STUDIES ON COMPOUNDS OF MEDICINAL INTEREST

A THESIS

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IN

THE FACULTY OF SCIENCE (CHEMISTRY)

BY

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UNDER THE GUIDANCE

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Statement under o. Ph. D. 7 of Saurashtra University

The work included in the thesis is my own work under the supervision of ***Dr. V. H. Shah*** and leads to some contribution in chemistry subsidised by a number of references.

Date. : - -2008
Place : Rajkot. ***(Janak J. Surani)***

This is to certify that the present work submitted for the Ph.D. Degree of Saurashtra University by ***Janak J. Surani*** is his own work and leads to advancement in the knowledge of chemistry.The thesis has been prepared under my supervision.

Date : - -2008
Place : Rajkot.

Dr. V. H. Shah(M.Sc. Ph.D.FIC),
Associate Professor,
Department of Chemistry,
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Dedicated
to my
beloved Family

ACKNOWLEDGEMENTS

" Shree Ganeshay Namah "

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

For his faith in me, his encourage, his motivation & inspiration made me to reach these heights, He is one and only Dr. V. H. SHAH, Professor, Department of Chemistry, Saurashtra University, Rajkot. My mentor, my guide reflects with his incredible personality and lightened up my life with indomitable determination. With his blessings, constant motivation and optimistic approach, I could complete my journey towards achieving my goal. His striving to make us not only better in our chosen field but good human being also. I pray to God that I may come to his expectations in present as well as in future.

I also owe to, from the deepest corner of heart, deepest sense of gratitude and indebtedness to Dr. P.H.Parsaniya, Head , Department of Chemistry, Saurashtra University, Rajkot, as I have been constantly benefited with their lofty research methodology and the motivation as well as their highly punctual, affectionate, and noncompromising nature which always inspired me in heading rapidly towards my goal and helped me achieving the aim of my present task very speedly.

Thanks are also due to other teaching and non-teaching staff of Department of Chemistry,for their kind help during my research work.

Who in this world can entirely and adequately thank the parents who have given me everything that I possess in this life. The life itself is their gift to me, so I am at loss of words in which to own my most esteemed father Shri Jivrajbhai and My loving mother Smt. Hansaben and most venerated late grand father Arajanbhai and late grand mother Gangaben. Also, I can never ever forget my beloved brother yogesh(natu) and sisters Chetana, and beloved fiancee Ekta, whose unstoping flow of love helped me to reach the goal.

I offer my heartful gratitude to Hitesh, Samir, Gaurang, Pranav, Manish, Amit, Haresh, Dipti, Chintan and all my Seniors for their support and much fruitful discussion at various stages.

I feel great pleasure to acknowledge my deepest sense of indebtedness to Ramgiri Bapu Bahuchraji Temple, and our Shri Raj Restaurant and Tulsi Group member, Mr.Chunibhai, Mr. Anwer kaka, Naresh, and Amit Kunadia by moral support.

I also remember well wishers and all those persons who helped me directly or indirectly for preparation of this work.

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I am profoundly indebted to Department of Chemistry, Saurashtra University for providing me the excellent laboratory facilities and kind furtherance for accomplishing this work.

Finally, each individual creature on this beautiful planet is created by God to fulfil a particular role. Whatever I have achieved in life is through His help, and an expression of His will. He showered His grace on me through some outstanding teachers and colleagues and when I pay my tributes to these fine persons, I am merely praising His glory. All this work is His work through a small person called Janak.

Janak J. Surani

CONTENTS

NOTES

1. All the temperatures are expressed in degree **centigrade** (^{0}C).
2. Melting points of all the compounds are uncorrected and have been recorded by **open capillary method.**
3. Room temperature, wherever mentioned, normally corresponds to **28^0 - 33 ^{0}C.**
4. Silica gel-G was used for preparing the TLC plates using different solvent systems.
5. **Infra red** spectra of all the compounds were scanned on **SHIMADZU-FOURIER TRANSFORM INFRA RED(FTIR)-8400 Spectrophotometer** using **KBr** disc.
6. **PMR** Spectra were recorded on **BRUKER Spectrophotometer(400 MHz)** using **TMS** as a internal standard and **$CDCl_3$,** and **DMSO-d_6** as solvents.
7. **^{13}C NMR** Spectra were recorded on **BRUKER Spectrophotometer(400 MHz)** using **$CDCl_3$,**and **DMSO-d_6** as solvents.
8. **MASS** spectra were recorded on **SHIMADZU-GCMS-QC-2010.**

SYNOPSIS

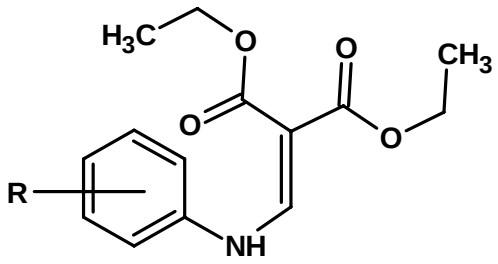
A comprehensive summary of the synthetic work is incorporated in the Ph.D. thesis with the entitled *"***STUDIES ON COMPOUNDS OF MEDICINAL INTEREST"** have been described. The synthetic work is presented in two parts which is summarized as under.

PART-I **(A) STUDIES ON 4-QUINOLONES.**
(B) STUDIES ON PYRIMIDO [2,1-b] [1,3] BENZOTHIAZOLE-4-ONES.
PART-II **STUDIES ON 1,4-DIHYDROPYRIDINES.**

PART- I (A) STUDIES ON 4-QUINOLONES.

4-Quinolones exhibit a wide spectrum of pharmacological profile such as antibacterial, antitubercular, antitumar, non-nucleoside inhibitors of human cytomegalo virus, new CB-2 cannabinoid receptors agonists, antimalarials, antifungal, antiinflammatory. Due to the various biological activities of 4-quinolones in medicinal chemistry, an attempt has been made to undertake the synthesis of 4-quinolones in **section I to VIII.**

SECTION - I: Preparation and biological evaluation of Diethyl-(substituted phenyl)-aminomethylene malonates.

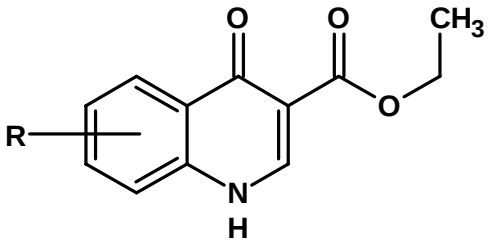


(Ia-j)

R=Substituted phenyl

Diethyl-(substituted phenyl)-aminomethylene malonates **(Ia-j)** have been prepared by the cyclocondensation of different substituted phenyl amines and diethyl ethoxy methylene malonate.

SECTION - II: Preparation and biological evaluation of Ethyl-substituted--1,4-dihydroquinoline-4-one-3-carboxylates.

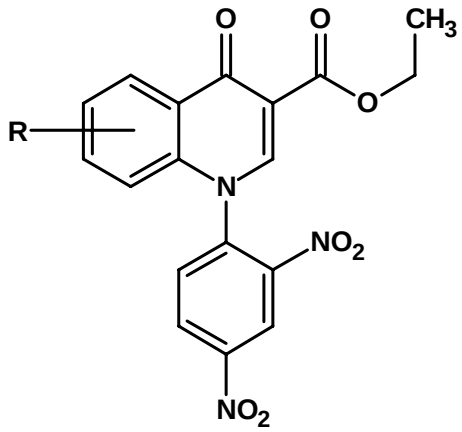


(IIa-j)

R=Substituted phenyl

Ethyl-substituted-1,4-dihydroquinoline-4-one-3-carboxylates **(IIa-j)** have been prepared by the cyclocondensation of different diethyl-(substituted phenyl)-aminomethylene malonates **(Ia-j)** in suitable solvent.

SECTION - III: Preparation and biological evaluation of Ethyl-1-N-(2,4-dinitrophenyl)-6,7,8-substituted-1,4-dihydroquinoline-4-one-3-carboxylates.

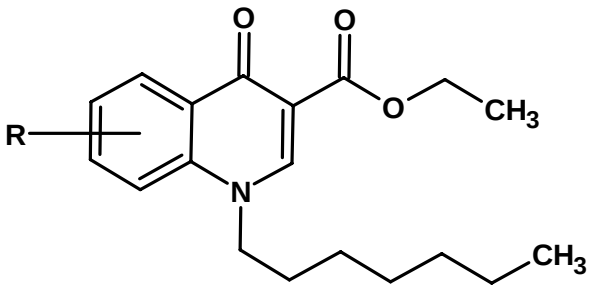


(IIIa-j)

R=Substituted phenyl

Ethyl-1-N-(2,4-dinitro phenyl)-6,7,8--substituted-1,4-dihydroquinoline-4-one-3-carboxylates **(IIIa-j)** have been prepared by the cyclocondensation of different ethyl-substituted-1,4-dihydroquinoline-4-one-3-carboxylates **(IIa-j)** with 1-chloro-2,4- dinitro benzene in the basic condition.

SECTION - IV: Preparation and biological evaluation of Ethyl-6,7,8-substituted-1-N-heptyl-1,4-dihydroquinoline-4-one-3-carboxylates.

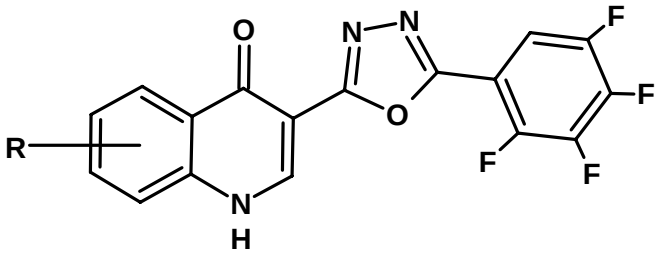


(IVa-j)

R=Substituted phenyl

Ethyl-6,7,8-substituted-1-N-heptyl-1,4-dihydroquinoline-4-one-3-carboxylates **(IVa-j)** have been prepared by the cyclocondensation of different ethyl-substituted-1,4-dihydroquinoline-4-one-3-carboxylates **(IIa-j)** and 1-bromo heptane in the presence of basic condition.

SECTION - V : Preparation and biological evaluation of Substituted-3-[5'-(2'',3'',4'',5''-tetrafluorophenyl)-1',3',4'-oxadiazol-2'-yl]-quinolone-4(1H)-ones.

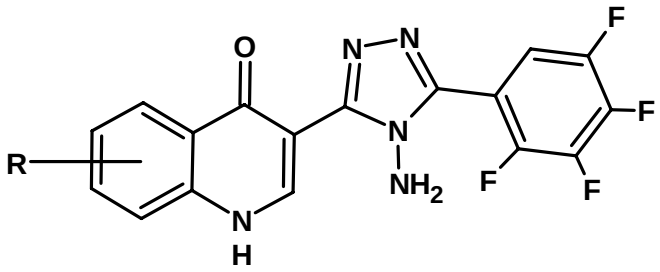


(Va-j)

R=Substituted phenyl

Substituted-3-[5'-(2'',3'',4'',5''-tetrafluorophenyl)-1',3',4'-oxadiazol-2'-yl]-substituted quinolone-4(1H)-ones **(Va-j)** have been synthesized by the cyclocondensation of 2,3,4,5-tetrafluoro benzoic acid with different substituted-1,4-dihydroquinoline-4-one-3-carbohydrazides which was prepared by the action of hydrazine hydrate on ethyl-substituted-1,4-dihydroquinoline-4-one-3-carboxylates **(IIa-j)**.

SECTION - VI : Preparation and biological evaluation of -3-[4'-amino-5'-(2'',3'',4'',5''-tetrafluorophenyl)-4H-1',2',4'-triazol-3'-yl]- Substituted-quinolone-4(1H)-ones.

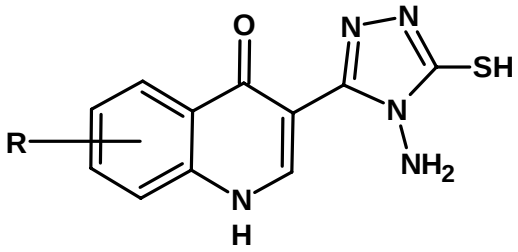


(VIa-j)

R=Substituted phenyl

3-[4'-amino-5'-(2'',3'',4'',5''-tetrafluorophenyl)-4H-1',2',4'-triazol-3'-yl]-Substituted-quinolone-4-(1H)-ones **(VIa-j).** have been prepared by the cyclocondensation of different substituted-3-[5'-(2'',3'',4'',5''-tetrafluoro phenyl)-1',3',4'-oxadiazol-2'-yl]-quinolone-4-(1H)-ones **(Va-j)** and hydrazine hydrate.

SECTION - VII : Preparation and biological evaluation of 3-[1'-N-amino-2'-mercapto-1',3',4'-triazol-5'-yl)-Substituted--quinolone-4-(1H)-ones.

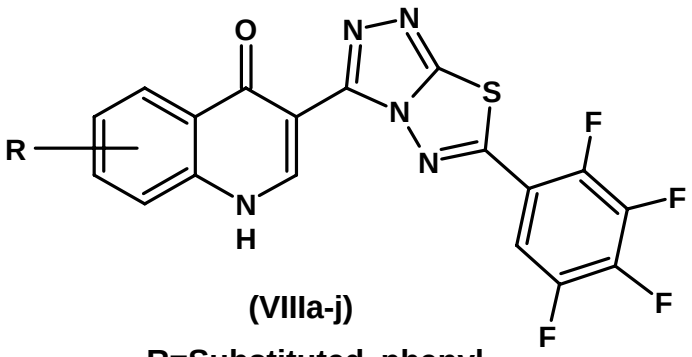


(VIIa-j)

R=Substituted phenyl

3-[1'-N-amino-2'-mercapto-1',3',4'-triazol-5'-yl)-Substituted-quinolone-4-(1H)-ones **(VIIa-j)** have been prepared by the cyclocondensation of different substituted 1,4-dihydroquinoline-4-one-3-carbohydrazides with carbon disulphide and pottassium hydroxide followed by the action of hydrazine hydrate.

SECTION - VIII : Preparation and biological evaluation of Substituted-3-[6'-(2'',3'',4'',5'',-tetrafloro phenyl)(1',2,',4')-triazolo-(3',a-b)[1',3',4']-thiadiazole-3-yl]-quinolone-4(1H)-ones.



(VIIIa-j)

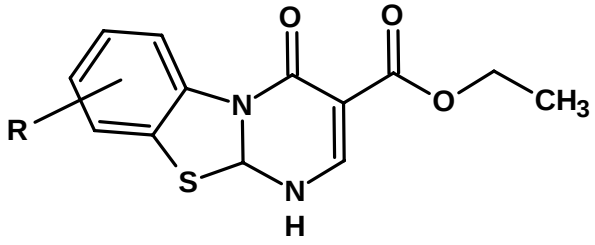
R=Substituted phenyl

Substituted-3-[6'-(2'',3'',4'',5'',-tetrafluoro phenyl)(1',2,',4')-triazolo-(3',a-b)[1',3',4']-thiadiazole-3-yl]-quinolone-4(1H)-ones **(VIIIa-j)** have been prepared by the cyclocondensation of different substituted-3-[1'-N-amino-2'-mercapto-1',3',4'-triazol-5'-yl)-quinolone-4-(1H)-ones **(VIIa-j)** and 2,3,4,5-tetrafluoro benzoic acid in the presence of phosphorous oxychloride.

PART - I (B)
STUDIES ON PYRIMIDO[2,1-b] [1,3] BENZOTHIAZOLE-4-ONES

Pyrimidines and benzothiazoles exhibit a wide spectrum of pharmacological profile such as antibacterial, antitubercular, antitumar, antimalarials, antifungal, antiinflammatory. Due to the various biological activities of Pyrimidines and benzothiazoles, the synthesis of Pyrimido(2,1-b)[1,3]benzothiazole-4-one having two heterocycles contaning pyrimidine and benzothiazole moieties have been undertaken which can be symmarized in the following section.

SECTION - I : Preparation and biological evaluation of 7,8,9-Ethyl-substituted-10a-dihydro-4H-pyrimido[2,1-b][1,3]benzothiazole-4-one-3-carboxylates.



(IXa-j)

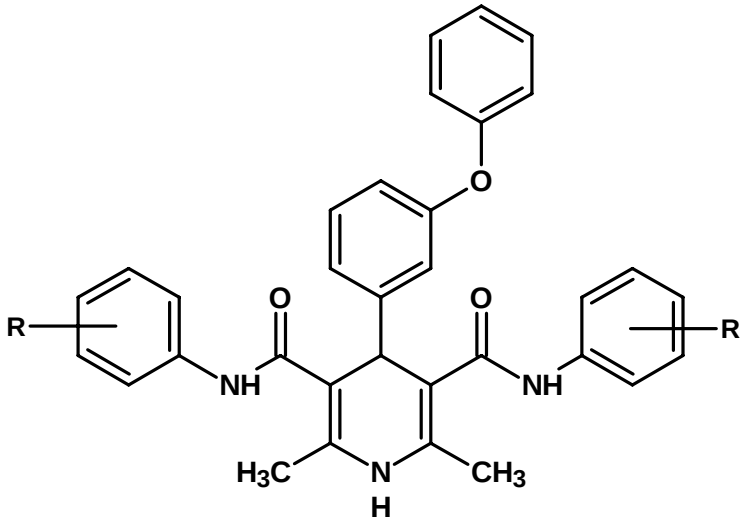
R=Substituted phenyl

7,8,9-Ethylsubstituted-10a-dihydro-4H-pyrimido[2,1-b][1,3]benzothiazole-4-one-3-carboxylates **(IXa-j)** have been prepared by the condensation of different substituted 2-amino benzothiazoles and diethyl ethoxy methylene malonate.

PART-II STUDIES ON 1,4-DIHYDROPYRIDINES

1,4-Dihydro pyridines are one of the most active class of compounds possessing diverse biological activity *viz*., calcium chanell blocker, cardiovascular, vasodilator, antihypertensive, antitubercular and anti-HIV activities. Promoted by above facts These valid observations lead us to synthesize some novel 1,4-dihydropyridines that have been described as under.

SECTION - I : Preparation and biological evaluation of 2,6-Dimethyl-3,5-N,N'-substituted-diphenyl carboxamido-4-(m-phenoxy-phenyl)-1,4-dihydropyridines.

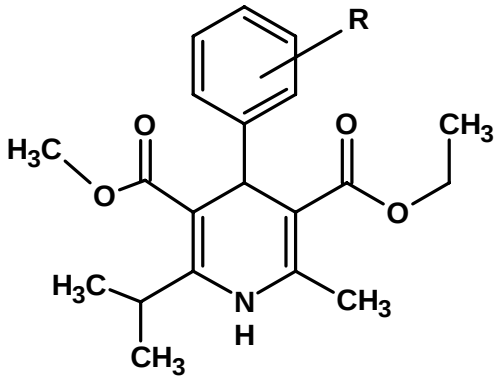


(Xa-j)

R=Substituted phenyl

2,6-Dimethyl-3,5-N,N'-substituted-diphenyl carboxamido-4-(m-phenoxy phenyl)-1,4-dihydropyridines **(Xa-j)** have been prepared by the cyclocondensation of one mole m-phenoxy benzaldehyde and two moles of substituted-N-phenyl butanamide-3-ones and ammonium hydroxide.

SECTION - II: Preparation and biological evaluation of 6-Methyl-2-isopropyl-4-(substituted phenyl)3-ethyl-5-methyl-1,4-di hydropyridine-dicarboxylates.

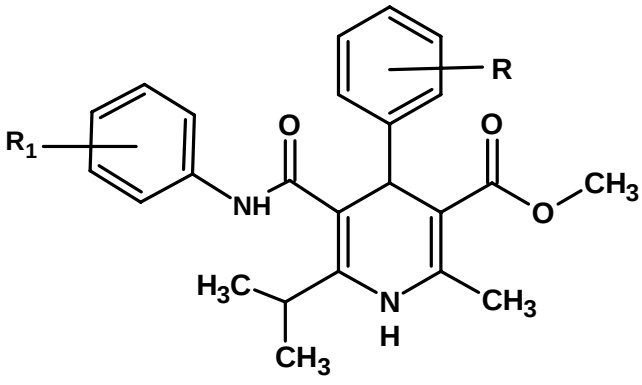


(XIa-j)

R=Substituted phenyl

6-Methyl-2-isopropyl-4-(substituted-phenyl)-5-ethyl-3-methyl-1,4-dihydro pyridine dicarboxylates **(XIa-j)** have been prepared by the cyclocondensation of one mole of ethyl-3-amino but-2-enoate and one mole of methyl-2-substituted-benzylidene-4-methyl-3-oxo-pentanoates.

SECTION - III : Preparation and biological evaluation of Methyl-2-isopropyl-6-methyl-3-(substituted-phenyl carboxamido)-4-substituted-phenyl-1,4-dihydropyridine-5-carboxylates.



(XIIa-j)

R & R_1= Substituted phenyl

Methyl-2-isopropyl-6-methyl-3-(substituted phenyl carboxamido)-4-substituted phenyl-1,4-dihydropyridine-5-carboxylates **(XIIa-j)** have been prepared by the cyclocondensation of one mole of methyl-3-amino but-2-enoate

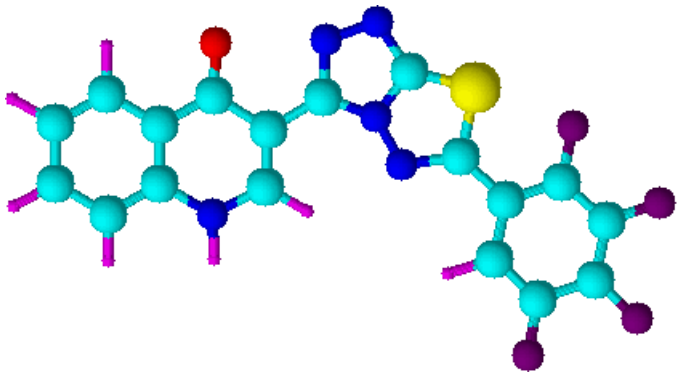
and different one mole of 2-substituted-benzylidene-4-methyl-3-oxo-N- phenyl pentanamides.

PURIFICATION AND CHARACTERISATION:

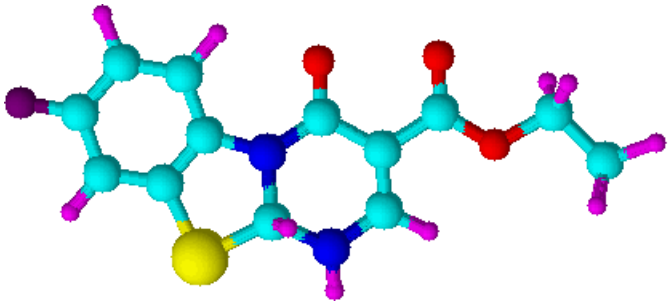
The purity of all the newly sythesized compounds have been checked by thin layer chromatography and constitution of newly synthesised compounds **(Ia-j) to (XIIa-j)** have been delineated by **Elemental analysis**, **FT IR, ^{1}H NMR,^{13}C NMR** and **Mass spectroscopy**.

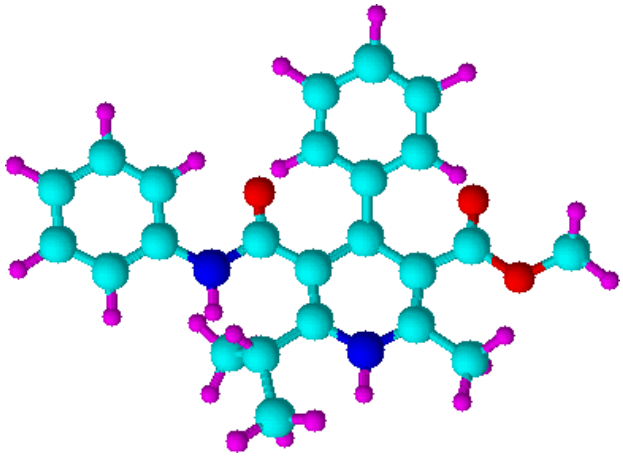
ANTIMICROBIAL ASSAY:

All the newly sythesized compounds **(Ia-j) to (XIIa-j)** have been screened for their ***in vitro*** therapeutic assay like antibacterial activities towards gram positive and gram negative bacterial strains and antifungal activites at different concentrations **(minimum inhibitory concentration).** The biological activites of synthesizied compounds have been compared with standard drugs.



STUDIES ON COMPOUNDS OF MEDICINAL INTEREST





"STUDIES ON COMPOUNDS OF MEDICINAL INTEREST"

(A) Drug

The word drug is derived from the French word "drogue" which means 'a dry herb. It is the single active chemical entity present in a medicine that is used for diagnosis, prevention, treatment / cure of a disease. This disease oriented definition of drug does not include contraceptives or use of drugs for improvement of health. According to "WHO" a drug may be defined as "Any substance or product which is used or intended to be used for modifying or exploring physiological system as pathological status for the benefit of the recipient".

(B) Pharmacology

Pharmacology is the science of drugs. In a broad sense, it deals with interaction of exogenously administered chemical molecules (drugs) with living system. It encompasses all aspects of knowledge about drugs, but most importantly those that are relevant to effective and safe use for medicinal purposes. For thousands of years most drugs were crude natural products of unknown composition and limited efficiency. Only the over effects of these substances on the body were rather imprecisely known, but how the same were produced was entirely unknown. Over the past 100 years or so, drugs have been purified, chemically characterized and a vast variety of highly potent and selective new drugs has been developed. The two main divisions of pharmacology are pharmacodynamics and pharmacokinetics.

(a) Pharmacodynamics : It is derived from the Greek word "dynamic" means power. What the drugs does to the body? This includes physiological and biochemical effects of drugs and their mechanism of action at macromolecular / sub cellular organ systems.

(b) Pharmacokinetics : It is derived from the Greek word 'Kinesis' means movement. What the body does to the drug? This refers to movements of the drug in and alternation of the drug by the body; includes absorption, distribution, binding / localization / storage, biotransformation and excretion of the drug.

Some other important aspects of pharmacology are given as under.

* ***Pharmacotherapeutics* :** It is the application of pharmacodynamic information together with knowledge of the disease for its prevention, mitigation or cure.

* ***Clinical Pharmacology :*** It is the scientific study of drug in man.It includes pharmacodynamic and pharmacokinetic investigation in healthy volunteers and in patients; evaluation of efficiency and safety of drugs and comparative trials with other forms of treatments; surveillance of patterns of drug uses, adverse effects, etc.

* ***Chemotherapy :*** It is the treatment of systemic infection / malignancy with specific drugs that have selective toxicity for the infecting organism / malignant cell with less effect on the host cells.

■ **Drugs in general, can thus be divided into :**

* ***Pharmacodynamic agents :*** These are chemical substances designed to have pharmacodynamic effect in the recipient.

* ***Chemotherapeutic agents :*** These are chemical substances designed for the treatment of infectious diseases or by the proliferation of malignant cells.

(c) Essential Drug Concept: The 'WHO' has defined Essential Drugs as "those that satisfy the healthcare needs of majority of the population; they should therefore be available at all times in adequate amounts and in appropriate dosage form".

It has been realized that only a handful of drugs out of the multitude available can meet the health needs of majority of the people in any

country, and that may be well tested and cheaper drugs are equally (or more) efficient and safe as their newer more expensive congeners. For optimum utilization of resources, governments (specially in developing countries) should concentrate on these drugs by identifying them as Essential Drugs. The "WHO" has laid down criteria guide selection of an essential drug :

(I) Adequate data on its efficiency and safety should be available from clinical studies.

(II) It should be available in a form in which quality, including bioavailability and stability on storage can be assured.

(III) Its choice should depend upon pattern of prevalent diseases; avail ability of facilities and trained personnel; financial resources; genetic, demographic and environmental factors.

(IV) In case of two or more similar drugs, choice should be made on the basis of their relative efficiency, safety, quality, price, availability and cost benefit ratio should be a major consideration.

(V) Choice may also be influenced by comparative pharmacokinetic proper ties and local facilities for manufacture and storage.

(VI) Most essential drug should be single compound. Fixed ratio combina tion products should be included only when dosage of each ingredient meets the requirements of a defined population group, and when the combination has a proven advantage.

(VII) Selection of essential drug should be a continuous process which should take into account the changing priorities for public health action, epide-miological condition as well as availability of better drugs/ formulations and progress in pharmacological knowledge.

(C) Drug Development

Many natural products by trial and error, came into practise for combat-ing human ailments existent during early human observation. With the advent of modern scientific approach, various plant medicines came under chemical scrutiny, ultimately leading to the isolation of active principles since early.

Such compounds either in extract form or in pure form became a part of pharmacopoeias. For instance, though the Chinese drug, Mauhang was in use

for over 5000 years for the treatment of various types of fever and respiratory ailments, its active principle, Ephidrine was isolated in 1887. In 1925 chemical investigations followed by pharmacological evaluation led this compound into the modern medicine. Similarly during this period, urea stibamine was introduced as the first drug in 1920 for the treatment of Kala-azar. In 1930, De Rauwolfia preparation were first employed for sedative and hypotensive properties.

A drug is a substance having abnormal effect on certain body functions eg. Strychnine stimulates the action of heart and aspirin retards its action. Since both of them effects abnormally, the two substances are known as drugs. Chemical sciences contributed extensively new discoveries leading to useful drugs since after 1930. The modern concept of drug discovery started in 1933 by Gerhand Domagk with his finding of **"Prontosil Red"**, a compound responsible for the antibacterial activity. The advent of **sulphonamides** drew the attention for the different activities of various chemicals for bacterial and human cells, this important factor prompted Florey and Chain in 1939 to investigate **penicillin** which was discovered ten years earlier by Alexander Fleming. The spectacular chemotherapeutical properties of penicillin and its dramatic war-time development for the treatment of wounds made **penicillin**, a most commonly used inexpensive drug.

A large number of important drugs have been introduced during the period of 1940 to 1980. This period is known as "Golden period" of new drug discovery. Thus starting from 1933 - the first antibacterial drug **prontosil** leading to various sulpha drugs; 1940 – **penicillin**; 1945 – **chloroquine** – **anti-malarial**; 1950 – **Methyldopa** – **anti-hypertensive;** 1967 – **chlorothiazine -diuretic**; 1958 - adrenergic beta blockers coronary vasodilatory; 1960 - semi synthetic **penicillin** -antibacterial; 1965 -**trimethoprim**-**antimicrobial**;1967-**disodium chromoglycoate** - antiallergic; 1972 - **cimetidine** H2– antagonist; 1975 -**verapamil**- calciumantagonist and 1981 - **captopril** - antihypertensive. There are some specific examples representing new therapeutic agent eg. **Metormine glipizide-**antidiabetic.

(D) Latest Drug Developments

The current interest in the creation of large, searchable libraries of organic compounds has captured the imagination of organic chemists and

the drug discovery community. In numerous laboratories the efforts are focused on the introduction of chemical diversity, which have been recently reviewed and pharmacologically interesting compounds have been identified from libraries of widely different compositions.

Today, the chief source of agents for the cure, the mitigation or the prevention of diseases are the organic compounds, natural or synthetic, together with so-called organometallics. Such agents have their origin in a number of ways **(a)** from naturally occurring materials - of both plant and animal origin, and **(b)** from the isolation of organic compounds synthesized in laboratory whose structures are closely related to those of naturally occurring compounds for eg. **atropine, steroids, morphine, cocaine** etc. that have been known to possess useful medicinal properties.

The process of drug design is extensively driven by the instinct and experience of pharmaceutical research scientists. It is often instructive to attempt to "capture" these experiences by analyzing the historical record that are successful drug design projects of the past. From this analysis, the inferences are drawn which play an important role in shaping our current and future projects. Towards this region, we would like to analyse the structures of a large number of drugs - the ultimate product of a successful drug design effort. Our goal for this is to begin to deconvolute this information in order to apply it to design of new drugs.

Different kinds of drugs are developed for different types of diseases *viz*. which can be defined with their names of the modern drugs are as under.

(a) Anticancer drugs

The drugs, which stops the abnormal growth of cell tissues in human body, are termed as anticancer drug. **Vinblastin** and **Busulphan** are the novel anticancer drugs.

(b) Hepatoprotective drugs

Drugs, which gives vitality to liver and protects liver by giving immunity power against antibodies, are termed as Hepatoprotective drug.

(c) Antimalarial drugs

Drugs, which kills the plasmodium causing malaria are called antimalarial drug. Combination of **Sulphamethoxazole** with **Pyrimethamine** is a novel antimalarial drug.

(d) Drug for meningitis

Drugs, which cures the inflammation of meningitis, are termed as meningitis drugs **Cifalexin** is a novel meningitis drug.

(e) Drug for typhoid

Drugs, which kills the bacteria of Salmonella typhi causing typhoid are known as typhoid drugs. A novel drug for typhoid is **Ciprofloxacin**.

(f) Antidiabetic drugs

Drugs, which converts the excess glucose of blood into glycogen are termed as antidiabetic drugs. Novel antidiabetic drugs are **Metformin, Glipizide** and **Gliclazide.**

(g) Antitubercular drugs

Drugs, which kills the bacteria of mycobacterium tuberculosis and thus cures lesions of pleural cavity. A novel antitubercular drug is **Ethambutol**.

(h) Antiasthamatic drugs

Drugs, which prevents the attack of asthama and gives relax respiration are called antiasthamatic drugs. Novel antiasthamatic drugs are **Ethophylline, Theophylline** and **Asmon**.

(i) Antihypertensive drugs

Drugs, which normalizes the blood pressure by dilating blood vessels are called antihypertensive drugs. Novel antihypertensive drugs are **Atenolol, Amlodipine** and **Nifedipine.**

(j) Anti-AIDS drugs

Drugs, which kills the viruses of AIDS i.e., HIV-1 and HIV-2 are called anti-AIDS drugs. Novel drugs are **Zidovudine, Acyclovir** and **Didanosine**.

Drugs, which neutralize the acid in stomach and stops excessive secretion of acid, are called antacid drugs. Novel antacid drugs are **Omeprazole** and **Lansoprazole.**

(I) Non steroidal antiinflammatory drugs (NSAID)

Drugs, which gives relief from fever, pain and inflammation are called NSAID. Novel NSAID are **Pyroxicam**, **Meloxicam** and **Nimesulide.**

Different kind of drugs generally used are designed as anaesthetic, antituberculostatic, antihypertensive, anticonvulsant, anthelmintic, antiinflammatory, sedative and hypnotics which prompted us to synthesise drugs having ***4-quinolones, pyrimido[2.1-b][1,3]benzothiazole-4-ones and 1,4-dihydro pyridines*** moieties as a better therapeutic activity.

■ **Aims and objectives of the present investigation are as follows.**

(a) To generate several biologically active moieties such as ***4-quinolones, pyrimido[2.1-b][1,3]benzothiazole-4-ones and 1,4-dihydro pyridines.***

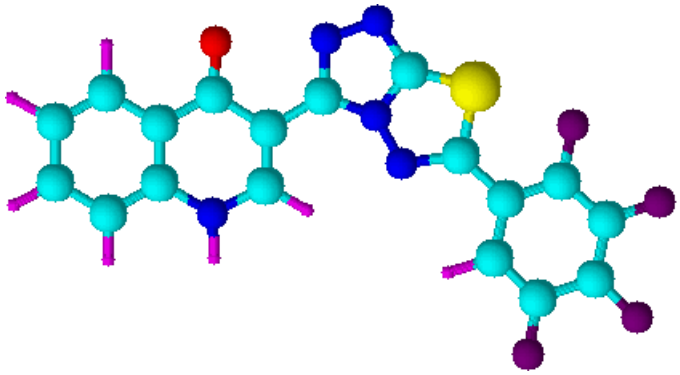
(b) To characterize these products for their structural assignment using various spectroscopic techniques like **IR, PMR** and **Mass** spectroscopy.

(c) To screen these new derivatives for their antimicrobial activity using different strains of bacteria and fungi and to compare antimicrobial activity with different known drugs at different concentrations for their MIC values.

In view of these facts, the research work presented in thesis are as follows.

PART-I **(A) STUDIES ON 4-QUINOLONES.**
(B) STUDIES ON PYRIMIDO [2,1-b] [1,3] BENZOTHIAZOLE -4-ONES.

PART-II **STUDIES ON 1,4-DIHYDROPYRIDINES.**



PART-I(A)

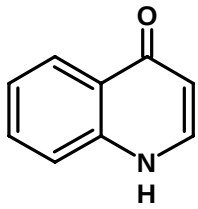
STUDIES ON

4-QUINOLONES

PART - I
STUDIES ON 4-QUINOLONES

INTRODUCTION:

Benzene ring when fused with 2,3-position of pyridine nucleus is known as quinoline. Quinoline carboxylic acid in which quinoline ring is substituted by oxo and carboxylic acid group at different positions are well documented in literature.The structure of 4-quinolone is depicted as under.



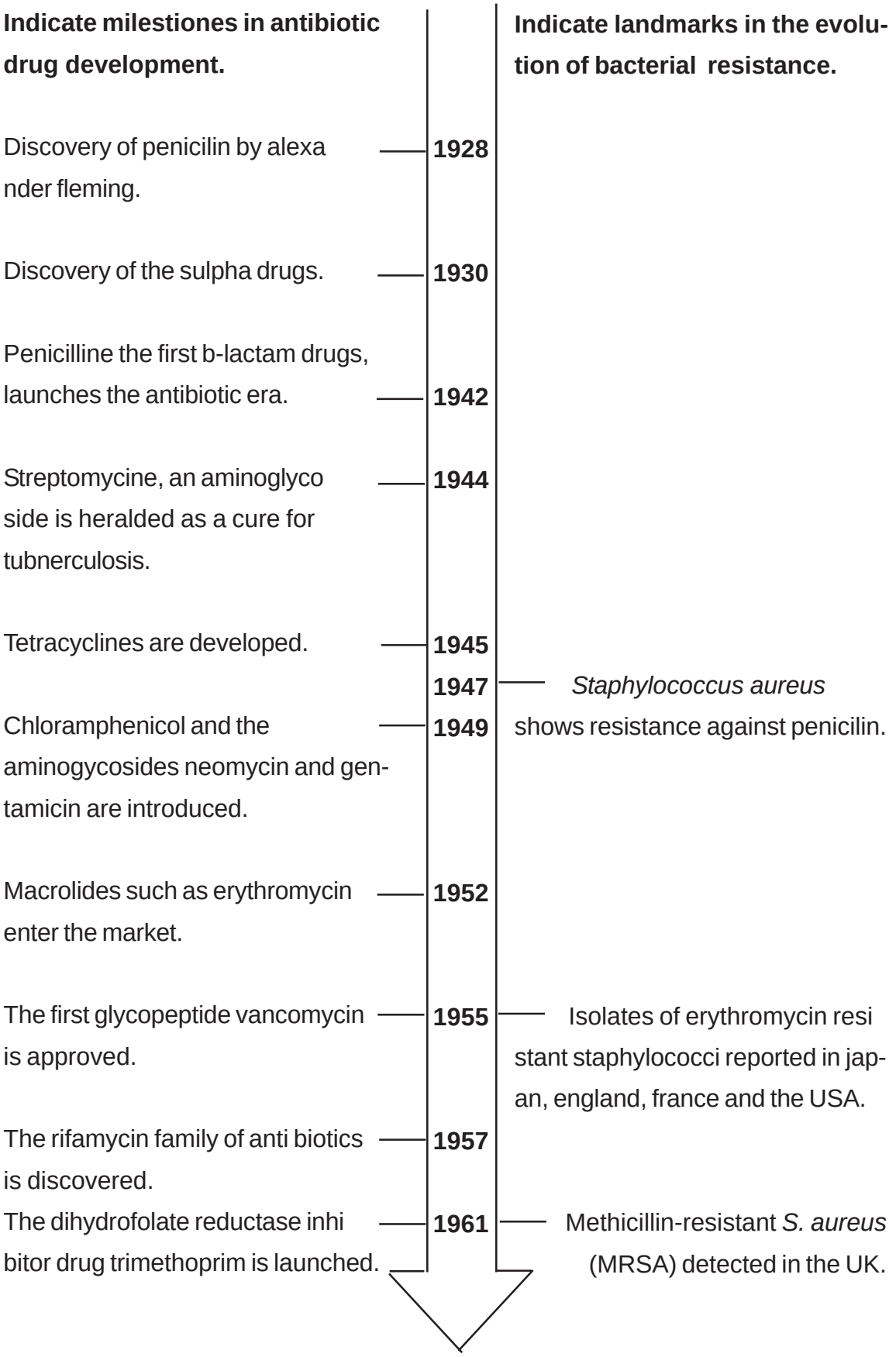
(1)

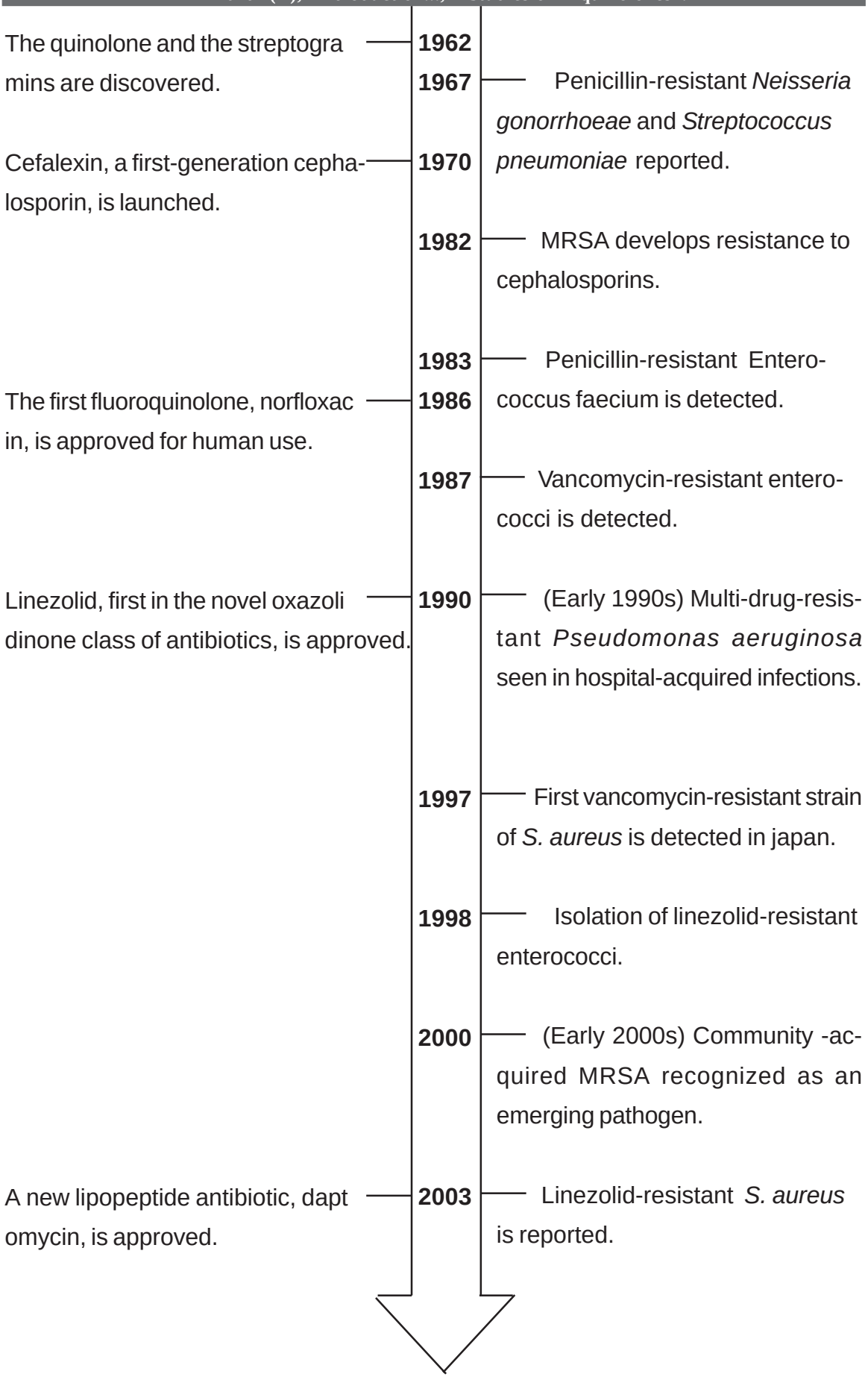
Quinolones constitute a large class of synthetic antimicrobial agents that are highly effective in the treatment of many types of infectious diseases, particularly those caused by bacteria. Quinolones are potent, broad specturem antibacterial agents. The early congeners of the quinolone antibiotics which is non-fluorinated at C-6 like nalidixic acid were limited to certain gram negative infections such as urinary tract infections. However, the modern generation of fluoroquinolones containing C-6 fluoro substituent and a cyclic basic amine moiety at C-7 surpass their predecessors in terms of spectrum of activity and potency. This has allowed for their use against a variety of gram-negative as well as some gram-positive pathogens. Quinolones are relatively easily prepared and administered via parenteral and oral routes and are well tolerated.

The rapid rise in bacterial resistance to the traditional antibiotics such as penicillin and tetracyclines and their derivatives has encouraged a continuing search for new classes of compound with novel modes of antibacterial activity.

The 4-quinolone antibiotics have emerged as an area of immense interest because of their broad spectrum of the ***in vivo activity*** and their ***in-vivo*** chemotherapeutic efficiency. Various structural modifications of this class of compounds have provided the new agents such as ciprofloxacin[1], ofloxacin[2], lomefloxacin[3] and sparfloxacin[4] which are considerably more potent and have a broader spectrum of antibacterial activity.

RACE-AGAINST TIME : THE INTRODUCTION OF NEW ANTIBIOTIC CLASSES AND THE EMERGENCE OF RESISTANCE.[5]




The quinolone and the streptogramins are discovered.
1962
1967
Penicillin-resistant Neisseria gonorrhoeae and Streptococcus pneumoniae reported.
Cefalexin, a first-generation cephalosporin, is launched.
1970
1982
MRSA develops resistance to cephalosporins.
1983
Penicillin-resistant Enterococcus faecium is detected.
The first fluoroquinolone, norfloxacin, is approved for human use.
1986
1987
Vancomycin-resistant enterococci is detected.
Linezolid, first in the novel oxazolidinone class of antibiotics, is approved.
1990
(Early 1990s) Multi-drug-resistant Pseudomonas aeruginosa seen in hospital-acquired infections.
1997
First vancomycin-resistant strain of S. aureus is detected in japan.
1998
Isolation of linezolid-resistant enterococci.
2000
(Early 2000s) Community -acquired MRSA recognized as an emerging pathogen.
A new lipopeptide antibiotic, daptomycin, is approved.
2003
Linezolid-resistant S. aureus is reported.

SYNTHETIC METHODS OF 4-QUINOLONES:-

Oldfield William (1969) synthesized 1-phenyl-4-oxo-1,4-dihydro-quinoline-3-carboxylic acids[6]. Different synthetic methods for the synthesis of 4-quinolone reported in the literature are as under:

(A). By the ethylation of 4-quinoline-3-carboxylic acid[7].

(B). By the treatment of substituted acetophenones with ethylcarbonate and triethylorthoformate followed by the condensation with substituted phenyl amine and further cyclization to afford 4-quinolone derivatives[8].

(C). By the reduction of 4-(3-nitro phenyl)pyridine followed by the condensation with diethyl ethoxy methylene malonate and on further cyclization yields substituted 4-quinolone-3-carboxylic acids[9].

(D). By the condensation of substituted anilines with dimethyl acetylene di carboxylate followed by thermal cyclization and hydrogenation[10].

(E). By the heating 4-Fluoro-2-methyl-N-(2,2,2-trifluoroethyl) aniline with polyphosphoric acid at 110º C to give 6-fluoro-4-oxo-1-(2,2,2-trifluoroethyl)-1,4-dihydroquinoline-3-carboxylic acid[11].

(F). By the condensation of 2,5-C_2H_5-(NH_2)$C_6H_3O(CH_2)_{17}CH_3$ with diethyl ethoxy methylene malonates followed by the cyclization with phosporous oxychloride to afford substituted quinolone-3-carboxylic acids[12].

(G). By the reaction of diethylethoxy methylene malonates with secondary aromatic amine in the presence of polyphosphoric acid to gives 4-quinolone-3-carboxylic acid[13].

(H). By the heating of N-(b-dicarboxy ethyl ethylene)-substituted aniline on heating at 250-255^{o} C affords 4-quinolone-3-carboxylic acid [14].

(I). By the condensation 2,4-dichloro-5-fluoro benzoyl chloride with malonic ester followed by decarboxylation and condensation with ethyl formate which on treatment with cyclopropyl amine followed by cyclization and reaction with piperazine yields ciprofloxacine[15].

(J). By the reaction of substituted acid chloride with diethyl malonate in the presence of magnesium followed by cyclization[16].

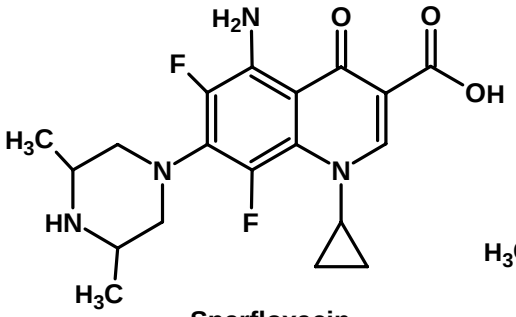
(k). By the reaction of N-Hydroxy succinimide ester of anthranillic acid with anions of ß-keto esters to give 4-oxo-3-quinoline carboxylic acid derivatives[17].

(L). By the reaction of ß-keto ester with p-anisidine in polyphosphoric acid affords 2-(phenoxy difluoromethyl)-6-methoxy 1H-quinoline-4-one[18].

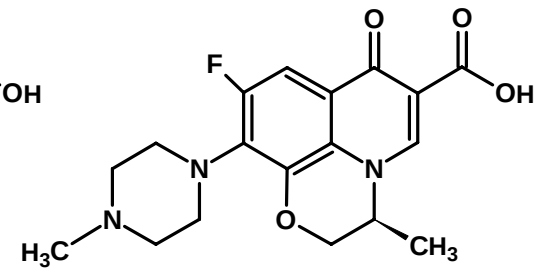
(M). 3-amino-2-phenyl-4(1H)-quinolones are obtained from anthranilamides[19].

(N). By the condensation of substituted acetophenones with cyclopropyl amine and dimethyl sulphate followed by the cyclization to afford 4-quinolone-3-carboxylates[20].

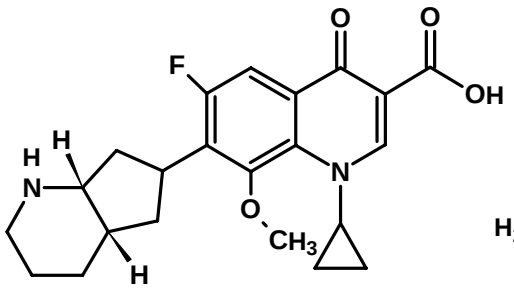
Some of the important 4-quinolones which are used in chemical trial can be summarized as under with several structures[21].



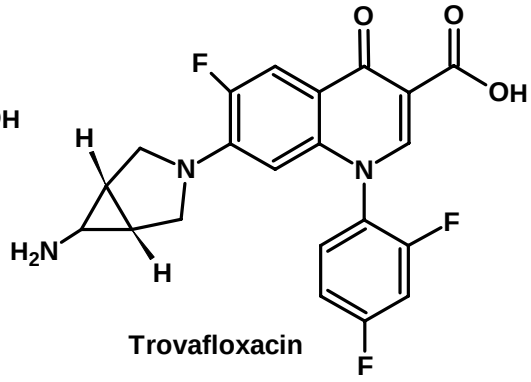
Sparfloxacin



S(-)Levofloxacin



Moxifloxacin



Trovafloxacin

(1) Nadifloxacin (antibacterial)
(2) Ciprofloxacin
(3) Gatifloxacin (antibacterial)
(4) Satifloxacin
(5) Ofloxacin(antibacterial)
(6) Garenoxacin
(7) Gemifloxacin
(8) Nalidixic acid (Urinary tract infe.)
(9) Cinoxacin
(10) Norfloxacin (Gyrase inhibitor)
(11) Enoxacin (Gyrase inhibitor)
(12) Lomefloxacin
(13) Temafloxacin
(14) Pefloxacin (Gyrase inhibitor)
(15) Enrofloxacin
(16) Flumequine
(17) Tosufloxacin
(18) Pipemidic acid (Urinary tract infe.)
(19) Amifloxacin
(20) Oxalinic acid (Gyrase inhibitor)
(21) Miloxacin
(22) Difloxacin
(23) Fleroxacin
(24) Alatrofloxacin mesilate
(25) Grepafloxacin
(26) Rufloxacin(antibacterial)
(27) Rosoxacin (antibiotic)
(28) Piromidic acid (chemotherapeutic)
(29) Flose quinon (vasodilator)
(30) Nedocronil (Antiallergic)

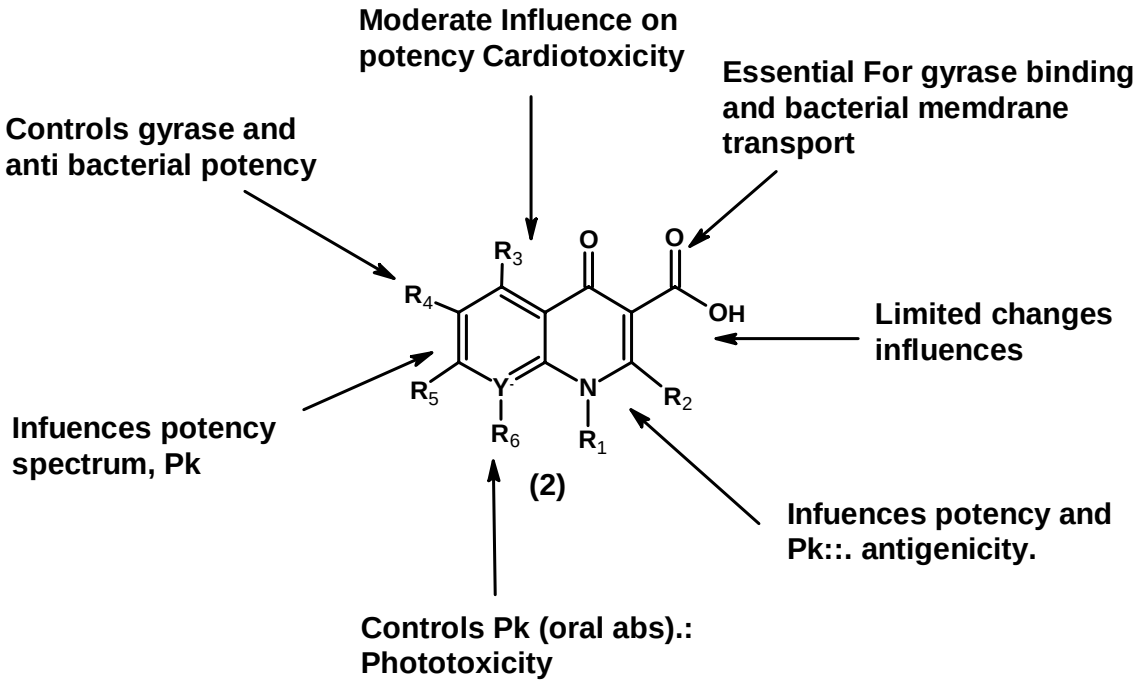
STRUCTURE- ACTIVITY RELATIONSHIP

The quinolone carboxylic acids constitute a class of extremely potent and orally active broad spectrum antibacterial agents[22-25]. These compounds have been shown to affect the bacterial growth by inhibiting the DNA gyrase, a key enzyme in bacterial DNA replication[26-27].

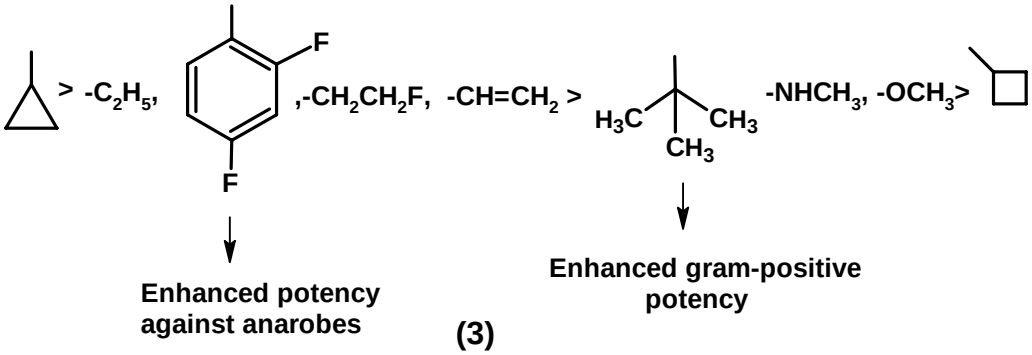
The substituiton of a piperazinyl ring at position 7 has rendered the molecule active against Pseudomonas and the presence of a fluorine atom at position 6 extends the activity of the molecule to some but not all gram-positive bacteria[29]. Streptococcus can be resistant[28]. Additions of alkyl chains to the nitrogen at position 1, increase the activity of the compounds. The substitution of hydrogen atoms by fluorines at position 8 of the ring and on the methyl of the alkyl chain diminishes the rate of degradation and decreases the rate of elimination.

It was widely believed that 3-carboxylic acid and 4-carbonyl were necessary for the antimicrobial activity of the compounds. However, Chu et.al.,[30] a showed that the transformation of existing molecules in 2,3,4,9-tetrahydroisothiazolo[5,4-b] quinoline-3,4-diones produces a significant increase in their biological activity[31].

Overview of SAR of Fluoroquinolones antibacterial drugs,[32,33].

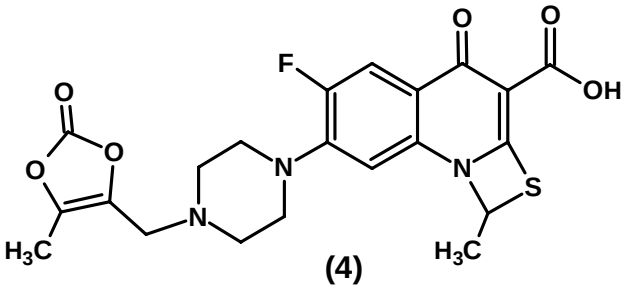


1. Subtituent at N-1 position: A compilation of active N-1 quinolone substituents is shown below with an emphasis on overall in vitro potency.



(3)

2. The simple replacement of C-2 hydrogen has generally to be disadvantageous,e.g., C-2 methyl or hydroxyl groups. However, some derivatives containing a suitable C-1 and C-2 ring have been shown to possess notable activity, e.g., Prulifloxacin.



(4)

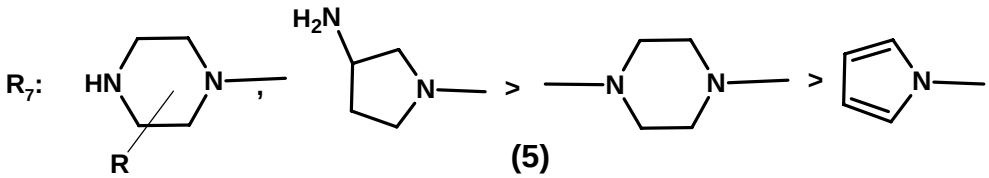
3. Without doubt, the C-3 carboxylic acid moiety is most commonly encountered. Other acidic groups such as sulphonic acid, phosponic acid, tetrazole as well as derivatisation as an ester results in a loss of antibacterial activity.

4. The C-4-oxo group of the quinolone nucleous appears to be essential for antibacterial activity. Replacement with 4-thioxo or sulphonyl group leads to a loss of activity.

5. The incorporation of an amino group at the C-5 position has proven to be benefical in terms of antibacterial activity. The order of activity at R_3: NH_2, CH_3>F, H>OH, OR, SH, SR.

6. The incorporation of a fluorine atom at the C-6 position of the quinolone is monumental, the order of activity at R_4: F.>Cl, Br, CH_3 >CN.

7. The introduction of a piperazine moiety at C-7 was a landmark devlopment. Other aminopyrrolidines also are compatible for activity..



(5)

8. A hydrogen atom at the C-8 or a nitrogen atom (a napthyridone) is the most common. In general, a C-8 fluoro substitutent offers good potency against gram-negative pathogens, while a C-8 methoxy moiety is active against gram-positive bacteria. The order of activity at R_6; F, Cl, OCH3, >H, CF3> methyl, vinyl, propagyl.

9. A halogen (F or Cl) at the 8-position improves oral absorption.

10. The joining of N-1 group to the C-8 position with oxazine ring leads to active ofloxacine.

MEDICINAL INTEREST OF 4-QUINOLONES

The research on 4-quinolones system is of current interest due to their valuable activities as Antibiotic, DNA gyrase inhibitors, Antibacterial etc. Besides the currently established drugs like Norfloxacin ,Ciprofloxacin. Many 4-quinolone derivatives have been synthesized world wide and have led to numerous second generation commercial product such as Ofloxacin, Gatifloxacin, Pipemidic acid. By the literature survey, it was found that 4-quinolones possess wide variety of biodynamic activity, which can be put forward as under.

[A] Analgesic activity[34-37]
[B] Antiallergic activity[38-42]
[C] Antiasthmatic activity[43-44]
[D] Antibacterial activity[45-63]
[E] Anticancer activity[64]
[F] Anticoccidial activity[36,49,65-66]
[G] Antiinflammatory activity[67-68]
[H] Antinaphylatetic activity[69]
[I] Antipyretic activity[34]
[J] Antirheumatism activity[34]
[K] Antispasmolytic activity[70]
[L] Antitumor activity[71-73]
[M] Antiulcer activity[74]
[N] Bacteriostatic activity[76]
[O] CNS depressant activity[35,77]
[P] Diuretic activity[77-78]
[Q] Hypnotic activity[79]

[R] Hypotensive activity[35]

[S] Pressure lowering activity[80]

[T] Tranquilizer activity[78]

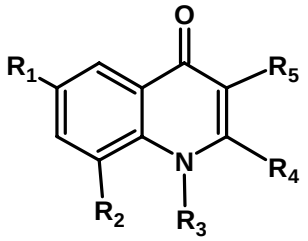
[U] Tuberculosis activity[80-81]

[V] Antimalarials[82]

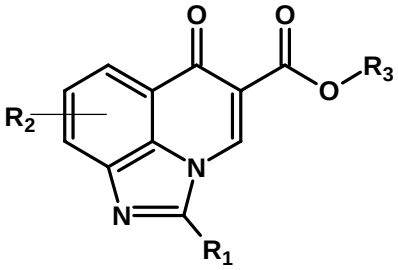
[W] Topoisomerase inhibitors[83-84]

[X] CB_2 cannabinoid receptors agonists[85]

Recently, K.S.Aithal et.al.,[86] have reported uses of norfloxacin for bone joint urinary tract, respiratory tract infection and also for maningitis. Antimicrobial and antifungal activity of 4-quinolones have been reported by M.B.Deshmukh et.al.,[87-88] Antiallergic activity studies of quinolone **(6)** and imidazoquinolinones **(7)** have been reported by N. P. Peet et.al.,[41] which established the SAR conclusion that amine and ester functions at the position 8 and 3 respectively were necessary for the significant antiallergic activity.

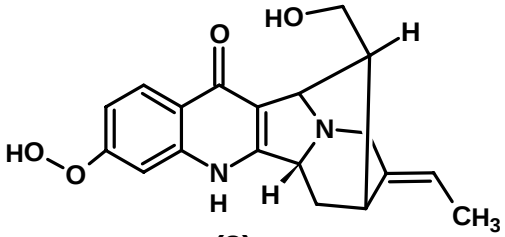


(6)



(7)

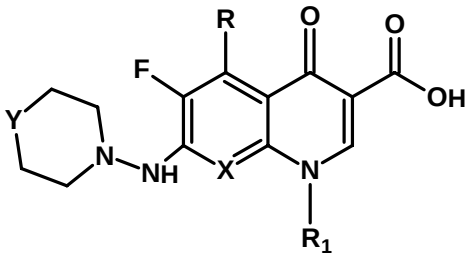
H. Takayama et.al.,[89] have isolated new alkaloid **(8)** from leaves of Gardneria nutans having a novel 4-quinolone ring skeleton.



(8)

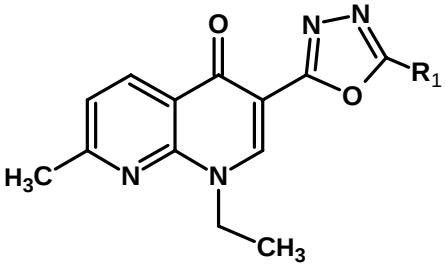
The alkaloid was obtained from crude basic fraction of the leaves of gardne -ria nutans in its unique structure having a 4-quinolone moiety.

R. Singh et. al.,[90] have reported the synthesis and antibacterial activity of 7-hydrazinoquinolones **(9)**.



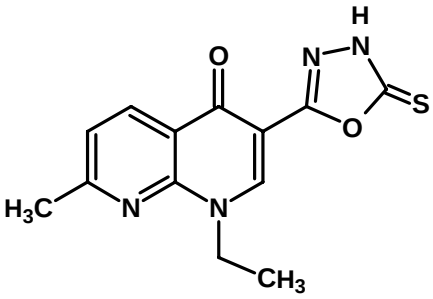
(9) **R and R_1=substituted phenyl, X=N,**

G. Gruver et. al.,[32] have designed the synthesis of 1,3,4-oxadiazoles and 1,3,4-oxadiazole-2-thione derivatives of nalidixic acid **(10)** and **(11)** as potent antibacterial and fungicidal agents.



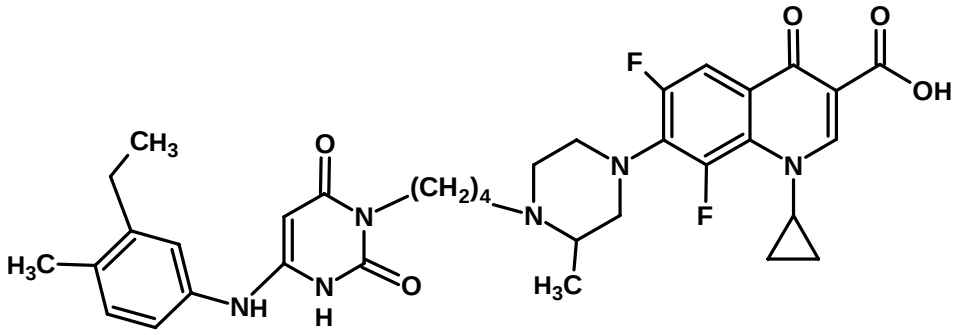
(10)

R1= p-Cl, p-OH, o,m-di nitro, phenyl



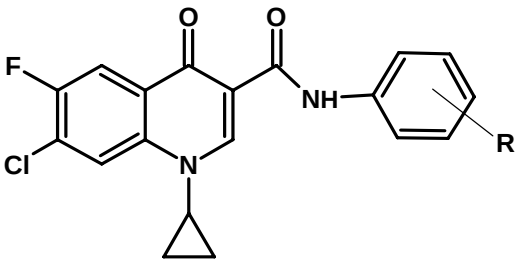
(11)

C. Zhi et. al.,[84] have reported the synthesis of a novel hybrid antibacterial agent **(12)** of 6-(3-ethyl-4-methylanilino)uracils (EMAU) and fluoroquinolones moiety (FQ) as potent DNA polymerase- topoisomerase inhibitors and showed that the resulting AU-FQ hybrid compounds were significantly more potent than the parent 'EMAU' compounds.



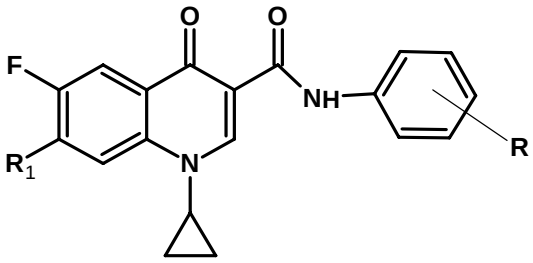
(12)

Recently, synthesis antimicrobial activity studies of novel amide derivatives of 4-quinolone **(13)** and **(14)** have been reported by H. I. Chauhan et.al.,[20].



(13)

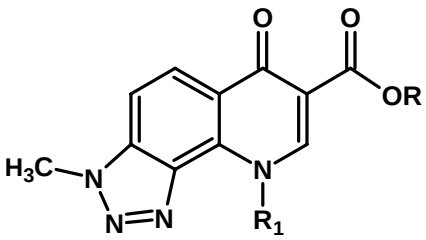
R=H,-OCH3,O-Cl,m-CH3,o-NO2----etc



(14)

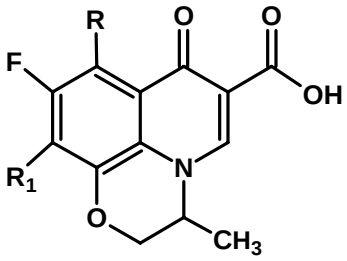
R_1=N-methyl piperazine,N-ethyl, morpholine.etc

A. Carta et.al.,[91] have studied the antitubercular activity of some new (1,2,3)- triazolo (4,5-h) quinolones **(15)** aganist the multidrug resistant *Mycobacterium tuberculosis* strains ($H_{37}Rv$).



(15) R and R_1=substituted phenyl

Recently, antimycobacterial and toxicological evaluation of novel ofloxacin derivatives **(16)** have been reported by M. Dinakaran et.al.,[92]



(16) R and R_1=substituted phenyl

In our further studies and in order to evaluate the biodynamic activities, synthesis of 4-quinolone derivatives was undertaken, which can be summarised in the following sections.

SECTION - I: PREPARATION AND BIOLOGICAL EVALUATION OF DIETHYL-(SUBSTITUTEDPHENYL)-AMINO METHYLENE-MALONATES.

SECTION - II: PREPARATION AND BIOLOGICAL EVALUATION OF ETHYL-SUBSTITUTED-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATES.

SECTION - III: PREPARATION AND BIOLOGICAL EVALUATION OF ET HYL-1-N-(2,4-DINITRO-PHENYL)-6,7,8-SUBSTITUTED-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATES.

SECTION - IV : PREPARATION AND BIOLOGICAL EVALUATION OF ETHYL-6,7,8-SUBSTITUTED-1-N-HEPTYL-1,4-DIHY-DRO QUINOLINE-4-ONE-3-CARBOXYLATES.

SECTION - V : PREPARATION AND BIOLOGICAL EVALUATION OF SUBSTITUTED-3-[5'-2'',3'',4'',5''-TETRAFLUOROPHEN YL)-1',3',4'-OXADIAZOL-2'-YL]- QUINOLONE-4(1H)-ONES.

SECTION - VI : PREPARATION AND BIOLOGICAL EVALUATION OF -3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRA FLUORO PHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]- SUBSTIT-UTED-QUINOLONE-4(1H)-ONES.

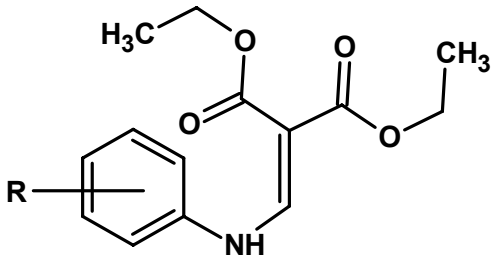
SECTION - VII : PREPARATION AND BIOLOGICAL EVALUATION OF 3-[1'-N-AMINO-2'- MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-SUBSTITUTED-QUINOLONE-4-(1H)-ONES.

SECTION - VIII : PREPARATION AND BIOLOGICAL EVALUATION OF SUBSTITUTED-3-[6'-(2'',3'',4'',5'',-TETRAFLUORO PHENYL)(1',2,',4')-TRIAZOLO-(3',a-b) [1',3',4']-THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONES.

SECTION - I

PREPARATION AND BIOLOGICAL EVALUATION OF DIETHYL-(SUBSTITUTED PHENYL)-AMINOMETHYLENE MALONATES.

Keeping in view of various biodynamic activities[34-85] of **4-quinolones** and in order to have highly potent therapeutic agents, the synthesis of **Diethyl-(substituted phenyl)-aminomethylene malonates (I_{a-j})** have been undertaken by the condensation of different **substituted phenyl amines** and **diethyl ethoxy methylene malonate.**



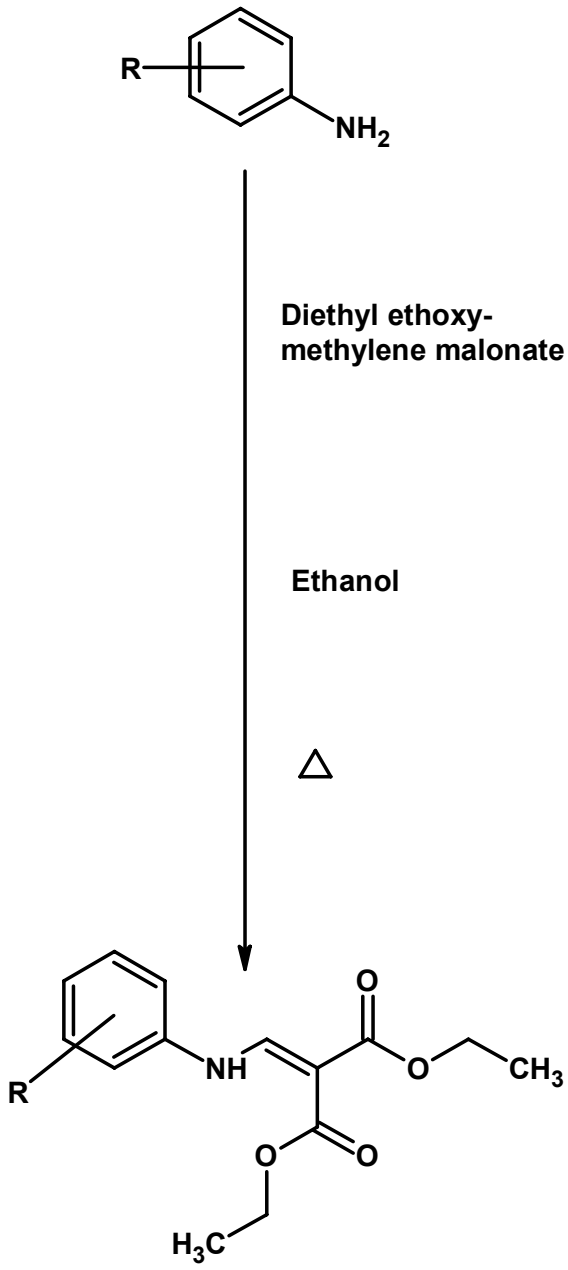
(Ia-j)

R=Substituted phenyl

The constitution of the products **(Ia-j)** have been delineated by **elemental analyses, IR, PMR** and **Mass** spectral data**.**

The products **(Ia-j)** were assayed for their ***in vitro*** biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** , ***S. aureus MTCC-96*** *and* ***B. subtillis MTCC-441*** **(Gram positive)** and ***E. coli MTCC-443*** **(Gram negative)** bacterial strains and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations.i.e.: 0(control), 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds **(Ia-j)** were compared with standard drugs *viz.*, **Amoxicillin, Chloramphenicol, Sparfloxacin, Levofloxacin**(antibacterial), **Griseofluvin, Fluconazole** (antifungal)**.**

REACTION SCHEME



(Ia-j)

R= substituted phenyl

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF DIETHYL-(SUBSTITUTED PHENYL)-AMINOMETHYLENE MALONATES.

(A) Preparation of Diethyl-(3-chloro-4-fluoro phenyl)-amino methylene malonate (I_d).

A mixture of 3-chloro-4-fluoro aniline (2.60 gm, 0.01 M) and diethyl ethoxy methylene malonate (1.06 ml, 0.01M) in ethanol (20 ml) was heated under reflux condition for 5 hrs. The rection mass was cooled at 0 to 5 ^{O}C temperature.The reaction mixture was poured into ice-water, filtered and washed with water and crystallized from ethanol. Yield : 84 %, M.P. : 64 ^{O}C, (Required : C, 53.26%; H, 4.79% N, 4.44%; for $C_{14}H_{15}NO_4ClF$, Found : C, 53.20%; H, 4.74% N, 4.40%.

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (2.0 : 8.0) = 0.62.
TLC solvent system R_{f_2} : Methanol : Toluene (0.5 : 9.5) = 0.46.

Similarly, other compounds **(I_{a-j})** were synthesized. The physical data are recorded in **Table No. 1.**

(C) Antimicrobial activity of Diethyl-(substitutedphenyl)-amino methylene malonates (I_{a-j}).

Antimicrobial activity testing was carried out by using cup-plate method[93], which has been described as under.

Antibacterial activity

S. pyogens MTCC-442 **,*S. aureus MTCC-96*** and ***B. subtillis MTCC-441*** (Gram positive bacteria) were grown in nutrient broth and ***E. coli MTCC-443*** (Gram negative bacteria) in Peptone water (PW, 1% bacteriological peptone and 0.5% NaCl in water) for 24 hrs., this gave an optimum growth of the test bacteria. Each purified compound was dissolved in dimethyl formamide

sterilized by filtration by using sintered glass filter and stored at 4^{O}C. Each agent was then added to molten nutrient agar in the following concentrations i.e, : 0 (control), 5, 25, 50, 100, 250 (µg/ml) and poured into sterile petridishes. The **pH** of the media was maintained at 7.2 -7.4. The inoculum consisted of an overnight grown broth culture of a bacterium diluted in such a manner that a 2 m.m. (internal diameter) loopful of the culture contain 10^5 colony-forming unit **(CFU)**. These were then spot inoculated on nutrient agar plates containing increasing amount of a compound, incubated at 37^{O}C for 24 hrs. For determination of the minimum inhibitory concentration**[94-95]**(MIC). Which are recorded as zones of inhibition in m.m. for bacterias in **Table No. 1A, 1B**.

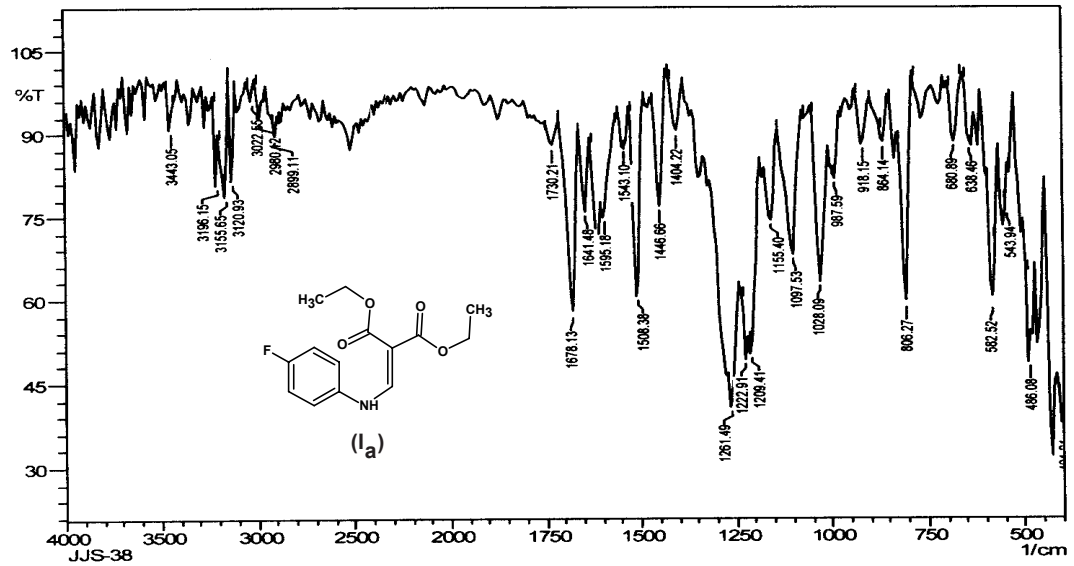
Antifungal activity

C. albicans MTCC-227 and ***A. niger MTCC-282*** was employed for testing antifungal activity using cup-plate method. The culture was maintained on Sabouraud's agar for 72 hrs., this gave an optimum growth of the test fungal spores. Each purified compound was dissolved in dimethyl formamide sterilized by filtration by using sintered glass filter and stored. Each agent was then added to Sabouraud's agar in the following concentrations i.e,: 0 (control), 5, 25, 50, 100, 250 (µg/ml) and poured into sterile petri dished. The inoculum consisted of an overnight grown broth culture of a bacterium diluted in such a mannerso that a 2 m.m. (internal diameter) loopful of the culture contain 105 colony-forming unit **(CFU)**. These were then spot inoculated on Sabouraud's agar plates containing increasing amount of a compound, incubated at 37^{O}C for 48 hrs. For determination of the minimum inhibitory concentration (MIC)**[94-95]**. Which are recorded as zones of inhibition in m.m. for fungi in **Table No. 1C.**

TABLE NO. 1 : PHYSICAL CONSTANTS OF DIETHYL-(SUBSTITUTED PHENYL)-AMINOMETHYLENE MALONATES (I_{a-j}).

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. ^oC 5	Yield % 6	R_f Value 7		% of Nitrogen Calcd. / Found 8
						R_{f_1}	R_{f_2}	
I_a	4-F-C_6H_4	$C_{14}H_{16}NO_4F$	281.0	50^o	87	0.66	0.49	4.98 / 4.93
I_b	3-Cl-C_6H_4	$C_{14}H_{16}NO_4Cl$	297.5	47^o	81	0.58	0.48	4.71 / 4.65
I_c	4-Cl-C_6H_4	$C_{14}H_{16}NO_4Cl$	297.5	46^o	89	0.52	0.47	4.71/ 4.64
I_d	3-Cl-4-F-C_6H_3	$C_{14}H_{15}NO_4ClF$	315.0	64^o	84	0.62	0.46	4.44 / 4.39
I_e	3,4-$(Cl)_2$-C_6H_3	$C_{14}H_{15}NO_4Cl_2$	332.0	57^o	86	0.58	0.48	4.22 / 4.15
I_f	4-NO_2-C_6H_4	$C_{14}H_{16}N_2O_6$	308.0	114^o	81	0.48	0.38	9.09 / 9.02
I_g	4-OCH_3-C_6H_4	$C_{15}H_{19}NO_5$	293.0	47^o	68	0.49	0.42	4.78 / 4.73
I_h	4-CH_3-C_6H_4	$C_{15}H_{19}NO_4$	277.0	51^o	81	0.44	0.40	5.05 / 5.00
I_i	2,3-$(CH_3)_2C_6H_3$	$C_{16}H_{21}NO_4$	291.0	52^o	83	0.41	0.38	4.81 / 4.78
I_j	-$C_{10}H_7$	$C_{18}H_{19}NO_4$	313.0	72^o	84	0.42	0.39	4.47 / 4.42

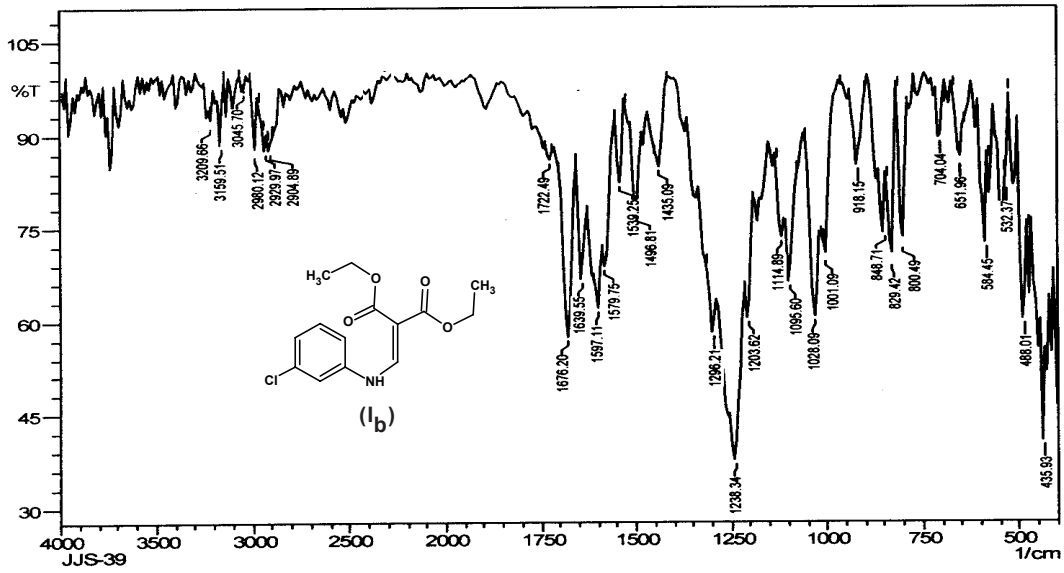
IR SPECTRAL STUDY OF DIETHYL-(p-FLUOROPHENYL)-AMINO METHYL-ENE MALONATE (I_a).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2980.8	2975 - 2850	96
	C-H (sym. str., m)	2899.6	2900 - 2800	96
	C-H (asym. def., m)	1446.4	1470 - 1435	96
	C-H (sym. def., m)	1404.1	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3022.5	3080 - 3010	97
	C=C & C-C (str., v)	1595.1	1600 - 1450	97
	C-H (i.p. def., m)	1155.0	1150 - 1050	97
	C-H (o.o.p. def., m)	806.5	825 - 800	97
	C-N (str., v)	1261.5	1340 - 1250	97
Amine	N-H (Astr., m)	3443.0	3500-3400	98
	N-H (str.,b)	3196.1-3120.9	3400 - 3000	98
	N-H (def., s,m)	1641.4	1650 - 1550	98
Ketone (ester)	C=O (str., b)	1730.2-1678.1	1740 - 1650	98
Subtitution	C-F (str., b)	1261-1097	1400 - 1080	99
Para(-4-) substituted	C-H (def., v,s)	864.14	800 - 850	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

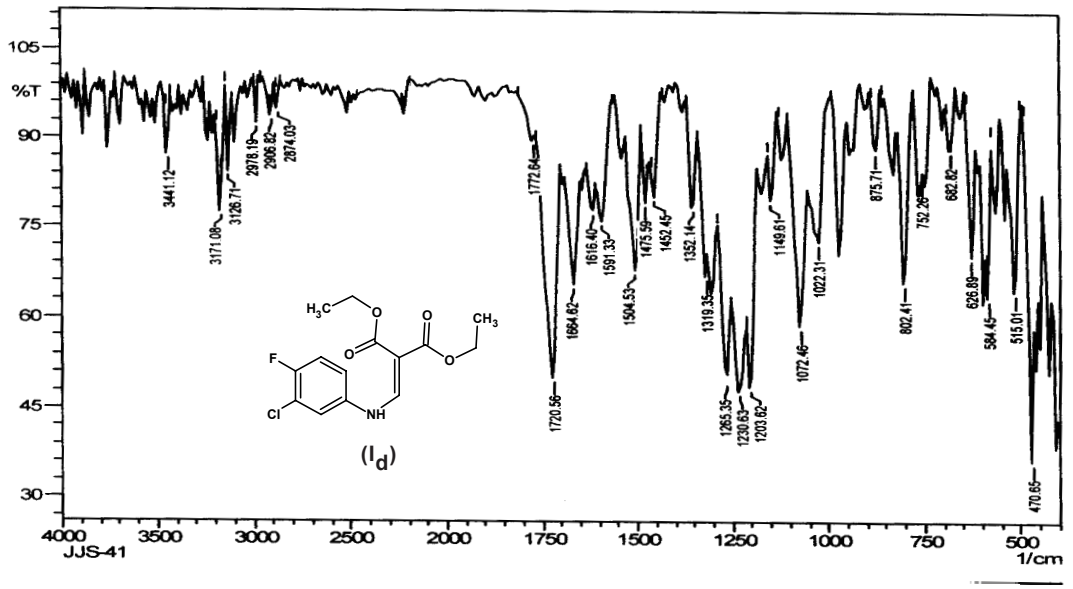
IR SPECTRAL STUDY OF DIETHYL-(*m*-CHLOROPHENYL)-AMINO METHYLENE MALONATE (I_b).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2929.8	2975 - 2850	96
	C-H (sym. str., m)	2904.6	2900 - 2800	96
	C-H (asym. def., m)	1435.4	1470 - 1435	96
	C-H (str., v)	3045.7	3080 - 3010	96
Aromatic and ring skeletal vibration	C=C & C-C (str., v)	1579.1	1600 - 1450	97
	C-H (i.p. def., m)	1095.6	1150 - 1050	97
	C-H (o.o.p. def., m)	829.4	825 - 800	97
	C-N (str., v)	1296.2	1340 - 1250	97
Amine	N-H (Astr., m)	3209.0	3500-3400	98
	N-H (str., b)	3209-3045	3400 - 3000	98
	N-H (def., s,m)	1639.5	1650 - 1550	98
Ketone (ester)	C=O (str., b)	1722.4-1676.2	1740 - 1650	98
Subtitution	C-Cl (str., b)	810-651	800-600	99
Meta(-3-) substituted	C-H (def., v,s)	829.4	880 - 830	99
		704.0	780-730	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

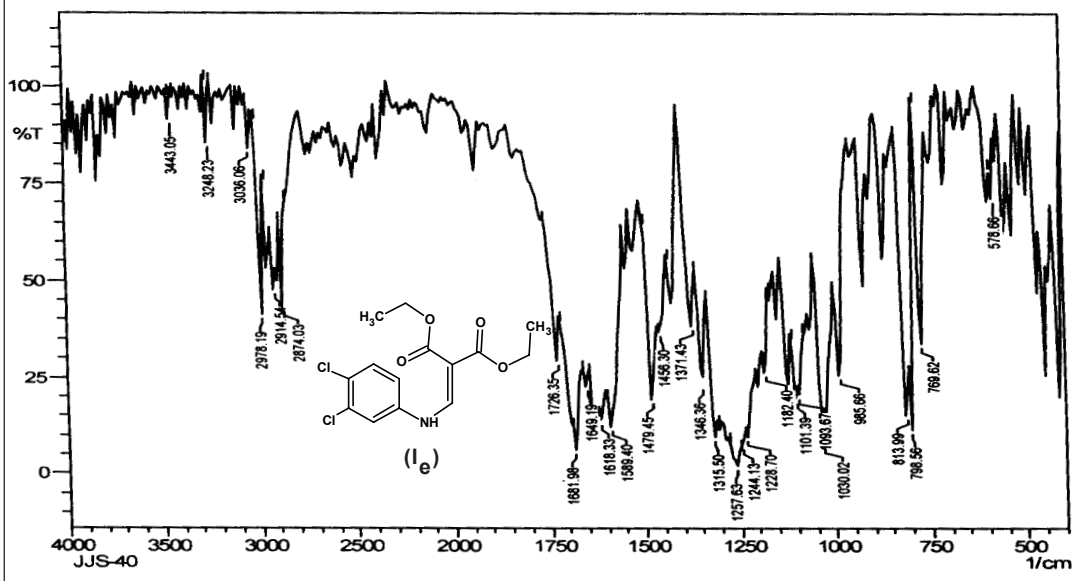
IR SPECTRAL STUDY OF DIETHYL-(3-CHLORO-4-FLUOROPHENYL)-AMINO METHYLENE MALONATE (I_d).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2906.8	2975 - 2850	96
	C-H (sym. str., m)	2874.6	2900 - 2800	96
	C-H (asym. def., m)	1452.4	1470 - 1435	96
	C-H (sym. def., m)	1352.1	1385 - 1300	96
Aromatic and ring skeletal vibration	C=C & C-C (str., v)	1591.1	1600 - 1450	97
	C-H (i.p. def., m)	1155.0	1150 - 1050	97
	C-H (o.o.p. def., m)	802.5	825 - 800	97
	C-N (str., v)	1319.3	1340 - 1250	97
Amine	N-H (Astr., m)	3441.1	3500-3400	98
	N-H (str., b)	3171-3126	3400 - 3000	98
	N-H (def., s,m)	1616.4	1650 - 1550	98
Ketone (ester)	C=O (str., b)	1720.5-1664.6	1740 - 1650	98
Halogen Subtitution	C-F (str., b)	1352-1149	1400 - 1080	99
	C-Cl(str., b)	802-662	800-600	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

IR SPECTRAL STUDY OF DIETHYL-(3,4-DICHLOROPHENYL)-AMINO-METHYLENE MALONATE (I_e).

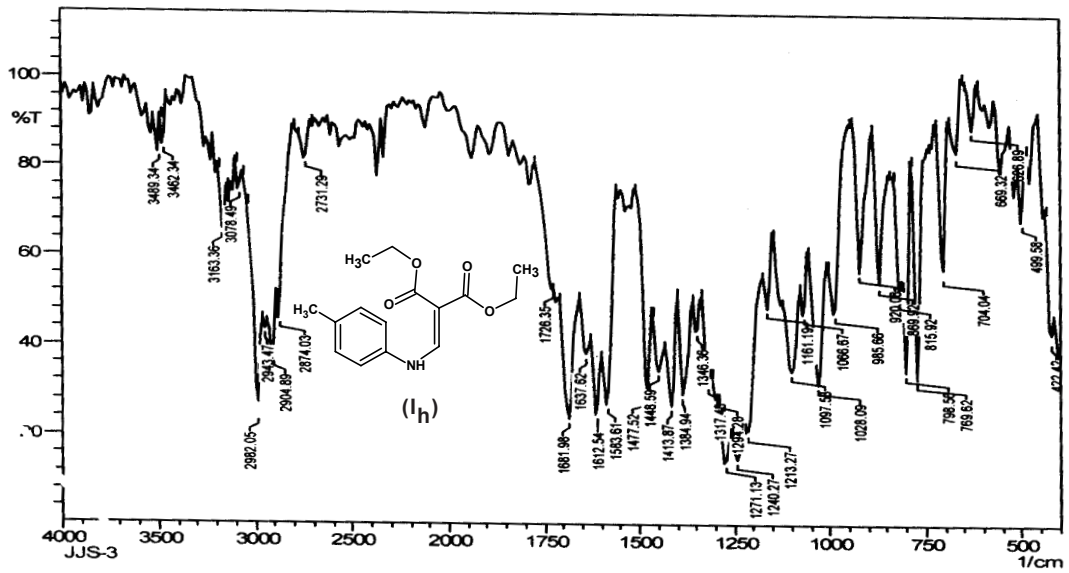


(I_e)

Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2914.5	2975 - 2850	96
	C-H (sym. str., m)	28747.0	2900 - 2800	96
	C-H (asym. def., m)	1479.4	1470 - 1435	96
	C-H (sym. def., m)	1450.3	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3036.0	3080 - 3010	97
	C=C & C-C (str., v)	1589.4	1600 - 1450	97
	C-H (i.p. def., m)	1101.3	1150 - 1050	97
	C-H (o.o.p. def., m)	813.9	825 - 800	97
	C-N (str., v)	1315.5	1340 - 1250	97
Amine	N-H (Astr., m)	3443.0	3500-3400	98
	N-H (str., b)	3248-3036	3400 - 3000	98
	N-H (def., s,m)	1618.3	1650 - 1550	98
Ketone (ester)	C=O (str., s)	1726.3-1681.9	1740 - 1650	98
Halogen Subtitution	C-Cl(str., b)	813-769	800-600	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

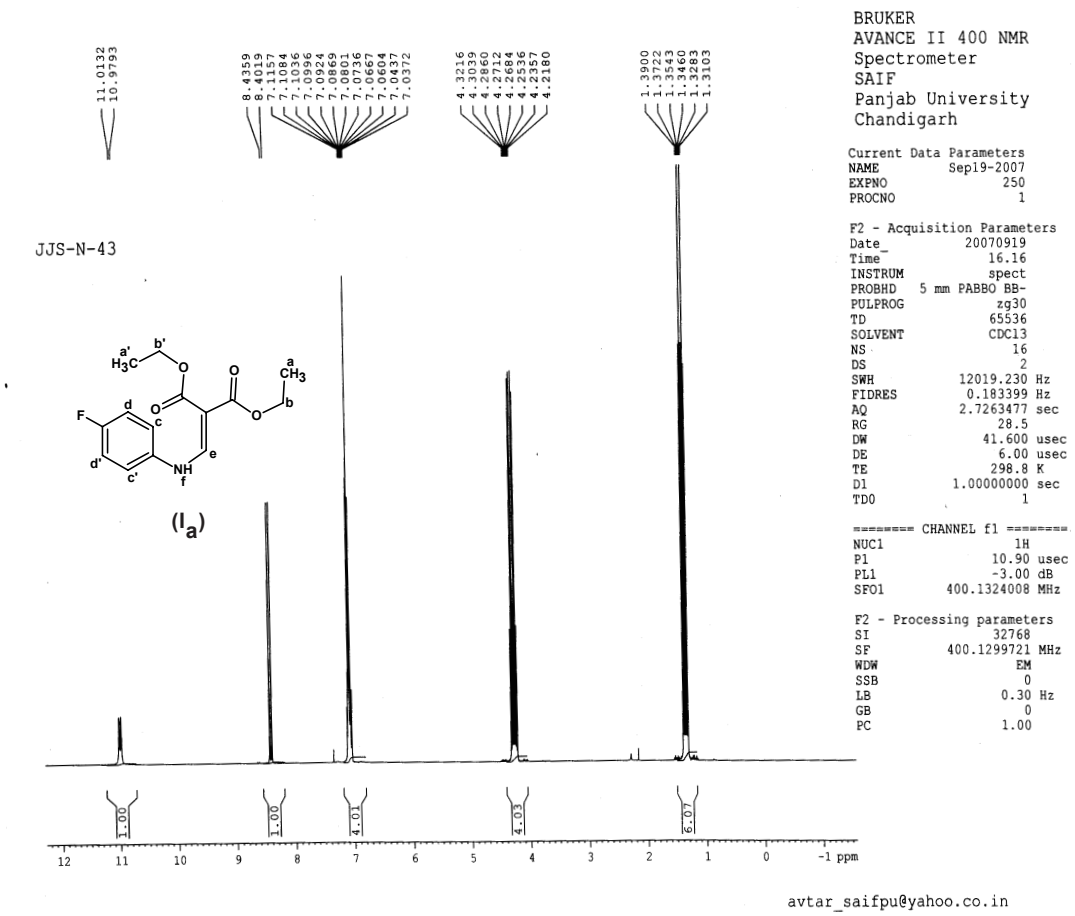
IR SPECTRAL STUDY OF DIETHYL-(*p*-METHYLPHENYL)-AMINO METHYLENE MALONATE (I_h).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2943.4	2975 - 2850	96
	C-H (sym. str., m)	2874.0	2900 - 2800	96
	C-H (asym. def., m)	1477.5	1470 - 1435	96
	C-H (sym. def., m)	1448.5	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3078.4	3080 - 3010	97
	C=C & C-C (str., v)	1583.6	1600 - 1450	97
	C-H (i.p. def., m)	1097.5	1150 - 1050	97
	C-H (o.o.p. def., m)	815.9	825 - 800	97
	C-N (str., v)	1271.1	1340 - 1250	97
Amine	N-H (Astr., m)	3489.3	3500-3400	98
	N-H (str., m)	3163-3078	3400 - 3000	98
	N-H (def., s,m)	1612.5	1650 - 1550	98
Ketone (ester)	C=O (str., s)	1726.3-1681.9	1740 - 1650	98
Para(-4-) substituted	C-H (def., v,s)	815.9	800 - 850	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

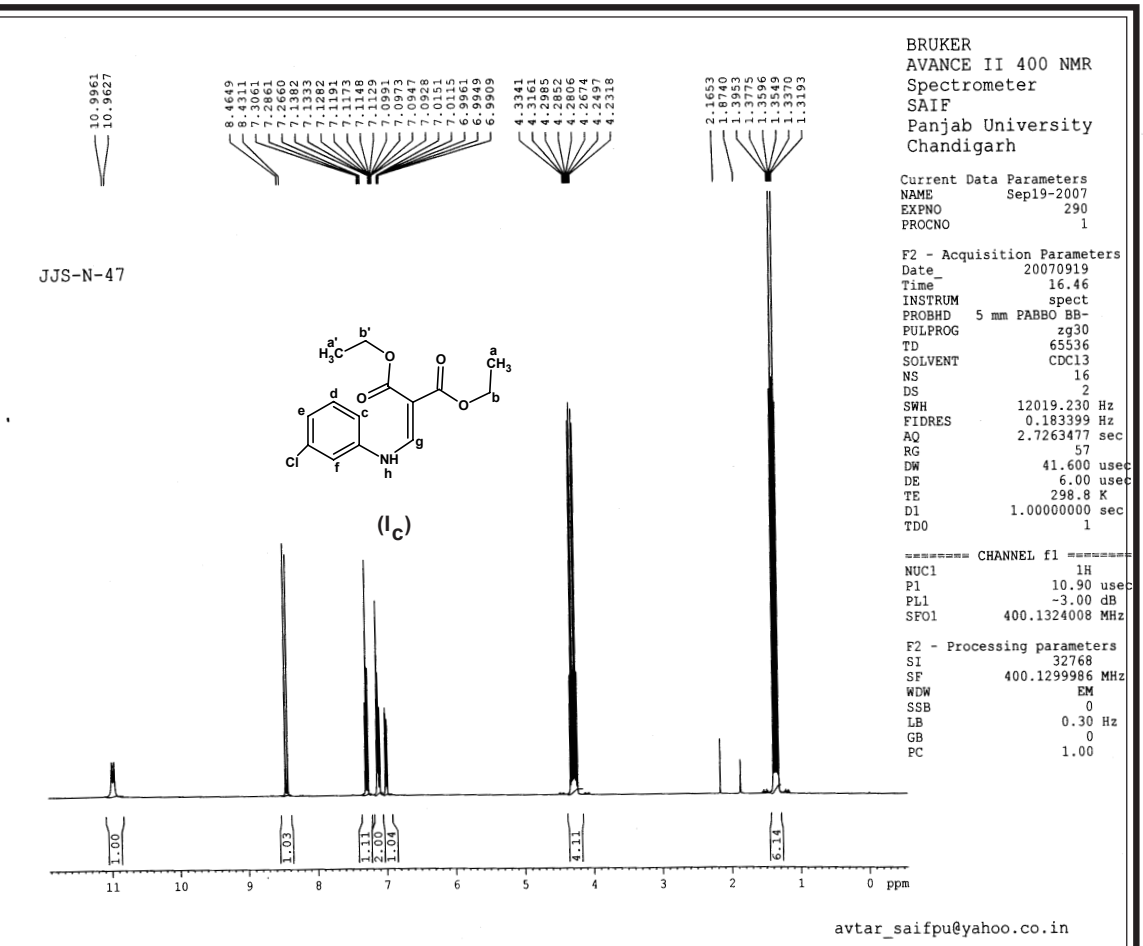
NMR SPECTRALSTUDY OF DIETHYL -(*p*-FLUOROPHENYL)-AMINO-METHYLENE MALONATE (I_a).



(I_a)

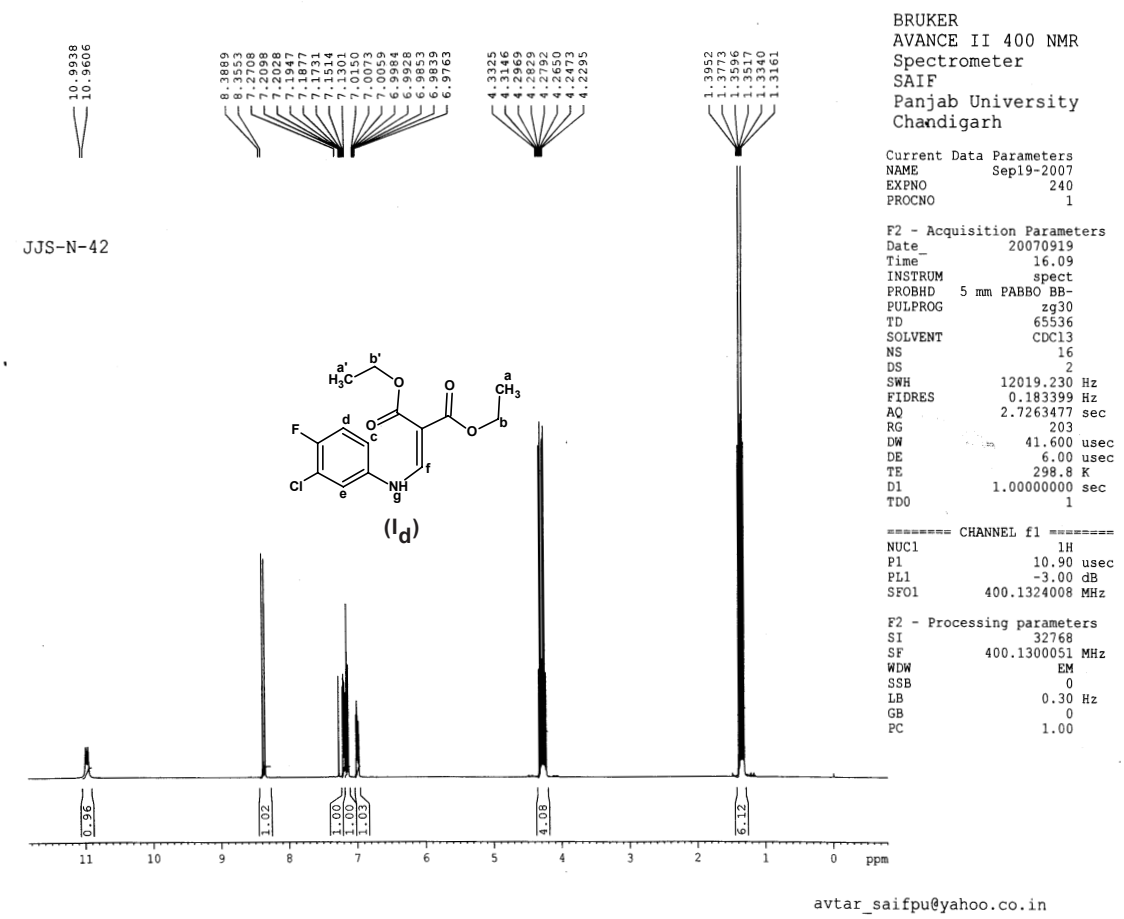
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.3103-1.3900	6H	triplet	- ($C\underline{H}_3$)(a,a')
2	4.2180-4.3216	4H	quartet	- $C\underline{H}_2$(b,b')
3	7.0372-7.1157	4H	multiplet	- Ar-$\underline{H}$(c,c',d,d')
4	8.4019-8.4359	1H	doublet	- NH-$\underline{C}\underline{H}$(e)
5	10.979-11.0132	1H	doublet	- N$\underline{H}$(f)

NMR SPECTRAL STUDY OF DIETHYL-(*m*-CHLOROPHENYL)-AMINO-METHYLENE MALONATE (I_C).



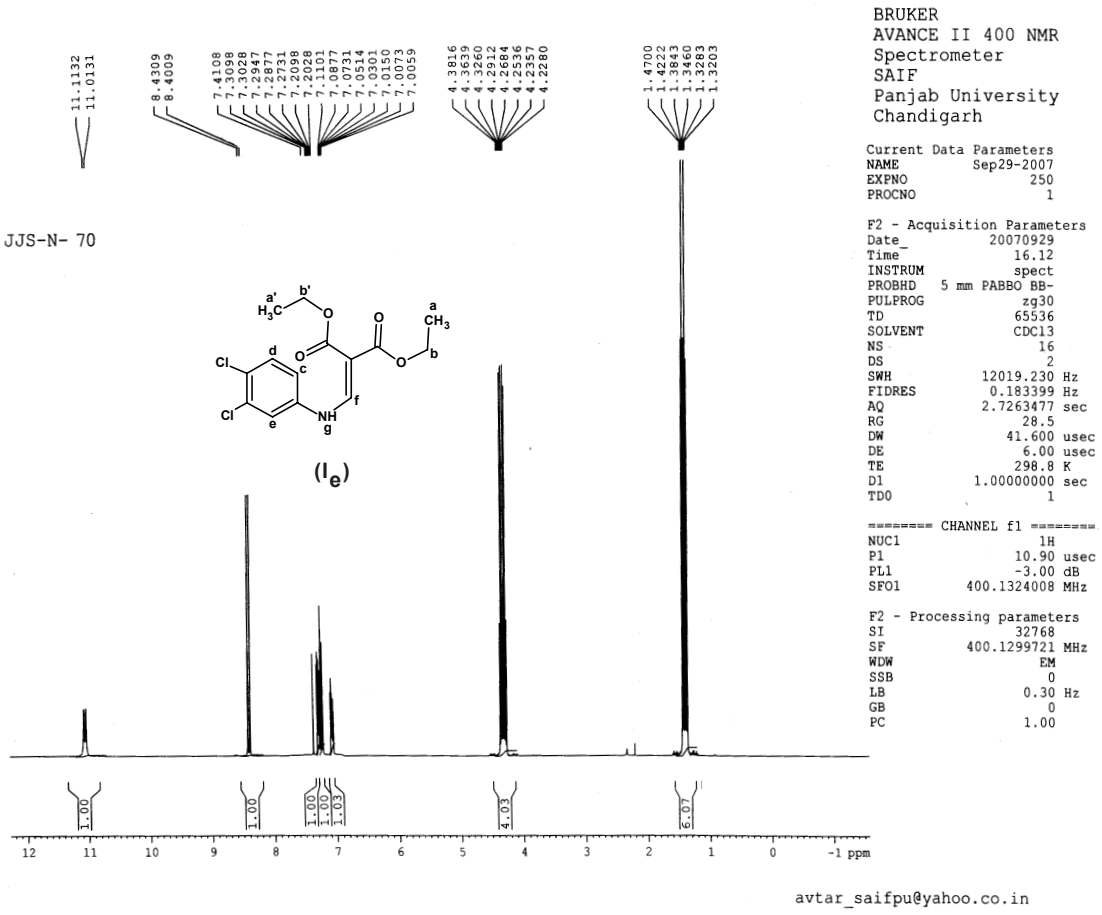
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.3193-1.3953	6H	triplet	- ($C\underline{H}_3$)(a,a')
2	4.2318-4.3341	4H	quartet	- $C\underline{H}_2$(b,b')
3	6.9909-7.0151	1H	triplet	- Ar-$\underline{H}$(f)
4	7.0928-7.1382	2H	multiplet	- Ar-$\underline{H}$(d,e)
5	7.2660-7.3061	1H	triplet	- Ar-$\underline{H}$(c)
6	8.4311-8.4649	1H	doublet	-NH-$\underline{CH}$(g)
7	10.9627-10.996	1H	doublet	- N$\underline{H}$(h)
8	2.1693	-	-	-Acetone

NMR SPECTRAL STUDY OF DIETHYL-(3-CHLORO-4-FLUOROPHENYL)-AMINO METHYLENE MALONATE (I_d).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.3161-1.6745	6H	triplet	- $(C\underline{H}_3)_{(a,a')}$
2	4.2295-4.3325	4H	quartet	- $C\underline{H}_{2(b,b')}$
3	6.9763-7.0150	1H	multiplet	- Ar-$\underline{H}_{(c)}$
4	7.1301-7.2098	1H	multiplet	- Ar-$\underline{H}_{(d)}$
5	7.2708	1H	singlet	- Ar-$\underline{H}_{(e)}$
6	8.3553-8.3889	1H	doublet	-NH-$\underline{CH}_{(f)}$
7	10.9606-10.993	1H	doublet	- $N\underline{H}_{(g)}$

NMR SPECTRAL STUDY OF DIETHYL-(3,4-DICHLOROPHENYL)-AMINO-METHYLENE MALONATE (I_e).

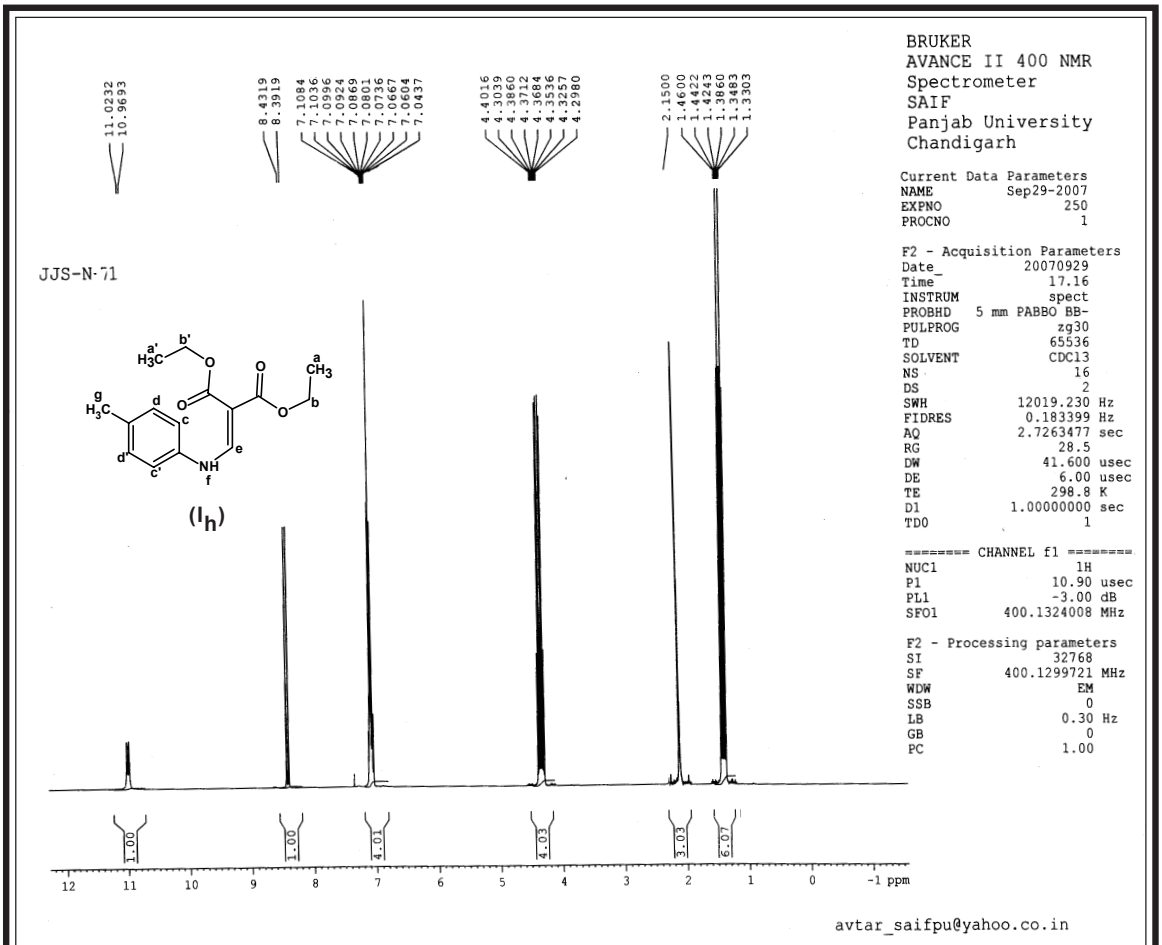


(I_e)

avtar_saifpu@yahoo.co.in

Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.3203-1.4700	6H	triplet	- $(C\underline{H}_3)_{(a,a')}$
2	4.2280-4.3816	4H	quartet	- $C\underline{H}_2$(b,b')
3	7.0059-7.1101	1H	multiplet	- Ar-$\underline{H}_{(c)}$
4	7.2028-7.3098	1H	multiplet	- Ar-$\underline{H}_{(d)}$
5	7.4108	1H	singlet	- Ar-$\underline{H}_{(e)}$
6	8.4009-8.4309	1H	doublet	-NH-$\underline{CH}_{(f)}$
7	11.0131-11.113	1H	doublet	- $N\underline{H}_{(g)}$

NMR SPECTRAL STUDY OF DIETHYL-(*p*-METHYLPHENYL)-AMINO-METHYLENE MALONATE (I_h).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.3303-1.4600	6H	triplet	- ($C\underline{H}_3$)$_{(a)}$
2	2.1500	3H	singlet	- $C\underline{H}_3$$_{(g)}$
3	4.2980-7.1084	4H	multiplet	- $C\underline{H}_2$$_{(b)}$
4	8.3919-8.4319	4H	multiplet	- Ar-$\underline{H}_{(c,c',d,d')}$
5	8.3919-8.4319	1H	doublet	-NH-$\underline{CH}_{(e)}$
6	10.9693-11.023	1H	doublet	- $N\underline{H}_{(f)}$

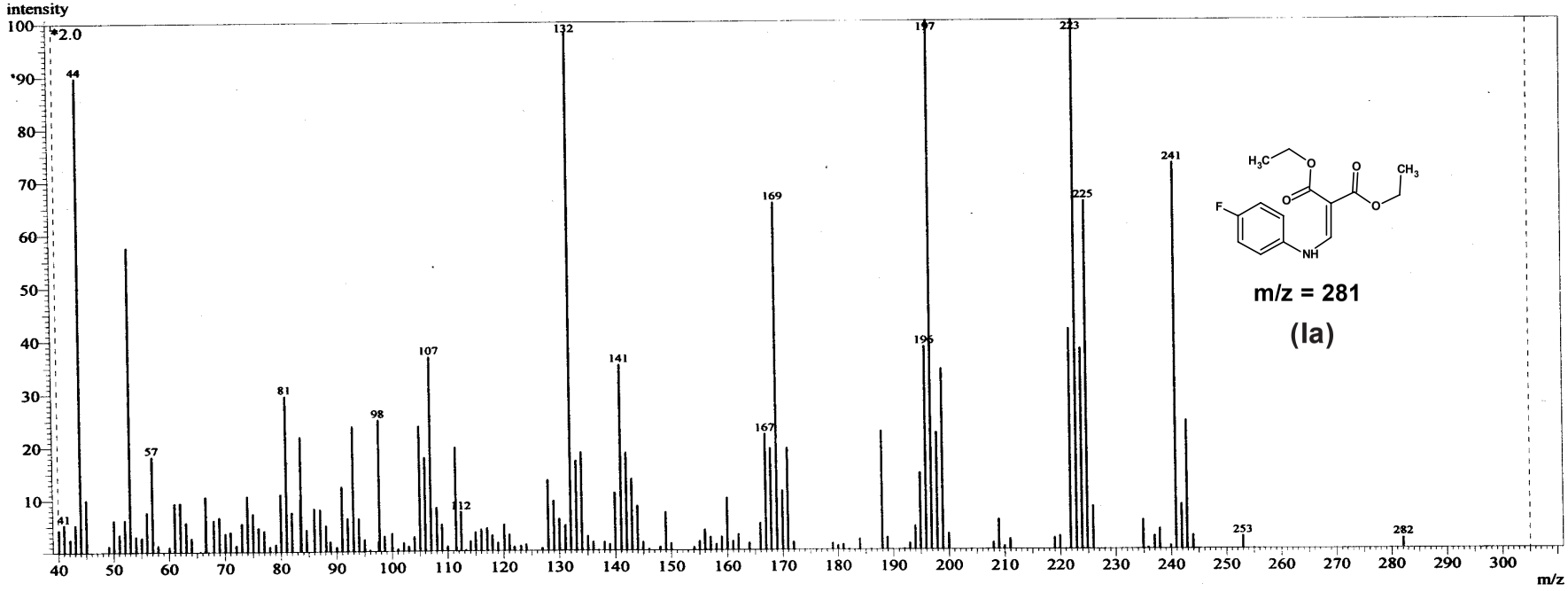
MASS SPECTRAL STUDY OF DIETHYL-(*p*-FLUORO PHENYL)-AMINO METHYLENE MALONATE (I_a).

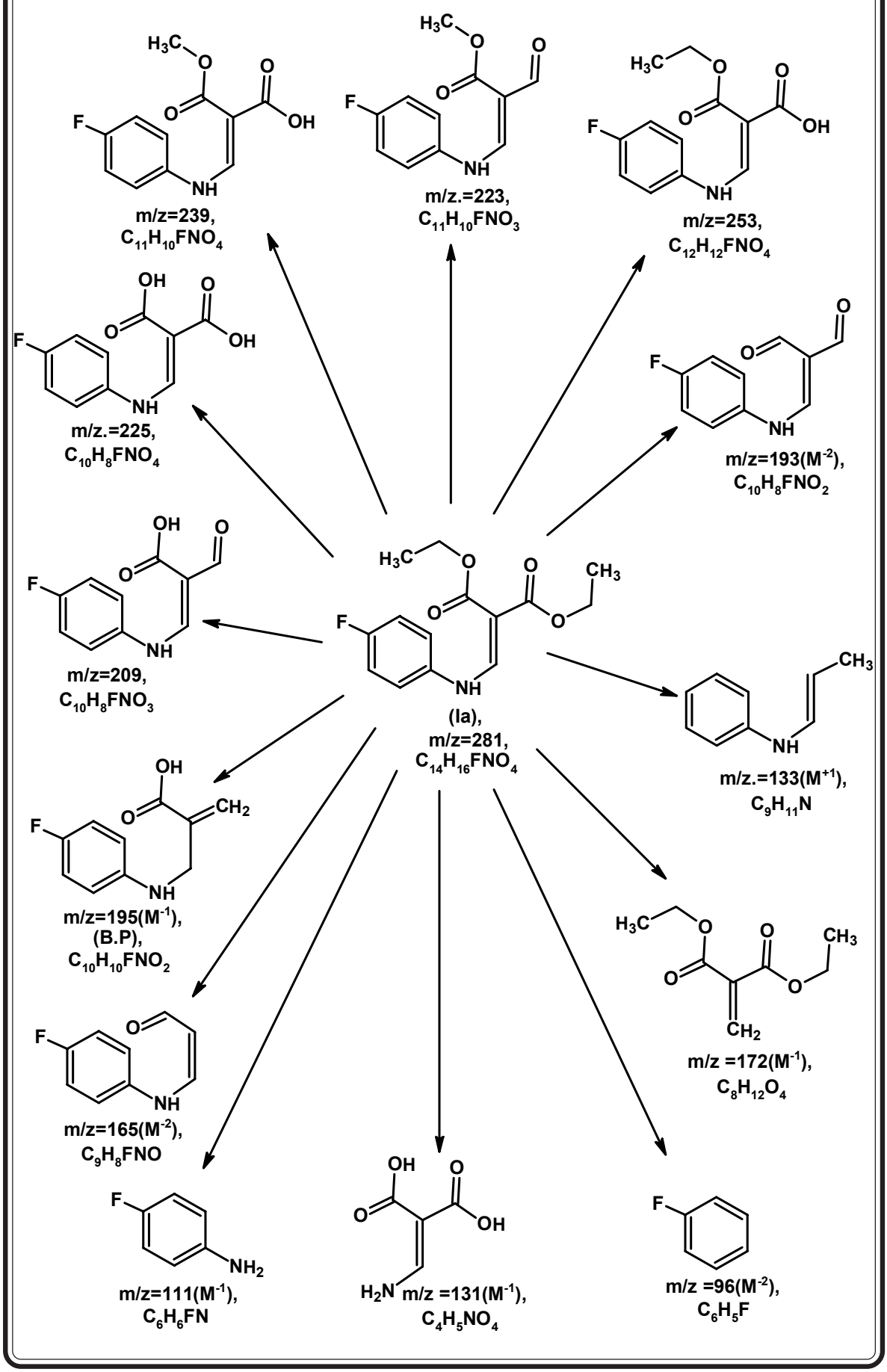
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 6/12/2006 3:58:50 PM
Sample Name	: JJS-M-34
Sample ID	: JJS-M-34
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-34.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune11.qgt

Line#:1 R.Time:8.7(Scan#:1003)
MassPeaks:161 BasePeak:223(55851)
RawMode:Averaged 0.3-14.6(5-1712)
BG Mode:None
intensity




m/z=239, C11H10FNO4
m/z.=223, C11H10FNO3
m/z=253, C12H12FNO4
m/z.=225, C10H8FNO4
m/z=193(M-2), C10H8FNO2
m/z=209, C10H8FNO3
(Ia), m/z=281, C14H16FNO4
m/z.=133(M+1), C9H11N
m/z=195(M-1), (B.P), C10H10FNO2
m/z =172(M-1), C8H12O4
m/z=165(M-2), C9H8FNO
m/z=111(M-1), C6H6FN
m/z =131(M-1), C4H5NO4
m/z =96(M-2), C6H5F

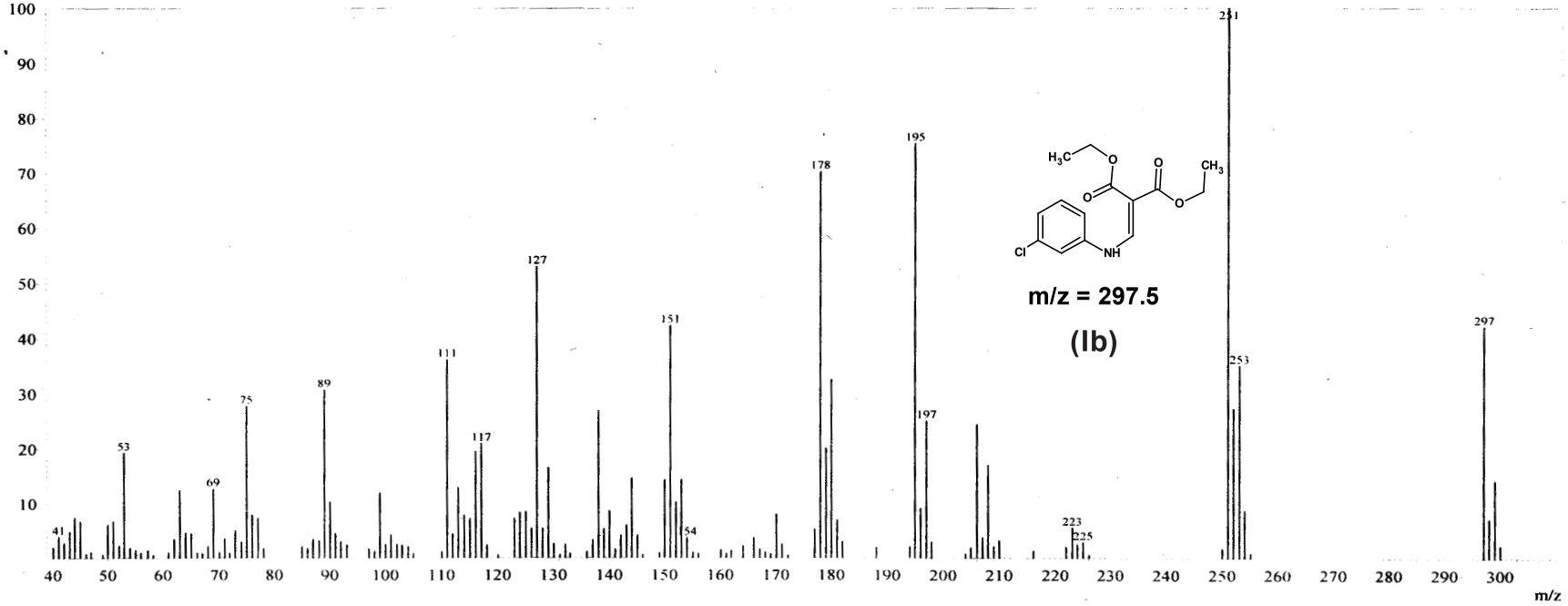
MASS SPECTRAL STUDY OF DIETHYL-(*m*-CHLORO PHENYL)-AMINO METHYLENE MALONATE (I_b).

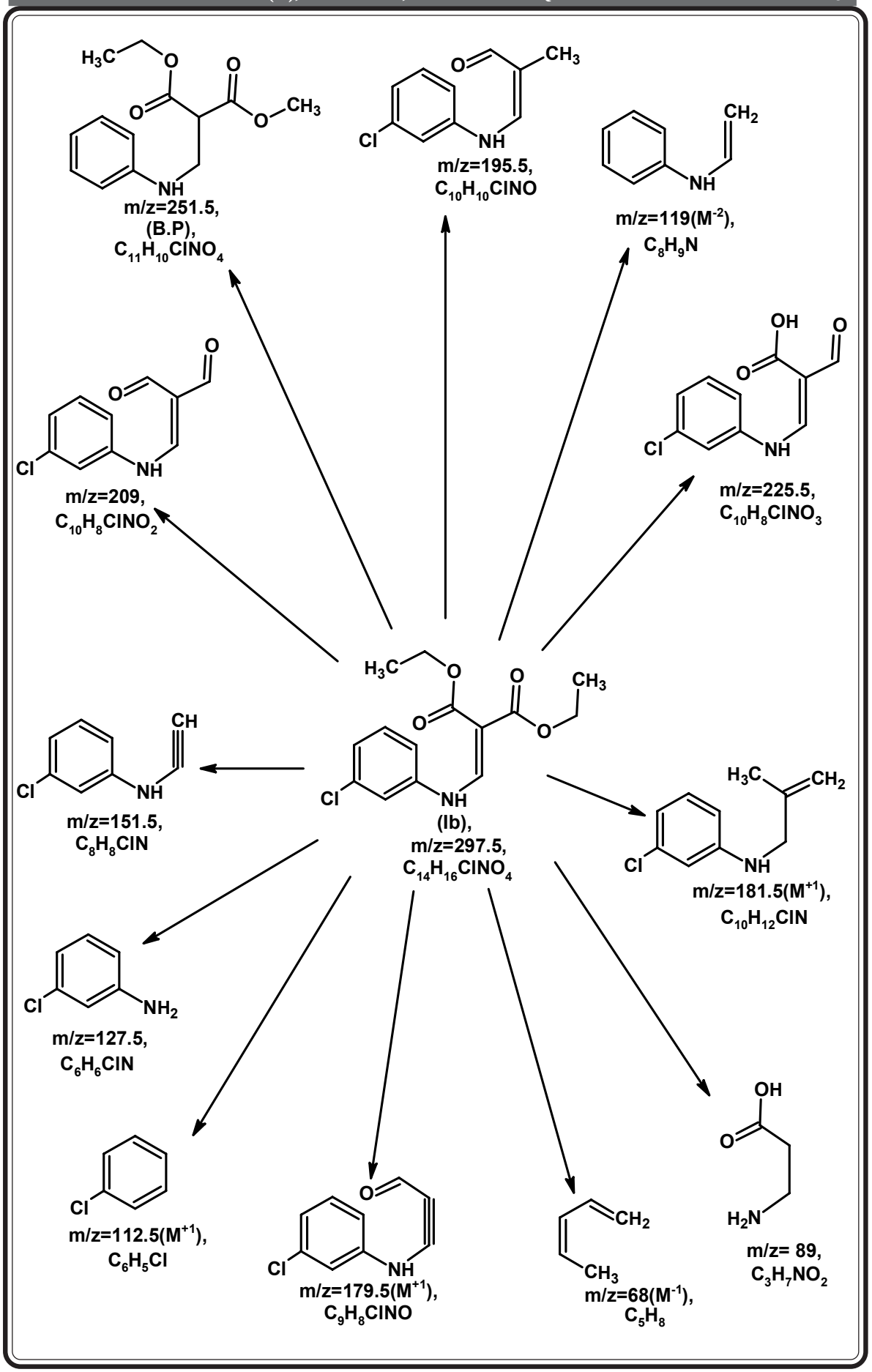
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 8/24/2007 12:33:43 PM
Sample Name	: JJS-MQ-15
Sample ID	: JJS-MQ-15
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-15.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune130807.qgt

Line#:1 R.Time:3.4(Scan#:367)
MassPeaks:140 BasePeak:251(210470)
RawMode:Single 3.4(367)
BG Mode:None
intensity




m/z=251.5, (B.P), $C_{11}H_{10}ClNO_4$
m/z=195.5, $C_{10}H_{10}ClNO$
m/z=119(M^{-2}), C_8H_9N
m/z=209, $C_{10}H_8ClNO_2$
m/z=225.5, $C_{10}H_8ClNO_3$
m/z=151.5, C_8H_8ClN
(Ib), m/z=297.5, $C_{14}H_{16}ClNO_4$
m/z=181.5(M^{+1}), $C_{10}H_{12}ClN$
m/z=127.5, C_6H_6ClN
m/z=112.5(M^{+1}), C_6H_5Cl
m/z=179.5(M^{+1}), C_9H_8ClNO
m/z=68(M^{-1}), C_5H_8
m/z= 89, $C_3H_7NO_2$

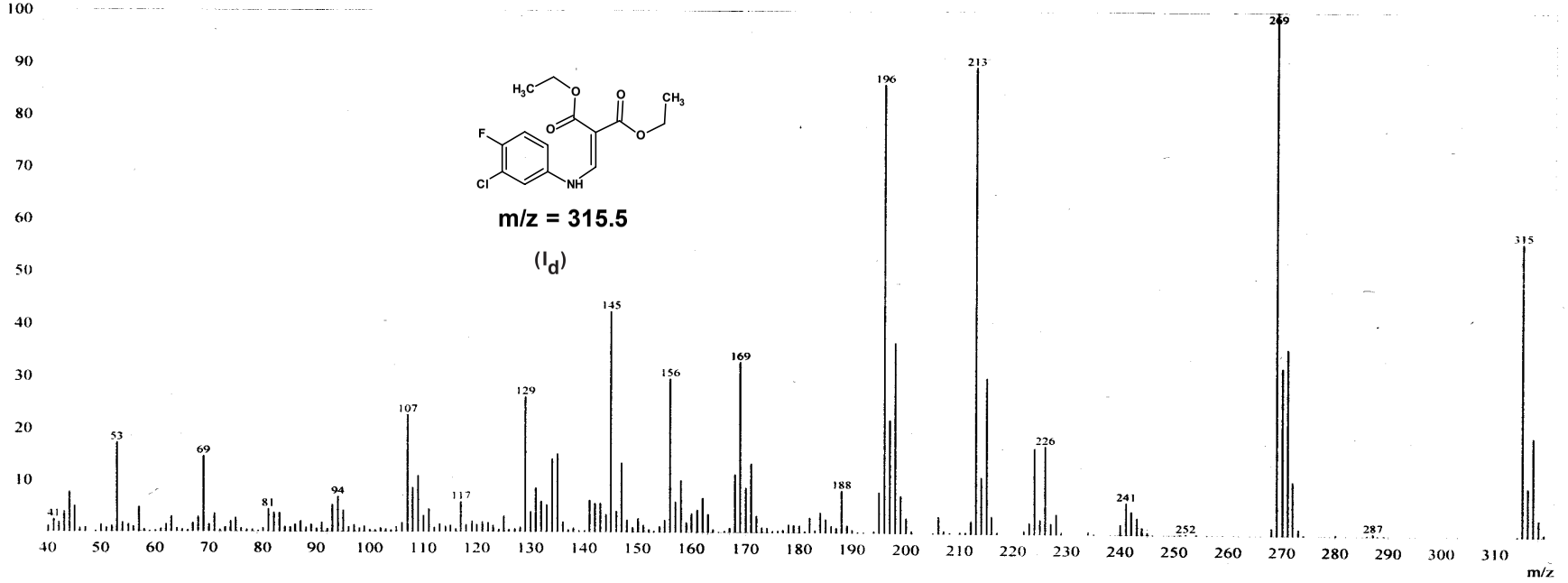
MASS SPECTRAL STUDY OF DIETHYL-(3-CHLORO-4-FLUOROPHENYL)-AMINO METHYLENE MALONATE (I_d).

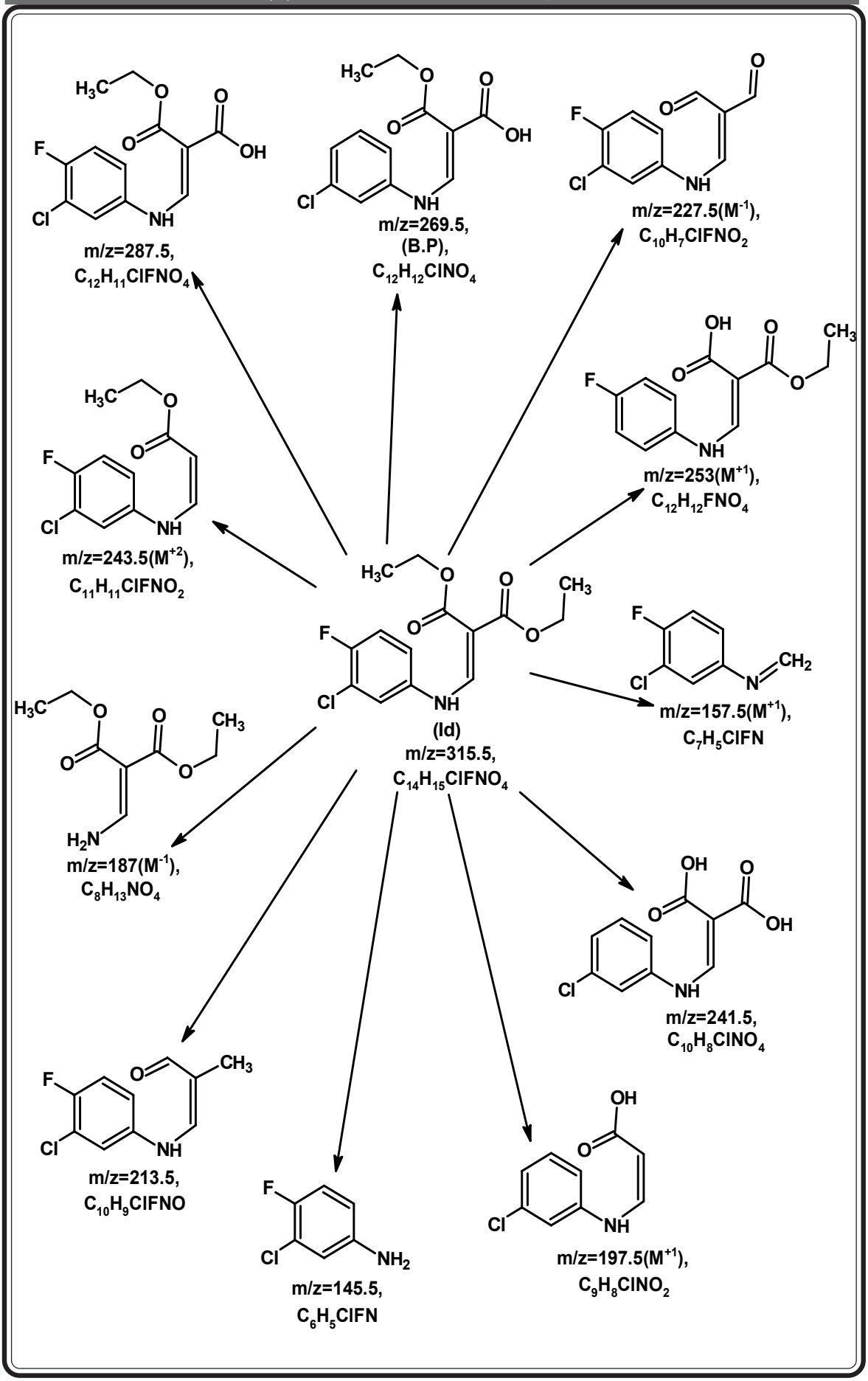
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 8/24/2007 11:46:45 AM
Sample Name : JJS-MQ-14
Sample ID : JJS-MQ-14
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-14.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune130807.qgt

Line#:1 R.Time:3.8(Scan#:420)
MassPeaks:209 BasePeak:269(534833)
RawMode:Averaged 3.4-4.1(371-460)
BG Mode:None
intensity




m/z=287.5,
$C_{12}H_{11}ClFNO_4$
m/z=269.5,
(B.P),
$C_{12}H_{12}ClNO_4$
m/z=227.5(M^{-1}),
$C_{10}H_7ClFNO_2$
m/z=253(M^{+1}),
$C_{12}H_{12}FNO_4$
m/z=243.5(M^{+2}),
$C_{11}H_{11}ClFNO_2$
(Id)
m/z=315.5,
$C_{14}H_{15}ClFNO_4$
m/z=157.5(M^{+1}),
C_7H_5ClFN
m/z=187(M^{-1}),
$C_8H_{13}NO_4$
m/z=241.5,
$C_{10}H_8ClNO_4$
m/z=213.5,
$C_{10}H_9ClFNO$
m/z=145.5,
C_6H_5ClFN
m/z=197.5(M^{+1}),
$C_9H_8ClNO_2$

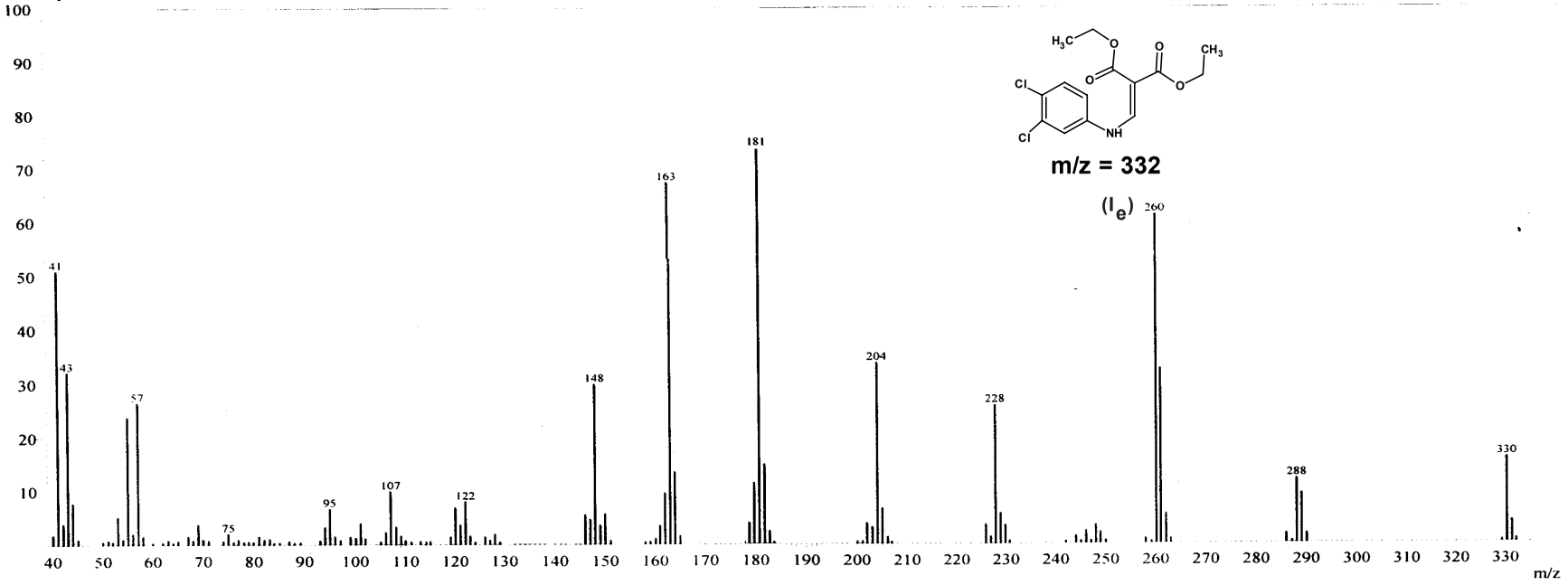
MASS SPECTRAL STUDY OF DIETHYL-(3,4-DICHLORO PHENYL)-AMINO METHYLENE MALONATE (I_e).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

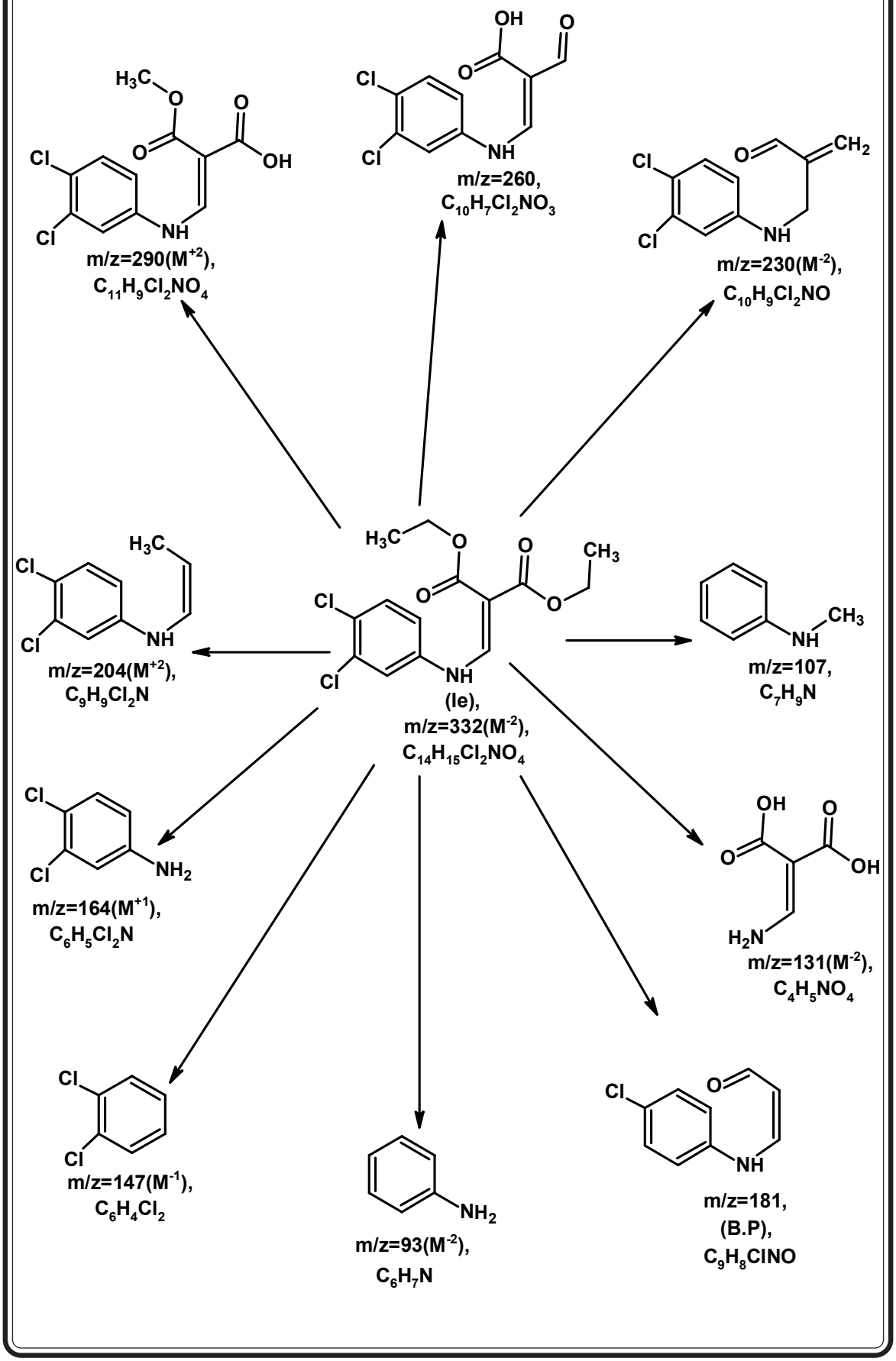
Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 9/22/2007 4:08:39 PM
Sample Name : JJS-MQ-29
Sample ID : JJS-MQ-29
Data File : C:\GCMSsolution\Data\V.H.SHAH\JS-MQ-29.QGD
Method File : C:\GCMSsolution\Data\Project1\D1.qgm
Tuning File : C:\GCMSsolution\System\Tune1\170907_01.qgt

Line#:1 R.Time:2.9(Scan#:313)
MassPeaks:162 BasePeak:181(399248)
RawMode:Single 2.9(313)
BG Mode:None
intensity



m/z = 332

(I_e)


m/z=290(M+2),
C11H9Cl2NO4
m/z=260,
C10H7Cl2NO3
m/z=230(M-2),
C10H9Cl2NO
m/z=204(M+2),
C9H9Cl2N
(Ie),
m/z=332(M-2),
C14H15Cl2NO4
m/z=107,
C7H9N
m/z=164(M+1),
C6H5Cl2N
m/z=131(M-2),
C4H5NO4
m/z=147(M-1),
C6H4Cl2
m/z=93(M-2),
C6H7N
m/z=181,
(B.P),
C9H8ClNO

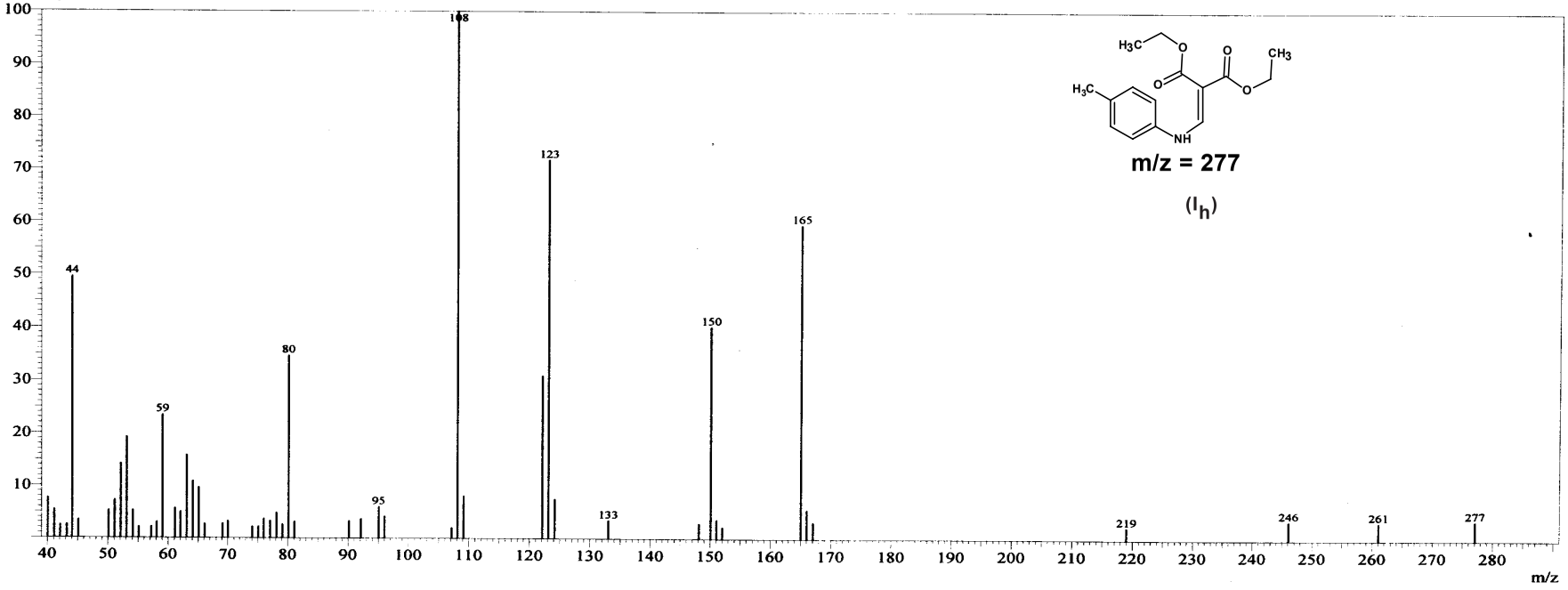
MASS SPECTRAL STUDY OF DIETHYL-(*p*-METHYL PHENYL)-AMINO METHYLENE MALONATE (I_h).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 7/10/2006 3:20:08 PM
Sample Name	: JJS-M-36
Sample ID	: JJS-M-36
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-36.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:8.2(Scan#:945)
MassPeaks:53 BasePeak:108(51246)
RawMode:Single 8.2(945)
BG Mode:None
intensity



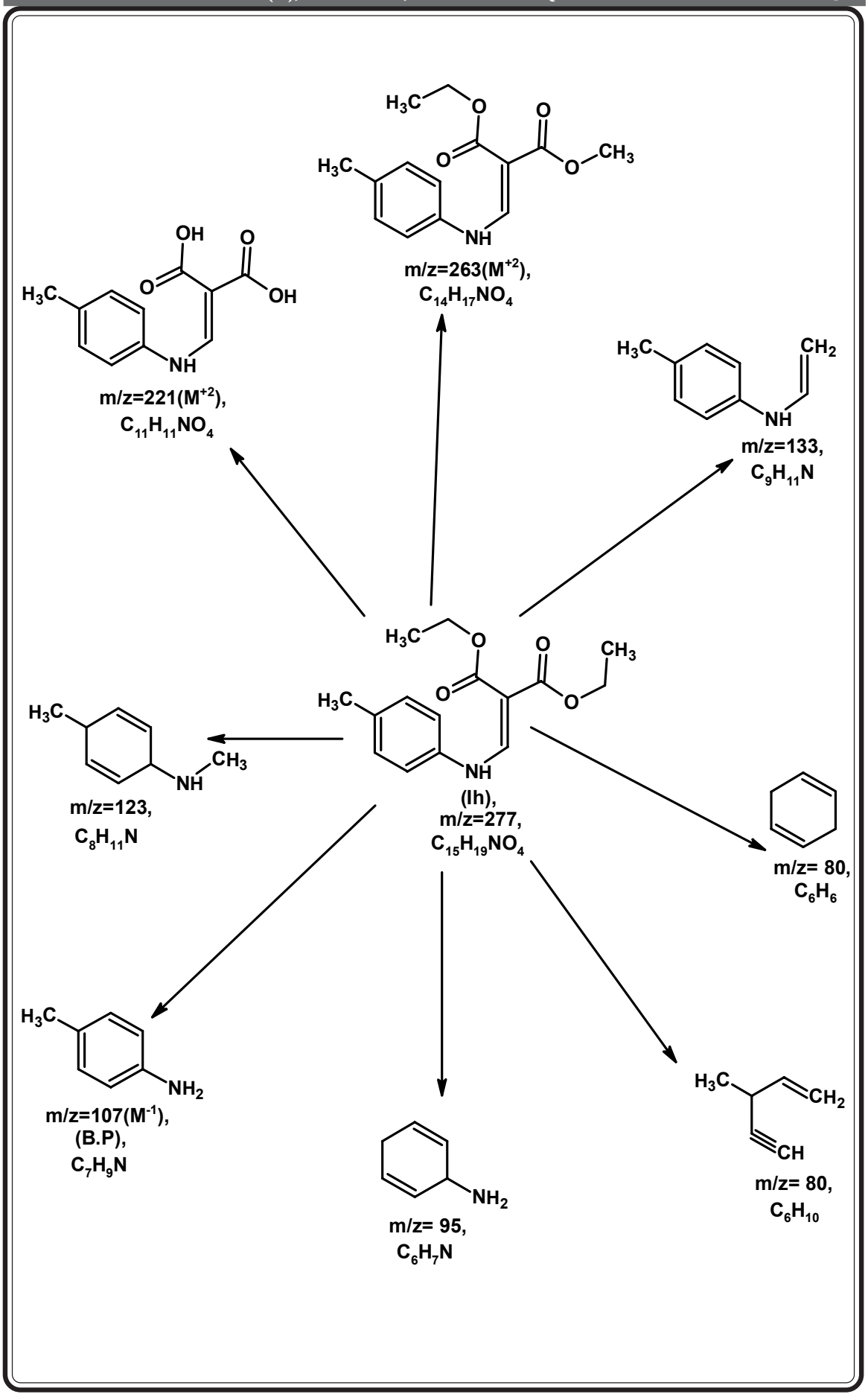

m/z=263(M+2),
C14H17NO4
m/z=221(M+2),
C11H11NO4
m/z=133,
C9H11N
m/z=123,
C8H11N
(Ih),
m/z=277,
C15H19NO4
m/z= 80,
C6H6
m/z=107(M-1),
(B.P),
C7H9N
m/z= 95,
C6H7N
m/z= 80,
C6H10

TABLE NO. 1A : COMPARATIVE ANTIMICROBIAL ACTIVITY OF DIETHYL -(SUBSTITUTED PHENYL)-AMINO METHYLENE MALONATES (I_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) S. pyogens MTCC- 442					S. aureus MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
Ia	4-F-C_6H_4	-	11	14	16	17	-	9	11	14	15
Ib	3-Cl-C_6H_4	-	10	13	15	16	-	8	10	13	13
Ic	4-Cl-C_6H_4	-	9	11	12	14	-	9	10	11	14
Id	3-Cl-4-F-C_6H_3	-	9	11	13	15	-	10	12	15	16
Ie	3,4-$(Cl)_2$-C_6H_3	-	8	10	13	16	-	8	10	12	14
If	4-NO_2-C_6H_4	-	9	10	12	14	-	7	8	10	13
Ig	2-OCH_3-C_6H_4	-	7	9	11	13	-	8	9	11	14
Ih	4-CH_3-C_6H_4	-	9	10	10	12	-	8	8	9	12
Ii	2,3-$(CH_3)_2$-C_6H_3	-	8	9	10	12	-	8	9	10	13
Ij	-$C_{10}H_7$	-	9	10	11	13	-	7	9	10	13

Comparative activity of (I_{a-j}) with known choosen standard drugs

Standard drug	Antibacterial activity									
				Ia					Id	Id
Amoxicilin	12	14	15	16	18	10	12	14	15	16
Chloramphenicol	14	15	18	19	24	14	17	20	21	24
Sparfloxacin	14	22	24	26	28	24	26	27	28	32
Levofloxacin	18	21	22	27	29	20	24	26	27	35

N.B.(-): No Activity

TABLE NO. 1B : COMPARATIVE ANTIMICROBIAL ACTIVITY OF DIETHYL -(SUBSTITUTED PHENYL)-AMINO METHYLENE MALONATES (I_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) B. subtillis MTCC- 441					E. Coli MTCC- 443				
		5	25	50	100	250	5	25	50	100	250
Ia	4-F-C_6H_4	-	9	11	12	14	-	6	6	7	8
Ib	3-Cl-C_6H_4	-	10	12	13	15	-	6	7	9	10
Ic	4-Cl-C_6H_4	-	8	10	11	13	-	8	9	11	11
Id	3-Cl-4-F-C_6H_3	-	8	9	11	12	-	8	9	10	12
Ie	3,4-$(Cl)_2$-C_6H_3	-	9	10	12	14	-	9	10	10	11
If	4-NO_2-C_6H_4	-	10	10	11	12	-	7	8	12	13
Ig	2-OCH_3-C_6H_4	-	10	11	12	13	-	6	7	9	11
Ih	4-CH_3-C_6H_4	-	8	9	10	12	-	6	7	8	12
Ii	2,3-$(CH_3)_2$-C_6H_3	-	10	10	11	12	-	5	6	8	10
Ij	-$C_{10}H_7$	-	10	11	13	15	-	6	7	8	9
Comparative activity of(I_{a-j}) with known choosen standard drugs											
Standard drug		**Antibacterial activity**									
Amoxicilin		12	15	16	18	19	11	14	16	18	20
Chloramphenicol		18	22	24	26	27	17	20	23	25	26
Sparfloxacin		22	24	25	26	29	20	22	25	26	28
Levofloxacin		24	26	28	29	31	23	25	26	29	30

N.B.(-): No Activity

TABLE NO. 1C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF DIETHYL-(SUBSTITUTED PHENYL)-AMINO METHYLENE MALONATES (I_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antifungal activity (Zones of inhibition in m.m.) C. albicans MTCC- 227					A.niger MTCC- 282				
		5	25	50	100	250	5	25	50	100	250
Ia	6-F	-	9	11	13	15	-	8	10	12	13
Ib	7-Cl	-	7	8	10	12	-	7	8	10	11
Ic	6-Cl	-	9	10	11	14	-	7	9	10	13
Id	7-Cl-6-F	-	11	13	15	17	-	12	14	15	17
Ie	6,7-$(Cl)_2$	-	6	8	10	11	-	8	9	10	12
If	6-NO_2	-	7	7	8	9	-	7	8	9	10
Ig	6-OCH_3	-	6	8	10	12	-	6	7	9	10
Ih	6-CH_3	-	5	6	8	10	-	7	9	10	11
Ii	7,8-$(CH_3)_2$	-	6	9	11	13	-	7	8	10	12
Ij	-C_4H_4	-	7	9	10	12	-	8	9	9	11

Comparative activity of (I_{a-j}) with known choosen standard drugs

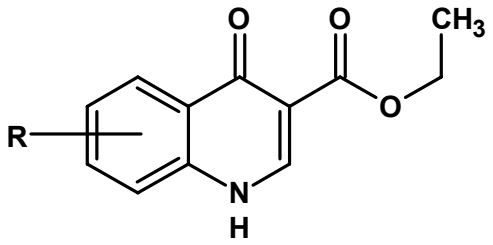
Standard drug	Antifungal activity									
Griseofulvin	16	18	21	23	25	17	19	21	22	23
Fluconazole	14	16	18	21	22	15	17	18	20	21

N.B.(-): No Activity

SECTION - II

PREPARATION AND BIOLOGICAL EVALUATION OF ETHYL-(SUBSTITUTED-1,4-DIHYDROQUINOLIN-4-ONE-3-CARBOXYLATES.

