6): δ 7.20 – 7.37 (m, 4H, Ar-H),
7.48 d , 2H , Ar-H), 7.65 – 7.84 (m , 4H , Ar-H),
7.88 (m, 4H , Ar-H), 11.4 (s , 2H, NH),
8.93-8.99 (s , 2H , CH)ppm. **[Fig.1]**

2,3-Bis-(2-nitrobenzylidenehydrazino)quinoxaline (3b):

Yield: (0.15 g, 68%), brownish crystal. M.P. 242°C.
IR (KBr):ν_{max} 1570-1540, 3058, 1675, 1620, 1600, 1470 cm^{-1}.
^{1}H NMR (300 MHz DMSO-d_6): δ 6.75 – 6.83 (m, 4H, Ar-H),
7.0 9 d , 2H , Ar-H), 7.25 – 7.28 (m , 4H , Ar-H),
7.50 (d , J = 7.5 Hz, 2H , Ar-H), 8.5 (s , 2H, NH),
8.3-8.4 (s , 2H , CH)ppm. [**Fig.2**]

2,3-Bis-(4-chlorobenzylidenehydrazino) quinoxaline (3c):

IR (KBr):ν_{max} 3237, 1686, 1537, 1421, 1363, 1265, 1158,
825 cm^{-1} [**Fig.3**]
^{1}H NMR (300 MHz DMSO-d_6): δ 6.91-6.98 (m, 4H, Ar-H),
7.19 d , 2H , Ar-H), 7.74 – 7.77 (m , 4H , Ar-H),
7.90(m, 4H , Ar-H), 9.9 (s , 2H, NH),
8.69 (s , 2H , CH)ppm. **[Fig.4]**

2,3-Bis- (4-methoxybenzylidene-hydrazino) quinoxaline (3d):

Yield 0.175 g, 75%) Orange Crystals. M.P. 164°C.
IR (KBr):ν_{max}3412, 2920, 1661, 1608, 1585, 1487, 1367,
1178 cm^{-1}.[**Fig.5**]
^{1}H NMR (300 MHz DMSO-d_6): δ 3.85 (s , 6H, O-CH_3), 7.1-7.9 (m ,
4H , Ar-H), 7.20-7.25 (m , 2H , Ar-H), 7.75-7.85 (m , 2H , Ar-H),
8.03 (d , 4H , J = 8 Hz, Ar-H), 8.76 (bs , 2H, NH),

8.95 (s , 2H , CH)ppm.

GCMS :(M+) 428, 366, 291, 212, 128 [**Fig.6**]

2,3-Bis-(2-hydroxybenzylidene hydrazino)quinoxaline(3e):

Yield: (0.18 g, 78%) Red crystals. M.P. 173°C.

IR (KBr):ν_{max} 3411, 2919, 1660, 1608, 1585, 1487, 1252 cm^{-1} [**Fig.7**]

^1H NMR (300 MHz, DMSO-d6): δ 4.6 (s , 2H , OH),

6.94 (t , 2H, J = 7.5 Hz, Ar-H), 7.05 (d , 2H , J = 8 Hz, Ar-H),

7.22-7.25 (m , 2H , Ar-H),7.35 (t , 2H , J = 7.5 Hz, Ar-H),

7.75-7.79 (m, 2H , Ar-H), 8.19 (d , 2H , J = 6.8 Hz, Ar-H),

8.5 (s , 2H , NH), 9.8 (s , 2H , CH)ppm.

GCMS (M+) : 399, 383, 265, 251, 178, 133 [**Fig.8**]

2,3-Bis-(2,3-dihydroxy benzylidenehydrazino)quinoxaline:

Yield: (0.186 g, 82%) Orange red crystal. M.P. 238°C.

IR (KBr):ν_{max} 3340, 2930, 2830, 1650, 1630, 1550, 1430 cm^{-1}.

^1H NMR (300 MHz DMSO- d_6): δ 4.05 (s, 1H , OH),

6.7-6.8(m, 2H, Ar-H), 7.2(d, J = 7.7 Hz, 2H, Ar-H),

7.24-7.28 (m, 2H, Ar-H), 7.56 (d, J = 7.7 Hz, 2H, Ar-H),

7.70-7.74 (m, 2H, Ar-H), 8.76 (bs, 2H, NH),

8.95 (s, 2H,CH) ppm.

2,3-Bis-(3,4-dihydroxybenzylidene hydrazino)quinoxaline

Yield: (0.13 g, 59%) red crystal. M.P. 230°C.

IR (KBr):ν_{max} 3010, 2972, 1671, 1654, 1639, 1597, 1517, 1283 cm^{-1}.

^1H NMR (300 MHz DMSO-d_6): δ 4.15(4H, OH),

6.71 (d , J= 8.2 Hz, 2H , Ar-H),7.0-7.12 (m, 4H, Ar-H),

7.35 (s, 2H, Ar-H), 7.50-7.56 (m, 2H, Ar-H),

8.69 (bs , 2H, NH), 8.51(s, 2H, CH), ppm.

2,3-Bis(2-pyridylmethylidene hydrazino)quinoxaline

Yield: (0.15 g, 69%) red crystal. M.P. 245°C.

IR (KBr):ν_{max} 3371, 3015, 2921, 1652, 1602, 1535, 1453 cm^{-1}.

^1H NMR (300 MHz DMSO-d_6): δ 7.29-7.41 (m , 3H , Ar-H),

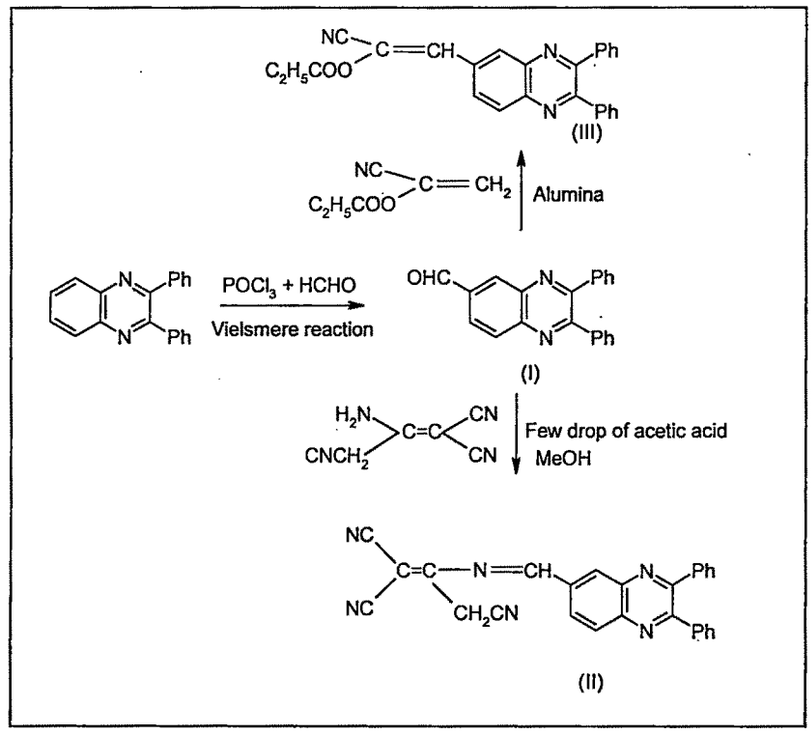
8.17-8.21 (m, 3H, Ar-H), 8.58-8.64 (m,3H, Ar-H),

8.89-8.95 (m, 3H,Ar-H), 8.6 (bs , 2H, NH), 8.04(s, 2H, CH), ppm.

