Ph. D. Thesis

# STUDIES ON SOME NEW HETEROCYCLIC ENTITIES OF MEDICINAL INTEREST

BY

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DEPARTMENT OF CHEMISTRY
(DST-FIST FUNDED & UGC-SAP SPONSORED)
SAURASHTRA UNIVERSITY
RAJKOT- 360 005
GUJARAT - (INDIA)
APRIL - 2009

# STUDIES ON SOME NEW HETEROCYCLIC ENTITIES OF MEDICINAL INTEREST

A THESIS
SUBMITTED TO THE
SAURASHTRA UNIVERSITY
FOR THE DEGREE OF

## DOCTOR OF PHILOSOPHY

IN

THE FACULTY OF SCIENCE (CHEMISTRY)

BY


## NILESHKUMAR K. GODVANI

UNDER THE GUIDANCE

OF

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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: -04-2009

Place: Rajkot **(Nileshkumar K. Godvani)**

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

The thesis has been prepared under my supervision.

Date: -04-2009

Place: Rajkot.

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DEDICATED
TO
MY FAMILY

# *ACKNOWLEDGEMENT*

*First and foremost I wish to bow my head humbly before* ***THE ALMIGHTY, "THE WONDERFUL CHEMIST"*** *of this lovely world. Without his blessings this task would have not been accomplished.*

*I feel great pleasure in expressing my deep and profound sense of gratitude to my research guide* ***Dr. Shipra Baluja*** *Associate Professor, Department of Chemistry, Saurashtra University for bringing me up to this stage of my career. It could hardly have become possible for me to venture in the domain of research without her continuous guidance, encouragement, motivative attitude, punctuality, and parental care. I feel honored and consider my self very lucky to work under her tutelage. She has been a guiding light to me during my research work will always remains so.*

*I wish to thanks to all the faculty members of this department. My sincere thanks are due to* ***Prof. P. H. Parsania*** *Head of the Department for providing me necessary facilities. I also thanks to all laboratory staff and administrative staff of this department for their timely help.*

*I wish to express my gratitude to* ***Dr. S. V. Chanda*** *Associate Professor, Department of Biosciences, Saurashtra University, Rajkot, for help in conducting biological activities.*

*I owe my special thanks to* ***Dr. K. P. Vaishnani, Dr. P. K. Kasundra, Dr. Asif Solanki, Dr. Nikunj Kachhadia, Dr. D. R. Godhani, Dr. F. D. Karia*** *for their selfless help, moral support and guidance during hours of need. I would never forget the company I had from my colleagues and friends* ***Anchal, Jagdish, Mehul, Nayan, Rahul*** *and* ***Ravi.***

*I am very much thankful to* ***Mr. Pankaj Kachhadia*** *and* ***Mr. Vijay Ram*** *for help me with instrumentation; S.A.I.F., C.I.L., Punjab University, Chandigadh, for NMR spectral analysis.*

*I am extremely thankful to my research colleagues and friends Vrajesh, Bharat, Viru, Jignesh, Matre, Manish, Kapil Dubal, Gaurang, Pranav, Chirag, Akshay, Jimmy, Naval, Raju, Dhawal, Satish, Rakesh, Savant, Punit, Bhuro,*

*Harsad, Suresh, Renish, Govind, Pankaj, Amit, Bhavesh, Piyush, Sandip, Rushit, Kapil, Lina, Pooja and Priti for their support.*

*I am specially thanks to Shaileshbhai and Shuklaji for their help during my research work.*

*I feel a deep sense of gratitude to* ***my parents*** *and* ***family members*** *for their untiring cooperation, which I received in the form of love, everlasting inspiration and moral support during the period of my study, which was instrumental for the successful completion of the work.*

*And finally, still there are many more Well Wishers, Friends, Relatives, who directly and indirectly rendered me valuable help and moral strength to complete this academic endeavor. I have deep reverence for all of them.*

***Nileshkumar K. Godvani***

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# Synopsis

# *SYNOPSIS*

# STUDIES ON SOME NEW HETEROCYCLIC ENTITIES OF MEDICINAL INTEREST

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

| | |
|---|---|
| Faculty | : Science |
| Subject | : Chemistry |
| Title | : **"STUDIES ON SOME NEW HETEROCYCLIC ENTITIES OF MEDICINAL INTEREST"** |
| Name of the Candidate | : **NILESHKUMAR K. GODVANI** |
| Registration number | : 3424 |
| Date of Registration | : 30th June 2006. |
| Name of the Guide | : Dr. Shipra Baluja<br>Associate Professor<br>Department of Chemistry<br>Saurashtra University<br>Rajkot-360 005. |
| Submitted to | : Saurashtra University |
| Place of work | : Department of Chemistry<br>Saurashtra University<br>Rajkot-360 005.<br>Gujarat (INDIA). |

Heterocyclic chemistry has seen unparallel progress owing to their wide natural occurrence, specific chemical reactivity and broad spectrum utility. These compounds show vital role in the field of pharmaceuticals because of their specific clinical reactivity, eg. epoxides, aziridines and β-lactams. The introduction of heterocyclic group into drugs may affect their physical properties, for example the dissociation constants of sulpha drugs or modify their patterns of absorption, metabolism, toxicity etc.

Taking in view of the applicability of heterocyclic compounds, the present work was undertaken to synthesize some new heterocycles bearing quinoline and triazole nucleus. All the synthesized compounds were characterized by IR, NMR and mass spectra. Further, physicochemical properties such as acoustical properties, density, refractive index, conductance, heat of solutions, thermal properties and dissociation constants of some compounds have also been studied. The antibacterial activity of these compounds has also been studied.

The present work is divided into four chapters.

**Chapter-1 General Introduction**

**Chapter-2 Synthesis and characterization**

**Part-1 Synthesis of Quinoline Derivatives**

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Section-II Synthesis of Aminopyrimidines

Section-III Synthesis of Cyanopyridines

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## CHAPTER – 1: GENERAL INTRODUCTION

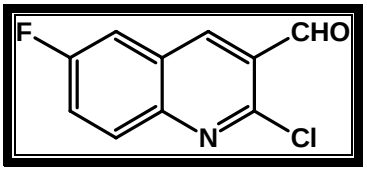
This chapter describes literature survey of synthesis, characterization, applications, physicochemical properties and antibacterial activities of heterocyclic compounds.

## CHAPTER – 2: SYNTHESIS AND CHARACTERIZATION

This chapter deals with synthesis and characterization of some quinoline and triazole derivatives.

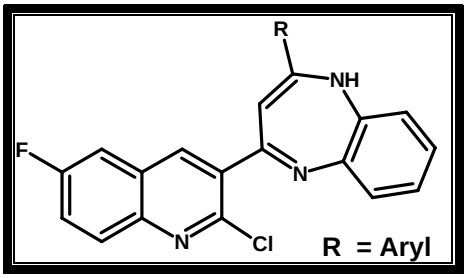
### PART – 1: SYNTHESIS OF QUINOLINE DERIVATIVES

The compounds containing quinoline ring system have been of great interest to synthetic and medicinal chemist for a long time due to the unique chemical and biological properties imparted by hetero atom because of their utilization as effective biologically active agent like antimalarial, antiviral, analgesic, antitumor etc. Quinoline contains a phenyl ring fused to a pyridine ring. Quinoline is also known as benzpyridine.

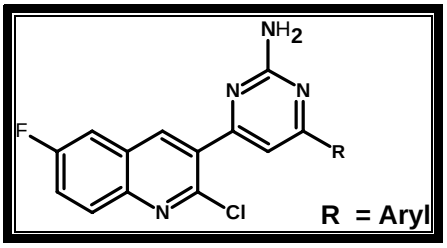



Thus, the important role displayed by quinoline and its derivatives for various therapeutic and biological activities prompted me to synthesize of some benzodiazepine, aminopyrimidine, cyanopyridine and isoxazole derivatives which are mentioned in following sections:

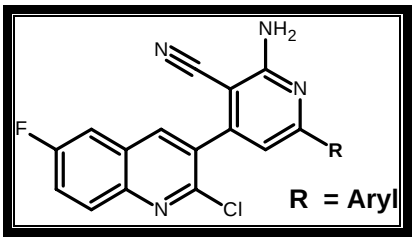
### Section-I Synthesis of 1,5-benzodiazepines



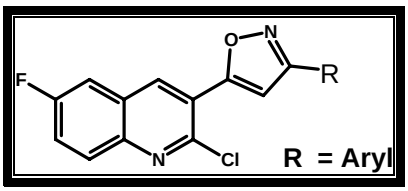
**Section-II Synthesis of aminopyrimidines**




**Section-III Synthesis of cyanopyridines**




**Section-IV Synthesis of isoxazoles**

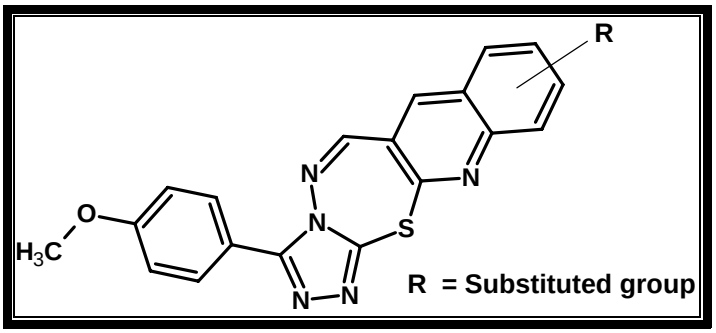



## PART – 2: SYNTHESES OF TRIAZOLE DERIVATIVES

Five membered ring with three nitrogen atoms is known as triazole. The chemistry of triazole derivatives have been of interest due to its useful applications in medicine, agriculture and industry. Further, some of these triazole are known to be used as analytical reagents, dyes and photographic chemicals and in the preparation of polymers.

Prompted by the biological activities of 1,2,4-triazole, in present work, an attempt has been made to synthesize new some 4-amino-3-mercapto 1,2,4-triazole derivatives.

From this triazole moiety, various 1,3,4- thiadiazepines have been synthesized.




**PART – 3: COMPARISON OF DIFFERENT METHODS OF SYNTHESIS**

In conventional synthesis method, the combination of solvents, a strong acid, and long reaction time makes this method environmentally hazardous. Thus, a simple and efficient procedure for the synthesis of heterocyclic system is required. Recently, Microwave-induced Organic Reaction Enhancement (MORE) chemistry has gained popularity as a non-conventional technique for rapid organic synthesis. Many researchers have reported the synthetic utility of MORE chemistry in routine organic synthesis. Compared to traditional processing of organic synthesis, microwave-enhanced chemistry saves significant time and very often improves conversions, clean product formation.

Further, a lot of interest has been generated on the use of ultrasound radiation in synthetic organic chemistry, which includes decrease of reaction time, increase of yield, lower reaction temperature, avoidance of phase transfer catalysis etc.

The synthesis of various benzodiazepines by Microwave, Ultrasound irradiation and Conventional thermal methods are compared.

## CHAPTER – 3: PHYSICO-CHEMICAL PROPERTIES

Some physicochemical properties of benzodiazepine and thiadiazepine derivatives have also been studied in dimethylformamide and tetrahydrofuran. The various physico chemical properties are discussed in the following six sections:

**Section-1 Acoustical Properties**

Acoustical properties of benzodiazepine and thiadiazepine derivatives in dimethylformamide and tetrahydrofuran were studied by measuring density, viscosity and sound velocity (at 2 MHz) at 298.15 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, solvation number etc. were evaluated and the results are discussed in the light of solvent – solute and solute – solute interactions.

**Section-2 Density and Refractive index**

Refractive index is a property of the material and is extremely useful in chemical analysis. Further, molar refraction is of great importance for the calculation of dipole moment. In this section, the density and refractive index of benzodiazepine and thiadiazepine derivatives were measured in dimethyl-formamide and tetrahydrofuran solutions at 298.15 K.

From the refractive index measurements, the density and refractive index of studied compounds were determined.

**Section-3 Conductance**

This section deals with the conductance measurement of solutions of benzodiazepine and thiadiazepine derivatives in dimethylformamide and tetrahydrofuran solutions over a wide range of concentration at 298.15 K. From these experimental values, equivalent conductance at infinite dilution for studied compounds was evaluated.

**Section-4 Heat of Solutions**

The molar heat of solution and melting temperature of a substance can be determined from the solubility measurement at different temperatures. In the present section, heat of solutions for benzodiazepine and thiadiazepine derivatives was determined at different temperatures (308.15-328.15 K) in dimethylformamide and tetrahydrofuran.

**Section-5 Thermal Properties**

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

**Section-6 Dissociation Constants**

This section deals with the dissociation constant of benzodiazepines and thiadiazepines in DMF-water and THF-water systems at 298.15 K.

## CHAPTER – 4: BIOLOGICAL ACTIVITIES

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

Signature of the Guide

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# Chapter -1

# General Introduction

## GENERAL INTRODUCTION

Man is not only a great inventor and builder, but he has also proved to be the most destructive force ever to appear on the face of the earth. Besides, less than ten percent of the population of this planet enjoys all the resources and determines the future course. Statistics show that the devastation of vast areas of remaining undeveloped surface of the world has been destroyed with inevitable extinction of thousands of plant and animal species. To overcome this alarming problem, the discovery of novel active compounds is a matter of urgency.

Organic chemists synthesized new compounds and there is an interest in the complex relationships between chemical structures and pharmacological actions. The search for chemical structures which exhibit physiological activity is a difficult goal of organic chemical approach. The compounds are subjected to screening for numerous types of biological and pharmacological actions. Open pathways for additional chemical research efforts in the expansion of the series and often leads to significant new medicinal products.

The determination of the structure of a biologically active molecule provides a two fold benefit to pharmacy and medicine. It makes possible research leading to synthesis and modification of the structure. Total synthesis is possible by the knowledge of chemical structure and in some instance it is economically important in reducing the cost of the drug.

The Chemistry of the heterocyclic compounds is as logical as that of aliphatic or aromatic compounds. The study of this class of compounds is of great interest both from the theoretical as well as practical point of view. A heterocyclic compound is one which possesses acyclic structure containing at least two different kinds of atoms in the ring. Mostly, carbon, nitrogen, oxygen and sulphur are present in the ring.

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.

Most of the alkaloids, pigments (such as indigo, haemoglobin, anthocyanin etc.), some well known drugs (like penicillin, streptomycin,

sulphathiazole, pyrenthrin, rotenmone, strychnine, reserpine, etc.) consists of heterocyclic ring system.

Many workers have been reported the application of heterocyclic compounds[1-6]. These compounds are useful in the field of medicine and used as a starting material for the synthesis of new drugs[7-18].

**AIMS AND OBJECTIVES:**

Looking to the applications of heterocyclic compounds, in the present work several entities have been designed, generated and were characterized using spectral studies. The details are as under.

- To synthesize several derivatives like benzodiazepines, aminopyrimidines, cyanopyridines, isoxazoles, thiadiazepines bearing quinoline and triazole nucleus.
- To compare synthesis of quinoline based benzodiazepines using microwave, ultrasound induced and conventional synthesis method.
- To characterize these synthesized compounds for structure elucidation IR, $^{1}$H NMR and Mass spectral studies.
- To study the physico chemical properties such as acoustical properties, density, refractive index, conductance, heat of solutions, thermal properties and dissociation constants of some compounds, in different solvents.
- To evaluate antibacterial activity of these synthesized compounds against different bacterial strains, in different solvents.

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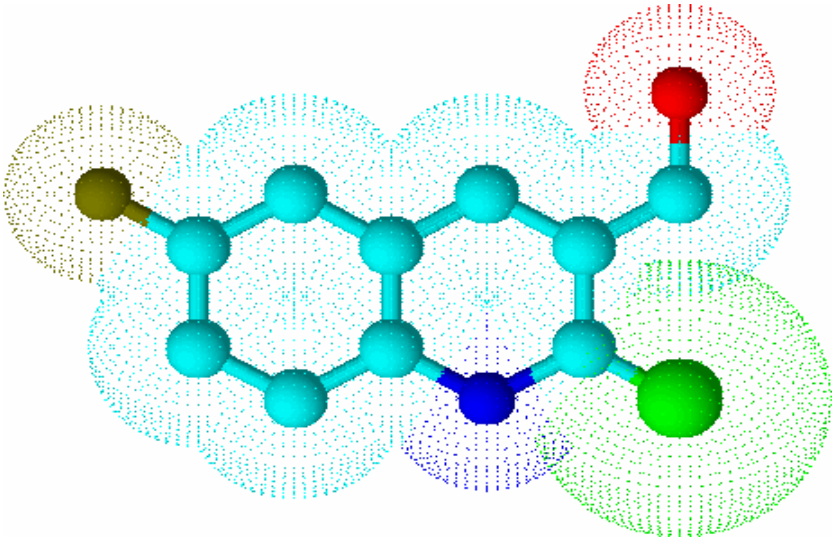
# Chapter -2

# Synthesis and Characterization

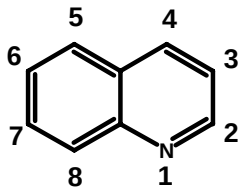


# Partr-1

# Synthesis of Quinoline Derivatives

## INTRODUCTION

Nitrogen containing heterocyclic compounds like quinoline has received considerable attention in recent years due to their biological and pharmaceutical activities. Quinoline contains a phenyl ring fused to a pyridine ring. Quinoline is also known as benzpyridine. The numbering system for the quinoline is as follows:




Different methods used for the synthesis of quinoline and its derivatives have been reported in literature[1-9]. Bangdiwala et al.[10] reported synthesis of 4-hydroxyquinoline. Raychaudhuri et al.[11] studied side products in the preparation of ethyl 7-chloro-4-hydroxyquinoline-3-carboxylate as a intermediate for chloroquine. Synthesis of quinolines with several substituents in the pyridine ring have also been reported by Moszew and co-workers[12]. A direct synthesis of quinoline derivatives from nitro compounds was done by Lachowicz et al.[13] Synthesis of substituted 7-chloroquinoline derivatives[14] and seleno-substituted quinolines[15] have also been reported.

Further, physicochemical study of various new complexes of hexachloroosmate anions with quinoline derivatives was documented by Craciunescu et al.[16] Cesaire et al.[17] studied ultraviolet absorption spectra of 4-amino-7-chloroquinoline derivatives as a function of pH. The structure-activity relationships in some new quinolone derivatives was studied by Leclerc et al.[18]

These quinoline derivatives are 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. Carissimi et al.[34] reported antibacterial and antifungal activities of 8-hydroxyquinolines. The antimycoplasmal[35], antimalarial[36,37] and antidepressant[38] properties of some of these derivatives have also been reported. The antimicrobial activities of a variety of these quinolines have

been studied by various workers[39-42]. Cai et al.[43] reported hypo-cholesterolemic activity of some thiophenyl quinolines.

Thus, the important role displayed by quinoline and its derivatives for various therapeutic and biological activities prompted us to synthesize some benzodiazepines, aminopyrimidine, cyanopyridines and isoxazole derivatives bearing quinoline nucleus in order to achieve compounds having better drug potential.

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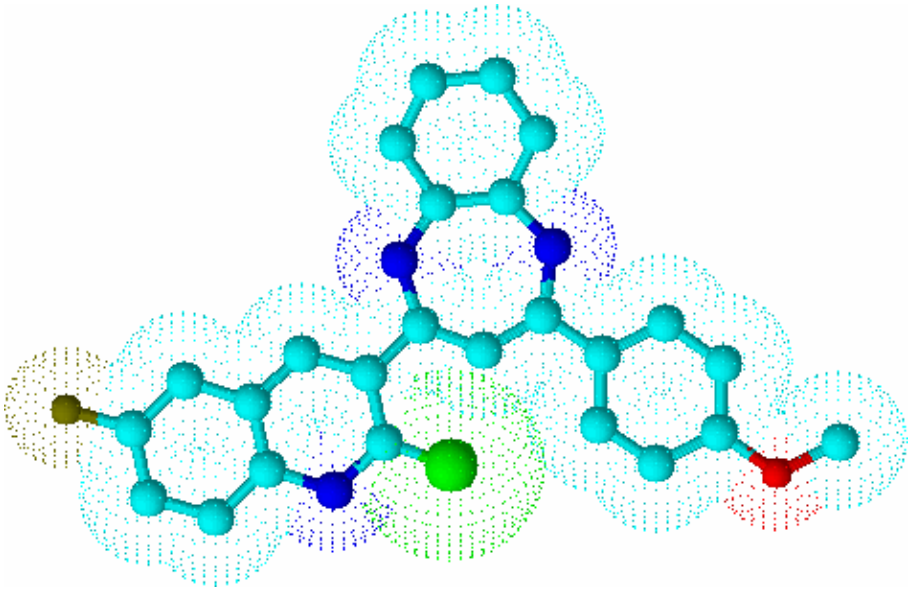


# Section-I

# Synthesis of 1,5-Benzodiazepines

## INTRODUCTION

1,5-benzodiazepine consists of a phenyl ring fused with seven membered heterocyclic ring having two nitrogen atoms at one and five positions.

Different methods have been reported for the synthesis of benzodiazepines and its derivatives[1-10]. Barltrop et al.[11] studied the chemistry of benzodiazepine and derivatives of benzotropone. Bell et al.[12] has reported the new synthesis of substituted benzodiazepin -2-one 4-oxide. Synthesis of some other substituted benzodiazepines has also been reported by Kaegi[13], Pastor et al[14] and Tsuchiya[15]. The solid phase and combinatorial synthesis of benzodiazepines on a solid support was done by Ellman[16]. Aromatic derivatives of 2,3-dihydro-1H-1,5-benzodiazepine have also been synthesized by Orlov et al.[17] Huang and Wang[18] documented a new route for synthesis of 1,5-benzodiazepines. Synthesis and spectral properties of substituted 1,5-benzodiazepines were also been studied by Cortes et al.[19] Guzen et al.[20] synthesized some 1,5-benzodiazepinic heterocycles by ultrasound enhanced method. Recently, synthesis of benzodiazepine derivatives has been reported by various other methods[21-31].

Further, these benzodiazepine derivatives are known to have wide spectrum of biological activities such as anticonvulsant[32], CNS active agent[33], neuroleptic[34], antihypertensive[35], antiproliferative[36], anti-inflammatory[37], cardiovascular[38], antiamnesic[39], antimicrobial[40], anthelmintic[40] etc.

Hester[41] reported sedative and antispasmodic effect of some triazole-benzodiazepines. Psychotropic activity of some 4-amino-1,5-benzodiazepines have also been studied by Bauer et al.[42]. Golik[43] has also worked on 2,4-benzodiazepine as a potent CNS agent. The structure-activity relationship studies of some benzodiazepines as oxytocin antagonist[44] and antitumor antibiotics[45] have been documented. The antimicrobial, antifungal and anthelmintic activities of 3H-1,5-benzodiazepine derivatives have been studied by Kumar et al.[46]. Recently, many workers[47-50] have been reported some other biologically active benzodiazepines.

## EXPERIMENTAL

### Synthesis of of 2-(2-chloro-6-fluoroquinolin-3-yl)-4-(4-methoxyphenyl)-1*H*-1,5-benzodiazepine.

**[A] Synthesis of *N*-(4-fluorophenyl)acetamide:**

A mixture of 4-fluoroaniline (0.01M) and acetic anhydride (0.01M) in absolute ethanol (20 ml) was refluxed in water bath for 2-3 hrs using $H_2SO_4$ as catalyst. The crude product was isolated and crystallized from absolute ethanol.

**[B] Synthesis of 2-chloro-6-fluoroquinoline-3-carbaldehyde:**

*N*- (4-fluorophenyl) acetamide (0.01M) was added in a mixture of Vilsmeier-Haack reagent (prepared by drop wise addition of 6.5 ml $POCl_3$ in ice cooled 2ml DMF) and refluxed for 27 hrs. The reaction mixture was poured into ice followed by neutralization using sodium bicarbonate. The crude product was isolated and crystallized from ethanol.

**[C] Synthesis of (2*E*)- 3- (2-chloro-6-fluoroquinolin-3-yl) -1- (4- methoxy phenyl) prop-2-en-1- one:**

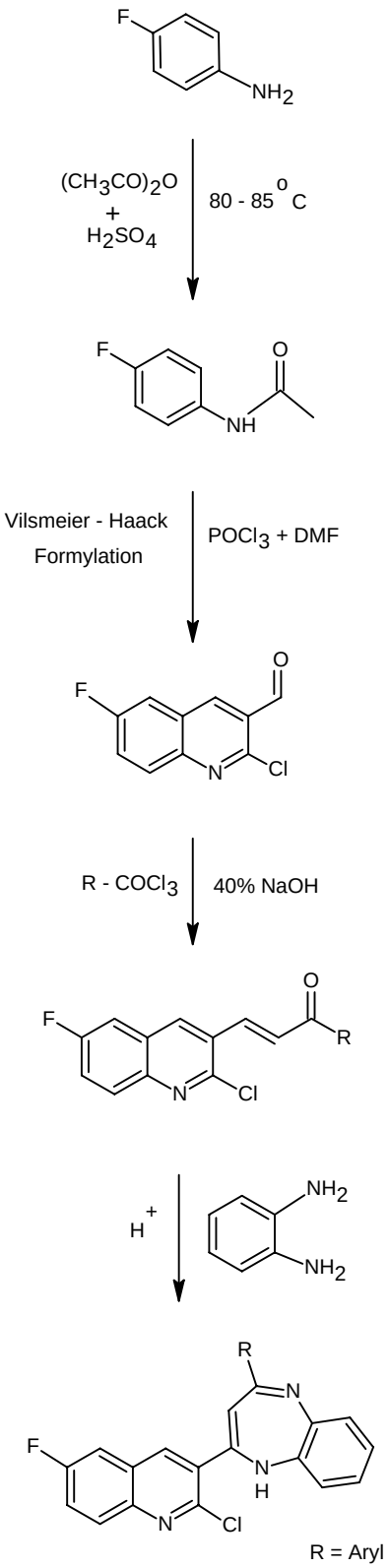
To a well stirred solution of 2-chloro-6-fluoroquinoline-3-carbaldehyde (0.01M) and p-methoxy-acetophenone (0.01M) in ethanol (25 ml), 40% NaOH was added till the solution became basic. The reaction mixture was stirred for 48 hrs. The contents were poured into ice, acidified, filtered and crystallized from ethanol.

**[D] Synthesis of of 2- (2-chloro-6-fluoroquinolin-3-yl) - 4- (4- methoxy phenyl)- 1*H*-1,5-benzodiazepine:**

A mixture of (2*E*) -3-(2-chloro-6-fluoroquinolin-3-yl) -1-(4- methoxy phenyl) prop-2-en-1- one, o-phenylenediamine (0.01 M) in ethanol (20ml) and glacial $CH_3COOH$ (3-4 drops) was refluxed for 8-10 hrs. The resulting mixture was poured on crushed ice. The product obtained was filtered and crystallized from ethanol.

Similarly, other substituted benzodiazepines have been prepared. The physical data for the synthesized compounds are reported in Table 1.1.

**REACTION SCHEME**




R = Aryl

**Table 1.1: Physical constants of benzodiazepines.**

| Sr. No. | Code | R | M.F. | M. Wt. (g/mol) | $R_f$* Value | M.P. $^oC$ | Yield % |
|---|---|---|---|---|---|---|---|
| **1** | **NBN-1** | 4-$OCH_3$-$C_6H_4$- | $C_{25}H_{17}ClFN_3O$ | 429.9 | 0.59 | 198 | 54 |
| **2** | **NBN-2** | 4-$NH_2$-$C_6H_4$- | $C_{24}H_{16}ClFN_4$ | 414.9 | 0.51 | 175 | 59 |
| **3** | **NBN-3** | 4-Br-$C_6H_4$- | $C_{24}H_{14}BrClFN_3$ | 478.7 | 0.66 | 232 | 49 |
| **4** | **NBN-4** | 4-$NO_2$-$C_6H_4$- | $C_{24}H_{14}ClFN_4O_2$ | 444.8 | 0.49 | 202 | 62 |
| **5** | **NBN-5** | 3-$NO_2$-$C_6H_4$- | $C_{24}H_{14}ClFN_4O_2$ | 444.8 | 0.64 | 215 | 57 |
| **6** | **NBN-6** | 4-OH-$C_6H_4$- | $C_{24}H_{15}ClFN_3O$ | 415.8 | 0.74 | 248 | 61 |
| **7** | **NBN-7** | 4-$CH_3$-$C_6H_4$- | $C_{25}H_{17}ClFN_3$ | 413.9 | 0.82 | 186 | 55 |
| **8** | **NBN-8** | 4-Cl-$C_6H_4$- | $C_{24}H_{14}Cl_2FN_3$ | 434.4 | 0.59 | 232 | 52 |
| **9** | **NBN-9** | 2-OH-$C_6H_4$- | $C_{24}H_{15}ClFN_3O$ | 415.8 | 0.63 | 177 | 58 |
| **10** | **NBN-10** | $C_6H_5$- | $C_{24}H_{15}ClFN_3$ | 399.8 | 0.70 | 182 | 62 |

* Ethyl acetate:Hexane: 2:8

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

**Infrared spectra:**

The IR spectra were recorded by SHIMADZU-FTIR-8400 Spectrophotometer in the frequency range of 4000-400 $cm^{-}1$ by KBr powder method. Figure 1.1 shows IR spectra of NBN-1. The IR spectral data for NBN-1 is given in Table 1.2. The spectral data for all other compounds are reported in Table 1.3.

**$^{1}$H NMR Spectra:**

The NMR spectra were recorded by BRUKER Spectrometer (400 MHz) using internal reference TMS and solvent $CDCl_3$/DMSO. Figure 1.2 shows NMR spectra of NBN-1. The spectral data for NBN-1 is given in Table 1.4.

**Mass spectra**:

The Mass spectra were recorded by GCMS-SHIMADZU-QP2010. Figure 1.3 shows mass spectra of NBN-1.The proposed mass fragmentation of the same compound is also given in Scheme 1.1.

**Figure 1.1 : IR spectra of 2-(2-chloro-6-fluoroquinolin-3-yl)-4-(4-methoxyphenyl)-1*H*-1,5-benzodiazepine (NBN-1).**

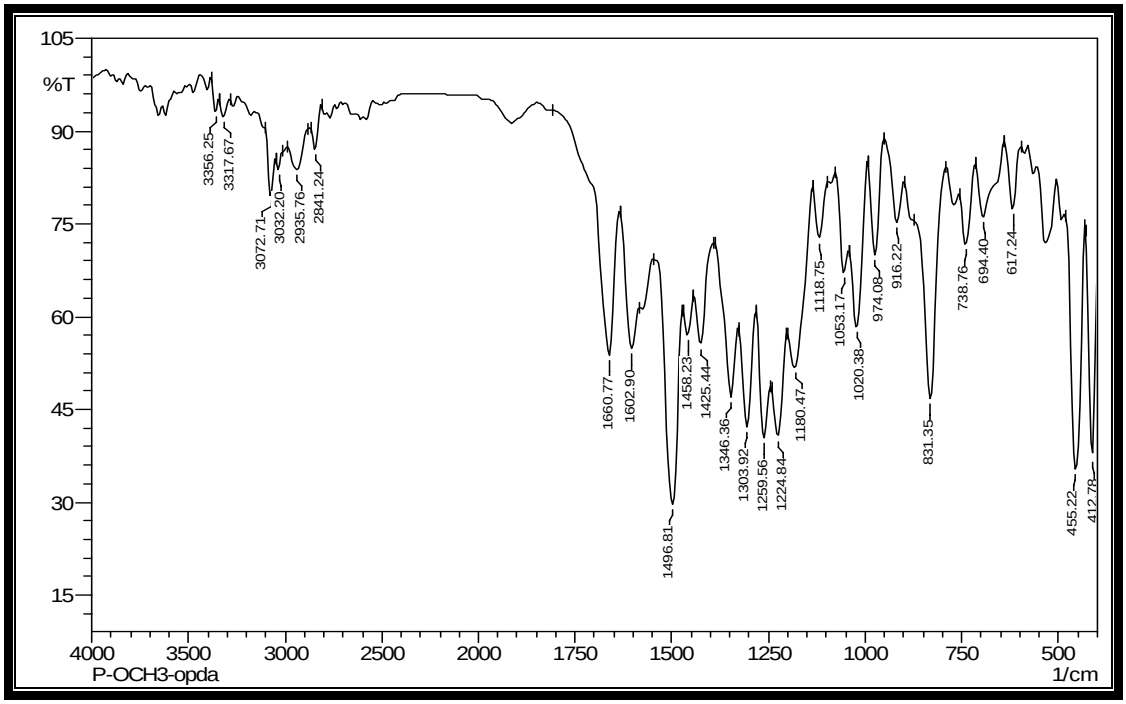


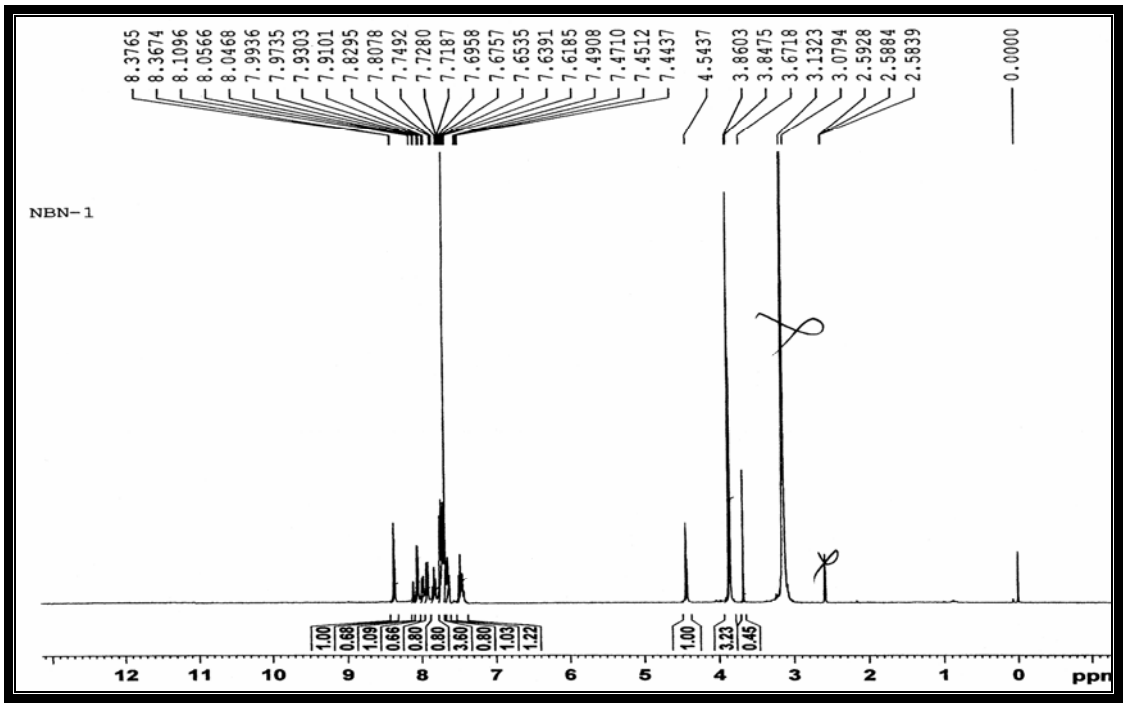

**Table 1.2: IR spectral data of 2-(2-chloro-6-fluoroquinolin-3-yl)-4-(4-methoxyphenyl)-1*H*-1,5-benzodiazepine (NBN-1).**

| Type | Vibration mode | Frequency in $cm^{-1}$ | |
|---|---|---|---|
| | | Observed | Reported[51,52] |
| Alkane (methyl) | C-H str. (asym.) | 2935.76 | 2975-2920 |
| | C-H str. (sym.) | 2841.24 | 2880-2860 |
| | C-H def. (asym.) | 1458.23 | 1470-1435 |
| | C-H def.(sym.) | 1346.36 | 1395-1370 |
| Aromatic | C-H str. | 3072.71 | 3100-3000 |
| | C=C str. | 1496.81 | 1585-1480 |
| | C-H i.p. def. | 1118.75 | 1125-1090 |
| | C-H o.o.p. def. | 831.35 | 860-810 |
| Quinoline+ Diazepine ring | C=N str. | 1660.77 | 1690-1640 |
| | C-N str. | 1303.92 | 1350-1200 |
| | N-H str. | 3317.67 | 3400-3200 |
| | N-H def. | 1602.90 | 1650-1550 |
| ether | C-O-C str. (asym.) | 1259.56 | 1275-1200 |
| | C-O-C str. (sym.) | 1020.38 | 1075-1020 |
| | C-F | 1224.84 | 1400-1000 |
| | C-Cl | 738.76 | 800-600 |

**Table 1.3: IR spectral data of synthesized benzodiazepines.**

| Compounds | *IR ν, ($cm^{-1}$)* | | | | |
|---|---|---|---|---|---|
| | **C=C** | **C=N** | **C-F** | **C-Cl** | **R** |
| **NBN-2** | 1503.21 | 1656.32 | 1238.42 | 758.12 | 3268.12 |
| **NBN-3** | 1515.45 | 1644.21 | 1235.25 | 754.61 | 545.23 |
| **NBN-4** | 1524.12 | 1647.64 | 1222.32 | 744.32 | 1325.25 |
| **NBN-5** | 1505.21 | 1640.65 | 1228.54 | 768.12 | 1330.21 |
| **NBN-6** | 1524.12 | 1651.58 | 1211.28 | 735.45 | 3312.35 |
| **NBN-7** | 1508.24 | 1653.54 | 1212.64 | 725.43 | 2938.12 |
| **NBN-8** | 1509.15 | 1647.52 | 1206.84 | 732.64 | 732.64 |
| **NBN-9** | 1501.78 | 1643.44 | 1205.12 | 735.54 | 3323.14 |
| **NBN-10** | 1514.52 | 1648.21 | 1230.25 | 738.71 | - |

**Figure 1.2: $^{1}$H NMR spectra of 2-(2-chloro-6-fluoroquinolin-3-yl)-4- (4-methoxyphenyl)-1*H*-1,5-benzodiazepine (NBN-1).**



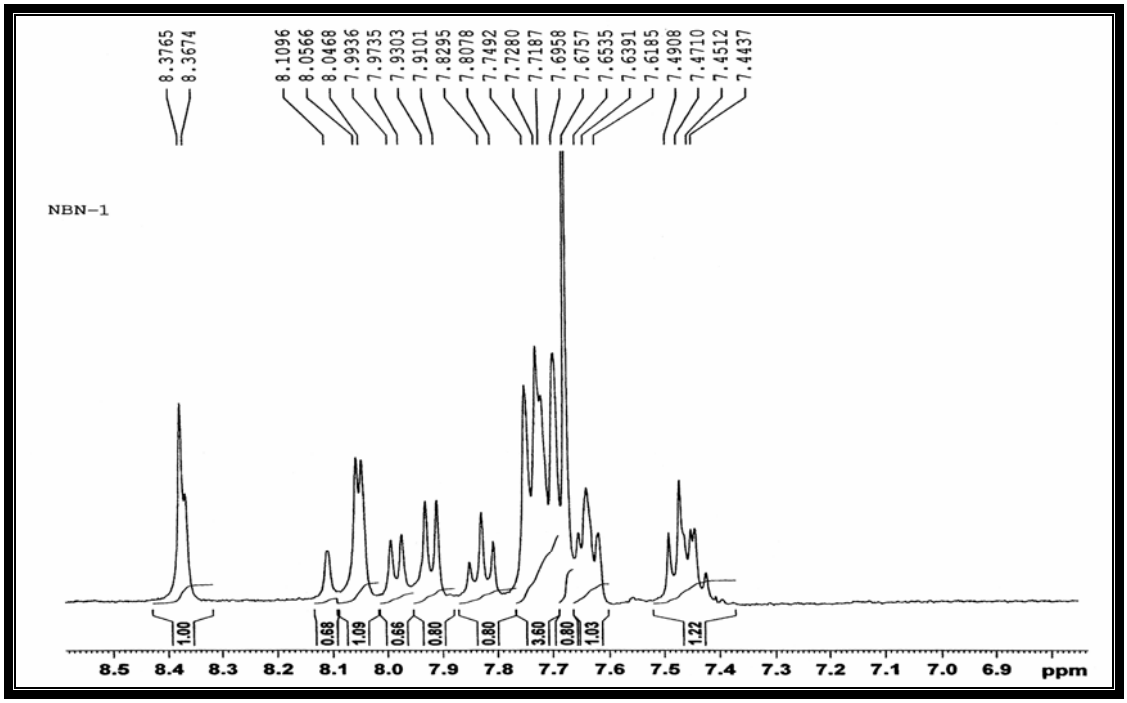
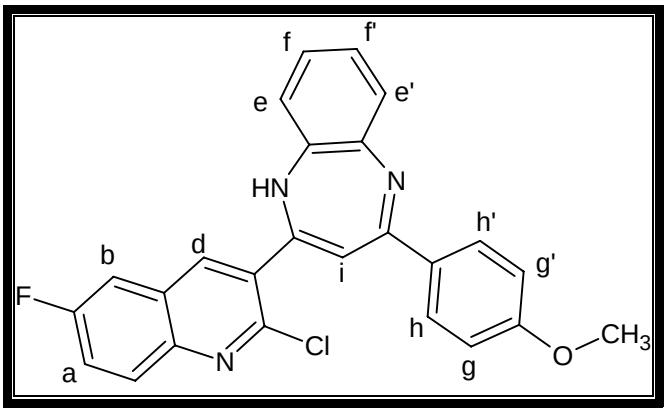
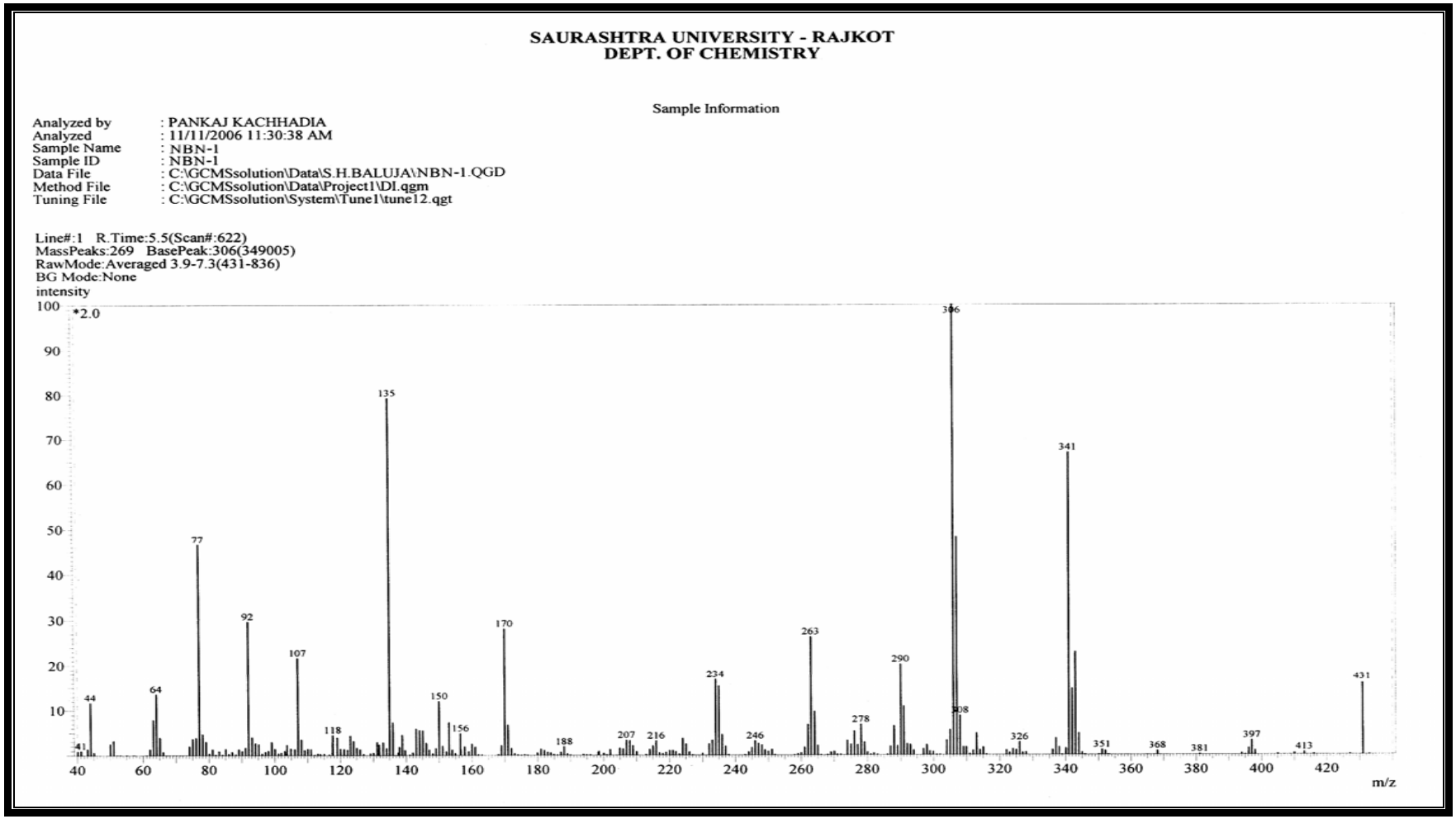



**Table 1.4: $^{1}$H NMR spectral data of 2-(2-chloro-6-fluoroquinolin-3-yl)-4-(4-methoxyphenyl)-1*H*-1,5-benzodiazepine (NBN-1).**

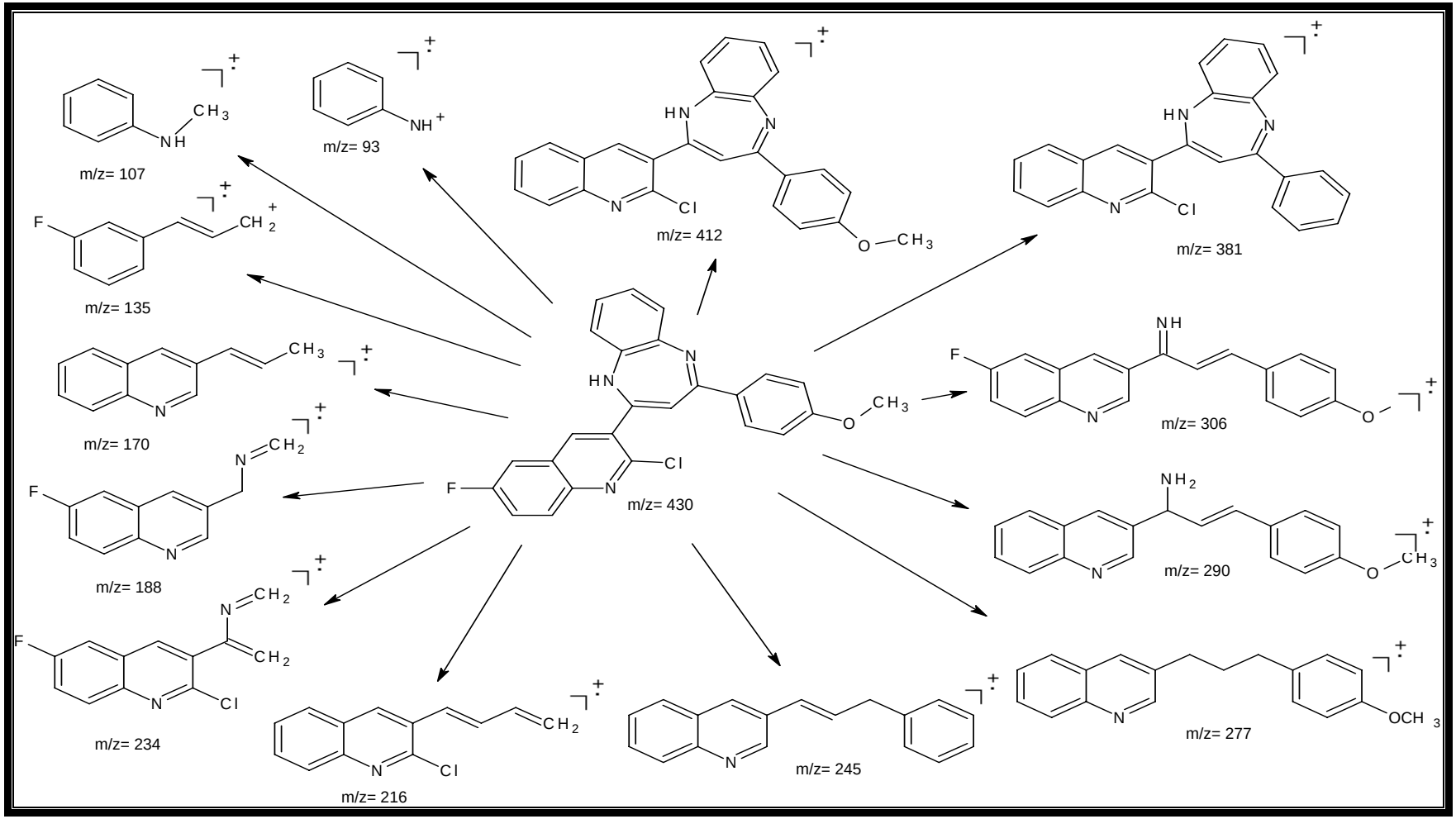



| Singal No. | Signal Position (δ ppm) | Relative No. of Protons | Multiplicity | Inference | *J* (Hz) |
|---|---|---|---|---|---|
| 1 | 3.86 | 3 | singlet | -OC$\underline{H}_3$ | - |
| 2 | 4.54 | 1 | singlet | $H_i$ | - |
| 3 | 7.44-7.49 | 1 | triplet | Ar-$H_f$ | - |
| 4 | 7.61-7.65 | 1 | triplet | Ar-$H_{f'}$ | - |
| 5 | 7.67-7.74 | 4 | multiplet | Ar-$H_{gg'hh'}$ | - |
| 6 | 7.80-7.82 | 1 | triplet | Ar-$H_a$ | - |
| 7 | 7.91-7.93 | 1 | doublet | Ar-$H_e$ | 8.08 |
| 8 | 7.97-7.99 | 1 | doublet | Ar-$H_{e'}$ | 8.04 |
| 9 | 8.04-8.10 | 2 | doublet | Ar-$H_{b+c}$ | 3.92 |
| 10 | 8.38 | 1 | singlet | Ar-$H_d$ | - |

**Figure 1.3: Mass spectra of2-(2-chloro-6-fluoroquinolin-3-yl)-4-(4-methoxyphenyl)-1*H*-1,5-benzodiazepine(NBN-1).**



**Scheme 1.1: Proposed mass fragmentation of 2-(2-chloro-6-fluoroquinolin-3-yl)-4-(4-methoxyphenyl)-1*H*-1,5-benzodiazepine (NBN-1).**



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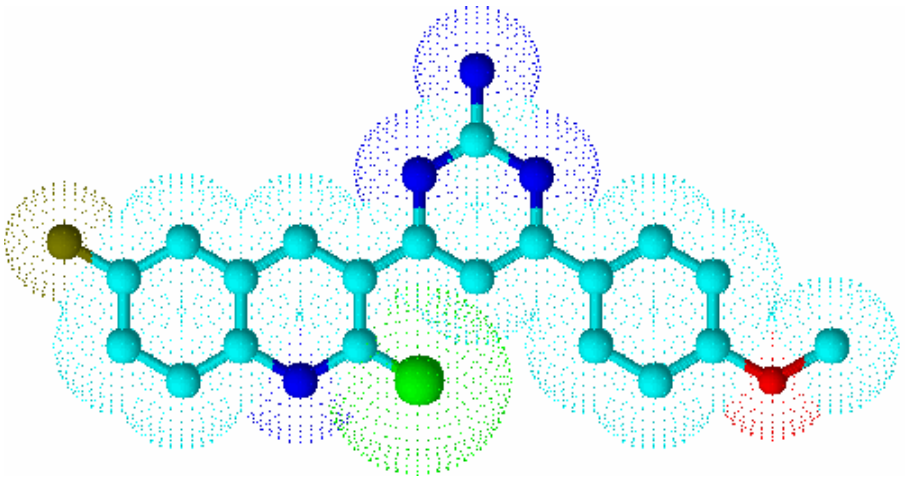
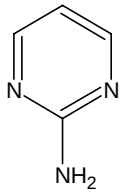


# Section-II

# Synthesis of Aminopyrimidines

## INTRODUCTION

2-Amino pyrimidine is the most important member of all the diazines as this ring system occurs widely in living organisms. Further, these derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activities.




2-Amino pyrimidine and its derivatives have been synthesized by different methods[1-6]. Shirai[7] has prepared these derivatives by the condensation of guanidine with propargylaldehyde whereas Ueda et al.[8] used Hilbert-Johnson procedure for the synthesis. El-Hashash et al.[9] have synthesized pyrimidine derivatives by a facile one-pot conversion method. Kidemet and co-workers[10] have reported a novel method for the synthesis of these derivatives under solvent-free conditions. Weber et al.[11] prepared these derivatives by solid-phase synthesis. Further, the synthesis of some metal complexes of 2- amino pyrimidine has also been documented[12-14]. Recently, some new amino pyrimidine derivatives have also been synthesized[15,16].

The FT-IR spectroscopic investigation of two dimensional polymeric complexes of 2- amino pyrimidine was documented by Akyuz[17]. Further, crystal[18], infrared and Raman spectroscopic[19] and thermochemical[12,20] studies of metal complexes of amino pyrimidine have also been reported.

As stated above, these amino pyrimidine derivatives are known to have wide spectrum of biological activities[21-25]. Buschauer[26] studied their antihistaminic activity whereas anthelmintic activity[27] has been reported by Chalquest. The antimicrobial activities of a variety of these amino pyrimidines have been studied by various workers[28-31]. Takahashi et al.[32] have reported cytokinin activity of some pyrimidine derivatives. Yoshioka et al.[33] have observed some of them as insecticide. The pesticidal and fungicidal activity of some amino pyrimidine derivatives have been reported by Obata et al.[34]. The fungicidal[35,36] and anticancer[37,38] activity of some other 4-aminopyrimidines have also been studied by other workers.

## EXPERIMENTAL

### Synthesis of 4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxyphenyl)-1,4-dihydropyrimidin-2-amine.

**[A] Synthesis of *N*-(4-fluorophenyl)acetamide:** Section-I [A]

**[B] Synthesis of 2-chloro-6-fluoroquinoline-3-carbaldehyde:** Section -I [B]

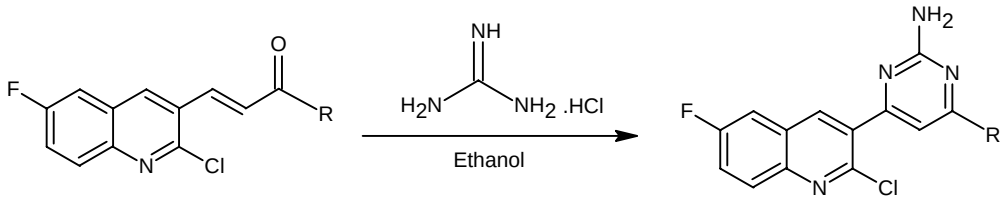
**[C] Synthesis of (2*E*)-3-(2-chloro-6-fluoroquinolin-3-yl)-1-(4- methoxy phenyl)prop-2-en-1- one:** Section -I [C]

**[D] Synthesis of 4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxyphenyl)-1,4-dihydropyrimidin-2-amine (NAP-1):**

A mixture of (2*E*) -3- ( 2- chloro- 6- fluoroquinolin – 3 –yl)-1-(4- methoxy phenyl) prop-2-en-1- one (0.01M) and guanidine hydrochloride (0.01M) in presence of potassium hydroxide (1 g) was refluxed in ethanol (20 ml) for 8-10 hours. The resulting mixture was poured on crushed ice. The product obtained was filtered and crystallized from ethanol.

Similarly, other substituted aminopyrimidines have been prepared.

**REACTION SCHEME**




The physical data are reported in Table 2.1.

The characterization was done by IR, NMR and mass spectral data. The instruments used are same as mentioned in Section-I. Figures 2.1, 2.2 and 2.3 show the IR, NMR and mass spectra for NAP-1. The IR and NMR spectral data for this compound is given in Tables 2.2 and 2.4 respectively. Table 2.3 shows the IR spectral data of all other synthesized compounds. The proposed mass fragmentation is reported in Scheme 2.1.

**Table 2.1: Physical constants of aminopyrimidines.**

| Sr. No. | Code | R | M.F. | M. Wt. (g/mol) | $R_f$* Value | M.P. $^oC$ | Yield % |
|---|---|---|---|---|---|---|---|
| **1** | **NAP-1** | 4-$OCH_3$-$C_6H_4$- | $C_{20}H_{14}ClFN_4O$ | 380.8 | 0.68 | 165 | 65 |
| **2** | **NAP-2** | 4-$NH_2$-$C_6H_4$- | $C_{19}H_{13}ClFN_5$ | 365.8 | 0.58 | 172 | 68 |
| **3** | **NAP-3** | 4-Br-$C_6H_4$- | $C_{19}H_{11}BrClFN_4$ | 429.7 | 0.55 | 181 | 62 |
| **4** | **NAP-4** | 4-$NO_2$-$C_6H_4$- | $C_{19}H_{11}ClFN_5O_2$ | 395.8 | 0.71 | 202 | 71 |
| **5** | **NAP-5** | 3-$NO_2$-$C_6H_4$- | $C_{19}H_{11}ClFN_5O_2$ | 395.8 | 0.63 | 241 | 74 |
| **6** | **NAP-6** | 4-OH-$C_6H_4$- | $C_{19}H_{12}ClFN_4O$ | 366.8 | 0.52 | 218 | 59 |
| **7** | **NAP-7** | 4-$CH_3$-$C_6H_4$- | $C_{20}H_{14}ClFN_4$ | 364.8 | 0.59 | 197 | 67 |
| **8** | **NAP-8** | 4-Cl-$C_6H_4$- | $C_{19}H_{11}Cl_2FN_4$ | 385.2 | 0.62 | 168 | 63 |
| **9** | **NAP-9** | 2-OH-$C_6H_4$- | $C_{19}H_{12}ClFN_4O$ | 366.8 | 0.68 | 174 | 68 |
| **10** | **NAP-10** | $C_6H_5$- | $C_{19}H_{12}ClFN_4$ | 350.8 | 0.71 | 194 | 72 |

* Acetone:Benzene: 2:8

**Figure 2.1: IR spectra of 4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxy-phenyl)-1,4-dihydropyrimidin-2-amine (NAP-1).**

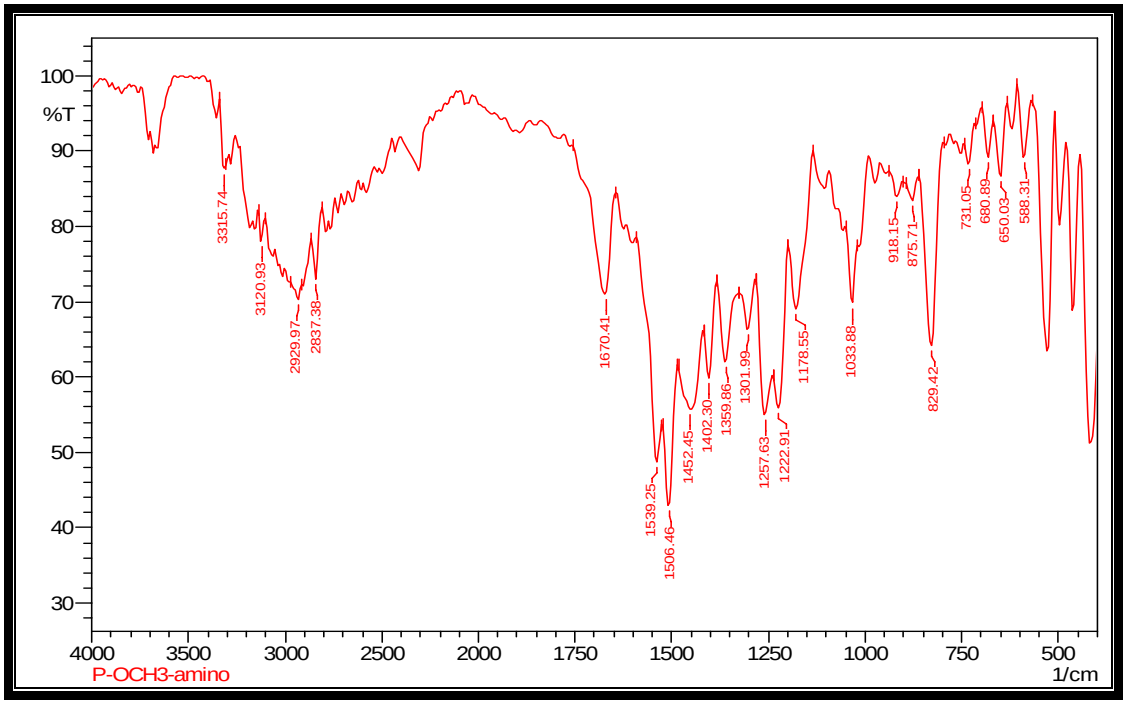


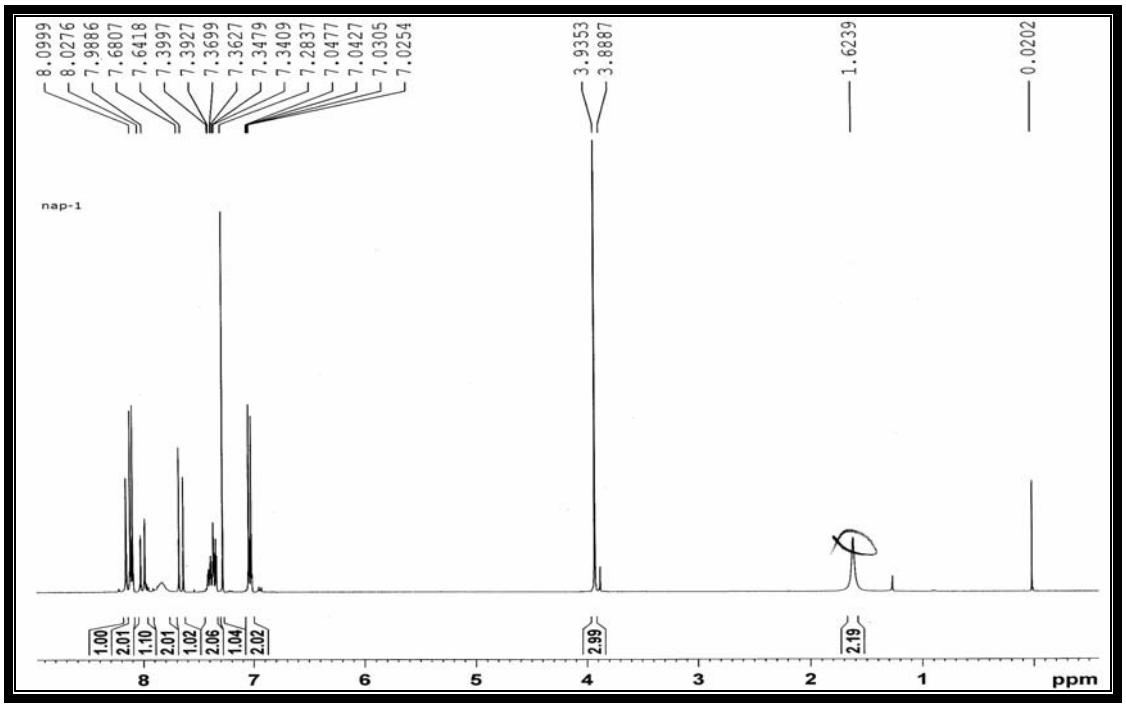

**Table 2.2: IR spectral data of 4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxyphenyl)-1,4-dihydropyrimidin-2-amine (NAP-1).**

| Type | Vibration mode | Frequency in $cm^{-1}$ | |
|---|---|---|---|
| | | Observed | Reported[39,40] |
| Alkane (methyl) | C-H str. (asym.) | 2929.97 | 2975-5920 |
| | C-H str. (sym.) | 2837.38 | 2880-2860 |
| | C-H def. (asym.) | 1452.45 | 1470-1435 |
| | C-H def.(sym.) | 1359.86 | 1395-1370 |
| Aromatic | C-H str. | 3120.93 | 3100-3000 |
| | C=C str. | 1506.46 | 1585-1480 |
| | C-H i.p. def. | 1033.88 | 1125-1090 |
| | C-H o.o.p. def. | 829.42 | 860-810 |
| Quinoline+ pyrimidine ring | C=N str. | 1670.41 | 1690-1640 |
| | C-N str. | 1257.63 | 1350-1200 |
| ether | C-O-C str. (asym.) | 1222.91 | 1275-1200 |
| | C-O-C str. (sym.) | 1033.88 | 1075-1020 |
| | C-F | 1178.55 | 1400-1000 |
| | C-Cl | 731.05 | 800-600 |
| Amine | N-H str. | 3315.74 | 3400-3200 |
| | N-H def. | 1539.25 | 1650-1590 |

**Table 2.3: IR spectral data of synthesized aminopyrimidines.**

| Compounds | *IR ν, ($cm^{-1}$)* | | | | |
|---|---|---|---|---|---|
| | **C=C** | **C-N** | **N-H** | **C-Cl** | **R** |
| **NAP-2** | 1515.35 | 1256.21 | 3268.54 | 735.62 | 3268.54 |
| **NAP-3** | 1524.32 | 1258.12 | 3278.25 | 731.05 | 560.12 |
| **NAP-4** | 1528.25 | 1257.63 | 3315.74 | 745.52 | 1334.53 |
| **NAP-5** | 1531.54 | 1248.25 | 3324.41 | 725.95 | 1330.21 |
| **NAP-6** | 1521.84 | 1257.63 | 3312.58 | 731.05 | 3322.35 |
| **NAP-7** | 1521.54 | 1242.54 | 3298.21 | 731.12 | 2939.12 |
| **NAP-8** | 1524.21 | 1238.25 | 3315.74 | 741.23 | 741.23 |
| **NAP-9** | 1534.89 | 1257.63 | 3268.12 | 721.56 | 3298.53 |
| **NAP-10** | 1527.32 | 1257.63 | 3265.52 | 728.26 | - |

**Figure 2.2: $^{1}$H NMR spectra of 4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxyphenyl)-1,4-dihydropyrimidin-2-amine (NAP-1).**



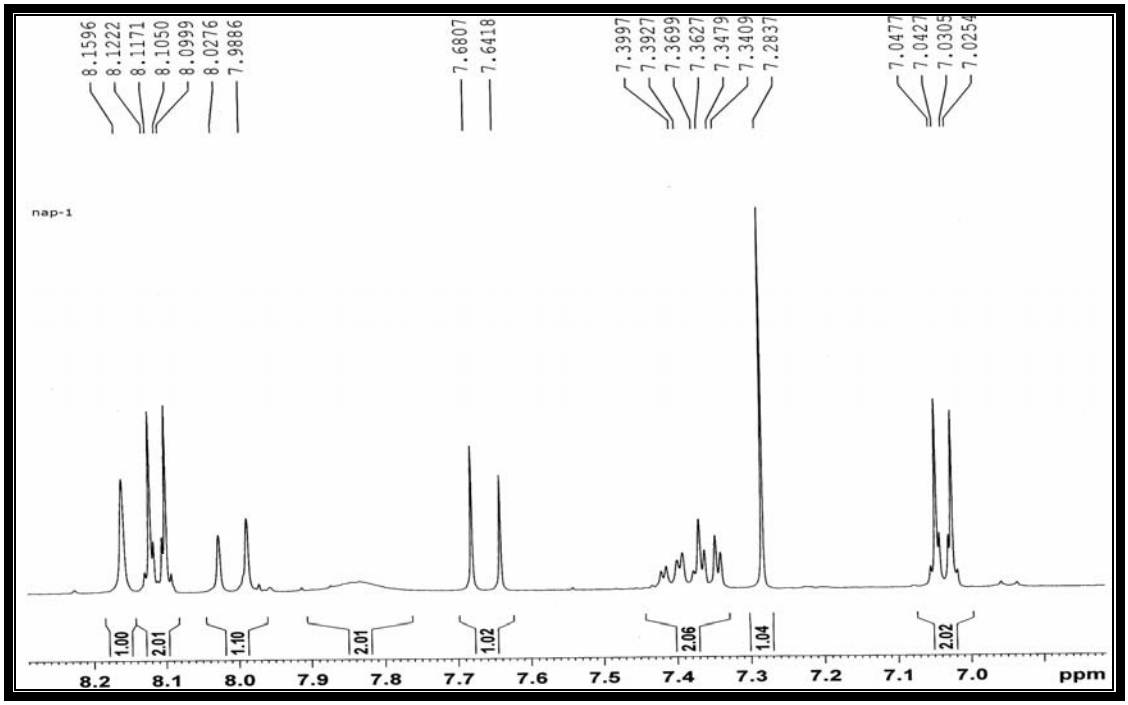
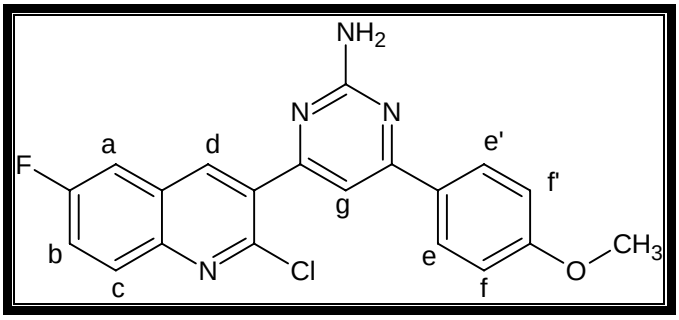
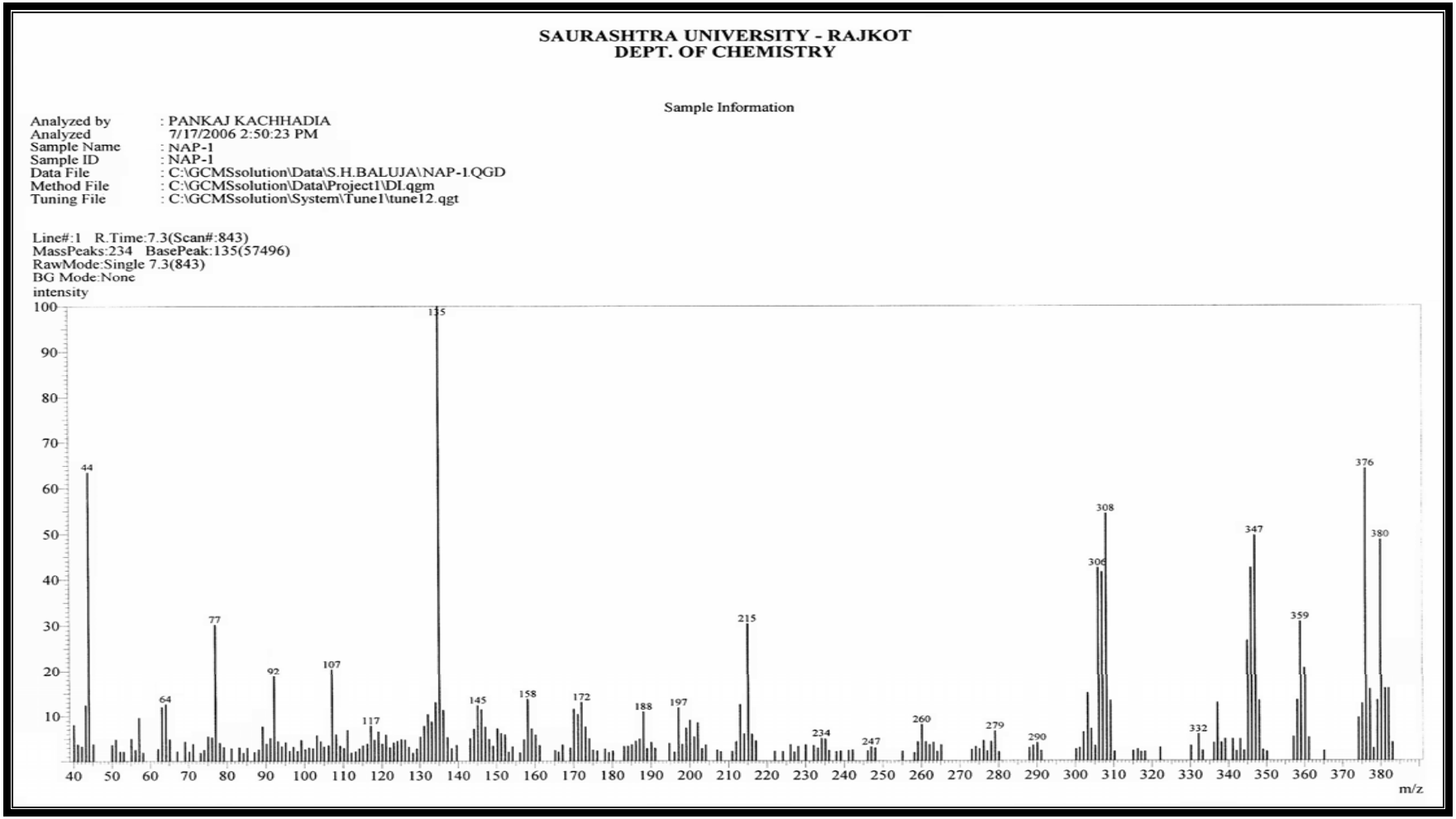



**Table 2.4: $^1$H NMR spectral data of 4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxyphenyl)-1,4-dihydropyrimidin-2-amine (NAP-1).**

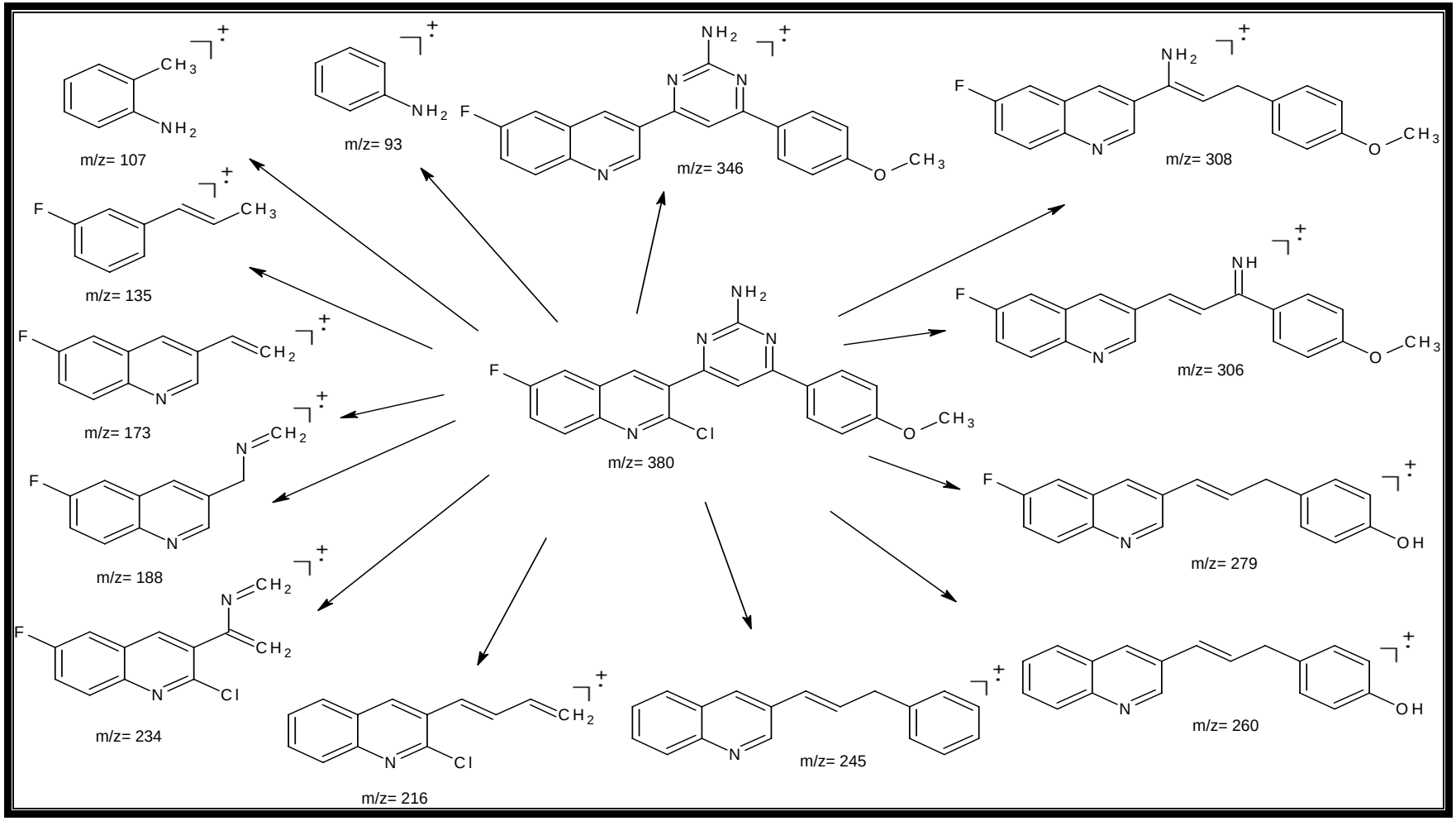



| Singal No. | Signal Position (δ ppm) | Relative No. of Protons | Multiplicity | Inference | *J* (Hz) |
|---|---|---|---|---|---|
| 1 | 3.94 | 3 | singlet | -OC$\underline{H}_3$ | - |
| 2 | 7.03-7.05 | 2 | doublet | Ar-$H_{ee'}$ | 6.99 |
| 3 | 7.28 | 1 | singlet | Ar-$H_g$ | - |
| 4 | 7.34-7.40 | 2 | multiplet | Ar-$H_{bc}$ | - |
| 5 | 7.64-7.68 | 1 | doublet | Ar-$H_a$ | 5.56 |
| 6 | 7.84 | 2 | Singlet | -N$\underline{H}$ | - |
| 7 | 8.10-8.12 | 2 | doublet | Ar-$H_{ff'}$ | 6.91 |
| 8 | 8.16 | 1 | Singlet | Ar-$H_d$ | - |

**Figure 2.3: Mass Spectra of 4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxyphenyl)-1,4-dihydropyrimidin-2-amine (NAP-1).**



**Scheme 2.1: Proposed mass fragmentation of 4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxyphenyl)-1,4-dihydro pyrimidin-2-amine (NAP-1).**



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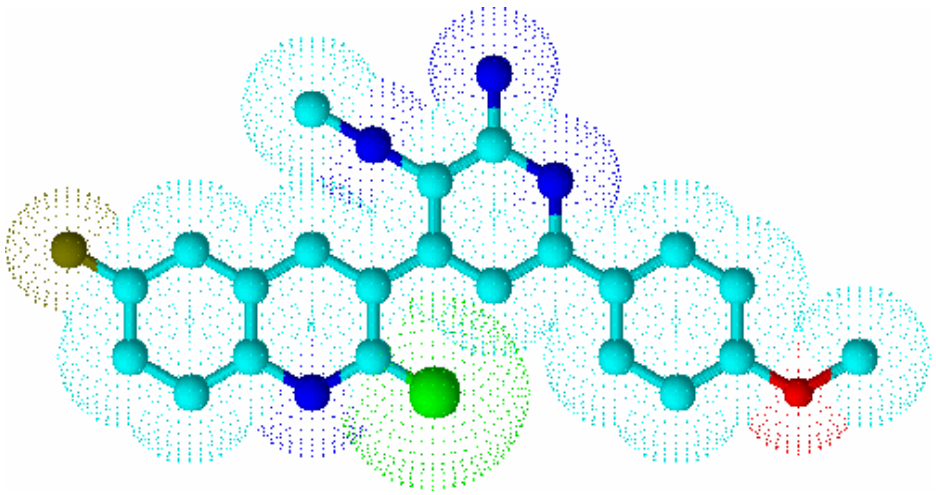


# Section-III

# Synthesis of Cyanopyridines

## INTRUDUCTION

Most of pyridine derivatives are synthesized by manipulation of pyridine and its simple homologues in a manner similar to chemistry of the benzenoid chemistry. However the simple pyridine compounds are prepared by the cyclization of aliphatic raw materials.

