STUDIES AND BIOLOGICAL EVALUATION OF SYNTHETIC THERAPEUTIC AGENTS

A THESIS

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IN

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BY

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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 ***Prof. V. H. Shah*** and leads to some contribution in chemistry subsidized by a number of references.

Date. : - -2009
Place : Rajkot.

(Mr. Manish J. Solanki)

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

Date : -05 - 2009
Place : Rajkot.

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Dedicated
To
My Family

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*The never ending process of enlightenment, which was initiated by my parents **Mr. Jamanbhai Solanki, Mrs. Madhuben Solanki** like angles drew me to this milestone and I am really staggered to realize, just how many efforts have been put in by them.It will not be out of place to pay grateful thanks to my Brothers **Mr. Jasmin and cousin Dr. Dharmesh** whose affection and loving care which have been always be a moving inspiration to me in fulfilling this research work and for their social sacrifice.*

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- Manish J. Solanki

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** to **33 ^{0}C.**
4. Silica gel-G was used for preparing the TLC plates using different solvant systems.
5. **Infra red** spectra of all the compounds were scanned on **SHIMADZU-FOURIER TRANSFORM INFRA RED (FT-IR)-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 solvants.
7. **^{13}C NMR** Spectra were recorded on **BRUKER Spectrophotometer(400 MHz)** using **$CDCl_3$,**and **DMSO-d_6** as solvants.
8. **MASS** spectra were recorded on **GC-MS-QC-2010.**

ABBREVIATIONS

(1) gl.= glacial.
(2) M.P= Melting point.
(3) B.P= Boiling point.
(4) BP= British pharmacopeis.
(5) DMSO= Dimethyl sulphoxide.
(6) DMSO-d_6= Dutereted dimethylsulphoxide.
(6) $CDCl_3$= Dutereted chloroform.
(7) DMF=Dimethylformamide.
(8) Aq.= Aqueous.
(8) s= Strong.
(9) m= Medium.
(10) br= Broad.
(11) sh= Sharp.
(12) dil.= Dilute.
(13) hrs.=hours.
(14) WHO= World health organization.
(15) E. coli = Escherichia coli.
(16) P. aeruginosa= Pseudomonas aeruginosa.
(17) S. aureus = Staphylococcus aureus.
(18) S.pyogenes = Streptococcus pyogenes.
(19) A. niger = Aspergillus niger.
(20) A. clavatus= Aspergillus clavatus.

CONTENTS

SYNOPSIS

STUDIES AND BIOLOGICAL EVALUATION OF SYNTHETIC THERAEUTIC AGENTS

.

A brief summary of the work to be incorporated in the thesis entitled, **" STUDIES AND BIOLOGICAL EVALUATION OF SYNTHETIC THERAPEUTIC AGENTS''** has been summarized as under.

PART-I : STUDIES ON 1,4-DIHYDRO PYRIDINES

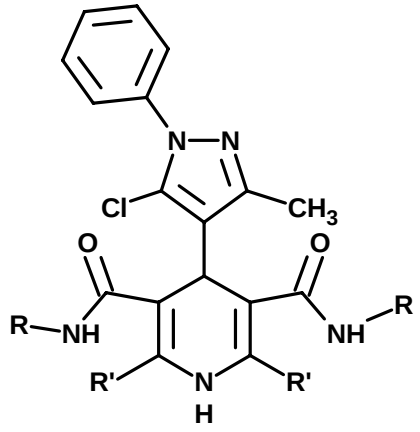
PART-II : STUDIES ON PHENOTHIAZINES

PART-III : STUDIES ON PYRIMIDINES

PART-I : STUDIES ON 1,4-DIHYDRO PYRIDINES

1,4-Dihydro pyridines are one of the most active class of compounds possessing diverse biological activity *viz*., calcium channel 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.

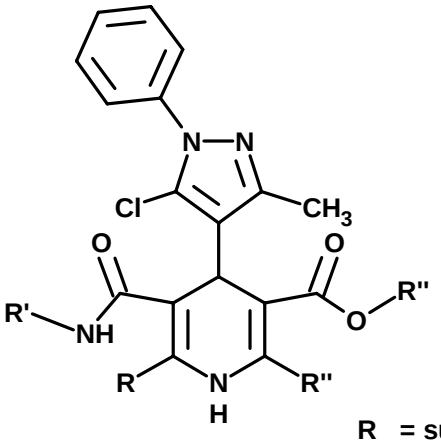
SECTION - I : Preparation and Biological evaluation of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-2,6-dimethyl/-isopropyl-3,5-disubstituted phenylcarbamoyl-1,4-dihydropyridines (I_{a-t}).



(I_{a-t}) R = substituted phenyl
R'= Methyl/Isopropyl

4-(5'-Chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-2,6-dimethyl/-6isopropyl-3,5-disubstituted phenylcarbamoyl-1,4-dihydropyridines (I_{a-t}) have been prepa- red by the cyclocondensation of one mole of **5-chloro-3-methyl-1-phenyl-pyrazole-4-carbaldehyde**, two moles of **N-(substituted -phenyl)-3-oxobutanamides/4-methyl 3-oxopetanamides** and **ammonia.**

SECTION - II : Preparation and biological evaluation of 4-(5'- Chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-2,6-dimethyl/6-isopropyl-2-methyl-3-carbmethoxy/ethoxy-5-substituted phenylcarbamoyl-1,4-dihydropyridines ($II_{a-n'}$).



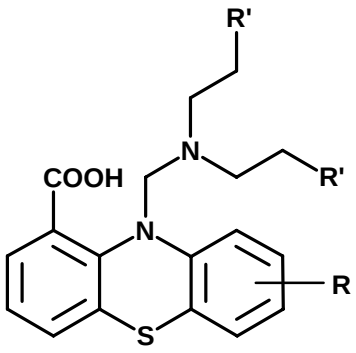
($II_{a-n'}$) R = substituted phenyl
R' = Methyl/ Isopropyl
R''= Methyl/ Ethyl

4-(5'-Chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-2,6-dimethyl/6-isopropyl-2-methyl-3-carbmethoxy/ethoxy-5-substituted phenyl-carbamoyl-1,4-dihydropyridine ($II_{a-n'}$) have been prepared by the condensation of **2-[(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-methylene]-3oxo-N-p-tolylbutanamide** and **methyl-3-aminobut-2-enoate/ ethyl-3-aminobut-2-enoate** in basic mediam.

PART-II : STUDIES ON PHENTOTHIAZINES DERIVATIVES

Phenothiazines possess a wide spectrum of pharmacological activites such as antituberculer, antitumor, anticonvulsant, tranquilizers, antiemetic etc. N-substituted phenothiazine nucleus causes a marked difference in activities and therefore phenothiazines with varied substituents has been synthesized and further their condensation reaction with secondary amine in presence of formaldehyde has been carried out and tested for activities in search of better medicinally interested agents.

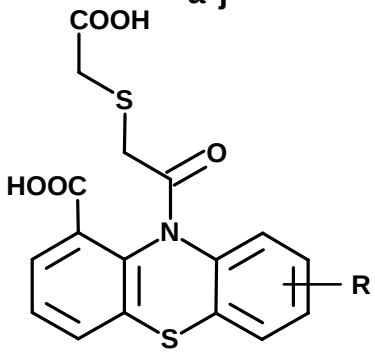
SECTION - I :Preparation and biological evaluation of 7/8/9-Substituted -10-N- [bis (2-chloroethyl/diethyl)-amino]-methyl phenothi azine-1- carboxylic acids (III_{a-t}).



(III_{a-t}) **R = H, o/m/p-CH_3,-OCH_3 and -NO_2**
R'= -H/ Cl

7/8/9-Substituted 10-N-[bis (2-chloroethyl/diethyl)-amino]-methyl-phenothiazine-1-carboxylic acids (III_{a-t}) have been prepared by the reaction of different **substituted phenothizines**, **dichloroethylamine/diethylamine, and formaldehyde** in acidic medium.

SECTION - II : Prepareation and biological evaluation of 7/8/9-Substituted-10-N-[(carboxymethyl)-sulfanylacetyl]-phenothiazine-1- carboxylic acids (IV_{a-j}).



(IV_{a-j}) **R = H, o/m/p-CH_3, -OCH_3,-NO_2**

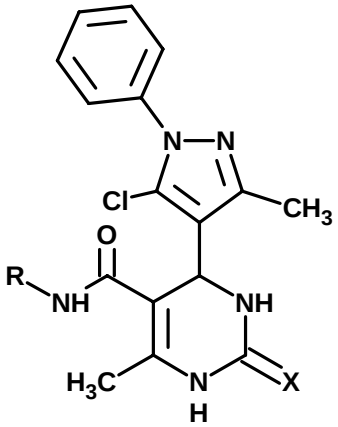
7/8/9-Substituted-10-N-[(carboxymethyl)-sulfanyl-acetyl]-phenothiazines-1-carboxylic acids (IV_{a-j}) have been prepared by the reaction of different substituted **phenothizines**,**chloroacetylchloride** and **thioglycollicacid** in **basic** media.

PART-III : STUDIES ON PYRIMIDINES

Pyrimidines represent one of the most active classes of compounds possessing a wide spectrum of biological activities *viz.,* significant *in vitro* activity against unrelated DNA and RNA viruses including Polio and Herpes viruses, diuretics, antitubercular, antihypertensive. Some pyrimidines, which

occurs as natural products like nucleic acids and vitamin-B and can be used as therapeutic agents for the treatment of AIDS and antitumor. In view of getting better theraputic agents baring pyrimidine nucleus, it was thought worthwhile to synthesize some newer pyrimidine derivatives which can be summarized as below.

Section-I : 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-6-methyl-2-oxo/-thio/-imino/-5-N-substituted phenyl carbamoyl-1, 2, 3,4-tetrahydro pyrimidines ($V_{a-d'}$).



($V_{a-d'}$) Where R= substituted phenyl X= O/ S/NH

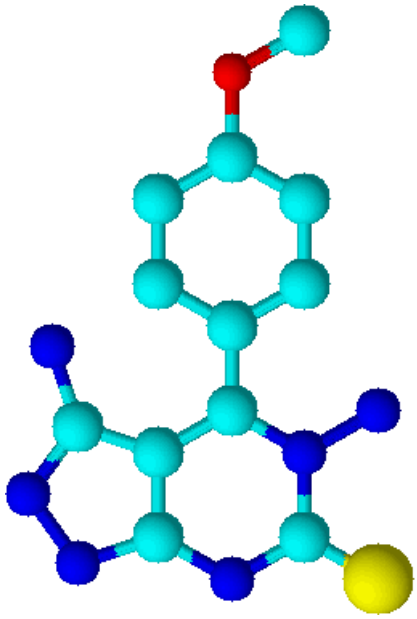
4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-6-methyl-2-oxo/-thio/-imino/-5-N-substituted phenylcarbamoyl-1,2,3,4-tetrahydro -pyrimidines ($V_{a-d'}$) have been prepared by the reaction of **5-chloro-3-methyl-1-phenyl-pyrazol-4-carbaldehyde**, **N-(substituted phenyl)-3-oxobutanamide** and **urea/ thiourea/ guanidine** in **acidic** media.

PURIFICATION AND STRUCTURAL CHARACTRISATION:

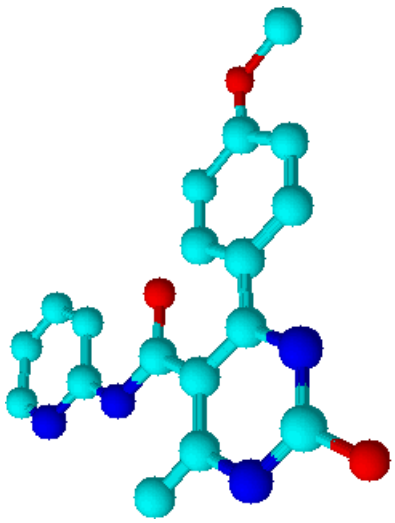
The purity of all compounds have been screened by thin layer chromatography using two different solvent systems **(R_{f_1} & R_{f_2})**. The constitution of newly synthesized compounds have been delineated by **elemental analysis, FT-IR, ^{1}H NMR** and **Mass spectoscopy.**

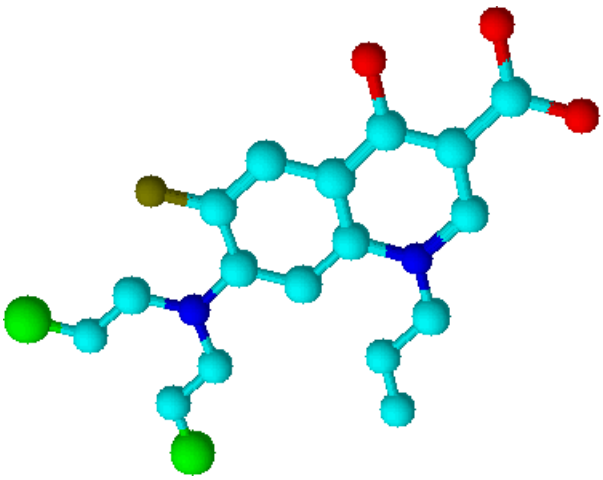
ANTIMICROBIAL ASSAY:

The purified organic compounds have been screened for their *in vitro* therapeutic assay like antibacterial activities towards Gram possitive and Gram negative bacterial strain and antifungal activity towards fungal strain at different concentrations **(Minimum Inhibitory Concentration)**. The biological activities of synthesized compounds have been compared with standard drugs at different concentrations.



STUDIES AND BIOLOGICAL EVALUATION OF SYNTHETIC THERAPEUTIC AGENT





STUDIES AND BIOLOGICAL EVALUATION OF SYNTHETIC THERAPEUTIC AGENTS

(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 move-

ments 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 inves tigation 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 infect ing 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 which are as follow :

(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 therapeuticagent eg. **Metormine glipizide-**anti diabetic.

(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 antima-

larial 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**.

(k) Antacid drugs:

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

(l) 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 ***1,4-Dihydropyridines, Phenothizines and Pyrimidines*** moieties as a better therapeutic activity.

■ **Aims and objectives of the present investigation are**

(a) To generate several biologically active heterocyclic moieties such as **14-Dihydropyridines, Phenothiazines and Pyrimidines.**

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

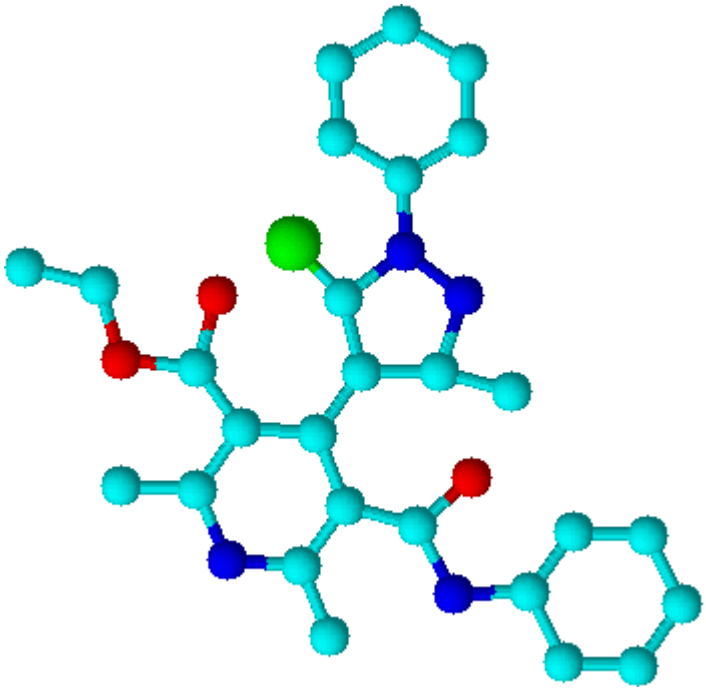
(c) To screen these purified new derivatives for their antimicrobial activity using different strains of bacteria and fungi and to compare antimicrobial activity against different known drugs at different concentrations for their MIC values.

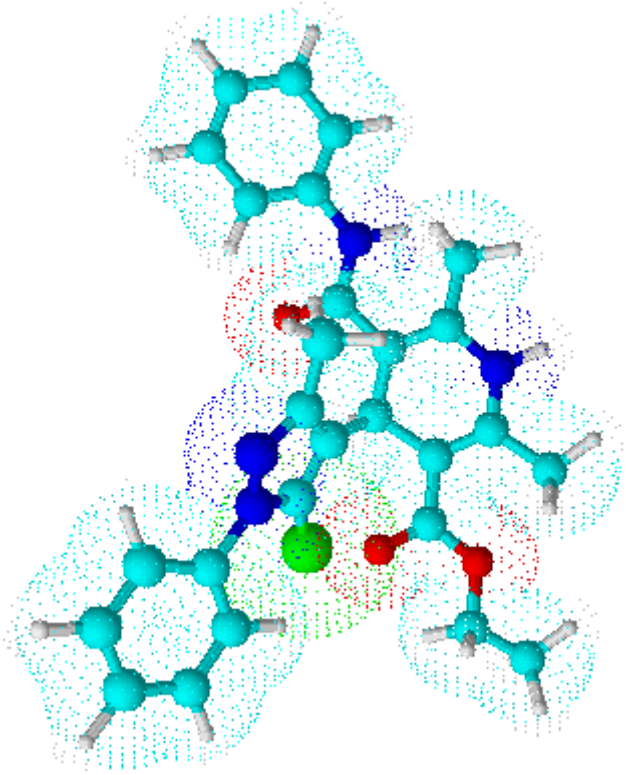
In view of these facts, the research work presented in thesis are as follows.

(I) STUDIES ON 1,4-DIHYDROPYRIDINES

(II) STUDIES ON PHENOTHIAZINES

(III) STUDIES ON PYRIMIDINES





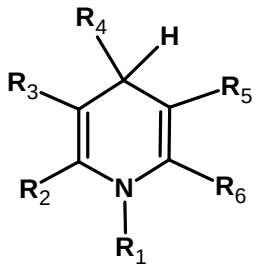
PART-I

STUDIES ON 1,4-DIHYDROPYRIDINES

PART - I
STUDIES ON 1,4-DIHYDROPYRIDINES

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 **(1).**



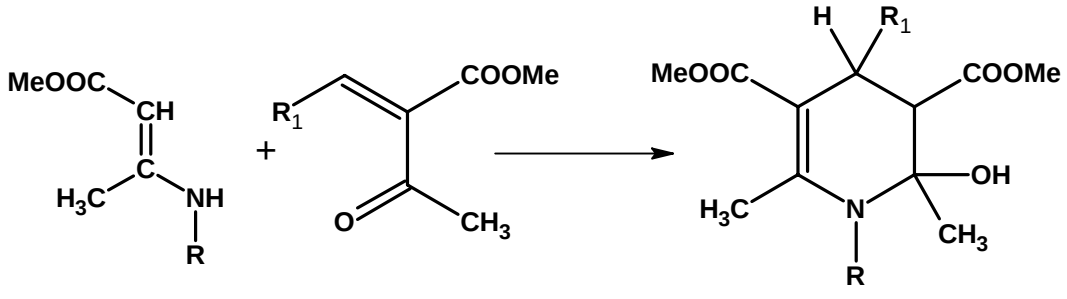
(1)

R_1, R_4 = H / Alkyl / Aryl
R_2, R_6 = Methyl, Isopropyl
R_3, R_5 = Acetyl /Carbmethoxy/ Carbethoxy / N-Aryl Carbamoyl

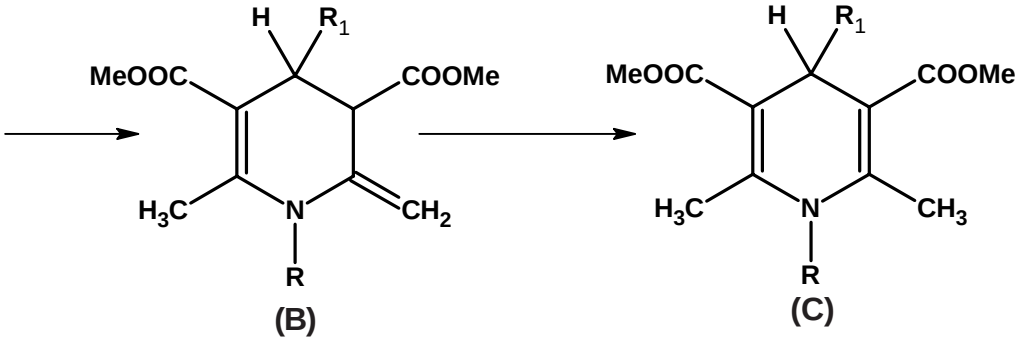
1,4-dihydropyridines contribute as an important class of compounds in medicinal chemistry, leading to several new drugs currently widely used especially as calcium channel antagonist[1] and other cardiovascular diseases also. .

SYNTHETIC METHODS OF DIHYDROPYRIDINE

B. Chekavichus et.al.,[2] has proposed following kind of successive intermidiate[2] in the Hantzsch synthesis of 1,4-dihydropyridines depicted as under.



(A)



R, R_1 = Alkyl / Aryl

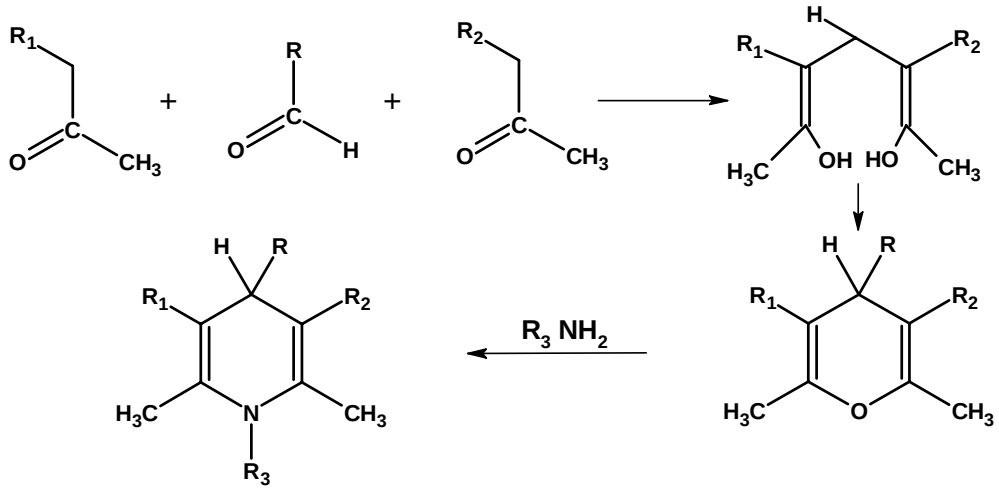
The synthesis of **1,4-dihydropyridines** involves following steps.

(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.

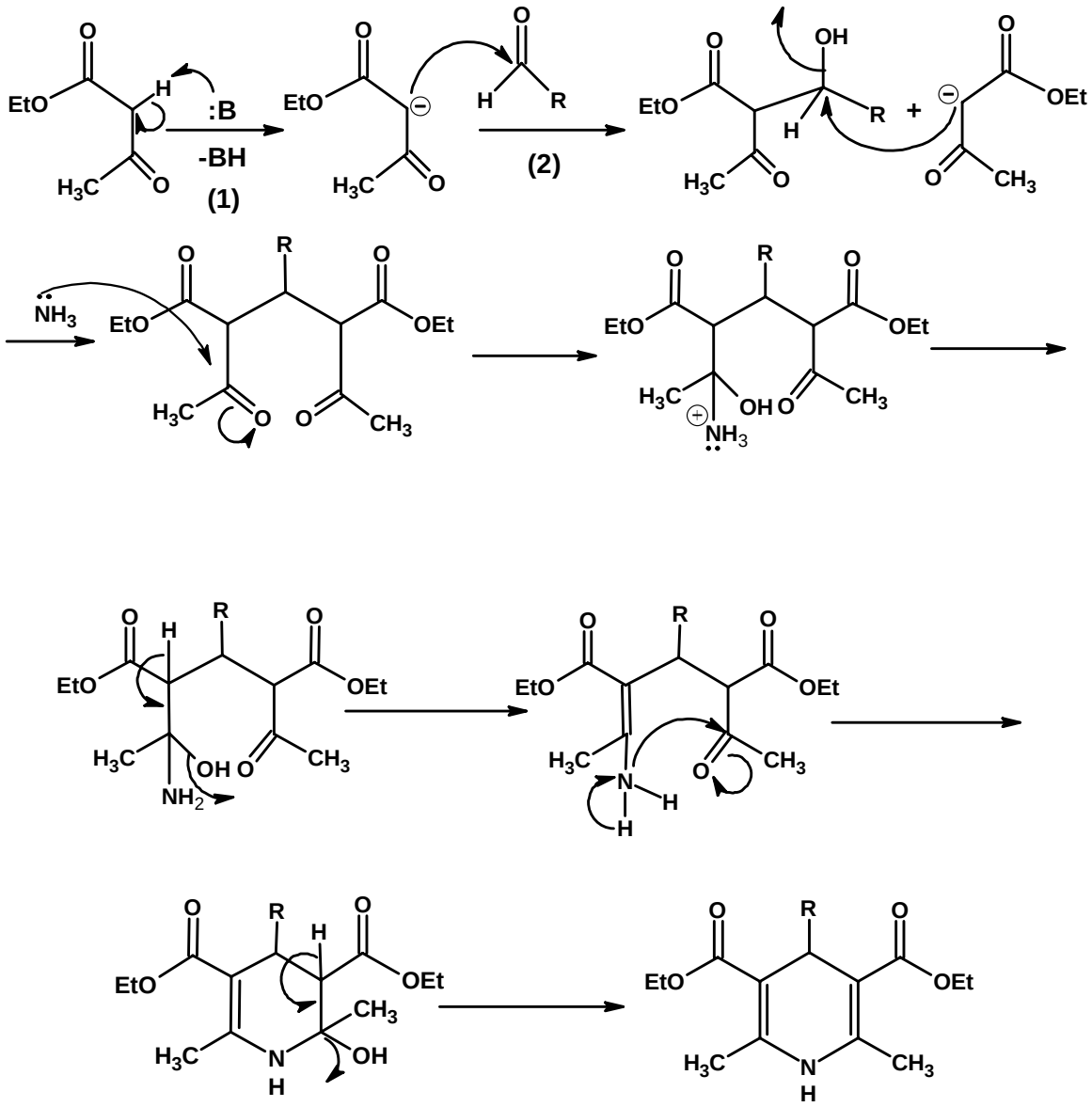


R, R_3 = H / Aryl / Aryl

R_1, R_2 = Carboxylate/ Arylcarbamoyl

MECHANISM:

The Mechanism of 1,4-dihydropyridine prepared by Hantzsch synthesis involves three steps can be depicted as follow:



(1) Abstraction of proton by base from ethyl acetoacetate to form nucleo phile.

(2) Attack of nucleophile on alkyl/aryl aldehyde molecule to yield β–keto ester.

(3) Condensation of NH_3 with β–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 acetoacetic ester and aromatic / aliphatic amine in presence of pyridine [3-6].

(2) By the condensation of aliphatic or aromatic aldehydes with 3-amino crotonate and 1,3-diketone [2,7-13].

(3) By the condensation of arylidene with 3-aminocrotonate[14].

(4) By the condensation of aliphatic or aromatic aldehydes with various 1,3-diketones in presence of ammonia or ammonium carbonate[15-17].

(5) By the condensation of α,β -unsaturated ketones with malononitrile and cyanoacetamide[18].

(6) By the condensation of o-nitrobenzaldehyde, β -amino butaricacid and methylpripiolate in gl. acetic acid[19].

(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 [20].

(8) By the regio and chemoselective addition of diphenyl cuprous cyanolithium ($Ph_2Cu(CN)Li_2$) to substituted N-alkylpyridium salts followed by acylation of the intermediate[21]

(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[22-24] .

(10) By the condensation of two moles of thiobarbituric acid, aromatic-amines and aromatic aldehydes[25-26].

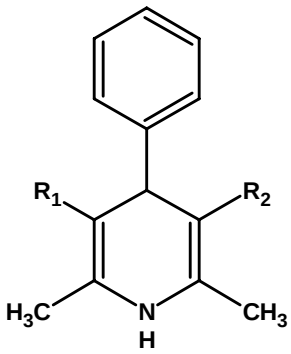
MEDICINAL INTEREST OF 1,4-DIHYDROPYRIDINE

The research on 1,4-dihydropyridine system is of current interest due to their valuable activities as calcium channel antagonist, vasodilator, cardiovascular etc. beside the currently established drugs Nifedipine[27-28], Nicardipine[29-30]. Many dihydropyridine derivatives have been synthesized world wide[31-33]. and have led to numerous second generation commercial product[34-

[41]such as Nimodipine[42-43],Nisodipine[44], Nitrendipine[45], Amlodopine[46], Felodipine[47], Isradipine[48], Manidipine[49] and Nelvadipine[50]. Some of their compounds are characterized by longer bioactivity of greater tissue selectivity. 1,4-dihydropyridine derivatives are associated with diverse biological activities which can be summerised as under.

[A] Antiarrythemic[51]
[B] Antiinflammatory[52]
[C] Antiallergic[53]
[D] Antiulcer[54]
[E] Antitumor[6]
[F] Vasodilator[55]
[G] Enzymetic[56-57]
[H] Calcium channel antagonist[58-60]
[I] Antihypertensive[61-62]
[J] Antihypolipemic[63]
[K] Antimayocardic ischemic[64]
[L] Cardiovascular[65]
[M] Photo induced relaxation[9,19]
[N] Antitubercular agents[66]

I. Nadeem et.al.,[10] **(2)** 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:



(2)

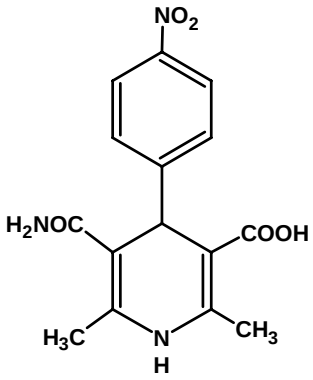
R_1=$COOCH_3$ / $COOC_2H_5$
R_2=$COOCH_3$ / $COOC_2H_5$
R_3 =Substituted phenyl

(1) Relative potency order for carbon number four (C-4) phenyl substituents in ortho and meta position is greater than para position.

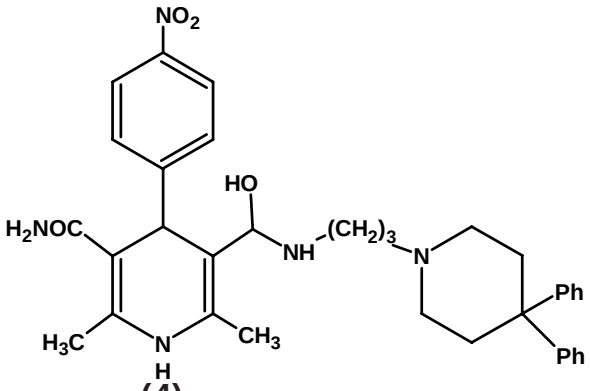
(2) Carbon number three(C-3) nitro substitutents decrease calcium channel antagonist activity.

G. Charles et.al.,[68] **(3)** have synthesized 1,4-dihydropyridines for treat ment of prostatic hyperplasia.

1,4-Dihydropyridine derivatives **(3)** have been found to be useful in treai-ng benign prostate hyperplasia inhibition of cholesterol synthesis **(4)** show-ed 'ki' of 1.9 m.mol/kg in reducing urethral pressure ***in vivo*** in dog.



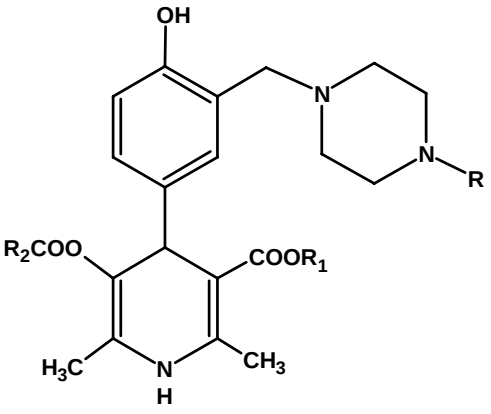
(3)



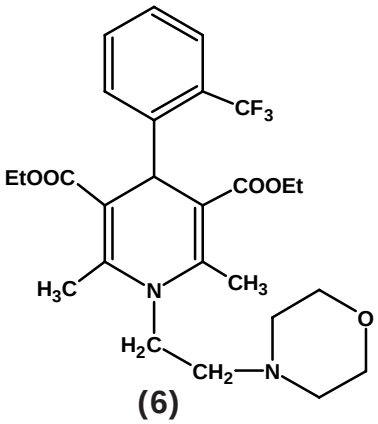
(4)

More recently B. M. Khadikar et.al.,[69] have synthesized 1,4-dihydropyridine derivatives **(5)** and tested its antihypertensive activity.

Out of many 1,4-dihydropyridine drugs only Flordipine **(6)** is N-substituted derivative that has proved to be very good calcium channel antagonist, contrary to the belief proposed by D.G.Triggle[70] 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.



(5)



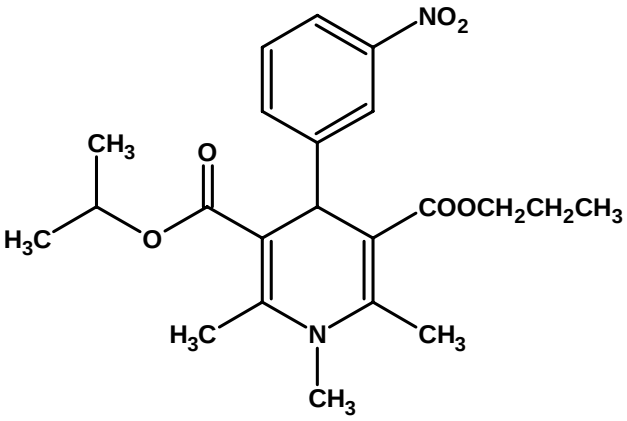
(6)

R_1,R_2=Methyl / ethyl

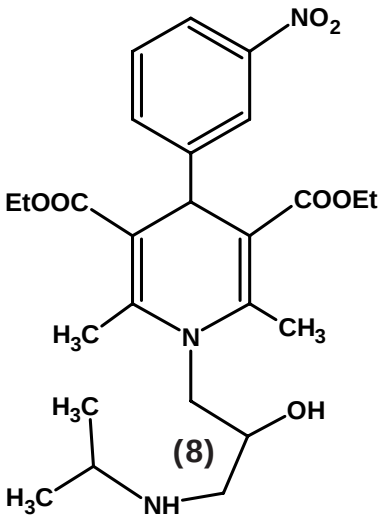
R=Alkyl / Aryl

N-methylnimodipine **(7)** was found to possess antidepressive[70] characteristics (20 mg.P.O reduce the immobile phase by approximately 22% com-

parison to control values), which provides excellent example of mechanism of action similar to that of Flordipine.V. Michael et.al.,[72] prepared antihypertensive and coronary vasodilator *N*-substituted 1,4-dihydropyridine **(8)**.

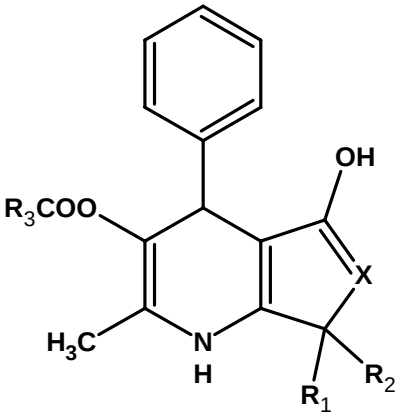


(7)

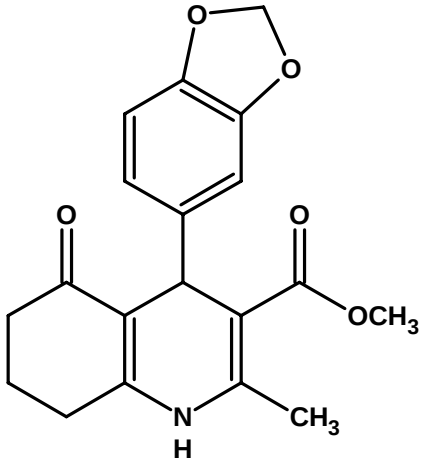


(8)

A. Daich et.al.,[73] have reported calcium antagonist effect of 1,4-dihydropyridines **(9)** and M. Suarez et.al.,[74] have synthesized calcium antagonist modulators 1,4-dihydropyridines **(10)**.



(9)

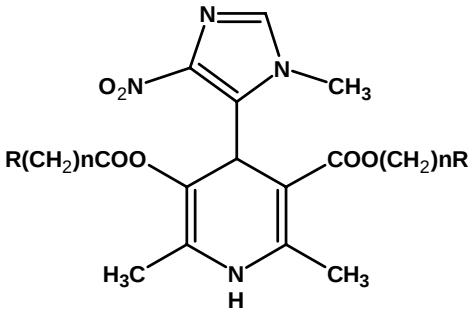


(10)

R_1,R_2,R_3= methyl / ethyl

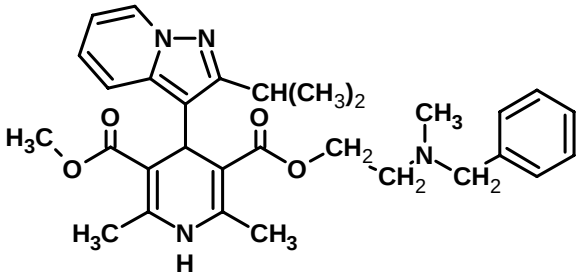
X=O, S, N

M.Sharifzadeh et.al.,[75] have prepared anticonvulsant 1,4-dihydropyridine**(11)** and K. Shigenobu et.al.,[76] prepared cardioprotective1,4-dihydropyridine**(12)**.



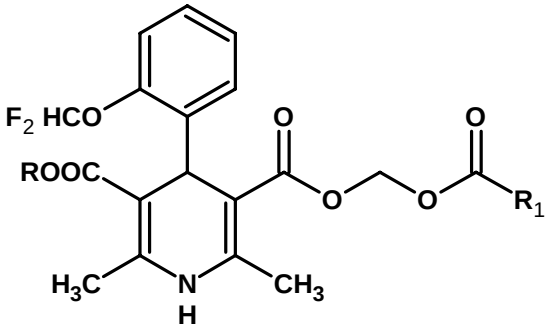
R = CH_3, $CH(CH_3)_2$,C_6H_5,$C(CH_3)_3$, C_6H_{11}; n = 1,2,3

(11)

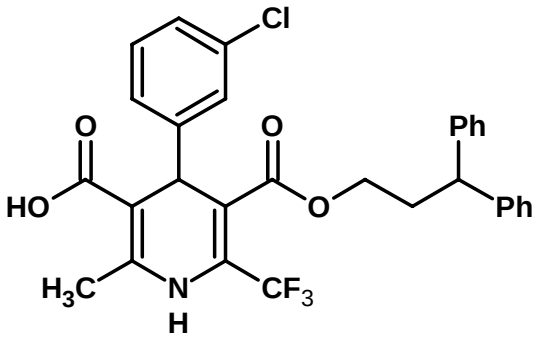


(12)

M. C. R. Franseen et.al.,[77] have synthesized 4-substituted-1,4-dihydropyridine-3,5-diesters **(13)** as Candida rugosa lipase.A.Takahara et.al.,[78] have designed the synthesis of N-type 1,4-dihydropyridines**(14)** and reported them as calcium channel blockers.



(13)

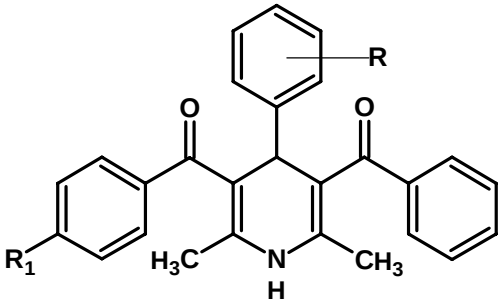


(14)

R = $(CH_2)_2O(CH_2)_2CH_3$; R_1=Et / Pr / iPr

R = CH_3; R_1=Et / Pr / iPr

A. Motohashi et al.,[79] 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 1,4-dihydropyridines 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 1,4-dihydropyridines.



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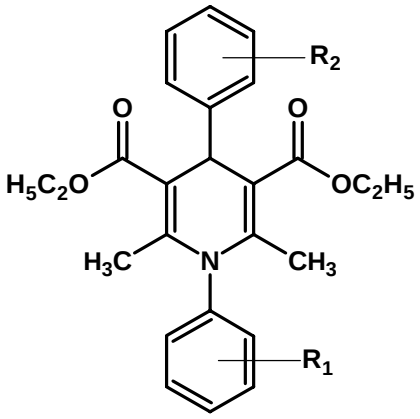
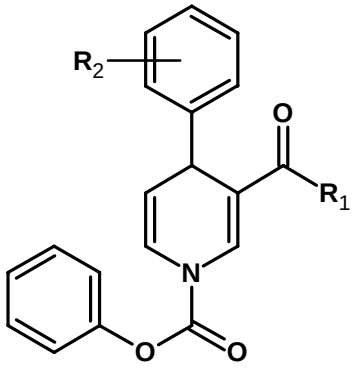


(16)

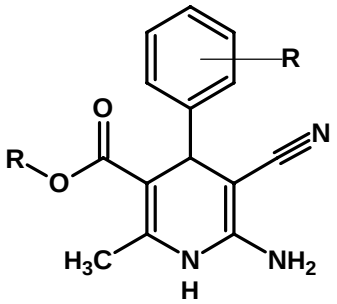
V.Burkhardt et., al have synthesized N-acyloxy-1,4- dihydropyridines **(17)** and evaluated as p-glycoprotein inhibitors.[80]



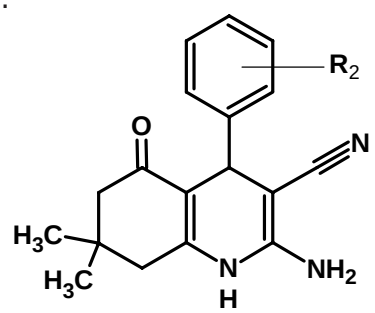
(17)

R_1= CH_3, C_2H_5 etc..
R_2= H,CH_3, NO_2

R. Leon et.al.,[83] have reported antihypertensive agents effect of 6-amino-1,4-dihydropyridines**(18)** and**(19)**.

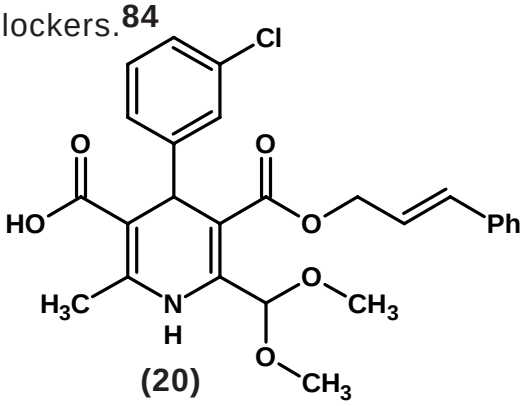


(18)



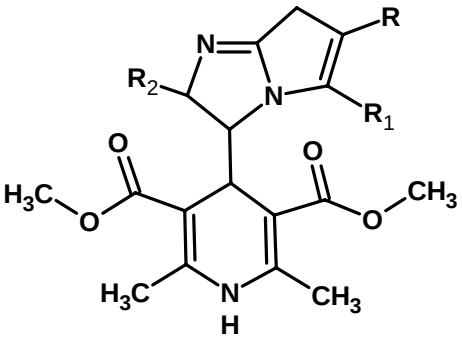
(19)

Y.Takshi et.al., have synthesized 1,4-dihydropiridines **(20)** and reported as calcium channel blockers.[84]



(20)

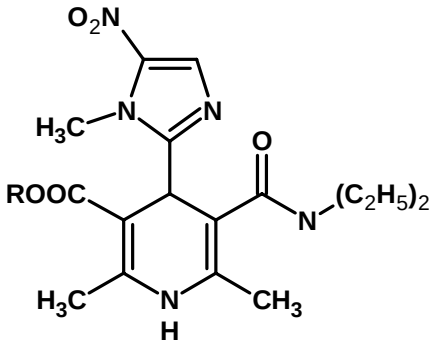
R.Budriesi et.al., have synthesized 4-imidazo[2,1-b]thiazol-1,4-dihydropyridine**(21)** and reported their cardiodepressant activity[85]



(21)

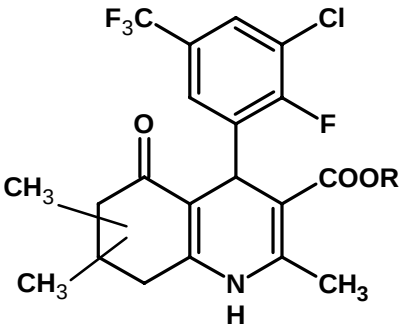
R_1=R_2=R_3= H,CH_3, Cl

Khoshneviszadeh et. al., have synthesized dihydropyridines (**22**) and reported their antitubercular activity[87]

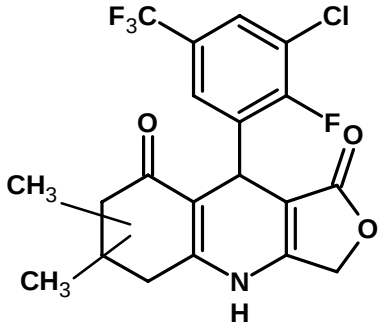


(22) **R=CH_3, C_2H_5 etc..**

Buelbuel et. al., have synthesized 1,4-dihydropyridines **(23),(24)** and reported their calcium antagonistic acitivity[88]

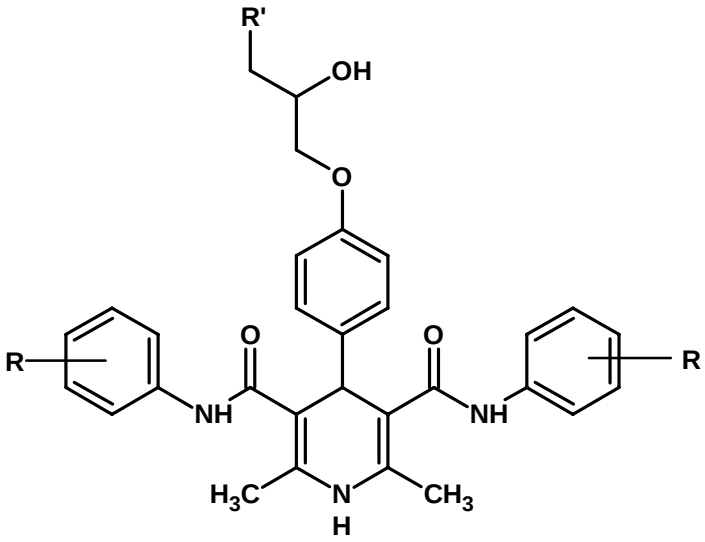


(23)



(24)

S.R.Pattan et. al., have synthesized 1,4-dihydropyridines(**25**) and tested for their anticonvulsant activity [86]



(25)

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.

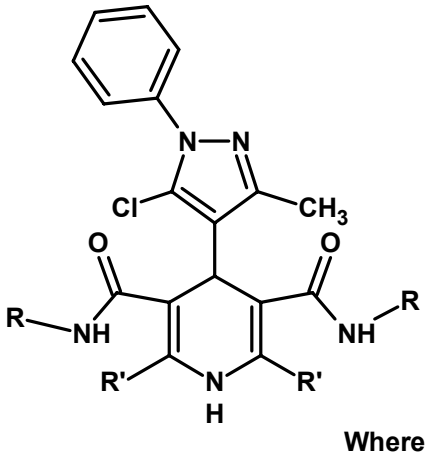
SECTION - I :PREPARATION AND BIOLOGICAL EVALUATION OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL/-ISOPROPYL-3,5-DISUBSTITUTED PHENYL- CARBAMOYL-1,4-DIHDROPYRIDINES.

SECTION - II:PREPARATION AND BIOLOGICAL EVALUATION OF 4-(5'-CHLORO-3'-METHYL-1'-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-/-6-ISOPROPYL/2-METHYL-3-CARBMETHOXY/ETHOXY-5-SUBSTITUTED PHENYLCARBAMOYL-1,4-DIHYDRO PYRIDINES.

SECTION-I

PREPARATION AND BIOLOGICAL EVALUATION OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL/-DIISOPROPYL-3,5-DISUBSTITUTED PHENYL CARBAMOYL-1,4-DIHYDROPYRIDINES(I_{a-t}).

1,4-Dihydropyridine derivatives represents one of the most active classes of compounds possessing wide spectrum of biodynamic activities[52-67]. In order to have potent therapeutic agents, the synthesis of **4-(5'-chloro-3'-methyl- 1'-N-phenyl-pyrazol-4'-yl)-2,6-dimethyl/-isopropyl-3,5-disubstituted phenylcarbamoyl-1,4-dihydropyridines (I_{a-t})**have been undertaken by the cyclocondensation of **one mole** of **5-chloro-3-methyl-1-N-phenyl-pyrazole-4-carbaldehyde** with **two moles** of **N-(substitutedphenyl)-3-oxobutanamides/4-methyl 3-oxopetanamides** in presence of **ammonia**.



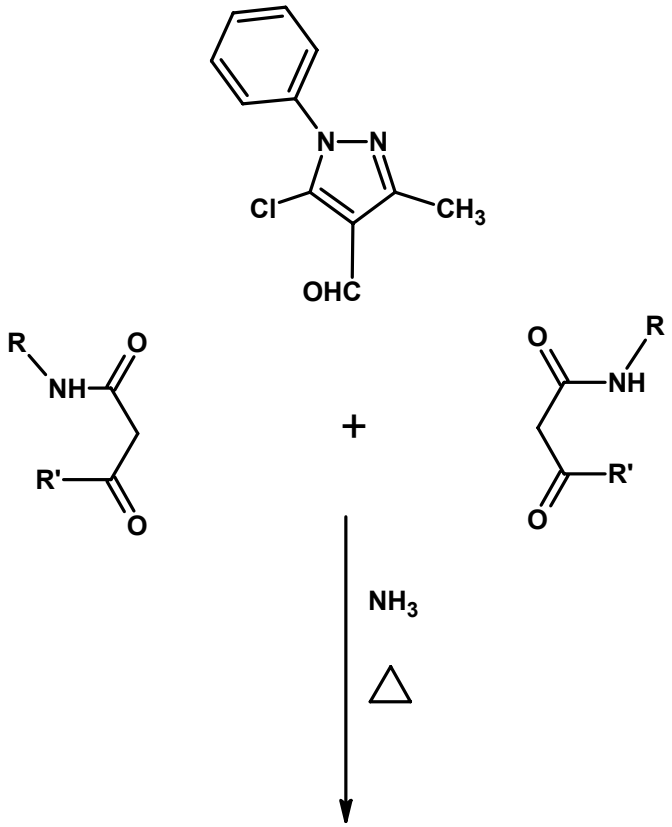
(I_{a-t})

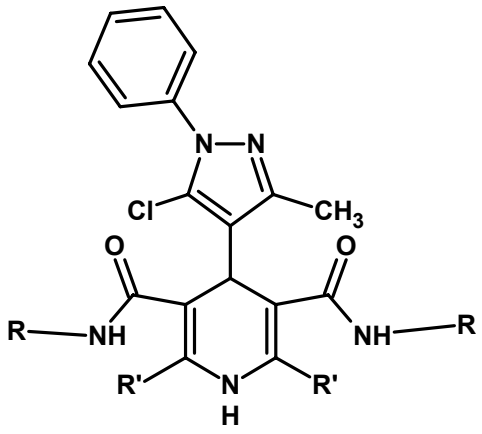
Where R= substituted phenyl and R' = -CH_3/ -$CH(CH_3)_2$

The constitution of the products **(I_{a-t})** have been delineated by **elemental analyses, IR, PMR** and **Mass** spectral data.

The products **(I_{a-t})** were assayed for their ***in vitro*** biological assay like antibacterial activity towards ***S. pyogens MTCC-443*, *S. aureus MTCC-96*** **and *P. aeruginosa MTCC-441* (Gram positive) and *E. coli MTCC-442* (Gram negative)** bacterial strains and antifungal activity towards ***Aspergillus niger MTCC-282*** **and *A. clavatus MTCC-1323*** at different concentrations i.e.: 0, 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds**(I_{a-t})** were compared with standard drugs,viz.,**Amplicilline,Chloramphenicol, Ciprofloxacin and Norfloxacin** (antibacterial)**, Greseofluvin, Nystatin** (antifungal)**.**

REACTION SCHEME





(I_{a-t})

R'= -CH_3/ $CH(CH_3)_2$
R = Substituted phenyl

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL/-ISOPROPYL-3,5-DISUBSTITUTED PHENYL CARBAMOYL-1,4-DIHYDROPYRIDINES (I_{a-t}).

Preparation of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-2,6-dimethyl/-isopropyl-3,5-di-(p-tolyl carbamoyl)-1,4-dihydropyridine (I_b)/(I_l):

(A) (i) Preparationof N-(p-tolyl)-3-oxobutanamide[81-82](1_b)

The synthesis of N-(4-methylphenyl)-3-oxobutanamide was undertaken according to the literature procedure. **Yield :**47 %, **M.P. :**113°C, (Required:**C**, 69.30%; **H**, 6.79%; **N**, 7.32% for $C_{11}H_{13}NO_2$, Found : **C**, 69.28%; **H**, 6.76 %; **N**, 7.27 %).

TLC solvent system Rf_1: Ethyl acetate : Hexane (1.5 : 8.5) = 0.60

TLC solvent system Rf_2: Methanol : Chloroform(0.5 : 9.5) = 0.48

(ii)Preparationof 4-methyl-N-(p-tolyl)-3-oxopetanamide[81-82] (1_l)

The synthesis of **4-methyl-N-(p-tolyl)-3-oxopetanamide** was undertaken according to the literature procedure.**Yield :**60 %, **M.P. :**128°C**,** (Required:**C**, 71.14%; **H**,7.75%; N, 6.38 % for $C_{13}H_{17}NO_2$, Found : **C**, 71.11 %; **H**, 7.73 %; **N**, 6.32 %).

TLC solvent system R_{f_1}: Ethyl acetate : Hexane (1.5 : 8.5) = 0.64

TLC solvent system R_{f_2}: Methanol : Chloroform(0.5 : 9.5) = 0.52

Similarly, other compounds **(1_{a-t})** were synthesized and physical data are recorded in talble no.1_A and 1_B

(B) (i) Preparation of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-2,6-dimethyl-3,5-di-(p-tolyl carbamoyl)-1,4-dihydropyridine(I_b):

A mixture of **N-(p-tolyl)-3-oxobutanamide (1_b)** (3.82 gm, 0.02 M), **5-chloro-3-methyl-1-N-phenyl-pyrazole-4-carbaldehyde**(2.20 gm, 0.01 M) and **ammonia** (5-7ml) in **methanol** (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 solid product so obtained was filtered, washed with water, dried and crystallized from suitable solvent. **Yield** : 56%, **M.P**. :191°C, (Required : **C**, 69.96 %; **H**, 5.65 %; **N**, 12.36 % for $C_{33}H_{32}N_5O_2Cl$, Found : **C**, 69.92 %; **H**, 5.63 %; **N**, 12.31 %).

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (3.0 : 7.0) = 0.48.
TLC solvent system R_{f_2} : Methanol : Chloroform(0.5 : 9.5) = 0.49**.**

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

(ii) Preparation of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-2,6-diisopropyl-3,5-di(p-tolyl carbamoyl)-1,4-dihydropyridine (I_l)

A mixture of **N-(p-tolyl)-4-methyl 3-oxopetanamide(1_l)** (4.32gm, 0.02M), **5-chloro-3-methyl-1-N-phenyl-pyrazole-4-carbaldehyde** (2.20 gm, 0.01 M) and **ammonia** (5-7ml) in **methanol** (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 solid product so obtained was filtered, washed with water, dried and crystallized from sutable solvent. **Yield** : 49%, **M.P**.:141°C,(Required :**C**, 71.36 %; **H**, 6.42 %; **N**, 11.25 % for $C_{37}H_{40}ClN_5O_2$, Found : **C**, 71.29 %; **H**, 6.40 %; **N**, 11.18 %).

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (3.0 : 7.0) = 0.51.
TLC solvent system R_{f_2} : Methanol : Chloroform(0.5 : 9.5) = 0.58**.**

Similarly, other compounds **(I_{k-t})** were synthesized. The physical data are recorded in **Table No.I_B**

(C) Antimicrobial activity of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-2,6-dimethyl/-isopropyl-3,5-disubstituted phenylcarbamoyl-1,4-dihydropyridines (I_{a-t}).

Antimicrobial activity testing was carried out as described under.The MIC values of test solution are recorded in **Table No. 1_a, 1_b, 1_c, 1_d, 1_e**, and **1_f.**

Evaluation Techniques :-

The following conditions must be met for the screening of antimicrobial activity:

- There should be intimate contcact between the test organisms and substance to be evaluated.
- Required conditions should be provided for the growth microor ganisms.
- Conditions should be same through the study.
- Aseptic/sterile environment should be maintained.

Various methods have been used from time to time by several workers to evaluate the antimicrobial activity. The evalutaion can be done by the following methods :

- Turbidometric method.
- Agar streak dilution method.
- Serial dilution method.
- Agar diffusion method.

Following Techniques are used as agar diffusion method:

- Agar cup method.
- Agar ditch method.
- Paper disc method.

We have used the Agar cup mehtod to evaluate the antibacterial activ ity.

It is one of the non automated in vitro bacterial susceptibility tests.

This classic method yields a zone of inhibition in mm results for the amount of antimicrobial agents that is needed to inhibit growth of specific microoganisms. It is carried out in petriplates.

DETERMINATION OF MINIMAL BACTERICIDAL CONCENTRATIONS BY AGAR CUP METHOD

MATERIALS AND METHOD:

1. **All the Synthesized Drugs were used for antibacterial test proce dures.**
2. **All necessary controls like :**
   - Drug Control
   - Vehicle control
   - Agar control
   - Organism control
   - Known antibacterial drugs control
   - All MTCC cultures were tested againts above mentioned known and unknown drugs.
   - Mueller hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test.
   - Inoculum size for the test strain was adjust to 10^8 Cfu [colony forming unit] per milliliter by comparing the turbidity.
   - Following common standard strains were used for the screening of an tibacterial and antifungal activities:

     The strains were procured from Institute of microbial technology, chandigarh.

-	**Escherichia coli**	**[Gram negative]**	**MTCC-442**
-	**Pseudomonas aeruginosa**	**[Gram negative]**	**MTCC-441**
-	**Staphylococcus aureus**	**[Gram Positive]**	**MTCC-96**
-	**Streptococcus pyogenes**	**[Gram Positive]**	**MTCC-443**
-	**Aspergillus niger**	**[Fungus]**	**MTCC-282**
-	**Aspergillus clavatus**	**[Fungus]**	**MTCC-1323**

(DMSO) was used as diluents/vehicle to get desired concentration of drugs to test upon standard bacterial strains.

ANTIBIOTIC ASSAY AS PER BRITISH PHARMOCOPEIAS (B.P.)

[Eur. method 2.7.] The potency of an antibiotic is estimated by comparing the inhibition of growth of sensitive micro-organisms produced by known concentrations of the antibiotic being examined and a reference substance.

The reference substances used in the assays are substances whose activity has been precisely determined with reference to the corresponding international stan-

dard or international reference preparation.