Keeping in view of various biodynamic activities[34-85] of **4-quinolones** and in order to have highly potent therapeutic agents, the synthesis of **Ethyl-substituted-1,4-dihydroquinolin-4-one-3-carboxylates (IIa-j)** have been undertaken by the condensation of different **diethyl-(substituted phenyl)-aminomethylene malonates (Ia-j)** in **dimethyl sulphoxide.**



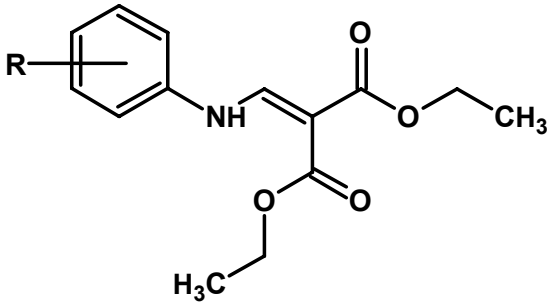
(IIa-j)

R=Substituted phenyl

The constitution of the products **(IIa-j)** have been delineated by **elemental analyses, IR, PMR** and **Mass** spectral data.

The products **(IIa-j)** were assayed for their ***in vitro*** biological assay like antibacterial activity towards ***S. pyogens MTCC-442, S. aureus MTCC-96 and B. subtillis MTCC-441*** **(Gram positive)** and ***E. coli MTCC-443*** **(Gram negative)** bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations .i.e.: 0(control), 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds **(IIa-j)** were compared with standard drugs viz.,**Amoxicillin,Chloramphenicol, Sparfloxacin,Levofloxacin**(antibacterial),**Griseofluvin, Fluconazole** (antifungal)**.**

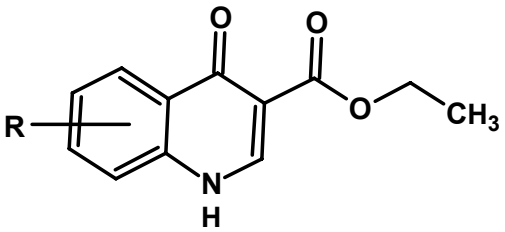
REACTION SCHEME



(Ia-j)
R=substituted phenyl

Dimethyl-
sulphoxide

△



(IIa-j)
R=substituted phenyl

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF ETHYL-(SUBSTITUTED-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATES.

(A) Preparation of Diethyl-(3-chloro-4-fluoro amino phenyl)-amino-methylene malonate (I_d).

Refere preparation, in Part-1, Section-I, **page No. 30.**

(B) Preparation of Ethyl-(7-chloro-6-fluoro-1,4-dihydroquinoline)-4-one-3-carboxylate (II_d).

A mixture of Diethyl-(3-chloro,4-fluorophenyl)-aminomethylene malonates (I_d) (3.15 gm,0.01M) and dimethyl sulphoxide (20 ml) was heated under stirring at 190 to 210^{O}C. The resulting mixture was then refluxed for 8 hrs. The reaction mixture was allowed to cool at room temperature. The reaction mixture was poured into ice-water, filtered and washed with water and crystalized from dimethyl formamide. The product was dried at 50-55 ^{O}C the white crystalline powder.. Yield : 53 %, M.P. : 289 ^{O}C, (Required: C, 53.45 %; H, 3.36 %; N, 5.19 % for $C_{12}H_9NO_3ClF$, Found: C, 53.41 %; H, 3.31 %; N, 5.17 %).

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (3.0 : 7.0) = 0.60.
TLC solvent system R_{f_2} : Methanol : Toluene (2.0 : 8.0) = 0.46.

Similarly, other compounds **(IIa-j)** were synthesized. The physical data are recorded in **Table No. 2**.

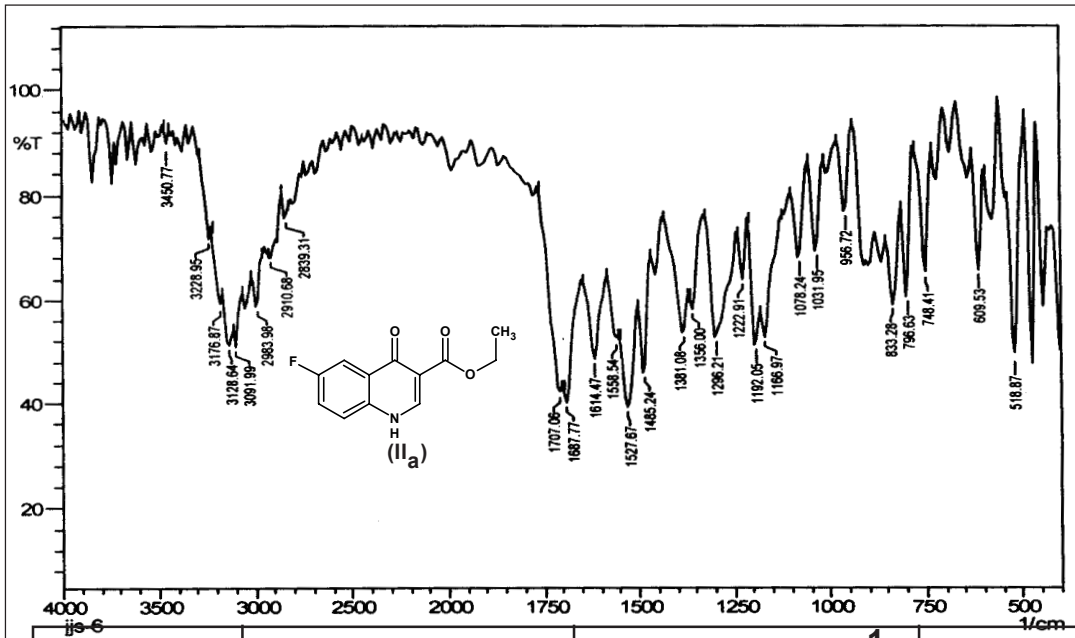
(B) Antimicrobial activity of Ethyl-(substituted-1,4-dihydroquinoline) -4-one-3-carboxylates (IIa-j).

Antimicrobial activity testing was carried out as described in Part-1(A), Section-I, page No. 30-31. The MIC values of test solution are recorded in **Table No. 2A, 2B** and **2C.**

TABLE NO. 2 : PHYSICAL CONSTANTS OF ETHYL-(SUBSTITUTED-1,4-DIHYDROQUINOLINE)-4-ONE-3-CARBOXYLATES (II_{a-j}).

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. °C 5	Yield % 6	R_f Value R_{f_1} 7	R_{f_2}	% of Nitrogen Calcd. / Found 8
II_a	6-F	$C_{12}H_{10}NO_3F$	235.0	289°	55	0.66	0.49	5.95 / 5.90
II_b	7-Cl	$C_{12}H_{10}NO_3Cl$	251.5	283°	57	0.58	0.48	5.57 / 5.50
II_c	6-Cl	$C_{12}H_{10}NO_3Cl$	251.5	284°	58	0.52	0.47	5.57 / 5.48
II_d	7-Cl-6-F	$C_{12}H_9NO_3ClF$	269.0	289°	53	0.62	0.46	5.20 / 5.15
II_e	6,7-$(Cl)_2$	$C_{12}H_9NO_3Cl_2$	286.0	271°	56	0.58	0.48	4.89 / 4.83
II_f	6-NO_2	$C_{12}H_{10}N_2O_5$	262.0	296°	51	0.48	0.38	10.68 /10.62
II_g	6-OCH_3	$C_{13}H_{13}NO_4$	247.0	274°	43	0.49	0.42	5.67 / 5.63
II_h	6-CH_3	$C_{13}H_{13}NO_3$	231.0	288°	57	0.44	0.41	6.06 / 6.00
II_i	7,8-$(CH_3)_2$	$C_{14}H_{15}NO_3$	281.0	271°	58	0.41	0.38	4.98 / 4.93
II_j	-	$C_{16}H_{13}NO_4$	267.0	235°	54	0.42	0.39	5.24 / 5.19

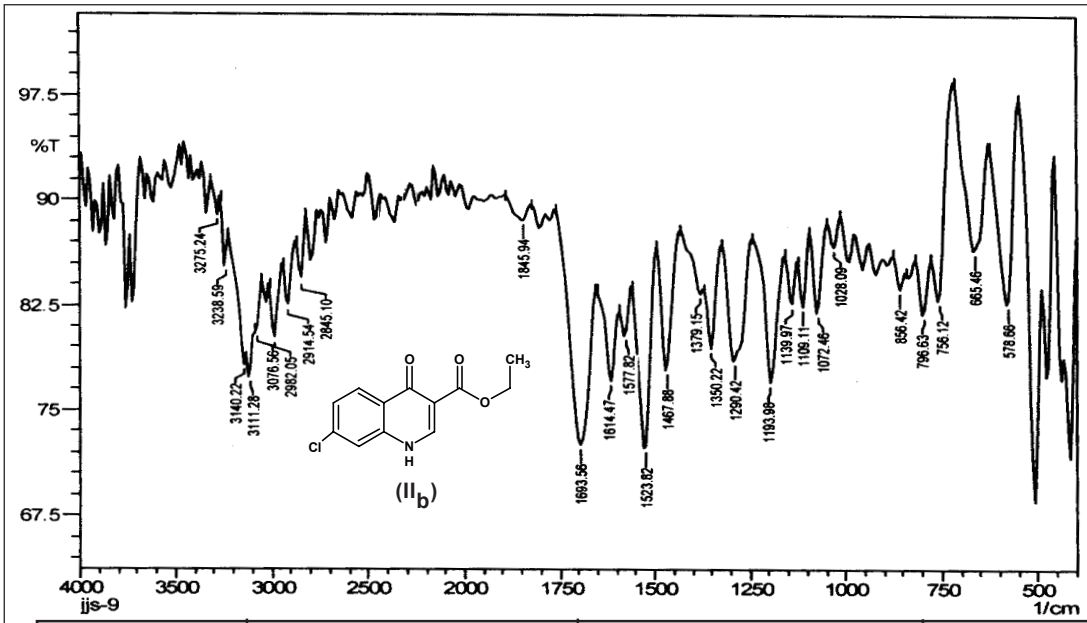
IR SPECTRAL STUDY OF ETHYL-6-FLUORO-1,4-DIHYDRO-QUINOLINE-4-ONE-3-CARBOXYLATES (II_a).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2910.6	2975 - 2850	96
	C-H (sym. str., m)	2839.3	2900 - 2800	96
	C-H (asym. def., m)	1485.2	1470 - 1435	96
	C-H (sym. def., m)	1381.0	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3091.9	3080 - 3010	97
	C=C & C-C (str., v)	1558.5	1600 - 1450	97
	C-H (i.p. def., m)	1078.2	1150 - 1050	97
	C-H (o.o.p. def., m)	833.2	825 - 800	97
	C-N (str., v)	1381.0	1340 - 1250	97
Amine	N-H (Astr., m)	3450.7	3500-3400	98
	N-H (str., b)	3228-3091	3400 - 3000	98
	N-H (def., s,m)	1614.4	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1687.7	1690 - 1640	98
(Ester)	C=O (str., s)	1707.0	1740 - 1650	98
Halogen Subtitution	C-F (str., b)	1381-1166	1400 - 1080	99
Para(-4-) substituted	C-H (def., v,s)	833.2	800 - 850	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

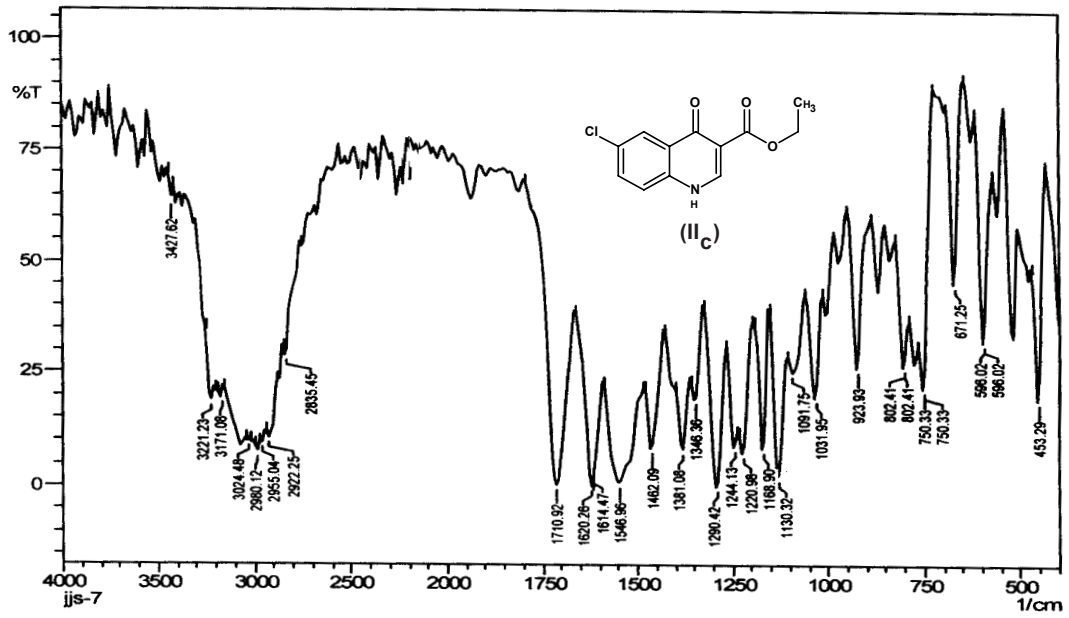
IR SPECTRAL STUDY OF ETHYL-7-CHLORO-1,4-DIHYDRO-QUINOLINE-4-ONE-3-CARBOXYLATE (II_b).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2914.5	2975 - 2850	96
	C-H (sym. str., m)	2845.1	2900 - 2800	96
	C-H (asym. def., m)	1467.8	1470 - 1435	96
	C-H (sym. def., m)	1379.1	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3076.5	3080 - 3010	97
	C=C & C-C (str., v)	1577.8	1600 - 1450	97
	C-H (i.p. def., m)	1139.9	1150 - 1050	97
	C-H (o.o.p. def., m)	796.6	825 - 800	97
	C-N (str., v)	1290.4	1340 - 1250	97
Amine	N-H (str., b)	3275-3076	3400 - 3000	98
	N-H (def., s,m)	1614.4	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1614.4	1690 - 1640	98
(Ester)	C=O (str., s)	1693.5	1740 - 1650	98
Halogen Subtitution	C-Cl(str., b)	796-665	800 - 600	99
Meta(-3-) substituted	C-H (def., v,s)	856.4	880 - 830	99
		756.1	780-730	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

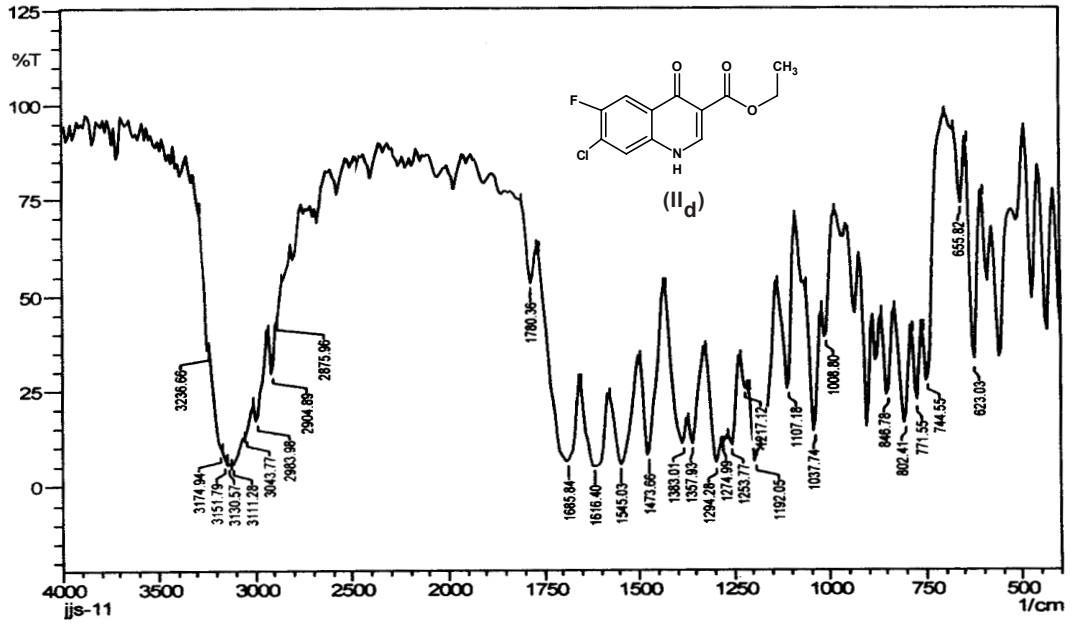
IR SPECTRAL STUDY OF ETHYL-6-CHLORO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (II_C).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2955.0	2975 - 2850	96
	C-H (sym. str., m)	2835.4	2900 - 2800	96
	C-H (asym. def., m)	1462.0	1470 - 1435	96
	C-H (sym. def., m)	1381.0	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3024.4	3080 - 3010	97
	C=C & C-C (str., v)	1462.0	1600 - 1450	97
	C-H (i.p. def., m)	1168.9	1150 - 1050	97
	C-H (o.o.p. def., m)	802.4	825 - 800	97
	C-N (str., v)	1290.4	1340 - 1250	97
Amine	N-H (Astr., m)	3427.6	3500-3400	98
	N-H (str., b)	3221-3024	3400 - 3000	98
	N-H (def., s,m)	1614.4	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1620.2	1690 - 1640	98
(Ester)	C=O (str., s)	1710.9	1740 - 1650	98
Para(-4-) substituted	C-H (def., v,s)	802.4	800 - 850	99
Halogen Subtitution	C-Cl(str., b)	802.4-671.2	800 - 600	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

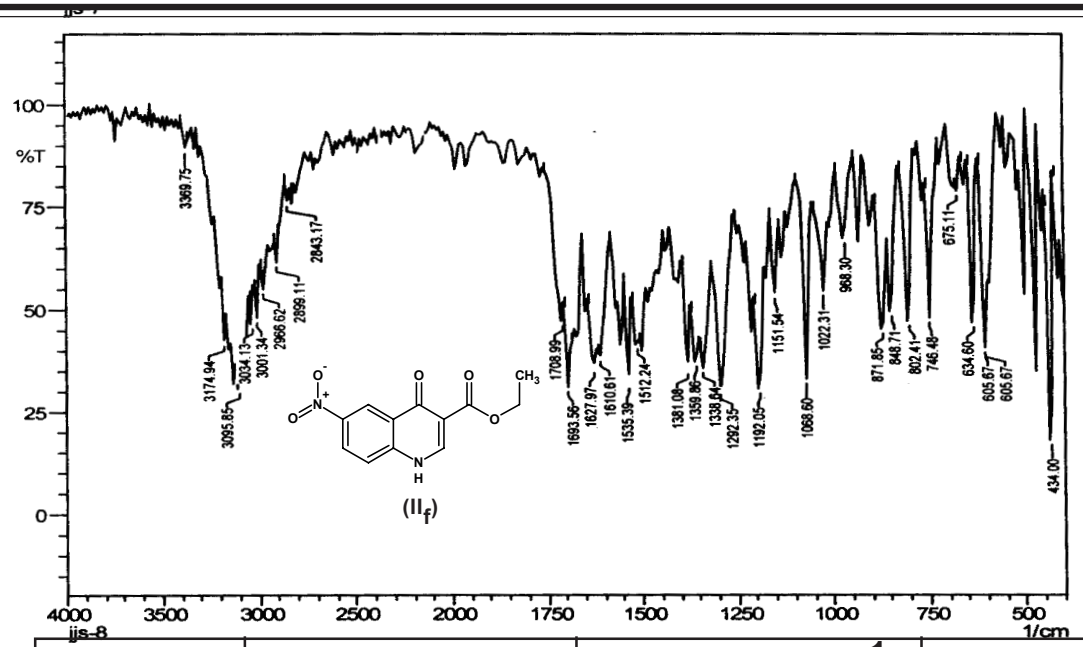
IR SPECTRAL STUDY OF ETHYL-7-CHLORO- 6-FLUORO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (II_d).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2904.8	2975 - 2850	96
	C-H (sym. str., m)	2875.9	2900 - 2800	96
	C-H (asym. def., m)	1473.6	1470 - 1435	96
	C-H (sym. def., m)	1383.0	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3043.7	3080 - 3010	97
	C=C & C-C (str., v)	1545.0	1600 - 1450	97
	C-H (i.p. def., m)	1107.1	1150 - 1050	97
	C-H (o.o.p. def., m)	802.4	825 - 800	97
	C-N (str., v)	1294.2	1340 - 1250	97
Amine	N-H (str., b)	3236-3043	3400 - 3000	98
	N-H (def., s,m)	1616.4	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1616.1	1690 - 1640	98
(Ester)	C=O (str., s)	1685.8	1740 - 1650	98
Halogen Subtitution	C-F (str.,b)	1383.1-1107.1	1400 - 1080	99
	C-Cl (str.,b)	802.4-623.0	800-600	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

IR SPECTRAL STUDY OF ETHYL-6-NITRO-1,4-DIHYDRO QUINOLINE-4-ONE-3-CARBOXYLATE (II_f).

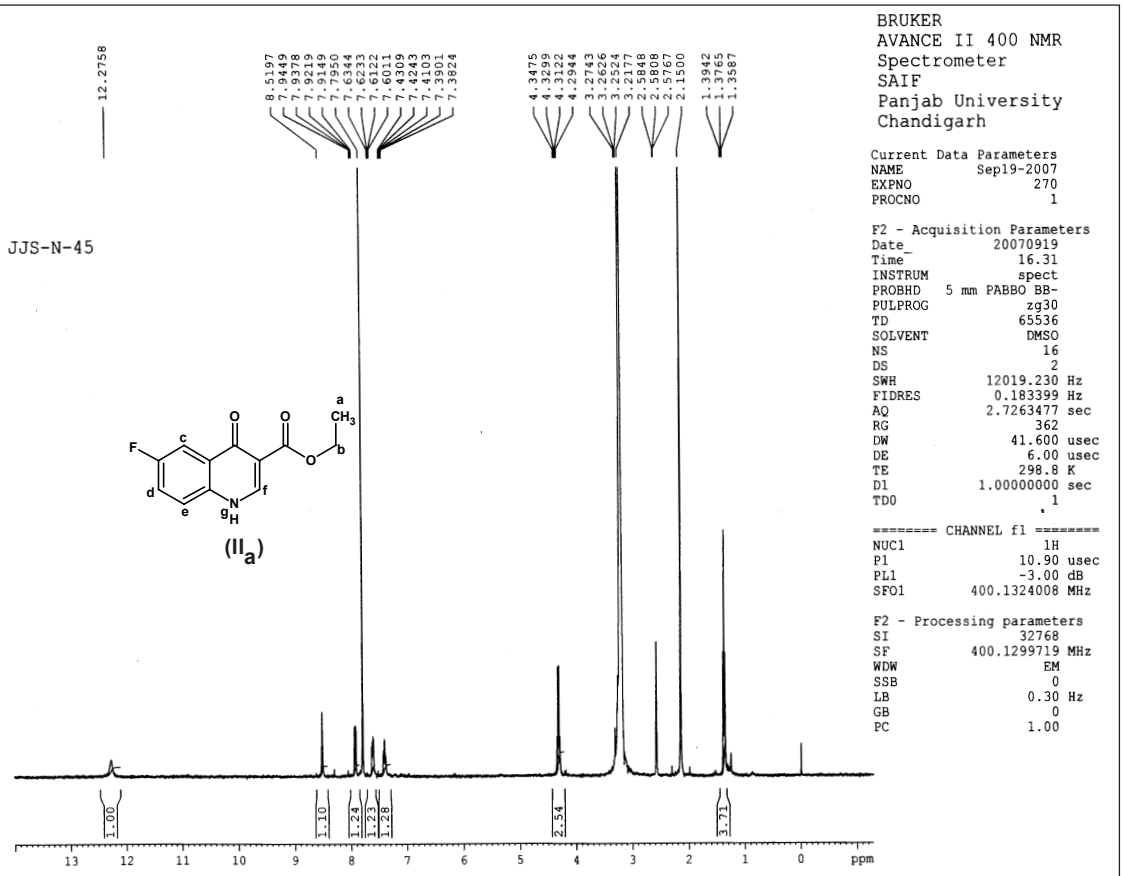


(II_f)

Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2966.6	2975 - 2850	96
	C-H (sym. str., m)	2899.1	2900 - 2800	96
	C-H (asym. def., m)	1512.2	1470 - 1435	96
	C-H (sym. def., m)	1381.0	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3034.1	3080 - 3010	97
	C=C & C-C (str., v)	1610.6	1600 - 1450	97
	C-H (i.p. def., m)	1151.5	1150 - 1050	97
	C-H (o.o.p. def., m)	802.4	825 - 800	97
	C-N (str., v)	1338.6	1340 - 1250	97
Amine	N-H (Astr., m)	3369.7	3500-3400	98
	N-H (str., b)	3174-3001	3400 - 3000	98
	N-H (def., s,m)	1627.9	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1693.5	1690 - 1640	98
(Ester)	C=O (str., s)	1708.9	1740 - 1650	98
Nitro Subtitution	C-NO_2 (Asym.str., s)	1535.3	1570 - 1500	99
	C-NO_2 (Sym.str., s)	1359.8	1370-1300	99
Para(-4-) substituted	C-H (def., v,s)	848.7	800 - 850	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

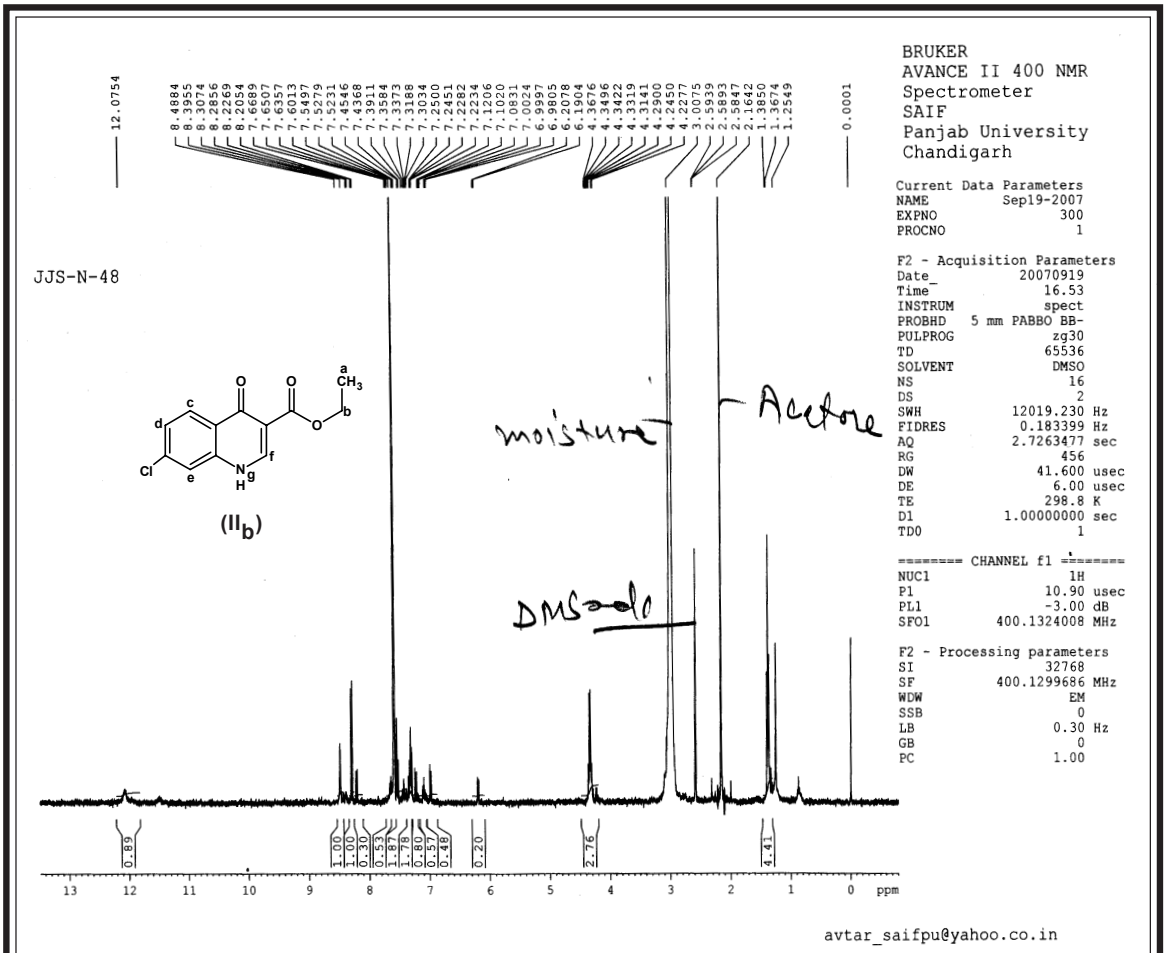
NMR SPECTRAL STUDY OF ETHYL-6-FLUORO-1,4-DIHYDRO-QUINOLINE-4-ONE-3-CARBOXYLATE (II_a).



avtar_saifpu@yahoo.co.in

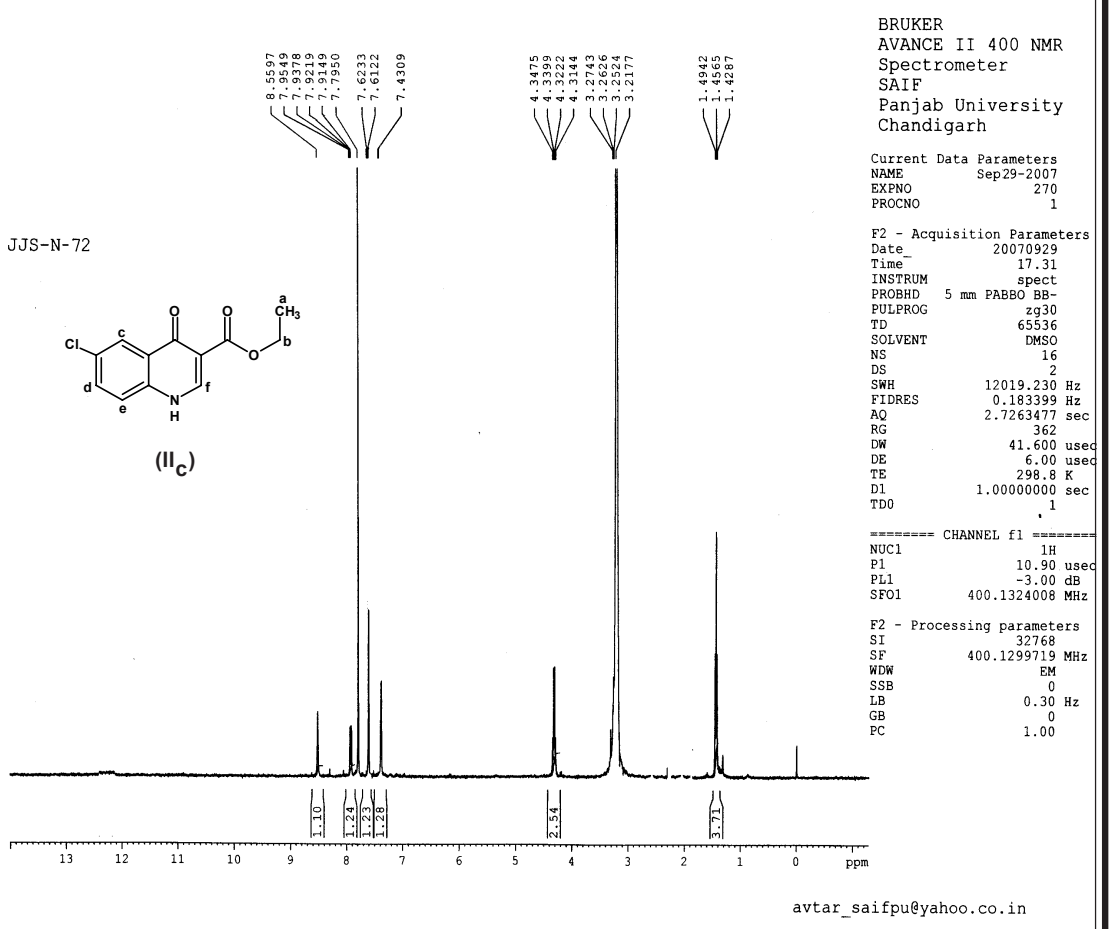
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.3587-1.3942	3H	triplet	- ($C\underline{H}_3$)(a)
2	4.2944-4.3475	2H	quartet	- $C\underline{H}_2$(b)
3	7.3824-7.4309	1H	multiplet	- Ar-$\underline{H}$(c)
4	7.6011-7.6344	1H	multiplet	- Ar-$\underline{H}$(d)
5	7.9149-7.9449	1H	multiplet	- Ar-$\underline{H}$(e)
6	8.5197	1H	singlet	-NH-$\underline{CH}$(f)
7	12.2758	1H	singlet	- N$\underline{H}$(g)
8	2.1500	-	-	-Acetone
9	2.5767.2	-	-	-DMSO-d_6
10	3.2177-3.2743	-	-	-Moisture

NMR SPECTRAL STUDY OF ETHYL-7-CHLORO-1,4-DIHYDRO-QUINOLINE-4-ONE-3-CARBOXYLATE (II_b).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.2549-1.3850	3H	triplet	- $(C\underline{H}_3)_{(a,)}$
2	4.2277-4.3676	2H	quartet	- $C\underline{H}_2$(b,)
3	7.3034-7.6689	2H	multiplet	- Ar-$\underline{H}_{(c,d)}$
4	8.2054-8.3074	1H	doublet	- Ar-$\underline{H}_{(e)}$
5	8.4884	1H	singlet	-NH-$\underline{C}H_{(f)}$
6	12.0754	1H	singlet	- $N\underline{H}_{(g)}$
7	2.1642	-	-	-Acetone
8	2.5847-2.5939	-	-	-DMSO-d_6
9	3.0075	-	-	-Moisture

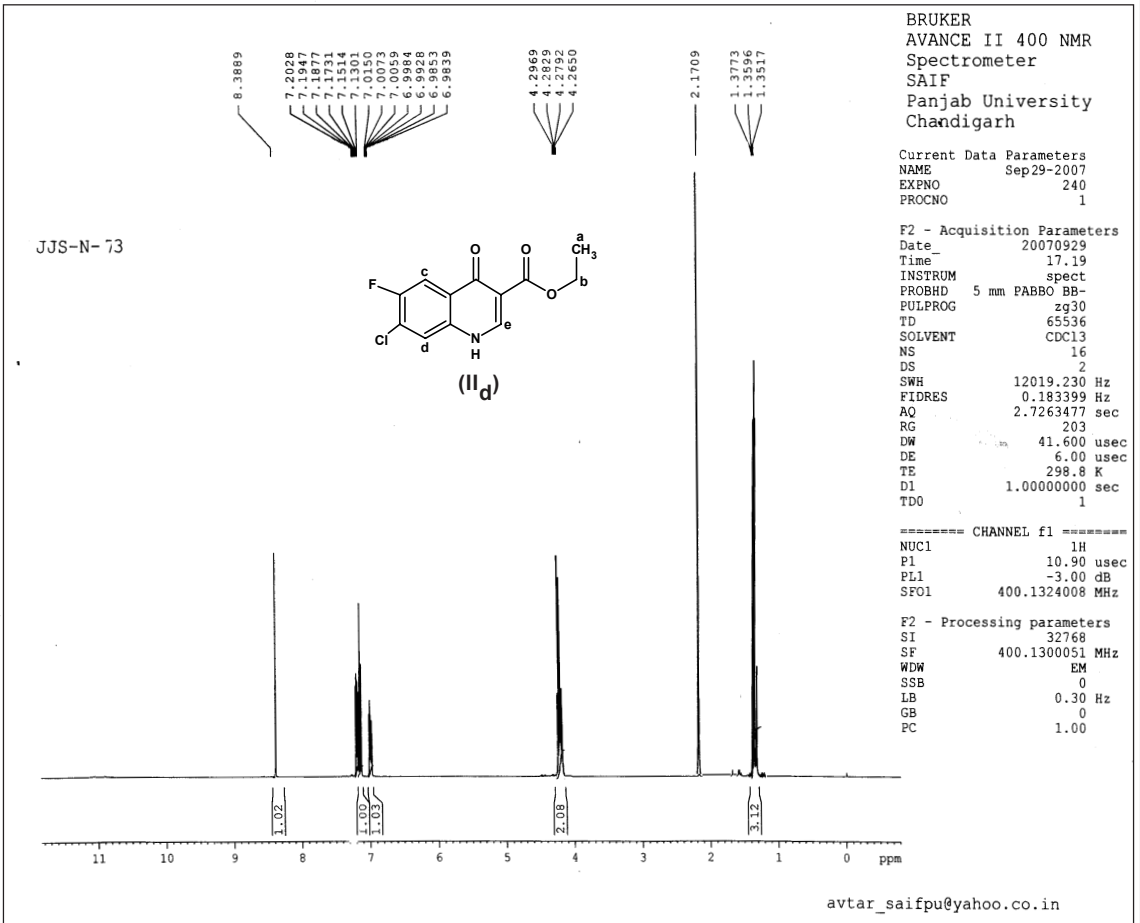
NMR SPECTRAL STUDY OF ETHYL-6-CHLORO-1,4-DIHYDRO-QUINOLINE-4-ONE-3-CARBOXYLATE (II_c).



avtar_saifpu@yahoo.co.in

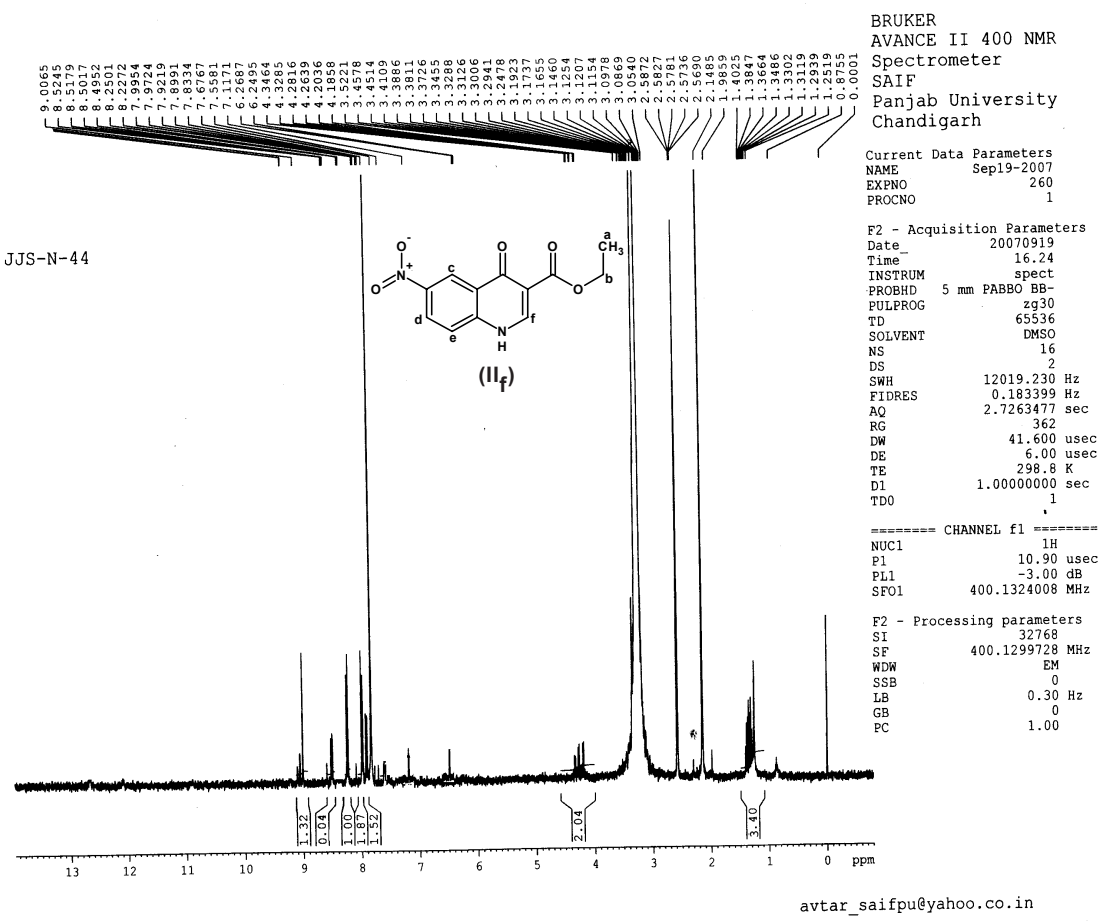
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.4287-1.4942	3H	triplet	- $(C\underline{H}_3)_{(a)}$
2	4.3144-4.3475	2H	quartet	- $C\underline{H}_{2(b)}$
3	7.4309	1H	singlet	- Ar-$\underline{H}_{(c)}$
4	7.6122-7.6233	1H	singlet	- Ar-$\underline{H}_{(e)}$
5	7.9149-7.9549	1H	doublet	-Ar-$\underline{H}_{(d)}$
6	8.5597	1H	singlet	-NH-$\underline{CH}_{(f)}$
7	3.2177-3.2743	-	-	-Moisture

NMR SPECTRAL STUDY OF ETHYL-7-CHLORO- 6-FLUORO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (II_d).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.3517-1.3773	3H	triplet	- ($C\underline{H}_3$)(a)
2	4.2650-4.2969	2H	quartet	- $C\underline{H}_2$(b)
3	6.9839-7.0150	1H	multiplet	- Ar-$\underline{H}$(c)
4	7.1301-7.2028	1H	multiplet	- Ar-$\underline{H}$(d)
5	8.3889	1H	singlet	-NH-$\underline{CH}$(e)
6	2.1709	-	-	-Acetone

NMR SPECTRAL STUDY OF ETHYL-6-NITRO-1,4-DIHYDRO-QUINOLINE-4-ONE-3-CARBOXYLATE (II_f).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.2519-1.4025	3H	multiplet	- $(C\underline{H}_3)_{(a)}$
2	4.1858-4.3464	2H	multiplet	- $C\underline{H}_{2(b)}$
3	7.8991	1H	multiplet	- Ar-$\underline{H}_{(d)}$
4	7.9954-8.2501	1H	doublet	- Ar-$\underline{H}_{(e)}$
5	8.4952-8.5245	1H	singlet	- Ar-$\underline{H}_{(c)}$
6	9.0065	1H	singlet	-NH-$\underline{CH}_{(f)}$
7	1.9859	-	-	-Acetone
8	2.5690-2.5872	-	-	-DMSO-d_6
9	3.0540	-	-	-Moisture

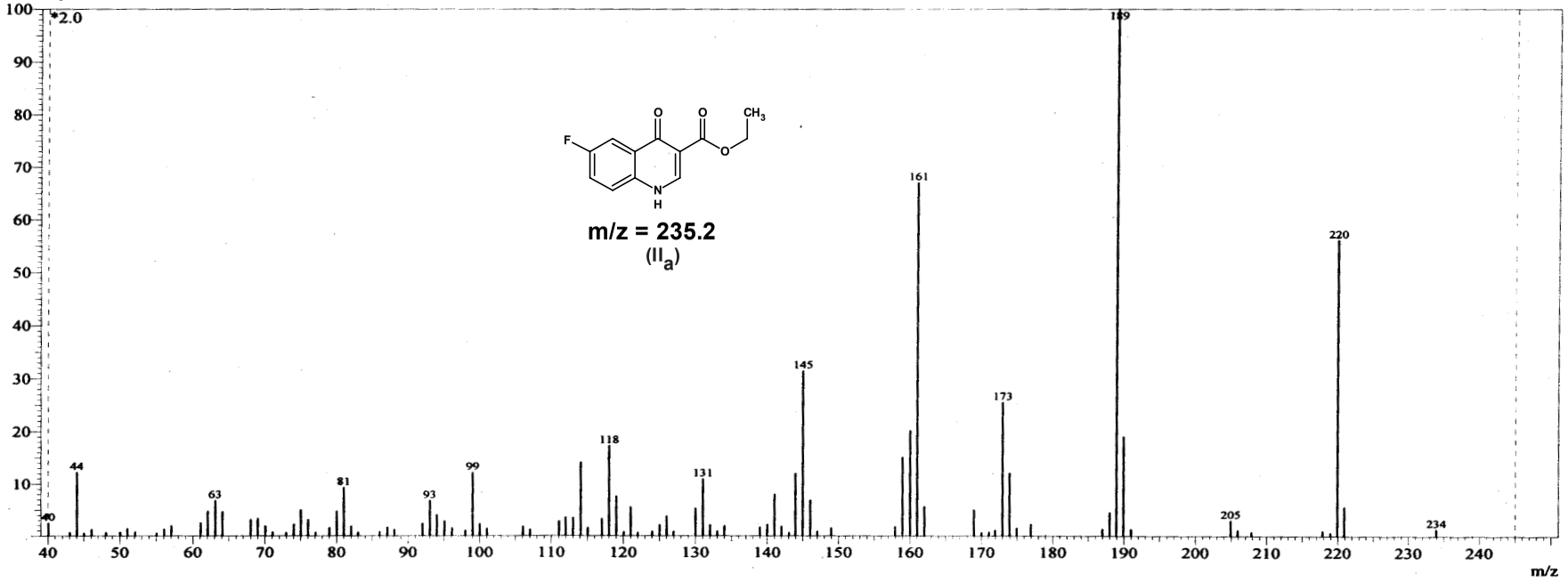
MASS SPECTRAL STUDY OF ETHYL- 6-FLUORO-1,4-DIHYDRO QUINOLINE-4-ONE-3-CARBOXYLATE (II_a).

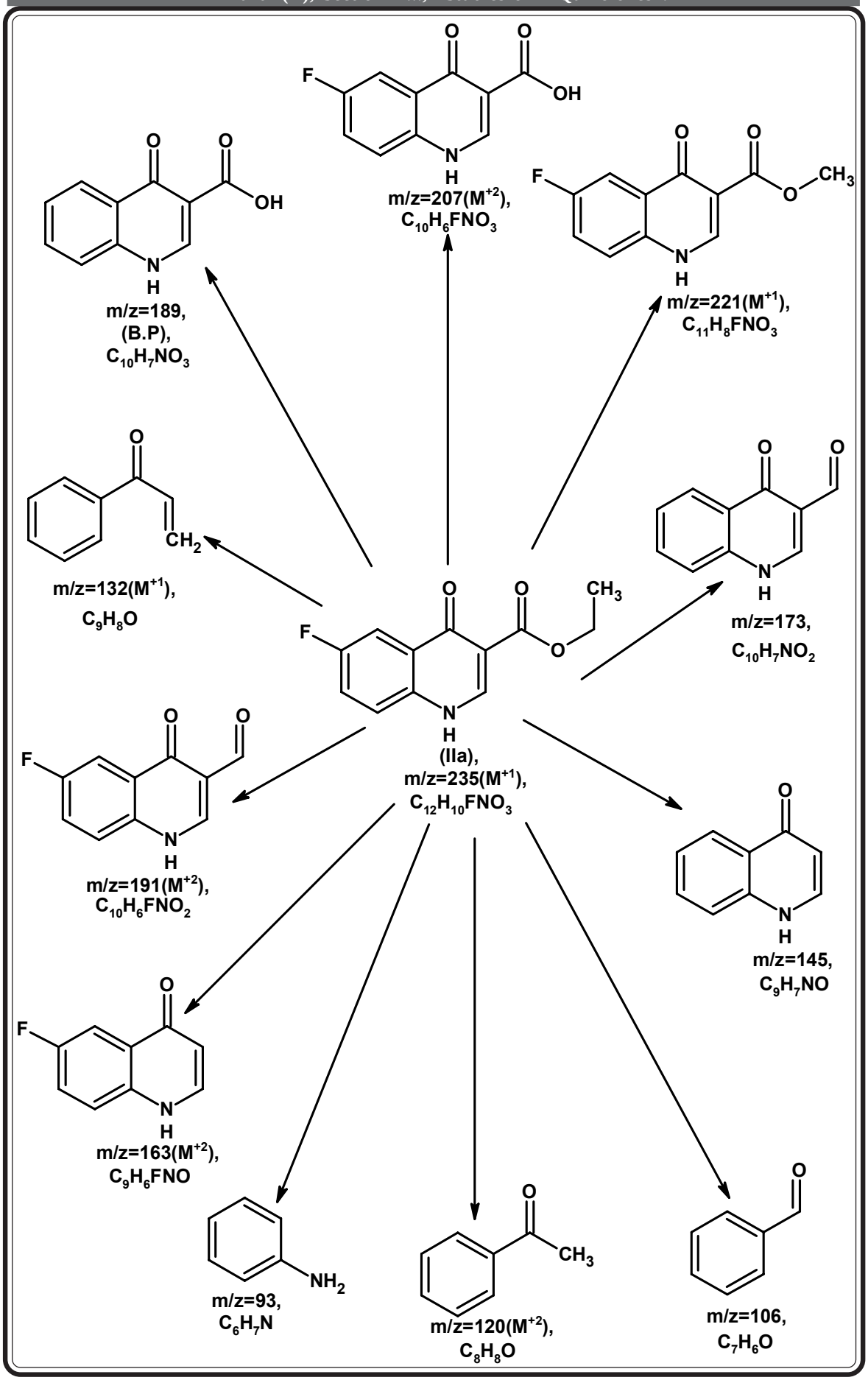
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 10/16/2006 3:02:22 PM
Sample Name	: JJS-M-56
Sample ID	: JJS-M-56
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-56.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:4.2(Scan#:470)
MassPeaks:100 BasePeak:189(406328)
RawMode:Single 4.2(470)
BG Mode:None
intensity




m/z=207(M+2), C10H6FNO3
m/z=189, (B.P), C10H7NO3
m/z=221(M+1), C11H8FNO3
m/z=132(M+1), C9H8O
m/z=173, C10H7NO2
(IIa), m/z=235(M+1), C12H10FNO3
m/z=191(M+2), C10H6FNO2
m/z=145, C9H7NO
m/z=163(M+2), C9H6FNO
m/z=93, C6H7N
m/z=120(M+2), C8H8O
m/z=106, C7H6O

MASS SPECTRAL STUDY OF ETHYL-7-CHLORO-1,4-DIHYDRO QUINOLINE-4-ONE-3-CARBOXYLATE (II_b).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 9/15/2005 2:45:50 PM
Sample Name : JJS-M-1
Sample ID : JJS-M-1
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-M-1.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune8.qgt

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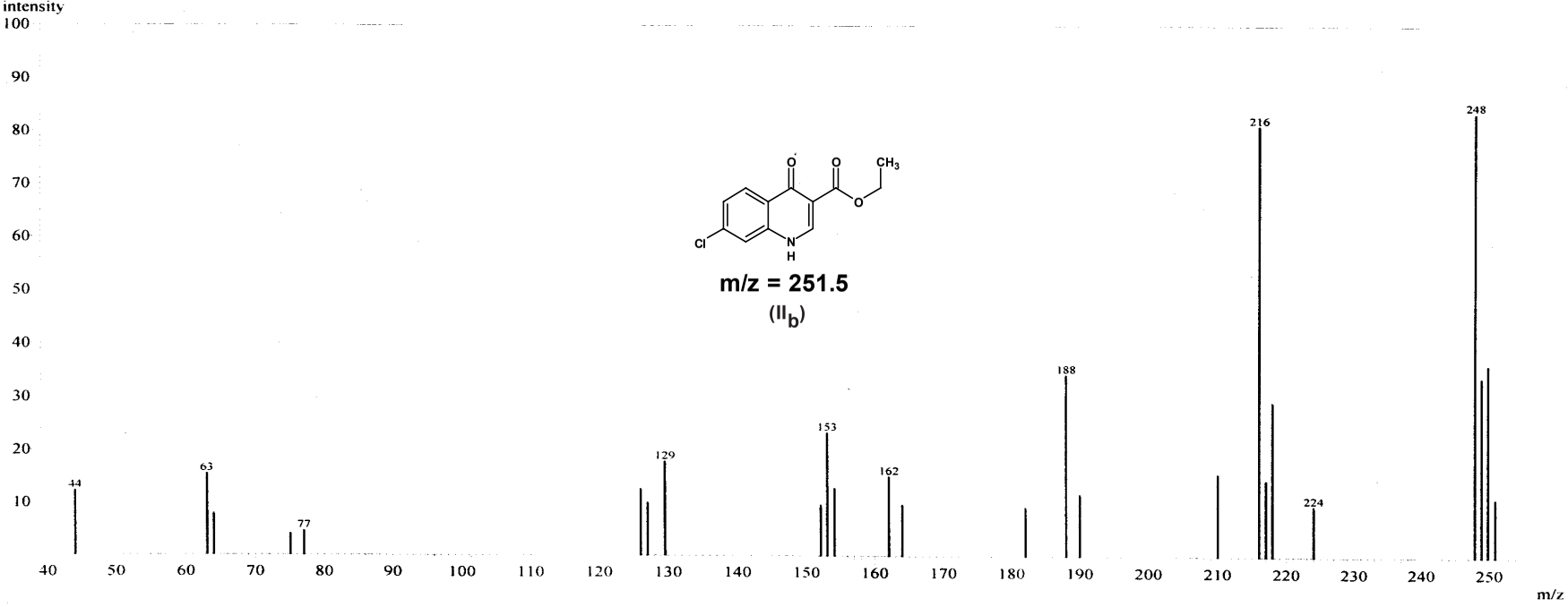
MassPeaks:26 BasePeak:244(11086)
RawMode:Averaged 4.0-5.0(445-563)
BG Mode:None
intensity



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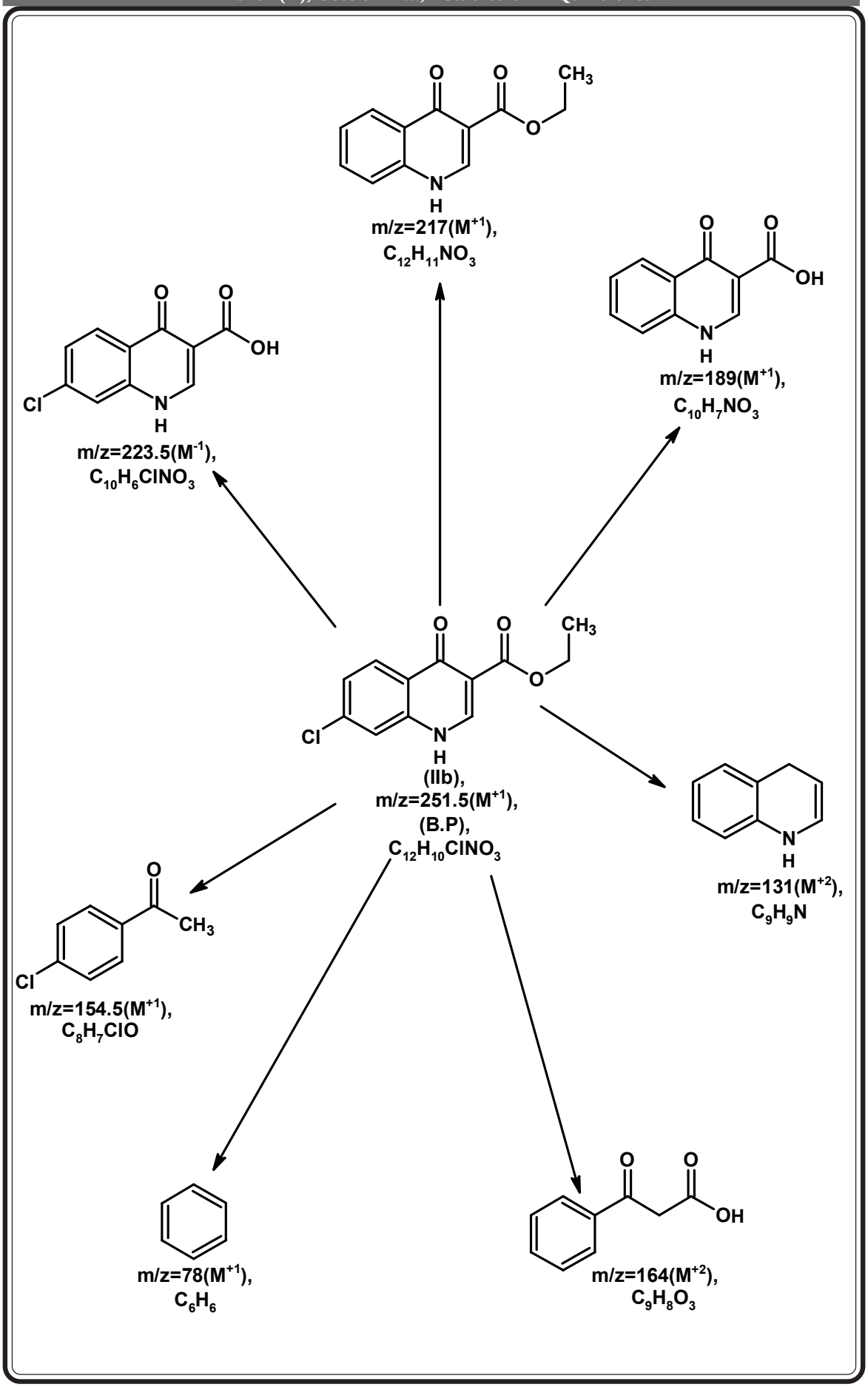
(II_b)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C12H11NO3
m/z=189(M+1),
C10H7NO3
m/z=223.5(M-1),
C10H6ClNO3
(IIb),
m/z=251.5(M+1),
(B.P),
C12H10ClNO3
m/z=131(M+2),
C9H9N
m/z=154.5(M+1),
C8H7ClO
m/z=78(M+1),
C6H6
m/z=164(M+2),
C9H8O3

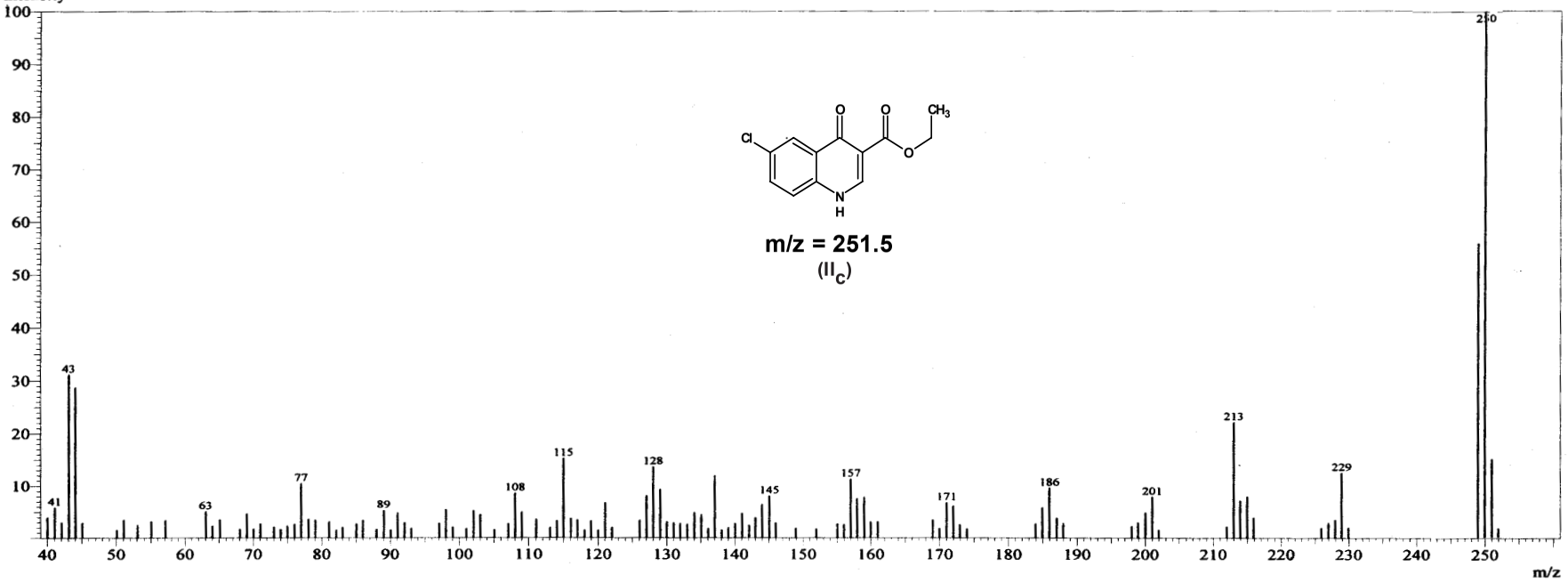
MASS SPECTRAL STUDY OF ETHYL-6-CHLORO-1,4-DIHYDRO QUINOLINE-4-ONE-3-CARBOXYLATE (II_c).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

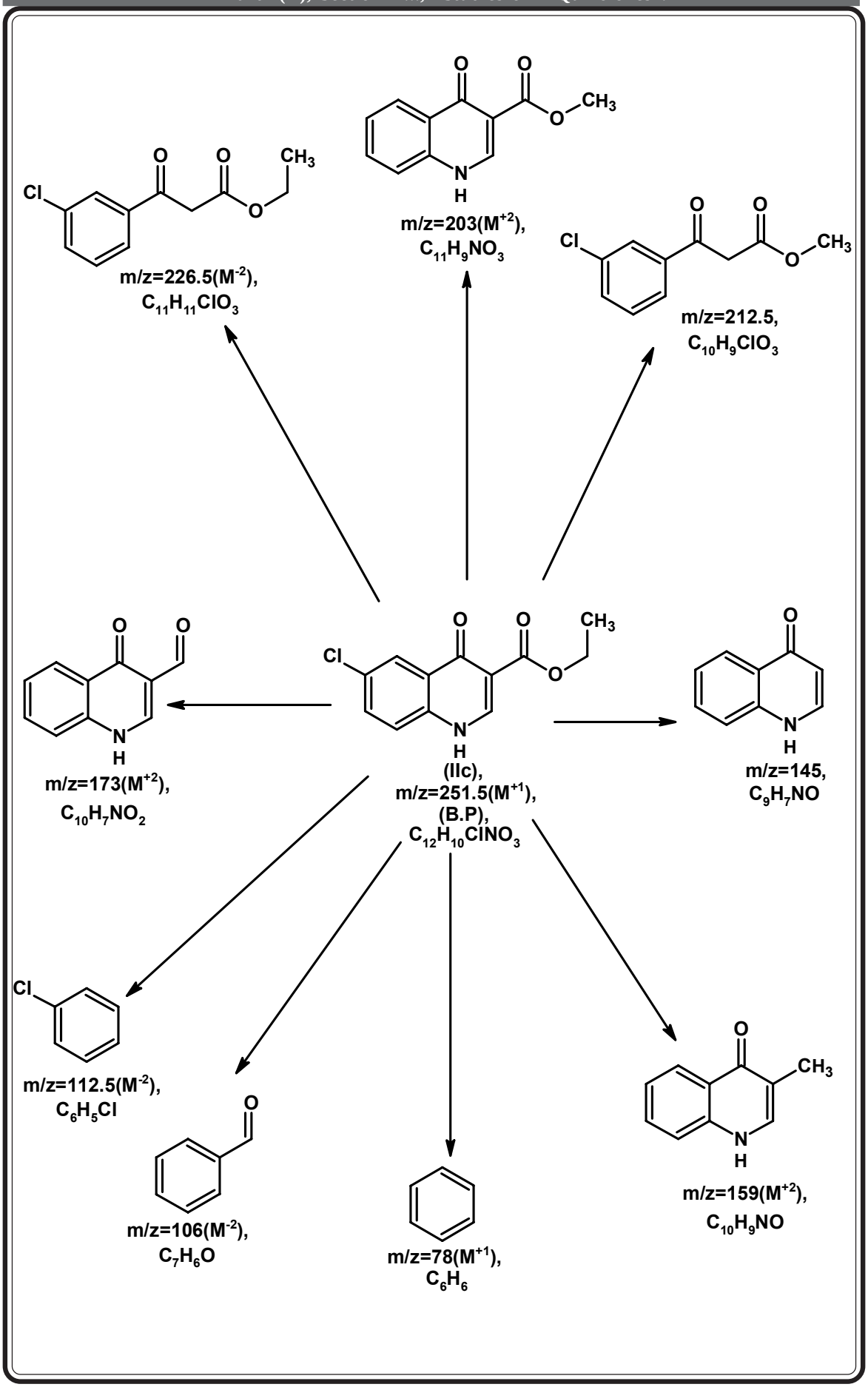
Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 10/16/2006 5:40:26 PM
Sample Name	: JJS-M-58
Sample ID	: JJS-M-58
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-58.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:5.7(Scan#:653)
MassPeaks:117 BasePeak:244(73066)
RawMode:Single 5.7(653)
BG Mode:None
intensity



m/z = 251.5
(II_c)


m/z=203(M+2),
C11H9NO3
m/z=226.5(M-2),
C11H11ClO3
m/z=212.5,
C10H9ClO3
m/z=173(M+2),
C10H7NO2
(IIc),
m/z=251.5(M+1),
(B.P),
C12H10ClNO3
m/z=145,
C9H7NO
m/z=112.5(M-2),
C6H5Cl
m/z=106(M-2),
C7H6O
m/z=78(M+1),
C6H6
m/z=159(M+2),
C10H9NO

MASS SPECTRAL STUDY OF ETHYL-7-CHLORO-6-FLUORO-1,4-DIHYDRO QUINOLINE-4-ONE-3-CARBOXYLATE (II_d).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 4/6/2006 12:01:57 PM
Sample Name	: JJS-M-25
Sample ID	: JJS-M-25
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-25.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune9.qgt

Line#:1 R.Time:6.3(Scan#:724)
MassPeaks:159 BasePeak:223(1248463)
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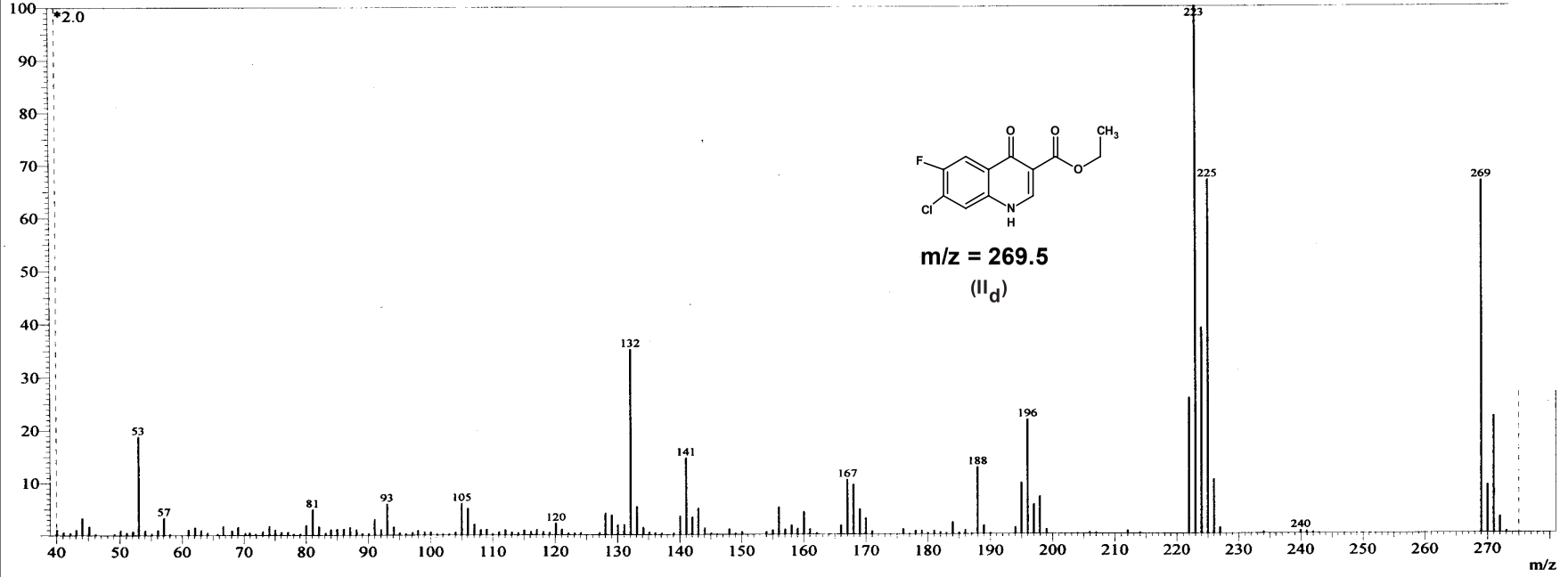
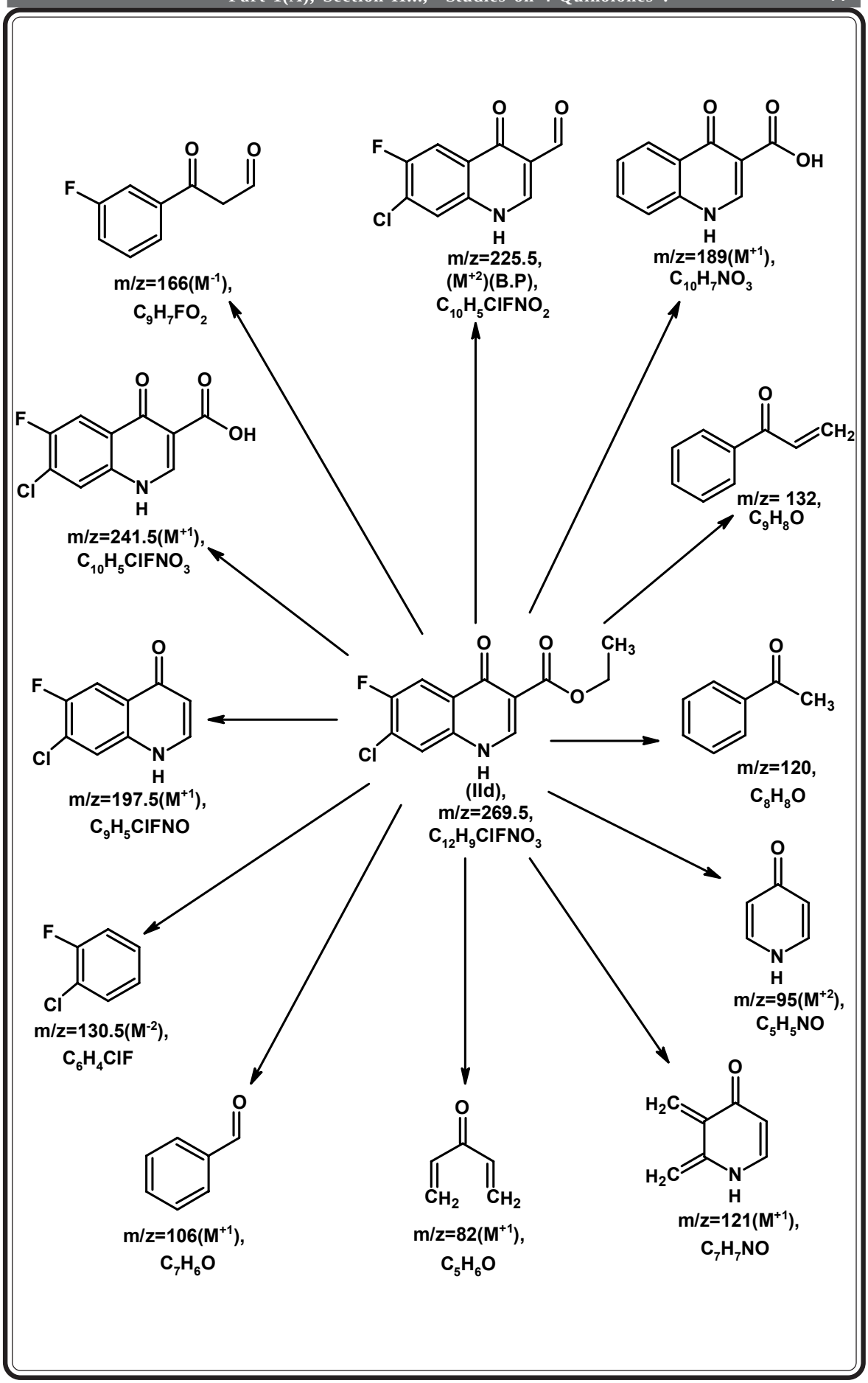
BG Mode:None
intensity



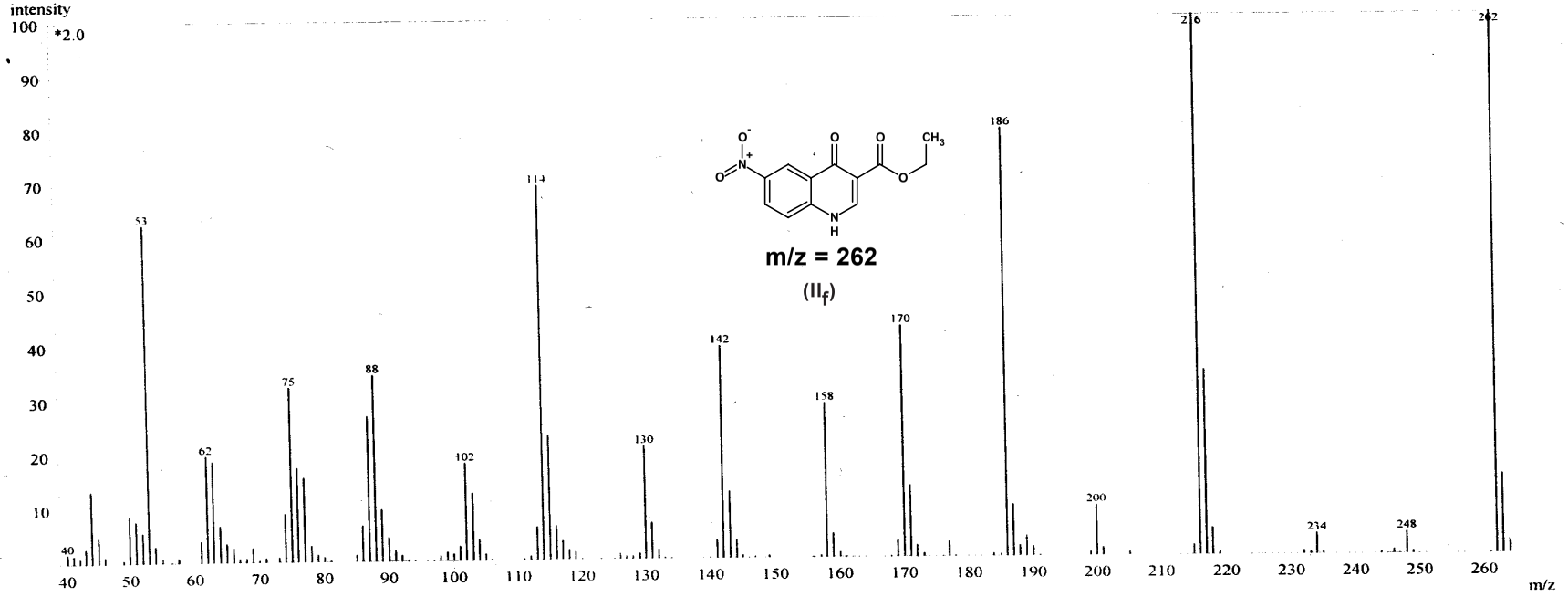

m/z=166(M-1),
C9H7FO2
m/z=225.5,
(M+2)(B.P),
C10H5ClFNO2
m/z=189(M+1),
C10H7NO3
m/z=241.5(M+1),
C10H5ClFNO3
m/z= 132,
C9H8O
m/z=197.5(M+1),
C9H5ClFNO
(IId),
m/z=269.5,
C12H9ClFNO3
m/z=120,
C8H8O
m/z=130.5(M-2),
C6H4ClF
m/z=95(M+2),
C5H5NO
m/z=106(M+1),
C7H6O
m/z=82(M+1),
C5H6O
m/z=121(M+1),
C7H7NO

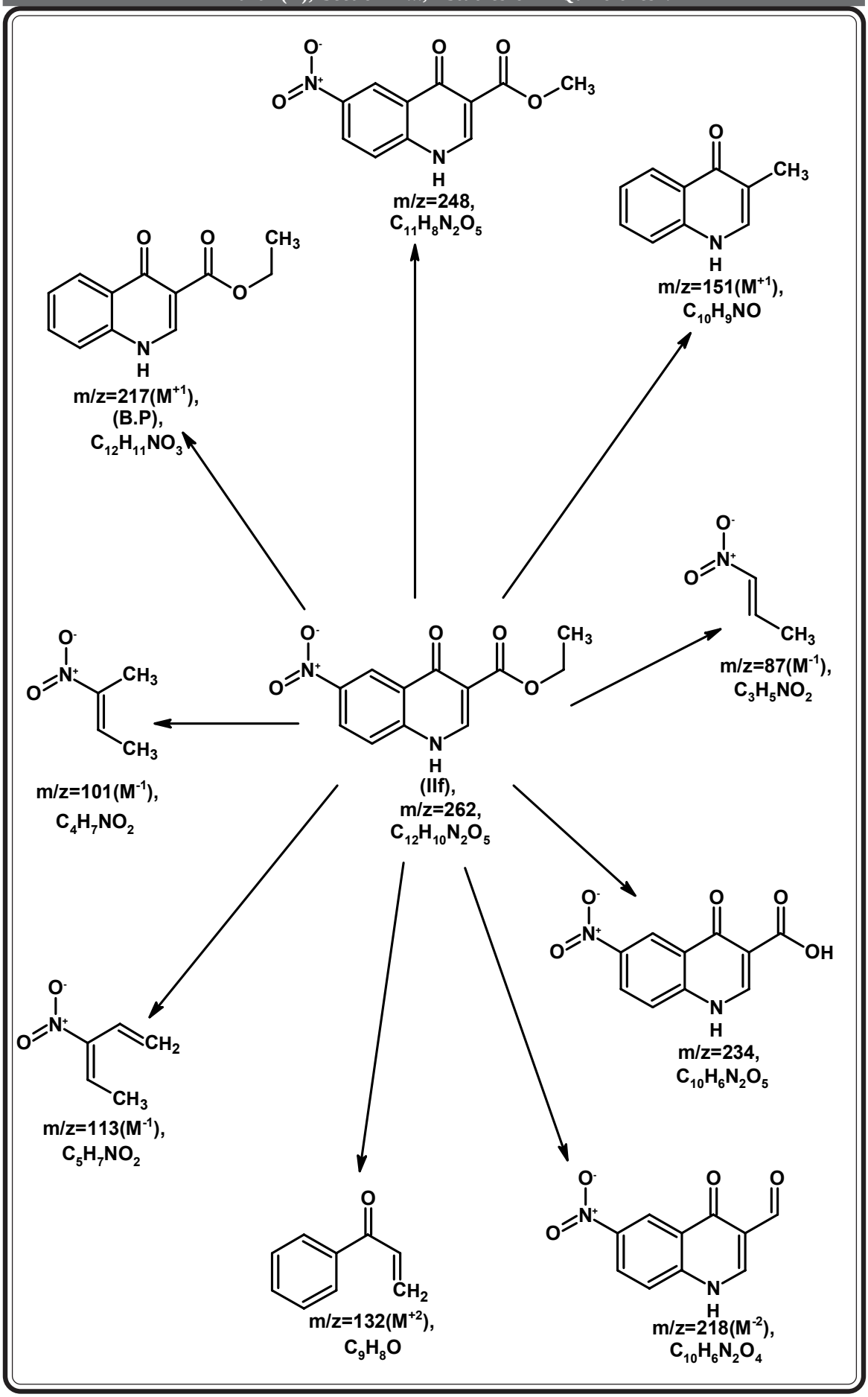
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 8/24/2007 1:08:15 PM
Sample Name : JJS-MQ-16
Sample ID : JJS-MQ-16
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-16.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune130807.qgt

Line#:1 R.Time:12.6(Scan#:1471)
MassPeaks:130 BasePeak:216(347302)
RawMode:Averaged 10.6-14.0(1237-1644)
BG Mode:None
intensity

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$C_{11}H_8N_2O_5$
m/z=151(M^{+1}),
$C_{10}H_9NO$
m/z=217(M^{+1}),
(B.P),
$C_{12}H_{11}NO_3$
m/z=87(M^{-1}),
$C_3H_5NO_2$
m/z=101(M^{-1}),
$C_4H_7NO_2$
(IIf),
m/z=262,
$C_{12}H_{10}N_2O_5$
m/z=234,
$C_{10}H_6N_2O_5$
m/z=113(M^{-1}),
$C_5H_7NO_2$
m/z=132(M^{+2}),
C_9H_8O
m/z=218(M^{-2}),
$C_{10}H_6N_2O_4$

TABLE NO. 2A : COMPARATIVE ANTIMICROBIAL ACTIVITY OF ETHYL-SUBSTITUTED-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATES (II_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) S. pyogens MTCC- 442					S. aureus MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
IIa	6-F	-	7	9	13	15	-	8	10	12	16
IIb	7-Cl	-	10	11	12	14	-	9	10	12	15
IIc	6-Cl	-	9	10	12	13	-	8	9	11	14
IId	7-Cl-6-F	-	10	11	14	14	-	11	13	15	15
IIe	6,7-$(Cl)_2$	-	10	12	11	16	-	7	8	8	12
IIf	6-NO_2	-	8	9	11	13	-	8	10	12	14
IIg	6-OCH_3	-	10	10	12	13	-	8	8	10	13
IIh	6-CH_3	-	9	11	13	14	-	7	8	9	11
IIi	7,8-$(CH_3)_2$	-	8	10	12	13	-	8	10	11	13
IIj	-C_4H_4	-	8	9	11	12	-	9	11	13	15

Comparative activity of (II_{a-j}) with known choosen standard drugs

Standard drug	Antibacterial activity									
									IIa	IIa
Amoxicilin	12	14	15	16	18	10	12	14	15	16
Chloramphenicol	14	15	18	19	24	14	17	20	21	24
Sparfloxacin	14	22	24	26	28	24	26	27	28	32
Levofloxacin	18	21	22	27	29	20	24	26	27	35

N.B.(-): No Activity

TABLE NO. 2B: COMPARATIVE ANTIMICROBIAL ACTIVITY OF ETHYL-SUBSTITUTED-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATES (II_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) B. Subtillis MTCC- 441					E.coli MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
IIa	6-F	-	11	11	12	14	-	6	7	9	9
IIb	7-Cl	-	10	12	13	16	-	7	8	10	11
IIc	6-Cl	-	10	11	12	14	-	5	6	8	10
IId	7-Cl-6-F	-	9	10	12	14	-	5	6	8	9
IIe	6,7-$(Cl)_2$	-	8	11	13	16	-	7	8	10	11
IIf	6-NO_2	-	8	10	11	13	-	7	7	9	10
IIg	6-OCH_3	-	8	9	10	13	-	6	7	9	10
IIh	6-CH_3	-	8	10	11	14	-	7	8	10	11
IIi	7,8-$(CH_3)_2$	-	9	9	10	12	-	5	5	7	8
IIj	-C_4H_4	-	8	10	12	15	-	7	7	8	9
Comparative activity of (II_{a-j}) with known choosen standard drugs											
Standard drug		**Antibacterial activity**									
Amoxiciline		12	15	16	18	19	11	14	16	18	20
Chloramphenicol		18	22	24	26	27	17	20	23	25	26
Sparfloxacin		22	24	25	26	29	20	22	25	26	28
Levofloxacin		24	26	28	29	31	23	25	26	29	30

N.B.(-): No Activity

TABLE NO. 2C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF ETHYL-SUBSTITUTED-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATES (II_{a-j}). (Different Inhibition Concentration in µg/ml).

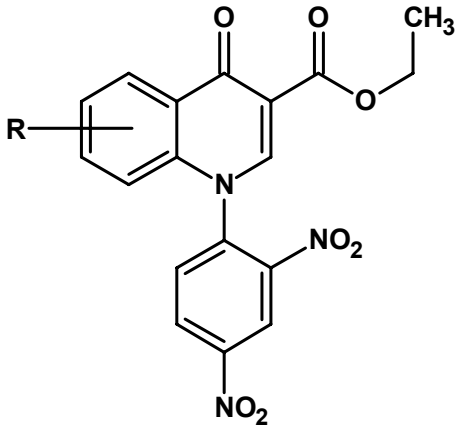
Compd No.	R	Antifungal activity (Zones of inhibition in m.m.) C. albicans MTCC- 227					A.niger MTCC- 282				
		5	25	50	100	250	5	25	50	100	250
IIa	6-F	-	7	10	13	15	-	8	10	11	14
IIb	7-Cl	-	6	8	10	12	-	7	8	9	11
IIc	6-Cl	-	10	11	13	14	-	8	9	10	13
IId	7-Cl-6-F	-	10	12	14	17	-	10	13	15	18
IIe	6,7-$(Cl)_2$	-	9	10	11	13	-	9	10	12	14
IIf	6-NO_2	-	6	7	8	10	-	8	9	10	11
IIg	6-OCH_3	-	7	9	10	12	-	7	8	9	12
IIh	6-CH_3	-	6	6	10	11	-	6	7	8	10
IIi	7,8-$(CH_3)_2$	-	6	9	11	14	-	8	10	11	13
IIj	-	-	7	9	11	13	-	8	9	10	13
Comparative activity of (II_{a-j}) with known choosen standard drugs											
Standard drug		**Antifungal activity**									
Griseofulvin		16	18	21	23	25	17	19	21	22	23
Fluconazole		14	16	18	21	22	15	17	18	20	21

N.B.(-): No Activity

SECTION - III

PREPARATION AND BIOLOGICAL EVALUATION OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-6,7,8-SUBSTITUTED-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATES.

Keeping in view, various properties[34-85] of **4-quinolone** and in order to have highly potent therapeutic agents, the synthesis of **Ethyl-1-N-(2,4-dinitro phenyl)-6,7,8-substituted-1,4-dihydroquinoline-4-one-3-carboxylates (IIIa-j)** have been accomplished by the cyclocondensation of different **ethyl-substituted-1,4-dihydroquinoline-4-one-3-carboxylates (IIa-j)** with **1-chloro-2,4-dinitro benzene** in the basic condition.



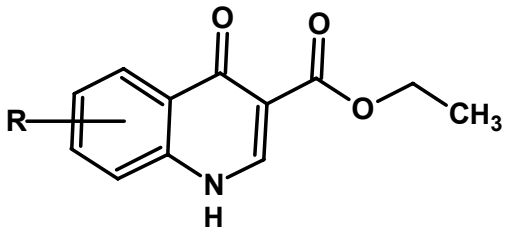
(IIIa-j)

R=Substituted phenyl

The constitution of the products **(IIIa-j)** have been delineated by **elemental analyses, IR, PMR** and **Mass** spectral data**.**

The products **(IIIa-j)** were assayed for their ***in vitro*** biological assay like antibacterial activity towards ***S. pyogens MTCC-442***,***S. aureus MTCC-96*** *and* ***B.subtillis MTCC-441*** **(Gram positive)** and ***E. coli MTCC-443*** **(Gram negative)** bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations .i.e.: 0(control), 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values.The biological activities of the synthesized compounds **(IIIa-j)** were compared with standard drugs viz., **Amoxicillin, Chloramphenicol, Sparfloxacin, Levofloxacin**(antibacterial), **Griseofluvin, Fluconazole** (antifungal).

REACTION SCHEME



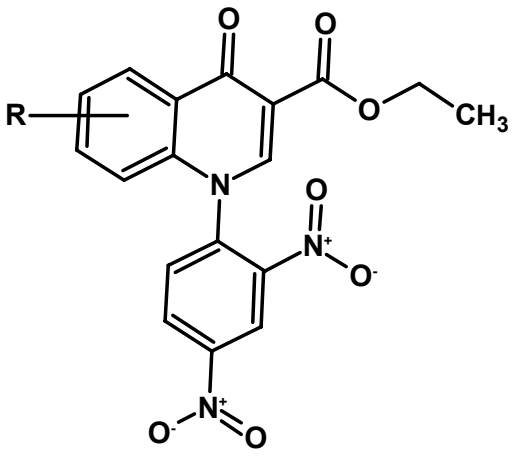
(IIa-j)
R=substituted phenyl

1-Chloro-2.4-dinitro benzene

Anhyd. K_2CO_3

Dimethyl-sulphoxide

△



(IIIa-j)
R=substituted phenyl

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF ETHYL-1-N-(2,4-DINITRO -PHENYL)-6,7,8-SUBSTITUTED-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATES.

(A) Preparation of Diethyl-(3-chloro-4-fluoro amino phenyl)-aminomethylene malonate (I_d).

For preparation, refer Part-1, Section-I, **page No.30.**

(B) Preparation of Ethyl-7-chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carboxylate (II_d).

For preparation, refer Part-1, Section-II, **page No.58.**

(C) Preparation of Ethyl-1-N-(2,4-dinitro phenyl)-7-chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carboxylate (IIIa-j).

A reaction mixture of Ethyl-7-chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carboxylates (II_d) (2.69 gm, 0.01 M) and anhydrous potassium carbonate (2.76 gm, 0.02M), in Dimethyl sulphoxide (20 ml) was stirred at 115 to120 ^{O}C for 1 hr. and then allowed to cool upto the temperature 50 to 60 ^{O}C. To this reaction mixture, the solution of 2,4-dinitro chlorobenzene (2.02 gm, 0.01M) and of dimethyl sulphoxide (6 ml) was added dropwise and the temperature was maintained at 50 to 60 ^{O}C for 8 hrs. The resulting mixture was poured onto crushed ice, filtered, washed with water and dried at 40 to 45 ^{o}C. The product was crystallized from ethanol. Yield : 64 %, M.P. : 228 ^{O}C, (Required : C,49.61%; H,2.54 %; N, 9.64 % for $C_{18}H_{11}N_3O_7ClF$ Found : C, 49.59 %; H, 2.51 %; N, 9.63%).

TLC solvent system R_{f_1} : Ethyl acetate : hexane(3.5 : 6.5) = 0.63**.**

TLC solvent system R_{f_2} : Methanol : Toluene(1.0 : 9.0) = 0.51**.**

Similarly, other compounds **(IIIa-j)** were synthesized. The physical data are recorded in **Table No. 3.**

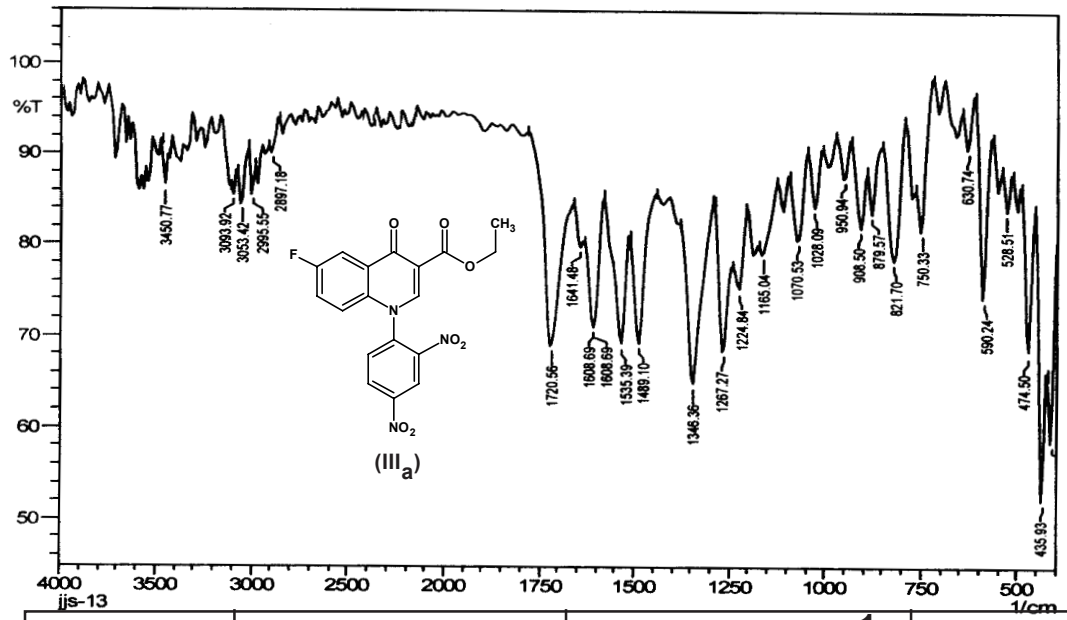
(B) Antimicrobial activity of Ethyl-1-N-(2,4-dinitro phenyl)-(6,7,8-substituted)-1,4-dihydroquinoline-4-one-3-carboxylates (IIIa-j).

Antimicrobial activity testing was carried out as described in Part-1(A), Section-I, page No.30-31. The MIC values of test solution are recorded in **Table No. 3A, 3B** and **3C.**

TABLE NO. 3 : PHYSICAL CONSTANTS OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-6,7,8-SUBSTITUTED-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATES (III_{a-j}).

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. ^oC 5	Yield % 6	R_f Value 7		% of Nitrogen Calcd. / Found 8
						R_{f_1}	R_{f_2}	
III_a	6-F	$C_{18}H_{12}N_3O_7F$	401.0	221^o	67	0.67	0.58	10.47 / 10.44
III_b	7-Cl	$C_{18}H_{12}N_3O_7Cl$	417.5	239^o	67	0.58	0.54	10.06 / 10.02
III_c	6-Cl	$C_{18}H_{12}N_3O_7Cl$	417.5	242^o	68	0.56	0.52	10.06 / 10.03
III_d	7-Cl-6-F	$C_{18}H_{11}N_3O_7ClF$	435.5	228^o	64	0.63	0.51	9.64 / 9.63
III_e	6,7-$(Cl)_2$	$C_{18}H_{11}N_3O_7Cl_2$	452.0	188^o	63	0.55	0.49	9.29 / 9.26
III_f	6-NO_2	$C_{18}H_{12}N_4O_9$	428.0	270^o	58	0.41	0.43	13.08 / 13.02
III_g	6-OCH_3	$C_{19}H_{15}N_3O_8$	413.0	113^o	53	0.51	0.53	10.17 / 10.15
III_h	6-CH_3	$C_{19}H_{15}N_3O_7$	397.0	105^o	62	0.63	0.47	10.58 / 10.55
III_i	7,8-$(CH_3)_2$	$C_{20}H_{17}N_3O_7$	411.0	178^o	60	0.46	0.43	10.22 / 10.20
III_j	-	$C_{22}H_{15}N_3O_7$	433.0	247^o	61	0.40	0.42	9.70 / 9.58

IR SPECTRAL STUDY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-6-FLUORO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (III_a).

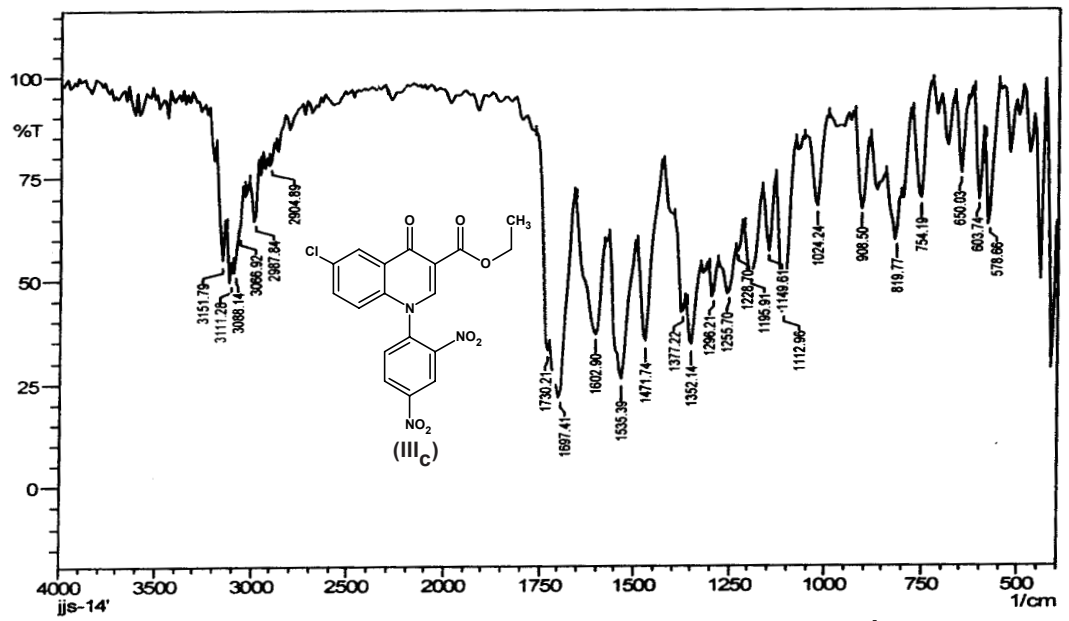


(III_a)

Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2995.5	2975 - 2850	96
	C-H (sym. str., m)	2897.1	2900 - 2800	96
	C-H (asym. def., m)	1489.1	1470 - 1435	96
	C-H (sym. def., m)	1346.3	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3053.5	3080 - 3010	97
	C=C & C-C (str., v)	1535.3	1600 - 1450	97
	C-H (i.p. def., m)	1165.0	1150 - 1050	97
	C-H (o.o.p. def., m)	821.7	825 - 800	97
	C-N (str., v)	1267.2	1340 - 1250	97
Amine	N-H (Astr., m)	3450.7	3500-3400	98
	N-H (str., b)	3093.9	3400 - 3000	98
	N-H (def., s,m)	1608.6	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1641.4	1690- 1640	98
(Ester)	C=O (str., s)	1720.5	1740 - 1650	98
Halogen Subtitution	C-F (str., b)	1348-1165	1400 - 1080	99
Para(-4-) substituted	C-H (def., v,s)	879.5	800 - 850	99
Nitro	C-NO_2(asym.str., s)	1535.3	1570-1500	99
	C-NO_2 (sym. str., s)	1346.3	1370-1300	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

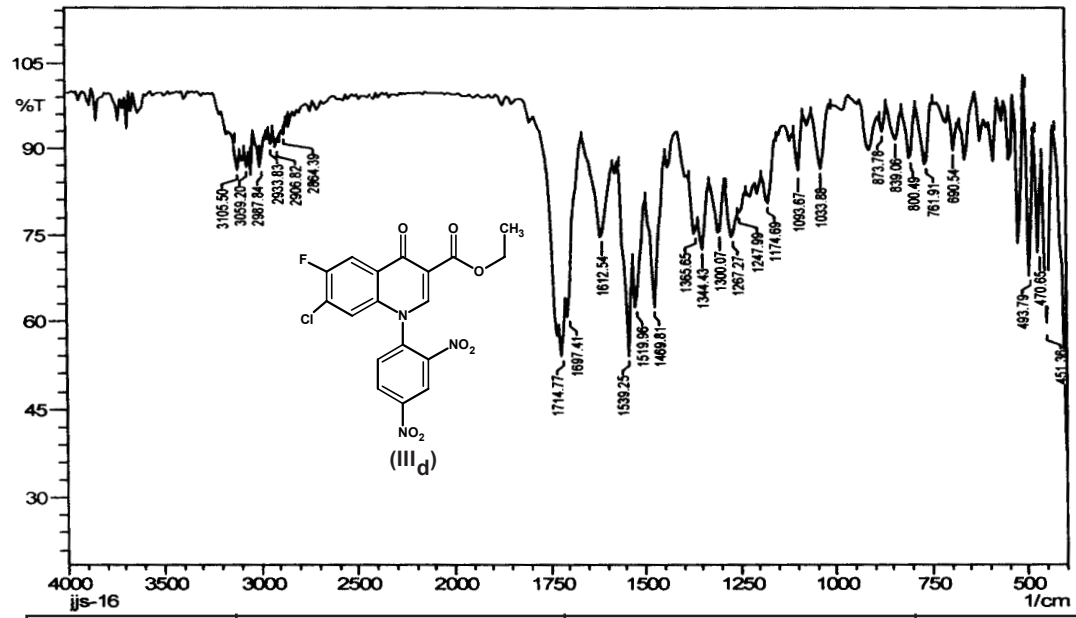
IR SPECTRAL STUDY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-6-CHLORO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (III_C).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2987.5	2975 - 2850	96
	C-H (sym. str., m)	2904.8	2900 - 2800	96
	C-H (asym. def., m)	1471.7	1470 - 1435	96
	C-H (sym. def., m)	1377.2	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3066.9	3080 - 3010	97
	C=C & C-C (str., v)	1535.3	1600 - 1450	97
	C-H (i.p. def., m)	1112.9	1150 - 1050	97
	C-H (o.o.p. def., m)	819.7	825 - 800	97
	C-N (str., v)	1352.1	1340 - 1250	97
Amine	N-H (str., b)	3151-3066	3400 - 3000	98
	N-H (def., s,m)	1602.6	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1697.4	1690 - 1640	98
(Ester)	C=O (str., s)	1730.2	1740 - 1650	98
Halogen Subtitution	C-Cl (str.,b)	754-603	800-600	99
Para(-4-) substituted	C-H (def., v,s)	819.7	800 - 850	99
Nitro	C-NO_2(asym.str., s)	1535.3	1570-1500	99
	C-NO_2 (sym. str., s)	1296.2	1370-1300	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

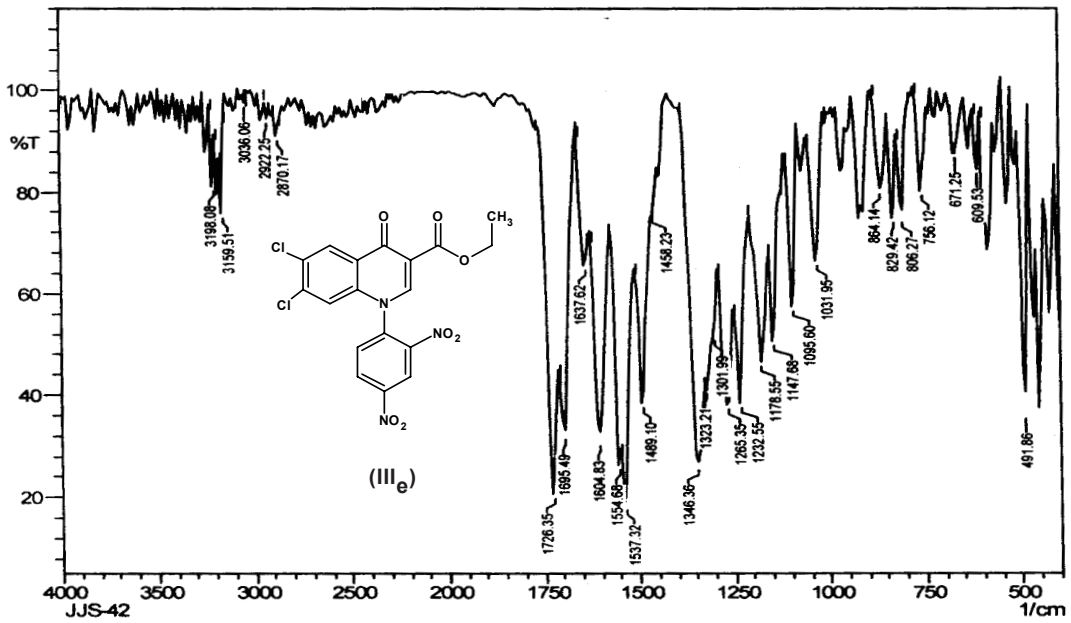
IR SPECTRAL STUDY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-7-CHLORO-6-FLUORO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (III_d).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2933.8	2975 - 2850	96
	C-H (sym. str., m)	2864.3	2900 - 2800	96
	C-H (asym. def., m)	1469.8	1470 - 1435	96
	C-H (sym. def., m)	1365.5	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3059.2	3080 - 3010	97
	C=C & C-C (str., v)	1539.2	1600 - 1450	97
	C-H (i.p. def., m)	1174.6	1150 - 1050	97
	C-H (o.o.p. def., m)	800.4	825 - 800	97
	C-N (str., v)	1267.2	1340 - 1250	97
Amine	N-H (str., b)	3105-3059	3400 - 3000	98
	N-H (def., s,m)	1612.5	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1697.4	1690 - 1640	98
(ester)	C=O (str., s)	1714.7	1740 - 1650	98
Halogen Subtitution	C-F (str., b)	1356-1033	1400 - 1080	99
	C-Cl (str., s)	761.9	800 - 600	99
Nitro	C-NO_2(asym.str., s)	1519.9	1570-1500	99
	C-NO_2 (sym. str., s)	1344.4	1370-1300	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

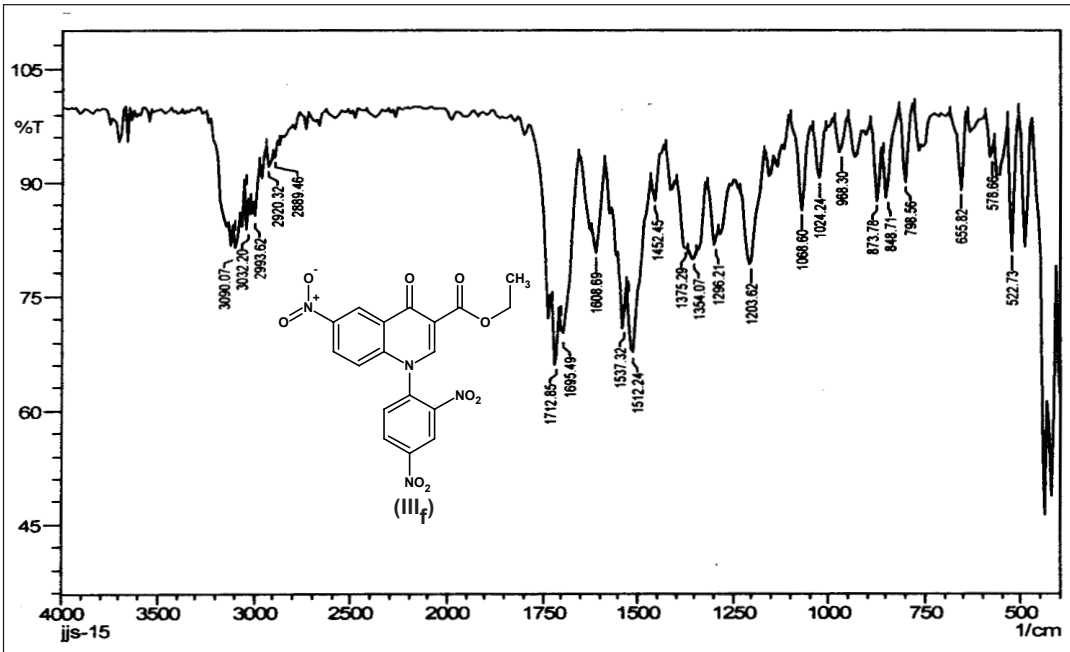
IR SPECTRAL STUDY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-6,7-DICHLORO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (III_e).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2922.2	2975 - 2850	96
	C-H (sym. str., m)	2870.1	2900 - 2800	96
	C-H (asym. def., m)	1489.1	1470 - 1435	96
	C-H (sym. def., m)	1346.3	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3036.0	3080 - 3010	97
	C=C & C-C (str., v)	1604.8	1600 - 1450	97
	C-H (i.p. def., m)	1047.6	1150 - 1050	97
	C-H (o.o.p. def., m)	806.2	825 - 800	97
	C-N (str., v)	1301.9	1340 - 1250	97
Amine	N-H (str., b)	3198.0	3400 - 3000	98
	N-H (def., s,m)	1554.6	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1695.4	1690 - 1640	98
(ester)	C=O (str., s)	1726.3	1740 - 1650	98
Halogen Subtitution	C-Cl (str., b)	806-609	800 - 600	99
Nitro	C-NO_2(asym.str., s)	1537.2	1570-1500	99
	C-NO_2 (sym. str., s)	1323.2	1370-1300	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

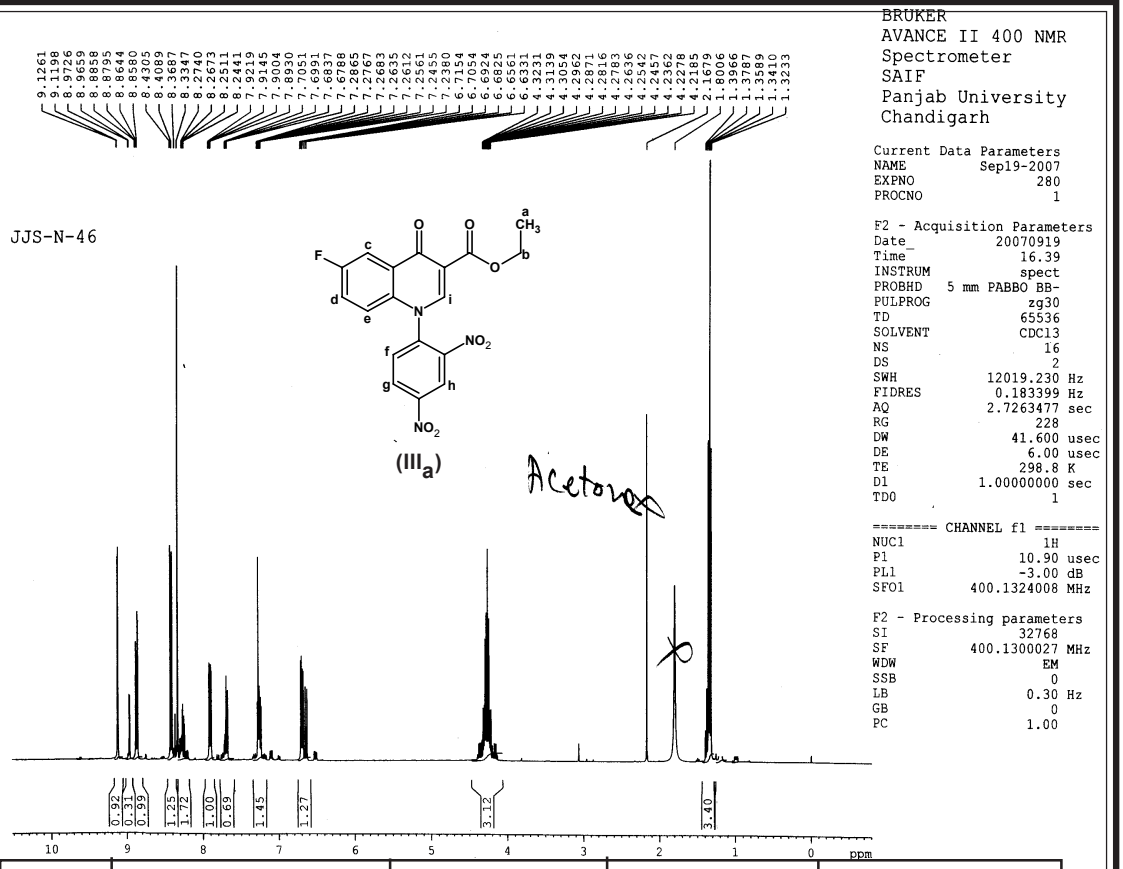
IR SPECTRAL STUDY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-6-NITRO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATES (III_f).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2920.3	2975 - 2850	96
	C-H (sym. str., m)	2889.4	2900 - 2800	96
	C-H (asym. def., m)	1452.4	1470 - 1435	96
	C-H (sym. def., m)	1375.2	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3032.2	3080 - 3010	97
	C=C & C-C (str., v)	1608.6	1600 - 1450	97
	C-H (i.p. def., m)	1068.6	1150 - 1050	97
	C-H (o.o.p. def., m)	798.5	825 - 800	97
	C-N (str., v)	1296.2	1340 - 1250	97
Amine	N-H (str.,b)	3090.0	3400 - 3000	98
	N-H (def., s,m)	1537.3	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1695.4	1690 - 1640	98
(ester)	C=O (str., s)	1712.8	1740 - 1650	98
Para(4)-Subtitution	C-H (def., v,s)	848.7	800 - 850	99
Nitro	C-NO_2(asym.str., s)	1512.2	1570-1500	99
	C-NO_2 (sym. str., s)	1354.0	1370-1300	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

NMR SPECTRAL STUDY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-6-FLUORO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (III_a).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.3233-1.3966	3H	multiplat	- $(C\underline{H}_3)_{(a)}$
2	4.2185-4.3231	2H	multiplat	- $C\underline{H}_{2(b)}$
3	6.6331-6.7154	1H	multiplat	- Ar-$\underline{H}_{(e)}$
4	7.2380-7.2865	1H	doublet	- Ar-$\underline{H}_{(d)}$
5	7.8930-7.9219	1H	doublet	- Ar-$\underline{H}_{(c)}$
6	8.2441-8.2740	1H	doublet	- Ar-$\underline{H}_{(f)}$
7	8.4089-8.4305	1H	doublet	- Ar-$\underline{H}_{(g)}$
8	8.8580-8.8858	1H	doublet	- Ar-$\underline{H}_{(h)}$
9	9.1198-9.1261	1H	doublet	-N-$\underline{CH}_{(i)}$
10	1.8006	-	-	-Moisture
11	2.1679	-	-	-Acetone
12	8.3687	-	-	-$CDCl_3$

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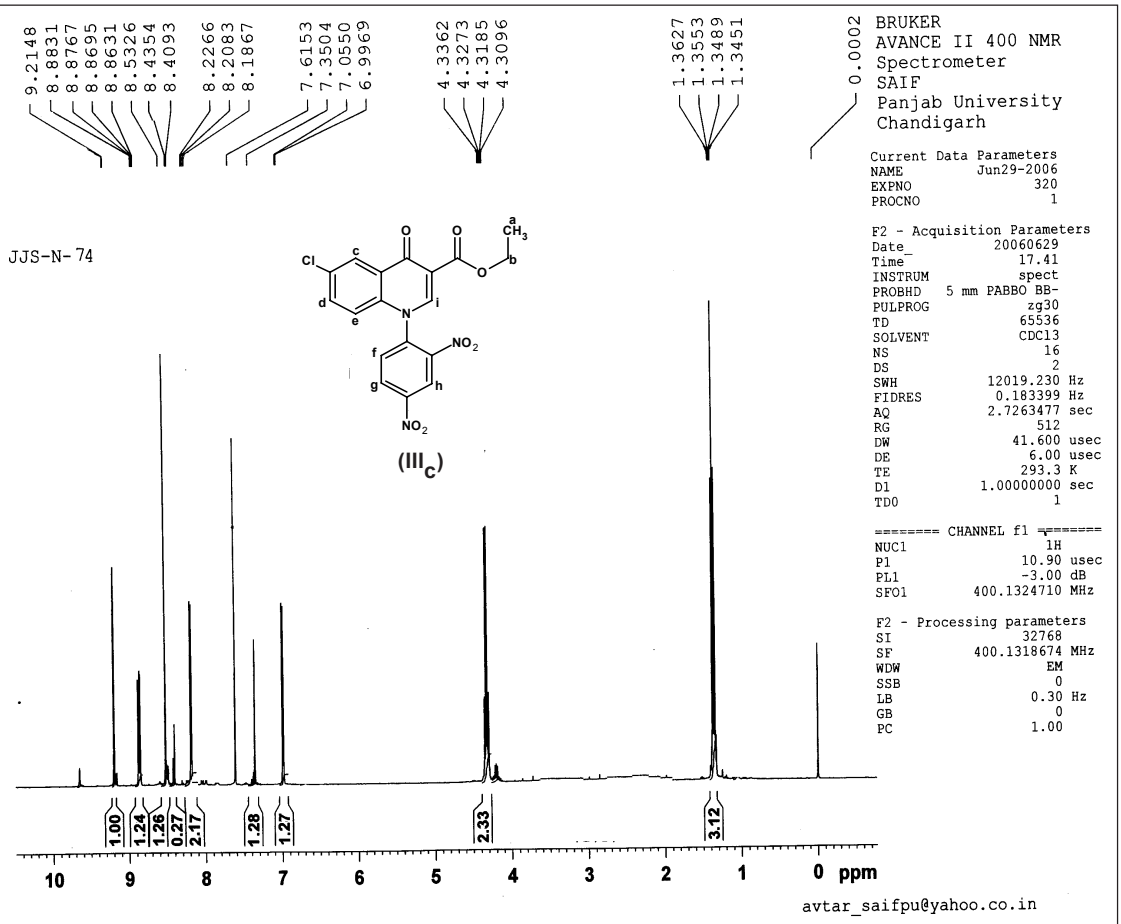
NMR SPECTRAL STUDY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-6-CHLORO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (III_c).



Current Data Parameters
NAME Jun29-2006
EXPNO 320
PROCNO 1

F2 - Acquisition Parameters
Date_ 20060629
Time 17.41
INSTRUM spect
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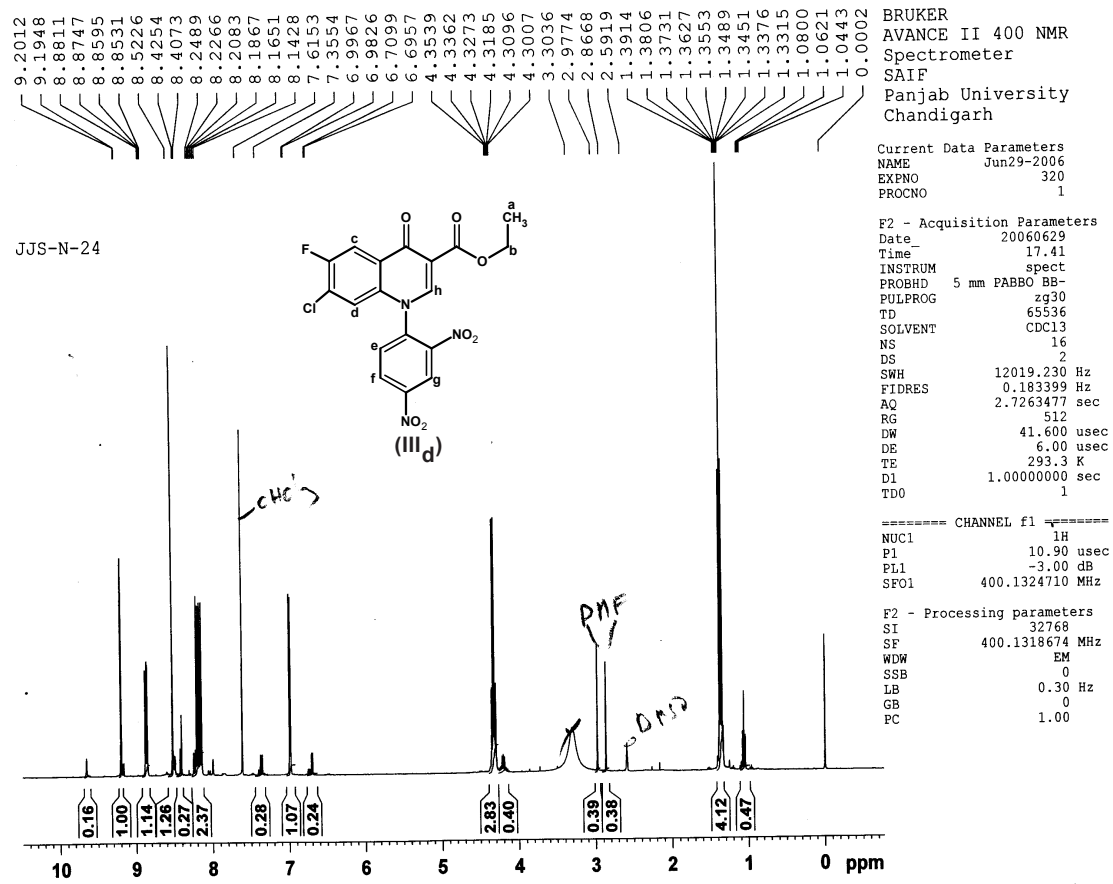
PULPROG zg30
TD 65536
SOLVENT CDCl3
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 512
DW 41.600 usec
DE 6.00 usec
TE 293.3 K
D1 1.00000000 sec
TD0 1

======== CHANNEL f1 ========
NUC1 1H
P1 10.90 usec
PL1 -3.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1318674 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.3451-1.3627	3H	triplet	- $(C\underline{H}_3)_{(a)}$
2	4.3096-4.3362	2H	quartet	- $C\underline{H}_2$(b)
3	6.9969-7.0550	1H	doublet	- Ar-$\underline{H}_{(e)}$
4	7.3504	1H	singlet	- Ar-$\underline{H}_{(c)}$
5	8.1867-8.2266	2H	doublet	- Ar-$\underline{H}_{(f,g)}$
6	8.5326	1H	singlet	- Ar-$\underline{H}_{(h)}$
7	8.8631-8.8831	1H	doublet	- Ar-$\underline{H}_{(d)}$
8	9.2148	1H	singlet	-N-$\underline{CH}_{(i)}$
9	7.6153	-	-	$-CDCl_3$

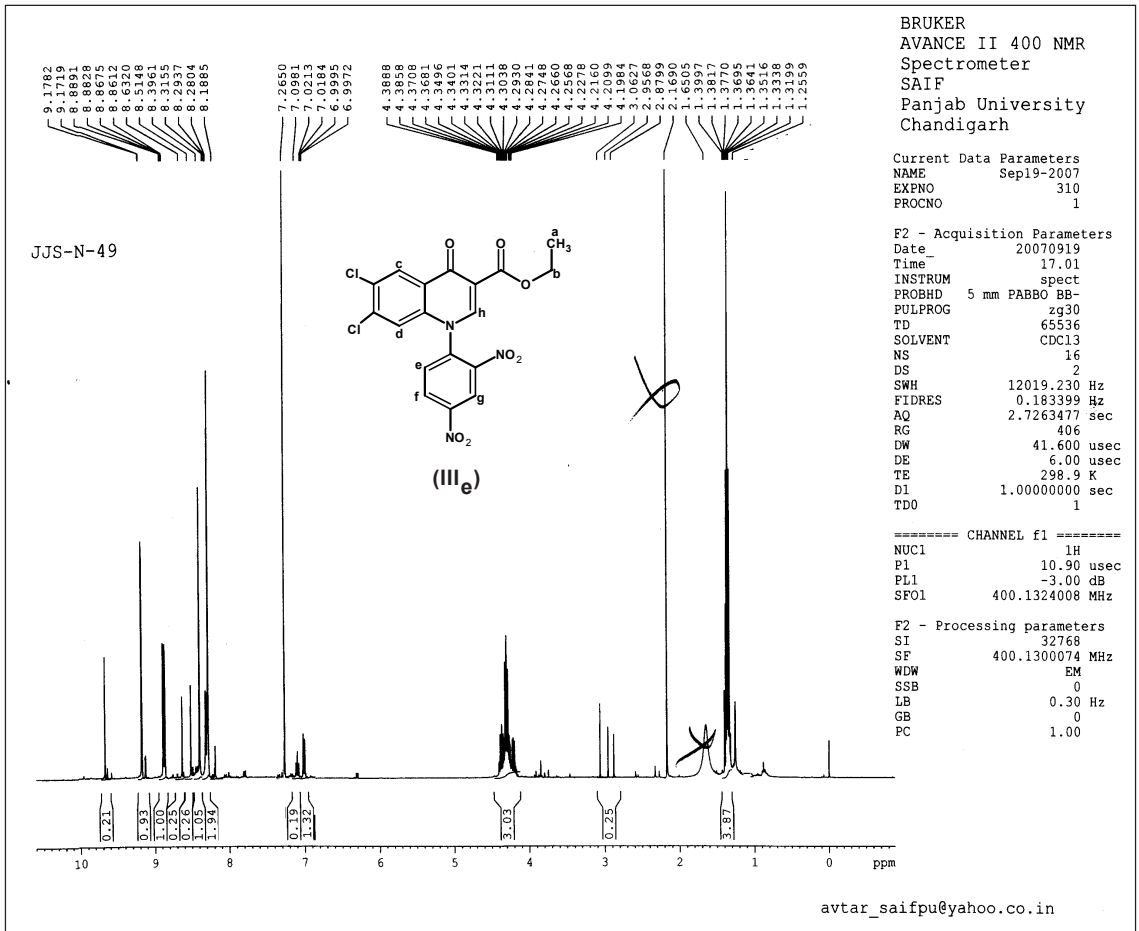
NMR SPECTRAL STUDY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-7-CHLORO-6-FLUORO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (III_d).



avtar_saifpu@yahoo.co.in

Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.3315-1.3914	3H	triplet	- ($C\underline{H}_3$)(a)
2	4.3007-4.3539	2H	quartet	- $C\underline{H}_2$(b)
3	6.6957-6.7099	1H	doublet	- Ar-$\underline{H}$(f)
4	8.1428-8.2489	2H	multiplet	- Ar-$\underline{H}$(c,d)
5	8.5226	1H	singlet	- Ar-$\underline{H}$(g)
6	8.8531-8.8811	1H	doublet	- Ar-$\underline{H}$(e)
7	9.2012	1H	doublet	-N-$\underline{C}H$(h)
8	2.5919	-	-	-DMSO-d_6
9	2.8668-2.9774	-	-	-DMF
10	7.6153	-	-	-$CDCl_3$

NMR SPECTRAL STUDY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-6,7-DI-CHLORO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (III_e).



