STUDIES OF SOME BIO-ACTIVE HETEROCYCLIC MOIETIES

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SAURASHTRA UNIVERSITY
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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Statement under O.Ph.D. 7 of Saurashtra University

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: -01-2010

Place: Rajkot **(Mehul P. Bhatt)**

This is to certify that the present work submitted for the Ph.D. Degree of Saurashtra University by **Mehul P. Bhatt** 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 RESEARCH
GUIDE
क्षीरदायै धनदायै
बुद्धिदायै नमो नमः।
यशोदायै कीर्तिदायै
धर्मदायै नमो नमः॥

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(MEHUL P. BHATT)

CONTENTS

SYNOPSIS

"Studies of Some Bioactive Heterocyclic Moieties"

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

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Heterocyclic compounds are organic compounds that contain a ring structure containing atoms in addition to carbon, such as sulfur, oxygen or nitrogen, as part of the ring. They may be either simple aromatic rings or non-aromatic rings.

These heterocyclic compounds constitute the largest and most varied family of organic compounds. Many of these compounds are of biological importance, such as nucleic acids and certain vitamins, hormones, and pigments. Further, these heterocyclic compounds are widely distributed in nature, which is essential to life. For example, DNA, Hemoglobin, Chlorophylls, vitamins etc. contains various types of heterocycles. Thus, heterocycles dominates the field of biochemistry and medicinal chemistry. Some of heterocyclic compounds are also used as chemical intermediates and solvents in the pharmaceutical, chemical, textile, dye-stuffs, petroleum, photography industries, agrochemicals and are of increasing importance in many others include polymers, adhesive, molecular engineering etc.

Thus, in the present work, some heterocyclic compounds have been synthesized and their physicochemical and biological properties were studied.

The present work is divided into following chapters:

- **Chapter - 1: General Introduction**
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CHAPTER - 1

GENERAL INTRODUCTION

This chapter describes literature survey of synthesis, characterization, applications, physicochemical studies and antibacterial activities of all the synthesized compounds.

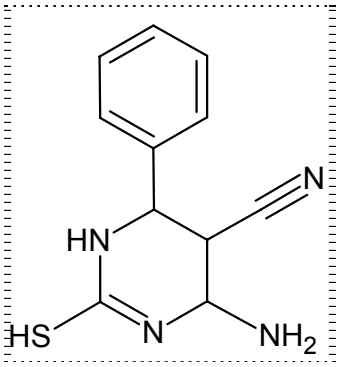
CHAPTER-2

SYNTHESIS AND CHARACTERIZATION

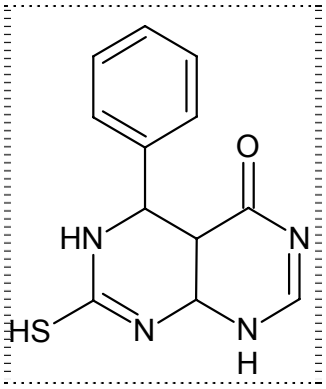
This chapter deals with synthesis and characterization of different bioactive heterocyclic compounds.

- **Part-1: Studies of some tetrahydropyrimidine derivatives.**

  Section-1: tetrahydropyrimidine

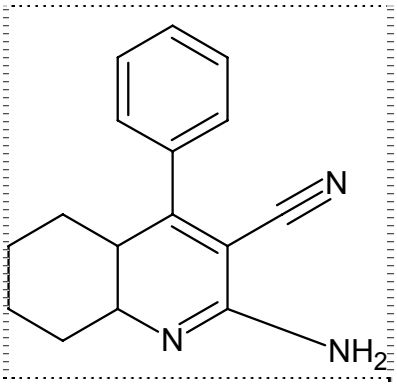


Section-2: tetrahydropyrimidopyrimidines.

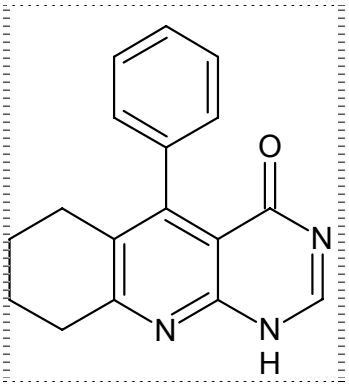


- **Part-2: Studies of some tetrahydroquinoline derivatives.**

  Section-1: Tetrahydroquinolines.

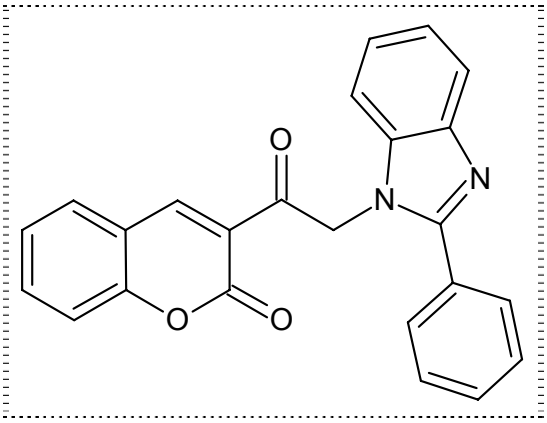


  Section-2: Pyrimidotetrahydroquinoline



- **Part-3: Studies of some benzimidazole derivatives.**

  Section-1: Condensation of benzimidazoles with acetyl coumarine derivative.



The characterization of all the synthesized compounds was done by IR, NMR and mass spectral data.

CHAPTER-3: PHYSICO CHEMICAL PROPERTIES

Some physico chemical properties of some compounds have also been studied. This chapter is further subdivided into eight sections.

Section-I: Acoustical Properties

In this chapter, density, sound velocity and viscosity of above synthesized tetrahydropyrimidines were measured in dimethylformamide and chloroform solutions of various concentrations at 303.15 K. From these experimental data, various acoustical parameters such as isentropic compressibility, Rao's molar sound function, specific acoustical impedance, internal pressure, Vander Waals constant, free volume, solution number etc. were evaluated and the results are discussed in terms of molecular interactions occurring in these solutions.

Section-II: Density and Refractive Index

Refractive index is a property of the material and is extremely useful in chemical analysis. In this chapter, the refractive index and density was measured in dimethylformamide and chloroform solutions at 303.15 K. From the refractive index measurements of solutions, the density and refractive

index of synthesized compounds were determined. The molar refraction of these compounds has also been evaluated from the density and refractive index values.

Section-III: Conductance

This chapter deals with the conductance measurement of solutions of tetrahydropyrimidine derivatives in dimethylformamide and chloroform solutions of different concentrations at 303.15 K. From these experimental values, specific conductance and equivalent conductance were evaluated.

Section-IV: Solubility

The molar heat of solution of a substance can be determined from the solubility measurement at different temperatures. In the present chapter, heat of solution for all the synthesized tetrahydropyrimidines were determined at different temperatures (293.15 -313.15 K) in methanol, ethanol and chloroform. From these experimental data various thermodynamic parameters were evaluated.

Section-V: Thermal Properties

This chapter describes the thermal properties of tetrahydropyrimidines. The Thermo Gravimetric Analysis (TGA) measurements and Differential Scanning Calorimeter (DSC) analysis were made. From these measurements, various kinetic parameters were evaluated. Further, thermal stability of various compounds were also determined.

Section-VI: Dissociation Constants

In this Chapter, the dissociation constant of some tetrahydropyrimidines were studied in methanol by using UV-Visible spectroscopy.

Section-VII: Partition coefficient.

Partition coefficient of ten tetrahydropyrimidine derivatives was determined by using UV-Visible spectroscopy.

CHAPTER–4: BIOLOGICAL ACTIVITIES

This chapter deals with antibacterial activity of all the synthesized compounds against different microbes.

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GENERAL INTRODUCTION

Heterocyclic compounds constitute the largest, most varied family of organic compounds and are very widely distributed in nature. They play a vital role in the metabolism of all the living cells. The study of heterocycles is of great interest both from the theoretical as well as practical stand point. A heterocyclic compound is one which possesses acyclic structure at least two different kinds of atoms in the ring. The most common types contain largely carbon atom, nitrogen, oxygen and sulphur but many other elements, including even bromine, chlorine can also be present. The heterocyclic containing the less common atoms have been subject to much investigation in recent years.

Heterocyclic chemistry and medicinal chemistry share a venerable common history. Many of the founders of heterocyclic systems had an intense interest not only in molecules from nature but also in the effects of synthetic compounds on living systems. The current interest in the creation of large, searchable libraries of organic compounds has captured the imagination of organic chemists and the drug discovery community. In numerous laboratories, the efforts are focused on the introduction of chemical diversity, which have been recently reviewed and pharmacologically interesting compounds have been identified from libraries of widely different compositions.

Today, the chief sources of agents for the cure, the improvement or the prevention of diseases are the heterocyclic compounds, natural or synthetic. Such agents have their origin in a number of ways (a) from naturally occurring materials - of both plant and animal origin, and (b) from the isolation of organic compounds synthesized in laboratory whose structures are closely related to those of naturally occurring compounds

Most of the alkaloids, pigments (such as indigo, haemoglobin, anthocyanin etc.), some well known drugs (like penicillin, streptomycin, sulphathiazole, pyrenthrin, rotenmone, strychnine, reserpine, etc.) consist of heterocyclic ring system. Heterocyclic compounds have great applicability in pharmaceutics because

they have specific chemical reactivity and provide false synthons in biosynthetic process or block the normal functioning of biological receptors.

Taking in view of the applicability of heterocyclic compounds, the present work was undertaken to synthesize some new heterocycles such as tetrahydro pyrimidine, tetrahydro quinoline, benzimidazole etc. Green chemistry aspect is used for the synthesis of some heterocyclic compounds.

AIMS AND OBJECTIVES:

- To synthesize several derivatives baring pyrimidine, quinoline, benzimidazole, coumarine nucleus.
- To characterize these synthesized compounds for structure elucidation by IR, ^{1}H NMR and Mass spectral studies.
- To study the physico chemical properties such as acoustical properties, density, refractive index, conductance, solubility, partition coefficient, thermal properties and dissociation constants of some compounds, in different solvents.
- To evaluate antibacterial activity of some of these synthesized compounds against different bacterial strains.

GENERAL REMARKS:

1. Melting points were recorded by open capillary method and are uncorrected.

2. Infrared spectra were recorded on SHIMADZU FTIR-8400 (Diffuse reflectance attachment) in the frequency range of 4000-400 cm-1 using KBr. Spectra were calibrated against the polystyrene absorption at 1610 cm^{-1}.

3. 1H NMR spectra were recorded on BRUKER AVANCE II 400 spectrometer. Making a solution of samples in DMSO d6 solvent using tetramethylsilane (TMS) as the internal standard unless otherwise mentioned, and are given in the δ scale.

4. Mass spectra were recorded on SHIMADZU GCMS-QP2010 spectrometer operating at 70 eV using direct injection probe technique.

5. Analytical thin layer chromatography (TLC) was performed on Merck precoated silica gel-G F254 aluminium plates. Visualization of the spots on TLC plates was achieved either by exposure to iodine vapor or UV light.

6. The chemicals used for the synthesis of products were purchased from Spectrochem, Sisco Research Laboratories (SRL), Thomas- Baker, SD fine chemicals and Loba chemie.

7. The structures and names of all the compounds given in the experimental section were generated using ACD Chemsketch version 11.0

INTRODUCTION

The intense activity in the field of pyrimidine chemistry during the past decade, from both academic and industrial laboratories, has prompted our interest in the Biginelli reaction. Pyrimidine is the trivial name for 1, 3-diazine where two meta CH units in benzene are replaced by nitrogen atom. The pyrimidine ring system undoubtedly belongs to the most important heterocycles in nature, as it represent the main structure of many biologically significant compounds, including nucleosides and nucleotides.

Tetrahydropyrimidine is higher saturated pyrimidine nucleus with two less double bonds. The tetrahydropyrimidines are small, highly soluble organic molecules, neutral at physiological pH, which do not interfere with normal cellular functions. They are zwitterion molecules, and the amidine group of the THPs is positively charged [1, 2].

Tetrahydropyrimidine has the great property of their synthetic compatibility. It can easily be modified [3]. Only few general methods for the synthesis of tetrahydropyrimidine-2- thione derivatives have been reported. In 1893, Biginelli [4] reported the synthesis of functionalized 3, 4-dihydro-pyrimidin-2(1*H*)-ones via three-component acid catalysed condensation reaction of an aromatic aldehyde, urea, and ethyl acetoacetate. In the past decade, this long neglected multicomponent reaction has experienced a remarkable revival, mainly due to the interesting pharmacological properties associated with this dihydropyrimidine [5]. The main disadvantage of this synthesis is the low yields of the desired pyrimidines. A very attractive approach to the synthesis of Biginelli compounds has been developed by Atwal and co-workers [6-8]. This approach is based on the reaction of arylidene of oxoesters with S-(4-methoxybenzyl)isothiourea or o-methylisourea in the presence of sodium bicarbonate followed by transformation of the obtained dihydropyrimidine derivatives into tetrahydropyrimidine derivative.

Many researchers have suggested various ways to synthesize various tetrahydropyrimidine derivatives in protic solvents or without solvent [9-16]. These compounds can also be synthesized by benzene like aprotic solvents [17]. Svetlik et al. have used the dialkyl acetone-1, 3-dicarboxylates as active

methylene compounds [18]. Some environmentally benign processes can be employed to synthesize the tetrahydropyrimidines. Neat reactants subjected to microwave radiation gave the required products more quickly and in better yields in comparison to traditional methodologies [19-22]. Under different reduction conditions, dihydropyrimidines are converted into tetrahydropyrimidine derivatives [23].

In recent years, tetrahydropyrimidine-2-thione derivatives received significant attention owing to their diverse range of biological properties [24]. These derivatives are reported to possess calcium antagonist [25-28], anti-inflammatory [29-31], analgesic [32], antitumor [33] antidepressant [34], antibacterial and antifungal effects [35-37]. Tetrahydropyrimidines are found to be accumulating in a significant amount and induces thermo tolerance in E. coli [38].

Over the past few years, several novel tetrahydropyrimidine like amidine derivatives have been synthesized and tested for muscarinic agonist activity in rat brain [39-41]. Several novel tetrahydropyrimidine derivatives exhibited muscarinic agonist activity in rat brain. Such compounds might be useful in treating Alzheimer's disease [42]. Chhillar et al. have synthesized three different tetrahydropyrimidine along with ten dihydropyridine derivatives and examined their activity against pathogenic strains of Aspergillus fumigatus and Candida albicans [43].

Thus, in sections 1 and 2, some new tetrahydroprimidines and tetra hydropyrimidopyrimidines have been synthesized and characterization of these synthesized compounds is done by IR, NMR and mass spectral data.

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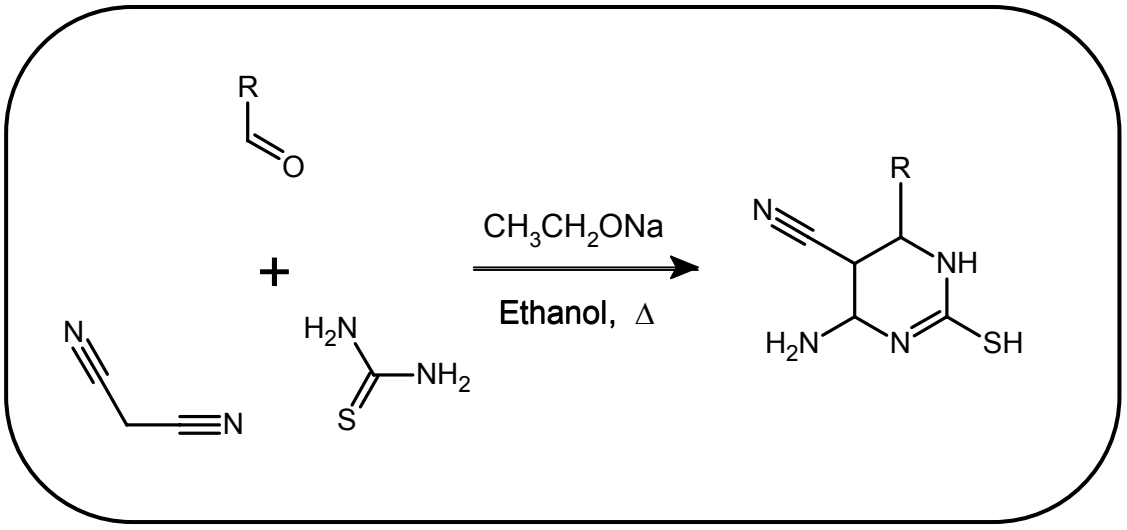
SYNTHESIS AND CHARACTERIZATION

Synthesis of 4-amino-6-aryl-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile:

First of all, sodium ethoxide was prepared by adding pieces of sodium metal in ethanol. To this solution (100 ml), malano nitrile (0.01 mole) and desired aldehyde (0.01 mole) was added. When the solution becomes clear, 0.76 gm of thiourea was mixed and the mixture was refluxed in a water bath for about 12 hours. The reaction mixture was then allowed to cool at room temperature and then poured into the crushed ice. The solution was neutralized with aqueous HCl solution and product was extracted in chloroform. Organic layer was washed with brine solution and anhydrous sodium sulphate was added to remove moisture from it. The product was recovered from chloroform solution by rota vapour under high vacuum condition. Solid product obtained was recrystalised from fresh chloroform.

Reaction Scheme:



Following compounds were synthesized through above reaction scheme.

MDT 1: 4-amino-6-(4-hydroxy-3-methoxyphenyl)-2-sulfanyl-1,4,5,6-tetrahydro -pyrimidine-5-carbonitrile

MDT 2: 4-amino-6-(4-methoxyphenyl)-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile

MDT 3: 4-amino-6-(4-hydroxyphenyl)-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile

MDT 4: 4-amino-6-(4-chlorophenyl)-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile

MDT 5: 4-amino-6-(3-chlorophenyl)-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile

MDT 6: 4-amino-6-(4-fluorophenyl)-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile

MDT 7: 4-amino-6-(3-nitrophenyl)-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile

MDT 8: 4-amino-6-phenyl-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile

MDT 9: 4-amino-6-(furan-2-yl)-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile

MDT 10: 4-amino-6-[(*Z*)-2-phenylethenyl]-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile

The various physical constants such as R_f value, melting point and percentage of yield for all the synthesized tetrahydropyrimidines are given in Table 1.1.

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

Table 1.1: Physical constants of compounds of MDT series.

Sr. No.	Code	R	M.F.	M. W. g	R_f* Value	M.P. ^oC	Yield %
1.	**MDT 1**	4-OH, 3-OCH_3-C_6H_4-	$C_{12}H_{14}N_4O_2S$	278.3	0.36	140	75
2.	**MDT 2**	4-OCH_3-C_6H_4-	$C_{12}H_{14}N_4OS$	262.3	0.41	118	82
3.	**MDT 3**	4-OH-C_6H_4-	$C_{11}H_{12}N_4OS$	248.3	0.38	190	78
4.	**MDT 4**	4-Cl-C_6H_4-	$C_{11}H_{11}ClN_4S$	266.8	0.45	168	69
5.	**MDT 5**	3-Cl-C_6H_4-	$C_{11}H_{11}ClN_4S$	266.8	0.42	157	67
6.	**MDT 6**	4-F-C_6H_4-	$C_{11}H_{11}FN_4S$	250.3	0.50	130	63
7.	**MDT 7**	3-NO_2-C_6H_4-	$C_{11}H_{11}N_5O_2S$	277.3	0.60	101	61
8.	**MDT 8**	C_6H_5-	$C_{11}H_{12}N_4S$	232.3	0.69	90	80
9.	**MDT 9**	4(α-C_4H_3O)-	$C_9H_{10}N_4OS$	222.3	0.32	81	83
10.	**MDT 10**	C_6H_4-CH=CH-	$C_{13}H_{14}N_4S$	258.3	0.72	164	58

* Ethyl acetate : Hexane **:** 3 : 7

Figure 1.1: IR spectra of 4-amino-6-(4-hydroxy-3-methoxyphenyl)-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (MDT 1).

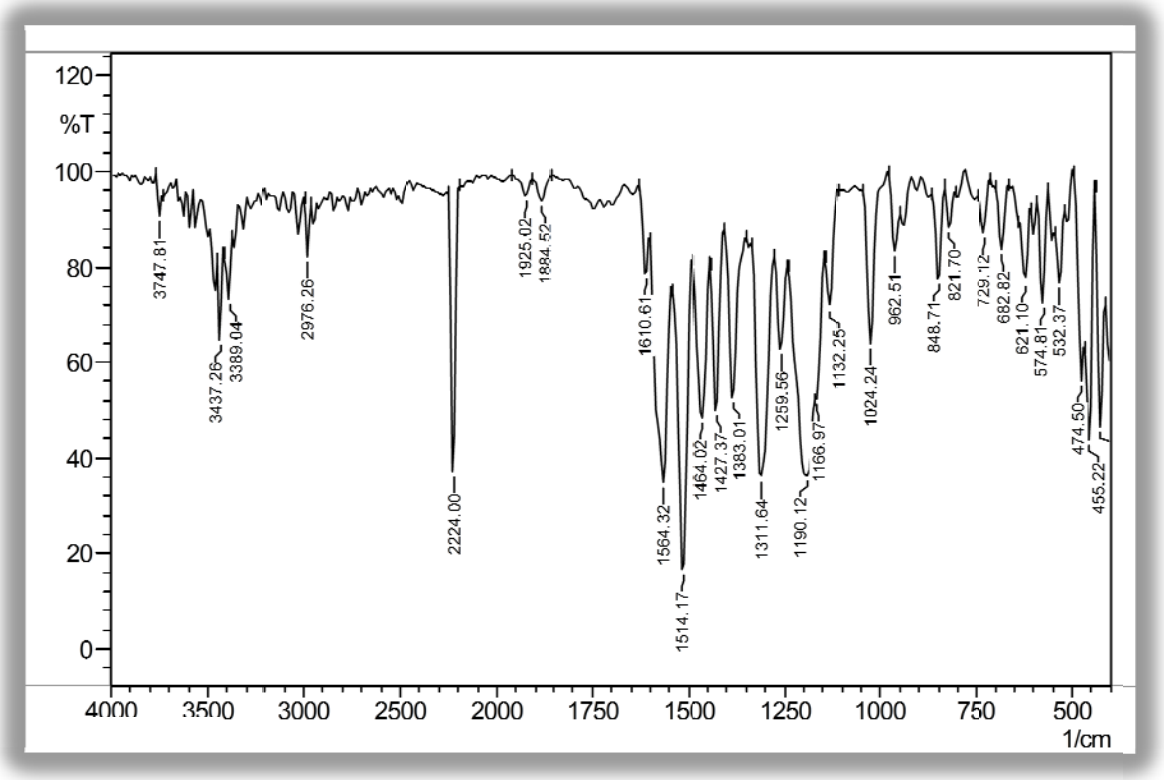


Table 1.2: IR spectral data of 4-amino-6-(4-hydroxy-3-methoxyphenyl)-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (MDT 1).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported*
Alkane (methyl)	C-H str. (asym.)	2976.26	2975-2920
	C-H str. (sym.)	2865.08	2880-2860
	C-H def. (asym.)	1464.02	1470-1435
	C-H def.(sym.)	1383.01	1395-1370
Aromatic	C-H str.	3082.00	3100-3000
	C=C str.	1514.17	1585-1480
	C-H i.p. def.	1132.25	1125-1090
	C-H o.o.p. def.	848.71	860-810
Hydroxy	O-H str.	1389.04	3650-3000
	O-H def.	1383.01	1410-1310
Primary amine	N-H str.	3437.26	3310-3500
	N-H ben	1610.61	1650-1590
ether	C-O-C str. (asym.)	1190.12	1400-1000
	C-O-C str. (sym.)	1024.24	1075-1020
C≡N	C≡N str	2224.00	2240-2220
Thiol	S-H str	2560.10	2600-2550

* (1) V. M. Parikh; "Absorption spectroscopy of organic molecule", Addition Wesley Pub. Co. London, 243-56 (1978).
(2) C. N. R. Rao; "Chemical application of Infrared Spectroscopy", Academic Press, New York (1963).

Table 1.3: IR spectral data of other synthesized tetrahydropyrimidines.

Compounds	*IR ν, (cm^{-1})*			
	C=C	**S-H**	**N-H**	**C≡N**
MDT 2	1515.15	2559.55	3438.28	2210.12
MDT 3	1520.25	2555.46	3436.25	2209.36
MDT 4	1518.57	2558.87	3439.14	2212.03
MDT 5	1514.32	2558.36	3429.98	2223.05
MDT 6	1516.62	2557.58	3431.25	2228..59
MDT 7	1517.49	2555.18	3438.56	2214.41
MDT 8	1514.48	2559.18	3425.26	2210.00
MDT 9	1519.15	2556.19	3422.23	2236.48
MDT 10	1518.18	2551.36	3421.59	2222..12

Figure 1.2: ^{1}H NMR spectra of 4-amino-6-(4-hydroxy-3-methoxyphenyl)-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (MDT 1).

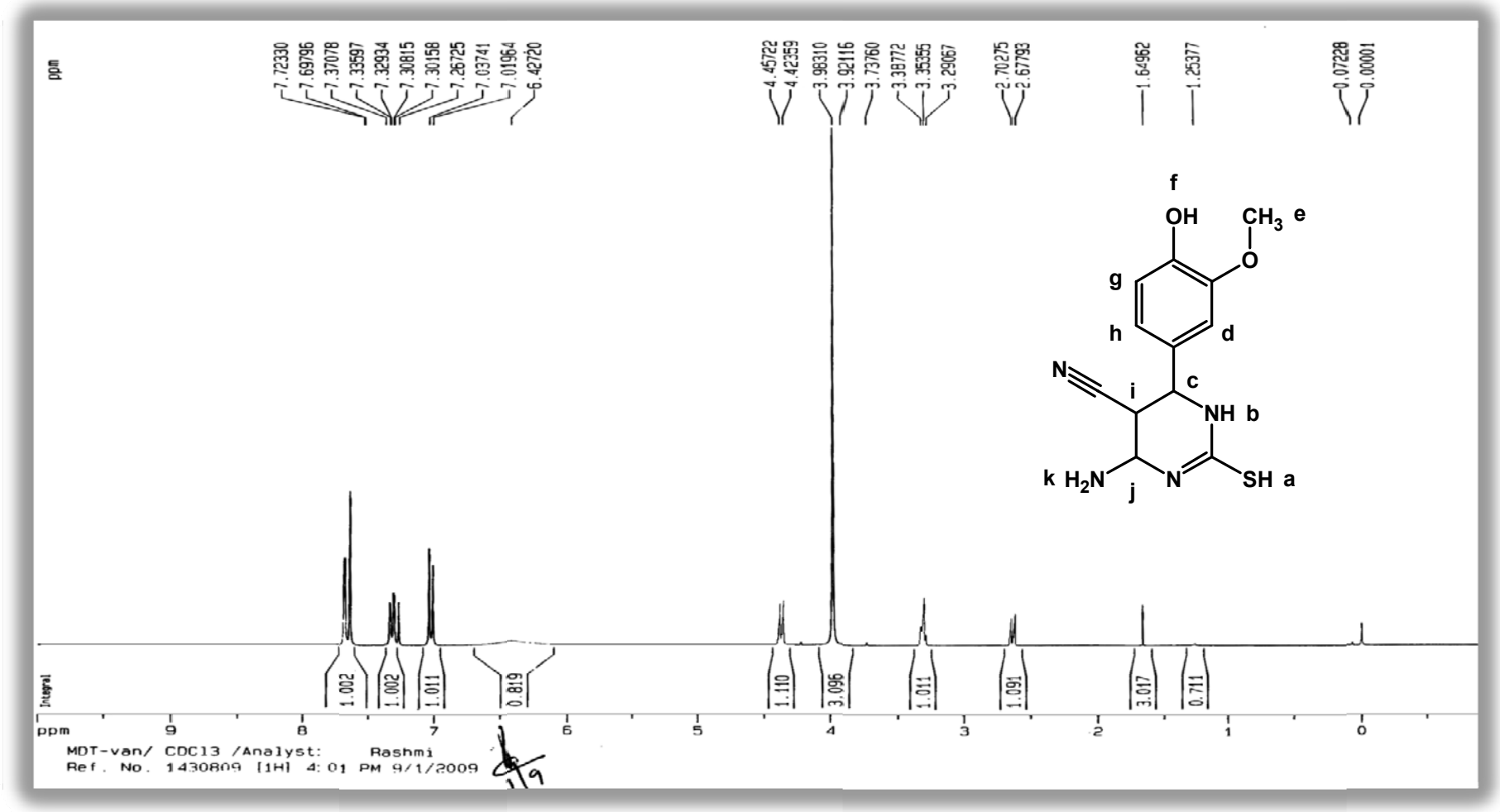
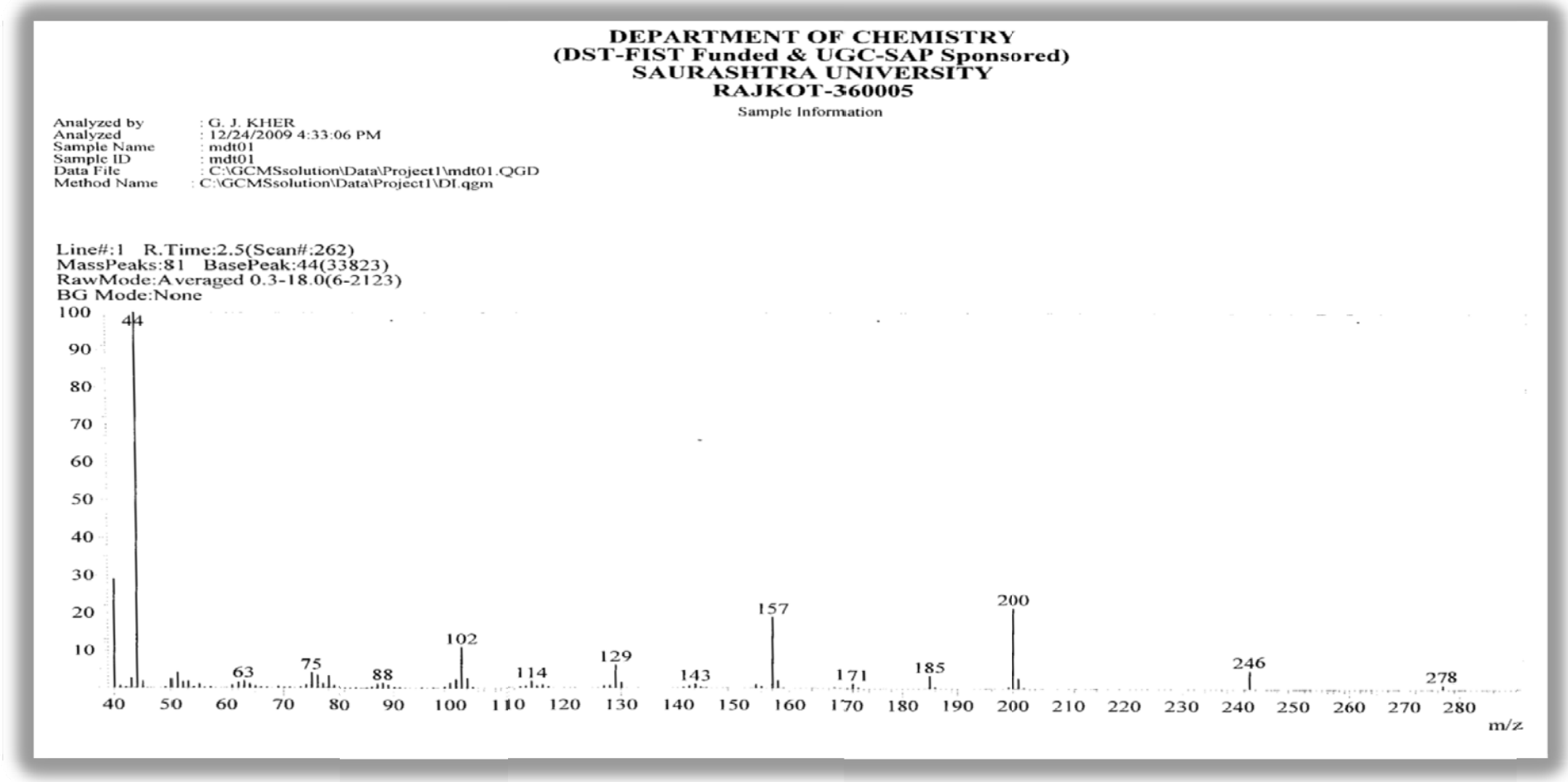


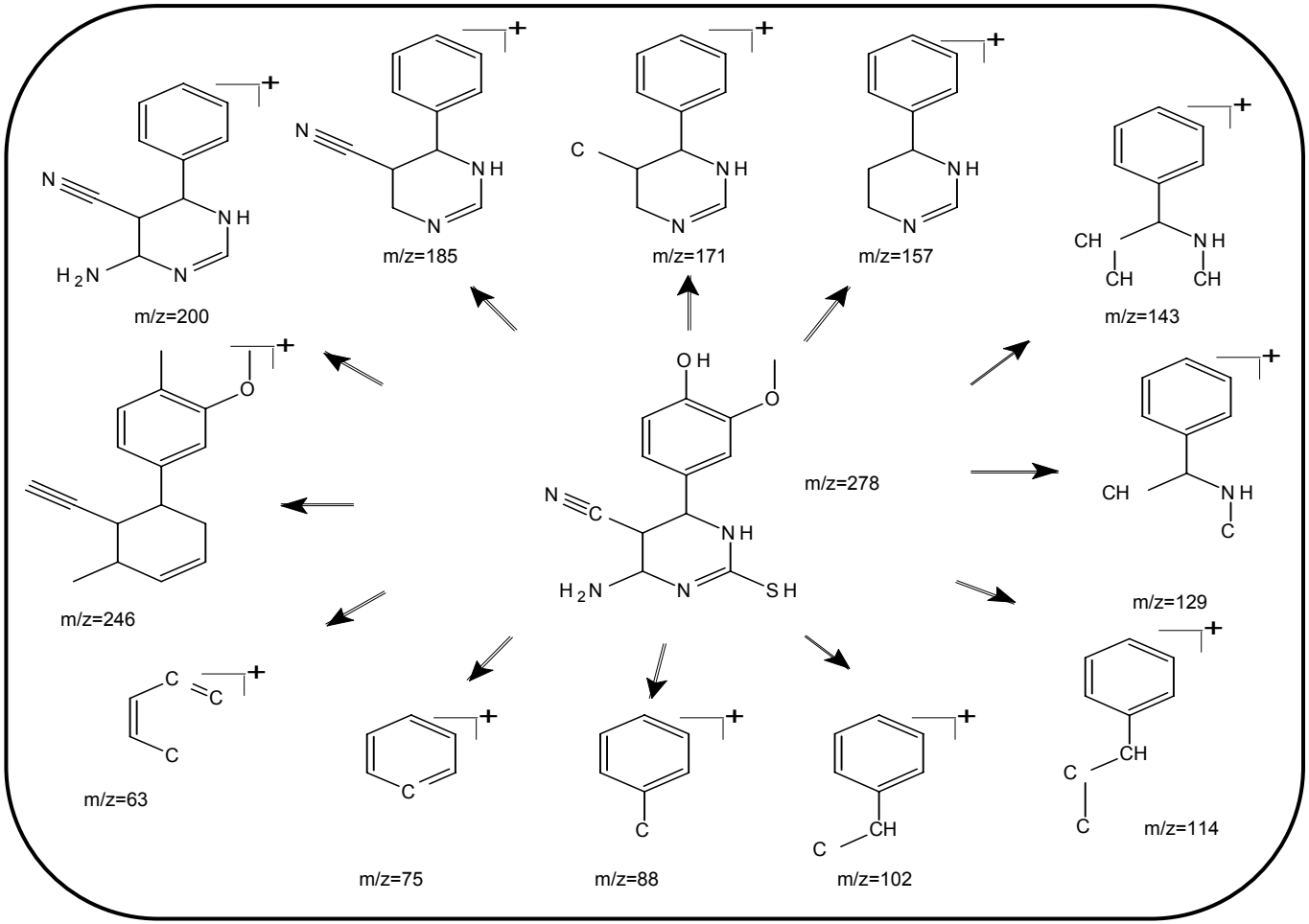
Table 1.4: ^{1}H NMR spectral data of 4-amino-6-(4-hydroxy-3-methoxy phenyl)-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (MDT 1).

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	*J* (Hz)
1	1.25	1	singlet	-S<u>H</u> (a)	-
2	1.65	3	singlet	-N<u>H</u> (b), -N<u>H</u>$_2$ (k)	-
3	2.68-2.70	1	doublet	-C<u>H</u>$_j$-	7.5
4	2.29-2.39	1	triplet	-C<u>H</u>$_i$-	-
5	3.98	3	singlet	-OC<u>H</u>$_3$	-
6	4.42-4.46	1	doublet	-C<u>H</u>$_c$-	10.1
7	6.43	1	singlet	-O<u>H</u>	-
8	7.02-7.04	1	doublet	Ar-<u>H</u>$_d$	2.33
9	7.27-7.33	1	triplet	Ar-<u>H</u>$_h$	-
10	7.70-7.72	1	doublet	Ar-<u>H</u>$_g$	7.6

Figure 1.3: Mass spectra of 4-amino-6-(4-hydroxy-3-methoxyphenyl)-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile (MDT 1).



Scheme 1.1: Proposed mass fragmentation of 4-amino-6-(4-hydroxy-3-methoxyphenyl)-2-sulfanyl-1,4,5,6-tetrahydro pyrimidine-5-carbonitrile (MDT 1).



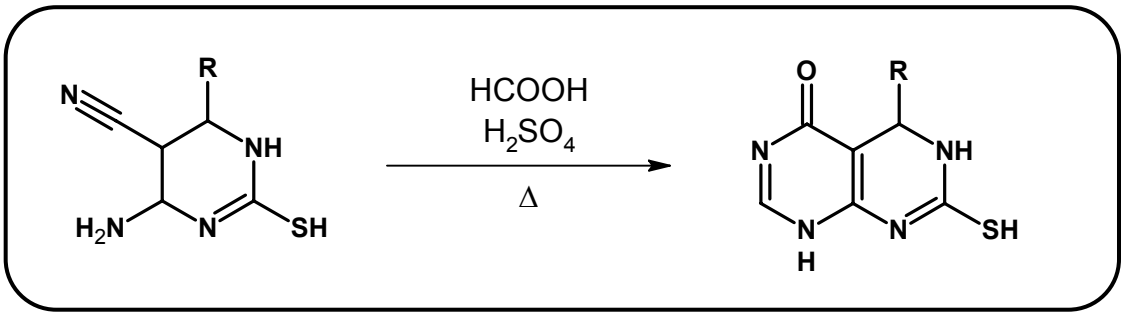
SYNTHESIS AND CHARACTERIZATION

Synthesis of 5-aryl-7-sulfanyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4(1H)-one:

Synthesis of 4-amino-6-aryl-2-sulfanyl-1,4,5,6-tetrahydropyrimidine-5-carbonitrile- Discussed in Section 1.

Synthesis of 5-aryl-7-sulfanyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4 (1H)-one- To the solution of recrystallized product (MDT series) obtained from section 1 (0.01 Mole) in formic acid (25 ml), 3-4 drops of sulphuric acid was added and the solution was refluxed in a water bath for 4 hours. Then, the reaction mixture was allowed to cool at room temperature and was neutralised with sodium bicarbonate carefully. From neutralized solution, product was extracted in the ethyl acetate. The organic layer was washed with brine solution and anhydrous sodium sulphate was added to remove moisture from it. The product was recovered from the solution with the help of rota vapour under high vacuum condition. The solid product obtained was recrystalised from methanol.

Reaction Scheme:



Following compounds were synthesized through above reaction scheme:

MPP 1: 5-(4-hydroxy-3-methoxyphenyl)-7-sulfanyl-5,6-dihydropyrimido [4,5-*d*] pyrimidin-4(3*H*)-one

MPP 2: 5-(4-methoxyphenyl)-7-sulfanyl-5,6-dihydropyrimido[4,5-*d*]pyrimi din-4 (3*H*)-one

MPP 3: 5-(4-hydroxyphenyl)-7-sulfanyl-5,6-dihydropyrimido[4,5-*d*]pyrimi din-4 (3*H*)-one

MPP 4: 5-(4-chlorophenyl)-7-sulfanyl-5,6-dihydropyrimido[4,5-*d*]pyrimidin-4 (3*H*)-one

MPP 5: 5-(3-chlorophenyl)-7-sulfanyl-5,6-dihydropyrimido[4,5-*d*]pyrimidin-4 (3*H*)-one

MPP 6: 5-(4-fluorophenyl)-7-sulfanyl-5,6-dihydropyrimido[4,5-*d*]pyrimidin-4-(3*H*)-one

MPP 7: 5-(3-nitrophenyl)-7-sulfanyl-5,6-dihydropyrimido[4,5-*d*]pyrimidin-4(3*H*) -one

MPP 8: 5-phenyl-7-sulfanyl-5,6-dihydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one

MPP 9: 5-(furan-2-yl)-7-sulfanyl-5,6-dihydropyrimido[4,5-*d*]pyrimidin-4(3*H*)-one

MPP 10: 5-(2-phenylethenyl)-7-sulfanyl-5,6-dihydropyrimido[4,5-*d*]pyrimi din-4(3*H*)-one

The various physical constants such as R_f value, melting point and percentage of yield for all the synthesized compounds of MTP series are given in Table 2.1.

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

Table 2.1: Physical constants of compounds of MDT series.

Sr. No.	Code	R	M.F.	M. W. g	R_f* Value	M.P. °C	Yield %
1.	**MPP 1**	4-OH, 3-OCH_3-C_6H_4-	$C_{13}H_{12}N_4O_3S$	304.3	0.19	98	67
2.	**MPP 2**	4-OCH_3-C_6H_4-	$C_{13}H_{12}N_4O_2S$	288.3	0.22	96	72
3.	**MPP 3**	4-OH-C_6H_4-	$C_{12}H_{10}O_2S$	274.3	0.20	86	68
4.	**MPP 4**	4-Cl-C_6H_4-	$C_{12}H_9ClN_4OS$	292.7	0.32	84	55
5.	**MPP 5**	3-Cl-C_6H_4-	$C_{12}H_9ClN_4OS$	292.7	0.36	92	59
6.	**MPP 6**	4-F-C_6H_4-	$C_{12}H_9FN_4OS$	276.3	0.29	102	58
7.	**MPP 7**	3-NO_2-C_6H_4-	$C_{12}H_9N_5O_3S$	303.3	0.45	85	66
8.	**MPP 8**	C_6H_5-	$C_{12}H_{10}N_4OS$	258.3	0.39	105	60
9.	**MPP 9**	4(α-C_4H_3O)-	$C_{10}H_8N_4O_2S$	248.3	0.17	65	69
10.	**MPP 10**	C_6H_4-CH=CH-	$C_{14}H_{12}N_4OS$	284.3	0.42	74	45

*Ethyl acetate : Hexane **:** 5 : 5

Figure 1.1: IR spectra of 5-(4-hydroxy-3-methoxyphenyl)-7-sulfanyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one (MPP 1).

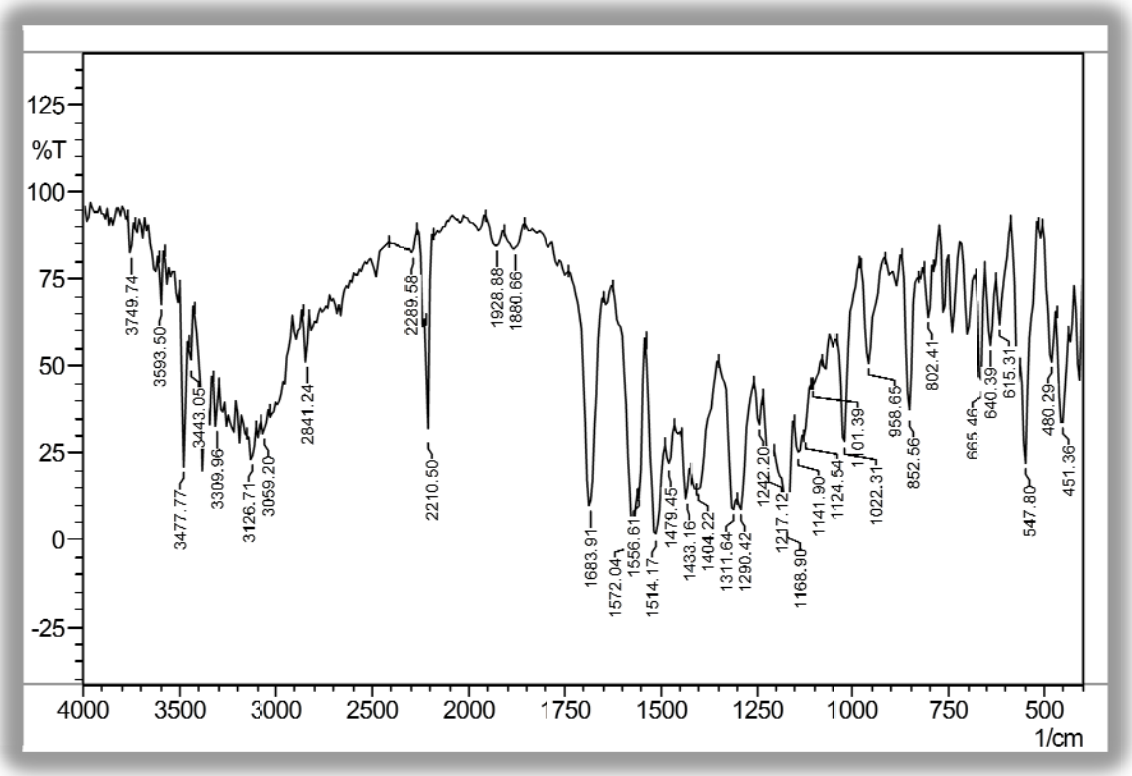


Table 1.2: IR spectral data of 5-(4-hydroxy-3-methoxyphenyl)-7-sulfanyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one (MPP 1).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported*
Alkane (methyl)	C-H str. (asym.)	-	2975-2920
	C-H str. (sym.)	2841.24	2880-2860
	C-H def. (asym.)	1479.45	1470-1435
	C-H def.(sym.)	1404.22	1395-1370
Aromatic	C-H str.	3059.20	3100-3000
	C=C str.	1514.17	1585-1480
	C-H i.p. def.	1556.61	1125-1090
	C-H o.o.p. def.	852.56	860-810
Ketone	C=Ostr.(cyclic)	1635.91	1710-1600
Hydroxy	O-H str.	3443.05	3650-3000
	O-H def.	1404.22	1410-1310
Amine (cyclic)	N-H str.	3477.77	3310-3500
ether	C-O-C str. (asym.)	1271.12	1400-1000
	C-O-C str. (sym.)	1022.31	1075-1020
Thiol	S-H str	2575.08	2600-2550

*(1) V. M. Parikh; "Absorption spectroscopy of organic molecule", Addition Wesley Pub. Co. London, 243-56 (1978).
(2) C. N. R. Rao; "Chemical application of Infrared Spectroscopy", Academic Press, New York (1963).

Table 2.3: IR spectral data of other synthesized pyrimidopyrimidines.

Compounds	*IR ν, (cm^{-1})*			
	C=C str	**S-H str**	**N-H str**	**C=O str (cyclo)**
MPP 2	1512.23	2571.59	3465.23	1630.23
MPP 3	1514.56	2569.26	3465.12	1625.14
MPP 4	1502.52	2574.13	3468.12	1622.78
MPP 5	1509.55	2575.23	3465.23	1631.33
MPP 6	1504.44	2571.46	3466.12	1629.82
MPP 7	1505.05	2569.19	3452.58	1624.39
MPP 8	1512.13	2573.38	3458.99	1631.31
MPP 9	1512.28	2548.27	3461.69	1632.25
MPP 10	1500.22	2565.22	3464.78	1635.52

Figure 2.2: ^{1}H NMR spectra of 5-(4-hydroxy-3-methoxyphenyl)-7-sulfanyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one (MPP 1).

