STUDIES ON SOME BIO-ACTIVE ORGANIC COMPOUNDS

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FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

THE FACULTY OF SCIENCE (CHEMISTRY)

BY

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UNDER THE GUIDANCE

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The work included in the thesis is my own work under the supervision of **Dr. Shipra Baluja** and leads to some contribution in chemistry subsidized by a number of references.

Date: -12-2009

Place: Rajkot **(Rahulkumar H. Bhalodia)**

This is to certify that the present work submitted for the Ph.D. Degree of Saurashtra University by **Rahulkumar H. Bhalodia** is his own work and leads to advancement in the knowledge of chemistry.

The thesis has been prepared under my supervision.

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Dedicated
to
My Family

ACKNOWLEDGEMENT

" Shree Ganeshay Namah "

Hats off to the Omnipresent, Omniscient and Almighty God, the glorious fountain and continuous source of inspirations! I offer salutations to him and my head bows with rapturous dedication from within my heart, to the Omnipotent Lord "Shree Krishna".

Firstly, I would like to express my sincere gratitude to my co-traveler and guide Dr. Shipra Baluja - Associate Professor, Department of Chemistry, Saurashtra University, Rajkot, for accepting me as her student and who made this research success. My mentor, my guide reflects with her incredible personality and lightened up my life with indomitable determination. With her blessings, constant motivation and optimistic approach, I could complete my journey towards achieving my goal. Her striving to make us not only better in our chosen field but good human being also. I pray to god that I may come to her expectations in present as well as in future.

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Rahul Bhalodia

CONTENTS

SYPNOSIS

SYNOPSIS

STUDIES ON SOME BIO-ACTIVE ORGANIC COMPOUNDS

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SYNOPSIS of the thesis to be submitted to the Saurashtra University for the degree of **Doctor of Philosophy** in Chemistry.

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Organic compounds are important constituents of many products eg., paints, drugs, plastics, food, explosives, petrochemicals etc. These molecules also exist in various natural products such as alkaloids and glycosides. Many of these organic compounds exhibit wide spectrum of biological activities such as antibacterial, antitubercular, anti HIV, anticancer, insecticidal, antiviral etc. These organic compounds can be aliphatic, biomolecules, polymers, heterocyclic etc.

Taking in view of the applicability of organic compounds, the present work was undertaken to synthesize some new heterocyclic compounds.

The present work is divided into four chapters.

Chapter-1 General Introduction

Chapter-2 Synthesis and characterization

Section-I Synthesis of Azomethines

Section-II Synthesis of Benzothiazole derivatives

Section-III Synthesis of Dihydropyrimidinones

Section-IV Synthesis of Dihydropyrimidinthiones

Section-v Synthesis of Thiazolidinones

Chapter-3 Physico chemical properties

Section-I Acoustical Properties

Section-II Solubility

Section-III Density and Refractive index

Section-IV Dissociation Constants

Section-V Thermal Properties

Section-VI Conductance

Chapter-4 Biological activities

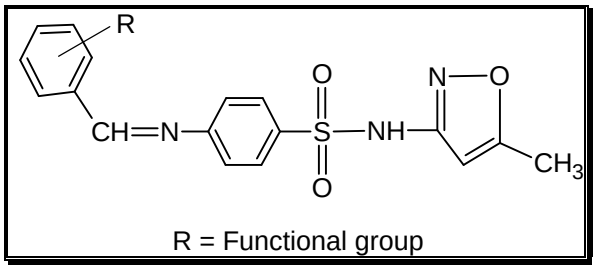
CHAPTER – 1: GENERAL INTRODUCTION

This chapter describes literature survey of synthesis, characterization, applications, physicochemical properties and antibacterial activities of heterocyclic compounds.

CHAPTER – 2: SYNTHESIS AND CHARACTERIZATION

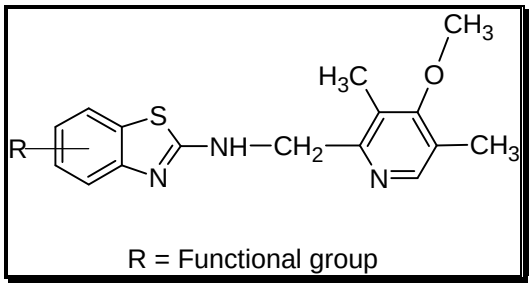
This chapter deals with synthesis and characterization of synthesized compounds. Characterization of these synthesized compounds was done by RI, Mass and NMR spectral data.

Section-I Synthesis of Azomethines



R = Functional group

Section-II Synthesis of Benzothiazole derivatives



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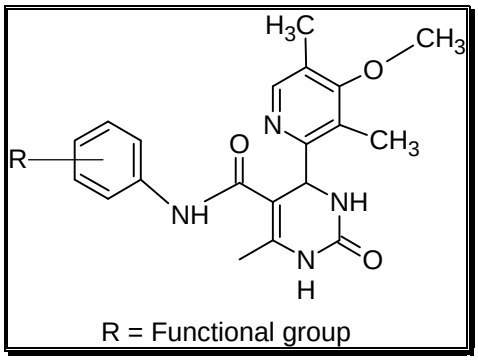
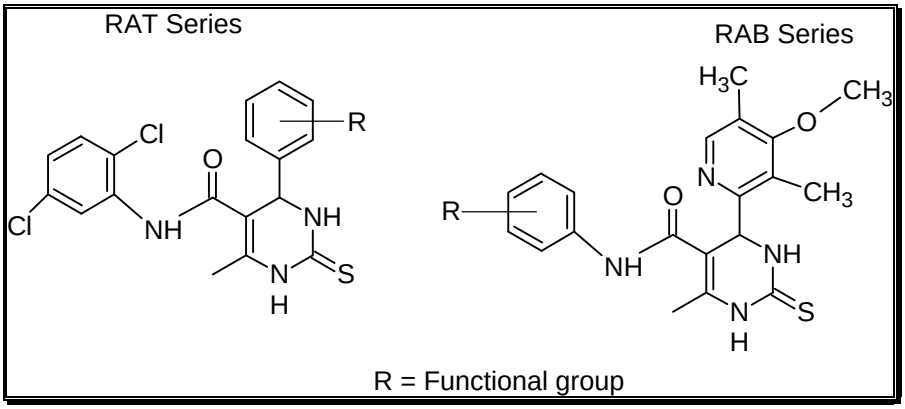
Section-III Synthesis of Dihydropyrimidinones

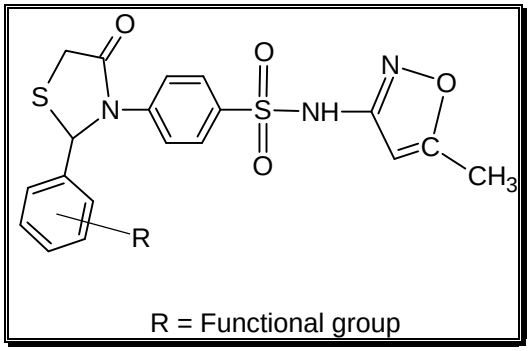


R = Functional group

Section-IV Synthesis of Dihydropyrimidinthiones



Section-v Synthesis of Thiazolidinones



CHAPTER – 3: PHYSICO-CHEMICAL PROPERTIES

Some physicochemical properties such as acoustical properties, solubility, density and refractive index, dissociation constants, thermal and conductance have also been studied in different solvents.

These properties were studied for solutions of different concentrations of **Dihydropyrimidinthiones derivatives** (**RAT series**) in **dimethylformamide** and **tetrahydrofuran at 308.15 K** and are discussed in different sections as following:

Section-1 Acoustical Properties

In this section, density, viscosity and ultrasound velocity were measured for solutions of different concentrations in both the solvents, DMF and THF. From these experimental data, various acoustical parameters like specific acoustical impedance (Z), isentropic compressibility (κ_S), inter molecular free length (L_f), molar compressibility (W), Rao's molar sound function (R_m), Vander Waals constant (b), relaxation strength (r), solvation number (S_n) apparent molar compressibility (ϕ_k) etc. were evaluated. The results are interpreted in terms of molecular interactions occurring in the solutions.

Section-2 Solubility

The solubility of various compounds of RAT series was determined at different temperatures (303.15-323.15 K) in dimethylformamide and tetrahydrofuran. Further, some thermodynamic parameters such as enthalpy, Gibb's energy and entropy of different solutions have been evaluated from the experimental data.

Section-3 Density and Refractive index

Refractive index is a property of the material and is extremely useful in chemical analysis. In this section, the density and refractive index of solutions of different concentrations of compounds of RAT series were measured in dimethylformamide and tetrahydrofuran at 308.15 K. From the density of solutions, densities of synthesized compounds were evaluated. The density of compounds were also evaluated theoretically and were compared with those obtained from experimental data.

Section-4 Dissociation Constants

This section deals with the dissociation constant of compounds of RAT series in DMF-water (60:40) system at different temperatures (298.15K, 308.15K and 318.15K) by Calvin Bjerrum pH titration technique. From the experimental data, dissociation constant were evaluated by average and half-integral method.

Further, some thermodynamic parameters such as enthalpy of solution, Gibb's energy change and entropy of solution have been evaluated from the observed dissociation constants.

Section-5 Thermal Properties

This section describes the thermal properties of RAT series compounds. The Thermo Gravimetric Analysis (TGA) and Differential Thermal Analysis (DSC) measurements were made. From these measurements, various kinetic parameters were evaluated. Further, thermal stability of various compounds were determined.

Section-6 Conductance

This chapter deals with the conductance measurement of solutions of different concentrations of Dihydropyrimidinthiones derivatives (RAT series) in dimethylformamide and tetrahydrofuran at 308.15 K. From these experimental values, specific conductance and equivalent conductance were measured.

CHAPTER – 4: BIOLOGICAL ACTIVITIES

In this chapter, antibacterial activity of synthesized compounds against some Gram positive and Gram negative bacteria in DMF and DMSO was studied.

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CHAPTER-1

GENERAL INTRODUCTION

GENERAL INTRODUCTION

The name organic was first used for all substances derived from living organisms i.e., plants and animals. Some of these substances are sugars, starches, oils, cellulose, fats, proteins, gums, dyes, alkaloids, fats, proteins, urea, gelatin etc. Such substances discovered and isolated from organic sources were studied under a branch of chemistry named organic chemistry.

Organic chemistry plays an importance part in our daily life because food, clothes, paper, ink, rubber, soap, perfumes, medicines etc. are indispensable to us for proper living. Organic compounds are important constituents of many products eg., paint, food, plastic, explosive, medicine, petrochemical, pesticide etc[1-5].

The study of organic chemistry is of utmost importance for chemists in order to synthesize drugs for the alleviation of human sufferings, for a biologist to understand the processes undergoing in the bodies of animals and plants, for a pharmacist in order to prepare good medicines and for a chemical manufacturer for developing industries of dyes, drugs, plastics, rubber, textiles, rayon, etc.

There are various types of organic compounds out of which heterocyclic compounds are one of the most important class. The study of heterocyclic compounds is of great interest both from the theoretical as well as practical point of view.

Many workers have been reported the applicability of heterocyclic compounds[6-15]. These compounds have great applicability in pharmaceutics because they have specific chemical reactivity. They resemble essential metabolism and they fit biological receptors and block their normal working[16]. These compounds are useful in the field of medicine and are used as a starting material for the synthesis of new drugs[17-25]. Various drugs such as penicillin, rotenmone, strychnine, resepine, sulphamethoxazole, ciprofloxacine, etc and pigments such as indigo, hemoglobin, anthocin etc. contain heterocyclic ring[26-28].

Taking in view of the applicability of heterocyclic compounds, in the present work several entities containing heterocyclic nucleus have been selected.

AIM AND OBJECTIVES:

- To synthesize some derivatives of 1-4-dihydropyrimidines, benzothaizole amine, thaizolidinones, sulphamethoxazole nucleus.
- To characterize these synthesized compounds for structure elucidation by IR, ^{1}H NMR and Mass spectral studies.
- To study the physicochemical properties such as acoustical properties, density and refractive index, solubility, dissociation constant, thermal properties and conductance of some dihydropyrimidinones (RAT series) in different solvents.
- To evaluated antibacterial activity of these synthesized compounds against different bacterial strains, in different solvents.

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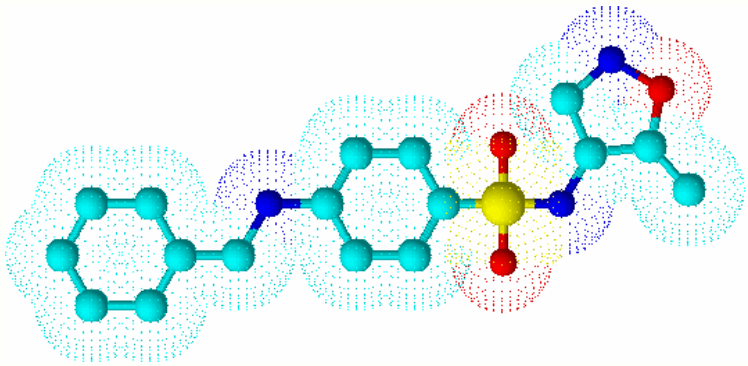
CHAPTER-2
SYNTHESIS AND CHARACTERIZATION



Section-I

Synthesis of Azomethines

INTRODUCTION

Azomethines are the compounds, which contain –C=N- group. These compounds are also known as imines or anils but most commonly, they are known as Schiff bases to honor Hugo Schiff[1], who synthesized these compounds first.

A lot of work has been done on this class of compounds due to its multi applicability. They are well known intermediate for the preparation of azetidinone[2], thiazolidinone[3], formazone[4], arylacetamide[5], metal complexes[6-8] and many other derivatives[9,10].

Further, these azomethines are known to be useful in complexing agent[11], perfumery[12], analytical reagent[13], as corrosion inhibitor[14], as a catalyst[15] and polymerization process[16]. Further, many workers reported a wide range of biological activity[17-19] of azomethines. Besides, several azomethines have been reported to possess remarkable antitumor[20], antibacterial[21], diuretic[22], insecticidal[23], anti-HIV[24], antiparasitic[25], anticancer[26], antimicrobial[27], antifunga[28], and anti-inflammatory[29] activities.

Genaral account of the summary of reaction of aldehydes with amine (aromatic or aliphatic) has been reviewed by Murry[30]. Some azomethines from amphetine and procaine were reported by Giovambattista and Rabassa[31]. Savich[32] at el. gave the detail study report of azomethines from 2-hydroxy-1-napthaldehyde and arylamides. Takeo and Yuhi[33] have been synthesized azomethines of 3,5-dibromosalicyladehyde. Some complexes of azomethines have also been synthesized from hetero aromatic amine and salicylaldehyde[34]. Sreenivasulu and Rao[35] have studied the characterization of azomethines and its ability of complexing with cadmium(II) by polaography. Electrochemical behavior of platinum complexes of azomethines has also been reported by Shagisultanova at el[36]. Parra at el[37]. have studied the mesomorphic properties of some azomethines compounds derived from phenyl and thienyl-1,3,4,-thiadiazole. Some other azomethines have also been synthesized by Hussain and Shaukat from p-dimethylamino cinnamaldehyde[38].

Recently, Tian at el. have synthesized and characterized 2-(3,4,5-tri methoxybenzylidenamino)ethanol azomethines[39] Yu and coworkers[40] studied

the synthesis of 3,3'-[α,ω alkanediylbis(nitrilomethylidyne)]bis[2-hydroxy-5-meth- ylbenzoic acid derivatives. Some novel azomethines derivatives of 2-aminobenzothiazole[41] and 4-methyl pyridine-2-amine[42] have also been reported. The spectral studied of azomethines have also been studied by various workers[43,44].

Sulfonamides have been used as antibacterial agents for last 60 years. Sulfamethoxazole (4-amino-N-(5-methylisoxazol-3-yl)-benzenesulfonamide), one of the sulfonamides is a class of drugs whose molecular structure contain the sulfanilamide analog[45]. Sulfamethoxazole is most often used as part of combination with Trimethoprim[46], which act synergistically against a wide variety of bacteria[47-49], although other combinations of sulfonamides are also available. It has found widespread use in animal husbandry[50] and, to a lesser extent[51], in the treatment of human infections such as bronchitis and urinary tract infections[52]. It is also applicable for antiseptique[53], atituberculr[54] and anti-inflammatory agent[55].

Thus, significant biological properties associated with azomethines derivatives have aroused considerable interest to design the compounds in which therapeutically active Sulfamethoxazole nucleus.

In the present section, some new azomethines have been synthesized containing Sulfamethoxazole nucleus.

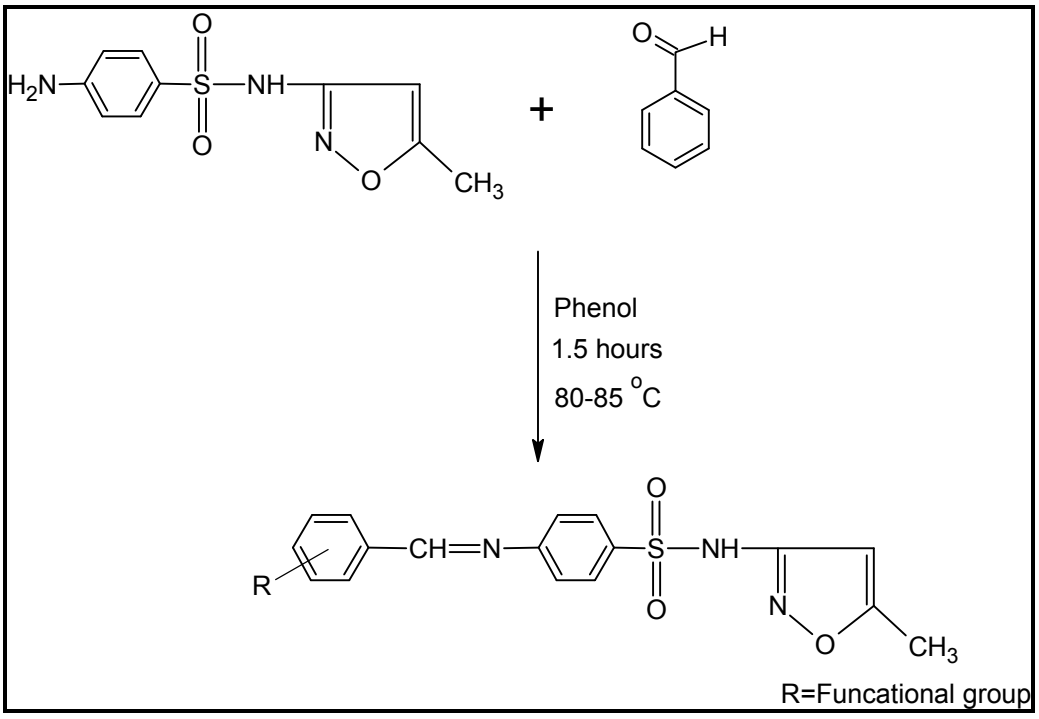
EXPERIMENTAL

Synthesis:

To an ethanolic solution of aldehydes (0.01mole). 0.01 mole of sulfamethoxazole and 1 ml of ethanolic phenol solution (0.1 moles) was added (drop wise). The mixture was stirred for 15 minutes and then was refluxed in water bath for 1.5 hours at 80-85 ^{o}C.

The resulting solution was cooled to room temperature and allowed to freeze for 30 minutes. The product was isolated by filtration and was recrystallized from ethanol.

REACTION SCHEME



The following azomethines have been synthesized from sulfamethoxazole.

1.	RSA-1:	4-[(4-methoxybenzylidene)amino]-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide
2.	RSA-2:	4-{[4-(dimethylamino)benzylidene]amino}-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide
3.	RSA-3:	4-[(4-fluorobenzylidene)amino]-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide
4.	RSA-4:	4-[(4-chlorobenzylidene)amino]-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide
5.	RSA-5:	N-(5-methyl-1,2-oxazol-3-yl)-4-[(3-nitrobenzylidene)amino]benzenesulfonamide
6.	RSA-6:	N-(5-methyl-1,2-oxazol-3-yl)-4-[(2-nitrobenzylidene)amino]benzenesulfonamide
7.	RSA-7:	4-(benzylideneamino)-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide
8.	RSA-8:	4-[(2-chlorobenzylidene)amino]-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide
9.	RSA-9:	4-[(3-chlorobenzylidene)amino]-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide
10.	RSA-10:	4-[(3-bromobenzylidene)amino]-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide

The various physical constants such as R_f value, melting point and percentage of yield for all synthesized Azomethiens are given in Table 1. The melting point was taken by open capillary method.

The characterization was done by IR, mass spectra and ^{1}H NMR.

Infrared spectra:

The IR spectra were recorded by SHIMADZU-FTIR-8400 spectrophotometer in the frequency range of 4000-400 cm^{-1} by KBr powder method. The IR spectra and data for RSA-1 is given in Figure 2.1.1 and Table 2.1.2 respectively. The spectral data for all other compounds are reported in Table 2.1.3.

Mass spectra:

The Mass spectra were recorded by GCMS-SHIMADZU-QP2010. Figure 2.1.2 shows mass spectra of RSA-1. The proposed mass fragmentation of RSA-1 is given in Scheme 2.1.1. The mass fragmentations of other compounds are also given separately.

^{1}H NMR Spectra:

The NMR spectra were recorded by BRUKER Spectrometer (400 MHz) using internal reference TMS and solvent $CDCl_3$/DMSO. Figure 2.1.3 shows NMR spectra of RSA-2. The spectral data for RSA-2 is given in Table 2.1.4.

Table 2.1.1: Physical constants of azomethines.

Sr. No.	Code	R	M.F.	M. Wt. (g/mol)	R_f* Value	M.P. °C	Yield %
1	**RSA-1**	4-OCH_3	$C_{18}H_{17}N_3O_4S$	371	0.42	171	86
2	**RSA-2**	4-$N(CH_3)_2$	$C_{19}H_{20}N_4O_3S$	384	0.48	202	92
3	**RSA-3**	4-F	$C_{17}H_{14}FN_3O_3S$	359	0.43	159	83
4	**RSA-4**	4-Cl	$C_{17}H_{14}ClN_3O_3S$	375	0.53	185	88
5	**RSA-5**	3-NO_2	$C_{17}H_{14}N_4O_5S$	386	0.58	211	90
6	**RSA-6**	2-NO_2	$C_{17}H_{14}N_4O_5S$	386	0.52	234	92
7	**RSA-7**	-H	$C_{17}H_{15}N_3O_3S$	341	0.61	131	80
8	**RSA-8**	2-Cl	$C_{17}H_{14}ClN_3O_3S$	375	0.67	241	84
9	**RSA-9**	3-Cl	$C_{17}H_{14}ClN_3O_3S$	375	0.60	238	80
10	**RSA-10**	3-Br	$C_{17}H_{14}BrN_3O_3S$	420	0.52	192	82

* Ethyl acetate: Hexane: 3:7

Figure 2.1.1: IR spectra of 4-{[(E)-(4-methoxyphenyl)methylidene]amino} -N-(5-methylisoxazol-3-yl)benzenesulfonamide (RSA-1).

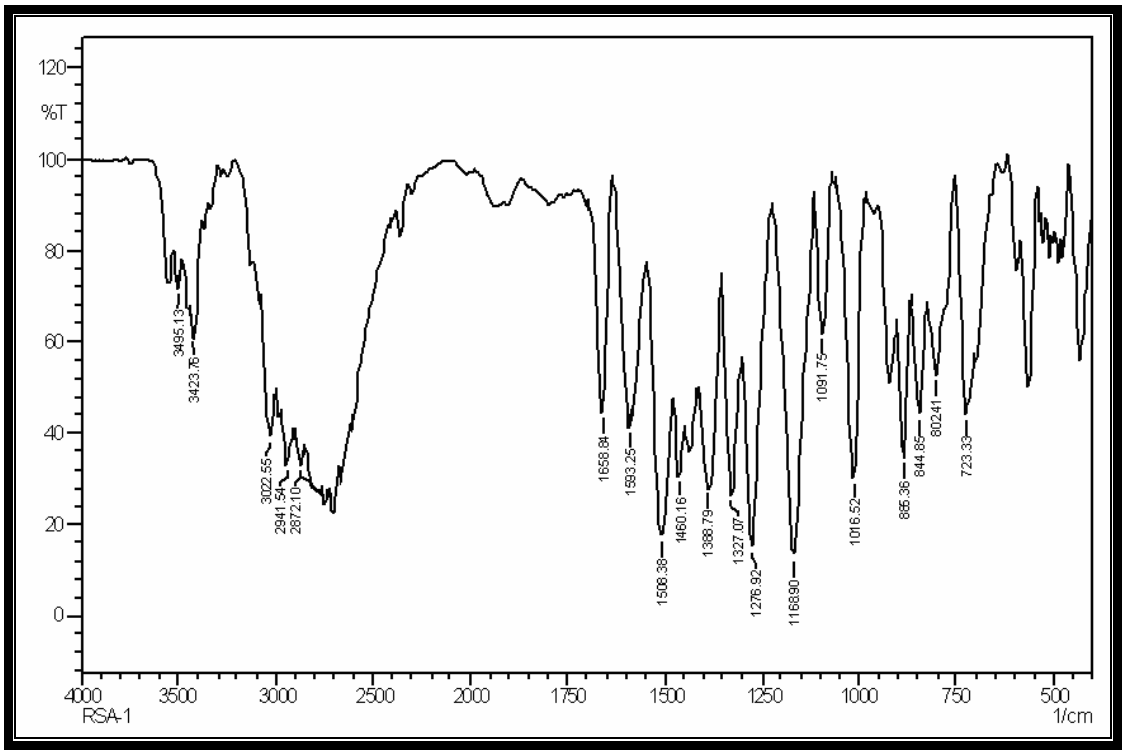


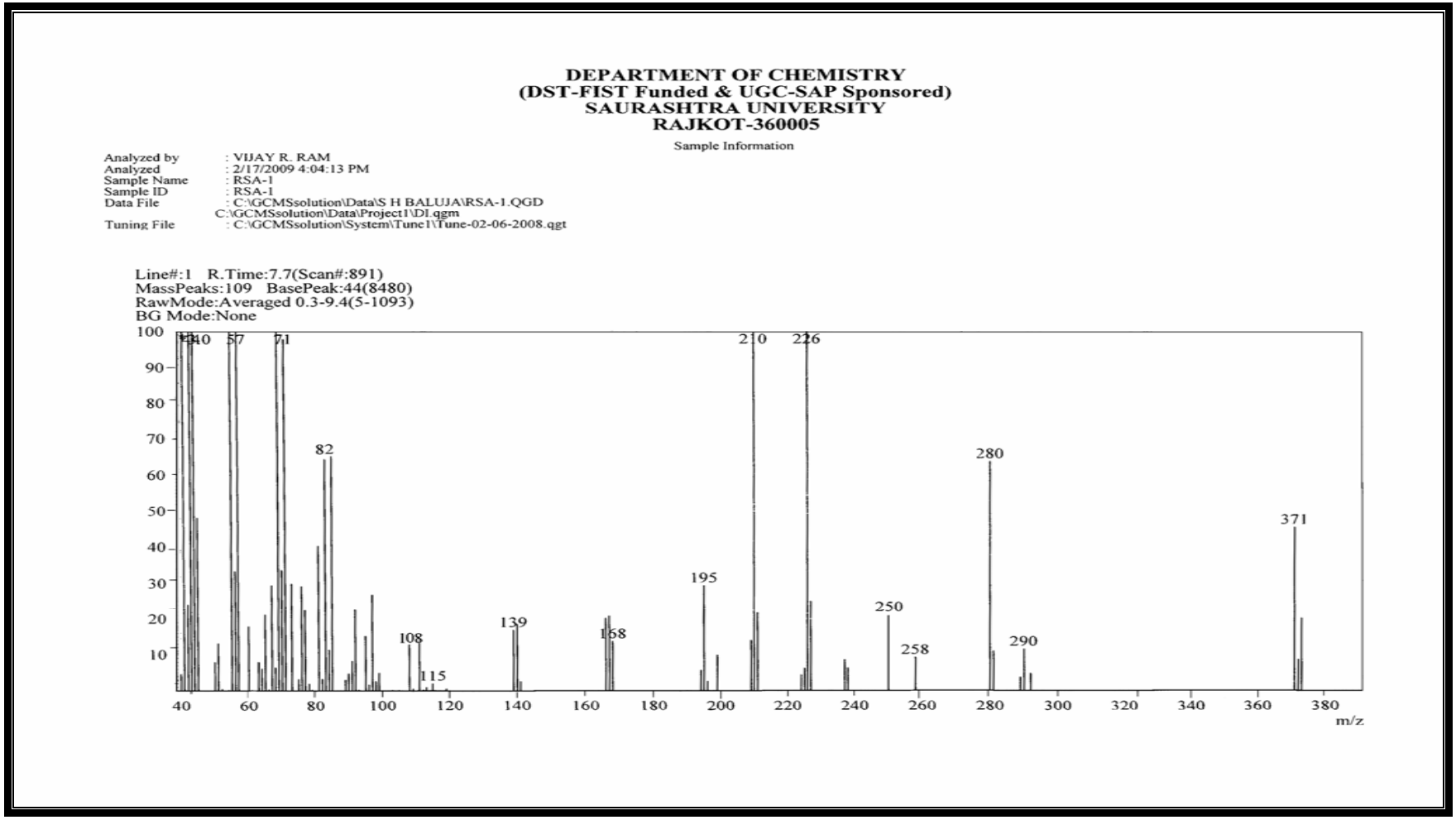
Table 2.1.2: IR spectral data of 4-{[(E)-(4-ethoxyphenyl)methylidene]amino}-N- (5-methylisoxazol-3-yl)benzenesulfonamide (RSA-1).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported[56,57]
Alkane	C-H str. (asym.)	2941.54	2975-2920
	C-H str. (sym.)	2872.10	2880-2860
	C-H def. (asym.)	1460.16	1500-1435
	C-H def.(sym.)	1388.79	1400-1370
Aromatic	C-H str.	3022.55	3200-3000
	C=C str.	1508.38	1585-1480
	C-H i.p. def.	1016.52	1125-1090
	C-H o.o.p. def.	844.85	860-810
Azomethine	C=N str.	1658.84	1690-1640
Sulfonamide	SO_2-NH (sym.)	1168.90	1180-1140
	SO_2-NH (asym.)	1327.07	1350-1300
Secondary amine	N-H (asym.)	3423.76	3500-3310
	N-H ben.	1593.25	1650-1550
ether	C-O-C str. (asym.)	1276.92	1300-1200
	N-O str.	1327.07	1400-1000

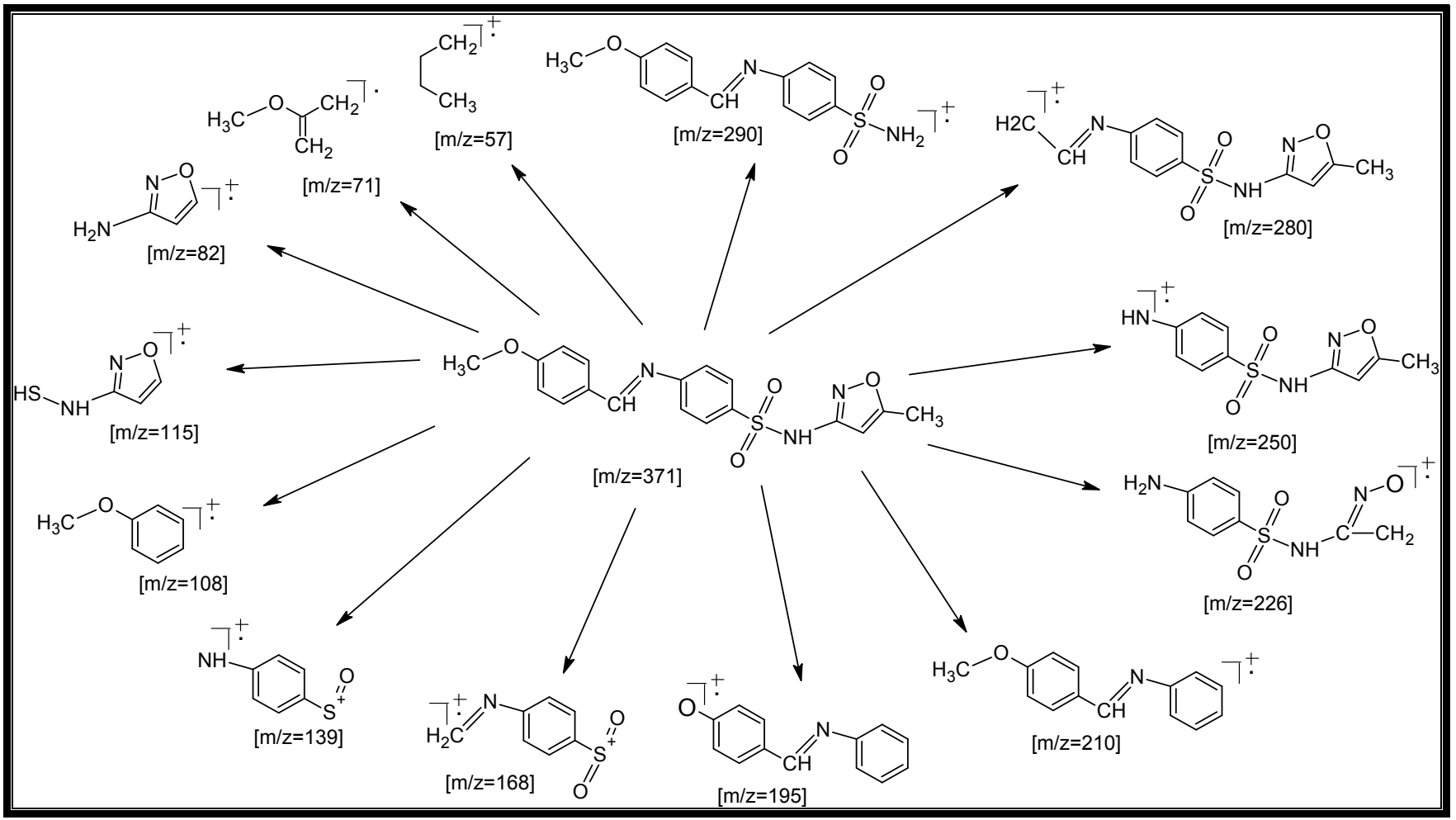
Table 2.1.3: IR spectral data of synthesized azomethines (RSA-3 to RSA-10).

Compounds	*IR ν, (cm^{-1})*			
	C=C (asym.)	**N-O Str.**	**C=N Str.**	**R**
RSA-2	1498.88	1037.74	1653.05	-
RSA-3	1538.16	1183.42	1673.45	1320.83
RSA-4	1489.10	1087.89	1656.91	700.18
RSA-5	1516.10	1109.11	1674.27	1340.57
RSA-6	1501.84	1112.53	1682.42	1358.73
RSA-7	1500.67	1203.84	1672.73	-
RSA-8	1534.37	1154.31	1679.54	732.15
RSA-9	1520.63	1167.50	1653.30	768.20
RSA-10	1532.54	1101.91	1666.89	553.08

Figure 2.1.2: Mass spectra of 4-{[(E)-(4-ethoxyphenyl)methylidene]amino}-N- (5-methylisoxazol-3-yl)benzenesulfonamide (RSA-1).



Scheme 2.1.1: Proposed mass fragmentation of 4-{[(E)-(4-ethoxyphenyl)methylidene]amino}-N- (5-methylisoxazol-3-yl)benzenesulfonamide (RSA-1).



Mass fragments (m/z value) of synthesized azomethiens (RSA-2 to RSA-10).

RSA-2: 371, 303, 271, 239, 223, 207, 189, 156, 148, 132, 119, 92.

RSA-3: 359, 317, 268, 246, 225, 198, 174, 156, 151, 140, 119, 108, 92.

RSA-4: 375, 360, 339, 293, 278, 262, 251, 214, 200, 161, 138, 113, 97,

RSA-5: 386, 370, 325, 304, 264, 251, 243, 237, 179, 155, 135, 122, 97.

RSA-6: 386, 371, 324, 304, 290, 250, 237, 225, 146, 133, 120, 97.

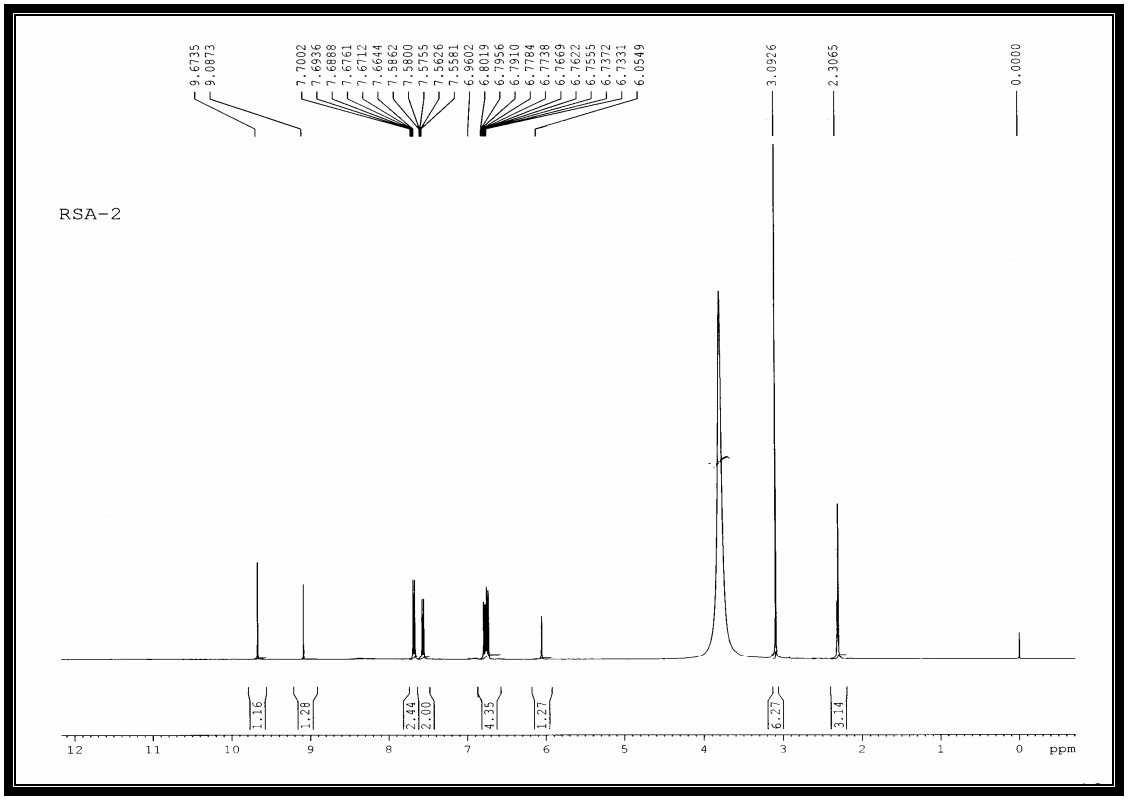
RSA-7: 341, 326, 301, 264, 259, 237, 155, 140, 104, 91, 77, 57.

RSA-8: 375, 360, 335, 293, 258, 237, 182, 161, 145, 138, 112, 91.

RSA-9: 375, 335, 294, 258, 239, 180, 162, 145, 111, 91.

RSA-10: 420, 405, 382, 340, 307, 260, 251, 237, 182, 161, 133, 91,

Figure 2.1.3: ^{1}H NMR spectra of 4-{[4-(dimethylamino)benzylidene] amino}-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide (RSA-2).



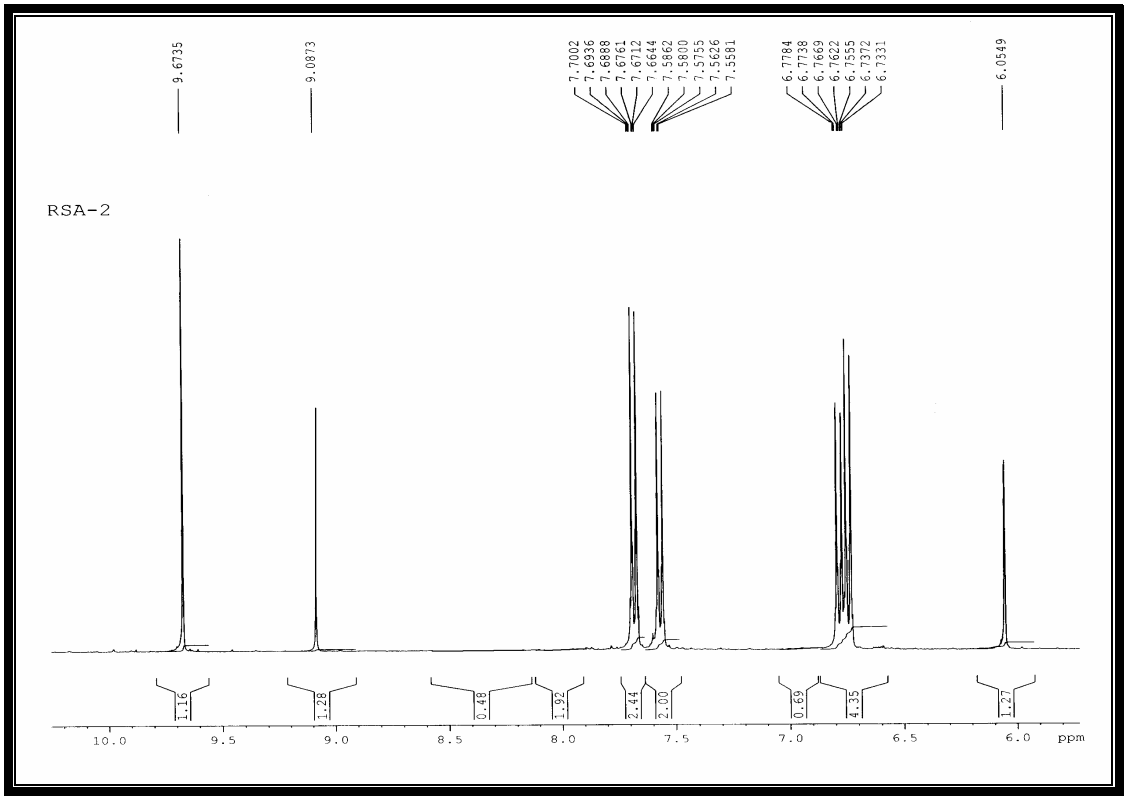
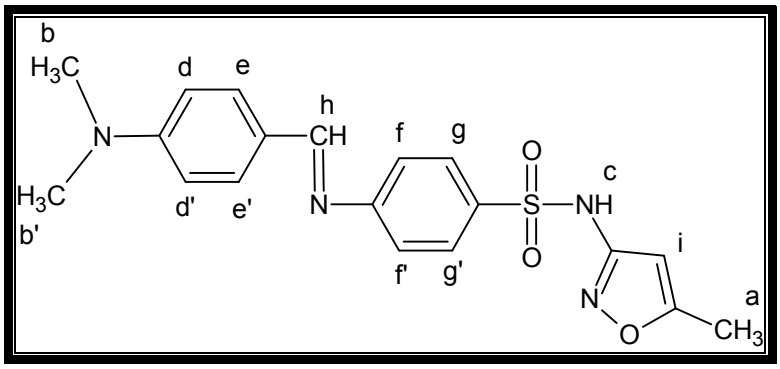


Table 2.1.4: ^{1}H NMR spectral data of 4-{[4-(dimethylamino)benzylidene] amino}-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide (RSA-2).



Singal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	*J* (Hz)
1	2.30	3	singlet	-C<u>H</u>$_3$ (a)	-
2	3.09	6	singlet	N-(C<u>H</u>$_3$)$_2$ (bb')	-
3	6.05	1	singlet	-N<u>H</u> (c)	-
4	6.73-6.75	4	double	Ar-H (dd')	8.96
5	6.76-6.77		doublet	Ar-H (ee')	6.48
6	7.55-7.57	2	doublet	Ar-H (ff')	6.96
7	7.66-7.67	2	doublet	Ar-H (gg')	4.68
8	9.08	1	singlet	N=CH (h)	-
9	9.67	1	singlet	H (i)	-

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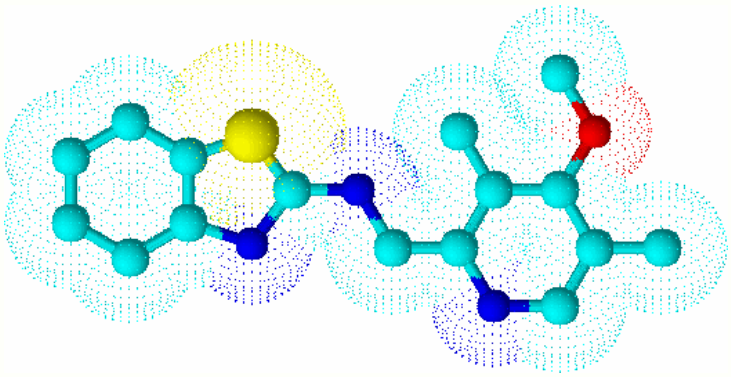
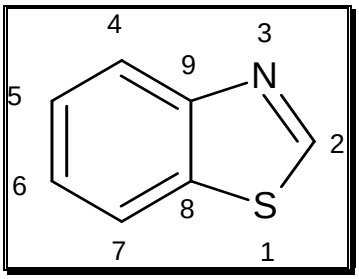


Section-II
Synthesis of Benzothiazole Derivatives

INTRODUCTION

The Benzothiazole is sulfur and nitrogen containing bicyclic ring system fused with phenyl ring. The study of benzothiazole derivatives is of considerable current interest due to their important biological and biophysical properties.



Benzothiazoles are a class of high production volume chemicals with various applications in industry[1,2]. The largest amount of benzothiazoles are used as vulcanization accelerators[3], such as 2-morpholinothiobenzothiazole in rubber production[4]. 2-Mercaptobenzothiazole is used in paper production as corrosion inhibittor[5], and 2-thiocyanomethylthiobenzothiazole is used as a substitute for chlorophenols in wood preservation and leather production[6]. Benzothiazoles are also added as antifreeze[7] and cooling liquids[8].

Further, Benzothiazole derivatives show a wide range of chemotherapeutic activity[9-11]. Many of the benzothiazole derivatives are used as antibacterial[12-15] and antifungal[16-19] agents. Substituted benzothaizols have been found to exhibit diverse biological activities such as antitumor[20,21], antimicrobial[22,23], anti-inflammatory[24,25], anthelmintic[26,27] antileishmanial[28,29] anticonvulsant[30], anti-HIV[31], antiviral[32], diuretics[33,34] etc.

One of the earliest and most valuable method for the synthesis of benzothiazole is the reaction of an o-amino thiaphenol with a carboxylic acid, its derivatives[35-38] or aldehydes[39-41]. The reaction of aldehydes and ketones has also been reported[42-44].

Further, literature survey shows that 2-aminobenzothiazole and some of its derivatives have been synthesized by many workers[45-50]. Davies and Sexton[51] have studied the synthesis of 1-thiolbenzothiazoles and its interaction with alcohols. Efros and Davidenkov[52] have reported the

preparation of 1-benzothiazolyl-3-methyl-5(4H)-pyrazolone. Bhargava and Baliga[53] have also synthesized some new 2-aminobenzothiazoles. Jenkins and coworkers[54] have synthesized the benzothiazole and benzoxazole rings. The Synthesis of 2-[2-(5-nitro-2-furyl)ethynyl] benzothiazole has also been reported by Yoshina et al.[55] Kim[56] has studied the thermostable copolymers of methyl methacrylate with 2-thiobenzothiazolethyl methacrylate. Halgas et al.[57] synthesized 3, 4, 6-substituted benzothiazolium salts and studied its antimicrobial activity. Maksimova and coworkers[58] have prepared the benzothiazole dye. Syntheses of 4-nitrophenyl benzothiazol-6-ylsulfides and 4-nitrophenyl benzothiazol-6-ylsulfones has been given by Kandeel[59]. Some complexes have also been synthesized by Mandal and coworkers from 2-(2'-pyridyl) benzothiazole[60]. Borisov et al.[61] have prepared (1E,3E)-1,4-diphenyl-1,3-butadiene by cycloaddition of 1,3- benzothiaz- ole-2-sulfenyl chloride. Some new benzothiazole derivatives of pyrimidines, acrylonitriles, coumarins have been synthesized[62] and studied their biological activities. Preparation of benzo[c]thiophene compounds containing benzimidazole, benzothiazole, and oxazole have reported by Clemen[63].

Thus, the important role displayed by benzothiazole and its derivatives for various therapeutic and biological activities encouraged to synthesize some new derivatives of benzothiazole.

In this section, some derivatives of benzothiazoles have been synthesized and their characterization was done by IR, NMR and mass spectra.

EXPERIMENTAL

Synthesis of 6-methoxy-N-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-1,3-benzothiazol-2-amine (RBT-1).

[A] Synthesis of 2-amino benzothiazole derivatives.

A solution of substituted aniline (1 mole) in chloro benzene was prepared in a three-necked, round-bottom flask fitted with a stirrer, reflux condenser, thermometer, and dropping funnel. Over a period of 5 minutes, 0.55 mole of concentrated sulfuric acid was added drop wise. To the finely divided suspension of substituted aniline sulfate, 1.1 moles of sodium thiocyanate was added and the mixture was heated for 3 hours at 100° (inside temperature) in an oil bath. The solution, which now contains the thio urea, was cooled to room temperature. To this mixture, 1.34 moles of sulfuryl chloride was added over a period of 15 minutes. Care was taken to avoid increase of temperature above 50°C. The mixture was kept at 50°C for 2 hours to remove all the evolved hydrogen chloride. The reaction mixture was then filtered to remove chloro benzene. The solid residue was then dissolved in hot water, and the remaining solvent (chloro benzene) was removed by a current of steam. The aqueous solution was filtered and was made alkaline by adding concentrated ammonium hydroxide. The precipitated substituted 2-amino benzothiazole was filtered and washed with water. The crude product was isolated and crystallized from absolute ethanol.

[B] Synthesis of 2-(chloromethyl)-4-methoxy-3,5-dimethylpyridine.

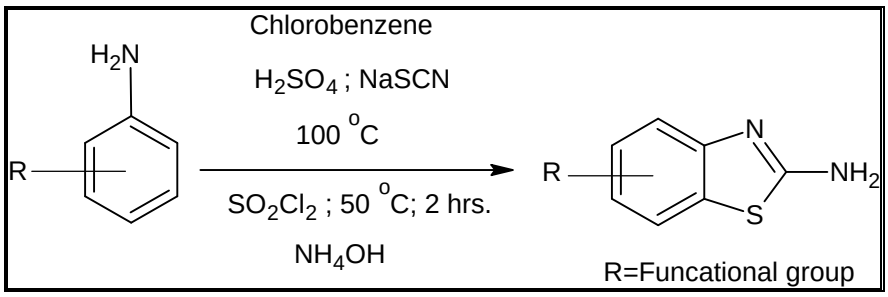
The solution of (4-methoxy-3,5-dimethylpyridin-2-yl)methanol (o.1 mole) in 50 ml of toluene was stirred for 10 minutes at room temperature. The reaction mixture was then cooled at 5-10^{o}C. To this mixture, thionyl chloride (0.1 mole) was added drop wise (the temperature dose not exceed 40^{o}C) and the mixture was stirred for 20 minutes at room temperature. The product was filtered and washed with toluene.

[C] Synthesis of 6-methoxy-N-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-1,3-benzothiazol-2-amine (RBT-1).

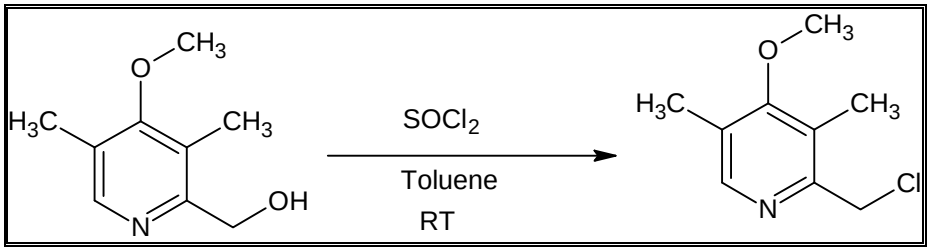
0.5 gm of sodium hydroxide was dissolved in 15 ml of methanol in a water bath. To this alkaline solution, 6-methoxy-1,3-benzothiazol-2-amine (0.01 mole) and 2-(chloromethyl)-4-methoxy-3,5-dimethylpyridine (0.01 mole) was added and was refluxed at 70^{o}C in water bath for 2 hours. The reaction mixture was then cooled at room temperature and poured in ice water. The solid product was filtered, washed with water and crystallized from ethanol.

REACTION SCHEME

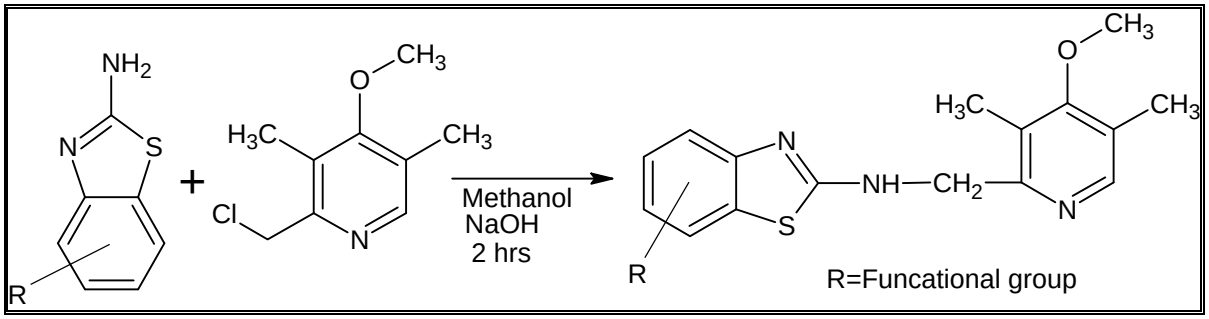
[A] Synthesis of 2-amino benzothiazole derivatives.



[B] Synthesis of 2-(chloromethyl)-4-methoxy-3,5-dimethylpyridine.



[C] Synthesis of 6-methoxy-N-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-1,3-benzothiazol-2-amine (RBT-1).



The following benzothiazole derivatives have been synthesized.

1. RBT-1: 6-methoxy-N-[(4-methoxy-3,5-dimethylpyridin-2-yl) methyl]-1,3-benzothiazol-2-amine
2. RBT-2: 6-chloro-N-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-1,3-benzothiazol-2-amine
3. RBT-3: 6-fluoro-N-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-1,3-benzothiazol-2-amine
4. RBT-4: N-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-6-nitro-1,3-benzothiazol-2-amine
5. RBT-5: N-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-6-methyl-1,3-benzothiazol-2-amine
6. RBT-6: 4-chloro-N-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-1,3-benzothiazol-2-amine
7. RBT-7: 4-bromo-N-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-1,3-benzothiazol-2-amine
8. RBT-8: 6-bromo-N-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-1,3-benzothiazol-2-amine
9. RBT-9: N-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-1,3-benzothiazol-2-amine

The various physical constants such as R_f value, melting point and percentage of yield for all synthesized benzothiazole derivatives are given in Table 2.2.1. All the melting point was taken by open capillary method.

The characterization was done by IR, mass spectra and ^{1}H NMR.

Infrared spectra:

The IR spectra were recorded by SHIMADZU-FTIR-8400 spectrophotometer in the frequency range of 4000-400 cm^{-1} by KBr powder method. The IR spectra and data for RBT-1 is given in Figure 2.2.1 and Table 2.2.2 respectively. The spectral data for all other compounds are reported in Table 2.2.3.

Mass spectra:

The Mass spectra were recorded by GCMS-SHIMADZU-QP2010. Figure 2.2.2 shows mass spectra of RBT-2. The proposed mass fragmentation of RBT-2 is given in Scheme 2.2.1. The mass fragmentations of other compounds are also given separately.

^{1}H NMR Spectra:

The NMR spectra were recorded by BRUKER Spectrometer (400 MHz) using internal reference TMS and solvent $CDCl_3$/DMSO. Figure 2.2.3 shows NMR spectra of RBT-2. The spectral data for RBT-2 is given in Table 2.2.4.

Table 2.2.1: Physical constants of Benzothiazole derivatives.

Sr. No.	Code	R	M.F.	M. Wt. (g/mol)	R_f* Value	M.P. °C	Yield %
1	**RBT-1**	4-OCH_3	$C_{17}H_{19}N_3O_2S$	329	0.50	212	60
2	**RBT-2**	4-Cl	$C_{16}H_{16}ClN_3OS$	333	0.61	181	72
3	**RBT-3**	4-F	$C_{16}H_{16}FN_3OS$	317	0.54	196	50
4	**RBT-4**	4-NO_2	$C_{16}H_{16}N_4O_3S$	344	0.48	233	42
5	**RBT-5**	4-CH_3	$C_{17}H_{19}N_3OS$	313	0.57	204	78
6	**RBT-6**	2-Cl	$C_{16}H_{16}ClN_3OS$	333	0.46	228	56
7	**RBT-7**	2-Br	$C_{18}H_{22}BrN_3OS$	378	0.38	178	62
8	**RBT-8**	4-Br	$C_{16}H_{16}BrN_3OS$	378	0.40	207	38
9	**RBT-9**	-H	$C_{16}H_{17}N_3OS$	299	0.66	215	68

* Methanol: Chloroform: 1.5:8.5

Figure 2.2.1: IR spectra of 6-methoxy-N-[(4-methoxy-3,5-dimethylpyridin -2-yl)methyl]-1,3-benzothiazol-2-amine (RBT-1).