Various methods for the synthesis of pyridine derivatives have been cited in the literature[1-10]. Synthesis of pyridine-2-sulphonhydrazide 1-oxide and alpha-(2-pyridylthio)acethydrazide and its 1-oxide were reported by Comrie and Mir[11]. Spitzner[12] have documented a simple synthesis of pyridine alkaloids. Ahmad et al.[13] have reported the synthesis of pyridine-3-aldoxime and pyridine-4-aldoxime. Synthesis of some pyridine derivatives from 3-formylchromone have also been documented by Haas and co-workers[14]. Solid-phase and combinatorial synthesis of pyridine derivatives have been studied by Patel et al.[15]. Further, vapor phase and microwave irradiation synthesis of pyridine derivatives have also been reported[16,17]. Recently, convenient synthesis of pyridine derivatives have been documented[18,19].

Literature survey shows that these derivatives exhibit various biological activities such as anticonvulsant[20,21], fungicidal[22], analgesic[23,24], anti-inflammatory[25,26], anticancer[27,28], antihypertensive[29,30], insecticidal[31,32], antiulcer[33,34], antitubercular[35], molluscicidal[36] etc. Graciunescu et al.[37] have reported antiepileptic activities and toxicological profiles of some complex salts of pyridine derivatives. The anti-inflammatory activities of some cyanopyridines have also been studied by Moeller and Gloxhuber[38]. Baldwin and co-workers[39] have reported the antihypertensive activity of some new cyanopyridines. The insecticidal[40] and antianexiety[41] activity of these derivatives have also been reported. Further, antimicrobial activity of some of these derivatives has been studied by various workers[42-46].

## EXPERIMENTAL

### Synthesis of 2-amino-4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxy phenyl) nicotinonitrile.

**[A] Synthesis of *N*-(4-fluorophenyl)acetamide:** Section-I [A]

**[B] Synthesis of 2-chloro-6-fluoroquinoline-3-carbaldehyde:** Section -I [B]

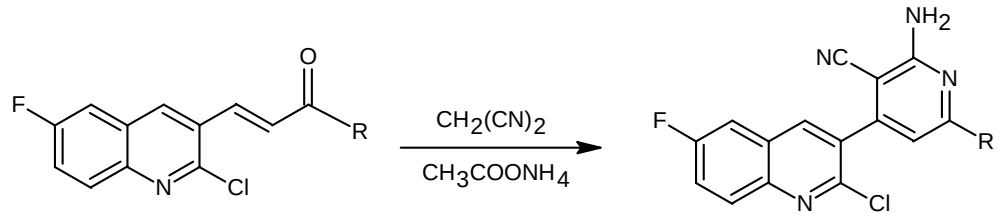
**[C] Synthesis of (2*E*)-3-(2-chloro-6-fluoroquinolin-3-yl)-1-(4-methoxy phenyl)prop-2-en-1- one:** Section -I [C]

**[D] Synthesis of 2-amino-4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxy phenyl) nicotinonitrile (NCP-1):**

A mixture of (2*E*) - 3- (2- chloro- 6-fluoroquinolin-3-yl) -1-(4- methoxy phenyl) prop-2-en-1-one (0.01 M), malononitrile (0.01 M) and ammonium acetate (0.08 M) in ethanol (30 ml) was refluxed for 10-12 hrs. The content was poured on crushed ice. The product obtained was filtered, washed with water and crystallized from ethanol.

Similarly, other substituted cyanopyridines have been prepared.

**REACTION SCHEME**




The physical data are reported in Table 3.1.

The characterization was done by IR, NMR and mass spectral data. The instruments used are same as mentioned in Section-I. Figures 3.1, 3.2 and 3.3 show the IR, NMR and mass spectra for NCP-1. The IR and NMR spectral data for this compound is given in Tables 3.2 and 3.4 respectively. Table 3.3 shows the IR spectral data of all other synthesized compounds. The proposed mass fragmentation is reported in Scheme 3.1.

**Table 3.1: Physical constants of cyanopiridines.**

| Sr. No. | Code | R | M.F. | M. Wt. (g/mol) | $R_f$* Value | M.P. °C | Yield % |
|---|---|---|---|---|---|---|---|
| **1** | **NCP-1** | 4-$OCH_3$-$C_6H_4$- | $C_{22}H_{14}ClFN_4O$ | 404.8 | 0.65 | 212 | 69 |
| **2** | **NCP-2** | 4-$NH_2$-$C_6H_4$- | $C_{21}H_{13}ClFN_5$ | 389.8 | 0.51 | 210 | 72 |
| **3** | **NCP-3** | 4-Br-$C_6H_4$- | $C_{21}H_{11}BrClFN_4$ | 453.7 | 0.49 | 225 | 75 |
| **4** | **NCP-4** | 4-$NO_2$-$C_6H_4$- | $C_{21}H_{11}ClFN_5O_2$ | 419.8 | 0.75 | 196 | 71 |
| **5** | **NCP-5** | 3-$NO_2$-$C_6H_4$- | $C_{21}H_{11}ClFN_5O_2$ | 419.8 | 0.69 | 178 | 63 |
| **6** | **NCP-6** | 4-OH-$C_6H_4$- | $C_{21}H_{12}ClFN_4O$ | 390.8 | 0.73 | 188 | 67 |
| **7** | **NCP-7** | 4-$CH_3$-$C_6H_4$- | $C_{22}H_{14}ClFN_4$ | 388.8 | 0.52 | 162 | 64 |
| **8** | **NCP-8** | 4-Cl-$C_6H_4$- | $C_{21}H_{11}Cl_2FN_4$ | 409.2 | 0.58 | 154 | 75 |
| **9** | **NCP-9** | 2-OH-$C_6H_4$- | $C_{21}H_{11}Cl_2FN_4$ | 409.2 | 0.47 | 202 | 79 |
| **10** | **NCP-10** | $C_6H_5$- | $C_{21}H_{12}ClFN_4$ | 374.8 | 0.45 | 187 | 81 |

*Ethyl acetate:Hexane: 2.5:7.5

**Figure 3.1: IR spectra of 2-amino-4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxyphenyl)nicotinonitrile (NCP-1).**

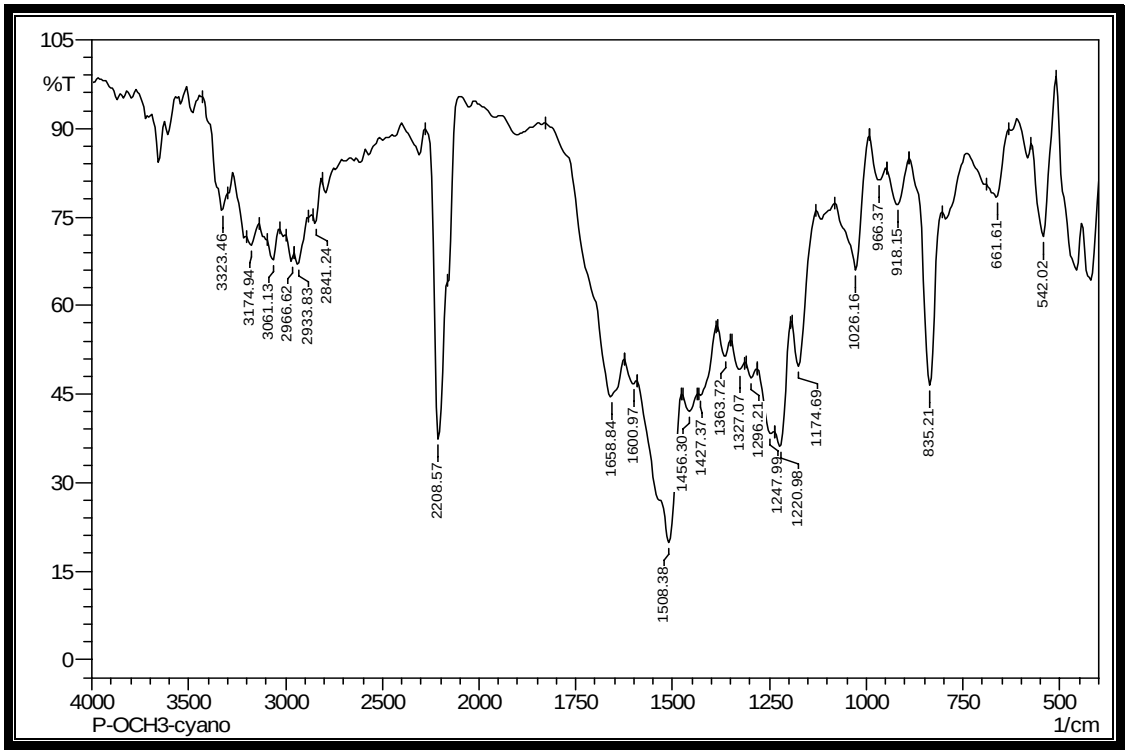


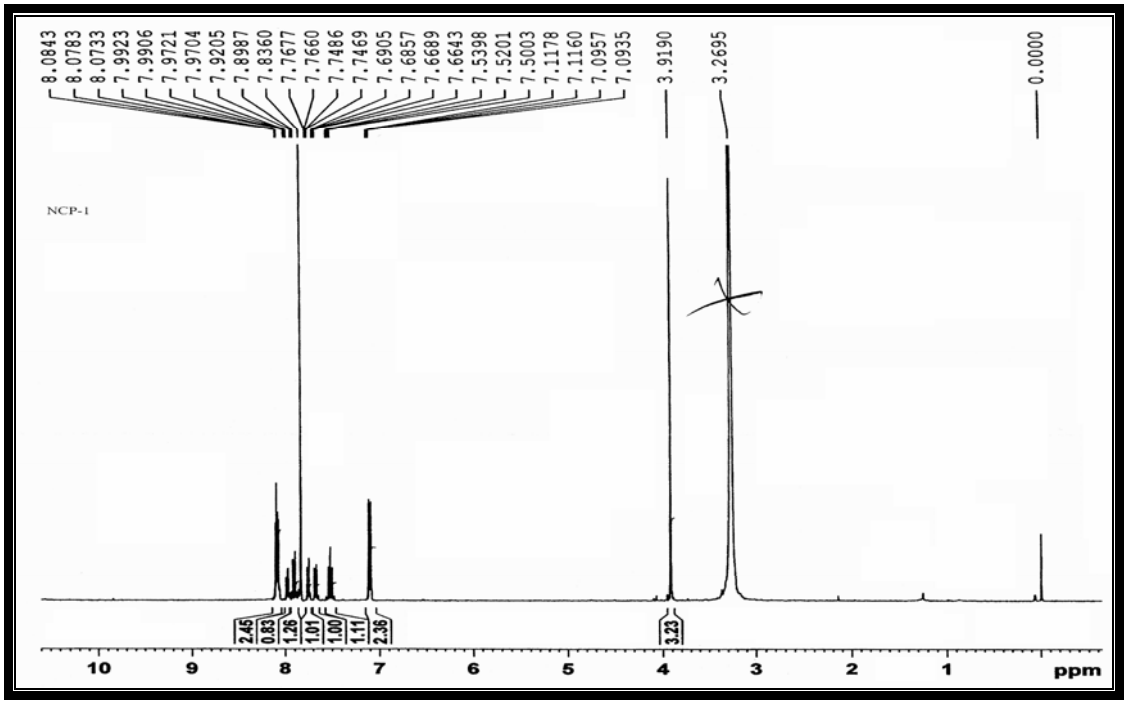

**Table 3.2: IR spectral data of 2-amino-4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxyphenyl)nicotinonitrile (NCP-1).**

| Type | Vibration mode | Frequency in $cm^{-1}$ | |
|---|---|---|---|
| | | Observed | Reported[47,48] |
| Alkane (methyl) | C-H str. (asym.) | 2933.83 | 2975-2920 |
| | C-H str. (sym.) | 2841.24 | 2880-2860 |
| | C-H def. (asym.) | 1456.30 | 1470-1435 |
| | C-H def.(sym.) | 1363.72 | 1395-1370 |
| Aromatic | C-H str. | 3061.13 | 3100-3000 |
| | C=C str. | 1508.38 | 1585-1480 |
| | C-H i.p. def. | 1026.16 | 1125-1090 |
| | C-H o.o.p. def. | 835.21 | 860-810 |
| Quinoline+ pyridine ring | C=N str. | 1658.84 | 1690-1640 |
| | C-N str. | 1247.99 | 1350-1200 |
| | C-N (Nitrile) str. | 2208.57 | 2240-2200 |
| ether | C-O-C str. (asym.) | 1220.98 | 1275-1200 |
| | C-O-C str. (sym.) | 1026.16 | 1075-1020 |
| | C-F | 1174.69 | 1400-1000 |
| | C-Cl | 661.61 | 800-600 |
| Amine | N-H str. | 3323.46 | 3400-3200 |
| | N-H def. | 1600.97 | 1650-1590 |

**Table 3.3: IR spectral data of synthesized cyanopyridines.**

| Compounds | *IR ν, ($cm^{-1}$)* | | | | |
|---|---|---|---|---|---|
| | **C=C** | **C≡N** | **N-H** | **C-Cl** | **R** |
| **NCP-2** | 1521.04 | 2232.14 | 3368.86 | 721.45 | 3368.86 |
| **NCP-3** | 1508.22 | 2208.57 | 3344.12 | 712.69 | 588.23 |
| **NCP-4** | 1511.23 | 2221.54 | 3323.48 | 724.62 | 1353.24 |
| **NCP-5** | 1508.22 | 2234.18 | 3315.64 | 668.52 | 1335.41 |
| **NCP-6** | 1528.64 | 2232.14 | 3298.78 | 688.24 | 3398.82 |
| **NCP-7** | 1522.08 | 2208.57 | 3275.63 | 678.64 | 2938.12 |
| **NCP-8** | 1508.22 | 2208.57 | 3304.12 | 731.60 | 731.60 |
| **NCP-9** | 1531.25 | 2204.12 | 3323.48 | 711.87 | 3313.52 |
| **NCP-10** | 1525.32 | 2234.51 | 3285.45 | 715.45 | - |

**Figure 3.2: $^{1}$H NMR spectra of 2-amino-4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxyphenyl)nicotinonitrile (NCP-1).**



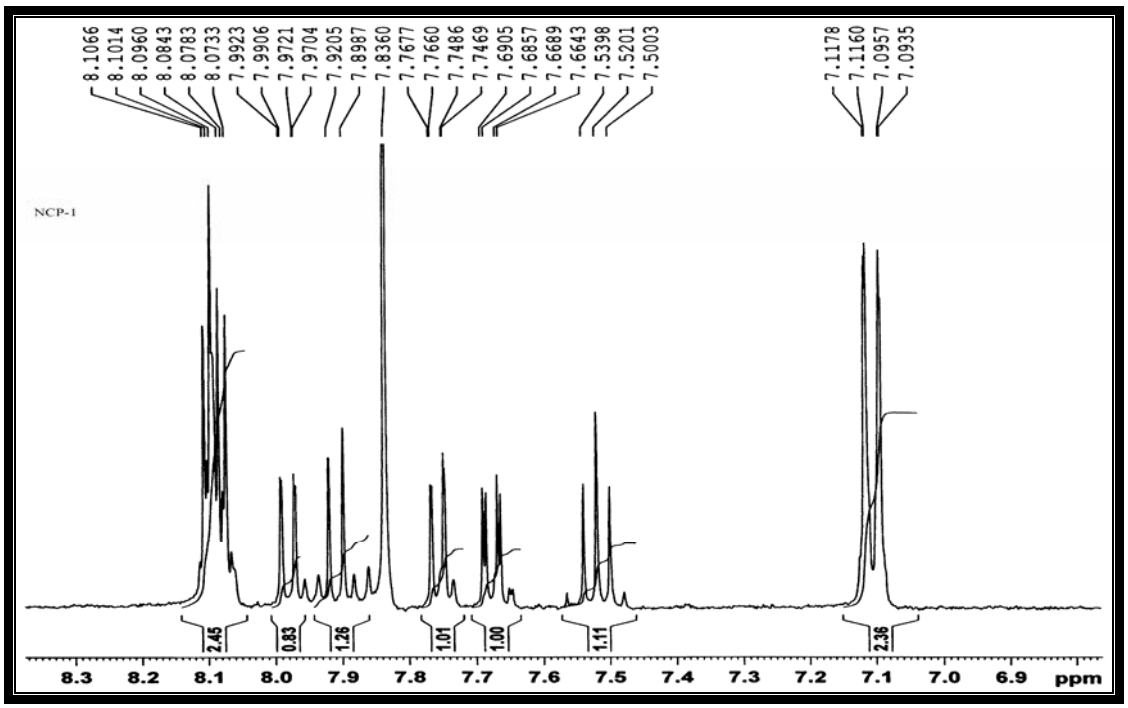
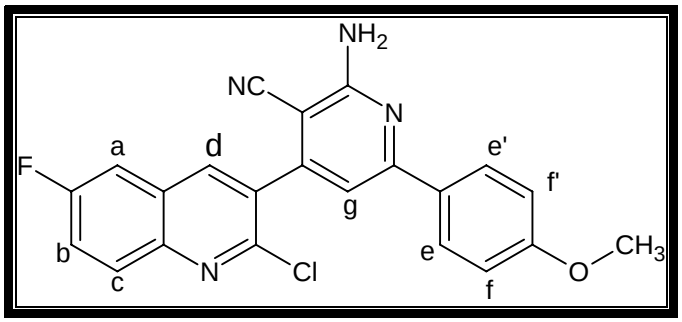
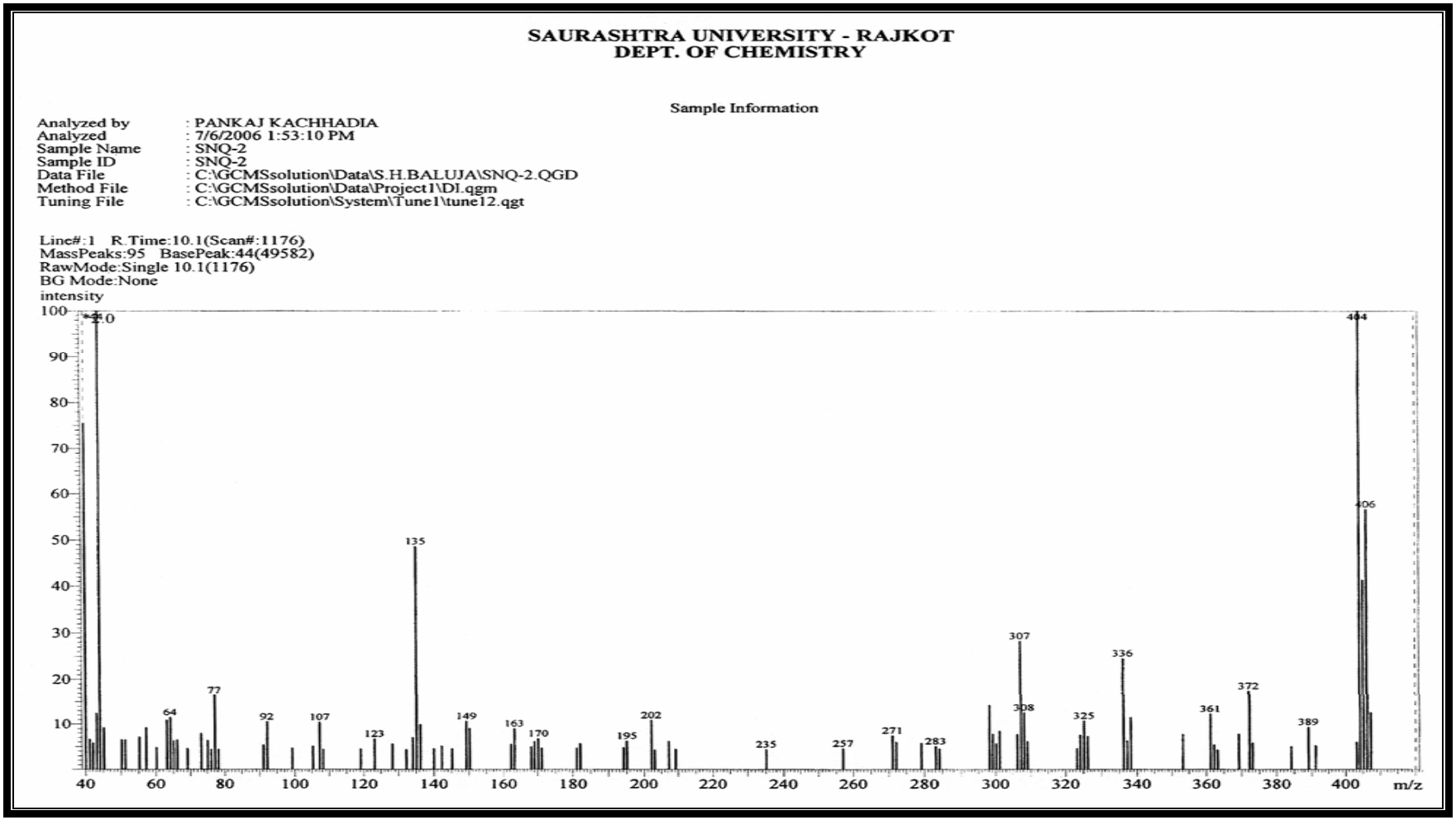



**Table 3.4:$^{1}$H NMR spectral data of 2-amino-4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxyphenyl)nicotinonitrile (NCP-1).**

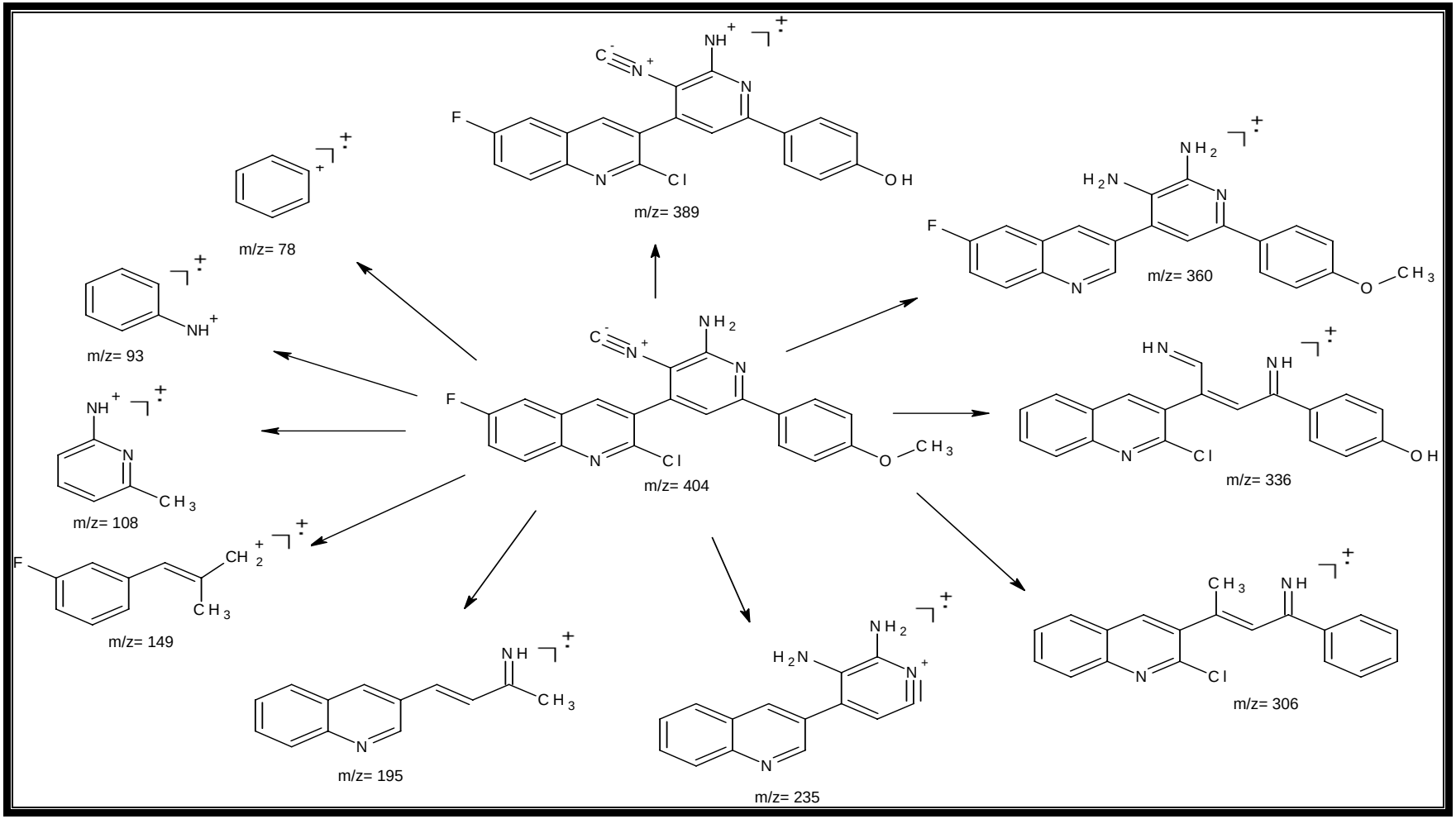



| Singal No. | Signal Position (δ ppm) | Relative No. of Protons | Multiplicity | Inference | *J* (Hz) |
|---|---|---|---|---|---|
| 1 | 3.92 | 3 | singlet | -OC$\underline{H}_3$ | - |
| 2 | 7.09-7.12 | 2 | doublet | Ar-$H_{ff'}$ | 8.88 |
| 3 | 7.50-7.54 | 1 | triplet | Ar-$H_b$ | - |
| 4 | 7.66-7.69 | 1 | doublet | Ar-$H_a$ | 8.82 |
| 5 | 7.75-7.77 | 1 | doublet | Ar-$H_c$ | 8.80 |
| 6 | 7.84-8.11 | 4 | multiplet | Ar-$H_{dgee'}$ | - |

**Figure 3.3: Mass Spectra of 2-amino-4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxyphenyl)nicotinonitrile (NCP-1).**



**Scheme 3.1: Proposed mass fragmentation of 2-amino-4-(2-chloro-6-fluoroquinolin-3-yl)-6-(4-methoxyphenyl) nicotinonitrile (NCP-1).**



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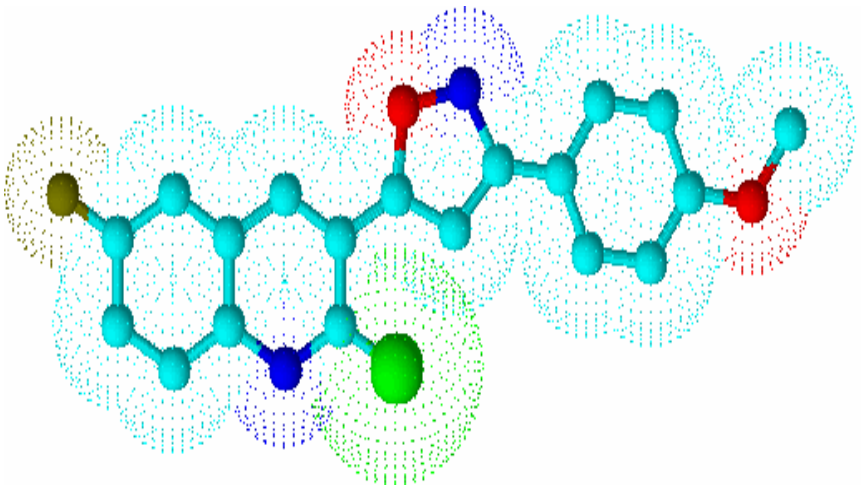


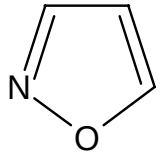
# Section-IV

# Synthesis of Isoxazoles

## INTRUDUCTION

Isoxazoles are a class of heterocyclic compounds containing two hetero atoms oxygen and nitrogen at one and two position in a five membered ring with two double bonds.

In 1888, Claisen first reported an isoxazole structure from a product of the reaction between 1,3 diketone and hydroxylamine[1]. It was shown to possess typical properties of an aromatic system but under certain reaction conditions, particularly in reducing or basic media, it becomes very highly labile.




Various methods for the synthesis of isoxazoles have been cited in the literature[2-10].

Quilico and Panizzi[11] have reported fulminic synthesis of isoxazole derivatives. Madikhanov et al.[12] and Simoni and co-workers[13] have reported synthesis of some isoxazole and isoxazoline derivatives. Synthesis of isoxazole derivatives of transition metals have also been studied by Kalinin et al.[14] Further, Molybdenum-mediated isoxazole compounds have been synthesized by Lin et al.[15] Lahvich and Koroleva[16] used isoxazole as a intermediates for the synthesis of 16-heteroprostanoid. Beebe[17] has synthesized polymer supported cyclic ethers by electrophilic cyclization of isoxazoles and furoisoxazoles. A solid-Phase synthesis of isoxazoles and isoxazolines has also reported by Kantorowski and Kurth[18]. Stereoselective synthesis of isoxazoles and pyrazoles has been done by Chiacchio et al.[19] Solid-phase synthesis of some isoxazole derivatives have also documented.[20,21] Microwave-assisted synthesis of isoxazole libraries were also reported by De Luca[22]. Various other methods for their synthesis have also been adopted[23-25]. Recently, by 1,3-dipolar cyclo addition also, isoxazole derivatives have been synthesized[26,27].

Further, literature survey shows that these derivatives exhibit various biological activities such as hypoglycemic[28], anticardiac[29], herbicidal[30], fungicidal[31], anti-inflammatory[32], hypolipidemic[33] inhibitory[34] etc. Regaila[35]

studied biological activity of some isoxazole derivatives. Dannhardt and co-workers[36] have reported muscarinic activity of some amino methylisoxazoles. Sayed et al.[37] have designed a dyestuffs containing isoxazole derivatives with biological activity. In vitro Antiprotozoal activity of dicationic 3,5-diphenylisoxazoles have also been studied[38]. Recently, antimicrobial and antitubercular activities of some new isoxazole derivatives have also been reported[39-41].

## EXPERIMENTAL

**Synthesis of 2-chloro-6-fluoro-3-[3-(4-methoxyphenyl) isoxazol-5-yl] quinoline.**

**[A] Synthesis of *N*-(4-fluorophenyl)acetamide:** Section-I [A]

**[B] Synthesis of 2-chloro-6-fluoroquinoline-3-carbaldehyde:** Section -I [B]

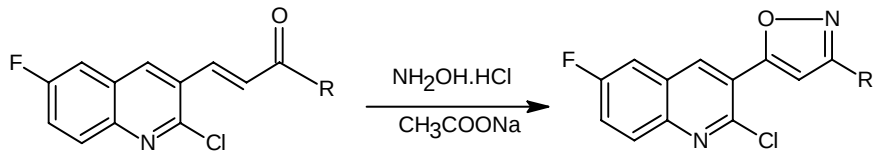
**[C] Synthesis of (2*E*)-3-(2-chloro-6-fluoroquinolin-3-yl)-1-(4-methoxy phenyl)prop-2-en-1- one:** Section -I [C]

**[D] Synthesis of 2-chloro-6-fluoro-3-[3-(4-methoxyphenyl) isoxazol-5-yl] quinoline (NISO-1).**

A solution of anhydrous sodium acetate (0.01 M) in minimum amount of hot acetic acid was added to a solution of hydroxylamine hydrochloride (0.01 M) in ethanol (20 ml). This solution was added to a solution of (2*E*)-3-(2-chloro-6-fluoroquinolin-3-yl)-1-(4-methoxy phenyl) prop-2-en-1- one (0.01 M) in ethanol (25 ml). The mixture was refluxed on a water bath for 10 hrs. The product was isolated and recrystallized from ethanol.

Similarly, other substituted isoxazoles have been prepared.

**REACTION SCHEME**




The physical data are reported in Table 4.1.

The characterization was done by IR, NMR and mass spectral data. The instruments used are same as mentioned in Section-I. Figures 4.1, 4.2 and 4.3 show the IR, NMR and mass spectra for NISO-1. The IR and NMR spectral data for this compound is given in Tables 4.2 and 4.4 respectively. Table 4.3 shows the IR spectral data of all other synthesized compounds. The proposed mass fragmentation is reported in Scheme 4.1.

**Table 4.1: Physical constants of isoxazoles.**

| Sr. No. | Code | R | M.F. | M. Wt. (g/mol) | $R_f$* Value | M.P. °C | Yield % |
|---|---|---|---|---|---|---|---|
| **1** | **NISO-1** | 4-$OCH_3$-$C_6H_4$- | $C_{19}H_{12}ClFN_2O_2$ | 354.8 | 0.57 | 171 | 71 |
| **2** | **NISO-2** | 4-$NH_2$-$C_6H_4$- | $C_{18}H_{11}ClFN_3O$ | 339.8 | 0.68 | 184 | 65 |
| **3** | **NISO-3** | 4-Br-$C_6H_4$- | $C_{18}H_9BrClFN_2O$ | 403.6 | 0.65 | 210 | 69 |
| **4** | **NISO-4** | 4-$NO_2$-$C_6H_4$- | $C_{18}H_9ClFN_3O_3$ | 369.7 | 0.61 | 168 | 72 |
| **5** | **NISO-5** | 3-$NO_2$-$C_6H_4$- | $C_{18}H_9ClFN_3O_3$ | 369.7 | 0.72 | 241 | 75 |
| **6** | **NISO-6** | 4-OH-$C_6H_4$- | $C_{18}H_{10}ClFN_2O_2$ | 340.7 | 0.75 | 222 | 64 |
| **7** | **NISO-7** | 4-$CH_3$-$C_6H_4$- | $C_{19}H_{12}ClFN_2O$ | 338.8 | 0.53 | 198 | 61 |
| **8** | **NISO-8** | 4-Cl-$C_6H_4$- | $C_{18}H_9Cl_2FN_2O$ | 359.2 | 0.68 | 212 | 64 |
| **9** | **NISO-9** | 2-OH-$C_6H_4$- | $C_{18}H_{10}ClFN_2O_2$ | 340.7 | 0.71 | 202 | 67 |
| **10** | **NISO-10** | $C_6H_5$- | $C_{18}H_{10}ClFN_2O$ | 324.7 | 0.78 | 235 | 58 |

*Ethyl acetate: Hexane: 2:8

**Figure 4.1: IR spectra of 2-chloro-6-fluoro-3-[3-(4-methoxyphenyl) Isoxazol-5-yl]quinoline (NISO-1).**

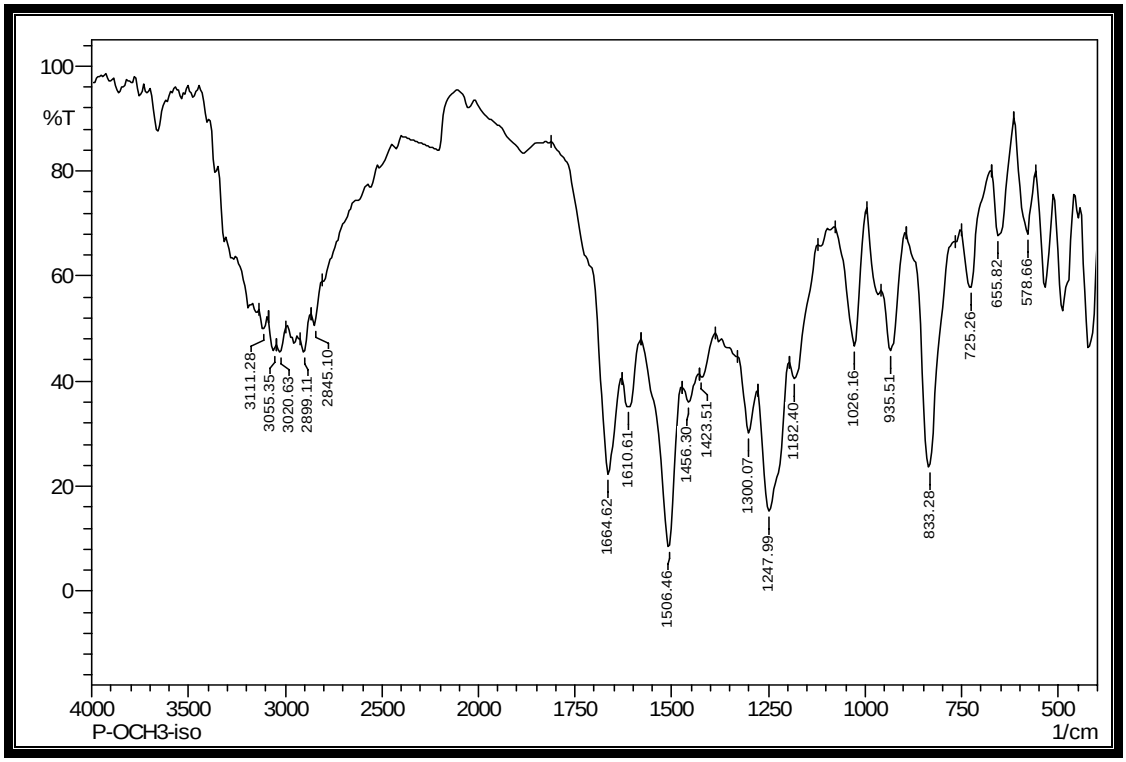


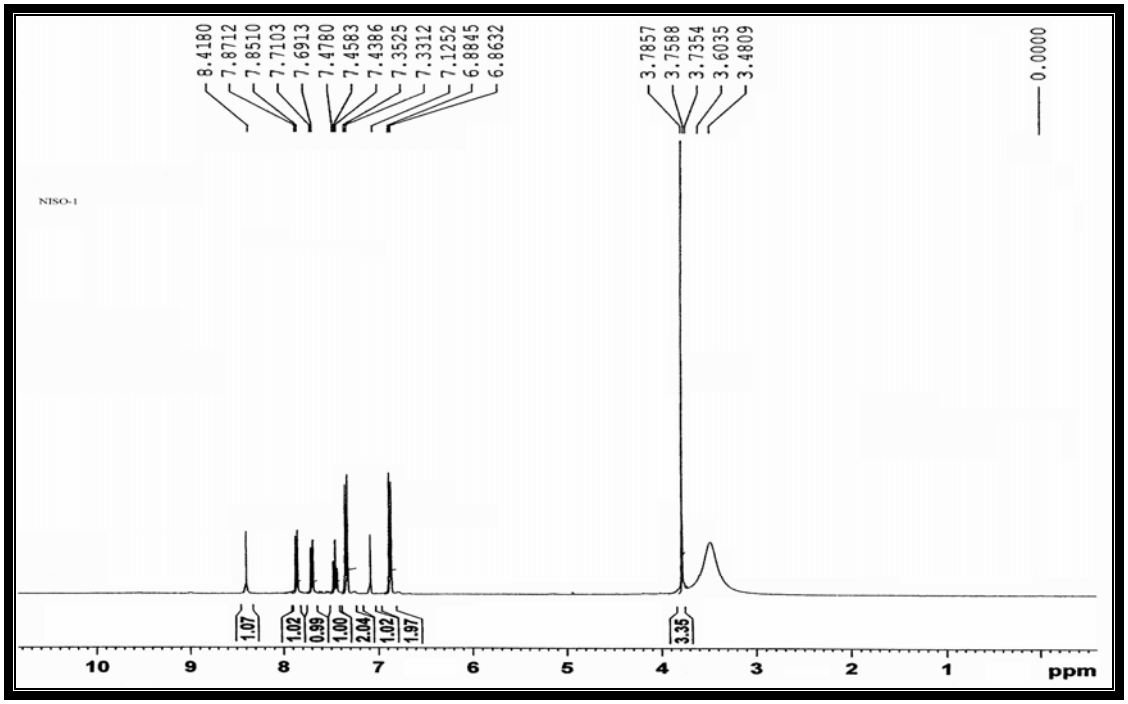

**Table 4.2: IR spectral data of 2-chloro-6-fluoro-3-[3-(4-methoxy phenyl)isoxazol-5-yl]quinoline (NISO-1).**

| Type | Vibration mode | Frequency in $cm^{-1}$ | |
|---|---|---|---|
| | | Observed | Reported[42,43] |
| Alkane (methyl) | C-H str. (asym.) | 2899.11 | 2975-2920 |
| | C-H str. (sym.) | 2845.10 | 2880-2860 |
| | C-H def. (asym.) | 1456.30 | 1470-1435 |
| | C-H def.(sym.) | 1423.51 | 1395-1370 |
| Aromatic | C-H str. | 3020.63 | 3100-3000 |
| | C=C str. | 1506.46 | 1585-1480 |
| | C-H i.p. def. | 1026.16 | 1125-1090 |
| | C-H o.o.p. def. | 833.28 | 860-810 |
| Quinoline+ oxazole ring | C=N str. | 1664.62 | 1690-1640 |
| | C-N str. | 1300.07 | 1350-1200 |
| | N-O str. | 833.28 | 850-800 |
| ether | C-O-C str. (asym.) | 1247.99 | 1275-1200 |
| | C-O-C str. (sym.) | 1026.16 | 1075-1020 |
| | C-F | 1182.40 | 1400-1000 |
| | C-Cl | 725.26 | 800-600 |

**Table 4.3: IR spectral data of synthesized isoxazoles.**

| Compounds | *IR ν, ($cm^{-1}$)* | | | | |
|---|---|---|---|---|---|
| | **C=C** | **C-N** | **N-O** | **C-Cl** | **R** |
| **NISO-2** | 1488.52 | 1311.25 | 824.57 | 741.36 | 3312.24 |
| **NISO-3** | 1524.21 | 1278.51 | 828.41 | 725.84 | 568.95 |
| **NISO-4** | 1498.63 | 1247.29 | 833.28 | 712.54 | 1334.51 |
| **NISO-5** | 1508.64 | 1325.54 | 812.62 | 724.41 | 1321.52 |
| **NISO-6** | 1522.65 | 1300.07 | 835.62 | 748.56 | 3333.41 |
| **NISO-7** | 1528.54 | 1308.98 | 812.62 | 745.35 | 2939.12 |
| **NISO-8** | 1531.54 | 1333.61 | 833.28 | 710.21 | 710.21 |
| **NISO-9** | 1514.38 | 1298.75 | 841.21 | 724.32 | 3333.41 |
| **NISO-10** | 1501.52 | 1300.07 | 833.28 | 732.52 | - |

**Figure 4.2: $^{1}$H NMR spectra of 2-chloro-6-fluoro-3-[3-(4-methoxy-phenyl)isoxazol-5-yl]quinoline (NISO-1).**



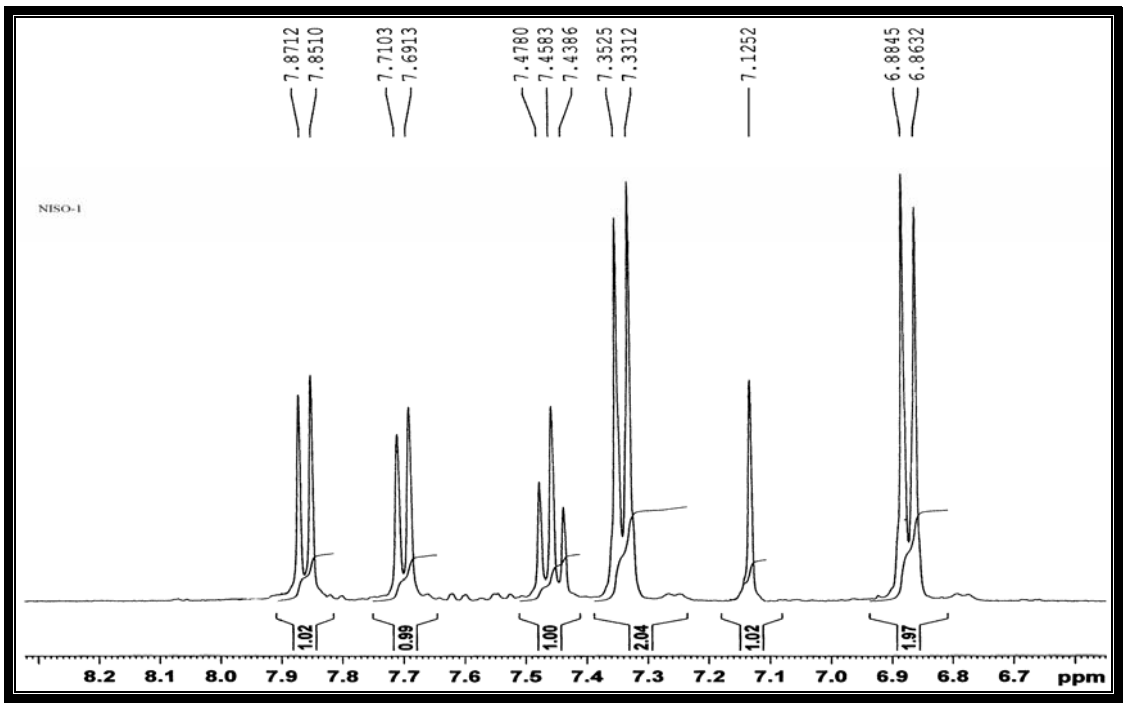
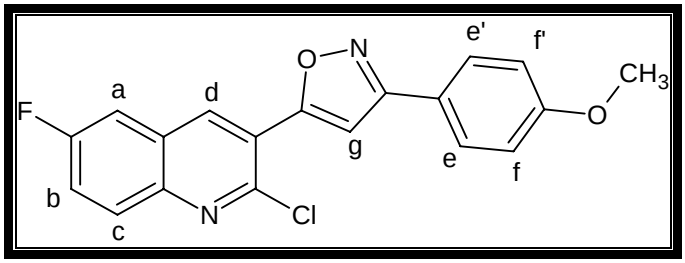
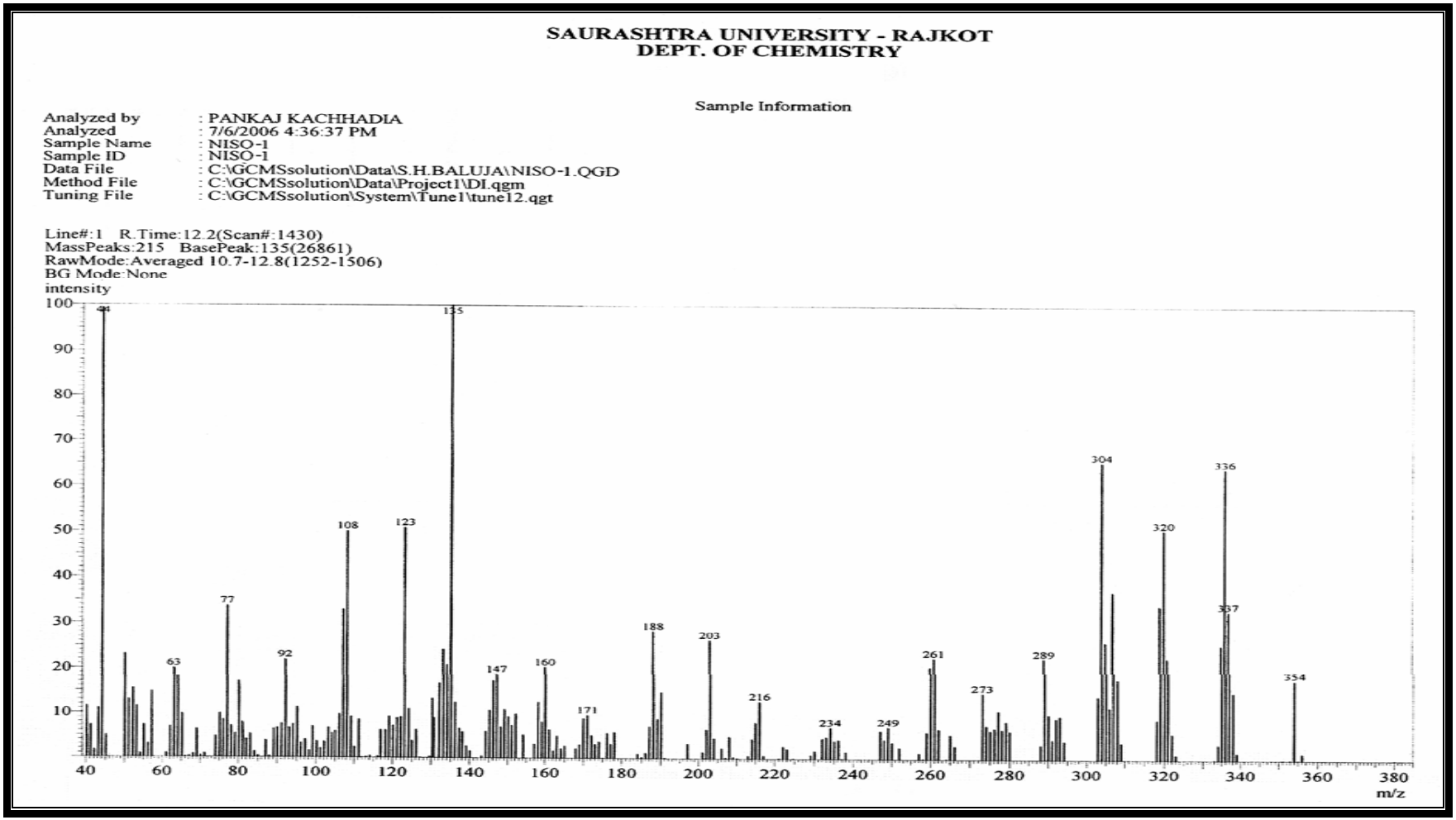



**Table 4.4: $^1$H NMR spectral data of 2-chloro-6-fluoro-3-[3-(4-methoxy - phenyl) isoxazol-5-yl]quinoline (NISO-1).**

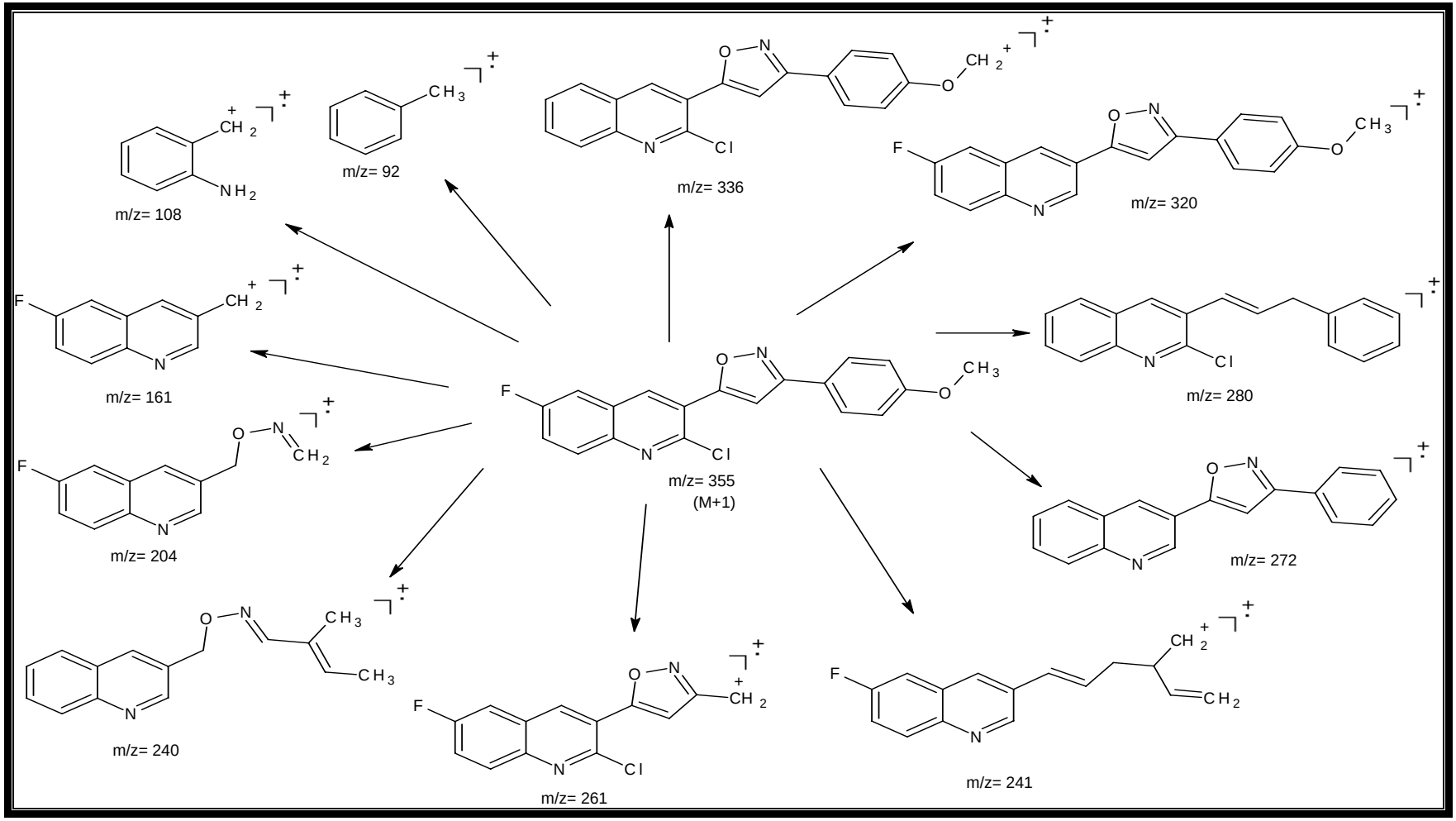



| Singal No. | Signal Position (δ ppm) | Relative No. of Protons | Multiplicity | Inference | *J* (Hz) |
|---|---|---|---|---|---|
| 1. | 3.79 | 3 | singlet | -OC$\underline{H}_3$ | - |
| 2. | 6.86-6.88 | 2 | doublet | Ar-$H_{ff'}$ | 8.52 |
| 3. | 7.13 | 1 | singlet | -$H_g$ | - |
| 4. | 7.33-7.35 | 2 | doublet | Ar-$H_{ee'}$ | 8.52 |
| 5. | 7.44-7.48 | 1 | triplet | Ar-$H_b$ | - |
| 6. | 7.69-7.71 | 1 | doublet | Ar-$H_a$ | 7.60 |
| 7. | 7.85-7.87 | 1 | doublet | Ar-$H_c$ | 8.08 |
| 8 | 8.42 | 1 | singlet | Ar-$H_d$ | - |

**Figure 4.3: Mass Spectra of 2-chloro-6-fluoro-3-[3-(4-methoxyphenyl)isoxazol-5-yl]quinoline (NISO-1).**



**Scheme 4.1: Proposed mass fragmentation of 2-chloro-6-fluoro-3-[3-(4-methoxyphenyl) isoxazol-5-yl]quinoline (NISO-1).**



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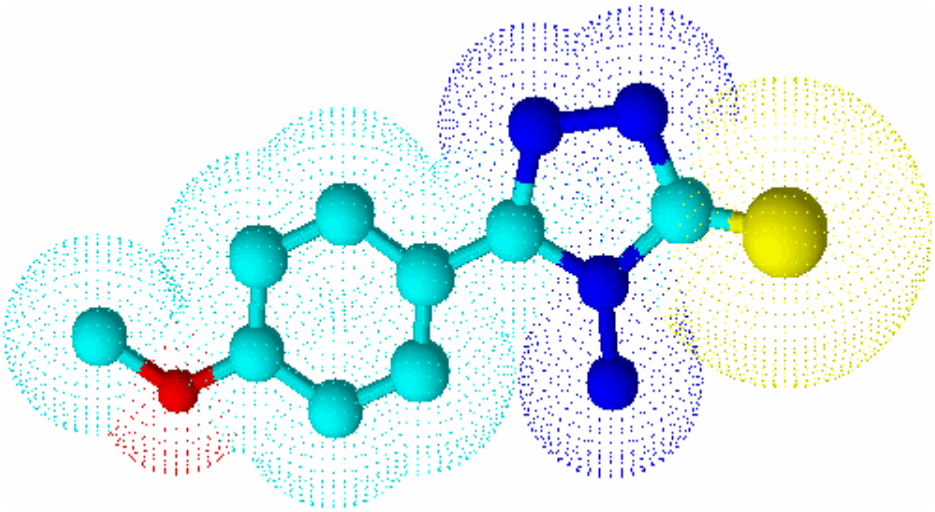

# Partr-2

# Synthesis of Triazole Derivatives

## INTRODUCTION

Triazole is one of a class of organic heterocyclic compounds having a five- membered diunsaturated ring structure with three nitrogen and two-carbon atoms. The simplest member of triazole family is triazole itself. It is white or pale yellow crystalline solid with a weak characteristic odor.

Literature survey reveals a lot about chemistry of 1,2,3 and 1,2,4-triazoles[1-6]. Various workers have synthesized triazole derivatives[7-17] using different methods. Bany and Dobosz[18] reported the synthesis of 1,2,4-triazole derivatives by the reaction of amidrazone hydrochlorides with s-triazine. Murakami and co-workers[19] synthesized 3-formyl-1,2,4-triazole nucleoside using diethoxy acetonitrile as a synthon. The electrochemical synthesis of some 1,2,4- triazole and 3-amino-1,2,4-triazole polychelates of divalent iron, cobalt and nickel have also been reported[20]. Radwan et al.[21] reported a new route for the synthesis of 1,2,4-triazole and 3,4-disubstituted cinnoline derivatives. Recently, synthesis of some new 1,2,4-triazoles have also been reported[22-26.]

Further, much attention has been focused on 1,2,4-triazole derivatives for their broad spectrum of biological activities such as antimicrobial, fungicidal, herbicidal, anticonvulsants, anticancer and plant growth regulatory activities[27-31]. These derivatives are also known to be an important and frequent insecticidal, agrochemical structural feature of many biological active compounds such as cytocrom p 450 enzyme inhibitors[32] and peptide analog inhibitors[33]. The biological activities of these compounds have been studied by various workers[34-44]. Lange and Tondys[45] reported some triazoles as new antituberculotic agents. Stenz et al.[46] studied the effect of triazoles on DNA- and RNA-containing bacteriophages and their hosts. The antiinflammatory[47] and herbicidal[48] activity of some other triazoles have also been studied. Sarhan et al.[49] reported antibacterial, analgesic, antipyretic, and antiinflammatory activities of some triazole derivatives. Crofton[50] reported a structure-activity relationship for the neurotoxicity of triazole fungicides. Recently, Yu et al.[51] and Yin et al.[52] studied antifungal and insecticidal activities of these derivatives. The lipophilicity, anticancer and antimicrobial properties of some fused triazoles has also been reported[53].

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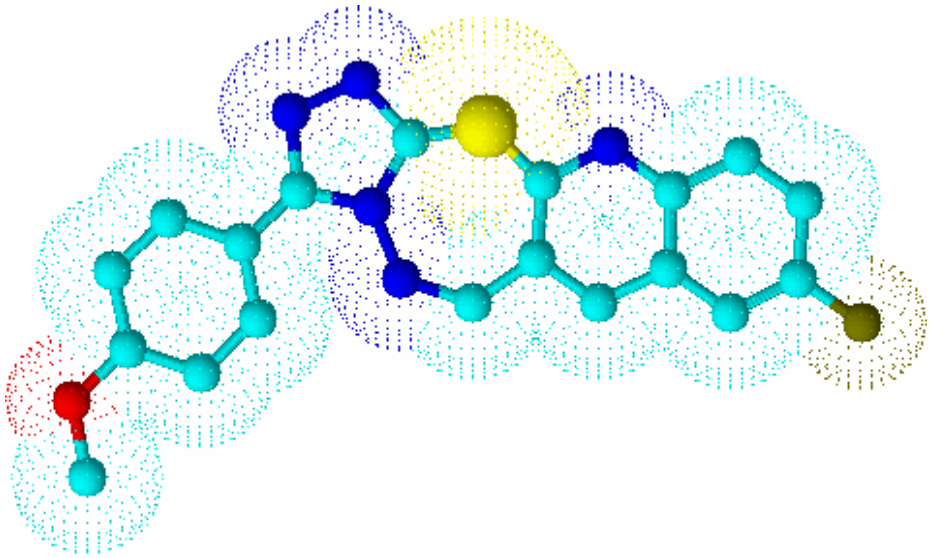
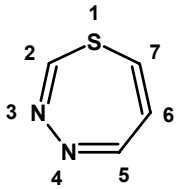


# Synthesis of 1,3,4-Thiadiazepines

## INTRODUCTION

The Chemistry of 1,3,4-thiadiazepine derivatives have been reviewed in last few years. The thiadiazepine ring system have one sulphur atom and two nitrogen atom at 1,3,4-position in seven membered heterocyclic ring. The interesting biological activities of these novel heterocycles have stimulated considerable research work in recent years leading to the synthetic utility of the derivatives of this ring system.




Different methods for the synthesis of these derivatives have been documented in literature[1-3]. Sandhu et al.[4] have prepared thiadiazepine derivatives by condensation of thiodiacetophenones with hydrazine hydrate in ethylene glycol. A symmetric pyrrolo thiadiazepine derivatives have also been prepared by Bolos et al.[5] Synthesis and characterization of zinc(II) and cadmium(II) halide complexes with 3,6-disubstituted-2,7-dihydro-1,4,5-thiadiazepine derivatives have been reported by Sandhu et al.[6] Corral and co-workers[7] have investigated a new method for the synthesis of chloro-substituted dibenzo thiadiazepines and their 5,6-dihydro derivatives. The synthesis of triazolo thiadiazepines have been carried out by using phase transfer catalysts[8]. Brukstus et al.[9] have synthesized triazole [1,3,4] thiadiazepine by the reaction of 4,6-dichloro-2-methyl thio pyrimidine-5-carboxyldehyde with 3-substituted -4-amino -1,2,4-triazole-5-thiones. Synthesis of quinolinethiadiazepine derivatives by condensation of 2-chloro-6-substituted quinoline-3-carboxaldehyde with thio- carbohydrazide in pyridine have been studied by Gururaja et. al.[10] Aly and his co-workers[11] have synthesized some new thiadiazepines by the reaction of N-imidoylthioureas with dimethyl acetylenedicarboxylate.

From the literature survey, it was revealed that 1,3,4-thiadiazepine are better therapeutic agents due to the presence of the -N=C-S group[12]. Various workers have been reported their various biological activities such as antitumor[13], antimicrobial[14], antidepressant[15], anti psychotic[16], antibacterial[17],

anticonvulsant[18], CCK antagonists[19], gastrin receptor antagonists[20] etc. These derivatives are also known to be found as potent drug in pharmaceutical industries. These derivatives are not only known for their potent antimicrobial activities[21] but they also act as excellent charge generating agent[22].

Wei et al.[23] have synthesized 1,2,5-benzothiadiazepine 1,1-dioxides and tested their antidepressant, anticonvulsant, and hypoglycemic activity. New dibenzothiadiazepine derivatives with antidepressant activities have been described by Giannotti et al.[24] Rao and Sastry[25] have reported biological activity of some other 1,3,4-thiadiazepines. The antibacterial[26] and anti-HIV[27] activity of some other 1,3,4-thiadiazepines have also been reported. Non nucleoside reverse transripatase activity of some thiadiazepines have been described by Artico et al.[28] Vice Susan[29] have prepared di-indolo thiadiazepine compounds as inflammation inhibitors, neoplasm inhibitors and pharmaceuticals for Psoriasis treatment., Swati has reported anticancer activity of thiadiazepine derivatives[30] whereas Lebegue et al.[31] have evaluated their antiproliferative activity toward the murine L1210 leukemia cell line. Ammar et al.[32] have discovered thiadiazepine derivatives as possible potential drug for fungal infection. Kalluraya B et al.[33] have synthesised thiadiazepines and screen for their antibacterial activities. Anthelmintic activity of 1,3,4-thiadiazepine have documented by Gururaja et al.[10] Ashutos singh and nizamudin[34] have prepared thiadiazepines and reported their molluscicidal activity. Antifungal activity of thiadiazepines have been studied by Anshu Dandia et al.[35] Kamble and Sudha[36] have discovered some 1,3,4-thiadiazepines as cardiovascular agent.

Thus, significant biological properties associated with thiadiazepine derivatives have aroused considerable interest to design the compounds in which therapeutically active triazole nucleus is incorporated and to study their biological activity.

## EXPERIMENTAL

### Synthesis of 3-(4-methoxyphenyl) 8,9-substituted-pyrido[3,2-*f*][1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazepine.

**[A] Synthesis of 4-methoxy benzoate:**

A solution of 4-methoxy benzoic acid (0.01M) in methanol (20 ml) and 0.5 ml conc. sulfuric acid was refluxed for 12 hrs. The content was cooled and poured on crushed ice. The product was filtered and treated with saturated sodium bicarbonate solution.

**[B] Synthesis of 4-methoxy benzoic acid hydrazide:**

A solution of 4-methoxy benzoate (0.01 M) in absolute ethanol was refluxed with 95% hydrazine hydrate (0.01M) for 8 hrs. in a water bath. The product was isolated and crystallized from ethanol.

**[C] Synthesis of potassium 4-methoxy benzoic acid hydrazide dithiocarbamate:**

An alcoholic solution of potassium hydroxide (0.015 M), absolute ethanol and the compound [B] was treated with carbon disulfide. This mixture was stirred for 12 hrs. It was then isolated with dry ether and the precipitated solid was filtered, washed with ether and dried.

**[D] Synthesis of 4-amino-5-(4-methoxy phenyl)-4H-1,2,4-triazole-3-thiol:**

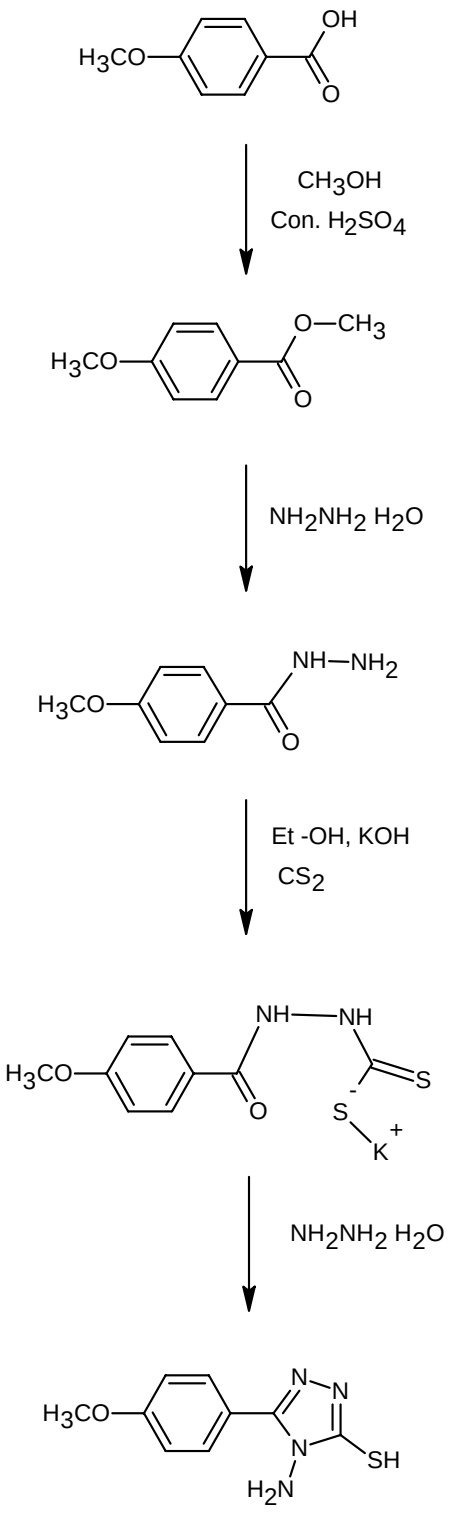
Above synthesized Potassium salt (0.01 M) was mixed with hydrazine hydrate and heated in oil bath for about 5 hrs till the evolution of $H_2S$ gas ceases. The reaction mixture was then poured onto crushed ice and treated with glacial acetic acid. The product was filtered and purified by KOH treatment and crystallized from ethanol.

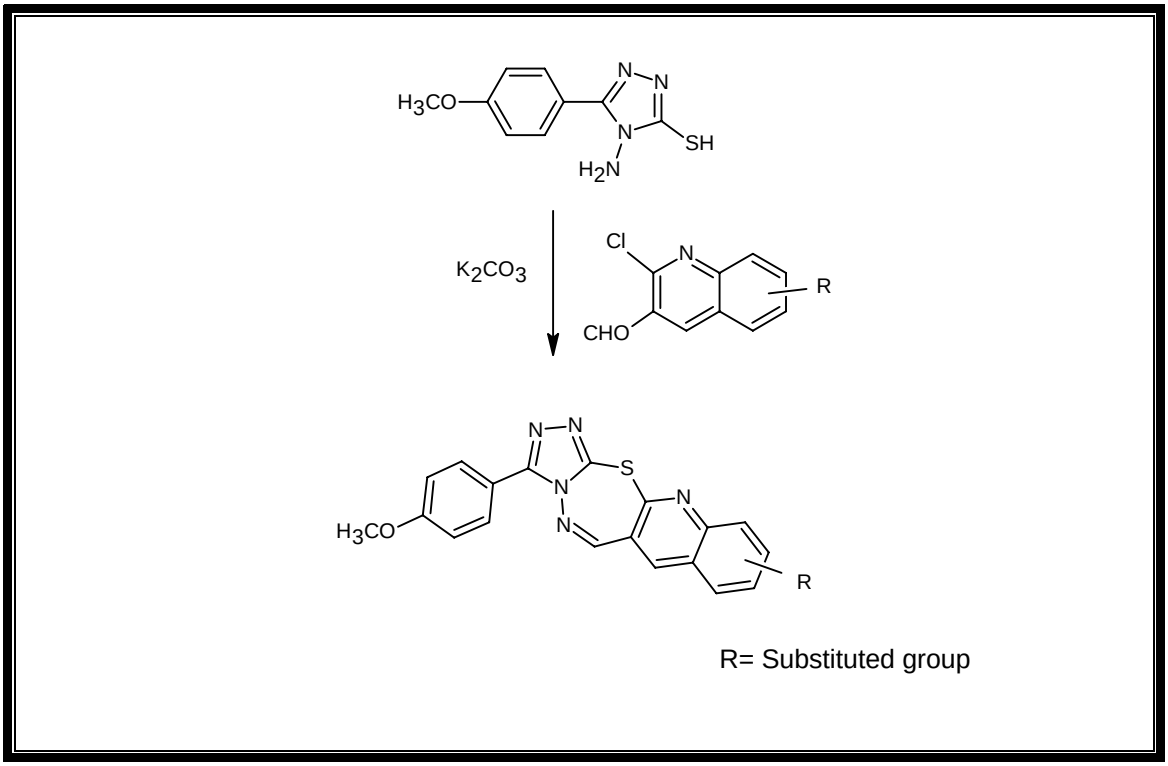
**[E] Synthesis of 3-(4-methoxyphenyl) 8,9-substituted-pyrido[3,2-*f*][1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazepine (NTD-1):**

To a mixture of 4-amino-5-(4-methoxy phenyl)-4H-1,2,4-triazole-3-thiol (0.01 M) and 2-chloro-6-fluoroquinoline-3-carbaldehyde (0.01 M) in DMF (20 ml), anhydrous $K_2CO_3$ (2.0 g) was added. The reaction mixture was stirred at 70-80 $^0$C for 2 hrs. It was then cooled and poured onto crushed ice. The product was isolated and recrystallized from methanol.

Similarly, other substituted thiadiazepines were prepared. The physical data for the synthesized compounds are reported in Table 1.

## REACTION SCHEME






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

**Infrared spectra:**

The IR spectra were recorded by SHIMADZU-FTIR-8400 Spectrophotometer in the frequency range of 4000-400 $cm^{-1}$ by KBr powder method. Figure 1 shows IR spectra of NTD-1. The IR spectral data for NTD-1 is given in Table 2. The spectral data for all other compounds are reported in Table 3.

**$^{1}$H NMR Spectra:**

The NMR spectra were recorded by BRUKER Spectrometer (400 MHz) using internal reference TMS and solvent $CDCl_3$/DMSO. Figure 2 shows NMR spectra of NTD-4. The spectral data for NTD-4 is given in Table 4.

**Mass spectra**:

The Mass spectra were recorded by GCMS-SHIMADZU-QP2010. Figure 3 shows mass spectra of NTD-1.The proposed mass fragmentation of the same compound is also given in Scheme 1.