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Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.3199-1.3997	3H	triplet	- ($C\underline{H}_3$)(a)
2	4.1984-4.3888	2H	quartet	- $C\underline{H}_2$(b)
3	6.9972-7.0213	1H	doublet	- Ar-$\underline{H}$(f)
4	8.2804-8.3155	2H	multiplet	- Ar-$\underline{H}$(c,d)
5	8.3961	1H	singlet	- Ar-$\underline{H}$(g)
6	8.8612-8.8891	1H	doublet	- Ar-$\underline{H}$(e)
7	9.1719-9.1782	1H	doublet	-N-$\underline{C}H$(h)
8	2.1690	-	-	-Acetone
9	7.2650	-	-	-$CDCl_3$

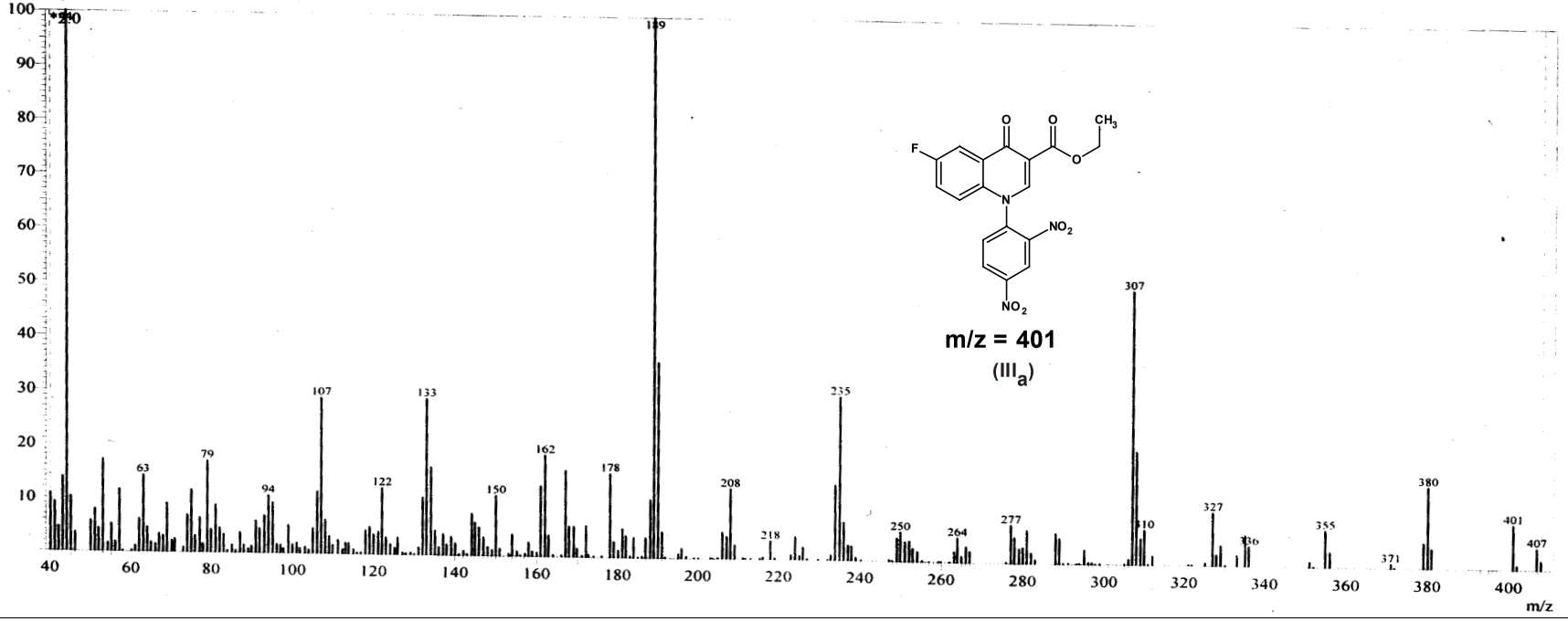
MASS SPECTRAL STUDY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-6-FLUORO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (III_a).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

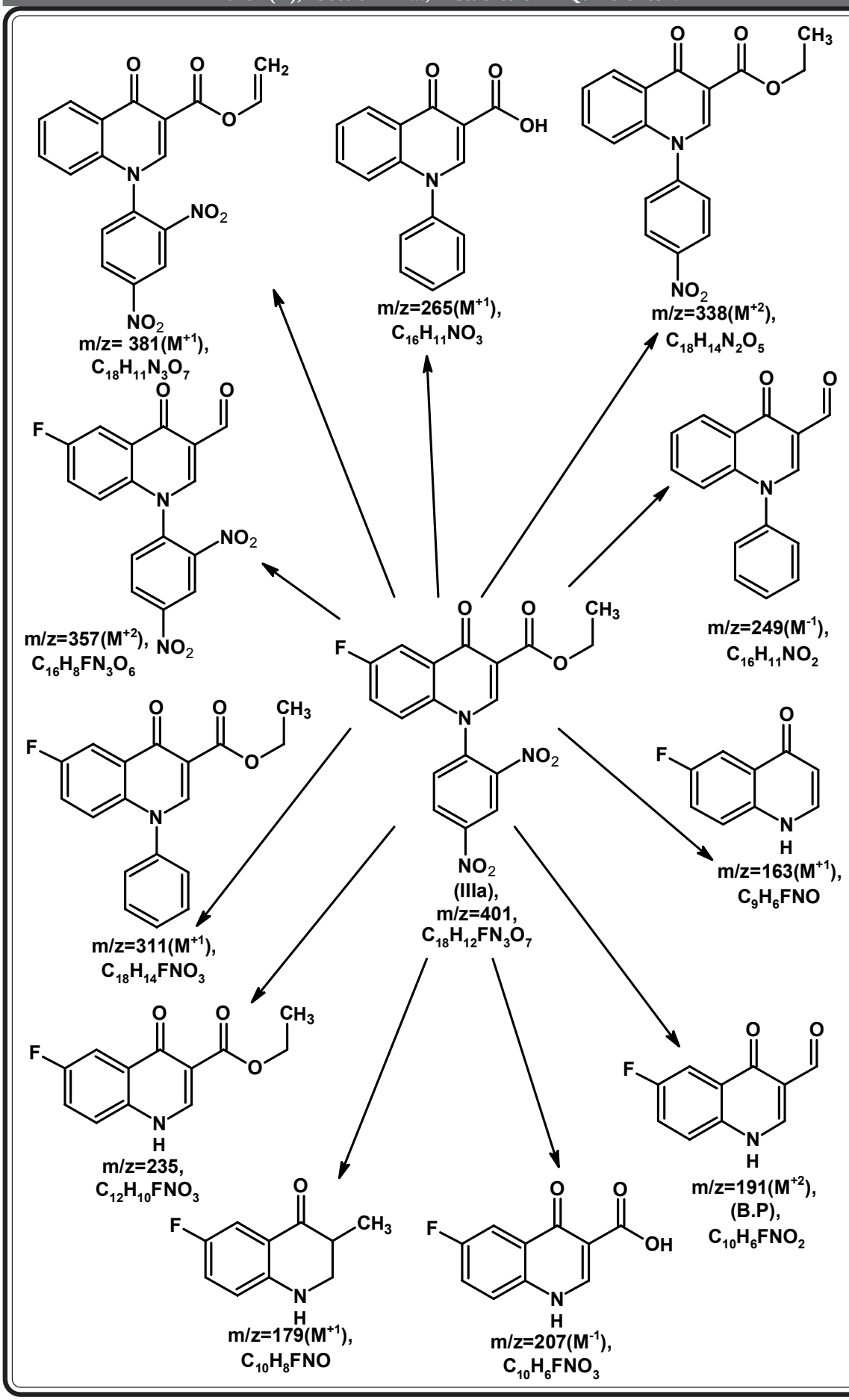
Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 8/24/2007 3:18:51 PM
Sample Name : JJS-MQ-18
Sample ID : JJS-MQ-18
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-18.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune130807.qgt

Line#:1 R.Time:6.3(Scan#:715)
MassPeaks:246 BasePeak:44(81470)
RawMode:Averaged 5.8-6.3(665-716)
BG Mode:None
intensity



m/z = 401
(III_a)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C18H11N3O7
m/z=265(M+1),
C16H11NO3
m/z=338(M+2),
C18H14N2O5
m/z=357(M+2),
C16H8FN3O6
m/z=249(M-1),
C16H11NO2
m/z=311(M+1),
C18H14FNO3
(IIIa),
m/z=401,
C18H12FN3O7
m/z=163(M+1),
C9H6FNO
m/z=235,
C12H10FNO3
m/z=191(M+2),
(B.P),
C10H6FNO2
m/z=179(M+1),
C10H8FNO
m/z=207(M-1),
C10H6FNO3

MASS SPECTRAL STUDY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-6-CHLORO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (III_c).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 8/24/2007 1:41:05 PM
Sample Name : JJS-MQ-17
Sample ID : JJS-MQ-17
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-17.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune130807.qgt

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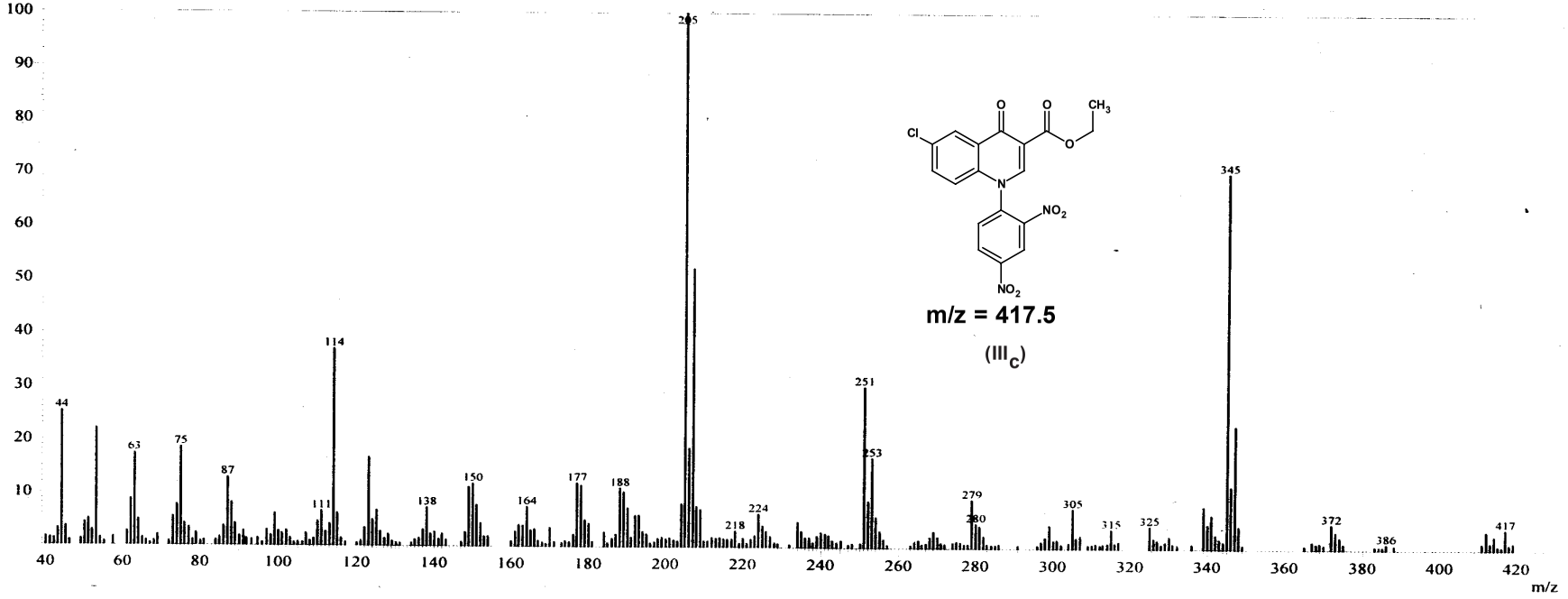
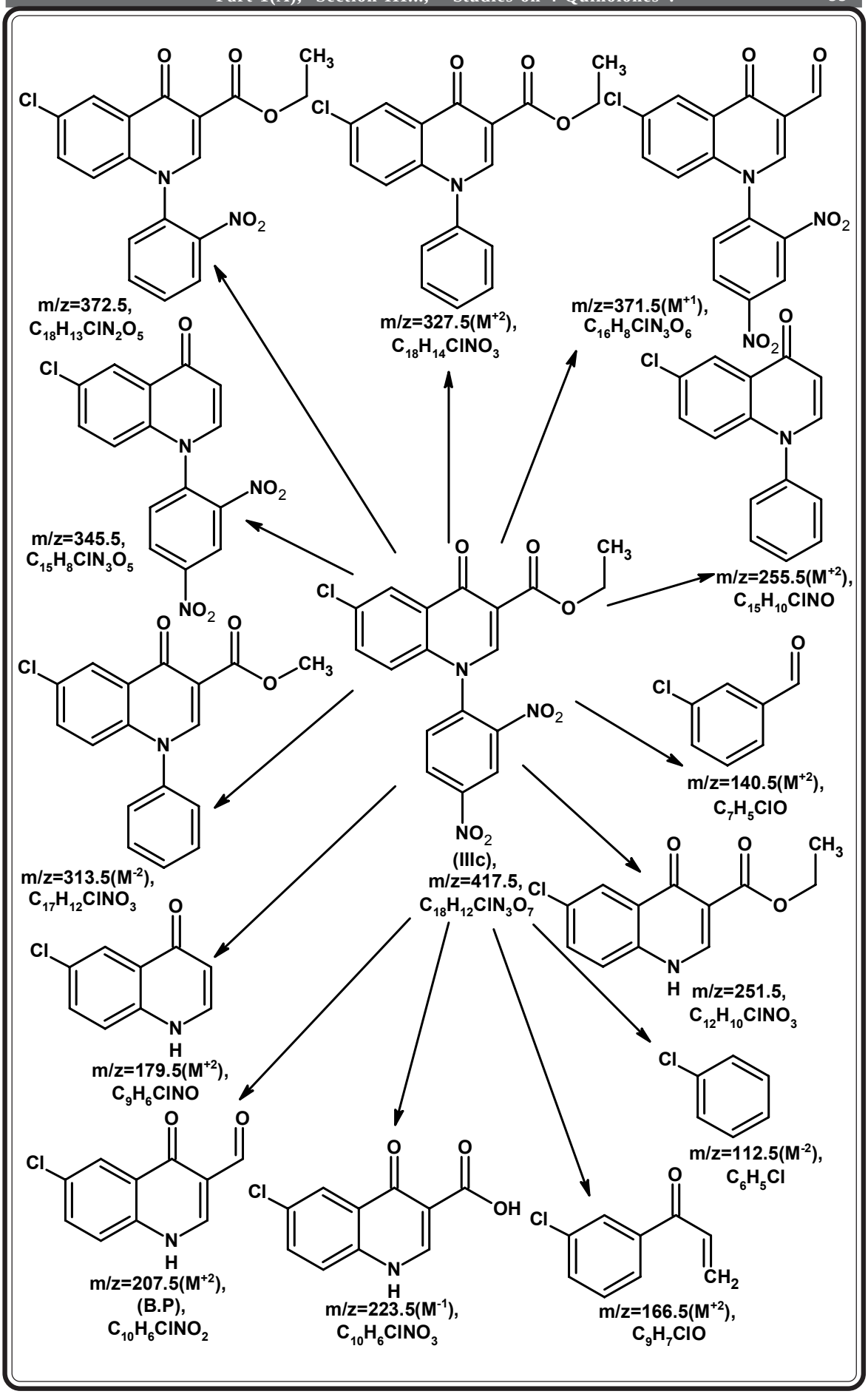
MassPeaks:274 BasePeak:205(221359)
RawMode:Single 10.3(1196)
BG Mode:None
intensity



m/z = 417.5

(III_c)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m/z=327.5(M+2),
C18H14ClNO3
m/z=371.5(M+1),
C16H8ClN3O6
m/z=345.5,
C15H8ClN3O5
m/z=255.5(M+2),
C15H10ClNO
m/z=313.5(M-2),
C17H12ClNO3
(IIIc),
m/z=417.5,
C18H12ClN3O7
m/z=140.5(M+2),
C7H5ClO
m/z=251.5,
C12H10ClNO3
m/z=179.5(M+2),
C9H6ClNO
m/z=112.5(M-2),
C6H5Cl
m/z=207.5(M+2),
(B.P),
C10H6ClNO2
m/z=223.5(M-1),
C10H6ClNO3
m/z=166.5(M+2),
C9H7ClO

MASS SPECTRAL STUDY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-7-CHLORO-6-FLUORO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (III_d).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 6/12/2006 3:16:55 PM
Sample Name	: JJS-M-33
Sample ID	: JJS-M-33
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-33.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune11.qgt

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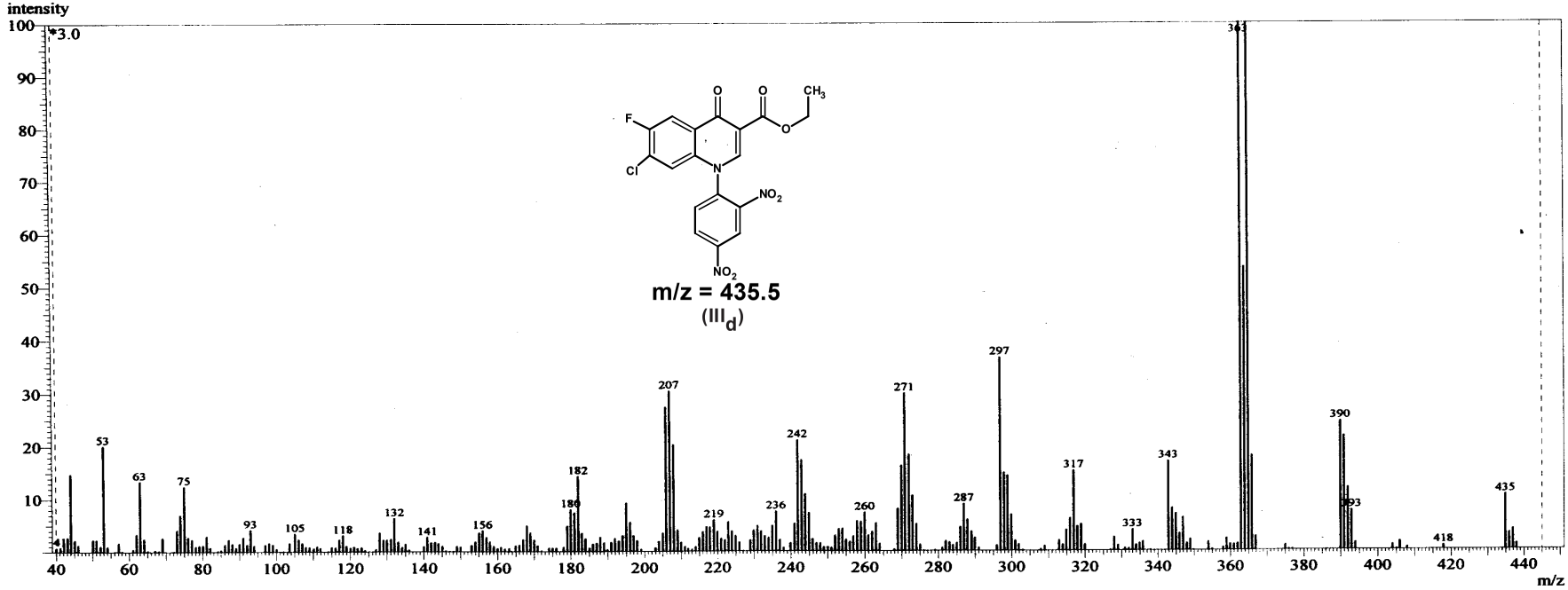
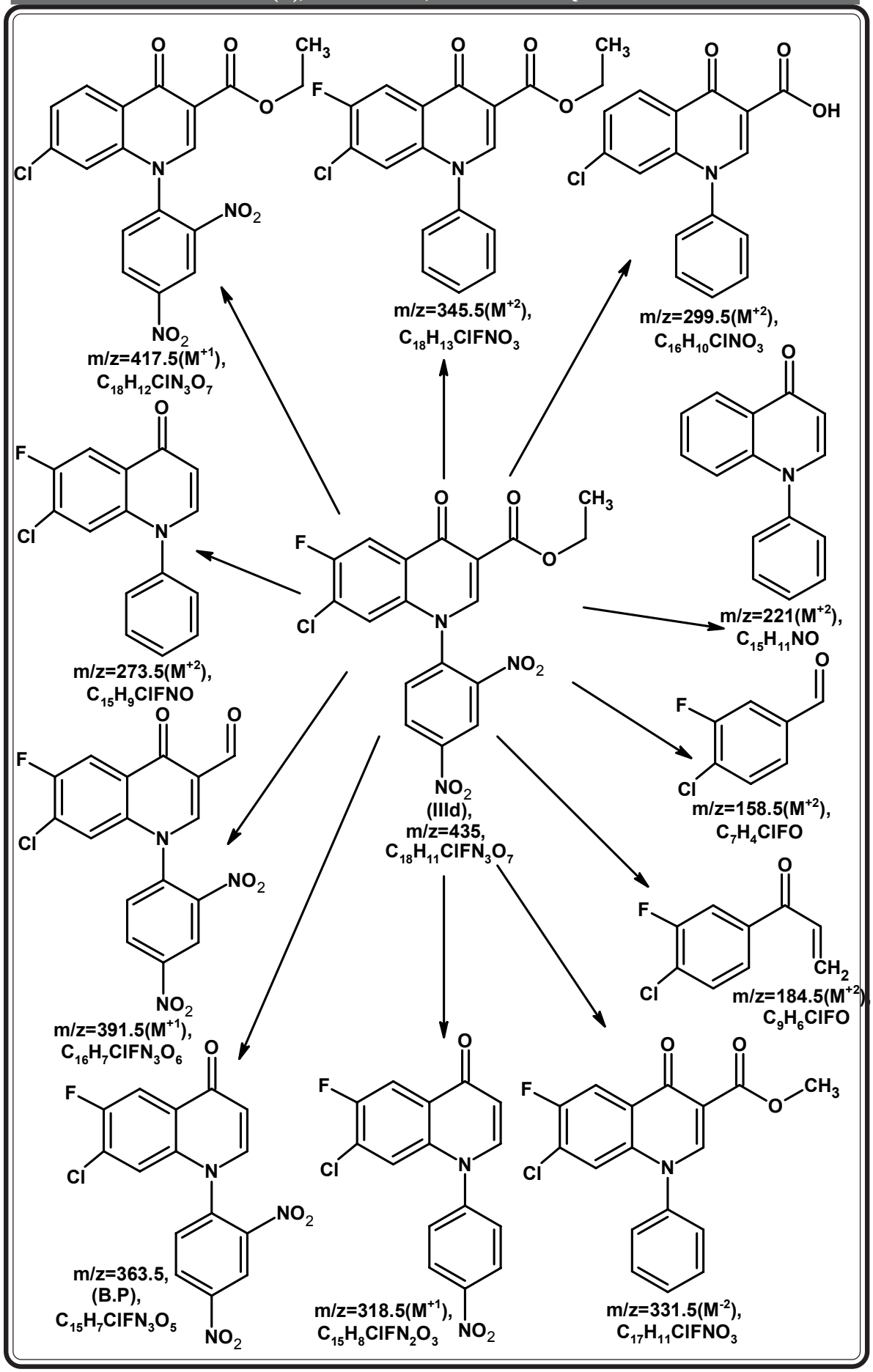
RawMode:Averaged 9.5-10.4(1107-1212)
BG Mode:None
intensity




m/z=417.5(M+1),
C18H12ClN3O7
m/z=345.5(M+2),
C18H13ClFNO3
m/z=299.5(M+2),
C16H10ClNO3
m/z=273.5(M+2),
C15H9ClFNO
m/z=221(M+2),
C15H11NO
(IIId),
m/z=435,
C18H11ClFN3O7
m/z=158.5(M+2),
C7H4ClFO
m/z=391.5(M+1),
C16H7ClFN3O6
m/z=184.5(M+2),
C9H6ClFO
m/z=363.5,
(B.P),
C15H7ClFN3O5
m/z=318.5(M+1),
C15H8ClFN2O3
m/z=331.5(M-2),
C17H11ClFNO3

MASS SPECTRAL STUDY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-6,7-DICHLORO-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (III_e).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 4/6/2006 12:30:05 PM
Sample Name	: JJS-M-26
Sample ID	: JJS-M-26
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-26.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune9.qgt

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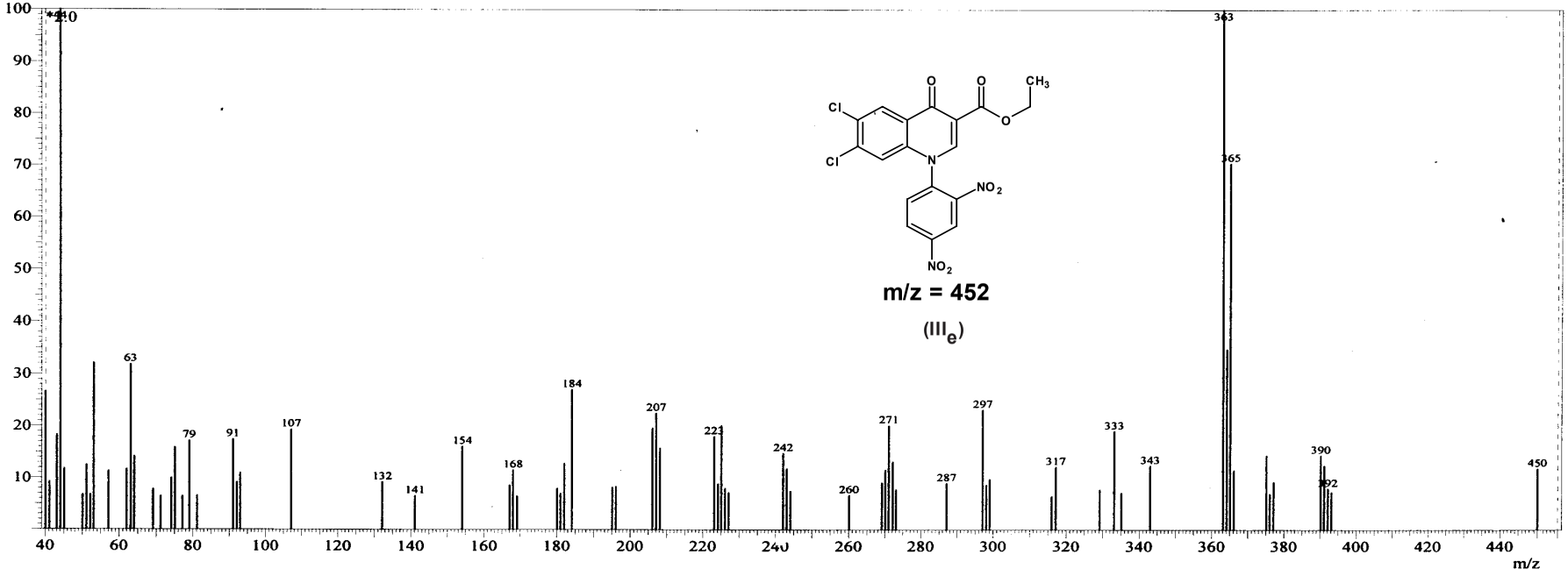
MassPeaks:75 BasePeak:363(31219)
RawMode:Single 8.5(981)
BG Mode:None
intensity



m/z = 452

(III_e)

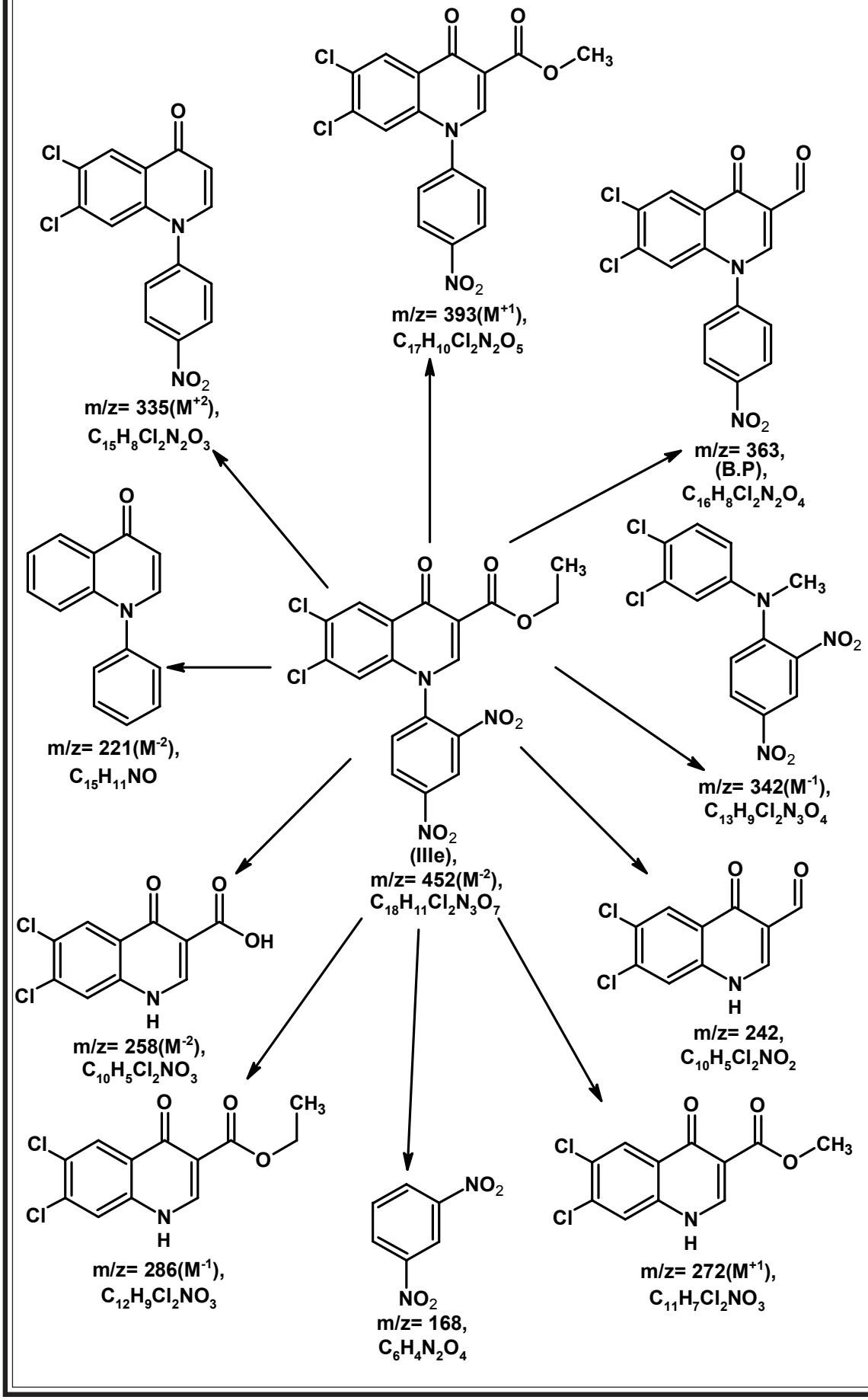

m/z= 393(M+1),
C17H10Cl2N2O5
m/z= 335(M+2),
C15H8Cl2N2O3
m/z= 363,
(B.P),
C16H8Cl2N2O4
m/z= 221(M-2),
C15H11NO
m/z= 342(M-1),
C13H9Cl2N3O4
(IIIe),
m/z= 452(M-2),
C18H11Cl2N3O7
m/z= 258(M-2),
C10H5Cl2NO3
m/z= 242,
C10H5Cl2NO2
m/z= 286(M-1),
C12H9Cl2NO3
m/z= 168,
C6H4N2O4
m/z= 272(M+1),
C11H7Cl2NO3

TABLE NO. 3A : COMPARATIVE ANTIMICROBIAL ACTIVITY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-6,7,8-SUBSTITUTED-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATES (III_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) S. pyogens MTCC- 442					S. aureus MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
III_a	6-F	-	12	14	16	18	-	9	11	13	15
III_b	7-Cl	-	13	13	15	17	-	10	12	14	18
III_c	6-Cl	-	9	10	12	14	-	8	10	12	17
III_d	7-Cl-6-F	-	10	12	14	16	-	11	13	17	19
III_e	6,7-$(Cl)_2$	-	11	13	15	17	-	7	8	10	16
III_f	6-NO_2	-	10	12	14	16	-	10	11	13	17
III_g	6-OCH_3	-	9	11	13	14	-	8	9	11	15
III_h	6-CH_3	-	9	10	12	13	-	9	10	12	16
III_i	7,8-$(CH_3)_2$	-	10	11	13	14	-	9	12	15	18
III_j	-C_4H_4	-	11	12	14	15	-	8	10	13	17

Comparative activity of (III_{a-j}) with known choosen standard drugs

Standard drug	Antibacterial activity									
				III a	III a				IIId IIIi	IIIb IIId IIIi
Amoxiciline	12	14	15	16	18	10	12	14	15	18
Chloramphenicol	14	15	18	19	24	14	17	20	21	24
Sparfloxacin	14	22	24	26	28	24	26	27	28	32
Levofloxacin	18	21	22	27	29	20	24	26	27	35

N.B.(-): No Activity

TABLE NO. 3B : COMPARATIVE ANTIMICROBIAL ACTIVITY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-6,7,8-SUBSTITUTED-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATES (III_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) B. Subtillis MTCC- 441					E.coli MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
III_a	6-F	-	10	11	13	16	-	7	8	10	12
III_b	7-Cl	-	10	12	14	17	-	8	8	11	13
III_c	6-Cl	-	9	10	12	15	-	7	7	9	10
III_d	7-Cl-6-F	-	10	11	13	17	-	6	8	10	11
III_e	6,7-$(Cl)_2$	-	11	12	14	17	-	7	8	10	12
III_f	6-NO_2	-	10	13	15	18	-	8	9	12	14
III_g	6-OCH_3	-	10	11	13	16	-	7	7	9	10
III_h	6-CH_3	-	9	10	12	15	-	7	7	9	11
III_i	7,8-$(CH_3)_2$	-	10	11	13	16	-	9	10	11	13
III_j	-C_4H_4	-	9	10	11	15	-	6	8	10	12

Comparative activity of (III_{a-j}) with known choosen standard drugs

Standard drug	Antibacterial activity									
Amoxiciline	12	15	16	18	19	11	14	16	18	20
Chloramphenicol	18	22	24	26	27	17	20	23	25	26
Sparfloxacin	22	24	25	26	29	20	22	25	26	28
Levofloxacin	24	26	28	29	31	23	25	26	29	30

N.B.(-): No Activity

TABLE NO. 3C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF ETHYL-1-N-(2,4-DINITRO-PHENYL)-6,7,8-SUBSTITUTED-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATES (III_{a-j}).(Different Inhibition Concentration in µg/ml).

Compd No.	R	Antifungal activity (Zones of inhibition in m.m.) C. albicans MTCC- 227					A.niger MTCC- 282				
		5	25	50	100	250	5	25	50	100	250
III_a	6-F	-	8	10	12	15	-	9	11	13	16
III_b	7-Cl	-	6	8	10	12	-	10	11	12	14
III_c	6-Cl	-	10	13	15	17	-	11	12	14	16
III_d	7-Cl-6-F	-	9	11	13	15	-	10	13	15	18
III_e	6,7-$(Cl)_2$	-	8	9	10	11	-	9	11	13	17
III_f	6-NO_2	-	7	9	10	13	-	8	9	11	12
III_g	6-OCH_3	-	5	7	8	11	-	8	9	11	14
III_h	6-CH_3	-	5	7	8	10	-	7	8	10	12
III_i	7,8-$(CH_3)_2$	-	6	8	10	12	-	8	9	11	13
III_j	-C_4H_4	-	7	9	11	14	-	9	11	13	15

Comparative activity of (III_{a-j}) with known choosen standard drugs

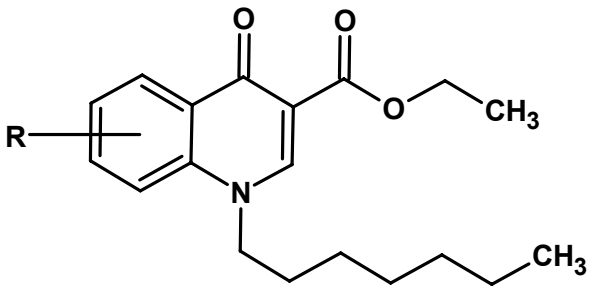
Standard drug	Antifungal activity									
Griseofulvin	16	18	21	23	25	17	19	21	22	23
Fluconazole	14	16	18	21	22	15	17	18	20	21

N.B.(-): No Activity

SECTION - IV

PREPARATION AND BIOLOGICAL EVALUATION OF ETHYL-6,7,8-SUBSTITUTED-1-N-HEPTYL-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATES.

Keeping in view of various biodynamic activities[34-85] of **4-quinolone** and in order to have highly potent therapeutic agents, the synthesis of **Ethyl-1-N-heptyl-6,7,8-substituted-1,4-dihydroquinoline-4-one-3-carboxylates (IVa-j)** have been prepared by the cyclocondensation of different **ethyl-substituted-1,4-dihydroquinoline-4-one-3-carboxylates (IIa-j)** and **1-bromo heptane** in the presence of basic condition.



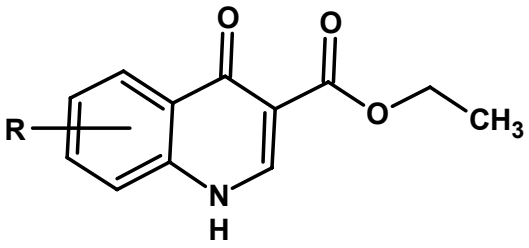
(IVa-j)

R=Substituted phenyl

The constitution of the products **(IVa-j)** have been delineated by **elemental analyses, IR, PMR** and **Mass** spectral data.

The products **(IVa-j)** were assayed for their ***in vitro*** biological assay like antibacterial activity towards ***S. pyogens MTCC-442 ,S. aureus MTCC-96 and B. subtillis MTCC-441*****(Gram positive)** and ***E. coli MTCC-443*** **(Gram negative)** bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** **and** ***Candida albicans MTCC-227*** at different concentrations.i.e.: 0(control),5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds **(IVa-j)** were compared with standard drugs viz.**,Amoxicillin, Chloramphenicol, Sparfloxacin, Levofloxacin**(antibacterial)**, Griseofluvin, Fluconazole** (antifungal)**.**

REACTION SCHEME



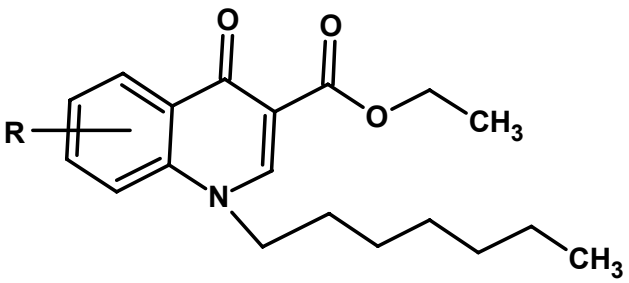
(IIa-j)
R=substituted phenyl

1-Bromo-heptane

Anhyd. K_2CO_3

Dimethyl-sulphoxide

△



(IVa-j)
R=substituted phenyl

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF ETHYL-6,7,8-SUBSTITUTED-1-N-HEPTYL-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATES.

(A) Preparation of Diethyl-(3-chloro-4-fluoro amino phenyl)-amino-methylene malonate (II_d).

For preparation, refer Part-1, Section-I, **page No.30.**

(B) Preparation of Ethyl-7-chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carboxylate (II_d).

For preparation, refer Part-1,Section-II, **page No.58**.

(C) Preparation of Ethyl-1-N-heptyl-7-chloro-6-fluoro-1,4-dihydro quinoline-4-one-3-carboxylate (IVd).

A mixture of Ethyl-7-chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carboxylates**(II_d)**.(2.69 gm, 0.01 M) and anhydrous potassium carbonate (2.76 gm, 0.02M)**,** in dimethyl sulphoxide (20 ml) was heated and stirred at 110 to120 ^{O}C for 1 hrs. and then allowed to cool up to the temp 60 to70^{O}C. To this reaction mixture, the solution of 1-bromo heptane (1.79 gm, 0.01M) in dimethyl sulphoxide (6 ml) was added dropwise and the temperature was maintained 95-100^{O}C for 8 hrs.The resulting mixture was poured on to crushed ice, filtered, washed with water and dried**.** The product was crystallized from ethanol. Yield : 47%, M.P. : 46 ^{O}C, (Required : C,62.04%; H,6.30 %; N,3.81 % for $C_{19}H_{23}NO_3ClF$ Found : C, 62.01 %; H, 6.27 %; N, 3.78%).

TLC solvent system R_{f_1} : Ethyl acetate :Hexane (5.0 : 5.0) = 0.54 **.**

TLC solvent system R_{f_2} : Methanol :Chloroform(0.5 : 9.5) = 0.59**.**

Similarly, other compounds **(IVa-j)** were synthesized. The physical data are recorded in **Table No. 4**.

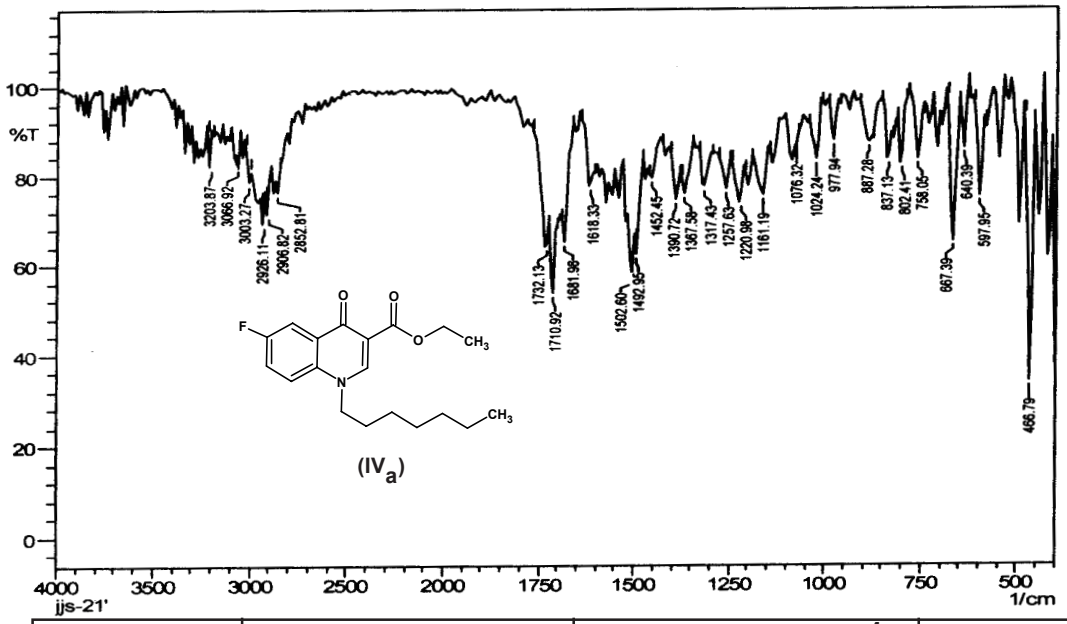
(D) Antimicrobial activity of Ethyl-6,7,8-substituted-1-N-heptyl-substituted-1,4-dihydroquinoline-4-one-3-carboxylates(IVa-j).

Antimicrobial activity testing was carried out as described in Part-1(A), Section-I, page No. 30-31. The MIC values of test solution are recorded in **Table No. 4A, 4B** and **4C.**

TABLE NO. 4 : PHYSICAL CONSTANTS OF ETHYL-6,7,8-SUBSTITUTED-1-N-HEPTYL-1,4-DIHYDROQUINOLINE-4-ON-3-CARBOXYLATES (IV_{a-j}).

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. ^oC 5	Yield % 6	R_f Value R_{f_1} 7	R_{f_2}	% of Nitrogen Calcd. / Found 8
IV_a	6-F	$C_{19}H_{24}NO_3F$	333.0	43^o	52	0.59	0.49	4.20 / 4.16
IV_b	7-Cl	$C_{19}H_{24}NO_3Cl$	349.5	57^o	54	0.57	0.52	4.00 / 3.95
IV_c	6-Cl	$C_{19}H_{24}NO_3Cl$	349.5	58^o	55	0.56	0.48	4.00/ 3.94
IV_d	7-Cl-6-F	$C_{19}H_{23}NO_3ClF$	367.5	46^o	47	0.61	0.62	3.81 / 3.75
IV_e	6,7-$(Cl)_2$	$C_{19}H_{23}NO_3Cl_2$	384.0	55^o	49	0.58	0.57	3.64 / 3.58
IV_f	6-NO_2	$C_{19}H_{24}N_2O_5$	360.0	186^o	53	0.49	0.47	7.77 / 7.73
IV_g	6-OCH_3	$C_{20}H_{27}NO_4$	345.0	61^o	50	0.53	0.51	4.06 / 4.00
IV_h	6-CH_3	$C_{20}H_{27}NO_3$	329.0	59^o	56	0.48	0.49	4.25 / 4.20
IV_i	7,8-$(CH_3)_2$	$C_{21}H_{29}NO_3$	343.0	63^o	58	0.47	0.46	4.08 / 4.02
IV_j	-	$C_{23}H_{27}NO_3$	365.0	123^o	51	0.46	0.49	3.83 / 3.80

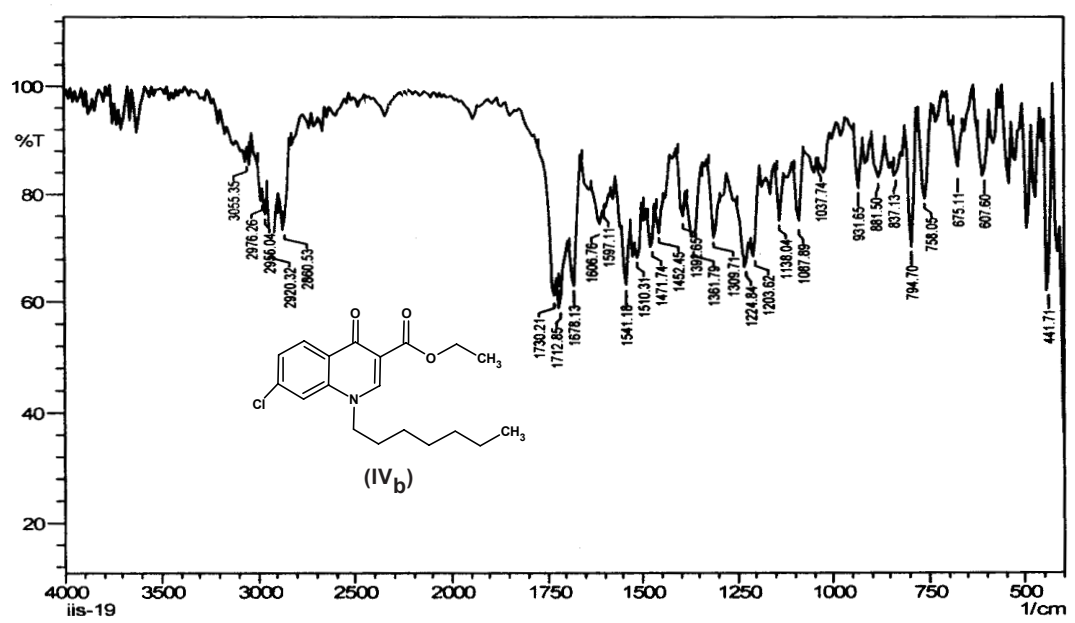
IR SPECTRAL STUDY OF ETHYL-6-FLUORO-1-N-HEPTYL-1,4-DIHYDRO-QUINOLINE-4-ONE-3-CARBOXYLATE (IV_a).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2906.8	2975 - 2850	96
	C-H (sym. str., m)	2852.8	2900 - 2800	96
	C-H (asym. def., m)	1452.4	1470 - 1435	96
	C-H (sym. def., m)	1367.5	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3066.9	3080 - 3010	97
	C=C & C-C (str., v)	1502.6	1600 - 1450	97
	C-H (i.p. def., m)	1124.2	1150 - 1050	97
	C-H (o.o.p. def., m)	802.4	825 - 800	97
	C-N (str., v)	1367.5	1340 - 1250	97
Amine	N-H (str., b)	3203-3003	3400 - 3000	98
	N-H (def., s,m)	1618.3	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1710.9	1710 - 1640	98
(ester)	C=O (str., s)	1732.1	1740 - 1650	98
Halogen Subtitution	C-F (str., b)	1390.7-1161.1	1400 - 1080	99
Para(-4-) substituted	C-H (def., v,s)	837.1	800 - 850	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

IR SPECTRAL STUDY OF ETHYL-7CHLORO-1-N-HEPTYL-1,4-DIHYDRO-QUINOLINE-4-ONE-3-CARBOXYLATE (IV_b).

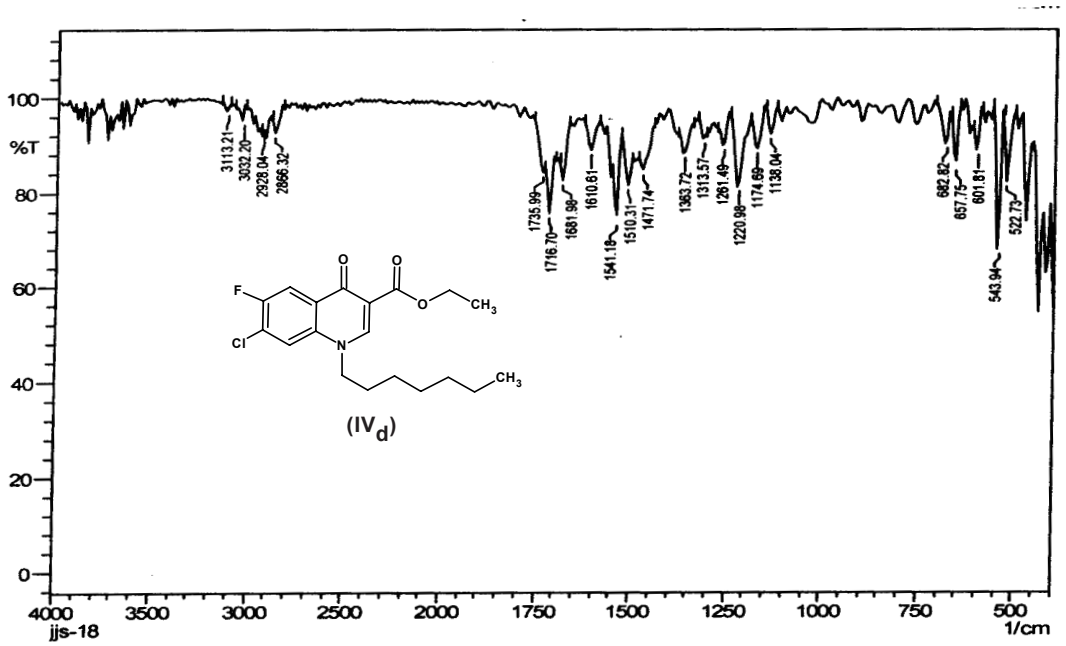


(IV_b)

Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2920.3	2975 - 2850	96
	C-H (sym. str., m)	2860.5	2900 - 2800	96
	C-H (asym. def., m)	1471.7	1470 - 1435	96
	C-H (sym. def., m)	1392.6	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3055.3	3080 - 3010	97
	C=C & C-C (str., v)	1510.3	1600 - 1450	97
	C-H (i.p. def., m)	1138.0	1150 - 1050	97
	C-H (o.o.p. def., m)	794.7	825 - 800	97
	C-N (str., v)	1361.7	1340 - 1250	97
Amine	N-H (str., b)	3055.3	3400 - 3000	98
	N-H (def., s,m)	1541.1	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1712.8	1710 - 1640	98
(ester)	C=O (str., s)	1730.2	1740 - 1650	98
Halogen Subtitution	C-Cl (str., b)	794-607	800-600	99
Para(-4-) substituted	C-H (def., v,s)	837.1	800 - 850	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

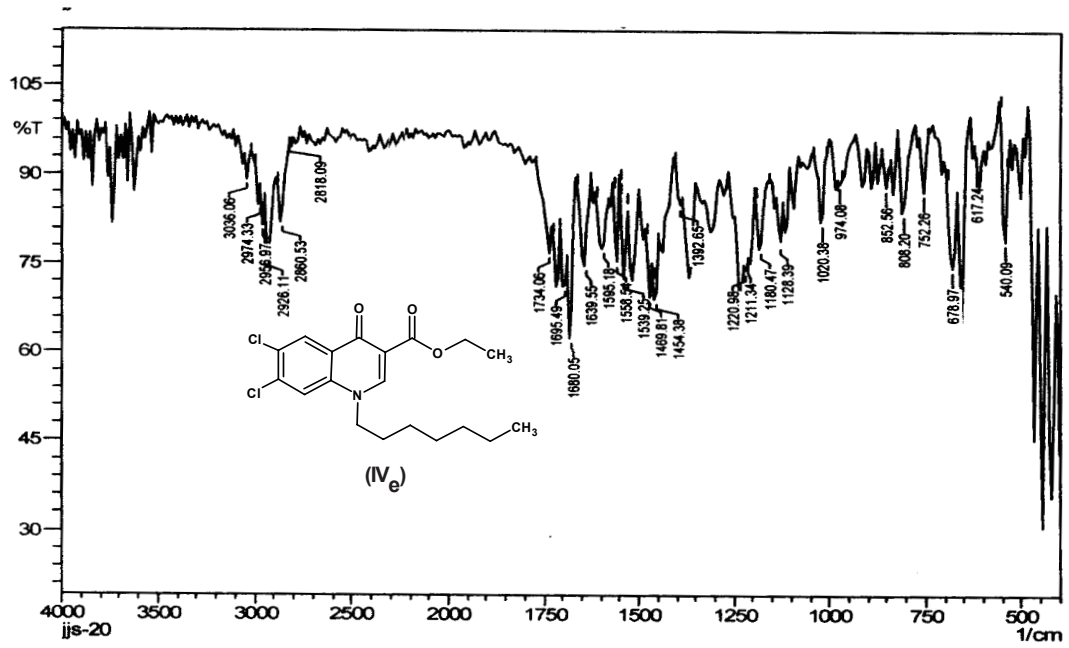
IR SPECTRAL STUDY OF ETHYL-7-CHLORO-6-FLUORO-1-N-HEPTYL-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (IV_d).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2928.0	2975 - 2850	96
	C-H (sym. str., m)	2866.3	2900 - 2800	96
	C-H (asym. def., m)	1471.7	1470 - 1435	96
	C-H (sym. def., m)	1363.5	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3032.2	3080 - 3010	97
	C=C & C-C (str., v)	1610.6	1600 - 1450	97
	C-H (i.p. def., m)	1174.6	1150 - 1050	97
	C-N (str., v)	1313.5	1340 - 1250	97
Amine	N-H (str., b)	3032.2	3400 - 3000	98
	N-H (def., s,m)	1541.5	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1716.7	1710 - 1640	98
(ester)	C=O (str., s)	1735.9	1740 - 1650	98
Halogen Subtitution	C-F (str.,b)	1363.7-1138.0	1400 - 1080	99
	C-Cl (str.,b)	682-601	800 - 600	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

IR SPECTRAL STUDY OF ETHYL-6,7-DICHLORO-1-N-HEPTYL-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (IV_e).

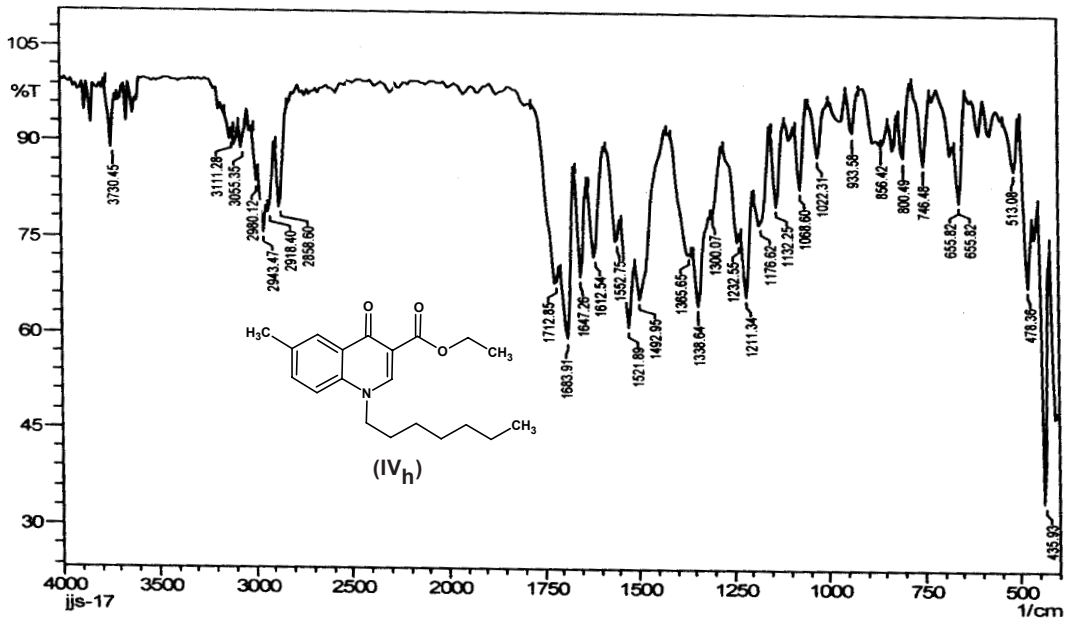


(IV_e)

Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2926.1	2975 - 2850	96
	C-H (sym. str., m)	2860.5	2900 - 2800	96
	C-H (asym. def., m)	1469.8	1470 - 1435	96
	C-H (sym. def., m)	1392.6	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3036.0	3080 - 3010	97
	C=C & C-C (str., v)	1595.1	1600 - 1450	97
	C-H (i.p. def., m)	1128.3	1150 - 1050	97
	C-H (o.o.p. def., m)	808.2	825 - 800	97
	C-N (str., v)	1392.6	1340 - 1250	97
Amine	N-H (str., b)	3036.0	3400 - 3000	98
	N-H (def., s,m)	1558.5	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1695.4	1710-1640	98
(ester)	C=O (str., s)	1734.0	1740 - 1650	98
Halogen Subtitution	C-Cl (str., b)	806-617	800-600	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

IR SPECTRAL STUDY OF ETHYL-6-METHYL-1-N-HEPTYL-1,4-DIHYDRO-QUINOLINE-4-ONE-3-CARBOXYLATE (IV_h).

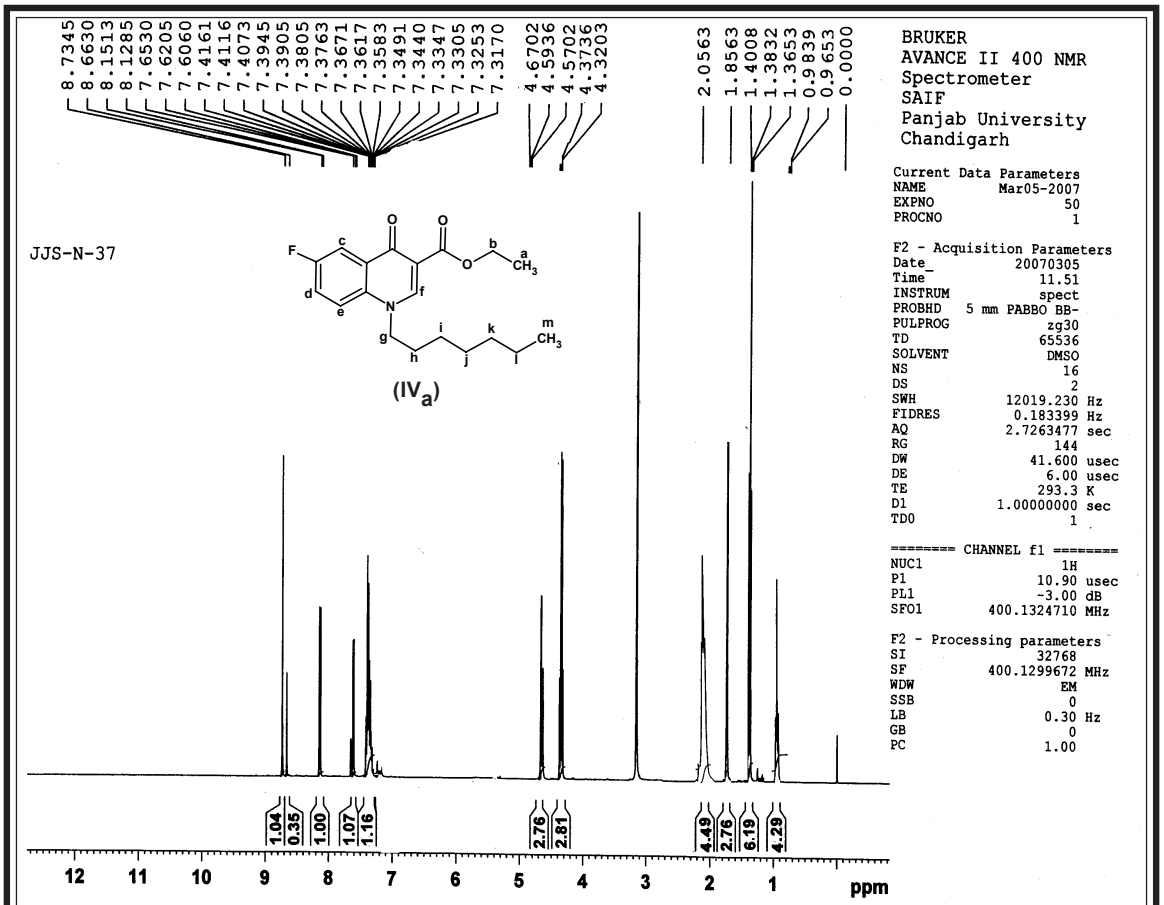


(IV_h)

Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2918.4	2975 - 2850	96
	C-H (sym. str., m)	2858.6	2900 - 2800	96
	C-H (asym. def., m)	1412.9	1470 - 1435	96
	C-H (sym. def., m)	1365.6	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3055.3	3080 - 3010	97
	C=C & C-C (str., v)	1552.7	1600 - 1450	97
	C-H (i.p. def., m)	1132.2	1150 - 1050	97
	C-H (o.o.p. def., m)	800.4	825 - 800	97
	C-N (str., v)	1338.6	1340 - 1250	97
Amine	N-H (str., b)	3111.2-3055.3	3400 - 3000	98
	N-H (def., s,m)	1612.5	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1683.9	1710 - 1640	98
(ester)	C=O (str., s)	1712.6	1740 - 1650	98
Para(4)-Subtitution	C-H (def., v,s)	856.4	800 - 850	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

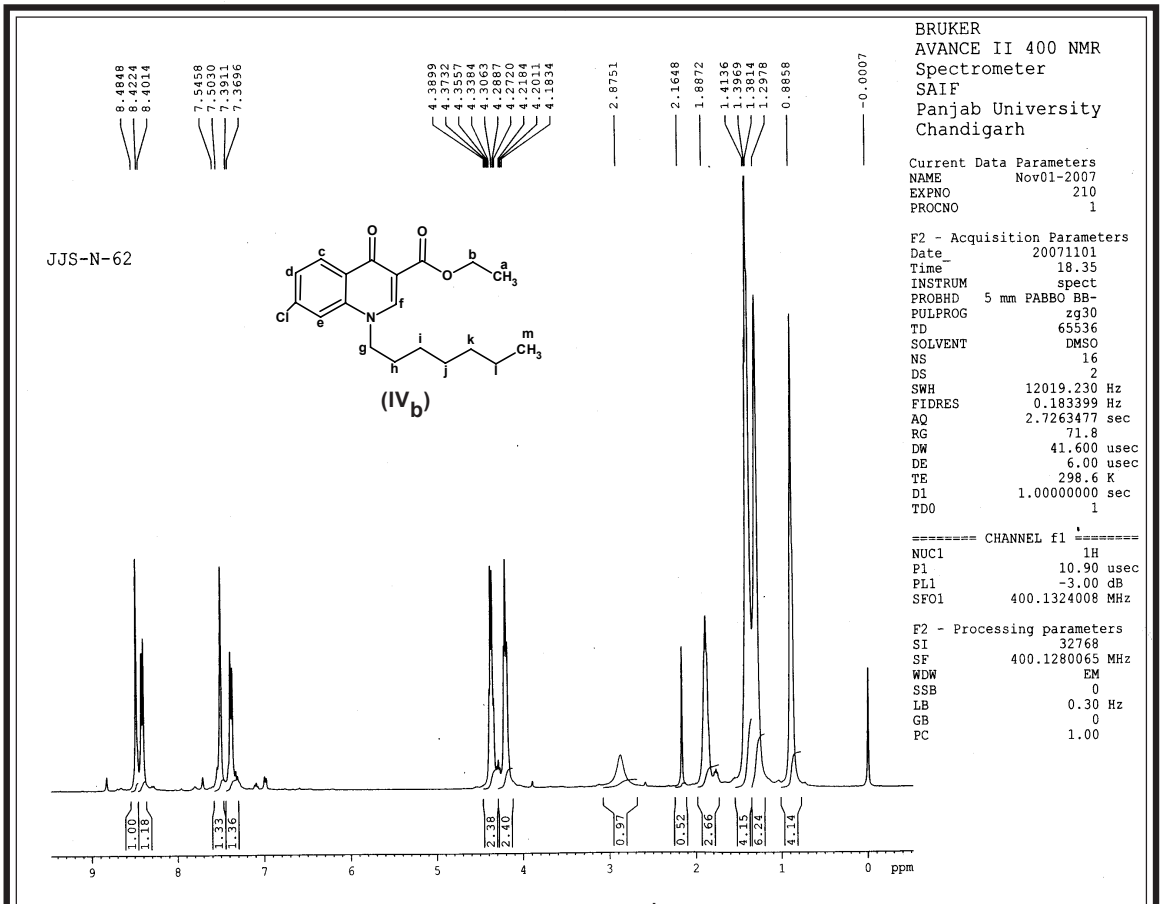
NMR SPECTRAL STUDY OF ETHYL-6-FLUORO-1-N-HEPTYL-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (IV_a).



avtar_saifpu@yahoo.co.in

Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	0.9653-0.9839	4H	triplet	- $CH_{2(i,j)}$
2	1.3653-1.4008	6H	triplet	- $CH_{3(a,m)}$
3	1.8563	2H	singlet	- $CH_{2(k)}$
4	2.0563	4H	triplet	- $CH_{2(h,l)}$
5	4.3203-4.3736	2H	triplet	- $CH_{2(g)}$
6	4.5936-4.6702	2H	quartet	-$CH_{2(b)}$
7	7.3170-7.4161	1H	multiplet	- Ar-$H_{(d)}$
8	7.6060-7.6530	1H	doublet	- Ar-$H_{(e)}$
9	8.1285-8.1513	1H	doublet	- Ar-$H_{(c)}$
10	8.6630-8.7345	1H	singlet	-N-$CH_{(f)}$
11	3.1452	-	-	-DMSO-d_6

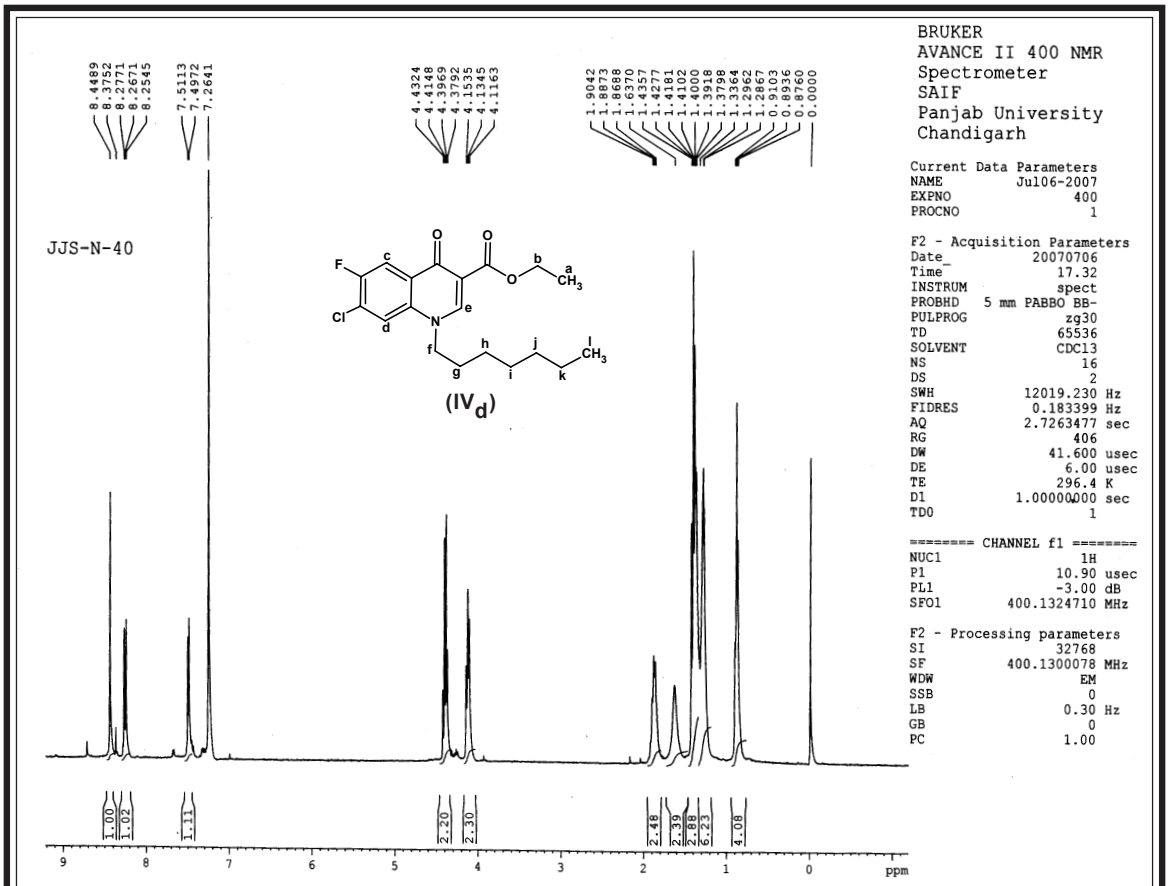
NMR SPECTRAL STUDY OF ETHYL-7-CHLORO-1-N-HEPTYL-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (IV_b).



avtar_saifpu@yahoo.co.in

Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	0.8858	4H	singlet	- $CH_{2(i,j)}$
2	1.2978	6H	singlet	- $CH_{3(a,m)}$
3	1.3814-1.4136	4H	triplet	- $CH_{2(h,l)}$
4	1.8872	2H	singlet	- $CH_{2(k)}$
5	4.1834-4.2720	2H	triplet	- $CH_{2(g)}$
6	4.3384-4.3899	2H	quartet	-$CH_{2(b)}$
7	7.3696-7.3911	1H	doublet	- Ar-$H_{(c)}$
8	7.5030	1H	singlet	- Ar-$H_{(d)}$
9	8.4014-8.4224	1H	doublet	- Ar-$H_{(e)}$
10	8.4848	1H	singlet	-N-$CH_{(f)}$
11	2.8751	-	-	-DMSO-d_6

NMR SPECTRAL STUDY OF ETHYL-7-CHLORO-6-FLUORO-1-N-HEPTYL--1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (IV_d).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	0.8760-0.9103	4H	triplet	- CH_2(h,i)
2	1.2867-1.3364	6H	triplet	- CH_3(a,l)
3	1.3364-1.4357	2H	multiplet	- CH_2(k)
4	1.6370	2H	singlet	- CH_2(j)
5	1.8688-1.9042	2H	triplet	- CH_2(g)
6	4.1163-4.1535	2H	triplet	- CH_2(f)
7	4.3792-4.4324	2H	quartet	- CH_2(b)
8	7.4972-7.5113	1H	doublet	- Ar-H(d)
9	8.2545-8.2771	1H	doublet	- Ar-H(c)
10	8.4489	1H	singlet	-N-CH(e)
11	7.2641	-	-	$-CDCl_3$

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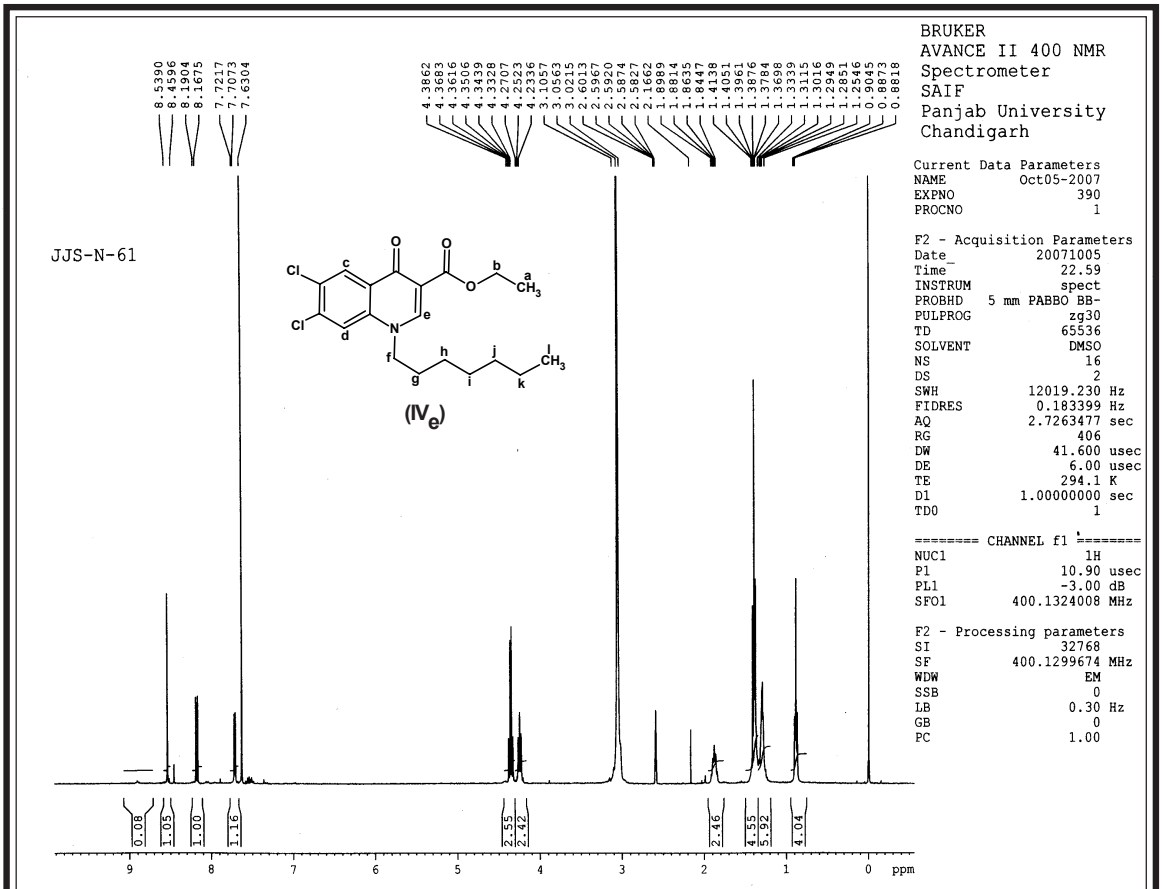
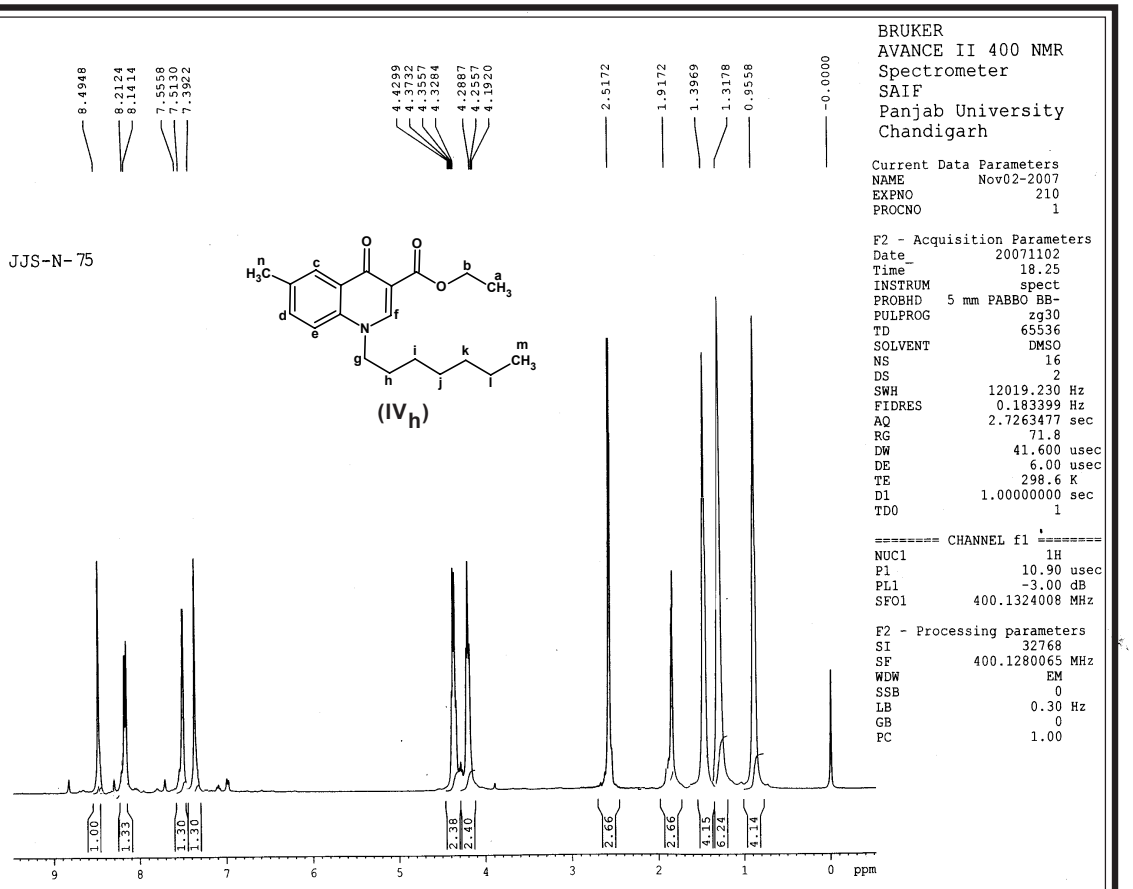
NMR SPECTRAL STUDY OF ETHYL-6,7-DICHLORO-1-N-HEPTYL-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (IV_e).



avtar_saifpu@yahoo.co.in

Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	0.8818-0.9045	4H	triplet	- $CH_{2(h,i)}$
2	1.2546-1.3339	6H	triplet	- $CH_{3(a,l)}$
3	1.3698-1.4138	4H	multiplet	- $CH_{2(j,k)}$
4	1.8447-1.8989	2H	singlet	- $CH_{2(g)}$
5	4.2336-4.2707	2H	triplet	- $CH_{2(f)}$
6	4.3328-4.3862	2H	triplet	- $CH_{2(e)}$
7	7.7073-7.7217	1H	quartet	- Ar-$H_{(c)}$
8	8.1675-8.1904	1H	doublet	- Ar-$H_{(d)}$
9	8.4596	1H	singlet	-N-$CH_{(e)}$
10	3.0215	-	-	-DMSO-d_6
11	7.6304	-	-	-$CDCl_3$

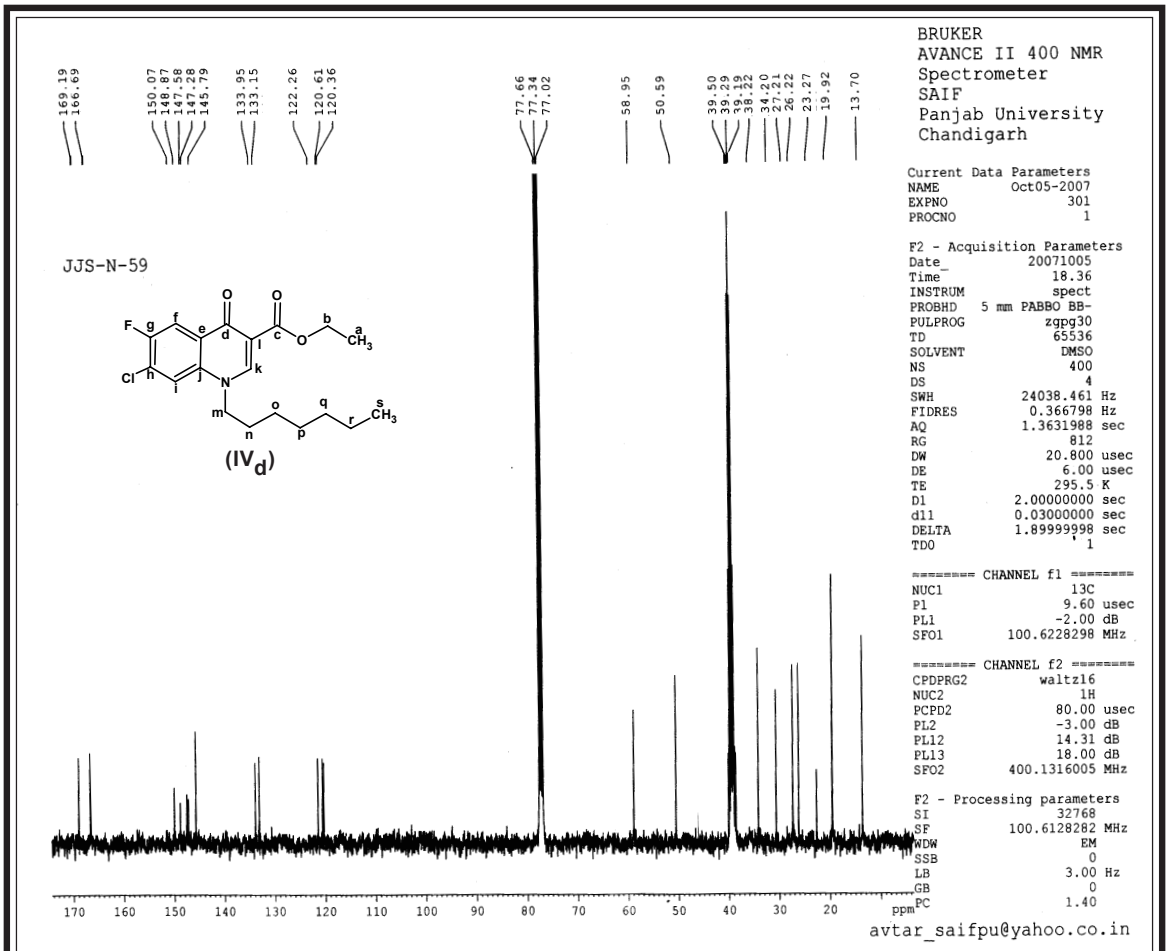
NMR SPECTRAL STUDY OF ETHYL-1-N-HEPTYL-6-METHYL-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (IV_h).



avtar_saifpu@yahoo.co.in

Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	0.9558	4H	singlet	- $CH_{2(i,j)}$
2	1.36178	6H	singlet	- $CH_{3(a,m)}$
3	1.3969	4H	singlet	- $CH_{2(k,l)}$
4	1.9172	2H	singlet	- $CH_{2(h)}$
5	2.5172	3H	singlet	- $CH_{2(n)}$
6	4.1920-4.2887	2H	triplet	-$CH_{2(g)}$
7	4.3284-4.4299	2H	quartet	-$CH_{2(b)}$
8	7.3922	1H	singlet	- Ar-$H_{(c)}$
9	7.5130-7.5558	1H	doublet	- Ar-$H_{(d)}$
10	8.1414-8.2124	1H	doublet	- Ar-$H_{(e)}$
11	8.4948	1H	singlet	-N-$CH_{(f)}$

^{13}CNMR SPECTRAL STUDY OF ETHYL-7-CHLORO-6-FLUORO-1-N-HEPTYL -1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (IV_d).



Serial No.	Signal Position (δ ppm)	Inference
1	13.70,19.92	- $\underline{C}H_3$(s,a)
2	23.27,2 66.22,27.21, 34.20, 38.22	- $\underline{C}H_2$(n to r)
3	50.59	- $\underline{C}H_2$(m)
4	58.95	-$C\underline{H}_2$(b)
5	120.38-150.7	- Ar-$\underline{C}$(e to l)
6	156.69	-$\underline{C}$ =O(d)
7	169.19	-$\underline{C}$ =O(c)

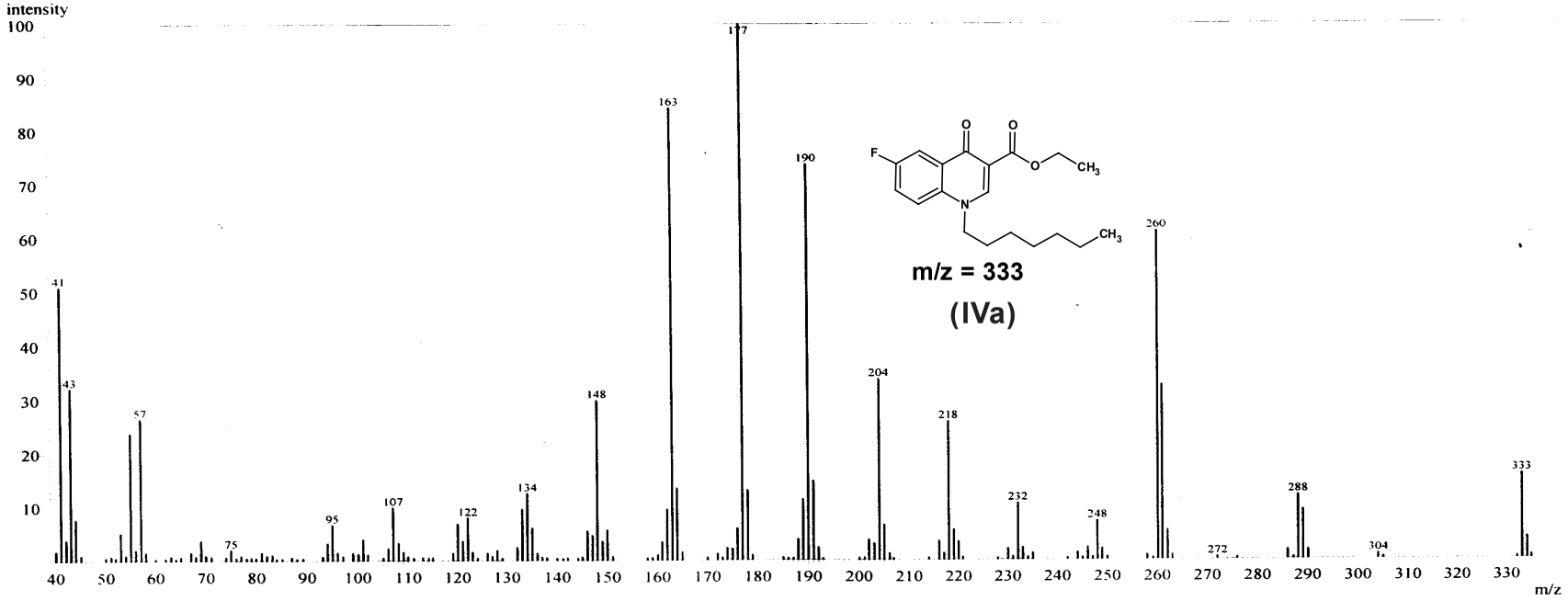
MASS SPECTRAL STUDY OF ETHYL-6-FLUORO-1-N-HEPTYL-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (IV_a).

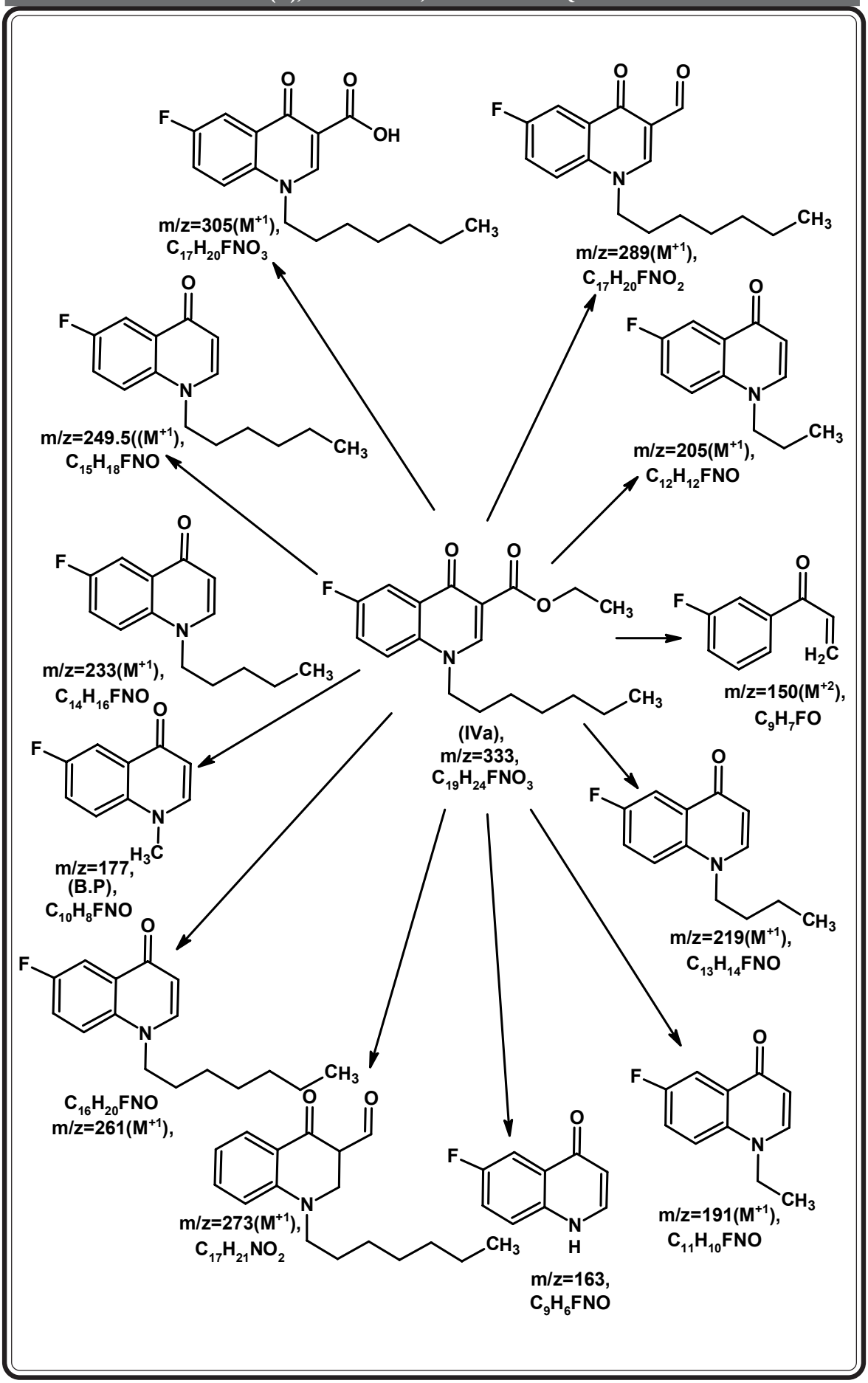
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 9/21/2007 4:08:39 PM
Sample Name	: JJS-MQ-19
Sample ID	: JJS-MQ-19
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-19.QGD
Method File	: C:\GCMSsolution\Data\Project1\D1.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\170907_01.qgt

Line#:1 R.Time:2.9(Scan#:313)
MassPeaks:162 BasePeak:177(399248)
RawMode:Single 2.9(313)
BG Mode:None
intensity




m/z=305(M+1),
C17H20FNO3
m/z=289(M+1),
C17H20FNO2
m/z=249.5((M+1),
C15H18FNO
m/z=205(M+1),
C12H12FNO
m/z=233(M+1),
C14H16FNO
(IVa),
m/z=333,
C19H24FNO3
m/z=150(M+2),
C9H7FO
m/z=177,
(B.P),
C10H8FNO
m/z=219(M+1),
C13H14FNO
C16H20FNO
m/z=261(M+1),
m/z=273(M+1),
C17H21NO2
m/z=163,
C9H6FNO
m/z=191(M+1),
C11H10FNO

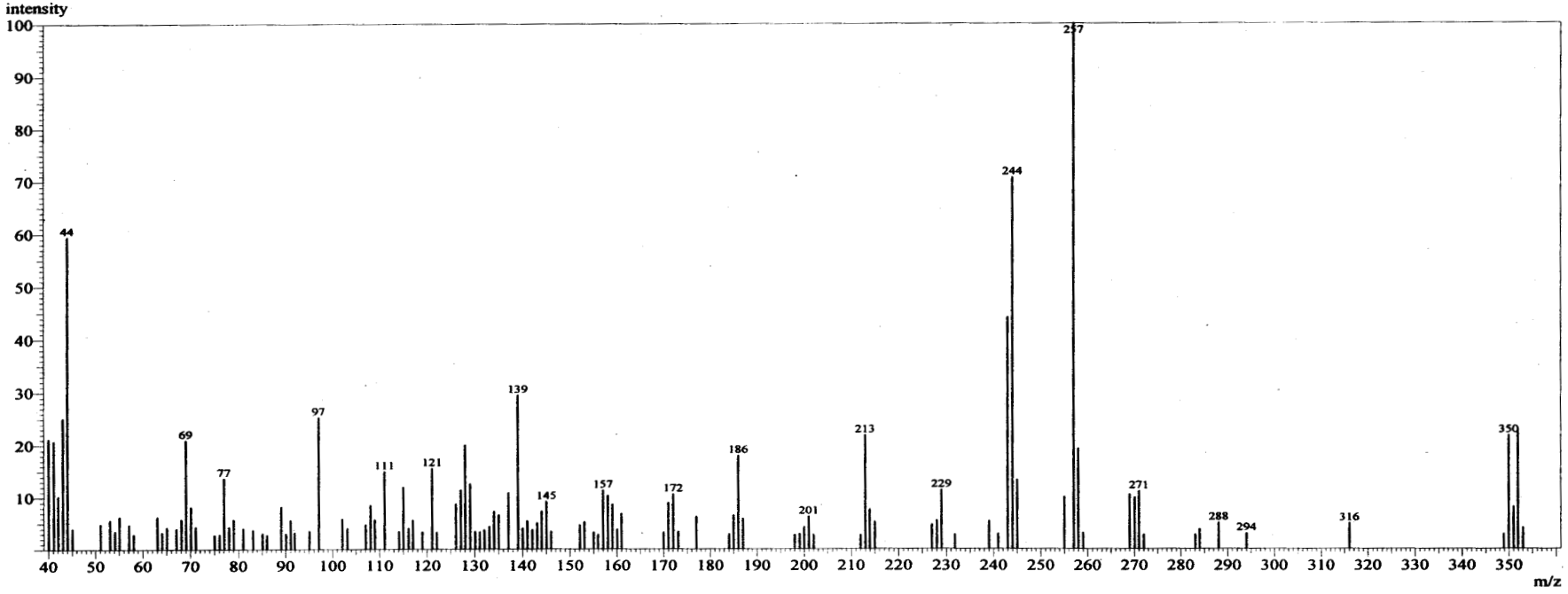
MASS SPECTRAL STUDY OF ETHYL-7CHLORO-1-N-HEPTYL-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (IV_b).

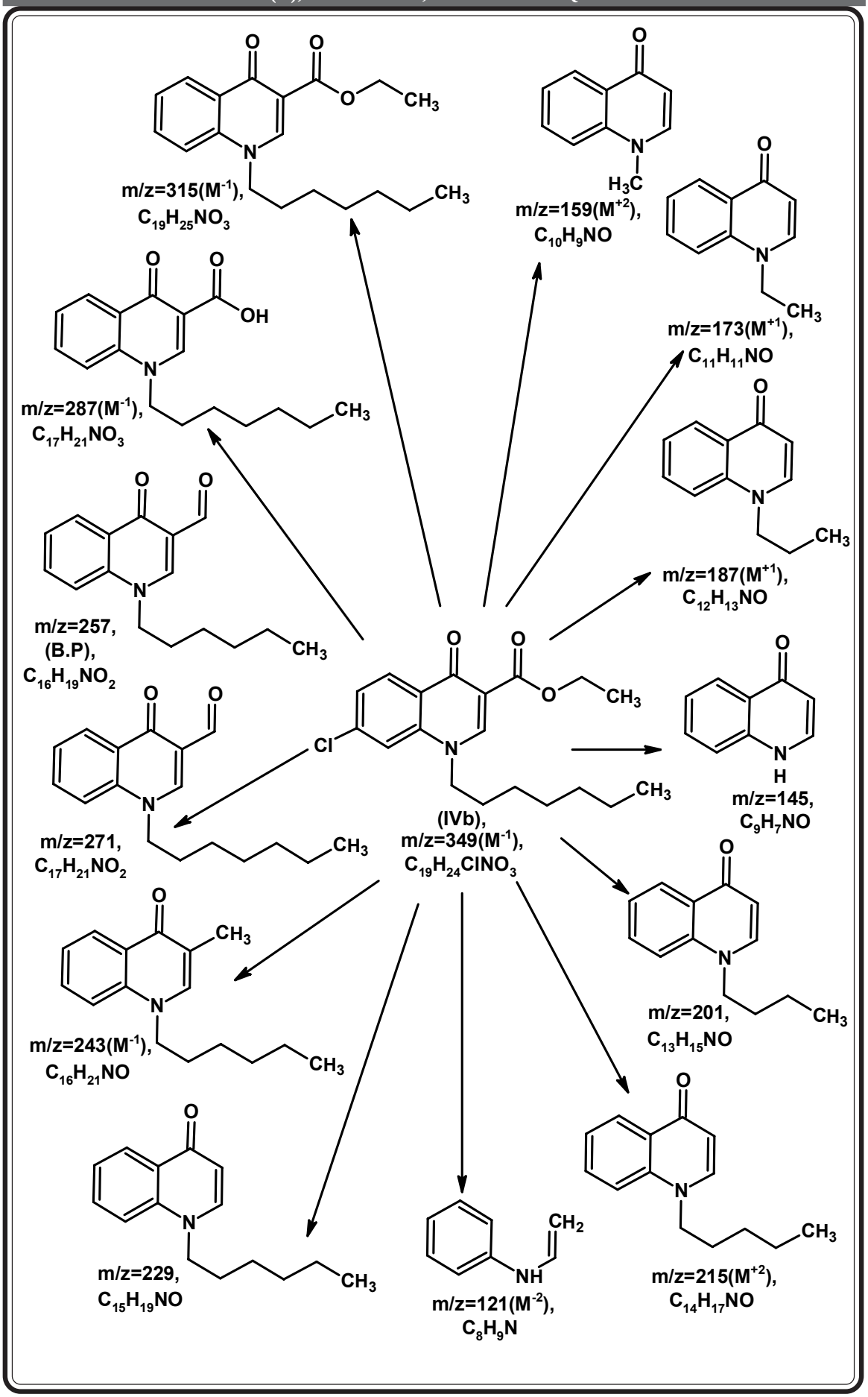
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 10/31/2006 2:28:16 PM
Sample Name	: JJS-M-63
Sample ID	: JJS-M-63
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-63.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:4.0(Scan#:449)
MassPeaks:121 BasePeak:257(37902)
RawMode:Single 4.0(449)
BG Mode:None
intensity




m/z=315(M-1), C19H25NO3
m/z=159(M+2), C10H9NO
m/z=173(M+1), C11H11NO
m/z=287(M-1), C17H21NO3
m/z=187(M+1), C12H13NO
m/z=257, (B.P), C16H19NO2
m/z=145, C9H7NO
m/z=271, C17H21NO2
(IVb), m/z=349(M-1), C19H24ClNO3
m/z=243(M-1), C16H21NO
m/z=201, C13H15NO
m/z=229, C15H19NO
m/z=121(M-2), C8H9N
m/z=215(M+2), C14H17NO

MASS SPECTRAL STUDY OF ETHYL-7-CHLORO-6-FLUORO-1-N-HEPTYL-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (IV_d).

SAURASHTRA UNIVERSITY - RAJKOT
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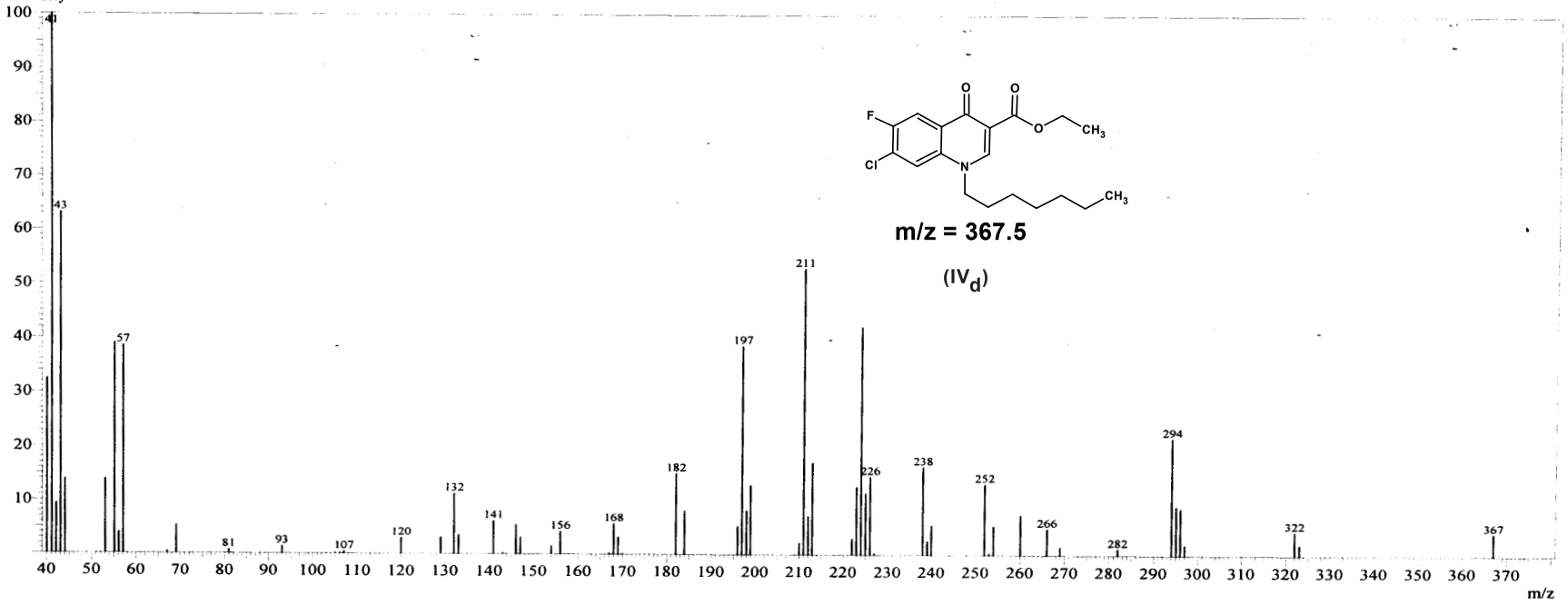
Sample Information

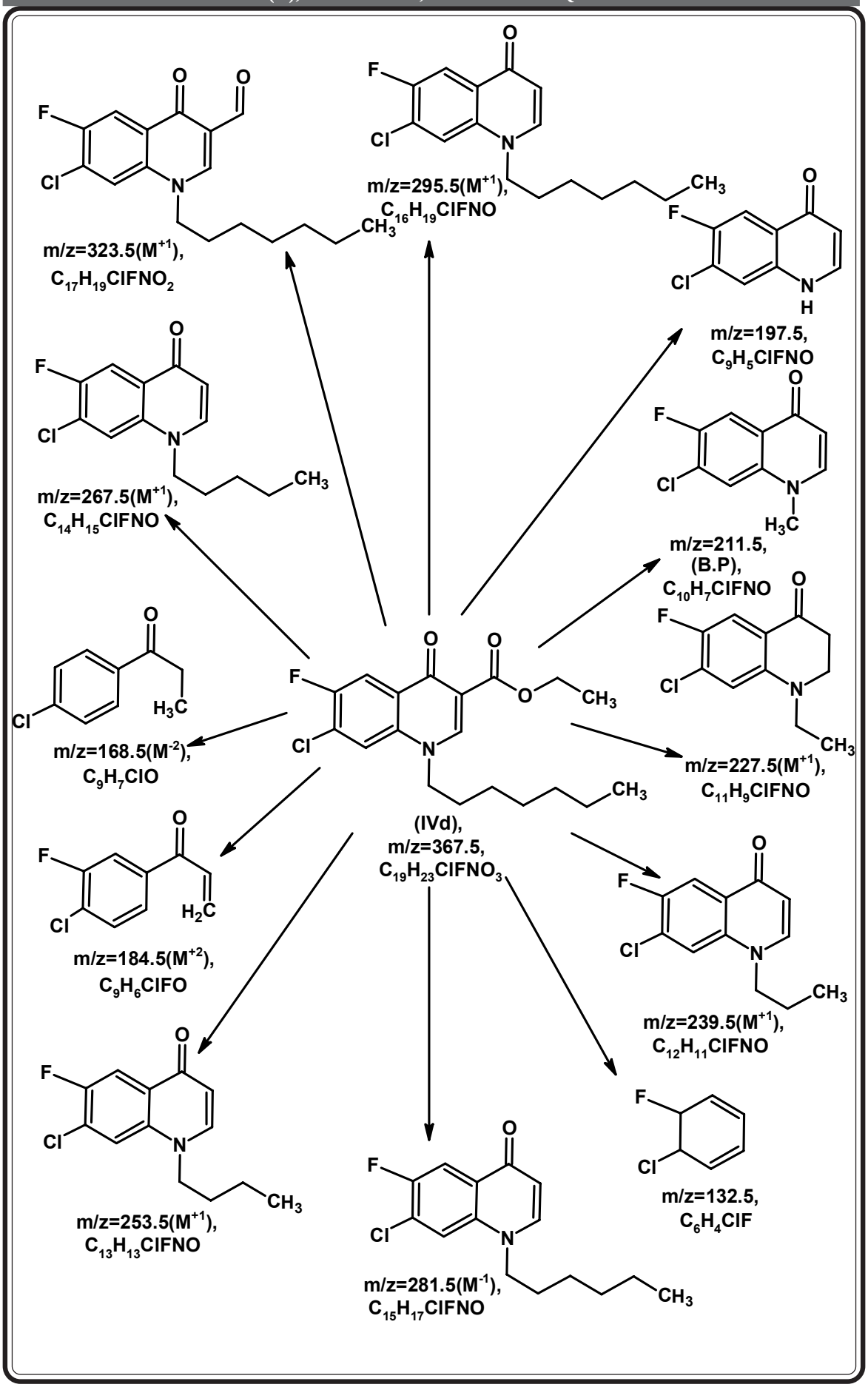
Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 4/18/2007 11:38:03 AM
Sample Name : JJS-MQ-7
Sample ID : JJS-MQ-7
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-7.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune121206.qgt

Line#:1 R.Time:1.0(Scan#:89)
MassPeaks:63 BasePeak:41(32176)
RawMode:Averaged 0.9-1.2(71-107)
BG Mode:None
intensity



m/z = 367.5

(IV_d)


m/z=323.5(M+1),
C17H19ClFNO2
m/z=295.5(M+1),
C16H19ClFNO
m/z=197.5,
C9H5ClFNO
m/z=267.5(M+1),
C14H15ClFNO
m/z=211.5,
(B.P),
C10H7ClFNO
m/z=168.5(M-2),
C9H7ClO
m/z=227.5(M+1),
C11H9ClFNO
(IVd),
m/z=367.5,
C19H23ClFNO3
m/z=184.5(M+2),
C9H6ClFO
m/z=239.5(M+1),
C12H11ClFNO
m/z=253.5(M+1),
C13H13ClFNO
m/z=281.5(M-1),
C15H17ClFNO
m/z=132.5,
C6H4ClF

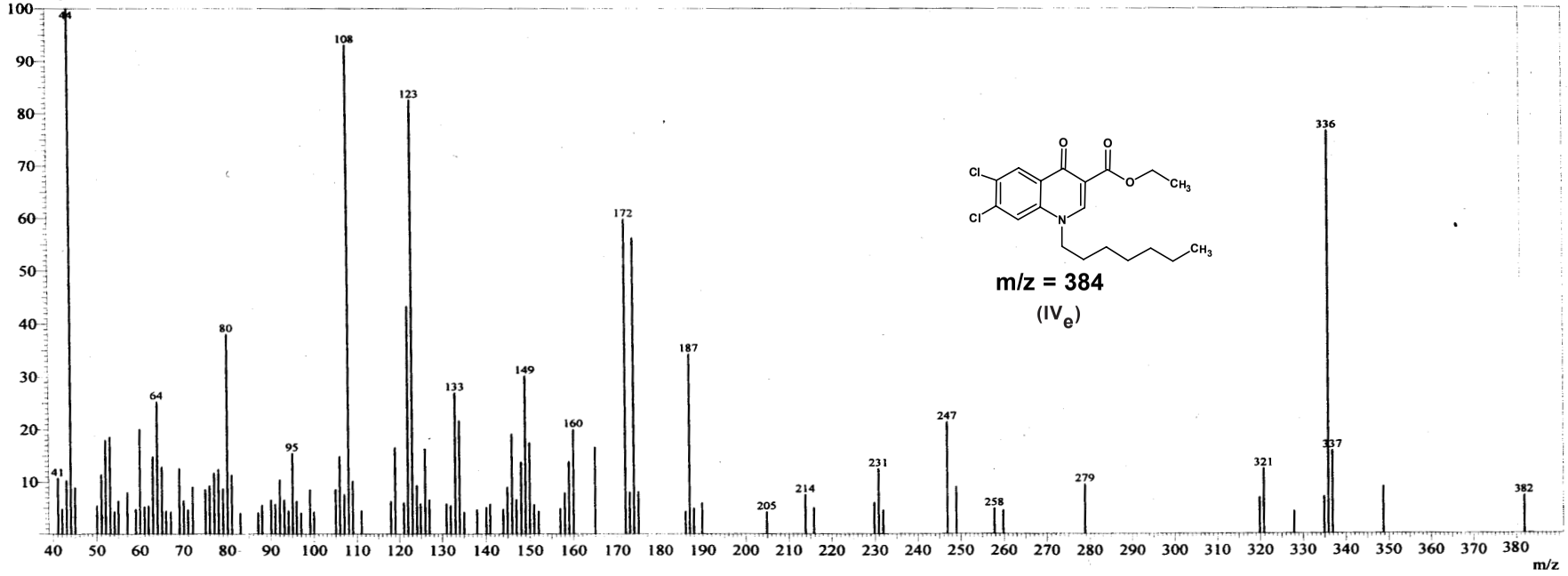
MASS SPECTRAL STUDY OF ETHYL-6,7-DICHLORO-1-N-HEPTYL-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (IV_e).

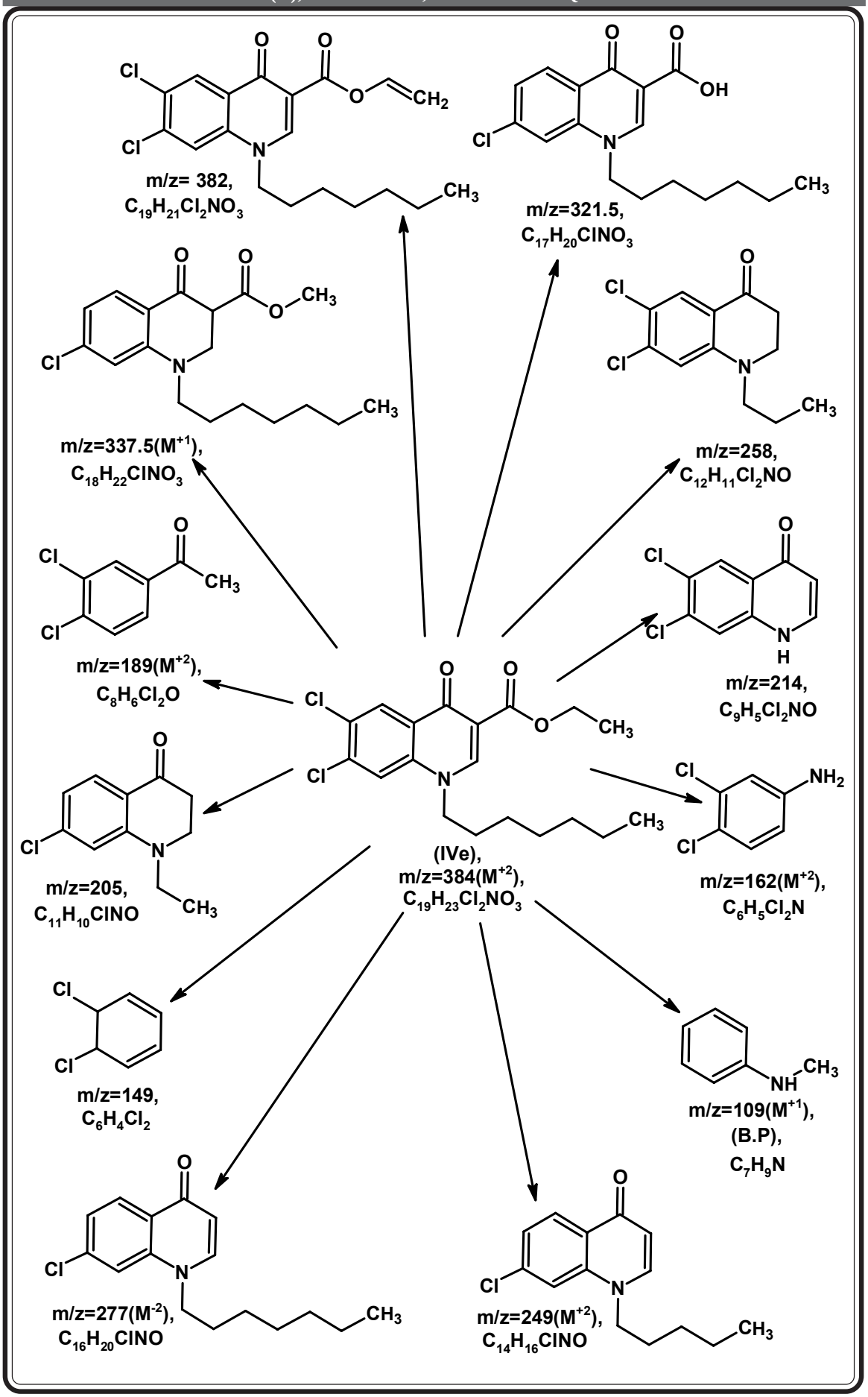
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 9/5/2006 5:06:54 PM
Sample Name : JJS-M-45
Sample ID : JJS-M-45
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-M-45.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:9.8(Scan#:1135)
MassPeaks:109 BasePeak:44(25548)
RawMode:Single 9.8(1135)
BG Mode:None
intensity




m/z= 382,
$C_{19}H_{21}Cl_2NO_3$
m/z=321.5,
$C_{17}H_{20}ClNO_3$
m/z=337.5(M^{+1}),
$C_{18}H_{22}ClNO_3$
m/z=258,
$C_{12}H_{11}Cl_2NO$
m/z=189(M^{+2}),
$C_8H_6Cl_2O$
m/z=214,
$C_9H_5Cl_2NO$
(IVe),
m/z=384(M^{+2}),
$C_{19}H_{23}Cl_2NO_3$
m/z=205,
$C_{11}H_{10}ClNO$
m/z=162(M^{+2}),
$C_6H_5Cl_2N$
m/z=149,
$C_6H_4Cl_2$
m/z=109(M^{+1}),
(B.P),
C_7H_9N
m/z=277(M^{-2}),
$C_{16}H_{20}ClNO$
m/z=249(M^{+2}),
$C_{14}H_{16}ClNO$

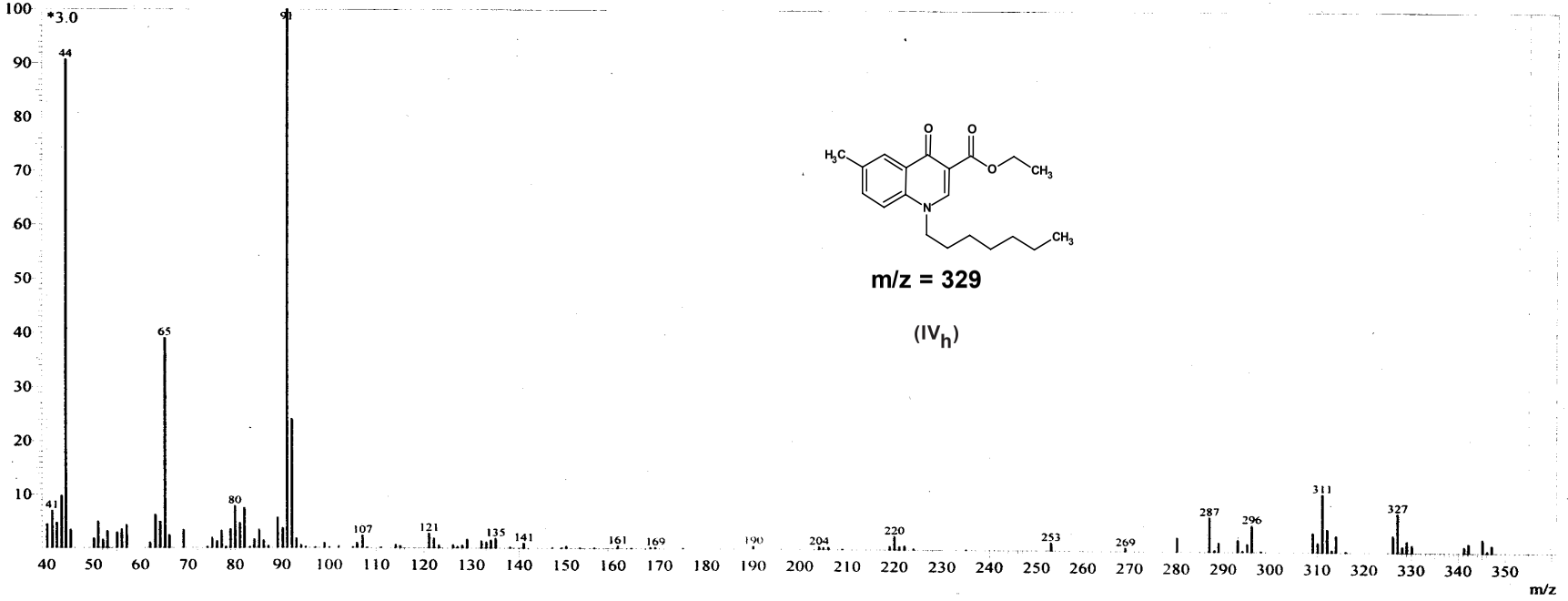
MASS SPECTRAL STUDY OF ETHYL-6-METHYL-1-N-HEPTYL-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOXYLATE (IV_h).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 7/13/2007 4:32:30 PM
Sample Name : JJS-MQ-11
Sample ID : JJS-MQ-11
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-11.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune190607.qgt

Line#:1 R.Time:11.5(Scan#:1342)
MassPeaks:113 BasePeak:91(132355)
RawMode:Averaged 9.9-12.1(1150-1417)
BG Mode:None
intensity



m/z = 329

(IV_h)

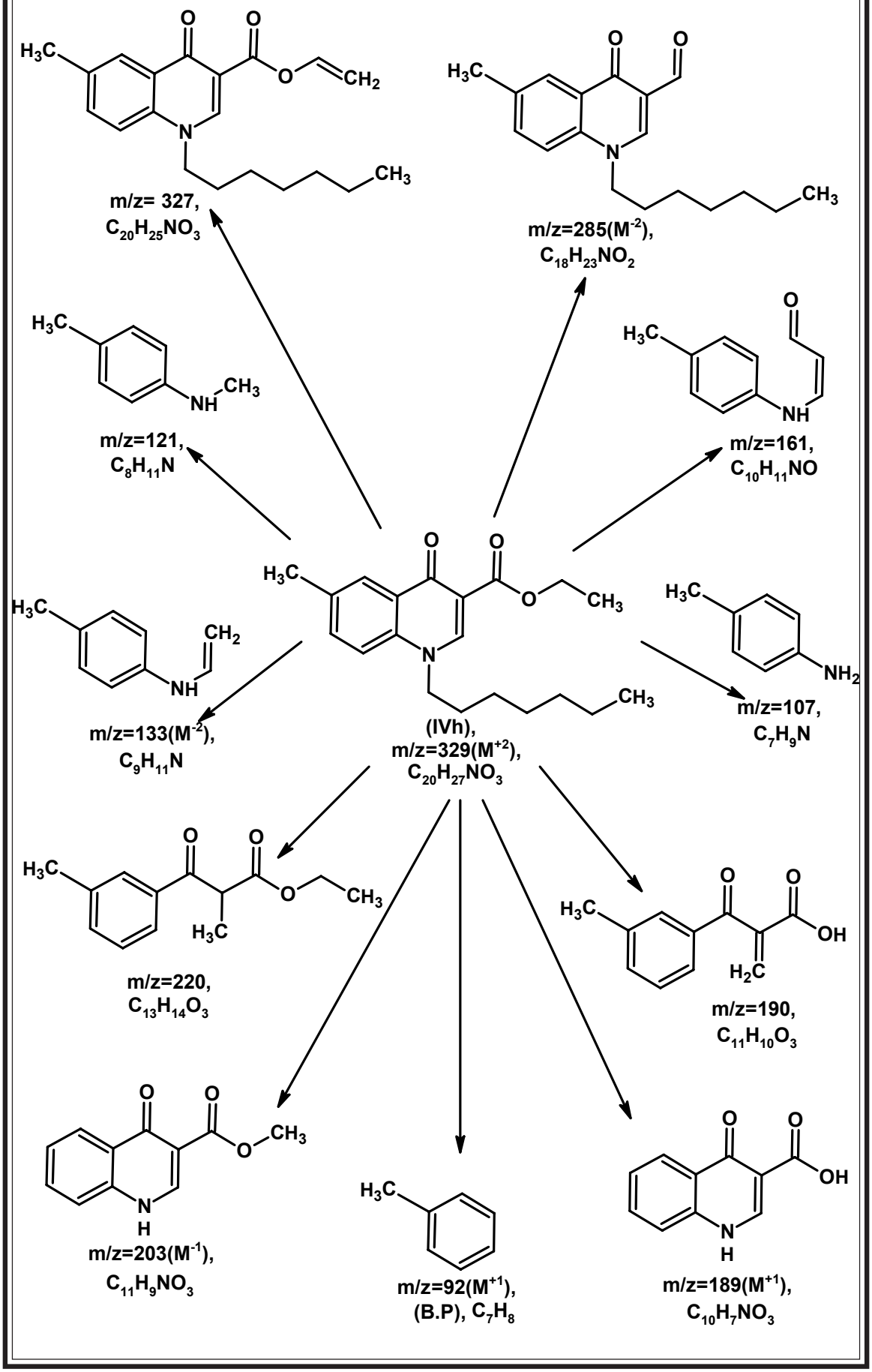

m/z= 327,
$C_{20}H_{25}NO_3$
m/z=285(M^{-2}),
$C_{18}H_{23}NO_2$
m/z=121,
$C_8H_{11}N$
m/z=161,
$C_{10}H_{11}NO$
m/z=133(M^{-2}),
$C_9H_{11}N$
(IVh),
m/z=329(M^{+2}),
$C_{20}H_{27}NO_3$
m/z=107,
C_7H_9N
m/z=220,
$C_{13}H_{14}O_3$
m/z=190,
$C_{11}H_{10}O_3$
m/z=203(M^{-1}),
$C_{11}H_9NO_3$
m/z=92(M^{+1}),
(B.P), C_7H_8
m/z=189(M^{+1}),
$C_{10}H_7NO_3$

TABLE NO. 4A : COMPARATIVE ANTIMICROBIAL ACTIVITY OF ETHYL-1-N-HEPTYL-SUBSTITUTED-1,4-DIHYDRO-QUINOLINE-4-ONE-3-CARBOXYLATES (IV_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) S. pyogens MTCC- 442					S. aureus MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
IV_a	6-F	-	9	10	11	14	-	9	11	14	16
IV_b	7-Cl	-	11	14	16	18	-	10	12	15	18
IV_c	6-Cl	-	12	13	15	19	-	9	11	13	17
IV_d	7-Cl-6-F	-	9	10	12	14	-	8	10	12	15
IV_e	6,7-$(Cl)_2$	-	10	12	15	18	-	7	8	10	13
IV_f	6-NO_2	-	9	10	12	17	-	8	8	9	12
IV_g	6-OCH_3	-	10	12	14	16	-	8	10	13	15
IV_h	6-CH_3	-	9	10	13	15	-	8	10	12	14
IV_i	7,8-$(CH_3)_2$	-	8	9	12	14	-	7	8	10	13
IV_j	-C_4H_4	-	9	10	12	14	-	9	10	11	14

Comparative activity of (IV_{a-j}) with known choosen standard drugs

Standard drug	Antibacterial activity									
				IV_b	IV_b IV_c IV_e				IV_b	IV_a IV_b IV_c
Amoxicilin	12	14	15	16	18	10	12	14	15	16
Chloramphenicol	14	15	18	19	24	14	17	20	21	24
Sparfloxacin	14	22	24	26	28	24	26	27	28	32
Levofloxacin	18	21	22	27	29	20	24	26	27	35

N.B.(-): No Activity

TABLE NO. 4B : COMPARATIVE ANTIMICROBIAL ACTIVITY OF ETHYL-1-N-HEPTYL-SUBSTITUTED-1,4-DIHYDRO-QUINOLINE-4-ONE-3-CARBOXYLATES (IV_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) B. Subtillis MTCC- 441					E.coli MTCC- 443				
		5	25	50	100	250	5	25	50	100	250
IV_a	6-F	-	10	12	14	17	-	7	8	10	11
IV_b	7-Cl	-	10	11	13	16	-	10	11	13	14
IV_c	6-Cl	-	9	10	12	15	-	8	9	10	10
IV_d	7-Cl-6-F	-	10	11	13	16	-	8	8	9	12
IV_e	6,7-$(Cl)_2$	-	11	12	15	18	-	8	7	8	9
IV_f	6-NO_2	-	9	11	13	15	-	6	9	10	10
IV_g	6-OCH_3	-	9	10	12	14	-	7	7	8	9
IV_h	6-CH_3	-	8	9	11	13	-	7	8	10	11
IV_i	7,8-$(CH_3)_2$	-	9	10	10	12	-	8	8	9	10
IV_j	-C_4H_4	-	8	9	11	14	-	6	10	11	13
Comparative activity of (IV_{a-j}) with known choosen standard drugs											
Standard drug		**Antibacterial activity**									
Amoxicilin		12	15	16	18	19	11	14	16	18	20
Chloramphenicol		18	22	24	26	27	17	20	23	25	26
Sparfloxacin		22	24	25	26	29	20	22	25	26	28
Levofloxacin		24	26	28	29	31	23	25	26	29	30

N.B.(-): No Activity

TABLE NO. 4C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF ETHYL-1-N-HEPTYL-SUBSTITUTED-1,4-DIHYDRO-QUINOLINE-4-ONE-3-CARBOXYLATES (IV_{a-j}). (Different Inhibition Concentration in µg/ml).

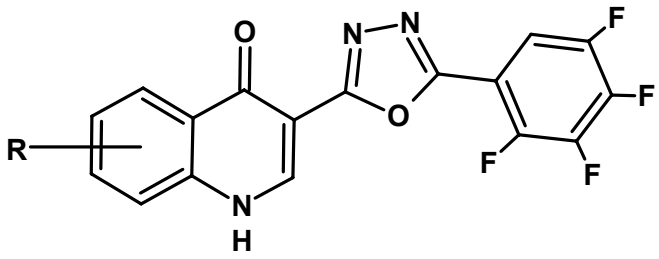
Compd No.	R	Antifungal activity (Zones of inhibition in m.m.) C. albicans MTCC- 227					A.niger MTCC- 282				
		5	25	50	100	250	5	25	50	100	250
IV_a	6-F	-	9	11	13	14	-	9	11	13	15
IV_b	7-Cl	-	7	9	10	13	-	8	9	10	12
IV_c	6-Cl	-	8	10	13	15	-	7	8	11	14
IV_d	7-Cl-6-F	-	10	11	12	16	-	9	12	14	17
IV_e	6,7-$(Cl)_2$	-	9	11	12	14	-	8	10	12	15
IV_f	6-NO_2	-	6	9	10	11	-	7	8	10	12
IV_g	6-OCH_3	-	7	9	10	13	-	8	10	11	14
IV_h	6-CH_3	-	8	10	11	12	-	7	8	9	11
IV_i	7,8-$(CH_3)_2$	-	7	9	10	13	-	8	10	11	14
IV_j	-C_4H_4	-	7	9	11	14	-	7	8	10	13
Comparative activity of (IV_{a-j}) with known choosen standard drugs											
Standard drug		Antifungal activity									
Griseofulvin		16	18	21	23	25	17	19	21	22	23
Fluconazole		14	16	18	21	22	15	17	18	20	21

N.B.(-): No Activity

SECTION - V

PREPARATION AND BIOLOGICAL EVALUATION OF SUBSTITUTED-3-[5'-(2'',3'',4'',5''-TETRAFLUOROPHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONES.

Keeping in view, various properties[34-85] of **4-quinolones** and in order to have highly potent therapeutic agents, the synthesis of **Substituted-3-[5'-(2'',3'',4'',5''-tetrafluorophenyl)-1',3',4'-oxadiazol-2'-yl]-substituted quinolone-4(1H)-ones(Va-j)** have been accomplished by the cyclocondensation of **2,3,4,5-tetrafluoro benzoic acid** with different **substituted-1,4-dihydroquinoline-4-one-3-carbo hydrazides** which was prepared by the action of **hydrazine hydrate** on **ethyl-substituted-1,4-dihydroquinoline-4-one-3-carboxylates (IIa-j).**



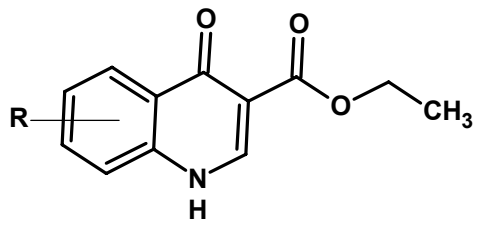
(Va-j)

R=Substituted phenyl

The constitution of the products **(Va-j)** have been delineated by **elemental analyses, IR, PMR** and **Mass** spectral data.

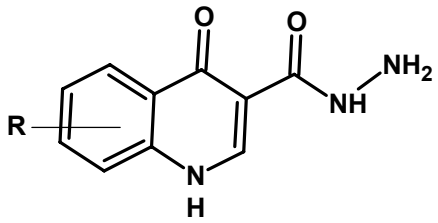
The products **(Va-j)** were assayed for their ***in vitro*** biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** , ***S. aureus MTCC-96*** *and* ***B. subtillis MTCC-441*** (Gram positive) and ***E. coli MTCC-443*** **(Gram negative)** bacterial strain and antifungal activity towards **Aspergillus niger MTCC-282** and **Candida albicans MTCC-227** at different concentrations i.e.: 0(control) 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds **(Va-j)** were compared with standard drugs,viz.,**Amoxicillin, Chloramphenicol, Sparfloxacin, Levofloxacin** (antibacterial)**, Griseofluvin, Fluconazole** (antifungal)**.**

REACTION SCHEME



(IIa-j)
R= substituted phenyl

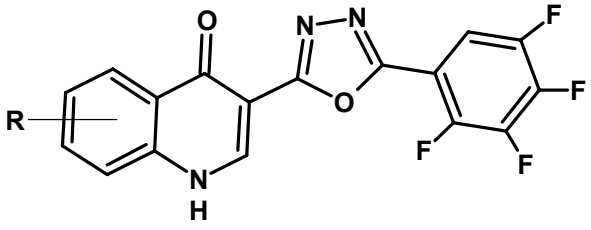
NH_2-NH_2 $2H_2O$



(5a-j)
R= substituted phenyl

Tetra fluoro-
benzoic acid

$POCl_3$



(Va-j)
R= substituted phenyl

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF SUBSTITUTED-3-[5'-(2'',3'',4'',5''-TETRAFLUOROPHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONES.

(A) Preparation of Diethyl-(3-chloro-4-fluoro amino phenyl)-amino-methylene malonate (I_d).

For preparation, refer Part-1, Section-I, **page No.30.**

(B) Preparation of Ethyl-7-chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carboxylate (II_d).

For preparation, refer Part-1, Section-II, **page No.58.**

(C) Preparation of 7-Chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carbohydrazide (5_d).

A mixture of Ethyl-7-chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carboxylate **(II_d)** (2.69 gm,0.01M) and hydrazine hydrate 80% (4.0 ml, 0.1 M) in ethanol (15 ml) and dimethyl formamide (10ml) was heated under reflux for 16 hrs.The excess of the solvent was removed by distillation and reaction mass was poured in to ice-cold water. The resulting product was filtered, dried and crystallized from dimethyl formamide. Yield : 74%, M.P. : 233 ^{O}C, (Required :C,46.98 %; H,2.76 %; N,16.44 % for $C_{10}H_7N_3O_2ClF$, Found : C, 46.93 %; H,2.72 %; N,16.39 %)**.**

TLC solvent system R_{f_1} : Ethyl acetate : Hexane(5.5 : 4.5) = 0.43**.**
TLC solvent system R_{f_2} : Methanol : Toluene(4.0 : 6.0) = 0.51 **.**

Similarly, other compounds **(5a-j)** were synthesized. The physical data are recorded in **Table No.5**.

(D) Preparation of 7-chloro-6-fluoro-3-[5'-(2'',3'',4'',5''-tetra fluoro-phenyl)-1',3',4'-oxadiazol-2'-yl]- quinolone-4(1H)-one (Vd).

A mixture of 7-chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carbohydrazide **(5_d)** (2.55 gm, 0.01 M) and 2,3,4,5- tetrafluoro benzoic acid (1.94 gm, 0.01M) in phosphorus oxychloride (15 ml) was heated under reflux for 6 to 7 hrs. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured on to crushed ice. The reaction mixture was neutralized with solution of 10% sodium bicarbonate. The resulting solid mass (brown red color precipitates) was filtered, washed with water, dried and crystallized from ethanol. Yield : 67 %, M.P. : 134 ^{O}C, (Required : C, 49.3 %; H, 1.22 %; N,10.16 % for $C_{17}H_5N_3O_2ClF_5$, Found : C, 49.0 %; H, 1.18 %; N,10.12 %).

TLC solvent system R_{f_1}: Ethyl acetate :Hexane(2.0 : 8.0) = 0.54**.**
TLC solvent system R_{f_2}: Methanol :Toluene(0.5 : 9.5) = 0.59**.**

Similarly, other compounds **(Va-j)** were synthesized. The physical data are recorded in **Table No. 5A**.

(E) Antimicrobial activity of Substituted-3-[5'-(2'',3'',4'',5''-tetra - fluoro phenyl)-1',3',4'-oxadiazol-2'-yl]-quinolone-4(1H)-ones (Va-j).

Antimicrobial activity testing was carried out as described in Part-1(A), Section-I, page No. 30-31. The MIC values of test solution are recorded in **Table No. 5B, 5C** and **5D.**

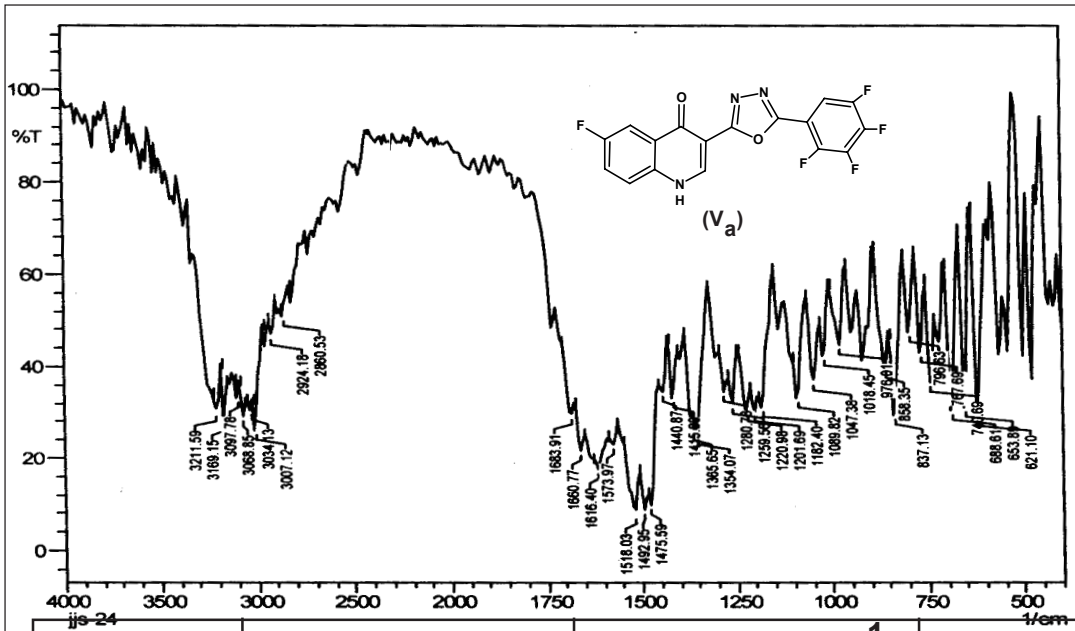
TABLE NO.5 : PHYSICAL CONSTANTS OF SUBSTITUTED-1,4-DIHYDROQUINOLINE-4-ONE-3-CARBOHY DRAZIDES (5_{a-j}).

Comp. No.	R	Molecular Formula	M.W.	M.P. ^{o}C	Yield %	R_f Value		% of Nitrogen Calcd. / Found
						R_{f_1}	R_{f_2}	
1	2	3	4	5	6	7		8
5_a	6-F	$C_{10}H_8N_3O_2F$	221.0	212^{o}	71	0.49	0.48	19.00 / 18.96
5_b	7-Cl	$C_{10}H_8N_3O_2Cl$	237.5	218^{o}	68	0.42	0.47	17.68 / 17.63
5_c	6-Cl	$C_{10}H_8N_3O_2Cl$	237.5	231^{o}	64	0.47	0.43	17.68/ 17.64
5_d	7-Cl-6-F	$C_{10}H_7N_3O_2ClF$	255.5	243^{o}	74	0.43	0.51	16.44 / 16.38
5_e	6,7-$(Cl)_2$	$C_{10}H_7N_3O_2Cl_2$	272.0	219^{o}	69	0.48	0.51	15.44 / 15.40
5_f	6-NO_2	$C_{10}H_8N_4O_4$	248.0	243^{o}	67	0.51	0.53	22.58 / 22.51
5_g	6-OCH_3	$C_{11}H_{11}N_3O_3$	233.0	198^{o}	62	0.49	0.48	18.03 / 17.97
5_h	6-CH_3	$C_{11}H_{11}N_3O_2$	217.0	241^{o}	64	0.53	0.49	19.35 / 19.30
5_i	7,8-$(CH_3)_2$	$C_{12}H_{13}N_3O_2$	231.0	229^{o}	69	0.59	0.47	18.18 / 18.13
5_j	-	$C_{14}H_{11}N_3O_2$	253.0	248^{o}	68	0.51	0.48	16.60 / 16.53

TABLE NO. 5A : PHYSICAL CONSTANTS OF SUBSTITUTED-3-[5'-(2'',3'',4'',5''-TETRAFLUOROPHENYL)-1',3',4'-OXADIAZOL-2'-YL]- QUINOLONE-4(1H)-ONES (V_{a-j}).

Comp. No.	R	Molecular Formula	M.W.	M.P. ^{o}C	Yield %	R_f Value		% of Nitrogen Calcd. / Found
1	2	3	4	5	6	R_{f_1}	R_{f_2} 7	8
V_a	6-F	$C_{17}H_6N_3O_2F_5$	379.0	198^{o}	63	0.51	0.42	11.08 / 11.03
V_b	7-Cl	$C_{17}H_6N_3O_2ClF_4$	395.5	172^{o}	71	0.48	0.47	10.62 / 10.55
V_c	6-Cl	$C_{17}H_6N_3O_2ClF_4$	395.5	167^{o}	72	0.49	0.51	10.62/ 10.57
V_d	7-Cl-6-F	$C_{17}H_5N_3O_2ClF_5$	413.5	134^{o}	67	0.53	0.52	10.16 / 10.10
V_e	6,7-$(Cl)_2$	$C_{17}H_5N_3O_2Cl_2F_4$	430.0	174^{o}	68	0.47	0.46	9.77 / 9.72
V_f	6-NO_2	$C_{17}H_6N_4O_4F_4$	406.0	129^{o}	62	0.43	0.41	13.79 / 13.73
V_g	6-OCH_3	$C_{18}H_9N_3O_3F_4$	391.0	149^{o}	60	0.53	0.52	10.74 / 10.70
V_h	6-CH_3	$C_{18}H_9N_3O_2F_4$	375.0	151^{o}	64	0.49	0.47	11.20 / 11.13
V_i	7,8-$(CH_3)_2$	$C_{19}H_{11}N_3O_2F_4$	389.0	157^{o}	66	0.49	0.43	10.80 / 10.74
V_j	-	$C_{21}H_9N_3O_2F_4$	411.0	157^{o}	67	0.51	0.48	10.22 / 10.15

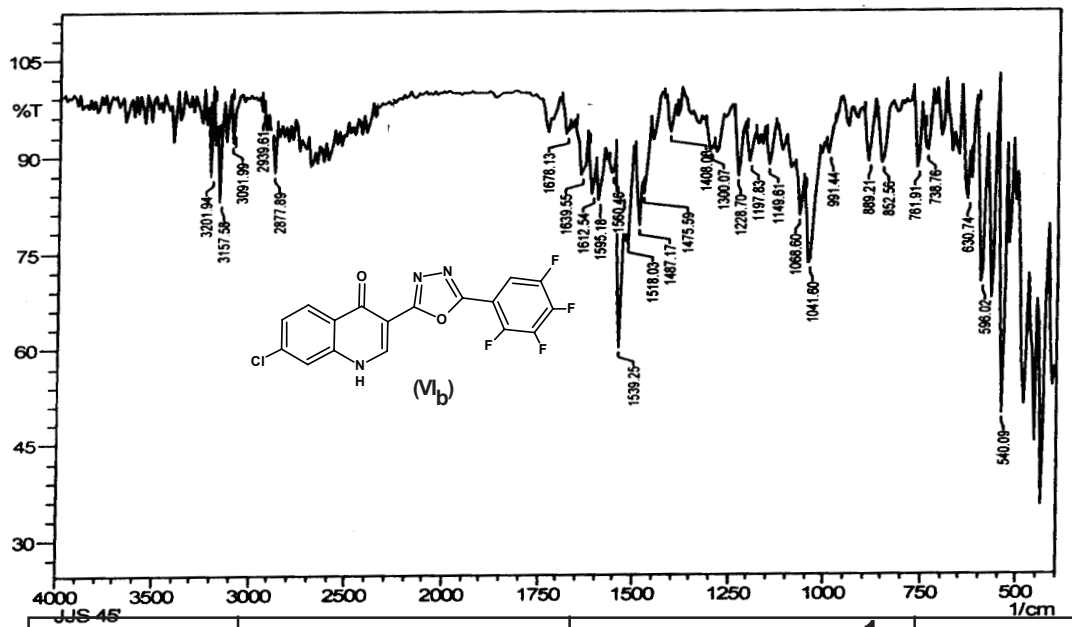
IR SPECTRAL STUDY OF 6-FLUORO-3-[5'-(2'',3'',4'',5''-TETRA FLUORO-PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONE (V_a).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2924.1	2975 - 2850	96
	C-H (sym. str., m)	2860.5	2900 - 2800	96
	C-H (asym. def., m)	1475.5	1470 - 1435	96
	C-H (sym. def., m)	1354.0	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3034.1	3080 - 3010	97
	C=C & C-C (str., v)	1573.9	1600 - 1450	97
	C-H (i.p. def., m)	1089.2	1150 - 1050	97
	C-H (o.o.p. def., m)	837.2	825 - 800	97
	C-N (str., v)	1280.7	1340 - 1250	97
	C=N (str., v)	1660.7	1690-1650	97
	N-N (def., v)	1201.6	1220 - 1020	97
4-Quinolone Moiety	N-H (str., b)	3211-3007	3400 - 3000	98
	N-H (def., s,m)	1616.4	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1683.9	1690 - 1640	98
Ether	C-O-C (asym.str., s)	1220.9	1275 - 1200	98
	C-O-C (sym. str., s)	1018.4	1075 - 1000	98
Halogen Subtitution	C-F (str., b)	1365.5-1089.8	1400 - 1080	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

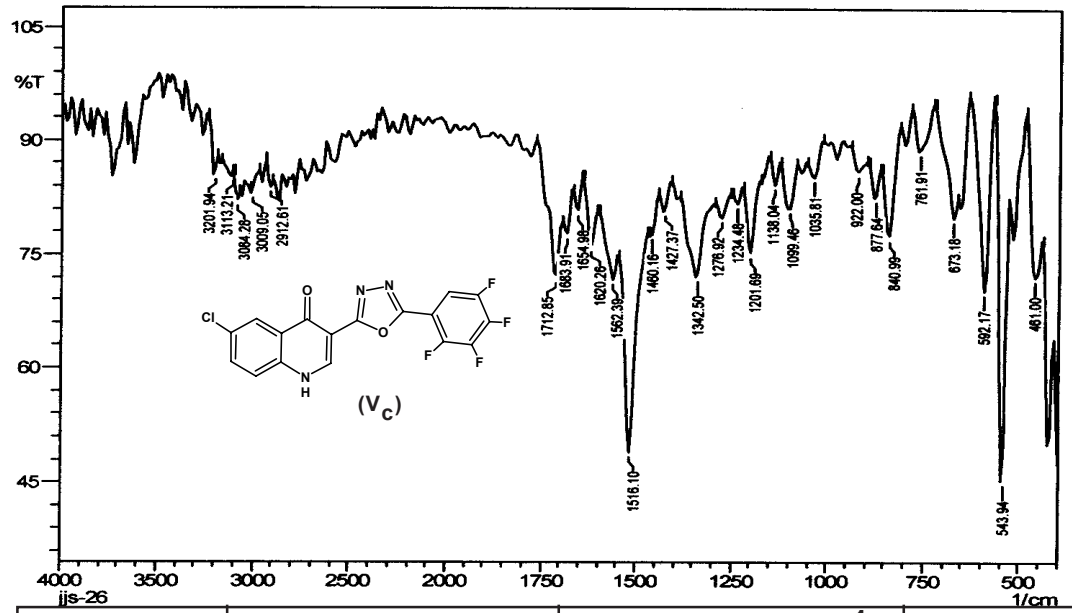
IR SPECTRAL STUDY OF 7-CHLORO-3-[5'-(2'',3'',4'',5''-TETRA FLUORO-PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONE (V_b).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2939.6	2975 - 2850	96
	C-H (sym. str., m)	2872.8	2900 - 2800	96
	C-H (asym. def., m)	1487.1	1470 - 1435	96
	C-H (sym. def., m)	1300.0	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3091.9	3080 - 3010	97
	C=C & C-C (str., v)	1595.1	1600 - 1450	97
	C-H (i.p. def., m)	1149.6	1150 - 1050	97
	C-H (o.o.p. def., m)	852.5	825 - 800	97
	C-N (str., v)	1300.7	1340 - 1250	97
	C=N (str., v)	1639.5	1690-1650	97
	N-N (def., v)	1068.6	1220 - 1020	97
4-Quinolone Moiety	N-H (str., b)	3201.9-3091.9	3400 - 3000	98
	N-H (def., s,m)	1639.5	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1678.1	1690 - 1640	98
Ether	C-O-C (asym.str., s)	1228.7	1275 - 1200	98
	C-O-C (sym. str., s)	1041.6	1075 - 1000	98
Halogen Subtitution	C-F (str., b)	1197.8	1400 - 1080	99
	C-Cl(sym. str, b)	761-630	800-600	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

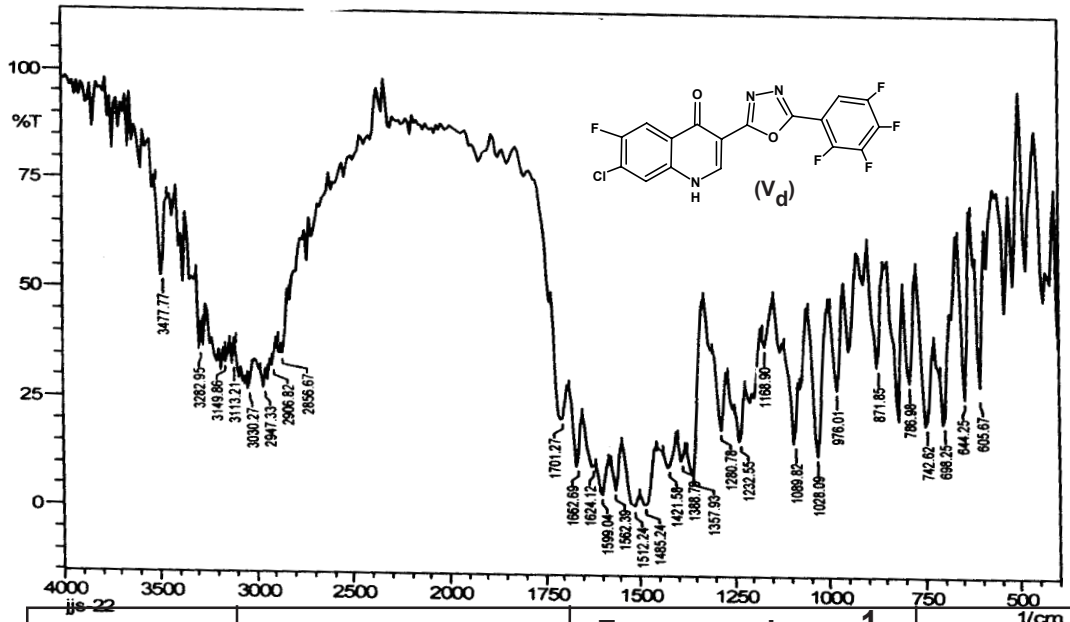
IR SPECTRAL STUDY OF 6-CHLORO-3-[5'-(2'',3'',4'',5''-TETRA FLUORO-PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONE (V_C).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2912.6	2975 - 2850	96
	C-H (sym. str., m)	2809.5	2900 - 2800	96
	C-H (asym. def., m)	1427.3	1470 - 1435	96
	C-H (sym. def., m)	1342.5	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3009.0	3080 - 3010	97
	C=C & C-C (str., v)	1562.3	1600 - 1450	97
	C-H (i.p. def., m)	1099.2	1150 - 1050	97
	C-H (o.o.p. def., m)	840.9	825 - 800	97
	C-N (str., v)	1272.9	1340 - 1250	97
	C=N (str., v)	1620.2	1690-1650	97
	N-N (def., v)	1201.6	1220 - 1020	97
4-Quinolone Moiety	N-H (str., b)	3201.9-3009.0	3400 - 3000	98
	N-H (def., s,m)	1562.3	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1712.8	1710 - 1650	98
Ether	C-O-C (asym.str., s)	1234.4	1275 - 1200	98
	C-O-C (sym. str., s)	1035.8	1075 - 1000	98
Halogen Subtitution	C-F (str., b)	1342.5-1099.4	1400 - 1080	99
	C-Cl(sym. str, b)	761-673	800-600	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

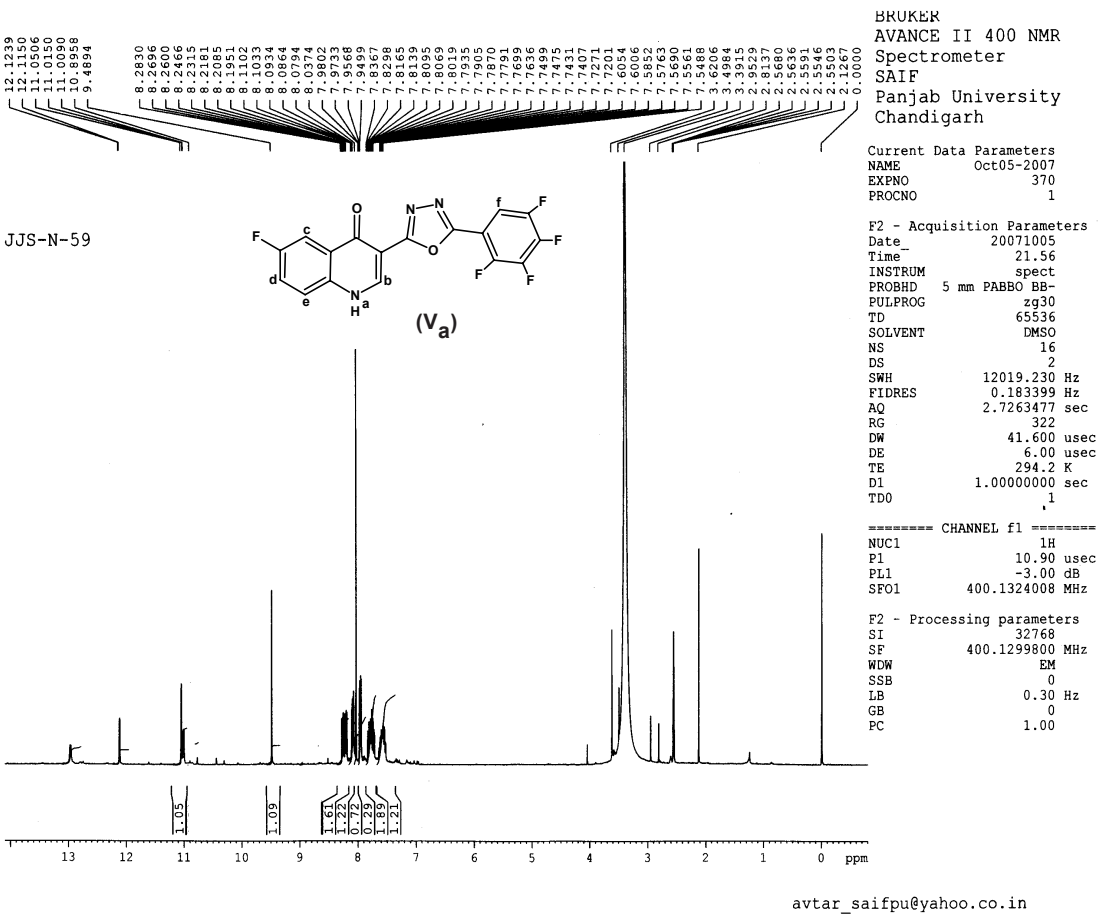
IR SPECTRAL STUDY OF 6-FLUORO-7-CHLORO-3-[5'-(2'',3'',4'',5''-TETRA FLUORO PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONE (V_d).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2947.3	2975 - 2850	96
	C-H (sym. str., m)	2856.6	2900 - 2800	96
	C-H (asym. def., m)	1421.5	1470 - 1435	96
	C-H (sym. def., m)	1357.9	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3030.2	3080 - 3010	97
	C=C & C-C (str., v)	1599.0	1600 - 1450	97
	C-H (i.p. def., m)	1089.8	1150 - 1050	97
	C-H (o.o.p. def., m)	810.2	825 - 800	97
	C-N (str., v)	1357.9	1340 - 1250	97
	C=N (str., v)	1662.6	1690-1650	97
	N-N (def., v)	1168.9	1220 - 1020	97
4-Quinolone Moiety	N-H (str., b)	3282.9-3030.2	3400 - 3000	98
	N-H (def., s,m)	1624.1	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1701.2	1710 - 1650	98
Ether	C-O-C (asym.str., s)	1232.5	1275 - 1200	98
	C-O-C (sym. str., s)	1028.0	1075 - 1000	98
Halogen Subtitution	C-F (str., b)	1388.7-1089.8	1400 - 1080	99
	C-Cl(sym. str, m)	786-605	800-600	99

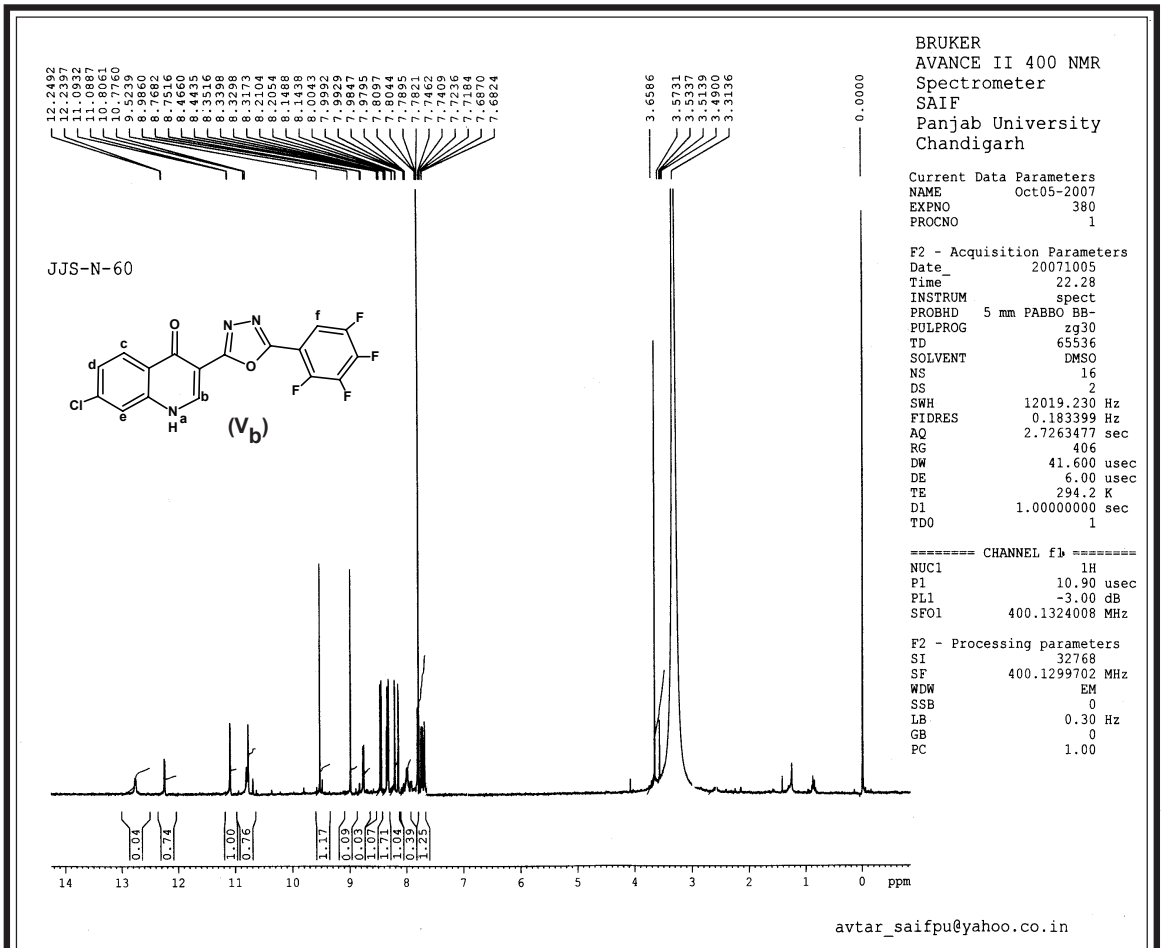
* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

NMR SPECTRAL STUDY OF 6-FLUORO-3-[5'-(2'',3'',4'',5''-TETRA-FLUORO PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONE-(V_a).



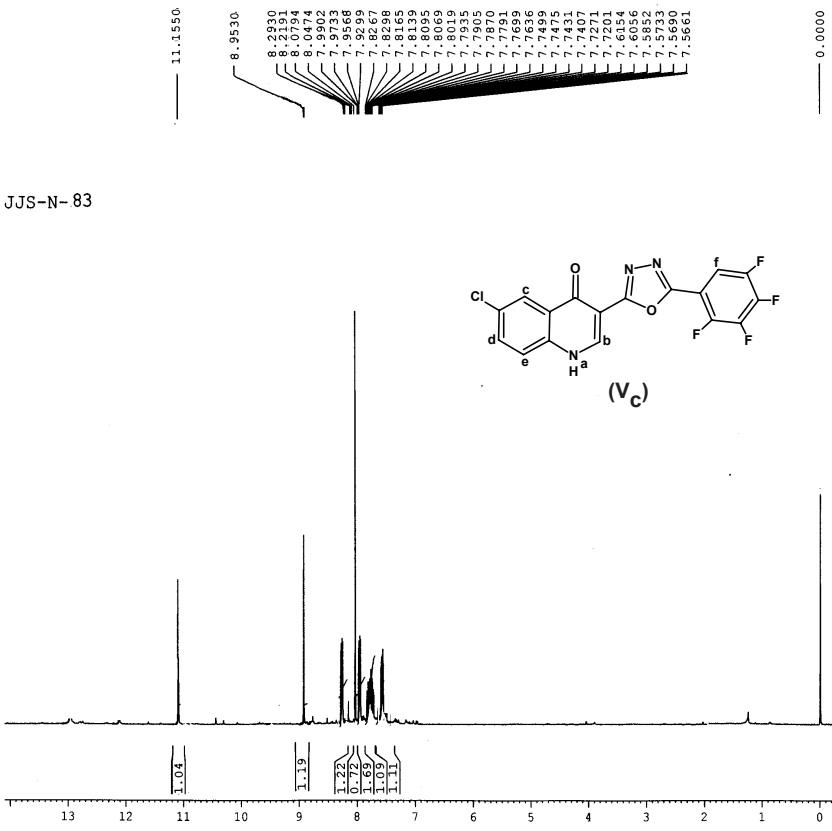
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	7.5488-7.5852	1H	multiplet	-Ar-H(c)
2	7.6006-7.8367	1H	multiplet	-Ar-H(d)
3	7.9499-8.2181	1H	multiplet	-Ar-H(f)
4	8.2315-8.2830	1H	multiplet	-Ar-H(e)
5	9.4894	1H	singlet	-NH-CH(b)
6	11.009-11.050	1H	doublet	-NH(a)
7	2.8137-3.6206	-	-	-DMSO-d_6

NMR SPECTRAL STUDY OF 7-CHLORO-3-[5'-(2'',3'',4'',5''-TETRA-FLUORO PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONE (V_b).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	7.6824-7.7462	1H	multiplet	-Ar-H(f)
2	7.9795-8.0043	1H	multiplet	-Ar-H(c)
3	8.1438-8.3516	1H	multiplet	-Ar-H(d)
4	8.4435-8.7682	1H	multiplet	-Ar-H(e)
5	9.5239	1H	singlet	-NH-CH(b)
6	10.776-11.093	1H	doublet	-NH(a)
7	3.3136-3.6586	-	-	-DMSO-d_6

NMR SPECTRAL STUDY OF 6-CHLORO-3-[5'-(2'',3'',4'',5''-TETRA-FLUORO PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONE (V_c).