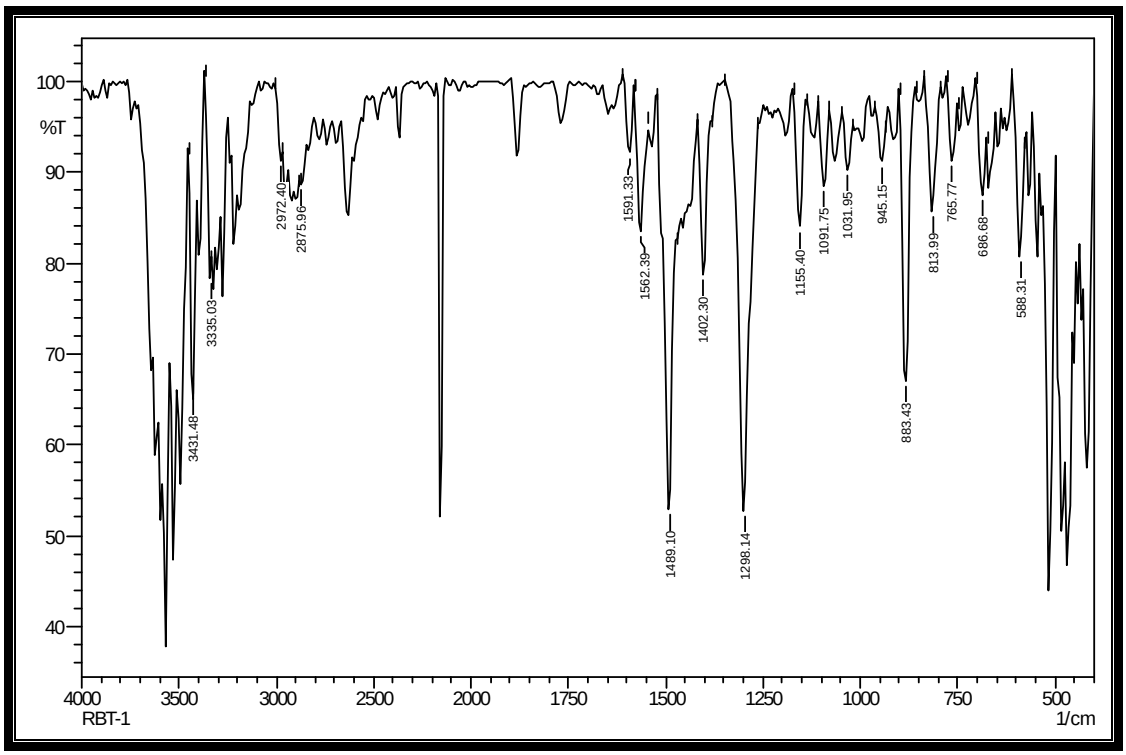


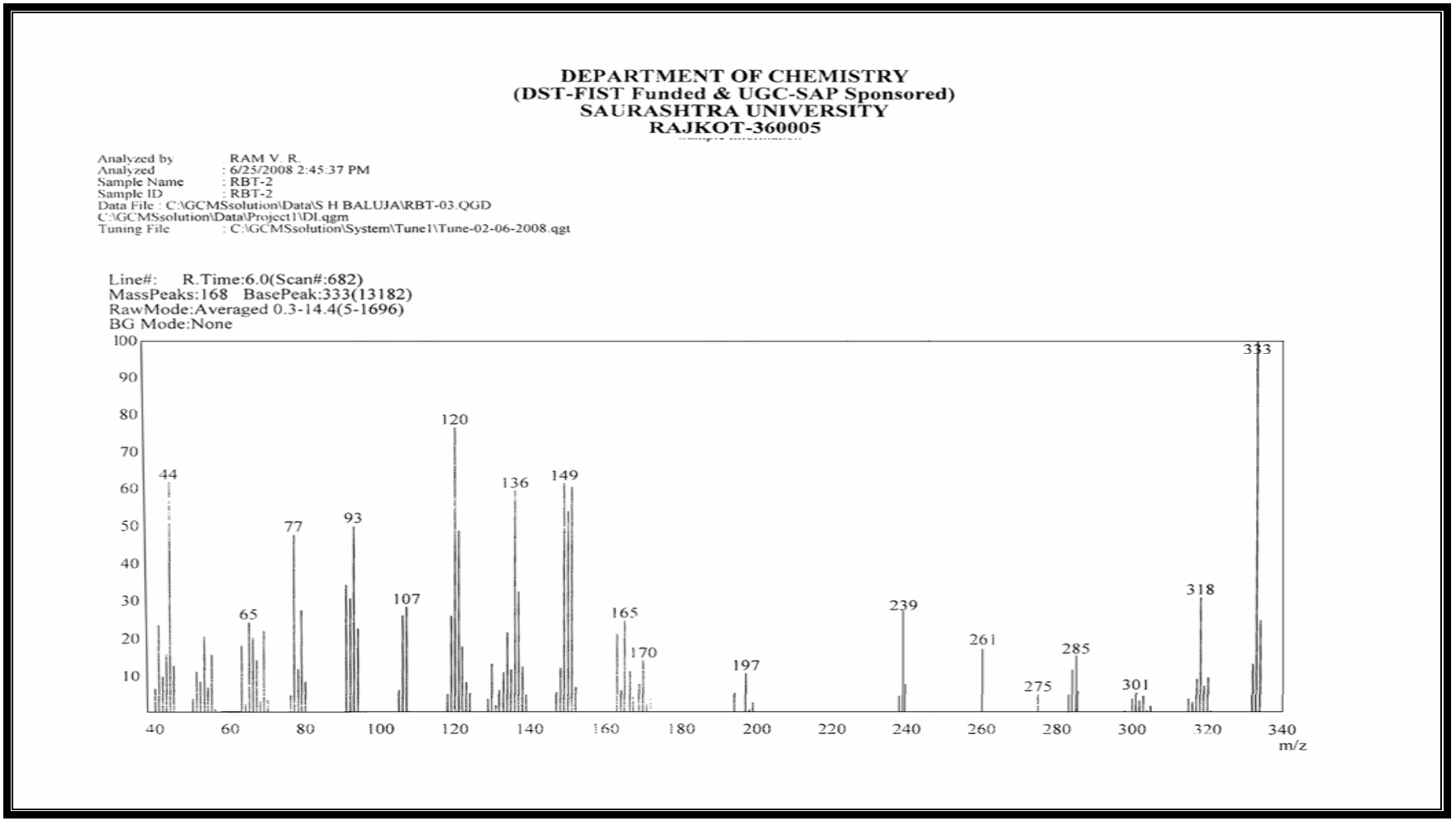
Table 2.2.2: IR spectral data of 6-methoxy-N-[(4-methoxy-3,5-dimethyl pyridine- 2-yl)methyl]-1,3-benzothiazol-2-amine (RBT-1).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported[64,65]
Alkane	C-H str. (asym.)	2972.40	2975-2920
	C-H str. (sym.)	2875.96	2880-2860
	C-H def. (asym.)	1489.10	1500-1435
	C-H def.(sym.)	1402.30	1400-1370
Aromatic	C-H str.	3198.09	3200-3000
	C=C str.	1562.39	1585-1480
	C-H i.p. def.	1155.40	1125-1090
	C-H o.o.p. def.	813.99	860-810
Secondary amine	-N-H (asym.)	3335.03	3500-3310
	-N-H (sym)	1591.33	1650-1550
Thaizole	C-S-C (sym.)	1031.95	1250-1010
	C-S-C o.o.p.def.	688.68	700-600
ether	C-O-C str. (asym.)	1298.14	1300-1200
	C-O-C str. (sym.)	1091.75	1100-1050

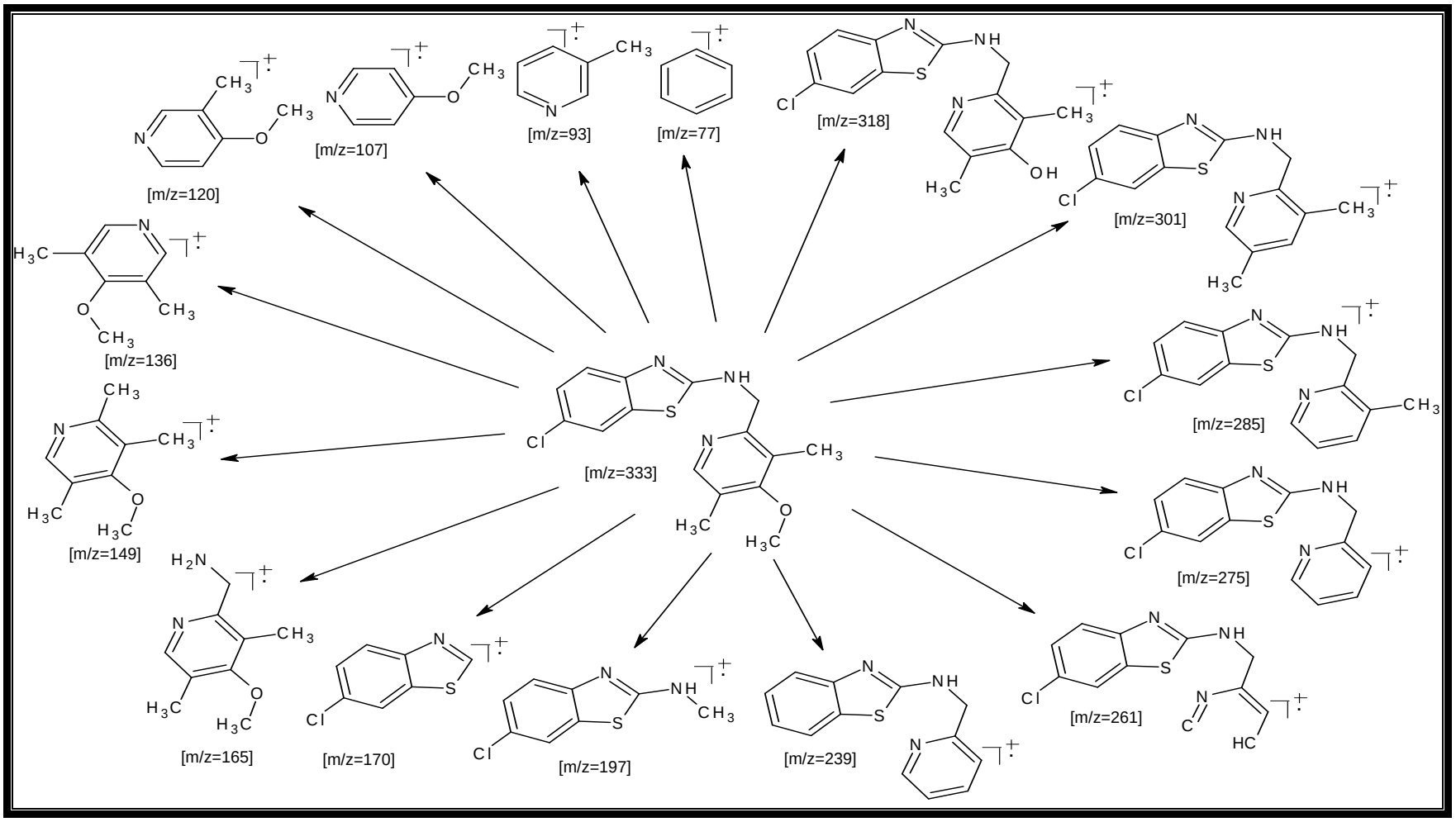
Table 2.2.3: IR spectral data of synthesized benzothaizole derivatives (RBT-2 to RBT-9).

Compounds	*IR ν, (cm^{-1})*				
	C=C str.	**-N-H (asym)**	**C-S-C (sym.)**	**C-O-C (asym.)**	**R**
RAT-2	1562.39	3335.03	1103.32	1278.85	777.34
RBT-3	1560.00	3300.12	1188.19	1257.63	1327.07
RBT-4	1573.97	3342.72	1118.75	1290.42	1344.43
RBT-5	1533.46	3337.08	1122.61	1280.61	-
RBT-6	1542.81	3321.50	1085.34	1264.74	532.05
RBT-7	1554.64	3365.71	1165.48	1279.09	632.70
RBT-8	1549.05	3311.76	1132.80	1284.00	650.87
RBT-9	1513.94	3350.09	1096.07	1260.40	-

Figure 2.2.2: Mass spectra of 6-chloro-N-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-1,3-benzothiazol-2-amine (RBT-2).



Scheme 2.2.1: Proposed mass fragmentation of 6-chloro-N-[(4-methoxy-3,5-dimethylpyridin-2-yl)methyl]-1,3-benzothiazol-2-amine (RBT-2).



Mass fragments (m/z value) of synthesized benzothiazole derivatives. (RBT-1 and RBT-3 to RBT-9).

RBT-1: 329, 314, 267, 225, 195, 164, 133, 107, 77.

RBT-3: 317, 301, 286, 255, 226, 180, 151, 122, 92.

RBT-4: 344, 299, 243, 231, 209, 180, 160, 134, 112, 77.

RBT-5: 313, 282, 256, 228, 200, 168, 136, 108, 91.

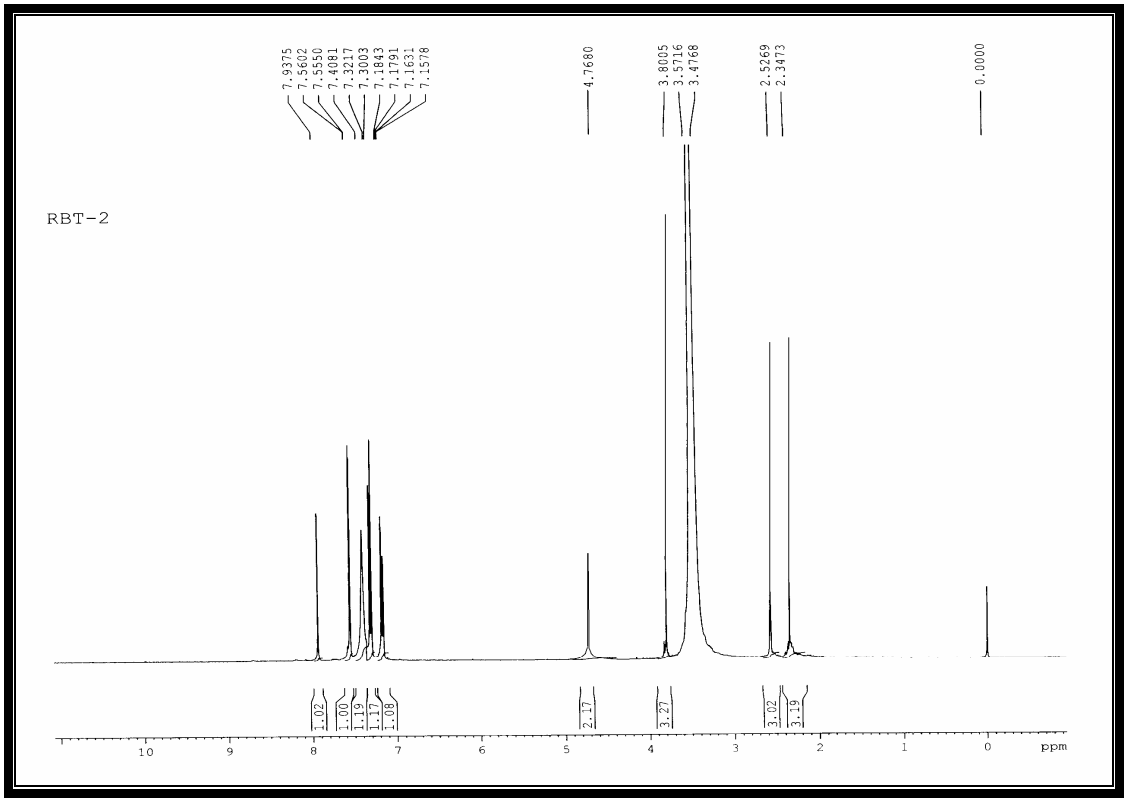
RBT-6: 333, 318, 298, 256, 232, 199, 164, 137, 109, 77.

RBT-7: 378, 342,m 312, 280, 266, 241, 217, 168, 152, 130, 109.

RBT-8: 378, 348, 324, 278, 254, 212, 190, 167, 138, 116, 91.

RBT-9: 299, 284, 253, 163, 134, 121, 105, 91,77.

Figure 2.2.3: ^{1}H NMR spectra of 6-chloro-N-[(4-methoxy-3,5-dimethylpyri din-2-yl)methyl]-1,3-benzothiazol-2-amine (RBT-2).



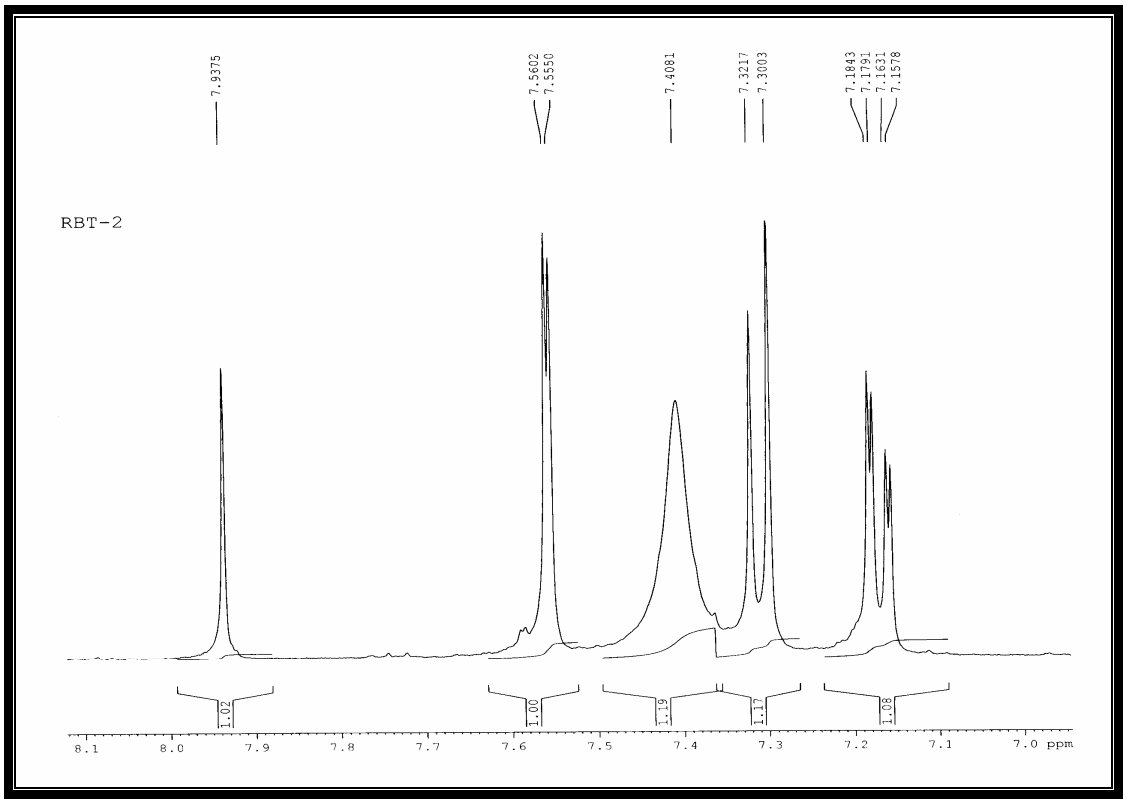
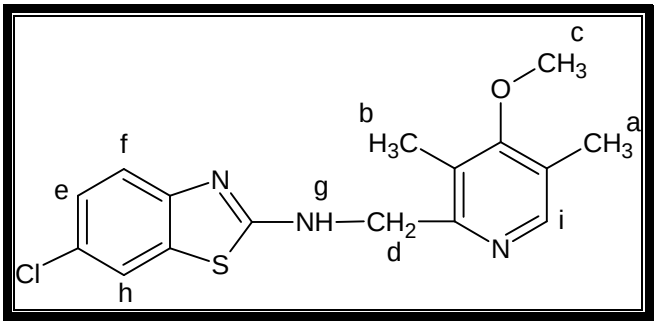


Table 2.2.4: ^{1}H NMR spectral data of 6-chloro-N-[(4-methoxy-3,5-dimethyl pyridin-2-yl)methyl]-1,3-benzothiazol-2-amine (RBT-2).



Singal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	*J* (Hz)
1	2.34	3	singlet	-C<u>H</u>$_3$ (a)	-
2	2.52	3	singlet	-C<u>H</u>$_3$ (b)	-
3	3.80	3	singlet	-OC<u>H</u>$_3$ (c)	-
4	4.76	2	singlet	-C<u>H</u>$_2$ (d)	-
5	7.15-7.16	1	doublet	Ar-H (e)	2.12
	7.17-1.18		doublet		2.08
6	7.30-7.32	1	doublet	Ar-H (f)	8.56
7	7.40	1	singlet	-N<u>H</u> (g)	-
8	7.55-7.56	1	doublet	Ar-H (h)	2.08
9	7.93	1	singlet	-H (i)	-

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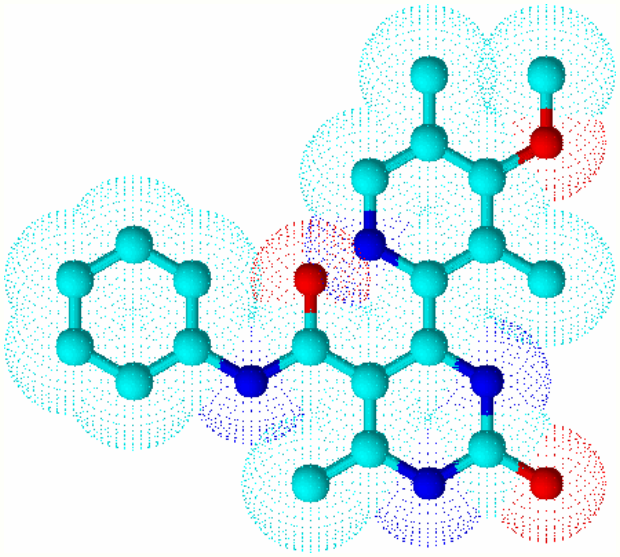


Section-III
Synthesis of
Dihydropyrimidinones

INTRODUCTION

Dihydropyrimidinones consists of a six membered heterocyclic ring having two nitrogen atoms at one and three positions. These compounds are synthesized by the most important multi-component reactions, known as Biginelli reaction. Biginelli reported the synthesis of functionalized 3,4-dihydropyrimidin-(1*H*)-ones (DHPMs) via three-component one-port, condensation reaction of an aromatic aldehyde, urea, and ethyl acetoacetate[1].

There are several methods used for the synthesis of dihydropyrimidinones[2-6]. Dihydropyrimidinones are synthesized by using Lewis acids as well as protic acid under classical reflux[7-10], solvent-free conditions[11-14], by microwave[15-18] or by ultrasound irradiation[19-22]. Recently, these methods are improved by using various catalyst such as indium(III) chloride[23], bismuth(III)[24], $CoCl_2$ $6H_2O$ or $LaCl_3$ $7H_2O$[25], silcasulfuric acid[26], clay-$SmCl_3$ $6H_2O$[27], ferrous chloride or nickel chloride[28], zinc perchlorate[29], $NaIO_4$[30] and ionic liquids[31]. However, in spite of their potential utility, many of these methods involve low yields, long reaction times, high temperature and expensive reagents.

Dihydropyrimidinones have been subjected to a large number of different modifications in order to obtain derivatives having different biological properties[32-36]. Several groups have studied the chemistry and pharmacological properties of dihydropyrimidinones derivatives. Dihydropyrimidinones are known to exhibit a wide range of biological activities such as antiviral[37], antitumour[38,39], antibacterial[40,41], and anti-inflammatory[42-44] properties. In addition, these compounds have emerged as potential calcium channel blockers[45], antihypertensive[46], α_{1a}–adrenergic antagonists[47] and neuropeptide antagonists[48]. Recently, these types of compounds have been isolated from marine alkaloids with interesting biological activities[49-51].

Janion and Shugard[52] have studied the effect of dihydropyrimidinones on some enzymes. Hardtmann and Kathawala[53] have studied of 4,6-Diaryl pyrimidin-2(1H)-ones as tranquilizers. The relation between the structure and cardiovascular activity of some dihydropyrimidinones have also been reported by Gitlina et al.[54] Vedernikova and coworkers[55] have studied the pharmacological applications of 4-oxo-1,4-dihydropyrimidines. Ziegler et al.[56]

have been synthesized 3-benzyloxy-6-hydroxy-3, 4-dihydro-4-pyrimidinones. Some 9-(aminoalkyl)-6,7-dihydropyrimido[2,1-f]purine-2,4,8 (1H,3H,9H)triones have been sythesised by Pawlowski and coworkers[57]. Lu et al.[58] have reported the synthesis of 3,4-dihydropyrimidin-2(1H)-ones using lanthanum chloride. Some 3,4-dihydropyrimidinones have been synthesized by using different methods[59-61]. Recently, synthesis of 4-(4-Cyano-2-thioaryl)-dihydro pyrimidinones and their uses in diseases of lung and cardiovascular systems have been reported by Nussbaum and coworkers[62]. Fustero et al.[63] have reported the new method for the synthesis of fluorinated 3,4-dihydro pyrimidinones.

With a view to getting better therapeutic agent, it was contemplated to synthesize some dihydropyrimidinones derivatives to enhance the overall activity of resulting compounds, which have been described in this section.

EXPERIMENTAL

Synthesis of N-(4-methoxyphenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl) -6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RAU-1).

[A] Synthesis of substituted 3-oxo-N-phenylbutanamide.

A mixture of substituted aniline (0.01 M) and ethyl aceto acetate (0.012 M) in 25 ml toluene was refluxed for 12 hours in presence of few drops of slurry of NaOH in water. The excess of toluene was distilled out and the reaction mixture was taken in hexane and stirred with glass rod. The product was isolated in hexane and filtered. The crude product was dried. This product was taken in aqueous NaOH solution and neutralized with dilute HCl. The recrystalisation was done in ethanol.

[B] Synthesis of 4-methoxy-3,5-dimethylpyridine-2-carbaldehyde.

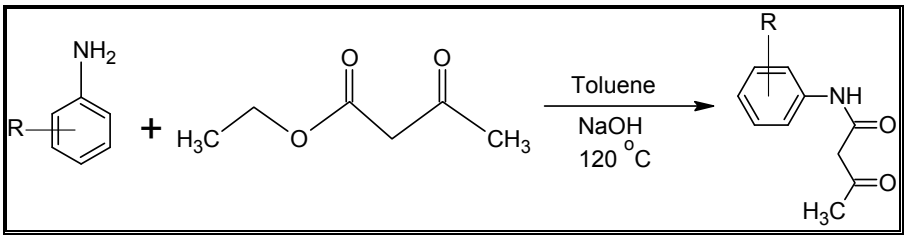
10 gm of (4-methoxy-3,5-dimethylpyridin-2-yl)methanol was taken in 60 ml of dichloromethane (MDC) in stopper flask and stirred. The mixture was heated at 30-35^{o} C. Then, 35 gm of MnO_2 was added over a period of 15 minutes. The reaction mixture was again stirred at 30-35^{o} C for 2 hours. The excess of toluene was distilled out and the liquid product of 4-methoxy-3,5-dimethylpyridine-2-carbaldehyde was isolated.

[C] Synthesis of N-(4-methoxyphenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RAU-1).

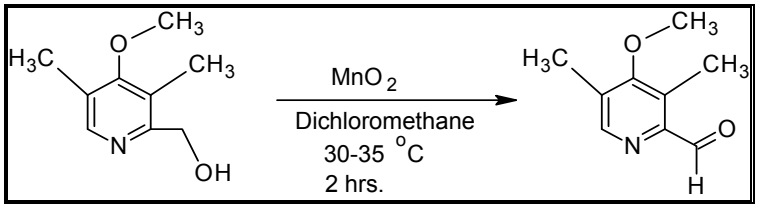
A solution of 4-methoxy-3,5-dimethylpyridine-2-carbaldehyde (0.01 M), substituted 3-oxo-N-phenylbutanamide (0.01 M) and urea (0.012 M) in methanol was refluxed for 12 hours in presence of few drops of concentrated HCl as catalyst. The product was isolated and recrystallized from DMF.

REACTION SCHEME

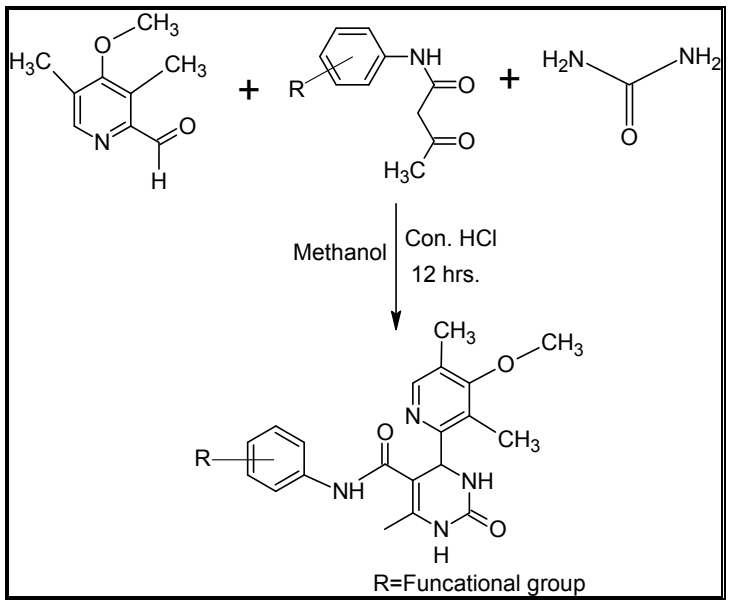
[A] Synthesis of substituted 3-oxo-N-phenylbutanamide.



[B] Synthesis of 4-methoxy-3,5-dimethylpyridine-2-carbaldehyde.



[C] Synthesis of N-(4-methoxyphenyl)-4-(4-methoxy-3,5-dimethylpyridin2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RAU-1).



The following dihydropyrimidinones have been synthesized.

1. RAU-1: N-(4-methoxyphenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbox amide
2. RAU-2: N-(4-chlorophenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbox amide
3. RAU-3: N-(3-chlorophenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbox amide
4. RAU-4: N-(4-hydroxyphenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbox amide
5. RAU-5: N-(2,5-dichlorophenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carb oxamide
6. RAU-6: N-(4-florophenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbox amide
7. RAU-7: N-(4-nitrophenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbox amide
8. RAU-8: 4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-oxo-N-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide
9. RAU-9: N-(4-methylphenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbox amide
10. RAU-10: N-(4-bromophenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carbox amide

The various physical constants such as R_f value, melting point and percentage of yield for all synthesized dihydropyrimidinones derivatives are given in Table 2.3.1. All the melting point was taken by open capillary method.

The characterization was done by IR, mass spectra and ^{1}H NMR.

Infrared spectra:

The IR spectra were recorded by SHIMADZU-FTIR-8400 spectrophotometer in the frequency range of 4000-400 cm^{-1} by KBr powder method. The IR spectra and data for RAU-1 is given in Figure 2.3.1 and Table 2.3.2 respectively. The spectral data for all other compounds are reported in Table 2.3.3.

Mass spectra:

The Mass spectra were recorded by GCMS-SHIMADZU-QP2010. Figure 2.3.2 shows mass spectra of RAU-2. The proposed mass fragmentation of RAU-2 is given in Scheme 2.3.1. The mass fragmentations of other compounds are also given separately.

^{1}H NMR Spectra:

The NMR spectra were recorded by BRUKER Spectrometer (400 MHz) using internal reference TMS and solvent $CDCl_3$/DMSO. Figure 2.3.3 shows NMR spectra of RAU-1. The spectral data for RAU-1 is given in Table 2.3.4.

Table 2.3.1: Physical constants of dihydropyrimidinones.

Sr. No.	Code	R	M.F.	M. Wt. (g/mol)	R_f* Value	M.P. °C	Yield %
1	**RAU-1**	4-OCH_3	$C_{21}H_{24}N_4O_4$	396	0.52	218	46
2	**RAU-2**	4-Cl	$C_{20}H_{21}ClN_4O_3$	400	0.43	254	45
3	**RAU-3**	3-Cl	$C_{20}H_{21}ClN_4O_3$	400	0.46	262	35
4	**RAU-4**	4-OH	$C_{20}H_{22}N_4O_4$	382	0.56	193	31
5	**RAU-5**	2,5-Dichloro	$C_{20}H_{20}Cl_2N_4O_3$	435	0.61	234	40
6	**RAU-6**	4-F	$C_{20}H_{21}FN_4O_3$	384	0.63	222	39
7	**RAU-7**	4-NO_2	$C_{20}H_{21}N_5O_5$	411	0.48	240	34
8	**RAU-8**	4-H	$C_{20}H_{22}N_4O_3$	366	0.37	206	56
9	**RAU-9**	4-CH_3	$C_{21}H_{24}N_4O_3$	380	0.46	187	53
10	**RAU-10**	4-Br	$C_{20}H_{21}BrN_4O_3$	445	0.54	267	44

***** Methanol: Chloroform 2.5:7.5

Figure 2.3.1: IR spectra of N-(4-methoxyphenyl)-4-(4-methoxy-3,5-dimeth ylpyridin-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RAU-1).

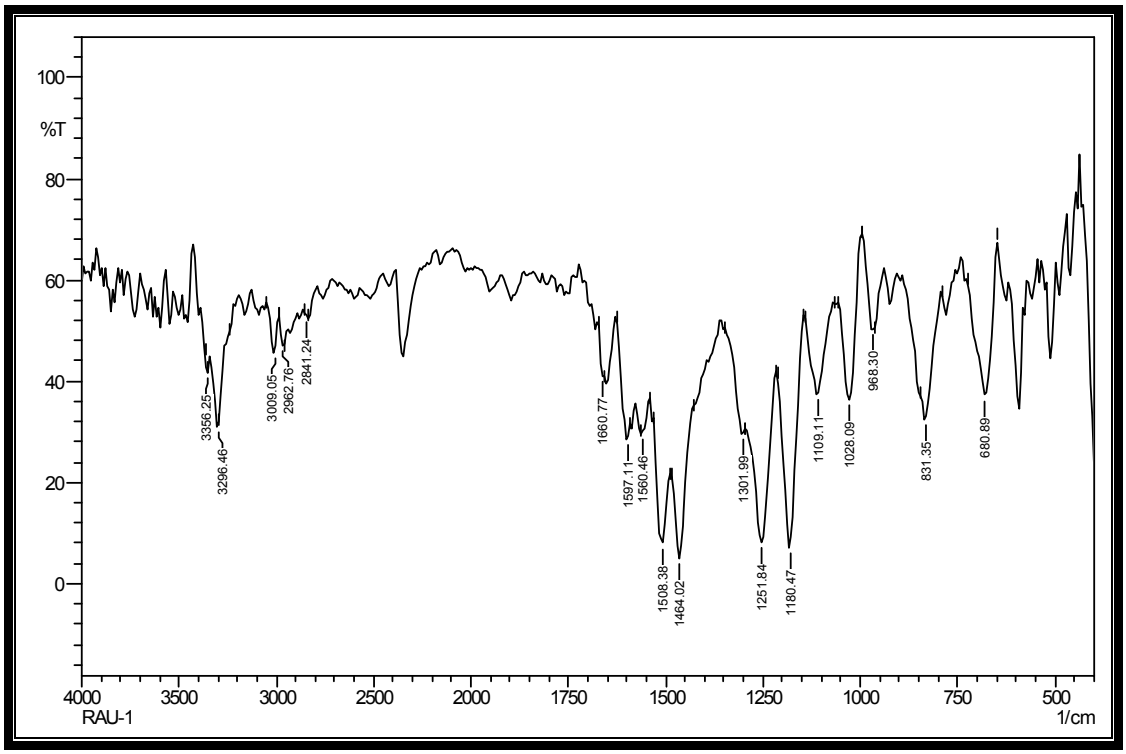


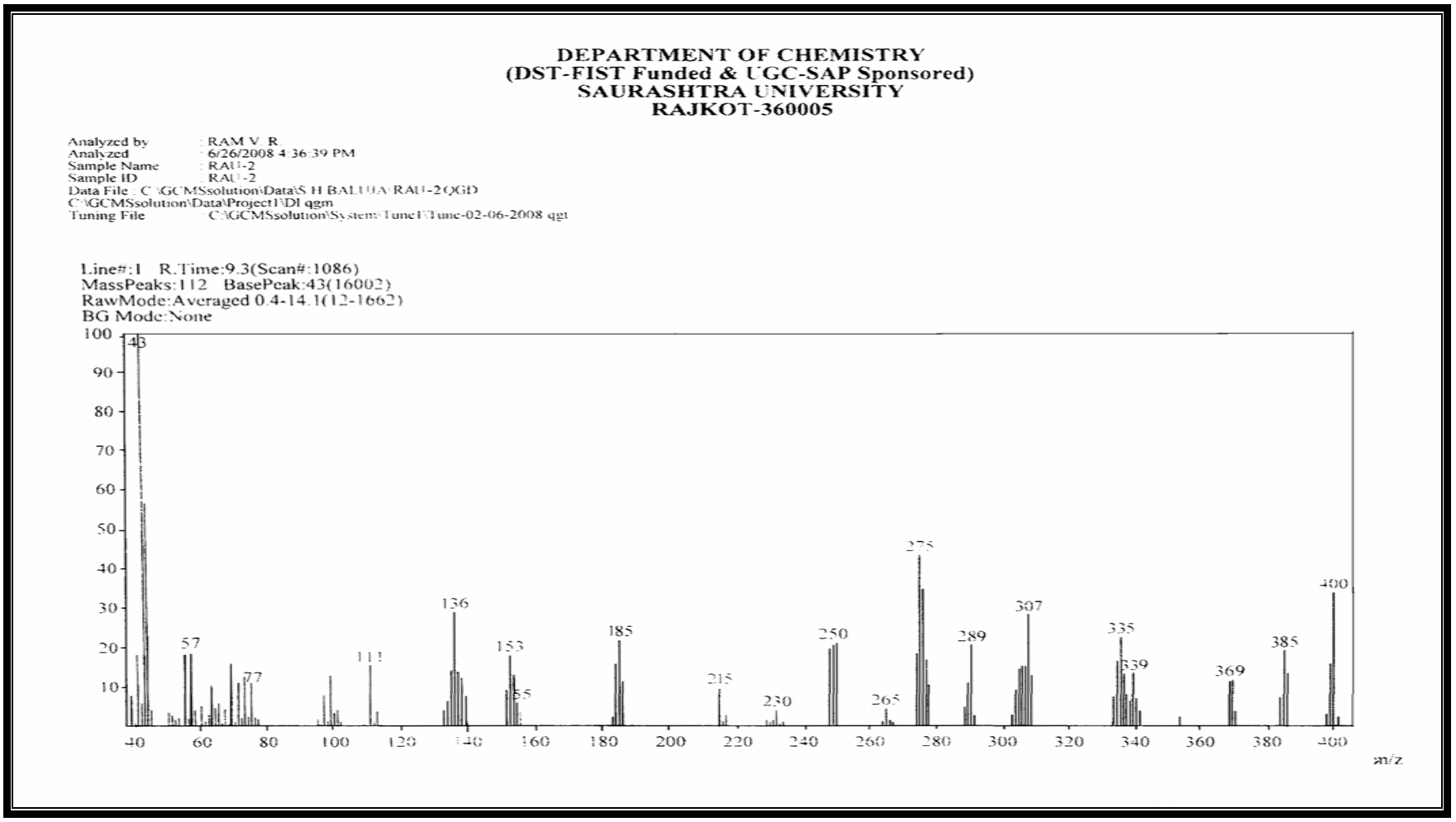
Table 2.3.2: IR spectral data of N-(4-methoxyphenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrim idine-5-carboxamide (RAU-1).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported[64,65]
Alkane	C-H str. (asym.)	2962.76	2975-2920
	C-H str. (sym.)	2841.24	2880-2860
	C-H def. (asym.)	1464.02	1500-1435
Aromatic	C-H str.	3155.65	3200-3000
	C=C str.	1508.38	1585-1480
	C-H i.p. def.	1109.11	1125-1090
	C-H o.o.p. def.	831.35	860-810
Ketones	C=O str.(cyclic)	1660.77	1740-1650
	C=O str. (alip.)	1597.11	1710-1550
Secondary amine	-N-H (asym.)	3296.64	3500-3300
	-N-H (sym)	1560.46	1650-1550
Ether	C-O-C str. (asym.)	1298.14	1400-1000
	C-O-C str. (sym.)	1091.75	1075-1020

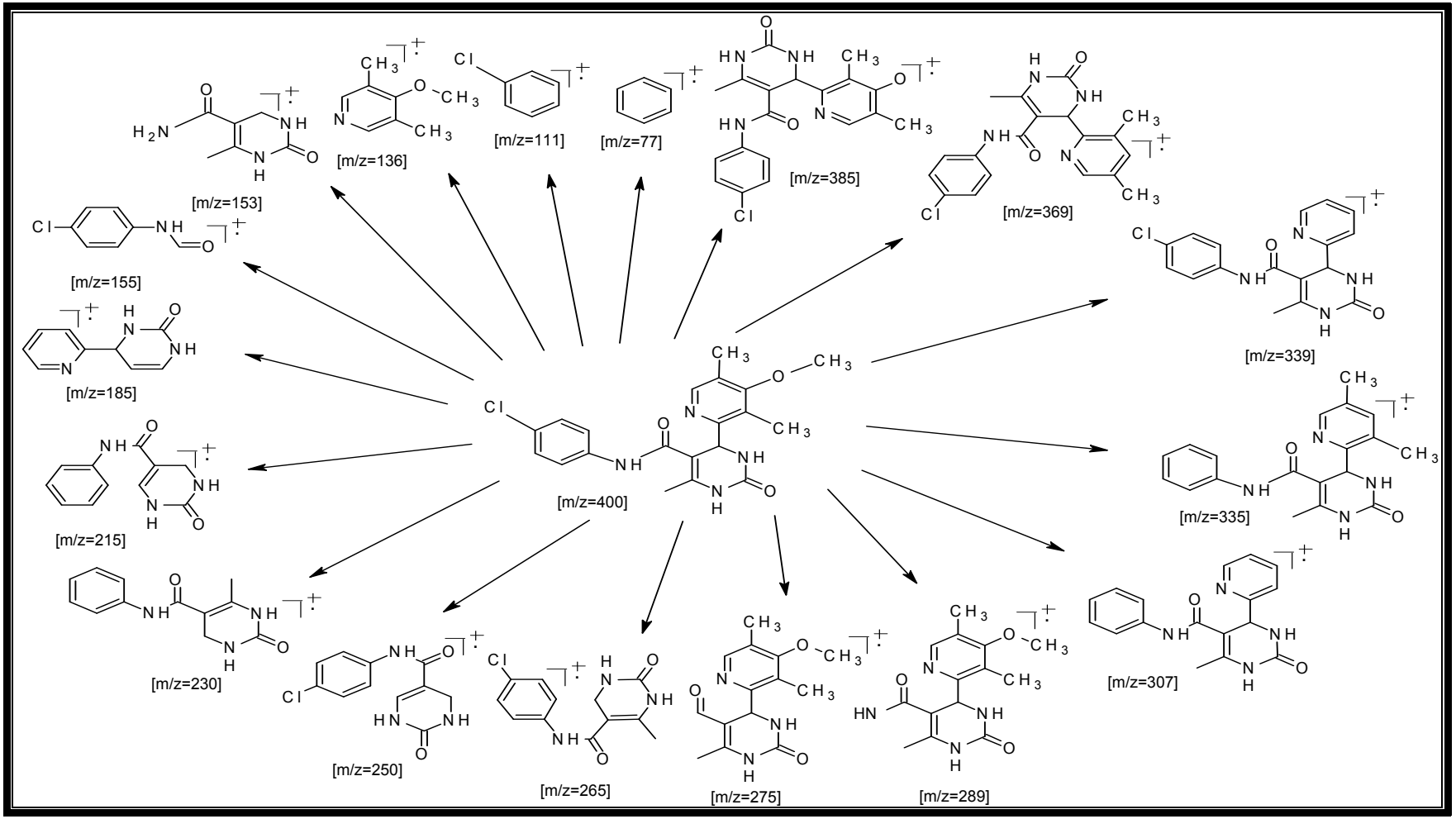
Table 2.3.3: IR spectral data of synthesized dihydropyrimidinones (RAU-2 to RAU-10).

Compounds	*IR ν, (cm^{-1})*		
	C=C str.	**-N-H (sym)**	**R**
RAU-2	1520	1590	752
RAU-3	1532	1591	764
RAU-4	1509	1610	3476
RAU-5	1512	1618	772
RAU-6	1524	1620	1188
RAU-7	1527	1609	1342
RAU-8	1521	1619	-
RAU-9	1508	1598	-
RAU-10	1510	1625	562

Figure 2.3.2: Mass spectra of N-(4-chlorophenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide (RAU-2).



Scheme 2.3.1: Proposed mass fragmentation of N-(4-chlorophenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2 -oxo -1,2,3,4- tetrahydro pyrimidine-5-carboxamide (RAU-2).



Mass fragment (m/z value) of other synthesized dihydropyrimidinones (RAU-1 and RAU-3 to RAU-10).

RAU-1: 396, 381, 365, 334, 319, 304, 260, 232, 203, 183, 164, 153.

RAU-3: 400, 356, 336, 308, 290, 276, 253, 232, 215, 186, 155, 138.

RAU-4: 382, 365, 334, 321, 304, 289, 259, 246, 186, 170, 155, 136.

RAU-5: 435, 420, 404, 368, 374, 303, 352, 299, 274, 246, 263, 228.

RAU-6: 384, 369, 353, 338, 304, 289, 246, 231, 200, 248.

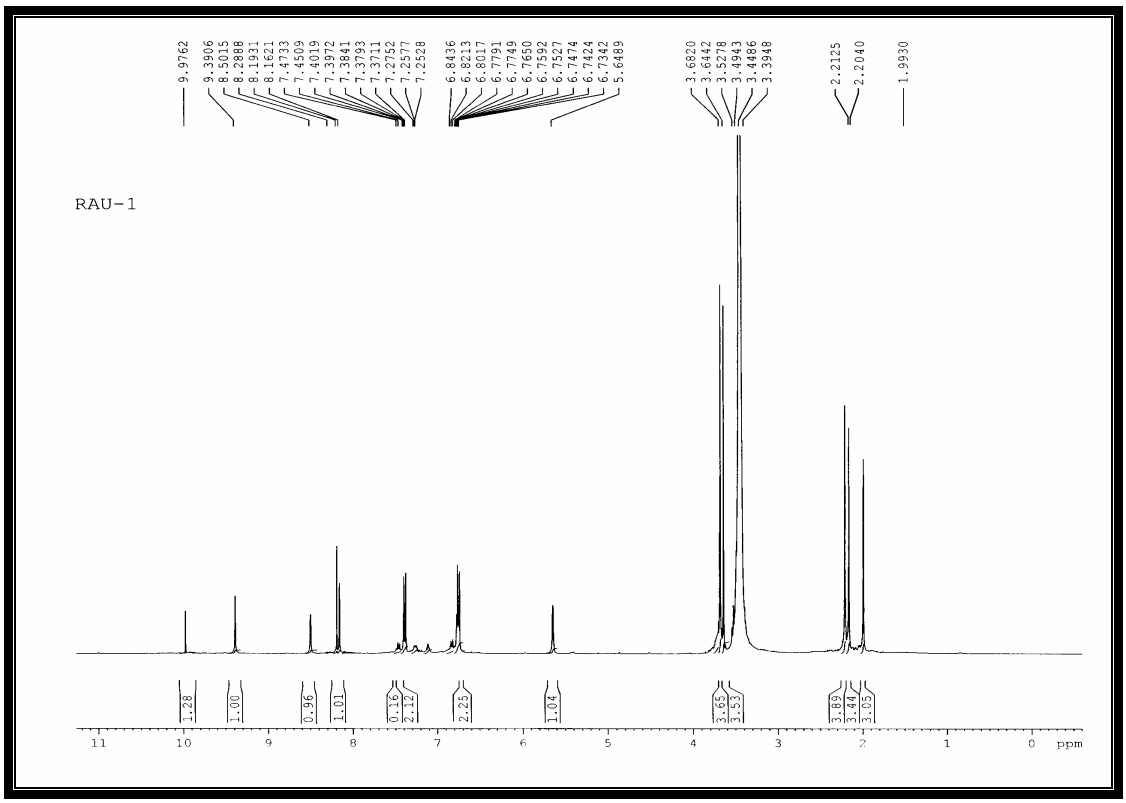
RAU-7: 411, 296, 380, 365, 364, 342, 332, 304, 290, 275, 240.

RAU-8: 366, 351, 335, 305, 289, 252, 230, 228, 243.

RAU-9: 380, 365, 349, 334, 304, 289, 246, 216, 170.

RAU-10: 445, 430, 414, 384, 365, 304, 309, 289, 274, 246.

Figure 2.3.3: ^{1}H NMR spectra of N-(4-methoxyphenyl)-4-(4-methoxy-3,5-di methylpyridin-2-yl)-6-methyl-2-oxo-1,2,3,4-trahydropyrimid ine-5-carboxamide (RAU-1).



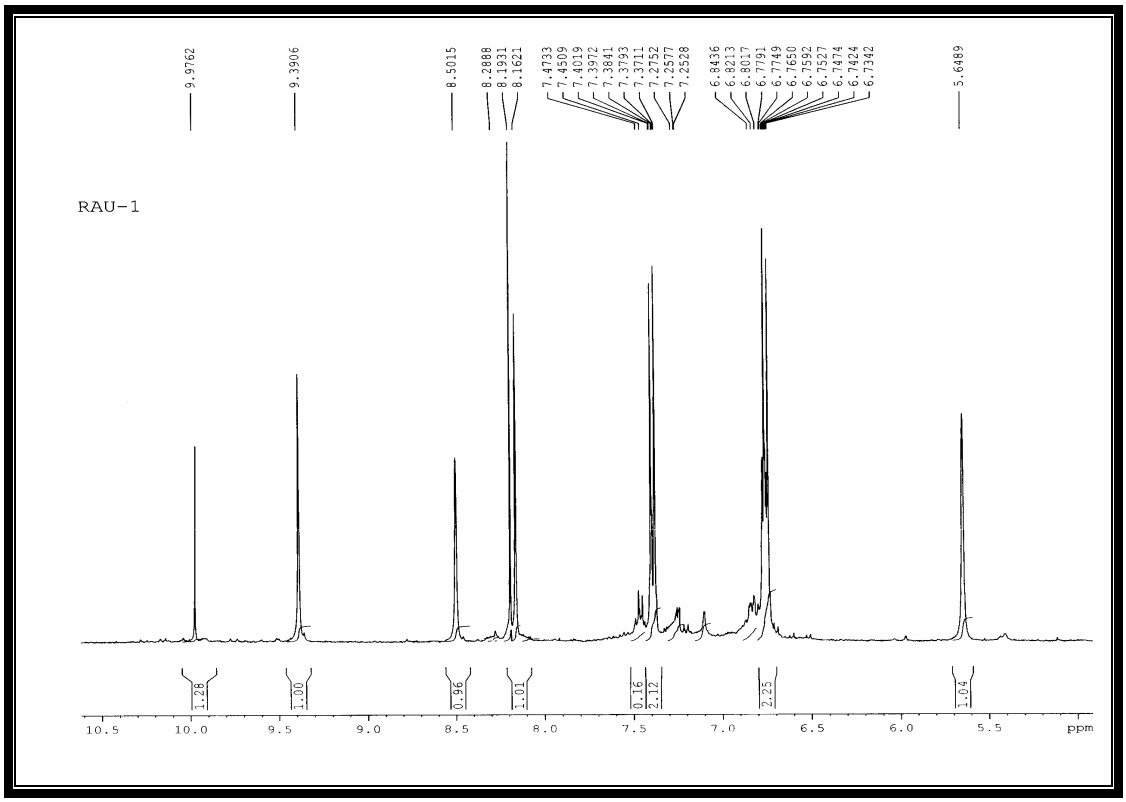
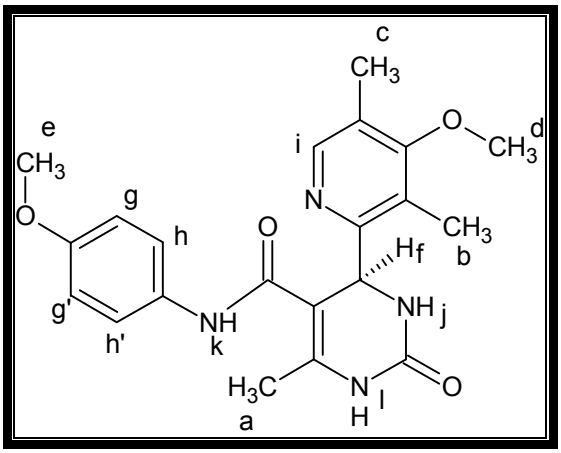


Table 2.3.4: ^{1}H NMR spectral data of N-(4-methoxyphenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-oxo-1,2,3,4-trahydropy rimidine-5-carboxamide (RAU-1).



Singal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	*J* (Hz)
1	1.99	3	singlet	-C<u>H</u>3 (a)	-
2	2.20	3	singlet	-C<u>H</u>3 (b)	-
3	2.21	3	singlet	-C<u>H</u>3 (c)	-
4	3.64	3	singlet	-OC<u>H</u>3 (d)	-
5	3.68	3	singlet	-OC<u>H</u>3 (e)	-
6	5.64	1	singlet	-CH (f)	-
7	6.73-6.74	2	doublet	Ar-H (gg')	5.28
8	7.37-7.38	2	doublet	Ar-H (hh')	5.2
9	8.16	1	singlet	Ar-H (i)	-
10	8.50	1	singlet	-NH (j)	-
11	9.39	1	singlet	-NH (k)	-
12	9.97	1	singlet	-NH (l)	-

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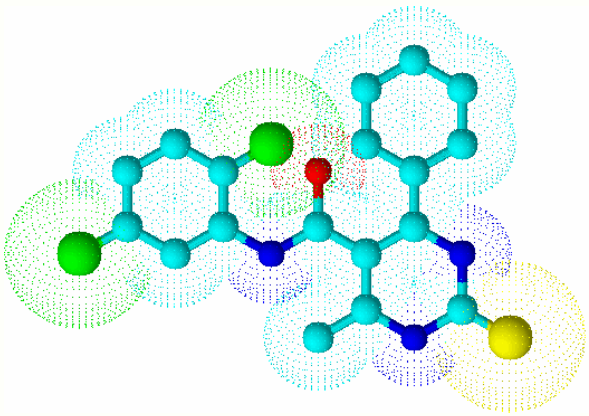


Section-IV
Synthesis of
Dihydropyrmidinthiones

INTRODUCTION

Dihydropyrimidinthiones and their derivatives are important classes of compounds in Dihydropyrimidine group. Dihydropyrimidinthiones consists of a six membered heterocyclic ring having two nitrogen atoms at one and three positions and also containing sulfur at second carbon. Biginelli reported the synthesis of 3,4-dihydropyrimidin-(1H)-thiones[1].

Over the past decade, dihydropyrimidin-2(1H)-thiones and their derivatives have attracted considerable attention in organic and medicinal chemistry as the dihydropyrimidine scaffold displays a fascinating array of pharmacological and therapeutic properties[2]. Thiourea itself was one of the first new drug employed to depress, the clinically over active thyroid in thyrotoxicosis[3] but some of the cyclic thiourea have been found better suited. All of these are prone of produce adverse reduction in susceptible patients and found more potent and less likely to produce side effect and is being used widely[4]. These dihydropyrimidinthiones compounds exist in a variety of natural and synthetic organic compounds and are known to possess a wide spectrum of biological and therapeutic properties[5-7] such as antibacterial[8], anti-viral[9], anti-tumor[10,11], anti-inflammatory[12], anti-fungal[13], antihypertensive[14], anti-HIV[15], as well as α_{1a}-antagonists[16,17], neuropeptide Y (NPY) antagonists[18], aggregation inhibitory activity[22] and anticarcinogencic[19] activity. These compounds are also used as analgesic[20], blood platelet[21] and calcium channel blockers[23]. The stereo chemical relationship between the aryl group and the dihydropyrimidine ring was found to be one of the factors having a pronounced effect on the biological activity[24,25]. Lukacs et al.[26] have reported the synthesis libraries of dihydropyrimidinone, dihydropyrimidinethione, dihydropyrimidothiazine and its biological activity. Shahrokni and coworkers[27] have reported the toxicity and efficacy of 5-fluorouracil. The photophysical of 5-ethoxycarbonyl-4-cinnamyl-6-methyl-3,4- dihydropyrimidine -2(1H)-thiones has also been reported[28].

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry for various reasons[29,30] In times where a premium is put on speed, diversity, and efficiency in the drug discovery process[31,32] , MCR strategies offer significant advantages over conventional

linear-type syntheses. MCR condensations involve three or more compounds reacting in a single event, but consecutively to form a new product, which contains the essential parts of all the starting materials.

In recent years, many workers have reported improvements in the Biginelli reaction include several methods and reagents[33-37], such as H2SO4[38], zirconium(IV) chloride[39], samarium chloride[40], boric acid[41], ytterbium(III) resin[42], 12-molybdophosphoric acid[43], silica triflate[44], covalently anchored sulfonic acid[45], phosphonic acid anhydride[46], trichloroisocyanuric acid[47] and N-butyl-N,N-dimethyl-α-phenyl ethyl ammonium bromide[48]. Most reported methods have shortcomings due to expensive reagents, long reaction times and unsatisfactory yields.

Recently, Hitchings et al.[49] have reported the synthesis of 2,6-diamino and 2-amino-6-hydroxy derivatives of 5-aryl-4,5-dihydropyrimidines. Konyukhov and coworkers[50] have synthesized 3,4-dihydropyrimidinethiones derivatives and studied their biological activity. Some compounds have also synthesized by Sammour et al.[51]. Vasudeva and coworkers[52] have also synthesized derivatives of benzopyrimidothiadiazines. Spectroscopic studies of the pyrimidine-2(1H)thione derivatives have been given by Al-Hajjar et al.[53]. Singh and Kumar[54] have studied the synthesis of 1,4-dihydropyrimidine-2(3H)-thiones/-ones with 1,2- and 1,3-binucleophiles. Postnov et al[55]. have used α,β-unsaturated ferrocenyl ketones in the synthesis of 4,6-disubstituted dihydropyrimidinethiones. Ultrasonic synthesis of 3,4-dihydropyrimidin-2(1H)-thiones have been reported by Gholap and coworkers[56]. Some new dihydropyrimidinones and their serivatives have also been synthesized by some workers[57-59].

In this section, the methods for the synthesis of 3,4-dihydropyrimidin-2(1H)-thiones by the one-pot three component condensation of aromatic aldehy- des, β-keto esterand thiourea in the presence of phenol are reported. Furher, the characterization of synthesized compounds are done by IR, NMR and mass spectral studies.

EXPERIMENTAL

Synthesis of RAT series:

Synthesis of N-(2,5-dichlorophenyl)-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RAT-1):

[A] Synthesis of N-(2,5-dichlorophenyl)-3-oxobutanamide.

