Synthesis of 5,6-Disubstitued Pyrimidines of Biological Importance

A Dissertation submitted in the partial fulfilment of the requirement for the Degree of Master of Philosophy (M.Phil) in Chemistry.

Submitted by
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The present studies are directed towards the development of novel methodologies for the synthesis of 5, 6-disubstitued pyrimidines.

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Tanvir Sultana

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Date: 20/09/2006

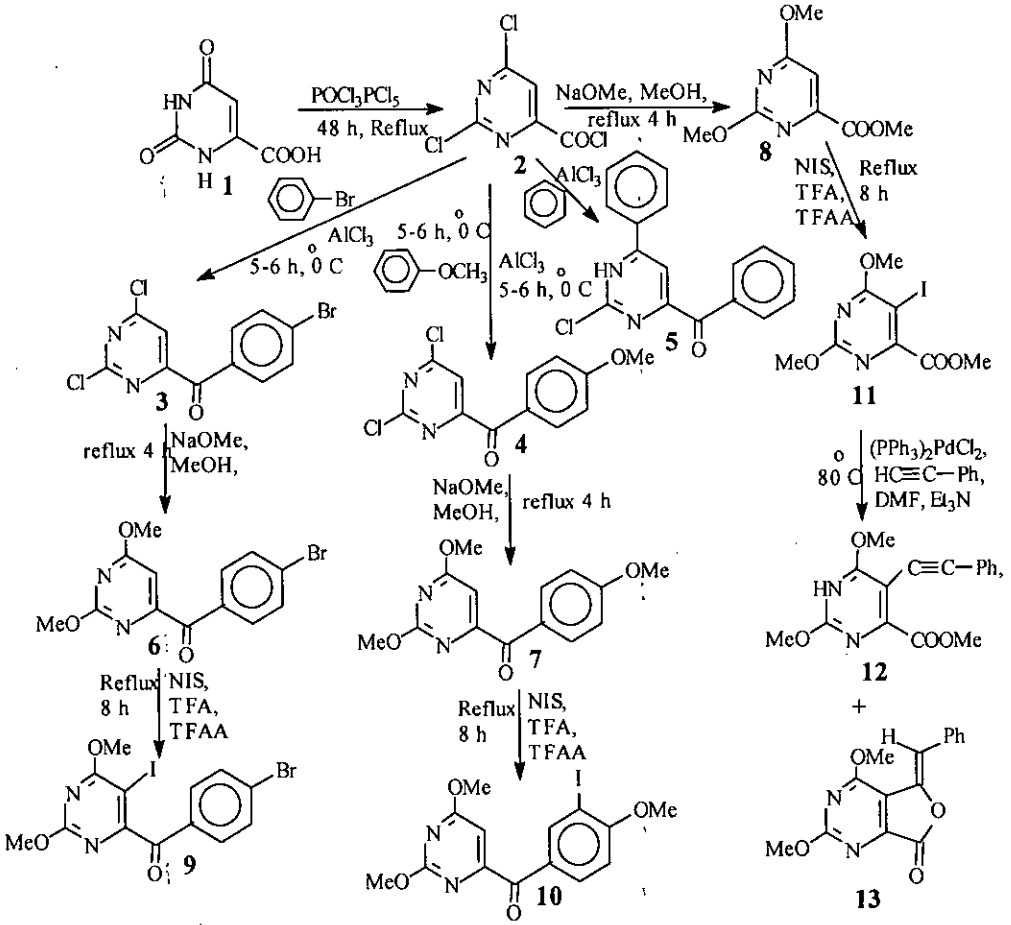
Contents

Iodination

Thesis title: Synthesis of 5, 6- Disubstituted Pyrimidines of Biological Importance

Abstract

In view of the significant biological activities of various 5 and 6- substituted uracils and related pyrimidine derivatives, a facile method for the synthesis of a number of 5, 6-disubstituted pyrimidines was developed (Scheme-1). 2, 4-Dichloro pyrimidine -6-carbonyl chloride **2** was synthesized by refluxing orotic acid **1** with phosphorus oxychloride and phosphorus pentachloride. Compound **2** underwent a smooth Friedel-Crafts reaction with a number of substituted benzene derivatives. 2, 4 Dichloro-6-*p*-bromobenzoyl pyrimidine **3** and 2, 4- dichloro-6-*p*-methoxy benzoyl pyrimidine **4** were converted to the corresponding dimethoxy pyrimidine 6 & 7 on treatment with sodium methoxide in methanol. 2, 4- Dicholoropyrimidine -6-carbonyl chloride was also converted to 2, 4- dimethyl -6-methyl orotate **8** by refluxing with sodium methoxide in methanol for 6 hr. The iodination reaction was attempted by several methods but only NIS-TFA-TFAA method gave the desired products. 2, 4-Dimethyl -5-iodo-6-*p*-bromobenzoyl pyrimidine **9** and 2, 4-dimethoxy-5-iodo-6-methyl orotate **11** were subjected to palladium-catalyzed reaction to yield 5-alkynyl substituted product and cyclized product. The structure of the synthesized products were established from their analytical and spectroscopic data.



(Scheme-1)

Prefatory Note

Analytical or laboratory grade solvents and chemicals were used in all experiments and these (orotic acid, TFA, TFAA, $(Ph_3P)_2$ $PdCl_2$, CuI, Et_3N, DMF, NIS, etc.) were procured from E. Merck (Germany) and Fluka (Switzerland). Reagent grade of chloroform, n-hexane, ethylacetate, methanol, ethanol etc. were purified by distillation at the boiling point of the respective solvent. Petroleum ether used during this research work had boiling point 40° – 60°C.

1. Purification of solvents and reagents

Dry methanol:

About 1.25gm of clean and dry magnesium turnings and 0.125 g of iodine were placed in a dry 500 ml round bottom flask containing 30 to 40 ml of reagent grade methanol. The flask was then fitted with a condenser carrying a calcium chloride guard tube on the top. The mixture was warmed until the iodine disappeared, Heating was continued until all the magnesium was converted into pasty mass methanolate. About 230 ml of commercial grade methanol was then added to the flask and refluxed the mixture for an additional hour. The resulting mixture was distilled off and the first 10 – 15 ml of distillate was discarded. Then the dry methanol was collected into a receiving flask from which it was stored into an air tight bottle.

$Mg + 2\ MeOH \rightarrow H_2 + Mg(OMe)_2$

$Mg(OMe)_2 + H_2O \rightarrow Mg(OH)_2 + 2\ MeOH$

2. Melting point

Melting points were determined on Gallenkamp (England) melting point apparatus (England) and paraffin oil bath .

3. Infra-red (IR) and UV spectra

The Infra-red spectra were recorded on KBr disc for films with a Shimadzu FTIR Spectrophotometer and the UV spectra were recorded in dry EtOH with a Shimadzu UV spectrophotometer at the Department of Chemistry, BUET, Dhaka, Bangladesh.

4. Nuclear Magnetic Resonance (NMR) Spectra

The NMR Spectroscopy is very widely used for the detailed investigation of an unknown compound. With the help of this spectroscopy the structure of unknown compound can be set up. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in deuteriochloroform ($CDCl_3$) with a Bruker DPX-400 spectrophotometer (400 MHz) using tetramethylsilane (TMS) as internal standard at the Bangladesh Council of Scientific and Industrial Research laboratories (BCSIR), Dhaka, Bangladesh and Iwate University, Morioka, Japan.

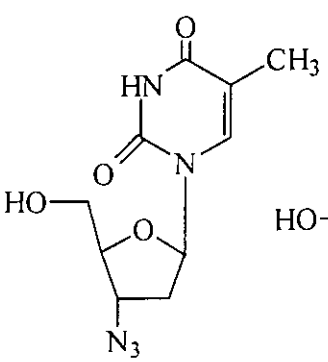
5. Drying

All organic extracts were dried over anhydrous sodium sulfate (Na_2SO_4) before concentration.

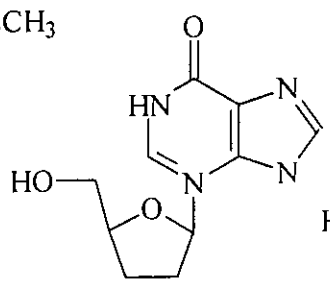
"Synthesis of 5,6-Disubstituted Pyrimidines of Biological Importance"
Background of the present work:

1.1 Introduction :

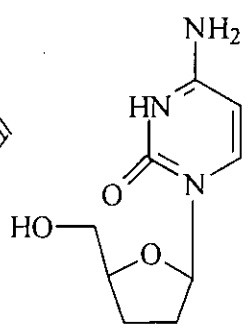
In the past few years the antiviral chemotherapy area has witnessed a remarkable production of antiviral compounds, particularly in the domain of the uracil bases and the nucleoside analogues. The acquired immunodeficiency syndrome (AIDS) was first recognized in 1981 [1] and has since become a major world wide epidemic. After the discovery that human immunodeficiency virus (HIV) is the causative agent of AIDS [2,3a-h,] numberous compounds have been reported to inhibit the application of human immunodeficiency virus (HIV) in vitro [3d,4.], yet only four agents have at this time been formally Licensed (in the USA) for clinical use in the treatment of AIDS[5]. These are zidovudine (3'-azido-2',3'-dideoxythy midine or azidothymidine 1 [AZT]; Retrovir)[6], didanosine(2',3-dideoxyinosine 2 [DD1]; videx)[7], zalcitabine (2',3'- dideoxycytidine 3 [DDC]; Hivid)[8], and stavudine (2',3'-didehydro-2',3'-dideoxy thymidine 4 [D4T]; zerit).



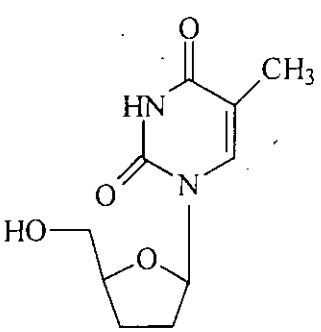
(1)
AZT, 1



(2)
DD1, 2



(3)
DDC, 3

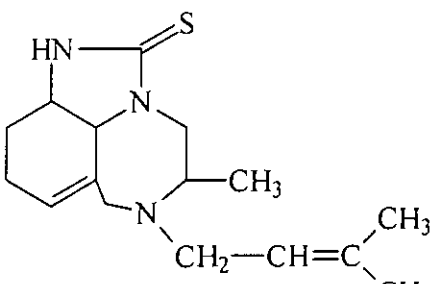


(4)
D4T, 4

The viral enzymes that have critical roles in the life cycle of the human immunodeficiency virus type-1(HIV-1) is the key target in the research for

effective drugs useful for AIDS therapy. One such enzyme is reverse transcriptase (RT) which contains both a DNA polymerase activity that can use either RNA or DNA as a template and a ribo nuclease H acivity [9,10]. A number of inhibitors of HIV-RT have been developed [11,12]. Generally these inhibitors can be divided into two classes:

1. Nucleoside analogues such as AZT **1** and DDC **3**.
2. Non nucleoside RT inhibitors (NNRT1) such as tetrahydroin dazo [4,5-I-jk] [1,4] benzodiazepin - 2 - (1H) – one (TIBO) 5 and 1 - [(2-hyroxyethoxy) methyl] – 6 - (phenylthio) thymine (HEPT) **6**.



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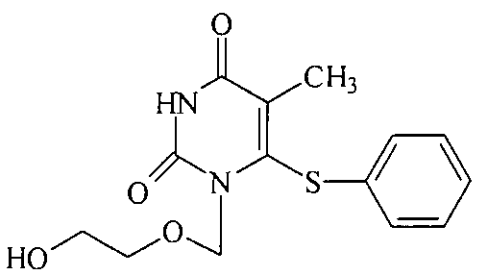


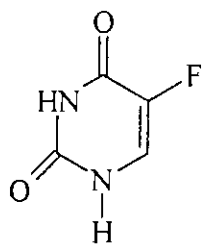
(6)

Here we shall scrutinize the Biological importance of some potent uracils and uridine derivatives substituted at C-5 and C-6 positions very briefly.

1.1.A. Biological Evaluation of 5-Substituted Uracil Derivatives and Nucleosides.

5-Flurouracil (5-Fu,7) and 5-fluoro-2′-deoxy uridine (5-Fud R, **8**) developed by Heidelberger[13,14] are used clinically for the treatment of breast colon and rectum Cancer, 5-Fu is known as an anti metabolic and believed to inhibit thymidylate synthase (TC) enzyme.

5-Iodo-2′-deoxyuridine (IDU, **9**) is utilized clinically in the tropical treatment of herpes simplex keradtitis [15], a sighttreatening eye infection . It is also effective against mucocutaneous HSV infection and vaccinia virus (VV).



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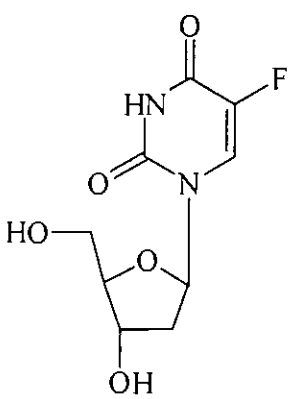

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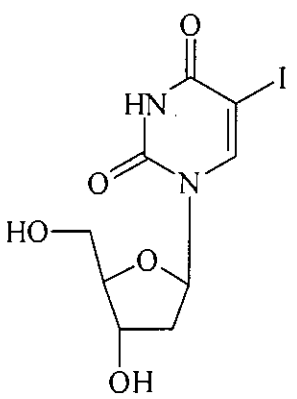
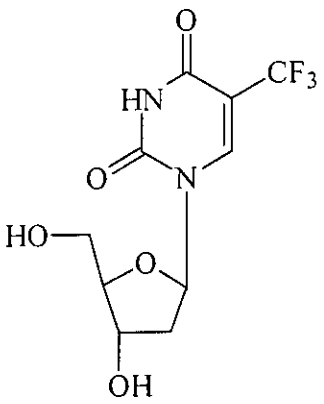


(9)

5-Trifluoromethyl-2′-deoxyuridine (TFT **10**) is an effective inhibitor of HSV[16] and used in the treatment of herpetic Keratitis, TFT, **10**, also exhibited in vitro action against human cytomegalo virus (HCMU)[17].

[E]-5-(2-bromovinyl) - 2′- deoxyuridine (BVDU,**11**) is the powerful inhibitor of HSV-1, VZV and pseudorabies virus,[18].BVDU,**11** is also active against bovid herpes virus type -1(BHV-1), simian varicella virus (SVV) and nuclear poly hedrosis virus (NPV)[18]. Robins et al[19] synthesized various 5-alkynyl -2′-deoxyuridines and observed that 5-ethynyl -2′-deoxyuridine **12** exibited excellent anticancer properties. (ID_{50} = 0.091 μg/ml in L1210

cells) and antiviral properties[20] against HSV-1 (ID_{50} = 0.6μg/ml), HSV 2 (ID_{50}=1.5μg/ ml) in all primary rabbit kidney cells in culture.



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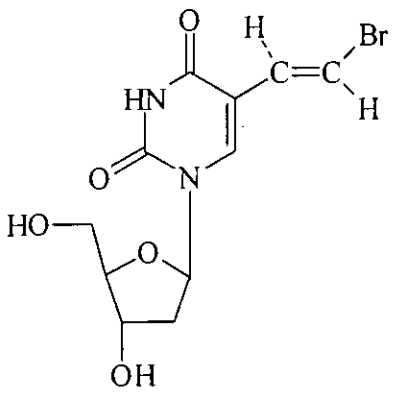

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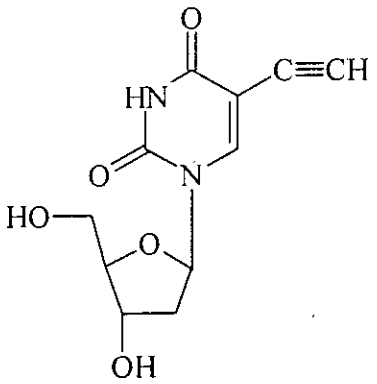
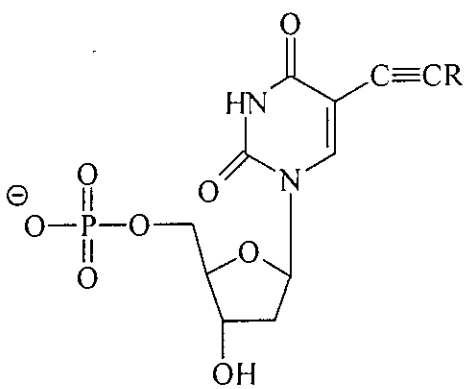


(12)

The 5-alkynyl -2′-deoxyuridines-5′-monophosphates 13 were found to be good inhibitors of T.S enzyme the 5-ethynyl derivative being the most effective [21] (Table-1).

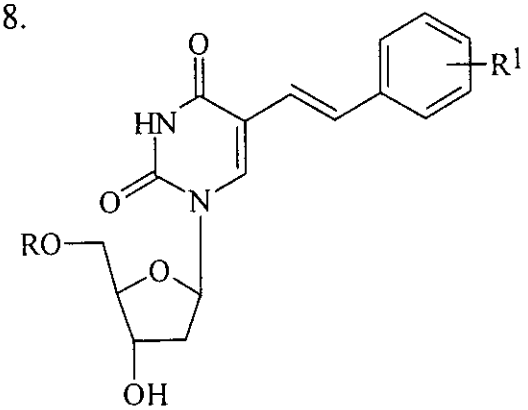
Table-1: Inhibition of TS enzyme by compound13.



(13)

	R	Ki (uM)
13a	H	0.1
13b	CH_2OH	3.0
13c	CH_2CH_2OH	1.9
13d	*n*-Bu	2.6
13e	Ph	2.0

A number of 5-styrul derivatives 14 a-c of d-Urd and d-UMP were synthesized by Bigge et al [22] and evaluated their inhibitory affects on L1210 cell growth [23]. The nucleosides 14 were found to be petent reversible inhibitors of TS enzyme very low value of ki/km ratio ranging from 0.035-0.08.



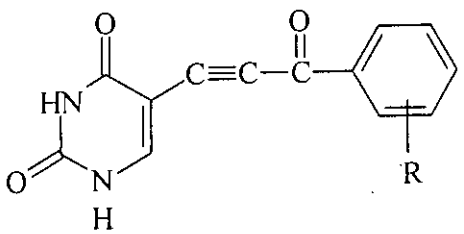
a $R = R^1 = H$

b $R = H, R^1 = NO_2$ (*m*)

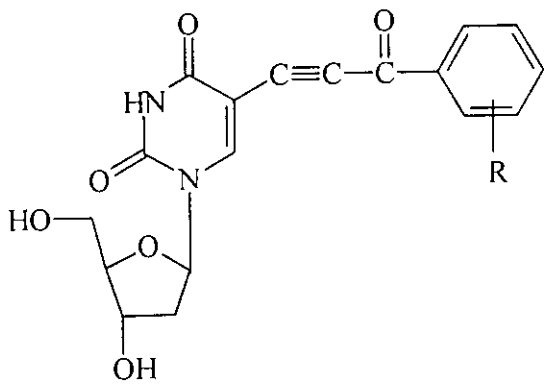
c $R = PO_3^{-2}, R` = N_3$ (*m*)

(14 a-c)

Kundu *et al*[24] developed a series of 5-acylethynyl uracils and their corresponding 2′-deoxyribonucleosides[25] 16. Compouds 15 displayed excellent anticancer properties in cell culture against CCRF-CEM human lymphoblastoid cells and L12110/0 mouse leukemia cell lines 24, while compounds 16 were comparatively less active.



(15 a-g)

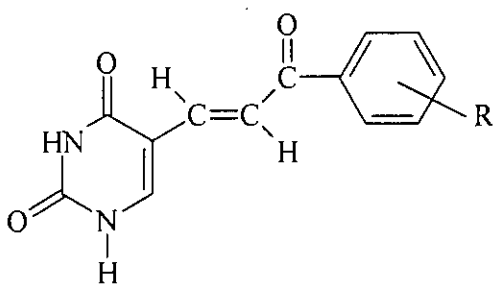


(16)

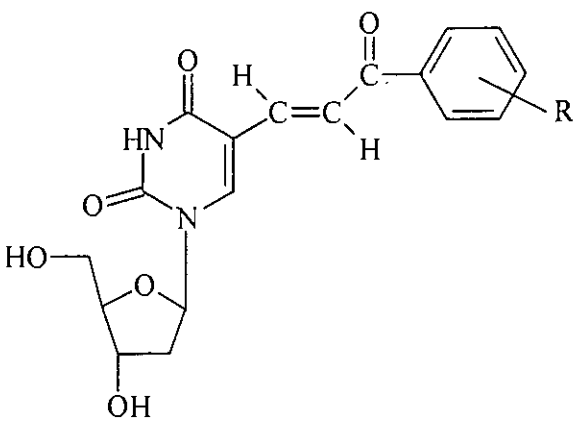
R= H, Me (*p*), OMe (*p*), Cl, Me (*o*), OMe (*o*).

Compounds **15a** and **15 b** were found to be as potent as the parent anticancer drug 5- fluorouracil (5-Fu) against Ehallich ascites carcinoma (EAC) cells in Swiss Albino mice in vitro. Compound **15** were also subjected to TS-inhibition studies and compound **15b** was found to be an effective inhibitor of TS enzyme[24].

Kundu *et al*[26] also synthesized (*E*)-5-(2-acylvinyl) uracils 17 and their corresponding 2′-deoxyribonucleosides[27] 18.



(17 a-d)



(18 a, b)

R= H, Me (*p*), OMe (*p*), $(OMe)_2$ (3, 4) .

Compound **17** showed moderate anticancer activities when tested in vitro against CCRFCEM human lymphosoblastoid cells, HT-29 colon carcinoma cell and L/1210/0 mouse leukemia cell and also found to inhibit the TS enzyme. Compound **18a** and **18b** were found to be weakly toxic against L1210/0 murine leukemia cells and human T-lymphocyte cells (Molt4/CB CEM) compounds **18** were also tested against various viral cell lines and did not show any appreciable antiviral selectivity against HIV-1 and HIV-2 in CEM cells and other viruses [27].

Although these drugs can extend the life of AIDS patients, non are capable of curing the disease, and serious sides effects are induced. For example, treatment with AZT leads to a suppression of bone–marrow

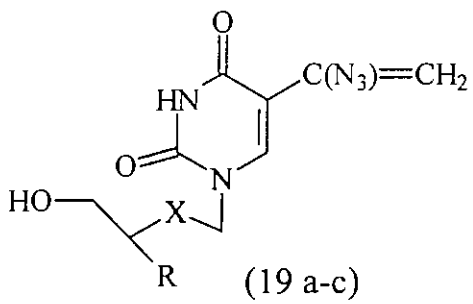
formation which often causes anemia and leucopenia, resulting in the need frequent blood transfusions[28].

The use of DD1, DDC, D4T is associated with painful sensory-motor peripheral neuropathy, as well as acute pancreatitis [29,30] and hepatotoxicity in some cases. The standard antiviral therapy for initiating treatment of patient with HIV infection AZT has also a very short half-life in the body, and high doses (250 mg) must be ingested every 4h to maintain a constant level of drug in the body. Long-term treatment of patients with all these drugs has led to emergence of drug-resistant HIV strain[31,32], more importantly. Therefore, the need for other promising AIDS drug candidates having improved selectivity and activity against HIV is extremely urgent[34.35].

A novel class of 5-substituted acyclic pyrimidine 19a-c synthesized by Rakesh Kumar *et al* [36] were found to be exhibit potent and selective in vitro anti HBV activity against duck hepatitis B virus (DHBV) infected primary duck hepatocyte at low concentration (EC_{50} = 0.01-0.1ug/ml range) (19c), the most active anti-DHBV agent, possessing a [4-hydroxy-3-(hydroxymethyl)-1-butyl] substituted at N-1, exhibited an activity [EC_{50} of 0.10-0.0μg/ml] comparable to that of reference compound (-)-β -L-2′3-dideoxy -3′-thiacytidine (3-TC) [EC_{50}=0.01-0.05 μg/ml). In contrast, related 5-[2-C1-azirinyl] uracil analogues (20b,c)[36] were devoid of anti-DHBV activity. The pyrimidine nucleoside (19a-c), 20b,c) exhibited no cytotoxic activity against a panel of 60 human cancer cell lines.

Table -2

In vitro Activity against Hepatitis B virus in primary Duck Hepalocyte Cultures (DHBV) and toxicity stationary and proliferating cell for 5-substituted uracil (19 a-c) and reference compounds.



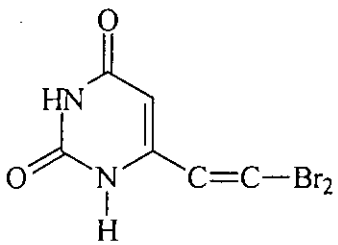
(19 a-c)

No	X	R	% inhibition at 10μg/ml[EC50 ()---g/ml][b]	Toxicity CC_{50}(μg/ml)		Cell proliferation IC(μg/ml)	
			DHBV primary duck hepatocytes	HFF[c]	Vero[e]	HFF[f]	$Daudi_g$
19a	0	H	84[0.01-0.1]	>100 d	>100	>100	>50
19b	0	CH_2OH	86[0.01-0.1]	>100	>200	100	>50
19c	C	CH_2OH	93[0.01-0.05]	>100	>200	>100	>50
3TC	-	-	96[0.01-0.50]	ND	>100	ND	ND

1.1B Biological evaluation of 6-substituted Pyrimidine and its derivatives:

6-Substituted uracil and nucleosides has less priority then 5-substituted uracils. But 6-substituted uracil have got much attention because of their possible use as anticancer and anti-AIDS agents [37,38]. Here we shall discuss the biological activity of some 6-substituted uracil and their nucleosides.

6-(2,2-dibromovinyl) uracil **21** and 6-Ethyl uracil **22** were synthesized and evaluated for their biological properties by Schroeder *et al* [39](compound **21** and **22** showed moderate antitumor activities)



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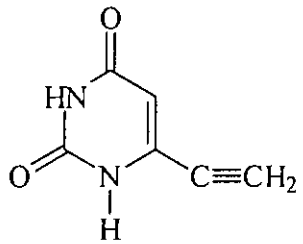
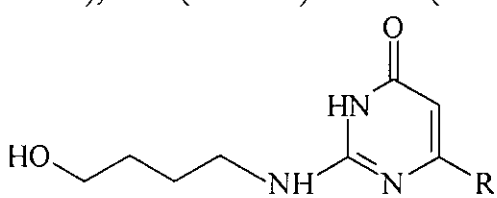
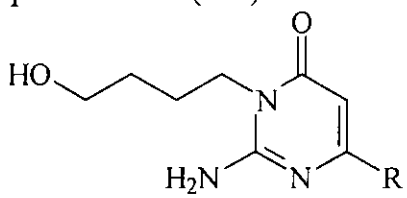


(22)

The solution and solid phase synthesis of substituted 2-(4-hydroxy butyl) amino-4-(3*H*)-pyrimidinones 23 as HIV-1 RT inhibitors was synthesized by Nizi *et al* [40].The evaluated compounds 23a-c and 24a-c in enzyme assays against recombinant HIV-1 RTS from both wild type (Wt) and clinically relevant mutant viruses resistant to T1BO/ neoirapine (L1001, K103N and V106A), using neoirapine as reference drug. The potentiality of 21b to inhibit the recombinant enzymes was found to be as follows: 410(wt), 525 (L1001), 840 (K103N) and 75 (V106A) reported as ki (nm) values.



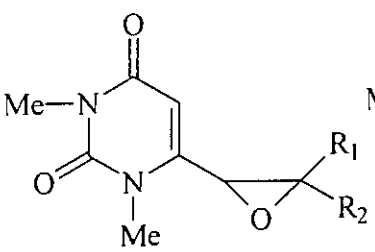
(23 a-c)



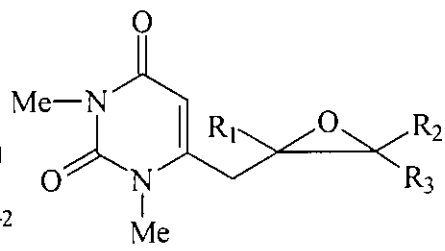
(24 a-c)

23,24 (a-c) R = Me, Br, $CH_2 Co_2 Me$.

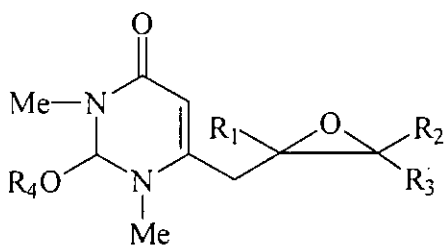
Saladino *et al* [41] synthesized several new 6-oxiranyl uracil 25 a-c, 6-methyloxiranyluracils 26 a-g and pyrimidine derivatives 27 a-d which were found to be a potent and selective antiviral against the parainfluenza 1(sendai) virus replication.



(25 a-c)



(26 a-g)



(27 a-d)

[25a-c] C: R_1 (R_2) = Me (Ph), H (Ph), Ph (H)

26a-g : R1 (R_2) [R_3] = Me (H) [H], Ph (H)[H], t-Bu (H) [H], Me (Me) [H], Me (Me) [H] (CH_2) {(CH_2)$_2$} [H], (CH)$_4$ {(CH_2)$_4$} [H].

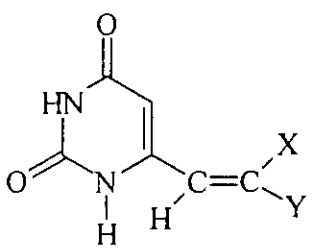
27a-d: R_1{R_2}(R_3)[R_4] = (CH_2)$_4$ {(CH_2)$_4$} (H)[n-pr], Ph{H}(H)[n-pr][cyclohesexyl, Me{H}(Me)[cyclohexyl].

All the compounds have been assayed for antiviral activity on parainflunza 1(sendai) virus replication in Madin Darby cnine kidney cells (MDCK cells) by the measure of the hamagglutinin units (HAV) in the supernatant of the infected cells. The flowing structure-activity relationships could be tentatively reported on the basis of above data;

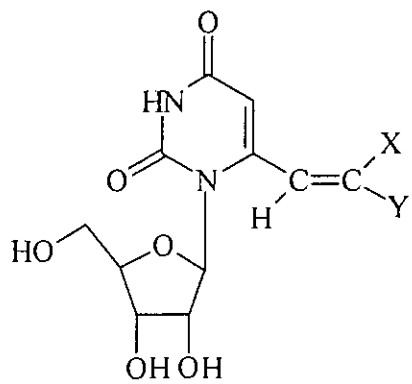
1) The N, N-dimethyl uracil scaffold very unusual for antiviral compound, along with C-6 substitution on the uracil ring, seems to be an important feature for active compounds.

2) The position, the substitution pattern, and the stereochemistry of the oxirane ring play an important role in modulating both the activity and the toxic effect of the products. In particular, 6-oxiranyl derivation 25a, and 25b are more active then corresponding 6-methyl oxiranyl derivatives.

6-Vinyl uracils 28 and their corresponding uridines 29 were synthesized by Megati *et al* [42] and 6- vinyluracil 28a was found to be able to inhibit the growth of L1210 in vitro.



(28)



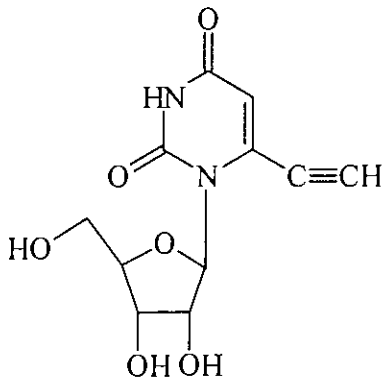
(29)

28a-f: X (Y) = H (H), H (Me), H (COOEt), Br (COOEt), Cl (COOEt);

27 a-d : X(Y)= H(H), H (Me), H(COOEt), Br(COOEt).

6 - (2-Bromo) vinylester **28e** and 6-(2-Chloro) vinylester **28f** of uracil inhibited the cell growth but not 6-vnilester derivative **28d**. In contrast with the free base **28**, the nucleosides **27 a-d** were found to be comparatively inactive.

6- Ethynyl uridine **30** was found to be barren of any cytostatic activity against murine (L1210 and FM 34) cells and human T-lympoblast Molt/4F and MT-4 cells in culture, while its 6-vinyl counterpart **29a** (X= Y= H) showed moderate activity [37].



(30)

A series of 6- substituted uracil acyclonucleoside was recently developed and 1-[(2-hydroxyethoxy)methyl]-6-phenylthiothymine (HEPT,6) and its analogues were found to be an excellent and specific inhibitors of HIV-1 virus type1. The anti-HIV-1 activity and citotoxicity of HEPT 6 were measured and compared with the known drugs like AZT, DDC and DDA which are under activity consideration as anti HIV agent (Table-3).

Table 3: Anti-HIV1 activity of HEPT and Nucleoside analogues in MT-4 cells.

Compound	$EC_{50}(\mu M)^a$	$CC_{50}(\mu M)^b$	SI^c
HEPT	7.0	740	106
AZT	0.016	20	1250
DDC	03	40	133
DDA	6.3	890	141

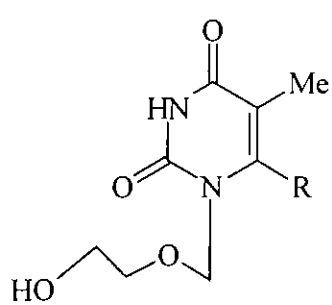
[a Ec_{50}, effective concentration required to achive 50% protection of MT-4 cells against cytopthic effect of HIV-1. bcc_{50}, cytotoxic concentration required to reduce viability of mockinfected MT-4 cells by 50% . CSI, selectivity index (ratio of CC_{50} / EC_{50})].

From the table-3 it is observed that HEPT shows inhibitory effect on the cytopathogenicity of HIV-1 (HTLV-111 Bstrain) in MT-4 cells. HEPT also exhibits comparable effective concentration (EC_{50}) and cytotoxic concentration (CC_{50}) to DDA, but less activity and cytotoxicity than AZT and DDC.

The inhibitor effects of HEPT against other retroviruses were observed the high specificity of HEPT against HIV-1, unlike the common drugs like AZT, DDC or DDA, DNA viruses and other retroviruses including HIV-2 remained unaffected by HEPT[44].

The excellent inhibitory effect of HEPT against HIV 1 encouraged the modifications of HEPT at various position (C-5,C-6, and also in the N-1 acylic chain).

Anti HIV-1 activity of HEPT analogues modified at C-6 position of compound **31** is shown in Table-4. It was found that replacement of phenylthio group by simple alkythio group **31 b** in HEPT afforded uniform inactivity **31**c showed comparable activity. Replacement of sulfur atom in HEPT by oxygen **31d**, nitrogen **31e** or halogen **31f** atoms gave poor results. On the other compound **31k** had considerable effect against HIV-1. Also modification at the c-6 modified analogues suggested the necessity of ring structure in the c-6 position for this compound to be effective against HIV-1[45].



