PART III

STUDIES ON PYRIMIDO THIAZINES

INTRODUCTION :

The biological activities of condensed pyrimidines as sedatives, antibacterials and antimalarials are well documented.[1-2] In particular, many thienopyrimidines have been evaluated pharmacologically and used as analgesic[3-7], anti-inflammatory[8-14], anticonvulsant[15-18] and antimicrobial agents[19-20]. Also,some thienopyrimidines have been found to show activity against many organisms.[21-22] 1,3-Disubstituted-2,4-dioxothieno[2,3-*d*]pyrimidine-1-acetic acids were evaluated as aldose reductase inhibitors and show significant AR inhibitory activity *in vitro*.Vega et al.[23] found that some thieno -[2,3-*d*] pyrimidines have analgesic, antipyritic and anti-inflammatory activity at concentrations lower than 50 mg/ml and have effect on the inhibition of Hellacell growth.More over, pyrimidothiazines have been the subject of chemical and biological studies on account of their interesting pharmacological properties. Such derivatives have analgesic,[24-26] antipyretic[27] and antiinflammatory[28-31] properties.

It is well known that pyrimidine and fused heterocyclic pyrimidine derivatives are of great biological interest, especially as antiviral, antitumor and antimicrobial agents.[32-35] Some series of pyrimido[2,1-*b*][1,3] thiazine and thiazolo[3,2-*a*]pyrimidine derivatives exhibited modest activity against Gram Positive bacterial strains.[36-38] Also, some thiazolo[3,2-*a*]pyrimidine were tested for their anti-inflammatory activities, and exerted moderate anti-inflammatory activity. In conjunction with our previous work on the synthesis of pyrimidine thione derivatives for biological evaluations a series involving a simple pyrimidine thione moiety is described.

Chandra Bhushan Mishra et al.[39] have reported 8-(furan-2-yl)-3-substituted thiazolo[5,4-*e*][1,2,4] triazolo[1,5-*c*] pyrimidine-2(3*H*)-thione derivatives as potential adenosine A_{2A} receptor antagonists

Imre Huber et al.[40] have synthesised alicycle-fused thiazolo and thiazino[2,3]-quinazolones and cycloalkylimino-3-thiazolinylthiazolidines.

Here,in this chapter new pyrimidothizene derivatves have been prepared by the condensation of N-(2,5-dimethylphenyl)-6-methyl-4-aryl-2-thioxo-1,2,3,4-tetrahydro - pyrimidine-5-carboxamides with 1,3-dibromopropane. The pyrimidothiazine compounds were reported for various pharmacological activities.[41-44]

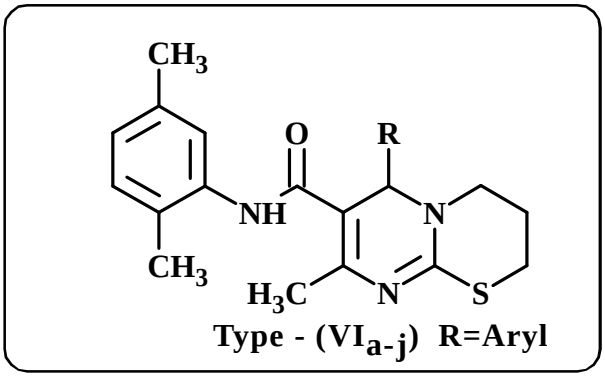
The work presented in one section which is as under:

SECTION-I : SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-ARYL-8-METHYL-N-(2,5-DIMETHYLPHENYL)-2,3,4,6-TETRAHYDROPYRIMIDO [2,1-b][1,3] THIAZINE-7-CARBOXAMIDES.

SECTION - I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 6-ARYL-8-METHYL-N-(2,5-DIMETHYLPHENYL)-2,3,4,6-TETRAHYDROPYRIMIDO[2,1-b][1,3] THIAZINE-7-CARBOXAMIDES.

It is well known that pyrimidine and fused heterocyclic pyrimidine derivatives are of great biological interest, especially as antiviral, antitumor and antimicrobial agents. Some series of pyrimido[2,1-*b*][1,3] thiazine and thiazolo[3,2-*a*]pyrimidine derivatives exhibited modest activity against Gram Positive bacterial strains.These valid observations led us to synthesise pyrimido[2,1-*b*][1,3] thiazine derivatives of type-(VI) by the cyclization of *N*-(2,5-dimethylphenyl)-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide with 1,2-dibromopropane in the presence of anhydrous potassium carbonate.