Part II

Synthesis of 2,3-diphenyl-7-(2-carbethoxy-2-cyano-ethylene) quinoxaline

Scheme IV a



Result and discussion:

The synthesis of compound (I) has been reported by Vilsmeier reaction. The structure of the compound was confirmed by sharp peak at 1704 cm^{-1} due to C=O (aldehyde). The compound (I) on reaction with ethyl cyanoacetate using alumina gave the compound (III). The appearance of CN band at 2265 and ester C=O at 1746 cm^{-1} in IR spectrum indicated the formation of 2,3-diphenyl-7-(2-carbethoxy-2-cyanoethylene) quinoxaline. The compound (I) again on reaction with malononitrile

dimer in acetic acid gave compound (II) that confirmed by its correct PMR by observing the signal at δ 3.45 due to $-CH_2$.

Experimental:

Synthesis of 2,3-diphenyl-7-formyl quinoxaline (II):

A mixture of 2,3-diphenyl quinoxaline (2.85 mole), dimethyl foramide (6 mole) was taken in a three necked round bottom flask fitted with a sealed stirrer, reflux condenser and dropping funnel. Then phosphorus oxychloride (3.2 mole) was added slowly to the stirred mixture. It was then heated for 2 hr on an oil bath. The reaction mixture was cooled in ice bath and neutralized to Congo red by adding aq. sodium acetate. The mixture then diluted with water and allowed to stand at 0 °C for 2 hrs. The cream coloured product separated out was filtered and recrystallized from alcohol. The yield (1.5 g, 68 %), M.P. 157 °C

IR (KBr)ν_{max}: 3056, 1704, 1526, 1441, 1346, 1218, 977 cm^{-1} [**Fig.9**]

Synthesis of malononitrile dimmer complex of quinoxaline (II):

The compound (I) on reaction with malononitrile dimmer in acetic acid gave compound III.

^{1}H NMR (300 MHz DMSO-d_6): δ 1.3(s, 1H), 3.4(s, 2H), 7.2-8.5(m, Ar-H) ppm [**Fig.10**]

2,3-Diphenyl-7-(2-carbethoxy-2-cyanoethylene)quinoxaline (III):

The targeted compound was synthesized by Knoevenagel condensation. In a round bottomed flask equipped with a guard tube a mixture of 2,3 diphenyl 7-formyl quinoxaline (0.500gm, 0.323 mmole) and ethyl cyanoacetate (0.174 gm, 0.113mmole) using alumina as a catalyst was

stirred for 3-4 hrs. The progress of the reaction was monitored by TLC. Reaction mixture then was extracted with ether and removal of ether under rotary evaporator gave white crystalline solid of 2,3-diphenyl-7-(2-carbethoxy-2-cyanoethylene)quinoxaline. M.P. 207 ^{0}C

The yield (0.36 g, 72%) (Elemental analysis: Calcd. C 80.97, H 8.61, N 3.42 % Observed: C 80.90, H 8.5, N 3.4 %)

IR (KBr): ν_{max} 2985, 2604, 2265, 1746, 1633, 1446, 1371, 1197, 1027, 976, 852 cm^{-1} [**Fig.11**]

^{1}H NMR (300 MHz DMSO-d_6): δ 1.25(s, 3H), 2.03(s, 2H), 2.58 (dd, CH), 7.43-7.96 (m, Ar-H) [**Fig.12**]

References:

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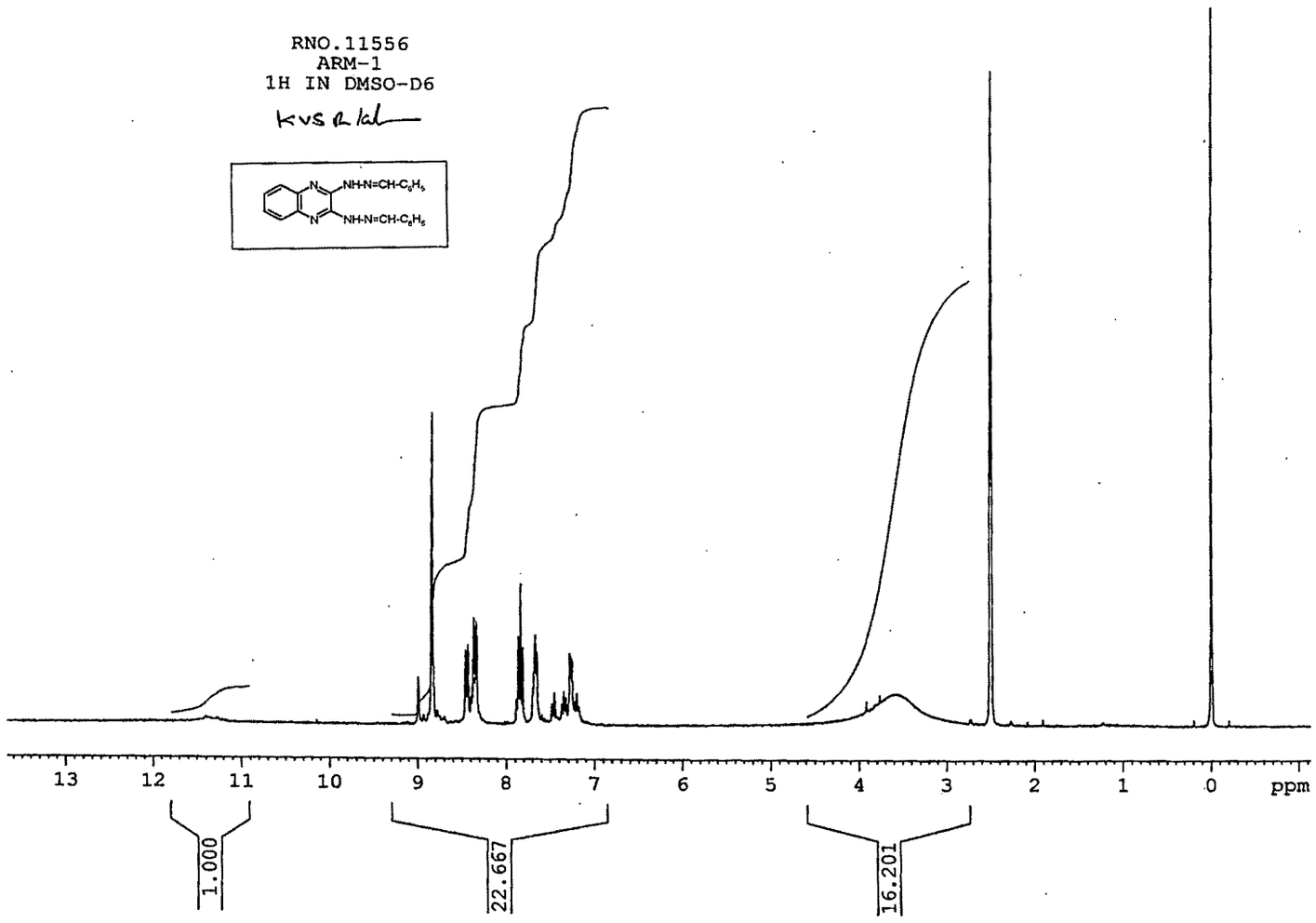