A mixture of 2,5-dichloro aniline (0.01 M) and ethyl acetoacetate (0.012 M) in 25 ml toluene was refluxed for 12 hours in presence of few drops of slurry of NaOH in water. The excess of toluene was distilled out and the reaction mixture was taken in hexane and was stirred with glass rod. The product was isolated in hexane and filtered. It was dried and dissolved in aqueous NaOH solution. On neutralization of this solution with dilute HCl, product was precipitated. The recrystalisation was done in ethanol.

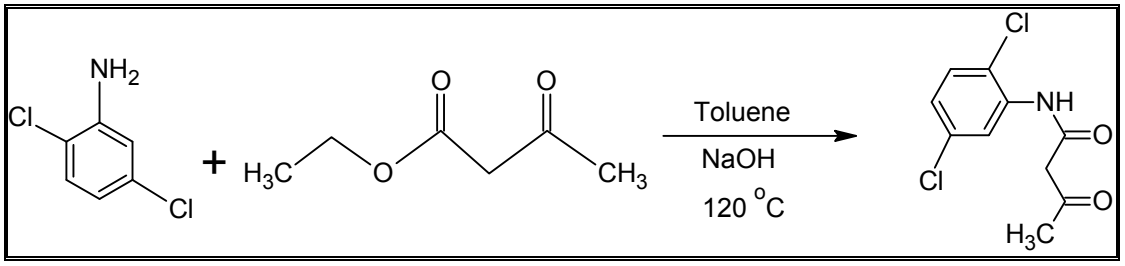
[B] Synthesis of N-(2,5-dichlorophenyl)-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RAT-1).

A solution of substituted benzaldehyde (0.01 M), N-(2,5-dichlorophenyl)-3-oxobutanamide (0.01 M) and thiaourea (0.012 M) in methanol was refluxed for 10 hours in presence of few drops of phenol as catalyst. The product was isolated and recrystallized from DMF.

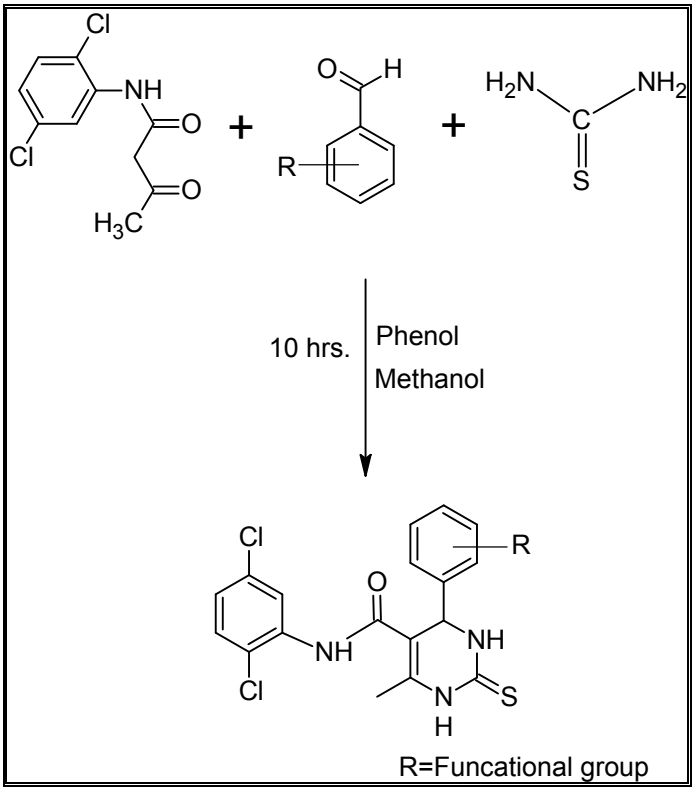
REACTION SCHEME

RAT series

[A] Synthesis of N-(2,5-dichlorophenyl)-3-oxobutanamide.



[B] Synthesis of N-(2,5-dichlorophenyl)-4-(4-methoxyphenyl)-6-methyl -2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RAT-1).



Synthesis of RAB series:

Synthesis of 4-(4-methoxy-3,5-dimethylpyridin-2-yl)N-(4-methoxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RAB-1).

[C] Synthesis of substituted 3-oxo-N-phenylbutanamide.

As per section-III, experiment [A].

[D] Synthesis of 4-methoxy-3,5-dimethylpyridine-2-carbaldehyde.

As per section-III, experiment [B].

[E] Synthesis of 4-(4-methoxy-3,5-dimethylpyridin-2-yl)N-(4-methoxy phenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RAB-1).

A solution of 4-methoxy-3,5-dimethylpyridine-2-carbaldehyde (0.01 M), substituted 3-oxo-N-phenylbutanamide (0.01 M) and thiaourea (0.012 M) in methanol was refluxed for 12 hours in presence of few drops of concentrated HCl as catalyst. The product was isolated and recrystallized from DMF.

REACTION SCHEME

RAB series

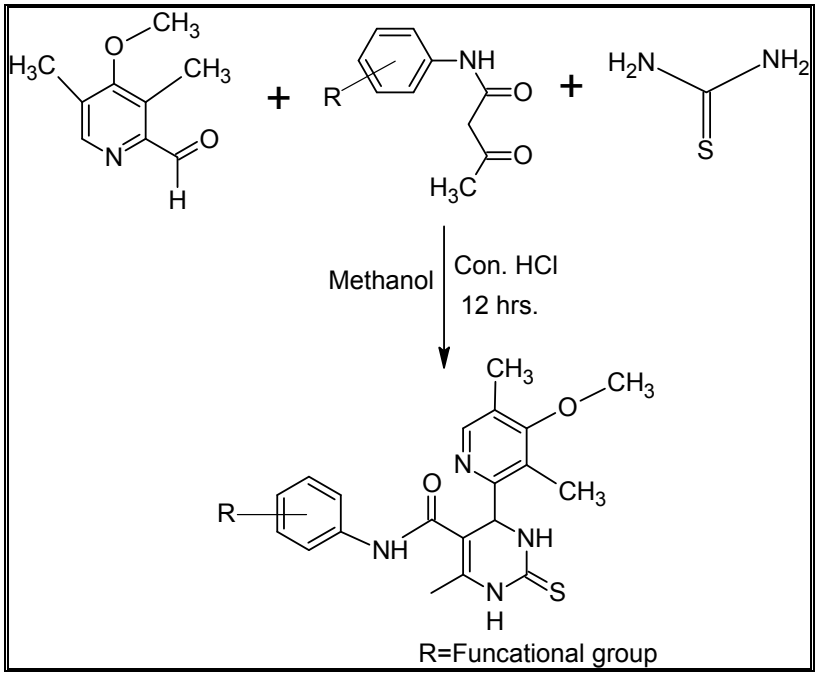
[C] Synthesis of substituted 3-oxo-N-phenylbutanamide.

As per section-III, reaction scheme [A]

[D] Synthesis of 4-methoxy-3,5-dimethylpyridine-2-carbaldehyde.

As per section-III, reaction scheme [B]

[E] Synthesis of 4-(4-methoxy-3,5-dimethylpyridin-2-yl)N-(4-methoxy phenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RAB-1).



The following dihydropyrimidinthiones have been synthesized.

1. RAT-1: N-(2,5-dichlorophenyl)-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
2. RAT-2: N-(2,5-dichlorophenyl)-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
3. RAT-3: N-(2,5-dichlorophenyl)-6-methyl-4-(4-methylphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
4. RAT-4: N-(2,5-dichlorophenyl)-4-(4-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide. 5. RAT-5: N-(2,5-dichlorophenyl)-4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
6. RAT-6: 4-(3-chlorophenyl)-N-(2,5-dichlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
7. RAT-7: N-(2,5-dichlorophenyl)-6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
8. RAT-8: 4-(2-chlorophenyl)-N-(2,5-dichlorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
9. RAT-9: N-(2,5-dichlorophenyl)-6-methyl-4-(2-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
10. RAT-10: N-(2,5-dichlorophenyl)-4-(2-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
11. RAB-1: 4-(4-methoxy-3,5-dimethylpyridin-2-yl)N-(4-methoxy phenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydro pyrimidine-5-carboxamide
12. RAB-2: N-(4-chlorophenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
13. RAB-3: N-(3-chlorophenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
14. RAB-4: N-(4-hydroxyphenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-

carboxamide

15. RAB-5: N-(2,5-dichlorophenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
16. RAB-6: N-(4-fluorophenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
17. RAB-7: N-(4-nitrophenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
18. RAB-8: 4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
19. RAB-9: N-(4-methylphenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide
20. RAB-10: N-(4-bromophenyl)-4-(4-methoxy-3,5-dimethylpyridin-2-yl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide

The various physical constants such as R_f value, melting point and percentage of yield for all synthesized dihydropyrimidinthiones are given in Table 2.4.1. The melting point was taken by open capillary method.

The characterization was done by IR, mass spectra and ^{1}H NMR.

Infrared spectra:

The IR spectra were recorded by SHIMADZU-FTIR-8400 spectrophotometer in the frequency range of 4000-400 cm^{-1} by KBr powder method. The IR spectra of RAT-1 and RAB-1 are given in Figures 2.4.1 and 2.4.2. IR spectral data are given in Tables 2.4.2 and 2.4.3 respectively. The spectral data for all other compounds are reported in Table 4.

Mass spectra:

The Mass spectra were recorded by GCMS-SHIMADZU-QP2010. Figures 2.4.3 and 2.4.4 shows mass spectra of RAT-2 and RAB-1 respectively and the proposed mass fragmentation of RAT-2 and RAB-1 are given in Schemes 2.4.1 and 2.4.2 respectively. The mass fragmentations of other compounds are also given separately.

^{1}H NMR Spectra:

The NMR spectra were recorded by BRUKER Spectrometer (400 MHz) using internal reference TMS and solvent $CDCl_3$/DMSO. Figures 2.4.3 and 2.4.4 shows NMR spectra of RAT-1 and RAB-1respectively. The spectral data for RAT-1 and RAB-1 are given in Tables 2.3.4 and 2.4.5.

Table 2.4.1: Physical constants of dihydropyrimidinthiones.

Sr. No.	Code	R	M.F.	M. Wt. (g/mol)	R_f* Value	M.P. °C	Yield %
1	**RAT-1**	4-OCH3	$C_{19}H_{17}Cl_2N_3O_2S$	422	0.51	180	56
2	**RAT-2**	-H	$C_{18}H_{15}Cl_2N_3OS$	392	0.62	194	61
3	**RAT-3**	4-CH_3	$C_{19}H_{17}Cl_2N_3OS$	406	0.42	211	53
4	**RAT-4**	4-F	$C_{18}H_{14}Cl_2N_3OS$	410	0.46	254	62
5	**RAT-5**	4-OH	$C_{18}H_{15}Cl_2N_3O_2S$	408	0.43	194	57
6	**RAT-6**	3-Cl	$C_{18}H_{14}Cl_3N_3OS$	426	0.46	167	60
7	**RAT-7**	3-NO_2	$C_{18}H_{14}Cl_2N_4O_3S$	437	0.57	235	48
8	**RAT-8**	2-Cl	$C_{18}H_{14}Cl_3N_3OS$	426	0.61	247	41
9	**RAT-9**	2-NO_2	$C_{18}H_{14}Cl_2N_4O_3S$	437	0.58	238	63
10	**RAT-10**	2-OH	$C_{18}H_{15}Cl_2N_3O_2S$	408	0.53	208	60
11	**RAB-1**	4-OCH_3	$C_{21}H_{24}N_4O_3S$	412	0.61	182	52
12	**RAB-2**	4-Cl	$C_{20}H_{21}ClN_4O_2S$	416	0.51	240	41
13	**RAB-3**	3-Cl	$C_{20}H_{21}ClN_4O_2S$	416	0.48	237	35
14	**RAB-4**	4-OH	$C_{20}H_{22}N_4O_3S$	398	0.43	175	48
15	**RAB-5**	2,5-Dichloro	$C_{20}H_{20}Cl_2N_4O_2S$	451	0.58	186	40
16	**RAB-6**	4-F	$C_{20}H_{21}FN_4O_2S$	400	0.61	231	36
17	**RAB-7**	4-NO_2	$C_{20}H_{21}N_5O_4S$	427	0.57	210	49
18	**RAB-8**	-H	$C_{20}H_{22}N_4O_2S$	382	0.53	196	43
19	**RAB-9**	4-CH_3	$C_{21}H_{24}N_4O_2S$	396	0.50	208	52
20	**RAB-10**	4-Br	$C_{20}H_{21}BrN_4O_2S$	461	0.43	219	46

* Methanol: Chloroform 2:8

Figure 2.4.1: IR spectra of N-(2,5-dichlorophenyl)-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carbox Amide (RAT-1).

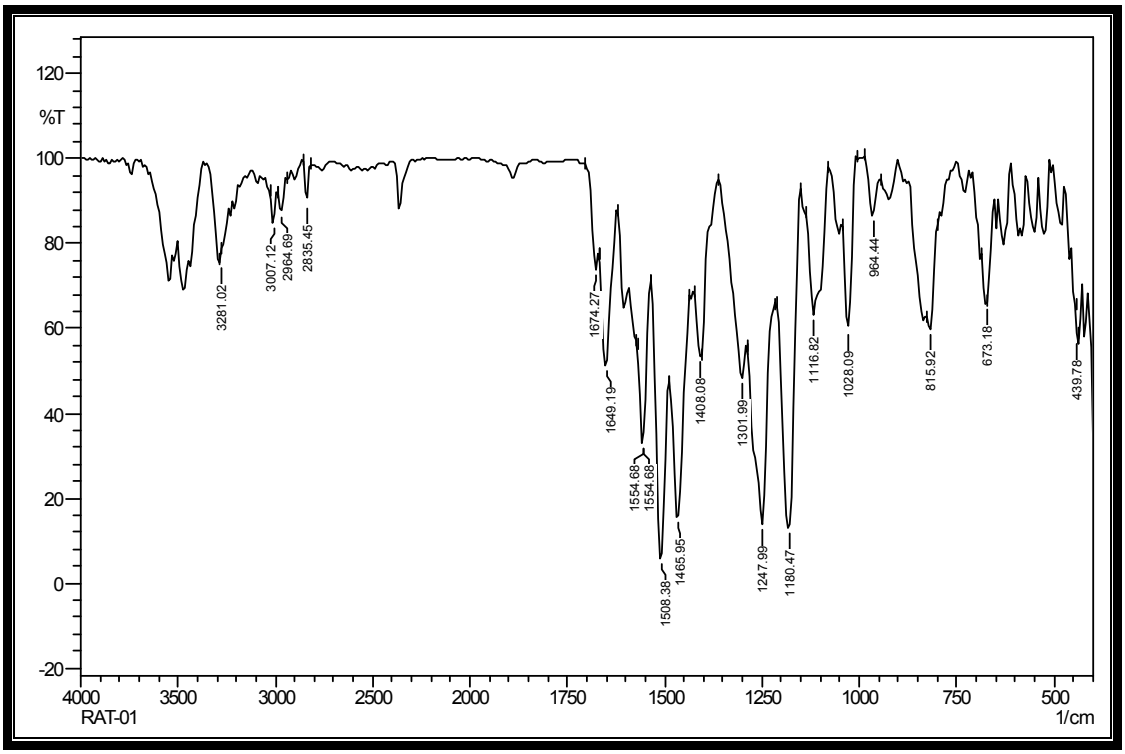


Table 2.4.2: IR spectral data of N-(2,5-dichlorophenyl)-4-(4-methoxyphe nyl)-6-methyl-2- thioxo-1,2,3,4-tetrahydropyrimidine-5-carb oxamide (RAT-1).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported[60,61]
Alkane	C-H str. (asym.)	2964.69	2975-2920
	C-H str. (sym.)	2835.45	2880-2860
	C-H def. (asym.)	1465.96	1500-1435
	C-H def.(sym.)	1408.08	1400-1370
Aromatic	C-H str.	3007.12	3200-3000
	C=C str.	1554.68	1585-1480
	C-H i.p. def.	1116.82	1125-1090
	C-H o.o.p. def.	815.92	860-810
Ketones	C=O str.	1674.27	1710-1550
Secondary amine	N-H (asym.)	3281.02	3400-3200
	N-H (sym)	1554.68	1650-1550
Ether	C-O-C str. (asym.)	1247.99	1400-1000
	C-O-C str. (sym.)	1028.09	1075-1020
Sulfur	C=S str.	1180.47	1200-1050
Chlorine	C-Cl str.	673.18	600-800

Figure 2.4.2: IR spectra of 4-(4-methoxy-3,5-dimethylpyridin-2-yl)N-(4-methoxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetra hydropyrimidine-5-carboxamide (RAB-1).

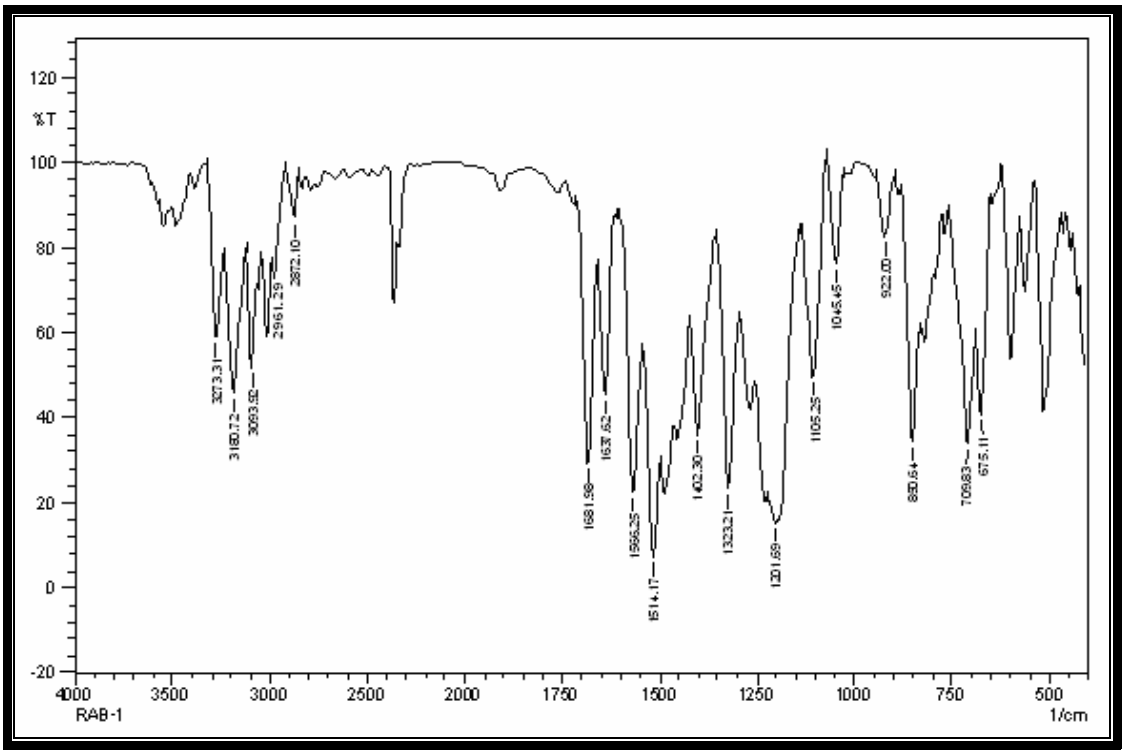


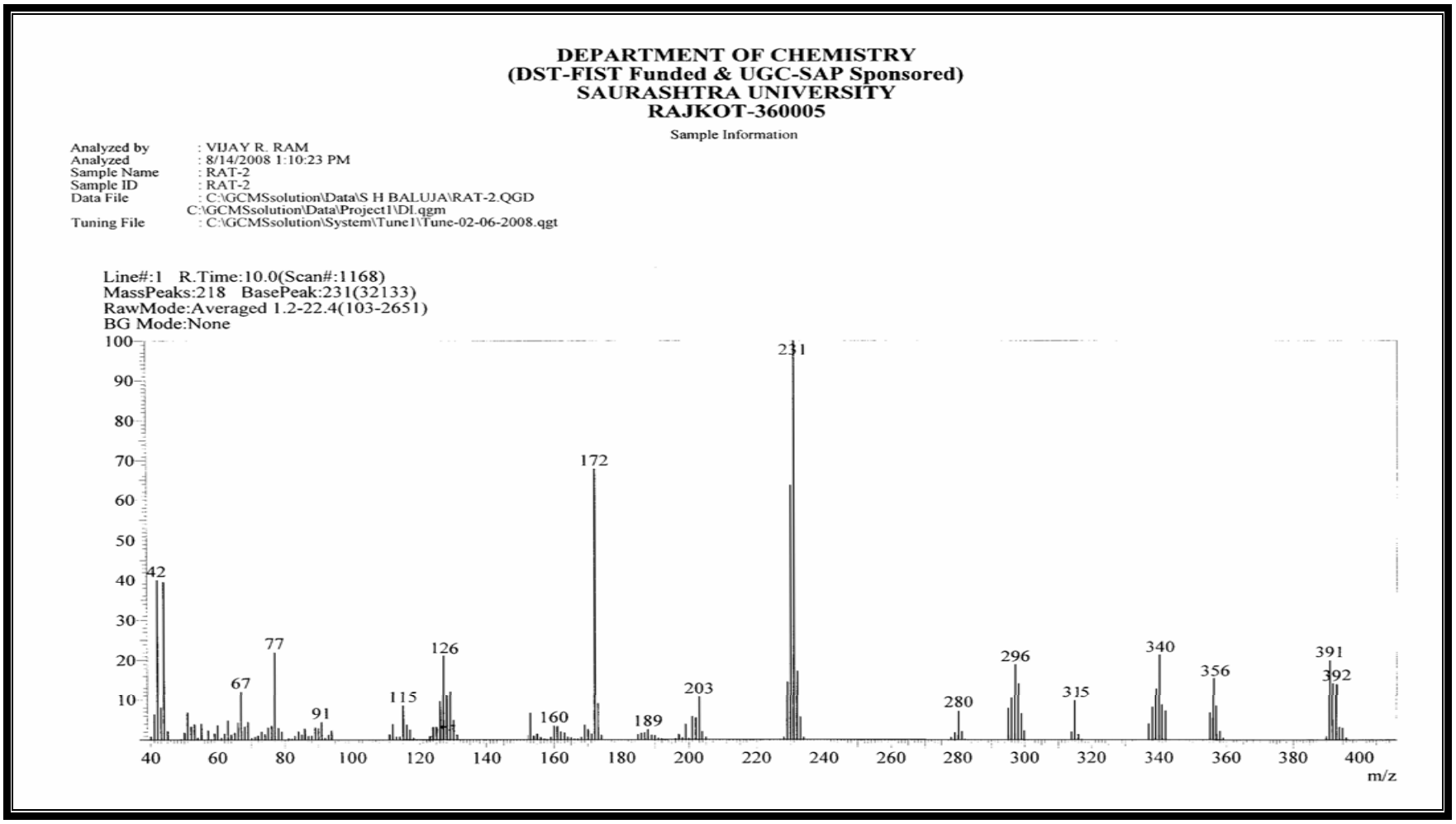
Table 2.4.3: IR spectral data of 4-(4-methoxy-3,5-dimethylpyridin-2-yl)N-(4-methoxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetra hydropyrimidine-5-carboxamide (RAB-1).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported[60,61]
Alkane	C-H str. (asym.)	2961.29	2975-2920
	C-H str. (sym.)	2872.10	2880-2860
	C-H def. (asym.)	1402.30	1500-1435
	C-H def.(sym.)	1323.21	1400-1370
Aromatic	C-H str.	3099.92	3200-3000
	C=C str.	1514.17	1585-1480
	C-H i.p. def.	1105.25	1125-1090
	C-H o.o.p. def.	850.64	860-810
Ketones	C=O str.	1681.98	1710-1550
Secondary amine	N-H (asym.)	3273.31	3500-3310
	N-H (syn.)	1566.25	1650-1550
Ether	C-O-C str. (asym.)	1201.69	1300-1200
	C-O-C str. (sym.)	1045.45	1075-1020
Sulfur	C=S str.	1105.25	1200-1050

Table 2.4.4: IR spectral data of synthesized dihydropyrimidinthaiones (RAT-2 to RAT-10 and RAB-2 to RAB-10).

Compounds	*IR ν, (cm^{-1})*				
	C=C str.	C=S str.	C=O str.	N-H (sym.)	R
RAT-2	1491	1188	1680	1577	-
RAT-3	1521	1188	1672	1566	-
RAT-4	1514	1105	1681	1566	1193
RAT-5	1508	1099	1681	1575	3282
RAT-6	1520	1164	1685	1572	771
RAT-7	1509	1142	1676	1581	1532
RAT-8	1511	1183	1680	1564	790
RAT-9	1524	1154	1681	1584	1521
RAT-10	1507	1114	1691	1570	3295
RAB-2	1537	1134	1682	1588	752
RAB-3	1524	1151	1710	1573	761
RAB-4	1555	1164	1723	1610	3310
RAB-5	1534	1142	1698	1594	782
RAB-6	1504	1124	1672	1620	1125
RAB-7	1564	1107	1691	1576	1534
RAB-8	1554	1131	1705	1610	-
RAB-9	1543	1146	1710	1587	-
RAB-10	1540	1151	1716	1593	663

Figure 2.4.3: Mass spectra of N-(2,5-dichlorophenyl)-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-Carboxamide (RAT-2).



Scheme 2.4.1: Proposed mass fragmentation of N-(2,5-dichlorophenyl)-6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydro pyri midine-5-carboxamide (RAT-2).

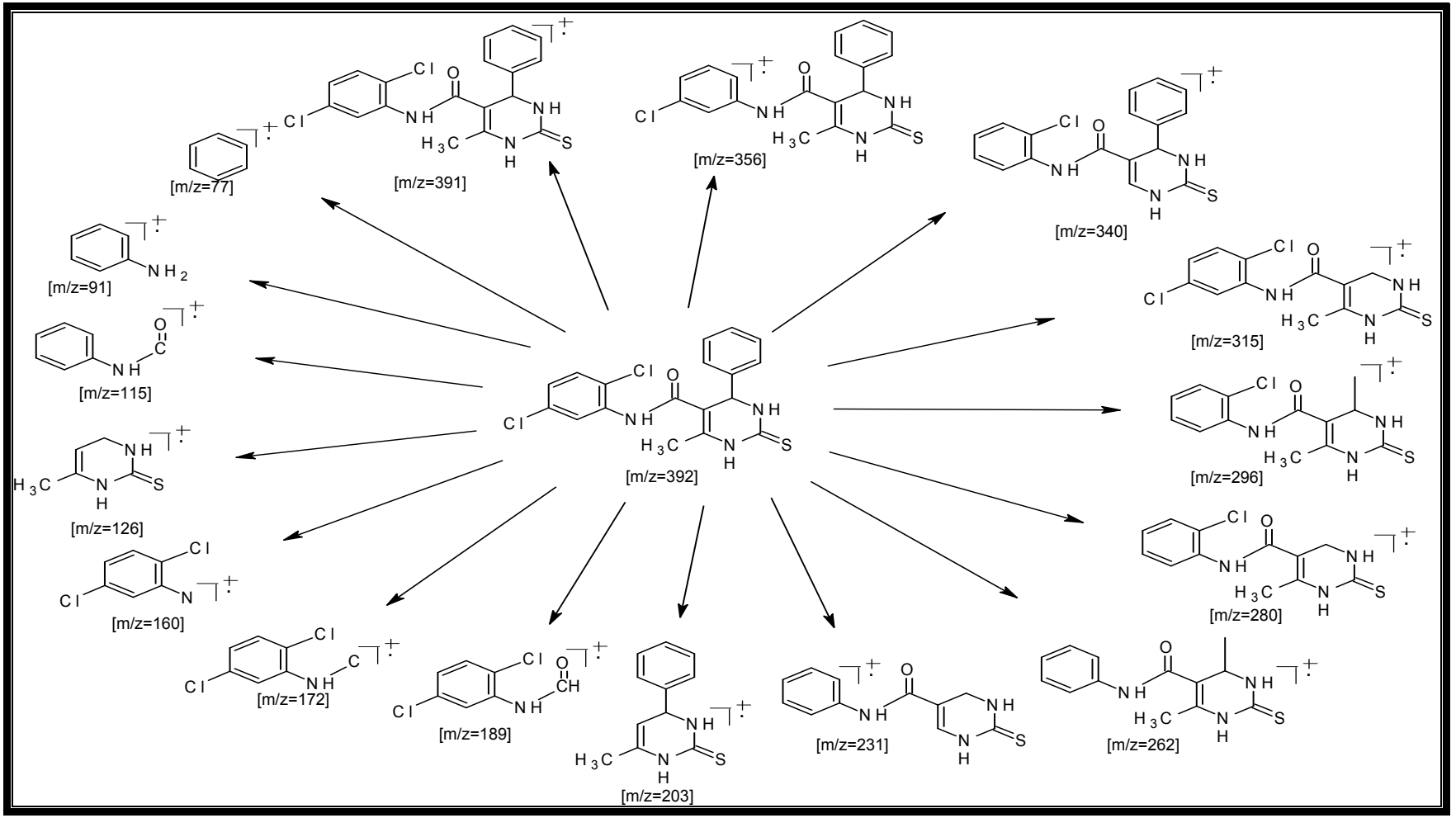
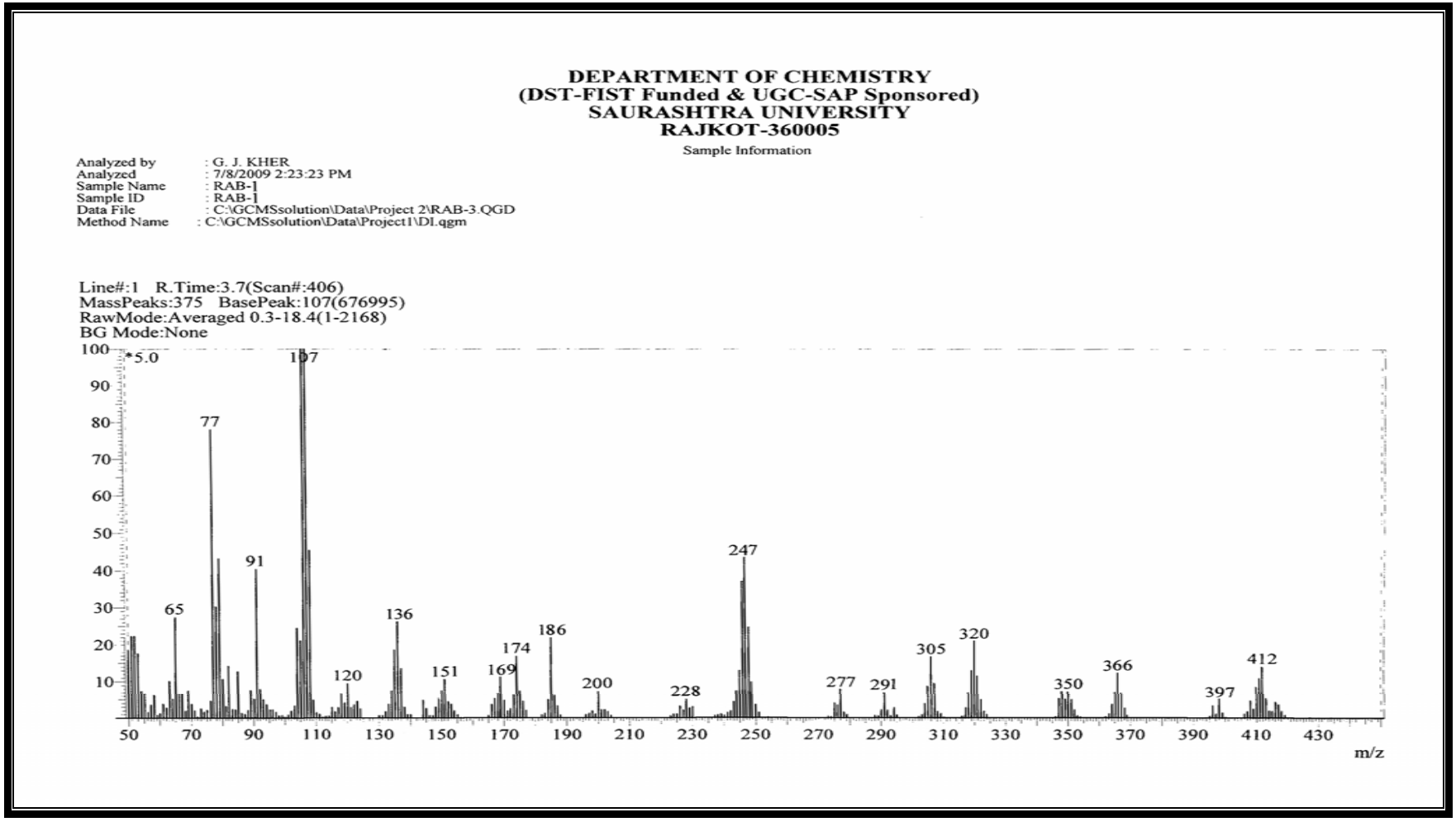
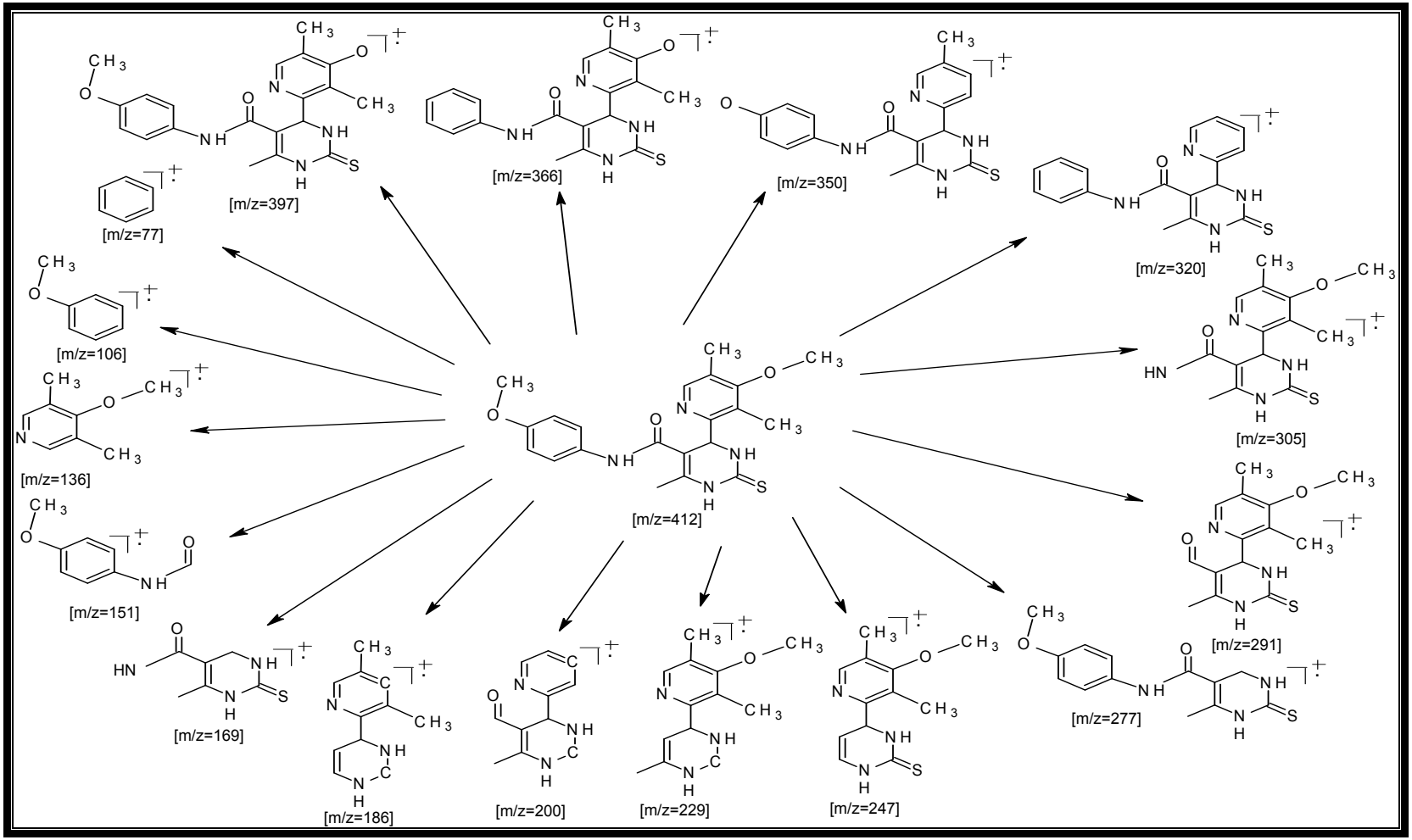


Figure 2.4.4: Mass spectra of 4-(4-methoxy-3,5-dimethylpyridin-2-yl)N-(4-methoxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2, 3,4-tetrahydropyrimidine-5-carboxamide (RAB-1).



Scheme 2.4.2: Proposed mass fragmentation of 4-(4-methoxy-3,5-dimethylpyridin-2-yl)N-(4-methoxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RAB-1).



Mass fragment (m/z value) of synthesizes dihydropyrimidinthiones.

RAT-1: 422, 379, 351, 345, 317, 303, 271, 261, 245, 231, 212, 202.

RAT-3: 406, 386, 245, 225, 211, 199, 187, 169, 161, 145, 126, 109.

RAT-4: 410, 394, 374, 354, 344, 328, 315, 293, 276, 249, 237, 221.

RAT-5: 408, 407, 391, 314, 289, 262, 245, 230, 221, 218, 202.

RAT-6: 426, 412, 390, 374, 360, 331, 314, 284, 267, 265, 239, 229.

RAT-7: 437, 421, 419, 401, 389, 314, 288, 276, 258, 248, 228, 217.

RAT-8: 426, 392, 374, 355, 336, 315, 289, 263, 241, 230, 207.

RAT-9: 437, 420, 395, 377, 356, 340, 316, 301, 283, 276, 254, 211.

RAT-10: 408, 407, 390, 356, 324, 305, 260, 246, 230, 218, 200.

RAB-2: 416, 401, 370, 335, 321, 318, 305, 278, 262, 245.

RAB-3: 416, 373, 355, 320, 337, 310, 303, 281, 232.

RAB-4: 398, 380, 365, 348, 318, 300, 288, 261, 245.

RAB-5: 451, 420, 403, 372, 366, 350, 315, 307, 274, 262, 231.

RAB-6: 400, 386, 370, 336, 303, 274, 264, 248, 220.

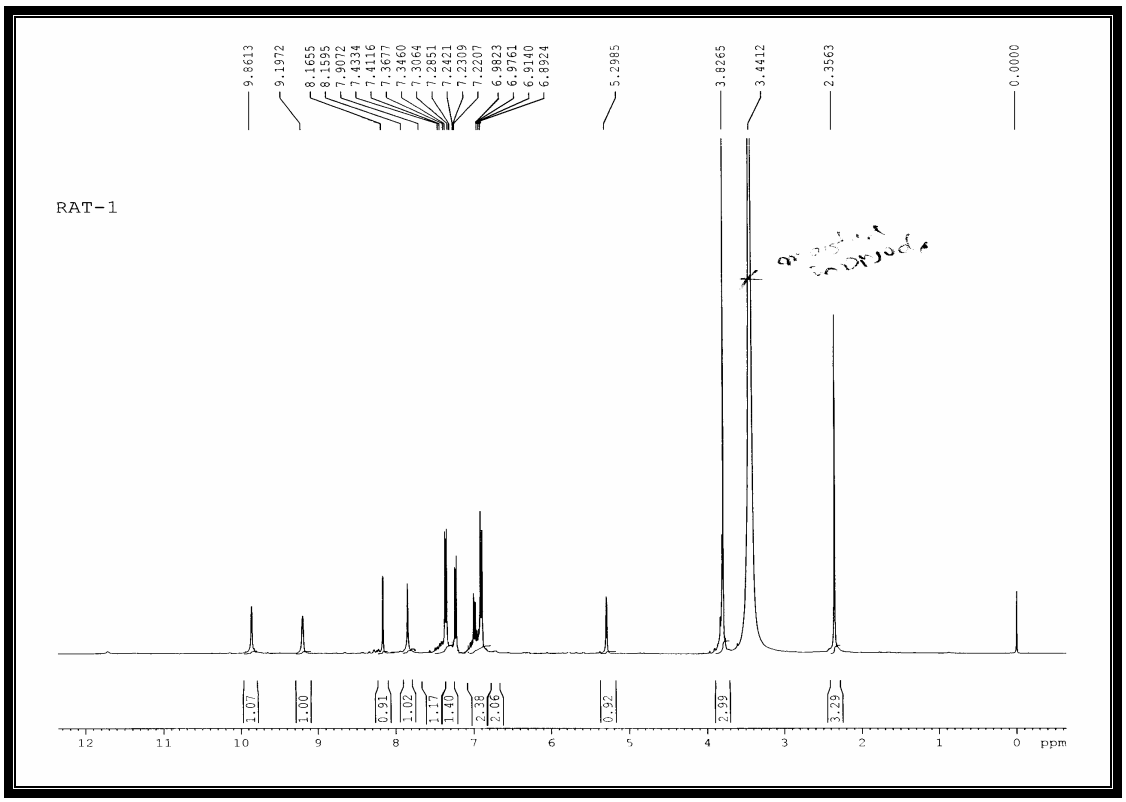
RAB-7: 427, 411, 395, 381, 365, 341, 320, 281, 244, 212.

RAB-8: 382, 350, 337, 320, 289, 247, 218.

RAB-9: 396, 350, 336, 304, 290, 261, 244, 226.

RAB-10: 461, 429, 401, 380, 351, 336, 302, 289, 262.

Figure 2.4.5: ^{1}H NMR spectra 4-(4-methoxy-3,5-dimethylpyridin-2-yl)N-(4-methoxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetra hydropyramidin e-5-carboxamide (RAT-1).



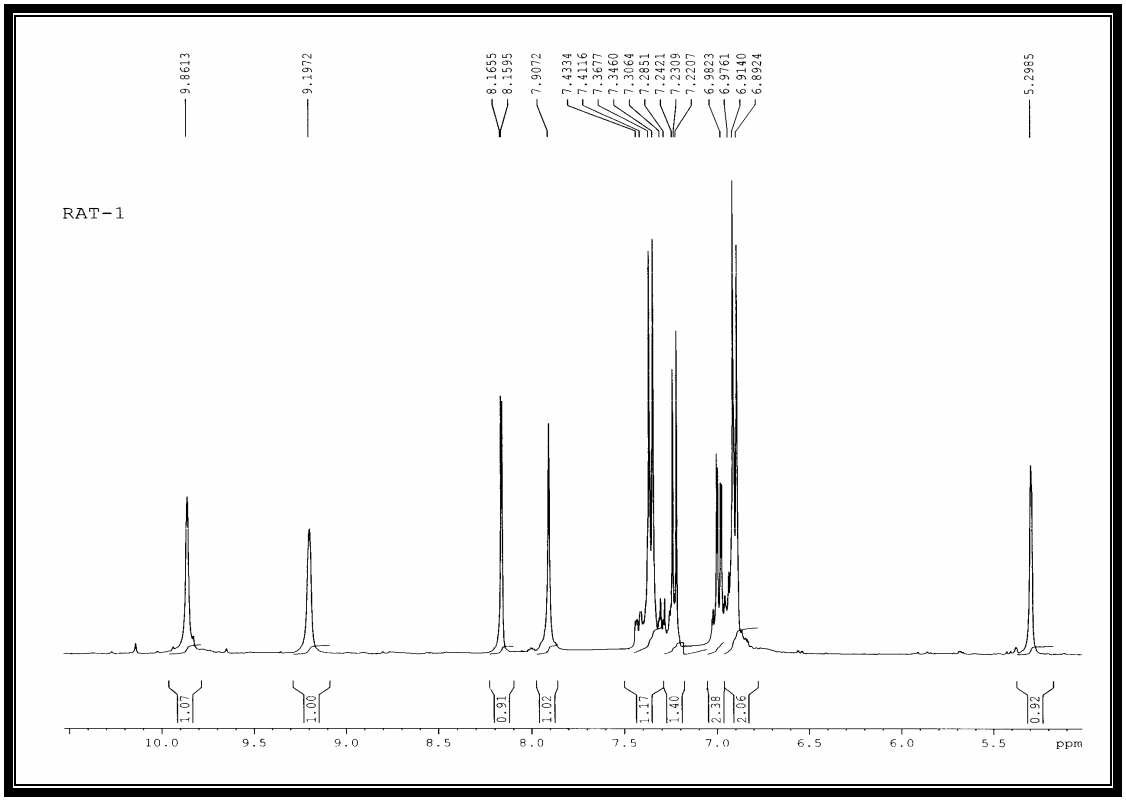
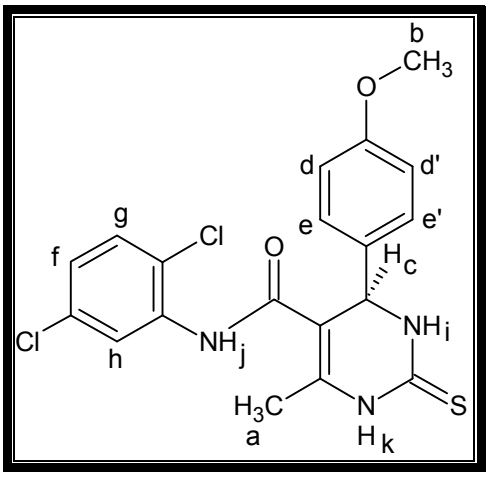


Table 2.4.4: ^{1}H NMR spectral data of 4-(4-methoxy-3,5-dimethylpyridin-2-yl)N-(4-methoxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RAT-1).



Singal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	*J* (Hz)
1	2.35	3	singlet	-C<u>H</u>$_3$ (a)	-
2	3.82	3	singlet	-OC<u>H</u>$_3$ (b)	-
3	5.29	1	singlet	-C<u>H</u> (c)	-
4	6.89-6.91	2	doublet	Ar-H (dd')	8.64
5	6.97-6.98	2	doublet	Ar-H (ee')	8.12
6	7.22-7.24	1	doublet	Ar-H (f)	8.56
7	7.34-7.36	1	doublet	Ar-H (g)	8.68
8	7.90	1	singlet	Ar-H (h)	-
9	8.15	1	singlet	-NH (j)	-
10	9.19	1	singlet	-NH (j)	-
11	9.86	1	singlet	-NH (k)	-

Figure 2.4.6: ^{1}H NMR spectra of 4-(4-methoxy-3,5-dimethylpyridin-2-yl)N-(4-methoxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RAB-1).

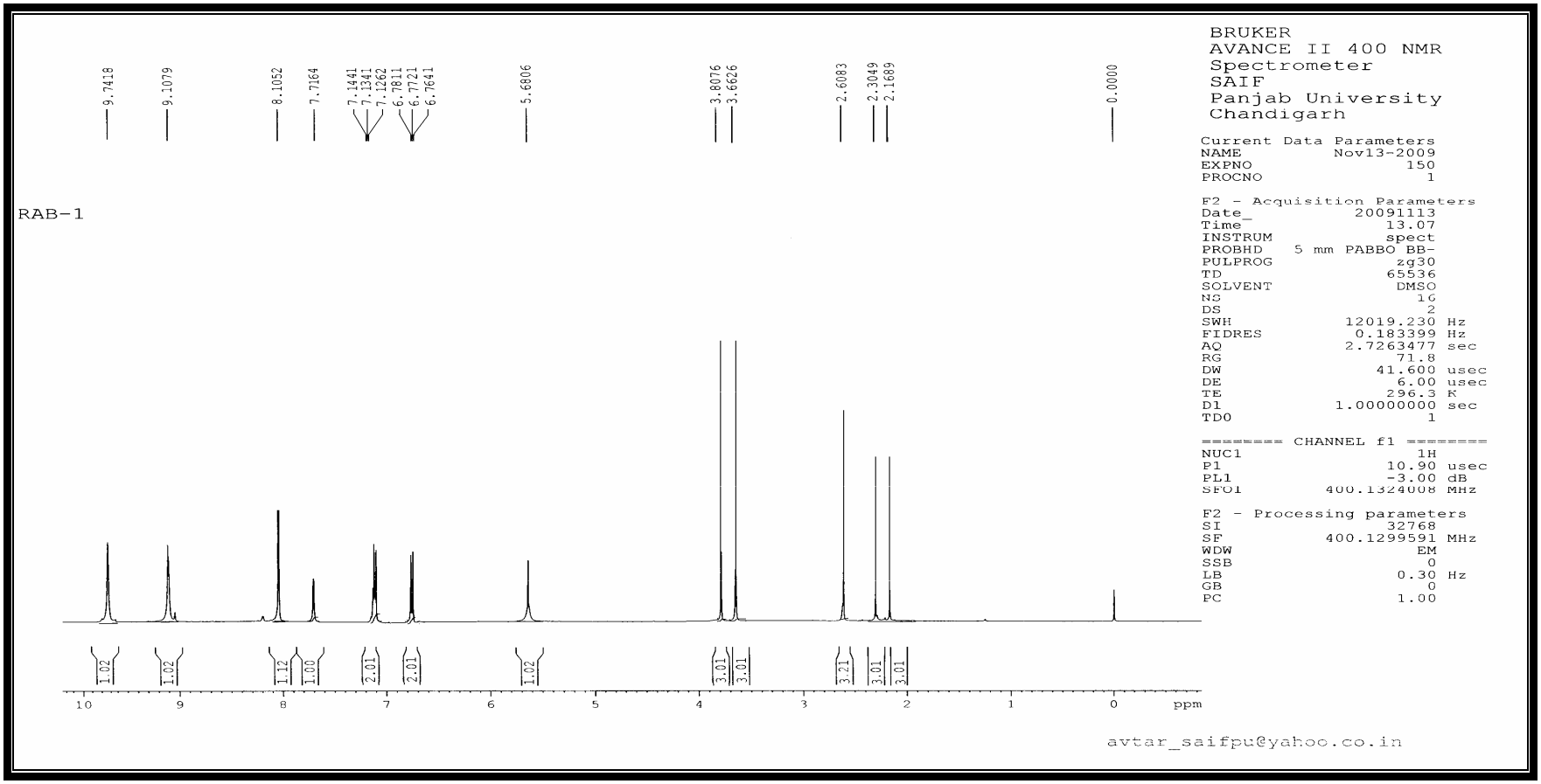
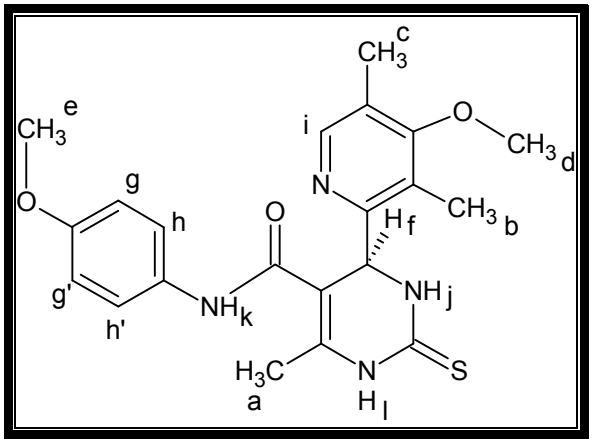


Table 2.4.5: ^{1}H NMR spectral data of 4-(4-methoxy-3,5-dimethylpyridin-2-yl)N-(4-methoxyphenyl)-6-methyl-N-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxamide (RAB-1).



Singal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	*J* (Hz)
1	2.13	3	singlet	-C<u>H</u>$_3$ (a)	-
2	2.30	3	singlet	-C<u>H</u>$_3$ (b)	-
3	2.60	3	singlet	-C<u>H</u>$_3$ (c)	-
4	3.66	3	singlet	-OC<u>H</u>$_3$ (d)	-
5	3.80	3	singlet	-OC<u>H</u>$_3$ (e)	-
6	5.68	1	singlet	-C<u>H</u> (f)	-
7	6.76-6.78	2	doublet	Ar-H (gg')	6.8
8	7.12-7.14	2	doublet	Ar-H (hh')	7.16
9	7.16	1	singlet	-H (i)	-
10	8.10	1	singlet	-NH (j)	-
11	9.10	1	singlet	-NH (k)	-
12	9.74	1	singlet	-NH (l)	

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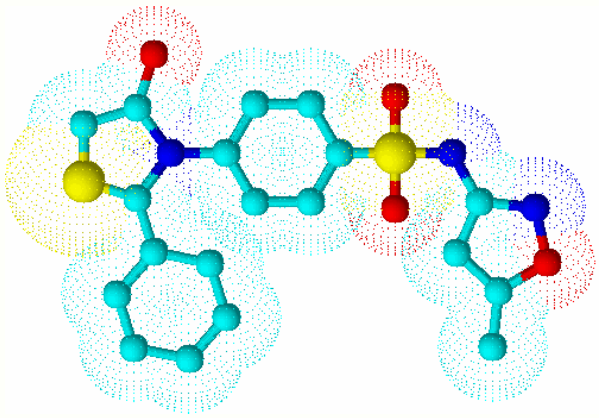
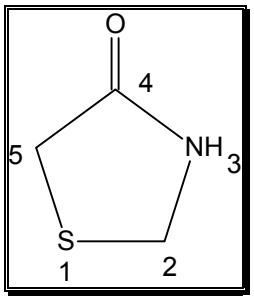


Section-V
Synthesis of Thiazolidinones

INTRODUCTION

Thiazolidinones are the derivatives of thiazolidine which belong to an important group of heterocyclic compounds containing sulfur and nitrogen in a five member ring. 4-Thiazolidinones are containing carbonyl group at 4-position[1]. Substituent in the 2, 3 and 5 position may be varied, but greatest difference in structure and properties is exerted by the groups attached to carbon atom in the 2-position and to nitrogen atom in the 3- position. General structure of 4-Thiazolidinones is given below:



A number of 4-thiazolidinone derivatives have been reported to possess diversified activities including hypoglycemic action[2-8]. Thiazolidinone ring is a main pharamacophoric group responsible for antidiabetic activity[9-11]. Compounds carrying the thiazolidinone ring have been reported to demonstrate a wide range of pharmacological activities which include anticonvulsant[12], antimicrobial[13,14], antiinflammatory[15], hypnotic[16], anti-hypertensive[17], antitumer[18] and antihistaminic[19] activities. Further, Singh[20] have reported the fungicidal activity of 5-methyl-3-aryl-2-arylimino-4-thiazolidinones and their acetoxymercuri derivatives. Pande and Saxena[21] have been measured the antiviral activity of 3-(substituted aminomethyl)-5-(nitrobenzylidene)- 4-thiazolidinone -2-thiones.

A lot of research work on thiazolidinones has been done in the past. The ucleus is also known as wonder nucleus because it gives out different derivatives with all different types of biological activities. Considerable confusion concerning the structure of 4-thiazolidinones exist in the early literature and noncyclic formulas were at first proposed for pseudothiohy-dantoin and for rhodanine[22]. Various optical and geometrical isomers are reported in the references[23]. A series of regioselective isomers has been

reported in someworks[24,25]. The carbonyl group of 4-thiazolidinone is highly unreactive. But in few cases 4-thiazolidinone on reaction with Lawesson's reagent gives corresponding 4-thione derivatives[26]. A detail study of tautomerism in 2-imnothiazolidine-4-one has been done by Akerblom[27].

Different methods for preparation of 4-thiazolidinone are available in literature. Kinetics of formation of 4-thiazolidinones by cyclocondensation reaction is given by Lawande and Arbad[28]. Ishimaru et al. have been used DBFOX-Ph/metal complexes as catalysts for enantioselective fluorination of 3-(2-arylacetyl)-2- thiazolidinones[29]. 4-thiazolidinones have been synthesized by using Phosphine was reported by Gabillet and coworkers[30]. Many workers have been reported the synthesis of 4-thiazolidinones under microwave irradiation[31,32].

Literature survey shows that, 4-thaizolidinone are synthesized by many workers[33-36]. Ram and coworkers[37] have been synthesized some 3-aryl-2-arylimino-4-thiazolidinones. Mane and Ingle[38] have reported the synthesis of 3-hydroxy-2-(substituted thiazolyl)-4-thiazolidinones. Roda et al.[39] have given the preparation of 2-aryl-3-[2'-isopropyl-5'-methylphenoxyacetylamino]-5H-methyl-4-thiazolidinones. Synthesis 2-aryl/alkyl-3-benzhydryl-4-thiazolidinone-s of have reported by Padia and Patel[40]. Solankee and coworkers[41] have synthesized 2-(phenylimino)-5-(ω -carboxyhexyl)-4-thiazolidinones. Shi and Wang[42] have studied the on synthesis of 3-aryl-5-benzoyl-2-thioxo- 4-thiazolidinones. Upma and Manrao[43] have studied the effect of chloro group on fungus with 4-thaizolidinone. Lata and Prakash[44] have reported the synthesis and biological evaluation of 4-thiazolidinones and their ketoazomethines. Synthesis of some novel bis-1,2,4-triazolo[3, 4 -b]-1,3, 4-thiadiazoles and bis-4-thiazolidinone derivatives from terephthalic dihydrazide have been reported by Palekar[45].

In this section, some derivatives of 4-thaizolidinones have been synthesized and their characterization was done by IR, NMR and mass spectra.

EXPERIMENTAL

Synthesis of 4-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzenesulfonamide (RSAT-1).

[A] Synthesis of 4-[(4-methoxybenzylidene)amino]-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide (RSA-1).

As per section-I.

[B] Synthesis of 4-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzenesulfonamide (RSAT-1).

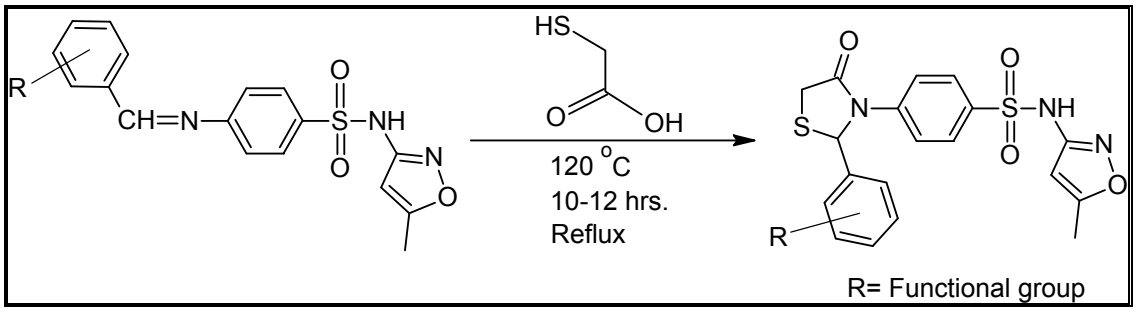
A mixture of 4-[(4-methoxybenzylidene)amino]-N-(5-methyl-1,2-oxazol-3-yl)be nzenesulfonamide (RSA-1) (0.01M) and thioglycolic acid 0.01M was heated at 120°C for 10-12 hrs. The reaction mixture was cooled and treated with 10% sodium bicarbonate solution. The solid product was thus separated, filtered and washed with water and crystallized from absolute ethanol.
Similarly other Schiff bases were condensed with thioglycolic acid.