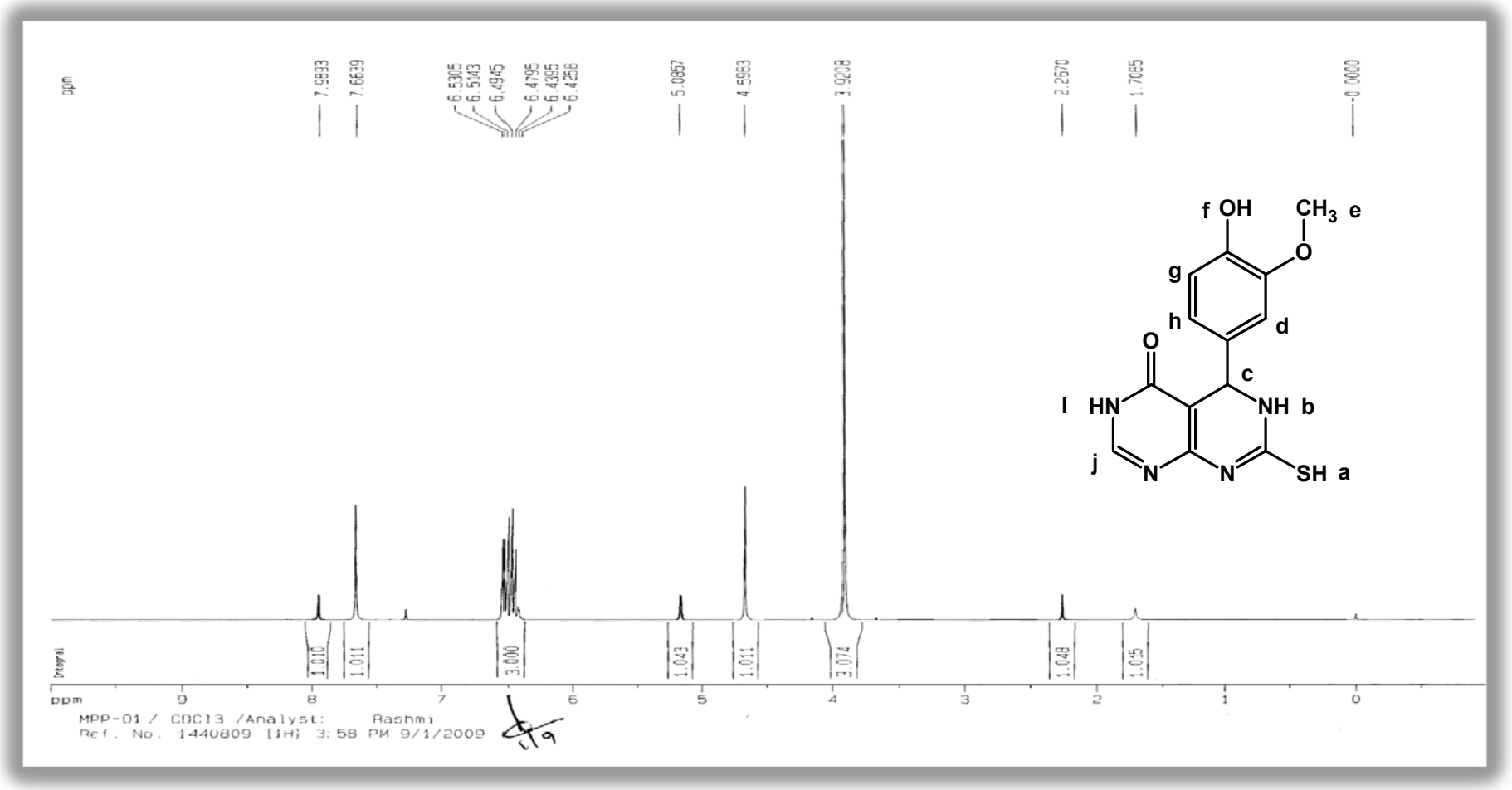
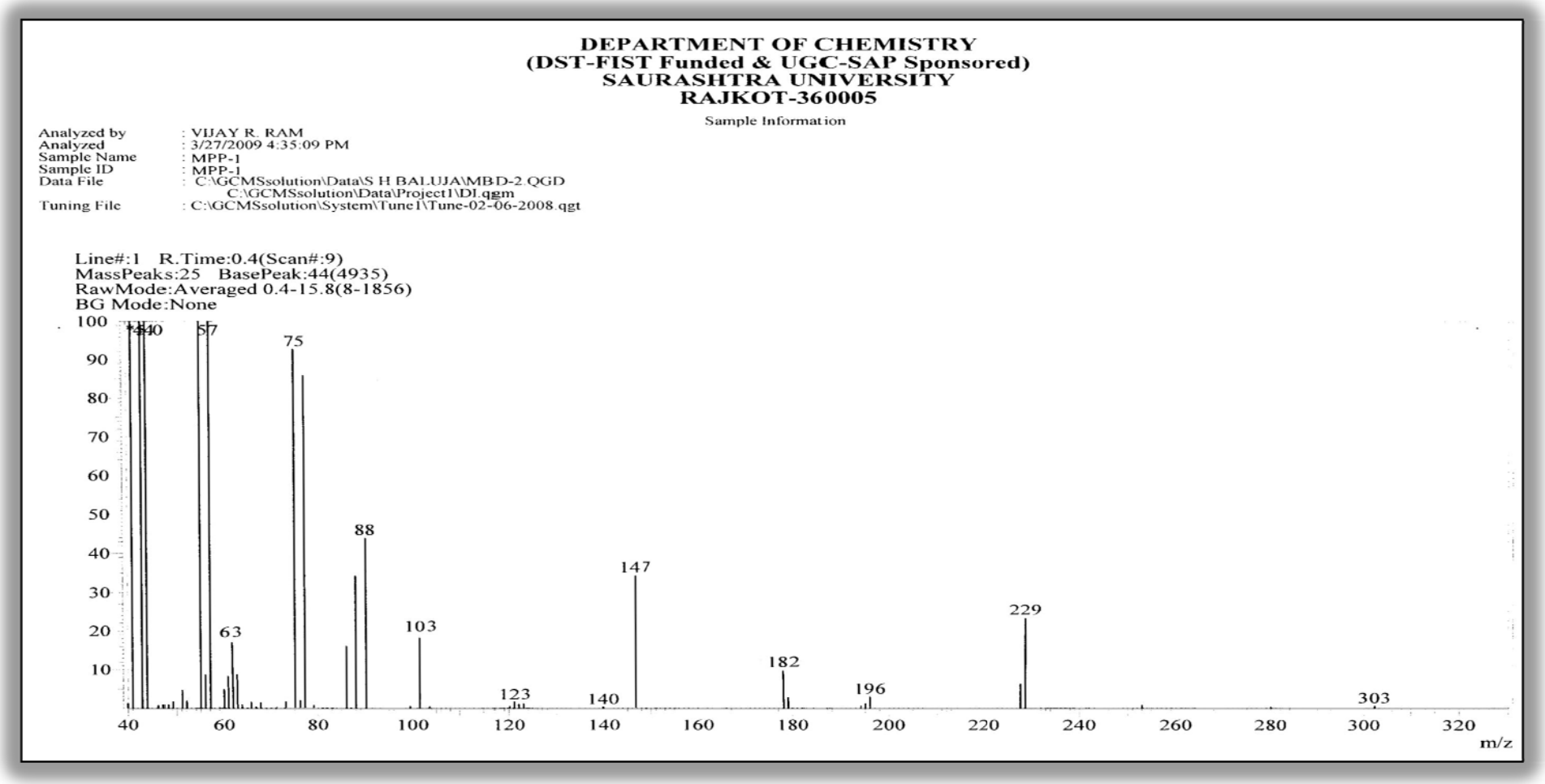


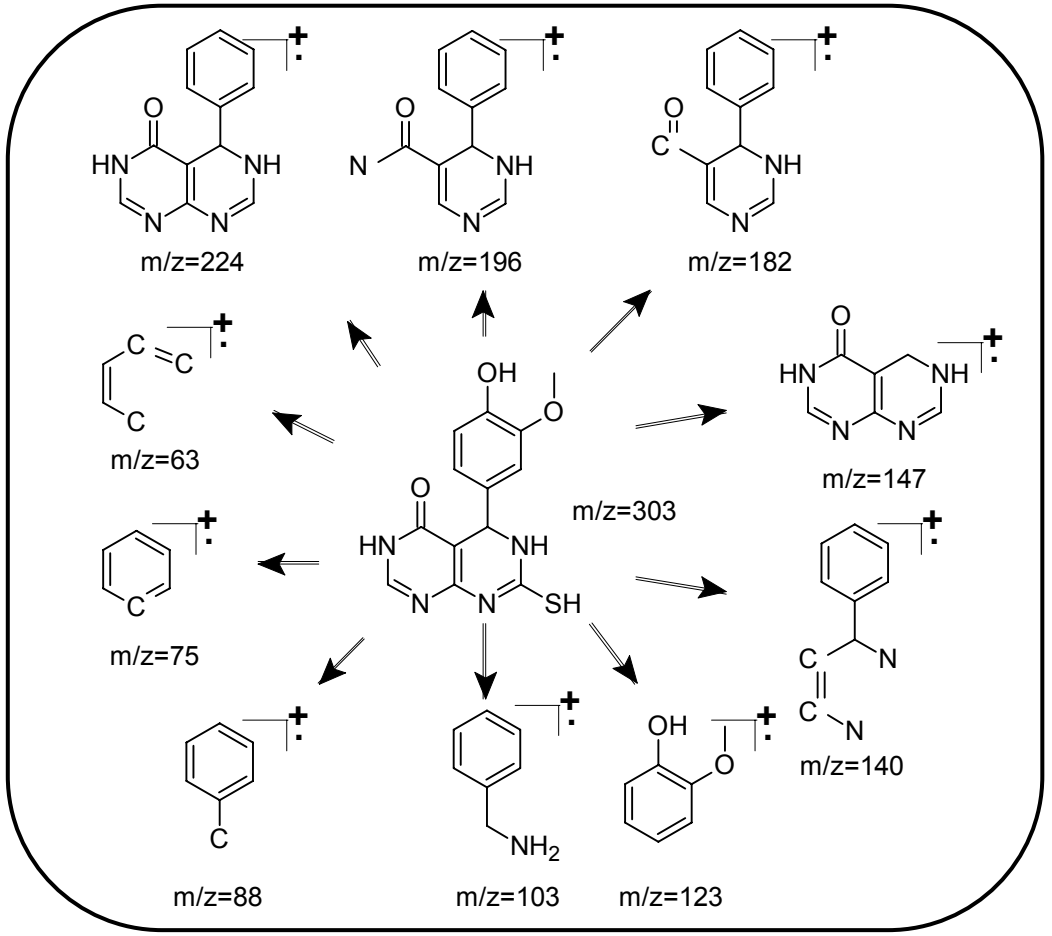
Table 1.4: ^{1}H NMR spectral data of 5-(4-hydroxy-3-methoxyphenyl)-7-sulfanyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one (MPP 1).

Singal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.71	1	singlet	-S<u>H</u> (a)
2	2.27	1	singlet	-N<u>H</u> (b)
3	3.92	3	singlet	-OC<u>H</u>$_3$ (e)
4	4.60	1	singlet	-C<u>H</u>$_c$-
5	5.09	1	singlet	-O<u>H</u>
6	6.43-6.53	3	multiplet	Ar-<u>H</u>$_{d,h,g}$
7	7.66	1	singlet	Ar-<u>H</u>$_j$
8	7.99	1	singlet	-N<u>H</u>- (I)

Figure 2.3: Mass spectra of 5-(4-hydroxy-3-methoxyphenyl)-7-sulfanyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one (MPP 1).



Scheme 2.1: Proposed mass fragmentation of 5-(4-hydroxy-3-methoxyphenyl)-7-sulfanyl-5,6-dihydropyrimido[4,5-d]pyrimidin-4(3H)-one (MPP 1).



INTRODUCTION

Quinoline is a well known molecule for chemists as its derivatives have been used as many drug molecules (e.g.; chloroquine, amidoquine, pamaquin, enrofloxacin, difloxacin, ofloxacin, etc.) or as precursor of many bioactive entities . Quinoline ring system is also found in alkaloid (e.g; cinchonan, chelidonine, etc.) like biological macromolecules.

Tetrahydroquinoline is also a useful molecule from pharmaceutical research point of view. Both 1,2,3,4-tetrahydroquinoline and 5,6,7,8-tetrahydroquinoline show reaction convenience and various types of activity. Unsubstituted 5,6,7,8-tetrahydroquinoline is a clear to yellow coloured liquid of boiling point 238^0 C.

Various researchers have indicated presence of many tetrahydroquinoline derivatives as transfer protein inhibitors [1], CRTH2 inhibitors [2], serine protease inhibitors [3], proton pump inhibitors [4], protein farnesyltransferase inhibitors [5, 6], allosteric inhibitors [7], etc. This moiety has also been reported as antagonists [8-13] and agonists [14, 15] of different types of receptors. Further, tetrahydroquinoline derivatives possess various types of activities like antidepressant [16], antiulcer [17], diuretic and antihypertensive [18], spasmogenic activity [19], gastrc antisecretory [20], analgesic [21], schistosomicidal [22, 23], antitussive, anorectic, and psychostimulant [24], antihistamine [25], antimalarial [26], antimicrobial [27], antifungal [28] etc. Asolkar et al. have reported some tetrahydroquinoline as antibiotic [29]. Some other tetrahydroquinoline have also been reported to possess anti-tubercular activity [30] and are useful in treatment of neurological and neurogenerative disorders [31]. Straten et al. have patented the four step preparation of a tetrahyddroquinoline derivative which can be used to control fertility [32]. These compounds are also known to be useful as cholesterol lowering agent [33].

Due to these all usefulness of tetrahydroquinoline, chemists are regularly attracted towards the synthesis [34, 35]. Different types of catalysts have been used to yield different products [36-38]. Many researchers have studied streochemical aspects of tetrahydroquinoline derivatives [39-43]. Dhar et al. [44] have performed SAR study whereas Salam et al. [45] have performed docking study of tetrahydroquinoline derivatives. Zalukaev et al. have studied

intramolecular interactions of discussed compound [46]. To synthesize this entity, green chemistry approaches like microwave irradiated reaction [47], solvent free catalytic reaction [48], multicomponent reaction (MCR) procedure etc. can also be employed.

Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry [49-53]. Recently when emphasis is put on speed, diversity, and efficiency in the drug discovery process [54], MCR strategies offer significant advantages over conventional linear-type syntheses [49-53]. In such reactions, three or more reactants come together in a single reaction vessel to form new products that contain portions of all the components [49-53]. So, in this section synthesis of tetrahydroquinolin were carried out by multicomponent reaction method.

These tetrahydroquinoline derivatives have also been used to synthesize pyrimidoquinolines [55-57]. These pyrimidoquinolines are important compounds because of their biological properties, which are known to depend mainly on the nature and position of substituent. Various biological properties such as antimalarial [58], anticancer [59], antimicrobial [60, 61], and anti-inflammatory activities [62, 63] etc. have been reported.

Our aim in the work presented herein was to synthesize pyrimido[4,5-b]quinolines using tetrahydroqinolinecarbonitriles as building blocks (Section-1). In section 2, synthesis of pyrimidoquinoline is discussed by cyclization of tetrahydroquinoline. The characterization of all the synthesized compounds were also done by IR, NMR and mass spectra.

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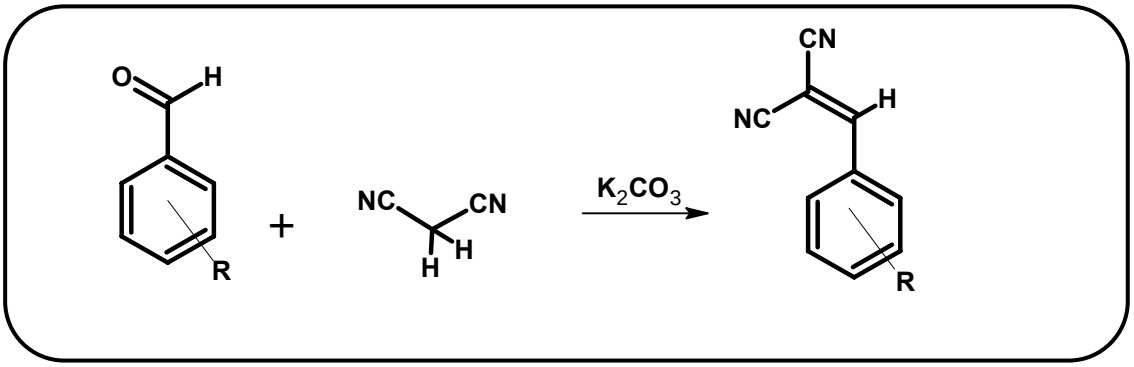
SYNTHESIS AND CHARACTERIZATION

Synthesis of 2-amino-4-aryl-5,6,7,8-tetrahydroquinoline-3carbonitrile:

Synthesis of benzylidenepropanedinitrile:

A mixture of vanillin (as aromatic aldehydes) (0.01M), malanonitrile (0.01M) and potassium carbonate (in excess) was crushed throughly by mortar pastel method for half an hour. To this solid mass, water was added to remove excess of potassium carbonate. The solution was then neutralized with aqueous hydrochloric acid solution. The resulting crude product was filtered and crystallized from dichloromethane.

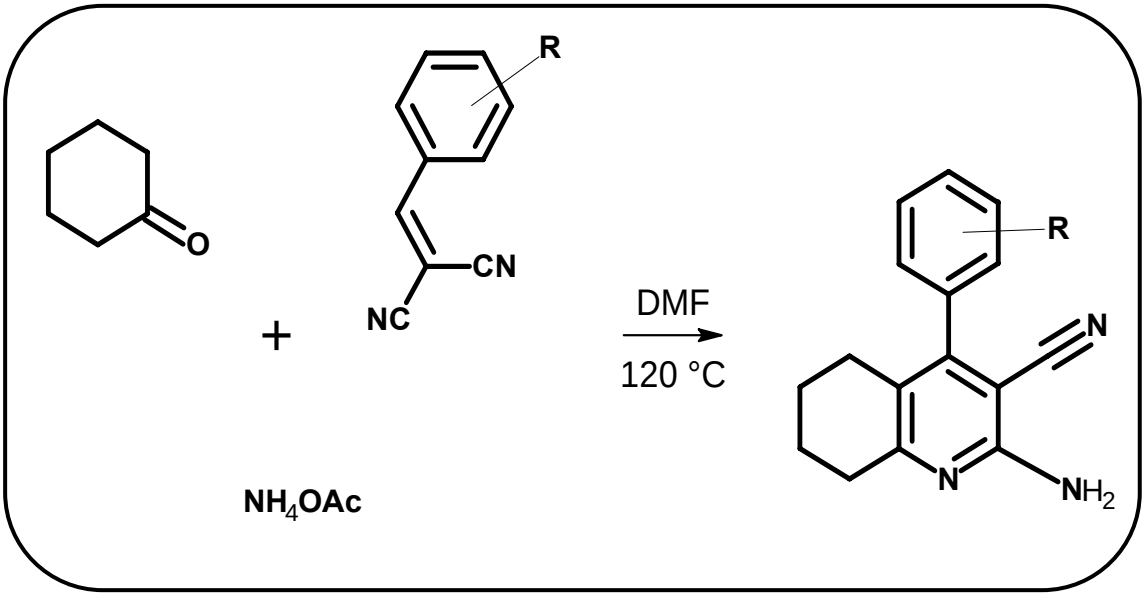
Reaction Scheme:



Synthesis of 2-amino-4aryl-5,6,7,8-tetrahydroquinoline-3-carbonitrile:

The above crystallized product (benzylidene propanedinitrile) was dissolved in N, N-dimethyl formamide. Equimolar amount of cyclohexanone was added to this solution with shaking. The resulting solution was then mixed with saturated solution of ammonium acetate in methanol and the mixture was refluxed at 150^0C for 4 hours. The reaction was monitored by TLC in the solvent system of EA : Hexane : 2:8. After completion of reaction, excess DMF was removed by rota vapour at high vacuum condition. The reaction mixture was then poured into ice and product was extracted in ethyl acetate. The organic layer was washed with brine solution and anhydrous sodium sulphate was added to remove moisture from it. The ethyl acetate was removed and solid product obtained was recrystalised from fresh ethanol.

Reaction Scheme:



Following compounds were synthesized through above reaction scheme.

MBH 1: 2-amino-4-(4-hydroxy-3-methoxyphenyl)-5,6,7,8-tetrahydro quino line-3-carbonitrile

MBH 2: 2-amino-4-(4-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbo nitrile

MBH 3: 2-amino-4-(4-hydroxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbo nitrile

MBH 4: 2-amino-4-(4-chlorophenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile

MBH 5: 2-amino-4-(3-chlorophenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile

MBH 6: 2-amino-4-(4-fluorophenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile

MBH 7: 2-amino-4-(3-nitrophenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile

MBH 8: 2-amino-4-phenyl-5,6,7,8-tetrahydroquinoline-3-carbonitrile

MBH 9: 2-amino-4-(3,4-dimethoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile

MBH 10: 2-amino-4-[4-(dimethylamino)phenyl]-5,6,7,8-tetrahydro quinoline-3-carbonitrile

The various physical constants such as R_f value, melting point and percentage of yield for all the synthesized compounds of MBH series are given in Table 3.1.

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

Table 3.1: Physical constants of compounds of MBH series.

Sr. No.	Code	R	M.F.	M. Wt. g	R_f* Value	M.P. °C	Yield %
1	**MBH 1**	4-OCH_3, 3-OH-	$C_{17}H_{17}N_3O_2$	295.4	0.42	218	65
2	**MBH 2**	4-OCH_3-	$C_{17}H_{17}N_3O$	279.4	0.35	258	63
3	**MBH 3**	4-OH-	$C_{16}H_{15}N_3O$	265.3	0.48	230	64
4	**MBH 4**	4-Cl-	$C_{16}H_{14}ClN_3$	283.8	0.45	210	73
5	**MBH 5**	3-Cl-	$C_{16}H_{14}ClN_3$	283.8	0.28	205	68
6	**MBH 6**	4-F-	$C_{16}H_{14}FN_3$	267.3	0.34	202	69
7	**MBH 7**	3-NO_2-	$C_{16}H_{14}N_4O_2$	294.3	0.56	210	78
8	**MBH 8**	H-	$C_{16}H_{15}N_3$	249.3	0.50	222	65
9	**MBH 9**	3, 4-Di OCH_3-	$C_{18}H_{19}N_3O_2$	309.4	0.39	195	58
10	**MBH 10**	4-N, N-Di CH_3-	$C_{18}H_{20}N_4$	292.4	0.30	188	61

* Ethyl acetate :Hexane **:** 3:7

Figure 3.1: IR spectra of 2-amino-4-(4-hydroxy-3-methoxyphenyl)-5,6,7,8-tetra hydroquinoline-3-carbonitrile (MBH 1).

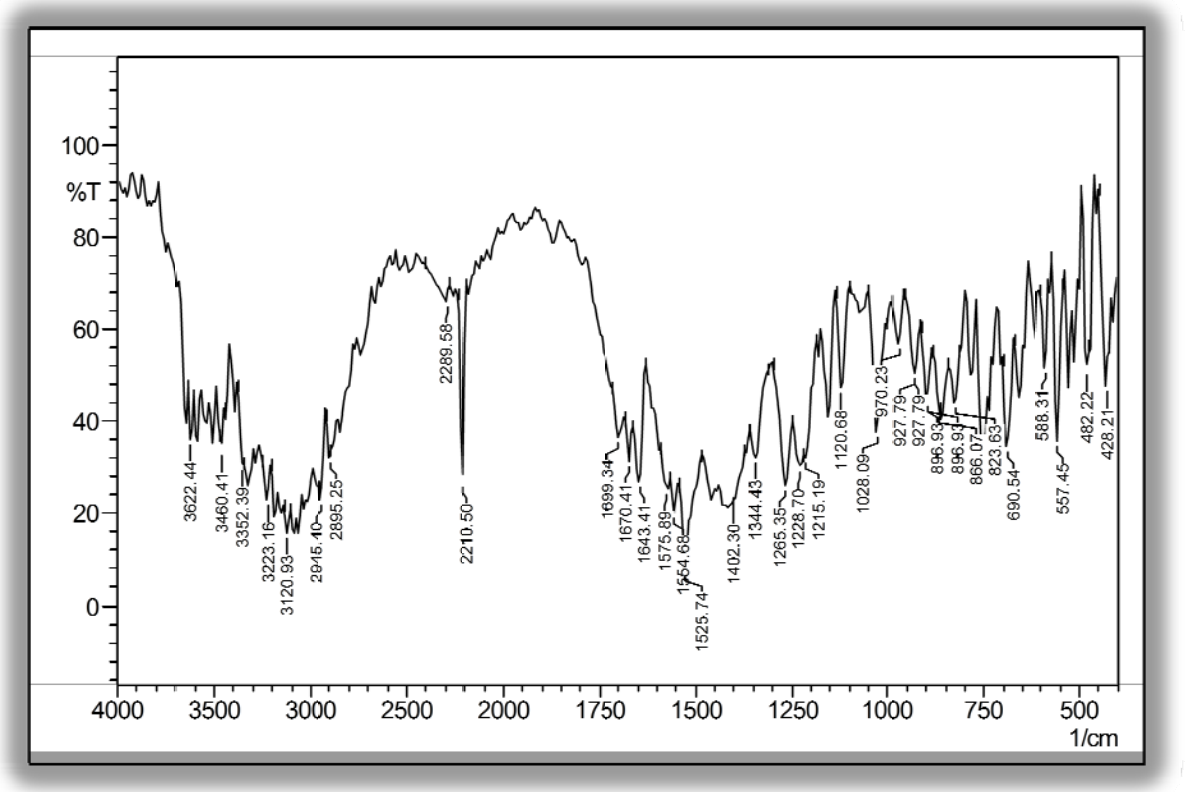


Table 3.2: IR spectral data of 2-amino-4-(4-hydroxy-3-methoxyphenyl)-5,6,7,8-tetra hydroquinoline-3-carbonitrile (MBH 1).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported*
Alkane (methyl)	C-H str. (asym.)	2945.40	2975-2920
	C-H str. (sym.)	2895.25	2880-2860
	C-H def. (asym.)	1476.50	1470-1435
	C-H def.(sym.)	1344.43	1395-1370
Aromatic	C-H str.	3120.93	3100-3000
	C=C str.	1525.74	1585-1480
	C-H i.p. def.	1120.68	1125-1090
	C-H o.o.p. def.	866.07	860-810
Hydroxy	O-H str.	3352.39	3650-3000
	O-H def.	1402.30	1410-1310
Primary amine	N-H str.	3460.41	3310-3500
	N-H ben	1643.41	1650-1590
Ether	C-O-C str. (asym.)	1215.19	1400-1000
	C-O-C str. (sym.)	1028.09	1075-1020
C≡N	C≡N str	2210.50	2240-2220
C=N	C=N str	1670.41	1690-1640

*(1) V. M. Parikh; "Absorption spectroscopy of organic molecule", Addition Wesley Pub. Co. London, 243-56 (1978).
(2) C. N. R. Rao; "Chemical application of Infrared Spectroscopy", Academic Press, New York (1963).

Table 3.3: IR spectral data of other synthesized tetrahydroquinollines.

Compounds	*IR ν, (cm^{-1})*			
	C=C str	**C=N str**	**N-H str**	**C≡N str**
MBH 2	1530.15	1672.56	3459.41	2215.32
MBH 3	1523.01	1665.32	3466.23	2211.54
MBH 4	1528.32	1675.19	3468.55	2215.26
MBH 5	1522.16	1671.87	3475.89	2218.51
MBH 6	1519.56	1670.54	3468.15	2209.33
MBH 7	1532.17	1672.33	3471.23	2212.12
MBH 8	1511.11	1672.45	3475.15	2205.14
MBH 9	1525.32	1673.26	3472.26	2213.94
MBH 10	1522.23	1674.54	3470.02	2209.09

Figure 3.2: ^{1}H NMR spectra of 2-amino-4-(4-hydroxy-3-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (MBH 1).

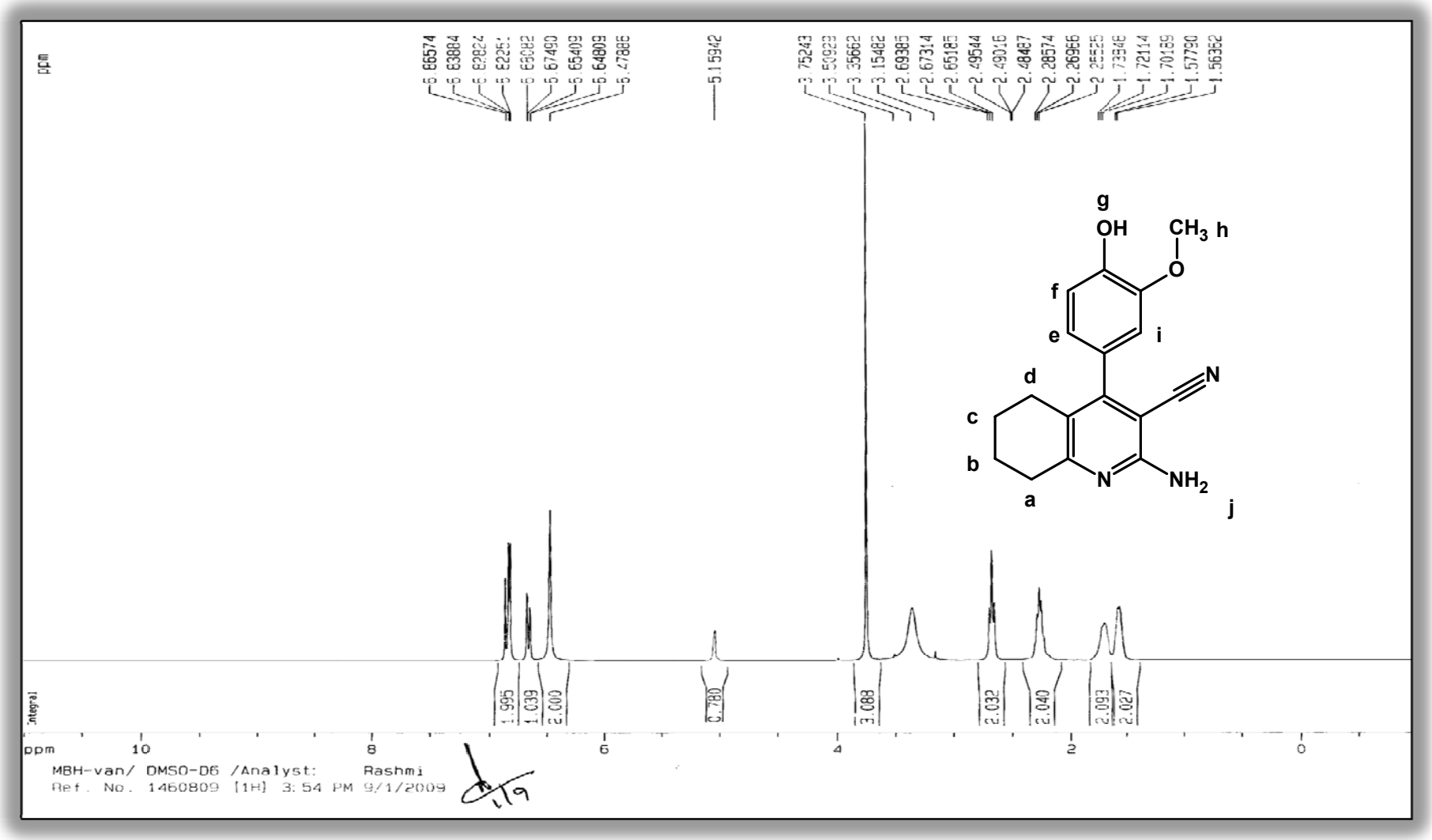
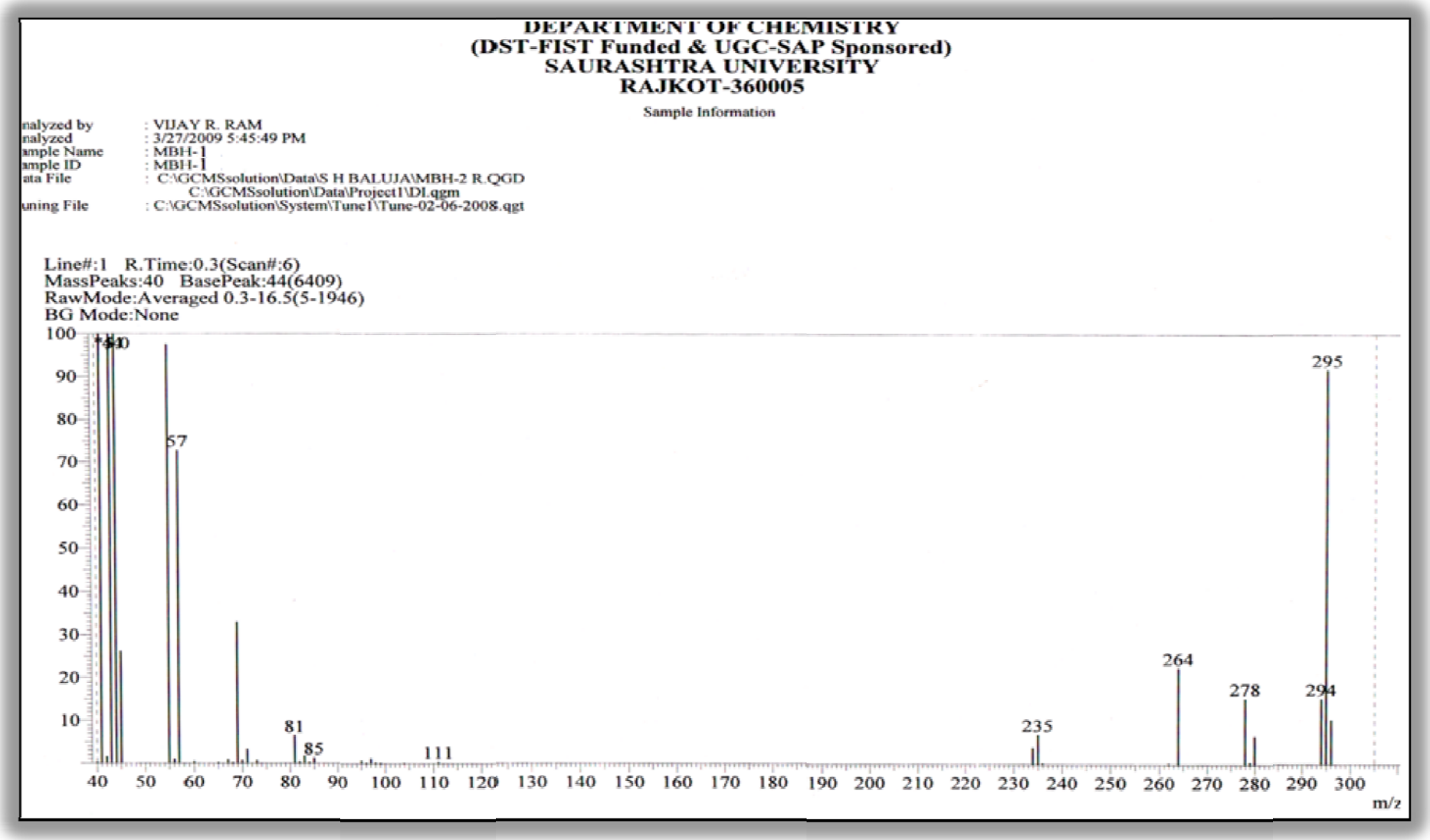


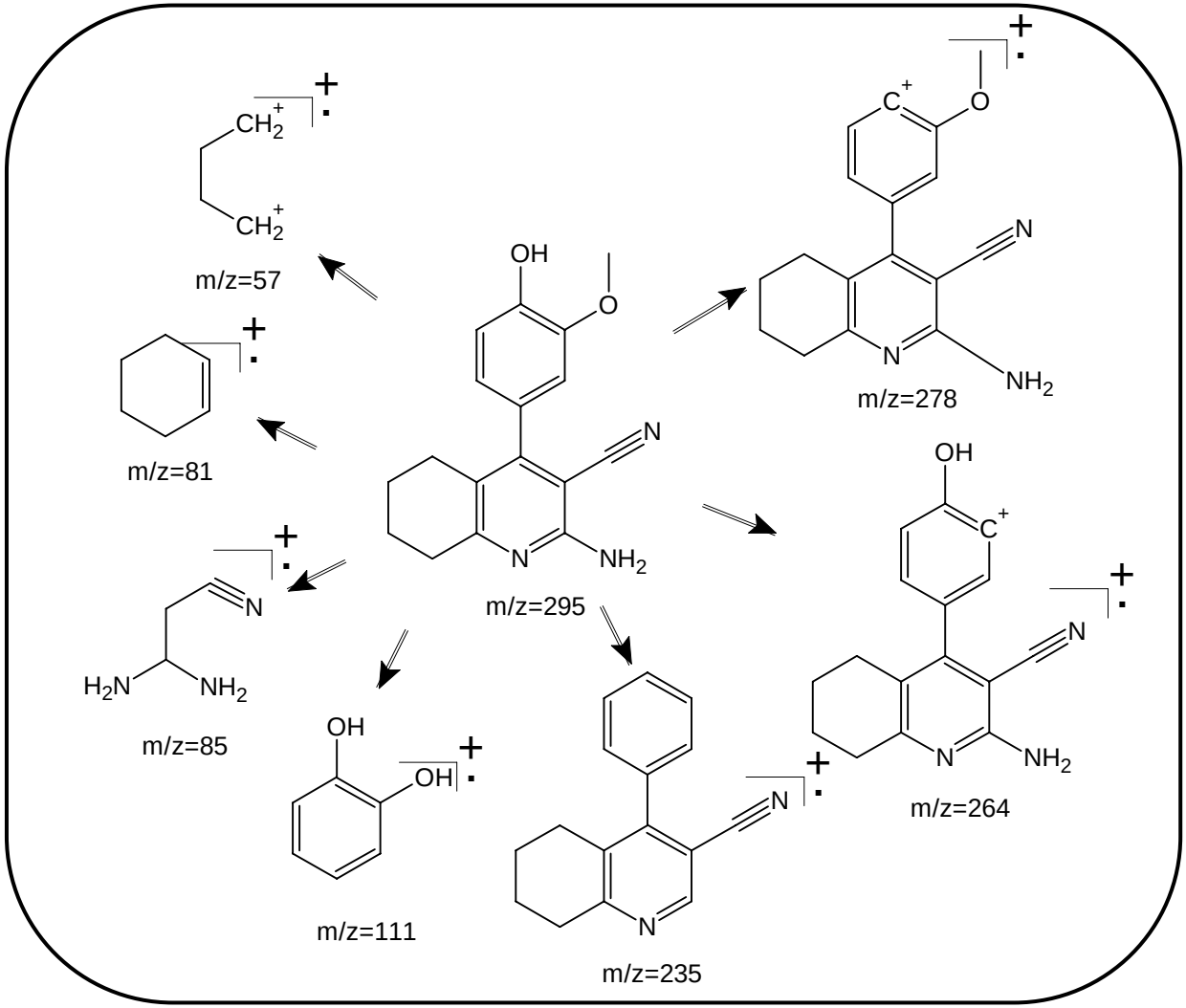
Table 3.4: ^{1}H NMR spectral data of 2-amino-4-(4-hydroxy-3-methoxy phenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (MBH 1).

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	J (Hz)
1	1.56-1.58	2	multiplet	-C<u>H</u>$_2$- (b)	-
2	1.70-1.74	2	multiplet	-C<u>H</u>$_2$- (c)	-
3	2.26-2.29	2	triplet	-C<u>H</u>$_2$- (d)	-
4	2.55-2.69	2	triplet	-C<u>H</u>$_2$- (a)	-
5	3.75	3	singlet	-OC<u>H</u>$_3$ (h)	-
6	5.16	1	singlet	-OH (g)	-
7	6.48	2	singlet	-NH$_2$ (j)	-
8	6.65-6.67	1	doublet	Ar-<u>H</u>$_f$	6.24
9	6.82-6.87	2	multiplet	Ar-<u>H</u>$_{e, i}$	-

Figure 3.3: Mass spectra of 2-amino-4-(4-hydroxy-3-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (MBH 1).



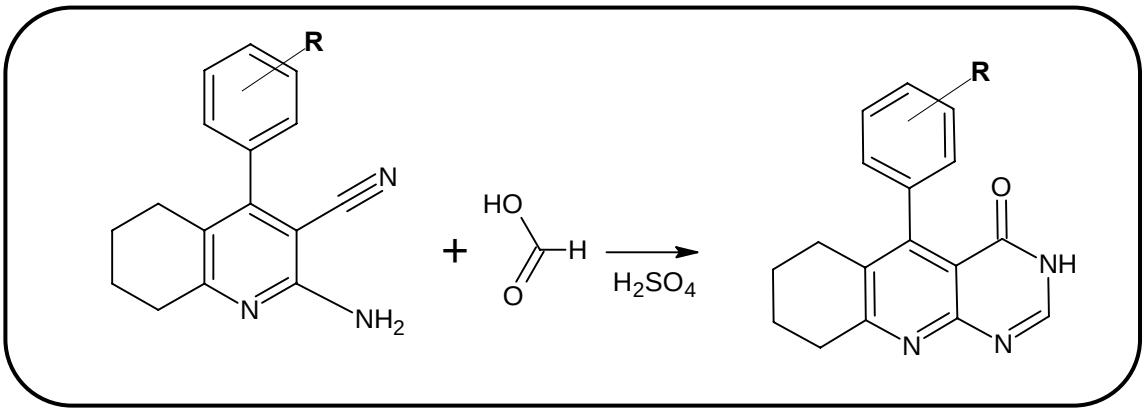
Scheme 3.1: Proposed mass fragmentation of 2-amino-4-(4-hydroxy-3-methoxyphenyl)-5,6,7,8-tetrahydroquinoline-3-carbonitrile (MBH 1).



Synthesis of 5-(4-aryl)-6,7,8,9-tetrahydropyrimido[4,5-*b*] quinolin-4(3*H*)-one:

To a solution of 2-amino-4-aryl-5,6,7,8-tetrahydroquinoline-3-carbonitrile in formic acid, 2-3 drops of H_2SO_4 was added and the solution mixture was refluxed for 4 hours in a water bath. The product was isolated from the reaction mass and recrystalised from methanol.

Reaction Scheme:



Following compounds were synthesized through above reaction scheme:

MBD 1: 5-(4-hydroxy-3-methoxyphenyl)-6,7,8,9-tetrahydropyrimido[4,5-*b*] quinolin-4(3*H*)-one

MBD 2: 5-(4-methoxyphenyl)-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4 (3*H*)-one

MBD 3: 5-(4-hydroxyphenyl)-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4 (3*H*)-one

MBD 4: 5-(4-chlorophenyl)-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4(3*H*) -one

MBD 5: 5-(3-chlorophenyl)-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4(3*H*) -one

MBD 6: 5-(4-fluorophenyl)-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4(3*H*)- one

MBD 7: 5-(3-nitrophenyl)-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4(3*H*)- one

MBD 8: 5-phenyl-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4(3*H*)-one

MBD 9: 5-(3,4-dimethoxyphenyl)-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin -4(3*H*)-one

MBD 10: 5-[4-(dimethylamino)phenyl]-6,7,8,9-tetrahydropyrimido[4,5-*b*]quin olin-4(3*H*)-one

The various physical constants such as R_f value, melting point and percentage of yield for all the synthesized tetrahydropyrimidines are given in Table 4.1.

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

Table 4.1: Physical constants of compounds of MBD series.

Sr. No.	Code	R	M.F.	M. Wt. g	R_f* Value	M.P. °C	Yield %
1	**MBD 1**	4-OCH_3, 3-OH-	$C_{18}H_{17}N_3O_3$	323.4	0.25	118	45
2	**MBD 2**	4-OCH_3-	$C_{18}H_{17}N_3O_2$	307.4	0.15	122	42
3	**MBD 3**	4-OH-	$C_{17}H_{15}N_3O_2$	293.3	0.21	125	45
4	**MBD 4**	4-Cl-	$C_{17}H_{14}ClN_3O$	311.8	0.33	109	43
5	**MBD 5**	3-Cl-	$C_{17}H_{14}ClN_3O$	311.8	0.26	105	40
6	**MBD 6**	4-F-	$C_{17}H_{14}FN_3O$	295.3	0.38	130	38
7	**MBD 7**	3-NO_2-	$C_{17}H_{14}N_4O_3$	322.3	0.45	113	41
8	**MBD 8**	H-	$C_{17}H_{15}N_3O$	277.3	0.30	129	49
9	**MBD 9**	3, 4-Di OCH_3-	$C_{19}H_{19}N_3O_3$	337.4	0.22	104	45
10	**MBD 10**	4-N, N-Di CH_3-	$C_{19}H_{20}N_4O$	320.4	0.31	99	41

* Ethyl acetate :Hexane **:** 5:5

Figure 4.1: IR spectra of 5-(4-hydroxy-3-methoxyphenyl)-6,7,8,9-tetrahydro pyrimido[4,5-*b*]quinolin-4(3*H*)-one (MBD 1).

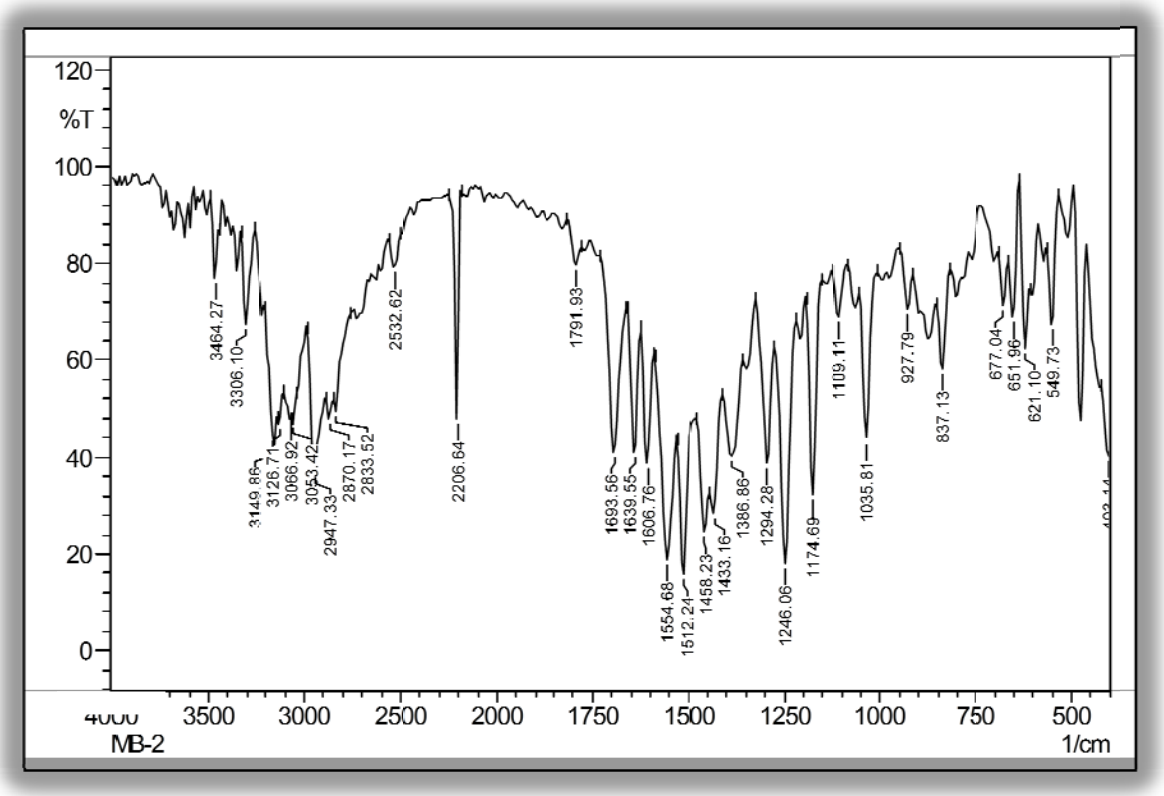


Table 4.2: IR spectral data of 5-(4-hydroxy-3-methoxyphenyl)-6,7,8,9-tetra hydropyrimido[4,5-*b*]quinolin-4(3*H*)-one (MBD 1).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported
Alkane (methyl)	C-H str. (asym.)	2947.33	2975-2920
	C-H str. (sym.)	2870.17	2880-2860
	C-H def. (asym.)	1458.23	1470-1435
	C-H def.(sym.)	1386.86	1395-1370
Aromatic	C-H str.	3053.42	3100-3000
	C=C str.	1512.24	1585-1480
	C-H i.p. def.	1109.11	1125-1090
	C-H o.o.p. def.	837.13	860-810
Ketone	C=O str (cyclic)	1693.56	1710-1600
Hydroxy	O-H str.	3306.10	3650-3000
	O-H def.	1386.68	1410-1310
Amine (cyclic)	N-H str.	3126.71	3310-3500
	N-H ben	1606.76	1650-1590
ether	C-O-C str. (asym.)	1284.82	1400-1000
	C-O-C str. (sym.)	1035.81	1075-1020
C=N	C=N str	1639.55	1690-1640

*(1) V. M. Parikh; "Absorption spectroscopy of organic molecule", Addition Wesley Pub. Co. London, 243-56 (1978).
(2) C. N. R. Rao; "Chemical application of Infrared Spectroscopy", Academic Press, New York (1963).