The assay must be desingned in a way that will permit examination of the validity of the mathematical model on which the potency equation is based. If a parallel-line model is chosen, the two log dose-response (or transformed response) lines of the preparation being examined and the reference preparation must be parallel; they must be linear over the range of doses used in the calculation. These conditions must be verified by validity tests for a given probability, usually P = 0.05. Other mathematical models, such

as the slope ratio model, may be used provided that proof of validity is demonstrated. Unless otherwise stated in the monograph, the fiducial limit of error (P=0.95) of the assay for potency are not less than 95 % and not more than 105 % of the estimated potency.

Carry out the assay by method A or method B unless otherwise speicified in the monograph.

A. DIFFUSION METHOD

1) Liquefy a medium suitable for the conditions of the assay and

2) Inoculate it at a suitable temperature, for example 48°C to 50°C for vegetative forms, with a known quantity of a suspension of micro-organisms sensitive to the antibiotic being examined such that clearly defined zones of inhibition of suitable diameter are provided with the concentrations of the antibiotic used for the assay.

3) Immediately pour into petri dishes or large rectangular dishes a quantity of the inoculated medium to form a uniform layer 2 mmm to 5 m thick. Alternatively, the medium may consist of two layers, only the upper layer being inoculated.

4) Store the dishes so that no appreciable growth or death of the micro-organisms occurs before the dishes are used and so that the surface of the medium is dry at the time of use.

5) Using the solvent and the buffer solution indicated in Table A-1, prepare solutions of the reference substance and of the antibiotic being examined having known concentrations and presumed to be of equal activity.

6) Apply the solutions to the surface of the medium, for example, in cavities prepared in the agar. The same volume of solution must be added to each cylinder or cavity.

OR

7) Alternatively, use sterile absorbent paper of suitable quality; impregnate the discs with the solutions of the reference substance or the soulutions of the antibiotic being examined and place on the surface of the agar.

8) In order to assess the validity of the assay, use not fever than doses of the reference substance and three doses of the antibiotic being examined having the same presumed activity as the doses of the reference substance.

9) It is preferable to use a series of doses in geometric progression. In routine assays when the linearity of the some system has been demonstrated over an adquate number of experiments using a three-point assay, a two-point assay may be sufficient, subject to agreement by the component authority. However, in all cases of dispute, athree point assay as decribed above must be applied.

10) Arrange the solutions on each petri dish on each rectangular dish according to a statistically suitable design, except for small petri dishes that cannot accommodate more than six solutions, arrange the solutions of the antibiotic being examined and the solutions of the reference substance in an alternate manner to avoid interaction of the more concentrated solutions.

11) Incubate at a suitable temperature for about 18 hours. A period of diffusion prior to incubation, usually 1 to 4 hours, at room temperature or at about 4°C, as appropriate, may be used to mininize the effects of the variation in time between the application of the solutions and to improve the regression slope.

12) Measure the diameters with a precision of at least 0.1 mm or the areas of the circular inhibition zones with a corresponding precision and calcuate the potency using appropriate statistical methods.

13) Use in each assay the number of replications per doses sufficient to ensure the required precision.

14) The assay may be repeated and the results combined statistically to obtain the required precision and to ascertain whether the potency of the antibiotic being examined is not less than the minimum required.

 # BUFFER SOLUTION

Weight / 1000 ml.

Adjust the pH by using 8.0 M phosphoric acid or 10.0 M potassium hydroxide.

Buffer No.	K_2HPO_4	KH_2PO_4	pH
B1	02.00	08.000	6.0
B2	16.73	00.523	8.0
B3	-	13.610	4.5
B4	20.00	80.000	6.0
B5	35.00	-	10.5
B6	13.60	04.000	7.0

Result and Discussion:

The products **(I_{a-t})** have been subjected to antibacterial activity towards ***S. pyogens MTCC-443*, *S. aureus MTCC-96* and *P. aeruginosa MTCC-441*** **(Gram positive) and *E. coli MTCC-442* (Gram negative)** bacterial strains and antifungal activity towards ***Aspergillus niger MTCC-282* and *A. clavatus MTCC-1323*** at different concentrations i.e.: 0, 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values.

The biological activities of the synthesized compounds **(I_{a-t})** were compared with standard drugs,viz.,**Amplicilline,Chloramphenicol, Ciprofloxacin and Norfloxacin** (antibacterial)**, Greseofluvin, Nystatin** (antifungal)**.**

The results of antimicrobial activity have been depicted on page no. **47** to **52**.

TABLE NO. 1_A: PHYSICAL CONSTANTS OF N-(SUBSTITUTED PHENYL)-3-OXOBUTANAMIDES(1_{a-j}).

Comp. No.	R	R'	Molecular Formula	M.W.	Yield %	M.P. ^oC	R_f Value R_{f_1}/R_{f_2}	% of Nitrogen Calcd. / Found
1	2	3	4	5	6	7	8	9
1_a	3-CH_3-C_6H_4	CH_3	$C_{11}H_{13}NO_2$	191.0	45	101	0.42/ 0.46	7.32 / 7.27
1_b	4-CH_3-C_6H_4	CH_3	$C_{11}H_{13}NO_2$	191.0	47	113	0.60 / 0.48	7.32 / 7.27
1_c	2,5-(CH_3)-C_6H_3	CH_3	$C_{12}H_{15}NO_2$	205.0	54	120	0.44/ 0.52	6.82 / 6.78
1_d	4-CH_3O-C_6H_4	CH_3	$C_{11}H_{13}NO_3$	207.0	46	116	0.47/ 0.49	6.75/ 6.72
1_e	3-Cl-C_6H_4	CH_3	$C_{10}H_{10}NO_2Cl$	211.5	57	107	0.53/ 0.58	6.61 / 6.58
1_f	4-Cl-C_6H_4	CH_3	$C_{10}H_{10}NO_2Cl$	211.5	58	133	0.64/ 0.51	6.61 / 6.58
1_g	2-F-C_6H_4	CH_3	$C_{10}H_{10}NO_2F$	195.5	43	89	0.46/ 0.48	7.17/ 7.13
1_h	4-F-C_6H_4	CH_3	$C_{10}H_{10}NO_2F$	195.5	61	92	0.69/ 0.52	7.17 / 7.14
1_i	3-O_2N-C_6H_4	CH_3	$C_{10}H_{10}N_2O_4$	222.0	58	157	0.41/ 0.43	12.60 /12.52
1_j	4-O_2N-C_6H_4	CH_3	$C_{10}H_{10}N_2O_4$	222.0	53	161	0.45/0.47	12.60 / 12.52

TLC solvent system Rf_1: Ethyl acetate : Hexane (1.5 : 8.5)

TLC solvent system Rf_2: Methanol : Chloroform(0.5 : 9.5)

TABLE NO. 1_B : PHYSICAL CONSTANTS OF 4-METHYL-N-(SUBSTITUTED PHENYL)-3-OXOPENTANAMIDES (1_{k-t}).

Comp. No.	R	R'	Molecular Formula	M.W.	Yield %	M.P. °C	R_f Value R_{f_1}/R_{f_2}	% of Nitrogen Calcd. / Found
1	2	3	4	5	6	7	8	9
1_k	3-CH_3-C_6H_4	$CH(CH_3)_2$	$C_{13}H_{17}NO_2$	219.0	45	101	0.42/ 0.66	6.38 / 6.32
1_l	4-CH_3-C_6H_4	$CH(CH_3)_2$	$C_{13}H_{17}NO_2$	219.0	60	128	0.64/ 0.52	6.38 /6.32
1_m	2,5-$(CH_3)_2C_6H_3$	$CH(CH_3)_2$	$C_{14}H_{19}NO_2$	233.0	63	117	0.43/ 0.54	6.00 / 5.96
1_n	4-CH_3O-C_6H_4	$CH(CH_3)_2$	$C_{13}H_{17}NO_3$	235.0	46	120	0.47/ 0.49	6.22 / 6.19
1_o	3-Cl-C_6H_4	$CH(CH_3)_2$	$C_{12}H_{14}NO_2Cl$	239.5	53	148	0.58/ 0.53	5.84 /5.78
1_p	4-Cl-C_6H_4	$CH(CH_3)_2$	$C_{12}H_{14}NO_2Cl$	239.5	57	133	0.67/ 0.54	5.84 / 5.78
1_q	2-F-C_6H_4	$CH(CH_3)_2$	$C_{12}H_{14}NO_2F$	223.0	53	94	0.46/ 0.48	6.27 / 6.23
1_r	4-F-C_6H_4	$CH(CH_3)_2$	$C_{12}H_{14}NO_2F$	223.0	60	98	0.65/ 0.48	6.27 / 6.23
1_s	3-O_2N-C_6H_4	$CH(CH_3)_2$	$C_{12}H_{14}N_2O_4$	250.0	52	158	0.45/ 0.48	11.19 /11.12
1_t	4-O_2N-C_6H_4	$CH(CH_3)_2$	$C_{12}H_{14}N_2O_4$	250.0	59	167	0.49/ 0.51	11.19 / 11.12

TLC solvent system Rf_1: Ethyl acetate : Hexane (1.5 : 8.5)

TLC solvent system Rf_2: Methanol : Chloroform(0.5 : 9.5)

TABLE NO. I_A: PHYSICAL CONSTANTS OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL- 3,5-DISUBSTITUTED PHENYLCARBAMOYL-1,4-DIHYDROPYRIDINES (I_{a-j}).

Comp. No. 1	R 2	R' 3	Molecular Formula 4	M.W. 5	Yield % 6	M.P. °C 7	R_f Value R_{f_1}/ R_{f_2} 8	% of Nitrogen Calcd. / Found 9
I_a	3-CH_3-C_6H_4	CH_3	$C_{33}H_{32}ClN_5O_2$	566.0	51	211	0.40/ 0.43	12.36 / 12.31
I_b	4-CH_3-C_6H_4	CH3	$C_{33}H_{32}ClN_5O_2$	556.0	56	191	0.48/ 0.49	12.36 / 12.31
I_c	2-5-$(CH_3)_2$-C_6H_3	CH3	$C_{35}H_{36}ClN_5O_2$	594.0	52	178	0.39/ 0.43	11.78/ 11.72
I_d	4-CH_3O-C_6H_4	CH3	$C_{33}H_{32}ClN_5O_4$	598.5	52	181	0.58/ 0.54	11.70 /11.64
I_e	3-Cl-C_6H_4	CH3	$C_{31}H_{26}Cl_3N_5O_2$	606.5	50	216	0.38/ 0.39	11.53 /11.48
I_f	4-Cl-C_6H_4	CH3	$C_{31}H_{26}Cl_3N_5O_2$	606.5	56	219	0.49/ 0.52	11.53 / 11.48
I_g	2-F-C_6H_4	CH3	$C_{31}H_{26}ClF_2N_5O_2$	574.0	53	186	0.41/ 0.43	12.19 /12.14
I_h	4-F-C_6H_4	CH3	$C_{31}H_{26}ClF_2N_5O_2$	574.5	51	185	0.61/ 0.58	12.19 /12.14
I_i	3-O_2N-C_6H_4	CH3	$C_{31}H_{26}ClN_7O_6$	628.0	59	199	0.62/ 0.59	15.53 /15.46
I_j	4-O_2N-C_6H_4	CH3	$C_{31}H_{26}ClN_7O_6$	628.0	58	205	0.52/ 0.56	15.53 /15.46

TLC solvent system Rf_1: Ethyl acetate : Hexane (1.5 : 8.5)

TLC solvent system Rf_2: Methanol : Chloroform(0.5 : 9.5)

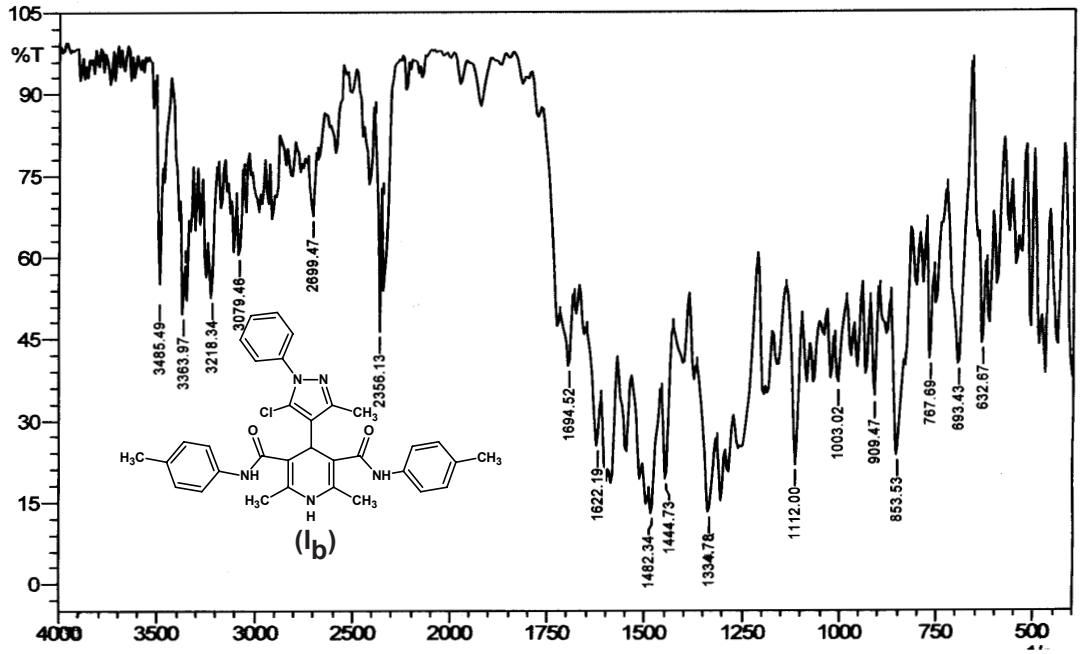
TABLE NO. I_B : PHYSICAL CONSTANTS OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIISOPROPYL- 3,5-DISUBSTITUTED PHENYL CARBAMOYL-1,4-DIHYDROPYRIDINES (I_{k-t}).

Comp. No.	R	R'	Molecular Formula	M.W.	Yield %	M.P. °C	R_f Value R_{f_1}/ R_{f_2}	% of Nitrogen Calcd. / Found
1	2	3	4	5	6	7	8	9
I_k	3-CH_3-C_6H_4	$CH(CH_3)_2$	$C_{37}H_{40}ClN_5O_2$	622.0	55	174	0.50/ 0.54	11.25 /11.18
I_l	4-CH_3-C_6H_4	$CH(CH_3)_2$	$C_{37}H_{40}ClN_5O_2$	622.0	49	141	0.51/ 0.58	11.25/11.18
I_m	2,5-$(CH_3)_2$-C_6H_3	$CH(CH_3)_2$	$C_{39}H_{44}ClN_5O_2$	650.0	64	148	0.47/ 0.53	10.76 / 10.70
I_n	4-CH_3O-C_6H_4	$CH(CH_3)_2$	$C_{37}H_{40}ClN_5O_4$	654.0	56	163	0.49/ 0.64	10.69 /10.62
I_o	3-Cl-C_6H_4	$CH(CH_3)_2$	$C_{35}H_{34}Cl_3N_5O_2$	663.5	61	175	0.48/ 0.61	10.55 /10.48
I_p	4-Cl-C_6H_4	$CH(CH_3)_2$	$C35H_{34}Cl_3N_5O_2$	663.5	51	143	0.44/ 0.59	10.55 / 10.48
I_q	2-F-C_6H_4	$CH(CH_3)_2$	$C_{35}H_{34}ClF_2N_5O_2$	630.0	53	194	0.47/ 0.42	11.09 /11.01
I_r	4-F-C_6H_4	$CH(CH_3)_2$	$C_{35}H_{34}ClF_2N_5O_2$	630.5	63	148	0.49/ 0.55	11.09/11.01
I_s	3-O_2N-C_6H_4	$CH(CH_3)_2$	$C_{35}H_{34}ClN_7O_6$	684.0	57	165	0.52/ 0.48	14.30 /14.23
I_t	4-O_2N-C_6H_4	$CH(CH_3)_2$	$C_{35}H_{34}ClN_7O_6$	684.0	47	158	0.53/ 0.60	14.30 /14.23

TLC solvent system Rf_1: Ethyl acetate : Hexane (1.5 : 8.5)

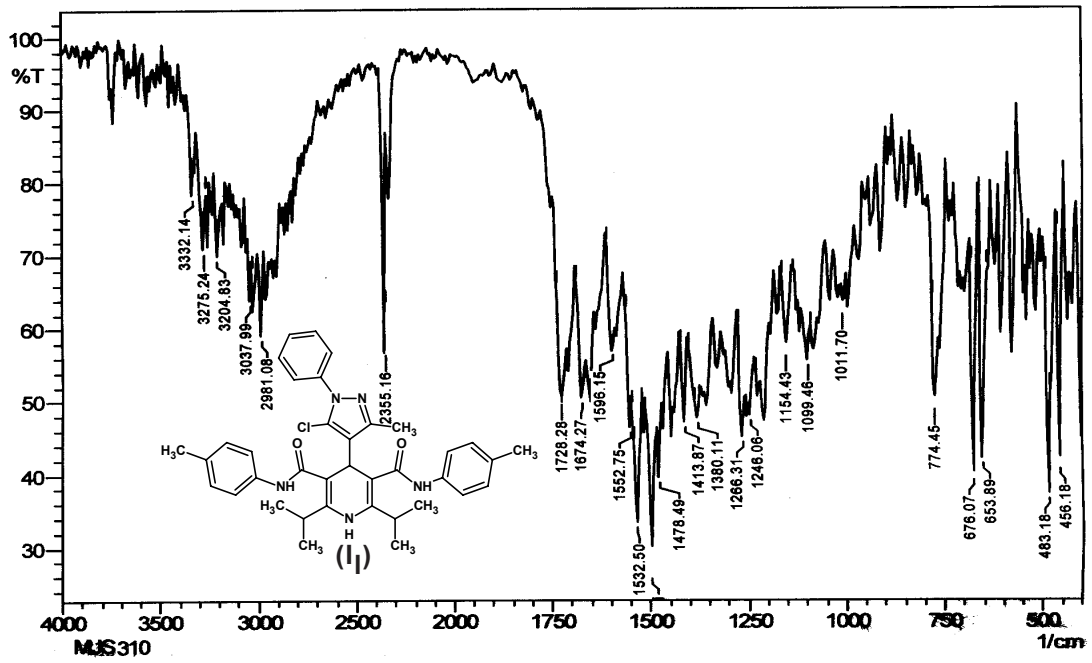
TLC solvent system Rf_2: Methanol : Chloroform(0.5 : 9.5)

IR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3,5-DI-(p-TOLYL CARBAMOYL)-1,4-DIHYDROPYRIDINE (I_b):



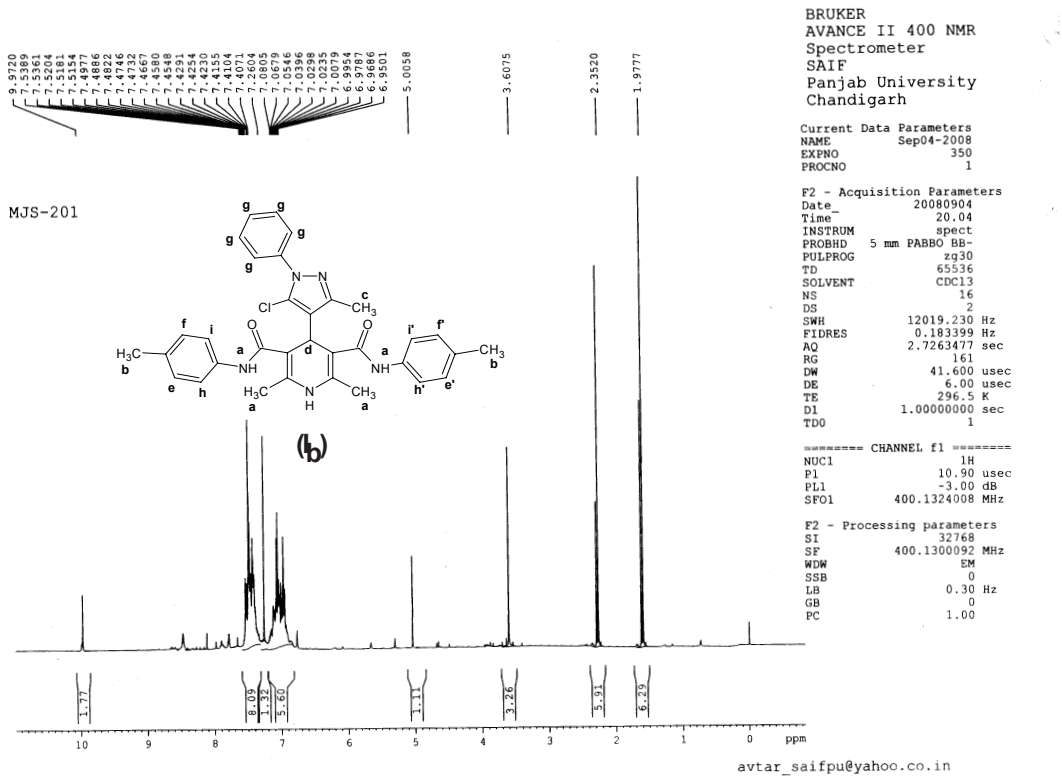
Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m)	2950.1	2975 - 2850	92
	C-H (sym. str., m)	2894.0	2900 - 2800	92
	C-H (asym. def., m)	1444.7	1470 - 1435	92
	C-H (sym. def., m)	1334.7	1385 - 1300	92
Aromatic and ring skeletal vibration	C=C & C-C (str., v)	1482.3	1600 - 1450	90
	C-H (i.p. def., m)	1112.0	1150 - 1050	90
	C-H (o.o.p. def., m)	804.5	825 - 800	90
	C-N (str., v)	1300.4	1340 - 1250	90
Pyridine Moiety	N-H (str., br.)	3363.9-3079.4	3400 - 3000	90
	N-H (def., s,m)	1622.1	1650 - 1525	90
Ketone				
Amide	C=O (str., s)	1694.5	1740 - 1650	90
Ester	C=O (str., s)	1674.2	1740 - 1650	90
Halogen Subtitution	C-Cl (str., br.)	767.6-632.6	800-600	89

IR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIISOPROPYL-3,5-DI-(p-TOLYLCARBAMOYL)-1,4-DIHYDROPYRIDINE (I_l):



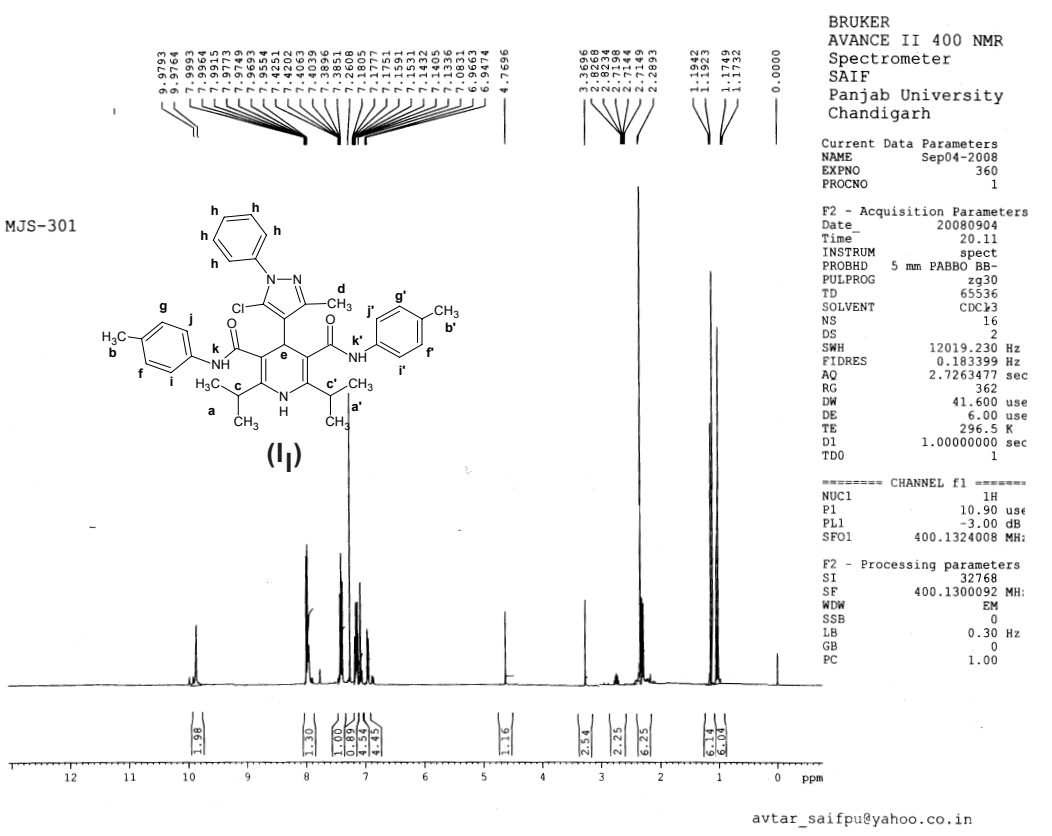
Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2981.0	2975 - 2850	92
	C-H (sym. str., m)	2800.0	2900 - 2800	92
	C-H (sym. def., m)	1380.1	1385 - 1300	92
Aromatic and ring skeletal vibration	C=C & C-C (str., v)	1478.4	1600 - 1450	90
	C-H (i.p. def., m)	1089.6	1150 - 1050	90
	C-H (o.o.p. def., m)	846.0	825 - 800	90
	C-N (str., v)	1299.9	1340 - 1250	90
Pyridine Moiety	N-H (str., br.)	3322.1	3400 - 3000	90
	N-H (def., s,m)	1598.6	1650 - 1525	90
Ketone Amide	C=O (str., s)	1674.2	1740 - 1650	90
Ester	C=O (str., s)	1728.2	1740 - 1650	90
Halogen Subtitution	C-Cl (str., br.	774.4-653.8	800-600	90
Para(-4-) substitution	C-H (def., v ,s)	808.2	850-800	89

NMR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3,5-DI-(p-TOLYL CARBAMOYL)-1,4-DIHYDROPYRIDINE (I_b):



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.9777	6H	singlet	- ($C\underline{H}_3$)$_{(a,a')}$
2	2.3520	6H	singlet	- ($C\underline{H}_3$)$_{(b,b')}$
3	3.6075	3H	singlet	- ($C\underline{H}_3$)$_{(c)}$
4	5.0058	1H	singlet	- Ar-$\underline{H}_{(d)}$
5	6.9501-7.0396	4H	multiplet	- Ar-$\underline{H}_{(e,e'-f,f')}$
6	7.0546-7.4104	5H	multiplet	- Ar-$\underline{H}_{(g)}$
7	7.4230-7.5389	4H	multiplet	- Ar-$\underline{H}_{(h,h'-i,i')}$
8	9.9720	2H	singlet	- N$\underline{H}_{(j,j')}$

NMR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIISOPROPYL-3,5-DI-(p-TOLYLCARBAMOYL)-1,4-DIHYDROPYRIDINE (I_l):



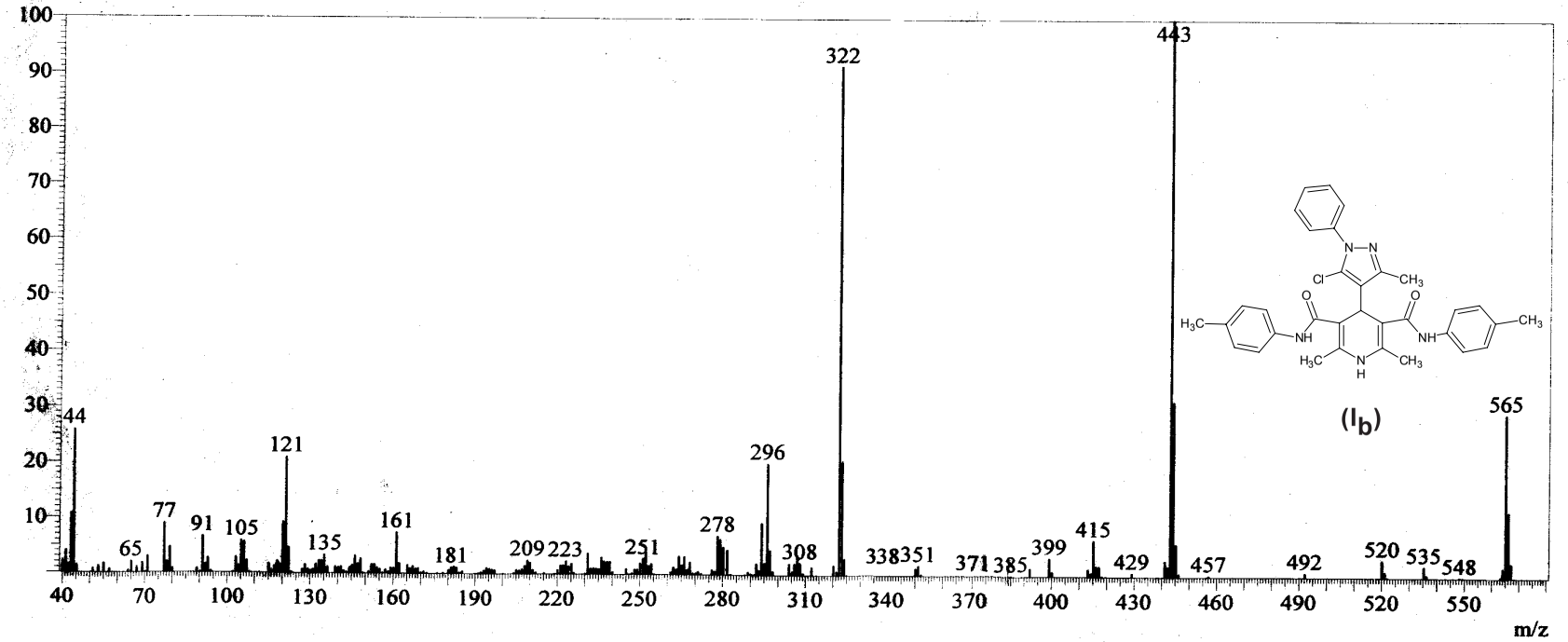
avtar_saifpu@yahoo.co.in

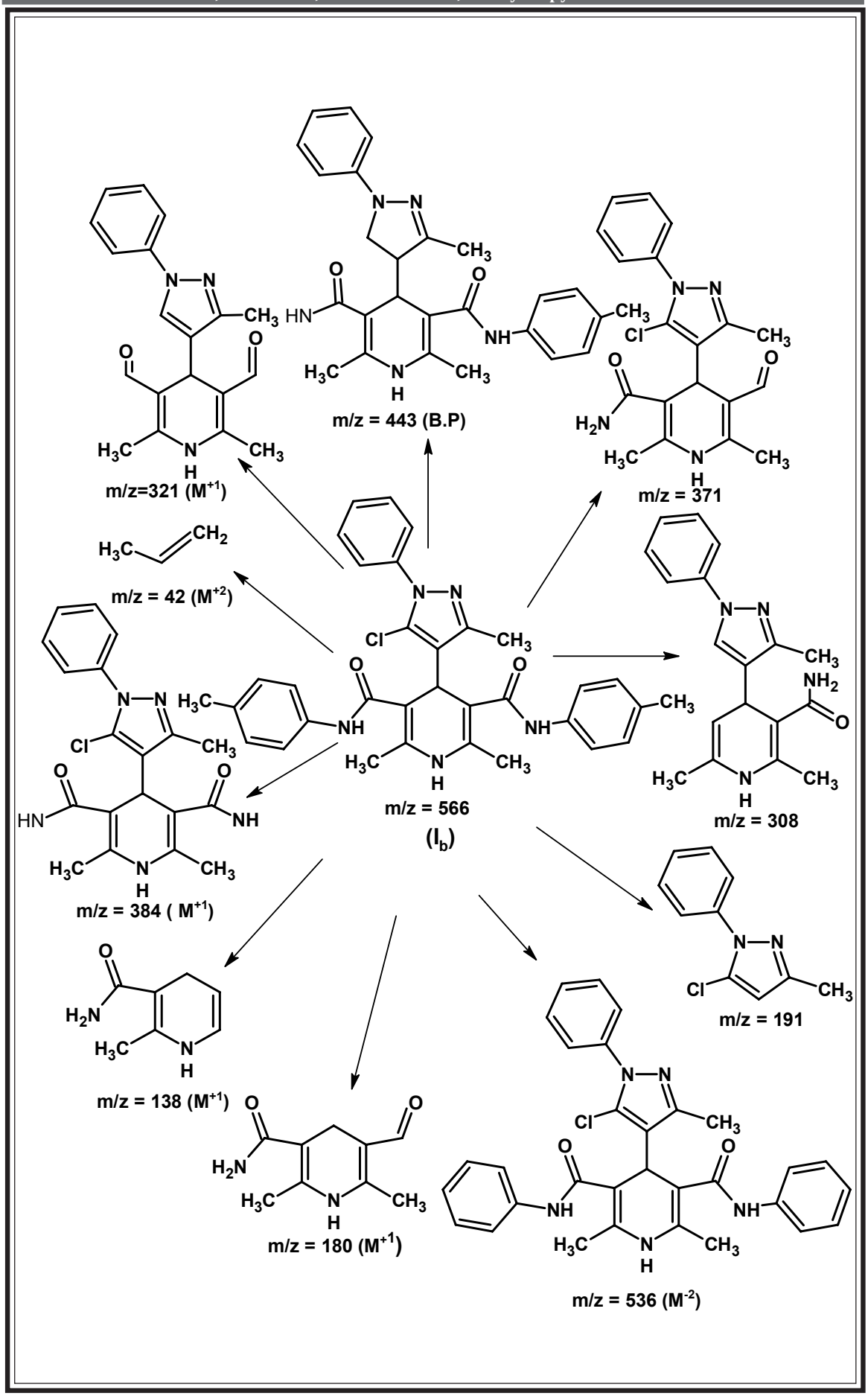
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.1732-1.1942	12H	doublet	- ($C\underline{H}_3$)$_{(a,a')}$
2	2.2893	6H	singlet	- ($C\underline{H}_3$)$_{(b,b')}$
3	2.7149-2.8268	2H	multiplet	- ($C\underline{H}$)$_{(c,c')}$
4	3.3696	3H	singlet	- ($C\underline{H}$)$_{(d)}$
5	4.7696	1H	singlet	- Ar-$\underline{H}_{(e)}$
6	6.9474-7.1805	4H	multiplet	- Ar-$\underline{H}_{(f,f'-g,g')}$
7	7.3851-7.4251	5H	multiplet	- Ar-$\underline{H}_{(h)}$
8	7.9554-7.9993	4H	multiplet	- Ar-$\underline{H}_{(i,i'-j,j')}$
9	9.9764-9.9793	2H	singlet	- N$\underline{H}_{(k,k')}$

MASS SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3,5-DI-(p-TOLYL CARBAMOYL)-1,4-DIHYDROPYRIDINE (I_b):

Analyzed by : PANKAJ KACHHADIA
Anaiyzed : 12/21/2007 1:49:49 PM
Sample Name : MJS-201
Sample ID : MJS-201
Data File : C:\GCMSsolution\Data\V.H.SHAH\MJS-201QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune121206.qgt

Line#:1 R.Time:10.0(Scan#:1161)
MassPeaks:224 BasePeak:443(97189)
RawMode:Averaged 8.7-11.5(1014-1349)
BG Mode:None

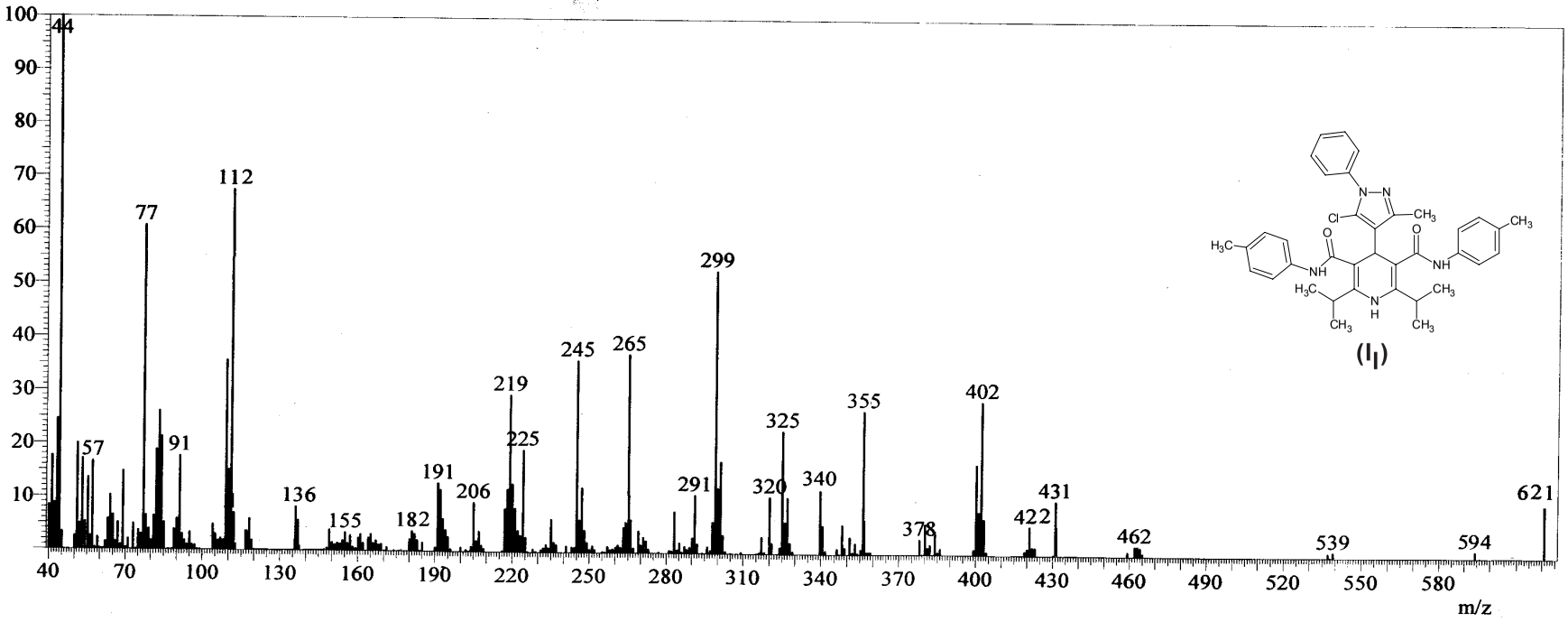



m/z = 443 (B.P)
m/z=321 (M+1)
m/z = 371
m/z = 42 (M+2)
m/z = 566
(Ib)
m/z = 308
m/z = 384 (M+1)
m/z = 191
m/z = 138 (M+1)
m/z = 180 (M+1)
m/z = 536 (M-2)

MASS SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZO L-4'-YL)-2,6-DIISOPROPYL-3,5-DI-(p-TOLYLCARBAMOYL)-1,4-DIHYD ROPYRIDINE (I_l):

Analyzed by : PANKAJ KACHHADIA
Analyzed : 11/20/2007 11:11:16 AM
Sample Name : MJS-201R
Sample ID : MJS-201R
Data File : C:\GCMSsolution\Data\V H SHAH\MJS-201 R.QGD
C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\Tune-02-06-2008.qgt

Line#:1 R.Time:8.4(Scan#:968)
MassPeaks:291 BasePeak:44(15205)
RawMode:Averaged 0.6-14.0(37-1650)
BG Mode:None



(I_l)

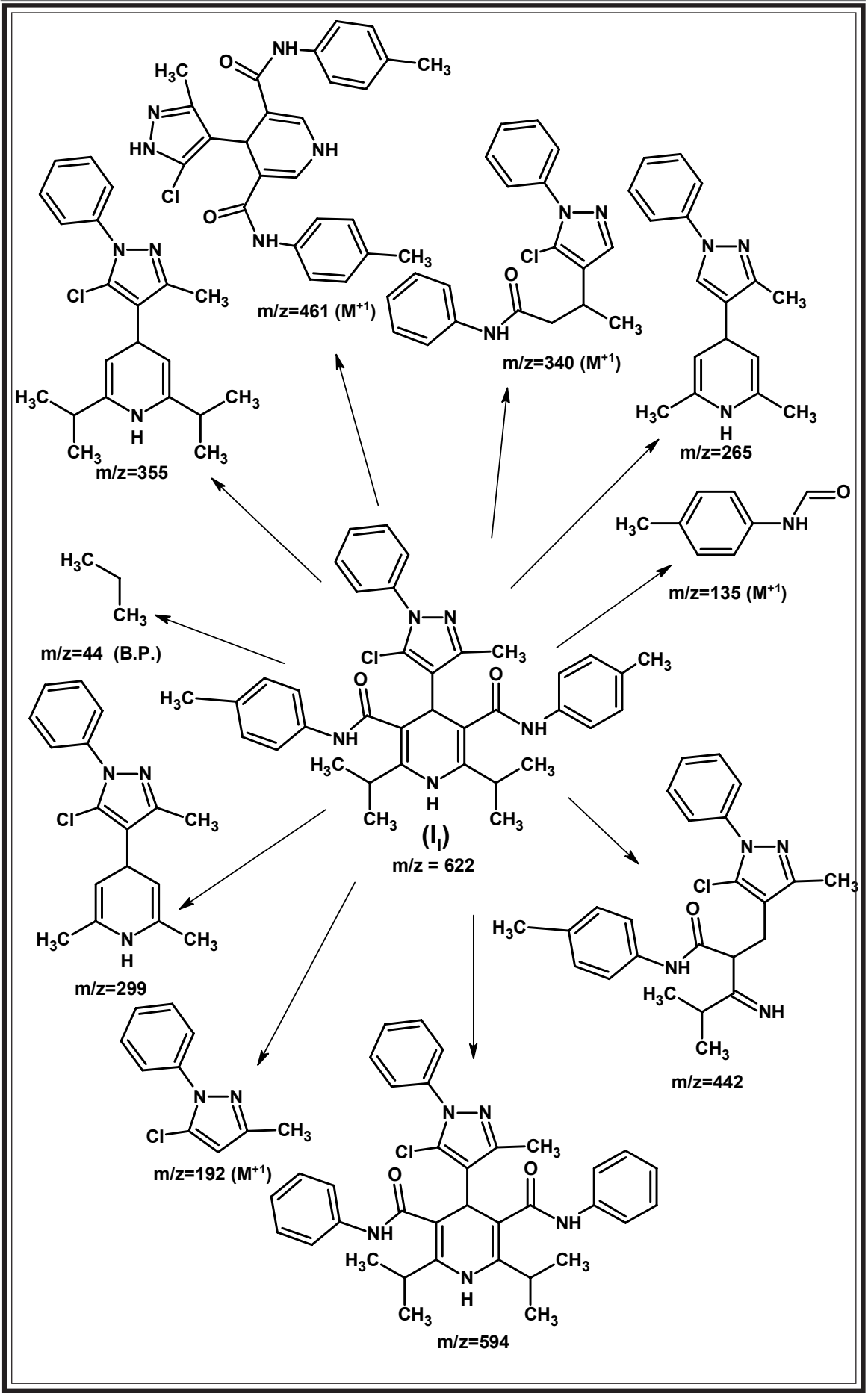

m/z=461 (M+1)
m/z=340 (M+1)
m/z=355
m/z=265
m/z=135 (M+1)
m/z=44 (B.P.)
(I1)
m/z = 622
m/z=299
m/z=442
m/z=192 (M+1)
m/z=594

TABLE NO. 1_a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL- 1'-N-PHENYL-PYRAZOL -4'-YL)-2,6-DIMETHY-3,5-DISUBSTITUTED PHENYLCARBAMOYL-1,4-DIHDROPYRIDINES (I_{a-j}).

(Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442					S. aureus MTCC-96				
			5	25	50	100	250	5	25	50	100	250
I_a	3-CH_3-C_6H_4	CH_3	-	12	14	16	18	-	12	15	18	19
I_b	4-CH_3-C_6H_4	CH_3	-	13	15	17	18	-	11	14	16	18
I_c	2,5-$(CH_3)_2$-C_6H_4	CH_3	-	11	14	17	19	-	12	14	15	17
I_d	4-CH_3O-C_6H_4	CH_3	-	11	14	15	18	-	12	16	17	19
I_e	3-Cl-C_6H_4	CH_3	-	12	14	18	21	-	10	13	15	17
I_f	4-Cl-C_6H_4	CH_3	-	11	14	16	19	-	11	13	15	16
I_g	2-F-C_6H_4	CH_3	-	12	14	16	21	-	11	15	16	18
I_h	4-F-C_6H_4	CH_3	-	12	14	15	18	-	12	14	14	16
I_i	3-O_2N-C_6H_4	CH_3	-	13	14	15	18	-	10	12	15	16
I_j	4-O_2N-C_6H_4	CH_3	11	14	16	17	19	-	12	14	15	16

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

Standard drug	Antibacterial activity									
	I_j	I_b I_i I_j	I_j	I_e	I_c I_e I_g I_j			I_a I_h I_b I_j I_c I_g I_d	I_a I_b I_d I_g	I_a I_b I_d I_g
Amoxiciline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
ciprofloxacin	16	19	21	21	22	17	19	21	22	22
Norfloxacin	18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

TABLE NO. 1_b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3,5-DISUBSTITUTED PHENYL CARBAMOYL-1,4-DIHYDROPYRIDINES (I_{a-j}).
(Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	Antibactrial activity (Zones of inhibition in mm) E. Coli MTCC-443 5	25	50	100	250	P. Aeruginosa MTCC-1688 5	25	50	100	250
I_a	3-CH_3-C_6H_4	CH_3	-	12	14	16	18	-	12	15	18	19
I_b	4-CH_3-C_6H_4	CH_3	-	13	15	17	18	-	11	14	16	18
I_c	2,5-$(CH_3)_2$-C_6H_4	CH_3	-	11	14	17	19	-	12	14	15	17
I_d	4-CH_3O-C_6H_4	CH_3	-	11	14	15	18	-	12	16	17	19
I_e	3-Cl-C_6H_4	CH_3	-	12	14	18	21	-	10	13	15	17
I_f	4-Cl-C_6H_4	CH_3	-	11	14	16	19	-	11	13	15	16
I_g	2-F-C_6H_4	CH_3	-	12	14	16	21	-	11	15	16	18
I_h	4-F-C_6H_4	CH_3	-	12	14	15	18	-	12	14	14	16
I_i	3-O_2N-C_6H_4	CH_3	-	13	14	15	18	-	10	12	15	16
I_j	4-O_2N-C_6H_4	CH_3	11	14	16	17	19	-	12	14	15	16

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

Standard drug	Antibacterial activity									
	I_j	I_b I_i I_j	I_j	I_e	I_c I_e I_g I_j			I_a I_h I_b I_j I_c I_g I_d	I_a I_b I_d I_g	I_a I_b I_d I_g
Amoxiciline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
ciprofloxacin	16	19	21	21	22	17	19	21	22	22
Norfloxacin	18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

TABLE NO. 1_C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL- 3,5-DISUBSTITUTED PHENYL CARBAMOYL-1,4-DIHYDROPYRIDINES (I_{a-j}).
(Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	Antibactrial activity (Zones of inhibition in mm) A. niger MTCC-282 5	25	50	100	250	A. clavatus MTCC-1323 5	25	50	100	250
I_a	3-CH_3-C_6H_4	CH_3	-	12	14	16	18	-	12	15	18	19
I_b	4-CH_3-C_6H_4	CH_3	-	13	15	17	18	-	11	14	16	18
I_c	2,5-$(CH_3)_2$-C_6H_4	CH_3	-	11	14	17	19	-	12	14	15	17
I_d	4-CH_3O-C_6H_4	CH_3	-	11	14	15	18	-	12	16	17	19
I_e	3-Cl-C_6H_4	CH_3	-	12	14	18	21	-	10	13	15	17
I_f	4-Cl-C_6H_4	CH_3	-	11	14	16	19	-	11	13	15	16
I_g	2-F-C_6H_4	CH_3	-	12	14	16	21	-	11	15	16	18
I_h	4-F-C_6H_4	CH_3	-	12	14	15	18	-	12	14	14	16
I_i	3-O_2N-C_6H_4	CH_3	-	13	14	15	18	-	10	12	15	16
I_j	4-O_2N-C_6H_4	CH_3	11	14	16	17	19	-	12	14	15	16

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

Standard drug	Antibacterial activity									
	I_j	I_b I_i I_j	I_j	I_e	I_c I_e I_g I_j	I_a I_b I_c I_d	I_h I_j I_g	I_a I_b I_d I_g	I_a I_b I_d I_g
Amplicilline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
ciprofloxacin	16	19	21	21	22	17	19	21	22	22
Norfloxacin	18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

TABLE NO. 1_d : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIISOPRPYL-3,5-DISUBSTITUTED PHENYL CARBAMOYL-1,4-DIHYDROPYRIDINES (I_{k-t}).
(Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442					S. aureus MTCC-96				
			5	25	50	100	250	5	25	50	100	250
I_k	3-CH_3-C_6H_4	$CH(CH_3)_2$	-	12	14	16	18	-	12	15	18	19
I_l	4-CH_3-C_6H_4	$CH(CH_3)_2$	-	13	15	17	18	-	11	14	16	18
I_m	2,5-$(CH_3)_2$-C_6H_4	$CH(CH_3)_2$	-	11	14	17	19	-	12	14	15	17
I_n	4-CH_3O-C_6H_4	$CH(CH_3)_2$	-	11	14	15	18	-	12	16	17	19
I_o	3-Cl-C_6H_4	$CH(CH_3)_2$	-	12	14	18	21	-	10	13	15	17
I_p	4-Cl-C_6H_4	$CH(CH_3)_2$	-	11	14	16	19	-	11	13	15	16
I_q	2-F-C_6H_4	$CH(CH_3)_2$	-	12	14	16	21	-	11	15	16	18
I_r	4-F-C_6H_4	$CH(CH_3)_2$	-	12	14	15	18	-	12	14	14	16
I_s	3-O_2N-C_6H_4	$CH(CH_3)_2$	-	13	14	15	18	-	10	12	15	16
I_t	4-O_2N-C_6H_4	$CH(CH_3)_2$	11	14	16	17	19	-	12	14	15	16

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

Standard drug	Antibacterial activity									
	I_j	I_b I_i I_j	I_j	I_e	I_c I_e I_g I_j			I_a I_h I_b I_j I_c I_g I_d	I_a I_b I_d I_g	I_a I_b I_d I_g
Ampliicilline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
ciprofloxacin	16	19	21	21	22	17	19	21	22	22
Norfloxacin	18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

TABLE NO. 1_e : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIISOPROPYL- 3,5 DISUBSTITUTED PHENYL CARBAMOYL-1,4-DIHYDROPYRIDINES (I_{k-t}).
(Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	Antibactrial activity (Zones of inhibition in mm)									
			E. Coli MTCC-443					P. Aeruginosa MTCC-1688				
			5	25	50	100	250	5	25	50	100	250
I_k	3-CH_3-C_6H_4	$CH(CH_3)_2$	-	12	14	16	18	-	12	15	18	19
I_l	4-CH_3-C_6H_4	$CH(CH_3)_2$	-	13	15	17	18	-	11	14	16	18
I_m	2,5-$(CH_3)_2$-C_6H_4	$CH(CH_3)_2$	-	11	14	17	19	-	12	14	15	17
I_n	4-CH_3O-C_6H_4	$CH(CH_3)_2$	-	11	14	15	18	-	12	16	17	19
I_o	3-Cl-C_6H_4	$CH(CH_3)_2$	-	12	14	18	21	-	10	13	15	17
I_p	4-Cl-C_6H_4	$CH(CH_3)_2$	-	11	14	16	19	-	11	13	15	16
I_q	2-F-C_6H_4	$CH(CH_3)_2$	-	12	14	16	21	-	11	15	16	18
I_r	4-F-C_6H_4	$CH(CH_3)_2$	-	12	14	15	18	-	12	14	14	16
I_s	3-O_2N-C_6H_4	$CH(CH_3)_2$	-	13	14	15	18	-	10	12	15	16
I_t	4-O_2N-C_6H_4	$CH(CH_3)_2$	11	14	16	17	19	-	12	14	15	16

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

Standard drug	Antibacterial activity									
	I_j	I_b I_i I_j	I_j	I_e	I_c I_e I_g I_j			I_a I_h I_b I_j I_c I_g I_d	I_a I_b I_d I_g	I_a I_b I_d I_g
Amplicilline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
ciprofloxacin	16	19	21	21	22	17	19	21	22	22
Norfloxacin	18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

TABLE NO. 1_f : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIISOPROPYL-3,5-DISUBSTITUTED PHENYL CARBAMOYL-1,4-DIHYDROPYRIDINES (I_{k-t}).

(Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	Antibactrial activity (Zones of inhibition in mm) A. niger MTCC-282					A. clavatus MTCC-1323				
			5	25	50	100	250	5	25	50	100	250
I_k	3-CH_3-C_6H_4	$CH(CH_3)_2$	-	12	14	16	18	-	12	15	18	19
I_l	4-CH_3-C_6H_4	$CH(CH_3)_2$	-	13	15	17	18	-	11	14	16	18
I_m	2,5-$(CH_3)_2$-C_6H_4	$CH(CH_3)_2$	-	11	14	17	19	-	12	14	15	17
I_n	4-CH_3O-C_6H_4	$CH(CH_3)_2$	-	11	14	15	18	-	12	16	17	19
I_o	3-Cl-C_6H_4	$CH(CH_3)_2$	-	12	14	18	21	-	10	13	15	17
I_p	4-Cl-C_6H_4	$CH(CH_3)_2$	-	11	14	16	19	-	11	13	15	16
I_q	2-F-C_6H_4	$CH(CH_3)_2$	-	12	14	16	21	-	11	15	16	18
I_r	4-F-C_6H_4	$CH(CH_3)_2$	-	12	14	15	18	-	12	14	14	16
I_s	3-O_2N-C_6H_4	$CH(CH_3)_2$	-	13	14	15	18	-	10	12	15	16
I_t	4-O_2N-C_6H_4	$CH(CH_3)_2$	11	14	16	17	19	-	12	14	15	16

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

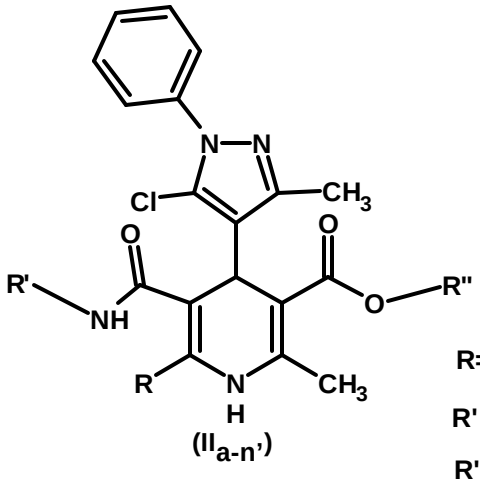
Standard drug	Antibacterial activity									
	I_j	I_b I_i I_j	I_j	I_e	I_c I_e I_g I_j			I_a I_h I_b I_j I_c I_g I_d	I_a I_b I_d I_g	I_a I_b I_d I_g
Amplicilline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
ciprofloxacin	16	19	21	21	22	17	19	21	22	22
Norfloxacin	18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

SECTION-II

PREPARATION AND BIOLOGICAL EVALUATION OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL/ 6-ISOPROPYL/ 2-METHYL-3-CARBMETHOXY/ EYHOXY-5-SUBSTITUTED PHENYLCARBAMOYL-1,4-DIHYDRO PYRIDINES($II_{a-n'}$).

1,4-Dihydropyridine derivatives represents one of the most active classes of compounds possessing wide spectrum of biodynamic activities[52-67]. In order to have potent therapeutic agents, the synthesis of **4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-2,6-dimethyl/6-isopropyl/2-methyl-3-carbmethoxy/ethoxy- 5-substituted phenylcarbamoyl-1,4-dihydropyridines ($II_{a'-n'}$)** have been undertaken by the condensation of **Ethyl/methyl-3-amino but-2-enoate** and **2-[(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl) methylene]-3-oxo-N-phenylbutanamide/ pantanamide** in basic media.



($II_{a-n'}$)

R= -CH_3/ -$CH(CH_3)_2$

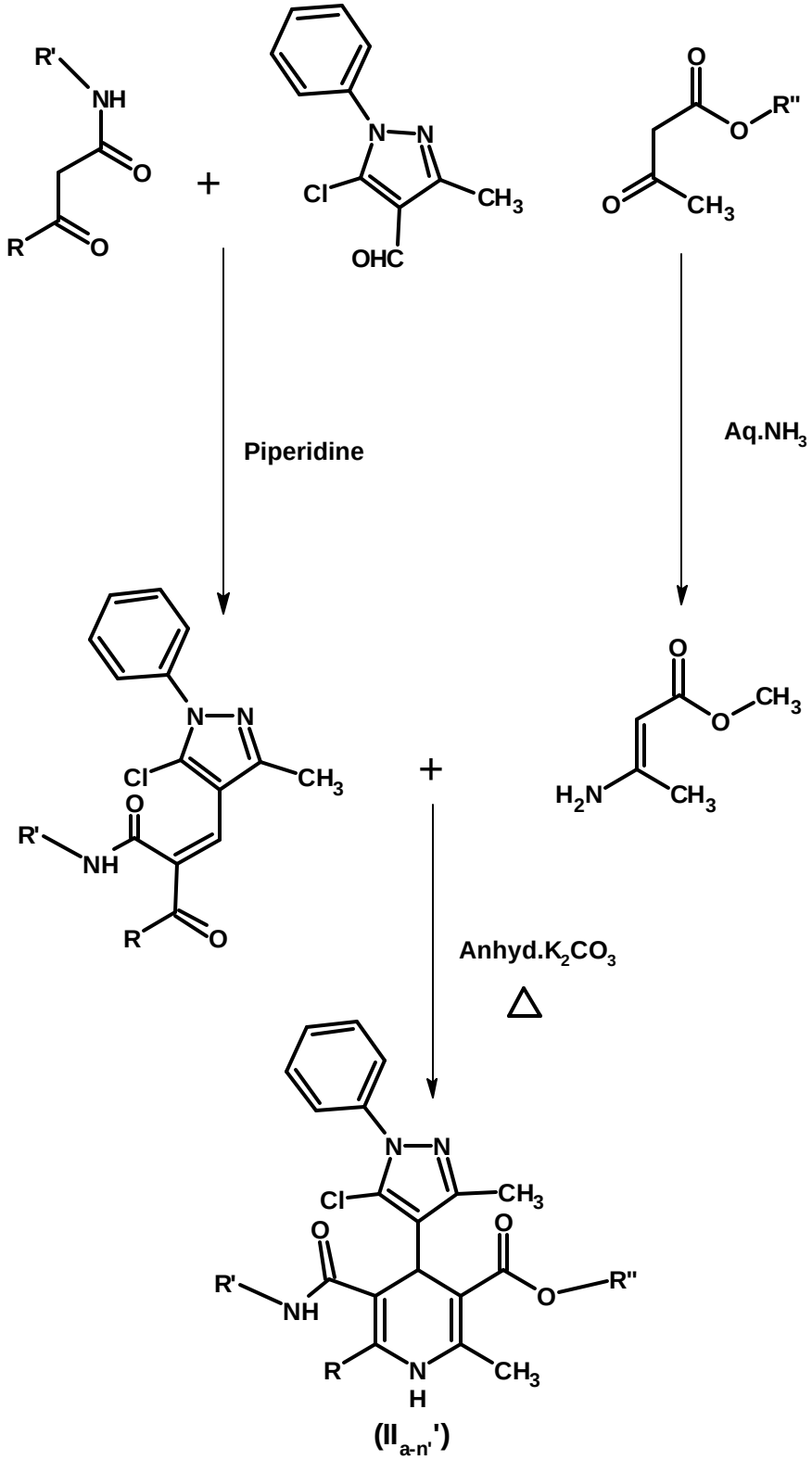
R' = Substituted phenyl

R"= -CH_3/ C_2H_5

The constitution of the products **($II_{a-n'}$)** have been delineated by **elemental analyses**, **IR, PMR** and **Mass** spectral data.