**Table 1: Physical constants of thiadiazepines.**

| Sr. No. | Code | R | M.F. | M. Wt. (g/mol) | $R_f$* Value | M.P. °C | Yield % |
|---|---|---|---|---|---|---|---|
| **1** | **NTD-1** | 4-F- | $C_{19}H_{12}FN_5OS$ | 377.4 | 0.49 | 198 | 50 |
| **2** | **NTD-2** | $C_4H4$- | $C_{23}H_{15}N_5OS$ | 409.5 | 0.61 | 214 | 55 |
| **3** | **NTD-3** | 3-$NO_2$- | $C_{19}H_{12}N_6O_3S$ | 404.4 | 0.52 | 224 | 45 |
| **4** | **NTD-4** | 4-$NO_2$- | $C_{19}H_{12}N_6O_3S$ | 404.4 | 0.53 | 174 | 40 |
| **5** | **NTD-5** | 4-$CH_3$- | $C_{20}H_{15}N_5OS$ | 373.4 | 0.50 | 220 | 60 |
| **6** | **NTD-6** | 2,5-diCl- | $C_{19}H_{11}Cl_2N_5OS$ | 428.3 | 0.58 | 241 | 48 |
| **7** | **NTD-7** | H- | $C_{19}H_{13}N_5OS$ | 359.4 | 0.59 | 238 | 50 |
| **8** | **NTD-8** | 4-$OCH_3$- | $C_{20}H_{15}N_5OS$ | 389.4 | 0.61 | 215 | 60 |
| **9** | **NTD-9** | 2,4-diCl- | $C_{19}H_{11}Cl_2N_5OS$ | 428.3 | 0.52 | 189 | 65 |
| **10** | **NTD-10** | 4-Br- | $C_{19}H_{12}BrN_5OS$ | 438.3 | 0.51 | 211 | 45 |

* Acetone:Benzene: 2:8

**Figure 1 : IR spectra of 3-(4-methoxyphenyl) 8,9-substituted-pyrido [3,2-*f*][1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazepine (NTD-1).**

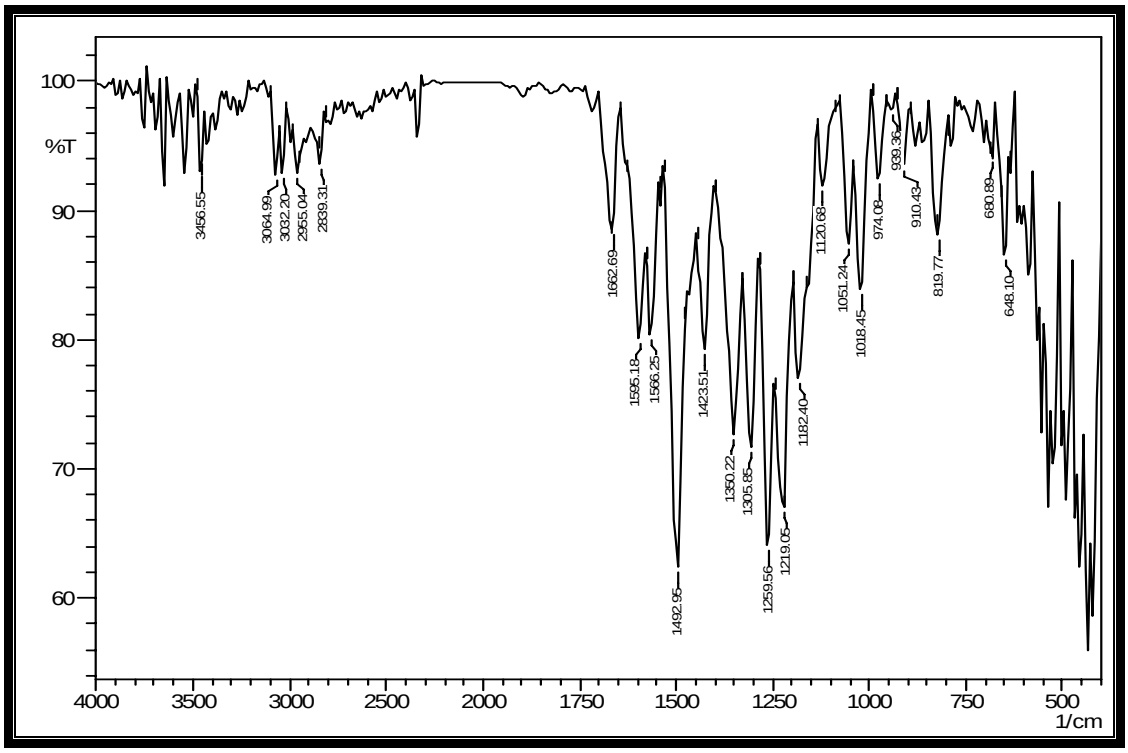


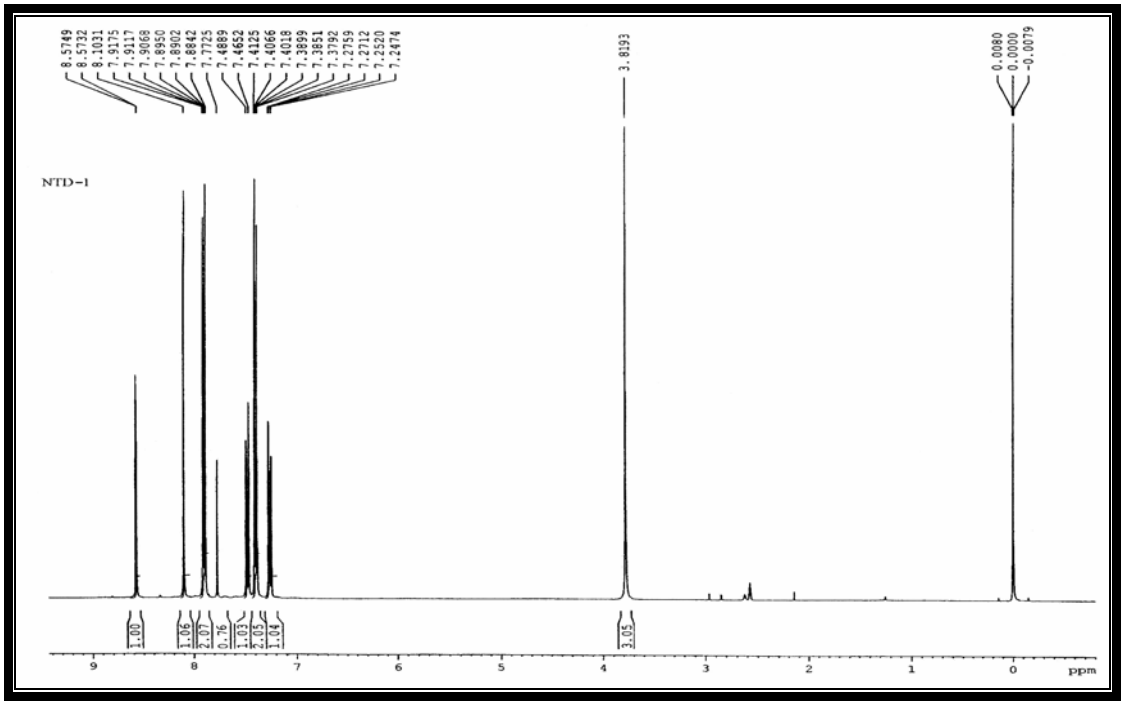

**Table 2: IR spectral data of 3-(4-methoxyphenyl) 8,9-substituted-pyrido[3,2-*f*][1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazepine (NTD-1).**

| Type | Vibration mode | Frequency in $cm^{-1}$ | |
|---|---|---|---|
| | | Observed | Reported[37,38] |
| Alkane (methyl) | C-H str. (asym.) | 2955.04 | 2975-2920 |
| | C-H str. (sym.) | 2839.31 | 2880-2860 |
| | C-H def. (asym.) | 1423.51 | 1470-1435 |
| | C-H def.(sym.) | 1350.22 | 1395-1370 |
| Aromatic | C-H str. | 3064.99 | 3100-3000 |
| | C=C str. | 1566.25 | 1585-1480 |
| | C-H i.p. def. | 1120.68 | 1125-1090 |
| | C-H o.o.p. def. | 819.77 | 860-810 |
| Triazole+ thiadiazepine ring | C=N str. | 1662.69 | 1690-1640 |
| | C-N str. | 1259.56 | 1350-1200 |
| | N-N str. | 1018.45 | 1050-1010 |
| | C-S-C str. | 1182.40 | 1250-1000 |
| | C-S-C def. | 648.10 | 700-600 |
| ether | C-O-C str. (asym.) | 1219.05 | 1275-1200 |
| | C-O-C str. (sym.) | 1051.24 | 1075-1020 |
| | C-F | 1305.85 | 1400-1000 |

**Table 3: IR spectral data of synthesized thiadiazepines.**

| Compounds | *IR ν, ($cm^{-1}$)* | | | | |
|---|---|---|---|---|---|
| | **C=C** | **N-N** | **C-S-C** | **C-O-C** | **R** |
| **NTD-2** | 1502.32 | 1023.73 | 1175.24 | 1222.54 | 1144.34 |
| **NTD-3** | 1485.52 | 1038.12 | 1170.65 | 1228.34 | - |
| **NTD-4** | 1498.64 | 1022.32 | 1162.35 | 1227.64 | 1334.51 |
| **NTD-5** | 1522.31 | 1042.47 | 1182.40 | 1219.05 | 1321.52 |
| **NTD-6** | 1524.85 | 1014.84 | 1195.23 | 12.08.21 | 2941.12 |
| **NTD-7** | 1512.32 | 1032.14 | 1220.74 | 1219.05 | 668.98 |
| **NTD-8** | 1508.12 | 1027.65 | 1182.40 | 1244.42 | 1244.42 |
| **NTD-9** | 1498.64 | 1038.12 | 1225.14 | 1248.65 | 712.04 |
| **NTD-10** | 1508.12 | 1022.32 | 1162.35 | 1219.05 | 572.95 |

**Figure 2: $^{1}$H NMR spectra of 3-(4-methoxyphenyl) 8,9-substituted-pyrido[3,2-*f*][1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazepine (NTD-4).**



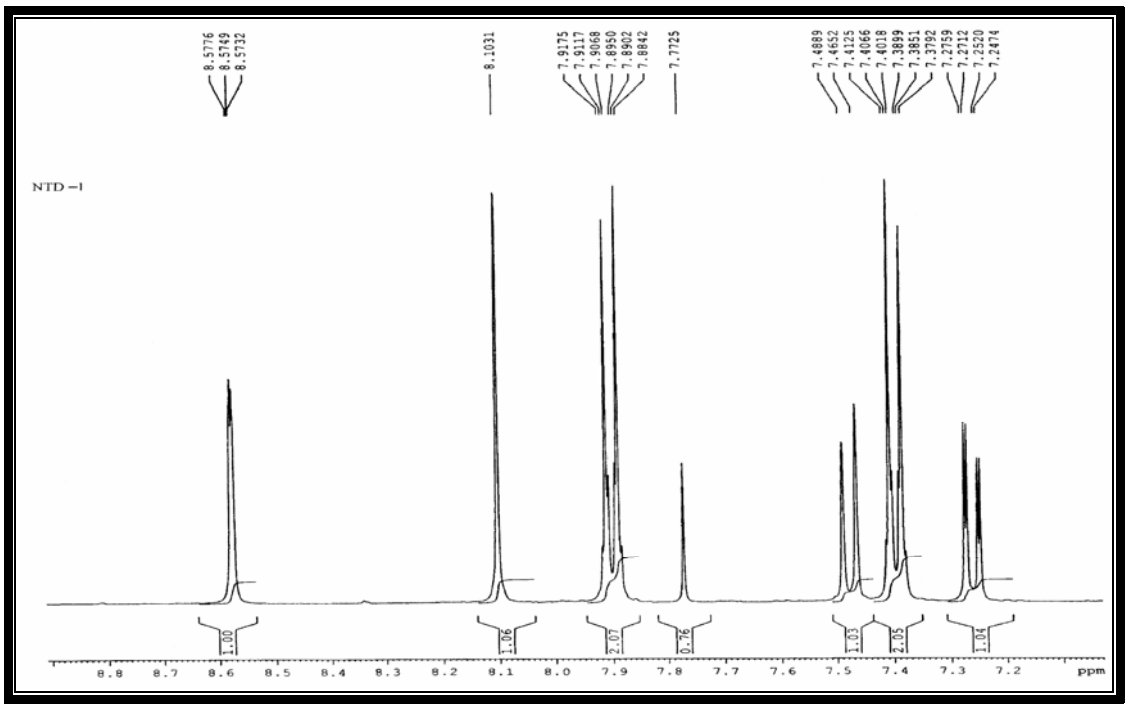
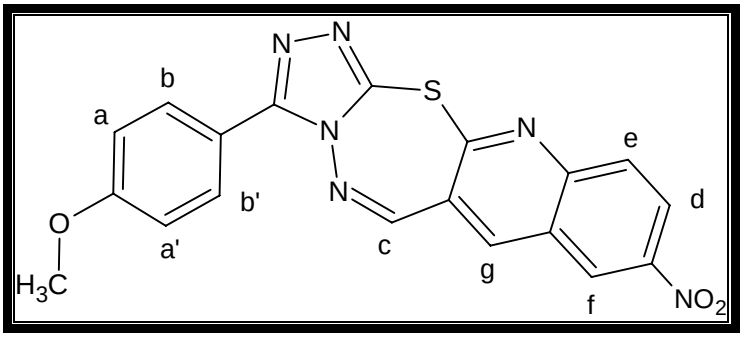
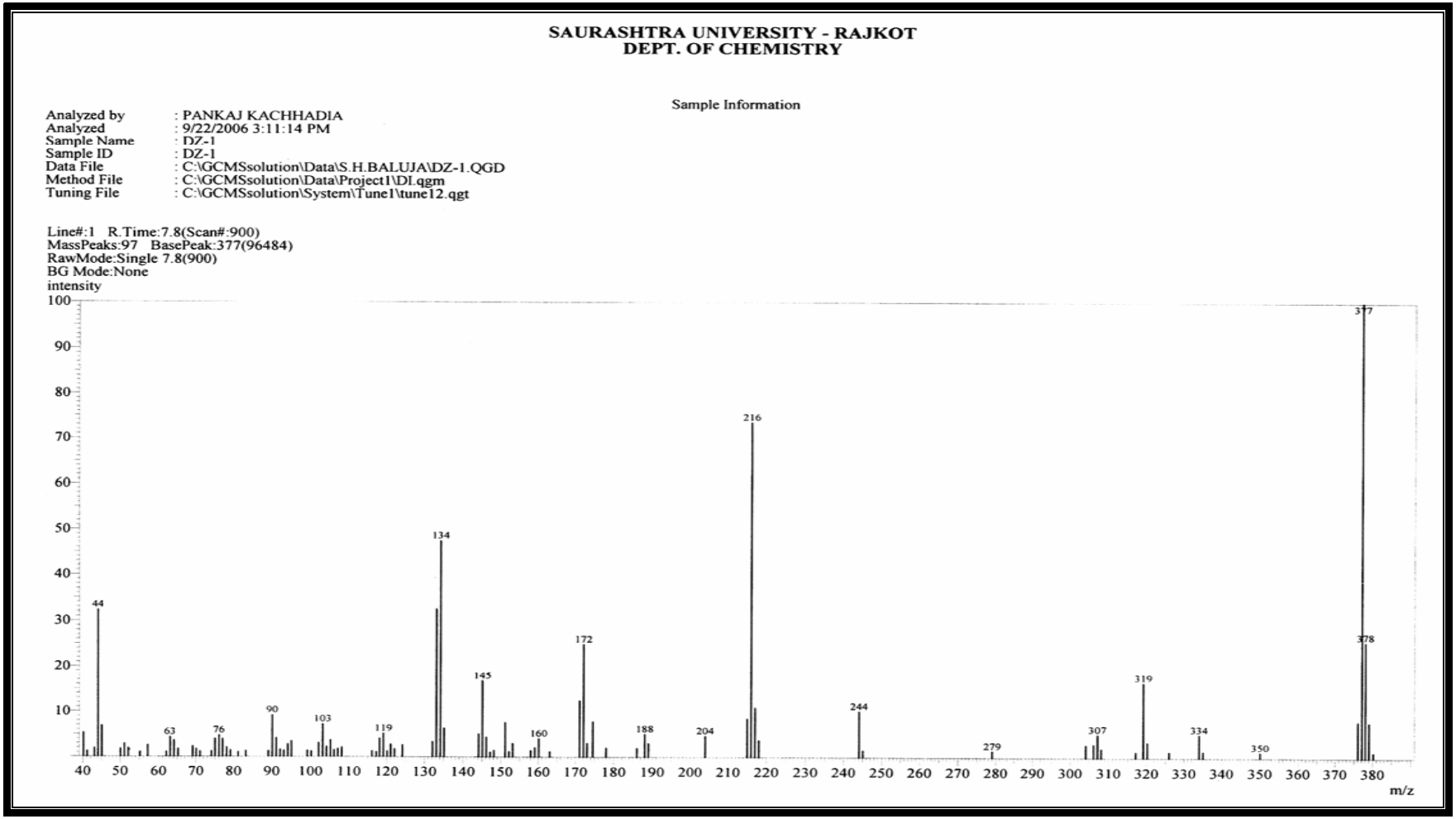



**Table 4: $^1$H NMR spectral data of 3-(4-methoxyphenyl) 8,9-substituted-pyrido[3,2-*f*][1,2,4] triazolo[3,4-*b*][1,3,4]thiadiazepine (NTD-4)**

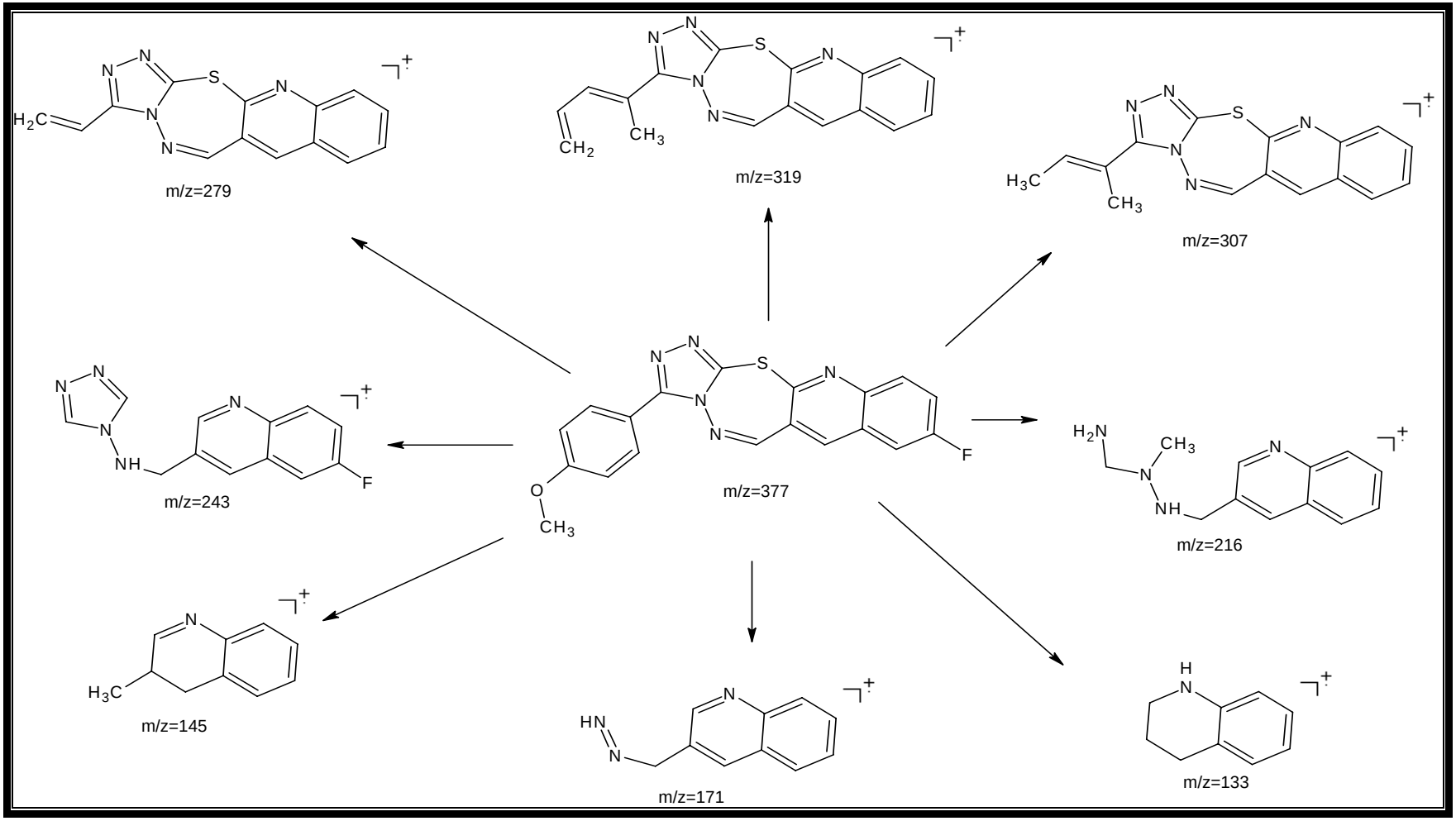



| Singal No. | Signal Position (δ ppm) | Relative No. of Protons | Multiplicity | Inference | *J* (Hz) |
|---|---|---|---|---|---|
| 1 | 3.82 | 3 | singlet | $OC\underline{H}_3$ | - |
| 2 | 7.25-7.27 | 1 | doublet | Ar-$H_a$ | 9.48 |
| 3 | 7.38-7.41 | 2 | doublet | Ar-$H_{bb'}$ | 8.60 |
| 4 | 7.47-7.49 | 1 | doublet | Ar-$H_{a'}$ | 8.60 |
| 5 | 7.77 | 1 | singlet | $H_c$ | - |
| 6 | 7.88-7.92 | 2 | doublet | Ar-$H_{de}$ | 8.56 |
| 7 | 8.10 | 1 | singlet | Ar-$H_f$ | - |
| 8 | 8.57 | 1 | singlet | Ar-$H_g$ | - |

**Figure 3: Mass spectra of 3-(4-methoxyphenyl) 8,9-substituted-pyrido[3,2-*f*][1,2,4] triazolo[3,4- *b*][1,3,4] thiadiazepine (NTD-1).**



**Scheme 1: Proposed mass fragmentation of 3-(4-methoxyphenyl) 8,9-substituted-pyrido[3,2-*f*][1,2,4] triazolo[3,4 *b*][1,3,4]thiadiazepine (NTD-1).**



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# Partr-3

# Comparision of Different Methods of Synthesis

## INTRODUCTION

Microwave chemistry is the science of applying microwave irradiation to chemical reactions[1-4]. Microwave-enhanced synthesis represents a fundamental step forward in the capabilities of synthetic chemistry. It allows organic chemists to work faster, generating higher yields with increased product purity, and to scale experiments up reliably from milligrams to much larger quantities without the need to alter reaction parameters. It offers much more precise control over conditions of temperature and pressure than any previous technology. Ultimately, by eliminating much of the time and effort from the process of performing chemical reactions, it allows chemists to focus on what is most important-the development of new compounds, or refined methods for generating known products.

Traditionally, organic synthesis is carried out by conductive heating with an external heat source (burner, electric plate heater, oil bath or heating mantle). This is a comparatively slow and inefficient method for transferring energy into the reaction system since it depends on convection currents and on the thermal conductivity of the various materials that must be penetrated, and results in the temperature of the reaction vessel being higher than that of the reaction mixture. In addition, a temperature gradient can develop within the sample and local overheating can lead to product, substrate or reagent decomposition.

In contrast, microwave irradiation produces efficient internal heating by direct coupling of microwave energy with the molecules of solvents, reagents or catalysts presented in the reaction mixture. Since the preceding vessels are typically made out of microwave-transparent materials the radiation passes through the walls of the vessel directly into the whole reaction mixture volume and an inverted temperature gradient as compared to conventional thermal heating results.

Microwave irradiation (microwave) consists in electromagnetic wave in the range 300 MHz to 300 GHz that corresponds to wavelengths of 1 cm to 1 m. The microwave region of the electromagnetic spectrum lies between infrared and radio frequencies. All domestic microwave ovens, microwave

reactors and other laboratory and industrial systems usually work at 2.45 GHz.

In the last few years, Microwave-induced Organic Reaction Enhancement (MORE) chemistry has gained popularity as a non-conventional technique for rapid organic synthesis[5]. The synthetic utility of MORE chemistry in routine organic synthesis have reported by many researchers[6-8]. Recently, some microwave enhanced synthesis of benzodiazepines have also been reported[9-13].

Further, a lot of interest has been generated on the use of ultrasound radiation in synthetic organic chemistry, which includes decrease of reaction time, increase of yield, lower reaction temperature, avoidance of phase transfer catalysis etc. Literature survey shows that few workers synthesized some compounds using ultrasonic technique[14-20], at lower reaction temperature and in less reaction time[21].

This prompted us to synthesize various substituted benzodiazepine derivatives using the Microwave-assisted (MW) method, Ultrasound irradiation (US) and Conventional thermal (Con.) method.

## EXPERIMENTAL

### Synthesis

***Conventional method:***

The experimental procedure and reaction scheme for the synthesis is already given in Section-I of Chapter-2 in experimental part.

***Microwave irradiation:***

1,5-benzodiazepines have also been synthesized by microwave irradiation. Microwave-assisted procedures were carried out in a domestic QPro-M microwave oven operating at 420 W. The reactants were same as conventional method. The reactions were completed within few minutes.

***Sonochemical Synthesis:***

In these case also, reactants were same as above. The synthesis was done using Ultrasonic Interferometer (Mittal Enterprise, New Delhi, Model No. F-81) operating at a frequency of 2 MHz. All the compounds were synthesized within few hours.

## RESULTS AND DISCUSSION

The reaction time and yield of different synthesized compounds by using microwave, ultrasonic waves and conventional techniques are reported in Table 1. It is observed that using microwave and ultrasonic waves, the reaction time is reduced considerably whereas % yield increased markedly.

Thus, microwave and ultrasonics proved to be better techniques than conventional method.

**Table 1: Comparison of % yield and reaction time of compounds synthesized by different methods.**

| Code | Yield % | | | Reaction time | | |
|---|---|---|---|---|---|---|
| | MW | US | Con. | MW min. | US hrs. | Con. hrs. |
| NBN-1 | 68 | 60 | 54 | 6 | 2.00 | 10 |
| NBN-2 | 74 | 62 | 59 | 6 | 2.25 | 10 |
| NBN-3 | 69 | 57 | 49 | 6 | 1.50 | 10 |
| NBN-4 | 81 | 70 | 62 | 7 | 2.10 | 9 |
| NBN-5 | 71 | 64 | 57 | 7 | 2.00 | 9 |
| NBN-6 | 78 | 70 | 61 | 6 | 2.25 | 8 |
| NBN-7 | 72 | 62 | 55 | 6 | 2.00 | 10 |
| NBN-8 | 74 | 59 | 52 | 7 | 2.15 | 10 |
| NBN-9 | 78 | 68 | 58 | 6 | 2.00 | 8 |
| NBN-10 | 76 | 69 | 62 | 6 | 2.30 | 10 |

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# Chapter -3

# Physico Chemical Properties


# Section-I

# Acoustical Properties

## INTRODUCTION

Ultrasonics is one of the fast developing areas in the field of modern science, which deals with sound waves having frequencies beyond the range of human hearing i.e. above 20 KHz (20,000 cycles per second). The term silent sound has also been used to denote ultrasonic waves[1]. Ultrasonic technique for its advantage of non-invasive capacity is widely accepted for many applications. It covers large domain of applications sectored into industrial, medical and scientific fields[2].

Due to its non-destructive nature in medicine, it is used in medicine for various diagnoses such as pediatrics[3], vascular diseases[4], brain diseases[5], urology[6], liver diseases[7] etc. Ultrasound therapy is also used in postmortem diagnosis[8]. Further, it is useful to obtain the information about bone microstructure[9], lung microstructure [10], proteins, blood cells[11] etc.

Now a day, lots of interest has been generated on the use of ultrasound radiation in synthetic organic chemistry[12,13], which causes decrease of reaction time, increase of yield, lower reaction temperature, avoidance of phase transfer catalysis etc[14,15].

This technique has also been used to study different materials[16], liquid crystals[17] and structure of solids[18-20].

Further, ultrasonic velocity measurements have been used to study the nature of molecular interactions in various binary[21-31] and ternary[32-37] liquid mixtures. Much work has been done in solutions of polymers[38-43], pharma materials[44-47], amino acids[48,49] and other electrolytes[50,56] and non electrolytes[57-61]. However, little work has been done for solutions of solid organic compounds[62-68].

## EXPERIMENTAL

The selected solvents DMF and THF for the present study are distilled by the reported procedure[69]. The synthesized compounds benzodiazepines and thiadiazepines were recrystallized before use.

The densities, viscosities and ultrasonic velocities of solvents and solutions of benzodiazepines and thiadiazepines of different concentrations were measured at 298.15 K by using pyknometer, an Ubbelohde suspended level viscometer and single frequency ultrasonic interferometer operating at 2 MHz, with the uncertainties of 0.0001 g/cm$^3$, $\pm$ 0.06 % and 0.01% respectively.

**Density measurements:**

The weight of distilled water, pure solvents and solutions of benzodiazepines and thiadiazepines were measured by using pyknometer. The densities were evaluated by using following equation:

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

**Viscosity Measurements:**

To determine the viscosity of solution, Ubbelohde viscometer[70] was used, which obeys Stoke's low[71]. The measured quantity of the distilled water / solvent / solution was placed in the viscometer, which was suspended in a thermostat at 298.15 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:

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

**Sound velocity measurement:**

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

The solvent / solution were filled in the measuring cell with quartz crystal and then micrometer was fixed. The circulation of water from the thermostat at 298.15 K was started and test solvent / solution in the cell is allowed to thermally equilibrate. The micrometer was rotated very slowly so as

to obtain a maximum or minimum of anode current (n). A number of maximum reading of anode current were counted. The total distntde (d) travel by the micrometer for n=10, was read. The wave length (λ) was determined according to the equation (3.1.3).

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

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

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

## RESULTS AND DISCUSSION

Tables 3.1.1 and 3.1.2 shows the experimental data of density ($\rho$), viscosity ($\eta$) and sound velocity ($U$) of pure solvents and solutions of synthesized benzodiazepine (NBN series) and thiadiazepine (NTD series) in DMF and THF at 298.15 K.

From these experimental data, various acoustical parameters like isentropic compressibility ($\kappa_S$), intermolecular free length ($L_f$), molar compressibility ($W$), Rao's molar sound function ($R_m$), Vander Waals constant ($b$), relaxation strength ($r$), apparent molar compressibility ($\phi_k$) etc., were evaluated using the following equations:

**1. Isentropic compressibility**:

Isentropic compressibility ($\kappa_s$) can be evaluated by the equation[72]:

$$\kappa_s = \frac{1}{U^2 \rho} \qquad \ldots (3.1.5)$$

**2. Intermolecular free path length:**

Jacobson[73] proposed an equation to calculate the intermolecular free path length ($L_f$), which is given below:

$$L_f = K_j \kappa_s^{1/2} \qquad \ldots (3.1.6)$$

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

**3. Molar compressibility:**

Molar compressibility ($W$) can be calculated by the following equation[74]:

$$W = \left( \frac{M}{\rho} \right) \kappa_s^{-1/7} \qquad \ldots (3.1.7)$$

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

$$M = M_1 W_1 + M_2 W_2 \qquad \ldots (3.1.8)$$

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

**Table 3.1.1: The density (*ρ*), ultrasonic velocity (*U*) and viscosity (*η*) of NBN series in DMF and THF at 298.15 K.**

| *Conc. M* | *Density ρ g.cm$^{-3}$* | *Velocity U. 10$^{-5}$ cm.s$^{-1}$* | *Viscosity η.10$^{3}$ poise* | *Density ρ g.cm$^{-3}$* | *Velocity U. 10$^{-5}$ cm.s$^{-1}$* | *Viscosity η.10$^{3}$ poise* |
|---|---|---|---|---|---|---|
| | ***DMF*** | | | ***THF*** | | |
| | ***NBN-1*** | | | ***NBN-1*** | | |
| ***0.00*** | 0.9449 | 1.4616 | 8.1418 | 0.8815 | 1.2780 | 4.6005 |
| ***0.01*** | 0.9484 | 1.4632 | 8.3884 | 0.8824 | 1.2724 | 4.6910 |
| ***0.02*** | 0.9502 | 1.4648 | 8.5529 | 0.8838 | 1.2656 | 4.7806 |
| ***0.04*** | 0.9531 | 1.4672 | 8.6999 | 0.8853 | 1.2668 | 4.8860 |
| ***0.06*** | 0.9567 | 1.4692 | 9.0562 | 0.8865 | 1.2784 | 4.9900 |
| ***0.08*** | 0.9592 | 1.4700 | 9.2257 | 0.8889 | 1.2828 | 5.1012 |
| ***0.10*** | 0.9668 | 1.4732 | 9.4051 | 0.8935 | 1.2872 | 5.2107 |
| | ***NBN-2*** | | | ***NBN-2*** | | |
| ***0.01*** | 0.9474 | 1.4684 | 8.1274 | 0.8832 | 1.2800 | 4.7177 |
| ***0.02*** | 0.9481 | 1.4700 | 8.3056 | 0.885 | 1.2812 | 4.7534 |
| ***0.04*** | 0.9492 | 1.4720 | 8.6402 | 0.8856 | 1.2824 | 4.7978 |
| ***0.06*** | 0.9524 | 1.4728 | 8.7901 | 0.8887 | 1.2844 | 4.8409 |
| ***0.08*** | 0.9565 | 1.4736 | 9.1068 | 0.8926 | 1.2860 | 5.0319 |
| ***0.10*** | 0.9638 | 1.4760 | 9.5469 | 0.8958 | 1.2892 | 5.0764 |
| | ***NBN-3*** | | | ***NBN-3*** | | |
| ***0.01*** | 0.9487 | 1.4660 | 8.2868 | 0.882 | 1.2784 | 4.7075 |
| ***0.02*** | 0.9534 | 1.4676 | 8.4246 | 0.8829 | 1.2792 | 4.7683 |
| ***0.04*** | 0.9593 | 1.4696 | 8.5619 | 0.8843 | 1.2800 | 4.8394 |
| ***0.06*** | 0.9615 | 1.4712 | 8.7359 | 0.8879 | 1.2812 | 4.9229 |
| ***0.08*** | 0.9629 | 1.4728 | 8.8910 | 0.8889 | 1.2824 | 5.0974 |
| ***0.10*** | 0.9691 | 1.4752 | 9.1326 | 0.8954 | 1.2832 | 5.2407 |
| | ***NBN-4*** | | | ***NBN-4*** | | |
| ***0.01*** | 0.9478 | 1.4660 | 8.2189 | 0.8824 | 1.2784 | 4.7917 |
| ***0.02*** | 0.9492 | 1.4676 | 8.3073 | 0.8838 | 1.2796 | 4.9113 |
| ***0.04*** | 0.9505 | 1.4692 | 8.3749 | 0.8866 | 1.2820 | 5.0543 |
| ***0.06*** | 0.9530 | 1.4712 | 8.5258 | 0.8892 | 1.2832 | 5.2194 |
| ***0.08*** | 0.9547 | 1.4720 | 8.6096 | 0.8929 | 1.2844 | 5.3883 |
| ***0.10*** | 0.9571 | 1.4732 | 8.7930 | 0.8949 | 1.2856 | 5.4117 |
| | ***NBN-5*** | | | ***NBN-5*** | | |
| ***0.01*** | 0.9509 | 1.4668 | 8.4186 | 0.8826 | 1.2788 | 4.6846 |
| ***0.02*** | 0.9529 | 1.4688 | 8.4766 | 0.8842 | 1.2792 | 4.7865 |
| ***0.04*** | 0.9548 | 1.4696 | 8.6266 | 0.8849 | 1.2816 | 4.8614 |
| ***0.06*** | 0.9581 | 1.4716 | 8.8062 | 0.8882 | 1.2836 | 4.9583 |
| ***0.08*** | 0.9619 | 1.4732 | 8.9225 | 0.8914 | 1.2848 | 5.0477 |
| ***0.10*** | 0.9662 | 1.4740 | 9.0236 | 0.8949 | 1.2864 | 5.1432 |

| ***Conc. M*** | ***Density ρ g.cm$^{-3}$*** | ***Velocity U. 10$^{-5}$ cm.s$^{-1}$*** | ***Viscosity η.10$^{3}$ poise*** | ***Density ρ g.cm$^{-3}$*** | ***Velocity U. 10$^{-5}$ cm.s$^{-1}$*** | ***Viscosity η.10$^{3}$ poise*** |
|---|---|---|---|---|---|---|
| | ***DMF*** | | | ***THF*** | | |
| | ***NBN-6*** | | | ***NBN-6*** | | |
| ***0.00*** | 0.9449 | 1.4616 | 8.1418 | 0.8815 | 1.2780 | 4.6005 |
| ***0.01*** | 0.9472 | 1.4628 | 8.4259 | 0.8822 | 1.2796 | 4.7869 |
| ***0.02*** | 0.9503 | 1.4636 | 8.5980 | 0.8845 | 1.2804 | 4.9152 |
| ***0.04*** | 0.9546 | 1.4648 | 8.7095 | 0.8886 | 1.2812 | 5.1107 |
| ***0.06*** | 0.9559 | 1.4664 | 8.8547 | 0.8922 | 1.2820 | 5.2144 |
| ***0.08*** | 0.9576 | 1.4672 | 8.9514 | 0.8947 | 1.2828 | 5.3538 |
| ***0.10*** | 0.9587 | 1.4680 | 9.1318 | 0.8998 | 1.2844 | 5.4794 |
| | ***NBN-7*** | | | ***NBN-7*** | | |
| ***0.01*** | 0.9463 | 1.4640 | 8.3899 | 0.8828 | 1.2792 | 4.7752 |
| ***0.02*** | 0.9490 | 1.4648 | 8.5501 | 0.8845 | 1.2792 | 4.8816 |
| ***0.04*** | 0.9510 | 1.4664 | 8.6646 | 0.8863 | 1.2792 | 5.0001 |
| ***0.06*** | 0.9545 | 1.4668 | 8.7772 | 0.8884 | 1.2796 | 5.0983 |
| ***0.08*** | 0.9581 | 1.4676 | 8.8872 | 0.8915 | 1.2800 | 5.2442 |
| ***0.10*** | 0.9622 | 1.4700 | 9.0676 | 0.8957 | 1.2808 | 5.4317 |
| | ***NBN-8*** | | | ***NBN-8*** | | |
| ***0.01*** | 0.9508 | 1.4636 | 8.2449 | 0.8845 | 1.2796 | 4.7470 |
| ***0.02*** | 0.9520 | 1.4648 | 8.3881 | 0.8882 | 1.2804 | 4.8344 |
| ***0.04*** | 0.9551 | 1.4664 | 8.5244 | 0.8897 | 1.2812 | 4.9366 |
| ***0.06*** | 0.9575 | 1.4676 | 8.7481 | 0.8917 | 1.2844 | 5.0344 |
| ***0.08*** | 0.9604 | 1.4684 | 8.8680 | 0.8929 | 1.2860 | 5.1506 |
| ***0.10*** | 0.9660 | 1.4700 | 9.1156 | 0.8956 | 1.2888 | 5.2494 |
| | ***NBN-9*** | | | ***NBN-9*** | | |
| ***0.01*** | 0.9482 | 1.4632 | 8.2665 | 0.8837 | 1.2784 | 4.7502 |
| ***0.02*** | 0.9529 | 1.4648 | 8.4121 | 0.8864 | 1.2792 | 4.8996 |
| ***0.04*** | 0.9546 | 1.4664 | 8.5320 | 0.8892 | 1.2796 | 5.0353 |
| ***0.06*** | 0.9578 | 1.4676 | 8.7306 | 0.893 | 1.2812 | 5.1285 |
| ***0.08*** | 0.9603 | 1.4696 | 8.8589 | 0.8946 | 1.2828 | 5.2095 |
| ***0.10*** | 0.9642 | 1.4712 | 9.0131 | 0.8973 | 1.2836 | 5.3314 |
| | ***NBN-10*** | | | ***NBN-10*** | | |
| ***0.01*** | 0.9464 | 1.4628 | 8.3267 | 0.8829 | 1.2780 | 4.6825 |
| ***0.02*** | 0.9489 | 1.4636 | 8.4690 | 0.8832 | 1.2792 | 4.7550 |
| ***0.04*** | 0.9523 | 1.4656 | 8.6362 | 0.8858 | 1.2800 | 4.8364 |
| ***0.06*** | 0.9563 | 1.4676 | 8.7614 | 0.8882 | 1.2816 | 4.9320 |
| ***0.08*** | 0.9591 | 1.4688 | 8.8478 | 0.8905 | 1.2836 | 5.0163 |
| ***0.10*** | 0.9612 | 1.4700 | 8.9972 | 0.8942 | 1.2852 | 5.1089 |

**Table 3.1.2: The density (*ρ*), ultrasonic velocity (*U*) and viscosity (*η*) of NTD series in DMF and THF at 298.15 K.**

| *Conc. M* | *Density ρ g.cm$^{-3}$* | *Velocity U. 10$^{-5}$ cm.s$^{-1}$* | *Viscosity η.10$^{3}$ poise* | *Density ρ g.cm$^{-3}$* | *Velocity U. 10$^{-5}$ cm.s$^{-1}$* | *Viscosity η.10$^{3}$ poise* |
|---|---|---|---|---|---|---|
| | ***DMF*** | | | ***THF*** | | |
| | ***NTD-1*** | | | ***NTD-1*** | | |
| ***0.00*** | 0.9449 | 1.4616 | 8.1418 | 0.8815 | 1.2780 | 4.6004 |
| ***0.01*** | 0.9480 | 1.4636 | 8.2777 | 0.8819 | 1.2804 | 4.6456 |
| ***0.02*** | 0.9511 | 1.4672 | 8.4194 | 0.8828 | 1.2820 | 4.7117 |
| ***0.04*** | 0.9535 | 1.4712 | 8.6052 | 0.8842 | 1.2840 | 4.7864 |
| ***0.06*** | 0.9572 | 1.4728 | 8.7436 | 0.8861 | 1.2856 | 4.9188 |
| ***0.08*** | 0.9611 | 1.4740 | 9.0109 | 0.8885 | 1.2868 | 5.1367 |
| ***0.10*** | 0.9645 | 1.4756 | 9.2732 | 0.8922 | 1.2888 | 5.2346 |
| | ***NTD-2*** | | | ***NTD-2*** | | |
| ***0.01*** | 0.9471 | 1.4624 | 8.2503 | 0.8823 | 1.2796 | 4.6410 |
| ***0.02*** | 0.9501 | 1.4648 | 8.3899 | 0.8842 | 1.2820 | 4.7067 |
| ***0.04*** | 0.9535 | 1.4668 | 8.5928 | 0.8854 | 1.2832 | 4.7832 |
| ***0.06*** | 0.9571 | 1.4688 | 8.7146 | 0.8882 | 1.2844 | 4.9141 |
| ***0.08*** | 0.9612 | 1.4700 | 8.9816 | 0.8916 | 1.2860 | 5.0665 |
| ***0.10*** | 0.9645 | 1.4708 | 9.2429 | 0.8951 | 1.2884 | 5.2342 |
| | ***NTD-3*** | | | ***NTD-3*** | | |
| ***0.01*** | 0.9478 | 1.4656 | 8.2872 | 0.8825 | 1.2808 | 4.6574 |
| ***0.02*** | 0.9498 | 1.4672 | 8.4275 | 0.8833 | 1.2820 | 4.7201 |
| ***0.04*** | 0.9525 | 1.4692 | 8.6376 | 0.8851 | 1.2836 | 4.8008 |
| ***0.06*** | 0.9553 | 1.4708 | 8.7595 | 0.8884 | 1.2856 | 4.9538 |
| ***0.08*** | 0.9583 | 1.4724 | 9.0138 | 0.8911 | 1.2880 | 5.1711 |
| ***0.10*** | 0.9628 | 1.4740 | 9.2684 | 0.8948 | 1.2908 | 5.3684 |
| | ***NTD-4*** | | | ***NTD-4*** | | |
| ***0.01*** | 0.9498 | 1.4652 | 8.3006 | 0.883 | 1.2792 | 4.7521 |
| ***0.02*** | 0.9532 | 1.4676 | 8.4514 | 0.8846 | 1.2804 | 4.8750 |
| ***0.04*** | 0.9562 | 1.4696 | 8.6649 | 0.8871 | 1.2812 | 4.9957 |
| ***0.06*** | 0.9588 | 1.4712 | 8.7718 | 0.8898 | 1.2828 | 5.0872 |
| ***0.08*** | 0.9622 | 1.4720 | 9.0296 | 0.8933 | 1.2844 | 5.1839 |
| ***0.10*** | 0.9670 | 1.4728 | 9.2773 | 0.8962 | 1.2856 | 5.3506 |
| | ***NTD-5*** | | | ***NTD-5*** | | |
| ***0.01*** | 0.9487 | 1.4664 | 8.3219 | 0.8824 | 1.2792 | 4.6281 |
| ***0.02*** | 0.9521 | 1.4680 | 8.4489 | 0.8841 | 1.2808 | 4.7378 |
| ***0.04*** | 0.9568 | 1.4700 | 8.6693 | 0.8854 | 1.2828 | 4.8188 |
| ***0.06*** | 0.9608 | 1.4712 | 8.8485 | 0.8879 | 1.2864 | 4.9770 |
| ***0.08*** | 0.9642 | 1.4728 | 8.9887 | 0.8908 | 1.2888 | 5.1800 |
| ***0.10*** | 0.9682 | 1.4744 | 9.2415 | 0.8944 | 1.2908 | 5.3524 |

| ***Conc. M*** | ***Density ρ g.cm$^{-3}$*** | ***Velocity U. 10$^{-5}$ cm.s$^{-1}$*** | ***Viscosity η.10$^{3}$ poise*** | ***Density ρ g.cm$^{-3}$*** | ***Velocity U. 10$^{-5}$ cm.s$^{-1}$*** | ***Viscosity η.10$^{3}$ poise*** |
|---|---|---|---|---|---|---|
| | ***DMF*** | | | ***THF*** | | |
| | ***NTD-6*** | | | ***NTD-6*** | | |
| ***0.00*** | 0.9449 | 1.4616 | 8.1418 | 0.8815 | 1.2780 | 4.6004 |
| ***0.01*** | 0.9470 | 1.4644 | 8.2689 | 0.8827 | 1.2796 | 4.6498 |
| ***0.02*** | 0.9502 | 1.4664 | 8.4114 | 0.8852 | 1.2808 | 4.7245 |
| ***0.04*** | 0.9543 | 1.4676 | 8.6125 | 0.8881 | 1.2824 | 4.8075 |
| ***0.06*** | 0.9558 | 1.4692 | 8.7308 | 0.8917 | 1.2844 | 4.9499 |
| ***0.08*** | 0.9577 | 1.4704 | 8.9791 | 0.8943 | 1.2868 | 5.1702 |
| ***0.10*** | 0.9591 | 1.4720 | 9.2213 | 0.8961 | 1.2884 | 5.2575 |
| | ***NTD-7*** | | | ***NTD-7*** | | |
| ***0.01*** | 0.9468 | 1.4636 | 8.3392 | 0.8824 | 1.2792 | 4.7268 |
| ***0.02*** | 0.9491 | 1.4652 | 8.4697 | 0.8838 | 1.2800 | 4.8101 |
| ***0.04*** | 0.9522 | 1.4664 | 8.6390 | 0.8857 | 1.2808 | 4.9936 |
| ***0.06*** | 0.9552 | 1.4668 | 8.8011 | 0.8880 | 1.2816 | 5.1222 |
| ***0.08*** | 0.9591 | 1.4676 | 8.9922 | 0.8911 | 1.2828 | 5.3075 |
| ***0.10*** | 0.9634 | 1.4700 | 9.2846 | 0.8936 | 1.2836 | 5.3806 |
| | ***NTD-8*** | | | ***NTD-8*** | | |
| ***0.01*** | 0.9492 | 1.4652 | 8.3613 | 0.8834 | 1.2796 | 4.6765 |
| ***0.02*** | 0.9532 | 1.4672 | 8.4959 | 0.8877 | 1.2804 | 4.7571 |
| ***0.04*** | 0.9561 | 1.4688 | 8.6515 | 0.8902 | 1.2812 | 4.8449 |
| ***0.06*** | 0.9583 | 1.4704 | 8.7942 | 0.8922 | 1.2844 | 4.9556 |
| ***0.08*** | 0.9621 | 1.4720 | 8.9827 | 0.8941 | 1.2860 | 5.1691 |
| ***0.10*** | 0.9662 | 1.4732 | 9.2455 | 0.8977 | 1.2888 | 5.2718 |
| | ***NTD-9*** | | | ***NTD-9*** | | |
| ***0.01*** | 0.9462 | 1.4636 | 8.2424 | 0.8829 | 1.2788 | 4.6508 |
| ***0.02*** | 0.9485 | 1.4652 | 8.3788 | 0.8858 | 1.2796 | 4.7277 |
| ***0.04*** | 0.9519 | 1.4668 | 8.5743 | 0.8882 | 1.2808 | 4.8080 |
| ***0.06*** | 0.9559 | 1.4680 | 8.7089 | 0.8915 | 1.2820 | 4.9488 |
| ***0.08*** | 0.9587 | 1.4692 | 8.9166 | 0.8936 | 1.2836 | 5.1662 |
| ***0.10*** | 0.9608 | 1.4700 | 9.0822 | 0.8962 | 1.2848 | 5.2581 |
| | ***NTD-10*** | | | ***NTD-10*** | | |
| ***0.01*** | 0.9482 | 1.4632 | 8.2773 | 0.8826 | 1.2784 | 4.7001 |
| ***0.02*** | 0.9517 | 1.4652 | 8.4164 | 0.8834 | 1.2792 | 4.7859 |
| ***0.04*** | 0.9555 | 1.4668 | 8.6181 | 0.8849 | 1.2804 | 4.8853 |
| ***0.06*** | 0.9595 | 1.4684 | 8.7573 | 0.8875 | 1.2816 | 5.0317 |
| ***0.08*** | 0.9632 | 1.4692 | 8.9909 | 0.8911 | 1.2836 | 5.2011 |
| ***0.10*** | 0.9665 | 1.4704 | 9.2095 | 0.8926 | 1.2852 | 5.3533 |

**4. Rao's molar sound function:**

Rao's molar sound function ($R_m$) can be evaluated by an equation given by Bagchi et al.[75]:

$$R_m = \left(\frac{M}{\rho}\right) U^{1/3} \qquad \ldots (3.1.9)$$

**5. Van der Waals Constant:**

Van der Waals constant ($b$) can be calculated as follows[76]:

$$b = \frac{M}{\rho}\left\{1 - \left(\frac{RT}{MU^2}\right)\left[\sqrt{1 + \frac{MU^2}{3RT}} - 1\right]\right\} \qquad \ldots (3.1.10)$$

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

**6. Relaxation Strength:**

The relaxation strength ($r$) can be calculated as follows[77]:

$$r = 1 - \left[\frac{U}{U_\infty}\right]^2 \qquad \cdots (3.1.11)$$

where $U_\infty$ = 1.6 x $10^5$ cm/sec.

**7. Solvation number:**

$$S_n = \frac{M_2}{M_1}\left[\frac{1-\kappa_s}{\kappa_{s1}}\right]\left[\frac{100 - X}{X}\right] \qquad \cdots (3.1.12)$$

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 $\kappa_{S1}$ and $\kappa_S$ are isentropic compressibility of solvent and solute respectively.

**8. Apparent Molar Compressibility ($\phi_K$):**

The apparent molar compressibility ($\phi_K$) of the solutions was calculated by the following equation:

$$\phi_K = \frac{\left(\rho_0\kappa_s - \rho\kappa_s^0\right)1000}{c\rho_0} + \frac{\kappa_s^0 M_2}{\rho_0} \qquad \ldots (3.1.13)$$

where $\rho_0$ and $\kappa_s^0$ are density and isentropic compressibility of pure solvent respectively, $c$ is the concentration of the solution and $M_2$ is the molecular weight of the compound.

Some of these calculated parameters are given in Tables 3.1.3 and 3.1.4. for benzodiazepines and thiadiazepines in DMF and THF respectively. Figures 3.1.1 and 3.1.2 show the variation of ultrasound velocity ($U$) with concentration in DMF and THF. It is observed that overall ultrasonic velocity ($U$) increases with concentration for all the compounds in both the solvents. However, in THF, for NBN-1, there is decrease in velocity at the beginning, which increases with increase in concentration. The velocity depends on intermolecular free length ($L_f$). The velocity increases with decrease in $L_f$ or vice versa. It is evident from Tables 3.1.3 and 3.1.4 that $L_f$ decrease continuously (except for NBN-1 in THF), which suggests that there is strong interaction between solvent (both DMF and THF) and compound molecules. For NBN-1 solutions in THF, the decrease of $U$ and increase in $L_f$ at lower concentration suggests the existence of solute-solute interactions.

This is further supported by isentropic compressibility ($\kappa_s$) and relaxation strength ($r$) values. The variation of isentropic compressibility ($\kappa_s$) with concentration of these compounds is also shown Figures 3.1.3 and 3.1.4 for all the solutions in both the solvents. Both isentropic compressibility ($\kappa_s$) and relaxation strength ($r$) (in Tables 3.1.3 and 3.1.4) are observed to decrease with concentration for all the compounds. The decrease of $\kappa_s$ with increasing concentration might be due to aggregation of solvent molecules around solute molecules indicating thereby the presence of solute-solvent interactions.

Figures 3.1.5 and 3.1.6 shows the linear variation of molar compressibility ($W$) with concentration. Tables 3.1.3 and 3.1.4 shows the variation of molar sound function ($R_m$) and Vander Waals constant ($b$) with concentration. The correlation coefficients for these parameters are in the range of 0.9993- 0.9999. This linear increase of these parameters suggests the absence of complex formation in these systems.

**Table 3.1.3: Some acoustical parameters of benzodiazepine derivatives in DMF and THF at 298.15 K.**

| | DMF | | | | THF | | | |
|---|---|---|---|---|---|---|---|---|
| Conc. M | $L_f$ $A^o$ | r | $R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$ | b $cm^3.mol^{-1}$ | $L_f$ $A^o$ | r | $R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$ | b $cm^3.mol^{-1}$ |
| | NBN-1 | | | | NBN-1 | | | |
| 0.00 | 0.1476 | 0.1655 | 4.0746 | 77.3503 | 0.1747 | 0.3620 | 4.1205 | 81.8016 |
| 0.01 | 0.1471 | 0.1637 | 4.1509 | 78.7711 | 0.1754 | 0.3676 | 4.2097 | 83.6946 |
| 0.02 | 0.1468 | 0.1619 | 4.2340 | 80.3184 | 0.1762 | 0.3743 | 4.2943 | 85.5290 |
| 0.04 | 0.1464 | 0.1591 | 4.4011 | 83.4426 | 0.1759 | 0.3731 | 4.4853 | 89.3044 |
| 0.06 | 0.1459 | 0.1568 | 4.5621 | 86.4568 | 0.1742 | 0.3616 | 4.6896 | 93.0893 |
| 0.08 | 0.1456 | 0.1559 | 4.7258 | 89.5414 | 0.1733 | 0.3572 | 4.8771 | 96.7016 |
| 0.10 | 0.1447 | 0.1522 | 4.8600 | 92.0173 | 0.1723 | 0.3528 | 5.0482 | 99.9793 |
| | NBN-2 | | | | NBN-2 | | | |
| 0.01 | 0.1467 | 0.1577 | 4.1535 | 78.7271 | 0.1743 | 0.3600 | 4.2067 | 83.4684 |
| 0.02 | 0.1465 | 0.1559 | 4.2352 | 80.2463 | 0.1739 | 0.3588 | 4.2908 | 85.1117 |
| 0.04 | 0.1462 | 0.1536 | 4.3983 | 83.2993 | 0.1737 | 0.3576 | 4.4721 | 88.6803 |
| 0.06 | 0.1459 | 0.1527 | 4.5484 | 86.1269 | 0.1731 | 0.3556 | 4.6394 | 91.9492 |
| 0.08 | 0.1455 | 0.1518 | 4.6915 | 88.8195 | 0.1726 | 0.3540 | 4.7989 | 95.0724 |
| 0.10 | 0.1447 | 0.1490 | 4.8150 | 91.1085 | 0.1718 | 0.3508 | 4.9624 | 98.2285 |
| | NBN-3 | | | | NBN-3 | | | |
| 0.01 | 0.1468 | 0.1605 | 4.1762 | 79.2007 | 0.1746 | 0.3616 | 4.2448 | 84.2606 |
| 0.02 | 0.1463 | 0.1587 | 4.2694 | 80.9387 | 0.1744 | 0.3608 | 4.3672 | 86.6724 |
| 0.04 | 0.1457 | 0.1564 | 4.4667 | 84.6403 | 0.1742 | 0.3600 | 4.6120 | 91.5119 |
| 0.06 | 0.1453 | 0.1545 | 4.6791 | 88.6336 | 0.1737 | 0.3588 | 4.8420 | 96.0450 |
| 0.08 | 0.1451 | 0.1527 | 4.8945 | 92.6804 | 0.1734 | 0.3576 | 5.0860 | 100.8535 |
| 0.10 | 0.1444 | 0.1499 | 5.0790 | 96.1213 | 0.1727 | 0.3568 | 5.2882 | 104.8410 |
| | NBN-4 | | | | NBN-4 | | | |
| 0.01 | 0.1469 | 0.1605 | 4.1633 | 78.9560 | 0.1746 | 0.3616 | 4.2241 | 83.8492 |
| 0.02 | 0.1466 | 0.1587 | 4.2554 | 80.6737 | 0.1743 | 0.3604 | 4.3256 | 85.8374 |
| 0.04 | 0.1464 | 0.1568 | 4.4442 | 84.2220 | 0.1737 | 0.3580 | 4.5268 | 89.7749 |
| 0.06 | 0.1460 | 0.1545 | 4.6260 | 87.6264 | 0.1733 | 0.3568 | 4.7255 | 93.6850 |
| 0.08 | 0.1458 | 0.1536 | 4.8093 | 91.0824 | 0.1727 | 0.3556 | 4.9148 | 97.4074 |
| 0.10 | 0.1455 | 0.1522 | 4.9874 | 94.4311 | 0.1724 | 0.3544 | 5.1126 | 101.2966 |
| | NBN-5 | | | | NBN-5 | | | |
| 0.01 | 0.1466 | 0.1596 | 4.1502 | 78.6926 | 0.1745 | 0.3612 | 4.2235 | 83.8298 |
| 0.02 | 0.1462 | 0.1573 | 4.2393 | 80.3462 | 0.1743 | 0.3608 | 4.3231 | 85.7967 |
| 0.04 | 0.1460 | 0.1564 | 4.4229 | 83.8098 | 0.1739 | 0.3584 | 4.5359 | 89.9636 |
| 0.06 | 0.1455 | 0.1541 | 4.5987 | 87.1021 | 0.1733 | 0.3564 | 4.7320 | 93.8047 |
| 0.08 | 0.1451 | 0.1522 | 4.7689 | 90.2928 | 0.1728 | 0.3552 | 4.9250 | 97.5994 |
| 0.10 | 0.1447 | 0.1513 | 4.9325 | 93.3731 | 0.1723 | 0.3536 | 5.1136 | 101.2966 |

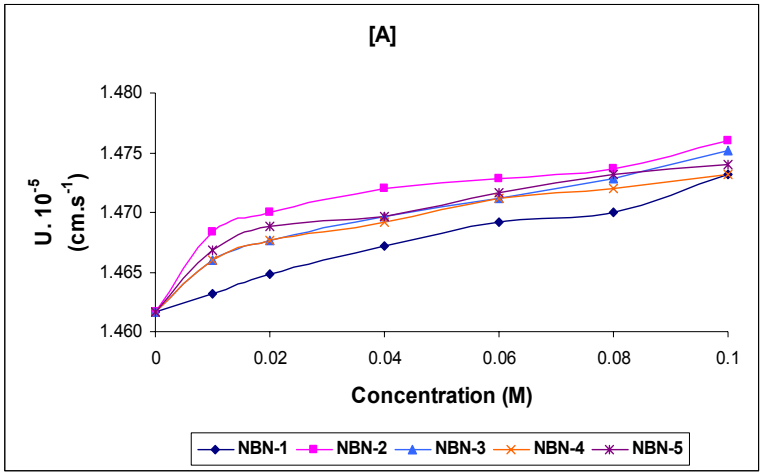
| | DMF | | | | THF | | | |
|---|---|---|---|---|---|---|---|---|
| **Conc. M** | $L_f$ $A^o$ | **r** | $R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$ | **b** $cm^3.mol^{-1}$ | $L_f$ $A^o$ | **r** | $R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$ | **b** $cm^3.mol^{-1}$ |
| | **NBN-6** | | | | **NBN-6** | | | |
| **0.00** | 0.1476 | 0.1655 | 4.0746 | 77.3503 | 0.1747 | 0.3620 | 4.1205 | 81.8016 |
| **0.01** | 0.1473 | 0.1641 | 4.1496 | 78.7525 | 0.1754 | 0.3676 | 4.2097 | 83.6946 |
| **0.02** | 0.1469 | 0.1632 | 4.2198 | 80.0700 | 0.1762 | 0.3743 | 4.2943 | 85.5290 |
| **0.04** | 0.1465 | 0.1619 | 4.3662 | 82.8259 | 0.1759 | 0.3731 | 4.4853 | 89.3044 |
| **0.06** | 0.1462 | 0.1600 | 4.5260 | 85.8271 | 0.1742 | 0.3616 | 4.6896 | 93.0893 |
| **0.08** | 0.1460 | 0.1591 | 4.6820 | 88.7694 | 0.1733 | 0.3572 | 4.8771 | 96.7016 |
| **0.10** | 0.1459 | 0.1582 | 4.8405 | 91.7573 | 0.1723 | 0.3528 | 5.0482 | 99.9793 |
| | **NBN-7** | | | | **NBN-7** | | | |
| **0.01** | 0.1472 | 0.1628 | 4.1538 | 78.8120 | 0.1743 | 0.3600 | 4.2067 | 83.4684 |
| **0.02** | 0.1469 | 0.1619 | 4.2251 | 80.1504 | 0.1739 | 0.3588 | 4.2908 | 85.1117 |
| **0.04** | 0.1466 | 0.1600 | 4.3820 | 83.0963 | 0.1737 | 0.3576 | 4.4721 | 88.6803 |
| **0.06** | 0.1463 | 0.1596 | 4.5286 | 85.8671 | 0.1731 | 0.3556 | 4.6394 | 91.9492 |
| **0.08** | 0.1459 | 0.1587 | 4.6727 | 88.5846 | 0.1726 | 0.3540 | 4.7989 | 95.0724 |
| **0.10** | 0.1454 | 0.1559 | 4.8135 | 91.2038 | 0.1718 | 0.3508 | 4.9624 | 98.2285 |
| | **NBN-8** | | | | **NBN-8** | | | |
| **0.01** | 0.1469 | 0.1632 | 4.1424 | 78.6030 | 0.1746 | 0.3616 | 4.2448 | 84.2606 |
| **0.02** | 0.1467 | 0.1619 | 4.2293 | 80.2300 | 0.1744 | 0.3608 | 4.3672 | 86.6724 |
| **0.04** | 0.1463 | 0.1600 | 4.3977 | 83.3925 | 0.1742 | 0.3600 | 4.6120 | 91.5119 |
| **0.06** | 0.1460 | 0.1587 | 4.5672 | 86.5832 | 0.1737 | 0.3588 | 4.8420 | 96.0450 |
| **0.08** | 0.1457 | 0.1577 | 4.7317 | 89.6873 | 0.1734 | 0.3576 | 5.0860 | 100.8535 |
| **0.10** | 0.1451 | 0.1559 | 4.8791 | 92.4461 | 0.1727 | 0.3568 | 5.2882 | 104.8410 |
| | **NBN-9** | | | | **NBN-9** | | | |
| **0.01** | 0.1471 | 0.1637 | 4.1455 | 78.6677 | 0.1746 | 0.3616 | 4.2241 | 83.8492 |
| **0.02** | 0.1466 | 0.1619 | 4.2089 | 79.8429 | 0.1743 | 0.3604 | 4.3256 | 85.8374 |
| **0.04** | 0.1463 | 0.1600 | 4.3678 | 82.8260 | 0.1737 | 0.3580 | 4.5268 | 89.7749 |
| **0.06** | 0.1460 | 0.1587 | 4.5173 | 85.6383 | 0.1733 | 0.3568 | 4.7255 | 93.6850 |
| **0.08** | 0.1456 | 0.1564 | 4.6696 | 88.4849 | 0.1727 | 0.3556 | 4.9148 | 97.4074 |
| **0.10** | 0.1451 | 0.1545 | 4.8118 | 91.1459 | 0.1724 | 0.3544 | 5.1126 | 101.2966 |
| | **NBN-10** | | | | **NBN-10** | | | |
| **0.01** | 0.1473 | 0.1641 | 4.1461 | 78.6877 | 0.1745 | 0.3612 | 4.2235 | 83.8298 |
| **0.02** | 0.1471 | 0.1632 | 4.2123 | 79.9288 | 0.1743 | 0.3608 | 4.3231 | 85.7967 |
| **0.04** | 0.1470 | 0.1609 | 4.3507 | 82.5169 | 0.1739 | 0.3584 | 4.5359 | 89.9636 |
| **0.06** | 0.1461 | 0.1587 | 4.4840 | 85.0074 | 0.1733 | 0.3564 | 4.7320 | 93.8047 |
| **0.08** | 0.1458 | 0.1573 | 4.6209 | 87.5773 | 0.1728 | 0.3552 | 4.9250 | 97.5994 |
| **0.10** | 0.1455 | 0.1559 | 4.7601 | 90.1919 | 0.1723 | 0.3536 | 5.1136 | 101.2966 |

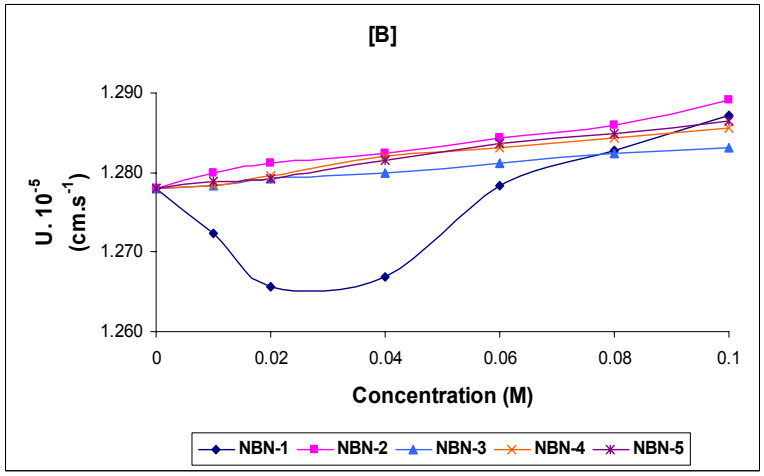
**Table 3.1.4: Some acoustical parameters of thiadiazepine derivatives in DMF and THF at 298.15 K.**

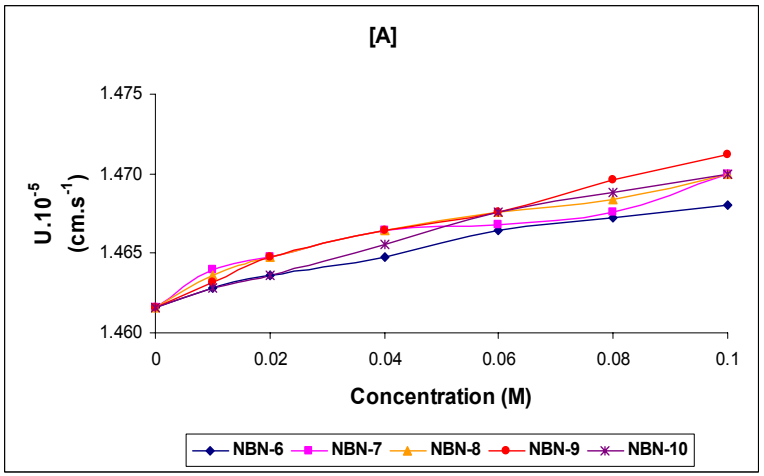
| | DMF | | | | THF | | | |
|---|---|---|---|---|---|---|---|---|
| Conc. M | $L_f$ $A^o$ | r | $R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$ | b $cm^3.mol^{-1}$ | $L_f$ $A^o$ | r | $R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$ | b $cm^3.mol^{-1}$ |
| | NTD-1 | | | | NTD-1 | | | |
| 0.00 | 0.1476 | 0.1655 | 4.0746 | 77.3503 | 0.1747 | 0.3620 | 4.1205 | 81.8016 |
| 0.01 | 0.1471 | 0.1632 | 4.1154 | 78.0897 | 0.1744 | 0.3596 | 4.1792 | 82.9153 |
| 0.02 | 0.1465 | 0.1591 | 4.1572 | 78.8178 | 0.1741 | 0.3580 | 4.2345 | 83.9781 |
| 0.04 | 0.1459 | 0.1545 | 4.2538 | 80.5762 | 0.1736 | 0.3560 | 4.3454 | 86.1313 |
| 0.06 | 0.1455 | 0.1527 | 4.3409 | 82.1962 | 0.1732 | 0.3544 | 4.4524 | 88.2168 |
| 0.08 | 0.1451 | 0.1513 | 4.4252 | 83.7699 | 0.1728 | 0.3532 | 4.5553 | 90.2277 |
| 0.10 | 0.1447 | 0.1495 | 4.5110 | 85.3647 | 0.1722 | 0.3512 | 4.6505 | 92.0650 |
| | NTD-2 | | | | NTD-2 | | | |
| 0.01 | 0.1473 | 0.1646 | 4.1468 | 78.7064 | 0.1744 | 0.3604 | 4.2079 | 83.5022 |
| 0.02 | 0.1468 | 0.1619 | 4.2161 | 79.9792 | 0.1739 | 0.3580 | 4.2904 | 85.0861 |
| 0.04 | 0.1464 | 0.1596 | 4.3622 | 82.7136 | 0.1736 | 0.3568 | 4.4635 | 88.4908 |
| 0.06 | 0.1459 | 0.1573 | 4.5053 | 85.3874 | 0.1732 | 0.3556 | 4.6264 | 91.6923 |
| 0.08 | 0.1455 | 0.1559 | 4.6427 | 87.9670 | 0.1727 | 0.3540 | 4.7841 | 94.7786 |
| 0.10 | 0.1451 | 0.1550 | 4.7818 | 90.5871 | 0.1720 | 0.3516 | 4.9398 | 97.8027 |
| | NTD-3 | | | | NTD-3 | | | |
| 0.01 | 0.1469 | 0.1609 | 4.1444 | 78.6051 | 0.1742 | 0.3592 | 4.2058 | 83.4343 |
| 0.02 | 0.1466 | 0.1591 | 4.2154 | 79.9216 | 0.1740 | 0.3580 | 4.2901 | 85.0795 |
| 0.04 | 0.1462 | 0.1568 | 4.3608 | 82.6402 | 0.1736 | 0.3564 | 4.4558 | 88.3300 |
| 0.06 | 0.1458 | 0.1550 | 4.5036 | 85.3170 | 0.1730 | 0.3544 | 4.6122 | 91.3817 |
| 0.08 | 0.1455 | 0.1531 | 4.6438 | 87.9403 | 0.1724 | 0.3520 | 4.7704 | 94.4585 |
| 0.10 | 0.1469 | 0.1513 | 4.7736 | 90.3656 | 0.1717 | 0.3492 | 4.9210 | 97.3688 |
| | NTD-4 | | | | NTD-4 | | | |
| 0.01 | 0.1468 | 0.1614 | 4.1352 | 78.4364 | 0.1744 | 0.3608 | 4.2016 | 83.3861 |
| 0.02 | 0.1463 | 0.1587 | 4.2002 | 79.6260 | 0.1741 | 0.3596 | 4.2817 | 84.9494 |
| 0.04 | 0.1459 | 0.1564 | 4.3431 | 82.2977 | 0.1737 | 0.3588 | 4.4422 | 88.1155 |
| 0.06 | 0.1455 | 0.1545 | 4.4859 | 84.9735 | 0.1733 | 0.3572 | 4.6008 | 91.2219 |
| 0.08 | 0.1452 | 0.1536 | 4.6221 | 87.5367 | 0.1727 | 0.3556 | 4.7526 | 94.1926 |
| 0.10 | 0.1468 | 0.1527 | 4.7483 | 89.9106 | 0.1723 | 0.3544 | 4.9053 | 97.1905 |
| | NTD-5 | | | | NTD-5 | | | |
| 0.01 | 0.1468 | 0.1600 | 4.1284 | 78.2864 | 0.1745 | 0.3608 | 4.1904 | 83.1630 |
| 0.02 | 0.1464 | 0.1582 | 4.1802 | 79.2394 | 0.1741 | 0.3592 | 4.2565 | 84.4396 |
| 0.04 | 0.1458 | 0.1559 | 4.2902 | 81.2879 | 0.1737 | 0.3572 | 4.3970 | 87.1816 |
| 0.06 | 0.1454 | 0.1545 | 4.4007 | 83.3586 | 0.1730 | 0.3536 | 4.5320 | 89.7740 |
| 0.08 | 0.1450 | 0.1527 | 4.5128 | 85.4513 | 0.1724 | 0.3512 | 4.6618 | 92.2894 |
| 0.10 | 0.1445 | 0.1508 | 4.6200 | 87.4510 | 0.1717 | 0.3492 | 4.7853 | 94.6852 |

| DMF | | | | | THF | | | |
|---|---|---|---|---|---|---|---|---|
| Conc. M | $L_f$ $A^o$ | r | $R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$ | b $cm^3.mol^{-1}$ | $L_f$ $A^o$ | r | $R_m.10^{-3}$ $cm^{-8/3}.s^{-1/3}$ | b $cm^3.mol^{-1}$ |
| NTD-6 | | | | | NBN-6 | | | |
| 0.00 | 0.1476 | 0.1655 | 4.0746 | 77.3503 | 0.1747 | 0.3620 | 0.3620 | 81.8016 |
| 0.01 | 0.1471 | 0.1623 | 4.1575 | 78.8752 | 0.1744 | 0.3604 | 0.3604 | 83.6483 |
| 0.02 | 0.1467 | 0.1600 | 4.2340 | 80.2889 | 0.1740 | 0.3592 | 0.3592 | 85.3534 |
| 0.04 | 0.1462 | 0.1587 | 4.3924 | 83.2706 | 0.1735 | 0.3576 | 0.3576 | 88.9305 |
| 0.06 | 0.1460 | 0.1568 | 4.5623 | 86.4601 | 0.1729 | 0.3556 | 0.3556 | 92.3775 |
| 0.08 | 0.1457 | 0.1554 | 4.7286 | 89.5862 | 0.1723 | 0.3532 | 0.3532 | 95.8905 |
| 0.10 | 0.1454 | 0.1536 | 4.8970 | 92.7438 | 0.1719 | 0.3516 | 0.3516 | 99.4670 |
| NTD-7 | | | | | NTD-7 | | | |
| 0.01 | 0.1472 | 0.1632 | 4.1287 | 78.3430 | 0.1745 | 0.3608 | 4.1844 | 4.1844 |
| 0.02 | 0.1469 | 0.1614 | 4.1803 | 79.2927 | 0.1742 | 0.3600 | 4.2452 | 4.2452 |
| 0.04 | 0.1465 | 0.1600 | 4.2871 | 81.2969 | 0.1739 | 0.3592 | 4.3693 | 4.3693 |
| 0.06 | 0.1462 | 0.1596 | 4.3923 | 83.2829 | 0.1736 | 0.3584 | 4.4903 | 4.4903 |
| 0.08 | 0.1459 | 0.1587 | 4.4918 | 85.1541 | 0.1731 | 0.3572 | 4.6058 | 4.6058 |
| 0.10 | 0.1453 | 0.1559 | 4.5891 | 86.9515 | 0.1728 | 0.3564 | 4.7229 | 4.7229 |
| NTD-8 | | | | | NTD-8 | | | |
| 0.01 | 0.1469 | 0.1614 | 4.1315 | 78.3670 | 0.1743 | 0.3604 | 4.1931 | 83.2088 |
| 0.02 | 0.1464 | 0.1591 | 4.1872 | 79.3880 | 0.1738 | 0.3596 | 4.2523 | 84.3660 |
| 0.04 | 0.1460 | 0.1573 | 4.3178 | 81.8338 | 0.1734 | 0.3588 | 4.3980 | 87.2385 |
| 0.06 | 0.1456 | 0.1554 | 4.4504 | 84.3161 | 0.1728 | 0.3556 | 4.5477 | 90.1332 |
| 0.08 | 0.1452 | 0.1536 | 4.5733 | 86.6127 | 0.1724 | 0.3540 | 4.6950 | 93.0130 |
| 0.10 | 0.1448 | 0.1522 | 4.6921 | 88.8389 | 0.1717 | 0.3512 | 4.8319 | 95.6569 |
| NTD-9 | | | | | NTD-9 | | | |
| 0.01 | 0.1473 | 0.1632 | 4.1604 | 78.9433 | 0.1745 | 0.3612 | 4.2134 | 83.6289 |
| 0.02 | 0.1469 | 0.1614 | 4.2407 | 80.4388 | 0.1741 | 0.3604 | 4.2982 | 85.2930 |
| 0.04 | 0.1465 | 0.1596 | 4.4036 | 83.4974 | 0.1737 | 0.3592 | 4.4823 | 88.9196 |
| 0.06 | 0.1461 | 0.1582 | 4.5605 | 86.4500 | 0.1732 | 0.3580 | 4.6592 | 92.4008 |
| 0.08 | 0.1457 | 0.1568 | 4.7216 | 89.4789 | 0.1728 | 0.3564 | 4.8416 | 95.9776 |
| 0.10 | 0.1455 | 0.1559 | 4.8846 | 92.5505 | 0.1724 | 0.3552 | 5.0185 | 99.4537 |
| NTD-10 | | | | | NTD-10 | | | |
| 0.01 | 0.1471 | 0.1637 | 4.1557 | 78.8615 | 0.1746 | 0.3616 | 4.2196 | 83.7600 |
| 0.02 | 0.1467 | 0.1614 | 4.2351 | 80.3322 | 0.1744 | 0.3608 | 4.3202 | 85.7389 |
| 0.04 | 0.1462 | 0.1596 | 4.4040 | 83.5053 | 0.1741 | 0.3596 | 4.5205 | 89.6860 |
| 0.06 | 0.1458 | 0.1577 | 4.5692 | 86.6054 | 0.1736 | 0.3584 | 4.7129 | 93.4746 |
| 0.08 | 0.1454 | 0.1568 | 4.7324 | 89.6835 | 0.1730 | 0.3564 | 4.8977 | 97.0903 |
| 0.10 | 0.1450 | 0.1554 | 4.8959 | 92.7575 | 0.1727 | 0.3548 | 5.0935 | 100.9289 |

**Figure 3.1.1: Variation of ultrasonic velocity (*U*) of benzodiazepines (NBN) with concentration in [A] DMF and [B] THF at 298.15 K.**