Table 4.3: IR spectral data of other synthesized tetrahydroquinoline - pyrimidine.

Compounds	*IR ν, (cm^{-1})*			
	C=C str	**C=N str**	**N-H str**	**C=O str (Cyclic)**
MBD 2	1513.13	1640.04	3127.22	1701.17
MBD 3	1519.15	1641.25	3129.91	1690.15
MBD 4	1514.12	1642.25	3131.35	1708.22
MBD 5	1512.55	1641.52	3130.84	1695.25
MBD 6	1511.11	1642.23	3125.21	1694.98
MBD 7	1512.45	1642.88	3124.24	1700.99
MBD 8	1513.35	1640.54	3126.36	1699.02
MBD 9	1514.41	1639.39	3129.28	1705.04
MBD 10	1509.09	1639.98	3127.61	1695.07

Figure 4.2: ^{1}H NMR spectra of 5-(4-hydroxy-3-methoxyphenyl)-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4(3*H*)-one (MBD 1).

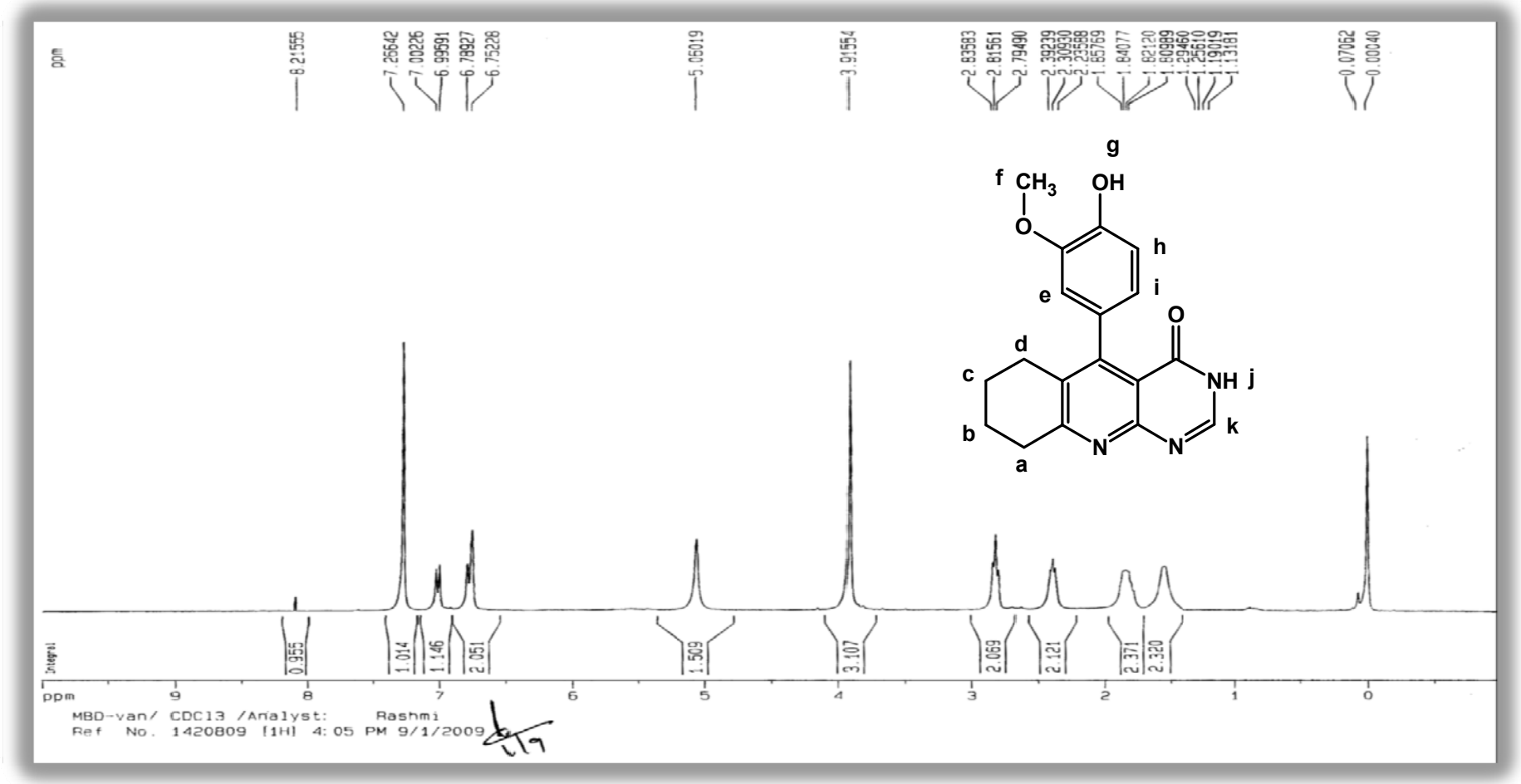
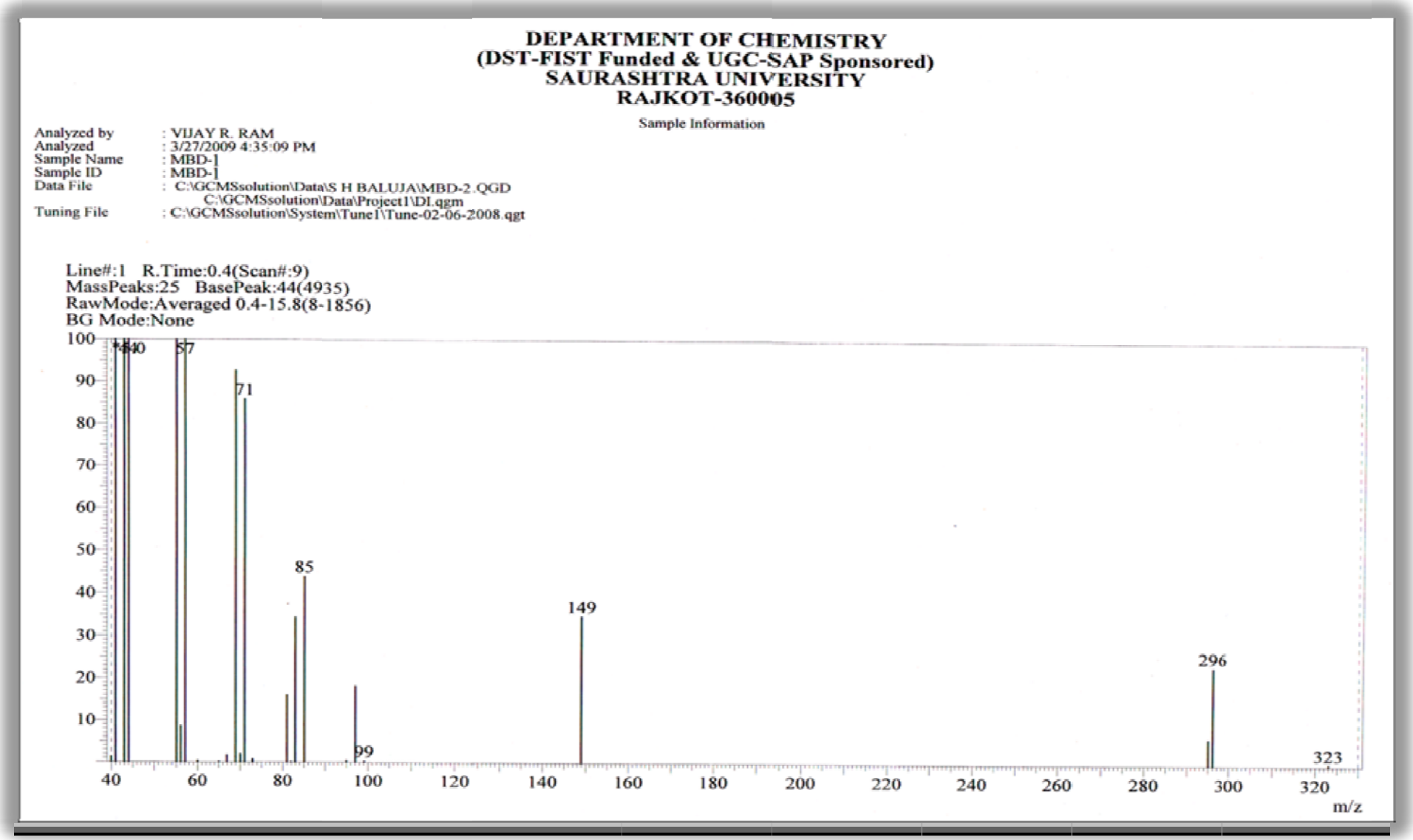


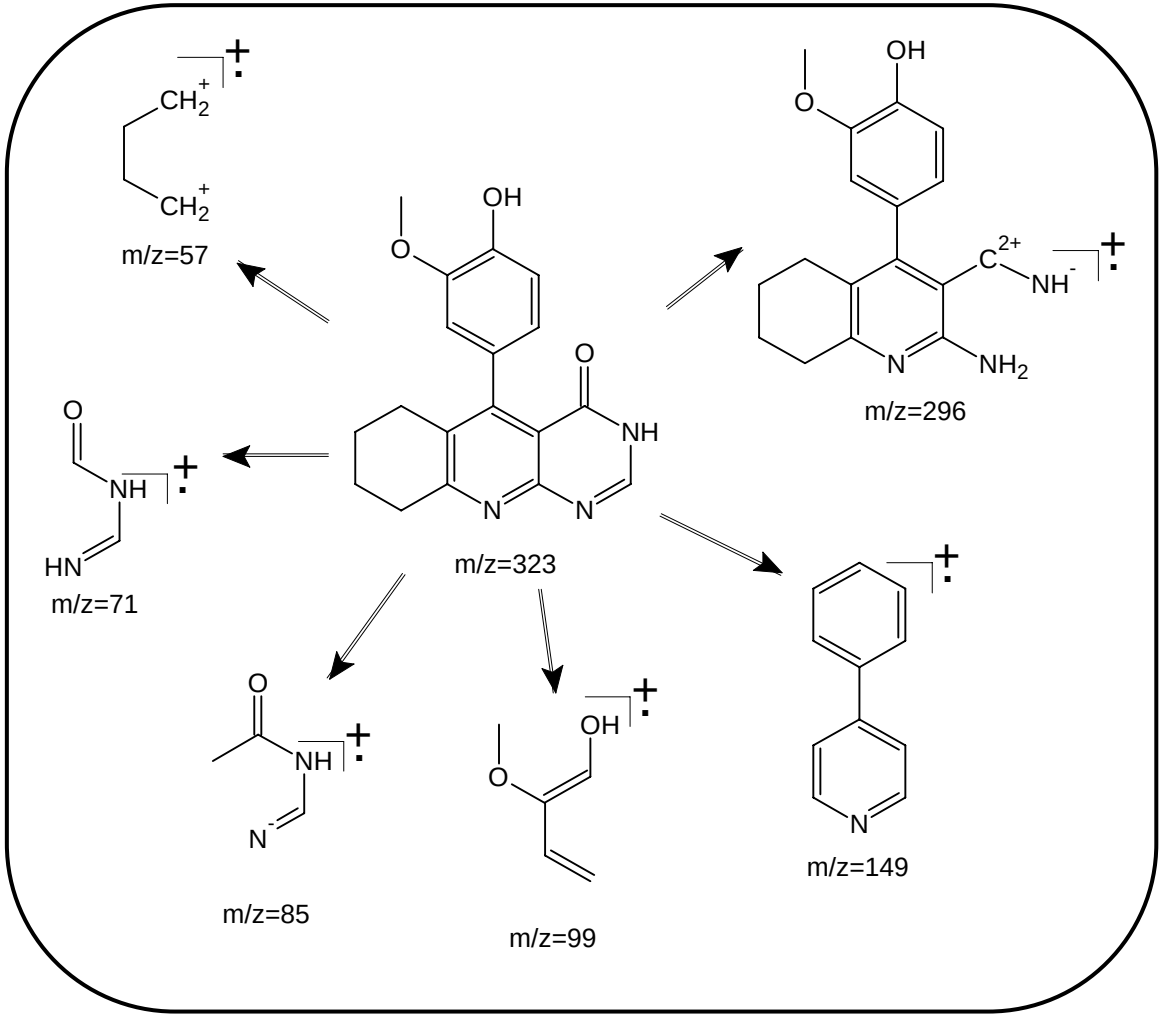
Table 4.4: ^{1}H NMR spectral data of 5-(4-hydroxy-3-methoxyphenyl)-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4(3*H*)-one (MBD 1).

Singal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	*J* (Hz)
1	1.13-1.30	2	multiplet	-C<u>H</u>$_2$-(b)	-
2	1.81-1.86	2	multiplet	-C<u>H</u>$_2$-(c)	-
3	2.24-2.39	2	triplet	-C<u>H</u>$_2$-(d)	-
4	2.80-2.84	2	triplet	-C<u>H</u>$_2$-(a)	-
5	3.92	3	singlet	-OC<u>H</u>$_3$ (f)	-
6	5.07	1	singlet	-O<u>H</u> (g)	-
7	6.75-6.79	2	doublet	Ar-<u>H</u> $_{h, i}$	11.1
8	6.99-7.02	1	doublet	Ar-<u>H</u> $_e$	7.9
9	7.27	1	singlet	-N<u>H</u> (j)	-
10	8.22	1	singlet	Ar-<u>H</u> $_k$	-

Figure 4.3: Mass spectra of 5-(4-hydroxy-3-methoxyphenyl)-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4(3*H*)-one (MBD 1).



Scheme 4.1: Proposed mass fragmentation of 5-(4-hydroxy-3-methoxyphenyl)-6,7,8,9-tetrahydropyrimido[4,5-*b*]quinolin-4(3*H*)-one (MBD 1).



INTRODUCTION

Benzimidazoles have been widely used since the 1960s as potent, orally active, safe, broad-spectrum anthelmintics agents in veterinary and human medicine and as antifungal agents in agriculture. Recently some drugs with benzimidazole ring system also used as antihistaminic, antiulcerative, protonpumpinhibitor, antiemetic etc. Mebendazole, thiabendazole, lobendazole, astemizole, omeprazpole, lansopraazole, domperidoone etc. are the some examples of drugs which possess benzimidazoole ring system. Maribavir, a novel antiviral agent in the benzimidazole drug class [1] which is currently in clinical development [2], have the potency to be used for the prevention of cytomegalovirus infections in transplant patients.

Compounds of benzimidazole class are efficient inhibitors of different biological processes [3, 11-13]. This is further confirmed by Fellenius et al. in rabbits [4] and by Sewing et al. in guinea pig [5]. Wooley et al have checked the biological effect caused by benzimidazole [6]. These derivatives also inhibit microtubule polymerization in vitro and in vivo in a similar fashion [7-10].

Benzimidazoles are known to possess various biological activities like antiprotozoal [14-17], antimicrobial [18, 19], antifungal [20, 21], antibacterial [20, 22, 23], antimicrotubule [24], antiproliferative [25], anti viral [26], anti HIV [27, 28] or fasciolicidal activity [29]. Literature survey shows that various chemists have synthesized derivatives of benzimidazoles [16, 30-34]. Most of them also evaluated synthesized compounds for different biological activities [35- 37].

Coumarin, a simple molecule, and its derivatives, have been known for more than a century. This class of compounds are known to prevent diseases, modulates growth and maturation and defence systems and may have anti-oxidant properties [38]. Various coumarin derivatives can be extracted from many natural products [39, 40]. These extracts shows anti HIV [41], antinoceceptive [42], antinflammatory [43], bronchodilator [44], anti oxidative [45] etc. activities. Therefore, coumarins always attract chemists to synthesize derivatives as precursor of novel drug. Such synthesized modified coumarins are noted to show various activities like anticarcenogenic [46], antimicrobial [47], antifungal [48],

antibacterial [49], antioxidant [50, 51], antiinfalammatory [52] etc. It is also used to inhibit many biological processes also [53-57]. So, chemists have regularly synthesized differently modified coumarins by applying variable conditions [58-65].

In this part, an attempt has made to synthesize compounds with the properties of both the moieties viz. benzimidazole and coumarin. In this section some derivatives of benzimidazoles have condenced with acetyl coumarin.

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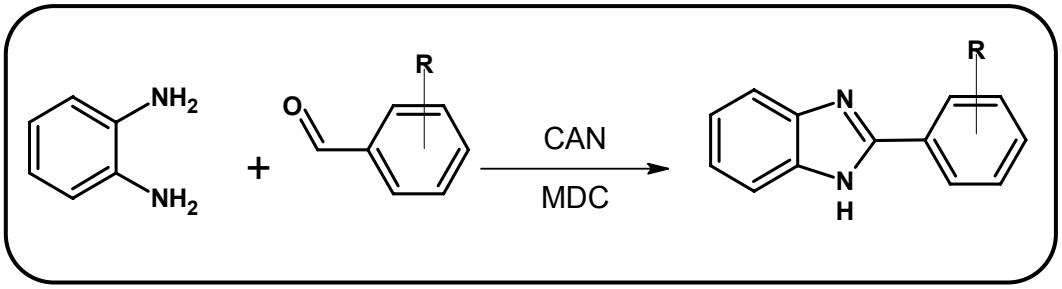
SYNTHESIS AND CHARACTERIZATION

Synthesis of 3-{[2-(4-aryl)-1*H*-benzimidazol-1-yl]acetyl}-2*H*-chromen-2-one

Synthesis of 2-(4-aryl)-1*H*-benzimidazole:

o-phenelinediamine (1.08 gm, 0.01 M) and aromatic aldehydes (1.52 gm, 0.01) were dissolved in appropriate amount of metheline dichloride (MDC). To this clear solution, 0.005 M of cerric ammonium nitrate (CAN) (2.74 gm) was added with constant stirring. The reaction mixture was stirred for 10-15 minutes and completion of reaction was checked with TLC in appropriate solvent system. After the completion of reaction, solvent was evaporated by rota vapour and residue was recrystallized from methanol.

Reaction Scheme:

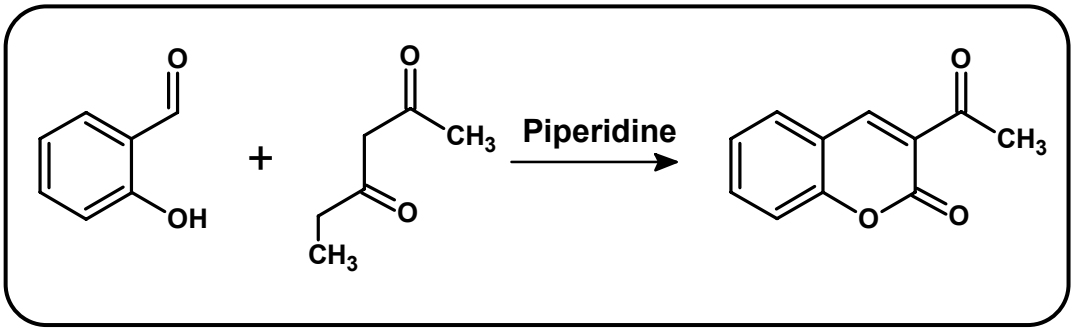


Synthesis of 3-(bromoacetyl)-2*H*-chromen-2-one:

Synthesis of 3-acetyl-2H-chromen-2-one:

To synthesize acetyl derivative coumarin, salicyldehyde (1.22 gm, 0.01M) and equivalent amount of ethyl aceto acetate (1.30 gms, 0.01M) was dissolved in methanol. The reaction mixture was stirred for 10 minutes after adding 2-3 drops of piperidin as catalyst. After completion of reaction (as observed by TLC), the mass was poured to the crushed ice. The product was extracted from solution with ethyl acetate. The solvent was evaporated and the crude product was recrystallized from ethanol.

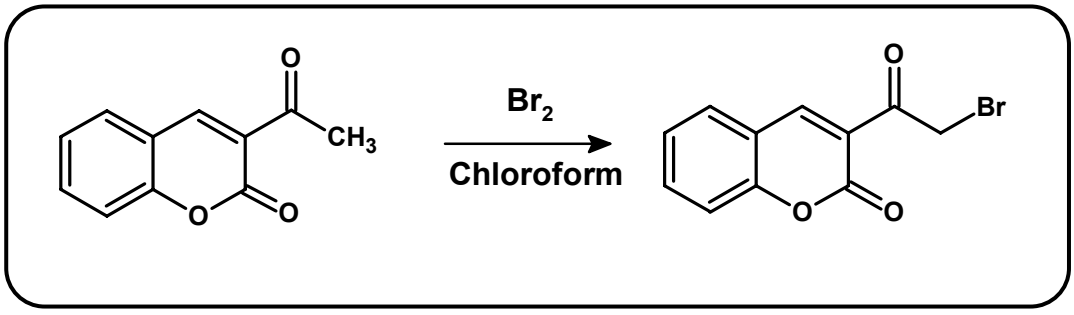
Reaction Scheme:



Bromination of 3-acetyl-2H-chromen-2-one:

The above product i.e., 3-acetyl-2H-chromen-2-one (1.88 gm, 0.01M) was dissolved in chloroform. To this solution, bromine solution (1.6 ml, 0.01M) in chloroform was added drop wise and temperature was maintained at about 0-5^0 C. After the addition of bromine solution, the solution was stirred at room temperature for half an hour. The resulting product was filtered and recrystallized from ethanol.

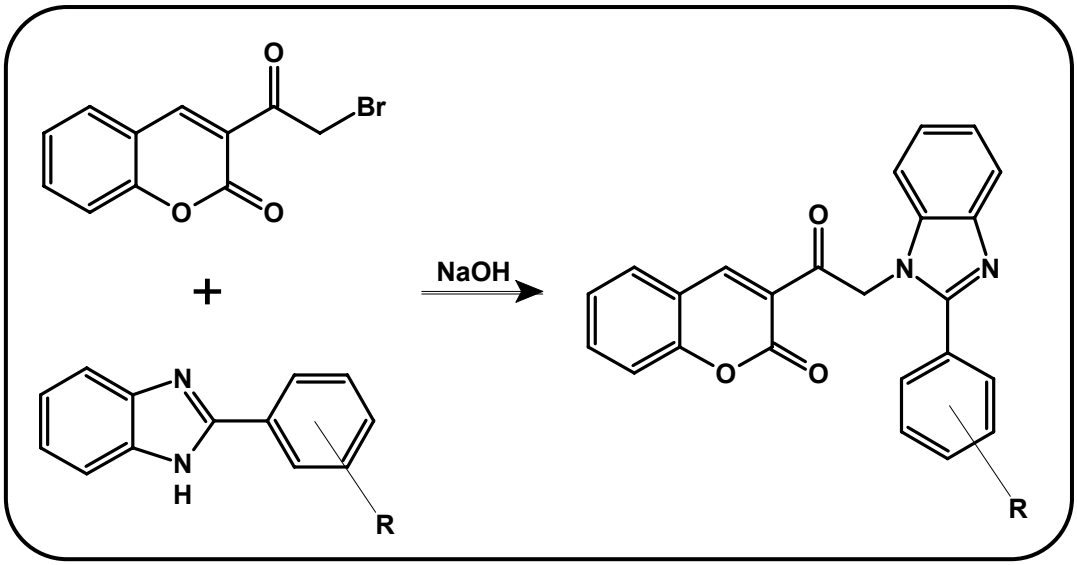
Reaction Scheme:



Condensation of 2-(4-aryl)-1H-benzimidazoles with 3-(bromoacetyl)-2*H*-chromen-2-one.

Equimolar amount of 2-(4-aryl)-1H-benzimidazoles with 3-(bromoacetyl)-2*H*-chromen-2-one was dissolved in the minimum amount of solvent. Small amount of sodium hydroxide was added to the solution and stirred by magnetic stirrer for about 3-4 hours. After completion of reaction, the product was extracted in ethyl acetate. The solution was evaporated to dryness and was recrystallized from ethanol.

Reaction Scheme:



Following compounds were synthesized through above reaction scheme:

MBB 1: 3-{[2-(4-hydroxy-3-methoxyphenyl)-1*H*-benzimidazol-1-yl]acetyl}-2*H*-chromen-2-one

MBB 2: 3-{[2-(4-methoxyphenyl)-1*H*-benzimidazol-1-yl]acetyl}-2*H*-chromen-2-one

MBB 3: 3-{[2-(4-hydroxyphenyl)-1*H*-benzimidazol-1-yl]acetyl}-2*H*-chromen-2-one

MBB 4: 3-{[2-(4-chlorophenyl)-1*H*-benzimidazol-1-yl]acetyl}-2*H*-chromen-2-one

MBB 5: 3-{[2-(3-chlorophenyl)-1*H*-benzimidazol-1-yl]acetyl}-2*H*-chromen-2-one

MBB 6: 3-{[2-(4-fluorophenyl)-1*H*-benzimidazol-1-yl]acetyl}-2*H*-chromen-2-one

MBB 7: 3-{[2-(3-nitrophenyl)-1*H*-benzimidazol-1-yl]acetyl}-2*H*-chromen-2-one

MBB 8: 3-[(2-phenyl-1*H*-benzimidazol-1-yl)acetyl]-2*H*-chromen-2-one

MBB 9: 3-{[2-(3,4-dimethoxyphenyl)-1*H*-benzimidazol-1-yl]acetyl}-2*H*-chromen-2-one

MBB 10: 3-{[2-[4-(dimethylamino)phenyl]-1*H*-benzimidazol-1-yl]acetyl}-2*H*-chromen-2-one

The various physical constants such as R_f value, melting point and percentage of yield for all the synthesized tetrahydropyrimidines are given in Table 5.1.

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

Table 5.1: Physical constants of compounds of MBB series.

Sr. No.	Code	R	M.F.	M. Wt. g	R_f* Value	M.P. °C	Yield %
1	**MBB 1**	4-OCH_3, 3-OH-	$C_{26}H_{20}N_2O_3$	408.5	0.35	278	45
2	**MBB 2**	4-OCH_3-	$C_{26}H_{20}N_2O_2$	392.5	0.32	265	49
3	**MBB 3**	4-OH-	$C_{25}H_{18}N_2O_2$	378.4	0.38	305	52
4	**MBB 4**	4-Cl-	$C_{25}H_{17}ClN_2$	396.9	0.25	315	41
5	**MBB 5**	3-Cl-	$C_{25}H_{17}ClN_2O$	396.9	0.19	322	40
6	**MBB 6**	4-F-	$C_{25}H_{17}FN_2O$	380.4	0.22	299	53
7	**MBB 7**	3-NO_2-	$C_{25}H_{18}N_2O$	362.4	0.41	329	43
8	**MBB 8**	H-	$C_{25}H_{18}N_2O$	362.4	0.29	285	54
9	**MBB 9**	3, 4-Di OCH_3-	$C_{27}H_{22}N_2O_3$	422.5	0.30	255	39
10	**MBB 10**	4-N, N-Di CH_3^-	$C_{27}H_{23}N_3O$	405.5	0.27	335	32

* Methanol : Hexane **:** 5:5

Figure 5.1: IR spectra of 3-{[2-(4-hydroxy-3-methoxyphenyl)-1*H*-benzimidazol-1-yl]acetyl}-2*H*-chromen-2-one (MBB 1).

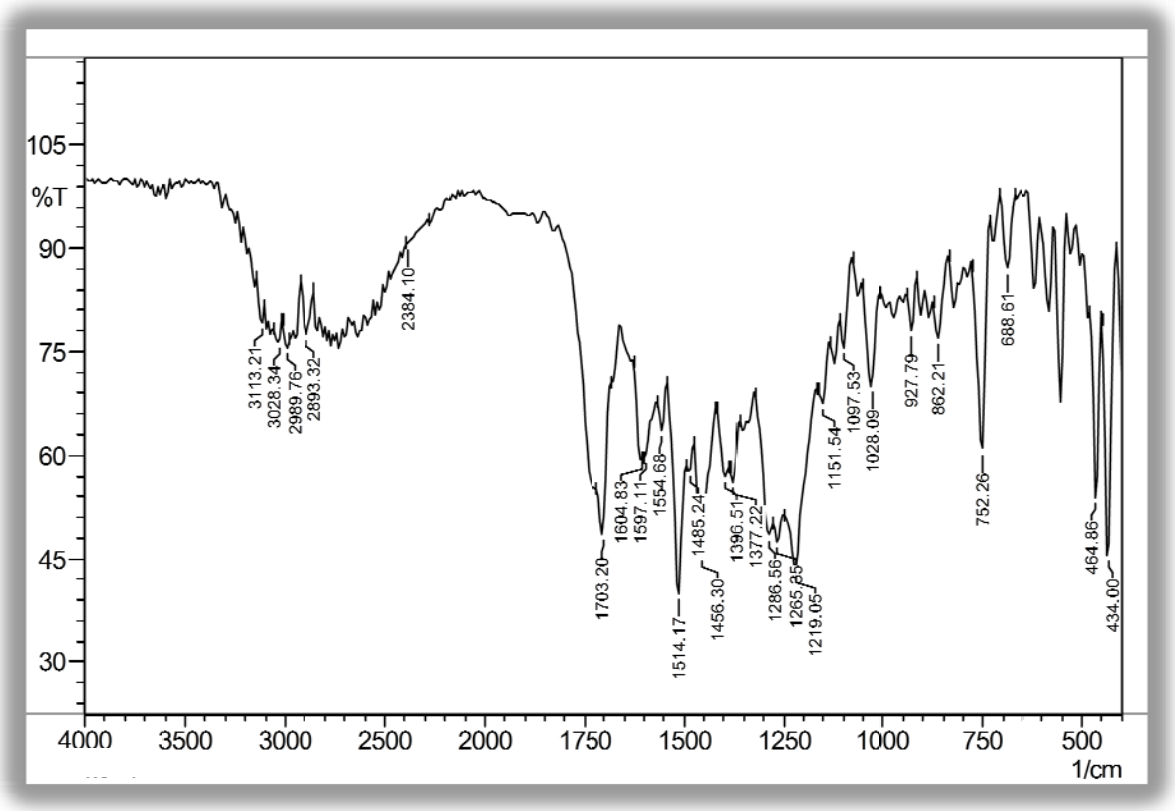


Table 5.2: IR spectral data of 3-{[2-(4-hydroxy-3-methoxyphenyl)-1*H*-benzimidazol-1-yl] acetyl}-2*H*-chromen-2-one (MBB 1).

Type	Vibration mode	Frequency in cm^{-1}	
		Observed	Reported*
Alkane (methyl)	C-H str. (asym.)	2989.76	2975-2920
	C-H str. (sym.)	2893.32	2880-2860
	C-H def. (asym.)	1456.30	1470-1435
	C-H def.(sym.)	1396.51	1395-1370
Aromatic	C-H str.	3028.34	3100-3000
	C=C str.	1514.77	1585-1480
	C-H i.p. def.	1097.53	1125-1090
	C-H o.o.p. def.	862.21	860-810
Ketones	C=O (cyclic).	1703.20	1710-1600
	C=O (Aliphatic)	1604.83	1725-1600
Hydroxy	O-H str.	3113.21	3650-3000
	O-H def.	1377.22	1410-1310
Imidazole ring	C=N str.	1632.88	1690-1640
	C-N str.	1265.35	1350-1200
ether	C-O-C str. (asym.)	1219.05	1400-1000
	C-O-C str. (sym.)	1028.09	1075-1020
	C-O-C str. (sym.)	1097.54	1090-1150

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Table 5.3: IR spectral data of other synthesized benzimidazole derivatives.

Compounds	*IR ν, (cm^{-1})*			
	C=C str	**C=O str (cyclic)**	**C=O str (aliphatic)**	**C-N str**
MBB 2	1515.11	1717.21	1615.03	1260.12
MBB 3	1525.44	1721,21	1622.12	1262.28
MBB 4	1528.02	1728.01	1625.12	1269.13
MBB 5	1499.71	1722.15	1608.02	1260.62
MBB 6	1524.12	1725.14	1615.39	1264.33
MBB 7	1520.23	1730.11	1613.19	1264.11
MBB 8	1546.17	1719.00	1611.28	1259.23
MBB 9	1505.79	1722.23	1610.22	1259.35
MBB 10	1517.32	1705.14	1601.59	1260.60

Figure 5.2: ^{1}H NMR spectra of 3-{[2-(4-hydroxy-3-methoxyphenyl)-1*H*-benzimidazol-1-yl]acetyl}-2*H*-chromen-2-one (MBB 1).

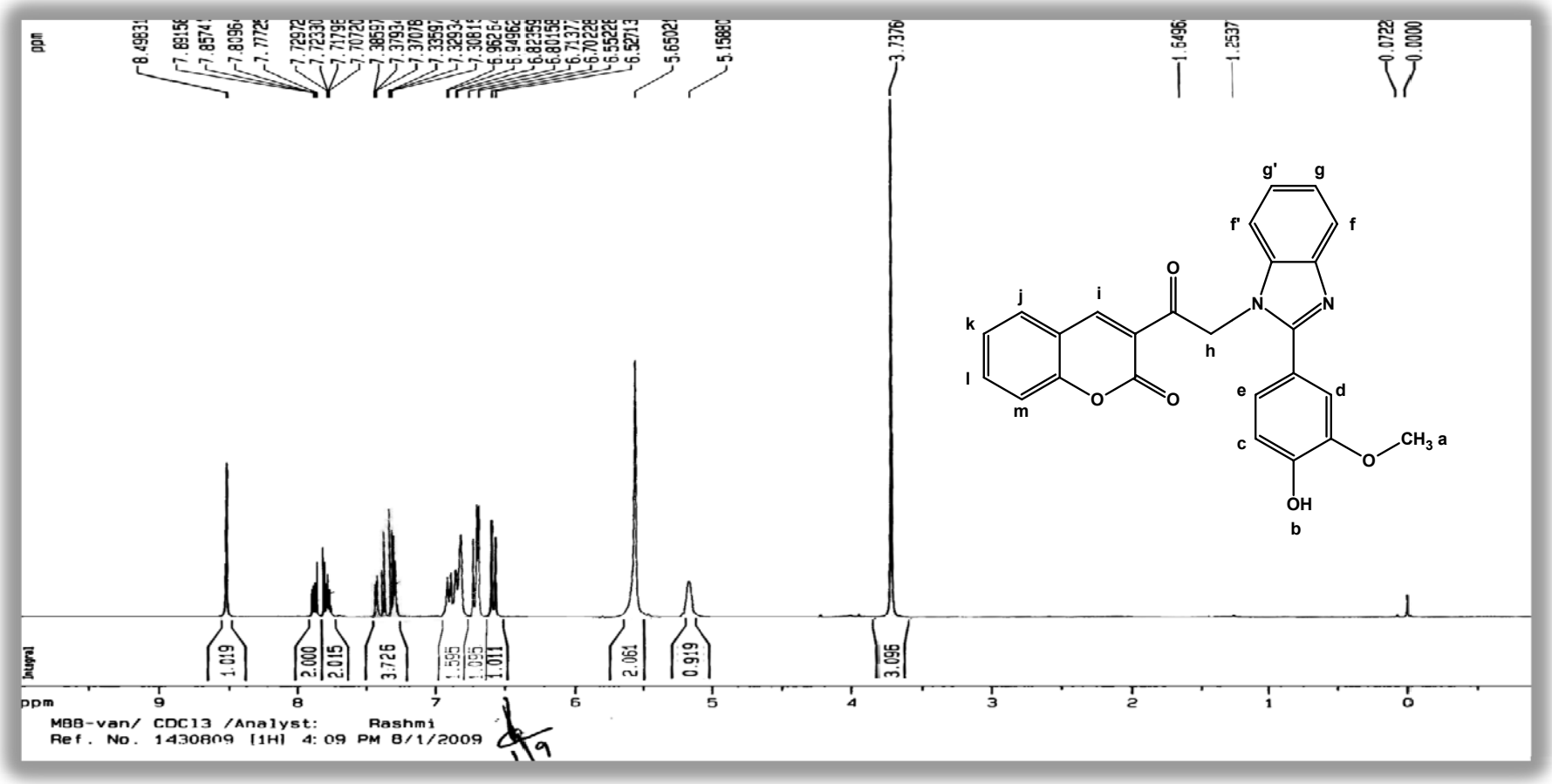
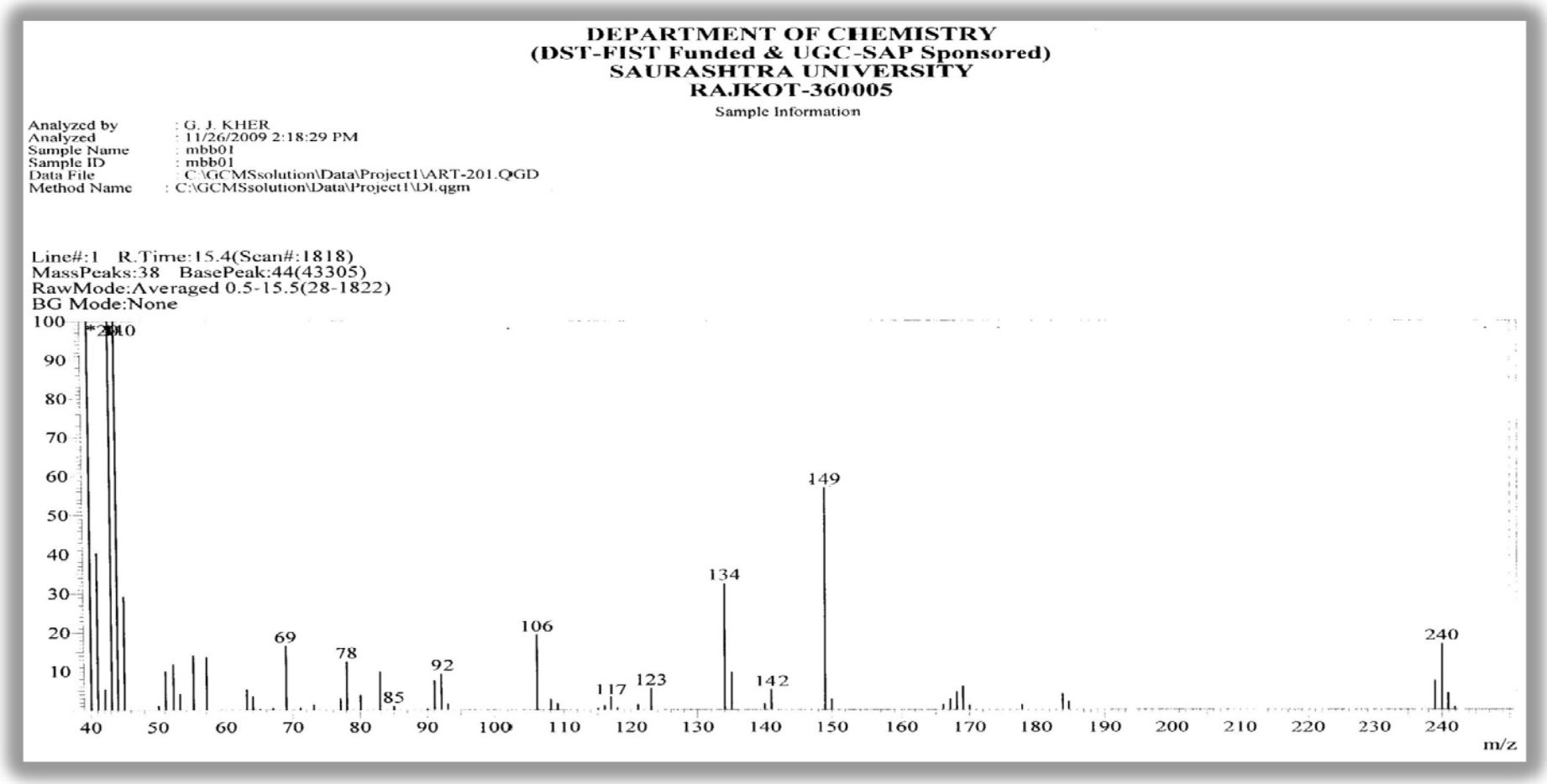


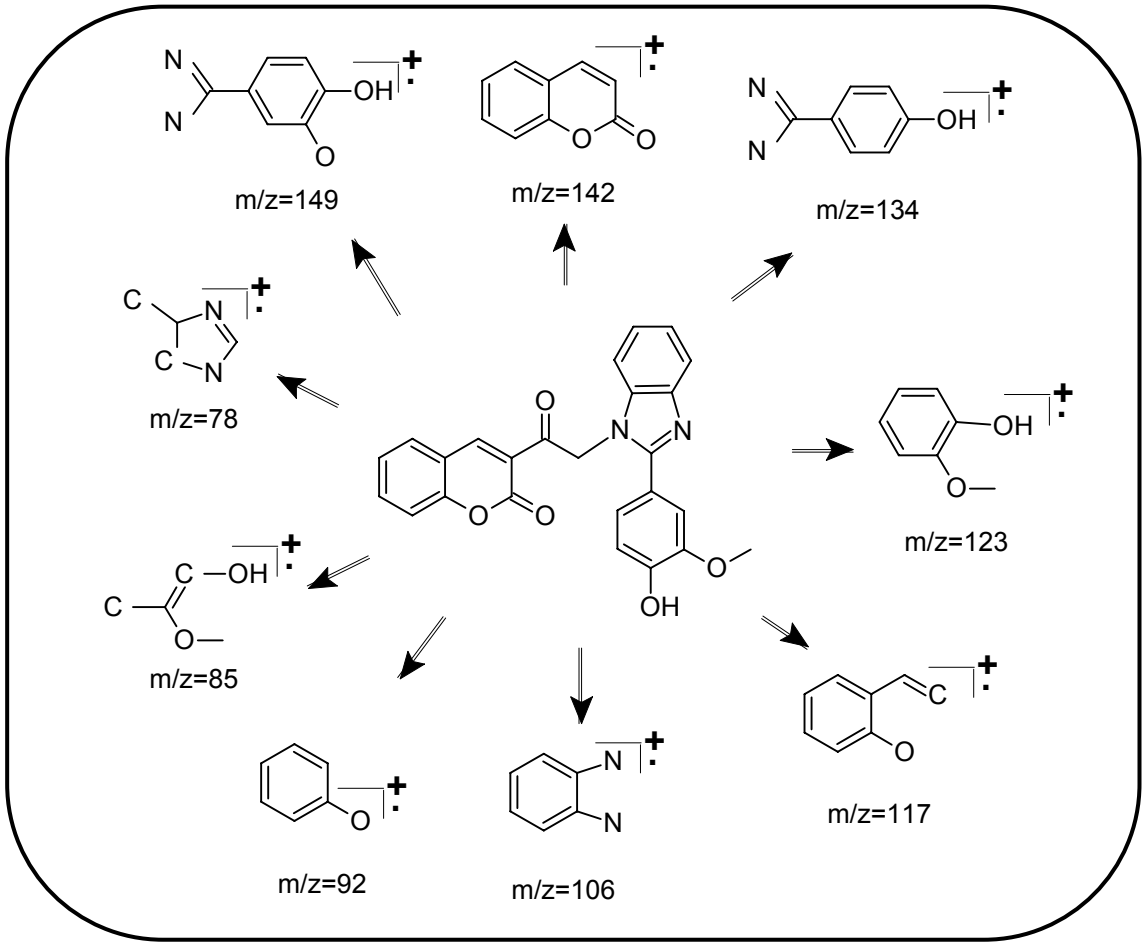
Table 5.4: ^{1}H NMR spectral data of 3-{[2-(4-hydroxy-3-methoxyphenyl)-1*H*-benzimidazol-1-yl]acetyl}-2*H*-chromen-2-one (MBB 1).

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference	*J* (Hz)
1	3.74	3	singlet	$-OCH_3$ (a)	-
2	5.15	1	singlet	-OH (b)	-
3	5.65	2	singlet	$-CH_2-$ (h)	-
4	6.53-6.56	1	doublet	Ar-Hc	7.55
5	6.70-6.71	1	doublet	Ar-H_d	3.27
6	6.81-6.96	1	double doublet	Ar-H_e	6.60 3.91
7	7.31-7.39	4	multiplet	Ar-$H_{j,k,l,m}$	-
8	7.71-7.73	2	multiplet	Ar-$H_{gg'}$	
9	7.78-7.79	2	multiplet	Ar-$H_{ff'}$	
10	8.5	1	singlet	Ar-H_i	-

Figure 5.3: Mass spectra of 3-{[2-(4-hydroxy-3-methoxyphenyl)-1*H*-benzimidazol-1-yl]acetyl}-2*H*-chromen-2-one (MBB 1).



Scheme 5.1: Proposed mass fragmentation of 3-{[2-(4-hydroxy-3-methoxyphenyl)-1*H*-benzimidazol-1-yl]acetyl}-2*H*-chromen-2-one (MBB 1).



INTRODUCTION

Ultrasonic studies deals with the waves of frequency above the range audible to the human ear, i.e., approximately 20, 000 Hertz.

Ultrasonic radiation is useful towards many directions of sciences. Ultrasonic waves are useful in industries for different physical treatments of industrially useful materials like agitation [(1)], dispersion [(2)], emulsification [(3)] etc. Ultrasound waves have also been used for cleaning **[(4)]** and to repair cracks **[(5)].**

Various researchers have checked the effect of ultrasound on human serum gamma globulin [(6)], aqueous solution of cytosine [(7)], other nucleic acid components [(8)]. Ultrasound is also useful as an aid for the extraction method of separating lutein from tagetes erecta flower [(9)]. Zhu et al. have improved the sludge's aerobic digestibility by ultrasonic treatment. Further, the digestion time was shortened [(10)] due to ultrasonic treatment. Ultrasonic rays are useful tool in medical field also. Ultrasonic radio-frequency spectrum analysis differentiates normal and edematous brain tissue from meningioma Intraoperatively [(11)]. It is also used for various diagnosis such as paediatrics [(12, 13)], vascular diseases [(14, 15)], brain diseases [(16)], ophthalmology [(17, 18)], in urology [(19, 20)], in cancer cell [(21, 22)] etc. Organic materials in landfill can also be degraded by ultrasound [(23)]. Pharmaceutical products are often present in wastewater treatment effluents, rivers, lakes and more rarely, in groundwater which can be treated by sonolysis [(24)]. It is also applied for inactivation of micro-organisms in food [(25-27)] and dairy industry [(28-30)].

Recently, a lot of interest has been generated on the use of ultrasound radiation in synthetic organic chemistry, because of its salient features like less reaction time, higher percentage of yield, lower reaction temperature, avoidance of phase transfer catalysis etc [(31-36)], which are compatible with green chemistry approach.

The structure of molecules and intermolecular attraction between molecules can be well understood through various thermodynamic parameters calculated through ultrasonic velocity measurements [(37)].

These ultrasonic measurements have been done for various pure liquids [38-40], liquid mixtures [41-44] and solutions of organic and inorganic compounds [45, 47], polymers [48], amino acids [49], drugs [50, 51] etc. The studies in some liquid crystals have also been done by Ayachit et al. [52].

In our laboratory, the ultrasonic studies of some compounds like Schiff bases [53], benzodiazepines [54], dihydropyrimidines [55] etc have been studied in different solvents.

In the present section, ultrasonic studies of compounds of MDT series have been studied in N, N dimethylformamide and chloroform solutions of various concentrations at 303.15 K with a view to understand molecular interactions in these solutions.

EXPERIMENTAL

Choice of Solvents:

N, N-Dimethylformamide (DMF) and chloroform ($CHCl_3$) have been chosen as solvents with different polarity and dielectric constants in the present work. These two solvents are of industrial interest because of their wide use as solvents and solubilising agents. These solvents are distilled by the reported procedure [56].