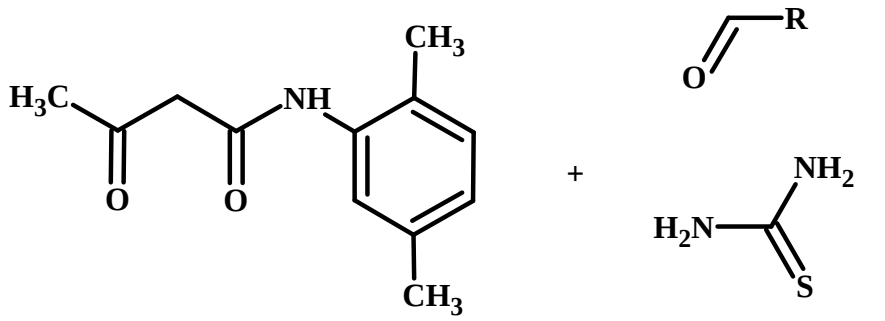


Type - (VI_{a-j}) R=Aryl

The constitution of the synthesized products(VI_{a-j}) have been characterized by using elemental analyses, infrared and ^1H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all compounds have been checked by thin layer chromatography.

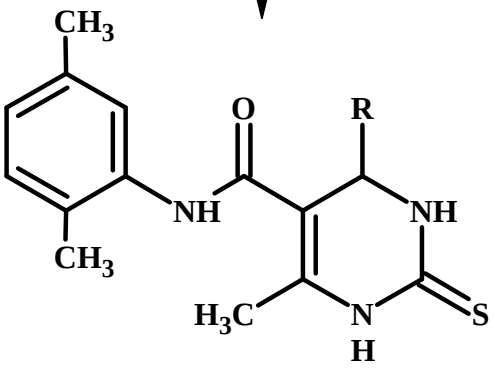
All the compounds have been evaluated for their antibacterial activity against Gram Positive bacteria like ***Staphytococcus aureus*** ,***Bacillus subtilis*** and Gram Negative bacteria like ***Escherichia coli***,***Salmonella paratyphi B*** and they were also evaluated for antifungal activity against ***A.niger*** and ***Candida albicans***. The antimicrobial activity of the synthesised compounds have been compared with standard drugs. Their antimicrobial effect was determined in higher dilutions using Agar Dilution Method **(Approved by NCCLs)**.