(31)

Table 4

Compound	R	Ec(μM)	CC_{50}(μM)	SI
31a	SPh	7.0	740	106
31b	SMe	>250	>250	~ 1
31c	SC_6H_{11}	8.2	664	81
31d	Oph	85	345	4
31e	NHPhI	>327	327	<1
31f	I	>80	400	>5
31g	C ≡CH	>5.5	5.5	<1
31h	C≡ CP	>14	14	~1
31i	CH =CH_2	>250	250	<1
31j	CH(OH)Ph	>400	400	<1
31k	CH_2Ph	23	352	15.3
31l	CH_2CH_2Pn	>444	444	<1

The modiffcation of HEPT at C-5 position by introducing methyl, iodo, ester, amido, ethynyl or vinyl groups resulted in increasing cytotoxicity with comparable EC_{50} values (Table-5). It was observed that 5-ethyl 32i and 5-isopropyl 30k analogues of HEPT were highly potent and selective inhibitors of HIV-1[46].

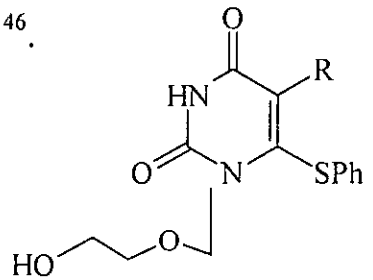
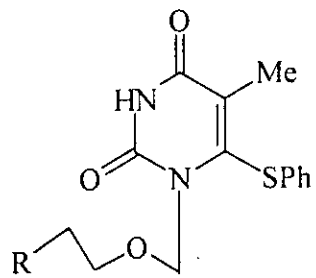


Table 5: Anti HIV-1 activity of (32) HEPT analogues Modified in c-5 positon of 32.

Compound	R	EC_{50}(μM)	CC_{50}(μM)	SI
32a	Me	70	740	106
32b	I	3.6	20	5.6
32c	COOMe	6.6	6.6	<1
32d	CONHPh	0.18	18	<1
32e	C ≡CH	>18	18	<1
32f	C ≡ CPh	>3.4	3.4	<1
32g	CH = CH_2	>250	>250	~1
32h	CH_2Ph	>23	23	<1
32i	Et	0.12	400	3300
32j	n-Pr	3.4	244	72
32k	*i* - Pr	0.063	231	3670

The N-1 acyclic side chain of HEPT was also varied and their antiviral activities were evaluated. It was found that O-acylated analogue 33b should comparable anti-HIV-1 activity with increase in cylotoxicity with respect to the parent compound HEPT. The deoxy HEPT analogues 32e-j was found to be more active and among this, the N-1 ethoxy methyl derivatives 33f showed high activity and moderate cell toxicity with selective index[47].

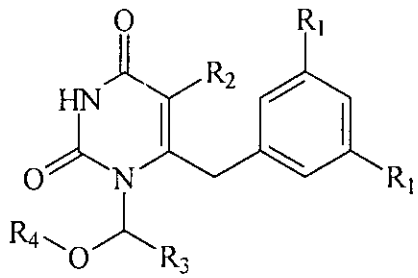


(33)

33 a-j: R= CH_2OH, CH_2OAC, CH_2OMe, CH_2OCHPn, H, Me, Et, CH_2F, CH_2N_3, Pr.

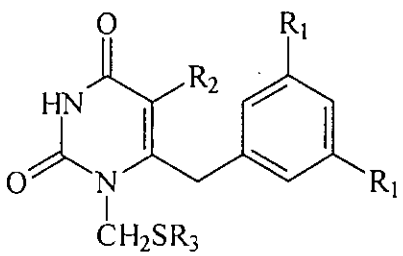
33	R_1	R_2	R_3
a	H	Et	Me
b	H	Et	Et
C	H	i-Pr	Me
d	H	i-Pr	Et
e	Me	Et	Me
F	Me	Et	Et

HEPT analogue 6-benzyl-1(ethoxymethyl)-5-isopropyuracil (MKC-442) 34a has been chosen as a candidate for clinical trails with AIDS patients[48] and 6-(3', 5'-dimethylbenzyl)-1(ethoxymethyl)-5 ethyluracil 34e(E-EBU-dM) showed excellent antiviral activitty[49]. Novel 6- 6- benzyluracil analogues of HEPT 34,35,36 including MKC-442 34d and E-EBU-dm 32e were recently synthesized and evaluated[50]. This results are summarized in Table-6 together with these of AZT.

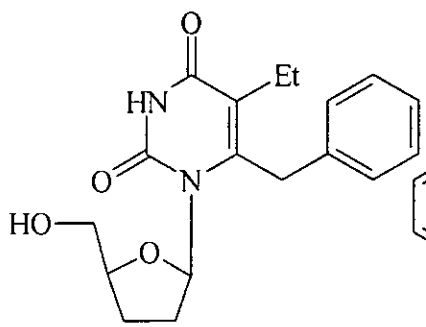


(34 a-g)

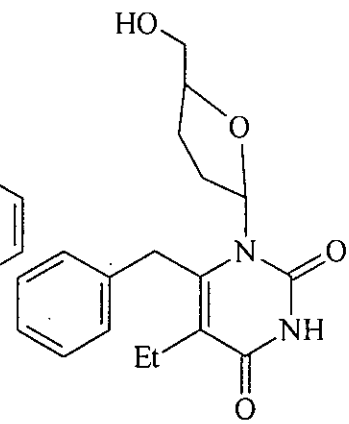
34	R_1	R_2	R_3	R_4
a	H	Et	Me	Me
b	H	Et	Me	Et
c	H	Et	Me	$(CH_2)OH$
d	H	i-Pr	H	Et
E	Me	Et	H	Et
f	Me	Et	Me	Me
g	Me	Et	Et	Et



(35 a-f)



(36 a)



(36 b)

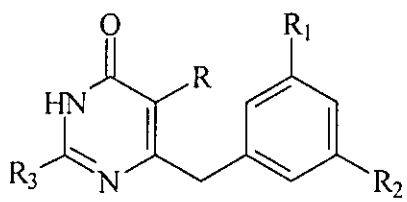
Table -6: Antiviral activity of HEPT analogues 34,35,36 and AZT against HIV-1 in MT-4 cells.

Compound	ED_{50}[a](μM)	CD_{50}[b](μM)	SI[c]
34a	>100	-	-
34b	>100	-	-
34c	>100	-	-
34d	0.005	141	28000
34e	0.004	100	25000
34f	2	100	50
34g	15	130	8.7
35a	0.002	32	16000
35b	0.040	37	925
35c	0.020	37	1850
35d	0.006	37	6200
35e	0.050	52	1.040
35f	0.004	68	17000
36a	37	52	14
36b	0.5	1	1
AZT	0.040	52	1300

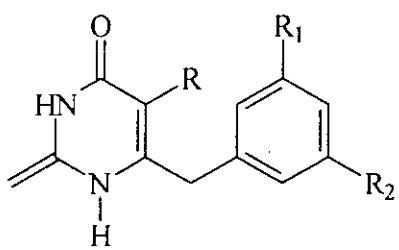
a: Effective dose of compound, achieving 50% inhibition of HIV-1 antigen production in MT -4 cultures.

b: Cytotoxic dose of compound, required to reduce the proliferation of normal uninfected MT-4 cells by 50%.

c: Selectivity index : ratio [CD_{50}/ED_{50}] . It was observed that the analogues 33 with Oxygen replaced with sulfur showed comparable activities and selectivities with those found for MKC-442 34d, and E-EBU-dM, 34e.



(37 a-i)



(38 a-c)

La Colla *et al*[50,51] developed a new class of non-nucleoside reverse transcriptase inhibitors (NNRTTs) viz. 3,4-dihydro -2-ackoxy-6-benzyn-4-oxopyrimidies (DABOs 37). Most of these DABO derivatives 37 were lacking of cytotoxicity in MT-4 cells, but selectivity inhibited the HIV-1 induced cytotathic effects (Table -7)

Table -7 : Cytotoxicity and Anti-HIV activity of DABOS 37 and 38 in HIV-infected MT4.

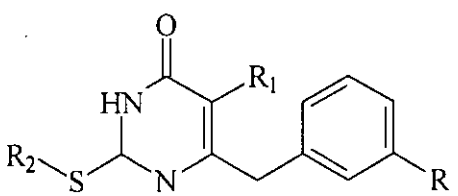
Compound	R	R_1	R_2	R_3	CC50[a]	EC50	SI[b]
37a	H	H	H	Me	>1000	>200	-
37b	H	H	H	Sec-butyl	344	5.5	62
37c	H	H	H	Cyclohexyl	157	9.0	17
37d	H	Me	H	Sec-butyl	>367	3.3	>111
37e	H	Me	H	Cyclohexyl	>335	0.8	418
37f	H	Me	Me	Sec-butyl	>349	2.7	>129
37g	H	Me	Me	Cyclohexyl	>320	1.1	>291
37h	Me	Me	H	Sec-butyl	>350	3.1	>113
37i	Me	Me	Me	Sec-butyl	>333	0.8	>416
38a	H	H	H	H	>1000	200	-
38b	H	Me	H	H	>463	92	5
38c	Me	Me	Me	H	>410	38	>11
HEPT	-	-	-	-	740	7	106
AZT	-	-	-	-	80	0.01	8000

a. CC50: Cytotoxic concentration, concentration required to reduce viability of mock infected MT-4 cells by 50% .

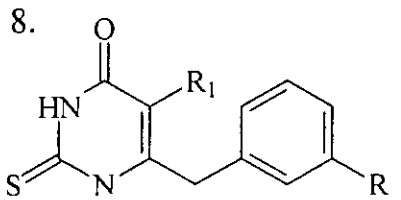
b. SI: Selectivity index (ratio of CC_{50}/EC_{50}).

The size of the alkoxy chain at the C-2 position of the pyrimidine ring appeared to be a determining factor for antiviral activity i.e. the increasing length of the derivatives **37c**, **37e**, **37g** showed better result. Again introduction of methyl group at the 3 –position in the benzyl moiety led to a significant increase in both potency and selectivity **37e**, **37i**.

To develop a more potential and selective compounds, the oxygen atom at C-2 position of pyrimidine ring was replaced by a sulfur atom yielding the thio analogues of DABO(S-DABOs 39)[53]. The antiviral activities of S-DABOs **39** and **40** are summarized in Table 8.



(39 a-g)



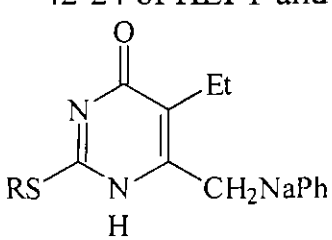
(40 a-c)

Table-8: Cytotoxicity and anti-HIV-1 activity of S-DABOs 39 and 6-Benzyl-2-thiouracils[40].

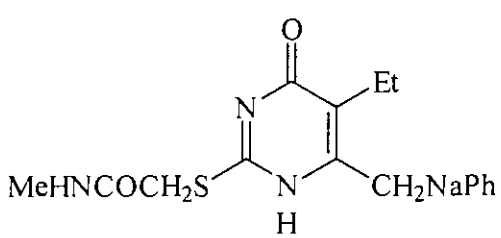
Compound	R	R_1	R_2	CC_5	EC_{50}	SI
39a	H	H	Sec-butyl	150	1.2	125
39b	H	H	Cyclohexyl	>330	0.8	>412
39c	H	Me	Sec-butyl	>347	0.6	>578
39d	H	Me	Cyclohexyl	>318	1.5	>212
39e	Me	H	Cyclohexyl	>333	0.6	>555
39f	Me	H	Cyclohexyl	318	0.6	>530
39g	Me	Me	Cyclohexyl	>318	0.6	>350
40a	Me	H	-	258	>258	<1
40b	H	Me	-	431	>108	<4
40c	Me	Me	-	284	>102	-

Most of the SDABOs 39 were found to be non-toxic in MT4 cells and when assayed in HIV-1 infected MT-4 cells, it behaved like the DABOs 37 did. Hence a large alkylthio group like Sec-butyl, cyclopentyl, cyclohexyl at C-2 position of pyrimidine ring and methyl, cyclohexyl at C-2 position of p yrimidine ring and methyl group at the 3′ position of the benzyl moiety increased the potency of S-DABO derivatives 39 than that of the DABO derivatives. The 6-benzyl-2-thiouracil derivatives 40 was found inactive as in previous case.

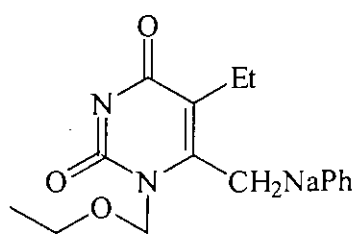
Danel et al[54] generated a number of anti HIV active napthyl analogues 41a-c, 42-24 of HEPT and DABO whose antiviral activities were evaluated.



(41 a-c)

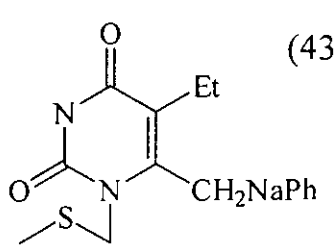


(42)



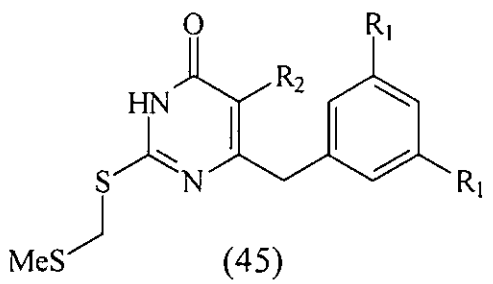
(43)

41	R
a	$MeSCH_2$
b	Et SCH_2
c	$MeOOCCH_2$



(44)

Vig *et al*[54] synthesized a novel dihidroalkoxybenzyl oxopyrimidine 45 a-d (S-DABO) derivatives targeting the non-nucleoside inhibitor (NNI) binding site of human immuno-deficiency virus (HIV) reverse transcriptase (RT) using a novel computer model for the NNI binding pocket and test for their RT inhibitor activity in cell free assays using purified recombinant HIV RT as well as for their anti HIV activity in HTL VIIIB infected peripheral blood mono nuclear cells [56].

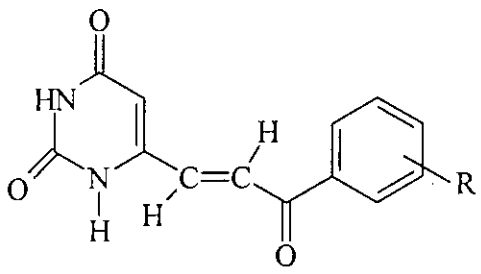


(45)

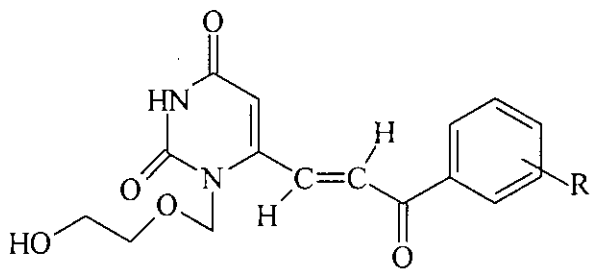
45	R_1	R_2
a	H	Me
b	H	Et
c	H	i-Pr
d	Me	I-Pr

Compound **45** which differ from compound **45c** by the addition of two methyl groups to the 6-benzyl ring providing a better hydrophobic contact with the NNI binding pocket was slightly more potent than compound **45c** in inhibiting recombinant HIVRT. However, compound **45d** failed to inhibit HIV replication in HTL VIIIB-infected cells as effectively as compound **45c**.

Kundu *et. al.*[57] recently developed the palladium catalyzed synthesized of [E]-6-(2-Acyl vinyl)-1-[(e-hydroxyethoxy)methyl]uracil and evaluated their antiviral and cytotoxic activities.



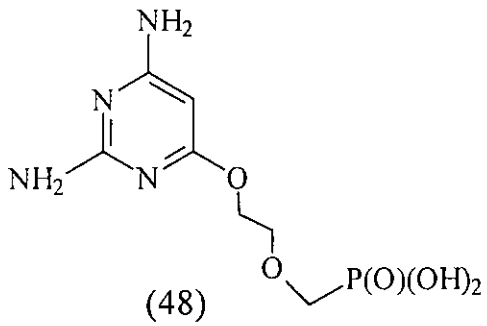
(46 a-c)



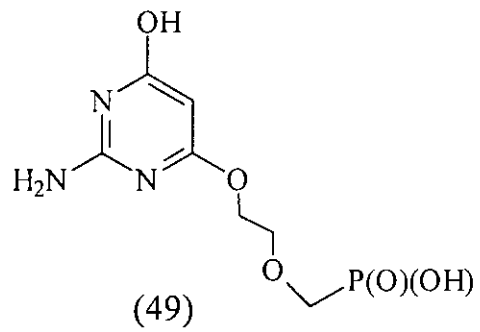
(47 a-d)

[E]-6-(2-acylvinyl) uracils 46a-c were found to be poorly cytostatic against murine leukemia (L 1210) and murine mammary carcinoma (FM3A)cells. However they were found to be distinctly inhibitory to human T-lymphocyte (Molt 4/C8 and CEM) cells proliferation. Compound 46b was found to be most toxic of three compounds tested. The acyclonucleosides 47a-d increased the cytotoxicity towards the murine cell lines, particularly L1210 cells.

H. Antonin *et al* [58] synthesized a group of 6-[2-(Phosphonomethoxy) alkoxy] pyrimidine among the 6-[2-(Phosphonomethoxy) ethyoxy] (PMEO) pyrimidine derivatives, several analogues showed a pronounced antiviral activities in cell culture. PMEO derivatives that carry ring [i,e, 48 and 49] emerged as the most active compounds. They were inhibitory to herpes simplex virus type -1 (HSV-1), HSV-2 and thymidine kinase(TK) deficient TK/HSV- 1 strain at EC_{50} values ranking between 6.5 and 24 μg/ml.



(48)



(49)

The compounds **48** and **49** were even more potent against two wild type VZV and two TK deficient VZV strains (EC_{50}:06-2.5 μg/ml)

Both 48 and 49 were exquisitely inhibitory to mononey murine sarcoma virus(MSV)in C3H/3T3cell cultures(EC_{50}:04-0.8 μg/ml)

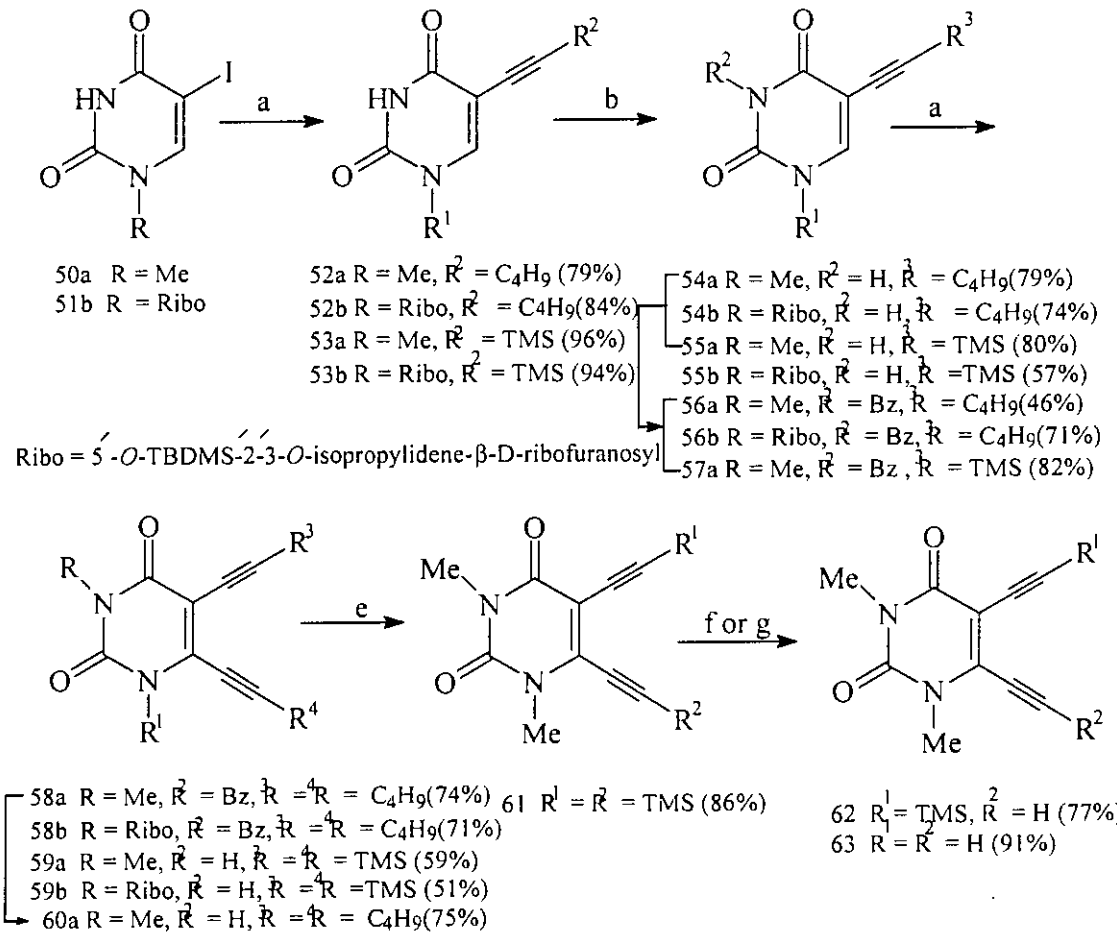
1.1C. Biological evaluation of 5,6-disubstituted Pyrimidines and related nucleosides:

Pyrimidine derivatives are widespread in medicinal natural products chemistry. A number of commercially important drugs incorporated in heterocycle. Specially substituted pyrimidines are valuable intermediates for drug discovery. Particularly, the preparation of 5,6-disubstituted pyrimidines is very difficult as process reported. Several synthetic routes of these compounds are known, some of them are described here. Bergman [59] cycloaromatization reaction is of interest both from a mechanistic point of view and because of its relevance to the mode of action of enediyne antibiotics including the esperamicins, calicheamicins, dynemicins, and kedarcidin. These DNA-cleaving molecules are among the most cytotoxic compounds known[60] and considerable efforts have been focused on the synthesis of analogs with enhanced properties for chemotherapeutic application[61].

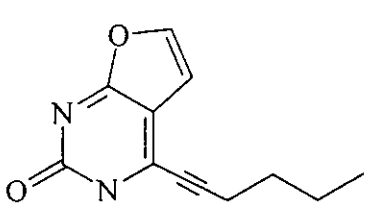
Russel and co-workers[62] reported the synthesis and Bergman cycloaromatization of three 5,6-bis (alkyn-1-yl) pyrimidine derivatives. Their synthesis started with 6-chloro-2,4-dimethoxypyrimidine and was not oriented to the preparation of nucleosides. Morris J. Robins et al [63] reported efficient syntheses of 5,6- bis (ethynyl) uracil derivatives and related nucleosides from uracil or uridine. [64a]

The respective 5-iodo -1-methyluracil (50a) or 5'-*O*-(tert-butyldimethy-5) iodo -2',3'-*O*-iso-propylideneuridine (50b) derivatives were readily obtained in 2-3 steps from uracil and uridine (Scheme 1)

Scheme -1



Scheme 1. Reagents: (a) H_3C CR/Pd(0), Cu(I). (b) (i) LDA, -78°C; (ii) I2, (c) BzCl/*i*Pr)$_2$N (d) NH_3/MeOH CH_2N_2/Et_2O, (f) NH_4F/THFMeOH[16]



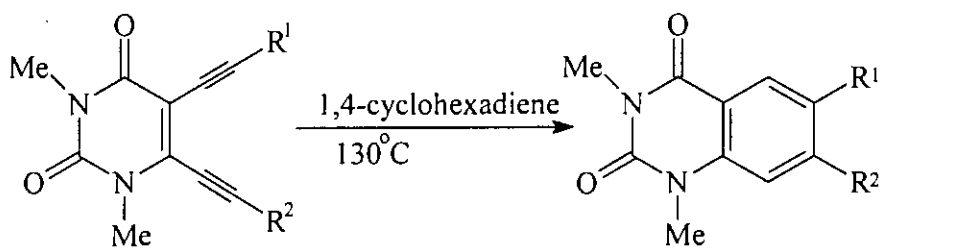
(64)

Sonogashira coupling [64,65] of 50a,b with TMS-ethyne or 1-hexyne proceeded smoothly to give 5-alkynyl derivatives **52a-53b** (79-96%). C-6-lithiation,[66] followed by treatment with iodine gave 5-(alkyn-1-yl)-6-iodo analogs **54a-55b** in good yields. Coupling of **54a** with 1-hexyne afforded minor amounts of 5,6-bis(hexyn-1-yl)derivative 60a, but the major product of this reaction was bicyclic compound **64** . Furano [2,3-*d*] pyrimidin-2-ones related to **64** are known byproducts of Sonogashira couplings 5-iodouracil subtracts [64,67] and variable amounts (10-15%) of the corresponding bicyclic pyrimidin-2-ones were observed when **52a,b** were prepared from **50a,b**. In the case of 52a,b cyclization was minimized with optimized reaction conditions, but coupling of the 6-iodo derivatives **54a,b** was considerably slower. The longer reaction times invariably gave furano[2,3-*d*] pyrimidin-2-ones as major products. The furan cyclization was circumvented by N^3-benzoylation of **54a,b**. The resulting **56a,b** underwent coupling to give **58a,b** without accompanying addition of O4 to the C5-alkynyl triple bond. Compound **55a** was N^3-benzoylated to give **57a**, but **59a,b** underwent coupling without formation of furano [2,3-*d*]pyrimidin-2-one products. Thus **59a,b** were prepared from **55a** or **55b** by direct coupling with (trimethyl silyl) acetylene. The N^3-benzoyl group was removed standard conditions, and treatment of **58a** with NH_3/MeOH gave **60a**(75%).

Attempts [68] to bis-desilylate **59a** gave intractable mixtures. Remarkably, N^3-methylation over came this problem and **63** was obtained in 91% yield upon treatment of **61** with NH_4F/MeOH. The C6-ethynyl TMS group was

selectively cleaved to give **62**(77%) with NH_4F/benzyltriethylammonium chloride (BTAC)/THF.

Enediynes **62** and **63** underwent thermal Bergman cycloaromatization in 1,4-cyclohexadiene at 130°C with half-lives of 8 and 2 h, respectively (sheme 2) compound **61** did not undergo Bergman cyclization under these conditions, and higher temperatures resulted in significant decomposition. Isolated yields of **65** and **66** were approximately 20%, and decomposition of starting material contributed to the modest yields.



62 R^1= TMS, R^2 = H
63 R^1= R^2 = H

65 R^1= TMS, R^2 = H ($t_{1/2}$ = 8h)
66 R^1= R^2 = H ($t_{1/2}$ = 2h)

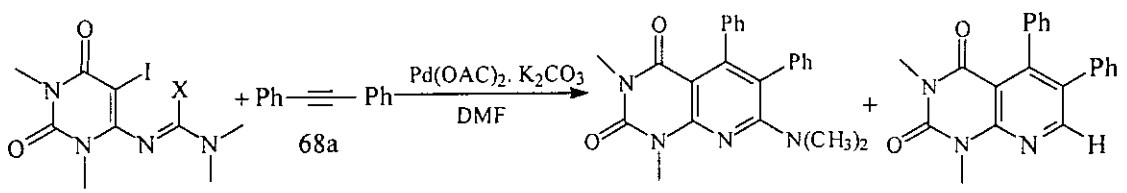
Scheme - 2

Activation energies for Bergman cycloaromatiozations have been correlated with the a,b distance between to two terminal alkynyl carbon atoms. Acyclic enedinynes with a,b-distances ›3.5 A were unreactive at 25°C and required heating of effect cyclization. In compounds **61-63**, the a,b distance is calculated to be approximately 4.1 A. Terminally substituted acylic enediynes exhibit increased activation barriers due to unfavorable steric interactions and entropic effects, and the relative reactivates of **61-63** are consistent with these observations. Morris J. Robins et al [63] have prepared 5,6-bis(alkyn-1-yl)-1-methyluracil derivatives and protected nucleosides via successive Sonogashira coupling of 5-and 6-iodo (uracil or uridine) analogs **51a,b** and 5**6a-56b**. Coupling of the 6-iodo derivatives was sluggish and

required longer reaction times resulted in increased formation of furano[2,3-*d*] pyrimidin-2-one byproducts from 5-(hexyn-l-yl) derivatives **54a,b**, but they were not observed with 5-(TMS-ethyn-l-yl) intermediates **53a,b or 55a,b.** The 5,6-bis(ethynl) derivatives underwent Bergaman cycloaromatization at elevated temperatures to give quinazoline-2,4-dine derivatives **65** and **66**. Connection of the two ethynylsubstituents to form fused bicyclic uracil-based enediynes should significantly lower activation barriers to Bergman cycloaromatization.

Recently, Yoon CM and his workers [69] reported an efficient method for the syntheses of pyrido[2,3-*d*]pyrimidines by the reactions of iodouracil, having a formamidine or acetamidine moiety, with various olefins in DMF using a catalytic amount of palladium acetate. [70, 71]

As a continuation of this work, the reactions of iodouracils having a formidine or actamidine moiety **67** with various acetylenes **68** were studied in the presence or absence of lithium chloride, which might play a crucial role in the reaction selectivity (scheme-3).

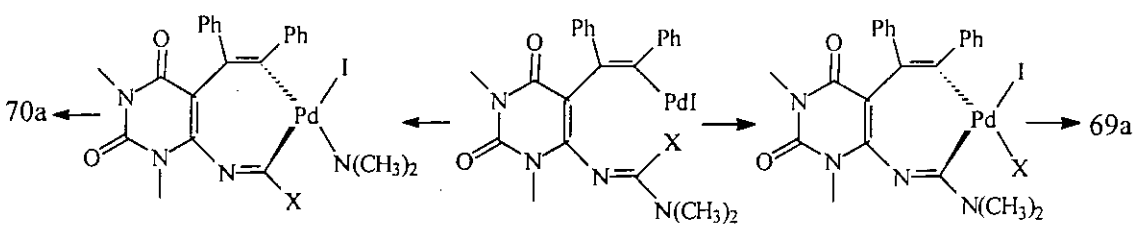


67a : X = H
67b : X = CH_3

69a 70a

Scheme - 3

The reaction of iodouracil **67a** with diphenylacetyene **68a** in DMF in the presence of palladium acetate as catalyst and potassium carbonate as base at 120°C gave two pyridopyrimidines **69a** (dehydrogenated one) and **70a** (deaminated one) in 67% and 27% yields, respectively . The selectivity was increased when the same reaction was tried in the presence of 1 equiv. of lithium chloride. Pyridopyrimidine **69a** was obtained in 93% yield and only amount of pyridopyrimidine **70a** was observed by TLC. A similar selectivity observed using 1 eqiv. of bromide instead of 1 equiv. of lithium chloride. However, selectivity was not observed at when tetra-*n*-butylammonium bromide or tera-*n*-butylammonium chloride was used instead of lithium bromide or lithium chloride. On the basis of these experimental results, the selectivity seems to be due to the lithium cation. Lithium cations in this reaction might prevent the insertion of palladium of intermediate I (X= H) into the C-N$(Me)_2$ bond to form intermediate II(X= H), which is necessary for the information of pyridopyridmidine **70a** (scheme 4).

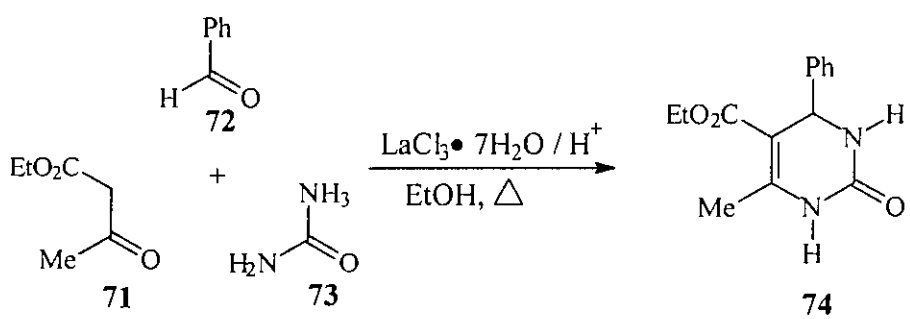


II I III

Scheme -4

The reaction of iodouracils having a formamidine moiety **67a** with acetylenes using palladium acetate in DMF in the presence of lithium chloride at 120°C gave pyrido pyrimidines with regioselectivity. The reaction of iodouracil having an acetamidine moiety **67b** with acetylenes without lithium chloride also gave pyrdopyrimidines.

The Biginelli reaction was first reported more than a century ago and recently reviewed [72] and involves the synthesis of 3,4-dihydrooyrimimdin-2(1H)-ones of type **74** by a very simple one-pot condensation reaction of ethyl acetoacetate **71**, benzaldethde **72** and urea **73** in ethanol. However, this one-pot, one-step protocol often provides only low to moderate yields of the target molecules **74** (scheme - 5), in particular when substituted aromatic or aliphatic aldehydes are employed.

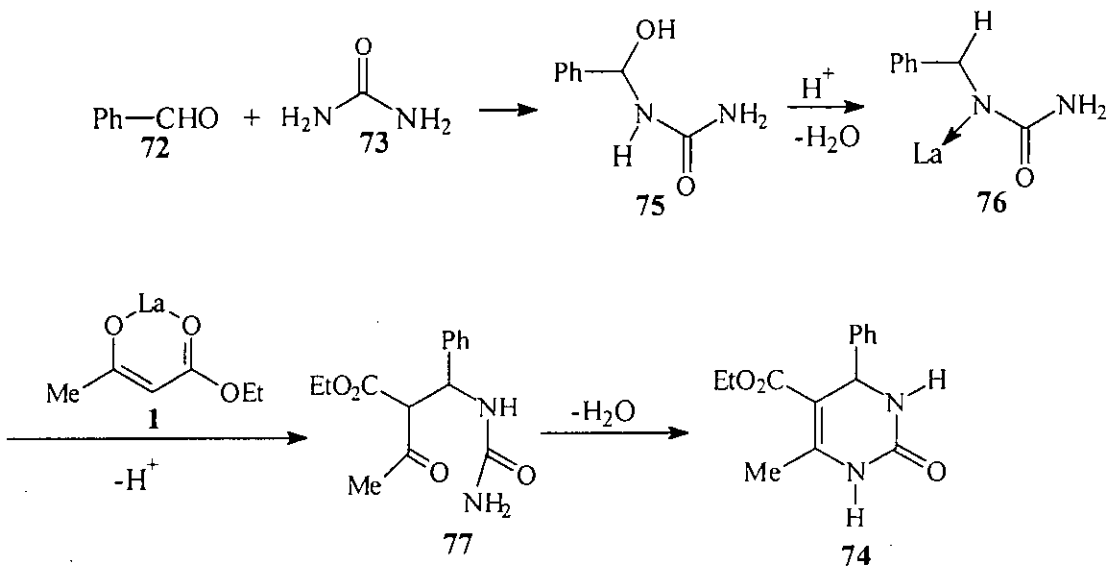


Scheme - 5

In the past decade, dihydropyrimidine derivatives have exhibited important pharmacological properties, e.g. as the integral backbones of several calcium channel blockers, antihypertensive agents, alpha-la-antagonists, and neuropeptide Y (NPY) antagonist. [73] Several improved procures for the preparation of DHPMs (Biginelli compounds) have recently been reported, either by modification of the classical one-pot Biginelli approach itself. [74-78] or by the development of novel, but more complex multistep strategies. [79] In addition, several combinatorial approach towards DHPMs **74** have been advanced using solid-phase or fluorous phase reaction conditions. [80]

Junlu, Yinjuan and coworker[81] have developed a simple and efficient method for the direct preparation of substituted dihydropyrimidinones using lanthanum chloride heptahydrate as a catalyst in good yields from readily available starting materials. This was a novel, one-pot combination that not only preserves the simplicity of Biginelli's one-pot reaction but also consistently produces excellent yields of the dihydropyrimidine -2(1*H*)-ones. In the presence of the $LaCl_3 7H_2O$(5 mmol), the reaction of β-keto ester 1(10mmol), aldehyde **72** (10mmol), and urea or thiourea **73** (15 mmol) was carried out in a one pot condensation employing refluxing EtOH, which had previously been employed successfully in the Biginelli condensation as solvent. After the reaction was completed, the dihydropyrimidines **74a**-t precipitated from the reaction mixture. Even for aliphatic aldehydes (i.e butyraldehyde and iso- butyraldehyde), which normally showed extremely poor yields in the Biginelli reaction,[82-83] 60% and 56% yields of the corresponding dihydropyrimidin-2(1H)-ones 4j and 4k could be obtained.