Fig. 1 NMR of 2,3-Bis (benziledene hydrazine) quinoxaline (3a)

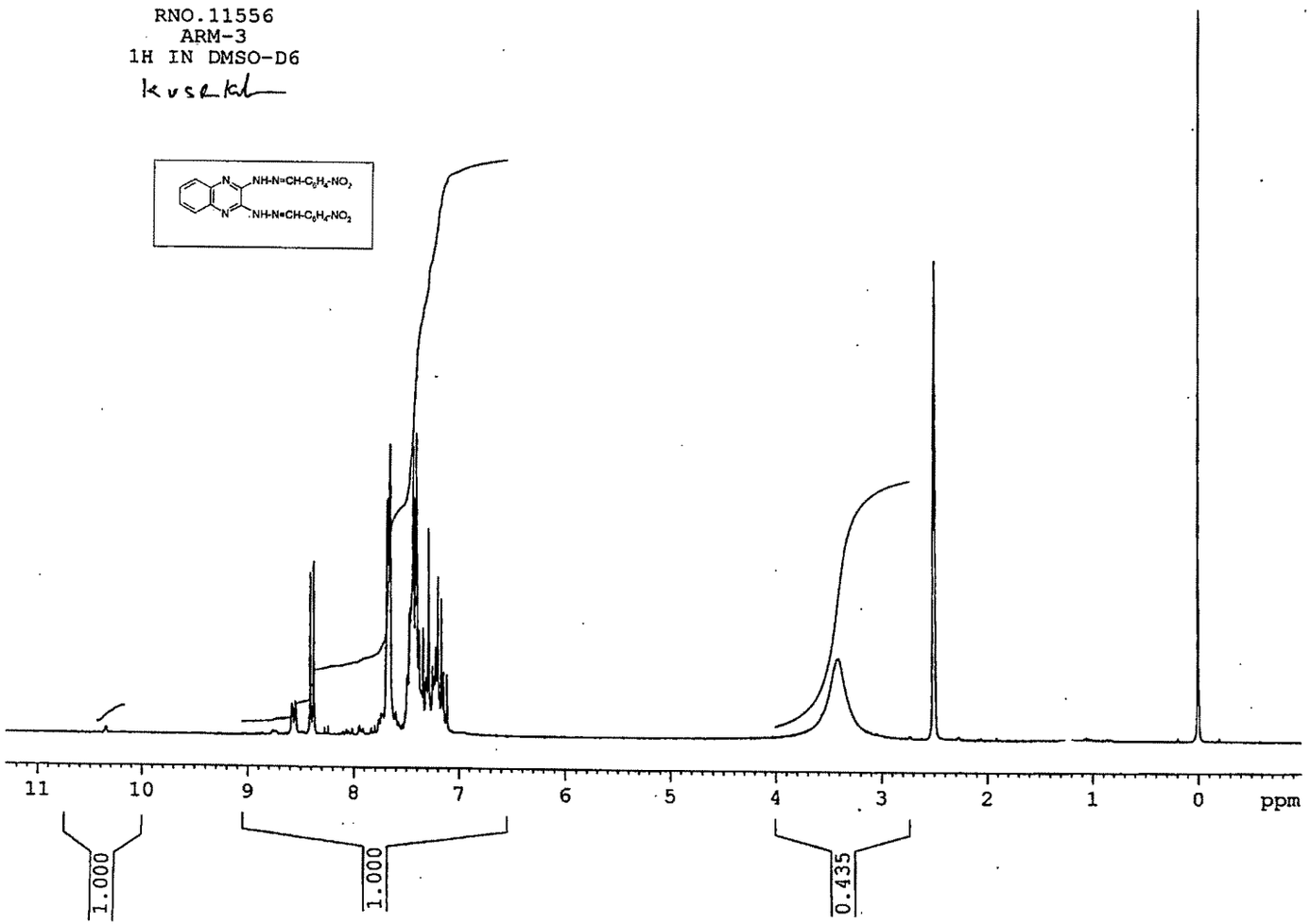


Fig. 2 NMR of 2,3-Bis (2-nitro benziledene hydrazine) quinoxaline(3b)

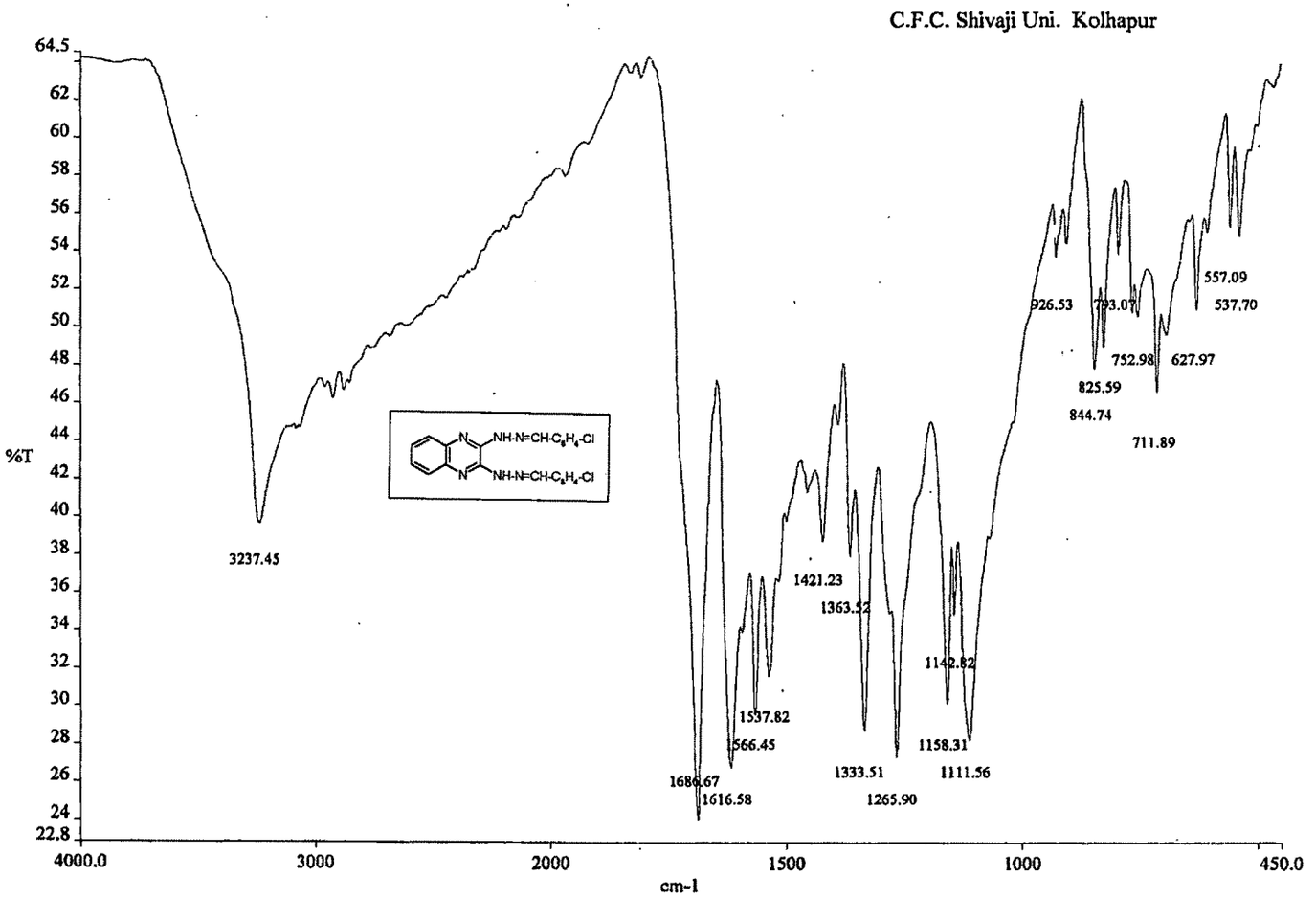


Fig. 3 IR of 2,3-Bis (4-chloro benziledene hydrazine) quinoxaline(3c)