The densities, viscosities and ultrasonic velocities of solvents and solutions of tetrahydropyrimidines of different concentrations were measured at 303.15 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 were measured by using pyknometer. The densities 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 [57] was used, which obeys Stoke's low [58]. The measured quantity of the distilled water / solvent / solution was placed in the viscometer, which was suspended in a thermostat at 303.15 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 and solutions were determined according to equation:

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

Sound velocity measurement:

Ultrasonic interferometer (Model No. F-81), Mittal Enterprise, New Delhi, working at frequency (F) 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 303.15 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 distance (d) travel by the micrometer for n=10, was read. The wave length (λ) was determined according to the equation (3.1.3).

$$\lambda = \frac{2d}{n} \quad \text{… (3.1.3)}$$

The sound velocity (U) of solvent and solutions were calculated from the wavelength and frequency (F) according to equation (3.1.4).

$$U = \lambda F \quad \text{... (3.1.4)}$$

In the present study, frequency F is 2 MHz.

RESULTS AND DISCUSSION

Tables 3.1.1 and 3.1.2 shows the experimental data of density (ρ), sound velocity (U) and viscosity (η) of pure solvents and solutions of synthesized compounds (MDT series) in DMF and chloroform at 303.15 K.

From these experimental data, various acoustical parameters like Specific acoustical impedance (Z), isentropic compressibility (κ_S), intermolecular free length (L_f), molar compressibility (W), Rao's molar sound function (R_m), Vander Waals constant (b), relaxation strength (r), solvation number (π), etc., were evaluated using the following equations:

1. Specific acoustical impedance:

Specific acoustical impedance (Z) can be calculated as:

$$Z = U\rho \qquad \ldots (3.1.5)$$

2. Isentropic compressibility:

Isentropic compressibility (κ_s) can be evaluated by the equation [59]:

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

3. Intermolecular free path length:

Jacobson [60] proposed an equation to calculate the intermolecular free path length (L_f), which is given below:

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

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

Table 3.1.1: The density (*ρ*), ultrasonic velocity (*U*) and viscosity (*η*) of MDT series in DMF at 303.15 K.

conc.	MDT 1	MDT 2	MDT 3	MDT 4	MDT 5	MDT 6	MDT 7	MDT 8	MDT 9	MDT 10
Density (ρ) (g.cm^{-3})										
0.00	0.9416	0.9416	0.9416	0.9416	0.9416	0.9416	0.9416	0.9416	0.9416	0.9416
0.01	0.9456	0.9448	0.9486	0.9494	0.9494	0.9454	0.9529	0.9507	0.9424	0.9562
0.02	0.9465	0.9452	0.9489	0.9503	0.9503	0.9458	0.9530	0.9507	0.9429	0.9565
0.04	0.9483	0.9461	0.9495	0.9520	0.9520	0.9467	0.9531	0.9508	0.9440	0.9571
0.06	0.9500	0.9470	0.9501	0.9538	0.9538	0.9476	0.9532	0.9509	0.9451	0.9576
0.08	0.9517	0.9479	0.9507	0.9555	0.9556	0.9484	0.9533	0.9510	0.9462	0.9581
0.10	0.9535	0.9489	0.9513	0.9573	0.9573	0.9494	0.9534	0.9511	0.9473	0.9587
Velocity (U.10^{-5}) (cm.s^{-1})										
0.00	1.4480	1.4480	1.4480	1.4480	1.4480	1.4480	1.4480	1.4480	1.4480	1.4480
0.01	1.4524	1.4584	1.4732	1.4544	1.4704	1.4520	1.4680	1.4712	1.4780	1.4696
0.02	1.4536	1.4560	1.4712	1.4556	1.4680	1.4524	1.4660	1.4704	1.4760	1.4716
0.04	1.4568	1.4540	1.4672	1.4584	1.4632	1.4540	1.4632	1.4696	1.4724	1.4764
0.06	1.4600	1.4520	1.4636	1.4612	1.4588	1.4552	1.4604	1.4688	1.4684	1.4808
0.08	1.4632	1.4496	1.4596	1.4640	1.4540	1.4564	1.4572	1.4680	1.4648	1.4852
0.10	1.4664	1.4488	1.4560	1.4672	1.4496	1.4580	1.4544	1.4672	1.4612	1.4900
Viscosity (η.10^{3}) (poise)										
0.00	5.7591	5.7591	5.7591	5.7591	5.7591	5.7591	5.7591	5.7591	5.7591	5.7591
0.01	6.0744	5.9308	6.7249	6.3664	6.9830	6.0309	6.3515	6.7800	5.7923	8.0902
0.02	6.2141	6.0389	6.7819	6.4059	7.0560	6.1333	6.4292	6.8123	5.8737	8.1222
0.04	6.4940	6.2506	6.8952	6.4868	7.2038	6.3404	6.5914	6.8787	6.0386	8.1880
0.06	6.7758	6.4651	7.0102	6.5671	7.3513	6.5466	6.7517	6.9442	6.2031	8.2537
0.08	7.0577	6.6784	7.1253	6.6485	7.5003	6.7541	6.9113	7.0105	6.3687	8.3197
0.10	7.3415	6.8938	7.2390	6.7301	7.6496	6.9622	7.0718	7.0769	6.5347	8.3856

Table 3.1.2: The density (*ρ*), ultrasonic velocity (*U*) and viscosity (*η*) of MDT series in chloroform at 303.15 K.

conc.	MDT 1	MDT 2	MDT 3	MDT 4	MDT 5	MDT 6	MDT 7	MDT 8	MDT 9	MDT 10
Density (ρ) ($g.cm^{-3}$)										
0.00	1.4713	1.4713	1.4713	1.4713	1.4713	1.4713	1.4713	1.4713	1.4713	1.4713
0.01	1.4713	1.4717	1.4714	1.4749	1.4720	1.4747	1.4800	1.4735	1.4809	1.4746
0.02	1.4715	1.4724	1.4718	1.4753	1.4723	1.4752	1.4801	1.4737	1.4813	1.4751
0.04	1.4721	1.4736	1.4727	1.4761	1.4730	1.4762	1.4803	1.4741	1.4820	1.4763
0.06	1.4726	1.4749	1.4736	1.4768	1.4736	1.4772	1.4805	1.4744	1.4827	1.4775
0.08	1.4731	1.4761	1.4745	1.4776	1.4743	1.4782	1.4807	1.4748	1.4834	1.4787
0.10	1.4737	1.4774	1.4754	1.4784	1.4750	1.4792	1.4809	1.4751	1.4841	1.4798
Velocity ($U.10^{-5}$) ($cm.s^{-1}$)										
0.00	0.9640	0.9640	0.9640	0.9640	0.9640	0.9640	0.9640	0.9640	0.9640	0.9640
0.01	0.9664	0.9676	0.9672	0.9652	0.9668	0.9688	0.9676	0.9644	0.9644	0.9648
0.02	0.9668	0.9680	0.9680	0.9652	0.9668	0.9692	0.9680	0.9656	0.9652	0.9652
0.04	0.9684	0.9692	0.9696	0.9660	0.9672	0.9700	0.9688	0.9684	0.9668	0.9668
0.06	0.9700	0.9704	0.9716	0.9664	0.9676	0.9708	0.9696	0.9712	0.9688	0.9680
0.08	0.9716	0.9716	0.9732	0.9668	0.9680	0.9716	0.9704	0.9740	0.9704	0.9692
0.10	0.9732	0.9732	0.9752	0.9676	0.9684	0.9724	0.9716	0.9772	0.9724	0.9708
Viscosity (η.10^{3}) (poise)										
0.00	20.7089	20.7089	20.7089	20.7089	20.7089	20.7089	20.7089	20.7089	20.7089	20.7089
0.01	29.0267	25.0234	26.0483	21.8259	21.3105	23.0004	21.2244	21.6914	21.6108	21.1902
0.02	30.2016	25.7452	27.3834	21.9701	21.4286	23.1473	22.0103	21.8389	23.0529	21.2239
0.04	32.5657	27.1960	30.0553	22.2716	21.6773	23.4406	23.5944	22.1467	25.9390	21.3038
0.06	34.9243	28.6437	32.7309	22.5672	21.9200	23.7406	25.1727	22.4480	28.8277	21.3774
0.08	37.2851	30.0998	35.4092	22.8630	22.1632	24.0345	26.7513	22.7500	31.7197	21.4576
0.10	39.6539	31.5585	38.0973	23.1652	22.4128	24.3354	28.3369	23.0581	34.6200	21.5378

4. Molar compressibility:

Molar compressibility (*W*) can be calculated by the following equation [61]:

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

The apparent molecular weight (*M*) of the solution can be calculated according to equation (3.1.8):

$$M = M_1 W_1 + M_2 W_2 \qquad \ldots (3.1.9)$$

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.

5. Rao's molar sound function:

Rao's molar sound function (R_m) can be evaluated by an equation given by Bagchi et al. [62]:

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

6. Van der Waals Constant:

Van der Waals constant (*b*) can be calculated as follows [63]:

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

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 [64]:

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

where U_∞ = 1.6 x 10^5 cm/sec.

8. Solvation number:

$$S_n = \frac{M_2}{M_1}\left[\frac{1-\kappa_s}{\kappa_{s1}}\right]\left[\frac{100-X}{X}\right] \qquad \cdots (3.1.13)$$

where *X* is the number of grams of solute in 100 gm of the solution. M_1 and M_2 are the molecular weights and κ_{S1} and κ_S are isentropic compressibility of solvent and solute respectively.

Figures 3.1.1 and 3.1.2 show the variation of ultrasound velocity (U) with concentration for compounds of MDT series in both the solvents. It is observed that in DMF (Figure 3.1.1), for MDT-1, MDT-4, MDT-6 and MDT-10, ultrasonic velocity increases with concentration whereas for MDT-2, MDT-3, MDT-5, MDT-7, MDT-8 and MDT-9 ultrasonic velocity decreases with concentration. The velocity depends on intermolecular free length (L_f). The velocity increases with decrease in L_f or vice versa. This fact is clearly shown in Table 3.1.3 for DMF. The L_f value decreases with concentration for MDT-1, MDT-4, MDT-6 and MDT-10 whereas for MDT-2, MDT-3, MDT-5, MDT-7, MDT-8 and MDT-9, it increases. The increase of U and decrease of L_f in solutions of MDT-1, MDT-4, MDT-6 and MDT-10, suggests that the solvent molecules interact strongly with compound molecules. Thus, ion-solvent (or solute-solvent) interactions predominate in these systems. However, in DMF solutions of MDT-2, MDT-3, MDT-5, MDT-7, MDT-8 and MDT-9, the increase on intermolecular free path length and decrease of ultrasonic velocity suggest the dominance of solute-solute interactions in these systems.

In chloroform solutions, velocity increases with concentration for all the studied compounds, as shown in Figure 3.1.2 whereas L_f values for all the compounds decreases with concentration (Table 3.1.4). Thus, in chloroform solutions also, solvent molecules interact strongly with all the compound molecules in all the systems.

This is further supported by isentropic compressibility (κ_s) and relaxation strength (r). The variation of isentropic compressibility (κ_s) with concentration of

Table 3.1.3: Some acoustical parameters of MDT series in DMF at 303.15 K.

conc.	MDT 1	MDT 2	MDT 3	MDT 4	MDT 5	MDT 6	MDT 7	MDT 8	MDT 9	MDT 10
Specific Acoustical Impedence ($Z.10^5$) (g.cm-2)										
0.00	1.3635	1.3635	1.3635	1.3635	1.3635	1.3635	1.3635	1.3635	1.3635	1.3635
0.01	1.3735	1.3778	1.3975	1.3808	1.3960	1.3727	1.3989	1.3987	1.3929	1.4053
0.02	1.3759	1.3762	1.3960	1.3832	1.3950	1.3737	1.3971	1.3980	1.3918	1.4076
0.04	1.3814	1.3757	1.3931	1.3884	1.3930	1.3765	1.3946	1.3974	1.3900	1.4130
0.06	1.3870	1.3751	1.3905	1.3936	1.3914	1.3789	1.3921	1.3967	1.3878	1.4180
0.08	1.3926	1.3741	1.3876	1.3989	1.3894	1.3813	1.3892	1.3961	1.3860	1.4230
0.10	1.3982	1.3747	1.3850	1.4045	1.3877	1.3842	1.3866	1.3955	1.3842	1.4284
Intermolecular free path length (L_f) (A^0)										
0.00	0.1492	0.1492	0.1492	0.1492	0.1492	0.1492	0.1492	0.1492	0.1492	0.1492
0.01	0.1484	0.1479	0.1461	0.1479	0.1463	0.1485	0.1463	0.1462	0.1461	0.1459
0.02	0.1482	0.1481	0.1463	0.1478	0.1465	0.1484	0.1465	0.1462	0.1463	0.1457
0.04	0.1478	0.1482	0.1466	0.1473	0.1468	0.1482	0.1468	0.1463	0.1465	0.1452
0.06	0.1473	0.1484	0.1470	0.1469	0.1472	0.1480	0.1470	0.1464	0.1469	0.1447
0.08	0.1469	0.1485	0.1473	0.1465	0.1475	0.1478	0.1474	0.1464	0.1471	0.1442
0.10	0.1464	0.1486	0.1476	0.1460	0.1478	0.1476	0.1476	0.1465	0.1474	0.1437
Relaxation Strength (r)										
0.00	0.1810	0.1810	0.1810	0.1810	0.1810	0.1810	0.1810	0.1810	0.1810	0.1810
0.01	0.1760	0.1692	0.1522	0.1737	0.1554	0.1764	0.1582	0.1545	0.1467	0.1564
0.02	0.1746	0.1719	0.1545	0.1724	0.1582	0.1760	0.1605	0.1554	0.1490	0.1541
0.04	0.1710	0.1742	0.1591	0.1692	0.1637	0.1742	0.1637	0.1564	0.1531	0.1485
0.06	0.1673	0.1764	0.1632	0.1660	0.1687	0.1728	0.1669	0.1573	0.1577	0.1434
0.08	0.1637	0.1792	0.1678	0.1628	0.1742	0.1714	0.1705	0.1582	0.1619	0.1384
0.10	0.1600	0.1801	0.1719	0.1591	0.1792	0.1696	0.1737	0.1591	0.1660	0.1328

Contd...

...Contd

conc.	MDT 1	MDT 2	MDT 3	MDT 4	MDT 5	MDT 6	MDT 7	MDT 8	MDT 9	MDT 10
Molar compressibility ($W.10^{-3}$) ($cm^{-1}.dyn^{-1}$)										
0.00	2.2948	2.2948	2.2948	2.2948	2.2948	2.2948	2.2948	2.2948	2.2948	2.2948
0.01	2.3067	2.3089	2.3055	2.2980	2.3052	2.3030	2.2983	2.2981	2.3173	2.2894
0.02	2.3237	2.3227	2.3178	2.3131	2.3186	2.3164	2.3152	2.3093	2.3259	2.3047
0.04	2.3578	2.3515	2.3423	2.3433	2.3454	2.3434	2.3495	2.3320	2.3431	2.3357
0.06	2.3918	2.3802	2.3669	2.3733	2.3721	2.3702	2.3838	2.3548	2.3599	2.3665
0.08	2.4255	2.4085	2.3912	2.4031	2.3983	2.3969	2.4178	2.3775	2.3769	2.3973
0.10	2.4590	2.4375	2.4156	2.4329	2.4244	2.4237	2.4519	2.4002	2.3937	2.4282
Van der Waals Constant (b) *($cm^3.mol^{-1}$)*										
0.00	77.6195	77.6195	77.6195	77.6195	77.6195	77.6195	77.6195	77.6195	77.6195	77.6195
0.01	77.9063	77.8981	77.5127	77.5380	77.5364	77.7905	77.3013	77.2707	77.9126	76.9376
0.02	78.4491	78.3957	77.9531	78.0180	78.0155	78.2305	77.8996	77.6586	78.2241	77.4191
0.04	79.5319	79.3879	78.8321	78.9714	78.9688	79.1062	79.0942	78.4349	78.8439	78.3804
0.06	80.6045	80.3770	79.7089	79.9173	79.9146	79.9827	80.2900	79.2109	79.4608	79.3413
0.08	81.6696	81.3613	80.5835	80.8557	80.8520	80.8551	81.4852	79.9875	80.0746	80.2981
0.10	82.7256	82.3417	81.4558	81.7867	81.7830	81.7204	82.6790	80.7621	80.6853	81.2537

Table 3.1.4: Some acoustical parameters of MDT series in chloroform at 303.15 K.

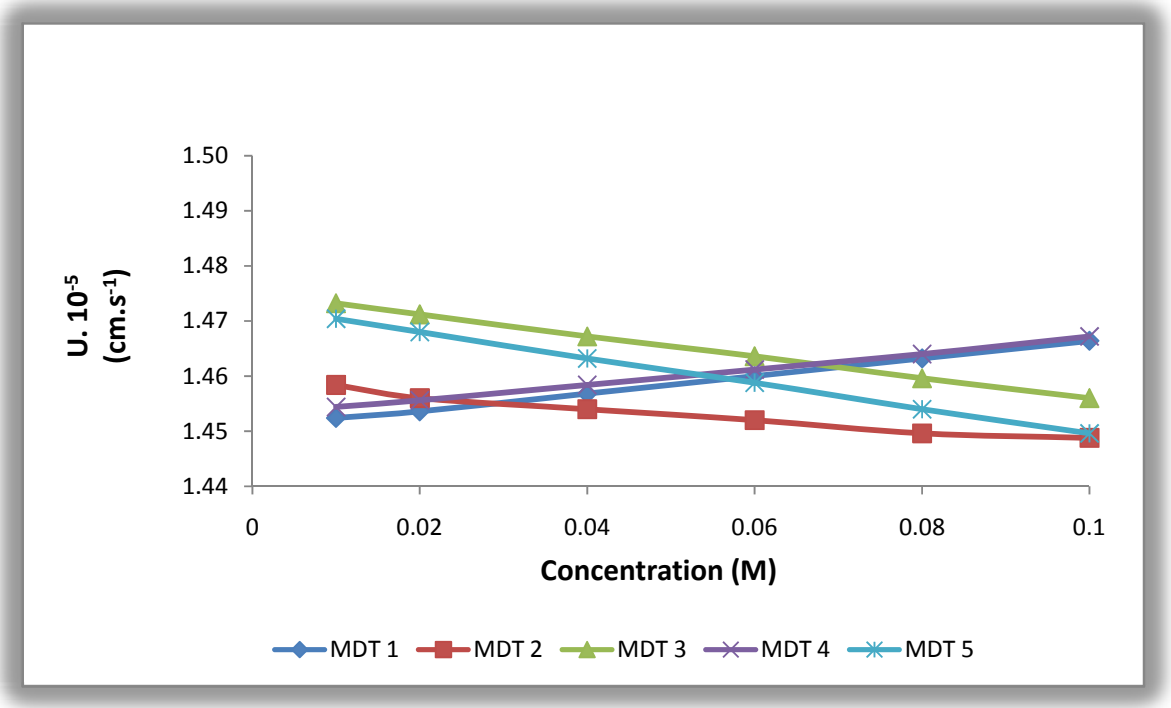
conc.	MDT 1	MDT 2	MDT 3	MDT 4	MDT 5	MDT 6	MDT 7	MDT 8	MDT 9	MDT 10
Specific Acoustical Impedence (Z) (g.cm-2)										
0.00	1.4183	1.4183	1.4183	1.4183	1.4183	1.4183	1.4183	1.4183	1.4183	1.4183
0.01	1.4218	1.4240	1.4231	1.4236	1.4231	1.4287	1.4321	1.4210	1.4282	1.4227
0.02	1.4227	1.4252	1.4247	1.4240	1.4234	1.4298	1.4328	1.4230	1.4297	1.4238
0.04	1.4256	1.4282	1.4279	1.4259	1.4247	1.4319	1.4341	1.4275	1.4328	1.4273
0.06	1.4284	1.4312	1.4317	1.4272	1.4259	1.4341	1.4355	1.4319	1.4364	1.4302
0.08	1.4313	1.4342	1.4349	1.4285	1.4271	1.4362	1.4369	1.4364	1.4395	1.4331
0.10	1.4342	1.4378	1.4388	1.4305	1.4284	1.4384	1.4388	1.4415	1.4432	1.4366
Intermolecular free path length (L_f) (A^0)										
0.00	0.1793	0.1793	0.1793	0.1793	0.1793	0.1793	0.1793	0.1793	0.1793	0.1793
0.01	0.1789	0.1786	0.1787	0.1789	0.1787	0.1782	0.1781	0.1791	0.1786	0.1789
0.02	0.1788	0.1785	0.1785	0.1788	0.1787	0.1781	0.1780	0.1789	0.1785	0.1788
0.04	0.1784	0.1782	0.1782	0.1786	0.1786	0.1779	0.1779	0.1783	0.1781	0.1785
0.06	0.1781	0.1779	0.1778	0.1785	0.1785	0.1777	0.1777	0.1778	0.1777	0.1782
0.08	0.1778	0.1776	0.1774	0.1784	0.1784	0.1775	0.1775	0.1772	0.1774	0.1779
0.10	0.1775	0.1772	0.1770	0.1782	0.1783	0.1773	0.1773	0.1766	0.1770	0.1775
Relaxation Strength (r)										
0.00	0.6370	0.6370	0.6370	0.6370	0.6370	0.6370	0.6370	0.6370	0.6370	0.6370
0.01	0.6352	0.6343	0.6346	0.6361	0.6349	0.6334	0.6343	0.6367	0.6367	0.6364
0.02	0.6349	0.6340	0.6340	0.6361	0.6349	0.6331	0.6340	0.6358	0.6361	0.6361
0.04	0.6337	0.6331	0.6328	0.6355	0.6346	0.6325	0.6334	0.6337	0.6349	0.6349
0.06	0.6325	0.6322	0.6312	0.6352	0.6343	0.6319	0.6328	0.6316	0.6334	0.6340
0.08	0.6312	0.6312	0.6300	0.6349	0.6340	0.6312	0.6322	0.6294	0.6322	0.6331
0.10	0.6300	0.6300	0.6285	0.6343	0.6337	0.6306	0.6312	0.6270	0.6306	0.6319

Contd...

...Contd

Molar compressibility (W.10^{-3}) (cm^{-1}. dyn^{-1})										
0.00	2.2763	2.2763	2.2763	2.2763	2.2763	2.2763	2.2763	2.2763	2.2763	2.2763
0.01	2.2834	2.2827	2.2822	2.2771	2.2821	2.2790	2.2725	2.2768	2.2665	2.2769
0.02	2.2888	2.2868	2.2861	2.2814	2.2865	2.2826	2.2780	2.2805	2.2694	2.2808
0.04	2.3001	2.2952	2.2939	2.2906	2.2956	2.2899	2.2891	2.2884	2.2750	2.2891
0.06	2.3115	2.3036	2.3020	2.2996	2.3047	2.2971	2.3002	2.2962	2.2810	2.2972
0.08	2.3229	2.3120	2.3098	2.3085	2.3138	2.3044	2.3113	2.3040	2.2866	2.3053
0.10	2.3343	2.3206	2.3178	2.3177	2.3229	2.3116	2.3226	2.3122	2.2925	2.3136
Van der Waals Constant Molar (b) *(cm^3.mol^{-1})*										
0.00	81.1395	81.1395	81.1395	81.1395	81.1395	81.1395	81.1395	81.1395	81.1395	81.1395
0.01	81.3352	81.2794	81.2748	81.1100	81.2730	81.0952	80.8511	81.1300	80.7077	81.1153
0.02	81.5163	81.4096	81.3905	81.2623	81.4282	81.2098	81.0370	81.2345	80.7866	81.2406
0.04	81.8774	81.6720	81.6235	81.5659	81.7386	81.4412	81.4109	81.4432	80.9442	81.4910
0.06	82.2403	81.9312	81.8543	81.8682	82.0485	81.6720	81.7841	81.6528	81.1019	81.7405
0.08	82.6015	82.1905	82.0861	82.1704	82.3566	81.9026	82.1576	81.8599	81.2577	81.9886
0.10	82.9621	82.4482	82.3162	82.4725	82.6647	82.1314	82.5298	82.0686	81.4154	82.2363

Figure 3.1.1: Variation of ultrasonic velocity (*U*) of MDT series with concentration in DMF at 303.15 K.



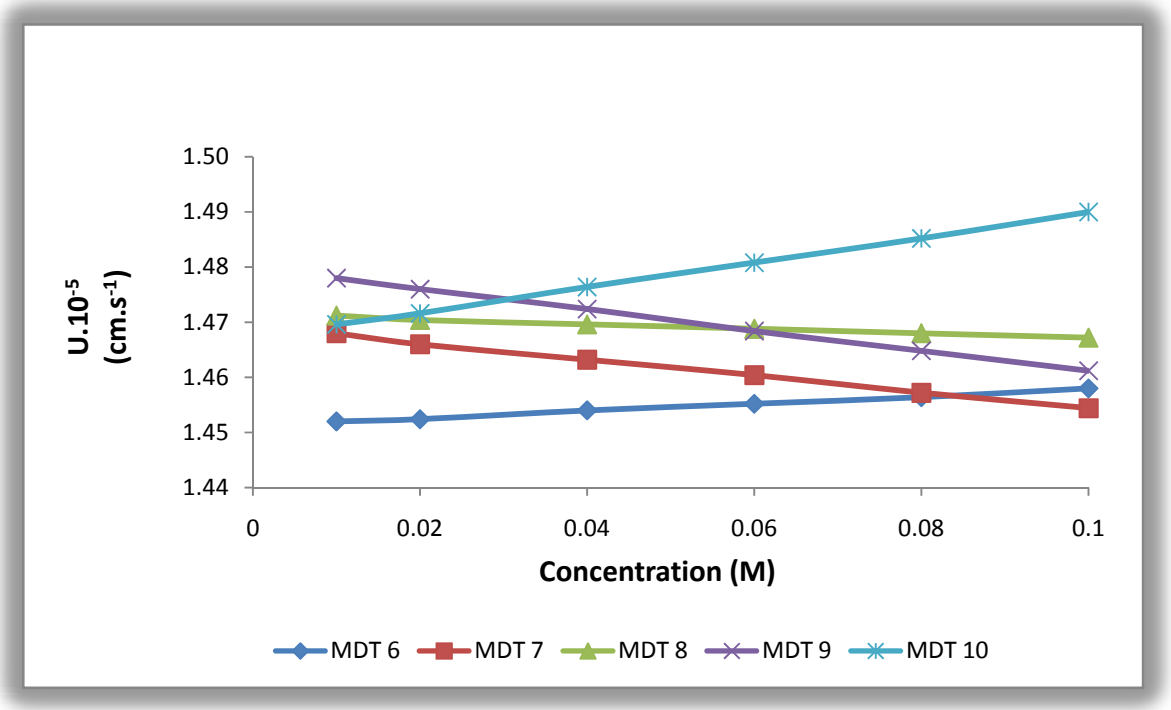
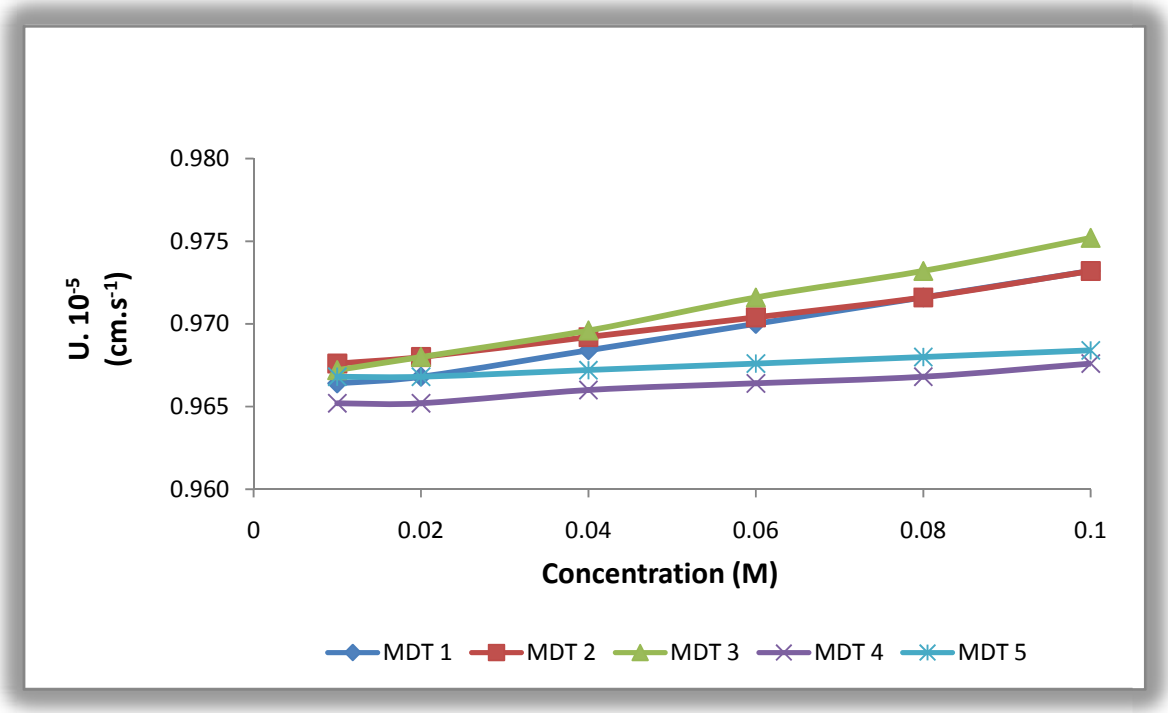


Figure 3.1.2: Variation of ultrasonic velocity (*U*) of MDT series with concentration in chloroform at 303.15 K.



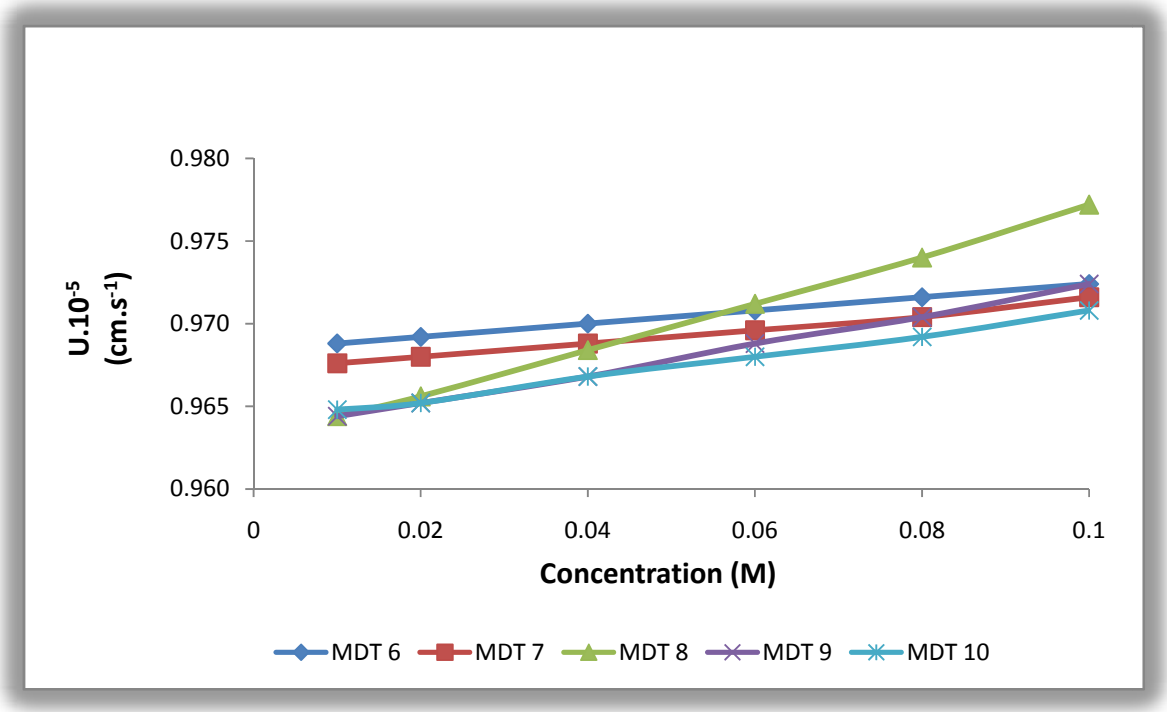
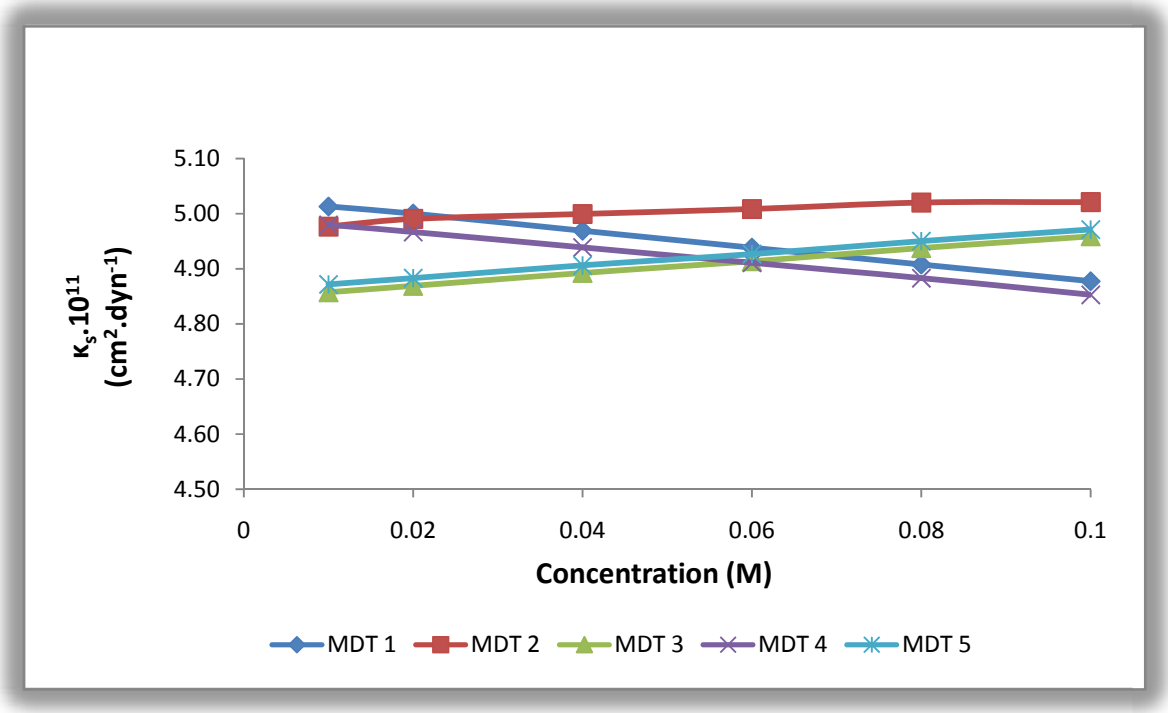


Figure 3.1.3: Variation of Isentropic compressibility (κ_S) of MDT series with concentration in DMF at 303.15 K.



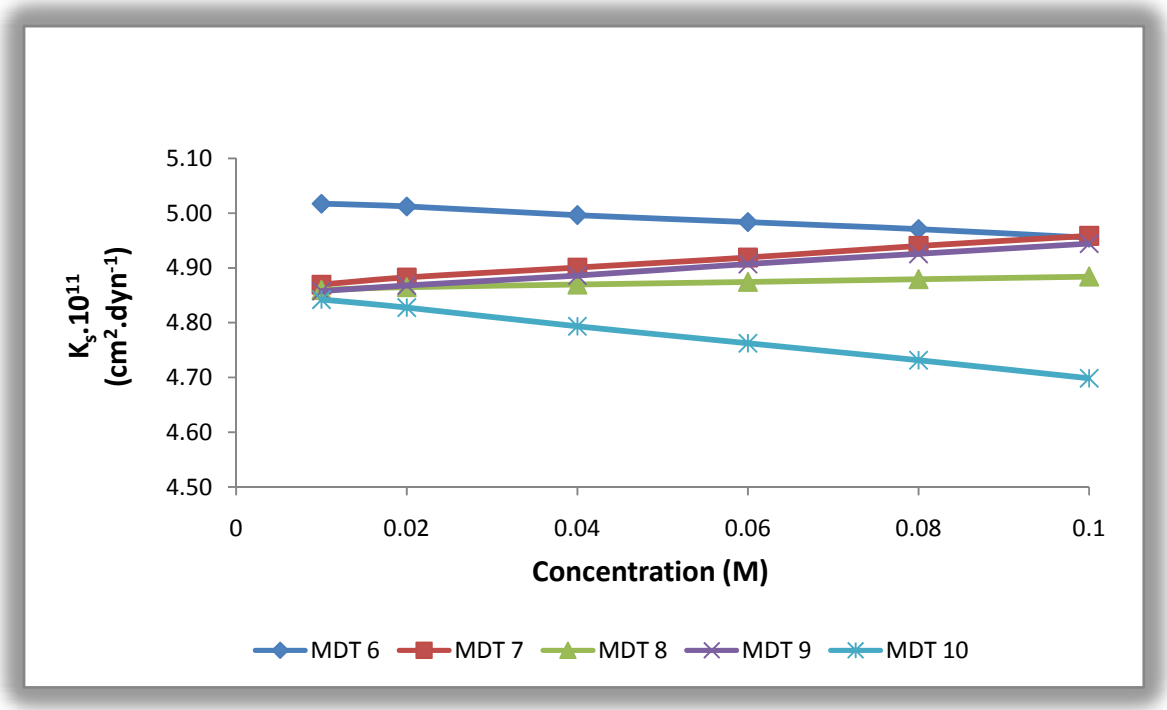
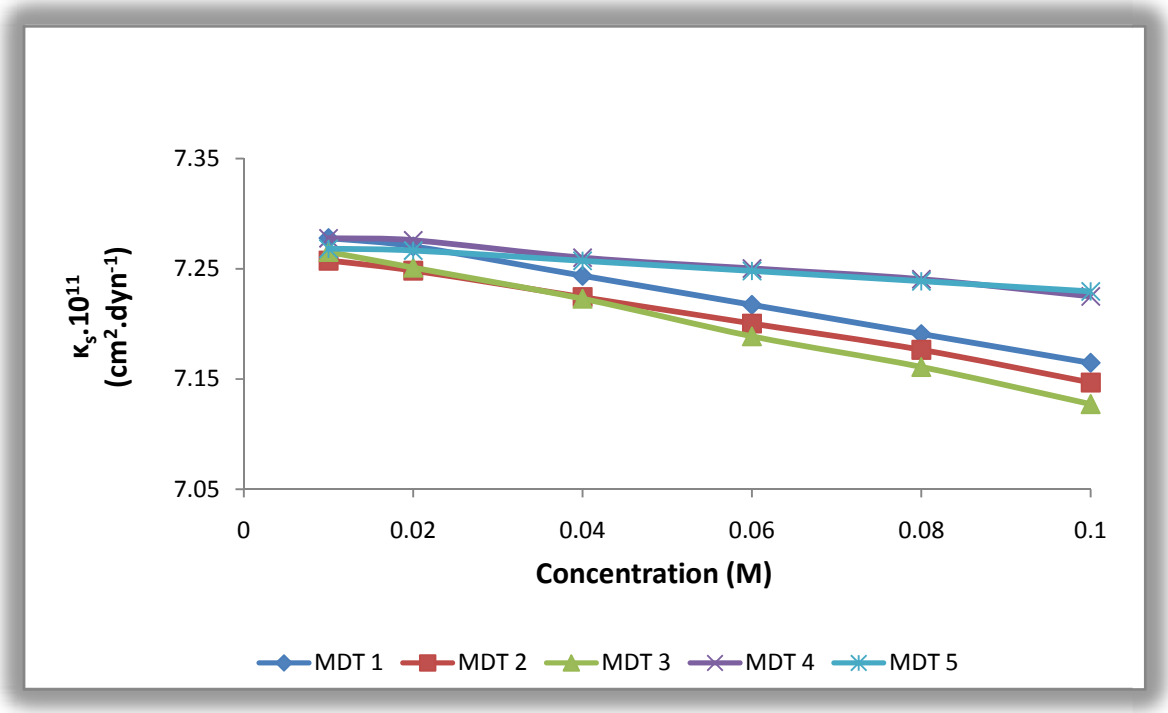


Figure 3.1.4: Variation of Isentropic compressibility (κ_S) of MDT series with concentration in chloroform at 303.15 K.



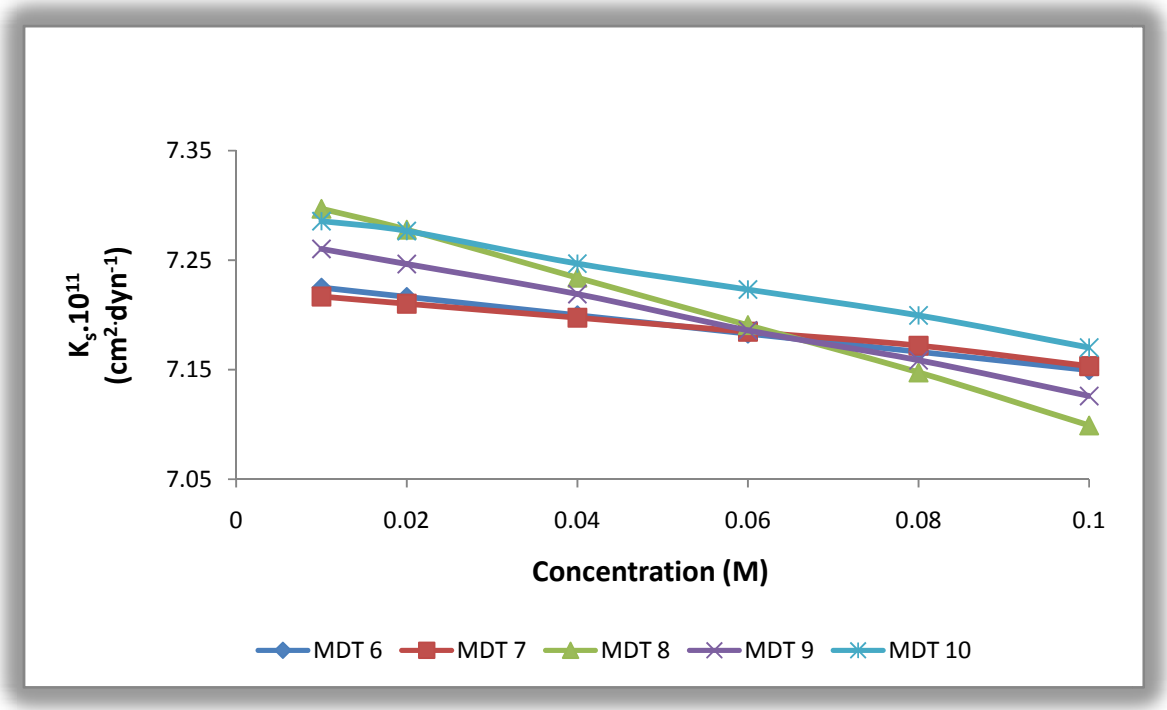
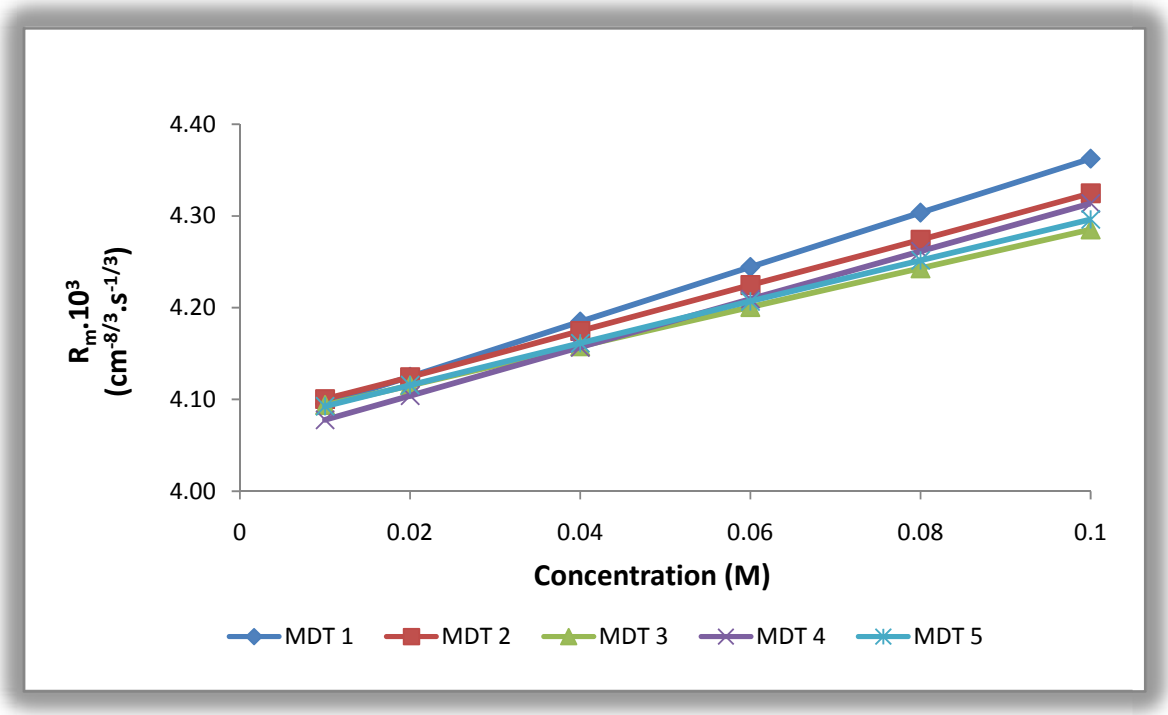


Figure 3.1.5: Variation of Rao's molar sound function (R_m) of MDT series with concentration in DMF at 303.15 K.