Recently, the mechanism of the Biginelli reaction was reinvestigated in detailed by Kappe [84] proposed and established that the first step in this reaction, the acid-catalyzed formation of an acylimine intermediate formed by reaction of the aldehyde with urea, was the key rate-limiting step. Interception of the minimum ion by ethyl acetoacetate produces an open-chain uriden which subsequently cyclized to the dihydropyrimidinones **74.** Because of the **74f** empty orbital in the lanthanum ion, a complex **76** can be formed through a coordinative bond and stabilized by lanthanum. So the proposed mechanism for the lanthanum promoted Biginelli reaction as follows (scheme 6).

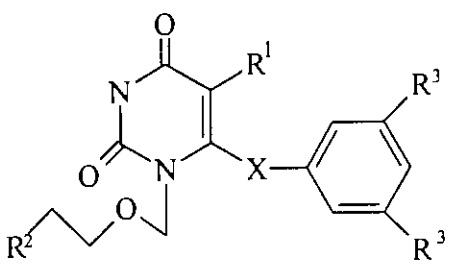


Scheme - 6

Present work: Synthesis of 5, 6-Disubstituted Pyrimidines of Biological Importance

2.1.A Rationale:

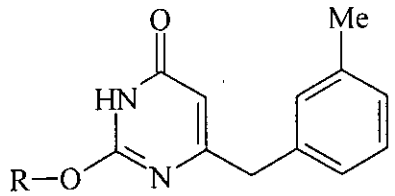
The studies on 6 – substituted uracils have been found limited in literature. The recent pandemic occurrence of AIDS and the discovery of 6-substituted uracils, e.g. 1– (2–hydroxyethoxy methyl) – 6 – (phenylthio) thymine (HEPT), **I**, and related compounds, such as E–EDU, **II**, I–EBU, **III**, E-EBU-dM, **IV**, which acts as specific inhibitors of HIV –1 (human immunodeficiency virus type 1), the causative agent of AIDS, have stimulated interest in 6-substituted uracil derivatives.



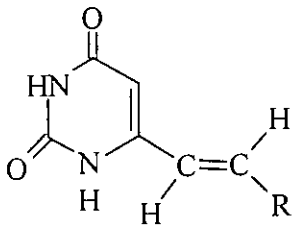
HEPT,	**I**,	X= S,	$R^1 = CH_3$,	R^2 = OH,	R^3 = H
E-EPU,	**II**,	X= S,	R^1 = Et,	R^2 = H,	$R^3 = CH_3$
I-EBU,	**III**,	X= CH_2,	R^1 = i-Pr,	$R^2 = R^3$ = H	
E-EBU-dM,	**IV**,	X= CH_2,	R^1 = Et,	R^2 = H,	$R^3 = CH_3$

Some pyrimidine derivatives, e.g. 3,4-dihydro-2-alkoxy-6-(3`-methylbenzyl) – 4 – oxopyrimidine (DABO), **V**, has shown considerable activities as inhibitors of HIV-1 RT.

The cytotoxic activities of 6-vinyluracil **VI** against L1210 mouse leukemia cells have shown. Recently 6- acyvinyl uracils **VII** were found highly cytotoxic against CCRF-CEM human lymthoblastoid cells.

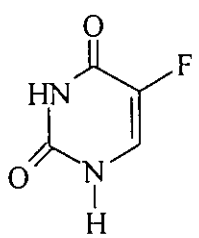


V

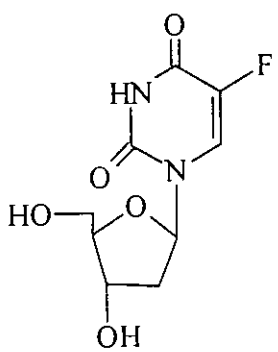


VI, R = H
VII, R = -COAr

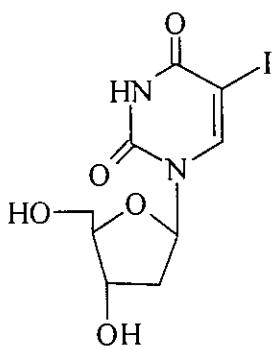
5 – Flurouracil (5-Fu, **VIII**) and 5-fluoro- 2′- deoxy uridine (5-Fudr, **IX**) are used clinically for the treatment of breast colon and rectum cancer, 5 – iodo – 2′–deoxyuridine (IDU, **X**) is utilized clinically in the tropical treatment of herpes simplex keradtatis, a sight treatening eye infection. It is also effective against mucocutaneous HSV infection and vaccinia virus (VV).



VIII

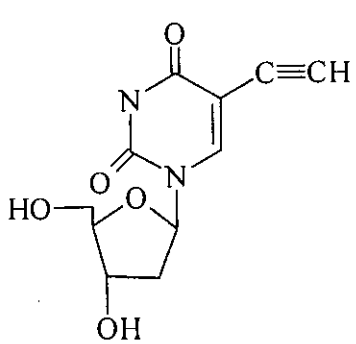


IX



X

5 – Ethynyl – 2′ deoxyuridine **XI** exibited excellent anticancer properties (ID_{50} = 0.091 μg/mL in L1210 cells and antiviral properties against HSV-1 in all primary rabbit kidney cells in culture.



XI

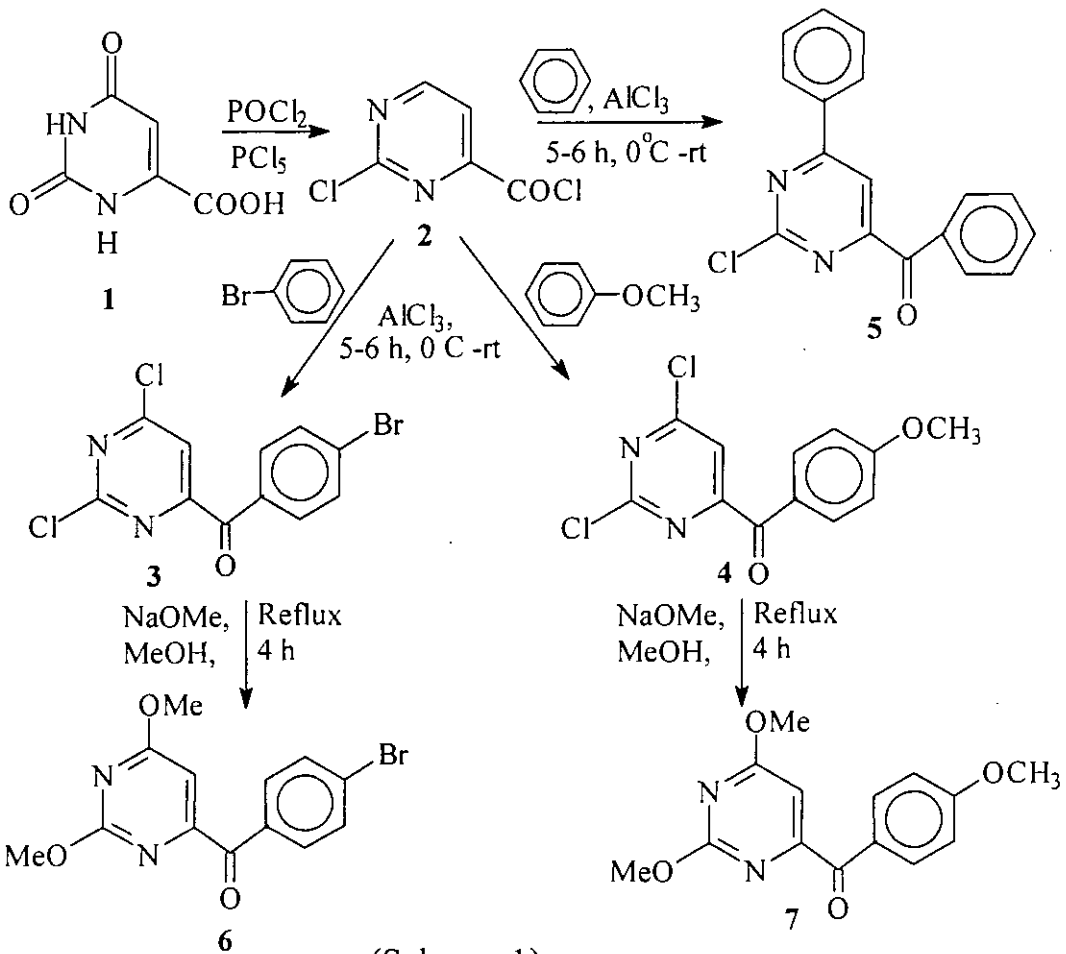
In view of the significant biological activity of various 5 and 6 – substituted uracils and related pyrimidine derivatives we became interested in developing methods for the synthesis of novel 5, 6- disubstituted uracils and pyrimidines. In this thesis a facile method for the synthesis of a number of 5, 6- disubstituted pyrimidine derivatives was planned.

2.1.B. Results and Discussion:

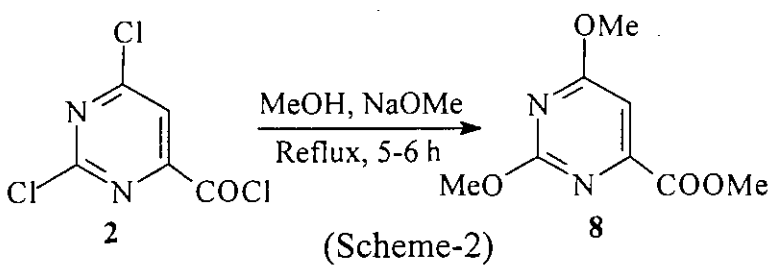
The 6-substituted pyrimidines were synthesised according to the reaction sequence as shown in the scheme **1** and **2**. 2, 4 -Dichloropyrimidine -6-carbonyl chloride **2** was synthesised according to the procedure of Gershon[85] by heating orotic acid **1** with phosphorus oxychloride and phosphorus pentachloride .Compound **2** underwent a smooth Friedel-Crafts reaction with a number of substituted benzene derivatives in the presence of anhydrous aluminium chloride in which the acid chloride moiety was found to react predominantly. The yields of the Friedel-Crafts products were good (70-87%). The Friedel-Crafts reaction took place at the *p*-position of the substituent on the benzene ring 2,4-Dichloropyrimidine-4-carbonyl chloride **2** showed Friedel-Crafts acylation reaction with benzene in which phenyl group was substituted at C-4 and C-6 position of the pyrimidine ring to yield disubstituted compounds **5**. The Friedel-Crafts reaction of 2, 4-dichloropyrimidine - 6 - carbonylchloride **2** and benzene derivatives with electron with drawing substituents on the benzene ring, e.g. benzophenon, *p*-nitrotoluene and 2-methyl benzaldehyde, however failed. Similarly, phenyl acetylene and styrene failed to give any identifiable products.

6-*p*-Bromobenzoyl-2,4- dichloropyrimidine **3** and 2,4- Dichloro - 6-*p*-methoxybenzoyl pyrimidine **4** were converted to the corresponding dimethoxy pyrimidines **6** & **7** on treatment with sodium methoxide in methanol.

2, 4- Dichloropyrimidine -6-carbonyl chloride was also converted to 2,4-dimethoxy pyrimidine 6-methyl carboxylate **8** by refluxing with sodium methoxide in methanol for 6 h.



(Scheme-1)



(Scheme-2)

2.1.C. Structure determination:

The structure of the compounds were established from their analytical and spectroscopic data. 2, 4- Dichloro pyrimidine -6- carbonyl chloride **2** was dense colourless liquid which was highly moisture sensitive.

2, 4- Dichloro-6-*p*-methoxyl benzoyl pyrimidine **4,** needle shape crystal, mp 110-112 °C. showed absorption at 1652.9 cm^{-1} for stretching of acyl ketone and at 1596.9 cm^{-1} for stretching of C=C in IR spectrum. The compound **4** exhibited chemical shift position at δ 7.8 as singlet for C-5 H in ^{1}H NMR spectrum.

2,4- Dichloro-6-*p*-bromobenzoyl pyrimidine **3,** colourless crystal, mp 118-119 °C., exhibited absorption at 1664.5 cm^{-1} for stretching of carbonyl group and absorption at 1587.3, 1548.7 cm^{-1} due to the stretching of C=C and C=N. Its UV spectrum showed λ_{max} at 284.80 nm for the conjugation of carbonyl group. In ^{1}HNMR spectrum of the compound chemical shift position at δ 7.88 (1H, S, C-5H) was obtained. Its ^{13}CNMR spectrum also showed the chemical shift at δ 188.1 for C=O. The CHN analysis confirmed the molecular formulae $C_{11}H_5N_2OBrCl_2$ of the compound **3.**

2-Chloro-4-phenyl-6-benzoyl pyrimidine **5,** yellow needles, mp 129-130 °C. The melting points of this compound **5** is identical with the literature value[108] The IR spectrum of the compound showed C=O stretching band at 1680 cm^{-1} and the absorption at 1600 and 1570 cm^{-1} for C=C and C=N stretching vibrations.

The ^{1}HNMR spectrum of the compound exhibited chemical shift position at 8.18 (s, 1H, C-5H) and 10 aromatic proton at the region of 7.39-8.15 as multiplet. The ^{13}CNMR spectrum showed chemical shift at δ 190.91 for

C=O group. The position of phenyl group was assigned at C-4 on the basis of the down field shift of the C-5 hydrogen in the ^{1}HNMR spectrum due to the deshielding effect of the phenyl groups at the C-4 position compared to the chemical shift of the C-5 H in other pyrimidines.

2,4-Dimethoxy-6-*p*-bromobenzoyl pyrimidine **6**, colourless needle, mp, 121-122 °C, showed absorption band at 1674.1 cm^{-1} due to carbonyl group stretching vibration and absorption band in the region 1582.5 and 1559.3 for the stretching vibration of C=C and C=N band. The UV spectrum of the compound gave the λ_{max} 277.20 nm for the conjugation of carbonyl group. Its ^{1}HNMR spectrum exhibited the chemical shift position at δ 4.01 and 4.04 for two OCH_3 group as singlet and at δ 6.93 singlet for C-5 H. In ^{13}CNMR spectrum of the compound the chemical shift at 190.8 for C=O, 54.3 and 55.1 for OCH_3 were obtained. The CHN analysis was compatible with the molecular formula $C_{13}H_{11}N_2BrO_3$.

2, 4-Dimethoxy-6-*p*-methoxybenzoyl pyrimidine **7**, light yellow needle, mp. 139-141 °C, showed absorption band at 1658.7 for C=O stretching vibration and in the region 1598.9 and 1558.4 for C=C and C=N band stretching vibrations. The UV spectrum of the compound showed λ_{max} 296.6 nm for the conjugation of carbonyl group. The ^{1}HNMR spectrum of the compound exhibited the chemical shift at δ 3.88 and 4.02 for two OCH_3 as singlet and at δ 6.85 for C-5 H as a singlet.

2,4-Dimethoxy-6-methyl orotate **8**, colourless needle, mp, 106-107 °C, showed absorption band at 1724.2 for C=O stretching and in the region 1600.8 and 1569.0 for C=C and C=N band stretching vibrations in the IR spectrum. In UV spectrum λ_{max} 280.40 nm was obtained.

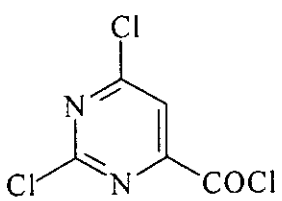
The ^{1}HNMR spectrum of the orotate showed the chemical shift positions at δ 3.97, 4.03 and 4.07 for OCH_3 as strong singlet and at δ 7.07 as a singlet for C-5H.

Its ^{13}CNMR spectrum also exhibited the chemical shift at δ 52.9, 54.3, 55.0 for three OCH_3 groups and at δ 172.7 for C=O. The CHN analysis was compatible with the molecular formula $C_8H_{10}N_2O_4$.

Experimental

2.1.D. Preparation of 2, 4 - dichloro pyrimidine – 6 - carbonyl chloride (2) :-

A mixture of 2, 4 – dioxo - 1, 3, 5 - trihydro - pyrimidine - 6 - carboxylic acid (orotic acid) 6g (0.345 mol) and phosphorus oxychloride 70 ml was refluxed for 24 h, then phosphorus penta chloride (22.93 g, 0.11 mol) was added in this mixture. The mixture was then refluxed for 24 h, The $POCl_3$ was removed under redused pressure. The residue was distilled with the help of short path distillation set. under reduced pressure and 5 g 2, 4 - dichloro pyrimidine-6-carbonyl chloride (2) was obtained as dense colourless liquid.

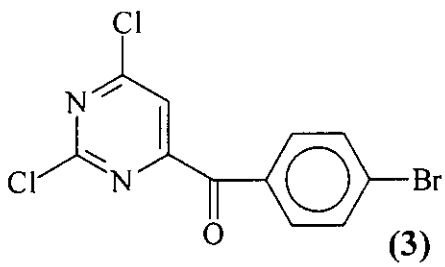


(2)

2.1.E. Synthesis of 2, 4 - dichloro-6-*p*-bromobenzoylpyrimidine (3)

To the aromatic compound, bromobenzene (60ml) anhydrous aluminium chloride (6g) was added at 0° C. To the cold solution 2, 4 - dichloro pyrimidine -6- Carbonyl chloride (6g) added dropwise. The mixture was then allowed to warm up to room temperature and stirred further at room temperature (25°C) for 2 hours. The mixture was then poured into cold hydrochloric acid solution (2 ml, 12N HCl in 60 ml water). The organic layer was separated and the aqueous layer was extracted with chloroform (3 × 25ml). The combined organic layer was washed with water, sodium

bicarbonate solution (10% 2x25 ml) and water again .It was dried over anhydrous Sodium Sulfate. After removal of solvent, the product was purified by column chromatography over silica gel and then it was crystallized. A niddle shape colorless crystal was obtained. yield 2g



(3)

Colourless needles (CCl_4) mp : 122-124°C.

IR: ν_{max} (KBr) 3112.9, 3070.5, 1664.5, 1587.3, 1548.7, 1519.8, 1401.2, 1325.0, 1303.8, 1325.0, 1246.9, 1217.0, 1181.3, 1071.4, 1011.6, 975.9, 847.7, 833.2, 790.8, 773.4, 742.5, 691.4, 606.6 and 484.1 cm^{-1}.

UV: λ_{max} 284.80 and 201.60 cm^{-1}.

^{1}HNMR (400 MHz $CDCl_3$) δ = 7.67(2H, br, d, *j* = 8.5Hz), 7.88 (1H, s,C-5H), 8.01(2H, br, d, *j* =8.5 Hz, Ar-H),

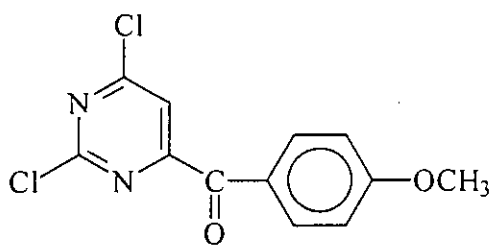
^{13}CNMR(100 MHz $CDCl_3$) δ = 119.7 (Py-CH), 130.2 , 132.0(Ar-H) , 132.4, 132.6 (Ar-C), 160.2 , 164.2 , 164.6 (Py-C), 188.1 (C=O).

Calcd for $C_{11}H_5N_2OBrCl_2$: C, 39.80; H 1.52; N, 8.44%,

Found: C, 39.73, H 1.58; N, 8.34%.

2.1.F. Synthesis of 2, 4- dichloro – 6 – *p* - methoxyl benzoyl pyrimidine (4) by Friedel-Craft Reaction:-

To the aromatic compound Anisol (60ml), anhydrous aluminium chloride (3 eq, 6g) was added at 0°C. To this cold solution 2, 4-dichloro pyrimidine-6- Carbonyl chloride (5g, 23.64 m.mol) added dropwise. The mixture was then allowed to warm up to room temperature and stirred further at room temperature (25°C) for 4 hours. This was then poured into cold hydrochloric acid solution (2 ml, 12N HCl in 60 ml water). The organic layer was separated and the aqueous layer was extracted with chloroform (3 ×25ml). The combined organic layer was washed with water, sodium bicarbonate solution(10% 2 × 25 ml) and water again .It was dried over anhydrous Sodium Sulfate. After removal of solvent, the product was purified by column chromatography over silica gel and then it was crystallized from tetrachloromethane. A needle shaped crystal was obtained.



(4)

Yellow crystals (CCl_4); mp : 110 -112°C

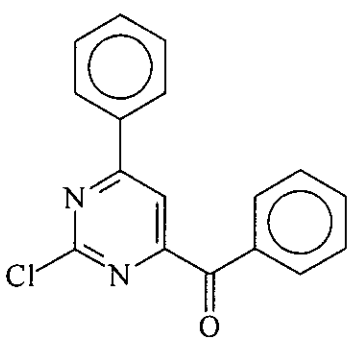
IR: ν_{max} (KBr) 1652.9, 1596.9, 1552.6, 1519.8, 1508.2, 1323.1, 1278.7, 1257.5, 1168.8, 1118.6, 1033.8, 846.7, 781.1 , 756.0, 746.4 and 607 cm^{-1}

UV (EtOH): λ_{max} 278.80, 224.60 and 205.00 nm

^{1}HNMR: (400 MHz, $CDCl_3$) δ_H 3.90 (s, 3H, $ArOCH_3$), 6.98 (d, J = 9 Hz, 2H, ArH), 7.80 (s, 1H, C-5H) , and 8.12 (d,J = 9Hz, 2H, ArH) ;

2.1.G. Preparation of 2-Chloro-4-phynyl – 6– benzoyl pyrimidine (5)

Anhydrous aluminium chloride (3 eq, 6g) was added at 0°C to the aromatic compound benzene (60ml). To this cold solution 2, 4-dichloro pyrimidine-6- Carbonyl chloride (5g, 23.64 m.mol) added dropwise. The mixture was then allowed to warm up to room temperature and stirred further at room temperature (25°C) for 4 hours. This was then poured into cold hydrochloric acid solution (2 ml, 12N HCl in 60 ml water). The organic layer was separated and the aqueous layer was extracted with chloroform (3 ×25ml). The combined organic layer was washed with water, sodium bicarbonate solution(10% 2 × 25 ml) and water again .It was dried over anhydrous Sodium Sulfate. After removal of solvent, the product was purified by column chromatography over silica gel and then it was crystallized from tetrachloromethane. A needle shaped crystal was obtained.



(5)

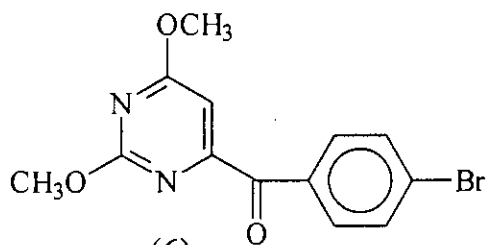
Yellow needles,mp 127-130°C

IR: ν_{max} (KBr) 300, 1680, 1600, 1570, 1515 and 1445 cm^{-1}

^{1}**HNMR:** (400 MHz, $CDCl_3$) δ_H 7.39 - 7.67 (m, 6H, Ar-H) 8.09 -8.15(m, 4H, Ar-H) and 8.18(s, 1H, C-5 H).

2.1.H. Preparation of 2, 4 – dimethoxy – 6 – *p* – bromobenzoyl Pyrimidine (6)

2,4-Dichloro-6-*p*-bromobenzoyl Pyrimidine **3** (1.6506 mmol) was added dropwise to an ice-cold solution of sodium (0.1138g) in dry methanol (30ml). The whole solution was stirred at room temperature for 4 hours. After completion of the reaction solvent was removed. A solid mass was obtained. To this solid mass 100 ml water was added and neutralized with the help of dil HCl. Then it was extracted with chloroform (50 ml × 3). The organic layer was then washed with water (twice), 10% $NaHCO_3$ (twice) and lastly with water (twice). It was dried over Na_2SO_4 (anhyd.) and filtered. After removal of chloroform the solid was then recrystallized with methanol. A needle shaped crystal was obtained.



(6)

Colourless needle (methanol) ; yield 450 mg. **mp:** 121-122°C;

IR: ν_{max} (KBr) 1674.1, 1582.5, 1559.3, 1484.1, 1463.9, 1395.4, 1386.4, 1349.1, 1259.4, 12054, 1105.1, 974.9, 835.3 and 763.8 cm^{-1}.

UV(EtOH) : λ_{max} 277.20 and 205.40 nm.

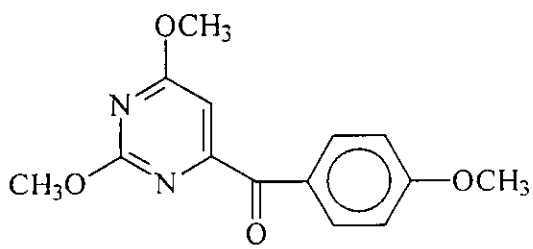
^{1}**HNMR:** (400MHz $CDCl_3$) δ_H : 4.01(3H, S, OCH_3), 4.04 (3H, s, OCH_3), 6.93 (1H,s ,C-5H), 7.63 (2H, d, *j* = 8.6 Hz, ArH), 8.00 (2H, d, *j* = 8.6 Hz;ArH),

^{13}**CNMR** (100 MHz $CDCl_3$) δ = 54.3(OCH_3), 55.1(OCH_3), 102.0(C-5H), 128.8(Ar-C), 132.2(Ar-CH), 133.9(Ar-C), 163.1, 165.0, 172.7 (Py-C), 190.8(C=O).

Calcd for $C_{13}H_{11}N_2BrO_3$: C, 48,32; H, 3.43; N, 8.67%, Found: C, 48.97; H, 3.42; N, 8.50%.

2.1.I. Synthesis of 2, 4-dimethoxy-6-*p*-methoxybenzoyl Pyrimidine 6

2,4-Dichloro- 6-*p*-methoxylbenzoyl Pyrimidine **4** (3.5g, 0.0283 mol) in dry methanol (50 ml) was added dropwise to an ice-cold solution of sodium (1.95 gm, 0.084 mol) in dry methanol (50ml). The whole solution was stirred at room temperature for 4 hours. After completion of the reaction the solvent was removed. A solid mass was obtained. To this solid mass 100 ml water was added and neutralized with the help of dil HCl . The solution should not much acidic since pyrimidine ring itself is basic. Then it was extracted with chloroform (50ml × 3). The organic layer was then washed with water (twice), 10% $NaHCO_3$ (twice) and lastly with water (twice). It was dried over Na_2SO_4 (anhyd.) and filtered. After removal of chloroform the solid mass was then recrystallized with methanol. A needles shaped crystal was obtained. yield 100 mg.



(7)

Light yellow needle (methanol) ; mp : 139-141°C

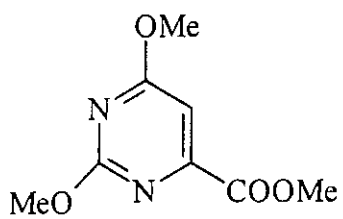
IR: ν_{max} (KBr) 3190, 1658.7, 1598.9, 1558.4, 1427.2, 1388.7, 1350.1, 1182, 1182.3, and 1095.5 cm^{-1}

UV(EtOH): λ_{max} 296.60 and 214.20 nm

^{1}HNMR: δ_H (400MHz, $CDCl_3$) 3.88 (s, 3H $ArOCH_3$) 4.02 (d, 3H, OCH_3), 4.03 (s. 3H, OCH_3), 6.85(s. H, C-5 H), 6.96 (d, J=8 Hz, 2H, ArH) 8.13 (d, J = 8 Hz, 2H, ArH)

2.1.J. Preparation of 2, 4 - dimethoxy -6- methyl orotate (8)

2,4-Dichloro pyrimidine -6 – carboxyl chloride **2** (1m mol) in dry methanol (50 ml) was added drop wise to an ice-cold solution of sodium (1.95g, 0.084 mol) in dry methanol (50 ml). The whole solution was stirred at room temperature for 4 hours. After completion of the reaction solvent was removed. A solid mass was obtained. To this solid mass 100 ml water was added and just neutralized with the help of dil HCl. Then it was extracted with chloroform (50ml × 3). The organic layer was then washed with water (twice), 10% $NaHCO_3$ (twice) and lastly with distilled water (twice). It was dried over Na_2SO_4 and filtered. After removal of chloroform the solid mass was then recrystallized with methanol A needle shaped crystal was obtained.



8

mp: 106-107 °C

IR: ν_{max} (KBr) 1724.2, 1600.8, 1569.0, 1439.0, 1435.9, 1393.5, 1271.0, 1286.4, 1353.9, 1119.6, 1125.1, 1102.2, 780.2, and 772.4 cm^{-1}

UV: λ_{max} 280.40 and 225.40 nm

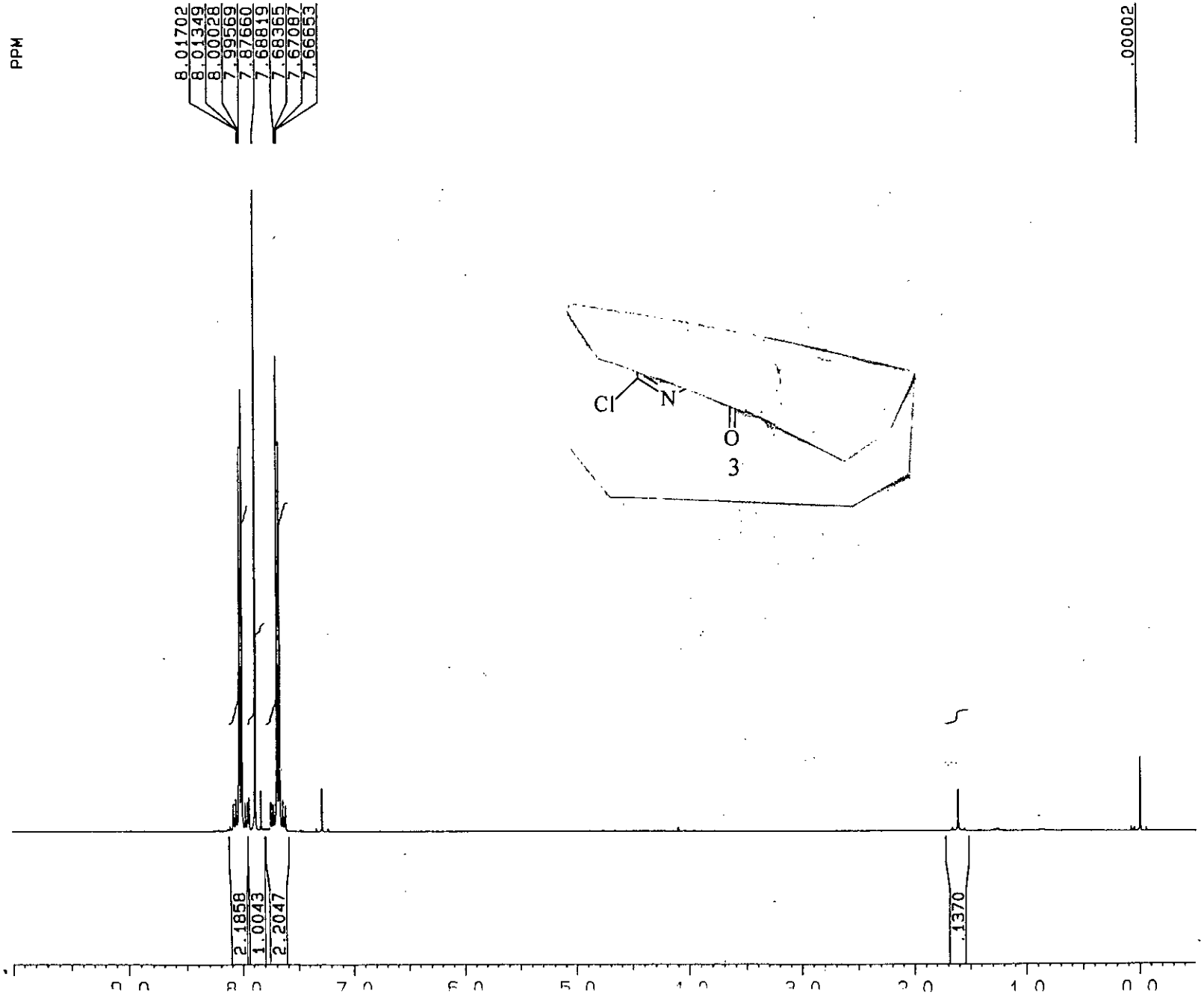
^{1}**HNMR:** (δ_H 400 MHz, $CDCl_3$) 3.97 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 4.07 (s, 3H, $COOCH_3$) , 7.07(s, 1H,C-5H)

^{13}**CNMR:** (100MHz, $CDCl_3$) 52.9(OCH_3), 54.3(OCH_3), 55.0($COOCH_3$), 103.1(Py-H), 156.7(Py-C), 164.4(Py-C), 165.7(Py-C), 172.7(C=O).

Calcd for $C_8H_{10}N_2O_4$, C, 48.48, H, 5.09, N, 14.14%,

Found: C, 48.90; H, 5.02, N, 13.76%.