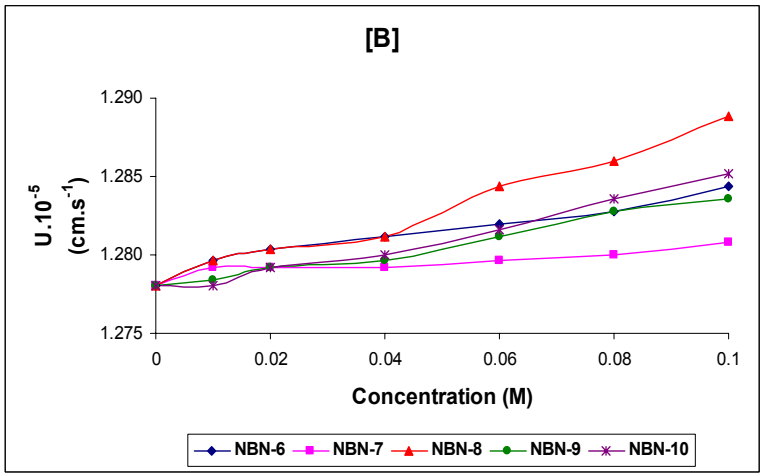
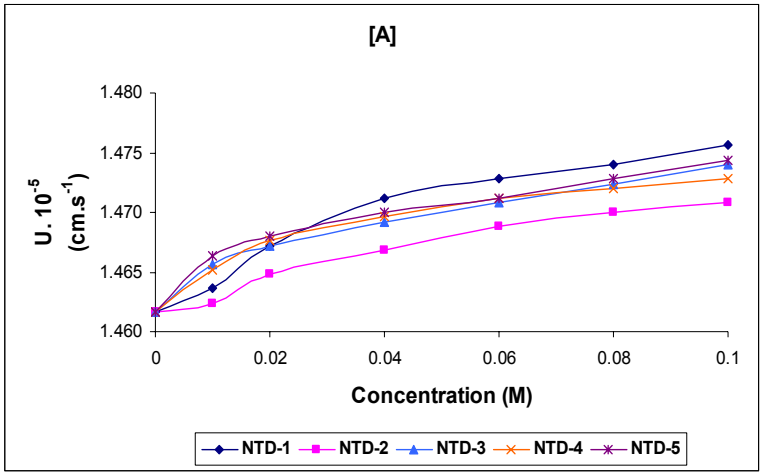
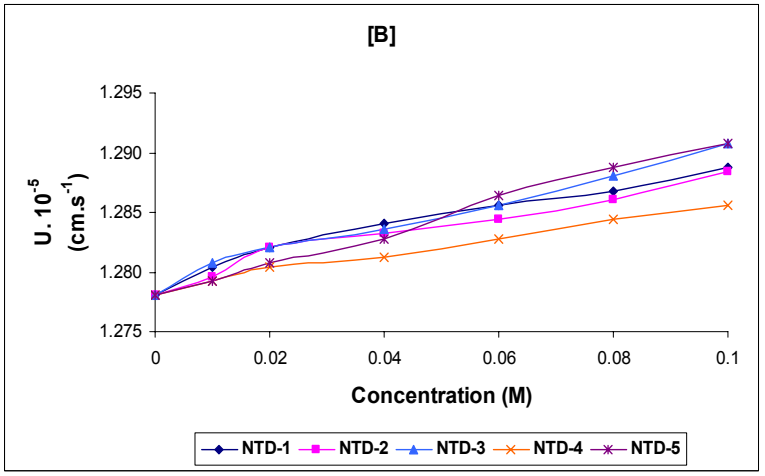
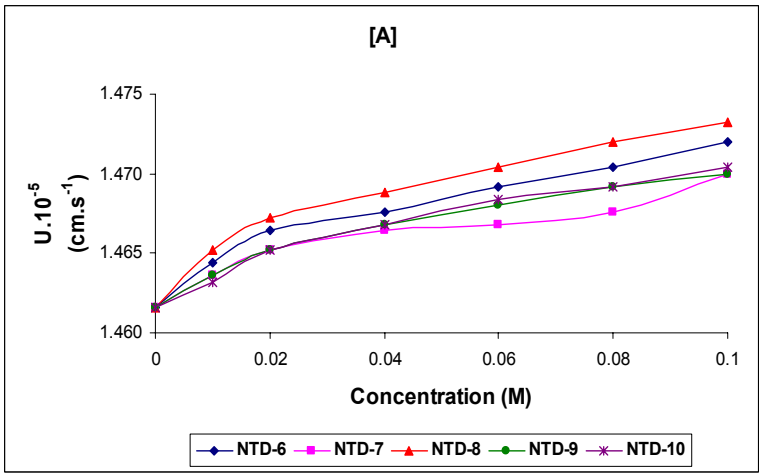



**Figure 3.1.2: Variation of ultrasonic velocity (*U*) of thiadiazepines (NTD) with concentration in [A] DMF and [B] THF at 298.15 K.**



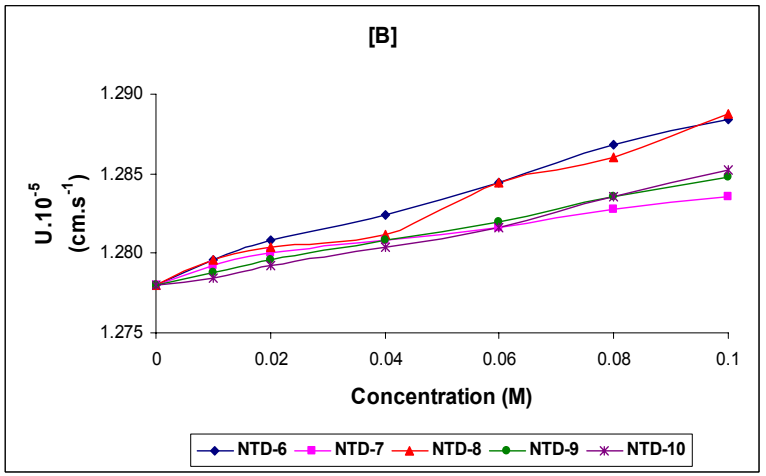



**Figure 3.1.3: Variation of Isentropic compressibility ($\kappa_s$) of benzodiazepines (NBN) with concentration in [A] DMF and [B] THF at 298.15 K.**

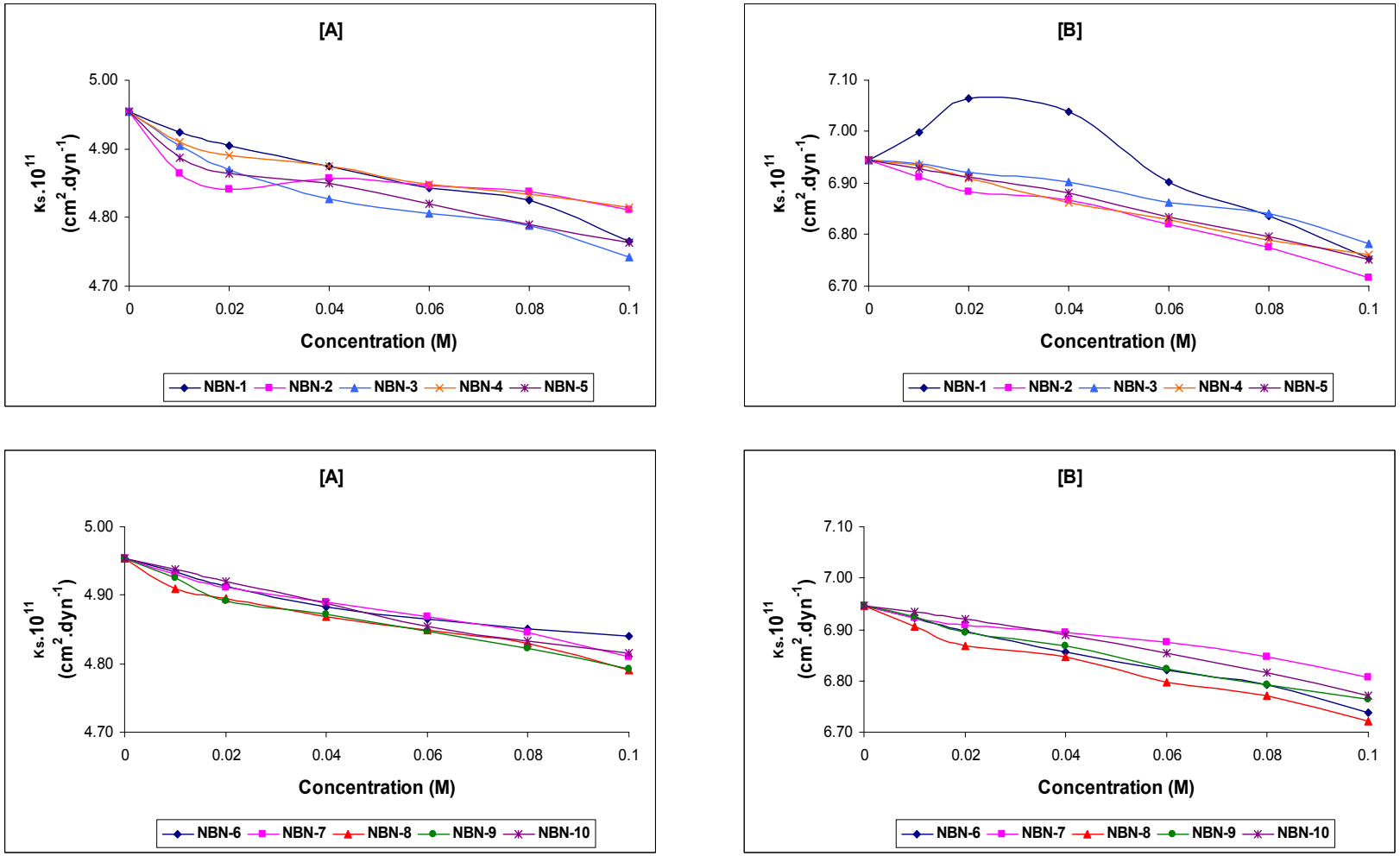


**Figure 3.1.4: Variation of Isentropic compressibility ($\kappa_s$) of thiadiazepines (NTD) with concentration in [A] DMF and [B] THF at 298.15 K.**

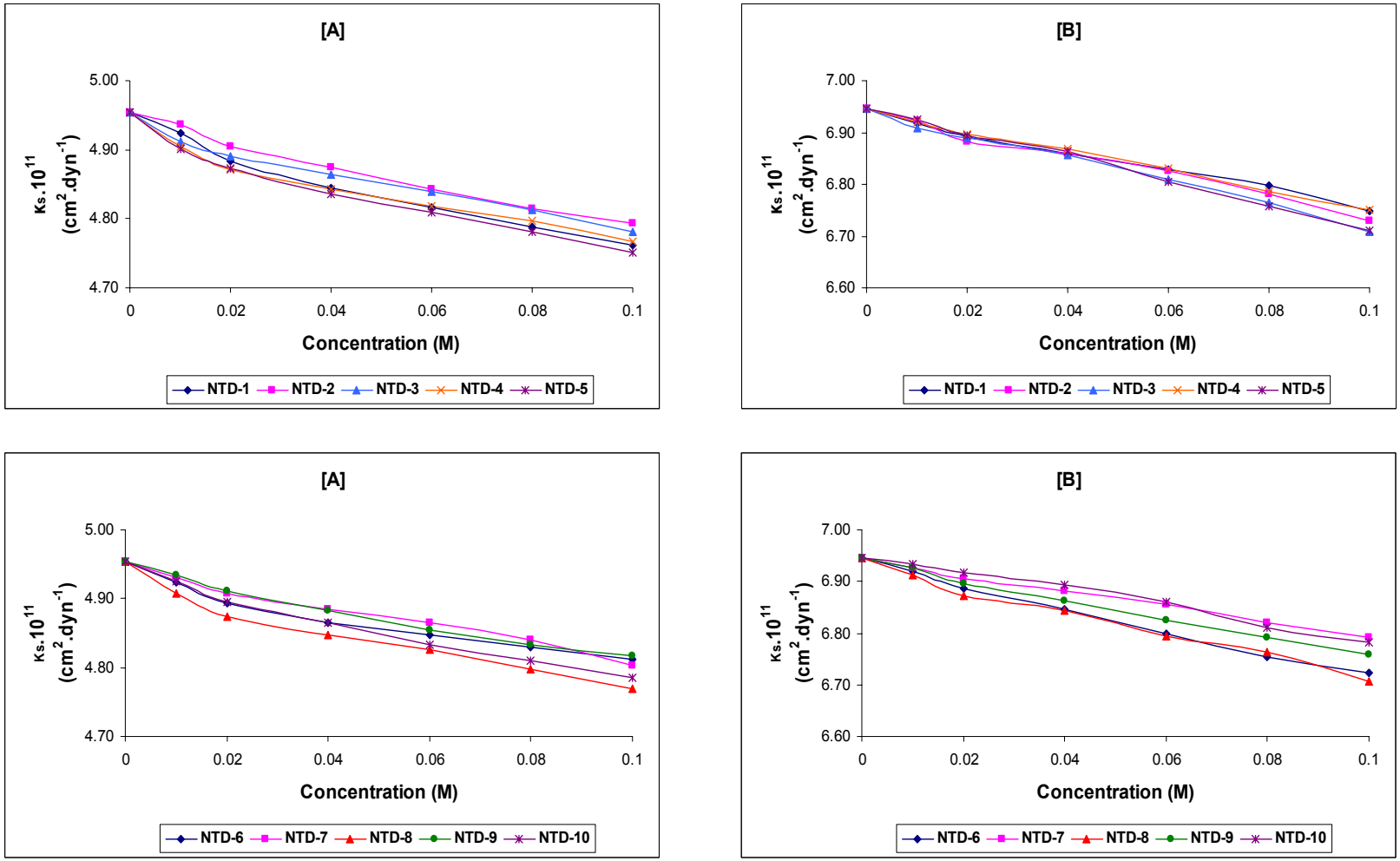


**Figure 3.1.5: Variation of Molar compressibility (*W*) of benzodiazepines (NBN) with concentration in [A] DMF and [B] THF at 298.15 K.**

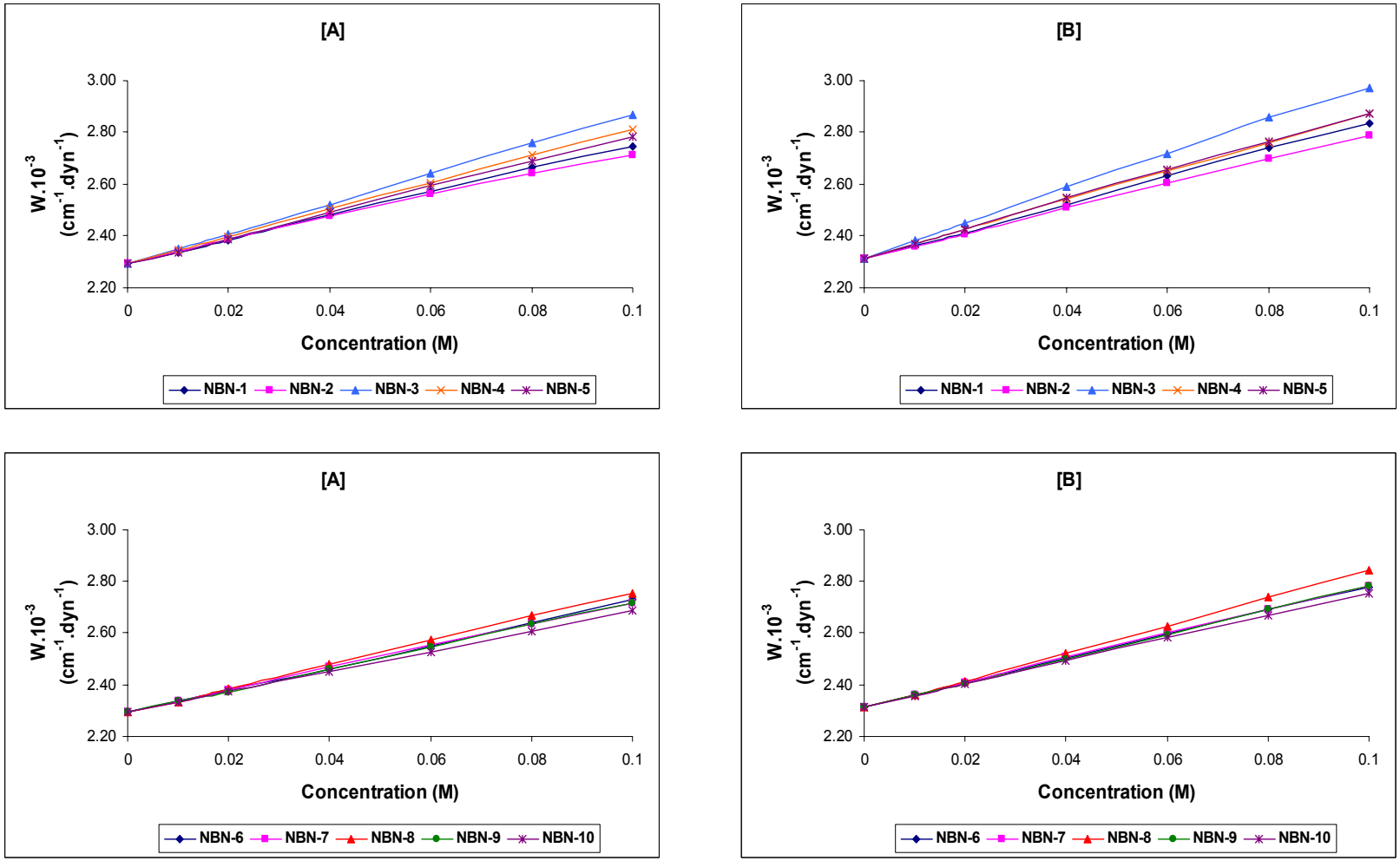
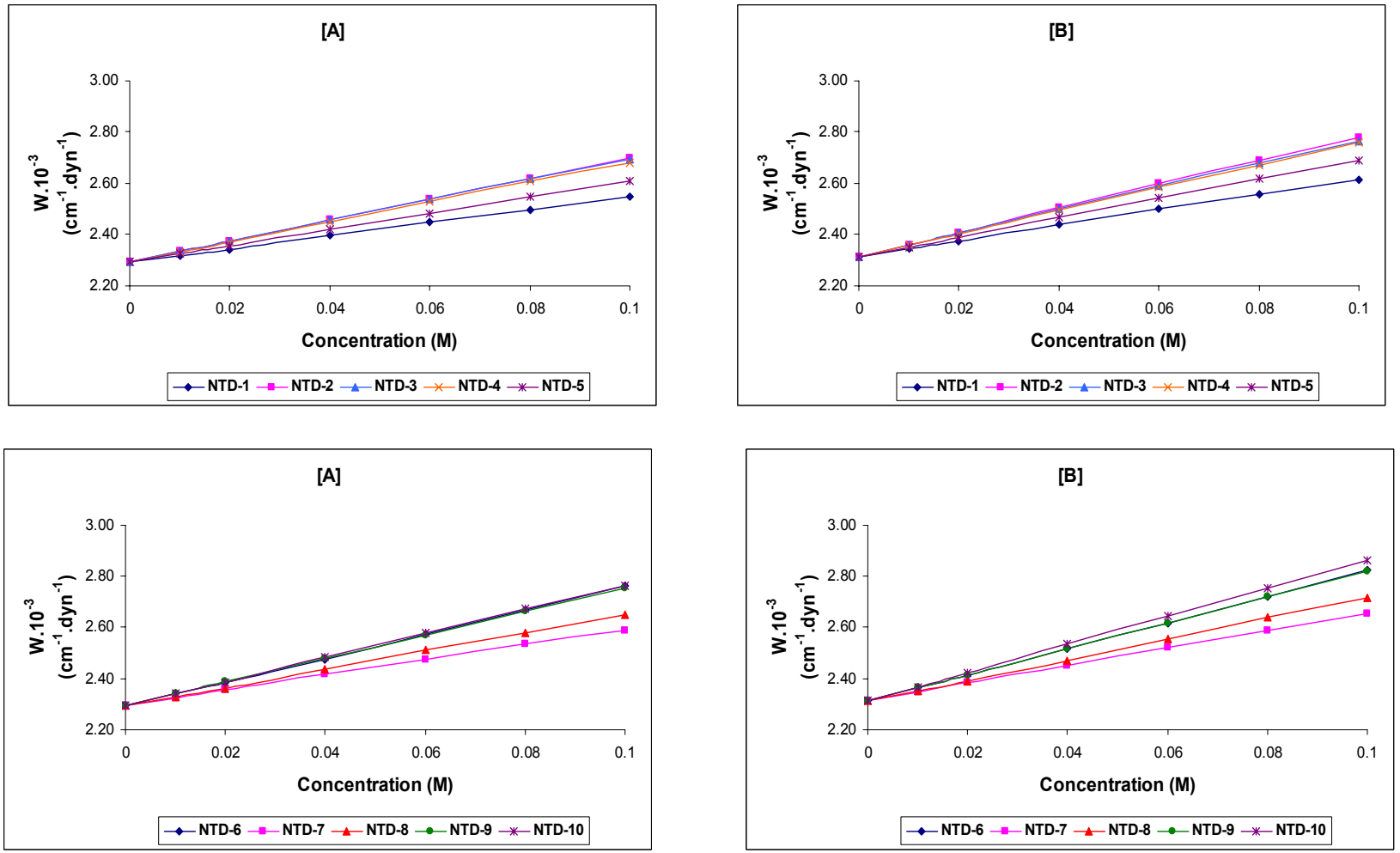


**Figure 3.1.6: Variation of Molar compressibility (*W*) of thiadiazepines (NTD) with concentration in [A] DMF and [B] THF at 298.15 K.**



Figures 3.1.7 and 3.1.8 show the variation of solvation number ($S_n$) with concentration. The solvation number is a measure of structure forming or structure breaking tendency of a solute in solutions. Figures 3.1.7 and 3.1.8 show that for both the series $S_n$ values are positive except for NBN-1 in THF solution at low concentrations. The positive $S_n$ is due to structure forming tendency whereas negative $S_n$ suggest structure breaking tendency. Except for NBN-1 solutions in THF, overall in all the systems solvation numbers are positive and increases nonlinearly, suggesting thereby overall structure forming tendency of these compounds.

In THF, for NBN-1, $S_n$ values are negative at the beginning but positive at higher concentrations. Further, these values are irregular. In this system, as mentioned above, ultrasonic velocity was also observed to decrease at lower concentration. Thus, the negative and decrease of solvation number further confirms the predominance of solute-solute interactions at lower concentrations. Thus, the compound NBN-1 exhibited structure breaking tendency at lower concentrations in THF. This may be due to methoxy group present in the compound. THF also contains lone pair of electrons on oxygen due to which, dipole-dipole interactions may exist causing negative $S_n$ values at low concentrations.

The isentropic compressibility of all the solutions were also fitted to the following Bachem's relation[78]:

$$\kappa_s = \kappa_s^0 + AC + BC^{3/2} \qquad \ldots (3.1.14)$$

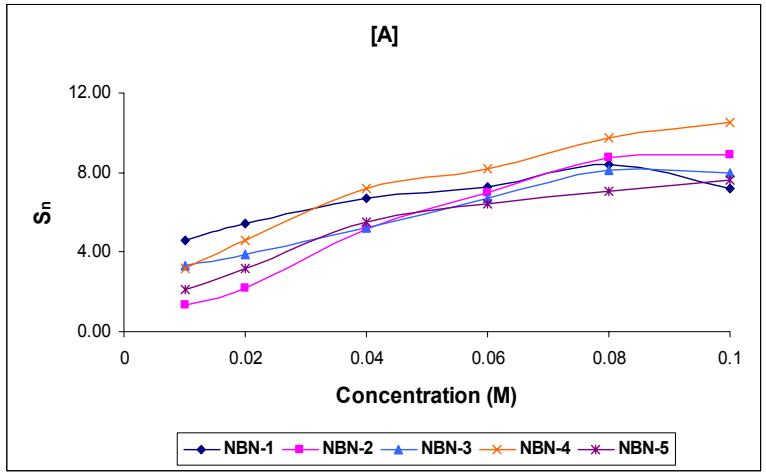
From the plot of $\left(\kappa_s - \kappa_s^0\right)/C$ verses $\sqrt{C}$, values of $A$ and $B$ were evaluated from the intercept and slope respectively. $\kappa_s^0$ is the isentropic compressibility of pure solvent.

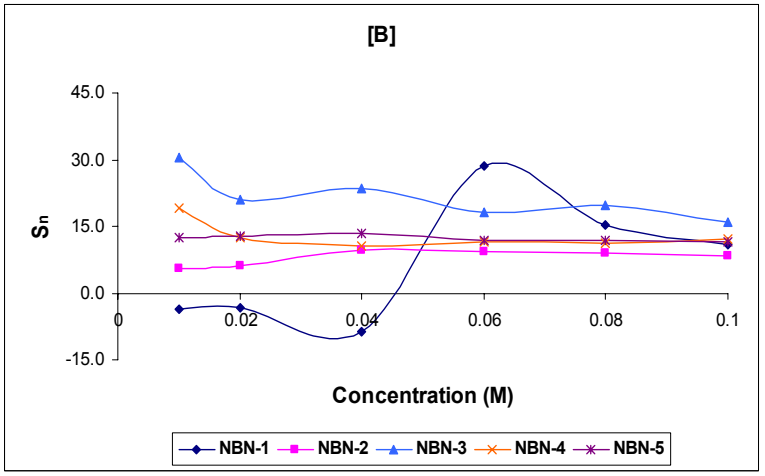
Further, the apparent molar compressibilities ($\phi_k$) of the solutions is fitted to Gucker's relation[79].

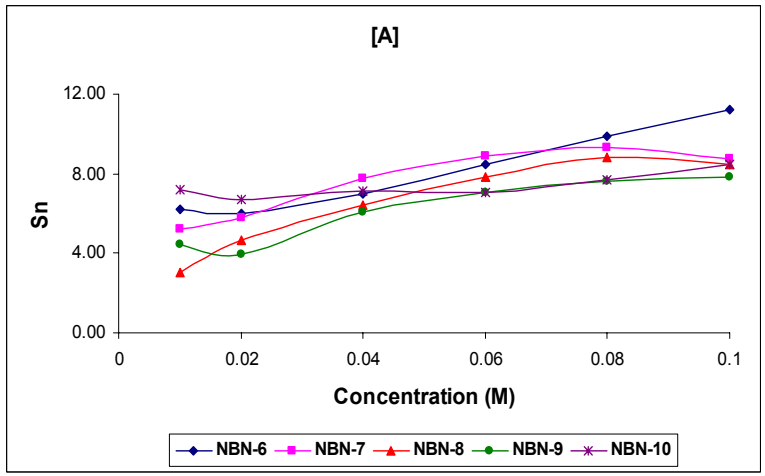
$$\phi_k = \phi^o_k + S_k \sqrt{C} \qquad \ldots (3.1.15)$$

From the plot of $\phi_k$ verses $\sqrt{C}$, $\phi^o_k$ and $S_k$ values are evaluated from the intercept and slope. All these values are given in Tables 3.1.7 and 3.1.8.

**Figure 3.1.7: Variation of Solvation Number ($S_n$)of benzodiazepines (NBN) with concentration in [A] DMF and [B] THF at 298.15 K.**



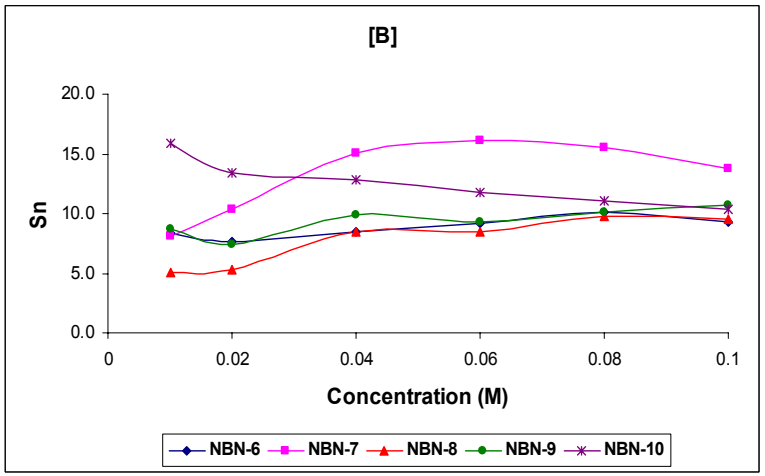
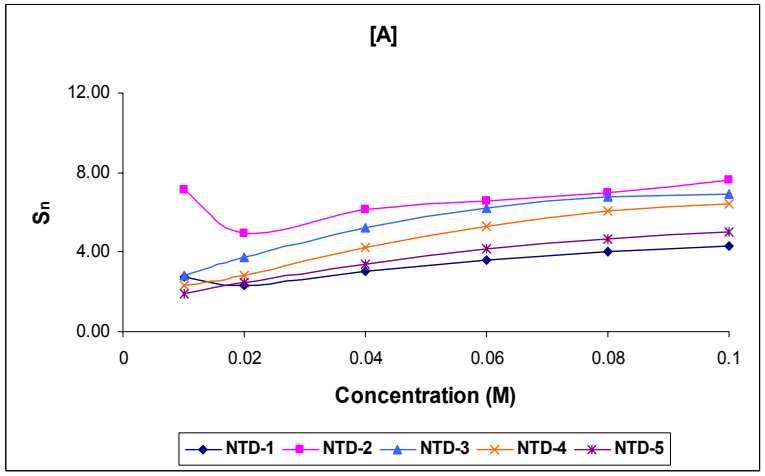
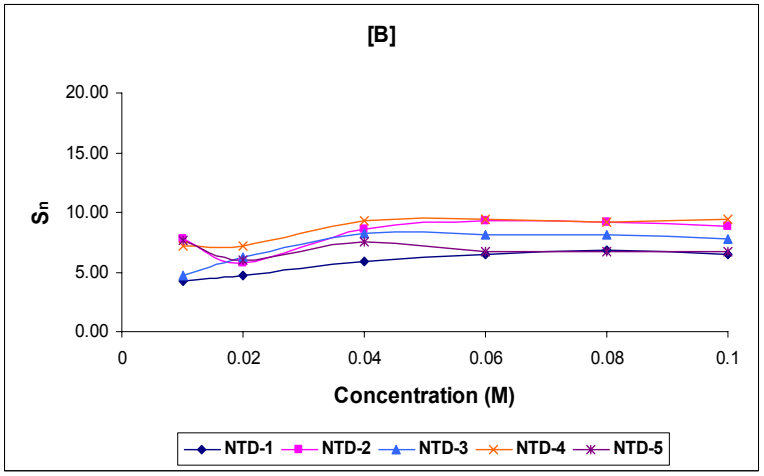
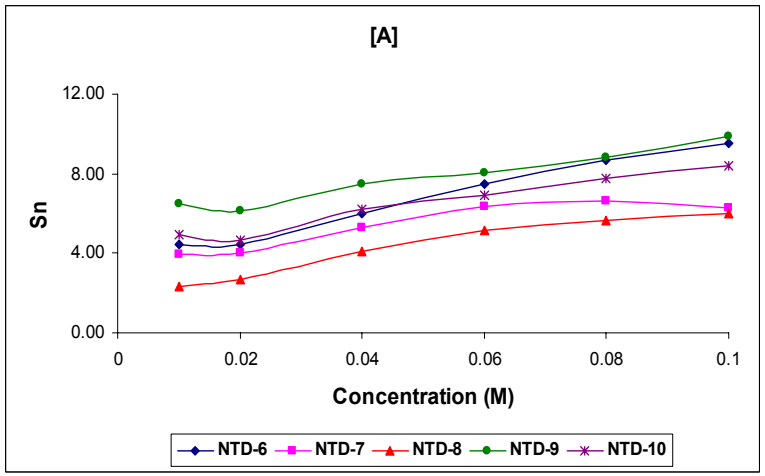



**Figure 3.1.8: Variation of Solvation Number ($S_n$) of thiadiazepines (NTD) with concentration in [A] DMF and [B] THF at 298.15 K.**



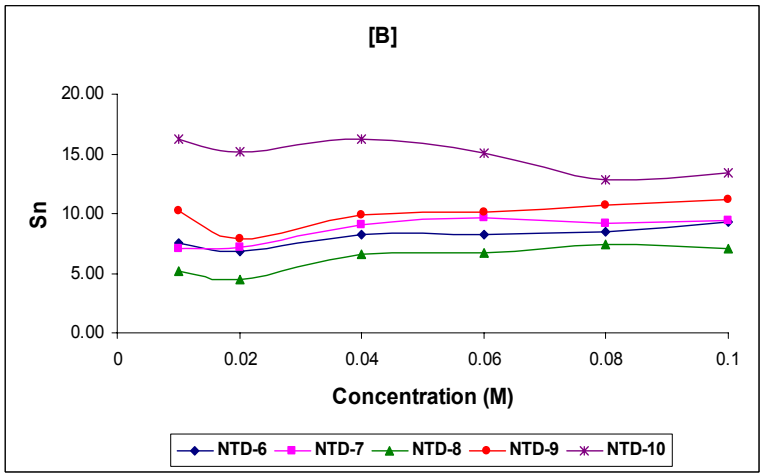



**Table 3.1.7: Bachem's constants *A* and *B*, $\phi^{o}_{k}$ and $S_k$ of benzodiazepines in DMF and THF at 298.15 K.**

| Compounds | $A \times 10^{11}$ $dyn^{-1}.cm^{3}.mol^{-1}$ | $B \times 10^{11}$ $dyn^{-1}.cm^{-1/2}.mol^{-3/2}$ | $\phi^{o}_{k} \times 10^{8}$ $dyn^{-1}.mol^{-1}$ | $S_k \times 10^{8}$ $dyn^{-1}cm^{-3/2}.mol^{-3/2}$ |
|---|---|---|---|---|
| | | ***DMF*** | | |
| ***NBN-1*** | -3.30 | 6.00 | -2.16 | 6.40 |
| ***NBN-2*** | -10.80 | 38.00 | -7.40 | 22.85 |
| ***NBN-3*** | -6.35 | 15.33 | -6.20 | 17.43 |
| ***NBN-4*** | -3.35 | 6.66 | -1.05 | 3.13 |
| ***NBN-5*** | -3.90 | 6.50 | -3.35 | 8.75 |
| ***NBN-6*** | -2.82 | 5.33 | -1.57 | 5.28 |
| ***NBN-7*** | -2.90 | 5.36 | -0.70 | 2.40 |
| ***NBN-8*** | -4.20 | 12.05 | -3.50 | 11.33 |
| ***NBN-9*** | -2.33 | 2.00 | -3.40 | 10.27 |
| ***NBN-10*** | -1.97 | 1.85 | -1.07 | 3.00 |
| | | ***THF*** | | |
| ***NBN-1*** | 9.00 | -57.33 | 7.20 | -21.42 |
| ***NBN-2*** | -3.90 | 6.50 | 1.48 | -4.93 |
| ***NBN-3*** | 0.43 | -4.00 | 3.28 | -7.28 |
| ***NBN-4*** | -2.46 | 1.93 | 1.24 | -2.88 |
| ***NBN-5*** | -1.52 | -1.30 | 1.66 | -3.66 |
| ***NBN-6*** | -2.79 | 2.30 | -0.49 | 0.83 |
| ***NBN-7*** | -3.16 | 5.46 | -0.94 | 8.80 |
| ***NBN-8*** | -2.83 | 1.97 | -2.15 | 0.75 |
| ***NBN-9*** | -0.72 | 3.33 | -1.00 | 3.90 |
| ***NBN-10*** | -2.91 | 3.50 | 1.68 | -3.75 |

**Table 3.1.8: Bachem's constants *A* and *B*, $\phi^{o}_{k}$ and $S_k$ of thiadiazepines in DMF and THF at 298.15 K.**

| Compounds | $A \times 10^{11}$ $dyn^{-1}.cm^{3}.mol^{-1}$ | $B \times 10^{11}$ $dyn^{-1}.cm^{-1/2}.mol^{-3/2}$ | $\phi^{o}_{k} \times 10^{8}$ $dyn^{-1}.mol^{-1}$ | $S_k \times 10^{8}$ $dyn^{-1}cm^{-3/2}.mol^{-3/2}$ |
|---|---|---|---|---|
| | | ***DMF*** | | |
| ***NTD-1*** | -4.59 | 8.79 | -4.73 | 11.83 |
| ***NTD-2*** | -2.96 | 4.37 | -2.36 | 6.11 |
| ***NTD-3*** | -4.87 | 10.99 | -3.39 | 9.85 |
| ***NTD-4*** | -6.16 | 14.71 | -6.30 | 18.40 |
| ***NTD-5*** | -6.19 | 14.23 | -5.75 | 14.86 |
| ***NTD-6*** | -3.90 | 8.11 | -3.80 | 12.67 |
| ***NTD-7*** | -2.81 | 4.70 | -2.06 | 5.39 |
| ***NTD-8*** | -5.79 | 13.53 | -6.12 | 17.76 |
| ***NTD-9*** | -2.48 | 3.39 | -1.47 | 4.67 |
| ***NTD-10*** | -3.55 | 6.04 | -3.71 | 10.55 |
| | | ***THF*** | | |
| ***NTD-1*** | -3.30 | 4.88 | -1.02 | 4.33 |
| ***NTD-2*** | -3.03 | 3.26 | 0.40 | -0.82 |
| ***NTD-3*** | -3.93 | 6.03 | -1.29 | 4.65 |
| ***NTD-4*** | -2.75 | 2.87 | -0.77 | 3.11 |
| ***NTD-5*** | -2.41 | 0.37 | -0.35 | 0.24 |
| ***NTD-6*** | -3.08 | 2.56 | -1.65 | 5.14 |
| ***NTD-7*** | -2.23 | 2.48 | -0.08 | 1.63 |
| ***NTD-8*** | -4.01 | 5.70 | -3.24 | 9.02 |
| ***NTD-9*** | -2.41 | 1.64 | -1.59 | 6.54 |
| ***NTD-10*** | -1.11 | -1.64 | 1.62 | -2.08 |

It is evident from Tables 3.1.7 and 3.1.8 that in DMF solutions, *A* and $\phi^{o}_{k}$ values are negative whereas *B* values are positive for all the compounds. The negative *A* and $\phi^{o}_{k}$ and higher *B* values indicates solute-solvent interactions. In THF solutions, except NBN-1, *A*, *B* and $\phi^{o}_{k}$ values again suggest the presence of solute-solvent interactions. Whereas in THF solutions of NBN-1, the predominance of solute-solute interactions is again proved.

The higher $S_k$ values are the indication of predominance of solute-solvent interactions as evident in DMF solutions. In THF solutions of NBN-1, $S_k$ values are more negative, which indicates predominant of solute-solute interaction dominates.

Thus, in the studied systems (benzodiazepines and thiadiazepines), in DMF and THF, solute-solvent interactions dominate except for NBN-1 where solute-solute interactions predominant in THF solutions.

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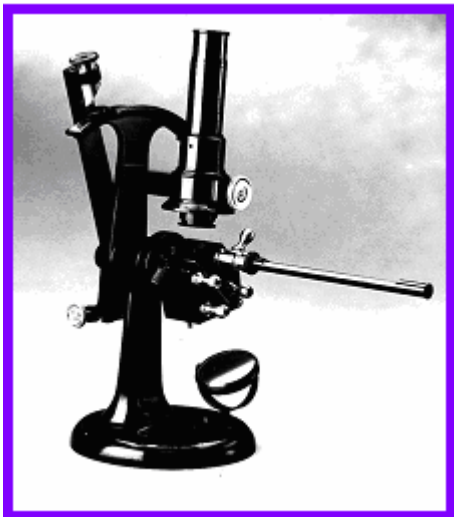


# Section-II

# Density and Refractive Index

## INTRODUCTION

The refractive index of a substance is defined as the ratio of the velocity of light in vacuum to its velocity in the given medium. It is one of the physical constants that can be used to describe a chemical species. Further, it is useful for the identification of crystalline substance. Specific and molar refractions have proved useful for analytical purposes since they are found to vary in a systematic way within homologous series of compounds. The molar refraction has been useful in structural studies. The molar refraction increases in regular increments with the number of carbon atoms within a homologous series. So, molar refraction of the compound can be considered as the sum of atomic increments and that, within certain limits, the contribution of each atom is the same in every molecule[1].

Literature survey shows that much work has been done in liquid mixtures[2-18] but scanty work has been reported for the solutions of organic, inorganic and polymeric materials[19-24]. Many workers have been reported refractive index of oils[25,26], amino acid[27], carboxylic acid[28], polymer[29,30], liquid crystals[31,32] and other materials[33,34] etc.

In the present section, the refractive index of solutions of benzodiazepines and thiadiazepines have measured in dimethylformamide and tetrahydrofuran 298.15 K. From the experimental data, the density and refractive index of the compounds have been evaluated.

## EXPERIMENTAL

The solvents DMF and THF were purified by fractionally distillation by the reported method[35]. For each compound, a series of solutions of different concentrations were prepared in these solvents.

The density and refractive index of pure solvents and solutions were measured by using pycnometer and Abbe refrectometer respectively at 298.15 K. The temperature was maintained by circulating water through jacket around the prisms of refractometer from an electronically controlled thermostatic water bath (NOVA NV-8550 E). The uncertainty of temperature was ± 0.1 $^{o}$C.

## RESULTS AND DISCUSSION

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

$$\frac{1}{\rho_{12}} = \frac{g_1}{\rho_1} + \frac{g_2}{\rho_2} \qquad \ldots (3.2.1)$$

where $\rho_{12}$ is the density of solution and $\rho_1$ and $\rho_2$ are the densities of solvent and solute respectively. Tables 3.2.1 – 3.2.4 shows the experimental values of densities and refractive index for all the studied solutions.

The density of these compounds were determined from the slope of the plot of $1/g_1\rho_{12}$ verses $g_2/g_1$. Figures 3.2.1 and 3.2.2 show the plot of $1/g_1\rho_{12}$ verses $g_2/g_1$ for benzodiazepine NBN-1 and thiadiazepine NTD-1 in DMF and THF respectively. The inverse of slope gives $\rho_2$. The densities of all the compounds evaluated from such plots are given in Tables 3.2.5 and 3.2.6 for both NBN and NTD series respectively in DMF and THF. Further, the density of compounds were evaluated by using the following equation (3.2.2),

$$\rho = KM/N_A \sum \Delta V_i \qquad \ldots (3.2..2)$$

where $\rho$ is the density of the compound, $K$ is packing fraction (0.599), M is the molecular weight of the compound, $N_A$ is the Avogadro's number and $\Delta V_i$ 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 Tables 3.2.5 and 3.2.6. The calculated volume increment $\Delta V_i$ for different atomic groups are given in Table 3.2.7.

Comparison of densities evaluated from graphs and those calculated from eq. (3.2.2) showed that calculated values are different from those evaluated graphically. Further, for the same compound, density in the two solvents is different. This suggests that solvent plays an important role. In solutions molecular interactions exist which differ in different solvents. These interactions differ due to different substitutions in compounds. The presence of these interactions have also observed in ultrasonic studies which is discussed in section I of chapter 2. Due to these interactions there may be some changes in volume which affects density.

**Table 3.2.1: The density ($\rho_{12}$) and refractive index ($n$) of NBN series in DMF at 298.15K.**

| *Conc. M* | $\rho_{12}$ $g.cm^{-3}$ | *n* | $\rho_{12}$ $g.cm^{-3}$ | *n* |
|---|---|---|---|---|
| | ***NBN-1*** | | ***NBN-6*** | |
| ***0.00*** | 0.9449 | 1.4270 | 0.9449 | 1.4270 |
| ***0.01*** | 0.9484 | 1.4290 | 0.9472 | 1.4275 |
| ***0.02*** | 0.9502 | 1.4295 | 0.9503 | 1.4285 |
| ***0.04*** | 0.9531 | 1.4300 | 0.9546 | 1.4292 |
| ***0.06*** | 0.9567 | 1.4310 | 0.9559 | 1.4300 |
| ***0.08*** | 0.9592 | 1.4315 | 0.9576 | 1.4315 |
| ***0.10*** | 0.9648 | 1.4320 | 0.9587 | 1.4338 |
| | ***NBN-2*** | | ***NBN-7*** | |
| ***0.01*** | 0.9474 | 1.4285 | 0.9463 | 1.4273 |
| ***0.02*** | 0.9481 | 1.4295 | 0.9490 | 1.4275 |
| ***0.04*** | 0.9492 | 1.4305 | 0.9510 | 1.4278 |
| ***0.06*** | 0.9524 | 1.4318 | 0.9545 | 1.4285 |
| ***0.08*** | 0.9565 | 1.4331 | 0.9581 | 1.4300 |
| ***0.10*** | 0.9638 | 1.4352 | 0.9622 | 1.4305 |
| | ***NBN-3*** | | ***NBN-8*** | |
| ***0.01*** | 0.9487 | 1.4277 | 0.9508 | 1.4278 |
| ***0.02*** | 0.9534 | 1.4284 | 0.9520 | 1.4290 |
| ***0.04*** | 0.9593 | 1.4302 | 0.9551 | 1.4302 |
| ***0.06*** | 0.9615 | 1.4307 | 0.9575 | 1.4314 |
| ***0.08*** | 0.9629 | 1.4320 | 0.9604 | 1.4328 |
| ***0.10*** | 0.9691 | 1.4332 | 0.9660 | 1.4342 |
| | ***NBN -4*** | | ***NBN-9*** | |
| ***0.01*** | 0.9478 | 1.4275 | 0.9482 | 1.4282 |
| ***0.02*** | 0.9492 | 1.4281 | 0.9529 | 1.4293 |
| ***0.04*** | 0.9505 | 1.4286 | 0.9546 | 1.4309 |
| ***0.06*** | 0.9530 | 1.4304 | 0.9578 | 1.4321 |
| ***0.08*** | 0.9547 | 1.4310 | 0.9603 | 1.4335 |
| ***0.10*** | 0.9571 | 1.4318 | 0.9642 | 1.4346 |
| | ***NBN -5*** | | ***NBN-10*** | |
| ***0.01*** | 0.9509 | 1.4290 | 0.9464 | 1.4280 |
| ***0.02*** | 0.9529 | 1.4297 | 0.9489 | 1.4292 |
| ***0.04*** | 0.9548 | 1.4309 | 0.9523 | 1.4306 |
| ***0.06*** | 0.9581 | 1.4321 | 0.9563 | 1.4315 |
| ***0.08*** | 0.9619 | 1.4332 | 0.9591 | 1.4326 |
| ***0.10*** | 0.9662 | 1.4343 | 0.9612 | 1.4335 |

**Table 3.2.2: The density ($\rho_{12}$) and refractive index (*n*) of NTD series in DMF at 298.15K.**

| *Conc. M* | $\rho_{12}$ *g.cm$^{-3}$* | *n* | $\rho_{12}$ *g.cm$^{-3}$* | *n* |
|---|---|---|---|---|
| | ***NTD-1*** | | ***NTD-6*** | |
| ***0.00*** | 0.9449 | 1.4270 | 0.9449 | 1.4270 |
| ***0.01*** | 0.9480 | 1.4280 | 0.9470 | 1.4278 |
| ***0.02*** | 0.9511 | 1.4287 | 0.9502 | 1.4284 |
| ***0.04*** | 0.9535 | 1.4293 | 0.9543 | 1.4292 |
| ***0.06*** | 0.9572 | 1.4305 | 0.9558 | 1.4299 |
| ***0.08*** | 0.9611 | 1.4312 | 0.9577 | 1.4310 |
| ***0.10*** | 0.9645 | 1.4318 | 0.9591 | 1.4319 |
| | ***NTD -2*** | | ***NTD-7*** | |
| ***0.01*** | 0.9471 | 1.4283 | 0.9468 | 1.4279 |
| ***0.02*** | 0.9501 | 1.4293 | 0.9491 | 1.4283 |
| ***0.04*** | 0.9535 | 1.4301 | 0.9522 | 1.4287 |
| ***0.06*** | 0.9571 | 1.4309 | 0.9552 | 1.4293 |
| ***0.08*** | 0.9612 | 1.4317 | 0.9591 | 1.4298 |
| ***0.10*** | 0.9645 | 1.4325 | 0.9634 | 1.4304 |
| | ***NTD -3*** | | ***NTD-8*** | |
| ***0.01*** | 0.9478 | 1.4285 | 0.9492 | 1.4281 |
| ***0.02*** | 0.9498 | 1.4290 | 0.9532 | 1.4288 |
| ***0.04*** | 0.9525 | 1.4294 | 0.9561 | 1.4299 |
| ***0.06*** | 0.9553 | 1.4302 | 0.9583 | 1.4308 |
| ***0.08*** | 0.9583 | 1.4310 | 0.9621 | 1.4314 |
| ***0.10*** | 0.9628 | 1.4319 | 0.9662 | 1.4322 |
| | ***NTD-4*** | | ***NTD-9*** | |
| ***0.01*** | 0.9498 | 1.4282 | 0.9462 | 1.4275 |
| ***0.02*** | 0.9532 | 1.4285 | 0.9485 | 1.4279 |
| ***0.04*** | 0.9562 | 1.4291 | 0.9519 | 1.4286 |
| ***0.06*** | 0.9588 | 1.4300 | 0.9559 | 1.4293 |
| ***0.08*** | 0.9622 | 1.4308 | 0.9587 | 1.4298 |
| ***0.10*** | 0.9670 | 1.4316 | 0.9608 | 1.4306 |
| | ***NTD-5*** | | ***NTD-10*** | |
| ***0.01*** | 0.9487 | 1.4287 | 0.9482 | 1.4282 |
| ***0.02*** | 0.9521 | 1.4300 | 0.9517 | 1.4289 |
| ***0.04*** | 0.9568 | 1.4309 | 0.9555 | 1.4296 |
| ***0.06*** | 0.9608 | 1.4318 | 0.9595 | 1.4304 |
| ***0.08*** | 0.9642 | 1.4331 | 0.9632 | 1.4312 |
| ***0.10*** | 0.9682 | 1.4345 | 0.9665 | 1.4320 |

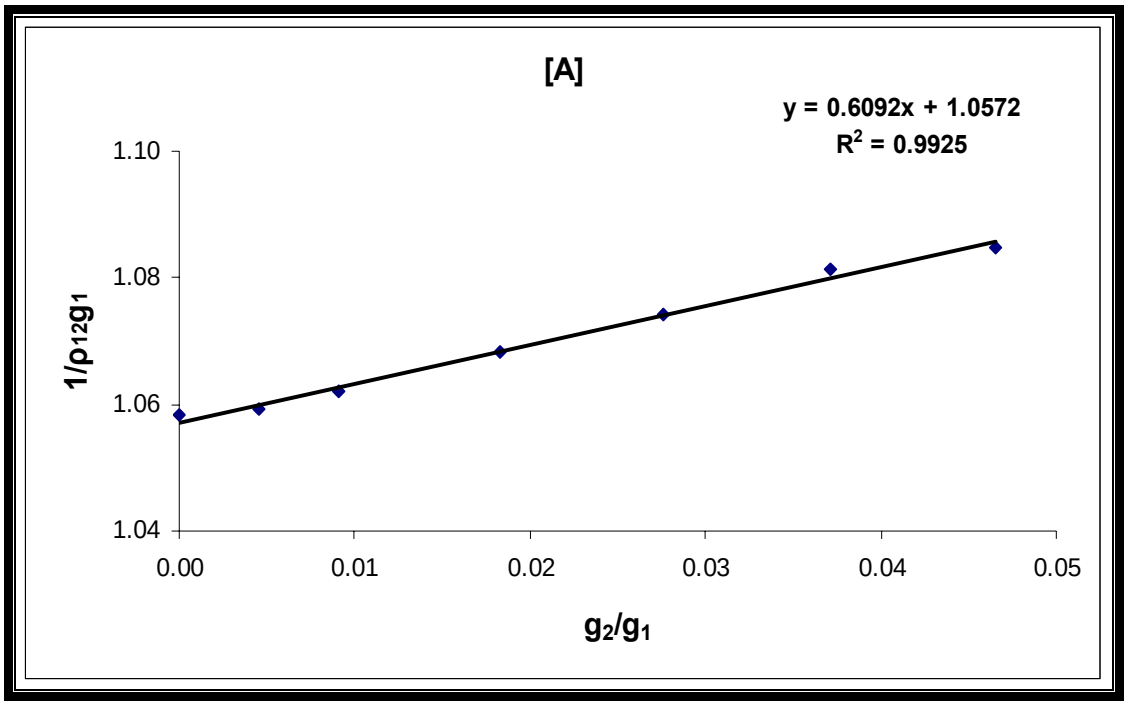
**Table 3.2.3: The density ($\rho_{12}$) and refractive index ($n$) of NBN series in THF at 298.15K.**

| *Conc. M* | $\rho_{12}$ $g.cm^{-3}$ | *n* | $\rho_{12}$ $g.cm^{-3}$ | *n* |
|---|---|---|---|---|
| | ***NBN-1*** | | | |
| ***0.00*** | 0.8815 | 1.4050 | 0.8815 | 1.4050 |
| ***0.01*** | 0.8824 | 1.4053 | 0.8822 | 1.4065 |
| ***0.02*** | 0.8838 | 1.4058 | 0.8845 | 1.4080 |
| ***0.04*** | 0.8853 | 1.4065 | 0.8886 | 1.4111 |
| ***0.06*** | 0.8865 | 1.4071 | 0.8922 | 1.4120 |
| ***0.08*** | 0.8889 | 1.4076 | 0.8947 | 1.4135 |
| ***0.10*** | 0.8935 | 1.4080 | 0.8998 | 1.4140 |
| | ***NBN-2*** | | | |
| ***0.01*** | 0.8832 | 1.4072 | 0.8828 | 1.4055 |
| ***0.02*** | 0.8850 | 1.4083 | 0.8845 | 1.4068 |
| ***0.04*** | 0.8856 | 1.4095 | 0.8863 | 1.4076 |
| ***0.06*** | 0.8887 | 1.4118 | 0.8884 | 1.4096 |
| ***0.08*** | 0.8926 | 1.4126 | 0.8915 | 1.4108 |
| ***0.10*** | 0.8958 | 1.4143 | 0.8957 | 1.4128 |
| | ***NBN-3*** | | | |
| ***0.01*** | 0.8820 | 1.4056 | 0.8845 | 1.4057 |
| ***0.02*** | 0.8829 | 1.4062 | 0.8882 | 1.4070 |
| ***0.04*** | 0.8843 | 1.4069 | 0.8897 | 1.4078 |
| ***0.06*** | 0.8879 | 1.4098 | 0.8917 | 1.4105 |
| ***0.08*** | 0.8889 | 1.4106 | 0.8929 | 1.4115 |
| ***0.10*** | 0.8930 | 1.4112 | 0.8956 | 1.4123 |
| | ***NBN -4*** | | | |
| ***0.01*** | 0.8824 | 1.4055 | 0.8837 | 1.4061 |
| ***0.02*** | 0.8838 | 1.4064 | 0.8864 | 1.4073 |
| ***0.04*** | 0.8866 | 1.4080 | 0.8892 | 1.4085 |
| ***0.06*** | 0.8892 | 1.4107 | 0.8930 | 1.4095 |
| ***0.08*** | 0.8929 | 1.4114 | 0.8946 | 1.4108 |
| ***0.10*** | 0.8949 | 1.4131 | 0.8973 | 1.4121 |
| | ***NBN -5*** | | | |
| ***0.01*** | 0.8826 | 1.4055 | 0.8829 | 1.4059 |
| ***0.02*** | 0.8842 | 1.4062 | 0.8832 | 1.4071 |
| ***0.04*** | 0.8849 | 1.4072 | 0.8858 | 1.4081 |
| ***0.06*** | 0.8882 | 1.4076 | 0.8882 | 1.4099 |
| ***0.08*** | 0.8914 | 1.4092 | 0.8905 | 1.4116 |
| ***0.10*** | 0.8949 | 1.4109 | 0.8942 | 1.4126 |

**Table 3.2.4: The density ($\rho_{12}$) and refractive index ($n$) of NTD series in THF at 298.15 K.**

| Conc. M | $\rho_{12}$ g.cm$^{-3}$ | n | $\rho_{12}$ g.cm$^{-3}$ | n |
|---|---|---|---|---|
| | | ***NTD-1*** | | |
| ***0.00*** | 0.8815 | 1.4050 | 0.8815 | 1.4050 |
| ***0.01*** | 0.8819 | 1.4058 | 0.8827 | 1.4055 |
| ***0.02*** | 0.8828 | 1.4063 | 0.8852 | 1.4064 |
| ***0.04*** | 0.8842 | 1.4067 | 0.8881 | 1.4072 |
| ***0.06*** | 0.8861 | 1.4072 | 0.8917 | 1.4084 |
| ***0.08*** | 0.8885 | 1.4077 | 0.8943 | 1.4098 |
| ***0.10*** | 0.8922 | 1.4082 | 0.8961 | 1.4115 |
| | | ***NTD -2*** | | |
| ***0.01*** | 0.8823 | 1.4066 | 0.8824 | 1.4056 |
| ***0.02*** | 0.8842 | 1.4073 | 0.8838 | 1.4066 |
| ***0.04*** | 0.8854 | 1.4082 | 0.8857 | 1.4074 |
| ***0.06*** | 0.8882 | 1.4094 | 0.8880 | 1.4094 |
| ***0.08*** | 0.8916 | 1.4102 | 0.8911 | 1.4106 |
| ***0.10*** | 0.8951 | 1.4115 | 0.8936 | 1.4125 |
| | | ***NTD -3*** | | |
| ***0.01*** | 0.8825 | 1.4071 | 0.8834 | 1.4061 |
| ***0.02*** | 0.8833 | 1.4080 | 0.8877 | 1.4073 |
| ***0.04*** | 0.8851 | 1.4088 | 0.8902 | 1.4083 |
| ***0.06*** | 0.8884 | 1.4095 | 0.8922 | 1.4090 |
| ***0.08*** | 0.8911 | 1.4101 | 0.8941 | 1.4104 |
| ***0.10*** | 0.8948 | 1.4109 | 0.8977 | 1.4120 |
| | | ***NTD-4*** | | |
| ***0.01*** | 0.8830 | 1.4056 | 0.8829 | 1.4057 |
| ***0.02*** | 0.8846 | 1.4062 | 0.8858 | 1.4070 |
| ***0.04*** | 0.8871 | 1.4075 | 0.8882 | 1.4083 |
| ***0.06*** | 0.8898 | 1.4090 | 0.8915 | 1.4091 |
| ***0.08*** | 0.8933 | 1.4104 | 0.8936 | 1.4105 |
| ***0.10*** | 0.8962 | 1.4120 | 0.8962 | 1.4118 |
| | | ***NTD-5*** | | |
| ***0.01*** | 0.8824 | 1.4062 | 0.8826 | 1.4063 |
| ***0.02*** | 0.8841 | 1.4072 | 0.8834 | 1.4068 |
| ***0.04*** | 0.8854 | 1.4079 | 0.8849 | 1.4077 |
| ***0.06*** | 0.8879 | 1.4085 | 0.8875 | 1.4086 |
| ***0.08*** | 0.8908 | 1.4092 | 0.8911 | 1.4099 |
| ***0.10*** | 0.8944 | 1.4106 | 0.8926 | 1.4110 |

**Figure 3.2.1: The variation of $1/g_1\rho_{12}$ with $g_2/g_1$ for NBN-1 in [A] DMF and [B] THF at 298.15 K.**



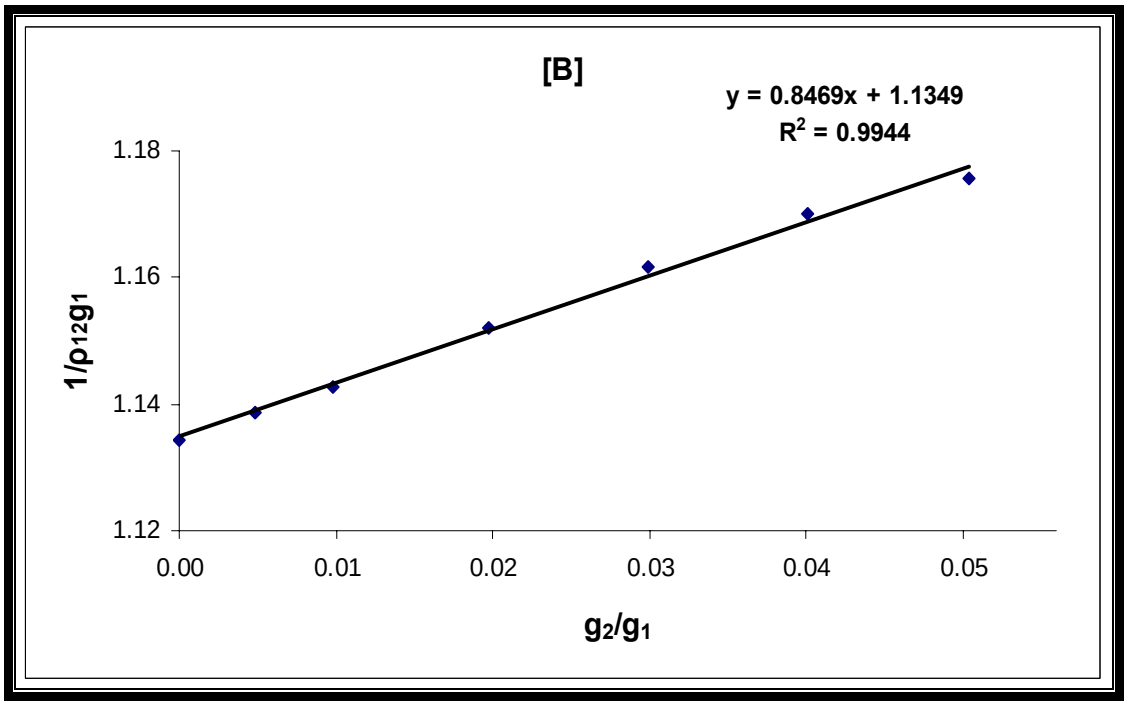
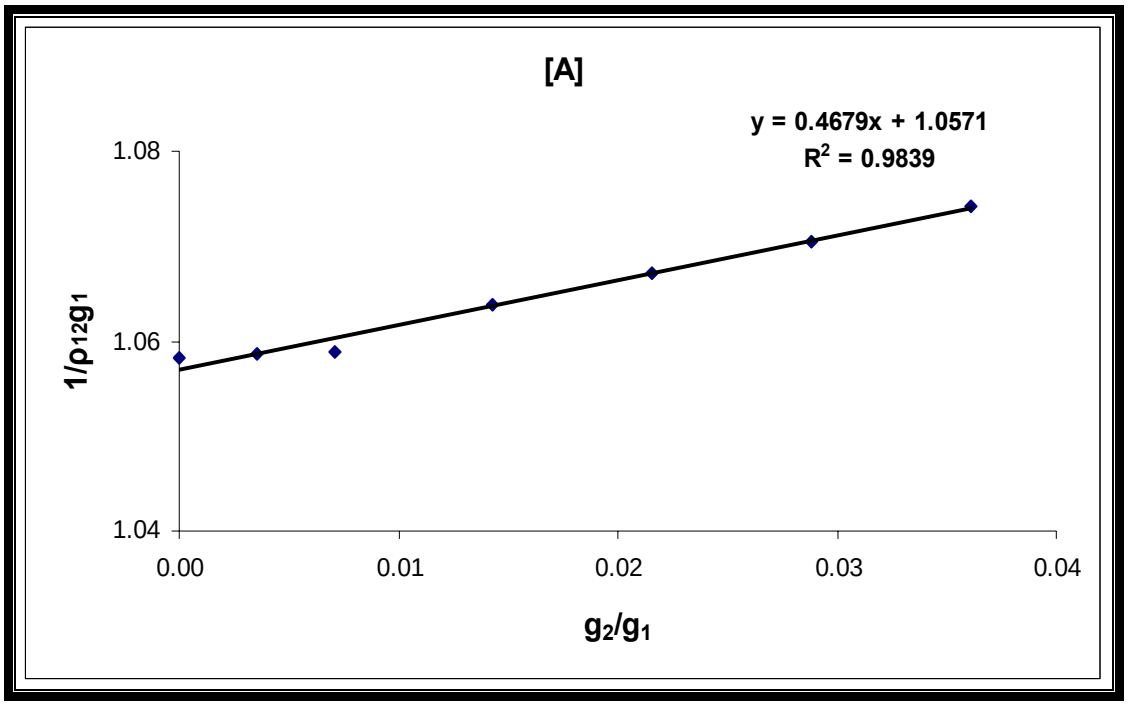



**Figure 3.2.2: The variation of $1/g_1\rho_{12}$ with $g_2/g_1$ for NTD-1 in [A] DMF and [B] THF at 298.15 K.**



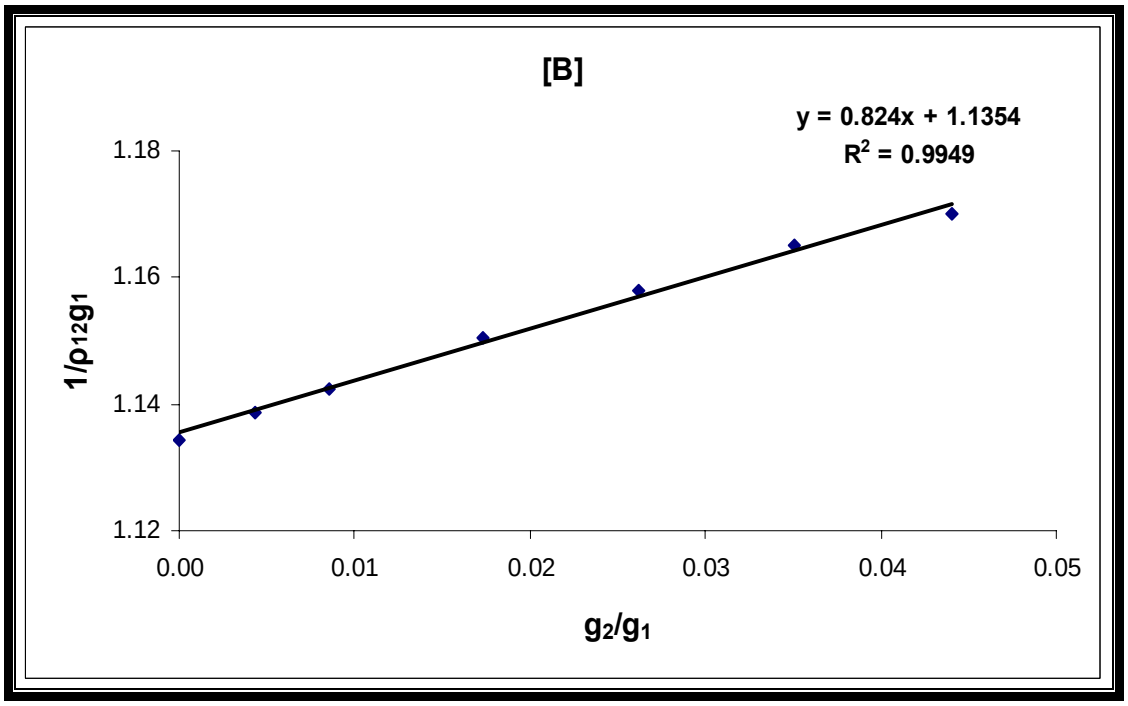



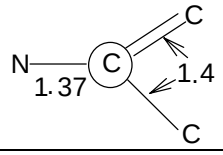
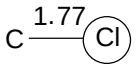
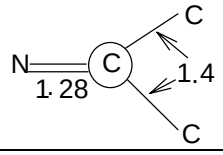
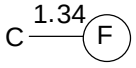
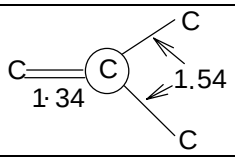
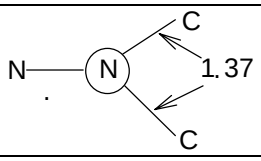
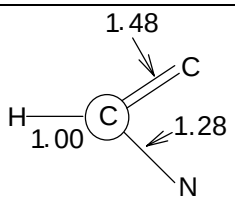
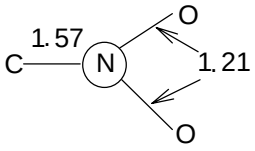
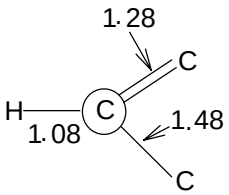
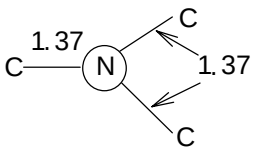
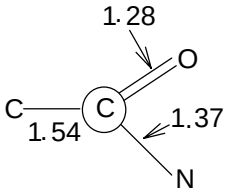
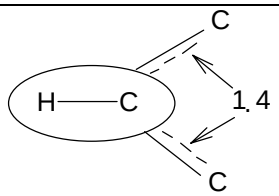
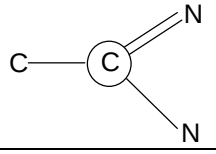
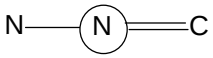
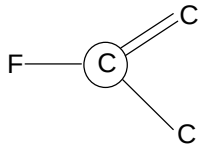
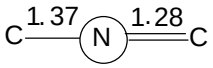
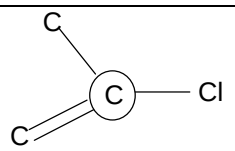
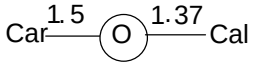
**Table 3.2.5: Experimental and calculated densities of NBN series in DMF and THF Solutions at 298.15 K.**

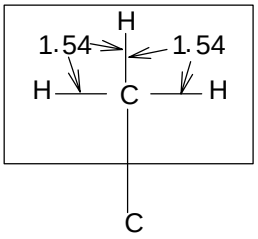
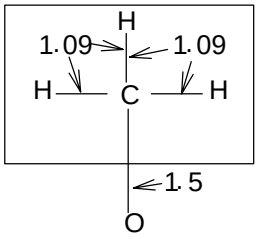
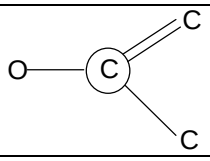
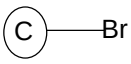
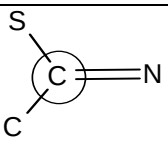
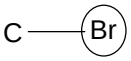
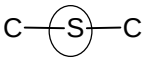
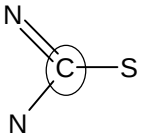
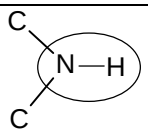
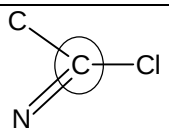
| *Compounds* | Density calculated from slope of Figure 3.2.1 in two solvents (g.cm$^{-3}$) | | Density (*g.cm*$^{-3}$) Calculated from Eq$^{n}$. 3.2.2 |
|---|---|---|---|
| | *DMF* | *THF* | |
| ***NBN-1*** | 1.6415 | 1.1808 | 1.0332 |
| ***NBN-2*** | 1.5898 | 1.3179 | 1.1125 |
| ***NBN-3*** | 1.7618 | 1.2063 | 1.1948 |
| ***NBN-4*** | 1.2612 | 1.2845 | 1.1320 |
| ***NBN-5*** | 1.6319 | 1.2470 | 1.1320 |
| ***NBN-6*** | 1.4083 | 1.5768 | 1.0474 |
| ***NBN-7*** | 1.5985 | 1.3041 | 1.0146 |
| ***NBN-8*** | 1.6228 | 1.2435 | 1.0709 |
| ***NBN-9*** | 1.6474 | 1.4098 | 1.0474 |
| ***NBN-10*** | 1.6383 | 1.2732 | 1.0253 |

**Table 3.2.6: Experimental and calculated densities of NTD series in DMF and THF Solutions at 298.15 K.**

| *Compounds* | Density calculated from slope of Figure 3.2.1 in two solvents (g.cm$^{-3}$) | | Density (*g.cm*$^{-3}$) Calculated from Eq$^{n}$. 3.2.2 |
|---|---|---|---|
| | *DMF* | *THF* | |
| ***NTD-1*** | 2.1372 | 1.2136 | 1.2537 |
| ***NTD-2*** | 1.8038 | 1.3080 | 1.1947 |
| ***NTD-3*** | 1.6064 | 1.3072 | 1.3568 |
| ***NTD-4*** | 1.8512 | 1.3808 | 1.3568 |
| ***NTD-5*** | 2.3844 | 1.3238 | 1.1932 |
| ***NTD-6*** | 1.4088 | 1.3831 | 1.3165 |
| ***NTD-7*** | 1.8921 | 1.3321 | 1.2180 |
| ***NTD-8*** | 1.8801 | 1.4455 | 1.2126 |
| ***NTD-9*** | 1.5446 | 1.3419 | 1.3165 |
| ***NTD-10*** | 1.8238 | 0.9856 | 1.4327 |

**Table 3.2.7 Volume increments of some atoms and groups of atoms.**

| Atoms or Atomic group | Volume Increments $(A^o)^3$ | Atoms or Atomic group | Volume Increments $(A^o)^3$ |
|---|---|---|---|
|  | 10.2 |  | 19.35 |
|  | 7.84 |  | 9.2 |
|  | 9.0 |  | 2.89 |
|  | 3.61 |  | 7.46 |
|  | 11.36 |  | 0.9 |
|  | 14.10 |  | 14.7 |
|  | 10.47 |  | 5.093 |
|  | 11.40 |  | 5.62 |
|  | 10.39 |  | 2.67 |

| Atoms or Atomic group | Volume Increments $(A^o)^3$ | Atoms or Atomic group | Volume Increments $(A^o)^3$ |
|---|---|---|---|
|   | 23.5 |   | 26.3 |
|   | 11.65 |   | 11.20 |
|   | 8.57 |   | 14.29 |
|   | 23.43 |   | 13.46 |
|   | 8.3 |   | 12.3 |

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

$$\left(MRD\right)_1 = \left[\frac{n^2-1}{n^2+1}\right]\frac{M}{\rho} \qquad \ldots (3.2.3)$$

where *n*, *M* and $\rho$ are refractive index, molecular weight and density of pure liquid respectively.

For solutions, the eq. (3.2.4) was used to determining molar refraction.

$$\left(MRD\right)_{12} = \left[\frac{n_{12}^2-1}{n_{12}^2+1}\right]\left[\frac{X_1M_1+X_2M_2}{\rho_{12}}\right] \qquad \ldots (3.2.4)$$

where $n_{12}$ and $\rho_{12}$ 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.

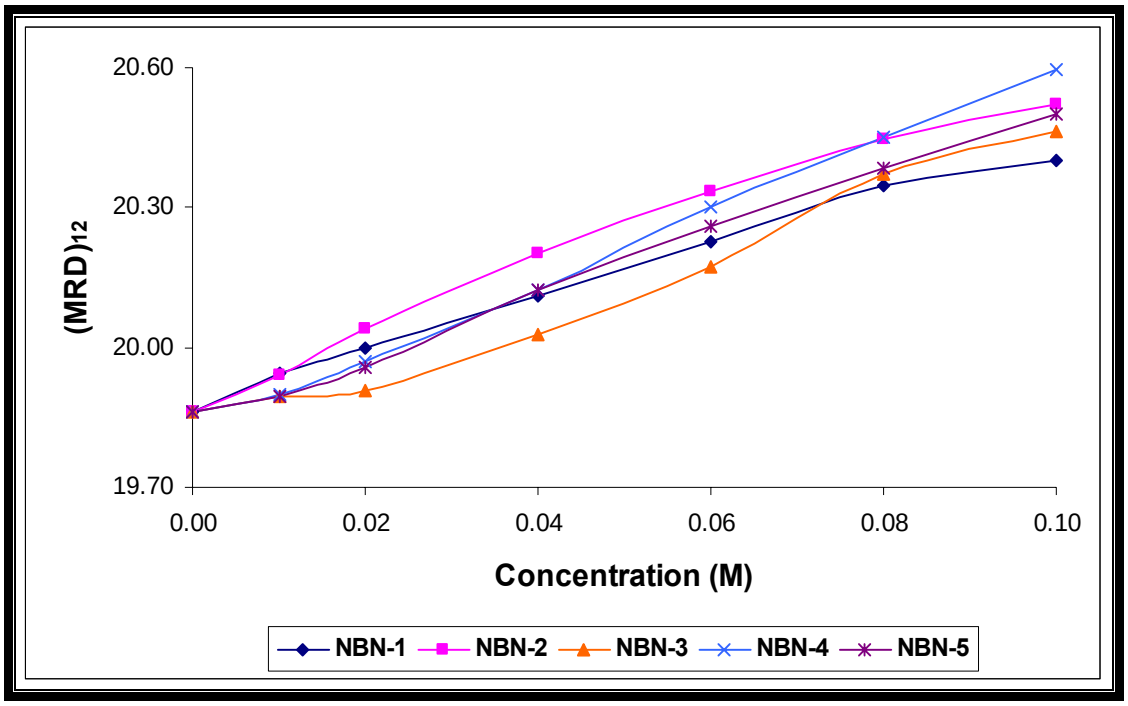
The plots of $(MRD)_{12}$ verses concentration for NBN and NTD series in DMF and THF are given in Figures 3.2.3 to 3.2.6. It is evident from these figures that $(MRD)_{12}$ increase with the increase in concentration. From the values of the molar refraction of solution and pure solvent, molar refraction of solid compounds were determined by following equation:

$$\left(MRD\right)_{12} = X_1\left(MRD\right)_1 + X_2\left(MRD\right)_2 \qquad \ldots (3.2.5)$$

From the density and molar refraction data, the refractive indexes of all the compounds were calculated from eq. (3.2.3). The molar refraction $(MRD)_2$ and refractive index of all the compounds are reported in Tables 3.2.8 and 3.2.9.

It is evident from Tables 3.2.8 and 3.2.9 that both $(MRD)_2$ and refractive index of compounds are different in each solvent. This again proves that in different solvents, intermolecular interactions are different, which affect these parameters. In some solvents, aggregation or hydrogen bonding takes place whereas in others, breakage of bonds takes place. As refractive index and molar refraction depends not only upon atomic refraction but also upon single, double or triple bonds, these parameters are affected by the type of interactions taking place in solution.