REACTION SCHEME



Ethanol

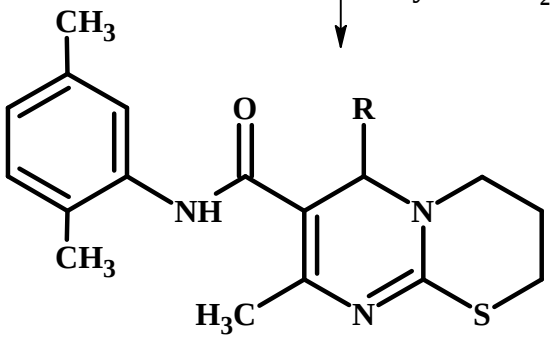
2-3 drops conc. HCl



$Br\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}Br$

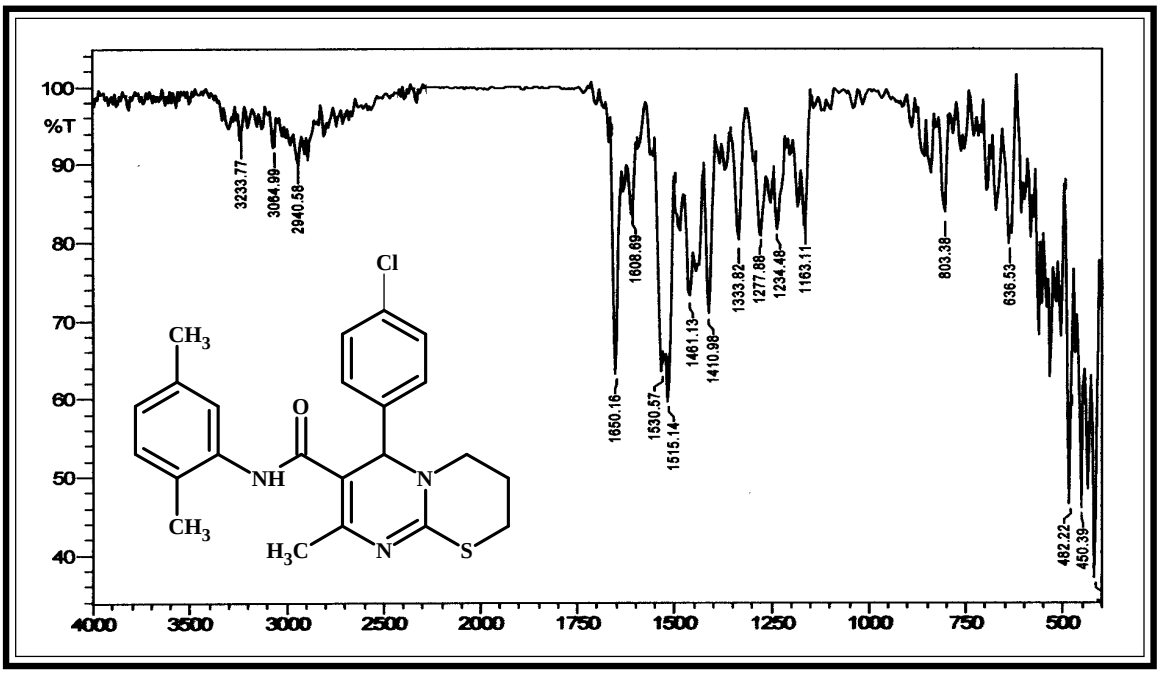
DMF,

Anhydrous K_2CO_3



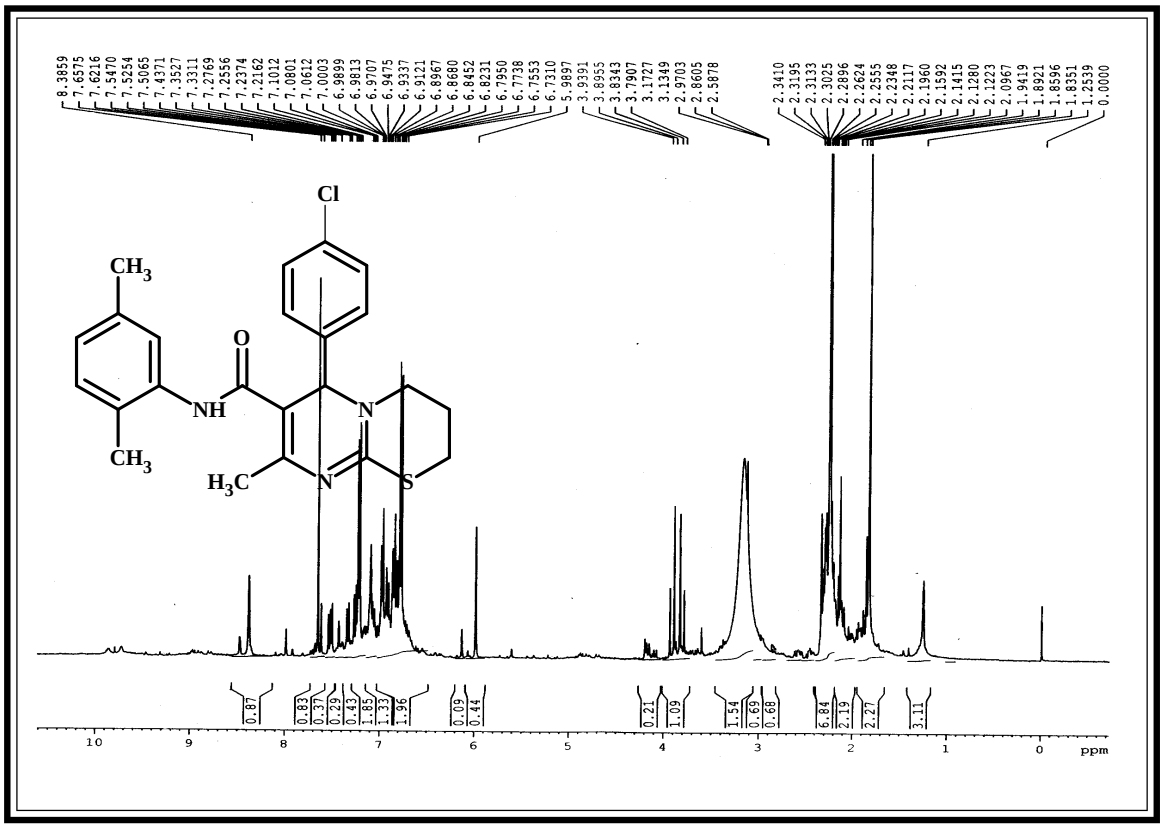
Type - ($VI_{a\text{-}j}$) R=Aryl

IR SPECTRAL STUDY OF 6-(4-CHLOROPHENYL)-8-METHYL-N-(2,5-DIMETHYLPHENYL)-2,3,4,6-TETRAHYDROPYRIMIDO[2,1-b][1,3] THIAZ-INE-7-CARBOXAMIDE.