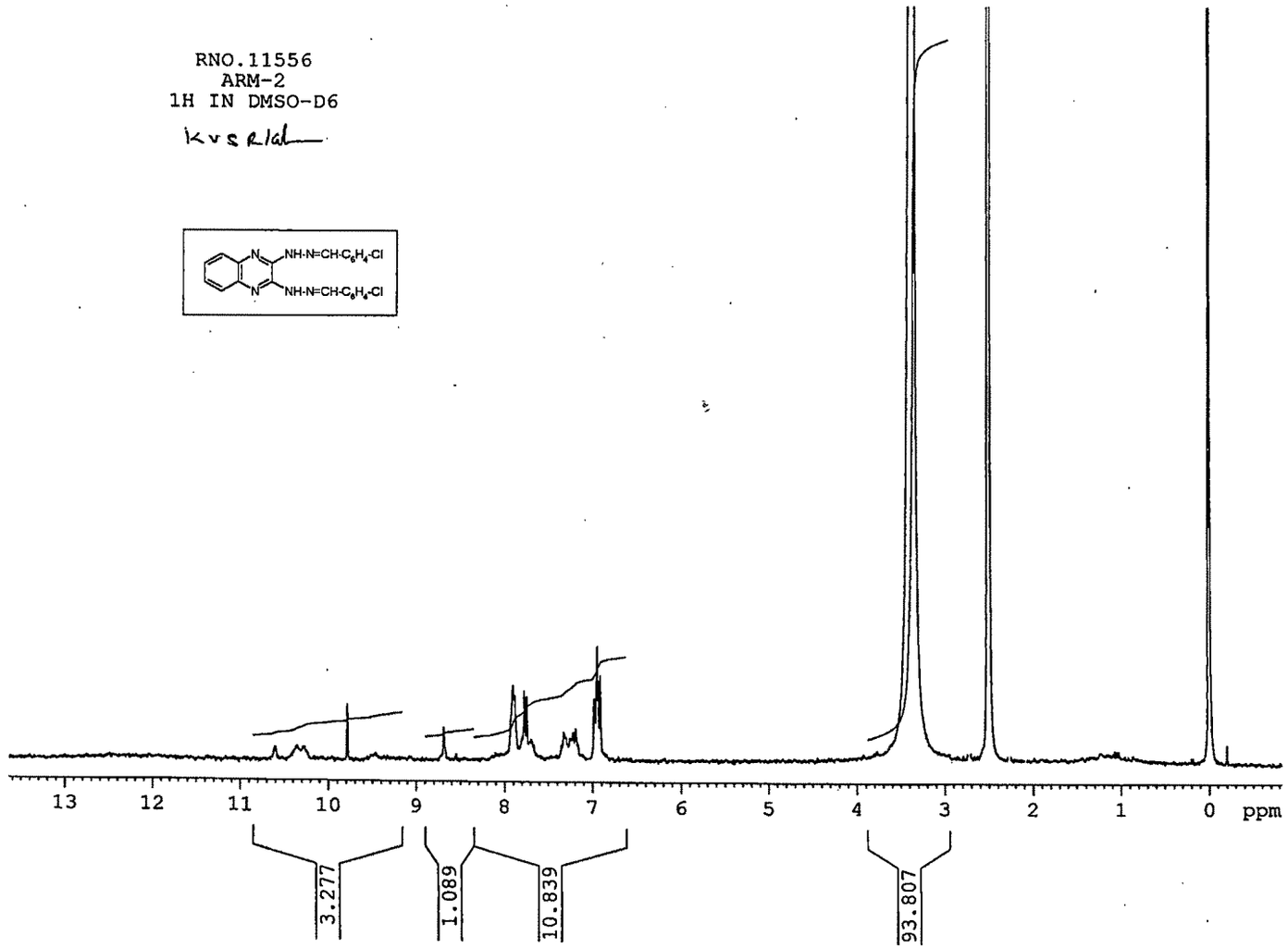


Fig. 4 NMR of 2,3-Bis (4-chloro benziledene hydrazine) quinoxaline(3c)