WKHAN-T13



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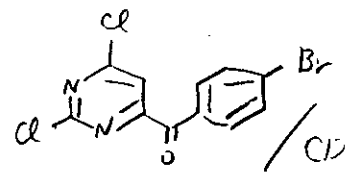

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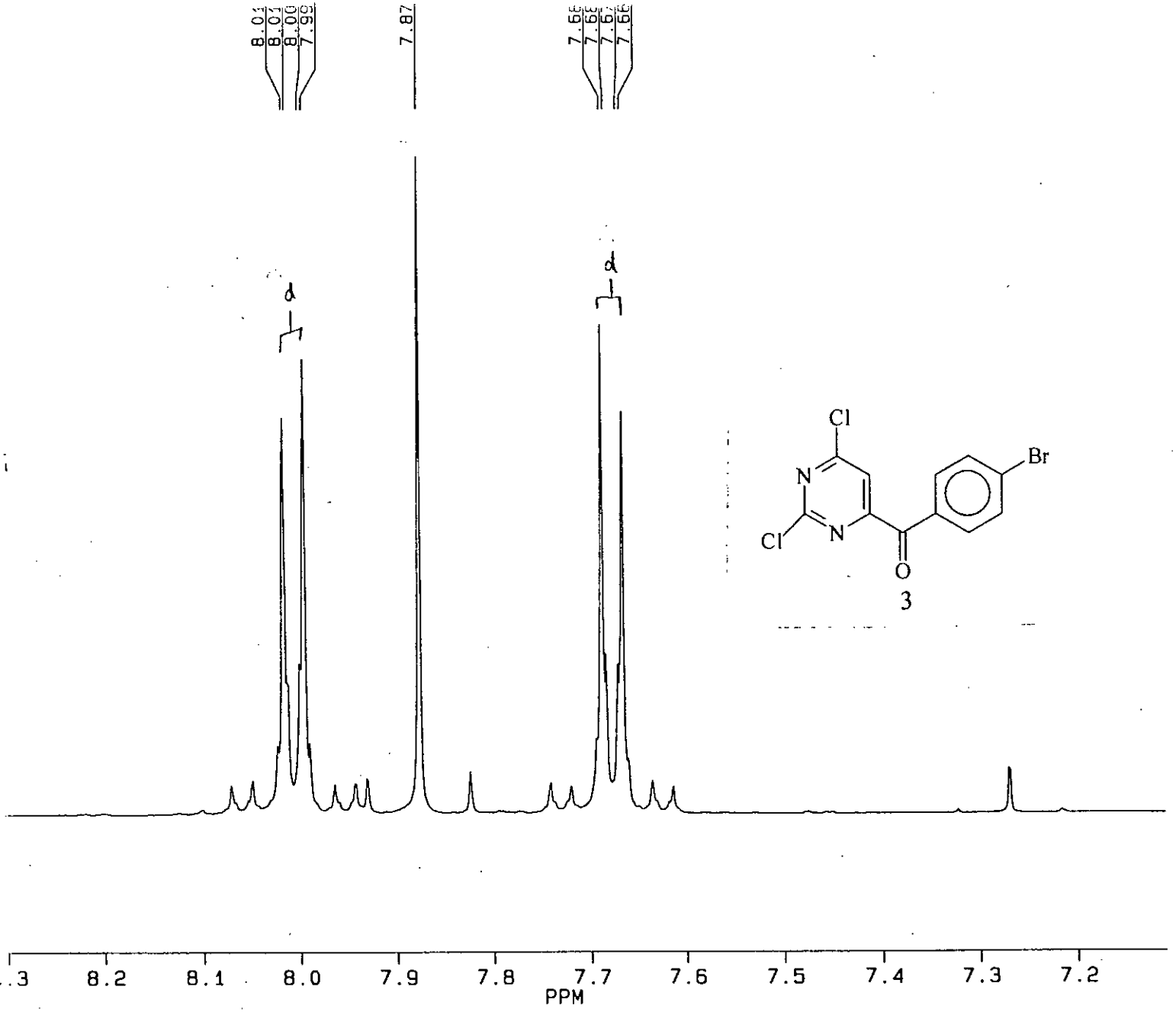
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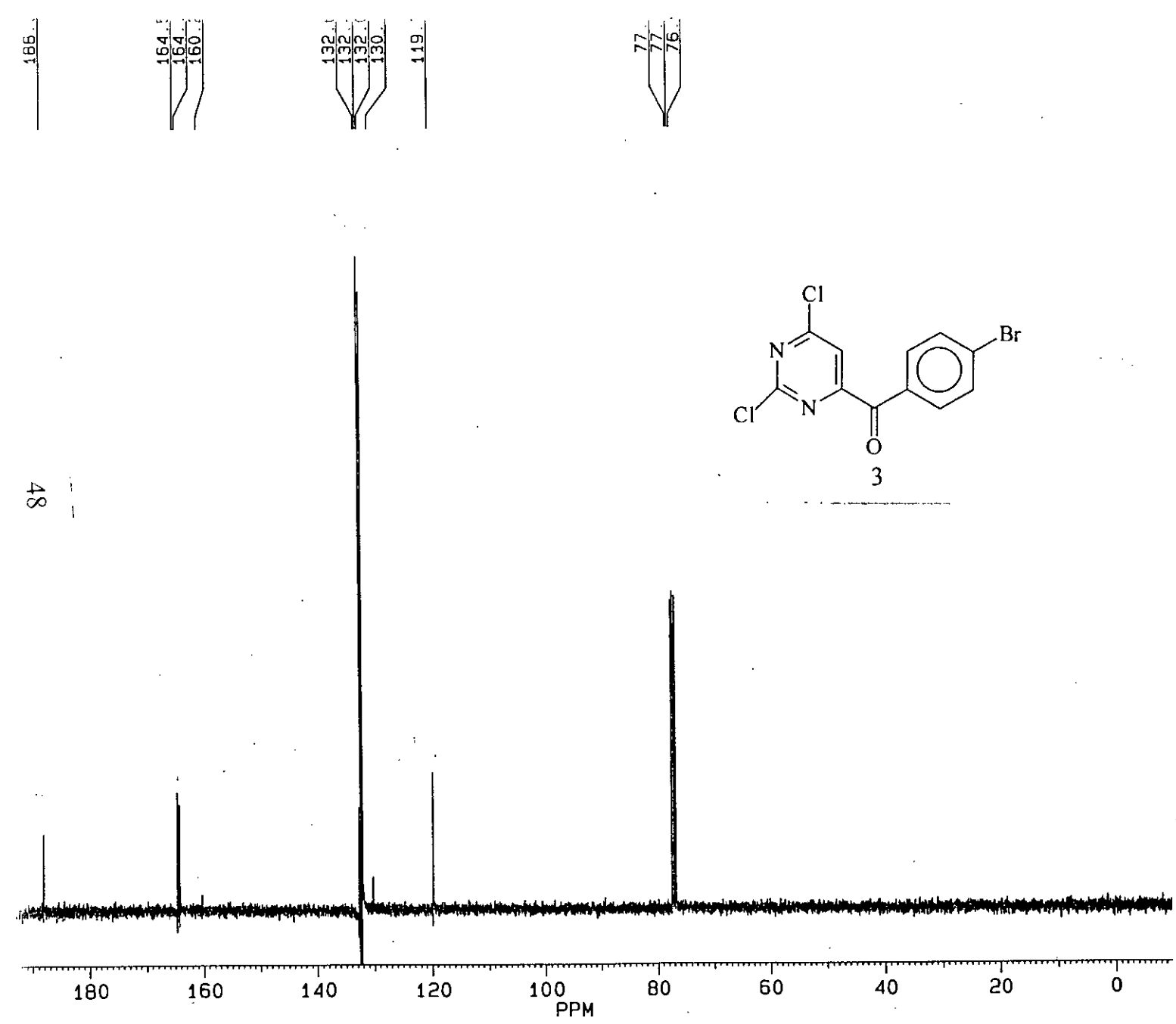

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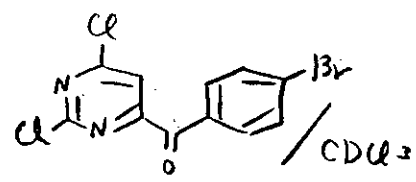

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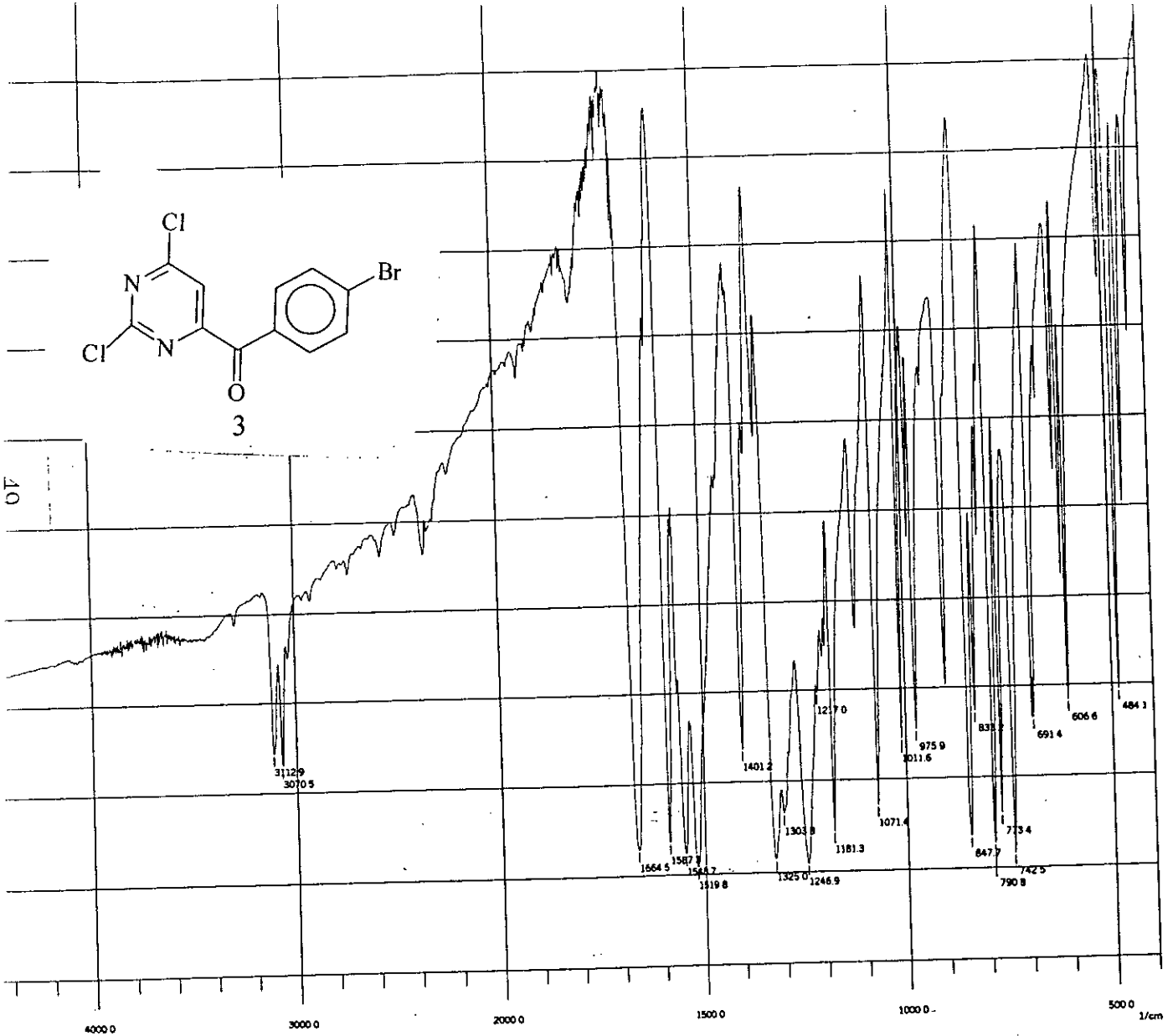

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T 13 27 May, 2003

LT IRS: T 13 27 May, 2003

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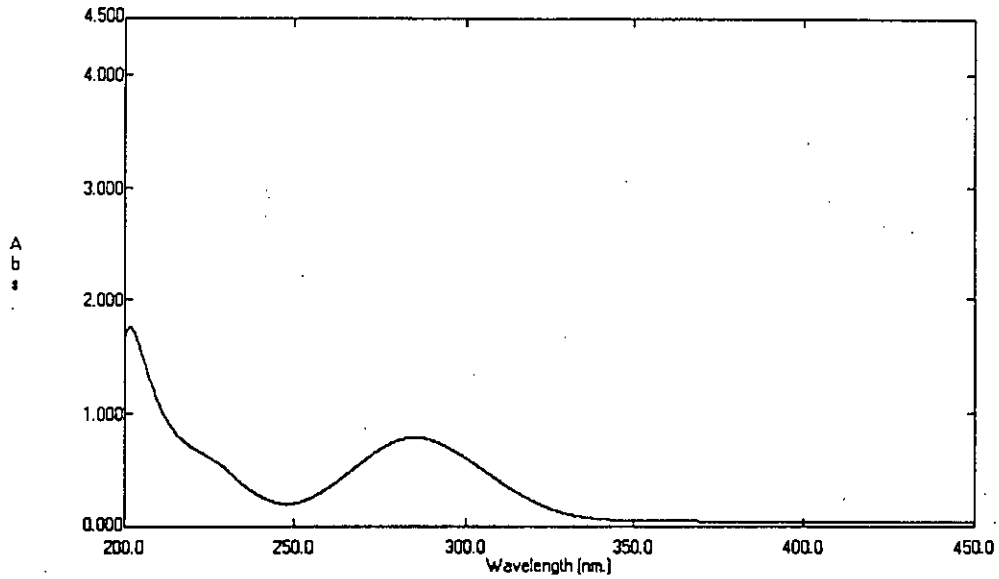

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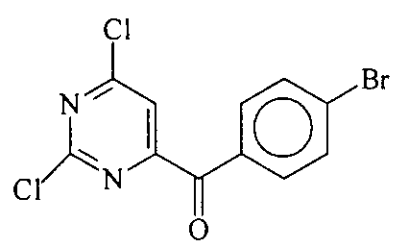

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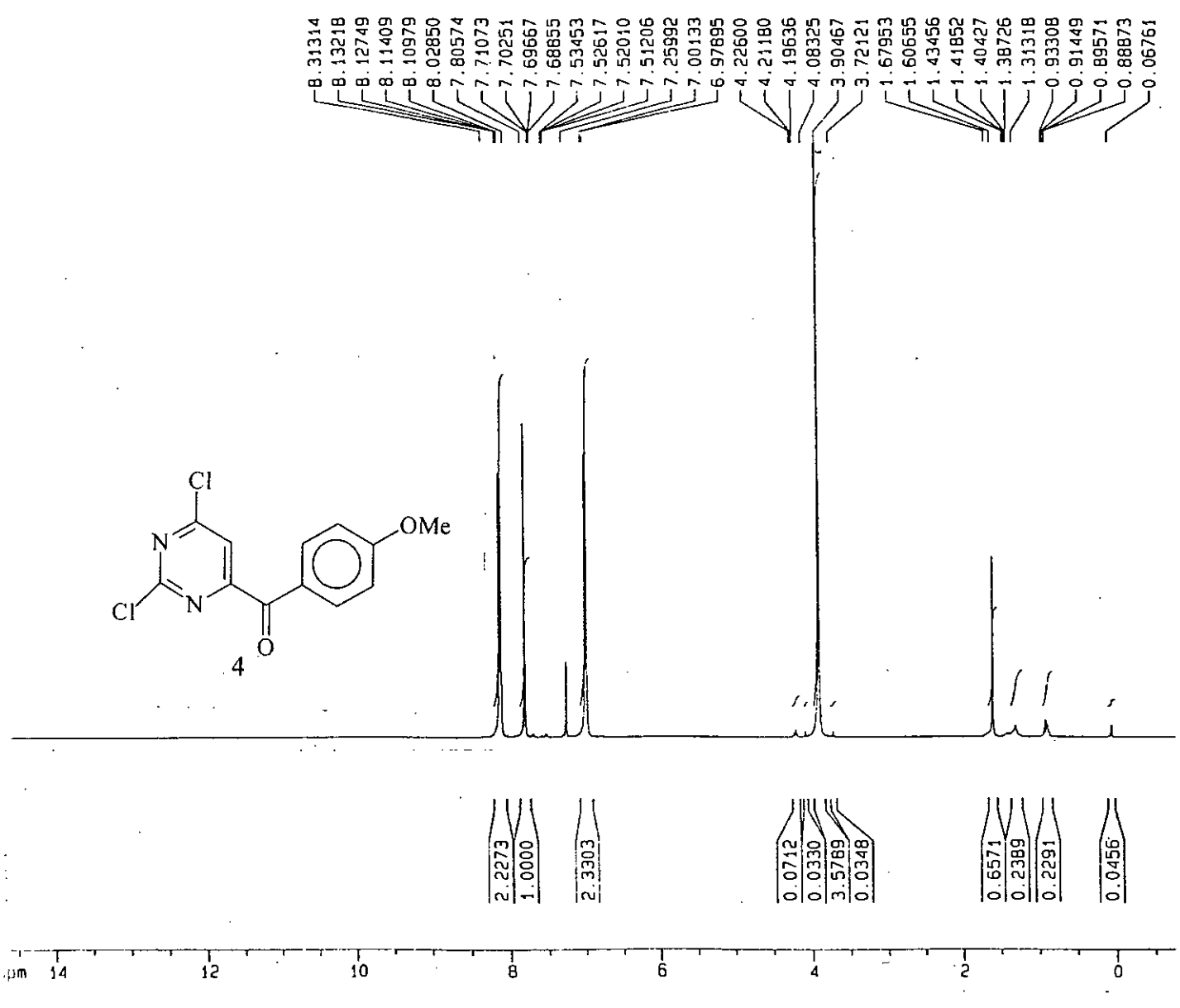

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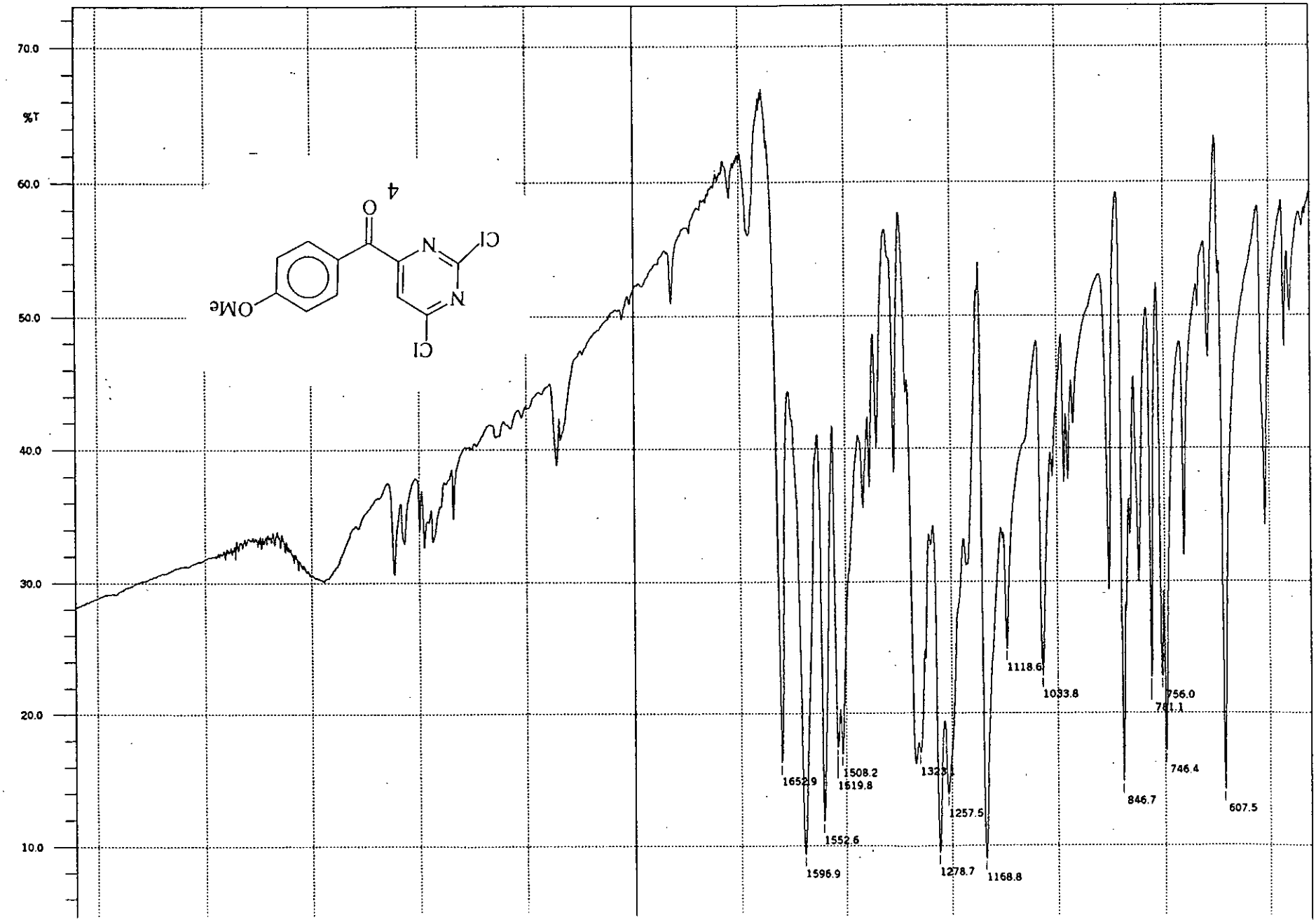
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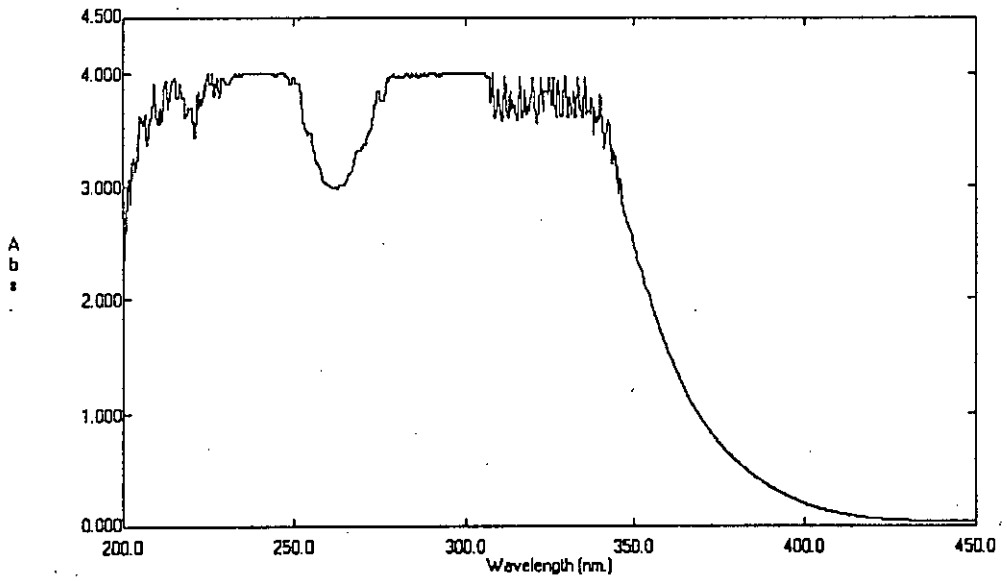

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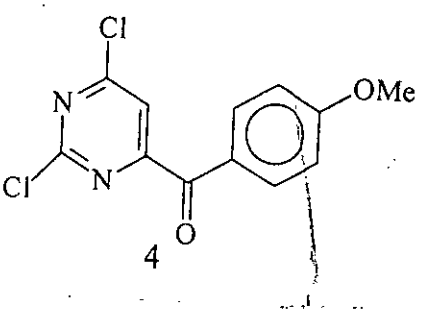

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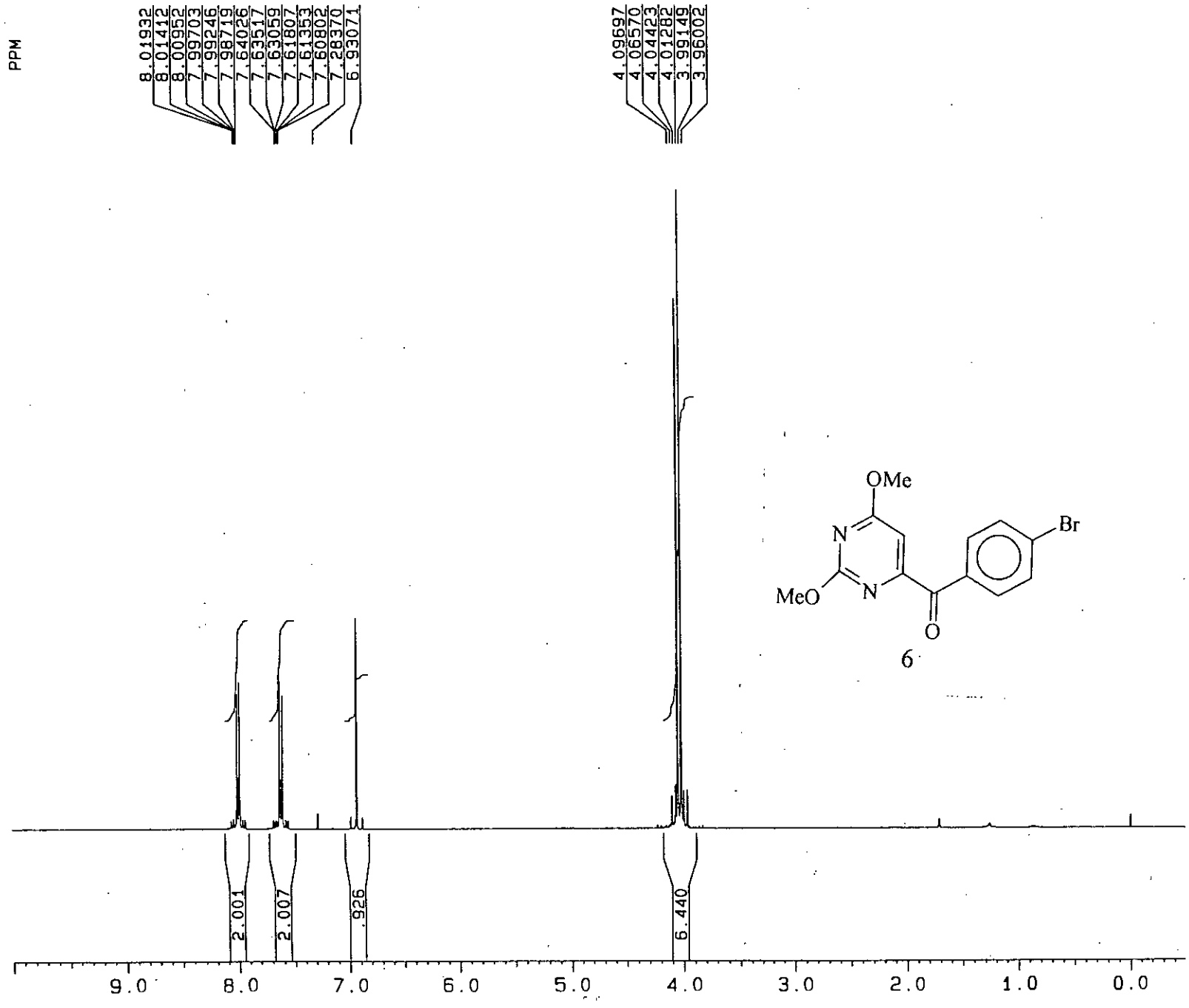

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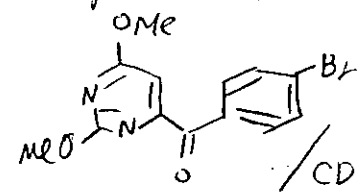

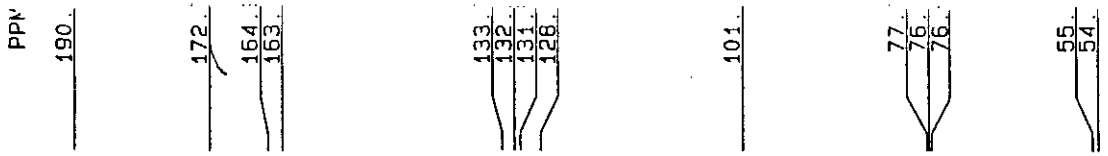

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DATE 28-1-4

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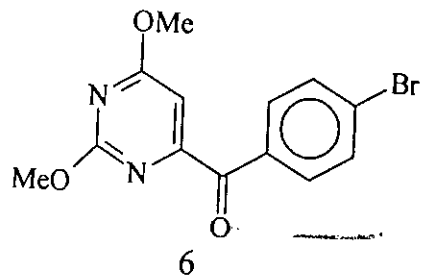

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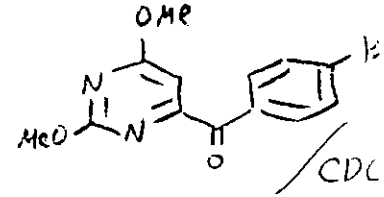

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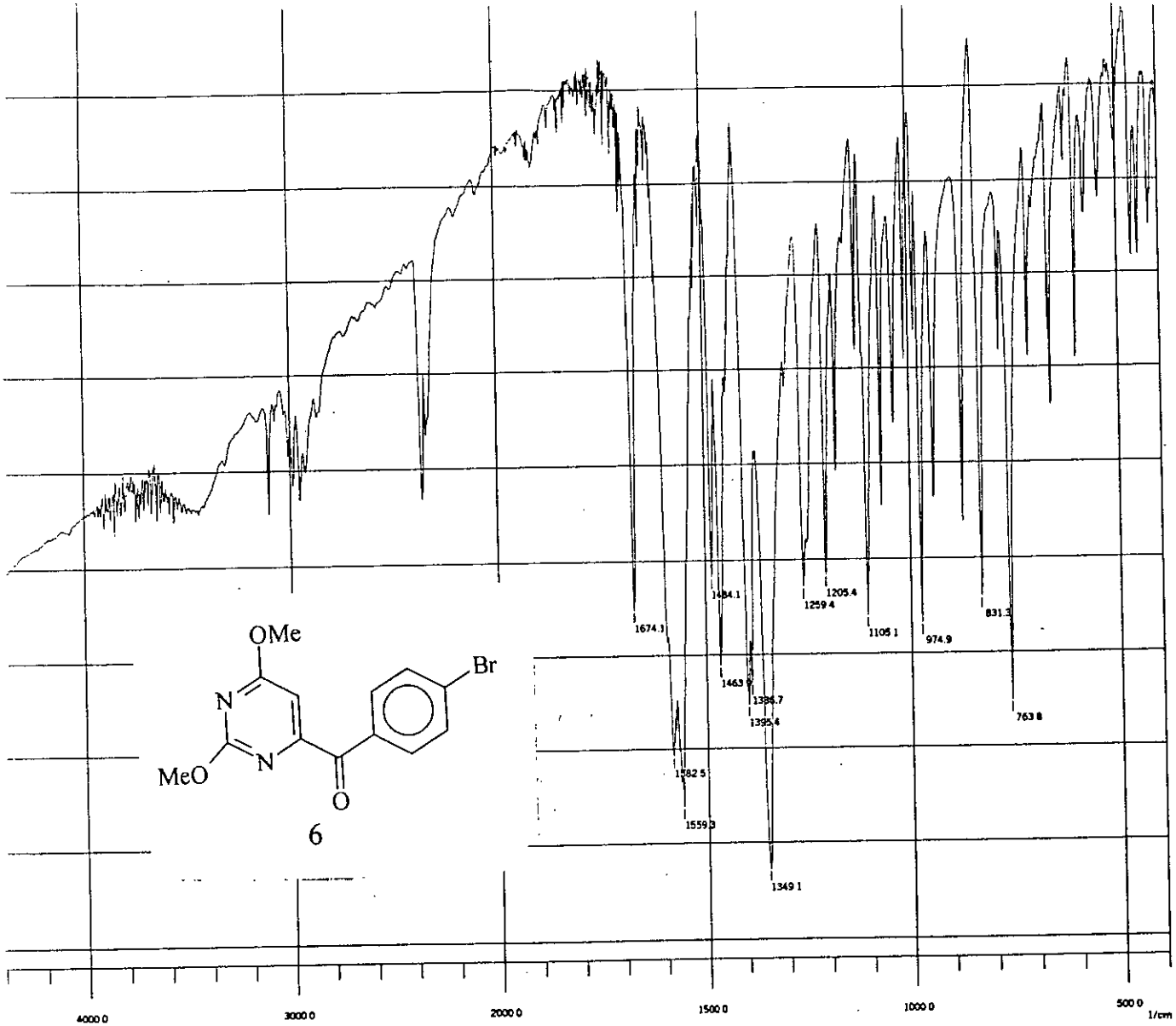

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3	974.9	31.628
4	1105.1	32.031
5	1205.4	34.158
6	1259.4	33.588
7	1349.1	18.629
8	1386.7	28.487
9	1395.4	27.302
10	1463.9	29.407
11	1484.1	34.152
12	1559.3	21.897
13	1582.5	24.653
14	1674.1	32.413

T 15, 7 June, 2003

IRS: T 15, 7 June, 2003

05/08/2003	Time:	19:29:07	NScans:	45
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1/cm	Ordinate:	%T	Apodization:	Happ
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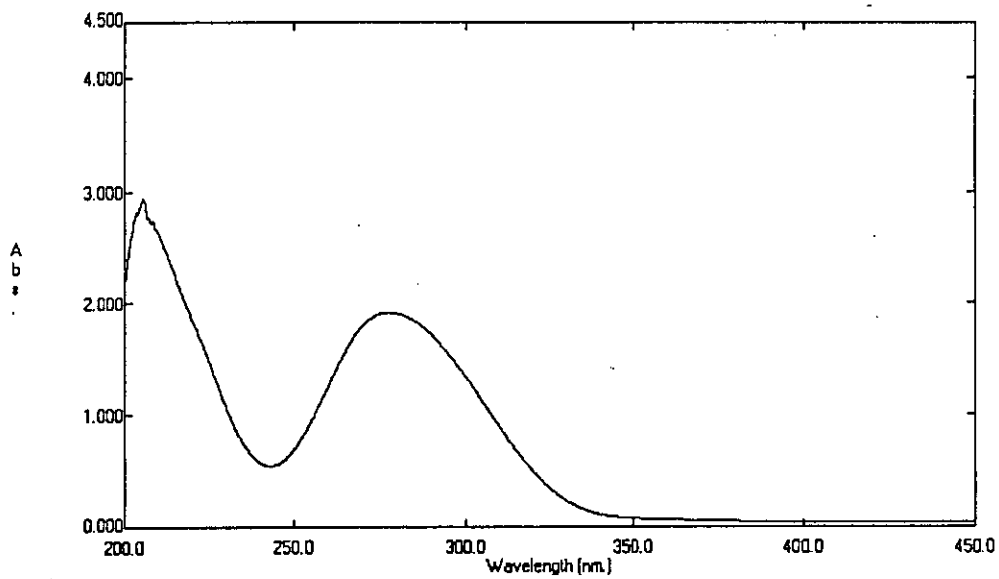

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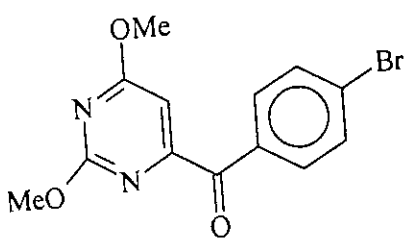