REACTION SCHEME

[A] Synthesis of 4-[(4-methoxybenzylidene)amino]-N-(5-methyl-1,2-oxazol-3-yl)benzenesulfonamide (RSA-1).

As per section-I.

[B] Synthesis of 4-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzenesulfonamide (RSAT-1).



The following thiazolidinones have been synthesized from sulfamethoxazole.

1. RSAT-1: 4-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzenesulfonamide
2. RSAT-2: 4-{2-[4-(dimethylamino)phenyl]-4-oxo-1,3-thiazolidin-3-yl}-N-(5-methylisoxazol-3-yl)benzenesulfonamide
3. RSAT-3: 4-[2-(4-fluorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzenesulfonamide
4. RSAT-4: 4-[2-(4-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzenesulfonamide
5. RSAT-5: N-(5-methylisoxazol-3-yl)-4-[2-(3-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]benzenesulfonamide
6. RSAT-6: N-(5-methylisoxazol-3-yl)-4-[2-(2-nitrophenyl)-4-oxo-1,3-thiazolidin-3-yl]benzenesulfonamide
7. RSAT-7: N-(5-methylisoxazol-3-yl)-4-(4-oxo-2-phenyl-1,3-thiazolidin-3-yl)benzenesulfonamide
8. RSAT-8: 4-[2-(2-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzenesulfonamide
9. RSAT-9: 4-[2-(3-chlorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzenesulfonamide
10. RSAT-10: 4-[2-(4-bromophenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzenesulfonamide

The various physical constants such as R_f value, melting point and percentage of yield for all synthesized Thiazolidinones are given in Table 2.5.1. The melting point was taken by open capillary method.

The characterization was done by IR, mass spectra and ^{1}H NMR.

Infrared spectra:

The IR spectra were recorded by SHIMADZU-FTIR-8400 spectrophotometer in the frequency range of 4000-400 cm^{-1} by KBr powder method. The IR spectra and data for RSAT-1 is given in Figure 2.5.1 and Table 2.5.2 respectively. The spectral data for all other compounds are reported in Table 2.5.3.

Mass spectra:

The Mass spectra were recorded by GCMS-SHIMADZU-QP2010. Figure 2.5.2 shows mass spectra of RSAT-1. The proposed mass fragmentation of RSAT-1 is given in Scheme 2.5.1. The mass fragmentations of other compounds are also given separately.

^{1}H NMR Spectra:

The NMR spectra were recorded by BRUKER Spectrometer (400 MHz) using internal reference TMS and solvent $CDCl_3$/DMSO. Figure 2.5.3 shows NMR spectra of RSAT-2. The spectral data for RSAT-1 is given in Table 2.5.4.

Table 2.5.1: Physical constants of thaizolidinones.

Sr. No.	Code	R	M.F.	M. Wt. (g/mol)	R_f* Value	M.P. °C	Yield %
1	**RSAT-1**	4-OCH_3	$C_{20}H_{19}N_3O_5S_2$	445	0.53	193	31
2	**RSAT-2**	4-$N(CH_3)_2$	$C_{21}H_{22}N_4O_4S_2$	458	0.42	274	24
3	**RSAT-3**	4-F	$C_{19}H_{16}FN_3O_4S_2$	433	0.61	234	29
4	**RSAT-4**	4-Cl	$C_{19}H_{16}ClN_3O_4S_2$	449	0.42	203	30
5	**RSAT-5**	3-NO_2	$C_{19}H_{16}N_4O_6S_2$	460	0.43	259	37
6	**RSAT-6**	2-NO_2	$C_{19}H_{16}N_4O_6S_2$	460	0.38	184	28
7	**RSAT-7**	H	$C_{19}H_{17}N_3O_4S_2$	415	0.46	238	23
8	**RSAT-8**	2-Cl	$C_{19}H_{16}ClN_3O_4S_2$	449	0.57	250	35
9	**RSAT-9**	3-Cl	$C_{19}H_{16}ClN_3O_4S_2$	449	0.40	286	34
10	**RSAT-10**	3-Br	$C_{19}H_{16}BrN_3O_4S_2$	494	0.52	281	28

* Hexene: Toluene: 7:3

Figure 2.5.1: IR spectra of 4-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzenesulfonamide (RSAT-1).

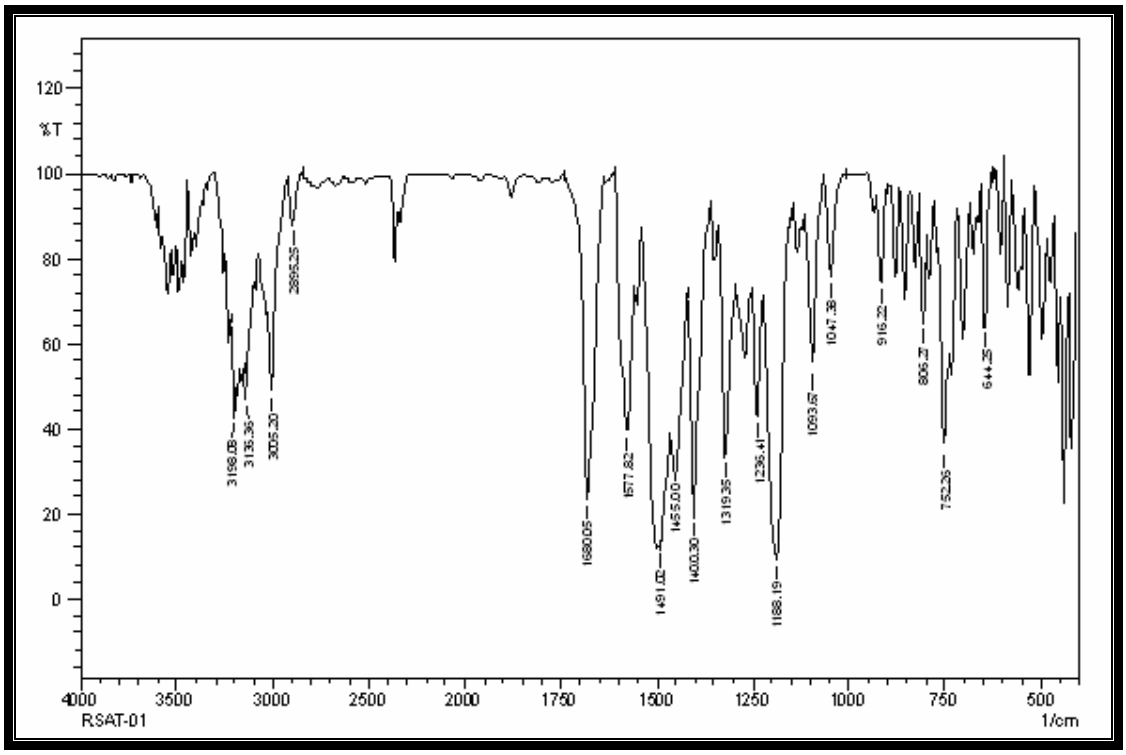


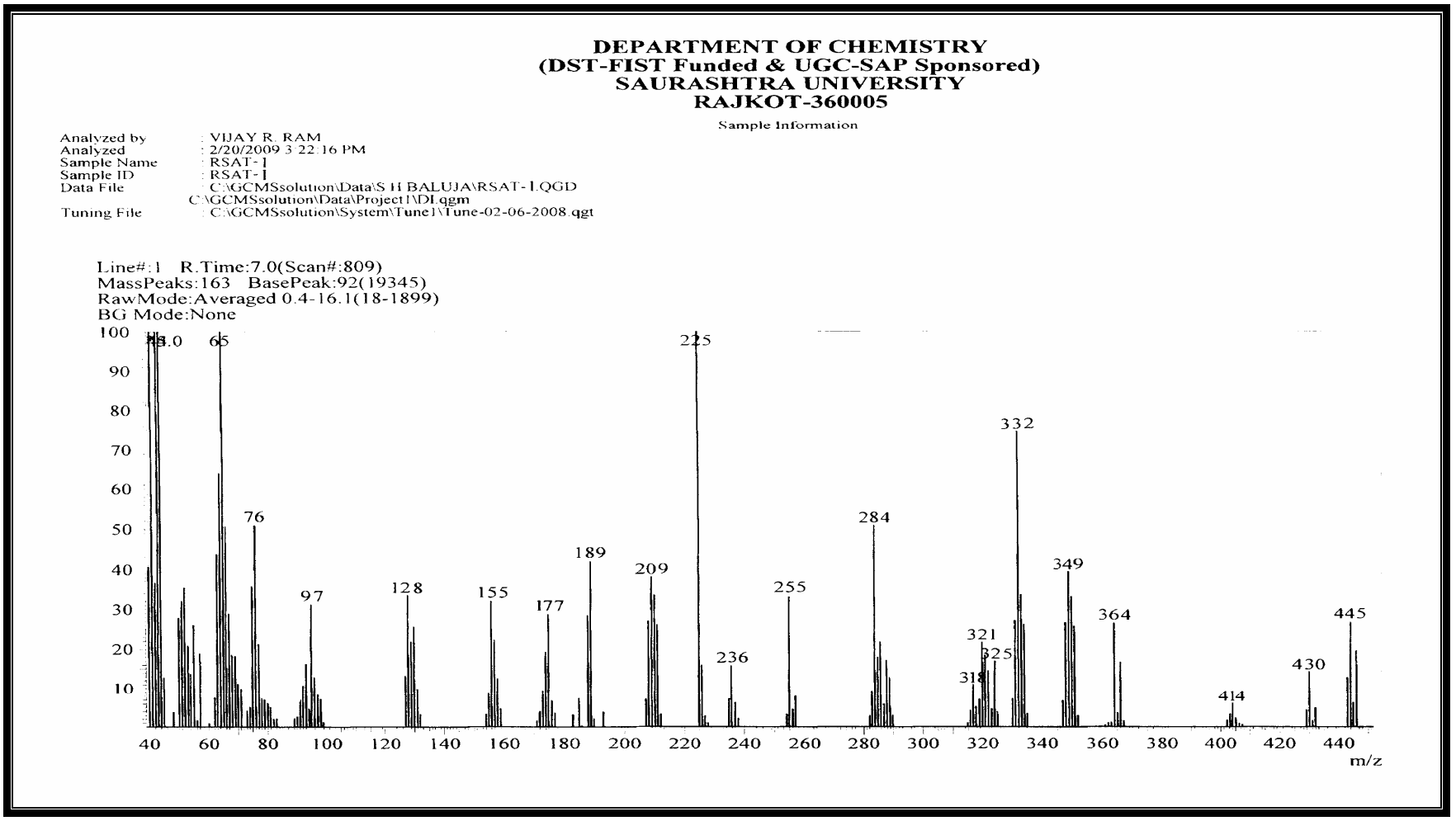
Table 2.5.2: IR spectral data of 4-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzenesulfonamide (RSAT-1).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported[46,47]
Alkane	C-H str. (sym.)	2895.25	2880-2860
	C-H def. (asym.)	1455.00	1500-1435
	C-H def.(sym.)	1400.30	1400-1370
Aromatic	C-H str.	3005.20	3200-3000
	C=C str.	1577.82	1585-1480
	C-H i.p. def.	1093.67	1125-1090
	C-H o.o.p. def.	806.27	860-810
Thaizolidinone	C=O str.	1660.05	1760-1655
	C-N str.	1188.19	1220-1020
	C-S-N str.	644.25	700-600
Sulfonamide	SO_2-NH (asym.)	1319.35	1350-1300
Secondary amine	N-H (asym.)	3410.00	3500-3310
ether	C-O-C str. (asym.)	1236.41	1300-1200
	N-O str.	1047.38	1400-1000

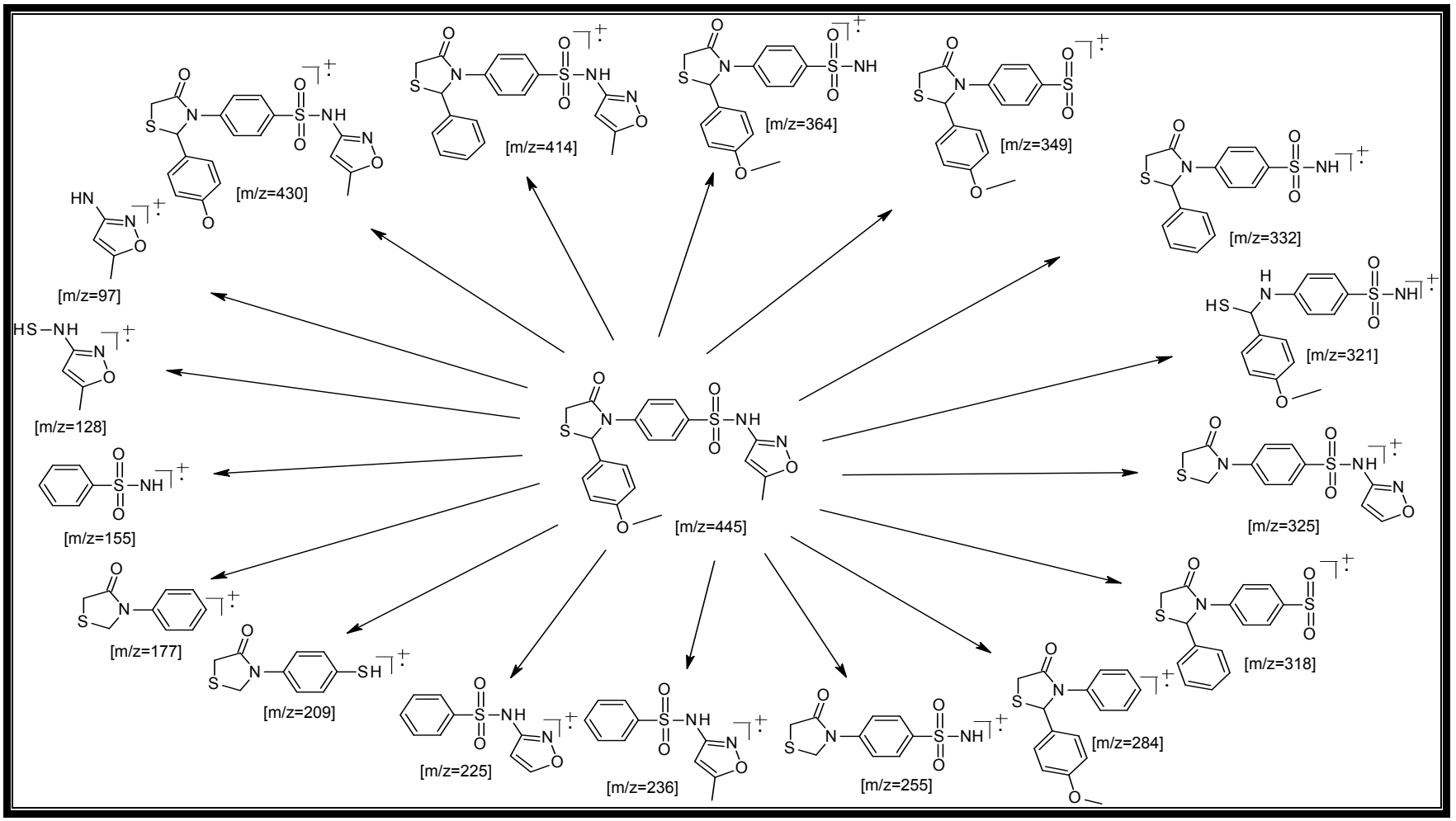
Table 2.5.3: IR spectral data of synthesized thiazolidinones (RSAT-2 to RSAT-10).

Compounds	*IR ν, (cm^{-1})*			
	C=C str.	**N-O str.**	**C=N (asym.)**	**R**
RSAT-2	1564	1064	3425	-
RSAT-3	1524	1058	3411	1326
RSAT-4	1532	1100	3464	709
RSAT-5	1548	1121	3436	1321
RSAT-6	1564	1092	3434	1342
RSAT-7	1524	1086	3451	-
RSAT-8	1560	1134	3427	740
RSAT-9	1532	1127	3467	761
RSAT-10	1544	1108	3472	569

Figure 2.5.3: Mass spectra 4-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzenesulfon amide (RSAT-1).



Scheme 2.5.1: Proposed mass fragmentation of 4-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-N-(5-methylisoxazol-3-yl)benzenesulfonamide (RSAT-1).



Mass fragments (m/z value) of synthesized thiazolidinones (RSAT- 2 to RSAT-9).

RSAT-2: 458, 443, 428, 414, 376, 361, 352, 338, 320, 315, 292.

RSAT-3: 433, 418, 414, 400, 388, 351, 338, 317, 304, 272, 253, 237.

RSAT-4: 449, 434, 414, 400, 367, 352, 338, 290, 288, 254, 238.

RSAT-5: 460, 444, 445, 414, 398, 378, 348, 318, 300, 276, 267.

RSAT-6: 460, 441, 413, 390, 364, 350, 327, 302, 276, 268.

RSAT-7: 415, 400, 372, 358, 338, 332, 317, 287, 254, 212.

RSAT-8: 449, 432, 414, 399, 351, 328, 288, 244, 231.

RSAT-9: 449, 430, 414, 384, 342, 338, 300, 276, 240, 228.

RSAT-10: 494, 479, 464, 444, 432, 412, 400, 382, 361, 354, 344, 320.

Figure 2.5.4: ^{1}H NMR spectra of 4-{2-[4-(dimethylamino)phenyl]-4-oxo-1,3-thiazolidin-3-yl}-N-(5-methylisoxazol-3-yl) benz enesulfonamide (RSAT-2).

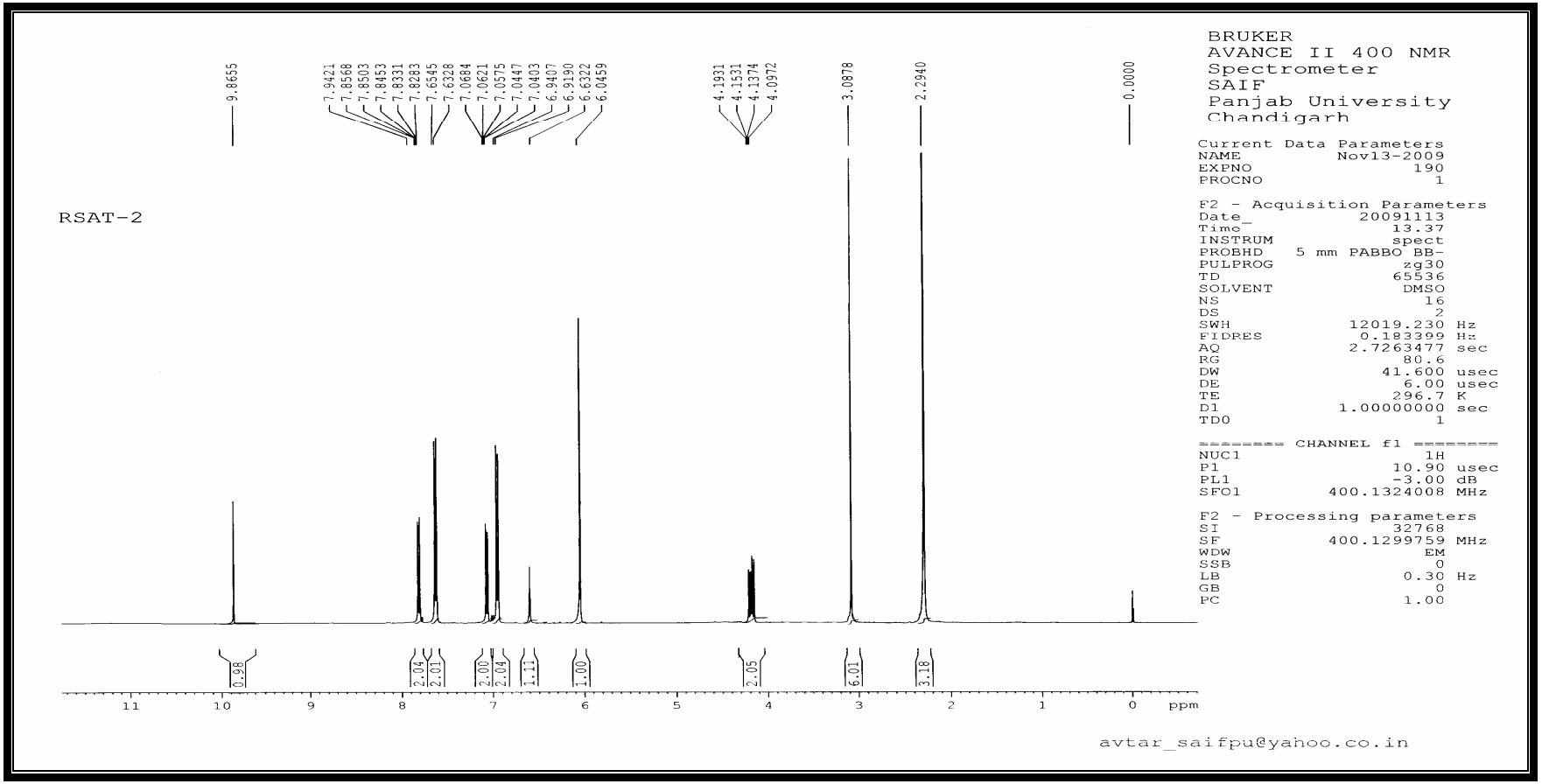
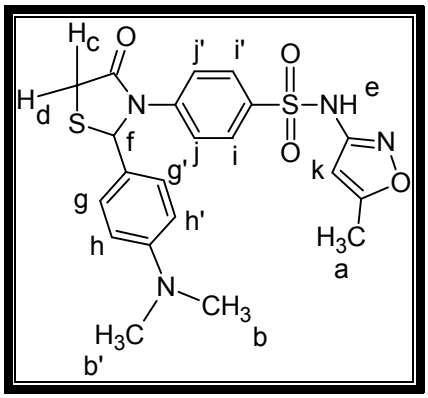


Table 2.5.4: ^{1}H NMR spectral data of 4-{2-[4-(dimethylamino)phenyl]-4-oxo-1,3-thiazolidin-3-yl}-N-(5-methylisoxazol-3-yl)benzene sulfonamide (RSAT-2).



Singal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	*J* (Hz)
1	2.29	3	singlet	-C<u>H</u>$_3$ (a)	-
2	3.08	6	singlet	N-(C<u>H</u>$_3$)$_2$ (bb')	-
3	4.09-4.13	2	doublet	-CH$_2$ (cd)	16.08
	4.15-4.19		doublet		16.00
4	6.04	1	singlet	-NH (e)	-
5	6.63	1	singlet	-H (f)	-
6	7.040-7.044	2	doublet	Ar-H (gg')	1.76
7	7.05-7.06	2	doublet	Ar-H (hh')	1.84
8	7.63-7.65	2	doublet	Ar-H (ii')	8.68
9	7.84-7.85	2	doublet	Ar-H (jj')	2.00
10	9.86	1	singlet	-H (k)	-

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CHAPTER-3
PHYSICO CHEMICAL PROPERTIES

Section-I

Acoustical Properties

INTRODUCTION

Ultrasonics is the science of sound waves deals with mechanical vibrations in a solid or fluid at a frequency higher than the range audible to humans 20 KHz (20,000 cycles per sec). It is also known as silent waves because human beings cannot hear these sound waves. However, bats, dogs, whales etc can hear these sound waves so these waves have been used in animal communication[1].

These ultrasonic vibrations have been used for a huge variety of applications. The industrial applications of ultrasound waves include welding of metals[2] and plastics[3], ultrasonic cleaning[4,] sono-chemistry[5,] polishing and cutting of mold steel[6-8], non-destructive material testing[9], thickness measurement[10], fluid level measurement[11] and medical imaging[12,] metal-forming processes[13], aircraft[14] and drawing[15] etc. For the extraction of various compounds also[16-19], ultrasonic waves have been used.

Ultrasonic measurement techniques are familiar to most people from their medical applications, it is used for various diagnosis such as brain diseases[20], dental disease[21], vascular diseases[22], in urology[23], in cancer[24] etc. It is also used in extraction of insulin[25], blood flow estimation[26], chemotherapy on rats[27], combination therapy[28] etc. This technique have also been used in herbal medicines[29] and skin therapy treatment[30]. Further, it is also applicable for the fetus in the imaging tissue anomalies in order to detect defects such as tumors [31].

In recent years, ultrasonic waves have been applicable to process monitoring and control, analyzing of milk composition[32], food processing[33] etc. A number of other applications in food industry have also been reported[34-38].

In materials science, these waves have been used for the determination of some properties of solids such as compressibility[39,40], specific heat ratios[41-43], elasticity[44-46] etc. In addition to these, ultrasonic waves provide valuable information about the structure of solids[47-49] and detecting effects in materials.

Now a days, lots of interest has been generated on the use of ultrasound radiation in synthetic organic chemistry, which includes decrease

of reaction time, increase of yield, lower reaction temperature, avoidance of phase transfer catalysis, nano particle synthesis etc[50-57].

In addition to these, Ultrasonic velocity measurements are used to study molecular interactions in pure liquids and binary / ternary mixtures[58-65] such as molecular association, dissociation etc. Further, equilibrium constant and some thermodynamic properties[66-69] of liquids and liquid mixtures can also be evaluated by ultrasonic measurements. It provides a powerful, effective and reliable tool to investigate the properties of solutions of polymers, carbohydrates, amino acids and organic and inorganic compounds.

Thus, in the present section, acoustical velocity studies of some dihydripirimidinones derivatives (RAT series) in N, N-dimethylformamide (DMF) and tetrahydrofuran (THF) solutions were done at 308.15K over a wide range of concentrations with a view to understand the molecular interactions in these solutions.

EXPERIMENTAL

The selected solvents, DMF and THF for the present study were distilled by the reported procedure[70]. The synthesized dihydropyrimidin thiones derivatives (RAT series) were recrystallized before use.

The densities, viscosities and ultrasonic velocities of pure solvents and solutions of diydropyririmidinthiones derivatives (RAT series) of different concentrations were measured at 308.15 K by using pyknometer, an Ubbelohde suspended level viscometer and single frequency ultrasonic interferometer operating at 2 MHz, with the uncertainties of 0.0001 g/cm^3, $\pm$ 0.06 % and 0.01% respectively.

Density measurements:

The weight of distilled water, pure solvents and solutions of synthesized compounds were measured by using pyknometer. The densities (ρ) were evaluated by using following equation:

$$\rho\left(g/cm^3\right) = \frac{\left(\text{wt. of solvent or solution}\right)\left(\text{density of water}\right)}{\left(\text{wt. of water}\right)} \quad \ldots (3.1.1)$$

Viscosity Measurements:

To determine the viscosity of solution, Ubbelohde viscometer[71] was used, which obeys Stoke's low[72]. The measured quantity of the distilled water / solvent / solution was placed in the viscometer, which was suspended in a thermostat at 308.15 K. The digital stopwatch, with an accuracy of $\pm$ 0.01 sec was used to determine flow time of solutions. Using the flow times (t) and known viscosity of standard water sample, the viscosity of solvent (η_1) and solutions (η_2) were determined according to equation:

$$\frac{\eta_1}{\eta_2} = \frac{t_1\rho_1}{t_2\rho_2} \quad \ldots (3.1.2)$$

Sound velocity measurement:

Ultrasonic interferometer, (Mittal Enterprise, New Delhi, Model No. F-81) working at frequency of 2 MHz was used to determine sound velocity.

The solvent / solution were filled in the measuring cell with quartz crystal and then micrometer was fixed. The circulation of water from the thermostat at 308.15 K was started and test solvent / solution in the cell is

allowed to thermally equilibrate. The micrometer was rotated very slowly so as to obtain a maximum or minimum of anode current (n). A number of maximum reading of anode current were counted. The total distntde (d) travel by the micrometer for n=10, was read. The wave length (λ) was determined by the equation:

$$\lambda = \frac{2d}{n} \qquad \ldots (3.1.3)$$

and sound velocity (U) of solvent and solutions were calculated by the equation:

$$U = \lambda F \qquad \ldots (3.1.4)$$

where F is the frequency, which is equal to 2 x 10^6 Hertz.

RESULTS AND DISCUSSION

Table 3.1.1 shows the experimental data of density (ρ), viscosity (η) and sound velocity (U) of pure solvents and solutions of compounds (RAT series) at 308.15 K.

From these experimental data, various acoustical parameters like specific acoustical impedance (Z), isentropic compressibility (κ_S), inter molecu -lar free length (L_f), molar compressibility (W), Rao's molar sound function (R_m), Vander Waals constant (b), relaxation strength (r), relative association (R_A), internal pressure (π), apparent molar compressibility (ϕ_k) etc., were evaluated using the following equations:

1. Specific acoustical impedance:

Specific acoustical impedance (Z) can be calculated as:

$$Z = U\rho \qquad \text{... (3.1.5)}$$

2. Isentropic compressibility:

Isentropic compressibility (κ_s) can be evaluated by the equation[73]:

$$\kappa_s = \frac{1}{U^2\rho} \qquad \text{… (3.1.6)}$$

3. Intermolecular free path length:

Jacobson[74] proposed an equation to calculate the intermolecular free path length (L_f), which is given below:

$$L_f = K_j \kappa_s^{1/2} \qquad \text{… (3.1.7)}$$

where K_J is Jacobson constant (=2.0965 X 10^{-6})

4. Molar compressibility:

Molar compressibility (W) can be calculated by the following equation[75]:

$$W = \left(\frac{M}{\rho}\right)\kappa_s^{-1/7} \qquad \text{… (3.1.8)}$$

The apparent molecular weight (M) of the solution can be calculated according to following equation:

$$M = M_1W_1 + M_2W_2 \qquad \text{… (3.1.9)}$$

where W_1 and W_2 are weight fractions of solvent and solute respectively. M_1 and M_2 are the molecular weights of the solvent and compounds respectively.

Table 3.1.1: The density (*ρ*), ultrasonic velocity (*U*) and viscosity (*η*) of RAT series in DMF and THF at 308.15 K.

Conc. M	Density ρ $g.cm^{-3}$	Velocity U. 10^{-5} $cm.s^{-1}$	Viscosity η.10^{3} poise	Density ρ $g.cm^{-3}$	Velocity U. 10^{-5} $cm.s^{-1}$	Viscosity η.10^{3} poise
	DMF			THF		
	RAT-1					
0.00	0.9338	1.4280	7.4521	0.8798	1.2152	4.7004
0.01	0.9413	1.4288	7.5964	0.8832	1.2172	4.8664
0.02	0.9433	1.4296	7.6368	0.8868	1.2232	4.9670
0.04	0.9470	1.4304	7.6961	0.8898	1.2268	5.1842
0.06	0.9481	1.4316	7.7658	0.8941	1.2300	5.3508
0.08	0.9523	1.4336	8.0506	0.8972	1.2336	5.4109
0.10	0.9569	1.4360	8.5263	0.9005	1.2384	5.6361
	RAT-2					
0.01	0.9427	1.4312	7.5886	0.8822	1.2196	4.9138
0.02	0.9447	1.4344	7.6723	0.8843	1.2252	5.0558
0.04	0.9453	1.4376	7.7378	0.8863	1.2336	5.1527
0.06	0.9466	1.4408	7.8234	0.8891	1.2380	5.3055
0.08	0.9485	1.4436	7.9607	0.8925	1.2448	5.4265
0.10	0.9494	1.4460	8.1469	0.8962	1.2616	5.6246
	RAT-3					
0.01	0.9409	1.4296	7.5822	0.884	1.2172	4.8685
0.02	0.9418	1.4328	7.6589	0.8864	1.2208	5.0264
0.04	0.9462	1.4352	7.7068	0.8886	1.2272	5.1773
0.06	0.9484	1.4368	7.9183	0.8917	1.2348	5.1542
0.08	0.9495	1.4400	8.1305	0.8941	1.2368	5.3098
0.10	0.9553	1.4424	8.6519	0.8978	1.2536	5.4791
	RAT-4					
0.01	0.9434	1.4272	7.9905	0.8832	1.2044	5.0384
0.02	0.9457	1.4284	8.3062	0.8861	1.2080	5.1401
0.04	0.9471	1.4340	8.5554	0.8900	1.2112	5.2127
0.06	0.9485	1.4460	8.8266	0.8948	1.2224	5.3405
0.08	0.9504	1.4516	9.1002	0.8981	1.2256	5.4700
0.10	0.9527	1.4568	9.4756	0.9002	1.2348	5.7679
	RAT-5					
0.01	0.9421	1.4344	7.8053	0.8845	1.2064	4.9954
0.02	0.9438	1.4364	8.0776	0.8872	1.2104	4.9499
0.04	0.9468	1.4412	8.3665	0.8898	1.2136	5.2735
0.06	0.9479	1.4500	8.6629	0.8925	1.2184	5.4307
0.08	0.9494	1.4568	8.8725	0.8960	1.2228	5.6706
0.10	0.9512	1.4668	9.1587	0.8991	1.2288	6.2512

Continue…..

….. Continue

Conc. M	Density ρ g.cm^{-3}	Velocity U. 10^{-5} cm.s^{-1}	Viscosity η.10^{3} poise	Density ρ g.cm^{-3}	Velocity U. 10^{-5} cm.s^{-1}	Viscosity η.10^{3} poise
	DMF			THF		
	RAT-6					
0.00	0.9338	1.4280	7.4521	0.8798	1.2152	4.7004
0.01	0.9431	1.4316	7.9467	0.8812	1.2244	4.9210
0.02	0.9448	1.4364	8.2397	0.8862	1.2316	5.1213
0.04	0.9454	1.4396	8.4966	0.8904	1.2380	5.2640
0.06	0.9481	1.4424	8.7833	0.8935	1.2428	5.5166
0.08	0.9521	1.4472	8.9578	0.8962	1.2500	5.7070
0.10	0.9574	1.4524	9.3023	0.8992	1.2572	5.8350
	RAT-7					
0.01	0.9431	1.4304	7.7128	0.8836	1.2172	4.9131
0.02	0.9454	1.4336	7.8145	0.8865	1.2232	5.0543
0.04	0.9471	1.4364	8.0239	0.8905	1.2276	5.1458
0.06	0.9489	1.4396	8.2055	0.8954	1.2332	5.2776
0.08	0.9506	1.4428	8.3513	0.8982	1.2376	5.5031
0.10	0.9514	1.4452	8.5413	0.9022	1.2420	5.7295
	RAT-8					
0.01	0.9413	1.4320	7.9164	0.8871	1.2192	4.8951
0.02	0.9437	1.4344	8.2130	0.8894	1.2256	4.9685
0.04	0.9450	1.4376	8.4718	0.8924	1.2292	5.0520
0.06	0.9486	1.4416	8.7180	0.8947	1.2352	5.2114
0.08	0.9533	1.4460	8.9762	0.8981	1.2368	5.3635
0.10	0.9552	1.4516	9.3024	0.9002	1.2396	5.5506
	RAT-9					
0.01	0.9420	1.4224	7.7340	0.8864	1.2184	4.9594
0.02	0.9456	1.4276	7.8505	0.8892	1.2236	5.1027
0.04	0.9482	1.4312	8.0585	0.8942	1.2292	5.2084
0.06	0.9512	1.4336	8.2477	0.8974	1.2356	5.4578
0.08	0.9532	1.4368	8.4036	0.9005	1.2424	5.5669
0.10	0.9563	1.4408	8.6078	0.9044	1.2472	5.7197
	RAT-10					
0.01	0.9442	1.4332	7.8025	0.8933	1.2112	4.9095
0.02	0.9445	1.4364	8.0634	0.8956	1.2136	5.0260
0.04	0.9452	1.4408	8.2816	0.8975	1.2184	5.1541
0.06	0.9493	1.4460	8.6128	0.8991	1.2232	5.2992
0.08	0.9513	1.4496	8.8516	0.9015	1.2252	5.5001
0.10	0.9535	1.4552	9.1483	0.9026	1.2288	5.6154

5. Rao's molar sound function:

Rao's molar sound function (R_m) can be evaluated by an equation given by Bagchi et al.[76].

$$R_m = \left(\frac{M}{\rho}\right) U^{1/3} \qquad \ldots (3.1.10)$$

6. Van der Waals Constant:

Van der Waals constant (b) can be calculated as follows[77]:

$$b = \frac{M}{\rho}\left\{1 - \left(\frac{RT}{MU^2}\right)\left[\sqrt{1 + \frac{MU^2}{3RT}} - 1\right]\right\} \qquad \ldots (3.1.11)$$

where R is the gas constant (=8.3143 JK^{-1} mol^{-1}) and T is the absolute temperature.

7. Relaxation Strength:

The relaxation strength (r) can be calculated as follows[78]:

$$r = 1 - \left[\frac{U}{U_\infty}\right]^2 \qquad \cdots (3.1.12)$$

where U_∞ = 1.6 x 10^5 cm $\cdot sec^{-1}$.

8. Relative Association (R_A):

$$R_A = \frac{\rho}{\rho_0}\left(\frac{U_0}{U}\right)^{1/3} \qquad \ldots (3.1.13)$$

where U, U_0 and ρ, ρ_0 are ultrasonic velocities and densities of solution and solvent respectively.

9. Internal Pressure:

Suryanarayana and Kuppuswamy[79] gave the following equation for evaluating internal pressure:

$$\pi = bRT\left[\frac{K_\eta}{U}\right]^{1/2} \frac{\rho^{2/3}}{M^{7/6}} \qquad \ldots (3.1.14)$$

where b is the packing factor (= 2). K is a constant (=4.28 X 10^9). The internal pressure (π) depends on temperature, density, ultrasonic velocity and specific heat at constant pressure.

10. Free Volume:

Free volume[80] can be calculated according to equation (3.1.15):

$$V_f = \left[\frac{MU}{K_n}\right]^{3/2} \quad \ldots (3.1.15)$$

11. Apparent Molar Compressibility (ϕ_k):

The apparent molar compressibility (ϕ_K) of the solutions was calculated by the following equation:

$$\phi_K = \frac{\left(\rho_0\kappa_s - \rho\kappa_s^0\right)1000}{c\rho_0} + \frac{\kappa_s^0 M_2}{\rho_0} \quad \ldots (3.1.16)$$

where ρ_0 and κ_s^0 are density and isentropic compressibility of pure solvent respectively, c is the concentration of the solution and M_2 is the molecular weight of the compound.

12. Solvation number:

$$S_n = \frac{M_2}{M_1}\left[\frac{1-\kappa_s}{\kappa_s^0}\right]\left[\frac{100-X}{X}\right] \quad \cdots (3.1.17)$$

where X is the number of grams of solute in 100 gm of the solution. M_1 and M_2 are the molecular weights of solvent and solute respectively.

Some of the calculated acoustical parameters are given in Tables 3.1.2 and 3.1.3 for compounds in DMF and THF solutions respectively.

Figure 3.1.1 shows the variation of ultrasound velocity (U) with concentration in DMF and THF. It is observed that overall ultrasonic velocity (U) increases with concentration for all the compounds in both the solvents. The velocity depends on intermolecular free length (L_f). Comparison of ultrasonic velocity and intermolecular free length (Tables 3.1.2 and 3.1.3) shows these two parameters are inversely related. Decrease in the free length causes velocity to increase or vice versa. It is evident from Tables 3.1.2 and 3.1.3 that L_f decrease continuously which is due to strong interaction between solvents and compound molecules. This causes velocity to increase.

The isentropic compressibility (κ_s) of the solutions in both the solvents is also found to decrease with increase of concentration, as shown in Figure 3.1.2. This phenomenon can be explained by assuming that the solvated

Table 3.1.2: Some acoustical parameters of RAT series in DMF at 308.15 K.

Conc. M	Z .10^{-5} g.cm^{-2}	L_f A^o	$R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$	*b* $cm^3.mol^{-1}$	*r*	R_A
			RAT-1			
0.00	1.3335	0.1519	4.0912	78.2697	0.2034	1.0000
0.01	1.3449	0.1512	4.1462	79.3078	0.2026	1.0078
0.02	1.3485	0.1509	4.2245	80.7909	0.2017	1.0098
0.04	1.3546	0.1506	4.3799	83.7459	0.2008	1.0136
0.06	1.3573	0.1504	4.5470	86.9172	0.1994	1.0145
0.08	1.3652	0.1498	4.6967	89.7378	0.1972	1.0185
0.10	1.3741	0.1492	4.8419	92.4603	0.1945	1.0228
			RAT-2			
0.01	1.3492	0.1508	4.1291	78.9375	0.1999	1.0088
0.02	1.3551	0.1503	4.1966	80.1681	0.1963	1.0102
0.04	1.3590	0.1499	4.3436	82.9134	0.1927	1.0101
0.06	1.3639	0.1495	4.4867	85.5822	0.1891	1.0107
0.08	1.3693	0.1491	4.6255	88.1731	0.1859	1.0121
0.10	1.3728	0.1488	4.7687	90.8528	0.1832	1.0125
			RAT-2			
0.01	1.3451	0.1511	4.1416	79.2058	0.2017	1.0072
0.02	1.3494	0.1507	4.2204	80.6525	0.1981	1.0074
0.04	1.3580	0.1501	4.3605	83.2827	0.1954	1.0116
0.06	1.3627	0.1498	4.5087	86.0808	0.1936	1.0136
0.08	1.3673	0.1494	4.6634	88.9691	0.1900	1.0140
0.10	1.3779	0.1487	4.7892	91.3186	0.1873	1.0196
			RAT-4			
0.01	1.3464	0.1512	4.1299	79.0253	0.2043	1.0105
0.02	1.3508	0.1509	4.2015	80.3738	0.2030	1.0126
0.04	1.3581	0.1502	4.3618	83.3303	0.1967	1.0128
0.06	1.3715	0.1488	4.5281	86.2690	0.1832	1.0115
0.08	1.3796	0.1481	4.6847	89.1367	0.1769	1.0122
0.10	1.3879	0.1474	4.8376	91.9358	0.1710	1.0135
			RAT-5			
0.01	1.3513	0.1505	4.2040	80.3085	0.1963	1.0074
0.02	1.3557	0.1502	4.3405	82.8776	0.1940	1.0087
0.04	1.3645	0.1495	4.6139	88.0005	0.1886	1.0108
0.06	1.3745	0.1485	4.9004	93.2761	0.1787	1.0099
0.08	1.3831	0.1477	5.1817	98.4765	0.1710	1.0100
0.10	1.3952	0.1465	5.4639	103.6024	0.1596	1.0096

Continue…..

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Conc. M	Z .10^{-5} g.cm^{-2}	L_f A^o	$R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$	b $cm^3.mol^{-1}$	r	R_A
			RAT-6			
0.00	1.3501	0.1519	4.1426	79.1881	0.2034	1.0000
0.01	1.3571	0.1508	4.2279	80.7268	0.1994	1.0091
0.02	1.3610	0.1501	4.4045	84.0375	0.1940	1.0098
0.04	1.3675	0.1497	4.5692	87.1241	0.1904	1.0097
0.06	1.3779	0.1492	4.7270	90.0330	0.1873	1.0119
0.08	1.3905	0.1484	4.8751	92.7418	0.1819	1.0151
0.10	1.3501	0.1.475	4.1426	79.1881	0.1760	1.0195
			RAT-7			
0.01	1.3490	0.1509	4.1466	79.2858	0.2008	1.0094
0.02	1.3553	0.1504	4.2325	80.8679	0.1972	1.0111
0.04	1.3604	0.1499	4.4130	84.2621	0.1940	1.0123
0.06	1.3660	0.1495	4.5923	87.6211	0.1904	1.0134
0.08	1.3715	0.1490	4.7711	90.9652	0.1868	1.0145
0.10	1.3750	0.1487	4.9535	94.3907	0.1841	1.0148
			RAT-8			
0.01	1.3479	0.1509	4.1511	79.3428	0.1990	1.0071
0.02	1.3536	0.1504	4.2310	80.8248	0.1963	1.0091
0.04	1.3585	0.1500	4.4045	84.0759	0.1927	1.0097
0.06	1.3675	0.1493	4.5657	87.0729	0.1882	1.0126
0.08	1.3785	0.1484	4.7189	89.9030	0.1832	1.0166
0.10	1.3866	0.1477	4.8874	92.9933	0.1769	1.0173
			RAT-9			
0.01	1.3399	0.1518	4.1438	79.3805	0.1972	1.0101
0.02	1.3499	0.1510	4.2256	80.8500	0.1949	1.0127
0.04	1.3571	0.1504	4.4021	84.1561	0.1922	1.0147
0.06	1.3636	0.1499	4.5735	87.3837	0.1859	1.0173
0.08	1.3696	0.1494	4.7495	90.6788	0.1832	1.0187
0.10	1.3778	0.1488	4.9184	93.8175	0.1742	1.0211
			RAT-10			
0.01	1.3532	0.1505	4.1312	78.9403	0.1976	1.0099
0.02	1.3567	0.1.501	4.2132	80.4465	0.1940	1.0095
0.04	1.3618	0.1496	4.3746	83.4435	0.1891	1.0092
0.06	1.3727	0.1488	4.5187	86.0894	0.1832	1.0124
0.08	1.3790	0.1482	4.6706	88.9091	0.1792	1.0137
0.10	1.3875	0.1475	4.8225	91.6820	0.1728	1.0147

Table 3.1.3: Some acoustical parameters of RAT series in THF at 308.15 K.

Conc. M	Z .10^{-5} g.cm^{-2}	L_f A^o	$R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$	*b* $cm^3.mol^{-1}$	r	R_A
RAT-1						
0.00	1.0691	0.1839	4.0591	81.9481	0.4232	1.0000
0.01	1.0750	0.1833	4.1395	83.5256	0.4213	1.0033
0.02	1.0847	0.1820	4.2223	85.0564	0.4155	1.0058
0.04	1.0916	0.1812	4.3969	88.4869	0.4121	1.0082
0.06	1.0997	0.1803	4.5615	91.7198	0.4090	1.0122
0.08	1.1068	0.1794	4.7309	95.0333	0.4056	1.0147
0.10	1.1152	0.1784	4.8985	98.2733	0.4009	1.0171
RAT-2						
0.01	1.0759	0.1830	4.1329	83.3364	0.4190	1.0015
0.02	1.0834	0.1820	4.2088	84.7383	0.4136	1.0024
0.04	1.0933	0.1805	4.3675	87.7326	0.4056	1.0024
0.06	1.1007	0.1796	4.5160	90.6090	0.4013	1.0043
0.08	1.1110	0.1783	4.6624	93.3762	0.3947	1.0063
0.10	1.1306	0.1755	4.8180	96.0615	0.3783	1.0060
RAT-3						
0.01	1.0760	0.1832	4.1280	83.2935	0.4213	1.0042
0.02	1.0821	0.1824	4.2063	84.7887	0.4178	1.0060
0.04	1.0905	0.1812	4.3734	88.0039	0.4117	1.0067
0.06	1.1011	0.1798	4.5358	91.0839	0.4044	1.0081
0.08	1.1058	0.1793	4.6937	94.2036	0.4025	1.0103
0.10	1.1255	0.1765	4.8609	97.1233	0.3861	1.0099
RAT-4						
0.01	1.0740	0.1835	4.1324	83.4087	0.4224	1.0036
0.02	1.0793	0.1829	4.2083	84.8943	0.4205	1.0064
0.04	1.0865	0.1820	4.3658	88.0049	0.4178	1.0100
0.06	1.0938	0.1813	4.5142	90.9560	0.4163	1.0150
0.08	1.1007	0.1805	4.6703	94.0190	0.4132	1.0179
0.10	1.1116	0.1789	4.8397	97.1868	0.4044	1.0177
RAT-5						
0.01	1.0752	0.1834	4.1917	84.6147	0.4228	1.0052
0.02	1.0792	0.1830	4.3321	87.4309	0.4220	1.0081
0.04	1.0848	0.1823	4.6259	93.2879	0.4194	1.0103
0.06	1.0896	0.1818	4.9144	99.0620	0.4178	1.0129
0.08	1.0956	0.1811	5.1944	104.6497	0.4159	1.0163
0.10	1.1048	0.1799	5.4793	110.2100	0.4102	1.0182

Continue…..

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Conc. M	Z .10^{-5} g.cm^{-2}	L_f A^o	$R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$	b $cm^3.mol^{-1}$	r	R_A
			RAT-6			
0.00	1.0691	0.1839	4.0591	81.9481	0.4232	1.0000
0.01	1.0789	0.1824	4.1593	83.7594	0.4144	1.0011
0.02	1.0914	0.1808	4.2389	85.1956	0.4075	1.0028
0.04	1.1023	0.1795	4.4148	88.5789	0.4013	1.0058
0.06	1.1104	0.1785	4.5924	92.0221	0.3967	1.0080
0.08	1.1203	0.1772	4.7734	95.4649	0.3896	1.0091
0.10	1.1305	0.1759	4.9509	98.8256	0.3826	1.0105
			RAT-7			
0.01	1.0755	0.1832	4.1451	83.6381	0.4213	1.0038
0.02	1.0844	0.1820	4.2387	85.3869	0.4155	1.0054
0.04	1.0932	0.1810	4.4237	89.0069	0.4113	1.0087
0.06	1.1042	0.1797	4.6020	92.4539	0.4059	1.0128
0.08	1.1116	0.1787	4.7883	96.0817	0.4017	1.0147
0.10	1.1205	0.1777	4.9647	99.5040	0.3974	1.0180
			RAT-8			
0.01	1.0816	0.1826	4.1251	83.1895	0.4194	1.0072
0.02	1.0900	0.1814	4.2161	84.8753	0.4132	1.0080
0.04	1.0969	0.1805	4.3936	88.3634	0.4098	1.0105
0.06	1.1051	0.1794	4.5761	91.8835	0.4040	1.0114
0.08	1.1108	0.1789	4.7449	95.2312	0.4025	1.0148
0.10	1.1159	0.1783	4.9212	98.6951	0.3998	1.0164
			RAT-9			
0.01	1.0800	0.1828	4.1331	83.3675	0.4201	1.0066
0.02	1.0880	0.1817	4.2257	85.1153	0.4152	1.0084
0.04	1.0992	0.1804	4.4057	88.6055	0.4098	1.0125
0.06	1.1088	0.1791	4.5934	92.2213	0.4036	1.0144
0.08	1.1188	0.1778	4.7802	95.7960	0.3970	1.0160
0.10	1.1280	0.1768	4.9571	99.2144	0.3924	1.0191
			RAT-10			
0.01	1.0820	0.1831	4.0784	82.4271	0.4270	1.0165
0.02	1.0869	0.1825	4.1550	83.9196	0.4247	1.0184
0.04	1.0935	0.1816	4.3200	87.1374	0.4201	1.0192
0.06	1.0998	0.1808	4.4856	90.3609	0.4155	1.0197
0.08	1.1045	0.1802	4.6423	93.4659	0.4136	1.0219
0.10	1.1091	0.1796	4.8076	96.7000	0.4102	1.0221

molecules are fully compressed by the electrical forces of the ions[81]. The compressibility of the solution is mainly due to the free solvent molecules. Due to solute-solvent interactions in the system, compressibility of the solution decreases with the increase in solute concentration. This is further confirmed by decrease of relaxation strength (r) and increase in specific impedance (Z) values (as reported in Tables 3.1.2 and 3.1.3). The increase in viscosity in both solvents also confirms the same. The association between solute and solvent molecules is further confirmed by relative association (R_A) values, which are found to increase continuously with concentration for all the compounds in both the solvents.

Further, Figure 3.1.3 shows variation of molar compressibility (W) with concentration for all the derivatives. There is linear increase in molar compressibility. Tables 3.1.2 and 3.1.3 shows that Vander Waal's constant (b) and Rao's molar sound function (R_m) also increases linearly with concentration for all the derivatives. The correlation coefficients for these parameters are in the range of 0.9800- 0.9979. The linear increase of these parameters suggests the absence of complex formation in these systems.

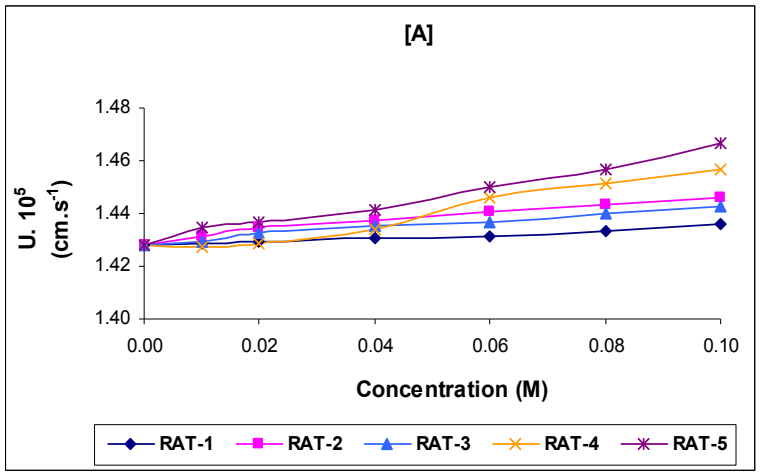
The interactions in a solution can also be confirmed by the solvation number, which is a measure of structure forming or structure breaking tendency of a solute in a solution. Figure 3.1.4 shows that for all the compounds, solvation number (S_n) increases with concentration. Further, these S_n values are positive for all the compounds in both the solvents. The positive S_n values suggest structure forming tendency of compounds in solution. This further confirms that there exist strong solute-solvent interactions in studied solutions.

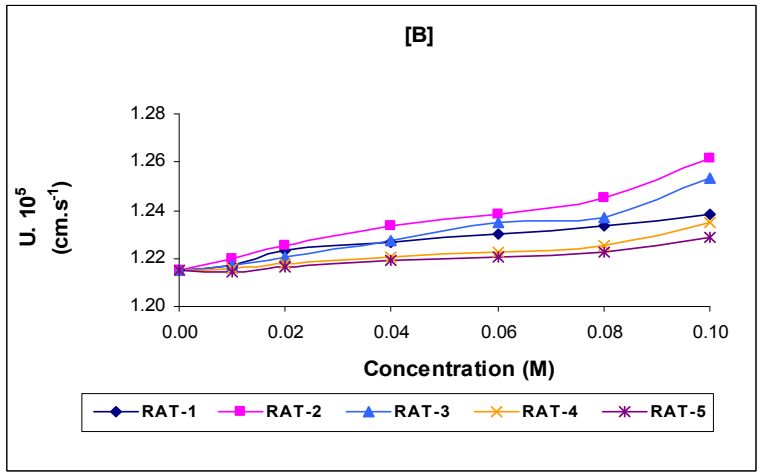
The isentropic compressibility of all the solutions were also fitted to the following Bachem's relation[82]:

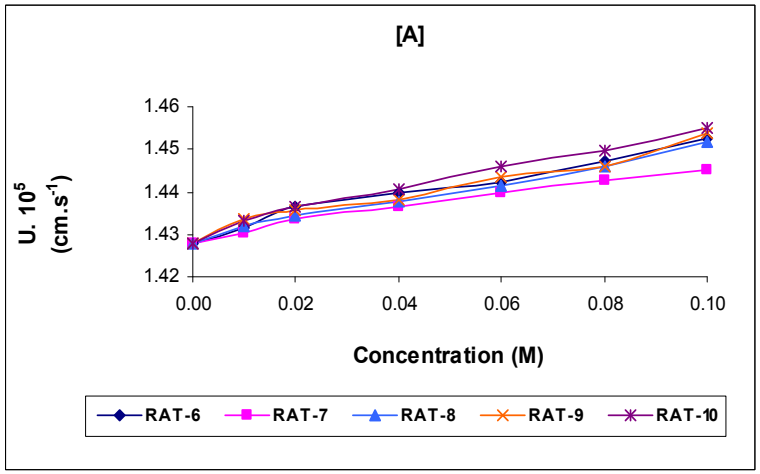
$$\kappa_s = \kappa_s^0 + AC + BC^{3/2} \qquad \ldots (3.1.18)$$

From the plot of $\left(\kappa_s - \kappa_s^0\right)/C$ verses $\sqrt{C}$, values of *A* and *B* were evaluated from the intercept and slope respectively. κ_s^0 is the isentropic compressibility of pure solvent.

Figure 3.1.1: Variation of ultrasonic velocity (*U*) of RAT series with concentration in [A] DMF and [B] THF at 308.15 K.







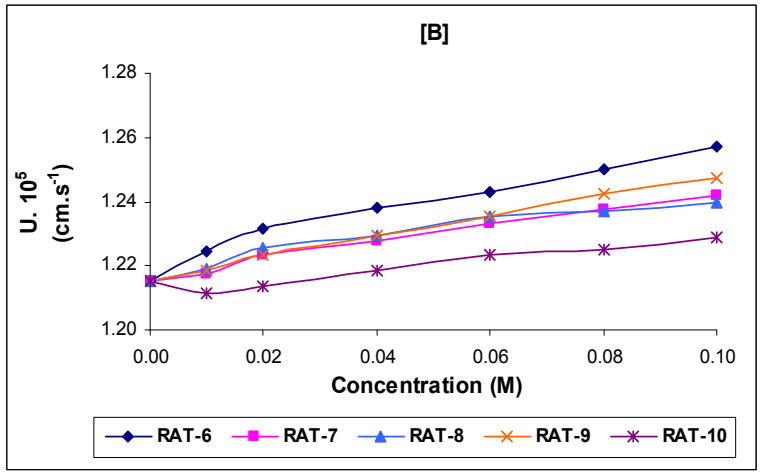


Figure 3.1.2: Variation of Isentropic compressibility (κ_s) of RAT series with concentration in [A] DMF and [B] THF at 308.15 K.