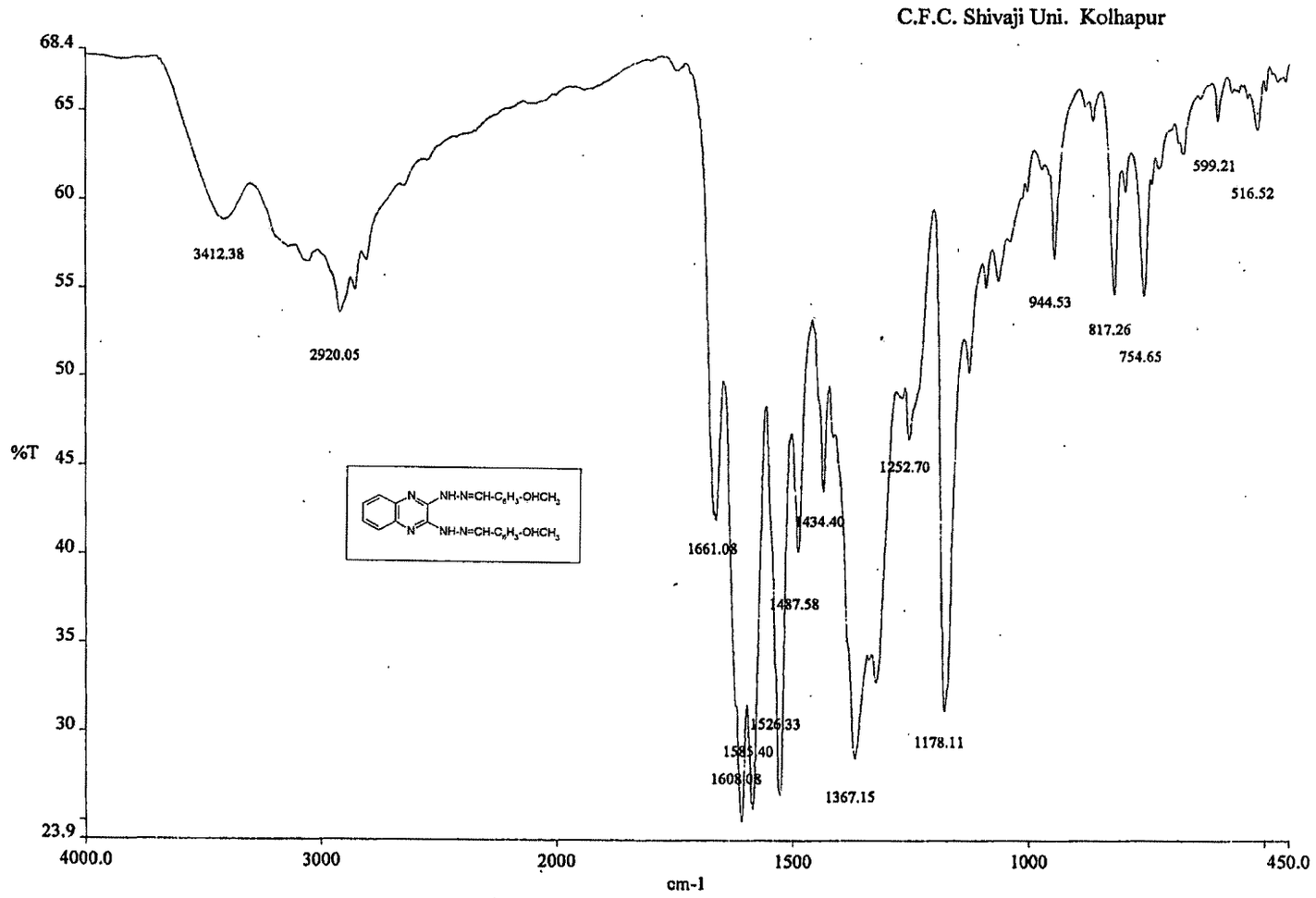


Fig. 5 IR of 2,3-Bis (4-methoxy benziledene hydrazine) quinoxaline(3d)

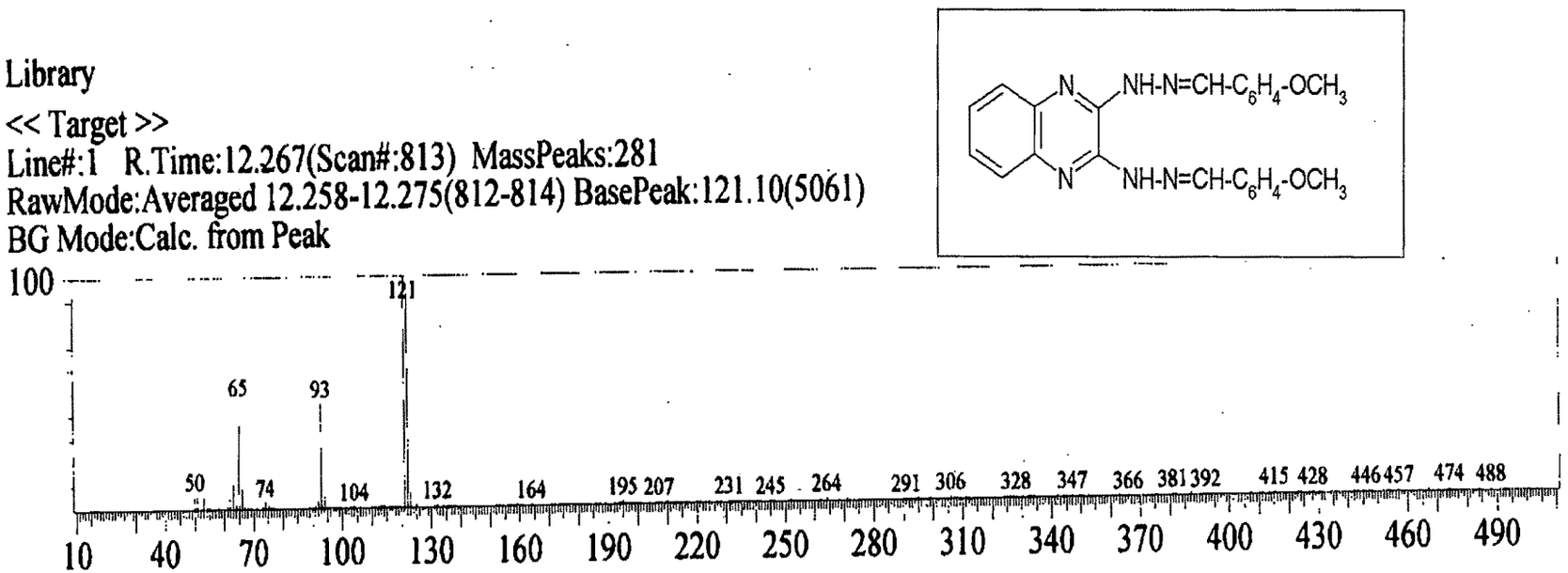


Fig. 6Mass spectra of 2,3-Bis (4-methoxy benziledene hydrazine) quinoxaline(3d)

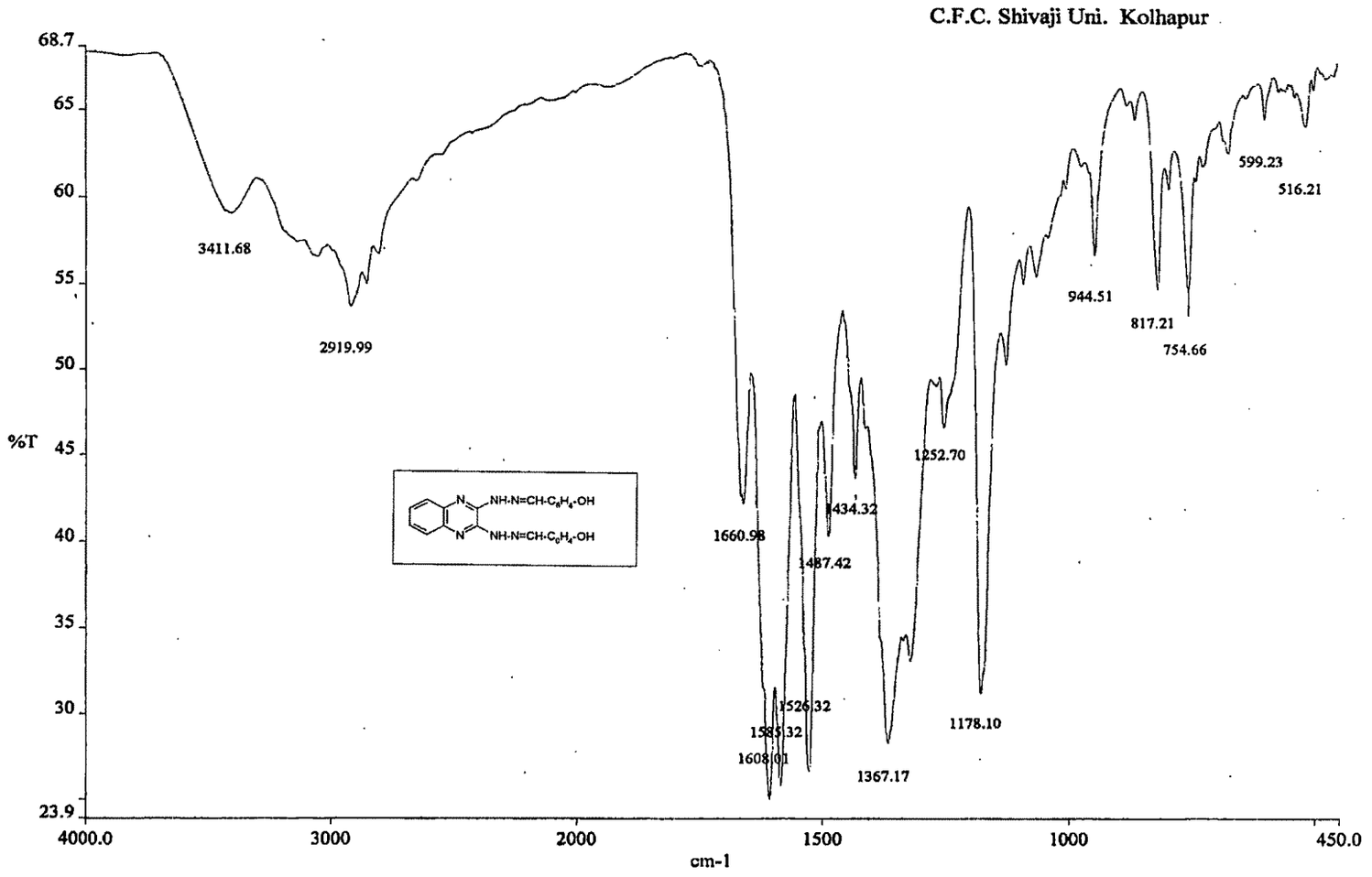
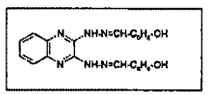