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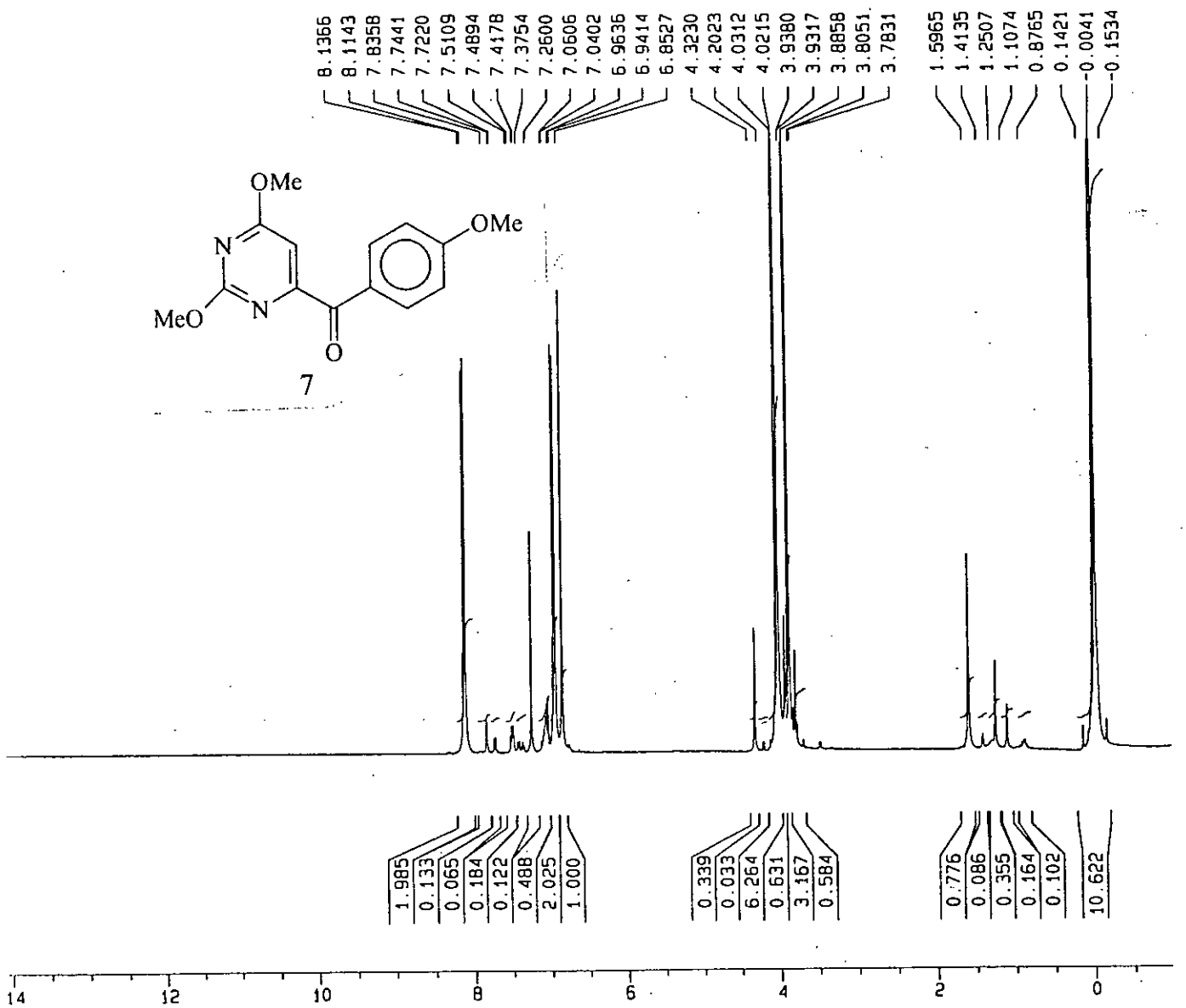

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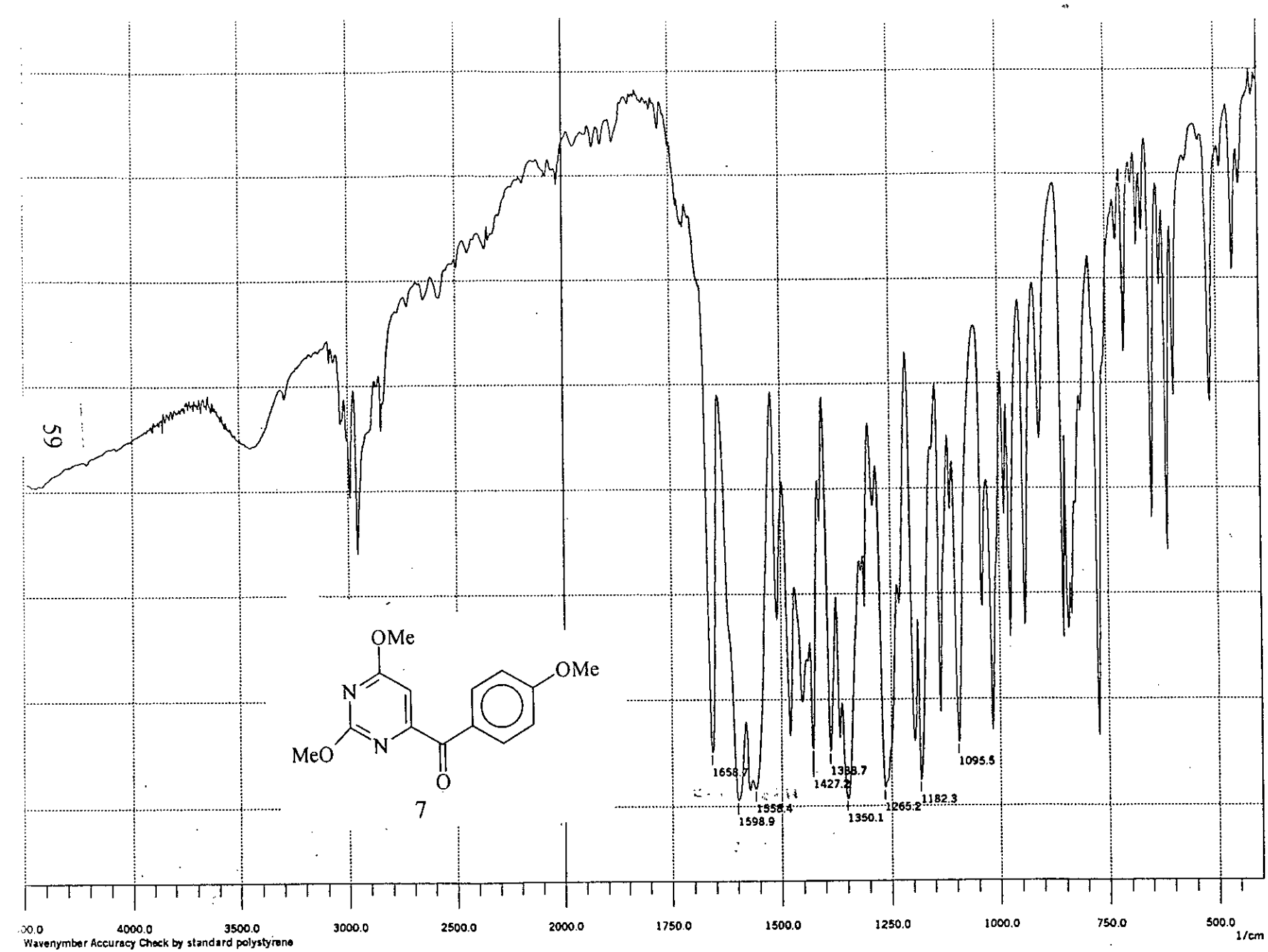
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N
O
OMe
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1265.2
1182.3
1095.5
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4000.0
3500.0
3000.0
2500.0
2000.0
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1500.0
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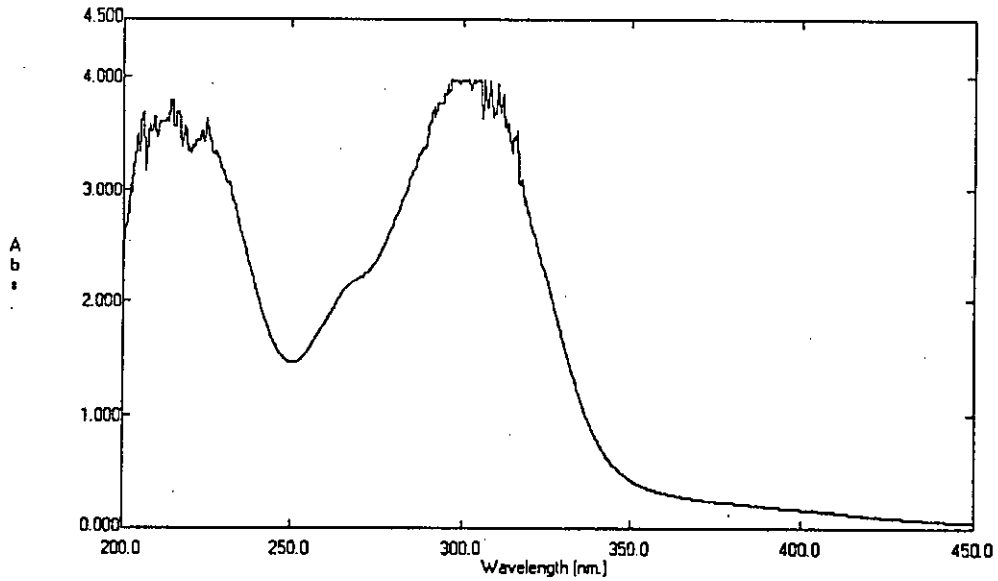
1000.0
750.0
500.0
1/cm
Wavenymber Accuracy Check by standard polystyrene



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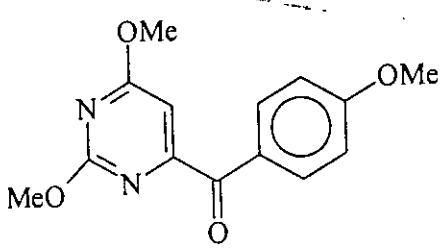

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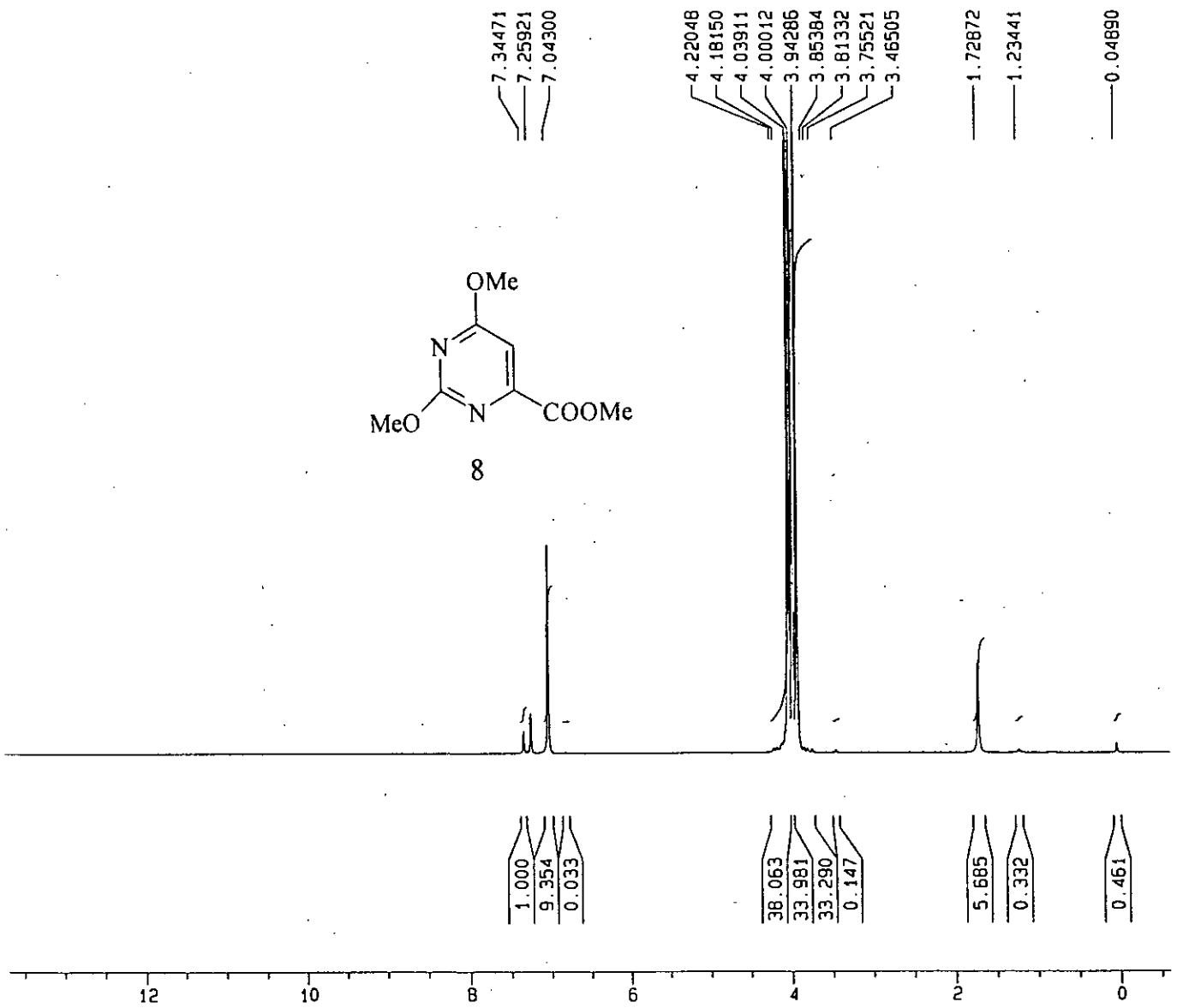

8

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PROCNO	1

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TE	310.0 K
D1	1.00000000 sec

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1D NMR plot parameters

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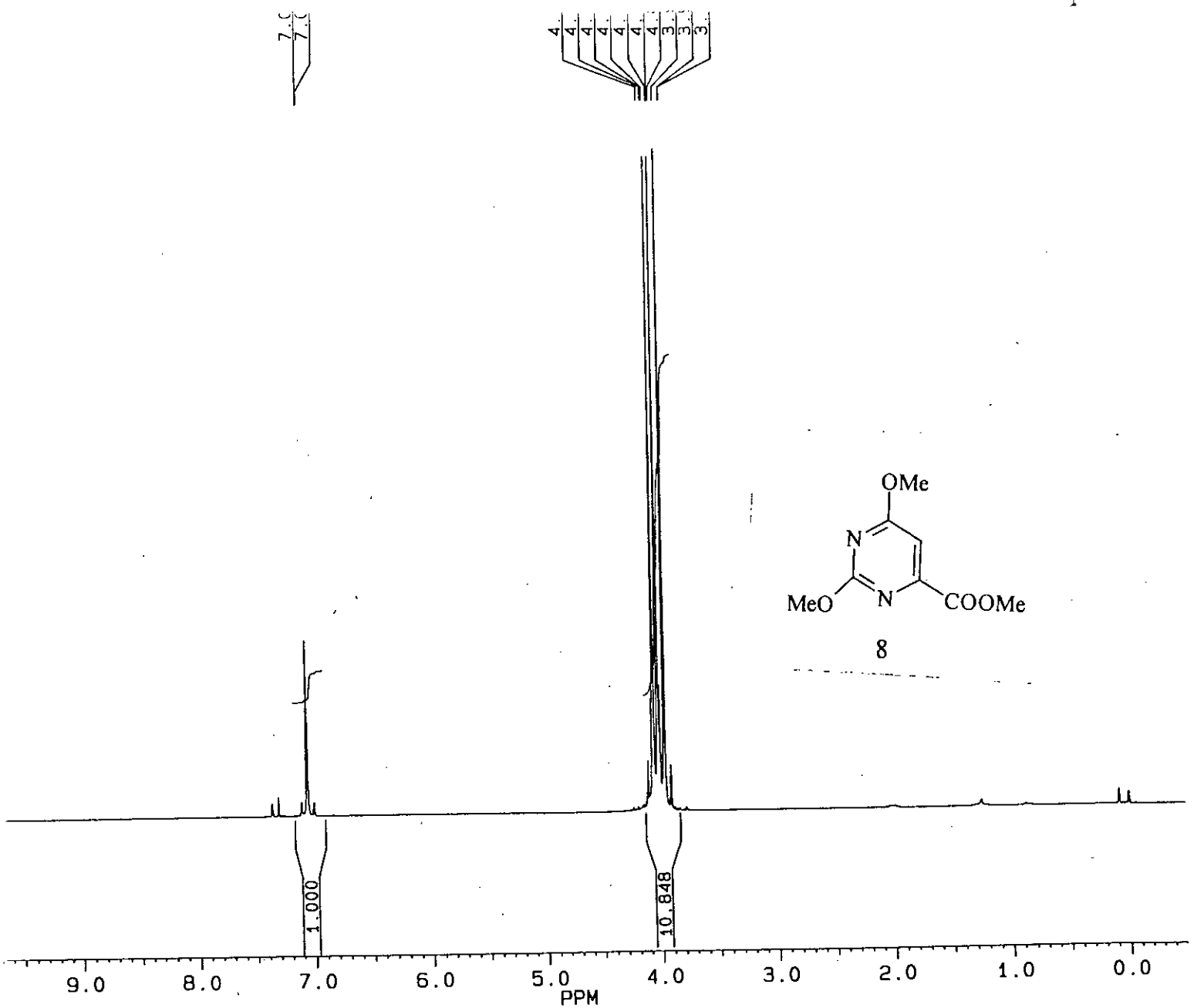

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DATE 19-1-4

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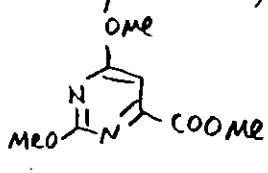
Sample - T10 / ^{1}H NMP



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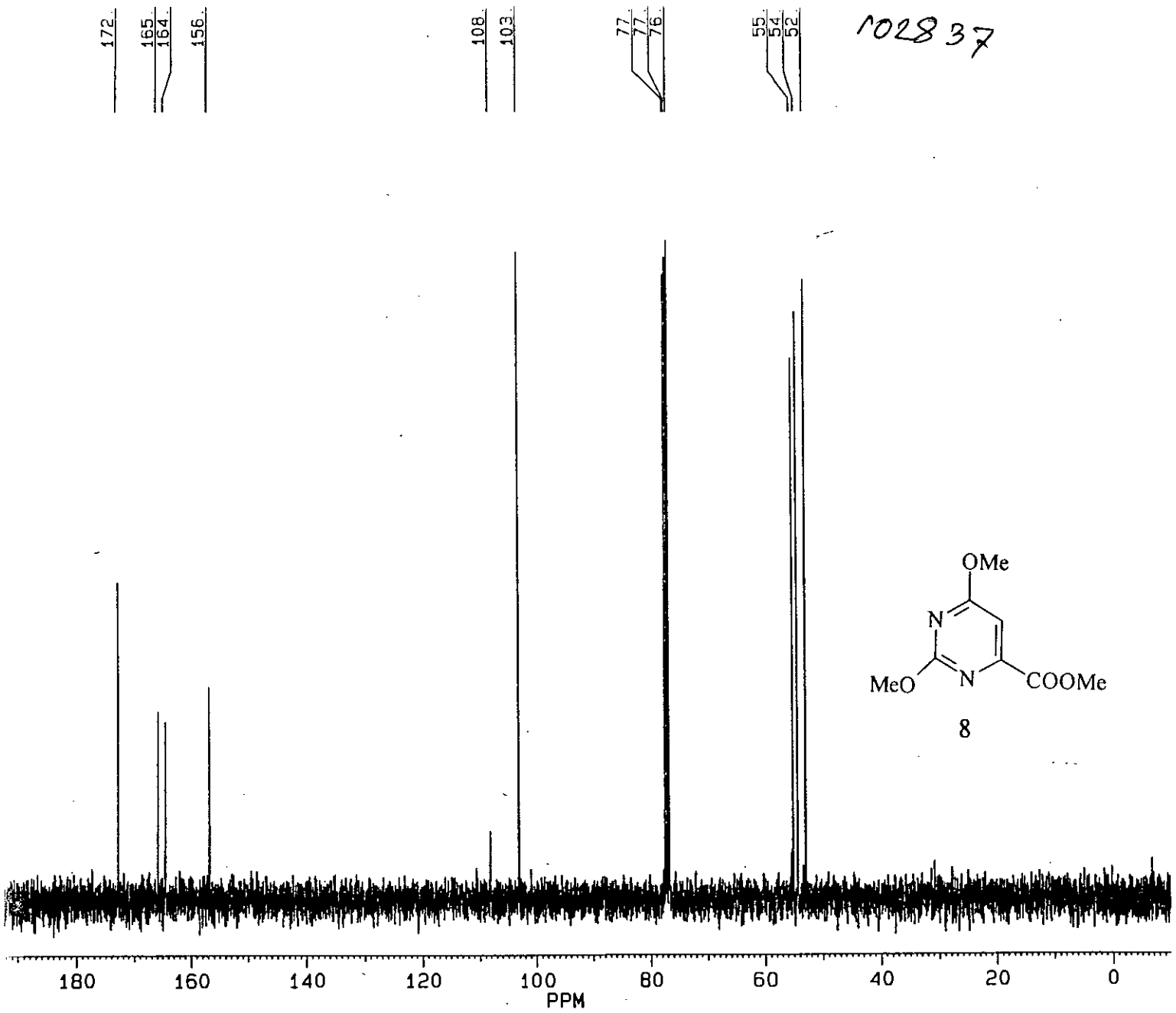

102837

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TE 297

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O2 6400.000
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CY 12.00
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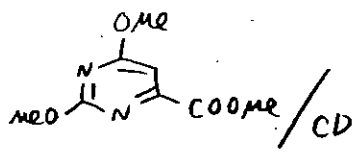
HZ/CM 960.379
PPM/CM 9.545
SR -121.19

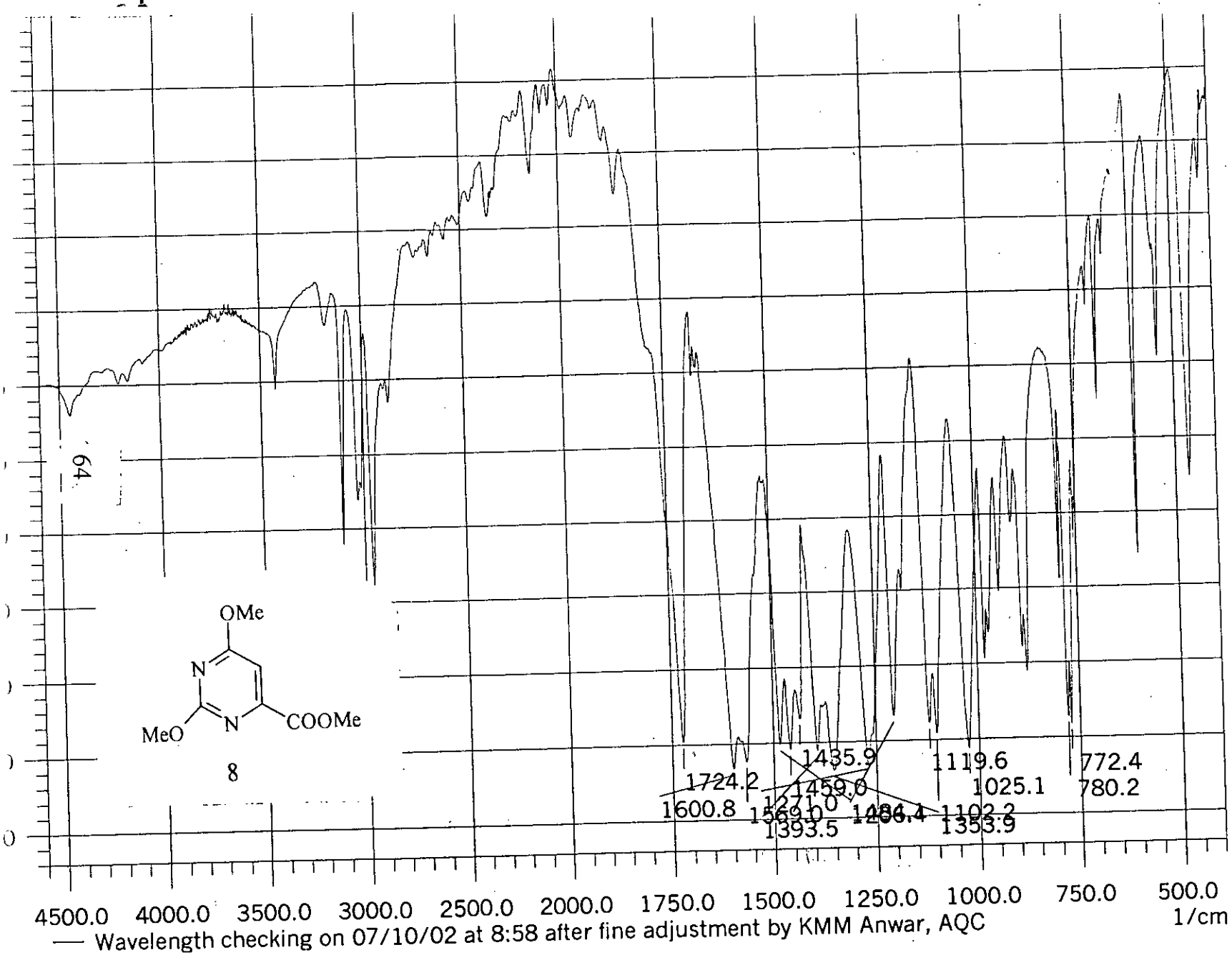
8

Sample – T10 / ^{13}C NMR



/ $CDCl_3$

complete Decoupling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1435.9
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1025.1
1102.2
1353.9
772.4
780.2
4500.0 4000.0 3500.0 3000.0 2500.0 2000.0 1750.0 1500.0 1250.0 1000.0 750.0 500.0
1/cm
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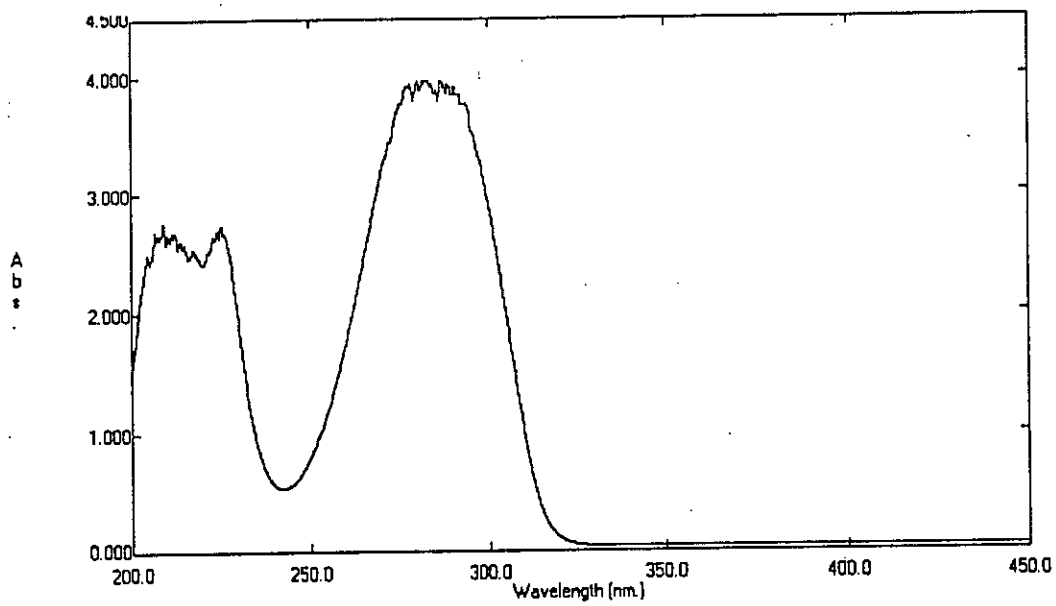

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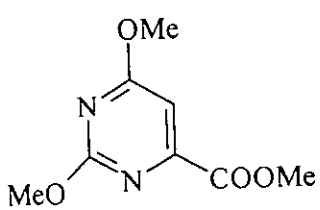


8

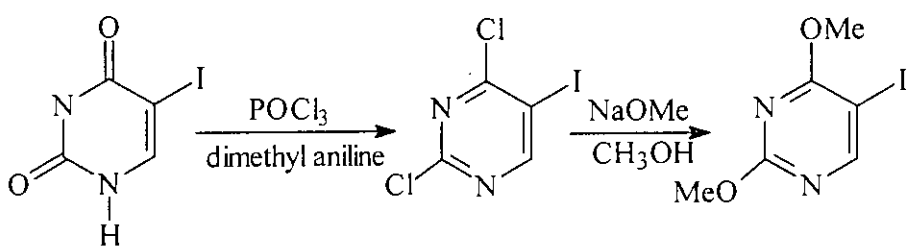
Iodination

2.2.A. Introduction :

5- Substituted derivatives of uracil have been of great importance because of their biological activity. 5-Fluorouracil[86] and the corresponding 2'-dexoy ribonucleoside are being used as anti-cancer agents whereas 5-iodo-2'deoxy uridine[87] is of importance as an antiviral agent. Various 5-alkyl substituted derivatives of uracil have been synthesized for both anticancer and antiviral properties[88]. Notable amongst them is (E)-5-(2-bromovinyl)-2'-deoxyuridine (BVDU)[89] which has been found to be one of the most potent drugs effective against herpes simplex virus type 1, (HSV-1).

Iodo derivatives of pyrimidines and uracils have been utilized for the synthesis of the corresponding carbon-substituted derivatives.[88,89] Thus the availablility of suitable iodo derivatives of pyrimidine and uracils becomes of importance. In connection with our studies on 5,6-disubstituted pyrimidines derivatives, we needed a large quantity of 5-substituted iodo-derivatives of pyrimidine.

The synthesis[90] of 2,4- dimethoxy-5-iodo-pyrimidine from 5-iodouracil **78** was performed by the treatment with phosphorus oxychloride and dimethyl aniline to convert it to 2,4-dichloro-5-iodo-pyrimidine **79** which on treatment with sodium methoxide in methanol was converted to 2,4-dimethoxy-5-iodo-pyrimidine **80** as shown scheme-3.

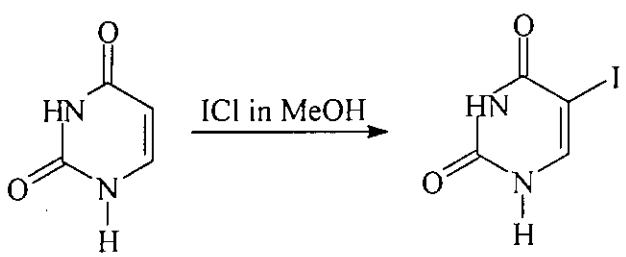


(78) (79) (80)

(Scheme-3)

On large scale synthesis of 2, 4-dimethoxy-5-iodo-pyrimidine, however, are found the method to be quite hazardous. 2, 4-Dichloro-5-iodopyrimidine was found to be highly toxic.

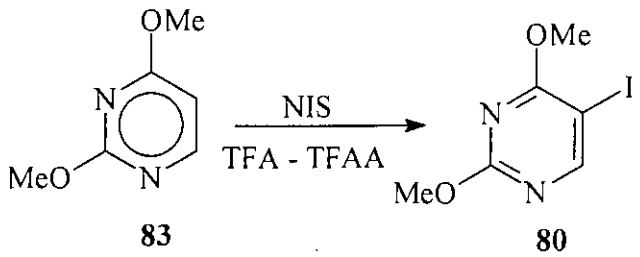
Iodine monochloride has been utilized for iodination of uracil nucleosides[91,92]. It was reported that uracil itself on refluxing with iodine monochloride in methanol yielded 5-iodiouracil in moderate yield (scheme–4). 2,4-dimethoxypyrimidine, however, on refluxing with iodine monochloride in methanol, did not give the desired 5-iodo-2, 4-dimethoxyprimidine. Iodination at C-5-position took place; however, concurrent removal of the methoxy groups led to 5-iodouracil (see scheme-4).



(81) (82)

(Scheme-4)

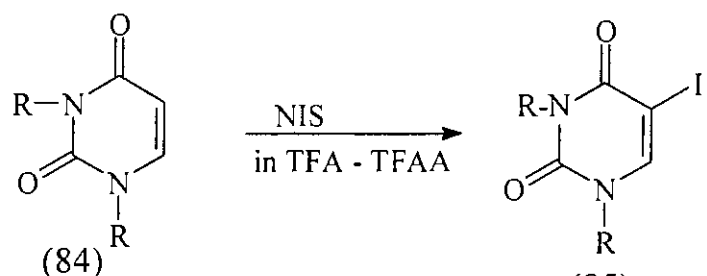
Although the use of *N*-iodosuccinimide[93] (NIS) in chloroform for the iodination of pyrimidines has been reported , there were difficulties with the iodination of several pyrimidines. We found that 2,4-dimethoxypyrimidine could not undergo iodination with NIS in chloroform even after eight hours of refluxing. However, substitution of chloroform with trifluoroacetic anhydride (TFA-TFAA) mixture as solvent led to successful iodination with NIS. Thus 2,4-dimethoxypyrimidine **83** can be efficiently iodinated with NIS in TFA-TFAA as shown in scheme-5.



83 **80**

(Scheme - 5)

NIS in TFA-TFAA could also be used for the iodination of uracil and its simple *N*-alkylderivatives (Scheme-6).



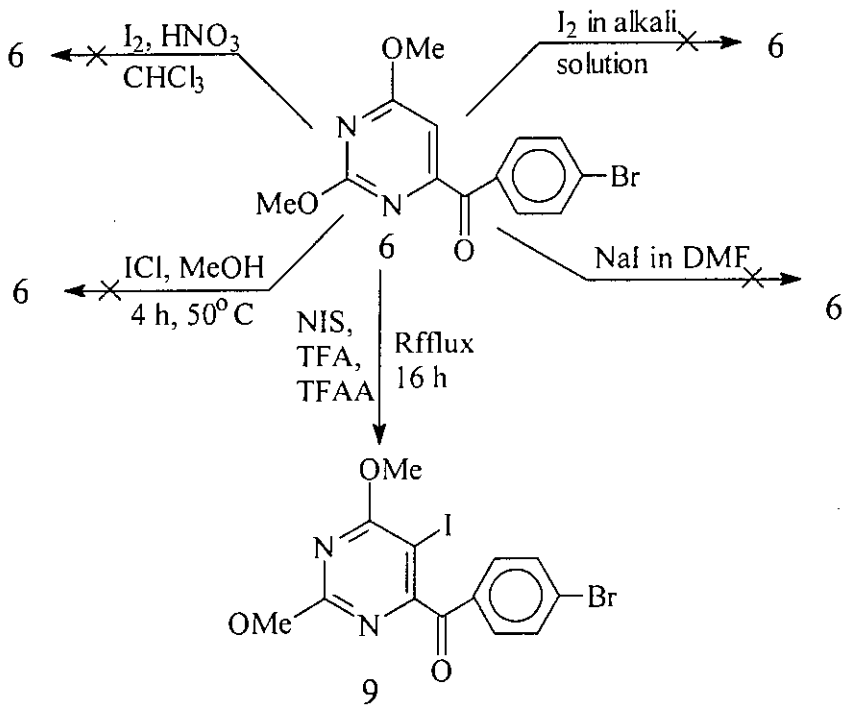
(84) (85)

R = H, CH_3, $CH_2C_6H_5$

(Scheme-6)

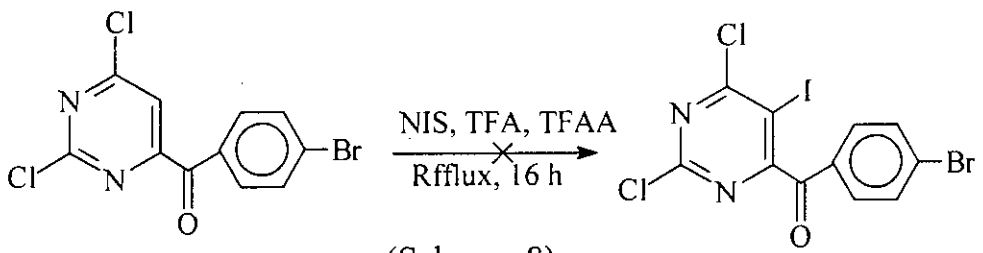
2.2.B. Results and Discussion:

In view of the extensive use of iodo derivatives of pyrimidine for the synthesis of the corresponding carbon-substituted derivatives, we attempted to synthesis 5-iodopyrimidines by using different methods. The iodination reaction was attempted by several methods but only NIS-TFA-TFAA method gave the desired products. The iodination of 2, 4-dimethoxy-6-*p*-bromo benzoyl pyrimidine was performed by the following methods(Schem-7).