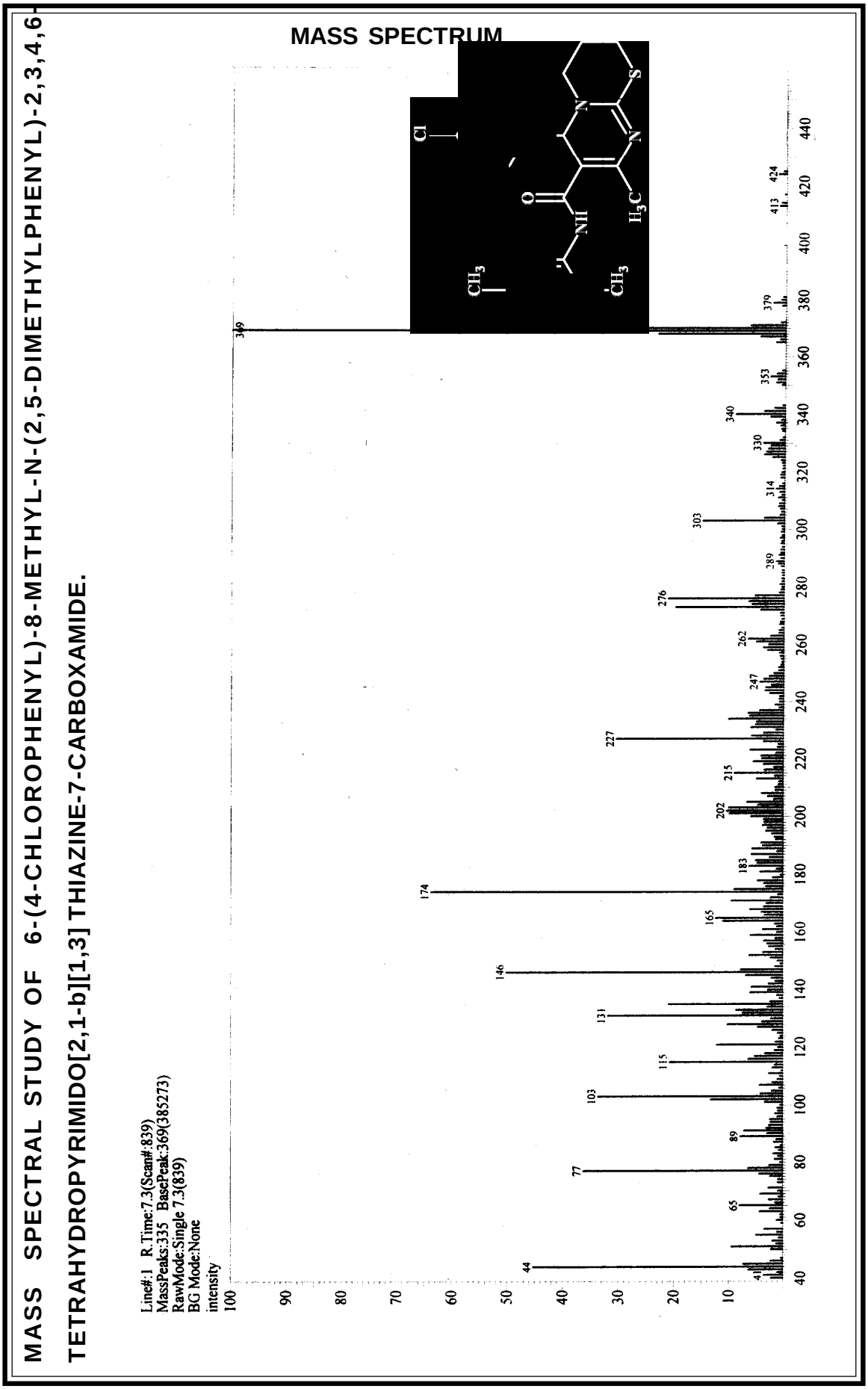
Type	Vibration Mode	Frequency in cm^{-1}		Ref. (Part-I)
		Observed	Reported	
Alkane	C-H str. (asym.)	2822	2975-2820	45
$-CH_3$	C-H str. (sym.)	2852	2900-2800	45
	C-H i.p.def. (asym.)	1461	1470-1400	45
	C-H o.o.p. def. (sym.)	1372	1390-1300	45
Aromatic	C-H str.	3064	3090-3010	46
and	C=C str.	1530	1600-1450	46
Pyrimido-				
thiazene	C=N str.	1605	1690-1570	46
moiety	C-S str.	1030	1031-1010	46
	C-N str.	1277	1310-1250	46
Amide	NH str.	3323	3410-3270	46
	NH def.	1625 (overlaped)	1647-1609	46
	C=O str. (amide)	1650	1650-1600	49