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters
NAME Oct07-2007
EXPNO 370
PROCNO 1

F2 - Acquisition Parameters
Date_ 20071007
Time 21.06
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 16
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 322
DW 41.600 usec
DE 6.00 usec
TE 294.2 K
D1 1.00000000 sec
TD0 1

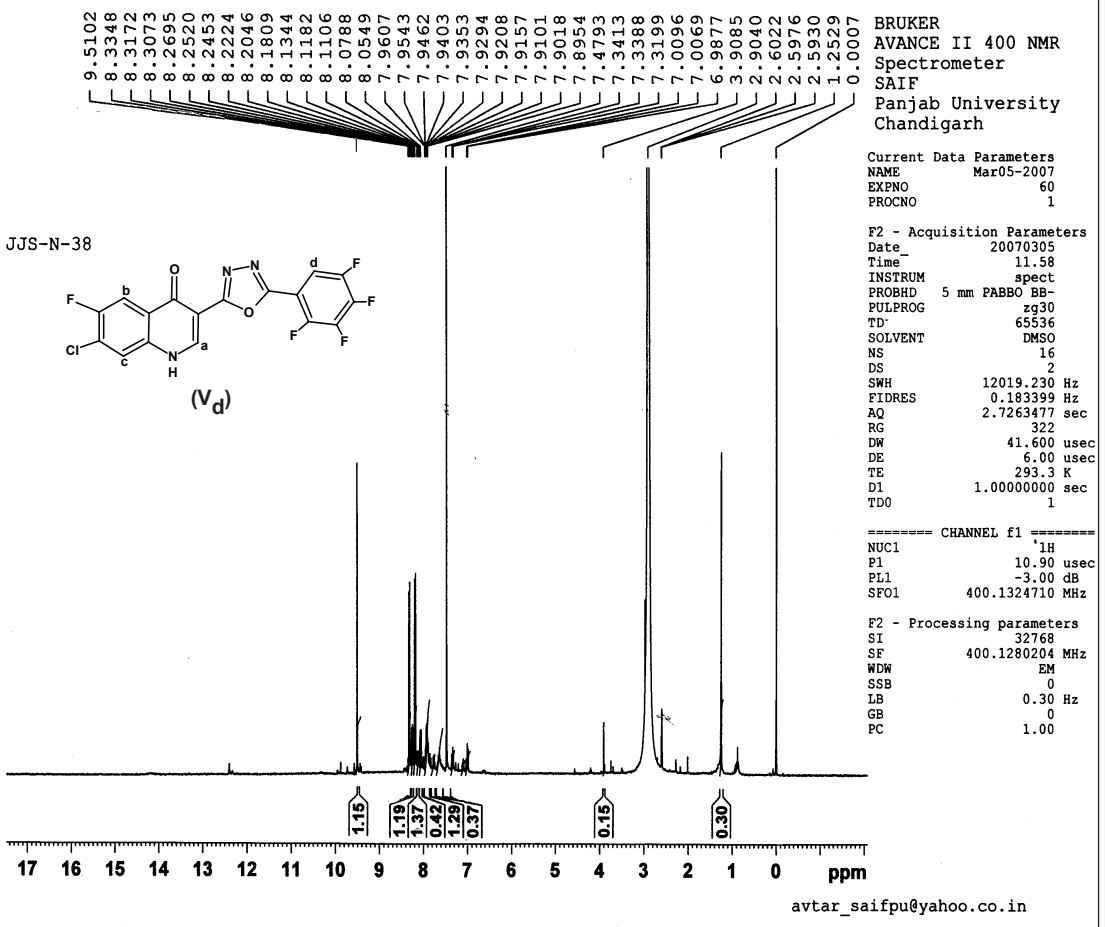
======== CHANNEL f1 ========
NUC1 1H
P1 10.90 usec
PL1 -3.00 dB
SFO1 400.1324008 MHz

F2 - Processing parameters
SI 32768
SF 400.1299800 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

avtar_saifpu@yahoo.co.in

Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	7.5661-7.6154	1H	multiplet	- Ar-H(c)
2	7.7271-7.8267	1H	multiplet	- Ar-H(f)
3	7.9299-7.9902	1H	doublet	- Ar-H(e)
4	8.2191-8.2930	1H	doublet	- Ar-H(d)
5	8.9530	1H	singlet	-NH-CH(b)
6	11.1550	1H	singlet	-NH(a)

NMR SPECTRAL STUDY OF 6-FLUORO-7-CHLORO-3-[5'-(2'',3'',4'',5''-TETRA FLUORO PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4-(1H)-ONE (V_d).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	7.8954-7.9607	1H	multiplet	- Ar-H(d)
2	8.0549-8.1344	1H	doublet	- Ar-H(b)
3	8.1809-8.3348	1H	doublet	- Ar-H(c)
4	9.5102	1H	singlet	- NH-CH(a)
5	2.5930-3.9085	-	-	- DMSO-d_6

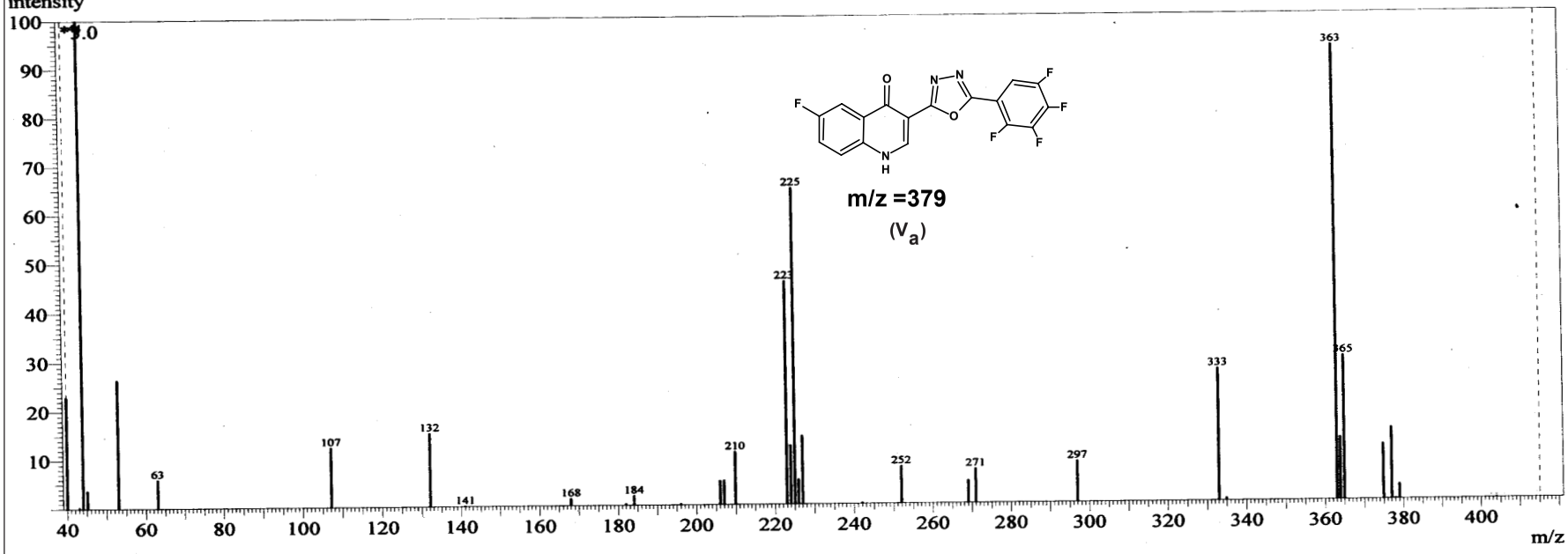
MASS SPECTRAL STUDY OF 6-FLUORO-3-[5'-(2'',3'',4'',5''-TETRAFLUORO PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONE (V_a).

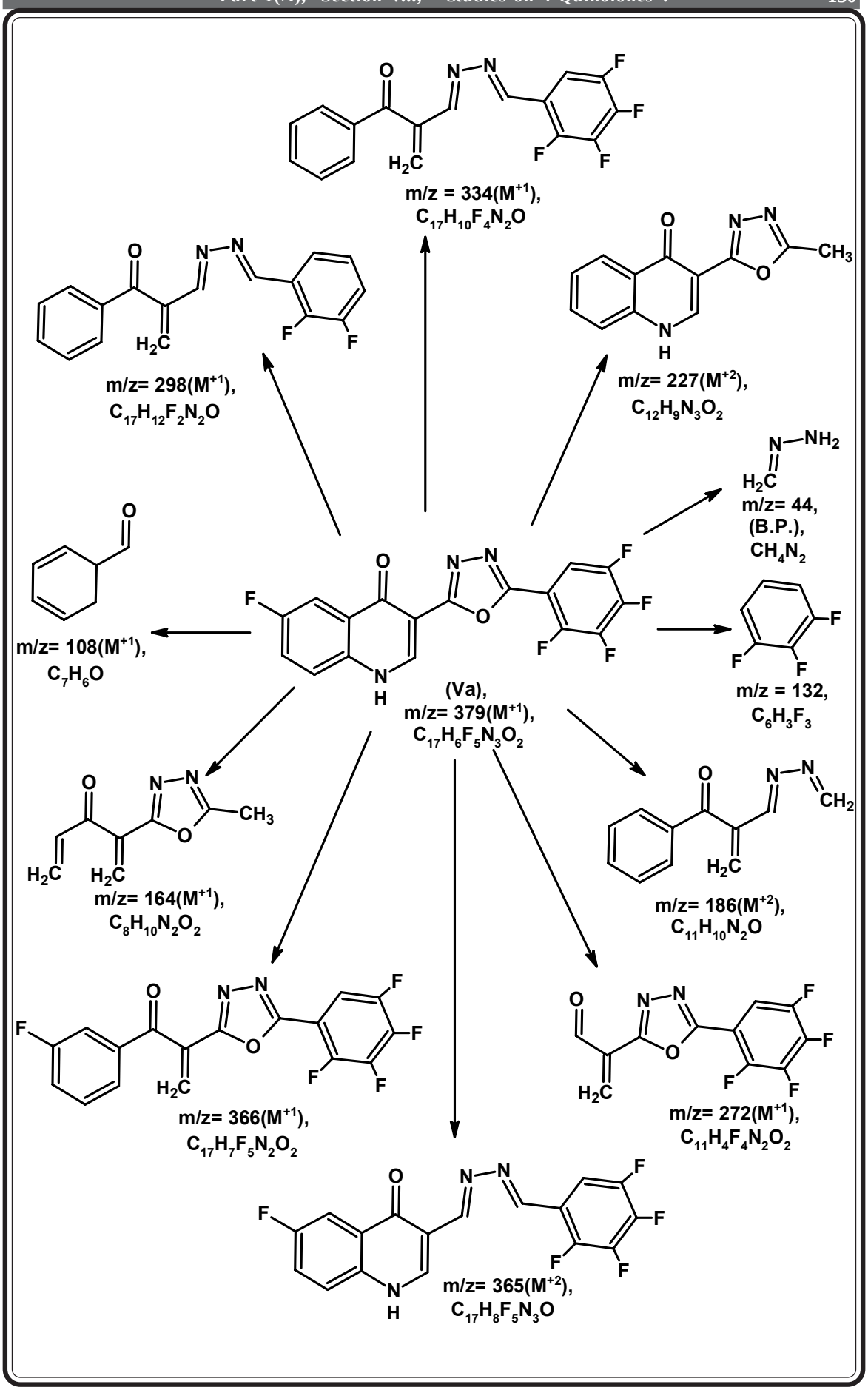
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 4/26/2006 4:30:07 PM
Sample Name	: JJS-M-30
Sample ID	: JJS-M-30
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-30.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune9.qgt

Line#:1 R.Time:8.8(Scan#:1024)
MassPeaks:35 BasePeak:44(19041)
RawMode:Averaged 6.3-11.3(718-1320)
BG Mode:None
intensity




m/z = 334(M+1),
C17H10F4N2O
m/z= 298(M+1),
C17H12F2N2O
m/z= 227(M+2),
C12H9N3O2
m/z= 44,
(B.P.),
CH4N2
m/z= 108(M+1),
C7H6O
(Va),
m/z= 379(M+1),
C17H6F5N3O2
m/z = 132,
C6H3F3
m/z= 164(M+1),
C8H10N2O2
m/z= 186(M+2),
C11H10N2O
m/z= 366(M+1),
C17H7F5N2O2
m/z= 272(M+1),
C11H4F4N2O2
m/z= 365(M+2),
C17H8F5N3O

MASS SPECTRAL STUDY OF 7-CHLORO-3-[5'-(2'',3'',4'',5''-TETRAFLUORO PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONE (V_b).

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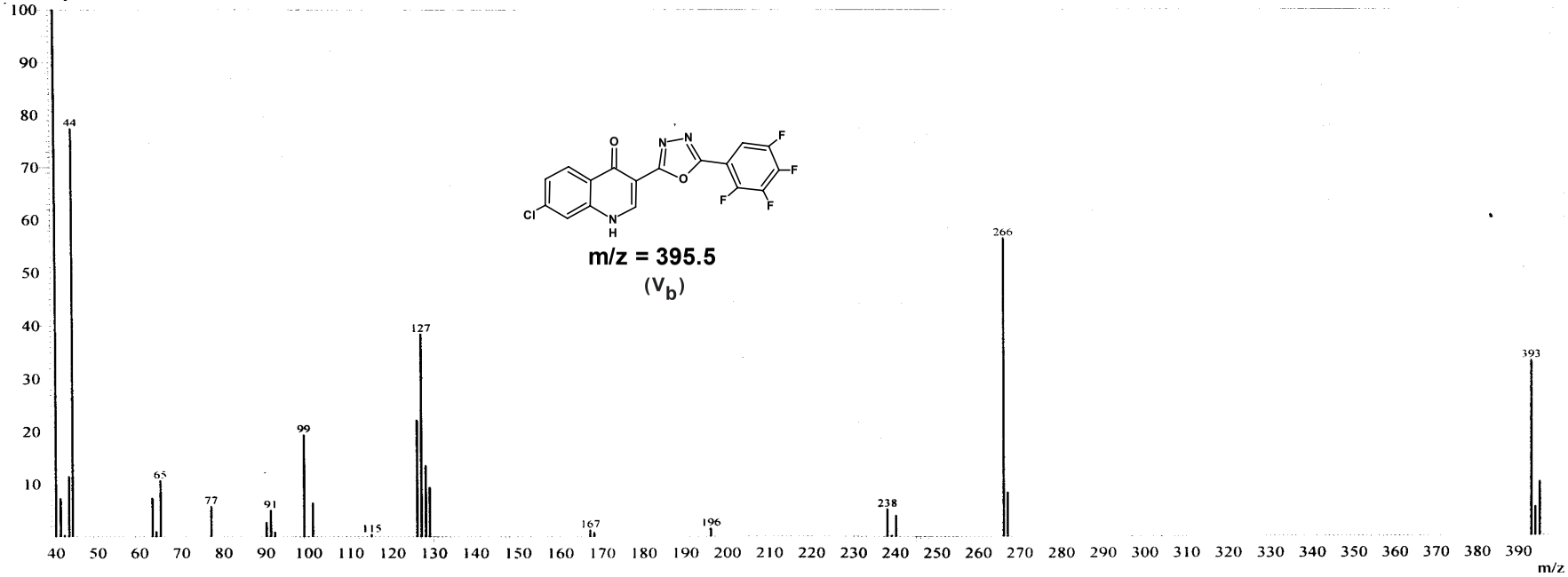
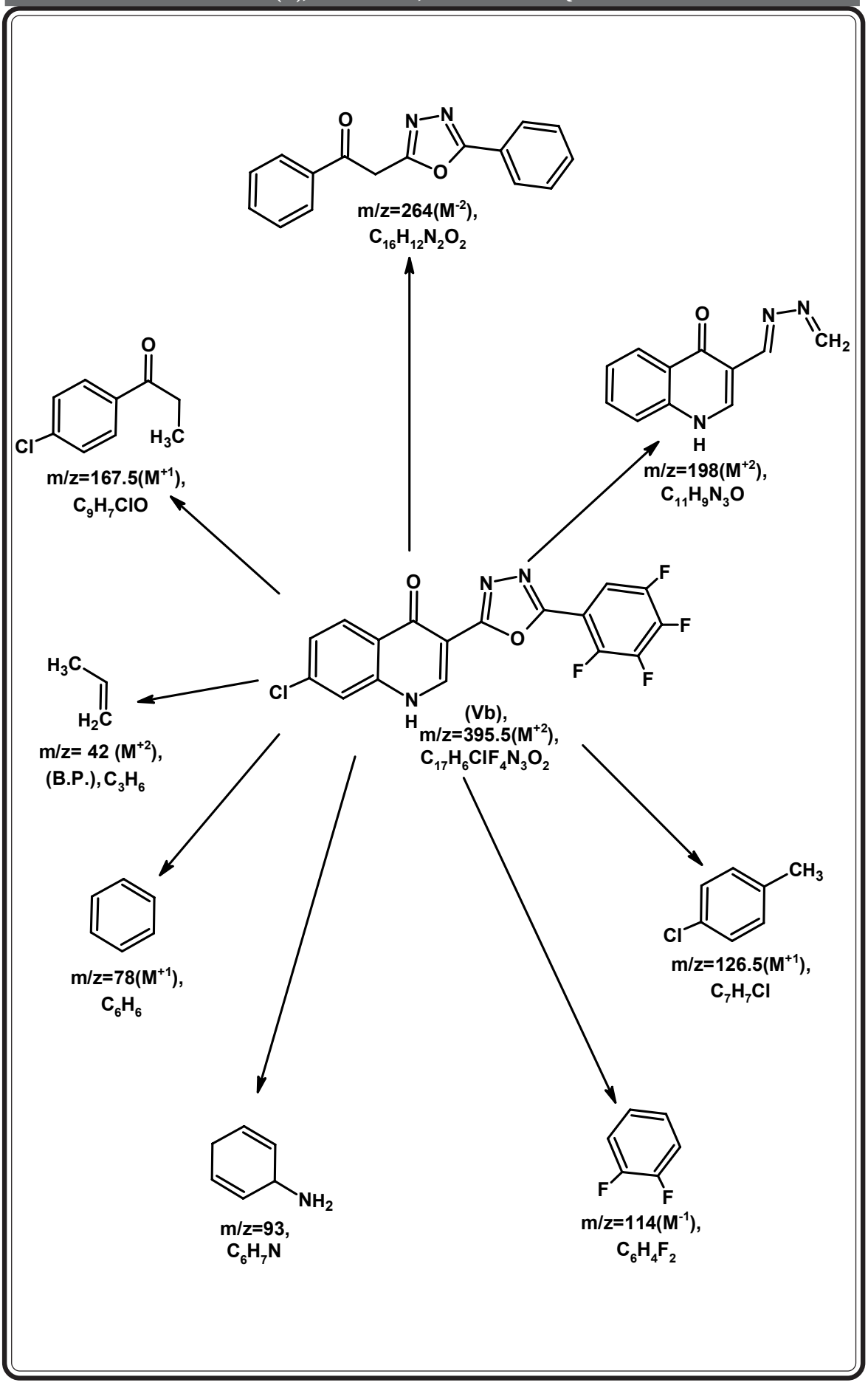
Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 4/18/2007 11:53:38 AM
Sample Name : JJS-MQ-9
Sample ID : JJS-MQ-9
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-9.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune121206.qgt

Line#:1 R.Time:3.0(Scan#:323)
MassPeaks:30 BasePeak:40(12393)
RawMode:Averaged 2.6-3.4(274-370)
BG Mode:None
intensity



m/z = 395.5
(V_b)


m/z=264(M-2),
C16H12N2O2
m/z=167.5(M+1),
C9H7ClO
m/z=198(M+2),
C11H9N3O
m/z= 42 (M+2),
(B.P.), C3H6
(Vb),
m/z=395.5(M+2),
C17H6ClF4N3O2
m/z=78(M+1),
C6H6
m/z=126.5(M+1),
C7H7Cl
m/z=93,
C6H7N
m/z=114(M-1),
C6H4F2

MASS SPECTRAL STUDY OF 6-CHLORO-3-[5'-(2'',3'',4'',5''-TETRAFLUORO PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONE (V_c).

SAURASHTRA UNIVERSITY - RAJKOT
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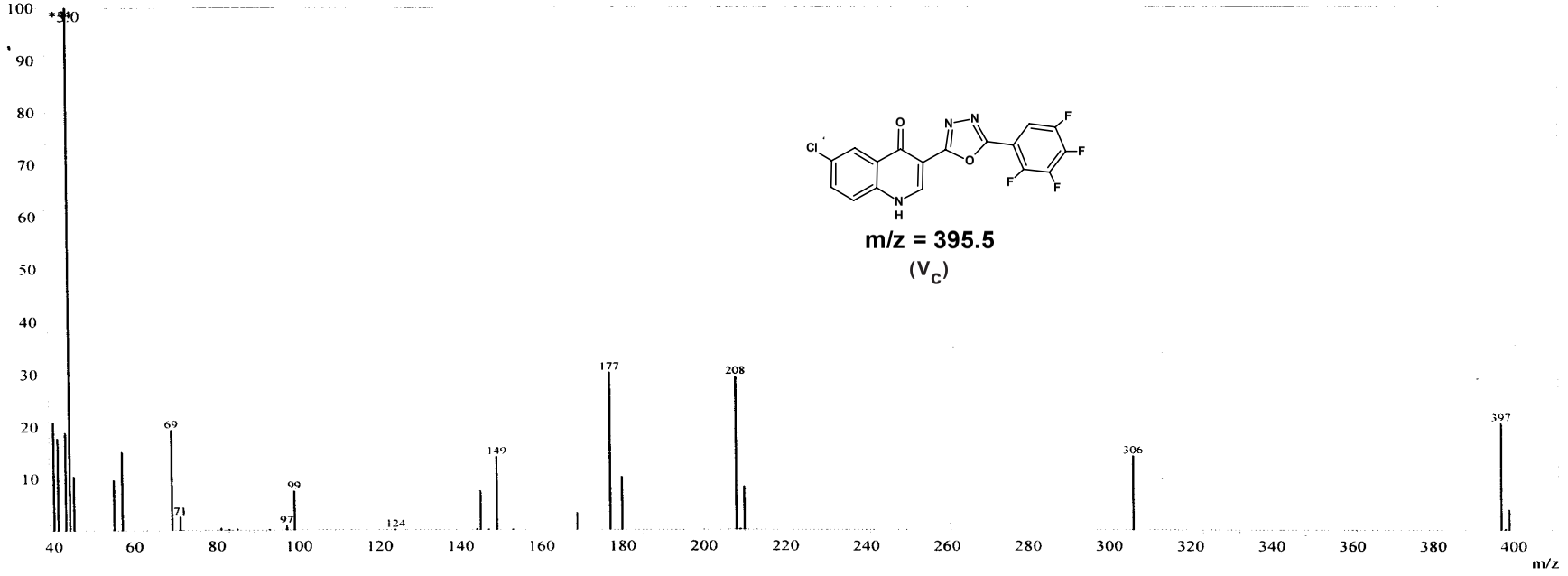
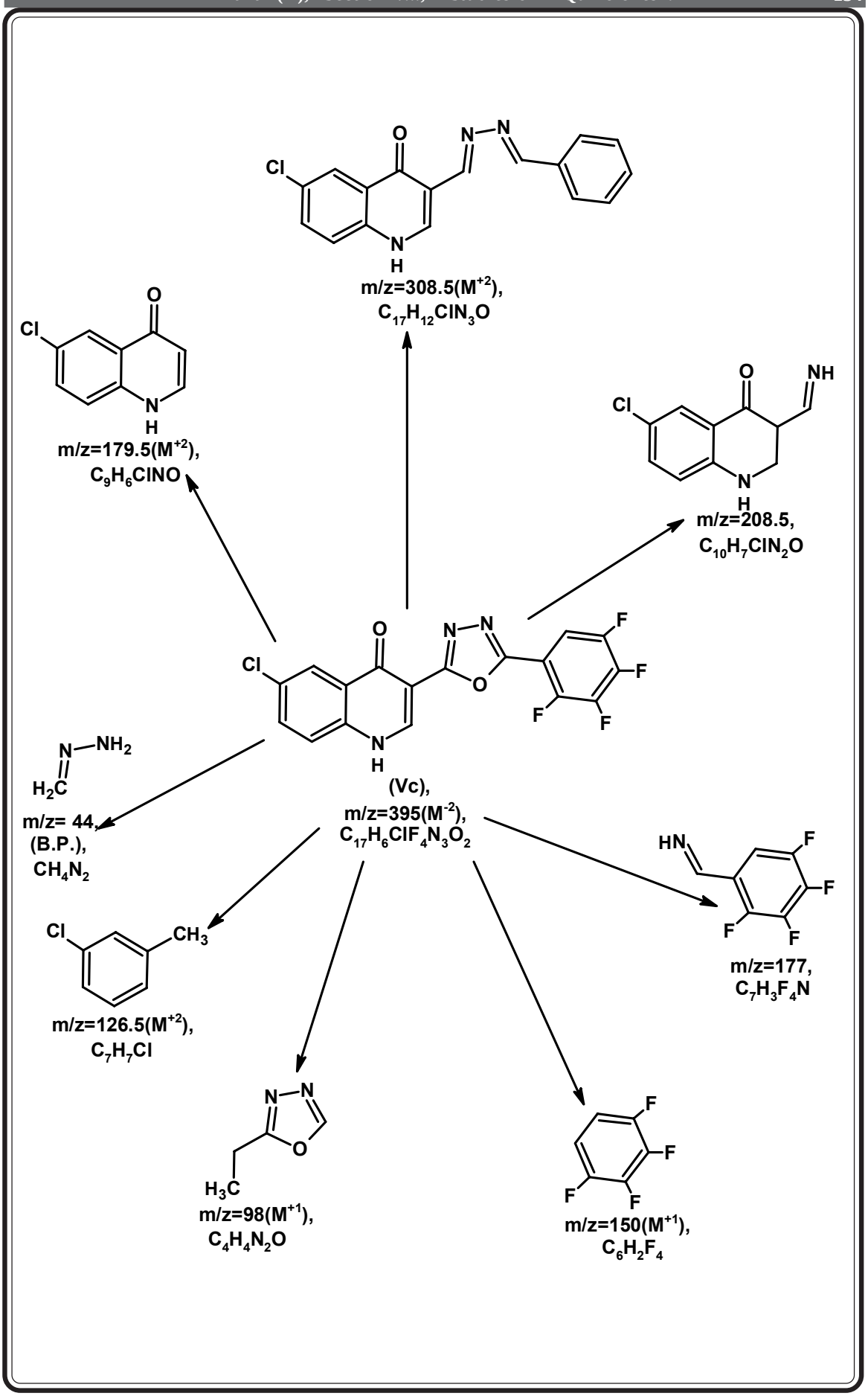
Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 9/21/2007 3:29:10 PM
Sample Name	: JJS-MQ-27
Sample ID	: JJS-MQ-27
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-27.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\170907_01.qgt

Line#:1 R.Time:5.3(Scan#:601)
MassPeaks:31 BasePeak:44(33882)
RawMode:Averaged 3.3-7.3(364-844)
BG Mode:None
intensity



m/z = 395.5
(V_c)


m/z=308.5(M+2),
C17H12ClN3O
m/z=179.5(M+2),
C9H6ClNO
m/z=208.5,
C10H7ClN2O
(Vc),
m/z=395(M-2),
C17H6ClF4N3O2
m/z= 44,
(B.P.),
CH4N2
m/z=126.5(M+2),
C7H7Cl
m/z=177,
C7H3F4N
m/z=98(M+1),
C4H4N2O
m/z=150(M+1),
C6H2F4

MASS SPECTRAL STUDY OF 7-CHLORO-6-FLUORO-3-[5'-(2'',3'',4'',5''-TETRAFLUORO PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONE (V_d).

SAURASHTRA UNIVERSITY - RAJKOT
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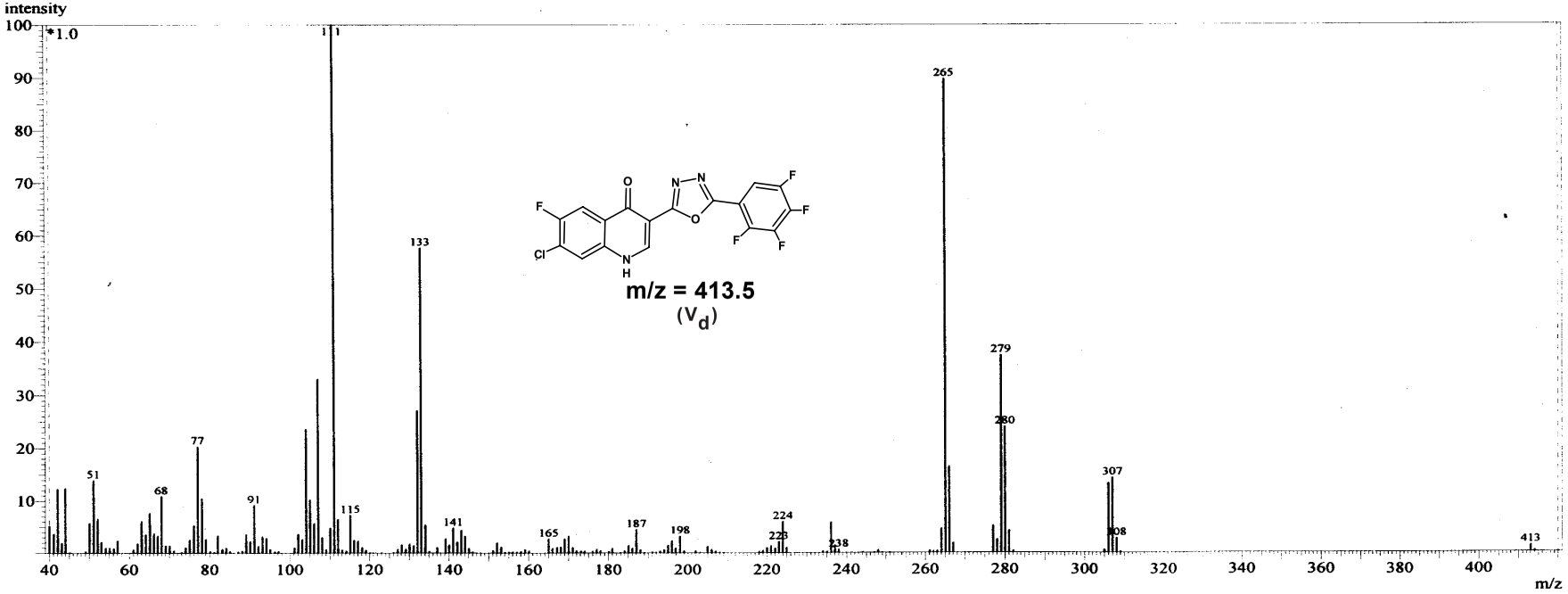
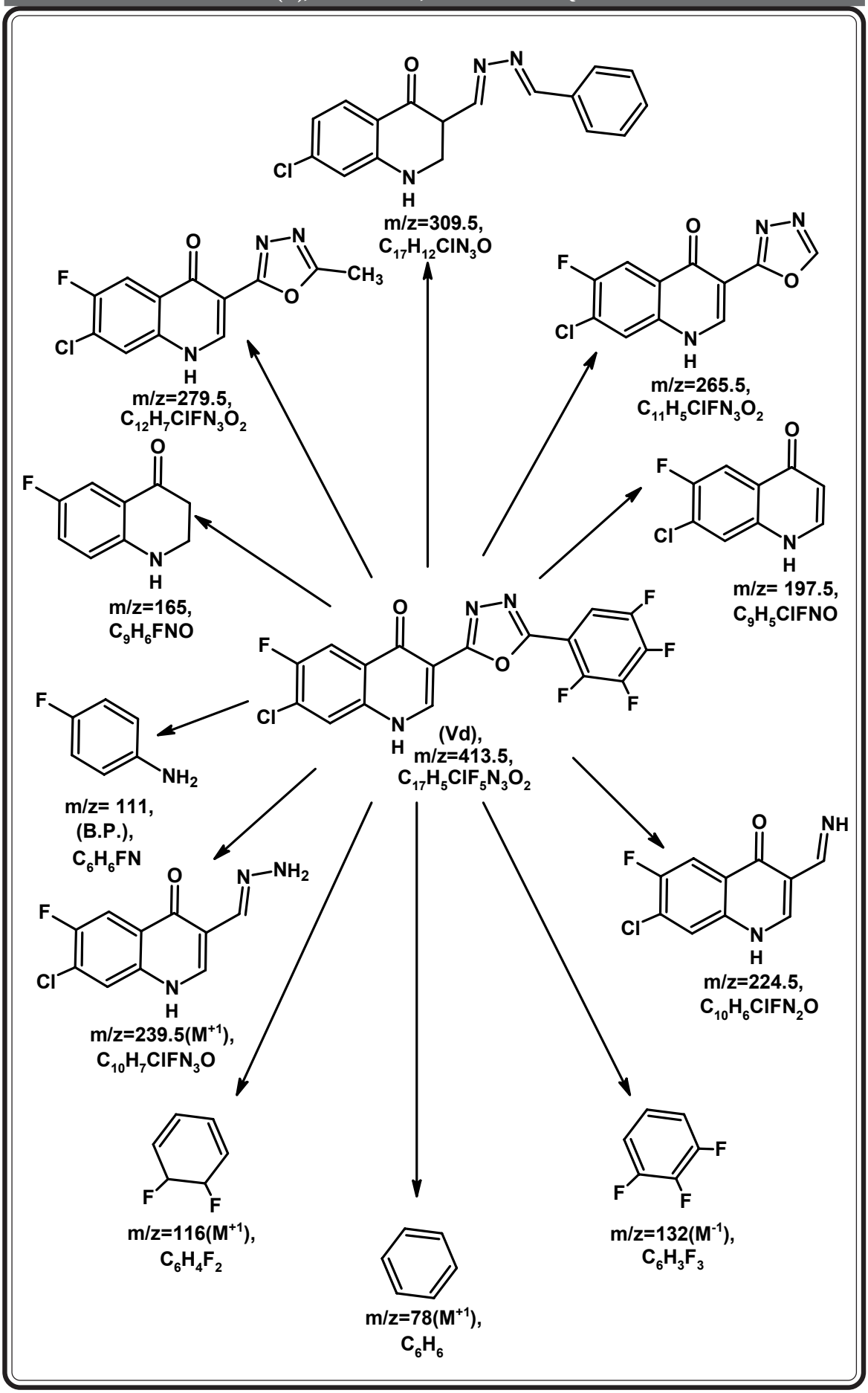
Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 9/4/2006 5:15:01 PM
Sample Name	: JJS-M-38
Sample ID	: JJS-M-38
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-38a.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:8.0(Scan#:925)
MassPeaks:175 BasePeak:111(185480)
RawMode:Averaged 6.8-9.2(776-1071)
BG Mode:None
intensity




m/z=309.5,
$C_{17}H_{12}ClN_3O$
m/z=279.5,
$C_{12}H_7ClFN_3O_2$
m/z=265.5,
$C_{11}H_5ClFN_3O_2$
m/z=165,
C_9H_6FNO
m/z= 197.5,
C_9H_5ClFNO
(Vd),
m/z=413.5,
$C_{17}H_5ClF_5N_3O_2$
m/z= 111,
(B.P.),
C_6H_6FN
m/z=239.5(M^{+1}),
$C_{10}H_7ClFN_3O$
m/z=224.5,
$C_{10}H_6ClFN_2O$
m/z=116(M^{+1}),
$C_6H_4F_2$
m/z=78(M^{+1}),
C_6H_6
m/z=132(M^{-1}),
$C_6H_3F_3$

MASS SPECTRAL STUDY OF 7-CHLORO-6-FLUORO-3-[5'-(2'',3'',4'',5''-TETRAFLUORO PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONE (V_e).

SAURASHTRA UNIVERSITY - RAJKOT
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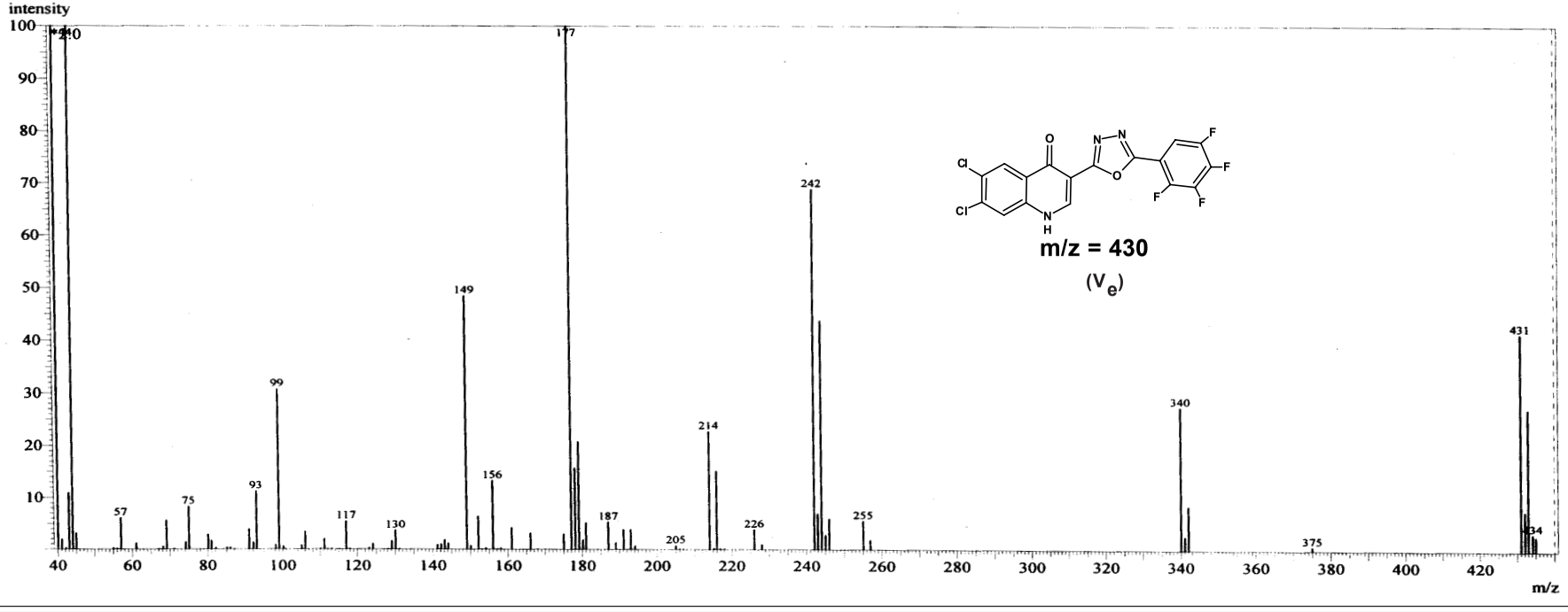
Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 1/2/2007 11:44:49 AM
Sample Name : JJS-MQ-2
Sample ID : JJS-MQ-2
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-2.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune121206.qgt

Line#:1 R.Time:5.0(Scan#:564)
MassPeaks:96 BasePeak:44(36083)
RawMode:Averaged 3.8-6.2(418-706)
BG Mode:None
intensity



m/z = 430

(V_e)

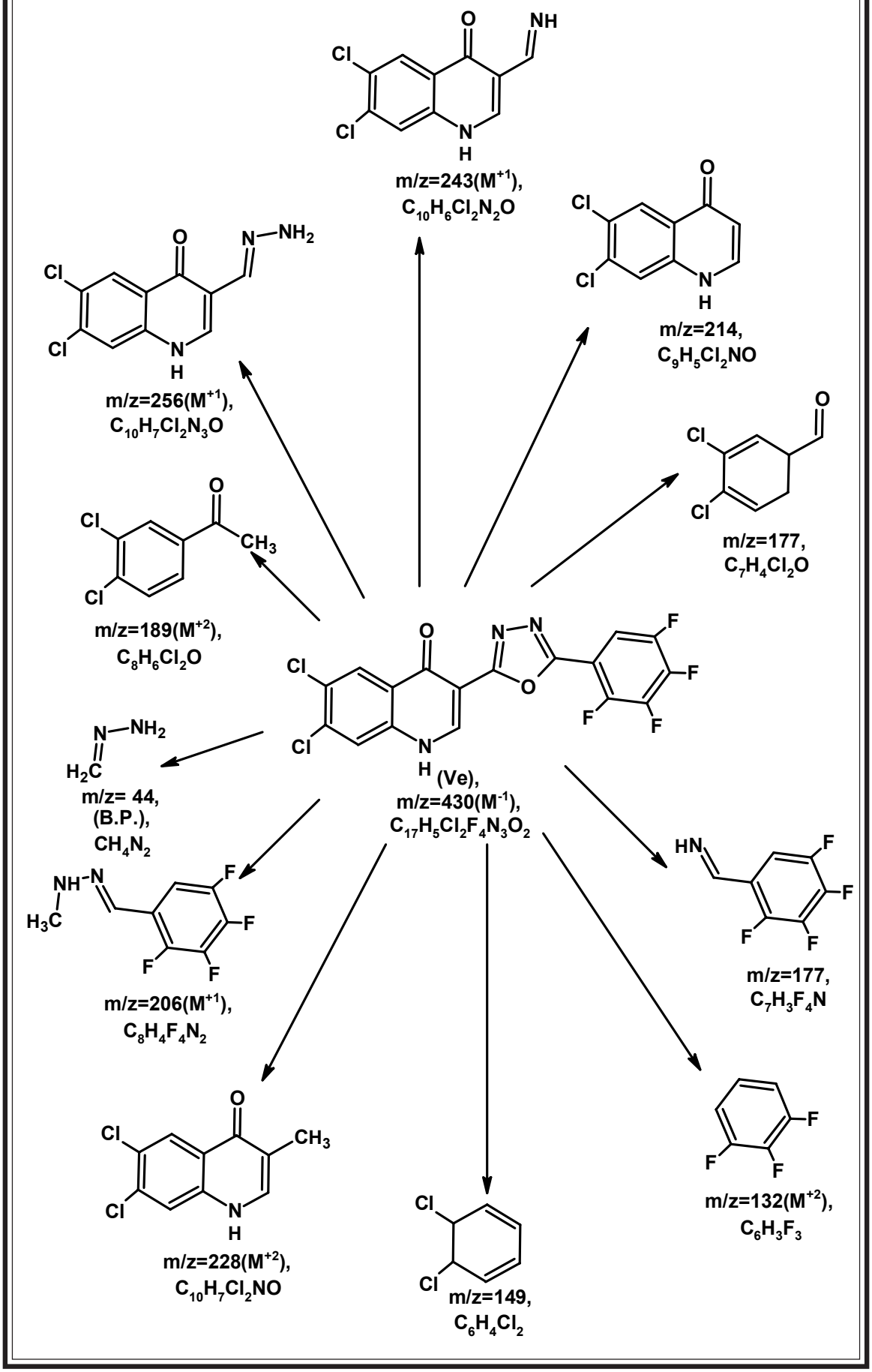

m/z=243(M+1),
C10H6Cl2N2O
m/z=214,
C9H5Cl2NO
m/z=256(M+1),
C10H7Cl2N3O
m/z=177,
C7H4Cl2O
m/z=189(M+2),
C8H6Cl2O
(Ve),
m/z=430(M-1),
C17H5Cl2F4N3O2
m/z= 44,
(B.P.),
CH4N2
m/z=206(M+1),
C8H4F4N2
m/z=177,
C7H3F4N
m/z=228(M+2),
C10H7Cl2NO
m/z=149,
C6H4Cl2
m/z=132(M+2),
C6H3F3

TABLE NO. 5B : COMPARATIVE ANTIMICROBIAL ACTIVITY OF SUBSTITUTED-3-[5'-(2'',3'',4'',5''-TETRA FLUORO-PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONES (V_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) S. pyogens MTCC- 442					S. aureus MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
Va	6-F	-	9	9	11	13	-	8	10	13	16
Vb	7-Cl	-	7	8	11	13	-	10	12	14	17
Vc	6-Cl	-	7	8	10	14	-	8	10	12	15
Vd	7-Cl-6-F	-	10	12	14	15	-	8	10	11	13
Ve	$6,7-(Cl)_2$	-	11	12	14	16	-	8	9	12	16
Vf	$6-NO_2$	-	10	11	13	17	-	9	10	12	17
Vg	$6-OCH_3$	-	9	10	12	14	-	10	12	14	15
Vh	$6-CH_3$	-	8	11	11	13	-	9	11	13	15
Vi	$7,8-(CH_3)_2$	-	8	10	12	14	-	10	12	14	15
Vj	-	-	9	11	13	15	-	8	10	11	13

Comparative activity of (V_{a-j}) with known choosen standard drugs

Standard drug	Antibacterial activity									
										$V_{a,b}$ $V_{e,f}$
Amoxicilin	12	14	15	16	18	10	12	14	15	16
Chloramphenicol	14	15	18	19	24	14	17	20	21	24
Sparfloxacin	14	22	24	26	28	24	26	27	28	32
Levofloxacin	18	21	22	27	29	20	24	26	27	35

N.B.(-): No Activity

TABLE NO. 5C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF SUBSTITUTED-3-[5'-(2'',3'',4'',5''-TETRA FLUORO-PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONES (V_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) B. Subtillis MTCC- 441					E.coli MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
Va	6-F	-	9	10	11	13	-	6	7	8	9
Vb	7-Cl	-	10	11	13	16	-	9	7	9	10
Vc	6-Cl	-	9	10	12	14	-	6	10	10	12
Vd	7-Cl-6-F	-	8	11	13	15	-	6	7	8	10
Ve	6,7-$(Cl)_2$	-	10	12	13	17	-	7	7	8	9
Vf	6-NO_2	-	9	10	11	15	-	9	8	10	11
Vg	6-OCH_3	-	9	11	12	13	-	8	10	11	13
Vh	6-CH_3	-	10	11	12	14	-	8	8	10	12
Vi	7,8-$(CH_3)_2$	-	10	12	13	16	-	6	10	11	12
Vj	-	-	11	13	15	18	-	7	7	8	11
Comparative activity of (V_{a-j}) with known choosen standard drugs											
Standard drug		Antibacterial activity									
Amoxicilin		12	15	16	18	19	11	14	16	18	20
Chloramphenicol		18	22	24	26	27	17	20	23	25	26
Sparfloxacin		22	24	25	26	29	20	22	25	26	28
Levofloxacin		24	26	28	29	31	23	25	26	29	30

N.B.(-): No Activity

TABLE NO. 5D: COMPARATIVE ANTIMICROBIAL ACTIVITY OF SUBSTITUTED-3-[5'-(2'',3'',4'',5''TETRA FLUORO-PHENYL)-1',3',4'-OXADIAZOL-2'-YL]-QUINOLONE-4(1H)-ONES (Va-j). (Different Inhibition Concentration in µg/ml)

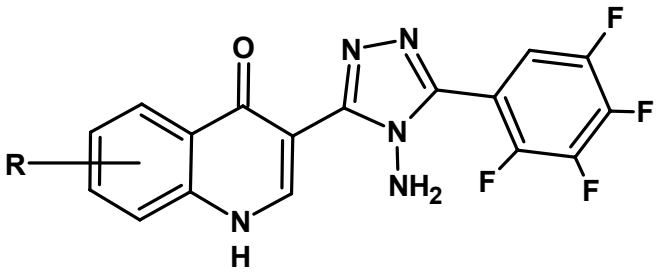
Compd No.	R	Antifungal activity (Zones of inhibition in m.m.) C. albicans MTCC- 227					A.niger MTCC- 282				
		5	25	50	100	250	5	25	50	100	250
Va	6-F	-	8	10	13	14	-	8	10	12	15
Vb	7-Cl	-	6	8	10	12	-	8	10	12	14
Vc	6-Cl	-	8	10	9	11	-	7	8	10	13
Vd	7-Cl-6-F	-	8	9	13	17	-	9	12	14	18
Ve	6,7-$(Cl)_2$	-	8	10	11	13	-	9	11	13	14
Vf	6-NO_2	-	6	7	12	14	-	8	9	11	15
Vg	6-OCH_3	-	7	9	9	11	-	7	8	9	10
Vh	6-CH_3	-	7	9	10	14	-	9	11	13	15
Vi	7,8-$(CH_3)_2$	-	8	10	11	13	-	7	8	10	12
Vj	-	-	7	9	13	14	-	7	9	11	13
Comparative activity of (V_{a-i}) with known choosen standard drugs											
Standard drug		**Antifungal activity**									
Griseofulvin		16	18	21	23	25	17	19	21	22	23
Fluconazole		14	16	18	21	22	15	17	18	20	21

N.B.(-): No Activity

SECTION - VI

PREPARATION AND BIOLOGICAL EVALUATION OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRA FLUORO PHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-SUBSTITUTED-QUINOLONE-4(1H)-ONES.

Keeping in view, various properties[34-85] of **4-quinolones** and in order to have highly potent therapeutic agents, the synthesis of **3-[4'-amino-5'-(2'',3'',4'',5''-tetrafluorophenyl)-4H-1',2',4'-triazol-3'-yl]-Substituted-quinolone-4-(1H)-ones (VIa-j)** have been accomplished by the cyclocondensation of different **substituted-3-[5'-(2'',3'',4'',5''-tetrafluorophenyl)-1',3',4'-oxadiazol-2'-yl]- quinolone-4-(1H)-ones (Va-j)** and **hydrazine hydrate**.



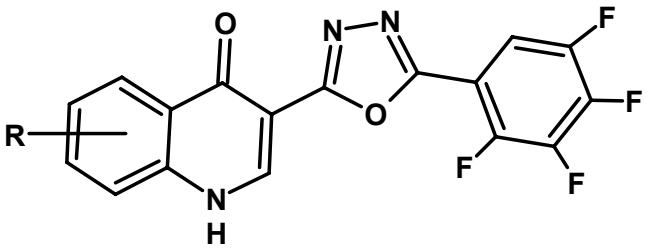
(VIa-j)

R=Substituted phenyl

The constitution of the products **(VIa-j)** have been delineated by **elemental analyses, IR, PMR** and **Mass** spectral data.

The products **(VIa-j)** were assayed for their ***in vitro*** biological assay like antibacterial activity towards ***S. pyogens MTCC-442, S. aureus MTCC-96*** **and** ***B. subtillis MTCC-441*** **(Gram positive)** and ***E. coli MTCC-443*** **(Gram negative)** bacterial strains and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations i.e.: 0(control), 5, 25, 50, 100, 250 (µg/ml) , for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds **(VIa-j)** were compared with standard drugs,viz., **Amoxicillin, Chloramphenicol, Sparfloxacin, Levofloxacin** (antibacterial)**, Griseofluvin, Fluconazole** (antifungal)**.**

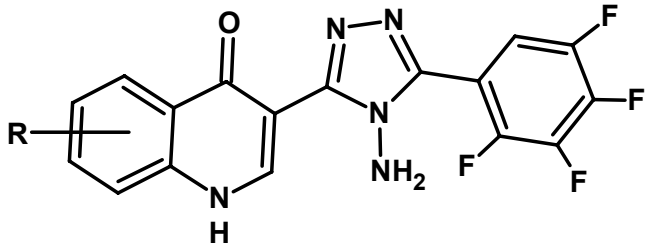
REACTION SCHEME



(Va-j)
R= substituted phenyl

NH_2-NH_2 $\cdot 2H_2O$

△



(VIa-j)
R= substituted phenyl

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRAFLUOROPHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-SUBSTITUTED-QUINOLONE-4(1H)-ONES.

(A) Preparation of Diethyl-(3-chloro-4-fluoro amino phenyl)-amino-methylene malonate (I_d).

For preparation, refer Part-1, Section-I, **page No. 30.**

(B) Preparation of Ethyl-7-chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carboxylate (II_d).

For preparation, refer Part-1, Section-II, **page No.58.**

(C) Preparation of 7-chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carbohydrazide (5_d).

For preparation, refer Part-1, Section-V, **page No.137.**

(D) Preparation of 3-[5'-(2'',3'',4'',5''-tetrafluorophenyl)-1',3',4'-oxadiazol-2'-yl]-7-chloro-6-fluoroquinolone-4(1H)-one (Vd).

For preparation, refer Part-1, Section-V, **page No.138**.

(E) Preparation of 3-[4'-amino-5'-(2'',3'',4'',5''-tetrafluorophenyl)-4H-1',2',4'-triazol-3'-yl]- 7-chloro-6-fluoro-quinolone-4-(1H)-one (VId).

A mixture of 7-chloro-6-fluoro-3-[5'-(2'',3'',4'',5''-tetrafluoro phenyl)-1',3',4'-oxadiazol-2'-yl]-7-chloro-6-fluoro-quinolone-4(1H)-one **(VId)** (2.55 gm, 0.01 M) in hydrazine hydrade 80 % (10 ml) was heated under reflux for 8 hrs.The reaction mass was allowed to cool at room temperature. The reaction mixture was poured on to crushed ice. The reaction mixture was neutralized with gl. acetic acid. The reaction mixture was filtered, washed with water and recrystallized from ethanol. Yield : 43 %, M.P.: 297 ^{O}C, (Required : C, 47.74 %; H,1.65 %; N,16.37 % for $C_{17}H_7N_5OClF_5$, Found : C, 47.70 %; H,1.61 %; N,16.32 %.

TLC solvent system R_{f_1} : Ethyl acetate : Hexane(2.5 : 7.5) = 0.49**.**

TLC solvent system R_{f_2} : Methanol : Toluene(1.0 : 9.0) = 0.42**.**

.

Similarly, other compounds **(VIa-j)** were synthesized. The physical data are recorded in **Table No.6**.

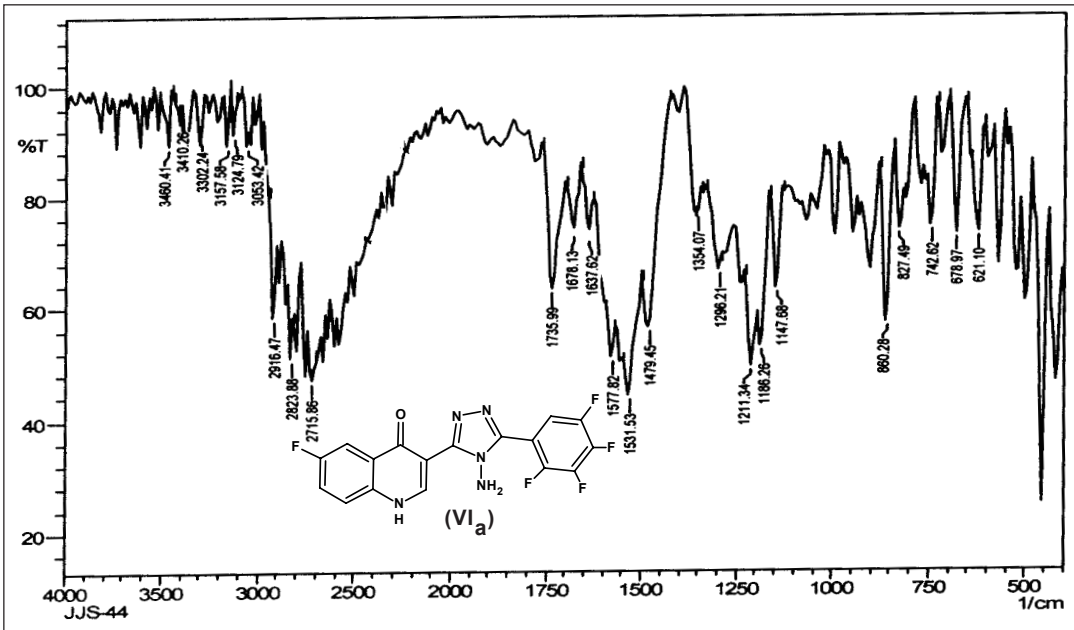
(F) Antimicrobial activity of 3-[4'-amino-5'-(2'',3'',4'',5''-tetra fluoro-phenyl)-4H-1',2',4'-triazol-3'-yl]-Substituted-quinolone-4-(1H)-ones (VIa-j).

Antimicrobial activity testing was carried out as described in Part-1(A), Section-I, page No. 30-31. The MIC values of test solution are recorded in **Table No. 6A, 6B** and **6C.**

TABLE NO. 6 : PHYSICAL CONSTANTS OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRAFLUOROPHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-SUBSTITUTED- QUINOLONE-4(1H)-ONES (VI_{a-j}).

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. ^oC 5	Yield % 6	R_f Value 7		% of Nitrogen Calcd. / Found 8
						R_{f_1}	R_{f_2}	
VI_a	6-F	$C_{17}H_8N_5OF_5$	393.0	293^o	44	0.57	0.49	17.81 / 17.78
VI_b	7-Cl	$C_{17}H_8N_5OClF_4$	409.5	291^o	41	0.53	0.47	17.09 / 17.03
VI_c	6-Cl	$C_{17}H_8N_5OClF_4$	409.5	289^o	48	0.51	0.48	17.09/ 17.07
VI_d	7-Cl-6-F	$C_{17}H_7N_5OClF_5$	427.5	297^o	43	0.49	0.42	16.37 / 16.32
VI_e	6,7-$(Cl)_2$	$C_{17}H_7N_5OCl_2F_4$	444.0	288^o	46	0.48	0.46	15.77 / 15.72
VI_f	6-NO_2	$C_{17}H_8N_6O_3F_4$	420.0	152^o	48	0.42	0.42	20.00 / 19.97
VI_g	6-OCH_3	$C_{18}H_{11}N_5O_2F_4$	405.0	153^o	43	0.51	0.46	17.28 / 17.22
VI_h	6-CH_3	$C_{18}H_{11}N_5OF_4$	389.0	145^o	42	0.47	0.42	17.99 / 17.93
VI_i	7,8-$(CH_3)_2$	$C_{19}H_{13}N_5OF_4$	403.0	143^o	47	0.46	0.44	17.37 / 17.32
VI_j	-	$C_{21}H_{11}N_5OF_4$	425.0	171^o	43	0.41	0.49	16.47 / 16.43

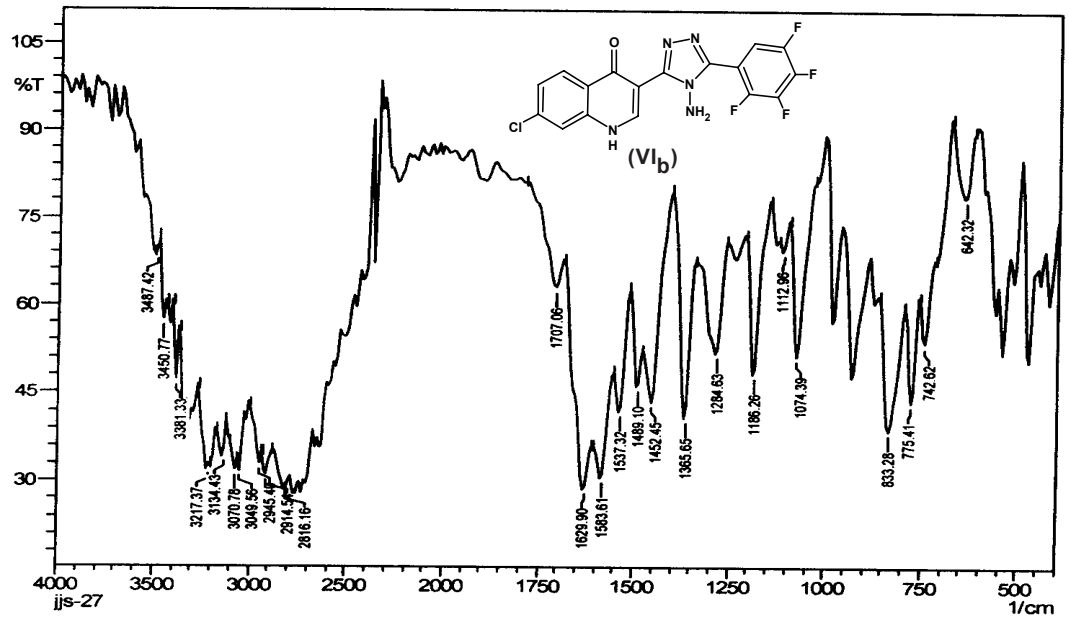
IR SPECTRAL STUDY OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRAFLUOROPHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-6-FLUORO-QUINOLINE-4-(1H)-ONE (VI_a).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2916.4	2975 - 2850	96
	C-H (sym. str., m)	2823.8	2900 - 2800	96
	C-H (asym. def., m)	1479.4	1470 - 1435	96
	C-H (sym. def., m)	1354.0	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3053.4	3080 - 3010	97
	C=C & C-C (str., v)	1531.5	1600 - 1450	97
	C-H (i.p. def., m)	1147.6	1150 - 1050	97
	C-H (o.o.p. def., m)	827.4	825 - 800	97
	C-N (str., v)	1296.2	1340 - 1250	97
	C=N (str., v)	1637.6	1690-1650	97
	N-N (def., v)	1092.6	1220 - 1020	97
4-quinolone moiety	N-H (str., b)	3410.2-3053.4	3400 - 3000	98
	N-H (def., s,m)	1637.6	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1676.1	1690 - 1650	98
Halogen Subtitution	C-F (str.,b)	1354.0-1147.6	1400 - 1080	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

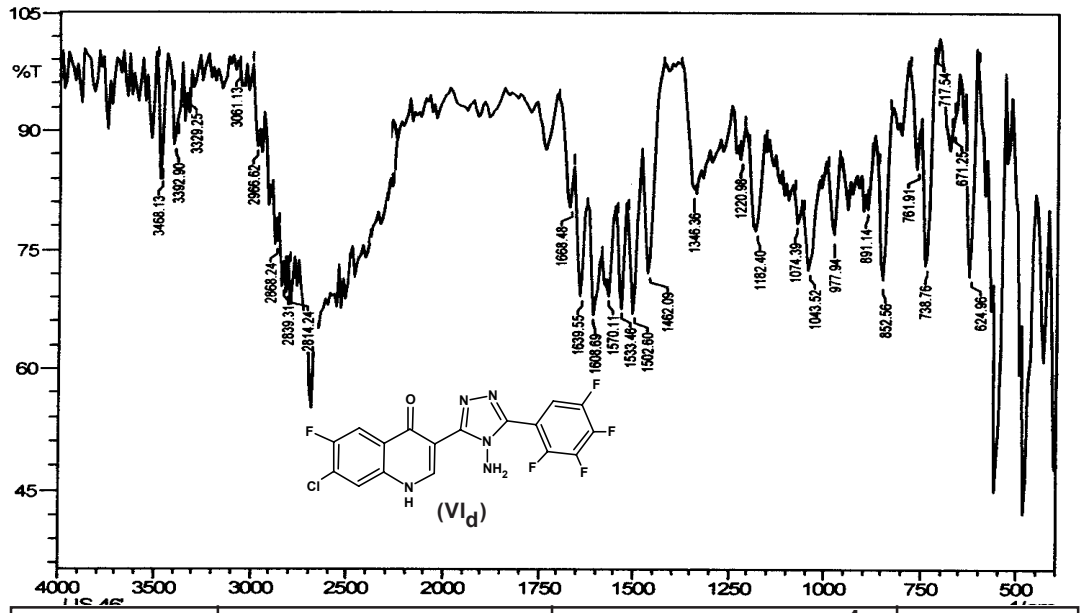
IR SPECTRAL STUDY OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRA FLUORO-PHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-7-CHLOROQUINOLINE-4(1H)-ONE (VI_b).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2914.5	2975 - 2850	96
	C-H (sym. str., m)	2816.1	2900 - 2800	96
	C-H (asym. def., m)	1452.4	1470 - 1435	96
	C-H (sym. def., m)	1365.5	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3049.5	3080 - 3010	97
	C=C & C-C (str., v)	1583.6	1600 - 1450	97
	C-H (i.p. def., m)	1112.9	1150 - 1050	97
	C-H (o.o.p. def., m)	833.2	825 - 800	97
	C-N (str., v)	1284.6	1340 - 1250	97
	C=N (str., v)	1629.9	1690-1650	97
	N-N (def., v)	1186.2	1220 - 1020	97
4-quinolone moiety	N-H (str., b)	3381.3-3049.5	3400 - 3000	98
	N-H (def., s,m)	1537.3	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1707.0	1710 - 1650	98
Halogen Subtitution	C-Cl (str., b)	775-642	800 - 600	99
	C-F (str.,b)	1365.6-1074.3	1400 - 1080	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

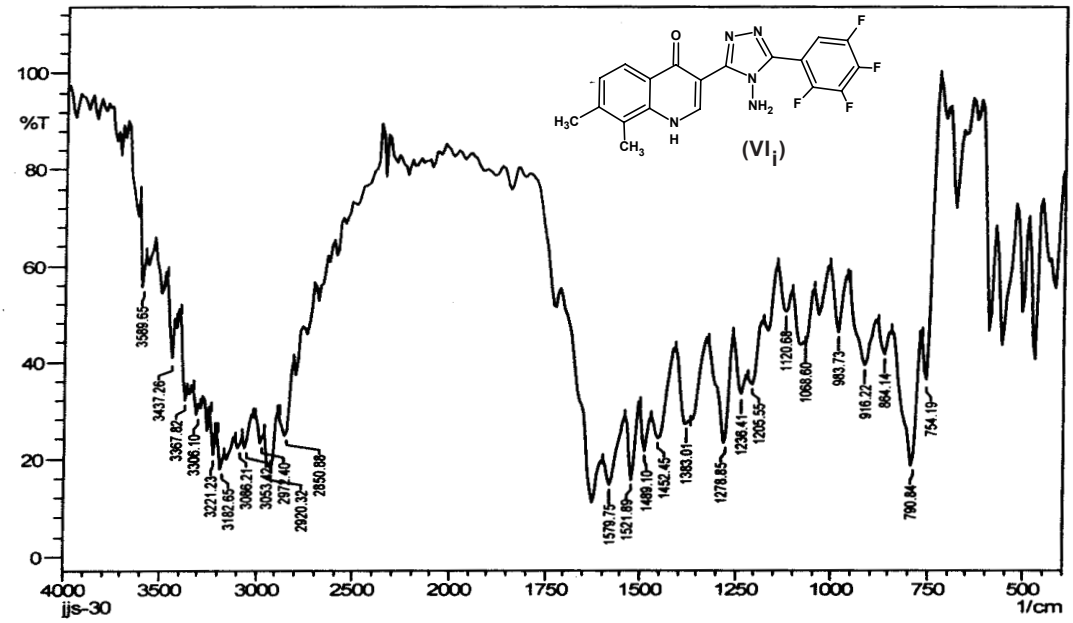
IR SPECTRAL STUDY OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRA FLUORO-PHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-6-FLUORO-7-CHLORO QUINOLINE-4(1H)-ONE (VI_d).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2966.6	2975 - 2850	96
	C-H (sym. str., m)	2808.2	2900 - 2800	96
	C-H (asym. def., m)	1462.0	1470 - 1435	96
	C-H (sym. def., m)	1346.3	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3061.7	3080 - 3010	97
	C=C & C-C (str., v)	1608.6	1600 - 1450	97
	C-H (i.p. def., m)	1182.4	1150 - 1050	97
	C-H (o.o.p. def., m)	852.5	825 - 800	97
	C-N (str., v)	1346.3	1340 - 1250	97
	C=N (str., v)	1639.5	1690-1650	97
	N-N (def., v)	1220.9	1220 - 1020	97
4-quinolone moiety	N-H (str., b)	3392.9-3061.1	3400 - 3000	98
	N-H (def., s,m)	1570.1	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1668.4	1690 - 1640	98
Halogen Subtitution	C-F (str., b)	1346.3-1074.3	1400 - 1080	99
	C-Cl (str., b)	761-624	800-600	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

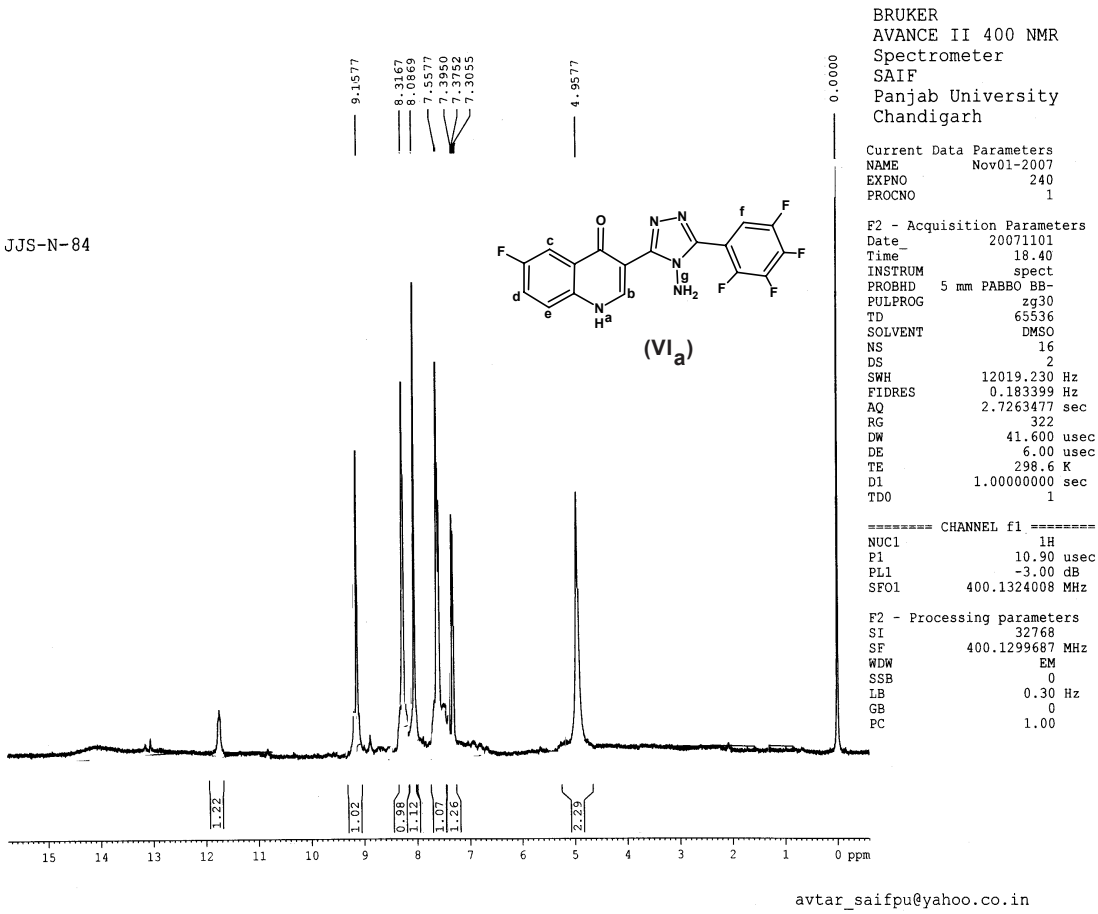
IR SPECTRAL STUDY OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRA FLUORO-PHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-7,8-DIMETHYLQUINLINE-4(1H)-ONE (VI_i).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2920.2	2975 - 2850	96
	C-H (sym. str., m)	2850.8	2900 - 2800	96
	C-H (asym. def., m)	1452.4	1470 - 1435	96
	C-H (sym. def., m)	1383.1	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3053.4	3080 - 3010	97
	C=C & C-C (str., v)	1579.7	1600 - 1450	97
	C-H (i.p. def., m)	11120.6	1150 - 1050	97
	C-H (o.o.p. def., m)	864.1	825 - 800	97
	C-N (str., v)	1278.8	1340 - 1250	97
	C=N (str., v)	1620.1	1690-1650	97
	N-N (def., v)	1205.5	1220 - 1020	97
4-quinolone moiety	N-H (str., b)	3367.8-3053.4	3400 - 3000	98
	N-H (def., s,m)	1579.7	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1670.3	1690 - 1640	98
Halogen Subtitution	C-F (str., b)	1383.4-1120.6	1400 - 1080	99

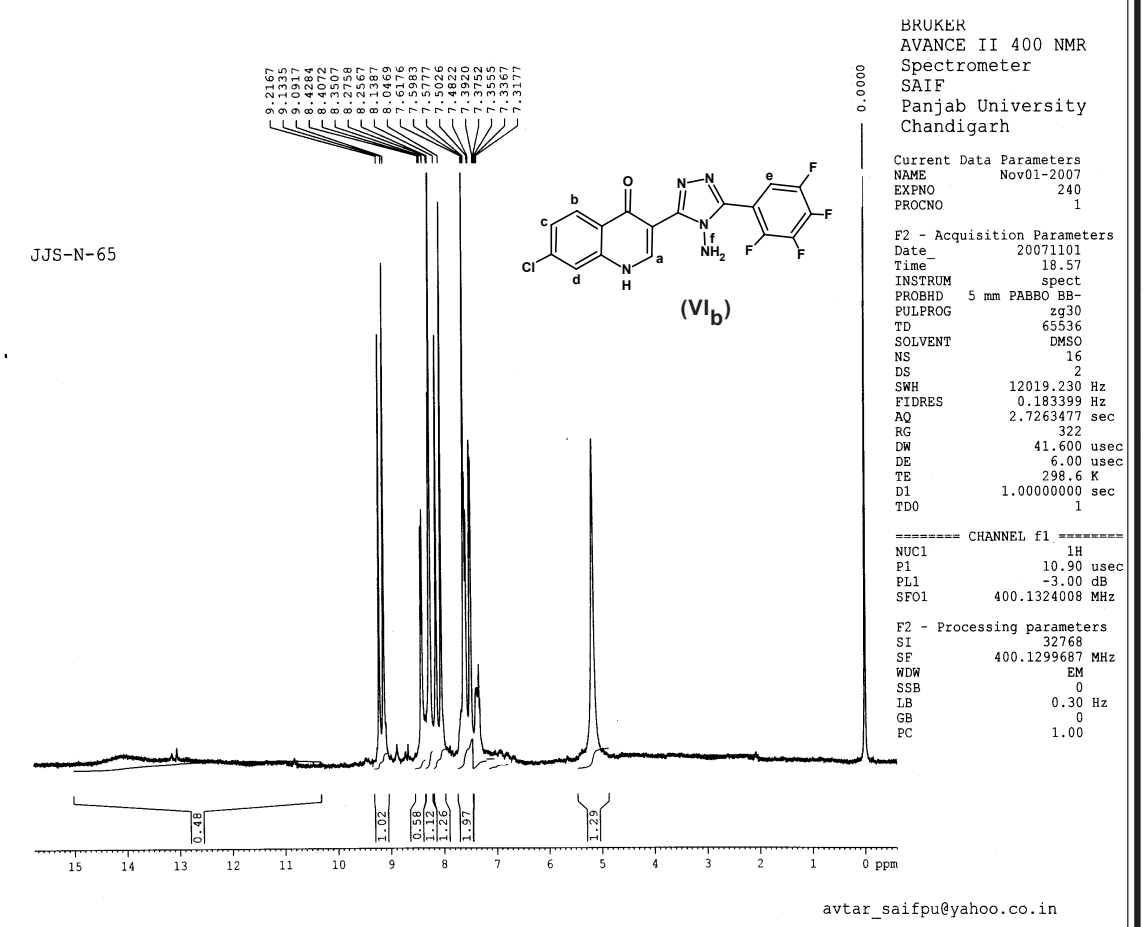
* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

NMR SPECTRAL STUDY OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRA FLUORO-PHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-6-FLUOROQUINOLINE-4(1H)-ONE (VI_a).



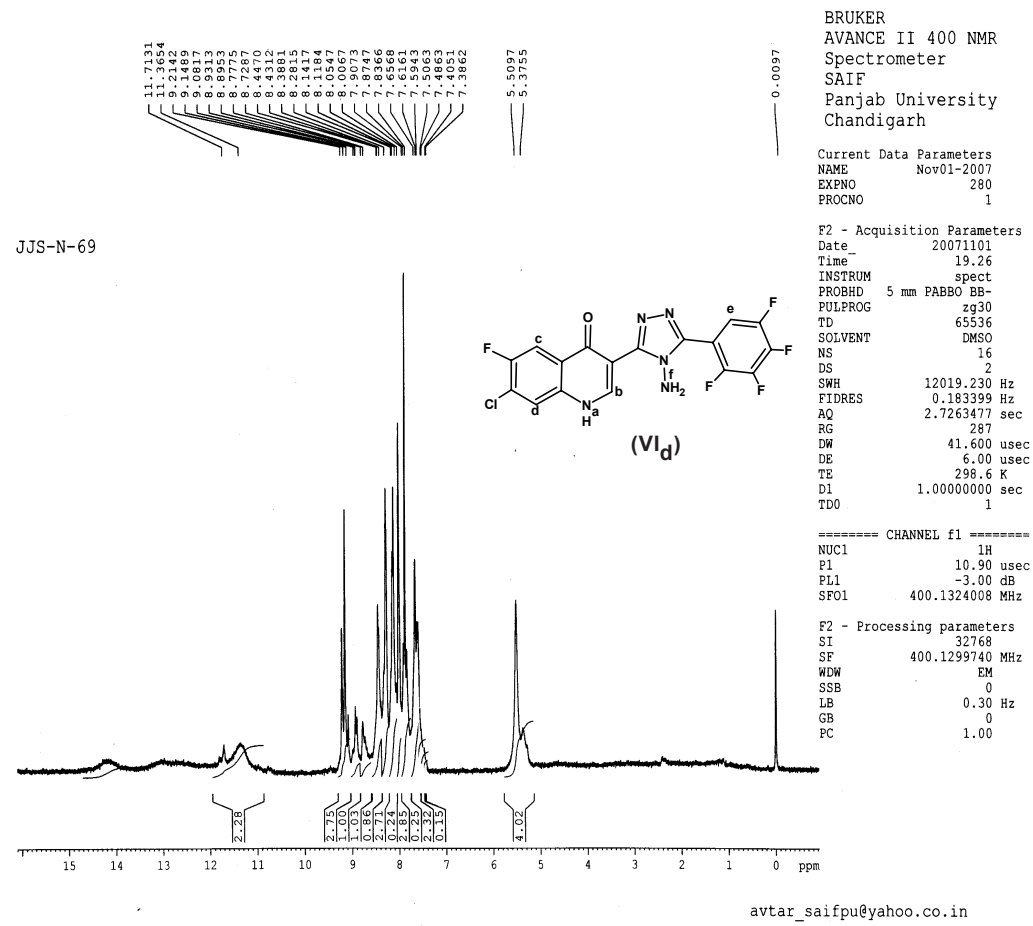
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	4.9577	2H	singlet	-N<u>H</u>2(g)
2	7.3055	1H	triplet	- Ar-<u>H</u>(d)
3	7.5577	1H	singlet	- Ar-<u>H</u>(f)
4	8.0869	1H	singlet	- Ar-<u>H</u>(c)
5	8.3167	1H	singlet	- Ar-<u>H</u>(e)
6	9.1577	1H	singlet	-NH-<u>CH</u>(b)
7	11.8038	1H	singlet	-N<u>H</u>(a)

NMR SPECTRAL STUDY OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRA FLUORO-PHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-7-CHLOROQUINOLINE-4(1H)ONE (VI_b).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	5.1723	2H	singlet	- NH_2(f)
2	7.3177-7.6176	2H	multiplet	- Ar-H(b,c)
3	8.0469-8.1387	1H	doublet	- Ar-H(e)
4	8.2567-8.4284	1H	doublet	- Ar-H(d)
5	9.0917-9.2167	1H	doublet	-NH-CH(a)

NMR SPECTRAL STUDY OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRA-FLUORO PHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-6-FLUORO-7-CHLORO-QUINOLINE-4(1H)-ONE (VI_d).



avtar_saifpu@yahoo.co.in

Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	5.5097	2H	singlet	- NH_2(f)
2	7.3862-7.5063	1H	triplet	- Ar-H(b)
3	7.9073-8.1417	1H	doublet	- Ar-H(c)
4	8.2815-8.7775	1H	doublet	- Ar-H(e)
5	8.8953-9.2142	1H	doublet	- NH-CH(b)
6	11.365-11.713	1H	singlet	- NH(a)

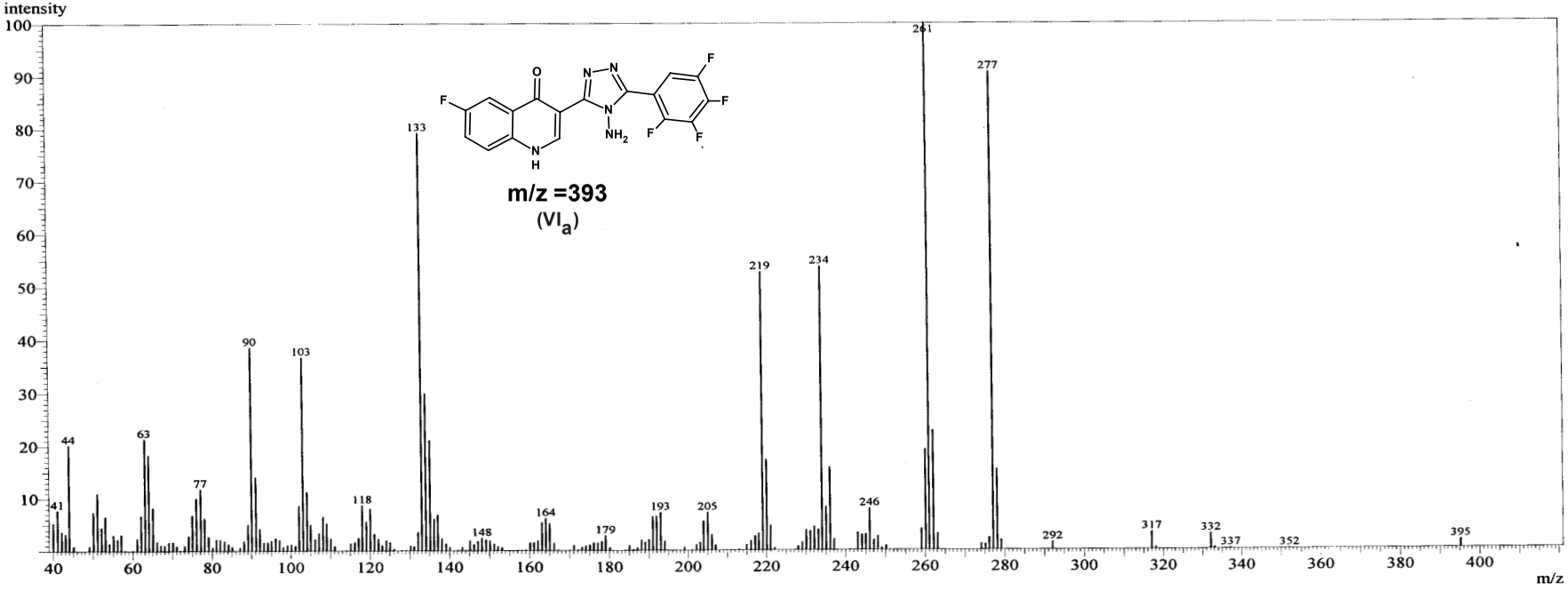
MASS SPECTRAL STUDY OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRAFLUORPHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-6-FLUOROQUINOLINE-4(1H)-ONE (VI_a).

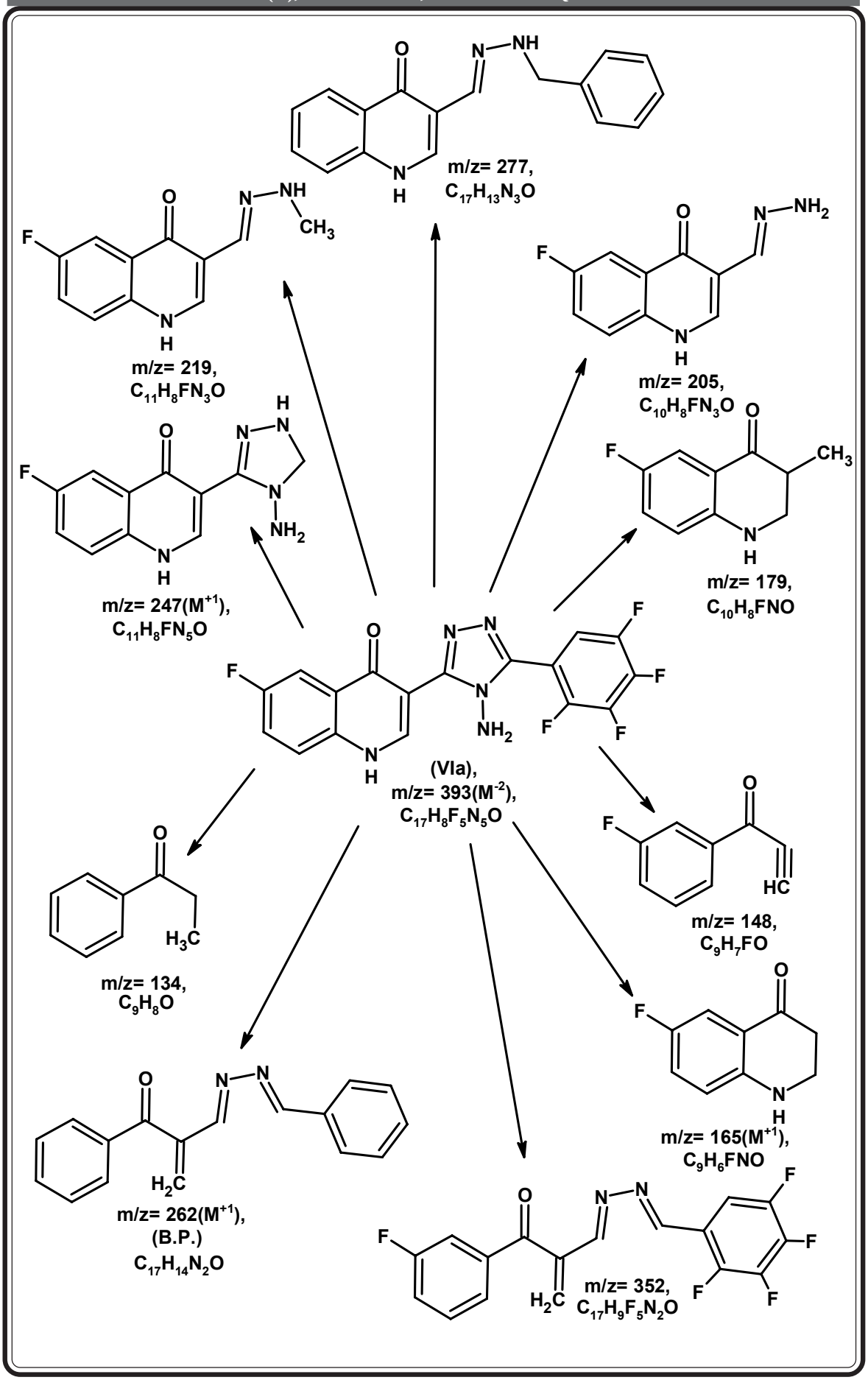
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 7/11/2006 1:36:09 PM
Sample Name : JJS-M-40
Sample ID : JJS-M-40
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-M-40.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:14.2(Scan#:1663)
MassPeaks:195 BasePeak:261(147266)
RawMode:Averaged 13.2-15.0(1544-1767)
BG Mode:None
intensity

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C17H13N3O
m/z= 219,
C11H8FN3O
m/z= 205,
C10H8FN3O
m/z= 247(M+1),
C11H8FN5O
m/z= 179,
C10H8FNO
(VIa),
m/z= 393(M-2),
C17H8F5N5O
m/z= 148,
C9H7FO
m/z= 134,
C9H8O
m/z= 165(M+1),
C9H6FNO
m/z= 262(M+1),
(B.P.)
C17H14N2O
m/z= 352,
C17H9F5N2O

MASS SPECTRAL STUDY OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRAFLUOROPHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-7-CHLORO QUINOLINE-4(1H)-ONE (VI_b).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 9/1/2005 11:35:08 AM
Sample Name	: JJS-2
Sample ID	: JJS-2
Data File	: C:\GCMSsolution\Data\Project1\JJS-2.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune8.qgt

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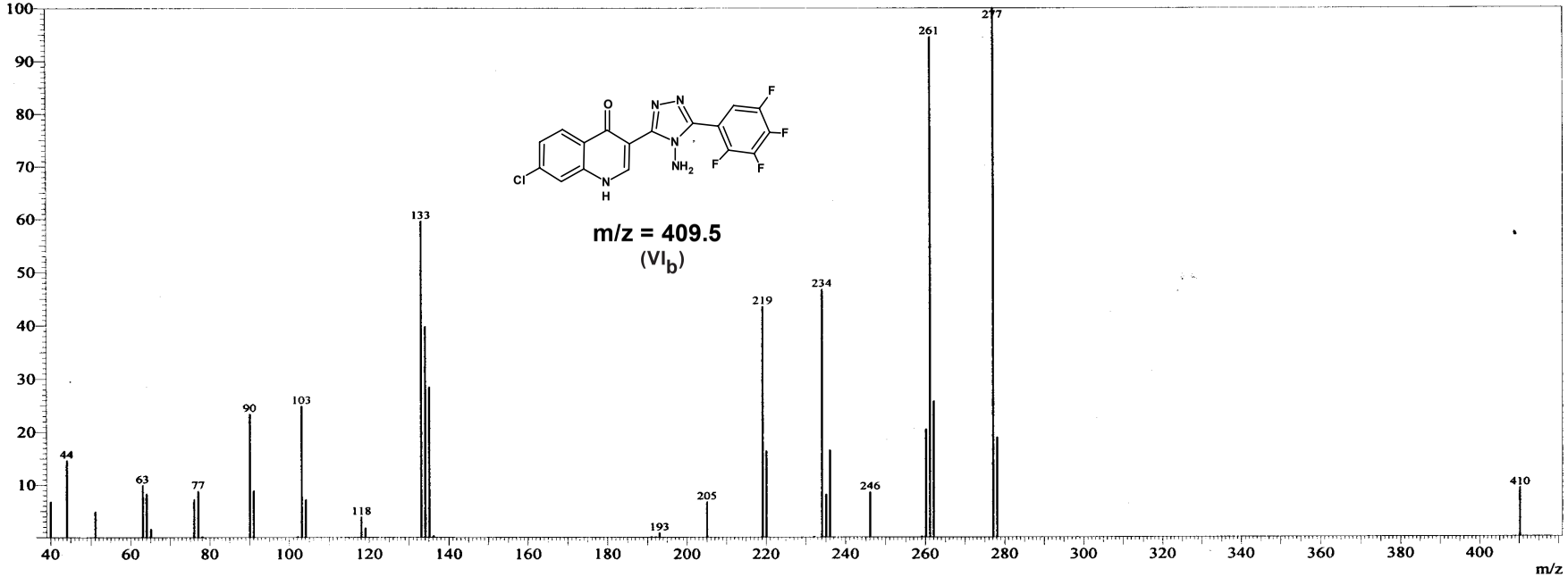
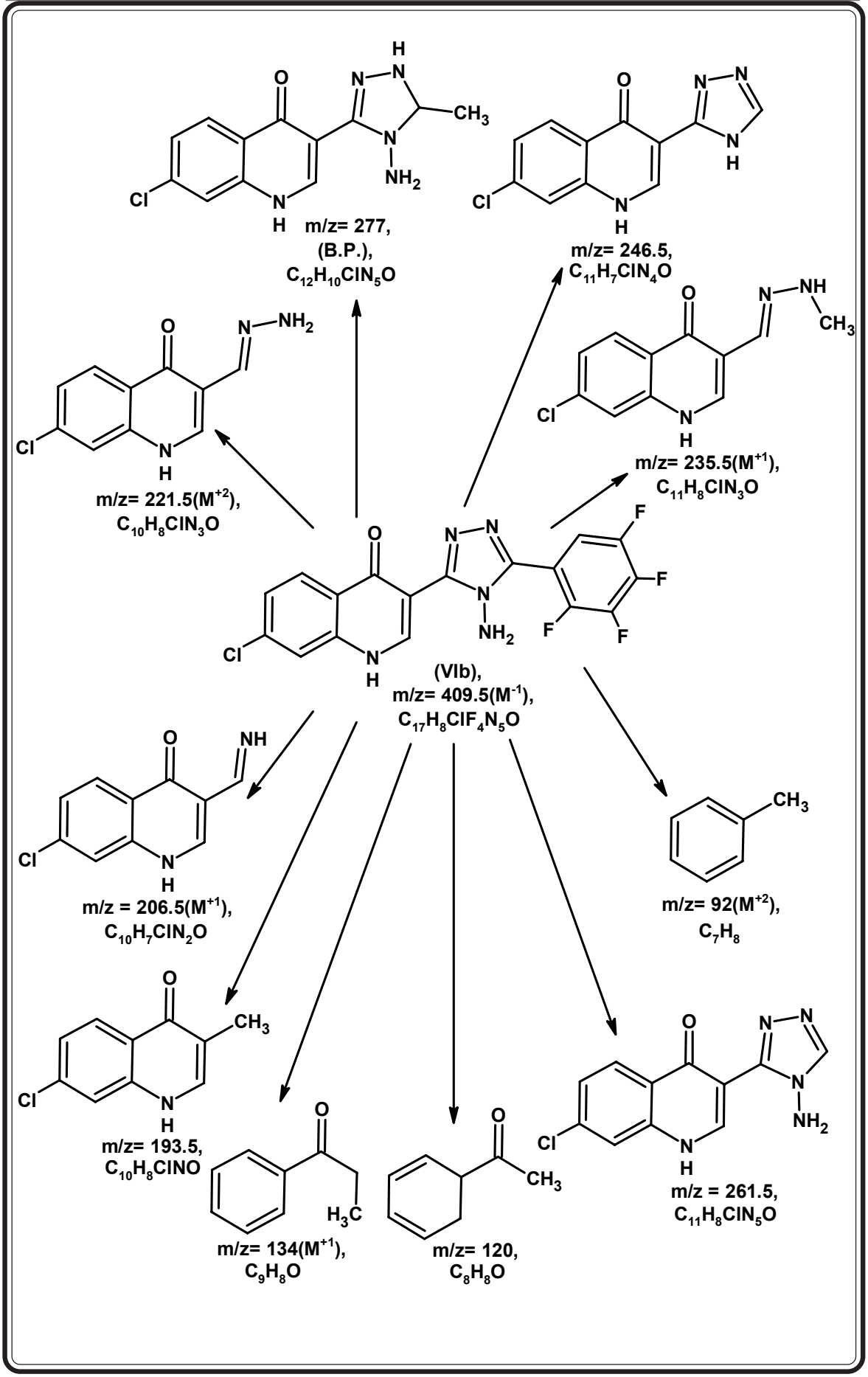
MassPeaks:38 BasePeak:277(17161)
RawMode:Averaged 16.1-17.0(1891-2010)
BG Mode:None
intensity




m/z= 277,
(B.P.),
$C_{12}H_{10}ClN_5O$
m/z= 246.5,
$C_{11}H_7ClN_4O$
m/z= 221.5(M^{+2}),
$C_{10}H_8ClN_3O$
m/z= 235.5(M^{+1}),
$C_{11}H_8ClN_3O$
(VIb),
m/z= 409.5(M^{-1}),
$C_{17}H_8ClF_4N_5O$
m/z = 206.5(M^{+1}),
$C_{10}H_7ClN_2O$
m/z= 92(M^{+2}),
C_7H_8
m/z= 193.5,
$C_{10}H_8ClNO$
m/z= 134(M^{+1}),
C_9H_8O
m/z= 120,
C_8H_8O
m/z = 261.5,
$C_{11}H_8ClN_5O$

MASS SPECTRAL STUDY OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRAFLUOROPHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-6-FLUORO-7-CHLOROQUINOLINE-4(1H)-ONE (VI_d).

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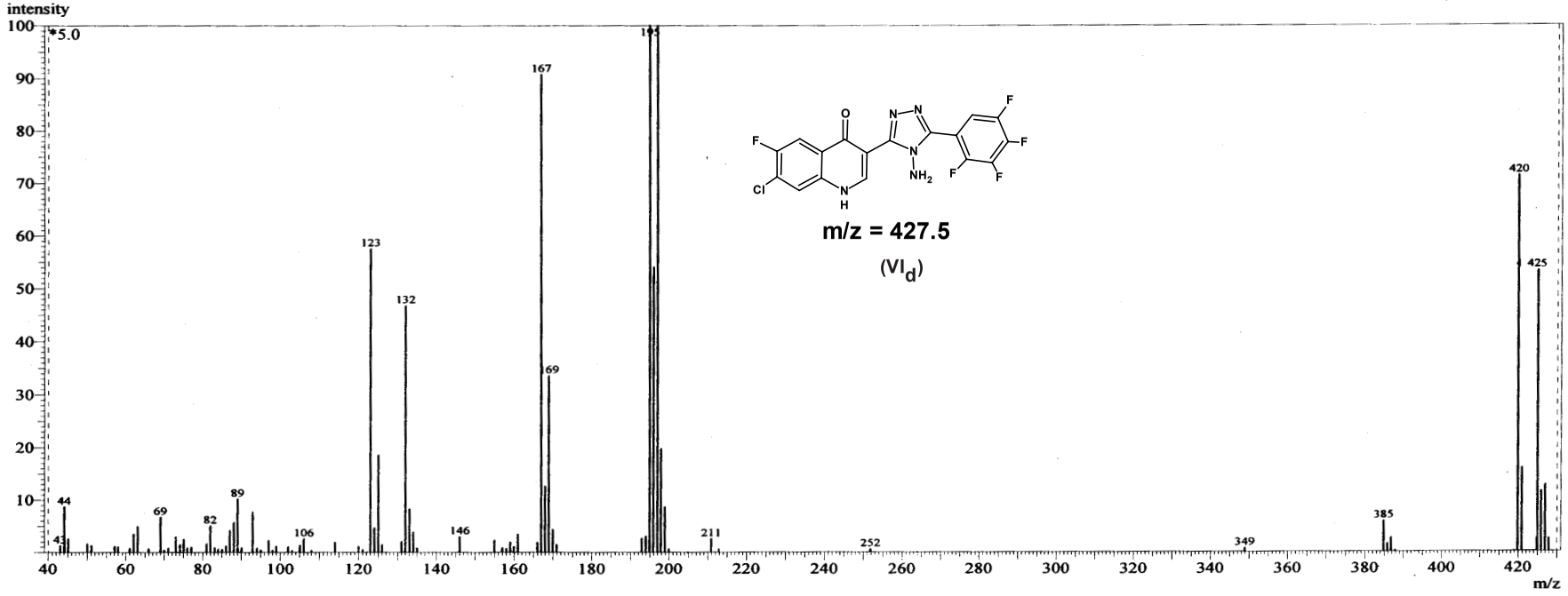
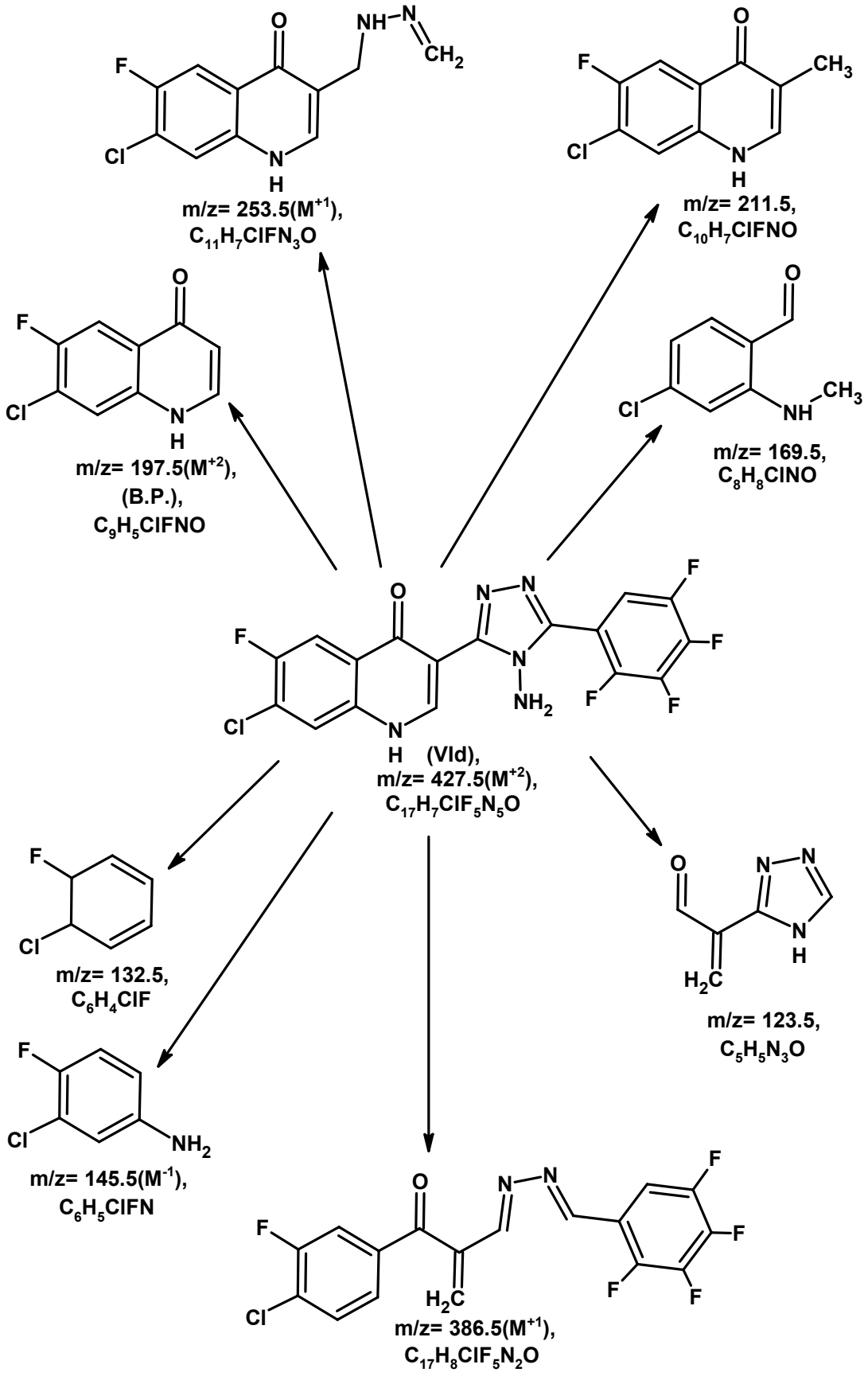
Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 12/24/2005 4:44:04 PM
Sample Name	: JJSM-10
Sample ID	: JJSM-10
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJSM-10.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune9.qgt

Line#:1 R.Time:9.3(Scan#:1087)
MassPeaks:90 BasePeak:195(541420)
RawMode:Averaged 7.8-10.4(902-1217)
BG Mode:None
intensity




m/z= 253.5(M+1),
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m/z= 211.5,
C10H7ClFNO
m/z= 197.5(M+2),
(B.P.),
C9H5ClFNO
m/z= 169.5,
C8H8ClNO
(VId),
m/z= 427.5(M+2),
C17H7ClF5N5O
m/z= 132.5,
C6H4ClF
m/z= 123.5,
C5H5N3O
m/z= 145.5(M-1),
C6H5ClFN
m/z= 386.5(M+1),
C17H8ClF5N2O

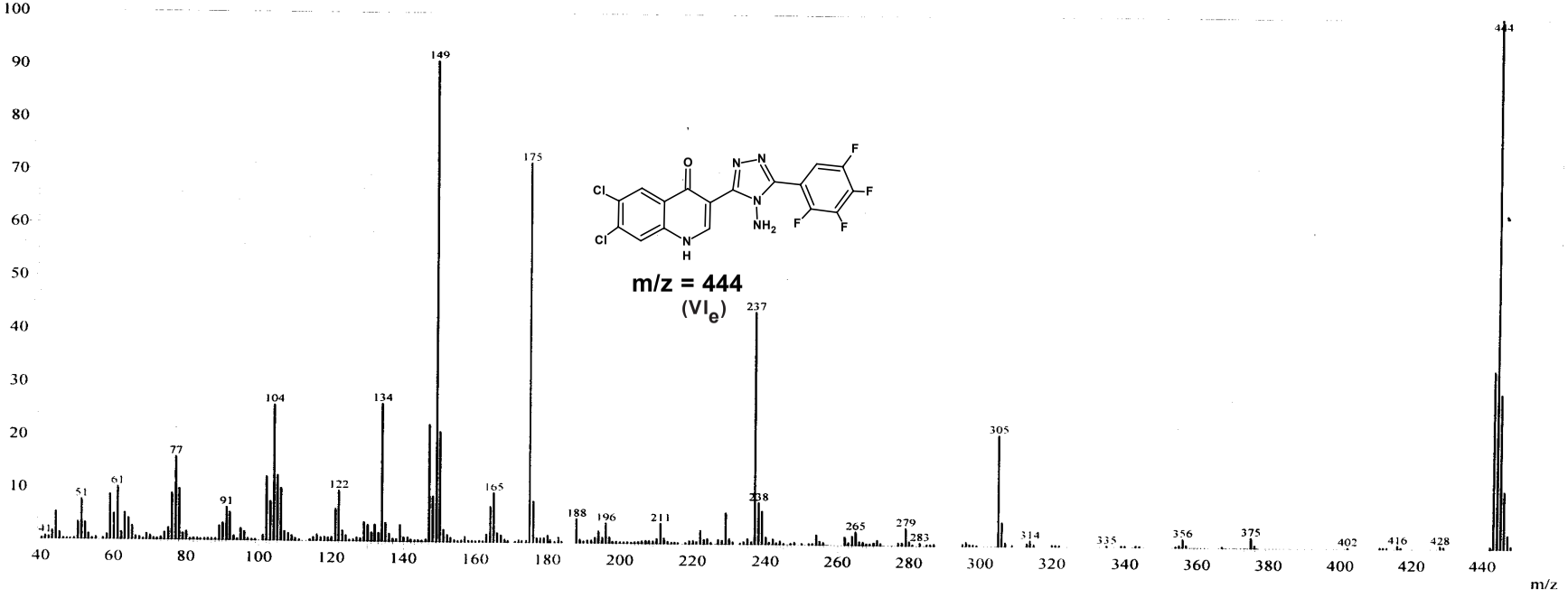
MASS SPECTRAL STUDY OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRAFLUOROPHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-6,7-DICHLOROQUINOLINE-4(1H)-ONE (VI_e).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 9/5/2006 3:16:26 PM
Sample Name : JJS-M-42
Sample ID : JJS-M-42
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-M-42.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:9.8(Scan#:1137)
MassPeaks:265 BasePeak:444(642544)
RawMode:Single 9.8(1137)
BG Mode:None
intensity



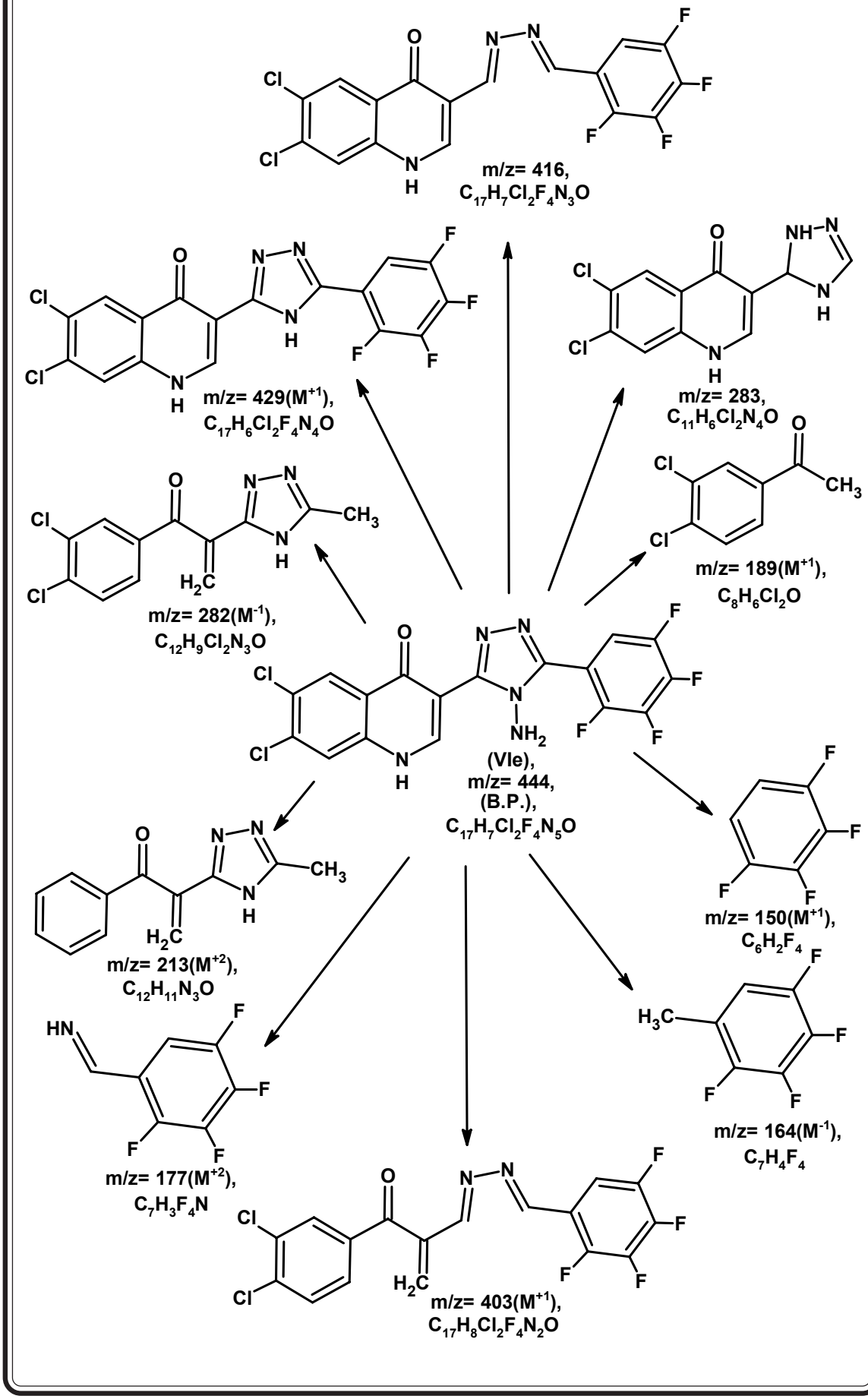

m/z= 416,
C17H7Cl2F4N3O
m/z= 429(M+1),
C17H6Cl2F4N4O
m/z= 283,
C11H6Cl2N4O
m/z= 282(M-1),
C12H9Cl2N3O
m/z= 189(M+1),
C8H6Cl2O
(VIe),
m/z= 444,
(B.P.),
C17H7Cl2F4N5O
m/z= 213(M+2),
C12H11N3O
m/z= 150(M+1),
C6H2F4
m/z= 177(M+2),
C7H3F4N
m/z= 164(M-1),
C7H4F4
m/z= 403(M+1),
C17H8Cl2F4N2O

TABLE NO. 6A : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRAFLUORO-PHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-SUBSTITUTED- QUINOLONE-4(1H)-ONE (VI_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) S. pyogens MTCC- 442					S. aureus MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
VIa	6-F	-	8	10	12	15	-	8	9	10	13
VIb	7-Cl	-	11	11	14	16	-	7	8	11	15
VIc	6-Cl	-	10	13	15	17	-	7	8	9	11
VId	7-Cl-6-F	-	13	11	13	15	-	8	8	9	12
VIe	$6,7-(Cl)_2$	-	10	14	16	18	-	8	10	12	16
VIf	$6-NO_2$	-	9	11	13	15	-	8	9	11	13
VIg	$6-OCH_3$	-	8	10	12	14	-	9	11	13	14
VIh	$6-CH_3$	-	9	9	11	13	-	7	8	9	11
VIi	$7,8-(CH_3)_2$	-	9	10	12	14	-	8	8	8	11
VIj	-	-	8	10	12	14	-	7	8	10	13

Comparative activity of (VI_{a-j}) with known choosen standard drugs

Standard drug	Antibacterial activity									
					V_e					V_e
Amoxicilin	12	14	15	16	18	10	12	14	15	16
Chloramphenicol	14	15	18	19	24	14	17	20	21	24
Sparfloxacin	14	22	24	26	28	24	26	27	28	32
Levofloxacin	18	21	22	27	29	20	24	26	27	35

N.B.(-): No Activity

TABLE NO. 6B : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRAFLUORO-PHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-SUBSTITUTED- QUINOLONE-4(1H)-ONE (VI_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) B. Subtillis MTCC- 441					E.coli MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
VIa	6-F	-	9	10	12	14	-	7	8	9	10
VIb	7-Cl	-	10	11	12	14	-	9	10	12	14
VIc	6-Cl	-	10	11	13	15	-	6	7	8	10
VId	7-Cl-6-F	-	9	10	11	13	-	5	6	7	8
VIe	6,7-$(Cl)_2$	-	9	10	11	12	-	8	9	11	13
VIf	6-NO_2	-	10	11	12	14	-	7	10	11	12
VIg	6-OCH_3	-	10	12	13	15	-	6	8	9	10
VIh	6-CH_3	-	9	10	11	13	-	6	9	11	13
VIi	7,8-$(CH_3)_2$	-	8	10	12	14	-	7	8	10	12
VIj	-	-	9	10	13	15	-	7	8	11	14
Comparative activity of (VI_{a-j}) with known choosen standard drugs											
Standard drug		**Antibacterial activity**									
Amoxicilin		12	15	16	18	19	11	14	16	18	20
Chloramphenicol		18	22	24	26	27	17	20	23	25	26
Sparfloxacin		22	24	25	26	29	20	22	25	26	28
Levofloxacin		24	26	28	29	31	23	25	26	29	30

N.B.(-): No Activity

TABLE NO. 6C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 3-[4'-AMINO-5'-(2'',3'',4'',5''-TETRAFLUORO-PHENYL)-4H-1',2',4'-TRIAZOL-3'-YL]-SUBSTITUTED-QUINOLONE-4(1H)-ONE (VI_{a-j}). (Different Inhibition-Concentration in µg/ml).

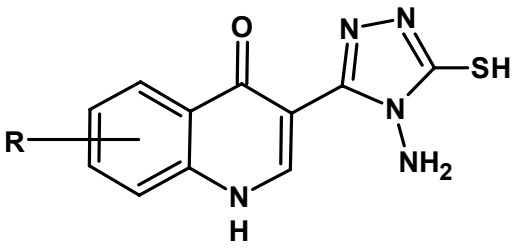
Compd No.	R	Antifungal activity (Zones of inhibition in m.m.) C. albicans MTCC- 227					A.niger MTCC- 282				
		5	25	50	100	250	5	25	50	100	250
VIa	6-F	-	7	9	11	13	-	7	8	10	13
VIb	7-Cl	-	8	10	11	13	-	8	9	11	14
VIc	6-Cl	-	6	8	13	16	-	7	9	12	15
VId	7-Cl-6-F	-	6	8	11	13	-	6	8	10	12
VIe	6,7-$(Cl)_2$	-	7	9	10	12	-	7	8	9	11
VIf	6-NO_2	-	6	8	11	13	-	8	9	11	14
VIg	6-OCH_3	-	5	7	9	11	-	6	7	8	10
VIh	6-CH_3	-	6	7	8	10	-	6	7	8	9
VIi	7,8-$(CH_3)_2$	-	6	8	10	13	-	7	9	10	12
VIj	-C_4H_4	-	8	10	11	14	-	6	9	12	16
Comparative activity of (VI_{a-j}) with known choosen standard drugs											
Standard drug		**Antifungal activity**									
Griseofulvin		16	18	21	23	25	17	19	21	22	23
Fluconazole		14	16	18	21	22	15	17	18	20	21

N.B.(-): No Activity

SECTION - VII

PREPARATION AND BIOLOGICAL EVALUATION OF-3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-SUBSTITUTED-QUINOLONE-4-(1H)-ONES.

Keeping in view, various biological properties[34-85] of **4-quinolones** and in order to have highly potent therapeutic agents, the synthesis of **3-[1'-N-amino-2'-mercapto-1',3',4'-triazol-5'-yl)-Substituted-quinolone-4-(1H)-ones (VIIa-j).** have been accomplished by the cyclocondensation of different **substituted 1,4-dihydroquinoline-4-one-3-carbohydrazides (5a-j), carbon disulphide** and **pottassium hydroxide** followed by the action of **hydrazine hydrate**.



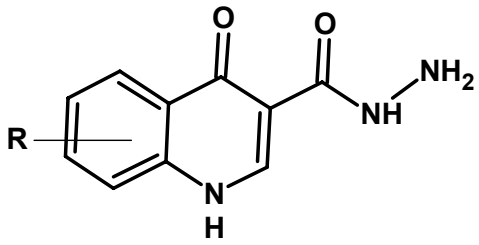
(VIIa-j)

R=Substituted phenyl

The constitution of the products **(VIIa-j)** have been delineated by **elemental analyses, IR, PMR** and **Mass** spectral data**.**

The products **(VIIa-j)** were assayed for their ***in vitro*** biological assay like antibacterial activity towards **S. pyogens MTCC-442 , S. aureus MTCC-96** and **B. subtillis MTCC-441(Gram positive)** and **E. coli MTCC-443 (Gram negative)** bacterial strains and antifungal activity towards **Aspergillus niger MTCC-282** and **Candida albicans MTCC-227** at different concentrations i.e. :0(control), 5, 25, 50,100, 250 (µg/ml), for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds **(VIIa-j)** were compared with standard drugs,viz., **Amoxicillin, Chloramphenicol, Sparfloxacin, Levofloxacin** (antibacterial)**, Griseofluvin, Fluconazole** (antifungal)**.**

REACTION SCHEME

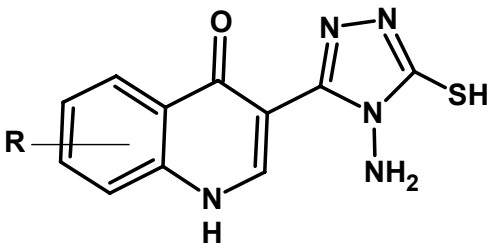


(5a-j)
R= substituted phenyl

(1) KOH, CS_2

(2) NH_2-NH_2 $2H_2O$

△



(VIIa-j)
R= substituted phenyl

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF SUBSTITUTED--3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-QUINOLONE-4-(1H)-ONES.

(A) Preparation of Diethyl-(3-chloro-4-fluoro amino phenyl)- amino methylene malonate (I_d).

For preparation, refer Part-1,Section-I, **page No. 30.**

(B) Preparation of Ethyl-7-chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carboxylate (II_d).

For preparation, refer Part-1,Section-II, **page No.58.**

(C) Preparation of 7-chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carbohydrazide (5_d).

For preparation, refer Part-1,Section-V, **page No.137.**

(D) Preparation of 7-chloro-6-fluoro-3-[1'-N-amino-2'-mercapto-1',3',4' -triazol-5'-yl)-quinolone-4-(1H)-one (VIId).

A mixture of 7-chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carbohydrazide **(5_d)** (2.55 gm, 0.01 M) and KOH (0.84 gm, 0.015 M) in absolute ethanol (30 ml), was stirred at 35 to 40 ^{O}C. Carbon disulphide (1.52 ml, 0.02 M) was added in to the reaction mixture within 30 minutes under stirring. The reaction mixture was then stirred at room tempreture for 8 hrs. under anhydrus condition. The white solid mass (dithiocarbamate) seprated out, which was filtered, washed with ethanol and dried.

This dithiocarbamate was dissolved in water (25 ml) and hydrazine hydrate (80%) (3.9 ml 0.1mol) was added to the resulting solution with stirring. The reaction mixture was heated under reflux for 8 hrs.The reaction mass was then allowed to cool at 35 to 40 ^{O}C and poured in to crushed ice. The pH was then adjusted between 5.5 to 6.5 by acidifying the mixture with Conc. hydro chloric acid at the temperature 0-5 ^{O}C. The creamish white solid so obtained was filtered, washed with water and recrystallized from dimethyl formamide**.** Yield : 85 %, M.P.: 289^{O}C, (Required : C, 42.38 %; H, 2.26 %; N, 22.47 % for

$C_{11}H_7N_5OSClF$, Found : C, 42.32 %; H, 2.24 %; N, 22.42%).

TLC solvent system R_{f_1} : Ethyl acetate : Hexane(4.0 : 6.0) = 0.57**.**
TLC solvent system R_{f_2} : Methanol : Toluene(1.5 : 8.5) = 0.52**.**

Similarly, other compounds **(VIIa-j)** were synthesized. The physical data are recorded in **Table No. 7**.

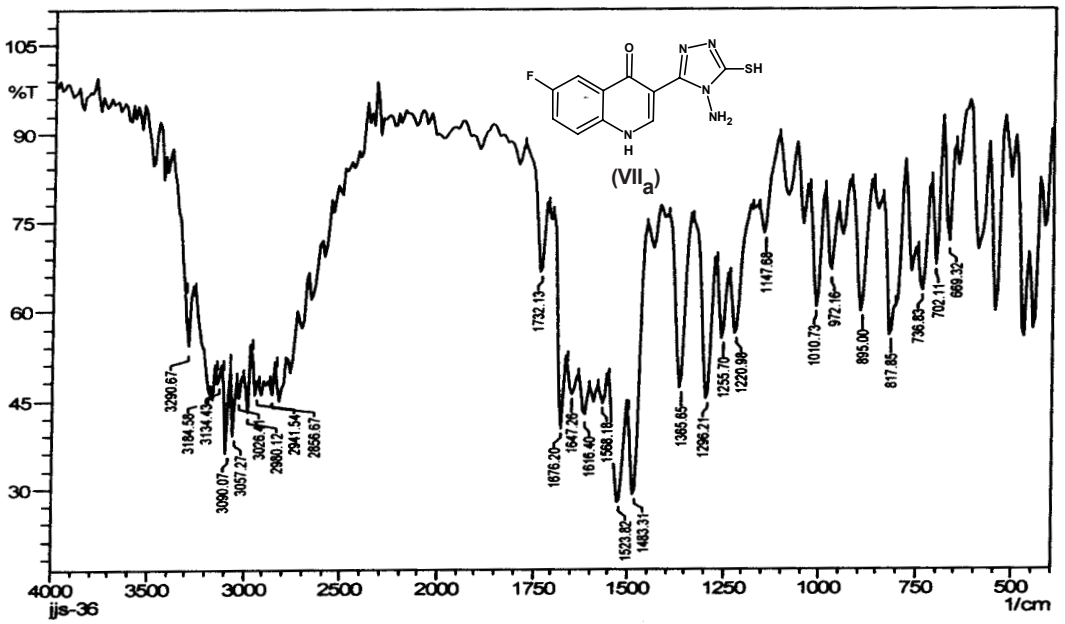
(E) Antimicrobial activity of Substituted-3-[1'-N-amino-2'-mercapto-1',3',4'-triazol-5'-yl)-quinolone-4-(1H)-ones (VIIa-j).

Antimicrobial activity testing was carried out as described in Part-1(A), Section-I, page No. 30-31. The MIC values of test solution are recorded in **Table No. 7A, 7B,** and **7C.**

TABLE NO. 7 : PHYSICAL CONSTANTS OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-SUBSTITUTED-QUINOLONE-4-(1H)-ONES (VII_{a-j}).

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. ^oC 5	Yield % 6	R_f Value R_{f_1} 7	R_{f_2}	% of Nitrogen Calcd. / Found 8
VII_a	6-F	$C_{11}H_8N_5OFS$	277.0	295^o	83	0.51	0.46	25.27 / 25.20
VII_b	7-Cl	$C_{11}H_8N_5OClS$	293.5	238^o	80	0.46	0.47	23.85 / 23.80
VII_c	6-Cl	$C_{11}H_8N_5OClS$	293.5	241^o	84	0.56	0.51	23.85/ 23.79
VII_d	7-Cl-6-F	$C_{11}H_7N_5OClSF$	311.5	289^o	85	0.57	0.52	22.47 / 22.42
VII_e	6,7-$(Cl)_2$	$C_{11}H_7N_5OCl_2S$	328.0	279^o	81	0.59	0.51	21.34 / 21.29
VII_f	6-NO_2	$C_{11}H_8N_6O_3S$	304.0	281^o	78	0.44	0.41	27.63 / 27.57
VII_g	6-OCH_3	$C_{12}H_{11}N_5O_2S$	289.0	251^o	59	0.46	0.49	24.22 / 24.19
VII_h	6-CH_3	$C_{12}H_{11}N_5OS$	273.0	241^o	75	0.51	0.43	25.64 / 25.59
VII_i	7,8-$(CH_3)_2$	$C_{13}H_{13}N_5OS$	287.0	285^o	79	0.56	0.42	24.39 / 24.32
VII_j	-	$C_{15}H_{11}N_5OS$	309.0	228^o	78	0.62	0.44	22.65 / 22.61

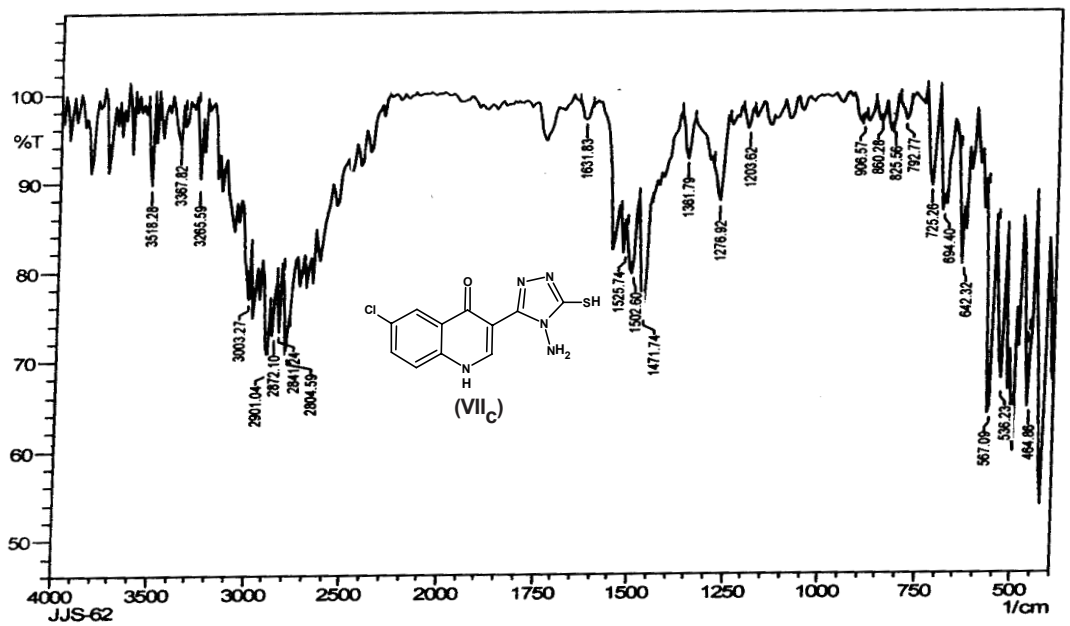
IR SPECTRAL STUDY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-6-FLUORO QUINOLONE-4-(1H)-ONE (VII_a).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2941.5	2975 - 2850	96
	C-H (sym. str., m)	2856.6	2900 - 2800	96
	C-H (asym. def., m)	1483.3	1470 - 1435	96
	C-H (sym. def., m)	1365.6	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3026.4	3080 - 3010	97
	C=C & C-C (str., v)	1525.7	1600 - 1450	97
	C-H (o.o.p. def., m)	817.8	825 - 800	97
triazole moiety	C-N (str., v)	1296.2	1340 - 1250	97
	C=N (str., v)	1647.2	1690-1650	97
	N-N (def., v)	1147.6	1220 - 1020	97
	C-S (str.m)	702.1	700-650	97
Quinolone moiety	N-H (str., b)	3290.6-3026.4	3400 - 3000	98
	N-H (def., s,m)	1616.4	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1676.2	1690 - 1640	98
Halogen Subtitution	C-F (str., b)	1365.6-1220.9	1400 - 1080	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

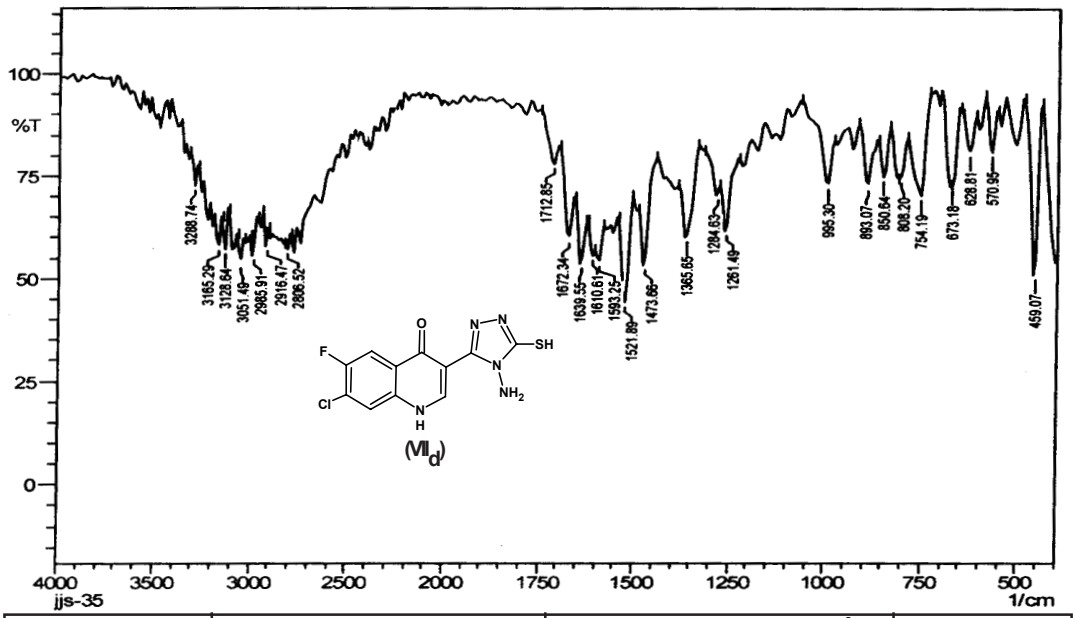
IR SPECTRAL STUDY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-6-CHLORO QUINOLONE-4-(1H)-ONE (VII_C).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2901.0	2975 - 2850	96
	C-H (sym. str., m)	2841.2	2900 - 2800	96
	C-H (asym. def., m)	1471.7	1470 - 1435	96
	C-H (sym. def., m)	1361.7	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3003.2	3080 - 3010	97
	C=C & C-C (str., v)	1525.7	1600 - 1450	97
	C-H (o.o.p. def., m)	825.5	825 - 800	97
triazole moiety	C-N (str., v)	1276.9	1340 - 1250	97
	C=N (str., v)	1631.8	1690-1650	97
	N-N (def., v)	1203.6	1220 - 1020	97
	C-S(str.m)	694.4	700-650	97
Quinolone moiety	N-H (str., b)	3367.8-3003.2	3400 - 3000	98
	N-H (def., s,m)	1560.1	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1631.8	1690 - 1640	98
Halogen Subtitution	C-Cl (str., b)	792- 642	800 - 600	99
	C-F (str., b)	1381.7-1203.6	1400 - 1080	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

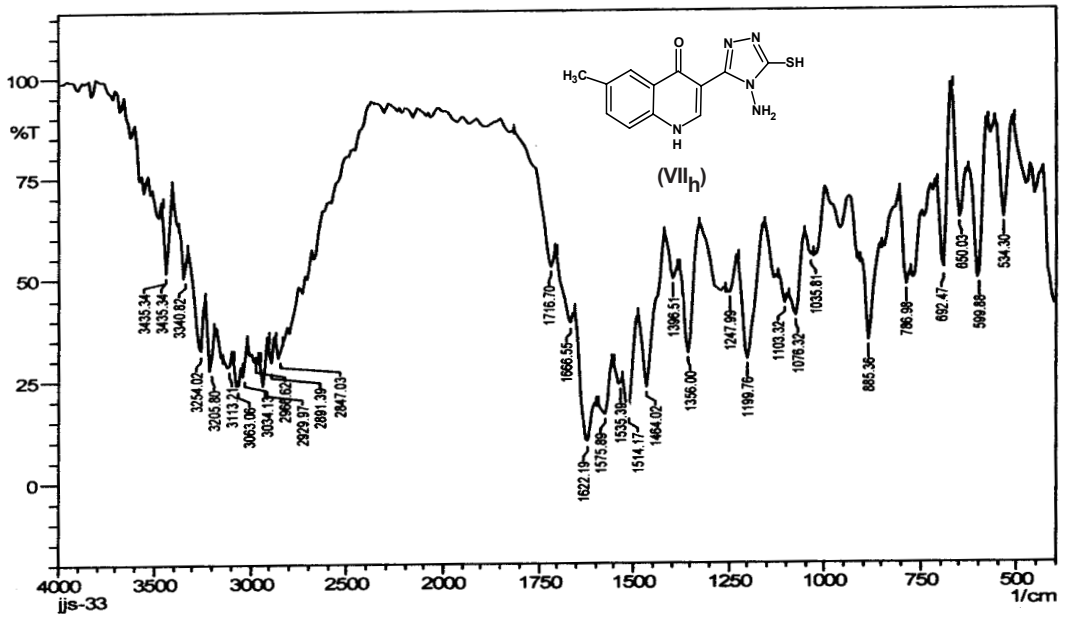
IR SPECTRAL STUDY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-7-CHLORO-6-FLUOROQUINOLONE-4-(1H)-ONE (VII_d).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2916.4	2975 - 2850	96
	C-H (sym. str., m)	2806.5	2900 - 2800	96
	C-H (asym. def., m)	1473.6	1470 - 1435	96
	C-H (sym. def., m)	1365.6	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3051.4	3080 - 3010	97
	C=C & C-C (str., v)	1521.8	1600 - 1450	97
	C-H (i.p. def., m)	1070.3	1150 - 1050	97
	C-H (o.o.p. def., m)	808.2	825 - 800	97
triazole moiety	C-N (str., v)	1284.6	1340 - 1250	98
	C=N (str., v)	1672.3	1690-1650	98
	N-N (def., v)	1190.5	1220 - 1020	98
	C-S(str.m)	673.1	700-650	98
Quinolone moiety	N-H (str., b)	3288.7-3051.4	3400 - 3000	98
	N-H (def., s,m)	1639.5	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1672.3	1690 - 1640	98
Halogen Subtitution	C-F (str., b)	1365.6-1261.4	1400-1000	99
	C-Cl (str., b)	808-628	800 - 600	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

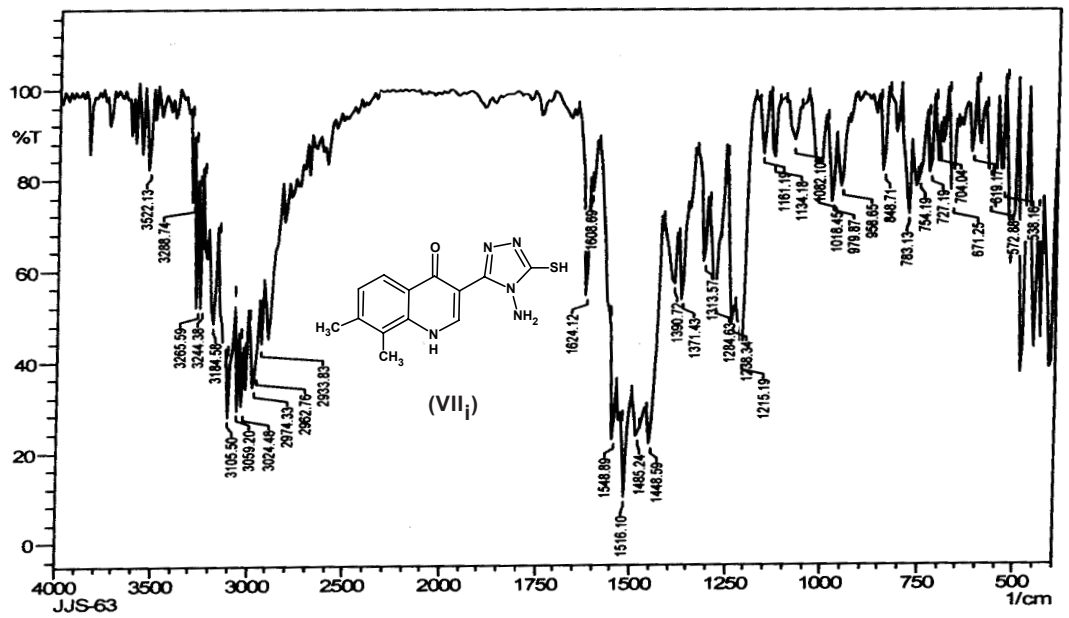
IR SPECTRALSTUDY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL--5'-YL)-6-METHYLQUINOLONE-4-(1H)-ONE (VII_h).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2966.6	2975 - 2850	96
	C-H (sym. str., m)	2847.0	2900 - 2800	96
	C-H (asym. def., m)	1464.0	1470 - 1435	96
	C-H (sym. def., m)	1396.5	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3034.1	3080 - 3010	97
	C=C & C-C (str., v)	1535.3	1600 - 1450	97
	C-H (i.p. def., m)	1103.3	1150 - 1050	97
	C-H (o.o.p. def., m)	885.3	825 - 800	97
triazole moiety	C-N (str., v)	1356.0	1340 - 1250	98
	C=N (str., v)	1666.5	1690-1650	98
	N-N (def., v)	1199.7	1220 - 1020	98
	C-S (str.m)	692.7	700-650	98
Quinolone moiety	N-H (str., b)	3340.8-3034.1	3400 - 3000	98
	N-H (def., s,m)	1622.1	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1716.7	1710 - 1650	98

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

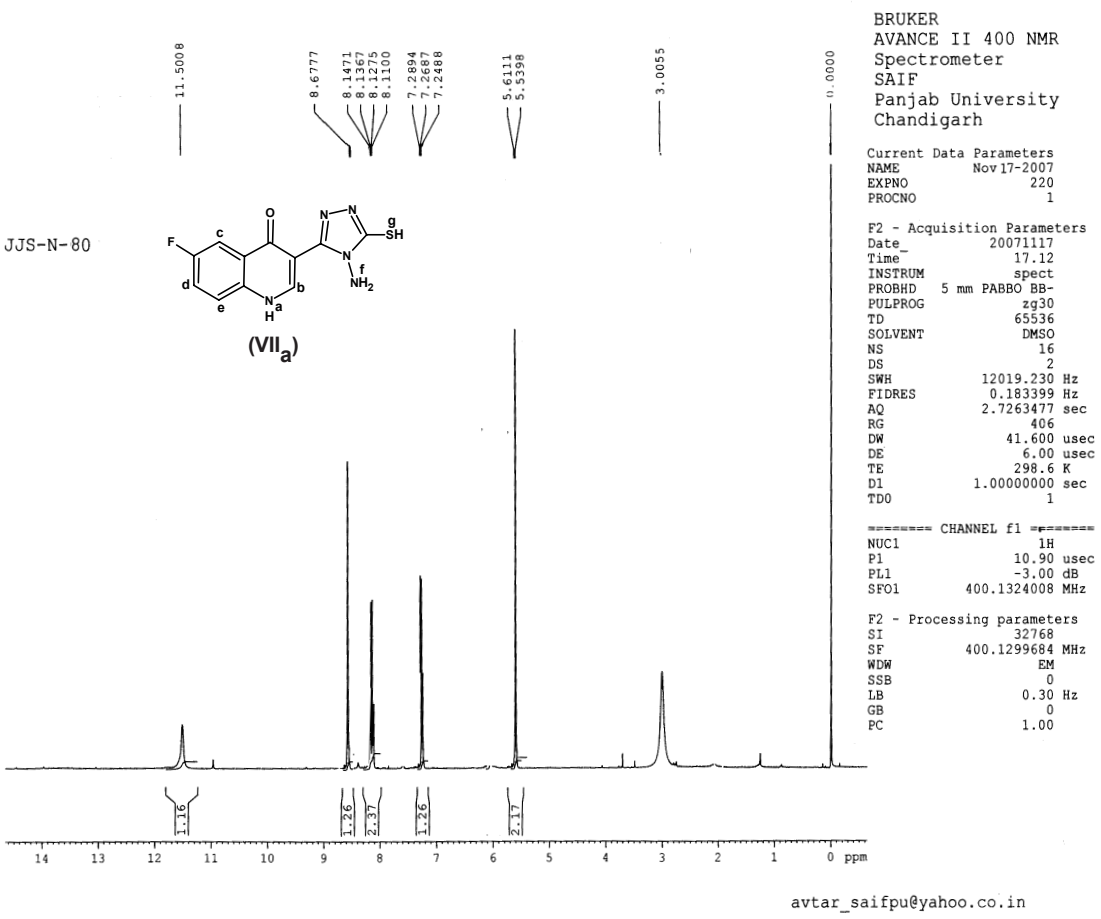
IR SPECTRAL STUDY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL--5'-YL)-7,8-DIMETHYLQUINOLONE-4-(1H)-ONE (VII_i).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2933.8	2975 - 2850	96
	C-H (sym. str., m)	2841.2	2900 - 2800	96
	C-H (asym. def., m)	1448.5	1470 - 1435	96
	C-H (sym. def., m)	1371.4	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3024.4	3080 - 3010	97
	C=C & C-C (str., v)	1608.9	1600 - 1450	97
	C-H (o.o.p. def., m)	848.7	825 - 800	97
triazole moiety	C-N (str., v)	1313.5	1340 - 1250	98
	C=N (str., v)	1624.1	1690-1650	98
	N-N (def., v)	1215.1	1220 - 1020	98
	C-S (str.m)	671.2	700-650	98
Quinolone moiety	N-H (str., b)	3288.7-3024.4	3400 - 3000	98
	N-H (def., s,m)	1548.8	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1624.1	1690 - 1640	98

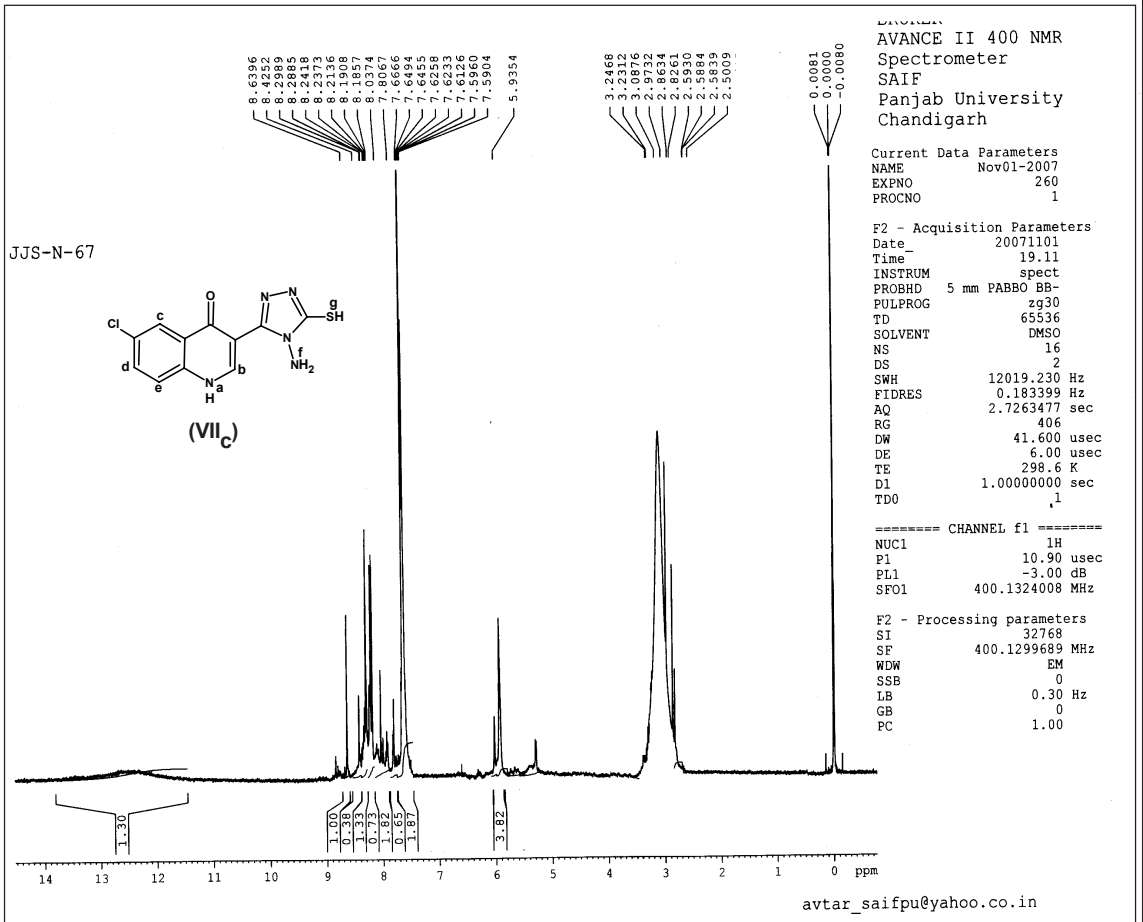
* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

NMR SPECTRAL STUDY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-6-FLUOROQUINOLONE-4-(1H)-ONE (VII_a).



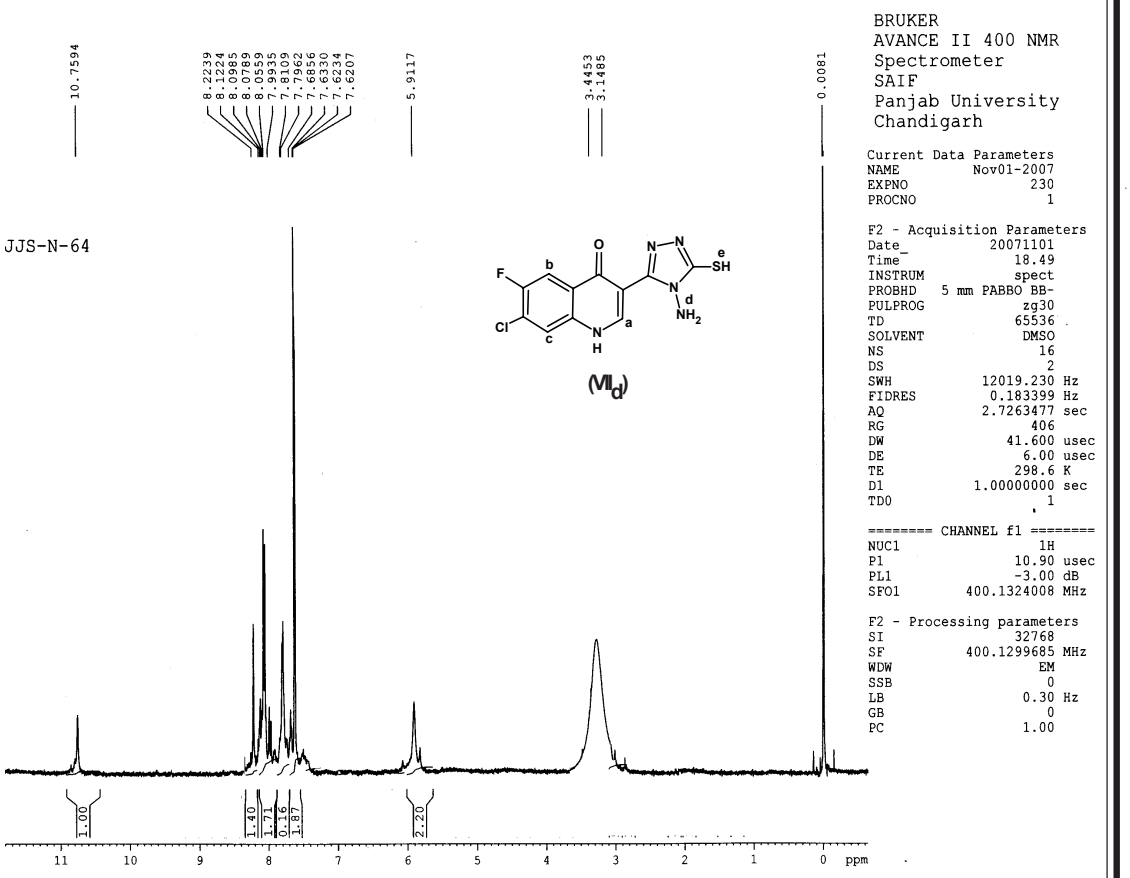
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	5.5398-5.6111	2H	singlet	- NH_2(f)
2	7.2488-7.2894	1H	triplet	- Ar-H(e)
3	8.1100-8.1471	2H	doublet	- Ar-H(c,d)
4	8.6777	1H	doublet	- NH-CH(b)
5	11.5008	1H	singlet	- SH(g)
6	3.0055	-	-	-DMSO-d_6

NMR SPECTRAL STUDY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-6-CHLOROQUINOLONE-4-(1H)-ONE (VII_c).



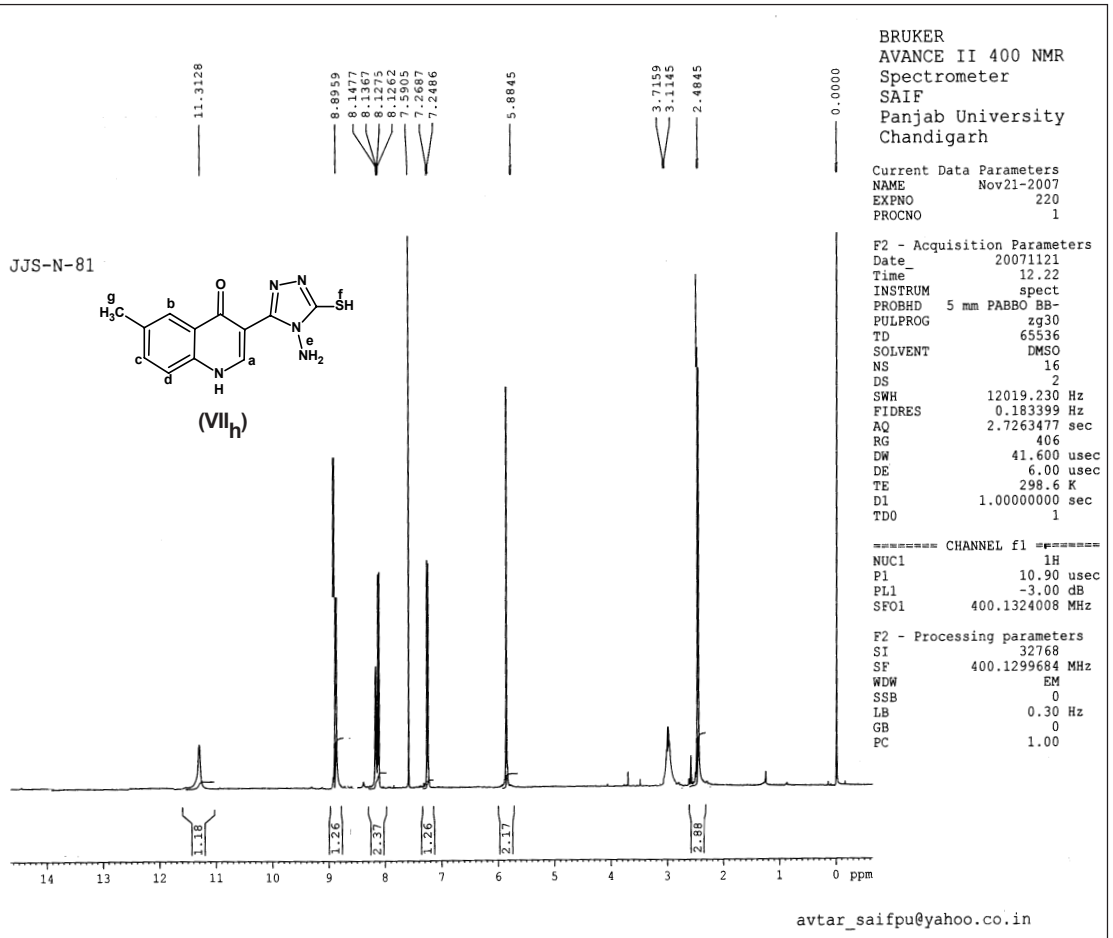
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	5.9354	2H	singlet	- NH_2(f)
2	7.5904-7.666	1H	multiplet	- Ar-H(c)
3	8.0374	1H	multiplet	- Ar-H(d)
4	8.1857-8.2989	1H	multiplet	- Ar-H(e)
5	8.6396	1H	singlet	- NH-CH(b)
6	2.5009-3.2468	-	-	-DMSO-d_6

NMR SPECTRAL STUDY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-7-CHLORO-6-FLUOROQUINOLONE-4-(1H)-ONE (VII_d).