The products **($II_{a-n'}$)** were assayed for their ***in vitro*** biological assay like antibacterial activity towards ***S. pyogens MTCC-443*, *S. aureus MTCC-96* and *P. aeruginosa MTCC-441* (Gram positive) and *E. coli MTCC-442* (Gram negative)** bacterial strains and antifungal activity towards ***Aspergillus niger MTCC-282* and *A. clavatus MTCC-1323*** at different concentrations i.e.: 0, 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds **($II_{a-n'}$)** were compared with standard drugs,viz. **Amoxicillin, Chloramphenicol, Ciprofloxacin and Norfloxacin** (antibacterial)**, Griseofluvin, Nystatin** (antifungal)**.**

REACTION SCHEME



($II_{a\text{-}n'}$')

R= -CH_3/-$CH(CH_3)_2$
R'= Substituted phenyl
R''= -CH_3/ C_2H_5

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL/-6-ISOPROPYL/2-METHYL-3-CARBMETHOXY/EYHOXY-5-SUBSTITUTED PHENYL-CARBAMOYL-1,4-DIHYDRO PYRIDINES ($II_{a-n'}$).

Preparation of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-2,6-dimethyl/-6-isopropyl/-2-methyl-3-carbethoxy/ethoxy-5-(p-tolyl carbamoyl)-1,4-dihydropyridine (II_b)/(II_l)/(II_v)/($II_{f'}$):

(A) (i) Preparation of 2-[(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl) methylene]-3oxo-N-p-tolylbutanamide (2_b).

A mixture of **N-(p-tolyl)-3-oxobutanamide** (1.91gm, 0.01 M), **5-chloro-3-methyl-1-N-phenyl-pyrazole-4-carbaldehyde** (2.20gm, 0.01 M) in 15 ml **methanol** and 3 to 4 drops of **piperidine** was stirred at room temperature for 24 hours.The reaction mixture was poured into ice called water. The solid product so obtained was filtered, washed with little cold methanol, dried and crystallized from methanol. **Yield** 66%, **M.P**. :118°C, (Required:**C**, 67.17%; **H**, 5.08%; **N**, 10.68% for $C_{22}H_{20}N_3O_2Cl$, Found : **C**, 67.20 %; **H**, 5.06 %; **N**, 10.63 %).

TLC solvent system R_{f_1}: Ethyl acetate : Hexane (9.0 :1.0) = 0.52**.**
TLC solvent system R_{f_2}: Methanol : Toluene (1.5 : 8.5) = 0.51.

Similarly, other compounds **(2_{a-t})** were synthesized and physical data are recorded in talble no.**2_A.**

(ii) Preparation of 2-[(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-methylene]-4-methyl-3oxo-N-p-tolylbutanamide (2_l).

A mixture of **4-methyl-N-(p-tolyl)-3-oxopetanamide** (2.19 gm, 0.01 M), **5-chloro-3-methyl-1-N-phenyl-pyrazole-4-carbaldehyde** (2.20gm, 0.01 M) in 15 ml **methanol** and 3 to 4 drops of **piperidine** was stirred at room tem-

perature for 24 hours.The reaction mixture was poured into called water so the solid product obtained was filtered and washed with little cold methanol, dried and crystallized from methanol. **Yield** :56 %, **M.P**.:108°C, (Required:**C**, 68.26%; **H**, 5.68%; **N**, 9.97% for $C_{24}H_{24}N_3O_2Cl$, Found : **C**, 68.29 %; **H**, 5.64 %; **N**, 9.92 %).

TLC solvent system R_{f_1}: Ethyl acetate : Hexane (9.0 :1.0) = 0.50**.**
TLC solvent system R_{f_2}: Methanol : Toluene (1.5 : 8.5) = 0.53

Similarly, other compounds **(2_{k-t})** were synthesized. The physical data are recorded in **Table No.2_B**.

(B) (i) Preparation of Methyl-3-aminobut-2-enoate.

A mixture of **methylacetoacetate** (1.16gm, 0.01 M), **ammonia solution** (25%) (2.72 ml, 0.04 mol) was stirred for 4 hours in ice bath. The solid product so obtained was filtered and dried. **Yield** : 68%, **M.P**.:45°C, (Required:**C**, 52.17%;**H**, 7.82%;**N**,12.17% for $C_5H_9NO_2$, Found :**C**, 52.20%; **H**, 7.79%; **N**,12.20%).

(ii) Preparation of Ethyl-3-aminobut-2-enoate.

A mixture of **ethylacetoacetate** (1.30gm, 0.01 M), **ammonia solution** (25%) (2.72 ml, 0.04 mol) was stirred for 6 hours in ice bath. The solid product so obtained was filtered it and dried. **Yield** : 58%, **M.P**.:35°C, (Required:**C**, 55.81%;**H**, 8.52%;**N**,10.85 for $C_6H_{11}NO_2$, Found :**C**, 55.75%; **H**, 8.49%; **N**,10.89%)

(C) (i) Preparation of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-2,6-dimethyl-3-carbmethoxy-5-(p-tolylcarbamoyl)-1,4-dihydropyridine (II_b).

A mixture of **2-[(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl) methylene]-3oxo-N-p-toylbutanamide** (1.97 gm,0.005 M), **methyl-3-aminobut-2-enoate** (0.70gm,0.006 M) and **anhydrous potassium carbonate** (1.37gm, 0.01 M) in **dimethyl formamide** (15 ml) was heated under reflux for 10 to12 hours.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** : 39%, **M.P**. :139°C, (Required : **C**, 66.12 %; **H**, 5.51 %; **N**, 11.40 % for **$C_{27}H_{27}N_4O_3Cl$,** Found : **C**, 66.10%; **H**, 5.48%; **N**, 11.35%).

TLC solvent system Rf_1: Ethyl acetate :Hexane (2.5 : 7.5) = 0.60.

TLC solvent system Rf_2 : Methanol :Chloroform (0.5 : 9.5) = 0.58

(ii) Preparation of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-6-isopropyl-2-methyl-3-carbmethoxy-5-(p-tolylcarbamoyl)-1,4-dihydropyridine (II_I).

A mixture of **2-[(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl) methylene]-4-methyl-3oxo-N-p-tolylbutanamide**(2.20 gm,0.005 M), **methyl-3-aminobut-2-enoate** (0.70gm,0.006 M) and **anhydrous potassium carbonate** (1.37 gm, 0.01 M) in **dimethyl formamide** (15 ml) was heated under reflux for 8 to10 hours.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**. :136°C, (Required : **C**, 67.05 %; **H**, 5.97 %; **N**, 10.78 % for **$C_{29}H_{31}N_4O_3Cl$**, Found : **C**, 67.08%; **H**, 5.94%; **N**, 10.72%).

TLC solvent system R_{f_1}: Ethyl acetate :Hexane (2.5 : 7.5) = 0.53.

TLC solvent system R_{f_2} : Methanol :Chloroform (0.5 : 9.5) = 0.41

(iii) Preparation of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-2,6-dimethyl-3-carbethoxy-5-(p-tolylcarbamoyl)-1,4-dihydropyridine (II_V).

A mixture of **2-[(5'-chloro-3'-methyl-1-N-phenyl-pyrazol-4'-yl)-methylene]-3oxo-N-p-tolylbutanamide**(1.97gm,0.005 M), **ethyl-3-aminobut-2-enoate** (0.78gm,0.006 M) and **anhydrous potassium carbonate** (1.37 gm, 0.01 M) in **dimethyl formamide** (15 ml) was heated under reflux for 12 to14 hours.The reaction was monitored by TLC. The reaction mixture was allowed to cool at room tempreture and poured into cold water. The solid product so obtained was filtered, washed with water, dried and cystallized from dimethyl formamide. **Yield** : 46%, **M.P**. :152°C, (Required : **C**, 66.53 %; **H**, 5.74 %; **N**,

11.08 % for $C_{28}H_{29}N_4O_3Cl$, Found : **C**, 66.56%; **H**, 5.72%; **N**, 11.02%).

TLC solvent system R_{f_1} : Ethyl acetate :Hexane (2.5 : 7.5) = 0.58.
TLC solvent system R_{f_2} : Methanol :Chloroform (0.5 : 9.5) = 0.48

(iv) Preparation of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl) -6-isopropyl-2-methyl-3-carbethoxy-5-(p-tolylcarbamoyl)-1,4-dihydro-pyridine ($II_{f'}$).

A mixture of 2**-[(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-methylene]-3oxo-N-p-tolylbutanamide**(2.20 gm,0.005 M), **ethyl-3-aminobut-2-enoate**. (0.78gm,0.006 M) and **anhydrous potassium carbonate** (1.37 gm, 0.01 M) in **dimethyl formamide** (15 ml) was heated under reflux for 12 to14 hours.The reaction was monitored by TLC. The reaction mixture was allowed to cool at room tempreture and poured into cold water. The solid product so obtained was filtered, washed with water, dried and cystallized from dimethyl formamide. **Yield** : 43%, **M.P.** :116°C,(Required : **C**, 67.54 %; **H**, 6.19 %; **N**, 10.50 % for $C_{30}H_{33}N_4O_3Cl$, Found : **C**, 67.56%; **H**, 6.17%; **N**, 10.46%).

TLC solvent system Rf_1: Ethyl acetate :Hexane (2.5 : 7.5) = 0.60.
TLC solvent system Rf_2 : Methanol :Chloroform (0.5 : 9.5) = 0.44
.

Similarly, other compounds **($II_{a-n'}$)** were synthesized. The physical data are recorded in **Table No.II_A,II_B,II_C and II_D**.

(D) Antimicrobial activity of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol -4'-yl)-2,6-dimethyl/6-isopropyl/2-methyl-3-carbmethoxy/ethoxy-5-substituted phenylcarbamoyl-1,4-dihydropyridines ($II_{a-n'}$).

Antimicrobial activity testing was carried out as described in Part-I, Section-I, page No. **30** to **33**. The MIC values of test solution are recorded in Table **No. 2_a, 2_b, 2_c..... and 2_l**

Result and Discussion:

The products **($II_{a-n'}$)** have been subjected to antibacterial activity towards ***S. pyogens MTCC-443*, *S. aureus MTCC-96* and *P. aeruginosa MTCC-441* (Gram positive) and *E. coli MTCC-442* (Gram negative)** bacterial strains and antifungal activity towards ***Aspergillus niger MTCC-282* and *A. clavatus MTCC-1323*** at different concentrations i.e.: 0, 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values.

The biological activities of the synthesized compounds **($II_{a-n'}$)** were compared with standard drugs,viz., **Amplicilline, Chloramphenicol, Ciprofloxacin and Norfloxacin** (antibacterial), **Greseofluvin, Nystatin** (antifungal).

The results of antimicrobial activity have been depicted on page no. **82** to **94**.

TABLE NO. 2_A : PHYSICAL CONSTANTS OF 2-[(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-METHYLENE]-3-OXO-N-PHENYLBUTANAMIDES (2_{a-j}).

Comp. No. 1	R 2	R' 3	Molecular Formula 4	M.W. 5	Yield % 6	M.P. °C 7	R_f Value R_f / R_{f_2} 8	% of Nitrogen Calcd. / Found 9
2_a	CH_3	3-CH_3-C_6H_4	$C_{22}H_{20}ClN_3O_2$	393.80	57	112	0.53/ 0.48	10.68 / 10.63
2_b	CH_3	4-CH_3-C_6H_4	$C_{22}H_{20}ClN_3O_2$	393.80	66	118	0.52/ 0.51	10.68 / 10.63
2_c	CH_3	2,5-$(CH_3)_2$-C_6H_3	$C_{23}H_{22}ClN_3O_2$	407.00	66	111	0.54/ 0.50	10.31/ 10.24
2_d	CH_3	4-CH_3O-C_6H_4	$C_{22}H_{20}ClN_3O_3$	409.80	63	121	0.56/ 0.54	10.26 / 10.21
2_e	CH_3	3-Cl-C_6H_4	$C_{21}H_{17}Cl_2N_3O_2$	414.30	56	117	0.58/ 0.47	10.14 / 10.08
2_f	CH_3	4-Cl-C_6H_4	$C_{21}H_{17}Cl_2N_3O_2$	414.30	61	138	0.54/ 0.55	10.14/ 10.08
2_g	CH_3	2-F-C_6H_4	$C_{21}H_{17}ClFN_3O_2$	397.80	58	141	0.50/ 0.54	10.57 / 10.51
2_h	CH_3	4-F-C_6H_4	$C_{21}H_{17}ClFN_3O_2$	397.80	67	131	0.48/ 0.53	10.57 / 10.51
2_i	CH_3	3-O_2N-C_6H_4	$C_{21}H_{17}ClN_4O_4$	424.85	67	128	0.44/ 0.57	13.20 / 13.14
2_j	CH_3	4-O_2N-C_6H_4	$C_{21}H_{17}ClN_4O_4$	424.85	59	107	0.53/ 0.49	13.20/ 13.14

TLC solvent system R_{f_1}: Ethyl acetate : Hexane (9.0 :1.0)

TLC solvent system R_{f_2}: Methanol : Toluene (1.5 : 8.5)

TABLE NO. 2_B : PHYSICAL CONSTANTS OF 2-[(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-METHYLENE]-4-METHYL-3-OXO-N-PHENYLPENTANAMIDES (2_{k-t}).

Comp. No.	R	R'	Molecular Formula	M.W.	Yield %	M.P. °C	R_f Value R_f / R_{f_2}	% of Nitrogen Calcd./Found
1	2	3	4	5	6	7	8	9
2_k	$CH(CH_3)_2$	3-CH_3-C_6H_4	$C_{24}H_{24}ClN_3O_2$	421.90	58	129	0.51/ 0.54	9.97 / 9.92
2_l	$CH(CH_3)_2$	4-CH_3-C_6H_4	$C_{24}H_{24}ClN_3O_2$	421.90	56	108	0.50/ 0.53	9.97 / 9.92
2_m	$CH(CH_3)_2$	2,5-(CH_3)-C_6H_3	$C_{25}H_{26}ClN_3O_2$	435.90	65	99	0.46/ 0.52	9.63/ 9.57
2_n	$CH(CH_3)_2$	4-CH_3O-C_6H_4	$C_{24}H_{24}ClN_3O_3$	437.00	52	101	0.54/ 0.57	9.61 / 9.54
2_o	$CH(CH_3)_2$	3-Cl-C_6H_4	$C_{23}H_{21}Cl_2N_3O_2$	422.30	53	131	0.56/ 0.52	9.50 / 9.44
2_p	$CH(CH_3)_2$	4-Cl-C_6H_4	$C_{23}H_{21}Cl_2N_3O_2$	422.30	52	111	0.54/ 0.48	9.50/9.44
2_q	$CH(CH_3)_2$	2-F-C_6H_4	$C_{23}H_{21}ClFN_3O_2$	425.80	57	104	0.49/ 0.43	9.86/ 9.77
2_r	$CH(CH_3)_2$	4-F-C_6H_4	$C_{23}H_{21}ClFN_3O_2$	425.80	62	106	0.42/ 0.43	9.86 / 9.77
2_s	$CH(CH_3)_2$	3-O_2N-C_6H_4	$C_{23}H_{21}ClN_4O_4$	452.80	63	121	0.46/ 0.48	12.36 / 12.31
2_t	$CH(CH_3)_2$	4-O_2N-C_6H_4	$C_{23}H_{21}ClN_4O_4$	452.80	58	115	0.50/ 0.48	12.36/ 12.31

TLC solvent system R_{f_1}: Ethyl acetate : Hexane (9.0 :1.0)

TLC solvent system R_{f_2}: Methanol : Toluene (1.5 : 8.5)

TABLE NO. II $_A$: PHYSICAL CONSTANTS OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL -3-CARBMETHOXY-5-(SUBSTITUTED PHENYLCARBAMOYL)-1,4-DIHYDROPYRIDINES (II$_{a-j}$).

Comp. No.	R	R'	R''	Molecular Formula	M.W.	Yield %	M.P. ^oC	R_f Value R_{f_1}/ R_{f_2}	% of Nitrogen Calcd. / Found
1	2	3	4	5	6	8	7	9	10
II_a	CH_3	3-CH_3-C_6H_4	CH_3	$C_{27}H_{27}ClN_4O_3$	490.90	37	121	0.53/ 0.41	11.40 / 11.35
II_b	CH_3	4-CH_3-C_6H_4	CH_3	$C_{27}H_{27}ClN_4O3$	490.90	39	139	0.60/ 0.58	11.40 / 11.35
II_c	CH_3	2,5-$(CH_3)_2$-C_6H_3	CH_3	$C_{28}H_{29}ClN_4O_3$	505.50	36	101	0.62/ 0.51	11.08 / 11.03
II_d	CH_3	4-CH_3O-C_6H_4	CH_3	$C_{27}H_{27}ClN_4O_4$	506.90	39	156	0.46/ 0.44	11.04 / 11.00
II_e	CH_3	3-Cl-C_6H_4	CH_3	$C_{26}H_{24}Cl_2N_4O_3$	511.40	36	132	0.54/ 0.49	10.95 / 10.90
II_f	CH_3	4-Cl-C_6H_4	CH_3	$C_{26}H_{24}Cl_2N_4O_3$	511.40	38	142	0.56/ 0.53	10.95 / 10.90
II_g	CH_3	2-F-C_6H_4	CH_3	$C_{26}H_{24}ClFN_4O_3$	494.90	39	109	0.48/ 0.46	11.31 / 11.26
II_h	CH_3	4-F -C_6H_4	CH_3	$C_{26}H_{24}ClFN_4O_3$	494.90	42	126	0.58/ 0.56	11.31 / 11.26
II_i	CH_3	3-O_2N-C_6H_4	CH_3	$C_{26}H_{24}ClN_5O_5$	521.95	45	148	0.52/ 0.42	13.41 / 13.32
II_j	CH_3	4-O_2N-C_6H_4	CH_3	$C_{26}H_{24}ClN_5O_5$	521.95	36	139	0.61/ 0.53	13.41 / 13.32

TLC solvent system R_{f_1}: Ethyl acetate : Hexane (9.0 :1.0)

TLC solvent system R_{f_2}: Methanol : Toluene (1.5 : 8.5)

TABLE NO. II_B :PHYSICAL CONSTANTS OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-ISOPROPYL-2-METHYL-3-CARBMETHOXY-5-(SUBSTITUTED PHENYLCARBAMOYL)-1,4- DIHYDROPYRIDINES (II_{k-t}).

Comp. No.	R	R'	R''	Molecular Formula	M.W.	Yield %	M.P. °C	R_f Value R_{f_1}/ R_{f_2}	% of Nitrogen Calcd. / Found
1	2	3	4	5	6	7	8	9	10
II_k	$CH(CH_3)_2$	3-CH_3-C_6H_4	CH_3	$C_{29}H_{31}ClN_4O_3$	519.00	37	123	0.46/ 0.49	10.78 / 10.72
II_l	$CH(CH_3)_2$	4-CH_3-C_6H_4	CH_3	$C_{29}H_{31}ClN_4O3$	519.00	38	136	0.53/ 0.41	10.78 / 10.72
II_m	$CH(CH_3)_2$	2,5-$(CH_3)_2$-C_6H_3	CH_3	$C_{30}H_{33}ClN_4O_3$	533.00	38	101	0.60/ 0.42	10.50 / 10.44
II_n	$CH(CH_3)_2$	4-CH_3O-C_6H_4	CH_3	$C_{29}H_{31}ClN_4O_4$	535.00	38	156	0.48/ 0.61	10.46 / 10.41
II_o	$CH(CH_3)_2$	3-Cl-C_6H_4	CH_3	$C_{28}H_{28}Cl_2N_4O_3$	539.40	37	132	0.52/ 0.47	10.38 / 10.30
II_p	$CH(CH_3)_2$	4-Cl-C_6H_4	CH_3	$C_{28}H_{28}Cl_2N_4O_3$	539.40	41	142	0.63/ 0.57	10.38 / 10.30
II_q	$CH(CH_3)_2$	2-F-C_6H_4	CH_3	$C_{28}H_{28}ClFN_4O_3$	523.00	38	109	0.49/ 0.42	10.70 / 10.63
II_r	$CH(CH_3)_2$	4-F -C_6H_4	CH_3	$C_{28}H_{28}ClFN_4O_3$	523.00	35	116	0.59/ 0.52	10.70 / 10.63
II_s	$CH(CH_3)_2$	3-O_2N-C_6H_4	CH_3	$C_{28}H_{28}ClN_5O_5$	550.00	40	148	0.49/ 0.51	12.72 / 12.64
II_t	$CH(CH_3)_2$	4-O_2N-C_6H_4	CH_3	$C_{28}H_{28}ClN_5O_5$	550.00	37	151	0.58/ 0.50	12.72 / 12.64

TLC solvent system R_{f_1}: Ethyl acetate : Hexane (9.0 :1.0)

TLC solvent system R_{f_2}: Methanol : Toluene (1.5 : 8.5)

TABLE NO. II_C : PHYSICAL CONSTANTS OF4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3-CARBETHOXY-5-(SUBSTITUTED PHENYLCARBAMOYL)-1,4-DIHYDRO PYRIDINES ($II_{u\text{-}d'}$).

Comp. No.	R	R'	R''	Molecular Formula	M.W.	Yield %	M.P. ^oC	R_f Value R_{f_1}/R_{f_2}	% of Nitrogen Calcd. / Found
1	2	3	4	5	6	7	8	9	10
II_u	CH_3	3-CH_3-C_6H_4	C_2H_5	$C_{28}H_{29}ClN_4O_3$	505.00	41	142	0.60/ 0.47	11.08 / 11.02
II_v	CH_3	4-CH_3-C_6H_4	C_2H_5	$C_{28}H_{29}ClN_4O_3$	505.00	46	152	0.58 / 0.48	11.08 / 11.02
II_w	CH_3	2,5-$(CH_3)_2$-C_6H_3	C_2H_5	$C_{29}H_{31}ClN_4O_3$	519.00	39	148	0.61/ 0.52	10.78 / 10.70
II_x	CH_3	4-CH_{3O}-C_6H_4	C_2H_3	$C_{28}H_{29}ClN_4O_4$	521.00	44	121	0.57/ 0.54	10.74 / 10.66
II_y	CH_3	3-Cl-C_6H_4	C_2H_5	$C_{27}H_{26}Cl_2N_4O_3$	525.00	40	140	0.51/ 0.46	10.65 / 10.57
II_z	CH_3	4-Cl -C_6H_4	C_2H_5	$C_{27}H_{26}Cl_2N_4O_3$	525.90	45	134	0.52/ 0.48	10.65 / 10.57
$II_{a'}$	CH_3	2-F-C_6H_4	C_2H_5	$C_{27}H_{26}ClFN_4O_3$	508.00	37	153	0.54/ 0.49	11.00 / 10.94
$II_{b'}$	CH_3	4-F-C_6H_4	C_2H_5	$C_{27}H_{26}ClFN_4O3$	508.00	38	131	0.52/ 0.50	11.00 / 10.94
$II_{c'}$	CH_3	3-O_{2N}-C_6H_4	C_2H_5	$C_{27}H_{26}ClN_5O_5$	535.00	33	138	0.48/ 0.53	13.06 / 13.00
$II_{d'}$	CH_3	4-O_{2N}-C_6H_4	C_2H_5	$C_{27}H_{26}ClN_5O_5$	535.00	43	147	0.62/ 0.49	13.06 / 13.00

TLC solvent system R_{f_1}: Ethyl acetate : Hexane (9.0 :1.0)

TLC solvent system R_{f_2}: Methanol : Toluene (1.5 : 8.5)

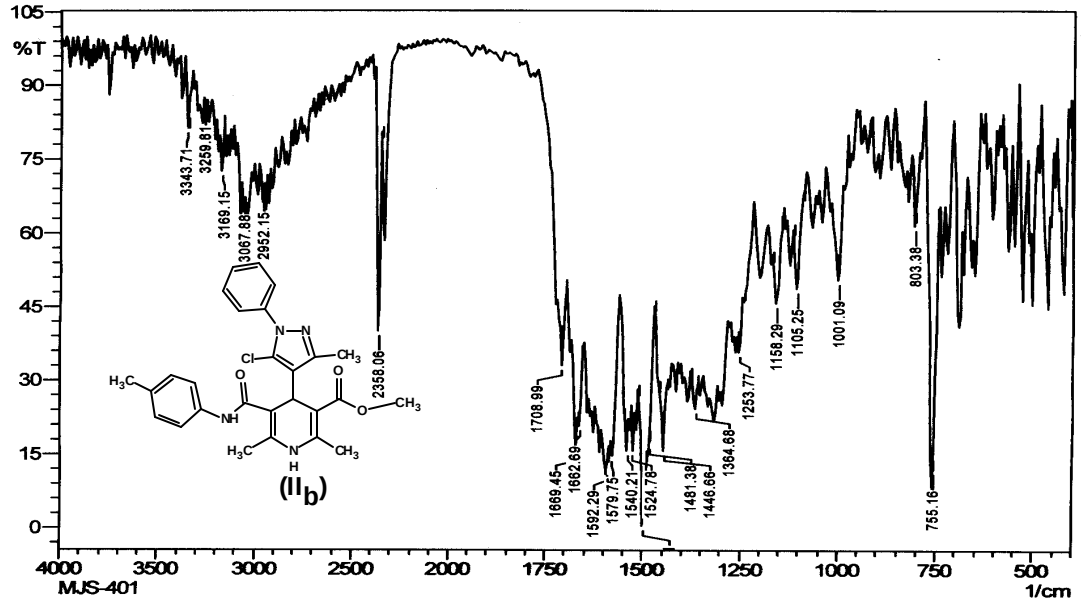
TABLE NO. II_D :PHYSICAL CONSTANTS OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-ISOPROPYL-2-METHYL-3-CARBETHOXY-5-(SUBSTITUTED PHENYLCARBAMOYL)-1,4- DIHYDROPYRIDINES ($II_{e'-n'}$).

Comp. No.	R	R'	R''	Molecular Formula	M.W.	Yield %	M.P. ^oC	R_f Value R_{f_1} / R_{f_2}	% of Nitrogen Calcd. / Found
1	2	3	4	5	6	7	8	9	10
$II_{e'}$	$CH(CH_3)_2$	3-CH_3-C_6H_4	C_2H_5	$C_{30}H_{33}ClN_4O_3$	533.60	41	112	0.61/ 0.48	10.50 / 10.44
$II_{f'}$	$CH(CH_3)_2$	4-CH_3-C_6H_4	C_2H_5	$C_{30}H_{33}ClN_4O3$	533.60	43	116	0.60/ 0.44	10.50 / 10.44
$II_{g'}$	$CH(CH_3)_2$	2,5-$(CH_3)_2$-C_6H_3	C_2H_5	$C_{31}H_{35}ClN_4O_3$	547.00	39	118	0.57/ 0.43	10.23 / 10.16
$II_{h'}$	$CH(CH_3)_2$	4-CH_3O-C_6H_4	C_2H_5	$C_{30}H_{33}ClN_4O_4$	549.00	38	111	0.58/ 0.46	10.20 / 10.12
$II_{i'}$	$CH(CH_3)_2$	3-Cl-C_6H_4	C_2H_5	$C_{29}H_{30}Cl_2N_4O_3$	553.00	42	122	0.49/ 0.54	10.11 / 10.05
$II_{j'}$	$CH(CH_3)_2$	4-Cl-C_6H_4	C_2H_5	$C_{29}H_{30}Cl_2N_4O_3$	553.00	46	134	0.51/ 0.49	10.11 / 10.05
$II_{k'}$	$CH(CH_3)_2$	2-F-C_6H_4	C_2H_5	$C_{29}H_{30}ClFN_4O_3$	537.00	48	131	0.48/ 0.51	10.42 / 10.36
$II_{l'}$	$CH(CH_3)_2$	4-F-C_6H_4	C_2H_5	$C_{29}H_{30}ClFN_4O_3$	537.40	45	109	0.50/ 0.53	10.42 / 10.36
$II_{m'}$	$CH(CH_3)_2$	3-O_{2N}-C_6H_4	C_2H_5	$C_{29}H_{30}ClN_5O_5$	564.00	40	108	0.47/ 0.49	12.41 / 12.35
$II_{n'}$	$CH(CH_3)_2$	4-O_{2N}-C_6H_4	C_2H_5	$C_{29}H_{30}ClN_5O_5$	564.00	40	105	0.61/ 0.52	12.41 / 12.35

TLC solvent system R_{f_1}: Ethyl acetate : Hexane (9.0 :1.0)

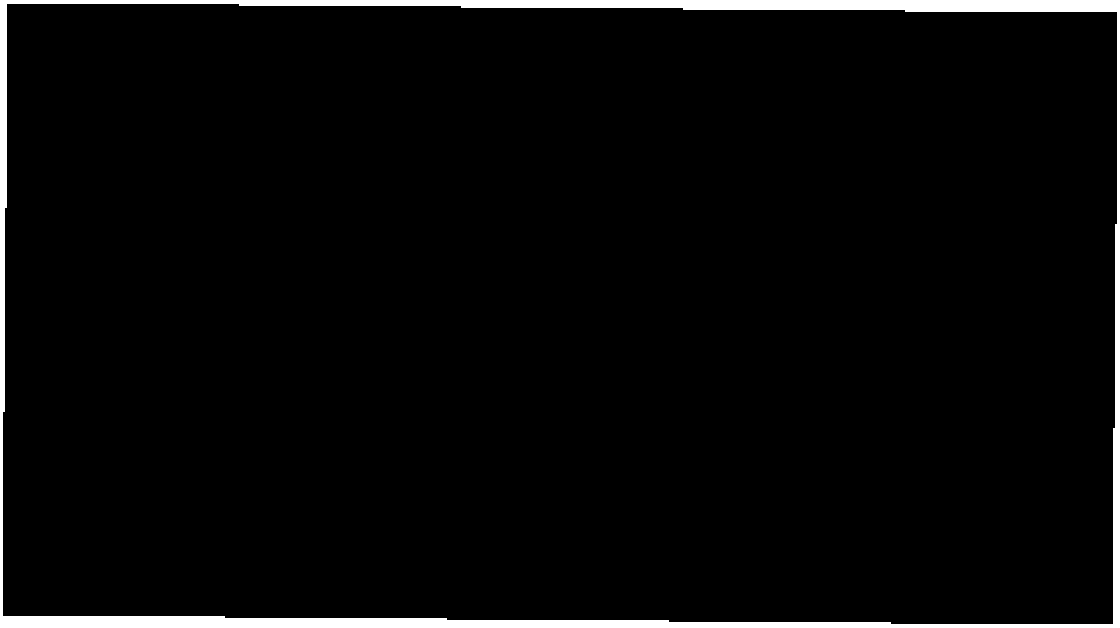
TLC solvent system R_{f_2}: Methanol : Toluene (1.5 : 8.5)

IR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3-CARBMETHOXY-5-(p-TOLYLCARBA-MOYL)-1,4-DIHYDROPYRIDINE (II_b):



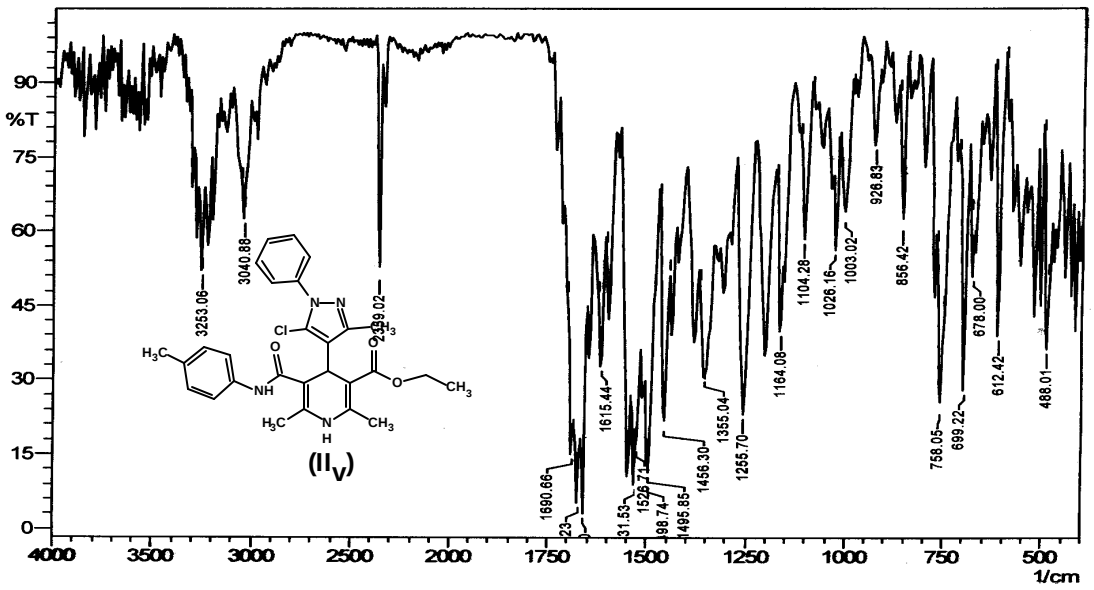
Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2952.1	2975 - 2850	92
	C-H (sym. str., m)	2892.1	2900 - 2800	92
	C-H (asym. def., m)	1446.6	1470 - 1435	92
	C-H (sym. def., m)	1364.7	1385 - 1300	92
Aromatic and ring skeletal vibration	C-H (str., v)	3067.8	3080 - 3010	90
	C=C & C-C (str., v)	1579.7	1600 - 1450	90
	C-H (i.p. def., m)	1105.2	1150 - 1050	90
	C-H (o.o.p. def., m)	803.4	825 - 800	90
	C-N (str., v)	1253.7	1340 - 1250	90
Pyridine Moiety	N-H (str., m)	3343.5	3400 - 3000	90
	N-H (def., s,m)	1592.3	1650 - 1550	90
Ketone Ester	C=O (str., s)	1708.9	1740 - 1650	90
Amide	C=O(str.,s)	1669.4	1700-1670	90
Halogen Subtitution	C-Cl (str., br.)	755.1	800-600	89
Para(-4-) substitution	C-H (def., v,s)	811.0	800 - 850	90

IR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-ISOPROPYL-2-METHYL-3-CARBMETHOXY-5-(p-TOLYLCARBAMOYL)-1,4-DIHYDROPYRIDINE (II_I):



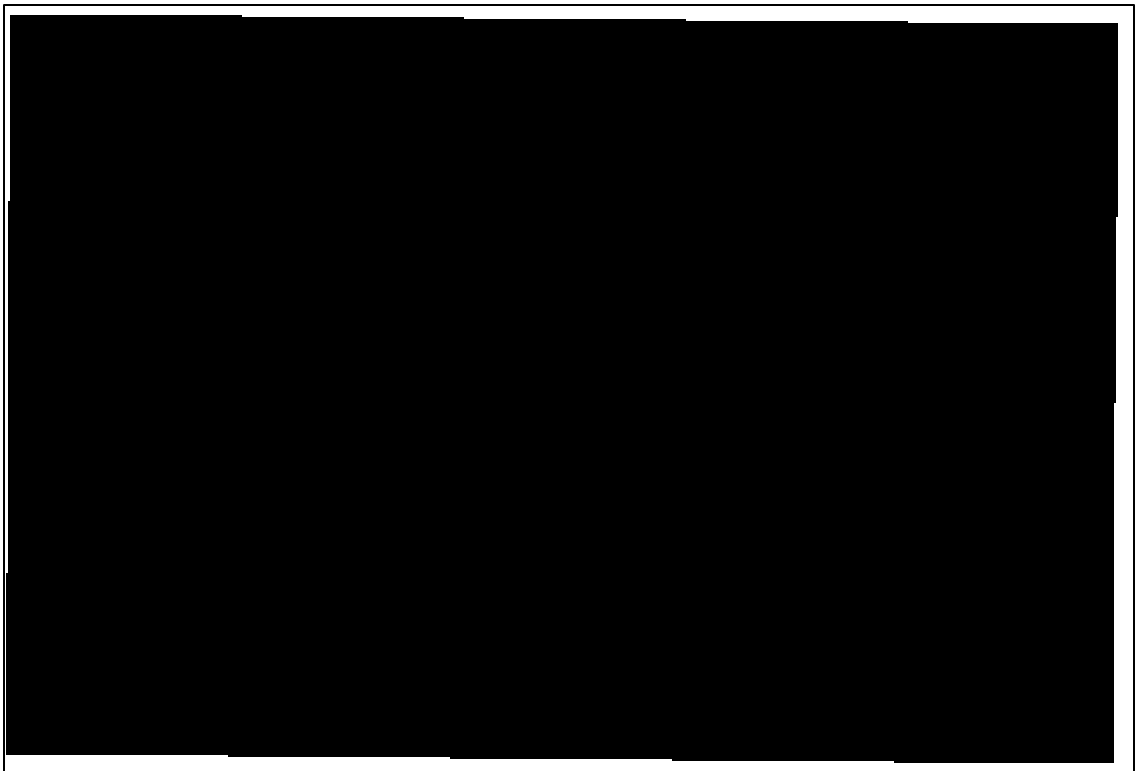
Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2981.0	2975 - 2850	92
	C-H (sym. str., m)	2850.0	2900 - 2800	92
	C-H (asym. def., m)	1478.4	1470 - 1435	92
	C-H (sym. def., m)	1380.1	1385 - 1300	92
Aromatic and ring skeletal vibration	C-H (str., v)	3037.9	3080 - 3010	90
	C=C & C-C (str., v)	1552.0	1600 - 1450	90
	C-H (i.p. def., m)	1099.4	1150 - 1050	90
	C-H (o.o.p. def., m)	812.9	825 - 800	90
	C-N (str., v)	1266.3	1340 - 1250	90
Pyridine Moiety	N-H (str., m)	3332.1	3400 - 3000	90
	N-H (def., s,m)	1596.1	1650 - 1550	90
Ketone Ester Amide	C=O (str., br.)	1728.2,	1740 - 1650	90
	C=O (str.,br.)	1674.2	1700-1670	90
Halogen Subtitution	C-Cl (str., b)	774.4-653.8	800-600	89
Para(-4-) substitution	C-H (def., v,s)	809.5	800 - 850	90

IR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3-CARBETHOXY-5-(p-TOLYLCARBA -MOYL)1,4-DIHYDROPYRIDINE (II_V):



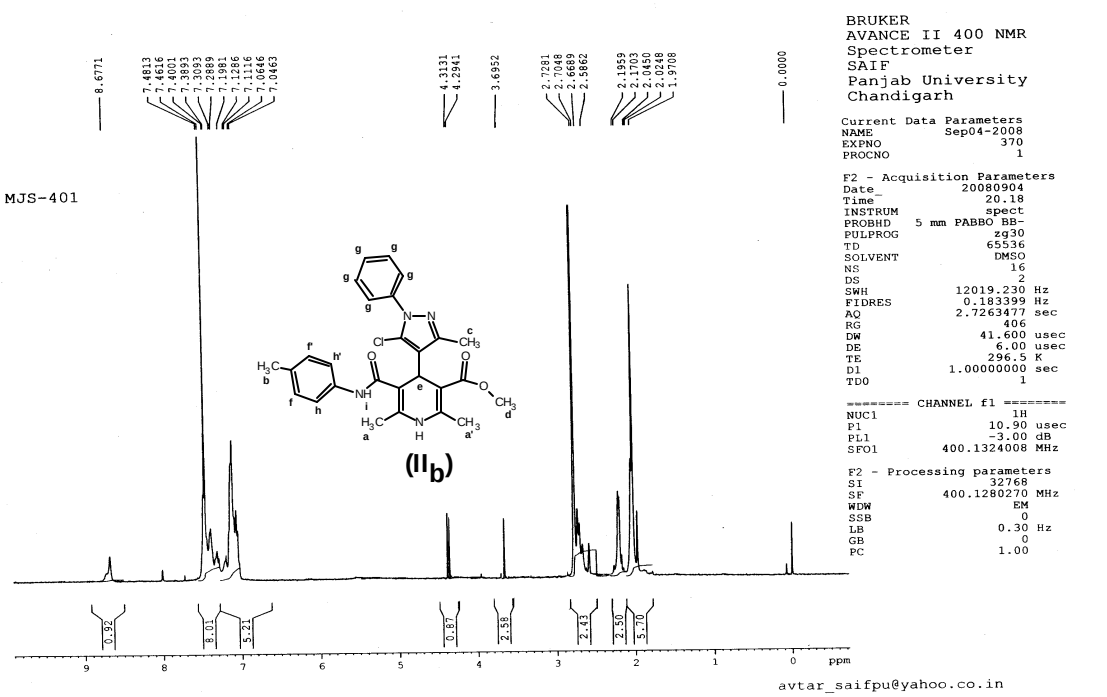
Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2973.3	2975 - 2850	92
	C-H (sym. str., m)	2870.1	2900 - 2800	92
	C-H (asym. def., m)	1456.3	1470 - 1435	92
	C-H (sym. def., m)	1355.0	1385 - 1300	92
Aromatic and ring skeletal vibration	C-H (str., v)	3040.9	3080 - 3010	90
	C=C & C-C (str., v)	1526.7	1600 - 1450	90
	C-H (i.p. def., m)	1104.1	1150 - 1050	90
	C-H (o.o.p. def., m)	758.9	825 - 800	90
	C-N (str., v)	1255.7	1340 - 1250	90
Pyridine Moiety	N-H (str., br.)	3253.0	3400 - 3000	90
	N-H (def., s,m)	1615.4	1650 - 1550	90
Ketone Ester	C=O (str., br.)	1690.0-1647.2	1740 - 1650	90
Halogen Subtitution	C-Cl (str., br.)	699.0-612.0	800-600	89
Pera substitution	C-H (def., v,s)	856.4	800 - 850	90

IR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-ISOPROPYL-2-METHYL-3-CARBETHOXY-5-(p-TOLYLCARBAMOYL)-1,4-DIHYDROPYRIDINE ($II_{f'}$):



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2945.4	2975 - 2850	92
	C-H (sym. str., m)	2841.2	2900 - 2800	92
	C-H (asym. def., m)	1450.5	1470 - 1435	92
	C-H (sym. def., m)	1344.4	1385 - 1300	92
Aromatic and ring skeletal vibration	C-H (str., v)	3061.1	3080 - 3010	90
	C=C & C-C (str., v)	1602.9	1600 - 1450	90
	C-H (i.p. def., m)	1095.6	1150 - 1050	90
	C-H (o.o.p. def., m)	833.2	825 - 800	90
	C-N (str., v)	1296.2	1340 - 1250	90
Pyridine Moiety	N-H (str., br.)	3417.9-3266.6	3400 - 3000	90
	N-H (def.,m)	1637.6	1650 - 1550	90
Ketone				
Ester	C=O (str., s)	1699.3	1740 - 1650	89
Amide	C=O (str., s)	1637.4	1700-1670	90
para(-4-) substitution	C-H (def., v,s)	833.2	850 - 800	90

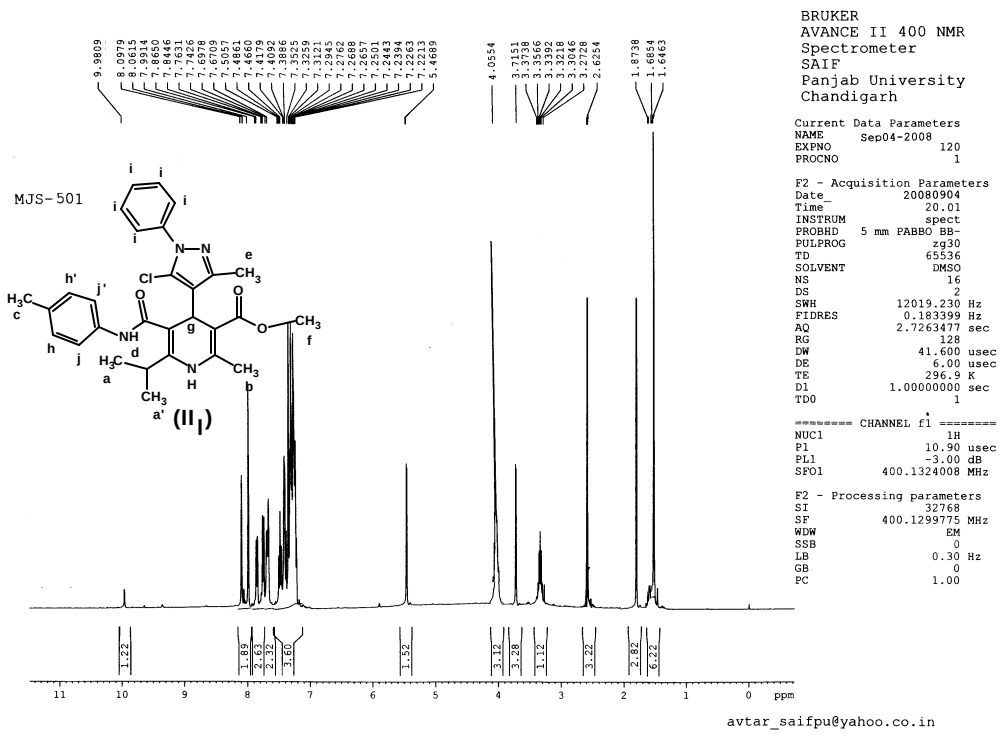
NMR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3-CARBMETHOXY-5-(p-TOLYLCARBA-MOYL)-1,4-DIHYDROPYRIDINE (II_b):



(II_b)

Serial No.	Signal Position (? ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.9708-	6H	singlet	- $(C\underline{H}_3)_{(a,a')}$
2	2.1954	3H	singlet	- $(C\underline{H}_3)_{(b)}$
3	2.2781	3H	singlet	- $(C\underline{H}_3)_{(c)}$
4	3.6952	3H	singlet	- $(C\underline{H}_3)_{(d)}$
5	4.431	1H	singlet	- $\underline{CH}_{(e)}$
6	7.0463-7.1286	2H	doublet	-Ar-$H_{(f,f)}$
7	7.1981-7.3093	5H	singlet	-Ar-$H_{(g)}$
8	7.3893-7.4813	2H	doublet	-Ar-$H_{(h,h')}$
9	8.6771	1H	singlet	-$NH_{(i)}$

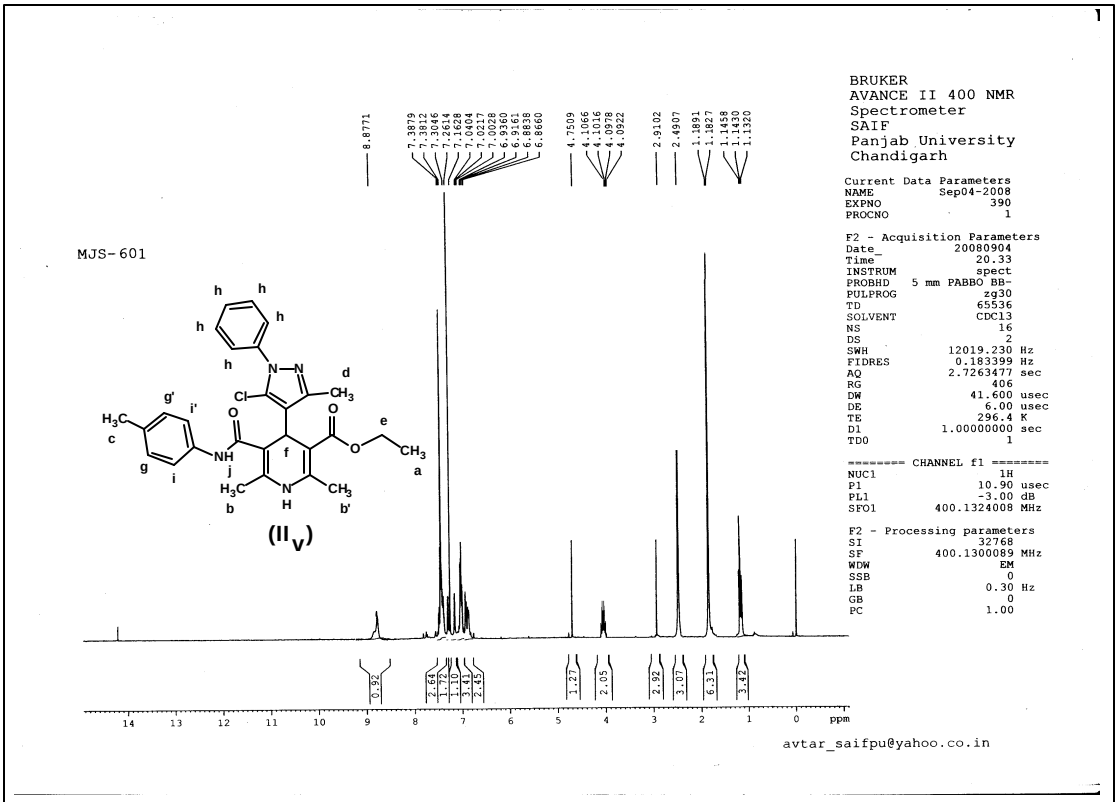
NMR SPECTRAL STUDY OF4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-ISOPROPYL-2-METHYL-3-CARBMETHOXY-5-(p-TOLYLCARBAMOYL)-1,4-DIHYDROPYRIDINE (II_I):



avtar_saifpu@yahoo.co.in

Serial No.	Signal Position (? ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.6463-1.6854	6H	doublet	$-(C\underline{H}_3)_{(a,a')}$
2	1.8738-1.0799	3H	singlet	$-(C\underline{H}_3)_{(b)}$
3	2.6254	3H	singlet	$-(C\underline{H}_3)_{(c)}$
4	3.2728-3.3738	1H	multiplate	$-(C\underline{H})_{(d)}$
5	3.7151	3H	singlet	$-\underline{CH}_3{}_{(e)}$
6	4.0554	3H	singlet	$-(C\underline{H}_3)_{(f)}$
7	5.4689	1H	singlet	$-(\underline{H})_{(g)}$
8	7.2213-7.3259	2H	doublet	$-Ar\text{-}H_{(h,h')}$
9	7.3525	5H	singlet	$-Ar\text{-}H_{(i)}$
10	7.4861-7.9914	2H	doublet	$-Ar\text{-}H_{(j,j')}$
11	9.9809	1H	singlet	$-NH_{(k)}$

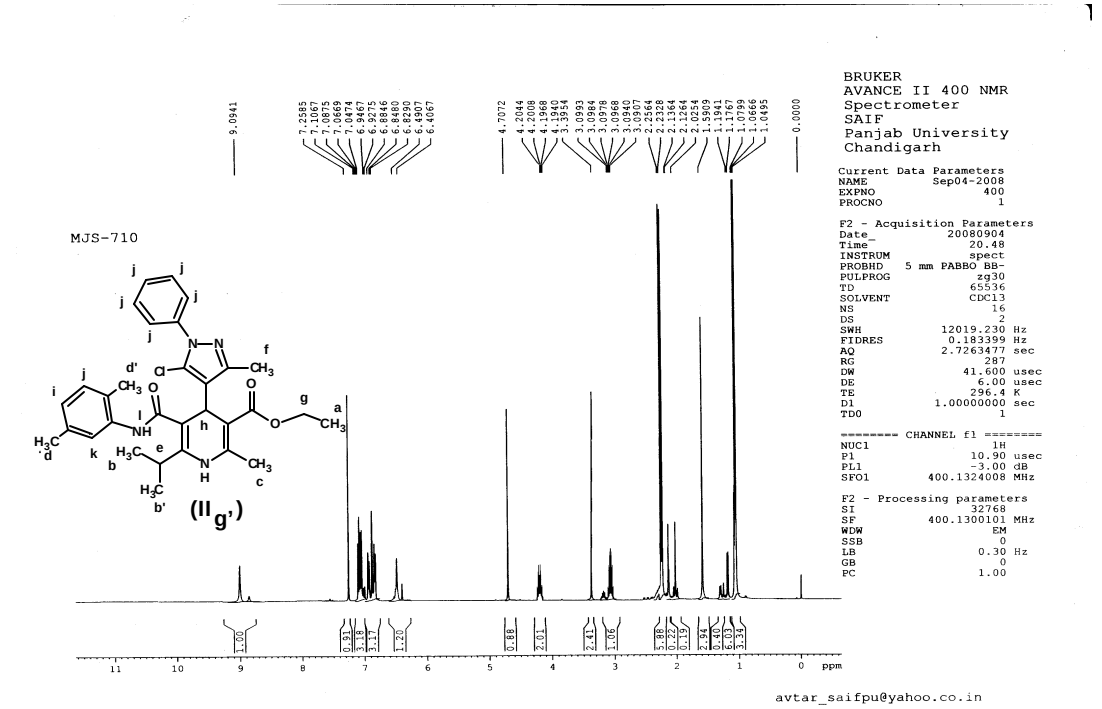
NMR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3-CARBETHOXY-5-(p-TOLYLCARBA -MOYL)-1,4-DIHYDROPYRIDINE (II_V):



(II_V)

Serial No.	Signal Position (? ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.1320-1.1458	3H	triplet	-($C\underline{H}_3$)$_{(a)}$
2	1.1827-1.1891	6H	singlet	-($C\underline{H}_3$)$_{(b,b')}$
3	2.4970	3H	singlet	-($C\underline{H}_3$)$_{(c)}$
4	2.9102	3H	singlet	-($C\underline{H}_3$)$_{(d)}$
5	4.0922-4.1060	2H	qurtaret	-($\underline{CH}_2$)$_{(e)}$
6	4.7509	1H	singlet	-$H_{(f)}$
7	6.8660-6.9360	2H	doublet	-Ar-$H_{(g,g')}$
8	7.0028-7.0404	5H	singlet	-Ar-$H_{(h)}$
9	7.1628-7.3839	2H	doublet	-Ar-$H_{(i,i')}$
10	8.8771	1H	singlet	-$NH_{(j)}$

NMR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-ISOPROPYL-2-METHYL-3-CARBETHOXY-5-(p-TOLYLCARBAMOYL)-1,4-DIHYDROPYRIDINE ($II_{g'}$):

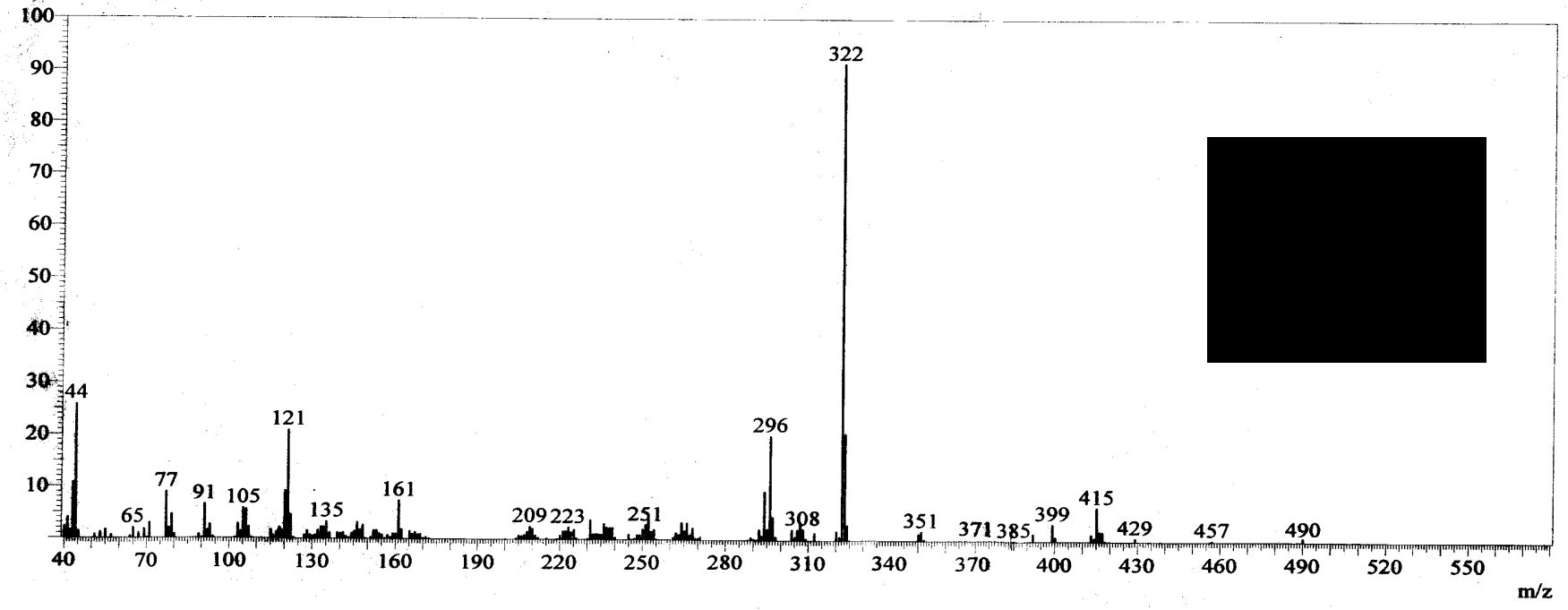


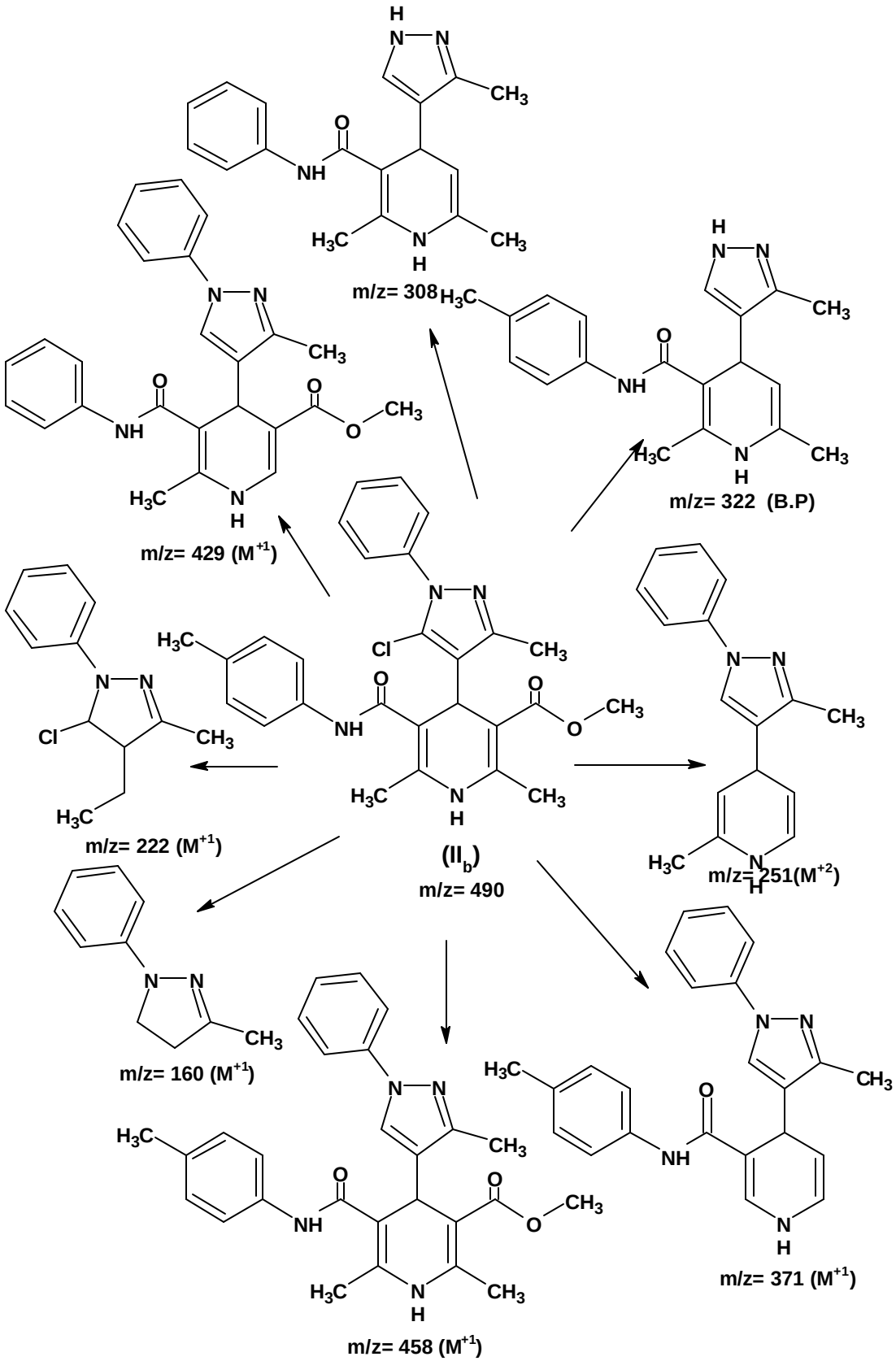
Serial No.	Signal Position (? ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.0495-1.0799	3H	triplet	$-(C\underline{H}_3)_{(a)}$
2	1.0495-1.0799	6H	doublet	$-(C\underline{H}_3)_{(b,b')}$
3	1.5909	3H	singlet	$-(C\underline{H}_3)_{(c)}$
4	2.2328-2.2564	6H	singlet	$-(C\underline{H}_3)_{(d,d')}$
5	3.0907-3.993	1H	multiplate	$-\underline{CH}_{(e)}$
6	3.3954	3H	singlet	$-(C\underline{H}_3)_{(f)}$
7	4.1940-4.2044	2H	qurtaret	$-(C\underline{H}_2)_{(g)}$
8	4.7072	1H	singlet	$-Ar-H_{(h)}$
9	6.4067-6.4907	1H	doublet	$-Ar-H_{(i)}$
10	6.8290-7.2585	6H	multiplate	$-Ar-H_{(j)}$
11	7.6735	1H	singlet	$-Ar-H_{(k)}$
12	9.0941	1H	singlet	$-NH_{(l)}$