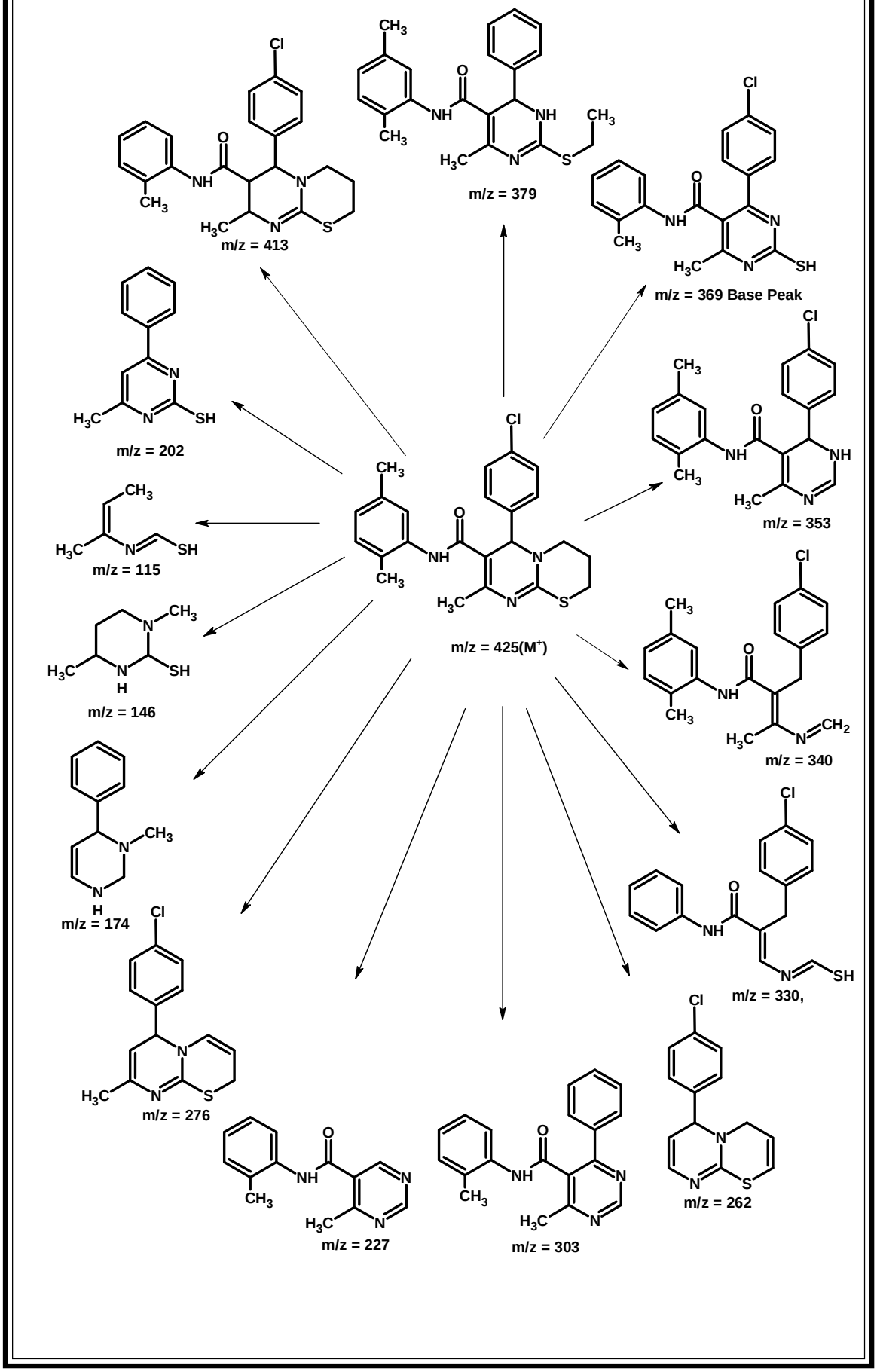
PMR SPECTRAL STUDY OF 6-(4-CHLOROPHENYL)-8-METHYL-N-(2,5-DIMETHYLPHENYL)-2,3,4,6-TETRAHYDROPYRIMIDO[2,1-b][1,3] THIAZ-INE-7-CARBOXAMIDE.



Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1.	1.25	1H	Singlet	CH
2.	1.89	3H	Singlet	CH_3
3.	2.26	3H	Singlet	CH_3
4.	2.34	3H	Singlet	CH_3
5.	2.31	2H	Doublet	CH_2
6.	2.58	2H	Doublet	CH_2
7.	3.79	2H	Quintet	CH_2
8.	5.98	1H	SInglet	Pyrimidine-H
9.	6.73-6.98	7H	Multiplet	Ar-H
10.	8.38	1H	Singlet	NH

MASS SPECTRAL STUDY OF 6-(4-CHLOROPHENYL)-8-METHYL-N-(2,5-DIMETHYLPHENYL)-2,3,4,6-TETRAHYDROPYRIMIDO[2,1-b][1,3] THIAZINE-7-CARBOXAMIDE.




m/z = 425(M+)
m/z = 413
m/z = 379
m/z = 369 Base Peak
m/z = 353
m/z = 340
m/z = 330,
m/z = 262
m/z = 303
m/z = 227
m/z = 276
m/z = 174
m/z = 146
m/z = 115
m/z = 202

EXPERIMENTAL

SYNTHESIS OF 6-ARYL-8-METHYL-N-(2,5-DIMETHYLPHENYL)-2,3,4,6-TETRAHYDROPYRIMIDO[2,1-b][1,3] THIAZINE-7-CARBOXAMIDE.