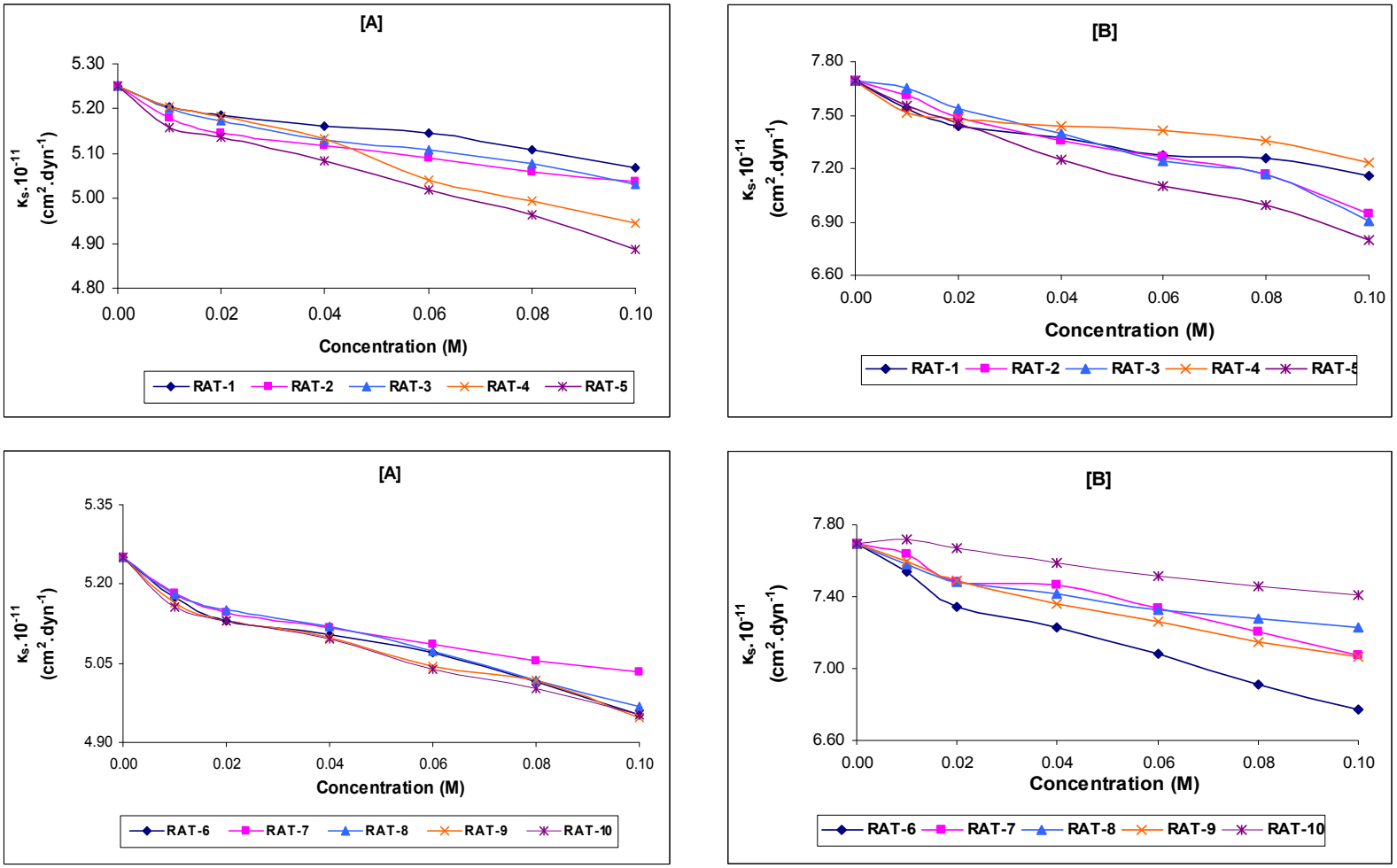
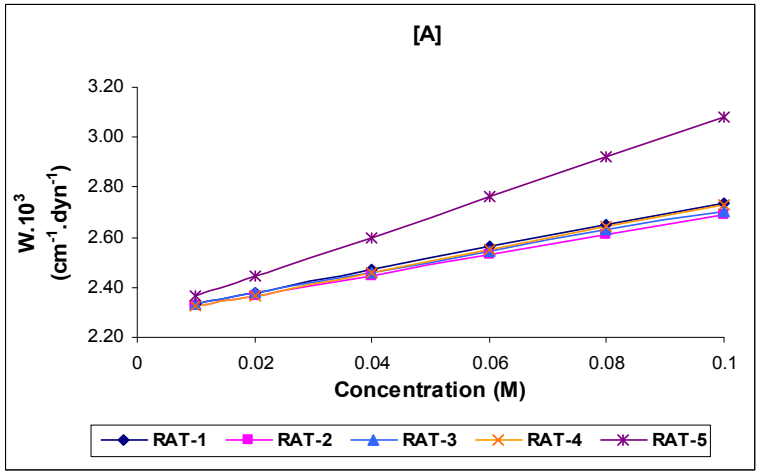
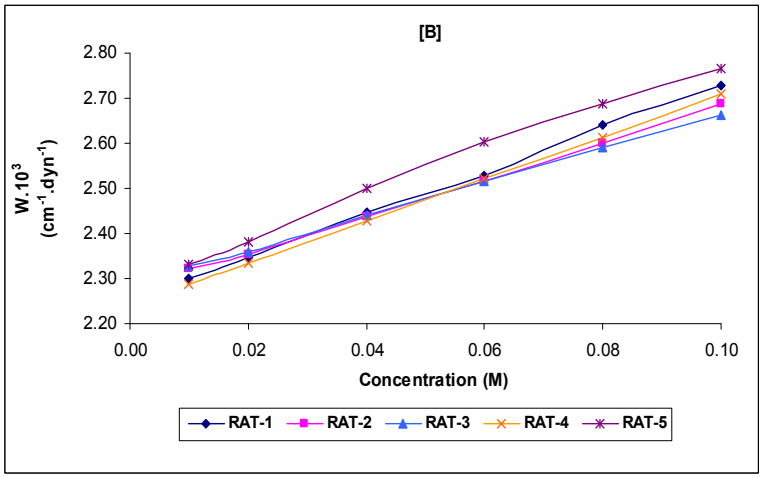
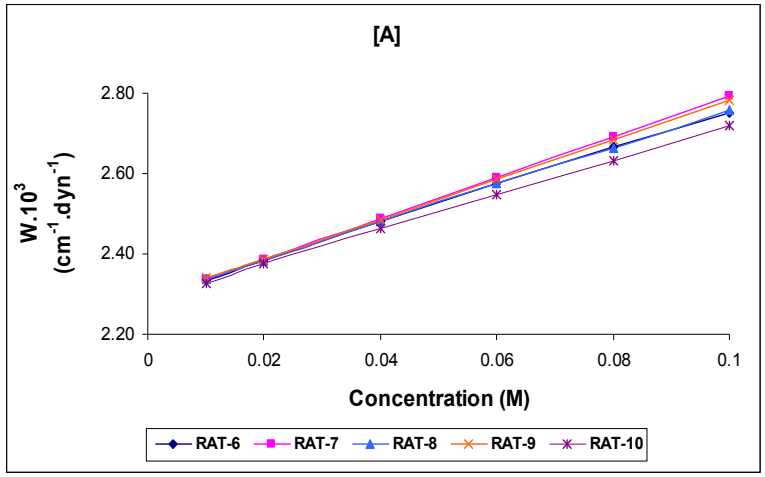
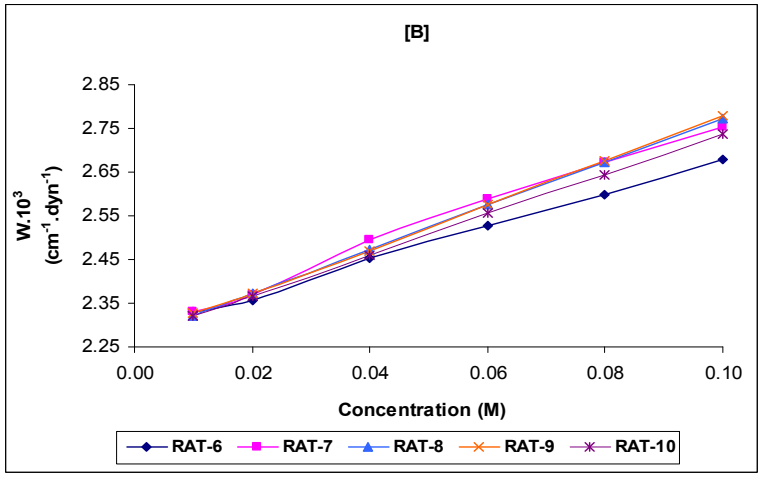


Figure 3.1.3: Variation of Molar compressibility (W) of RAT with concentration in [A] DMF and [B] THF at 308.15 K.









Further, the apparent molar compressibility (ϕ_k) of the solutions is fitted to Gucker's relation[83].

$$\phi_k = \phi^o_k + S_k \sqrt{C} \quad \text{… (3.1.19)}$$

From the plot of ϕ_k verses $\sqrt{C}$, ϕ^o_k and S_k values are evaluated from the intercept and slope.

The apparent molar volumes Φ_V of the solutions were calculated by the following equation:

$$\Phi_v = M/\rho - [1000(\rho-\rho_0)/\rho c] \quad \text{…. (3.1.20)}$$

and were fitted in the relation:

$$\Phi_V = \Phi_V^o + S_v C \quad \text{…. (3.1.21)}$$

From the plot of Φ_V verses C, Φ_V^o and S_v values were calculated from the intercept and slope respectively. S_v is the measure of solute-solvent interaction. All these values are given in Table 3.1.4.

It is evident from Table 3.1.4 that in DMF solutions, *A,* ϕ^o_k, and Φ_V^o values are negative whereas *B* and ϕ^o_k values are positive for all the compounds. The negative *A,* ϕ^o_k , Φ_V^o and positive *B* values indicate solute-solvent interactions in studied systems. This is again confirmed by the positive and higher S_k *and* S_v values, which are known as interaction parameters.

Thus, in the studied systems, solute-solvent interactions dominate in both DMF and THF solutions.

Figure 3.1.4: Variation of Solvation Number (S_n) of RAT series with concentration in [A] DMF and [B] THF at 308.15 K.

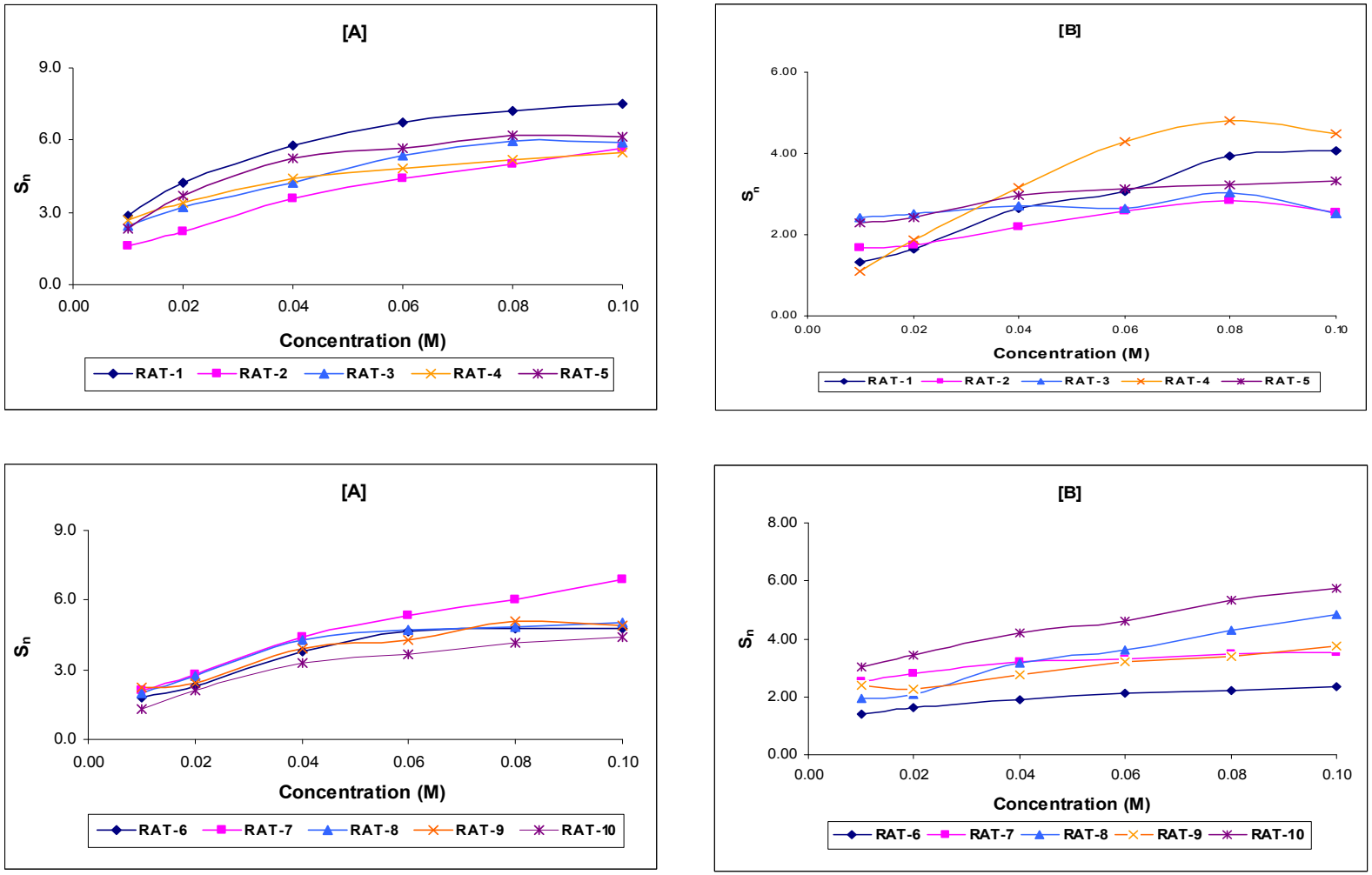


Table 3.1.4: Bachem's constants *A* and *B*, ϕ^{o}_{k} and S_k, Φ_V^{o} and S_v of RAT series DMF and THF at 308.15 K.

Comp.	$A \times 10^{11}$ $dyn^{-1}.cm^{3}$ mol^{-1}	$B \times 10^{11}$ $dyn^{-1}.cm^{-1/2}$ $mol^{3/2}$	$\phi^{o}_{k} \times 10^{8}$ $dyn^{-1}.mol^{1}$	$S_k \times 10^{8}$ $dyn^{-1}cm^{-3/2}$ $mol^{3/2}$	Φ_V^{o}	S_v
			DMF			
RAT-1	-5.38	12.96	-3.15	6.19	-721.00	10115.25
RAT-2	-8.83	23.16	-12.6	41.10	-782.20	9917.54
RAT-3	-6.07	13.63	-8.23	25.30	-407.32	3764.68
RAT-4	-4.70	5.68	-8.83	24.64	-618.00	6772.78
RAT-5	-10.02	23.14	-12.55	38.99	-521.00	5602.04
RAT-6	-9.27	22.64	-5.13	7.65	-537.65	5560.84
RAT-7	-8.42	21.43	-12.22	39.82	-545.71	5104.91
RAT-8	-8.02	18.61	-10.48	31.55	-466.93	4365.00
RAT-9	-3.83	5.83	-6.01	17.29	-608.97	6180.61
RAT-10	-10.76	27.60	-14.97	49.91	-524.55	5334.67
			THF			
RAT-1	-20.24	51.44	-33.04	99.86	-1098.06	11063.82
RAT-2	-14.38	28.22	-15.25	32.44	-531.96	4487.24
RAT-3	-8.42	3.43	-9.46	7.03	-491.67	1562.06
RAT-4	-4.77	1.77	-22.44	73.84	-1094.05	10218.58
RAT-5	-28.8	0.18	-16.59	40.80	-1785.39	10025.34
RAT-6	-20.34	37.15	-18.27	25.61	-960.14	5218.38
RAT-7	-14.23	28.05	-19.27	45.73	-766.20	5187.94
RAT-8	-14.56	32.95	-18.31	52.85	-690.00	6086.35
RAT-9	-12.06	18.41	-15.44	33.50	-663.37	4796.00
RAT-10	-3.31	1.52	-2.55	6.97	-317.46	2664.52

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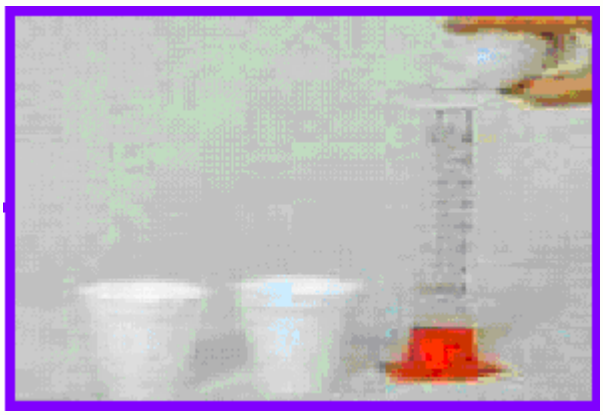


Section-II
Solubility

INTRODUCTION

Chemical such as trade-sales coating, pharmaceuticals, cosmetics and foodstuffs are produced as multicomponent chemical mixture. Often these mixtures or formulations include polymers and low molecular components of high and low boiling points. Basic knowledge of the miscibility of the various components is required to meet environmental, shelf life and product quality specifications. In this regard, solubility has played an important role in the development of stable commercial chemical formulation as well as for assessing phase segregation during product synthesis.

In 1936, Joel Hildebrand proposed[1] a simple definition for a "solubility" that would provide a systemic description of the miscibility behavior of solvents. The solubility of drug is essential information in drug discovery and is important in the preparation of drug formulation stages in the pharmaceutical industry. There are many methods for solubilization of drugs including cosolvency, surface active agents, salt information, complexation, hydrotropism, crystal engineering and preparation of soluble prodrug, and more recently, the addition of ionic liquids[2-9].

The extensive information on the thermodynamic properties of organic compounds is needed not only their use in many industrial processes but also for the advancement of theoretical developments through an understanding of the intermolecular forces in solution for structure-property relationship.

The process of dissolving is a process which involves the breaking and making of bonds and that involves energy which is in the form of heat. Thus, the process of dissolution is accompanied by the heat change i.e., enthalpy change (ΔH_{sol}). The interpretation of these heat transfer found in the literature,[10–15] may not be sufficient to provide a realistic picture of the interactions in solution. In most cases, the small values of the heat transfer results from the approximate cancellation of the component entropy and enthalpy contributions. These separate contributions can be calculated, if precise solubility data at different temperatures are available.

From the solubility measurements, melting temperature of a substance can also be determined[16]. Literature serve, shows that many researchers have been worked on solubility of some gases[17], organic compounds[18-20],

amino acids [21,22], polymers[23-25], ionic liquids[26,27], inorganic compounds[28-31], drugs[32-35], etc. In our laboratory, heat of solution of some synthesized heterocyclic compounds and drugs has also been determined[36,37]. From the solubility data, some thermodynamic parameters have also been reported[38-45].

In the present work, the solubility for some dihydropyrimidinthiones derivatives (RAT series) was determined in N, N-dimethylformamide (DMF) and tetrahyrofuran (THF) at different temperatures (303.15 to 323.15 K). Further, some thermodynamic parameters such as enthalpy, Gibb's energy and entropy have also been evaluated from the solubility data.

EXPERIMENTAL

The solubility of Dihydropyrimidinthiones derivatives (RAT series) has been studied in DMF and THF. These solvents were purified and fractionally distilled prior to use by the reported method[46].

The solubilities were measured by a gravimetric method[47]. For each measurement, an excess mass of dihydropyrimidinthiones was added to a known mass of solvent. Then, the equilibrium cell was heated to a constant temperature with continuous stirring. After few hours when the temperature of the water bath approached constant value, the actual value of the temperature was recorded. The stirring was stopped and the solution was kept still for 2 h. A portion of this solution was filtered and by a preheated injector, 2 ml of this clear solution was taken in another weighted measuring vial (m_0). The vial was quickly and tightly closed and weighted (m_1) to determine the mass of the sample (m_1- m_0). Then, the vial was covered with a piece of filter paper to prevent dust contamination. Then, the vial was kept at room temperature to evaporate the solvent. After the solvent in the vial had completely evaporated, the vial was dried and reweighed (m_2) to determine the mass of the constant residue solid (m_2- m_0). All the weights were taken using an electronic balance (Mettler Toledo AB204-S, Switzerland) with an accuracy of $\pm$ 0.0001 g. Thus, the solid concentration of the sample solution of mole fraction, x, could be determined from equation 3.2.1.

$$x = \frac{(m_2 - m_0)/M_1}{(m_2 - m_0)/M_1 + (m_1 - m_2)/M_2} \quad \text{.. (3.2.1)}$$

where M_1 is the molar mass of dihydropyrimidinthiones and M_2 is the molar mass of the solvent.

RESULTS AND DISCUSSION

Tables 3.2.1 and 3.2.2 shows, the solubility *(x)* of synthesized compounds in the DMF and THF respectively. It is evident from these Tables that the solubility increases with temperature in both the solvents. Comparison of solubility of these compounds in DMF and THF shows that overall solubility is greater in DMF than that in THF. The dielectric constant and dipole moment of DMF (36.71, 3.86) are greater than that of THF (7.58, 1.75). Thus, these properties of solvent play an important role on the solubility. Figure 3.2.1 shows the variation of mole fraction solubility (x) against temperature for RAT-1 in DMF and THF.

The temperature dependence solubility in solvents is described by the modified Apelblat equation[48, 49]

$$\ln x = A + BT \qquad \text{..... (3.2.2)}$$

where *x* is the mass fraction solubility of compounds; *T* is the absolute temperature and *A*, and *B* are the coefficients. The values of these coefficients are given in Table 3.2.3. Using these values of *A* and *B*, calculated solubilities x_c were evaluated and are reported in Tables 3.2.1 and 3.2.2.

The percentage relative deviations *(%RD)* between the experimental and calculated values of solubilities are also calculated by equation 3.2.3 and are given in Tables 3.2.1 and 3.2.2.

$$\%\ \textit{Relative Deviation} = \left(\frac{x - x_c}{x}\right) \cdot 100 \qquad \text{..... (3.2.3)}$$

Using these solubility values at different temperature in both the solvents, some thermodynamic parameter such as enthalpy, Gibb's energy and entropy have also been calculated.

According to van't Hoff equation[50], the standard enthalpy change of solution is obtained from the slope the *ln x* versus *1/T* plot. However, in recent thermodynamic treatments, some modifications have been introduced in the van't Hoff equation to diminish the propagation of errors and consequently to separate the chemical effects from those due to statistical treatment used when enthalpy-entropy compensation plots are developed[51]. For this reason,

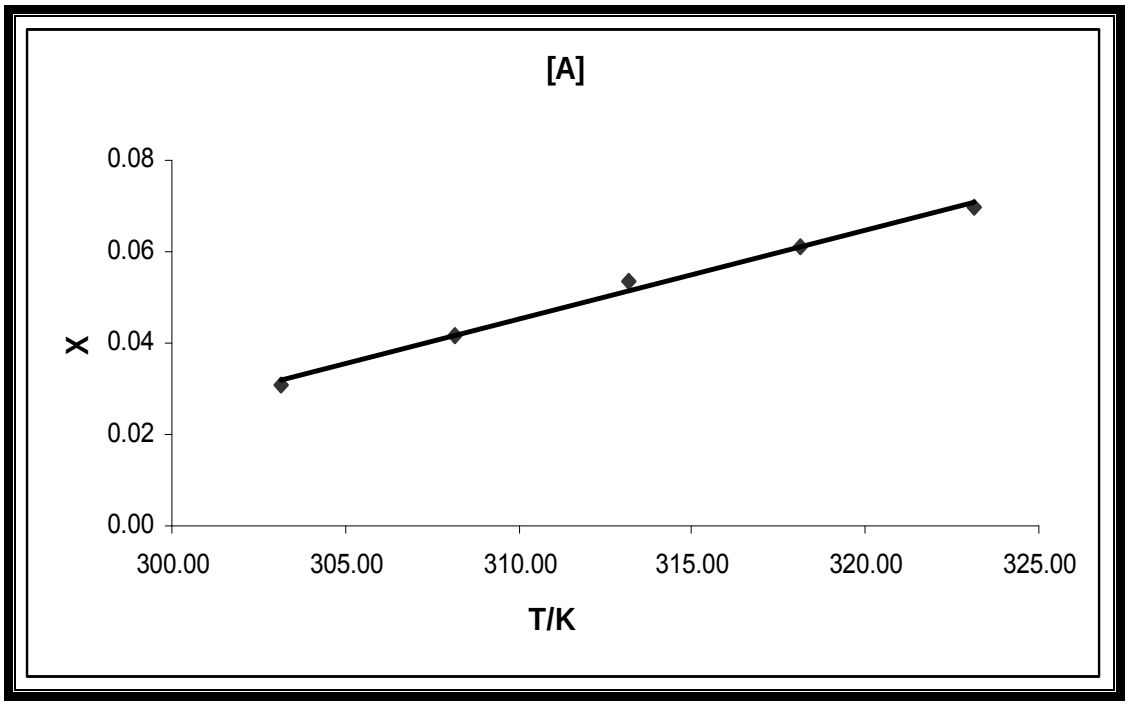
Table 3.2.1: The experimental solubility *(x)*, calculated solubility *(x_c)* and % relative deviation *(RD)* of RAT series in DMF at different temperatures.

Temp. K	x. 10^2	$x_c.10^2$	% RD	x. 10^2	$x_c.10^2$	%RD
	RAT-1			RAT-6		
303.15	3.1033	3.3084	-6.6070	2.8855	2.8470	1.3346
308.15	4.1796	4.0387	3.3707	3.5512	3.5921	-1.1524
313.15	5.3378	4.9302	7.6361	4.4767	4.5321	-1.2373
318.15	6.1341	6.0186	1.8834	5.6319	5.7182	-1.5315
323.15	6.9475	7.3472	-5.7535	7.2467	7.2146	0.4425
	RAT-2			RAT-7		
303.15	3.5019	3.4570	1.2828	3.0000	3.2309	-7.6979
308.15	4.4062	4.2264	4.0789	4.0419	3.9461	2.3691
313.15	5.3104	5.1672	2.6971	5.1641	4.8197	6.6693
318.15	6.4375	6.3173	1.8679	5.9361	5.8866	0.8340
323.15	7.6503	7.7234	-0.9549	6.7250	7.1896	-6.9082
	RAT-3			RAT-8		
303.15	2.9576	2.8728	2.8692	3.1007	2.9877	3.6445
308.15	3.2212	3.2487	-0.8535	3.7634	3.7116	1.3766
313.15	3.6787	3.6739	0.1329	4.4530	4.6109	-3.5460
318.15	4.1851	4.1546	0.7291	5.8554	5.7281	2.1745
323.15	4.6965	4.6983	-0.0393	7.3654	7.1160	3.3853
	RAT-4			RAT-9		
303.15	2.9652	2.8622	3.3075	2.2067	2.2680	-2.7804
308.15	3.1794	3.2684	-2.8006	3.0681	2.9194	4.8472
313.15	3.7468	3.7258	0.5612	3.9468	3.7578	4.7900
318.15	4.0482	4.2472	-4.9150	4.9705	4.8369	2.6876
323.15	4.9589	4.8413	2.3662	6.0478	6.2260	-2.9465
	RAT-5			RAT-10		
303.15	3.3579	3.4195	-1.8338	3.1697	3.3657	-6.1808
308.15	4.2091	4.2079	0.0303	4.0114	3.9436	1.6889
313.15	5.1011	5.1780	-1.5073	4.8826	4.6208	5.3608
318.15	6.4807	6.3718	1.6796	5.4430	5.4143	0.5281
323.15	7.6321	7.8409	-2.7352	6.0075	6.3440	-5.6018

Table 3.2.2: The experimental solubility *(x)*, calculated solubility *(x_c)* and % relative deviation *(RD)* of RAT series in THF at different temperatures.

Temp. K	x. 10^2	$x_c.10^2$	%RD	x. 10^2	$x_c.10^2$	% RD
	RAT-1			RAT-6		
303.15	3.8427	3.8944	-1.3459	7.9882	7.9987	-0.1321
308.15	4.6809	4.5700	2.3688	9.1685	8.8575	3.3923
313.15	5.5446	5.3626	3.2792	10.3143	9.8084	4.9048
318.15	6.4393	6.2931	2.2701	11.0636	10.8615	1.8270
323.15	7.2983	7.3849	-1.1855	11.4847	12.0276	-4.7277
	RAT-2			RAT-7		
303.15	3.8905	3.9590	-1.7627	5.8449	5.8741	-0.4986
308.15	4.9825	4.8451	2.7584	6.6823	6.5734	1.6302
313.15	6.0185	5.9294	1.4792	7.3915	7.3559	0.4808
318.15	7.4377	7.2565	2.4363	8.2394	8.2317	0.0937
323.15	8.6098	8.8805	-3.1439	9.0926	9.2117	-1.3093
	RAT-3			RAT-8		
303.15	4.7033	4.7055	-0.0468	2.1180	2.0995	0.8742
308.15	5.7597	5.8486	-1.5435	2.8161	2.7187	3.4578
313.15	7.1539	7.2693	-1.6126	3.6401	3.5205	3.2852
318.15	9.0958	9.0352	0.6667	4.6049	4.5589	1.0008
323.15	11.0525	11.2300	-1.6058	5.7744	5.9034	-2.2341
	RAT-4			RAT-9		
303.15	2.9890	3.0323	-1.4477	3.2051	3.1260	2.4682
308.15	3.8176	3.6832	3.5211	3.8546	3.7875	1.7394
313.15	4.6254	4.4739	3.2763	4.7952	4.5891	4.2994
318.15	5.4863	5.4342	0.9494	5.6862	5.5602	2.2148
323.15	6.3585	6.6008	-3.8101	6.5467	6.7370	-2.9064
	RAT-5			RAT-10		
303.15	4.9367	4.9918	-1.1175	4.2472	4.1582	2.0961
308.15	5.7410	5.7047	0.6335	4.5860	4.6788	-2.0249
313.15	6.6063	6.5193	1.3176	5.0537	5.2647	-4.1767
318.15	7.4356	7.4502	-0.1962	5.8883	5.9240	-0.6057
323.15	8.2244	8.5140	-3.5209	6.7587	6.6658	1.3749

Figure 3.2.1: The mole fraction solubility (x) against temperature (T/K) for RAT-1 in [A] DMF and [B] THF.



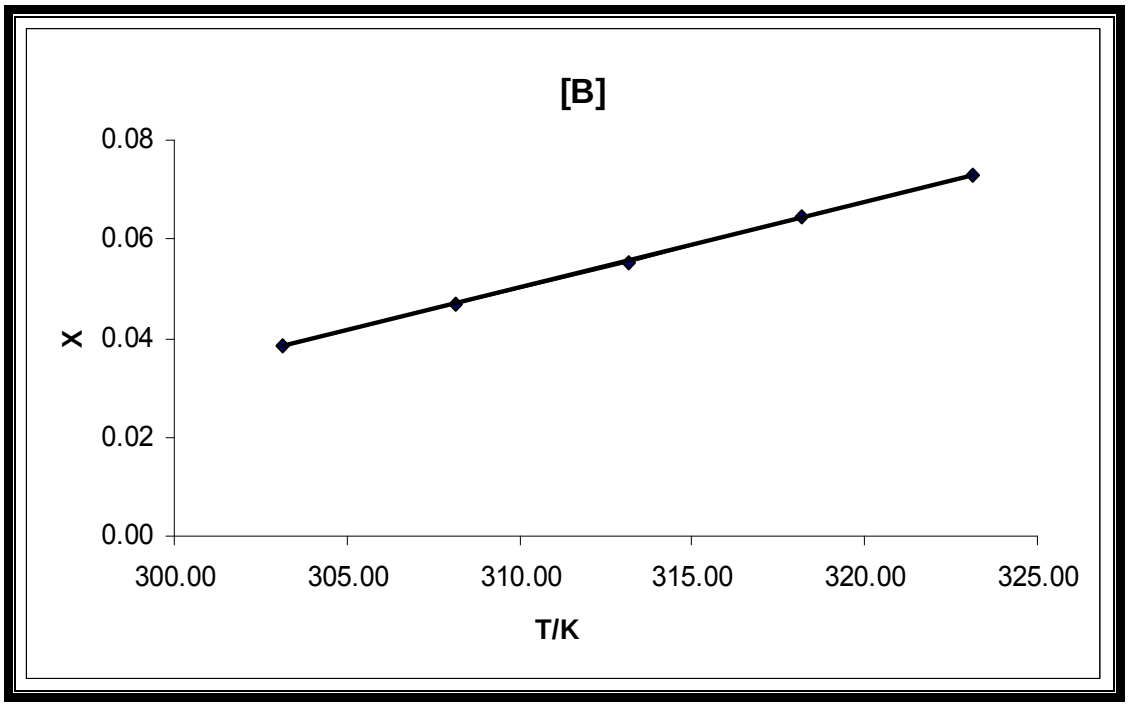


Table 3.2.3: Coefficient *A* and *B* of RAT series in DMF and THF from equation 3.2.2.

Compounds	***A***	***B***	***A***	***B***
	DNF		***THF***	
RAT-1	-15.5047	0.0399	-12.9472	0.0320
RAT-2	-15.1075	0.0388	-15.2808	0.0398
RAT-3	-10.7297	0.0237	-16.1934	0.0433
RAT-4	-11.2465	0.0254	-14.8278	0.0374
RAT-5	-15.9565	0.0415	-10.7493	0.0256
RAT-6	-17.5209	0.0461	-8.0351	0.0183
RAT-7	-15.5586	0.0400	-9.4557	0.0219
RAT-8	-16.6677	0.0434	-18.9763	0.0500
RAT-9	-18.9179	0.0500	-14.4467	0.0363
RAT-10	-13.0020	0.0317	-10.3353	0.0236

the mean harmonic temperature (T_{hm}) is used in the van't Hoff analysis, which is calculated by the following equation.

$$T_{hm} = \frac{n}{\sum_{i}^{n}\left(1/T\right)} \quad \text{..... (3.2.4)}$$

where *n* is the number of temperatures studied and *T* is absolute temperature of the experiment. In the present case, the T_{hm} value obtained is 308 K.

So, the modified van't Hoff equation is [52, 53].

$$\frac{\partial \ln x}{\partial\left(1/T - 1/T_{hm}\right)_P} = -\frac{\Delta H_{sol}}{R} \quad \text{..... (3.2.5)}$$

where ΔH_{sol} is the heat of solution and *R* is the gas constant.

Figure 3.2.2 shows the van't Hoff plots for RAT-1 in DMF and THF solutions. The slope of these linear plots gives the values of ΔH_{sol} whereas Gibb's free energy of dissolution (ΔG_{sol}) were evaluated from the intercept using the following equation[53].

$$\Delta G_{sol} = -RT_{hm}.\ intercept \quad \text{..... (3.2.6)}$$

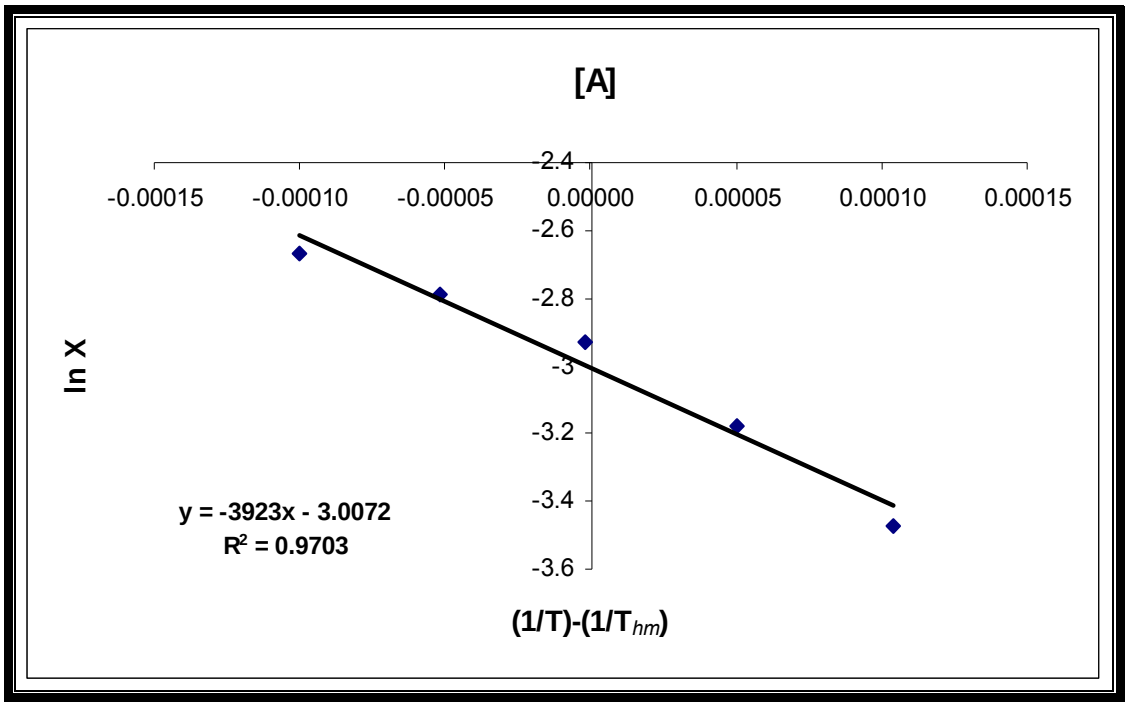
Using these evaluated ΔH_{sol} and ΔG_{sol} values, the entropies of solutions ΔS_{sol} were obtained from equation[54] .

$$\Delta S_{sol} = \frac{\Delta H_{sol} - \Delta G_{sol}}{T_{hm}} \quad \text{..... (3.2.7)}$$

All these thermodynamic parameters are given in Table 3.2.4.

It is evident from Table 3.2.4 that for all the compounds ΔH_{sol} , ΔG_{sol} and ΔS_{sol} values are positive. The positive ΔH_{sol} is due to absorption of energy i.e. endothermic dissolution of compounds takes place. This causes decrease in solubility as evident by comparing theoretical and experimental values, which may be due to Van Der Waals and Lwis acid-base interactions between solute and solvent[54]. The positive ΔH_{sol} and ΔS_{sol} values in both solvents, suggest that solubility of compounds is entropy driving process[55]. Further, the positive values of ΔG_{sol} indicate that the dissolution process is not spontaneous[55].

Figure 3.2.2: van't Hoff plots for for RAT-1 in [A] DMF and [B] THF.



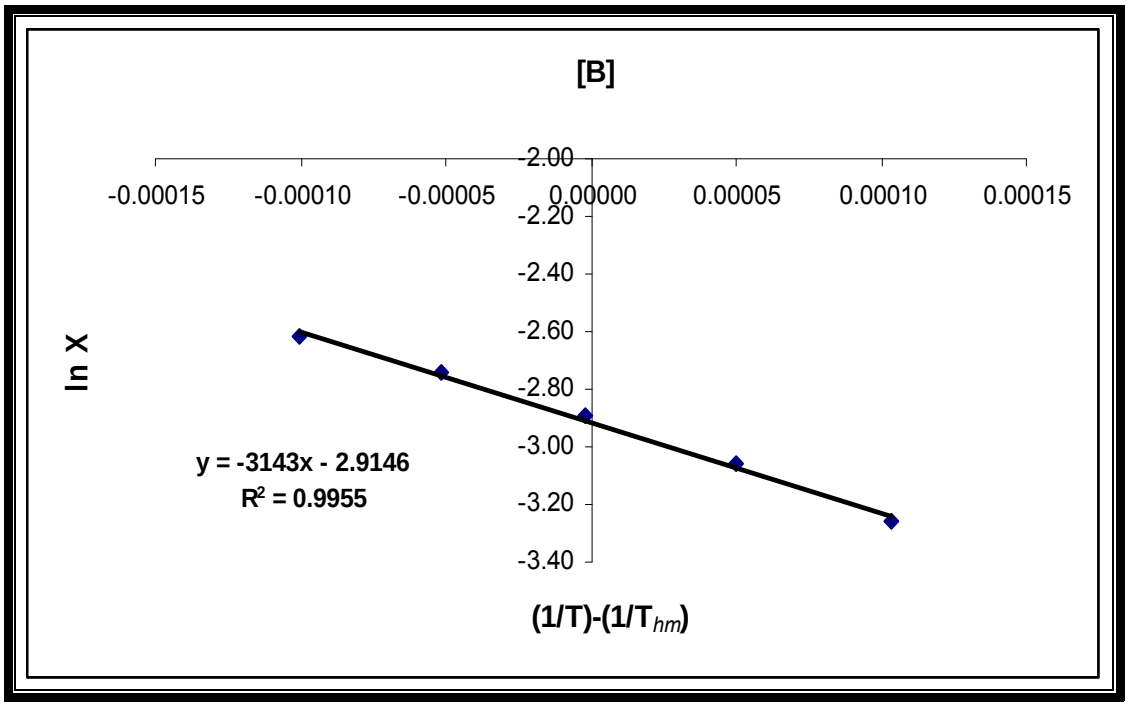


Table 3.2.4: The thermodynamic parameters of compounds in DMF and THF.

Compound code	ΔH_{sol} kJ.mol^{-1}	ΔG_{sol} kJ.mol^{-1}	ΔS_{sol} J.mol^{-1}.K^{-1}	ΔH_{sol} kJ.mol^{-1}	ΔG_{sol} kJ.mol^{-1}	ΔS_{sol} J.mol^{-1}.K^{-1}
	DMF			THF		
RAT-1	7.7950	1.8702	18.9296	6.2451	1.8126	14.1619
RAT-2	7.5655	1.8312	18.3208	7.7532	1.7546	19.1655
RAT-3	4.6720	2.0621	8.3386	8.4288	1.6354	21.7049
RAT-4	5.4745	2.0586	10.9139	7.3008	1.9288	17.1634
RAT-5	8.0759	1.8466	19.9026	4.9875	1.7015	10.4988
RAT-6	8.7445	1.9052	21.8517	3.5730	1.4371	6.8242
RAT-7	7.8079	1.8908	18.9049	4.2591	1.6224	8.4242
RAT-8	8.4443	1.9044	20.8950	9.7301	2.0731	24.4640
RAT-9	9.7442	2.0320	24.6405	7.0814	1.9064	16.5343
RAT-10	6.1875	1.9167	13.6451	4.5782	1.8349	8.7648

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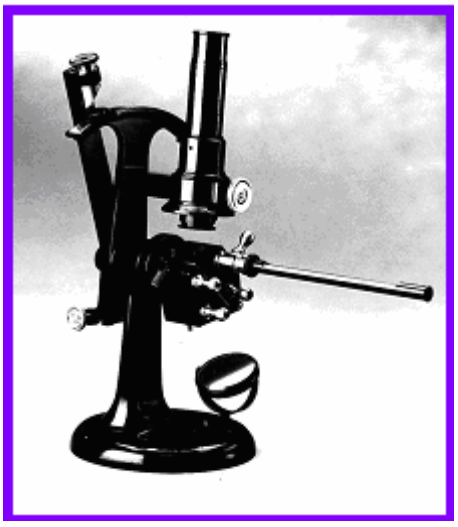


Section-III

Density and Refractive Index

INTRODUCTION

In 1621, Willebrord Snell, discovered the sinusoidal relationship between the angle of incidence and the angle of refraction when a light ray passes from one optically transparent medium to another. From that the refractive index of a medium is a measure of how much the speed of light is reduced inside the medium. It is a fundamental physical property of a substance, which depends upon temperature and the wavelength of the light used.

It is one of the physical constants that can be used to describe a chemical species. Further, it is useful for the identification of crystalline substance. Refractive index has used to measure solids, liquids, and gases. Most commonly it is used to measure the concentration of a solute in a solution. Specific and molar refractions have proved useful for analytical purposes since they are found to vary in a systematic way within homologous series of compounds. The molar refraction has been useful in structural studies. It is useful to identify a particular substance, purity of component and measurement of concentration. It also determines isotropic and anisotropic behavior of the crystal compounds. Various thermodynamic properties of chemical materials can be evaluated by refractive index.

Literature survey shows that much work has been done in liquid mixtures[1-15] and various polymers[16-20]. Many workers have been reported refractive index of amino acid[21-24], vitamins[25-27], medicine materials[28,29], complex refractive index[30-32], plant extracts[33,34], organic and inorganic compounds[35-38] etc.

By using the refractive index, Rangappa studied the milk constant[39]. Masuko and Awaya have been reported simple method for assaying sugars of silage materials[40]. Kashmiri and co-workers[41] studied the physico-chemical analysis of different types of honey produced in Pakistan. Glucose and fructose levels of grape skin have been reported by Varandas et al.[42].

Further, Deich[43] have been reported refractive index of C_6H_5X (X=halogen group). Kinart at al.[44] studied the refractive index of 1-butyl-3-methylimidazolium tetrafluoroborate and 1-butyl-2,3-dimethylimidazolium tetra

-fluoroborate. The refractive index of 1,4:3,6-Dianhydrohexitol-basedpolycarb -onate yhave been reported by Yamaoka and Nukui[45].

In the present section, the refractive indexes of solutions of RAT series have measured in N, N-dimethylformamide (DMF) and tetrahydrofuran (THF) at 308.15 K.

EXPERIMENTAL

The solvents DMF and THF were purified by fractionally distillation by the reported method[46]. For each compound, a series of solutions of different concentrations were prepared in these solvents.

The density and refractive index of pure solvents and solutions were measured by using pycnometer and Abbe refrectometer respectively at 308.15 K. The temperature was maintained by circulating water through jacket around the prisms of refractometer from an electronically controlled thermostatic water bath (NOVA NV-8550 E). The uncertainty of temperature was ± 0.1 ^{o}C.

RESULTS AND DISCUSSION

The density of solution (ρ_{12}) is related to densities of the solvent, solute and their weight fractions g_1 and g_2 according to the equation:

$$\frac{1}{\rho_{12}} = \frac{g_1}{\rho_1} + \frac{g_2}{\rho_2} \qquad \ldots (3.3.1)$$

where ρ_{12} is the density of solution and ρ_1 and ρ_2 are the densities of solvent and solute respectively. Tables 3.3.1 and 3.3.2 shows the experimental values of densities and refractive index for all the studied solutions.

The density of these compounds were determined from the slope of the plot of $1/g_1\rho_{12}$ verses g_2/g_1. Figure 3.3.1 shows the plot of $1/g_1\rho_{12}$ verses g_2/g_1 for RAT-1, in DMF and THF respectively at 308.15K. The inverse of slope gives ρ_2. The densities of all the compounds evaluated from such plots are given in Table 3.3.4 for all the compounds in DMF and THF. Further, the density of compounds were evaluated by using the following equation[47]:

$$\rho = KM/N_A \sum \Delta V_i \qquad \ldots (3.3.2)$$

where ρ is the density of the compound, K is packing fraction (0.599), M is the molecular weight of the compound, N_A is the Avogadro's number and ΔV_i is the volume increment of the atoms and atomic groups present in the compound. The calculated volume increment ΔV_i for different atomic groups are given in Table 3.3.3.The density of all the studied compounds have been evaluated from equation (3.3.2) and are reported in Table 3.3.4.

Comparison of densities evaluated from graphs and those calculated from eq. (3.3.2) showed that calculated values are different from those evaluated graphically. Further, for the same compound, density in the two solvents is different. This suggests that solvent plays an important role. In solutions molecular interactions exist which differ in different solvents due to different substitutions in compounds. The presence of these interactions have also been observed in ultrasonic studies which are discussed in section I of chapter 2. Due to these interactions, there may be some changes in volume which affects density.

Table 3.3.1: The density (ρ_{12}) and refractive index (*n*) of RAT series in DMF at 308.15K.

Conc. M	ρ_{12} $g.cm^{-3}$	g_1	g_2	*n*
		RAT-1		
0.00	0.9338	1.0000	0.0000	1.4239
0.01	0.9413	0.9955	0.0045	1.4241
0.02	0.9433	0.9910	0.0090	1.4249
0.04	0.9470	0.9822	0.0178	1.4261
0.06	0.9481	0.9733	0.0267	1.4275
0.08	0.9523	0.9645	0.0355	1.4289
0.10	0.9569	0.9559	0.0441	1.4313
		RAT-2		
0.01	0.9427	0.9958	0.0042	1.4242
0.02	0.9447	0.9917	0.0083	1.4248
0.04	0.9453	0.9834	0.0166	1.4259
0.06	0.9466	0.9751	0.0249	1.4273
0.08	0.9485	0.9669	0.0331	1.4291
0.10	0.9494	0.9587	0.0413	1.4308
		RAT-3		
0.01	0.9409	0.9957	0.0043	1.4243
0.02	0.9418	0.9914	0.0086	1.4248
0.04	0.9462	0.9828	0.0172	1.4257
0.06	0.9484	0.9743	0.0257	1.4268
0.08	0.9495	0.9658	0.0342	1.4289
0.10	0.9553	0.9575	0.0425	1.4292
		RAT-4		
0.01	0.9434	0.9957	0.0043	1.4247
0.02	0.9457	0.9913	0.0087	1.4255
0.04	0.9471	0.9827	0.0173	1.4265
0.06	0.9485	0.9740	0.0260	1.4277
0.08	0.9504	0.9655	0.0345	1.4286
0.10	0.9527	0.9569	0.0431	1.4298
		RAT-5		
0.01	0.9421	0.9957	0.0043	1.4249
0.02	0.9438	0.9913	0.0087	1.4256
0.04	0.9468	0.9827	0.0173	1.4269
0.06	0.9479	0.9742	0.0258	1.4289
0.08	0.9494	0.9656	0.0344	1.4292
0.10	0.9512	0.9571	0.0429	1.4311

Continue…..

….. Continue

Conc. M	ρ_{12} *g.cm^{-3}*	g_1	g_2	*n*
		RAT-6		
0.00	0.9338	1.0000	0.0000	1.4239
0.01	0.9431	0.9955	0.0045	1.4250
0.02	0.9448	0.9910	0.0090	1.4258
0.04	0.9454	0.9820	0.0180	1.4270
0.06	0.9481	0.9730	0.0270	1.4282
0.08	0.9521	0.9642	0.0358	1.4291
0.10	0.9574	0.9555	0.0445	1.4305
		RAT-7		
0.01	0.9431	0.9954	0.0046	1.4253
0.02	0.9454	0.9907	0.0093	1.4264
0.04	0.9471	0.9815	0.0185	1.4276
0.06	0.9489	0.9723	0.0277	1.4290
0.08	0.9506	0.9632	0.0368	1.4308
0.10	0.9514	0.9540	0.0460	1.4320
		RAT-8		
0.01	0.9413	0.9955	0.0045	1.4242
0.02	0.9437	0.9910	0.0090	1.4247
0.04	0.9450	0.9820	0.0180	1.4269
0.06	0.9486	0.9730	0.0270	1.4289
0.08	0.9533	0.9642	0.0358	1.4295
0.10	0.9552	0.9554	0.0446	1.4312
		RAT-9		
0.01	0.9420	0.9954	0.0046	1.4243
0.02	0.9456	0.9907	0.0093	1.4269
0.04	0.9482	0.9816	0.0184	1.4272
0.06	0.9512	0.9724	0.0276	1.4281
0.08	0.9532	0.9633	0.0367	1.4309
0.10	0.9563	0.9543	0.0457	1.4320
		RAT-10		
0.01	0.9514	0.9957	0.0043	1.4245
0.02	0.9536	0.9915	0.0085	1.4251
0.04	0.9558	0.9830	0.0170	1.4255
0.06	0.9578	0.9746	0.0254	1.4271
0.08	0.9590	0.9662	0.0338	1.4289
0.10	0.9602	0.9578	0.0422	1.4319

Table 3.3.2: The density (ρ_{12}) and refractive index (*n*) of RAT series in THF at 308.15K.

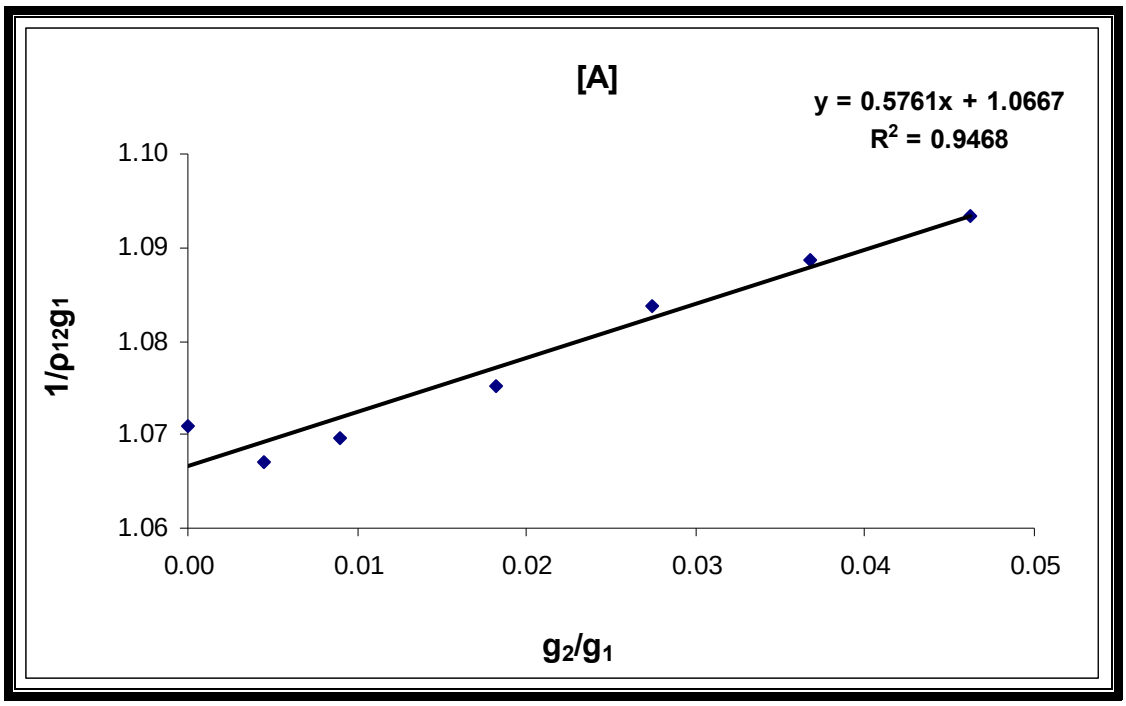
Conc. M	ρ_{12} $g.cm^{-3}$	g_1	g_2	*n*
		RAT-1		
0.00	0.8798	1.0000	0.0000	1.4016
0.01	0.8832	0.9953	0.0047	1.4038
0.02	0.8868	0.9906	0.0094	1.4043
0.04	0.8898	0.9813	0.0187	1.4059
0.06	0.8941	0.9720	0.0280	1.4076
0.08	0.8972	0.9628	0.0372	1.4082
0.10	0.9005	0.9537	0.0463	1.4097
		RAT-2		
0.01	0.8822	0.9956	0.0044	1.4032
0.02	0.8843	0.9912	0.0088	1.4041
0.04	0.8863	0.9825	0.0175	1.4057
0.06	0.8891	0.9739	0.0261	1.4063
0.08	0.8925	0.9653	0.0347	1.4076
0.10	0.8962	0.9568	0.0432	1.4082
		RAT-3		
0.01	0.8840	0.9955	0.0045	1.4035
0.02	0.8864	0.9910	0.0090	1.4053
0.04	0.8886	0.9820	0.0180	1.4069
0.06	0.8917	0.9730	0.0270	1.4083
0.08	0.8941	0.9641	0.0359	1.4098
0.10	0.8978	0.9554	0.0446	1.4111
		RAT-4		
0.01	0.8832	0.9954	0.0046	1.4031
0.02	0.8861	0.9909	0.0091	1.4044
0.04	0.8900	0.9818	0.0182	1.4069
0.06	0.8948	0.9729	0.0271	1.4087
0.08	0.8981	0.9639	0.0361	1.4093
0.10	0.9002	0.9550	0.0450	1.4118
		RAT-5		
0.01	0.8845	0.9954	0.0046	1.4056
0.02	0.8872	0.9909	0.0091	1.4061
0.04	0.8898	0.9819	0.0181	1.4082
0.06	0.8925	0.9729	0.0271	1.4092
0.08	0.8960	0.9640	0.0360	1.4122
0.10	0.8991	0.9552	0.0448	1.4138

Continue…..

….. Continue

Conc. M	ρ_{12} ***g.cm^{-3}***	g_1	g_2	***n***
		RAT-6		
0.00	0.8798	1.0000	0.0000	1.4016
0.01	0.8812	0.9952	0.0048	1.4036
0.02	0.8862	0.9905	0.0095	1.4052
0.04	0.8904	0.9811	0.0189	1.4065
0.06	0.8935	0.9718	0.0282	1.4079
0.08	0.8962	0.9625	0.0375	1.4091
0.10	0.8992	0.9532	0.0468	1.4108
		RAT-7		
0.01	0.8836	0.9951	0.0049	1.4034
0.02	0.8865	0.9903	0.0097	1.4049
0.04	0.8905	0.9806	0.0194	1.4059
0.06	0.8954	0.9711	0.0289	1.4070
0.08	0.8982	0.9616	0.0384	1.4082
0.10	0.9022	0.9522	0.0478	1.4098
		RAT-8		
0.01	0.8871	0.9953	0.0047	1.4031
0.02	0.8894	0.9905	0.0095	1.4046
0.04	0.8924	0.9811	0.0189	1.4056
0.06	0.8947	0.9718	0.0282	1.4079
0.08	0.8981	0.9625	0.0375	1.4086
0.10	0.9002	0.9533	0.0467	1.4112
		RAT-9		
0.01	0.8864	0.9951	0.0049	1.4034
0.02	0.8892	0.9903	0.0097	1.4048
0.04	0.8942	0.9807	0.0193	1.4058
0.06	0.8974	0.9712	0.0288	1.4066
0.08	0.9005	0.9617	0.0383	1.4079
0.10	0.9044	0.9523	0.0477	1.4091
		RAT-10		
0.01	0.8933	0.9963	0.0037	1.4032
0.02	0.8956	0.9926	0.0074	1.4038
0.04	0.8975	0.9852	0.0148	1.4046
0.06	0.8991	0.9779	0.0221	1.4061
0.08	0.9015	0.9705	0.0295	1.4075
0.10	0.9026	0.9631	0.0369	1.4082

Figure 3.3.1: The variation of $1/g_1\rho_{12}$ with g_2/g_1 for RAT-1 in [A] DMF and [B] THF at 308.15 K.