**Figure 3.2.3: The plots of molar refraction $(MRD)_{12}$ against concentration of NBN series in DMF solutions at 298.15 K.**



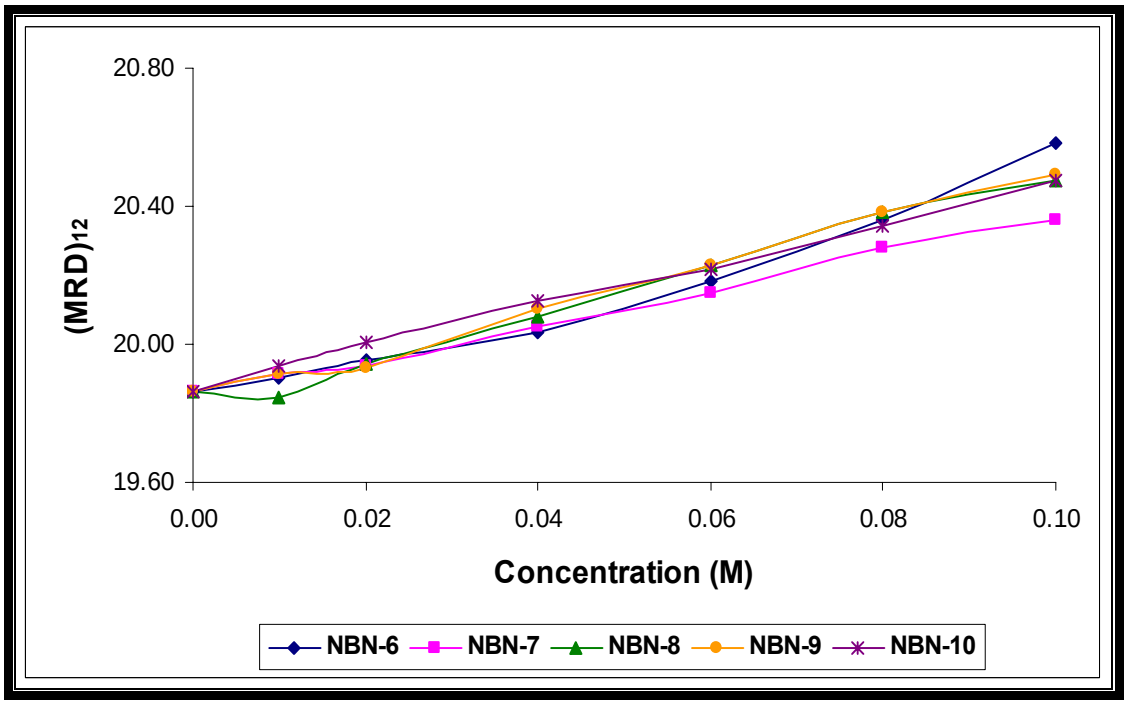
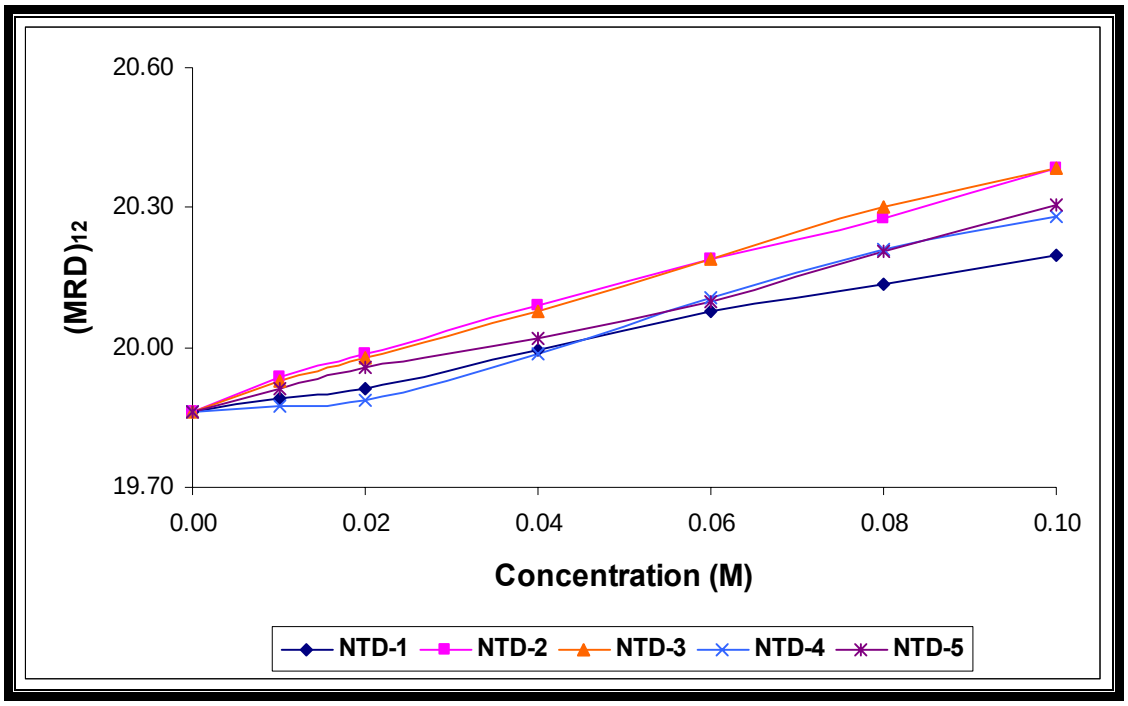



**Figure 3.2.4: The plots of molar refraction $(MRD)_{12}$ against concentration of NTD series in DMF solutions at 298.15 K.**



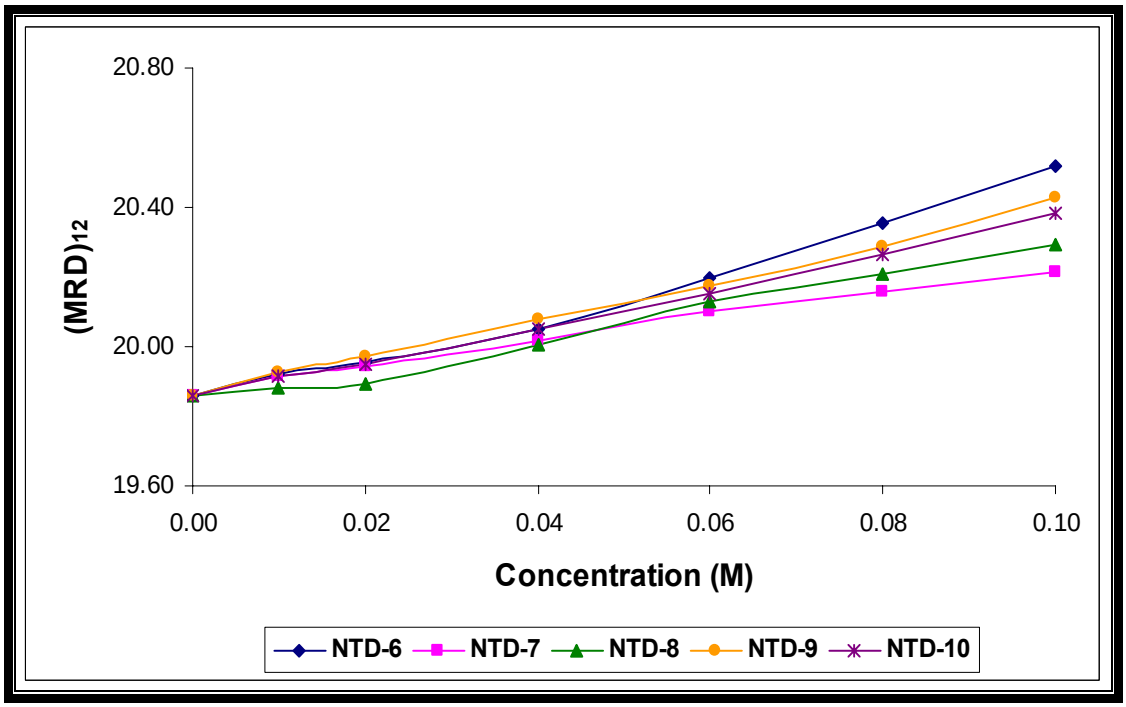
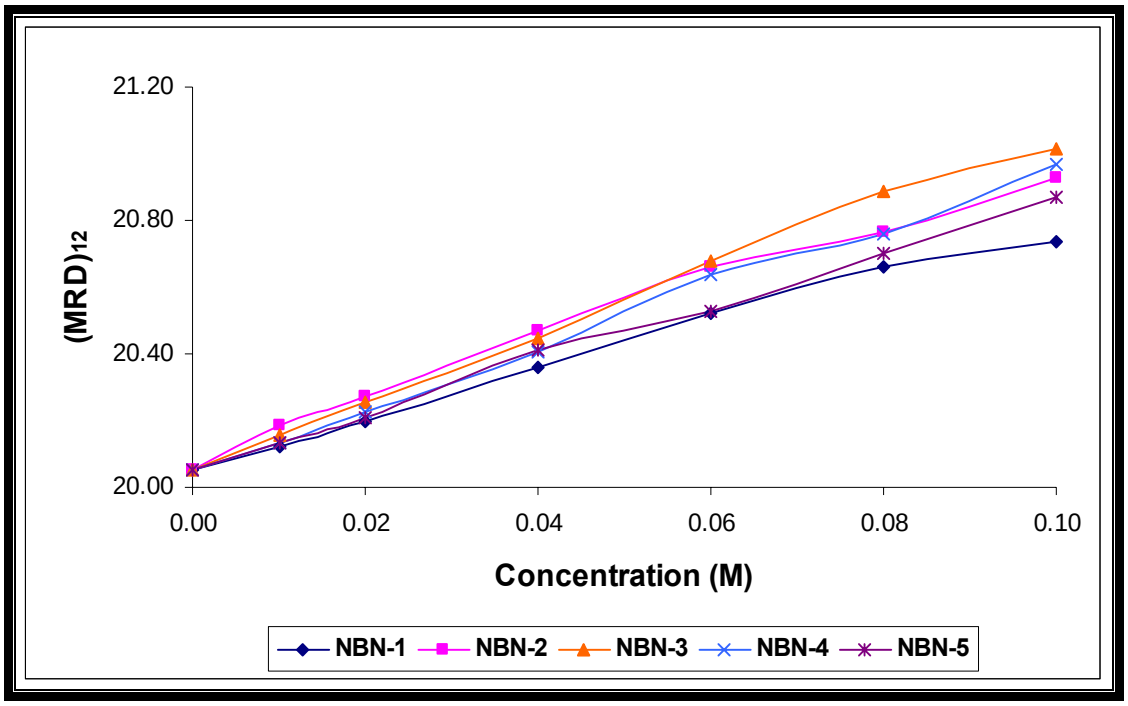



**Figure 3.2.5: The plots of molar refraction $(MRD)_{12}$ against concentration of NBN series in THF solutions at 298.15 K.**



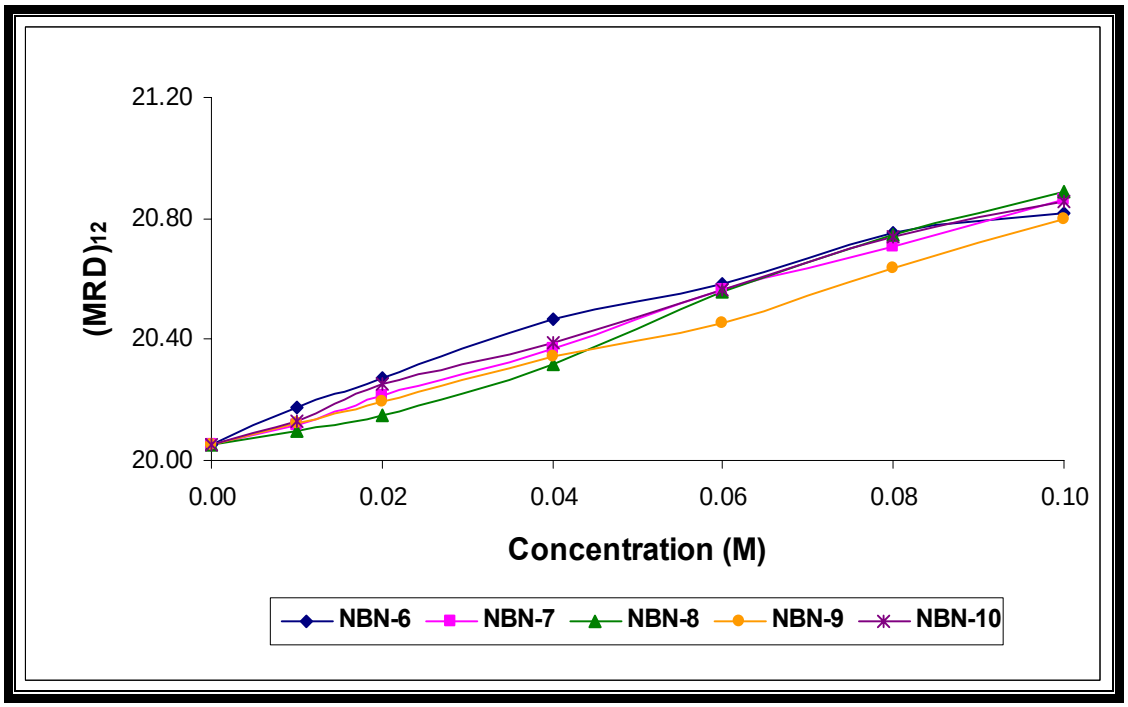
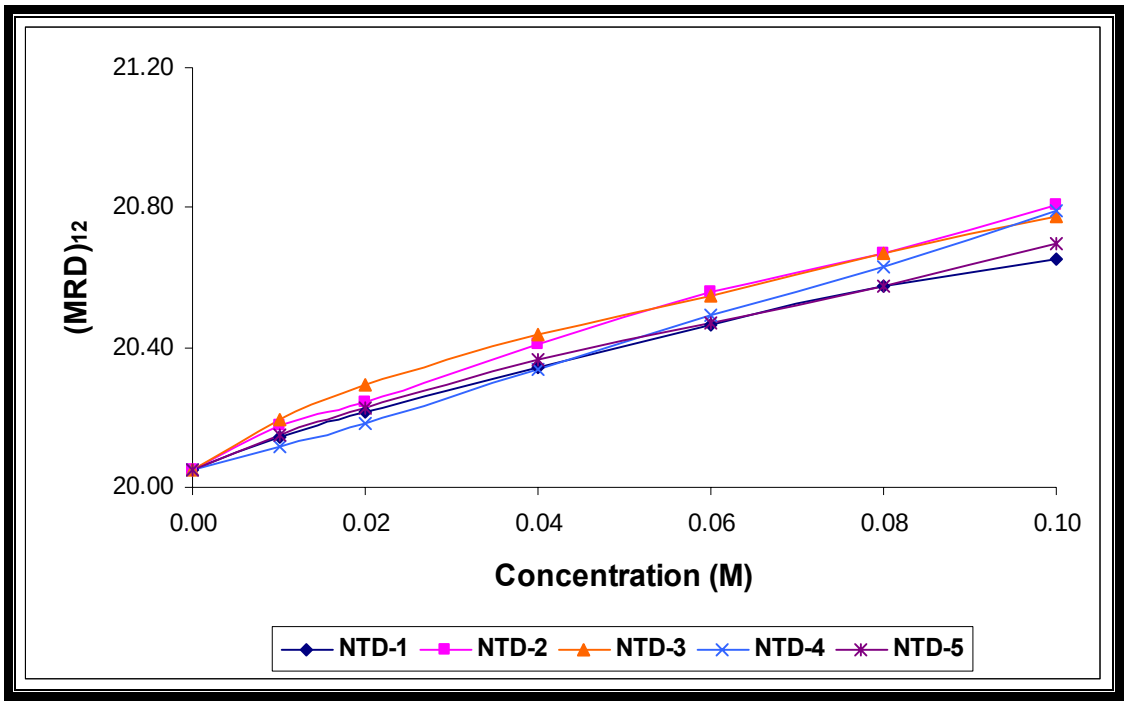



**Figure 3.2.6: The plots of molar refraction $(MRD)_{12}$ against concentration of NTD series in THF solutions at 298.15 K.**



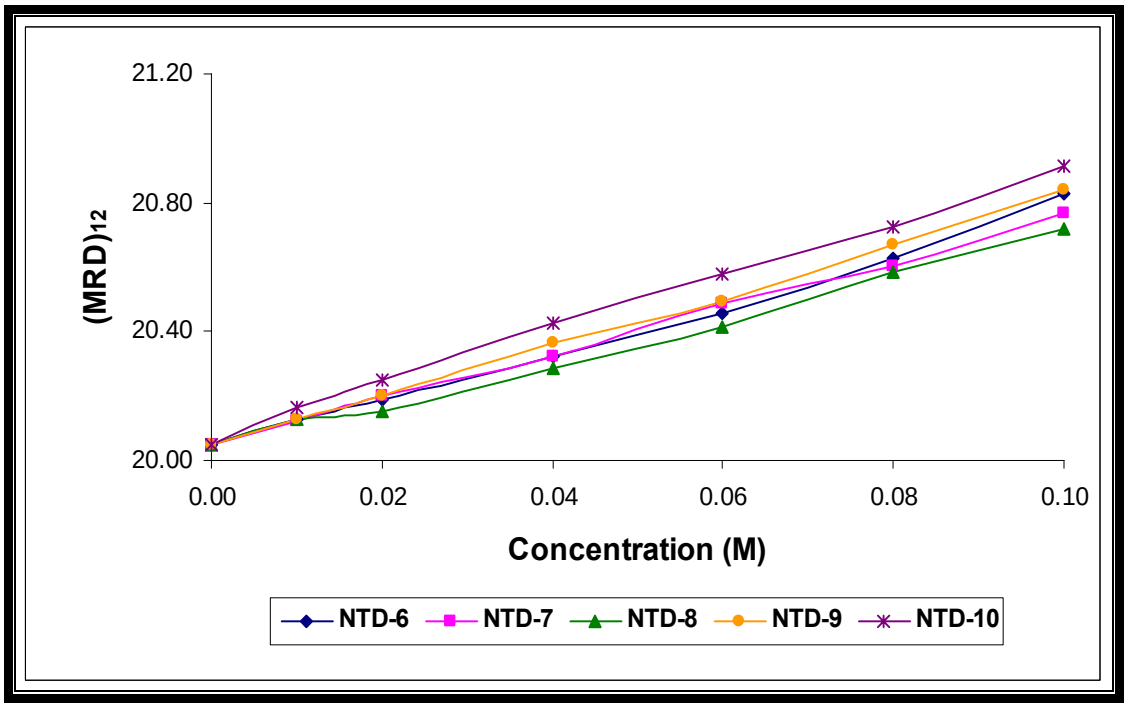



**Table 3.2.8: Molar refraction *(MRD)$_2$* and refractive index *(n)* of 0.1M solution of NBN series in DMF and THF at 298.15 K.**

| Compounds | Solvents | | | |
|---|---|---|---|---|
| | DMF | | THF | |
| | *(MRD$_2$)* | *n* | *(MRD$_2$)* | *n* |
| ***NBN-1*** | 88.92 | 1.5942 | 102.14 | 1.4729 |
| ***NBN-2*** | 104.35 | 1.7315 | 125.14 | 1.7258 |
| ***NBN-3*** | 96.81 | 1.6306 | 134.23 | 1.5912 |
| ***NBN-4*** | 112.93 | 1.5531 | 129.60 | 1.6713 |
| ***NBN-5*** | 101.25 | 1.6648 | 117.88 | 1.5748 |
| ***NBN-6*** | 111.18 | 1.6765 | 112.66 | 1.7989 |
| ***NBN-7*** | 83.77 | 1.5602 | 117.16 | 1.6597 |
| ***NBN-8*** | 98.28 | 1.6562 | 120.33 | 1.6058 |
| ***NBN-9*** | 100.39 | 1.7262 | 109.52 | 1.6646 |
| ***NBN-10*** | 98.45 | 1.7398 | 116.38 | 1.6629 |

**Table 3.2.9: Molar refraction *(MRD)$_2$* and refractive index *(n)* of 0.1M solution of NTD series in DMF and THF at 298.15 K.**

| Compounds | Solvents | | | |
|---|---|---|---|---|
| | DMF | | THF | |
| | *(MRD$_2$)* | *n* | *(MRD$_2$)* | *n* |
| ***NTD-1*** | 63.52 | 1.6387 | 92.21 | 1.5048 |
| ***NTD-2*** | 86.79 | 1.6901 | 110.65 | 1.6248 |
| ***NTD-3*** | 86.88 | 1.6066 | 106.87 | 1.6073 |
| ***NTD-4*** | 73.86 | 1.5914 | 108.83 | 1.6656 |
| ***NTD-5*** | 77.39 | 1.9826 | 97.77 | 1.6098 |
| ***NTD-6*** | 103.46 | 1.5962 | 113.09 | 1.6511 |
| ***NTD-7*** | 65.14 | 1.6018 | 106.23 | 1.7171 |
| ***NTD-8*** | 75.12 | 1.6454 | 100.48 | 1.6687 |
| ***NTD-9*** | 92.00 | 1.5778 | 114.41 | 1.6359 |
| **NTD-10** | 86.54 | 1.6396 | 122.97 | 1.4651 |

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

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# Section-III

# Conductance

## INTRODUCTION

Conductance of an electric current through an electrolyte solution involves migration of positively charged species towards the cathode and negatively charged species towards the anode. The conductance is a measure of the current that results from the application of a given electrical force and depends directly on the number of charged particles in the solution. Since all ions present in the solution contribute to the conductance process, conductance is an additive property of a solution depending on all the ions present. It is widely applicable for titration reactions involving ions, from which one can calculate the dissociation constant of weak electrolytes, solubility of sparingly soluble salt and rate of reactions that proceed with the formation or disappearance of ions etc. In acid-base titrations, this technique is also useful to determine relative strength of the two weak acids or bases, degree of hydrolysis, basicity of organic acid etc.

Literature survey shows that conductance of many inorganic and organic compounds have been measured in aqueous and non-aqueous solvents[1-29]. Various workers used this technique to analyzed agricultural products[30], for controlling the purification of glycerol by ion exchange[31], to study the dissociation constants of 2-chromonecarboxylic acid and its sodium salt[32] etc. It is also used to determination of the dissociation constant and limiting equivalent conductance of weak electrolytes[33], electroosmotic flow[34], for studying conformational changes in polyelectrolytes in aqueous solutions[35] etc.

Many workers have been reported the conductance study of synthetic compounds[36-47]. However, scanty work has been reported on benzo-diazepine[48,49]. Recently, conductance of some Schiff bases have been measured by Kaya[50] and Bhatt et al.[51]. Further, in our laboratory some conductance measurements have been done for Schiff bases[52].

In the present section, conductance of all the synthesized benzo-diazepines and thiadiazepines were measured in dimethylformamide and tetrahydrofuran at 298.15 K.

## EXPERIMENTAL

The solvents DMF and THF were purified by fractionally distillation by the method reported in the literature [53].

The solutions of different concentrations were prepared for each compound in DMF and THF and the conductance of each solution was measured by using Equip-tronics Conductivity Meter (Model No. 664) having cell constant 0.86 $cm^{-1}$ at 298.15 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 ($\kappa$), which is then used for the calculation of equivalent conductance ($\lambda_c$).

The equations used for calculating specific conductance ($\kappa$) and equivalent conductance ($\lambda_c$) are:

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

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

where $\theta$ is the cell constant (= 0.86) and *c* is the concentration (g.equi./lit.) of solution.

Tables 3.3.1 to 3.3.4 show the equivalent conductance of all the studied compounds in DMF and THF at 298.15K along with measured conductance (*k*). The variation of conductance with concentration for these compounds in both the solvents are given in Figures 3.3.1 to 3.3.4. For studied compounds, conductivities are observed to be less in THF than those in DMF. Further, for all the studied systems, conductance increases with concentration.

The equivalent conductance ($\lambda_c$) is plotted against $\sqrt{C}$ for all studied compounds and is shown in Figures 3.3.5 to 3.3.8. In both DMF and THF, usually $\lambda_c$ increases with dilution. But for certain compounds, $\lambda_c$ do not increase continuously but bend downward at low concentrations giving rise to maximum. This typical behavior may be due to interactions within the molecule thereby causing constriction within the molecule or due to association between solute with solvent molecules. It is evident from these figures that some compounds behave as strong electrolytes whereas most of them exhibited weak electrolytic behavior. Further, the behavior is different in different solvents.

For the systems where $\lambda_c$ values increase with dilution, $\lambda_0$ values were evaluated by extrapolation. These values are compared with those determined by an alternate procedure using the following equation:

$$k = k_0 + \lambda_0 c + c\phi_{(c)} \qquad \ldots\ldots (3.3.3)$$

**Table 3.3.1: The Conductance (*k*) and equivalent conductance ($\lambda_C$) of NBN series in DMF at 298.15 K.**

| Conc. M | $k.10^5$ mho | $\lambda_C$ mho.cm$^2$.equi.$^{-1}$ | $k.10^5$ mho | $\lambda_C$ mho.cm$^2$.equi.$^{-1}$ | $k.10^5$ mho | $\lambda_C$ mho.cm$^2$.equi.$^{-1}$ | $k.10^5$ mho | $\lambda_C$ mho.cm$^2$.equi.$^{-1}$ | $k.10^5$ mho | $\lambda_C$ mho.cm$^2$.equi.$^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| | ***NBN-1*** | | ***NBN-2*** | | ***NBN-3*** | | ***NBN-4*** | | ***NBN-5*** | |
| ***0.000*** | 2.24 | - | 2.24 | - | 2.24 | - | 2.24 | - | 2.24 | - |
| ***0.001*** | 2.46 | 1.8920 | 2.36 | 1.0320 | 2.45 | 1.8060 | 2.40 | 1.3760 | 2.87 | 5.4180 |
| ***0.002*** | 2.61 | 1.5910 | 2.64 | 1.7200 | 2.69 | 1.9350 | 2.83 | 2.5370 | 3.39 | 4.9450 |
| ***0.004*** | 2.78 | 1.1610 | 3.27 | 2.2145 | 3.08 | 1.8060 | 3.66 | 3.0530 | 4.24 | 4.3000 |
| ***0.006*** | 2.84 | 0.8600 | 3.79 | 2.2217 | 3.44 | 1.7200 | 4.32 | 2.9813 | 4.93 | 3.8557 |
| ***0.008*** | 3.45 | 1.3008 | 4.28 | 2.1930 | 3.78 | 1.6555 | 5.06 | 3.0315 | 5.54 | 3.5475 |
| ***0.010*** | 4.08 | 1.5824 | 4.77 | 2.1758 | 4.38 | 1.8404 | 5.68 | 2.9584 | 5.86 | 3.1132 |
| ***0.020*** | 5.83 | 1.5437 | 6.74 | 1.9350 | 5.19 | 1.2685 | 8.49 | 2.6875 | 8.07 | 2.5069 |
| ***0.040*** | 8.54 | 1.3545 | 8.33 | 1.3094 | 7.15 | 1.0557 | 11.82 | 2.0597 | 11.12 | 1.9092 |
| ***0.060*** | 11.13 | 1.2742 | 11.73 | 1.3602 | 8.29 | 0.8672 | 14.71 | 1.7874 | 14.00 | 1.6856 |
| ***0.080*** | 13.67 | 1.2287 | 13.57 | 1.2180 | 9.54 | 0.7848 | 17.43 | 1.6329 | 16.60 | 1.5437 |
| ***0.100*** | 16.54 | 1.2298 | 14.32 | 1.0389 | 10.34 | 0.6966 | 19.69 | 1.5007 | 18.60 | 1.4070 |
| | ***NBN-6*** | | ***NBN-7*** | | ***NBN-8*** | | ***NBN-9*** | | ***NBN-10*** | |
| ***0.001*** | 2.24 | - | 2.24 | - | 2.24 | - | 2.24 | - | 2.24 | - |
| ***0.002*** | 2.52 | 2.4080 | 2.43 | 1.6340 | 2.30 | 0.5160 | 2.46 | 1.8920 | 2.45 | 1.8060 |
| ***0.004*** | 2.97 | 3.1390 | 2.85 | 2.6230 | 2.78 | 2.3220 | 2.68 | 1.8920 | 2.78 | 2.3220 |
| ***0.006*** | 3.23 | 2.1285 | 3.18 | 2.0210 | 3.67 | 3.0745 | 3.12 | 1.8920 | 3.35 | 2.3865 |
| ***0.008*** | 3.59 | 1.9350 | 3.34 | 1.5767 | 4.43 | 3.1390 | 3.38 | 1.6340 | 4.25 | 2.8810 |
| ***0.010*** | 3.98 | 1.8705 | 3.78 | 1.6555 | 5.12 | 3.0960 | 3.59 | 1.4513 | 6.19 | 4.2463 |
| ***0.020*** | 4.35 | 1.8146 | 4.22 | 1.7028 | 5.73 | 3.0014 | 4.17 | 1.6598 | 7.85 | 4.8246 |
| ***0.040*** | 6.11 | 1.6641 | 4.68 | 1.0492 | 8.52 | 2.7004 | 5.89 | 1.5695 | 9.61 | 3.1691 |
| ***0.060*** | 8.99 | 1.4513 | 6.39 | 0.8923 | 11.74 | 2.0425 | 6.97 | 1.0170 | 11.24 | 1.9350 |
| ***0.080*** | 11.46 | 1.3215 | 7.70 | 0.7826 | 13.96 | 1.6799 | 8.13 | 0.8442 | 12.96 | 1.5365 |
| ***0.100*** | 13.07 | 1.1642 | 8.55 | 0.6783 | 15.69 | 1.4459 | 9.72 | 0.8041 | 14.24 | 1.2900 |

**Table 3.3.2: The Conductance (*k*) and equivalent conductance ($\lambda_C$) of NBN series in THF at 298.15 K.**

| ***Conc. M*** | ***k.10$^5$ mho*** | ***$\lambda_C$ mho.cm$^2$.equi.$^{-1}$*** | ***k.10$^5$ mho*** | ***$\lambda_C$ mho.cm$^2$.equi.$^{-1}$*** | ***k.10$^5$ mho*** | ***$\lambda_C$ mho.cm$^2$.equi.$^{-1}$*** | ***k.10$^5$ mho*** | ***$\lambda_C$ mho.cm$^2$.equi.$^{-1}$*** | ***k.10$^5$ mho*** | ***$\lambda_C$ mho.cm$^2$.equi.$^{-1}$*** |
|---|---|---|---|---|---|---|---|---|---|---|
| | ***NBN-1*** | | ***NBN-2*** | | ***NBN-3*** | | ***NBN-4*** | | ***NBN-5*** | |
| ***0.000*** | 0.021 | - | 0.021 | - | 0.021 | - | 0.021 | - | 0.021 | - |
| ***0.001*** | 0.041 | 0.1746 | 0.024 | 0.0284 | 0.025 | 0.0370 | 0.062 | 0.3500 | 0.042 | 0.1815 |
| ***0.002*** | 0.062 | 0.1776 | 0.030 | 0.0374 | 0.029 | 0.0331 | 0.091 | 0.2997 | 0.060 | 0.1694 |
| ***0.004*** | 0.095 | 0.1593 | 0.040 | 0.0404 | 0.040 | 0.0404 | 0.142 | 0.2595 | 0.091 | 0.1505 |
| ***0.006*** | 0.130 | 0.1564 | 0.048 | 0.0390 | 0.047 | 0.0374 | 0.192 | 0.2454 | 0.115 | 0.1340 |
| ***0.008*** | 0.170 | 0.1606 | 0.057 | 0.0390 | 0.058 | 0.0401 | 0.240 | 0.2354 | 0.128 | 0.1155 |
| ***0.010*** | 0.184 | 0.1400 | 0.067 | 0.0397 | 0.067 | 0.0397 | 0.283 | 0.2253 | 0.163 | 0.1221 |
| ***0.020*** | 0.383 | 0.1557 | 0.113 | 0.0397 | 0.111 | 0.0388 | 0.423 | 0.1729 | 0.283 | 0.1127 |
| ***0.040*** | 0.403 | 0.0821 | 0.164 | 0.0308 | 0.183 | 0.0349 | 0.728 | 0.1520 | 0.492 | 0.1013 |
| ***0.060*** | 0.425 | 0.0579 | 0.218 | 0.0282 | 0.253 | 0.0333 | 0.895 | 0.1253 | 0.702 | 0.0976 |
| ***0.080*** | 0.442 | 0.0453 | 0.248 | 0.0244 | 0.282 | 0.0281 | 1.093 | 0.1152 | 0.922 | 0.0969 |
| ***0.100*** | 0.468 | 0.0384 | 0.285 | 0.0227 | 0.297 | 0.0237 | 1.271 | 0.1075 | 0.964 | 0.0811 |
| | ***NBN-6*** | | ***NBN-7*** | | ***NBN-8*** | | ***NBN-9*** | | ***NBN-10*** | |
| ***0.001*** | 0.021 | - | 0.021 | - | 0.021 | - | 0.021 | - | 0.021 | - |
| ***0.002*** | 0.034 | 0.1127 | 0.023 | 0.0172 | 0.039 | 0.1548 | 0.042 | 0.1840 | 0.026 | 0.0421 |
| ***0.004*** | 0.048 | 0.1144 | 0.028 | 0.0301 | 0.051 | 0.1269 | 0.062 | 0.1767 | 0.030 | 0.0391 |
| ***0.006*** | 0.068 | 0.1017 | 0.037 | 0.0344 | 0.069 | 0.1032 | 0.084 | 0.1361 | 0.040 | 0.0417 |
| ***0.008*** | 0.086 | 0.0925 | 0.044 | 0.0331 | 0.096 | 0.1072 | 0.111 | 0.1293 | 0.051 | 0.0423 |
| ***0.010*** | 0.104 | 0.0888 | 0.051 | 0.0324 | 0.114 | 0.0994 | 0.114 | 0.1003 | 0.061 | 0.0429 |
| ***0.020*** | 0.120 | 0.0847 | 0.057 | 0.0310 | 0.126 | 0.0903 | 0.116 | 0.0820 | 0.070 | 0.0424 |
| ***0.040*** | 0.205 | 0.0791 | 0.085 | 0.0273 | 0.207 | 0.0800 | 0.119 | 0.0420 | 0.114 | 0.0401 |
| ***0.060*** | 0.341 | 0.0688 | 0.142 | 0.0259 | 0.298 | 0.0596 | 0.222 | 0.0432 | 0.262 | 0.0518 |
| ***0.080*** | 0.503 | 0.0691 | 0.170 | 0.0213 | 0.374 | 0.0506 | 0.484 | 0.0664 | 0.315 | 0.0421 |
| ***0.100*** | 0.604 | 0.0627 | 0.209 | 0.0202 | 0.436 | 0.0446 | 0.612 | 0.0635 | 0.326 | 0.0328 |

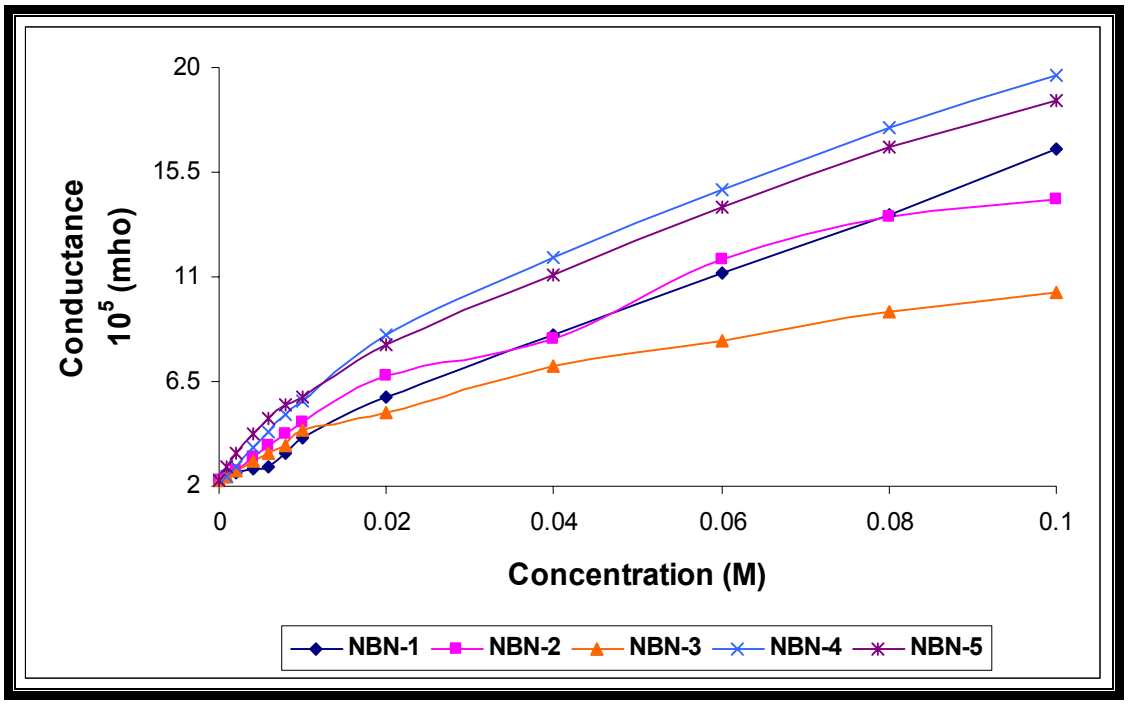
**Table 3.3.3: The Conductance (*k*) and equivalent conductance ($\lambda_C$) of NTD series in DMF at 298.15 K.**

| Conc. M | $k.10^5$ mho | $\lambda_C$ $mho.cm^2.equi.^{-1}$ | $k.10^5$ mho | $\lambda_C$ $mho.cm^2.equi.^{-1}$ | $k.10^5$ mho | $\lambda_C$ $mho.cm^2.equi.^{-1}$ | $k.10^5$ mho | $\lambda_C$ $mho.cm^2.equi.^{-1}$ | $k.10^5$ mho | $\lambda_C$ $mho.cm^2.equi.^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| | NTD-1 | | NTD-2 | | NTD-3 | | NTD-4 | | NTD-5 | |
| 0.000 | 2.24 | - | 2.24 | - | 2.24 | - | 2.24 | - | 2.24 | - |
| 0.001 | 2.38 | 1.2040 | 3.11 | 7.4820 | 2.52 | 2.4080 | 2.64 | 3.4400 | 2.81 | 4.9020 |
| 0.002 | 2.50 | 1.1180 | 3.86 | 6.9660 | 2.72 | 2.0640 | 2.95 | 3.0530 | 3.37 | 4.8590 |
| 0.004 | 2.66 | 0.9116 | 5.25 | 6.4715 | 3.12 | 1.8920 | 4.12 | 4.0420 | 4.03 | 3.8485 |
| 0.006 | 2.76 | 0.7453 | 6.34 | 5.8767 | 3.51 | 1.8203 | 5.04 | 4.0133 | 4.61 | 3.3970 |
| 0.008 | 2.93 | 0.7418 | 7.12 | 5.2460 | 3.92 | 1.8060 | 6.12 | 4.1710 | 5.02 | 2.9885 |
| 0.010 | 3.09 | 0.7310 | 8.10 | 5.0396 | 4.52 | 1.9608 | 7.42 | 4.4548 | 5.54 | 2.8380 |
| 0.020 | 4.64 | 1.0320 | 9.98 | 3.3282 | 5.98 | 1.6082 | 9.54 | 3.1390 | 7.82 | 2.3994 |
| 0.040 | 7.22 | 1.0707 | 12.03 | 2.1049 | 7.35 | 1.0987 | 12.23 | 2.1479 | 11.06 | 1.8963 |
| 0.060 | 9.57 | 1.0506 | 13.73 | 1.6469 | 8.99 | 0.9675 | 14.11 | 1.7014 | 13.70 | 1.6426 |
| 0.080 | 11.67 | 1.0137 | 15.27 | 1.4007 | 10.54 | 0.8923 | 15.92 | 1.4706 | 16.00 | 1.4792 |
| 0.100 | 14.07 | 1.0174 | 16.32 | 1.2109 | 12.34 | 0.8686 | 17.03 | 1.2719 | 18.10 | 1.3640 |
| | NTD-6 | | NTD-7 | | NTD-8 | | NTD-9 | | NTD-10 | |
| 0.001 | 2.24 | - | 2.24 | - | 2.24 | - | 2.24 | - | 2.24 | - |
| 0.002 | 2.73 | 4.2140 | 2.53 | 2.4940 | 2.49 | 2.1500 | 2.73 | 4.2140 | 2.50 | 2.2360 |
| 0.004 | 3.22 | 4.2140 | 2.75 | 2.1930 | 2.67 | 1.8490 | 3.04 | 3.4400 | 2.81 | 2.4510 |
| 0.006 | 3.93 | 3.6335 | 3.29 | 2.2575 | 2.98 | 1.5846 | 3.83 | 3.4185 | 3.67 | 3.0745 |
| 0.008 | 4.99 | 3.9417 | 3.85 | 2.3077 | 3.36 | 1.6053 | 5.01 | 3.9703 | 4.64 | 3.4400 |
| 0.010 | 5.88 | 3.9130 | 4.46 | 2.3865 | 3.62 | 1.4835 | 6.44 | 4.5150 | 5.73 | 3.7518 |
| 0.020 | 7.04 | 4.1280 | 5.32 | 2.6488 | 4.13 | 1.6254 | 7.72 | 4.7128 | 7.23 | 4.2914 |
| 0.040 | 9.11 | 2.9541 | 7.55 | 2.2833 | 5.87 | 1.5609 | 10.82 | 3.6894 | 9.58 | 3.1562 |
| 0.060 | 11.59 | 2.0103 | 9.12 | 1.4792 | 6.93 | 1.0084 | 12.84 | 2.2790 | 11.44 | 1.9780 |
| 0.080 | 13.76 | 1.6512 | 10.13 | 1.1309 | 8.15 | 0.8471 | 14.92 | 1.8175 | 13.16 | 1.5652 |
| 0.100 | 15.87 | 1.4652 | 11.54 | 0.9998 | 9.74 | 0.8063 | 16.65 | 1.5491 | 14.44 | 1.3115 |

**Table 3.3.4: The Conductance (*k*) and equivalent conductance ($\lambda_C$) of NTD series in THF at 298.15 K.**

| Conc. M | $k.10^5$ mho | $\lambda_C$ $mho.cm^2.equi.^{-1}$ | $k.10^5$ mho | $\lambda_C$ $mho.cm^2.equi.^{-1}$ | $k.10^5$ mho | $\lambda_C$ $mho.cm^2.equi.^{-1}$ | $k.10^5$ mho | $\lambda_C$ $mho.cm^2.equi.^{-1}$ | $k.10^5$ mho | $\lambda_C$ $mho.cm^2.equi.^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|---|
| | NTD-1 | | NTD-2 | | NTD-3 | | NTD-4 | | NTD-5 | |
| 0.000 | 0.021 | - | 0.021 | - | 0.021 | - | 0.021 | - | 0.021 | - |
| 0.001 | 0.045 | 0.2090 | 0.033 | 0.1058 | 0.026 | 0.0404 | 0.027 | 0.0516 | 0.041 | 0.1737 |
| 0.002 | 0.066 | 0.1948 | 0.043 | 0.0955 | 0.028 | 0.0314 | 0.034 | 0.0559 | 0.063 | 0.1823 |
| 0.004 | 0.099 | 0.1679 | 0.056 | 0.0759 | 0.041 | 0.0426 | 0.053 | 0.0688 | 0.087 | 0.1419 |
| 0.006 | 0.125 | 0.1492 | 0.070 | 0.0705 | 0.049 | 0.0403 | 0.081 | 0.0860 | 0.122 | 0.1441 |
| 0.008 | 0.154 | 0.1434 | 0.087 | 0.0714 | 0.063 | 0.0455 | 0.111 | 0.0968 | 0.152 | 0.1413 |
| 0.010 | 0.174 | 0.1314 | 0.115 | 0.0810 | 0.087 | 0.0569 | 0.145 | 0.1066 | 0.183 | 0.1393 |
| 0.020 | 0.222 | 0.0864 | 0.178 | 0.0676 | 0.182 | 0.0694 | 0.319 | 0.1281 | 0.303 | 0.1213 |
| 0.040 | 0.280 | 0.0557 | 0.266 | 0.0527 | 0.276 | 0.0549 | 0.489 | 0.1006 | 0.456 | 0.0935 |
| 0.060 | 0.360 | 0.0486 | 0.375 | 0.0507 | 0.345 | 0.0464 | 0.651 | 0.0903 | 0.547 | 0.0754 |
| 0.080 | 0.425 | 0.0434 | 0.527 | 0.0544 | 0.427 | 0.0436 | 0.732 | 0.0764 | 0.675 | 0.0703 |
| 0.100 | 0.515 | 0.0425 | 0.712 | 0.0594 | 0.538 | 0.0445 | 0.845 | 0.0709 | 0.761 | 0.0636 |
| | NTD-6 | | NTD-7 | | NTD-8 | | NTD-9 | | NTD-10 | |
| 0.001 | 0.021 | - | 0.021 | - | 0.021 | - | 0.021 | - | 0.021 | - |
| 0.002 | 0.033 | 0.1058 | 0.032 | 0.0946 | 0.038 | 0.1479 | 0.042 | 0.1840 | 0.028 | 0.0593 |
| 0.004 | 0.045 | 0.1041 | 0.052 | 0.1333 | 0.051 | 0.1299 | 0.060 | 0.1681 | 0.032 | 0.0477 |
| 0.006 | 0.066 | 0.0970 | 0.076 | 0.1183 | 0.066 | 0.0968 | 0.084 | 0.1361 | 0.042 | 0.0460 |
| 0.008 | 0.081 | 0.0866 | 0.104 | 0.1183 | 0.089 | 0.0979 | 0.121 | 0.1436 | 0.054 | 0.0466 |
| 0.010 | 0.097 | 0.0812 | 0.141 | 0.1291 | 0.111 | 0.0970 | 0.154 | 0.1433 | 0.063 | 0.0454 |
| 0.020 | 0.115 | 0.0812 | 0.179 | 0.1359 | 0.134 | 0.0972 | 0.190 | 0.1453 | 0.074 | 0.0452 |
| 0.040 | 0.228 | 0.0890 | 0.275 | 0.1092 | 0.204 | 0.0787 | 0.315 | 0.1264 | 0.142 | 0.0522 |
| 0.060 | 0.324 | 0.0651 | 0.371 | 0.0753 | 0.295 | 0.0589 | 0.434 | 0.0888 | 0.249 | 0.0490 |
| 0.080 | 0.370 | 0.0500 | 0.489 | 0.0671 | 0.372 | 0.0503 | 0.504 | 0.0692 | 0.285 | 0.0378 |
| 0.100 | 0.425 | 0.0434 | 0.625 | 0.0649 | 0.432 | 0.0442 | 0.589 | 0.0611 | 0.335 | 0.0338 |

**Figure 3.3.1: The variation of Conductance with concentration for NBN series in DMF at 298.15 K.**



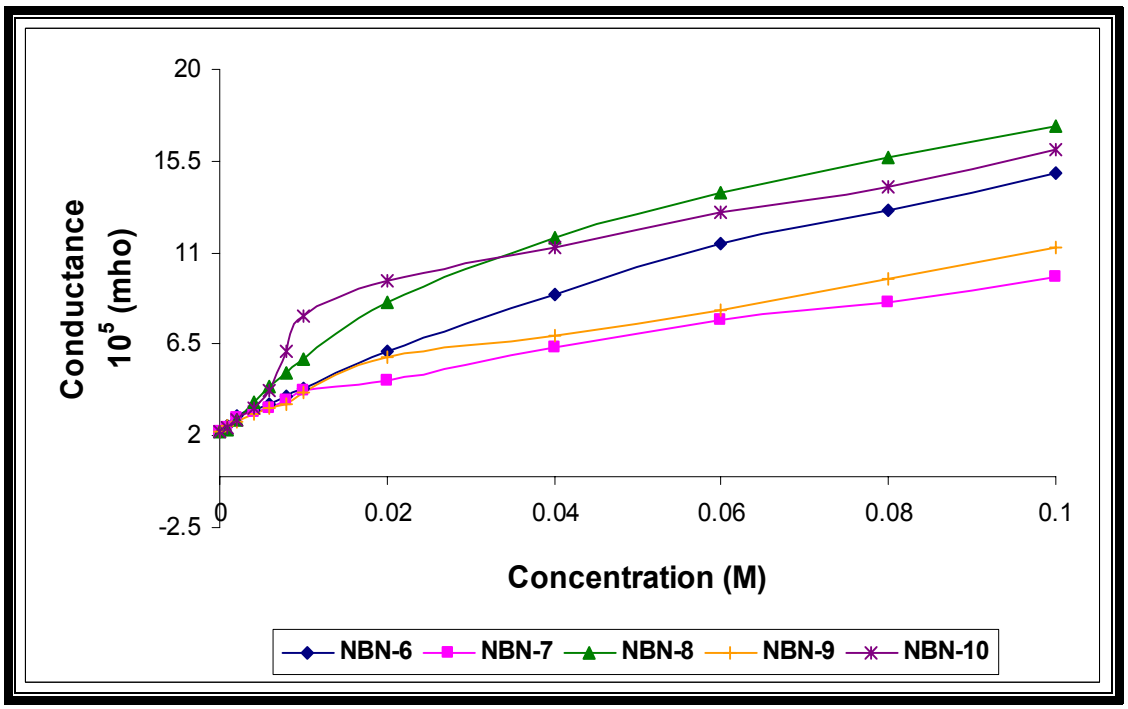
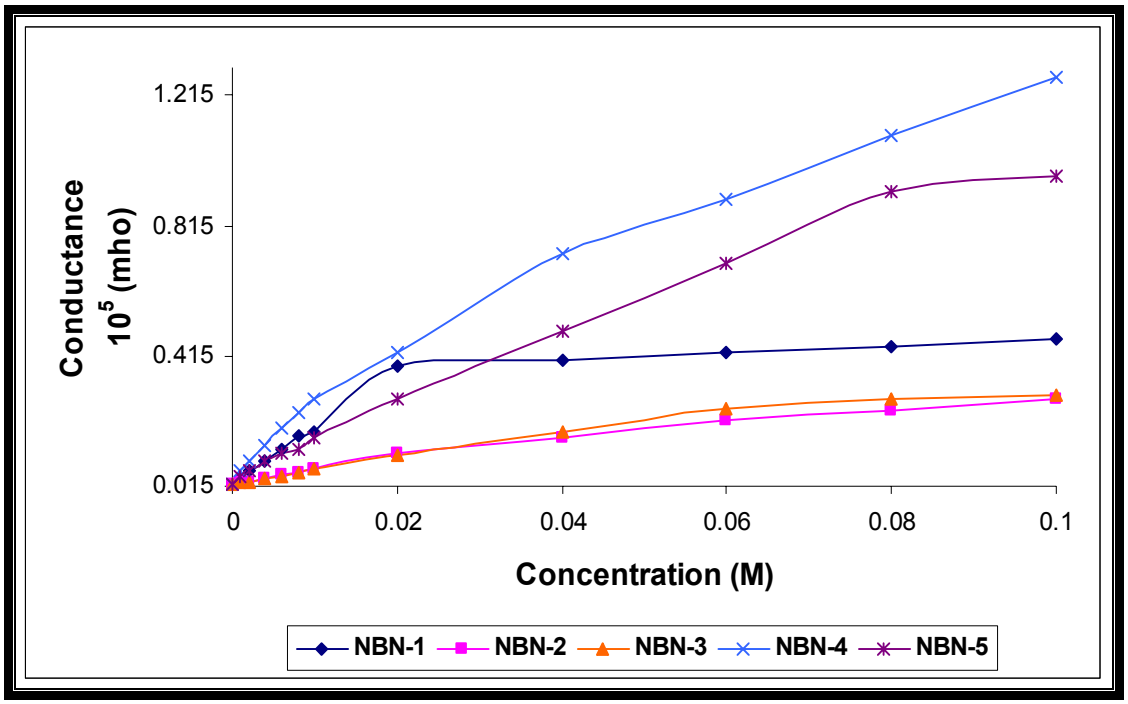



**Figure 3.3.2: The variation of Conductance with concentration for NBN series in THF at 298.15 K.**



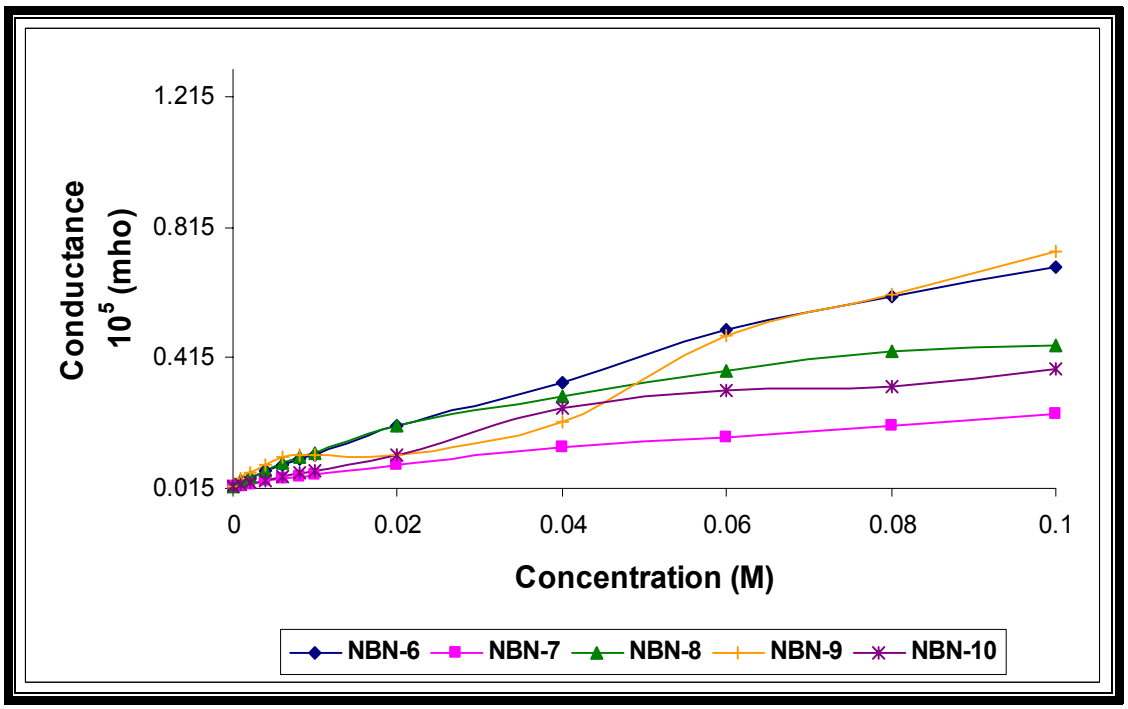
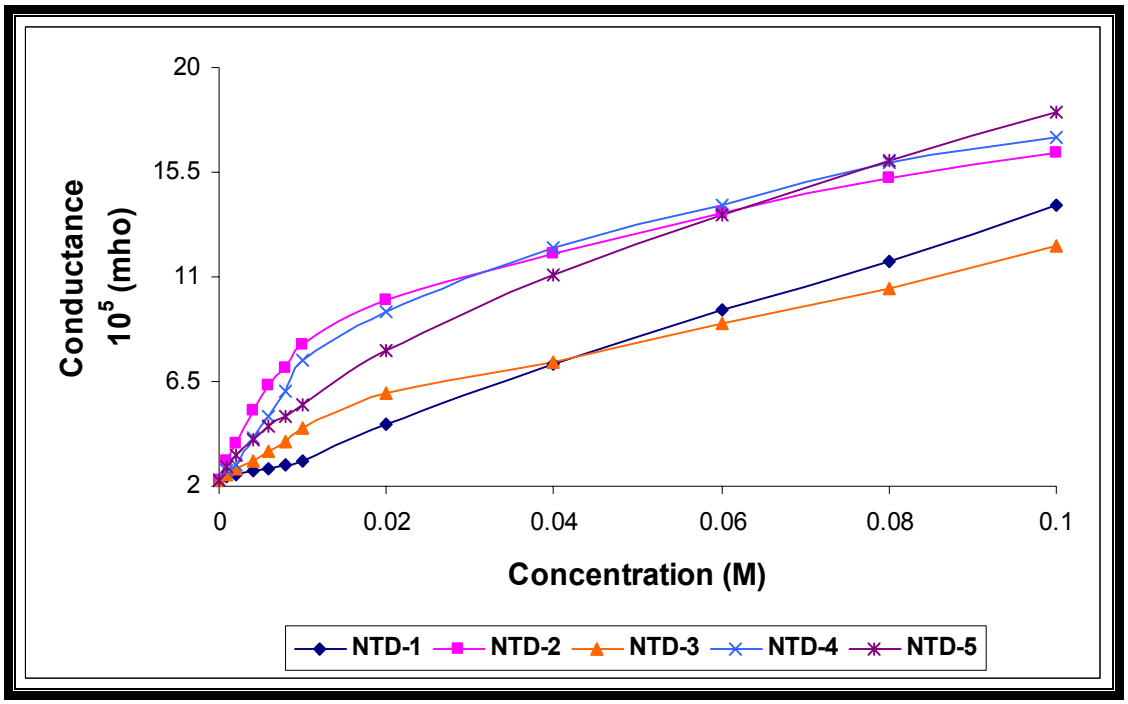



**Figure 3.3.3: The variation of Conductance with concentration for NTD series in DMF at 298.15 K.**



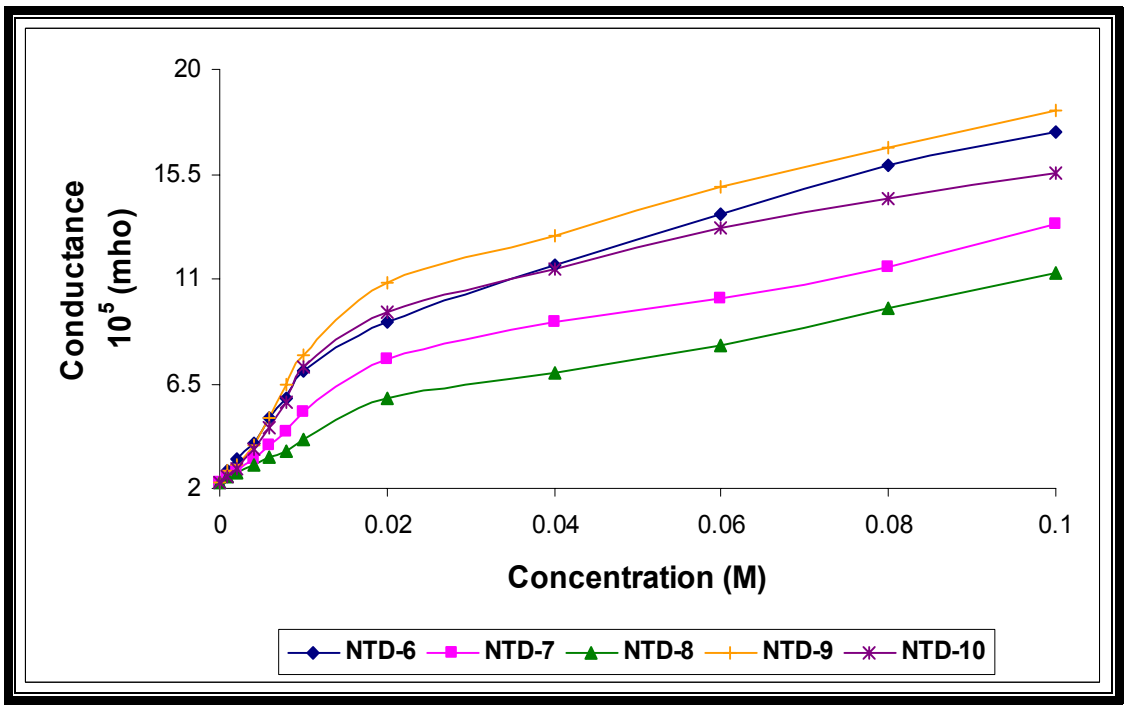
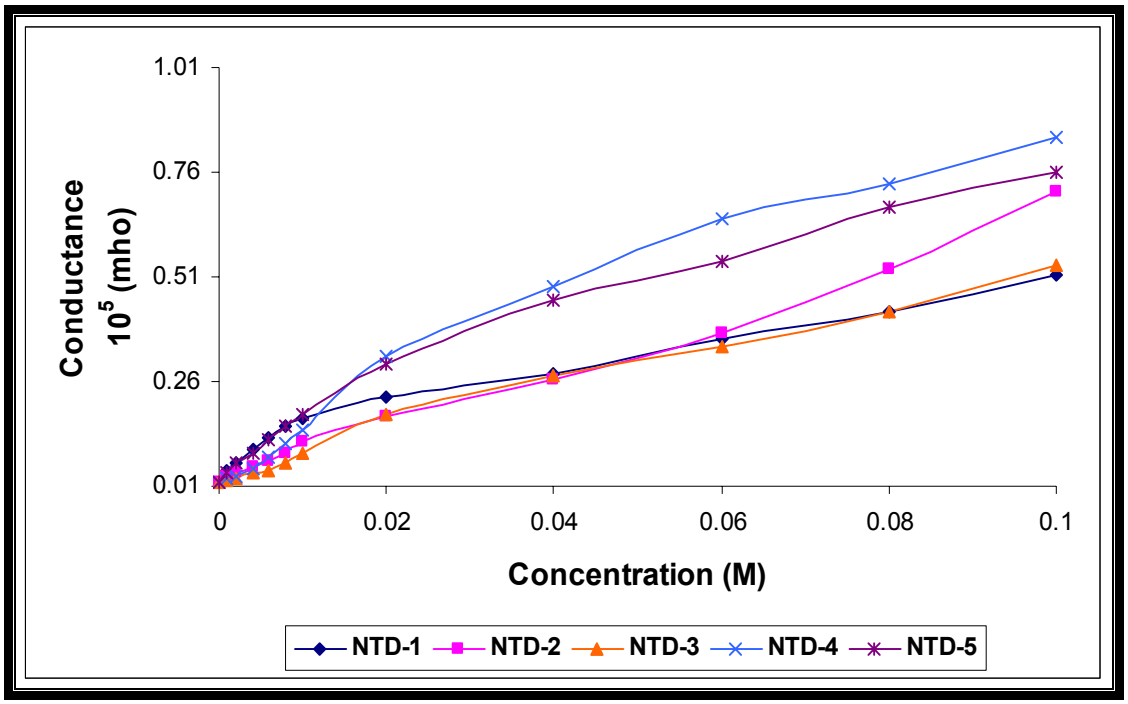



**Figure 3.3.4: The variation of Conductance with concentration for NTD series in THF at 298.15 K.**



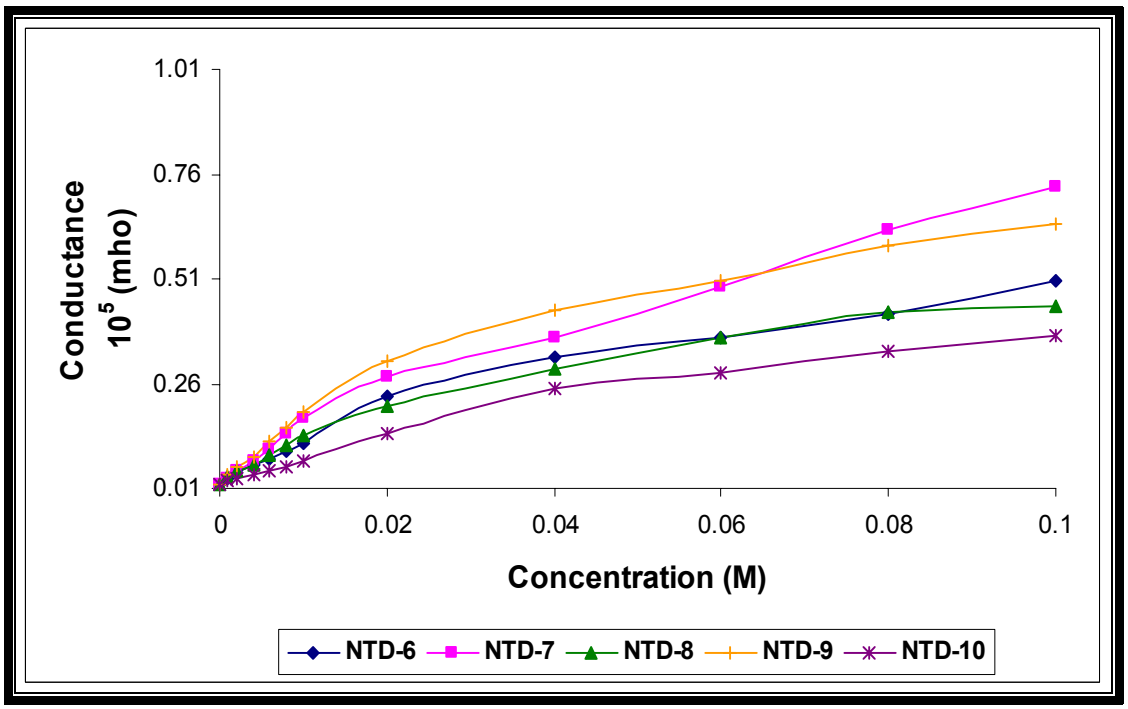
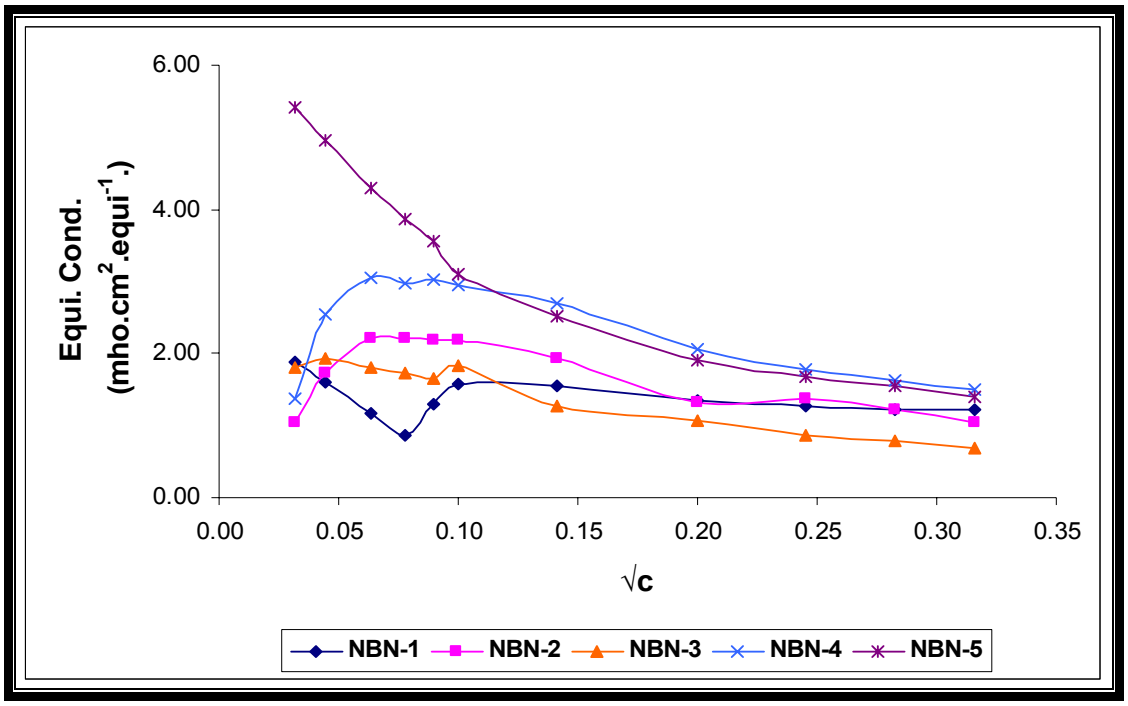



**Figure 3.3.5**: **The variation of equivalent conductance with √C for NBN series in DMF at 298.15 K.**



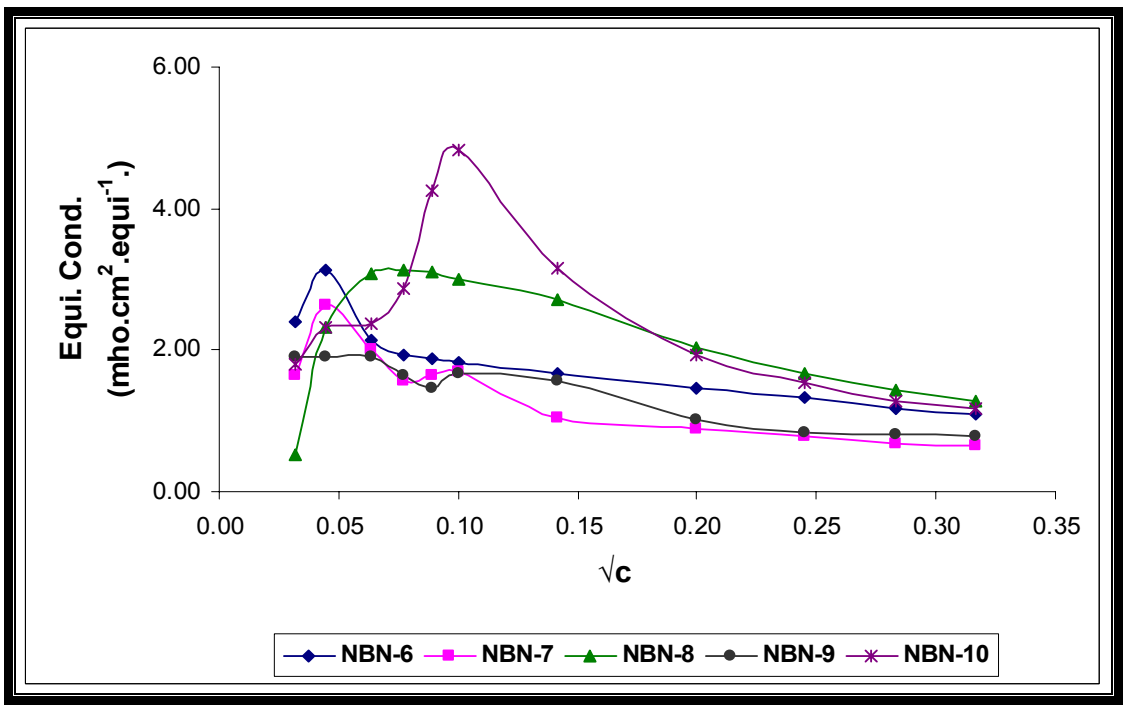
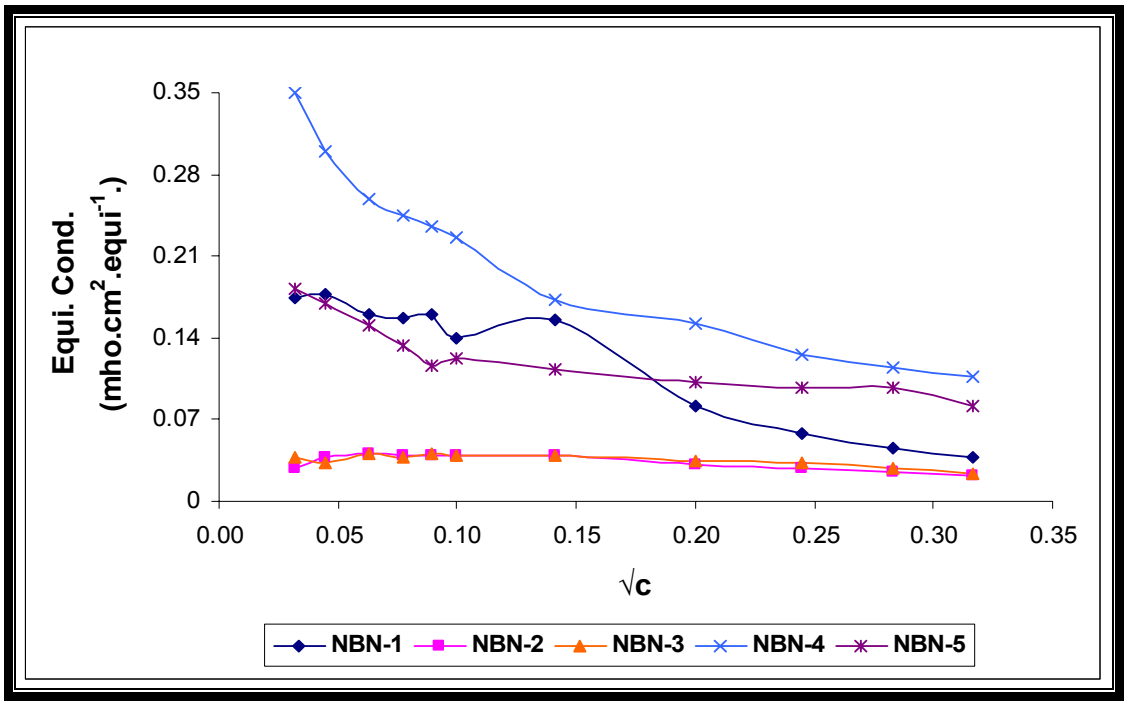



**Figure 3.3.6**: **The variation of equivalent conductance with √C for NBN series in THF at 298.15 K.**



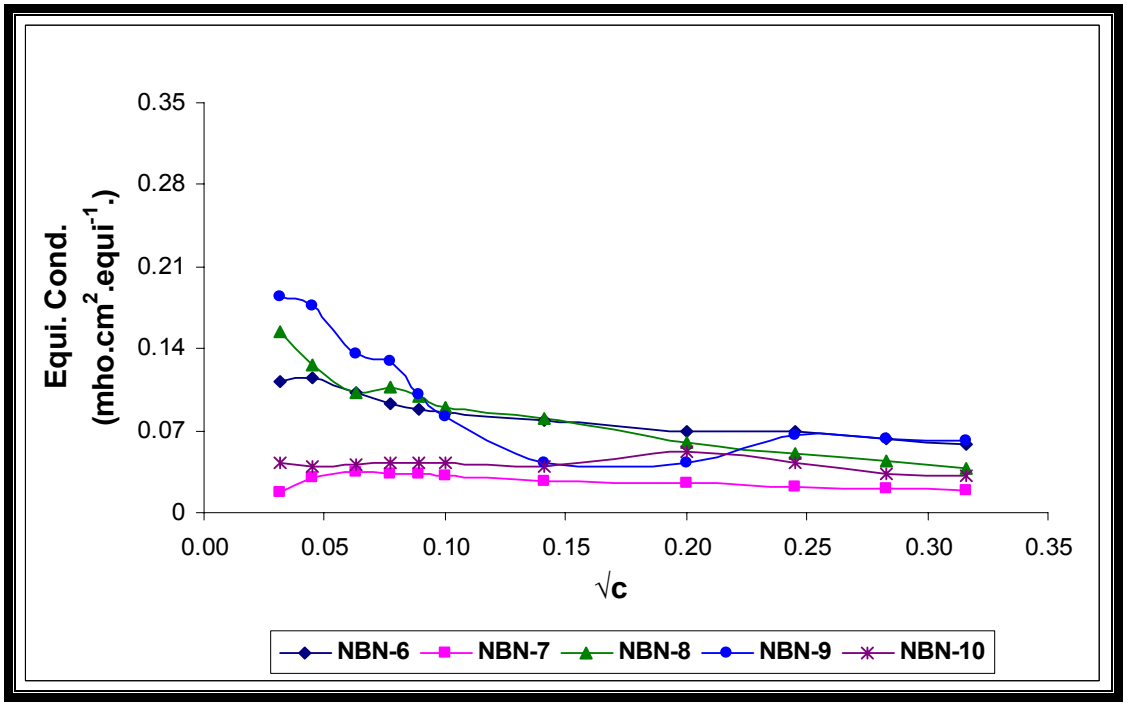
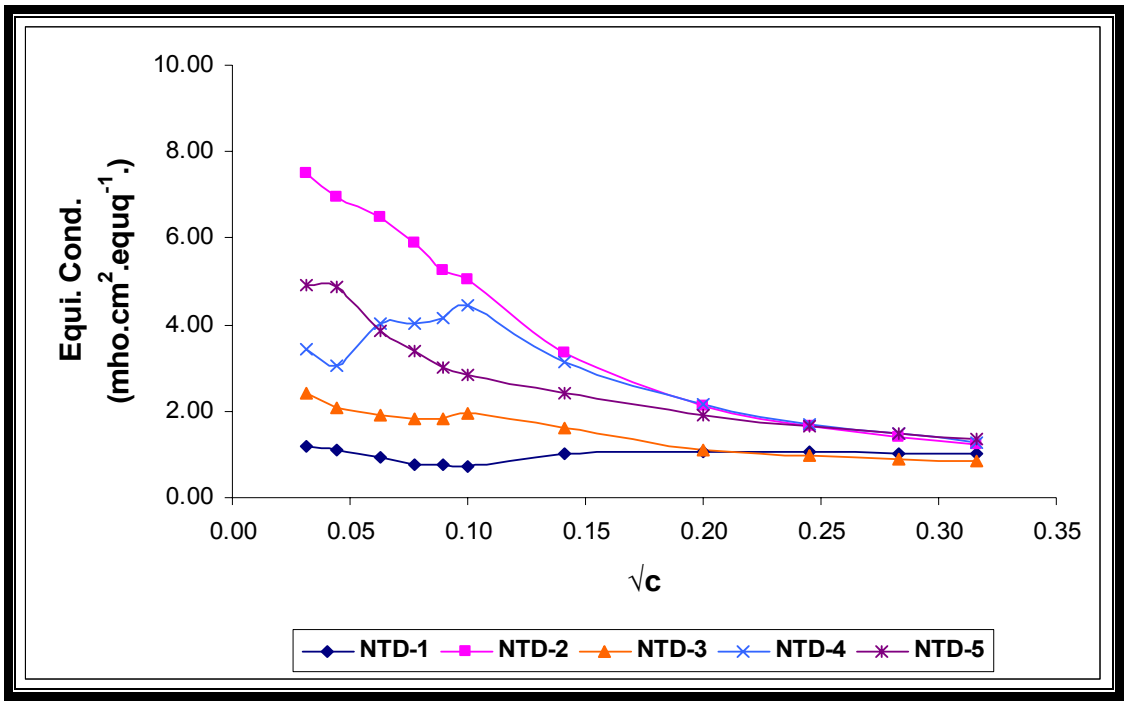



**Figure 3.3.7**: **The variation of equivalent conductance with √C for NTD series in DMF at 298.15 K.**



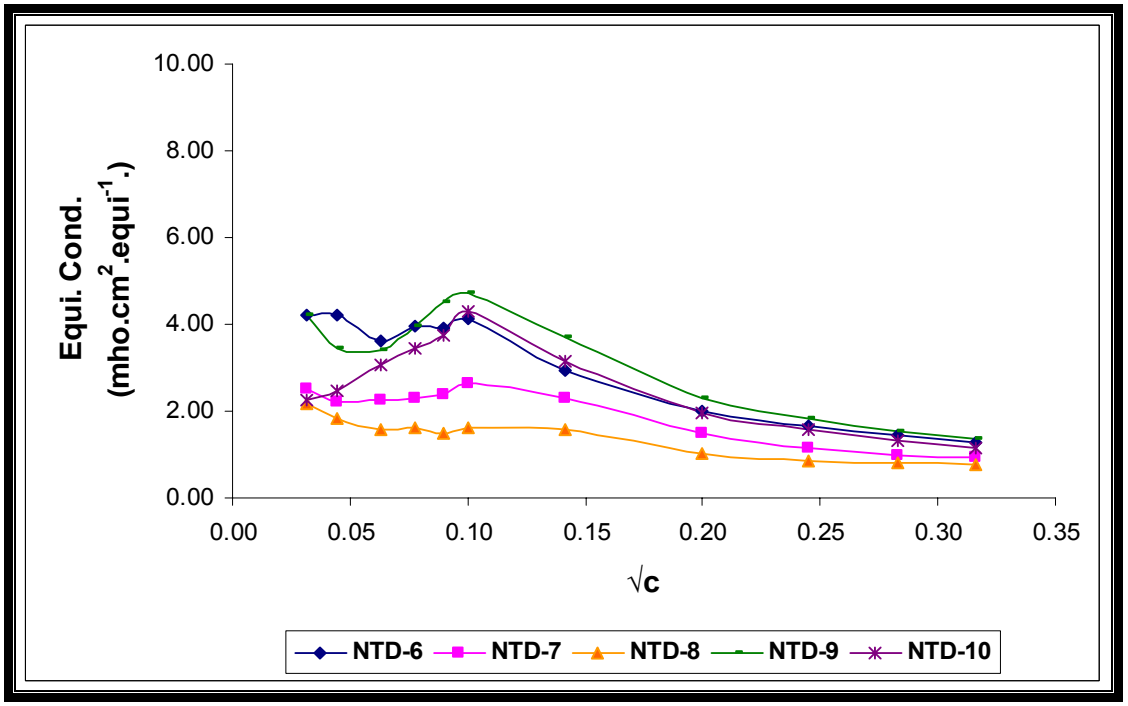
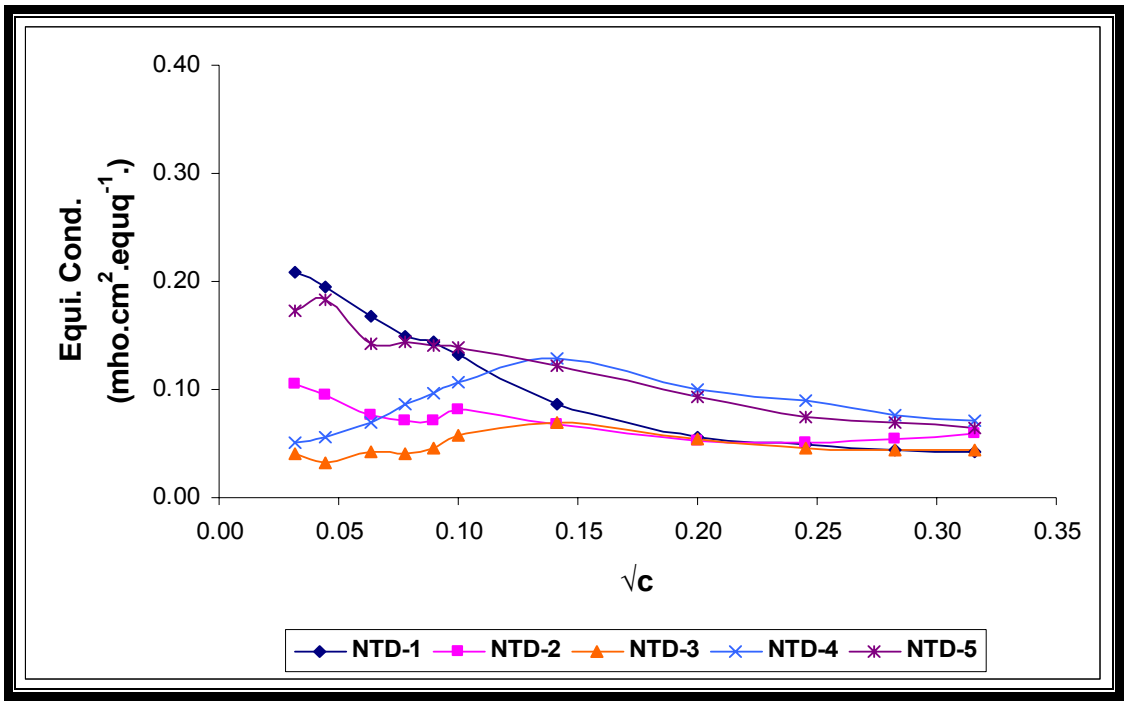
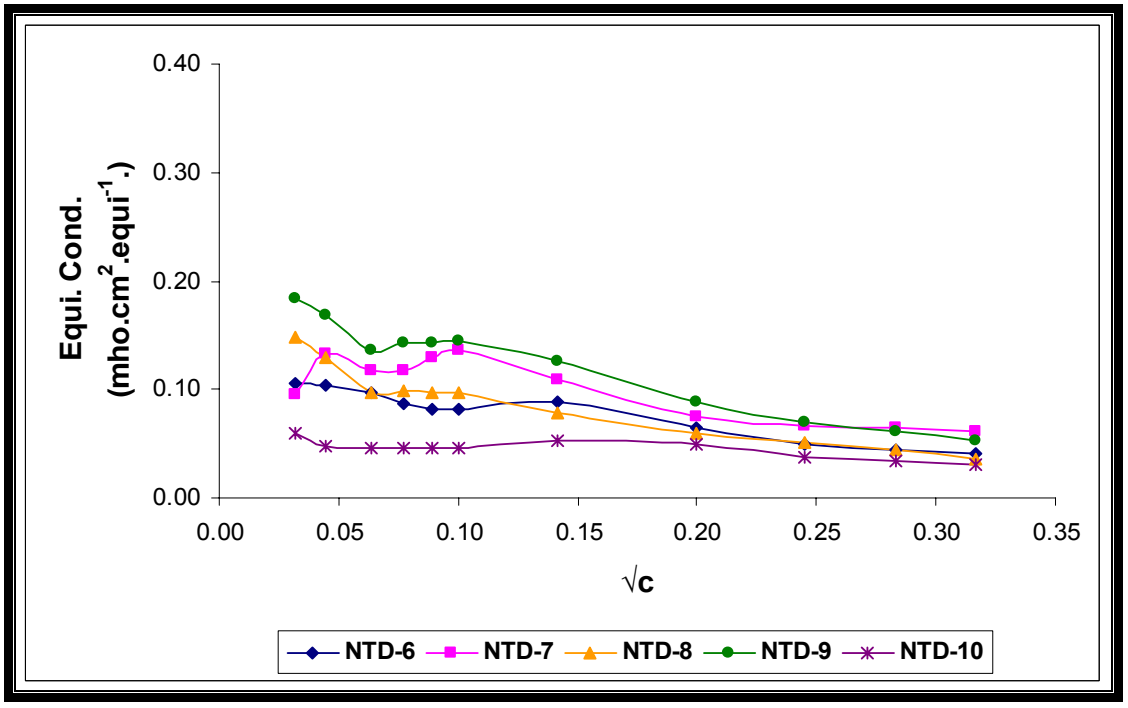



**Figure 3.3.8**: **The variation of equivalent conductance with √C for NTD series in THF at 298.15 K.**



where $k$ and $k_0$ are the electrolytic conductivity of the solutions and solvent respectively. $c$ is the equivalent concentration and the function $\Phi_{(c)}$ denotes the effect of interionic interactions. The limiting conductivity can be determined accurately from the slope, $dk/dc$ of plot of $k$ verses $c$, provided other derivatives ($dk_0/dc$) and $d[c\Phi_{(c)}]/dc$ in differential form of equation (3.3.3) are neglected as compared to $\lambda_0$, which can be determined from differential form of equation (3.3.3) is

$$\frac{dk}{dc} = \frac{dk_0}{dc} + \lambda_0 + \frac{d\left[c\phi_{(c)}\right]}{dc} \qquad \ldots\ldots (3.3.4)$$

Tables 3.3.5 and 3.3.6 shows the $\lambda_0$ values for all studied compounds along with those determined by extrapolation. For those system in which $\lambda_c$ decreases at low concentrations, $\lambda_0$ could not be evaluated. Comparison of $\lambda_0$ values in Table 3.3.5 show that for most of the systems, values are in good agreement. However, for some cases, deviations are significant suggesting thereby that above equations (3.3.3) and (3.3.4) are not valid for these systems.