Synthesis of 6-(4-chlorophenyl)-8-methyl-N-(2,5-dimethylphenyl)-2,3,4,6-tetrahydropyrimido[2,1-b][[1,3] thiazine-7-carboxamide.

(A) Synthesis of ***N*-(2,5-dimethylphenyl)-3-oxobutanamide:**

The synthesis is mentioned in part-I section-I.

(B) Synthesis *N*-(2,5-dimethylphenyl)-4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

The synthesis is mentioned in part-II section-I(B).

(C) Synthesis of 6-(4-chlorophenyl)-8-methyl-N-(2,5-dimethyl phenyl)-2,3,4,6 -tetrahydropyrimido[2,1-b][[1,3] thiazine-7-carboxamide.

A mixture of *N*-(2,5-dimethylphenyl)-6-(4-hydroxyphenyl)-4-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (1.67 g, 0.005M), dibromopropane (2.10 g, 0.01 M) and 2-3 drops of CH_3COOH in DMF (15 ml) was refluxed for 8-9 hrs. The reaction mixture was poured into ice cold water and neutralise with base.Thus the product was so obtained it was isolated and crystallised from ethanol. Yield 60%, m.p. 146^oC. ($C_{23}H_{24}ClN_3OS$: Required : C, 64.79%; H, 5.63%; N, 09.85%; found : C, 64.57%; H, 5.48%; N, 09.50%).The purity of the compound was checked by TLC.

Similarly other substituted Pyrimidothiazine derivatives were synthesized. The physical datas are recorded in Table No.VI.

(D) Antimicrobial activity of 6-Aaryl-8-methyl-N-(2,5-dimethylphenyl)-2,3,4,6-tetrahydropyrimido[2,1-b][1,3]thiazine-7-carboxamides.

Antimicrobial testing was carried out as described in part-I,section-I.(Refrences part-1,53,54)

The antimicrobial activities of the synthesised compounds are recorded in table no.VI(A)&(B).

TABLE-VI : PHYSICAL CONSTANTS OF OF 6-ARYL-8-METHYL-N-(2,5-DIMETHYLPHENYL)-2,3,4,6-TETRAHYDRO PYRIMIDO [2,1-b][1,3] THIAZINE-7-CARBOXAMIDES.

Sr. No.	R	Molecular Formula	Molecular Weight	M. P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found
1	2	3	4	5	6	7	8
VIa	4-NO_2-C_6H_4	$C_{23}H_{24}N_4O_3S$	436.50	105	60	12.82	12.67
VIb	4-OCH_3-C_6H_4	$C_{24}H_{27}N_3O_2S$	421.50	127	58	09.96	09.51
VIc	4-OH-C_6H_4	$C_{23}H_{25}N_3O_2S$	407.50	186	54	10.30	10.05
VId	4-F-C_6H_4	$C_{23}H_{24}FN_3OS$	409.50	109	59	10.25	09.94
VIe	4-Cl-C_6H_4	$C_{23}H_{24}ClN_3OS$	426.00	146	60	09.85	09.50
VIf	3-NO_2-C_6H_4	$C_{23}H_{24}N_4O_3S$	436.50	189	61	12.82	12.67
VIg	3-Cl-C_6H_4	$C_{23}H_{24}ClN_3OS$	426.00	200	63	09.85	09.50
VIh	2-NO_2-C_6H_4	$C_{23}H_{24}N_4O_3S$	436.50	171	61	12.82	12.67
VIi	2-Cl-C_6H_4	$C_{23}H_{24}ClN_3OS$	426.00	095	57	09.85	09.50
VIj	2-OH-C_6H_4	$C_{23}H_{25}N_3O_2S$	407.50	107	51	10.30	10.05

ANTIMICROBIAL ACTIVITY OF OF 6-ARYL-8-METHYL-N-(2,5-DIMETHYLPHENYL)-2,3,4,6-TETRAHYDROPYRIMIDO-[2,1-b][1,3] THIAZINE-7-CARBOXAMIDES. **TABLE NO-VI(A) ANTIBACTERIALACTIVITY**