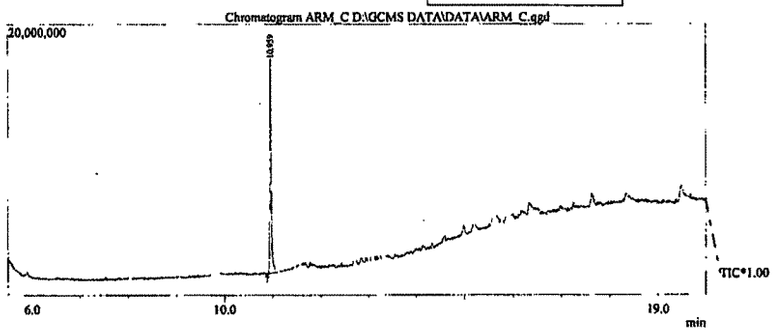
Fig. 5 IR of 2,3-Bis (2-hydroxy benziledene hydrazine) quinoxaline (3e)

SHIVAJI UNIVERSITY, Kolhapur
Common Facility Center

Sample Information

Analyzed by	: Admin
Analyzed	: 1/16/2007 1:00:13 PM
Sample Name	: ARM_C
Sample ID	: ARM_C
Injection Volume	: 1.000
Data File	: D:\GCMS DATA\DATA\ARM_C.qgd
Method File	: D:\GCMS DATA\METHODS\mali.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\PFTBA.qgt





Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Name
1	6.409	6.325	6.533	26054732	15.92	
2	6.698	6.650	6.775	11757853	7.18	
3	10.959	10.883	11.075	32280446	19.72	
4	11.216	11.075	11.425	31551340	19.27	
5	11.563	11.325	11.633	11043626	6.75	
6	13.068	13.000	13.167	9028579	5.52	
7	15.625	15.517	15.725	13280040	8.11	
8	15.886	15.817	16.042	19284532	11.78	
9	16.336	16.208	16.375	9412009	5.75	
				163693377	100.00	

Fig. 7 GC of 2,3-Bis (2-hydroxy benziledene hydrazine) quinoxaline (3e)

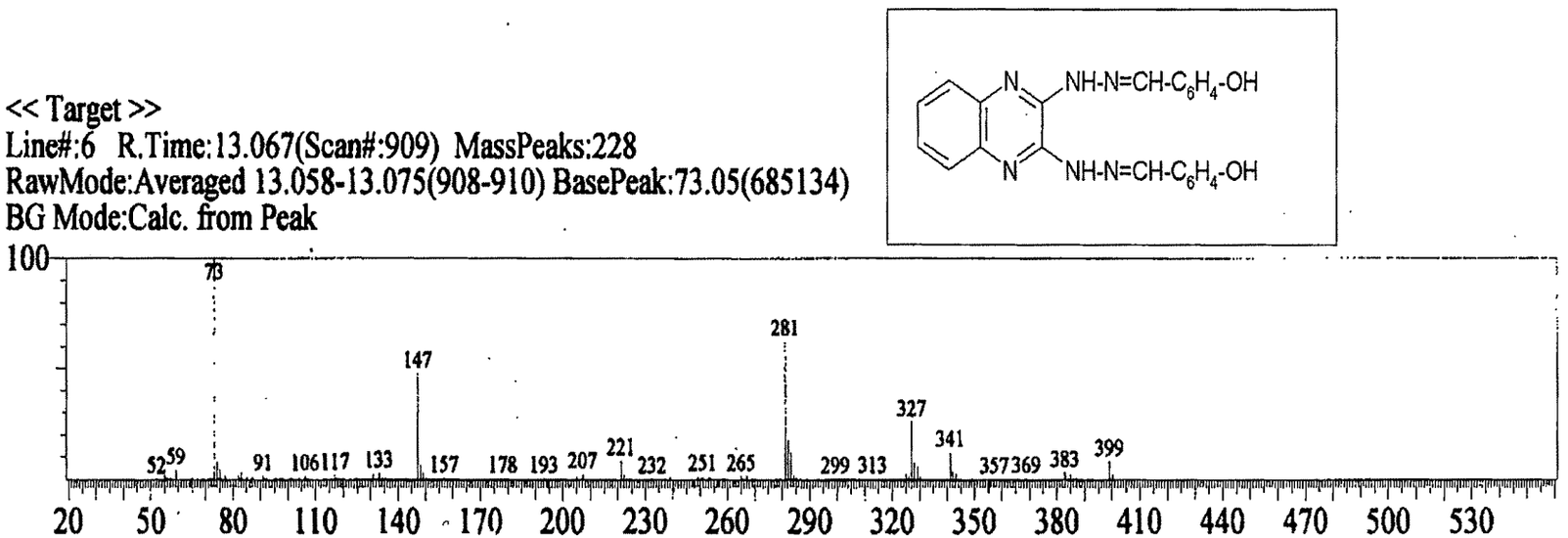


Fig. 8 Mass spectra of 2,3-Bis (2-hydroxy benziledene hydrazine) quinoxaline (3e)