**Table 3.3.5: The limiting equivalent conductance ($\lambda_0$) of all the compounds in DMF and THF at 298.15 K.**

| *Compound Code* | $\lambda_0$ *mho.cm$^2$.equi.$^{-1}$* from graph | $\lambda_0 10^3$ *mho.cm$^2$.equi.$^{-1}$* from eq. (3.3.4) | $\lambda_0$ *mho.cm$^2$.equi.$^{-1}$* from graph | $\lambda_0 10^3$ *mho.cm$^2$.equi.$^{-1}$* from eq. (3.3.4) |
|---|---|---|---|---|
| | *DMF* | | *THF* | |
| ***NBN -1*** | 2.15 | 1.63 | - | 0.168 |
| ***NBN -2*** | - | 2.63 | - | 0.047 |
| ***NBN -3*** | 2.35 | 2.05 | - | 0.047 |
| ***NBN -4*** | - | 3.57 | 0.410 | 0.257 |
| ***NBN -5*** | 5.75 | 3.63 | 0.200 | 0.134 |
| ***NBN -6*** | 2.65 | 2.02 | 0.125 | 0.097 |
| ***NBN -7*** | 1.95 | 1.88 | - | 0.037 |
| ***NBN -8*** | 4.50 | 3.71 | 0.165 | 0.105 |
| ***NBN -9*** | 2.40 | 1.81 | 0.210 | 0.096 |
| ***NBN -10*** | 6.70 | 5.50 | - | 0.050 |
| ***NTD-1*** | 1.23 | 0.80 | 0.230 | 0.151 |
| ***NTD-2*** | 8.10 | 5.77 | 0.108 | 0.159 |
| ***NTD-3*** | 2.55 | 2.17 | - | 0.062 |
| ***NTD-4*** | - | 5.16 | - | 0.124 |
| ***NTD-5*** | 5.65 | 3.17 | 0.205 | 0.087 |
| ***NTD-6*** | - | 4.69 | 0.116 | 0.092 |
| ***NTD-7*** | - | 2.98 | - | 0.156 |
| ***NTD-8*** | 2.50 | 1.79 | 0.155 | 0.108 |
| ***NTD-9*** | - | 5.44 | 0.200 | 0.165 |
| ***NTD-10*** | - | 4.92 | - | 0.052 |

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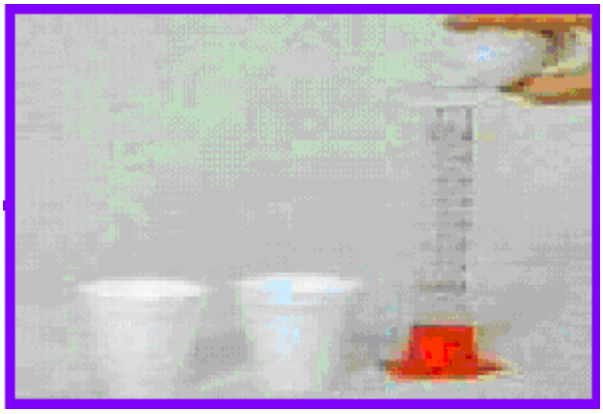


# *Section-IV*

# *Heat of Solutions*

## INTRODUCTION

The extensive information on the thermodynamic properties of organic compounds is needed not only their use in many industrial processes but also for the advancement of theoretical developments through an understanding of the intermolecular forces-solution structure-property relationship. Solubility data is an important information in drug discovery, drug formulation and crystallization-based separation investigations. In modeling the dependence of protonation and complex formation constants on medium using different approaches, it is often necessary to know the activity coefficients of neutral species, but data for nonelectrolytes are not so readily found as those for electrolytes[1].

The dissolution of a solute in a solvent is accompanied by the heat change. If the heat is absorbed, i.e., the solution is cooler, the enthalpy change ($\Delta H$) would be positive. If the heat is evolved, solution is warmer and so ($\Delta H$) would be negative. Thus, the heat of solution is defined as the change in enthalpy, when one mole of substance is dissolved in specified quantity of solvent at a given temperature.

The molar heat of solution and melting temperature of a substance can be determined from the solubility measurements at different temperatures[2]. The heat of solution for many organic and inorganic compounds, complexes, polymers etc. have also been reported [3-11]. The thermodynamic properties of several electrolytes in different solvents have been studied by many workers[12-15]. Regosz and Fini et al. studied the heat of solution of benzodiazepine derivetives[16,17]. Further, the heat of solutions of some heterocyclic compounds have also been reported[18-20]. In our laboratory, heat of solution of some organic compounds has also been determined[21, 22].

In the present work, solubility and heat of solutions for benzodiazepine and thiadiazepine derivatives was determined at different temperatures (308.15-328.15K) in dimethylformamide (DMF) and tetrahydrofuran (THF). Using these data, Gibb's free energy and entropy of different solutions have also been evaluated.

## EXPERIMENTAL

The heat of solution of benzodiazepines and thiadiazepines have been studied in DMF and THF. These solvents were purified and fractionally distilled prior to use by the method reported in the literature [23].

The saturated solution of each compound was prepared in DMF and THF at a desired temperature. A portion of this solution was filtered. From the filtrate, a known volume (say 10 ml) was transferred in a preweighted beaker. The weight of beaker along with solution was taken and the solvent was evaporated to dryness at room temperature until a constant weight is obtained. All the masses were taken using an electronic balance (Mettler Toledo AB204-S, Switzerland) with an uncertainty of ± 0.0001 g. This gives the weight of solute present in the known volume of solution. Three replicate measurements were carried out at a particular temperature and average value of weight was taken for calculation. The experiment was repeated at other temperatures also. Subtraction of weight of solute from the weight of solution gives the weight of solvent in a known volume of saturated solution.

## RESULTS AND DISCUSSION

The solubility *(x)* of synthesized compounds (NBN and NTD series) in the studied solvents are given in Tables 3.4.1 – 3.4.4. It is evident from the Tables that the solubility of both the series increases with temperature in both the solvents. Comparison of solubility of these compounds in DMF and THF shows that overall solubility is greater in DMF than that in THF. The dielectric constant and dipole moment of DMF (36.71, 3.86) are greater than that of THF (7.58, 1.75). Thus, these properties of solvent play an important role on the solubility, as expected.

The temperature dependence solubility in solvents is described by the modified Apelblat equation [24,25]

$$\ln x = A + B(T/K) \qquad \text{..... (3.4.1)}$$

where *x* is the mass fraction solubility of compounds; *T* is the absolute temperature and *A*, and *B* are the coefficients. The values of these coefficients are given in Tables 3.4.5 and 3.4.6. Using these values of *A* and *B*, calculated solubilities $x_c$ were evaluated and are also reported in Tables 3.4.1-3.4.4.

The relative deviations *(RD)* between the experimental and calculated values of solubilities are also calculated by equation 3.4.2 and are given in Tables 3.4.1 to 3.4.4.

$$\textit{Relative Deviation} = \left( \frac{x - x_c}{x} \right) \qquad \text{..... (3.4.2)}$$

Further, relative average deviations *(ARD)* and root-mean-square deviations *(rmsd)* were also calculated by equations 3.4.3 and 3.4.4 and are listed in Table 3.4.5 and 3.4.6.

$$ARD = \frac{1}{N} \sum_{i}^{N} \frac{x_i - x_c}{x_i} \qquad \text{..... (3.4.3)}$$

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

where *N* is the number of experimental points.

**Table 3.4.1: The experimental solubility *(x),* calculated solubility *($x_c$)* and relative deviation *(RD)* of NBN series in DMF at different temperatures.**

| ***Temp. K*** | ***x. $10^3$*** | ***$x_c.10^3$*** | ***100 RD*** | ***x. $10^3$*** | ***$x_c.10^3$*** | ***100 RD*** |
|---|---|---|---|---|---|---|
| | ***NBN-1*** | | | ***NBN-6*** | | |
| ***308.15*** | 8.2052 | 8.1170 | -0.2429 | 8.6549 | 8.6407 | -0.0525 |
| ***318.15*** | 8.3482 | 8.2479 | -0.2705 | 8.8099 | 8.7976 | -0.0475 |
| ***328.15*** | 8.4785 | 8.3809 | -0.2608 | 8.9745 | 8.9574 | -0.0587 |
| | ***NBN-2*** | | | ***NBN-7*** | | |
| ***308.15*** | 5.7425 | 5.7254 | -0.0757 | 14.0619 | 14.2602 | 0.3104 |
| ***318.15*** | 5.9393 | 5.8939 | -0.1678 | 14.1964 | 14.4035 | 0.3225 |
| ***328.15*** | 6.0876 | 6.0673 | -0.0835 | 14.3336 | 14.5482 | 0.3320 |
| | ***NBN-3*** | | | ***NBN-8*** | | |
| ***308.15*** | 10.2983 | 10.1730 | -0.2856 | 8.9506 | 9.0020 | 0.1033 |
| ***318.15*** | 10.3210 | 10.2138 | -0.2463 | 9.1125 | 9.1471 | 0.0627 |
| ***328.15*** | 10.3894 | 10.2547 | -0.3036 | 9.2392 | 9.2946 | 0.1098 |
| | ***NBN-4*** | | | ***NBN-9*** | | |
| ***308.15*** | 6.3061 | 6.2805 | -0.0983 | 11.3231 | 11.3394 | 0.0141 |
| ***318.15*** | 6.4330 | 6.4394 | 0.0017 | 11.4135 | 11.4305 | 0.0151 |
| ***328.15*** | 6.6308 | 6.6024 | -0.1035 | 11.5053 | 11.5222 | 0.0150 |
| | ***NBN-5*** | | | ***NBN-10*** | | |
| ***308.15*** | 9.4340 | 9.4778 | 0.0812 | 7.1074 | 7.0427 | -0.2031 |
| ***318.15*** | 9.5564 | 9.6402 | 0.1699 | 7.2230 | 7.1562 | -0.2065 |
| ***328.15*** | 9.7571 | 9.8055 | 0.0889 | 7.3433 | 7.2716 | -0.2177 |

**Table 3.4.2: The experimental solubility *(x)*, calculated solubility *($x_c$)* and relative deviation *(RD)* of NBN series in THF at different temperatures.**

| *Temp. K* | *x. $10^3$* | *$x_c.10^3$* | *100 RD* | *x. $10^3$* | *$x_c.10^3$* | *100 RD* |
|---|---|---|---|---|---|---|
| | ***NBN-1*** | | | ***NBN-6*** | | |
| ***308.15*** | 7.1791 | 7.2212 | 0.1005 | 8.3079 | 8.2570 | -0.1463 |
| ***318.15*** | 7.4480 | 7.4560 | 0.0038 | 8.4631 | 8.4491 | -0.0528 |
| ***328.15*** | 7.6520 | 7.6984 | 0.1062 | 8.7021 | 8.6457 | -0.1552 |
| | ***NBN-2*** | | | ***NBN-7*** | | |
| ***308.15*** | 5.1797 | 5.1851 | 0.0020 | 12.5896 | 12.4064 | -0.3532 |
| ***318.15*** | 5.3290 | 5.3591 | 0.0894 | 12.7214 | 12.5436 | -0.3406 |
| ***328.15*** | 5.5325 | 5.5388 | 0.0040 | 12.8822 | 12.6823 | -0.3775 |
| | ***NBN-3*** | | | ***NBN-8*** | | |
| ***308.15*** | 9.0696 | 8.9647 | -0.2654 | 8.0121 | 7.9309 | -0.2292 |
| ***318.15*** | 9.2280 | 9.1366 | -0.2305 | 8.1516 | 8.0588 | -0.2562 |
| ***328.15*** | 9.4281 | 9.3118 | -0.2841 | 8.2788 | 7.9309 | -0.2461 |
| | ***NBN-4*** | | | ***NBN-9*** | | |
| ***308.15*** | 5.6661 | 5.6229 | -0.1658 | 9.8062 | 9.6901 | -0.2758 |
| ***318.15*** | 5.8304 | 5.7999 | -0.1200 | 9.9349 | 9.8267 | -0.2557 |
| ***328.15*** | 6.0315 | 5.9825 | -0.1777 | 10.0927 | 9.9652 | -0.2949 |
| | ***NBN-5*** | | | ***NBN-10*** | | |
| ***308.15*** | 8.4438 | 8.4557 | 0.0115 | 6.1796 | 6.2506 | 0.2066 |
| ***318.15*** | 8.6304 | 8.6438 | 0.0146 | 6.3121 | 6.3768 | 0.1834 |
| ***328.15*** | 8.8233 | 8.8360 | 0.0124 | 6.4276 | 6.5056 | 0.2210 |

**Table 3.4.3: The experimental solubility *(x),* calculated solubility *($x_c$)* and relative deviation *(RD)*of NTD series in DMF at different temperatures.**

| *Temp. K* | *x. $10^3$* | *$x_c.10^3$* | *100 RD* | *x. $10^3$* | *$x_c.10^3$* | *100 RD* |
|---|---|---|---|---|---|---|
| | ***NTD-1*** | | | ***NTD-6*** | | |
| ***308.15*** | 14.2460 | 14.7085 | -0.3133 | 12.7107 | 12.8762 | 0.2784 |
| ***318.15*** | 14.4646 | 14.9158 | -0.3641 | 12.9237 | 13.0838 | 0.2653 |
| ***328.15*** | 14.6932 | 15.1261 | -0.3368 | 13.1139 | 13.2948 | 0.2982 |
| | ***NTD-2*** | | | ***NTD-7*** | | |
| ***308.15*** | 14.8923 | 14.7085 | -0.3133 | 18.1494 | 18.0536 | -0.1501 |
| ***318.15*** | 15.1337 | 14.9158 | -0.3641 | 18.4367 | 18.2532 | -0.2685 |
| ***328.15*** | 15.3288 | 15.1261 | -0.3368 | 18.5622 | 18.4551 | -0.1632 |
| | ***NTD-3*** | | | ***NTD-8*** | | |
| ***308.15*** | 10.1179 | 10.2211 | 0.2028 | 7.8366 | 7.8734 | 0.0785 |
| ***318.15*** | 10.3674 | 10.6169 | 0.5025 | 8.0482 | 8.0646 | 0.0243 |
| ***328.15*** | 10.9072 | 11.0280 | 0.2258 | 8.2204 | 8.2605 | 0.0832 |
| | ***NTD-4*** | | | ***NTD-9*** | | |
| ***308.15*** | 15.5787 | 15.5586 | -0.0490 | 19.2778 | 19.2672 | -0.0321 |
| ***318.15*** | 15.8460 | 15.7779 | -0.1219 | 19.4483 | 19.4413 | -0.0272 |
| ***328.15*** | 16.0242 | 16.0003 | -0.0541 | 19.6295 | 19.6170 | -0.0341 |
| | ***NTD-5*** | | | ***NTD-10*** | | |
| ***308.15*** | 10.0550 | 10.0599 | -0.0074 | 4.5013 | 4.4876 | -0.0744 |
| ***318.15*** | 10.3322 | 10.3145 | -0.0555 | 4.6498 | 4.6382 | -0.0646 |
| ***328.15*** | 10.5713 | 10.5756 | -0.0090 | 4.8096 | 4.7937 | -0.0800 |

**Table 3.4.4: The experimental solubility *(x)*, calculated solubility *($x_c$)* and relative deviation *(RD)* of NTD series in THF at different temperatures.**

| *Temp. K* | *x. $10^3$* | *$x_c.10^3$* | *100 RD* | *x. $10^3$* | *$x_c.10^3$* | *100 RD* |
|---|---|---|---|---|---|---|
| | ***NTD-1*** | | | ***NTD-6*** | | |
| ***308.15*** | 12.1214 | 12.2328 | 0.1893 | 11.0702 | 11.0063 | -0.1466 |
| ***318.15*** | 12.3680 | 12.4549 | 0.1415 | 11.3257 | 11.2286 | -0.2102 |
| ***328.15*** | 12.5595 | 12.6811 | 0.2021 | 11.5276 | 11.4554 | -0.1588 |
| | ***NTD-2*** | | | ***NTD-7*** | | |
| ***308.15*** | 12.4871 | 12.4061 | -0.1665 | 15.2052 | 15.3301 | 0.1775 |
| ***318.15*** | 12.7620 | 12.6061 | -0.2998 | 15.4321 | 15.5462 | 0.1586 |
| ***328.15*** | 12.9007 | 12.8094 | -0.1813 | 15.6297 | 15.7653 | 0.1897 |
| | ***NTD-3*** | | | ***NTD-8*** | | |
| ***308.15*** | 8.0517 | 7.9813 | -0.2001 | 6.8535 | 6.9609 | 0.2942 |
| ***318.15*** | 8.2913 | 8.1833 | -0.2917 | 7.0118 | 7.1300 | 0.3191 |
| ***328.15*** | 8.4705 | 8.3904 | -0.2172 | 7.1835 | 7.3031 | 0.3166 |
| | ***NTD-4*** | | | ***NTD-9*** | | |
| ***308.15*** | 13.4135 | 13.4414 | 0.0302 | 15.4641 | 15.6520 | 0.2717 |
| ***318.15*** | 13.5878 | 13.6309 | 0.0557 | 15.7087 | 15.8568 | 0.2078 |
| ***328.15*** | 13.7929 | 13.8230 | 0.0329 | 15.8608 | 16.0642 | 0.2896 |
| | ***NTD-5*** | | | ***NTD-10*** | | |
| ***308.15*** | 7.6167 | 7.5775 | -0.1238 | 4.0451 | 4.0408 | -0.0374 |
| ***318.15*** | 7.8390 | 7.8082 | -0.0991 | 4.2011 | 4.2057 | 0.0020 |
| ***328.15*** | 8.0906 | 8.0460 | -0.1329 | 4.3824 | 4.3773 | -0.0395 |

**Table 3.4.5: Coefficient *A* and *B* of equation 3.4.1, Relative Average Deviation *(ARD)*, and root Mean Square Deviation *(rmsd)* of NBN series in DMF and THF.**

| *Compounds* | *A* | *B* | $10^9$ *rmsd* | *100 ARD* |
|---|---|---|---|---|
| | | ***DMF*** | | |
| ***NBN-1*** | -5.31 | 0.0016 | 18.21 | -0.2581 |
| ***NBN-2*** | -6.05 | 0.0029 | 1.82 | -0.1090 |
| ***NBN-3*** | -4.71 | 0.0004 | 30.24 | -0.2785 |
| ***NBN-4*** | -5.84 | 0.0025 | 1.14 | -0.0667 |
| ***NBN-5*** | -5.18 | 0.0017 | 7.75 | 0.1133 |
| ***NBN-6*** | -5.31 | 0.0018 | 0.45 | -0.0529 |
| ***NBN-7*** | -4.56 | 0.0010 | 85.51 | 0.3216 |
| ***NBN-8*** | -5.20 | 0.0016 | 4.62 | 0.0919 |
| ***NBN-9*** | -4.73 | 0.0008 | 0.52 | 0.0147 |
| ***NBN-10*** | -5.45 | 0.0016 | 9.62 | -0.2091 |
| | | ***THF*** | | |
| ***NBN-1*** | -5.92 | 0.0032 | 2.62 | 0.0701 |
| ***NBN-2*** | -6.28 | 0.0033 | 0.63 | 0.0318 |
| ***NBN-3*** | -5.31 | 0.0019 | 21.92 | -0.2600 |
| ***NBN-4*** | -6.14 | 0.0031 | 3.45 | -0.1545 |
| ***NBN-5*** | -5.45 | 0.0022 | 0.37 | 0.0128 |
| ***NBN-6*** | -5.51 | 0.0023 | 3.85 | -0.1181 |
| ***NBN-7*** | -4.73 | 0.0011 | 70.21 | -0.3571 |
| ***NBN-8*** | -5.33 | 0.0016 | 15.51 | -0.2438 |
| ***NBN-9*** | -5.06 | 0.0014 | 27.30 | -0.2754 |
| ***NBN-10*** | -5.70 | 0.002 | 10.21 | 0.2037 |

**Table 3.4.6: Coefficient *A* and *B* of equation 3.4.1, Relative Average Deviation *(ARD)*, and root Mean Square Deviation *(rmsd)* of NTD series in DMF and THF.**

| *Compounds* | *A* | *B* | $10^9$ *rmsd* | *100 AAD* |
|---|---|---|---|---|
| | | ***DMF*** | | |
| ***NTD-1*** | -4.73 | 0.0015 | 77.82 | -0.3417 |
| ***NTD -2*** | -4.65 | 0.0014 | 81.61 | -0.3381 |
| ***NTD -3*** | -5.76 | 0.0038 | 58.32 | 0.3104 |
| ***NTD -4*** | -4.60 | 0.0014 | 3.74 | -0.0750 |
| ***NTD -5*** | -5.37 | 0.0025 | 0.24 | -0.0240 |
| ***NTD -6*** | -4.85 | 0.0016 | 57.12 | 0.2806 |
| ***NTD -7*** | -4.35 | 0.0011 | 36.32 | -0.1939 |
| ***NTD -8*** | -5.58 | 0.0024 | 2.21 | 0.0620 |
| ***NTD -9*** | -4.23 | 0.0009 | 0.25 | -0.0311 |
| ***NTD -10*** | -6.42 | 0.0033 | 0.47 | -0.0730 |
| | | ***THF*** | | |
| ***NTD -1*** | -4.96 | 0.0018 | 23.51 | 0.1776 |
| ***NTD -2*** | -4.88 | 0.0016 | 26.12 | -0.2159 |
| ***NTD -3*** | -5.60 | 0.0025 | 15.33 | -0.2363 |
| ***NTD -4*** | -4.74 | 0.0014 | 2.31 | 0.0396 |
| ***NTD -5*** | -5.81 | 0.0030 | 2.92 | -0.1186 |
| ***NTD -6*** | -5.13 | 0.0020 | 12.44 | -0.1719 |
| ***NTD -7*** | -4.61 | 0.0014 | 31.32 | 0.1753 |
| ***NTD -8*** | -5.71 | 0.0024 | 26.52 | 0.3099 |
| ***NTD -9*** | -4.56 | 0.0013 | 65.71 | 0.2564 |
| ***NTD -10*** | -6.74 | 0.0040 | 0.04 | -0.0250 |

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

$$T_{hm} = \frac{n}{\sum_{i}^{n}\left(1/T\right)} \qquad \text{..... (3.4.5)}$$

where *n* is the number of temperatures studied and *T* is absolute temperature of the experiment. In the present case, the $T_{hm}$ value obtained is 318 K.

So, the modified van't Hoff equation is[27,28].

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

where $\Delta H_s$ is the heat of solution and *R* is the gas constant.

Figures 3.4.1 and 3.4.2 show the van't Hoff plots for NBN-1 (benzodiazepine) and NTD-1 (thiadiazepine) respectively, in DMF and THF solutions. From these linear plots, $\Delta H_s$ values were calculated from the slope of straight line. From the intercept of these plots $\Delta G$ values were evaluated by the equation.[27]

$$\Delta G = -RT_{hm}.\ intercept \qquad \text{..... (3.4.7)}$$

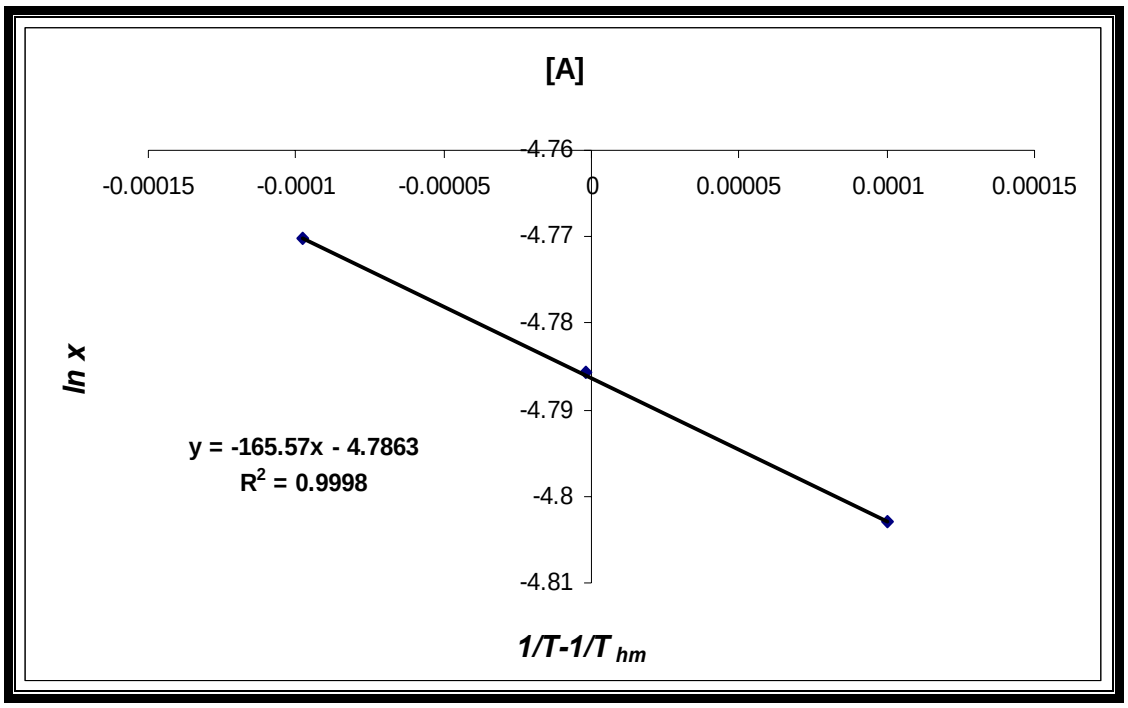
Using these evaluated $\Delta H_s$ and $\Delta G$ values, the entropies of solutions $\Delta S$ were obtained from equation 3.4.8.

$$\Delta S = \frac{\Delta H_s - \Delta G}{T_{hm}} \qquad \text{..... (3.4.8)}$$

All these thermodynamic parameters are given in Tables 3.4.7 and 3.4.8.

It is evident from tables that for all the compounds $\Delta H_s$ and $\Delta G$ values are positive whereas $\Delta S$ values are negative. When stronger bonds are broken and weaker bonds are formed, energy is consumed and so, $\Delta H_s$ becomes positive[29]. This indicates endothermic dissolution of compounds

**Figure 3.4.1: van't Hoff plots for for NBN-1 in [A] DMF and [B] THF.**



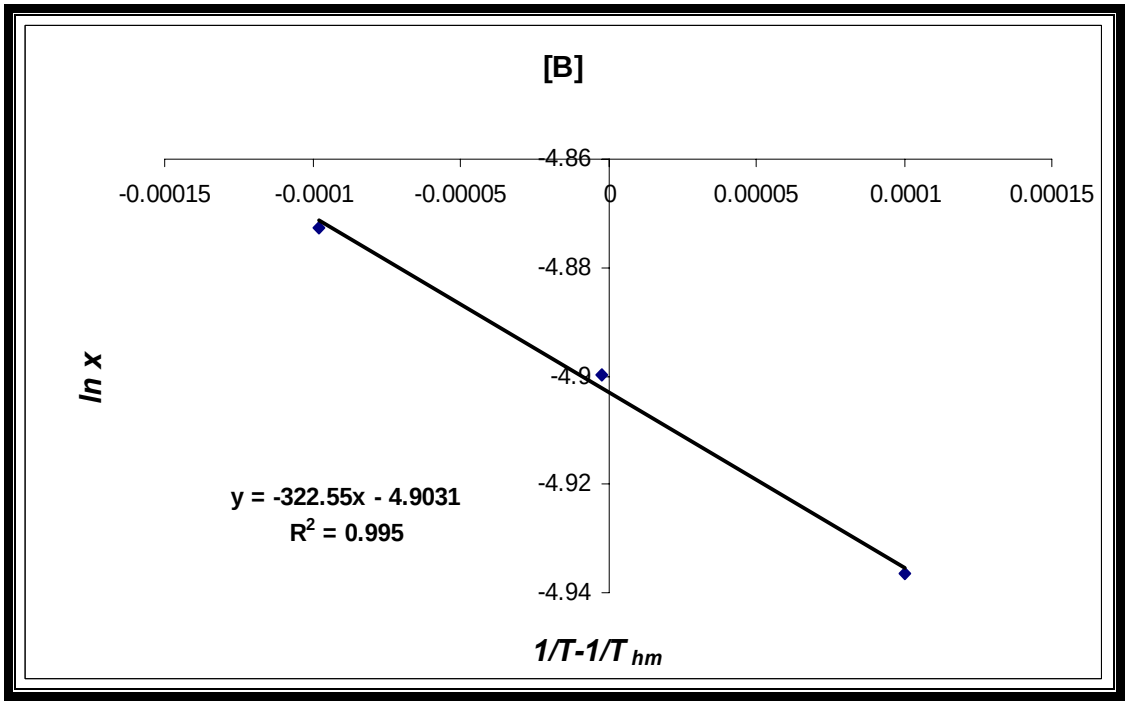
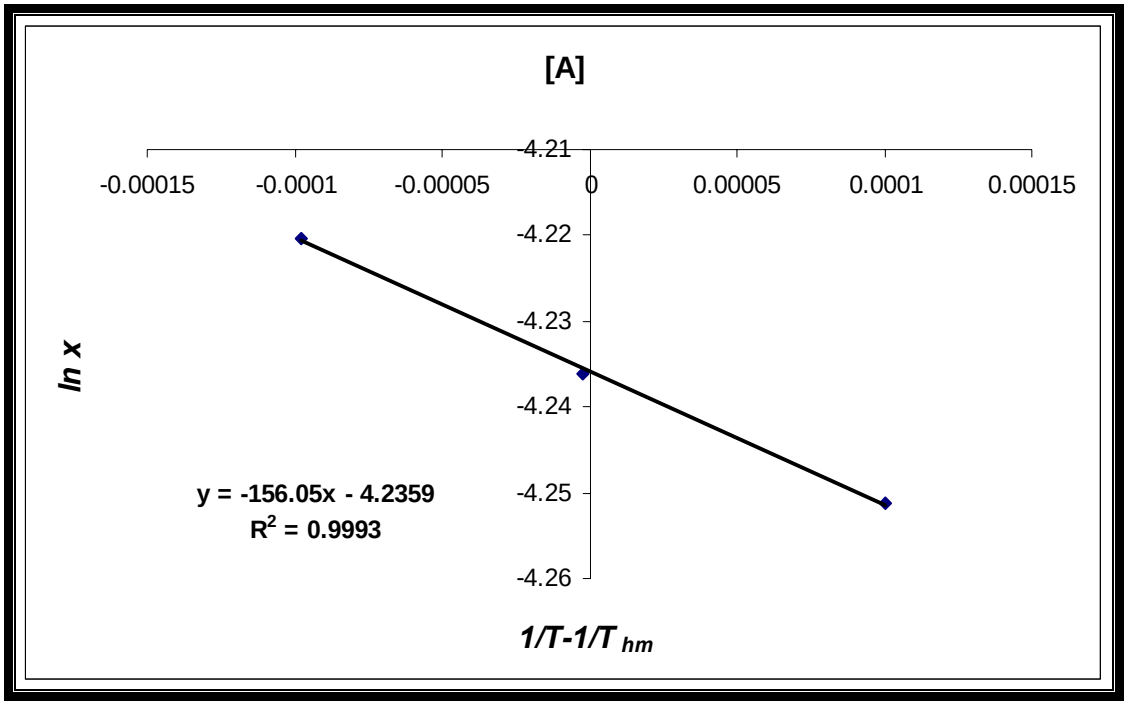



**Figure 3.4.2: van't Hoff plots for for NTD-1 in [A] DMF and [B] THF.**



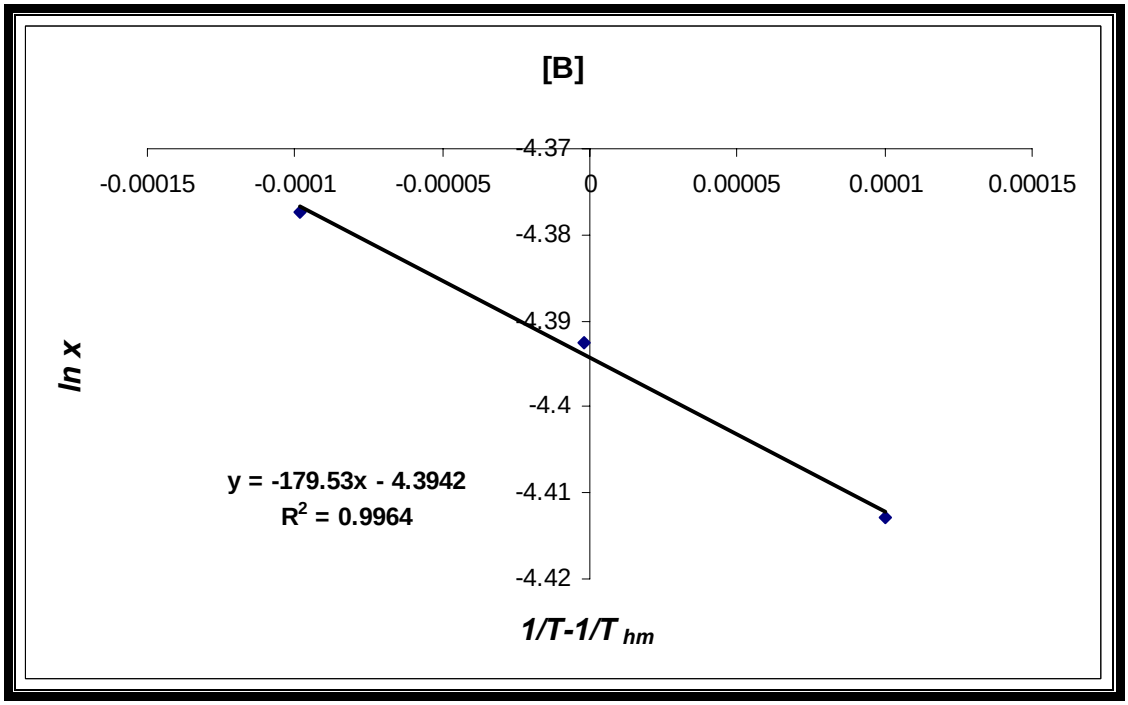



**Table 3.4.7: The thermodynamic function of NBN series in DMF and THF at 318 K *($T_{hm}$).***

| Compound code | $\Delta H_s$ cal.mol$^{-1}$ | $\Delta G$ kcal.mol$^{-1}$ | $\Delta S$ cal.mol$^{-1}$.K$^{-1}$ | $\Delta H_s$ cal.mol$^{-1}$ | $\Delta G$ kcal.mol$^{-1}$ | $\Delta S$ cal.mol$^{-1}$.K$^{-1}$ |
|---|---|---|---|---|---|---|
| | DMF | | | THF | | |
| NBN-1 | 328.98 | 3.0243 | -8.4759 | 640.91 | 3.0975 | -7.7291 |
| NBN-2 | 586.32 | 3.2406 | -8.3499 | 660.18 | 3.3091 | -8.3152 |
| NBN-3 | 87.82 | 2.8913 | -8.8070 | 388.50 | 2.9620 | -8.0838 |
| NBN-4 | 502.69 | 3.1901 | -8.4353 | 626.48 | 3.2523 | -8.2462 |
| NBN-5 | 363.78 | 2.9913 | -8.2569 | 441.01 | 3.0043 | -8.0554 |
| NBN-6 | 192.03 | 2.6897 | -7.8499 | 464.06 | 3.0167 | -8.0125 |
| NBN-7 | 318.69 | 2.9700 | -8.3365 | 230.29 | 2.7591 | -7.9454 |
| NBN-8 | 160.11 | 2.8276 | -8.3839 | 328.59 | 3.0404 | -8.5245 |
| NBN-9 | 336.97 | 2.9399 | -8.1724 | 288.63 | 2.9154 | -8.2526 |
| NBN-10 | 327.51 | 3.1169 | -8.7661 | 395.11 | 3.2021 | -8.8246 |

**Table 3.4.8: The thermodynamic function of NTD series in DMF and THF at 318 K *($T_{hm}$).***

| Compound code | $\Delta H_s$ cal.mol$^{-1}$ | $\Delta G$ kcal.mol$^{-1}$ | $\Delta S$ cal.mol$^{-1}$.K$^{-1}$ | $\Delta H_s$ cal.mol$^{-1}$ | $\Delta G$ kcal.mol$^{-1}$ | $\Delta S$ cal.mol$^{-1}$.K$^{-1}$ |
|---|---|---|---|---|---|---|
| | DMF | | | THF | | |
| NTD-1 | 310.07 | 2.6779 | -7.4410 | 356.73 | 2.7769 | -7.6106 |
| NTD-2 | 290.16 | 2.6493 | -7.4175 | 328.05 | 2.7570 | -7.6445 |
| NTD-3 | 750.87 | 2.8884 | -6.6905 | 509.59 | 3.0297 | -7.9274 |
| NTD-4 | 283.47 | 2.6202 | -7.3497 | 279.63 | 2.7174 | -7.6595 |
| NTD-5 | 502.77 | 2.8906 | -7.5080 | 605.28 | 3.0651 | -7.7272 |
| NTD-6 | 313.53 | 2.7491 | -7.6564 | 406.70 | 2.8325 | -7.6286 |
| NTD-7 | 226.50 | 2.5245 | -7.2311 | 276.49 | 2.6369 | -7.4206 |
| NTD-8 | 480.24 | 3.0485 | -8.0764 | 471.69 | 3.1356 | -8.3705 |
| NTD-9 | 181.29 | 2.4907 | -7.2580 | 254.71 | 2.6257 | -7.4577 |
| NTD-10 | 664.45 | 3.3953 | -8.5803 | 802.99 | 3.4595 | -8.3430 |

where the enthalpy term contributes to an unfavorable positive value of $\Delta G$[29]. Thus, positive values of $\Delta G$ indicates that the dissolution process is not spontaneous[29,30].

The negative value of entropy indicates less randomness in solutions[29].

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# Section-V

# Thermal Properties

## INTRODUCTION

Studies on thermal properties of substances are of great importance from both scientific and practical of view. Scientific and technological achievements together with demands based on industrial requirement have permitted the development of various types of materials that can withstand at much higher temperatures and more corrosive environments.

These thermal properties can be studied by various thermal techniques which are among the most powerful experimental tools developed during the last century. These techniques are able to characterize a wide range of materials and material properties. In these techniques, the change in properties of material are followed as a function of temperature when it is heated at constant predetermined rate under specified ambient atmospheric conditions.

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

In the present study, thermal analysis is done by DSC and TGA techniques.

DSC is a versatile thermal technique used to provide quantitative and qualitative information about physical and chemical changes involving endothermic or exothermic processes or heat capacity changes. It also provides useful information about crystallinity, stability of crystallites, glass transition temperature[1], cross-linking and heat of polymerization etc.

In TGA, the mass of sample is recorded as a function of temperature or time, when it is subjected to a programmed temperature change in a specified atmosphere. The plot of mass change versus temperature is known as thermogram or TG curve. TG curves are characteristic for a given compound because of unique sequence of physicochemical reactions which occur over definite temperature ranges and at rates that are a function of molecular structure. The changes in weight are due to various physical and chemical changes which lead to the evolution of volatile products or the formation of heavier reaction products[2].

Literature survey shows that thermal analysis of various types of compounds such as drugs[3-6], polymers[7-10], catalyst[11-12], nuclear fuel[13], pharma materials[14-18], dyes[19-20], fertilizers[21], inorganic[22-24] and organic[25-27] compounds have been reported. Recently, a number of investigators[28-37]have studied the thermal properties of various materials. However, the little works have done on the thermal properties of benzodiazepine derivatives[38-42].

In the present study, thermal properties of some new synthesized benzodiazepines have been studied by DSC and TGA techniques.

Using thermograms, various kinetic parameters have also been evaluated.

## THEORY

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

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

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

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

The constant *K* is assumed to have the Arrhenius form:

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

*C* can also be defined as:

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

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

Equation (3.5.3) can be written as:

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

$W/W_0$ is known as residual weight fraction.

Thus, the rate of conversion is,

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

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

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

where *n* is the order of the reaction.

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

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

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

where $A$ is the frequency factor, $\beta$ 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 [43] and Anderson-Freeman Method [44]:**

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

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

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

Anderson and Freeman then derived the following equation by using equation (3.5.8):

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

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

**2. Sharp-Wentworth method [45]:**

To analyse the TGA data for first order kinetics (n=1), Sharp and Wentworth gave the relation:

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

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

**3. Chatterjee Method[46]:**

Based on the weight units, the following relation was developed by Chatterjee:

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

where $W_1$ and $W_2$ are the sample weights.

**4. Horowitz and Metzger method[47] :**

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

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

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

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

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

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

## EXPERIMENTAL

Thermo gravimetric analysis (TGA) and Differential Scanning Calorimetry (DSC) measurements were made on the instrument “Pyris-1, Perkin Elmer Thermal Analysis” at the heating rate of 10°C/min in nitrogen atmosphere for all the benzodiazepines.

## RESULTS AND DISCUSSION

The TGA thermo grams of NBN-9 and NBN-10 are given in Figure 3.5.1. Various thermal properties such as initial decomposition temperature (IDT), the decomposition temperature range and the maximum degradation along with the percentage weight loss and Exo / Endo transitions are reported in Table 3.5.1.

For some compounds, degradation is single step process whereas for others, it is multistep process. For NBN-3, NBN-4 and NBN-9, multi step degradation takes place.

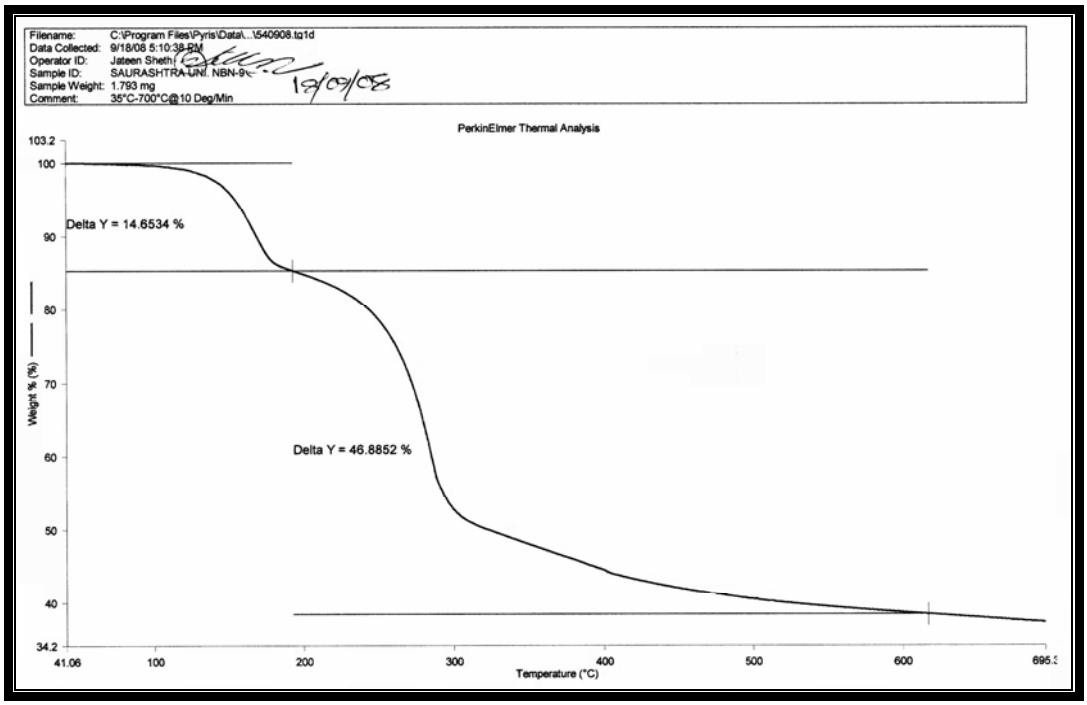
Table 3.5.1 shows that NBN-10 is unstable whereas NBN-8 is most stable followed by NBN-6. NBN-10 has no side chain or no substitution. While in other compounds, various substituent groups are attached. This suggests that absence of substituent decreases the stability of the present studied compounds. When chloro group is present at para position (as in NBN-8), stability is highest which is followed by the presence of hydroxyl group at para position (as in NBN-6). The presence of other groups also shows significant stability.

Further, Table 3.5.1 shows DSC data along with the melting temperature determined by open capillary method. It is observed that the melting temperatures determined by the two methods are in good agreement. The heat of reaction is found to be maximum for NBN-3 and minimum for NBN-5. However, no correlation could be established between heat of reaction, kinetic parameters, melting temperature, thermal stability and substitution group

Various kinetic parameters, such as order of the degradation (*n*), energy of activation (*E*), frequency factor (*A*) and entropy change ($\Delta S^o$) have also been calculated from the thermograms for each step and are reported in Table 3.5.2.

It is evident from Tables 3.5.2 that order of reaction is quite different in different steps for different benzodiazepines. For single step degradation compound, order of reaction varies from 1.21 to 5.5, whereas for multi steps it varies from 1.6 to 14.

**Figure 3.5.1: The TGA graphs of NBN-9 and NBN-10.**



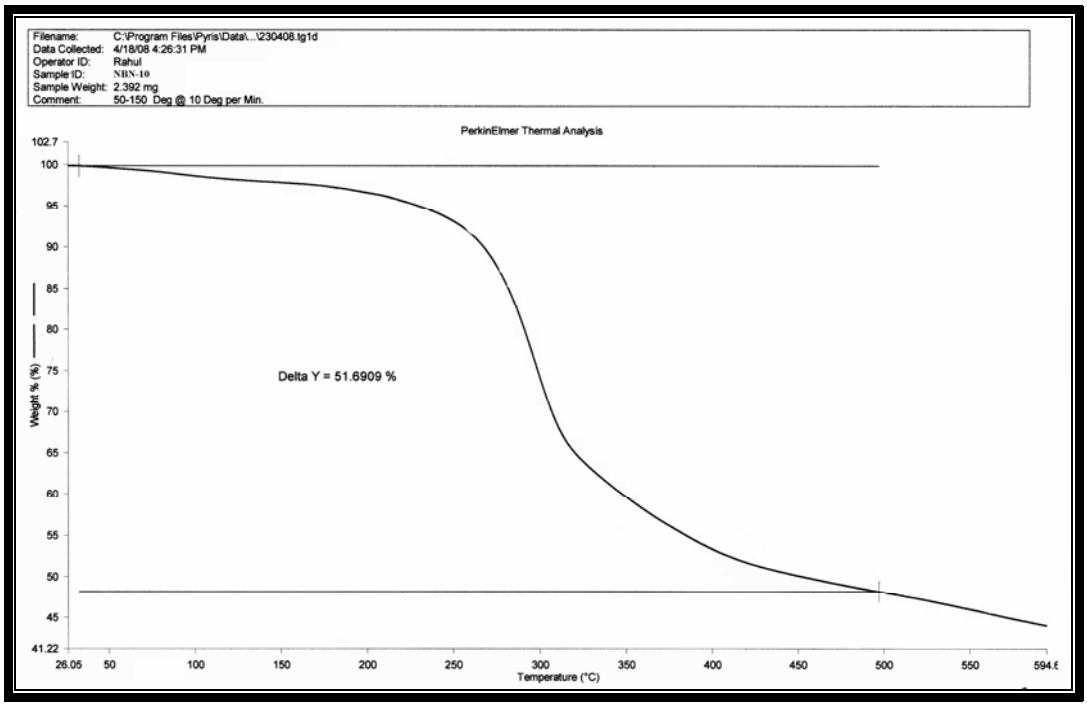
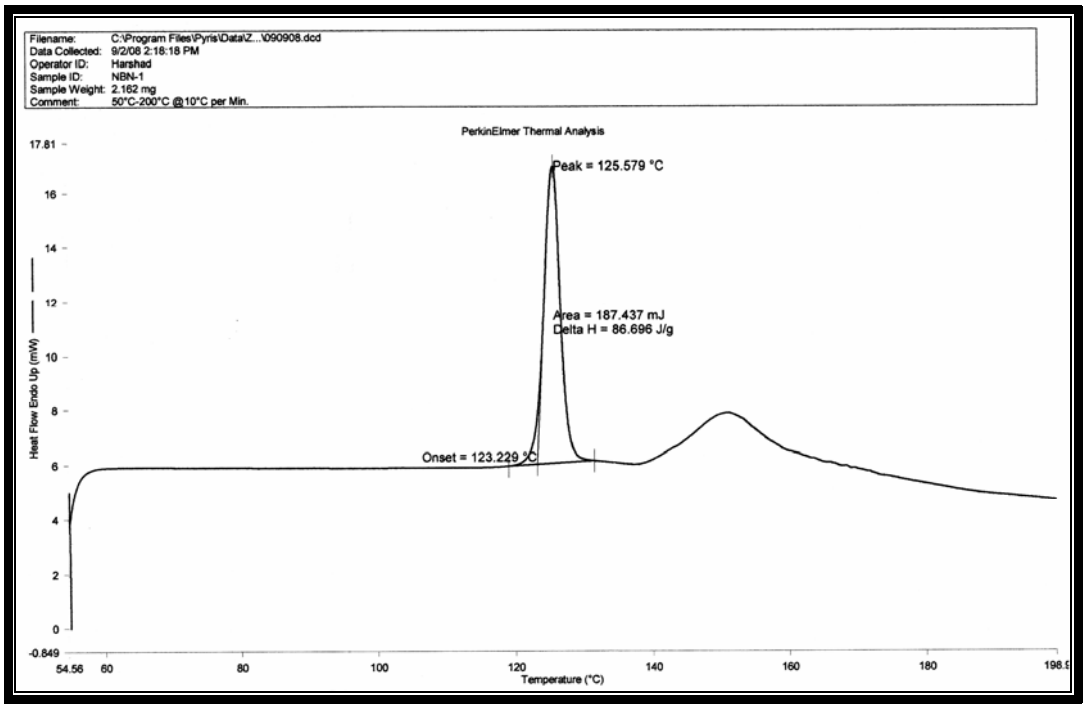



**Figure 3.5.2: The DSC graphs of NBN-1 and NBN-2.**



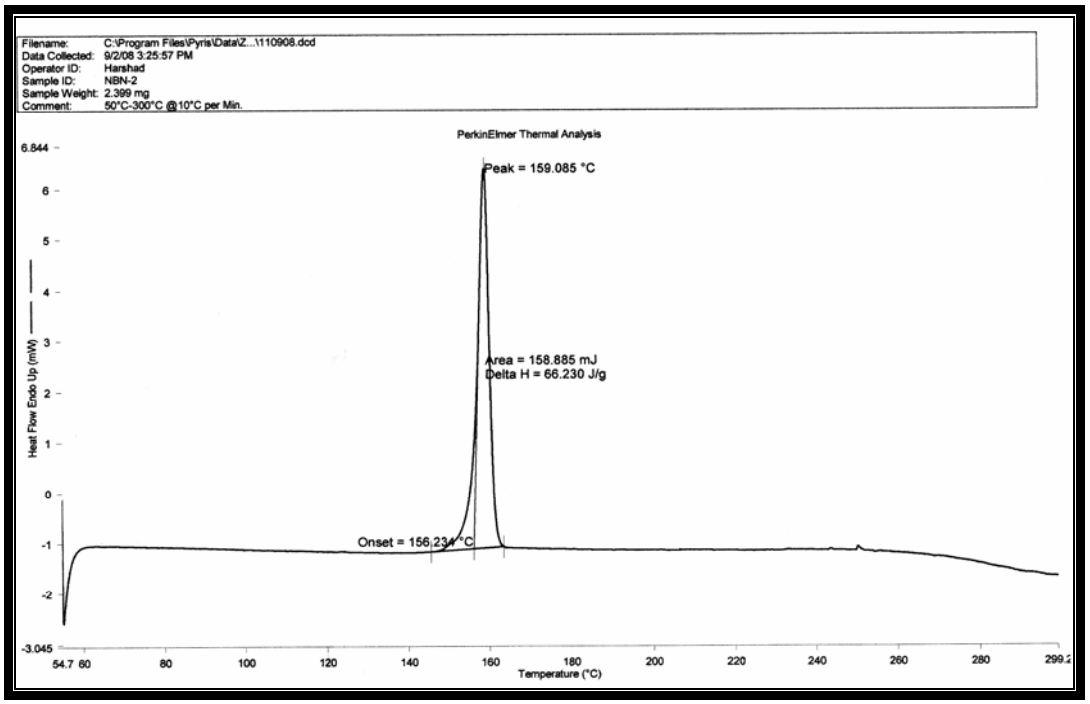



**Table 3.5.1: TGA/DSC data for synthesized NBN series.**

| ***Comp. Code*** | ***Amt. mg.*** | ***Initial Decomp. Temp. $^oC$*** | ***Decomp. range $^oC$*** | ***% Wt. loss*** | ***Residual Wt. Loss mg.*** | ***Transition*** | ***DSC $^0C$*** | ***Open capillary method $^0C$*** | ***$\Delta H$ $J.g^{-1}$*** |
|---|---|---|---|---|---|---|---|---|---|
| ***NBN-1*** | 4.547 | 140 | 140-450 | 41.11 | 1.8693 | Endo. | 125.58 | 128 | 86.70 |
| ***NBN-2*** | 4.687 | 150 | 150-450 | 37.20 | 1.7433 | Endo. | 159.09 | 160 | 66.23 |
| ***NBN-3*** | 10.895 | 185 | 185-728 | 98.00 | 10.6769 | Endo.<br>Exo. | 168.57<br>238.21 | 232 | 66.86<br>188.40 |
| ***NBN-4*** | 10.7415 | 181 | 181-705 | 94.00 | 10.0970 | Endo.<br>Endo.<br>Exo | 90.28<br>204.53<br>274.05 | 202 | 6.15<br>26.01<br>191.2 |
| ***NBN-5*** | 2.069 | 173 | 173-397 | 92.00 | 1.9035 | Endo. | 165.78 | 165 | 8.19 |
| ***NBN-6*** | 1.747 | 202 | 202-494 | 45.00 | 0.7862 | Endo. | 227.96 | 228 | 102.69 |
| ***NBN-7*** | 3.253 | 142 | 142-500 | 47.80 | 1.5549 | Endo.<br>Exo. | 167.73<br>223.11 | 166 | 65.21<br>165.18 |
| ***NBN-8*** | 3.023 | 277 | 277-561 | 51.00 | 1.5417 | Endo. | 239.95 | 232 | 70.80 |
| ***NBN-9*** | 1.793 | 158 | 158-426 | 57.50 | 1.0309 | Endo.<br>Endo. | 118.20<br>265.19 | 117 | 39.31<br>98.51 |
| ***NBN-10*** | 2.392 | 100 | 100-496 | 52.74 | 1.2615 | Endo. | 262.90 | 262 | 99.87 |

**Table 3.5.2: The kinetic parameters of benzodiazepine derivatives.**

| ***Comp. code*** | ***n*** | ***E*** ***kJ.mol$^{-1}$*** | ***A*** ***s$^{-1}$*** | ***$\Delta S$*** ***J.mol$^{-1}$.K$^{-1}$*** |
|---|---|---|---|---|
| ***NBN-1*** | 1.25 | 136.05 | 5.89 X $10^{11}$ | 128.13 |
| ***NBN-2*** | 4.63 | 223.76 | 7.53 X $10^{21}$ | 322.32 |
| ***NBN-3 1$^{nd}$ step*** | 9.1 | 24.704 | 0.7855 | -102.17 |
| ***NBN-3 2$^{nd}$ step*** | 1.2 | 340.47 | 4.18 X $10^{18}$ | 255.33 |
| ***NBN-4 1$^{st}$ step*** | 14 | 339.49 | 2.65 X $10^{34}$ | 562.71 |
| ***NBN-4 2$^{nd}$ step*** | 6 | 45.73 | 87.44 | -62.07 |
| ***NBN-4 3$^{rd}$ step*** | 1.6 | 241.86 | 7.81 X $10^{12}$ | 145.62 |
| ***NBN-5*** | 1.79 | 556.87 | 9.87 X $10^{51}$ | 898.37 |
| ***NBN-6*** | 1.21 | 138.54 | 4.87 X $10^{9}$ | 86.71 |
| ***NBN-7*** | 2.68 | 450.03 | 2.81 X $10^{44}$ | 754.41 |
| ***NBN-8*** | 5.5 | 38.24 | 241.37 | -51.43 |
| ***NBN-9 1$^{st}$ step*** | 2 | 667.08 | 6.3 X $10^{105}$ | 1932.79 |
| ***NBN-9 2$^{nd}$ step*** | 6.1 | 94.99 | 1.92 X $10^{8}$ | 106.14 |
| ***NBN-10*** | 1.78 | 449.16 | 1.11 X $10^{41}$ | 688.63 |

For single step degradation compounds, energy of activation (*E*) is maximum for NBN-5 and minimum for NBN-8. The frequency factor (*A*) also varies in the same order. For multi step degradation compounds, In first and second steps, energy of activation is found to be maximum for NBN-9 and minimum for NBN-3. The frequency factor A follows the same order.

Further, change in entropy ($\Delta S^{0}$) for all these reactions were calculated by equation (3.5.14) and are reported in Table 3.3.2. These values are both positive and negative for different compounds. The positive values of $\Delta S^{0}$ indicate that the transition state is less ordered than the original compound whereas negative value of $\Delta S^{0}$ corresponds to an increase in the order of transition state than the reactants.

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# Section-VI

# Dissociation Constants

## INTRODUCTION

The term ionization constant means those constant, which are used to measure the strength of acid and bases. They are often known as dissociation constants.

The dissociation or ionization constant is determined by determining one of the species, at equilibrium. The activity or concentration of the others can be calculated from the amount of the acid or base initially introduced and the stoichiometry of the acid base equilibrium.

Literature survey shows that various methods are applicable to determine dissociation constant. Hansen and Hafliger have been determined dissociation constant of a weak acid using a dissolution rate method[1]. Kovach et al. have studied the dissociation constants of organic electrolytes using the Fuoss-Kraus method[2]. Uhrova et al.[3] reported separation methods (HPLC and CE) for the determination of dissociation constants. Various workers have been determined the dissociation constant by capillary electrophoresis[4], NMR methods[5], feedback-based flow ratiometry[6], spectrophotometric[7], interfacial Fourier transform infrared spectroscopy[8] methods. For very high or very low acid strengths, spectrophotometer method is considered to be an ideal method but this method is also more time consuming. It is applicable if at least one of the species at equilibrium absorbs characteristically in the ultraviolet or visible region and the relevant ionic species show absorption maxima at different wavelengths.

Potentiometry is mostly used for the determination of dissociation 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[9]. For this measurement, glass and calomel electrodes have been used and carbonate free potassium hydroxide is the best alkali to use as a titrant.

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

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

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

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.

Literature survey shows that many workers studied the dissociation constant of many complex substances[10-14] using different methods. Spectrophotometric determination of the dissociation constant of different systems have been reported by various workers[15-18]. Delahay and Vielstich studied the Kinetics of the dissociation of weak acids and bases by polarography and voltammetry technique[19]. The distribution coefficients and dissociation constants of a series of barbituric acid derivatives have been reported by Leyda et al.[20] Further, Dauphin and co-workers[21] reported the application of conductometry to the study of dissociation constants of 2-chromonecarboxylic acid and its sodium salt. Funasaki[22] reported the dissociation constants of acid-base indicators on the micellar surface of dodecyldimethylamine oxide. Levitt[23] 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[24-30] have been studied by various workers.

In the present work, the dissociation constant of all synthesized benzodiazepine (NBN series) and thiadiazepines (NTD series) are studied in dimethyl formamide and tetrahydrofuran at 298.15 K by Calvin Bjerrum *pH* titration technique.

## EXPERIMENTAL

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

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

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

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

A systronic *pH* meter (Model No. EQ 664) was used for the pH determination. The systronic glass electrode and a saturated calomel electrode were used as indicator and reference electrodes respectively. Before operation, the glass electrode was immersed in 0.1 M HCl for twenty minutes. Then, it was washed thoroughly with distilled water.

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/THF + 4.0 ml $NaNO_3$ (1.0 M).

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

Thus, total volumes ($V^0$) in each set = 40.0 ml and Solvent : water ratio 60:40 (v/v).

The above mentioned solutions were allowed to attain a constant temperature (298.15 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:

$$TK_j^{\ H} = \frac{\left[LH_j\right]}{\left\{\left[LH_{j-1}\right]\left[H\right]\right\}} \quad \text{... (3.6.1)}$$

$TK_j^H$ 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 $\beta_j^H$ is given by:

$$T\beta_j^H = \frac{\left[LH_j\right]}{\left[L\right]\left[H\right]^j} \quad \text{... (3.6.2)}$$

and it refers to the reaction:

$$L + JH \leftrightarrow LH_j$$

The stoichiometric proton-ligand stability constant is given by:

$$K_j^{\ H} = \frac{\left[LH_j\right]}{\left\{\left[LH_{j-1}\right]\left[H\right]\right\}} \quad \text{... (3.6.3)}$$

and

$$\beta_j^{\ H} = \frac{\left[LH_j\right]}{\left[L\right]\left[H\right]^j} \quad \text{... (3.6.4)}$$

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[31] 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] + 2$K_1^H$ $K_2^H$ $[H]^2$ + .....J$K_1^H$ $K_2^H$ [H] ... $K_j^H$ $[H]^j$} / {1 + $K_1^H$ [H] + $K_1^H$ $K_2^H$ $[H]^2$.....$K_1^H K_2^H$.....$K_j^H$ $[H]^j$ ... (3.6.5)

From equation (3.6.4), we can write

$$\bar{n}_H = \frac{\sum_{j=1}^{\eta} j\beta_j^H [H]^j}{\sum_{j=1}^{\eta} \beta_j^H [H]^j} \quad : \left(\beta_0^H = 1\right) \qquad \ldots (3.6.6)$$

Equation (3.6.6) 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[32] 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[33] 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:

$$-\log\left[H^{+}\right] = B + \log f + \log U_H^0 \qquad \text{... (3.6.7)}$$

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

Equation (3.6.7) can be written as:

$$1/anti\log B = [H^{+}]\, fU_H^0 \qquad \text{... (3.6.8)}$$

$$\therefore \left[H^{+}\right] = \frac{1}{\left[anti\log B\right]\left[fU_H^0\right]} \qquad \text{... (3.6.9)}$$

Substituting for $[H^+]$ in equation (3.6.5) we get,

$\bar{n}_H$ = $(K_1^H/f\,U^0_H)[1/\text{antilog B}] + ....+ ((JK_1^H\,K_2^H...K_J^H)/(f\,U^0_H)^J)[1/\text{antilogB}]^J$
$/(1+K_1^H/f\,U^0_H))[1/\text{antilog B}]+..+ ((K_1^HK_2^H...K_J^H)/(f\,U^0_H)J)[1/\text{antilogB}]$ ...(3.6.10)

$$K_j^H = fU_H^0.pK_j^H \qquad \text{... (3.6.11)}$$

$$\beta_j^H = fU_H^0.p\beta_j^H \qquad \text{... (3.6.12)}$$

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:

$$\log K_1 = \left(\bar{n}_H\right)_{0.5} \quad \ldots \text{ (3.6.13)}$$

$$\log K_2 = \left(\bar{n}_H\right)_{1.5} \quad \ldots\ldots \text{ (3.6.14)}$$

2. Mid point slope method:

For $H_2L$ type ligands:

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

or $$\log K_1 K_2 = 2pL_1 \quad \ldots \text{ (3.6.15)}$$

From the measured mid-point slope, $D$, the ratio $K_1/K_2$ can be calculated by eq. (3.6.16):

$$D = \frac{-4.606}{\left(2 + \sqrt{\left(K_1 / K_2\right)}\right)} \quad \ldots \text{ (3.6.16)}$$

The individual values of $K_1$ and $K_2$ were obtained by using $K_1/K_2$ values and relation (3.6.15).

## 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 NBN-1 and NTD-1 are shown in figures 3.6.1. and 3.6.2 respectively in different solvents.

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

$$\overline{n_H} = Y - \left\{\left(V''-V'\right)\left(N^0+E^0\right)\right\} \Big/ \left\{\left(V^0+V'\right)T_L^0\right\} \qquad \text{...(3.6.17)}$$

where *Y* is the number of displaceable protons per ligand molecule. For all the compounds, *Y* is taken as one. *V'* and *V"* are the volume of alkali required at the same *pH* for both acid and ligand titration curves respectively. $V^0$ is the initial volume of the test solution. $N^0$, $E^0$ and $T^0_L$ are the initial concentration of the alkali, acid and ligand respectively.

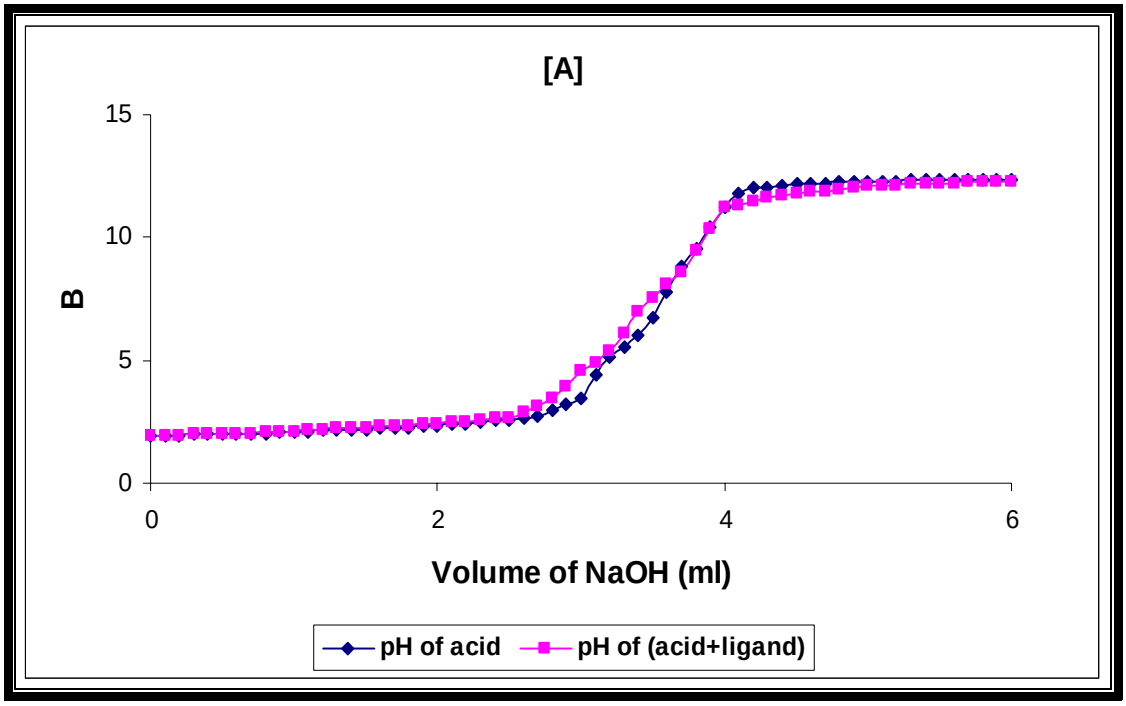
The calculated values of $\overline{n_H}$ for all the studied compounds are given in Tables 3.6.1 to 3.6.4 for both the solvent systems. It is evident from Tables that $\overline{n_H}$ values are in between zero and one for all the systems except NBN-6 and NBN-9 for which, the values of $n_H$ extend 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 NBN-6 and NBN-9. 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. The general plots for the variation of $\overline{n_H}$ with B of NBN-1 and NTD-1 are given in Figures 3.6.3 and 3.6.4 in both the solvent systems respectively.

Further, the $\log \bar{n}_H \Big/ \left(\bar{n}_H - 1\right)$ values are plotted against *B* as shown in Figures 3.6.5 and 3.6.6. The plots are straight lines from which $\log pK_1^H$ values were calculated at several *B* values, by the following equation.

$$\log pK_1^H = B + \log \bar{n}_H \Big/ \left(\bar{n}_H - 1\right) \qquad \text{… (3.6.18)}$$

The average $pk_1^H$ value is also reported in Tables 3.6.1 -3.6.4 for all compounds. It is evident from tables that these $pk_1^H$ values are in agreement with that obtained by the Figures 3.6.3 and 3.6.4. *i. e*., at $\overline{n_H}$ = 0.5.