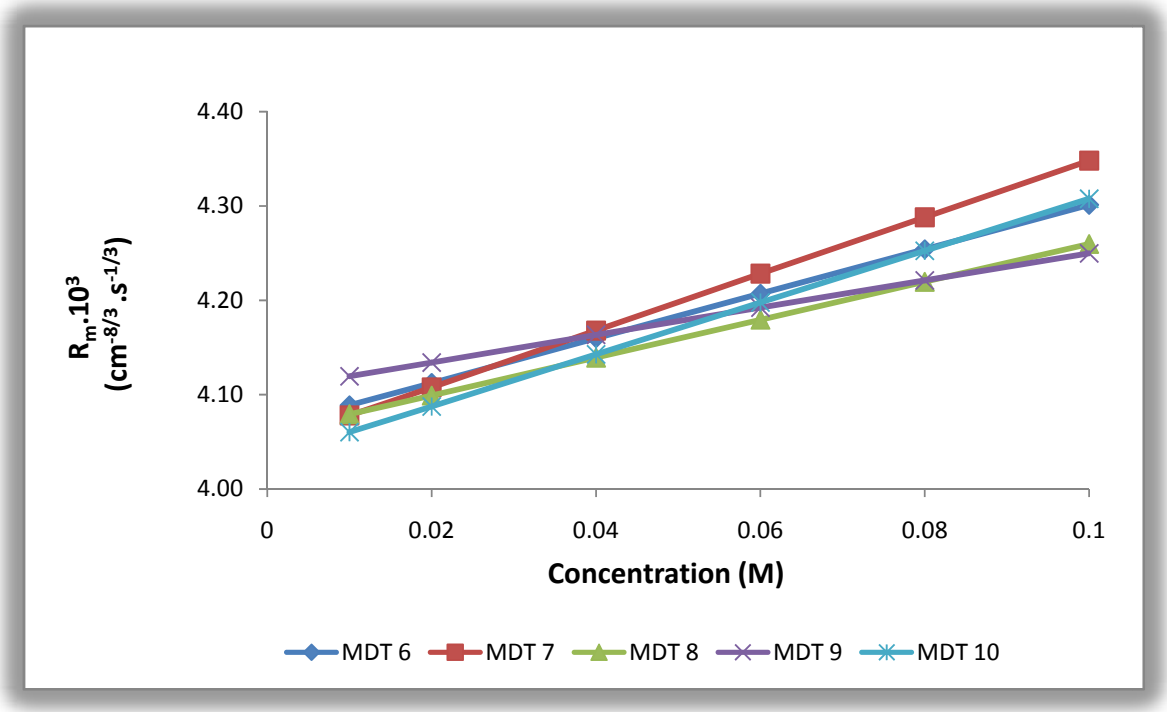
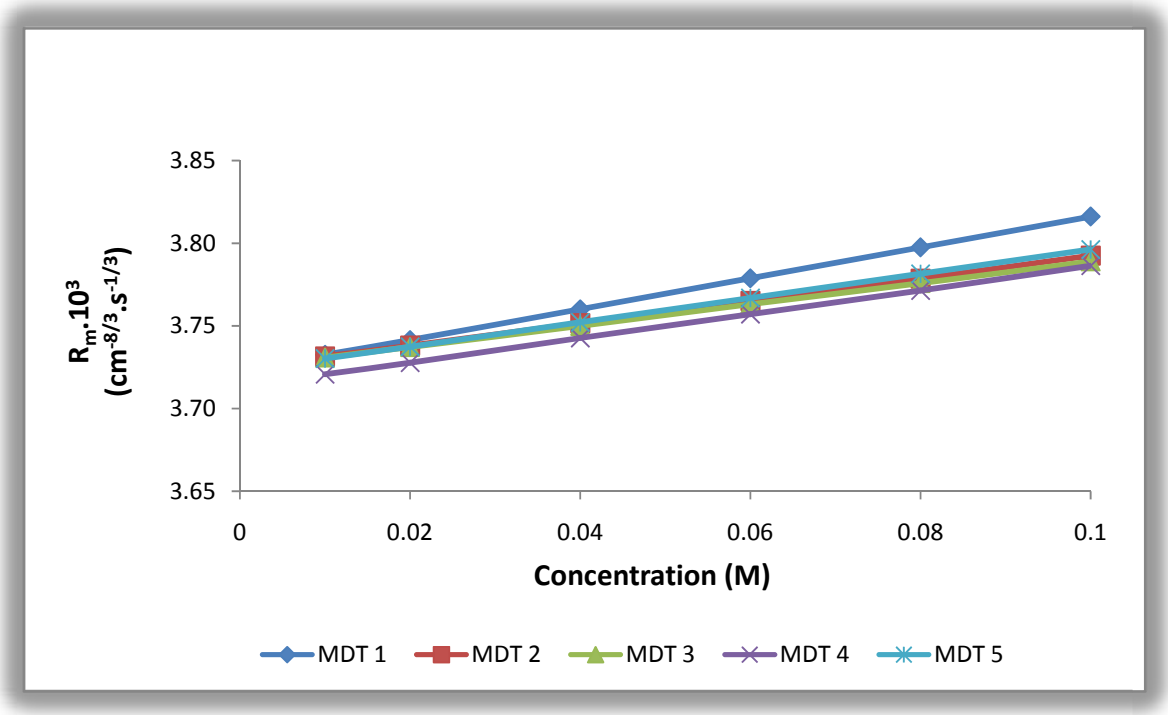
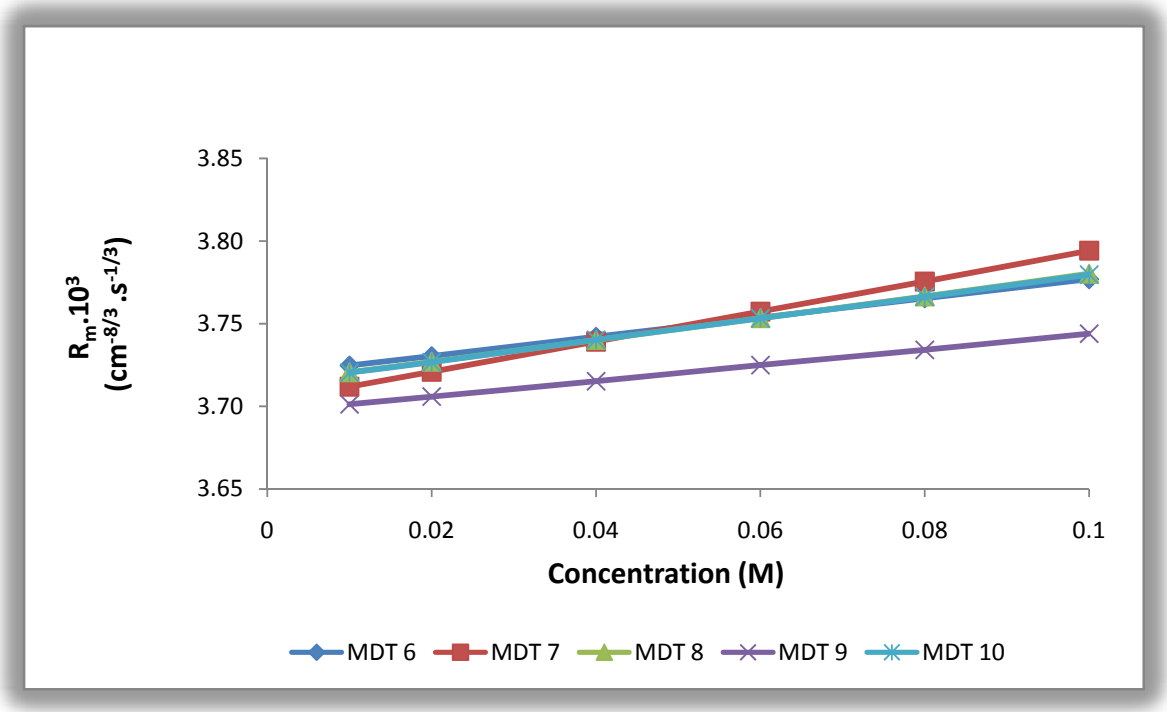


Figure 3.1.6: Variation of Rao's molar sound function (R_m) of MDT series with concentration in chloroform at 303.15 K.





these compounds is shown in Figures 3.1.3 and 3.1.4 for both solvents. In DMF, κ_s values decrease for the compounds MDT-1, MDT-4, MDT-6 and MDT-10 whereas it increases for MDT-2, MDT-3, MDT-5, MDT-7, MDT-8 and MDT-9. In chloroform, for all the compounds, κ_s values decrease as concentration increases. Similar results are observed for relaxation strength (r) in both the solvents (as shown in Tables 3.1.3 and 3.1.4).

The decreases of κ_s and r with increasing concentration might be due to aggregation of solvent molecules around solute molecules indicating thereby the presence of ion (solute) -solvent interactions. The increase of acoustical impedance (Z) (Tables 3.1.3 and 3.1.4) further confirms the solute-solvent interactions in above said systems. The reverse nature of κ_s , r and Z is due to solute-solute interactions in the system (as observed in DMF solutions of MDT-2, MDT-3, MDT-5, MDT-7, MDT-8 and MDT-9.

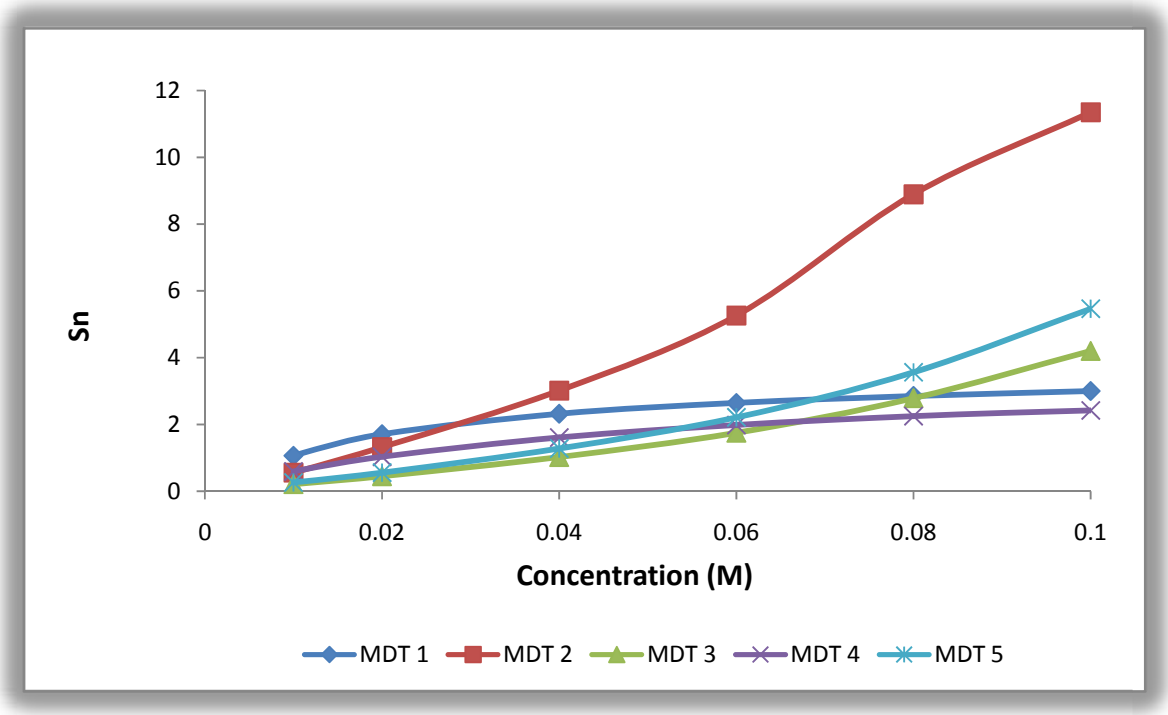
Further, Rao's molar sound function (R_m) is observed to increase linearly in both the solvents for all the studied compounds as shown in Figures 3.1.5 and 3.1.6. The molar compressibility (W) and Vander Waal's constant (b) are observed to increase linearly with concentration for all the compounds in both the solvents (0.9990-1.0000). The linear increase shows absence of complex formation in these systems.

The behaviour of solute in a particular solvent is also studied by the solvation number (S_n). Figures 3.1.7 and 3.1.8 show the variation of solvation number with concentration in both the solvents. As evident from figures, the solvation number is positive for all the compounds and it increases with concentration for all compounds except for MDT-8 in chloroform solution. The increase of solvation number is due to structure forming tendency whereas reverse is true for structure braking tendency in a solution. Thus, the positive and increase of S_n suggests that all the studied compounds (except for MDT-8 in chloroform solution) exhibit structure forming tendency in the studied solvents. Although increase in compressibility (κ_s), intermolecular free length (L_f), relaxation strength (r) and decrease of velocity (U), viscosity (η) in MDT-2, MDT-3, MDT-5, MDT-7, MDT-8 and MDT-9 in DMF suggest

existence of solute-solute interactions, increase of solvation number with concentration suggest that solute-solvent interactions also exist in these systems. The type of interaction depends on the functional groups present in the solute, the structure of solute as well as on the solvent molecule. MDT-8 does not contain any substitution in aromatic ring due to which, this compound may not be able to interact as much as other compounds with chloroform. This results in a decrease of S_n with concentration in this system.

Thus, in DMF solutions, both solute-solvent and solute-solute interactions exist in MDT-2, MDT-3, MDT-5, MDT-7, MDT-8 and MDT-9. However, these systems also exhibit structure forming tendency. All other compounds show solute-solvent interactions and hence structure forming tendency in DMF. In chloroform, all the compounds (except for MDT-8) show structure forming tendency whereas structure breaking tendency is exhibited by MDT-8.

Figure 3.1.7: Variation of solvation number (S_n) of MDT series with concentration in DMF at 303.15 K.



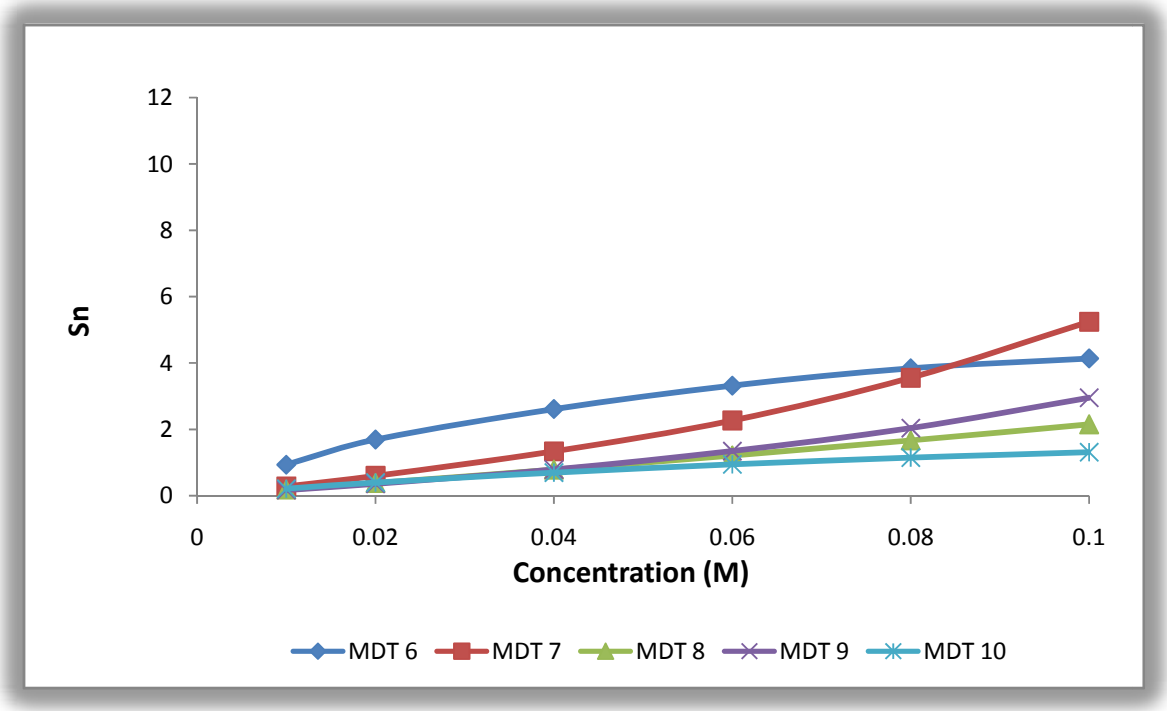
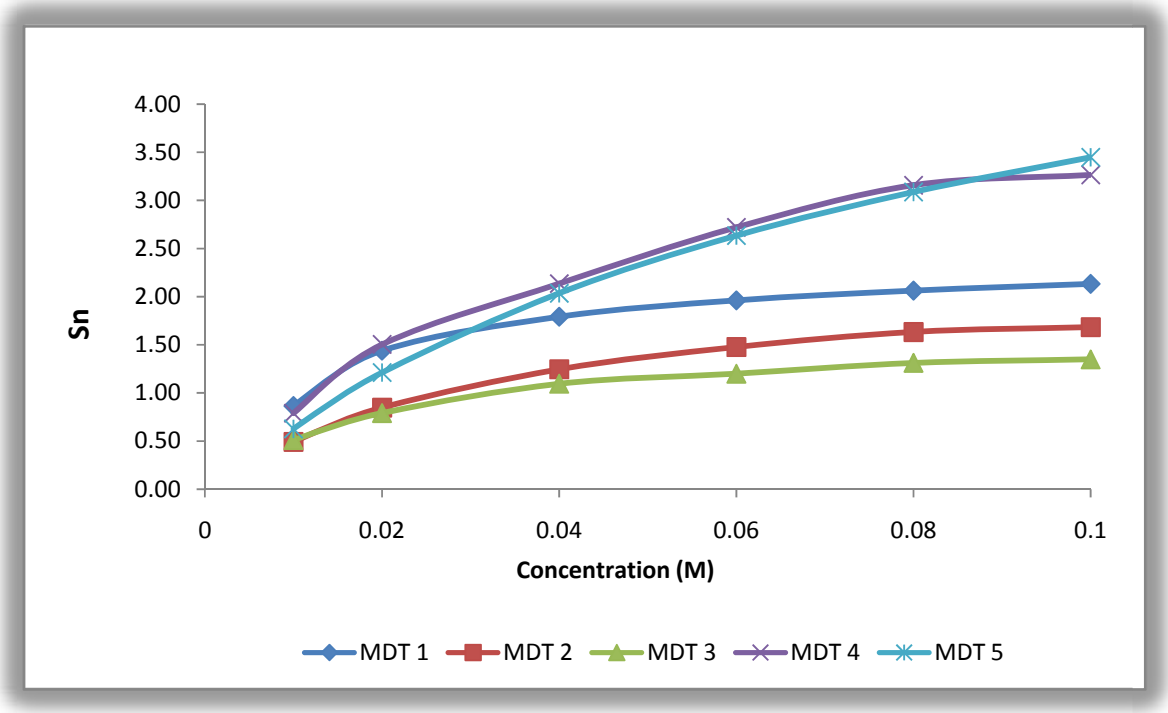
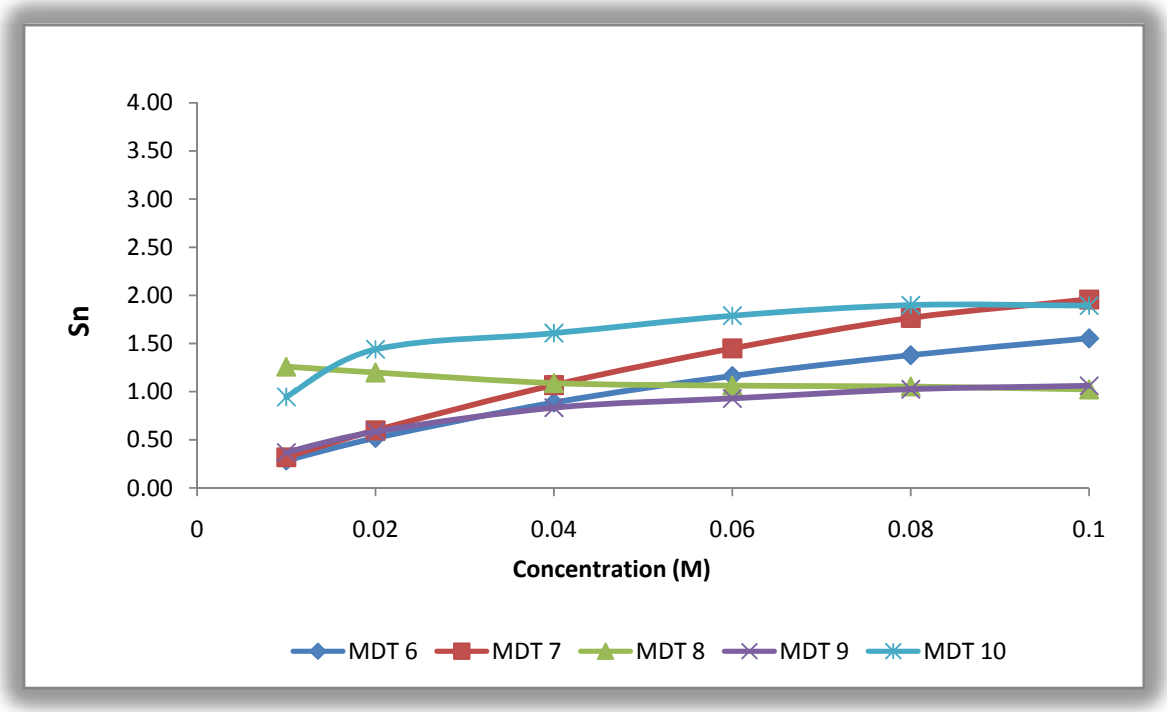


Figure 3.1.8: Variation of solvation number (S_n) of MDT series with concentration in chloroform at 303.15 K.





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INTRODUCTION

The refractive index is a characteristic property of a substance, which depends upon temperature and the wavelength of the light used. It decreases with increasing temperature and wavelength.

Refractive index is a very useful method to determine the structure and identity of unknown compounds. It also determines isotropic and anisotropic behaviour of the crystal by the arrangement of atoms [1]. From the refractive Index values, thermodynamics properties of chemical materials can be computed with the help of the measurement of density, molecular mass and specific volume. The number of atoms, groups, radicals and bonds present in the compound can also be calculated by refractive index measurement. Generally, refractive index is a unit less number. Most compounds gives refractive index values between 1.3000 and 1.7000, but some materials give negative refractive index values and are known as meta materials. These materials were first demonstrated for microwave frequencies [2].

Refractive index measurements are useful in various industries to control manufacturing processes such as fermentation [3], dyes [4], canning [5] and preservation of food, determination of purity of polar substances [6] and for the identification or assaying of some solids, liquids or constituents of a solution. A very well known application is to determine the thickness of film [7-11]. Thus, this property has been used to study various substances. Dinar et al. have studied refractive index of atmospheric aerosol [12]. Recently, Wittmann et al. has checked the refractive index of semiconductor materials [13]. Hubbezoglu et al. have concluded that colour changes were found to be stronger in materials with larger refractive indices by checking the effect of bleaching of dental composite resins on refractive index [14]. A very sensitive process of grating of some photonic crystal fibre occurs with regular observation in change of refractive index [15]. An increase of the position of the impurity in a spherical quantum dot can be identified by the total refractive index changes [16].

Literature survey shows that various researchers have regularly evaluated the refractive index of different liquid solutions [17-24].The refractive index of some

organic compounds [25, 26], inorganic salts [27, 28], organic-inorganic hybrid materials [29], polymeric materials [30-32], optical fibres [33-35], photosensitive materials [36], nanomaterials [37, 38], holographic materials [39] membrane protein [40] and other materials [41, 42] have also been determined. Solomko and Galadzhii have studied refractive index of water-acetone- alcohol systems [43]. Refractive index of some aliphatic alcohols with dioxane has also been reported by Sherstneva and Koleboshin [44]. Refractive index of methyl isobutyl ketone + pentanols has also been measured by Riggio et al. [45]. Aal-Wahaibi et al. reported refractive index of ternary system: Isopropyl alcohol + Cyclohexane + Water [46]. Campos et al. determined the refractive index of Formamide + Water system [47].

In the present section, the density and refractive index of synthesized tetrahydropyrimidine were measured in N, N-dimethylformamide and chloroform solutions of different concentrations. Further, molar refraction have been evaluated. From these data, the refractive index and density of compounds were determined

EXPERIMENTAL

The solvents N. N-dimethyformamide and chloroform were of LR grade and are fractionally distilled by the reported method [51]. All the studied synthesized compounds (MDT 1-10) were recrystalized from chloroform. For each compound, a series of solutions of different concentrations were prepared in DMF and chloroform solvents.

The density and refractive index of solutions were measured by using pyknometer and Abbe refractometer respectively. Study of refractive index and density was completed at constant temperature viz. 303.15 K, which is 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 $\pm 0.1^{o}$ C. Mettler Toledo AB204-S, Switzerland electronic balance with uncertainty of $\pm$ 0.0001 g, was used for all the weights taken for density measurements.

The results are given in Table 3.5.1.

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:

$$\frac{1}{\rho_{12}} = \frac{g_1}{\rho_1} + \frac{g_2}{\rho_2} \quad \ldots (3.5.1)$$

where ρ_{12} is the density of solution and ρ_1 and ρ_2 are the densities of solvent and solute respectively. Table 3.5.1 shows the experimental values of densities and refractive index for all the ten synthesized tetrahydropyrimidine in different solutions.

The slope of the plot of $1/g_1\rho_{12}$ verses g_2/g_1 gives the density of these compounds. The plot of $1/g_1\rho_{12}$ verses g_2/g_1 is given in Figure 3.5.1 for MDT-1 in DMF and chloroform respectively. The densities of all the synthesized compounds were evaluated from the slope of such plots. The inverse of slope gives density of compound (ρ_2). Table 3.5.2 shows these calculated densities for all the compounds. Further, the density of compounds were calculated by using the following equation (3.5.2),

$$\rho = KM / N_A \sum \Delta V_i \quad \ldots (3.5.2)$$

ρ indicates the density of the compound, K is packing fraction which is equal to 0.599, M is for 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 density of all the studied compounds have been evaluated and reported in Table 3.5.2. The calculated volume increment ΔV_i for different atomic groups are given in Table 3.5.3.

Comparison of densities evaluated from graphs and those calculated from eq. (3.5.2) showed that calculated values are different from those evaluated graphically. For the same compound, density in the two different solvents is different. This suggests that one has to consider the role of solvent in the measurement of the physical parameters of any solutions. It is because of the

Table 3.5.1: The density (ρ_{12}) and refractive index (n) of MDT series in DMF at 303.15 K.

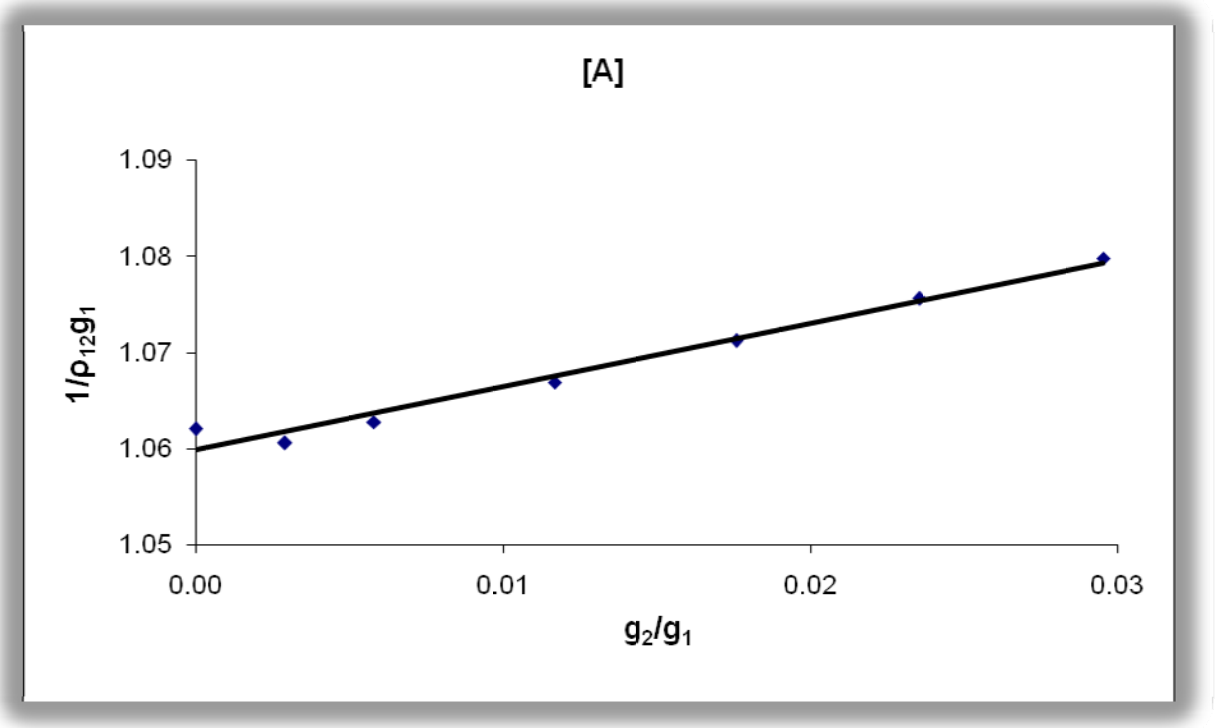
	DMF		Chloroform	
Conc.(M)	ρ_{12} ($g.cm^{-3}$)	N	ρ_{12} ($g.cm^{-3}$)	n
MDT 1				
0.00	0.9416	1.4121	1.4713	1.4397
0.01	0.9456	1.4231	1.4713	1.4402
0.02	0.9465	1.4239	1.4715	1.4410
0.04	0.9483	1.4247	1.4721	1.4421
0.06	0.9500	1.4255	1.4726	1.4433
0.08	0.9516	1.4265	1.4731	1.4448
0.10	0.9535	1.4273	1.4737	1.4458
MDT 2				
0.01	0.9448	1.4223	1.4717	1.4399
0.02	0.9452	1.4229	1.4724	1.4404
0.04	0.9461	1.4238	1.4736	1.4414
0.06	0.9470	1.4248	1.4749	1.4423
0.08	0.9479	1.4259	1.4761	1.4433
0.10	0.9489	1.4268	1.4774	1.4443
MDT 3				
0.01	0.9486	1.4212	1.4714	1.4400
0.02	0.9489	1.4228	1.4718	1.4406
0.04	0.9495	1.4230	1.4727	1.4417
0.06	0.9501	1.4242	1.4736	1.4428
0.08	0.9507	1.4252	1.4745	1.4440
0.10	0.9513	1.4263	1.4754	1.4450
MDT 4				
0.01	0.9494	1.4219	1.4749	1.4415
0.02	0.9503	1.4223	1.4753	1.4416
0.04	0.9520	1.4231	1.4761	1.4420
0.06	0.9538	1.4239	1.4768	1.4423
0.08	0.9555	1.4250	1.4776	1.4425
0.10	0.9573	1.4255	1.4784	1.4428
MDT 5				
0.01	0.9494	1.4203	1.4720	1.4409
0.02	0.9503	1.4208	1.4723	1.4410
0.04	0.9520	1.4217	1.4730	1.4413
0.06	0.9538	1.4226	1.4736	1.4416
0.08	0.9556	1.4235	1.4743	1.4418
0.10	0.9573	1.4244	1.4750	1.4421

Continue…..

.... Continue

Conc.(M)	ρ_{12} ($g.cm^{-3}$)	n	ρ_{12} ($g.cm^{-3}$)	n
MDT 6				
0.00	0.9416	1.4121	1.4713	1.4397
0.01	0.9454	1.4211	1.4747	1.4412
0.02	0.9458	1.4215	1.4752	1.4414
0.04	0.9467	1.4222	1.4762	1.4418
0.06	0.9476	1.4230	1.4772	1.4425
0.08	0.9484	1.4237	1.4782	1.4426
0.10	0.9494	1.4244	1.4792	1.4430
MDT 7				
0.01	0.9529	1.4191	1.4800	1.4408
0.02	0.9530	1.4200	1.4801	1.4412
0.04	0.9531	1.4217	1.4803	1.4420
0.06	0.9532	1.4234	1.4805	1.4426
0.08	0.9533	1.4252	1.4807	1.4433
0.10	0.9534	1.4269	1.4809	1.4440
MDT 8				
0.01	0.9506	1.4225	1.4735	1.4408
0.02	0.9507	1.4228	1.4737	1.4411
0.04	0.9508	1.4234	1.4741	1.4416
0.06	0.9509	1.4239	1.4744	1.4421
0.08	0.9510	1.4245	1.4748	1.4426
0.10	0.9511	1.4251	1.4751	1.4431
MDT 9				
0.01	0.9424	1.4164	1.4809	1.4397
0.02	0.9429	1.4175	1.4813	1.4400
0.04	0.9440	1.4195	1.4820	1.4406
0.06	0.9451	1.4214	1.4827	1.4412
0.08	0.9462	1.4234	1.4834	1.4418
0.10	0.9473	1.4253	1.4841	1.4424
MDT 10				
0.01	0.9562	1.4233	1.4746	1.4396
0.02	0.9565	1.4238	1.4751	1.4398
0.04	0.9571	1.4244	1.4763	1.4399
0.06	0.9576	1.4251	1.4775	1.4401
0.08	0.9581	1.4257	1.4787	1.4402
0.10	0.9587	1.4262	1.4798	1.4404

Figure 3.5.1: The variation of $1/g_1\rho_{12}$ with g_2/g_1 for MDT-1 in [A] DMF and [B] chloroform at 303.15 K.



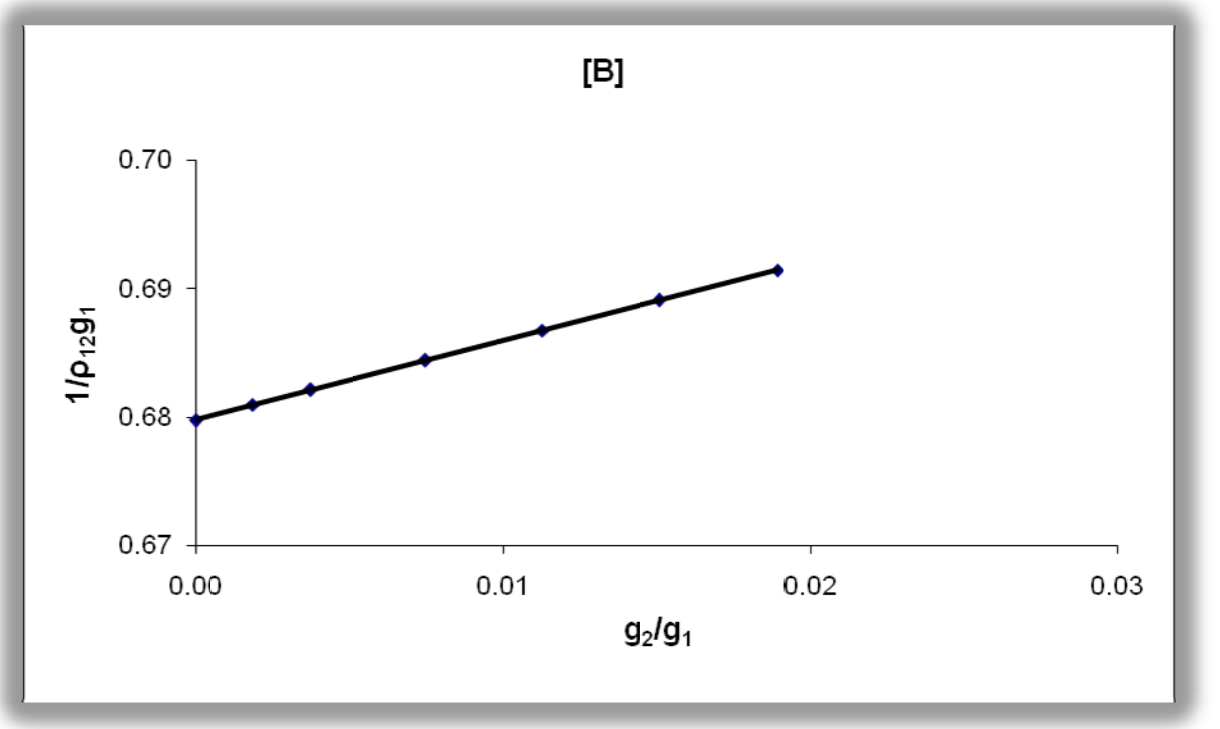
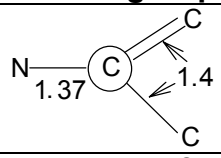
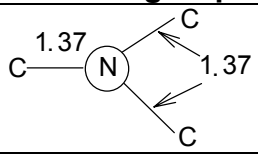
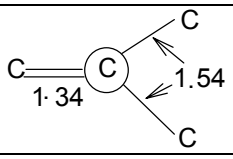
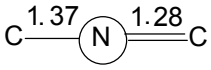
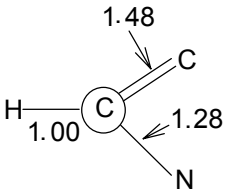
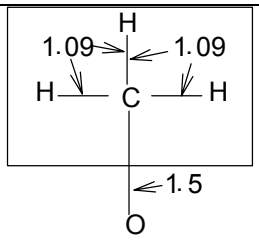
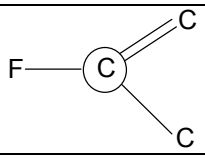
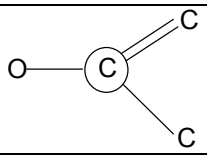
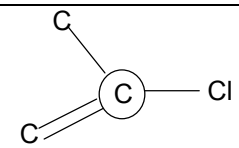
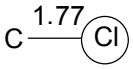
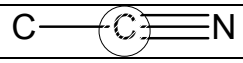
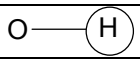
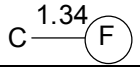
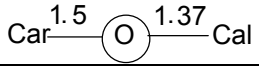
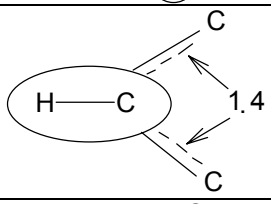
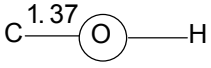
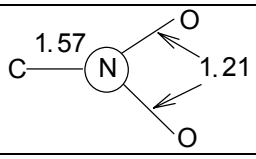
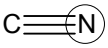
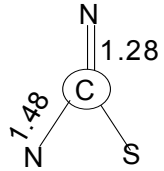
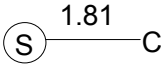
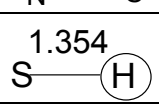


Table 3.5.2: Experimental and calculated densities of MDT series in DMF and chloroform solutions at 303.15 K.

Compounds	Density ($g.cm^{-3}$) calculated from slope of Fig. 3.5.1 in two solvents		Density ($g.cm^{-3}$) calculated from Eq^{n}. 3.5.2
	DMF	Chloroform	
MDT 1	1.5175	1.6234	1.2960
MDT 2	1.2270	1.9380	1.2624
MDT 3	1.2870	1.7825	1.3163
MDT 4	1.7953	1.8692	1.3565
MDT 5	1.7699	1.6978	1.3565
MDT 6	1.2610	2.0121	1.3351
MDT 7	1.2438	1.8519	1.3664
MDT 8	1.2315	1.6892	1.2787
MDT 9	1.2642	2.4213	1.5300
MDT 10	1.5974	2.0661	1.3877

Table 3.5.3: 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		0.9
	9.0		5.62
	3.61		26.3
	11.40		11.65
	10.39		19.35
	15.9		4.7
	9.2		2.67
	14.7		5.36
	7.46		10.0
	13.46		3.92
	4.8		

facts that, in every solution molecular interactions exist which differ with different solvents. This is further confirmed by acoustical parameter which is already discussed in Section I. Generally, intermolecular interactions do not affect the density but due to the presence of different substituted groups in solutes, interactions differ in different solvents which may cause change in volume thereby affecting the density of solute in a particular solvent.

The molar refraction of a pure liquid $(MRD)_1$ can be calculated by the following equation:

$$\left(MRD\right)_1 = \left[\frac{n^2-1}{n^2+1}\right]\frac{M}{\rho} \qquad \ldots (3.5.3)$$

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

For solutions, the eq. (3.5.4) was used to determining molar refraction.

$$\left(MRD\right)_{12} = \left[\frac{n_{12}^2-1}{n_{12}^2+1}\right]\left[\frac{X_1M_1 + X_2M_2}{\rho_{12}}\right] \qquad \ldots (3.5.4)$$

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.

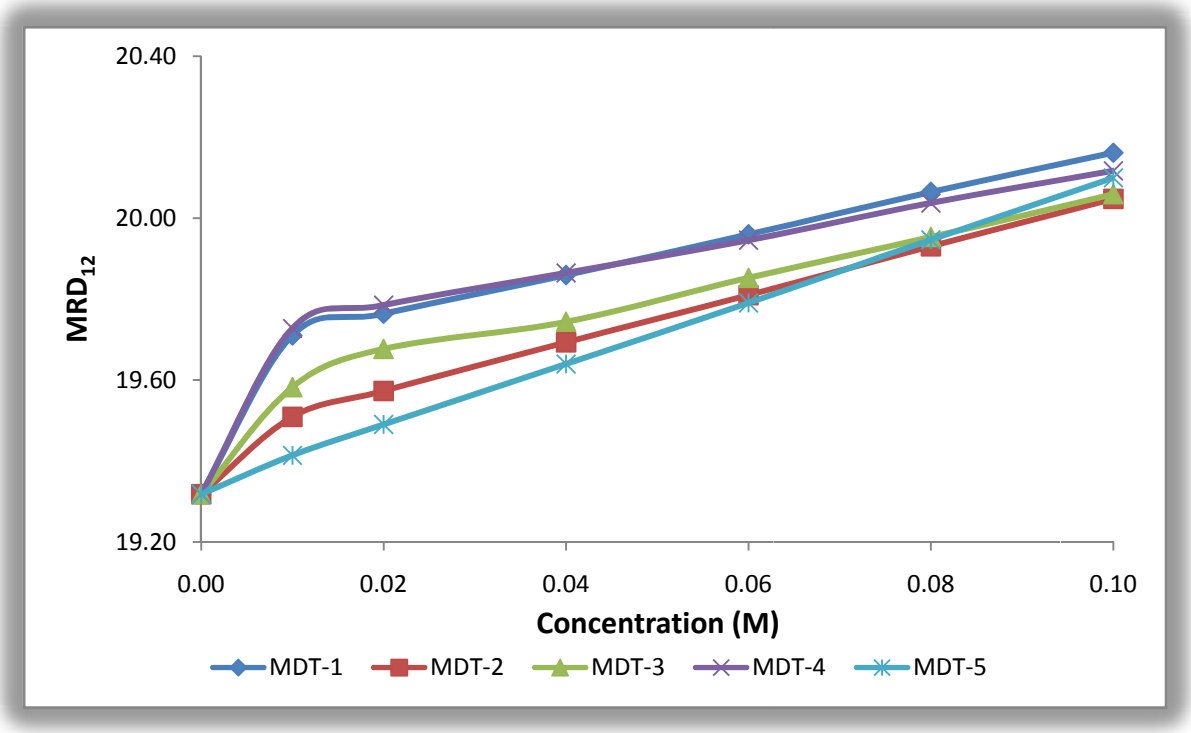
The plots of $(MRD)_{12}$ verses concentration for all the studied compounds in DMF and chloroform are given in Figures 3.5.2 and 3.5.3. It is evident from these figures that $(MRD)_{12}$ increases with the increase in concentration. From the values of the molar refraction of solution and pure solvent, molar refraction of solid compounds were determined by following equation:

$$\left(MRD\right)_{12} = X_1\left(MRD\right)_1 + X_2\left(MRD\right)_2 \qquad \ldots (3.5.5)$$

From the density and molar refraction data, the refractive indexes of all the compounds were calculated from eq. (3.5.3). The molar refraction $(MRD)_2$ and refractive index of all the compounds are reported in Table 3.5.4 for 0.1 M solution.

Each solvent interacts differently with different functional groups, so that $(MRD)_2$ and refractive index of compounds is different in each solvent, as shown in Table 3.5.4. As discussed above, in different solvents intermolecular interactions are different, which affect these parameters. In some solvents, aggregation or hydrogen bonding takes place whereas in others, breakage of bonds takes place. The refractive index and molar refraction depends not only upon atomic refraction but also upon single, double or triple bonds. However, it is reported that bond refraction is more effective than atomic refraction [52, 53]. Further, bond polarity also causes change in molar refraction. Thus, type of solvent affects the refractive Index and molar refraction of a solute.

Figure 3.5.2: The plots of molar refraction $(MRD)_{12}$ against concentration of MDT series in DMF solutions at 303.15 K.



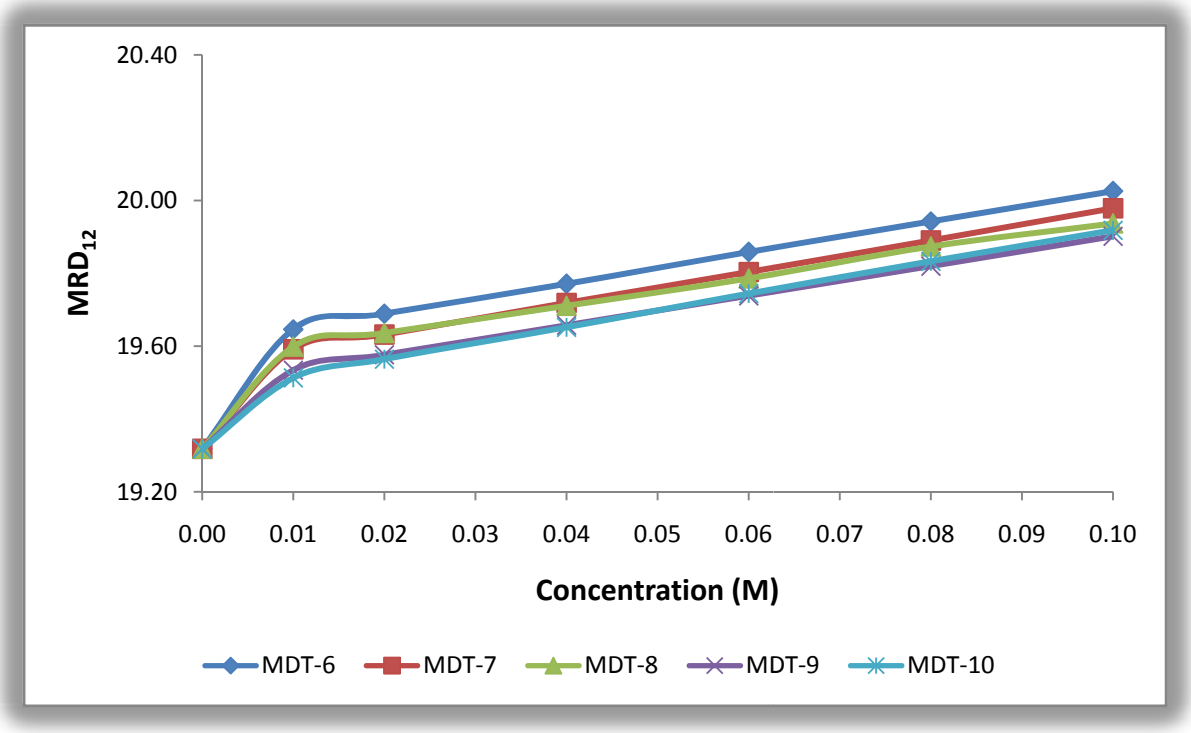
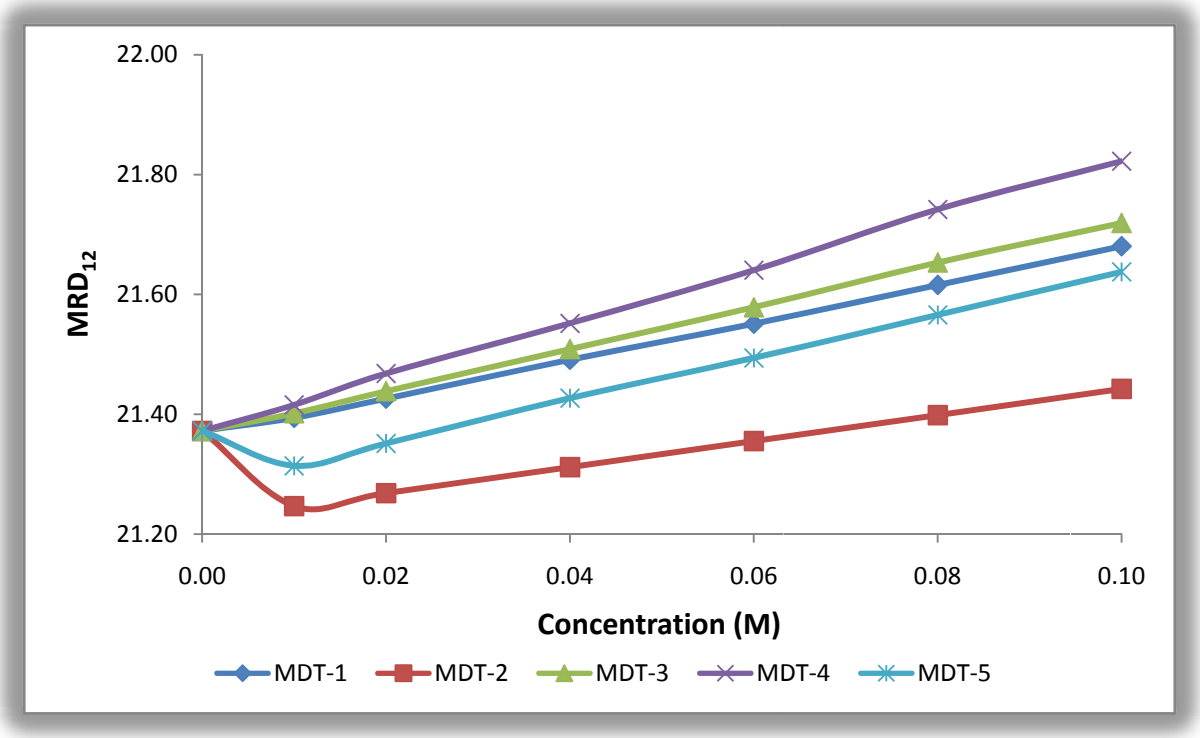


Figure 3.5.3: The plots of molar refraction $(MRD)_{12}$ against concentration of MDT series in chloroform solutions at 303.15 K.