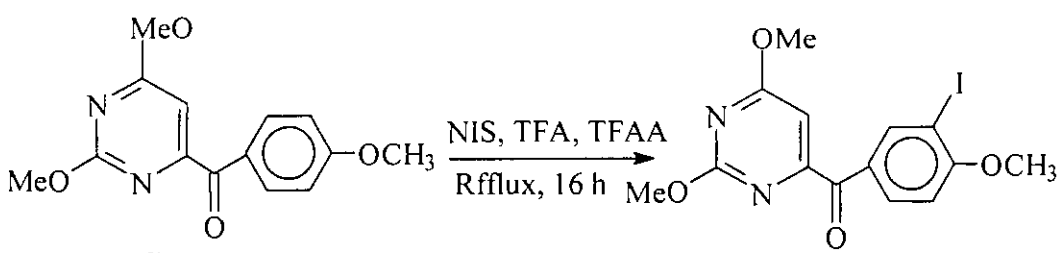
(Scheme-7)

The iodination reaction of 2, 4 dichloro-6-*p*-bromobenzoyl pyrimidine was also carried out by using NIS-TFA-TFAA under refluxing condition but desired compound 5-iodo pyrimidine was not obtained(Schem-8).



(Scheme-8)

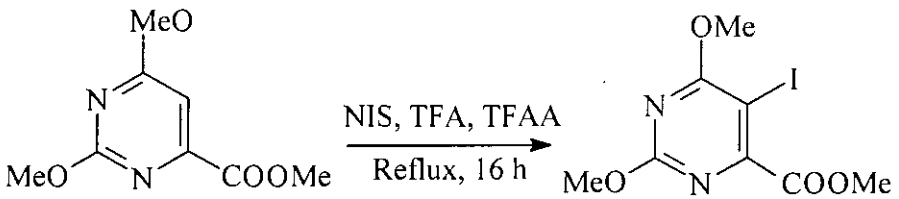
When 2, 4-dimethoxy-6-*p*-anisoyl pyrimidine **7** was subjected to iodination reaction utilizing NIS-TFA-TFAA under the same condition instead of 5-iodopyrimidine yielded 2, 4 – dimethoxy – 6 – *p* – methoxy – m – iodo benzoyl pyrimidine **10**.



7 10

(Scheme -9)

2,4-Dimethoxy-6-methyl orotate **8** was subjected to iodination reaction using NIS-TFA-TFAA under the same condition to afford 2,4-dimethyoxy-5-iodo 6-methyl orotate **11**.



8 (Scheme-10) 11

N-Iodosuccinimide in trifluoroacetic acid and trifluoroacetic anhydride was found to be an excellent reagent for the iodonation at C-5 position of 2, 4-dimethoxy –6-substituted pyrimidine.

2.2.C. Structure determination:

The structure of the compounds was established from their analytical and spectroscopic data. 2, 4 -Dimethoxy-5-iodo-6-*p*-bromobenzoyl pyrimidine **9** colourless crystal, mp 185-186 °C, showed absorption band at 1681.8 for C=O stretching vibration and in the region 1576.7 and 1588.3 for C=C and C=N stretching vibration in IR spectrum.

In ^{1}HNMR spectrum of the compound the chemical shift position at δ 3.97 and 4.10 for OCH_3 as singlet and at 7.62 (d, 2H) and 7.73 (d, 2H) for aromatic proton were obtained. No peak was obtained for C-5H.

The ^{13}CNMR spectrum of the compound showed chemical shift at δ 191.9 for C=O and at 55.6 and 55.7 for two OCH_3 groups.

2,4-Dimethoxy-6-*p*-methoxy-*m*-iodobenzoyl pyrimidine 10 was crystalline compound. Its melting point was 118-119 °C. The IR spectrum of the compound showed absorption band at 1651 cm^{-1} for C=O and in the region 1577.7 and 1562.25 for C=C and C=N stretching vibration.

In the ^{1}HNMR spectrum of the compound the chemical shift position at δ 6.89 as a singlet for C-5 H was observed which confirmed that the iodination did not take place at C-5 position but iodination took place at the meta position of the benzene ring.

The ^{13}CNMR spectrum of the compound showed chemical shift at δ 54.4, 55.3 and 56.7 for three OCH_3 groups and at δ 102.17 for Py C-5 H and 189.0 for C=O. The chemical shift at δ 102.1 indicated that iodination did not take place at C-5 position of the pyrimidine ring.

2,4-Dimethoxy-5-iodo-6-methyl orotate **11**, crystalline solid, mp 167-168 °C, showed absorption band at 1728 for C=O stretching vibration in IR spectrum. The ^{1}HNMR spectrum of the compound did not show any chemical shift for C-5 H. It only showed the chemical shift position as strong singlet for three OCH_3 group.

The ^{13}CNMR spectrum of the compound also did not show any chemical shift for C-5 H.

The CHN analysis also confirmed the molecular formula of the compound **11**.

2.2.D. Experimental

General Procedure :

2.2.D.(i) Preparation of 2, 4 – dimethoxy – 5 - iodo – 6 – *p* - bromobenzoyl pyrimidine (9)

Iodine monochloride in methanol (Method A):

A mixture of iodine monochloride (400mg, 2.46 mmol) and 2, 4-dimethoxy -6-*p*-bromobenzoyl pyrimidine (500 mg, 1.6954 mmol) in methanol (6ml) was refluxed for 4h. The solvent was removed and the residue was crystallized from hot methanol.

IR, UV, ^{1}HNMR, ^{13} CNMR spectra of this compound was indistinguishable from those of the same compound. No desired product could be isolated.

Sodium Iodied in DMF (Method B) :

A mixture of 2, 4-dimethoxy -6-*p*-bromobenzoyl pyrimidine (500 mg, 1.6954 mmol) and dry NaI (0.447g) in dry DMF (5ml) was refluxed under N_2 atm. for 2h. The solvent was then removed at high temperature under reduced pressure. The residue was triturated with water and filtered, Crystallized from methanol. Starting materials was obtained but no iodinated product was isolated.

Iodine in KI and KOH (Method C)

A mixture of 2, 4-dimethoxy -6-*p*-bromobenzoyl pyrimidine (500 mg, 1.6954 mmol) and dry I_2 (757.42 mg) in KI (1M, 5 ml), KOH (2M, 2 ml)

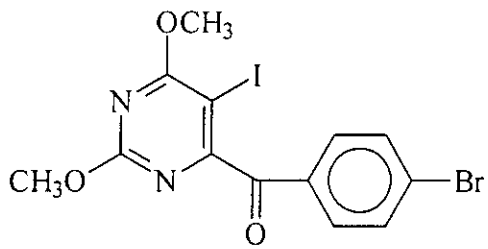
and DMF (5 ml) was refluxed for 2h. The solvent was then removed at high temperature under reduced pressure. The residue was triturated with water and filtered, Crystallized from methanol. No iodinated product could be isolated.

Iodine in HNO_3, $CHCl_3$ (Method D):

A mixture of 2, 4-dimethoxy -6-*p*-bromobenzoyl pyrimidine (500 mg, 1.6954 mmol) and I_2 (757.42 mg) in $CHCl_3$ (20 ml) and HNO_3 (2M, 1.6 ml) was refluxed for 1h. The solvent was then removed at high temperature under reduced pressure. The residue was triturated with water and filtered, Crystallized from methanol. The desired product could not be isolated.

***N*-Iodo succiniamide (NIS) in Trifluroacetic acid and trifloro acetic anhydrate mixture (Method E):**

A mixture of 2, 4-dimethoxy -6-*p*-bromobenzoyl pyrimidine (500 mg, 1.6954 mmol) trifluoroacetic acid (50 ml) and trifluoroacetic anhydride (1 ml) was refluxed for 20 minutes. *N*-Iodosuccinimide (1.2 equiv, 457.74 mg) was added and the reaction mixture was further refluxed for 8 hours. The progress of this reaction was observed with TLC. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue left was dissolved in chloroform (300ml), and successively washed with water (50 ml), saturated sodium bicarbonate (2×40 ml), saturated sodium thiosulfates (2 × 40 ml) and water (2 × 40 ml). The chloroform layer was dried over Sodium sulfate and concentrated to dryness to give 1.15g crude mass. The crude mass was crystallized from methanol.



(9)

mp: 185-186 °C

IR: ν_{max} (KBr) 2958.0, 1681.8, 1576.7, 1588.3, 1555.5, 1479.3, 1449.4, 1403.1, 1379.0, 1364.5, 1248.8, 1227.6, 1069.5, 1017.4, 1010.6, 979.8, 931.6, 849.6, 784.0 and 768.6 cm^{-1}

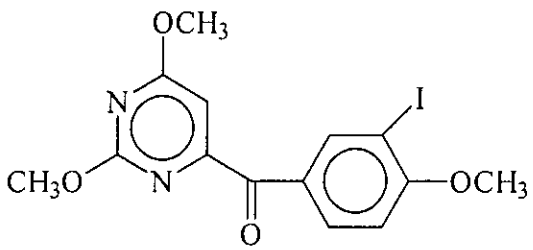
^{1}HNMR: (400MHz, $CDCl_3$)δ_H, 3.97 (s,3H,OCH_3), 4.10(s,3H,OCH_3), 7.62(d, 2H, J = 7.2 Hz, Ar-H), 7.73(d, 2H, J = 7.2 Hz, ArH).

^{13}CNMR: (400MH_z, $CDCl_3$) δ_C 55.6 (OCH_3), 55.7(OCH_3), 65.68, 129.9(Ar-C), 131.6, 132.27, 133.33 (Ar-CH), 165.8, 168.6, 169.7(Py-C), 191.8 (C= O).

2.2.D.(ii). Synthesis of 2,4-dimethoxy - 6 - *p* - methoxy - *m* -iodobenzoyl pyrimidine (10)

A mixture of 2,4 dimethoxy-6-p-methoxybenzoyl Pyrimidine 200 mg, (0.7296 mmol), trifluoroacetic acid (5 ml) and trifluoroacetic anhydride (1ml) was refluxed for 20 minutes. N-Iodosuccinimide (186.88 mg) was added and the reaction mixture was further refluxed for 8 hours. The progress of this reaction was monitored with tlc. The reaction mixture was allowed to cool to room temperature and the solvent was removed under

reduced pressure. The residue left was dissolved in chloroform (300 ml), and successively washed with water (50 ml), saturated sodium bicarbonate (2 × 40 ml), saturated sodium thiosulfate (2 × 40 ml) and water (2× 40 ml) . The chloroform solution was dried over sodium sulfate. After removal of solvent the solid mass ware crystallized from methanol. (130 mg. yield)



(10)

mp = 1181-119 °C

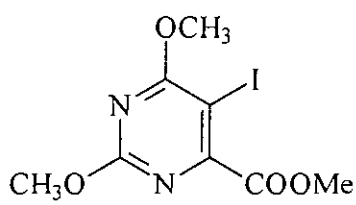
IR: ν_{max} (KBr) 1651.0, 1577.7, 1562.25, 1477.4, 1380.9, 1352. 0, 1269.1, 1201.6, 1049.2 and 767.6 cm^{-1}

^{1}HNMR: (400MHz,$CDCl_3$) δ_H 3.96 (s, 3H $ArOCH_3$), 4.03 (6H,C-2, OCH_3 and C-4 OCH_3), 6.69 (dd, J = 2.0 Hz, Ar-H), 6.86 (d, 1H, J = 8.6 Hz, Ar-H), 6.89 (s,1H,C-5H), 8.69. (dd, J = 2.0 Hz, 1H, ArH), 8.16 (dd, 1H, J = 8.6 Hz, ArH).

^{13}CNMR: δ_H (400MHz, $CDCl_3$) 54.47 (OCH_3) 55.34 (OCH_3) 56.78 (OCH_3) 102.17 (Py-C-5H), 110.02 (Ar-CH), 129.86 (ArC), 133.23 (Ar-H), 142.87, 162.27, 63.75 (Py-C) and 189.03 (C=O).

2.2.D.(iii). Preparation of 2, 4 – dimethoxy – 5 – iodo – 6 – methyl arotate (11)

A mixture of 2,4-dimethoxy-6-carbomethoxy-pyrimidine (2.2 g 0.1138 mmol) trifluoroacetic acid (50ml) and trifluoroacetic anhydride (1ml) was refluxed for 20 minutes. N-Iodosuccinimide (1.2eq, 3.07 g) was added and the reaction mixture was farther refluxed for 8 hours. The progress of this reaction was observed with TLC. The reaction mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure. The residue left was dissolved in chloroform (300ml), and successively washed with water (50ml), saturated sodium bicarbonate (2×40 ml), saturated sodium thiosulfates (2×40 ml) and water (2×40 ml). The chloroform layer was dried over Sodium sulfate and concentrated to dryness to give 1.15g crude mass. The crude mass was crystallized from methanol .



11

mp: 167-168°C.

IR: ν_{max} (KBr) 1728.1, 1553.6, 1486.1, 1454.2, 1437.8, 1383.8, 1354.9, 1234.4, 1198.7, 1169.7, 1108.0, 1039.6, 1016.4, 965.3 and 786.9 cm^{-1}.

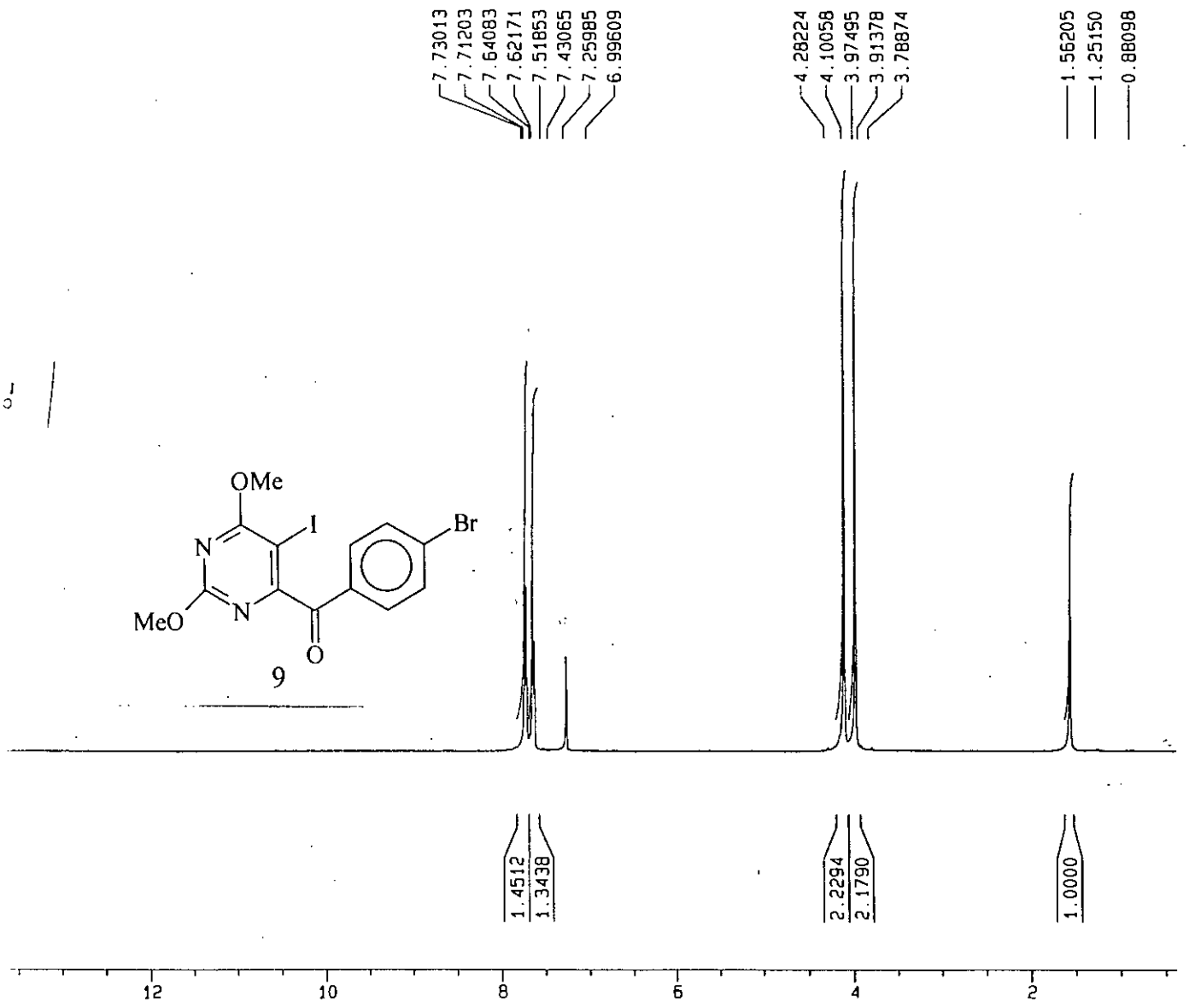
UV(EtOH) : λ_{max} 286.80 and 234.80 nm.

^{1}**HNMR:** (400 MHz, $CDCL_3$) δ_H 3.92 (3H, OCH_3), 3.95(3H, OCH_3), 4.00(3H, $COOCH_3$).

^{13}**CNMR:** (100MHz $CDCl_3$) δ_C 53.0(OCH_3), 54.3(OCH_3), 55.5(OCH_3), 66.57, 103.6, 162.0, 165.38, 169.97(C=O).

Calcd : $C_8H_9N_2O_4I$ (C, 29.65, H, 2.80; N, 8.64%.)

Found: C, 30.17, H, 2.80, N, 8.66%.



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EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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PULPROG	zg30
TD	32768
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DS	0
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	362
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

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

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

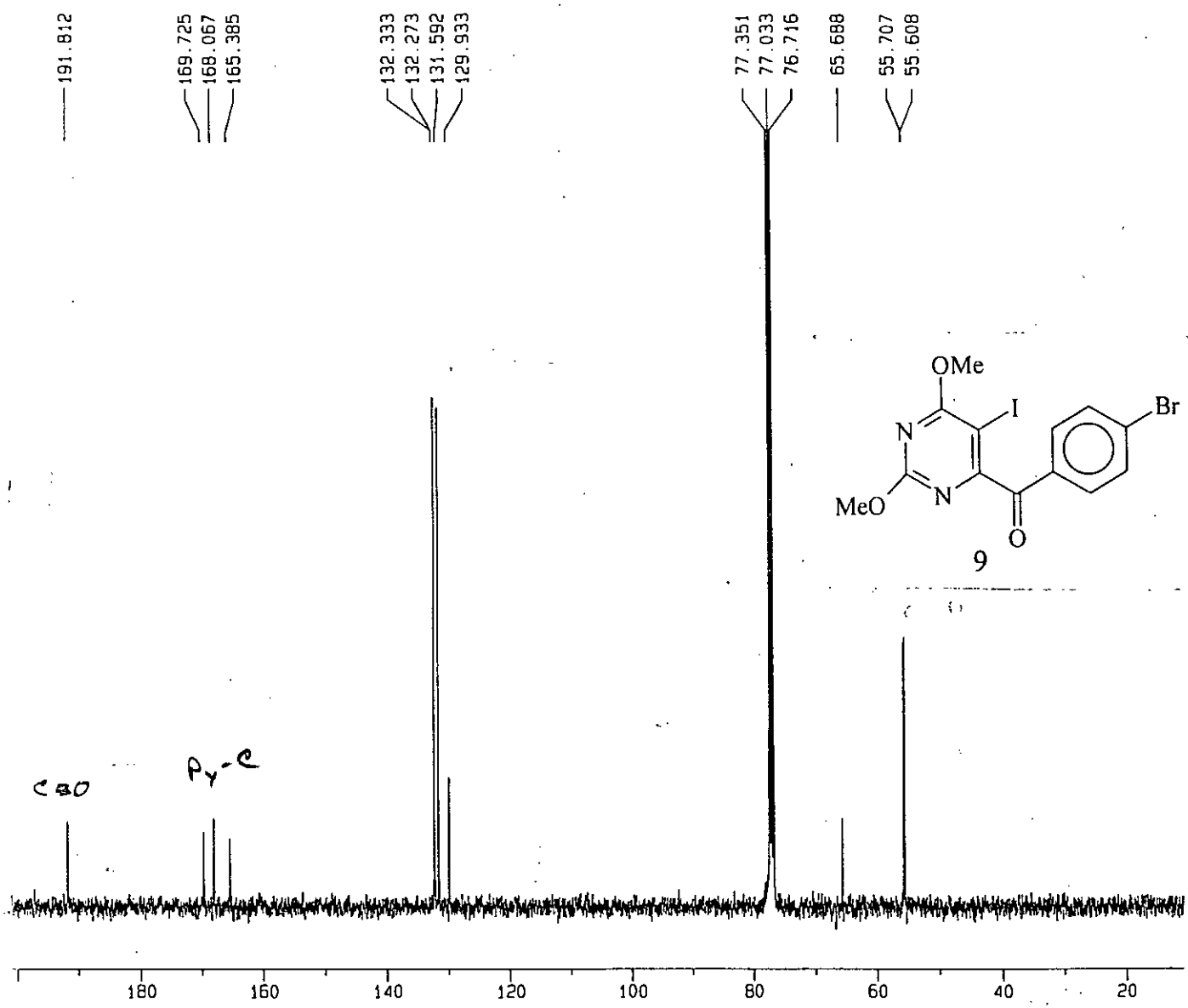
F2 - Processing parameters

SI	32768
SF	400.1400086 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	14.330 ppm
F1	5734.02 Hz
F2P	0.382 ppm
F2	152.66 Hz
PPMCM	0.69743 ppm/cm
HZCM	279.06839 Hz/cm

Analytical, BCSIR, 13C Spectrum T-16 in CDCl3, Tanvir, BUET



9

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Current Data Parameters
NAME                  A1179
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
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PULPROG             zgpg30
TD                     32768
SOLVENT                CDCl3
NS                      1113
DS                         2
SWH               24154.590 Hz
FIDRES             0.737140 Hz
AQ                 0.6783476 sec
RG                     16384
DW                  20.700 usec
DE                   6.00 usec
TE                  300.0 K
D1                1.50000000 sec
d11               0.03000000 sec
d12               0.00002000 sec

********** CHANNEL f1 **********
NUC1                     13C
P1                    8.30 usec
PL1                  -6.00 dB
SFO1           100.6253045 MHz

********** CHANNEL f2 **********
CPDPRG2              waltz16
NUC2                     1H
PCPD2                80.00 usec
PL2                  -6.00 dB
PL12                 16.00 dB
PL13                 120.00 dB
SFO2           400.1400000 MHz

F2 - Processing parameters
SI                     32768
SF             100.6152815 MHz
WDW                       EM
SSB                        0
LB                    2.50 Hz
GB                         0
PC                      1.40

1D NMR plot parameters
CX                    20.00 cm
F1P                 210.009 ppm
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F2P                  10.840 ppm
F2                 1090.65 Hz
PPMCM                9.95847 ppm/cm
HZCM              1001.97418 Hz/cm
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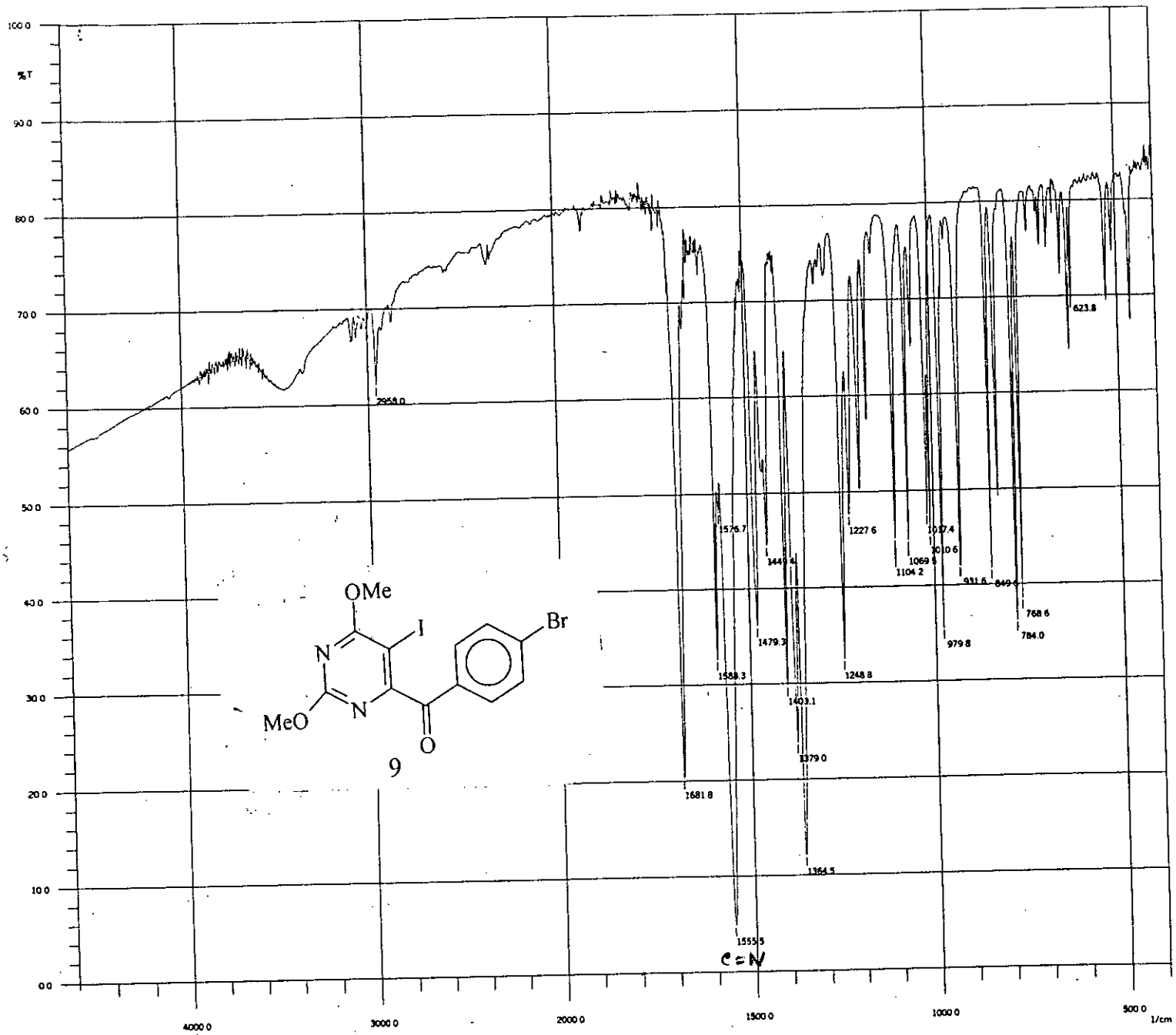

Peaktable of T16.IRS, 22 Peaks
Threshhold: 50, Noise: 2, No Range Selection

No.	Pos. (1/cm)	Inten. (%T)
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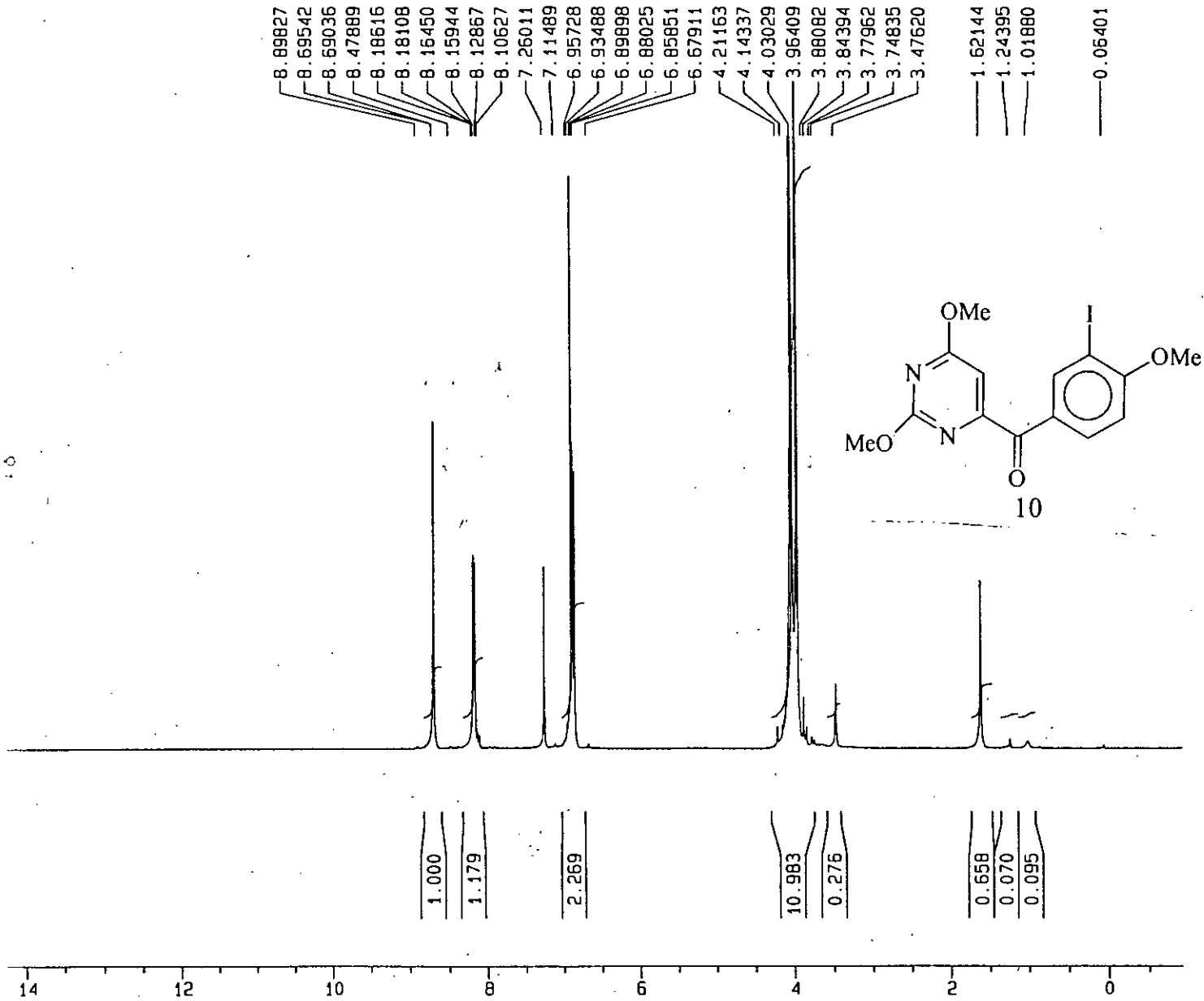
2	768.6	38.462
3	784.0	36.151
4	849.6	41.682
5	931.6	42.000
6	979.8	35.453
7	1010.6	45.391
8	1017.4	47.530
9	1069.5	44.843
10	1104.2	45.013
11	1227.6	47.611
12	1248.8	32.441
13	1364.5	12.073
14	1379.0	23.825
15	1403.1	29.787
16	1449.4	44.499
17	1479.3	36.050
18	1555.5	4.867
19	1576.7	47.998
20	1588.3	32.563
21	1681.8	20.252
22	2958.0	62.097

T16, 16June, 2003



NAME	A76B
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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PULPROG	zg30
TD	32768
SOLVENT	Aceton
NS	128
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FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	64
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

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

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

F2 - Processing parameters

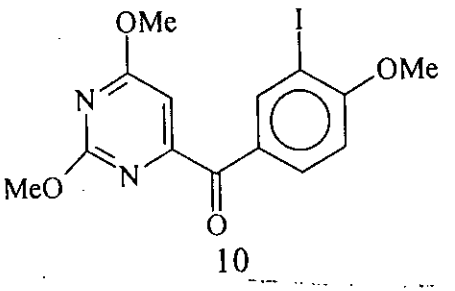
SI	32768
SF	400.1400092 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

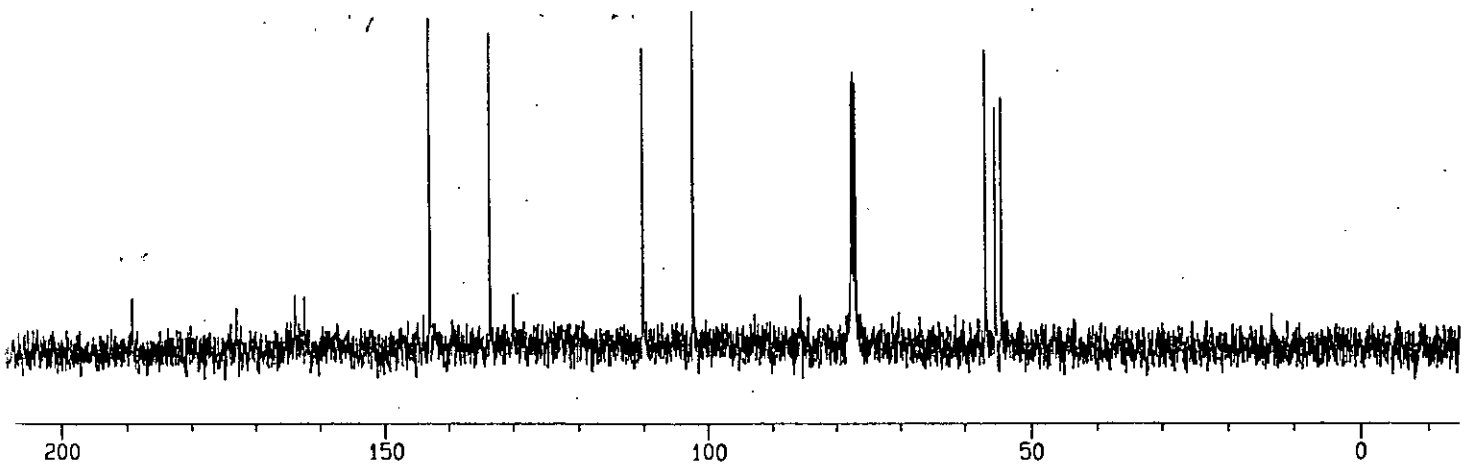
CX	20.00 cm
F1P	14.865 ppm
F1	5948.10 Hz
F2P	-0.911 ppm
F2	-364.61 Hz
PPMCM	0.78881 ppm/cm
HZCM	315.63547 Hz/cm

Analytical, BCSIR Lab. Dhaka 13C Spectrum T-6 in CDCL3 Tanvir BUET.