**Figure 3.6.1: The plot of pH (B) against volume of NaOH for NBN-1 in [A] DMF and [B] THF at 298.15 K.**



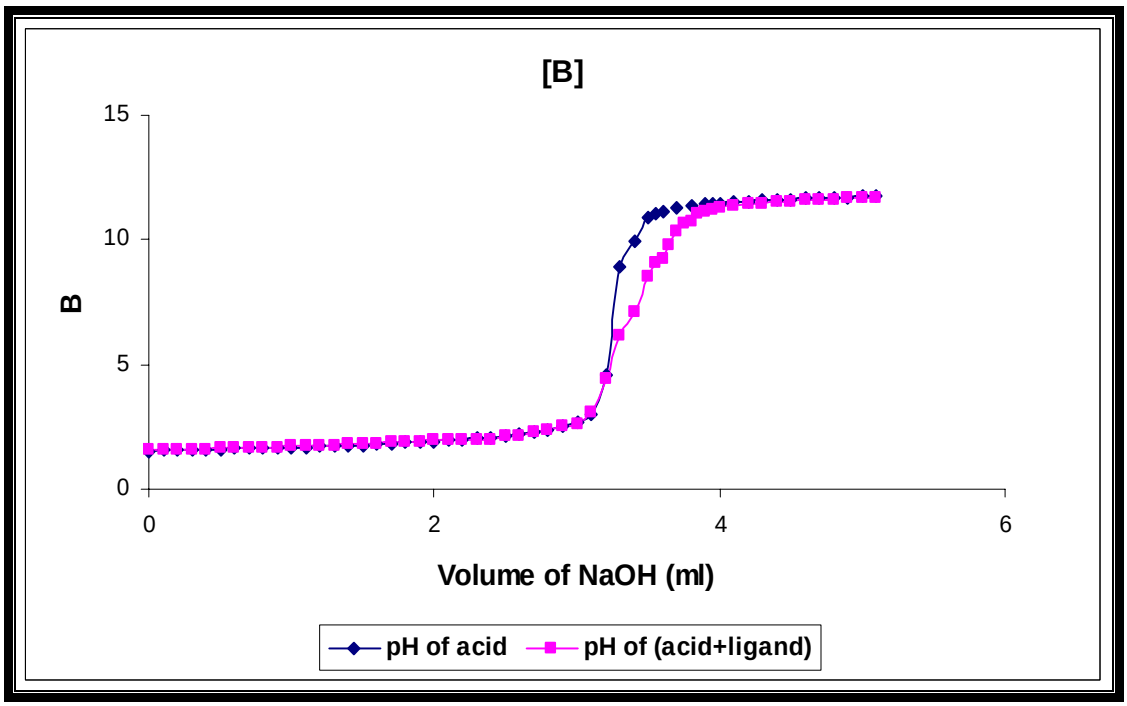
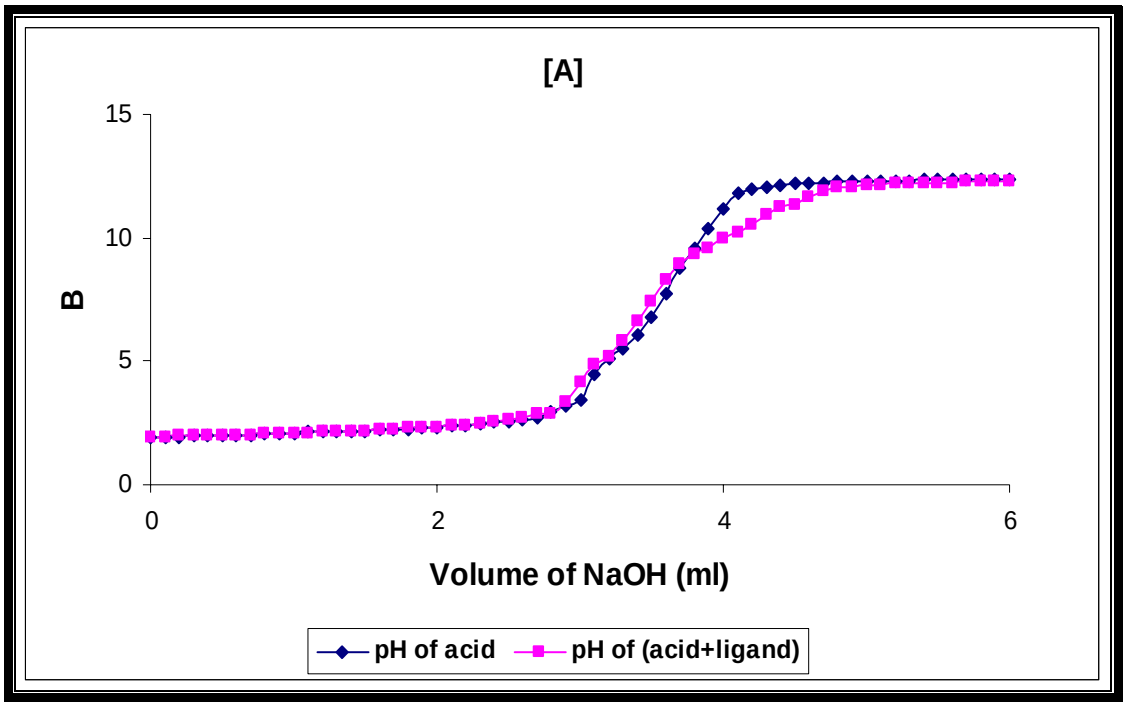



**Figure 3.6.2: The plot of pH (B) against volume of NaOH for NTD-1 in [A] DMF and [B] THF at 298.15 K.**



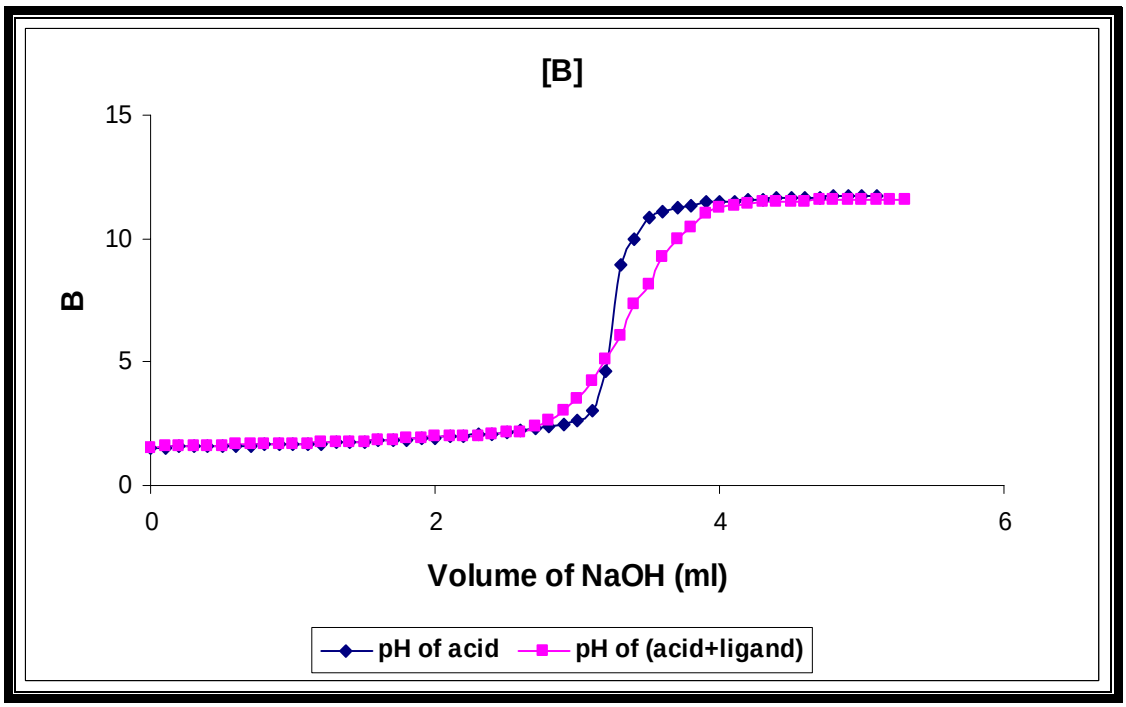



**Table 3.6.1: The *pH (B)*, $n_H$, $log\ pK_1^H$ and other terms for NBN series in DMF at 298.15 K.**

| *B* | *V'* | *V''* | *V''-V'* | $n_H$ | $log\ n_H/(1-n_H)$ | $log\ pK_1^H$ |
|---|---|---|---|---|---|---|
| | | | ***NBN-1*** | | | |
| 9.8 | 4.398 | 4.502 | 0.104 | 0.7423 | 0.4595 | 10.2595 |
| 9.9 | 4.420 | 4.546 | 0.126 | 0.6880 | 0.3434 | 10.2434 |
| 10.0 | 4.441 | 4.581 | 0.140 | 0.6535 | 0.2755 | 10.2755 |
| 10.1 | 4.461 | 4.624 | 0.163 | 0.5967 | 0.1702 | 10.2702 |
| 10.2 | 4.485 | 4.667 | 0.182 | 0.5500 | 0.0871 | 10.2871 |
| 10.3 | 4.504 | 4.701 | 0.197 | 0.5131 | 0.0227 | 10.3227 |
| 10.4 | 4.513 | 4.729 | 0.216 | 0.4662 | -0.0588 | 10.3412 |
| 10.5 | 4.522 | 4.755 | 0.233 | 0.4243 | -0.1325 | 10.3675 |
| 10.6 | 4.532 | 4.781 | 0.249 | 0.3849 | -0.2035 | 10.3965 |
| 10.7 | 4.541 | 4.795 | 0.254 | 0.3727 | -0.2261 | 10.4739 |
| | | | ***NBN-2*** | | | |
| 10.0 | 4.441 | 4.581 | 0.14 | 0.6535 | 0.2755 | 10.2755 |
| 10.1 | 4.461 | 4.612 | 0.151 | 0.6264 | 0.2245 | 10.3245 |
| 10.2 | 4.485 | 4.649 | 0.164 | 0.5945 | 0.1661 | 10.3661 |
| 10.3 | 4.504 | 4.690 | 0.186 | 0.5403 | 0.0701 | 10.3701 |
| 10.4 | 4.513 | 4.712 | 0.199 | 0.5082 | 0.0143 | 10.4143 |
| 10.5 | 4.522 | 4.729 | 0.207 | 0.4886 | -0.0199 | 10.4801 |
| 10.6 | 4.532 | 4.748 | 0.216 | 0.4665 | -0.0584 | 10.5416 |
| 10.7 | 4.541 | 4.781 | 0.240 | 0.4073 | -0.1629 | 10.5371 |
| 10.8 | 4.550 | 4.813 | 0.263 | 0.3506 | -0.2677 | 10.5323 |
| | | | **NBN-3** | | | |
| 9.1 | 4.168 | 4.263 | 0.095 | 0.7634 | 0.5087 | 9.6087 |
| 9.2 | 4.180 | 4.282 | 0.102 | 0.7460 | 0.4680 | 9.6680 |
| 9.3 | 4.189 | 4.315 | 0.126 | 0.6863 | 0.3401 | 9.6401 |
| 9.4 | 4.205 | 4.354 | 0.149 | 0.6292 | 0.2297 | 9.6297 |
| 9.5 | 4.301 | 4.477 | 0.176 | 0.5630 | 0.1100 | 9.6100 |
| 9.6 | 4.333 | 4.532 | 0.199 | 0.5062 | 0.0108 | 9.6108 |
| 9.7 | 4.364 | 4.583 | 0.219 | 0.4570 | -0.0749 | 9.6251 |
| 9.8 | 4.398 | 4.653 | 0.255 | 0.3682 | -0.2345 | 9.5655 |
| 9.9 | 4.420 | 4.702 | 0.282 | 0.3017 | -0.3645 | 9.5355 |
| 10.0 | 4.441 | 4.726 | 0.285 | 0.2946 | -0.3793 | 9.6207 |
| | | | ***NBN-4*** | | | |
| 9.0 | 4.158 | 4.310 | 0.152 | 0.6214 | 0.2151 | 9.2151 |
| 9.1 | 4.168 | 4.333 | 0.165 | 0.5891 | 0.1564 | 9.2564 |
| 9.2 | 4.180 | 4.351 | 0.171 | 0.5742 | 0.1299 | 9.3299 |
| 9.3 | 4.189 | 4.380 | 0.191 | 0.5245 | 0.0427 | 9.3427 |
| 9.4 | 4.205 | 4.401 | 0.196 | 0.5123 | 0.0213 | 9.4213 |
| 9.5 | 4.301 | 4.513 | 0.212 | 0.4736 | -0.0459 | 9.4541 |
| 9.6 | 4.333 | 4.559 | 0.226 | 0.4392 | -0.1061 | 9.4939 |
| 9.7 | 4.364 | 4.613 | 0.249 | 0.3826 | -0.2078 | 9.4922 |
| 9.8 | 4.398 | 4.652 | 0.254 | 0.3707 | -0.2298 | 9.5702 |
| | | | ***NBN-5*** | | | |
| 9.1 | 4.168 | 4.290 | 0.122 | 0.6962 | 0.3601 | 9.4601 |
| 9.2 | 4.180 | 4.310 | 0.130 | 0.6763 | 0.3200 | 9.5200 |
| 9.3 | 4.189 | 4.330 | 0.141 | 0.6490 | 0.2670 | 9.5670 |
| 9.4 | 4.205 | 4.370 | 0.165 | 0.5894 | 0.1570 | 9.5570 |
| 9.5 | 4.301 | 4.50 | 0.199 | 0.5059 | 0.0102 | 9.5102 |
| 9.6 | 4.333 | 4.540 | 0.207 | 0.4864 | -0.0237 | 9.5763 |

***Continue.....***

***……Continue***

| ***B*** | ***V'*** | ***V''*** | ***V''-V'*** | $n_H$ | $log\ n_H/(1-n_H)$ | $log\ pK_1^H$ |
|---|---|---|---|---|---|---|
| 9.7 | 4.364 | 4.590 | 0.226 | 0.4396 | -0.1054 | 9.5946 |
| 9.8 | 4.398 | 4.620 | 0.222 | 0.4500 | -0.0872 | 9.7128 |
| 9.9 | 4.420 | 4.680 | 0.260 | 0.3561 | -0.2572 | 9.6428 |
| ***NBN-6*** | | | | | | |
| 6.4 | 3.451 | 3.600 | 0.149 | 1.6228 | 0.4159 | 6.8159 |
| 6.5 | 3.465 | 3.620 | 0.155 | 1.6077 | 0.4225 | 6.9225 |
| 6.6 | 3.478 | 3.640 | 0.162 | 1.5901 | 0.4305 | 7.0305 |
| 6.7 | 3.491 | 3.660 | 0.169 | 1.5726 | 0.4388 | 7.1388 |
| 6.8 | 3.505 | 3.690 | 0.185 | 1.5322 | 0.4592 | 7.2592 |
| 6.9 | 3.514 | 3.710 | 0.196 | 1.5045 | 0.4745 | 7.3745 |
| 7.0 | 3.525 | 3.726 | 0.201 | 1.4920 | 0.4818 | 7.4818 |
| 7.1 | 3.535 | 3.740 | 0.205 | 1.4820 | 0.4878 | 7.5878 |
| 7.2 | 3.544 | 3.758 | 0.214 | 1.4594 | 0.5020 | 7.7020 |
| 7.3 | 3.555 | 3.770 | 0.215 | 1.4570 | 0.5035 | 7.8035 |
| 9.6 | 3.806 | 4.390 | 0.584 | 0.5335 | 0.0583 | 9.6583 |
| 9.7 | 3.819 | 4.400 | 0.581 | 0.5415 | 0.0723 | 9.7723 |
| 9.8 | 3.830 | 4.420 | 0.59 | 0.5193 | 0.0335 | 9.8335 |
| 9.9 | 3.842 | 4.435 | 0.593 | 0.5122 | 0.0211 | 9.9211 |
| 10.0 | 3.854 | 4.450 | 0.596 | 0.5050 | 0.0088 | 10.0088 |
| 10.1 | 3.865 | 4.470 | 0.605 | 0.4828 | -0.0298 | 10.0702 |
| 10.2 | 3.877 | 4.490 | 0.613 | 0.4632 | -0.0640 | 10.1360 |
| 10.3 | 3.889 | 4.520 | 0.631 | 0.4185 | -0.1428 | 10.1572 |
| 10.4 | 3.900 | 4.540 | 0.640 | 0.3964 | -0.1827 | 10.2173 |
| ***NBN-7*** | | | | | | |
| 9.7 | 3.819 | 3.861 | 0.042 | 0.8946 | 0.9286 | 10.6286 |
| 9.8 | 3.830 | 3.900 | 0.07 | 0.8243 | 0.6714 | 10.4714 |
| 9.9 | 3.842 | 3.935 | 0.093 | 0.7667 | 0.5166 | 10.4166 |
| 10.0 | 3.854 | 3.969 | 0.115 | 0.7115 | 0.3921 | 10.3921 |
| 10.1 | 3.865 | 4.000 | 0.135 | 0.6615 | 0.2909 | 10.3909 |
| 10.2 | 3.877 | 4.043 | 0.166 | 0.5838 | 0.1470 | 10.3470 |
| 10.3 | 3.889 | 4.082 | 0.193 | 0.5163 | 0.0283 | 10.3283 |
| 10.4 | 3.900 | 4.102 | 0.202 | 0.4938 | -0.0107 | 10.3893 |
| 10.5 | 3.913 | 4.125 | 0.212 | 0.4689 | -0.0540 | 10.4460 |
| 10.6 | 3.925 | 4.141 | 0.216 | 0.4591 | -0.0712 | 10.5288 |
| ***NBN-8*** | | | | | | |
| 9.2 | 3.754 | 3.912 | 0.158 | 0.6028 | 0.1811 | 9.3811 |
| 9.3 | 3.768 | 3.931 | 0.163 | 0.5903 | 0.1587 | 9.4587 |
| 9.4 | 3.781 | 3.95 | 0.169 | 0.5754 | 0.1320 | 9.5320 |
| 9.5 | 3.795 | 3.991 | 0.196 | 0.5077 | 0.0134 | 9.5134 |
| 9.6 | 3.806 | 4.020 | 0.214 | 0.4626 | -0.0650 | 9.5350 |
| 9.7 | 3.819 | 4.040 | 0.221 | 0.4452 | -0.0955 | 9.6045 |
| 9.8 | 3.830 | 4.070 | 0.240 | 0.3977 | -0.1803 | 9.6197 |
| 9.9 | 3.842 | 4.110 | 0.268 | 0.3276 | -0.3123 | 9.5877 |
| ***NBN-9*** | | | | | | |
| 6.0 | 3.394 | 3.532 | 0.138 | 1.6502 | 0.4045 | 6.4045 |
| 6.1 | 3.410 | 3.562 | 0.152 | 1.6148 | 0.4194 | 6.5194 |
| 6.2 | 3.424 | 3.598 | 0.174 | 1.5592 | 0.4453 | 6.6453 |
| 6.3 | 3.438 | 3.632 | 0.194 | 1.5087 | 0.4721 | 6.7721 |
| 6.4 | 3.451 | 3.671 | 0.220 | 1.4431 | 0.5128 | 6.9128 |
| 6.5 | 3.465 | 3.703 | 0.238 | 1.3977 | 0.5459 | 7.0459 |

***Continue.....***

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| ***B*** | ***V'*** | ***V''*** | ***V''-V'*** | $n_H$ | $log\ n_H/(1-n_H)$ | $log\ pK_1^H$ |
|---|---|---|---|---|---|---|
| 6.6 | 3.478 | 3.735 | 0.257 | 1.3498 | 0.5865 | 7.1865 |
| 6.7 | 3.491 | 3.758 | 0.267 | 1.3247 | 0.6106 | 7.3106 |
| 9.4 | 3.781 | 4.332 | 0.551 | 0.6156 | 0.2045 | 9.6045 |
| 9.5 | 3.795 | 4.354 | 0.559 | 0.5960 | 0.1688 | 9.6688 |
| 9.6 | 3.806 | 4.378 | 0.572 | 0.5637 | 0.1112 | 9.7112 |
| 9.7 | 3.819 | 4.402 | 0.583 | 0.5365 | 0.0635 | 9.7635 |
| 9.8 | 3.830 | 4.420 | 0.590 | 0.5193 | 0.0335 | 9.8335 |
| 9.9 | 3.842 | 4.452 | 0.610 | 0.4695 | -0.0530 | 9.8470 |
| 10.0 | 3.854 | 4.483 | 0.629 | 0.4223 | -0.1361 | 9.8639 |
| 10.1 | 3.865 | 4.512 | 0.647 | 0.3775 | -0.2172 | 9.8828 |
| 10.2 | 3.877 | 4.543 | 0.666 | 0.3303 | -0.3069 | 9.8931 |
| ***NBN-10*** | | | | | | |
| 9.4 | 3.781 | 3.91 | 0.129 | 0.6759 | 0.3192 | 9.7192 |
| 9.5 | 3.795 | 3.95 | 0.155 | 0.6107 | 0.1955 | 9.6955 |
| 9.6 | 3.806 | 3.97 | 0.164 | 0.5882 | 0.1548 | 9.7548 |
| 9.7 | 3.819 | 4.01 | 0.191 | 0.5205 | 0.0357 | 9.7357 |
| 9.8 | 3.83 | 4.03 | 0.2 | 0.4981 | -0.0034 | 9.7966 |
| 9.9 | 3.842 | 4.06 | 0.218 | 0.4530 | -0.0818 | 9.8182 |
| 10.0 | 3.854 | 4.08 | 0.226 | 0.4331 | -0.1169 | 9.8831 |
| 10.1 | 3.865 | 4.11 | 0.245 | 0.3856 | -0.2023 | 9.8977 |
| 10.2 | 3.877 | 4.15 | 0.273 | 0.3156 | -0.3362 | 9.8638 |

**Table 3.6.2: The *pH (B), $n_H$, log $pK_1^H$* and other terms for NBN series in THF at 298.15 K.**

| *B* | *V'* | *V''* | *V''-V'* | $n_H$ | *log $n_H/(1-n_H)$* | *log $pK_1^H$* |
|---|---|---|---|---|---|---|
| | | | | ***NBN-1*** | | |
| 8.2 | 3.283 | 3.466 | 0.183 | 0.5349 | 0.0608 | 8.2608 |
| 8.3 | 3.286 | 3.475 | 0.189 | 0.5197 | 0.0343 | 8.3343 |
| 8.4 | 3.288 | 3.479 | 0.191 | 0.5146 | 0.0255 | 8.4255 |
| 8.5 | 3.289 | 3.483 | 0.194 | 0.5070 | 0.0122 | 8.5122 |
| 8.6 | 3.293 | 3.488 | 0.195 | 0.5045 | 0.0079 | 8.6079 |
| 8.7 | 3.296 | 3.492 | 0.196 | 0.5020 | 0.0035 | 8.7035 |
| 8.8 | 3.297 | 3.505 | 0.208 | 0.4716 | -0.0495 | 8.7505 |
| 8.9 | 3.301 | 3.518 | 0.217 | 0.4487 | -0.0894 | 8.8106 |
| 9.0 | 3.305 | 3.532 | 0.227 | 0.4234 | -0.1341 | 8.8659 |
| 9.1 | 3.32 | 3.549 | 0.229 | 0.4185 | -0.1428 | 8.9572 |
| 9.2 | 3.325 | 3.561 | 0.236 | 0.4008 | -0.1746 | 9.0254 |
| | | | | ***NBN-2*** | | |
| 8.7 | 3.295 | 3.482 | 0.187 | 0.5249 | 0.0433 | 8.7433 |
| 8.8 | 3.297 | 3.489 | 0.192 | 0.5122 | 0.0212 | 8.8212 |
| 8.9 | 3.299 | 3.494 | 0.195 | 0.5046 | 0.0080 | 8.9080 |
| 9.0 | 3.305 | 3.506 | 0.201 | 0.4894 | -0.0184 | 8.9816 |
| 9.1 | 3.316 | 3.512 | 0.196 | 0.5023 | 0.0039 | 9.1039 |
| 9.2 | 3.325 | 3.522 | 0.197 | 0.4998 | -0.0003 | 9.1997 |
| 9.3 | 3.335 | 3.536 | 0.201 | 0.4898 | -0.0177 | 9.2823 |
| 9.4 | 3.345 | 3.549 | 0.204 | 0.4823 | -0.0308 | 9.3692 |
| 9.5 | 3.354 | 3.563 | 0.209 | 0.4697 | -0.0527 | 9.4473 |
| | | | | ***NBN-3*** | | |
| 7.5 | 3.268 | 3.42 | 0.152 | 0.6136 | 0.2008 | 7.7008 |
| 7.6 | 3.269 | 3.429 | 0.16 | 0.5932 | 0.1639 | 7.7639 |
| 7.7 | 3.271 | 3.438 | 0.167 | 0.5755 | 0.1321 | 7.8321 |
| 7.8 | 3.273 | 3.445 | 0.172 | 0.5628 | 0.1096 | 7.9096 |
| 7.9 | 3.276 | 3.456 | 0.18 | 0.5425 | 0.0740 | 7.9740 |
| 8.0 | 3.278 | 3.475 | 0.197 | 0.4993 | -0.0012 | 7.9988 |
| 8.1 | 3.281 | 3.489 | 0.208 | 0.4714 | -0.0498 | 8.0502 |
| 8.2 | 3.283 | 3.501 | 0.218 | 0.4460 | -0.0942 | 8.1058 |
| 8.3 | 3.286 | 3.522 | 0.236 | 0.4003 | -0.1756 | 8.1244 |
| 8.4 | 3.289 | 3.535 | 0.246 | 0.3749 | -0.2220 | 8.1780 |
| | | | | ***NBN-4*** | | |
| 7.3 | 3.262 | 3.44 | 0.178 | 0.5474 | 0.0826 | 7.3826 |
| 7.4 | 3.265 | 3.446 | 0.181 | 0.5398 | 0.0693 | 7.4693 |
| 7.5 | 3.268 | 3.453 | 0.185 | 0.5297 | 0.0516 | 7.5516 |
| 7.6 | 3.269 | 3.461 | 0.192 | 0.5119 | 0.0207 | 7.6207 |
| 7.7 | 3.271 | 3.468 | 0.197 | 0.4992 | -0.0014 | 7.6986 |
| 7.8 | 3.273 | 3.472 | 0.199 | 0.4941 | -0.0102 | 7.7898 |
| 7.9 | 3.276 | 3.492 | 0.216 | 0.4510 | -0.0855 | 7.8145 |
| 8.0 | 3.278 | 3.496 | 0.218 | 0.4459 | -0.0943 | 7.9057 |
| 8.1 | 3.281 | 3.501 | 0.22 | 0.4409 | -0.1032 | 7.9968 |
| 8.2 | 3.283 | 3.506 | 0.223 | 0.4333 | -0.1166 | 8.0834 |
| | | | | ***NBN-5*** | | |
| 7.4 | 3.265 | 3.439 | 0.174 | 0.5576 | 0.1005 | 7.5005 |
| 7.5 | 3.268 | 3.444 | 0.176 | 0.5526 | 0.0916 | 7.5916 |
| 7.6 | 3.269 | 3.456 | 0.187 | 0.5246 | 0.0428 | 7.6428 |
| 7.7 | 3.271 | 3.462 | 0.191 | 0.5145 | 0.0251 | 7.7251 |

***Continue.....***

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| ***B*** | ***V'*** | ***V''*** | ***V''-V'*** | ***$n_H$*** | ***log $n_H/(1-n_H)$*** | ***log $pK_1^H$*** |
|---|---|---|---|---|---|---|
| 7.8 | 3.273 | 3.471 | 0.198 | 0.4967 | -0.0058 | 7.7942 |
| 7.9 | 3.276 | 3.488 | 0.212 | 0.4611 | -0.0677 | 7.8323 |
| 8.0 | 3.278 | 3.501 | 0.223 | 0.4332 | -0.1167 | 7.8833 |
| 8.1 | 3.281 | 3.518 | 0.237 | 0.3977 | -0.1803 | 7.9197 |
| 8.2 | 3.283 | 3.529 | 0.246 | 0.3748 | -0.2222 | 7.9778 |
| ***NBN-6*** | | | | | | |
| 5.4 | 3.218 | 3.380 | 0.162 | 1.5877 | 0.3791 | 5.3791 |
| 5.5 | 3.221 | 3.390 | 0.169 | 1.5699 | 0.3864 | 5.4864 |
| 5.6 | 3.223 | 3.400 | 0.177 | 1.5495 | 0.3941 | 5.5941 |
| 5.7 | 3.225 | 3.420 | 0.195 | 1.5038 | 0.4114 | 5.7114 |
| 5.8 | 3.228 | 3.430 | 0.202 | 1.4860 | 0.4316 | 5.8316 |
| 5.9 | 3.23 | 3.440 | 0.210 | 1.4656 | 0.4401 | 5.9401 |
| 6.0 | 3.232 | 3.450 | 0.218 | 1.4453 | 0.4502 | 6.0502 |
| 6.1 | 3.234 | 3.460 | 0.226 | 1.4250 | 0.4750 | 6.1750 |
| 8.0 | 3.278 | 3.785 | 0.507 | 0.7114 | 0.3918 | 8.3917 |
| 8.1 | 3.281 | 3.813 | 0.532 | 0.6479 | 0.2648 | 8.3648 |
| 8.2 | 3.283 | 3.834 | 0.551 | 0.5997 | 0.1755 | 8.3755 |
| 8.3 | 3.286 | 3.850 | 0.564 | 0.5667 | 0.1166 | 8.4166 |
| 8.4 | 3.289 | 3.881 | 0.592 | 0.4957 | -0.0075 | 8.3925 |
| 8.5 | 3.290 | 3.910 | 0.620 | 0.4246 | -0.1320 | 8.3680 |
| 8.6 | 3.292 | 3.935 | 0.643 | 0.3662 | -0.2382 | 8.3618 |
| 8.7 | 3.295 | 3.951 | 0.656 | 0.3333 | -0.3011 | 8.3989 |
| 8.8 | 3.297 | 3.972 | 0.675 | 0.2851 | -0.3992 | 8.4008 |
| ***NBN-7*** | | | | | | |
| 8.0 | 3.278 | 3.46 | 0.182 | 0.5374 | 0.0651 | 8.0651 |
| 8.1 | 3.281 | 3.463 | 0.182 | 0.5374 | 0.0652 | 8.1652 |
| 8.2 | 3.283 | 3.469 | 0.186 | 0.5273 | 0.0475 | 8.2475 |
| 8.3 | 3.286 | 3.473 | 0.187 | 0.5248 | 0.0431 | 8.3431 |
| 8.4 | 3.289 | 3.478 | 0.189 | 0.5197 | 0.0343 | 8.4343 |
| 8.5 | 3.29 | 3.487 | 0.197 | 0.4994 | -0.0010 | 8.4990 |
| 8.6 | 3.292 | 3.492 | 0.200 | 0.4918 | -0.0142 | 8.5858 |
| 8.7 | 3.295 | 3.498 | 0.203 | 0.4842 | -0.0274 | 8.6726 |
| 8.8 | 3.297 | 3.505 | 0.208 | 0.4716 | -0.0495 | 8.7505 |
| 8.9 | 3.299 | 3.512 | 0.213 | 0.4589 | -0.0716 | 8.8284 |
| ***NBN-8*** | | | | | | |
| 7.5 | 3.268 | 3.426 | 0.158 | 0.5983 | 0.1730 | 7.6730 |
| 7.6 | 3.269 | 3.439 | 0.170 | 0.5678 | 0.1185 | 7.7185 |
| 7.7 | 3.271 | 3.45 | 0.179 | 0.5450 | 0.0783 | 7.7783 |
| 7.8 | 3.273 | 3.463 | 0.190 | 0.5170 | 0.0296 | 7.8296 |
| 7.9 | 3.276 | 3.47 | 0.194 | 0.5069 | 0.0120 | 7.9120 |
| 8.0 | 3.278 | 3.482 | 0.204 | 0.4815 | -0.0322 | 7.9678 |
| 8.1 | 3.281 | 3.494 | 0.213 | 0.4587 | -0.0720 | 8.0280 |
| 8.2 | 3.283 | 3.504 | 0.221 | 0.4383 | -0.1076 | 8.0924 |
| 8.3 | 3.286 | 3.518 | 0.232 | 0.4104 | -0.1573 | 8.1427 |
| ***NBN-9*** | | | | | | |
| 5.1 | 3.211 | 3.340 | 0.129 | 1.6716 | 0.3960 | 5.4960 |
| 5.2 | 3.213 | 3.360 | 0.147 | 1.6258 | 0.4146 | 5.6146 |
| 5.3 | 3.216 | 3.380 | 0.164 | 1.5826 | 0.4340 | 5.7340 |
| 5.4 | 3.218 | 3.400 | 0.182 | 1.5368 | 0.4568 | 5.8568 |
| 5.5 | 3.221 | 3.420 | 0.199 | 1.4935 | 0.4809 | 5.9809 |
| 5.6 | 3.223 | 3.440 | 0.217 | 1.4477 | 0.5097 | 6.1097 |
| 5.7 | 3.225 | 3.460 | 0.235 | 1.4020 | 0.5425 | 6.2425 |

***Continue.....***

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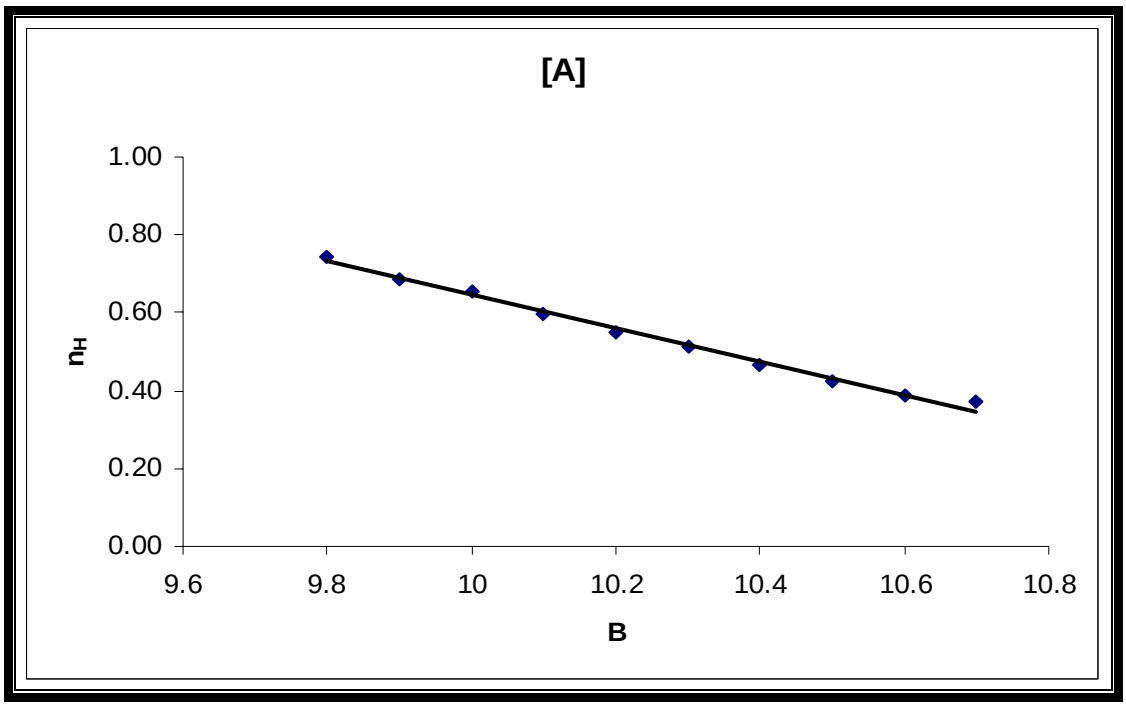
| ***B*** | ***V'*** | ***V''*** | ***V''-V'*** | $n_H$ | $log\ n_H/(1-n_H)$ | $log\ pK_1^H$ |
|---|---|---|---|---|---|---|
| 5.8 | 3.228 | 3.480 | 0.252 | 1.3587 | 0.5783 | 6.3783 |
| 5.9 | 3.230 | 3.500 | 0.270 | 1.3130 | 0.6227 | 6.5227 |
| 7.9 | 3.276 | 3.844 | 0.568 | 0.5562 | 0.0981 | 7.9981 |
| 8.0 | 3.278 | 3.856 | 0.578 | 0.5309 | 0.0537 | 8.0537 |
| 8.1 | 3.281 | 3.864 | 0.583 | 0.5183 | 0.0318 | 8.1318 |
| 8.2 | 3.283 | 3.870 | 0.587 | 0.5082 | 0.0142 | 8.2142 |
| 8.3 | 3.286 | 3.891 | 0.605 | 0.4626 | -0.0652 | 8.2348 |
| 8.4 | 3.289 | 3.908 | 0.619 | 0.4271 | -0.1276 | 8.2724 |
| 8.5 | 3.290 | 3.921 | 0.631 | 0.3966 | -0.1822 | 8.3178 |
| **NBN-10** | | | | | | |
| 7.9 | 3.276 | 3.455 | 0.179 | 0.5450 | 0.0784 | 7.9784 |
| 8.0 | 3.278 | 3.462 | 0.184 | 0.5323 | 0.0562 | 8.0562 |
| 8.1 | 3.281 | 3.469 | 0.188 | 0.5222 | 0.0386 | 8.1386 |
| 8.2 | 3.283 | 3.476 | 0.193 | 0.5095 | 0.0165 | 8.2165 |
| 8.3 | 3.286 | 3.483 | 0.197 | 0.4994 | -0.0011 | 8.2989 |
| 8.4 | 3.289 | 3.490 | 0.201 | 0.4892 | -0.0187 | 8.3813 |
| 8.5 | 3.29 | 3.496 | 0.206 | 0.4766 | -0.0408 | 8.4592 |
| 8.6 | 3.292 | 3.505 | 0.213 | 0.4588 | -0.0717 | 8.5283 |

**Figure 3.6.3: The plot of $n_H$ against B for NBN-1 in [A] DMF and [B] THF at 298.15K.**



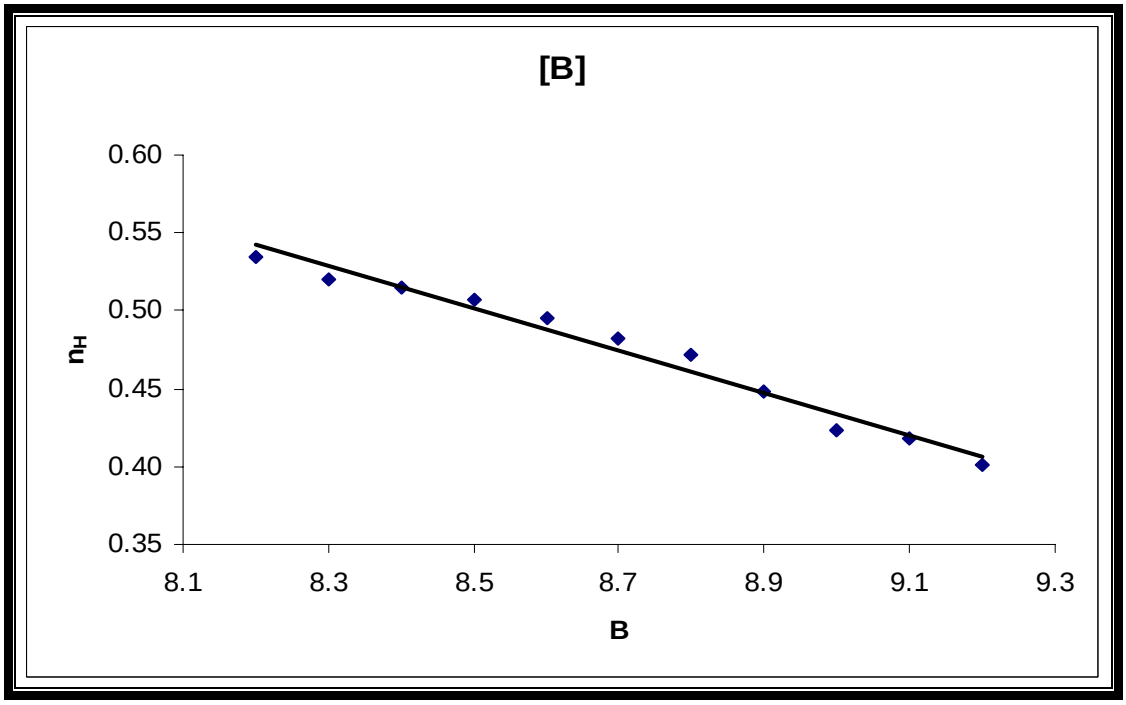
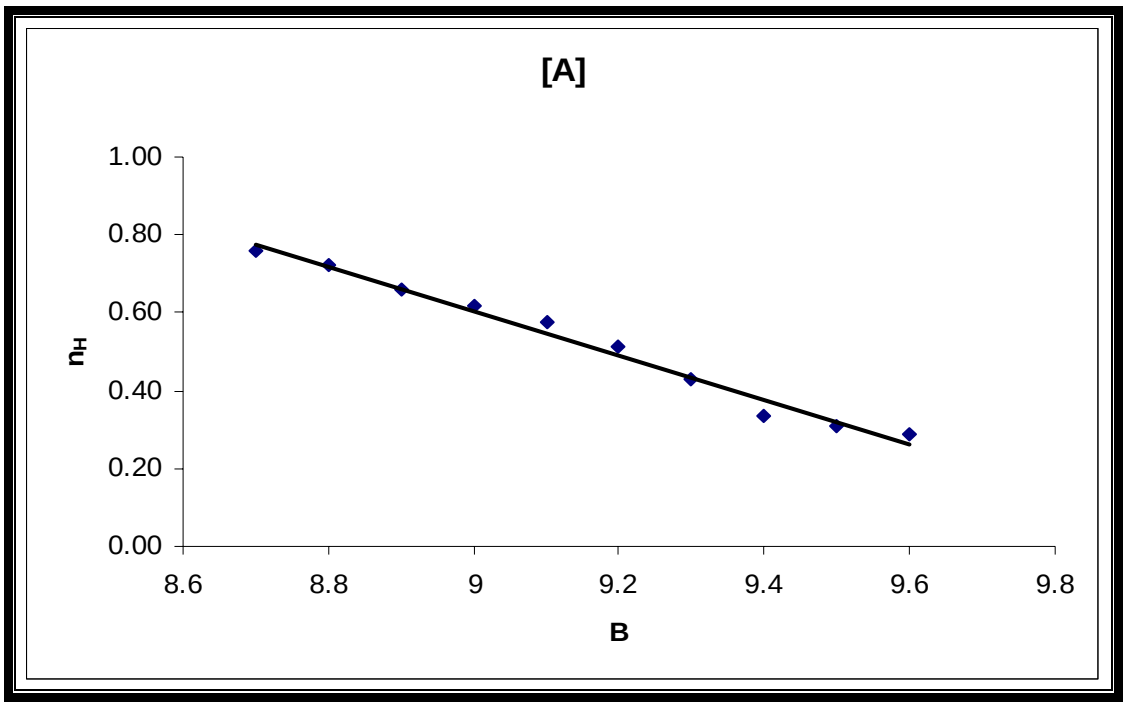
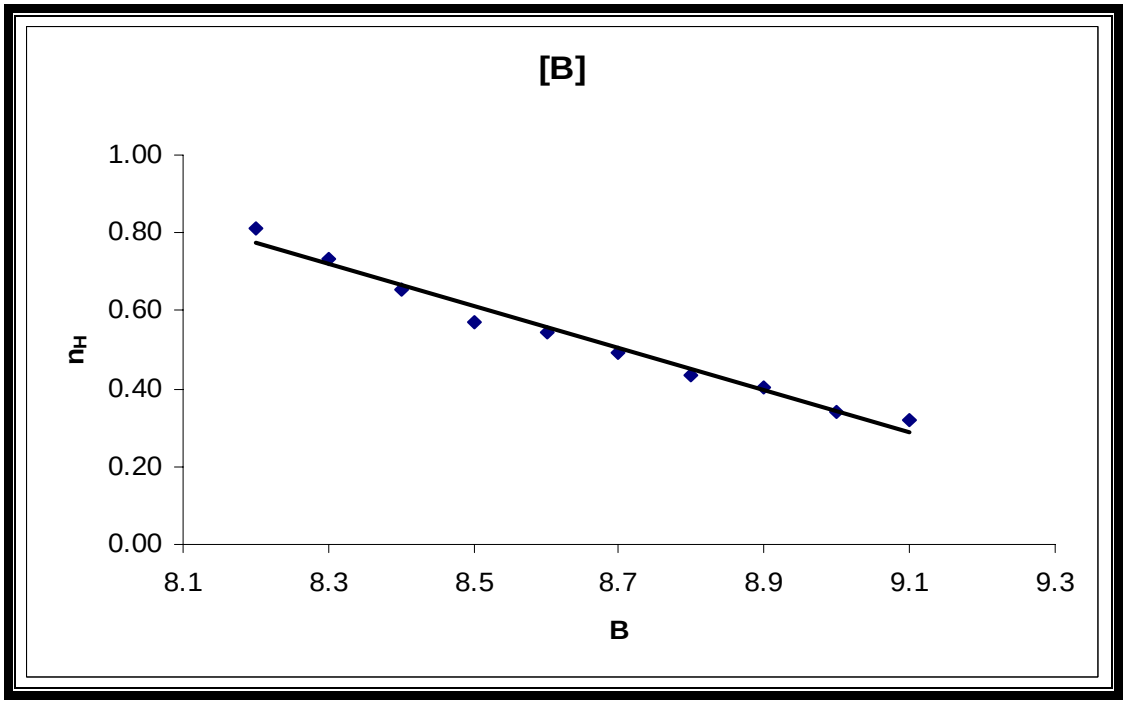



**Figure 3.6.4: The plot of $n_H$ against B for (NTD-1) in [A] DMF and [B] THF at 298.15 K.**



For NBN-6 and NBN-9, the proton-ligand constants were calculated by solving equation 3.6.1. For all the points below $\overline{n_H}$ =1, the following equation was used

$$log\ pK_1^H = B + log\,\bar{n}_H \big/ \left(\bar{n}_H - 1\right) \quad \ldots (3.6.19)$$

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

$$logpK_2^H = B + log\left[\left(\bar{n}_H - 1\right)\big/\left(2 - \bar{n}_H\right)\right] \quad \ldots (3.6.20)$$

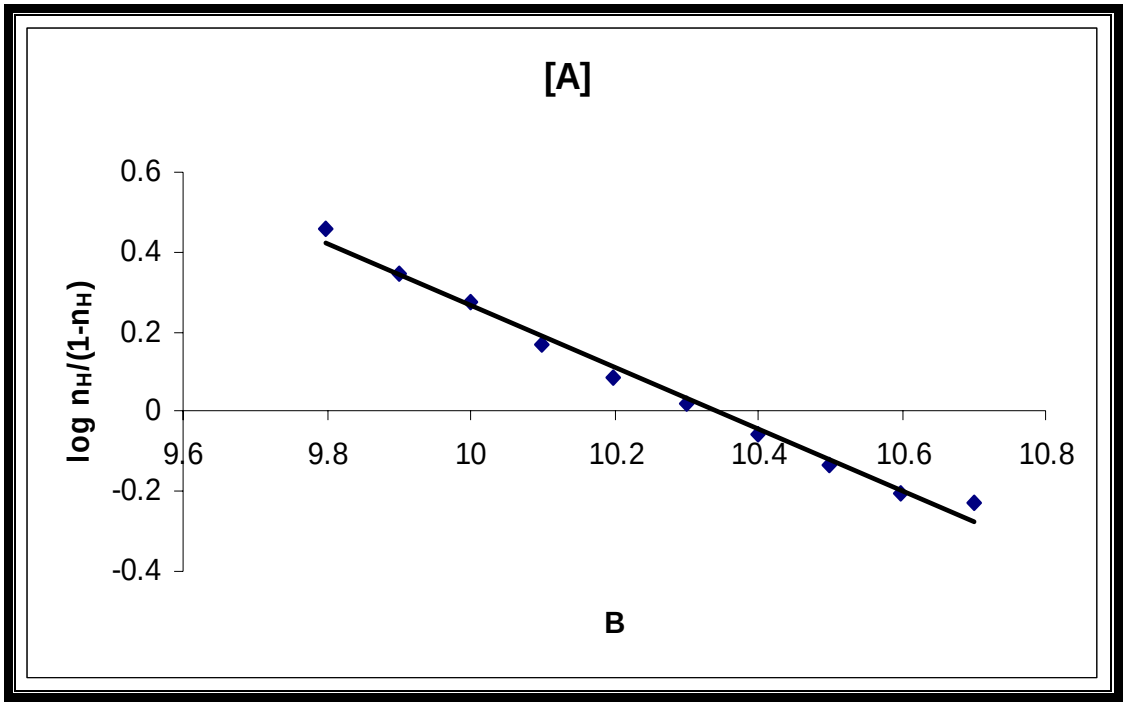
From the various values of $\log pK_1^H$ (or *log* $pK_2^H$) calculated for a system, the average value was calculated. The values of *log* $pK_1^H$ and *log* $pK_2^H$ calculated by these two methods i.e., half-integral method and average method are given in Table 3.6.5 for both the solvent systems. It is observed that in most of the systems, the calculated values by these two methods are in good agreement.

Out of all systems studied, NBN-6 and NBN-9 are of $H_2L$ type whereas others are of *HL* type. The comparison of $pK_1^H$ values of *HL* type ligand shows that the dissociation constant depends upon the type of solvent used. The values are different in different solvent systems. Further, the order of dissociation or acidic constants is different in each solvent system.

Thus, 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.

Comparison of $pK_1^H$ values of NBN series shows that in both the solvent, NBN-4 is more acidic which contains p-nitro group. However, NBN-2 is most basic in both the systems. It contains p-amino group. NBN-6 and NBN-9 both contain hydroxyl groups at para and ortho positions respectively. But, NBN-9 is found to be more acidic than NBN-6. However, for NTD series, in both solvent systems, NTD-5 is more basic in both the systems as expected. It contains p-methyl group. But, NTD-4 is found to be more acidic as it contains p-nitro group. Thus, it is concluded that different compounds exhibit different dissociation constant which also depends upon the type and position of substituent group.

**Figure 3.6.5: The plot of log $n_H/(1-n_H)$ against B for ( NBN-1) in [A] DMF and [B] THF at 298.15K.**



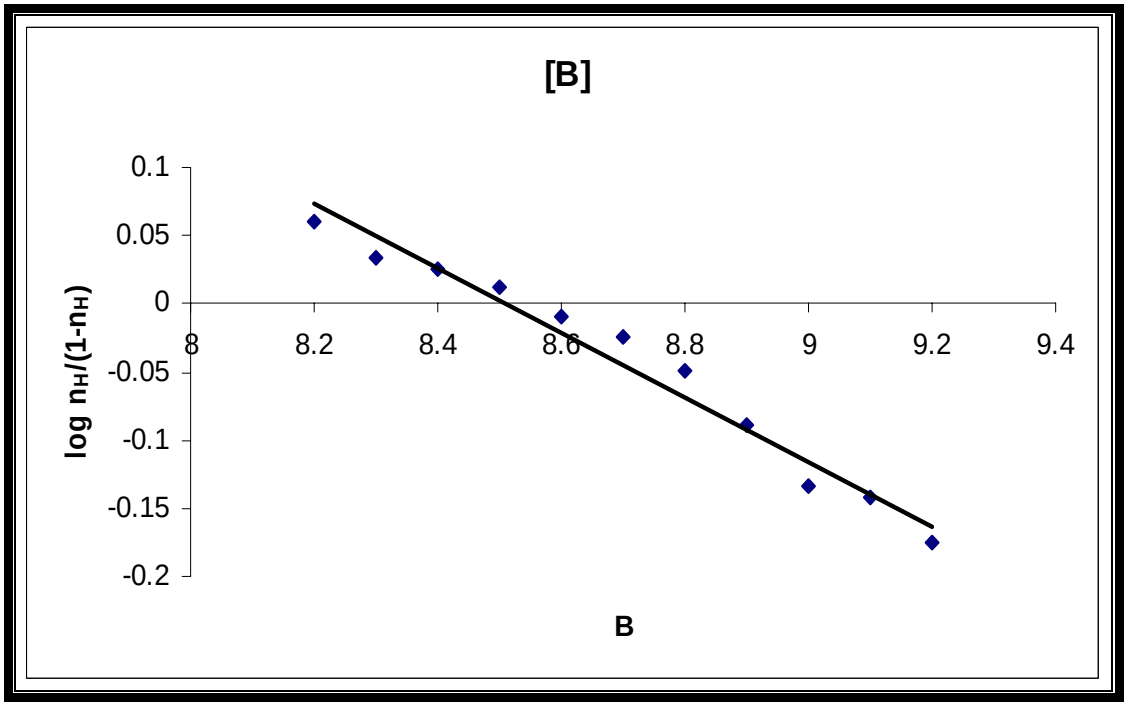
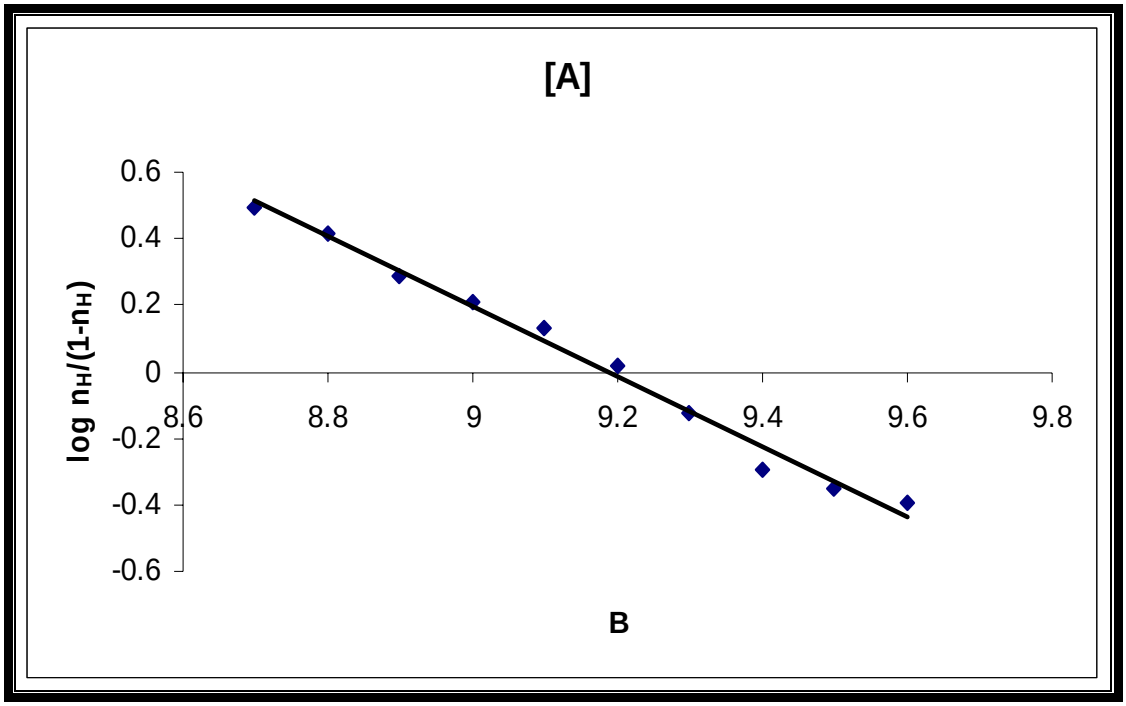



**Figure 3.6.6: The plot of log $n_H/(1-n_H)$ against B for (NTD-1) in [A] DMF and [B] THF at 298.15K.**



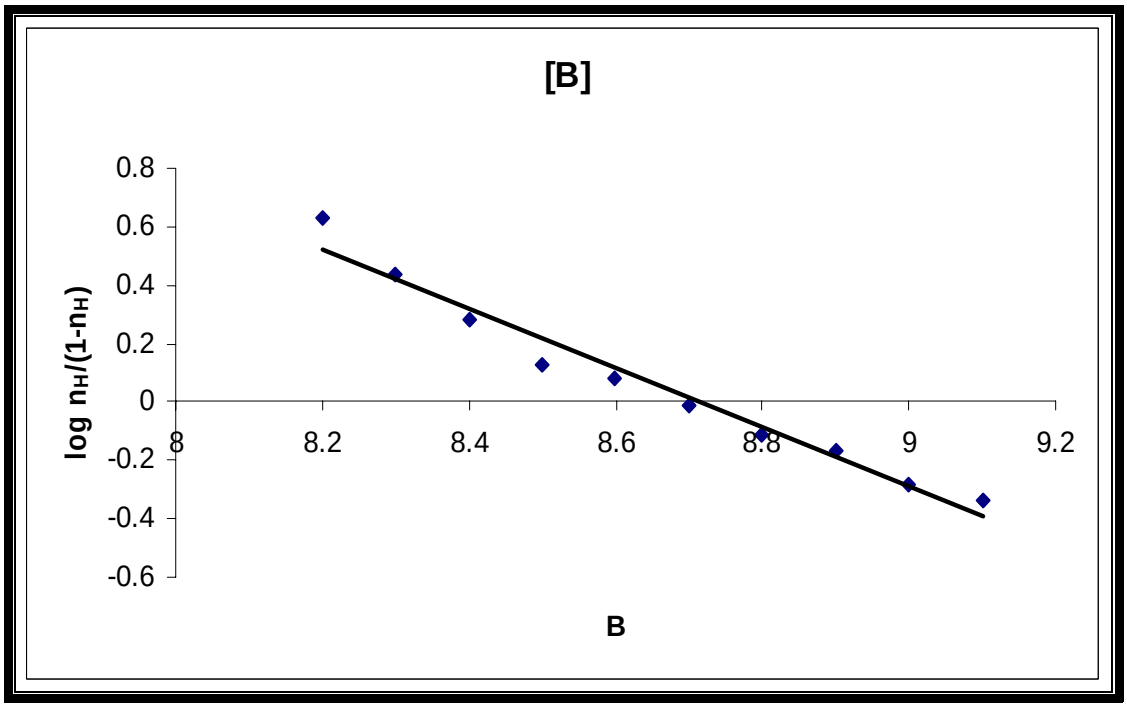



**Table 3.6.3: The *pH (B), $n_H$, log $pK_1^H$* and other terms for NTD series in DMF at 298.15 K.**

| *B* | *V'* | *V''* | *V''-V'* | $n_H$ | *log $n_H/(1-n_H)$* | *log $pK_1^H$* |
|---|---|---|---|---|---|---|
| | | | ***NTD-1*** | | | |
| 8.7 | 4.124 | 4.221 | 0.097 | 0.7582 | 0.4963 | 9.1963 |
| 8.8 | 4.137 | 4.249 | 0.112 | 0.7209 | 0.4120 | 9.2120 |
| 8.9 | 4.146 | 4.282 | 0.136 | 0.6611 | 0.2902 | 9.1902 |
| 9.0 | 4.158 | 4.311 | 0.153 | 0.6189 | 0.2105 | 9.2105 |
| 9.1 | 4.168 | 4.338 | 0.170 | 0.5766 | 0.1342 | 9.2342 |
| 9.2 | 4.180 | 4.376 | 0.196 | 0.5120 | 0.0208 | 9.2208 |
| 9.3 | 4.189 | 4.419 | 0.23 | 0.4275 | -0.1269 | 9.1731 |
| 9.4 | 4.205 | 4.472 | 0.267 | 0.3356 | -0.2966 | 9.1034 |
| 9.5 | 4.301 | 4.580 | 0.279 | 0.3072 | -0.3531 | 9.1469 |
| 9.6 | 4.333 | 4.620 | 0.287 | 0.2879 | -0.3933 | 9.2067 |
| | | | ***NTD-2*** | | | |
| 11.3 | 4.597 | 4.711 | 0.114 | 0.7188 | 0.4076 | 11.7076 |
| 11.4 | 4.609 | 4.743 | 0.134 | 0.6695 | 0.3067 | 11.7067 |
| 11.5 | 4.622 | 4.780 | 0.158 | 0.6105 | 0.1952 | 11.6952 |
| 11.6 | 4.634 | 4.809 | 0.175 | 0.5687 | 0.1201 | 11.7201 |
| 11.7 | 4.650 | 4.842 | 0.192 | 0.5269 | 0.0469 | 11.7469 |
| 11.8 | 4.662 | 4.862 | 0.200 | 0.5074 | 0.0129 | 11.8129 |
| 11.9 | 4.675 | 4.887 | 0.212 | 0.4780 | -0.0382 | 11.8618 |
| 12.0 | 4.690 | 4.922 | 0.232 | 0.4289 | -0.1243 | 11.8757 |
| 12.1 | 4.706 | 4.949 | 0.243 | 0.4020 | -0.1723 | 11.9277 |
| 12.2 | 4.752 | 5.010 | 0.258 | 0.3658 | -0.2389 | 11.9611 |
| | | | ***NTD-3*** | | | |
| 8.6 | 4.115 | 4.242 | 0.127 | 0.6833 | 0.3340 | 8.9340 |
| 8.7 | 4.124 | 4.269 | 0.145 | 0.6385 | 0.2471 | 8.9471 |
| 8.8 | 4.137 | 4.305 | 0.168 | 0.5813 | 0.1425 | 8.9425 |
| 8.9 | 4.146 | 4.343 | 0.197 | 0.5091 | 0.0159 | 8.9159 |
| 9.0 | 4.158 | 4.382 | 0.224 | 0.4420 | -0.1012 | 8.8988 |
| 9.1 | 4.168 | 4.415 | 0.247 | 0.3848 | -0.2037 | 8.8963 |
| 9.2 | 4.180 | 4.453 | 0.273 | 0.3203 | -0.3268 | 8.8732 |
| 9.3 | 4.189 | 4.479 | 0.29 | 0.2781 | -0.4143 | 8.8857 |
| 9.4 | 4.205 | 4.522 | 0.317 | 0.2112 | -0.5723 | 8.8277 |
| | | | ***NTD-4*** | | | |
| 8.3 | 4.084 | 4.203 | 0.119 | 0.7031 | 0.3743 | 8.6743 |
| 8.4 | 4.093 | 4.235 | 0.142 | 0.6457 | 0.2608 | 8.6608 |
| 8.5 | 4.102 | 4.268 | 0.166 | 0.5860 | 0.1508 | 8.6508 |
| 8.6 | 4.115 | 4.301 | 0.186 | 0.5362 | 0.0630 | 8.6630 |
| 8.7 | 4.124 | 4.325 | 0.201 | 0.4989 | -0.0019 | 8.6981 |
| 8.8 | 4.137 | 4.351 | 0.214 | 0.4667 | -0.0580 | 8.7420 |
| 8.9 | 4.146 | 4.380 | 0.234 | 0.4169 | -0.1456 | 8.7544 |
| 9.0 | 4.158 | 4.398 | 0.240 | 0.4021 | -0.1722 | 8.8278 |
| 9.1 | 4.168 | 4.428 | 0.260 | 0.3525 | -0.2641 | 8.8359 |
| 9.2 | 4.180 | 4.452 | 0.272 | 0.3228 | -0.3218 | 8.8782 |
| | | | **NTD-5** | | | |
| 11.6 | 4.634 | 4.763 | 0.129 | 0.6821 | 0.3315 | 11.9315 |
| 11.7 | 4.65 | 4.797 | 0.147 | 0.6378 | 0.2458 | 11.9458 |
| 11.8 | 4.662 | 4.825 | 0.163 | 0.5985 | 0.1735 | 11.9735 |
| 11.9 | 4.675 | 4.860 | 0.185 | 0.5445 | 0.0775 | 11.9775 |
| 12.0 | 4.69 | 4.895 | 0.205 | 0.4954 | -0.0080 | 11.9920 |

***Continue.....***

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| ***B*** | ***V'*** | ***V''*** | ***V''-V'*** | $n_H$ | $log\ n_H/(1-n_H)$ | $log\ pK_1^H$ |
|---|---|---|---|---|---|---|
| 12.1 | 4.706 | 4.928 | 0.222 | 0.4538 | -0.0805 | 12.0195 |
| 12.2 | 4.752 | 4.985 | 0.233 | 0.4273 | -0.1272 | 12.0728 |
| 12.3 | 4.811 | 5.060 | 0.249 | 0.3888 | -0.1965 | 12.1035 |
| 12.4 | 4.948 | 5.221 | 0.273 | 0.3319 | -0.3038 | 12.0962 |
| ***NTD-6*** | | | | | | |
| 9.6 | 3.806 | 4.391 | 0.585 | 0.5310 | 0.0540 | 9.6540 |
| 9.7 | 3.819 | 4.401 | 0.582 | 0.5390 | 0.0679 | 9.7679 |
| 9.8 | 3.83 | 4.421 | 0.591 | 0.5168 | 0.0291 | 9.8291 |
| 9.9 | 3.842 | 4.435 | 0.593 | 0.5122 | 0.0211 | 9.9211 |
| 10.0 | 3.854 | 4.458 | 0.604 | 0.4850 | -0.0261 | 9.9739 |
| 10.1 | 3.865 | 4.472 | 0.607 | 0.4778 | -0.0385 | 10.0615 |
| 10.2 | 3.877 | 4.492 | 0.615 | 0.4582 | -0.0728 | 10.1272 |
| 10.3 | 3.889 | 4.522 | 0.633 | 0.4135 | -0.1518 | 10.1482 |
| 10.4 | 3.900 | 4.541 | 0.641 | 0.3938 | -0.1872 | 10.2128 |
| ***NTD-7*** | | | | | | |
| 11.1 | 3.987 | 4.138 | 0.151 | 0.6224 | 0.2170 | 11.3170 |
| 11.2 | 4.000 | 4.165 | 0.165 | 0.5875 | 0.1536 | 11.3536 |
| 11.3 | 4.018 | 4.201 | 0.183 | 0.5427 | 0.0743 | 11.3743 |
| 11.4 | 4.035 | 4.234 | 0.199 | 0.5029 | 0.0050 | 11.4050 |
| 11.5 | 4.053 | 4.261 | 0.208 | 0.4806 | -0.0337 | 11.4663 |
| 11.6 | 4.069 | 4.295 | 0.226 | 0.4359 | -0.1120 | 11.4880 |
| 11.7 | 4.086 | 4.334 | 0.248 | 0.3812 | -0.2104 | 11.4896 |
| 11.8 | 4.110 | 4.368 | 0.258 | 0.3566 | -0.2563 | 11.5437 |
| ***NTD-8*** | | | | | | |
| 10.4 | 3.900 | 4.012 | 0.112 | 0.7194 | 0.4088 | 10.8088 |
| 10.5 | 3.913 | 4.056 | 0.143 | 0.6418 | 0.2533 | 10.7533 |
| 10.6 | 3.925 | 4.094 | 0.169 | 0.5768 | 0.1344 | 10.7344 |
| 10.7 | 3.938 | 4.135 | 0.197 | 0.5068 | 0.0118 | 10.7118 |
| 10.8 | 3.950 | 4.164 | 0.214 | 0.4644 | -0.0620 | 10.7380 |
| 10.9 | 3.962 | 4.192 | 0.230 | 0.4245 | -0.1322 | 10.7678 |
| 11.0 | 3.975 | 4.235 | 0.260 | 0.3496 | -0.2696 | 10.7304 |
| 11.1 | 3.987 | 4.265 | 0.278 | 0.3048 | -0.3581 | 10.7419 |
| ***NTD-9*** | | | | | | |
| 9.0 | 4.158 | 4.312 | 0.154 | 0.6164 | 0.2059 | 9.2059 |
| 9.1 | 4.168 | 4.334 | 0.166 | 0.5866 | 0.1519 | 9.2519 |
| 9.2 | 4.180 | 4.352 | 0.172 | 0.5718 | 0.1255 | 9.3255 |
| 9.3 | 4.189 | 4.382 | 0.193 | 0.5196 | 0.0340 | 9.3340 |
| 9.4 | 4.205 | 4.402 | 0.197 | 0.5098 | 0.0170 | 9.4170 |
| 9.5 | 4.301 | 4.515 | 0.214 | 0.4686 | -0.0546 | 9.4454 |
| 9.6 | 4.333 | 4.554 | 0.221 | 0.4517 | -0.0843 | 9.5157 |
| 9.7 | 4.364 | 4.615 | 0.251 | 0.3776 | -0.2169 | 9.4831 |
| 9.8 | 4.398 | 4.654 | 0.256 | 0.3657 | -0.2391 | 9.5609 |
| ***NTD-10*** | | | | | | |
| 10.0 | 4.441 | 4.809 | 0.181 | 0.5520 | 0.0906 | 10.0906 |
| 10.1 | 4.461 | 4.622 | 0.204 | 0.4953 | -0.0082 | 10.0918 |
| 10.2 | 4.485 | 4.665 | 0.213 | 0.4733 | -0.0464 | 10.1536 |
| 10.3 | 4.504 | 4.698 | 0.222 | 0.4513 | -0.0849 | 10.2151 |
| 10.4 | 4.513 | 4.726 | 0.240 | 0.4069 | -0.1636 | 10.2364 |
| 10.5 | 4.522 | 4.753 | 0.256 | 0.3675 | -0.2358 | 10.2642 |
| 10.6 | 4.532 | 4.778 | 0.260 | 0.3578 | -0.2541 | 10.3459 |
| 10.7 | 4.541 | 4.792 | 0.285 | 0.2962 | -0.3760 | 10.3240 |

**Table 3.6.4: The *pH (B), $n_H$, log $pK_1^H$* and other terms for NTD series in THF at 298.15 K.**

| *B* | *V'* | *V''* | *V''-V'* | $n_H$ | *log $n_H/(1-n_H)$* | *log $pK_1^H$* |
|---|---|---|---|---|---|---|
| | | | ***NTD-1*** | | | |
| 8.2 | 3.283 | 3.358 | 0.075 | 0.8094 | 0.6280 | 8.8280 |
| 8.3 | 3.286 | 3.392 | 0.106 | 0.7306 | 0.4333 | 8.7333 |
| 8.4 | 3.288 | 3.423 | 0.135 | 0.6569 | 0.2822 | 8.6822 |
| 8.5 | 3.289 | 3.458 | 0.169 | 0.5706 | 0.1234 | 8.6234 |
| 8.6 | 3.293 | 3.472 | 0.179 | 0.5452 | 0.0787 | 8.6787 |
| 8.7 | 3.296 | 3.495 | 0.199 | 0.4944 | -0.0097 | 8.6903 |
| 8.8 | 3.297 | 3.519 | 0.222 | 0.4360 | -0.1118 | 8.6882 |
| 8.9 | 3.301 | 3.536 | 0.235 | 0.4030 | -0.1706 | 8.7294 |
| 9.0 | 3.305 | 3.564 | 0.259 | 0.3421 | -0.2840 | 8.7160 |
| 9.1 | 3.320 | 3.589 | 0.269 | 0.3169 | -0.3335 | 8.7665 |
| | | | ***NTD-2*** | | | |
| 10.8 | 3.494 | 3.601 | 0.107 | 0.7294 | 0.4306 | 11.2306 |
| 10.9 | 3.515 | 3.642 | 0.127 | 0.6790 | 0.3253 | 11.2253 |
| 11.0 | 3.551 | 3.689 | 0.138 | 0.6514 | 0.2716 | 11.2716 |
| 11.1 | 3.589 | 3.749 | 0.160 | 0.5962 | 0.1693 | 11.2693 |
| 11.2 | 3.649 | 3.822 | 0.173 | 0.5640 | 0.1118 | 11.3118 |
| 11.3 | 3.749 | 3.951 | 0.202 | 0.4921 | -0.0137 | 11.2863 |
| 11.4 | 3.849 | 4.062 | 0.213 | 0.4657 | -0.0597 | 11.3403 |
| 11.5 | 4.042 | 4.273 | 0.231 | 0.4231 | -0.1347 | 11.3653 |
| 11.6 | 4.361 | 4.612 | 0.251 | 0.3776 | -0.2170 | 11.2830 |
| 11.7 | 4.820 | 5.092 | 0.272 | 0.3324 | -0.3028 | 11.1972 |
| | | | ***NTD-3*** | | | |
| 8.1 | 3.281 | 3.386 | 0.105 | 0.7331 | 0.4389 | 8.5389 |
| 8.2 | 3.283 | 3.418 | 0.135 | 0.6569 | 0.2821 | 8.4821 |
| 8.3 | 3.286 | 3.445 | 0.159 | 0.5959 | 0.1688 | 8.4688 |
| 8.4 | 3.289 | 3.462 | 0.173 | 0.5604 | 0.1054 | 8.5054 |
| 8.5 | 3.29 | 3.480 | 0.19 | 0.5172 | 0.0299 | 8.5299 |
| 8.6 | 3.292 | 3.500 | 0.208 | 0.4715 | -0.0496 | 8.5504 |
| 8.7 | 3.295 | 3.520 | 0.225 | 0.4283 | -0.1253 | 8.5747 |
| 8.8 | 3.297 | 3.541 | 0.244 | 0.3801 | -0.2124 | 8.5876 |
| 8.9 | 3.299 | 3.568 | 0.269 | 0.3166 | -0.3341 | 8.5659 |
| 9.0 | 3.305 | 3.582 | 0.277 | 0.2964 | -0.3755 | 8.6245 |
| | | | ***NTD-4*** | | | |
| 7.7 | 3.271 | 3.402 | 0.131 | 0.6670 | 0.3016 | 8.0016 |
| 7.8 | 3.273 | 3.419 | 0.146 | 0.6289 | 0.2290 | 8.0290 |
| 7.9 | 3.276 | 3.438 | 0.162 | 0.5882 | 0.1549 | 8.0549 |
| 8.0 | 3.278 | 3.452 | 0.174 | 0.5577 | 0.1008 | 8.1008 |
| 8.1 | 3.281 | 3.465 | 0.184 | 0.5324 | 0.0563 | 8.1563 |
| 8.2 | 3.283 | 3.480 | 0.197 | 0.4993 | -0.0011 | 8.1989 |
| 8.3 | 3.286 | 3.492 | 0.206 | 0.4765 | -0.0408 | 8.2592 |
| 8.4 | 3.289 | 3.508 | 0.219 | 0.4435 | -0.0986 | 8.3014 |
| 8.5 | 3.290 | 3.521 | 0.231 | 0.4130 | -0.1526 | 8.3474 |
| 8.6 | 3.292 | 3.539 | 0.247 | 0.3724 | -0.2267 | 8.3733 |
| 8.7 | 3.295 | 3.551 | 0.256 | 0.3496 | -0.2697 | 8.4303 |
| | | | ***NTD-5*** | | | |
| 11.0 | 3.551 | 3.688 | 0.137 | 0.6540 | 0.2764 | 11.2764 |
| 11.1 | 3.589 | 3.745 | 0.156 | 0.6063 | 0.1876 | 11.2876 |
| 11.2 | 3.649 | 3.819 | 0.170 | 0.5716 | 0.1252 | 11.3252 |

***Continue.....***

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| ***B*** | ***V'*** | ***V''*** | ***V''-V'*** | ***$n_H$*** | ***log $n_H/(1-n_H)$*** | ***log $pK_1^H$*** |
|---|---|---|---|---|---|---|
| 11.3 | 3.749 | 3.932 | 0.183 | 0.5399 | 0.0694 | 11.3694 |
| 11.4 | 3.849 | 4.048 | 0.199 | 0.5008 | 0.0014 | 11.4014 |
| 11.5 | 4.042 | 4.273 | 0.231 | 0.4231 | -0.1347 | 11.3653 |
| 11.6 | 4.361 | 4.612 | 0.251 | 0.3776 | -0.2170 | 11.2830 |
| 11.7 | 4.820 | 5.092 | 0.272 | 0.3324 | -0.3028 | 11.1972 |
| ***NTD-6*** | | | | | | |
| 9.1 | 3.316 | 3.453 | 0.137 | 0.6521 | 0.2728 | 9.3728 |
| 9.2 | 3.325 | 3.473 | 0.148 | 0.6242 | 0.2204 | 9.4204 |
| 9.3 | 3.335 | 3.49 | 0.155 | 0.6066 | 0.1880 | 9.4880 |
| 9.4 | 3.345 | 3.519 | 0.174 | 0.5584 | 0.1020 | 9.5020 |
| 9.5 | 3.354 | 3.543 | 0.189 | 0.5205 | 0.0356 | 9.5356 |
| 9.6 | 3.364 | 3.560 | 0.196 | 0.5028 | 0.0049 | 9.6049 |
| 9.7 | 3.373 | 3.582 | 0.209 | 0.4699 | -0.0523 | 9.6477 |
| 9.8 | 3.382 | 3.601 | 0.219 | 0.4447 | -0.0965 | 9.7035 |
| 9.9 | 3.392 | 3.619 | 0.227 | 0.4245 | -0.1321 | 9.7679 |
| 10.0 | 3.401 | 3.642 | 0.241 | 0.3892 | -0.1958 | 9.8042 |
| ***NTD-7*** | | | | | | |
| 10.7 | 3.481 | 3.597 | 0.116 | 0.7065 | 0.3816 | 11.0816 |
| 10.8 | 3.494 | 3.628 | 0.134 | 0.6611 | 0.2902 | 11.0902 |
| 10.9 | 3.515 | 3.665 | 0.150 | 0.6208 | 0.2141 | 11.1141 |
| 11.0 | 3.551 | 3.728 | 0.177 | 0.5529 | 0.0923 | 11.0923 |
| 11.1 | 3.589 | 3.788 | 0.199 | 0.4978 | -0.0038 | 11.0962 |
| 11.2 | 3.649 | 3.870 | 0.221 | 0.4431 | -0.0994 | 11.1006 |
| 11.3 | 3.749 | 4.005 | 0.256 | 0.3563 | -0.2568 | 11.0432 |
| 11.4 | 3.849 | 4.131 | 0.282 | 0.2926 | -0.3834 | 11.0166 |
| 11.5 | 4.042 | 4.349 | 0.307 | 0.2332 | -0.5169 | 10.9831 |
| ***NTD-8*** | | | | | | |
| 9.9 | 3.392 | 3.547 | 0.155 | 0.6071 | 0.1889 | 10.0889 |
| 10.0 | 3.401 | 3.569 | 0.168 | 0.5742 | 0.1299 | 10.1299 |
| 10.1 | 3.413 | 3.587 | 0.174 | 0.5591 | 0.1032 | 10.2032 |
| 10.2 | 3.425 | 3.608 | 0.183 | 0.5364 | 0.0634 | 10.2634 |
| 10.3 | 3.437 | 3.625 | 0.188 | 0.5239 | 0.0416 | 10.3416 |
| 10.4 | 3.447 | 3.652 | 0.205 | 0.4810 | -0.0331 | 10.3669 |
| 10.5 | 3.459 | 3.670 | 0.211 | 0.4659 | -0.0593 | 10.4407 |
| 10.6 | 3.47 | 3.685 | 0.215 | 0.4559 | -0.0767 | 10.5233 |
| 10.7 | 3.481 | 3.702 | 0.221 | 0.4409 | -0.1031 | 10.5969 |
| ***NTD-9*** | | | | | | |
| 8.6 | 3.292 | 3.427 | 0.135 | 0.6570 | 0.2822 | 8.8822 |
| 8.7 | 3.295 | 3.445 | 0.150 | 0.6189 | 0.2106 | 8.9106 |
| 8.8 | 3.297 | 3.458 | 0.161 | 0.5910 | 0.1598 | 8.9598 |
| 8.9 | 3.299 | 3.487 | 0.188 | 0.5224 | 0.0389 | 8.9389 |
| 9.0 | 3.305 | 3.502 | 0.197 | 0.4996 | -0.0007 | 8.9993 |
| 9.1 | 3.316 | 3.524 | 0.208 | 0.4718 | -0.0491 | 9.0509 |
| 9.2 | 3.325 | 3.547 | 0.222 | 0.4364 | -0.1112 | 9.0888 |
| 9.3 | 3.335 | 3.569 | 0.234 | 0.4060 | -0.1652 | 9.1348 |
| 9.4 | 3.345 | 3.582 | 0.237 | 0.3985 | -0.1787 | 9.2213 |
| 9.5 | 3.354 | 3.604 | 0.25 | 0.3657 | -0.2392 | 9.2608 |

***Continue…..***

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| ***B*** | ***V'*** | ***V''*** | ***V''-V'*** | $n_H$ | $log\ n_H/(1-n_H)$ | $log\ pK_1^H$ |
|---|---|---|---|---|---|---|
| | | | ***NTD-10*** | | | |
| 9.4 | 3.345 | 3.422 | 0.077 | 0.8046 | 0.6146 | 10.0146 |
| 9.5 | 3.354 | 3.461 | 0.107 | 0.7285 | 0.4287 | 9.9287 |
| 9.6 | 3.364 | 3.501 | 0.137 | 0.6525 | 0.2736 | 9.8736 |
| 9.7 | 3.373 | 3.542 | 0.169 | 0.5714 | 0.1249 | 9.8249 |
| 9.8 | 3.382 | 3.581 | 0.199 | 0.4954 | -0.0080 | 9.7920 |
| 9.9 | 3.392 | 3.625 | 0.233 | 0.4093 | -0.1593 | 9.7407 |
| 10.0 | 3.401 | 3.642 | 0.252 | 0.3613 | -0.2474 | 9.7526 |
| 10.1 | 3.413 | 3.653 | 0.282 | 0.2855 | -0.3985 | 9.7015 |

**Table 3.6.5: The *log* $pK_1^H$ values for all the studied compounds calculated by different methods.**

| Compounds | DMF | | THF | |
|---|---|---|---|---|
| | Half-integral method | Average log $pK_1^H$ | Half-integral method | Average log $pK_1^H$ |
| NBN-1 | 10.31 | 10.32 | 8.71 | 8.66 |
| NBN-2 | 10.42 | 10.43 | 9.17 | 9.14 |
| NBN-3 | 9.62 | 9.61 | 8.01 | 7.96 |
| NBN-4 | 9.38 | 9.39 | 7.70 | 7.73 |
| NBN-5 | 9.57 | 9.57 | 7.78 | 7.76 |
| NBN-6 | 9.97($n_H$=0.5)<br>7.02 ($n_H$=1.5) | 9.97($n_H$=0.5)<br>7.31($n_H$=1.5) | 8.39 ($n_H$=0.5)<br>5.73 ($n_H$=1.5) | 8.38 ($n_H$=0.5)<br>5.94 ($n_H$=1.5) |
| NBN-7 | 10.42 | 10.43 | 8.52 | 8.50 |
| NBN-8 | 9.52 | 9.53 | 7.93 | 7.90 |
| NBN-9 | 9.77 ($n_H$=0.5)<br>6.30 ($n_H$=1.5) | 9.78 ($n_H$=0.5)<br>6.84 ($n_H$=1.5) | 8.22 ($n_H$=0.5)<br>5.47 ($n_H$=1.5) | 8.20 ($n_H$=0.5)<br>5.92 ($n_H$=1.5) |
| NBN-10 | 9.78 | 9.796 | 8.30 | 8.26 |
| NTD-1 | 9.19 | 9.18 | 8.69 | 8.71 |
| NTD-2 | 11.82 | 11.80 | 11.32 | 11.28 |
| NTD-3 | 8.92 | 8.90 | 8.54 | 8.54 |
| NTD-4 | 8.72 | 8.74 | 8.21 | 8.20 |
| NTD-5 | 12.01 | 12.01 | 11.35 | 11.31 |
| NTD-6 | 9.89 | 9.96 | 9.61 | 9.58 |
| NTD-7 | 11.42 | 11.43 | 11.07 | 11.06 |
| NTD-8 | 10.74 | 10.75 | 10.37 | 10.33 |
| NTD-9 | 9.38 | 9.39 | 9.04 | 9.04 |
| NTD-10 | 10.23 | 10.25 | 9.84 | 9.83 |

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# Chapter-4

# Biological Activities

## INTRODUCTION

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

As mentioned in Chapter 2, benzodiazepines, aminopyrimidines, cyanopyridines, isoxazoles and thiadiazepines are known for a wide variety of biological activities.