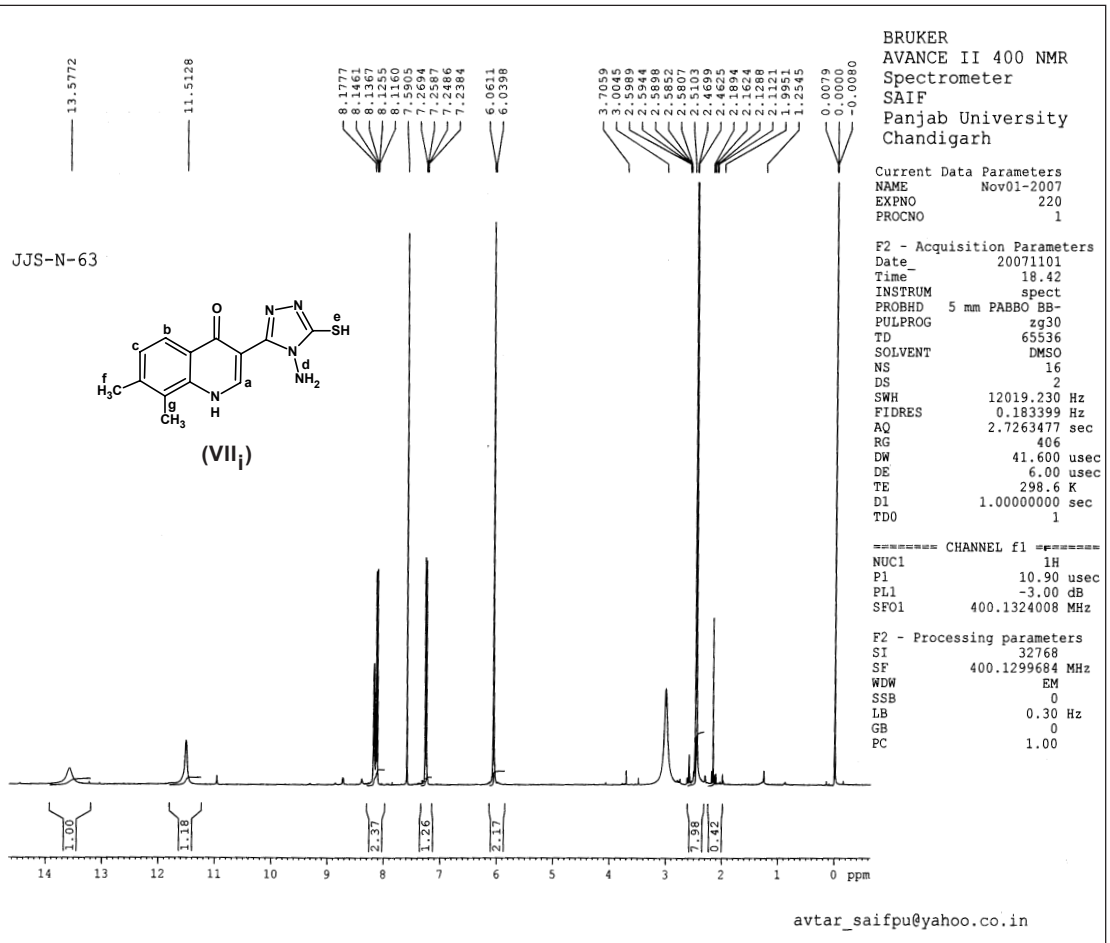
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	5.9117	2H	singlet	- NH_2(d)
2	7.6207-7.6330	1H	multiplet	- Ar-H(c)
3	8.0559-8.1224	1H	multiplet	- Ar-H(b)
4	8.2239	1H	multiplet	-NH-CH(a)
5	10.7594	1H	singlet	-SH(e)
.6	3.1485-3.4453	-	-	-DMSO-d_6

NMR SPECTRAL STUDY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-6-METHYLQUINOLONE-4-(1H)-ONE (VII_h).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	2.4845	3H	singlet	- CH_3(g)
2	5.8845	2H	singlet	- NH_2(e)
3	7.2486-7.2687	1H	doublet	- Ar-H(b)
4	8.1262-8.1477	2H	multiplet	- Ar-H(c,d)
5	8.8959	1H	singlet	-NH-CH(a)
6	11.3128	1H	singlet	-SH(f)
7	3.1145-3.3145	-	-	-DMSO-d_6
8	7.5903	-	-	-$CDCl_3$

NMR SPECTRAL STUDY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-7,8-DIMETHYLQUINOLONE-4-(1H)-ONE (VII_i).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	2.4623-2.5103	6H	singlet	- CH_3(f,g)
2	6.0398-6.0611	2H	singlet	- NH_2(d)
3	7.2384-7.2694	1H	multiplet	-NH-CH(a)
4	8.1160-8.1777	2H	multiplet	- Ar-H(b,c)
5	11.5128	1H	singlet	-SH(e)
6	3.0045	-	-	-DMSO-d_6
7	7.5903	-	-	-$CDCl_3$

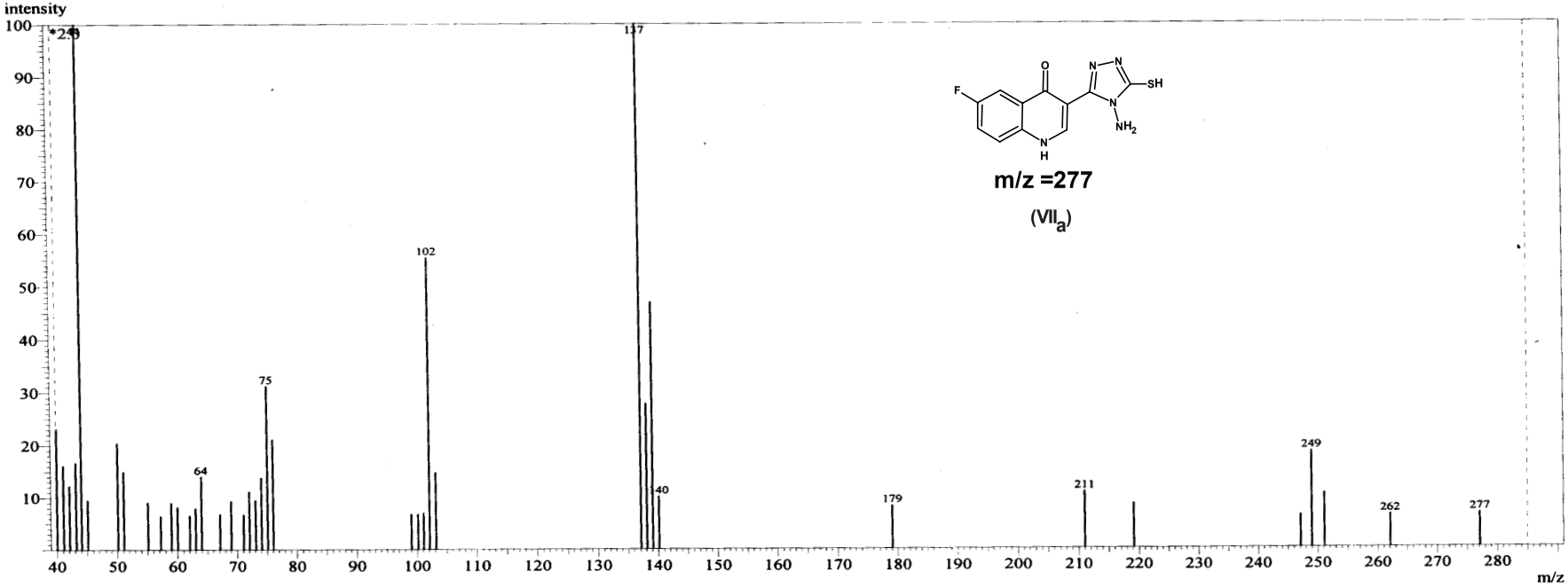
MASS SPECTRAL STUDY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-6-FLUOROQUINOLONE-4-(1H)-ONE (VII_a).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

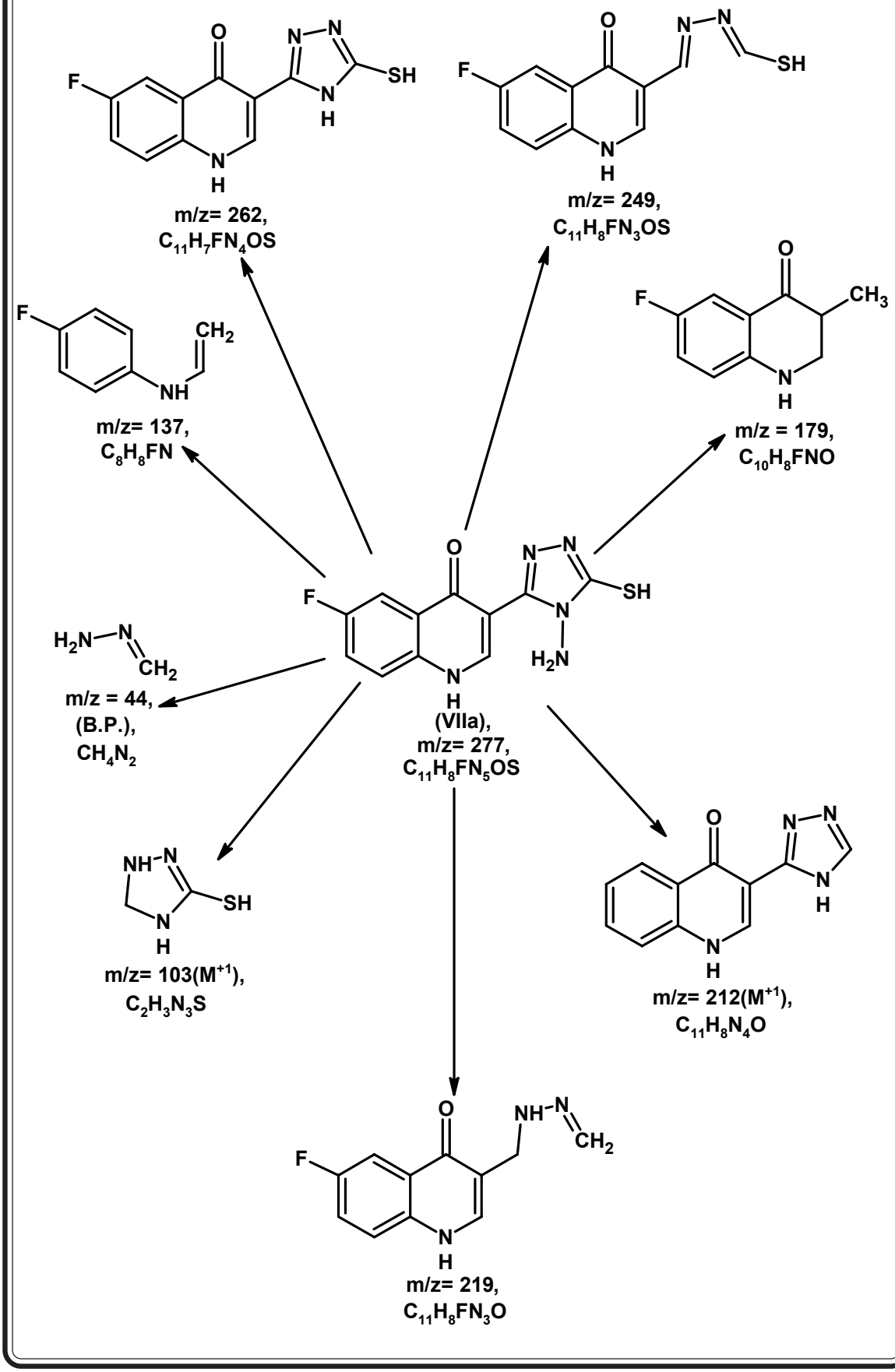
Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 7/11/2006 12:59:19 PM
Sample Name	: JJS-M-39
Sample ID	: JJS-M-39
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-39.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:14.9(Scan#:1750)
MassPeaks:40 BasePeak:44(32746)
RawMode:Single 14.9(1750)
BG Mode:None
intensity



m/z =277

(VII_a)


m/z= 262,
$C_{11}H_7FN_4OS$
m/z= 249,
$C_{11}H_8FN_3OS$
m/z= 137,
C_8H_8FN
m/z = 179,
$C_{10}H_8FNO$
m/z = 44,
(B.P.),
CH_4N_2
(VIIa),
m/z= 277,
$C_{11}H_8FN_5OS$
m/z= 103(M^{+1}),
$C_2H_3N_3S$
m/z= 212(M^{+1}),
$C_{11}H_8N_4O$
m/z= 219,
$C_{11}H_8FN_3O$

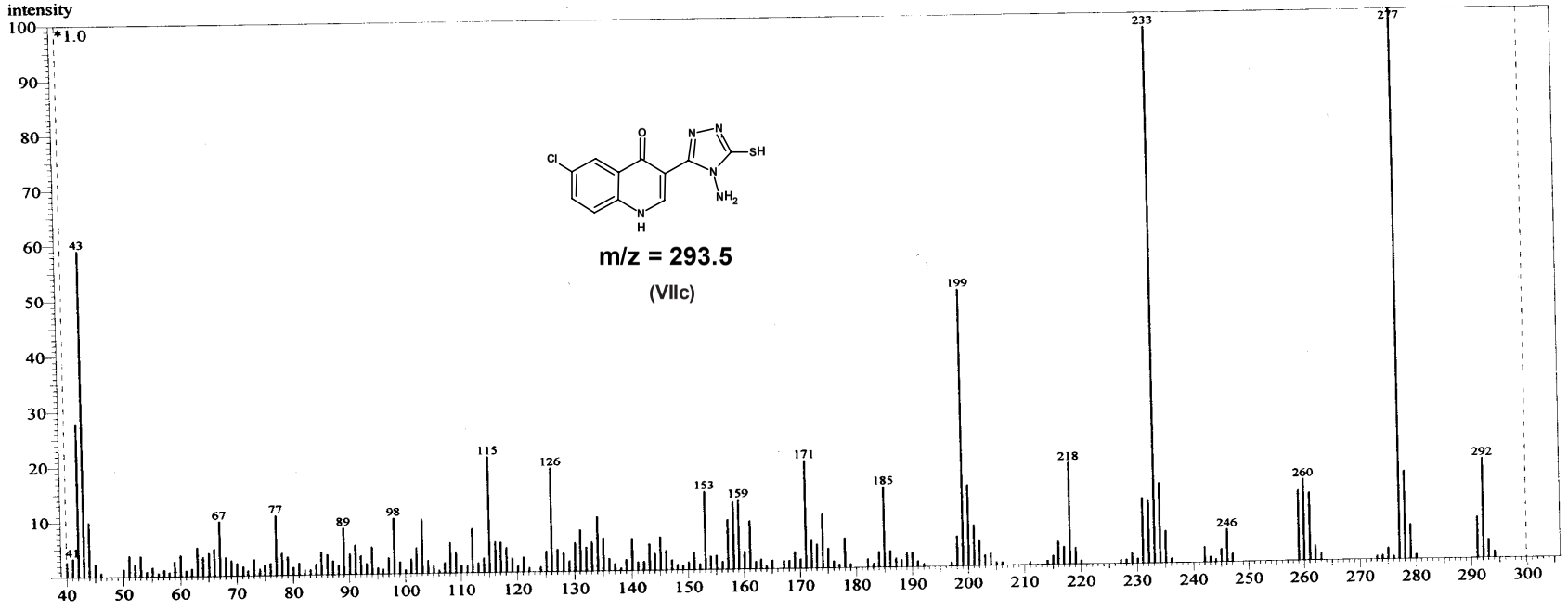
MASS SPECTRAL STUDY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-6-CHLOROQUINOLONE-4-(1H)-ONE (VII_c).

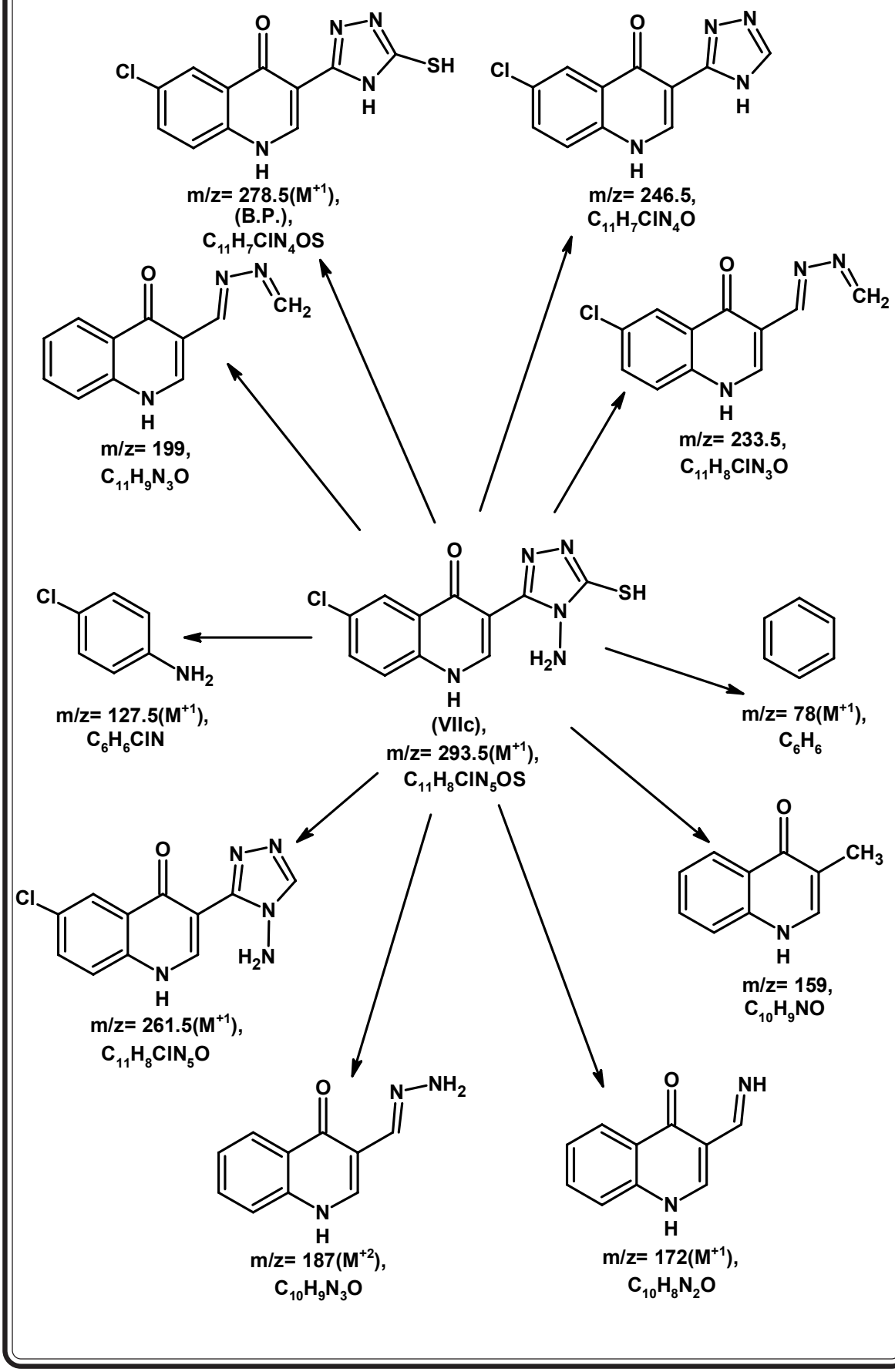
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 4/6/2006 2:50:11 PM
Sample Name	: JJS-M-28
Sample ID	: JJS-M-28
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-28.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune9.qgt

Line#:1 R.Time:4.6(Scan#:517)
MassPeaks:204 BasePeak:277(255214)
RawMode:Single 4.6(517)
BG Mode:None
intensity




m/z= 278.5(M+1),
(B.P.),
C11H7ClN4OS
m/z= 246.5,
C11H7ClN4O
m/z= 199,
C11H9N3O
m/z= 233.5,
C11H8ClN3O
m/z= 127.5(M+1),
C6H6ClN
(VIIc),
m/z= 293.5(M+1),
C11H8ClN5OS
m/z= 78(M+1),
C6H6
m/z= 261.5(M+1),
C11H8ClN5O
m/z= 159,
C10H9NO
m/z= 187(M+2),
C10H9N3O
m/z= 172(M+1),
C10H8N2O

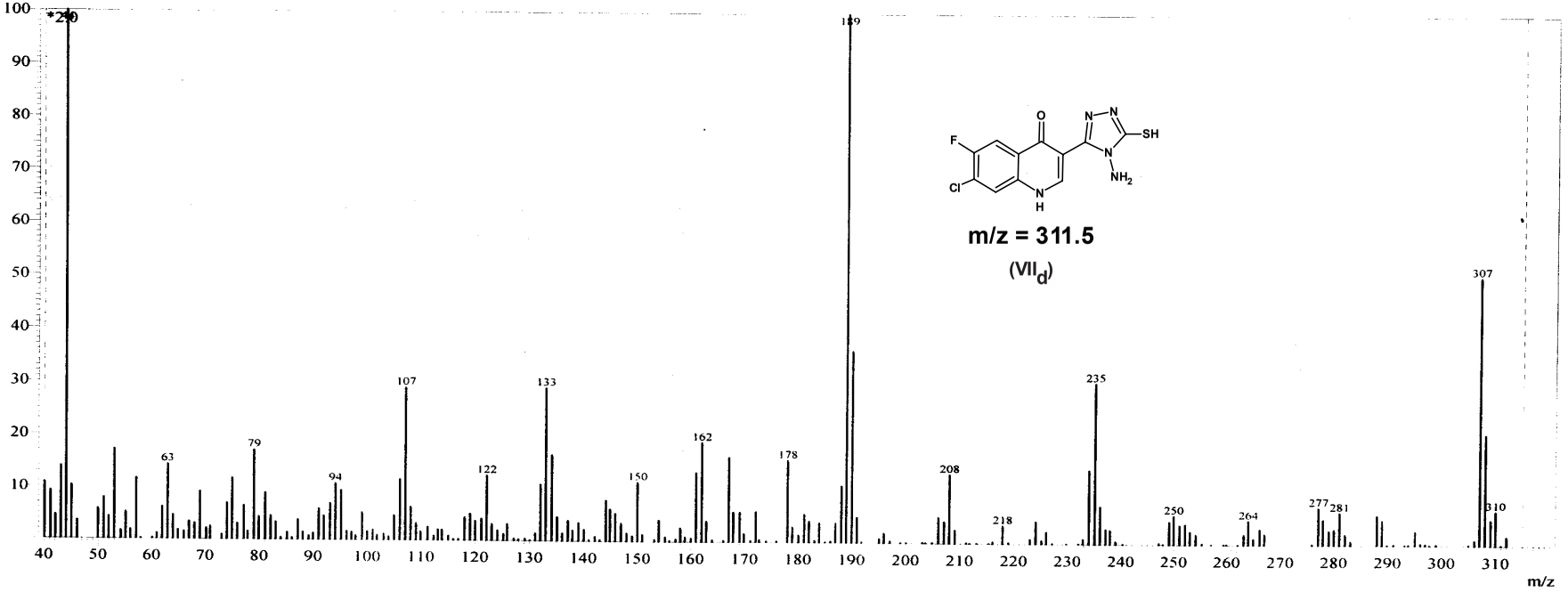
MASS SPECTRAL STUDY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-7-CHLORO-6-FLUOROQUINOLONE-4-(1H)-ONE (VII_d).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

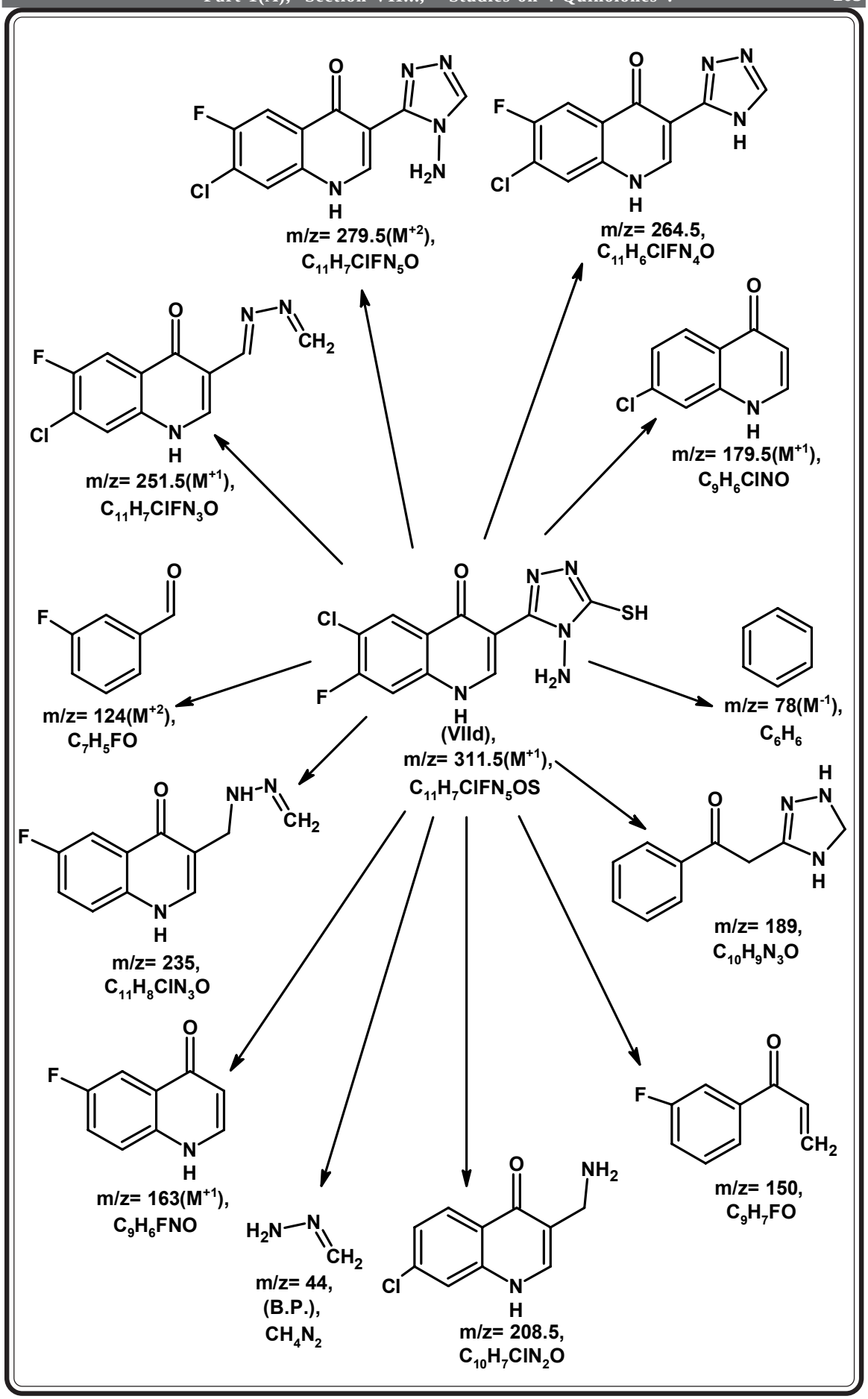
Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 8/24/2007 3:18:51 PM
Sample Name	: JJS-MQ-18
Sample ID	: JJS-MQ-18
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-18.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune130807.qgt

Line#:1 R.Time:6.3(Scan#:715)
MassPeaks:223 BasePeak:44(81470)
RawMode:Averaged 5.8-6.3(665-716)
BG Mode:None
intensity



m/z = 311.5

(VII_d)


m/z= 279.5(M+2),
C11H7ClFN5O
m/z= 264.5,
C11H6ClFN4O
m/z= 251.5(M+1),
C11H7ClFN3O
m/z= 179.5(M+1),
C9H6ClNO
m/z= 124(M+2),
C7H5FO
(VIId),
m/z= 311.5(M+1),
C11H7ClFN5OS
m/z= 78(M-1),
C6H6
m/z= 235,
C11H8ClN3O
m/z= 189,
C10H9N3O
m/z= 163(M+1),
C9H6FNO
m/z= 44,
(B.P.),
CH4N2
m/z= 208.5,
C10H7ClN2O
m/z= 150,
C9H7FO

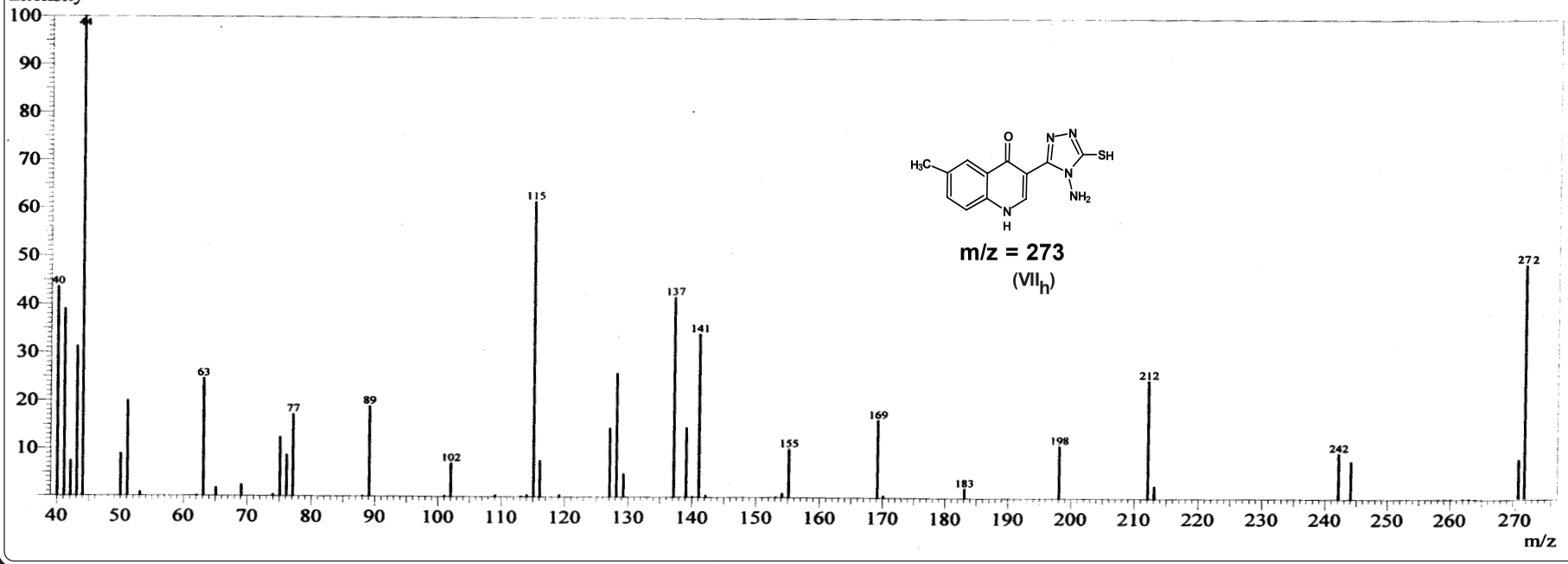
MASS SPECTRAL STUDY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-6-METHYLQUINOLONE-4-(1H)-ONE (VII_h).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

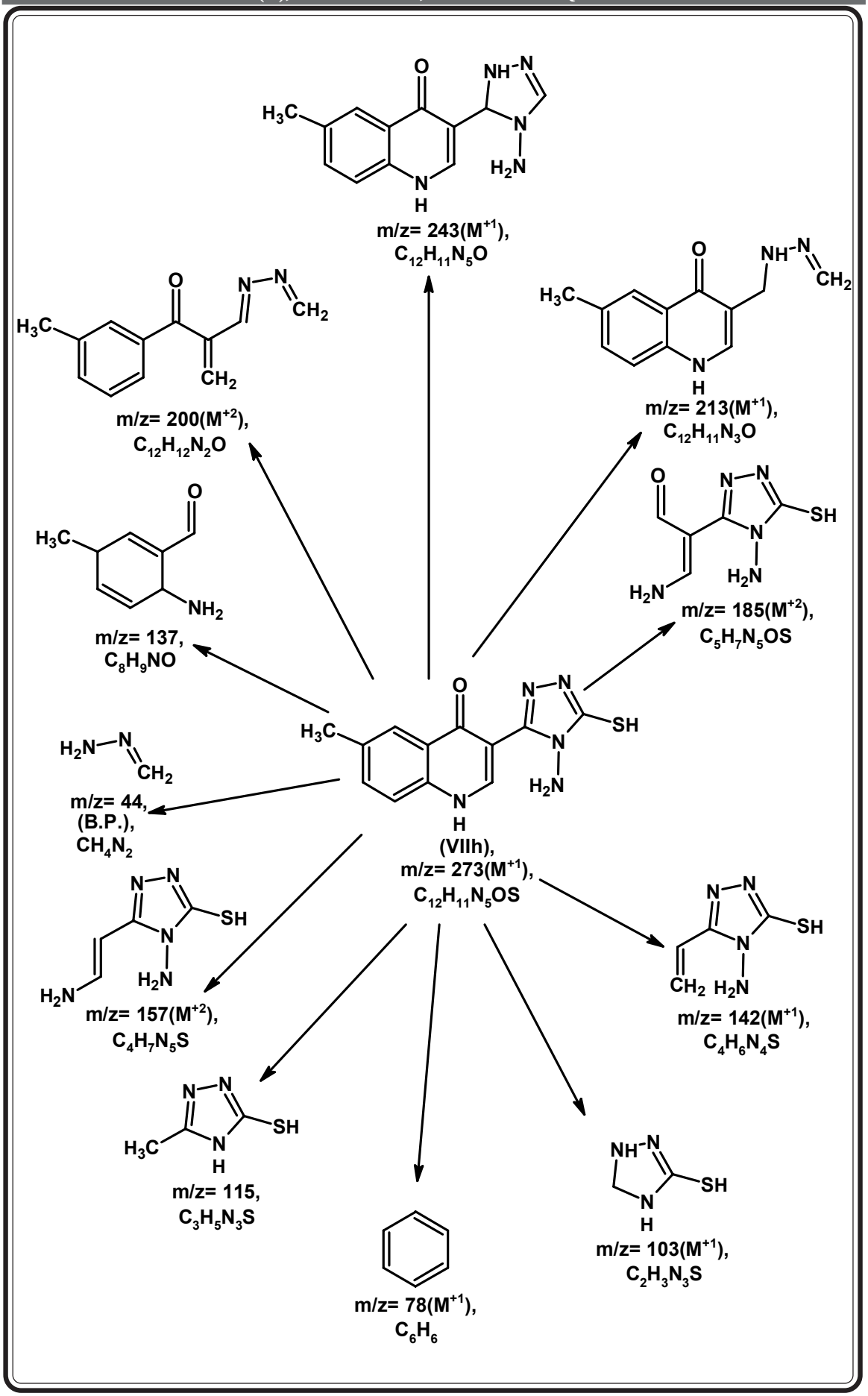
Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 1/16/2007 2:06:35 PM
Sample Name	: JJS-9
Sample ID	: JJS-9
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-9.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune121206.qgt

Line#:1 R.Time:10.2(Scan#:1194)
MassPeaks:48 BasePeak:44(5937)
RawMode:Averaged 7.4-12.2(858-1427)
BG Mode:None
intensity



m/z = 273
(VII_h)


m/z= 243(M+1),
C12H11N5O
m/z= 200(M+2),
C12H12N2O
m/z= 213(M+1),
C12H11N3O
m/z= 137,
C8H9NO
m/z= 185(M+2),
C5H7N5OS
m/z= 44,
(B.P.),
CH4N2
(VIIh),
m/z= 273(M+1),
C12H11N5OS
m/z= 157(M+2),
C4H7N5S
m/z= 142(M+1),
C4H6N4S
m/z= 115,
C3H5N3S
m/z= 78(M+1),
C6H6
m/z= 103(M+1),
C2H3N3S

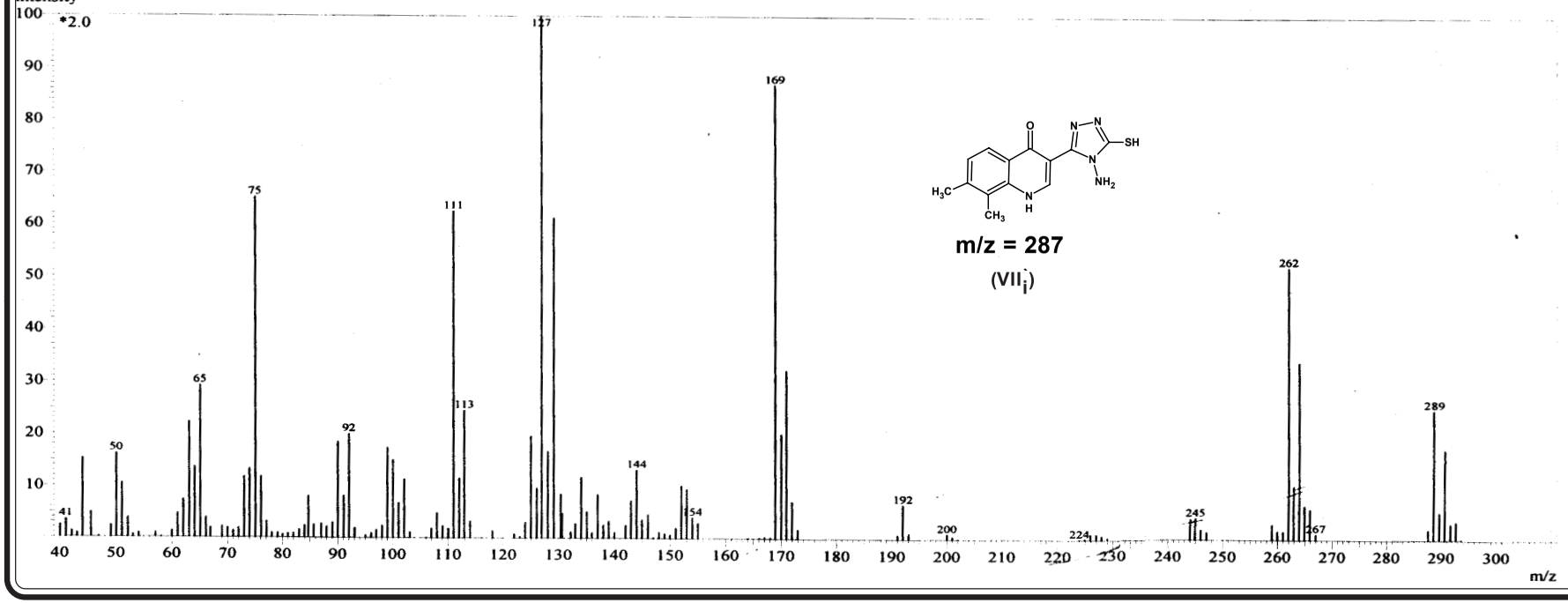
MASS SPECTRAL STUDY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-6-DIMETHYLQUINOLONE-4-(1H)-ONE (VII_i).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 9/25/2006 11:45:27 AM
Sample Name	: JJS-M-50
Sample ID	: JJS-M-50
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-50.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:3.9(Scan#:428)
MassPeaks:143 BasePeak:127(316420)
RawMode:Averaged 3.5-4.2(382-474)
BG Mode:None
intensity



m/z = 287

(VII_i)

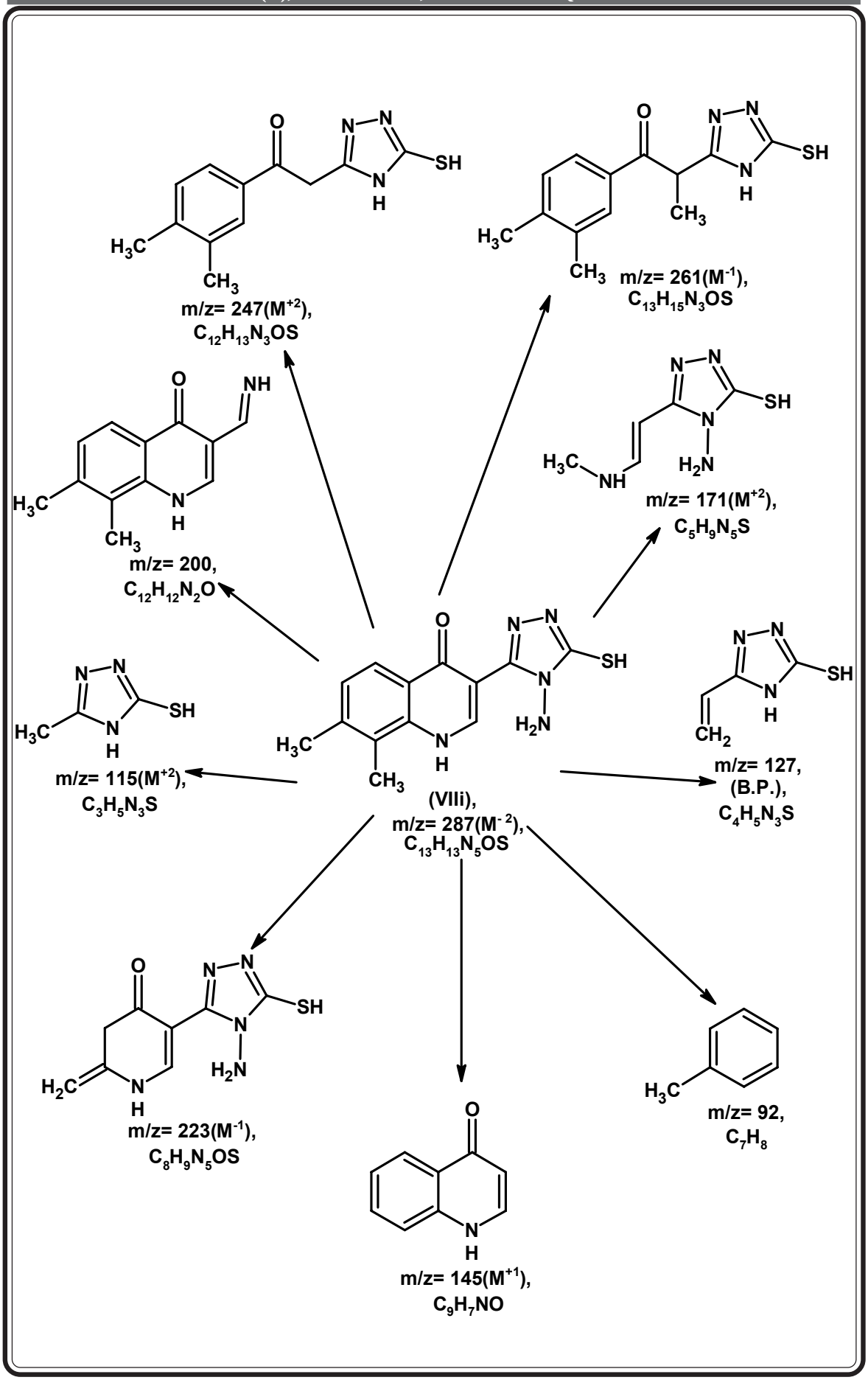

m/z= 247(M+2), C12H13N3OS
m/z= 261(M-1), C13H15N3OS
m/z= 200, C12H12N2O
m/z= 171(M+2), C5H9N5S
m/z= 115(M+2), C3H5N3S
(VIIi), m/z= 287(M-2), C13H13N5OS
m/z= 127, (B.P.), C4H5N3S
m/z= 223(M-1), C8H9N5OS
m/z= 145(M+1), C9H7NO
m/z= 92, C7H8

TABLE NO. 7A : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-SUBSTITUTED-QUINOLONE-4-(1H)-ONES (VII_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) S. pyogens MTCC- 442					S. aureus MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
VII_a	6-F	-	10	11	13	14	-	8	10	12	16
VII_b	7-Cl	-	8	9	11	13	-	8	10	10	13
VII_c	6-Cl	-	9	10	12	14	-	9	11	12	15
VII_d	7-Cl-6-F	-	8	9	10	12	-	8	9	11	13
VII_e	6,7-$(Cl)_2$	-	9	10	12	14	-	8	11	13	16
VII_f	6-NO_2	-	9	11	13	15	-	9	11	14	15
VII_g	6-OCH_3	-	10	10	12	14	-	7	8	10	13
VII_h	6-CH_3	-	8	9	11	13	-	7	8	9	12
VII_i	7,8-$(CH_3)_2$	-	9	10	11	12	-	8	9	10	14
VII_j	-	-	8	9	10	11	-	8	10	12	14
Comparative activity of (VII_{a-j}) with known choosen standard drugs											
Standard drug		**Antibacterial activity**									
											v_a / v_e
Amoxicilin		12	14	15	16	18	10	12	14	15	16
Chloramphenicol		14	15	18	19	24	14	17	20	21	24
Sparfloxacin		14	22	24	26	28	24	26	27	28	32
Levofloxacin		18	21	22	27	29	20	24	26	27	35

N.B.(-): No Activity

TABLE NO. 7B : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3 ', 4'-TRIAZOL-5'-YL)-SUBSTITUTED-QUINOLONE-4-(1H)-ONES (VII_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.)									
		B. Subtillis MTCC- 441					E.coli MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
VII_a	6-F	-	9	10	12	14	-	6	7	8	15
VII_b	7-Cl	-	10	12	13	15	-	7	6	8	11
VII_c	6-Cl	-	9	11	13	16	-	6	7	10	13
VII_d	7-Cl-6-F	-	8	10	11	13	-	7	7	9	12
VII_e	6,7-$(Cl)_2$	-	9	10	11	12	-	7	6	7	8
VII_f	6-NO_2	-	8	9	9	11	-	6	6	7	7
VII_g	6-OCH_3	-	8	9	10	12	-	6	8	10	10
VII_h	6-CH_3	-	9	10	12	14	-	7	6	8	11
VII_i	7,8-$(CH_3)_2$	-	8	9	10	11	-	6	8	10	14
VII_j	-	-	10	11	12	14	-	7	8	11	13
Comparative activity of (VII_{a-j}) with known choosen standard drugs											
Standard drug		**Antibacterial activity**									
Amoxicilin		12	15	16	18	19	10	12	12	15	16
Chloramphenicol		18	22	24	26	27	14	17	20	21	24
Sparfloxacin		22	24	25	26	29	24	26	27	28	32
Levofloxacin		24	26	28	29	31	20	24	26	27	35

N.B.(-): No Activity

TABLE NO.7C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 3-[1'-N-AMINO-2'-MERCAPTO-1',3',4'-TRIAZOL-5'-YL)-SUBSTITUTED-QUINOLONE-4-(1H)-ONES (VII_{a-j}). (Different Inhibition Concentration in µg/ml).

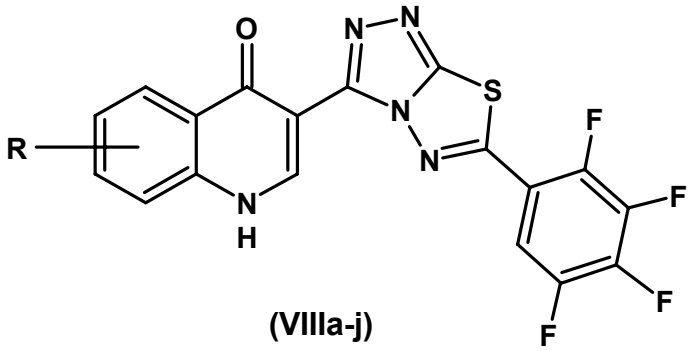
Compd No.	R	Antifungal activity (Zones of inhibition in m.m.) C. albicans MTCC- 227					A. niger MTCC- 282				
		5	25	50	100	250	5	25	50	100	250
VII_a	6-F	-	5	7	9	11	-	7	9	10	12
VII_b	7-Cl	-	5	7	8	10	-	7	8	10	11
VII_c	6-Cl	-	6	8	10	12	-	8	9	10	12
VII_d	7-Cl-6-F	-	7	9	11	14	-	8	10	12	14
VII_e	6,7-$(Cl)_2$	-	7	8	10	11	-	7	8	9	10
VII_f	6-NO_2	-	6	7	8	12	-	6	7	8	10
VII_g	6-OCH_3	-	7	9	11	14	-	7	9	11	13
VII_h	6-CH_3	-	6	8	10	12	-	7	8	9	10
VII_i	7,8-$(CH_3)_2$	-	5	7	8	10	-	6	8	10	12
VII_j	-C_4H_4	-	6	8	9	11	-	7	9	9	11
Comparative activity of(VII_{a-j}) with known choosen standard drugs											
Standard drug		Antifungal activity									
Griseofulvin		16	18	21	23	25	17	19	21	22	23
Fluconazole		14	16	18	21	22	15	17	18	20	21

N.B.(-): No Activity

SECTION - VIII

PREPARATION AND BIOLOGICAL EVALUATION OF SUBSTITUTED-3-[6'-(2'',3'',4'',5''-TETRAFLUOROPHENYL)(1',2,',4')-TRIAZOLO-(3',a-b)[1',3',4']-THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONES.

Keeping in view, various biological properties[34-85] of 4-quinolone and in order to have highly potent therapeutic agents, the synthesis of **Substituted-3-[6'-(2'',3'',4'',5'',-tetrafluoro phenyl)(1',2,',4')-triazolo-(3',a-b)[1',3',4']-thiadiazole-3-yl]-quinolone-4(1H)-ones (VIIIa-j)** have been accomplished by the cyclocondensation of different **substituted-3-[1'-N-amino-2'-mercapto-1',3',4'-triazol-5'-yl)-quinolone-4-(1H)-ones (VIIa-j)** and **2,3,4,5-tetrafluoro benzoic acid** in the presence of phosphorous oxychloride.



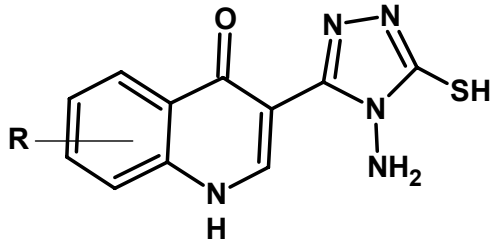
(VIIIa-j)

R=Substituted phenyl

The constitution of the products **(VIIIa-j)** have been delineated by **elemental analyses,IR, PMR** and **Mass** spectral data**.**

The products **(VIIIa-j)** were assayed for their ***in vitro*** biological assay like antibacterial activity towards **S.pyogens MTCC-442** , **S.aureus MTCC-96 and B.subtillis MTCC-441 (Gram positive)** and **E. coli MTCC-443 (Gram negative)** bacterial strains and antifungal activity towards **Aspergillus niger MTCC-282** and **Candida albicans MTCC-227** at different concentrationsi.e. :0(control), 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds **(VIIIa-j)** were compared with standard drugs viz., **Amoxicillin, Chloramphenicol, Sparfloxacin, Levofloxacin** (antibacterial)**, Griseofluvin, Fluconazole** (antifungal)**.**

REACTION SCHEME

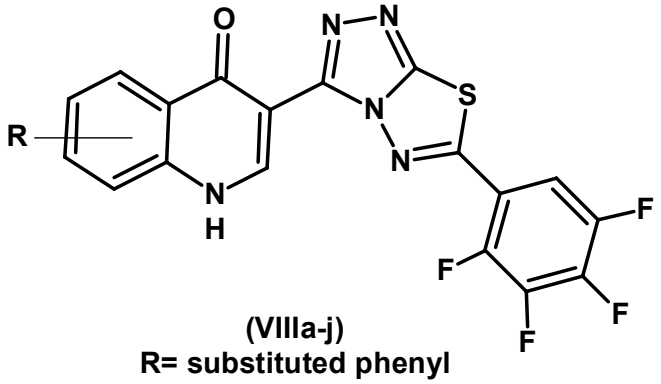


(VIIa-j)
R= substituted phenyl

Tetra fluoro-
benzoic acid

$POCl_3$

△



(VIIIa-j)
R= substituted phenyl

EXPERIMENTAL

PREPARATION AND BIOLOGICAL SCREENING OF SUBSTITUTED-3-[6'-(2'',3'',4'',5'',-TETRAFLUOROPHENYL)(1',2,',4')-TRIAZOLO-(3',a-b)[1',3',4']-THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONES.

(A) Preparation of Diethyl-(3-chloro-4-fluoro amino phenyl)-amino-methylene malonate (I_d).

For preparation, refer Part-1,Section-I, **page No.30.**

(B) Preparation of Ethyl-7-chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carboxylate (II_d).

For preparation, refer Part-1, Section-II, **page No.58.**

(C) Preparation of 7-chloro-6-fluoro-1,4-dihydroquinoline-4-one-3-carbohydrazide (5_d).

For preparation, refer Part-1, Section-V, **page No.137.**

(D) Preparation of 7-chloro-6-fluoro-3-[1'-N-amino-2'-mercapto-1',3'-4'-triazol-5'-yl)-quinolone-4-(1H)-one (VIId).

For preparation, refer Part-1, Section-VII, **page No.187.**

(E) Preparation of 7-chloro-6-fluoro-3-[6'-(2'',3'',4'',5'',-tetrafluorophenyl)(1',2,',4')-triazolo-(3',a-b)[1',3',4']-thiadiazole-3-yl]-quinolone-4(1H)-one (VIIId).

A mixture of 7-chloro-6-fluoro-3-[1'-N-amino-2'-mercapto-1',3',4'-triazol-5'-yl)-quinolone-4-(1H)-one (**VIId)** (3.11gm,0.01 M) and 2,3,4,5-tetra fluoro benzoic acid (1.94 gm,0.01M) in phosphourus oxychloride (15 ml) was heated under reflux for 8 hrs. The rection was monitored by TLC. After the completion of reaction, the reaction mixture was allowed to cool at room temprature and then poured on to crushed ice. The pH was then adjusted to neutral by dropwise addition of 10% sodium bicarbonate solution. The brown red colour precipitates so obtained was filtered, washed with water, dried.The product was crystallized from ethanol. Yield : 65 %, M.P. : 83 ^{O}C, (Required : C, 46.02 %; H, 1.07 %; N,14.91 % for $C_{18}H_5N_5OSClF_5$, Found : C, 45.98 %; H, 1.02 %; N,14. 88%).

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (2.0 : 8.0) = 0.57.
TLC solvent system R_{f_2} : Methanol : Chloroform(0.5 : 9.5 = 0.52**.**

Similarly, other compounds **(VIIIa-j)** were synthesized. The physical data are recorded in **Table No. 8.**

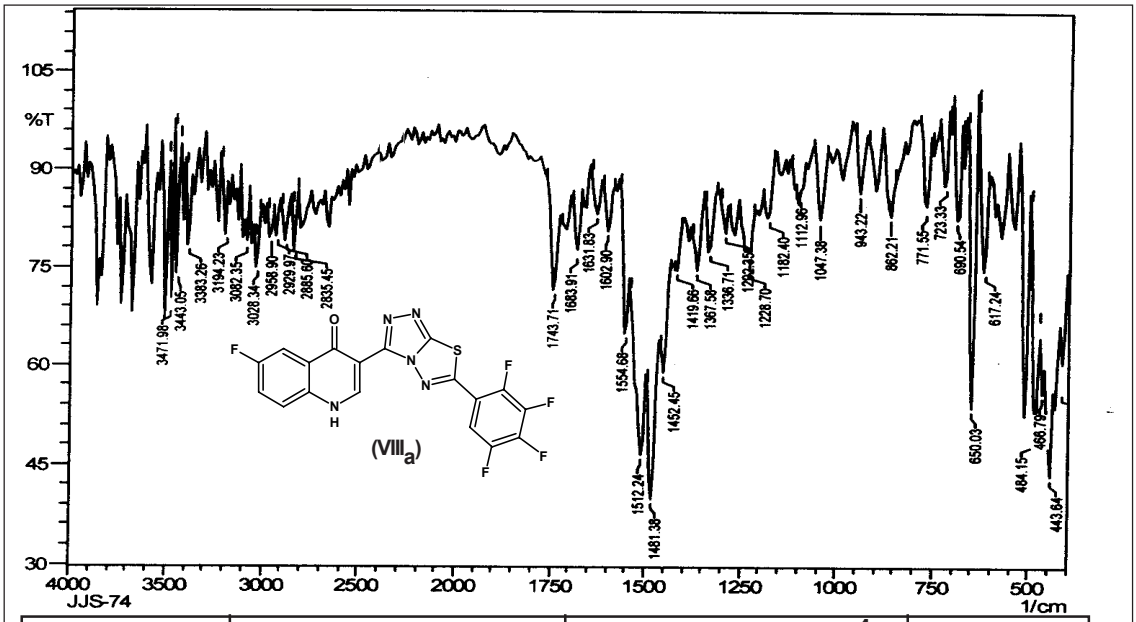
(B) Antimicrobial activity of Substituted-3-[6'-(2'',3'',4'',5'',-tetrafluoro phenyl)(1',2,',4')-triazolo-(3',a-b)[1',3',4']-thiadiazole-3-yl]-quinolone-4(1H)-ones (VIIIa-j)

Antimicrobial activity testing was carried out as described in Part-1(A), Section-I, page No. 30-31.The MIC values of test solution are recorded in **Table No. 8A, 8B** and **8C.**

TABLE NO. 8 : PHYSICAL CONSTANTS OF SUBSTITUTED-3-[6'-(2'',3'',4'',5'',-TETRA FLUORO-PHENYL)(1',2,',4')-TRIAZOLO-(3',a-b)[1',3',4']-THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONES ($VIII_{a-j}$).

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. ^{o}C 5	Yield % 6	R_f Value 7		% of Nitrogen Calcd. / Found 8
						R_{f_1}	R_{f_2}	
$VIII_a$	6-F	$C_{18}H_6N_5OF_5S$	435.0	165^{o}	67	0.51	0.46	16.09 / 16.03
$VIII_b$	7-Cl	$C_{18}H_6N_5OF_4SCl$	451.5	145^{o}	68	0.46	0.47	15.50 / 15.43
$VIII_c$	6-Cl	$C_{18}H_6N_5OF_4SCl$	451.5	149^{o}	66	0.56	0.51	15.50/ 15.44
$VIII_d$	7-Cl-6-F	$C_{18}H_5N_5OF_5SCl$	469.5	84^{o}	65	0.57	0.52	14.91 / 14.85
$VIII_e$	6,7-$(Cl)_2$	$C_{18}H_5N_5OF_4SCl_2$	486.0	93^{o}	67	0.59	0.51	14.40 / 14.37
$VIII_f$	6-NO_2	$C_{18}H_6N_6O_3F_4S$	462.0	172^{o}	60	0.44	0.41	18.18 / 18.13
$VIII_g$	6-OCH_3	$C_{19}H_9N_5O_2F_4S$	447.0	141^{o}	58	0.46	0.49	15.66 / 15.60
$VIII_h$	6-CH_3	$C_{19}H_9N_5OF_4S$	431.0	136^{o}	62	0.51	0.43	16.24 / 16.20
$VIII_i$	7,8-$(CH_3)_2$	$C_{20}H_{11}N_5OSF_4$	445.0	139^{o}	68	0.56	0.42	15.73 / 15.65
$VIII_j$	-	$C_{22}H_9N_5OF_4S$	467.0	168^{o}	61	0.62	0.44	14.99 / 14.92

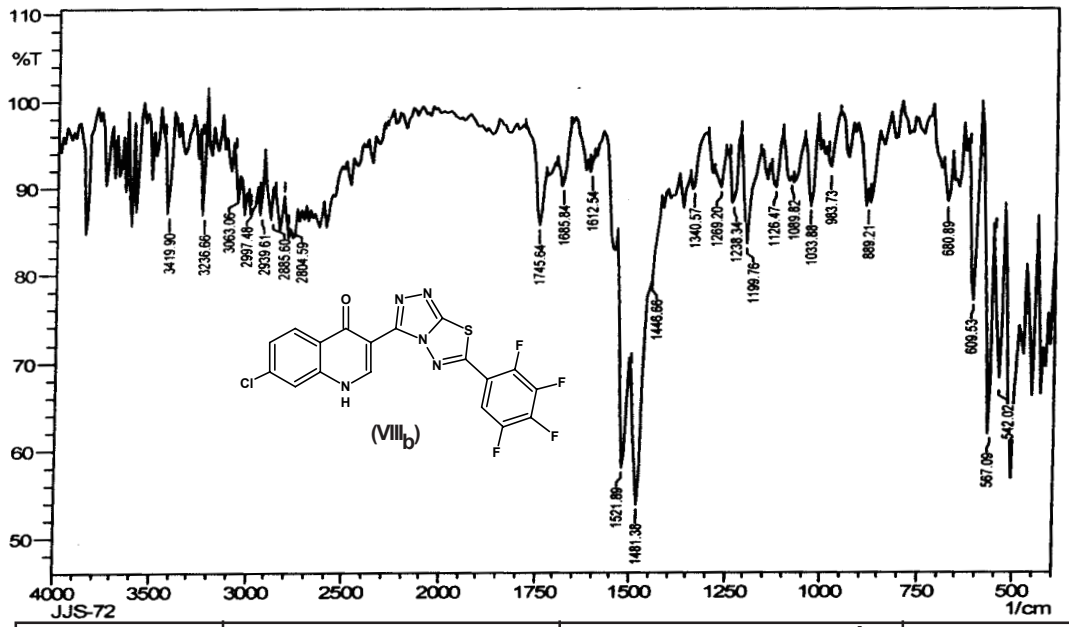
IR SPECTRAL STUDY OF 6-FLUORO-3-[6'-(2'',3'',4'',5'',-TETRA-FLUORO-PHENYL (1',2,',4')-TRIAZOLO-(3',4'-b)[1',3',THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONE ($VIII_a$).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2929.9	2975 - 2850	96
	C-H (sym. str., m)	2885.4	2900 - 2800	96
	C-H (asym. def., m)	1452.4	1470 - 1435	96
	C-H (sym. def., m)	1367.5	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3028.3	3080 - 3010	97
	C=C & C-C (str., v)	1554.6	1600 - 1450	97
	C-H (o.o.p. def., m)	862.2	825 - 800	97
	C-H (i.p. def., m)	1112.9	1150 - 1050	97
thiadiazole moiety	C-N (str., v)	1336.7	1340 - 1250	98
	C=N (str., v)	1631.8	1690-1650	98
	N-N (def., v)	1182.4	1220 - 1020	98
	C-S-C(str.m)	650.0	700-650	98
4-quinolone moiety	N-H (str., b)	3383.2-3028.3	3400 - 3000	98
	N-H (def., s,m)	1602.9	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1683.9	1690- 1640	98
Halogen Subtitution	C-F (str., b)	1367.5-1047.3	1400-1000	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

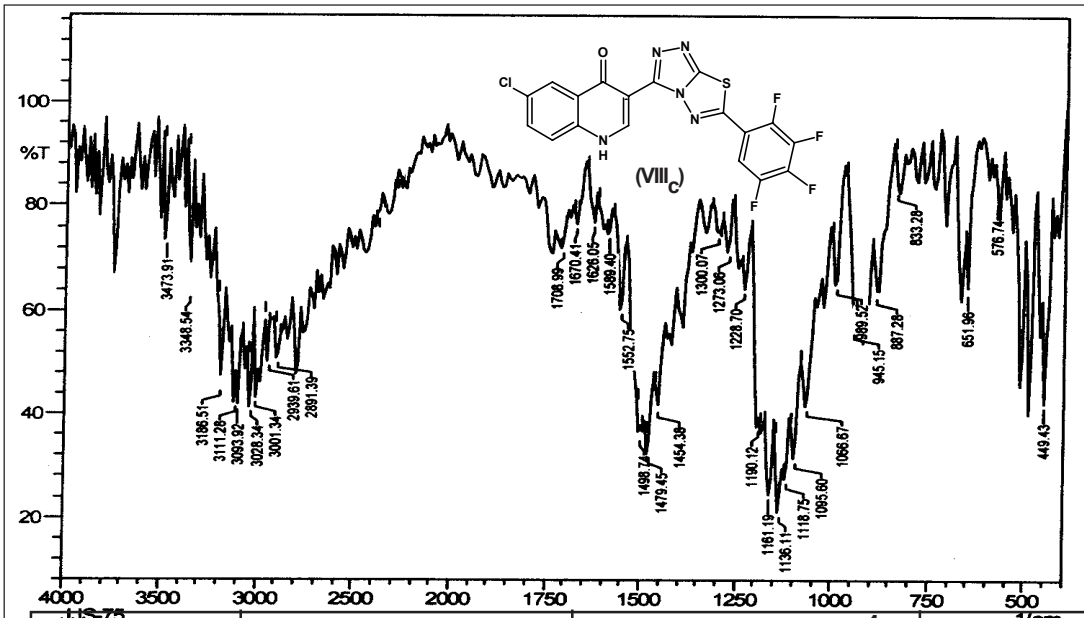
IR SPECTRAL STUDY OF 7-CHLORO-3-[6'-(2'',3'',4'',5'',-TETRA-FLUORO PHENYL (1',2,',4')-TRIAZOLO-(3',4'-b)[1',3',4']-THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONE ($VIII_b$).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2939.6	2975 - 2850	96
	C-H (sym. str., m)	2885.6	2900 - 2800	96
	C-H (asym. def., m)	1446.6	1470 - 1435	96
	C-H (sym. def., m)	1340.5	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3063.0	3080 - 3010	97
	C=C & C-C (str., v)	1521.8	1600 - 1450	97
	C-H (i.p. def., m)	1126.4	1150 - 1050	97
thiadiazole moiety	C-N (str., v)	1340.5	1340 - 1250	98
	C=N (str., v)	1612.5	1690-1650	98
	N-N (def., v)	1199.7	1220 - 1020	98
	C-S-C(str.m)	680.8	700-650	98
4-quinolone moiety	N-H (str., b)	3236.6-3063.0	3400 - 3000	98
	N-H (def., s,m)	1612.5	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1685.8	1690 - 1640	98
Halogen Subtitution	C-F (str., b)	1340.5-1033.8	1400-1000	99
	C-Cl (str., b)	609.5	800-600	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

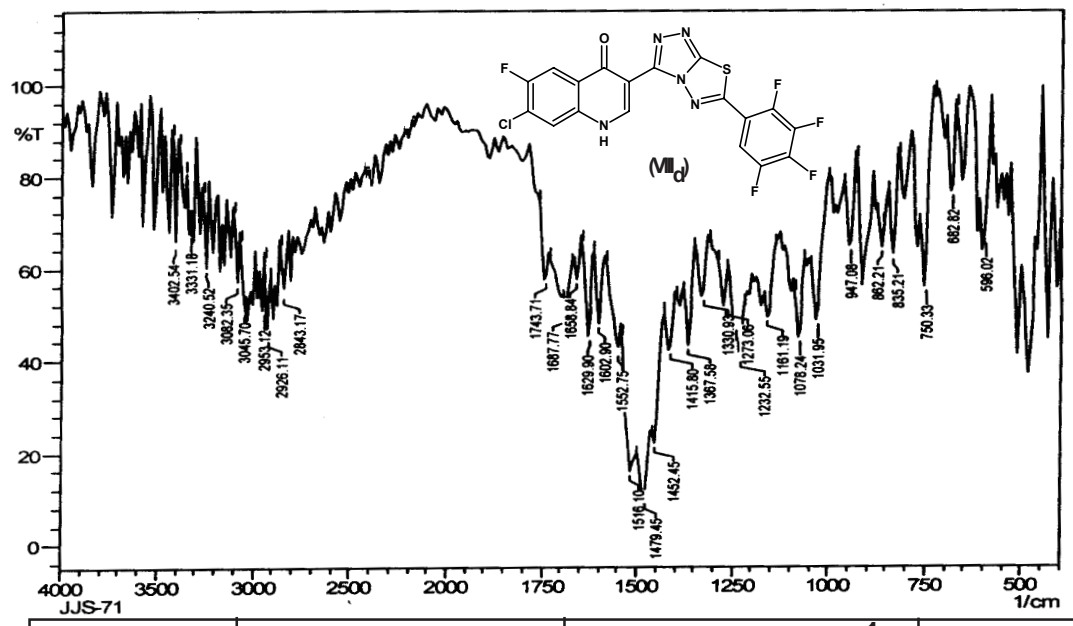
IR SPECTRAL STUDY OF 6-CHLORO-3-[6'-(2'',3'',4'',5'',-TETRA-FLUORO PHENYL (1',2,',4')-TRIAZOLO-(3',4'-b)[1',3',4']-THIADIAZOLE--3-YL]-QUINOLONE-4(1H)-ONE ($VIII_C$).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2939.6	2975 - 2850	96
	C-H (sym. str., m)	2891.3	2900 - 2800	96
	C-H (asym. def., m)	1454.3	1470 - 1435	96
	C-H (sym. def., m)	1300.7	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3028.3	3080 - 3010	97
	C=C & C-C (str., v)	1589.4	1600 - 1450	97
	C-H (o.o.p. def., m)	833.2	825 - 800	97
	C-H (i.p. def., m)	1118.7	1150 - 1050	97
thiadiazole moiety	C-N (str., v)	1361.7	1340 - 1250	98
	C=N (str., v)	1670.4	1690-1650	98
	N-N (def., v)	1136.1	1220 - 1020	98
	C-S-C(str.m)	651.9	700-650	98
4-quinolone moiety	N-H (str., b)	3348.5-3001.3	3400 - 3000	98
	N-H (def., s, m)	1626.0	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1708.9	1690 - 1640	98
Halogen Subtitutiond	C-F (str., b)	1300.0-1066.6	1400-1000	99
	C-Cl(str., b)	833.2-651.9	800-600	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

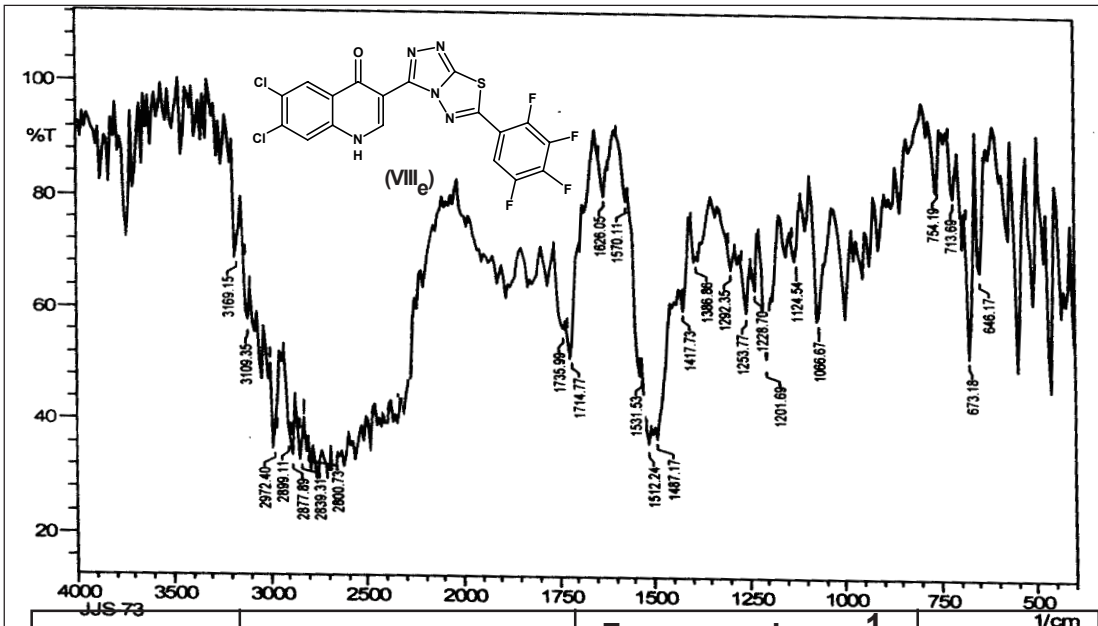
IR SPECTRAL STUDY OF 7-CHLORO-6-FLUORO-3-[6'-(2'',3'',4'',5''-,-TETRA FLUOROPHENYL (1',2,',4')-TRIAZOLO-(3',4'-b)[1',3',4']-THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONE ($VIII_d$).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2926.1	2975 - 2850	96
	C-H (sym. str., m)	2843.1	2900 - 2800	96
	C-H (asym. def., m)	1452.4	1470 - 1435	96
	C-H (sym. def., m)	1367.5	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3045.7	3080 - 3010	97
	C=C & C-C (str., v)	1552.7	1600 - 1450	97
	C-H (o.o.p. def., m)	835.2	825 - 800	97
	C-H (i.p. def., m)	1078.2	1150 - 1050	97
thiadiazole moiety	C-N (str., v)	1330.9	1340 - 1250	98
	C=N (str., v)	1658.5	1690-1650	98
	N-N (def., v)	1161.2	1220 - 1020	98
	C-S-C(str.m)	682.8	700-650	98
4-quinolone moiety	N-H (str., b)	3402.5-3045.7	3400 - 3000	98
	N-H (def., s,m)	1602.9	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1687.7	1690 - 1640	98
Halogen Subtitutiond	C-F (str., b)	1367.5-1031.9	1400-1000	99
	C-Cl (str., b)	750.3	800-600	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

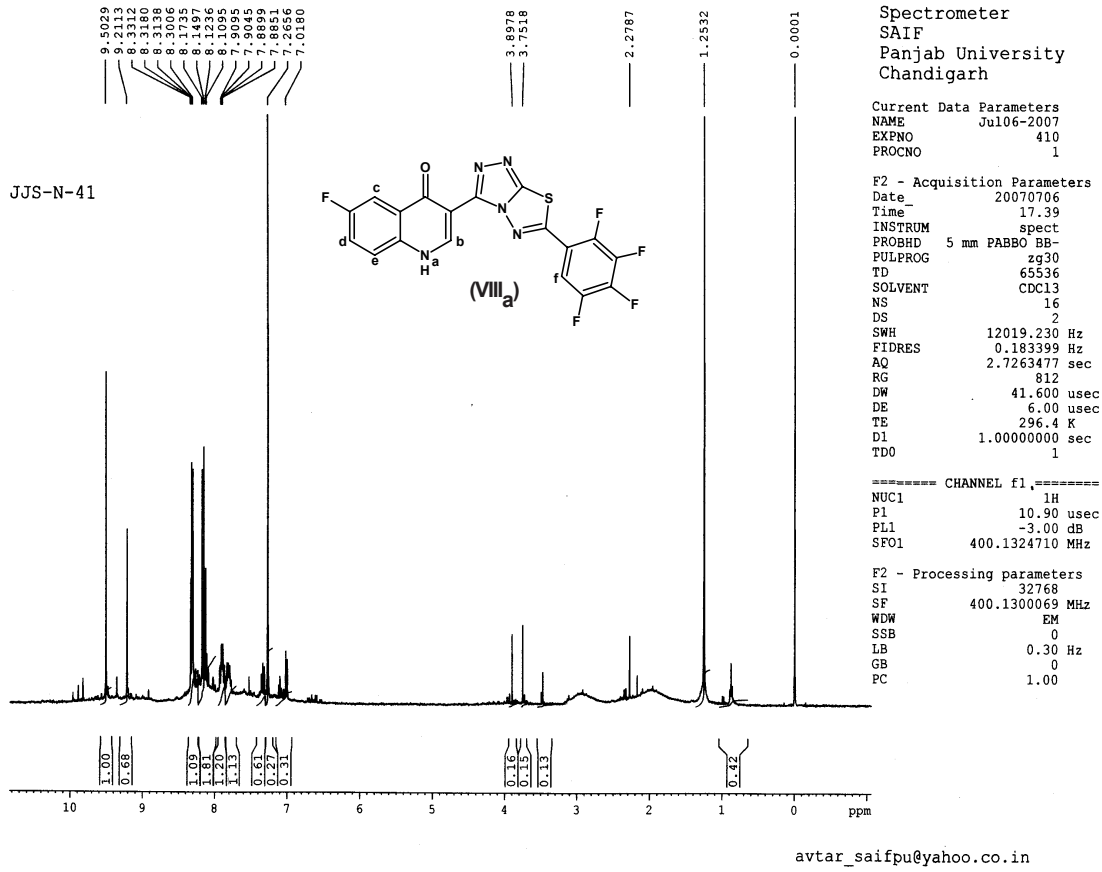
IR SPECTRAL STUDY OF 6,7-DICHLORO-3-[6'-(2'',3'',4'',5'',-TETRA-FLUORO PHENYL (1',2,',4')-TRIAZOLO-(3',4'-b)[1',3',4']-THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONE ($VIII_e$).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2972.4	2975 - 2850	96
	C-H (sym. str., m)	2839.3	2900 - 2800	96
	C-H (asym. def., m)	1417.7	1470 - 1435	96
	C-H (sym. def., m)	1383.8	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3065.3	3080 - 3010	97
	C=C & C-C (str., v)	1531.5	1600 - 1450	97
	C-H (o.o.p. def., m)	850.2	825 - 800	97
	C-H (i.p. def., m)	1124.5	1150 - 1050	97
thiadiazole moiety	C-N (str., v)	1292.3	1340 - 1250	98
	C=N (str., v)	1626.0	1690-1650	98
	N-N (def., v)	1124.5	1220 - 1020	98
	C-S-C(str.m)	673.1	700-650	98
4-quinolone moiety	N-H (str., b)	3169.1	3400 - 3000	98
	N-H (def., s,m)	1626.0	1650 - 1550	98
Ketone (4-quinolone)	C=O (str., s)	1714.7	1740 - 1650	98
Halogen Subtitutiond	C-F (str., b)	1386.8-1066.6	1400-1000	99
	C-Cl (str., b)	754.1-646.1	800-600	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

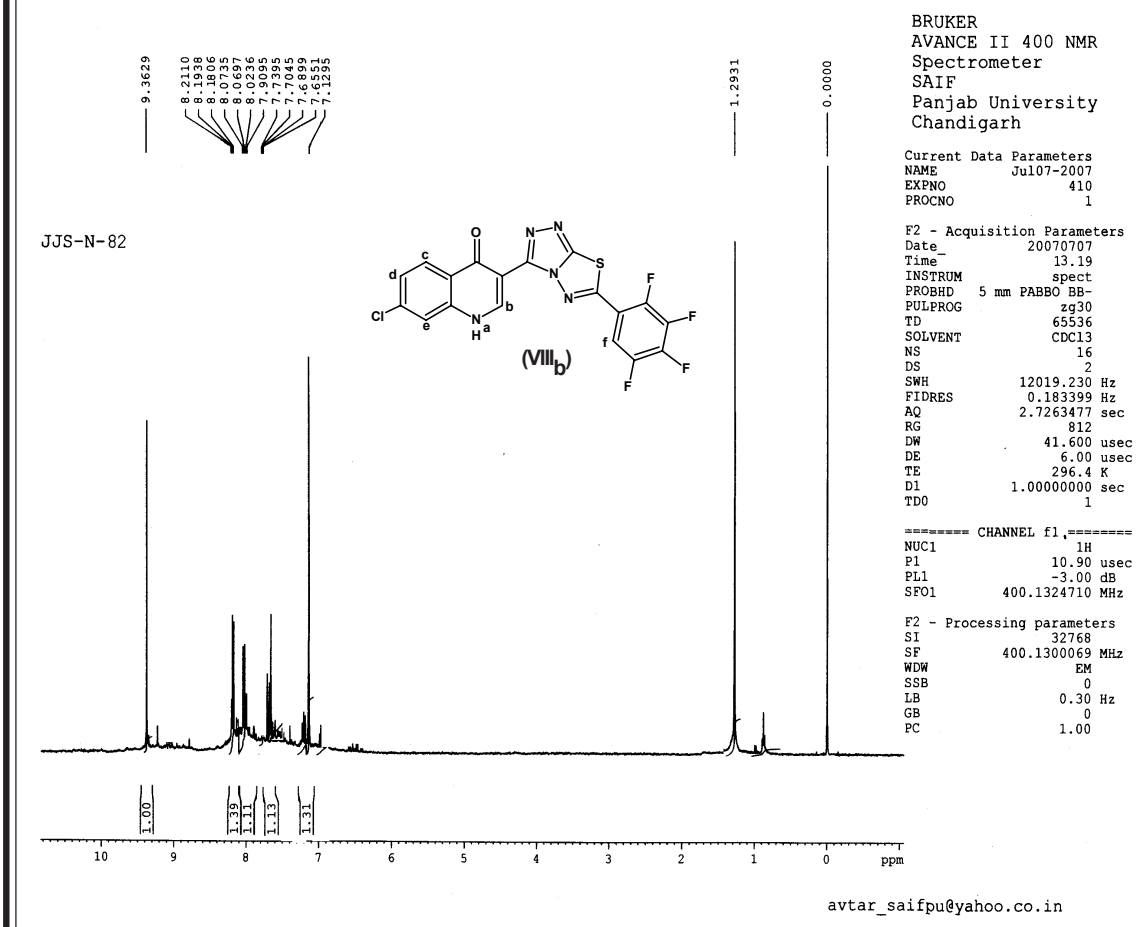
NMR SPECTRAL STUDY OF 6-FLUORO-3-[6'-(2'',3'',4'',5'',-TETRA-FLUORO PHENYL (1',2,',4')-TRIAZOLO-(3',4'-b)[1',3',4']-THIADIAZOLE-3-YL]- QUINOLONE-4(1H)-ONE ($VIII_a$).



avtar_saifpu@yahoo.co.in

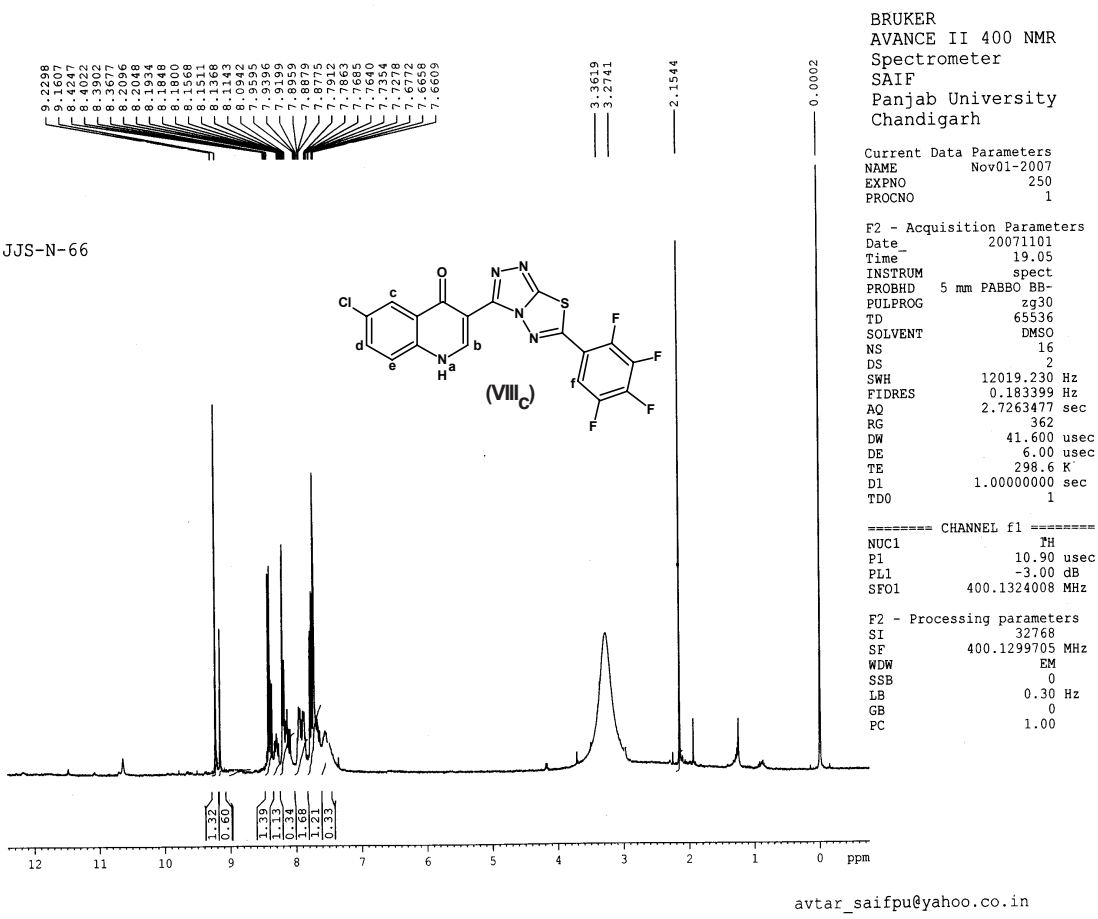
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	7.8851-7.9095	2H	multiplet	- Ar-H(d,e)
2	8.1095-8.1735	1H	multiplet	- Ar-H(c)
3	8.3006-8.3312	1H	multiplet	- Ar-H(f)
4	9.5029	1H	singlet	-NH-CH(b)
5	7.2656	-	-	$-CDCl_3$

NMR SPECTRAL STUDY OF 7-CHLORO-3-[6'-(2'',3'',4'',5'',-TETRA-FLUORO PHENYL(1',2,',4')-TRIAZOLO-(3',4'-b)[1',3',4']-THIADIAZOLE-3-YL] QUINOLONE-4(1H)-ONE ($VIII_b$).



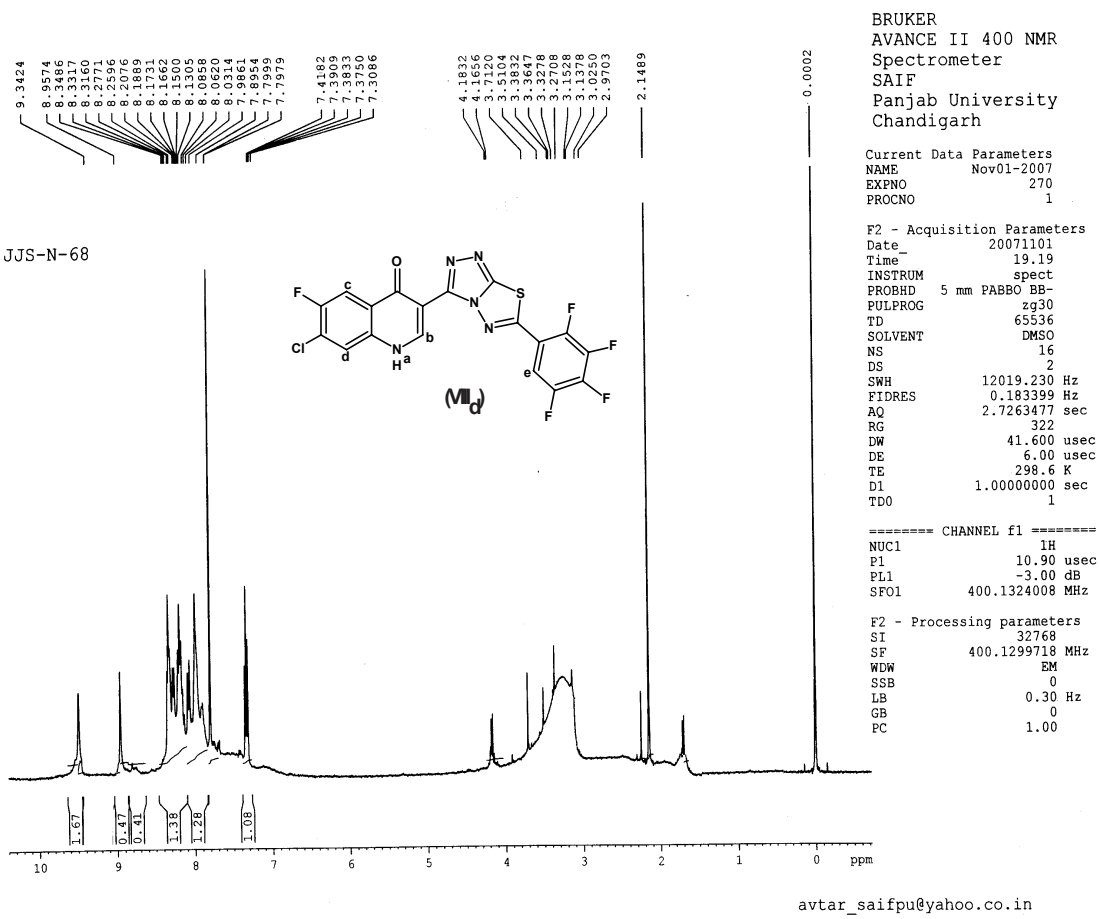
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	7.1295	1H	singlet	- Ar-H(e)
2	7.6551-7.7395	1H	multiplet	- Ar-H(c)
3	7.9095-8.0735	1H	multiplet	- Ar-H(d)
4	8.1806-8.2110	1H	doublet	- Ar-H(f)
5	9.3629	1H	singlet	- NH-CH(b)

NMR SPECTRAL STUDY OF 6-CHLORO-3-[6'-(2'',3'',4'',5'',-TETRA-FLUORO PHENYL (1',2,',4')-TRIAZOLO-(3',4'-b)[1',3',4']-THIADI-AZOLE-3-YL] -QUINOLONE-4(1H)-ONE ($VIII_c$).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	7.7278-7.7912	1H	multiplet	- Ar-H(e)
2	7.8775-7.9595	1H	multiplet	- Ar-H(d)
3	8.0942-8.2096	1H	multiplet	- Ar-H(c)
4	8.2096-8.4247	1H	doublet	- Ar-H(f)
5	9.2298	1H	singlet	- NH-CH(b)
6	3.2741-3.3619	-	-	-DMSO-d_6

NMR SPECTRAL STUDY OF 7-CHLORO-6-FLUORO-3-[6'-(2'',3'',4'',5'',-TETRA FLUORO PHENYL(1',2,',4')-TRIAZOLO-(3',4'-b)[1',3',4']-THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONE ($VIII_d$).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	7.3086-7.4182	1H	multiplet	- Ar-H(c)
2	7.8954-8.0858	1H	multiplet	- Ar-H(d)
3	8.1305-8.3486	1H	multiplet	- Ar-H(e)
4	9.3424	1H	singlet	- NH-CH(b)
5	2.9703 -3.7120	-	-	-DMSO-d_6
6	7.7979	-	-	-$CDCl_3$

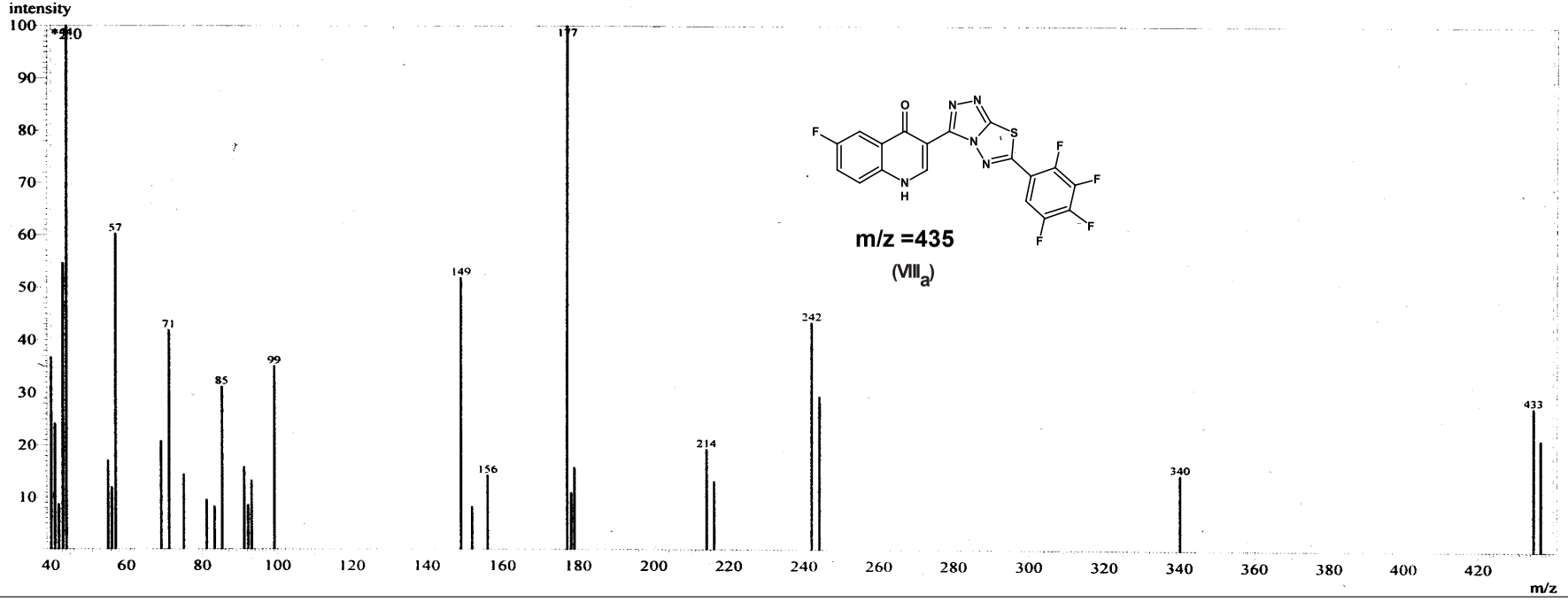
MASS SPECTRAL STUDY OF 6-FLUORO-3-[6'-(2'',3'',4'',5'',-TETRAFLUOROPHENYL(1',2,',4')-TRIAZOLO-(3',4'-b)[1',3',4']-THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONE ($VIII_a$).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

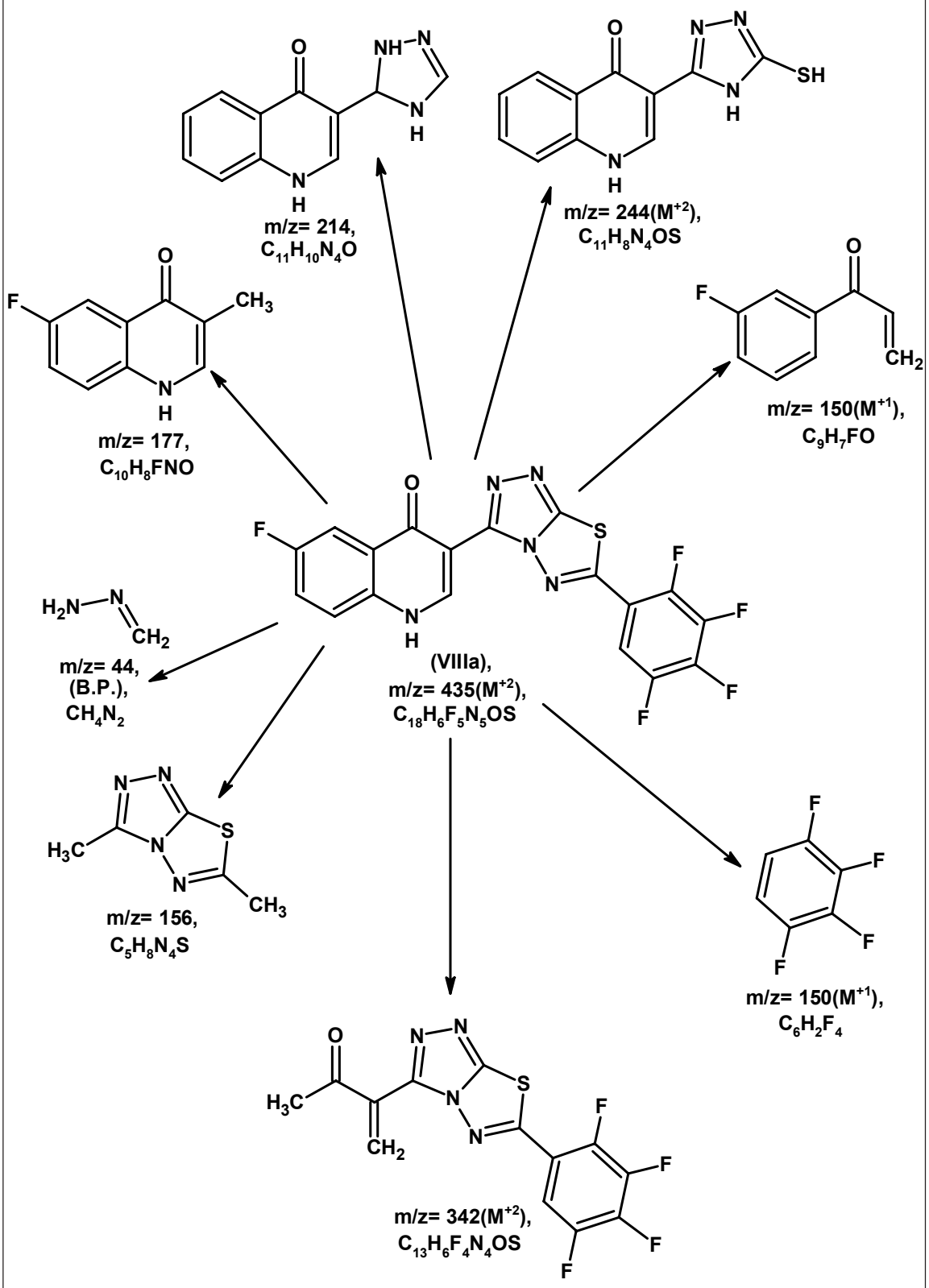
Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 1/2/2007 2:02:10 PM
Sample Name	: JJS-MQ-5
Sample ID	: JJS-MQ-5
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-5.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune121206.qgt

Line#:1 R.Time:3.0(Scan#:319)
MassPeaks:31 BasePeak:44(24636)
RawMode:Single 3.0(319)
BG Mode:None
intensity



m/z =435

($VIII_a$)


m/z= 214,
$C_{11}H_{10}N_4O$
m/z= 244(M^{+2}),
$C_{11}H_8N_4OS$
m/z= 177,
$C_{10}H_8FNO$
m/z= 150(M^{+1}),
C_9H_7FO
m/z= 44,
(B.P.),
CH_4N_2
(VIIIa),
m/z= 435(M^{+2}),
$C_{18}H_6F_5N_5OS$
m/z= 156,
$C_5H_8N_4S$
m/z= 150(M^{+1}),
$C_6H_2F_4$
m/z= 342(M^{+2}),
$C_{13}H_6F_4N_4OS$

MASS SPECTRAL STUDY OF 7-CHLORO-3-[6'-(2'',3'',4'',5'',-TETRAFLUOROPHE NYL (1',2,',4')-TRIAZOLO-(3',4'-b)[1',3',4']-THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONE ($VIII_b$).

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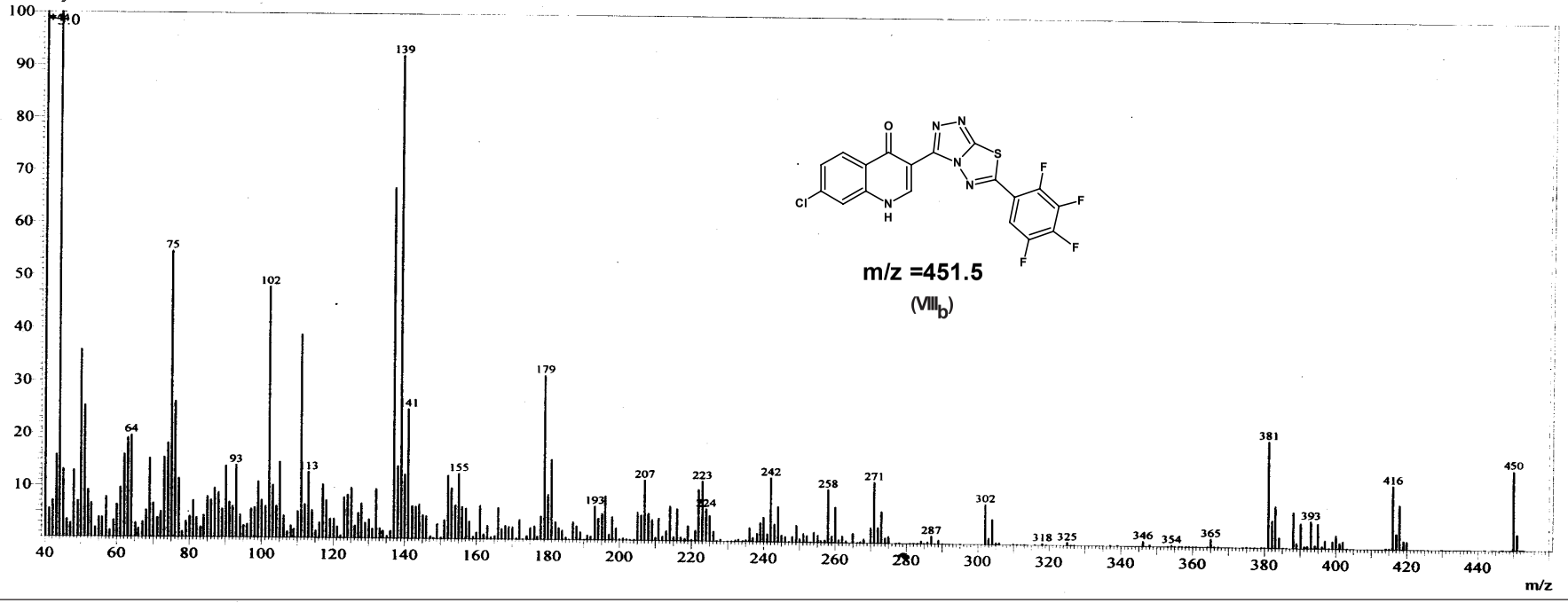
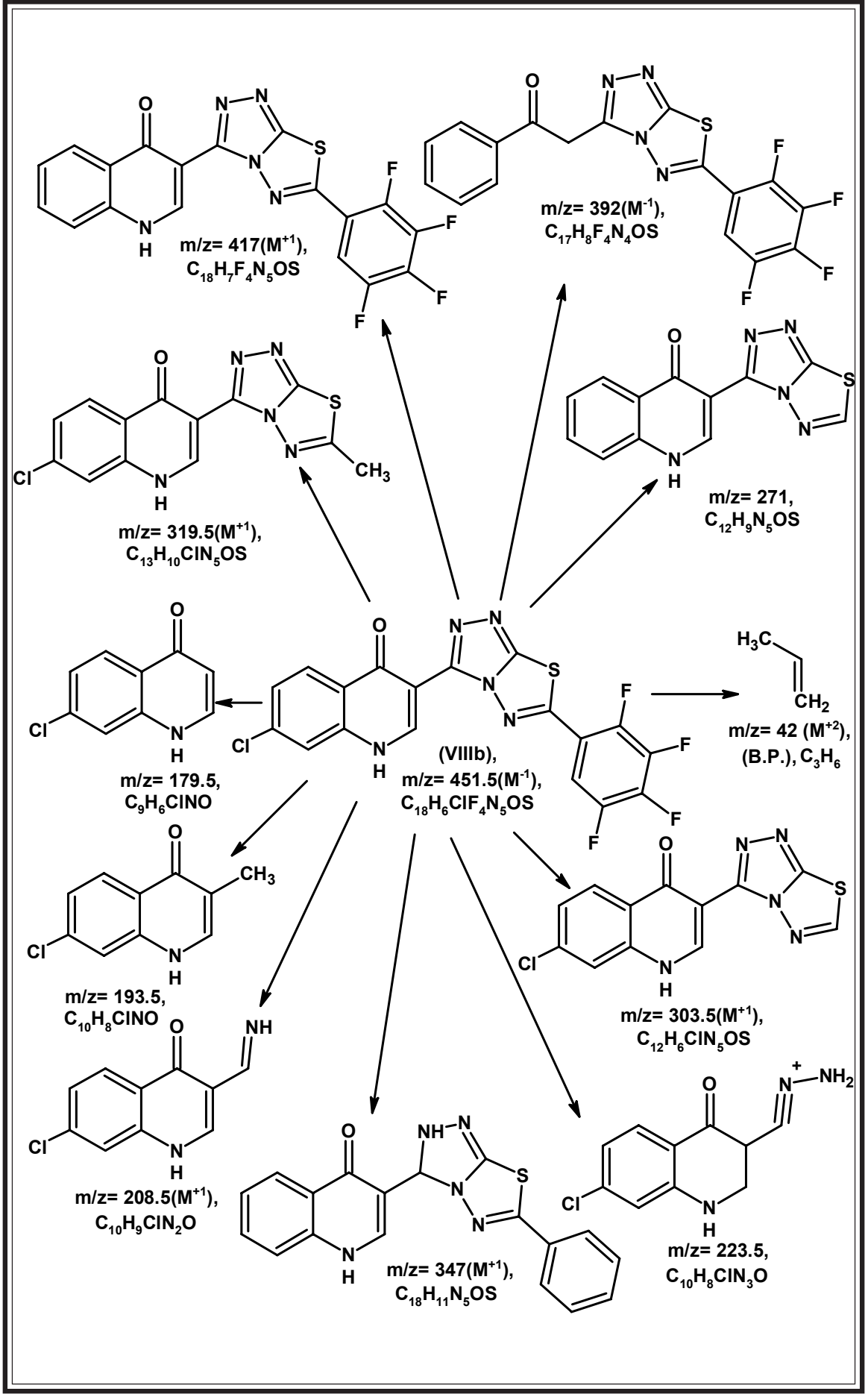
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 1/2/2007 12:19:50 PM
Sample Name : JJS-MQ-3
Sample ID : JJS-MQ-3
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-3.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune121206.qgt

Line#:1 R.Time:12.0(Scan#:1410)
MassPeaks:322 BasePeak:40(157679)
RawMode:Averaged 8.5-16.6(987-1956)
BG Mode:None
intensity




m/z= 417(M+1),
C18H7F4N5OS
m/z= 392(M-1),
C17H8F4N4OS
m/z= 319.5(M+1),
C13H10ClN5OS
m/z= 271,
C12H9N5OS
m/z= 179.5,
C9H6ClNO
(VIIIb),
m/z= 451.5(M-1),
C18H6ClF4N5OS
m/z= 42 (M+2),
(B.P.), C3H6
m/z= 193.5,
C10H8ClNO
m/z= 303.5(M+1),
C12H6ClN5OS
m/z= 208.5(M+1),
C10H9ClN2O
m/z= 347(M+1),
C18H11N5OS
m/z= 223.5,
C10H8ClN3O

MASS SPECTRAL STUDY OF 6-CHLORO-3-[6'-(2'',3'',4'',5''-TETRAFLUOROPHE NYL (1',2,',4')-TRIAZOLO-(3',4'-b)[1',3',4']-THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONE ($VIII_c$).

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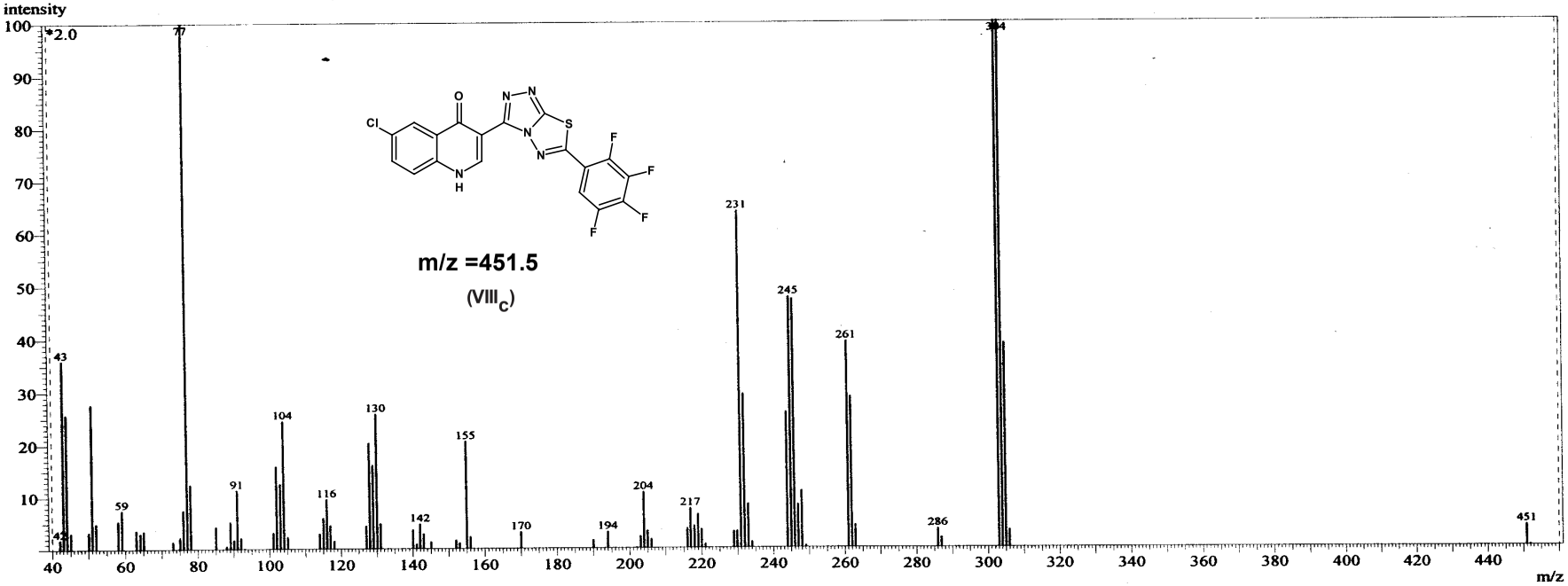
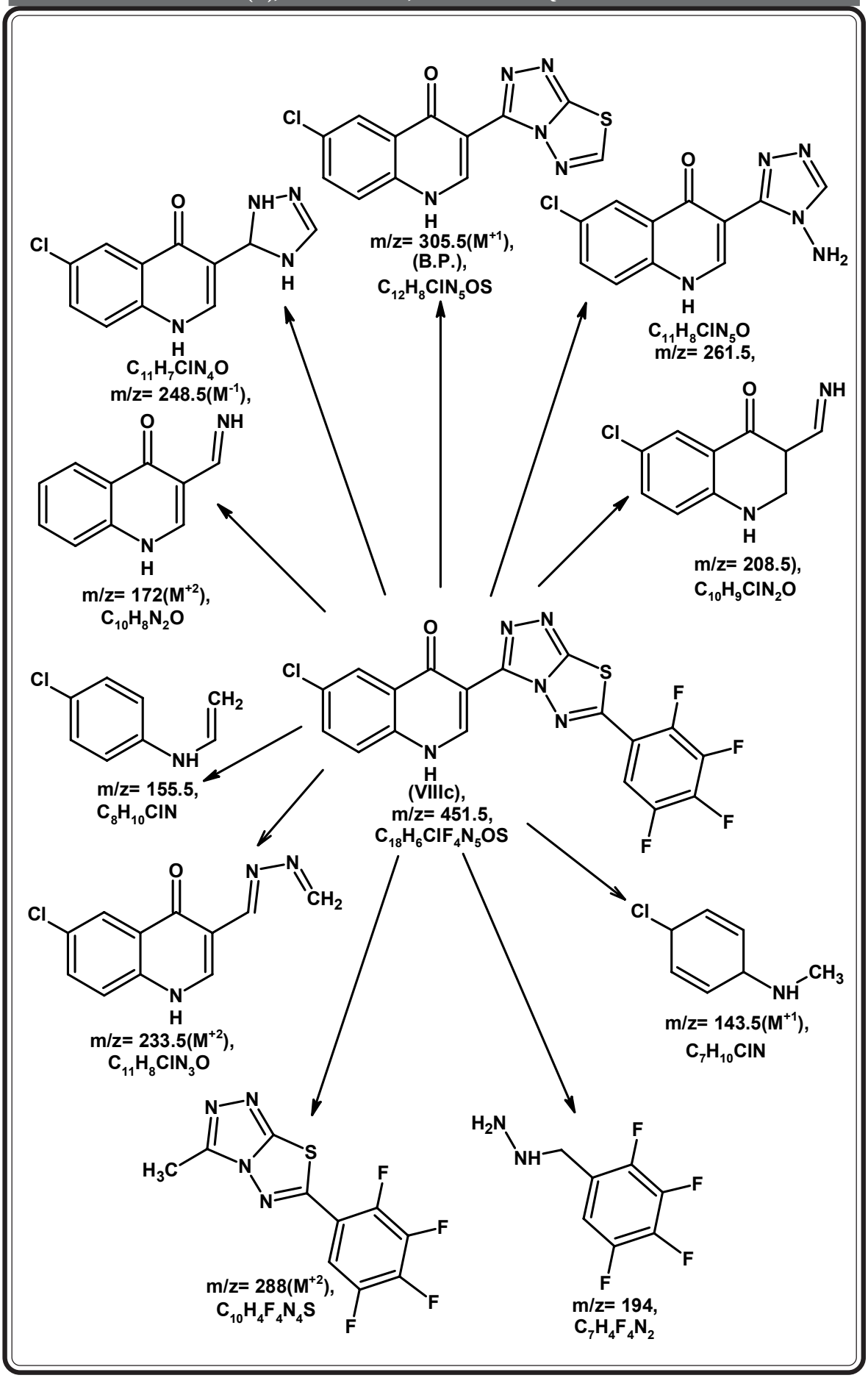
Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 12/24/2005 10:28:02 PM
Sample Name	: JJSM-13
Sample ID	: JJSM-13
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJSM-13.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune9.qgt

Line#:1 R.Time:8.9(Scan#:1034)
MassPeaks:86 BasePeak:304(67702)
RawMode:Averaged 7.3-9.7(843-1126)
BG Mode:None
intensity




m/z= 305.5(M+1),
(B.P.),
C12H8ClN5OS
C11H7ClN4O
m/z= 248.5(M-1),
C11H8ClN5O
m/z= 261.5,
m/z= 172(M+2),
C10H8N2O
m/z= 208.5),
C10H9ClN2O
m/z= 155.5,
C8H10ClN
(VIIIc),
m/z= 451.5,
C18H6ClF4N5OS
m/z= 233.5(M+2),
C11H8ClN3O
m/z= 143.5(M+1),
C7H10ClN
m/z= 288(M+2),
C10H4F4N4S
m/z= 194,
C7H4F4N2

MASS SPECTRAL STUDY OF 7-CHLORO-6-FLUORO-3-[6'-(2'',3'',4'',5'',-TETRAFLUOROPHENYL (1',2,',4')-TRIAZOLO-(3',4'-b)[1',3',4']-THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONE ($VIII_d$).

SAURASHTRA UNIVERSITY - RAJKOT
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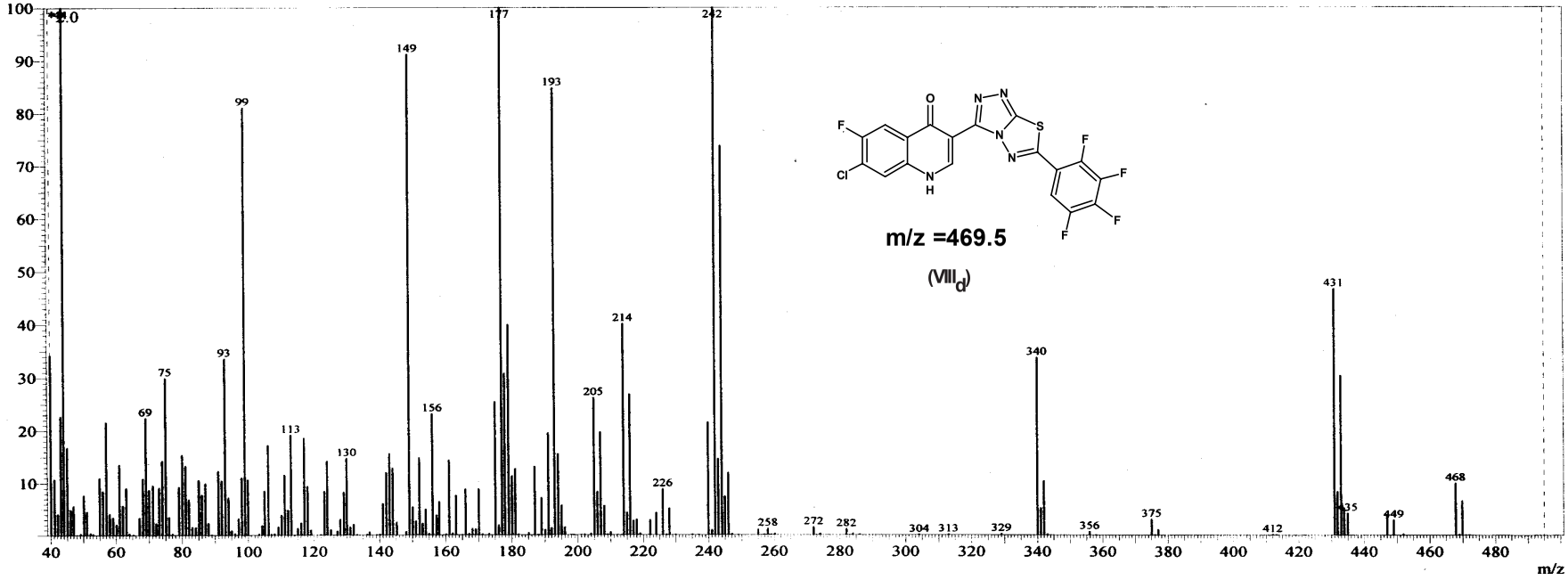
Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 1/2/2007 2:02:10 PM
Sample Name	: JJS-MQ-5
Sample ID	: JJS-MQ-5
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-5.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune121206.qgt

Line#:1 R.Time:6.2(Scan#:712)
MassPeaks:212 BasePeak:177(32464)
RawMode:Averaged 4.8-9.0(535-1041)
BG Mode:None
intensity



m/z =469.5

($VIII_d$)

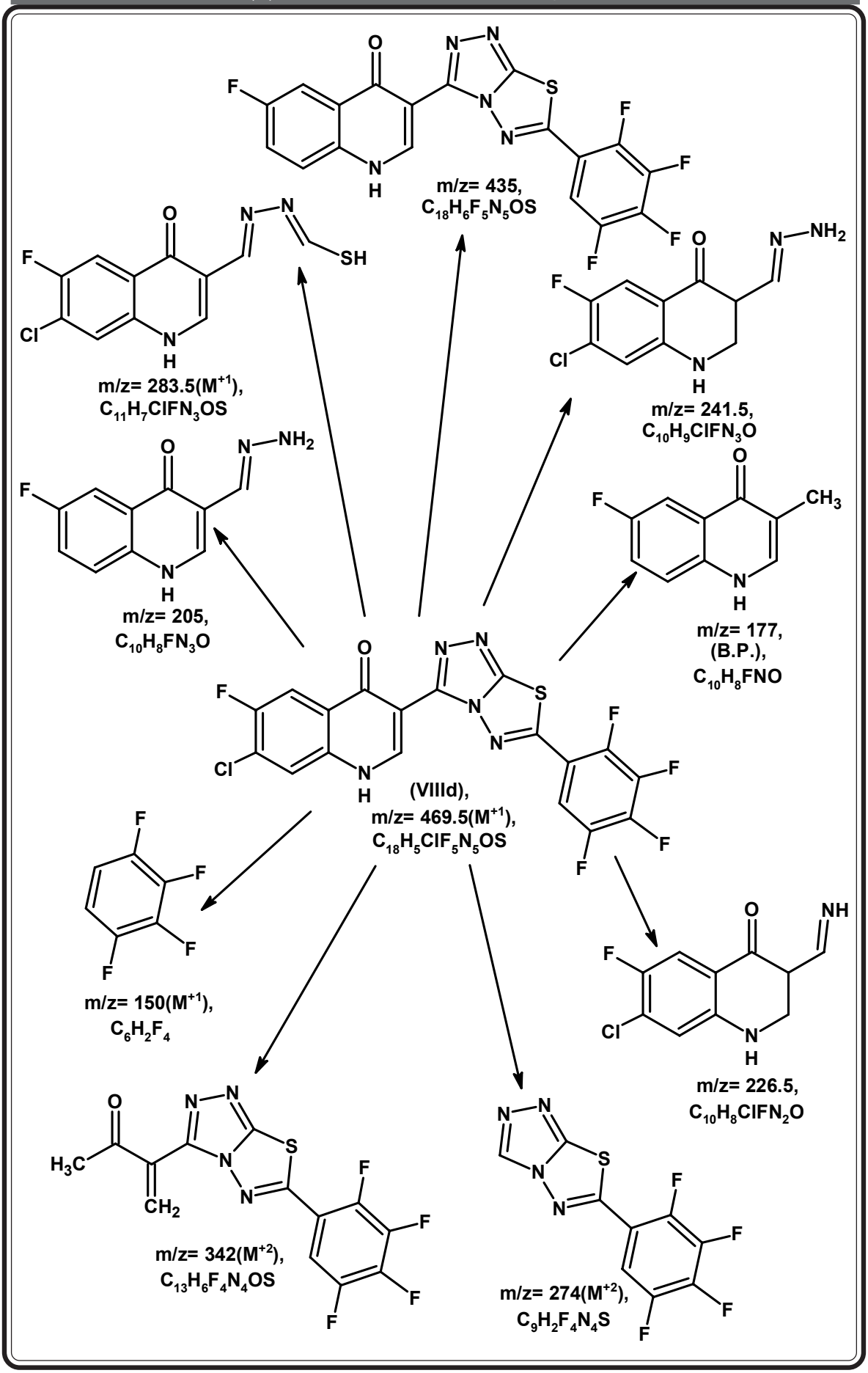

m/z= 435,
C18H6F5N5OS
m/z= 283.5(M+1),
C11H7ClFN3OS
m/z= 241.5,
C10H9ClFN3O
m/z= 205,
C10H8FN3O
m/z= 177,
(B.P.),
C10H8FNO
(VIIId),
m/z= 469.5(M+1),
C18H5ClF5N5OS
m/z= 150(M+1),
C6H2F4
m/z= 226.5,
C10H8ClFN2O
m/z= 342(M+2),
C13H6F4N4OS
m/z= 274(M+2),
C9H2F4N4S

TABLE NO. 8A : COMPARATIVE ANTIMICROBIAL ACTIVITY OF SUBSTITUTED-3-[6'-(2'',3'',4'',5'',-TETRA FLUORO-PHENYL)(1',2,',4')-TRIAZOLO-(3',a-b)[1',3',4']-THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONE ($VIII_{a-j}$).

(Different- Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) S. pyogens MTCC- 442					S. aureus MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
$VIII_a$	6-F	-	8	10	12	14	-	9	11	13	17
$VIII_b$	7-Cl	-	10	12	14	16	-	10	13	17	20
$VIII_c$	6-Cl	-	10	12	14	17	-	11	13	15	18
$VIII_d$	7-Cl-6-F	-	9	11	12	15	-	10	12	16	18
$VIII_e$	6,7-$(Cl)_2$	-	9	10	12	14	-	8	10	12	14
$VIII_f$	6-NO_2	-	8	10	11	13	-	9	11	13	15
$VIII_g$	6-OCH_3	-	8	9	10	14	-	9	11	14	15
$VIII_h$	6-CH_3	-	9	10	12	13	-	10	12	14	14
$VIII_i$	7,8-$(CH_3)_2$	-	8	9	10	12	-	9	11	13	15
$VIII_j$	-	-	8	8	9	11	-	9	10	12	15

Comparative activity of($VIII_{a-j}$) with known choosen standard drugs

Standard drug	Antibacterial activity										
										V_b $V_{c,d}$	$V_{a,b}$ $V_{c,d}$
Amoxicilin	12	14	15	16	18	10	12	14	15	16
Chloramphenicol	14	15	18	19	24	14	17	20	21	24
Sparfloxacin	14	22	24	26	28	24	26	27	28	32
Levofloxacin	18	21	22	27	29	20	24	26	27	35

N.B.(-): No Activity

TABLE NO. 8B : COMPARATIVE ANTIMICROBIAL ACTIVITY OF SUBSTITUTED-3-[6'-(2'',3'',4'',5'',-TETRA FLUORO-PHENYL)(1',2,',4')-TRIAZOLO-(3',a-b)[1',3',4']-THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONE ($VIII_{a-j}$).

(Different- Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.)									
		B. Subtillis MTCC- 441					E.coli MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
$VIII_a$	6-F	-	10	12	13	16	-	7	7	9	10
$VIII_b$	7-Cl	-	10	11	12	15	-	6	7	8	9
$VIII_c$	6-Cl	-	10	12	14	17	-	6	6	7	8
$VIII_d$	7-Cl-6-F	-	9	10	12	14	-	6	6	7	8
$VIII_e$	6,7-$(Cl)_2$	-	10	12	13	16	-	6	9	10	12
$VIII_f$	6-NO_2	-	10	11	12	15	-	8	7	9	10
$VIII_g$	6-OCH_3	-	10	12	13	17	-	9	10	13	16
$VIII_h$	6-CH_3	-	9	10	11	13	-	8	9	10	11
$VIII_i$	7,8-$(CH_3)_2$	-	8	9	10	12	-	8	10	13	14
$VIII_j$	-C_4H_4	-	10	11	13	16	-	9	8	9	10
Comparative activity of ($VIII_{a-j}$) with known choosen standard drugs											
Standard drug		**Antibacterial activity**									
Amoxicilin		12	15	16	18	19	11	14	16	18	20
Chloramphenicol		18	22	24	26	27	17	20	23	25	26
Sparfloxacin		22	24	25	26	29	20	22	25	26	28
Levofloxacin		24	26	28	29	31	23	25	26	29	30

N.B.(-): No Activity

TABLE NO. 8C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF SUBSTITUTED-3-[6'-(2'',3'',4'',5'',-TETRA FLUORO-PHENYL)(1',2,',4')-TRIAZOLO-(3',a-b)[1',3',4']-THIADIAZOLE-3-YL]-QUINOLONE-4(1H)-ONE ($VIII_{a-j}$). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antifungal activity (Zones of inhibition in m.m.) C. albicans MTCC- 227					A. niger MTCC-282				
		5	25	50	100	250	5	25	50	100	250
$VIII_a$	6-F	-	7	9	11	13	-	7	8	9	10
$VIII_b$	7-Cl	-	7	8	9	11	-	7	8	10	11
$VIII_c$	6-Cl	-	6	8	10	12	-	8	9	10	12
$VIII_d$	7-Cl-6-F	-	6	9	11	13	-	8	10	11	13
$VIII_e$	6,7-$(Cl)_2$	-	8	10	12	14	-	8	9	10	11
$VIII_f$	6-NO_2	-	6	8	9	10	-	8	10	12	15
$VIII_g$	6-OCH_3	-	10	10	11	13	-	9	11	12	14
$VIII_h$	6-CH_3	-	9	11	13	15	-	6	8	9	10
$VIII_i$	7,8-$(CH_3)_2$	-	6	8	10	11	-	7	10	10	12
$VIII_j$	-C_4H_4	-	7	9	11	13	-	7	9	11	13
Comparative activity of(VII_{a-j}) with known choosen standard drugs											
Standard drug		Antifungal activity									
Griseofulvin		16	18	21	23	25	17	19	21	22	23
Fluconazole		14	16	18	21	22	15	17	18	20	21

N.B.(-): No Activity

References

1. Wise R., Andrews J. M., Edwards L. J., Antimicorb. Agents Chemother. **23**, 559-564, (1983).
2. Hayakawa I., Hiramitsu T., Tanaka Y., Chem.Pharm.Bull.**32**, 4907-4913,(1984).
3. Chin N.X., Novelli A., Neu H.C., Antimicorb. Agents Chemother. **32**, 656-662, (1988).
4. Miyamato T., Matsumoto J., Chiba K., Egawa H., Shibamori K., Minamida A., Nishimura Y., Okada H., Kataoka M., Fujita M., Hirose T., Nakano J., J.Med.Chem.Vol.-**33**,1645-1656, (1900).
5. Drug Discovery, nature Reviews, Antibacterials Vol.-**6** ,No.-1 ,10-11, (Jan-2007).
6. Oldfield William (Lilly Industries Ltd.)., Brit., 1, 147, 336 (Cl.C07d). Chem. Abstr., **71**, 49795, (1969).
7. Albert R; Kesseler H. J.; Chem.Ther., **7(4)**, 345-9 (1972) (Ger.); Chem. Abstr., **78**, 38520, (1973).
8. Keitaro senga Ravindra. P. raio, Roland K. Robing. J. Med. Chem.Vol.-**18**, No.3, (1975).
9. Lesher G. Y; Carabateas P. M.; U.S. 3, 907, 808 (Cl.260-87R,C07d); Chem. Abstr., **84**, 43880, (1976).
10. Wright j. B; Johnson H. G.; J. Med. Chem., **20 (1)**,166-9, (1977); Chem.Abstr., **86**, 25930, (1977).
11. Lee K.T.; U.S. 4,146,625 (Cl.424-258; A 01 N 9/22); Chem .Abstr., **91**, 5125,(1979).
12. Knoechel H; Schubert W; Teubner H; Huebler D; ChemnitiusK. H; Stopsack H.; Ger(East)., **134**, 225 (Cl. C. 07 D 215/54); Chem .Abstr., **91**, 39349, (1979).
13. Ishikawa H; Tabusa Fujio; Nakagawa K.; Ger Offen., **3**,007,006 (Cl. C 07D 215/56); Chem. Abstr., 9323263, (1980).
14. Mushika Y; Tani J; Totaro Y; Oshima S.; Eur. Pat., 28698(Cl. C 07 D 215/56); Chem. Abstr., **95**, 187094, (1981).
15. Grohe K; Zeiler H. J;Metzger K.;Ger. Offen., 3, 007, 006 (Cl. C 07 D 401/04); Chem. Abstr., **99**, 53790, (1983).
16. Michael engler, guido rusing, fritz sorgel and Olrike Hoizgrabe, Antimicrobial agents and chemotherapy, Vol. no.-**42**, no.-**5**, 1151-1159, (may-1998).
17. Christos,mrrsos. Alexandros Zogratos. and olga igglessi markopoulo, Chem. Pharm. Bull. **48(2)**, 211-214, (2000).
18. S. ya. Solodukhin, A. S. Peregudov. E. V. Vorontsov and N. D. Chkanikov Molecules, **9**, 164-169, (2004).
19. Pavel. Hradil. Martin. grepl. Jan Hlavoc. Mlroslov Soural. Michal. Malon and Valerio Bertolo si J. Org. Chem. **71**, 819-822, (2005) .
20. H. I. Chauhan, N. B. Patel, &. A. L. Patel Indian journal of chemistry vol.**46B**,126-134 (Jan-2007).
21. Pharmaceutical Substanes, Synthesis, Patents. Applications, Axel Kleemann and Jurgenzngel. (4^{th} edition).
22. Mitscher L. A., Devasthle P. V., Zovod R. M., Springer, Berlin, 115-146, (1990).
23. Wentland M. P., Siporin C., Heifetz C. L., Domagala J. M. The New Generation of Quinolones, Marcel Dekker, New York, 1-44, (1990).

24. Chu D. T. W., Fernandes P. B., Academic press, San Diego, **21**, 39-144, (1991).
25. Sanchez J. P., Gogliotti R. D., Domagala J. M., Gracheck S. J., Huband M. D., Sesmi J. A., Cohen M. A., J. Med. Chem. **38**, 4478-4487,(1995) .
26. Palumbo M., Gatto B., Zagotto G., Trends Microbiol, **1**, 232-235,(1993).
27. Fan J. Y., Sun D.K., Yu H., Kerwin S. M., Hurley L.H., J. Med. Chem. **38**, 408-424,(1995) .
28. Neer T. M. ; J. Am. Vet. Med. As-soc., **193**, 577-580, (1988).
29. Berg J.; In Proc. west vet. Conf, Las Vegas, nevadfa: Mobay Corporation, (1988).
30. Chu D., Fernadez P., Claiborne A., Shen L., Pernet A.; DrugsExp. Clin.res., **14**,379-383,(1988).
31. G. Sarkozy. Vet. med. Zech. **46**, 257-274 (9-10) (2001).
32. Gaurav grover and suvarana.g.kini.journal of Heterocyclic chemistryvol.**12**, 289-290 Jan-march (2003).
33. D. Sriram, P. Yogeeswari, Medicinal Chemistry pp.no.289-290.
34. Aries, Robert.,Fr., 1, 543, 405 (Cl. C 07 d, A 61k); Chem.Abstr., **71**, 124278, (1969).
35. Loev Bernard., U.S. 3,462,438 (Cl. 260-287, C07d).
36. Ferrini Pier G; Hass G.; Rossi A.; Swiss., 578, 536 (Cl. C 07 D 215/56); Chem.Abstr., 29659,(1977).
37. Hall C.M; Wright J. B;Johnson H. G;Taylor A. J.; J. Med.Chem., **20(10)**, 1337-43, (1977); Chem.Abstr.,**87**,135158,(1977).
38. Goeschke R;Ferrini P. G;Sallmann A.;Eur. Pat., EP, 62 ,001(Cl. C 07 D215/56); Chem. Abstr.,160599, (1983).
39. Hazard R; Dicker I. D;Ingali A. H; Eup.Pat.EP.,104,108(Cl. C 07 D 311/24); **101**,72627,(1984).
40. Nippon Shinyaku Co.,Ltd.Jpn.Kokkai Tokkyo Koho JP 58, 219,166 [83,219,166] (Cl. C 07 D215/48); Chem. Abstr. **100**,191752, (1984).
41. Norton. p. peet. Larry. E. baugh Shyar Sunder and jin.e.lewis J. Med. Chem. vol. **28**, No-3,298-302,(1985).
42. Goschke R; Ferrini P.G; Sallmann A.; Can.CA,1,192,554(Cl. C 07 D 215/56); Chem.Abstr.,**104**,168378,(1986).
43. G.C. Kamdar, D.J. Bhatt, A.R.Parikh, J. Indian Chem. Soc. 61,79 (1984): Chem. Abstr.,**103**,53884,(1985).
44. Nagano Y; Murakami M.; Japan Kokkai., 7326771.; Chem.Abstr., **78**, 159470, (1973).
45. Kobalyashi R.;Isagai K; Nakayoichi;Seki T.;japan Kokkai., 7, 684,476(Cl. C 07 D 401/06);Chem.Abstr., **86**,72466(1977).
46. Minami S;Matsumoto J;Sugita M;Shimizu M;Takase Y; Nakamura S ;Japan. Kokkai. ,**75**,160,285 (Cl.C07D 401/04);Chem.Abstr.,**87**,68427w,(1977).
47. Kyorin Pharmaceutical Co.,Ltd.; Belg.863, 429(Cl.C07D) ; Chem. Abstr., **89** ,

180050w, (1978).

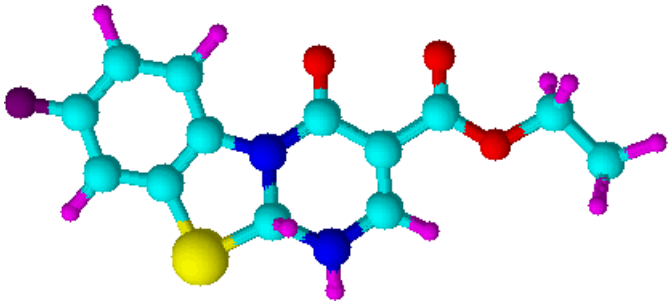
48. R.H.Mizzoni,R.A.Lucas. R. Smith, D.C. Mapiesden and G.Destevens.J. Med.Chem .Vol.-**13**, (1970). J.Med.Chem.Vol.-**22**,No.**11**, 1354-1357,(1979).
49. Lester. A. Mitscher, Daniel.L.Flynn.H.Eugene gracey and Steven.D.Drake. J.Med.Chem.Vol.-**22**,No.11, 1354-1357,(1979).
50. Irikura T;Suzus S; ItoA;Koga H.;Fr.Demande.,2,424,919(Cl.C07D401/04)Chem. Abstr., **92**,215294j (1980).
51. Hiroshi Koga. Akira Itoh. satoshi murayama. Seigo Suzue.and TsutomuIhkan. J.Med.Chem., **23**,1358-1363,(1980).
52. Nakanishi S.;Eur.Pat.EP., 314, 362 (Cl.C07D401/04); Chem.Abstr. ,**112**, 55628x (1990).
53. Coromines J.P;Constansa J.F; Pinol A.C.; Fr.Demande FR 2,625, 200(Cl.07 D 401/ 04); Chem.Abstr.,55635x (1990).
54. Jun.Segawa. Kenji Kazuno, Masakuni Ozaki and masahiro Kise.J.Med.Chem. **35**,4727-4735(1992).
55. Jun.Segawa. Kenji Kazuno, Masakuni Ozaki and masahiro Kise.J.Med.Chem.**35**,4727-4735(1992).
56. V.H. Shah,, A.R.Parikh, J.Inst.Chem. 58,141, (1986):Chem.Abstr.,**109**,22697d, (1988).
57. V.B.Gaur, V.H. Shah,, A.R.Parikh, J.Inst.Chem. 62,157,(1990):Chem.Abstr.,**124**, 164173g ,(1991).
58. Gaurav grover and suvarana.g.kini.journal of Heterocyclic chemistry vol.**12**,289-290 Jan-march(2003).
59. Alireza foroumadi Fatemeh.soltani,mohammod hasan,moshoti,Rogheeyeh Ashrof-Askari.**58**,1023-1028,(2003).
60. Jae wook. lee, Gui. Taek.Lim. and Kilsun., Lee ; Journal of the KoreanChemical Soceity, Vol, **47**, No. 5,(2003).
61. Yoshikaza Asahina,Khiro Araya.Kazuhiko Lwase, and Takayo shiIshizaki. J. Med.Chem. **48**, 3443-3446, (2005).
62. Eric stern. Jean. Francois Goossens ,Philippe Chavatte, PutrickDepreux, Jean- pierre Henichart. J Med.Chem.stern.et.al. a-j (2005).
63. N.B.Patel,P.R.Bhagat Indian journal of Heterocyclic chemistry vol.**16**,,205-206Oct-Dec-(2006).
64. Ito Y;Kato H;Yasuda SW; Yoshida Y.;Jpn.Kokkai Tokkyo Koho Jp.,570,467 [93,70,467](Cl.07D 513/04); Chem.Abstr.,**119**.139203n (1993).
65. Patchett. A.A;clark.R.Lj Rogers E.F; U.S.3,542,851 (cl.260-471;(otc); Chem. abstr.,**74**,72712p (1971).
66. Y.J. Fernandes. H.Parekh. J.Inst. Chemists, **63**,199 (1991).
67. Allais Andre (Roussel-uclaf);Fr.M.6 103 (Cl.A61 KgCO7d). Chem.abstr.,**71**,12474c

(1969).

68. Bernasconi Raymond;Ger.oflfem.,2,017,470 (Cl.C07d); Chem.abstr.,**74**,6358j (1971) 0, 508-12(1984);
69. Li Hj Lu Y;Liang X.;Yaoxue xuebao,**19(7)**, 508-12 ,Chem.abstr. ,**101**, 230328w (1984).
70. Bosert F;Vater W.;ger.offen., 2 ,033,148 (Cl.C07d);Chem.abstr., **75**, 98459c (1971).
71. Voronova V.A;Kauss V.;Tezisy Dokl.Resp.Konf.Molodykh Uch.Khim.,2nd,**1**,14,-15(1977);Chem .Abstr., **89**,109013(1978).
72. Daniel.T.W. Chu., Eva Pthuleac. Robert E. Maleczka. J.O.and Andre.G.pernet. J.Med.Chem. Vol.-**28**, No.11, 1558-1504, (1985).
73. Yoshikazu , Asahina. Takayashi Ishizaki. J.Med.Chem.**48**, 3194-3202,(2005).
74. Munson H.R.Jr;Alphin R.S.; U.S. US 4,343,804(Cl.424-258;A 61 K 31/47); Chem.Abstr.,**98**,143284 (1983).
75. Leroi E.L.;S.African., 68, 04, 576;Chem.abstr.,**71**,124277(1969).
76. Hanifin,J.W.Jr;Capuzzi R.A;Cohen E.;US.3,470186(Cl.260-287;Cl.07 d,A 61K); Chem.Abstr.,**71**,124275 (1969).
77. Loewe H.;Entwickl.,Wirkung, Darstell.,Zweite Auflage.,4,2231-6(1972) (Ger.); Chem. Abstr.,77, 92755(1972).
78. Nishimura Hareki; Nagai Yasutaka;Nakamura Keiji.;Japan., 6916373 (Cl.16E 432).; Chem. Abstr.,**71**,124273(1969).
79. Kutter Eberhard; Griss Gerhard; Grell Wolfgang;Kleemann Manfr ed. ;Ger., 1,919,570 (Cl.C 07d, A61 k); Chem.Abstr., **74**,22711 (1971).
80. Champseix A; Gueremy C; Le fur J.;Ger.Offen.,**2**,727,144(Cl. A61K31/445); Chem. Abstr., **88**, 121003(1978).
81. Movrin M;Majsinger D;Medic saric M.; Sci.Pharm.,46(2); Chem.Abstr. **89**,190856 (1978).
82. Karl A. Roseman,maribeth. M.gould. Warner, M-Linfield and Ben.E.Edwards Vol.no.-**3**,230-233,(1977).
83. Mark.P.Wentland Suzanne.C.Aldous. Peter.H. Dorft ,Jemes.B.Rakeand Susan.A.Coughlin. J.Med.Chem.**36**,2801-2809,(1993).
84. Chengxin Zhi, George.E.wright,Richard Bethell,Caroline Cadilhae,Richard Storer. J.Med.Chem .**49**,1455-1465, (2006).
85. Yasunori Tsuzuki Koh-Ichiro Shibanori, shigeki Kashimoto, and Katsumi chiba. J. Med.Chem.Vol.-**47**, 2097-2104,(2004).
86. K.S. Aithal ; N. Udupa and K. K. Sreenivasan.; Indian J Chem., **35B**, 864-6,(1996).
87. M. B. Deshmukh and B. S. Shinde.; Indian J Hetero. Chem., **5**, 235-6 (1996).
88. M. B. Deshmukh; M.A. Shelar; J.S. Jadhav; B.S. Shinde and S.H. Patil.; Indian J

Hetero. chem., **6**, 184,(1997).

89. Hiromitsu. takayama, wataru nittas mariko kitajima, Norio Aimi and Shin - Chiroakai,,journal of Natural products.vol.**57**, No.4 pp-521-523, april(1994).
90. Rajeshwar singh ,George thomas, Akio Hyodo, ronald GeorgeMicetich, Eur.J. Med. Chem.**33**, 697-703, (1998).
91. Antonio Carta, Michele palomba, Bianca paglietti ,Stefania Zanetti, Bioorganic & Med.Chem.Letters.**17**, Issue 17, 4791-4794, (2007).
92. Marugesan Dinakaran,Palaniappan Senthilkumar, Arnab China, Valakunja, Bioor ganic & Med.Chem.Letters.**18**, Issue 3,1229-1236, (2008).
93. A.L. Barry ; *The antimicrobic susceptibility test, Principle and Practices* {ELBS 4th Edition), 180-193.
94. Dastidar, S.G., Chaudhary, A., Annadurai, S. et al., In vitro and in vivo antimicro bial action of fluphenazine., *J. Chem.- other.* **7**, 201 (1995).
95. Mausmi Kawase, Bharat Varu, Anamik Shah, Noboru Motohashi, Satoru Tani, Satsuo Saito et al.: *Arzneim. Forsch. / Drug Res.*, **61(1)**, 67-71, (2001).
96. D.H.Williams and L.Fleming, "spectroscopic method of organic chemistry", 2nd, edition,London.
97. F.V.Loffe:Khim, geterokeikl, soidin. **6**,1089 (1968).
98. N.B.Calthup. L.H.Poly and stephen.C. wiberely, "introduction of IR and raman spectroscopy' Academic press inter.edu. (1964).
99. V.M.parikh, Absorption spectroscopy of organic molecules; Addission wesley publishing company, 243-258, (1978).



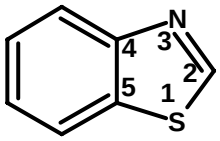
PART-I(B)

STUDIES ON PYRIMIDO [2,1-b][1,3]BENZOTHIAZOLE-4-ONES

PART - I(B)
STUDIES ON PYRIMIDO[2,1-b] [1,3] BENZOTHIAZOLE -4-ONES

INTRODUCTION:

Thiazole is a five membered heterocyclic ring system having sulfur and nitrogen as heteroatoms.The benzthiazole ring system bears phenyl ring fused with thiazole ring as indicated in the structure **(17)**.

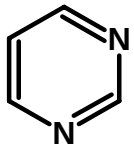


benzo thiazole

(17)

The history of the true thiazole series begins in 1879 with the work of Hoffmann, who prepared derivatives of benzthiazole such as 2-chlorobenzthiazole.2-phenylbenzthiazole[100] containing the thiazole nucleus were first reported by Hantzsh et.al., in a series of papers begining in 1887[101].

Pyrimidine **(18)** is a six membered heterocyclic compound consisting of two nitrogen atoms at 1 and 3 positions of heterocyclic ring.



pyrimidine
(18)

Generally pyrimidine derivatives such as 2-hydroxy-substituted-pyrimidines, 2-mercapto-substituted-pyrimidines and 2-amino-substituted-pyrimidines were studied. Pyrimidines have been isolated from the nucleic acid hydrolysates.

Pyrimidines are among those molecules that make life possible, have been some of the building blocks of DNA and RNA. Several analogues of pyrimidines have been used as compounds that interfere with the synthesis and functioning of nucleic acids e.g. fluorouracil, which has been used in cancer treatment. Also there are some thiouracil derivatives, which produce ad-

verse reduction in susceptible patients and found more potent and less likely to produce side effects and is being widely used[102]. There are several other important groups of pyrimidines with medicinal uses.

SYNTHETIC ASPECT OF BENZTHIAZOLE :

(A) By the condesation of o-amino thiophenol with a carboxylic acid or its derivatives or an aldehyde[103-114].

(B) By the Cyclisation of Benzenecarbothiaoamide in aqueous alkali with potassium ferricyaninde to give 2,3-dihydrobenz thiazoles[115-117].

(C) By the spontaneous Cyclisation of o-thiocyanato arylamines to pro duce 2-aminobenzthiazoles with good yields[118-119].

(D) By the Condensation of o-aminothiaphenol reacts with aromatic 1,2-diketones in boiling methanol yielding 2-aroyl-2-arylbenzothiazolines on boiling in acetic acid affords corresponding 2-arylbenzothiazole[120]

(E) By the Condensation of arylthiourea liquid bromine in chloroform to affords 2-aminobenzothioazole[121].

(F) By the Cyclisation of o-Nitroaryl thiocyantes to 2-aminobenzothia-zole[122].

SYNTHETIC METHODS FOR PYRIMIDINES

Various methods for synthesis of pyrimidines which are reported in the literature are as follows.

(a) By the condensation of urea and malonic acid led to formation of pyrimidine[123].

(b) By the condensation of malonic ester and urea led to formation of pyrimidine[124].

(c) By the condensation of formamidine with phenylazomalononitrile led to formation of 4,5,6-triaminopyrimidine[125].

(d) By the condensation of aromatic aldehydes,ß-ketoester or substituted ß-ketoester with urea or thiourea led to formation of pyrimidines[126].

(e) By the condensation of thiourea and substituted ß-ketoester in pres ence of sodium ethoxide led to formation of 2-mercaptopyrimidines[127].

(f) By the condensation of chalcones with dicyandiamide in presence of piperidine led to formation of pyrimidines[128].

(g) By thermal or microwave irridiation of thiourea and substituted ß-ketoester in presence of dimethylformamide led to formation of substituted tetrahydropyrimidines[129].

(h) One pot synthesis of aromatic aldehydes,ß-ketoester or substituted ß-ketoester with urea or thiourea led to formation of substituted dihydro pyrimidin-2-ones catalysed by $CuCl_2$[130].

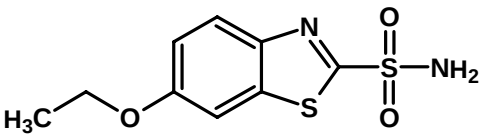
(i) One pot synthesis of aromatic aldehydes,ß-ketoester or substituted ß-ketoester with urea or thiourea led to formation of 3,4-dihydro pyrimidin-2-(1H)-ones/thiones under microwave irradiation[131].

(j) One pot synthesis of aromatic aldehydes,ß-ketoester or substituted ß-ketoester with urea or thiourea led to formation of dihydro pyrimidin-2-(1H)- ones catalysed by Tin (II) chloride ($SnCl_2$)[131].

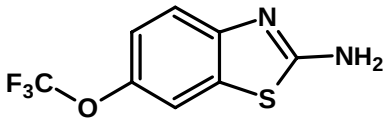
(k) One pot synthesis of aromatic aldehydes,ß-ketoester or substituted ß-ketoester with urea or thiourea led to formation of 3,4-dihydro pyrimidin-2-(1H)-ones by microwave induced eco-friendly solvent free biginelli reaction catalysed by calcium chloride[132].

MEDICINAL INTEREST OF BENZOTHIAZOLE :-

Some well known drugs which are having benzthiazole nucleus.



Ethoxzolamide
(Drug for glucoma and macular



Rifuzole
Antiglutamate" Anticonvulsant"

Literature survey revealed that various benzthiazoles have resulted in many potential drugs and are known to exhibit a broad spectrum of therapeutic activities such as :

[A] Antiinflammatory activity[133-134].
[B] Antimalarials[135-137].
[C] Antisepticactivity[138-139]
[D] Antidepressant activity[140].
[E] Antitumor activity[141-142]
[F] Antimicrobialactivity[143-144]
[G] Analgesic,Antipyretic activity[145].
[H] Pesticidal[146].

[I] Anticonvulsant activity[147-148].

[J] Anticancer activity[149-150].

[K] Immunosuppresive agent[151-152].

[L] Antiviral[153].

[M] Herbicidal[154].

[N] Neuroprotective agents[155-156].

[O] Antitubercularactivity[157-163].

[P] Antibacterialactivity[164-166].

[Q] Antifungalactivity[167].

[R] Anthelminticactivity[168].

[S] Local Anaestheticactivity[169-170].

[T] Antihistaminicactivity[169].

[U] Antiasthamicactivity[171].

[V] AntiUlceractivity[172].

MEDICINAL INTEREST OF PYRIMIDINES

In medicinal chemistry, pyrimidine derivatives have been very well known for their therapeutic applications. The presence of pyrimidine base in the thymine, cytosine and uracil, which are the essential building blocks of nucleic acids, DNA and RNA is one possible reason for their activity. The literature indicates the compounds having pyrimidine nucleus possess broad range of biological activities, like 5-fluorouracil as anticancer; idoxuridines and trifluoridine as antiviral; zidovudine and stavudine as antiHIV; trimethoprim, sulphamethazine and sulphadiazine as antibacterial; sulphadoxin as antimalarial and antibacterial; minoxidil and prazosin as antihypertensive; barbiturates eg. phenobarbitone as sedative, hypnotics and anticonvulsant; propylthiouracil as antithyroid; thionzylamine as H_1-antihistamine; and toxoflavin and fervennuline as antibiotics.

Some of the therapeutic activities of pyrimidine derivatives can be summarized as follows.

[A] Antithyroid[173-174]

[B] Antitumor[175-177]

[C] Antihypertensive[178-180]

[D] Antiinflammatory1[181-183]

[E] Diuretic[184]

[F] Antimalarial[185-187]

[G] Antispasmodic[188]

[H] Anticonvulsant[189]

[I] Antineoplastic[190]

[J] Anthelmintic[191]

[K] Cardiovascular[192-194]

[L] Antitubercular[195]

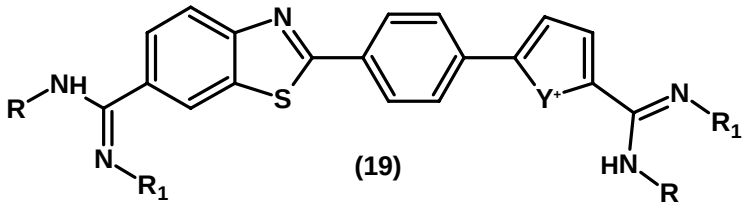
[M] Antiviral[196-197]

[N] Antihistamine[198]

[O] Anti-HIV[199-200]

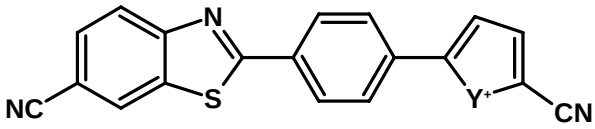
[P] Antimicrobial[201-220]

L. raeane et.al.,[221]. have prepared benzthiazole derivatives **(19)** and **(20),** which have been found to possess Anti HIV activity. J. Hofmann et. al.,[150]. have synthesised benzthiazole derivatives **(21)** as potent anticancer agents.