MASS SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3-CARBMETHOXY-5-(p-TOLYLCARBAMOYL)-1,4-DIHYDROPYRIDINE (II_b):

Analyzed by : VIJAY R. RAM
Analyzed : 5/12/2008 5:05:04 PM
Sample Name : MJS- 401
Sample ID : MJS- 401
Data File : C:\GCMSsolution\Data\V H SHAH\MJS-401QGD
C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\Tune-28-04-2008.qgt

Line#:1 R.Time:10.0(Scan#:1161)
MassPeaks:224 BasePeak:322(97189)
RawMode:Averaged 8.7-11.5(1014-1349)
BG Mode:None

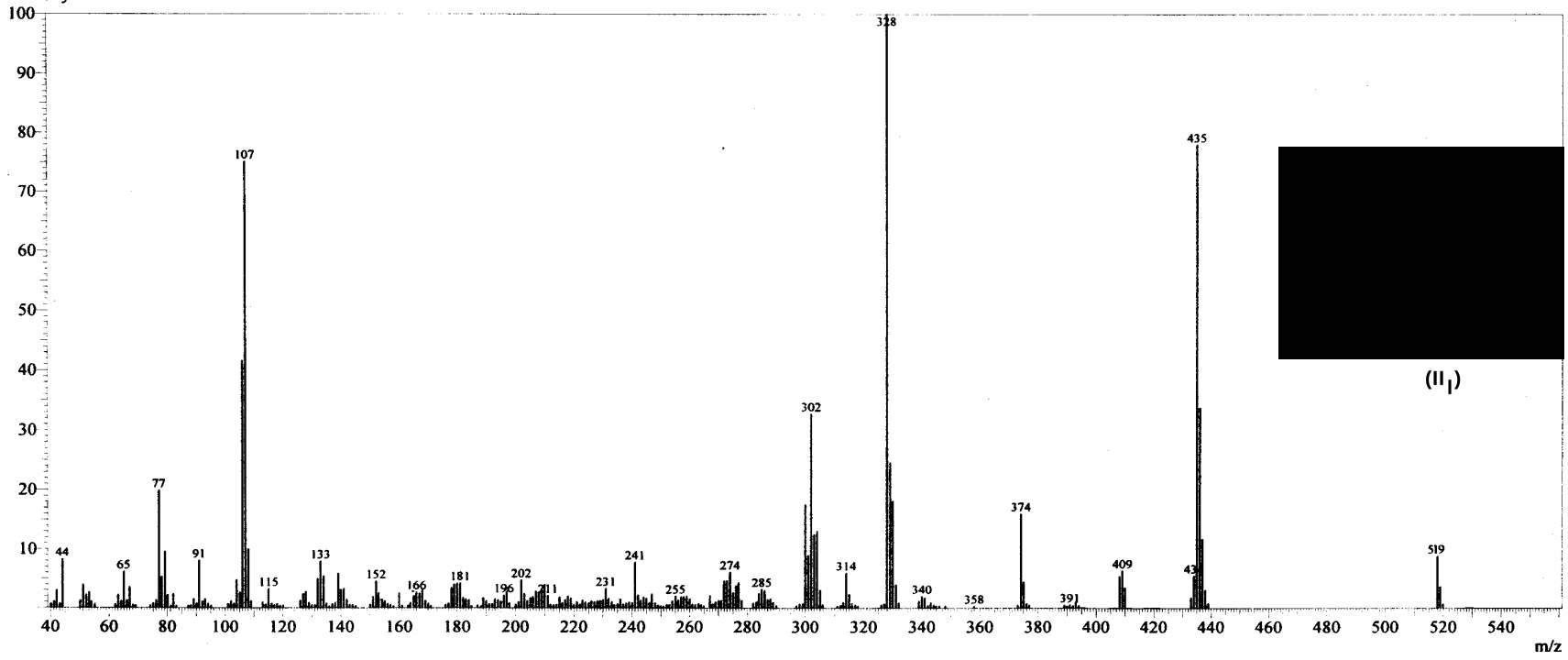



m/z= 308
m/z= 322 (B.P)
m/z= 429 (M+1)
m/z= 222 (M+1)
(IIb)
m/z= 490
m/z= 251(M+2)
m/z= 160 (M+1)
m/z= 371 (M+1)
m/z= 458 (M+1)

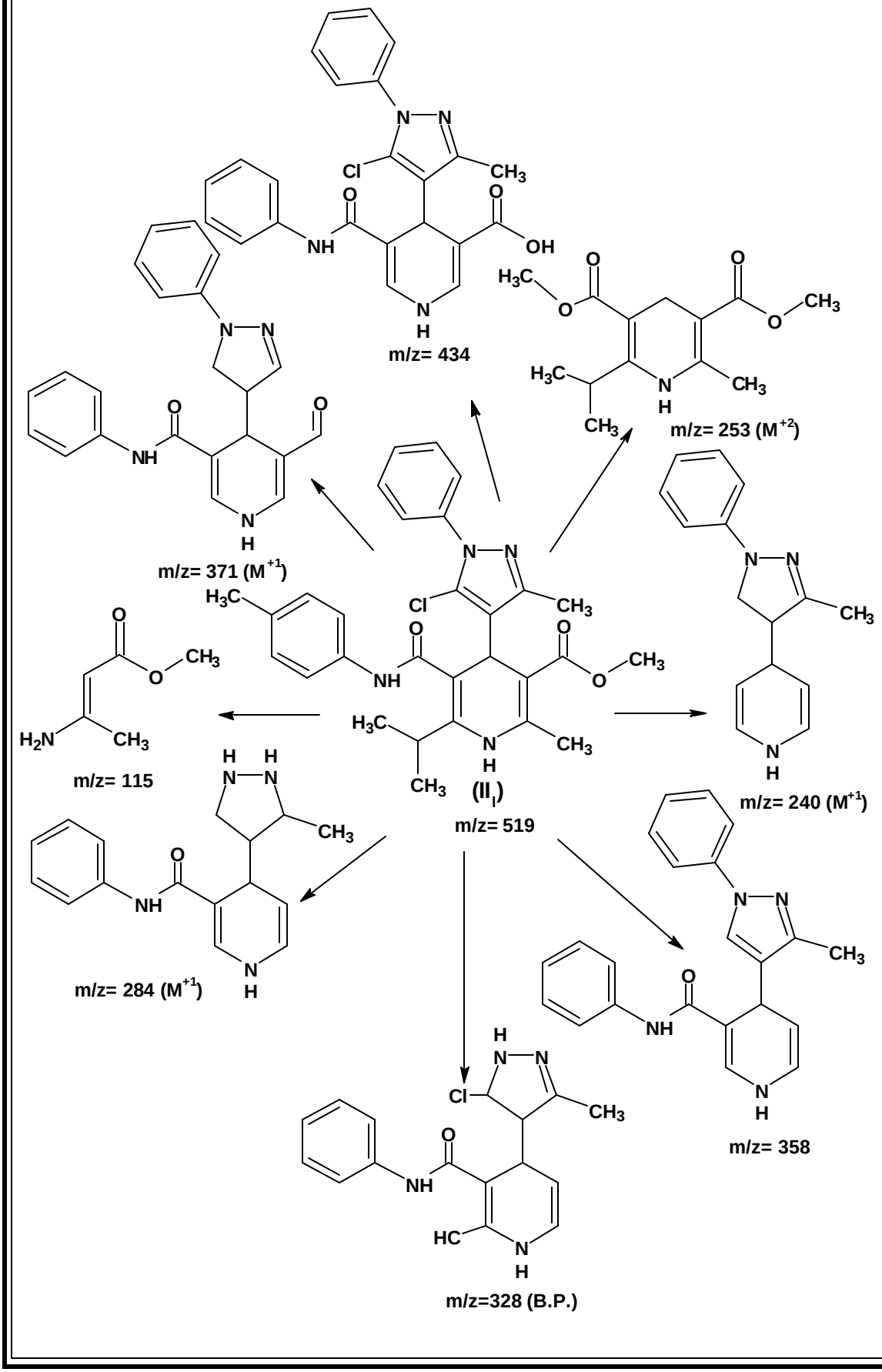
MASS SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-ISOPROPYL-2-METHYL-3-CARBMETHOXY-5-(p-TOLYLCARBAMOYL)-1,4-DIHYDROPYRIDINE (II_I):

Analyzed by : VIJAY R. RAM
Anaiyzed : 9/23/2008 3:08:04 PM
Sample Name : MJS-501
Sample ID : MJS-501
Data File : C:\GCMSsolution\Data\V.H.SHAH\MJS-501.QGD
Method File : C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\tune12.qgt

Line#:1 R.Time:10.6(Scan#:1234)
MassPeaks:282 BasePeak:328(372248)
RawMode:Single 10.6(1234)
BG Mode:None
intensity



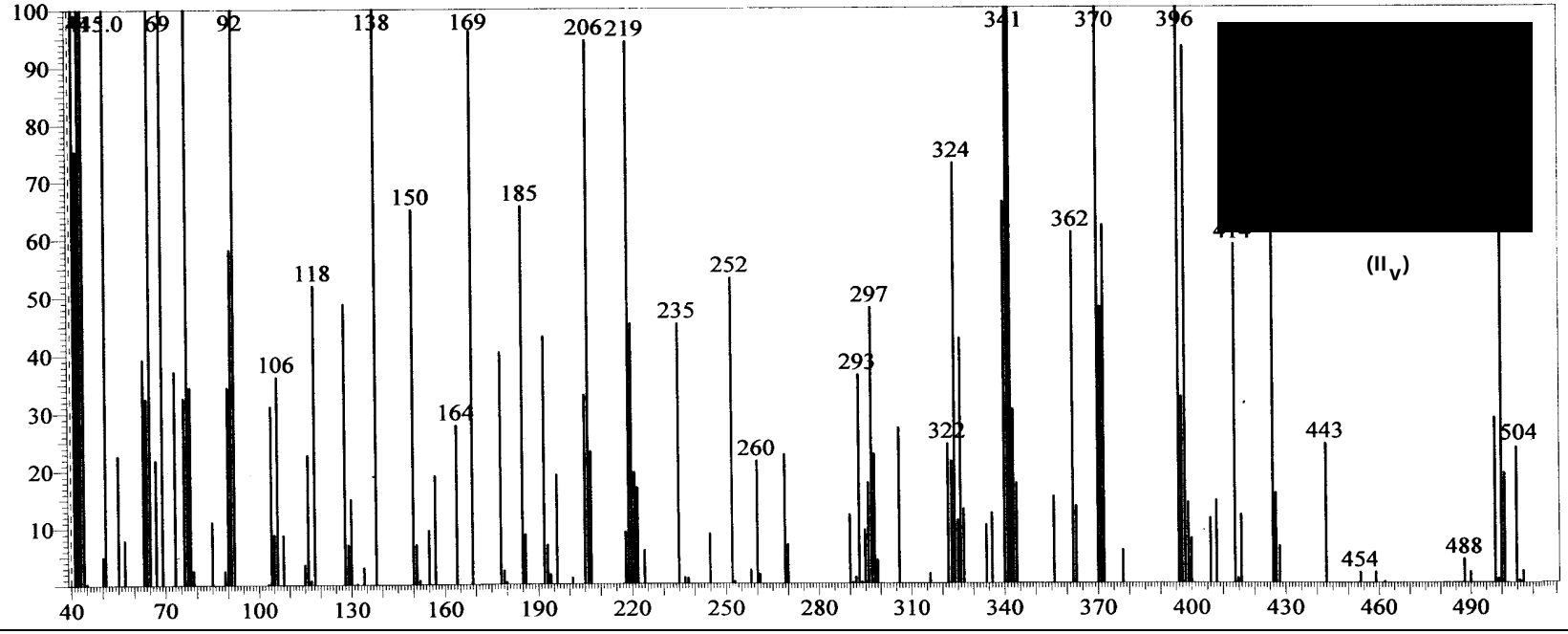
(II_I)

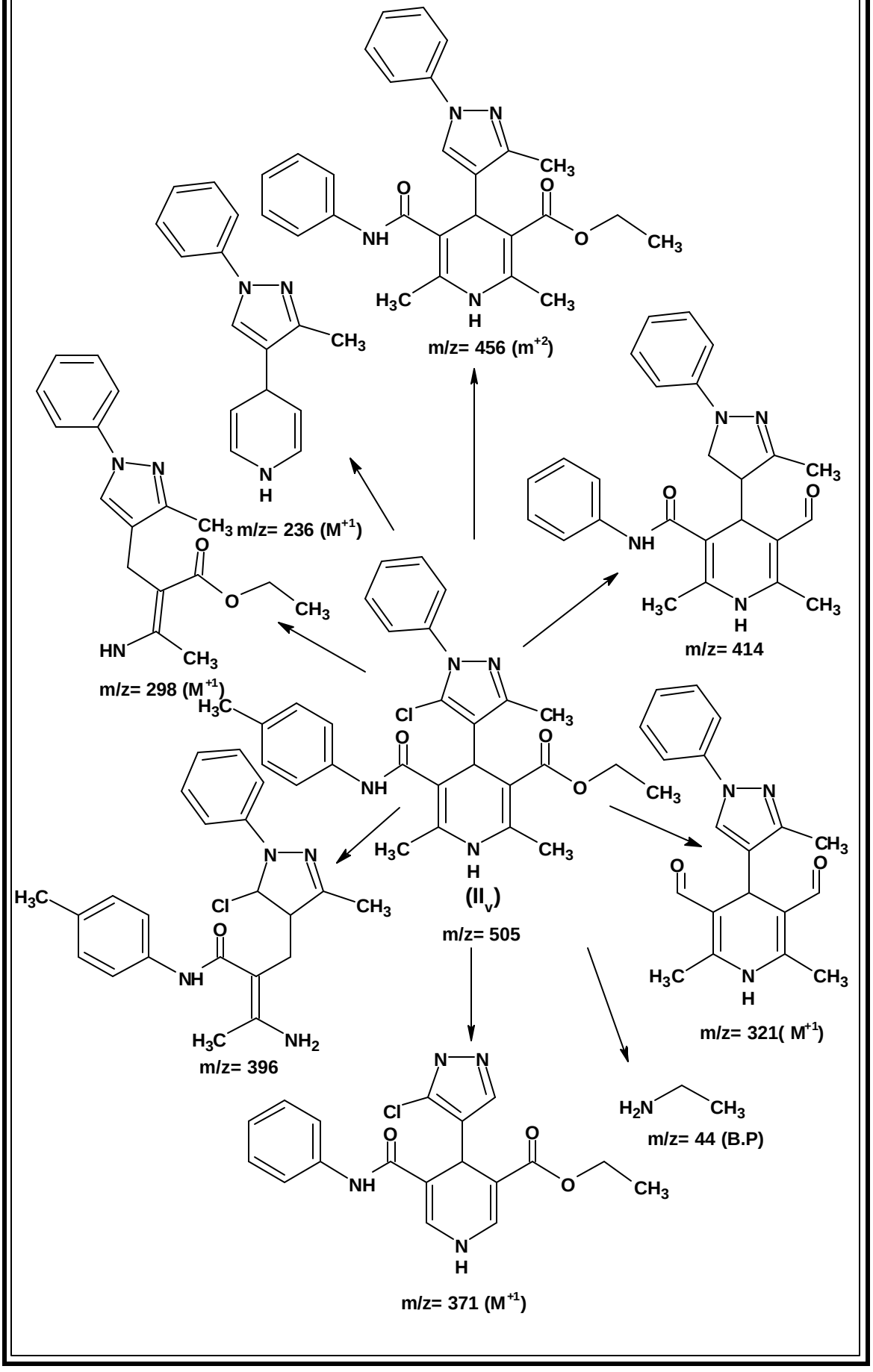

m/z= 434
m/z= 253 (M+2)
m/z= 371 (M+1)
m/z= 115
m/z= 240 (M+1)
(II$_l$)
m/z= 519
m/z= 284 (M+1)
m/z= 358
m/z=328 (B.P.)

MASS SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3-CARBETHOXY-5-(p-TOLYLCARBAMOYL)-1,4-DIHYDROPYRIDINE (II_V):

Analyzed by : VIJAY R. RAM
Analyzed : 10/23/2008 1:55:22 PM
Sample Name : MJS-601
Sample ID : MJS-601
Data File : C:\GCMSsolution\Data\Project1\MJS-601.QGD
C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\Tune-02-06-2008.qgt

Line#:1 R.Time:9.6(Scan#:1115)
MassPeaks:145 BasePeak:44(12424)
RawMode:Averaged 0.5-22.3(30-2644)
BG Mode:None




m/z= 456 (m+2)
m/z= 236 (M+1)
m/z= 414
m/z= 298 (M+1)
(IIv)
m/z= 505
m/z= 396
m/z= 321(M+1)
m/z= 44 (B.P)
m/z= 371 (M+1)

MASS SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-ISOPROPYL-2-METHYL -3-CARBETHOXY-5-(p-TOLYLCARBAMOYL)-1,4-DIHYDROPYRIDINE ($II_{f'}$):

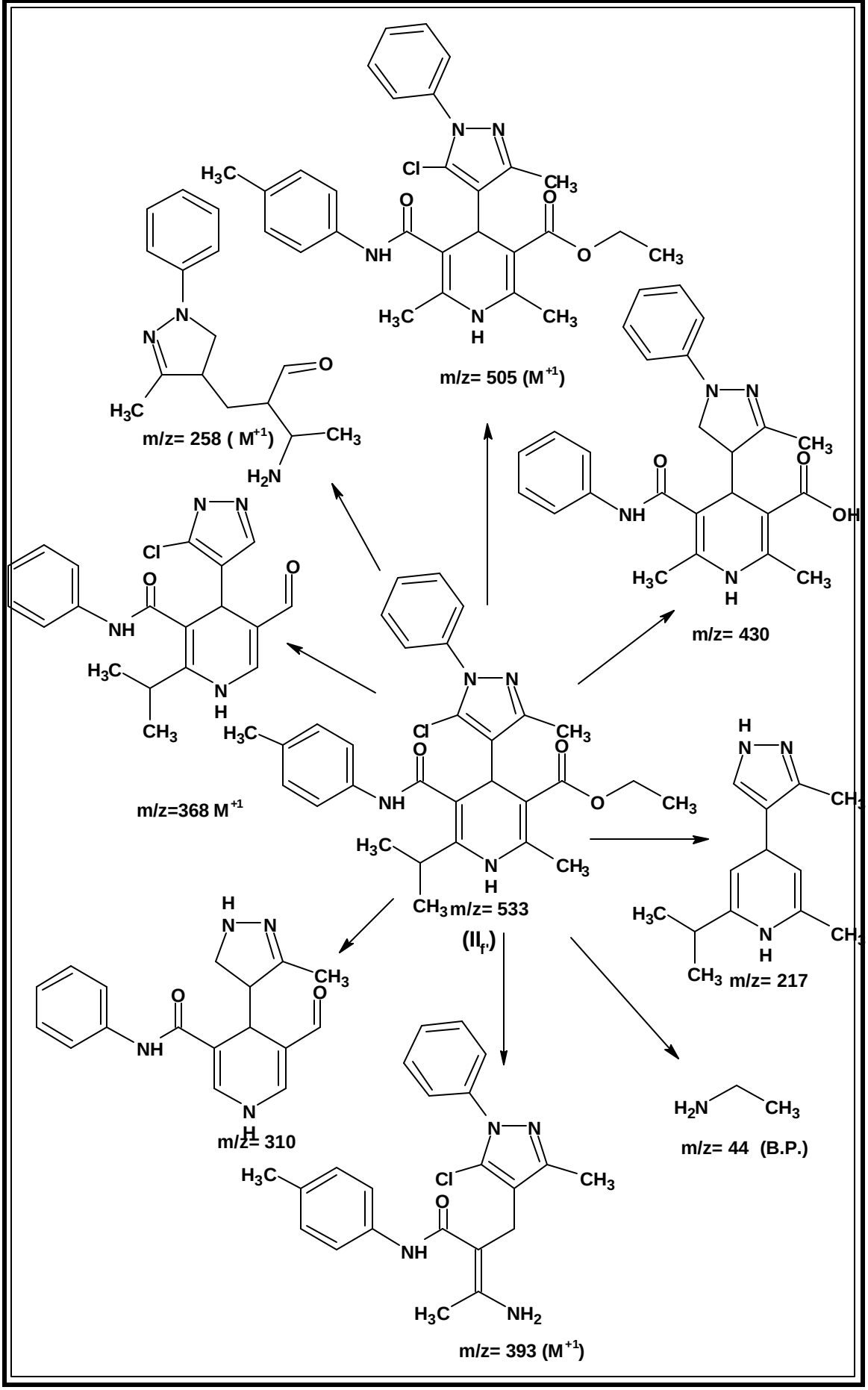

m/z= 505 (M+1)
m/z= 258 (M+1)
m/z= 430
m/z=368 M+1
m/z= 533
(IIf.)
m/z= 217
m/z= 310
m/z= 44 (B.P.)
m/z= 393 (M+1)

TABLE NO. 2_a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3-CARBMETHOXY- 5-SUBSTITUTED PHENYLCARBAMOYL-1,4-DIHYDRO PYRIDINES (II_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	R''	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442					S. aureus MTCC-96				
				5	25	50	100	250	5	25	50	100	250
II_a	CH_3	3-CH_3-C_6H_4	CH_3	-	12	14	15	17	-	11	14	15	17
II_b	CH_3	4-CH_3-C_6H_4	CH_3	-	11	14	17	19	-	12	13	14	16
II_c	CH_3	2,5-$(CH_3)_2$-C_6H_3	CH_3	-	12	13	14	16	-	12	13	15	16
II_d	CH_3	4-OCH_3-C_6H_4	CH_3	-	10	11	14	17	-	11	12	14	16
II_e	CH_3	3-Cl-C_6H_4	CH_3	-	12	14	15	17	-	11	13	15	18
II_f	CH_3	4-Cl-C_6H_4	CH_3	-	12	13	16	17	-	12	13	14	17
II_g	CH_3	2-F-C_6H_4	CH_3	-	11	13	14	15	-	12	13	14	17
II_h	CH_3	4-F-C_6H_4	CH_3	-	11	13	17	19	-	10	12	14	15
II_i	CH_3	3-NO_2-C_6H_4	CH_3	-	11	14	17	19	-	12	13	16	17
II_j	CH_3	4-NO_2-C_6H_4	CH_3	-	10	12	15	17	-	11	13	15	17

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

Standard drug	Antibacterial activity									
	II_b II_h II_i					II_a				II_d
Ampiciline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
ciprofloxacin	16	19	21	21	22	17	19	21	22	22
Norfloxacin	18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

TABLE NO. 2_b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3-CARBMETHOXY- 5-SUBSTITUTED PHENYLCARBAMOYL-1,4-DIHYDRO PYRIDINES (II_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	R''	Antibactrial activity (Zones of inhibition in mm) E. Coli MTCC-443					P. Aeruginosa MTCC-1688				
				5	25	50	100	250	5	25	50	100	250
II_a	CH_3	3-CH_3-C_6H_4	CH_3	-	12	14	15	18	-	11	12	14	17
II_b	CH_3	4-CH_3-C_6H_4	CH_3	-	15	17	19	25	-	13	14	15	18
II_c	CH_3	2,5-$(CH_3)_2$-C_6H_3	CH_3	-	15	17	19	24	-	12	15	18	20
II_d	CH_3	4-OCH_3-C_6H_4	CH_3	-	15	16	18	22	-	15	16	17	20
II_e	CH_3	3-Cl-C_6H_4	CH_3	-	12	12	14	15	-	10	11	14	16
II_f	CH_3	4-Cl-C_6H_4	CH_3	-	11	13	15	16	-	11	15	18	21
II_g	CH_3	2-F-C_6H_4	CH_3	-	17	18	18	19	-	12	13	15	17
II_h	CH_3	4-F-C_6H_4	CH_3	-	12	13	16	17	-	11	11	14	16
II_i	CH_3	3-NO_2-C_6H_4	CH_3	-	11	12	14	16	-	14	17	18	20
II_j	CH_3	4-NO_2-C_6H_4	CH_3	-	15	15	18	26	-	12	15	20	23

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

Standard drug	Antibacterial activity									
		II_b II_c II_d IIg IIj	II_b II_c II_d II_g	II_b IIc	II_b II_c II_d II_j		II_d	II_c II_d II_f II_j	II_c II_g II_i II_j	II_c II_d II_f II_i II_j
Ampiciline	14	15	16	19	20	14	15	15	18	20
Chloramphenicol	14	17	23	23	23	14	17	18	19	21
ciprofloxacin	20	23	28	28	28	20	23	24	26	27
Norfloxacin	22	25	26	29	29	18	19	21	23	23

N.B.(-): No Activity

TABLE NO. 2_C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3-CARBMETHOXY- 5-SUBSTITUTED PHENYLCARBAMOYL-1,4-DIHYDRO PYRIDINES (II_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	R''	Antifungal activity (Zones of inhibition in mm) A. niger MTCC-282					A. clavatus MTCC-1323				
				5	25	50	100	250	5	25	50	100	250
II_a	CH_3	3-CH_3-C_6H_4	CH_3	-	18	19	20	21	-	18	20	21	23
II_b	CH_3	4-CH_3-C_6H_4	CH_3	-	17	18	20	21	-	13	15	16	18
II_c	CH_3	2,5-$(CH_3)_2$-C_6H_3	CH_3	-	17	19	21	22	-	12	15	18	20
II_d	CH_3	4-OCH_3-C_6H_4	CH_3	-	20	21	23	23	-	18	19	21	23
II_e	CH_3	3-Cl-C_6H_4	CH_3	-	17	19	20	22	-	17	20	20	23
II_f	CH_3	4-Cl-C_6H_4	CH_3	-	18	19	21	23	-	18	19	20	23
II_g	CH_3	2-F-C_6H_4	CH_3	-	17	19	20	21	-	16	17	19	20
II_h	CH_3	4-F-C_6H_4	CH_3	-	15	17	18	20	-	17	19	21	22
II_i	CH_3	3-NO_2-C_6H_4	CH_3	-	18	21	22	23	-	16	17	18	21
Ii_j	CH_3	4-NO_2-C_6H_4	CH_3	-	15	18	21	22	-	13	15	19	21
Comparative activity of (II_{a-j}) with known choosen standard drugs													
Standard drug				**Antibacterial activity**									
Greseofulvin				19	23	25	25	28	18	21	22	22	24
Nystain				18	19	24	29	29	18	21	24	25	26

N.B.(-): No Activity

TABLE NO. 2 $_d$: COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-ISOPROPYL-2-METHYL-3-CARBMETHOXY- 5-SUBSTITUTED PHENYLCARBAMOYL-1,4-DIHYDRO PYRIDINES (II_{k-t}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	R''	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442 5	25	50	100	250	S. aureus MTCC-96 5	25	50	100	250
II_k	$CH(CH_3)_2$	3-CH_3-C_6H_4	CH_3	-	12	14	17	18	-	12	13	15	16
II_l	$CH(CH_3)_2$	4-CH_3-C_6H_4	CH_3	-	12	14	15	17	-	13	14	15	16
II_m	$CH(CH_3)_2$	2,5-$(CH_3)_2$-C_6H_3	CH_3	-	11	13	14	18	-	12	15	16	17
II_n	$CH(CH_3)_2$	4-OCH_3-C_6H_4	CH_3	-	12	14	16	18	-	12	15	16	17
II_o	$CH(CH_3)_2$	3-Cl-C_6H_4	CH_3	-	12	13	14	16	-	11	13	15	16
II_p	$CH(CH_3)_2$	4-Cl-C_6H_4	CH_3	-	12	15	18	19	-	11	13	16	18
II_q	$CH(CH_3)_2$	2-F-C_6H_4	CH_3	-	12	14	16	17	-	11	14	15	17
II_r	$CH(CH_3)_2$	4-F-C_6H_4	CH_3	-	11	14	16	19	-	11	12	15	17
II_s	$CH(CH_3)_2$	3-NO_2-C_6H_4	CH_3	-	11	13	15	18	-	12	13	15	17
Ii_t	$CH(CH_3)_2$	4-NO_2-C_6H_4	CH_3	-	12	13	15	17	-	11	12	14	15

Comparative activity of (II_{k-t}) with known choosen standard drugs

Standard drug	Antibacterial activity									
				II_p	II_p II_r			II_l II_m II_n II_q	II_m II_n II_p	II_p
Amoxiciline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
ciprofloxacin	16	19	21	21	22	17	19	21	22	22
Norfloxacin	18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

TABLE NO. 2 $_e$: COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-ISOPROPYL-2-METHYL-3-CARBMETHOXY- 5-SUBSTITUTED PHENYLCARBAMOYL-1,4-DIHYDRO PYRIDINES (II_{k-t}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	R''	Antibactrial activity (Zones of inhibition in mm) E. Coli MTCC-443 5	25	50	100	250	P. Aeruginosa MTCC-1688 5	25	50	100	250
II_k	$CH(CH_3)_2$	3-CH_3-C_6H_4	CH_3	-	11	13	17	17	-	10	12	15	18
II_l	$CH(CH_3)_2$	4-CH_3-C_6H_4	CH_3	-	11	13	15	15	-	10	13	14	16
II_m	$CH(CH_3)_2$	2,5-$(CH_3)_2$-C_6H_3	CH_3	-	11	14	16	17	-	11	14	17	19
II_n	$CH(CH_3)_2$	4-OCH_3-C_6H_4	CH_3	-	15	17	16	17	-	10	14	15	18
II_o	$CH(CH_3)_2$	3-Cl-C_6H_4	CH_3	-	11	12	15	16	-	12	14	15	17
II_p	$CH(CH_3)_2$	4-Cl-C_6H_4	CH_3	-	09	11	13	14	-	09	11	13	15
II_q	$CH(CH_3)_2$	2-F-C_6H_4	CH_3	-	13	14	15	16	-	10	14	17	21
II_r	$CH(CH_3)_2$	4-F-C_6H_4	CH_3	-	12	14	15	16	-	11	12	15	18
II_s	$CH(CH_3)_2$	3-NO_2-C_6H_4	CH_3	-	15	17	18	18	-	11	13	15	16
II_t	$CH(CH_3)_2$	4-NO_2-C_6H_4	CH_3	-	12	15	19	21	-	08	11	14	15

Comparative activity of (II_{k-t}) with known choosen standard drugs

Standard drug	Antibacterial activity									
		II_k II_s	II_n	II_t	II_t					II_q
Ampliciine	14	15	16	19	20	14	15	15	18	20
Chloramphenicol	14	17	23	23	23	14	17	18	19	21
ciprofloxacin	20	23	28	28	28	20	23	24	26	27
Norfloxacin	22	25	26	27	29	18	19	21	23	23

N.B.(-): No Activity

TABLE NO. 2_f : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-ISOPROPYL-2-METHYL-3-CARBMETHOXY- 5-SUBSTITUTED PHENYLCARBAMOYL-1,4-DIHYDRO PYRIDINES(II_{k-t}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	R''	Antifungal activity (Zones of inhibition in mm)									
				A. niger MTCC-282					A. clavatus MTCC-1323				
				5	25	50	100	250	5	25	50	100	250
II_k	$CH(CH_3)_2$	3-CH_3-C_6H_4	CH_3	-	16	17	18	22	-	16	18	20	22
II_l	$CH(CH_3)_2$	4-CH_3-C_6H_4	CH_3	-	15	17	21	22	-	16	17	20	21
II_m	$CH(CH_3)_2$	2,5-$(CH_3)_2$-C_6H_3	CH_3	-	17	20	22	22	-	18	19	21	21
II_n	$CH(CH_3)_2$	4-OCH_3-C_6H_4	CH_3	-	15	18	20	21	-	17	18	18	22
II_o	$CH(CH_3)_2$	3-Cl-C_6H_4	CH_3	-	17	20	21	22	-	13	15	17	20
II_p	$CH(CH_3)_2$	4-Cl-C_6H_4	CH_3	-	19	22	22	23	-	13	16	18	19
II_q	$CH(CH_3)_2$	2-F-C_6H_4	CH_3	-	17	18	20	22	-	17	18	20	21
II_r	$CH(CH_3)_2$	4-F-C_6H_4	CH_3	-	17	21	22	23	-	17	19	20	21
II_s	$CH(CH_3)_2$	3-NO_2-C_6H_4	CH_3	-	15	18	18	19	-	16	18	20	21
Ii_t	$CH(CH_3)_2$	4-NO_2-C_6H_4	CH_3	-	17	18	20	21	-	18	20	21	22
Comparative activity of (II_{k-t}) with known choosen standard drugs													
Standard drug				**Antibacterial activity**									
				II_p									
Greseofulvin				19	23	25	25	28	18	21	22	22	24
Nystatin				18	19	24	29	29	18	21	24	25	26

N.B.(-): No actviity

TABLE NO. 2 g : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL 4'-YL)-2,6-DIMETHYL-3-CARBETHOXY- 5-SUBSTITUTED PHENYLCARBAMOYL-1,4-DIHYDRO PYRIDINES ($II_{u-d'}$). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	R''	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442					S. aureus MTCC-96				
				5	25	50	100	250	5	25	50	100	250
II_u	CH_3	3-CH_3-C_6H_4	C_2H_5	-	12	13	16	18	-	12	15	17	18
II_v	CH_3	4-CH_3-C_6H_4	C_2H_5	-	11	14	15	16	-	11	13	15	16
II_w	CH_3	2,5-$(CH_3)_2$-C_6H_3	C_2H_5	-	12	13	16	18	-	11	15	16	17
II_x	CH_3	4-OCH_3-C_6H_4	C_2H_5	-	11	12	15	17	-	11	13	14	17
II_y	CH_3	3-Cl-C_6H_4	C_2H_5	-	12	13	14	18	-	11	12	15	16
II_z	CH_3	4-Cl-C_6H_4	C_2H_5	-	12	15	18	19	-	11	12	16	17
$II_{a'}$	CH_3	2-F-C_6H_4	C_2H_5	-	12	13	15	17	-	12	14	15	17
$II_{b'}$	CH_3	4-F-C_6H_4	C_2H_5	-	12	14	16	17	-	12	14	15	17
$II_{c'}$	CH_3	3-NO_2-C_6H_4	C_2H_5	-	13	14	16	17	-	12	14	15	17
$II_{d'}$	CH_3	4-NO_2-C_6H_4	C_2H_5	-	12	13	15	16	-	11	12	15	16

Comparative activity of ($II_{u-d'}$) with known choosen standard drugs

Standard drug	Antibacterial activity									
				II_z				II_u II_w $II_{a'}$ $II_{b'}$ $II_{c'}$	II_u II_w II_z	II_u
Amoxiciline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
ciprofloxacin	16	19	21	21	22	17	19	21	22	22
Norfloxacin	18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

TABLE NO. 2_h : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3-CARBETHOXY- 5-SUBSTITUTED PHENYLCARBAMOYL-1,4-DIHYDRO PYRIDINES ($II_{u-d'}$). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	R''	Antibactrial activity (Zones of inhibition in mm) E. Coli MTCC-443					P. Aeruginosa MTCC-1688				
				5	25	50	100	250	5	25	50	100	250
II_u	CH_3	3-CH_3-C_6H_4	C_2H_5	-	15	15	18	19	-	10	14	17	20
II_v	CH_3	4-CH_3-C_6H_4	C_2H_5	-	14	16	17	19	-	10	13	15	17
II_w	CH_3	2,5-$(CH_3)_2$-C_6H_3	C_2H_5	-	15	17	19	22	-	09	13	15	19
II_x	CH_3	4-OCH_3-C_6H_4	C_2H_5	-	12	15	18	20	-	12	15	17	21
II_y	CH_3	3-Cl-C_6H_4	C_2H_5	-	12	14	17	19	-	13	13	15	17
II_z	CH_3	4-Cl-C_6H_4	C_2H_5	-	10	12	15	17	-	14	15	20	23
$II_{a'}$	CH_3	2-F-C_6H_4	C_2H_5	-	13	13	15	16	-	10	12	13	15
$II_{b'}$	CH_3	4-F-C_6H_4	C_2H_5	-	11	11	14	15	-	11	12	13	15
$II_{c'}$	CH_3	3-NO_2-C_6H_4	C_2H_5	-	13	15	17	21	-	12	14	18	21
$II_{d'}$	CH_3	4-NO_2-C_6H_4	C_2H_5	-	13	18	20	22	-	15	17	19	22

Comparative activity of ($II_{u-d'}$) with known choosen standard drugs

Standard drug	Antibacterial activity									
		II_u II_w	II_v II_w $II_{d'}$	II_w $II_{d'}$	II_w II_x $II_{c'}$ $II_{d'}$		$II_{d'}$	II_x II_z $II_{d'}$	II_z $II_{c'}$ $II_{d'}$	II_u II_x II_z $II_{c'}$ $II_{d'}$
Amoxiciline	14	15	16	19	20	14	15	15	18	20
Chloramphenicol	14	17	23	23	23	14	17	18	19	21
ciprofloxacin	20	23	28	28	28	20	23	24	26	27
Norfloxacin	22	25	26	27	29	18	19	21	23	23

N.B.(-): No Activity

TABLE NO. 2_i : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3-CARBETHOXY- 5-SUBSTITUTED PHENYLCARBAMOYL-1,4-DIHYDRO PYRIDINES ($II_{u-d'}$). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	R''	Antifungal activity (Zones of inhibition in mm) A. niger MTCC-282					A. clavatus MTCC-1323				
				5	25	50	100	250	5	25	50	100	250
II_u	CH_3	3-CH_3-C_6H_4	C_2H_5	-	18	19	20	21	-	18	20	21	23
II_v	CH_3	4-CH_3-C_6H_4	C_2H_5	-	18	20	22	23	-	18	21	21	24
II_w	CH_3	2,5-$(CH_3)_2$-C_6H_3	C_2H_5	-	15	18	21	22	-	13	16	19	21
II_x	CH_3	4-OCH_3-C_6H_4	C_2H_5	-	16	17	18	22	-	16	18	20	22
II_y	CH_3	3-Cl-C_6H_4	C_2H_5	-	15	17	21	22	-	16	17	20	21
II_z	CH_3	4-Cl-C_6H_4	C_2H_5	-	17	20	22	23	-	18	19	21	22
$II_{a'}$	CH_3	2-F-C_6H_4	C_2H_5	-	18	20	21	24	-	15	18	17	20
$II_{b'}$	CH_3	4-F-C_6H_4	C_2H_5	-	18	21	23	24	-	15	16	17	23
$II_{c'}$	CH_3	3-NO_2-C_6H_4	C_2H_5	-	20	22	23	25	-	19	23	23	25
$II_{d'}$	CH_3	4-NO_2-C_6H_4	C_2H_5	-	16	19	21	22	-	15	18	20	22

Comparative activity of ($II_{u-d'}$) with known choosen standard drugs

Standard drug	Antibacterial activity									
		$II_{c'}$					$II_{c'}$	$II_{c'}$	II_v $II_{c'}$	
Greseofulvin	19	23	25	25	28	18	21	22	22	24
Nystatin	18	19	24	29	29	18	21	24	25	26

N.B.(-): No Activity

TABLE NO. 2_j : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3-CARBETHOXY- 5-SUBSTITUTED PHENYLCARBAMOYL-1,4-DIHYDRO PYRIDINES ($II_{e'-n'}$). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	R''	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442					S. aureus MTCC-96				
				5	25	50	100	250	5	25	50	100	250
$II_{e'}$	$CH(CH_3)_2$	3-CH_3-C_6H_4	C_2H_5	-	11	13	14	16	-	11	12	13	16
$II_{f'}$	$CH(CH_3)_2$	4-CH_3-C_6H_4	C_2H_5	-	12	14	15	16	-	12	13	16	18
$II_{g'}$	$CH(CH_3)_2$	2,5-$(CH_3)_2$-C_6H_3	C_2H_5	-	11	14	15	19	-	11	13	14	15
$II_{h'}$	$CH(CH_3)_2$	4-OCH_3-C_6H_4	C_2H_5	-	11	13	15	18	-	12	14	15	16
$II_{i'}$	$CH(CH_3)_2$	3-Cl-C_6H_4	C_2H_5	-	12	14	17	18	-	11	12	15	17
$II_{j'}$	$CH(CH_3)_2$	4-Cl-C_6H_4	C_2H_5	-	11	14	16	18	-	12	15	17	19
$II_{k'}$	$CH(CH_3)_2$	2-F-C_6H_4	C_2H_5	-	12	13	17	19	-	11	13	15	16
$II_{l'}$	$CH(CH_3)_2$	4-F-C_6H_4	C_2H_5	-	12	13	15	17	-	11	14	15	16
$II_{m'}$	$CH(CH_3)_2$	3-NO_2-C_6H_4	C_2H_5	-	11	14	16	17	-	12	13	14	15
$II_{n'}$	$CH(CH_3)_2$	4-NO_2-C_6H_4	C_2H_5	-	12	13	15	16	-	12	13	15	16

Comparative activity of ($II_{e'-n'}$) with known choosen standard drugs

Standard drug	Antibacterial activity									
					$II_{k'}$			$II_{h'}$, $II_{j'}$	$II_{f'}$, $II_{j'}$	$II_{f'}$, $II_{j'}$
Amoxiciline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
ciprofloxacin	16	19	21	21	22	17	19	21	22	22
Norfloxacin	18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

TABLE NO. 2_k : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3-CARBETHOXY- 5-SUBSTITUTED PHENYLCARBAMOYL-1,4-DIHYDRO PYRIDINES($II_{e'-n'}$). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	R''	Antibactrial activity (Zones of inhibition in mm) E. Coli MTCC-443					P. Aeruginosa MTCC-1688				
				5	25	50	100	250	5	25	50	100	250
$II_{e'}$	$CH(CH_3)_2$	3-CH_3-C_6H_4	C_2H_5	-	13	13	15	17	-	11	12	15	16
$II_{f'}$	$CH(CH_3)_2$	4-CH_3-C_6H_4	C_2H_5	-	13	17	19	21	-	12	14	16	18
$II_{g'}$	$CH(CH_3)_2$	2,5-$(CH_3)_2$-C_6H_3	C_2H_5	-	11	14	16	18	-	12	14	15	17
$II_{h'}$	$CH(CH_3)_2$	4-OCH_3-C_6H_4	C_2H_5	-	12	16	18	19	-	11	14	17	19
$II_{i'}$	$CH(CH_3)_2$	3-Cl-C_6H_4	C_2H_5	-	12	14	16	17	-	11	14	15	17
$II_{j'}$	$CH(CH_3)_2$	4-Cl-C_6H_4	C_2H_5	-	10	13	15	17	-	11	13	15	16
$II_{k'}$	$CH(CH_3)_2$	2-F-C_6H_4	C_2H_5	-	11	13	15	16	-	11	12	14	16
$II_{l'}$	$CH(CH_3)_2$	4-F-C_6H_4	C_2H_5	-	13	15	16	19	-	12	14	15	16
$II_{m'}$	$CH(CH_3)_2$	3-NO_2-C_6H_4	C_2H_5	-	12	14	17	20	-	12	14	15	17
$II_{n'}$	$CH(CH_3)_2$	4-NO_2-C_6H_4	C_2H_5	-	10	14	17	19	-	13	14	15	18

Comparative activity of ($II_{e'-n'}$) with known choosen standard drugs

Standard drug	Antibacterial activity									
			$II_{f'}$, $II_{h'}$		$II_{f'}$, $II_{m'}$					
Amoxiciline	14	15	16	29	20	14	15	15	18	20
Chloramphenicol	14	17	23	23	23	14	17	18	19	21
ciprofloxacin	20	23	28	28	28	20	23	24	26	27
Norfloxacin	22	25	26	27	29	18	19	21	23	23

N.B.(-): No Activity

TABLE NO. 2_I : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METHYL-1'-N-PHENYL-PYRAZOL-4'-YL)-2,6-DIMETHYL-3-CARBETHOXY- 5-SUBSTITUTED PHENYLCARBAMOYL-1,4-DIHYDRO PYRIDINES ($II_{e'-n'}$). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	R''	Antifungal activity (Zones of inhibition in mm) A. niger MTCC-282					A. clavatus MTCC-1323				
				5	25	50	100	250	5	25	50	100	250
$II_{e'}$	$CH(CH_3)_2$	3-CH_3-C_6H_4	C_2H_5	-	18	20	22	23	-	23	23	23	24
$II_{f'}$	$CH(CH_3)_2$	4-CH_3-C_6H_4	C_2H_5	-	19	23	24	25	-	17	19	20	21
$II_{g'}$	$CH(CH_3)_2$	2,5-$(CH_3)_2$-C_6H_3	C_2H_5	-	19	21	23	24	-	20	23	22	25
$II_{h'}$	$CH(CH_3)_2$	4-OCH_3-C_6H_4	C_2H_5	-	18	20	21	23	-	18	18	22	23
$II_{i'}$	$CH(CH_3)_2$	3-Cl-C_6H_4	C_2H_5	-	20	21	22	24	-	15	17	20	21
$II_{j'}$	$CH(CH_3)_2$	4-Cl-C_6H_4	C_2H_5	-	22	22	22	27	-	16	18	19	29
$II_{k'}$	$CH(CH_3)_2$	2-F-C_6H_4	C_2H_5	-	18	20	22	24	-	18	20	21	22
$II_{l'}$	$CH(CH_3)_2$	4-F-C_6H_4	C_2H_5	-	21	22	23	23	-	19	20	21	23
$II_{m'}$	$CH(CH_3)_2$	3-NO_2-C_6H_4	C_2H_5	-	18	18	19	22	-	18	20	21	22
$II_{n'}$	$CH(CH_3)_2$	4-NO_2-C_6H_4	C_2H_5	-	18	20	21	22	-	20	21	22	23
Comparative activity of ($II_{e'-n'}$) with known choosen standard drugs													
Standard drug				**Antibacterial activity**									
					$II_{f'}$,$II_{i'}$, $II_{g'}$, $II_{i'}$, $II_{j'}$					$II_{e'}$	$II_{e'}$, $II_{g'}$	$II_{e'}$, $II_{g'}$, $II_{h'}$, $II_{n'}$	$II_{e'}$, $II_{g'}$, $II_{j'}$	
Greseofulvin				19	23	25	25	28	18	21	22	22	24
Nystatin				18	19	24	29	29	18	21	24	25	26

N.B.(-): No Activity

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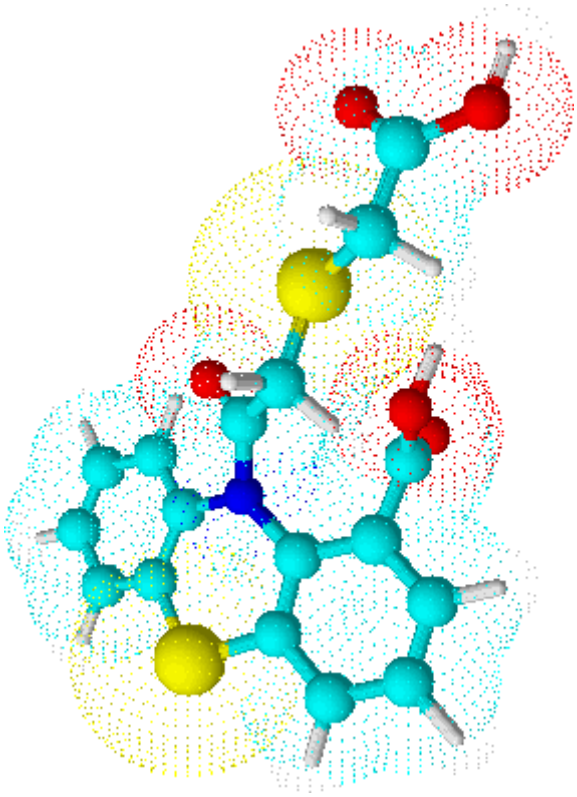


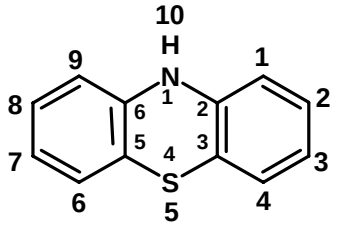
PART-II

STUDIES ON PHENOTHIAZINES

PART - II
STUDIES ON PHENOTHIAZINES

INTRODUCTION

When two **benzene nucleus** are fused with 2,3 and 5,6 positions of **thiazine** is called as **phenothiazine**. **Phenothiazine (26)** is also known as **thiodiphenyl amine**. The structure and numbering of **phenothiazine** is given bellow.



(26)

A. Benthsen[93] has synthesized **phenothiazine** by the reaction of **diphenylamine** and **sulfur** in the presence of catalytic amount of **iodine** particles in 1883. The most important application of **phenothiazine** are as an anthelmintic[90,91] and insecticidal agents.

Different methods of synthesis for some substituted phenothiazines are as follows.

(a) By the action of **diphenylamine** with **sulfur[93].**

(b) By the action of **diphenylamine** with **thionyl chloride[94,95]**.

(c) By the action of **2-amino thiophenol** with **2,4,6-trinitro chloro benzene** in presence of **sodium hydroxide** solution[96].

(d) By the action of **2-amino thiophenol** with **2,5-dinitro chloro benzene** in presence of **sodium acetate** solution[97].

(e) By the action of **2-amino-2'-iodo-4-4'-dinitro diphenyl sulphide** in presence of **cuprous iodide** and **sodium carbonate[98]**.

(f) By the action **phenothiazine** in **glacial acetic acid** with **sodium nitrite[99]**.

(g) By the action of **3-nitro phenothiazine** in **glacial acetic acid** with **hydrogenchloride[97]**.

(h) By action of **3,7-dinitro phenothiazine** in **dil. HCl** with **tin/zinc** - metal[100].

(i) By the oxidative cyclisation of **2-amino-4-chloro-3-methyl benzene thiol** with **2-halo/2,6-dibromo/chloro nitro benzene**[101].

(j) By the reaction of **2-formamido-5'-methoxy-2'-nitro-4-trifluromethyl diphenyl sulphide** in presence of **ethanolic sodium hydroxide**[102].

(k) By the reaction of **3,4-dichloro-2-formamido-2'-nitro-4'-bromo diphenylsulphide** in presence of **ethanolic potassium hydroxide**[103].

(l) By the reaction of **4-nitrodiphenylamine-2-sulfinic acid** in presence of **dilute sulfuric acid**[104].

(m) By the reaction of **aniline**, **hydriquinol** and **sulfur**[105].

(n) By the reaction of **N-(4-methyl phenyl)-[1,3]-benzodioxol-5-amine** with **sulfur** and **iodine** in **o-dichloro benzene**[106].

Applications of phenothiazines

Phenothiazine exhibited different types of agrochemical activities which are described as under.

(a) Larvicidal activity[107]

(b) Fungicidal activity[108-110]

(c) Acracidal activity[111,112]

(d) Plant growth rgulator [113].

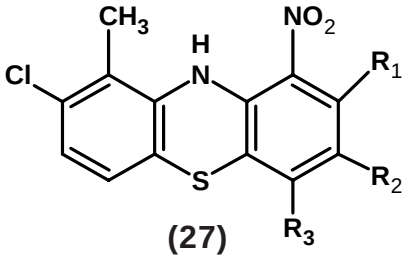
Therapeutic Importance

Phenothiazine derivatives showed a wide range of different types of therapeutic properties which are as follows.

(a) Antitmicrobial activity[119-121]
(b) Anthelmintic activity[122,123]
(c) Bactericidal activity[124,125]
(d) Antidepressant activity[126]
(e) Antitumour activity[127-130]
(f) Anticancer activity[131,132,183]
(g) Antitubarcular activity[133-135]
(h) Antileprotic activity[136]
(i) Sedative activity[137]
(j) Antiinflammatory activity[138-141]
(k) Tranquilizers[142,143]
(l) Antipsychotropic activity[144,145]
(m) Antiviral activity [146,147]
(n) Antidiabetic activity[148]
(o) Antifungal activity[149]
(p) Antimalarial activity[150,151]
(r) Lipid peroxidation inhibitors and cytoprotective activity[158]
(s) Antitrypanosomal activity[153]

Phenothiazine derivatives have been reported as a valuable human medicine in the treatment of parkinson's disease[96]

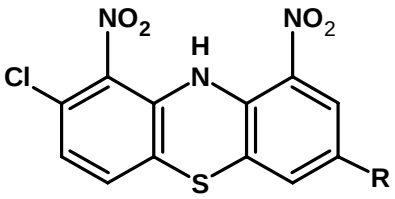
R.K.Rathore et. al.,[138] have synthesized **phenothiazine** derivatives **(27)** and **(28)** reported as tranquilizers.



(27)

R_1,R_3 = H, Br

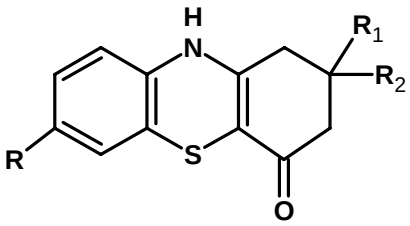
R_2 = H, NO_2, Cl, COOH



(28)

R = H, NO_2, Cl

P.J.Rosenthal et. al.,[146] have synthesized **phenothiazine** derivatives **(29)**, **(30)** and reported their antimalarial activity.

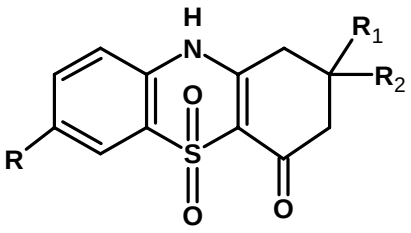


(29)

R = Cl, F

R_1= H, CH_3

R_2= H, CH_3, Aryl



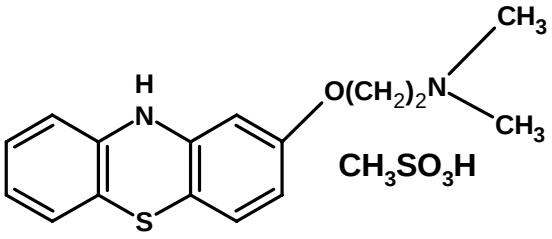
(30)

R = Cl, F

R_1= H, CH_3,

R_1= CH_3, Aryl

M.J.Yu et. al., have [148] synthesized **phenothiazine** derivatives **(31)**, **(32)**, **(33)**, **(34)**, **(35)**, **(36)**, **(37)**, **(38)**, **(39)**, **(40)** and reported as lipid peroxidation inhibitors and cytoprotective agents.



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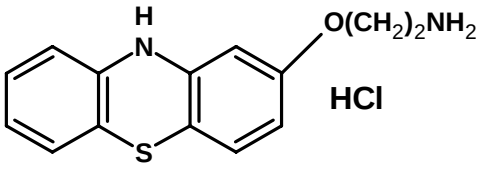

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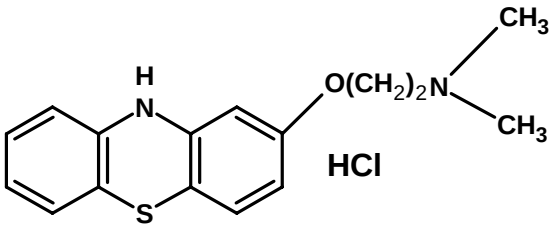

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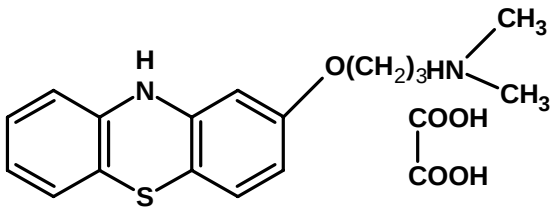
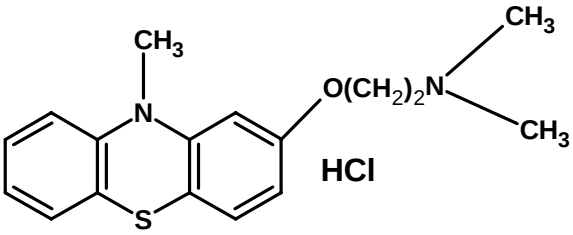
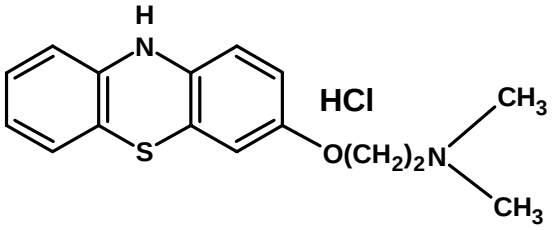


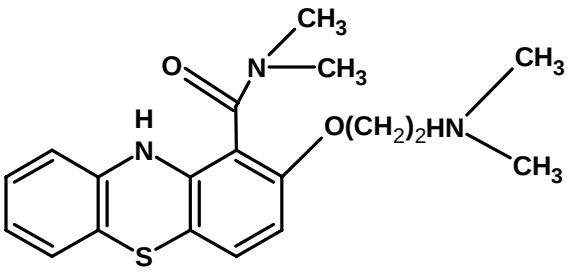
(34)



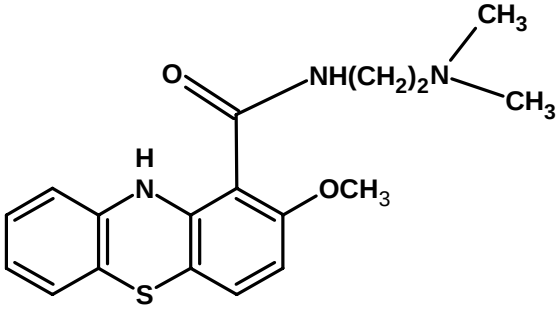
(35)



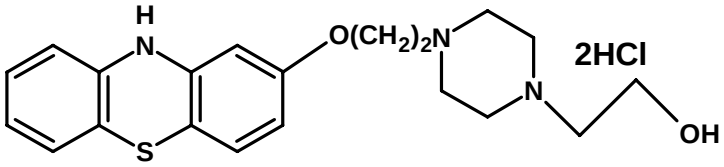
(36)



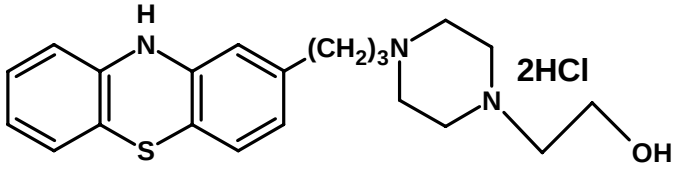
(37)



(38)



(39)



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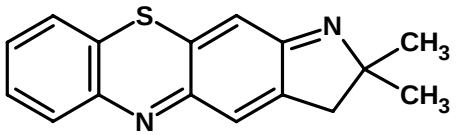
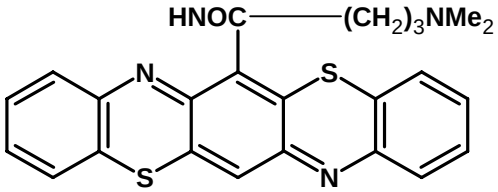


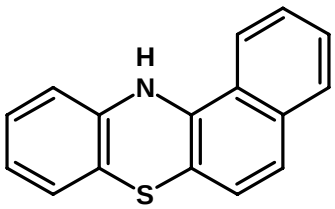
(41)

O.F.Ginzburg et. al.,[151] have synthesized **phenothiazine** derivatives **(42)** and reported as antitumor activity.