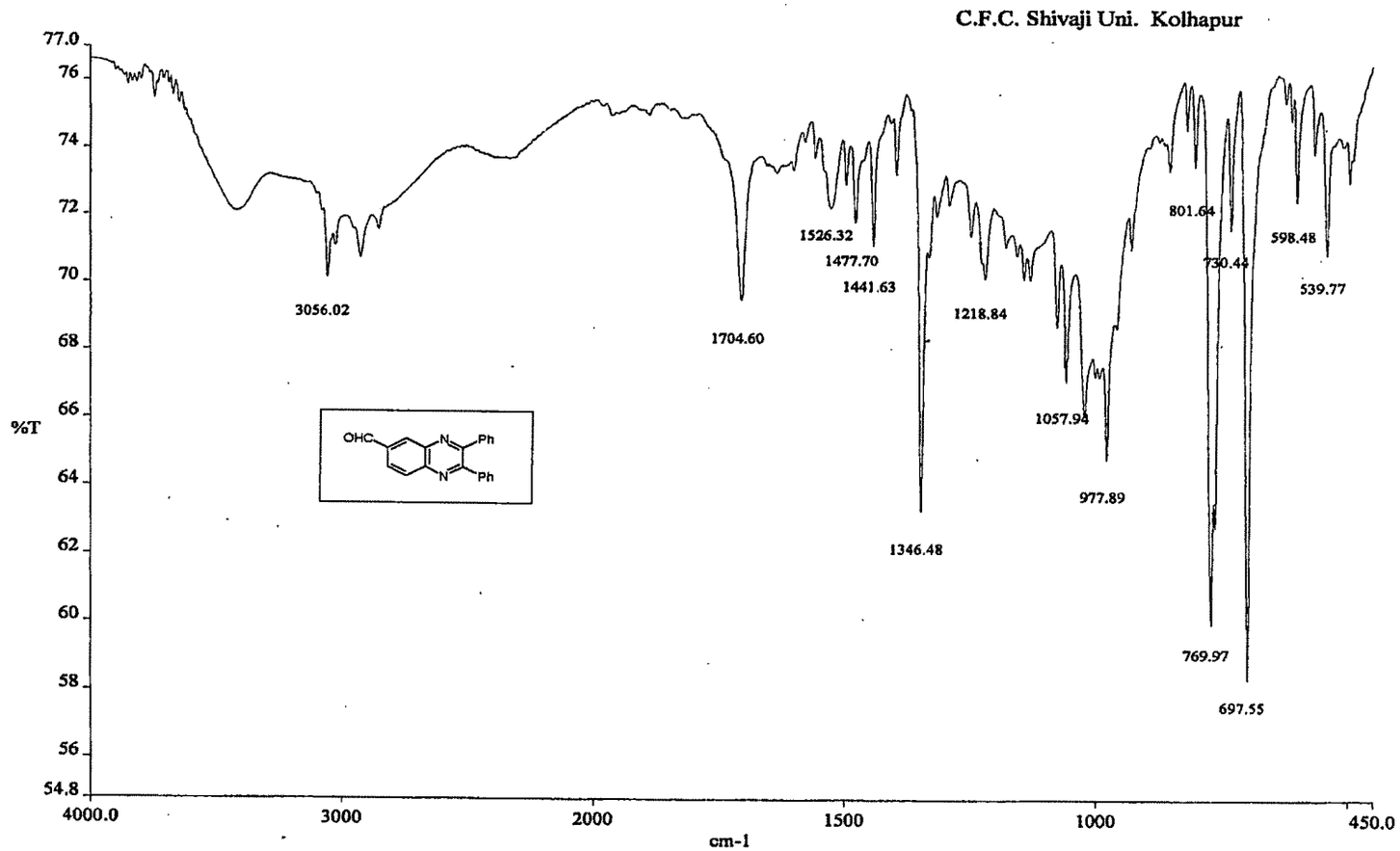


Fig. 9 IR of 2,3-diphenyl-7-formyl quinoxaline (II)