Compd No.	R	Gram Positive								Gram Negative							
		S. aureus μg/ml				*B.Subtilis* μg/ml				*E.Coli* μg/ml				*S.Paratyphi B* μg/ml			
		2000	1000	500	250	2000	1000	500	250	2000	1000	500	250	2000	1000	500	250
VI_a	4-NO_2-C_6H_4	+	+	+	-	+	+	+	-	+	+	+	-	+	+	+	-
VI_b	4-OCH_3-C_6H_4	+	+	-	-	+	+	-	-	+	+	+	-	+	+	+	-
VI_c	4-OH-C_6H_4	+	+	+	-	+	+	+	-	+	+	+	-	+	+	+	-
VI_d	4-F-C_6H_4	+	+	+	+	+	+	+	+	+	+	+	-	+	+	+	+
VI_e	4-Cl-C_6H_4	+	+	+	-	+	+	-	-	+	+	-	-	+	+	+	-
VI_f	3-NO_2-C_6H_4	+	+	+	+	+	+	-	-	+	+	+	-	+	+	-	-
VI_g	3-Cl-C_6H_4	+	+	-	-	+	+	+	+	+	+	-	-	+	+	-	-
VI_h	2-NO_2-C_6H_4	+	+	+	-	+	+	+	-	+	+	-	-	+	+	+	-
VI_i	2-Cl-C_6H_4	+	+	+	+	+	+	+	-	+	+	+	-	+	+	-	-
VI_j	2-OH-C_6H_4	+	+	+	-	+	+	+	-	+	+	+	-	+	+	-	-

Reference drugs:	*S. aureus*	*B.Subtilis*	*E.Coli*	*S.Paratyphi B*
Ciprofloxacin	1.9	7.8	0.4	1.4

ANTIMICROBIAL ACTIVITY OF 6-ARYL-8-METHYL-N-(2,5-DIMETHYLPHENYL)-2,3,4,6-TETRAHYDROPYRIMIDO [2,1-b][1,3] THIAZINE-7-CARBOXAMIDES.

TABLE NO-VI(B) ANTIFUNGALACTIVITY

Compd No.	R	*A.niger* μg/ml				*C.albicans* μg/ml			
		2000	1000	500	250	2000	1000	500	250
VI_a	4-NO_2-C_6H_4	+	+	+	+	+	+	+	+
VI_b	4-OCH_3-C_6H_4	+	+	+	+	+	+	+	-
VI_c	4-OH-C_6H_4	+	+	+	-	+	+	+	-
VI_d	4-F-C_6H_4	+	+	+	+	+	+	+	+
VI_e	4-Cl-C_6H_4	+	+	+	+	+	+	+	-
VI_f	3-NO_2-C_6H_4	+	+	-	-	+	+	-	-
VI_g	3-Cl-C_6H_4	+	+	-	-	+	+	+	+
VI_h	2-NO_2-C_6H_4	+	+	+	+	+	+	-	-
VI_i	2-Cl-C_6H_4	+	+	+	-	+	+	+	+
VI_j	2-OH-C_6H_4	+	+	+	+	+	+	+	-

Reference drugs:	*A.niger*	*C.albicans*
Fluconazol	0.7	0.4

CONCLUSION:

ANTIMICROBIAL ACTIVITY

From the result of experiments using newly synthesized organic compounds it is clear that all of the compounds were highly active at lower dillution i.e. high concentration like 2000 μg/ml and 1000 μg/ml conc.of compounds.

In the series VI_{a-j} almost eight compounds VI_a,VI_c,VI_d,VI_e,VI_f,VI_h,VI_i and VI_j were found active at 500 μg/ml conc. against *Staphylococcus aureus* (in which R= 4-NO_2-C_6H_4, 4-OH-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4,3-NO_2-C_6H_4, 2-NO_2-C_6H_4, 2-Cl-C_6H_4 and 2-OH-C_6H_4). *B.Subtilis* was inhibited at 500 μg/ml conc. by seven compounds VI_a,VI_c,VI_d,VI_g,VI_h,VI_i and VI_j (in which R= 4-NO_2-C_6H_4, 4-OH-C_6H_4, 4-F-C_6H_4, 3-Cl-C_6H_4, 2-NO_2-C_6H_4, 2-Cl-C_6H_4 and 2-OH-C_6H_4). So,six compounds VI_a,VI_c,VI_d,VI_h,VI_i and VI_j were active against both cultures *B.Subtilis* and *S.aureus* (in which R= 4-NO_2-C_6H_4, 4-OH-C_6H_4, 4-F-C_6H_4, 2-NO_2-C_6H_4, 2-Cl-C_6H_4 and 2-OH-C_6H_4).