(42)

T.Kurihara et. al[152] have synthesized 12H-benzo[a]phenothiazine**(43)**,**9-Methyl-12H-benzo[a]phenothiazine(44)**,**10-Methyl-12H-benzo[a] phenothiazine(45)**,**11-Methyl-12H-benzo[a]phenothiazine (46)**,**5-Oxo-5H-benzo[a]phenothiazine(47)**,**6-Hydroxy-5-Oxo-12H-benzo[a]phenothiazine(48)**,**6-Methyl-5-Oxo-5H-benzo[a]phenothiazine (49)**,**5H-benzo[a][1,4] benzo- thiazino-[3,2-c]phenothiazine(50)** and evaluted as antitumour agent.



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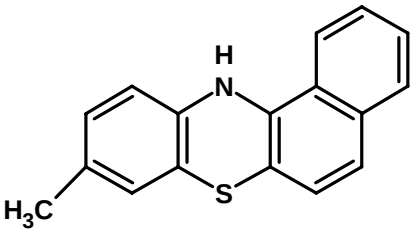

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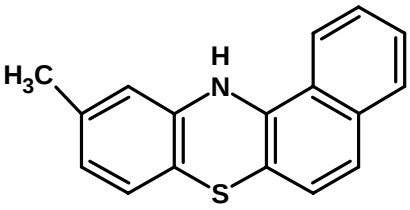

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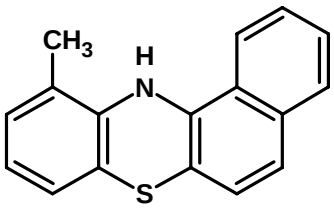
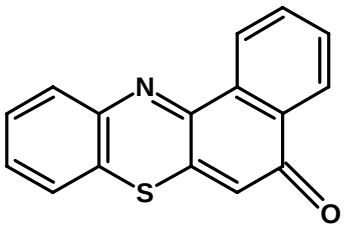


(46)



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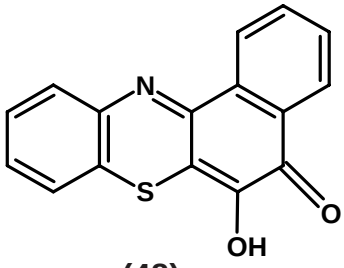

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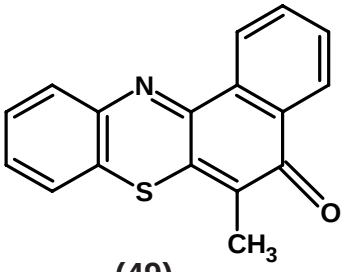
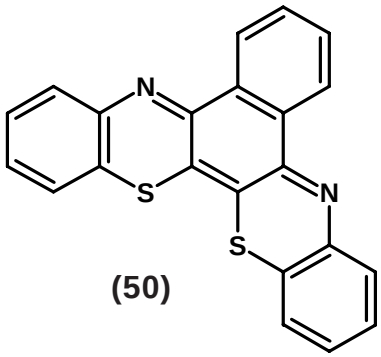
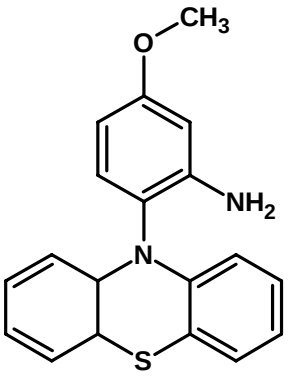


(49)

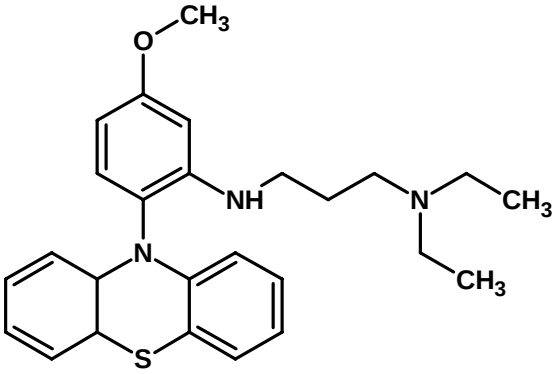


(50)

H, davida. shirley. et., al have synthesized 10-(2'-Amino)-phenylphenothiazine.**(51)**,and10-(2'-γ-Diethyaminopropy1amino)-phenylphenothiazine **(52)** and evaluated as antimalerial agents

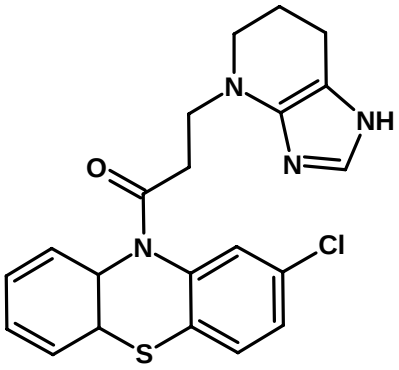


(53)



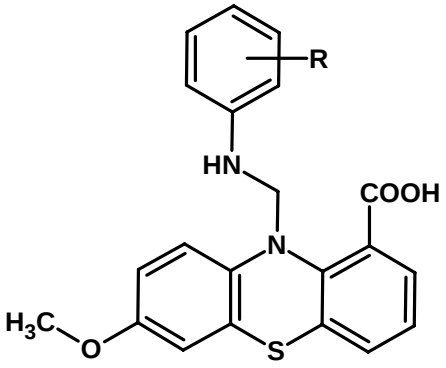
(54)

Yu.M.Yutilov et. al., have synthesized 5-[(2-Chlorophenothiazin-10-yl) carbonyl]-spinaceamine(**55)**



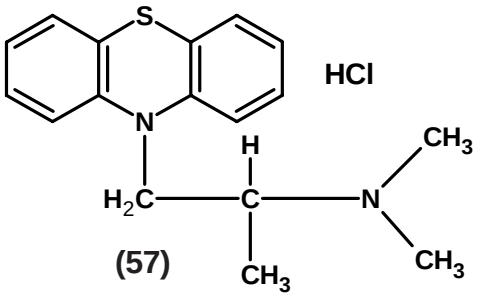
(55)

V.R.Radadiya et.al.,[153]have synthesized 10-(arylaminomethyl)-3-methoxy- pheothiazine-9-carboxylic acid **(56)** and evaluated as antiibacterial agents. [144]



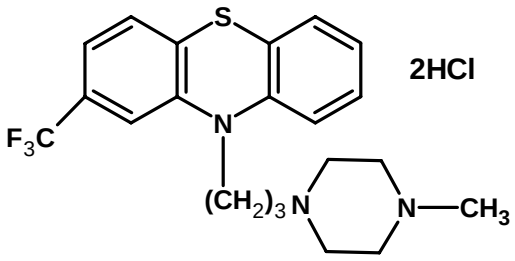
(56)

Receenty more than 40 drugs of **phenothiazine** class are now in clinical use. They are applied as antihistamine, sedative, antiemetic, antipsychotic, neuroleptic, agents. Since last two decades studies devoted to the **phenothiazine** class of compounds have been stimulated due to their promasing activities. Some **phenothiazine** drugs which are now in clinically uses are given bellow.



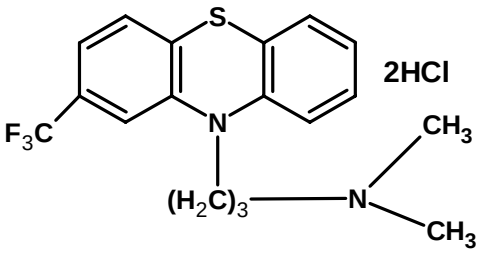
(57)

Promethazine hydrochloride
(Histamine H_1-receptor antagonist, antiemetic)



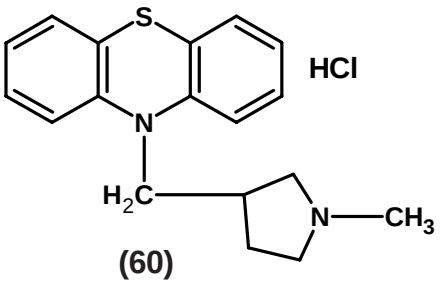
(58)

Trifluoperazine hydrochloride
(antipsychotic,antiemetic)



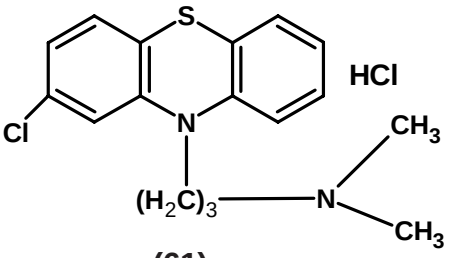
(59)

Triflupromazine hydrochloride
(antipsychotic,antiemetic)



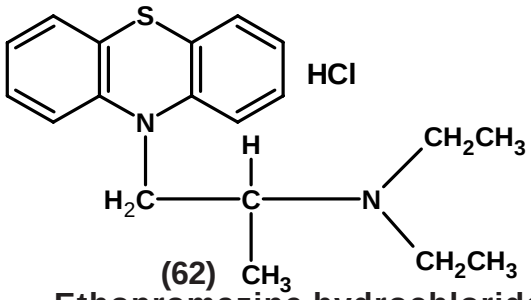
(60)

Methdilazinehydrochloride
(antiprouritic)



(61)

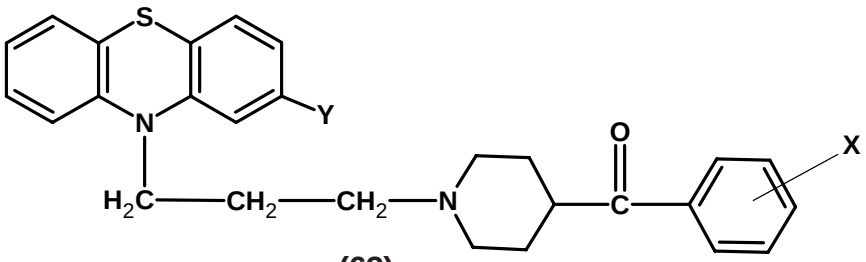
Chlorpromazine hydrochloride
(antipsychotic,antiemetic)



(62)

Ethopromazine hydrochloride
(antiparkinsonian)

W.J. Welsted et al., [154] have synthesized **phenothiazine (63)** and reported as neuroleptic agent.

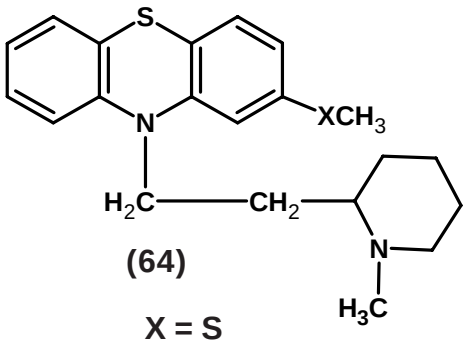


(63)

X = F/Cl

Y = H/F/Cl/$COCH_3$/CF_3

E.M. Haves et al.,[156] have synthesized **phenothiazine (64), (65)** and reported as antipsychotic agent, which are differ onyl in the oxidation state of the sulfur atom of the ring 2-substituent.

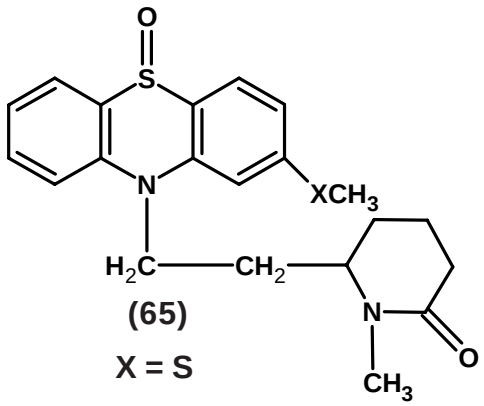


(64)

X = S

X= SO

X = SO_2



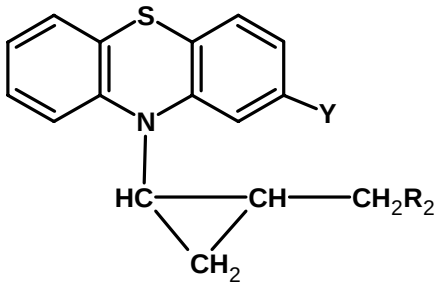
(65)

X = S

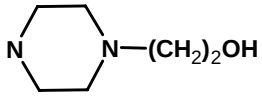
X= SO

X = SO_2

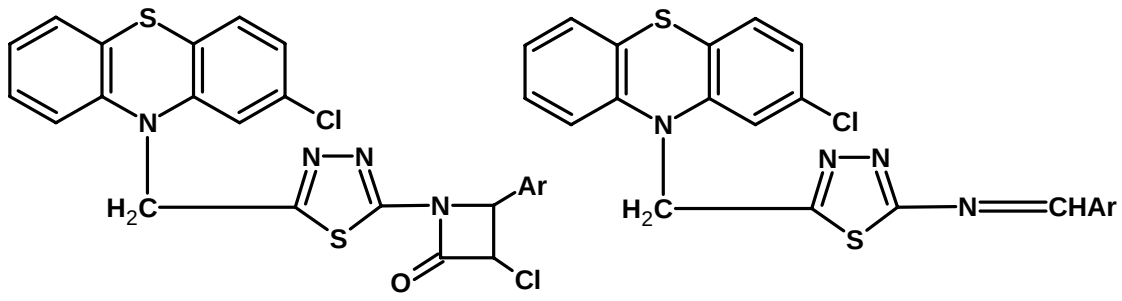
C. Kaiser et al., [157] have synthesized **phenothiazine (66)** and reported as potential antidepressant agent.



(66)

X = H, Cl, CF_3, SCH_3 **R_2= NMe_2, NHMe, NH_2,** 

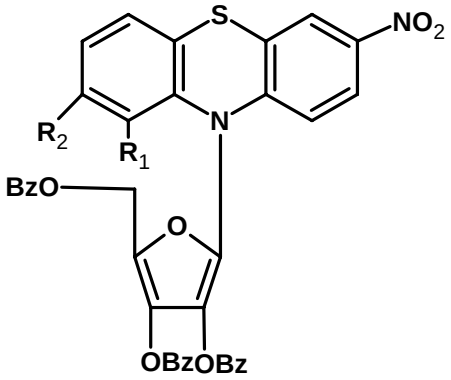
S.K. Shrivastava et.al.,[160] have synthesized **phenothiazine** derivative **(67)** and **(68)** reported as antimicrobial and antiinflammatory agent.



(67) **(68)**

Ar =substituted phenyl

A.K. Yadav et al., [161] have synthesized **phenothiazine (69)** and reported as antimicrobail agent.

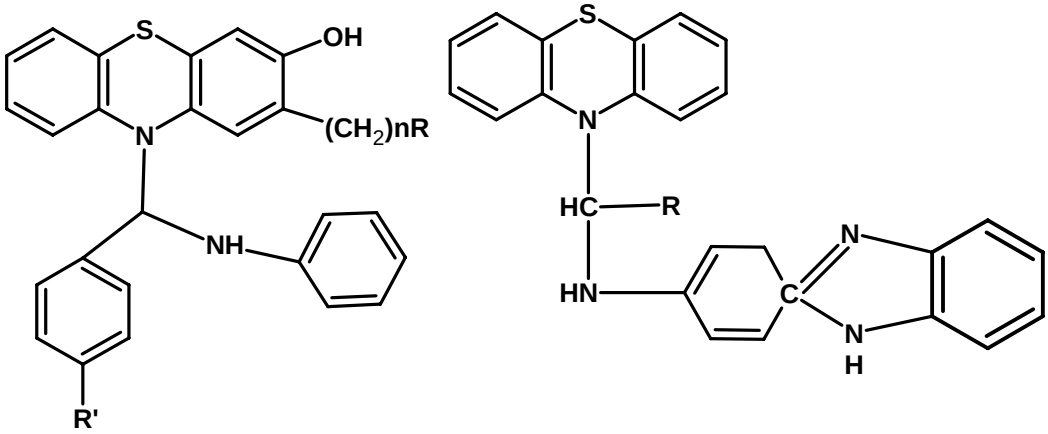


R_1 = H, Br, Cl

Bz = Benzoyl

(69)

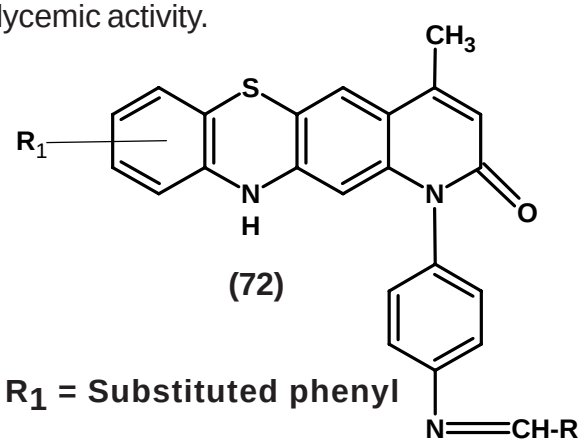
V.K. Pandey et.al., [162] have reported **phenothiazine (70)** , **(71)** as antiviral agents.



(70) **(71)**

R'= Substituted phenyl **R= Substituted phenyl**

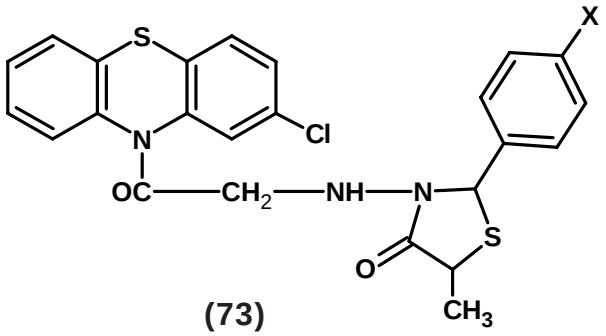
V.K. Pandey et.al., [163] have synthesized **phenothiazine (72)** and reported their hypoglycemic activity.



(72)

R, R_1 = Substituted phenyl

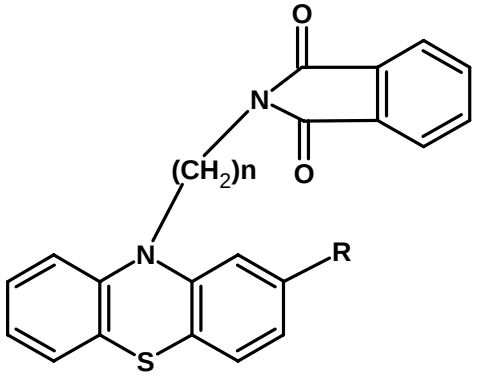
R. Tilak et.al., [165] have reported **phenothiazine** derivative **(73)** as antiinflammatory activity .



(73)

X = Cl, Br

N. Motohashi et al., [171-174] have synthesized **phenothiazine (74), (75)** and reported as antitumor agent.

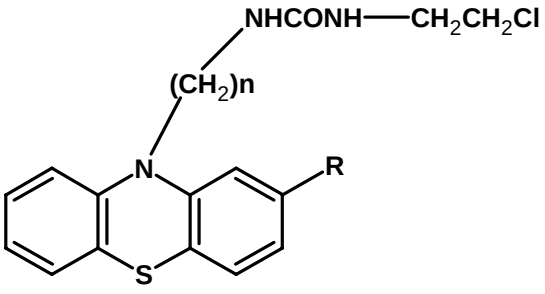


(76)

R = H, n = 3, R = H, n = 4

R = Cl, n = 3, R = Cl, n = 4

R = Cl, n = 3, R = Cl, n = 4



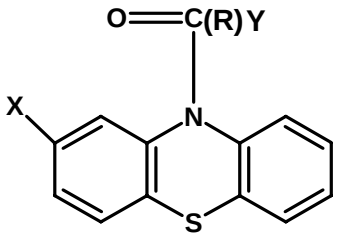
(77)

R = H, n = 3, R = H, n = 4

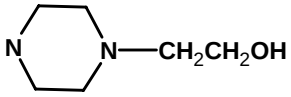
R = CF_3, n = 3, R = CF_3 , n = 4

R = CF_3, n = 3, R = CF_3 , n = 4

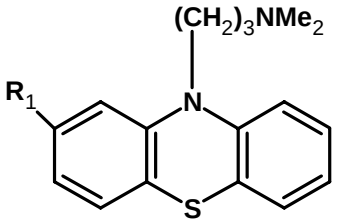
V.N. Sharma et al., [178] have synthesized **phenothiazine (78)** and eveluated as local anaesthetics



(78)

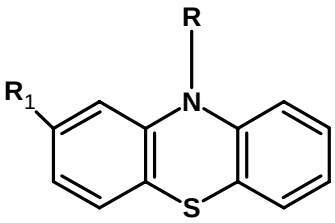
X = H, Cl **Y = NHC(CH3)3,** 

K.T.Douglas et al., [179] hvae synthesized **phenothiazines(79), (80)** and eveluated as antitrypanosomal and antileishmanial agents **.**



(79)

R_1 = H, Cl, CF_3, $COCH_3$, COOH/ CH_2OH, $CONH_2$

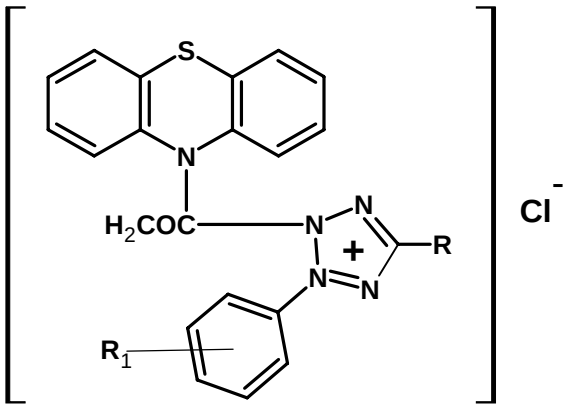


(80)

R_1= H

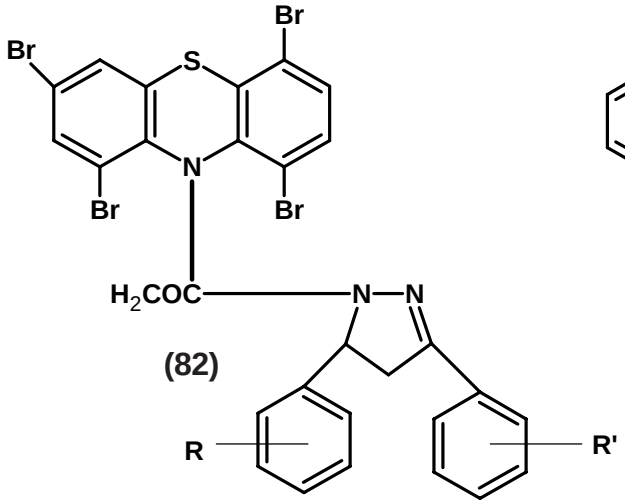
R = $(CH_2)_3NH_2$, $CH_2C(CH_3)_2N(CH_3)_2$ $(CH_2)_3NHCH_3$, $(CH_2)_3N$, $(CH_2)_2NEt_2$

K. Shanker et al., [179] hvae synthesized **phenothiazine (81)** and reported as local anaesthetics **.**



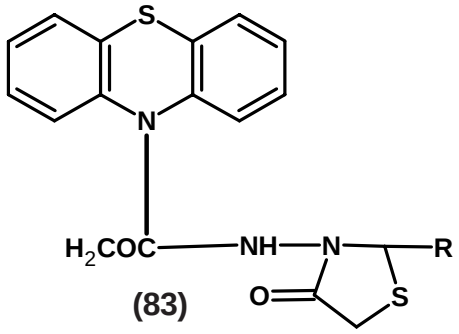
(81) **R_1 = CH_3, R = Aryl**

N.C. Desai et al., [181] have synthesized **phenothiazines (82), (83), (84)** and reported as antimicribial and antitubercular agent **.**



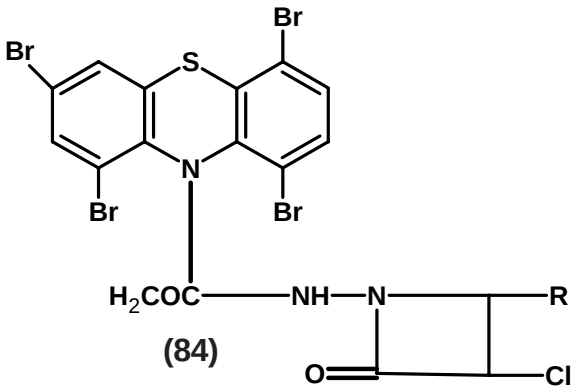
(82)

R' = H, Cl, R = Substituted phenyl



(83)

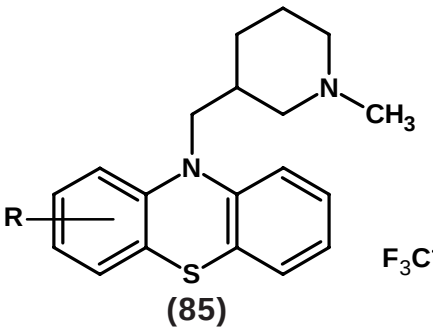
R = Substituted phenyl



(84)

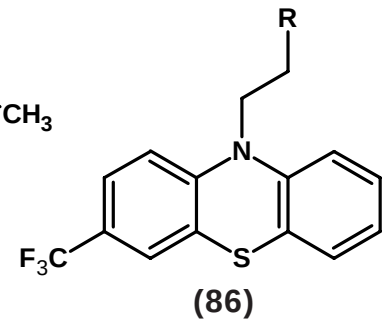
R = Substituted phenyl

M. Peter.B. et., al[182] have synthesized phenothiazines **(85),(86),(87)** and reported as antitubercular agent[171] **.**



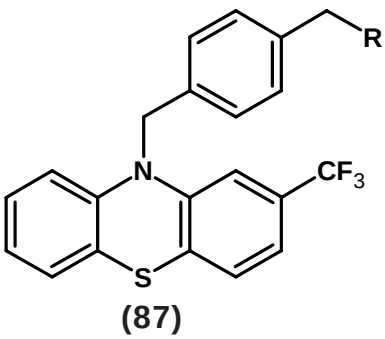
(85)

R=H, CH_3, Cl



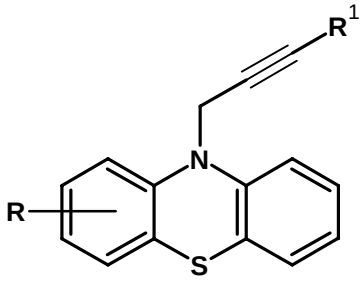
(86)

R=$N(CH_3)_2$, $N(Et)_2$



(87)

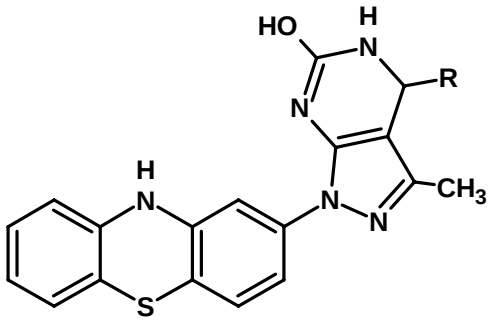
B.Alessandra et.,al[183] have synthesized N-substituted phenothiazine-es **(88)** and tested for antitumor activitiy.



(88)

R1= substituted phenyl

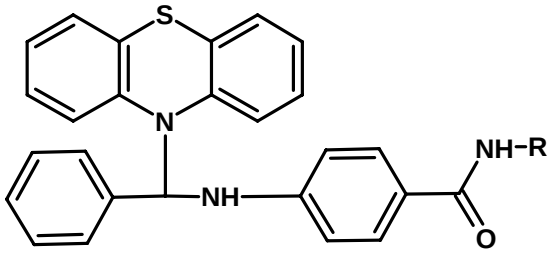
Trivedi A.R et., al[184] have synthesized 2-heterocycle-substituted-phenothiazines **(89)** and reported their antitubercular activity·



(89)

R= Substituted phenyl

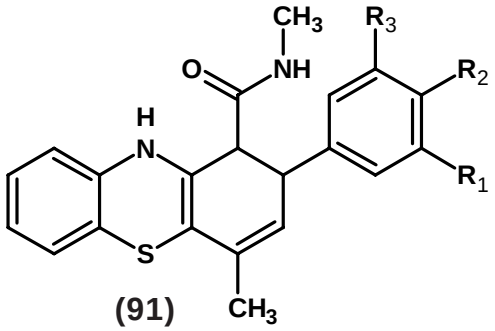
M.D.Bhanushli et al.,[185] have synthesized N-substituted phenothiaz-ines **(90)** and reported their antifungal and antibacterial activity.



(90)

R= 4-chlorophenyl, 4-chloro-3-fluro phenyl, 4-nitrophenyl, 4-carboxy phenyl, 4-carboxy-3-hydroxyphenyl.

Y.S. Sandanandan et., al [186] have synthesized substituted 10-H - phenothiazines **(91)** and reported their anti inflammatory activity**.**



(91)

(a) $R_1=R_2=R_3=H$ **(b)** $R_1=CH_3, R_2=R_3=H$

(c) $R_1=Cl, R_2=R_3=H$ **(d)** $R_1=H, R_2=R_3=Cl$

(e) $R_1=OCH_3, R_2=R_3=H$ **(f)** $R_1=R_2=H, R_3=OCH_3$

(g) $R_1=H, R_2=R_3=OCH_2\text{-}O\text{-}$ **(h)** $R_1=R_2=H, R_3=NO_2$

In view of procuring potent biodynamic agent and after reviewing recent litrature survey on 10-substituted **phenothiazines** for their various method of synthesis and different pharmacological activities, synthesis of **phenothiazines** have been under taken which can be summerised in the following section as under.

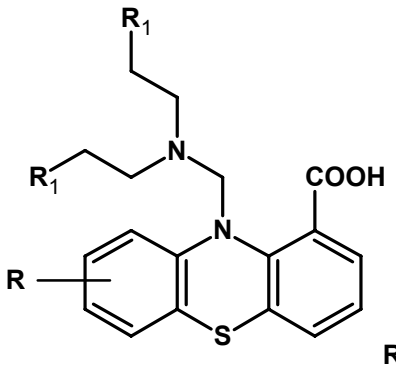
SECTION-I: PREPARATION AND BIOLOGICAL EVALUATION OF 7/8/9-SUBSTITUTED-10-N-[BIS(2-CHLOROETHYL/DIETHYL) -AMINO]-METHYL-PHENOTHIAZINE-1-CARBOXYLIC ACIDS.

SECTION-II : PREPARATION AND BIOLOGICAL EVALUATION OF 7/8/9-SUBSTTUTED-10-N-[(CARBOXYMETHYL)SULFANYL]-ACETYL-PHENOTHIAZINE-1-CARBOXYLIC ACIDS.

SECTION - I

PREPARATION AND BIOLOGICAL EVALUATION OF 7/8/9-SUBSTITUTED 10-N-[BIS-(2-CHLOROETHYL/ETHYL)-AMINO]-METHYL-PHENOTHIZINE-1-CARBOXYLIC ACIDS (III_{a-t}).

Recent litrature survey on substituted **phenothiazines** for their other applications[97-109] and various pharmacological profile[110-170] suggest to structually redesign and synthesize some newer bioactive **phenothiazines**. The synthesis of **7/8/9/-substituted10-N-[bis-(2-chloroethyl/ethyl)-amino] methyl-phenothiazines (III_{a-t})** have been under taken by the reaction of **7/8/9-substituted 1-Carboxy phenothiazines**, **formaldehyde and 2-chloro-N-(2-chloroethyl) ethanamine / diethyl amine** in acidic media, which is known as **Mannich** reaction.



(III_{a-t})

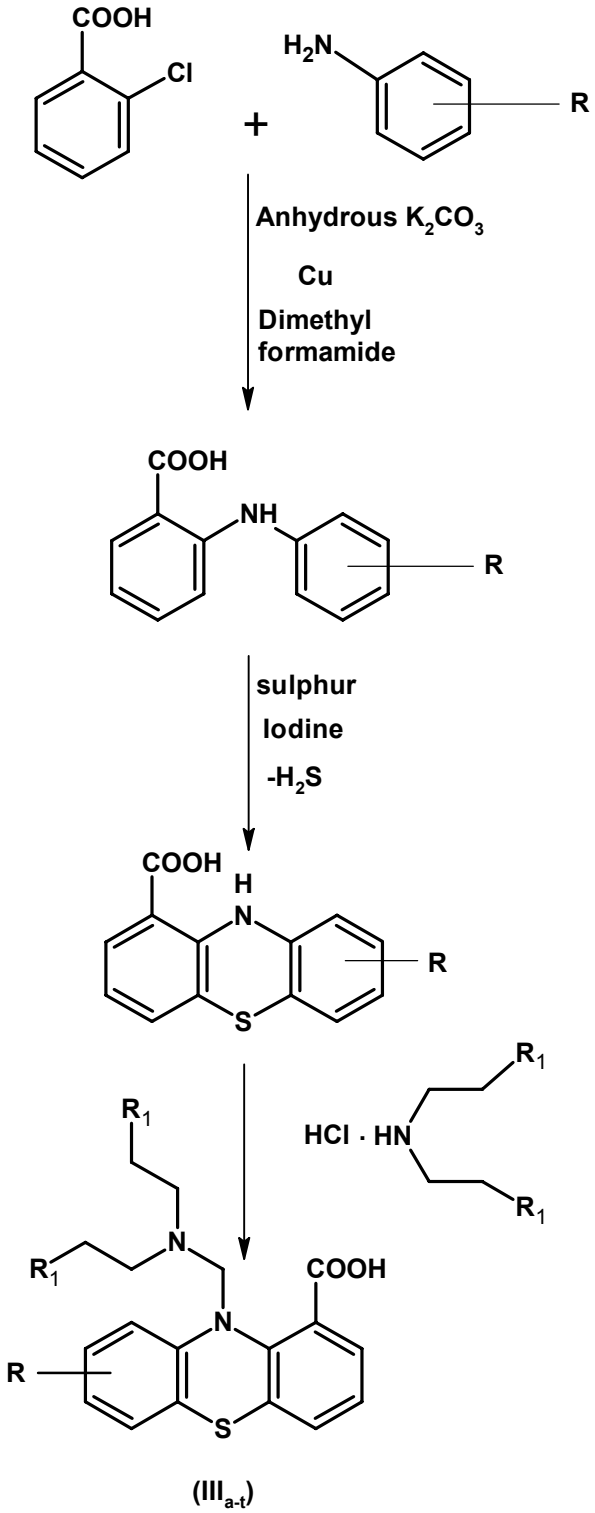
R= o/m/p-CH_3,-OCH_3,-NO_2

R_1= -Cl/-H

The constitution of the products **(III_{a-t})** have been delineated by elemental analyses, IR, PMR and Mass spectral data

The products **(III_{a-t})** were assayed for their ***in vitro*** biological assay like antibacterial activity towards ***S. pyogens MTCC-443*, *S. aureus MTCC-96* and *P. aeruginosa MTCC-441*** **(Gram positive) and *E. coli MTCC-442* (Gram negative)** bacterial strains and antifungal activity towards ***Aspergillus niger MTCC-282* and *A. clavatus MTCC-1323*** at different concentrations i.e.: 0, 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds **(III_{a-t})** were compared with standard drugs,viz., **Amplicillin, Chloramphenicol, Ciprofloxacin and Norfloxacin** (antibacterial)**, Greseofluvin, Nystatin** (antifungal)..

REACTION SCHEME



(III_{a-t})

R = o/m/p $-CH_3$, $-OCH_3$ and $-NO_2$

R_1 = -Cl/-H

EXPERIMENTAL

PREPARATION OF 7/8/9-SUBSTITUTED-10-N-[BIS-(2-CHLOROETHYL/ETHYL)-AMNIO]-METHYL-PHENOTHIZINE-1-CARBOXYLIC ACIDS (III_{a-t}).

Preparation of 10-N-[bis-(2-chloroethyl/ethyl)-amino]-methyl-7-methyl-phenothiazine-1-carboxylic acid (III_b)/(III_l).

(A) Preparation of 1-Carboxy-4'-methyl diphenylamine(3_b).

A mixture of **2-chloro benzoic acid** (1.56gm, 0.01M) and **p-toludine** (1.07gm, 0.01M) in **dimethyl formamide**(20ml) was refluxed in presence of anhydrous **potassium carbonate** (2gm) and **copper powder** (0.20gm) for two hours using an oil bath. The mixture was filtered and residue was washed with 10.0 ml hot **dimethyl formamide**. The filtrate so obtained was pourd into ice cold water and followed by acidification with 10.0 ml **dil. hydrochloric acid**. The precipitated acid was then dried in air and recrystallized from **ethanol**. **Yield** : 69%, **M.P**. : 158°C, (Required : **C**, 73.92%; **H**, 5.72%; **N**, 6.17% for $C_{14}H_{13}NO_2$, Found : **C**: 73.87%; **H**, 5.67%; **N**, 6.13%)

TLC solvent system Rf_1**: Ethyl acetate : Hexane (2.4 : 7.6) =** 0.59
TLC solvent system Rf_2**: Acetone : Bezene (0.5 : 9.5) =** 0.65

Similarly, other compounds (3_{a-j}) were synthesized. The physical data are recorded in Table No.3_A

(B) Preparation of 1-Carboxy-7-methyl phenothiazine (3_l).

A mixture of **1-carboxy-4'-methyl diphenyl amine** (2.27gm, 0.01M), **sulfur powder** (0.64gm, 0.02M) and **iodine** (0.3gm) in **1,2-dichloro benzene** (20ml) was refluxed for five hours in oil bath. The reaction mixture was distilled to remove excess solvent. The product so obtained was recrystal-

lized from **toluene**. **Yield** : 58%, **M.P**. : 96°C, (Required : **C**, 65.30%; **H**, 4.27%; **N**, 5.44% for $C_{14}H_{11}NO_2S$, Found :C: 65.24%; H, 4.21%; N, 5.36%)

TLC solvent system Rf_1: Ethyl acetate : Hexane (2.4 : 7.6) = 0.53

TLC solvent system Rf_2: Acetone : Bezene (0.5 : 9.5) = 0.62

Similarly, other compounds (3_{k-t}) were synthesized. The physical data are recorded in Table No. 3_B.

(C) (i) Preparation of 10-N-[bis-(2-chloroethyl)amino]-methyl-7-methyl-phenothiazine-1-carboxylic acid (III_b):

A mixture of **1-carboxy-7-methyl phenothiazine** (2.57gm, 0.01M), **2-chloro-*N*-(2-chloroethyl) ethanamine hydrochloride** (1.78 gm,0.01M) and **formaldehyde** (2-3 ml) in 20.0 ml of dioxane was refluxed for 8 to10 hours. The reaction mixture was cooled and pourd in to cold water. The product so obtained was filtered, dried and crystallized from **dioxane.Yield** : 49%, **M.P.** : 119°C (Required : **C**, 55.42%; **H**, 4.86%; **N**, 6.80% for $C_{19}H_{20}Cl_2N_2O_2S$, Found : **C**: 55.37%; **H**, 4.77%; **N**, 6.74%)

TLC solvent system Rf_1: Ethyl acetate : Hexane (2.4 : 7.6) = 0.39

TLC solvent system Rf_2: Acetone : Bezene (0.5 : 9.5) = 0.51

(ii)Preparation of 10-N-[bis-(ethyl)-amino]-methyl-7-methyl-phenothiazine-1-carboxylic acid (III_l):

A mixture of **1-carboxy-7-methyl phenothiazine** (2.57gm, 0.01M), **diethyl amine** (1.5 ml, 0.015 M)**, formaldehyde** (2-3 ml) and 4 to 5 drops of **conc. HCl** in 20 ml of dixoane was refluxed for 8 to 10 hours. The reaction mixture was cooled and pourd in to cold water. The product so obtained was filtered, dried and crystallized from **dioxane.**Yield : 41%, **M.P**. : 133°C, (Required : **C**, 70.27%; **H**, 6.42%; **N**, 8.17% for $C_{19}H_{22}N_2O_2S$, Found : **C**: 70.21%; **H**, 6.35%; **N**, 8.12%)

TLC solvent system Rf_1: Ethyl acetate : Hexane (2.4 : 7.6) = 0.51

TLC solvent system Rf_2: Acetone : Bezene (0.5 : 9.5) = 0.48

(D) Antimicrobial activity of Substituted 7/8/9-substituted-10-N-[bis-(2-chloroethyl/ethyl)-amino]-methyl-phenothiazine-1-carboxylic acids (III_{a-t}).

Antimicrobial activity testing was carried out as described in **Part-I, Section-I**, page No. **31-34.** The MIC values of test solution are recorded in **Table No.** 3_a, 3_b, 3_c, 3_d, 3_e and 3_f.

Result and Discussion:

The products **(III_{a-t})** have been subjected to antibacterial activity towards ***S. pyogens MTCC-443*, *S. aureus MTCC-96*** **and** ***P. aeruginosa MTCC-441*** **(Gram positive)** and ***E. coli MTCC-442*** **(Gram negative)** bacterial strains and antifungal activity towards ***Aspergillus niger MTCC-282*** **and** ***A. clavatus MTCC-1323*** at different concentrations i.e.: 0, 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values.

The biological activities of the synthesized compounds**(III_{a-t})** were compared with standard drugs,viz.,**Amplicilline,Chloramphenicol, Ciprofloxacin and Norfloxacin** (antibacterial)**, Greseofluvin, Nystatin** (antifungal)**.**

The results of antimicrobial activity have been depicted on page no. **132** to **137**.

TABLE NO. 3_A : PHYSICAL CONSTANTS OF SUBSTITUTED 1-CARBOXY DIPHENYLAMINES (3_{a-j})

Comp. No.	R	Molecular Formula	M.W.	Yield %	M.P. °C	R_f Value R_{f_1} / R_{f_2}	% of Nitrogen Calcd. / Found
1	2	3	4	5	6	7	8
3_a	H	$C_{13}H_{11}NO_2$	213.0	70	97	0.52/ 0.57	6.57/ 6.52
3_b	4-CH_3	$C_{14}H_{13}NO_2$	227.0	69	158	0.59/ 0.65	6.17/ 6.13
3_c	3-CH_3	$C_{14}H_{13}NO_2$	227.0	71	164	0.64/ 0.60	6.17/ 6.11
3_d	2-CH_3	$C_{14}H_{13}NO_2$	227.0	68	143	0.60/ 0.58	6.17/ 6.12
3_e	4-OCH_3	$C_{14}H_{13}NO_3$	243.0	76	188	0.46/ 0.50	5.76/ 6.72
3_f	3-OCH_3	$C_{14}H_{13}NO_3$	243.0	75	108	0.50/ 0.54	5.76/ 5.70
3_g	2-OCH_3	$C_{14}H_{13}NO_3$	243.0	67	126	0.58/ 0.61	5.76/ 5.71
3_h	4-NO_2	$C_{13}H_{10}N_2O_4$	258.0	62	192	0.54/ 0.59	5.86/ 4.88
3_i	3-NO_2	$C_{13}H_{10}N_2O_4$	258.0	71	185	0.61/ 0.57	5.82/ 4.82
3_j	2-NO_2	$C_{13}H_{10}N_2O_4$	258.0	60	121	0.53/ 0.62	5.88/ 4.92

TLC solvent system Rf_1: Ethyl acetate : Hexane (2.4 : 7.6)

TLC solvent system Rf_2: Acetone : Bezene (0.5 : 9.5)

TABLE NO. 3_B : PHYSICAL CONSTANTS OF 7/8/9-SUBSTITUTED-1-CARBOXY PHENOTHIAZINES (3_{k-t})

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	Yield % 5	M.P. °C 6	R_f Value R_{f_1} / R_{f_2} 7	% of Nitrogen Calcd. / Found 8
3_k	H	$C_{13}H_9NO_2S$	243.0	63	123	0.48/ 0.55	5.76/ 5.70
3_l	4-CH_3	$C_{14}H_{11}NO_2S$	257.0	58	96	0.53/ 0.62	5.44/ 5.36
3_m	3-CH_3	$C_{14}H_{11}NO_2S$	257.0	66	113	0.58/ 0.53	5.45/ 5.39
3_n	2-CH_3	$C_{14}H_{11}NO_2S$	257.0	49	186	0.60/ 0.64	5.45/ 5.39
3_o	4-OCH_3	$C_{14}H_{11}NO_3S$	273.0	60	172	0.42/ 0.48	5.13/ 5.07
3_p	3-OCH_3	$C_{14}H_{11}NO_3S$	273.0	54	101	0.56/ 0.50	5.13/ 5.07
3_q	2-OCH_3	$C_{14}H_{11}NO_3S$	273.0	68	146	0.50/ 0.46	5.13/ 5.08
3_r	4-NO_2	$C_{13}H_8N_2O_4S$	288.0	52	175	0.48/ 0.52	5.06/ 5.01
3_s	3-NO_2	$C_{13}H_8N_2O_4S$	288.0	64	168	0.52/ 0.58	5.06/ 5.00
3_t	2-NO_2	$C_{13}H_8N_2O_4S$	288.0	50	186	0.54/ 0.56	5.08/ 5.01

TLC solvent system Rf_1: Ethyl acetate : Hexane (2.4 : 7.6)

TLC solvent system Rf_2: Acetone : Bezene (0.5 : 9.5)

TABLE NO. III_A : PHYSICAL CONSTANTS OF 7/8/9-SUBSTITUTED-10-N-[BIS-(2-CHLOROETHYL)-AMINO]-METHYL-PHENOTHIAZINE 1-CARBOXYLIC ACIDS (III_{a-j}).

Comp. No.	R	R_1	Molecular Formula	M.W.	M.P. ^oC	Yield %	R_f Value R_{f_1} / R_{f_2}	% of Nitrogen Calcd. / Found
1	2	3	4	5	6	7	8	9
III_a	H	Cl	$C_{18}H_{18}N_2O_2Cl_2S$	397.0	130°	50	0.49 / 0.49	7.05 / 7.01
III_b	4-CH_3	Cl	$C_{19}H_{20}N_2O_2Cl_2S$	411.5	119°	49	0.39 / 0.51	6.80 / 6.74
III_c	3-CH_3	Cl	$C_{19}H_{20}N_2O_2Cl_2S$	411.0	130°	46	0.38 / 0.50	6.81 / 6.75
III_d	2-CH_3	Cl	$C_{19}H_{20}N_2O_2Cl_2S$	411.0	141°	48	0.43 / 0.53	6.81/ 6.76
III_e	4-OCH_3	Cl	$C_{19}H_{20}N_2O_3Cl_2S$	427.0	135°	39	0.47 / 0.49	6.55 / 6.48
III_f	3-OCH_3	Cl	$C_{19}H_{20}N_2O_3Cl_2S$	427.0	143°	38	0.48 / 0.41	6.55 / 6.48
III_g	2-OCH_3	Cl	$C_{19}H_{20}N_2O_3Cl_2S$	427.0	154°	46	0.42 / 0.46	6.55/ 6.49
III_h	4-NO_2	Cl	$C_{18}H_{17}N_3O_4Cl_2S$	442.0	175°	48	0.51 / 0.47	9.50 / 9.42
III_i	3-NO_2	Cl	$C_{18}H_{17}N_3O_4Cl_2S$	442.0	145°	53	0.46 / 0.48	9.50 /9.41
III_j	2-NO_2	Cl	$C_{18}H_{17}N_3O_4Cl_2S$	442.0	152°	44	0.44 / 0.52	9.50 / 9.42

TLC solvent system Rf_1: Ethyl acetate : Hexane (2.4 : 7.6)

TLC solvent system Rf_2: Acetone : Bezene (0.5 : 9.5)

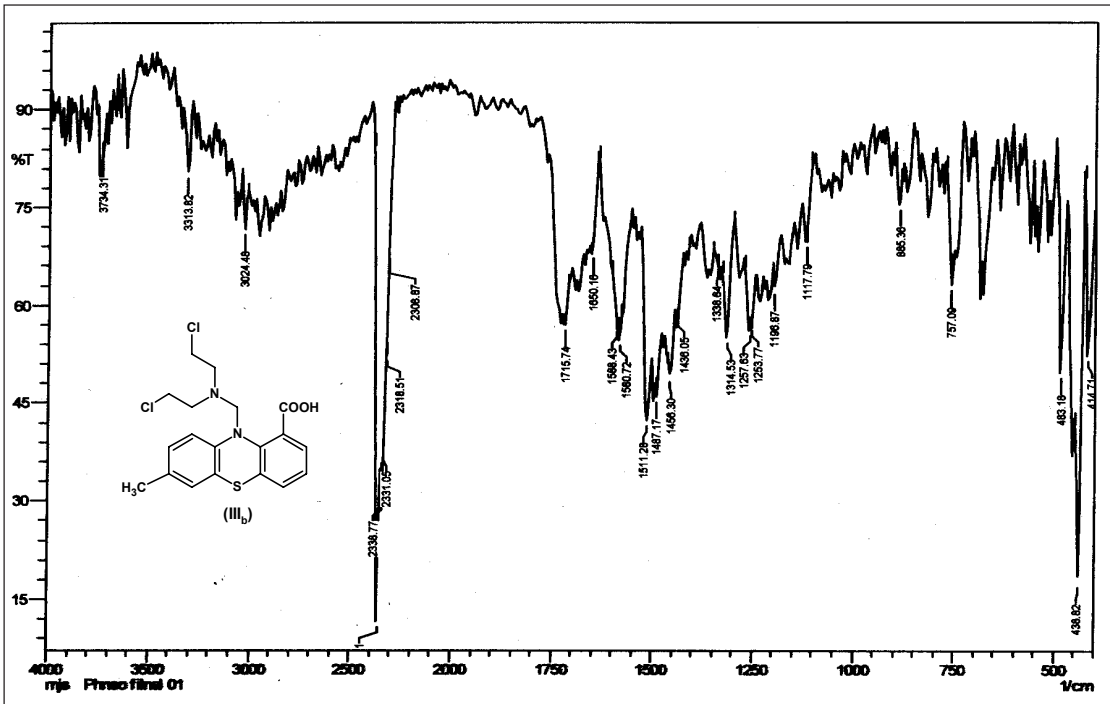
TABLE NO. III_B : PHYSICAL CONSTANTS OF 7/8/9-SUBSTITUTED-10-N-[BIS-(ETHYL)-AMINO]- METHYL-PHENOTHIAZINES-1-CARBOXYLIC ACIDS (III_{k-t}).