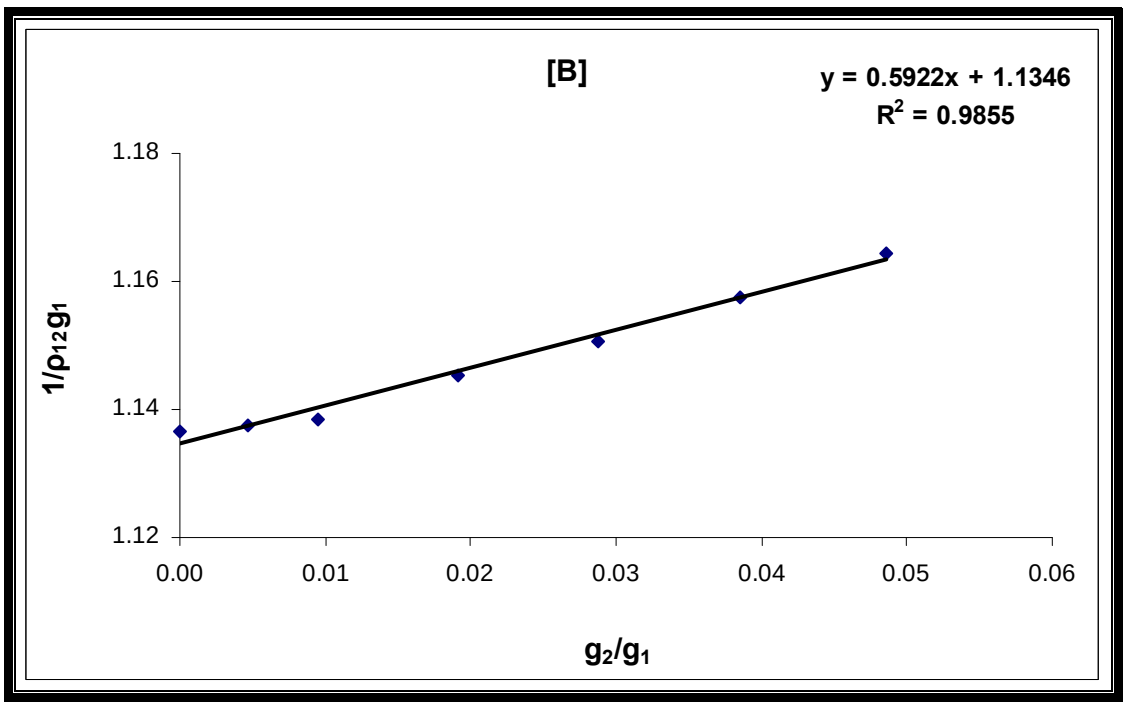


Table 3.3.3: Volume increments of some atoms and groups of atoms.

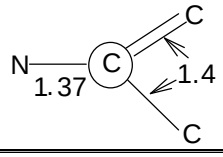
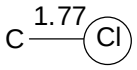
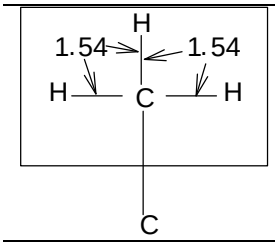
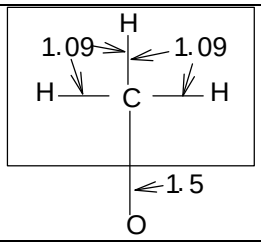
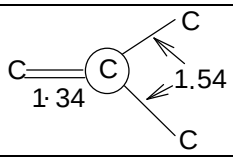
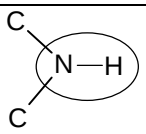
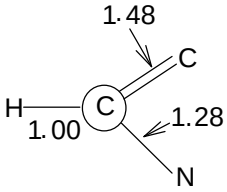
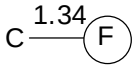
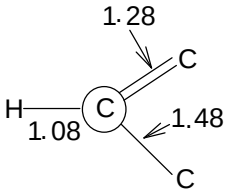
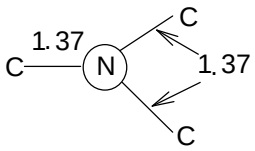
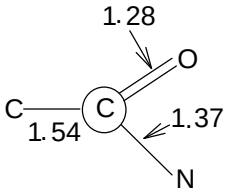
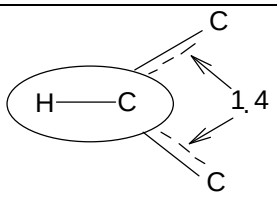
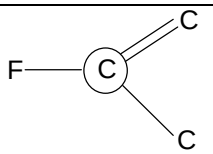
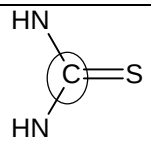
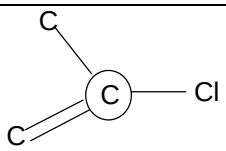
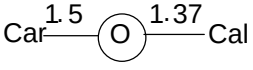
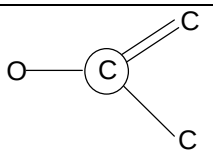
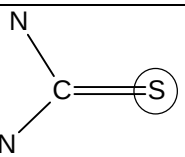
Atoms or Atomic group	Volume Increments $(A^o)^3$	Atoms or Atomic group	Volume Increments $(A^o)^3$
	10.2		19.35
	23.5		26.3
	9.0		8.3
	3.61		9.2
	11.36		0.9
	14.10		14.7
	11.40		3.44
	10.39		2.67
	11.65		3.35

Table 3.3.4: Experimental and calculated densities of RAT series in DMF and THF Solutions at 308.15 K.

Compounds	Density calculated from slope of Figure 3.3.1 ($g.cm^{-3}$)		Density ($g.cm^{-3}$) Calculated from Eq^{n}. 3.3.2
	DMF	*THF*	
RAT-1	1.7358	1.6886	1.3512
RAT-2	1.3335	1.4658	1.3682
RAT-3	1.6717	1.4804	1.3782
RAT-4	1.4420	1.7781	1.4649
RAT-5	1.4205	1.5618	1.4731
RAT-6	1.6642	1.6393	1.4689
RAT-7	1.3714	1.7655	1.4689
RAT-8	1.6753	1.5265	1.4714
RAT-9	1.6554	1.8272	1.5120
RAT-10	1.3767	1.8103	1.4732

Further, The molar refraction of a pure liquid $(MRD)_1$ were calculated by the following equation:

$$\left(MRD\right)_1 = \left[\frac{n^2-1}{n^2+1}\right]\frac{M}{\rho} \qquad \ldots (3.3.3)$$

where n, M and ρ are refractive index, molecular weight and density pure liquid respectively.

For solutions, the following equation was used to determining molar refraction:

$$\left(MRD\right)_{12} = \left[\frac{n_{12}^2-1}{n_{12}^2+1}\right]\left[\frac{X_1M_1+X_2M_2}{\rho_{12}}\right] \qquad \ldots (3.3.4)$$

where n_{12} and ρ_{12} are refractive index and density of solution respectively. X_1 and X_2 are the mole fractions and M_1 and M_2 are the molecular weight of the solvent and solute respectively.

The plots of $(MRD)_{12}$ verses concentration for RAT series in DMF and THF are given in Figures 3.3.2 and 3.3.3. It is evident from these figures that $(MRD)_{12}$ increase with the increase in concentration. From the values of the

molar refraction of solution and pure solvent, molar refraction of solid compounds were determined by following equation:

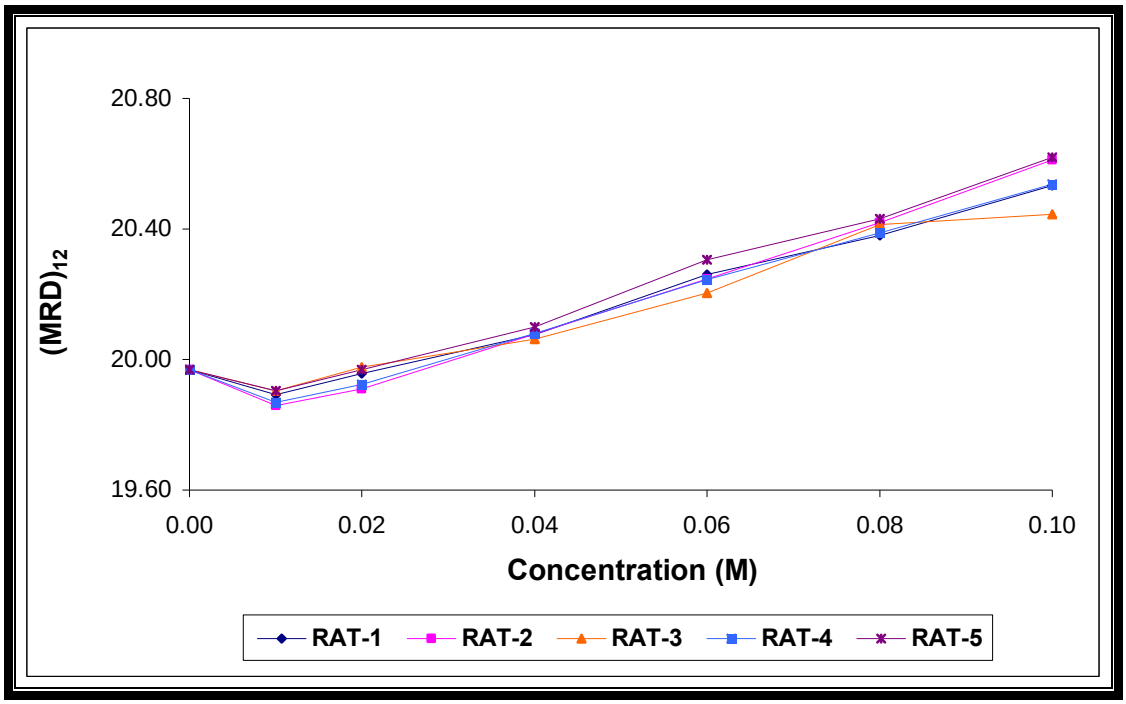
$$(MRD)_{12} = X_1 (MRD)_1 + X_2 (MRD)_2 \quad \ldots (3.3.5)$$

From the density and molar refraction data, the refractive indexes of all the compounds were calculated from eq. (3.3.3). The molar refraction $(MRD)_2$ and refractive index of all the compounds are reported in Table 3.3.5, for 0.1M solution.

It is evident from Table 3.3.5 that both $(MRD)_2$ and refractive index of compounds are different in each solvent. This again proves that in different solvents, intermolecular interactions are different, which affect these parameters. In some solvents, there may be intraction between solute and solvent molecules where as in others breakage of bonds may take place. As refractive index and molar refraction depends not only upon atomic refraction but also upon single, double or triple bonds, these parameters are affected by the type of interactions taking place in solution. Further, bond polarity also causes change in molar refraction. Thus, type of solvent affects the refractive index and molar refraction of a solute.

However, it is reported that bond refraction is more effective than atomic refraction. Further, bond polarity also causes change in molar refraction. Thus, type of solvent affects the refractive Index and molar refraction of a solute.

Figure 3.3.2: The plots of molar refraction $(MRD)_{12}$ against concentration of RAT series in DMF solutions at 308.15 K.



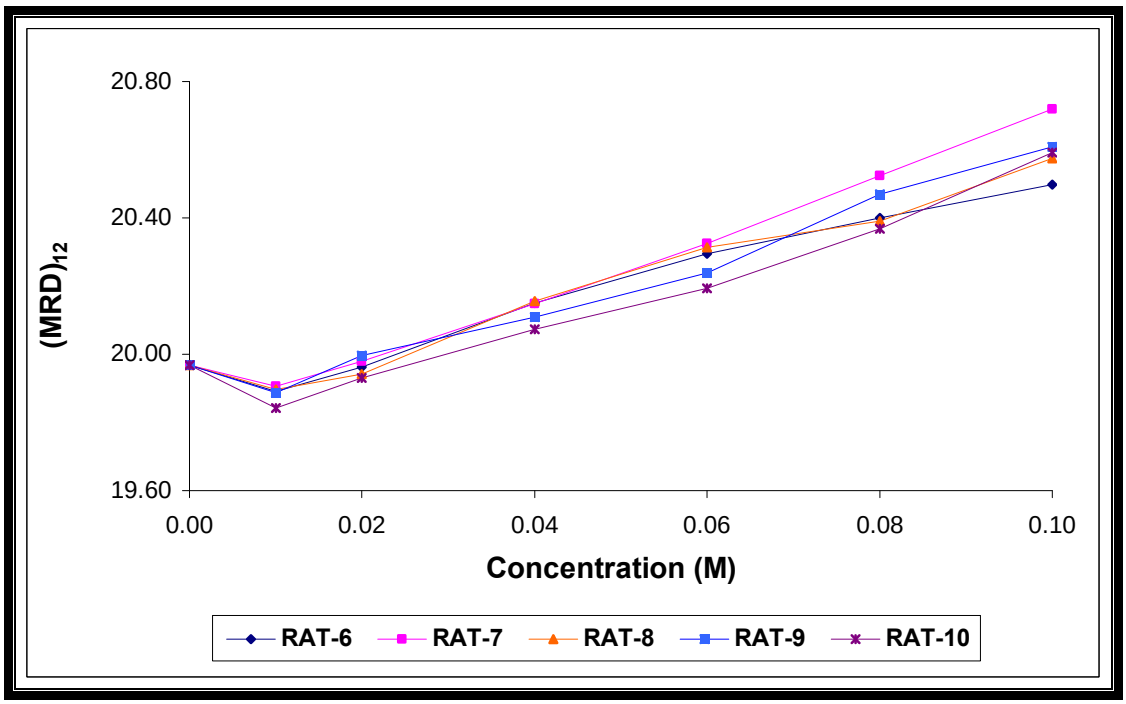
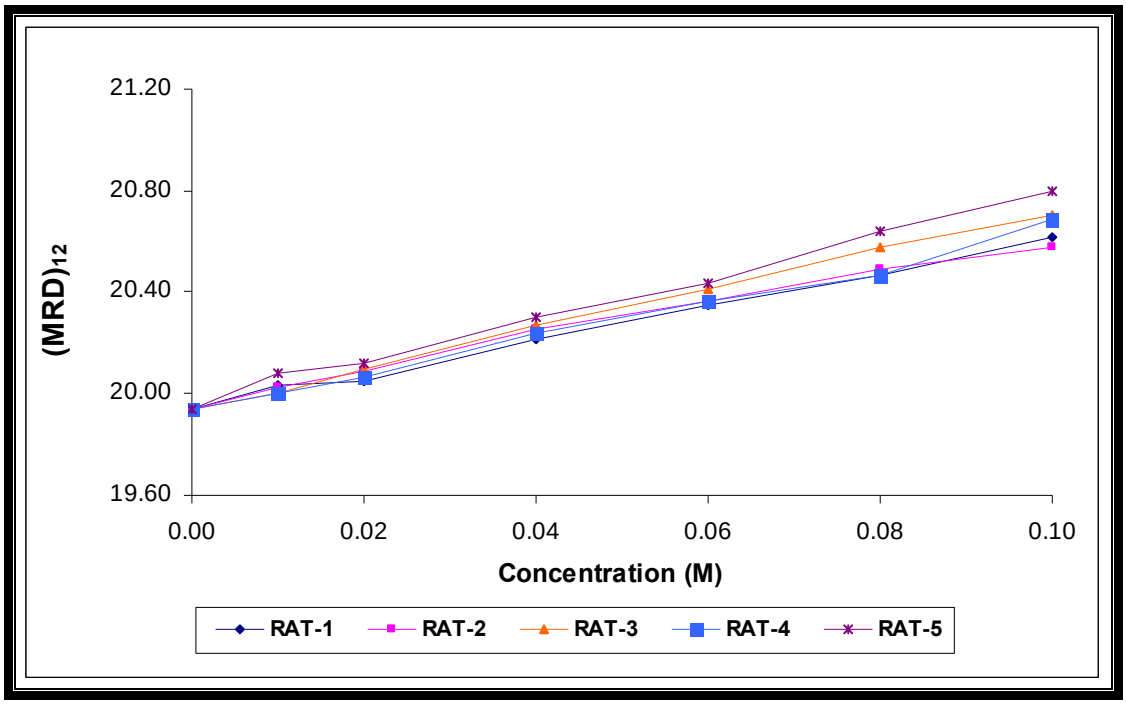


Figure 3.3.3: The plots of molar refraction *(MRD)*$_{12}$ against concentration of RAT series in THF solutions at 308.15 K.



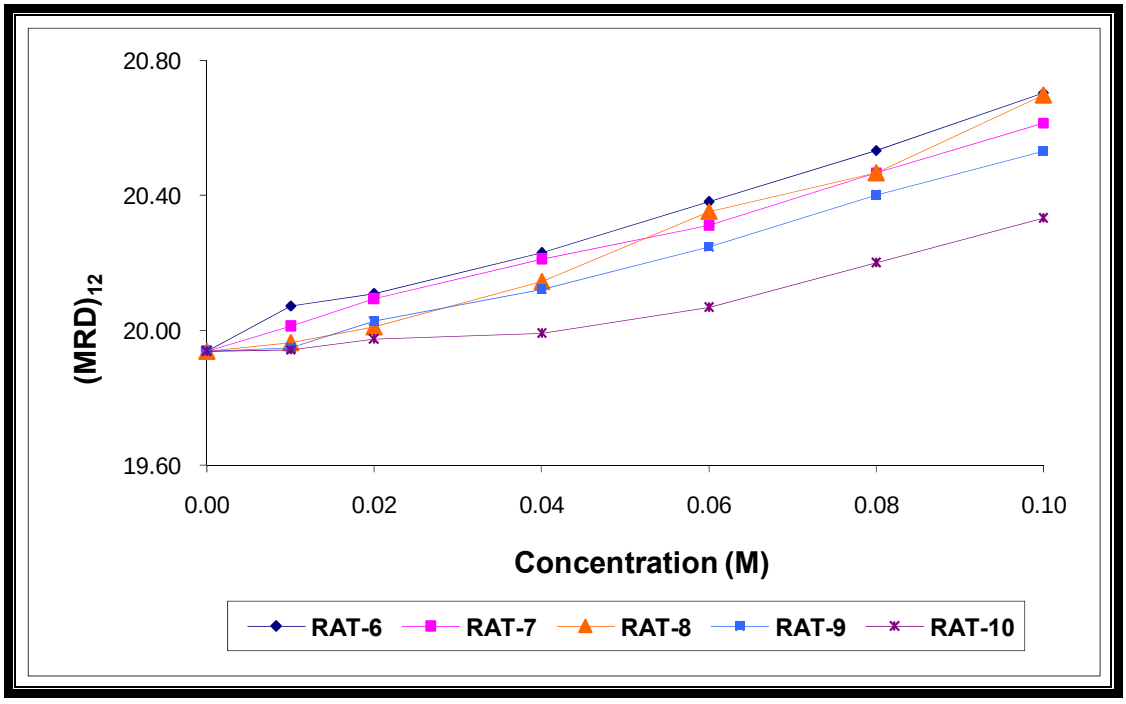


Table 3.3.5: Molar refraction *$(MRD)_2$* and refractive index *(n)* of 0.1M solution of RAT series in DMF and THF at 308.15 K.

Compounds	Solvents			
	DMF		THF	
	(MRD_2)	n	(MRD_2)	n
RAT-1	91.0744	1.6724	102.4883	1.7566
RAT-2	100.7345	1.6012	98.1486	1.6551
RAT-3	80.0690	1.5734	113.1660	1.7628
RAT-4	91.4046	1.5561	111.3178	1.9494
RAT-5	101.7629	1.6267	124.5989	1.9328
RAT-6	86.6130	1.5919	113.1603	1.8205
RAT-7	113.8506	1.6333	102.4138	1.7656
RAT-8	96.2845	1.6817	112.5131	1.7397
RAT-9	100.4741	1.6862	92.4797	1.7004
RAT-10	99.5083	1.5863	78.7481	1.6159

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Section-IV

Dissociation Constants

INTRODUCTION

The term dissociation constant is used to measure the strength of acid and bases. This is also known as ionization or acidity constant. The dissociation constant deals with the tendency of a compound to dissociate. Dissociation is the process by which the compound or ion is split into two components that are also ions or compounds

The dissociation constant of organic reagent plays a fundamental role in many analytical procedures such as acid- base titration, solvent extraction, complex formation, ion transport etc. It has been shown that the acid-base properties affect the toxicity[1], chromatographic retention behavior, and pharmaceutical properties[2] of organic acids and bases. Much of the theoretical foundation of modern organic chemistry is based on the observation of the effects on acid-base equilibrium of changing molecular structure[3].

For the measurement of dissociation constants, various methods have been reported. Mehrotra and Upadhyaya[4] have used conductometric method for the determination of the dissociation constant. Uhrova et al.[5] reported separation methods for the determination of dissociation constants. Tanaka et al.[6] maasured the ionization constant of weak acids by feedback-based flow ratiometry method. Lebron-Paler[7] reported the acid dissociation constant by Spectroscopic Method. Zevatskii[8] and coworkers represent the calculations of dissociation constants by empirical and quantum-chemical DFT methods. Various workers have been determined the dissociation constant by capillary electrophoresis[9], NMR methods[10], potentiometric method[11] etc.

For very high or very low acid strengths, spectrophotometer method is considered to be an ideal method but this method is also more time consuming. It is applicable if at least one of the species at equilibrium absorbs characteristically in the ultraviolet or visible region and the relevant ionic species show absorption maxima at different wavelengths.

Potentiometry is mostly used for the determination of dissociation constant of acids because it is economical in time. Further, it can be used for acids of pK_a range from 2 to 11 units[12]. For this measurement, glass and calomel electrodes have been used and carbonate free potassium hydroxide is the best alkali to use as a titrant.

The potential generated by the hydrogen ions, in the solution of an acid in a given medium is measured by an electronic potentiometer assembly. The relationship between the potential of glass electrode and the pH of the solution has the general form:

$$-\log[H^+] = pH = \frac{E_0 - E_c}{0.0591} \text{ at } 25^\circ C$$

where E_0 is the observed potential and E_c is the potential of the calomel electrode. The various terms in above equation change with time. So, this electrode cannot be used as a primary standard. However, it does provide a very convenient way of comparing the pH of a series of solutions. So, it is calibrated before and after use with a pair of known buffers, the pH of one of which must lie near to the pH region to be measured. The correctness of the results depends upon the exactness of the calibration of pH-meter.

Literature survey shows that different workers studied the dissociation constant of acids, bases, amino acids, cellulose derivatives, vitamins etc[13-22]. Bell et al.[23] have studied the dissociation constant of formic acid. Ong et al.[24] have reported the dissociation constants of pyridine penta carboxylic acid. Perlmutter and Tapuhi[25] have determined the acid constant of trichloroacetic acids. Corradini and coworkers[26] have studied the ionization constant of picric acid. The dissociation constant of 1-hydroxy-2-pyridinone-6-carboxylic acid was studied by Thipyapong et al.[27].

Some of the thermodynamic parameters have also been evaluated with the help of dissociation constant[28-35]. Boodts and Lison[36] have studied new computerized method for the determination of thermodynamic dissociation constants from experimental data. Basaran and coworkers[37] have reported the determination of the thermodynamic dissociation constant of chloroacetic acid. Sallam et al[38] have also reported dissociation constants of some dyes with thermodynamic functions. Bari and coworkers[39] measured dissociation constants and thermodynamic parameters of 8-aminoquinoline. El-Naggar[40] has determined the first and second dissociation constants and related thermodynamic functions of adipic acid. The thermodynamic properties of H_3PO_4 over a wide range of temperatures and pressures were studied by Ballerat-Busserolles et al.[41]. Versteeg and Geert[42] studied the dissociation constants and thermodynamic properties of amines and alkanolamines.

In the present work, the dissociation constant of all synthesized dihydropyrimidinthiones derivatives (RAT series) are studied in DMF at different temperatures (298.15 - 318.15 K) by Calvin Bjerrum pH titration technique.

EXPERIMENTAL

All solutions used for the titration are prepared using distilled water. Following are the concentrations of the solutions used for the titration. The chemicals used were of B.D.H Analar grade.

Solutions	**Concentration (M)**
Nitric acid	1.0
Sodium hydroxide	0.5
Sodium nitrate	1.0
Ligand (in DMF)	0.1

Nitric acid and sodium hydroxide were standardized by titrating with 0.1 N NaOH and 0.05 M succinic acid solution respectively.

The buffer solutions used for the calibration of pH meter were 0.05 M potassium hydrogen phthalate and 0.01 M Borax buffer.

A Systronic *pH* meter (Model No. EQ 664) was used for the pH determination. The Systronic glass electrode and a saturated calomel electrode were used as indicator and reference electrodes respectively. Before operation, the glass electrode was immersed in 0.1 M HCl for twenty minutes. Then, it was washed thoroughly with distilled water. The *pH* meter was calibrated with buffer solution of known pH. A constant temperature was maintained to ± 0.05 K by using a digital controller Nova Inst. (Model No. NV 8550 E).

Calvin Bjerrum pH titration:

The following sets of mixtures were prepared for titration:

(I) 2 ml HNO_3 (1.0M) + 4 ml water + 30 ml DMF + 4.0 ml $NaNO_3$ (1.0 M).

(ii) 2 ml HNO_3 (1.0M) + 4 ml water + 28 ml DMF + 2.0 ml ligand solution (0.1M) + 4.0 ml $NaNO_3$ (1.0 M).

Thus, total volumes (V^0) in each set = 40.0 ml and Solvent : Water ratio 60:40 (v/v). The solvent used for the study was DMF.

The above mentioned solutions were allowed to attain a definite temperature and then titrated against standard NaOH solution (0.5 M). The same experiment was repeated at different temperatures, i.e., at 298.15 K, 308.15K and 318.15K.

THEORY

In the present work ligands are of *HL* type. Thus, the equilibria are,

$$L + H \leftrightarrow HL$$

In general, these equations can be represented as:

$$LH_{j-1} + H \leftrightarrow LH_j$$

The thermodynamic proton-ligand stability constant (TK_j^H) is given by:

$$TK_j^{\ H} = \frac{\left[LH_j\right]}{\left\{\left[LH_{j-1}\right]\left[H\right]\right\}} \quad \text{... (3.4.1)}$$

TK_j^H is reciprocal of the thermodynamic dissociation constant of the acid LH_j dissociating as:

$$LH_i = LH_{i-1} + H$$

The overall thermodynamic proton-ligand stability constant β_j^H is given by:

$$T\beta_j^H = \frac{\left[LH_j\right]}{\left[L\right]\left[H\right]^j} \quad \text{... (3.4.2)}$$

and it refers to the reaction:

$$L + JH \leftrightarrow LH_j$$

The stoichiometric proton-ligand stability constant is given by:

$$K_j^{\ H} = \frac{\left[LH_j\right]}{\left\{\left[LH_{j-1}\right]\left[H\right]\right\}} \quad \text{... (3.4.3)}$$

and

$$\beta_j^{\ H} = \frac{\left[LH_j\right]}{\left[L\right]\left[H\right]^j} \quad \text{... (3.4.4)}$$

An inert electrolyte is used to determine the stability constant in a particular salt medium. Sodium nitrate is mostly preferred as supporting electrolyte, because of very slight complexing tendency of nitrate ion. Generally, the competition between nitrate ion and the ligand under study is minor importance. The molar concentrations are used in place of activities.

For the determination of dissociation constants, Bjerrum[43] introduced a relation for the determination of $\bar{n}_H$, which is defined as average number of hydrogen bound to each ligand.

$\bar{n}_H$ = $\{K_1^H [H] + 2K_1^H K_2^H [H]^2 + ...JK_1^H K_2^H [H] ... K_j^H [H]^j\} / \{1 + K_1^H [H] + K_1^H K_2^H [H]^2.....K_1^H K_2^H.....K_j^H [H]^j$ ... (3.4.5)

From equation (3.6.4), we can write

$$\bar{n}_H = \frac{\sum_{j=1}^{\eta} j\beta_j^H [H]^j}{\sum_{j=1}^{\eta} \beta_j^H [H]^j} \quad : \left(\beta_0^H = 1\right) \qquad \ldots (3.4.6)$$

Equation (3.4.6) is called Bjerrum formation function of the system.

The determination of dissociation constants from experimental data comprises the following three steps: (i) evaluation of formation curve of the system (ii) calculation of stoichiometric K`s of the system by direct solution of the formation function and (iii) conversion of stoichiometric constants into thermodynamic constants.

When the system consists of a ligand, which is a conjugated base of a weak acid, the pH-metric method introduced by Bjerrum has been widely used. This method is known as "Bjerrum-Calvin pH titration technique".

In this technique, the concentration of H^+ ions is measured. Thus, a large amount of data can be obtained in a short period of time. The Irving and Rossotti method[44] has some advantages, such as:

(i) valid for both pure water and for the mixed solvents.

(ii) conversion of pH-meter reading in to stoichiometric hydrogen ion concentration is not necessary.

(iii) not necessary to know the stoichiometric concentration of neutral salt added to maintain the ionic strength constant.

Due to these advantages, this method is used in the present work. The pH-meter is standardized using an aqueous buffer. The *pH* is measured for two solutions:

(1) A mixture containing a mineral acid, a chelating agent and a neutral electrolyte to keep ionic strength constant and

(2) A mixture same as above but without the chelating agent, when titrated against an alkali solution.

After each addition of standard alkali, the *pH* meter reading is noted using a glass electrode-saturated calomel electrode combination. For both the titrations, same initial volume of the mixture and same standard alkali is used.

The titration curves obtained in the above two titrations are designated as the reagent or ligand titration curve and the acid titration curve respectively.

The possible hydrolysis reactions are ignored because (i) fresh reagent solutions were used in *pH* titrations, (ii) titration times were of the order of one hour, (iii) there were no observable drifts with time in the meter readings and (iv) the concentrations of the mineral acid or alkali in the solutions were small.

Usually, a *pH*-meter calibrated with an aqueous buffer is used for aqueous solutions only. However, for the mixed aqueous media, especially aqueous dioxane solutions, van Uitert and Haas gave a relation between the glass electrode reading pH in dioxane-water medium and the stoichiometric hydrogen ion concentration of the same in mixture of varied composition and ionic strength. They reported the relation:

$$-\log\left[H^{+}\right] = pH + \log f + \log U_H^0 \qquad \text{... (3.4.7)}$$

where *f* is the activity coefficient of the hydrogen ions in the solvent mixture under consideration at the same temperature and ionic strength, and U_H^0 is a correction factor at zero ionic strength, which depends only on the solvent composition and temperature. U_H^0 is taken as unity in aqueous media. The meter reading in any aqueous dioxane solution can, therefore, be converted into hydrogen ion concentration using equation (3.4.7), provided that correction factor for the appropriate solvent, salt medium, and temperature, has been determined. Equation (3.4.7) can be written as:

$$1/anti\log pH = [H^{+}]\, fU_H^0 \qquad \text{... (3.4.8)}$$

$$\therefore \left[H^{+}\right] = \frac{1}{\left[anti\log pH\right]\left[fU_H^0\right]} \qquad \text{... (3.4.9)}$$

Substituting for $[H^+]$ in equation (3.4.5) we get,

$\bar{n}_H$ = $(K_1^H/f\,U^0{}_H)[1/\text{antilog pH}] + \ldots + ((JK_1^H\,K_2^H \ldots K_J^H)/(f\,U^0{}_H)^J)[1/\text{antilog pH}]^J/(1+K_1^H/f\,U^0{}_H))[1/\text{antilog pH}] + \ldots + ((K_1^H K_2^H \ldots K_J^H)/(f\,U^0{}_H)J)[1/\text{antilog pH}]$

...(3.4.10)

$$K_j^H = fU_H^0 . pK_j^H \qquad \text{... (3.4.11)}$$

$$\beta_j^H = fU_H^0 . p\beta_j^H \qquad \text{... (3.4.12)}$$

The proton-ligands constant, $p_{Kj}{}^H$ can be obtained by the following methods:

1. Interpolation at half $\bar{n}_H$ values:

At the following $\bar{n}_H$ values, log K_1 and log K_2 can be determined:

$$\log K_1 = \left(\bar{n}_H\right)_{0.5} \quad \ldots \text{(3.4.13)}$$

$$\log K_2 = \left(\bar{n}_H\right)_{1.5} \quad \ldots\ldots \text{(3.4.14)}$$

2. Mid point slope method:

For H_2L type ligands:

$$K_1 K_2 [L]^2 = 1$$

or $$\log K_1 K_2 = 2pL_1 \quad \ldots \text{(3.4.15)}$$

From the measured mid-point slope, D, the ratio K_1/K_2 can be calculated by eq. (3.4.16):

$$D = \frac{-4.606}{\left(2 + \sqrt{\left(K_1 / K_2\right)}\right)} \quad \ldots \text{(3.4.16)}$$

The individual values of K_1 and K_2 were obtained by using K_1/K_2 values and relation (3.4.15).

RESULTS AND DISCUSSION

Figure 3.4.1 shows that typical titrations curve of the acid in the absence and presence of compound RAT-1 at [A] 298.15K, [B] 308.15K and [C] 318.15K. It can be seen that for the same volume of NaOH added the compound titration curves showed a lower pH value than the titration curve of free acid.

From these titration curves, the average number of protons associated with the ligand ($\overline{n_H}$) can be calculated by the following equation given by Irving and Rossotti[44].

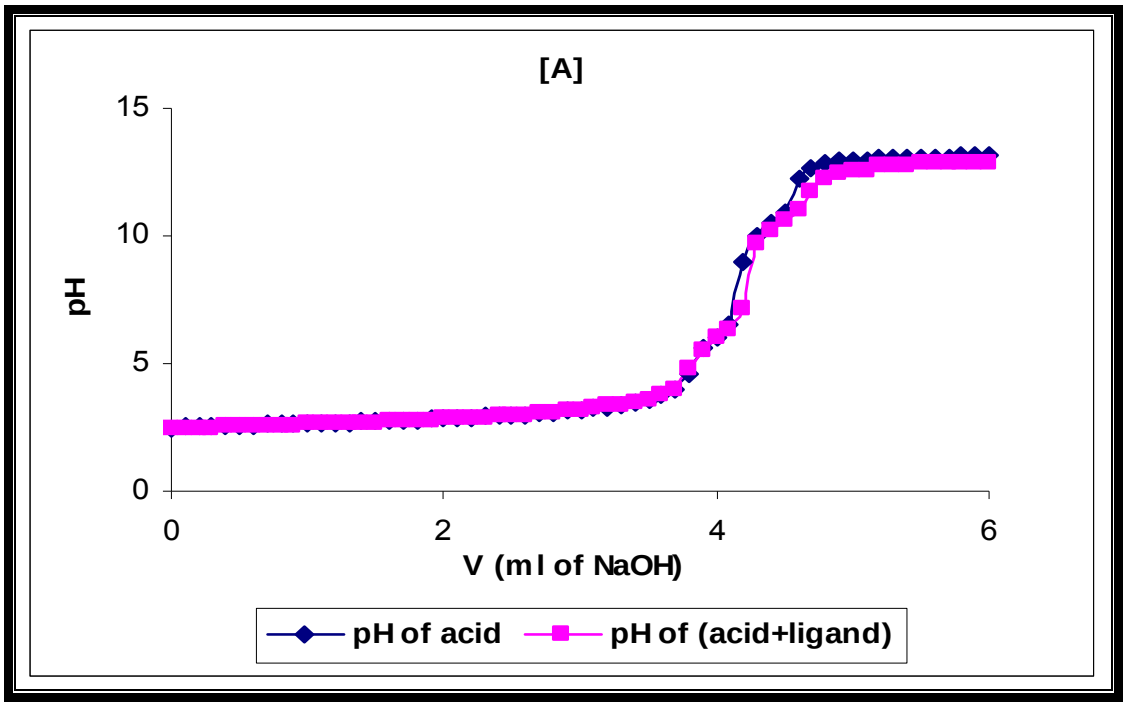
$$\overline{n_H} = Y - \left\{\left(V'' - V'\right)\left(N^0 + E^0\right)\right\} \Big/ \left\{\left(V^0 + V'\right)T_L^0\right\} \quad \ldots (3.4.17)$$

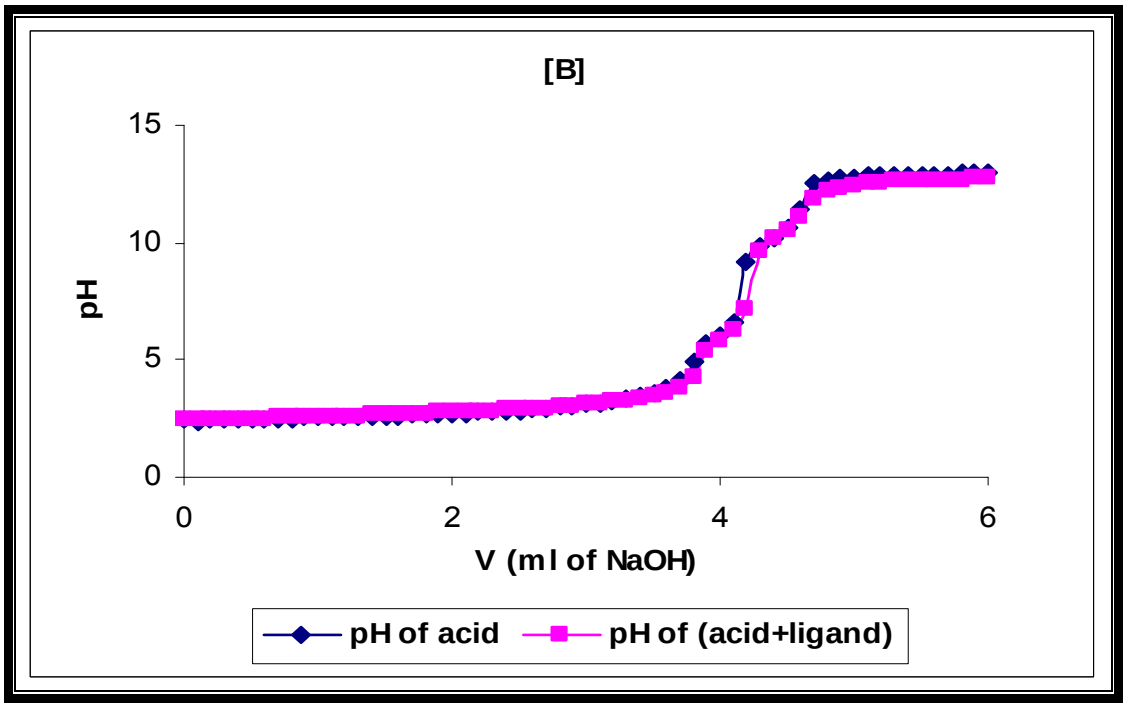
where Y is the number of displaceable protons per ligand molecule. For RAT-5 and RAT-10, Y is taken as two whereas other compounds Y is equal to one. V' and V" are the volume of alkali required at the same pH for both acid and ligand titration curves respectively. V^0 is the initial volume of the test solution. N^0, E^0 and T^0_L are the initial concentration of the alkali, acid and ligand respectively.

The calculated values of $\overline{n_H}$ for all the studied compounds are given in Tables 3.4.1 to 3.4.3 for all temperature systems. It is evident from Tables that the values of $\overline{n_H}$ are found to be between 0 to 1 for all the compounds except RAT-5 and RAT-10 where $\overline{n_H}$ values are between 0 to 2. The value of $\overline{n_H}$ between 0 and 2 suggests that compound have two replaceable protons whereas $\overline{n_H}$ value between 0 and 1 is due to one replaceable proton.

Figure 3.4.2 shows the plot of $\overline{n_H}$ values against pH for RAT-1. The pK_1^H value was evaluated at $\overline{n_H}$ =0.5 i.e., by half-integral method for all the compounds with Y=1. However, for compound RAT-5 and RAT-10 where Y=2, pK_1^H value was evaluated at $\overline{n_H}$ =0.5 and $\overline{n_H}$ =1.5.
Further, the $\log \bar{n}_H \Big/ \left(\bar{n}_H - 1\right)$ values are plotted against B as shown in Figure 3.4.3. The plots are straight lines from which $\log pK_1^H$ values were calculated at several pH values, by the following equation:

Figure 3.4.1: The plot of pH (B) against volume of NaOH for RAT-1 in DMF at [A] 298.15K [B] 308.15K and [C] 318.15K.





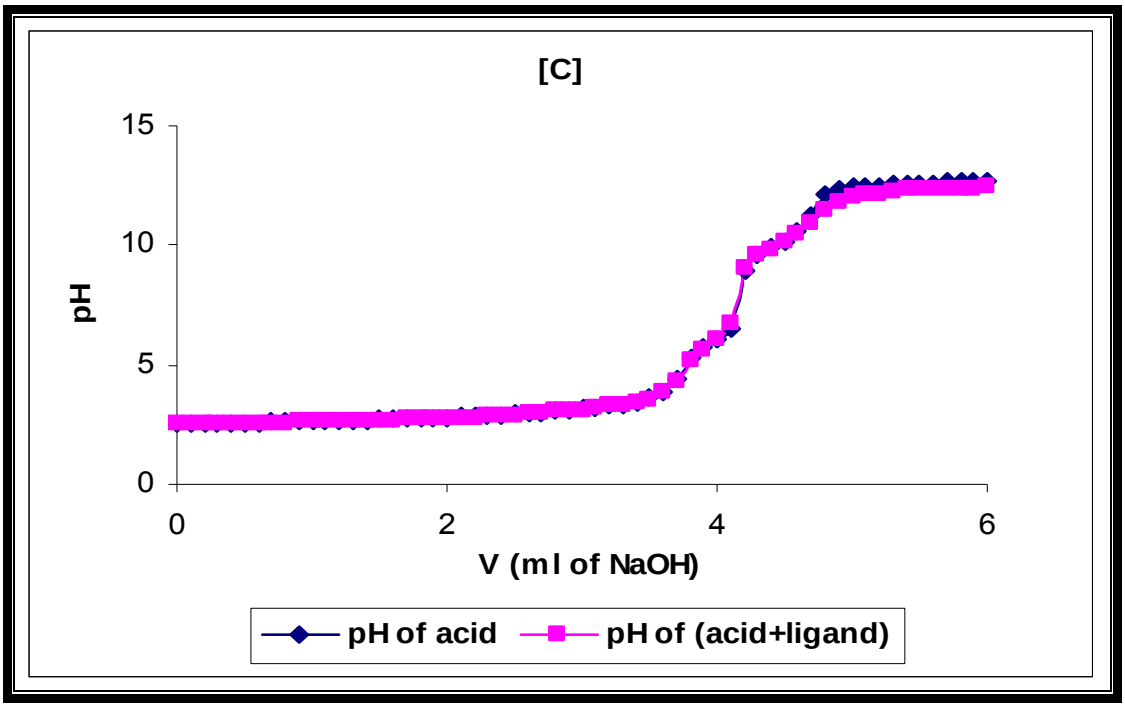

[C]
15
10
5
0
pH
0
2
4
6
V (ml of NaOH)
pH of acid
pH of (acid+ligand)

Table 3.4.1: The *pH*, n_H, pK_1^H and other terms for RAT series in DMF at 298.15K.

pH	*V'*	*V''*	*V''-V'*	n_H	$\log n_H/(1-n_H)$	pK_1^H
RAT-1						
11.7	4.5578	4.6936	0.1358	0.6657	-0.5286	11.9992
11.8	4.5656	4.7106	0.1450	0.6432	-0.5371	12.0560
11.9	4.5734	4.7319	0.1585	0.6102	-0.5503	12.0946
12.0	4.5812	4.7532	0.1720	0.5772	-0.5645	12.1352
12.1	4.5891	4.7745	0.1854	0.5445	-0.5796	12.1775
12.2	4.5969	4.7957	0.1988	0.5118	-0.5958	12.2205
12.3	4.6130	4.8400	0.2270	0.4431	-0.6347	12.2007
12.4	4.6348	4.8900	0.2552	0.3746	-0.6818	12.1775
12.5	4.6565	4.9615	0.3050	0.2538	-0.7980	12.0316
12.6	4.6783	4.9904	0.3121	0.2369	-0.8196	12.0920
12.7	4.7006	5.0230	0.3224	0.2122	-0.8546	12.1303
RAT-2						
11.2	4.5487	4.6600	0.1113	0.7252	-0.5078	11.6214
11.3	4.5266	4.6800	0.1534	0.6210	-0.5459	11.5145
11.4	4.5344	4.7002	0.1658	0.5905	-0.5587	11.5589
11.5	4.5422	4.7250	0.1828	0.5486	-0.5777	11.5846
11.6	4.5500	4.7500	0.2000	0.5062	-0.5988	11.6107
11.7	4.5578	4.7750	0.2172	0.4638	-0.6223	11.6370
11.8	4.5656	4.8002	0.2346	0.4209	-0.6489	11.6615
11.9	4.5734	4.8238	0.2504	0.3821	-0.6762	11.6912
12.0	4.5812	4.8476	0.2664	0.3427	-0.7076	11.7171
RAT-3						
10.4	4.2777	4.3787	0.1009	0.7493	-0.5000	10.8754
10.5	4.2804	4.4002	0.1198	0.7024	-0.5155	10.8729
10.6	4.2831	4.4217	0.1386	0.6557	-0.5324	10.8798
10.7	4.2858	4.4435	0.1577	0.6083	-0.5511	10.8912
10.8	4.2886	4.4652	0.1766	0.5614	-0.5717	10.9072
10.9	4.2913	4.4870	0.1957	0.5140	-0.5947	10.9243
11.0	4.2940	4.5031	0.2091	0.4807	-0.6126	10.9665
11.1	4.2967	4.5109	0.2142	0.4681	-0.6198	11.0445
11.2	4.2995	4.5187	0.2192	0.4557	-0.6271	11.1228
11.3	4.3096	4.5396	0.2300	0.4290	-0.6437	11.1759
11.4	4.3217	4.5627	0.241	0.4019	-0.6619	11.2273
RAT-4						
9.7	4.2796	4.3875	0.1079	0.7320	-0.5056	10.1363
9.8	4.2833	4.3979	0.1146	0.7153	-0.5111	10.2002
9.9	4.2870	4.4174	0.1304	0.6761	-0.5248	10.2196
10.0	4.2907	4.4391	0.1484	0.6314	-0.5418	10.2338
10.1	4.2944	4.4609	0.1665	0.5865	-0.5604	10.2518
10.2	4.2981	4.4826	0.1845	0.5419	-0.5809	10.2729
10.3	4.3053	4.5050	0.1997	0.5042	-0.5998	10.3073
10.4	4.3158	4.5300	0.2142	0.4683	-0.6197	10.3449
10.5	4.3263	4.5550	0.2287	0.4325	-0.6415	10.3819
10.6	4.3368	4.5800	0.2432	0.3966	-0.6656	10.4178
10.7	4.3474	4.6029	0.2555	0.3663	-0.6883	10.4619
10.8	4.3579	4.6171	0.2592	0.3572	-0.6955	10.5449
10.9	4.3684	4.6314	0.2630	0.3480	-0.7031	10.6273

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pH	***V'***	***V''***	***V''-V'***	***n_H***	***log $n_H/(1-n_H)$***	***pK_1^H***
			RAT-5			
7.1	4.0717	4.2008	0.1291	1.6778	0.6974	7.8166
7.2	4.0780	4.2187	0.1407	1.6489	0.6185	7.8717
7.3	4.0843	4.2300	0.1457	1.6364	0.5884	7.9533
7.4	4.0906	4.2482	0.1576	1.6068	0.5238	8.0114
7.5	4.0969	4.2677	0.1708	1.5739	0.4623	8.0675
7.6	4.1019	4.2852	0.1833	1.5428	0.4119	8.1282
7.7	4.1059	4.3012	0.1953	1.5129	0.3692	8.1922
7.8	4.1093	4.3110	0.2017	1.4970	0.3484	8.2737
7.9	4.1130	4.3424	0.2294	1.4280	0.2705	8.2973
8.0	4.1167	4.3605	0.2438	1.3921	0.2364	8.3599
8.1	4.1204	4.3801	0.2597	1.3525	0.2025	8.4199
8.2	4.1241	4.4075	0.2834	1.2935	0.1582	8.4626
8.3	4.1278	4.4378	0.3100	1.2272	0.1151	8.5009
8.9	4.1500	4.5990	0.4490	0.8813	-0.0490	8.7964
9.0	4.1537	4.6209	0.4672	0.8361	-0.0668	8.8563
9.1	4.1574	4.6533	0.4959	0.7647	-0.0943	8.8917
9.2	4.1611	4.6958	0.5347	0.6681	-0.1315	8.9004
9.3	4.1648	4.7205	0.5557	0.6159	-0.1521	8.9484
9.4	4.1685	4.7488	0.5803	0.5548	-0.1771	8.9842
9.5	4.1722	4.7785	0.6063	0.4902	-0.2051	9.0114
9.6	4.1759	4.7882	0.6123	0.4753	-0.2118	9.0938
9.7	4.1796	4.7963	0.6167	0.4645	-0.2169	9.1808
9.8	4.1833	4.8213	0.6380	0.4116	-0.2427	9.2135
9.9	4.1870	4.8512	0.6642	0.3465	-0.2784	9.2213
10.0	4.1907	4.8808	0.6901	0.2822	-0.3199	9.2156
10.1	4.1944	4.9012	0.7068	0.2408	-0.3515	9.2363
10.2	4.1981	4.9183	0.7202	0.2076	-0.3810	9.2637
			RAT-6			
10.1	3.6276	3.7766	0.1490	0.6243	-0.5446	10.3206
10.2	3.6621	3.8235	0.1614	0.5934	-0.5574	10.3641
10.3	3.6966	3.8711	0.1745	0.5607	-0.5720	10.4060
10.4	3.7220	3.9065	0.1845	0.5358	-0.5838	10.4623
10.5	3.7463	3.9452	0.1989	0.4999	-0.6021	10.4998
10.6	3.7707	3.9837	0.2130	0.4647	-0.6218	10.5386
10.7	3.7951	4.0210	0.2259	0.4326	-0.6414	10.5822
10.8	3.8195	4.0522	0.2327	0.4159	-0.6523	10.6524
10.9	3.8439	4.0860	0.2421	0.3926	-0.6685	10.7105
			RAT-7			
10.8	3.8195	3.9413	0.1218	0.6942	-0.5183	11.1561
10.9	3.8439	3.9802	0.1363	0.6580	-0.5315	11.1843
11.0	3.8683	4.0167	0.1484	0.6279	-0.5432	11.2272
11.1	3.8927	4.0532	0.1605	0.5978	-0.5556	11.2721
11.2	3.9184	4.1017	0.1833	0.5409	-0.5813	11.2712
11.3	3.9447	4.1443	0.1996	0.5004	-0.6019	11.3006
11.4	3.9711	4.1800	0.2089	0.4774	-0.6145	11.3607
11.5	3.9974	4.2179	0.2205	0.4487	-0.6313	11.4106
11.6	4.0474	4.2869	0.2395	0.4019	-0.6619	11.4273
11.7	4.1000	4.3490	0.2490	0.3789	-0.6786	11.4854
11.8	4.1313	4.3889	0.2576	0.3579	-0.6950	11.5462

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pH	***V'***	***V''***	***V''-V'***	***n_H***	***log $n_H/(1-n_H)$***	***pK_1^H***
RAT-8						
9.4	3.4765	3.6208	0.1443	0.6349	-0.5404	9.6403
9.5	3.4961	3.6530	0.1569	0.6032	-0.5533	9.6819
9.6	3.5160	3.6834	0.1674	0.5768	-0.5647	9.7346
9.7	3.5360	3.7240	0.1880	0.5250	-0.5891	9.7434
9.8	3.5560	3.7508	0.1948	0.5080	-0.5978	9.8140
9.9	3.5760	3.7892	0.2132	0.4618	-0.6235	9.8335
10.0	3.5960	3.8190	0.2230	0.4373	-0.6384	9.8906
10.1	3.6276	3.8593	0.2317	0.4158	-0.6524	9.9523
10.2	3.6621	3.9087	0.2466	0.3787	-0.6787	9.9850
RAT-9						
9.6	3.5160	3.6730	0.1570	0.6031	-0.5533	9.7818
9.7	3.5360	3.6999	0.1639	0.5859	-0.5607	9.8507
9.8	3.5560	3.7302	0.1742	0.5601	-0.5723	9.9048
9.9	3.5760	3.7591	0.1831	0.5378	-0.5828	9.9658
10.0	3.5960	3.7878	0.1918	0.5161	-0.5937	10.0279
10.1	3.6276	3.8272	0.1996	0.4967	-0.6038	10.0943
10.2	3.6621	3.8701	0.2080	0.4760	-0.6153	10.1582
10.3	3.6966	3.9083	0.2117	0.4671	-0.6204	10.2427
10.4	3.7220	3.9464	0.2244	0.4354	-0.6396	10.2872
10.5	3.7463	3.9833	0.2370	0.4041	-0.6604	10.3313
10.6	3.7707	4.0173	0.2466	0.3803	-0.6776	10.3879
10.7	3.7951	4.0494	0.2543	0.3613	-0.6923	10.4525
RAT-10						
8.6	3.3783	3.4518	0.0735	1.8136	1.3872	8.6021
8.7	3.3836	3.4838	0.1002	1.7459	0.9527	8.8001
8.8	3.3889	3.5237	0.1348	1.6583	0.6427	8.9244
8.9	3.3942	3.5579	0.1637	1.5850	0.4821	8.9921
9.0	3.3995	3.5979	0.1984	1.4971	0.3485	9.1235
9.1	3.4176	3.6398	0.2222	1.4370	0.2797	9.2354
9.2	3.4373	3.6908	0.2535	1.3580	0.2070	9.3649
9.3	3.4569	3.7554	0.2985	1.2444	0.1257	9.3956
9.4	3.4765	3.8040	0.3275	1.1714	0.0829	9.5024
10.0	3.5960	4.0884	0.4924	0.7576	-0.0970	10.1842
10.1	3.6276	4.1563	0.5287	0.6670	-0.1320	10.2375
10.2	3.6621	4.2219	0.5598	0.5897	-0.1627	10.3465
10.3	3.6966	4.2897	0.5931	0.5070	-0.1976	10.3995
10.4	3.7220	4.3485	0.6265	0.4238	-0.2365	10.4563
10.5	3.7463	4.4051	0.6588	0.3434	-0.2802	10.6231
10.6	3.7707	4.4544	0.6837	0.2818	-0.3201	10.6982

Table 3.4.2: The *pH*, n_H, pK_1^H and other terms for RAT series in DMF at 308.15 K.

pH	*V'*	*V''*	*V''-V'*	n_H	$\log n_H/(1-n_H)$	pK_1^H
RAT-1						
11.7	4.6248	4.6788	0.0540	0.8671	-0.4660	12.5144
11.8	4.6343	4.6906	0.0563	0.8614	-0.4675	12.5935
11.9	4.6438	4.7074	0.0636	0.8435	-0.4723	12.6316
12.0	4.6533	4.7444	0.0911	0.7760	-0.4917	12.5397
12.1	4.6629	4.7815	0.1186	0.7087	-0.5134	12.3861
12.2	4.6724	4.8278	0.1554	0.6187	-0.5469	12.2102
12.3	4.6819	4.8833	0.2014	0.5064	-0.5987	12.0111
12.4	4.6914	4.9636	0.2722	0.3341	-0.7150	11.7004
12.5	4.7062	4.9966	0.2904	0.2901	-0.7571	11.6113
12.6	4.7898	5.0906	0.3007	0.2664	-0.7831	11.5600
12.7	4.8714	5.1850	0.3136	0.2366	-0.8200	11.4912
RAT-2						
10.8	4.519	4.5846	0.0656	0.8379	-0.4738	11.5134
10.9	4.5316	4.6286	0.0970	0.7604	-0.4965	11.4015
11.0	4.5443	4.6643	0.1200	0.7037	-0.5151	11.3756
11.1	4.5570	4.7003	0.1433	0.6462	-0.5360	11.3617
11.2	4.5696	4.7313	0.1617	0.6009	-0.5542	11.3778
11.3	4.5823	4.7625	0.1802	0.5554	-0.5744	11.3966
11.4	4.5949	4.7938	0.1989	0.5094	-0.5971	11.4163
11.5	4.6057	4.8089	0.2032	0.4989	-0.6026	11.4981
11.6	4.6152	4.8200	0.2048	0.4951	-0.6047	11.5914
11.7	4.6248	4.8311	0.2063	0.4915	-0.6067	11.6852
11.8	4.6343	4.8422	0.2079	0.4876	-0.6088	11.7785
11.9	4.6438	4.8533	0.2095	0.4838	-0.6109	11.8719
12.0	4.6533	4.8644	0.2111	0.4800	-0.6130	11.9652
RAT-3						
10.1	4.3632	4.6139	0.2507	0.3784	-0.6790	9.8844
10.2	4.3895	4.6278	0.2383	0.4095	-0.6567	10.0410
10.3	4.4146	4.6417	0.2271	0.4375	-0.6382	10.1909
10.4	4.4390	4.6556	0.2166	0.4638	-0.6223	10.3371
10.5	4.4634	4.6694	0.2060	0.4904	-0.6073	10.4833
10.6	4.4878	4.6833	0.1955	0.5166	-0.5934	10.6289
10.7	4.5063	4.6972	0.1909	0.5282	-0.5876	10.7490
10.8	4.5190	4.7048	0.1858	0.5409	-0.5813	10.8712
10.9	4.5316	4.7107	0.1791	0.5576	-0.5734	11.0005
11.0	4.5443	4.7167	0.1724	0.5743	-0.5658	11.1300
11.1	4.5570	4.7226	0.1656	0.5912	-0.5584	11.2602
RAT-4						
9.7	4.3460	4.6195	0.2735	0.3216	-0.7263	9.3758
9.8	4.3660	4.6248	0.2588	0.3583	-0.6946	9.5470
9.9	4.3860	4.6339	0.2479	0.3856	-0.6736	9.6978
10.0	4.4073	4.6431	0.2358	0.4159	-0.6523	9.8525
10.1	4.4317	4.6523	0.2206	0.4539	-0.6282	10.0196
10.2	4.4561	4.6615	0.2054	0.4918	-0.6065	10.1857
10.3	4.4805	4.6706	0.1901	0.5299	-0.5867	10.3520
10.4	4.5038	4.6798	0.1760	0.5650	-0.5700	10.5135
10.5	4.5226	4.6790	0.1564	0.6136	-0.5490	10.7008
10.6	4.5415	4.6802	0.1387	0.6575	-0.5317	10.8832