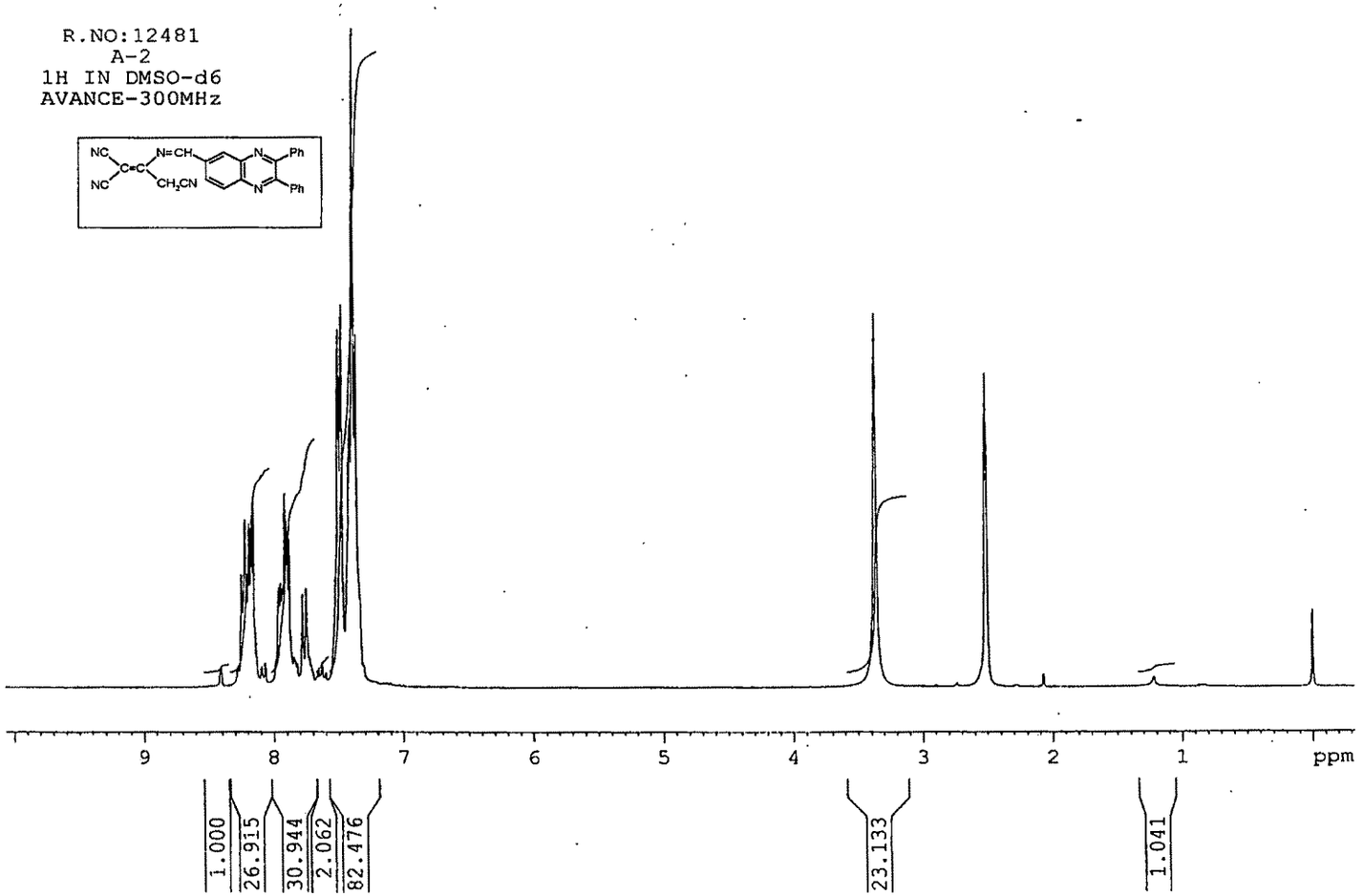


Fig. 10 NMR of Malononitrile dimmer complex of quinoxaline

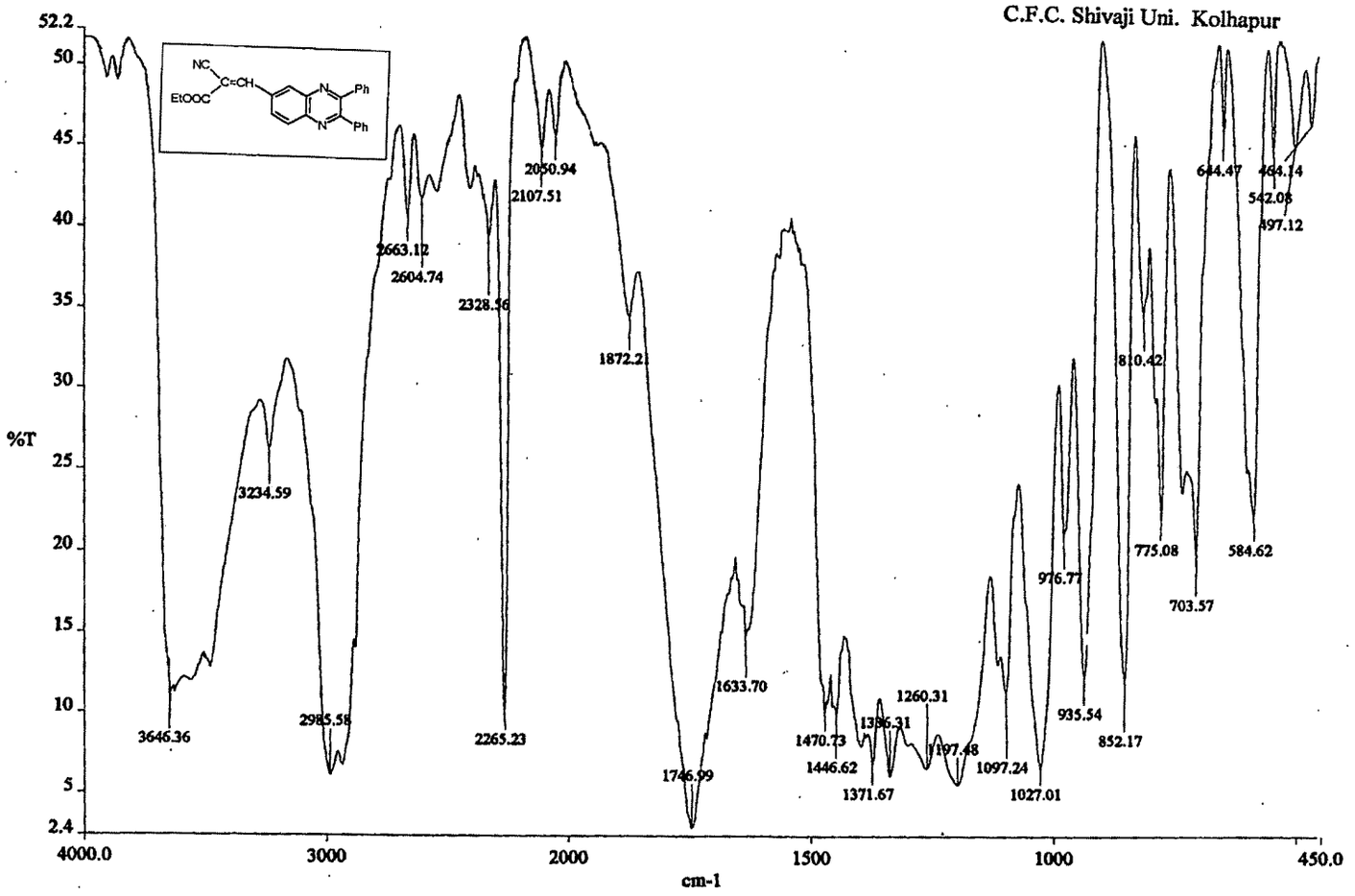


Fig. 11 IR of 2,3-diphenyl-7-(2-carbethoxy-2-cyanoethylene) quinoxaline (III)

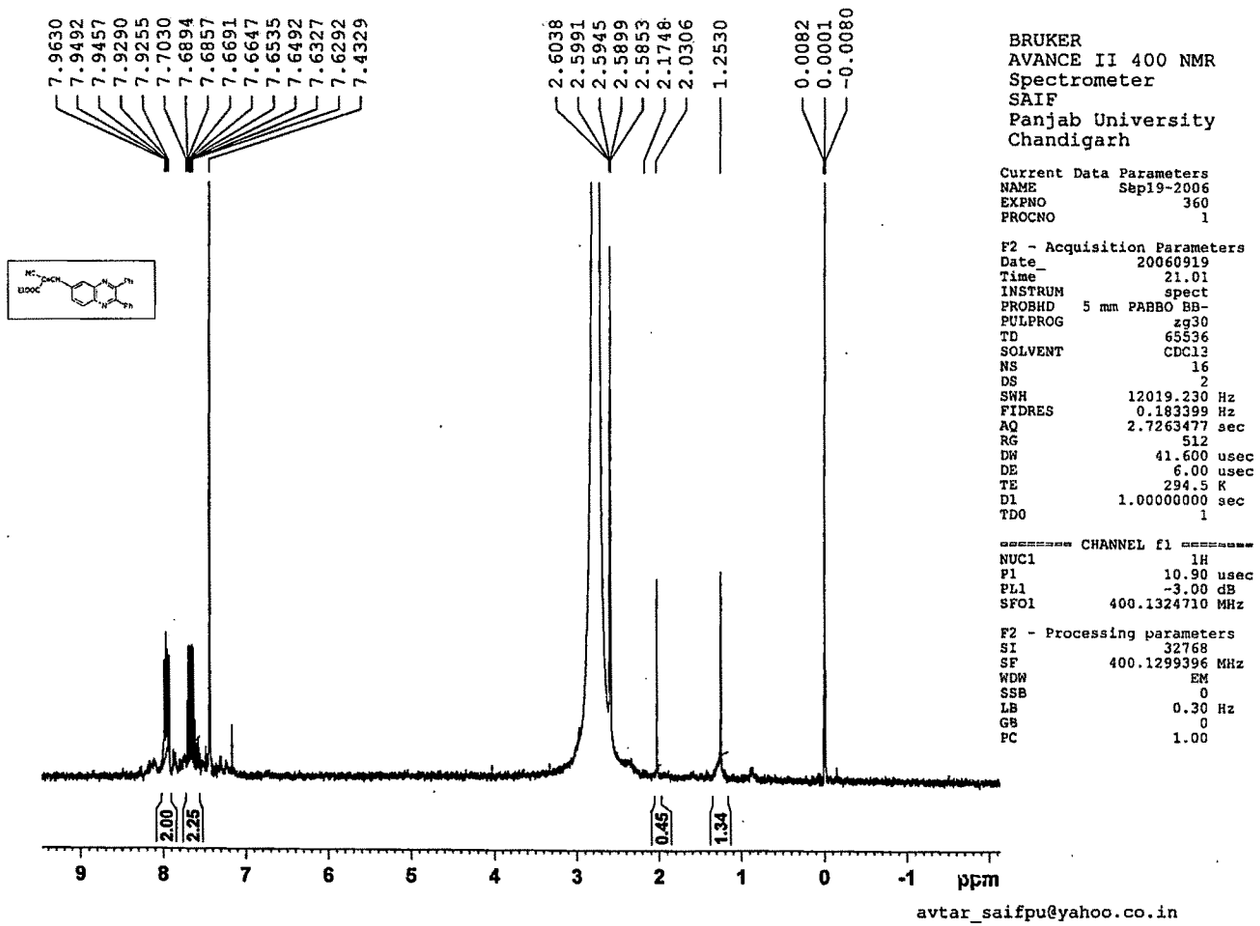


Fig. 12 PMR of 2,3-diphenyl-7-(2-carbethoxy-2-cyanoethylene) quinoxaline (III)