Comp. No.	R	R_1	Molecular Formula	M.W.	M.P. ^oC	Yield %	R_f Value R_{f_1}/ R_{f_2}	% of Nitrogen Calcd. / Found
1	2	3	4	5	6	7	8	9
III_k	H	H	$C_{18}H_{20}N_2O_2S$	328.0	151^o	39	0.47 / 0.51	8.53 / 8.48
III_l	4-CH_3	H	$C_{19}H_{22}N_2O_2S$	342.0	133^o	41	0.51 / 0.48	8.17 / 8.12
III_m	3-CH_3	H	$C_{19}H_{22}N_2O_2s$	342.0	138^o	37	0.39 / 0.49	8.18 / 8.13
III_n	2-CH_3	H	$C_{19}H_{22}N_2O_2S$	342.0	143^o	43	0.44 / 0.51	8.18/ 8.14
III_o	4-OCH_3	H	$C_{19}H_{22}N_2O_3S$	358.0	135^o	46	0.48 / 0.49	7.82 / 7.76
III_p	3-OCH_3	H	$C_{19}H_{22}N_2O_3S$	358.0	173^o	47	0.49 / 0.46	7.82 / 7.76
III_q	2-OCH_3	H	$C_{19}H_{22}N_2O_3S$	358.0	164^o	45	0.46 / 0.41	7.82/ 7.77
III_r	4-NO_2	H	$C_{18}H_{19}N_3O_4S$	373.0	166^o	45	0.50 / 0.45	11.29 /11.24
III_s	3-NO_2	H	$C_{18}H_{19}N_3O_4S$	373.0	178^o	50	0.45 / 0.45	11.29 /11.24
III_t	2-NO_2	H	$C_{18}H_{19}N_3O_4S$	373.0	120^o	44	0.48 / 0.50	11.29 / 11.23

TLC solvent system Rf_1: Ethyl acetate : Hexane (2.4 : 7.6)

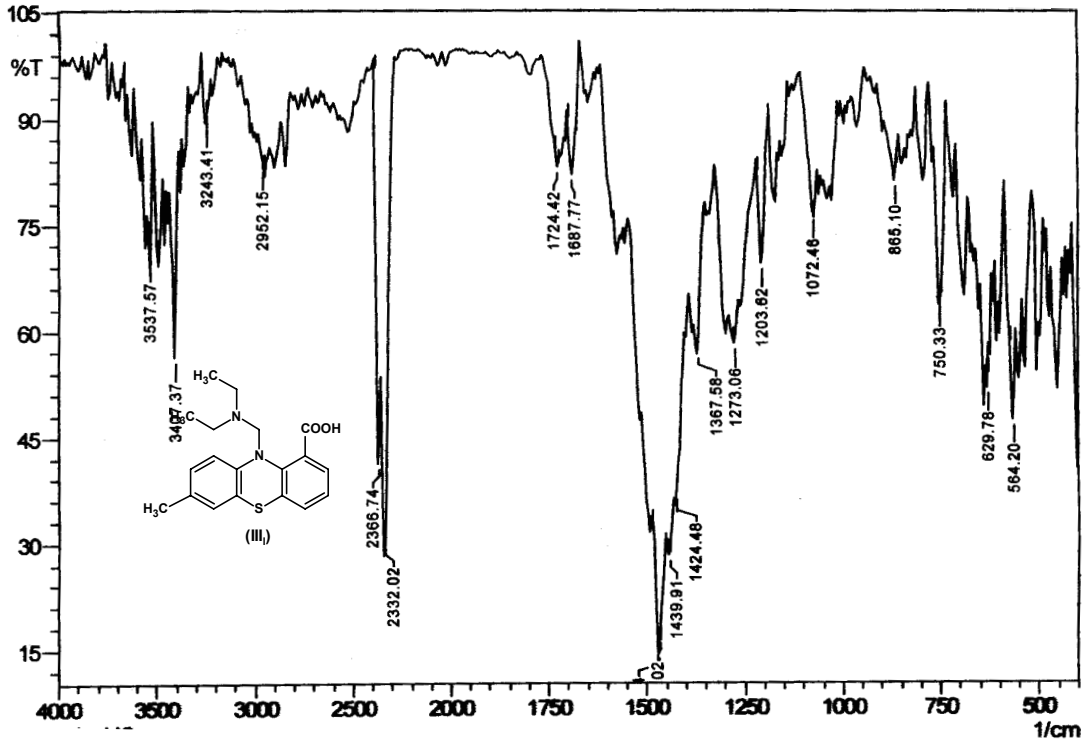
TLC solvent system Rf_2: Acetone : Bezene (0.5 : 9.5)

IR SPECTRAL STUDY OF 10-N-[BIS-(2-CHLOROETHYL)-AMINO]-METHYL-7-METHYL-PHENOTHIZINE-1-CARBOXYLIC ACID (III_b):



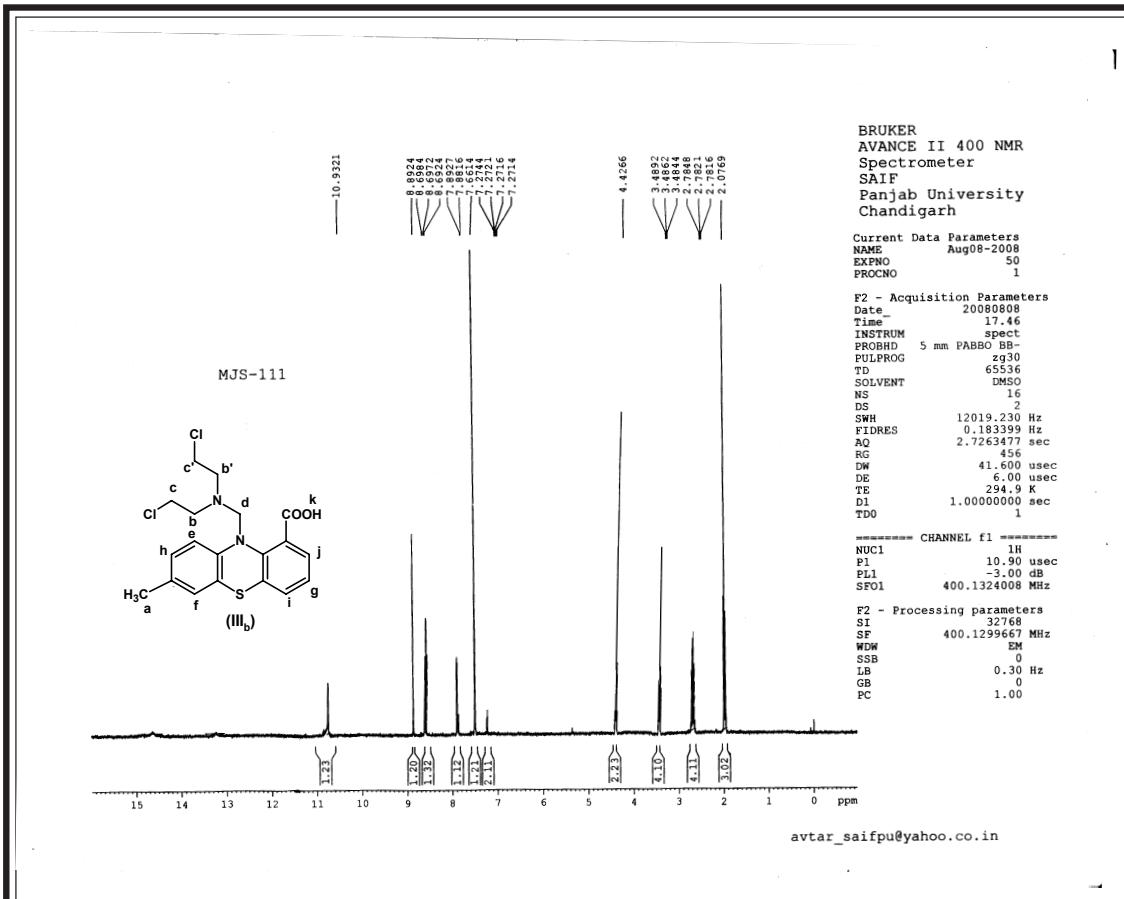
Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2979.1	2975 - 2850	92
	C-H (sym. str., m)	2880.0	2900 - 2800	92
	C-H (asym. def., m)	1456.3	1470 - 1435	92
	C-H (sym. def., m)	1314.5	1385 - 1300	92
Aromatic and ring skeletal vibration	C-H str	3031.5-3024.4	3080 - 3030	90 90
	C=C & C-C (str., v)	1511.2	1600 - 1450	90
	C-H (i.p. def., m)	1117.7	1150 - 1050	90
	C-H (o.o.p. def., m)	835.3	825 - 800	90
	C-N (str., v)	1338.6	1380 - 1332	
Carbonyl Acid	C=O (str., s)	1660.7-	1690 - 1650	89
	C=O (str., s)	1715.7		
Halogen Subtitution	C-Cl (str., b)	757.0 760.0	800-600	90 90
Thioether	C-S-C (str., s)	1196.3 1117.7	1200-1050	

IR SPECTRAL STUDY OF 10-N-[BIS-(ETHYL)-AMINO]-METHYL-7-METHYL-PHENOTHIAZINE-1-CARBOXYLIC ACID (III_I):



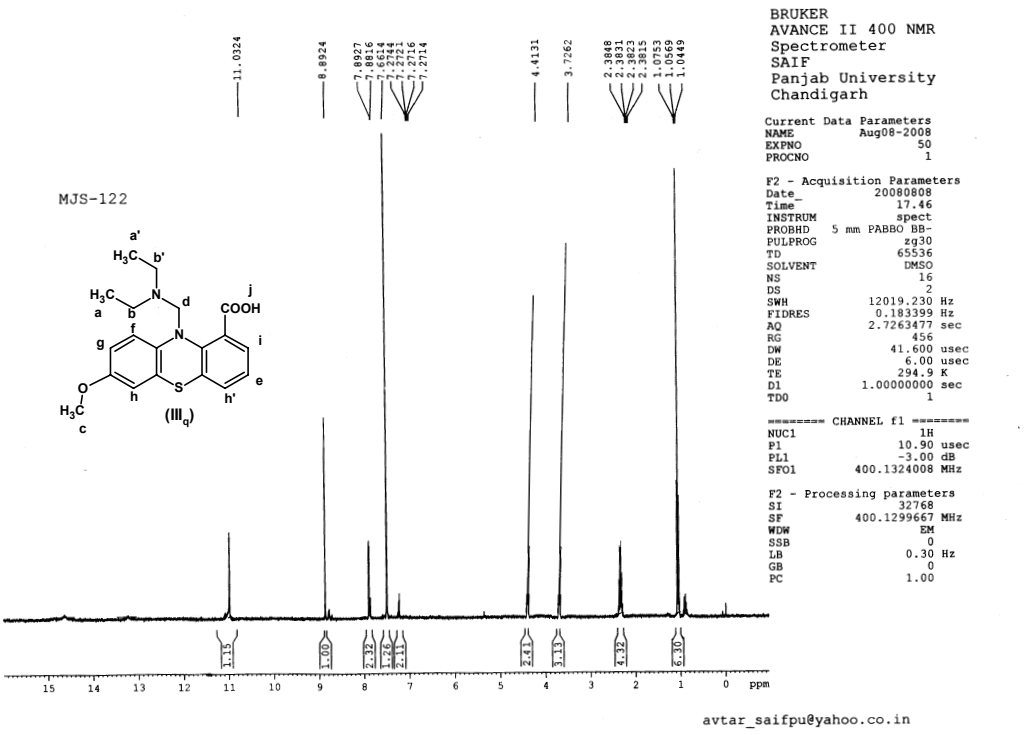
Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2952.1	2975 - 2850	92
	C-H (sym. str., m)	2814.0	2900 - 2800	92
	C-H (asym. def., m)	1439.0	1470 - 1435	92
	C-H (sym. def., m)	1367.5	1385 - 1300	92
Aromatic and ring skeletal vibration	C=C & C-C (str., v)	1472.0	1600 - 1450	90
	C-H (i.p. def., m)	1072.4	1150 - 1050	90
	C-H (o.o.p. def., m)	865.1	825 - 800	90
	C-N (str., v)	1267.5	1380 - 1332	90
Carbonyl Acid	C=O (str., s)	1687.7	1690 - 1650	89
Thioether	C-S-C (str., s)	1160.2	1200-1050	90

NMR SPECTRAL STUDY OF 10-N-[BIS-(2-CHLOROETHYL)-AMINO]-METHYL-7-METHYL-PHENOTHIZINE-1-CARBOXYLIC ACID(III_b):



Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	2.0769	3H	singlet	- $(C\underline{H}_3)_{(a)}$
2	2.7816-2.7848	4H	triplet	- $(C\underline{H}_2)_{2(b,b')}$
3	3.4844-3.4892	4H	triplet	- $(C\underline{H}_2)_{2(c,c')}$
4	4.4286	2H	singlet	- $(C\underline{H}_2)_{(d)}$
5	7.2714-7.2744	2H	multiplet	- Ar-$\underline{H}_{(e,f)}$
6	7.6614	1H	singlet	- Ar-$\underline{H}_{(g)}$
7	7.8816-7.8927	1H	doublet	- Ar-$\underline{H}_{(h)}$
8	8.6924-8.6984	1H	singlet	- Ar-$\underline{H}_{(i)}$
9	8.8924	1H	singlet	- Ar-$\underline{H}_{(j)}$
10	10.9321	1H	singlet	- COO$\underline{H}_{(k)}$

NMR SPECTRAL STUDY OF 10-N-[BIS-(ETHYL)-AMINO]-METHYL-7-METHOXY-PHENOTHIAZINE-1-CARBOXYLIC ACID (III_q):

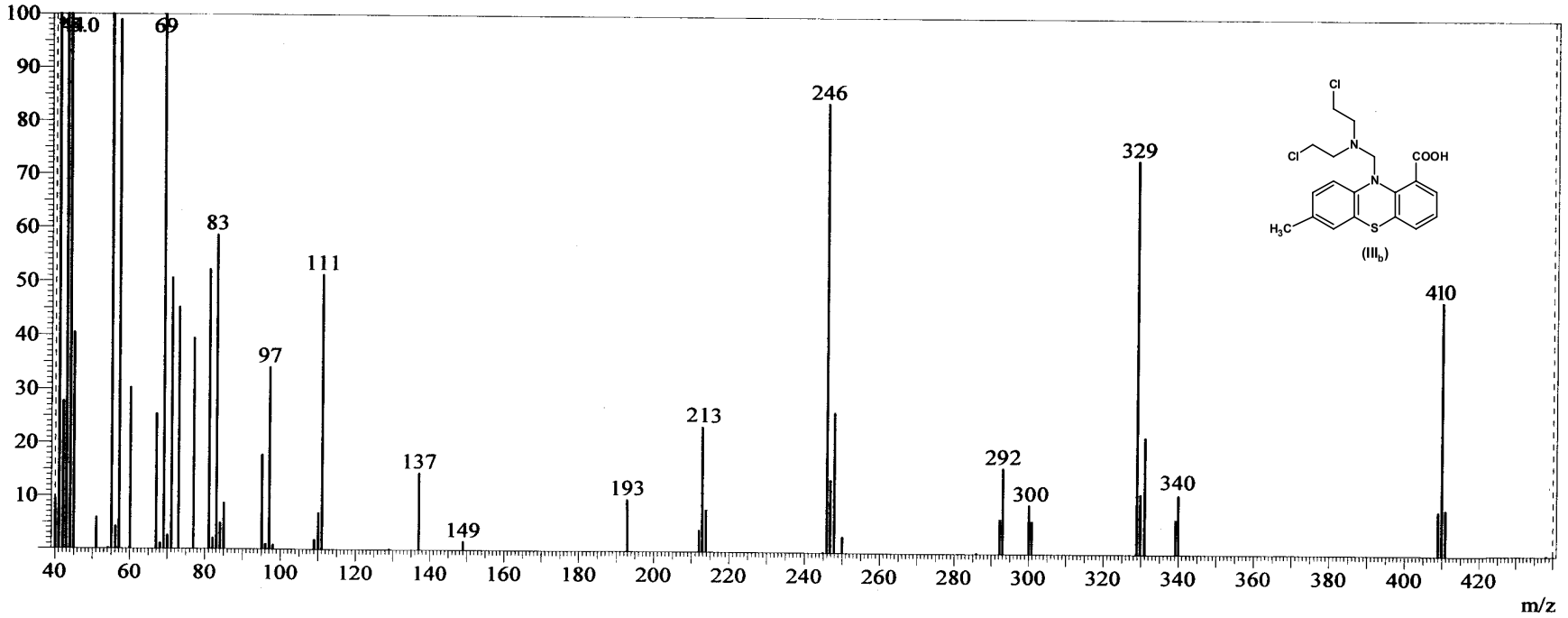


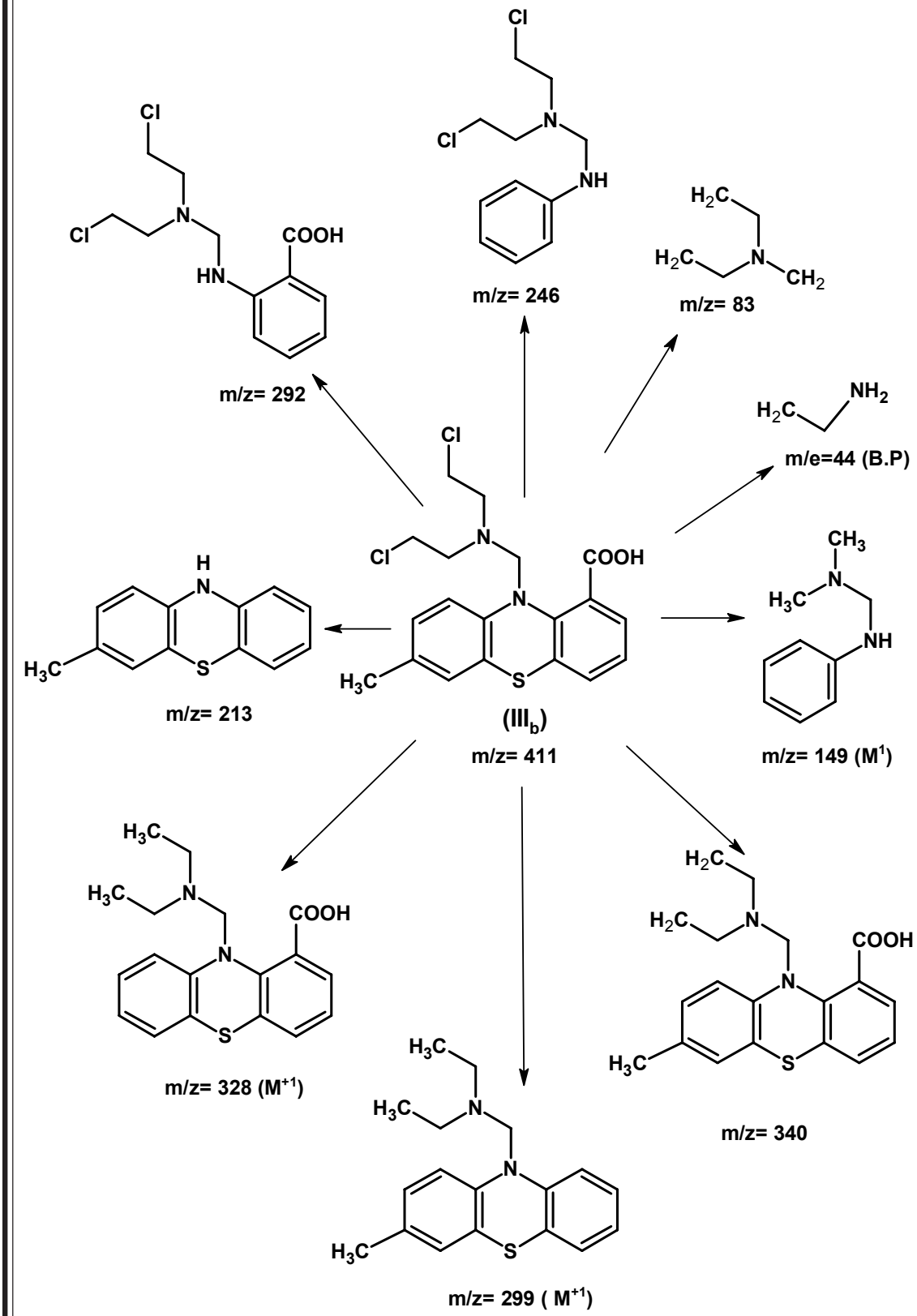
Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.0449-1.0753	6H	triplet	- 2($C\underline{H}_3$)$_{(a,a')}$
2	2.3815-2.3848	4H	quartret	- ($C\underline{H}_2$)$_{(b,b')}$
3	3.7262	3H	singlet	- ($OC\underline{H}_3$)$_{(c)}$
4	4.4131	2H	singlet	- ($C\underline{H}_2$)$_{(d)}$
5	7.2714-7.2744	2H	doublet	- Ar-$\underline{H}_{(e,f)}$
6	7.6614	1H	singlet	- Ar-$\underline{H}_{(g)}$
7	7.8816-7.8947	2H	doublet	- Ar-$\underline{H}_{(h,h')}$
8	8.8974	1H	singlet	- Ar-$\underline{H}_{(i)}$
9	11.0324	1H	singlet	- $COOH_{(j)}$

MASS SPECTRAL STUDY OF 10-N-[BIS-(2-CHLOROETHYL)-AMINO]-METHYL-7-METHYL-PHENOTHIZINE-1-CARBOXYLIC ACID (III_b):

Analyzed by : VIJAY R. RAM
Analyzed : 11/28/2008 1:32:01 PM
Sample Name : MS-2
Sample ID : MS-2
Data File : C:\GCMSsolution\Data\Project1\MSPPA-2.QGD
C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\Tune-02-06-2008.qgt

Line#:1 R.Time:8.6(Scan#:991)
MassPeaks:50 BasePeak:44(12576)
RawMode:Averaged 0.4-11.1(10-1296)
BG Mode:None




Cl
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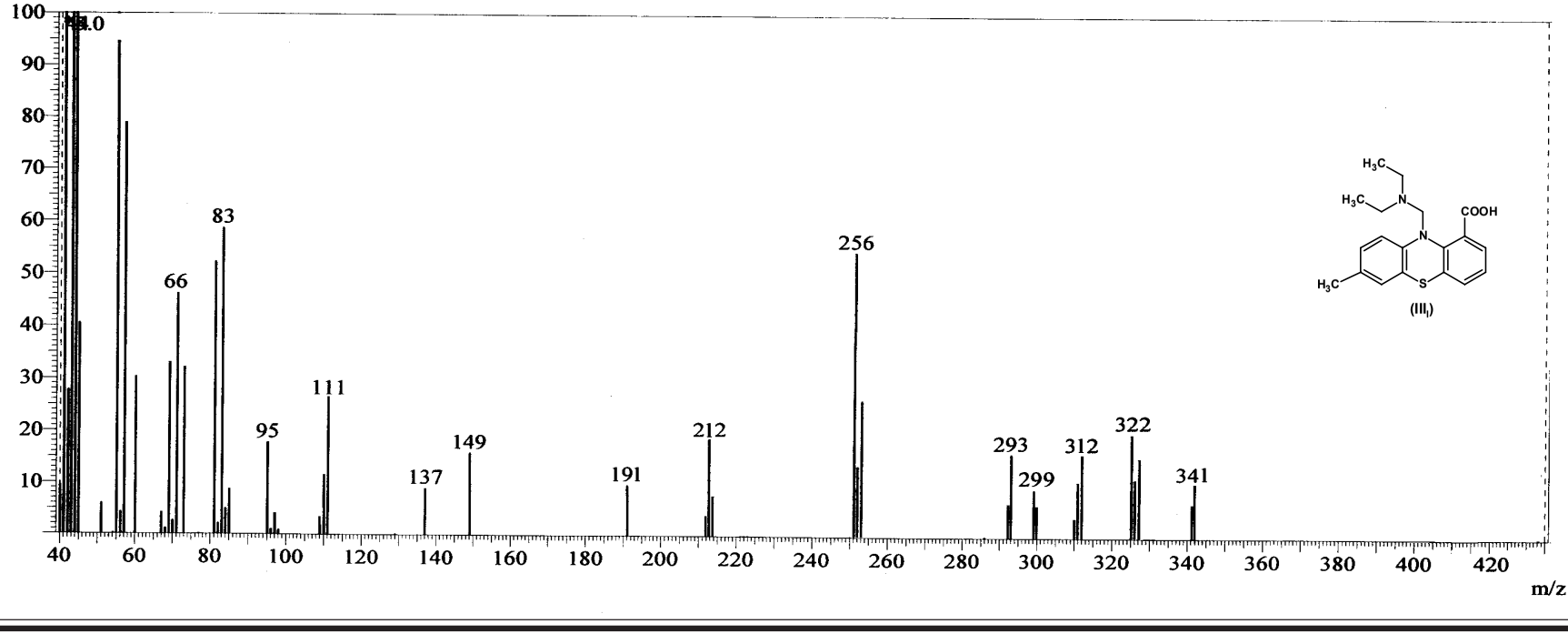
N
NH
m/z= 246
Cl
Cl
N
HN
COOH
m/z= 292
H2C
H2C
N
CH2
m/z= 83
NH2
H2C
m/e=44 (B.P)
Cl
Cl
N
COOH
N
H3C
S
H
N
H3C
S
m/z= 213
(IIIb)
m/z= 411
CH3
N
H3C
NH
m/z= 149 (M1)
H3C
H3C
N
COOH
N
S
m/z= 328 (M+1)
H2C
H2C
N
COOH
N
H3C
S
m/z= 340
H3C
H3C
N
N
H3C
S
m/z= 299 (M+1)

MASS SPECTRAL STUDY OF 10-N-[BIS-(ETHYL)-AMINO]-METHYL-7-METHYL-PHENOTHIAZINE-1-CARBOXYLIC-ACID (III_1):

Analyzed by : VIJAY R. RAM
Analyzed : 5/12/2008 1:05:04 PM
Sample Name : MS-821
Sample ID : MS-821
Data File : C:\GCMSsolution\Data\Project1\MSPPA-2.QGD
C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\Tune-02-06-2008.qgt

Line#:1 R.Time:8.6(Scan#:1161)
MassPeaks:50 BasePeak:44(12576)
RawMode:Averaged 0.4-11.1(10-1296)
BG Mode:None



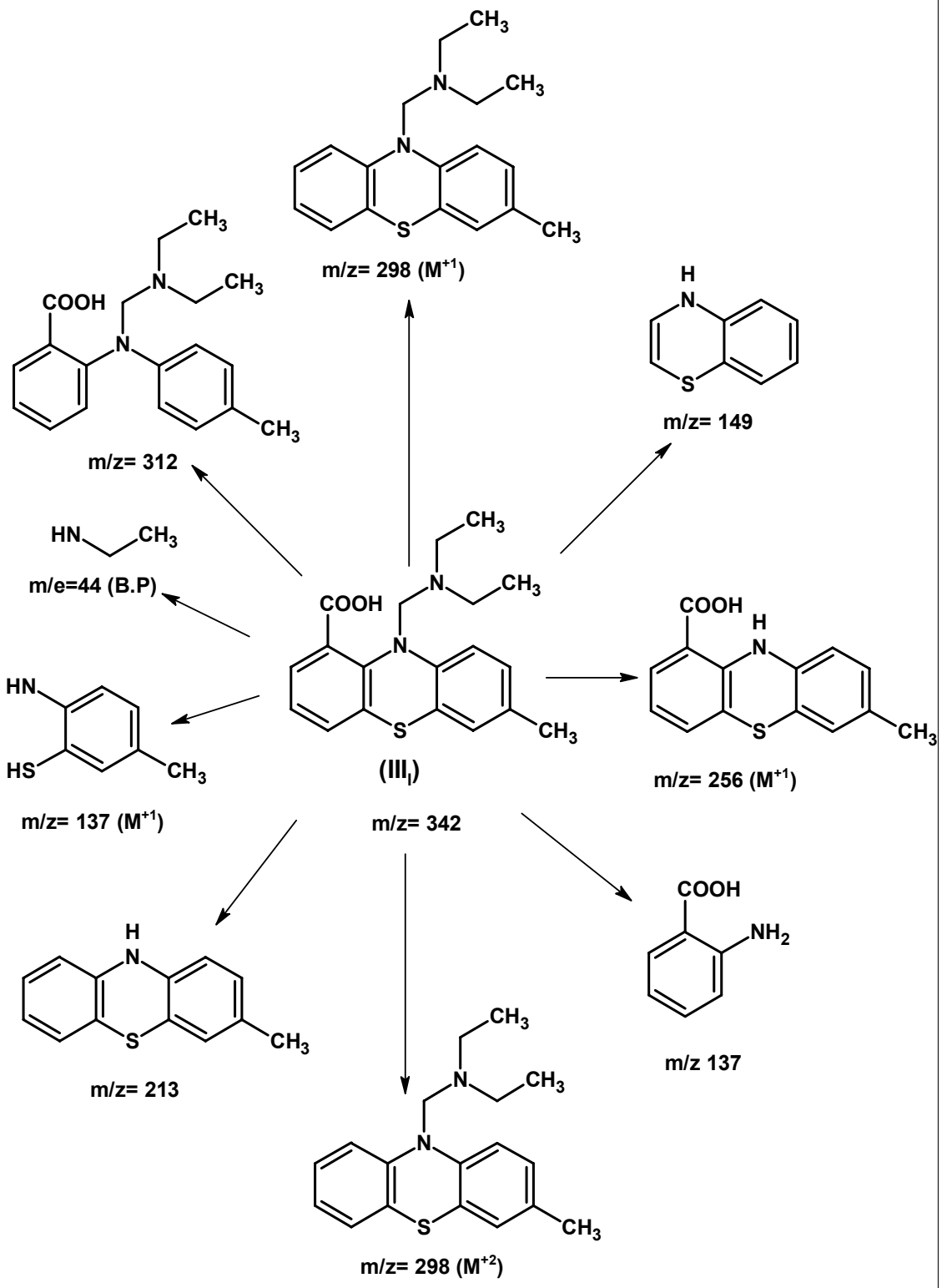

m/z= 298 (M+1)
m/z= 312
m/z= 149
m/e=44 (B.P)
m/z= 137 (M+1)
(III$_l$)
m/z= 342
m/z= 256 (M+1)
m/z= 213
m/z 137
m/z= 298 (M+2)

TABLE NO. 3_a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 7/8/9-SUBSTITUTED-10-N-[BIS-(2-CHLOROETHYL)-AMNIO]-METHYL PHENOTHIZINE-1-CARBOXYLIC ACIDS (III_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442 5	25	50	100	250	S. aureus MTCC-96 5	25	50	100	250
III_a	H	Cl	-	10	11	14	15	-	09	10	12	15
III_b	4-CH_3	Cl	-	11	13	15	16	-	10	12	14	17
III_c	3-CH_3	Cl	-	10	11	13	15	-	10	11	15	16
III_d	2-CH_3	Cl	-	10	14	16	18	-	10	12	13	15
III_e	4-OCH_3	Cl	-	11	12	13	15	-	11	12	13	14
III_f	3-OCH_3	Cl	-	10	12	13	15	-	10	11	15	17
III_g	2-OCH_3	Cl	-	10	12	16	17	-	10	11	14	17
III_h	4-NO_2	Cl	-	10	12	15	16	-	10	12	14	15
III_i	3-NO_2	Cl	-	11	13	15	16	-	11	14	15	16
III_j	2-NO_2	Cl	-	12	14	15	17	-	11	13	14	16

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

Standard drug	Antibacterial activity									
								III_i		
Amplicilline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
ciprofloxacin	16	19	21	21	22	17	19	21	22	22
Norfloxacin	18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

TABLE NO. 3_b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 7/8/9-SUBSTITUTED-10-N-[BIS-(2-CHLOROETHYL)-AMNIO]-METHYLPHE- NOTHIZINE-1-CARBOXYLIC ACIDS (III_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	Antibactrial activity (Zones of inhibition in mm) E. Coli MTCC-443					P. Aeruginosa MTCC-1688				
			5	25	50	100	250	5	25	50	100	250
III_a	H	Cl	-	13	15	16	19	-	12	13	15	17
III_b	4-CH_3	Cl	-	14	16	17	18	-	11	13	16	18
III_c	3-CH_3	Cl	-	12	14	15	17	-	13	14	17	18
III_d	2-CH_3	Cl	-	15	17	18	20	-	12	13	16	17
III_e	4-OCH_3	Cl	-	13	17	19	20	-	15	17	18	20
III_f	3-OCH_3	Cl	-	13	15	17	19	-	13	16	17	20
III_g	2-OCH_3	Cl	-	14	16	17	18	-	13	15	17	19
III_h	4-NO_2	Cl	-	12	13	15	18	-	14	16	17	18
III_i	3-NO_2	Cl	-	14	17	18	20	-	12	13	15	18
III_j	2-NO_2	Cl	-	14	15	17	19	-	14	17	18	20

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

Standard drug	Antibacterial activity									
		III_d	III_b III_g III_e III_b III_i III_d III_e		III_d III_e III_i		III_e	III_e III_f III_g III_h III_j	III_i III_j	III_e III_f III_j
Amoxiciline	14	15	16	19	20	14	15	15	18	20
Chloramphenicol	14	17	23	23	23	14	17	18	19	21
Sparfloxacin	20	23	28	28	28	20	23	24	26	27
Levofloxacin	22	25	26	27	29	18	19	21	23	23

N.B.(-): No Activity

TABLE NO. 3_C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 7/8/9-SUBSTITUTED-10-N-[BIS-(2-CHLOROETHYL)-AMNIO]-METHYLPHE- NOTHIZINE-1-CARBOXYLIC ACIDS (III_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	Antifungal activity (Zones of inhibition in mm) A. niger MTCC-282					A. clavatus MTCC-1323				
			5	25	50	100	250	5	25	50	100	250
III_a	H	Cl	-	14	15	18	20	-	14	15	18	19
III_b	4-CH_3	Cl	-	15	18	21	22	-	13	16	19	21
III_c	3-CH_3	Cl	-	16	17	18	22	-	16	17	19	20
III_d	2-CH_3	Cl	-	15	17	21	22	-	16	17	18	19
III_e	4-OCH_3	Cl	-	17	20	22	27	-	18	19	20	21
III_f	3-OCH_3	Cl	-	15	17	19	20	-	14	15	17	20
III_g	2-OCH_3	Cl	-	17	18	20	22	-	18	23	23	25
III_h	4-NO_2	Cl	-	18	19	21	22	-	17	18	19	20
III_i	3-NO_2	Cl	-	20	21	22	28	-	18	20	21	22
III_j	2-NO_2	Cl	-	15	18	19	21	-	17	18	18	22

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

Standard drug	Antifungal activity									
		III_i					III_g	III_g	III_g	
Griseofulvin	19	23	25	25	28	18	21	22	22	24
Nystatin	18	19	24	29	29	18	21	24	25	26

N.B.(-): No Activity

TABLE NO. 3_d:COMPARATIVE ANTIMICROBIAL ACTIVITY OF 7/8/9-SUBSTITUTED-10-N-[BIS-(ETHYL)-AMNIO]-METHYL-PHENOTHIZINE-1-CARBOXYLIC ACIDS (III_{k-t}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442 5	25	50	100	250	S. aureus MTCC-96 5	25	50	100	250
III_k	H	H	-	11	12	15	18	-	11	13	15	16
III_l	4-CH_3	H	-	10	12	14	18	-	11	15	16	18
III_m	3-CH_3	H	-	12	14	16	19	-	12	14	16	17
III_n	2-CH_3	H	-	10	12	13	18	-	11	14	15	17
III_o	4-OCH_3	H	-	11	12	17	21	-	12	13	15	18
III_p	3-OCH_3	H	-	12	13	15	19	-	12	13	15	17
III_q	2-OCH_3	H	-	10	11	14	21	-	11	14	15	16
III_r	4-NO_2	H	-	12	14	15	18	-	11	12	15	18
III_s	3-NO_2	H	-	10	13	15	18	-	12	13	14	17
III_t	2-NO_2	H	-	11	13	17	19	-	11	13	15	16

Comparative activity of (III_{k-t}) with known choosen standard drugs

Standard drug	Antibacterial activity									
					III_m III_o III_p III_q III_t			III_l III_m III_n III_q	III_l III_m	III_l III_o III_q
Amlicilline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
ciprofloxacin	16	19	21	21	22	17	19	21	22	22
Norfloxacin	18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

TABLE NO. 3_e:COMPARATIVE ANTIMICROBIAL ACTIVITY OF 7/8/9-SUBSTITUTED-10-N-[BIS-(ETHYL)-AMNIO]-METHYL-PHENOTHIZINE-1-CARBOXYLIC ACIDS (III_{k-t}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	Antibactrial activity (Zones of inhibition in mm) E. Coli MTCC-443 5	25	50	100	250	P. Aeruginosa MTCC-1688 5	25	50	100	250
III_k	H	H	-	12	14	15	19	-	13	15	16	19
III_l	4-CH_3	H	-	15	16	18	20	-	12	14	15	17
III_m	3-CH_3	H	-	14	15	17	20	-	11	12	15	17
III_n	2-CH_3	H	-	13	14	17	19	-	14	15	17	20
III_o	4-OCH_3	H	-	12	14	17	20	-	13	15	19	21
III_p	3-OCH_3	H	-	13	15	17	18	-	11	12	14	17
III_q	2-OCH_3	H	-	14	17	18	21	-	12	16	17	20
III_r	4-NO_2	H	-	13	15	17	20	-	13	15	17	18
III_s	3-NO_2	H	-	14	15	17	21	-	10	14	16	18
III_t	2-NO_2	H	-	12	13	18	19	-	13	15	18	19

Comparative activity of (III_{k-t}) with known choosen standard drugs

Standard drug	Antibacterial activity									
			III_l III_q	III_l	III_l, III_r III_m,III_s III_o III_q			III_k,III_t III_n, III_o III_q III_r	III_o III_t	III_n III_o III_q
Ampicilline	14	15	16	19	20	14	15	15	18	20
Chloramphenicol	14	17	23	23	23	14	17	18	19	21
Sparfloxacin	20	23	28	28	28	20	23	24	26	27
Levofloxacin	22	25	26	27	29	18	19	21	23	23

N.B.(-): No Activity

TABLE NO. 3_f: COMPARATIVE ANTIMICROBIAL ACTIVITY OF 7/8/9-SUBSTITUTED-10-N-[BIS-(ETHYL)-AMNIO]-METHYL-PHENOTHIZINE-1-CARBOXYLIC ACIDS (III_{k-t}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	R'	Antifungal activity (Zones of inhibition in mm) A. niger MTCC-282					A. clavatus MTCC-1323				
			5	25	50	100	250	5	25	50	100	250
III_k	H	H	-	17	18	19	21	-	15	16	17	18
III_l	4-CH_3	H	-	19	22	22	25	-	13	16	18	19
III_m	3-CH_3	H	-	17	18	20	21	-	17	18	20	21
III_n	2-CH_3	H	-	17	21	22	23	-	17	19	21	25
III_o	4-OCH_3	H	-	15	18	18	19	-	16	18	20	21
III_p	3-OCH_3	H	-	17	18	19	20	-	18	20	22	22
III_q	2-OCH_3	H	-	18	19	20	21	-	18	20	21	23
III_r	4-NO_2	H	-	17	18	20	21	-	13	15	16	17
III_s	3-NO_2	H	-	17	19	21	22	-	12	15	17	18
III_t	2-NO_2	H	-	18	21	23	23	-	17	19	20	23

Comparative activity of (III_{k-t}) with known choosen standard drugs

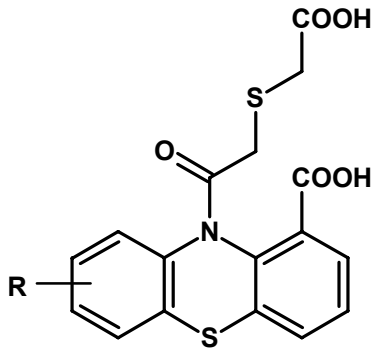
Standard drug	Antifungal activity									
		III_l							III_p	III_n
Griseofulvin	19	23	25	25	28	18	21	22	22	24
Nystatin	18	19	24	29	29	18	21	24	25	26

N.B.(-): No Activity

SECTION - II

PREPARATION AND BIOLOGICAL SCREENING OF 7/8/9-SUBSTITUTED-10-N-[(CARBOXYMETHYL)-SULFANYL]-ACETYL-PHENOTHIAZINE-1-CARBOXYLIC ACIDS (IV_{a-j}).

Recent litrature survey on substituted **phenothiazines** for their other applications[97-109] and various pharmacological profile[110-170] suggest to structually redesign and synthesize some newer bioactive **phenothiazines**. The synthesis of **7/8/9-Substituted-10-N-[(carboxymethyl)-sulfanyl]-acetyl-phenothiazine-1-carboxylic acids (IV_{a-j})** have been under taken by the reaction of **7/8/9-Substituted-1-Carboxy phenothiazines**, **chloroacetyl chloride followed by the action of thioglycollic acid** in basic media.

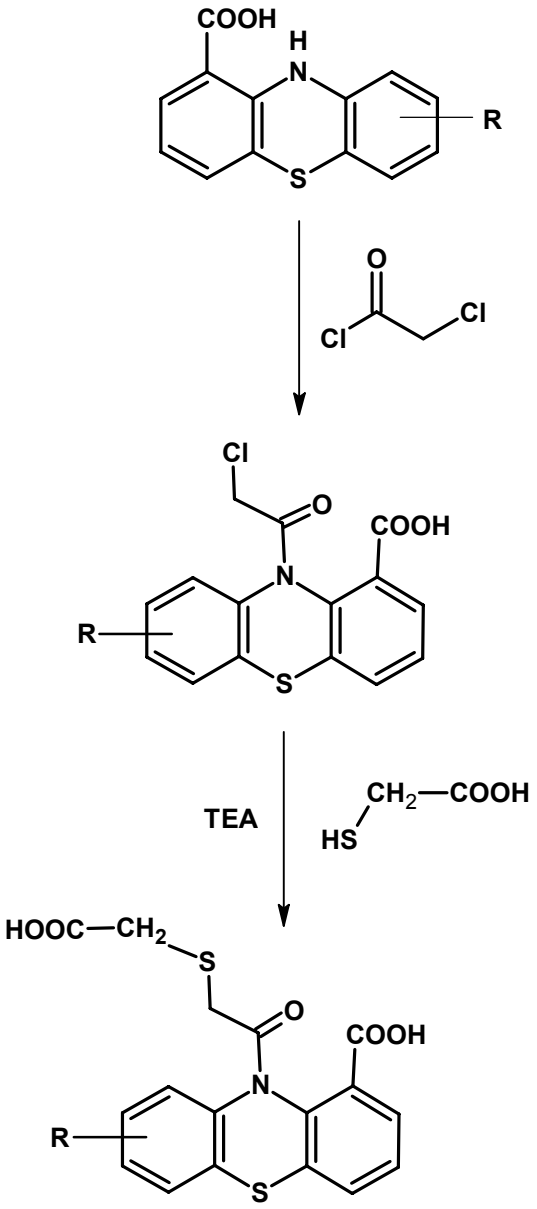


(IV_{a-j}) **R=H, o//,p-CH_3, OCH_3, NO_2**

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

The products **(IV_{a-j})** were assayed for their ***in vitro*** biological assay like antibacterial activity towards ***S. pyogens MTCC-443*****, *S. aureus MTCC-96* and *P. aeruginosa MTCC-441* (Gram positive) and *E. coli MTCC-442* (Gram negative)** bacterial strains and antifungal activity towards ***Aspergillus niger MTCC-282* and *A. clavatus MTCC-1323*** at different concentrations i.e.: 0, 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds **(IV_{a-j})** were compared with standard drugs,viz., **Amplicillin, Chloramphenicol, Ciprofloxacin and Norfloxacin** (antibacterial)**, Griseofluvin, Nystatin** (antifungal)..

REACTION SCHEME



(IV_{a-j})

R = o/m/p,-H, CH_3, -OCH_3 and -NO_2

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 7/8/9-SUBSTITUTED-10-N-[(CARBOXYMETHYL)-SULFANYL]-ACETYL-PHENOTHIAZINE-1-CARBOXYLIC ACIDS (IV_{a-j}).

Preparation of 10-N-[(carboxymethyl)-sulfanyl]-acetyl-7-methyl-phenothiazine-1-carboxylic acid (IV_b):

(A) Preparation of 1-Carboxy-4'-methyl diphenylamine.

1-Carboxy-4'-methyl diphenylamine has been prepared according to procedure cited in section-I, part-II page no.**115**

Similarly, other compounds (3_{a-j}) were synthesized. The physical data are recorded in Table No.3_A

(B) Preparation of 1-Carboxy-7-methyl phenothiazine .

1-Carboxy-7-methyl phenothiazine has been prepared according to procedure cited in section-I, part -II page no**115.**

Similarly, other compounds (3_{k-t}) were synthesized. The physical data are recorded in Table No. 3_B.

(C) Preparation of 10-[(carboxymethyl)-sulfanyl]-acetyl-7-methyl-phenothiazine-1-carboxylic acid (IV_b):

A mixture of **1-carboxy-7-methyl phenothiazine** (2.70gm, 0.01M), **chloroacetyl chloride** (1.2 ml 0.012 M) in 10.0 ml of toluene was stirred at 30^0C for 10 to 12 hours.and monitored the reaction by TLC. After completion of the reaction, a solution of **thioglycolic acid** (0.8 ml 0.012 M) in 5.0 ml of toluene is added and refluxed the mixture for 5 hours. The reaction was monitored by TLC. After completion of reaction the excess toluene was distilled out and remaining slurry was treated with hexane. The solid product so obtained was filtered, dried and crystallized from tlouene.**Yield** : 38%, **M.P**. 118°C, (**Required** : **C**, 55.46 %; **H**, 3.85 %; **N**, 3.59 % for $C_{18}H_{15}NO_5S_2$, Found : **C**, 55.50%; **H**, 3.88%; **N**, 3.56%).

TLC solvent system : Ethyl acetate :Hexane = 1.0 : 9.0= 0.46
TLC solvent system : Acetone : Bezene = 8.0 : 1.5= 0.61

(D) Antimicrobial activity of 7/8/9-substituted 10-N-[(carboxymethyl) -sulanyl]-acetyl-phenothizine-1-carboxylic acids(IV_{a-j}):

Antimicrobial activity testing was carried out as described in **Part-I(A), Section-I,** page No. **31** to **34**. The MIC values of test solution are recorded in **Table No. 4_a, 4_b,** and **4_c.**

Result and Discussion:

The products**(IV_{a-j})** have been subjected to antibacterial activity towards ***S. pyogens MTCC-443*, *S. aureus MTCC-96*** **and** ***P. aeruginosa MTCC-441*** **(Gram positive) and** ***E. coli MTCC-442*** **(Gram negative)** bacterial strains and antifungal activity towards ***Aspergillus niger MTCC-282*** **and** ***A. clavatus MTCC-1323*** at different concentrations i.e.: 0, 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values.

The biological activities of the synthesized compounds**(IV_{a-j})** were compared with standard drugs,viz.,**Amplicilline,Chloramphenicol, Ciprofloxacin and Norfloxacin** (antibacterial)**, Greseofluvin, Nystatin** (antifungal)**.**

The results of antimicrobial activity have been depicted on page no. **147** to **149**.

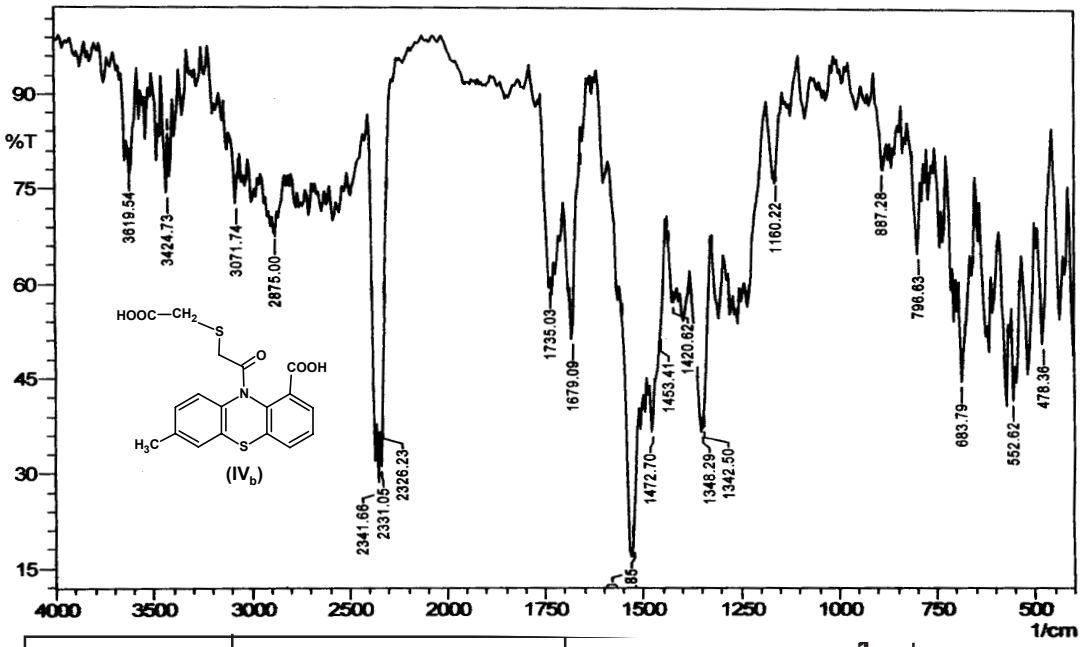
TABLENO.IV_A:PHYSICALCONSTANTSOF 7/8/9-SUBSTITUTED-10-N-(CARBOXYMETHYL)-SULFANYL]-ACETYL-PHENOTHIAZINE-1-CARBOXYLIC ACIDS (IV_{a-j}).

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	Yield % 6	M.P. °C 5	R_f Value R_{f_1} / R_{f_2} 7	% of Nitrogen Required/Found 8
IV_a	H	$C_{17}H_{13}NO_5S_2$	375	46	99	0.50 / 0.55	3.73 / 3.73
IV_b	4-CH_3	$C_{18}H_{15}NO_5S_2$	389	38	118	0.46 / 0.61	3.59 / 3.56
IV_c	3-CH_3	$C_{18}H_{15}NO_5S_2$	389	39	124	0.49 / 0.62	3.17 / 3.56
IV_d	2-CH_3	$C_{18}H_{15}NO_5S_2$	389	32	123	0.61 / 0.59	3.17 / 3.56
IV_e	4-OCH_3	$C_{18}H_{15}NO_6S_2$	405	45	128	0.48 / 0.55	3.45 / 3.41
IV_f	3-OCH_3	$C_{18}H_{15}NO_6S_2$	405	46	118	0.53 / 0.50	3.45 / 3.41
IV_g	2-OCH_3	$C_{18}H_{15}NO_6S_2$	405	43	116	0.52 / 0.59	3.45 / 3.41
IV_h	4-NO_2	$C_{17}H_{12}N_2O_7S_2$	420	49	112	0.52 / 0.61	3.33 / 3.31
IV_i	3-NO_2	$C_{17}H_{12}N_2O_7S_2$	420	39	125	0.60 / 0.52	3.33 / 3.31
IV_j	2-NO_2	$C_{17}H_{12}N_2O_7S_2$	420	32	111	0.55 / 0.45	3.33 / 3.31

TLC solvent system Rf_1: Ethyl acetate : Hexane (2.4 : 7.6)

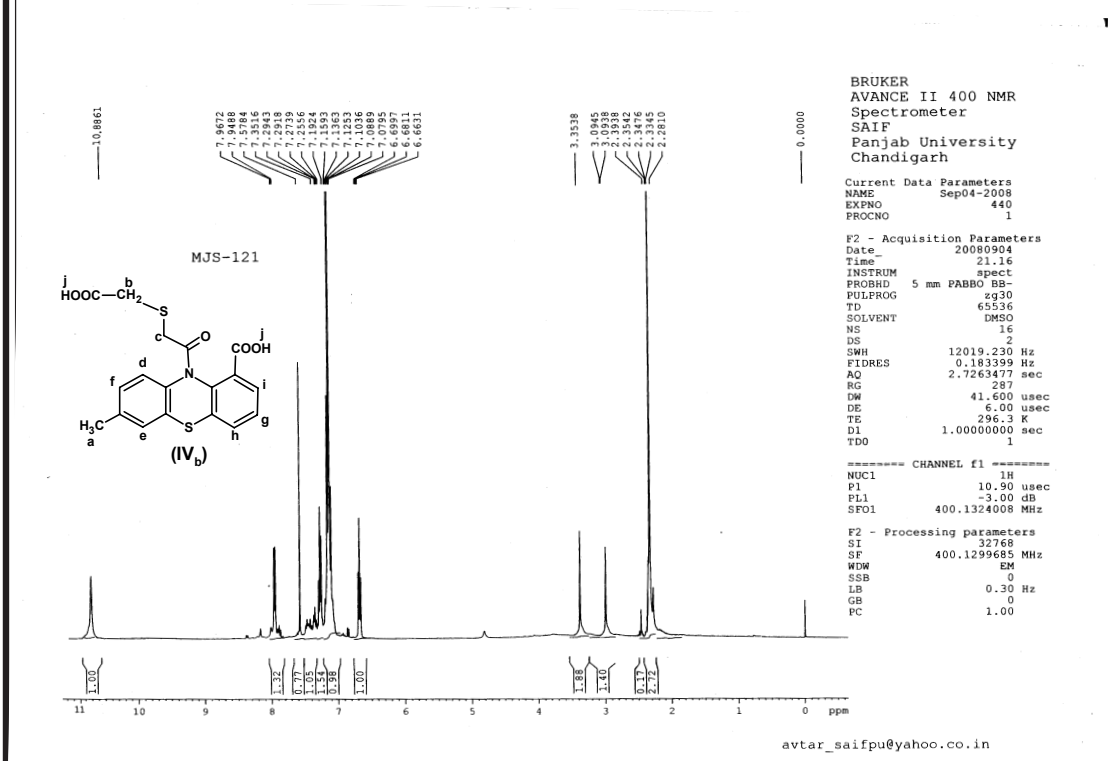
TLC solvent system Rf_2: Acetone : Bezene (0.5 : 9.5)

IR SPECTRA OF 10-N-[(CARBOXYMETHYL)-SULFANYL]-ACETYL-7-METHYL-PHENOTHIAZINE-1-CARBOXYLIC ACID (IV_b):



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (methyl and methylene)	C-H (asym. str., m s)	2952.1	2975 - 2850	92
	C-H (sym. str., m)	2804.0	2900 - 2800	92
	C-H (asym. def., m)	1466.3	1470 - 1435	92
	C-H (sym. def., m)	1367.5	1385 - 1300	92
Aromatic and ring skeletal vibration	C=C & C-C (str., v)	1590.7	1600 - 1450	90
	C-H (i.p. def., m)	1072.4	1150 - 1050	90
	C-H (o.o.p. def., m)	811.5	825 - 800	90
	C-N (str., v)	1273.0	1340 - 1250	907
Carbonyl Keton Acid	C=O (str., s)	1724	1725 - 1700	89
	C=O (str., s)	1687.7		
Halogen Subtitution	C-Cl (str., br.)	757.0 760.0	800-600	90
Sulfur	C-S (str., s)	1196.3 1117.7	1200-1050	90

NMR SPECTRAL STUDY OF 10-N-[(CARBOXYMETHYL)-SULFANYL]-ACETYL-7-METHYL-PHENOTHIAZINE-1-CARBOXYLIC ACID (IV_b):

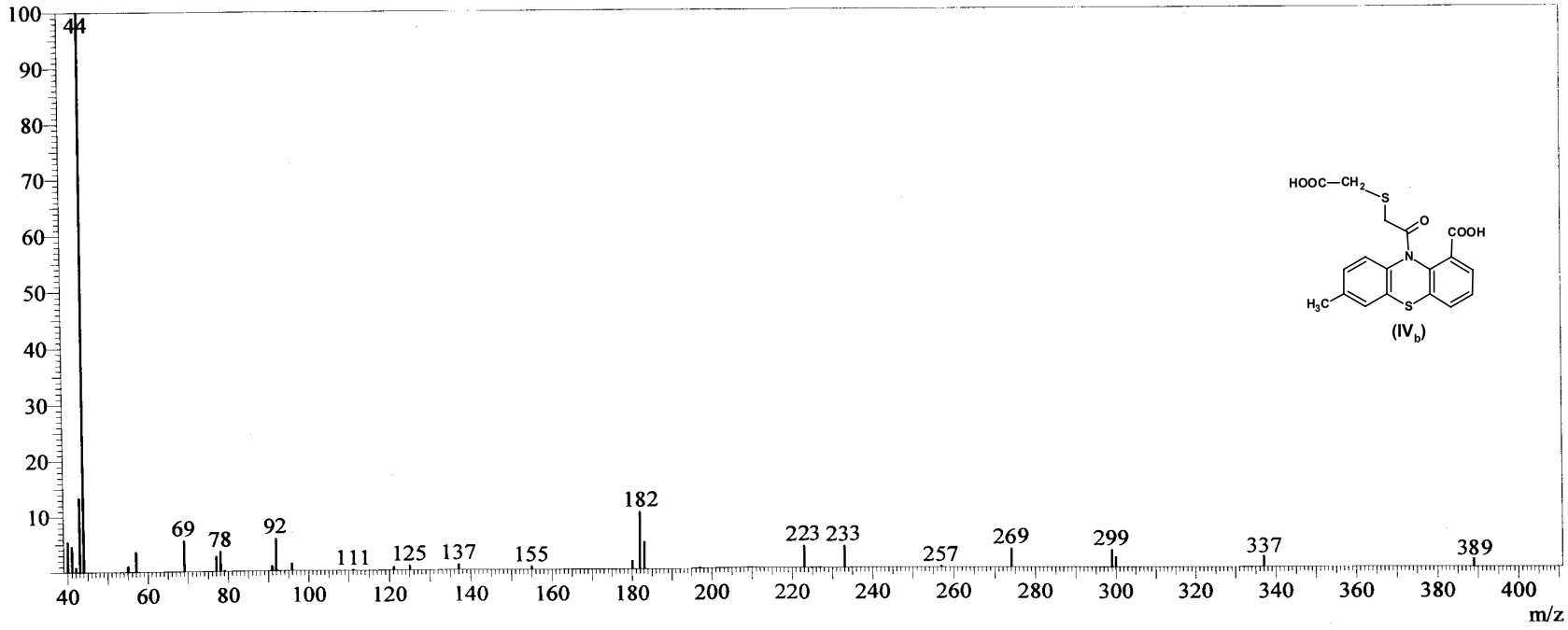


Serial No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	Inference
1	2.2810-2.3938	3H	singlet	- ($C\underline{H}_3$)$_{(a)}$
2	3.0938-3.0945	2H	singlet	- ($C\underline{H}_2$)$_{(b)}$
3	3.3528	2H	singlet	- ($C\underline{H}_2$)$_{(c)}$
4	6.6631-6.6997	1H	multiplet	- Ar-$\underline{H}_{(d)}$
5	7.0795-7.1593	1H	multiplet	- Ar-$\underline{H}_{(e)}$
6	71924	1H	singlet	- Ar-$\underline{H}_{(f)}$
7	7.2556-7.3516	1H	multiplet	- Ar-$\underline{H}_{(g)}$
8	7.5784	1H	singlet	- Ar-$\underline{H}_{(h)}$
9	7.9488-7.9672	1H	singlet	- Ar-$\underline{H}_{(i)}$
10	10.8861	1H	singlet	- COO$\underline{H}_{(j)}$

MASS SPECTRAL STUDY OF 10-N-[(CARBOXYMETHYL)-SULFANYL]-ACETYL-7-METHYL-PHENOTHIAZINE-1-CARBOXYLIC ACID (III_b).

Analyzed by : VIJAY R. RAM
Analyzed : 1/4/2009 11:56:55 AM
Sample Name : MS-12
Sample ID : MS-12
Data File : C:\GCMSsolution\Data\V H SHAH\G-16-2.QGD
C:\GCMSsolution\Data\Project1\DI.qgm
Tuning File : C:\GCMSsolution\System\Tune1\Tune-02-06-2008.qgt

Line#:1 R.Time:11.0(Scan#:1280)
MassPeaks:30 BasePeak:44(13946)
RawMode:Averaged 0.4-13.0(17-1528)
BG Mode:None



(IV_b)

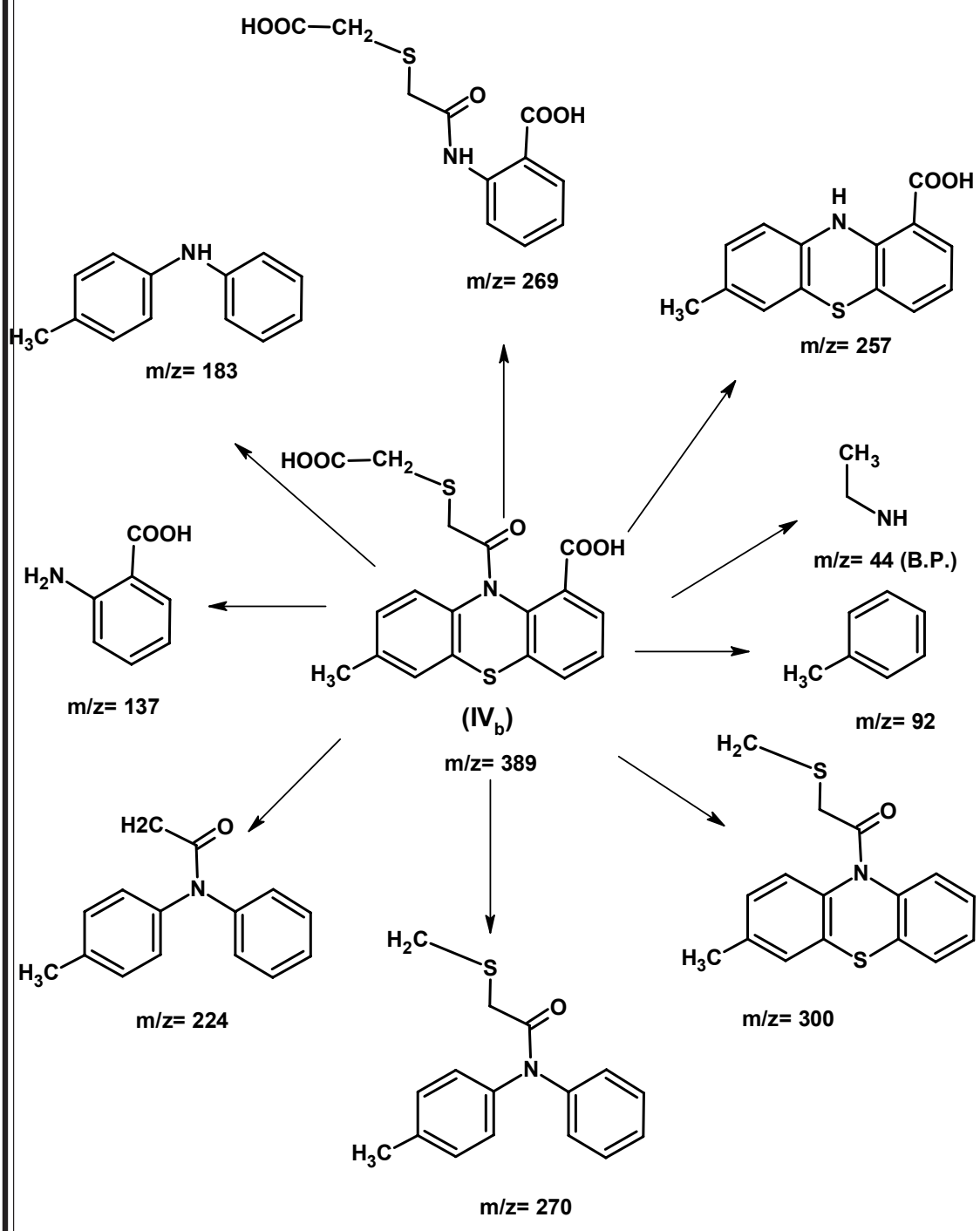

HOOC—CH2
S
O
COOH
NH
m/z= 269
NH
H3C
m/z= 183
COOH
H
N
H3C
S
m/z= 257
HOOC—CH2
S
O
COOH
N
H3C
S
(IVb)
m/z= 389
CH3
NH
m/z= 44 (B.P.)
COOH
H2N
m/z= 137
H3C
m/z= 92
H2C
O
N
H3C
m/z= 224
H2C
S
O
N
H3C
S
m/z= 300
H2C
S
O
N
H3C
m/z= 270

TABLE NO. 4_a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 7/8/9-SUBSTITUTED 10-N-[(CARBOXYMETHYL)-SULFA- NYL]-ACETYL-PHENOTHIAZINE-1-CARBOXYLIC ACIDS (IV_{a-j}).
(Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442					S. aureus MTCC-96				
		5	25	50	100	250	5	25	50	100	250
IV_a	H	-	11	14	17	19	-	10	11	14	15
IV_b	4-CH_3	-	11	14	17	18	-	10	13	16	17
IV_c	3-CH_3	-	10	12	15	16	-	11	13	14	15
IV_d	2-CH_3	-	12	15	17	18	-	12	13	15	16
IV_e	4-OCH_3	-	12	14	15	16	-	13	14	15	16
IV_f	3-OCH_3	-	11	13	14	17	-	12	13	15	17
IV_g	2-OCH_3	-	12	14	15	18	-	12	14	13	17
IV_h	4-NO_2	-	12	13	14	17	-	11	14	15	16
IV_i	3-NO_2	-	12	15	16	19	-	11	13	16	17
IV_j	2-NO_2	-	12	14	17	17	-	11	14	15	17

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

Standard drug	Antibacterial activity									
	IV_a IV_i					IV_e	IV_e IV_g IV_h IV_j	IV_b IV_i		
Ampicilline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
Ciprofloxacin	16	19	21	21	22	17	19	21	22	22
Norfloxacin	18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

TABLE NO. 4_b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 7/8/9- SUBSTITUTED- 10-N-[(CARBOXYMETHYL)-SULFANYL]-ACETYL-PHENOTHIAZINE-1-CARBOXYLIC ACIDS.(IV_{a-j}).
(Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) E. Coli MTCC-443					P. Aeruginosa MTCC-1688				
		5	25	50	100	250	5	25	50	100	250
IV_a	H	-	12	15	16	20	-	10	14	16	17
IV_b	4-CH_3	-	13	15	17	20	-	11	14	15	18
IV_c	3-CH_3	-	14	16	19	21	-	10	12	15	17
IV_d	2-CH_3	-	13	15	16	19	-	12	16	17	18
IV_e	4-OCH_3	-	12	13	15	21	-	11	12	17	19
IV_f	3-OCH_3	-	12	15	18	19	-	10	12	15	18
IV_g	2-OCH_3	-	10	13	15	19	-	10	12	14	20
IV_h	4-NO_2	-	11	12	15	21	-	10	13	15	17
IV_i	3-NO_2	-	12	15	19	21	-	12	14	16	19
IV_j	2-NO_2	-	14	16	17	18	-	11	15	16	18

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

Standard drug	Antibacterial activity									
			IV_c IV_j	IV_c IV_i	IV_a IV_b IV_c IV_h IV_i			IV_d IV_j		IV_g
Ampicilline	14	15	16	19	20	14	15	15	18	20
Chloramphenicol	14	17	23	23	23	14	17	18	19	21
Ciprofloxacin	20	23	28	28	28	20	23	24	26	27
Norfloxacin	22	25	26	27	29	18	19	21	23	23

N.B.(-): No Activity

TABLE NO. 4_C : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 7/8/9-SUBSTITUTED-10-N-[(CARBOXYMETHYL) SULFANYL]-ACETYL-PHENOTHIAZINE-1-CARBOXYLIC ACIDS (IV_{a-j}).
(Different Inhibition Concentration in µg/ml).