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pH	***V'***	***V''***	***V''-V'***	***n_H***	***log $n_H/(1-n_H)$***	***pK_1^H***
			RAT-5			
7.1	4.1756	4.3175	0.1419	1.6467	0.6130	7.7684
7.2	4.1837	4.3354	0.1517	1.6223	0.5564	7.8330
7.3	4.1919	4.3545	0.1626	1.5953	0.5012	7.8957
7.4	4.2000	4.3845	0.1845	1.5408	0.4089	7.9258
7.5	4.2048	4.4001	0.1953	1.5140	0.3706	7.9935
7.6	4.2097	4.4138	0.2041	1.4922	0.3423	8.0681
7.7	4.2145	4.4576	0.2431	1.3952	0.2391	8.0630
7.8	4.2193	4.4953	0.2760	1.3134	0.1725	8.0817
7.9	4.2242	4.5128	0.2886	1.2822	0.1504	8.1519
8.9	4.2725	4.7835	0.5110	0.7304	0.6130	7.7684
9.0	4.2773	4.8253	0.5480	0.6386	0.5564	7.8330
9.1	4.2821	4.8523	0.5702	0.5836	0.5012	7.8957
9.2	4.2870	4.8746	0.5876	0.5405	0.4089	7.9258
9.3	4.2918	4.8952	0.6034	0.5014	0.3706	7.9935
9.4	4.2966	4.9125	0.6159	0.4706	0.3423	8.0681
9.5	4.3066	4.9357	0.6291	0.4381	0.2391	8.0630
9.6	4.3260	4.9670	0.6410	0.4093	0.1725	8.0817
9.7	4.3460	4.9914	0.6454	0.3991	0.1504	8.1519
			RAT-6			
10.0	3.8610	4.0265	0.1655	0.5849	-0.5611	10.1490
10.1	3.8732	4.0475	0.1743	0.5630	-0.5709	10.2100
10.2	3.8854	4.0675	0.1821	0.5436	-0.5800	10.2759
10.3	3.8976	4.0867	0.1891	0.5261	-0.5886	10.3455
10.4	3.9242	4.1250	0.2008	0.4971	-0.6036	10.3950
10.5	3.9545	4.1598	0.2053	0.4862	-0.6095	10.4761
10.6	3.9848	4.2013	0.2165	0.4586	-0.6254	10.5279
10.7	4.0071	4.2293	0.2222	0.4446	-0.6338	10.6033
10.8	4.0214	4.2557	0.2343	0.4145	-0.6532	10.6501
			RAT-7			
10.7	4.0071	4.1529	0.1458	0.6356	-0.5401	10.9415
10.8	4.0214	4.1783	0.1569	0.6079	-0.5513	10.9905
10.9	4.0357	4.2068	0.1711	0.5726	-0.5666	11.0270
11.0	4.0500	4.2310	0.1810	0.5480	-0.5779	11.0837
11.1	4.0643	4.2543	0.1900	0.5257	-0.5888	11.1447
11.2	4.0786	4.2831	0.2045	0.4897	-0.6076	11.1820
11.3	4.0929	4.3122	0.2193	0.4529	-0.6288	11.2179
11.4	4.1104	4.3388	0.2284	0.4304	-0.6428	11.2784
11.5	4.1312	4.3679	0.2367	0.4100	-0.6563	11.3419
			RAT-8			
9.1	3.7184	3.8614	0.1430	0.6402	-0.5383	9.3502
9.2	3.7388	3.8910	0.1522	0.6172	-0.5475	9.4075
9.3	3.7592	3.9203	0.1611	0.5950	-0.5567	9.4671
9.4	3.7796	3.9516	0.1720	0.5678	-0.5687	9.5186
9.5	3.8000	3.9834	0.1834	0.5394	-0.5820	9.5686
9.6	3.8122	4.0103	0.1981	0.5026	-0.6007	9.6046
9.7	3.8244	4.0315	0.2071	0.4802	-0.6129	9.6655
9.8	3.8366	4.0528	0.2162	0.4575	-0.6260	9.7260
9.9	3.8488	4.0773	0.2285	0.4268	-0.6451	9.7719
10.0	3.8610	4.0983	0.2373	0.4049	-0.6598	9.8327
10.1	3.8732	4.1204	0.2472	0.3802	-0.6776	9.8878

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pH	***V'***	***V''***	***V''-V'***	***n_H***	***log $n_H/(1-n_H)$***	***pK_1^H***
RAT-9						
9.4	3.7796	3.9166	0.1370	0.6558	-0.5323	9.6799
9.5	3.8000	3.9459	0.1459	0.6336	-0.5409	9.7378
9.6	3.8122	3.9665	0.1543	0.6126	-0.5494	9.7990
9.7	3.8244	3.9872	0.1628	0.5914	-0.5583	9.8605
9.8	3.8366	4.0100	0.1734	0.5649	-0.5701	9.9134
9.9	3.8488	4.0348	0.1860	0.5334	-0.5850	9.9581
10.0	3.8610	4.0590	0.1980	0.5034	-0.6002	10.0060
10.1	3.8732	4.0820	0.2088	0.4765	-0.6150	10.0591
10.2	3.8854	4.1026	0.2172	0.4556	-0.6272	10.1226
10.3	3.8976	4.1236	0.2260	0.4337	-0.6407	10.1841
10.4	3.9242	4.1616	0.2374	0.4055	-0.6594	10.2338
10.5	3.9545	4.2027	0.2482	0.3789	-0.6786	10.2853
10.6	3.9848	4.2427	0.2579	0.3550	-0.6973	10.3407
RAT-10						
8.6	3.6539	3.7693	0.1154	1.7092	0.8006	8.8231
8.7	3.6652	3.8073	0.1421	1.6420	0.6017	8.9540
8.8	3.6764	3.8451	0.1687	1.5751	0.4644	8.9991
8.9	3.6876	3.8831	0.1955	1.5078	0.3623	9.0420
9.0	3.6989	3.9270	0.2281	1.4258	0.2683	9.1204
9.1	3.7184	3.9826	0.2642	1.3352	0.1889	9.2284
9.2	3.7388	4.0415	0.3027	1.2387	0.1221	9.4573
9.9	3.8488	4.3470	0.4982	0.7502	-0.0999	9.9783
10.0	3.8610	4.3851	0.5241	0.6856	-0.1247	10.0173
10.1	3.8732	4.4231	0.5499	0.6213	-0.1499	10.1538
10.2	3.8854	4.4835	0.5981	0.5008	-0.2003	10.2239
10.3	3.8976	4.5260	0.6284	0.4253	-0.2358	10.3315
10.4	3.9242	4.5754	0.6512	0.3692	-0.2654	10.4548
10.5	3.9545	4.6331	0.6786	0.3017	-0.3064	10.5496

Table 3.4.3: The *pH*, n_H, pK_1^H and other terms for RAT series in DMF at 318.15 K.

pH	*V'*	*V''*	*V''-V'*	n_H	$\log n_H/(1-n_H)$	pK_1^H
RAT-1						
11.7	4.746	4.8563	0.1103	0.7295	-0.5064	12.1309
11.8	4.7575	4.8875	0.13	0.6814	-0.5229	12.1302
11.9	4.769	4.94	0.171	0.5814	-0.5626	12.0428
12.0	4.7805	5.01	0.2295	0.4391	-0.6372	11.8937
12.1	4.792	5.0225	0.2305	0.4368	-0.6387	11.9897
12.2	4.8158	5.0899	0.2741	0.3313	-0.7175	11.8950
12.3	4.8684	5.1605	0.2921	0.2885	-0.7587	11.9080
12.4	4.95	5.2535	0.3035	0.2623	-0.7879	11.9508
RAT-2						
10.8	4.6324	4.8138	0.1814	0.5529	-0.5756	10.8923
10.9	4.6459	4.8310	0.1851	0.5439	-0.5799	10.9765
11.0	4.6596	4.8483	0.1887	0.5352	-0.5841	11.0613
11.1	4.6730	4.8655	0.1925	0.5260	-0.5886	11.1452
11.2	4.6865	4.8828	0.1963	0.5168	-0.5933	11.2292
11.3	4.7001	4.9000	0.1999	0.5081	-0.5978	11.3140
11.4	4.7115	4.9200	0.2085	0.4870	-0.6091	11.3775
11.5	4.7230	4.9350	0.2120	0.4786	-0.6138	11.4627
11.6	4.7345	4.9498	0.2153	0.4706	-0.6183	11.5488
11.7	4.7460	4.9623	0.2163	0.4683	-0.6197	11.6448
11.8	4.7575	4.9803	0.2228	0.4876	-0.6291	11.7171
RAT-3						
9.9	3.9712	4.0879	0.1167	0.7081	-0.5136	10.2848
10.0	4.0007	4.1375	0.1368	0.6580	-0.5315	10.2842
10.1	4.0212	4.2000	0.1788	0.5532	-0.5755	10.1928
10.2	4.0501	4.2313	0.1812	0.5475	-0.5781	10.2828
10.3	4.0765	4.2625	0.1860	0.5358	-0.5838	10.3623
10.4	4.0999	4.2938	0.1939	0.5163	-0.5935	10.4284
10.5	4.1000	4.3074	0.2074	0.4827	-0.6115	10.4699
10.6	4.1352	4.3467	0.2115	0.4729	-0.6170	10.5528
10.7	4.1785	4.3959	0.2174	0.4587	-0.6253	10.6281
10.8	4.1805	4.4152	0.2347	0.4156	-0.6525	10.6520
10.9	4.2057	4.4544	0.2487	0.3811	-0.6769	10.6895
RAT-4						
9.5	4.2836	4.4207	0.1371	0.6594	-0.5310	9.7870
9.6	4.2973	4.4552	0.1579	0.6079	-0.5513	9.7904
9.7	4.3267	4.4867	0.1600	0.6029	-0.5534	9.8814
9.8	4.3600	4.5350	0.1750	0.5661	-0.5695	9.9154
9.9	4.3933	4.5885	0.1952	0.5163	-0.5935	9.9284
10.0	4.4421	4.6425	0.2004	0.5040	-0.5999	10.0069
10.1	4.4947	4.7038	0.2091	0.4831	-0.6113	10.0706
10.2	4.5200	4.7423	0.2223	0.4507	-0.6301	10.1142
10.3	4.5422	4.7808	0.2386	0.4108	-0.6558	10.1433
10.4	4.5644	4.8039	0.2395	0.4088	-0.6571	10.2398
10.5	4.5867	4.8360	0.2493	0.3850	-0.6741	10.2965

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pH	V'	V''	V''-V'	n_H	log $n_H/(1-n_H)$	pK_1^H
			RAT-5			
6.9	3.5956	3.7120	0.1164	1.7063	0.7901	7.6642
7.0	3.6024	3.7372	0.1348	1.6599	0.6472	7.6885
7.1	3.6073	3.7645	0.1572	1.6035	0.5171	7.7068
7.2	3.6121	3.7821	0.1700	1.5712	0.4577	7.7640
7.3	3.6170	3.8135	0.1965	1.5044	0.3579	7.7823
7.4	3.6218	3.8562	0.2344	1.4089	0.2519	7.7772
7.5	3.6267	3.8894	0.2627	1.3376	0.1907	7.8052
7.6	3.6316	3.9173	0.2857	1.2797	0.1487	7.8496
7.7	3.6364	3.9305	0.2941	1.2586	0.1347	7.9299
8.7	3.6850	4.1945	0.5095	0.7171	-0.1126	8.4474
8.8	3.6898	4.2115	0.5217	0.6865	-0.1244	8.5182
8.9	3.6947	4.2435	0.5488	0.6184	-0.1511	8.5509
9.0	3.6995	4.2790	0.5795	0.5413	-0.1827	8.5695
9.1	3.7148	4.3089	0.5941	0.5051	-0.1984	8.6287
9.2	3.7311	4.3382	0.6071	0.4729	-0.2130	8.6909
9.3	3.7475	4.3683	0.6208	0.4390	-0.2290	8.7491
9.4	3.7639	4.4002	0.6363	0.4007	-0.2484	8.7988
9.5	3.7803	4.4247	0.6444	0.3809	-0.2589	8.8716
			RAT-6			
9.8	3.8302	3.9827	0.1525	0.6173	-0.5474	10.0076
9.9	3.8419	4.0057	0.1638	0.5890	-0.5593	10.0563
10.0	3.8535	4.0277	0.1742	0.5630	-0.5709	10.1101
10.1	3.8651	4.0469	0.1818	0.5441	-0.5798	10.1768
10.2	3.8767	4.0675	0.1908	0.5217	-0.5908	10.2377
10.3	3.8884	4.0893	0.2009	0.4965	-0.6039	10.2939
10.4	3.9000	4.1128	0.2128	0.4668	-0.6205	10.3422
10.5	3.9125	4.1347	0.2222	0.4434	-0.6346	10.4012
10.6	3.9250	4.1588	0.2338	0.4145	-0.6532	10.4500
10.7	3.9375	4.1800	0.2425	0.3929	-0.6683	10.5110
10.8	3.9500	4.2032	0.2532	0.3663	-0.6883	10.5619
			RAT-7			
10.5	3.9125	4.0633	0.1508	0.6222	-0.5454	10.7168
10.6	3.9250	4.0862	0.1612	0.5963	-0.5562	10.7694
10.7	3.9375	4.1069	0.1694	0.5759	-0.5651	10.8329
10.8	3.9500	4.1305	0.1805	0.5482	-0.5778	10.8841
10.9	3.9625	4.1535	0.1910	0.5221	-0.5906	10.9384
11.0	3.9750	4.1752	0.2002	0.4992	-0.6025	10.9986
11.1	3.9875	4.1993	0.2118	0.4703	-0.6185	11.0484
11.2	4.0000	4.2222	0.2222	0.4445	-0.6339	11.1032
11.3	4.0172	4.2498	0.2326	0.4187	-0.6504	11.1576
11.4	4.0345	4.2755	0.2410	0.3980	-0.6647	11.2202
11.5	4.0517	4.3031	0.2514	0.3722	-0.6837	11.2730
			RAT-8			
8.9	3.7135	3.8643	0.1508	0.6205	-0.5461	9.1136
9.0	3.7270	3.8898	0.1628	0.5905	-0.5587	9.1589
9.1	3.7405	3.9157	0.1752	0.5594	-0.5726	9.2037
9.2	3.7541	3.9375	0.1834	0.5389	-0.5823	9.2678
9.3	3.7676	3.9601	0.1925	0.5162	-0.5936	9.3281
9.4	3.7811	3.9825	0.2014	0.4940	-0.6053	9.3895
9.5	3.7946	4.0080	0.2134	0.4640	-0.6222	9.4373
9.6	3.8070	4.0315	0.2245	0.4363	-0.6390	9.4887
9.7	3.8186	4.0560	0.2374	0.4040	-0.6604	9.5312
9.8	3.8302	4.0769	0.2467	0.3809	-0.6771	9.5890

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pH	***V'***	***V''***	***V''-V'***	***n_H***	***log $n_H/(1-n_H)$***	***pK_1^H***
RAT-9						
9.4	3.7811	3.9371	0.1560	0.6081	-0.5512	9.5907
9.5	3.7946	3.9593	0.1647	0.5863	-0.5605	9.6515
9.6	3.8070	3.9810	0.1740	0.5631	-0.5709	9.7102
9.7	3.8186	4.0004	0.1818	0.5436	-0.5800	9.7760
9.8	3.8302	4.0227	0.1925	0.5169	-0.5932	9.8293
9.9	3.8419	4.0429	0.2010	0.4957	-0.6044	9.8925
10.0	3.8535	4.0650	0.2115	0.4695	-0.6190	9.9469
10.1	3.8651	4.0871	0.2220	0.4433	-0.6346	10.0011
10.2	3.8767	4.1072	0.2305	0.4221	-0.6482	10.0636
10.3	3.8884	4.1294	0.2410	0.3960	-0.6661	10.1166
10.4	3.9000	4.1511	0.2511	0.3708	-0.6848	10.1704
RAT-10						
8.5	3.6714	3.7781	0.1067	1.7312	0.8869	8.5247
8.6	3.6810	3.8118	0.1308	1.6706	0.6766	8.6249
8.7	3.6905	3.8482	0.1577	1.6030	0.5161	8.7750
8.8	3.7000	3.8882	0.1882	1.5263	0.3876	8.9173
8.9	3.7135	3.9409	0.2274	1.4278	0.2703	9.0011
9.0	3.7270	3.9775	0.2505	1.3698	0.2169	9.1591
9.1	3.7405	4.0269	0.2864	1.2798	0.1487	9.2805
9.8	3.8302	4.3136	0.4834	0.7868	-0.0858	9.8834
9.9	3.8419	4.3665	0.5246	0.6838	-0.1254	9.9935
10.0	3.8535	4.4069	0.5534	0.6119	-0.1537	10.1935
10.1	3.8651	4.4539	0.5888	0.5235	-0.1904	10.2604
10.2	3.8767	4.4856	0.6089	0.4735	-0.2127	10.3007
10.3	3.8884	4.5198	0.6314	0.4175	-0.2397	10.4285
10.4	3.9000	4.5621	0.6621	0.3410	-0.2817	10.4952

$$\log pK_1^H = pH + \log[\overline{n_H} / (\overline{n_H} - 1)] \quad \ldots (3.4.18)$$

The calculated pk_1^H values are reported in Tables 3.4.1 to 3.4.3 for all compounds along with those obtained by half-integral method. From these log pK_1^H values, the average value of pK_1^H was calculated. Further, It is evident from Tables 3.4.1 to 3.4.3 that these pk_1^H values are in agreement with that obtained by half-integral method.

For RAT-5 and RAT-10, the proton-ligand constants were calculated by solving equation (3.4.1). For all the points below $\overline{n_H}$ =1, the following equation was used

$$log\ pK_1^H = pH + log\, \bar{n}_H / (\bar{n}_H - 1) \quad \ldots (3.4.19)$$

where as for all the points above $\overline{n_H}$ =1, the equation used was:

$$logpK_2^H = pH + log[(\bar{n}_H - 1)/(2 - \bar{n}_H)] \quad \ldots (3.4.20)$$

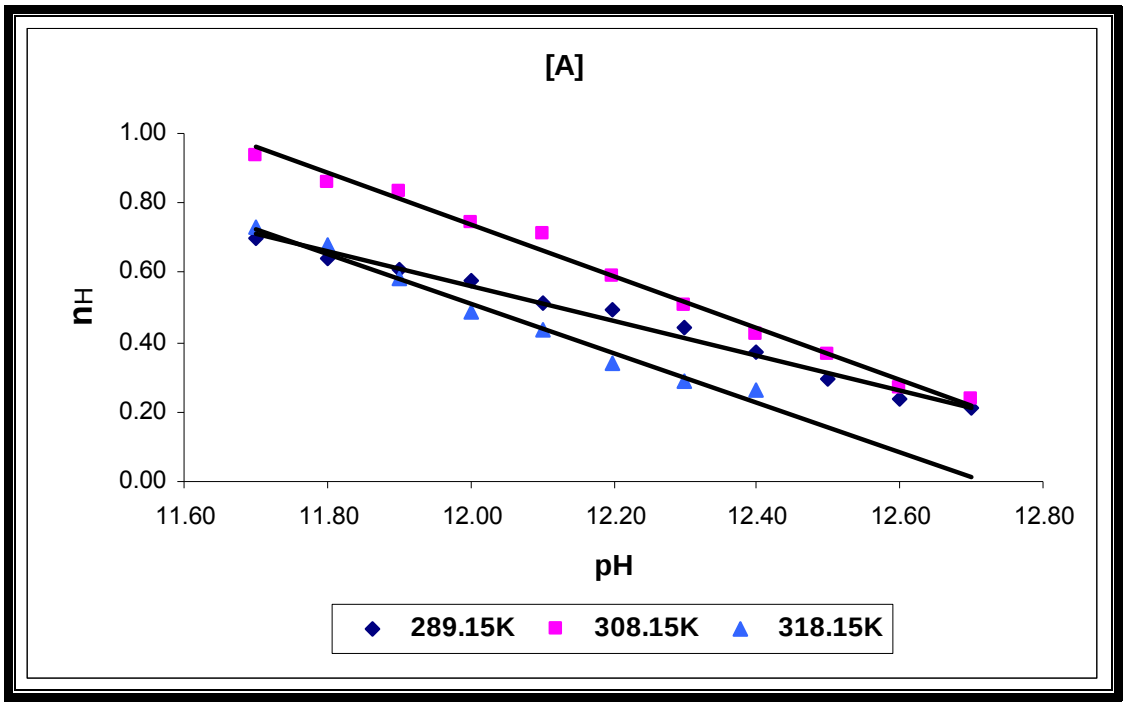
From the various values of $\log pK_1^H$ (or $log\ pK_2^H$) calculated for a system, the average value was calculated.

Table 3.4.4 shows the dissociation constant of compounds by both average and half-integral method at different temperatures. It is observed that the pK^H value decreases with increasing temperature, i.e. the acidity of the compounds increases, independently of the nature of the substituent[46]. Further, pK_1^H is minimum in RAT-5 and maximum in RAT-1 suggesting thereby maximum dissociation in RAT-5 which contains hydroxy group. RAT-1 contains $–OCH_3$ group which decreases dissociation. RAT-5 is found to be more acidic than other compounds as expected as it contains –OH group. Overall, RAT-1 is more basic and RAT-5 is most acidic. Thus, presence of different substituents influences the dissociation of the compound due to inductive effect.

Further, some thermodynamic parameters such as enthalpy of solution, Gibb's energy change and entropy of solution have also been evaluated from dissociation constants at different temperatures for these systems.

The enthalpy changes (ΔH) for the dissociation process were evaluated[47] from the slope of the plot pK_1^H vs. 1/T.

Figure 3.4.2: The plot of n_H against pH for [A] RAT-1 and [B] RAT-2 in DMF at different temperatures.



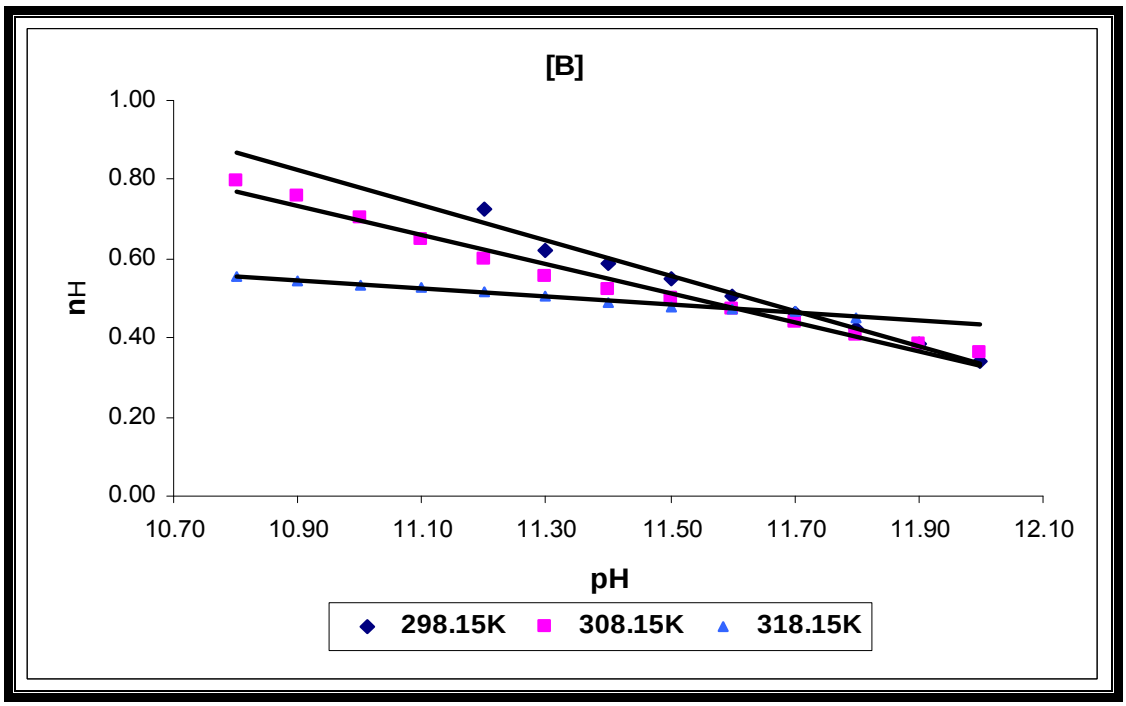
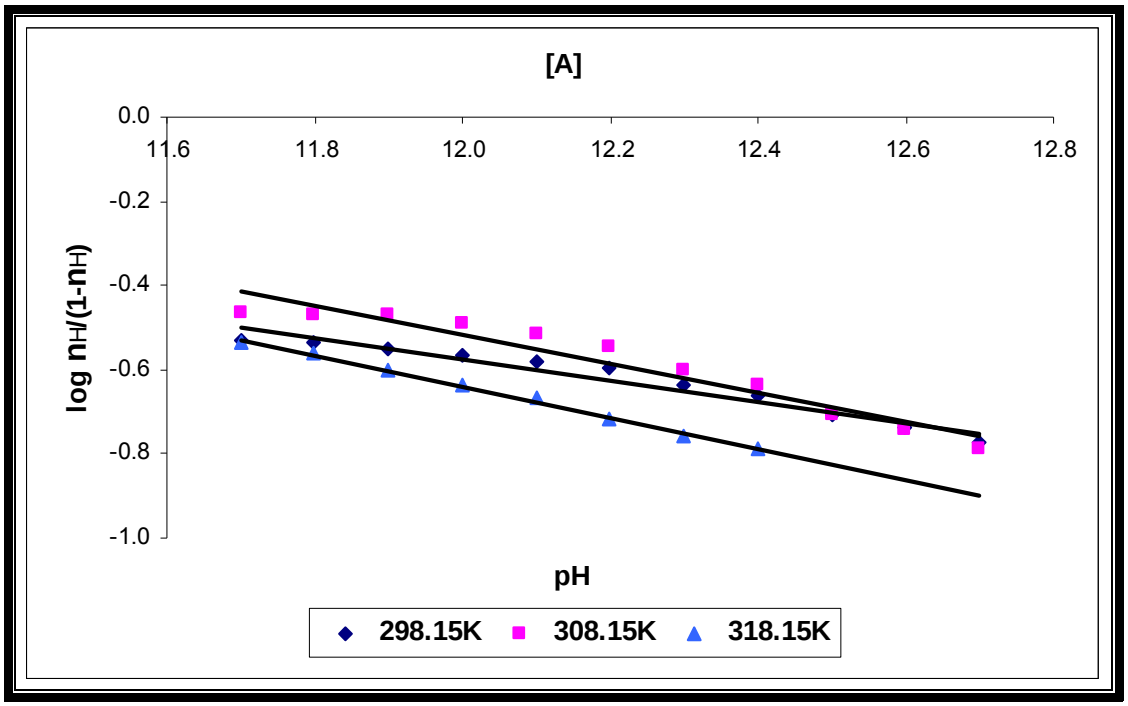


Figure 3.4.3: The plot of log $n_H/(1-n_H)$ against B for [A] RAT-1 and [B] RAT-2 in DMF at different temperatures.



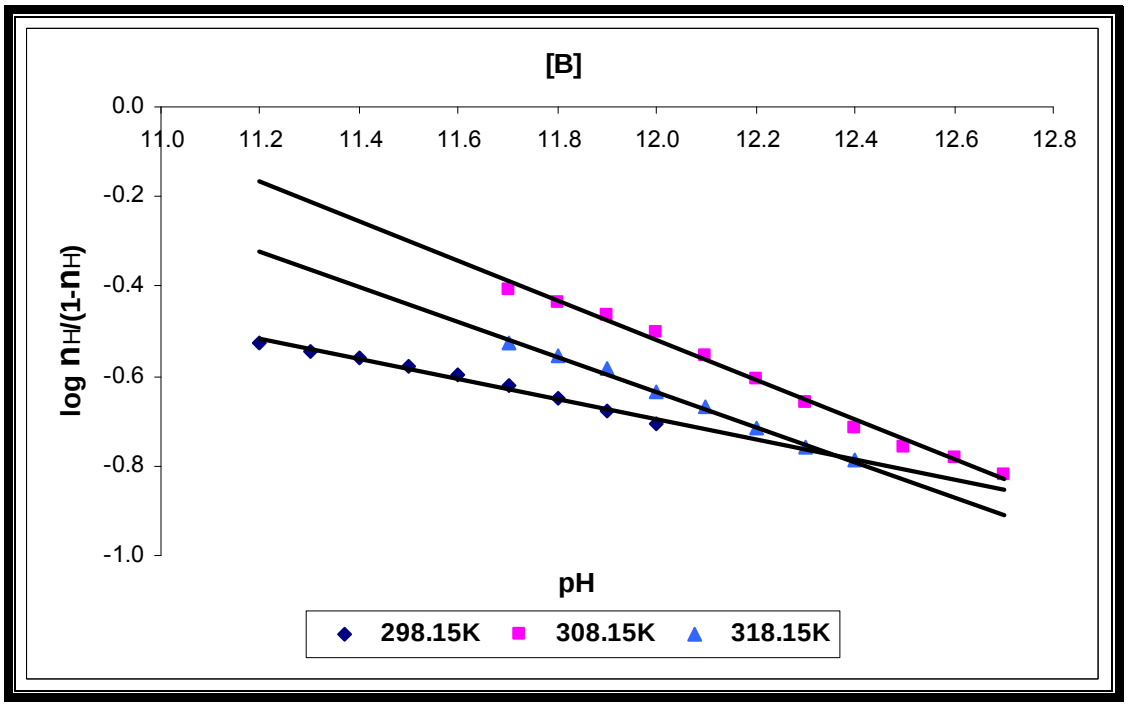


Table 3.4.4: The pK_1^H values for all the studied compounds calculated by different methods in DMF at different temperatures.

Comp. code	T/K	Half-intergal method pK_1^H	Average method pK_1^H	Comp. code	T/K	Half-intergal method pK_1^H	Average method pK_1^H
RAT-1	298.15	12.12	12.11	***RAT-6***	298.15	10.50	10.50
	308.15	12.11	12.00		308.15	10.41	10.40
	318.15	11.99	12.01		318.15	10.27	10.28
RAT-2	298.15	11.62	11.62	***RAT-7***	298.15	11.35	11.33
	308.15	11.55	11.50		308.15	11.14	11.34
	318.15	11.31	11.33		318.15	11.00	10.99
RAT-3	298.15	10.98	11.03	***RAT-8***	298.15	9.82	9.88
	308.15	10.57	11.50		308.15	9.64	9.62
	318.15	10.47	10.47		318.15	9.37	9.38
RAT-4	298.15	10.33	10.30	***RAT-9***	298.15	10.09	10.12
	308.15	10.11	10.20		308.15	10.00	10.01
	318.15	10.01	10.02		318.15	9.87	9.89
RAT-5	298.15	8.18 (n_H=1.5) 9.05 (n_H=0.5)	8.00 (n_H=1.5) 9.20 (n_H=0.5)	***RAT-10***	298.15	9.14 (n_H=1.5) 10.47 (n_H=0.5)	9.10 (n_H=1.5) 10.42 (n_H=0.5)
	308.15	7.96 (n_H=1.5) 8.85 (n_H=0.5)	7.80 (n_H=1.5) 8.80 (n_H=0.5)		308.15	9.10 (n_H=1.5) 10.20 (n_H=0.5)	9.09 (n_H=1.5) 10.24 (n_H=0.5)
	318.15	7.75 (n_H=1.5) 8.64 (n_H=0.5)	7.68 (n_H=1.5) 8.62 (n_H=0.5)		318.15	8.96 (n_H=1.5) 10.18 (n_H=0.5)	8.90 (n_H=1.5) 10.22 (n_H=0.5)

Table 3.4.5. Thermodynamic parameters for the dissociation of RAT series in DMF-Water mixture at different temperatures.

compounds	*T/K*	ΔG_{Hal} kJ mol^{-1}	ΔG_{Ave} kJ mol^{-1}	ΔH_{Hal} kJ mol^{-1}	ΔH_{Ava} kJ mol^{-1}	$-\Delta S_{Hal}$ J mol^{-1} K^{-1}	$-\Delta S_{Aval}$ J mol^{-1} K^{-1}
RAT-1	298.15	67.045	67.101	12.764	11.488	187.73	192.33
	308.15	70.802	71.451			188.34	194.59
	318.15	73.160	73.039			189.84	193.47
RAT-2	298.15	64.332	64.332	26.805	26.511	129.79	130.80
	308.15	67.852	68.147			133.21	135.12
	318.15	69.018	68.896			132.68	133.23
RAT-3	298.15	61.066	60.789	47.807	47.330	45.65	46.55
	308.15	61.952	62.424			45.71	48.98
	318.15	63.779	63.779			50.02	51.70
RAT-4	298.15	57.190	57.190	27.850	28.720	101.47	98.46
	308.15	60.181	59.650			104.92	100.38
	318.15	61.038	60.977			104.32	101.39
RAT-5	298.15	44.291 50.934	45.287 50.104	42.549 37.017	39.420 39.889	6.03 48.13	20.29 35.33
	308.15	46.021 50.921	46.965 52.213			11.27 48.37	24.49 40.01
	318.15	46.783 52.510	47.210 52.632			13.31 48.70	24.49 40.05
RAT-6	298.15	58.132	58.132	60.704	60.705	130.94	131.88
	308.15	61.421	61.362			133.54	134.23
	318.15	62.561	62.622			132.93	133.97
RAT-7	298.15	62.838	62.727	65.191	65.527	100.18	106.58
	308.15	65.728	66.908			103.39	113.58
	318.15	67.008	66.947			104.16	110.13
RAT-8	298.15	54.367	54.699	56.108	56.199	46.16	40.19
	308.15	56.877	56.759			51.46	44.39
	318.15	57.078	57.139			50.48	44.19
RAT-9	298.15	55.862	56.028	58.329	58.445	118.70	102.71
	308.15	59.001	59.060			121.57	106.22
	318.15	60.124	60.246			121.28	106.61
RAT-10	298.15	50.602 57.966	50.381 57.689	13.05 20.51	17.09 20.15	129.89 129.54	115.13 129.83
	308.15	53.691 60.181	53.632 60.417			131.89 128.74	118.59 130.69
	318.15	54.581 62.013	54.215 62.256			130.54 130.45	116.69 132.35

Using the following equation, Gibbs energy changes (ΔG) have been evaluated[47].

$$\Delta G = 2.303\ RT\ pK^{H} \quad \ldots (3.4.21)$$

From these ΔG and ΔH values, entropy values (ΔS) were calculated using the relationship[47], assuming ΔH to be independent of temperature[48]

$$\Delta S = (\Delta H - \Delta G) / T \quad \ldots. (3.4.22)$$

All these thermodynamic parameters are reported in Table 3.4.5 for both average and half-integral methods. It is observed that for both methods, values are in good agreement with each other.

The positive value of ΔH indicates that dissociation process is endothermic and is accompanied by absorption of heat. Further, ΔG values are positive indicating thereby that the dissociation process is not spontaneous. However, negative value of ΔS is due to the increased order.

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Section-V
Thermal Properties

INTRODUCTION

Today, an impressive array of powerful, elegant ant automated tools is available with physical and material scientists for obtaining qualitative and quantitative information about the composition, structure and characteristics of materials. Among the several instruments and techniques, thermal analysis has grown rapidly in recent years.

Thermal analysis is the generic name used to describe a series of analytical techniques which measure physical and chemical changes in materials as a function of temperature and time. These thermal properties can be studied by various thermal techniques which are among the most powerful experimental tools developed during the last century. These techniques are able to characterize a wide range of materials and material properties[1,2].

Some of the most commonly used techniques are Differential Scanning Calorimetry (DSC), Differential Thermal Analysis (DTA), Thermo Gravimetric Analysis (TGA), Evolved Gas Detection (EGD), Evolved Gas Analysis (EGA) etc.

Thermogravimetric analysis (TGA) is one of the most widely used thermal analysis techniques which specifically measure the weight changes (gains and losses) in materials. In TGA, the mass of sample is recorded as a function of temperature or time. The plot of mass change versus temperature is known as thermogram or TG curve. TG curves are characteristic for a given compound because of unique sequence of physicochemical reactions which occur over definite temperature ranges and at rates that are a function of molecular structure[3]. The changes in weight are due to various physical and chemical changes. Such measurements provide information about the material's thermal stability[4] as well as the material's composition[5]. TGA technique is used to estimate the product's life time[6-8]. The TGA decomposition kinetics method[9] uses the data from experiments run at several heating rates to calculate kinetic parameters[10-13] including activation energy and specific rate constant.

Literature survey shows that thermal analysis of various types of compounds such as polymers[14,15], geological materials[16], electronic circuit boards[17], coals[18], drugs[19], pharmaceutical material[20,21], catalyst[22,23], nuclear

fuel[24-27], dyes[28,29], fertilizers[30-32], inorganic[33-35] and organic[36-41] compounds have been reported. Current areas of applications include environmental measurements[42], composition analysis, product reliability[43] and dynamic properties[44]. Further, various reversible and non-reversible reactions[45], the decomposition of compounds at definite conditions[46], the decomposition of molecules adsorbed on a surface, phase transitions[47] etc. can also be studied.

This method can not distinguish the actual nature of the material evolved in the course of the process and is also handicapped in resolving overlapped thermal events[48]. This is the limitation of this technique.

In the present section, thermal properties of some dihydropyrimidin thiones (RAT series) have been studied TGA technique.

THEORY

From TGA curves, various kinetic parameters can be evaluated by several methods. In all these methods, it is assumed that thermal and diffusion barriers are negligible because small quantity of material is used. The shape of any TGA curve depends on the nature of apparatus and the way in which it is used. Further, Arrhenius equation is valid in all these methods.

The kinetic treatments are generally based on the relationship of the type:

$$dC/dt = K f(C) \quad \text{... (3.5.1)}$$

where C is the degree of conversion, t is time and K is rate constant. $f(C)$ is a temperature independent function of C.

The constant K is assumed to have the Arrhenius form:

$$K = A e^{-E/RT} \quad \text{... (3.5.2)}$$

C can also be defined as:

$$C = 1-(W/W_0) \quad \text{... (3.5.3)}$$

where W_0 and W are the initial weight at $t=0$ and weight at any time t of the material.

Equation (3.5.3) can be written as:

$$(W/W_0) = (1-C) \quad \text{... (3.5.4)}$$

W/W_0 is known as residual weight fraction.

Thus, the rate of conversion is,

$$dC/dt = - (1/W_0)(dW/dt) \quad \text{... (3.5.5)}$$

For homogeneous kinetics, the conversion is assumed to be of the form:

$$f(C) = (1-C)^n \quad \text{... (3.5.6)}$$

where n is the order of the reaction.

Substituting the values from equation (3.5.2) and (3.5.6) in equation (3.5.1) gives:

$$dC/dt = A\, e^{-E/RT}\, (1-C)^n$$

or $$dC/dt = (A/\beta)\, e^{-E/RT}\, (1-C)^n \quad \text{... (3.5.7)}$$

where A is the frequency factor, β is the rate of heating and E is the energy of activation.

Various methods for single and multiple heating rates have been reported. The methods of single heating rate are as follows:

1. Freeman-Carroll[49] and Anderson-Freeman Method[50]:

At a single heating rate, Freeman and Carroll gave the following relation to analysis TGA data :

$$\ln (dC/dt)/\ln (1-C) = n\text{-}E/R\ [(1/T/(\Delta \ln(1-C)] \quad \text{... (3.5.8)}$$

A plot of left hand side against $(1/T)/(\Delta \ln(1-C))$ gives a straight line with a slope equal to $-E/R$ and the intercept is equal to n.

Above equation (3.5.8) is modified by Anderson and Freeman in the following form:

$$(\Delta \ln[dC/dt]) = n\ (\Delta \ln(1-C)) - E/R\ \Delta(1/T) \quad \text{... (3.5.9)}$$

The plot of $(\Delta \ln[dC/dt])$ against $(\Delta \ln(1-C))$ for equal intervals of $\Delta(1/T)$ gives a straight line with slope equal to n and intercept $-E/R\Delta(1/T)$.

2. Sharp-Wentworth method[51]:

For order kinetics (n=1), Sharp and Wentworth gave the relation:

$$\log [(dC/dt)/(1-C)] = \log (A/\beta) - (E/2.303R).(1/T) \quad \text{... (3.5.10)}$$

The plot of $\log [(dC/dt)/(1-C)]$ against $1/T$ would be a straight line with slope equal to $-(E/2.303R)$ and intercept equal to $\log (A/\beta)$.

3. Chatterjee Method[52]:

Chatterjee gave the following relation to determine the order of reaction (n).

$$n = [\log(dW/dt)_1 - \log(dW/dt)_2] / (\log W_1 - \log W_2) \quad \text{... (3.5.11)}$$

where W_1 and W_2 are the sample weights.

4. Horowitz and Metzger method[53] :

In this method, the value of energy of activation E can be determined from a single TG curve by the relation:

$$ln\,[ln(1-C)^{-1}] = (E/RT_s^2)\theta \quad \text{... (3.5.12)}$$

where $\theta = T-T_s$. T_s is the temperature at which the rate of decomposition is maximum. The frequency factor A and entropy change ΔS can be determined by the following equations:

$$ln\,E - ln\,(RT_s^2) = ln\,A - ln\beta - E/RT_s \quad \text{... (3.5.13)}$$

$$A = (k_bT / h)\, e^{\Delta S/R} \quad \text{... (3.5.14)}$$

where k_b is Boltzmann constant and h is Planck's constant.

EXPERIMENTAL

Thermo gravimetric analysis (TGA) made on the instrument "Pyris-1, Perkin Elmer Thermal Analysis" at the heating rate of 10°C/min in nitrogen atmosphere for all the RAT series.

RESULTS AND DISCUSSION

The TGA thermo grams of are given in Figure 3.5.1. Various thermal properties such as initial decomposition temperature (IDT), the decomposition temperature range and the maximum degradation along with the percentage weight loss are reported in Table 3.5.1.

For most of the compounds, degradation is single step process. However, for compounds RAT-1 and RAT-6, multi step degradation takes place.

The thermal stability can not be decided by weight loss for RAT-1 and RAT-6, because degradation is multi step process (Figures 1 and 3). Further, the variation in the trend of thermal decomposition might be interpreted by taking into account some interactions (structural as well as electronic) and also because of several experimental factors.

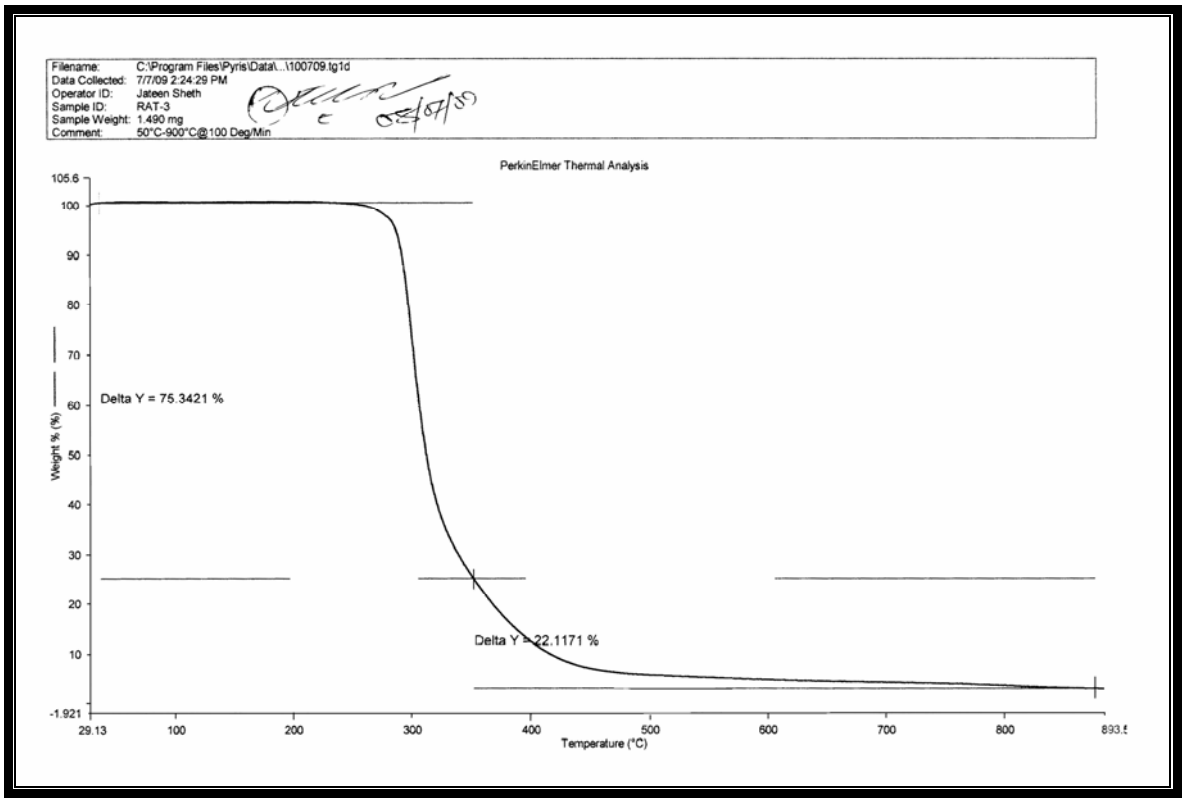
Looking to the initial decomposition temperature in Table 3.5.1, RAT-10 is most unstable and RAT-2 is most stable. RAT-10 contains 2-OH group whereas RAT-2 is without substitution. Thus, the absence of any functional group to aryl ring increases the stability.

The decomposition continues up to approximately 800 and up for RAT-2, RAT-3 and RAT-4. RAT-2 is without any functional group. Whereas RAT-3 and RAT-4 contain 4-methyl and 4-fluoro groups respectively which increase the decomposition temperature.

Comparison of RAT-5 and RAT-10 shows that RAT-5 is more stable than RAT-10. Both these compounds contain hydroxyl group. In RAT-5, it is at 4 position whereas in RAT-10, it is at 2-position. RAT-6 and RAT-8 contain chloro group at 4- and 2- positions respectively. The initial decomposition temperature is higher for RAT-8 but decomposition range is higher for RAT-6 containing 3-chloro group. Similarly, RAT-7 and RAT-9 contain nitro group at 4- and 2- positions respectively. In this case, RAT-9 is unstable than RAT-7. Again, decomposition range is higher for RAT-7 containing 3-nitro group. This suggests that position of functional groups also affect the stability. Thus, the presence of group at ortho (2-) position decreases the stability.

From thermograms, various kinetic parameters, such as order of the degradation (n), energy of activation (E), frequency factor (A) and entropy

Figure 3.5.1: The TGA graphs of RAT-3 and RAT-6.



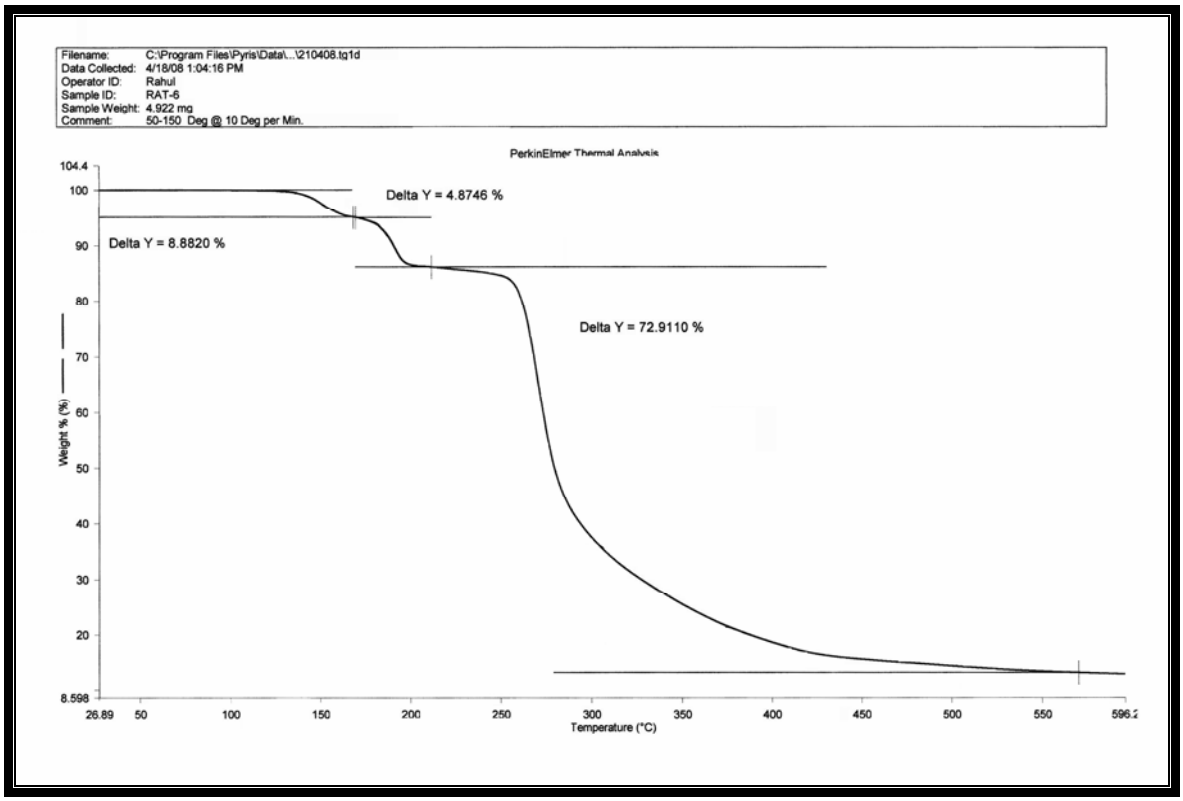


Table 3.5.1: TGA data for synthesized RAT series.

Comp. Code	*Amt. mg.*	*Initial Decomp. Temp. (^oC)*	*Decomp. range (^oC)*	*% Wt. loss*	*Residual Wt. Loss mg.*	*Max Degrad. Temp (^oC)*
RAT-1	2.230	188	188-621	99.74	2.222	1051.65
RAT-2	5.827	280	280-792	98.75	5.754	739.15
RAT-3	1.490	255	255-824	98.80	1.472	718.15
RAT-4	2.727	230	230-665	99.21	2.705	717.15
RAT-5	2.916	167	167-820	81.76	2.384	710.15
RAT-6	4.922	125	125-548	86.24	4.244	691.15
RAT-7	9.423	200	200-600	61.31	5.777	717.15
RAT-8	7.493	178	178-400	79.74	5.974	641.15
RAT-9	4.406	146	146-400	65.44	2.883	540.65
RAT-10	5.800	98	98-500	64.94	3.766	611.15

Table 3.5.2: The kinetic parameters of RAT series.

Comp. code	*n*	*E* *kJ.mol^{-1}*	*A* *s^{-1}*	*ΔS* *J.mol^{-1}.K^{-1}*
RAT-1 1st step	1.98	97.4230	3.4511 X 10^3	-34.5081
RAT-1 2nd step	1.96	58.7213	24.3891	-76.6816
RAT-2	2.90	25.9388	1.8345	-94.2612
RAT-3	2.68	82.4707	9.0470 X 10^4	-4.1805
RAT-4	2.02	49.3677	2.1480 X 10^2	-54.4111
RAT-5	4.08	14.8903	0.2086	-112.0020
RAT-6 1st step	1.19	98.6705	3.3603 X 10^6	26.1914
RAT-6 2nd step	15.31	37.4961	30.3864	-70.3638
RAT-6 3rd step	4.09	3.3015	0.0069	-95.6127
RAT-7	2	34.0375	11.3220	-78.8791
RAT-8	1.95	64.0843	1.4720 X 10^4	-18.3345
RAT-9	6.95	18.9933	0.0056	-139.776
RAT-10	7.75	46.4652	6.6107 X 10^2	-43.7351

change (ΔS) have also been evaluated for each step and are reported in Table 3.5.2.

It is evident from Table 3.5.2 that order of reaction is quite different for all the compounds. For single step decomposition, order of reaction varies from 1.95 to 7.75. For RAT-1 compound, the order of reaction is almost same for both steps, difference is only of 0.02. However, much change is observed for different steps in RAT-6.

For single step degradation, energy of activation (E) is maximum for RAT-3 and minimum for RAT-5. The values of frequency factor (A) are also showed variation in first step. The frequency factor is maximum for RAT-3 and minimum for RAT-9. For multi step degradation, in both RAT-1 and RAT-6, energy of activation and frequency factor is higher for the first step.

Further, change in entropy (ΔS) for all the compounds are calculated by equation 3.5.14. It is observed that entropy change is negative for all compounds except RAT-6 for the first step. The negative ΔS values indicate that the activation compound has a more ordered or more rigid structure than the reactants and reaction is slower than the normal. Whereas the positive ΔS values indicate that the transition state is in less ordered state[54].

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Section-VI
Conductance

INTRODUCTION

Electrical conductance of an electrolyte solution is a measure of the solution's ability to conduct electricity and it is based on Ohm's law. It is a property of ionic solutions. From a macroscopic point of view, ionic conductance of solution is similar to electron or hole conductance through solid object. In the latter cases, electrons are moving without ion cores, while in the former, charges are moving as ions.

Although water itself is a very poor conductor of electricity, the presence of ionic spices in solution increases the conductance considerably. The conductance of such electrolytic solutions depends on the concentration of the ions, nature of the ions presents (though their charges and mobility), temperature and viscosity of the medium.

The conductometry is widely applicable for acid-base titration reactions for determine relative strength of the two weak acids or bases[1], solubility of sparingly soluble salt[2], for determination of the dissociation constant[3] of weak electrolytes, and in determining equilibrium constant, rates of reactions that proceed with the formation or disappearance of ions and also used to determined interionic forces etc[4-6].

This technique is also useful to various biological processes[7-10]. D'Errico[11] used this technique for regulation of the osmotic pressure in the animal organism. Poole[12] have studied the conductivity of glass. The specific conductivity of hydrogen clay sols have also been reported by Mitra and Ghosh[13]. The interactions of Gum karaya (neutral salts) and nonelectrolytes[14] and of sucrose with some multivalent ions[15] have also been studied by this technique.

Literature survey shows that conductance of many inorganic and organic compounds have been measured in aqueous and non-aqueous solvents[16-27]. Karelson and Kuura[28] have reported the conductivity of lithium chloride solutions in ethanol. Toshmatov et al.[29] have reported the diffusion of fluoride ions in a potassium yttrium fluoride crystal and sodium fluoride-yttrium fluoride solid solutions at high temperatures by this technique. Liu and coworkers[30] have studied the conductance of sodium ethanolate. The thermal conductivity of various other materials has also been measured[31-33].

Further, Calinescu et al.[34] have reported conductivity of 4-hydroxy-5-methoxy-isophthaldehyde-bis(dimethylhydrazone) complexes. The conductance of o-nitrophenol, 1-nitroso-2 naphthol and 8-hydroxyquinoline complexes were studied by Prakash and Eqbal[35]. Zhang and coworkers[36] studied the thermal decomposition reaction kinetics of complexes of $[Sm(o\text{-}MOBA)_3$ $bipy]_2H_2O$ and $[Sm(m\text{-}MOBA)_3bipy]_2H_2O$ by conductometry. Macinnis et al.[37] have measured the conductance of sodium dihydroxybenzoates of aqueous solutions. The electrolysis method for producing 4-aminophenol was reported by Zan[38]. Zhao and coworkers[39] studied the characterization of Schiff bases derived from adamantine amine and o-vanillin. Doyle[40] have reported the conductance of thiazole derivatives.

In the present section, conductance of all the synthesized dihydropyrimidinthiones (RAT series) were measured in N, N-dimethyl formamide (DMF) and tetrahydrofuran (THF) at 308.15 K.

EXPERIMENTAL

The solvents DMF and THF were purified by fractionally distillation by the method reported in the literature[41].

The solutions of different concentrations were prepared for each compound in DMF and THF and the conductance of each solution was measured by using Elico Conductivity Meter (Model No. CM 180) at 308.15 K. The measured conductance was corrected by subtracting the conductance of pure solvent.

RESULTS AND DISCUSSION

The measured conductance (*k*) of each solution after correction was used to determine the specific conductance (κ), which is then used for the calculation of equivalent conductance (λ_c).

The equations used for calculating specific conductance (κ) and equivalent conductance (λ_c) are:

$$\kappa = k\theta \qquad \ldots(3.6.1)$$

$$\lambda_c = 1000\frac{\kappa}{C} \qquad \ldots (3.6.2)$$

where θ is the cell constant and *c* is the concentration (g.equi./lit.) of solution. For DMF solutions, cell constant θ was 0.96 cm^{-1} where as for THF, it was 0.98 cm^{-1}.

These equivalent conductance values of all the RAT series derivatives in DMF and THF are reported in Tables 3.6.1 and 3.6.2 along with measured conductance (k). In THF, the relatively low conductivities are due to greater electro relaxation effect owing to the higher permittivity of THF, which contributes interionic repulsions to a larger extent[42]. It is observed that for all the systems studied, conductance increases with concentration (as also shown in Figures. 3.6.1 and 3.6.2).

The equivalent conductance (λ_c) is plotted against $\sqrt{C}$ for all compounds as shown in Figures 3.6.3 and 3.6.4. For all the dihydropyrimi-denthiones (RAT series) derivatives, the equivalent conductance increases with concentration in both the solvents. It is obvious from figures that all derivatives behave as weak electrolytes in both the solvents.

For weak electrolytes, it is difficult to determine λ_0. However, in the studied solutions of compounds, λ_0 values are evaluated approximately by extrapolation method. These values are compared with those determined by an alternate procedure using the following equation.

$$k = k_0 + \lambda_0 c + c\phi_{(c)} \qquad \ldots\ldots (3.6.3)$$

where k and k_0 are the electrolytic conductivity of the solutions and solvent respectively. c is the equivalent concentration and the function $\Phi_{(c)}$ denotes the effect of interionic interactions.