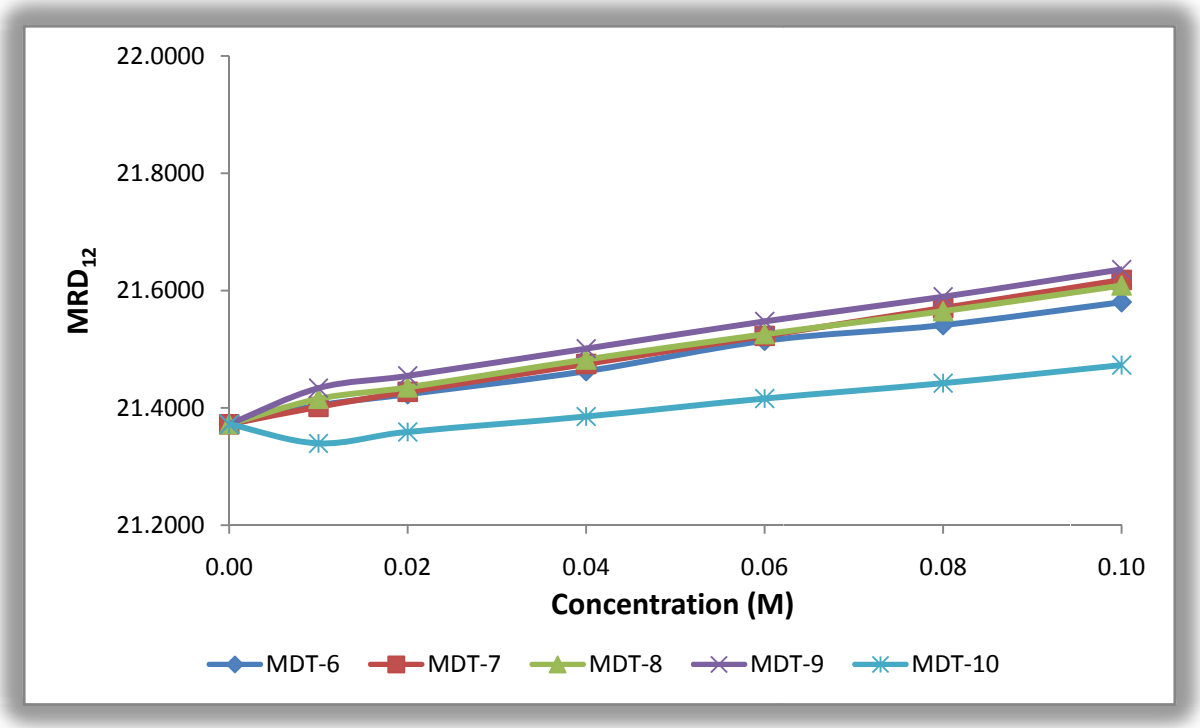


Table 3.5.4: Calculated molar refraction and refractive index of 0.1 M solution of MDT compounds in DMF and chloroform at 303.15 K.

Compounds	Solvents			
	DMF		Chloroform	
	$(MRD)_2$	n	$(MRD)_2$	n
MDT 1	121.6168	1.7680	76.5282	1.4703
MDT 2	127.0079	1.6448	59.2671	1.4469
MDT 3	114.3017	1.5263	64.0095	1.3921
MDT 4	99.0076	1.7553	50.4572	1.3539
MDT 5	94.4151	1.7361	53.7491	1.3576
MDT 6	109.8296	1.5803	47.0155	1.3722
MDT 7	119.4055	1.5820	54.0534	1.3677
MDT 8	104.1181	1.5317	51.6345	1.3419
MDT 9	112.6901	1.6026	30.0622	1.2799
MDT 10	96.7712	1.6999	33.7944	1.2784

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INTRODUCTION

Electrical conductance is a useful method to characterise the properties of ionic solution. This property is useful for physico-chemical analysis. The conductance of electrolytic solutions depends on the concentration of the ions and also on the nature of the ions present. Conductance measurements were among the first to be used for determining dissociation constants, solubility products and other properties of electrolyte solutions. This technique is also used for determining the ionization constant of weak electrolytes, equilibrium constants, rates of reactions that proceed with the formation or disappearance of ions, and to study of interionic forces. The relative strengths of the two acids or bases, solubility of sparingly soluble salts, degree of hydrolysis, basicity of organic acids etc. have also been studied by conductometric techniques [1-4]. Lyashchenko and Lileev relate electric conductivity of aqueous solutions of guanidinium salts with rotational mobility of water molecules [5]. Reaction rates in a radiation-induced chemical reaction can also be studied by means of conductivity measurements [6]. Dey et al have studied the effect of substituents on the solvational behavior of organic compound with the help of conductometric and solubility measurements [7].

Conductometry is also useful to various biological processes [8-10]. It is used to determine micro amounts of carbon in aqueous phase [11], ascorbic acid in vitamin C tablet [12], carbon in uranium carbide and its solution in nitric acid [13], enzymatic degradation of microbial biofilm [14], dye-surfactant ion pair formation in aqueous solutions [15] etc. Morita et al reported ionic conductance of polymeric electrolytes and of polymeric composite solid electrolytes [16]. Arjomandi and Holze have characterized polymers on gold electrodes In situ [17]. Myllyniemi et al. have used an indirect conductometric screening method for the detection of antibiotic residues in bovine kidneys [18]. Stanisz has used conductometric technique to determine electrolyte and osmotic permeability coefficients [19]. Mehta et al. have used this method to study interactions between diclofenac sodium and cyclodextrin molecules in aqueous media [20]. Gil et al have studied micellization of surfactant system by conductometric method [21]. Literature survey shows that conductance of many inorganic and organic compounds have

been measured in aqueous [22-27] and non–aqueous solvents [28-31]. Jha and Saxena have performed conductance study of mixed halocobaltates in acetonitrile [32]. Mukherjee and Datta have checked the effects of conductance on mobility of ions [33]. Recently, conductance of some Schiff bases in DMF has been measured at different temperatures by Grzeszcuk and Bator [34]. Further, in our laboratory, some conductance measurements have been done for Schiff bases **[35, 36].** However, not much data was available for heterocyclic ring systems.

Thus, in present work, conductances of tetrahydropyrimidine derivatives in different solutions have measured by using N, N-dimethylformamide and chloroform as a solvent at 303.15 K.

EXPERIMENTAL

All the solvents used were distilled prior to use. The solutions of different concentrations were prepared for each compound in DMF and chloroform and the conductance of each solution was measured by using Equiptronics Conductivity Meter (Model No. EQ-664) having cell constant 0.89 cm^{-1} at 303.15 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:

$$\kappa = k\theta \qquad \ldots (3.3.1)$$

$$\lambda_c = 1000\frac{\kappa}{C} \qquad \ldots (3.3.2)$$

where θ is the cell constant (= 0.89 cm^{-1}) and c is the concentration (g.equi./lit.) of solution.

These equivalent conductance values of all the tetrahydropyrimidines in DMF and chloroform at 303.15 K are reported in Tables 3.3.1 and 3.3.2 along with measured conductance (k) except for chloroform solutions of MDT-1 and MDT-3, where conductance is almost same as that of pure solvent. Figures 3.3.1 to 3.3.2 show the variation of conductance with concentration in both the solvents. Conductivities of all studied compounds are observed to be less in DMF than those in chloroform. Further, for all the systems studied, conductance increases with concentration. Figures 3.3.1 and 3.3.2 show that for most of the compounds, there is sharp increase in conductance with concentration. However, at higher concentration, the values increase very slowly.

The equivalent conductance (λ_c) is plotted against $\sqrt{C}$ for all studied compounds and is shown in Figures 3.3.3 and 3.3.4. In both DMF and chloroform solutions, usually λ_c increases with dilution In DMF solutions, for most of the systems, at lower concentrations, the change in λ_c values is very less and in figures it appears as almost constant whereas at higher concentrations it decreases. In chloroform solutions, for most of the compounds much increase or decrease is observed at lower concentrations. For MDT-2 and MDT-6, at lower concentrations, the change in equivalent conductance is not significant whereas for MDT-4, MDT-5 and MDT-7, after 0.10 N, λ_c decreases and bend downward at

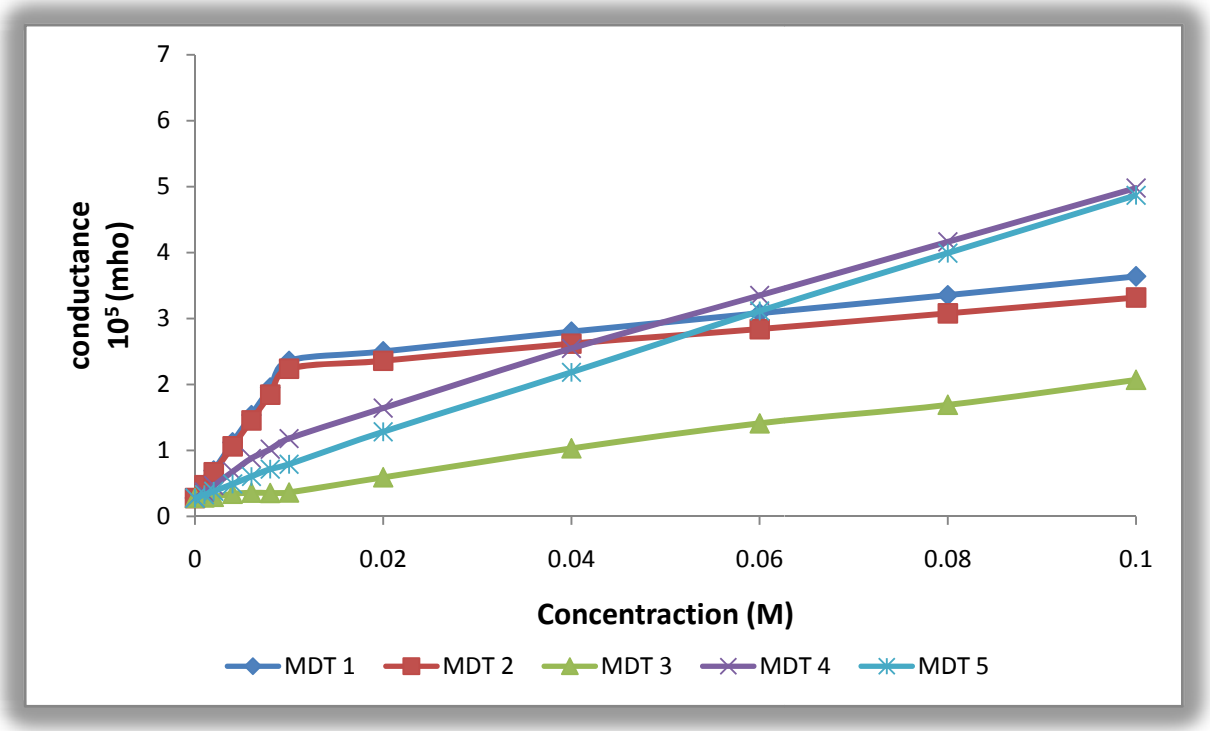
Table 3.3.1: The conductance (k) and equivalent conductance (λ_C) of MDT series in DMF at 303.15 K.

Conc. C (g/lit)	$k.10^5$ $(\Omega)^{-1}$	λ_C (cm^2/Ω.equiv.)	$k.10^5$ $(\Omega)^{-1}$	λ_C (cm^2/Ω.equiv.)	$k.10^5$ $(\Omega)^{-1}$	λ_C (cm^2/Ω.equiv.)	$k.10^5$ $(\Omega)^{-1}$	λ_C (cm^2/Ω.equiv.)	$k.10^5$ $(\Omega)^{-1}$	λ_C (cm^2/Ω.equiv.)
	MDT 1		**MDT 2**		**MDT 3**		**MDT 4**		**MDT 5**	
0.000	0.28	---	0.28	---	0.28	---	0.28	---	0.28	---
0.001	0.49	1.8512	0.47	1.7444	0.29	0.0712	0.37	0.8010	0.33	0.4539
0.002	0.69	1.8512	0.67	1.7444	0.30	0.0757	0.47	0.8455	0.38	0.4539
0.004	1.12	1.8757	1.06	1.7444	0.34	0.1402	0.68	0.8900	0.49	0.4762
0.006	1.54	1.8675	1.46	1.7459	0.36	0.1202	0.88	0.8915	0.61	0.4851
0.008	1.95	1.8634	1.85	1.7455	0.36	0.0857	1.02	0.8244	0.72	0.4884
0.010	2.36	1.8530	2.24	1.7462	0.36	0.0748	1.18	0.8028	0.79	0.4557
0.020	2.50	0.9897	2.36	0.9265	0.59	0.1393	1.64	0.6070	1.28	0.4472
0.040	2.80	0.5614	2.62	0.5211	1.03	0.1675	2.55	0.5049	2.19	0.4243
0.060	3.08	0.4158	2.84	0.3800	1.41	0.1681	3.35	0.4558	3.12	0.4210
0.080	3.36	0.3423	3.08	0.3117	1.69	0.1572	4.17	0.4324	3.99	0.4133
0.100	3.64	0.2992	3.32	0.2707	2.07	0.1595	4.98	0.4185	4.87	0.4087
	MDT 6		**MDT 7**		**MDT 8**		**MDT 9**		**MDT 10**	
0.001	0.29	0.0979	0.28	0.0000	0.41	1.1926	0.30	0.1602	0.51	2.0915
0.002	0.31	0.1424	0.28	0.0044	0.55	1.1926	0.31	0.1602	0.75	2.0915
0.004	0.34	0.1424	0.28	0.0089	0.81	1.1926	0.35	0.1602	1.22	2.0915
0.006	0.37	0.1291	0.28	0.0089	1.08	1.1941	0.39	0.1617	1.69	2.0930
0.008	0.38	0.1101	0.29	0.0089	1.35	1.1937	0.42	0.1613	2.16	2.0926
0.010	0.39	0.0997	0.29	0.0089	1.62	1.1944	0.46	0.1620	2.63	2.0933
0.020	0.61	0.1455	0.42	0.0632	1.88	0.7107	0.81	0.2376	3.05	1.2335
0.040	1.05	0.1709	0.68	0.0894	2.39	0.4690	1.52	0.2755	3.88	0.8014
0.060	1.40	0.1660	0.95	0.0997	2.90	0.3885	2.22	0.2882	4.71	0.6579
0.080	1.74	0.1624	1.22	0.1042	3.40	0.3474	2.93	0.2945	5.55	0.5861
0.100	2.06	0.1586	1.48	0.1070	3.92	0.3241	3.63	0.2983	6.38	0.5431

Table 3.3.2: The conductance (k) and equivalent conductance (λ_C) of MDT series in chloroform at 303.15 K.

Conc. c (g/lit)	$k.10^7$ $(\Omega)^{-1}$	λ_C (cm^2/Ω.equiv.)	$k.10^7$ $(\Omega)^{-1}$	λ_C (cm^2/Ω.equiv.)	$k.10^7$ $(\Omega)^{-1}$	λ_C (cm^2/Ω.equiv.)	$k.10^7$ $(\Omega)^{-1}$	λ_C (cm^2/Ω.equiv.)
	MDT 2		**MDT 4**		**MDT 5**		**MDT 6**	
0.000	8.40	---	8.40	---	8.40	---	8.40	---
0.001	8.50	8.9000	8.50	8.9000	8.50	8.9000	8.50	8.9000
0.002	8.60	8.9000	8.50	4.4500	8.50	4.4500	8.60	8.9000
0.004	8.80	8.9000	8.70	6.6750	8.60	4.4500	8.80	8.9000
0.006	9.00	8.9000	8.90	7.4167	8.80	5.9333	9.00	8.9000
0.008	9.20	8.9000	9.10	7.7875	8.90	6.6750	9.20	8.9000
0.010	9.40	8.9000	9.30	8.0100	9.00	6.2300	9.40	8.9000
0.020	9.40	4.4500	9.30	4.0050	9.10	3.1150	9.40	4.4500
0.040	9.50	2.4475	9.30	2.0025	9.10	1.5575	9.40	2.2250
0.060	9.50	1.6317	9.40	1.4833	9.20	1.1867	9.50	1.6317
0.080	9.60	1.3350	9.40	1.1125	9.20	0.8900	9.50	1.2238
0.100	9.60	1.0680	9.50	0.9790	9.30	0.8010	9.50	0.9790
	MDT 7		**MDT 8**		**MDT 9**		**MDT 10**	
0.001	8.50	8.9000	8.50	8.9000	8.50	8.9000	8.50	8.9000
0.002	8.60	8.9000	8.60	8.9000	8.60	8.9000	8.60	8.9000
0.004	8.70	6.6750	8.80	8.9000	8.90	11.1250	8.90	11.1250
0.006	8.80	5.9333	9.10	10.3833	9.20	11.8667	9.20	11.8667
0.008	9.00	6.6750	9.30	10.0125	9.50	12.2375	9.40	11.1250
0.010	9.20	7.1200	9.60	10.6800	9.80	12.4600	9.70	11.5700
0.020	9.20	3.5600	9.60	5.3400	9.80	6.2300	9.70	5.7850
0.040	9.30	2.0025	9.80	3.1150	9.90	3.3375	9.80	3.1150
0.060	9.40	1.4833	9.90	2.2250	9.90	2.2250	9.90	2.2250
0.080	9.50	1.2238	10.00	1.7800	10.00	1.7800	10.00	1.7800
0.100	9.70	1.1570	10.20	1.6020	10.10	1.5130	10.10	1.5130

Figure 3.3.1: The variation of conductance (k) with concentration for MDT series in DMF at 303.15 K.



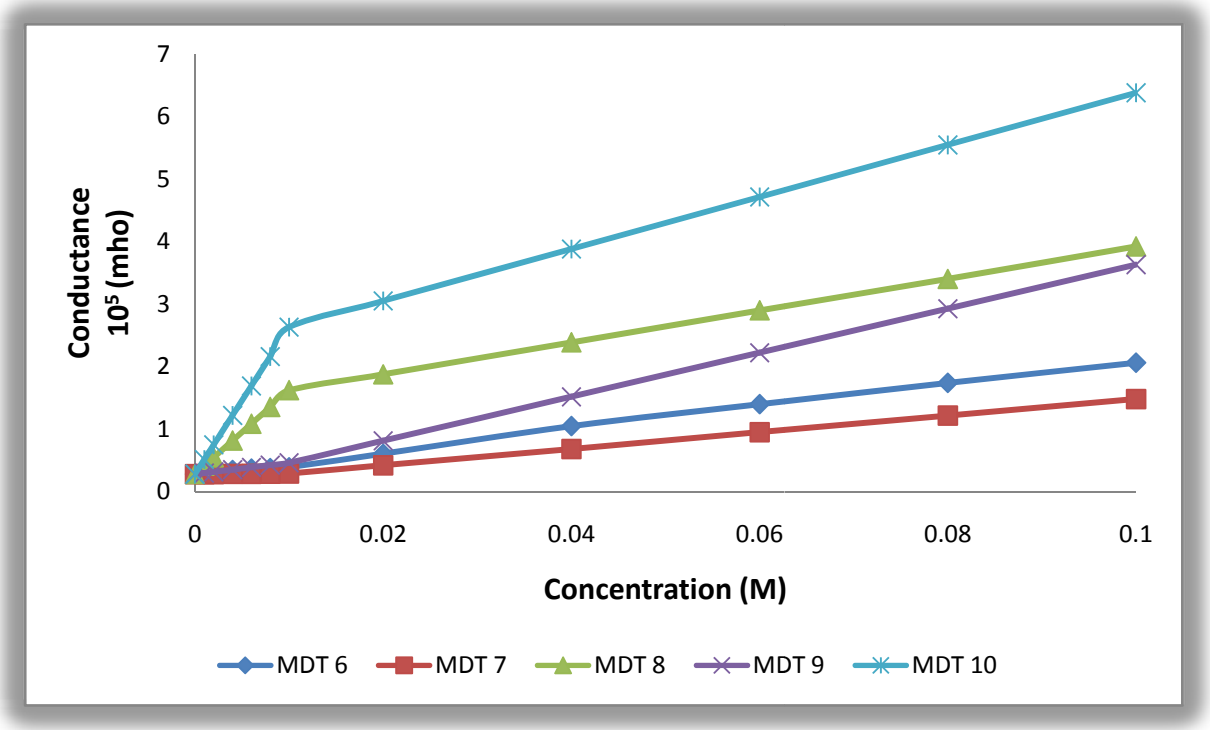
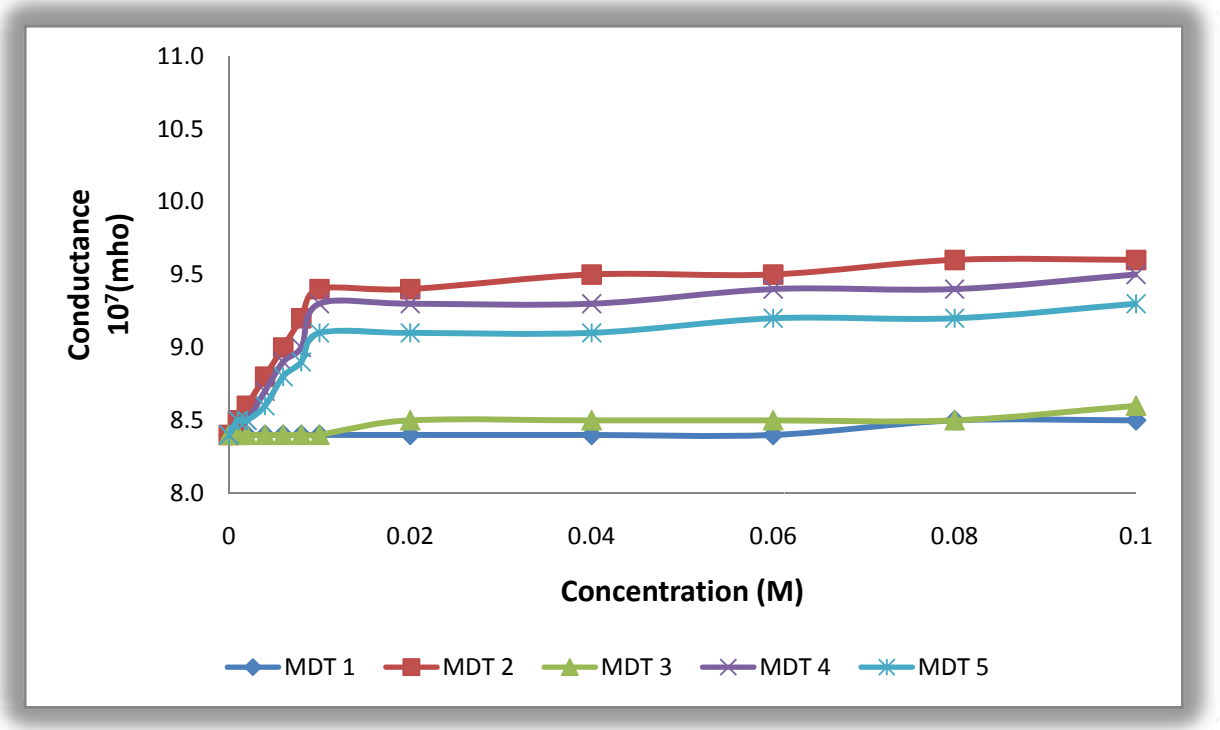


Figure 3.3.2: The variation of Conductance (k) with concentration for MDT series in chloroform at 303.15 K.



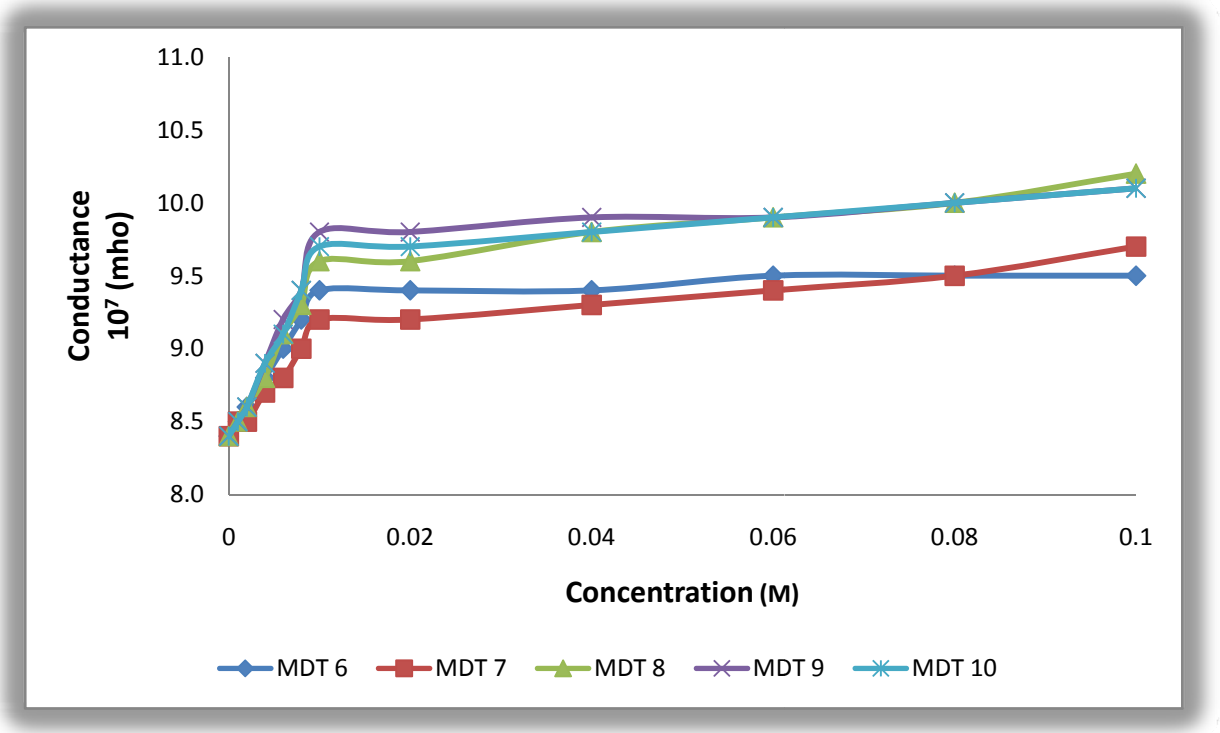
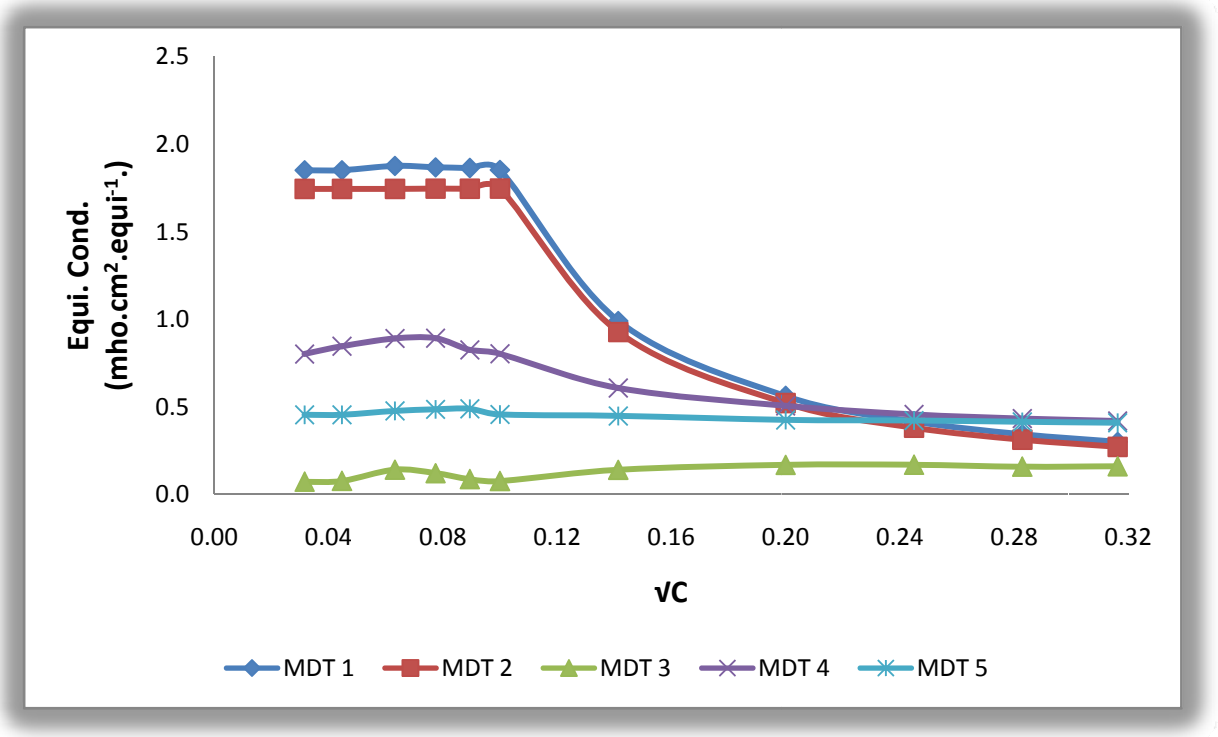


Figure 3.3.3: **The variation of equivalent conductance (λ_C) with $\sqrt{C}$ for MDT series in DMF at 303.15 K.**



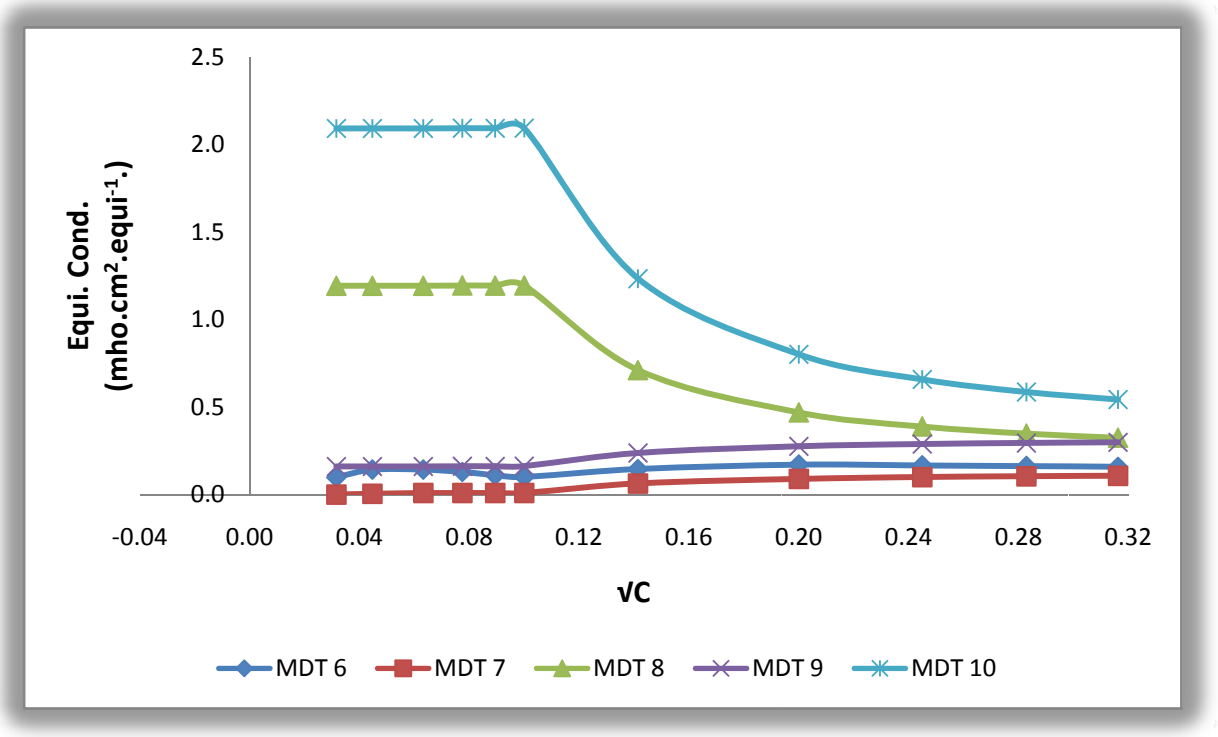
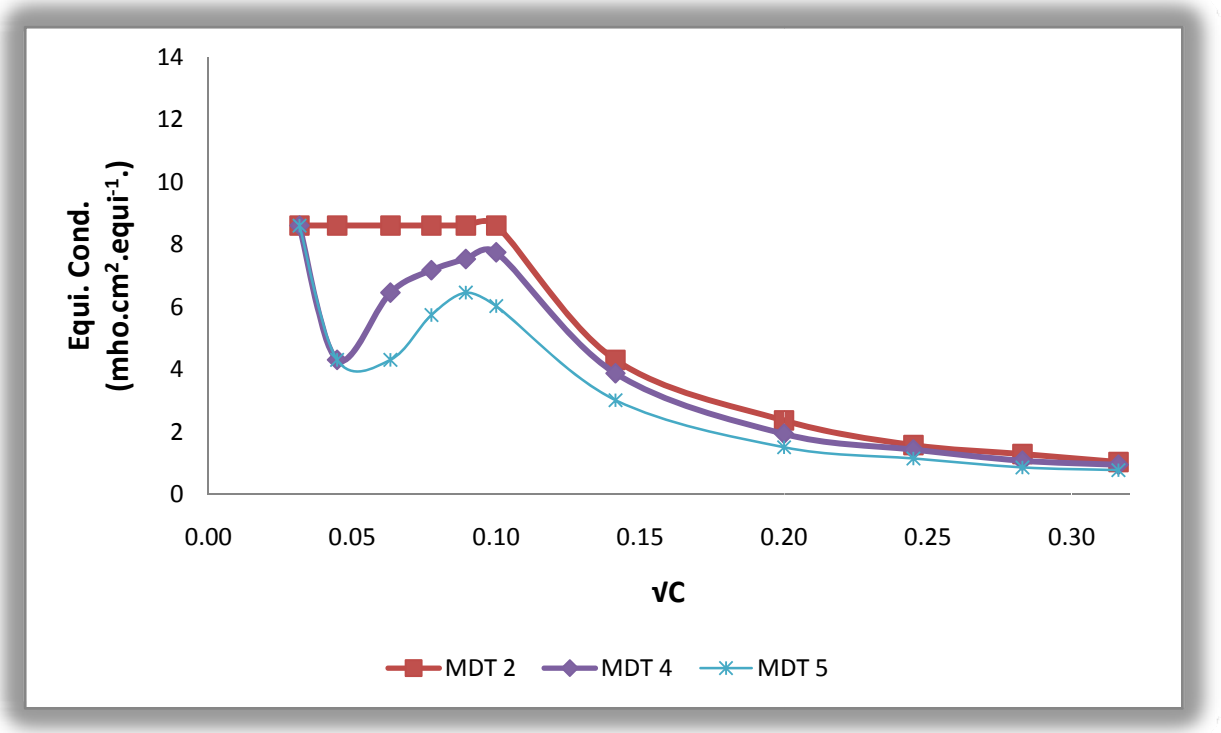
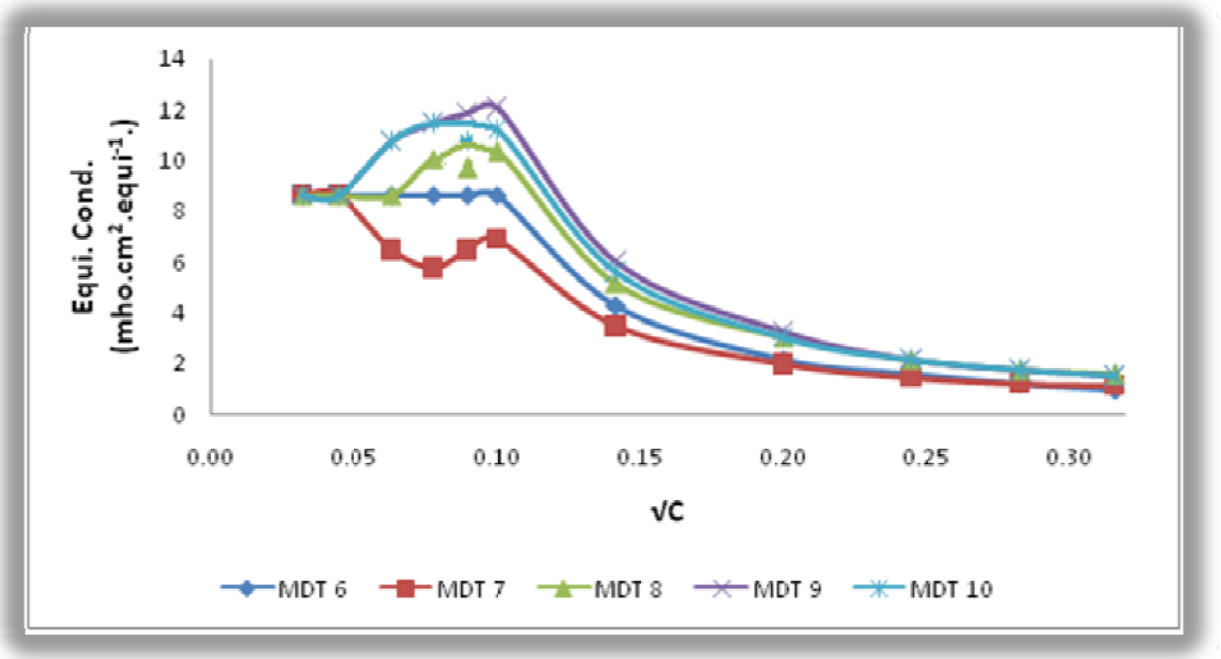


Figure 3.3.4: **The variation of equivalent conductance (λ_C) with $\sqrt{C}$ for MDT series in chloroform at 303.15 K.**





low concentrations. For rest of the compounds (MDT-8, MDT-9 and MDT-10) λ_c increases after 0.10 N and then decreases.

This typical behaviour may be due to interactions within the molecule thereby causing constriction within the molecule or due to association between solute with solvent molecules. Similar behaviour was observed by Singh et al. [37] . Haffner et al. [38] have also reported such abnormal behaviour in the studied systems and interpreted the results in terms of aggregation or complex formation at lower concentration range. This suggests that all the studied compounds exhibit weak electrolytic behaviour in DMF and chloroform solutions. So the equivalent conductance at infinite dilution for these compounds cannot be evaluated.

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INTRODUCTION

The addition of solute in a solvent causes a change in the heat of solution, which is also known as enthalpy change (ΔH). If the heat is absorbed i.e., the solution is cooler then ΔH is positive. If the heat is evolved i.e., the solution is warmer and ΔH is negative.

Heat of solution is an important parameter of solubility study, which is a key factor for study the behaviour of many species and effect occurs in the surrounding medium due to it. Various thermodynamic parameters can also be evaluated from heat of solution [1-9]. The molar heat of solution and melting temperature of a substance can also be determined from the solubility measurements at different temperatures [10]. The interaction between resin and asphaltene micelles can be understood by solubility parameters during peptization study of gas oil [11]. Gamse et al have studied Organic Flame Retardants in Supercritical CO at different temperatures and pressures [12].

Computations and observations of solubility parameter is a very useful term in pharmaceutical industries. The solubility behavior of drugs remains one of the most challenging aspects in formulation development [13]. Solubility study has been used to determine the ocular doses of different fluoroquinolones [14]. Simonelli et al have made solubility study to characterize the form of sulfathiazole controlling the rate of dissolution when sulfathiazole coprecipitated with povidone [15].

Solubility proves to be a hopeful study for biologists also. Tanford et al have studied the effects of aqueous urea [16, 17] and ethylene glycol solutions [18] on protein denaturation on the basis of solubility studies of amino acids and their derivatives. It is also reported that solubility play an important role in rapid interchange and turnover of bone mineral in the presence of fluctuating serum levels of calcium and phosphate [19]. Perutz et al have studied the solubility of the haemoglobin of sickle-cell anaemia patients [20]. Nozaki and Tanford have studied the solubility of amino acids, diglycine, and triglycine in aqueous guanidine hydrochloride solutions [21]. Zager [22] have used the solubility study to study the urine pH affects myoglobin (M)-induced renal injury in rats. The

presence of a small amount of contaminant in both chymotrypsinogen B and chymotrypsin B has also been determined by solubility study [23]. The solubility studies of some biological compounds have also been reported by GC method [24].

In our laboratory, study of solubility and evaluation of some thermodynamic parameters from solubility data is expanding from some synthesized bioactive heterocyclic compounds [25, 26], some biological compounds [27] to drug Active Pharmaceutical Ingredients (APIs) molecules [28, 29].

In the present chapter, solubility study of some tetrahydropyrimidine derivatives (MDT 1-10) have been done in methanol, ethanol and chloroform at various temperatures (293.15 to 313.15 K).

EXPERIMENTAL

All the synthesized compounds were recrystallized in chloroform. Methanol and ethanol are solvents of choice due to its dependence upon solubility and relative permeability. All the solvents were purified by fractional distillation and its purity was checked by HPLC.

The gravimetric method [30] was used to study the solubility. An excess mass of compound was added to a known mass of solvent. The solution was heated to a constant temperature with continuous stirring. After, at least 3 hr the stirring was stopped and the solution was kept at a constant temperature for 2 hr. A portion of this solution was filtered and by a preheated injector, 5 ml of this clear solution was taken to preweighted 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). To prevent dust contamination, the vial was covered with a piece of filter paper. After completely dryness of vial mass, the vial was reweighed (m_2) to determine the mass of the constant residue solid (m_2- m_0). All the weights taken using Mettler Toledo AB204-S, Switzerland electronic balance with uncertainty of $\pm$ 0.0001 g. The procedure was repeated three times at each temperature.

Using the weights of compounds (residues) and solvents, the mole fraction (x) of the compound in the solution is determined from equation 1.

$$x = \frac{(m_2 - m_0)/M_1}{(m_2 - m_0)/M_1 + (m_1 - m_2)/M_2} \quad \text{... (3.4.1)}$$

where M_1 and M_2 are the molar mass of compound and solvent respectively. This practical was repeated three times at each temperatures and an average value is given in Table 3.4.1.

It is obvious from Table 3.4.1 that there is an increase in solubility with temperature for all the compounds in the studied solvents. The temperature dependence of solubility in solvents is described by the modified Apelblat equation [31, 32].

$$\ln x = A + B\,(T/K) \quad \text{...(3.4.2)}$$

where x is the mass fraction solubility of compound, T is the absolute temperature and A and B are the parameters. The results of calculated solubility x_{ci} are also given in Table 3.4.1. Comparison between the experimental solubility and calculated solubility (x_{ci}) has been made which gives similar behaviour as reported in literature [33, 34].

Further absolute average deviations (AAD) and root-mean-square deviations (RMSD) were calculated by equations (3) and (4) are listed in Table 3.4.2.

$$AAD = \frac{1}{N}\sum_i^N \frac{x_i - x_{ci}}{x_i} \quad \text{... (3.4.3)}$$

$$RMSD = \left[\sum_{i=1}^{N} \frac{(x_{ci} - x_i)^2}{N-1}\right]^{1/2} \quad \text{... (3.4.4)}$$

where N is the number of experimental points and x_{ci} is the calculated solubility.

In Table 3.4.1 the relative deviations (RD) between the experimental and calculated values of solubility are mentioned which was calculated by equation (3.4.5).

$$\textit{Relative Deviation} = \left(\frac{x - x_{ci}}{x} \right) \quad \text{... (3.4.5)}$$

According to van't Hoff analysis, 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 [31]. For this reason, the mean harmonic temperature (T_{hm}) is used in the van't Hoff analysis, which is calculated by modified van't Hoff equation.

The enthalpy of solution (ΔH_{sol}) was calculated by modified Van't Hoff equation [10].

$$\frac{\partial \ln x}{\partial \left(1/T - 1/T_{hm} \right)_P} = -\frac{\Delta H_{Sol}}{R} \quad \text{... (3.4.6)}$$

where T is the experimental temperature and R is gas constant. T_{hm} is the mean harmonic temperature which is given as

$$T_{hm} = \frac{n}{\sum_{i}^{n} \left(1/T \right)} \quad \text{... (3.4.7)}$$

where n is the number of experimental temperatures. In the present case, the T_{hm} value obtained is only 302.99 K. The slope of the plot of ln *x* versus ($1/T$-$1/T_{hm}$) gives the value of ΔH_{sol}.

The Gibbs energy change (ΔG_{sol}) for the solubility process was then evaluated from intercept of the above plot using following relation [35].

$$\Delta G_{sol} = -RT.\ intercept \quad \text{... (3.4.8)}$$

Table 3.4.1: The experimental solubility (x), calculated solubility (x_c) and relative deviation (RD) of MDT series in methanol at different temperatures.

Temp. K	x. 10^3	$x_c.10^3$	x. 10^3	$x_c.10^3$
	MDT 1		**MDT 6**	
293.15	5.0027	5.0309	2.9765	2.6330
298.15	5.0167	5.0460	3.3969	2.9391
303.15	5.0337	5.0612	3.8218	3.2808
308.15	5.0474	5.0764	4.2439	3.6622
313.15	5.0611	5.0916	4.6704	4.0880
	MDT 2		**MDT 7**	
293.15	2.1561	1.6945	2.5740	2.5814
298.15	2.2855	1.7814	2.5826	2.5918
303.15	2.4118	1.8727	2.5945	2.6022
308.15	2.5478	1.9687	2.6032	2.6126
313.15	2.6774	2.0696	2.6152	2.6231
	MDT 3		**MDT 8**	
293.15	4.4797	3.6202	2.7468	2.8062
298.15	4.6153	3.7118	3.0801	3.1012
303.15	4.7537	3.8057	3.4193	3.4273
308.15	4.8889	3.9021	3.7579	3.7877
313.15	5.0237	4.0008	4.0991	4.1860
	MDT 4		**MDT 9**	
293.15	1.3729	1.0733	12.722	12.567
298.15	1.4164	1.1005	12.777	12.617
303.15	1.4449	1.1283	12.829	12.668
308.15	1.5000	1.1569	12.884	12.719
313.15	1.5439	1.1862	12.941	12.770
	MDT 5		**MDT 10**	
293.15	3.3490	2.7182	5.5568	4.6902
298.15	3.3750	2.7318	5.7198	4.8089
303.15	3.4008	2.7455	5.7340	4.9306
308.15	3.4614	2.7593	6.0485	5.0554
313.15	3.4520	2.7731	6.2107	5.1834

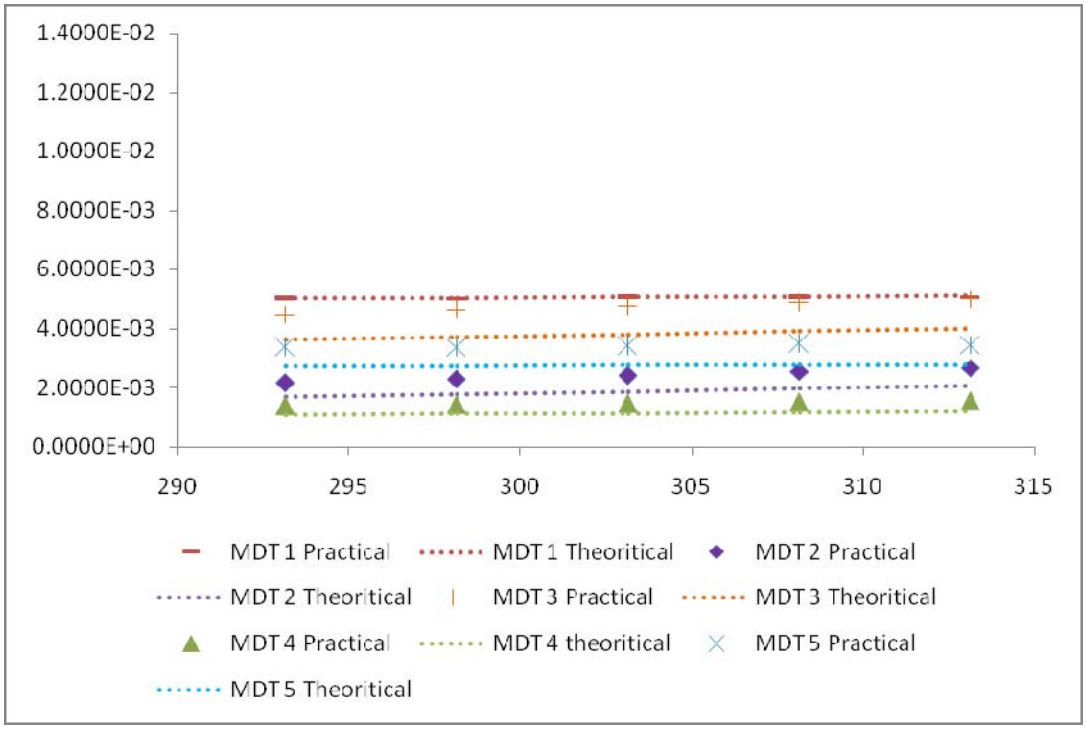
Table 3.4.2: The experimental solubility (x), calculated solubility (x_c) and relative deviation (RD) of MDT series in ethanol at different temperatures.