Compd No.	R	Antifungal activity (Zones of inhibition in mm)									
		A. niger MTCC-282					A. clavatus MTCC-1323				
		5	25	50	100	250	5	25	50	100	250
IV_a	H	-	19	23	23	24	-	17	20	23	28
IV_b	4-CH_3	-	18	20	20	21	-	18	20	20	21
IV_c	3-CH_3	-	19	19	21	24	-	16	18	21	21
IV_d	2-CH_3	-	18	18	20	23	-	19	20	20	22
IV_e	4-OCH_3	-	18	20	22	23	-	18	21	23	22
IV_f	3-OCH_3	-	15	18	21	22	-	13	16	21	24
IV_g	2-OCH_3	-	16	17	18	22	-	16	18	18	17
IV_h	4-NO_2	-	15	17	21	22	-	16	17	16	17
IV_i	3-NO_2	-	17	20	22	23	-	18	19	23	23
IV_j	2-NO_2	-	15	17	18	20	-	14	17	18	20

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

Standard drug	Antifungal activity									
		IV_a IV_c							IV_a IV_e IV_i	IV_a IV_f
Greseofulvin	19	23	25	25	28	18	21	22	22	24
Nystatin	18	19	24	29	29	18	21	24	25	26

N.B.(-): No Activity

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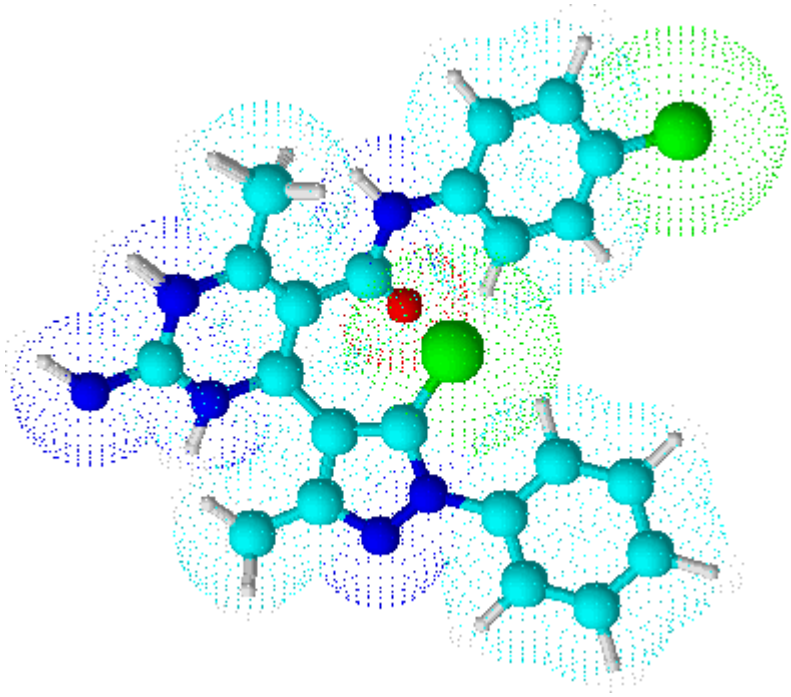


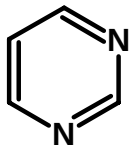
PART-III

STUDIES ON PYRIMIDINES

PART - III
STUDIES ON PYRIMIDINES

INTRODUCTION

Pyrimidine **(92)** is a six membered heterocyclic compound consisting of two nitrogen atoms at one (1) and three (3) positions of heterocyclic ring.

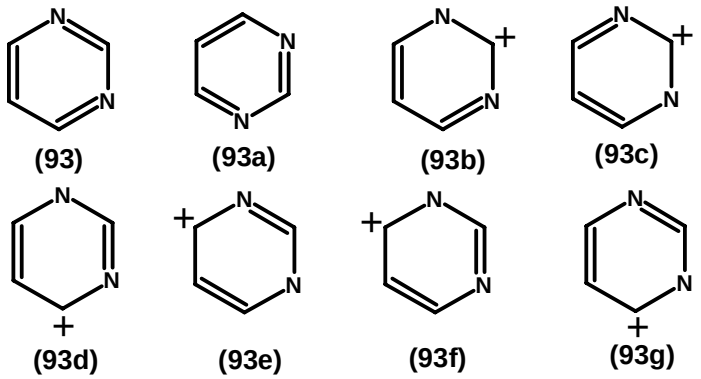


pyrimidine
(92)

Generally pyrimidine derivatives such as 2-hydroxy-substituted-pyrimidine, 2-mercapto-substituted-pyrimidine and 2-amino-substituted-pyrimidine are 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 adverse reduction in susceptible patients and found more potent and less likely to produce side effects and is being widely used[187]. There are several other important groups of pyrimidines with medicinal uses.

Pyrimidine ring carrying various substituents may be built up from two or three aliphatic fragments by the principle synthesis or by a variety of other syntheses, which are complimentary rather than alternative to it. An alternative method of synthesis is the isomerisation or break down of another heterocycles such as hydration of purine, but such methods are rarely used. Pyrimidine is best considered as a resonance hybrid to which the uncharged equivalent Kekule structures **(93)** and **(93a)** and charged structures **(93b)** and **(93g)** contributes. The self consistent π (pi) electron densities required for the ground state of pyrimidine are 0.776, 0.825 and 1.103 for positions 2, 4 and 5 respectively[197]. Despite considerable localization of π (pi) electrons at nitrogen atoms of pyrimidines the ring system is still sufficiently aromatic to possess substantial stability. This has a great advantage in the primary synthesis of pyrimidines.



(93) (93a) (93b) (93c)

(93d) (93e) (93f) (93g)

The first primary synthesis from aliphatic fragments was carried out by Frankland et.al., in 1848. Since then a many distinct primary synthetic methods have been devised[186,188-191,194,196,199,201,202,205]. It is also possible to prepare pyrimidines from other heterocyclic compounds such as pyrrole[187], imidazole[189], isoxazole and oxazole[193,195], pyridine[203], pyrazine[204], 1,3,5-triazine[198], oxazine[200], thiazine[206] by different processes.

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[209].

(b) By the condensation of malonic ester and urea led to formation of pyrimidine[210].

(c) By the condensation of formamidine with phenylazomalononitrile led to formation of 4,5,6-triaminopyrimidine[208].

(d) By the condensation of aromatic aldehydes,ß-ketoester or substituted ß-ketoester with urea or thiourea led to formation of pyrimidines[207].

(e) By the condensation of thiourea and substituted ß-ketoester in pres ence of sodium ethoxide led to formation of 2-mercaptopyrimidines[211].

(f) By the condensation of chalcones with dicyandiamide in presence of piperidine led to formation of pyrimidines[212].

(g) By thermal or microwave irridiation of thiourea and substituted ß-ketoester in presence of dimethylformamide led to formation of substituted tetrahydropyrimidines[213].

(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 $CuCl_2$[214].

(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[215].

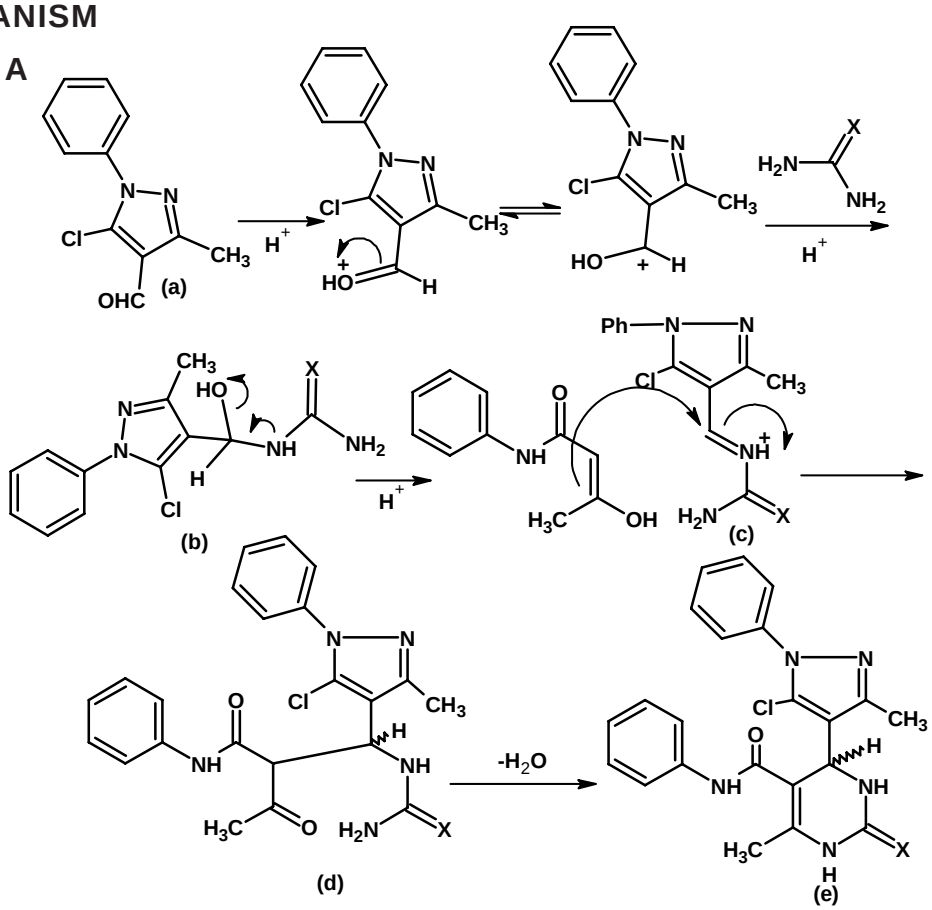
(j) One pot synthesis of aromatic aldehydes,ß-ketoester or substituted ß-ketoester with urea or thiourea led to formation of dihydro pyrimidin-2-(1H)- ones catalysed by Tin (II) chloride ($SnCl_2$)[215].

(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[216].

The mechanism of formation of pyrimidine can be depicted as under:

MECHANISM

PATH - A



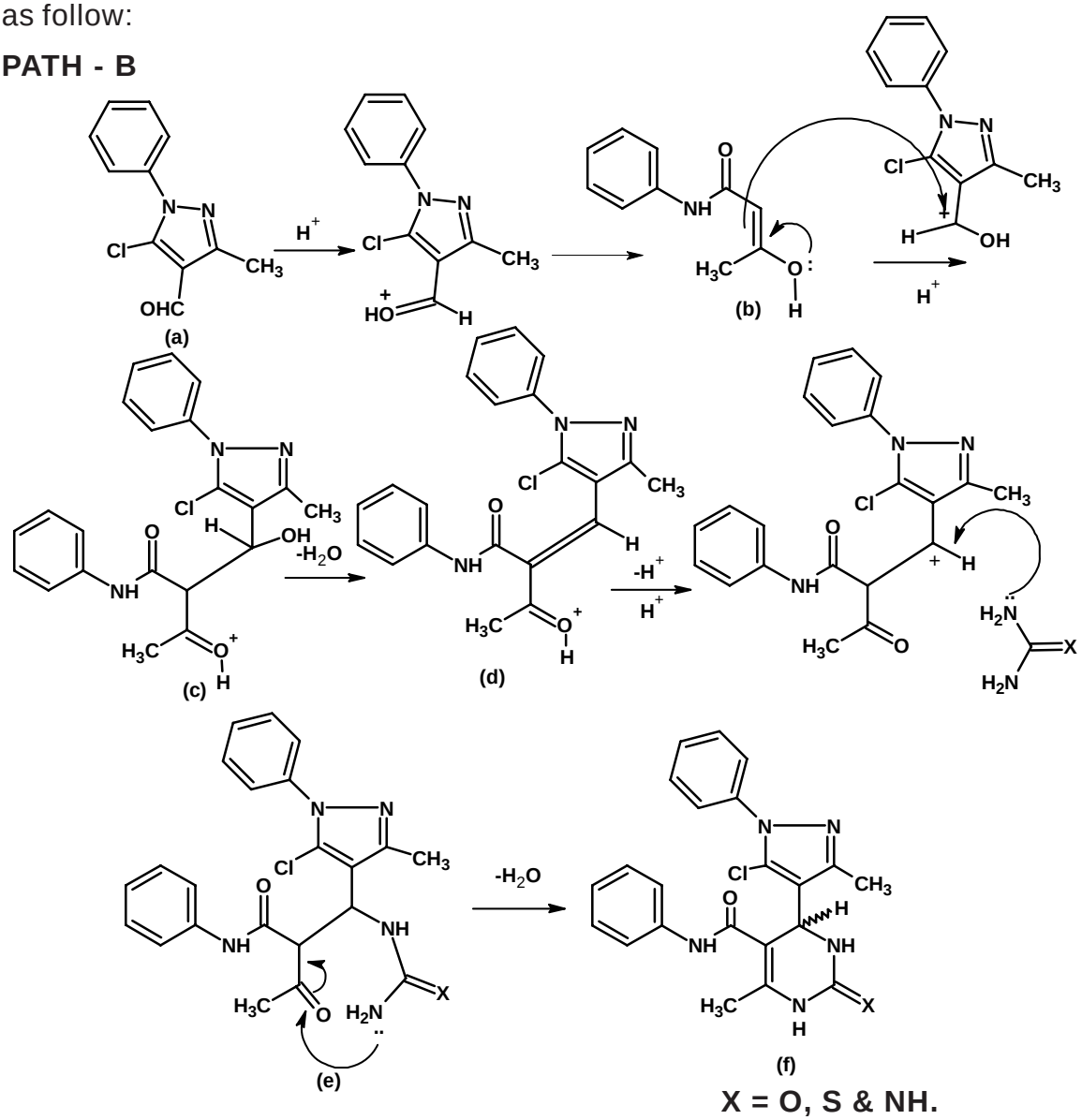
X = O, S & NH.

The present work is explained by considering basic mechanism of multicomponents biginelli reaction. This includes the condensation of substituted benzaldehydes **(a)** with either urea or thiourea or guanidine to form hemiaminal **(b)** with some similarities to the mannich condensation. Hemiaminal **(b)** undergoes dehydration in presence of acid catalyst to produce iminium

cation **(c)** as a intermediate. The enamine (iminium cation) **(c)** generated acts as an electrophile for the nucleophilic addition of keto enol of 4-methyl-oxo-*N*-phenylpentanamide with removal of proton to produce **(d)**. The intermediate **(d)** undergoes intramolecular condensation in presence of acid between oxygen of ketone and amino group of urea or thiourea or guanidine to give the cyclised targeted product **(e)**.

Another mechanism of formation of pyrimidine can also be presented as follow:

PATH - B

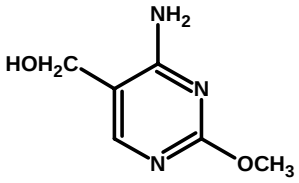


This mechanism includes the condensation of pyrazoline aldehydes **(a)** with keto-enol of 3-oxo-*N*-phenylbutanamide **(b)** to form intermidiate **(c)** with some similarities to the aldol condensation. Intermidiate **(c)** udergoes dehydration in presence of acid catalyst to produce arylidine **(d)**. The condensation of arylidine **(d)** with either urea or thiourea or guanidine

to form hemiaminal intermidiate **(e)**. Hemiaminal intermidiate **(e)** undergoes intramolecular condensation in presence of acid between oxygen of ketone and amino group of urea or thiourea or guanidine to give cyclised targeted product **(f)**.

PHARMACOLOGICAL IMPORTANCE OF PYRIMIDINES

Numerous pyrimidines are well known drugs for variety of diseases. They may be placed in four categories viz. barbiturates, sulfonamides, antimicrobials and antitumor agents. Uracil, thymine, alloxan, vicine and divicine, cytosine, chroticacid, willardiline, tetradotoxine, becimethrian **(94)**, blasticidine **(95)**, cougerotin, amicetin, bamicetin and plicacetin, phleomicine, blemycin and related families **(96)**.



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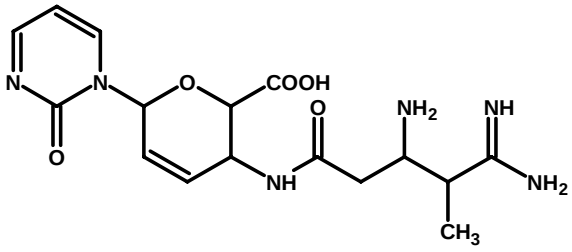


(95)

(96)

Pyrimidine derivatives have wide varieties of usages. Pyrimidine ring system is also present in Vitamin B_2 and folic acid. Pyrimidine ring system having a mercapto group occupy a unique position in medicinal chemistry.[233] These types of derivatives play a vital role in biological processes[219-221] as well as synthetic drugs.[218]

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

(a) **Antithyroid**[231,232] (b) **Antitumor**[224,253-254]

(c) **Antihypertensive**[234,245-246] (d) **Antiinflammatory1**[244,280-281]

(e) **Diuretic**[223] (f) **Antimalarial**[225,227,230]

(g) **Antispasmodic**[226] (h) **Anticonvulsant**[255]

(i) **Antineoplastic**[235,273,333,334] (j) **Anthelmintic**[239]

(k) **Antimicrobial**[222,236-240,247,256-279,331]

(l) **Cardiovascular**[248-250] (m) **Antiviral**[241,270-273,333]

(n) **Platelet aggregation inhibitor**[228,229]

(o) **Antihistamine**[242,243,332] (p) **Anti-HIV**[251,282,330]

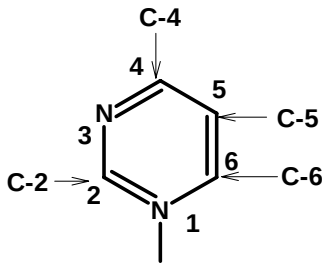
(q) **Antitubercular**[252]

The basis of any rational drug discovery programme is fundamently, the Medicinal Chemistry. Although the synthesis of modified nucleic acids has been a subject of interest for some time, the intense focus on the medicinal chemistry of oligonucleotides dates perhaps to not more than five years. As a result of this, the scope of medicinal chemistry has recently been expanded enormously, but the biological data of supporting the conclusions about synthetic strategies have just begun to emerge.

Modifications in the base, sugar and phosphate moeities of oligonucleotides and oligonucleotide conjugates have been reported. The subjects of medicinal chemical programmes include approaches to create enhanced affinity and more selective affinity for RNA or duplex structures, the ability to cleave nucleic acid targets, enhanced nuclease stability, cellularuptake and distribution, *in vivo* tissue distribution, metabolism and clearance. Although substantial progress in the medicinal chemistry of oligonucleotides has been made in the past three years, it is not yet possible to reach the conclusion about the therapeutic ability of the novel modifications. Preliminary data on effects on nuclease stability and hybridization properties for a few modifications and activity *in vitro* suggest that the next generation of oligonucleotides may display substantially improved potencies and selectivity.

PYRIMIDINE MODIFICATIONS (Nucleotide)

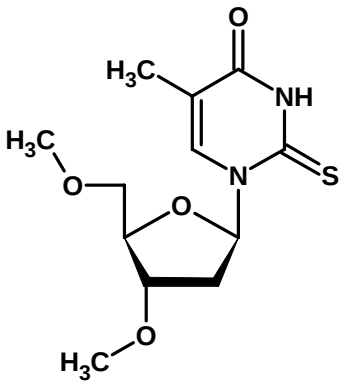
A relatively large number of modified pyrimidines have been synthesized and now incorporated into oligonucleotides and evaluated. The principle sites of modification are C-2, C-4, C-5 and C-6 **(97)**. These and other nucleoside analogues have recently been thoroughly reviewed.[308]



sites of pyrimidine Modification

(97)

In as much as the C2 position is involved in Watson-Crick hybridization, oligonucleotides containing C2 alkyl modified pyrimidines have shown unattractive hybridization characters. However, an oligonucleotide containing 2-thiothymidine **(98)** was found to hybridize well to DNA and, in fact even better to RNA with a thermal melting temperature (ΔT_m) value of 1.5°C/modification. In a different study, oligoribonucleotides with 2'-o-methyl-2-thiouridine **(99)** exhibited a thermal melting temperature (ΔT_m) value of +5.5°C/modification when hybridized against RNA resulting from a highlly preoganized RNA-like C3'-endo conformation (attributed to the combination of 2-thio modification and 2'-o-Mesubstituent). Oligonucleotides with this modification also exhibit better hybridization discrimination for the wobble uracil-guanosine (U-G) base pair formation compared to the normal uracil-adenine (U-A) base pair. This selectivity is a result of weaker hydrogen bonding and increased steric bulk of the 2-thiocarbonyl group.[306]



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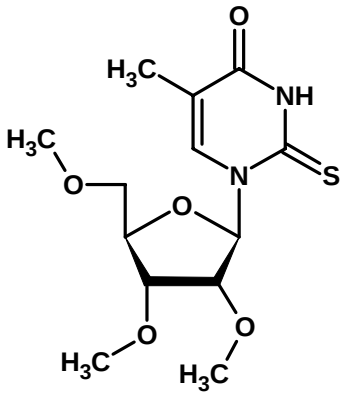
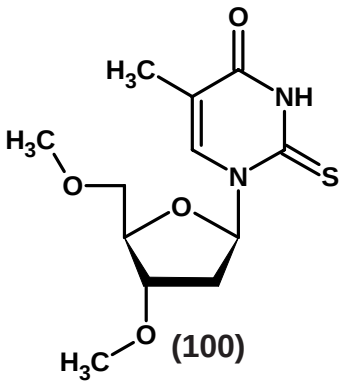


(99)

In contrast, the pyrimidine modifications in 4-position with interesting properties have been reported. 4-Thiopyrimidines **(100,101)** have been incorporated into oligonucleotides with no significant negative effect on hybridization.However, recent studies have shown destabilization in the normal uracil-adenine (U-A) base pair formation and stabilization of the wobble uracil-guanosine (U-G) base pair for 4-thiouridine. A bicyclic and an 4-methoxy analog of cytosine were shown to hybridize with both purine bases in DNA with thermal melting temperature (Tm) values approximately equal to that of natural base pairs. Additionally, a fluorescent base has been incorporated into

oligonucleotides and shown to enhance DNA-DNA duplex stability.[307]



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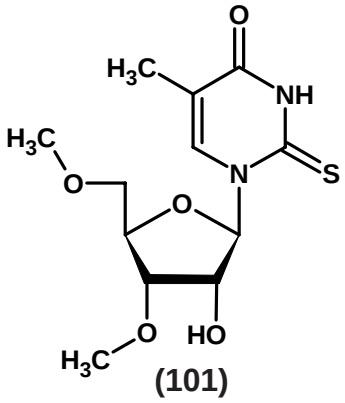
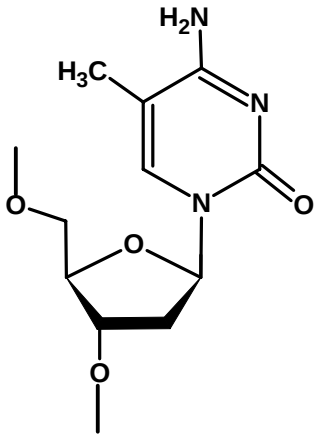


(101)

The pyrimidine modification at C_5 position including halogenated nucleosides have been reported. Although the stability of duplexes may be enhanced by incorporation 5-halogenated uracil containing nucleosides, the occasional mispairing with guanidine and the potential that the oligonucleotide might degrade and release toxic nucleosides analogs cause concern. Oligo-nucleotides containing 5-propynylpyrimidine **(102,103,103)** modification have been shown to enhance the duplex stability thermal melting temperature (ΔT_m = 1.6°C/modification), and support RNase H activity. The 5-heteroaryl-pyrimidines were also shown to increase the stability of duplexes. A more dramatic influence was reported for the tricyclic 2'-deoxycytidine analoges, termed phenoxazine, exhibiting an enhancement of 2-5°C/modification, depending on the positioning of the modified bases.[296]



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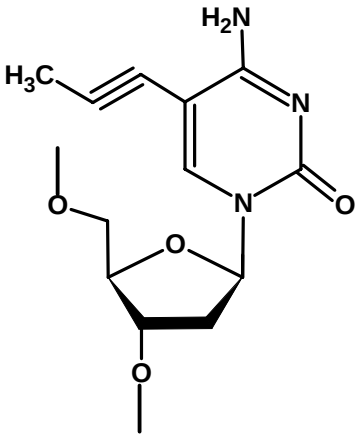

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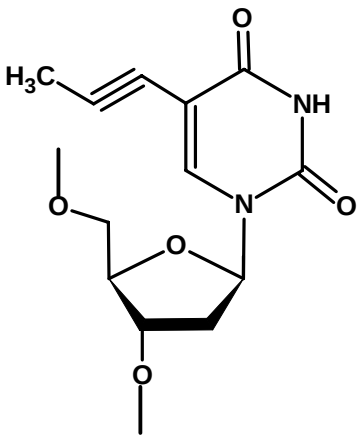
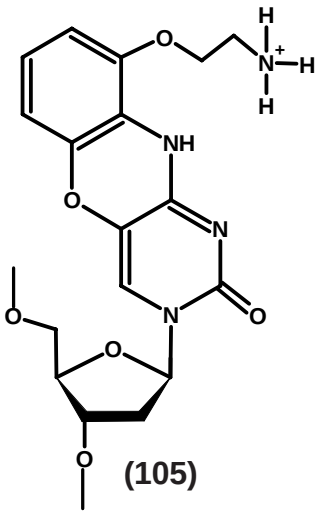


(104)

As expected, modifications in the C_6 position of pyrimidines are highly dupled destabilizing. Oligonucleotides containing 6-azapyrimidines **(105)** have been shown not only to reduce the thermal melting temperature (T_m) value by 1-2°C per modification, but also to enhance the nuclease stability of oligonucleotides and to support E. coli RNase H-induced deradation of RNA targets.[309]



(105)

PYRIMIDINE MODIFICATIONS (Non-nucleotide)

The increasing interest in the early 1970s in properties and use of interferon (IFN) together with the difficulty in producing useful amounts of interferon (IFN) led to the search for agents that would induce IFN in the host. Precedenced at that time for interferon (IFN) inducers included viruses and bacterial wall constituents and entities of large molecular weight such as the polynucleotides. There were also several examples of low molecular weight substances such as certain antibiotics and the antiviral agent, tilorone.[292] In 1976 it was reported that 6-methyl pyrimidinone(2-amino-5-bromo-6-methyl-4-(3H)pyrimidinone, ABMP) induced circulating levels of interferon (IFN) in several animal specis upon oral or intraperitoneal administration.[287] Subsequent structure-activity studies yielded a more potent and less toxic 6-phenyl ananlog called ABPP or bropirimine (2-amino-5-bromo-6-phenyl-4-(3H)pyrimidinone) (figure 1 and Table 1).[285,291] Bropirimine and related 6-aryl analogs were examined extensively for efficacy in virus and tumor models, along with their immunomodulatory properties and overall pharmacological effects.[297]

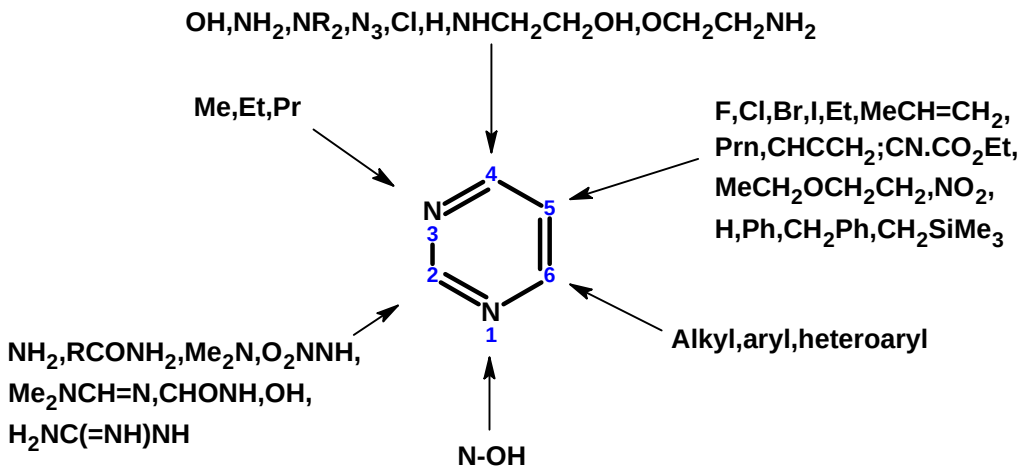


Figure 1 : Preliminary SAR of antiviral activity of pyrimidinones

Table - I

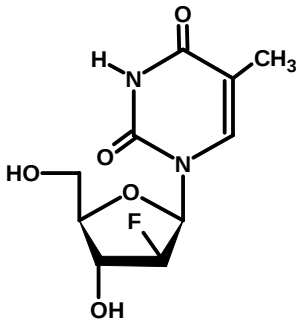
Antiviral Activity

	monosubstituted	Disubstituted	Heterocyclic
Active	2-F,OMe, Me	3,5-OMe	1-Naphthyl
	3-F,OMe, Cl, NO_2	2,5-Cl_2	2-Pyrazyl
	Me, CF_3, $MeCH_2CH_2O$,	3,5-OMe	2,3-pyridyl
	Br,I	3,4-Cl_2	2-Furyl
	4-F, Cl	3,5-Cl_2	
Inactive	4-Me, CN, Butyl,	2,3-OMe	2-Napthyl
	OH,OCH_2ph, OMe		1-Furyl
			4-Pyridyl
			2-Quinoline

As with the polynucleotides, the pyrimidinones exhibited significant activity against interferon (IFN) sensitive viruses such as Semliki Forest virus *in vivo.* However, in addition, they exhibited prophylactic and therapeutic activity upon either local or systemic administration to rodents infected with a variety of DNA viruses, such as the herpes viruses (HSV-1, HSV-2 , CMV and pseudorabies), and when administered intranasally for upper respiratory infections, such as infectious bovine rhinortacheites, influenza A and para-influenza-3. Particularly interestion activity was noted with bropirimine on intravaginal administration in protection against HSV-2 intravaginal infection in guinea pigs, an important model for genital herpes in humans.[298] Bropirimine also exhibited activity when given either intraperitoneally or orally to mice infected with Listera monocytogenes. The efficacy in this model was not abrogated by the addition of anti-interferon (IFN) antibody.[293]

PYRIMIDINES AS ANTITUMOUR AGENTS

A number of other pyrimidine antagonists displaying antitumour activity, in which the base is conjugated to a modified suger ring have been reported. Although D-Arabinofuranosyl uridine (ara-uridine) shows no useful acitivity, and 5-bromo- and 5-iodo-D-arabinofuranosyl uridine inhibit the growth of sarcoma 180 and L1210 cells in culture.[284] Other thymidine analogues with similar activity include 5-azidomethyl-,5-aminomethyl and 5-hydroxymethyl-2'-deoxyu-ridine[286]. 3'-Amino-3'-deoxy thymidine[288] and 3'-amino-2',3'-dideoxycy-tidine[182] also posses strong activity against L1210 leukaemia 2'-Deoxy-2'-fluoro-5-methyl-1-B-D-arabinofuranosyluracil (FMAU; 40) is highly active against arabinofuranosyl cytidine (ara-C) resistant L1210 and P815 cell lines both *in vitro* and *in vivo*.[295] 2-B-D-Ribofuranosylthiazole-4-carboxamide (Tiazofurin; 41) has aroused much interest recently for its activity against solid tumour such as lung carcinoma. It is metabolized to an analogue of NAD in which the thiazole-4-carboxamide moiety replaces the nicotinamide ring. However, it also depresses the synthesis of DNA and RNA, and thus merits inclusion as an antagonist of normal purine and pyrimidine metabolism.[294]



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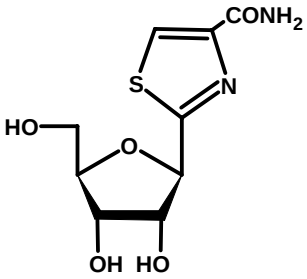


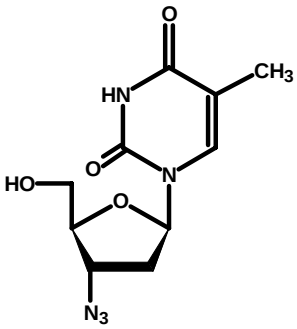
(107)

PYRIMIDINES AS ANTI-HIV AGENTS

The strategy of designing nucleoside analogs that are selective for viral DNA polymerases is the most well-studied and successful approch to viral chemotherapy, and has led to the discovery of several clinically useful antiviral drugs. This strategy, however, has inherent limitations. Human DNA polymerases also required dNTP's and the chemical mechanisms of polymerization by the viral and human enzymes are similar. Nucleoside analogs often

have significant host toxicity that is probably related to inhibition of host cell DNA synthesis. Nevertheless, these compounds constitute the major class of antiviral drugs, and this approach is likely to yield additional active compounds in the near future. For the long term, however, other strategies may ultimately lead tonmmore selective agent withn lower toxicity.

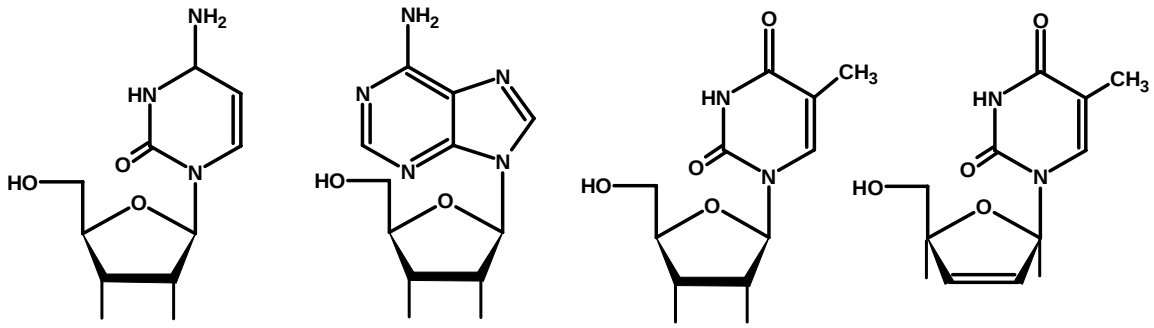
Obviously, the key to design analogue with a lower affinity for the host enzyme than the viral enzyme, which requires that there be structural differences between the enzyme active sites. For reverse transcriptase, the most well studied inhibitor is 3'-azido-3'-deoxythymidine (AZT; 42), which is currently used clinically to treat AIDS.[317,318]



(108)

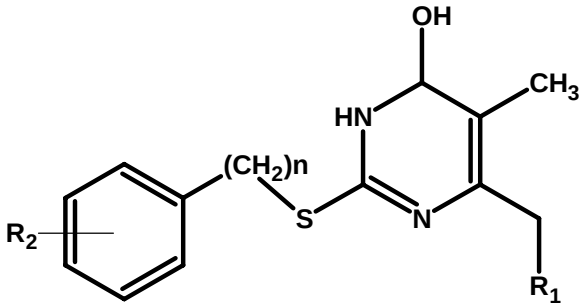
3'-azido-3'-deoxythymidine (AZT) inhibits HIV reverse transcriptase with an IC50 of 40nM[300], but is 100-300 times less active against mammalian DNA polymerase α and DNA polymerase γ. The reason for this selectivity is not clear since 3'-azido-3'-deoxythymidine (AZT) is a chain terminator for mammalian DNA polymerases and inhibits normal cellular DNA synthesis.[290] Several other dideoxynucleoside analogs have been shown to be potent inhibitors of HIV replication *in vitro*.[301,305] In general, these compounds have the same mechanism of action as 3'-azido-3'-deoxythymidine (AZT), that is, intracellular conversion to the triposphate derivative and subsquent inhibition of HIV reverse transcriptase.

Some of these compounds are simply analogs of the nautral 2'-deoxynucleoside in which the 3'-OH group has been replaced with a hydrogen, such as 2',3'-dideoxycytidine**(109)**, 2',3'-dideoxyadenosine**(110)** and 2',3'-dideoxythymidine **(111).** Other analogs contain a 2'-3' double bond, such as 2'3'-didehydro-2',3'-dideoxythymidine **(112).** Several related analogs with other modifications to the ribose ring or the heterocyclic base moiety have also been reported to have activity against HIV or HIV reverse transcriptase.[195,196]



(109) **(110)** **(111)** **(112)**

R. A. Nugent et. al.,[310] have synthesized pyrimidine thioethers **(113)** and evaluated for inhibitory properties against wild-type HIV-1 reverse transcriptase.



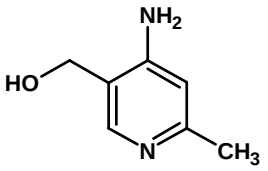
R_1= 2,6-$(Cl)_2$, 4-F
R_2=4-OCH_3,4-NO_2, 4-CN, 4-Br

(113)

PYRIMIDINE AS ANTIBIOTICS :

There are few examples of pyrimidine antibiotics. The simplest of all is bacimethrin (5-hydroxymethyl-2-methoxypyrimidin-4-amine) (**114**), which is active against several staphylococcal infections[311]. Gourgetin (**115**), a cytosine derivative is active against mycobacteria as well as several Gram-positive and Gram-negative bacteria[312]. There are more derivatives of cytosine,namely amicetin (**116**) and plicacetin (**117**), which exhibit activity against acid fast and Gram-positive bacteria as well as some other organisms[311].Puromycin has a wide spectrum of antitrypanosomal activity. Aminogly- coside antibiotics phleomycin , bleomycin and related families are wide-spectrum antibiot-

ics containing the pyrimidine ring. Another antibiotic tubercidine is reported to exhibit antitumour properties[312]. In addition, they have antineoplastic activity. Bleom ycin is already in clinical use against certain tumours like Hodgkin's lymphoma and disseminated testicular cancer[313].



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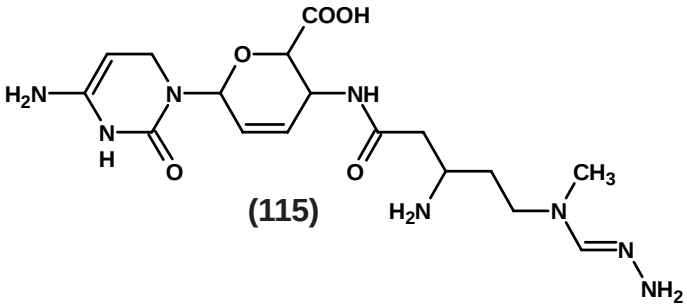

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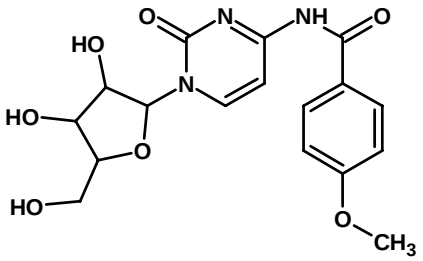

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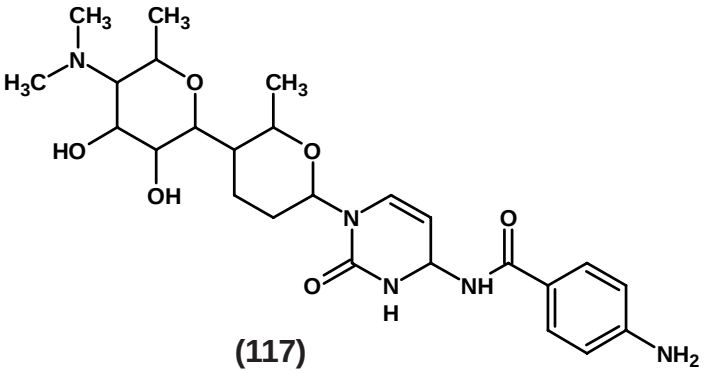
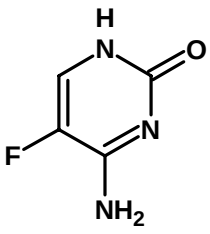


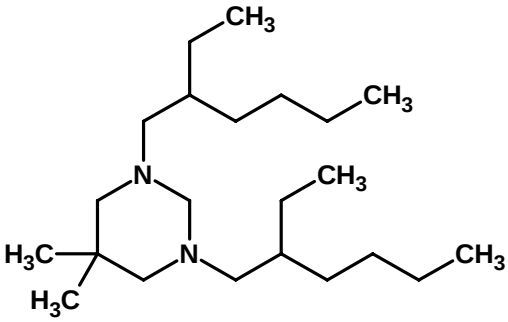
(117)

PYRIMIDINE AS ANTIFUNGALS :

Pyrimidines also exhibit antifungal properties. Flucytosine (**118**)[314] is a fluorinated pyrimidine used as nucleosidal anti fungal agent for the treatment of serious systemic infections caused by susceptible strains of candida and cryptococcus[315].Hexitidine[316] (**119**) is mainly used for the treatment of aphthous ulceration.



(**118**)



(**119**)

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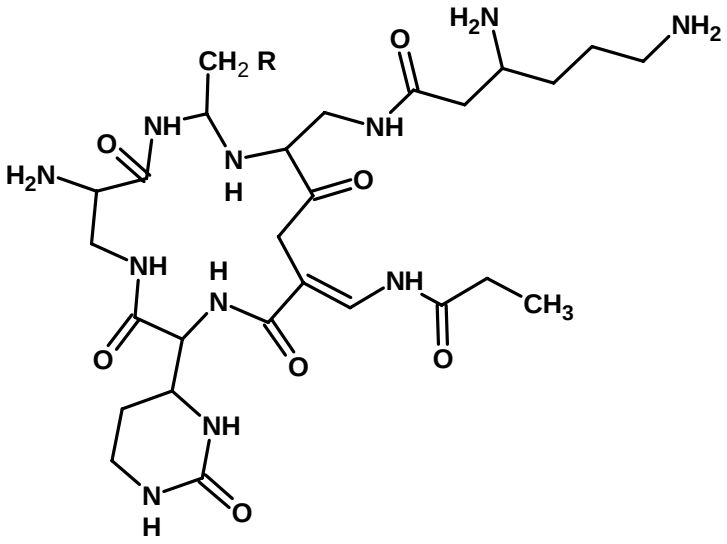
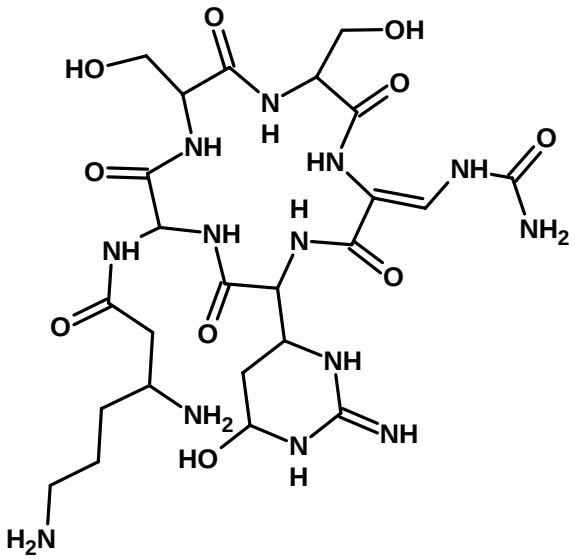
PYRIMIDINE AS ANTITUBERCULAR:

Capreomycin (**120**) produced by *Streptomyces capreolus* is a second-line bacteriostatic antituberculin drug containing pyrimidine[317,318].



(120)

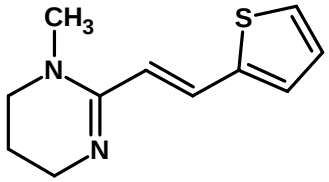
Viomycin (**121**) is more tuberculostatic than *p*-aminosalicyclic acid. It is effective in the treatment of experimental tuberculosis



(**121**)

PYRIMIDINE AS ANTHELMENTICS :

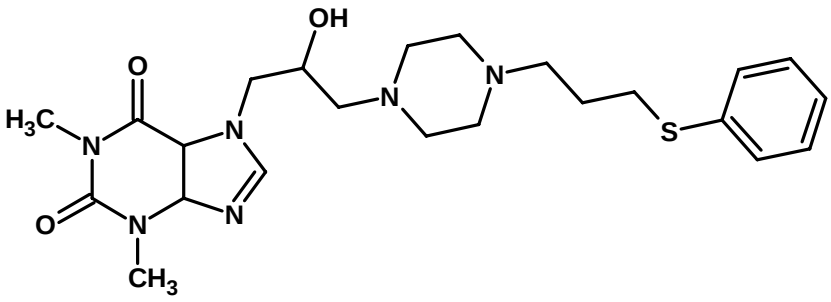
These drugs have the ability of ridding the body of parasitic worms. Pyrantel pamoate (**122**) is a depolarizing neuromuscular blocking agent that causes spastic paralysis in helminthes and is employed in the treatment of infestations caused by pinworms and roundworms[319].



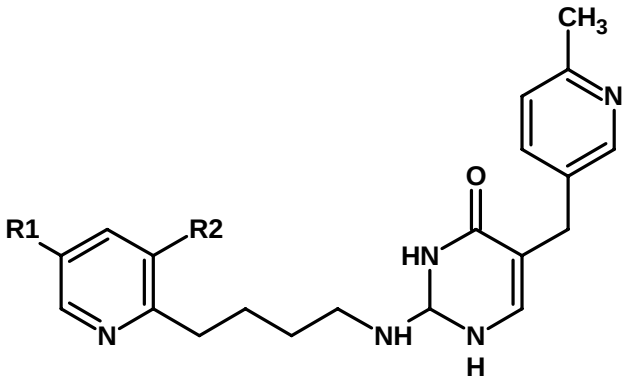
(122)

PYRIMIDINE AS ANTIHISTAMINIC :

Taziphylline (**123**) is ten times more potent than either astemizole or terfenadine in its affinity for H1-histaminebinding site and appears to be devoid of CNS activity[320].Another pyrimidine containing antihistaminic drug, temelastine (**124a**) is comparable to mepyramine[321]. Radiolabelled studies have indicated that it does not penetrate the CNS appreciably. Icotidine (**124b**) , a structural analogue of temelastine lacks CNS activity and is a dual antagonist of both H1 and H2 receptors[322].



(123)

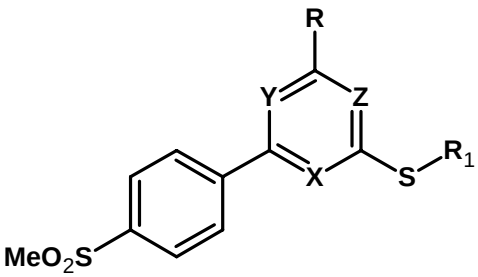


(124a), R_1=Br, R_2 = -CH_3

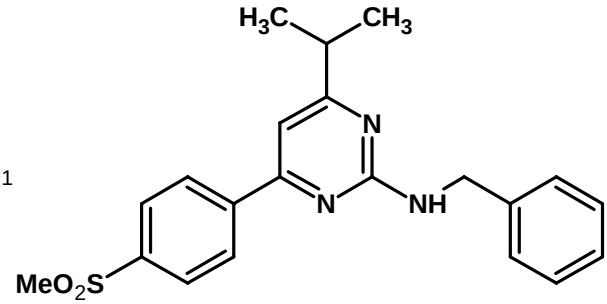
(124b), R_1=H, R_2 = -OCH_3

A family of trisubstituted pyrimidines has been described as selective COX-2 inhibitors. To explore the usefulness of pyrimidine derivatives as potential NSAIDs. Aurelio Orjales et. al.,[323] have synthesized novel pyrimidine derivatives **(125)** and **(126).**

In vitro biological evaluation of these compounds has provided information to determine the structural features necessary for COX-2 inhibitory activity.

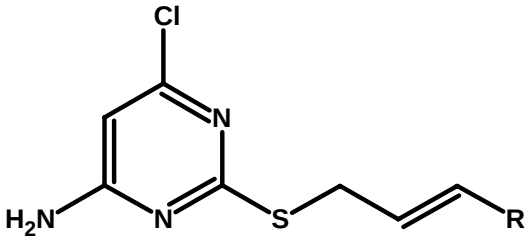


(125) Y=CH; X=Z=N



(126) Y=Z=N; X=CH

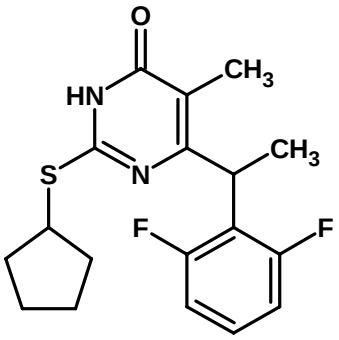
F. Manetti et. al.,[324] have synthesized novel pyrimidines **(127)** with nanomolar activity toward recombinant HIV-1 and mutant HIV-1 strains.



R = Ph, Me, CO_2Me, $CONMe_2$, $CONEt_2$

(127)

D.Rotili et al.,[325] have synthesized 6-substituted-[1-(2,6-difluorophenyl]pyrimidinones **(128,129)** and tested against endogenous, nontelomeric reverse transcriptase (endo-RT) in human differentiating cell systems to investigate their antiproliferative and cytodifferentiating activity.



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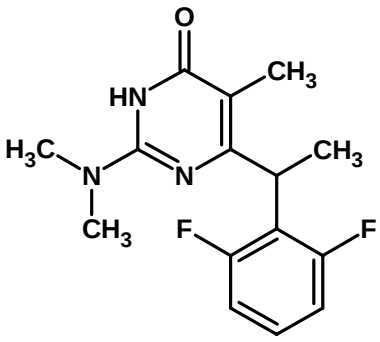
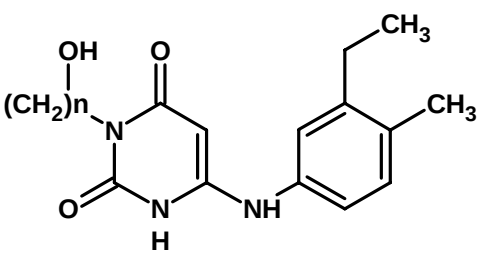
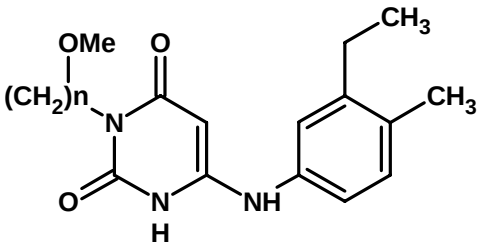


(129)

R. Storer et al.,[326] have synthesized 3-substituted-6-(3-ethyl-4-methylanilino)uracils **(130,131)** screened for their capacity to inhibit the replication-specific bacterial DNA plymerase IIIC (pol IIIC) and the growth of Gram+ bacteria in culture.

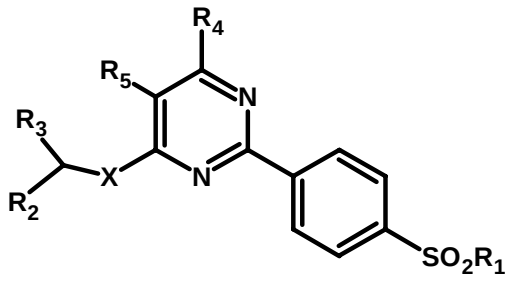


(130) n = 2,3,4.



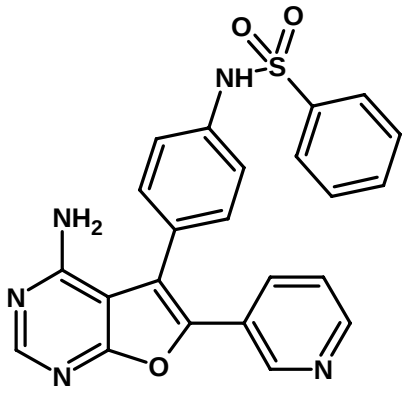
(131) n = 2,3,4.0

A.Orjales et al.,[327] have synthesized new series of 2-(4-methylsulfonylphenyl)and 2-(4-sulfamoylphenyl)pyrimidines **(132)** and evaluated for their ability to inhibit cyclooxygenase-2 (COX-2).



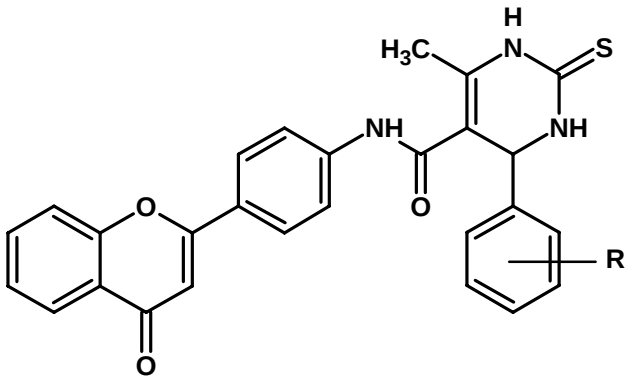
(132)

Y.Miyazaki et al.,[328] have synthesized 4-amino-5,6-furo [2,3-d] pyrimidines **(133)** and identified as inhibitors of glycogen synthase kinase-3B (GSK-3B).



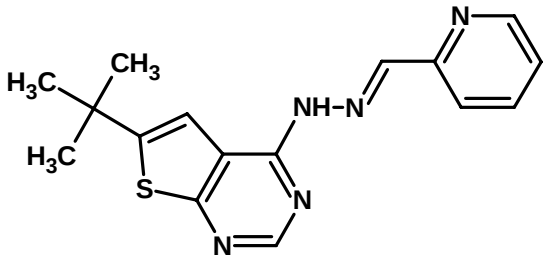
(133)

Recently, S.M.Bhalekar et al.,[329] have synthesized cromon pyrimidines **(134)** and reported their anitbectarial activity



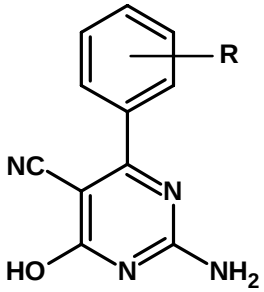
(134)

H. Takao et al.,[335] have synthesized 2-Pyridinecarboxaldehyde [6-(tert-butyl)thieno[2,3-d]pyrimidine-4-yl]hydrazone derivatives **(135)** and identified as cyclin-dependent kinase 4 inhibitors



(135)

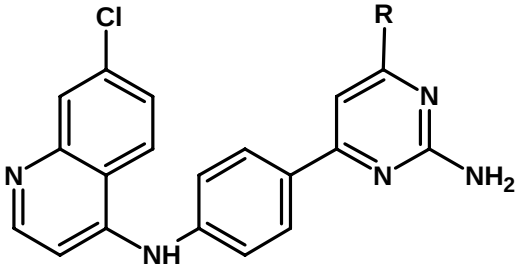
M.B.Deshmukh et al.,[336] have synthesized 2-amino-5cyano-6-hydroxyl-4-aryl pyrimidines **(136)** and reported their antibacterial activity.



(136)

R= -Cl, -NO_2, -OCH_3, -OH

M.Sharma et al.,[337] have synthesized quinolinyl pyrimidines**(137)** and evaluated for antitubercular and antimalarial activity.



(137)

R= 4-isopropyl phenyl, 3-pyridyl, 4-thiomethyl

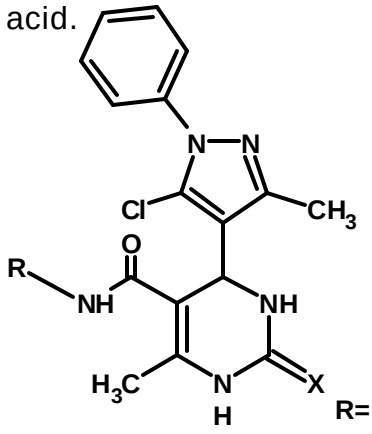
In view of procuring highly potent biodynamic agents and after reviewing recent literature survey on oxo / thio / iminopyrimidines for their various methods of synthesis and different pharmacological activities, synthesis of pyrimidines have been undertaken which can be summarized in the following one section as follows:

SECTION- I : PREPARATION AND BIOLOGICAL EVALUATION OF 4-(5'-CHLORO-3'-METYL-1'-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-OXO-/THIO-/IMINO-5-N-SUBSTITUTED-PHENYLCARBAMOYL-1,2,3,4-TETRAHYDRO PYRIMIDINES.

SECTION - III

PREPARATION AND BIOLOGICAL EVALUATION OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-OXO/-THIO/-IMINO-5-N-SUBSTITUTED-PHENYLCARBAMOYL-1,2,3,4-TETRAHYDRO PYRIMIDINES ($V_{a-d'}$).

Keeping in view of wide spectrum **biodynamic activities**[116-174] of pyrimidines and with a view to have potent therapeutic agents, the synthesis of **4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-6-methyl-2-oxo-/thio-/imino-5-N-substituted phenyl carbamoyl-1,2,3,4-tetrahydro pyrimidines ($V_{a-d'}$)** have been synthesized by the condensation of different ***N*-substituted phenyl-2-oxobutanamides, 5-chloro-3-methyl-1-N-phenyl-pyrazole-4-carbaldehyde**, and **urea/thiourea/ guanidine** in the presence of catalytical amount of acid.