At 250 μg/ml conc. *S. aureus* was inhibited by three compounds VI_d,VI_f and VI_i (in which R= 4-F-C_6H_4, 3-NO_2-C_6H_4 and 2-Cl-C_6H_4).*B.Sutilis* was inhibited by two compounds VI_d and VI_g (in which R= 4-F-C_6H_4 and 3-Cl-C_6H_4).So, it is obvious from the data obtained that compounds VI_d,VI_f,VI_g and VI_i (R= 4-F-C_6H_4, 4-Cl-C_6H_4, 3-NO_2-C_6H_4, 3Cl-C_6H_4 and 2-Cl-C_6H_4) were highly active among all the compounds.

For Gram Negative bacteria in the series VI_{a-j} almost seven compounds VI_a,VI_b,VI_c,VI_d, VI_f,VI_i and VI_j were found active at 500 μg/ml conc. against *E.Coli* (in which R= 4-NO_2-C_6H_4, 4-OCH_3-C_6H_4, 4-OH-C_6H_4, 4-F-C_6H_4, 3-NO_2-C_6H_4, 2-Cl-C_6H_4 and 2-OH-C_6H_4). *S.Paratyphi B*. was inhibited at 500 μg/ml conc. by six compounds VI_a,VI_b,VI_c,VI_d,VI_e and VI_h (in which R= 4-NO_2-C_6H_4, 4-OCH_3-C_6H_4, 4-OH-C_6H_4, 4-F-C_6H_4, 4-Cl-$C_6H_4$and 2-NO_2-C_6H_4).So,nine compounds VI_a,VI_b,VI_c,VI_d, VI_e,VI_f,VI_h,VI_i and VI_j were active against both cultures *E.Coli* and *S.Parathyphi B.* (in which R= 4-NO_2-C_6H_4, 4-OCH_3-C_6H_4, 4-OH-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4,3-NO_2-C_6H_4, 2-NO_2-C_6H_4, 2-Cl-C_6H_4 and 2-OH-C_6H_4).

At 250 μg/ml conc. *E.Coli* was not inhibited by any compounds. *S.Parathyphi* B was killed by one compound VI_d (in which R= 4-F-C_6H_4). So, it is obvious from the data obtained that compound V_d (in which R= 4-F-C_6H_4) was highly active among all the compounds.

Antifungal activity for the series VI_{a-j} almost eight compounds VI_a,VI_b,VI_c, VI_d, VI_e,VI_h,VI_i and VI_j were found active at 500 μg/ml conc. against *A.niger* (in which R= 4-NO_2-C_6H_4, 4-OCH_3-C_6H_4, 4-OH-C_6H_4, 4-F-C_6H_4, 4-Cl-C_6H_4, 2-NO_2-C_6H_4, 2-Cl-C_6H_4 and 2-OH-C_6H_4).*C.albicans* was inhibited by eight compounds VI_a,VI_b,VI_c, VI_d,VI_f,VI_g,VI_i and VI_j (R= 4-NO_2-C_6H_4, 4-OCH_3-C_6H_4, 4-OH-C_6H_4, 4-F-C_6H_4,4-CI-C_6H_4, 3-CI-C_6H_4, 2-Cl-C_6H_4 and 2-OH-C_6H_4).So,seven compounds VI_a,VI_b,VI_c,VI_d,VI_e,VI_i and VI_j were active against both the cultures *A. niger* and *C.albicans* (R= 4-NO_2-C_6H_4, 4-OCH_3-C_6H_4, 4-OH-C_6H_4, 4-F-C_6H_4, 4-CI-C_6H_4, 2-Cl-C_6H_4 and 2-OH-C_6H_4).

At the conc. of 250 μg/ml *A.niger* was inhibited by six compounds VI_a,VI_b,VI_d,VI_e,VI_h and VI_j (in which R= 4-NO_2-C_6H_4, 4-OCH_3-C_6H_4, 4-F-C_6H_4, 4-CI-C_6H_4, 2-NO_2-C_6H_4 and 2-OH-C_6H_4). *C.albicans* was inhibited by four compounds VI_a, VI_d,VI_g and VI_i (R= 4-NO_2-C_6H_4, 4-F-C_6H_4, 3-CI-C_6H_4 and 2-Cl-C_6H_4) .So, it is obvious from the data obtained that compounds VI_a,VI_b,VI_d, VI_e,VI_g,VI_h,VI_i and VI_j (R= 4-NO_2-C_6H_4, 4-OCH_3-C_6H_4, 4-F-C_6H_4,4-CI-C_6H_4, 3-CI-C_6H_4, 2-NO_2-C_6H_4, 2-Cl-C_6H_4 and 2-OH-C_6H_4) were highly active among all the compounds.