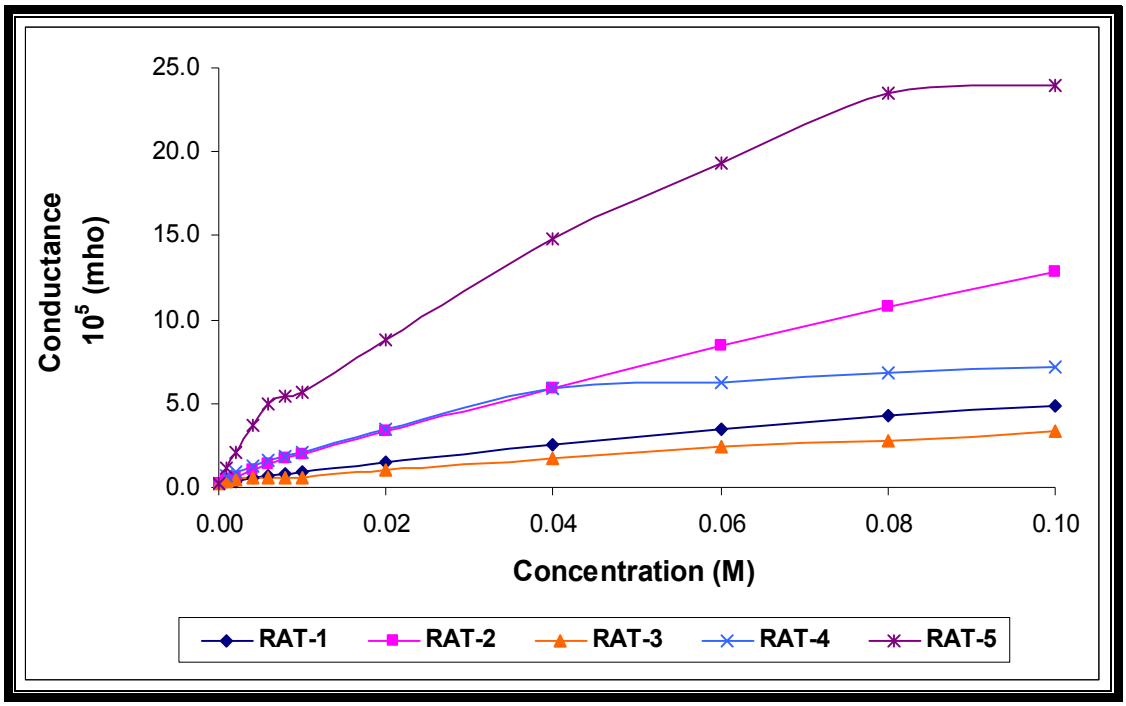
Table 3.6.1: The conductance (*k*) and equivalent conductance (λ_C) of RAT series in DMF at 308.15 K.

Conc. M	***k·10⁵ mho***	***λ_C mho.cm².equi.⁻¹***	***k·10⁵ mho***	***λ_C mho.cm².equi.⁻¹***	***k·10⁵ mho***	***λ_C mho.cm².equi.⁻¹***	***k·10⁵ mho***	***λ_C mho.cm².equi.⁻¹***	***k·10⁵ mho***	***λ_C mho.cm².equi.⁻¹***
	RAT-1		***RAT-2***		***RAT-3***		***RAT-4***		***RAT-5***	
0.000	0.200	-	0.200	-	0.200	-	0.200	-	0.200	-
0.001	0.325	1.2250	0.420	2.1560	0.380	1.7640	0.715	5.0470	1.200	9.5616
0.002	0.391	0.9359	0.624	2.0776	0.480	1.3720	0.910	3.4790	2.040	8.8128
0.004	0.550	0.8575	0.997	1.9527	0.605	0.9923	1.320	2.7440	3.720	8.4384
0.006	0.656	0.7448	1.340	1.8620	0.610	0.6697	1.580	2.2540	5.000	7.6736
0.008	0.790	0.7228	1.700	1.8375	0.612	0.5047	1.820	1.9845	5.410	6.2472
0.010	0.900	0.6860	1.910	1.6758	0.630	0.4214	2.090	1.8522	5.700	5.2762
0.020	1.500	0.6370	3.350	1.5435	1.030	0.4067	3.500	1.6170	8.800	4.1261
0.040	2.500	0.5635	5.900	1.3965	1.740	0.3773	5.900	1.3965	14.800	3.5030
0.060	3.500	0.5390	8.450	1.3475	2.410	0.3610	6.300	0.9963	19.300	3.0554
0.080	4.300	0.5023	10.800	1.2985	2.820	0.3210	6.800	0.8085	23.500	2.7955
0.100	4.900	0.4606	12.800	1.2348	3.300	0.3038	7.200	0.6860	24.000	2.2844
	RAT-6		***RAT-7***		***RAT-8***		***RAT-9***		***RAT-10***	
0.001	0.900	6.8208	0.568	3.4944	0.817	5.8848	0.418	2.0544	0.665	4.4256
0.002	1.420	5.9584	0.614	1.9680	1.020	3.9168	0.577	1.7904	1.000	3.8208
0.004	1.780	3.8612	0.728	1.2576	1.080	2.1024	0.752	1.3152	1.610	3.3744
0.006	1.830	2.6558	0.880	1.0816	1.380	1.8816	0.830	1.0016	2.120	3.0656
0.008	1.900	2.0776	0.980	0.9312	1.410	1.4472	0.980	0.9312	2.570	2.8392
0.010	2.050	1.8091	1.090	0.8506	1.620	1.3594	1.000	0.7642	2.980	2.6650
0.020	3.190	1.4631	1.630	0.6845	2.500	1.1021	1.500	0.6221	3.530	1.5965
0.040	4.800	1.1260	2.240	0.4886	4.000	0.9110	2.500	0.5510	4.970	1.1438
0.060	5.620	0.8846	3.000	0.4474	5.000	0.7674	3.400	0.5114	6.390	0.9898
0.080	6.010	0.7112	3.130	0.3511	5.500	0.6355	4.500	0.5155	7.680	0.8971
0.100	6.600	0.6268	3.440	0.3107	6.250	0.5804	5.600	0.5180	8.270	0.7743

Table 3.6.2: The conductance (k) and equivalent conductance (λ_C) of RAT series in THF at 308.15 K.

Conc. M	$k \cdot 10^5$ mho	λ_C mho.cm^2.equi.$^{-1}$	$k \cdot 10^5$ mho	λ_C mho.cm^2.equi.$^{-1}$	$k \cdot 10^5$ mho	λ_C mho.cm^2.equi.$^{-1}$	$k \cdot 10^5$ mho	λ_C mho.cm^2.equi.$^{-1}$	$k \cdot 10^5$ mho	λ_C mho.cm^2.equi.$^{-1}$
	RAT-1		***RAT-2***		***RAT-3***		***RAT-4***		***RAT-5***	
0.000	0.024	-	0.024	-	0.024	-	0.024	-	0.024	-
0.001	0.098	0.7003	0.101	0.7595	0.185	1.5181	0.169	1.3677	0.132	1.0199
0.002	0.101	0.3643	0.107	0.4092	0.318	1.3842	0.181	0.7403	0.224	0.9424
0.004	0.146	0.2879	0.133	0.2683	0.425	0.9435	0.209	0.4359	0.385	0.8495
0.006	0.177	0.2405	0.173	0.2442	0.498	0.7434	0.285	0.4097	0.507	0.7575
0.008	0.192	0.1980	0.195	0.2101	0.535	0.6010	0.341	0.3731	0.551	0.6198
0.010	0.207	0.1726	0.200	0.1730	0.580	0.5231	0.390	0.3445	0.570	0.5137
0.020	0.377	0.1661	0.320	0.1453	1.030	0.4731	0.620	0.2804	0.880	0.4026
0.040	0.701	0.1592	0.590	0.1388	1.740	0.4034	1.010	0.2318	1.480	0.3423
0.060	0.886	0.1351	0.860	0.1366	2.410	0.3739	1.260	0.1937	1.930	0.2987
0.080	0.955	0.1095	1.080	0.1294	2.840	0.3309	1.590	0.1841	2.350	0.2734
0.100	1.180	0.1087	1.280	0.1231	3.340	0.3118	1.900	0.1764	2.400	0.2234
	RAT-6		***RAT-7***		***RAT-8***		***RAT-9***		***RAT-10***	
0.001	0.187	1.5369	0.127	0.9729	0.367	3.2289	0.282	2.4299	0.287	2.4769
0.002	0.292	1.2620	0.144	0.5664	0.594	2.6814	0.454	2.0234	0.450	2.0046
0.004	0.380	0.8378	0.168	0.3396	0.972	2.2290	0.729	1.6579	0.684	1.5522
0.006	0.504	0.7528	0.188	0.2577	1.240	1.9059	0.828	1.2604	0.853	1.2996
0.008	0.595	0.6715	0.210	0.2191	1.540	1.7819	0.945	1.0828	0.972	1.1145
0.010	0.660	0.5983	0.235	0.1988	1.670	1.5477	1.040	0.9555	1.010	0.9273
0.020	1.120	0.5154	0.372	0.1638	2.650	1.2345	1.520	0.7034	1.720	0.7974
0.040	1.720	0.3987	0.561	0.1263	3.940	0.9204	2.690	0.6266	2.220	0.5162
0.060	2.270	0.3520	0.725	0.1099	4.210	0.6559	3.420	0.5321	2.860	0.4444
0.080	2.730	0.3180	0.878	0.1004	4.970	0.5812	4.280	0.5001	3.440	0.4014
0.100	2.990	0.2789	1.000	0.0918	5.550	0.5195	5.070	0.4744	3.510	0.3277

Figure 3.6.1: The variation of conductance with concentration for RAT series in DMF at 308.15 K.



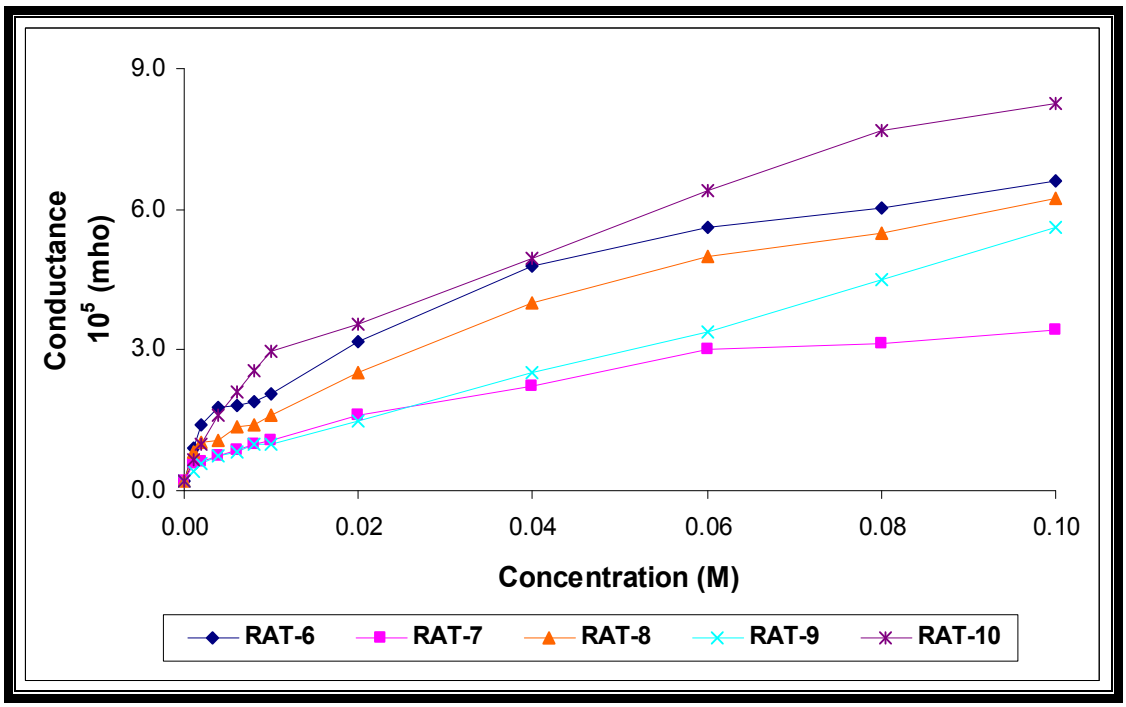
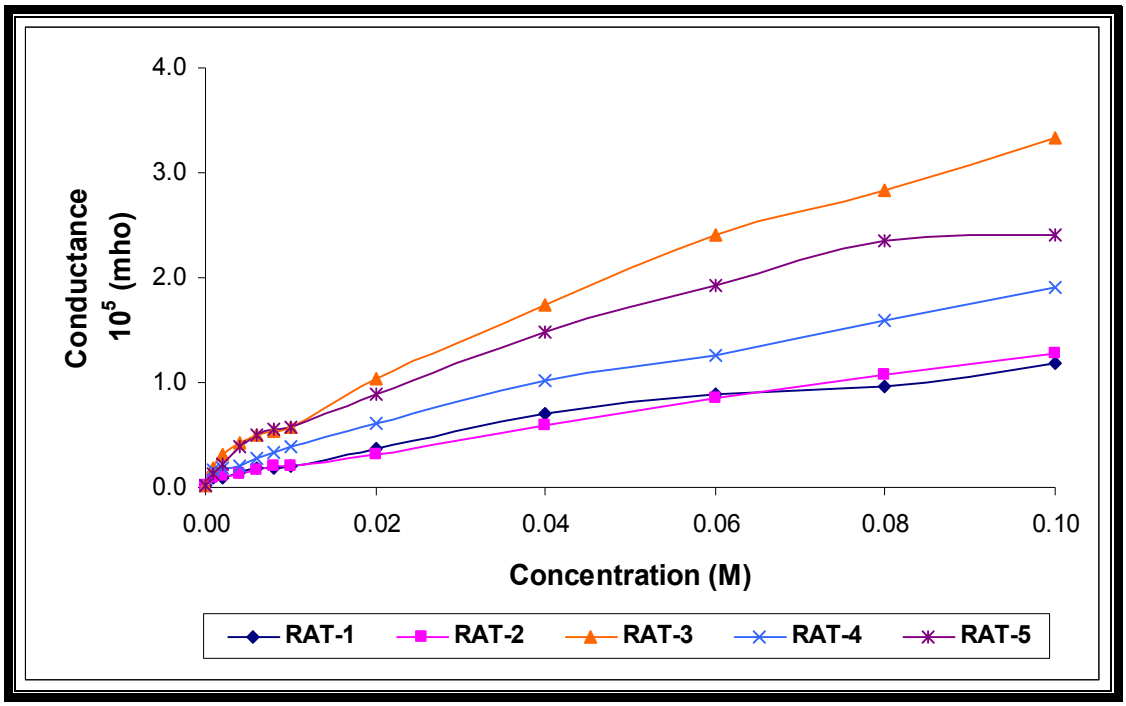


Figure 3.6.2: The variation of conductance with concentration for RAT series in THF at 308.15 K.



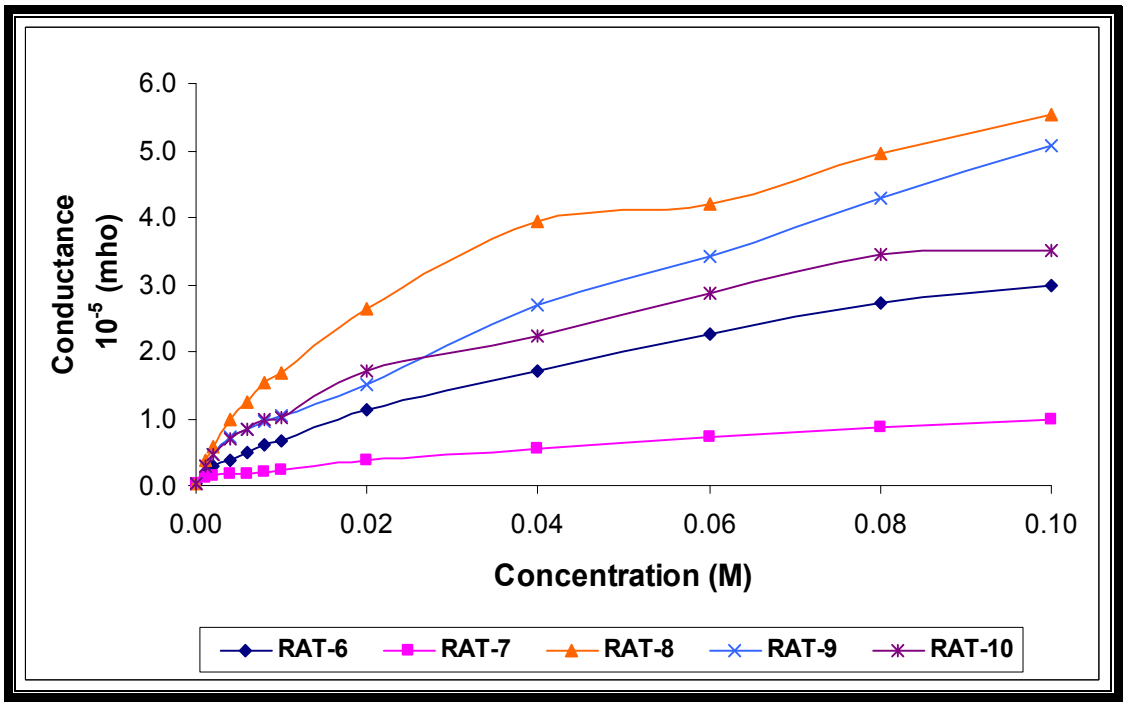
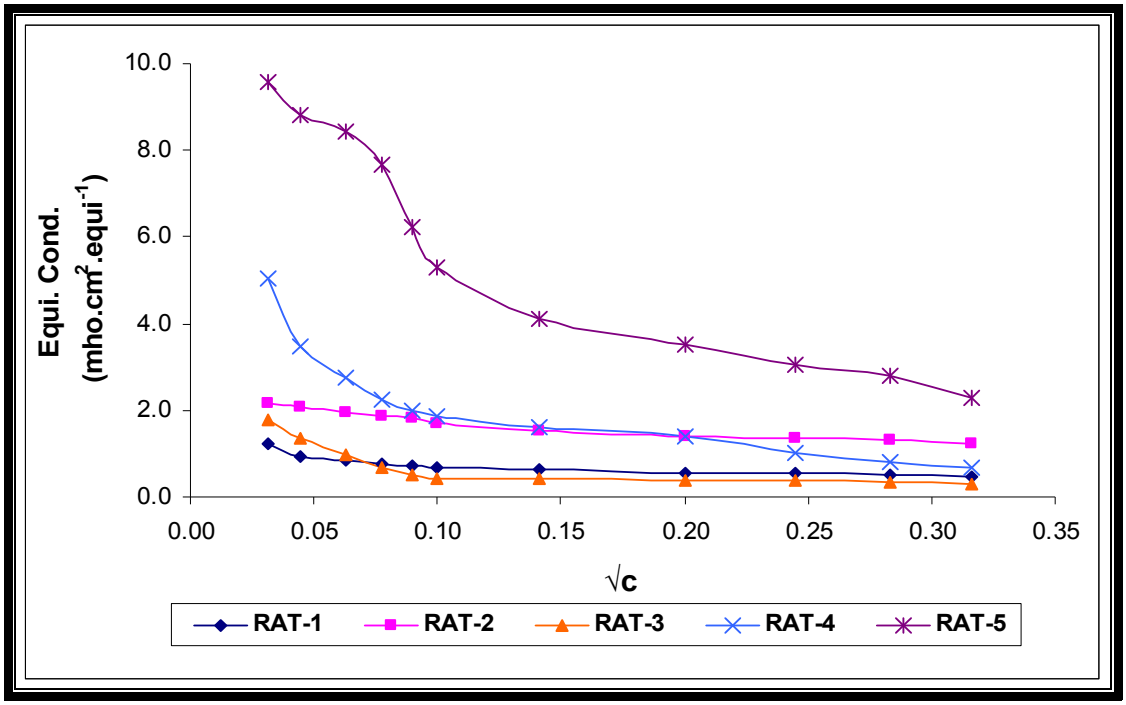


Figure 3.6.3: **The variation of equivalent conductance with √C for RAT series in DMF at 308.15 K.**



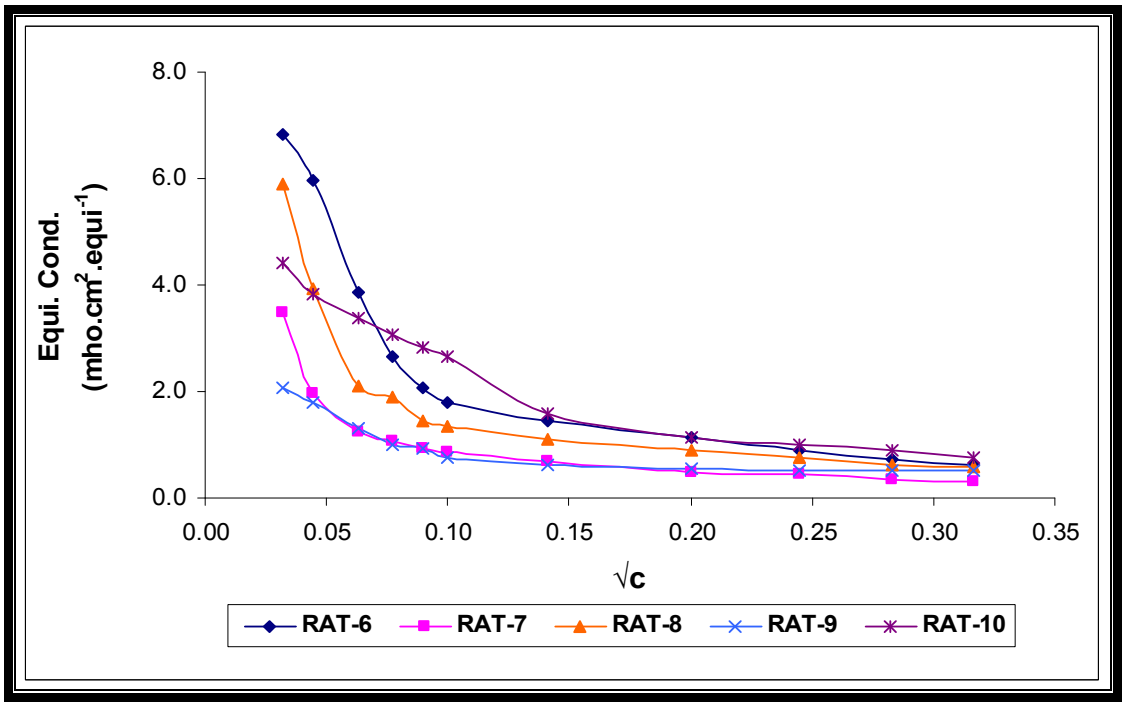
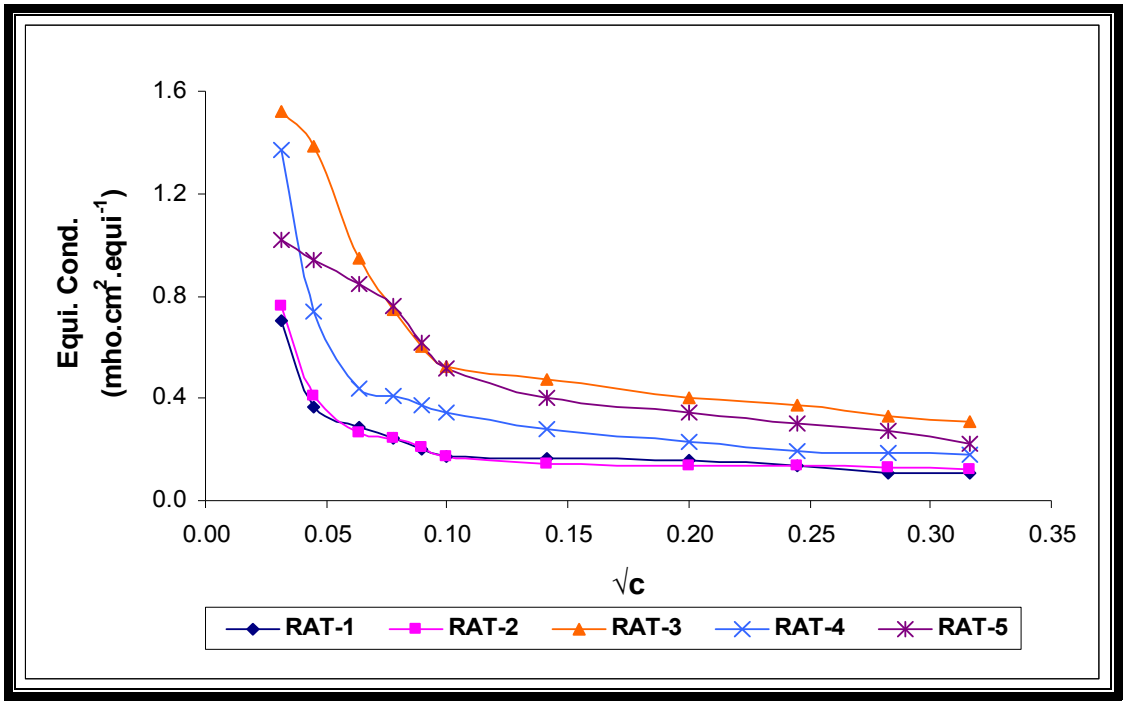
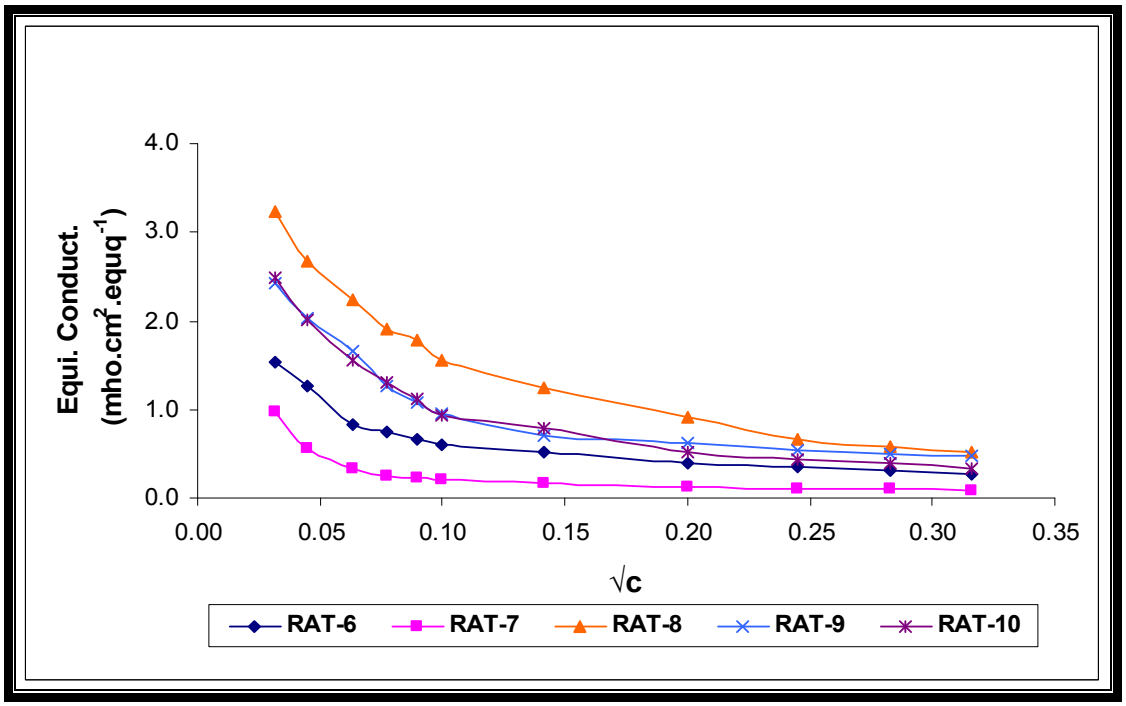


Figure 3.6.4: **The variation of equivalent conductance with √C for RAT series in THF at 308.15 K.**





The limiting conductivity can be determined accurately from the slope, dk/dc of plot of k verses c, provided other derivatives (dk_0/dc) and $d[c\Phi_{(c)}]/dc$ in differential form of equation (3.6.3) are neglected as compared to λ_0, which can be determined from differential form of equation (3.6.3) is

$$\frac{dk}{dc} = \frac{dk_0}{dc} + \lambda_0 + \frac{d\left[c\phi_{(c)}\right]}{dc} \qquad \text{….. (3.6.4)}$$

These λ_0 values are reported in Table 3.6.3 along with those determined by extrapolation.

From Table 3.6.3., it is observed that in both the solvents, calculated values of limiting equivalent conductance (λ_0) are in good agreement with those evaluated graphically suggesting thereby that equation 3.6.3 is applicable for the studied systems.

Table 3.6.3: The limiting equivalent conductance (λ_0) of RAT series in DMF and THF at 308.15 K.

Compound Code	λ_0 *mho.cm^2.equi.$^{-1}$* **from graph**	$\lambda_0 10^3$ *mho.cm^2.equi.$^{-1}$* **from eq. (3.6.4)**	λ_0 *mho.cm^2.equi.$^{-1}$* **from graph**	$\lambda_0 10^3$ *mho.cm^2.equi.$^{-1}$* **from eq. (3.6.4)**
	DMF		***THF***	
RAT-1	-	0.67	0.18	0.16
RAT-2	-	1.73	0.14	0.15
RAT-3	0.56	0.48	0.54	0.50
RAT-4	1.75	1.73	0.33	0.31
RAT-5	5.67	5.65	0.57	0.55
RAT-6	1.55	1.54	0.58	0.59
RAT-7	0.75	0.75	0.24	0.26
RAT-8	1.12	1.14	1.62	1.61
RAT-9	0.71	0.75	0.92	0.95
RAT-10	2.60	2.72	0.90	0.95

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CHAPTER-4

BIOLOGICAL ACTIVITIES

INTRODUCTION

Biological activity is an expression describing the beneficial or adverse effects of a drug on living matter. Biological Activity Spectrum of a compound represents the pharmacological effects[1], physiological[2] and biochemical mechanisms[3] of action, specific toxicity which can be revealed in compounds interaction with biological system. Further, it describes the intrinsic properties of the compound which depends on its structure. Most of known biologically active substances have many biological activities such as antibacterial[4-6], anti-inflammatory[7-9], antifungal[10-12], anti-HIV[13,14], antipyretic[15,16], antitumor[17-19] etc.

When the drug is a complex chemical mixture, this activity is exerted by the substance's active ingredient or pharmacophore but can be modified by the other constituents. The main kind of biological activity is a substance's toxicity. Activity is generally dosage-dependent and it is not uncommon to have effects ranging from beneficial to adverse for one substance when going from low to high doses.

As mentioned in Chapter 2, dihydropytrimidinones and dihydropyrim-idinthiones are known for a wide variety of biological activities. In the present chapter, the antibacterial and antifungal activities of the synthesized dihydropytrimidinones and dihydropyrimidinthiones (RAT series) have been screened against some Gram positive, Gram negative bacterial stains and fungus.

EXPERIMENTAL

The antibacterial and antifungal activities of dihydopyrimidinethiones (RAT series) and dihydropyrimidinones were studied in DMF and DMSO.

All the compounds were recrystallized prior to use. The solvents, DMF and DMSO were also purified before use by standard method[20].

For all the compounds, agar well diffusion method was used.

Test Microorganisms:

The compounds were tested for its antibacterial and antifungal activities against Gram positive bacteria viz. *Bacillus cereus* ATCC11778 (BC), *Micrococcus flavus* ATCC10240 (MF), Gram negative bacteria viz. *Proteus mirabilis* NCIM2241 (PM), Escherichina coli NCIM 2241 (EC) and Fungus viz. *Cryptococcus luteolus* ATCC 32044 (CL), *Candida tropicalis* ATCC 4563 (CT).

Microorganisms and Fungus were obtained from National Chemical Laboratory (NCL), Pune, India and were maintained at 4°C on nutrient agar slants.

Preparation of test compounds:

The solutions were prepared at a concentration of 1 mg/μl for all the compounds.

Preparation of the plates and microbiological assay:

The antibacterial and antifungal evaluation was done by agar well diffusion method[21,22] using Mueller Hinton Agar No.2 as the nutrient medium. The agar well diffusion method was preferred to be used in this study because it was found to be better than the disc diffusion method as suggested by Parekh et al.[3] The bacterial strains were activated by inoculating a loop full of test strain in 25 ml of N-broth and the same was incubated for 24 h in an incubator at 37^{o} C. 0.2 ml of the activated strain was inoculated in Mueller Hinton Agar. Mueller Hinton Agar kept at 45^{o}C was then poured in the Petri dishes and allowed to solidify. After solidification of the media, 0.85 cm ditch was made in the plates using a sterile cork borer and these were completely filled with the test solution. The plates were incubated for 24 h at 37^{o}C. The mean value obtained for the three wells was used to calculate the zone of growth inhibition of each sample. The controls were maintained for each bacterial strain and each solvent. The inhibition zone formed by these compounds against the particular test bacterial and fungal strain determined the antibacterial activities of these synthesized compounds.

RESULTS AND DISCUSSION

Dihydropyrimidinonthiones (RAT series) :

Figure 4.1 shows inhibition against Gram positive bacteria in DMF and DMSO. It is observed that against *B. cereus*, in DMF all the compounds exhibited inhibition whereas in DMSO, RAT-10 showed no inhibition at all. Further, against *B. cereus*, in DMF, RAT-5 shows maximum inhibition whereas in DMSO, RAT-9 exhibited maximum inhibition. However, for *M. flavus*, RAT-10 showed maximum inhibition in both the solvents.

The inhibition depends on type of bacterial strain, solvent as well as structure of compound. All the compounds in RAT series contain the same central moiety with different side chains. So, in a particular solvent, for a particular strain side chain plays important role in inhibition.

In the present study, against *B. cereus*, p-hydroxy group is most effective in inhibition which is present in RAT-5. Whereas p-methyl is least effective which is present in RAT-3. However, for *M. flavus*, in DMF solution, o-hydroxy (as in RAT-10) is most effective and no substitution (as in RAT-2) had no effect at all.

In DMSO, o-hydroxy (as in RAT-10) is most effective against both *B. cereus* and *M. flavus*. Again, p-methyl (as in RAT-3) and no substitution (as in RAT-2) had no effect at all against *M. flavus*. Thus, *M. flavus* is the resistant bacteria in DMSO.

Figure 4.2 shows inhibition against Gram negative bacteria in DMF and DMSO. It is observed that against *E. coli, in DMF,* RAT-1 and in DMSO RAT-9 showed maximum inhibition. In DMSO, most of the studied compounds had no effect against *E. Coli.* RAT-1 contain p-OCH_3 group and RAT-9 contain o-nitro group. Thus, these groups increase inhibition against *E. coli* in DMF and DMSO respectively.

For *P. mirabills,* In DMF, RAT-2, RAT-3 and RAT-8 showed almost same inhibition. Rest of the compounds had no effect at all. Whereas in DMSO, only RAT-6 showed no inhibition. RAT-5 and RAT-10 showed same maximum inhibition. As mentioned above, RAT-2 and RAT-3 contain no

Figure 4.1: Antibacterial activity of dihydropyrimidinthiones (RAT series) against Gram positive bacteria in DMF and DMSO.

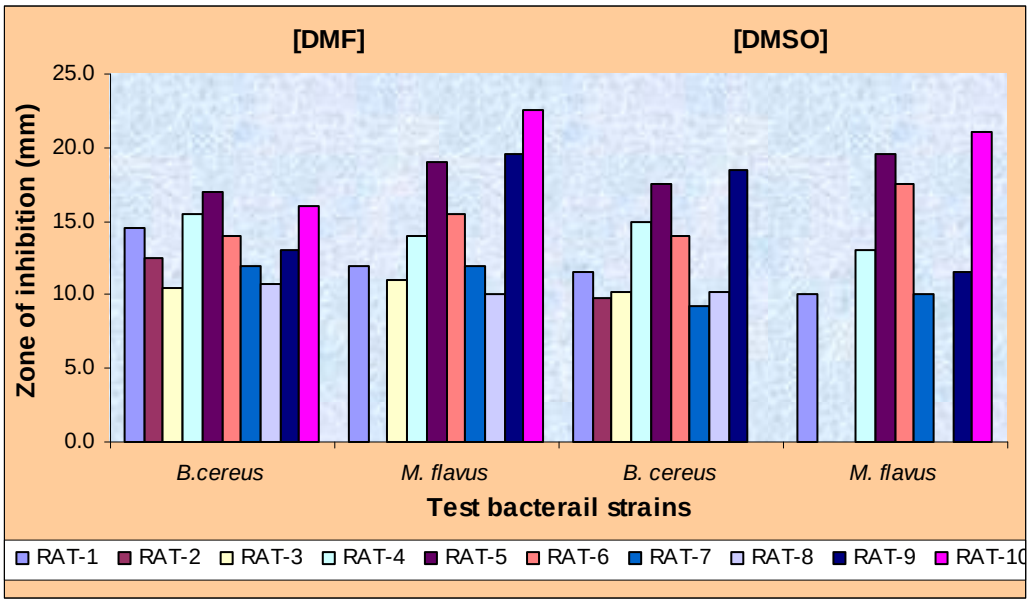
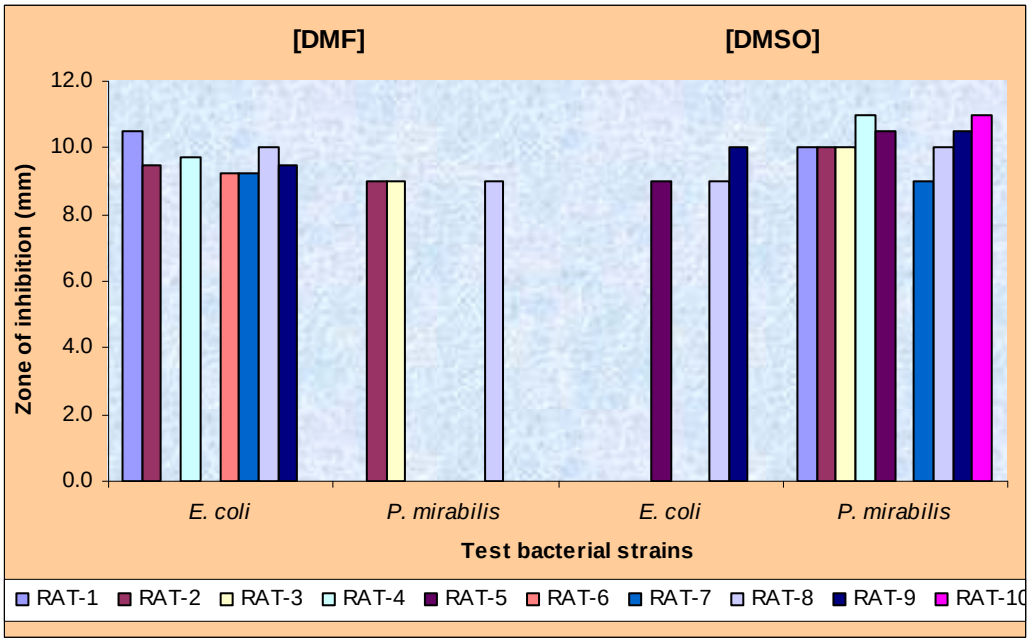


Figure 4.2: Antibacterial activity of dihydropyrimidinthiones (RAT series) against Gram negative bacteria in DMF and DMSO.



substitution and p-methyl group respectively whereas RAT-8 contain o-chloro group. This indicates that these groups, which were not effective against Gram positive bacteria is effective against Gram negative bacteria. Further, in DMSO against *P.mirabills,* p-fluoro (as in RAT-4) and o-hydroxyl group (as in RAT-10) is most effective.

Thus, in DMF, *P. mirabills* is most resistant bacteria whereas in DMSO, *E. Coli* is resistant.

Figure 4.3 shows inhibition against fungus in DMF and DMSO. For *C. luteolus,* inhibition is maximum in both DMF and DMSO. RAT-9 showed the maximum inhibition in both DMF and DMSO. RAT-2 and RAT-3 showed minimum inhibition in DMF whereas in DMSO, RAT-1 and RAT-2 exhibited no inhibition at all. Thus, o- nitro group is effective for this fungal strain in both the solvents. Whereas compound with p-methoxy group (RAT-1) and compound having no substitution group (RAT-2) is not effective in DMSO.

For *C. tropicalis*, all the compounds have showed almost same results of inhibition in DMF and DMSO. However, in DMSO, RAT-5 has slightly more inhibition than others. Thus, all compounds exhibited activity against *C. tropicalis* and activity is maximum for p-hydroxyl group and minimum for compound which not having substitution group in DMSO.

Thus, in DMF the presence of p-hydroxyl and p-methoxy groups are most effective against Gram positive and Gram negative bacteria. Whereas in DMSO, o-nitro group increased inhibition against both Gram positive and Gram negative bacteria in the studied compounds. Against studied fungal strains also, o-nitro group increased inhibition.

Overall, in case of RAT series, although there is slight change in inhibition in the two solvents, the presence of substituent groups affects inhibition and inhibition is maximum for compounds having hydroxyl, methoxy and nitro groups. Minimum inhibition is observed for compounds having chloro group and compounds having no substitution.

Figure 4.3: Antifungal activity of dihydropyrimidinthiones (RAT series) in DMF and DMSO.

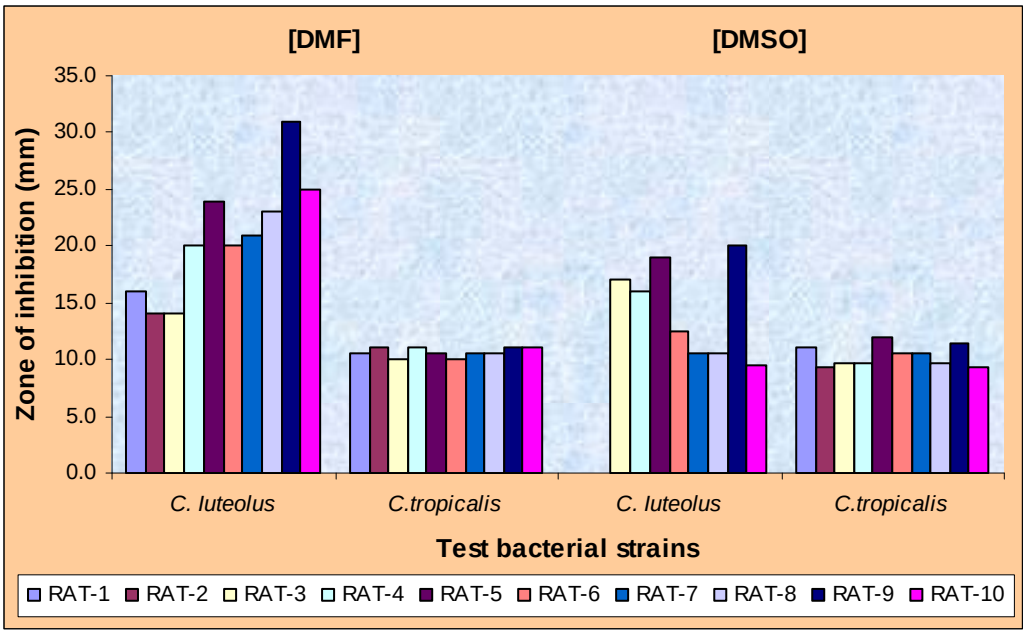
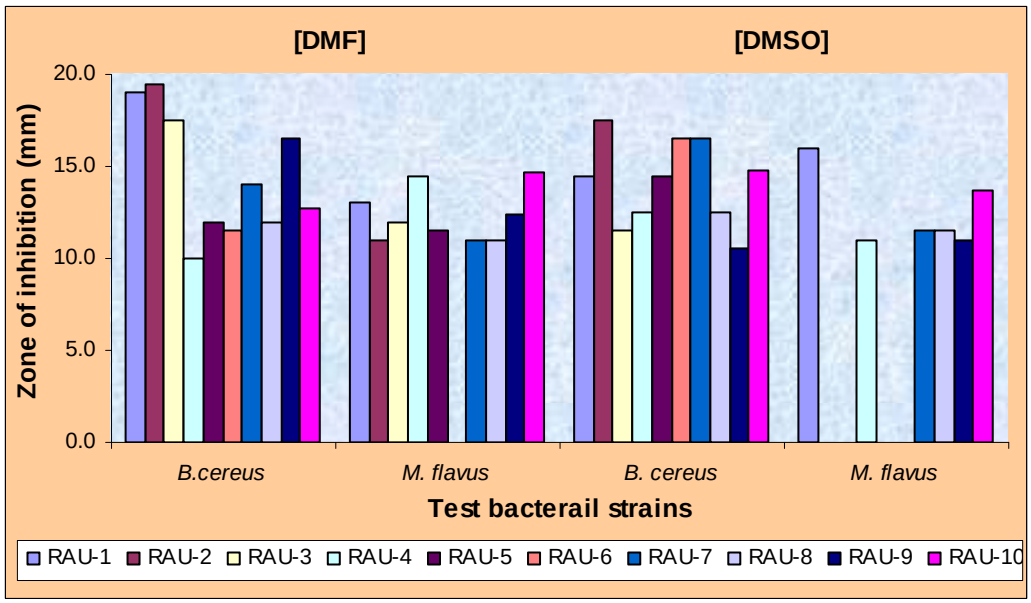


Figure 4.4: Antibacterial activity of dihydropyrimidinones against Gram positive bacteria in DMF and DMSO.



Dihydropyrimidinones:

Figure 4.4 shows the zone of inhibition against Gram positive bacteria in DMF and DMSO. It is evident that for both solvents, RAU-2 showed maximum inhibition against *B. cereus.* Minimum is observed by RAU-4 in DMF and RAU-9 in DMSO. RAU-2 contains p-chloro group which is found to be most effective against *B. cereus* in comparison to other groups. RAU-4 and RAU-9 contain p-hydroxy and p-methyl groups respectively. Thus, *B. cereus* is more resistant against hydroxyl and methyl group.

For *M. flavus,* RAU-10 in DMF and RAU-1 showed maximum inhibition. This bacteria is most resistant against RAU-6 in DMF and RAU-2, RAU-3, RAU-5 and RAU-6 in DMSO.

Against Gram negative bacteria, RAU-8 and RAU-10 exhibited maximum inhibition against *E. coli* (as shown in Figure 4.5) in DMF and DMSO respectively. RAU-3 and RAU-6 in DMF and RAU-4 and RAU-5 in DMSO exhibited no inhibition against *E. coli.* Thus, no substitution (as in RAU-8) and p-bromo group (as in RAU-10) is most effective against this bacteria. m-chloro (as in RAU-3) and p-fluoro (as in RAU-6) could not affect in DMF whereas p-hdroxy (as in RAU-4) and 2,5-dichloro (as in RAU-5) groups had no effect in DMSO.

For *P. mirabilis*, RAU-7 and RAU-10 showed maximum inhibition in DMF and DMSO respectively. Rau-1, RAU-3 and RAU-5 had no effect on *P. mirabilis* in DMF Whereas in DMSO all compounds exhibited inhibition. Thus, E. coli is more resistant bacteria in DMSO and *P. mirabilis* is more resistant bacteria in DMF.

Figure 4.6 shows zone of inhibition against fungal strains in DMF and DMSO. RAU-1 observed maximum inhibition against *C. luteolus* in both DMF and DMSO. Whereas RAU-6 showed minimum inhibition against *C. luteolus* in DMF. In DMSO, RAU-4 and RAU-6 showed no inhibition at all. RAU-1 contains p-methoxy group which is found to be most effective against *C. luteolus.*

For C. tropicalis, inhibition is much less than *C. luteolus* in both the solvents. In both the solvents, RAU-10 containing p-bromo group exhibited

Figure 4.5: Antibacterial activity of dihydropyrimidinones against Gram negative bacteria in DMF and DMSO.

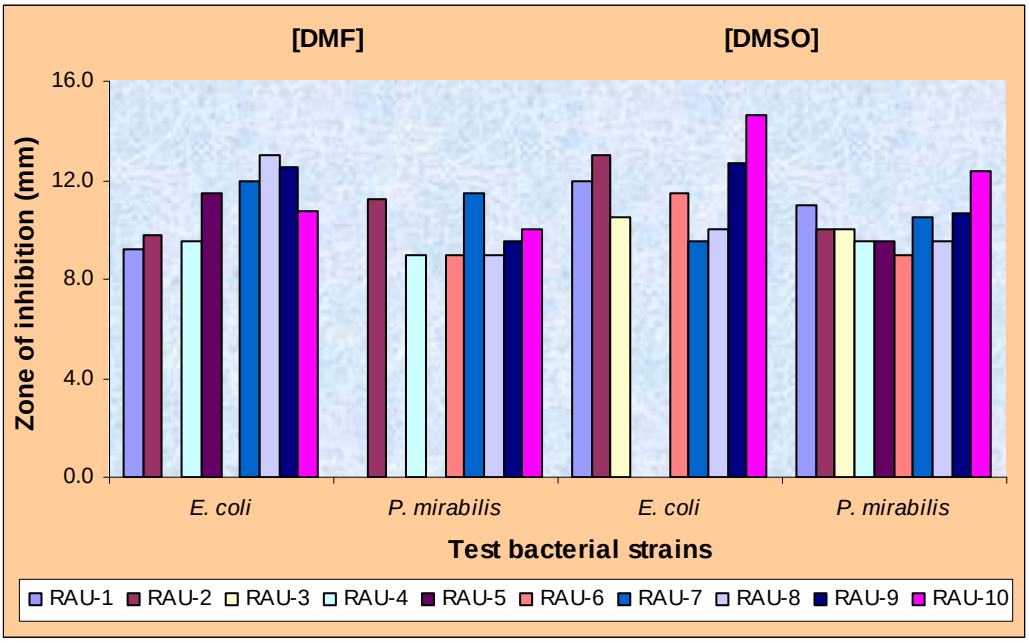
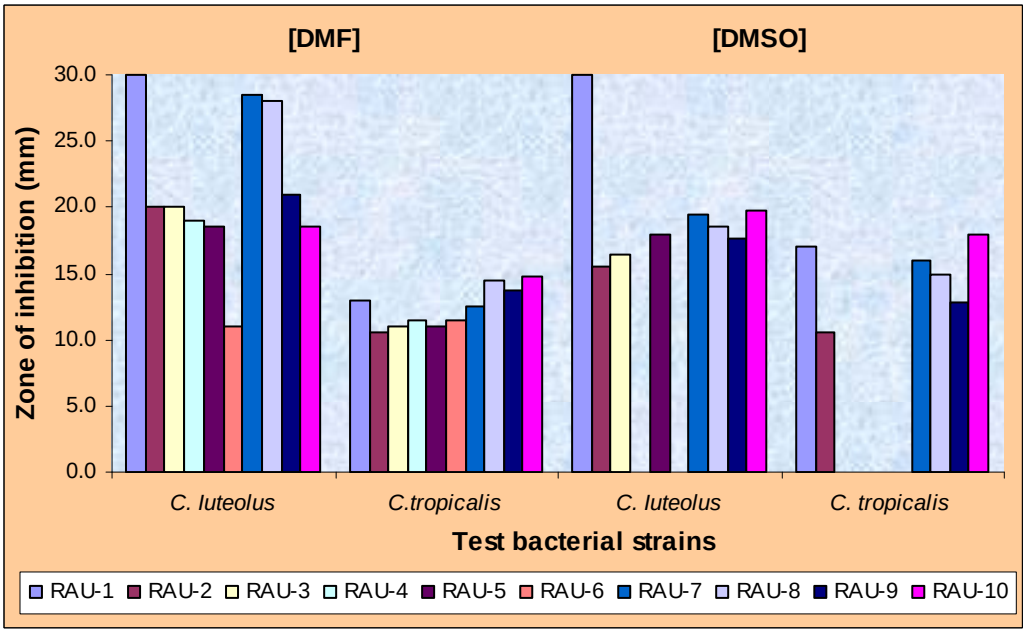


Figure 4.6: Antifungal activity of dihydropyrimidinones in DMF and DMSO.



maximum inhibition. In DMF, all the compounds showed inhibition whereas in DMSO, RAU-3, RAU-4, RAU-5 and RAU-6 had no effect at all.

Overall, the studied compounds exhibited more inhibition against fungal strains than bacterial strains.

In both the solvents, p-chloro group increases the inhibition against *B. cereus* whereas p-bromo in DMF and p-methoxy in DMSO is most effective against *M. flavus*. P-fluoro group had no effect at all in DMF whereas in DMSO, p-chloro, m-chloro, p-fluoro groups are found to be ineffective. Against Gram negative bacteria *E. Coli*, when there is no substitution, inhibition is highest in DMF whereas in DMSO, p-bromo increases the inhibition. For this bacteria, the presence of m-chloro and p-fluoro groups shows no effect in DMF whereas in DMSO, p-hydroxy and 2,5-dichloro groups had no effect. Against *P. mirabilis*, in DMSO again p-bromo increases the inhibition whereas in DMF p-nitro is most effective. P-methoxy, m-chloro and 2,5-dichloro groups had no effect against this bacteria in DMF.

In case of fungal strains, p-methoxy for *C.luteolus* and p-bromo for *C. tropicalis* is found to be most effective in both the solvents. Against *C. luteolus*, all compounds exhibited inhibition in DMF whereas in DMSO, p-hydroxy and p-fluoro groups are not effective at all. Against *C. tropicalis*, again all compounds exhibited inhibition in DMF whereas in DMSO, p-hydroxy, m-chloro, 2,5-dichloro and p-fluoro groups showed no inhibition at all.

Thus, in the studied bacterial and fungal stains, in the studied compounds, overall, p- hydroxy, m-chloro, 2,5-dichloro and p-fluoro groups had little or no effect at all in both the solvents.

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A COMPREHENSIVE SUMMARY OF THE WORK

A COMPREHENSIVE SUMMARY OF THE WORK

The present work is divided into four chapters.

CHAPTER-1: This chapter deals with the general introduction of heterocyclic compounds. The importance of heterocyclic compounds in pharmaceutical and biological field is given along with the aims and objective of the present work.

CHAPTER-2: This chapter deals with the synthesis of azomethines, benzothaizole derivatives, dihydropyrimidinones, dihydropyrimidinthiones and thiazolidinones. All the synthesized compounds are characterized by IR, mass and NMR spectral data.

CHAPTER-3: For the synthesized dihydropyrimidinthiones (**RAT series**), some physicochemical properties such as acoustical properties, solubility, density, refractive index, dissociation constants, thermal propertied, conductance etc. are studied in this chapter over a wide range of concentration. For all physicochemical properties, DMF and THF are used as solvent. The various properties are given in different sections.

Section-I: This section deals with the acoustical properties of RAT series at 308.15K in solutions of DMF and THF over a wide range of concentration. From the various evaluated acoustical parameters, it is concluded that in the studied compounds, solute-solvent interactions dominate.

Section II: This section describes that solubility of all studied compounds in DMF and THF at different temperatures (303.15-323.15 K). It is observed that the solubility of all the compounds increases linearly with temperature in both the solvents. Overall, solubility is greater in DMF than that in THF. The dielectric constant and dipole moment of DMF (36.71, 3.86) are greater than that of THF (7.58, 1.75). Thus, these properties of solvent play an important role on the solubility. Further, some thermodynamic parameters such as enthalpy (ΔH_{sol}), Gibb's energy (ΔG_{sol}) and entropy (ΔS_{sol}) of different

solutions have been evaluated. For all the compounds ΔH_{sol} , ΔG_{sol} and ΔS_{sol} values are positive. The positive value of ΔH_{sol} indicates absorption of energy i.e. endothermic dissolution of compounds. The positive ΔH_{sol} and ΔS_{sol} values in both solvents, suggest that solubility of compounds is entropy driving process. Further, the positive values of ΔG_{sol} indicate that the dissolution process is not spontaneous.

Section III: In this section, density and refractive index of the solutions of compounds of RAT series were measured at 308.15 K. The evaluated experimental densities are found to be different than those calculated theoretically, which may due to solvation of ions. Further, densities of same compound are different in both the solvents. This may be due to different interactions in different solvents, as discussed in section I.

Section IV: In this section, the dissociation constant of compounds of RAT series were studied in DMF : water (60:40) system at different temperatures (i.e., 298.15, 308.15 and 318.15). The dissociation constants were evaluated by average and half-integral method. The results obtained by these two methods are in good agreement. The dissociation constant is observed to decrease with increase in temperature. Further, dissociation constant is found to be maximum for RAT-5 containing p–OH group and minimum for RAT-1 which contains p–OCH_3 group. Thus, RAT-5 is more acidic and RAT-1 is more basic.

Further, from dissociation constant data, some thermodynamic parameters such as enthalpy (ΔH), Gibb's energy (ΔG) and entropy (ΔS) were evaluated for both the methods. The values are in good agreement for both the methods. Again, positive ΔH indicates that the dissociation process is endothermic whereas positive ΔG indicates that dissociation process is not spontaneous. The negative values of ΔS is due to increased order.

Section V: The thermal properties of compounds, measured by TGA were discussed in this section. From the thermograms of the all compounds, it is

observed that for RAT-1 and RAT-6, multi steps degradation takes place whereas for other compounds, degradation is single step process.

Further, RAT-2 is found to be more stable whereas RAT-10 is most unstable. RAT-10 contains 2-OH group whereas there is no substitution group in RAT-2. Thus, absence of any functional group to aryl ring increases the stability. The position of functional groups also affects the stability and it is observed that the presence of groups at 2-position decreases the stability. Various kinetic parameters such as order of reaction, energy of activation, frequency factor, entropy etc., were also calculated from thermograms. It is observed that order of reaction is quite different for all the compounds. For single step, energy of activation is maximum for RAT-3 and minimum for RAT-5. For RAT-1 and RAT-6, energy of activation and frequency factor is higher for the first step. The positive ΔS values indicated that the activation compounds has a more ordered or more rigid structure than the reactant and reaction is slower than the normal.

Section VI: This section deals with the conductance of solution of compounds of RAT series at 308.15 K in DMF and THF over a wide range of concentration. The equivalent conductances for all the compounds were also evaluated. All the compounds are found to exhibit weak electrolytic nature in both the solvents. However, the limiting equivalent conductances (λ_0) were evaluated by both extrapolation of plot of λ_c versus $\sqrt{C}$ and by theoretical method. The values are found to be in good agreement.

CHAPTER-4: The antibacterial and antifungal activity of dihydropyrimidin thiones (RAT series) and dihydropyrimidinones (RAU series) in DMF and DMSO are studied in this chapter. Different bacterial strains behave differently in different solvents. Further, the presences of different substituents also affect inhibition.

LIST OF PUBLISHESD AND ACCEPTE PAPERS

Published Papers:

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6. Solubility of Ofloxacin in 1,2-dichloromethane, chloroform, carbontetra chloride and water from (293.15 to 313.15) K, Shipra Baluja, **Rahul Bhalodia**, Ravi Gajera, Nayan Vekariya and Mehul Bhatt, J. Chem. Eng. Data, In press (2009).
7. Adiabatic Compressibilities of some synthesized derivatives of dihydro pyrimidines in N, N-Dimethylformamide and Dimethylsulfoxide at 298.15 K, Shipra Baluja, **Rahul Bhalodia** and Ravi Gajera, Russ. J. Phys. Chem., In Press, (2010).