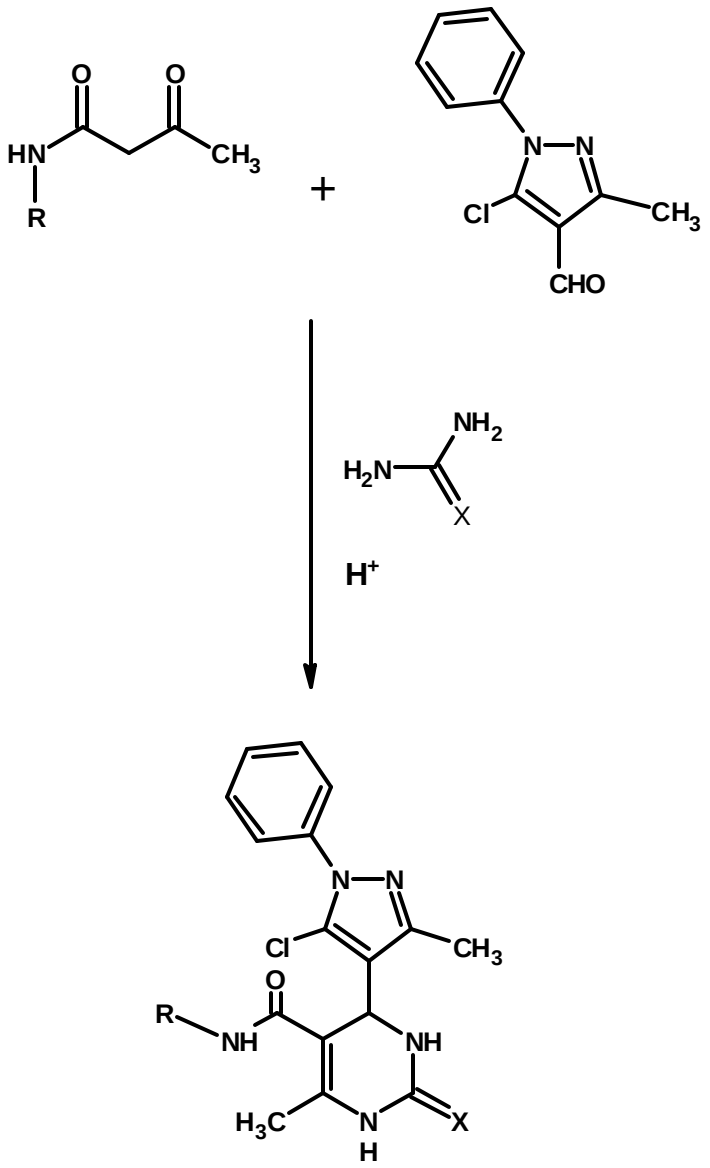
($V_{a-d'}$) **R= Substututed phenyl**

X= O/ S/ NH

The constitution of the products **($V_{a-d'}$)** have been delineated by **elemental analyses, IR, PMR** and **Mass** spectral data.

The products **($V_{a-d'}$)** were assayed for tfor their ***in vitro*** biological assay like antibacterial activity towards ***S. pyogens MTCC-443*, *S. aureus MTCC-96* and *P. aeruginosa MTCC-441* (Gram positive) and *E. coli MTCC-442* (Gram negative)** bacterial strains and antifungal activity towards ***Aspergillus niger MTCC-282* and *A. clavatus MTCC-1323*** at different concentrations i.e.: 0, 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds **($V_{a-d'}$)** were compared with standard drugs,viz., **Amplicillin, Chloramphenicol, Ciprofloxacin and Norfloxacin** (antibacterial)**, Greseofluvin, Nystatin** (antifungal)**.**

REACTION SCHEME



($V_{a\text{-}d'}$)

R=Substituted phenyl

X= O / S / NH

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-OXO/-THIO/-IMINO-5-N-SUBSTITUTED PHENYL CARBAMOYL-1,2,3,4-TETRAHYDRO PYRIMIDINES ($V_{a-d'}$)

Preparation of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-6-methyl-2-oxo/-thio/-imino-5-N-(p-tolyl)-1,2,3,4-tetrahydro pyrimidine (V_b)/(V_l)/(V_v):

(A) Preparationof N-(4-methylphenyl)-3-oxobutanamide (1_b).

N-(4-methylphenyl)-3-oxobutanamide has been prepared according to the procedure cited in **Part - I, Section - I, Page No.28**

(B) (i) Preparation of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-6-methyl-2-oxo-5-N-(p-tolyl)-1,2,3,4-tetrahydro pyrimidine (V_b).

A mixture of ***N*-(4-methyl phenyl)-3-oxobutanamide** (2.22 gm, 0.01M), **5-chloro-3-methyl-1-N-phenyl-pyrazole-4-carbaldehyde** (2.20 gm, 0.01 M), **urea** (0.90 gm, 0.015 M) and catalytic amount of HCl in dimethylformamide (10 ml) was heated under reflux condition for 8 to10 hrs. The reaction mixture was kept at room temperature for 24 hrs. The yellow crystalline product so obtained was filtered and crystallized from dimethylformamide. **Yield** : 55 %, **M.P**. : 232°C, (Required : **C**, 63.31%; **H**, 5.04%; **N**, 16.05% for $C_{23}H_{22}N_5ClO_2$ Found : **C**, 63.65 %; **H**, 5.03 %; **N**, 15.97 %).

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (4.0 : 6.0) = 0.57.
TLC solvent system R_{f_2} : Methanol : Chloroform (1.0 : 9.0) = 0.63.

Similarly, other compounds **(V_{a-j})** were synthesized. The physical data are recorded in **Table-V_A**.

(ii) Preparation of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-6-methyl-2-thio-5-N-(p-tolyl)-1,2,3,4-tetrahydro pyrimidine (V_l).

A mixture of ***N*-(4-methylphenyl)-3-oxobutanamide** (2.22 gm, 0.01M), **5-chloro-3-methyl-1-N-phenyl-pyrazole-4-carbaldehyde** (2.20 gm, 0.01 M), **thiourea** (1.14 gm, 0.015 M) and catalytic amount of HCl in dimethylformamide (15 ml) was heated under reflux condition for 10 to12 hrs. The reaction mixture was kept at room temperature for 24 hrs. The yellow crystalline product so obtained was filtered and crystallized from dimethylformamide. **Yield** : 50 %, **M.P**. : 224°C, (Required : **C**, 61.06%; **H**, 4.86%; **N**, 15.49% for $C_{23}H_{22}N_5ClOS$ Found : **C**, 61.02 %; **H**, 4.83 %; **N**, 15.40 %).

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (4.0 : 6.0) = 0.47.
TLC solvent system R_{f_2} : Methanol : Chloroform (1.0 : 9.0) = 0.53.

Similarly, other compounds **(V_{k-t})** were synthesized and the physical data are recorded in **Table-V_B**.

(iii) Preparation of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl) -6-methyl-2-imino-5-N-(p-tolyl)-1,2,3,4-tetrahydro pyrimidine (V_v).

A mixture of ***N*-(4-methylphenyl)-3-oxobutanamide** (2.22 gm, 0.01M), **5-chloro-3-methyl-1-N-phenyl-pyrazole-4-carbaldehyde** (2.20 gm, 0.01 M), **guanidinehydrochloride** (1.43 gm, 0.015 M) and catalytic amount of HCl in dimethylformamide (15 ml) was heated under reflux condition for 12 to14 hrs. The reaction mixture was kept at room temperature for 24 hrs. The product so obtained was filtered and crystallized from dimethylformamide. **Yield** : 52 %, **M.P**. : 244°C, (Required : **C**, 63.45%; **H**, 5.28%; **N**, 19.31% for $C_{23}H_{23}N_6ClO$ Found : **C**, 63.43 %; **H**, 5.25 %; **N**, 19.25 %).

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (4.0 : 6.0) = 0.51.
TLC solvent system R_{f_2} : Methanol : Chloroform (1.0 : 9.0) = 0.60.

Similarly, other compounds **($V_{u-d'}$)** were synthesized and the physical data are recorded in **Table-V_C**.

(D) Antimicrobial activity of 4-(5'-chloro-3'-methyl-1'-N-phenyl-pyrazol-4'-yl)-6-methyl-2-oxo-/thio-/imino-5-N-substituted phenyl-carbamoyl-1,2,3,4-tetrahydro pyrimidines ($V_{a-d'}$):

Antimicrobial activity testing was carried out as described in **Part - I, Section - I, page No. 31-33.** The **MIC** values of test solution are recorded in **Table No.** $5_a, 5_b, 5_c, 5_d, 5_e, 5_f, 5_g, 5_h$ and 5_i.

Result and Discussion:

The products**($V_{a-d'}$)** have been subjected to antibacterial activity towards ***S. pyogens MTCC-443*, *S. aureus MTCC-96*** **and** ***P. aeruginosa MTCC-441*** **(Gram positive) and** ***E. coli MTCC-442*** **(Gram negative)** bacterial strains and antifungal activity towards ***Aspergillus niger MTCC-282*** **and** ***A. clavatus MTCC-1323*** at different concentrations i.e.: 0, 5, 25, 50, 100, 250 (µg/ml) for their MIC (Minimum Inhibitory Concentration) values.

The biological activities of the synthesized compounds**($V_{a-d'}$)** were compared with standard drugs,viz.,**Amplicilline,Chloramphenicol, Ciprofloxacin and Norfloxacin** (antibacterial)**, Greseofluvin, Nystatin** (antifungal)**.**

The results of antimicrobial activity have been depicted on page no. **194** to **202**.

TABLE NO. V_A : PHYSICAL CONSTANTS OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-OXO-5-N-SUBSTITUTED PHENYLCARBAMOYL-1,2,3,4-TETRAHYDROPYRIMIDINES (V_{a-j}).

Comp. No.	R	Molecular Formula	M.W.	Yield %	M.P. °C	R_f Value R_{f_1} / R_{f_2}	% of Nitrogen Cal/ Found
1	2	3	4	5	6	7	8
V_a	3-CH_3-C_6H_4	$C_{23}H_{22}ClN_5O_2$	435.90	51	212	0.53/ 0.59	16.05 /15.97
V_b	4-CH_3-C_6H_4	$C_{23}H_{22}ClN_5O_2$	435.90	55	232	0.57 / 0.63	16.05 / 15.97
V_c	2,5-$(CH_3)_2C_6H_3$	$C_{24}H_{24}ClN_5O_2$	449.00	59	191	0.59 / 0.66	15.55/ 15.47
V_d	4-OCH_3-C_6H_4	$C_{23}H_{22}ClN_5O_3$	451.00	60	259	0.49 / 0.53	15.49 / 15.40
V_e	3-Cl-C_6H_4	$C_{22}H_{19}Cl_2N_5O_2$	456.30	58	212	0.51/ 0.58	15.34 /15.26
V_f	4-Cl-C_6H_4	$C_{22}H_{19}Cl_2N_5O_2$	456.30	57	253	0.61/ 0.68	15.34 /15.26
V_g	2-F-C_6H_4	$C_{22}H_{19}ClFN_5O_2$	439.80	49	203	0.56 / 0.61	15.91 / 15.85
V_h	4-F-C_6H_4	$C_{22}H_{19}ClFN_5O_2$	439.80	59	231	0.52 / 0.59	15.91 / 15.85
V_i	3-NO_2-C_6H_4	$C_{22}H_{19}ClN_6O_4$	466.80	49	259	0.51/ 0.57	17.86 / 17.90
V_j	4-NO2-C6H4	$C_{22}H_{19}ClN_6O_4$	466.80	38	278	0.57/ 0.62	17.99 / 17.90

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (4.0 : 6.0)

TLC solvent system R_{f_2} : Methanol : Chloroform (1.0 : 9.0)

TABLE NO. V_B : PHYSICAL CONSTANTS OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-THIO-5-N-SUBSTITUTED PHENYLCARBAMOYL-1,2,3,4-TETRAHYDRO PYRIMIDINES (V_{k-t}).

Comp. No.	R	Molecular Formula	M.W.	Yield %	M.P. °C	R_f Value R_{f_1} / R_{f_2}	% of Nitrogen Cal/ Found
1	2	3	4	6	5	7	8
V_k	3-CH_3-C_6H_4	$C_{23}H_{22}ClN_5OS$	451.9	51	212	0.43 / 0.59	15.49 / 15.40
V_l	4-CH_3-C_6H_4	$C_{23}H_{22}ClN_5OS$	451.90	50	224	0.47 / 0.53	15.49 / 15.40
V_m	2,5-$(CH_3)_2$-C_6H_3	$C_{24}H_{24}ClN_5OS$	465.90	49	218	0.49 / 0.56	15.02/ 14.96
V_n	4-CH_3O-C_6H_4	$C_{22}H_{19}N_5OSClF$	467.90	56	239	0.59 / 0.54	14.96 / 14.88
V_o	3-Cl-C_6H_4	$C_{22}H_{19}Cl_2N_5OS$	472.30	60	222	0.41/ 0.50	14.82 /14.76
V_p	4-Cl-C_6H_4	$C_{22}H_{19}Cl_2N_5OS$	472.30	54	243	0.51/ 0.58	14.82 /14.76
V_q	2-F-C_6H_4	$C_{22}H_{19}ClFN_5OS$	455.90	52	203	0.46 / 0.56	15.35 / 15.27
V_r	4-F-C_6H_4	$C_{22}H_{19}ClFN_5OS$	455.90	53	221	0.50 / 0.59	13.35 / 15.27
V_s	3-O_2N-C_6H_4	$C_{22}H_{19}ClN_6O_3S$	482.90	49	249	0.48 / 0.57	17.39 / 17.30
V_t	4-O_2N-C_6H_4	$C_{22}H_{19}ClN_6O_3S$	482.90	41	262	0.53 / 0.58	17.39 / 17.30

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (4.0 : 6.0)

TLC solvent system R_{f_2} : Methanol : Chloroform (1.0 : 9.0)

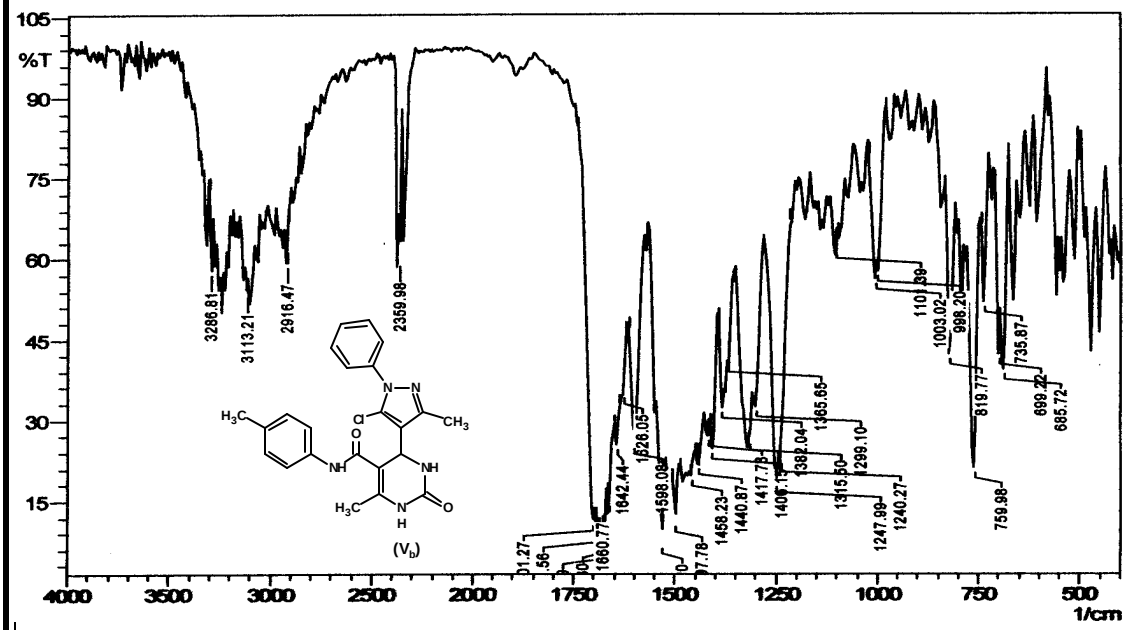
TABLE NO. V_C : PHYSICAL CONSTANTS OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-IMINO-5-N-SUBSTITUTED PHENYLCARBAMOYL-1,2,3,4-TETRAHYDRO PYRIMIDINS ($V_{u\text{-}d'}$).

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	Yield % 5	M.P. ^oC 6	R_f Value R_{f_1} / R_{f_2} 7	% of Nitrogen Cal/ Found 8
V_u	3-CH_3-C_6H_4	$C_{23}H_{23}ClN_6O$	434.90	49	232	0.53/ 0.59	19.31 /19.25
V_v	4-CH_3-C_6H_4	$C_{23}H_{23}ClN_6O$	434.90	52	244	0.51 / 0.60	19.31 / 19.25
V_w	2,5-$(CH_3)_2$-C_6H_3	$C_{24}H_{25}ClN_6O$	448.80	58	261	0.58 / 0.62	18.71/ 18.65
V_x	4-CH_3O-C_6H_4	$C_{23}H_{23}ClN_6O_2$	450.90	61	259	0.49 / 0.52	18.62 / 18.55
V_y	3-Cl-C_6H_4	$C_{22}H_{20}Cl_2N_6O$	455.30	53	212	0.51 / 0.56	18.44 /18.37
V_z	4-Cl-C_6H_4	$C_{22}H_{20}Cl_2N_6O$	455.30	57	253	0.61 / 0.66	18.44/ 18.37
$V_{a'}$	2-F-C_6H_4	$C_{22}H_{20}ClFN_6O$	438.80	52	273	0.56 / 0.60	19.14 / 19.07
$V_{b'}$	4-F-C_6H_4	$C_{22}H_{20}ClFN_6O$	438.80	61	280	0.52 / 0.58	19.14 / 19.07
$V_{c'}$	3-O_2N-C_6H_4	$C_{22}H_{20}ClN_7O_3$	465.90	58	261	0.51 /0.56	21.03 / 21.96
$V_{d'}$	4-O_2N-C_6H_4	$C_{22}H_{20}ClN_7O_3$	465.90	50	248	0.57 / 0.61	21.03 / 20.96

TLC solvent system R_{f_1} : Ethyl acetate : Hexane (4.0 : 6.0)

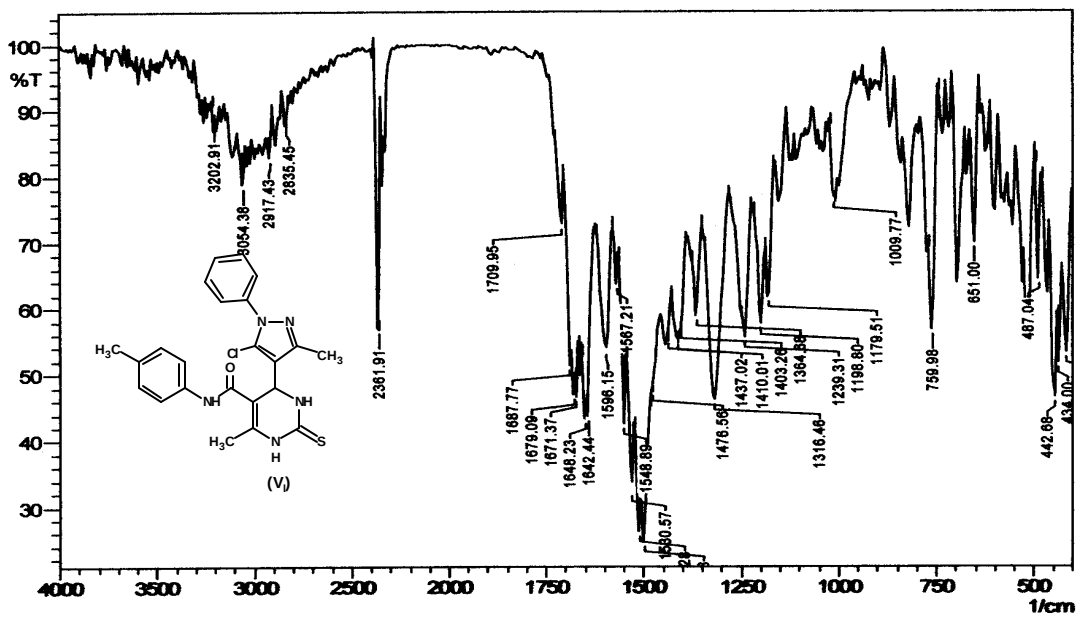
TLC solvent system R_{f_2} : Methanol : Chloroform (1.0 : 9.0)

IR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-OXO-5-N-(p-TOLYL)-1,2,3,4-TETRAHYDRO-PYRIMIDINE (V_b):



Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (Dimethyl)	C-H (asym. str., m s)	2916.40	2975 - 2850	92
	C-H (sym. str., m)	2880.00	2900 - 2800	92
	C-H (asym. def., m)	1440.87	1460 - 1400	92
	C-H (sym. def., m)	1382.04	1385 - 1300	92
Aromatic and ring skeletal vibration	C-H (str., v)	3113.21	3080 - 3010	90
	C=C & C-C (str., v)	1598.08	1600 - 1450	90
	C-H (i.p. def., m)	1101.39	1150 - 1050	90
	C-H (o.o.p. def., m)	819.77	825 - 800	90
Pyrimidine Moiety	C-N-C (str., v)	1315.50	1360 - 1310	90
	C=N (str.,v)	1556.61	1690 - 1650	90
	C-N (str., v)	1327.07	1340 - 1250	90
	N-H (str., br.)	3286.76-	3310 - 3500	90
	N-H (def., s,m)	1598.32	1650 - 1550	90
Ketone (Amide)	C=O (str., br.)	1660.69	1740 - 1650	89
Halogen	C-Cl (str., br.)	759.98-	800 - 600	90

IR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-THIO-5-N-(p-TOLYL)-1,2,3,4-TETRAHYDRO-PYRIMIDINE (V_I):

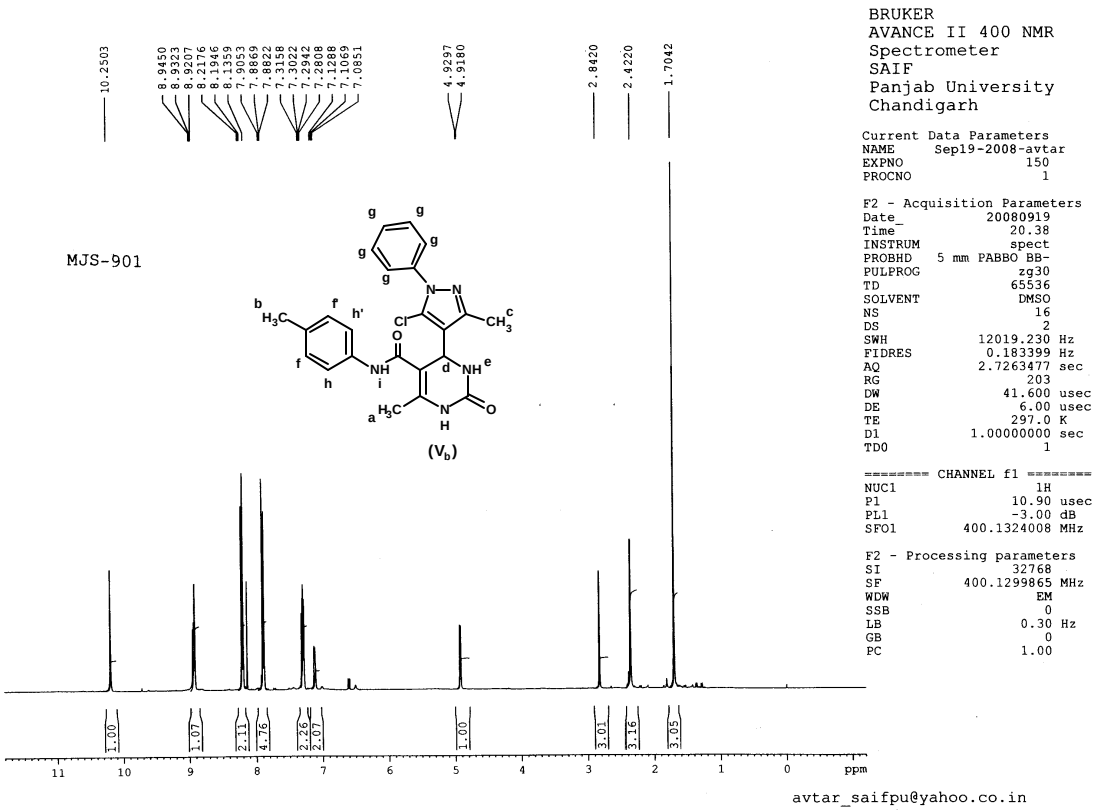


Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (Dimethyl)	C-H (asym. str., m s)	2970.48	2975 - 2850	92
	C-H (sym. str., m)	2889.46	2900 - 2800	92
	C-H (asym. def., m)	1446.66	1460 - 1400	92
	C-H (sym. def., m)	1307.78	1385 - 1300	92
Aromatic and ring skeletal vibration	C-H (str., v)	3240.52	3080 - 3010	90
	C=C & C-C (str., v)	1500.67	1600 - 1450	90
	C-H (i.p. def., m)	1111.03	1150 - 1050	90
	C-H (o.o.p. def., m)	804.34	825 - 800	90
Pyrimidine Moiety	C-N-C (str., v)	1307.78	1360 - 1310	90
	C=N (str., v)	1629.90	1690 - 1650	90
	C-N (str., v)	1234.48	1340 - 1250	90
	N-H (str., br.)	3363.97-3477.77	3310 - 3500	90
	N-H (def., s,m)	1583.61	1650 - 1550	90
Ketone (Amide)	C=O (str., br.)	1629.90	1740 - 1650	89
Halogen	C-Cl (str., br.)	688.61-758.05	800 - 600	90

IR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-IMINO-5-N-(p-TOLYL)-1,2,3,4-TETRAHYDRO-PYRIMIDINE (V_V):

Type	Vibration mode	Frequency in cm^{-1}		Reference
		Observed	Reported	
Alkane (Dimethyl)	C-H (asym. str., m s)	2906.82	2975 - 2850	92
	C-H (sym. str., m)	2833.52	2900 - 2800	92
	C-H (asym. def., m)	1448.59	1460 - 1400	92
	C-H (sym. def., m)	1377.22	1385 - 1300	92
Aromatic and ring skeletal vibration	C-H (str., v)	3066.92	3080 - 3010	90
	C=C & C-C (str., v)	1523.82	1600 - 1450	90
	C-H (i.p. def., m)	1054.13	1150 - 1050	90
	C-H (o.o.p. def., m)	802.00	825 - 800	90
Pyrimidine Moiety	C-N-C (str., v)	1336.71	1360 - 1310	90
	C=N (str., v)	1604.83	1690 - 1650	90
	C-N (str., v)	1261.49	1340 - 1250	90
	N-H (str., br.)	3338.89-3441.12	3310 - 3500	90
	N-H (def., s,m)	1595.18	1650 - 1550	90
Ketone (Amide) Subtitution	C=O (str., br.)	1713.81	1740 - 1650	89
Halogen	C-Cl(str., br.)	699.22-760.94	800 - 600	90

PMR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PY-RAZOL-4'-YL)-6-METHYL-2-OXO-5-N-(p-TOLYL)-1,2,3,4-TETRAHYDRO-PYRIMIDINE (V_b):

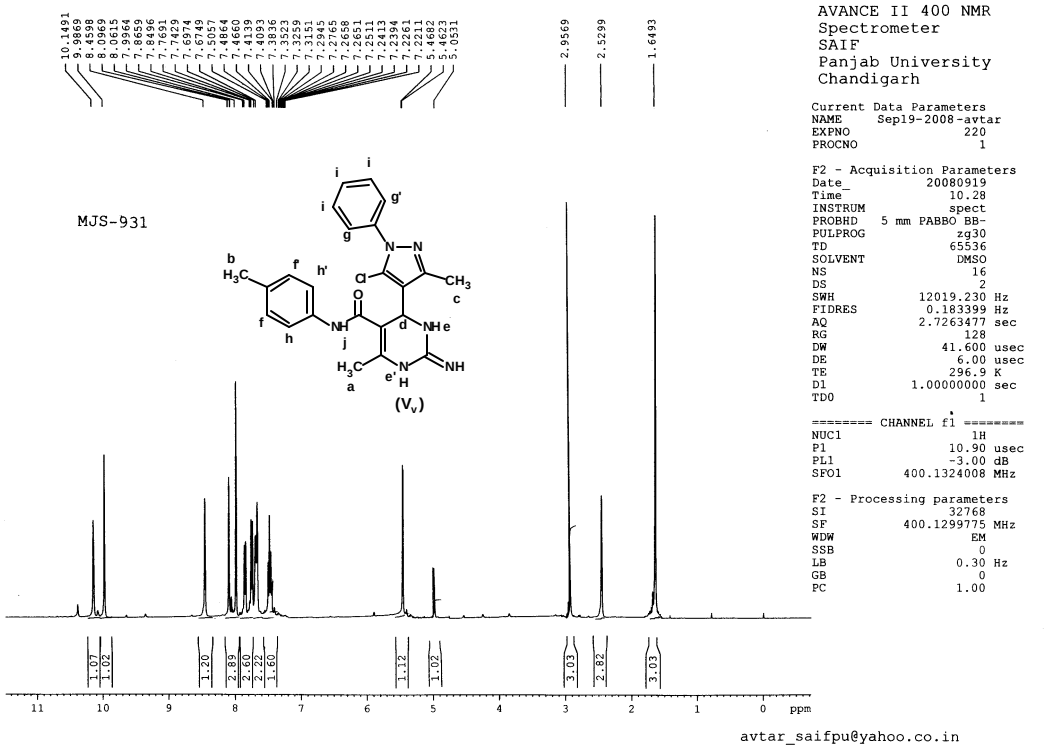


Serial No.	Signal Position (? ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.7042	3H	singlet	- C<u>H</u>$_{3(a)}$
2	2.4220	3H	singlet	- C<u>H</u>$_{3(b)}$
3	2.8420	3H	singlet	- C<u>H</u>$_{3(c)}$
4	4.9297	1H	singlet	- C<u>H</u>$_{(d)}$
5	7.0851-7.1288	2H	singlet	- N<u>H</u>$_{(e,e')}$
6	7.2808-7.3158	2H	multiplet	- Ar-<u>H</u>$_{(f,f')}$
7	7.8822-7.9053	5H	multiplet	- Ar-<u>H</u>$_{(g)}$
8	8.1359-8.2176	2H	singlet	- Ar-<u>H</u>$_{(h,h')}$
9	10.2503	1H	singlet	- N<u>H</u>$_{(i)}$

PMR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PY-RAZOL-4'-YL)-6-METHYL-2-THIO-5-N-(p-TOLYL)-1,2,3,4-TETRAHYDRO-PYRIMIDINE (V_I):

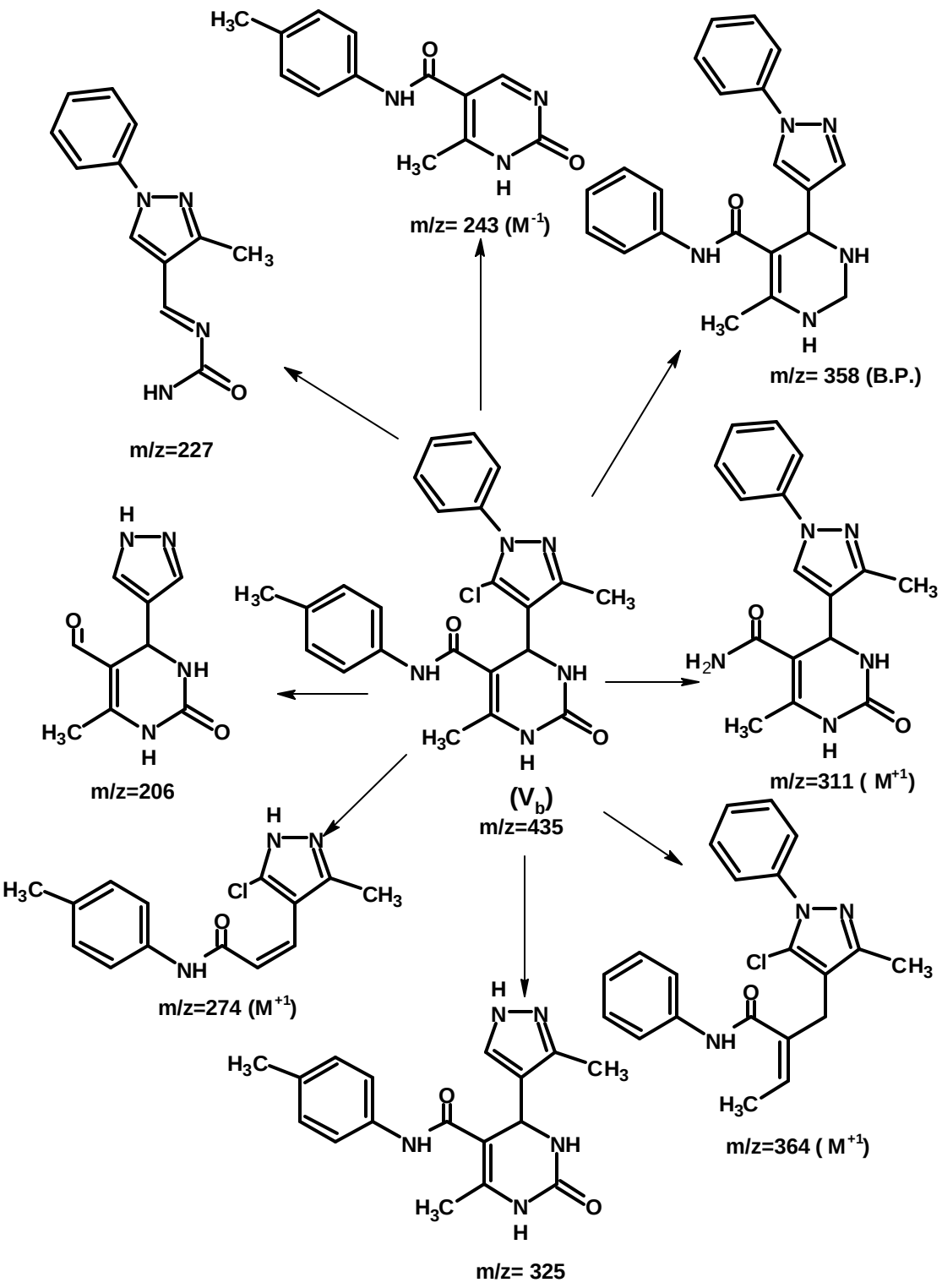
Serial No.	Signal Position (? ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.6669	3H	singlet	- C<u>H</u>$_3$(a)
2	2.4664	3H	singlet	- C<u>H</u>$_3$(b)
3	2.8721	3H	singlet	- C<u>H</u>(c)
4	5.0772	1H	singlet	- C<u>H</u>(d)
5	7.2442-7.2529	2H	singlet	- N<u>H</u>(e,e')
6	7.4177-7.4383	2H	doublet	- Ar-<u>H</u>(f,f')
7	7.5393-7.6528	5H	multiplet	- Ar-<u>H</u>(g)
8	7.9669-7.9818	1H	singlet	- Ar-<u>H</u>(h)
9	8.1711-8.2023	1H	singlet	- Ar-<u>H</u>(i)
10	9.8464	1H	singlet	- N<u>H</u>(j)

PMR SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PY-RAZOL-4'-YL)-6-METHYL-2-IMINO-5-N-(p-TOLYL)-1,2,3,4-TETRAHYDRO - PYRIMIDINE (V_V):

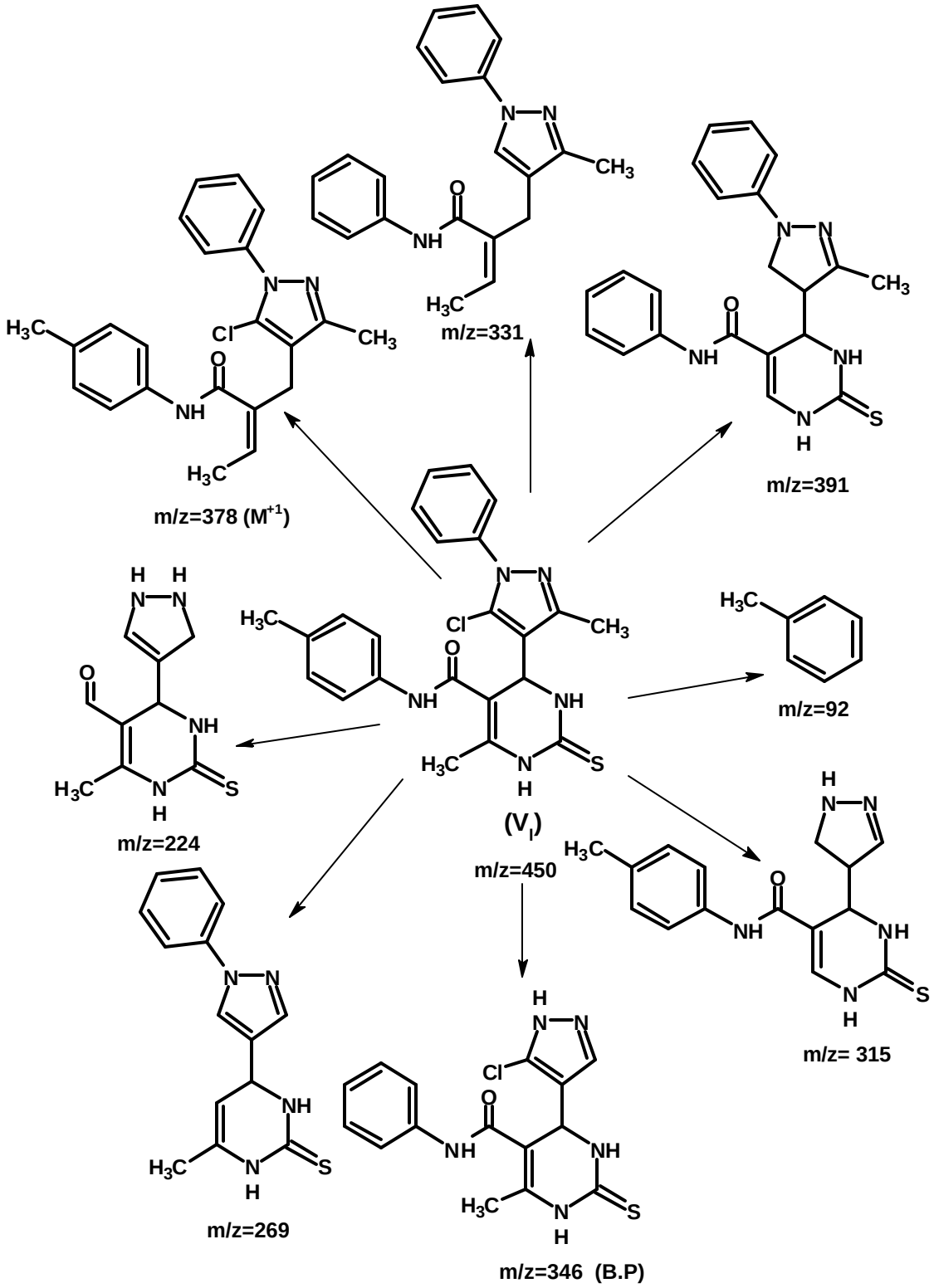


Serial No.	Signal Position (? ppm)	Relative No. of Protons	Multiplicity	Inference
1	1.6493	3H	singlet	- C<u>H</u>3(a)
2	2.5299	3H	singlet	- C<u>H</u>3(b)
3	2.9569	1H	singlet	- C<u>H</u>(c)
4	5.0531	1H	singlet	- Ar-<u>H</u>(d)
5	5.4623-5.4682	2H	doublet	- N<u>H</u>(e,e')
6	7.2394-7.3259	2H	multiplet	- Ar-<u>H</u>(f,f')
7	7.3856-7.5057	2H	multiplet	- Ar-<u>H</u>(g,g')
8	7.6749-7.7691	2H	multiplet	- Ar-<u>H</u>(h,h')
9	7.8496-8.4598	3H	multiplet	-Ar-<u>H</u>(i)
10	10.1491	1H	singlet	- N<u>H</u>(j)

MASS SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-OXO-5-N- (p-TOLYL)-1,2,3,4-TETRAHYDRO PYRIMIDINE (V_b).


m/z= 243 (M-1)
m/z=227
m/z= 358 (B.P.)
m/z=206
(Vb)
m/z=435
m/z=311 (M+1)
m/z=274 (M+1)
m/z=364 (M+1)
m/z= 325

MASS SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-THIO-5-N-(p-TOLYL)-1,2,3,4-TETRAHYDRO PYRIMIDINE (V_I).


m/z=331
m/z=378 (M+1)
m/z=391
m/z=92
m/z=224
(Vl)
m/z=450
m/z= 315
m/z=269
m/z=346 (B.P)

MASS SPECTRAL STUDY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-IMINO-5-N-(p-TOLYL)-1,2,3,4-TETRAHYDRO PYRIMIDINE (V_V').

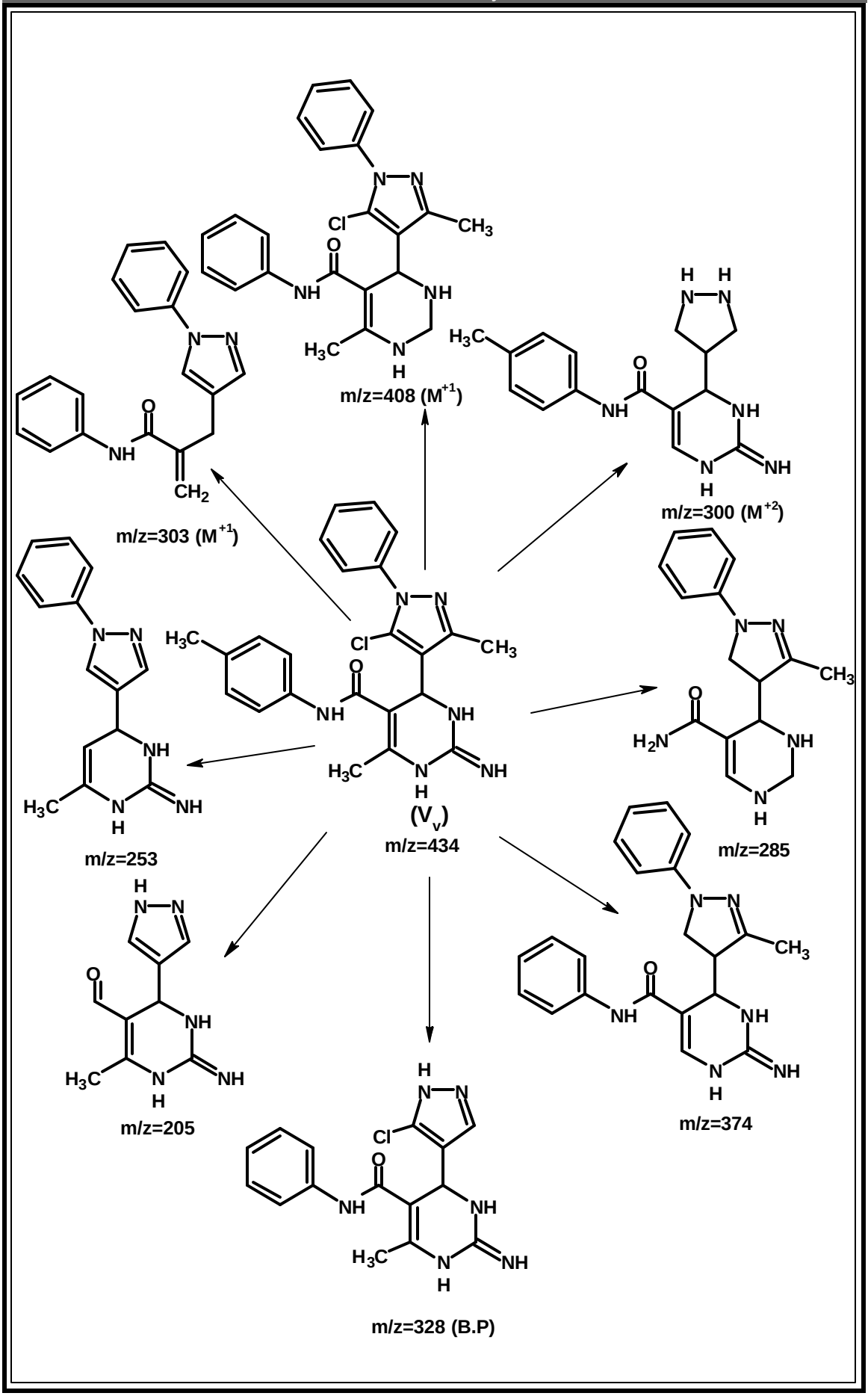

m/z=408 (M+1)
m/z=303 (M+1)
m/z=300 (M+2)
m/z=253
(Vv)
m/z=434
m/z=285
m/z=205
m/z=374
m/z=328 (B.P)

TABLE NO. 5_a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-OXO-5-N-SUBSTITUTED PHENYL CARBAMOYL-1,2,3,4-TETRAHYDRO PYRIMIDINES (V_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)									
		S. pyogens MTCC-442					S. aureus MTCC-96				
		5	25	50	100	250	5	25	50	100	250
V_a	3-CH_3-C_6H_4	-	10	11	13	15	-	11	12	13	15
V_b	3-CH_3-C_6H_4	-	12	13	15	16	-	13	14	15	17
V_c	2,5-$(CH_3)_2$-C_6H_3	-	12	14	16	17	-	12	13	14	17
V_d	4-CH_3O-C_6H_4	-	11	13	14	15	-	12	13	14	17
V_e	3-Cl-C_6H_4	-	11	12	14	19	-	10	13	14	15
V_f	4-Cl-C_6H_4	-	11	14	17	19	-	12	13	16	17
V_g	2-F-C_6H_4	-	10	12	15	17	-	11	13	15	17
V_h	4-F-C_6H_4	-	12	14	15	18	-	12	13	15	16
V_i	3-O_2N-C_6H_4	-	12	13	16	17	-	13	14	16	17
V_j	4-O_2N-C_6H_4	-	10	13	14	16	-	11	13	16	17

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

Standard drug	Antibactrial activity									
					V_e V_f		V_b V_i	V_b V_i	V_f V_i V_j	
Amplicilline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
Ciprofloxacin	16	19	21	21	22	17	19	21	22	22
Norfloxacin	18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

TABLE NO. 5_b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-OXO-5-N-SUBSTITUTED PHENYL CARBAMOYL-1,2,3,4-TETRAHYDRO PYRIMIDINES. (V_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)									
		E. Coli MTCC-443					P. Aeruginosa MTCC-1688				
		5	25	50	100	250	5	25	50	100	250
V_a	3-CH_3-C_6H_4	-	12	14	15	17	-	10	12	14	16
V_b	3-CH_3-C_6H_4	-	10	14	16	19	-	12	13	15	18
V_c	2,5-$(CH_3)_2$-C_6H_3	-	11	15	18	20	-	11	15	18	20
V_d	4-CH_3O-C_6H_4	-	12	15	17	19	-	11	13	15	17
V_e	3-Cl-C_6H_4	-	13	17	19	23	-	12	13	14	17
V_f	4-Cl-C_6H_4	-	13	17	18	22	-	12	14	18	20
V_g	2-F-C_6H_4	-	14	16	19	23	-	11	14	16	17
V_h	4-F-C_6H_4	-	17	19	19	24	-	12	15	17	19
V_i	3-O_2N-C_6H_4	-	12	14	15	15	-	11	13	14	15
V_j	4-O_2N-C_6H_4	-	10	13	15	16	-	12	13	15	17

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

Standard drug	Antibacterial activity									
		V_h	V_e V_f V_g V_h	V_e V_g V_h	V_c V_e V_f V_g V_h			V_c V_h	V_c V_f	V_c V_f
Amplicilline	14	15	16	19	20	14	15	15	18	20
Chloramphenicol	14	17	23	23	23	14	17	18	19	21
Ciprofloxacin	20	23	28	28	28	20	23	24	26	27
Norfloxacin	22	25	26	27	29	18	19	21	23	23

N.B.(-): No Activity

TABLE NO. 5_c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-OXO-5-N-SUBSTITUTED PHENYL CARBAMOYL-1,2,3,4-TETRAHYDRO PYRIMIDINES (V_{a-j}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antifungal activity (Zones of inhibition in mm)									
		A. niger MTCC-282					A. clavatus MTCC-1323				
		5	25	50	100	250	5	25	50	100	250
V_a	3-CH_3-C_6H_4	-	19	20	21	23	-	20	21	23	25
V_b	3-CH_3-C_6H_4	-	18	20	21	22	-	15	16	18	20
V_c	2,5-$(CH_3)_2$-C_6H_3	-	19	21	22	23	-	15	18	20	23
V_d	4-CH_3O-C_6H_4	-	21	23	23	25	-	19	21	23	24
V_e	3-Cl-C_6H_4	-	19	20	22	23	-	20	20	23	25
V_f	4-Cl-C_6H_4	-	19	21	23	24	-	19	20	23	24
V_g	2-F-C_6H_4	-	19	20	21	22	-	17	19	20	22
V_h	4-F-C_6H_4	-	17	18	20	22	-	19	21	22	23
V_i	3-O_2N-C_6H_4	-	21	22	23	23	-	17	18	21	23
V_j	4-O_2N-C_6H_4	-	18	21	22	23	-	15	19	21	22

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

Standard drug	Antifungal activity									
		V_a V_g V_c V_i V_d V_e V_f					V_a V_d V_e V_f V_h	V_a V_d V_e V_f		
Greseofulvin	19	23	25	25	28	18	21	22	22	24
Nystatin	18	19	24	29	29	18	21	24	25	26

N.B.(-): No Activity

TABLE NO. 5_d : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-THIO-5-N-SUBSTITUTED PHENYL CARBAMOYL-1,2,3,4-TETRAHYDRO PYRIMIDINES (V_{k-t}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442					S. aureus MTCC-96				
		5	25	50	100	250	5	25	50	100	250
V_k	3-CH_3-C_6H_4	-	12	14	17	18	-	10	13	14	17
V_l	3-CH_3-C_6H_4	-	10	13	14	16	-	11	12	15	16
V_m	2,5-$(CH_3)_2$-C_6H_3	-	12	15	18	19	-	12	13	14	16
V_n	4-CH_3O-C_6H_4	-	12	14	15	17	-	12	14	16	17
V_o	3-Cl-C_6H_4	-	12	14	15	17	-	11	13	15	16
V_p	4-Cl-C_6H_4	-	11	12	14	17	-	12	14	15	17
V_q	2-F-C_6H_4	-	12	13	15	18	-	11	12	14	15
V_r	4-F-C_6H_4	-	12	13	15	18	-	12	15	17	18
V_s	3-O_2N-C_6H_4	-	11	14	15	16	-	11	13	15	16
V_t	4-O_2N-C_6H_4	-	12	13	16	18	-	11	15	16	17

Comparative activity of (V_{k-t}) with known choosen standard drugs

Standard drug	Antibactrial activity									
				V_m	V_n			V_n V_p V_r V_t	V_n V_r V_t	V_r
Amplicilline	11	14	16	18	19	10	13	14	16	18
Chloramphenicol	10	13	19	20	20	12	14	19	20	21
Ciprofloxacin	16	19	21	21	22	17	19	21	22	22
Norfloxacin	18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

TABLE NO. 5$_e$: COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-THIO-5-N-SUBSTITUTED PHENYL CARBAMOYL-1,2,3,4-TETRAHYDRO PYRIMIDINES (V_{k-t}) (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) E. Coli MTCC-443					P. Aeruginosa MTCC-1688				
		5	25	50	100	250	5	25	50	100	250
V_k	3-CH_3-C_6H_4	-	08	11	12	14	-	10	12	15	16
V_l	3-CH_3-C_6H_4	-	10	14	15	16	-	12	13	15	17
V_m	2,5-$(CH_3)_2$-C_6H_3	-	08	13	15	17	-	11	12	14	15
V_n	4-CH_3O-C_6H_4	-	10	13	16	17	-	12	13	15	16
V_o	3-Cl-C_6H_4	-	15	16	17	18	-	13	15	18	20
V_p	4-Cl-C_6H_4	-	11	13	15	17	-	10	12	13	15
V_q	2-F-C_6H_4	-	12	15	18	20	-	13	15	16	17
V_r	4-F-C_6H_4	-	09	13	14	16	-	11	14	15	17
V_s	3-O_2N-C_6H_4	-	10	13	15	17	-	09	11	15	16
V_t	4-O_2N-C_6H_4	-	11	13	15	16	-	09	13	15	18

Comparative activity of (V_{k-t}) with known choosen standard drugs

Standard drug	Antibacterial activity									
		V_o	V_o		V_q			V_o V_q	V_o	V_o
Amplicilline	14	15	16	19	20	14	15	15	18	20
Chloramphenicol	14	17	23	23	23	14	17	18	19	21
Ciprofloxacin	20	23	28	28	28	20	23	24	26	27
Norfloxacin	22	25	26	27	29	18	19	21	23	23

N.B.(-): No Activity

TABLE NO. 5_f : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-THIO-5-N-SUBSTITUTED PHENYL CARBAMOYL-1,2,3,4-TETRAHYDRO PYRIMIDINES (V_{k-t}). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antifungal activity (Zones of inhibition in mm) A. niger MTCC-282					A. clavatus MTCC-1323				
		5	25	50	100	250	5	25	50	100	250
V_k	3-CH_3-C_6H_4	-	17	18	22	23	-	18	20	22	23
V_l	3-CH_3-C_6H_4	-	17	21	22	24	-	17	20	21	22
V_m	2,5-$(CH_3)_2$-C_6H_3	-	20	22	22	25	-	19	21	21	24
V_n	4-CH_3O-C_6H_4	-	18	20	21	23	-	18	18	22	23
V_o	3-Cl-C_6H_4	-	20	21	22	30	-	15	17	20	31
V_p	4-Cl-C_6H_4	-	22	22	23	26	-	16	18	19	21
V_q	2-F-C_6H_4	-	18	20	22	23	-	18	20	21	22
V_r	4-F-C_6H_4	-	20	22	23	23	-	19	20	21	23
V_s	3-O_2N-C_6H_4	-	18	18	19	22	-	18	20	21	22
V_t	4-O_2N-C_6H_4	-	18	20	21	22	-	20	21	22	24

Comparative activity of (v_{k-t}) with known choosen standard drugs

Standard drug	Antifungal activity									
		V_m	V_o V_p V_r		V_o				V_n V_t	V_m V_t
Greseofulvin	19	23	25	25	28	18	21	22	22	24
Nystatin	18	19	24	29	29	18	21	24	25	26

N.B.(-): No Activity

TABLE NO. 5_g : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-IMINO-5-N-SUBSTITUTED PHENYL CARBAMOYL-1,2,3,4-TETRAHYDRO PYRIMIDINES ($V_{u-d'}$). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442					S. aureus MTCC-96				
		5	25	50	100	250	5	25	50	100	250
V_u	3-CH_3-C_6H_4	-	11	12	14	17	-	11	12	13	17
V_v	3-CH_3-C_6H_4	-	12	13	14	18	-	11	12	15	16
V_w	2,5-$(CH_3)_2$-C_6H_3	-	12	14	15	17	-	12	13	14	16
V_x	4-CH_3O-C_6H_4	-	12	14	15	17	-	12	14	16	17
V_y	3-Cl-C_6H_4	-	11	12	14	17	-	11	12	15	16
V_z	4-Cl-C_6H_4	-	12	13	15	18	-	12	13	14	16
$V_{a'}$	2-F-C_6H_4	-	12	13	15	18	-	12	14	16	17
$V_{b'}$	4-F-C_6H_4	-	11	14	15	16	-	11	13	15	16
$V_{c'}$	3-O_2N-C_6H_4	-	12	13	16	18	-	12	14	15	17
$V_{d'}$	4-O_2N-C_6H_4	-	11	12	14	17	-	11	12	14	15
Comparative activity of ($V_{u-d'}$) with known choosen standard drugs											
Standard drug		**Antibactrial activity**									
									V_x $V_{a'}$ $V_{a'}$	V_x $V_{a'}$	
Amplicilline		11	14	16	18	19	10	13	14	16	18
Chloramphenicol		10	13	19	20	20	12	14	19	20	21
Ciprofloxacin		16	19	21	21	22	17	19	21	22	22
Norfloxacin		18	19	20	21	21	19	22	25	26	28

N.B.(-): No Activity

TABLE NO. 5_h : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-IMINO-5-N-SUBSTITUTED PHENYL CARBAMOYL-1,2,3,4-TETRAHYDRO PYRIMIDINES ($V_{u\text{-}d'}$). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)									
		E. Coli MTCC-443					P. Aeruginosa MTCC-1688				
		5	25	50	100	250	5	25	50	100	250
V_u	3-CH_3-C_6H_4	-	10	15	16	18	-	11	12	14	15
V_v	3-CH_3-C_6H_4	-	12	13	15	17	-	12	14	15	16
V_w	2,5-$(CH_3)_2$-C_6H_3	-	10	13	14	15	-	10	15	17	18
V_x	4-CH_3O-C_6H_4	-	12	14	15	17	-	11	13	15	16
V_y	3-Cl-C_6H_4	-	12	14	17	19	-	11	12	15	17
V_z	4-Cl-C_6H_4	-	11	12	15	17	-	12	14	17	20
$V_{a'}$	2-F-C_6H_4	-	15	18	20	22	-	11	14	16	18
$V_{b'}$	4-F-C_6H_4	-	12	15	18	20	-	10	15	17	18
$V_{c'}$	3-O_2N-C_6H_4	-	09	13	14	16	-	11	13	15	16
$V_{d'}$	4-O_2N-C_6H_4	-	10	13	15	17	-	11	12	15	17

Comparative activity of ($V_{u\text{-}d'}$) with known choosen standard drugs

Standard drug	Antibacterial activity									
			$V_{a'}$	$V_{a'}$	$V_{a'}$ $V_{b'}$			V_w $V_{c'}$		V_z
Amplicilline	14	15	16	19	20	14	15	15	18	20
Chloramphenicol	14	17	23	23	23	14	17	18	19	21
Coprofloxacin	20	23	28	28	28	20	23	24	26	27
Norfloxacin	22	25	26	27	29	18	19	21	23	23

N.B.(-): No Activity

TABLE NO. 5_i : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 4-(5'-CHLORO-3'-METYL-1'-N-PHENYL-PYRAZOL-4'-YL)-6-METHYL-2-IMINO-5-N-SUBSTITUTED PHENYL CARBAMOYL-1,2,3,4-TETRAHYDRO PYRIMIDINES ($V_{u-d'}$). (Different Inhibition Concentration in µg/ml).

Compd No.	R	Antifungal activity (Zones of inhibition in mm)									
		A. niger MTCC-282					A. clavatus MTCC-1323				
		5	25	50	100	250	5	25	50	100	250
V_u	3-CH_3-C_6H_4	-	19	20	21	23	-	20	21	23	24
V_v	3-CH_3-C_6H_4	-	20	22	23	25	-	21	21	24	25
V_w	2,5-$(CH_3)_2$-C_6H_3	-	21	22	23	23	-	16	19	21	28
V_x	4-CH_3O-C_6H_4	-	18	21	22	23	-	18	20	22	23
V_y	3-Cl-C_6H_4	-	17	18	22	23	-	17	20	21	22
V_z	4-Cl-C_6H_4	-	17	21	22	24	-	19	21	22	28
$V_{a'}$	2-F-C_6H_4	-	20	22	22	25	-	16	19	21	28
$V_{b'}$	4-F-C_6H_4	-	18	20	22	23	-	18	20	22	23
$V_{c'}$	3-O_2N-C_6H_4	-	20	21	21	30	-	17	20	21	22
$V_{d'}$	4-O_2N-C_6H_4	-	20	22	22	24	-	18	20	22	23

Comparative activity of ($V_{u-d'}$) with known choosen standard drugs

Standard drug	Antifungal activity									
		V_u V_f V_g $V_{a'}$ $V_{c'}$ $V_{d'}$					V_v	V_u V_v V_x V_z $V_{b'}$ $V_{d'}$	V_u V_v V_w V_z $V_{a'}$	
Griseofulvin	19	23	25	25	28	18	21	22	22	24
Nystatin	18	19	24	29	29	18	21	24	25	26

N.B.(-): No Activity

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