189.038
163.757
162.274
142.878
133.469
129.866
110.027
102.178
85.526
77.475
77.156
76.839
56.787
55.340
54.476



10



Current Data Parameters

NAME	A768
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

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SOLVENT	CDCl3
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DS	0
SWH	24154.590 Hz
FIDRES	0.737140 Hz
AQ	0.6783476 sec
RG	16384
DW	20.700 usec
DE	6.00 usec
TE	300.0 K
D1	1.50000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

********** CHANNEL f1 **********

NUC1	13C
P1	6.60 usec
PL1	-6.00 dB
SFO1	100.6253045 MHz

********** CHANNEL f2 **********

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

F2 - Processing parameters

SI	32768
SF	100.6152721 MHz
WDW	EM
SSB	0
LB	2.50 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	216.613 ppm
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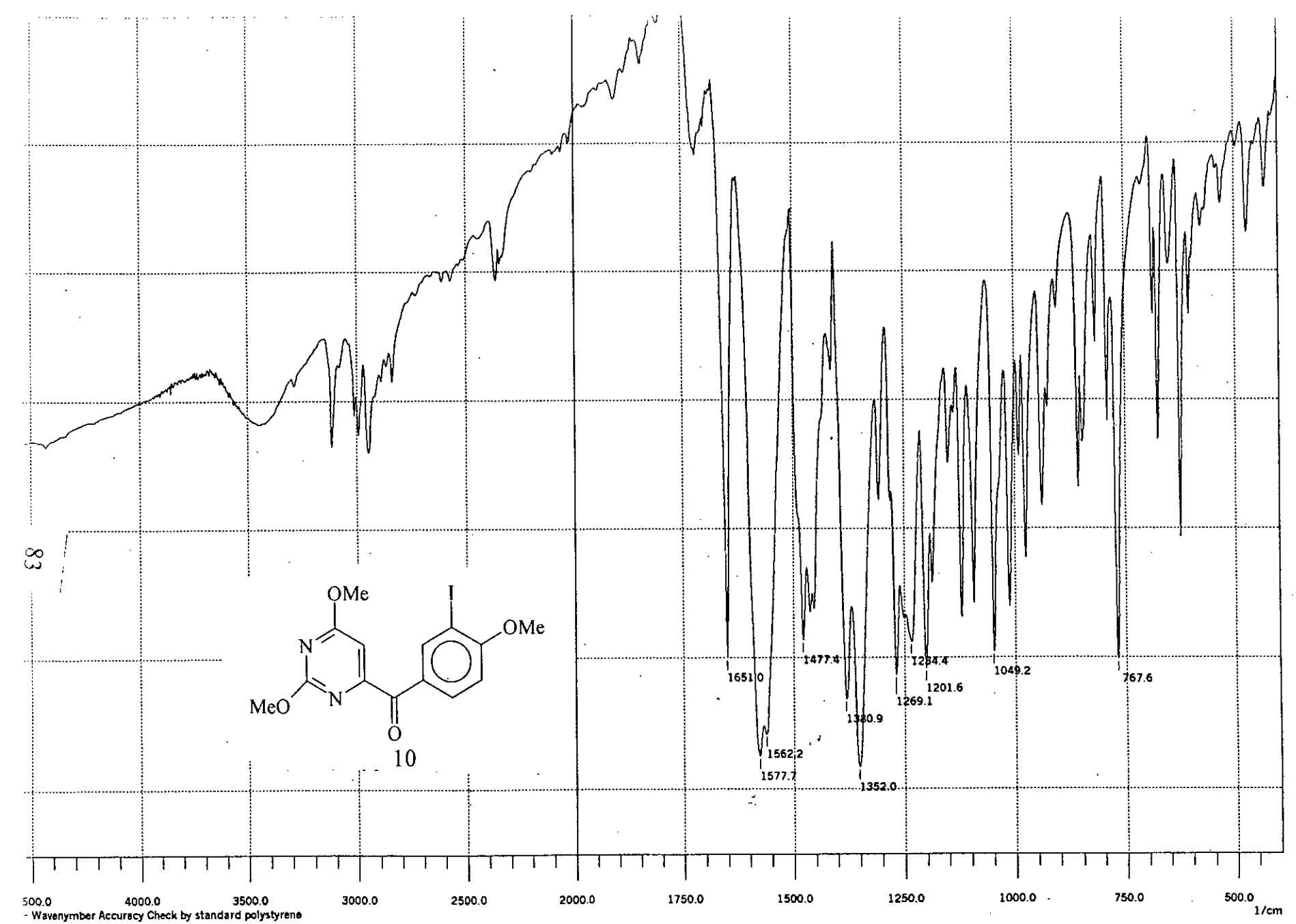
F2P	-14.583 ppm
F2	-1467.30 Hz
PPMCM	11.55984 ppm/cm
HZCM	1163.09595 Hz/cm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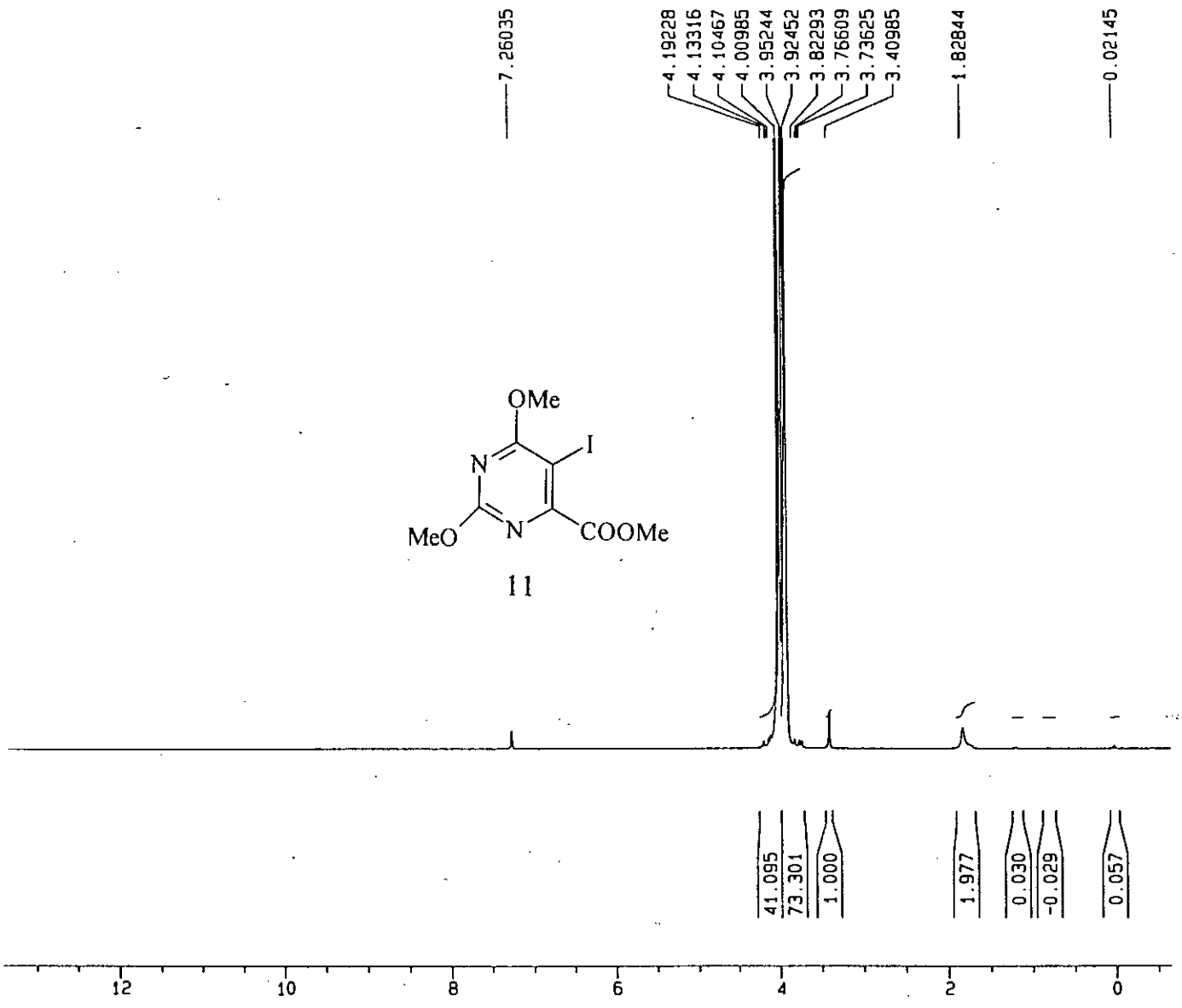
1577.7
1477.4
1380.9
1352.0
1269.1
1234.4
1201.6
1049.2
767.6
4000.0
3500.0
3000.0
2500.0
2000.0
1750.0
1500.0
1250.0
1000.0
750.0
500.0
1/cm
- Wavenymber Accuracy Check by standard polystyrene

OMe
I
OMe
N
N
MeO
O

10



11

Current Data Parameters

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EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

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TD	32768
SOLVENT	CDCl3
NS	128
DS	0
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	90.5
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

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

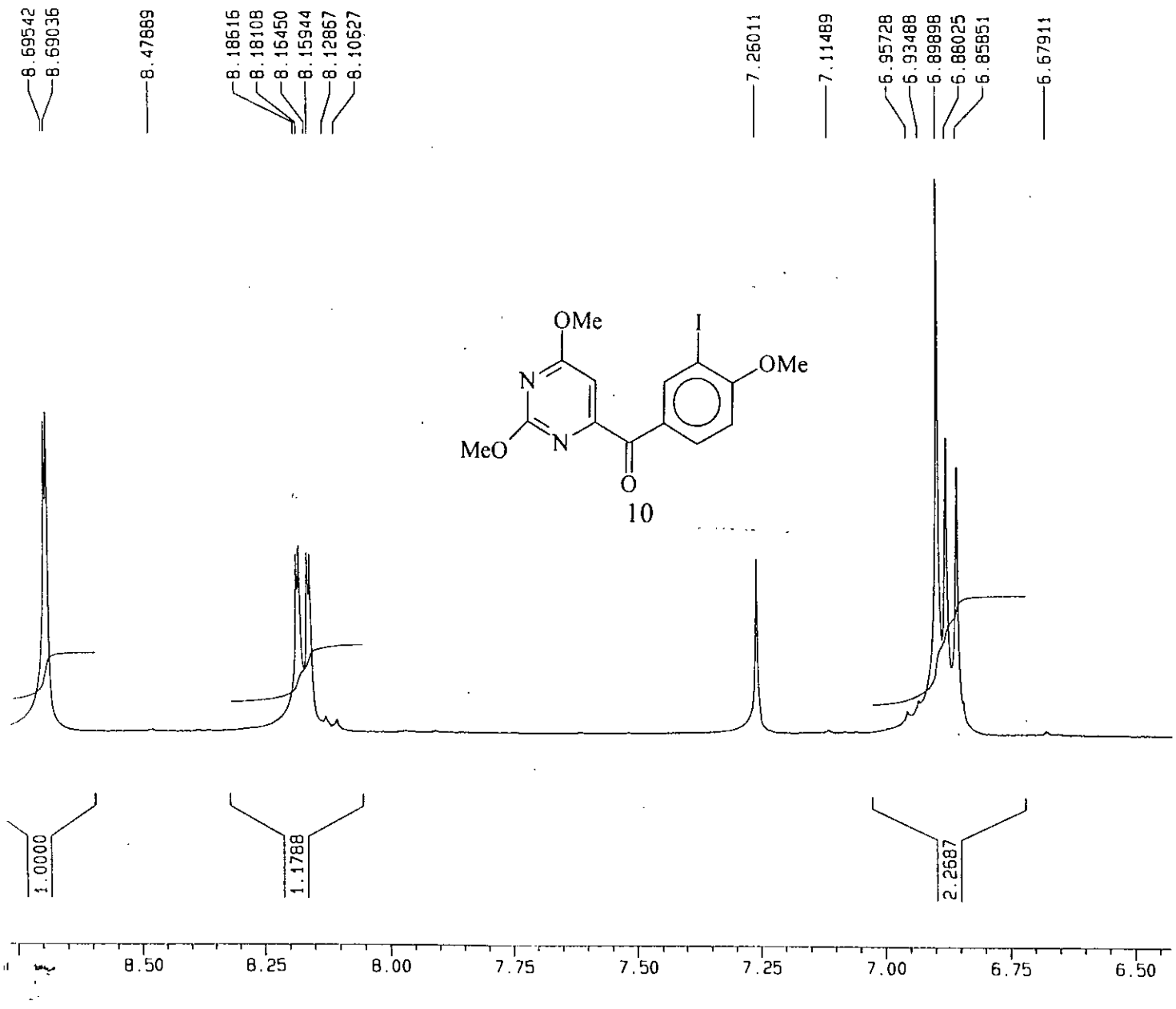
NUC1	1H
P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428010 MHz

F2 - Processing parameters

SI	32768
SF	400.1400083 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	14.217 ppm
F1	5688.93 Hz
F2P	-0.645 ppm
F2	-257.94 Hz
PPMCM	0.74310 ppm/cm
HZCM	297.34320 Hz/cm



Current Data Parameters

NAME	A768
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20020904
Time	13.23
INSTRUM	dpx400
PROBHD	5 mm Multinuc
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	128
DS	0
SWH	6410.256 Hz
FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	64
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

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

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

F2 - Processing parameters

SI	32768
SF	400.1400092 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
F1P	8.833 ppm
F1	3534.27 Hz
F2P	6.428 ppm
F2	2572.01 Hz
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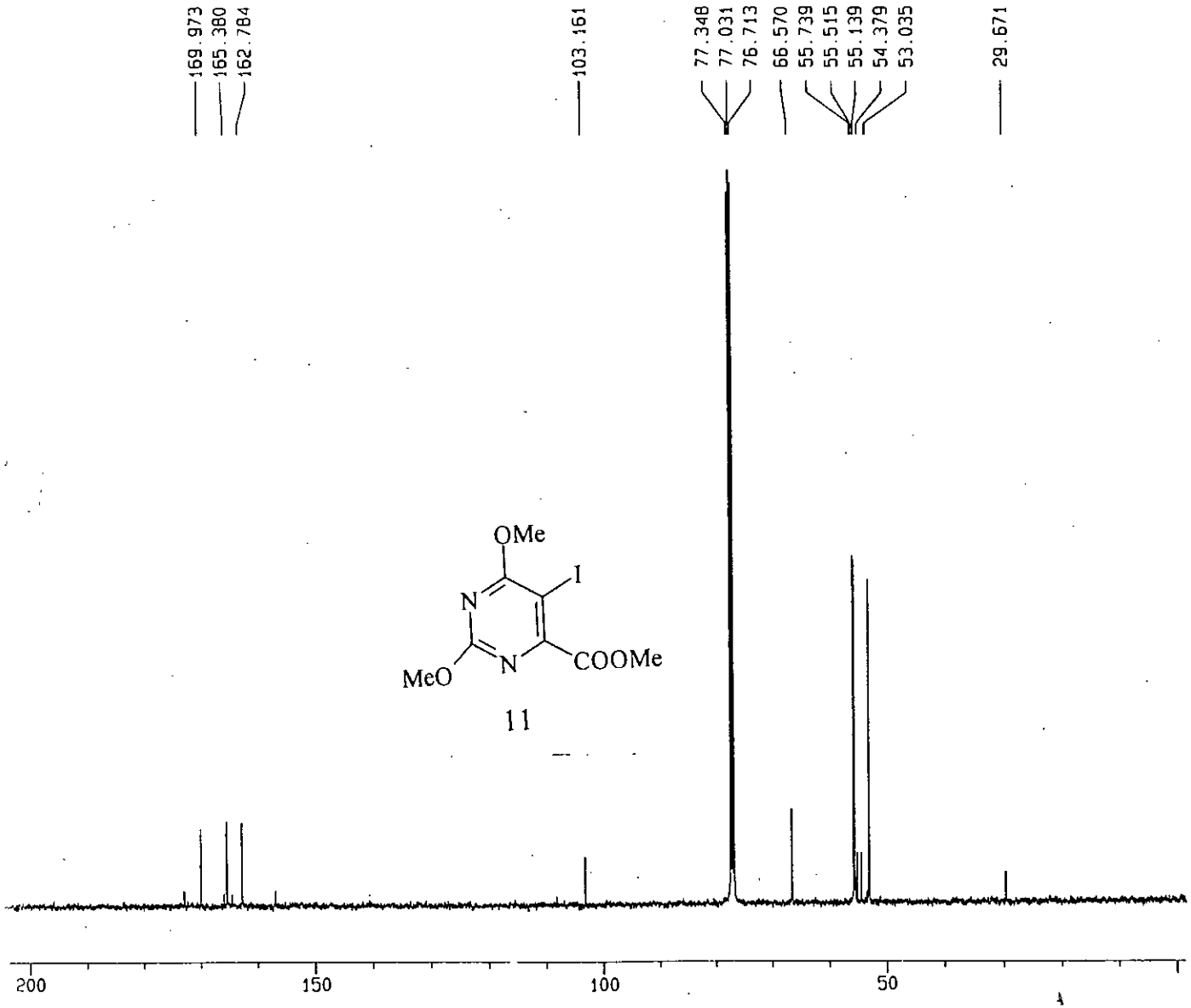
HZCM	48.11267 Hz/cm

Analytical, BCSIR, 13C Spectrum T-11 in COCl3, Tanvir, BUET



Current Data Parameters

NAME	A1723
EXPNO	2
PROCNO	1

F2 - Acquisition Parameters

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FIDRES	0.737140 Hz
AQ	0.6783476 sec
RG	16384
DW	20.700 usec
DE	6.00 usec
TE	300.0 K
D1	1.50000000 sec
d11	0.03000000 sec
d12	0.00002000 sec

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

NUC1	13C
P1	8.30 usec
PL1	-6.00 dB
SF01	100.6253045 MHz

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

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

F2 - Processing parameters

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

1D NMR plot parameters

CX	20.00 cm
F1P	213.004 ppm
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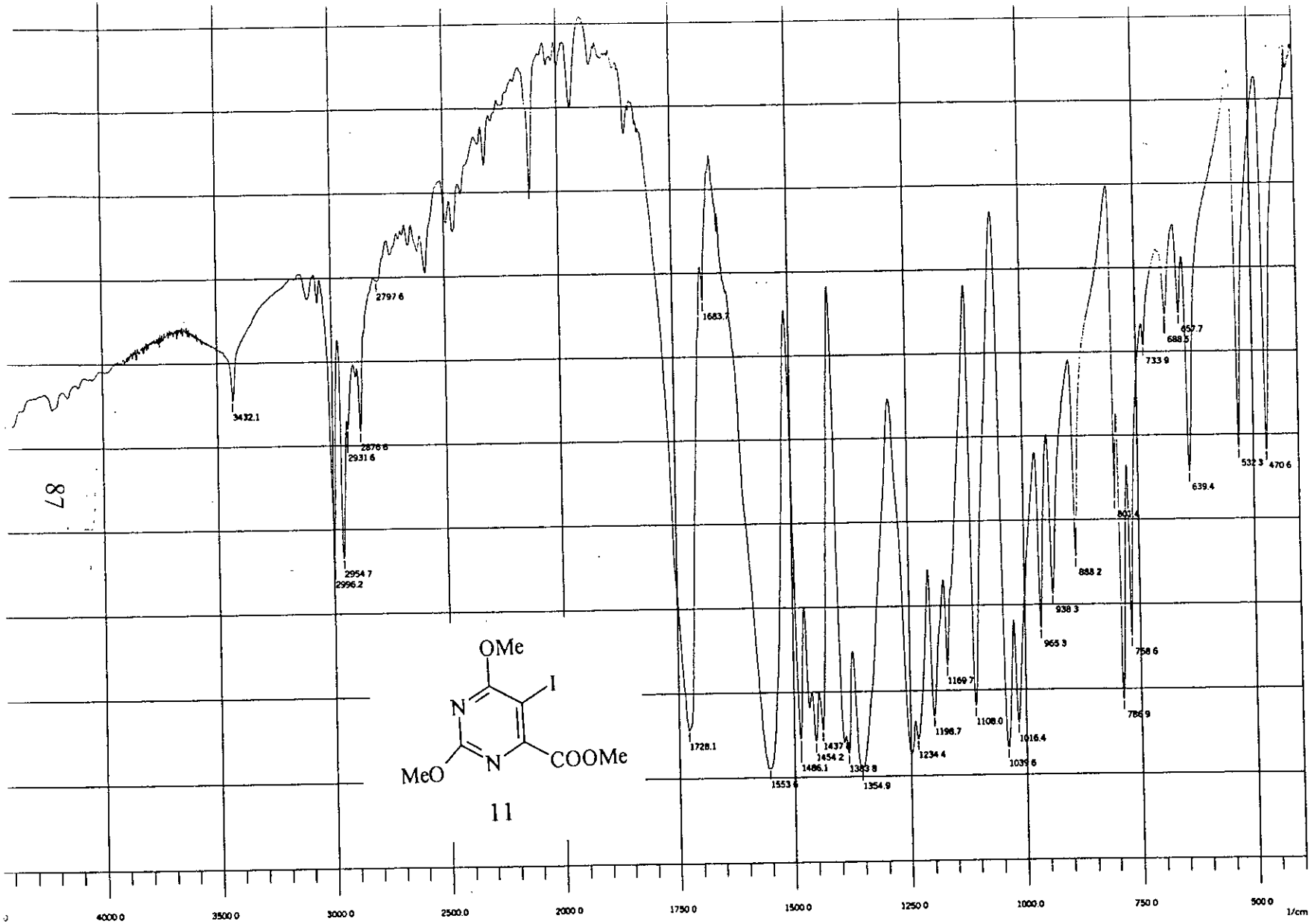
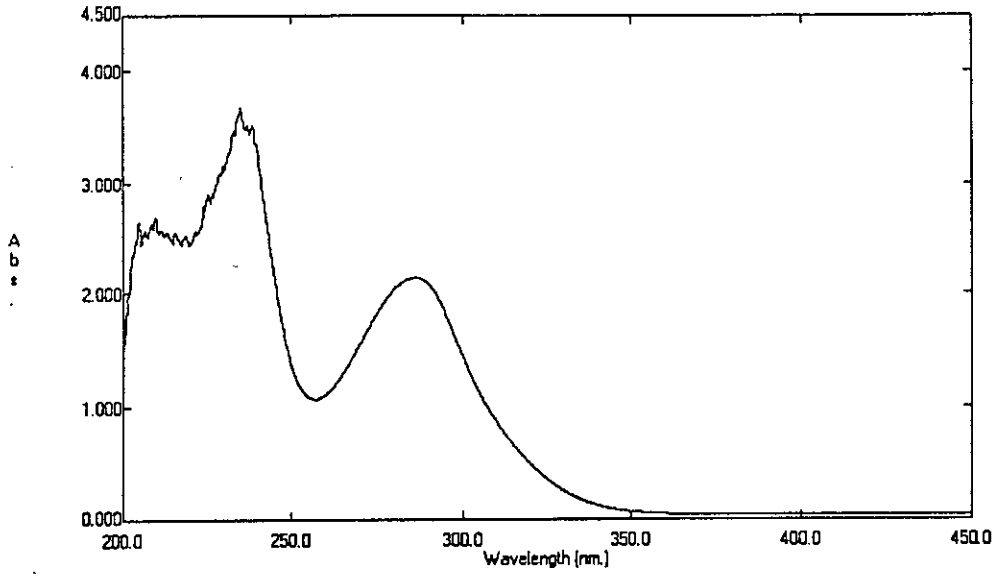
F2P	-1.553 ppm
F2	-156.26 Hz
PPMCM	10.72784 ppm/cm
HZCM	1079.38416 Hz/cm



TIRS: T-11, 12 April, 2003

03/13/2003	Time:	12:17:21	NScans:	45
HYPER IR	User:	SHIMADZU	Detector:	standard
1/cm	Ordinate:	%T	Apodization:	Happ
400.20	Max:	4599.91	Range:	1/cm
4358	Data Interval:	0.96434	Resolution:	2.0
auto	Aperture:	auto	Mirror Speed:	2.8(low)



File Name: TS-T11

Created: 11:00 08/15/04
Data: Original

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Scan Speed: Fast
Slit Width: 2.0
Sampling Interval: 0.2

No.	Wavelength (nm.)	Abs.
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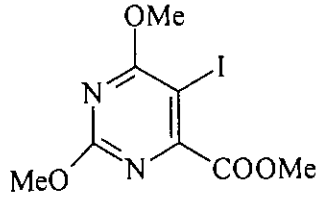
2	234.80	3.6747
3	209.60	2.6848



11

2.3. Preparation of 5-substituted pyrimidine derivatives through palladium catalyzed reaction:

2.3.A. Introduction:

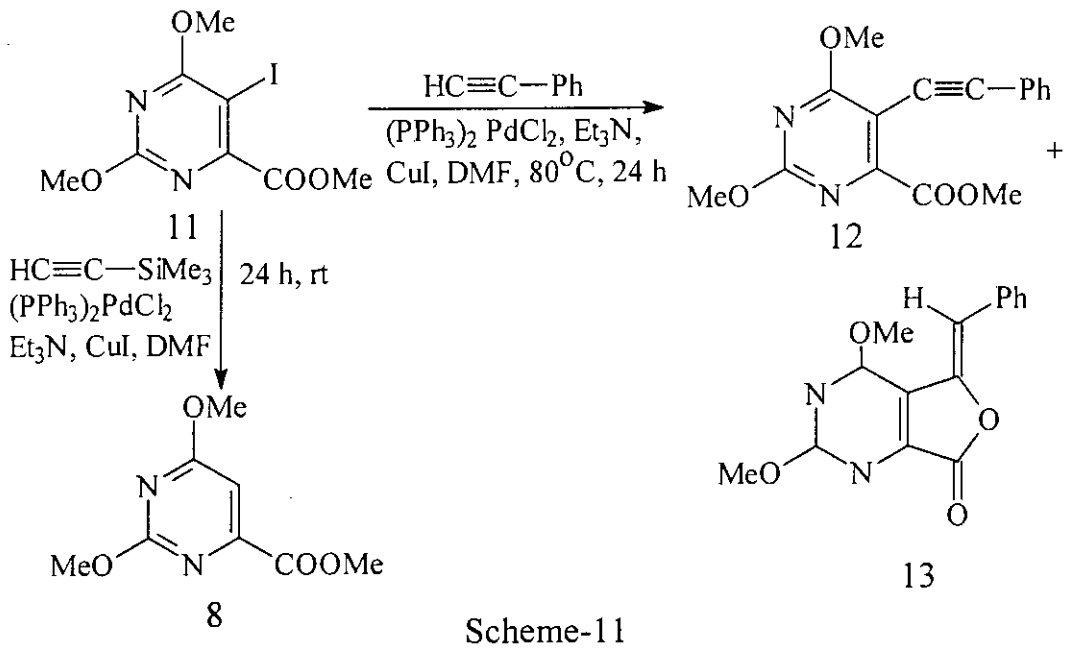
There are relatively few basic type reactions that generate a new carbon-carbon bond, although this is one of the most critical operations in the synthesis of organic molecules. Acetylenes and vinylic derivatives are versatile compounds in the synthetic organic chemistry and hence various methods for their synthesis have been explored. A conventional method for the preparation of arylacetylene derivatives is the coupling reaction of arylhalides with copper(I)acetylides, known as Castro reaction[94]. The cross coupling of organotin reagents with variety of organic electrophiles, catalyzed by palladium, provides a novel method for generating a carbon-carbon bond[95] known as Still coupling. The palladium-catalyzed coupling of haloarenes and haloalkenes with alkenes known as the Heck reaction is well-established[96].The Sonogashira coupling reaction of terminal alkynes with arylhalides provides an efficient route to arylalkynes[97]. Numerous applications to natural product syntheses have been reported, including the construction of complex enediyne antibiotics[98]. The synthesis of methyl enyonates and enynones is of interest as the alkyl enynone moiety has been found in naturally occurring compounds and they are useful synthetic intermediates[99]. T. Jeffery has established palladium catalyzed vinylation of vinylic halides[100] and vinylation of acetylenic iodides under solid-liquid phase-transfer conditions[101].

Palladium catalyzed reaction have been extensively used for carboannulation[102] and heteroannulation[103] processes. Several research

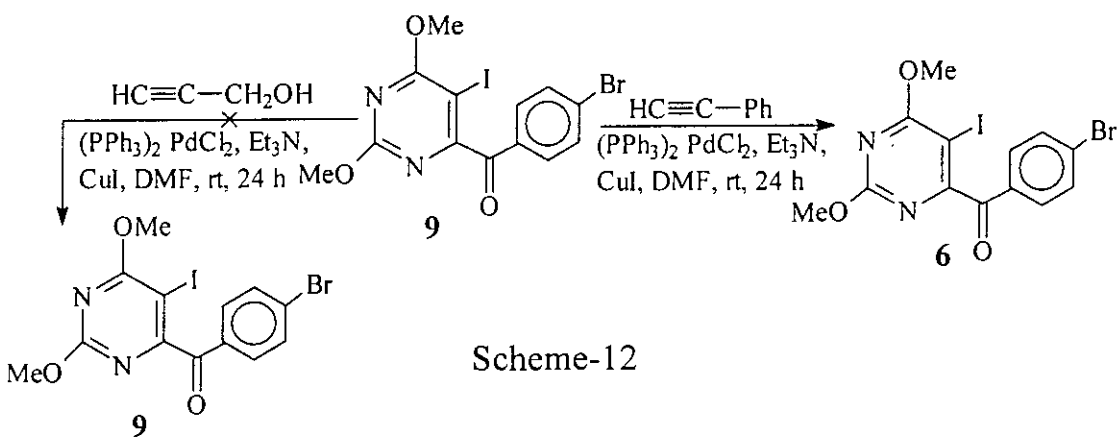
groups have reported the synthesis of aromatic heterocycles via palladium - catalyzed annulation of internal alkynes[104]. Others have shown that palladium-catalyzed cyclization are valuable synthetic tools for the preparation of a wide variety of heterocycles[105] using vinylic compounds, terminal alkynes and other substrates. In recent years, our group has developed methods for the synthesis of benzofused heterocyclic compounds, for example benzofurans[106] and isoindolinone[107] by palladium-catalyzed reaction.

2.3.B. Results and Discussion:

In continuation of our studies on the synthesis of various heterocyclic compounds through palladium-catalyzed reactions using terminal alkynes, we became interested in the palladium catalyzed carboannulation for the synthesis of 5-substituted pyrimidines. A new strategy for the regio-selective synthesis of 5-alkynyl pyrimidine derivatives through the palladium catalyzed condensation of 2,4-dimethoxy-5-iodo-6-methyl orotate 11 and 2,4- dimethoxy-5-iodo-6-*p*-bromobenzoyl pyrimidine **9** with terminal alkynes and subsequent cyclization (Scheme - 11).



Scheme-11



Scheme-12

The reactions were usually carried out by heating a mixture of 5-iodo pyrimidine derivatives **11** , **9** and alkynes in DMF at room temperature for 24 h in the presence of bis(triphenyl phosphine)palladium (II) chloride copper(I) iodide and triethyl amine. The reaction between 2,4-dimethoxy-5-iodo-6-methylorotate **11** and phenylacetylene gave 2, 4-dimethoxy-5- phenyl ethynyl-6-methylorotate **12** and 2, 4-dimethoxypyrimidinyl-3-(*Z*) benzylidene thalide **13**. But in case of trimethyl silyl acetylene only deiodinated product of 2, 4-dimethoxy-6-methylorotate **8** was obtained

under the same reaction condition. The palladium catalyzed reaction of 2, 4-dimethoxy-5- iodo-6-*p*-bromobenzoyl pyrimidine **9** with phenylacetylene and propargyl alcohol did not afford the desired condensed or cyclized product but it gave the deiodinated product **6** and unreacted starting material **9**. From the results of the palladium catalyzed reactions it might be assumed that the presence of two bulky group at **5** and **6** position of the pyrimidine ring developed a steric effect and hindered the coupling reaction.

2.3.C. Characterization of the products:

2, 4- Dimethoxy - 5- phenyl ethynyl - 6- methyl orotate **12**, light yellow solid, mp. 91-93 °C, showed strong absorption band at 1733.9 cm^{-1} for C=O stretching vibration and the absorption band in the region 1583.4 and 1542.0 for C=C and C=N stretching vibrations.

The ^{1}HNMR spectrum of the compound exhibited chemical shift at δ 3.9, 4.04 and 4.09 for OCH_3 as singlet. The chemical shift at 7.3 and 7.5 as multiplet for 5-aromatic proton. No peak was observed for C- 5H of pyrimidine ring which confirmed the coupling of ethynyl group.

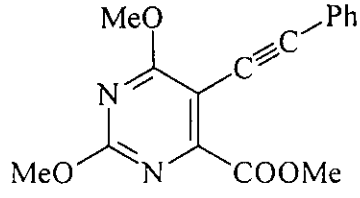
The ^{13}CNMR spectrum of the compound showed chemical shift at δ 171.7 for C=O, 52.1, 55.2 for OCH_3 and it also showed the chemical shift position for the aromatic carbons.

2, 4- Dimethoxypyrimidinyl -3-(*Z*) benzylidene thalide **13**, light yellow solid, mp 82-83 °C, showed absorption band at 1729.1 cm^{-1} for C=O in the thalide ring. The UV-spectrum of the compound gave λ_{max} at 345.8, 276.2, 249.4 nm. The ^{1}HNMR spectrum of the compound showed chemical shift at δ 3.96and 4.02 for OCH_3 and at δ 7.01 as singlet for vinylic proton at 3-position of thalide ring.

2.3. D. Experimental

Preparation of pyrimidine -3- *(Z)*-benzylilidine thalide (13)

A mixture of 2,4 dimethoxy-5-Iodo-6-methyl orotate (150 mg, 0.4587 mmol) bis (triphenyl phosphine) palladium (11) choride (3.5 mol %) copper (II) iodide (0.00698g) and triethyl amine (0.1859g, 4 eq) was stirred in DMF (10ml) under nitrogen atmosphere for 1 hour, then phenylacetyline (0.1925g,3eq) was added to the reaction mixture. The progress of the reaction was monitored by TLC (n-hexane-chloroform 1:1). After completion of the reaction the mixture was evaporated to dryness under reduced pressure and the residue was extracted with chloroform (3×50 ml). The combined organic layer was washed with distilled water (3×50ml), dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. The residue was latter purified by column chromatography. Two fraction were obtained one is condensed product and another is cyclized products.



12

2, 4-Dimethoxy-5-phenylthynyl-6-methyl orotate 12 (fraction A).

mp: 91- 93°C

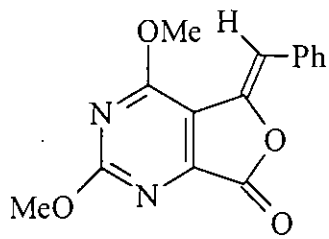
UV(EtOH): λ_{max} 360.60, 322.40, 310.80 and 220.20 nm.