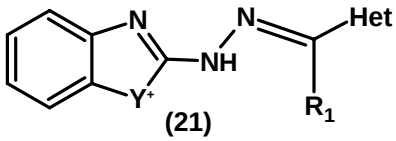
(19)

Y=S,O, R=Me_2CH,R_1=H



(20)

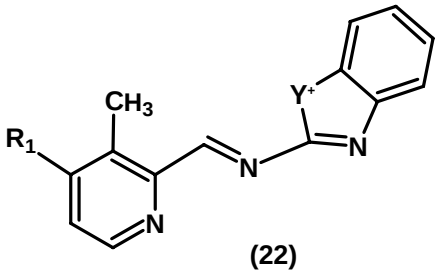
X=S,O.



(21)

X=S,N,O, Het= Quinolinyl, Isoquinolinyl, 2-Pyridyl

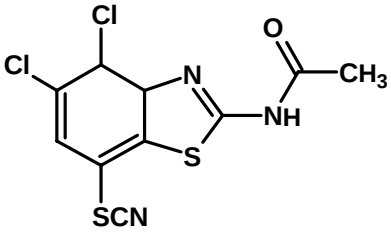
Recently, K.Thomas et.al.,[222]. have synthesised benzthiazole derivatives of type**(22)** as antihelicobacterpylori agent.



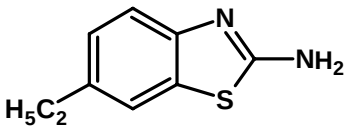
(22)

Y=S,R_1=$S(CH_2CH_2O)_3CH_3$

R.J.Alamino et. al.,[223-224] have synthesized a series of thiocynato benzothiazole, as a novel antiparasitic agents. The anthelmintic activity of the compound **(23)** was determined against as carissuum and hymenolepisnana in the mouse, and the result of the testing the activity data of **(23)** against these two helminthes failed to establish any structure-activity relationships. only compound 6-ethyl-2-aminobenzothiazole **(24)** had comparable activity to the reference drugs d, l-tetramisole and bunamidine[225].

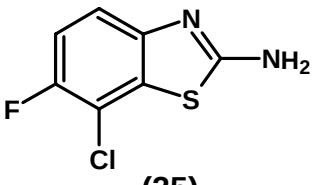


(23)

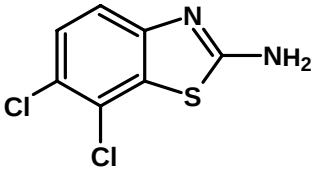


(24)

The antifungal activity of **(23)** was determined in sabourauds liquid medium BBL and the MIC values were tested against a number of yeast species. The most active compound tested were **(25)** and **(26)** and in addition, both significantly inhibited the growth of Candida albicans and micros Porum conis in the agar diffusion-cylinder cup test[226].



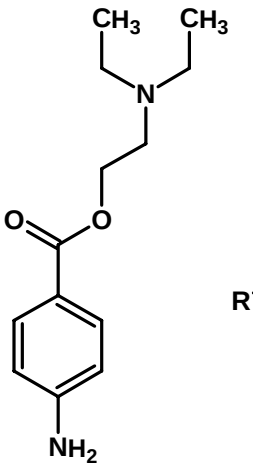
(25)



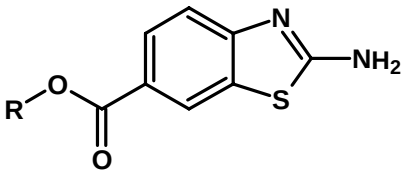
(26)

The vitamin, thiamine is the only natural product found to posses the thiazole nucleus[227].Sulfathiazole, the most potent sulfa drug in general use and promizol (4-aminophenyl-2-aminothiazolyl-5-sulfone)[228]a tuberculotherapeutic agent, are among the best-known thiazoles used in present-day medicine. The versatility of the thiazole is further demonstrated by the fact that some of these compounds possess antimalarial activity[229] that 2-(4-thiazolyl)-ethylamine has biological properties similar to those of histamine[230] and that 2-aminothiazole exhibits antithyroid activity[231].

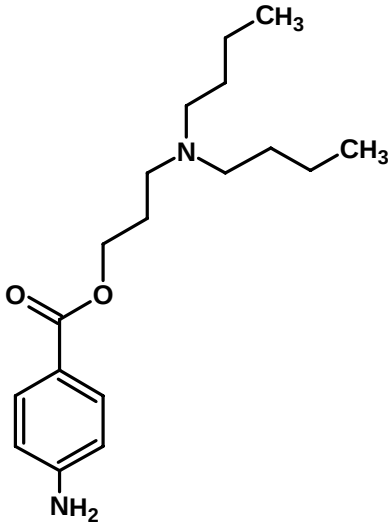
2-amino-6-carboxy benzothiazole **(28)**, is parent scaffold of the two well known local anesthetics, procaine **(27)** and butyn **(29)**.



(27)



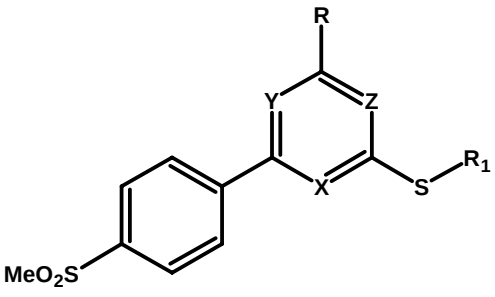
(28)

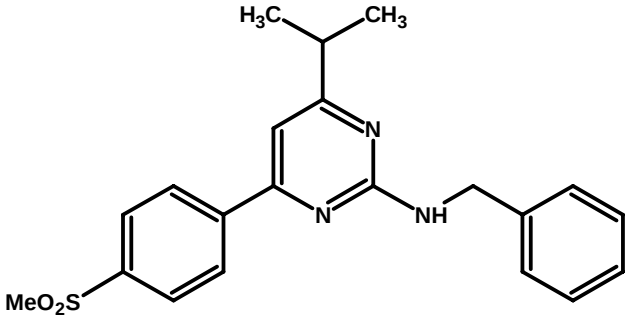


(29)

P. Khalili et. al.,[232] have carried out biochemical and pharmacokinetic evaluation of a novel nitric oxide donor pyrimidine nucleoside hybrid drug as a potential anticancer / antiviral agent. Rostom S.A.et al.,[233] have synthesized and screened certain 2-(benzoxazol-2-yl-amino)-3H-4-oxopyrimidines for ***in vitro*** anti-HIV activity.

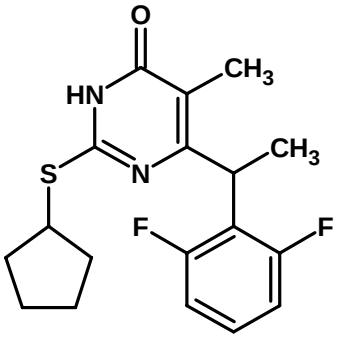
A family of trisubstituted pyrimidines has been described as selective COX-2 inhibitors. To explore the usefulness of pyrimidine derivatives as potential NSAIDs, A. Orjales et. al.,[234] have synthesized novel pyrimidine derivatives **(30)** and **(31)**. ***In vitro*** biological evaluation of these compounds has provided information to determine the structural features necessary for COX-2 inhibitory activity.

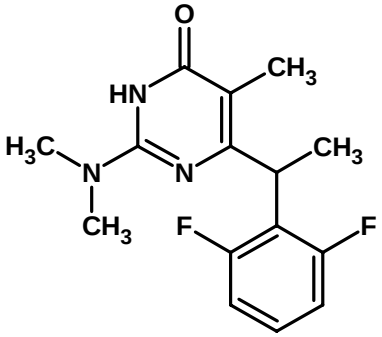




(30) Y = CH; X, Z = N **(31)** Y, Z = N; X = CH

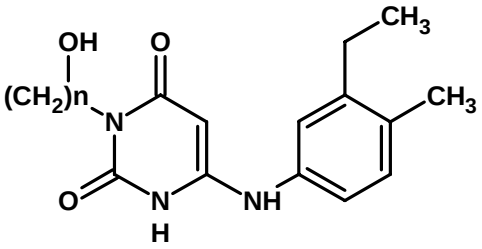
D.Rotili et al.,[235] have synthesized 6-substituted-[1-(2,6-difluorophenyl]pyrimidinones **(32,33)** and tested against endogenous, nontelomeric reverse transcriptase (endo-RT) in human differentiating cell systems to investigate their antiproliferative and cytodifferentiating activity.

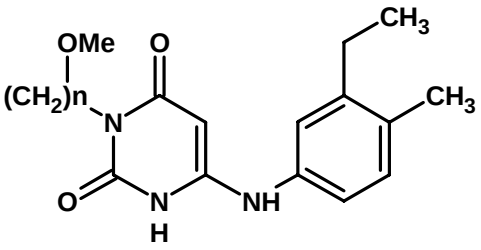




(32) **(33)**

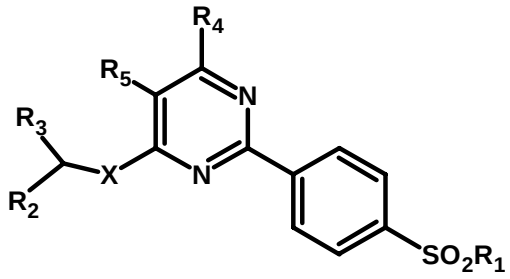
R. Stoorer et al.,[236] have synthesized 3-substituted-6-(3-ethyl-4-methylanilino)uracils **(34,35)** screened for their capacity to inhibit the replication-specific bacterial DNA plymerase IIIC (pol IIIC) and the growth of Gram+ bacteria in culture.





(34) n = 2,3,4. **(35) n = 2,3,4.0**

A.Orjales et al.,[237] have synthesized new series of 2-(4-methylsulfonylphenyl) and 2-(4-sulfamoylphenyl) pyrimidines **(36)** and evaluated for their ability to inhibit cyclooxygenase-2 (COX-2).



(36)

After persuing exostive literature survey it was found that not attempt was made to synthesis fused benzthiazole with any heterocycles moities and evaluated for biological profile.

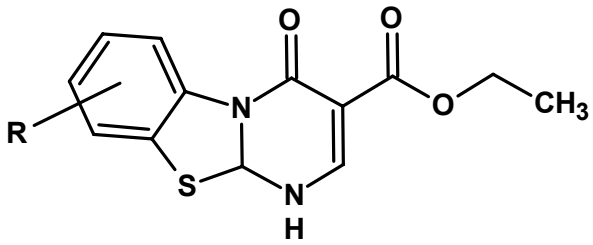
This part includes the synthesis and biological studies in benzthiaozole is fused with pyrimidine and its biological activity is evaluated which can be summarized in the following section.

SECTION - I : PREPARATION AND BIOLOGICAL EVALUATION OF 7,8,9-ETHYL-SUBSTITUTED-10a-DIHYDRO-4H-PYRIMIDO[2,1-b][1,3]BENZOTHIAZOLE-4-ONE-3-CARBOXYLATES.

SECTION - I

PREPARATION AND BIOLOGICAL EVALUATION OF ETHYL-7,8,9-SUBSTITUTED-10a-DIHYDRO-4H-PYRIMIDO[2,1-b][1,3]BENZOTHIAZOLE-4-ONE-3-CARBOXYLATES.

Keeping in view of various biodynamic activities[133-220] of **pyrimido[2,1-b] [1,3] benzothiazole-4-ones** and in order to have highly potent therapeutic agents, the synthesis of **Ethyl-7,8,9-substituted-10a-dihydro-4H-pyrimido[2,1-b][1,3]benzothiazole-4-one-3-carboxylates (IXa-j)** have been accomplished by the condensation of **different-4,5,6-substituted 2-amino benzothiazoles and diethyl ethoxy methylene malonate.**



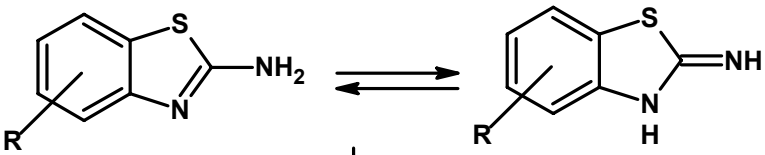
(IXa-j)

R=Substituted phenyl

The constitution of the products **(IXa-j)** have been delineated by **elemental analyses, IR, PMR** and **Mass** spectral data.

The products **(IXa-j)** were assayed for their ***in vitro*** biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** , ***S. aureus MTCC-96,*** **and** ***B. subtillis MTCC-441*** (Gram positive) and ***E. coli MTCC-443*** (Gram negative) bacterial strains and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations i.e.:0(control), 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds **(IXa-j)** were compared with standard drugs,,viz. **Amoxicillin, Chloramphenicol, Sparfloxacin, Levofloxacin**(antibacterial)**, Griseofluvin, Fluconazole** (antifungal)**.**

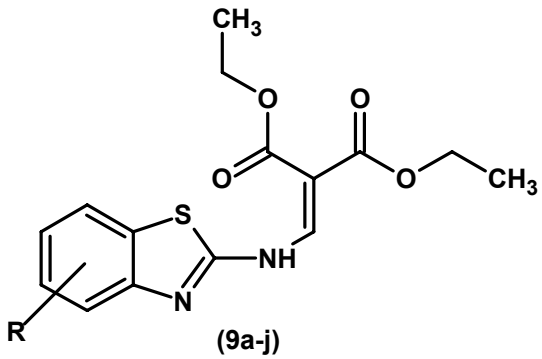
REACTION SCHEME



Diethyl ethoxy-
methylene malonate

Ethanol

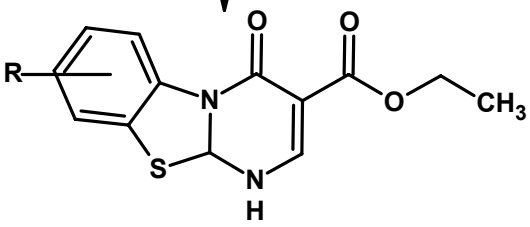
△



(9a-j)
R=substituted phenyl

Dimethyl-
sulphoxide

△



(IXa-j)
R=substituted phenyl

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF ETHYL-7,8,9-SUBSTITUTED-10a-DIHYDRO-4H-PYRIMIDO[2,1-b][1,3]BENZOTHIAZOLE-4-ONE-3-CARBOXYLATES.

(A) Preparation of 4,5,6-substituted- 2-amino-1,3- benzothiazole.

For preparation, of 4,5,6-substituted- 2-amino-1,3- benzothiazole refer in literature[121],

(B) Preparation of diethyl {[(6-methoxy-1,3-benzothiazol-2-yl)amino] methylene} malonate (9a-j).

A mixture of 6-methoxy- 2-amino-1,3- benzothiazole (1.80 gm, 0.01 M), and diethyl ethoxy methylene malonate (1.06 ml, 0.01M) in ethanol (20ml) was heated under reflux for 4 hrs. The rection mixture was then allowed to cool at 0 to 5 ^{O}C temperature. The rection mixture was poured in to ice-water, filtered, washed with water, dried and recrystallized from ethanol:water (3:1). Yield : 52 %, M.P.: 89 ^{O}C,(Required : C, 54.85 %; H, 5.18 %; N, 7.99 % for $C_{16}H_{18}N_2O_5S$, Found : C, 54.81 %; H, 5.12 %; N, 7.92 %).

TLC solvent system R_{f_1} : Ethyl acetate : Hexane(1.0 : 9.0) = 0.59.
TLC solvent system R_{f_2} : Methanol : Toluene(1.5 : 8.5) = 0.56.

Similarly, other compounds **(9a-j)** were synthesized. The physical data are recorded in **Table No.9**.

(C) Preparation of Ethyl 8-methoxy-10a-dihydro-4H-pyrimido[2,1-b][1,3]benzothiazole-4-one-3-carboxylate (IXa-j).

A mixture of diethyl {[(6-methoxy-1,3-benzothiazole-2-yl)amino] methylene} malonate (3.50gm, 0.01 M) in dimethyl sulphoxide(20 ml) was heated with stirring and the reaction mixture was then refluxed for 8 hrs. The resulting mixture

was allowed to cool at room temperature. The reaction mixture was poured in ice-cold water, filtered, washed with water and crystallized from Dimethyl formamide. The product was dried at 45-50 ^{O}C**.** Yield : 45 %, M.P. : 189 ^{O}C, (Required : C, 54.89 %; H, 4.61 %; N, 9.14 % for $C_{14}H_{14}N_2O_4S$, Found : C, 54.83 %; H, 4.58 %; N, 9.10 %).

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (3.0 : 7.0) = 0.51.
TLC solvent system R_{f_2} : Methanol : Toluene (1.0 : 9.0) = 0.38.

Similarly, other compounds **(IXa-j)** were synthesized. The physical data are recorded in **Table No.9A**.

(D) Antimicrobial activity of Ethyl-7,8,9-substituted-10a-dihydro-4H-pyri mido[2,1-b][1,3]benzothiazole-4-one-3-carboxylates (IXa-j) .

Antimicrobial activity testing was carried out as described in Part-1(A), Section-I, page No.30-31. The MIC values of test solution are recorded in **Table No.9B, 9C** and **9D.**

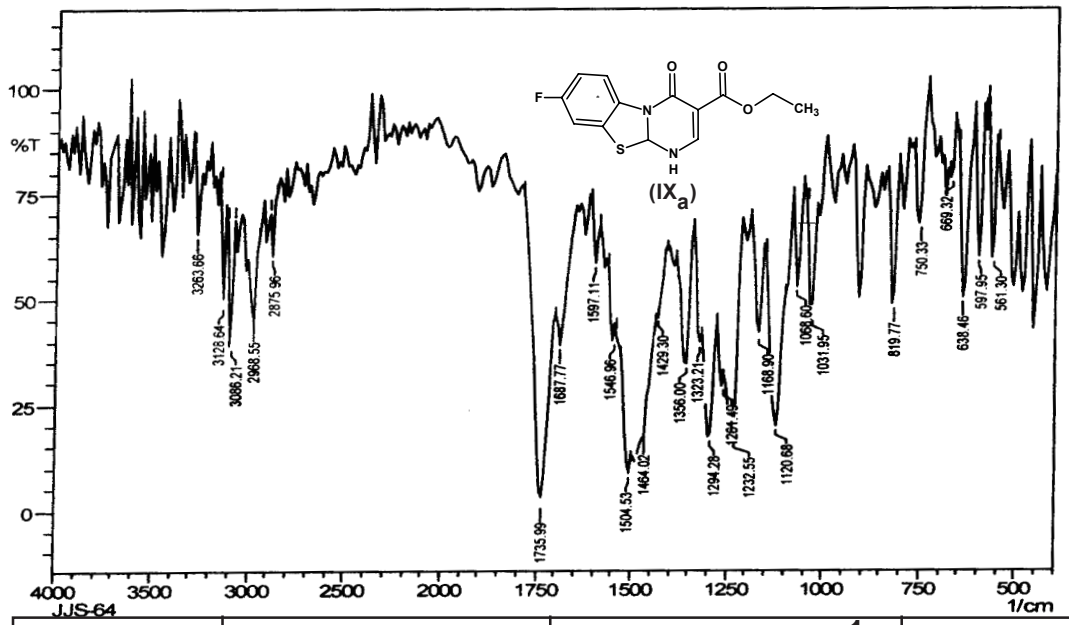
TABLE NO. 9 : PHYSICAL CONSTANTS OF DIETHYL {[(4,5,6-SUBSTITUTED-1,3-BENZOTHIAZOL-2-YL)AMINO]- METHYLENE} MALONATE (9a-j).

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. ^{o}C 5	Yield % 6	R_f Value 7		% of Nitrogen Calcd. / Found 8
						R_{f_1}	R_{f_2}	
9_a	6-F	$C_{15}H_{15}FN_2O_4S$	338.0	83^{o}	48	0.41	0.50	8.28 / 8.24
9_b	5-Cl	$C_{15}H_{15}ClN_2O_4S$	354.5	88^{o}	42	0.58	0.49	7.90 / 7.85
9_c	6-Cl	$C_{15}H_{15}ClN_2O_4S$	354.5	84^{o}	54	0.52	0.48	7.90 / 7.86
9_d	5-Cl-6-F	$C_{15}H_{14}ClFN_2O_4S$	372.5	98^{o}	65	0.54	0.51	7.51 / 7.46
9_e	5,6-$(Cl)_2$	$C_{15}H_{14}Cl_2N_2O_4S$	389.0	103^{o}	61	0.48	0.52	7.20/ 7.15
9_f	6-NO_2	$C_{15}H_{15}N_3O_6S$	365.0	117^{o}	58	0.51	0.44	11.50 / 11.44
9_g	5-OCH_3	$C_{16}H_{18}N_2O_5S$	350.0	92^{o}	57	0.47	0.40	7.99/ 7.92
9_h	6-OCH_3	$C_{16}H_{18}N_2O_5S$	350.0	89^{o}	52	0.43	0.39	7.99 / 7.91
9_i	6-CH_3	$C_{16}H_{18}N_2O_4S$	334.0	94^{o}	54	0.48	0.42	8.38/ 8.34
9_j	4,5-$(CH_3)_2$	$C_{19}H_{20}N_2O_4S$	348.0	86^{o}	56	0.51	0.48	8.04/ 8.00

TABLE NO. 9A : PHYSICAL CONSTANTS OF ETHYL-6,7,8-SUBSTITUTED-10a-DIHYDRO-4H-PYRIMIDO[2,1-b] [1,3]BENZOTHIAZOLE-4-ONE-3-CARBOXYLATES (IX_{a-j}).

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. °C 5	Yield % 6	R_f Value 7		% of Nitrogen Calcd. / Found 8
						R_{f_1}	R_{f_2}	
IX_a	8-F	$C_{13}H_{11}N_2O_3FS$	294.0	153°	39	0.63	0.43	9.52 / 9.48
IX_b	7-Cl	$C_{13}H_{11}N_2O_3ClS$	310.5	144°	44	0.58	0.42	9.01 / 8.98
IX_c	8-Cl	$C_{13}H_{11}N_2O_3ClS$	310.5	139°	40	0.56	0.38	9.01 / 8.97
IX_d	7-Cl-8-F	$C_{13}H_{10}N_2O_3ClFS$	328.5	180°	43	0.49	0.41	8.52 / 8.47
IX_e	7,8-$(Cl)_2$	$C_{13}H_{10}N_2O_3Cl_2S$	345.0	191°	47	0.52	0.42	8.12 / 8.07
IX_f	8-NO_2	$C_{13}H_{11}N_3O_5S$	321.0	232°	41	0.43	0.40	13.08 / 13.04
IX_g	7-OCH_3	$C_{14}H_{14}N_2O_4S$	306.0	175°	43	0.51	0.38	9.15 / 9.09
IX_h	8-OCH_3	$C_{14}H_{14}N_2O_4S$	306.0	188°	45	0.58	0.39	9.15 / 9.10
IX_i	8-CH_3	$C_{14}H_{14}N_2O_3S$	290.0	117°	44	0.49	0.35	9.65 / 9.61
IX_j	6,7-$(CH_3)_2$	$C_{15}H_{16}N_2O_3S$	304.0	121°	46	0.53	0.40	9.21 / 9.14

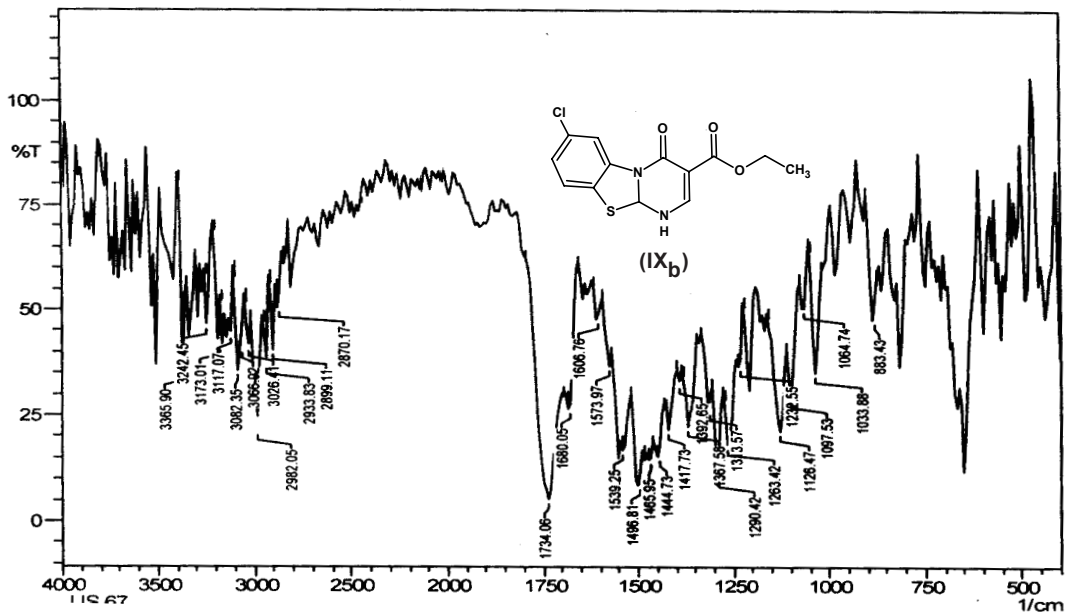
IR SPECTRAL STUDY OF ETHYL-8-FLUORO-10a-DIHYDRO-4H-PYRIMIDO[2,1-b][1,3]BENZOTHIAZOLE-4-ONE-3-CARBOXYLATE (IX_a).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2968.5	2975 - 2850	96
	C-H (sym. str., m)	2875.9	2900 - 2800	96
	C-H (asym. def., m)	1464.0	1470 - 1435	96
	C-H (sym. def., m)	1356.0	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3086.2	3080 - 3010	97
	C=C & C-C (str., v)	1546.9	1600 - 1450	97
	C-H (i.p. def., m)	1120.6	1150 - 1050	97
	C-H (o.o.p. def., m)	819.7	825 - 800	97
pyrimido[2,1-b][1,3] benzothiazole	C-N (str., v)	1323.2	1340 - 1250	97
	C-S-C(str.m)	669.3	700-650	97
	N-H (str., b)	3263.6-3086.2	3400 - 3000	98
	N-H (def., s,m)	1597.1	1650 - 1550	98
Ketone pyrimido ester	C=O (str., s)	1687.7	1690 - 1640	98
	C=O (str., s)	1735.9	1740 - 1650	98
Halogen Subtitution	C-F (str.,b)	1356.0-1120.6	1400 - 1080	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

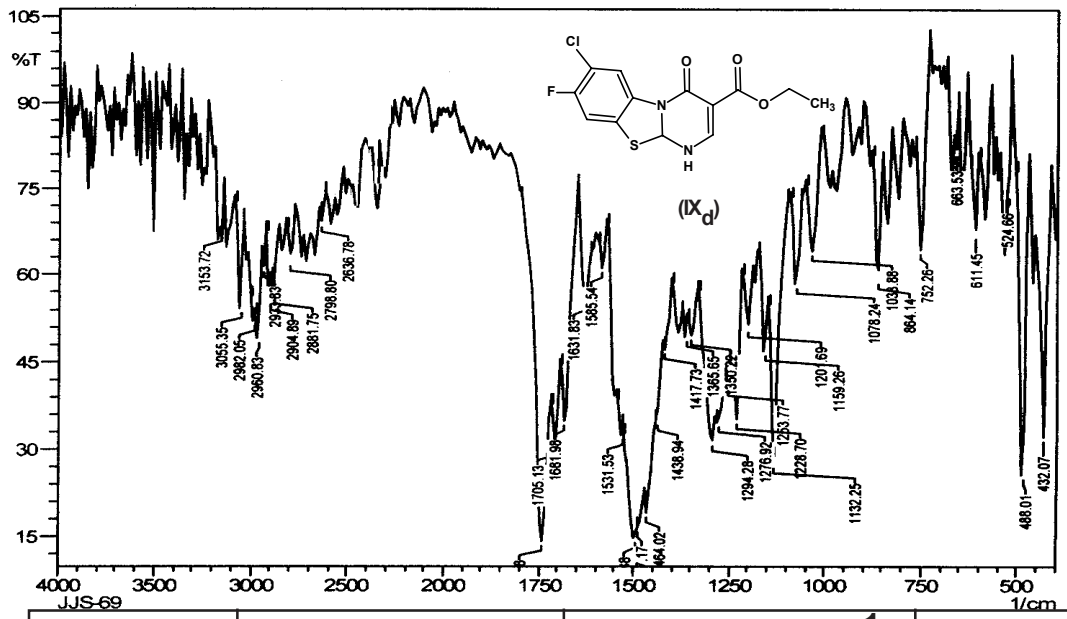
IR SPECTRAL STUDY OF ETHYL-7-CHLORO-10a-DIHYDRO-4H-PYRIMIDO[2,1-b][1,3]BENZOTHIAZOLE-4-ONE-3-CARBOXYLATE (IX_b).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2933.8	2975 - 2850	96
	C-H (sym. str., m)	2870.1	2900 - 2800	96
	C-H (asym. def., m)	1444.7	1470 - 1435	96
	C-H (sym. def., m)	1367.5	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3026.4	3080 - 3010	97
	C=C & C-C (str., v)	1573.9	1600 - 1450	97
	C-H (i.p. def., m)	1097.5	1150 - 1050	97
	C-H (o.o.p. def., m)	826.7	825 - 800	97
pyrimido[2,1-b][1,3] benzothiazole	C-N (str., v)	1290.4	1340 - 1250	97
	C-S-C(str.m)	653.2	700-650	97
	N-H (str., b)	3365.9-3066.0	3400 - 3000	98
	N-H (def., s,m)	1606.7	1650 - 1550	98
Ketone pyrimido ester	C=O (str., s)	1680.0	1690 - 1640	98
	C=O (str., s)	1734.0	1740 - 1650	98
Halogen Subtitution	C-Cl (str., b)	805.2	800-600	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

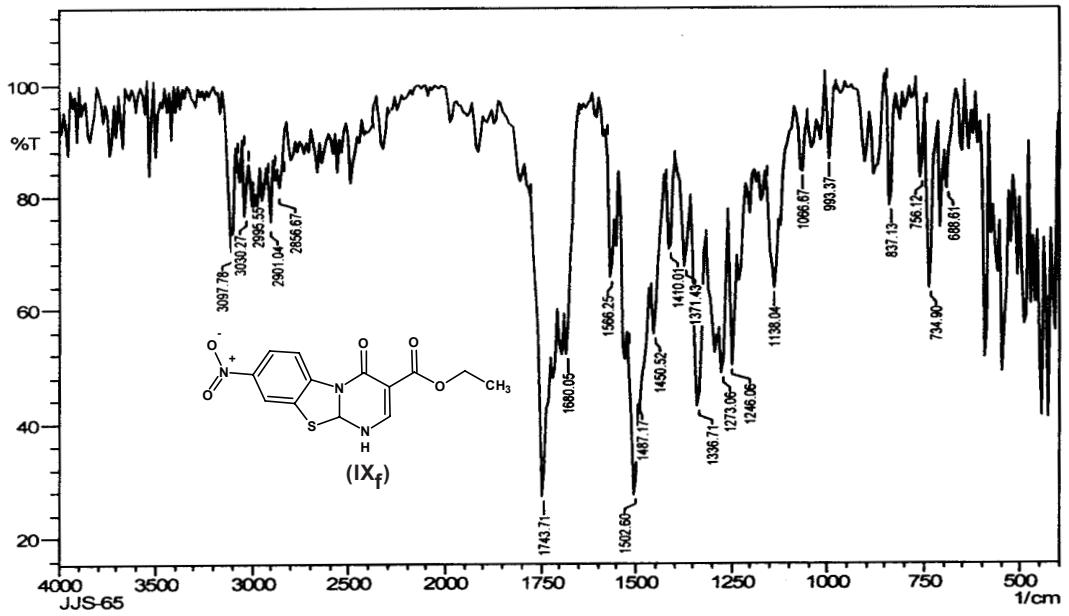
IR SPECTRAL STUDY OF ETHYL-7-CHLORO-8-FLUORO-10a-DI-HYDRO-4H-PYRIMIDO [2,1-b][1,3]BENZOTHIAZOLE-4-ONE-3-CARBOXYLATE (IX_d).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2933.8	2975 - 2850	96
	C-H (sym. str., m)	2881.7	2900 - 2800	96
	C-H (asym. def., m)	1438.9	1470 - 1435	96
	C-H (sym. def., m)	1365.5	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3055.3	3080 - 3010	97
	C=C & C-C (str., v)	1585.5	1600 - 1450	97
	C-H (i.p. def., m)	1132.5	1150 - 1050	97
	C-H (o.o.p. def., m)	864.1	825 - 800	97
pyrimido[2,1-b][1,3] benzothiazole	C-N (str., v)	1350.2	1340 - 1250	97
	C-S-C(str.m)	663.5	700-650	97
	N-H (str., b)	3153.7-3055.3	3400 - 3000	98
	N-H (def., s,m)	1585.5	1650 - 1550	98
Ketone pyrimido ester	C=O (str., s)	1681.9	1690 - 1640	98
	C=O (str., s)	1705.1	1740 - 1650	98
Halogen Subtitution	C-Cl (str., b)	752-611	800-600	99
	C-F (str., b)	1159.2	1400 - 1080	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

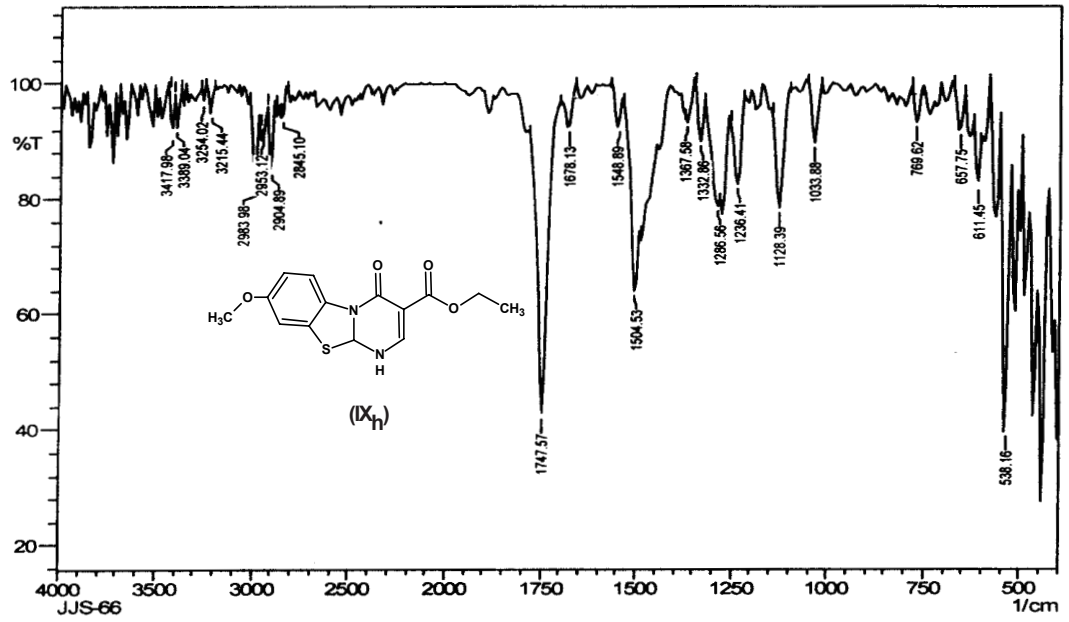
IR SPECTRAL STUDY OF ETHYL-8-NITRO-10a-DIHYDRO-4H-PYRIMIDO [2,1-b][1,3] BENZOTHIAZOLE-4-ONE-3-CARBOXYLATE (IX_f).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2901.0	2975 - 2850	96
	C-H (sym. str., m)	2856.6	2900 - 2800	96
	C-H (asym. def., m)	1450.5	1470 - 1435	96
	C-H (sym. def., m)	1371.4	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3030.2	3080 - 3010	97
	C=C & C-C (str., v)	1566.2	1600 - 1450	97
	C-H (i.p. def., m)	1138.0	1150 - 1050	97
	C-H (o.o.p. def., m)	837.1	825 - 800	97
pyrimido[2,1-b][1,3] benzothiazole	C-N (str., v)	1336.7	1340 - 1250	97
	C-S-C(str.m)	688.6	700-650	97
	N-H (str., b)	3097.7	3400 - 3000	98
	N-H (def., s,m)	1566.2	1650 - 1550	98
Ketone pyrimido ester	C=O (str., s)	1680.0	1690 - 1640	98
	C=O (str., s)	1743.7	1740 - 1650	98
Nitro Subtitution	C-NO_2 (asym str.,s)	1502.6	1570-1500	99
	C-NO_2 (sym str., s)	1336.7	1370-1300	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

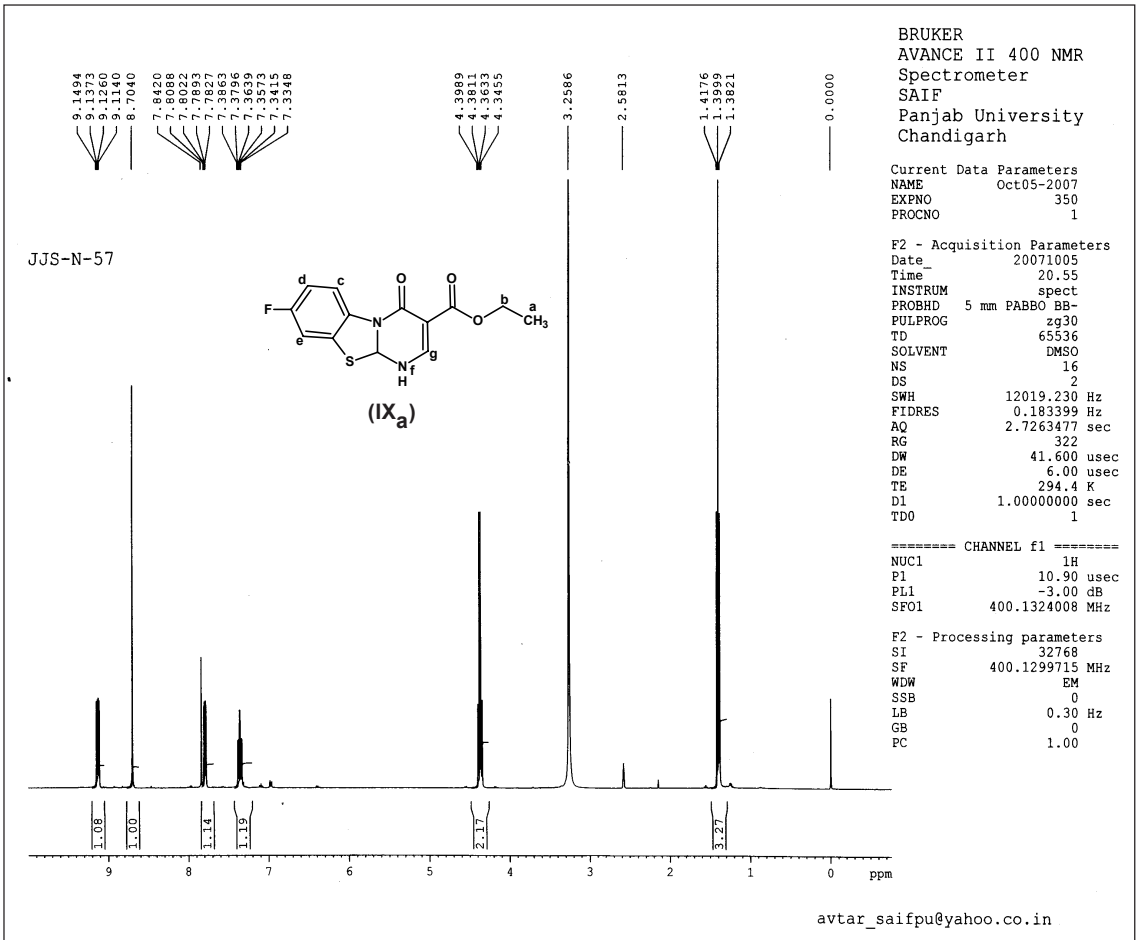
IR SPECTRAL STUDY OF ETHYL-8-METHOXY-10a-DIHYDRO-4H-PYRIMIDO [2,1-b][1,3]BENZOTHIAZOLE-4-ONE-3-CARBOXYLATE (IX_h).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2904.8	2975 - 2850	96
	C-H (sym. str., m)	2845.1	2900 - 2800	96
	C-H (asym. def., m)	-	1470 - 1435	96
	C-H (sym. def., m)	1367.5	1385 - 1300	96
Aromatic and ring skeletal vibration	C=C & C-C (str., v)	1548.8	1600 - 1450	97
	C-H (i.p. def., m)	1128.3	1150 - 1050	97
pyrimido[2,1-b][1,3] benzothiazole	C-N (str., v)	1286.5	1340 - 1250	97
	C-S-C(str.m)	657.7	700-650	97
	N-H (str., m)	3417.9-3215.4	3400 - 3000	98
	N-H (def., s,m)	1504.5	1650 - 1550	98
Ketone pyrimido ester	C=O (str., s)	1678.1	1690 - 1640	98
	C=O (str., s)	1747.5	1740 - 1650	98

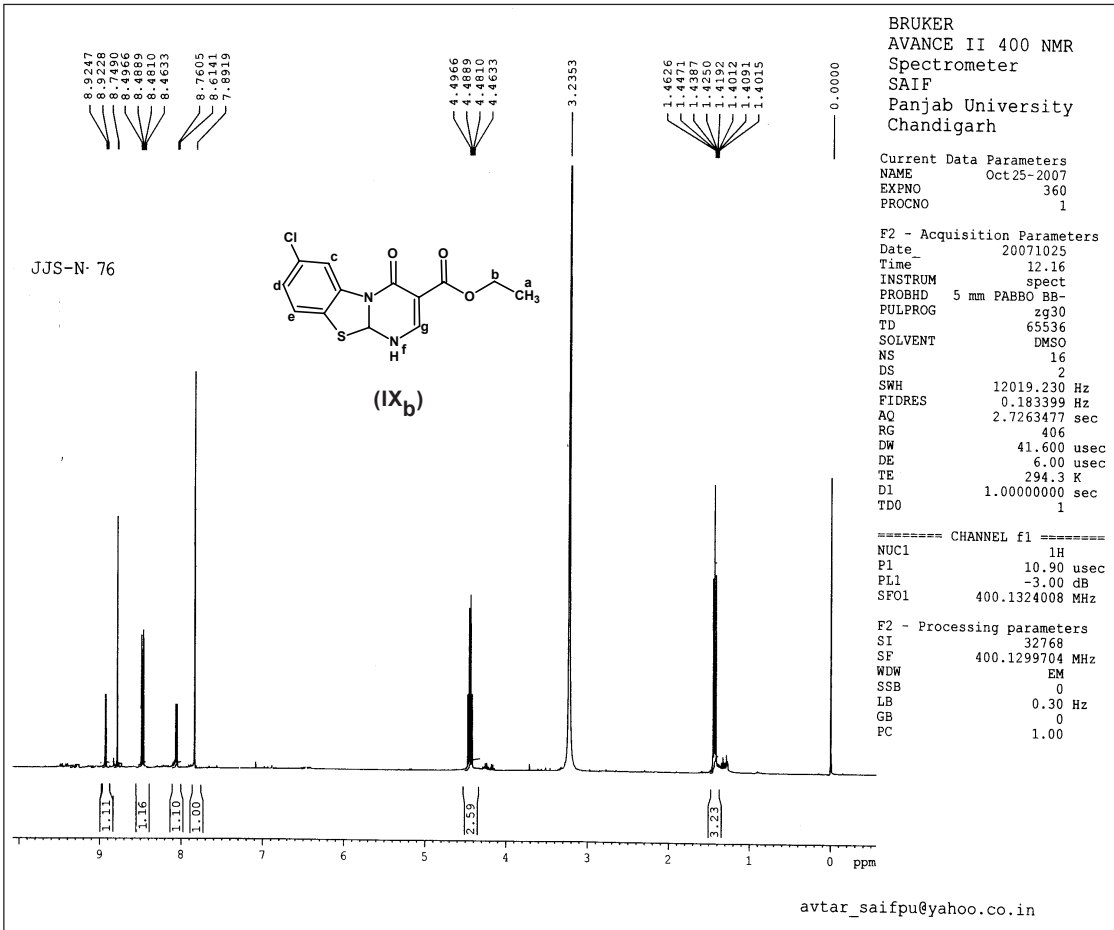
* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

NMR SPECTRAL STUDY OF ETHYL-8-FLUORO-10a-DIHYDRO-4H-PYRIMIDO [2,1-b][1,3] BENZOTHIAZOLE-4-ONE-3-CARBOXYLATE (IX_a).



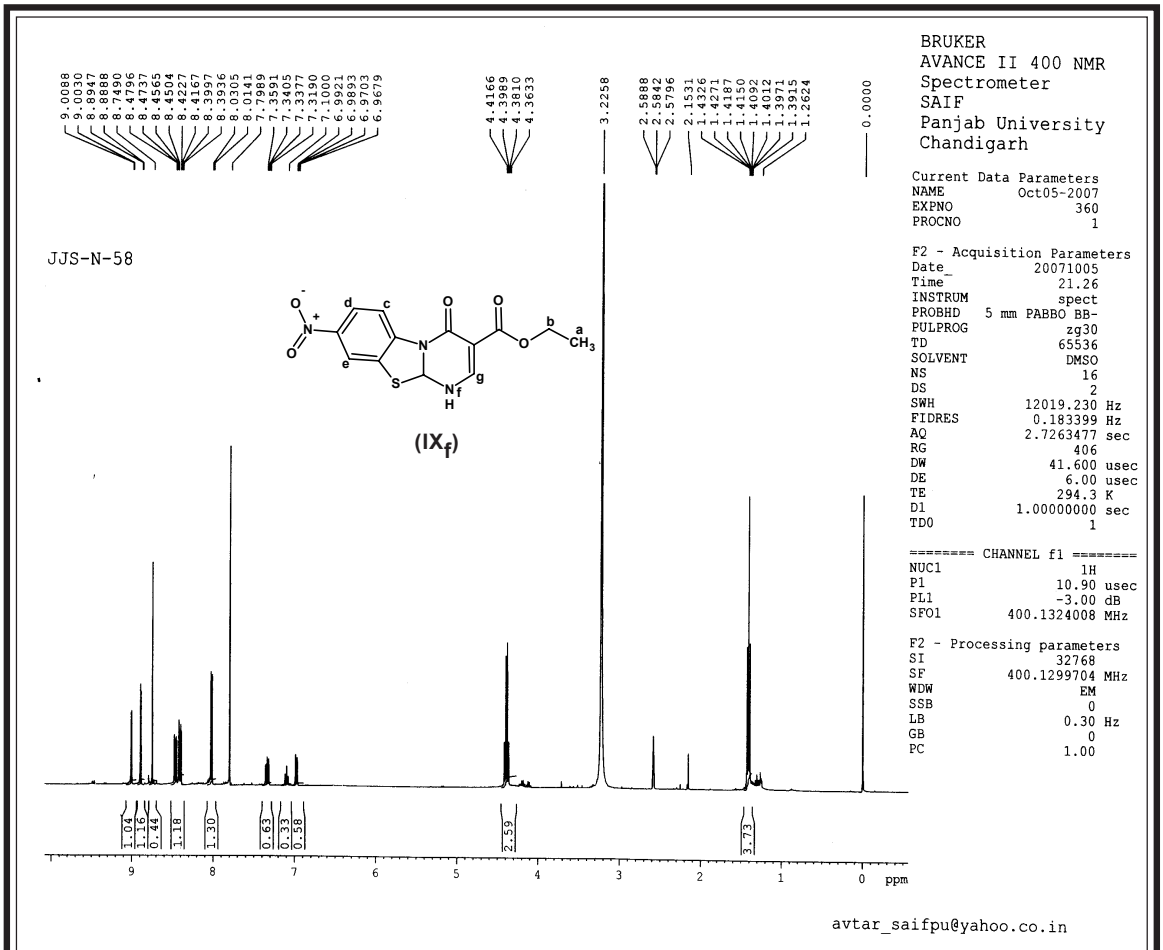
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.3821-1.4176	3H	triplet	- CH_3(a)
2	4.3455-4.3989	2H	quartet	- OCH_2(b)
3	7.3348-7.3863	1H	multiplet	- Ar-H(c)
4	7.7827-7.8420	1H	doublet	- Ar-H(e)
5	8.7040	1H	singlet	- NH-CH(g)
6	9.1140-9.1494	1H	doublet	- Ar-H(d)
7	3.2586	-	-	-DMSO-d_6

NMR SPECTRAL STUDY OF ETHYL-7-CHLORO-10a-DIHYDRO-4H-PYRIMIDO [2,1-b][1,3] BENZOTHIAZOLE-4-ONE-3-CARBOXYLATE (IX_b).



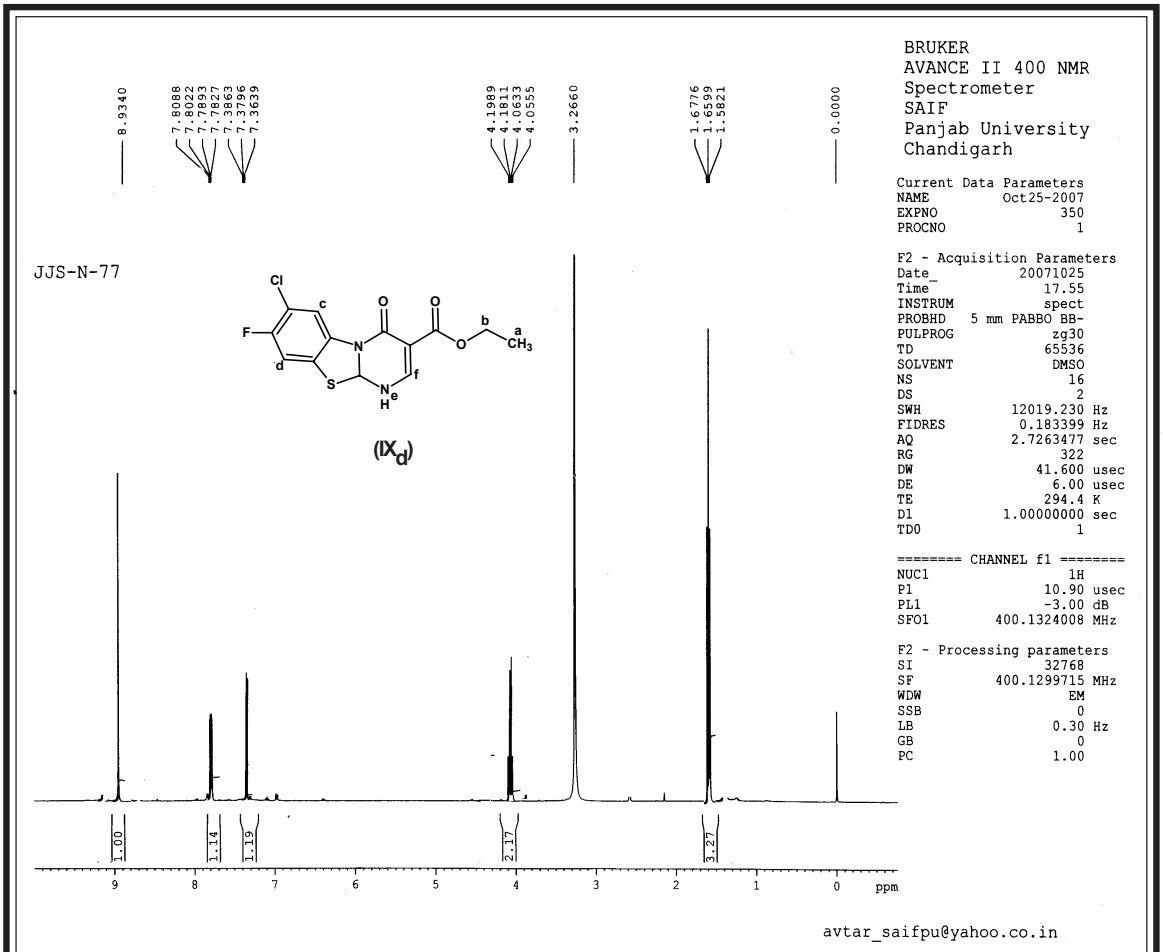
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.4015-1.4626	3H	triplet	- $C\underline{H}_3$(a)
2	4.4633-4.4966	2H	quartet	- $OC\underline{H}_2$(b)
3	7.8919	1H	singlet	- Ar-$\underline{H}$(c)
4	8.6141-8.7605	1H	doublet	- Ar-$\underline{H}$(e)
5	8.4633-8.4966	1H	doublet	- Ar-$\underline{H}$(d)
6	8.9228-8.9247	1H	singlet	- NH-$\underline{CH}$(g)
7	3.2353	-	-	-DMSO-d_6

NMR SPECTRAL STUDY OF ETHYL-8-NITRO-10a-DIHYDRO-4H-PYRIMIDO[2,1-b][1,3] BENZOTHIAZOLE-4-ONE-3-CARBOXYLATE (IX_f).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.3915-1.4326	3H	triplet	- $C\underline{H}_{3(a)}$
2	4.3633-4.4166	2H	quartet	- $OC\underline{H}_{2(b)}$
3	8.0141-8.0305	1H	doublet	- Ar-$\underline{H}_{(c)}$
4	8.3936-8.4737	1H	multiplet	- Ar-$\underline{H}_{(d)}$
5	8.8888-8.8947	1H	doublet	- Ar-$\underline{H}_{(e)}$
6	9.0030-9.0088	1H	doublet	- NH-$\underline{CH}_{(g)}$
7	3.2258	-	-	-DMSO-d_6

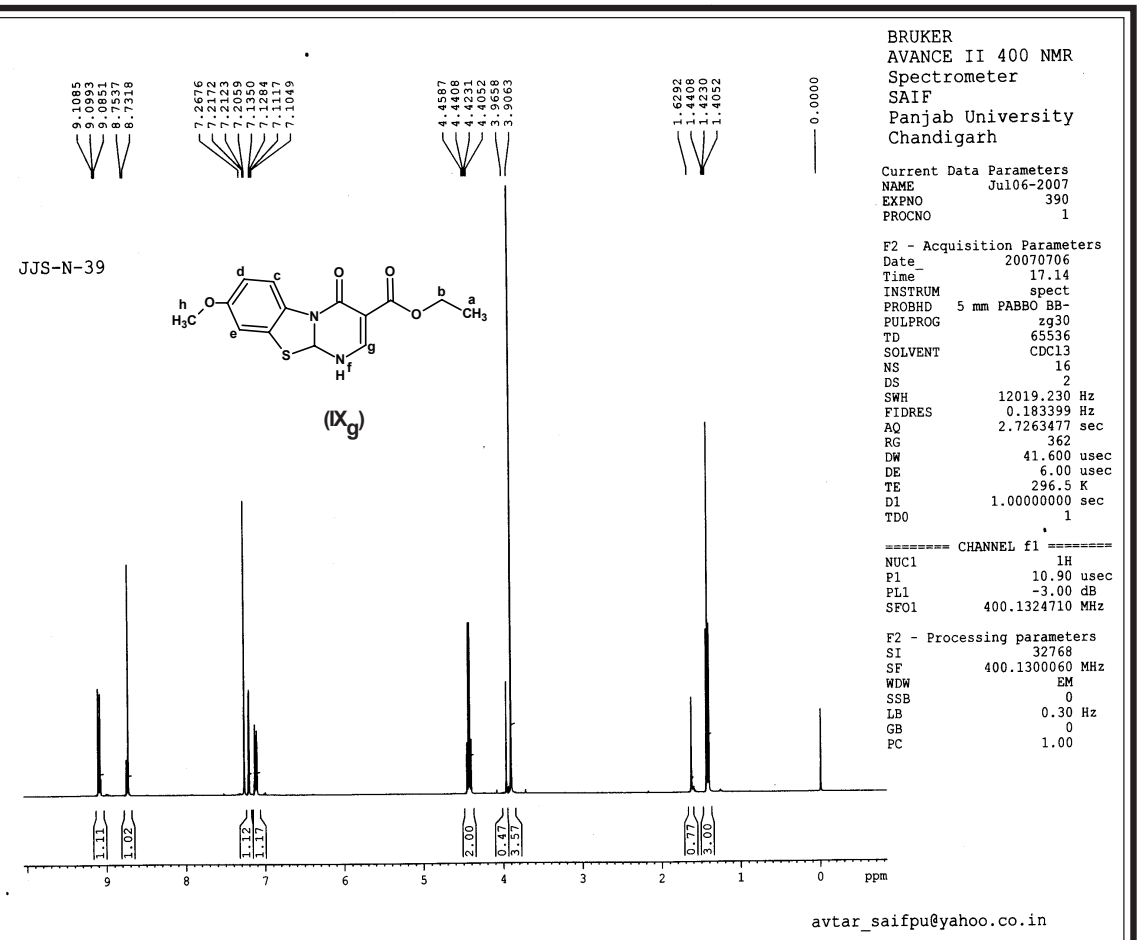
NMR SPECTRAL STUDY OF ETHYL-7-CHLORO-8-FLUORO-10a-DIHYDRO-4H-PYRIMIDO [2,1-b][1,3]BENZOTHIAZOLE-4-ONE-3-CARBOXYLATE (IX_d).



avtar_saifpu@yahoo.co.in

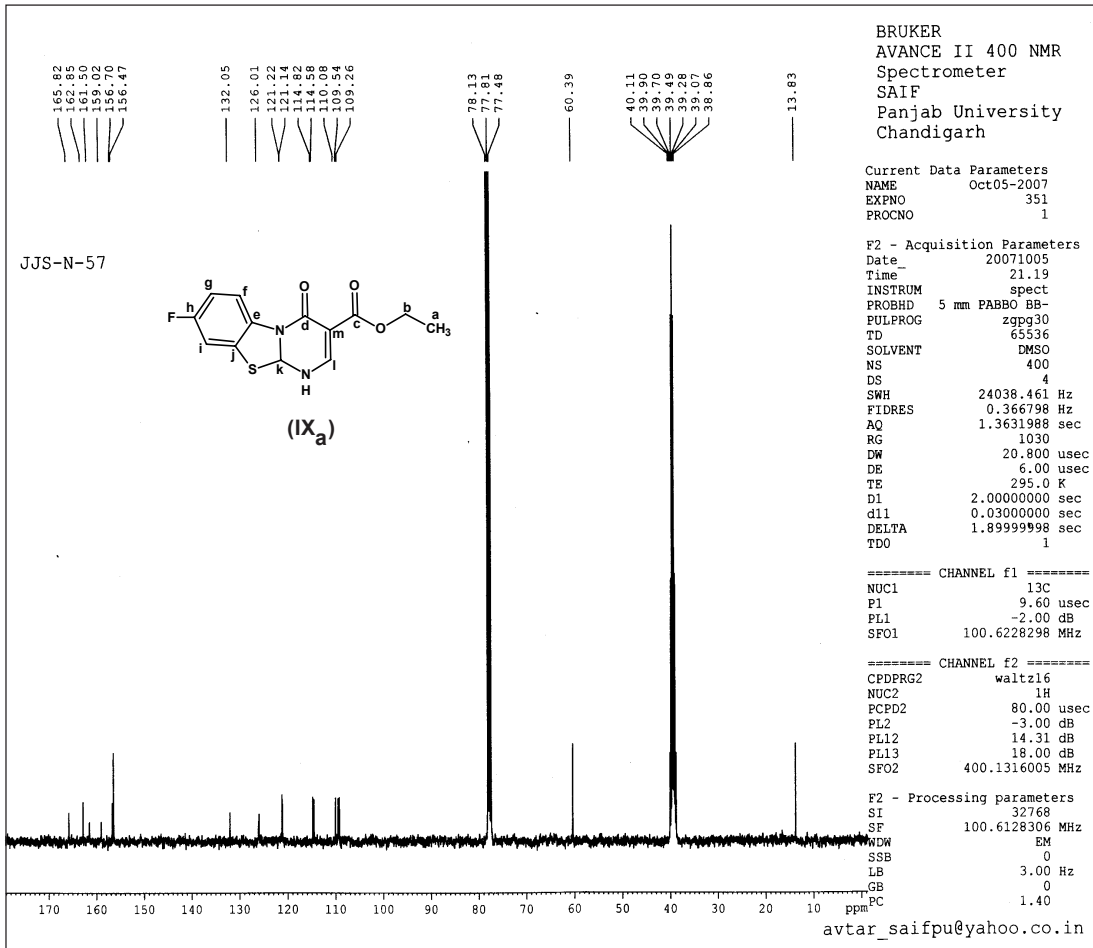
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.5821-1.6776	3H	triplet	- $C\underline{H}_{3(a)}$
2	4.0555-4.1989	2H	quartet	- $OC\underline{H}_{2(b)}$
3	7.3639-7.3863	1H	doublet	- Ar-$\underline{H}_{(d)}$
4	7.7827-7.8088	1H	triplet	- Ar-$\underline{H}_{(c)}$
5	8.9340	1H	singlet	- NH-$\underline{CH}_{(f)}$
6	3.2660	-	-	- DMSO-d_6

NMR SPECTRAL STUDY OF ETHYL-8-METHOXY-10a-DIHYDRO-4H-PYRIMIDO[2,1-b][1,3] BENZOTHIAZOLE-4-ONE-3-CARBOXYLATE (IXg).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.4052-1.4408	3H	triplet	- CH_3(a)
2	3.9063	3H	singlet	- OCH_3(h)
3	4.4052-4.4587	2H	quartet	- OCH_2(b)
4	7.1049-7.1350	1H	doublet	- Ar-H(c)
5	7.2059-7.2172	1H	doublet	- Ar-H(d)
6	8.7318-8.7537	1H	singlet	- NH-CH(g)
7	9.0851-9.1085	1H	triplet	- Ar-H(e)

^{13}C NMR SPECTRAL STUDY OF ETHYL-8-FLUORO-10a-DIHYDRO-4H-PYRIMIDO[2,1-b][1,3] BENZOTHIAZOLE-4-ONE-3-CARBOXYLATE (IX_a).



Serial No.	Signal Position (δ ppm)	Inference
1	13.83	- $\underline{C}H_{3(a)}$
2	60.39	- $\underline{C}H_{2(b)}$
3	1093.2-161.5	- Ar-$\underline{C}H_{(e\ to\ m)}$
4	162.8	-$\underline{C}$ =$O_{(d)}$
5	165.8	-$\underline{C}$ =$O_{(c)}$

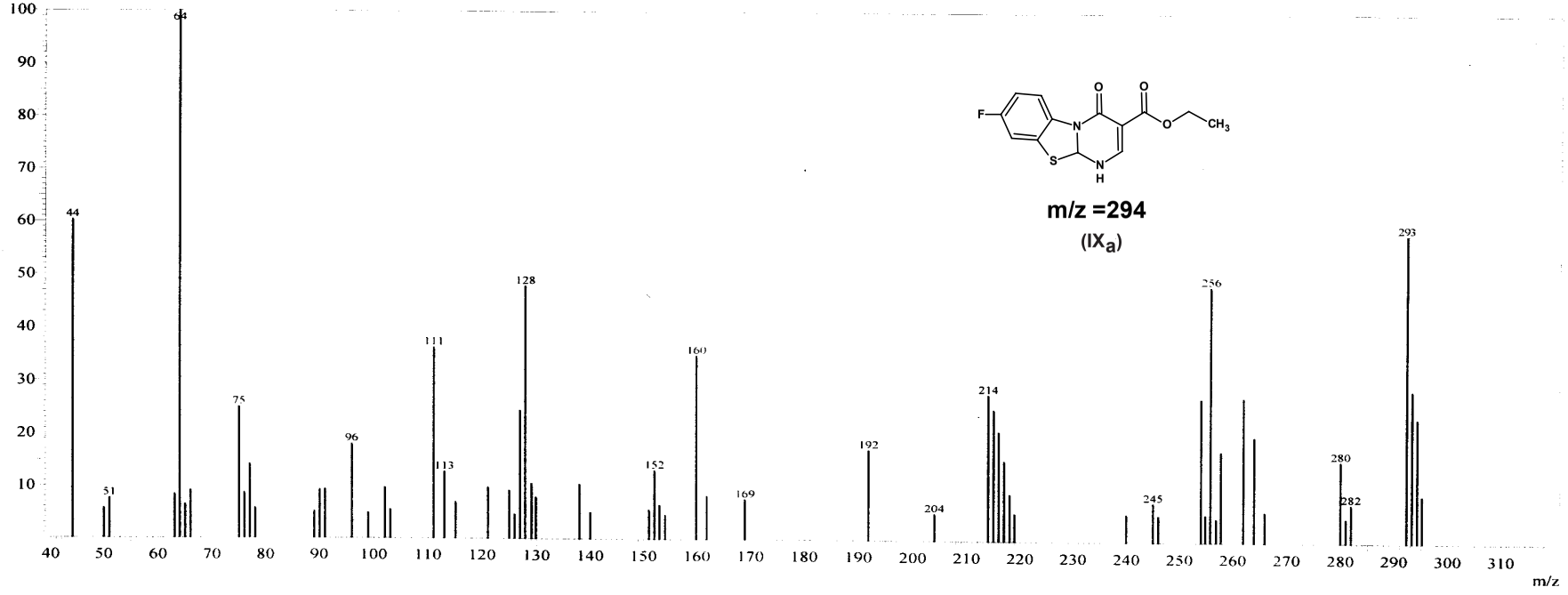
MASS SPECTRAL STUDY OF ETHYL-8-FLUORO-10a-DIHYDRO-4H-PYRIMIDO [2,1-b][1,3]BENZOTHIAZOLE-4-ONE-3-CARBOXYLATE (IX_a).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

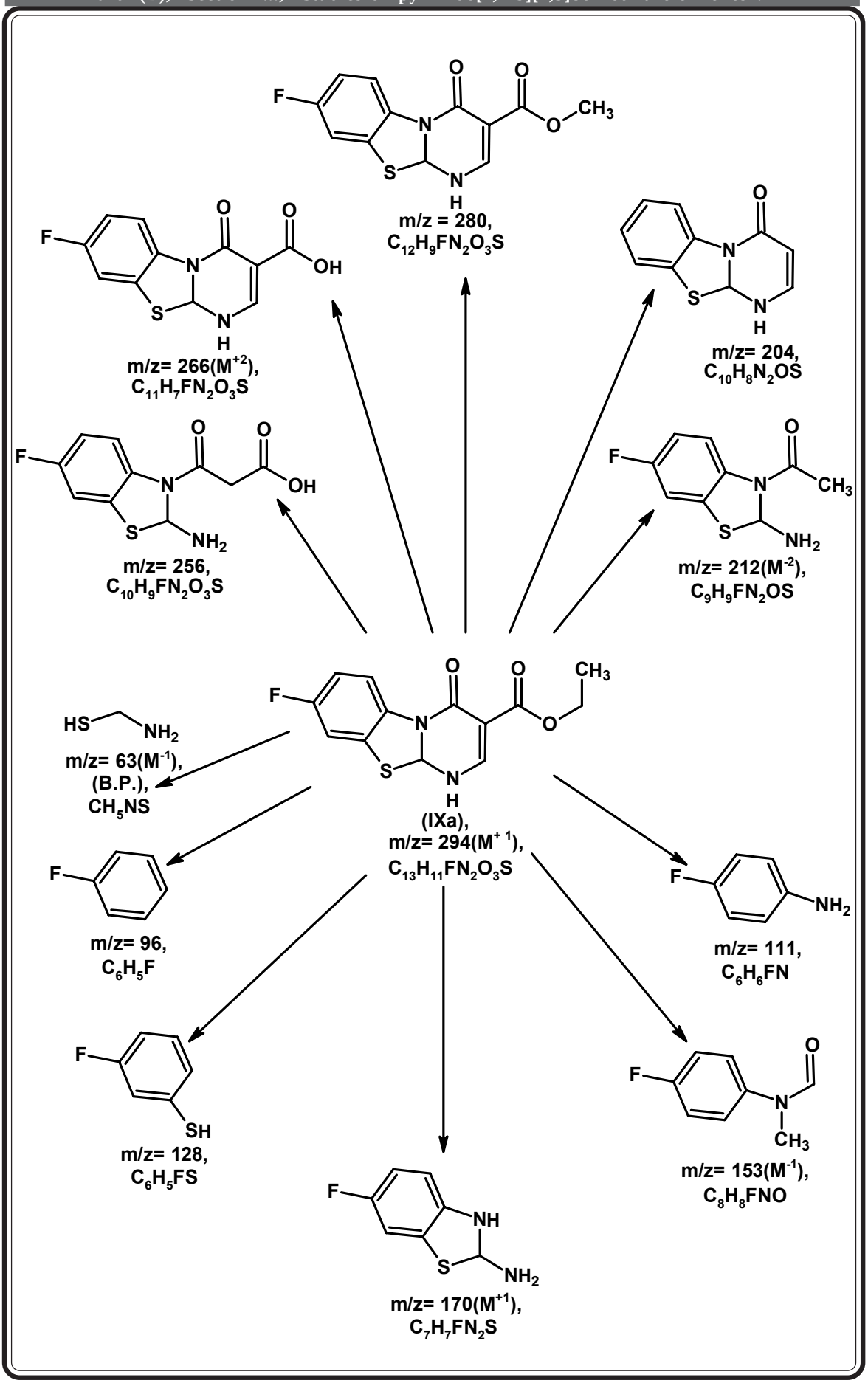
Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 9/5/2006 3:57:42 PM
Sample Name	: JJS-M-43
Sample ID	: JJS-M-43
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-43.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:4.1(Scan# 457)
MassPeaks:64 BasePeak:64(22769)
RawMode:Single 4.1(457)
BG Mode:None
intensity



m/z =294
(IX_a)


m/z = 280,
C12H9FN2O3S
m/z= 266(M+2),
C11H7FN2O3S
m/z= 204,
C10H8N2OS
m/z= 256,
C10H9FN2O3S
m/z= 212(M-2),
C9H9FN2OS
HS NH2
m/z= 63(M-1),
(B.P.),
CH5NS
(IXa),
m/z= 294(M+1),
C13H11FN2O3S
m/z= 96,
C6H5F
m/z= 111,
C6H6FN
m/z= 128,
C6H5FS
m/z= 153(M-1),
C8H8FNO
m/z= 170(M+1),
C7H7FN2S

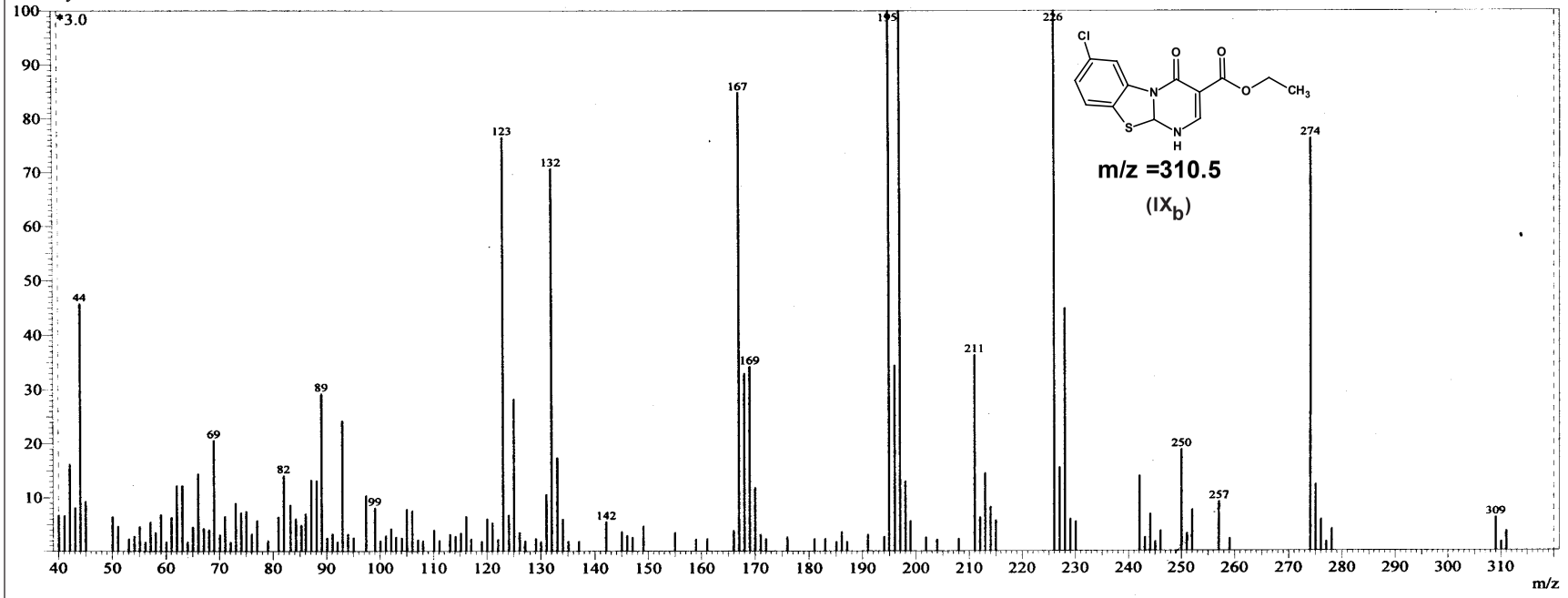
MASS SPECTRAL STUDY OF ETHYL-7-CHLORO-10a-DIHYDRO-4H-PYRIMIDO [2,1-b][1,3] BENZOTHIAZOLE-4-ONE-3-CARBOXYLATE (IX_b).

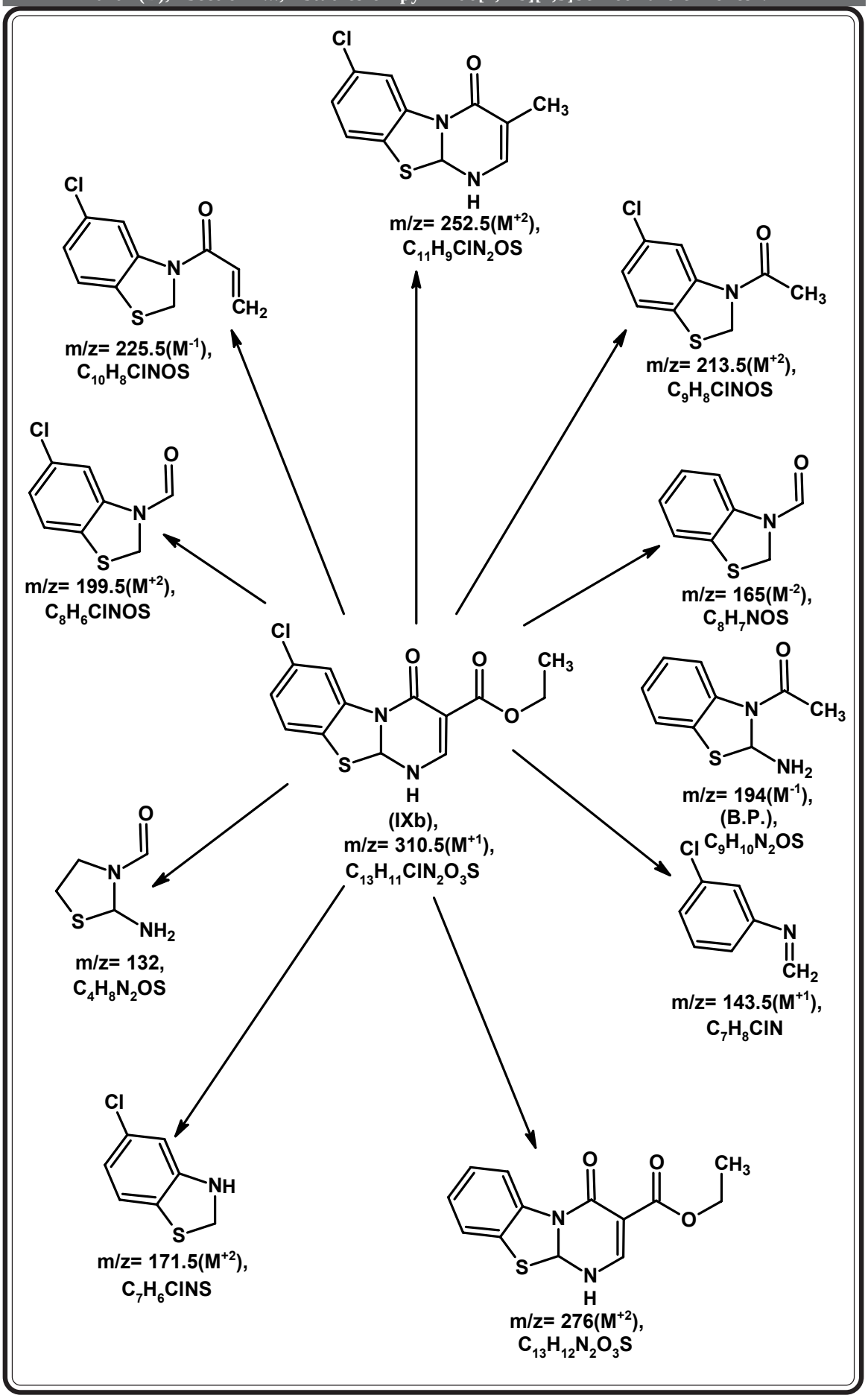
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 2/2/2006 11:58:32 AM
Sample Name	: JJS-M-17
Sample ID	: JJS-M-17
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-17.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune9.qgt

Line#:1 R.Time:1.8(Scan#:176)
MassPeaks:143 BasePeak:195(184298)
RawMode:Single 1.8(176)
BG Mode:None
intensity




m/z= 252.5(M+2),
C11H9ClN2OS
m/z= 225.5(M-1),
C10H8ClNOS
m/z= 213.5(M+2),
C9H8ClNOS
m/z= 199.5(M+2),
C8H6ClNOS
m/z= 165(M-2),
C8H7NOS
(IXb),
m/z= 310.5(M+1),
C13H11ClN2O3S
m/z= 194(M-1),
(B.P.),
C9H10N2OS
m/z= 132,
C4H8N2OS
m/z= 143.5(M+1),
C7H8ClN
m/z= 171.5(M+2),
C7H6ClNS
m/z= 276(M+2),
C13H12N2O3S

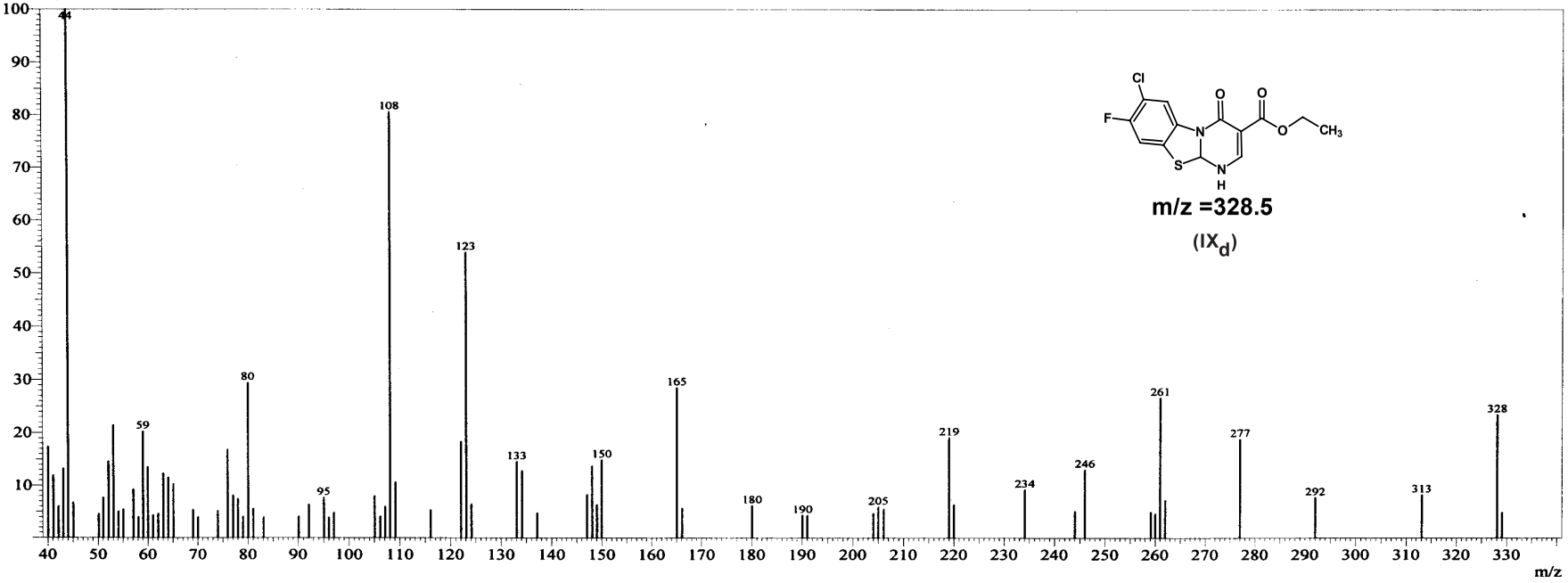
MASS SPECTRAL STUDY OF ETHYL-7-CHLORO-8-FLUORO-10a-DIHYDRO-4H-PYRIMIDO [2,1-b][1,3] BENZO-THIAZOLE-4-ONE-3-CARBOXYLATE (IX_d).

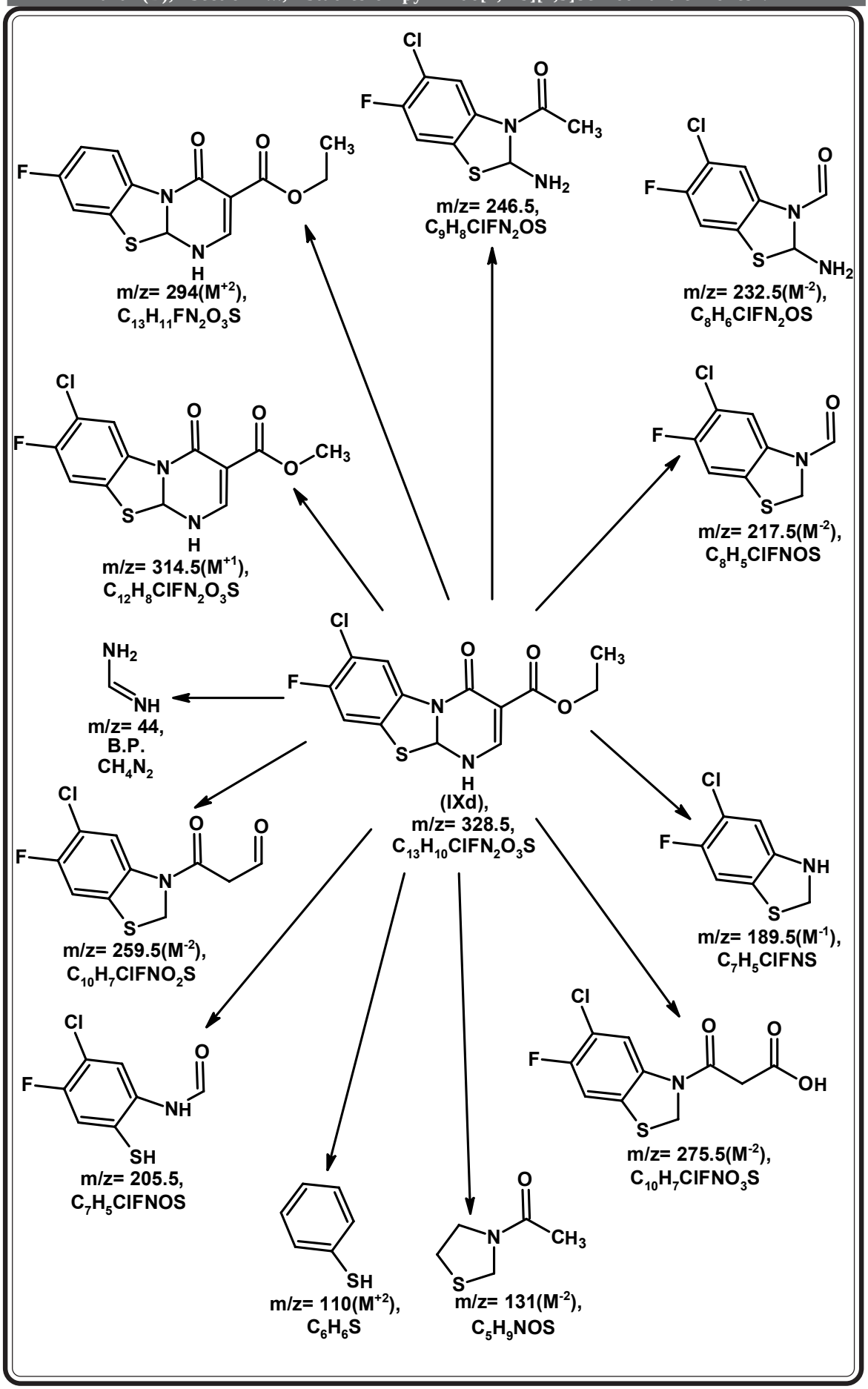
SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 7/10/2006 3:59:32 PM
Sample Name	: JJS-M-37
Sample ID	: JJS-M-37
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-37.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:11.5(Scan#:1343)
MassPeaks:74 BasePeak:44(26293)
RawMode:Single 11.5(1343)
BG Mode:None
intensity

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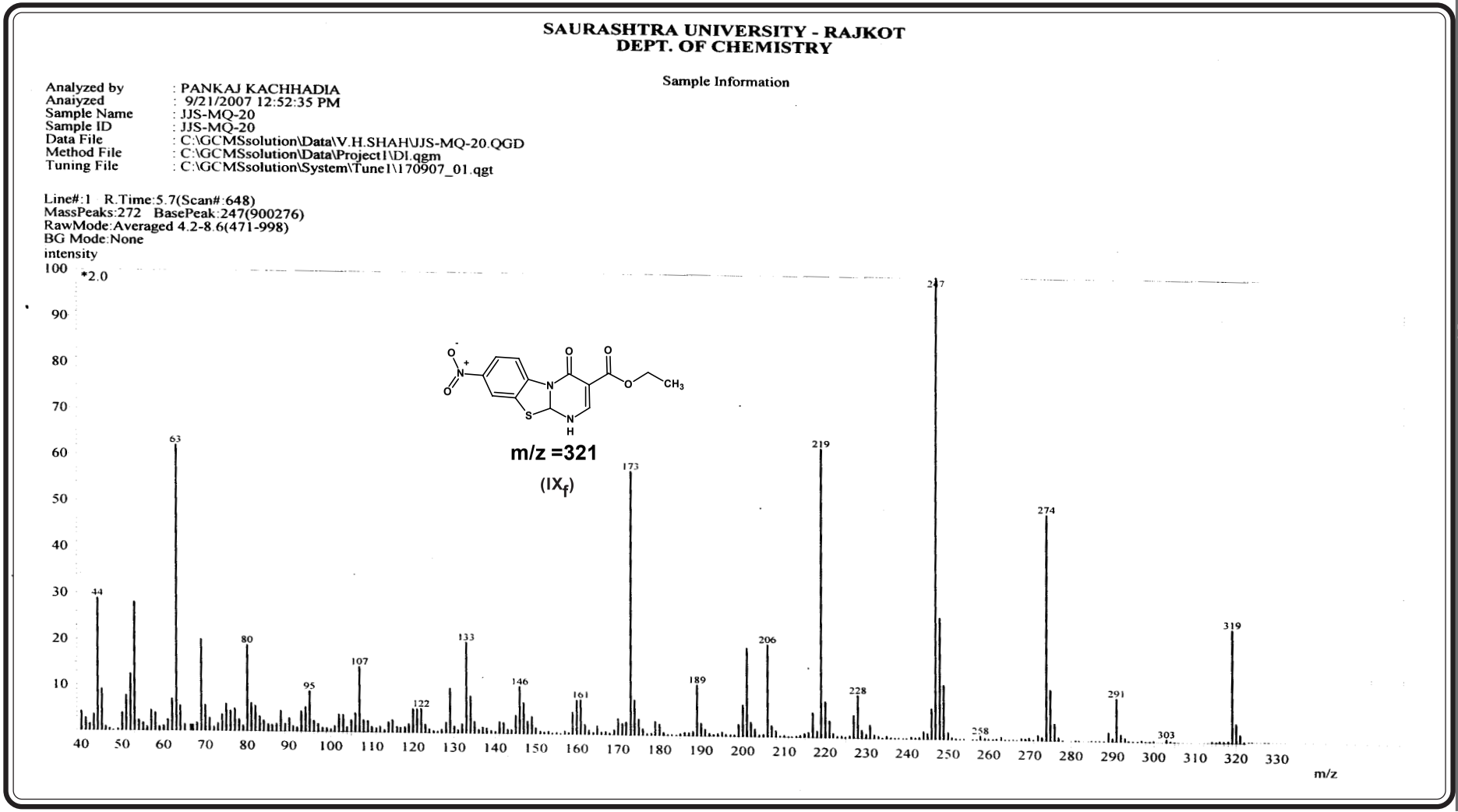
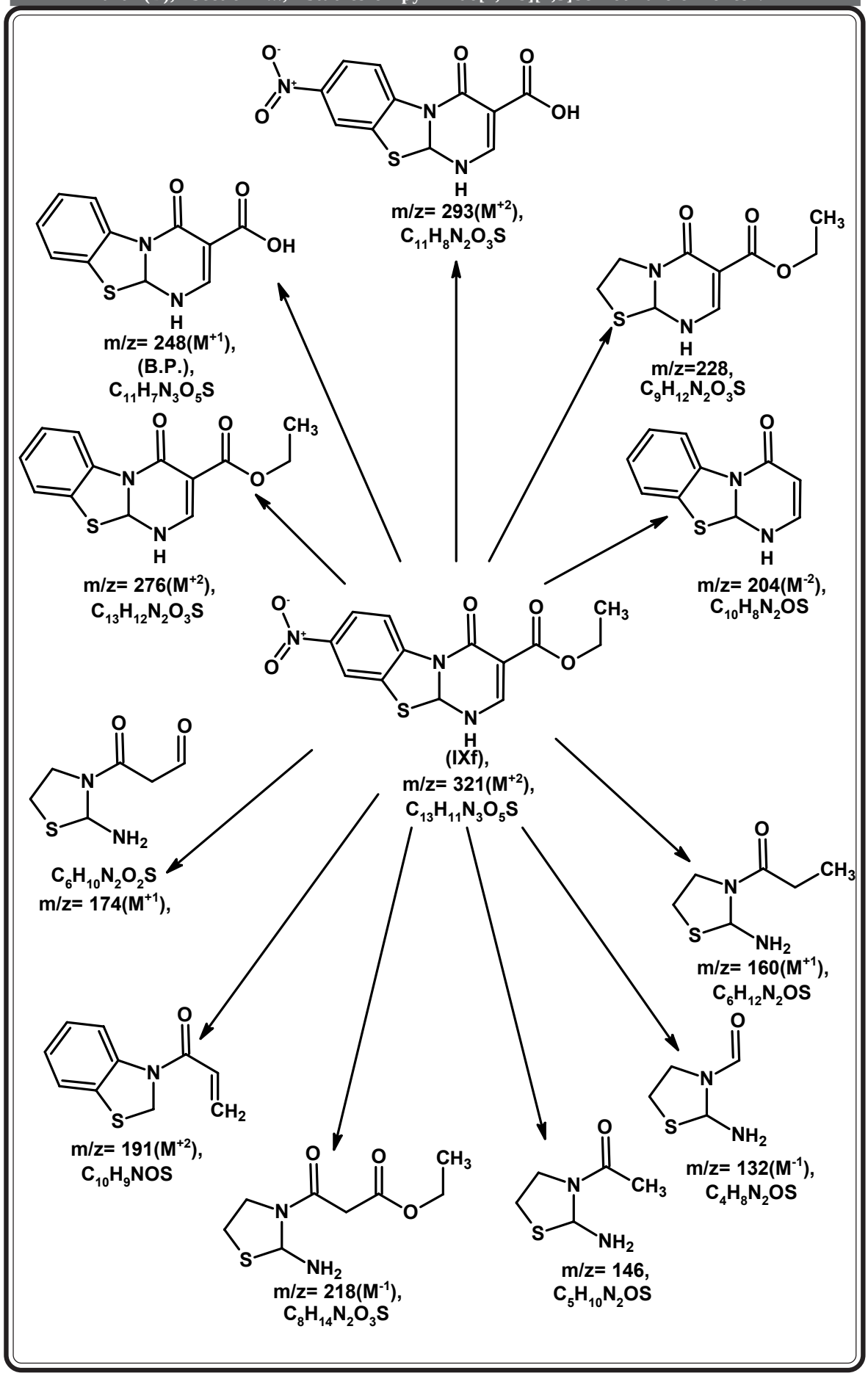
C13H11FN2O3S
m/z= 246.5,
C9H8ClFN2OS
m/z= 232.5(M-2),
C8H6ClFN2OS
m/z= 314.5(M+1),
C12H8ClFN2O3S
m/z= 217.5(M-2),
C8H5ClFNOS
m/z= 44,
B.P.
CH4N2
(IXd),
m/z= 328.5,
C13H10ClFN2O3S
m/z= 259.5(M-2),
C10H7ClFNO2S
m/z= 189.5(M-1),
C7H5ClFNS
m/z= 205.5,
C7H5ClFNOS
m/z= 275.5(M-2),
C10H7ClFNO3S
m/z= 110(M+2),
C6H6S
m/z= 131(M-2),
C5H9NOS

MASS SPECTRAL STUDY OF ETHYL-8-NITRO-10a-DIHYDRO-4H-PYRIMIDO [2,1-b][1,3]BENZOTHIAZOLE-4-ONE-3-CARBOXYLATE (IX_f).

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m/z= 248(M+1),
(B.P.),
C11H7N3O5S
m/z=228,
C9H12N2O3S
m/z= 276(M+2),
C13H12N2O3S
m/z= 204(M-2),
C10H8N2OS
(IXf),
m/z= 321(M+2),
C13H11N3O5S
C6H10N2O2S
m/z= 174(M+1),
m/z= 160(M+1),
C6H12N2OS
m/z= 191(M+2),
C10H9NOS
m/z= 132(M-1),
C4H8N2OS
m/z= 218(M-1),
C8H14N2O3S
m/z= 146,
C5H10N2OS

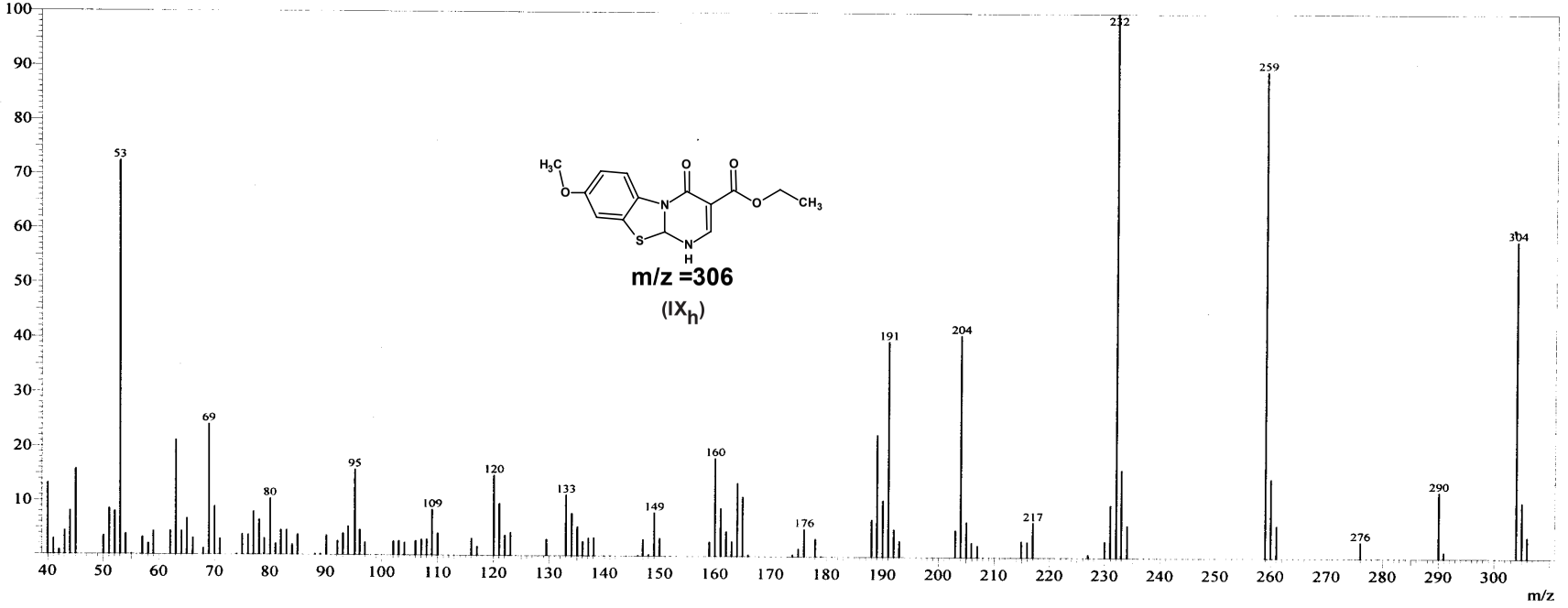
MASS SPECTRAL STUDY OF ETHYL-8-METHOXY-10a-DIHYDRO-4H-PYRIMIDO [2,1-b][1,3]BENZOTHIAZOLE-4-ONE-3-CARBOXYLATE (IX_h).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

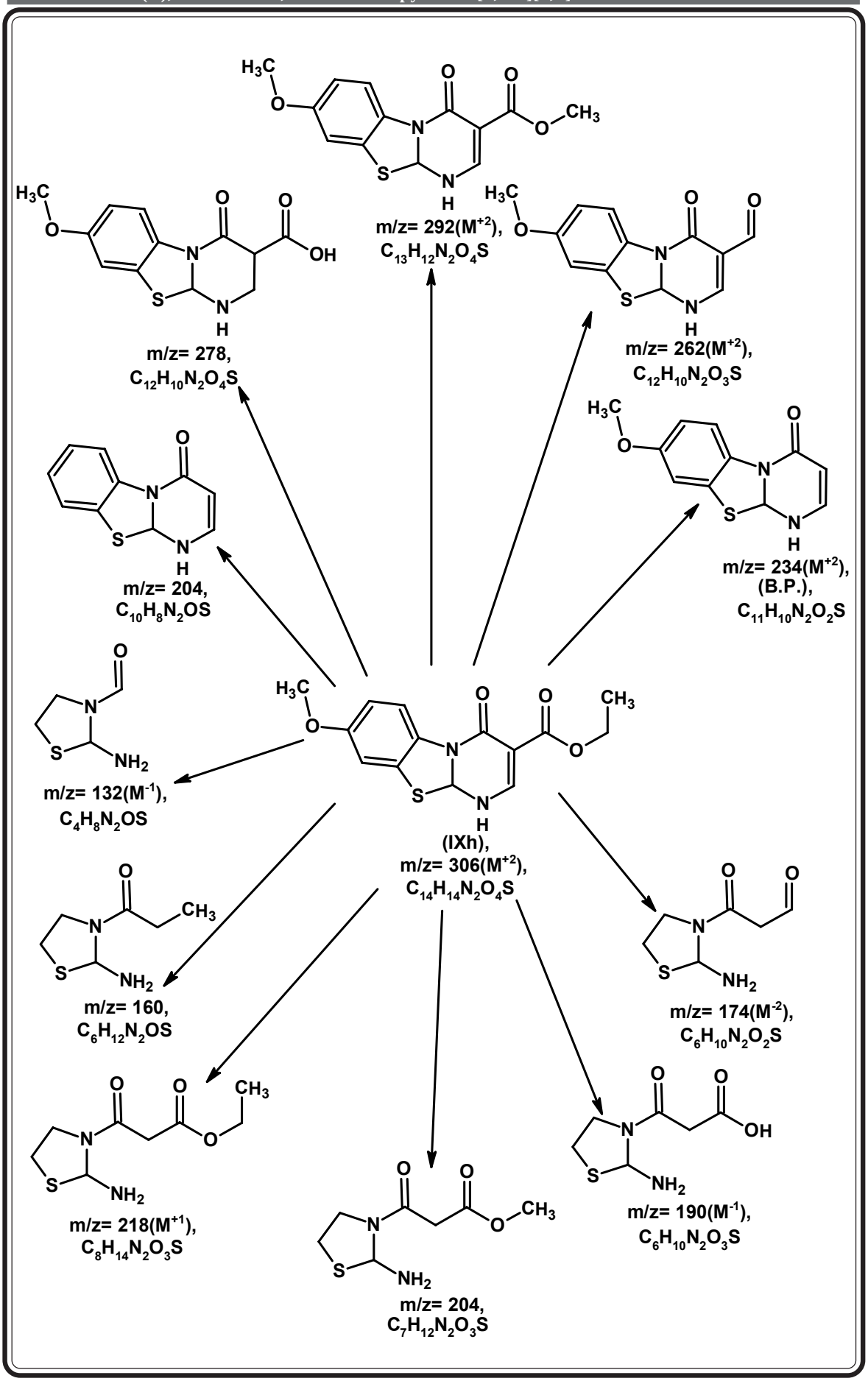
Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 4/18/2007 11:43:42 AM
Sample Name : JJS-MQ-8
Sample ID : JJS-MQ-8
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-8.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune121206.qgt

Line#:1 R.Time:1.4(Scan#:129)
MassPeaks:114 BasePeak:232(51956)
RawMode:Averaged 1.3-1.8(125-185)
BG Mode:None
intensity



m/z =306

(IX_h)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m/z= 278,
C12H10N2O4S
m/z= 262(M+2),
C12H10N2O3S
m/z= 204,
C10H8N2OS
m/z= 234(M+2),
(B.P.),
C11H10N2O2S
m/z= 132(M-1),
C4H8N2OS
(IXh),
m/z= 306(M+2),
C14H14N2O4S
m/z= 160,
C6H12N2OS
m/z= 174(M-2),
C6H10N2O2S
m/z= 218(M+1),
C8H14N2O3S
m/z= 204,
C7H12N2O3S
m/z= 190(M-1),
C6H10N2O3S

TABLE NO. 9B : COMPARATIVE ANTIMICROBIAL ACTIVITY OF ETHYL-SUBSTITUTED-10a-DIHYDRO-4H-PRIMIDO-[2,1-b] [1,3] BENZOTHIAZOLE-4-ONE-3-CARBOXYLATES (IX_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) S. pyogens MTCC- 442					S. aureus MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
IX_a	7-F	-	9	10	11	14	-	8	11	13	16
IX_b	6-Cl	-	9	10	12	16	-	10	12	14	17
IX_c	7-Cl	-	12	14	16	20	-	8	10	12	14
IX_d	6-Cl-7-F	-	11	13	15	18	-	11	13	16	18
IX_e	6,7-$(Cl)_2$	-	10	12	14	17	-	8	12	15	15
IX_f	7-NO_2	-	10	11	14	16	-	8	9	11	14
IX_g	6-OCH_3	-	9	12	13	15	-	8	10	12	15
IX_h	7-OCH_3	-	10	10	12	14	-	9	10	13	14
IX_i	7-CH_3	-	8	11	12	14	-	9	11	14	16
IX_j	5,6-$(CH_3)_2$	-	8	9	11	13	-	8	9	11	14

Comparative activity of(IX_{a-j}) with known choosen standard drugs

Standard drug	Antibacterial activity									
				v_c	v_c v_d				v_d v_e	$v_{a,b}$ $v_{d,i}$
Amoxicilin	12	14	15	16	18	10	12	14	15	16
Chloramphenicol	14	15	18	19	24	14	17	20	21	24
Sparfloxacin	14	22	24	26	28	24	26	27	28	32
Levofloxacin	18	21	22	27	29	20	24	26	27	35

N.B.(-): No Activity

TABLE NO. 9C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF ETHYL-SUBSTITUTED-10a-DIHYDRO-4H-PRIMIDO-[2,1-b] [1,3] BENZOTHIAZOLE-4-ONE-3-CARBOXYLATES (IX_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.)									
		B. Subtillis MTCC- 441					E.coli MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
IX_a	7-F	-	11	12	14	17	-	8	10	11	14
IX_b	6-Cl	-	11	12	14	18	-	9	11	12	15
IX_c	7-Cl	-	9	10	12	15	-	7	10	15	19
IX_d	6-Cl-7-F	-	11	13	14	16	-	6	8	13	17
IX_e	6,7-$(Cl)_2$	-	10	11	12	14	-	8	11	11	14
IX_f	7-NO_2	-	10	12	13	14	-	9	10	10	11
IX_g	6-OCH_3	-	10	11	12	13	-	7	9	10	11
IX_h	7-OCH_3	-	9	10	11	12	-	6	8	9	10
IX_i	7-CH_3	-	8	9	10	11	-	5	7	8	12
IX_j	5,6-$(CH_3)_2$	-	7	8	9	10	-	5	7	9	10
Comparative activity of (IX_{a-j}) with known choosen standard drugs											
Standard drug		**Antibacterial activity**									
Amoxicilin		12	15	16	18	19	11	14	16	18	20
Chloramphenicol		18	22	24	26	27	17	20	23	25	26
Sparfloxacin		22	24	25	26	29	20	22	25	26	28
Levofloxacin		24	26	28	29	31	23	25	26	29	30

N.B.(-): No Activity

TABLE NO. 9D : COMPARATIVE ANTIMICROBIAL ACTIVITY OF ETHYL-SUBSTITUTED-10a-DIHYDRO-4H-PRIMIDO-[2,1-b] [1,3] BENZOTHIAZOLE-4-ONE-3-CARBOXYLATES (IX_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antifungal activity (Zones of inhibition in m.m.)									
		C. albicans MTCC- 227					A. niger MTCC- 282				
		5	25	50	100	250	5	25	50	100	250
IX_a	7-F	-	7	8	10	12	-	9	10	12	14
IX_b	6-Cl	-	9	11	13	15	-	10	12	15	17
IX_c	7-Cl	-	9	13	14	18	-	11	14	16	18
IX_d	6-Cl-7-F	-	9	10	11	14	-	9	10	11	13
IX_e	6,7-$(Cl)_2$	-	8	10	12	14	-	8	10	12	13
IX_f	7-NO_2	-	6	9	10	12	-	9	11	13	15
IX_g	6-OCH_3	-	5	8	11	13	-	7	8	9	11
IX_h	7-OCH_3	-	5	7	10	12	-	6	7	9	10
IX_i	7-CH_3	-	5	7	8	10	-	8	9	10	12
IX_j	5,6-$(CH_3)_2$	-	6	8	9	11	-	7	8	10	11
Comparative activity of (IX_{a-j}) with known choosen standard drugs											
Standard drug		Antifungal activity									
Griseofulvin		16	18	21	23	25	17	19	21	22	23
Fluconazole		14	16	18	21	22	15	17	18	20	21

N.B.(-): No Activity

References

100. Hoffmann, Ber.,**12**,1126, 2359, (1879); **13**, 8 (1880).
101. Hantzsch.et.al., Ber., **20**, 3118, 3336, (1887).
102. Mc Gavack, T.H.J. Chevalley, S. Keni-gsberg, and S. Pearsib; *Bull N. Y. Med. Coll.,* **16,** 58 (1953).
103. Bogert.et.al., J. Am. Chem. Soc.,**46**, 1308 (1924)
104. De Smet, Bull. Soc. Chim. Belges, **58**, 472 (1949); Chem. abstr., **45**, 607 (1951).
105. Kiprianov, J. Gen. Chem. (U.S.S.R), **19**, 1515 (1949);Chem. abstr., **44**, 1097 (1950).
106. Hauser, Helv. Chem. Acta.,**11**, 198 (1928).
107. Lankelma et al., J. Am. Chem.Soc., **53**, 309, 2654 (1931); **58**, 609 (1936).
108. Zubarovskii, J. Gen. Chem. (U.S.S.R), **17**, 613 (1947);Chem. abstr., **42**, 906 (1948).
109. Kiprianov, Suitnik, J. Gen. Chem. (U.S.S.R), **6**, 232 (1936); Chem. abstr., **30**, 4859 (1936).
110. Petitcolas et. al., Bull. Soc. Chim. France, 103, (1949).
111. Wallach, Ann., **259**, 300 (1890).
112. Bogert and Abrahamson, J. Am. Chem.Soc., **44**, 826 (1922).
113. Bottcher and Bauer, Ann., **568**, 218 (1950).
114. Hunter, J. Chem. Soc.,125 (1930),.
115. Bogert and Naiman, *J. Am. Chem. Soc*., **57**, 1529 (1935).
116. Khunyants and Benevolenskaya, J.Gen. Chem. (U.S.S.R), **7**, 2471 (1937); Chem. abstr., **32**, 2119 (1938).
117. Mercury, Vincent and sherrill, J. Am. Chem.Soc., **68**, 1594 (1946).
118. Kaufmann et al., Sarch. Pharm., **266**,197(1928); 267, 192 (1929); 273, 31 (1935).
119. White and Brewster, Trans.Kansas Acad.Sci., **42**, 241 (1939);Chem.abstr., **34**, 5447 (1940).
120. N.Sonoda, G. Yamamoto, K. Natsukawa, K. Kondo and S. Murai; *Tetrahedron Lett.*, (1975).
121. Hugerschoff, H. *Chem. Ber.*, ***34,*** 3130, **1901**. (b) Hugerschoff, H. *Chem. Ber.*, ***6,*** 3121.(1903)**.**
122. Robert J. Alaimo ; *J. Heterocyclic Chem.* 7, (1973).
123. Acheson, *"An Introduction to the chemistry of Heterocyclic compounds", Inter Science* (1969).
124. A. I. Vogel, *"Vogel's Text book of Practical Organic Chemistry",* 5th Ed., (1994).
125. Badger *"Chemistry of Heterocyclic Compounds", Academic Press* (1961).
126. Biginelli, *Gazz Chem. Ital.,* **23,** 360 (1983); *Atti. Accad. Lincei,* **(5)3,** 195 (1894).
127. Y. M. Elkholy, A.H. Elassar and M.H. Elnagdi; *Hetero. Commun.,* **3** (2)**,**151 (1997).
128. P. Sharma, K.F. Hussain, S. Sukhwal, S. Kothari; *Ind. J. Chem.,* **35(B),** 966-968 (1999).
129. B. Kumar, B. Kaur, J. Kaur, A. Parmar, R.D. Anand, H. Kumar; *Ind. J.Chem.,* **41(B),**

1526-1530 (2002).

130. Yan-Feng Li, Li-Jan Li, Ji- Tai Li; *Chemistry; An Indian Journal*, **1(9),** 628 (2004).

131. Sanjay Kumar, Anil saini & Jagir S. Sandha, *Ind. J. Chem.*, **43B**, 1485 (2004).

132. Anup Mishra, G. Agnihotri, Mudhusudar S. K., *Ind. J. Chem.*, **43B**, 2018 (2004).

133. M.P.Sugrue,P.Garthpran,C.shmit,N.P.Viader;J.Pharmacol.Exp.ther.,**232**,534(1935).

134. S.N.Sawhney, R.K.Tomer.Om Prakash, Indra prakash and S.P. Singh, IndianJ. Chem.Sect-B,**19B**(5),415-417 (1980);Chem.Abstr.,**94**,30612j (1981).

135. stuckwisch, J.Am. Chem.Soc., **71**, 3417, (1949).

136. wiselosel. Ed. Survey of Antimalarial Drugs, vol. Ii, part-I, 938-939 (1941-1945).

137. Thomas H. Porter, Karl Folkers, Philip Stotter; J. Med.Chem.**16(11)**, 1314-16(1973) .Chem.abstr.,**79**,142801s(1973).

138. Browing, Conel, et.al., Proc.Roy .Soc., 3336,(1950).

139. Saburo Veno, Takao Kawasaki, Shimogo; Ger Offen, **2**,026,452(Cl. C07D) 63,Dec.-1970; Chem.abstr., **74**, 42349d (1971).

140. J. C. Sharp, J.P.Palmer, E. D.Evans; J. Med.Chem.**15(5)**, 523-9 (1972)
. Chem.abstr., **77**, 43068k (1972).

141. F.Risso, M. Santagati; Farmaco, Ed,sci., **31(1)**, 41-8, (1976) ,Chem.abstr., **84**, 90090r (1976).

142. Ian Hutchinson, Mei-sze chug; J. Med.Chem.**44(9)**,1446-1455 (2001) Chem.abstr. ,**135**, 573 (2001).

143. Klaus Wgher, Hans Schpinpflag, Earnst Paul; Ger Offen, **2**, 136,923. ;Chem.abstr ., **78**, 97633e (1973).

144. O.W. Wolters, H.Schwan, J.B.Bicking; J. Med.Chem. **32**, 2486 (1989).

145. Eberlein,Wolgang, Guenther Trummlitz, Wolfhand Engel; Chem.abstr., **46**, 68983k (1982).

146. Alison Mary, Smith; Brit. UK Pat. Appl. GB (Cl. C07D3 07/64); Chem .abstr., **125**, 86634u (1996).

147. Francois Audiau, Claude Gueremy, patrick jimonet, Serge Mignani, Eur. Pat. Appl. EP,375,510,Chem.Abstr., **114**, 6491e (1991).

148. Jean Claude Hardy, Jean Bouquerel, Patrick Nemecek; PCT Int. Appl.WO 99,05,147 (Cl.C07D513/06); Chem.abstr., **130**,139337m (1999).

149. B. dash, M.Patra and S.Praharaj , Indian J. Chem. sect- B, **19B**, 894-897(1980); Chem. Abstr., **94**,156804s (1981) .

150. Johann Hofmann, Gottried Heinisch, Johnny Easmon; PCT Int. Appl.WO 01,94,340 (Cl.C07D403); Chem.abstr.,**136**, 20073f (2002).

151. Toshiyasu Mase, Hideki Arima, Kenichi tomioka; J. Med.Chem. **29(3)**, 386-94 (1986) Chem. abstr.,**104**, 109547a (1986).

152. Horst Liebig, Guenter Dransch, Al-fred. Grafe; Ger Offen, **2**,135,54 (Cl. C07D);

Chem.abstr., 97630b (1973).

153. El-Sherbeny Magda A; Arzheim-Forsch; Chem. Abstr., **134**, 71558; (2001)

154. Guido Mayer, U L F Misslifz; PCT Int. Appl.WO 02, 48**,** 140 (Cl. C07D413/06), (2002).

155. Nigel Greig, Mark Mattson, Xiaoxian Zhy; PCT Int. Appl.WO 0204,409 Cl.C07C277 /00); Chem.abstr.,**136**, 118442q (2002).

156. Bernard Barlaam, Peter Bernstein, Catly Dantzman; PCT Int. Appl.WO 0251,821, (Cl. C07D263/57); Chem.abstr., **137**, 78945d (2002).

157. Mayer Rev. Medicale France Mov. 3-19, (1941).

158. Enrico Del Pianto (Univ. Rome) Ricerca,Sci., **20**,1491-1493 (1950).

159. Moys, Schwartz and bioeckinger, Bioeckinger, Bratislava, Lekarske Listy, **43**, II(6), 325-332 (1963).

160. Feedlander and French, Proc.Soc.Exptl. Biol. Med., **66**, 362-365 (1947).

161. Masamichi Sasati, Kekkatu, **32**, 201-205 (1957).

162. E.Holbova and z.Odlerova (Inst.Chem. Komensky Univ. 816-850, Bratislava Czech) Chem.Abstr., **94**, 30613 k(1981).

163. K. Waisser, N.Houngbedji, Z.Odlerova,W. Thiel, R.Mayer, Pharmazine, **45(2)**, 141-142, (1990); Chem.Abstr., 113, 196v (1990).

164. Ballio, Farm.Sci.E.tec.(pavia), **6**, 200-208, (1951); Chem.Abstr., **45**, 39021(1951).

165. R.A. Kulkarni and V.V. Save, J.Ind.Chem.Soc., **45**, 429-431, (1988).

166. K.M. Ghoniem, S.El.Basil, A.N.Usman, M.M. Said, S.A.megahed, Egypt.J.Pharm. Sci.**31**, 237-246 (1990); Chem.Abstr., **114**, 42624j (1991).

167. T. Kuchta, E.Sidoova, Cesk.Farm.**38** (7), 310-311 (1989); Chem.Abstr., **112**, 73654 (1990).

168. Ilhan Isikdag, Umit Ucueu, Turk Saglik Doga, Bilimleri Derg, **14(1)**, 158-168(1990); Chem.Abstr.,**113**,184199c (1990).

169. Tsatsas, et al., Bull. Soc.Chim.france, 730-737, (1962).

170. J. S. Upadhyaya. Indian J. Pharm.Sci., **42(5)**, 133-135 (1980); Chem.Abstr., **95**, 807909 (1981) .

171. David J. anderson, U.S. US 4,783,346, Chem.Abstr., **112**, 178982r (1990) .

172. Tomoya Machinami, Kazue Yasufuka, Masashi Shibahara, Jpn.Kokai Tokkya Koho Jp. 02, **167**, 268, (90,167,268); Chem.Abstr.,**113**, 191360b (1990) .

173. D. S. Matteson, M.S. Bleenbaum, R.A. Bechtold, R.J. Willsek; *J. Org. Chem.,* **43,** 950 (1978).

174. A. R. Katritzky, C. W. Rees; *'Comprehensive Heterocyclic Chemistry',* **3,** 152 (1982).

175. C.C. Heidelberger, N.C. Chaudhari, P. Dannberg, D. Mooren, L. Griesgach, R. Duchinsky, R. I. Schnitzer, E. Pleven; *Scheiner Nature,* **179,** 663 (1957).

176. Okada,Hirochi, Kato, Masanari, Koyanagi; *Chem. Pharm. Bull.,* 1999, **47**(3), 430, (Eng); *Chem. Abstr.,* **130,** 352240f (1999).

177. T. V. Safonova, A.F. Keremov, Yu. A. Ershova; *Khim. Farm. Zn.,* **32**(12), 11, (1998). (Eng); *Chem. Abstr.,* **131,** 18975e (1999).

178. L. Vio and M.G. Mamolo Farmaco; *Ed. Sce.,* **38** (4), 255, (1983); *Chem. Abstr.,* **99,** 88139e (1983).

179. J. B. Press and R.K. Rushell; *U.S. Pat*., **4,** 670, 560, (1987), *Chem.Abstr.,***107,** 115604v (1987).

180. R. K. Rushell, J.B. Press, R.A. Rampnlla, J.J. Mancnally, R. Falotiko; *J. Med. Chem.,* **31,** 1786 (1988).

181. O. Nakaguti, N. Shimazaki, M. Shimazaki and M. Nakatuka; *Eur. Pat. Appl.,* Ep-168, 005 (1986); *Chem. Abstr.,* **105.** 191118p (1986).

182. S. S. Bahekar, D. B. Shinde; *Acta Pharm*., **53**, 223-229 (2003).

183. W. Max, B. Murty, E. Peter, W. Klaur; *Novartis Pharma., Switz; PCT Int.* WO 03 **63**, 871 (Cl.A61K31/505) 2003; *Chem. Abstr.,* **139,** 164802c (2003)..

184. V. Papesch, E.F. Schroeder; *US Pat.* 2724559 (1956), *Chem. Abstr.,* **50,** 1370 (1956).

185. P. Steilbuck, R. Baltzly and H.M. Hood; *J. Org. Chem.,* **28,** 1983 (1963).

186. H. M. Hood; *Brit. Pat.* 957, 797 (1964); *Chem. Abstr.,* **61,** 3122 (1964).

187. N. Tokutake; *Brit. Pat.* 146836B, *Chem. Abstr.,* **87,** 102370j (1977).

188. C. J. Chappel and C. VanSeemann; *Prog. Med. Chem.,* **3,** 89 (1963).

189. B. G. Ugarkar, J. M. Dare, J. J. Kopcho; *J. Med. Chem.,* **43,** 2883-93 (2000).

190. R. Kotva and J. Krepelka; *Cellect. Czech. Chem. Commun.,* **48(I),** 1, 137-43, 299-303, 304-311 (1983); *Chem. Abstr.,* **98,** 160668a-670v (1983).

191. B. De'Souza and J.J. Galay; *Eur. Pat.* 105**,** 029 (1984); *Chem. Abstr.,* **101,** 72748b (1984).

192. M. Kurono; **Jp** 62**,** 267, 272 (1987); *Chem. Abstr.,* **109,** 37382t (1988).

193. K. Atwal; **US** 4**,** 769, 371 (1988); *Chem. Abstr.,* **110,** 114853a (1989).

194. Chotto and A. Mizuno ; *Eur. Pat.* Ep. **195,** 374 (1988); *Chem. Abstr.,* **110,** 231653w (1989).

195. M.K. Jani. B.R. Shah. N.K. Undavia, P.B. Trivedi; *Chem. Abstr.,* **121,** 35513p (1994).

196. A. Kreutzberger and M. Sellheim; *Che. Zig.* **108** (7-8), 253-5, (1984); *Chem. Abstr.,* **102,** 24572p (1985).

197. Jaen, Ju an C; *Tularik Inc. usa PCT Int. Appl.* WO 02 64, 096 (Cl. A61K) 2002;

198. Smith Kline and French Lab. Ltd.; *Chem. Abstr.,* **103,** 22613z (1985).

199. Okabe M., Sun, R.C. and Zenehoff G.B.; *J. Org. Chem.,* **56,** 4393 (1991).

200. K. Noriyuki, M. Hitoshi; Shionogi & Co. Ltd., *Japan PCT Int. Appl.* WO 03 47**,** 564 (Cl. A61K31/343) 2002; *Chem. Abstr.,* **139,** 36532c (2003).

201. G. W. Anderson, IF.Halverstadt, WH, Miller RO, Rohlin; *J. Am. Chem.Soc.,***67,** 2197 (1945).

202. Calas, Michele, Pages, Cecile and Barhier, Alain; *Eur. J. Med. Chem., Chem. Ther.,***18 (1)** (Fr.) (1983); *Chem. Abstr.,* **99,** 53686d (1983).

203. Guo, Huiyan, Yu. Zhili and Su. Shengmao; *Yzoxue Xuebao* **18** (3), 185-90 (Ch.); *Chem. Abstr.,* **99,** 70673r (1983).

204. A. Stuart, T. Paterson and B. Roth; *J. Med. Chem.,* **26** (5), 667-73 (1983); *Chem. Abstr.,* **98,** 16066y (1983).

205. R. Kotva, J. Krepelka; *Czech. C.S.,* **224,** 239 (1984); *Chem. Abstr.,* **102,** 45974m (1985).

206. V. K. Ahuwalia, H.R. Sharma and R. Tyagi; *Ind. J. Chem.* **26-B(7),** 697-699 (1987);*Chem. Abstr.,* **109,** 6474y (1988).

207. J. M. Parmar, J.J. Modha, A.R. Parikh; *Ind. J. Chem.* **38-B**, 440-444(1999).

208. O. A. Fathlla; *Ind. J. Chem.,* **40**(B), 37-42 (2001).

209. L. R. Patil, V.S. Ingle, S.P. Bondge, V.E. Bhingolikar; *Ind. J. Het. Chem.,* **11,** 131(2001).

210. J. M. Parmar, J.J. Modha, A.R. Parikh; *J. Inst. Chemist (India);* **73**(1), (2001).

211. D. N. Nagar, K.H. Sikotra and V.H. Shah; *J. Inst. Chemist (India);* **73**(3), 93 (2001).

212. D. N. Nagar, K.H. Sikotra and V.H. Shah; *J. Inst. Chemist (India);* **73** (4), 132 (2001).

213. H. S. Patel, V.K. Patel, B.C. Dixit; *Oriental J. Chem.,* **17**(3), 411-414 (2001).

214. N. J. Datta, R.C. Khunt and A.R. Parikh; *Oriental J. Chem.,* **18** (1), 131-134 (2001).

215. C. S. Andotra, S. Kaur and J. Khajuria; *Ind. J. Het. Chem.,* **12** (1), 77-78 (2002).

216. E. S. Devi, E.O. Prakash, J.T. Rao; *J. Inst. Chemist (India);* **74**(5), 167 (2002).

217. B. Kaspar, G. P. Sorana, I. Khalid; *Chem. Abstra.,* **136,** 151176q (2002).

218. H. M. F. Madkour, M.A.I. Salem, E.A. Soliman, N.F.H. Mahmoud; *Phosphorus Sulfur and Silicon and the Related Elements*,**170,** 15-27 (2002). *Chem. Abstra.,***136,** 183780y (2002).

219. S. Tsuneyuki, H. Toshihide, M. Toru, K. Tsutomu, H. Shinsuke; *Ono Pharmaceutic Co.Ltd., Japan PCT Int. Appl.* WO 02 **51**, 815, (Cl.C07D239/47) (2002); *Chem. Abstr.,* **137,**78963h (2002).

220. E. Martin, Z. Hugo, C. Fredrik, A. Peter; *Syngenta participations A. G.;Switz. PCT Int. Appl.* WO 02 53**,** 560 (Cl. C07D401/04)(2002); *Chem. Abstra.,***137,** 169533j (2002).

221. Livio Racane, Kulenovic Tralic, Lelja; Heterocycles, 2001, **55 (11)**, 2085-2098; Chem. Abstr., **136**, 216685b (2002).

222. Kuhler Thomas, Swanson Marianne, Christenson Beritte; J. Med. Chem. **45**, 4282, (2002)

223. R. J. Alamino, C. J. Hatton, and M. K. Eckman, *J.Med. Chem.*, **13**, 554 (1970).

224. R. J. Alamino and C. J. Hatton, *J. Med.Chem.,***15**,108, (1972).

225. R. J. Alamino, *J. Hetrocycl. Chem.*,**8**,309 (1971).

226. D. C. Grove and W. A. Randall, "Assay Method of Antibiotics: A Laboratory Manual " Medical Encyclopedia, New York, N. Y., (1955).

227. G. L. Jenkins and W. H. Hartung, "The Chemistry of OrgenicMedicinal Products, " John Wiley and Sons, Inc, New York, N. *Y., 617-621, (1944).*

228. L. L. Bambas, This Journal~AL, **67**, 671 (1945).

229. F. Brody and M. T. Bogert. ibid., **65**, 1080, (1943).

230. H. Erlenmeyer and M. Muller, *Helv. Chim. Acta,* **28**, 922, (1945).

231. D. Bovet, J. Bablet and J. Foumel, *Ann. insf. Pasteur, 72,* Jan.-Feb. (1946); (b) **37**, Oct. 7 (1945).

232. P. Khalili, E. Naimi, W. Y. Sun, E. E. Knaus and L. I. Wiebe, *Eur. J. Pharm. Sci.*, **19**, 305-313 (2003).

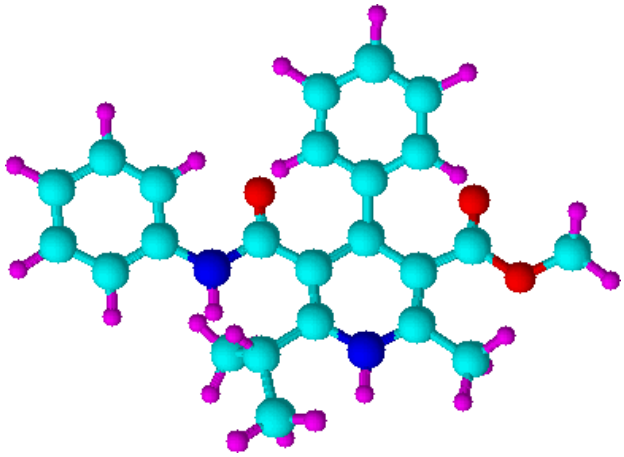
233. Rostom, S. A., Fahmy, H. T., Saudi, M. N.; *Scientia Phatmaceutica,* **71**(2), 57-74 (2003).

234. Aurelio Orjales, Ramon Mosquera, Agustin Berisa, M. Teresa Nunez, Beatriz Lopez and M. Carmen Dieguez; *FAES FARMA S.A., Department of Research,Bilbao,Spain,* (2004).

235. S.Bartonlini, A.Mai, M. Artico, N. Paesano, D. Rotili; *J. Med. Chem.*, **48**, 6776-6778 (2005).

236. C.Zhi, Z. Long, A. Manikowski, N.C.Brown, P.M. Tarantino, K. Holm, E. J. Dix, G. E. Wright, K.A.Foster, M.M.Butler, W.A.LaMarr, D.J.Skow, I.Motorina, S.Lamothe, R.Storer;*J. Med. Chem.*, **48**, 7063-7074 (2005).

237. A.Orjales, R.Mosquera, B.Lopaz, R.Olivera, L.Labeaga, M.T.Nunez; *Bioorganic & Med.Chem.,* **16(5)**,2183-2199 (2008).



PART-II

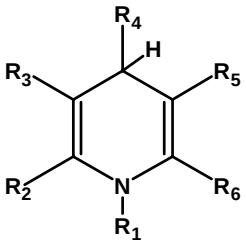
STUDIES ON

1,4-DIHYDROPYRIDINES

PART - II
STUDIES ON 1,4-DIHYDROPYRIDINE DERIVATIVES

INTRODUCTION

In 1,4-dihydropyridine structure either imino (NH) or substituted nitrogen atom is present at the one position and hydrogen atom at the four position of the six membered heterocyclic ring which can be represented as under **(37).**



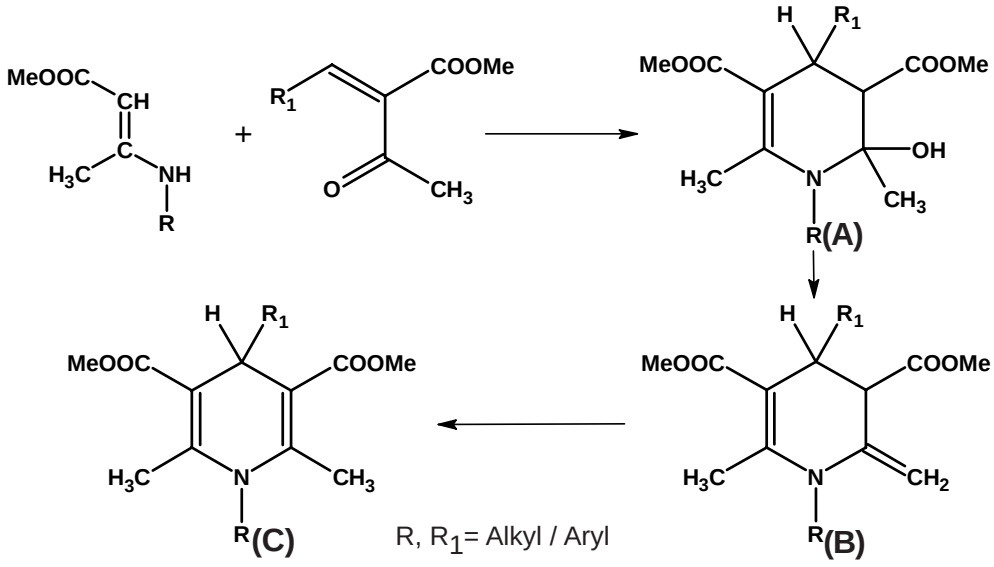
(37)

R_1, R_4 = H / Alkyl / Aryl
R_2, R_6 = Methyl, Isopropyl
R_3, R_5 = Acetyl /Carbmethoxy/ Carbethoxy / N-Aryl Carbamoyl

1,4-dihydropyridines contribute as an important class of compounds in medicinal chemistry, leading to several new drugs currently widely used especially as calcium channel antagonist[238] and other cardiovascular diseases also.

SYNTHETIC METHODS OF DIHYDROPYRIDINE

B. Chekavichus et.al.,[239] has proposed following kind of successive intermidiate[2] in the Hantzsch synthesis of 1,4-dihydropyridines depicted as under.



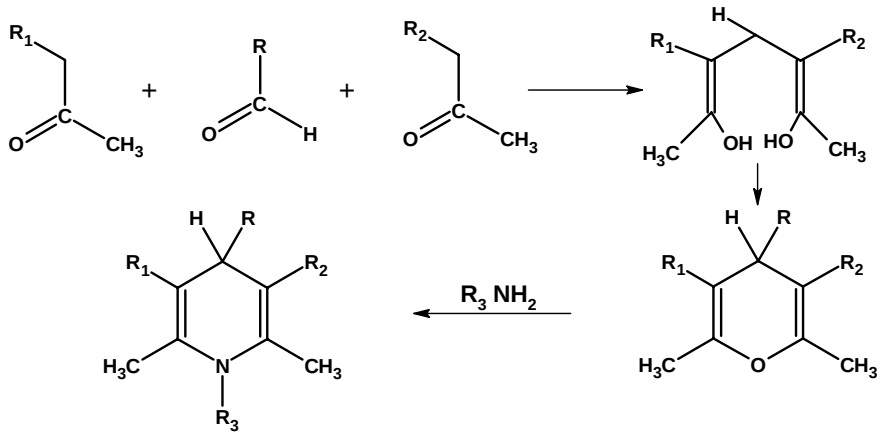
The synthesis of **1,4-dihydropyridines** involves following steps.

(1) Intermediate **(A)** involves cyclisation of 3-arylaminocrotonate and arylidene followed by the rearrangement of hydrogen.

(2) Intermediate **(B)** involves dehydration of **(A)** with loss of equimolar quan tity of water.

(3) Intermediate **(C)** involves isomerisation of intermediate of **(B)** and obt ained regio and stereo selective 1,4-dihydropyridine as a final product.

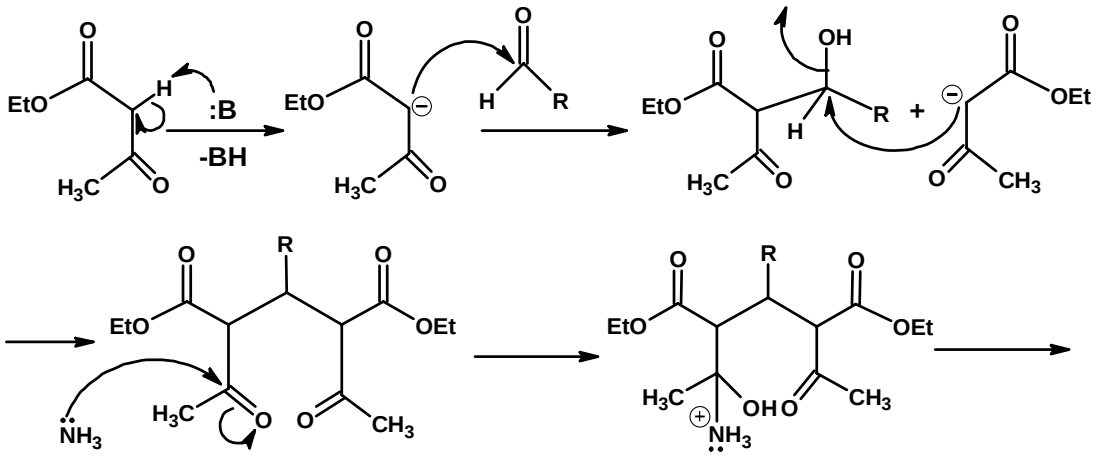
It has been observed that in the presence of piperidine as a catalyst, pyran was formed as an intermediate by the cyclocondensation of aliphatic or aromatic aldehydes with 1,3-diketones, followed by the dehydration of pyran through the reaction with aliphatic or aromatic amines afforded final product. Formation of intermediate is proved by ^{1}H NMR and Mass spectral data.

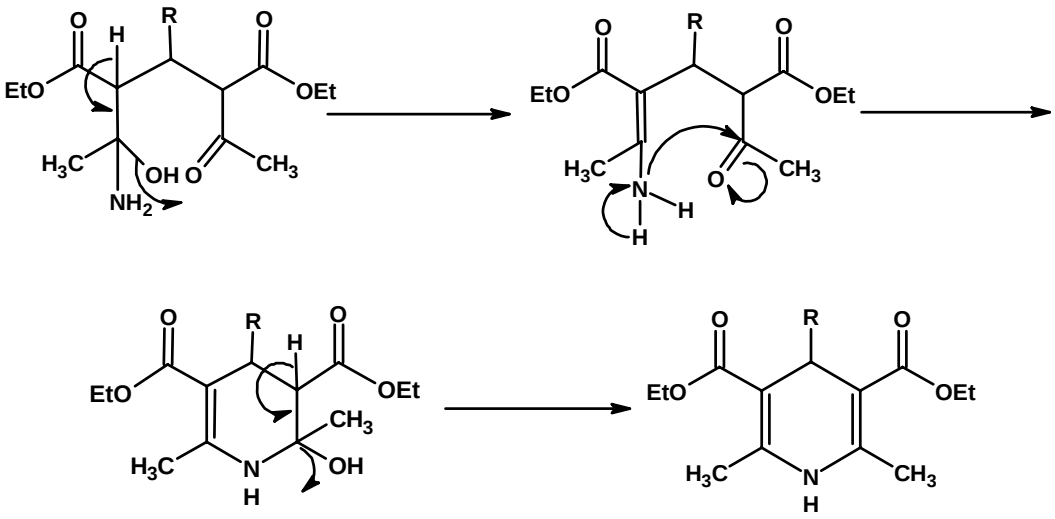


R, R_3 = H / Aryl / Aryl

R_1, R_2 = Carboxylate/ Arylcarbamoyl

MECHANISM





(1) Abstraction of proton by base from ethyl acetoacetate form nucleophile.

(2) Attack of nucleophile on aldehyde molecule to yield bis-keto ester.

(3) Condensation of NH_3 with bis-keto ester with removel of water molecule to give 1,4-dihydropyridine derivative.

SYNTHETIC METHODS OF 1,4-DIHYDROPYRIDINES

Different synthetic methods for the synthesis of 1,4-dihydropyridines are as follows.

(1) By the condensation of aromatic or aliphatic aldehydes with acetoacet-icester and aromatic / aliphatic amine in presence of pyridine **240-243**.

(2) By the condensation of aliphatic or aromatic aldehydes with 3-amino crotonate and 1,3-diketone **239,244-250**.

(3) By the condensation of arylidene with 3-aminocrotonate**251**.

(4) By the condensation of aliphatic or aromatic aldehydes with various 1,3-diketones in presence of ammonia or ammonium carbonate**252-254**.

(5) By the condensation of α,β -unsaturated ketones with malononitrile and cyanoacetamide**255**.

(6) By the condensation of o-nitrobenzaldehyde, β -amino butaricacid and methylpripiolate in gl. acetic acid**256**.

(7) By the knoevenagel condensation of benzaldehyde with acetoacetice ster in presence of β-alanine as catalyst and subsequent

cyclocondensation of the resulting benzylidene with 3-amino crotonate **257**.

(8) By the regio and chemoselective addition of $Ph_2Cu(CN)Li_2$ to substituted N-alkylpyridium salts followed by acylation of the intermediate**258**

(9) By the condensation of 1,3-diketones ,alkyl or aryl aldehydes with aq. ammonium hydroxide in the presence of piperidine or piperidyl acetate or potassium acetate or potassium carbonate or gl.acetic acid**259-261** .

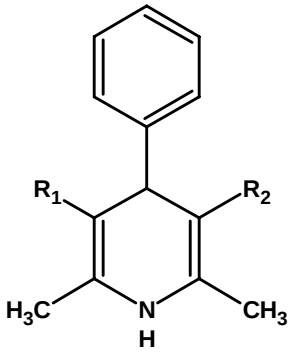
(10) By the condensation of two moles of thiobarbituric acid, aromatic-amines and aromatic aldehydes**262-263**.

MEDICINAL INTEREST 0F 1,4-DIHYDROPYRIDINE

The research on 1,4-dihydropyridine system is of current interest due to their valuable activities as calcium channel antagonist, vasodilator, cardio-vascular etc. beside the currently established drugs Nifedipine**264-265**, Nicardipine**266-267** Many dihydropyridine derivatives have been synthesized world wide**268-271**. and have led to numerous second generation commercial product**272-279**.such as Nimodipine**280-281**, Nisodipine**282**, Nitrendipine**283**,Amlodopine**284**,Felodipine**285**,Isradipine**286**, Manidipine**287** and Nelva- dipine**288**. Some of their compounds are characterized by longer bioactivity of greater tissue selectivity. 1,4-dihydropyridine derivatives are associated with diverse biological activities viz.

[A] Antiarrythemic[289]
[B] Antiinflammatory[290]
[C] Antiallergic[291]
[D] Antiulcer[292]
[E] Antitumor[243]
[F] Vasodilator[293]
[G] Enzymetic[294-295]
[H]Calcium channel antagonist [296-298]
[I] Antihypertensive[299-300]
[J] Antihypolipemic[301]
[K] Antimayocardic ischemic[302]
[L] Cardiovascular[303]
[M] Photo induced relaxation[246,256]
[N] Antitubercular agents[304]

I. Nadeem et.al.,**[247] (38)** have demonstrated the structure activity relationship of calcium channel and photo induced relaxation of novel 1,4-dihydropyridines. Activities of calcium channel antagonists ***in vitro*** were detected and conclusion about structure-activity relationship (SARs), was drawn as under:



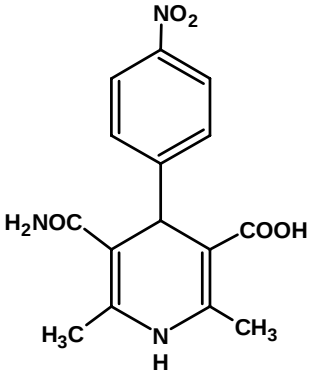
R_1=$COOCH_3$ / $COOC_2H_5$
R_2=$COOCH_3$ / $COOC_2H_5$
R_3 =Substituted phenyl

(38)

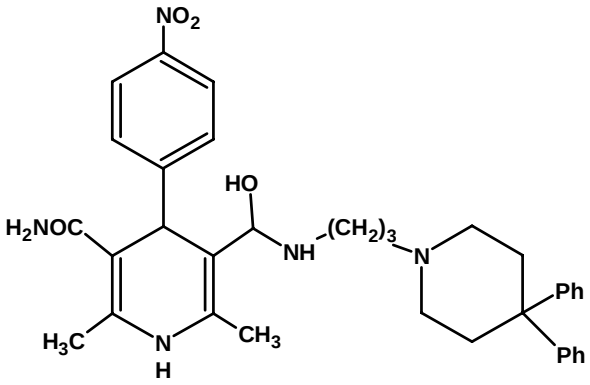
(1) Relative potency order for C-4 phenyl substituents in ortho and meta-position is greater then para position.

(2) C-3 nitro substitutents decrease calcium channel antagonist activity.

G. Charles et.al.,[305] **(39)** have synthesized 1,4-dihydropyridines for treatment of prostatic hyperplasia.



(39)



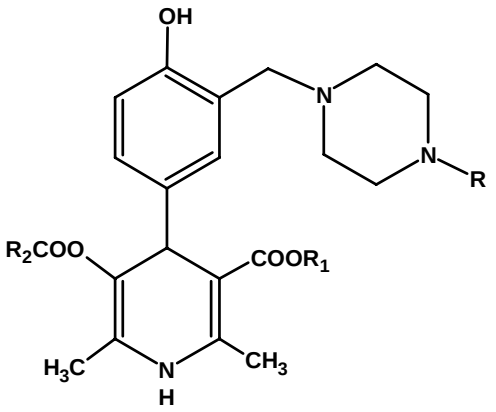
(40)

Dihydropyridine derivatives **(39)** have been found to be useful in treaing benign prostate hyperplasia inhibition of cholesterol synthesis **(40)** showed 'ki' of 1.9 m.mol/kg in reducing urethral pressure ***in vivo*** in dog.

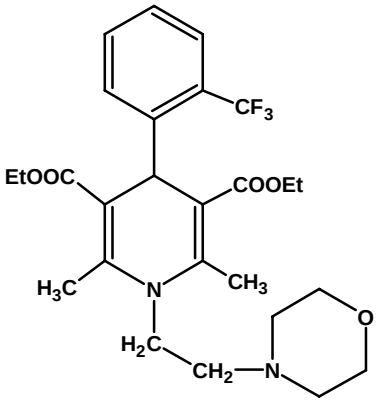
More recently B. M. Khadikar et.al.,[306] have synthesized 1,4-dihydropyridine derivatives **(41)** and tested its biological activity.

Out of many 1,4-dihydropyridine drugs only Flordipine **(42)** is N-substituted derivative that has proved to be very good calcium channel antagonist, contrary to the belief proposed by D.J.Triggle[307] that N-substituted 1,4-

dihydropyridine do not show good antihypertensive activity, probably the concept of that time and -NH was belived to be essential for calcium channel antagonism.



(41)

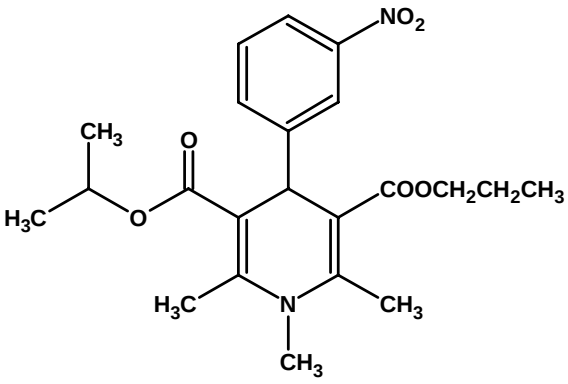


(42)

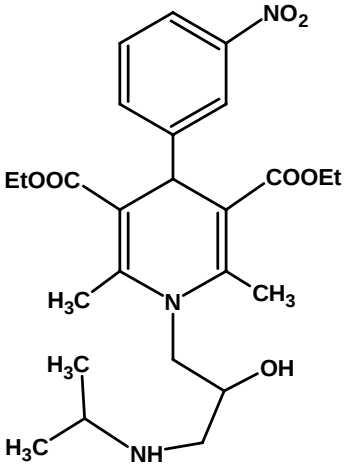
R_1,R_2=Methyl / ethyl

R=Alkyl / Aryl

N-methylnimodipine **(43)** was found to possess antidepressive[308] characteristics (20 mg.P.O reduce the immobile phase by approximately 22% comparison to control values), which provides excellent example of mechanism of action similar to that of Flordipine.



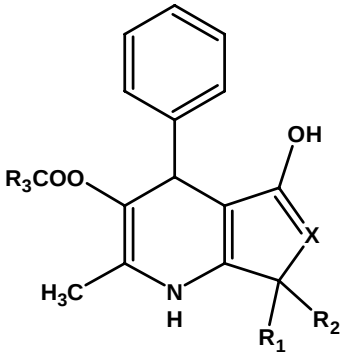
(43)



(44)

V. Michael et.al.,[309] prepared antihypertensive and coronary vasodilator *N*-substituted 1,4-dihydropyridine **(44)**.

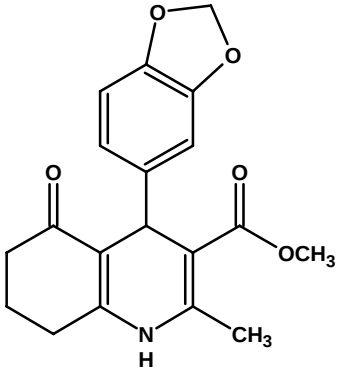
A. Daich et.al.,[310] have reported calcium antagonist effect of 1,4-dihydro-pyridines **(45)** and M. Suarez et.al.,[311] have synthesized calcium antagonist modulators 1,4-dihydropyridines **(46)**.



(45)

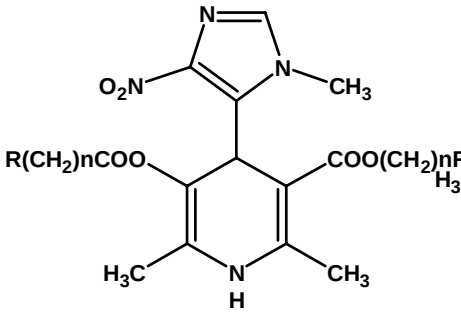
R_1,R_2,R_3= methyl / ethyl

X=O, S, N



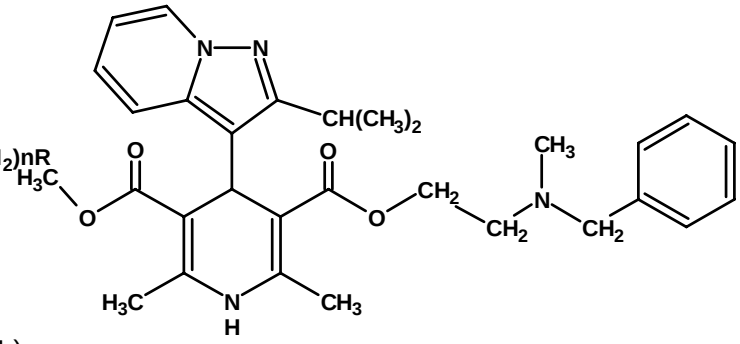
(46)

M. Sharifzadeh et.al.,[312] have prepared anticonvulsant 1,4-dihydropyridine**(47)** and K. Shigenobu et.al.,[313] prepared cardioprotective 1,4-dihydropyridine**(48)**.



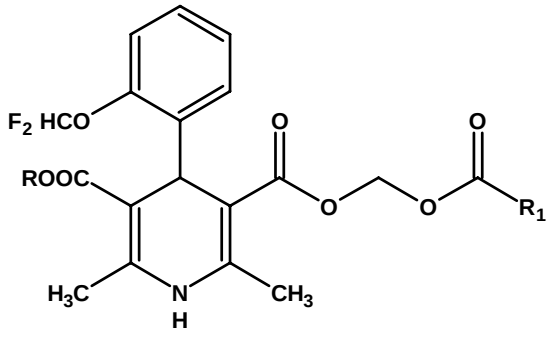
R = CH_3, $CH(CH_3)_2$,C_6H_5,$C(CH_3)_3$, C_6H_{11}; n = 1,2,3

(47)



(48)

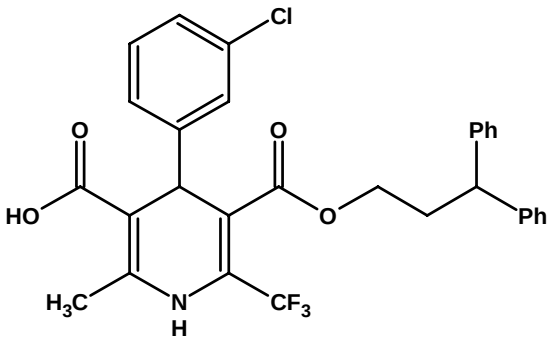
M. C. R. Franseen et.al.,[314] have synthesized 4-substituted-1,4-dihydro-pyridine-3,5-diesters **(49)** as Candida rugosa lipase.