In the present chapter, the antibacterial activities of the synthesized compounds have been screened against some Gram positive and Gram negative bacterial stains.

## EXPERIMENTAL

The antibacterial activities of all synthesized compounds were studied in DMF and DMSO.

All the synthesized compounds were re crystallized prior to use. The solvents, DMF and DMSO were also purified before use by standard method[1].

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

**Test Microorganisms:**

The synthesized compounds were tested for its antibacterial activity against Gram positive bacteria viz. *Bacillus cereus* ATCC11778, *Micrococcus flavus* ATCC10240, *Staphylococcus epidermidis* ATCC12228, and *Staphylococcus aureus* ATCC29737 and Gram negative bacteria viz. *Proteus mirabilis* NCIM2241, *Salmonella typhimurium* ATCC23564, *Citrobacter freundii* ATCC10787 and *Klebsiella pneumoniae* NCIM2719.

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[2,3] using Mueller Hinton Agar No.2 as the nutrient medium. The agar well diffusion method was preferred to be used in this study because it was found to be better than the disc diffusion method as suggested by Parekh et al.[3] The bacterial strains were activated by inoculating a loop full of test strain in 25 ml of N-broth and the same was incubated for 24 h in an incubator at 37$^{o}$ C. 0.2 ml of the activated strain was inoculated in Mueller Hinton Agar. Mueller Hinton Agar kept at 45$^{o}$C was then poured in the Petri dishes and allowed to solidify. After solidification of the media, 0.85 cm ditch was made in the plates using a sterile cork borer and these were completely filled with the test solution. The plates were incubated for 24 h at 37$^{o}$C. The mean value

obtained for the three wells was used to calculate the zone of growth inhibition of each sample. The controls were maintained for each bacterial strain and each solvent. The inhibition zone formed by these compounds against the particular test bacterial strain determined the antibacterial activities of these synthesized compounds.

## RESULTS AND DISCUSSION

### 1,5-BENZODIAZEPINES

Figure 4.1 shows inhibition against Gram positive bacteria in DMSO. It is observed that against *B. cereus*, NBN-10 shows maximum inhibition whereas NBN-6 and NBN-9 exhibited minimum inhibition. NBN-1 and NBN-2 showed no inhibition at all. In NBN-10, the side chain has no substitution group whereas NBN-6 and NBN-9 possess p-hydroxy and o-hydroxy groups. Thus, when there is no substitution group attached to side chain, the compound showed maximum inhibition against *B. cereus*.

For *M. flavus*, again NBN-10 showed maximum inhibition and NBN-9 showed minimum inhibition. Thus, in this case also, absence of any group is most effective and o-hydroxy is least effective.

Against *S. epidermidis*, only NBN-10 exhibited inhibition. Other compounds had no effect at all.

Thus, in DMSO *S. epidermidis* is most resistant bacteria and compound having no substitution group is most effective.

Figure 4.2 shows inhibition against Gram positive bacteria in DMF. Against *B. cereus* and *M. flavus* all compounds shows inhibition and maximum is observed for NBN-3 and NBN-5 for *B. cereus* and NBN-10 for *M. flavus* respectively. Thus, for *B. cereus* p-bromo group (as in NBN-3) and m-nitro (as in NBN-5) are most effective whereas for *M. flavus* absence of any group (as in NBN-10) is most effective. For *S. epidermidis*, again only NBN-10 exhibited activity. Other compounds had no effect on this bacterium.

Thus, in DMF also, *S. epidermidis* is most resistant bacteria. For *M. flavus* and *S. epidermidis*, compound having no substitution group is most effective.

Against Gram negative bacteria in DMSO, Figure 4.3 shows zone of inhibition for the studied compounds. It is evident that all compounds exhibited activity against *P. mirabilis* and activity is maximum for NBN-10 which has no substitution group. Against *S. typhimurium*, again only NBN-10 showed activity. For *K. pneumoniae*, NBN-3 had no effect and maximum is again observed by NBN-10. Thus, for the studied Gram negative bacteria, in DMSO

**Figure 4.1: Antibacterial activity of benzodiazepines against Gram positive bacteria in DMSO.**

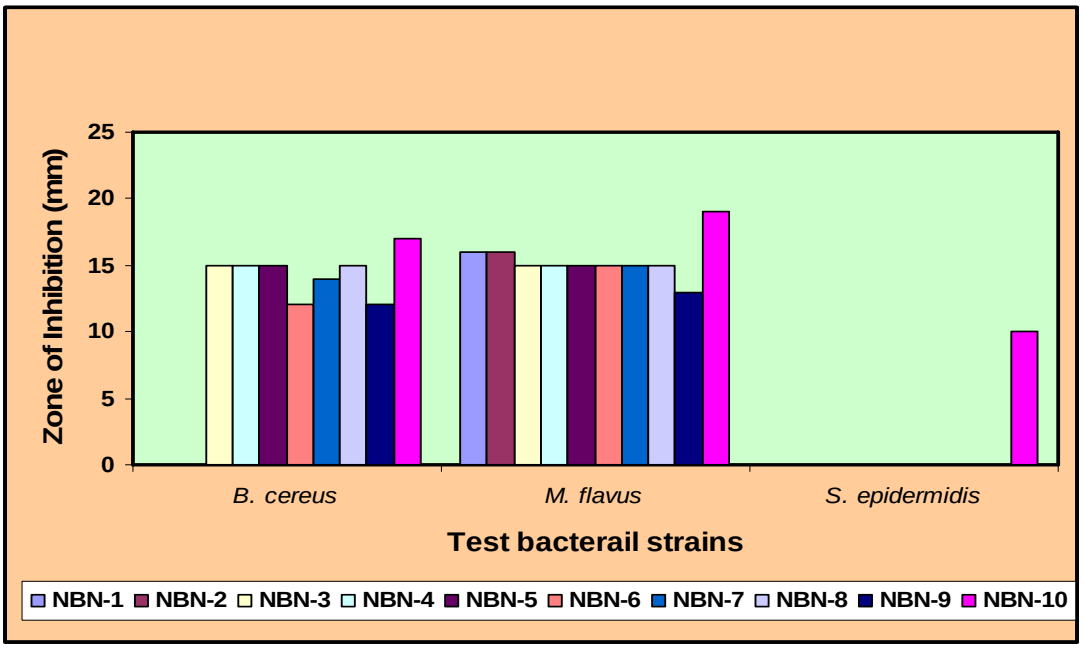



**Figure 4.2: Antibacterial activity of benzodiazepines against Gram positive bacteria in DMF.**

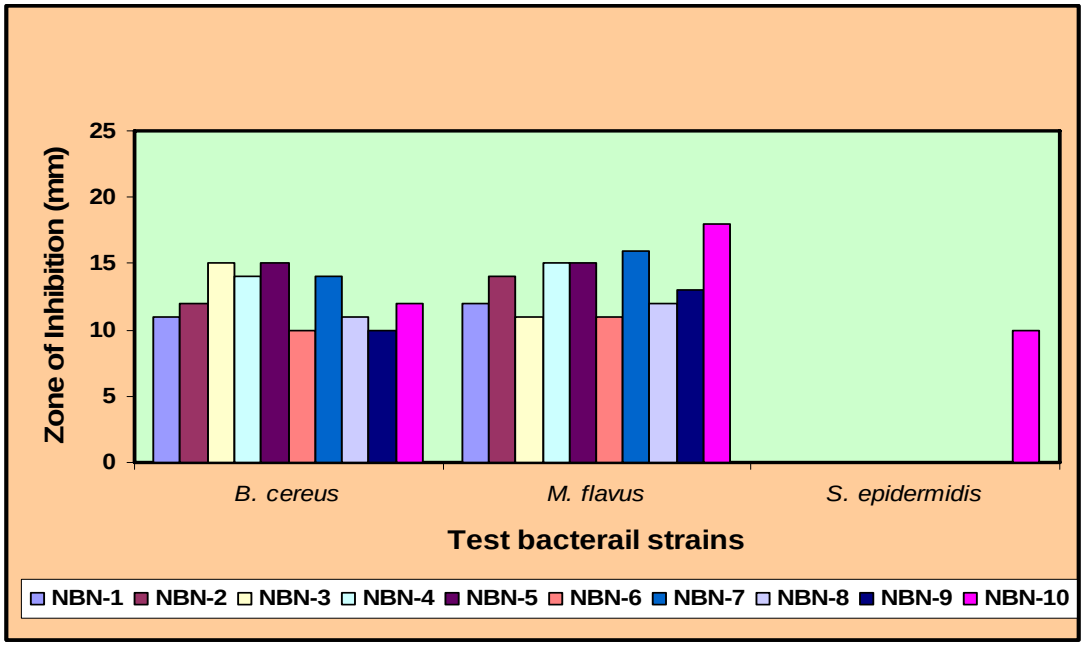


**Figure 4.3: Antibacterial activity of benzodiazepines against Gram negative bacteria in DMSO.**

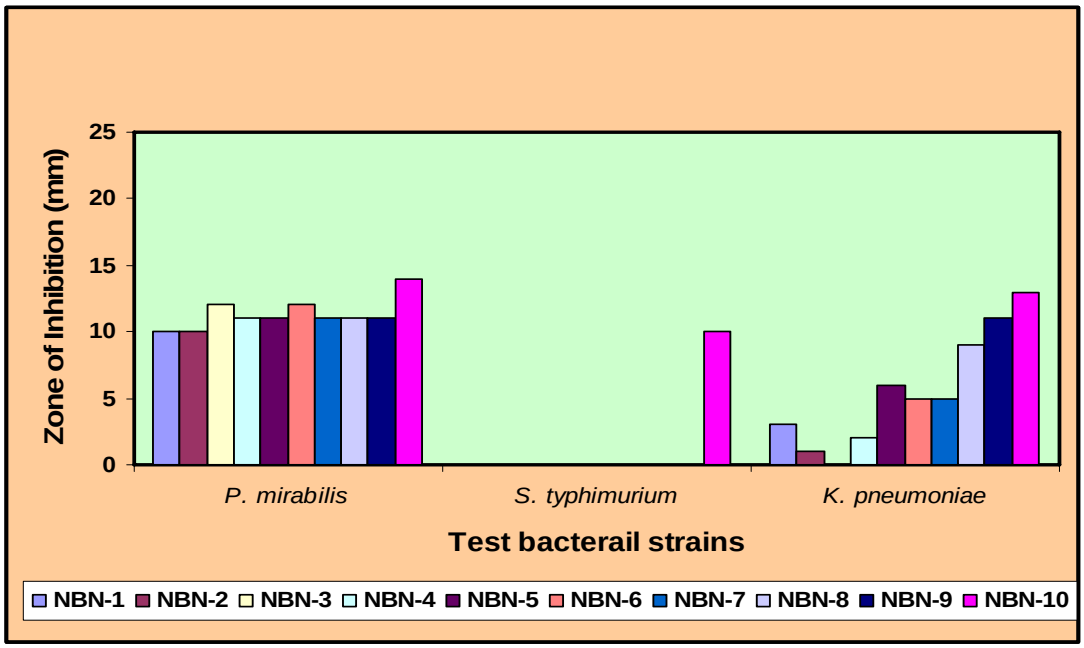
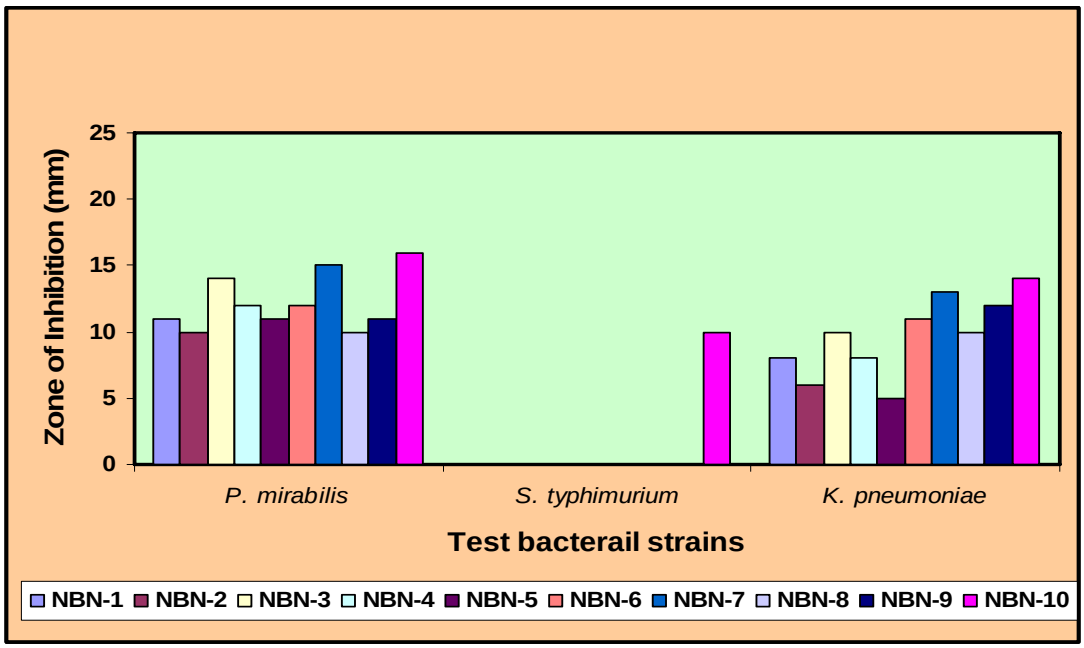



**Figure 4.4: Antibacterial activity of benzodiazepines against Gram negative bacteria in DMF.**



NBN-10 is most effective and *S. typhimurium* is most resistant bacteria. It is concluded that when there is no group attached to side chain, inhibition is maximum.

Figure 4.4 shows zone of inhibition against Gram negative bacteria in DMF. It is evident that for all the three bacteria, NBN-10 showed maximum activity. Against *P. mirabilis*, minimum is observed by NBN-1 and NBN-2. For *K. pneumoniae,* NBN-5 showed minimum inhibition. For *S. typhimurium,* other compounds had no effect at all. Thus in DMF also, *S. typhimurium* is most resistant bacteria and compound with no substitution group is most effective.

So overall, in case of NBN series although there is slight change in inhibition in the two solvents, the presence of substituents group effects inhibition and when there is no substitution group in the side change, compound exhibited maximum inhibition.

**AMINOPYRIMIDINES**

Figure 4.5 shows zone of inhibition against Gram positive bacteria in DMSO. It is observed that NAP-8 exhibited maximum inhibition against all the studied Gram positive bacteria. The maximum inhibition is against *M. flavus*. NAP-8 contains p-chloro group in side chain. Against *B. cereus*, only NAP-6 showed no inhibition. However, against *M. flavus* and S. aureus, many compounds are not effective. Thus, in DMSO for these Gram positive bacteria, p-chloro group in side chain is most effective. *S. aureus* is most resistant bacteria.

In DMF, Figure 4.6 shows zone of inhibition against Gram positive bacteria. Again NAP-8 showed maximum inhibition against *B. cereus* and *S. aureus*. However, against *M. flavus* NAP-9 showed slightly more inhibition. Figure 4.5 and 4.6 show inhibition is greater in DMF than in DMSO. In DMF, all the compounds showed inhibition against studied Gram positive bacteria.

Figure 4.7 and 4.8 show zone of inhibition against Gram negative bacteria in DMSO and DMF respectively. In DMSO, NAP-4, NAP-6 and NAP-7 showed no inhibition at all and NAP-8 exhibited maximum inhibition. Against *S. typhimurium* and *C. freundii* only NAP-6 and NAP-2 respectively showed inhibition. Other compounds had no effect at all. Whereas in DMF, all the

**Figure 4.5: Antibacterial activity of aminopyrimidines against Gram positive bacteria in DMSO.**

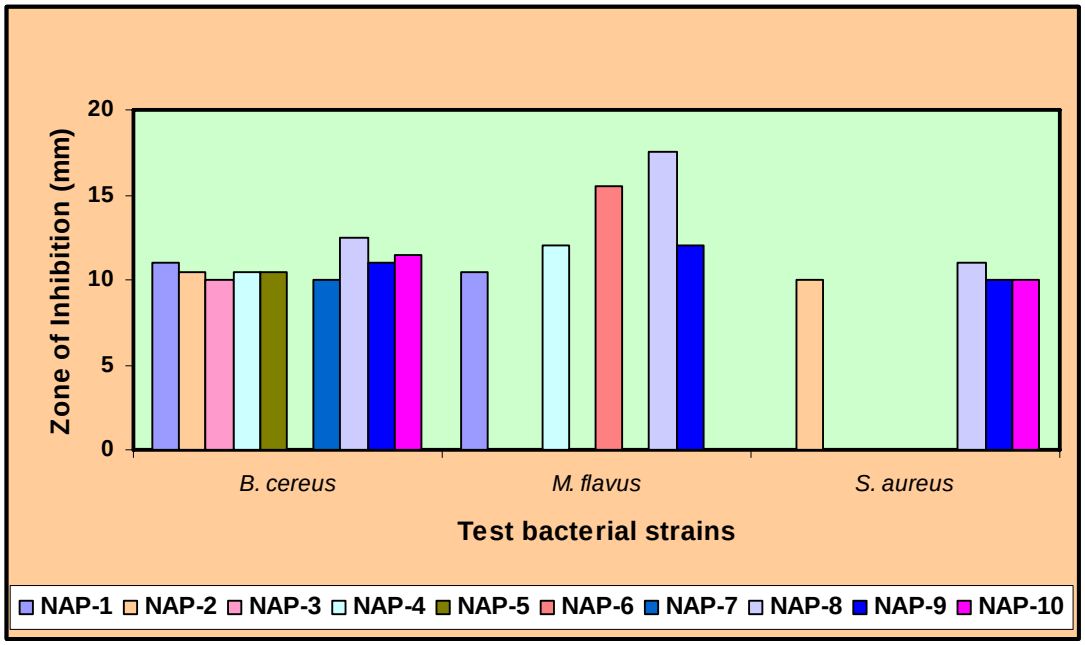



**Figure 4.6: Antibacterial activity of aminopyrimidines against Gram positive bacteria in DMF.**

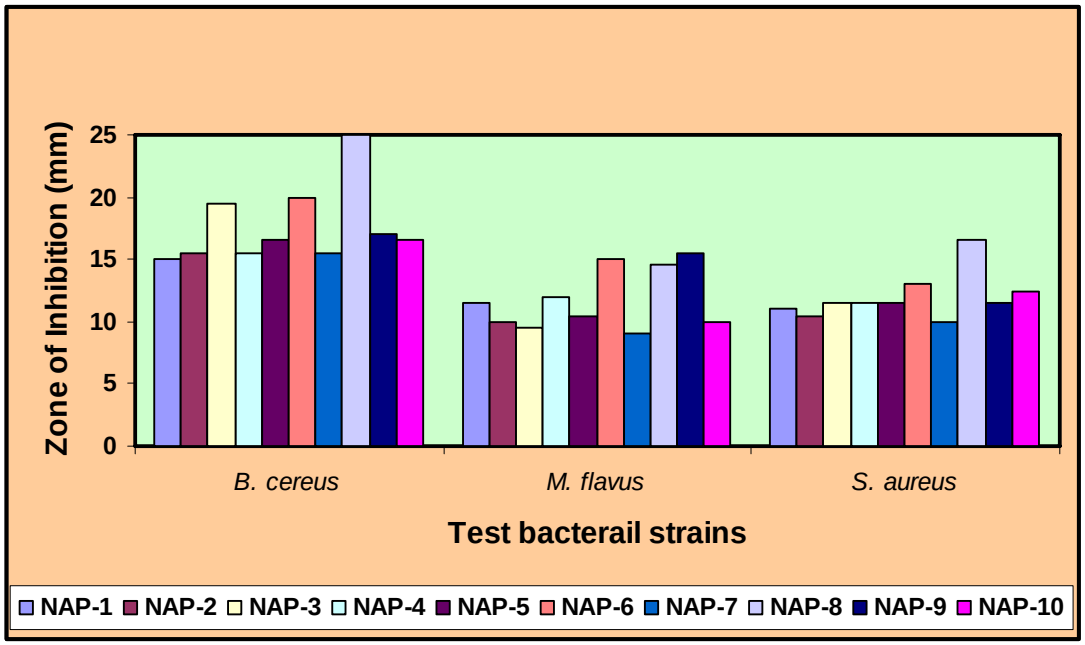


**Figure 4.7: Antibacterial activity of aminopyrimidines against Gram negative bacteria in DMSO.**

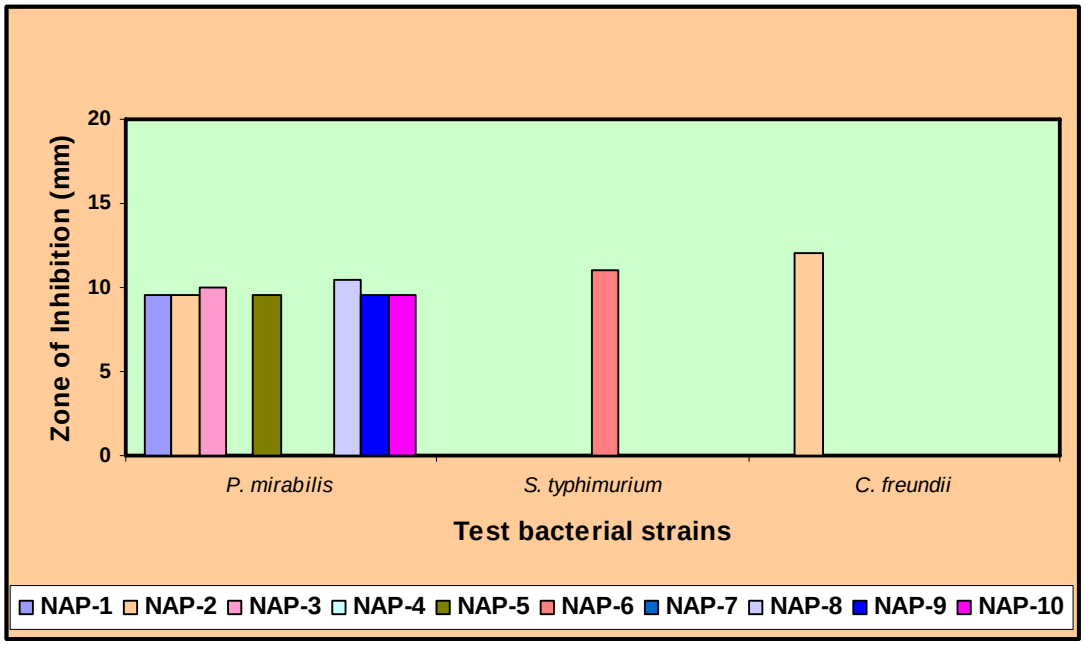
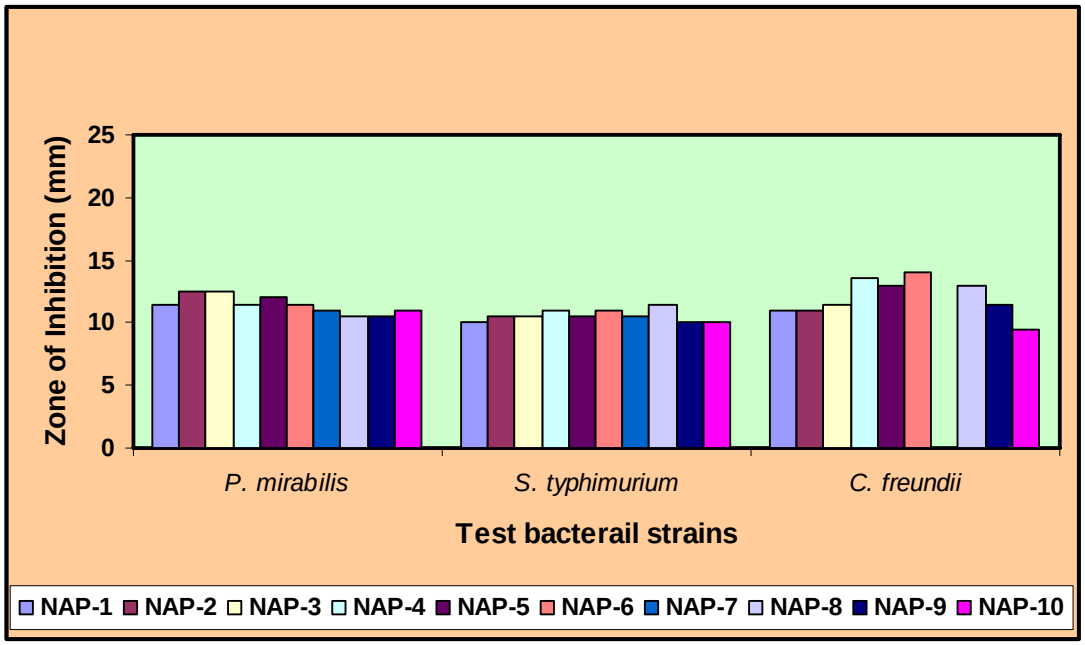



**Figure 4.8: Antibacterial activity of aminopyrimidines against Gram negative bacteria in DMF.**



compounds exhibited inhibition against the studied Gram negative bacteria except NAP-7 for *C. freundii*. Against *P. mirabilis* inhibition is more for NAP-2 and NAP-3. NAP-8 showed maximum inhibition for *S. typhimurium* and NAP-6 showed maximum against *C. freundii*. Overall, there is not much difference in activity of these compounds against studied bacteria.

Thus, in this series of compounds, solvent and substitution play an important role in inhibition. Against both Gram positive bacteria, DMF is good solvent. NAP-8 contains p-chloro substitution which is found to be most effective in both DMSO and DMF against Gram positive bacteria.

Against Gram negative bacteria also, DMF is found to be good solvent where almost all the substituents are effective. However, p-amino, p- bromo, p-chloro and p-hydroxy groups are proved to be slightly better than others.

**CYANOPYRIDINES**

Figure 4.9 showed inhibition against Gram positive bacteria in DMSO. In DMSO, against *B. cereus* except NCP-4 others showed inhibition and inhibition is again maximum for NCP-8 followed by NCP-6. There is no inhibition observed by any compounds against *M. flavus* and *S. aureus*.

In DMF, all the compounds exhibited inhibition against *B. cereus* and *S. aureus* as shown in Figure 4.10. Further, maximum activity is for NCP-8. Against *M. flavus*, only NCP-9 and NCP-10 exhibited inhibition and inhibition is same for both the compounds.

Thus, for this NCP series also, DMF is good solvent and overall p-chloro substitution is most effective against studied Gram positive bacteria.

In case of Gram negative bacteria, Figure 4.11 shows zone of inhibition in DMSO. The studied compounds donot exhibit any activity against *S. typhimurium* and *C. freundii*. However, only NCP-3, NCP-4 and NCP-8 showed same inhibition for *P. mirabilis*. Thus, p-bromo, P-nitro and p-chloro substitution affect *P. mirabilis*.

Figure 4.12 shows that in DMF, all the compounds showed activity against all the three gram negative bacteria. For *P. mirabilis*, inhibition is almost similar for all the compounds. For *S. typhimurium* maximum is for NCP-10 and minimum for NCP-5, NCP-6 and NCP-7. Thus, when there is no

**Figure 4.9: Antibacterial activity of cyanopyridines against Gram positive bacteria in DMSO.**

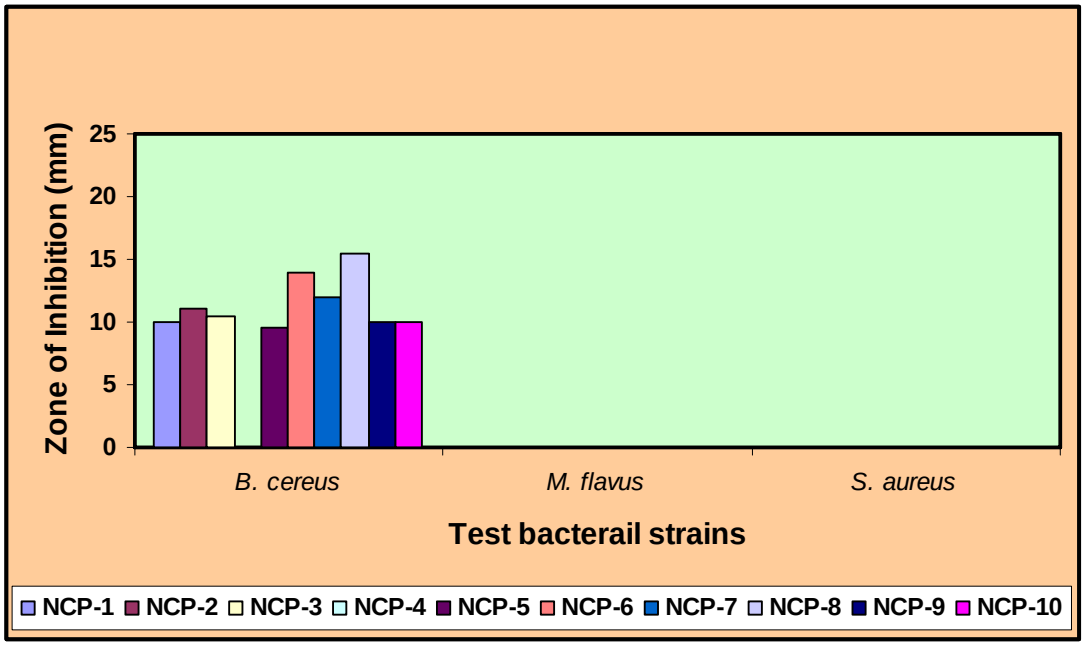



**Figure 4.10: Antibacterial activity of cyanopyridines against Gram positive bacteria in DMF.**

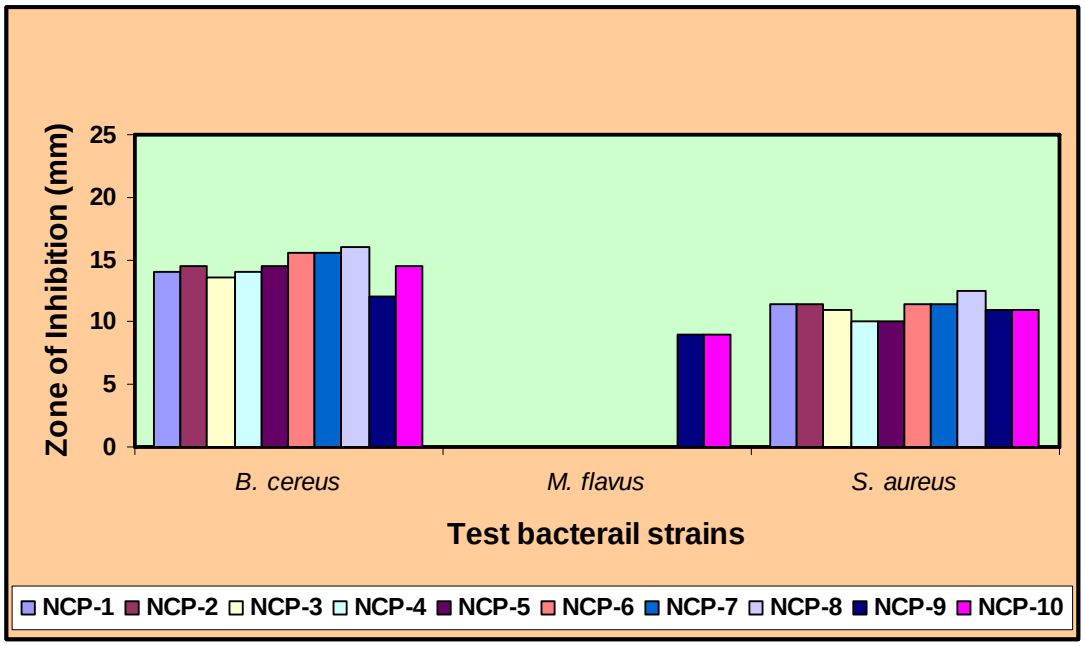


**Figure 4.11: Antibacterial activity of cyanopyridines against Gram negative bacteria in DMSO.**

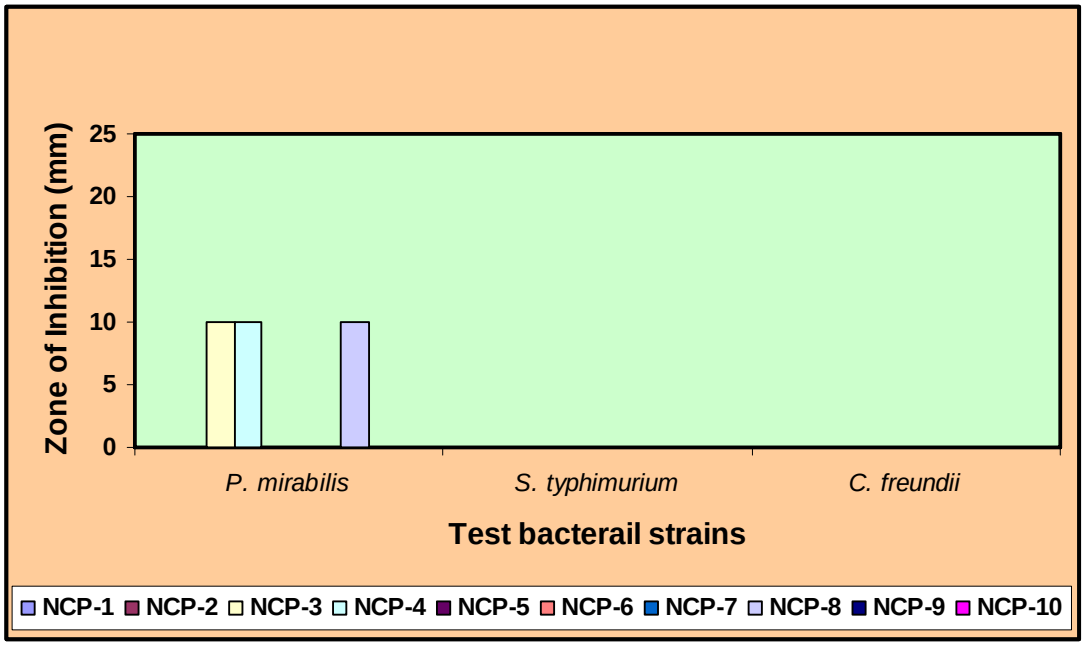
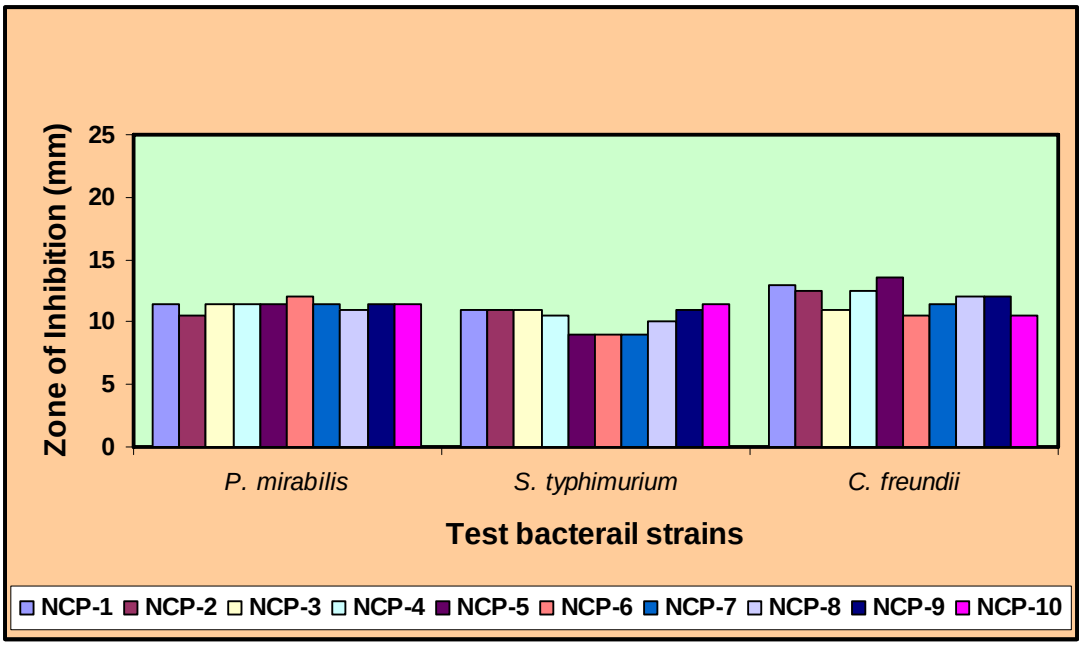



**Figure 4.12: Antibacterial activity of cyanopyridines against Gram negative bacteria in DMF.**



substitution group present (as in NCP-10), it is most effective for this bacteria. Against *C. freundii*, maximum inhibition is for NCP-5 and minimum for NCP-6 and NCP-10. Thus, m-nitro is more effective for *C. freundii* than others. Overall, DMF is good solvent for Gram negative bacteria.

**ISOXAZOLES**

Figure 4.13 shows inhibition against Gram positive bacteria in DMSO. It is evident from Figure that for *B. cereus*, only NISO-2, NISO-4, NISO-5 and NISO-6 showed inhibition. Other compounds had no effect at all. Further, NISO-2 having p-amino group showed greater inhibition. Against *M. flavus* only NISO-5 showed inhibition. Thus, m-nitro group (in NISO-5) is the only group effective against M. flavus. For *S. aureus*, all compounds exhibited no inhibition. Thus, *S. aureus*, is most resistant bacteria in DMSO.

In DMF, Figure 4.14 shows inhibition against Gram positive bacteria. Against *B. cereus*, all compounds exhibited inhibition and maximum inhibition is for NISO-6 containing p-hydroxy group. Minimum inhibition is observed by NISO-3 and NISO-4 containing p-bromo and p-nitro group. Against *M. flavus*, NISO-5 show maximum activity followed by similar activity of NISO-1, NISO-3 and NISO-4. Whereas NISO-7, NISO-8 and NISO-10 shows similar minimum activity. NISO-2 and NISO-9 showed no activity at all. Thus, in this case m-nitro group is most effective. For *S. aureus*, again all compounds showed inhibition and it is maximum for NISO-6. NISO-8 and NISO-9 showed minimum activity. Thus, for *S. aureus* also p-hydroxy is most effective and p-chloro and o-hydroxy had minimum effect.

Thus in DMF, NISO-5 and NISO-6 are most effective compounds which contains m-nitro and p-hydroxy group respectively.

Figures 4.15 and 4.16 shows zone of inhibition against Gram negative bacteria in DMSO and DMF respectively. In DMSO, against *P. mirabilis* only NISO-1, NISO-2 and NISO-7 showed inhibition which is of same magnitude. Others compounds showed no inhibition at all. For *S. typhimurium* NISO-1, NISO-5, NISO-6 and NISO-8 showed inhibition. Other compounds had no effect on this bacterium. Maximum inhibition is for NISO-1 and minimum for NISO-8. Thus, for *S. typhimurium* p-methoxy substitution is most effective.

**Figure 4.13: Antibacterial activity of isoxazoles against Gram positive bacteria in DMSO.**

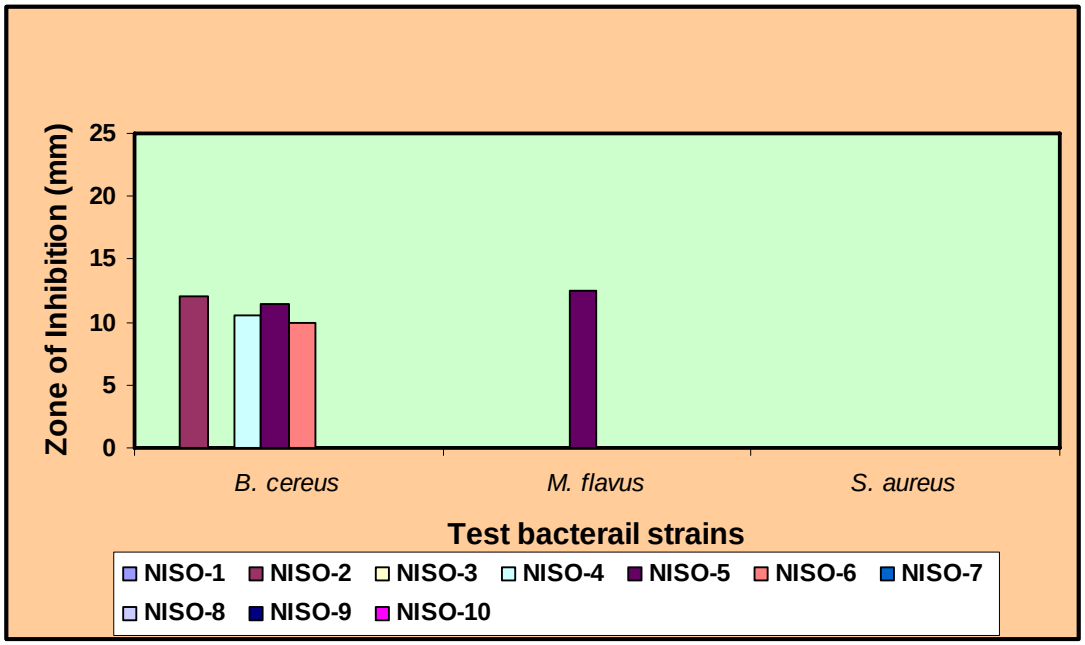



**Figure 4.14: Antibacterial activity of isoxazoles against Gram positive bacteria in DMF.**

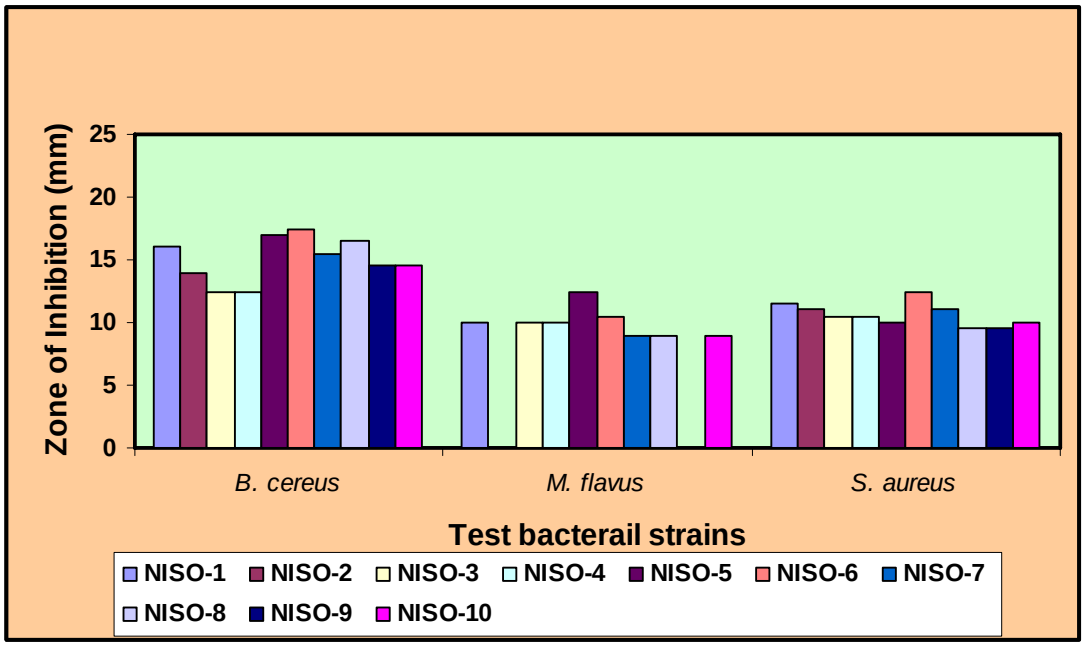


**Figure 4.15: Antibacterial activity of isoxazoles against Gram negative bacteria in DMSO.**

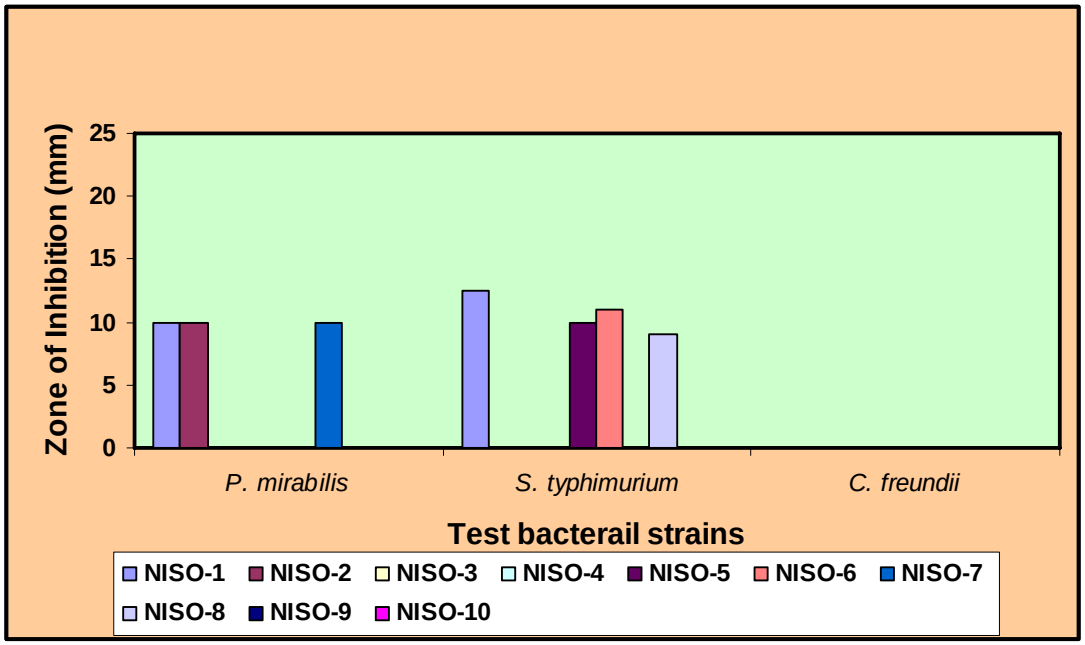
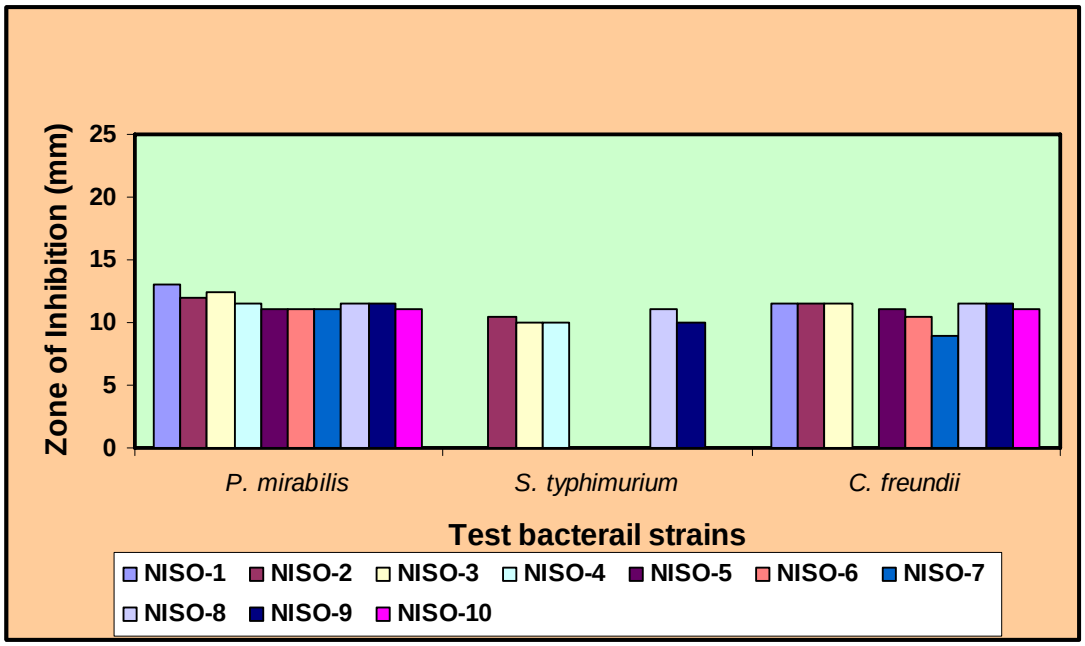



**Figure 4.16: Antibacterial activity of isoxazoles against Gram negative bacteria in DMF.**



which is in NISO-1. No inhibition is observed against *C. freundii* by any compounds. Thus, in DMSO, *C. freundii* is most resistant bacteria.

In DMF, all compounds showed almost similar inhibition against *P. mirabilis*. Against *S. typhimurium*, NISO-8 show maximum activity followed by NISO-2 whereas NISO-3, NISO-4 and NISO-9 show similar minimum activity while NISO-1, NISO-5, NISO-6, NISO-7 and NISO-10 shows no activity. Against *C. freundii*, all the compounds show almost similar average activity except NISO-4. Thus, all substitutions are effective for *C. freundii* except p-nitro (as in NISO-4). Thus, in DMF, *S. typhimurium* is most resistant bacteria.

**1,3,4-THIADIAZEPINES**

Figure 4.17 shows zone of inhibition in DMSO against Gram positive bacteria. Against *B. cereus* NTD-6 showed maximum inhibition followed by NTD-1. NTD-2, NTD-3, NTD-4, NTD-5, NTD-8 and NTD-10 had no effect at all. NTD-6 contains 2,5-dichloro group which is proved to be most effective in DMSO. For *M. flavus*, NTD-3, NTD-4, NTD-6, NTD-7, NTD-8 and NTD-10 showed no inhibition. Maximum is observed by NTD-1 having p-fluoro group. Against *S. aureus*, except NTD-8 and NTD-10, other compounds showed inhibition and maximum is observed by NTD-6. Thus for *S. aureus* also, 2,5-dichloro group is most effective.

Figure 4.18 shows zone of inhibition against Gram positive bacteria in DMF. It is observed that NTD-1 to NTD-5 and NTD-7 had no effect against *B. cereus*. For other compounds, little inhibition is observed which is higher for NTD-6 having 2,5-dichloro group. Against *M. flavus*, NTD-7, NTD-8 and NTD-10 showed no inhibition. Others showed some activity which is higher for NTD-9 having 2,4-dichloro group. For *S. aureus*, again few compounds exhibited little inhibition. However, inhibition is significant against NTD-6 having 2,5-dichloro group.

In DMF, against Gram positive bacteria, inhibition is less than those in DMSO. Thus, DMSO is good solvent for these compounds. Overall 2,5-dichloro substitution (as in NTD-6) is proved to most effective in both the solvents.

**Figure 4.17: Antibacterial activity of thiadiazepines against Gram positive bacteria in DMSO.**

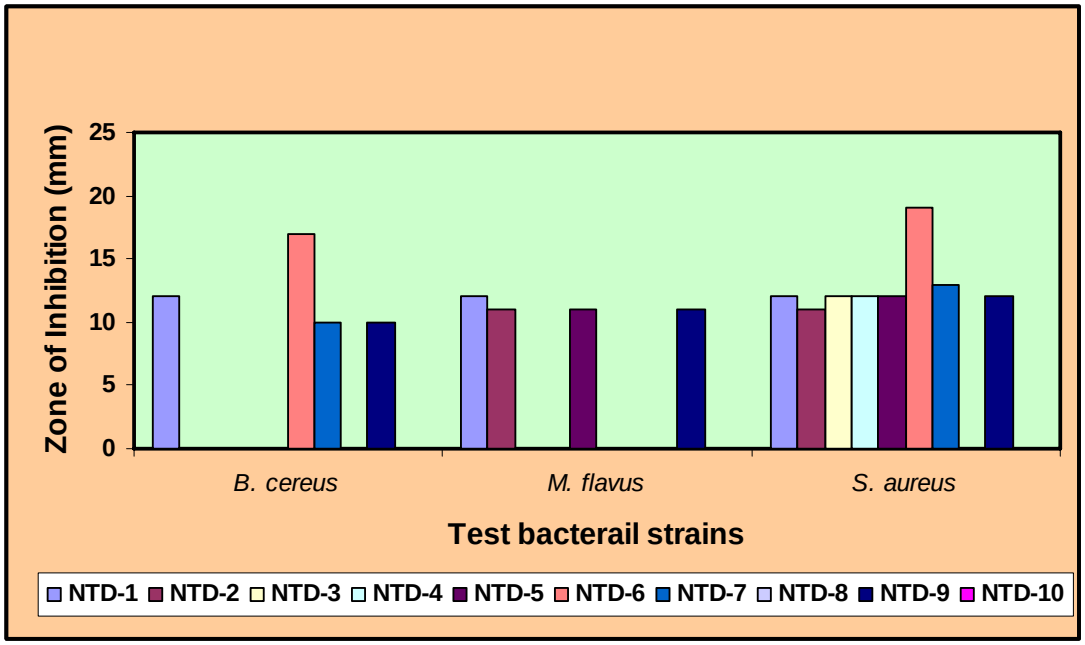
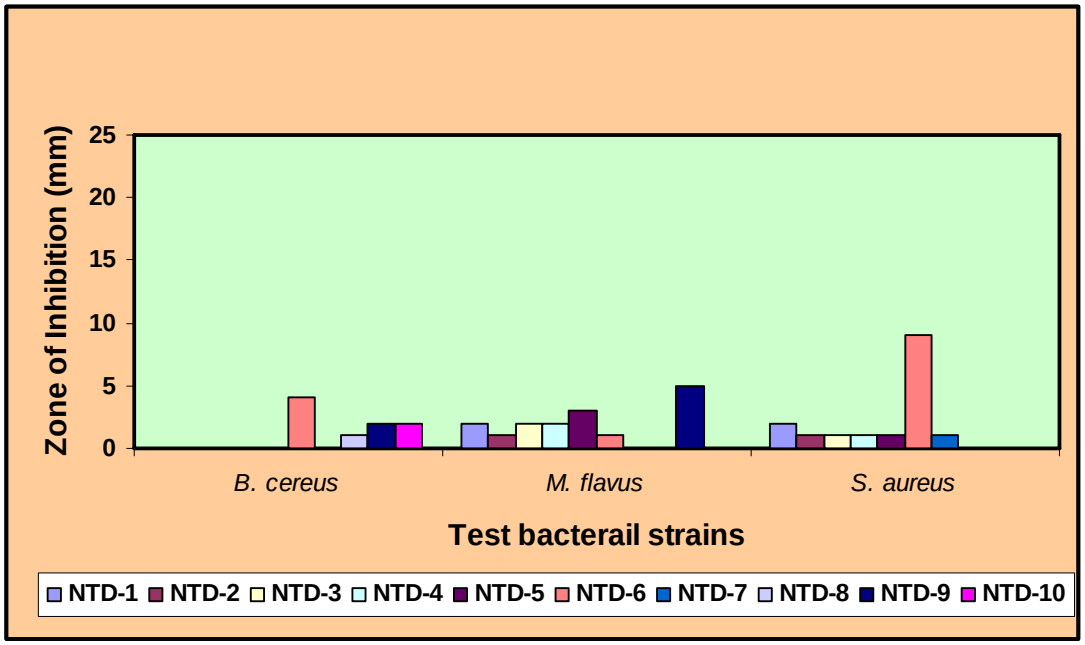



**Figure 4.18: Antibacterial activity of thiadiazepines against Gram positive bacteria in DMF.**



Against Gram negative bacteria Figures 4.19 and 4.20 show zone of inhibition in DMSO and DMF. It is clear from these figures that n DMSO, slight activity is observed for both *K. pneumoniae* and *P. mirabilis* for some compounds. However, in DMF, only NTD-7 and NTD-6 exhibited activity for *K. pneumoniae* and *P. mirabilis* respectively and these activities are also very very less which is not very significant.

So, it is concluded that in both solvents, Gram negative bacteria *K. pneumoniae* and *P. mirabilis* are resistant.

**Figure 4.19: Antibacterial activity of thiadiazepines against Gram negative bacteria in DMSO.**

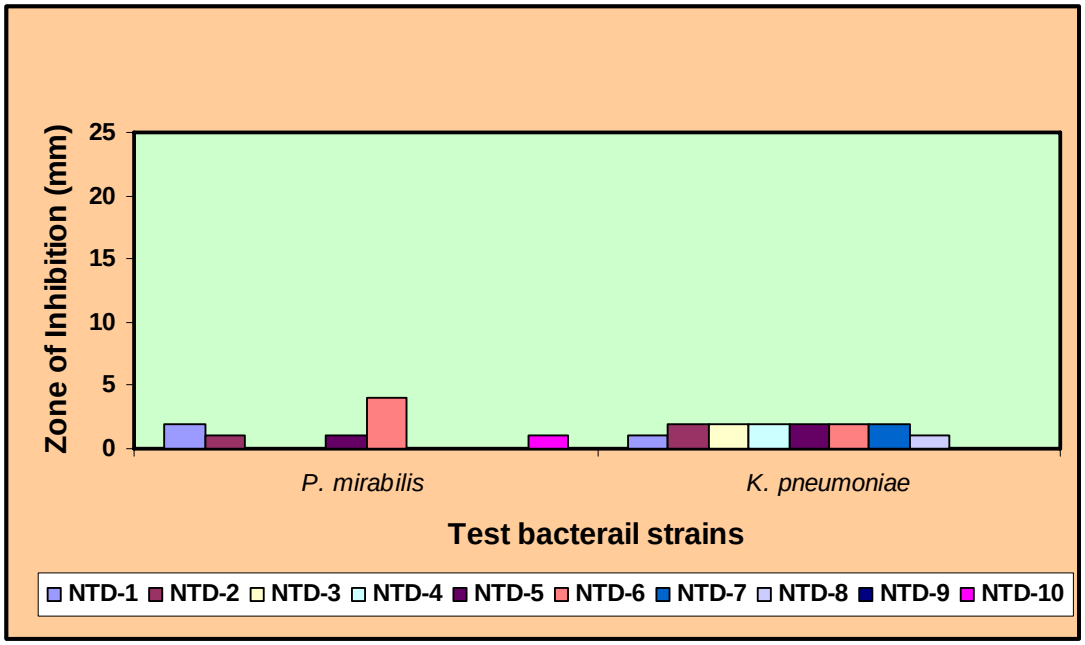
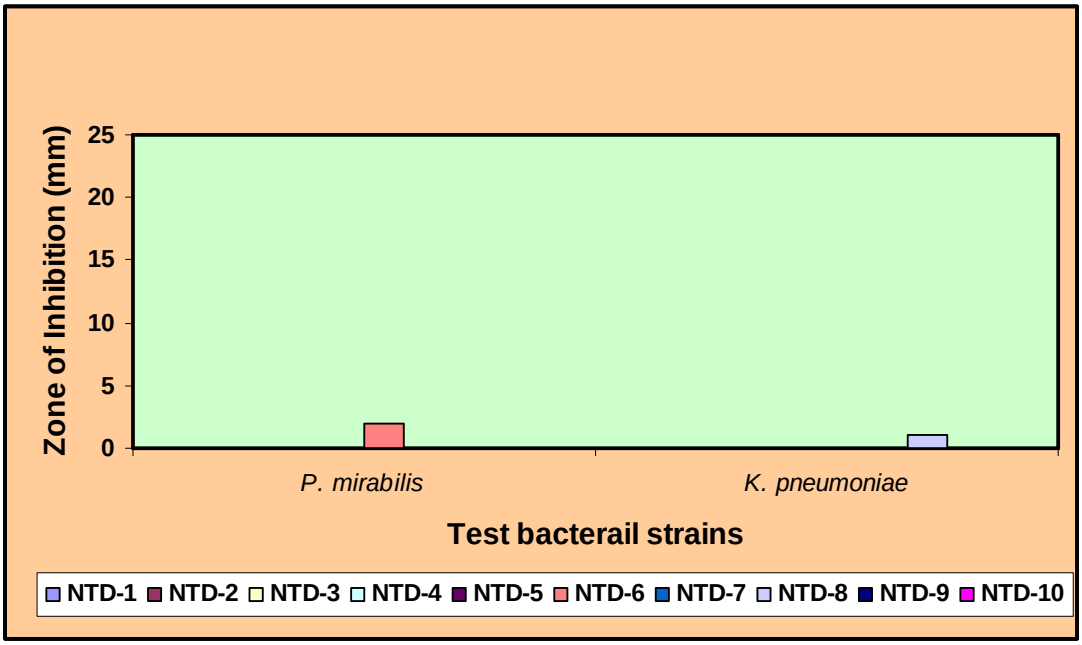



**Figure 4.20: Antibacterial activity of thiadiazepines against Gram negative bacteria in DMF.**



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# A Comprehensive Summary of the Work

## 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 aims and objective of the present work.

**CHAPTER - 2**: **Part-1** deals with the synthesis of benzodiazepines, aminopyrimidines, cyanopyridines and isoxazoles bearing quinoline moiety whereas in **Part-2** synthesis of thiadiazepines having triazole moiety are described along with their physical constant data. In both the parts I and II, the characterizations of synthesized compounds are done by IR, NMR and mass spectral data. The spectra and the characteristic peak positions of IR and NMR spectra of some compounds are reported. Further, mass spectra and possible fragmentation schemes are given in this chapter.

**Part-3** deals with the comparison of synthesis of benzodiazepines by conventional, microwave and ultrasound irradiation methods. It is observed that both microwave and ultrasound methods give comparatively good yield of products than conventional method. Further, by using these techniques, reaction time is reduced to few minutes (in microwave) and to few hours (in ultrasound technique).

**CHAPTER - 3**: The physicochemical properties of synthesized benzodiazepines and thiadiazepines were also studied. The different properties are given in different sections. For the study of all physicochemical properties, DMF and THF are used.

***Section-I***: This section describes the acoustical properties of benzodiazepines and thiadiazepines in solutions at 298.15 K. The various acoustical parameters helped to understand the different types of interactions occurring in the solutions. It is observed that for both the series, in the studied solvents, solute-solvent interactions dominate.

***Section-II:*** In this section, the densities of benzodiazepines and thiadiazepines were measured in DMF and THF solutions at 298.15 K. The experimental density values are found to be different than those calculated

theoretically for all the studied systems, which may be due to solvation of ions in solutions. In solutions of different solvents, density is found to be different due to different interactions. The molar refraction and refractive index of compounds are also found to be different in each solvent.

***Section-III:*** This section deals with the conductance of studied compounds in solutions of DMF and THF at 298.15 K. It is observed that for all the studied compounds, conductivities are less in THF than in DMF. Further, all the studied compounds are weak electrolytes in nature.

***Section-IV:*** This section describes the heat of solution of all the studied compounds in DMF and THF at different temperatures (308.15 -328.15 K). It is observed that the solubility of all the compounds increases linearly with temperature in both the solvents. Comparison of solubility of these compounds in DMF and THF shows that overall solubility is greater in DMF than in THF. The Gibb's free energy and entropy of different solutions have also been evaluated. $\Delta H_s$ and $\Delta G$ values are found to be positive whereas $\Delta S$ values are negative. Positive $\Delta H_s$ indicates endothermic dissolution of compounds. Whereas positive $\Delta G$ suggests that the dissolution process is not spontaneous. Further, the negative values of entropy indicate less random ness in solutions.

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***Section-V:*** The thermal properties of synthesized benzodiazepines are described in this section. DSC and TGA thermo grams were scanned at the heating rate of $10^0$ C per minute. It is observed that thermal stability depends on the presence of substituents in the compound. From all the studied compounds NBN-10 is unstable whereas NBN-8 is most stable followed by NBN-6. NBN-10 has no side chain or no substitution. While in other compounds, various substituents are attached. This suggests that absence of substituent decreases the stability of the studied compounds. When chloro group is present at para position (as in NBN-8), stability is highest which is followed by the presence of hydroxyl group at para position (as in NBN-6). The presence of other groups also shows significant stability.

Further, the melting points determined by DSC and by open capillary methods are found to be in good agreement. The heat of reaction is found to be maximum for NBN-3 and minimum for NBN-5. However, no correlation could be established between heat of reaction, kinetic parameters, melting temperature, thermal stability and substitution group

Various kinetic parameters such as order of reaction, energy of activation, frequency factor and entropy change were also calculated for each step. The order of reaction is quite different in different steps for different compounds. Further, the change in entropy values is found to be both positive and negative in different steps. 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-VI:*** In this section, the dissociation constants of benzodiazepines and thiadiazepines in water-DMF and water-THF mixtures are reported at 298.15 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.

Comparison of $pK_1^H$ values of NBN series shows that in both the solvent, NBN-4 is more acidic which contains p-nitro group. However, NBN-2 is most basic in both the systems as expected due to the presence of p-amino group. NBN-6 and NBN-9 both contain hydroxyl groups at para and ortho positions respectively. But, NBN-9 is found to be more acidic than NBN-6. However, for NTD series, in both solvent systems, NTD-5 is more basic in both the systems as expected. It contains p-methyl group. But, NTD-4 is found to be more acidic as it contains p-nitro group.

**CHAPTER - 4:** The antibacterial activities of all the synthesized compounds in DMF and DMSO are explained in this chapter. Different bacterial strains behave differently in different solvents. Further, presence of different substituents also affects inhibition.

# LIST OF PUBLISHED/ACCEPTED/COMMUNICATED PAPERS

## ***Published papers***

1 **Thermodynamic studies of some α-naphthyl amine derivatives in DMF and THF solution at 313.15 K,** Shipra Baluja, Nilesh Godvani and Nirmal Pandya, *Ultra chemistry,* **39(2)**, 131-136 (2007).

2 **Thermal profile and decomposition kinetics of some new schiff bases of 5-amino isopthalic acid,** S. Baluja, P. Kasundra and N. Godvani, *Acta ciencia indica,* **XXXIV**, 99 (2008).

3 **Antibacterial activity of *Punica Granatum* Stem,** R. nair, Y. Vaghaisya, N. Godvani, A. Solanki, S. Baluja and S. Chanda, *Plant archives*, **8**, 671-673 (2008).

4 **Synthesis and antibacterial evaluation of some schiff bases,** J. Javiya, N. Godvani, J. Parekh, S.Chanda and S. Baluja. *Acta ciencia indica,* **XXXIV**, 413 (2008).

## ***Accepted papers***

5 **Thermal profile and decomposition kinetics of some new schiff bases derived from 4-amino antipyrine,** Shipra Baluja, Jagdish Movaliya and Nilesh Godvani, *Int. J. Appl. Chem.*

6 **Preparation, characterization and antibacterial activities of some metal complexes containing Schiff bases of triazole derivatives,** Shipra Baluja, Nikunj Kachhadia, Nilesh Godvani, Ratish Nair, Sumitra Chanda and Parag Ajudia *Institution of Chemist.*

7 **Acoustical studies of some derivatives of 1,5-benzodiazepines at 298.15,** S. Baluja, J. Movaliya and N. Godvani, *Russ. J. Phy. Chem.*

8 **Thermodynamic and acoustical studies of aqueous solutions of some amino acids at 308.15K,** Shipra Baluja, Nikunj Kachhadia, Nilesh Godvani and Asif Solanki, *J. Pure and Appl. Chem.*

***Communicated papers***

1 **Solubility of some synthetic benzodiazepines in N, N-dimethyl formamide and tetrahydrofuran from (308.15 to 328.15) K**, Shipra Baluja, Ravi Gajera, Rahul Bhalodia, Nilesh Godvani, *J. Chem. Eng. Data*., Manuscript ID: je-2009-00065x.

2 **Studies of molecular interactions in solutions of Loperamide drug at 308.15 K** Shipra Baluja, and Nilesh Godvani and Jagdish Movaliya.

3 **Antibacterial studies of some metal chelates of 1,2,4- triazole schiff bases** Shipra Baluja, Nikunj Kachhadia, Asif Solanki, Sumitra Chanda and Nilesh Godvani .

4 **Excess thermodynamic properties of binary mixtures of Acetophenone with methanol, hexane, DMF and THF at T= 308.15 K** Shipra Baluja, Jagdish Movalia and Nilesh Godvani.

5 ***In vitro* antibacterial activity of Schiff bases of quinoline aldehyde S**. Baluja, N. Godvani, R. Gajera, J. Parekh, Y. Vaghasiya, S. Chanda and M. Bhatt.

6 **Synthesis and antibacterial activity of some chalcones** Shipra Baluja*, Nilesh Godvani, Mehul Bhatt, Jigna Parekh, Sumitra Chanda and Ravi Gajera.

7 **Synthesis, characterization and antibacterial activity of some thiazolidinones** Shipra Baluja, Nilesh Godvani, Ravi Gajera and Mehul Bhatt.

8 **Molecular interactions in DMF solutions of some pyrazole Schiff bases at 308.15 K** Shipra Baluja, Nilesh Godvani and Jayesh Javiya.

9 **Studies of molecular interactions in solution of phenylephrine drug at 308.15 K** Shipra Baluja, Jagdish Movaliya and Nilesh Godvani.

10 **Dissociation constants of some pyrazole schiff bases in DMF and THF** Shipra Baluja, Nilesh Godvani, and Jayesh Javiya*.*

# LIST OF PAPERS PRESENTED IN DIFFERENT CONFERENCES/SYMPOSIA

***Poster presentation***

1 "Antibacterial studies of some metal chelates of 1,2,4-triazole Schiff bases", Shipra Baluja, Asif Solanki, Sumitra chanda, Nilesh Godvani and Nikunj Kachhadia, 2nd International Symposium on Drug Discovery and Process Research, K. L. E. Society's College of Pharmacy, Belgaum Feb., 10-12, 2006 **(International)**

2 "Antibacterial study of Punica Granatum stem", Nilesh Godvani, Nikunj Kachhadia, Sumitra Chanda, Asif Solanki and Shipra Baluja, 2nd International Symposium on Drug Discovery and Process Research, K. L. E. Society's College of Pharmacy, Belgaum Feb., 10-12, 2006 **(International)**

3 "Study of molecular interactions of Loperamide drug in different solvents at 308.15 K", Shipra Baluja, Nilesh Godvani and Jagdish Movaliya, XVI International Conference on Chemical Thermodynamics, Suzdal, Russia, 1-6 July, 2007. **(International)**

4 "Acoustical studies of some derivatives of 1,5-benzodiazepines at 298.15 K", (Part-1) Shipra Baluja, Jagdish Movaliya and Nilesh Godvani, XVI International Conference on Chemical Thermodynamics, Suzdal, Russia, 1-6 July, 2007. **(International)**

5 "Acoustical studies of binary mixtures of acetophenone at 308.15K",Shipra Baluja, Asif Solanki , Nikunj Kachhadia, Nilesh Godvani and Anchal Kulshrestha, 2nd National Conference on Thermodynamics of Chemistry and Biological Systems, Veer Narmad South Gujarat University, Surat, 30th Octo.- 1st Nov. 2006. **(National).**

6 "Excess thermodynamic properties of binary mixtures of acetophenone with methanol, hexane, DMF and THF at 308.15 K" Jagdish Movalia, Nilesh Godvani and Shipra Baluja, 3rd National conference on thermodynamics of chemical and biological systems, Nagpur University, Nagpur, 16-17 Octo- 2008. **(National)**

7 "Molecular interactions in DMF solutions of some pyrazole Schiff bases at 308.15 K", Nayan Vekariya, Nilesh Godvani, Jayesh Javiya and Shipra Baluja, 3rd National conference on thermodynamics of chemical and biological systems, Nagpur University, Nagpur, 16-17 Octo- 2008. **(National)**

***Oral presentation***

1 "Study of molecular interactions in solutions of Phenylephrine drug at 308.15 K", Shipra Baluja, Jagdish Movaliya and Nilesh Godvani, 20th International Conference on Chemical Thermodynamics" (20th ICCT), Warsaw, Poland, 3-8 August, 2008. **(International)**

2 **"**Acoustical studies of some derivatives of 1,5-Benzodiazepines at 298.15 K" (Part-2) Nilesh Godvani, Jagdish Movalia and Shipra Baluja, 3rd National conference on thermodynamics of chemical and biological systems, Nagpur University, Nagpur, 16-17 Octo- 2008. **(National),** Procceding of the 3rd NCTCBS-2008.

3 "Density, viscosity and speed of sound of solutions of some imidazolinone derivatives in DMSO at 308.15K", Shipra Baluja, Nilesh Godvani, Asif Solanki and Nikunj Kachhadia, 2nd National Conference on Thermodynamics of Chemistry and Biological Systems, Veer Narmad South Gujarat University, Surat, 30th Octo.-1st Nov. 2006. **(National).**