IR: ν max (KBr) 2957.6, 2926.8, 1733.9, 1583.4, 1560.3, 1569.9, 1542.0, 1482.2, 1462.9, 1441.7, 1384.8, 1363.6, 1300.9, 1258.5, 1205.4, 1174.6, 1083.0, 1040.5, 773.4, 763.8 cm^{-1}.

^{1}HNMR: (400MHz, $CDCl_3$) δ_H : 3.96, 4.04, 4.09(OCH_3), 7.3(m, Ar-H), 7.5 (m, Ar-H).

^{13}CNMR(100 MHz,$CDCl_3$) δc: 52.9, 55.1, 55.2(OCH_3), 122.91, 128.36, 128.76, 131.66, 158.90, 163.30, 164.45, 171.76(C=O),

pyrimidine -3- *(Z)*-benzylilidine thalide 13 (fraction B)



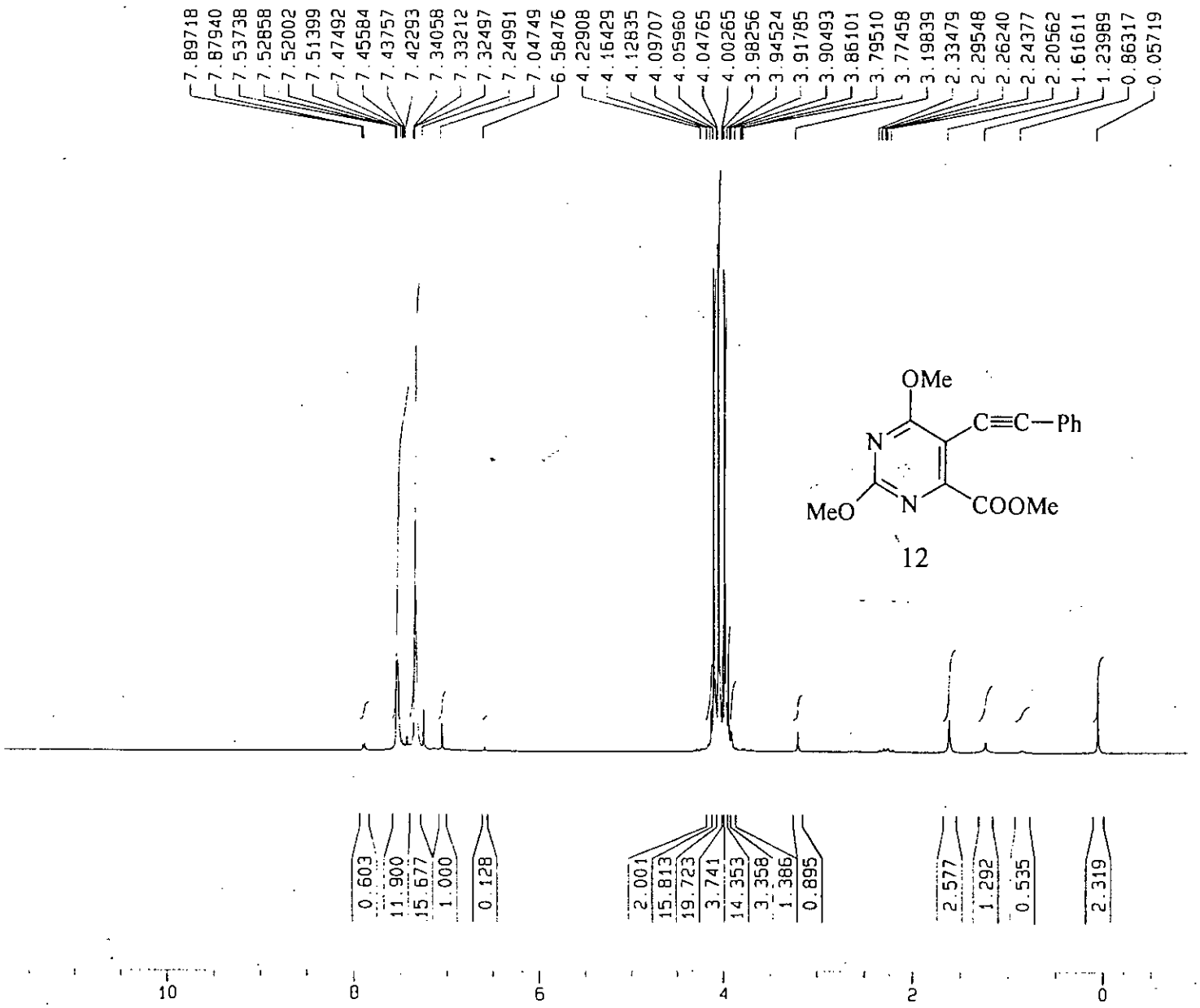
13

mp: 82-83°C

UV(EtOH): λ_{max} 345.8, 176.2 and 249.4 nm.

IR: ν max (KBr) 2957.6, 2926.8, 1739.1, 1554.5, 1447.0, 1343.8, 1355.9, 766.8 cm^{-1}.

^{1}HNMR: (400MHz, $CDCl_3$) δ_H : 3.96(3H, OCH_3) 4.02 (3H, OCH_3) 7.01(s, 1H= CH-vinylich H), 7.3 (m, 1H, ArH), 7.41(m 3H, ArH), 7.8 (d, J=8Hz, 1H ArH).



12

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RG	128
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

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PL1	-6.00 dB
SFO1	400.1428010 MHz

F2 - Processing parameters

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WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.40

1D NMR plot parameters

CX	20.00 cm
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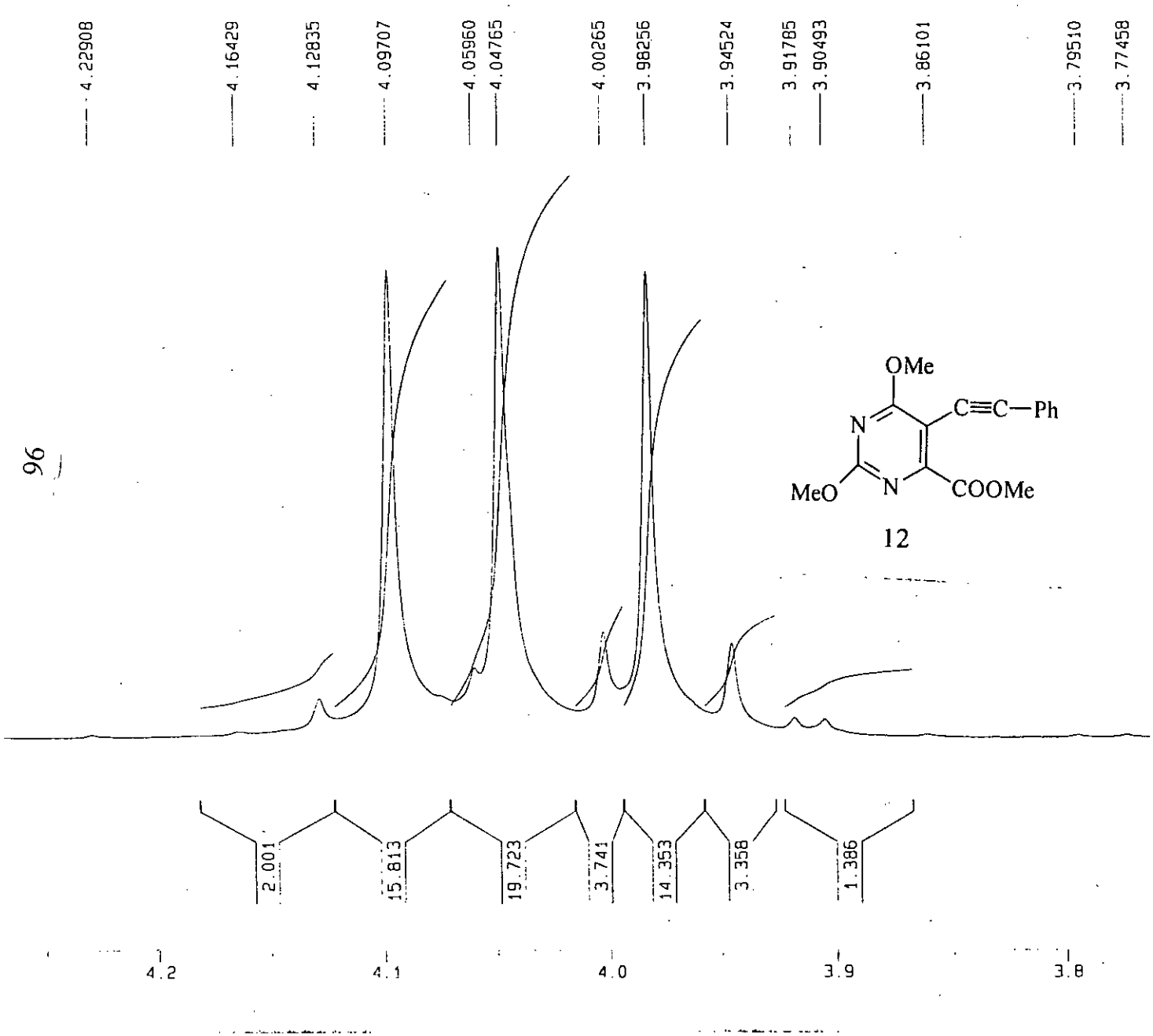

96

12

EXPNO	1
PROCNO	1

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FIDRES	0.195625 Hz
AQ	2.5559540 sec
RG	128
DW	78.000 usec
DE	6.00 usec
TE	310.0 K
D1	1.00000000 sec

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

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P1	8.30 usec
PL1	-6.00 dB
SFO1	400.1428010 MHz

F2 - Processing parameters

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SSB	0
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1D NMR plot parameters

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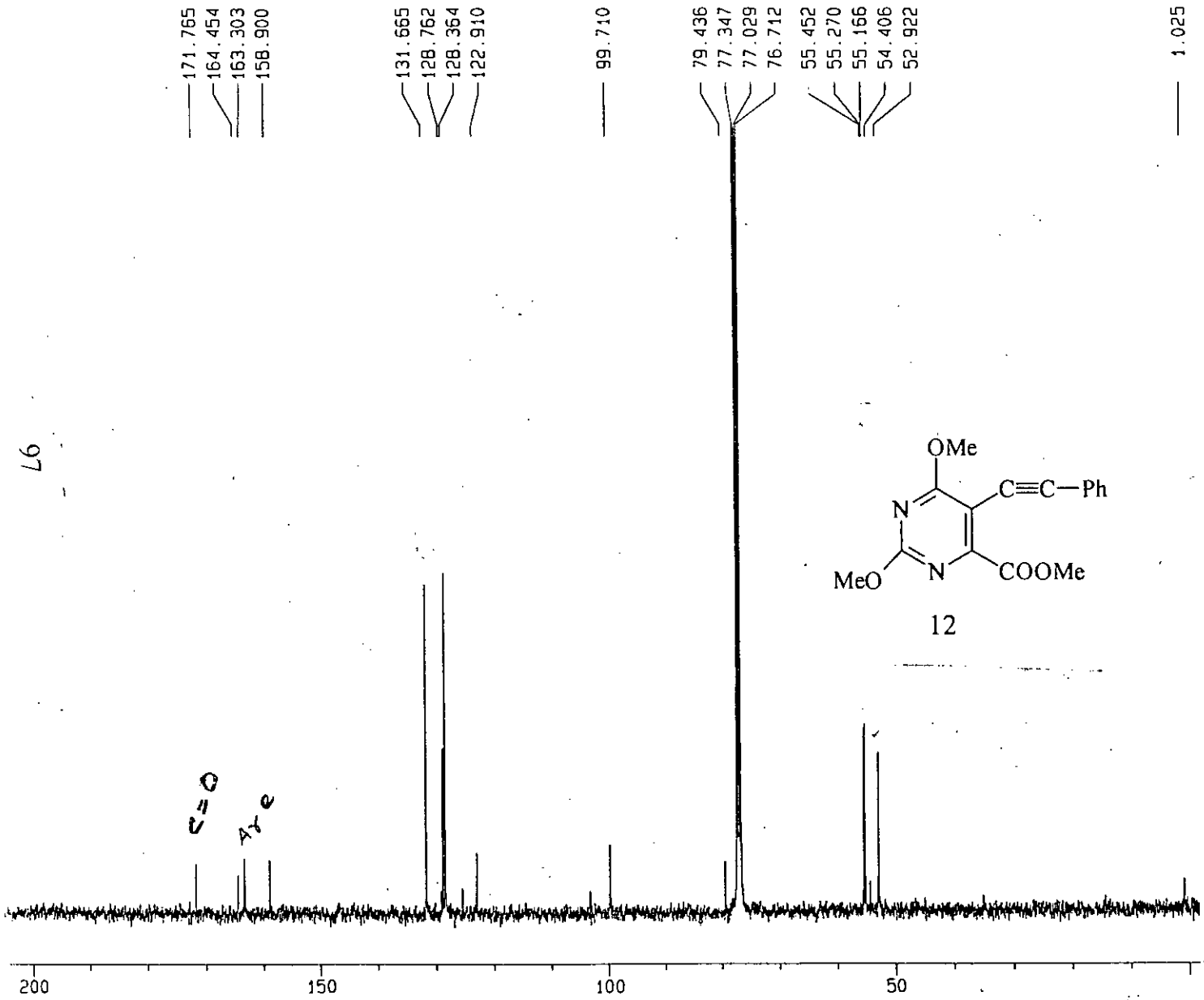

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EXPNO	2
PROCNO	1

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TE	300.0 K
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d11	0.03000000 sec
d12	0.00002000 sec

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PL1	-6.00 dB
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========== CHANNEL f2 ==========

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PL12	16.00 dB
PL13	120.00 dB
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F2 - Processing parameters

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GB	0
PC	1.40

1D NMR plot parameters

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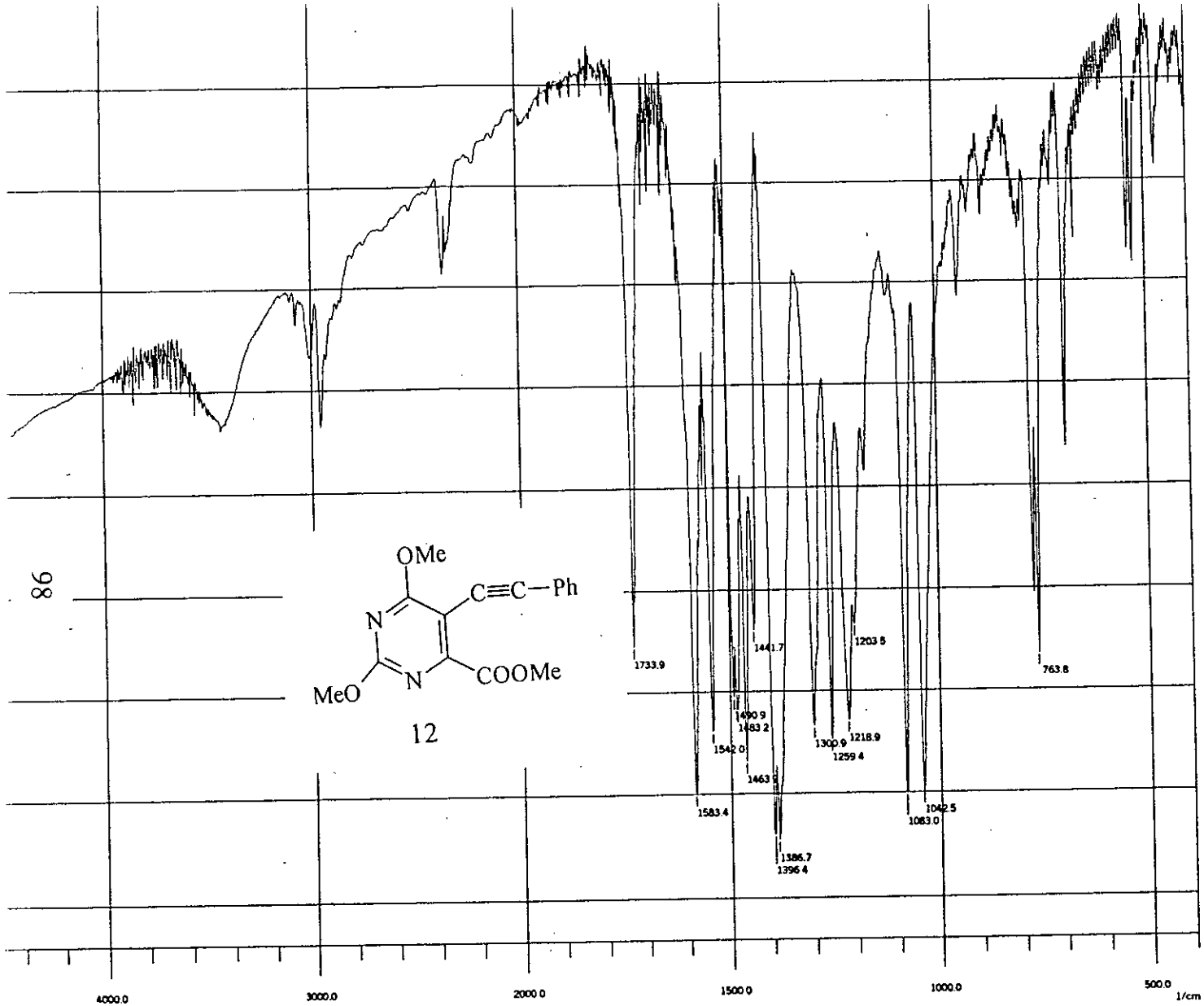

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8	1386.7	37.798
9	1396.4	38.056
10	1441.7	48.029
11	1463.9	41.591
12	1483.2	44.113
13	1490.9	44.718
14	1542.0	43.070
15	1583.4	40.011
16	1733.9	47.256

T-25b, June 13. 2004

b IRS: T-25b, June 13. 2004

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	1/cm	Ordinate:	%T	Apodization:	Happ
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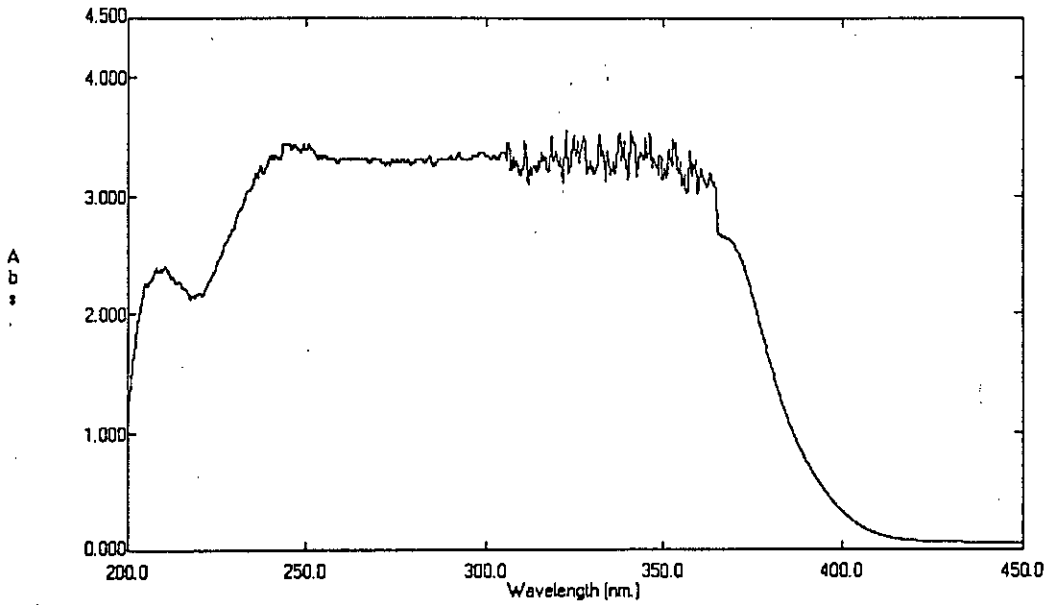

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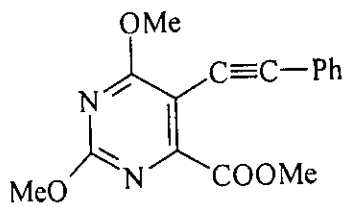

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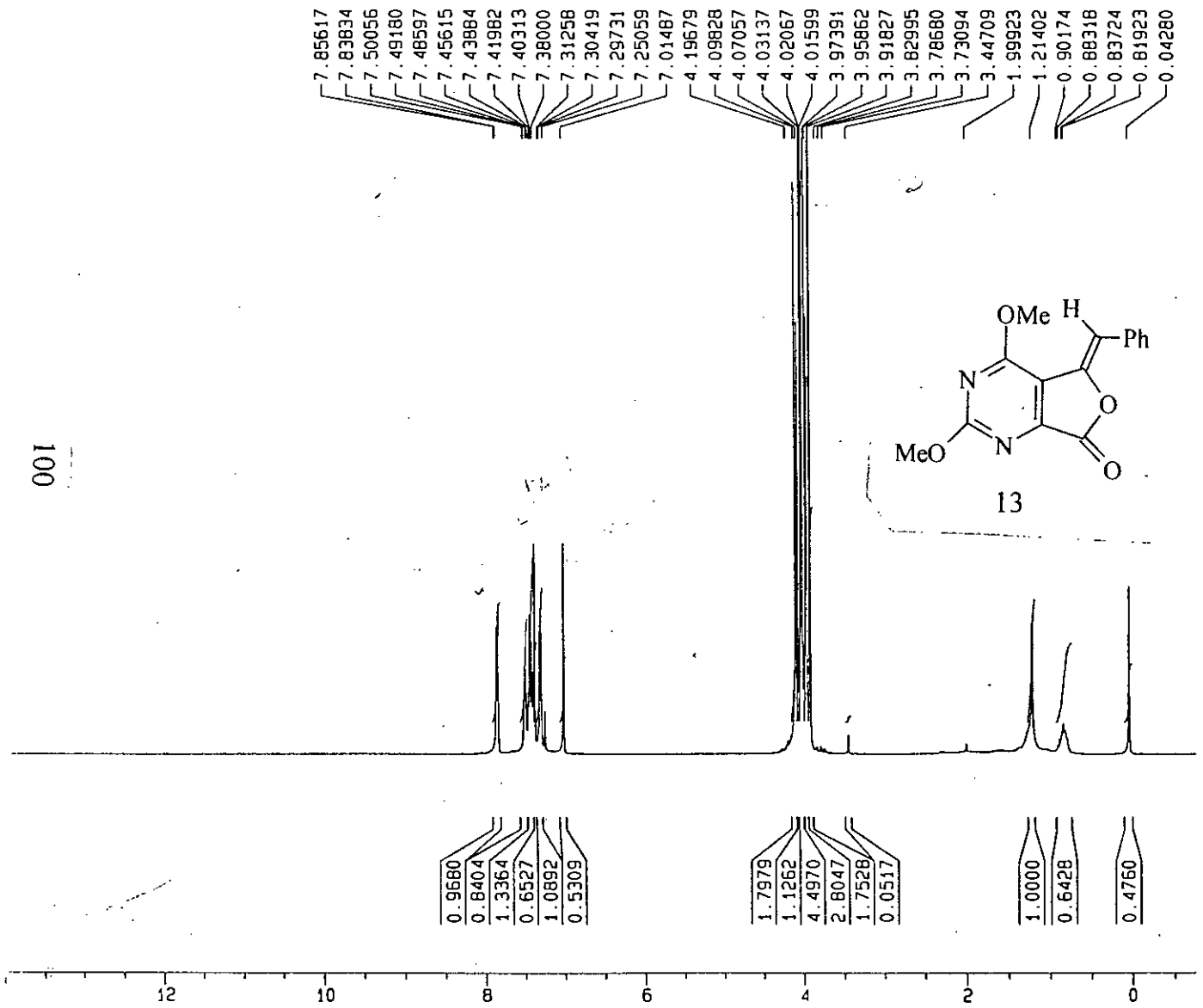

13

Current Data Parameters

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PROCNO	1

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TE	310.0 K
D1	1.00000000 sec

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PL1	-6.00 dB
SFO1	400.1428010 MHz

F2 - Processing parameters

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SSB	0
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GB	0
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1D NMR plot parameters

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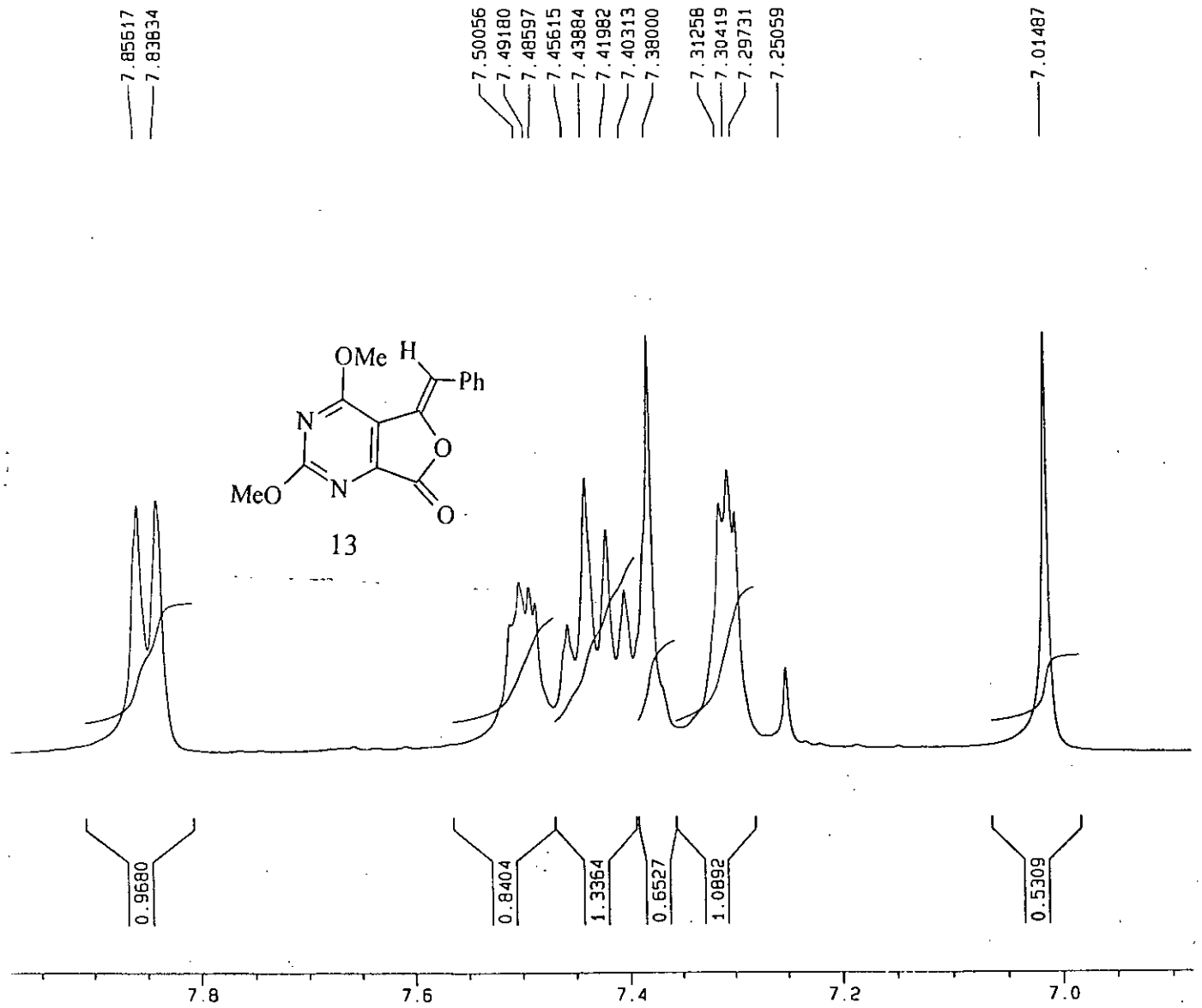

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PROCNO	1

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

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F2 - Processing parameters

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GB	0
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1D NMR plot parameters

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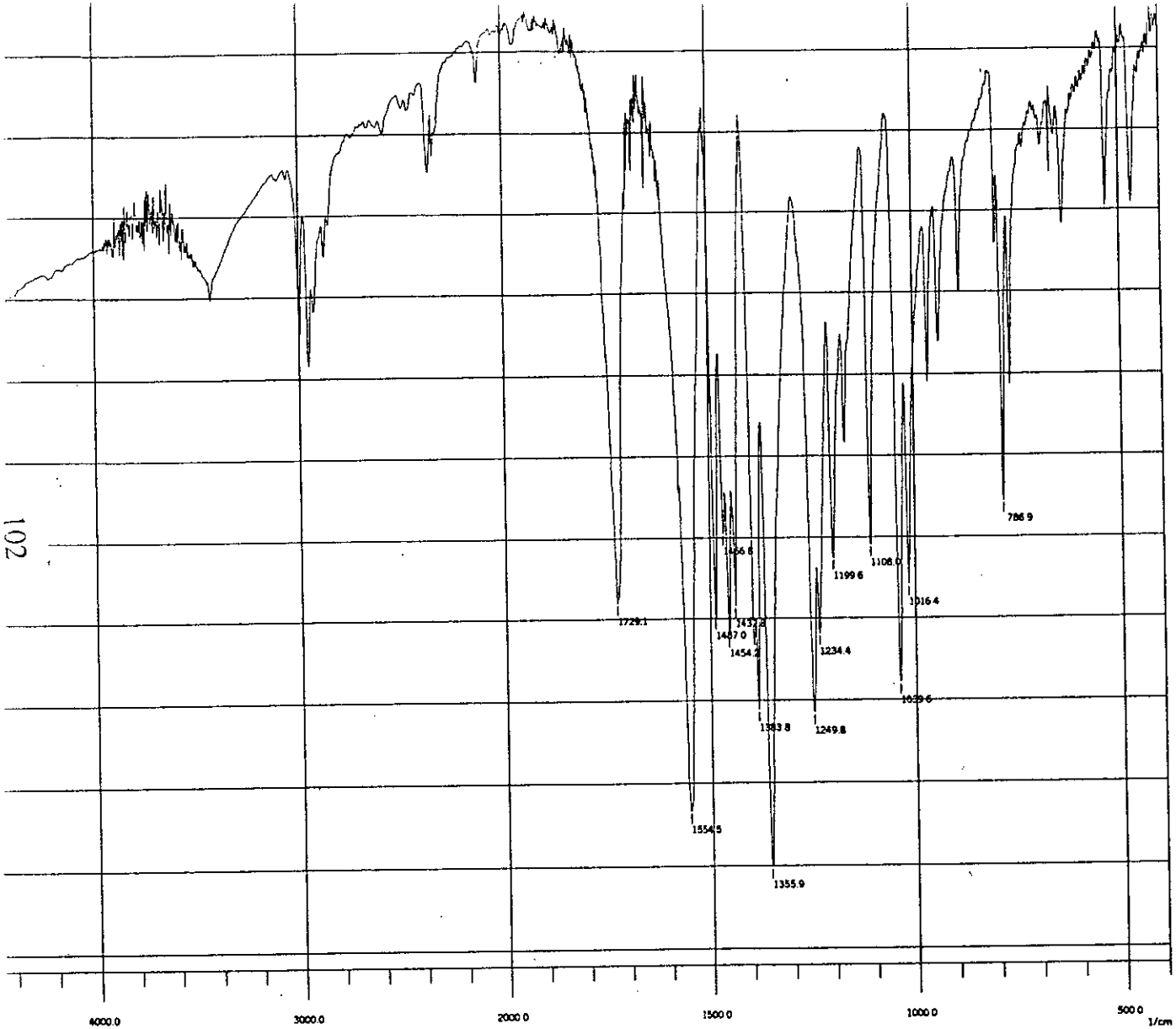

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8	1355.9	24.949
9	1383.8	34.420
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11	1454.2	38.964
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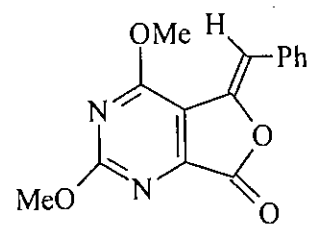
T-17, 15.Sep 2003



13

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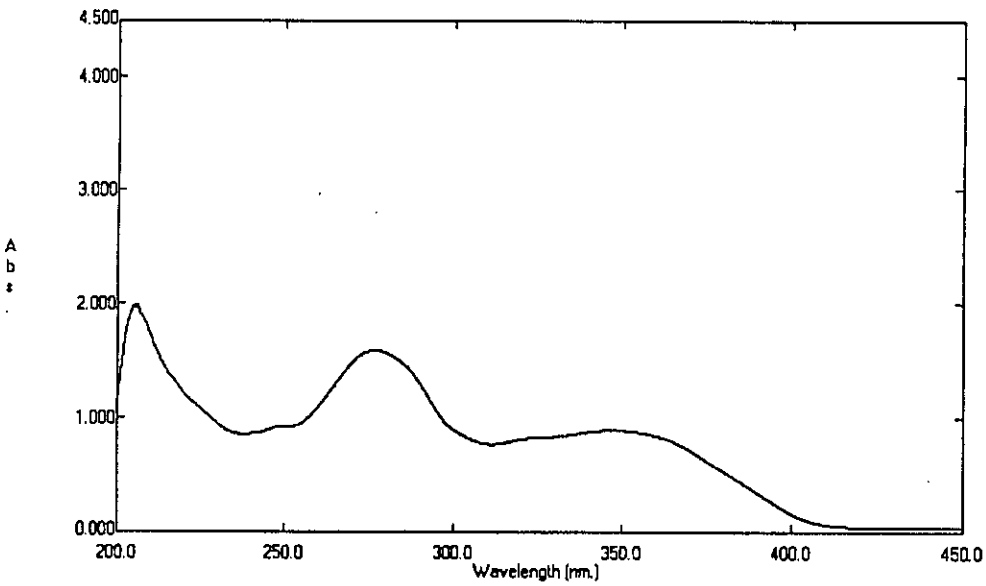

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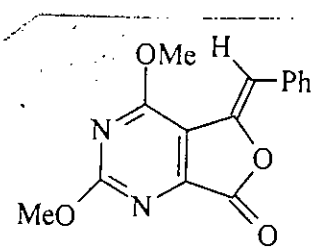

13

Conclusion

In this thesis, we have demonstrated a convenient and facile method for the synthesis of 2, 4-dichloro-6-*p*-aroyl-pyrimidine and 2,4- dicholoro-6-methyl orotate and their corresponding 2, 4-dimethoxy pyrimidine. Iodonation at C-5 position also described here. *N*-iodosuccinimide in trifluoroacetic acid and trifluoroacetic anhydride was found to be an excellent reagents for the iodination at C-5 position of 2, 4-dimethoxy -6-aroyl pyrimidine and 2, 4-dimethoxy-6-methyl orotate. 5-Iodo pyrimidine derivatives were subjected to coupling reaction with terminal alkynes through palladium-catalyzed reactions to yield condensed product 5-alkynyl pyrimidine and cyclized product pyrimidinyl thalite. The most important features of the synthesis are that readily available starting materials are used under relatively mild reaction conditions. Also, no toxic and hazardous compounds are produced by these syntheses. A variety of functional groups can be introducted at the C-5 and C-6 position of the pyrimidine ring by this procedure. Through this methodology biologically important uracil and pyrimidine derivatives can be easily synthesized. This method will be attractive to both organic and medicinal chemists.

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