R = $(CH_2)_2O(CH_2)_2CH_3$; R_1=Et / Pr / iPr

R = CH_3; R_1=Et / Pr / iPr

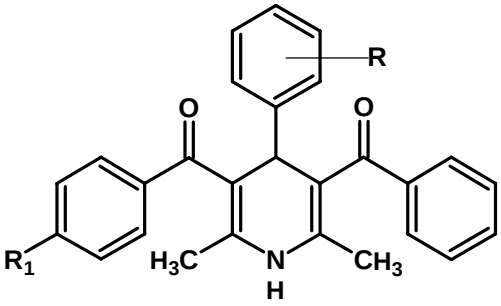
(49)



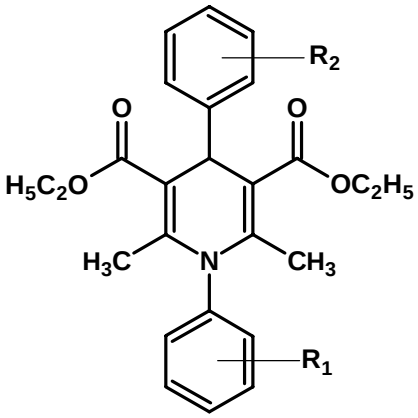
(50)

A.Takahara et.al.,[315] have designed the synthesis of N-type 1,4-dihydropyridines**(50)** and reported them as calcium channel blockers.

A. Motohashi et al.,[316] Dihydropyridines with N-phenyl substitution and tested for tumor specific cytotoxicity and *mdr* reversal activity to find out the effects of N-phenyl substitution on activity. Asymmetric BzDHPs with different substitution on benzoyl aromatic ring were synthesized and evaluated for tumor specific cytotoxicity. In continuation, dihydropyridines with phenyl carbamoyl side chain on one arm and –CN, -COOEt, -COOMe side chain on other arm were also synthesized and evaluated as mdr reversal dihydropyridines.

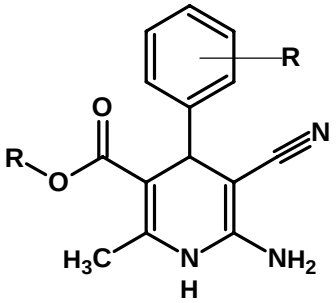


(51)

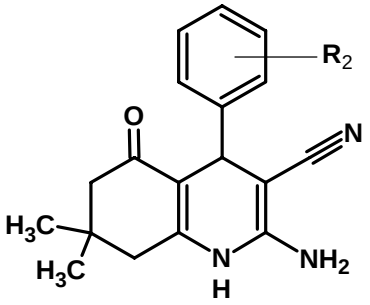


(52)

R. pattan et.al.,[317] have reported antihypertensive agents effect of 6-amino-1,4-dihydropyridines**(53) &(54)**.



(53)



(54)

In view of procuring highly potent biodynamic agents and after reviewing literature survey on 1,4-dihydropyridines for their various methods of synthesis and different biological activities, synthesis of 1,4-dihydropyridines have been under taken, which can be summarized in the following sections as under.

SECTION - I : Preparation and biological evaluation of 2,6-Dimethyl-3,5-N,N'-substituted-diphenyl carboxamido-4-(m-phenoxy- phenyl)-1,4-dihydropyridines.

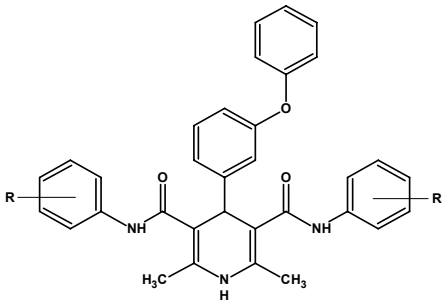
SECTION - II: Preparation and biological evaluation of 6-Methyl-2-isopropyl-4-(substituted phenyl) 3-ethyl-5-methyl-1,4-di hydropyridine-dicarboxylates.

SECTION - III : Preparation and biological evaluation of Methyl-2-isopropyl-6-methyl-3-(substituted-phenyl carboxamido)- 4-substituted-phenyl-1,4-dihydropyridine-5-carboxylates.

SECTION-I

PREPARATION AND BIOLOGICAL EVALUATION OF 2,6-DIMETHYL-3,5-N,N'-SUBSTITUTED-DIPHENYLCARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-DIHYDROPYRIDINES.

1,4-Dihydro-pyridine derivatives represents one of the most active classes of compounds possessing wide spectrum of biodynamic activities.[289-304] In order to have potent therapeutic agents, the synthesis of **2,6-Dimethyl-3,5-N,N'-substituted-diphenyl carboxamido-4-(m-phenoxy-phenyl)-1,4-dihydropyridines (X_{a-j}).** have been undertaken by the condensation of **m-phenoxy benzaldehyde** and **substituted- N-phenylbutanamide-3-ones** in the basic condition.



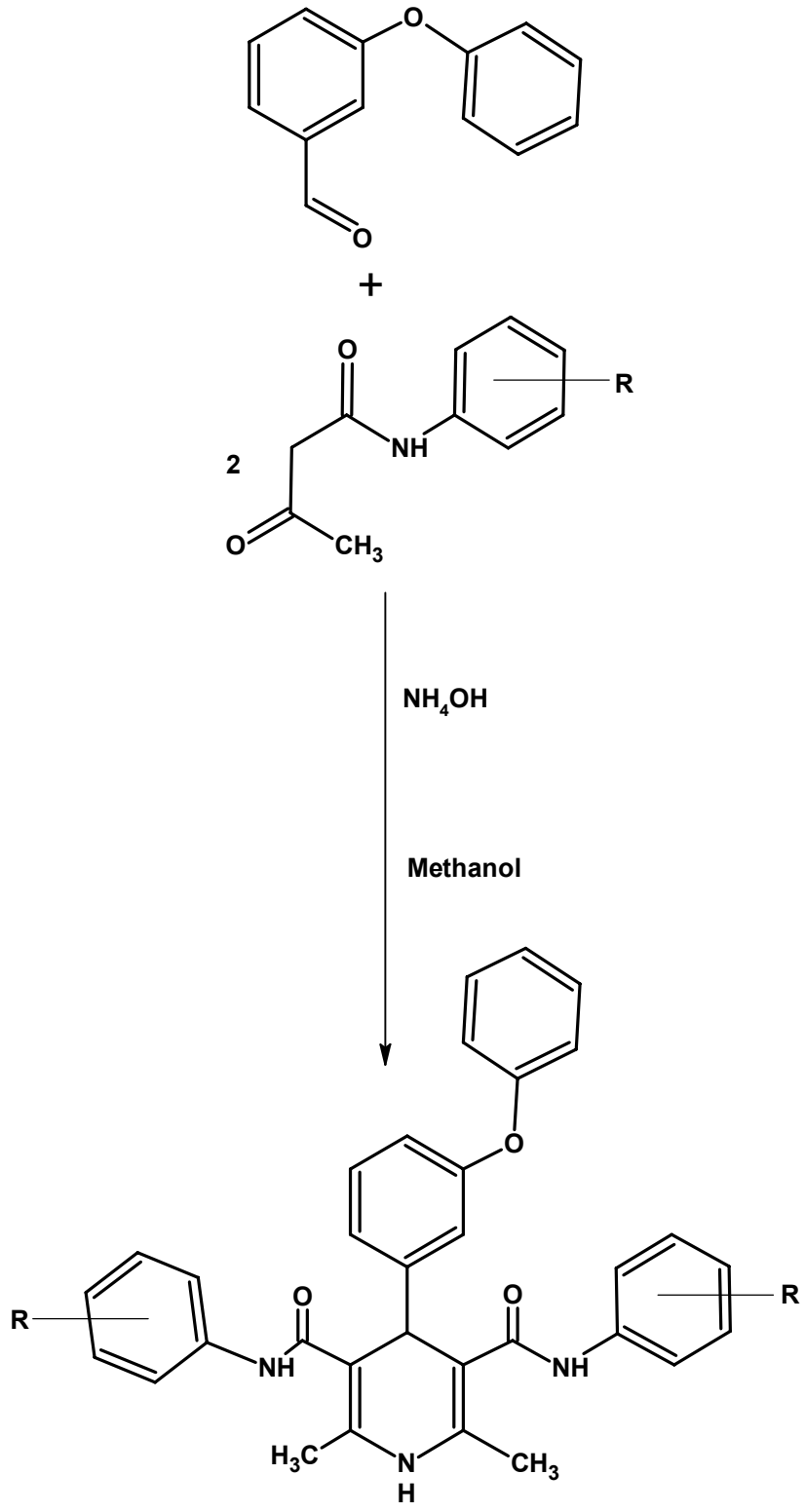
(Xa-j)

R=Substituted phenyl

The constitution of the products **(X_{a-j})** have been delineated by **elemental analyses, IR, PMR** and **Mass** spectral data.

The products **(X_{a-j})** were assayed for their ***in vitro*** biological assay like antibacterial activity towards ***S.pyogens MTCC-442, S.aureus MTCC-96*** **and** ***B.subtillis MTCC-441*** **(Gram positive)** and ***E.coli MTCC-443*** **(Gram negative)** bacterial strains and antifungal activity towards **Aspergillus niger MTCC-282 and Candida albicans MTCC-227** at different concentrations i.e. : 0 (control), 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds **(X_{a-j})** were compared with standard drugs,viz., **Amoxicillin, Chloramphenicol, Sparfloxacin, Levofloxacin** (antibacterial)**, Griseofluvin, Fluconazole** (antifungal)**.**

REACTION SCHEME



(Xa-j)
R=substituted phenyl

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 2,6-DIMETHYL-3,5-N,N'-SUBSTITUTED-DIPHENYLCARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-DIHYDROPYRIDINES.

(A) Preparation of N-substituted-phenyl butanamide-3-ones.

For preparation, of N-substituted-phenyl butanamide-3-ones has been under taken according to literature[318-319].

Similarly, other compounds **(10_{a-j})** were synthesized. The physical data are recorded in **Table No.10.**

(B) Preparation of 2,6-Dimethyl-3,5-N,N'-p-p'-dichloro-diphenyl carboxamido-4-(*m*-phenoxy- phenyl)-1,4-dihydropyridine (X_c).

A mixture of *m*-phenoxy benzaldehyde (1.98gm, 0.01 M), N-p-chlorophenyl butanamide-3-one (2.11 gm, 0.02 M) in methanol (15ml) and liquor ammonia solution (1 ml) was heated under reflux for 8 hrs. The reaction was monitored by TLC. After the completion of reaction, the reaction mixture was poured in to crushed ice-water. The solid product so obtained was filtered, washed with water and crystallized from Methanol. Yield : 51 %, M.P. :132 °C, (Required : C, 67.81%; H, 4.66%; N, 7.19 % for $C_{33}H_{27}N_3O_3Cl_2$, Found :C, 67.78%; H, 4.61%; N, 7.15 %).

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (4.0 : 6.0) = 0.59.
TLC solvent system R_{f_2} : Methanol : Toluene (1.0 : 9.0) = 0.43.

Similarly, other compounds **(X_{a-j})** were synthesized. The physical data are recorded in **Table No.10A.**

(C) Antimicrobial activity of 2,6-Dimethyl-3,5-N,N'-substituted-diphenyl carboxamido-4-(*m*-phenoxy- phenyl)-1,4-dihydropyridine (X_{a-j}).

Antimicrobial activity testing was carried out as described in Part-1(A), Section-I, page No. 30-31. The MIC values of test solution are recorded in **Table No. 10B, 10C** and **10D.**

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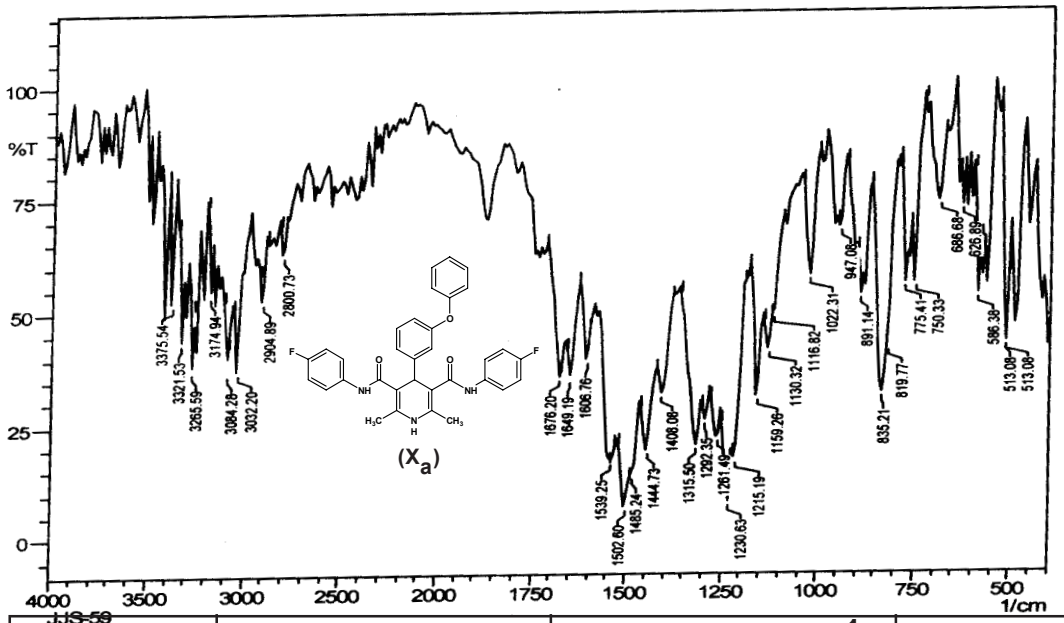
TABLE NO. 10 : PHYSICAL CONSTANTS OF N-SUBSTITUED-PHENYL BUTANAMIDE -3-ONES (10a-j).

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. °C 5	Yield % 6	R_f Value R_{f_1}	R_{f_2} 7	% of Nitrogen Calcd. / Found 8
10_a	4-F	$C_{10}H_{10}NO_2F$	195	92°	61	0.69	0.52	7.18 / 7.15
10_b	3-Cl	$C_{10}H_{10}NO_2Cl$	211	107°	57	0.53	0.58	6.63 / 6.58
10_c	4-Cl	$C_{10}H_{10}NO_2Cl$	211	133°	58	0.64	0.51	6.63/ 6.57
10_d	3-Cl-4-F	$C_{10}H_9NO_2ClF$	229	123°	45	0.51	0.54	6.11 / 6.07
10_e	3,4-$(Cl)_2$	$C_{10}H_9NO_2Cl_2$	246	132°	64	0.59	0.49	5.69 / 5.64
10_f	3-NO_2	$C_{10}H_{10}N_2O_4$	222	157°	58	0.41	0.43	12.61/ 12.56
10_g	4-NO_2	$C_{10}H_{10}N_2O_4$	222	161°	53	0.45	0.47	12.61/ 12.57
10_h	2,4-$(NO_2)_2$	$C_{10}H_9N_3O_6$	267	183°	61	0.38	0.49	15.73 / 15.68
10_i	4-CH_3	$C_{11}H_{13}NO_2$	191	113°	47	0.60	0.48	7.32/ 7.28
10_j	2,3-$(CH_3)_2$	$C_{12}H_{15}NO_2$	205	103°	56	0.57	0.47	6.82/ 6.77

TABLE NO. 10A : PHYSICAL CONSTANTS OF 2,6-DIMETHYL-3,5-N,N'-SUBSTITUTED-DIPHENYL-CARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-DIHYDROPYRIDINES (X_{a-j})..

Comp. No.	R	Molecular Formula	M.W.	M.P. °C	Yield %	R_f Value		% of Nitrogen Calcd. / Found
1	2	3	4	5	6	R_{f_1} 7	R_{f_2}	8
X_a	4-F	$C_{33}H_{27}N_3O_3F_2$	551.0	179°	54	0.51	0.48	7.62 / 7.58
X_b	3-Cl	$C_{33}H_{27}N_3O_3Cl_2$	584.0	130°	53	0.58	0.42	7.19 / 7.12
X_c	4-Cl	$C_{33}H_{27}N_3O_3Cl_2$	584.0	132°	51	0.59	0.43	7.19/ 7.13
X_d	3-Cl-4-F	$C_{33}H_{25}N_3O_3Cl_2F_2$	620.0	138°	48	0.53	0.45	6.77 / 6.71
X_e	3,4-$(Cl)_2$	$C_{33}H_{25}N_3O_3Cl_4$	653.0	139°	52	0.56	0.51	6.43 / 6.38
X_f	3-NO_2	$C_{33}H_{27}N_5O_7$	605.0	133°	49	0.43	0.52	11.57 /11.51
X_g	4-NO_2	$C_{33}H_{27}N_5O_7$	605.0	129°	58	0.48	0.43	11.57 /11.52
X_h	2,4-$(NO_2)_2$	$C_{33}H_{25}N_7O_{11}$	697.0	141°	42	0.41	0.40	14.10 / 14.05
X_i	4-CH_3	$C_{35}H_{33}N_3O_3$	543.0	211°	49	0.45	0.38	7.73 / 7.67
X_j	2,3-$(CH_3)_2$	$C_{37}H_{37}N_3O_3$	571.0	176°	48	0.42	0.39	7.35 / 7.29

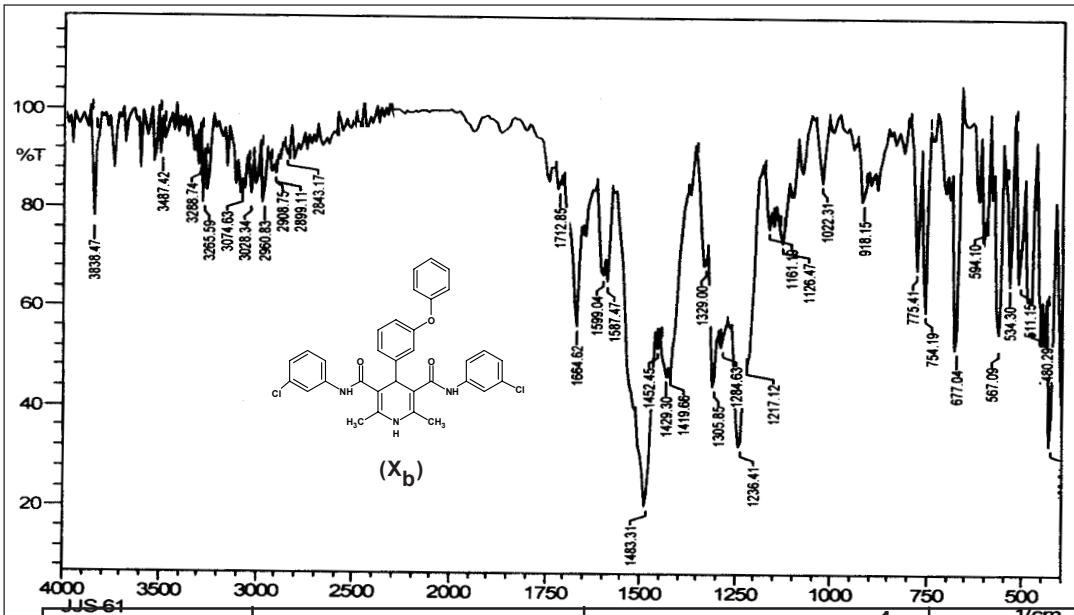
IR SPECTRAL STUDY OF 2,6-DIMETHYL-3,5-N,N'-*p*-*p*'-DIFLUORO-DIPHENYL CARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-DIHYDROPYRIDINE (X_a).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2904.8	2975 - 2850	96
	C-H (sym. str., m)	2800.7	2900 - 2800	96
	C-H (asym. def., m)	1444.7	1470 - 1435	96
	C-H (sym. def., m)	1315.5	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3032.2	3080 - 3010	97
	C=C & C-C (str., v)	1502.6	1600 - 1450	97
	C-H (i.p. def., m)	1116.8	1150 - 1050	97
	C-H (o.o.p. def., m)	819.7	825 - 800	97
	C-N (str., v)	1315.5	1340 - 1250	97
Amine	N-H (str., b)	3375.5-3084.2	3400 - 3000	98
	N-H (def., s,m)	1606.6	1650 - 1550	98
Ketone Amide	C=O (str., s)	1676.2	1740 - 1650	98
Ether	Ph-O-Ph (asym.str.,s)	1230.6	1275 - 1200	98
	Ph-O-Ph (sym. str., s)	1022.3	1075 - 1000	98
halogen Subtitution	C-F (str., b)	1315.5-1116.8	1400-1080	99
Pera(-4-) substitution	C-H (def., v,s)	835.2	850-800	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

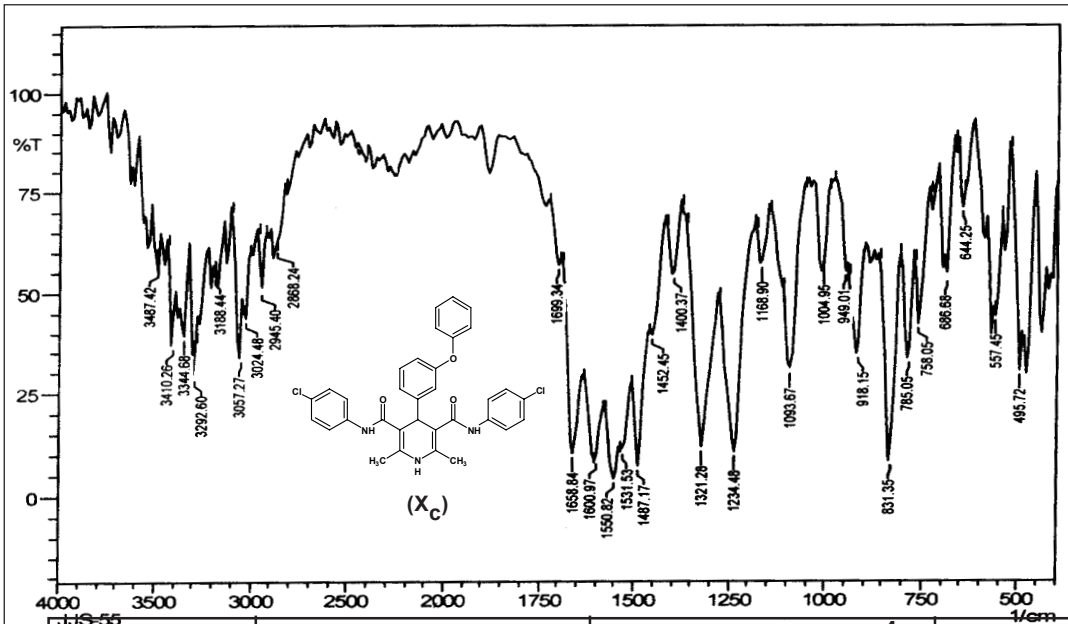
IR SPECTRAL STUDY OF 2,6-DIMETHYL-3,5-N,N'-*m*-*m*'-DICHLORO-DIPHENYL CARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-DIHYDROPYRIDINE (X_b).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2908.7	2975 - 2850	96
	C-H (sym. str., m)	2899.1	2900 - 2800	96
	C-H (asym. def., m)	1452.4	1470 - 1435	96
	C-H (sym. def., m)	1305.8	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3028.3	3080 - 3010	97
	C=C & C-C (str., v)	1483.3	1600 - 1450	97
	C-H (i.p. def., m)	1125.4	1150 - 1050	97
	C-N (str., v)	1329.0	1340 - 1250	97
Amine	N-H (str.,b)	3288.7-3074.6	3400 - 3000	97
	N-H (def., s,m)	1599.0	1650 - 1550	97
Ketone Amide	C=O (str., s)	1664.6	1740 - 1650	98
Ether	Ph-O-Ph (asym.str.,s)	1236.4	1275 - 1200	98
	Ph-O-Ph (sym. str., s)	1022.3	1075 - 1000	98
halogen Subtitution	C-Cl (str., b)	775-677	800-600	99
Meta(-3-) substitution	C-H (def., v,s)	870.1	880 - 830	99
		754.1	780-730	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

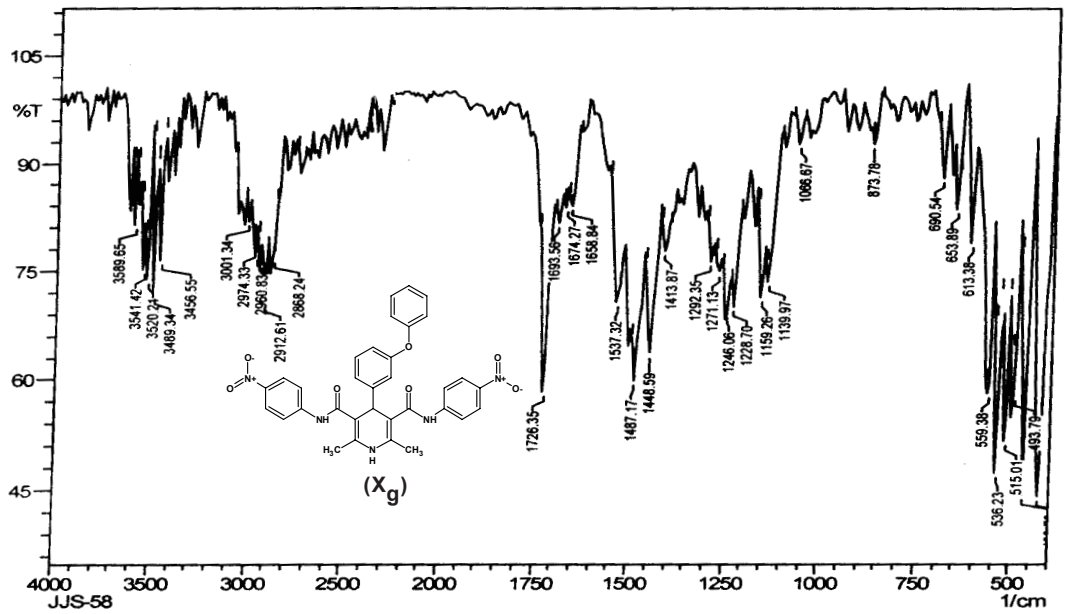
IR SPECTRAL STUDY OF 2,6-DIMETHYL-3,5-N,N'-*p*-*p*'-DICHLORO-DIPHENYL CARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-DIHYDROPYRIDINE (X_c).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2945.4	2975 - 2850	96
	C-H (sym. str., m)	2868.2	2900 - 2800	96
	C-H (asym. def., m)	1452.4	1470 - 1435	96
	C-H (sym. def., m)	1321.2	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3024.4	3080 - 3010	97
	C=C & C-C (str., v)	1600.9	1600 - 1450	97
	C-H (i.p. def., m)	1093.9	1150 - 1050	97
	C-H (o.o.p. def., m)	831.3	825 - 800	97
	C-N (str., v)	1234.4	1340 - 1250	97
Amine	N-H (str., b)	3410.2-3057.2	3400 - 3000	97
	N-H (def., s,m)	1600.9	1650 - 1550	97
Ketone Amide	C=O (str., s)	1699.3	1740 - 1650	98
Ether	Ph-O-Ph (asym.str.,	1234.4	1275 - 1200	98
	Ph-O-Ph (sym. str., s)	1004.9	1075 - 1000	98
halogen Subtitution	C-Cl (str., s)	785.0-644.2	800-600	99
Pera(-4-) substitution	C-H (def., v,s)	831.3	850-800	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

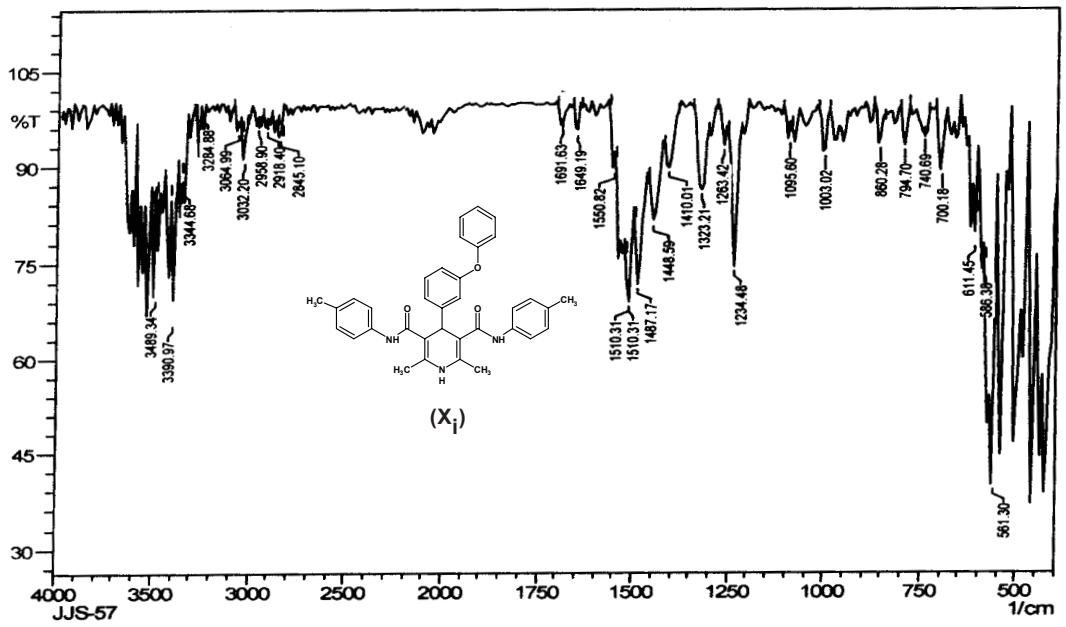
IR SPECTRAL STUDY OF 2,6-DIMETHYL-3,5-N,N'-*p*-*p*'-DINITRO-DIPHENYL CARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-HYDRO PYRIDINE-(X_g).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2960.8	2975 - 2850	96
	C-H (sym. str., m)	2868.2	2900 - 2800	96
	C-H (asym. def., m)	1448.5	1470 - 1435	96
	C-H (sym. def., m)	1292.3	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3001.3	3080 - 3010	97
	C=C & C-C (str., v)	1537.3	1600 - 1450	97
	C-H (i.p. def., m)	1139.9	1150 - 1050	97
	C-H (o.o.p. def., m)	811.3	825 - 800	97
	C-N (str., v)	1271.1	1340 - 1250	97
Amine	N-H (str., b)	3456.5	3400 - 3000	97
	N-H (def., s,m)	1658.8	1650 - 1550	97
Ketone Amide	C=O (str., s)	1726.3	1740 - 1650	98
Ether	Ph-O-Ph (asym.str.)	1228.7	1275 - 1200	98
	Ph-O-Ph (sym. str., s)	1066.6	1075 - 1000	98
Nitro Subtitution	C-NO_2 (asym str., s)	1537.3	1570-1500	99
	C-NO_2 (sym str., s)	1292.9	1370-1290	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

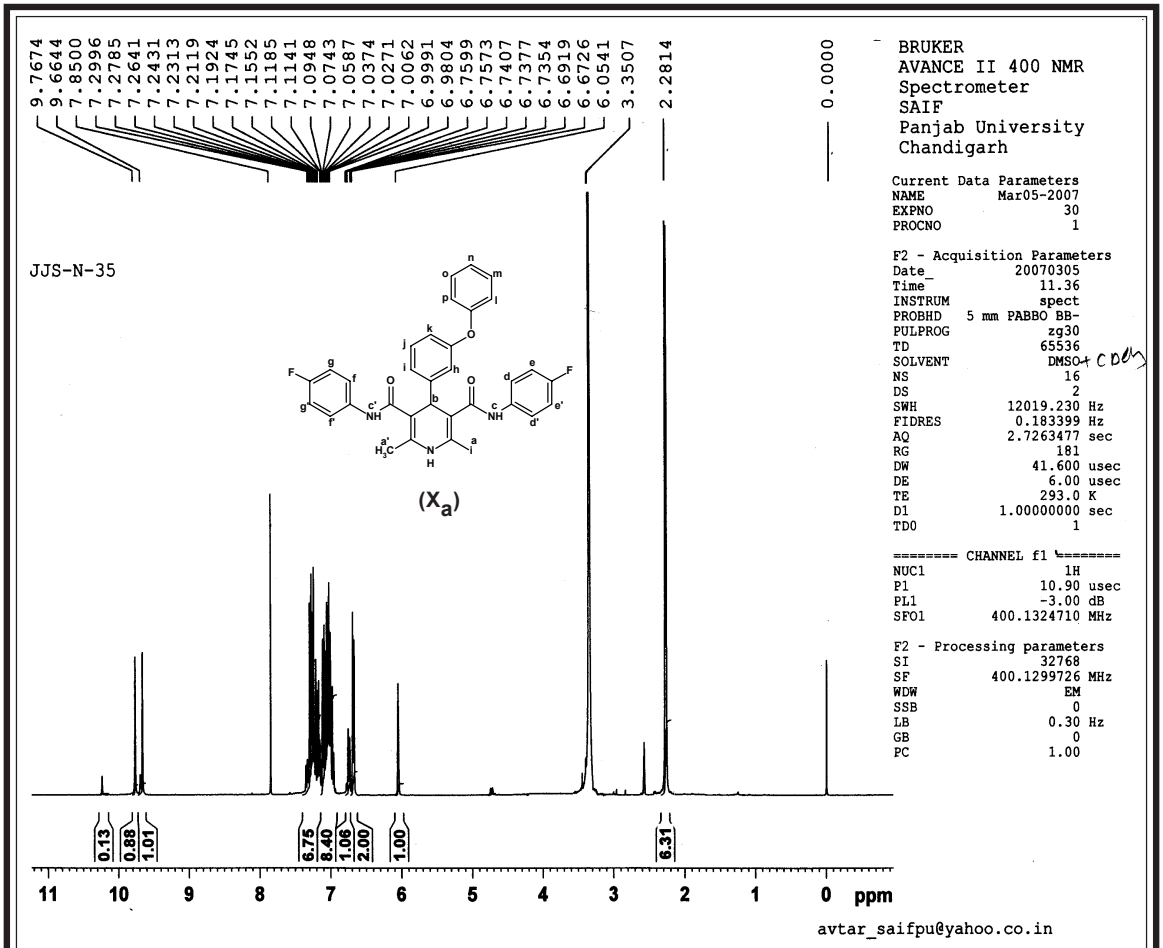
IR SPECTRAL STUDY OF 2,6-DIMETHYL-3,5-N,N'-*p*-*p*'-DIMETHYL-DIPHENYL CARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-DIHYDROPYRIDINE (X_i).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2918.4	2975 - 2850	96
	C-H (sym. str., m)	2845.1	2900 - 2800	96
	C-H (asym. def., m)	1448.5	1470 - 1435	96
	C-H (sym. def., m)	1323.2	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3032.2	3080 - 3010	97
	C=C & C-C (str., v)	1550.8	1600 - 1450	97
	C-H (i.p. def., m)	1095.6	1150 - 1050	97
	C-H (o.o.p. def., m)	794.7	825 - 800	97
	C-N (str., v)	1323.2	1340 - 1250	97
Amine	N-H (str., b)	3390.9-3064.9	3400 - 3000	97
	N-H (def., s,m)	1649.1	1650 - 1550	97
Ketone Amide	C=O (str., s)	1691.6	1740 - 1650	98
Ether	Ph-O-Ph (asym.str.,	1234.4	1275 - 1200	98
	Ph-O-Ph (sym. str., s)	1003.0	1075 - 1000	98
Pera(-4-) substituted	C-H (def., v,s)	860.2	850-800	99

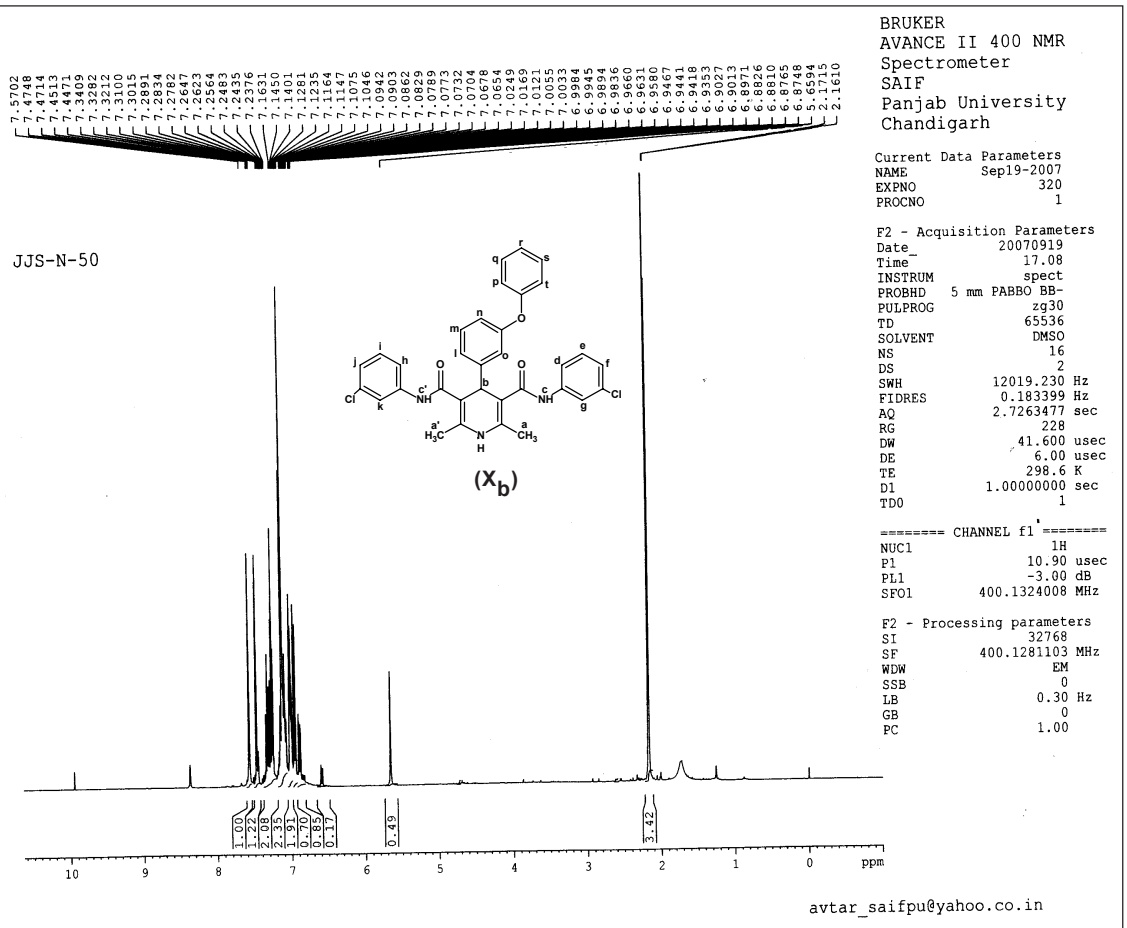
* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

NMR SPECTRAL STUDY OF 2,6-DIMETHYL-3,5-N,N'-*p*-*p*'-DIFLUORO-DIPHENYL CARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-DIHYDRO-PYRIDINE (X_a).



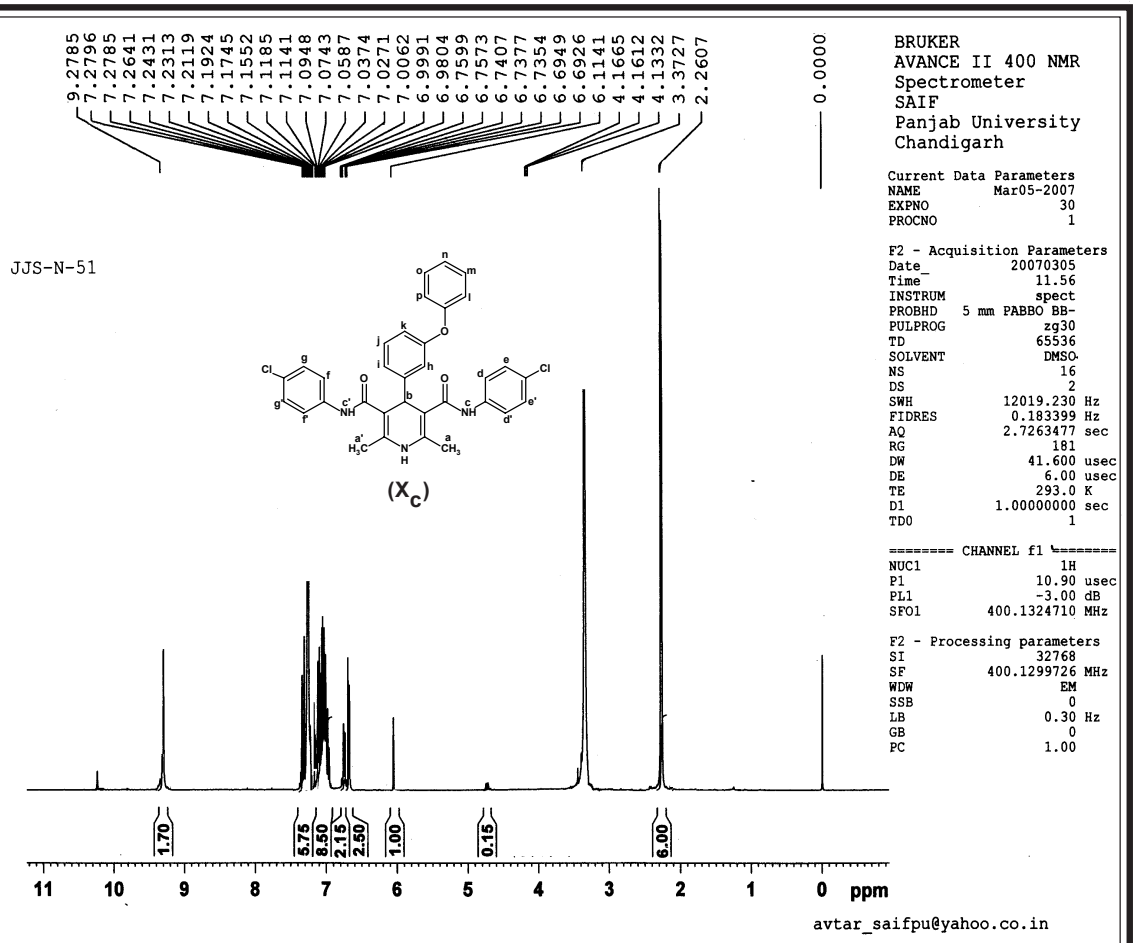
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	2.2814	6H	singlet	- ($C\underline{H}_3$)$_{(a,a')}$
2	6.0541	1H	singlet	- Ar-$\underline{H}_{(b)}$
3	6.6726-6.7407	2H	multiplet	- Ar-$\underline{H}_{(i,k)}$
4	6.7573-6.7599	1H	multiplet	- Ar-$\underline{H}_{(j)}$
5	6.9804-7.1552	8H	multiplet	-Ar-$\underline{H}_{(dd'-gg')}$
6	7.1745-7.2996	6H	multiplet	- Ar-$\underline{H}_{(h,\ l\ -p)}$
7	9.6644-9.7674	2H	doublet	- Ar-$\underline{H}_{(c,c')}$
8	3.3507	-	-	-DMSO-d_6
9	7.8500	-	-	-$CDCl_3$

NMR SPECTRAL STUDY OF 2,6-DIMETHYL-3,5-N,N'-*m*-*m*'-DICHLORO-DI PHENYL CARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-DIHYDRO-PYRIDINE (X_b).



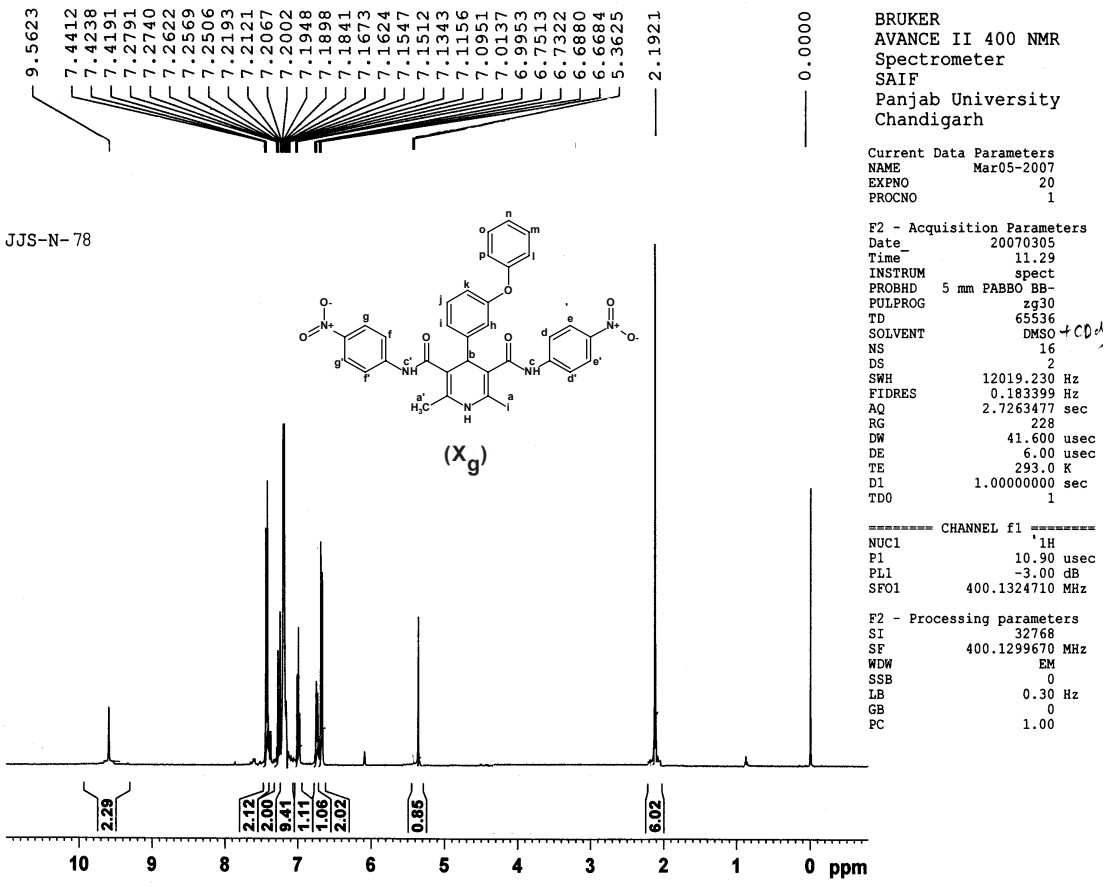
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	2.1610	6H	singlet	- ($C\underline{H}_3$)(a,a')
2	5.6594	1H	singlet	- Ar-$\underline{H}$(b)
3	6.8810-6.9027	1H	multiplet	-Ar-$\underline{H}$(r)
4	6.9353-6.9660	1H	multiplet	-Ar-$\underline{H}$(m)
5	6.9836-7.0249	4H	multiplet	-Ar-$\underline{H}$(h-k)
6	7.0654-7.1631	4H	multiplet	-Ar-$\underline{H}$(d-g)
7	7.2376-7.3409	4H	multiplet	-Ar-$\underline{H}$(o-n)
8	7.4714-7.4748	2H	singlet	-Ar-$\underline{H}$(p,t)
9	7.5702	2H	singlet	-Ar-$\underline{H}$(q,s)

NMR SPECTRAL STUDY OF 2,6-DIMETHYL-3,5-N,N'-*p*-*p*'-DICHLORO-DI PHENYL CARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-DIHYDRO-PYRIDINE (X_c).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	2.2607	6H	singlet	- $(C\underline{H}_3)_{(a,a')}$
2	6.1141	1H	singlet	- Ar-$\underline{H}_{(b)}$
3	6.6926-6.7407	2H	doublet	- Ar-$\underline{H}_{(h,i)}$
4	6.7573-6.7599	2H	multiplet	- Ar-$\underline{H}_{(j,k)}$
5	6.9804-7.1552	8H	multiplet	Ar-$\underline{H}_{(dd'-gg')}$
6	7.1745-7.2796	5H	multiplet	- Ar-$\underline{H}_{(l-p)}$
7	9.2785	2H	singlet	- $N\underline{H}_{(c,c')}$
8	3.3727	-	-	-DMSO-d_6

NMR SPECTRAL STUDY OF 2,6-DIMETHYL-3,5-N,N'-*p*-*p*'-DINITRO-DIPHENYL CARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-HYDRO PYRIDINE (X_g).



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters
NAME Mar05-2007
EXPNO 20
PROCNO 1

F2 - Acquisition Parameters
Date_ 20070305
Time 11.29
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO + CDCl
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DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 228
DW 41.600 usec
DE 6.00 usec
TE 293.0 K
D1 1.00000000 sec
TD0 1

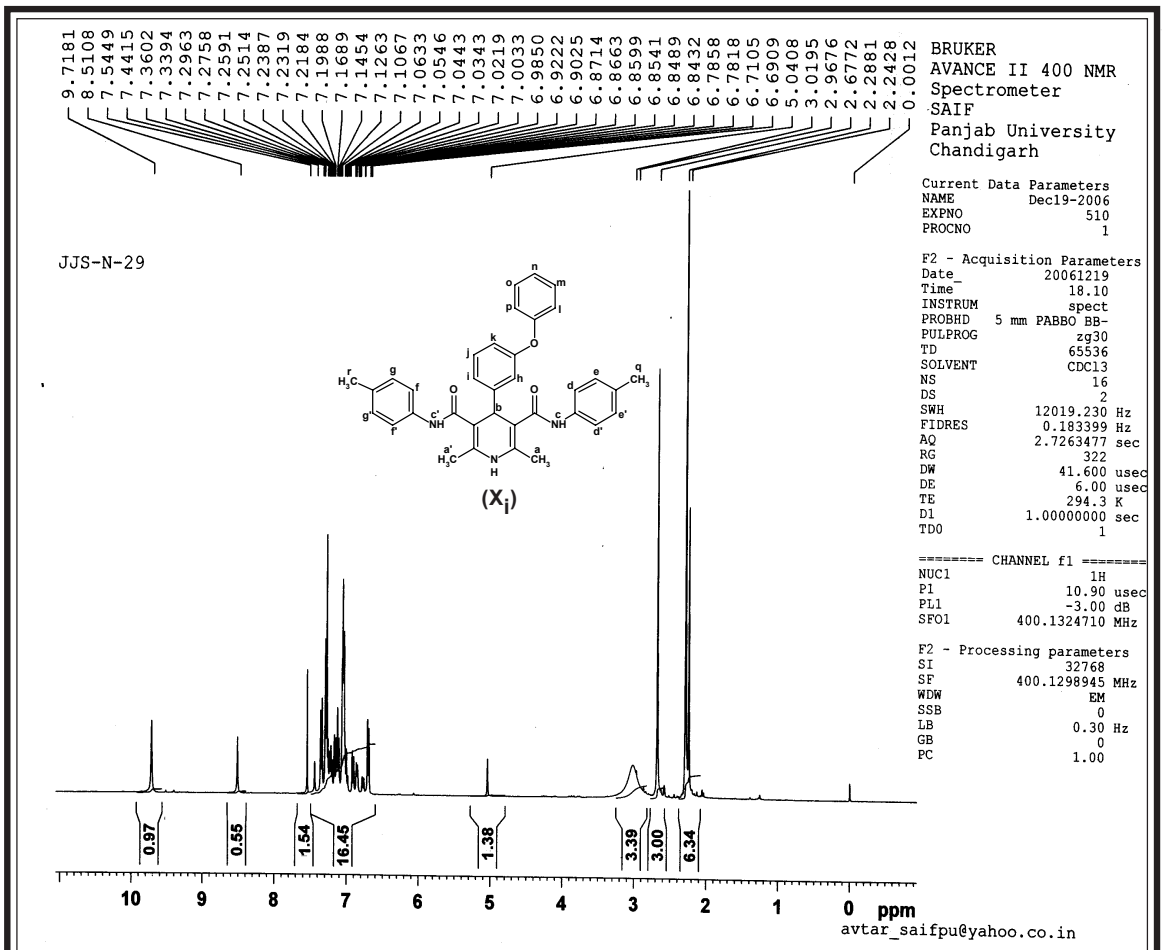
======== CHANNEL f1 ========
NUC1 1H
P1 10.90 usec
PL1 -3.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 32768
SF 400.1299670 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00

avtar_saifpu@yahoo.co.in

Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	2.1921	6H	singlet	- ($C\underline{H}_3$)$_{(a,a')}$
2	5.3625	1H	singlet	- Ar-$\underline{H}_{(b)}$
3	6.6684-6.6880	2H	doublet	- Ar-$\underline{H}_{(i)}$
4	6.7322-6.7513	1H	doublet	- Ar-$\underline{H}_{(j,k)}$
5	6.9953-7.0951	1H	doublet	- Ar-$\underline{H}_{(h)}$
6	7.1156-7.2569	9H	multiplet	Ar-$\underline{H}_{(dd'-gg')}$
7	7.2622-7.2791	2H	multiplet	- Ar-$\underline{H}_{(l-p)}$.
8	7.4191-7.4412	2H	doublet	- Ar-$\underline{H}_{(l-p)}$
9	9.5623	2H	singlet	- N$\underline{H}_{(c,c')}$

NMR SPECTRAL STUDY OF 2,6-DIMETHYL-3,5-N,N'-*p*-*p*'-DIMETHYL- DI-PHENYL CARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-DIHYDRO-PYRIDINE (X_i).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	2.2881	6H	singlet	- ($C\underline{H}_3$)(a,a')
2	2.6772	3H	singlet	- Ar-$\underline{H}$(q)
3	2.9676-3.0195	3H	doublet	- Ar-$\underline{H}$(r)
4	5.0408	1H	singlet	- Ar-$\underline{H}$(b)
5	6.6909-7.4415	16H	multiplet	- Ar-$\underline{H}$(e-p)
6	7.5449	1H	singlet	- Ar-$\underline{H}$(h)
7	9.7181	2H	singlet	- N$\underline{H}$(c,c')

MASS SPECTRAL STUDY OF 2,6-DIMETHYL-3,5-N,N'-*p*-*p*'-DIFLUORO-DIPHENYL CARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-DIHYDROPYRIDINE (X_a).

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Sample Information

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Anaiyzed	: 12/24/2005 5:32:46 PM
Sample Name	: JJSM-12
Sample ID	: JJSM-12
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Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune9.qgt

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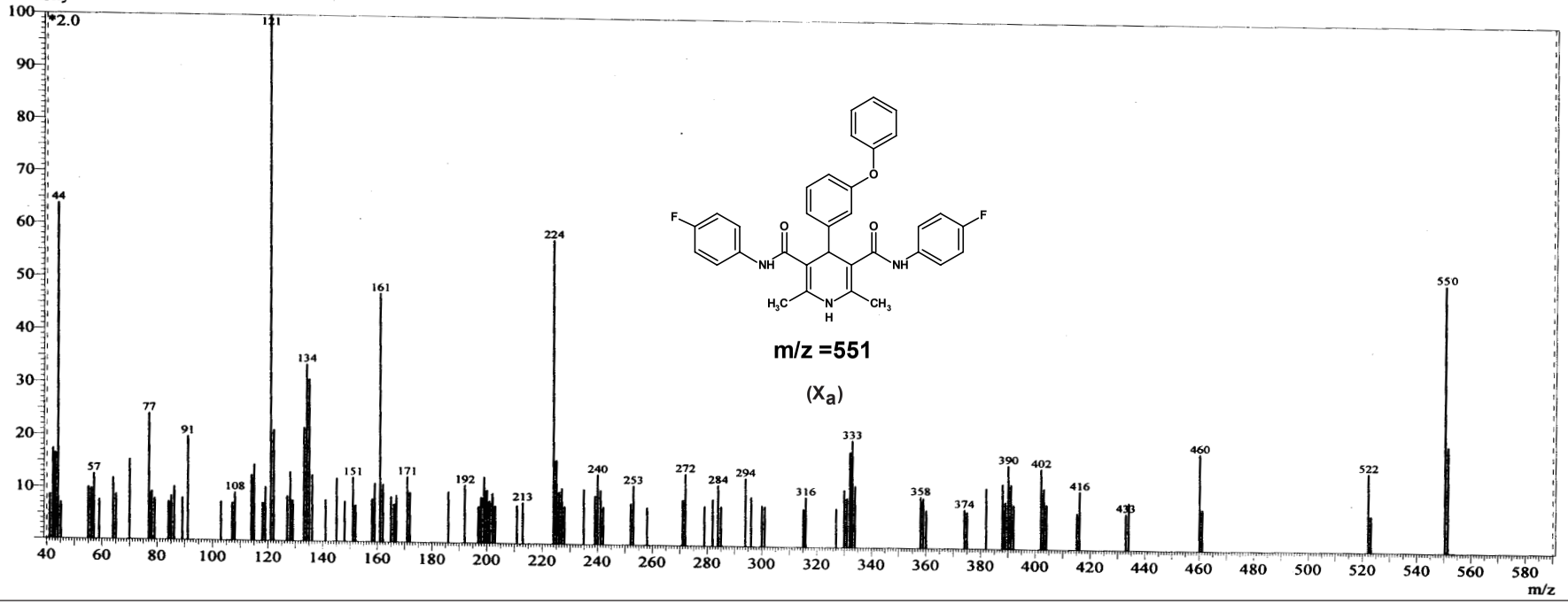
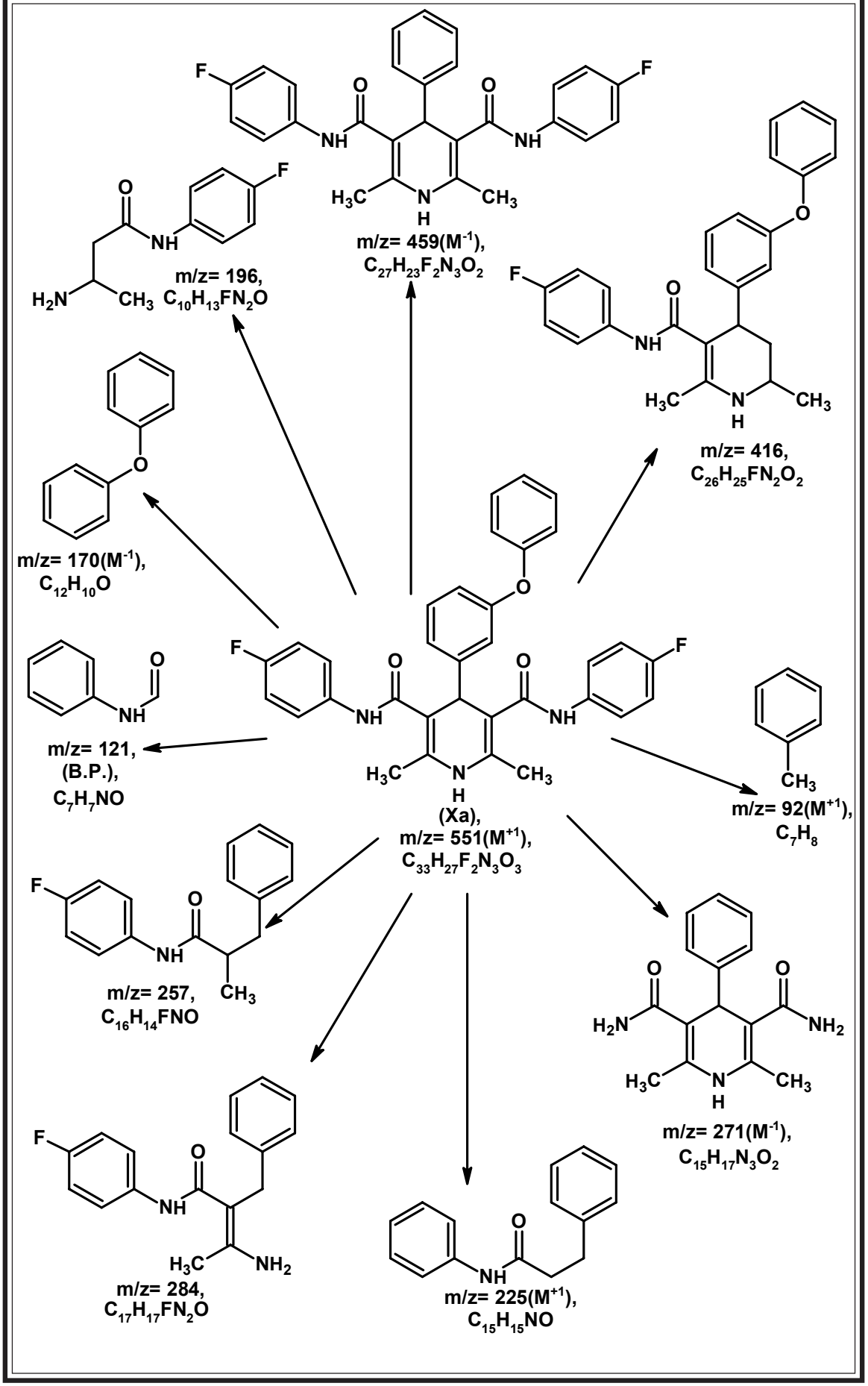
MassPeaks:116 BasePeak:121(29192)
RawMode:Single 9.6(1115)
BG Mode:None
intensity



m/z =551

(X_a)


m/z= 459(M-1),
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m/z= 196,
C10H13FN2O
m/z= 416,
C26H25FN2O2
m/z= 170(M-1),
C12H10O
m/z= 121,
(B.P.),
C7H7NO
(Xa),
m/z= 551(M+1),
C33H27F2N3O3
m/z= 92(M+1),
C7H8
m/z= 257,
C16H14FNO
m/z= 271(M-1),
C15H17N3O2
m/z= 284,
C17H17FN2O
m/z= 225(M+1),
C15H15NO

MASS SPECTRAL STUDY OF 2,6-DIMETHYL-3,5-N,N'-*m*-*m*'-DICHLORO-DIPHENYL CARBOXAMIDO-4-(m-PHENOXY-PHENYL)-1,4-DIHYDROPYRIDINE (X_b).

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Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 9/28/2007 4:32:48 PM
Sample Name	: JJS-MQ-29
Sample ID	: JJS-MQ-29
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Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\170907_01.qgt

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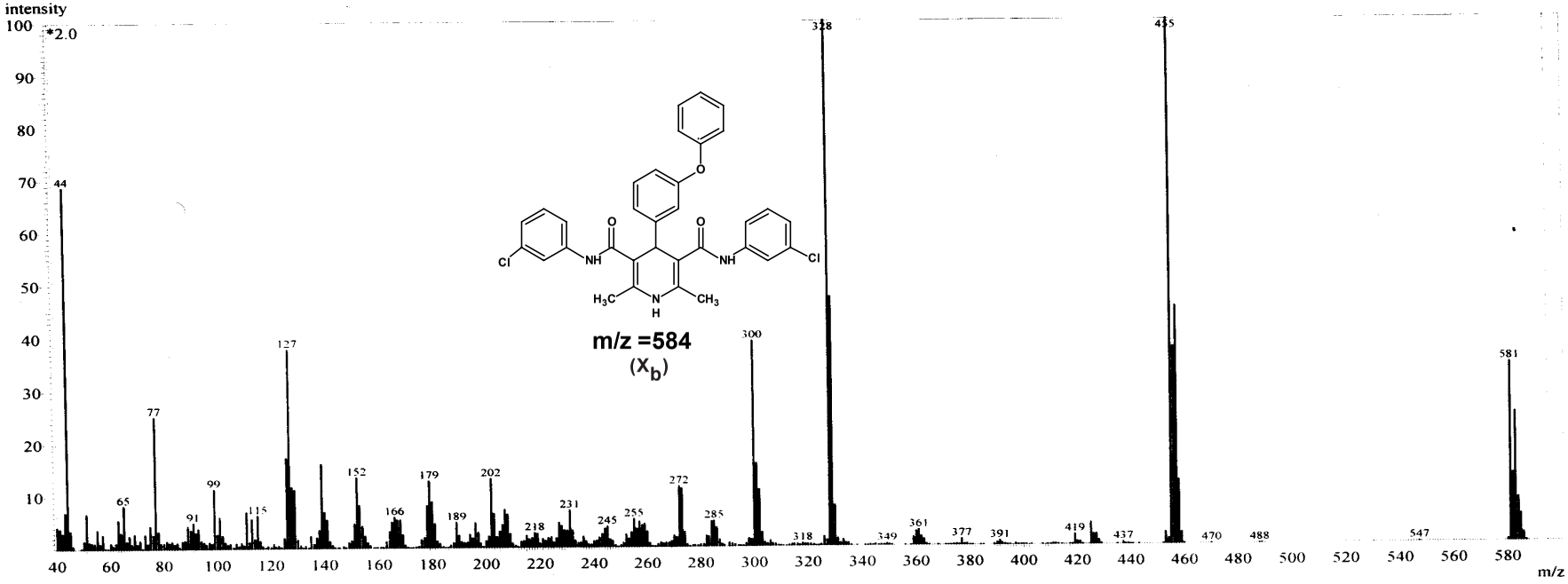
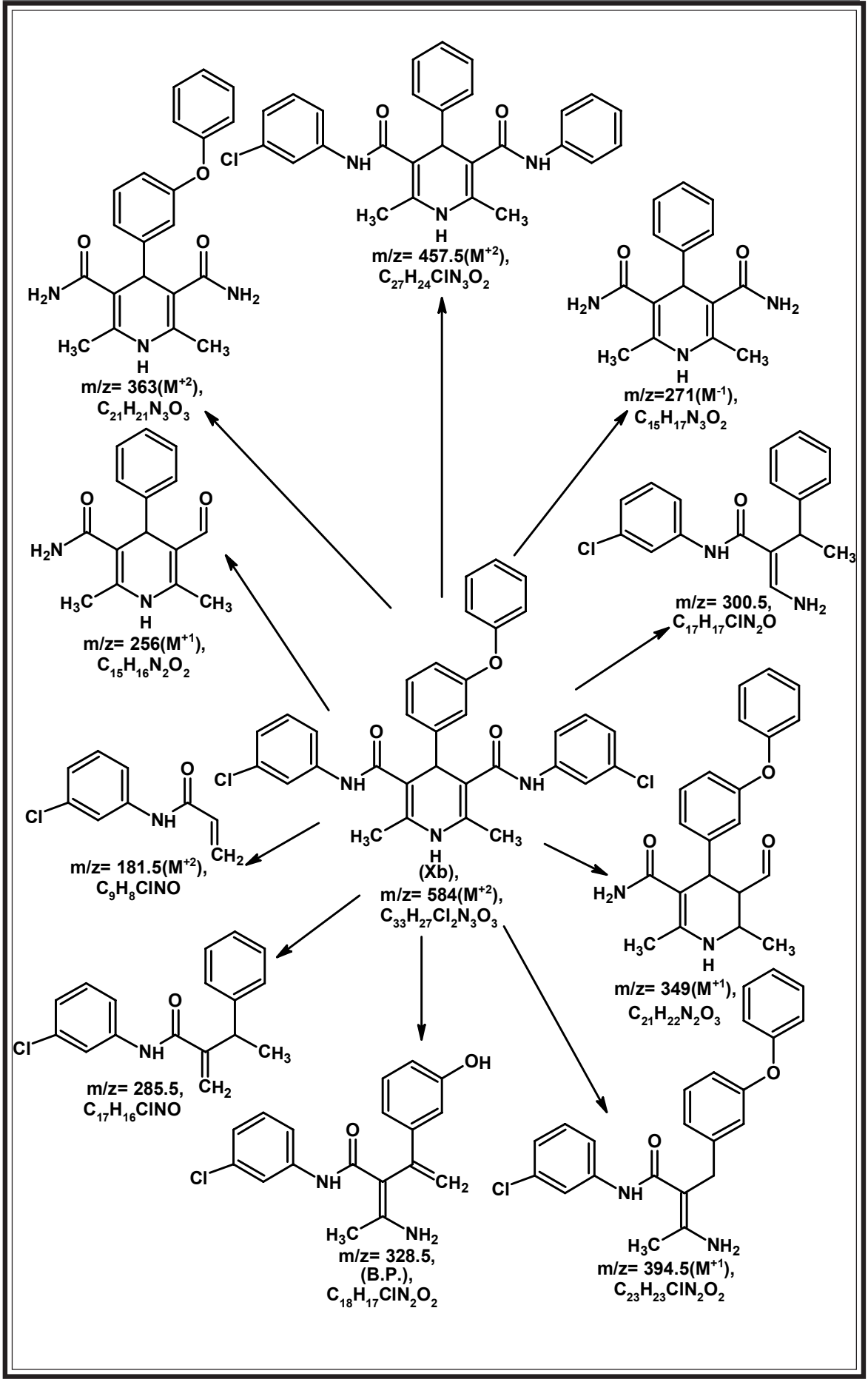
RawMode:Averaged 9.8-12.2(1139-1423)
BG Mode:None
intensity

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m/z= 363(M+2),
C21H21N3O3
m/z=271(M-1),
C15H17N3O2
m/z= 256(M+1),
C15H16N2O2
m/z= 300.5,
C17H17ClN2O
m/z= 181.5(M+2),
C9H8ClNO
(Xb),
m/z= 584(M+2),
C33H27Cl2N3O3
m/z= 349(M+1),
C21H22N2O3
m/z= 285.5,
C17H16ClNO
m/z= 328.5,
(B.P.),
C18H17ClN2O2
m/z= 394.5(M+1),
C23H23ClN2O2

MASS SPECTRAL STUDY OF 2,6-DIMETHYL-3,5-N,N'-*p*-*p*'-DICHLORO-DIPHENYL CARBOXAMIDO-4-(*m*-PHENOXY PHENYL)-1,4-DIHYDROPYRIDINE (X_c).

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Sample Information

Analyzed by	: PANKAJ KACHHADIA
Analyzed	: 10/16/2006 10:52:35 AM
Sample Name	: JJS-M-51
Sample ID	: JJS-M-51
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Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune12.qgt

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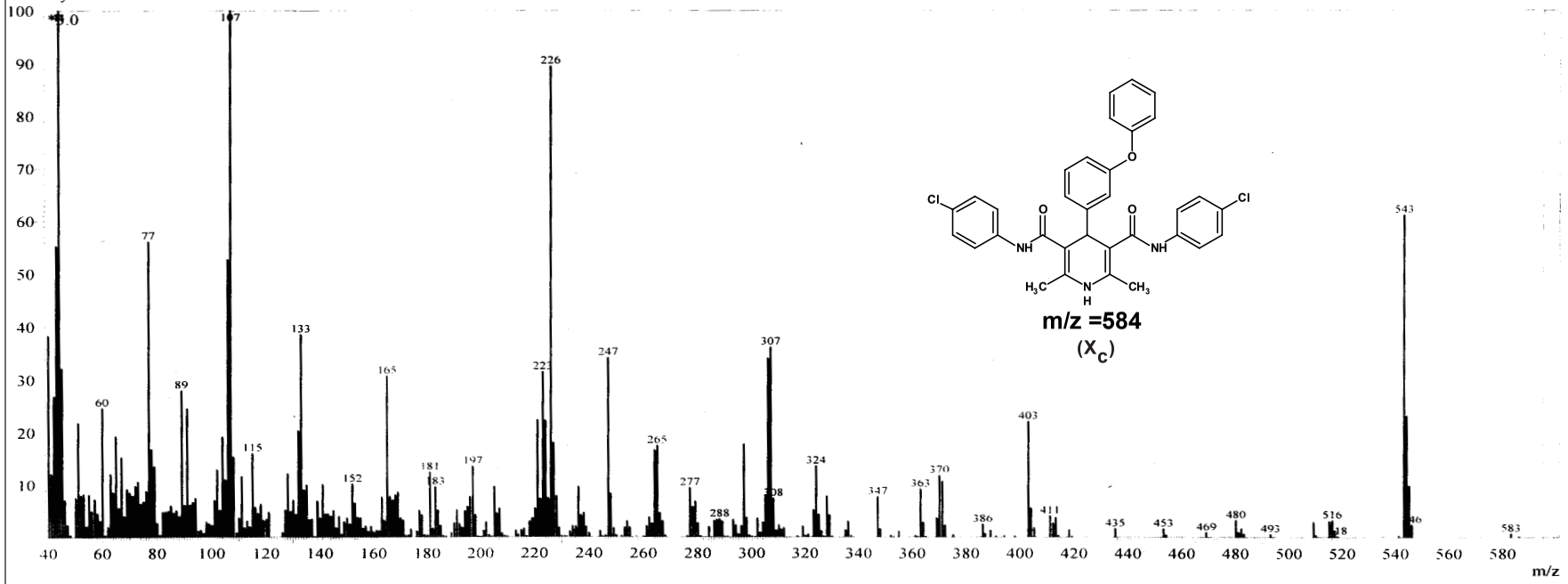
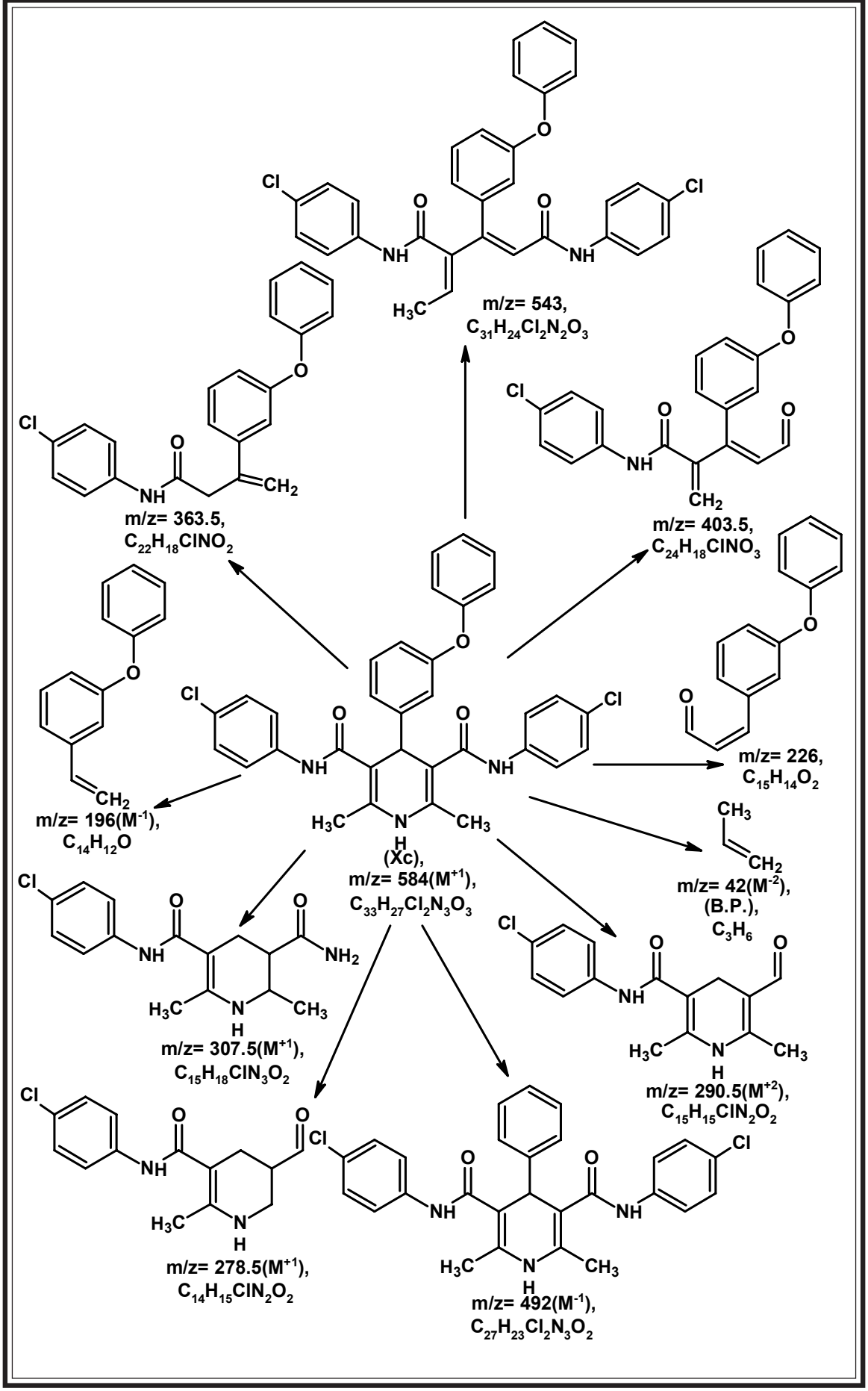
intensity



m/z =584
(X_c)


m/z= 543,
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m/z= 363.5,
$C_{22}H_{18}ClNO_2$
m/z= 403.5,
$C_{24}H_{18}ClNO_3$
m/z= 226,
$C_{15}H_{14}O_2$
m/z= 196(M^{-1}),
$C_{14}H_{12}O$
(Xc),
m/z= 584(M^{+1}),
$C_{33}H_{27}Cl_2N_3O_3$
m/z= 42(M^{-2}),
(B.P.),
C_3H_6
m/z= 307.5(M^{+1}),
$C_{15}H_{18}ClN_3O_2$
m/z= 290.5(M^{+2}),
$C_{15}H_{15}ClN_2O_2$
m/z= 278.5(M^{+1}),
$C_{14}H_{15}ClN_2O_2$
m/z= 492(M^{-1}),
$C_{27}H_{23}Cl_2N_3O_2$

MASS SPECTRAL STUDY OF 2,6-DIMETHYL-3,5-N,N'-*p*-*p*'-DIMETHYL-DIPHENYL CARBOXAMIDO-4-(*m*-PHENOXY PHENYL)-1,4-DIHYDROPYRIDINE (X_i).

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Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 9/23/2006 3:08:04 PM
Sample Name	: JJS-M-46
Sample ID	: JJS-M-46
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Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune12.qgt

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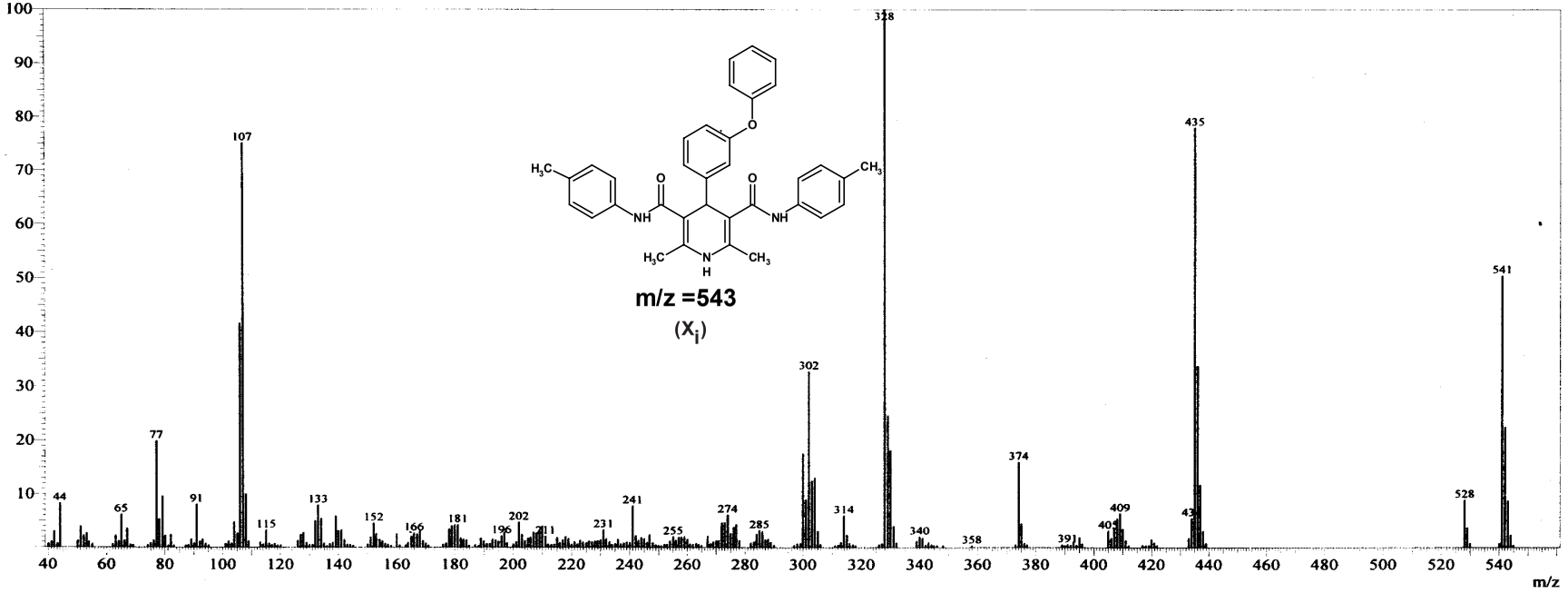
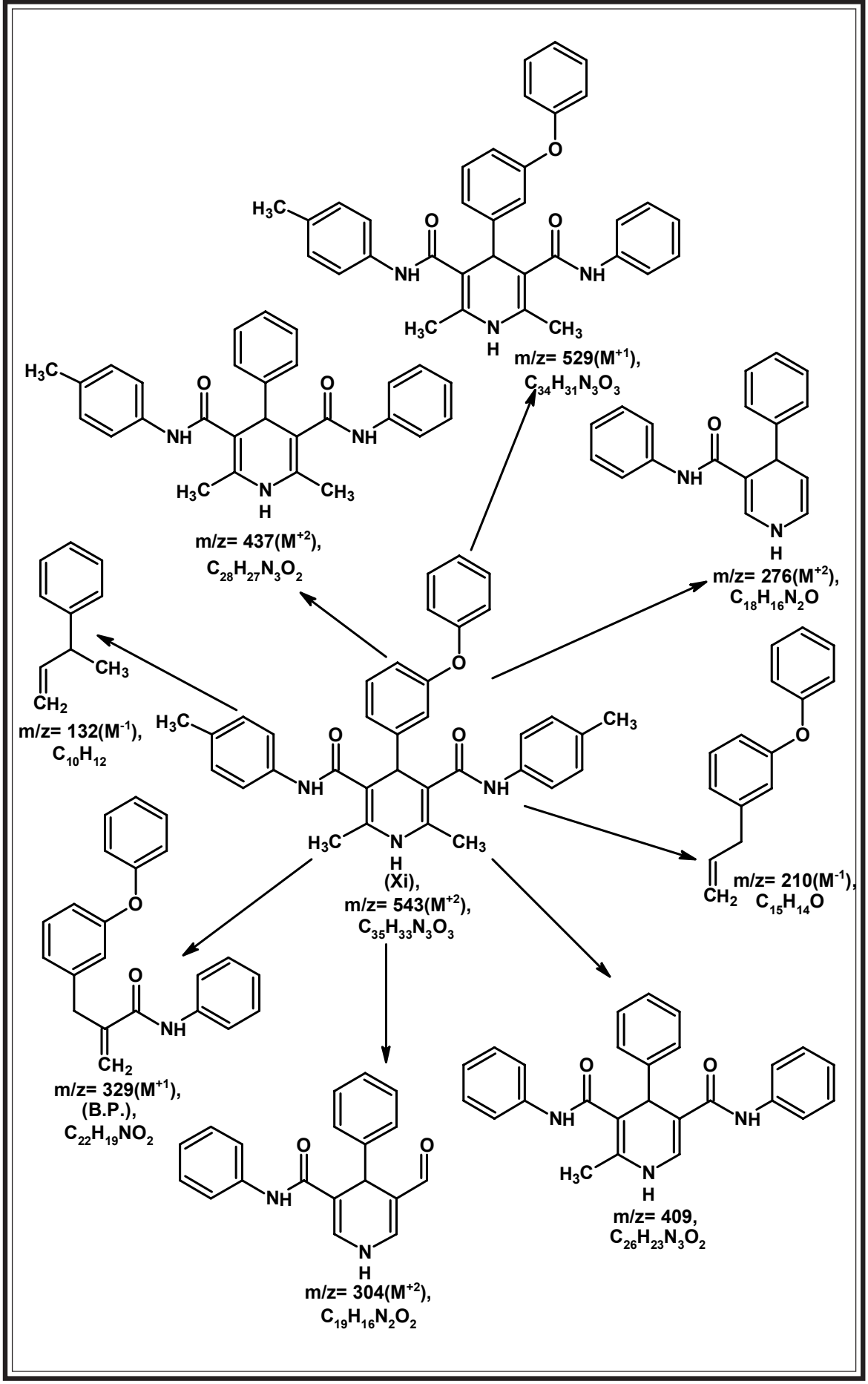
RawMode:Single 10.6(1234)
BG Mode:None
intensity

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C34H31N3O3
m/z= 437(M+2),
C28H27N3O2
m/z= 276(M+2),
C18H16N2O
m/z= 132(M-1),
C10H12
(Xi),
m/z= 543(M+2),
C35H33N3O3
m/z= 210(M-1),
C15H14O
m/z= 329(M+1),
(B.P.),
C22H19NO2
m/z= 304(M+2),
C19H16N2O2
m/z= 409,
C26H23N3O2

TABLE NO. 10B : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2,6-DIMETHYL-3,5-N,N'-SUBSTITUTED-DIPHENYL CARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-DIHYDROPYRIDINES (X_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) S. pyogens MTCC- 442					S. aureus MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
X_a	4-F	-	9	10	12	14	-	9	11	14	16
X_b	3-Cl	-	8	9	11	13	-	9	11	13	15
X_c	4-Cl	-	9	10	11	13	-	8	9	11	13
X_d	3-Cl-4-F	-	8	9	10	12	-	8	8	10	13
X_e	3, 4-$(Cl)_2$	-	8	9	10	12	-	8	9	11	14
X_f	3-NO_2	-	9	10	12	14	-	8	10	12	15
X_g	4-NO_2	-	10	12	14	16	-	9	11	13	15
X_h	2,4-$(NO_2)_2$	-	10	11	13	17	-	10	12	14	17
X_i	4-CH_3	-	9	10	12	14	-	11	13	15	18
X_j	2,3-$(CH_3)_2$	-	9	10	11	14	-	8	10	13	17

Comparative activity of (X_{a-j}) with known choosen standard drugs

Standard drug	Antibacterial activity										
										x_i	$x_{a,h}$ $x_{i,j}$
Amoxicilin	12	14	15	16	18	10	12	14	15	16
Chloramphenicol	14	15	18	19	24	14	17	20	21	24
Sparfloxacin	14	22	24	26	28	24	26	27	28	32
Levofloxacin	18	21	22	27	29	20	24	26	27	35

N.B.(-): No Activity

TABLE NO.10C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2,6-DIMETHYL-3,5-N,N'-SUBSTITUTED-DIPHENYL CARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-DIHYDROPYRIDINES (X_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.)									
		B. Subtillis MTCC- 441					E.coli MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
X_a	4-F	-	9	10	11	13	-	8	10	12	14
X_b	3-Cl	-	7	9	10	12	-	7	9	11	12
X_c	4-Cl	-	9	11	12	14	-	9	11	14	19
X_d	3-Cl-4-F	-	10	11	12	15	-	8	10	13	18
X_e	3, 4-$(Cl)_2$	-	10	11	13	16	-	9	9	11	17
X_f	3-NO_2	-	9	10	12	14	-	8	10	12	14
X_g	4-NO_2	-	8	10	11	13	-	7	8	10	12
X_h	2,4-$(NO_2)_2$	-	8	9	11	13	-	6	8	10	11
X_i	4-CH_3	-	9	9	10	12	-	6	7	8	10
X_j	2,3-$(CH_3)_2$	-	10	11	12	14	-	7	7	11	13
Comparative activity of (X_{a-j}) with known choosen standard drugs											
Standard drug		Antibacterial activity									
Amoxicilin		12	15	16	18	19	11	14	16	18	20
Chloramphenicol		18	22	24	26	27	17	20	23	25	26
Sparfloxacin		22	24	25	26	29	20	22	25	26	28
Levofloxacin		24	26	28	29	31	23	25	26	29	30

N.B.(-): No Activity

TABLE NO. 10D : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2,6-DIMETHYL-3,5-N,N'-SUBSTITUTED-DIPHENYL CARBOXAMIDO-4-(*m*-PHENOXY-PHENYL)-1,4-DIHYDROPYRIDINES (X_{a-j}). (Different Inhibition Concentration in µg/ml).

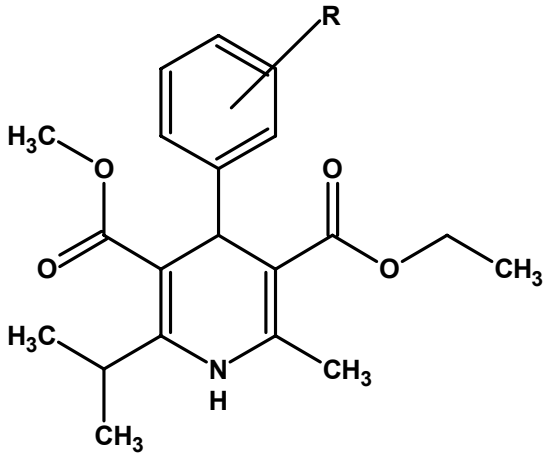
Compd No.	R	Antifungal activity (Zones of inhibition in m.m.)									
		C. albicans MTCC- 227					A. niger MTCC- 282				
		5	25	50	100	250	5	25	50	100	250
X_a	4-F	-	8	10	11	13	-	7	8	10	12
X_b	3-Cl	-	8	10	11	14	-	8	8	9	11
X_c	4-Cl	-	7	8	9	11	-	6	7	9	10
X_d	3-Cl-4-F	-	6	9	10	12	-	8	9	10	11
X_e	3, 4-$(Cl)_2$	-	6	10	11	13	-	8	10	11	14
X_f	3-NO_2	-	7	8	9	11	-	9	9	11	13
X_g	4-NO_2	-	8	8	9	11	-	7	8	10	12
X_h	2,4-$(NO_2)_2$	-	5	7	8	10	-	9	10	12	14
X_i	4-CH_3	-	5	8	10	12	-	9	11	13	15
X_j	2,3-$(CH_3)_2$	-	6	8	10	11	-	7	8	9	10
Comparative activity of (X_{a-j}) with known choosen standard drugs											
Standard drug		Antifungal activity									
Griseofulvin		16	18	21	23	25	17	19	21	22	23
Fluconazole		14	16	18	21	22	15	17	18	20	21

N.B.(-): No Activity

SECTION-II

PREPARATION AND BIOLOGICAL EVALUATION OF 6-METHYL-2-ISOPROPYL-4-SUBSTITUTED PHENYL 3-ETHYL-5-METHYL-1,4-DIHYDROPYRIDINE-DICARBOXYLATES.

1,4-Dihydro-pyridine derivatives represents one of the most active classes of compounds possessing wide spectrum of biodynamic activities[289-304]. In order to have potent therapeutic agents, the synthesis of **6-Methyl-2-isopropyl-4-substituted phenyl 3-ethyl-5-methyl-1,4-di hydropyridine-dicarboxylates (XIa-j)** have been undertaken by the condensation of **ethyl-3-amino but-2-enoate** and **methyl-2-substituted- benzylidene-4-methyl-3-oxo-pentanoates.**



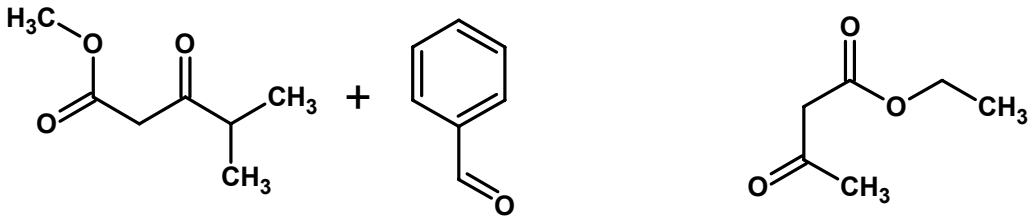
(XIa-j)

R=Substituted phenyl

The constitution of the products **(XIa-j)** have been delineated by **elemental analyses**, **IR, PMR** and **Mass** spectral data.

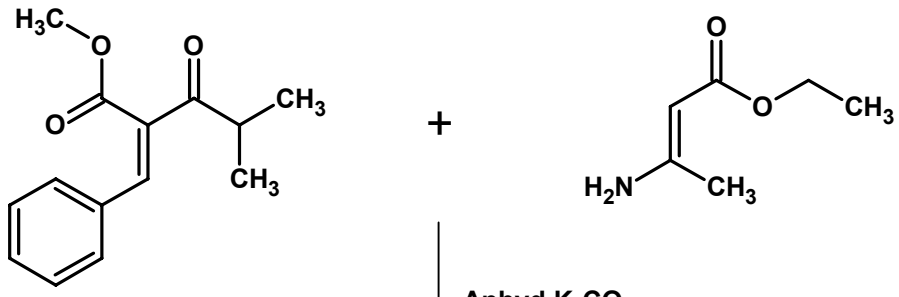
The products **(XIa-j)** were assayed for their ***in vitro*** biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** **,** ***S. aureus MTCC-96*** **and** ***B. subtillis MTCC-441*** **(Gram positive) and** ***E. coli MTCC-443*** **(Gram negative)** bacterial strains and antifungal activity towards **Aspergillus niger MTCC-282 and Candida albicans MTCC-227** at different concentrations i.e.: 0(control) , 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds**(XIa-j)** were compared with standard drugs,viz., **Amoxicillin, Chloramphenicol, Sparfloxacin, Levofloxacin**(antibacterial)**, Griseofluvin, Fluconazole** (antifungal)**.**

REACTION SCHEME



Piperidine

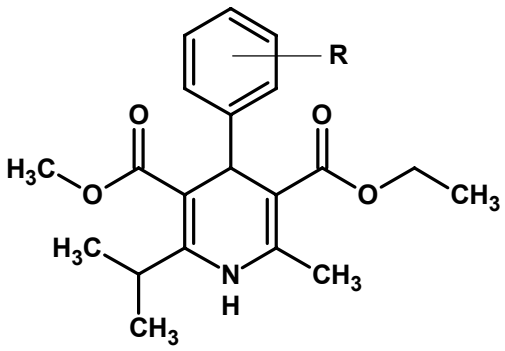
Aq.NH_3



(11a-j)
R=substituted phenyl

Anhyd.K_2CO_3

△



(XIa-j)
R=substituted phenyl

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 6-METHYL-2-ISO-PROPYL-4-SUBSTITUTED PHENYL 3-ETHYL-5-METHYL-1,4-DI HYDROPYRIDINE-DICARBOXYLATES.

(A) Preparation of Ethyl(2z)-2-(*m*-nitro benzylidene)-4-methyl-3-oxopentanoate.

A mixture of ethyl 4-methyl-3-oxopentanoate (1.58 gm, 0.01 M), m-nitro benzaldehyde (1.51 gm, 0.01 M) in ethanol (20 ml) in the presence of piperidine was stirred at 25-35°C for 10 to 12 hrs. The reaction was monitored by TLC. The reaction mixture was poured in to water, filtered, washed with water, dried and recrystallized from ethanol. Yield : 42%, M.P. : 132°C, (Required : C, 60.64 %; H, 5.45 %; N, 5.05% for $C_{14}H_{15}NO_5$, Found :C, 60.59%; H, 5.41%; N, 5.00%).

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (9.0 :1.0) = 0.53**.**
TLC solvent system R_{f_2} : Methanol : Toluene (1.5 : 8.5) = 0.56.

Similarly, other compounds **(11a-j)** were synthesized. The physical data are recorded in **Table No.11**.

(B) Preparation of Ethyl (2*E*)-3-aminobut-2-enoate.

A mixture of ethyl aceto acetate (1.30gm, 0.01 M), ammonia solution (25%) (2.72 ml, 0.04 mol) in methanol (10ml) in the presence of catalytic amount of acetic acid was stirred for 2 hrs. It got separated into two layers of water and product. The two layers were separated with the help of separatory funnel.The separated layer was Ethyl (2*E*)-3-aminobut-2-enoate. Yield : 58%, M.P.:29°C, (Required:C, 55.80%;H, 8.58%;N,10.84 for $C_6H_{11}NO_2$, Found :C, 55.75%; H, 8.52%; N,10.79%).

(C) Preparation of 6-Methyl-2-isopropyl - 4(*m*-nitro phenyl) 3-ethyl-5-methyl-1,4-di hydropyridine-dicarboxylate (Xla-j) .

A mixture of Ethyl(2z)-2-(*m*-nitrobenzylidene)-4-methyl-3-oxopentanoate. (2.77 gm,0.01 M), Ethyl (2*E*)-3-aminobut-2-enoate.(1.52gm,0.012 M) and Anhydrous potassium carbonate (2.74 gm, 0.02 M) in dimethyl formamide (20 ml) was heated under reflux for 8 to10 hrs.The reaction was monitored by TLC. The reaction mixture was allowed to cool at room tempreture. The solid product so obtained was filtered, washed with water, dried and cystallized from dimethyl formamide. Yield : 38%, M.P. :128°C, (Required : C, 61.84 %; H, 6.23 %; N, 7.21 % for $C_{20}H_{24}N_2O_4$, Found : C, 61.78%; H, 6.16%; N, 7.17%).

TLC solvent system R_{f_1} : Ethyl acetate :Hexane (2.5 : 7.5) = 0.48.
TLC solvent system R_{f_2} : Methanol :Chloroform (0.5 : 9.5) = 0.44 **.**

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Similarly, other compounds **(Xla-j)** were synthesized. The physical data are recorded in **Table No.11A**.

(B) Antimicrobial activity of 6-Methyl-2-isopropyl -4-substituted phenyl 3-ethyl-5-methyl-1,4-di hydropyridine-dicarboxylate (Xla-j).

Antimicrobial activity testing was carried out as described in Part-1(A), Section-I, page No. 30-31. The MIC values of test solution are recorded in Table **No. 11B, 11C** and **11D**.

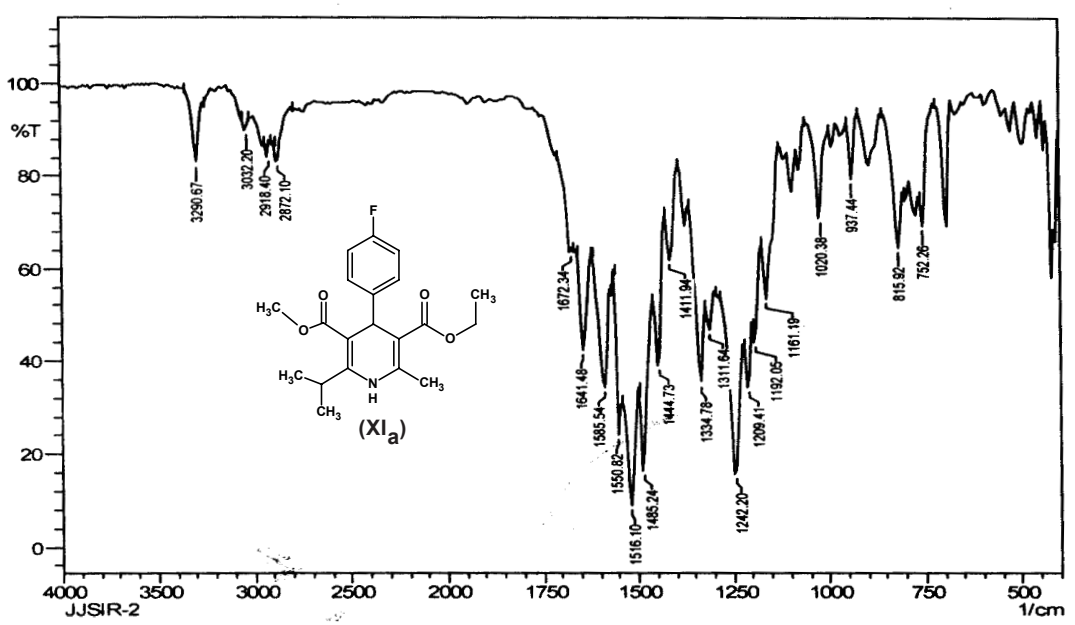
TABLE NO. 11 : PHYSICAL CONSTANTS OF ETHYL(2Z)-2-(SUBTITUTED BENZYLIDENE)-4-METHYL-3-OXOPENTANOATES (11_{a-j}).

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. ^{o}C 5	Yield % 6	R_f Value R_{f_1}	R_{f_2} 7	% of Hydrogen Calcd. / Found 8
11_a	4-F	$C_{14}H_{15}O_3F$	250.0	122^{o}	46	0.53	0.52	6.04 / 6.00
11_b	3-Cl	$C_{14}H_{15}O_3Cl$	266.5	128^{o}	42	0.58	0.53	5.67 / 5.62
11_c	4-Cl	$C_{14}H_{15}O_3Cl$	266.5	132^{o}	38	0.48	0.43	5.67/ 5.61
11_d	4-Br	$C_{14}H_{15}O_3Br$	311.0	108^{o}	52	0.42	0.48	4.86 / 4.81
11_e	3-NO_2	$C_{14}H_{15}NO_5$	277.0	132^{o}	42	0.53	0.56	5.45 / 5.41
11_f	4-NO_2	$C_{14}H_{15}NO_5$	277.0	148^{o}	53	0.48	0.46	5.45 / 5.39
11_g	4-CH_3	$C_{15}H_{18}O_3$	246.0	128^{o}	38	0.52	0.50	7.37 / 7.32
11_h	4-OCH_3	$C_{15}H_{18}O_4$	262.0	123^{o}	43	0.53	0.48	6.92 / 6.88
11_i	2,3-$(CH_3)_2$	$C_{16}H_{20}O_3$	260.0	138^{o}	47	0.47	0.49	7.74 / 7.69
11_j	3-OC_6H_5	$C_{20}H_{20}O_4$	324.0	141^{o}	45	0.44	0.50	6.21/ 6.17

TABLE NO. 11A : PHYSICAL CONSTANTS OF 6-METHYL-2-ISOPROPYL-4-SUBSTITUTED PHENYL-3-ETHYL-5-METHYL-1,4-DI HYDROPYRIDINE-DICARBOXYLATES (XI_{a-j}).

Comp. No.	R	Molecular Formula	M.W.	M.P. °C	Yield %	R_f Value		% of Nitrogen
						R_{f_1}	R_{f_2}	Calcd. / Found
1	2	3	4	5	6	7		8
XI_a	4-F	$C_{20}H_{24}NO_4F$	361.0	136°	37	0.62	0.58	3.88 / 3.84
XI_b	3-Cl	$C_{20}H_{24}NO_4Cl$	377.5	132°	41	0.63	0.53	3.70 / 3.67
XI_c	4-Cl	$C_{20}H_{24}NO_4Cl$	377.5	138°	37	0.58	0.53	3.70 / 3.65
XI_d	4-Br	$C_{20}H_{24}NO_4Br$	422.0	111°	35	0.59	0.56	3.31 / 3.29
XI_e	3-NO_2	$C_{20}H_{24}N_2O_4$	388.0	128°	38	0.48	0.44	7.21 / 7.17
XI_f	4-NO_2	$C_{20}H_{24}N_2O_4$	388.0	124°	36	0.49	0.48	7.21 / 7.16
XI_g	4-CH_3	$C_{21}H_{27}NO_4$	357.0	143°	37	0.46	0.41	3.92 / 3.89
XI_h	4-OCH_3	$C_{21}H_{27}NO_5$	373.0	121°	37	0.52	0.49	3.75 / 3.71
XI_i	2,3-$(CH_3)_2$	$C_{22}H_{29}NO_4$	376.0	148°	38	0.49	0.46	3.72 / 3.65
XI_j	3-OC_6H_5	$C_{26}H_{29}NO_5$	435.0	161°	38	0.60	0.51	3.21 / 3.18

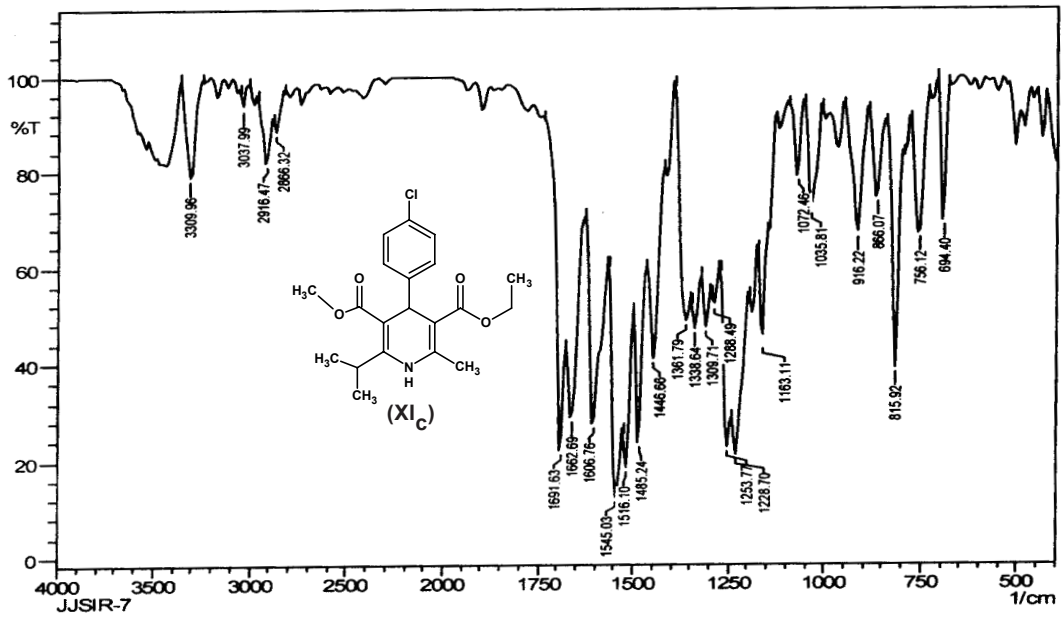
IR SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-*4-(p*-FLUORO PHENYL)-3-ETHYL-5-METHYL-1,4-DI HYDROPYRIDINE DICARBOXYLATE (XI_a).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2918.4	2975 - 2850	96
	C-H (sym. str., m)	2872.1	2900 - 2800	96
	C-H (asym. def., m)	1444.7	1470 - 1435	96
	C-H (sym. def., m)	1334.7	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3032.2	3080 - 3010	97
	C=C & C-C (str., v)	1585.5	1600 - 1450	97
	C-H (i.p. def., m)	1161.1	1150 - 1050	97
	C-H (o.o.p. def., m)	815.9	825 - 800	97
	C-N (str., v)	1311.6	1340 - 1250	97
Pyridine Moiety	N-H (str., m)	3290.5	3400 - 3000	97
	N-H (def., s,m)	1641.4	1650 - 1550	97
Ketone	C=O (str., s)	1672.3	1740 - 1650	98
Ester				
Halogen Subtitution	C-F (str., b)	1411.9-1161.1	1400 - 1080	99
Para(-4-) substitution	C-H (def., v,s)	879.5	800 - 850	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

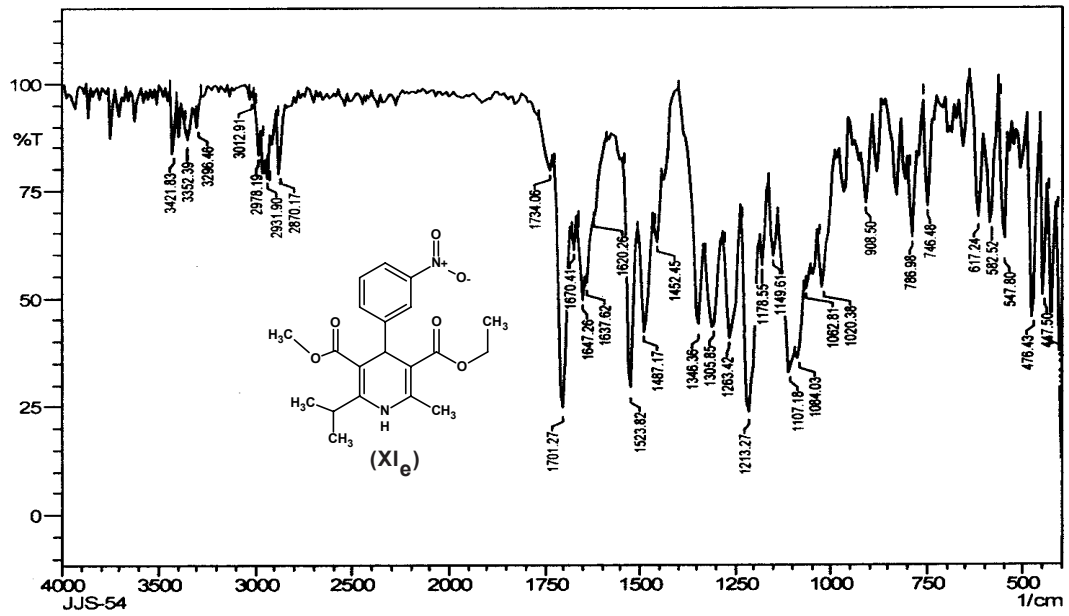
IR SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-4-(*p*-CHLORO PHENYL)-3-ETHYL-5-METHYL-1,4-DI HYDROPYRIDINE-DICARBOXYLATE (XI_C).



Type	Vibration mode C-H (asym. str., m s)	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (sym. str., m)	2916.4	2975 - 2850	96
	C-H (asym. def., m)	2866.3	2900 - 2800	96
	C-H (sym. def., m)	1446.6	1470 - 1435	96
		1361.7	1385 - 1300	96
	C-H (str., v)			
Aromatic and ring skeletal vibration	C=C & C-C (str., v)	3037.9	3080 - 3010	97
	C-H (i.p. def., m)	1545.0	1600 - 1450	97
	C-H (o.o.p. def., m)	1072.4	1150 - 1050	97
	C-N (str., v)	815.9	825 - 800	97
		1309.7	1340 - 1250	97
Pyridine Moiety	N-H (str., m)			
	N-H (def., s,m)	3309.9	3400 - 3000	97
		1606.7	1650 - 1550	97
Ketone Ester	C=O (str., b)	1691.6, 1662.6	1740 - 1650	98
Halogen Subtitution	C-Cl (str., b)	756.1-694.4	800-600	99
Para(-4-) substitution	C-H (def., v,s)	879.5	800 - 850	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

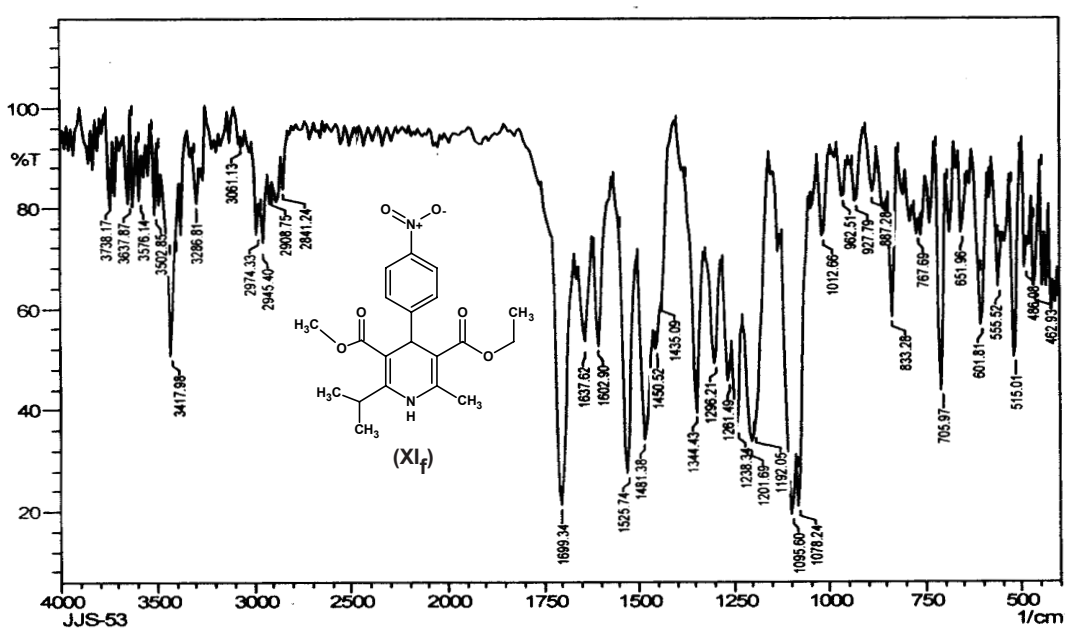
IR SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-4-(*m*-NIRTO PHENYL--3-ETHYL-5-METHYL-1,4-DI HYDROPYRIDINE-DICARBOXYLATE (XI_e).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2931.9	2975 - 2850	96
	C-H (sym. str., m)	2870.1	2900 - 2800	96
	C-H (asym. def., m)	1452.4	1470 - 1435	96
	C-H (sym. def., m)	1348.3	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3012.9	3080 - 3010	97
	C=C & C-C (str., v)	1523.8	1600 - 1450	97
	C-H (i.p. def., m)	1107.1	1150 - 1050	97
	C-H (o.o.p. def., m)	786.9	825 - 800	97
	C-N (str., v)	1305.8	1340 - 1250	97
Pyridine Moiety	N-H (str., b)	3352.9-3286.4	3400 - 3000	97
	N-H (def., s,m)	1620.2	1650 - 1550	97
Ketone Ester	C=O (str., b)	1734.0-1647.2	1740 - 1650	98
Meta(-3-) substitution	C-H (def., v,s)	786.9	880 - 830	99
		746.4	780-730	99
Nitro substitution	C-NO_2(asym.str., s)	1523.8	1570-1500	99
	C-NO_2 (sym. str., s)	1346.3	1370-1300	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

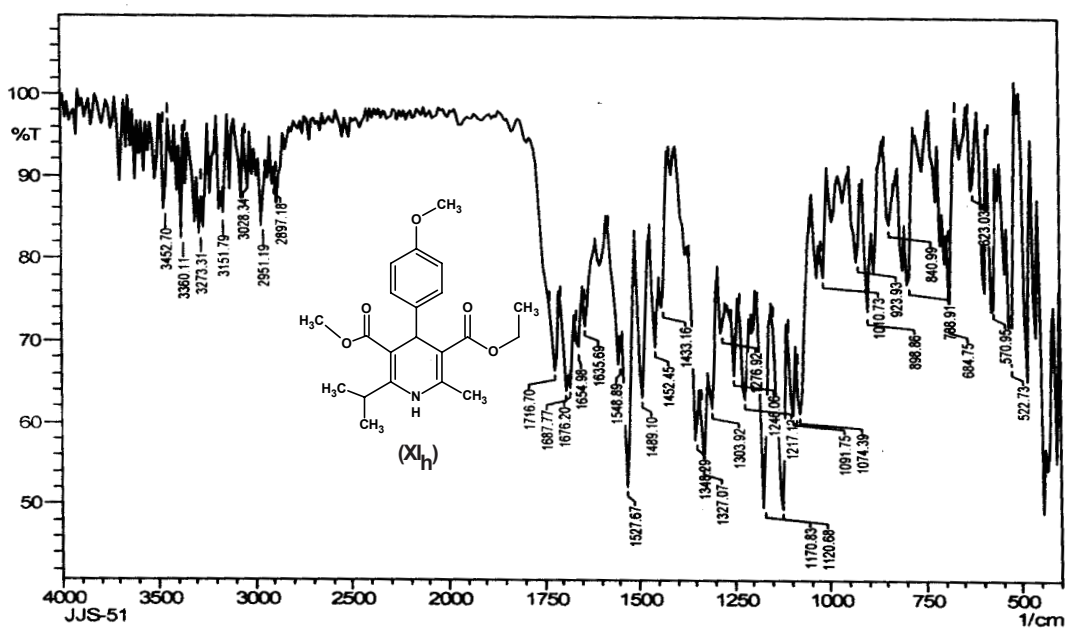
IR SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-*4-(p*-NITRO PHENYL-) -3-ETHYL-5-METHYL-1,4-DI HYDROPYRIDINE-DICARBOXYLATE (XI_f).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2945.4	2975 - 2850	96
	C-H (sym. str., m)	2841.2	2900 - 2800	96
	C-H (asym. def., m)	1450.5	1470 - 1435	96
	C-H (sym. def., m)	1344.4	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3061.1	3080 - 3010	97
	C=C & C-C (str., v)	1602.9	1600 - 1450	97
	C-H (i.p. def., m)	1095.6	1150 - 1050	97
	C-H (o.o.p. def., m)	833.2	825 - 800	97
	C-N (str., v)	1296.2	1340 - 1250	97
Pyridine Moiety	N-H (str., b)	3417.9-3266.6	3400 - 3000	97
	N-H (def.,m)	1637.6	1650 - 1550	97
Ketone Ester	C=O (str., s)	1699.3	1740 - 1650	98
para(-4-) substitution	C-H (def., v,s)	833.2	850 - 800	99
Nitro substitution	C-NO_2(asym.str., s)	1525.7	1570-1500	99
	C-NO_2 (sym. str., s)	1344.3	1370-1300	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

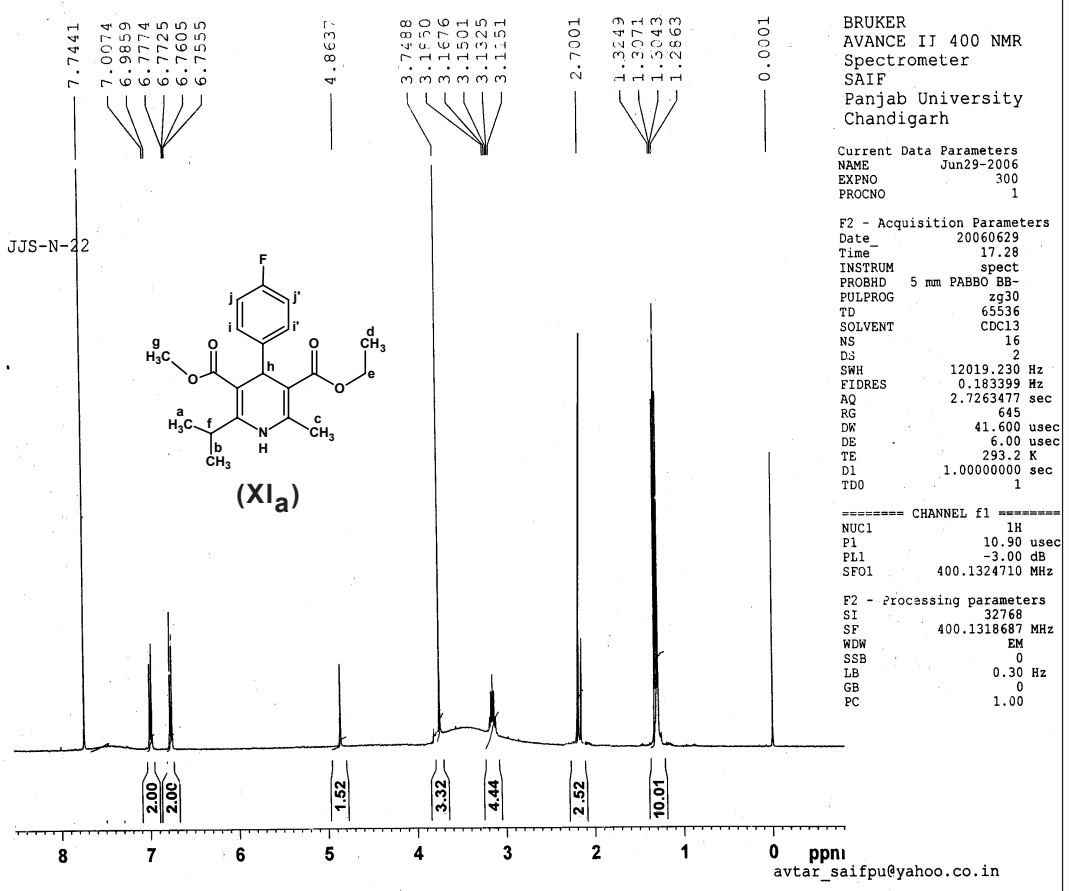
IR SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-*4-(p*-METHOXY PHENYL)-3-ETHYL-5-METHYL-1,4-DI HYDROPYRIDINE-DICARBOXYLATE (XI_h).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2951.1	2975 - 2850	96
	C-H (sym. str., m)	2897.1	2900 - 2800	96
	C-H (asym. def., m)	1452.4	1470 - 1435	96
	C-H (sym. def., m)	1348.3	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H (str., v)	3028.3	3080 - 3010	97
	C=C & C-C (str., v)	1548.8	1600 - 1450	97
	C-H (i.p. def., m)	1120.6	1150 - 1050	97
	C-H (o.o.p. def., m)	840.9	825 - 800	97
	C-N (str., v)	1327.0	1340 - 1250	97
Pyridine Moiety	N-H (str., b)	3360.1-3273.7	3400 - 3000	97
	N-H (def., s,m)	1635.6	1650 - 1550	97
Ketone Ester	C=O (str.,b)	1716.1-1654.9	1740 - 1650	98
Ether	Ph-O-C(asym. str., m)	1217.1	1275-1200	98
	Ph-O-C(sym. str., s)	1074.3	1075-1000	98
Para(-4-) substitution	C-H (def., v, s)	840.9	850 - 800	99

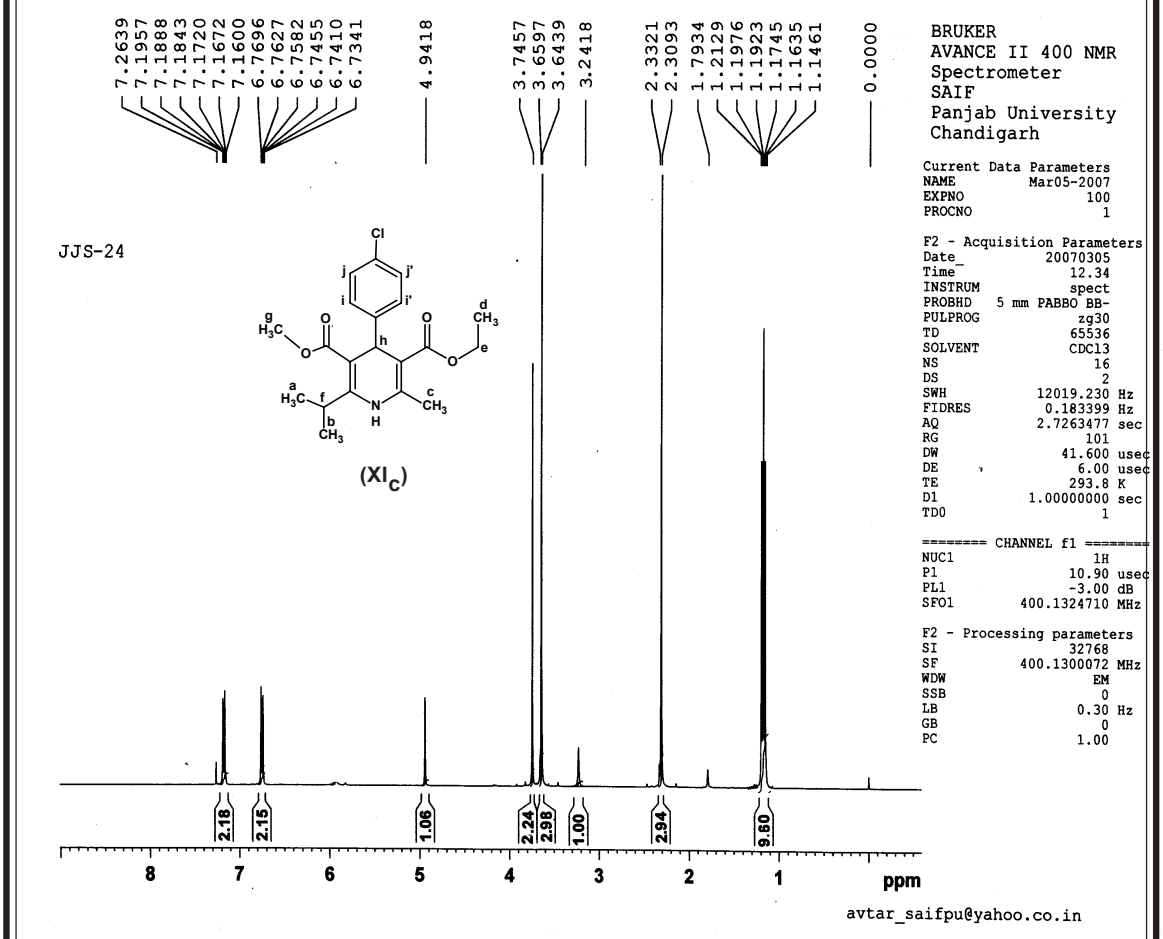
* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

NMR SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-4-*(p*-FLUORO-PHENYL)-3-ETHYL-5-METHYL-1,4-DI HYDROPYRIDINE-CARBOXY-LATE (XI_a).



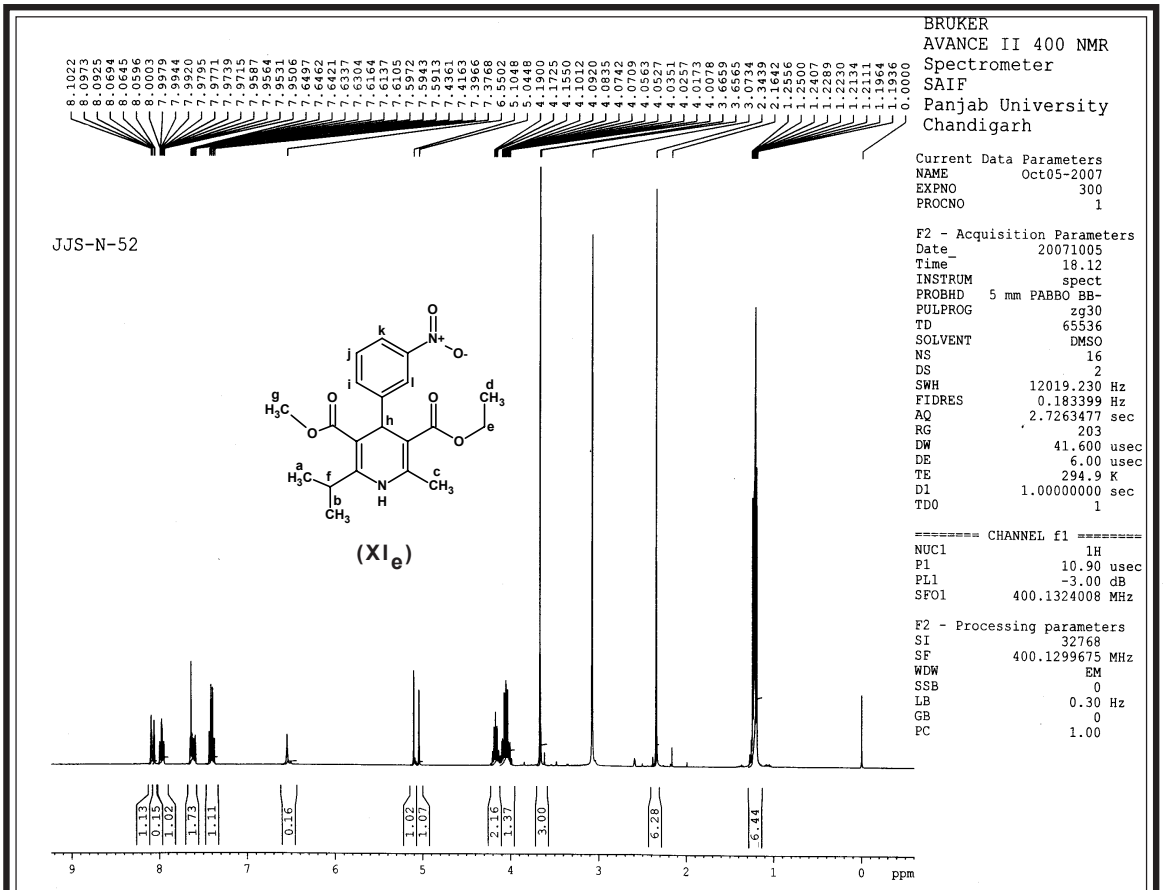
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.2863-1.3249	9H	quatret	- $(C\underline{H}_3)_{(a,b,d)}$
2	2.7001	3H	singlet	- $(C\underline{H}_3)_{(c)}$
3	3.1151-3.1850	3H	multiplet	- $(C\underline{H}_3)_{(e,f)}$
4	3.7488	3H	singlet	- $(C\underline{H}_3)_{(g)}$
5	4.8637	1H	singlet	- Ar-$\underline{H}_{(h)}$
6	6.7555-6.7774	2H	doublet	Ar-$\underline{H}_{(i, i')}$(J=8.76)
7	6.9859-7.0074	2H	doublet	Ar-$\underline{H}_{(j, j')}$(J=8.60)
8	7.7441	-	-	-$CDCl_3$

NMR SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-*4-(p*-CHLORO-PHENYL)-3-ETHYL-5-METHYL-1,4-DI HYDROPYRIDINE-DICARBO-XYLATE (XI_C).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.1461-1.2129	9H	quatret	- ($C\underline{H}_3$)$_{(a,b,d)}$
2	2.3093-2.3321	3H	singlet	- ($C\underline{H}_3$)$_{(c)}$
3	3.2418	1H	singlet	- ($C\underline{H}_3$)$_{(f)}$
4	3.6439-3.6597	3H	singlet	- ($C\underline{H}_3$)$_{(g)}$
5	3.7457	2H	singlet	- Ar-$\underline{H}_{(e)}$
6	4.9418	1H	singlet	- Ar-$\underline{H}_{(h)}$
7	6.7582-6.7341	2H	doublet	Ar-$\underline{H}_{(i, i')}$(J=9.64)
8	7.1600-7.1843	2H	doublet	Ar-$\underline{H}_{(j, j')}$(J=9.73)

NMR SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-*4-(m*-NIRTO PHENYL)-3-ETHYL-5-METHYL-1,4-DI HYDROPYRIDINE-DICARBOXYLATE (XI_e).



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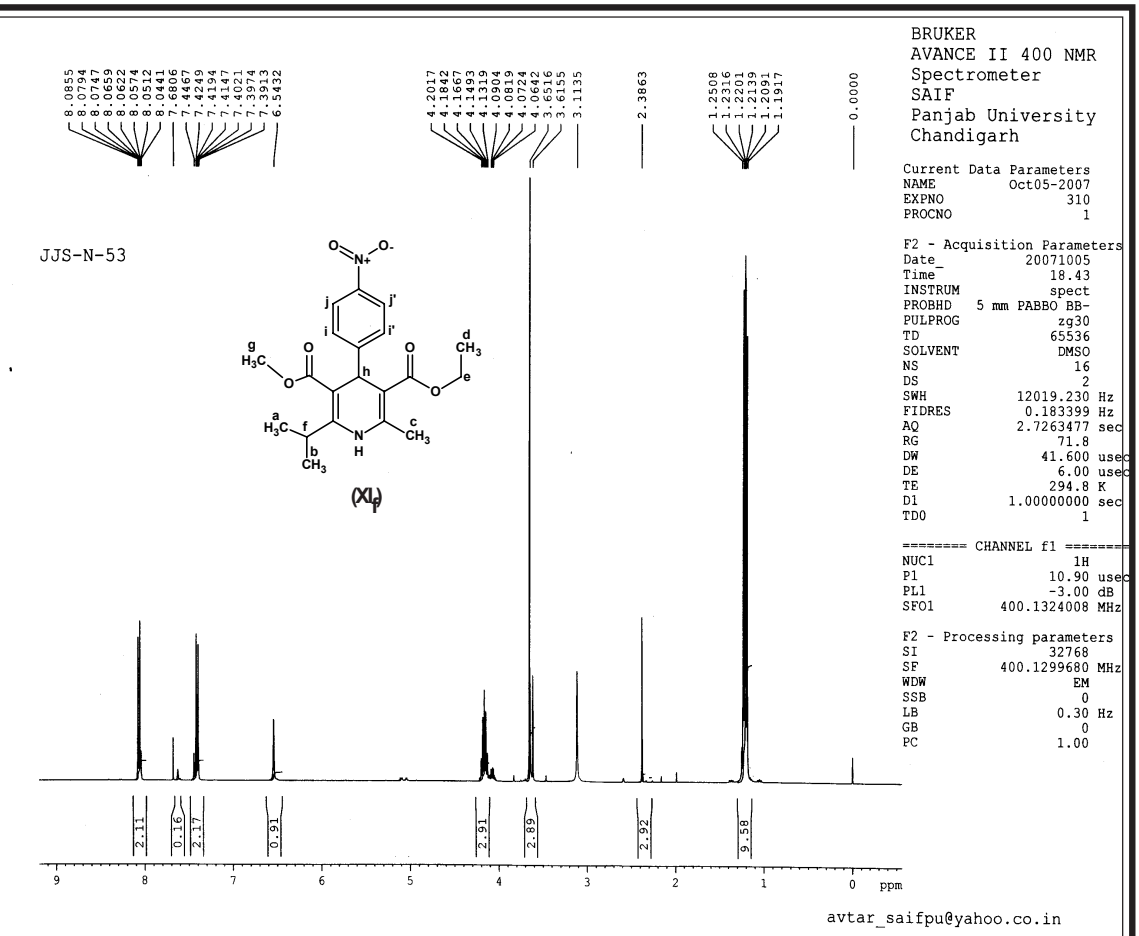
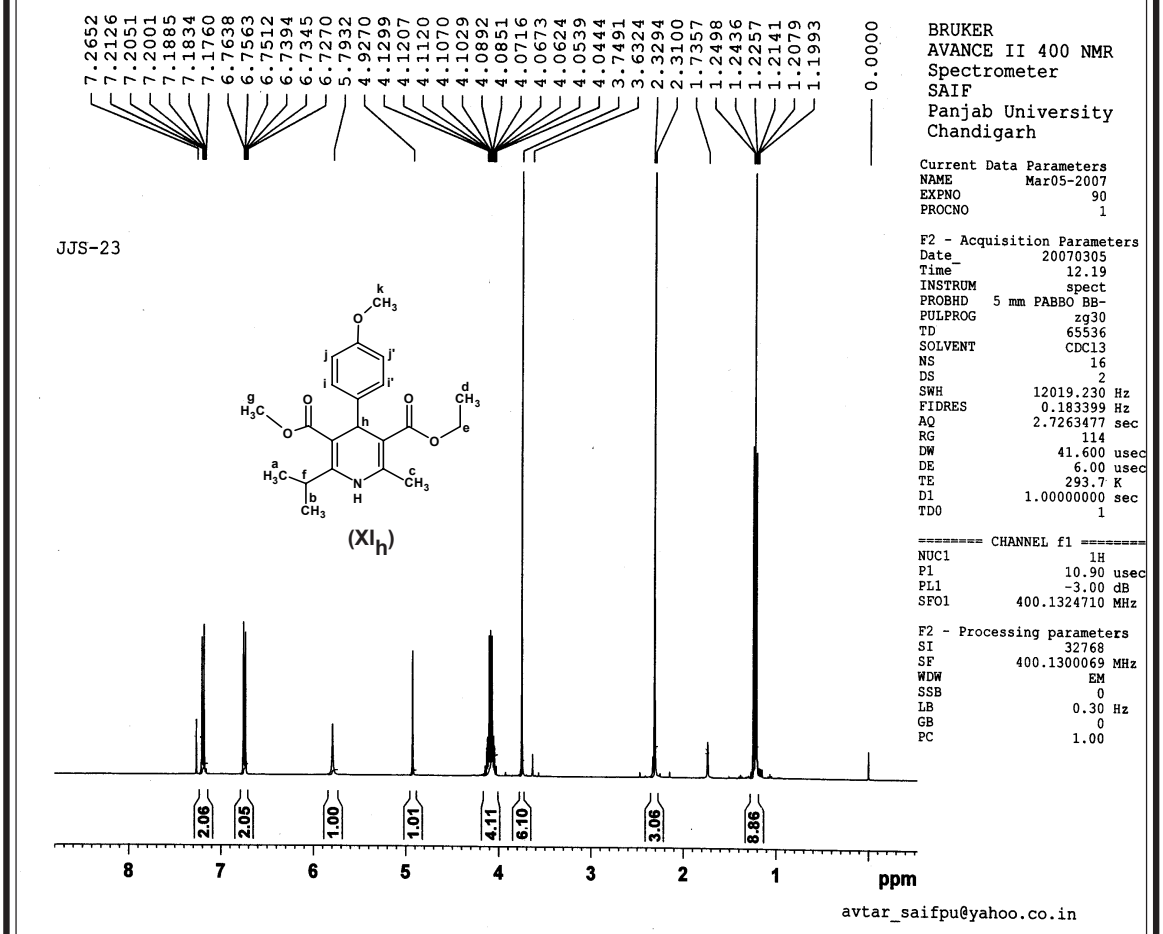
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.1936-1.2556	6H	multiplet	- ($C\underline{H}_3$)$_{(a,b)}$
2	2.3439	6H	singlet	- ($C\underline{H}_3$)$_{(c,d)}$
3	3.6563-3.6659	3H	singlet	- ($C\underline{H}_3$)$_{(g)}$
4	4.0078-4.1012	1H	multiplet	- ($C\underline{H}_3$)$_{(f)}$
5	4.1550-4.1900	2H	multiplet	- Ar-$\underline{H}_{(e)}$
6	5.0448-5.1048	2H	doublett	- Ar-$\underline{H}_{(h)}$
7	7.3768-7.5972	1H	multiplet	- Ar-$\underline{H}_{(j)}$
8	7.61057.6497	1H	multiplet	- Ar-$\underline{H}_{(i)}$
9	7.9531-8.0003	1H	multiplet	- Ar-$\underline{H}_{(k)}$
10	8.0596-8.1022	1H	multiplet	- Ar-$\underline{H}_{(l)}$
11	3.0734	-	-	-DMSO-d_6

NMR SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-*4-(p*-NITRO PHENYL)-3-ETHYL-5-METHYL-1,4-DI HYDROPYRIDINE-DICARBOXYLATE-(XI_f).



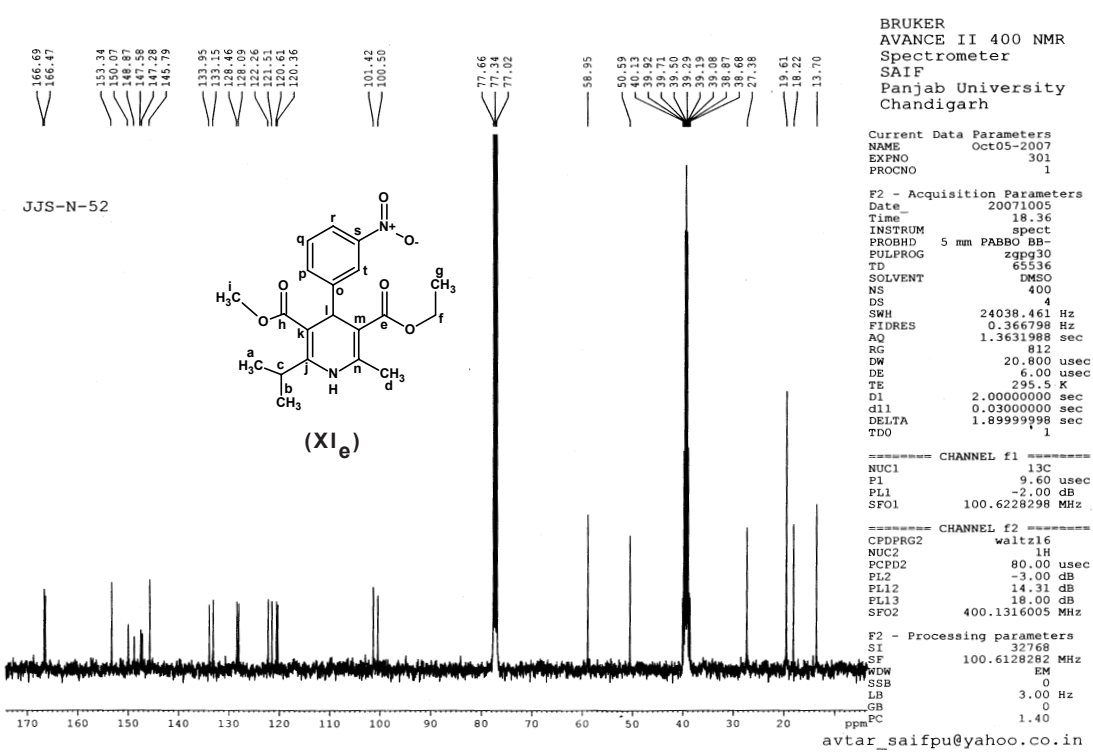
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.1917-1.2508	9H	quatret	- ($C\underline{H}_3$)$_{(a,b,d)}$
2	2.3863	3H	singlet	- ($C\underline{H}_3$)$_{(c)}$
3	3.6155-3.6516	3H	singlet	- ($C\underline{H}_3$)$_{(g)}$
4	4.0642-4.2017	3H	multiplet	- ($C\underline{H}_3$)$_{(e,f)}$
5	6.5432	1H	singlet	- Ar-$\underline{H}_{(h)}$
6	7.3913-7.4147	2H	doublet	Ar-$\underline{H}_{(i, i')}$(J=9.36)
7	8.0622-8.0855	2H	doublet	Ar-$\underline{H}_{(j, j')}$(J=9.32)
8	3.1135	-	-	-DMSO-d_6

NMR SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-*4-(p*-METHOXY-PHENYL)-3-ETHYL-5-METHYL-1,4-DI HYDROPYRIDINE-DICARBOXY-LATE (XI_h).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.1993-1.2498	9H	quatret	- ($C\underline{H}_3$)(a,b,d)
2	2.3100-2.3294	3H	singlet	- ($C\underline{H}_3$)(c)
3	3.7491	6H	singlet	- ($C\underline{H}_3$)(g,k)
4	4.0444-4.1299	3H	multiplet	- ($C\underline{H}_3$)(e,f)
5	4.9270	1H	singlet	- Ar-$\underline{H}$(h)
6	6.7394-6.7638	2H	doublet	Ar-$\underline{H}$(i, i')(J=9.76)
7	7.1760-7.2001	2H	doublet	Ar-$\underline{H}$(j, j')(J=9.64)
8	7.2652	-	-	-$CDCl_3$

^{13}CNMR SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-*4-(m*-NIRTO-PHENYL)-3-ETHYL-5-METHYL-1,4-DIHYDROPYRIDINE-DICARBO-XYLATE (XI_e).



Serial No.	Signal Position (δ ppm)	Inference
1	13.70	- $\underline{C}H_{3(g)}$
2	18.22	- $\underline{C}H_{3(d)}$
3	19.61	- $\underline{C}H_{3(a,b)}$
4	27.38	-$\underline{C}H_{(c)}$
5	50.59	-$\underline{C}H_{3(i)}$
6	58.95	-$\underline{C}H_{2(f)}$
7	100.5-153.3	- Ar-$\underline{C}$(j to t)
8	1663.4-166.6	-$\underline{C}$ =O$_{(e,h)}$

MASS SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-*4*-(*p*-FLUORO PHENYL)- 3-ETHYL-5-METHYL-1,4-DI HYDRO-PYRIDINE-DICARBOXYLATE (XI_a).

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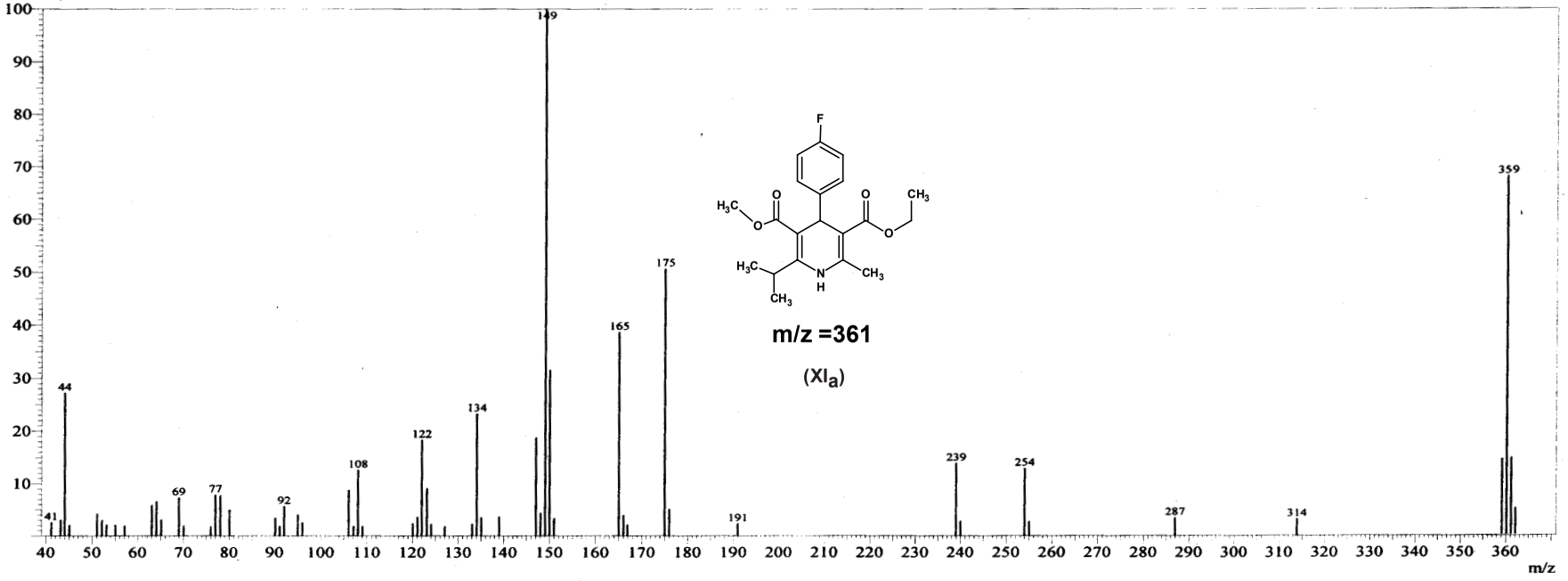
Sample Information

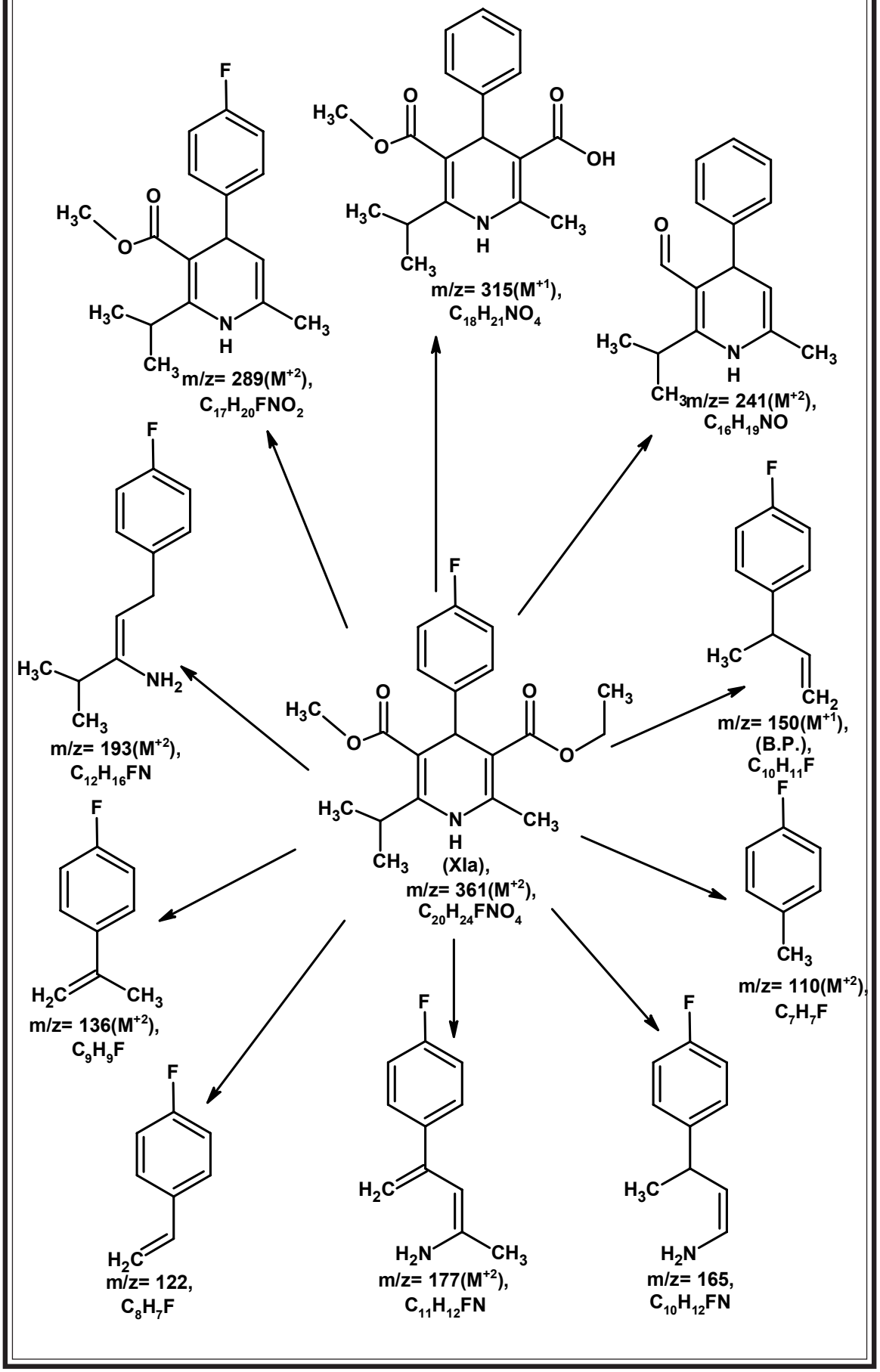
Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 10/5/2006 2:48:07 PM
Sample Name : JJS-M-41
Sample ID : JJS-M-41
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-M-41.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:4.7(Scan#:526)
MassPeaks:58 BasePeak:149(60188)
RawMode:Single 4.7(526)
BG Mode:None
intensity



m/z =361

(XI_a)


m/z= 315(M+1),
C18H21NO4
m/z= 289(M+2),
C17H20FNO2
m/z= 241(M+2),
C16H19NO
m/z= 193(M+2),
C12H16FN
m/z= 150(M+1),
(B.P.),
C10H11F
(XIa),
m/z= 361(M+2),
C20H24FNO4
m/z= 136(M+2),
C9H9F
m/z= 110(M+2),
C7H7F
m/z= 122,
C8H7F
m/z= 177(M+2),
C11H12FN
m/z= 165,
C10H12FN

MASS SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-*4*-(*p*-CHLORO-PHENYL) 3-ETHYL-5-METHYL-1,4-DI HYDRO-PYRIDINE-DICARBOXYLATE (XI_C).