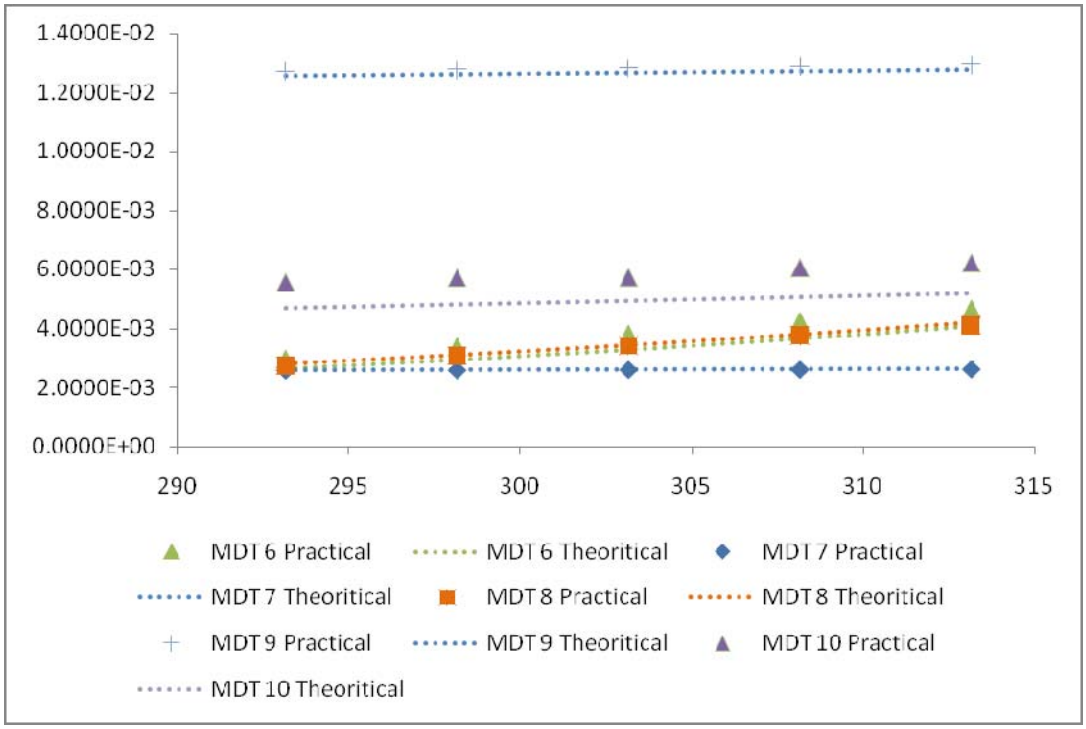
Temp. K	x. 10^3	$x_c.10^3$	x. 10^3	$x_c.10^3$
	MDT 1		**MDT 6**	
293.15	3.0494	2.9831	2.9892	2.7675
298.15	3.0648	2.9980	3.1606	2.9123
303.15	3.0842	3.0130	3.3346	3.0646
308.15	3.0984	3.0281	3.5005	3.2250
313.15	3.1167	3.0433	3.6690	3.3937
	MDT 2		**MDT 7**	
293.15	1.4552	1.4752	3.3474	2.8199
298.15	1.6219	1.6222	3.4640	2.9058
303.15	1.7898	1.7838	3.5815	2.9943
308.15	1.9589	1.9615	3.6999	3.0854
313.15	2.1291	2.1570	3.8192	3.1794
	MDT 3		**MDT 8**	
293.15	2.6002	2.1726	4.0836	4.0783
298.15	2.7047	2.2499	4.0900	4.0845
303.15	2.8096	2.3301	4.0965	4.0906
308.15	2.9151	2.4130	4.1026	4.0967
313.15	3.0209	2.4990	4.1306	4.1029
	MDT 4		**MDT 9**	
293.15	1.0794	0.9110	2.3117	2.0906
298.15	1.1596	0.9674	2.3637	2.1329
303.15	1.2391	1.0272	2.4163	2.1759
308.15	1.3124	1.0907	2.4694	2.2199
313.15	1.3907	1.1581	2.5231	2.2647
	MDT 5		**MDT 10**	
293.15	5.8600	5.7304	5.8880	4.9087
298.15	7.3140	6.7921	7.6133	6.0556
303.15	8.7677	8.0504	9.3768	7.4703
308.15	10.221	9.5419	11.190	9.2156
313.15	11.658	11.310	12.858	11.369

Table 3.4.3: Coefficient A and B of equation 2, Relative Average Deviation (ARD), and root Mean Square Deviation (rmsd) of MDT series in methanol and ethanol.

Compounds	A	B	10^8 rmsd	100 ARD
Methanol				
MDT 1	-5.469	0.0006	0.0209	0.0006
MDT 2	-9.313	0.01	7.3130	-0.0089
MDT 3	-7.088	0.005	22.369	-0.0177
MDT 4	-8.304	0.005	2.6778	-0.0050
MDT 5	-6.202	0.001	10.975	-0.0117
MDT 6	-12.39	0.022	6.4896	-0.0090
MDT 7	-6.195	0.0008	0.0017	0.0001
MDT 8	-11.74	0.02	0.0623	0.0007
MDT 9	-4.612	0.0008	0.6629	-0.0037
MDT 10	-6.829	0.005	21.339	-0.0179
Ethanol				
MDT 1	-6.109	0.001	0.1213	-0.0012
MDT 2	-12.09	0.019	0.0062	0.0001
MDT 3	-8.185	0.007	5.7206	-0.0081
MDT 4	-10.52	0.012	1.0675	-0.0031
MDT 5	-15.13	0.034	6.9337	-0.0102
MDT 6	-8.881	0.0102	1.6770	-0.0045
MDT 7	-7.631	0.006	8.6080	-0.0104
MDT 8	-5.591	0.0003	0.0045	-0.0002
MDT 9	-7.344	0.004	1.4450	-0.0040
MDT 10	-17.63	0.042	65.689	-0.0340

Figure 3.4.1: Plot of ln x vs T/K for MDT-1 methanol.





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

$$\Delta S_{sol} = \frac{\Delta H_{sol} - \Delta G_{sol}}{T_{hm}} \quad \text{... (3.4.9)}$$

All these thermodynamic parameters are given in Table 3.4.4.

It is evident from Table 3.4.4 that for all the compounds ΔH_{sol}, ΔG_{sol} and ΔS_{sol} values are positive. When stronger bonds are broken and weaker bonds are formed, energy is consumed. So, ΔH_{sol} becomes positive [36]. This indicates endothermic dissolution of compounds where the enthalpy term contributes to an unfavourable positive value of ΔG_{sol}. Thus, positive value of ΔG_{sol} indicates that the dissolution process is not spontaneous [36, 37]. The negative value of entropy indicates less randomness in solutions [36].

Table 3.4.4: The thermodynamic function of MDT series in methanol and ethanol at 302.99 K (T_{hm}).

Comp. code	ΔH_{sol} cal.mol^{-1}	ΔG_{sol} kcal.mol^{-1}	ΔS_{sol} cal.mol^{-1}.K^{-1}	ΔH_{sol} cal.mol^{-1}	ΔG_{sol} kcal.mol^{-1}	ΔS_{sol} cal.mol^{-1}.K^{-1}
	Methanol			Ethanol		
MDT-1	0.4470	14.8302	-47.4715	0.8234	14.8302	-46.2293
MDT-2	8.2716	11.2998	-9.9946	14.5079	11.2998	10.5884
MDT-3	4.3782	14.9547	-34.9077	5.7225	14.9547	-30.4706
MDT-4	4.4605	15.1652	-35.3311	9.6276	15.1652	-18.2769
MDT-5	1.1565	11.7306	-34.8997	26.1558	11.7306	47.6106
MDT-6	17.1684	11.6039	18.3658	7.8177	11.6039	-12.4963
MDT-7	0.6058	12.4475	-39.0835	5.0308	12.4475	-24.4787
MDT-8	15.2645	12.5825	8.8520	0.2333	12.5825	-40.7585
MDT-9	0.6463	12.8354	-40.2299	3.3762	12.8354	-31.2199
MDT-10	4.2493	12.4669	-27.1221	32.1004	12.4669	64.8002

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INTRODUCTION

Thermal analysis has been proved to be a key method in the study and characterisation of various materials and finds wide applications in industrial and research fields. In thermal analysis, specific physical properties of any material are measured as a function of time or temperature. By these measurements, one can calculate transition temperature, weight loss, energy of transition, dimensional changes, modulus changes viscoelectric properties etc.

There are various methods of thermal analysis. Some of them are differential Scanning Calorimetry (DSC), Differential Thermal Analysis (DTA), Thermo Gravimetric Analysis (TGA), Evolved Gas Detection (EGD), Evolved Gas Analysis (EGA) etc.

Interest in thermogravimetry has increased in recent years because of the commercial availability of automatic, continuously recording thermo-balances. In dynamic thermogravimetry, a sample is subjected to conditions of continuous increase in temperature, usually linear with time, whereas in isothermal or static thermogravimetry the sample is maintained at a constant temperature for a period of time [(1)]. For present study, dynamic thermogravimetry has been applied.

The Differential Scanning Calorimeter records the difference in electric power required to keep a test sample and reference material at equal temperatures as they are heated or cooled at constant rate. The power difference shows up during physical or chemical transitions in the sample and is equivalent to the thermal energy absorbed or released during the transition [(1)].

Various researchers have regularly studied the thermal behaviour of various compounds like rubber [(2)], reinforced polymer composite [(3)], monomers [(4)],some nano composites [(5)], sugarcane [(6)], starch blends [(7)], coal [(8)], alumina, titania and zirconia membranes [(9)], semi-conducting composites[(10)], some catalysts [(11)], crystals[(12, 13)], alloys[(14)], drugs [(15-18)], pharma materials [(19-23)], dyes[(24, 25)], fertilizers [(26)], inorganic [(27-29)], organic compounds [(30-32)] etc. In medical field, Thermal analysis of some human body materials have also been studied [(33)].

Blasi et al have compared the devolatilization kinetics of softwood and hardwood [34] by TGA. Thermal stability of some Fluorene-Based conjugated polymers has been studied by Zena et al [35]. Deterioration of historical parchments can be studied by various thermal analysis techniques [36]. Horowitz and Metzgera have given new mathematical interpretation of thermo gravimetric traces to determine the kinetic parameters of pyrolysis reactions which is also applicable to polymeric systems [37]. In our laboratory, thermal studies of various bioactive heterocyclic compounds have been done [38].

In the present section, thermal properties of some tetrahydropyrimidines have been studied by TGA and DSC methods.

Theory

Various kinetic parameters can be calculated from thermo grams of particular compound by several methods. All these methods can be applied by assuming that thermal and diffusion barriers affects least because small quantity of material is used for analysis. The shape of any TGA curve indicates the nature of apparatus and the way in which it is used. Arrhenius equation is valid in all these methods. .

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

$$dC/dt = K f(C) \quad \text{... (3.6.1)}$$

where C represents 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:

$$K = A e^{-E/RT} \quad \text{... (3.6.2)}$$

The degree of concentration C can be given by:

$$C = 1-(W/W_0) \quad \text{... (3.6.3)}$$

where W_0 and W are the initial weight of compound at t=0 and weight at any time t. Equation (3.6.3) can be written as:

$$(W/W_0) = (1-C) \quad \text{... (3.6.4)}$$

W/ W_0 is known as residual weight fraction. Thus, the rate of conversion is,

$$dC/dt = - (1/W_0) (dW/dt) \quad \text{... (3.6.5)}$$

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

$$f(C) = (1-C)^n \quad \text{... (3.6.6)}$$

where n is the order of the reaction.

Substituting the values from equation (3.6.2) and (3.6.6) in equation (3.6.1) gives:

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

or $$dC/dt = (A/\beta)\, e^{-E/RT} (1-C)^n \quad \text{... (3.6.7)}$$

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 [38] and Anderson-Freeman Method [39]:

From the thermogram obtained at a single heating rate, the energy of activation E and order of reaction n can be evaluated using the following Freeman-Carroll equation:

$$\ln (dC/dt)/\ln (1-C) = n - E/R\, [(1/T/(\Delta \ln(1-C)] \quad \text{... (3.6.8)}$$

A plot of ln (dC/dt)/ln (1-C) against (1/T)/(Δln(1-C)) gives a straight line with a slope equal to -E/R and the intercept is equal to n.

Using equation (8), the following equation was derived by Anderson and Freeman:

$$(\Delta \ln [dC/dt]) = n\, (\Delta \ln (1-C)) - E/R\, \Delta(1/T) \quad \text{... (3.6.9)}$$

The plot of (Δln[dC/dt]) against (Δln(1-C)) for equal intervals of Δ(1/T) gives a straight line with slope equal to n and intercept -E/RΔ(1/T).

2. Sharp-Wentworth method [40]:

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

$$\log [(dC/dt)/(1-C)] = \log (A/\beta) - (E/2.303R).(1/T) \quad \text{... (3.6.10)}$$

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/β). Where β is heating rate.

3. Chatterjee Method [41]:

In this method, order of reaction can be calculated by the equation:

$$n = [\log(dW/dt)_1 - \log(dW/dt)_2] / (\log W_1 - \log W_2) \quad \text{... (3.6.11)}$$

where W_1 and W_2 are the sample weights. This equation was given be Chatterjee.

4. Horowitz and Metzger method [37]:

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

$$\ln [\ln(1-C)^{-1}] = (E/RT_s^2)\,\theta \quad \text{... (3.6.12)}$$

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:

$$\ln E - \ln (RT_s^2) = \ln A - \ln\beta - E/RT_s \quad \text{... (3.6.13)}$$

$$A = (k_b T / h)\, e^{\Delta S/R} \quad \text{... (3.6.14)}$$

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

EXPERIMENTAL

Thermo gravimetric analysis (TGA) measurements were made on the instrument “Perkin Elmer Thermal Analysis” in nitrogen atmosphere. The heating rate was 20^0C/min for all the synthesized compounds.

RESULTS AND DISCUSSION

The TGA thermograms of MDT-1 and MDT-2 are given in Figure 3.6.1. From thermograms of all the studied compounds, various thermal properties such as initial decomposition temperature, the decomposition temperature range, the maximum degradation, the percentage weight loss etc were determined and are reported in Table 1.

For all the compounds, degradation is single step process. Further, almost all the compounds, degration temperature is less than 200 ^{0}C. Out of ten compounds, MDT-10 is most unstable which is followed by MDT-5. MDT-7 is the most stable compound which is followed by MDT-1. All the studied compounds have the same central moiety but substitution groups are different. MDT-10 contains cinnamaldehyde as substitution to aromatic ring. Thus, cinnamaldehyde makes the compound unstable whereas chloro group at meta position (as in MDT-5) makes it a little bit less stable. However, the presence of nitro group at meta position increases the stability as is the case for MDT-7. The variation in the trend of thermal decomposition might be interpreted by taking into account some intermolecular interactions (structural as well as electronic) and also because of several experimental factors.

Further, from the thermograms, various kinetic parameters, such as order of the degradation (n), energy of activation (E), frequency factor (A) and entropy change (ΔS) have also been calculated and are reported in Table 3.6.2. It is evident that order of reaction is quite different in each studied compound. The order of reaction varies from 0.21 to 7.54. The value is minimum for MDt-2 and maximum for MDt-4.

The energy of activation (E) is highest for MDT-5 containing chloro group at meta position and minimum for MDT-8 which is without any substitution group. The frequency factor (A) is also highest for MDT-5 but minimum for MDT-10.

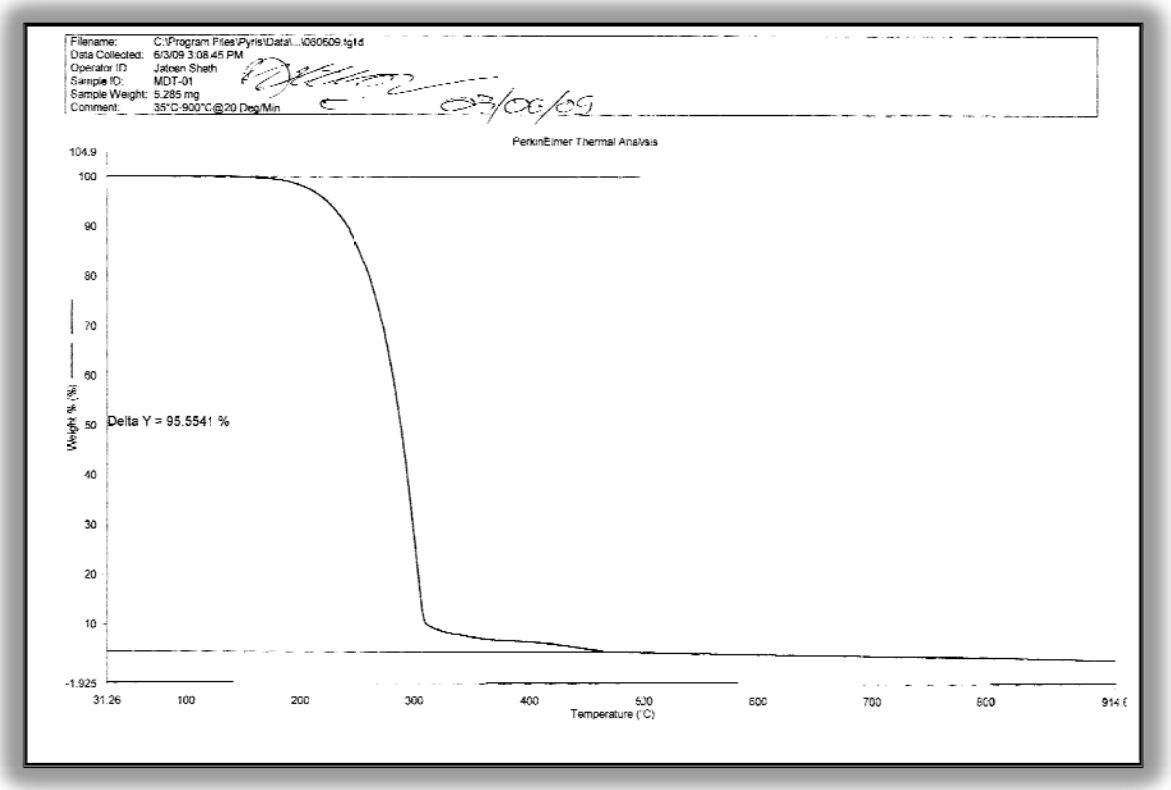
Further, change in entropy (ΔS^0) for all these reactions were also calculated by equation (14) and are reported in Tables 3.6.2. The entropy change (ΔS^0) is found to be both positive and negative. For MDT-1, MDT-2, MDT-4, MDT-5, MDT-6 and MDT-9, the values are positive whereas for others,

ΔS^0 values are negative. The positive value of ΔS^0 indicates that the transition state is less ordered than the original compound whereas negative value of ΔS^0 corresponds to an increase in the order of transition state than the reactants [42].

Further, DSC of MDT-1 and MDT-2 are shown in Figure 2. From DSC, melting points of all the compounds are determined and are given in Table 1 along with melting points determined by open capillary method. There is good agreement between the values evaluated from DSC and those determined by open capillary method.

Thus, the degradation in the studied compounds is single step process with different order of reaction. Further, thermal stability depends upon the type of substituent present.

Figure 3.6.1: The TGA graphs of MDT 1 and MDT 2.



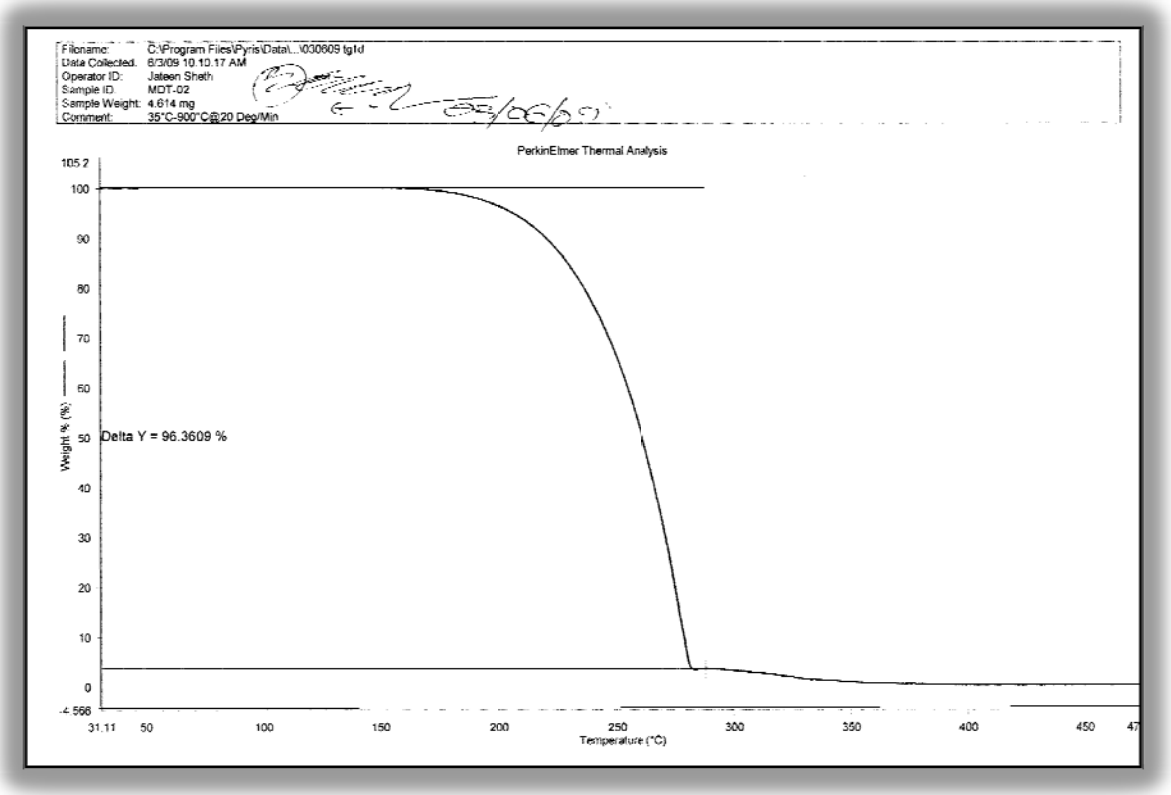


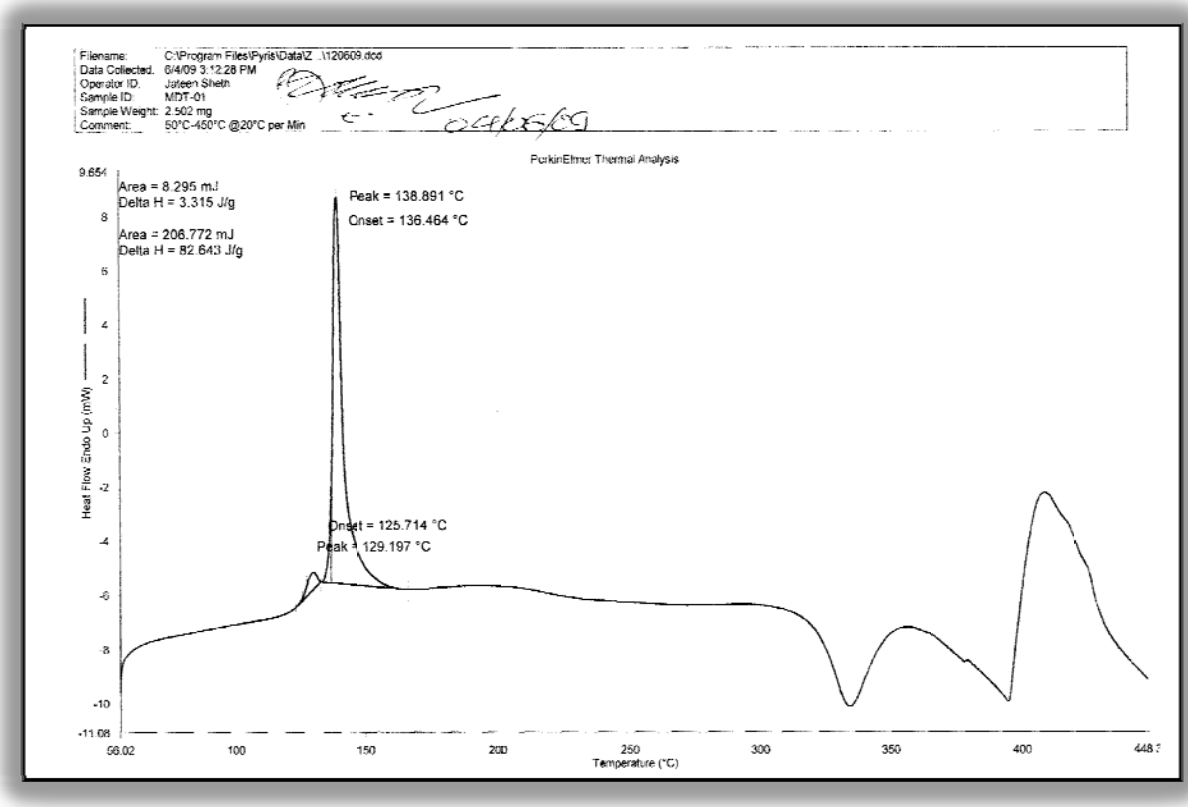
Table 3.6.1: TGA data for MDT 1-10.

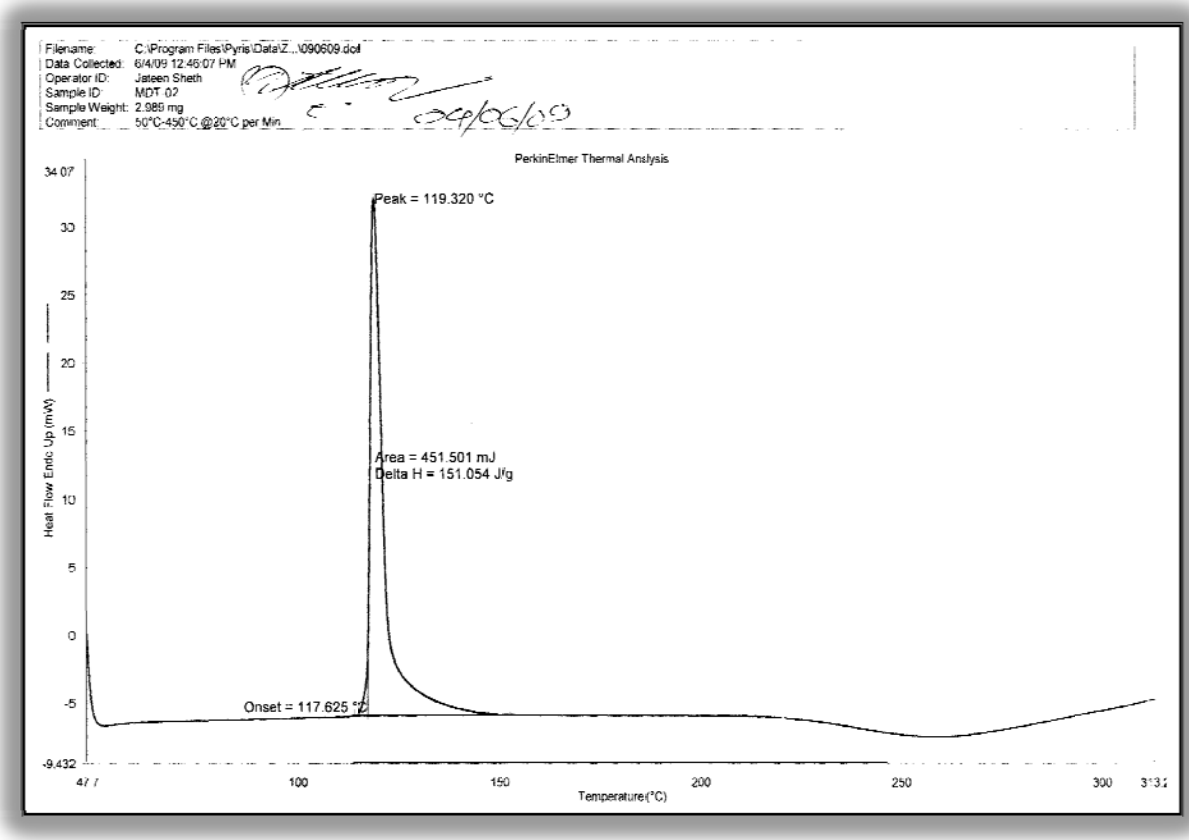
Compound Code	Amount (mg.)	Initial Decomp. Temp. (°C)	Decomp. Range (°C)	% Wt. loss	Residual wt. loss (mg.)	Max. Degradation Temp. (°C)	Transition	DSC Temp. (°C)	Open capillary M.P. °C
MDT 1	5.285	168.52	168.52-310.91	95.55	5.0500	310.91	Endo	138.891	140
MDT 2	4.614	132.72	132.72-280.91	96.36	4.4461	280.91	Endo	119.320	118
MDT 3	0.912	159.43	159.43-281.3	94.76	0.8642	281.3	Endo	190.574	190
MDT 4	6.505	99.87	99.87-200.00	97.24	6.3255	200.00	Endo	167.132	168
MDT 5	4.009	83.49	83.49-161.27	97.50	3.9088	161.27	Endo	156.850	157
MDT 6	3.401	125.00	125.00-234.09	99.34	3.3786	234.09	Endo	130.874	130
MDT 7	2.103	169.64	169.64-287.50	64.55	1.3575	287.50	Endo	98.679	101
MDT 8	2.734	123.33	123.33-233.33	98.46	2.6919	233.33	Endo	89.816	90
MDT 9	2.105	96.88	96.88-205.16	99.07	2.0855	205.16	Endo	79.863	81
MDT 10	2.656	78.19	78.19-418.18	64.48	1.7125	418.18	Endo	162.168	164

Table 3.6.2: The kinetic parameters for MDT 1-10 for 1st step.

Comp. code	n	E (kJ)	A (Sec^{-1})	Δs^o (J^{-1})
MDT 1	2.65	392.5162	8.33×10^{34}	571.16
MDT 2	0.22	598.6519	3.05×10^{56}	984.42
MDT 3	2.84	16.03654	9.60×10^{-01}	-97.25
MDT 4	7.73	620.6761	5.25×10^{68}	1219.97
MDT 5	0.21	681.7723	1.95×10^{82}	1480.47
MDT 6	0.27	564.66634	1.76×10^{58}	1018.86
MDT 7	5.87	28.788971	2.50×10^{01}	-70.24
MDT 8	2.28	7.7862273	1.09×10^{-01}	-114.55
MDT 9	1.58	29.586866	1.25×10^{02}	-55.54
MDT 10	7.54	8.1166256	3.96×10^{-02}	-125.60

Figure 3.6.2: The DSC graphs of MDT 1 and MDT 2.





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INTRODUCTION

The acidic or basic strength of material can be highlighted by the dissociation constants. They are also known as acidity constant, ionization constant or formation constant. The dissociation or ionization constant is determined by determining one of the species, at equilibrium. The activity or concentration of the other species can be calculated from the amount of the acid or base initially introduced and the stoichiometry of the acid base equilibrium.

Various methods have been developed for the measurement of dissociation constants, such as potentiometry including pH metry [(1)] spectrophotometry [(2)], conductometry [(3)], solubility measurements [(4)], cryoscopy [(5)], measurements of the rates of acid catalyzed hydrolysis of esters [(6)], measurement of the relative distribution of an acid between two immiscible solvents [(7)], dissociation constant by capillary electrophoresis[(8)], NMR methods[(9)], feedback-based flow ratiometry [(10)], interfacial fourier transform infrared spectroscopy [(11)] .

Spectrophotometry is an ideal method when a substance is not soluble enough for potentiometry or when its pK_a value is particularly low or high [(12-15)]. Various saperation methods are also useful for the determination of dissociation constants [(16)]. Bai and Zhang have evaluated the dissociation constants of naphthols in β -cyclodextrin by fluorescence method [(17)]. Hansen and Hafliger have determined dissociation constant of a weak acid using a dissolution rate method [(18)]. Nasser and Mohammad have predicted the acidic dissociation constant of some organic compounds using linear and nonlinear QSPR methods [(19)]. Al-Alwan et al. have studied the effects of medium on the dissociation constants of malic and tartaric acids [(20).]

Potentiometry is mostly used for the determination of dissociation constants of acids because it is economical in time. Further, it can be used for acids of pK_a range from 2 to 11 units [(21)]. For this measurement, glass and calomel electrodes have been used and carbonate free potassium hydroxide is the best alkali to use as a titrant. But, for very low pK_a values, this method does not give accurate results. In such cases, more sensitive instruments should be

used. The activity of the hydrogen ions is measured directly by pH metry. So, one can get reliable values of dissociation constant by this method. However, there are certain difficulties in mixed aqueous media and nonaqueous media.

There are many applications of dissociation constants. The nature of the functional groups can be determined by simple comparison of acidity or dissociation constant of the unknown compound with those of known compounds. The dissociation or formation constant also provide useful informations about tautomeric equilibria [22, 23], solvent-solute interactions [24] etc. Kinetics study of the dissociation of weak acids and bases is possible by polarography and voltammetry technique [25]. The distribution coefficients and dissociation constants of a series of barbituric acid derivatives have been reported by Leyda et al. [26] Funasaki [27] reported the dissociation constants of acid-base indicators on the micellar surface of dodecyldimethylamine oxide. Levitt [28] studied the determination of the dissociation constant and limiting equivalent conductance of a weak electrolyte from conductance measurements on the weak electrolyte. Further, in last few years dissociation constant of many substances [29-35] have been studied by various workers.

In the present work, the dissociation constant of tetrahydropyrimidine have studied in dimethyl formamide – water system at 303.15 K.

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 Elico pH meter (Model No. Li 610) was used for the pH determination. PPC (CL 51) Combined electrode was used as electrode. Before operation, the electrode was immersed in 0.1 M HCl for twenty minutes. Then, it was washed thoroughly with distilled water.

Before measurement, the pH meter was calibrated with buffer solution of known pH.

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 (0.1M) + 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 DMF : water ratio 60:40 (v/v).

The above mentioned solutions were allowed to attain a constant temperature (303.15 K) and then titrated against standard NaOH solution (0.5 M) under an inert atmosphere of nitrogen.

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:

$$TK_j^H = \frac{\left[LH_j\right]}{\left\{\left[LH_{j-1}\right]\left[H\right]\right\}} \quad \text{... (3.7.1)}$$

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:

$$T\beta_j^H = \frac{\left[LH_j\right]}{\left[L\right]\left[H\right]^j} \quad \text{... (3.7.2)}$$

and it refers to the reaction:

$$L + JH \leftrightarrow LH_j$$

The stoichiometric proton-ligand stability constant is given by:

$$K_j^H = \frac{\left[LH_j\right]}{\left\{\left[LH_{j-1}\right]\left[H\right]\right\}} \quad \text{... (3.7.3)}$$

and

$$\beta_j^H = \frac{\left[LH_j\right]}{\left[L\right]\left[H\right]^j} \quad \text{... (3.7.4)}$$

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

$$\bar{n}_H = \{K_1^H [H] + 2K_1^H K_2^H [H]^2 + ...JK_1^H K_2^H [H] ... K_j^H [H]^j\} / \{1 + K_1^H [H] + K_1^H K_2^H [H]^2.....K_1^H K_2^H.....K_j^H [H]^j \quad ... (3.7.5)$$

From equation (3.7.4), we can write

$$\bar{n}_H = \frac{\sum_{j=1}^{\eta} j\beta_j^H [H]^j}{\sum_{j=1}^{\eta} \beta_j^H [H]^j} \quad : \left(\beta_0^H = 1\right) \qquad \ldots (3.7.6)$$

Equation (3.7.6) is called Bjerrum formation function of the system.

The determination of dissociation or formation 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, by potentiometer, 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 [37] 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. In this method, the pH-meter is standardized using an aqueous buffer. The pH (B) 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 (B) 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 [38] gave a relation between the glass electrode reading B 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:

$$-\log\left[H^{+}\right] = pH + \log f + \log U_H^0 \qquad \text{... (3.7.7)}$$

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 (3.7.7), provided that correction factor for the appropriate solvent, salt medium, and temperature, has been determined.

Equation (3.7.7) can be written as:

$$1/anti\log pH = [H^+]\, fU_H^0 \qquad \text{... (3.7.8)}$$

$$\therefore \left[H^+\right] = \frac{1}{\left[anti\log pH\right]\left[\, fU_H^0\,\right]} \qquad \text{... (3.7.9)}$$

Substituting for $[H^+]$ in equation (3.7.5) we get,

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

$/(1+K_1^H/f\ U^0_H))[1/\text{antilog B}]$+..+ $((K_1^HK_2^H...K_J^H)/(f\ U^0_H)J)[1/\text{antilogpH}]$ ...(3.7.10)

$$K_j^H = fU_H^0.pK_j^H \qquad \text{... (3.7.11)}$$

$$\beta_j^H = fU_H^0.p\beta_j^H \qquad \text{... (3.7.12)}$$

The proton-ligand 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:

$$\log K_1 = \left(\bar{n}_H\right)_{0.5} \qquad \text{… (3.7.13)}$$

$$\log K_2 = \left(\bar{n}_H\right)_{1.5} \qquad \text{... (3.7.14)}$$

2. Midpoint slope method:

For H_2L type ligands:

$$K_1K_2[L]^2 = 1$$

or $$\log K_1K_2 = 2pL_1 \qquad \text{... (3.7.15)}$$

From the measured mid-point slope, D, the ratio K_1/K_2 can be calculated by eq. (3.7.16):

$$D = \frac{-4.606}{\left(2 + \sqrt{\left(K_1 / K_2\right)}\right)} \quad \text{... (3.7.16)}$$

The individual values of K_1 and K_2 were obtained by using K_1/K_2 values and relation (3.7.15).

RESULTS AND DISCUSSION

The titration curves obtained in the above two titrations are designated as the acid titration curve and ligand or reagent titration curve respectively. The titration curves for MDT 1 and MDT 2 are shown in Figure 3.7.1.

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

$$\overline{n_H} = Y - \left\{\left(V''-V'\right)\left(N^0+E^0\right)\right\} \Big/ \left\{\left(V^0+V'\right)T_L^0\right\} \quad \text{... (3.7.17)}$$

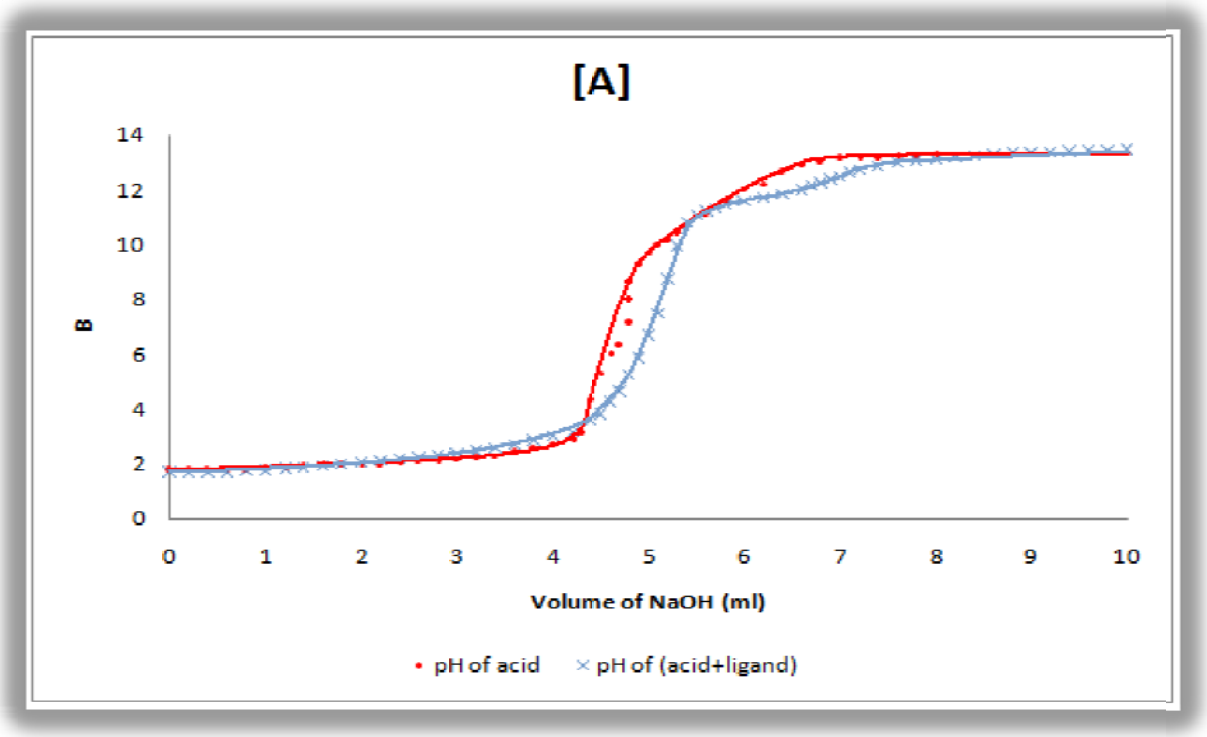
where *Y* is the number of displaceable protons per ligand molecule. *V'* and *V"* are the volume of alkali required at the same pH for both acid and ligand titration curves respectively. V^0 is the initial volume of the test solution. N^0, E^0 and T^0_L are the initial concentration of the alkali, acid and ligand respectively. For MDT 1 and MDT 3, value of Y is 2. Whereas for other compounds, Y is equal to one.

The calculated values of $\overline{n_H}$ for all the studied compounds are given in Table 3.7.1. It is evident from table that $\overline{n_H}$ values are in between zero and one for all the system except MDT 1 and MDT 3 for which, the values of n_H extend over the range from 0 to 2 indicating two dissociation steps. The pK_1^H values at $\overline{n_H}$ = 0.5 were evaluated for each systems except MDT 1 and MDT 3. For these two compounds, the pK_1^H and pK_2^H were calculated at $\overline{n_H}$ = 0.5 and $\overline{n_H}$ = 1.5 respectively. The general plots for the variation of $\overline{n_H}$ with B of MDT 1 and MDT 2 are given in Figure 3.7.2.

Further, the $\log \bar{n}_H \Big/ \left(1-\bar{n}_H\right)$ values are plotted against B as shown in Figure 3.7.3. The plots are straight lines from which $\log pK_1^H$ values were calculated at several B values, by the following equation.

$$\log pK_1^H = pH + \log \bar{n}_H \Big/ \left(1-\bar{n}_H\right) \quad \text{… (3.7.18)}$$

Figure 3.7.1: The plot of pH (B) against volume of NaOH for MDT 1 and MDT 2 in DMF at 303.15 K.



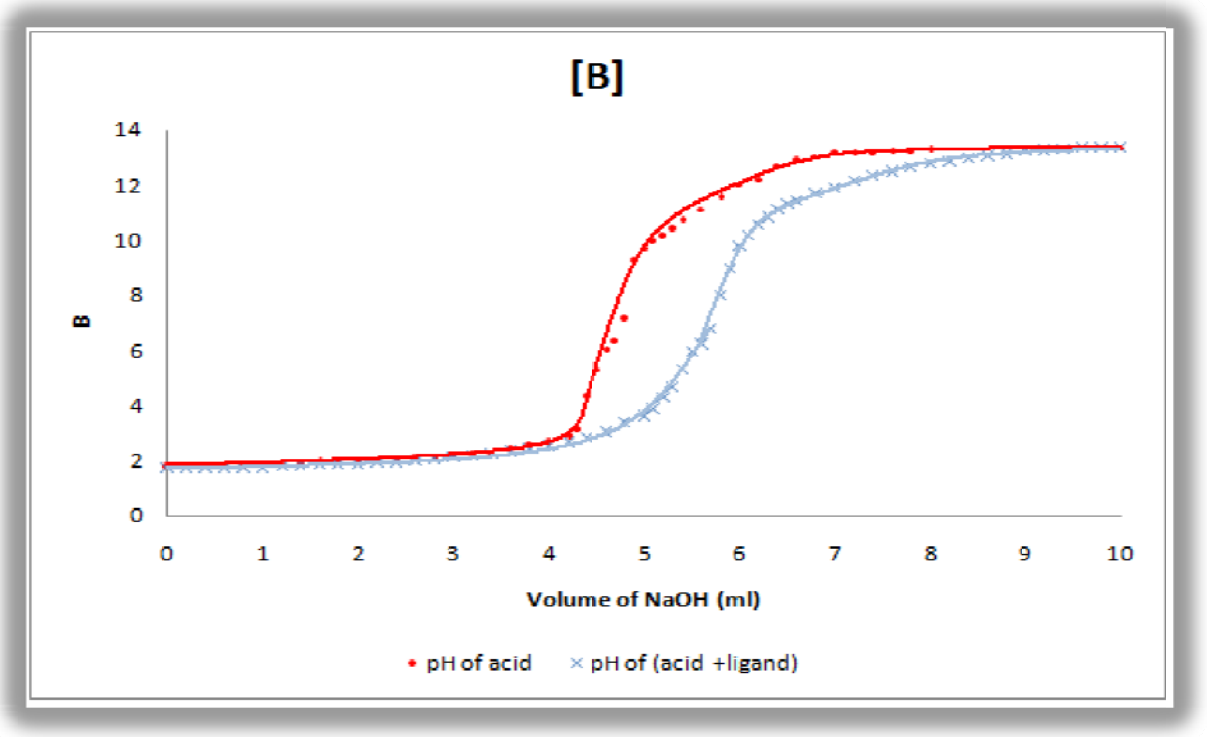


Table 3.7.1: The pH (B), n_H, log pK_1^H and other terms for MDT series in DMF at 303.15 K.

B	V'	V''	V''-V'	n_H	log $n_H/(1-n_H)$	log pK_1^H
MDT 1						
5.40	5.7286	5.8227	0.0941	1.7736	1.0994	6.2941
5.45	5.7526	5.8947	0.1421	1.6584	0.6430	6.0861
5.50	5.7765	5.9667	0.1902	1.5430	0.4121	5.9784
5.55	5.7989	6.0468	0.2479	1.4046	0.2478	5.8727
5.60	5.8213	6.1269	0.3056	1.2664	0.1398	5.7871
5.65	5.8426	6.2039	0.3613	1.1331	0.0626	5.7163
5.70	5.8638	6.2808	0.417	0.9999	-0.0001	5.6499
5.75	5.8851	6.3577	0.4726	0.8670	-0.0547	5.5838
5.80	5.9064	6.4346	0.5282	0.7343	-0.1060	5.5136
11.10	4.4780	5.0700	0.5920	0.5359	-0.1850	10.6272
11.20	4.4880	5.0867	0.5987	0.5197	-0.1920	10.7262
11.30	4.4980	5.1029	0.6049	0.5047	-0.1986	10.8251
11.40	4.5125	5.1190	0.6065	0.5012	-0.2001	10.9243
11.50	4.5281	5.1352	0.6071	0.5003	-0.2006	11.0232
11.60	4.5437	5.1513	0.6076	0.4995	-0.2009	11.1223
11.70	4.5594	5.1674	0.6080	0.4991	-0.2011	11.2218
11.80	4.575	5.1835	0.6085	0.4984	-0.2014	11.3210
MDT 2						
4.90	4.4580	4.6406	0.1826	0.5482	-0.5778	4.9840
5.00	4.4680	4.6563	0.1883	0.5342	-0.5846	5.0595
5.10	4.4780	4.6719	0.1939	0.5205	-0.5914	5.1356
5.20	4.4880	4.6875	0.1995	0.5067	-0.5985	5.2117
5.30	4.4980	4.7030	0.2050	0.4932	-0.6057	5.2882
5.40	4.5125	4.7212	0.2087	0.4843	-0.6106	5.3726
5.50	4.5281	4.7435	0.2134	0.4729	-0.6170	5.4528
MDT 3						
5.40	4.5125	4.2593	-0.2532	1.3743	0.2207	5.7417
5.50	4.5281	4.2963	-0.2318	1.4274	0.2699	5.8967
5.60	4.5437	4.3265	-0.2172	1.4636	0.3084	6.0360
5.70	4.5594	4.3559	-0.2035	1.4976	0.3492	6.1744
5.80	4.5750	4.3853	-0.1897	1.5319	0.3957	6.3149
5.90	4.5906	4.4143	-0.1763	1.5651	0.4473	6.4561
6.00	4.6121	4.4429	-0.1692	1.5828	0.4780	6.5791
12.05	6.0316	5.5437	-0.4879	0.8341	-0.0676	11.9045
12.10	6.0842	5.5507	-0.5335	0.7266	-0.1089	11.8563
12.15	6.1368	5.5577	-0.5791	0.6193	-0.1507	11.8018
12.20	6.1895	5.5648	-0.6247	0.5123	-0.1953	11.7370
12.25	6.2200	5.5718	-0.6482	0.4573	-0.2202	11.7220
12.30	6.2450	5.5789	-0.6661	0.4156	-0.2407	11.7188
12.35	6.2700	5.5859	-0.6841	0.3737	-0.2629	11.7113

Contd...