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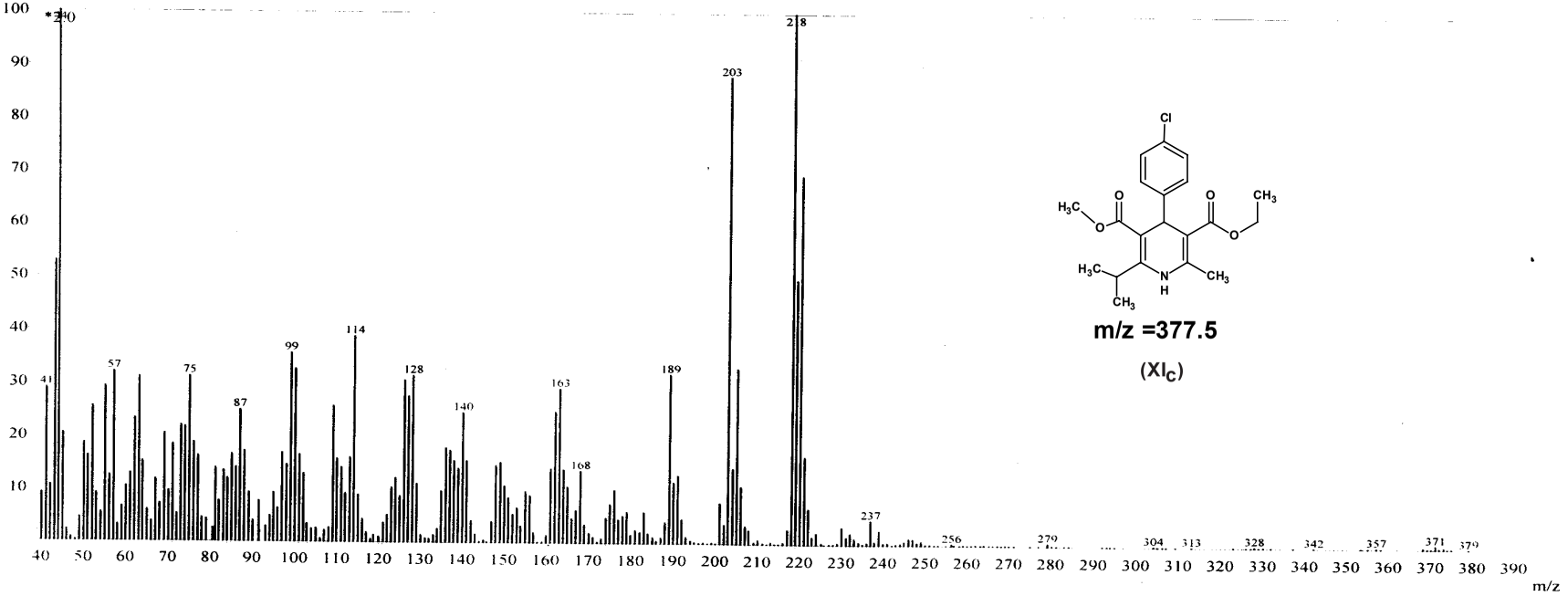
Sample Information

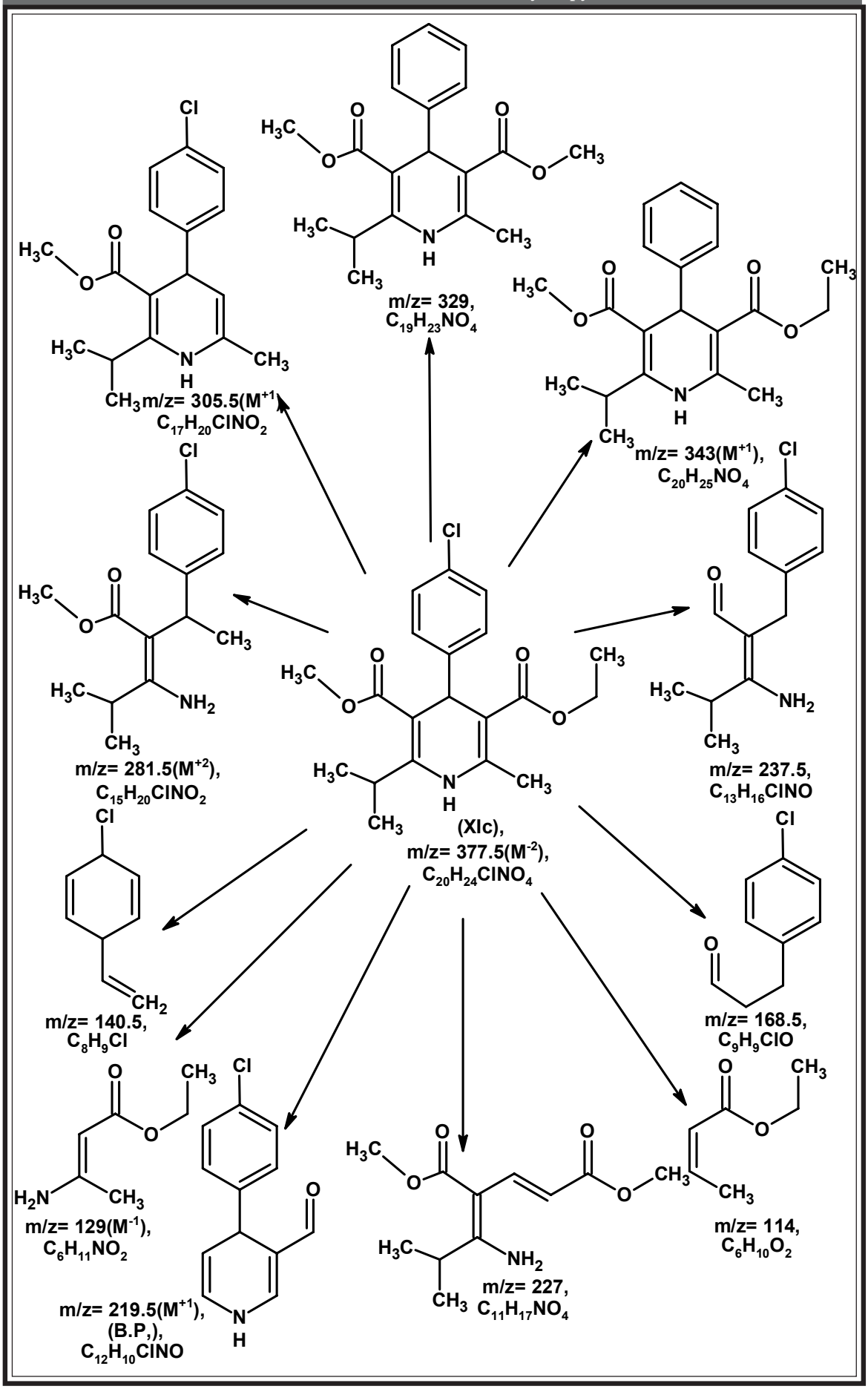
Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 9/28/2007 3:22:01 PM
Sample Name : JJS-MQ-28
Sample ID : JJS-MQ-28
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-28.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\170907_01.qgt

Line#:1 R.Time:10.3(Scan#:1195)
MassPeaks:270 BasePeak:218(163271)
RawMode:Averaged 4.7-18.1(530-2132)
BG Mode:None
intensity



m/z =377.5

(XI_C)


m/z= 329,
C19H23NO4
m/z= 305.5(M+1)
C17H20ClNO2
m/z= 343(M+1),
C20H25NO4
m/z= 281.5(M+2),
C15H20ClNO2
m/z= 237.5,
C13H16ClNO
(XIc),
m/z= 377.5(M-2),
C20H24ClNO4
m/z= 140.5,
C8H9Cl
m/z= 168.5,
C9H9ClO
m/z= 129(M-1),
C6H11NO2
m/z= 219.5(M+1),
(B.P,),
C12H10ClNO
m/z= 227,
C11H17NO4
m/z= 114,
C6H10O2

MASS SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-*4-(m*-NIRTO PHENYL) 3-ETHYL-5-METHYL-1,4-DI HYDRO-PYRIDINE -DICARBOXYLATE (XI_e).

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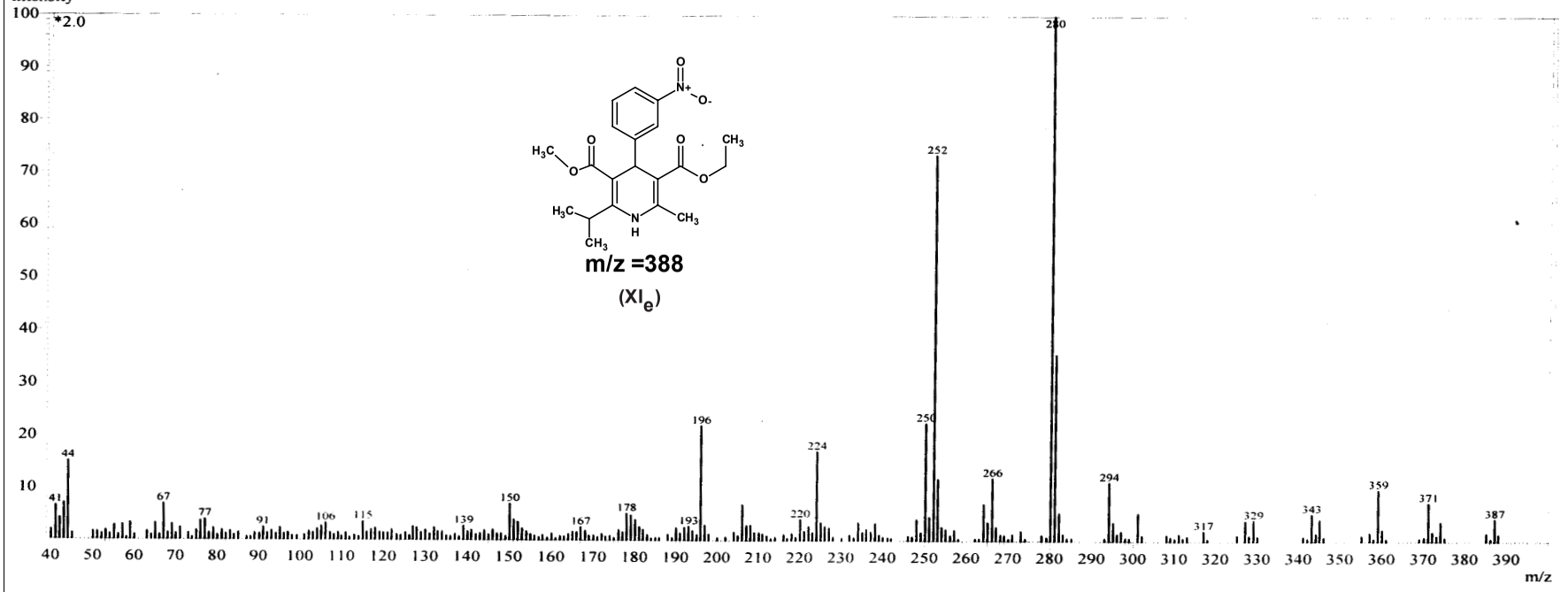
Sample Information

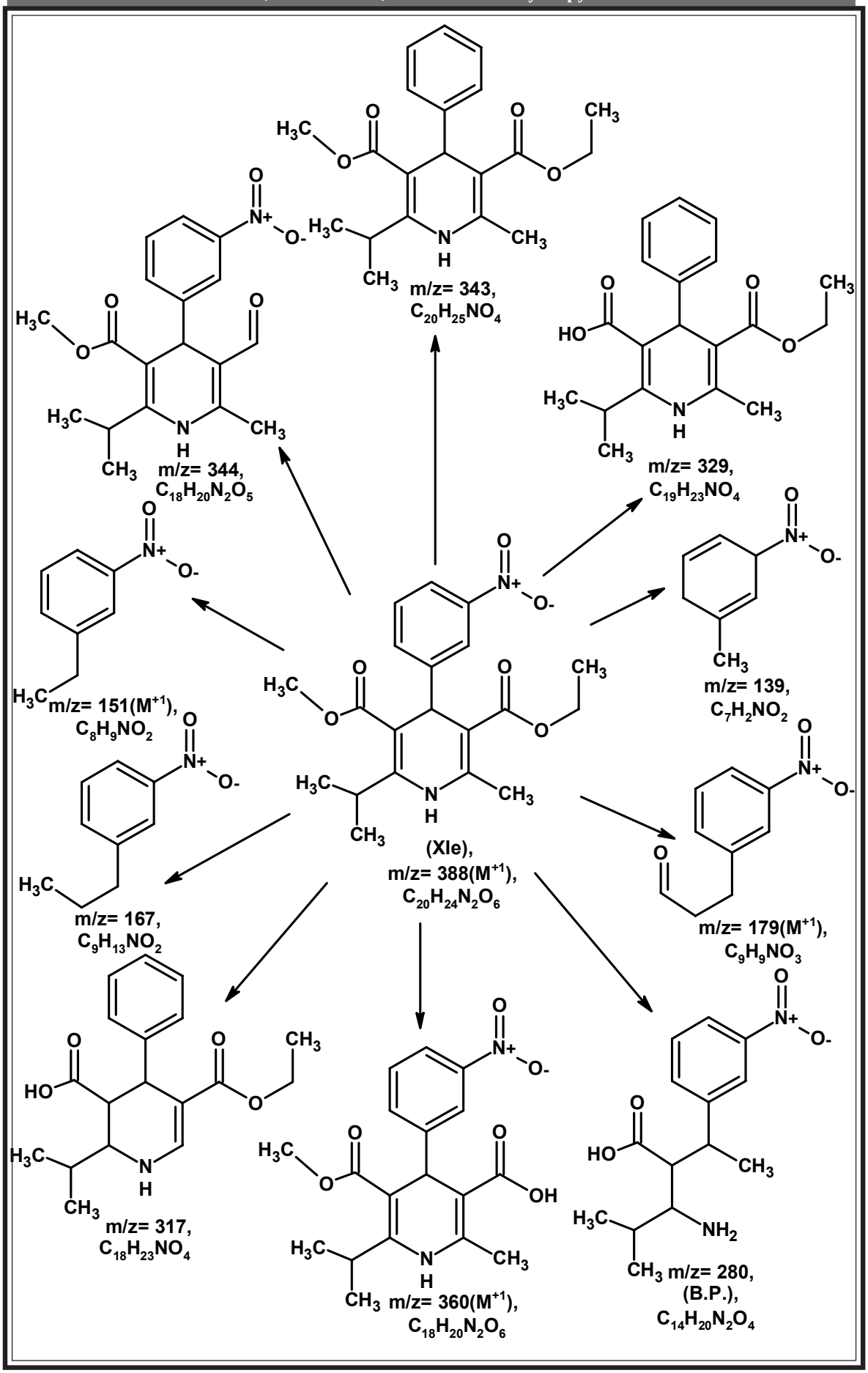
Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 9/21/2007 1:39:25 PM
Sample Name : JJS-MQ-24
Sample ID : JJS-MQ-24
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-24.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\170907_01.qgt

Line#:1 R.Time:3.4(Scan#:377)
MassPeaks:265 BasePeak:280(561877)
RawMode:Single 3.4(377)
BG Mode:None
intensity



m/z =388

(XI_e)


m/z= 343,
C20H25NO4
m/z= 344,
C18H20N2O5
m/z= 329,
C19H23NO4
m/z= 151(M+1),
C8H9NO2
m/z= 139,
C7H2NO2
(XIe),
m/z= 388(M+1),
C20H24N2O6
m/z= 167,
C9H13NO2
m/z= 179(M+1),
C9H9NO3
m/z= 317,
C18H23NO4
m/z= 360(M+1),
C18H20N2O6
m/z= 280,
(B.P.),
C14H20N2O4

MASS SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-*4-(p*-NITRO PHENYL) 3-ETHYL-5-METHYL-1,4-DI HYDRO-PYRIDINE-DICARBOXYLATE (XI_f).

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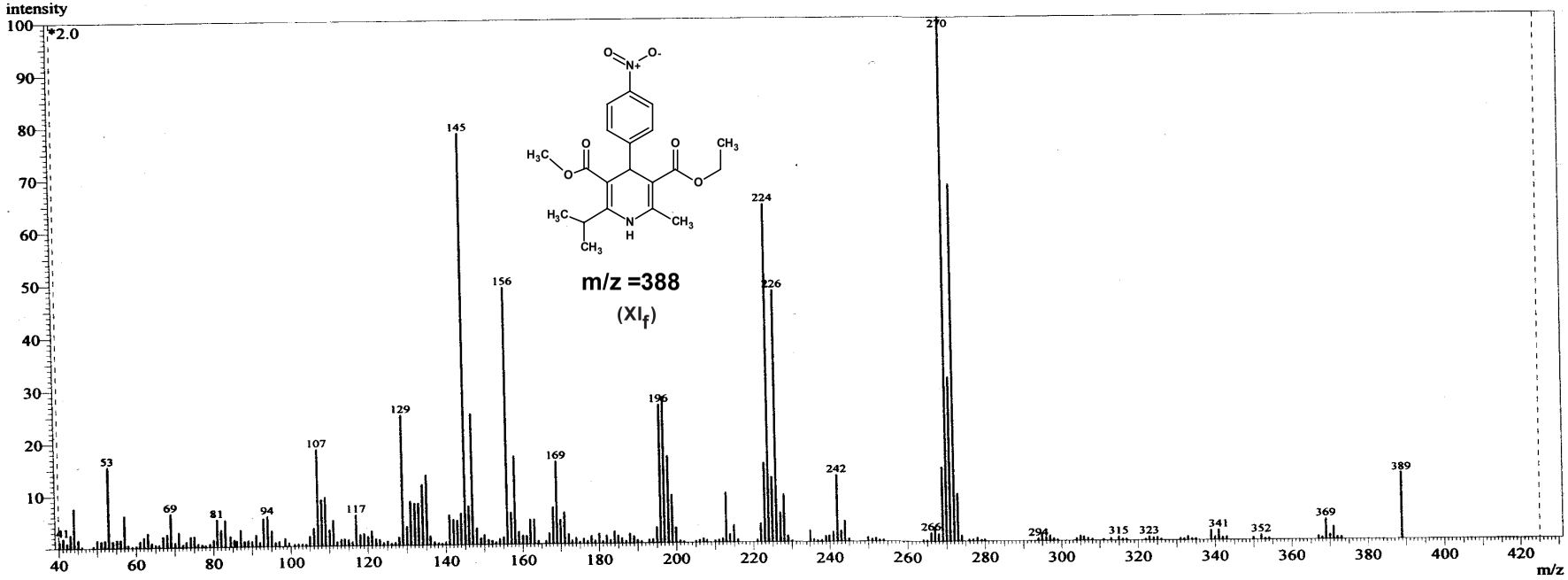
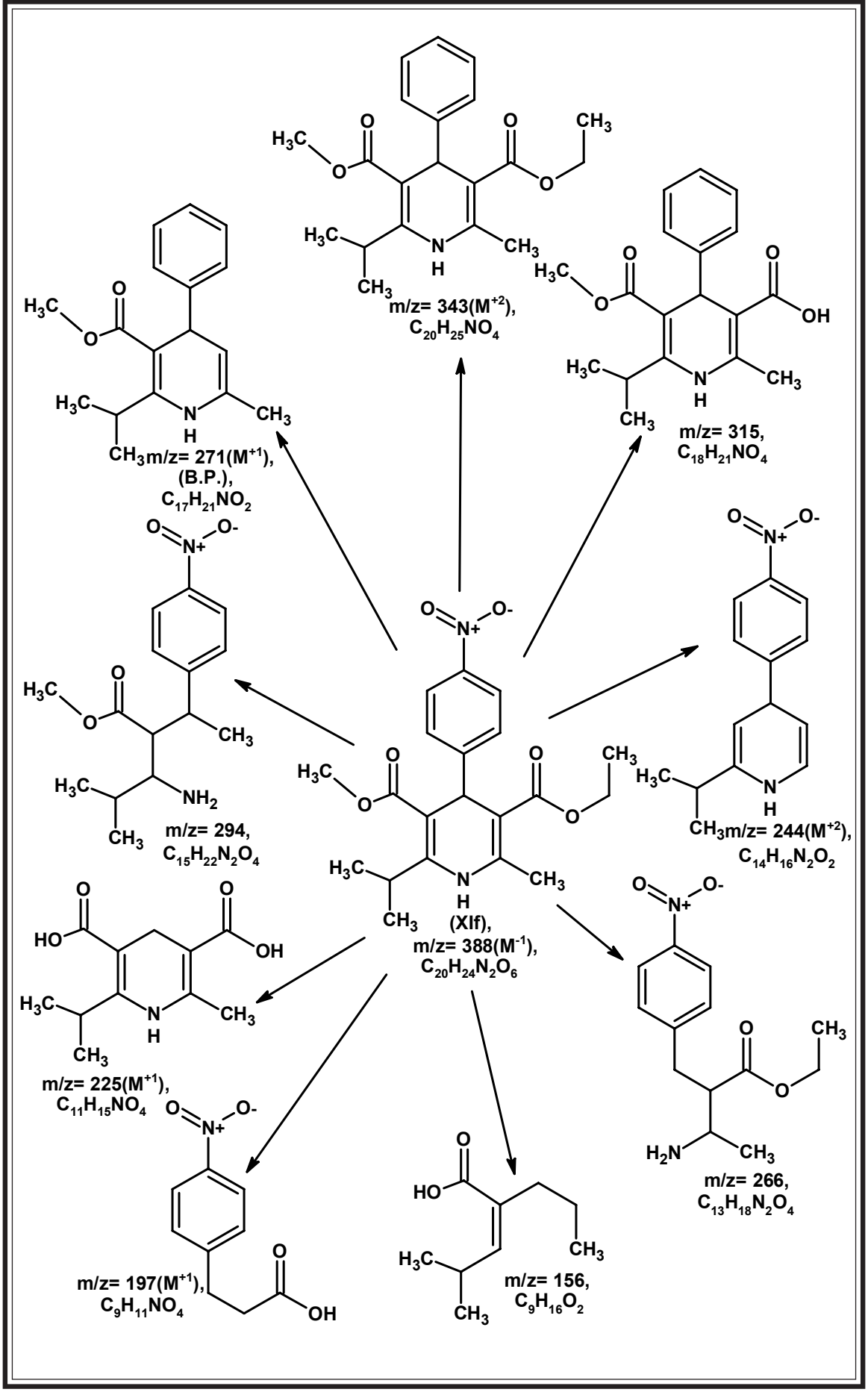
Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 2/1/2006 3:41:26 PM
Sample Name	: JJS-M-15
Sample ID	: JJS-M-15
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-15.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune9.qgt

Line#:1 R.Time:3.6(Scan#:393)
MassPeaks:261 BasePeak:270(971029)
RawMode:Single 3.6(393)
BG Mode:None
intensity




m/z= 343(M+2), C20H25NO4
m/z= 315, C18H21NO4
m/z= 271(M+1), (B.P.), C17H21NO2
m/z= 294, C15H22N2O4
m/z= 244(M+2), C14H16N2O2
(XIf), m/z= 388(M-1), C20H24N2O6
m/z= 225(M+1), C11H15NO4
m/z= 266, C13H18N2O4
m/z= 197(M+1), C9H11NO4
m/z= 156, C9H16O2

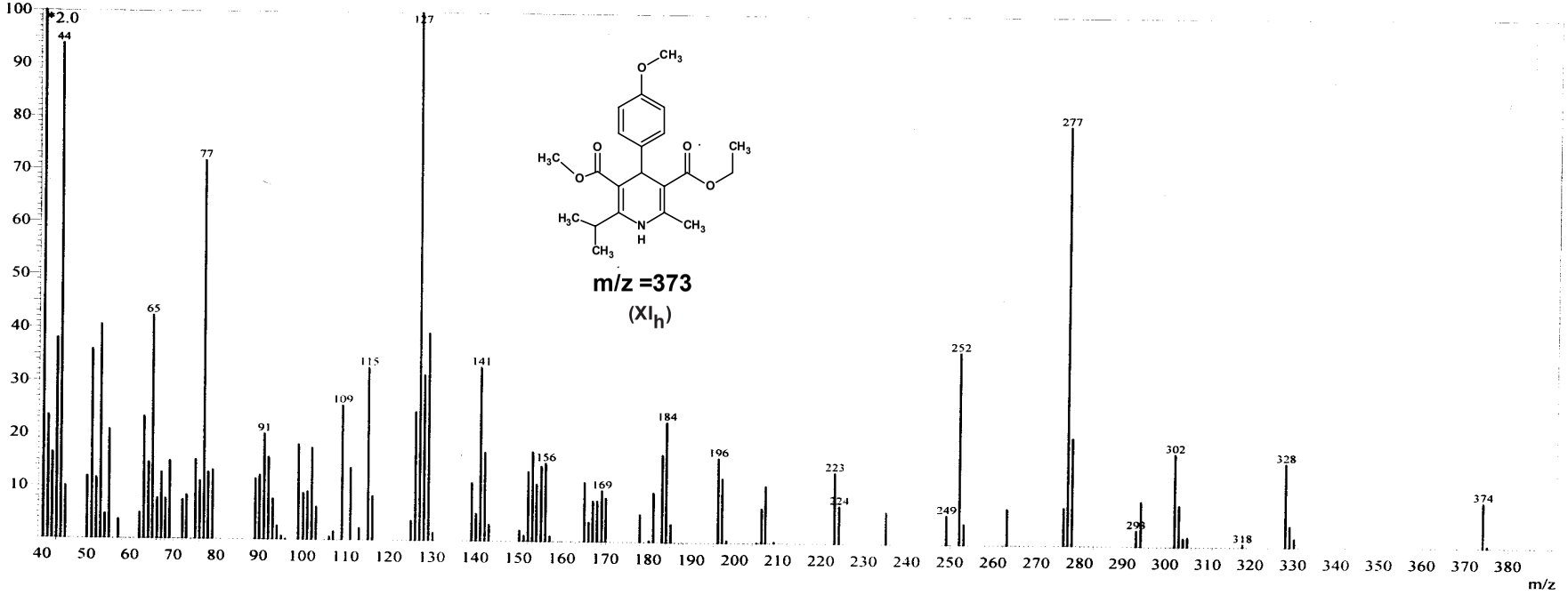
MASS SPECTRAL STUDY OF 6-METHYL-2-ISOPROPYL-*4-(p*-METHOXY PHENYL)-3-ETHYL-5-METHYL-1,4-DI-HYDRO PYRIDINE-DICARBOXYLATE (XI_h).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 4/18/2007 12:08:39 PM
Sample Name	: JJS-MQ-10
Sample ID	: JJS-MQ-10
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-10.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune121206.qgt

Line#:1 R.Time:2.5(Scan#:269)
MassPeaks:108 BasePeak:40(31986)
RawMode:Averaged 2.1-2.8(222-304)
BG Mode:None
intensity



m/z =373
(XI_h)

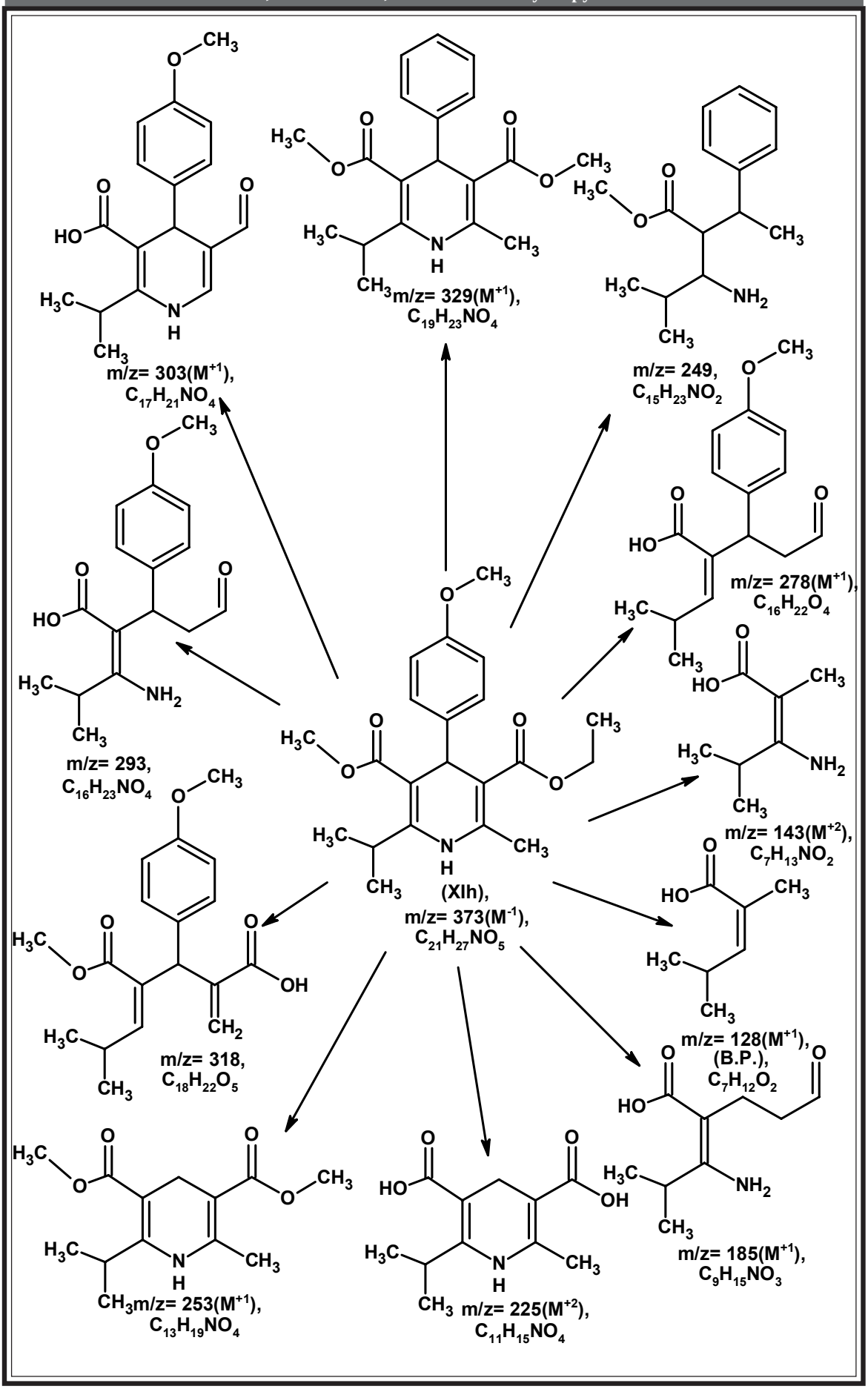

m/z= 303(M+1), C17H21NO4
m/z= 329(M+1), C19H23NO4
m/z= 249, C15H23NO2
m/z= 293, C16H23NO4
m/z= 278(M+1), C16H22O4
m/z= 143(M+2), C7H13NO2
(XIh), m/z= 373(M-1), C21H27NO5
m/z= 318, C18H22O5
m/z= 128(M+1), (B.P.), C7H12O2
m/z= 185(M+1), C9H15NO3
m/z= 253(M+1), C13H19NO4
m/z= 225(M+2), C11H15NO4

TABLE NO. 11B : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 6-METHYL-2-ISOPROPYL-4-SUBSTITUTED PHENYL-3-ETHYL-5-METHYL-1,4-DI HYDROPYRIDINE-DICARBOXYLATES (XI_{a-j}) .(Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.) S. pyogens MTCC- 442					S. aureus MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
XI_a	4-F	-	10	11	13	15	-	8	9	10	12
XI_b	3-Cl	-	9	10	12	15	-	8	9	11	14
XI_c	4-Cl	-	10	11	14	16	-	9	10	12	13
XI_d	4-Br	-	10	12	13	16	-	7	8	10	14
XI_e	3-NO_2	-	9	11	14	17	-	8	9	10	14
XI_f	4-NO_2	-	8	11	13	15	-	7	8	9	13
XI_g	4-CH_3	-	9	10	12	14	-	8	10	13	17
XI_h	4-OCH_3	-	8	9	10	14	-	9	11	14	17
XI_i	2,3-$(CH_3)_2$	-	8	9	11	13	-	9	10	12	16
XI_j	3-OC_6H_5	-	10	10	12	14	-	7	8	10	14

Comparative activity of(XI_{a-j}) with known choosen standard drugs

Standard drug	Antibacterial activity									
										Xlg,h Xli
Amoxicilin	12	14	15	16	18	10	12	14	15	16
Chloramphenicol	14	15	18	19	24	14	17	20	21	24
Sparfloxacin	14	22	24	26	28	24	26	27	28	32
Levofloxacin	18	21	22	27	29	20	24	26	27	35

N.B.(-): No Activity

TABLE NO. 11C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 6-METHYL-2-ISOPROPYL-4-SUBSTITUTED-PHENYL-3-ETHYL-5-METHYL-1,4-DI HYDROPYRIDINE-DICARBOXYLATES (XI_{a-j}). (Different Inhibition-Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in m.m.)									
		B. Subtillis MTCC- 441					E.coli MTCC- 96				
		5	25	50	100	250	5	25	50	100	250
XI_a	4-F	-	9	11	12	14	-	7	8	8	9
XI_b	3-Cl	-	10	12	13	15	-	7	8	10	10
XI_c	4-Cl	-	7	9	10	12	-	7	8	10	13
XI_d	4-Br	-	8	9	10	12	-	8	10	12	16
XI_e	3-NO_2	-	8	10	11	13	-	6	7	8	10
XI_f	4-NO_2	-	10	11	12	14	-	10	15	17	22
XI_g	4-CH_3	-	9	10	11	13	-	9	12	13	18
XI_h	4-OCH_3	-	10	10	11	13	-	8	10	11	14
XI_i	2,3-$(CH_3)_2$	-	8	10	10	12	-	9	10	12	14
XI_j	3-OC_6H_5	-	7	8	9	11	-	7	8	10	12

Comparative activity of (XI_{a-j}) with known choosen standard drugs

Standard drug	Antibacterial activity									
										XI_f
Amoxicilin	12	15	16	18	19	11	14	16	18	20
Chloramphenicol	18	22	24	26	27	17	20	23	25	26
Sparfloxacin	22	24	25	26	29	20	22	25	26	28
Levofloxacin	24	26	28	29	31	23	25	26	29	30

N.B.(-): No Activity

TABLE NO. 11D : COMPARATIVE ANTIMICROBIAL ACTIVITY OF6-METHYL-2-ISOPROPYL-4-SUBSTITUTED PHENYL-3-ETHYL-5-METHYL-1,4-DI HYDROPYRIDINE-DICARBOXYLATES (XI_{a-j}). (Different Inhibition Concentration in µg/ml).

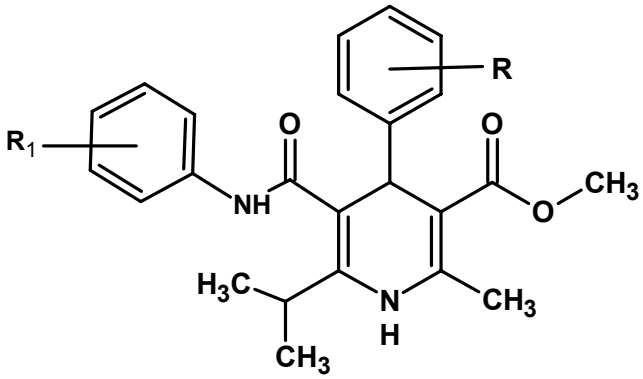
Compd No.	R	Antifungal activity (Zones of inhibition in m.m.) C. albicans MTCC- 227					A. niger MTCC- 282				
		5	25	50	100	250	5	25	50	100	250
XI_a	4-F	-	5	7	10	12	-	6	7	9	10
XI_b	3-Cl	-	5	7	8	10	-	8	9	11	12
XI_c	4-Cl	-	7	8	9	11	-	7	8	9	11
XI_d	4-Br	-	6	8	10	13	-	9	11	13	14
XI_e	3-NO_2	-	8	10	13	15	-	8	10	12	15
XI_f	4-NO_2	-	8	10	11	12	-	8	9	11	13
XI_g	4-CH_3	-	9	10	12	14	-	8	10	12	14
XI_h	4-OCH_3	-	9	11	11	13	-	7	9	10	11
XI_i	2,3-$(CH_3)_2$	-	7	8	9	11	-	7	8	9	10
XI_j	3-OC_6H_5	-	7	7	8	10	-	7	8	9	11
Comparative activity of (XI_{a-j}) with known choosen standard drugs											
Standard drug		Antifungal activity									
Griseofulvin		16	18	21	23	25	17	19	21	22	23
Fluconazole		14	16	18	21	22	15	17	18	20	21

N.B.(-): No Activity

SECTION-III

PREPARATION AND BIOLOGICAL SCREENING OF METHYL-2-ISO-PROPYL-6-METHYL-3-(SUBSTITUTED-PHENYLCARBOXAMIDO-4-SUB-STITUTED-PHENYL-1,4-DIHYDROPYRIDINE-5-CARBOXYLATES.

1,4-Dihydro-pyridine derivatives represents one of the most active classes of compounds possessing wide spectrum of biodynamic activities[289-304]. In order to have potent therapeutic agents, the synthesis of **Methyl-2-isopropyl-6-methyl-3-(substituted phenyl carboxamido)-4-substituted phenyl-1,4-dihydropyridine-5-carboxylates (XIIa-j)** have been undertaken by the cyclocondensation of one mole of **methyl-3-amino but-2-enoate** with different one mole of **2-substituted-benzylidene-4-methyl-3-oxo-N-phenyl pentanamides.**



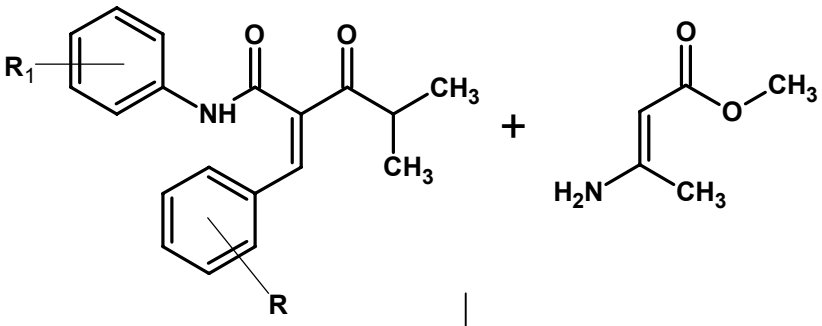
(XIIa-j)

R & R_1= Substituted phenyl

The constitution of the products **(XIIa-j)** have been delineated by **elemental analyses, IR, PMR** and **Mass** spectral data.

The products **(XIIa-j)** were assayed for their ***in vitro*** biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** **,** ***S. aureus MTCC-96*** **and** ***B. subtillis MTCC-441*** **(Gram positive) and** ***E. coli MTCC-443*** **(Gram negative)** bacterial strains and antifungal activity towards **Aspergillus niger MTCC-282 and Candida albicans MTCC-227** at different concentrations i.e.: 0(control), 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds **(XIIa-j)** were compared with standard drugs,viz., **Amoxicillin, Chloramphenicol, Sparfloxacin, Levofloxacin**(antibacterial)**,Griseofluvin, Fluconazole** (antifungal)**.**

REACTION SCHEME

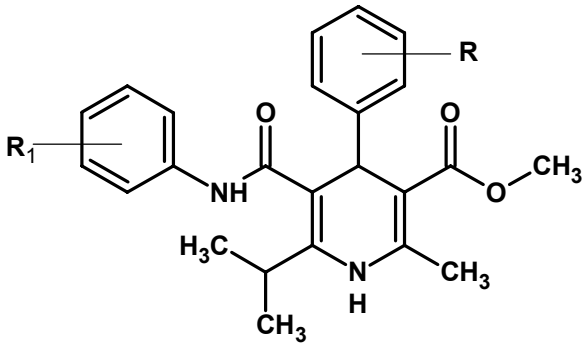


(12a-j)
R , R_1= substituted phenyl

Dimethyl-
formamide

Anhyd. K_2CO_3

△



(XIIa-j)
R , R_1= substituted phenyl

EXPERIMENTAL

PREPARATION AND BIOLOGICAL SCREENING OF METHYL-2-ISO-PROPYL-6-METHYL-3-(SUBSTITUTED-PHENYLCARBOXAMIDO-4-SUBSTITUTED-PHENYL-1,4-DIHYDROPYRIDINE-5-CARBOXYLATES.

(A) Preparationof 3-4-dichloro-phenyl-4-methyl-3-oxopentanamide.

The synthesis of 3-4-dichloro-phenyl-4-methyl-3-oxopentanamide was undertaken according to the literature procedure.[318-319]. Yield :54 %, M.P. :153°C, (Required:C, 52.57%; H, 4.78%; N, 5.11% for $C_{12}H_{13}NO_2Cl_2$, Found : C, 52.52 %; H, 4.68 %; N, 6.52 %).

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (1.0 : 9.0) = 0.48.
TLC solvent system R_{f_2} : Methanol : Chloroform(0.5 : 9.5) = 0.51.

Similarly, other compounds were synthesized.

(B) Preparation of *N*-(3,4-dichlorophenyl)-4-methyl-2-(*m*-nitrobenzylidene)-3-oxopentanamide (12_f).

For preparation, refer Part-II, Section-II, page No. 326-327.

Yield: 47%, M.P.:183°C, (Require:C, 56.04%; H, 3.96%; N, 6.88 % for $C_{19}H_{16}N_2O_4Cl_2$, Found : C, 56.00 %; H, 3.91 %; N, 6.81%).

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (2.5 : 7.5) = 0.48.
TLC solvent system R_{f_2} : Methanol :Chloroform(1.0 : 9.0) = 0.41.

Similarly, other compounds **(12_{1-10})** were synthesized. The physical data are recorded in **Table No.12.**

(C) Preparation of Methyl (2*E*)-3-aminobut-2-enoate.

For preparation, refer Part-II, Section-II, page No.326-327.

Yield : 72%, M.P.: 81°C, (Required : C,52.16%; H, 7.88%; N,12.17% for $C_5H_9NO_2$, Found : C,52.09 %; H, 7.82%; N,12.11%).

(D) Preparation of Methyl-2-isopropyl-6-methyl-3-(3,4-dichloro phenyl carboxamido)-4-substituted phenyl-1,4-dihydropyridine-5-carboxylate (XIIa-j).

A mixture of N-(3,4-dichlorophenyl)-4-methyl-2-(m-nitrobenzylidene)-3-oxopentanamide **(12_f)** (4.07 gm, 0.01 M), methyl (2E)-3-aminobut-2-enoate (1.38 gm, 0.012 M) and potassium carbonate (2.74 gm, 0.02 M) in dimethyl formamide (20 ml) was heated under reflux condition for 8 to 10 hrs. The reaction was monitored by TLC. The reaction mixture was allowed to cool at room temperature. The reaction mixture was then poured in to cold water. The solid product so obtained was filtered, washed with water, dried and crystallized from dimethyl formamide. Yield : 49%, M.P. :198°C, (Required : C, 57.15 %; H, 4.60 %; N, 8.83 % for $C_{20}H_{24}N_2O_4$, Found : C, 57.08 %; H, 4.53 %; N, 8.78 %).

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (3.0 : 7.0) = 0.62.
TLC solvent system R_{f_2} : Methanol : Chloroform(0.5 : 9.5) = 0.59**.**

Similarly, other compounds **(XIa-j)** were synthesized. The physical data are recorded in **Table No.12A.**

(E) Antimicrobial activity of Methyl-2-isopropyl-6-methyl-3-(substituted phenyl carboxamido)-4-substituted phenyl-1,4-dihydropyridine-5-carboxylates (XIIa-j).

Antimicrobial activity testing was carried out as described in Part-I(A), Section-I, page No. 30-31. The MIC values of test solution are recorded in **Table No. 12B, 12C** and **12D.**

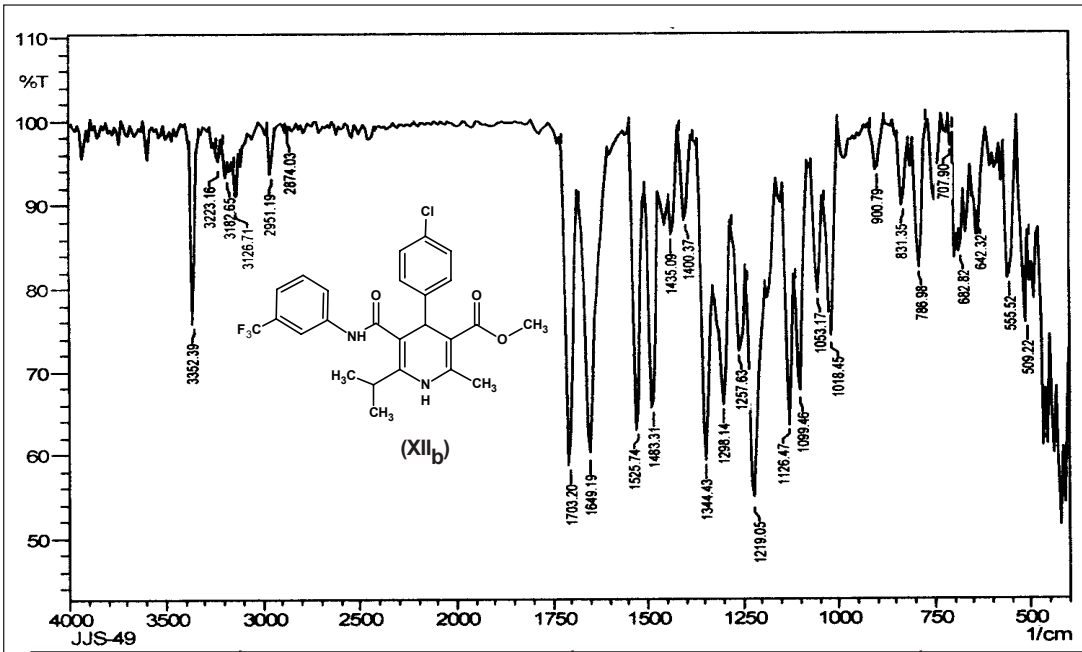
TABLE NO. 12 : PHYSICAL CONSTANTS OF *N*-(3,4-DICHLOROPHENYL)-4-METHYL-2-(m,-NITROBENZYLIDENE)-3-OXOPENTANAMIDE (12_{a-j}).

Comp. No.	R	R_1	Molecular Formula	M.W.	M.P. ^oC	Yield %	R_f Value		% of Nitrogen Calcd. / Found
1	2	3	3	4	5	6	R_{f_1}	R_{f_2} 7	8
12_a	4-F	3-CF_3	$C_{20}H_{17}NO_2F_4$	379.0	161^o	39	0.49	0.49	3.69 / 3.62
12_b	4-Cl	3-CF_3	$C_{20}H_{17}NO_2ClF_3$	395.5	163^o	41	0.39	0.51	3.54 / 3.49
12_c	3-NO2	3-CF_3	$C_{20}H_{17}N_2O_4F_3$	406.0	178^o	37	0.38	0.50	6.89 / 6.82
12_d	4-F	3-4-$(Cl)_2$	$C_{19}H_{16}NO_2Cl_2F$	380.0	153^o	43	0.43	0.53	3.68 / 3.63
12_e	4-Cl	3-4-$(Cl)_2$	$C_{19}H_{16}NO_2Cl_3$	396.5	175^o	46	0.47	0.49	3.53 / 3.49
12_f	3-NO_2	3-4-$(Cl)_2$	$C_{19}H_{16}N_2O_4Cl_2$	407.0	183^o	47	0.48	0.41	6.88 / 6.83
12_g	4-F	4-NO_2	$C_{19}H_{17}N_2O_4F$	356.0	194^o	45	0.42	0.46	7.86 / 7.82
12_h	3-Cl	4-NO_2	$C_{19}H_{17}N_2O_4Cl$	372.5	198^o	51	0.51	0.47	7.51 / 7.47
12_i	4-Cl	4-NO_2	$C_{19}H_{17}N_2O_4Cl$	372.5	205^o	53	0.46	0.48	7.51 /7.46
12_j	3-NO_2	4-NO_2	$C_{19}H_{17}N_3O_6$	383.0	278^o	54	0.44	0.52	10.96 / 10.91

TABLE NO. 12A : PHYSICAL CONSTANTS OF METHYL-2-ISOPROPYL-6-METHYL-3-(SUBSTITUTED-PHENYL CARBOXAMIDO)-4-SUBSTITUTED-PHENYL-1,4-DIHYDROPYRIDINE-5-CARBOXYLATES (XII_{a-j}).

Comp. No.	R	R_1	Molecular Formula	M.W.	M.P. °C	Yield %	R_f Value		% of Nitrogen
							R_{f_1}	R_{f_2}	Calcd. / Found
1	2	3	3	4	5	6	7		8
XII_a	4-F	3-CF_3	$C_{25}H_{24}N_2O_3F_4$	476.0	211°	36	0.48	0.49	5.88 / 5.82
XII_b	4-Cl	3-CF_3	$C_{25}H_{24}N_2O_3ClF_3$	492.5	189°	36	0.49	0.52	5.68 / 5.61
XII_c	3-NO2	3-CF_3	$C_{25}H_{24}N_3O_5F_3$	503.0	191°	38	0.52	0.56	8.34/ 8.29
XII_d	4-F	3-4-$(Cl)_2$	$C_{24}H_{23}N_2O_3Cl_2F$	477.0	214°	41	0.61	0.58	5.87 / 5.81
XII_e	4-Cl	3-4-$(Cl)_2$	$C_{24}H_{23}N_2O_3Cl_3$	493.5	205°	42	0.58	0.54	5.67 / 5.62
XII_f	3-NO_2	3-4-$(Cl)_2$	$C_{24}H_{23}N_3O_5Cl_2$	504.0	198°	49	0.62	0.59	8.33 / 8.28
XII_g	4-F	4-NO_2	$C_{24}H_{24}N_3O_5F$	453.0	178°	41	0.40	0.42	9.27 / 9.21
XII_h	3-Cl	4-NO_2	$C_{24}H_{24}N_3O_5Cl$	469.5	192°	40	0.38	0.39	8.94 / 8.88
XII_i	4-Cl	4-NO_2	$C_{24}H_{24}N_3O_5Cl$	469.5	199°	43	0.41	0.43	8.94 / 8.87
XII_j	3-NO_2	4-NO_2	$C_{24}H_{24}N_4O_7$	480.0	194°	42	0.39	0.43	11.66 / 11.60

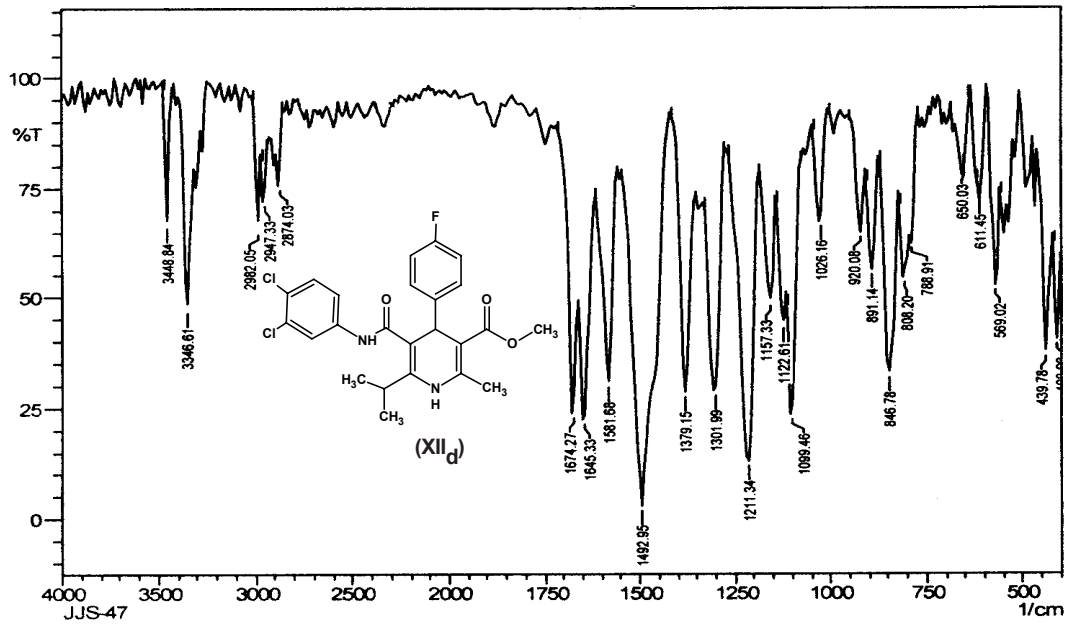
IR SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(*m*-TRIFLUOROMETHYL-PHENYL CARBOXAMIDO)-*p*-CHLOROPHENYL-1,4-DI HYDRO PYRIDINE-5-CARBOXYLATE (XII_b).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2951.1	2975 - 2850	96
	C-H (sym. str., m)	2874.0	2900 - 2800	96
	C-H (asym. def., m)	1435.0	1470 - 1435	96
	C-H (sym. def., m)	1344.3	1385 - 1300	96
Aromatic and ring skeletal vibration	C=C & C-C (str., v)	1525.7	1600 - 1450	97
	C-H (i.p. def., m)	1126.4	1150 - 1050	97
	C-H (o.o.p. def., m)	831.5	825 - 800	97
	C-N (str., v)	1344.4	1340 - 1250	97
Pyridine Moiety	N-H (str., b)	3352.3-3126.7	3400 - 3000	98
	N-H (def., s,m)	1525.7	1650 - 1525	98
Ketone				
Amide	C=O (str., s)	1703.2	1740 - 1650	98
Ester	C=O (str., s)	1649.1	1740 - 1650	98
Halogen Subtitution	C-Cl (str., b)	786.9-642.3	800-600	99
Para(-4-) substitution	C-H (def., v,s)	831.3	850-800	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

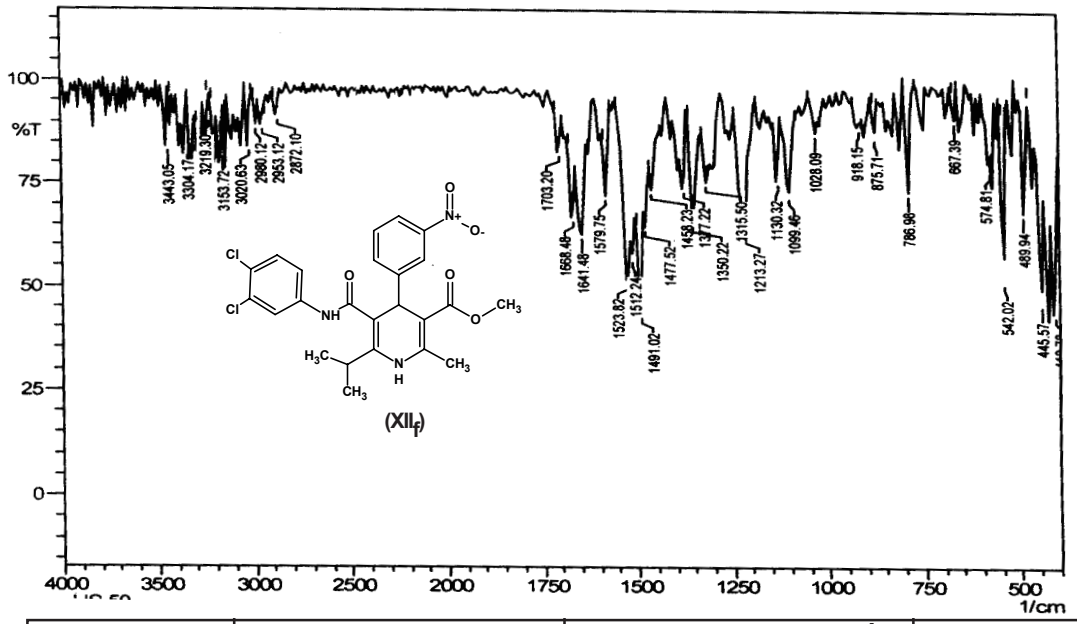
IR SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(3,4-DICHLOROPHENYL CARBOXAMIDO)-*p*-FLUOROPHENYL-1,4-DIHYDROPYRIDINE-5-CARBOXYLATE (XII_d).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2947.3	2975 - 2850	96
	C-H (sym. str., m)	2874.0	2900 - 2800	96
	C-H (sym. def., m)	1379.1	1385 - 1300	96
Aromatic and ring skeletal vibration	C=C & C-C (str., v)	1492.9	1600 - 1450	97
	C-H (i.p. def., m)	1122.6	1150 - 1050	97
	C-H (o.o.p. def., m)	846.7	825 - 800	97
	C-N (str., v)	1301.9	1340 - 1250	97
Pyridine Moiety	N-H (str., b)	3346.6	3400 - 3000	98
	N-H (def., s,m)	1581.6	1650 - 1525	98
Ketone Amide	C=O (str., s)	1674.2	1740 - 1650	98
Ester	C=O (str., s)	1645.3	1740 - 1650	98
Halogen Subtitution	C-F (str., b)	1379.1-1099.4	1400-1080	99
Para(-4-) substitution	C-H (def., v ,s)	808.2	850-800	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

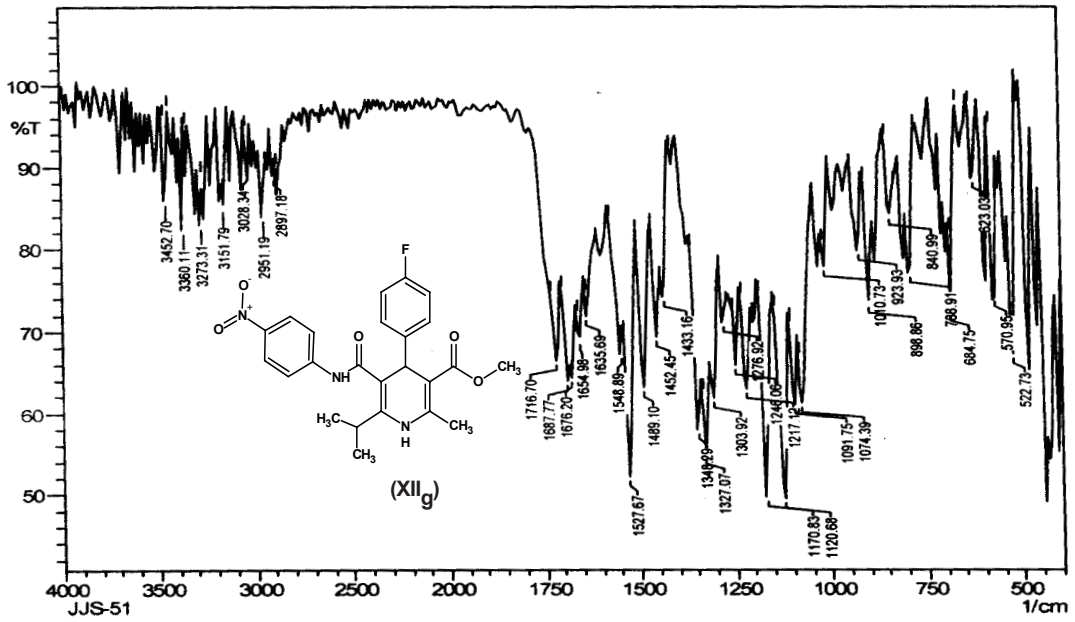
IR SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(3,4-DICHLOROPHENYL CARBOXAMIDO)-*m*-NITROPHENYL-1,4-DI HYDRO-PYRIDINE-5-CARBOXYLATE (XII_f).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2953.1	2975 - 2850	96
	C-H (sym. str., m)	2872.1	2900 - 2800	96
	C-H (asym. def., m)	1458.2	1470 - 1435	96
	C-H (sym. def., m)	1350.2	1385 - 1300	96
Aromatic and ring skeletal vibration	C-H(str., s)	3020.6	3080-3010	97
	C=C & C-C (str., v)	1579.7	1600 - 1450	97
	C-H (i.p. def., m)	1130.3	1150 - 1050	97
	C-H (o.o.p. def., m)	786.9	825 - 800	97
	C-N (str., v)	1315.5	1340 - 1250	97
Pyridine Moiety	N-H (str., b)	3304.1-3153.7	3400 - 3000	98
	N-H (def., s,m)	1523.8	1650 - 1525	98
Ketone Amide	C=O (str., s)	1703.2	1740 - 1650	98
Ester	C=O (str., s)	1668.4	1740 - 1650	98
Halogen Subtitution	C-Cl (str., b)	786.9-667.3	800-600	99
Nitro substitution	C-NO2 (asym.str.)	1512.2	1570-1500	99
	C-NO2 (asym.str.)	1350.2	1370-1300	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

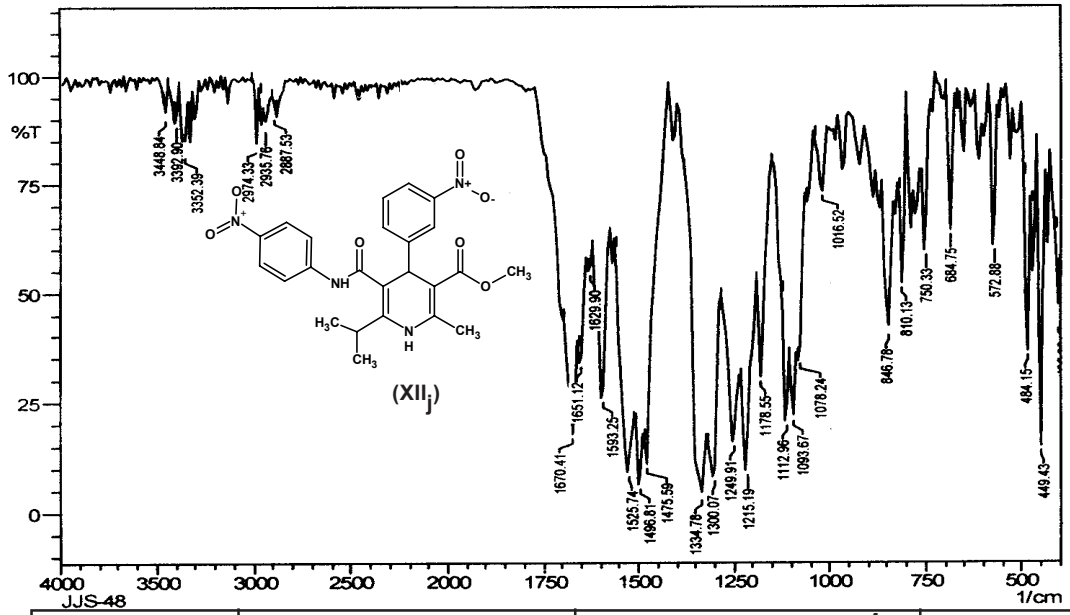
IR SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(4-NITRO METHENE-PHENYL CARBOXAMIDO)-*p*-FLUOROPHENYL-1,4-DIHYDRO PYRIDINE-5-CARBOXYLATE (XII_g).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2951.1	2975 - 2850	96
	C-H (sym. str., m)	2897.1	2900 - 2800	96
	C-H (asym. def., m)	1452.4	1470 - 1435	96
	C-H (sym. def., m)	1348.2	1385 - 1300	96
Aromatic and ring skeletal vibration	C=C & C-C (str., v)	1527.6	1600 - 1450	97
	C-H (i.p. def., m)	1120.6	1150 - 1050	97
	C-H (o.o.p. def., m)	840.9	825 - 800	97
	C-N (str., v)	1327.0	1340 - 1250	97
Pyridine Moiety	N-H (str., b)	3360.1-3151.7	3400 - 3000	98
	N-H (def., s,m)	1635.6	1650 - 1525	98
Ketone Amide	C=O (str., s)	1716.7	1740 - 1650	98
Ester	C=O (str., b)	1687.7-1654.9	1740 - 1650	98
Halogen Subtitution	C-F (str., b)	1348.2-1074.3	1400-1080	99
Para(-4-) substitution	C-H (def., v,s)	840.9	850-800	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

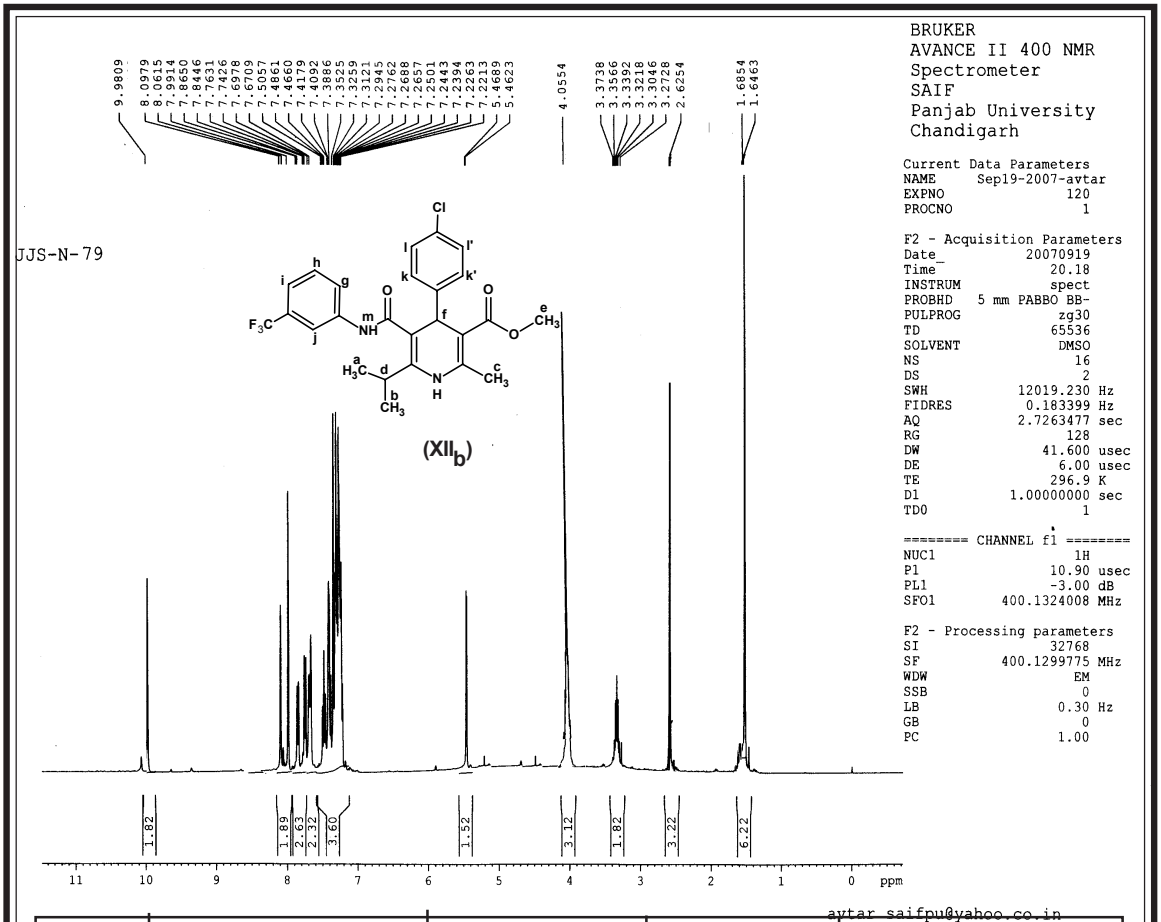
IR SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(*p*-NITRO PHENYL CARBOXAMIDO)-*m*-NITROPHENYL-1,4-DI HYDRO-PYRIDINE-5-CARBOXYLATE (XII_j).



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2935.7	2975 - 2850	96
	C-H (sym. str., m)	2887.5	2900 - 2800	96
	C-H (asym. def., m)	1475.5	1470 - 1435	96
	C-H (sym. def., m)	1334.7	1385 - 1300	96
Aromatic and ring skeletal vibration	C=C & C-C (str., v)	1593.2	1600 - 1450	97
	C-H (i.p. def., m)	1112.9	1150 - 1050	97
	C-H (o.o.p. def., m)	810.1	825 - 800	97
	C-N (str., v)	1300.7	1340 - 1250	97
Pyridine Moiety	N-H (str., b)	3448.8-3352.3	3400 - 3000	98
	N-H (def., s,m)	1629.9	1650 - 1525	98
Ketone Amide	C=O (str., s)	1670.4	1740 - 1650	98
Ester	C=O (str., s)	1651.1	1740 - 1650	98
Nitro substituted	C-NO2 (asym.str.)	1525.7	1570-1500	99
	C-NO2 (asym.str.)	1334.7	1370-1300	99
Meta(-3-) substituted	C-H (def., v, s)	846.7	880-830	99
		750.3	780-730	99

* Abbreviations : s = strong, m = medium, w = weak, v = variable, b = broad, sh = sharp.

NMR SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(3-*m*-TRIFLUOROMETHENE-PHENYL CARBOXAMIDO)-*p*-CHLORO-PHENYL-1,4-DIHYDRO PYRIDINE-5-CARBOXYLATE (XII_b).



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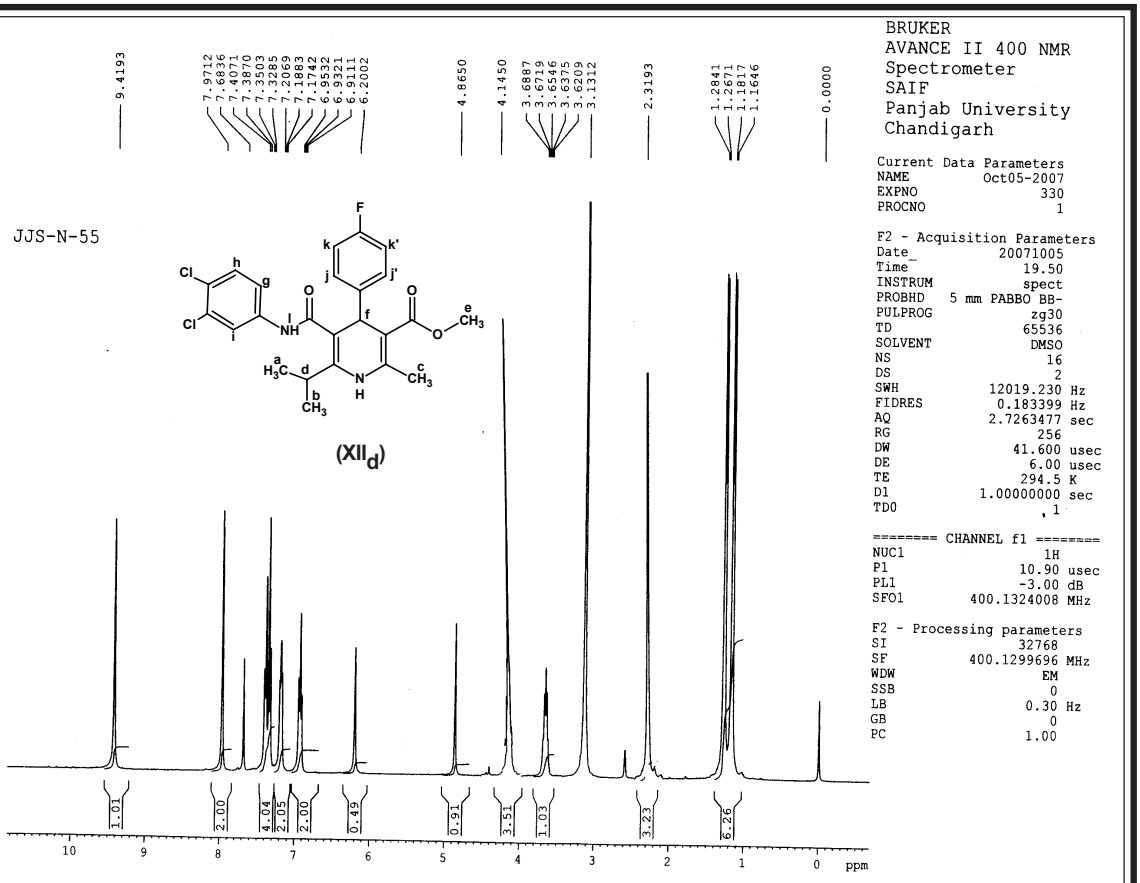
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.6463-1.6854	6H	singlet	- $(C\underline{H}_3)_{(a,b)}$
2	2.6254	3H	singlet	- $(C\underline{H}_3)_{(c)}$
3	3.2728-3.3738	1H	multiplet	- $(C\underline{H})_{(d)}$
4	4.0554	3H	singlet	- $(C\underline{H}_3)_{(e)}$
5	5.4623-5.4689	1H	singlet	- Ar-$\underline{H}_{(f)}$
6	7.2213-7.5057	3H	multiplet	- Ar-$\underline{H}_{(g,h,i)}$
7	7.7426-7.7631	2H	doublet	Ar-$\underline{H}_{(k,k')}$(J=8.2)
8	7.8446-7.8650	2H	doublet	Ar-$\underline{H}_{(l,l')}$(J=8.16)
9	8.0979	1H	singlet	- Ar-$\underline{H}_{(j)}$
10	9.9809	1H	singlet	- N$\underline{H}_{(m)}$

NMR SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(3,4-DICHLOROPHENYL CARBOXAMIDO)-4-FLUOROPHENYL-1,4-DI-HYDRO PYRIDINE-5-CARBOXYLATE (XII_d).



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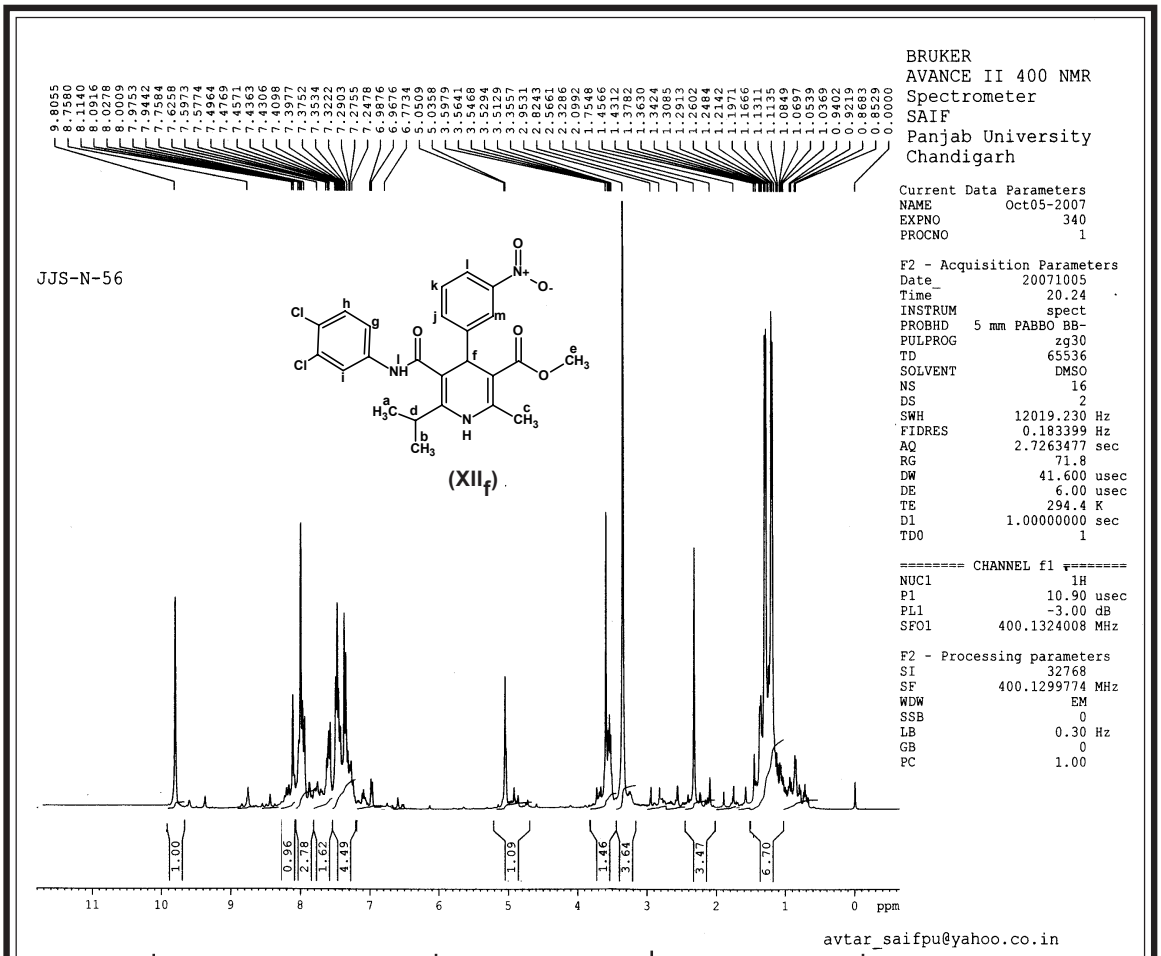
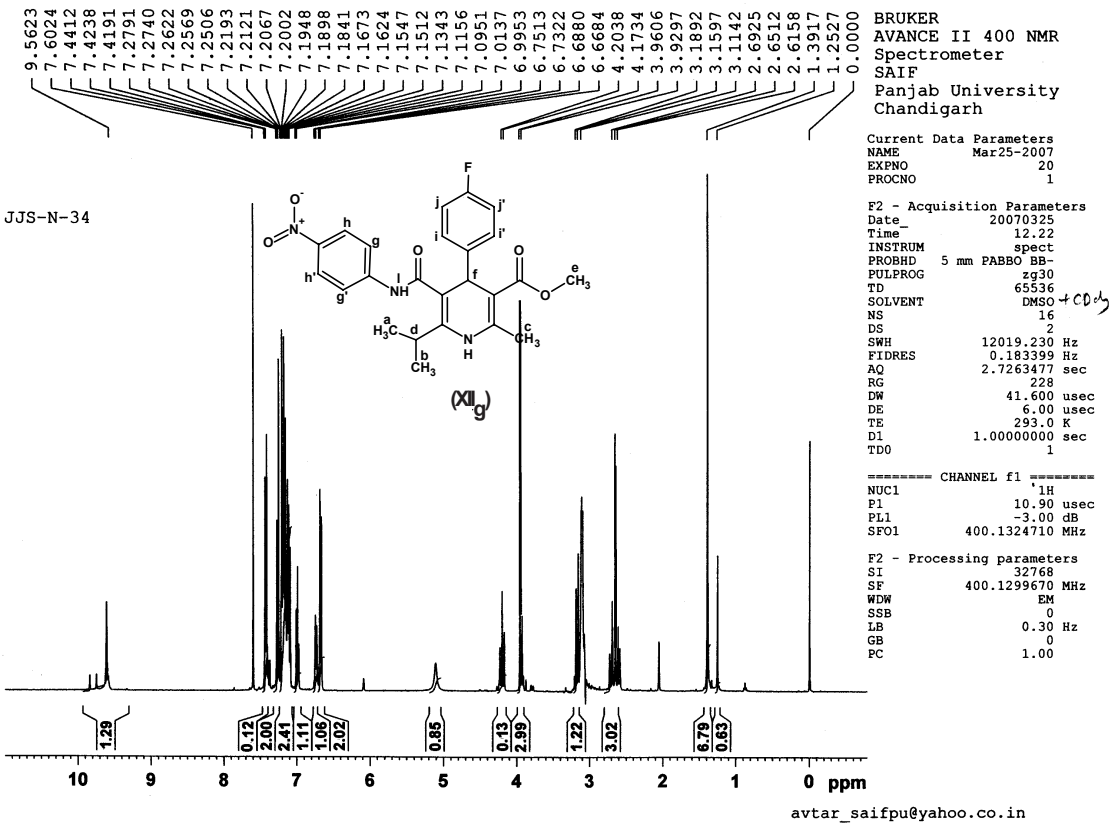
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.1646-1.2841	6H	doublet	- ($C\underline{H}_3$)$_{(a,b)}$
2	2.3193	3H	singlet	- ($C\underline{H}_3$)$_{(c)}$
3	3.6209-3.6887	1H	multiplet	- ($C\underline{H}$)$_{(d)}$
4	4.1450	3H	singlet	- ($C\underline{H}_3$)$_{(e)}$
5	4.8650	1H	singlet	- Ar-$\underline{H}_{(f)}$
6	6.9111-6.9532	2H	doublet	- Ar-$\underline{H}_{(j,j')}$
7	7.1742-7.2069	2H	doublet	- Ar-$\underline{H}_{(k,k')}$
8	7.3285-7.4071	2H	multiplet	- Ar-$\underline{H}_{(g,h)}$
9	7.9712	1H	singlet	- Ar-$\underline{H}_{(i)}$
10	9.4193	1H	singlet	- N$\underline{H}_{(l)}$
11	3.1312	-	-	-DMSO-d_6

NMR SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(3,4-DICHLOROPHENYL CARBOXAMIDO)-*m*-NITROPHENYL-1,4-DI-HYDRO PYRIDINE-5-CARBOXYLATE (XII_f).



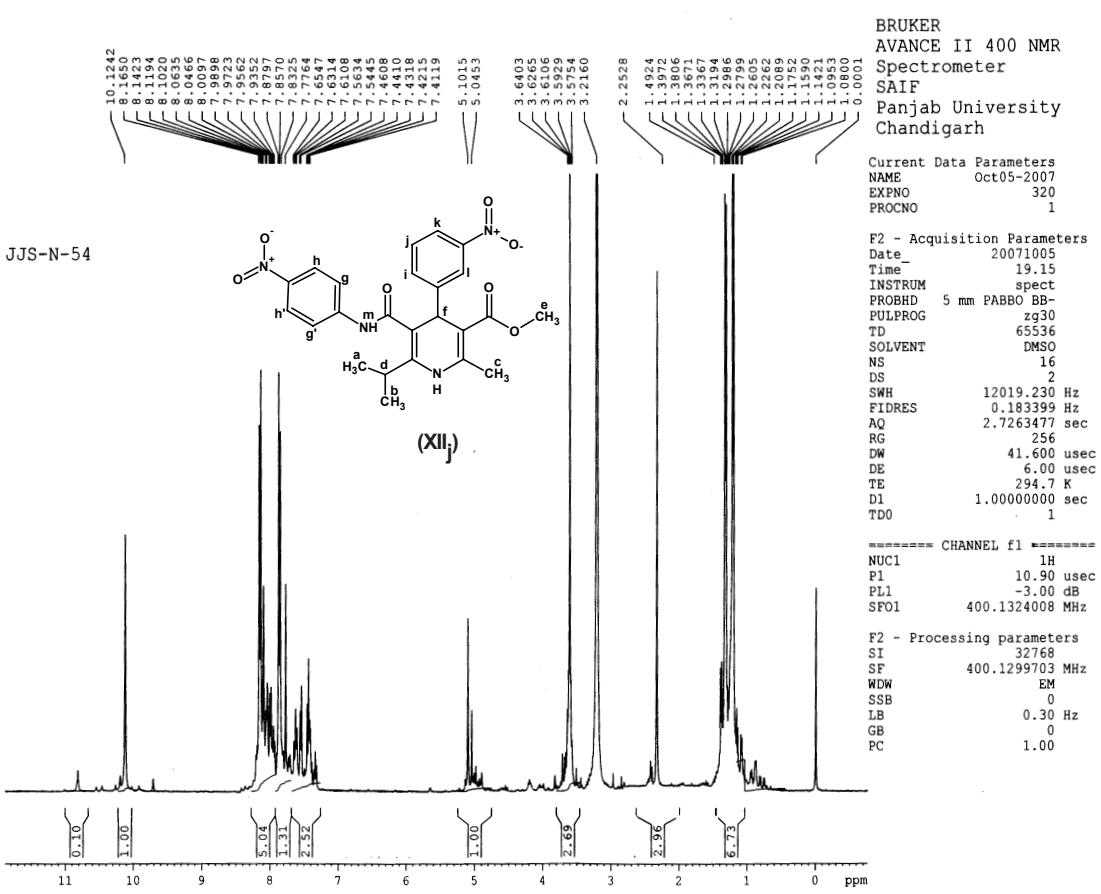
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.0369-1.1666	6H	doublet	- $(C\underline{H}_3)_{(a,b)}$
2	2.3286	3H	singlet	- $(C\underline{H}_3)_{(c)}$
3	3.3557	3H	singlet	- $(C\underline{H}_3)_{(e)}$
4	3.5468-3.5979	1H	multiplet	- $(C\underline{H})_{(d)}$
5	5.03558-5.0509	1H	singlet	- Ar-$\underline{H}_{(f)}$
6	7.2755-7.5973	4H	multiplet	- Ar-$\underline{H}_{(j\ to\ m)}$
7	7.6258	1H	multiplet	- Ar-$\underline{H}_{(i)}$
8	7.9442-8.1140	2H	multiplet	- Ar-$\underline{H}_{(g,h)}$
9	9.8055	1H	singlet	- N$\underline{H}_{(l)}$

NMR SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(*p*-NITRO PHENYL CARBOXAMIDO)-*p*-FLUOROPHENYL-1,4-DIHYDRO-PYRIDINE-5-CARBOXYLATE (XII_g).



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.3917	6H	singlet	- ($C\underline{H}_3$)$_{(a,b)}$
2	2.6158-2.6925	3H	multiplet	- ($C\underline{H}_3$)$_{(c)}$
3	3.1142-3.1892	1H	multiplet	- ($C\underline{H}$)$_{(d)}$
4	3.9297-3.9606	3H	singlet	- ($C\underline{H}_3$)$_{(e)}$
5	5.1136	1H	singlet	- Ar-$\underline{H}_{(f)}$
6	6.6684-6.880	2H	doublet	- Ar-$\underline{H}_{(g,g')}$
7	6.7322-6.7513	1H	doublet	- Ar-$\underline{H}_{(i,i')}$
8	6.9953-7.2791	3H	multiplet	- Ar-$\underline{H}_{(j,j')}$
9	7.4191-7.4412	2H	doublet	- Ar-$\underline{H}_{(h,h')}$
10	9.5623	1H	singlet	- N$\underline{H}_{(m)}$
11	7.6024	-	-	-$CDCl_3$

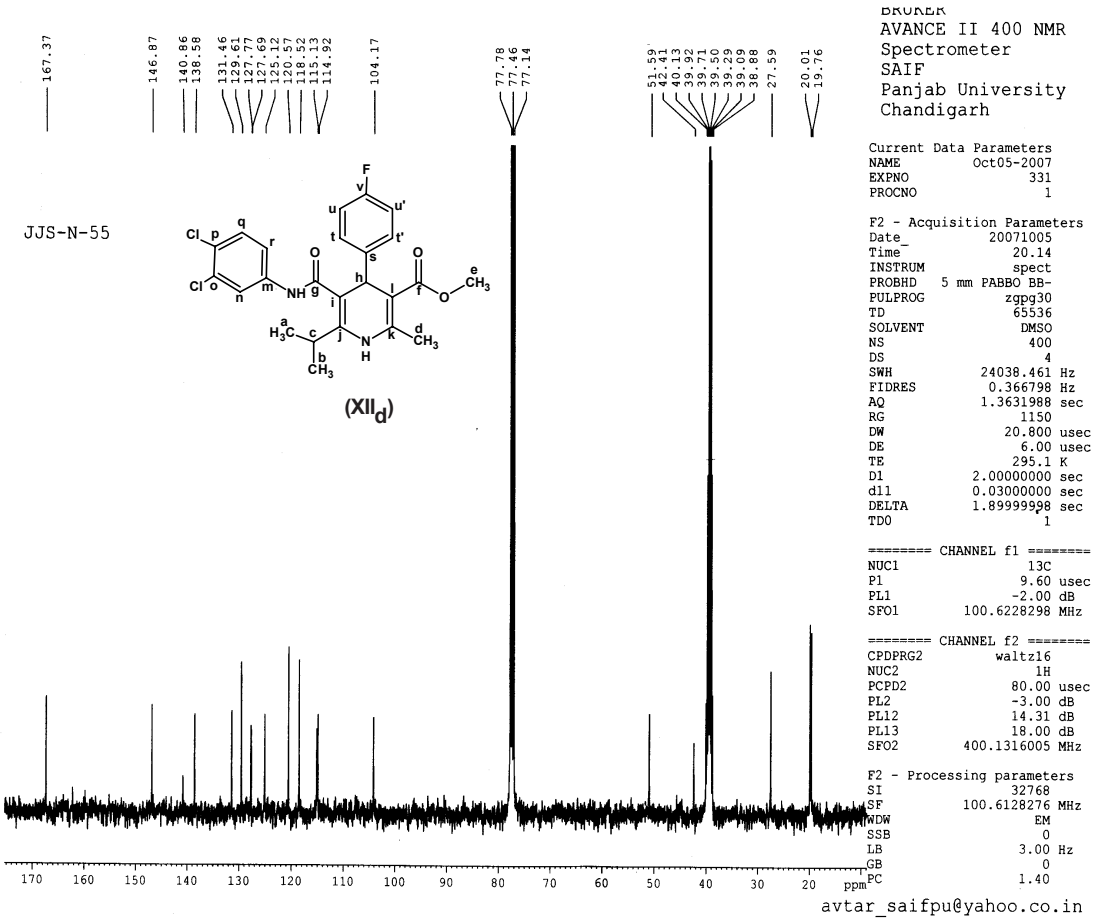
NMR SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(*p*-NITRO PHENYL CARBOXAMIDO)-*m*-NITROPHENYL-1,4-DIHYDRO-PYRIDINE-5-CARBOXYLATE (XII_j).



avtar_saifpu@yahoo.co.in

Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.0800-1.39725	6H	doublet	- (CH_3)$_{(a,b)}$
2	2.2528	3H	singlet	- (CH_3)$_{(c)}$
3	3.5754-3.6403	3H	singlet	- (CH_3)$_{(e)}$
4	5.0453-5.1015	1H	singlet	- (CH)$_{(d)}$
5	7.4119-7.6547	2H	multiplet	- Ar-H$_{(i,j)}$
6	7.7764-7.8797	1H	multiplet	- Ar-H$_{(k)}$
7	7.9352-8.1650	5H	multiplet	-Ar-H$_{(gg'-hh',l)}$
8	10.1242	1H	singlet	- NH$_{(m)}$
9	3.2160	-	-	-DMSO-d_6

^{13}CNMR SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(3,4-DICHLOROPHENYLCARBOXAMIDE)-*p*-FLUOROPHENYL-1,4-DIHYDRO- PYRIDINE-5-CARBOXYLATE (XII_d).



Serial No.	Signal Position (δ ppm)	Inference
1	19.76,20.01	- $\underline{C}H_{3(a,b)}$
2	27.59	- $\underline{C}H_{3(d)}$
3	42.41	- $\underline{C}H_{(c)}$
4	51.59	-$C\underline{H}_{2(e)}$
5	104.17	- Ar-$\underline{C}_{(h)}$
6	114.92-146.87	- Ar-$\underline{C}_{(i\ to\ v)}$
7	167.37	-$\underline{C}$ =O(f , g)

MASS SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(*m*-TRIFLUOROMETHYL-PHENYL CARBO-XAMIDO)-*p*-CHLOROPHENYL-1,4-DI HYDRO PYRIDINE-5-CARBOXYLATE (XII_b).

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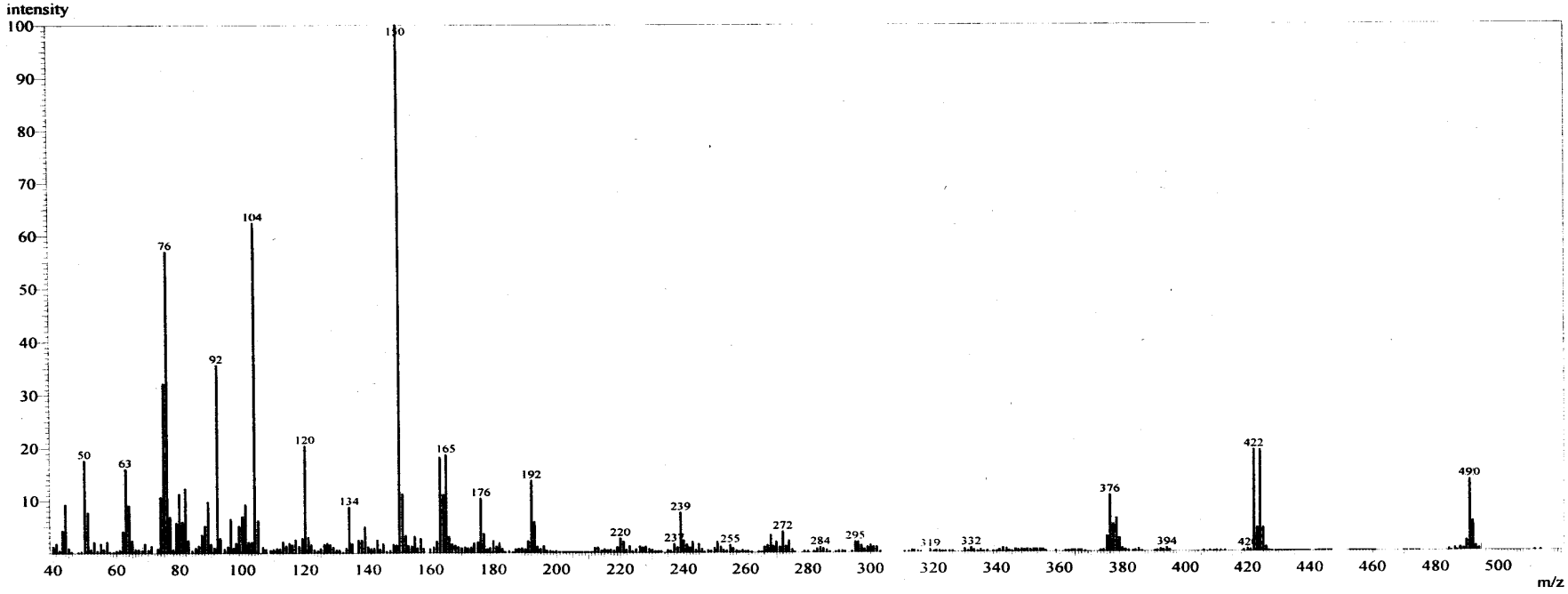
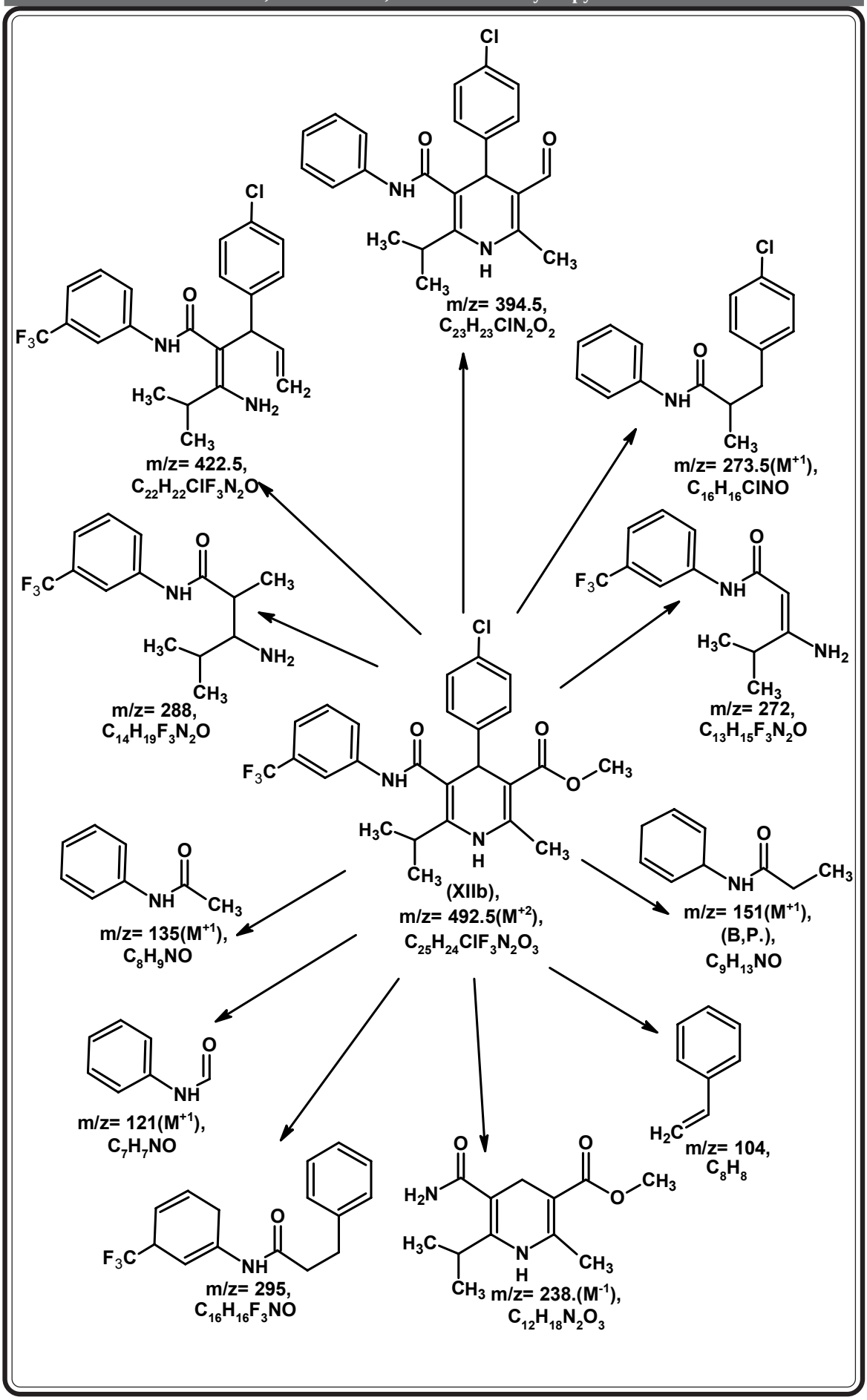
Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 8/25/2007 4:19:46 PM
Sample Name : JJS-49
Sample ID : JJS-49
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-49.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune130807.qgt

Line#:1 R.Time:7.4(Scan#:858)
MassPeaks:382 BasePeak:150(1143540)
RawMode:Single 7.4(858)
BG Mode:None
intensity




m/z= 394.5,
$C_{23}H_{23}ClN_2O_2$
m/z= 422.5,
$C_{22}H_{22}ClF_3N_2O$
m/z= 273.5(M^{+1}),
$C_{16}H_{16}ClNO$
m/z= 288,
$C_{14}H_{19}F_3N_2O$
m/z= 272,
$C_{13}H_{15}F_3N_2O$
(XIIb),
m/z= 492.5(M^{+2}),
$C_{25}H_{24}ClF_3N_2O_3$
m/z= 135(M^{+1}),
C_8H_9NO
m/z= 151(M^{+1}),
(B,P.),
$C_9H_{13}NO$
m/z= 121(M^{+1}),
C_7H_7NO
m/z= 104,
C_8H_8
m/z= 295,
$C_{16}H_{16}F_3NO$
m/z= 238.(M^{-1}),
$C_{12}H_{18}N_2O_3$

MASS SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(3,4-DICHLOROPHENYL CARBOXAMIDO)-*p*-FLUOROPHENYL-1,4-DI HYDRO PYRIDINE-5-CARBOXYLATE (XII_d).

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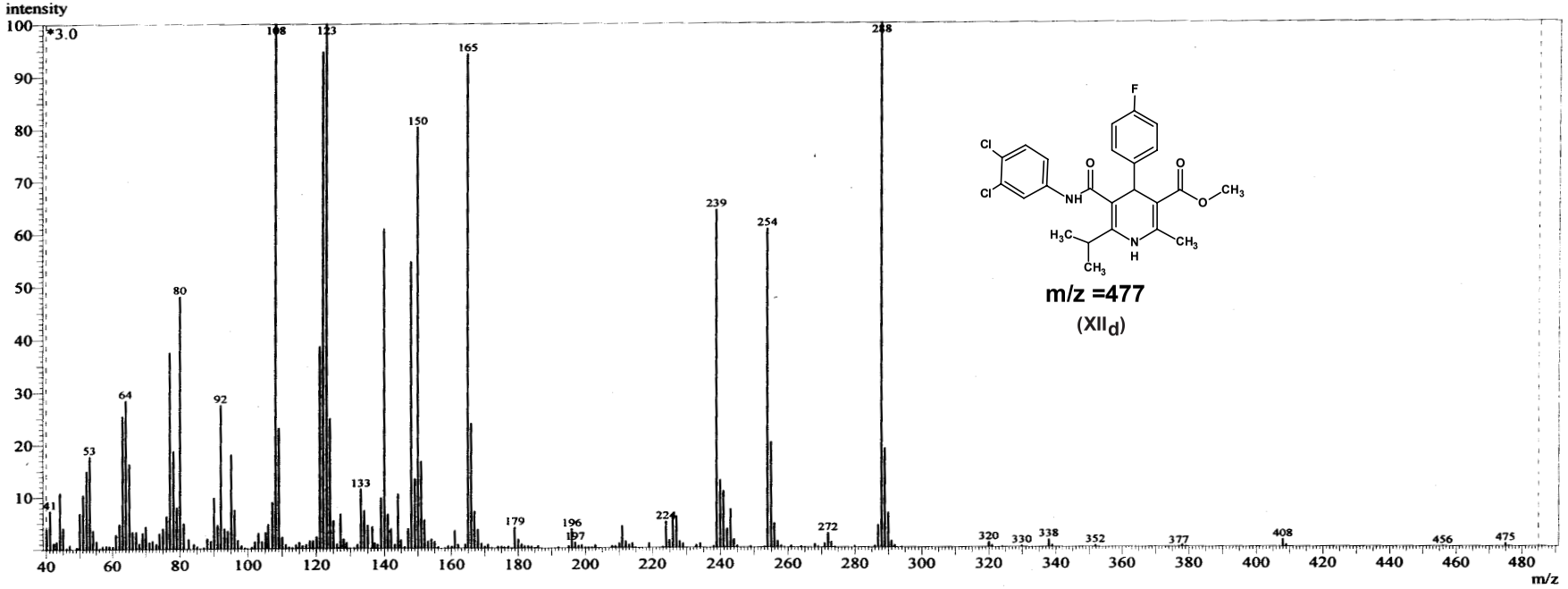
DEPT. OF CHEMISTRY

Sample Information

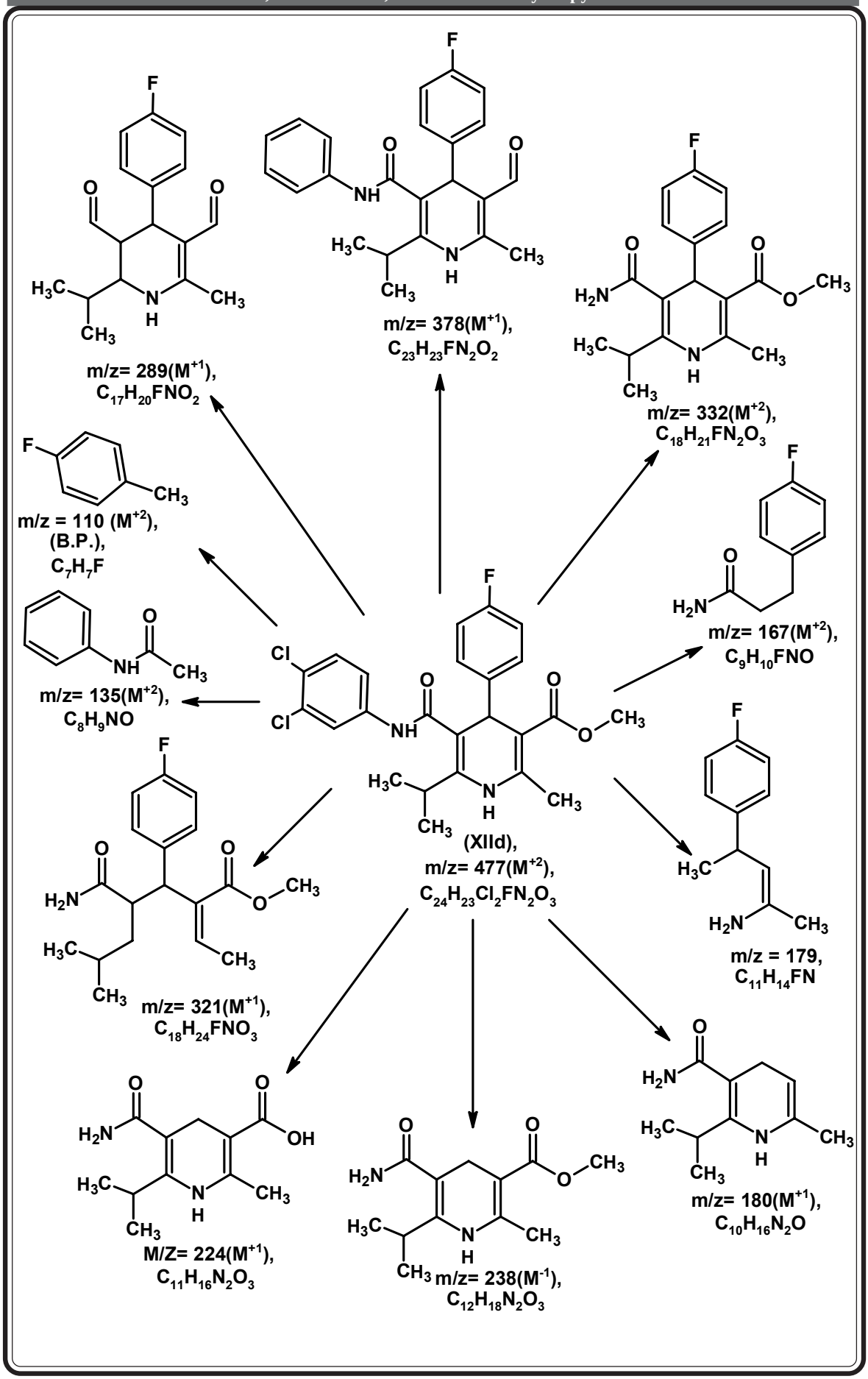
Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 10/31/2006 4:15:22 PM
Sample Name	: JJS-M-67
Sample ID	: JJS-M-67
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-67.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:6.5(Scan#:748)
MassPeaks:220 BasePeak:108(818884)
RawMode:Averaged 5.2-7.6(585-879)
BG Mode:None
intensity



m/z =477

(XII_d)


m/z= 289(M+1), C17H20FNO2
m/z= 378(M+1), C23H23FN2O2
m/z= 332(M+2), C18H21FN2O3
m/z = 110 (M+2), (B.P.), C7H7F
m/z= 167(M+2), C9H10FNO
m/z= 135(M+2), C8H9NO
(XIId), m/z= 477(M+2), C24H23Cl2FN2O3
m/z = 179, C11H14FN
m/z= 321(M+1), C18H24FNO3
M/Z= 224(M+1), C11H16N2O3
m/z= 238(M-1), C12H18N2O3
m/z= 180(M+1), C10H16N2O

MASS SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(3,4-DICHLOROPHENYL CARBOXAMIDO)-*m*-NITRO PHENYL-1,4-DI HYDRO PYRIDINE-5-CARBOXYLATE (XII_f).

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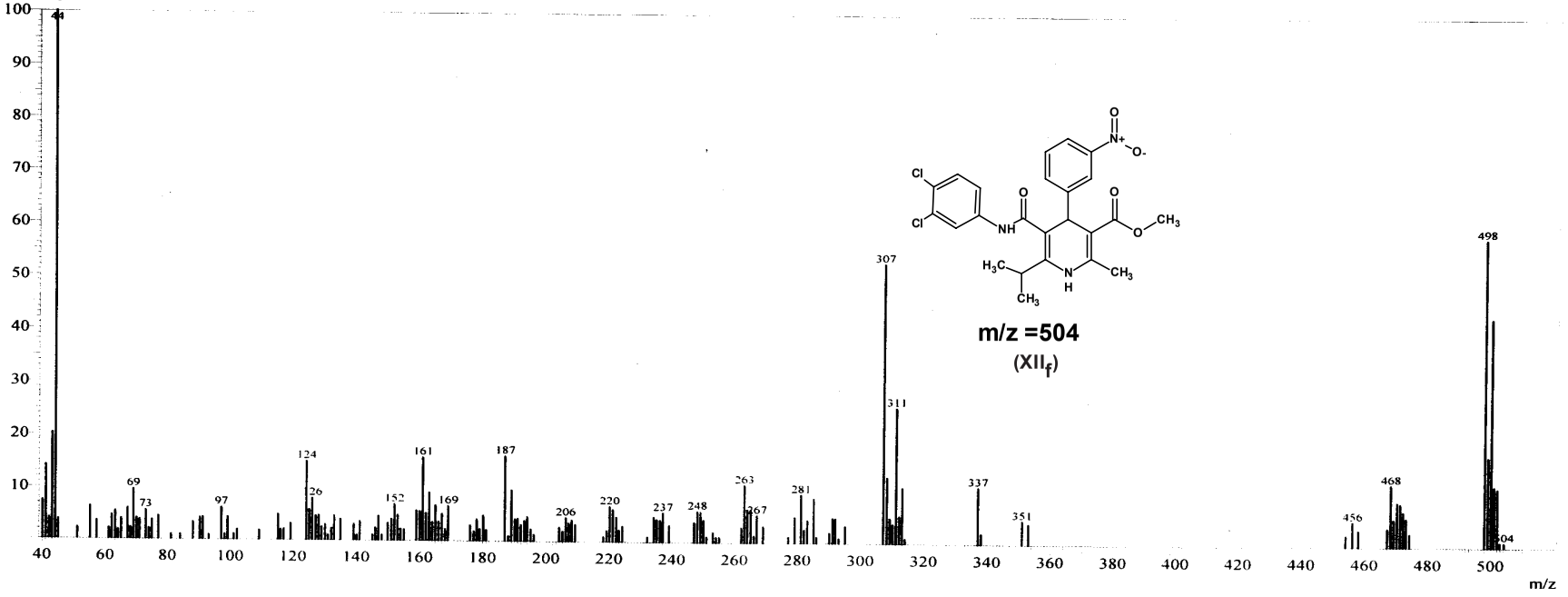
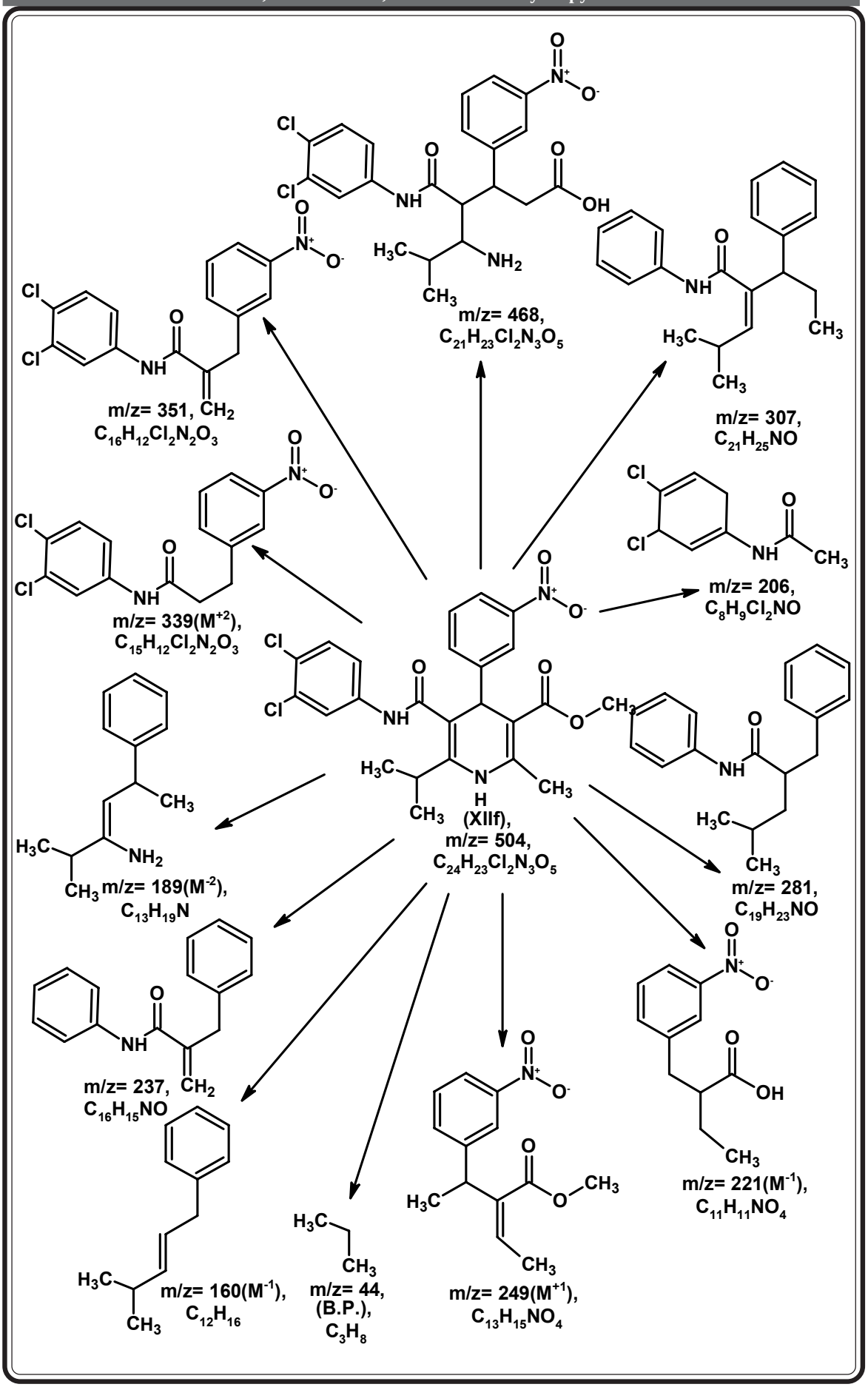
Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 9/21/2007 2:53:35 PM
Sample Name : JJS-MQ-26
Sample ID : JJS-MQ-26
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-26.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\170907_01.qgt

Line#:1 R.Time:11.1(Scan#:1300)
MassPeaks:166 BasePeak:44(37030)
RawMode:Averaged 11.1-11.1(1299-1301)
BG Mode:None
intensity



m/z =504
(XII_f)


m/z= 468,
C21H23Cl2N3O5
m/z= 351, CH2
C16H12Cl2N2O3
m/z= 307,
C21H25NO
m/z= 339(M+2),
C15H12Cl2N2O3
m/z= 206,
C8H9Cl2NO
(XIIf),
m/z= 504,
C24H23Cl2N3O5
m/z= 189(M-2),
C13H19N
m/z= 281,
C19H23NO
m/z= 237, CH2
C16H15NO
m/z= 221(M-1),
C11H11NO4
m/z= 160(M-1),
C12H16
m/z= 44,
(B.P.),
C3H8
m/z= 249(M+1),
C13H15NO4

MASS SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(*p*-NITROPHENYL CARBOXAMIDO)-*p*-FLUORO PHENYL-1,4-DI HYDRO PYRIDINE-5-CARBOXYLATE (XII_g).

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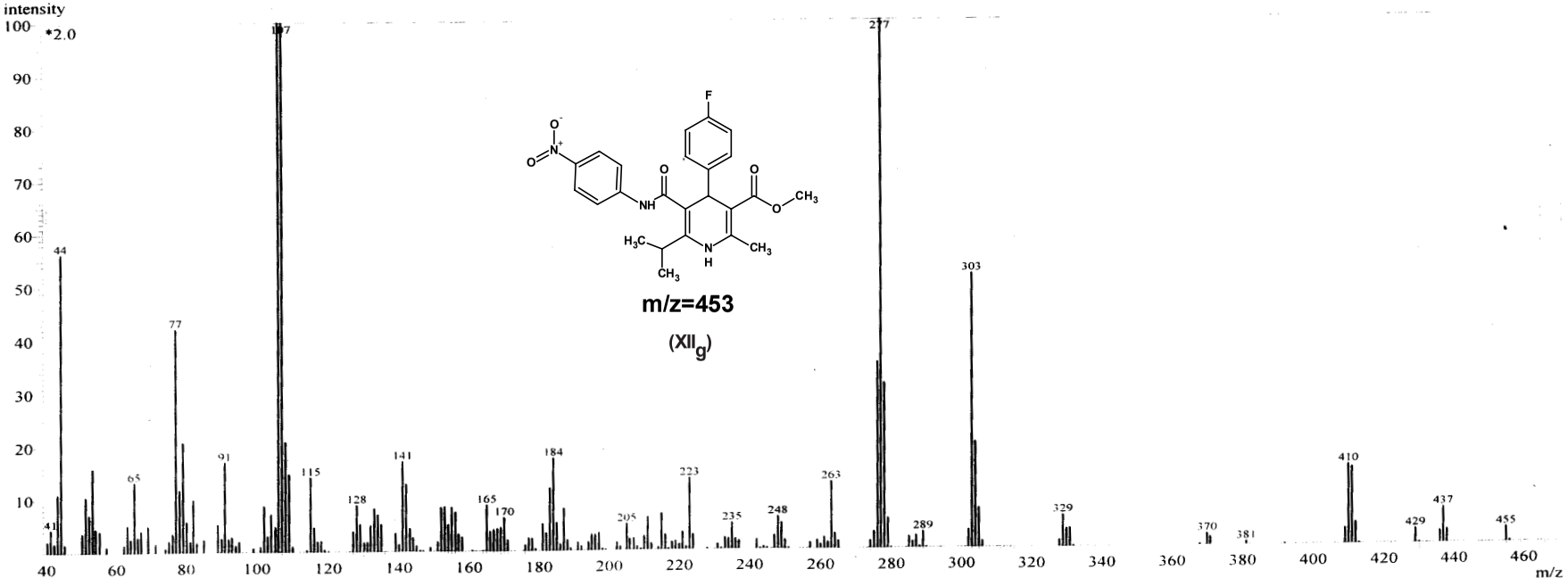
Sample Information

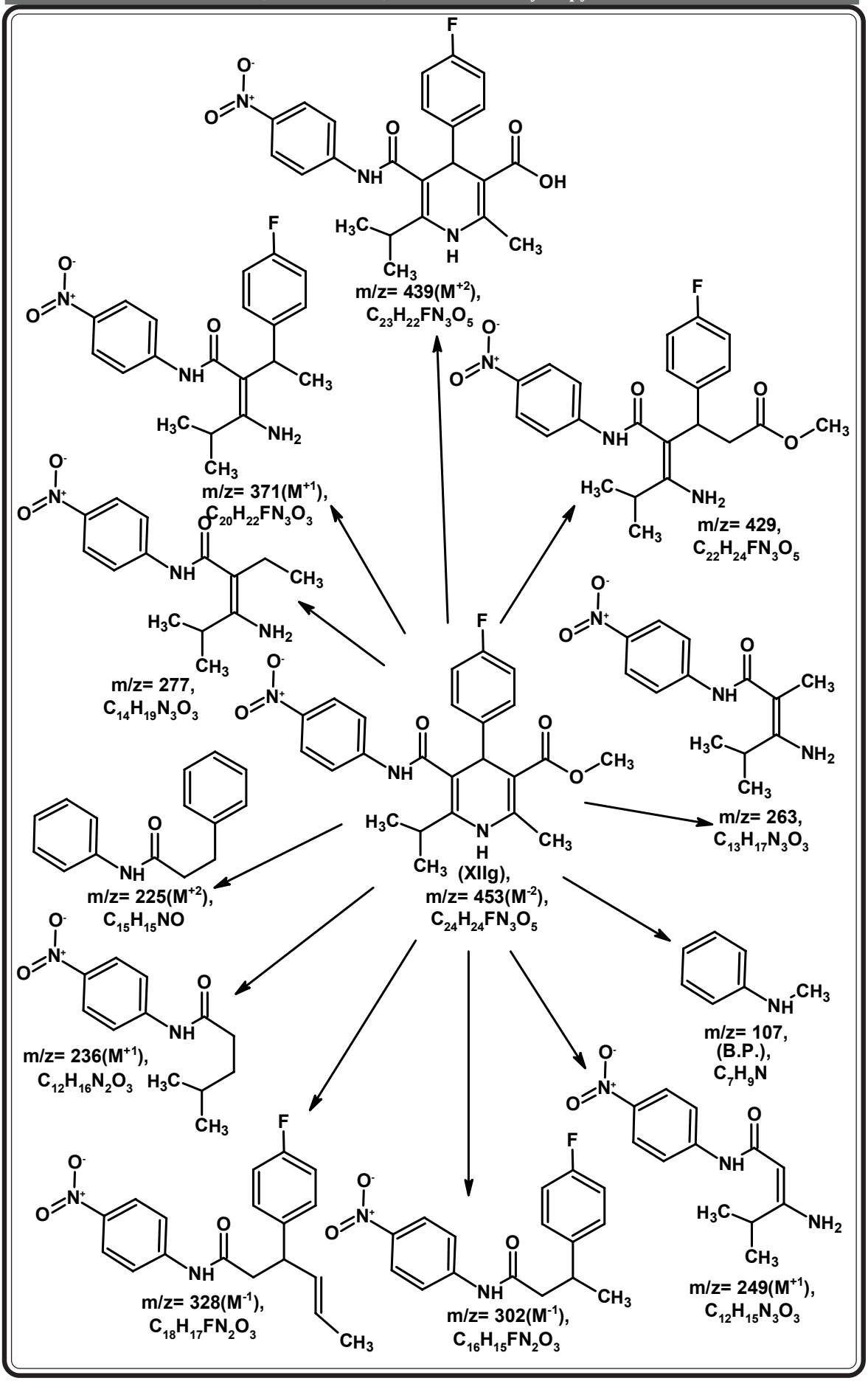
Analyzed by	: PANKAJ KACHHADIA
Anaiyzed	: 9/23/2006 4:47:45 PM
Sample Name	: JJS-M-48
Sample ID	: JJS-M-48
Data File	: C:\GCMSsolution\Data\V.H.SHAH\JJS-M-48.QGD
Method File	: C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File	: C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:11.2(Scan#:1305)
MassPeaks:200 BasePeak:107(178365)
RawMode:Averaged 10.3-12.0(1203-1407)
BG Mode:None
intensity



m/z=453

(XII_g)


m/z= 439(M+2),
C23H22FN3O5
m/z= 371(M+1),
C20H22FN3O3
m/z= 429,
C22H24FN3O5
m/z= 277,
C14H19N3O3
m/z= 263,
C13H17N3O3
(XIIg),
m/z= 453(M-2),
C24H24FN3O5
m/z= 225(M+2),
C15H15NO
m/z= 107,
(B.P.),
C7H9N
m/z= 236(M+1),
C12H16N2O3
m/z= 328(M-1),
C18H17FN2O3
m/z= 302(M-1),
C16H15FN2O3
m/z= 249(M+1),
C12H15N3O3

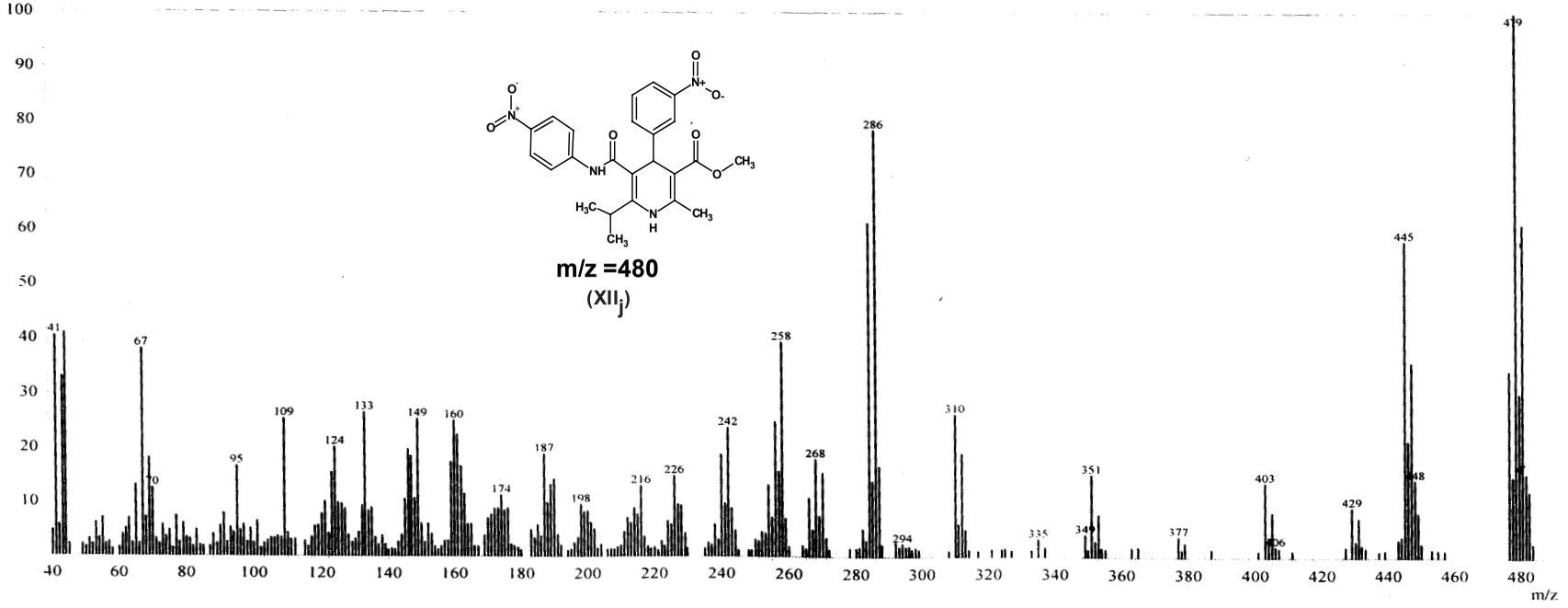
MASS SPECTRAL STUDY OF METHYL-2-ISOPROPYL-6-METHYL-3-(*p*-NITRO-PHENYL CARBOXAMIDO)-*m*-NITRO-PHENYL-1,4-DI HYDRO PYRIDINE-5-CARBOXYLATE (XII_j).

SAURASHTRA UNIVERSITY - RAJKOT
DEPT. OF CHEMISTRY

Sample Information

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 9/21/2007 2:12:35 PM
Sample Name : JJS-MQ-25
Sample ID : JJS-MQ-25
Data File : C:\GCMSsolution\Data\V.H.SHAH\JJS-MQ-25.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\170907_01.qgt

Line#:1 R.Time:10.4(Scan#:1214)
MassPeaks:291 BasePeak:473(99963)
RawMode:Single 10.4(1214)
BG Mode:None
intensity



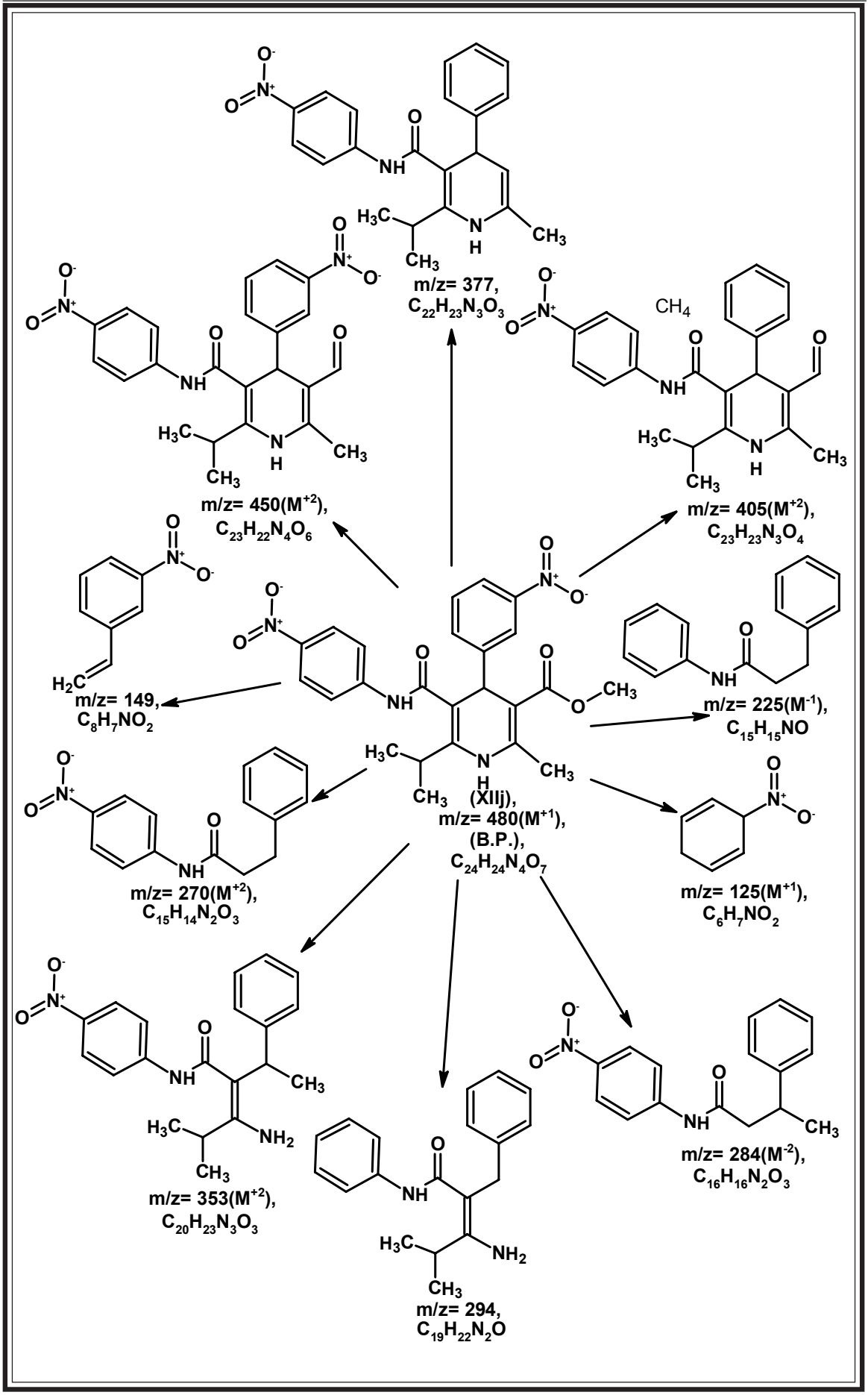

m/z= 377,
C22H23N3O3
m/z= 450(M+2),
C23H22N4O6
m/z= 405(M+2),
C23H23N3O4
m/z= 149,
C8H7NO2
m/z= 225(M-1),
C15H15NO
(XIIj),
m/z= 480(M+1),
(B.P.),
C24H24N4O7
m/z= 270(M+2),
C15H14N2O3
m/z= 125(M+1),
C6H7NO2
m/z= 353(M+2),
C20H23N3O3
m/z= 284(M-2),
C16H16N2O3
m/z= 294,
C19H22N2O

TABLE NO. 12B : COMPARATIVE ANTIMICROBIAL ACTIVITY OF METHYL-2-ISOPROPYL-6-METHYL-3-(SUBSTITUTED-PHENYL CARBOXAMIDO)-*4*-SUBSTITUTED-PHENYL-1,4-DIHYDROPYRIDINE-5-CARBOXYLATES (XII_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R_1	Antibactrial activity (Zones of inhibition in m.m.) S. pyogens MTCC- 442					S. aureus MTCC- 96				
			5	25	50	100	250	5	25	50	100	250
XII_a	4-F-C_6H_4	3-CF_3-C_6H_4	-	8	8	10	12	-	9	11	13	17
XII_b	4-Cl-C_6H_4	3-CF_3-C_6H_4	-	8	9	11	13	-	10	12	14	17
XII_c	3-NO_2-C_6H_4	3-CF_3-C_6H_4		10	10	12	14		8	10	12	16
XII_d	4-F-C_6H_4	3,4-$(Cl)_2$-C_6H_3	-	9	11	13	15	-	8	11	13	15
XII_e	4-Cl-C_6H_4	3,4-$(Cl)_2$-C_6H_3	-	9	10	12	14	-	9	10	11	14
XII_f	3-NO_2-C_6H_4	3,4-$(Cl)_2$-C_6H_3	-	10	12	14	16	-	9	11	14	15
XII_g	4-F-C_6H_4	4-NO_2-C_6H_4	-	11	13	15	17	-	11	13	15	19
XII_h	3-Cl-C_6H_4	4-NO_2-C_6H_4	-	8	9	11	14	-	8	10	12	16
XII_i	4-Cl-C_6H_4	4-NO_2-C_6H_4	-	9	10	11	13	-	8	9	11	12
XII_j	3-NO_2-C_6H_4	4-NO_2-C_6H_4	-	8	8	10	12	-	9	10	13	15

Comparative activity of (XII_{a-j}) with known choosen standard drugs

Standard drug	Antibacterial activity									
									XII_g	$XII_{a,b}$ $XII_{c,g}$ XII_h
Amoxicilin	12	14	15	16	18	10	12	14	15	16
Chloramphenicol	14	15	18	19	24	14	17	20	21	24
Sparfloxacin	14	22	24	26	28	24	26	27	28	32
Levofloxacin	18	21	22	27	29	20	24	26	27	35

N.B.(-): No Activity

TABLE NO. 12C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF METHYL-2-ISOPROPYL-6-METHYL-3-(SUBSTITUTED-PHENYL CARBOXAMIDO)-*4*-SUBSTITUTED-PHENYL-1,4-DIHYDROPYRIDINE-5-CARBOXYLATES (XII_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R_1	Antibactrial activity (Zones of inhibition in m.m.) B. subtillis MTCC- 441					E. Coli MTCC- 443				
			5	25	50	100	250	5	25	50	100	250
XII_a	4-F-C_6H_4	3-CF_3-C_6H_4	-	9	10	11	14	-	7	8	9	11
XII_b	4-Cl-C_6H_4	3-CF_3-C_6H_4	-	10	11	12	15	-	6	7	13	15
XII_c	3-NO_2-C_6H_4	3-CF_3-C_6H_4	-	8	9	10	13	-	8	10	9	10
XII_d	4-F-C_6H_4	3,4-$(Cl)_2$-C_6H_3	-	7	8	9	12	-	7	8	13	16
XII_e	4-Cl-C_6H_4	3,4-$(Cl)_2$-C_6H_3	-	8	9	10	11	-	8	10	8	11
XII_f	3-NO_2-C_6H_4	3,4-$(Cl)_2$-C_6H_3	-	8	10	11	14	-	5	7	13	18
XII_g	4-F-C_6H_4	4-NO_2-C_6H_4	-	9	10	11	13	-	9	11	12	16
XII_h	3-Cl-C_6H_4	4-NO_2-C_6H_4	-	8	9	10	12	-	8	10	11	13
XII_i	4-Cl-C_6H_4	4-NO_2-C_6H_4	-	8	10	10	11	-	7	9	10	12
XII_j	3-NO_2-C_6H_4	4-NO_2-C_6H_4	-	7	9	10	12	-	6	8	9	10
Comparative activity of (XII_{a-j}) with known choosen standard drugs												
Standard drug			**Antibacterial activity**									
Amoxicilin			12	15	16	18	19	11	14	16	18	20
Chloramphenicol			18	22	24	26	27	17	20	23	25	26
Sparfloxacin			22	24	25	26	29	20	22	25	26	28
Levofloxacin			24	26	28	29	31	23	25	26	29	30

N.B.(-): No Activity

TABLE NO. 12D : COMPARATIVE ANTIMICROBIAL ACTIVITY OF METHYL-2-ISOPROPYL-6-METHYL-3-(SUBSTITUTED-PHENYL CARBOXAMIDO)-4-SUBSTITUTED-PHENYL-1,4-DIHYDROPYRIDINE-5-CARBOXYLATES (XII_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R_1	Antifungal activity (Zones of inhibition in m.m.) C. albicans MTCC- 227					A. niger MTCC- 282				
			5	25	50	100	250	5	25	50	100	250
XII_a	4-F-C_6H_4	3-CF_3-C_6H_4	-	8	10	10	12	-	8	9	11	14
XII_b	4-Cl-C_6H_4	3-CF_3-C_6H_4	-	8	10	11	14	-	8	10	12	15
XII_c	3-NO_2-C_6H_4	3-CF_3-C_6H_4	-	5	10	12	14	-	8	9	11	13
XII_d	4-F-C_6H_4	3,4-$(Cl)_2$-C_6H_3	-	6	8	11	13	-	7	8	10	12
XII_e	4-Cl-C_6H_4	3,4-$(Cl)_2$-C_6H_3	-	7	8	12	14	-	8	10	12	14
XII_f	3-NO_2-C_6H_4	3,4-$(Cl)_2$-C_6H_3	-	7	9	10	13	-	9	11	13	15
XII_g	4-F-C_6H_4	4-NO_2-C_6H_4	-	6	9	11	14	-	8	9	11	13
XII_h	3-Cl-C_6H_4	4-NO_2-C_6H_4	-	7	8	9	11	-	7	8	10	12
XII_i	4-Cl-C_6H_4	4-NO_2-C_6H_4	-	7	8	10	12	-	8	10	12	13
XII_j	3-NO_2-C_6H_4	4-NO_2-C_6H_4	-	6	8	10	12	-	6	8	10	12
Comparative activity of (XII_{a-j}) with known choosen standard drugs												
Standard drug			**Antifungal activity**									
Griseofulvin			16	18	21	23	25	17	19	21	22	23
Fluconazole			14	16	18	21	22	15	17	18	20	21

N.B.(-): No Activity

REFERENCES

238. Huang, Fu Chin, Clara J., Jones Howart; *Chem. Abstr*., **101**, 110747(1984).

239. B.Chekavichus et.al.; (Latvin institue of organic synthesis, Riga. Latvia, LV-1006); *Chem. Heterocycl. Compd*. (N.V.) (Pud. 1998), **33** (7), (1997) 799-Sou(Eng.); *Chem, Abstr*., **128**, No.11, 127907t-562 (1996).

240. Hermandez- Gallegoes, F. PA Lehmann, E. Hung, F. Posadas, E. Herman dez Gallegos; *Eur. J. Med. Chem*., 355-364 (1995).

241. K.Ohsumi, K. Ohishi, Y. Morinaga, R. Nakagava, Y. Suga, T. Sekiyama, T. Tsuji, T. Tsurui; *Chem. Pharm. Bull.*, **13** (5), 818-828 (1995).

242. F.Bossert et.al; Ger. Offen., 1,923,990; *Chem. Abstr*., **74**,53543p (1971).

243. A. Zidermane, G. Duburs. A. Zibere, Lat. V PSR; Zinat. Akad. Vestes, **4**, 77 (1970), *Chem. Abstr*., **75,** 47266 (1971).

244. S. M. Jain, R. Kant, S. Devi, K. L. Dhar, S. Singh, S. Bani, G. B. Singh; *Ind. J.Chem*. **29B**, 95-97 (1990).

245. Harada K, Kawahara J, Okada Y, Uzamaki H, Kusaka M, Tokiwa T; *Jpn. J. Pharmacol.*, Nov; **78** (3), 261-8 (1990).

246. Miri Ramin, Howlett Susan E., Knaus Edward E. (Faculty of Pharmacy,Pharmaceutical Sciences, University Alberta, Edmonton, AB Can. T6G2N8); *Arch. Pharm.,* (Weinhein, Ger.) 1997, 330 (9-10), 290-294 (Eng.); *Chem. Abstr*., **128**, No. 6, 61409-530 (1998).

247. I. Nadeem et.al.; (Faculty of Pharmacy, Pharmaceutical Sciences University of Albe-rta, Edmonton, AB Can. T6G2N8), Drug Dev. Res. 1997, 42 (3/4), 120-130 (Eng);*Chem. Abstr*., **128**, No. 26, 321541j-570 (1998).

248. K. Isamu et.al; (department of Chemistry, Faculty Engineering, Gifu University, Ja pan, (501) 1997, (11), 1321-1324 (Eng.); *Chem. Abstr*.,**128**, No. 8,88763w-561(1998).

249. Niwa Seili et.al. (Ajinomoto Co., Inc, Japan); PCT Int. Appl., WO 19 32,446 (CI.C0 7d211/30), 1 July 1999, Jp Appl. 1998/303, 067, 23 Oct.1998; 101, pp (Japan); *Chem.Abstr*., **131**, No. 6, 73562t-738(1999).

250. S. G. Jagadeesh, G. L. David Krupadanam and G. Srimannarayana; *Ind. J. Chem*., **36**(2), 965 (1997).

251. C. Safak, I. Sahin, R. Sunal; Arzneim-forsch/ Drug Res., **40(1)**, 119-122 (1940).

252. Hernandez-Gallegos, F.PA Lehmann, E. Hung, F. Posadas, E. Hernandez-Gallegos; *Eur.J. Med. Chem*., **30**, 355-364 (1995).

253. P. Murugan and V. T. Ramakrishnan; *Indian J. Chem*., **40B**, pp.78 -781 (2001).

254. A. Shah, H. Geraiya, Y. Motohshi, M. Kawase, S. Saito, H. Sakagami, K. Saton, Y. Tada; *J. Anticancer,* **203**, 323-78 (2000).

255. A. V. Sauin et.al., (Department of Chemistry, Moscow state Univ.,Moscow , Rusia (119894); *Rus. J. Org. Chem.*, 1997, **33** (2), 205-212 (Eng.); *Chem. Abstr*., **128**, No.13, 153990j-587 (1998).

256. Fujii Hirofumi, Hayashi Shunichi (Nitto Denko Corp., Japan); Jpn. Kokai,Tokkyo Koho JPW 175,953 (98 175,953) (Cl.C07D 211/90,30 June 998, Appl. 96/340,123, 19 Dec. 1996; 13 pp. Japan; *Chem. Abstr.*, **129**, No.8, 95407a-690 (1998).

257. Castelli, Eugenio et.al.; PCT.Int. Appl. Wo 95 07,698(Cl. C07D 211/90), 26 Feb. 1998, IT Appl. 96/1, 708, 23- Aug.1996, 20 pp.(Eng.); *Chem. Abstr.*, **123**, No.16, 192556s-517 (1998).

258. Bennasar, M-Liuisa et.al.(Laboratory of Organic Chemistry, Faculty of Pharmacy, Univ. of Barcelona, Barcelona Spain 08028); *Tetradedron Lett.,* 1998, 39(50), 9275-9278 (Eng.); *Chem. Abstr.*, **130**, No.10, 124977w-709 (1999).

259. G. Inoue; Nippon Kagaku Zasshi, **79**, 1243-6 (1958); *Chem. Abstr.*, **54**, 24716 (1960).

260. G. Inoue; Nippon Kagaku Zasshi, **80**, 1061-3 (1959); *Chem. Abstr.*, **55**, 3586 (1961).

261. G. Inoue, N. Sugiyama, T. Ozawa; *Nippon Kagaku Zasshi*, **82**, 1272-4(1961); *Chem. Abstr.*, **57**, 15067 (1960).

262. V. K. Ahluwalia and Umashankar Dasl, *Ind. J. Chem., Sect-B*, **35B**, 852 (1996).

263. V. K. Ahluwalia and Pooja Sharma and Bindu Goyal; *Ind. J. Chem.*, **36B**,1059 (1997).

264. R. Nanda Kumar, T. Suresh and P. S. Mohan; *Oriented J. Chem.*, Vol.**18(1)**, 93-96 (2002).

265. Vater W., Kroneberg G., Hoffmeifer F., Kaller H., Meng K., Oberdorf A., Plus W,Schlossmann K. and Stoepelk K.; *Arzneim-forsch*, **22**, (1972).

266. Iwanami M. et.at.; *Chem. Pharm. Bull*, **27**, 1426 (1979).

267. Takenaka T., Usnda S. Nomara T., Maeno H. and Sado T.*; Arzneim-forsch*, **26**, 2172 (1976).

268. Bossert F. and Vater W.; *Med. Res. Rev*. **9**, 291 (1989).

269. Kastrons V., Vitolins R. and Duburs G.; *Khim Farm Zh*, **24**, 14 (1990).

270. Triggle D. J. et. al.; *Med. Res. Rev*. **9**, 123 (1989).

271. Janis R. A, Silver P. and Triggle D. J.; *Adv. Drug Res*., **16**, 307 (1987).

272. Oht Suka M., Yokota M., Kodama I., Yamada K. and Shibata S.; *Gen. Pharmacol.* **20**, 539 (1989).

273. Sausing A. and Duburs G.; *Heterocycles*, **27**, 269 (1988).

274. Bossert F. Meyer H. and Wehinger E.; *Angew. chem*., **93**, 755 (1981).

275. Bossert F. Meyer H. and wehinger E.; *Angew. Chem*., Int. Ed. Engl., **93**, 762 (1987).

276. Stout D. M. and Meners; A I, *Chem. Rev.*, **82**, 223 (1982).

277. Kuthan J. and Kurfurst A.; Ind. *Eng. Chem. Prod Res. Dev*., **21**,191 (1982).

278. Eisner U. and Kuthan J. *; Chem. Rev.*, **72**, 1 (1972).

279. Freedman D. D. and Waters D. D.*; Drugs*, **34**, 578 (1987).

280. Kazda S. and Towart R. ; *Br. J. pharmacol*., **72**, pp. 582-83 (1981).

281. Tanaka K. et. al.; *Arzneim-forsch*, **32**, 1529 (1982).

282. Kazda s. et. al.; *Arzneim-forsch*, **30**, 2144 (1980).

283. Stoepel K., Heise A. and Kazda S.; *Arzneim-forsch*, **31**, 2056 (1981).

284. Arrowsmith J. E. et.al; *Pharmacologist*, **27**, 290 (1985).

285. Nyborg N. C. B. and Mulvany M. J.; *J. Cardiovase. Pharmacol*., **6**, 499 (1984).

286. Hof R. P., Scholtusik G., loutzenhiser R., Vuorela H. J. and Neumann P.; *J.cardiovase. Pharmacol.*, **6**, 394,(1984).

287. Meguro K., Aizawa M.,Sohda T., kawamatsu Y., and Nagaoka A.; *Chem. Pharm. Bull.*, **33**, 3787(1985).

288. Furuta T., Shibata S., kodama I. And Yamada K.; *J. Cardiovase. Pharmacol*., **5**, 836 (1983).

289. H. Masakatu, K. Kenichi, S. Yasuchiko, H. Masakazu, K. Osumu, H. Hiroyoshi; *Chem. Abstr*., **130**, No. 3, 24915f-579 (1999).

290. R. C. Johnson, D. J. Taylor, V. A. Kenneth, C. soan; US Pat. 4, 758, 669, *Chem. Abstr.*, **109**, 149336 (1988).

291. K. Cooper, F.M. Jonatham;Eur. Pat. Appl. EP 294, 274, U S Pat. 4, 758, 669,*Chem Abstr*., **110**, 231441 (1989).

292. F. Marco, Z. Andrea, G. Carmelo, M. Germini; Eur. Pat. 272, 693; *Chem. Abstr*.,**109**, 190259 (1988).

293. E. Wehinger, H. Meyer, A. Knorr, K. Stanislaw; *Chem. Abstr.,* 107, 217482 (1987).

294. Marchalin Stefan, et.al. (department of chemistry, Solvak Tech. Univ., Bartialava, Solvakia SK. (81237); *Heterocycles* 1998, 1943-1958 (Eng.), Japan ; *Chem. Abstr.*, **131**, No.3, 24915f-569 (1999).

295. Fujii Masayuki et.al. (Department of chemistry, Kinki univ., Fukuoka,(Japan 820); Trends *Heterocycl. Chem*., 1997, 5, 17- 36(Eng.), Research Trands; *Chem. Abstr.*, **130**, No.6. 66006-669 (1999).

296. Miwa Seiji et.al., (Ajinomato co. inc. Japan); PCT Int. Appl. Wo 99 32,446 (Cl.C07d 211/90), 1, July 1999, Jp Appl. 1998/303, 067, 23 Oct.1998 101 pp. (Japan); *Chem. Abstr*., **130**, No.6, 73562-738 (1999).

297. V. K. Ahluwalia and Bindu Goyal; *Ind. J. Chem.,* Vol. **35B**, Oct (1996), pp.1021-1025.

298. R. K. Khajuria et.al.; *Ind. J. Chem.* Vol. **32B**, Sept. 1993, pp. 981-983.

299. Nagarathnam, Dhanapalau et.al. (Department of Chemistry, pharmaceuticology and Pharmaceutical, Operations, Sunaptic Pharmaceutical corpration, Paramus, NT 07652 USA);*J.Med.Chem.,*1998,42(26), 5320-333(Eng), *American Chemical Society' ,Chem. Abstr*.,**130**(9), 110137-87 (1999).

300. Zhang Sauqi et. al. (Department of Pharmacy, Xijing Hospital, fourthmiitary medical Univ. (CITY 186, Peop. Rep. China) Yaexue Vuebao1998, 33(10) 789-792(ch); *Chem. Abstr.,* 130, No.12 ,15 3554m -648 (1999).

301. Kulbhushan Rana, Balbir kaur and Baldev Kumar; *Ind. J. Chem*., **43B**, 1553 (2004).

302. Z. M. Yan, Y. M. Ding, Y. Xuebao; *Chem. Abstr.,* **106**, 32859 (1987).

303. Karup, Gunnal et.al. (A/S Gea Pharmaceutic Fabrik, Den.); PCT Int;Appl. Wo 99 25, 688 (CI. C07D 211/90),27 May 1999, DK Appl. 1997/1,299, 14 Nov . 1997; 37 pp.(Eng); *Chem. Abstr*., **131**, No. 1, 5189b-627(1999).

304. H. Gevariya , B. Desai , V. Vora, A. K. Shah; *Hetero cycliccommunication* , **7**(5), 481 (2002).

305. Gluchowski Charles et.al. (Synaptic Pharma. Co. USA); U. S. US 5,767,131 (Cl. 514-318; A01N 43/46) 16 Jan. 1998, WO Appl. 94 / US, 3, 852, 5 Apr. 1994; 160 pp.; *Chem. Abstr*., **129**(6), 67709p-661(1998).

306. B. M. Khadilkar et.al. ; *Ind. J. Chem*. , Vol. **40B**, pp. 82-86, Jan. 2001.

307. D.G.Triggle ; Drugs acting on icon channels and membranes, *Comprehensivemedicinal chemistry,* **3**,1047 (1990).

308. H. Meyer et.al; DE 4133257 and EP 5336603 (Bayer A. G.).

309. V. Michael et.al; *Ger. Offen.,* 2, 405,658; *Chem. Abstr*., **81**, 169440b (1974).

310. A. Daich, Milostav Chudik, Stefan Marchlin, Peter Knesl and Bernard Decroix, *J. Het.Chem*.,**37**, 1549 (2000).

311. M. Suarez, Yamila Verdecia, Estael Ochoa, Nazario Martin, RobertoMartinez ; *J. Het.Chem.,* **37**, 735 (2000).

312. M. Sharifzadeh, A. Shafiee, N. Rastkari;*Daru*, **12 (2)**, (2004).

313. K. Shiganobu, H. Tanaka;*Cardiovascular Drug Reviews*, **18(2)**, 93-102 (2000).

314. M. C. R. Franseen, A. Sobolev, A. de Groot; *J. Org. Chem.*, **67**, 401-10 (2002).

315. A. Takahara, T. Yamamoto, S. Niwa;*Bioorganic & Med. Chem. Lett.*, **16 (4)**, 798-802 (2006).

316. Engi, H.; Sakagami, H.; Kawase, M.; Parecha, A.; Manvar, D.; Kothari, H.; Adlakha, P.; Shah, A.;Motohashi, N.; Ocsovszki, I.; Molnar, J.; *In Vivo* **20**, 637-44, 2006.

317. Rafael Leon,Manuela G.Lopez, Mercedes Villarroya, Euro. J. of Med. Chem.**43**,668-674,(2008)

318. G.V. Jadhav, *J. Indian Chem. Soc*.; **7**, 669-671 (1930).

319. B. Desai, D. Sureja, Y. Naliapara, A. Shah, A. K. Saxenab, *Bioorganic & Med. Chem*.; **9,** 1993–1998 (2001).