...Contd

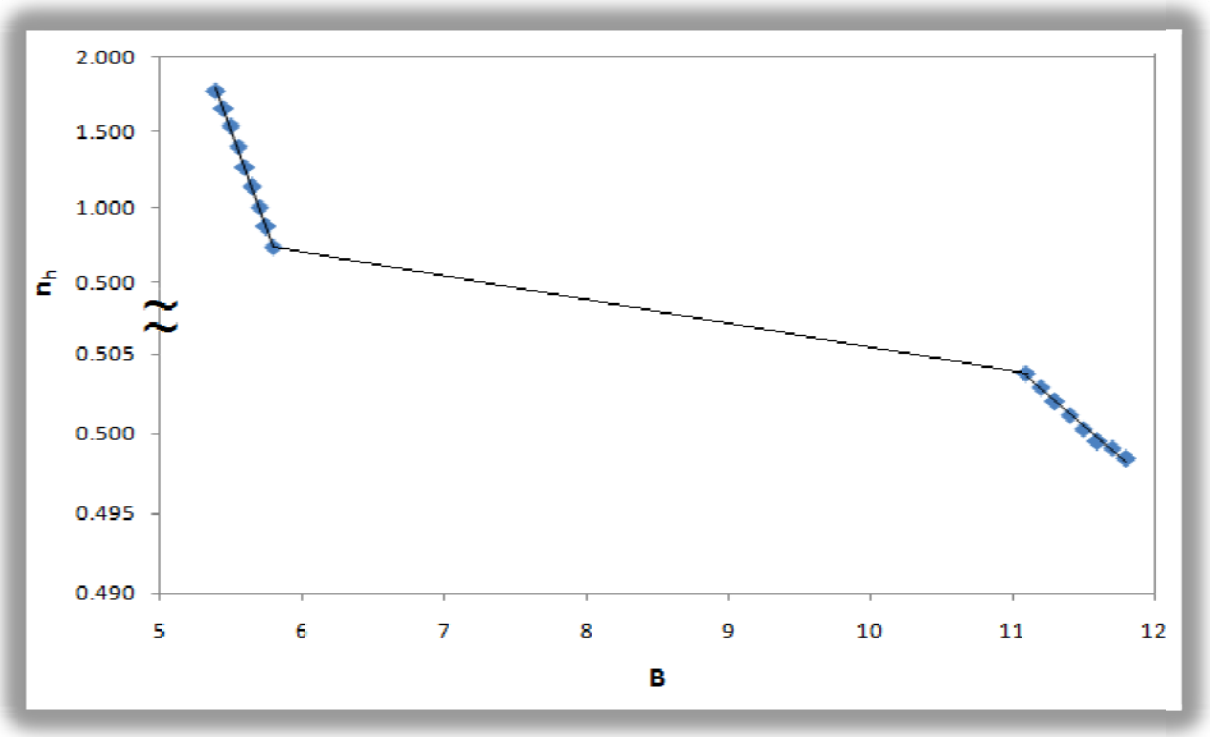
B	V'	V''	V''-V'	n_H	log $n_H/(1-n_H)$	log pK_1^H
MDT 4						
4.70	4.4380	4.5311	0.0931	0.7695	-0.4937	5.2236
4.80	4.4480	4.5639	0.1159	0.7132	-0.5118	5.1956
4.90	4.4580	4.5967	0.1387	0.6568	-0.5319	5.1819
5.00	4.4680	4.6474	0.1794	0.5562	-0.5741	5.0981
5.10	4.4780	4.7000	0.222	0.4510	-0.6299	5.0145
5.20	4.4880	4.7526	0.2646	0.3458	-0.7050	4.9230
5.30	4.4980	4.8071	0.3091	0.2359	-0.8209	4.7896
MDT 5						
5.00	4.4680	5.0034	0.5354	0.6756	-0.5250	5.3186
5.10	4.4780	5.0379	0.5599	0.6153	-0.5483	5.3040
5.20	4.4880	5.0724	0.5844	0.5550	-0.5746	5.2960
5.30	4.4980	5.1069	0.6089	0.4948	-0.6049	5.2909
5.40	4.5125	5.1414	0.6289	0.4459	-0.6331	5.3056
5.50	4.5281	5.1759	0.6478	0.3997	-0.6634	5.3234
5.60	4.5437	5.2273	0.6836	0.3119	-0.7354	5.2563
MDT 6						
5.20	4.4880	4.6550	0.1670	0.5871	-0.5602	5.3528
5.30	4.4980	4.6800	0.1820	0.5501	-0.5769	5.3873
5.40	4.5125	4.7050	0.1925	0.5243	-0.5895	5.4422
5.50	4.5281	4.7263	0.1982	0.5104	-0.5966	5.5180
5.60	4.5437	4.7467	0.2030	0.4987	-0.6028	5.5977
5.70	4.5594	4.7671	0.2077	0.4873	-0.6090	5.6779
5.80	4.5750	4.7876	0.2126	0.4754	-0.6156	5.7572
MDT 7						
5.80	4.3817	4.4963	0.1146	0.7160	-0.5109	6.2015
5.90	4.3900	4.5333	0.1433	0.6449	-0.5365	6.1591
6.00	4.3983	4.5704	0.1721	0.5736	-0.5661	6.1288
6.10	4.4080	4.6039	0.1959	0.5147	-0.5943	6.1256
6.20	4.4180	4.6235	0.2055	0.4911	-0.6069	6.1845
6.30	4.4280	4.6431	0.2151	0.4674	-0.6202	6.2433
6.40	4.4380	4.6627	0.2247	0.4438	-0.6343	6.3019
MDT 8						
6.10	4.3817	4.4990	0.1173	0.7093	-0.5132	6.4873
6.20	4.3900	4.5382	0.1482	0.6328	-0.5412	6.4363
6.30	4.3983	4.5722	0.1739	0.5692	-0.5681	6.4209
6.40	4.4080	4.6040	0.1960	0.5145	-0.5945	6.4252
6.50	4.4180	4.6357	0.2177	0.4609	-0.6240	6.4319
6.60	4.4280	4.6675	0.2395	0.4070	-0.6583	6.4366
6.70	4.4380	4.6992	0.2612	0.3534	-0.6986	6.4377
6.80	4.4480	4.7310	0.2830	0.2996	-0.7473	6.4313

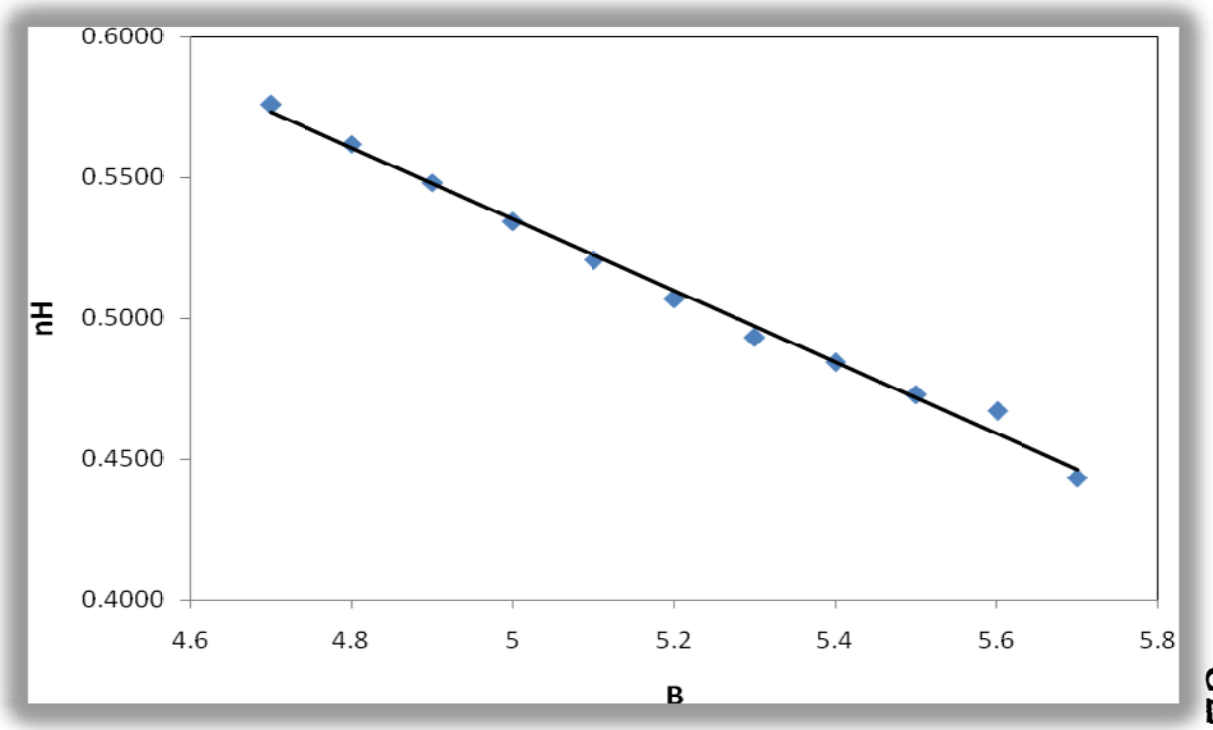
Contd...

...Contd

B	V'	V''	V''-V'	n_H	log $n_H/(1-n_H)$	log pK_1^H
MDT 9						
6.10	4.3817	4.5147	0.133	0.6704	-0.5269	6.4083
6.20	4.3900	4.5486	0.1586	0.6070	-0.5517	6.3888
6.30	4.3983	4.5825	0.1842	0.5436	-0.5800	6.3760
6.40	4.4080	4.6164	0.2084	0.4838	-0.6109	6.3718
6.50	4.4180	4.6494	0.2314	0.4269	-0.6450	6.3722
6.60	4.4280	4.6816	0.2536	0.3721	-0.6838	6.3728
6.70	4.4380	4.7139	0.2759	0.3170	-0.7305	6.3667
MDT 10						
6.00	4.3733	4.5067	0.1334	0.6693	-0.5273	6.3062
6.10	4.3817	4.5400	0.1583	0.6077	-0.5514	6.2900
6.20	4.3900	4.5733	0.1833	0.5458	-0.5790	6.2797
6.30	4.3983	4.6067	0.2084	0.4837	-0.6109	6.2716
6.40	4.4080	4.6400	0.2320	0.4253	-0.6461	6.2693
6.50	4.4180	4.6733	0.2553	0.3678	-0.6871	6.2647
6.60	4.4280	4.7048	0.2768	0.3147	-0.7327	6.2619

Figure 3.7.2: The plot of n_H against B for MDT 1 and MDT 2 in DMF at 303.15K.





The average pK_1^H value is also reported in Table 3.7.1 for all compounds. It is evident from tables that these pK_1^H values are in agreement with that obtained by half-integral method *i. e*., at $\overline{n_H}$ = 0.5.

For MDT 1 and MDT 3, the proton-ligand constants were calculated by solving equation 3.7.1. For all the points below $\overline{n_H}$ =1, the following equation was used

$$log\ pK_1^H = pH + log\,\bar{n}_H/(\bar{n}_H - 1) \quad \ldots (3.7.19)$$

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

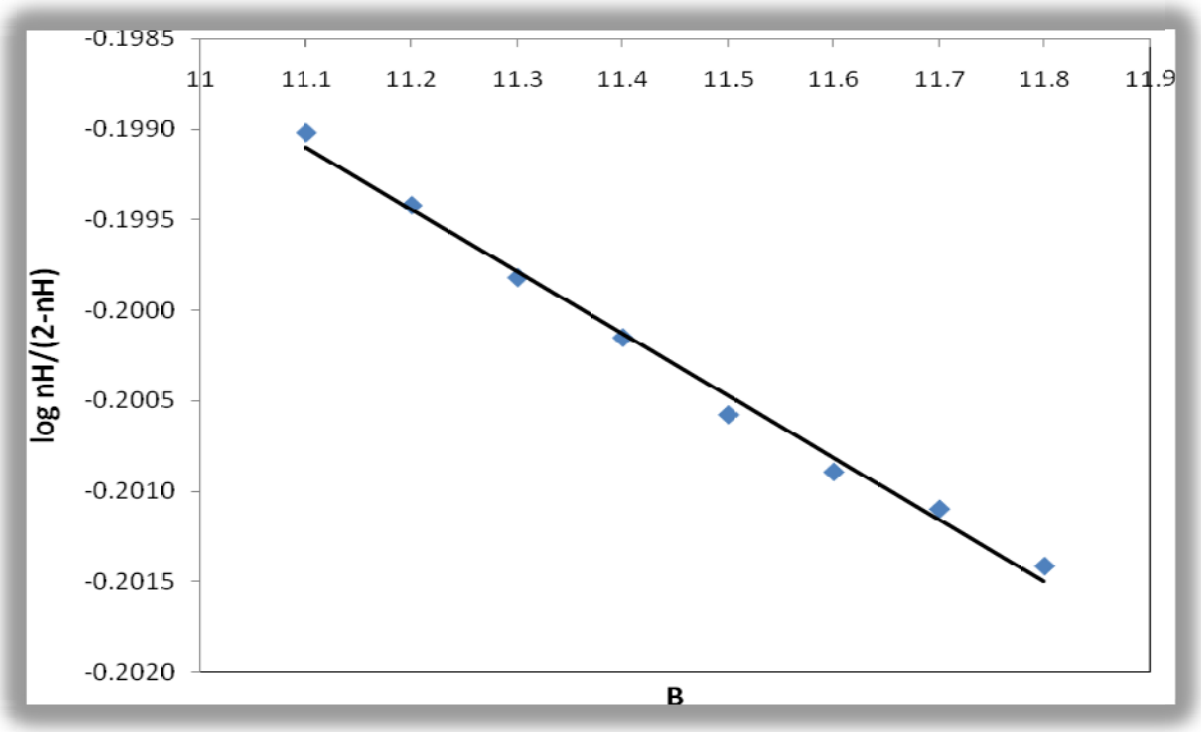
$$logp\,K_2^H = pH + log\left[(\bar{n}_H - 1)/(2 - \bar{n}_H)\right] \quad \ldots (3.7.20)$$

From the various values of $\log pK_1^H$ (or $\log pK_2^H$), the average value was calculated. The values of $\log pK_1^H$ and $\log pK_2^H$ calculated by the two methods i.e., half-integral method and average method are given in Table 3.7.2. It is observed that in most of the systems, the values are in good agreement. However, deviations are observed for MDT 1 and MDT 3.

Out of all systems studied, MDT 1 and MDT 3 are of *H_2L* type whereas others are of *HL* type. So, a variation in the single titration curve occurs in MDT 1 and MDT 3 is observed which is due to ionisation of more than one acidic group on a molecule [39]. MDT 1 and MDT 3 both contain hydroxyl groups at para positions. But, MDT 1 is found to be more acidic than MDT 3. This suggests that presence of methoxy group increases the acidic character. This is in agreement with the results obtained for quinoline azodyes and their metal complexes [40]. Yoda has reported that alteration of hydroxy group with any other functional group can also change the dissociation of rate of the compounds [41].

Comparison of pK_1^H values of MDT series shows that, MDT 5 is more acidic which contains m-chloro group. However, MDT 8 and MDT 9 are most basic. MDT 8 contains phenyl ring without substitution, whereas in MDT 9, furan substitution is present. From these results, it is concluded that different compounds exhibit different dissociation constant which also depends upon the type and position of substituent group [42]. This is due to inductive or mesomeric effect of functional groups.

Figure 3.7.3: The plot of log $n_H/(2-n_H)$ against B for MDT 1 and log $n_H/(1-n_H)$ in against B for MDT 2 in DMF at 303.15K.



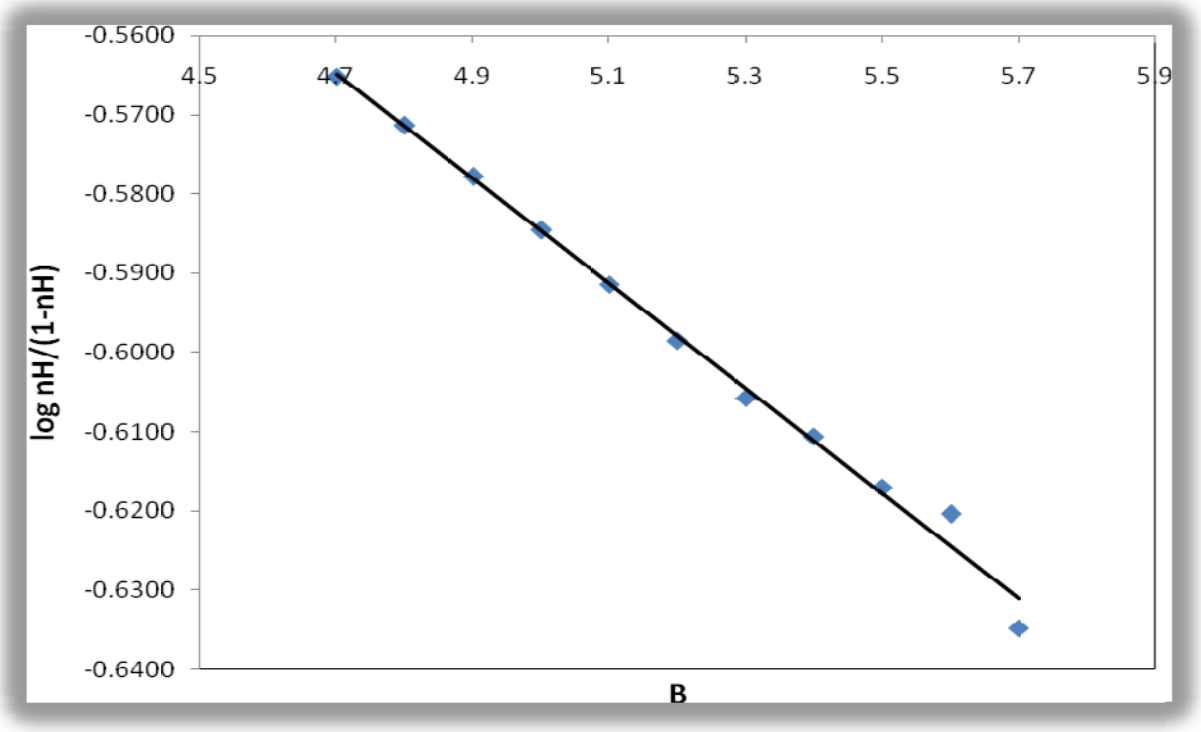


Table 3.7.2: The log pK_1^H values for all the studied compounds calculated by different methods.

Compounds	log pK_1^H			log pK_1^H	
	Half-integral method	Average method		Half-integral method	Average method
MDT 1	5.50 (n_H=1.5) 11.50 (n_H=0.5)	5.83 (n_H=1.5) 11.02 (n_H=0.5)	**MDT 6**	5.50	5.53
MDT 2	5.20	5.22	**MDT 7**	6.20	6.20
MDT 3	5.70 (n_H=1.5) 12.20 (n_H=0.5)	5.80 (n_H=1.5) 11.78 (n_H=0.5)	**MDT 8**	6.40	6.44
MDT 4	5.30	5.26	**MDT 9**	6.40	6.38
MDT 5	5.00	5.01	**MDT 10**	6.30	6.28

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INTRODUCTION

The partition coefficient is a measure of the tendency of the substance to prefer a non-aqueous medium rather than aqueous medium. Partition coefficient term may also be narrated as distribution coefficient. Partition coefficient, unlike solubility, measures the differential ability of a solute to dissolve in two insoluble phases. The value of partition coefficient is a measure of hydrophobicity and hydrophilicity of the solute. Normally, one of the solvents chosen is water while the second is hydrophobic [(1)]. Other hydrophobic organic solvents like chloroform, ether, and hexane can also be used. But n-octanol is an important molecule both for biological and environmental reasons [(1)]. Collander has studied the partition coefficient of organic compounds in alcohols higher than octanol [(2)]. n-octanol is an amphiphilic liquid at room temperature, in which one end is hydrophilic and the other is hydrophobic. Due to this property, it is pharmaceutically useful. It is a model of phospholipid membranes [(3, 4)]. The octanol - water partition coefficient is also used to determine bioavailability and environmental fate. Finizio et al. have used octanol-air partition coefficient as a predictor of partitioning of semi-volatile organic chemicals to aerosols like pollutants [(5)]. Miller et al. have correlated the octanol-water partition coefficient and aqueous solubility [(6)].

Many other industries take into account the partition coefficient or distribution coefficients for a number of applications such as in the formulation of make-up, topical ointments, dyes, hair colours and many other consumer products. In metallurgy, the partition coefficient is an important factor in determining how different impurities are distributed between molten and solidified metal [(7)]. Partition coefficient of rare earth elements collected from the terrestrial basalt and lunar basalt has been studied [(8)].

Partition coefficients are used extensively in medicinal chemistry, drug design, ecotoxicology and environmental chemistry. Governmental and international agencies like U.S. Environmental Protection Agency, OECD (Organization for Economic Cooperation and Development) recognized the partition coefficient method as a physical property of organic pollutants [(9-11)]. This

property is also useful in crop science research [12]. Partition coefficients of 221 pesticides and pesticide metabolites have been measured [13].

Partition coefficient plays an important role in the pharmaceutical research. It is a key tool to draw the transport map of drug in living body. The distribution coefficient has a strong influence on ADME properties (Absorption, Distribution, Metabolism, and Excretion) of the drug. The hydrophobicity of a compound (as measured by its distribution coefficient) plays a major role in determining where drugs are distributed within the body after adsorption. Further, their metabolism and excretion process can also be studied. For drug, the ideal distribution coefficient is usually intermediate (neither too hydrophobic nor too hydrophilic) [14-16].

Partition coefficient is also useful to determine more useful analogue of drug molecule. [17]. Ong et al. have studied the partition phenomena to predict drug membrane permeability by immobilized artificial membranes [18]. Membrane permeability of some biological compounds has also been checked by this method [19].

The traditional method to determine the parttion coefficient is known as Shake-Flask method which is a well recognized method [9]. There are several other methods to measure the partition coefficient like stir flask method [20], vial-equilibration method [21], reversed-phase HPLC, reversed-phase TLC, slow-stirring partition methods and column generator method[11], micellar electro kinetic capillary chromatography [22], Counter-current chromatography (CCC) [23], Microemulsion electrokinetic chromatography (MEEKC) [24] etc.

In the present study, partition coefficients of tetra hydropyrimidines have been studied in n-octanol-water system by UV spectroscopy at different pH. The partition coefficient is highly influenced by pH. So, in the present study, a wide range of pH (0.84 to 8.0) is selected. For 0.84 pH, 0.1 N HCl was taken whereas for 6.0, 7.4 and 8.0, phosphate buffer was used. These values of pH are selected due to their existence in human body. As HCl exists in gastric juice in stomach, 0.1 N HCl is taken. Blood has 7.4 pH, so the study is done at pH 7.4. Further, the middle and upper range of body pH is 6.0 and 8.0 respectively, so study was done at these all pH also.

EXPERIMENTAL

n-Octanol is of analytical grade. The purity of solvent was checked by GC and found to be 99.8%. Distilled water was used throughout for all experiments.

Preparation of standard solution:-

10 mg sample was dissolved in n-octanol to give 100 ml solution of 100 ppm. This solution was known as standard solution. Suitable dilutions were made from this standard solution (2 μg to 20 μg).

Measurement:-

λ_{max} values were measured using UV spectrophotometer (Shimadzu, UV-1700, Pharmaspec) from this solution. For each compound, absorbance (OD) was measured at respective λ_{max} value and the calibration curve of OD versus concentration of compounds was drawn.

Determination of Partition coefficient:-

A known amount of the compound under investigation was dissolved in n-octanol at a concentration not higher than 20 μg. Equal volumes of this solution and water is mixed in oven dried stoppered flask and the mixture was stirred for 24 hrs. at room temperature. After 24 hrs., the solution was transferred into 60 ml of separating funnel and allowed to stand in order to separate the aqueous and organic layers. The organic layer will be upper one while lower will be aqueous. The organic layer was then analyzed by UV spectrophotometer. Using calibration curve, the concentration of compounds in organic layer was then evaluated.

THEORY

Partition coefficient (P) is defined as the ratio of the compounds in organic phase to that present in the aqueous phase. i.e., [25]

$$P = \frac{C_{org}}{C_{aq}} \qquad \ldots (3.5.1)$$

where C_{org} and C_{aq} are concentration of solute in organic and aqueous phases respectively.

In the present case, concentrations were determined by UV measurement so, equation (3.5.1) written as [26]:

$$P = \frac{B_E}{B_E - A_E} \qquad \ldots (3.5.2)$$

where B_E= Absorbance before extraction and A_E=Absorbance after extraction. From equation (3.5.2) log P were calculated for each set of experiment.

RESULTS AND DISCUSSION

The values of log P for the studied compounds at different pH are given in Table 3.71 and Figure 3.5.1. The log P value depends upon the hydrophilic and hydrophobic character of compounds. log P values have inverse relation with hydrophilisity of compounds.

Table 3.5.1 shows that compounds with higher log P value is hydrophobic whereas those with lower log P values are hydrophilic.

Observations suggest that for MDT-5 exhibited maximum hydrophobicity in most of the pH. Whereas MDT-1 is highly hydrophilic at all pH. Thus, MDT-1 will be easily absorbed in blood than MDT-5 which is likely to be accumulated in fatty tissues [27, 28]. The substitution in compound affects its nature. All the compounds have same central moiety with different substituents. Thus, the presence of vanillin group (as in MDT-1) increases the hydrophilic character whereas 3-chlorobenzene causes an increase in hydrophobicity.

Overall, the decreasing order of hydrophobicity of compounds is: MDT-5 > MDT-4 > MDT-10 > MDT-6 > MDT- 8 > MDT-2 > MDT-7 > MDT-3 > MDT-1.

In 0.1N HCl-octanol system, MDT-10 is slightly more hydrophobic than MDT-5 whereas MDT-1 is highly hydrophilic in nature. Thus, in gastric juice also, MDT-10 will not be absorbed whereas MDT-1 can be easily absorbed. Thus, at lower pH, cinnamaldehyde also causes hydrophobicity in a compound.

At 6.0 and 8.0 pH, the trend is same as in water i.e., MDT-5 containing 3-chloro benzene is highly hydrophobic and MDT-1 containing vanillin group is more hydrophilic.

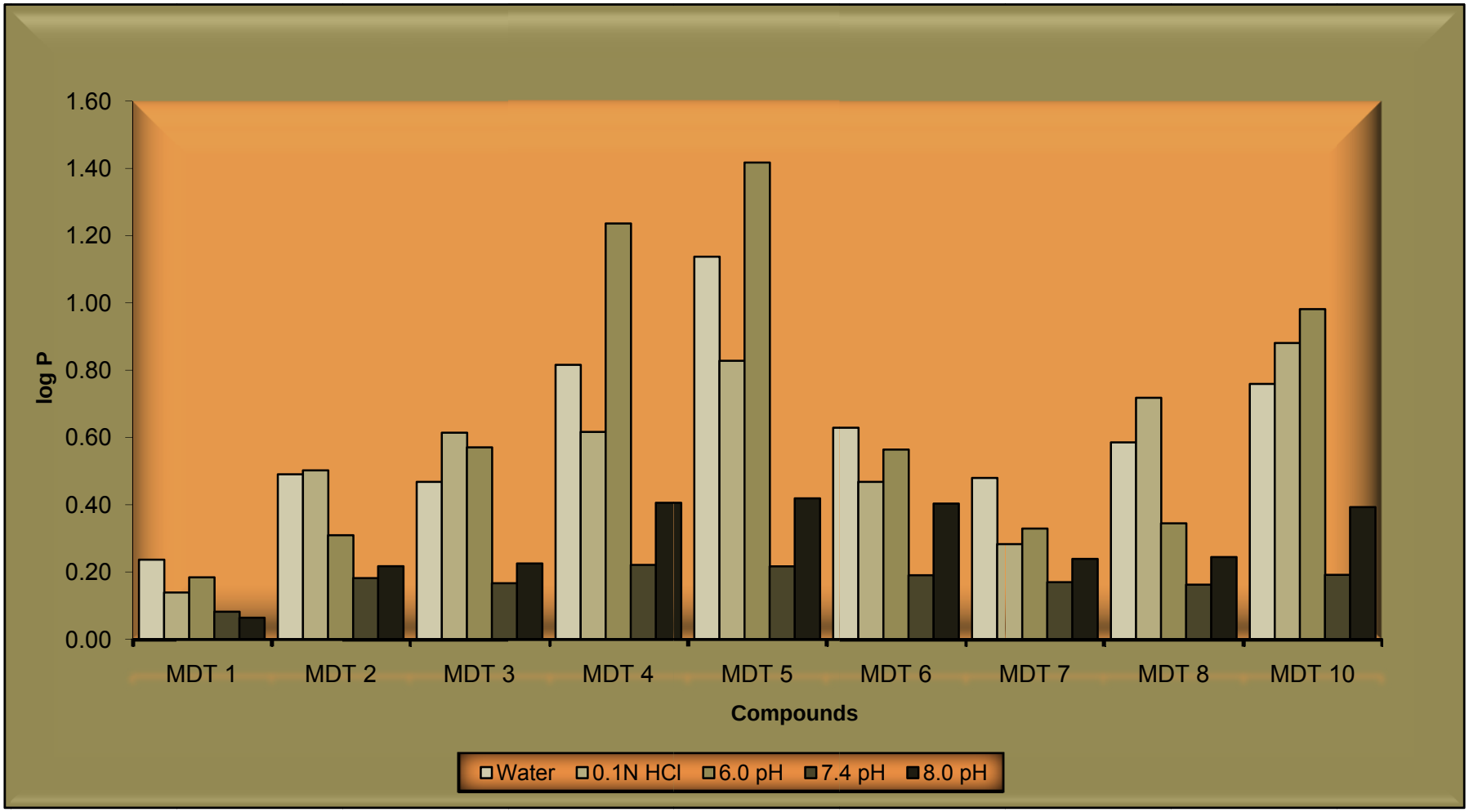
In 7.4 pH range, again MDT-4 and MDT-5 exhibited maximum hydrophobic character.

Over all study of partition coefficients of tetra hydro pyrimidine derivatives shows that MDT-5 is most hydrophobic compounds and MDT-1 is most hydrophilic compounds at all studied medium. Thus, there is no apparent effect of pH on the order of partition coefficients of the studied compound having different substitutions.

Table 3.5.1: log P values for compounds of MDT series.

Compounds Code	Max absorption Wavelength (nm)	log P				
		Water	0.1N HCl	6.0 pH	7.4 pH	8.0 pH
MDT 1	381	0.2366	0.1392	0.1844	0.0821	0.0640
MDT 2	349	0.4905	0.5021	0.3094	0.1820	0.2173
MDT 3	361	0.4682	0.6142	0.5706	0.1668	0.2255
MDT 4	320	0.8158	0.6167	1.2361	0.2213	0.4059
MDT 5	205	1.1374	0.8279	1.4175	0.2170	0.4191
MDT 6	312	0.6288	0.4681	0.5639	0.1905	0.4033
MDT 7	261	0.4797	0.2831	0.3294	0.1699	0.2390
MDT 8	309	0.5853	0.7181	0.3447	0.1627	0.2446
MDT 10	203	0.7593	0.8808	0.9817	0.1915	0.3931

Figure 3.5.1: log P values of compounds of MDT series.



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INTRODUCTION

Biological activity spectrum of a compound represents the pharmacological effects, physiological and biochemical mechanisms of action, specific toxicity which can be revealed in compound's interaction with biological system. Further, it describes the intrinsic properties of the compound which depends on its structure.

Pyrimidines are always an attraction point for researchers because of its efficiency towards various pharmacological usages. Pyrimidine nucleosides are known to possess various activities like anti-HIV [1], antiviral [2-6], antitumour [7, 8], antibacterial [9] anti-inflammatory [10], adrenoceptor antagonists [11-14] etc. Many researchers have worked on antimicrobial activity of dihydropyrimidine moiety. Fathalla and co-workers [15] have reported the antibacterial and anticancer activity of pyrimidine derivatives. 3,4dihydropyrimidinone derivatives have reported to possess the antimicrobial activity [16]. Shinde and Bahekar have studied the anti-inflammatory activity of pyrimidine derivatives [17]. Patil et al. have synthesized various derivatives of reduced pyrimidines and screened for various biological activities [18].

The quinoline derivatives are also known to have wide spectrum of therapeutic activities such as: antiulcer [19, 20], anti-HIV [21], antihypertensive [22], antimalarial [23-25], antihistamine [26, 27], diuretic [28, 29], herbicidal [30], anticancer [31, 32] cardiovascular [33] etc. Smith et al have used tetrahydroquinoline as ligand for control of gene expression [34]. Lombardo et al have characterised tetrahydroquinoline derivatives as transferase inhibitors [35]. This moiety is also known to show the antioxidant activity [36].

So, in the present chapter, antibacterial activities of some synthesized compounds have been screened against some Gram positive and Gram negative bacteria. Sixteen compounds from tetrahydropyrimidine and tetrahedroquinoline derivatives have chosen for evaluation and compared.

The solvent DMSO was also purified before use by standard method [37]. All the synthesized compounds were recrystallized prior to use. For all the compounds, agar well diffusion method was used.

Test Microorganisms:

The synthesized compounds were tested for its antibacterial activity against two Gram positive bacteria *Stephylococus epidermidis* MTCC2639 and *Bacillus subtilis* MTCC1790 and two Gram negative bacteria *Escharichia coli* MTCC729 and *Shigella flexneri* MTCC1457.

Microorganisms 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 evaluation was done by agar well diffusion method [38, 39] 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 [39]. 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 strain determined the antibacterial activities of these synthesized compounds.

RESULTS AND DISCUSSION

Table 1 shows the antibacterial activity of tetrahydropyrimidine derivatives (MDT series) against Gram positive and Gram negative bacteria. It is evident from Table 1 that MDT2, MDT5 and MDT6 showed activity against *S. epidermidis* whereas other compounds could not affect at all. The activity shown by MDT2, MDT 5 and MDT 6 are very less. Further, MDT 5 and MDT 6 show equal inhibition.

All the compounds of MDT series contain same central moiety but different substitution. These substitutions are aryl ring with different functional groups. MDT5 contains m-chloro group whereas in MDT6 p-flouro group is present. In MDT2, methoxy group is present at para position. Thus, activity is affected by these functional groups.

However, *B. subtilis* remained unaffected by all the studied tetrahydropyrimidine compounds. Thus, B. subtilis is resistant bacteria for the studied compounds where not a single group could affect these Gram positive bacteria.

Both the negative bacteria (*E. coli* and *S. flexneri*) could not be affected by the studied tetrahydropyrimidine compounds.

Table 2 shows the activity of studied tetrahydroquinoline compounds (MBH series) against Gram positive and Gram negative bacteria. In this case, compounds from MBH 1 to MBH 5 showed activity against *S. epidermidis*. Other three compounds had no effect on this bacterium. Further, activity is maximum for MBH 1. This compound contains vanillin as a side chain. MBH 4 containing p-chloro group showed least activity. Thus, vanillin is most effective group in against *S. epidermidis*. Against *B. subitilis,* only MBH 4 showed activity which contained p-chloro group. Thus, B. subtilis is resistant bacteria for the studied compounds

It is concluded that for both MDT and MBH series, p-chloro group is effective against *S. epidemicis* and *B. subtilis* is resistant bacteria. For both series, 7^{th} and 8^{th} compounds had no effect at all.

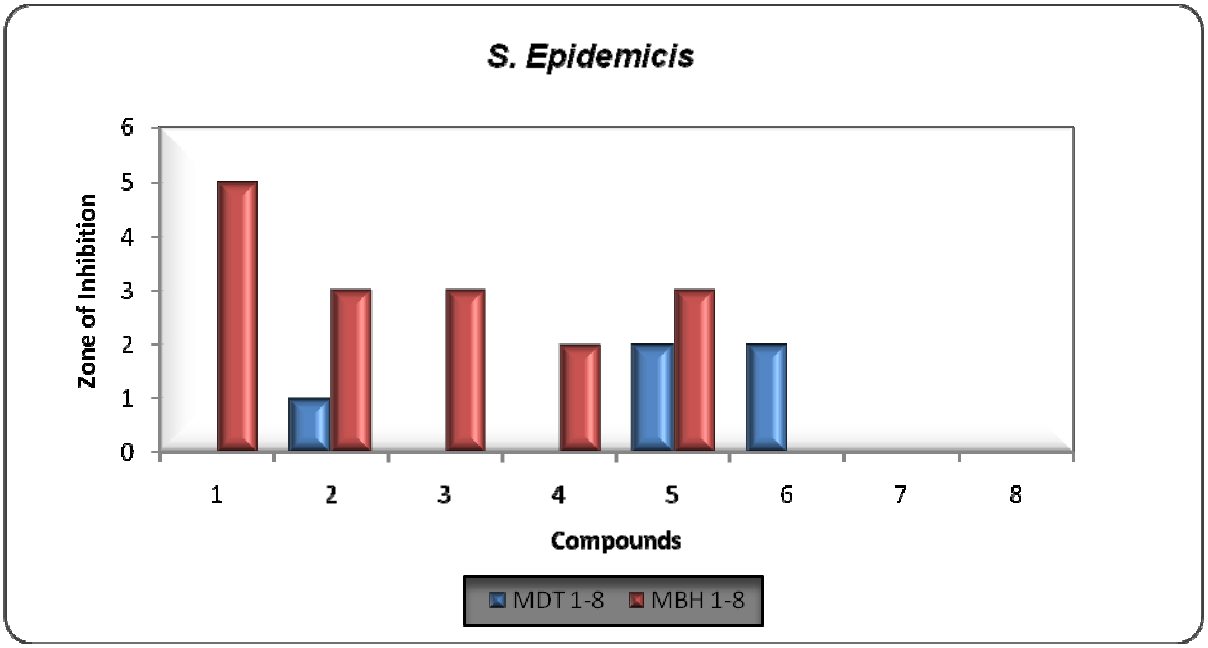
Table 1: Antibacterial activity of compounds of MDT series in DMSO.

Compounds	Test Bacterial Strain			
	Gram Positive		Gram Nagative	
	S. epidermidis	*B. subtilis*	*E. coli*	*S. flexneri*
MDT 1	-	-	-	-
MDT 2	1	-	-	-
MDT 3	-	-	-	-
MDT 4	-	-	-	-
MDT 5	2	-	-	-
MDT 6	2	-	-	-
MDT 7	-	-	-	-
MDT 8	-	-	-	-

Table 2: Antibacterial activity of compounds of MBH series in DMSO.

Compounds	Test Bacterial Strain			
	Gram Positive		Gram Nagative	
	S. epidermidis	*B. subtilis*	*E. coli*	*S. flexneri*
MBH 1	5	-	-	-
MBH 2	3	-	-	-
MBH 3	3	-	-	-
MBH 4	2	1	-	-
MBH 5	3	-	-	-
MBH 6	-	-	-	-
MBH 7	-	-	-	-
MBH 8	-	-	-	-

Figure 1: Comparison of activity of compounds of MDT series and MBH series against *S. Epidemicis*.



Comparison of activity in MDT and MBH series is shown in Figure 1. It is observed that MBH series is slightly more effective than MDT series against Gram positive bacteria. Thus, tetrahydroquinoline nucleus (in MBH series) is more fatal than tetrahydropyrimidine moiety.

So, it is concluded that for both the series of compounds, *S. epidermidis* is most susceptible bacteria and both Gram negative bacteria (*E. coli* and *S. flexneri*) are the most resistant. Overall, MBH series is more effective than the MDT series in Gram Positive bacteria. For both series, 7^{th} and 8^{th} compounds had no effect at all.

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A COMPREHENSIVE SUMMARY OF THE WORK

The present work is divided into following chapters:

Chapter-1

This chapter describes the importance of heterocyclic compounds with aim and objective of the present work.

Chapter-2

This chapter divided into following parts:

Part-1: Part-1 of this chapter deals with the synthesis of tetrahydropyrimidine derivatives. This part consists of two sections. The first section describes the synthesis and characterization of tetrahydropyrimidine derivatives and in the second section, synthesis of pyrimidopyrimidines by cyclization of these tetrahydropyrimidines have discussed. The synthesized compounds are characterized by IR, NMR and mass spectral data. The physical constant data of the synthesized compounds are also reported.

Part-2: In this Part, synthesis and characterization of tetrahydroquinoline derivatives and their cyclization to synthesize pyrimidoquinoline are described in two different sections along with their physical constant data. The synthesized compounds are characterized by IR, NMR and mass spectral data.

Part-3: 3-{[2-aryl-1H-benzimidazol-1-yl]acetyl}-2H-chromen-2-one are synthesized by the condensation of two different heterocyclic compounds, i.e; benzimidazole and coumarine. The characterization is done by IR, NMR and mass spectral data.

Chapter-3

This chapter deals with the physicochemical properties of synthesized tetrahydropyrimidines in different solvents. The different properties are given in different sections.

Section-1:

This section deals with the acoustical properties of tetrahydropyrimidines (MDT 3 series) over a wide range of concentrations at 308.15K in DMF and $CHCl_3$. For this, density, viscosity and ultrasonic velocity of solutions are measured. Various acoustical parameters are evaluated from the experimental data to understand different types of interactions occurring in the solutions. It is observed that for the studied compounds, in both solvents i.e., DMF and chloroform, different compounds showed different behaviour. In DMF, both solute-solute and solute-solvent interactions exist in solutions of different compounds. In chloroform, most of the compounds exhibited solute-solvent interactions.

Section-2:

In this section, the refractive index and densities of compounds have been measured in DMF and chloroform solutions of various concentrations at 303.15K. From the experimental density of solutions, density of solid compounds was evaluated and was compared with those observed theoretically. The values of evaluated density are found to be different than those calculated theoretically for all the studied systems. This may be due to different interactions in different solvents. Further, the molar refraction and refractive index of compounds were evaluated, which are also found to be different in each solvent.

Section-3:

This section deals with the conductance of studied compounds in DMF and $CHCl_3$ at 303.15K. It is observed that conductivities of studied compounds are higher in DMF than the other solvent. Further, these compounds exhibit weak electrolytic nature in the studied solvents.

Section-4:

This section describes the solubility of all the studied compounds in methanol and ethanol at different temperatures (293.15 -313.15 K). It is observed that the solubility of all the compounds increases linearly with temperature in both the solvents. The thermodynamic parameters such as Gibb's energy

(ΔG_{sol}), enthalpy (ΔH_{sol}) and entropy (ΔS_{sol}) for the dissolution process in the two solvents were also evaluated for all the compounds. It is observed that enthalpy and Gibb's energy are positive for all the compounds whereas entropy values are both negative and positive. The positive enthalpy indicates endothermic dissolution of compounds whereas positive ΔG_{sol} suggests that the dissolution process is not spontaneous. Further, the negative values of entropy indicate less randomness in solutions.

Section-5:

The thermal properties of synthesized tetrahydropyrimidines are described in this section. DSC and TGA thermo gram were scanned at the heating rate of 20°C per minute. It is observed that thermal stability depends on the presence of substituents in the compound. MDT 10 having cinnamaldehyde is found to be most unstable whereas MDT 7 having nitro group is most stable. Further, the melting points determined by DSC and by open capillary methods are found to be in good agreement. From thermograms, various kinetic parameters such as order of reaction, energy of activation, frequency factor and entropy change were also calculated. The order of reaction is quite different for different compounds. Further, the entropy is found to be both positive and negative in different compounds. The positive values of entropy change indicate that the transition state is less ordered than the original compound whereas negative value of entropy change corresponds to an increase in the order of transition state than the reactants.

Section-6:

In this section, the dissociation constants of tetrahydropyrimidines compounds are studied in water-DMF mixtures at 303.15 K. The dissociation or acidic constant depends not only on the solvent but also on the type of substituent groups present in the compound. Different groups interact differently with the solvent, which affect their dissociation.

Out of all systems studied, MDT 1 and MDT 3 are of H_2L type whereas others are of *HL* type. MDT 1 and MDT 3, both contain hydroxyl groups at para

positions. But, MDT 1 is found to be more acidic than MDT 3. This suggests that presence of methoxy group increases the acidic character.

Among other compounds of HL type, MDT 5 is more acidic which contains m-chloro group. However, MDT 8 and MDT 9 are most basic. MDT 8 contains phenyl ring without substitution, whereas in MDT 9, furan substitution is present. From these results, it is concluded that compounds having different substitution groups exhibit different dissociation constant, which is due to inductive or mesomeric effect of functional groups.

Section-7:

This section describes partition coefficient of tetrahydropyrimidines compounds, which has been studied in n-octanol-water system by UV spectroscopy at different pH. From the study, it is concluded that MDT-5 is most hydrophobic compounds and MDT-1 is most hydrophilic compounds at all studied medium.

Chapter-4:

The antimicrobial activities of tetrahydropyrimidines (MDT series) and tetrahydroquinoline compounds (MBH series) are studied in DMSO in this chapter. Different Gram positive and Gram negative bacterial strains are used for the study. All the studied Gram negative bacteria remained unaffected by the studied compounds. But, the presence of different substituents at different positions in phenyl ring affects inhibition towards Gram Positive bacteria. Comparison between tetrahydropyrimidine and tetrahydroquinoline nucleus shows that the tetrahydriquinoline nucleus is more effective than tetrahydropyrimidine nucleus for studied bacterial strains.

List of Published/Accepted/Communicated Papers

1. Solubility of Enrofloxacin Sodium in various solvents at various Temperature. **S. Baluja**, R. Bhalodia, **M. Bhatt**, N. Vekaria and R. Gajera; J. Chem. Eng. Data, 53, 2008, 2897-2899.

2. Solubility of Difloxacine in Acetone, Methanol and Ethanol from (293.15 to 313.15 K). **S. Baluja**, R. Bhalodia, N. Vekaria, R. Gajera and **M. Bhatt** ; J. Chem. Eng. Data, 54, 2009, 1091-1093.

3. Solubility of ofloxacin in 1,2-dichloromethane, chloroform, carbontetrach -loride and water from 293.15 to 313.15 k. **S. Baluja**, **M. Bhatt**, R. Gajera, R. Bhalodia and N. Vekariya; J. Chem. Eng. Data, Manuscript ID: je-2009-00540d, 2009 (In press).

4. Solubility of cholesterol in some alcohols from 293.15 to 318.15 k. **S. Baluja**, **M. Bhatt**, N. Vekariya, R. Gajera and R. Bhalodia; J. Pharm. Sci. Manuscript No.: SRL-AASR-2009-511, 2009 (In Press)

5. Cholesterol: An ultrasonic study in different solvents at 308.15 k. S. Chanda, R. Bhalodia, **S. Baluja** and **M. Bhatt**; Int. J. Appl. Chem., 2009 (In Press)

6. Theoritical comparision of viscosity in binary solution at 298.15 k. **S. Baluja**, N. Vekariya and **M. Bhatt**; Int. J. Appl. Chem. Manuscript Code No: #822, 2009 (In Press).

7. The Solution Heat and Conductance of Some Azomethines Nonaqueous Solutions at 308.15 K. **S. Baluja** and **M. Bhatt**; Russian Journal of Physical Chemistry, 83(13), 2009, 2230- 2232.

8. Synthesis and antibacterial activity of some chalcones. **S. Baluja**, N. Godvani, S. Chanda, Y. Vaghasiya, J. Parekh, R. Gajera, **M. Bhatt**. J. Ind. Chem. Soc., 2009 (In press).

9. Synthesis, characterization and antibacterial activity of some thiazolidinones. **S. Baluja**, N. Godvani, S. Chanda, Y. Vaghasiya, J. Parekh, R. Gajera, **M. Bhatt**. J. Chem. Pharm. Sci., 2009, (In press).

List of Papers Presented in Different Conferences

1. "Ultrasonic Studies of antiprotozoal Drug in protic and aprotic solvents at 308.15K" Shipra Baluja, Anchal Kulshrestha and Mehul Bhatt; 3rd National Conference on NCTCBS, Nagpur (2009).

2. "Cholesterol: An ultrasonic study in different solvents at 308.15." S. Chanda, R. Bhalodia, **S. Baluja** and **M. Bhatt;** 20th International Conference on Chemical Thermodynamics, Warsaw, Poland (2008)