STUDIES ON COMPOUNDS OF MEDICINAL INTEREST

A THESIS
SUBMITTED TO THE
SAURASHTRA UNIVERSITY
FOR THE DEGREE OF

Doctor of Philosophy

IN THE FACULTY OF SCIENCE (CHEMISTRY)
BY

BHARAT G. PATEL

UNDER THE GUIDANCE
OF

Dr. V. H. SHAH
Associate Professor

DEPARTMENT OF CHEMISTRY
SAURASHTRA UNIVERSITY
RAJKOT - 360 005.
INDIA(2004)

Gram : UNIVERSITY

Phone & Fax No. : 0281-2578512
Fax No. : 0281-2577663

SAURASHTRA UNIVERSITY

University Road.
Rajkot - 360 005.

Dr. V. H. Shah
M.Sc.; Ph.D., F.I.C.
Associate Professor,
Department of Chemistry

Residence :
Dr. V. H. Shah
PA-8,professor's Quarters
Sau. University Campus
Rajkot - 360 005.
GUJARAT (INDIA)

No. :

Date : **10-06-2004**

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

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

(Mr. Bharat G. Patel)

Date. : -06-2004
Place : Rajkot.

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

Date : -06-2004
Place : Rajkot.

Dr. V. H. Shah
Associate Professor
Department of Chemistry
Saurashtra University
Rajkot - 360 005.

ACKNOWLEDGEMENT

I wish to make devote supplication to THE ALMIGHTY for his benediction, but for HIS inspiration this task would not have been accomplished.

I express my deep sense of gratitude to my eminent guide ***Dr. V. H. SHAH,*** *M.Sc., Ph. D., F. I. C. Associate Professor, Department of Chemistry, Saurashtra University - Rajkot, for his propaedentical teaching, Sagacious guidance, creative criticism, perpetual encouragement and painstanstaking expert supervision throughout the research work brought my efforts to fruition.*

I am grateful to ***Prof. H. H. Parekh,*** *Professor and Head, Department of Chemistry, Saurashtra University - Rajkot, for and providing research facilities.*

I am heartly thankful to Dr. Ketan Sikotra, Dr. Kishor Ahir, Dr. Naresh Ravat, Dr. Tushar Metha, Mr. Nilesh Doshi (late), Mr. Axay Dave, Mr. Arif Siddiqui, Mr. Vimal Bhuva, Mr. Vijay Lunagariya, Mr. Shailesh Vaghasia, Mr.Vrajlal Gothalia, Mr. Hitesh Mathukia and my all other colleagues who have helped me directly or indirectly for the completion of my research.

I would like to express my sincere thanks and gratitude to all teaching and non-teaching staff members for their kind co-operation during my research work.

I am thankful to the authorities of R.S.I.C.-Chandigarh and C.D.R.I.-Lucknow for providing necessary instrumental facilities of PMR, IR and Mass spectral analysis.

I am thankful to Dr. Darshita P. Shah (MD, Pathology), Mehta diagnostic and research guidance centre, Rajputpara - Rajkot for providing valuable guidance for antimicrobial activity.

The never ending process of enlightenment, which was initiated by my parents like an angle, 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, sister Roshani and uncle, 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.

A bunch of thanks to my dear friend Mr. Vishal Patidar for their co-operation and effort in giving the present shape of thesis.

Finally, I am thankful to Dr. K. G. Mavani, Vice Chancellor, Saurashtra University - Rajkot for providing research as well as hostel facilities.

Mr. Bharat G. Patel

M. Sc.

CONTENTS

Section-III : Preparation and biological evaluation of 1,2,3,4,6,7,8,9-octahydro-10-aryl-5-(*m*-nitrophenyl)-2,8-dimercapto-4,6-dioxo-5H,10H-pyrodo[2,3-d : 6,5-d']dipyrimidines

SYNOPSIS

A brief summary of the work to be incorporated in the thesis entitled "**STUDIES ON COMPOUNDS OF MEDICINAL INTEREST''** has been summarized as under.

(A) STUDIES ON PYRIMIDINE DERIVATIVES

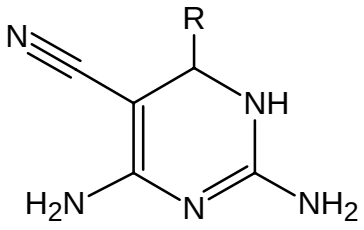
(B) STUDIES ON PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINES

(A) STUDIES ON PYRIMIDINE DERIVATIVES

Pyrimidines represents 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 etc. Some pyrimidines, which occur as natural product like nucleic acids and vitamin-B and can be used as therapeutic agent for the treatment of AIDS and antitumor. Keeping in association of pyrimidines with varied activities, it was thought worthwhile to synthesize some newer pyrimidines and its derivatives which can be summarized as below.

PART - I : STUDIES ON PYRIMIDINES

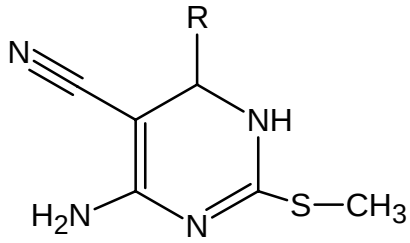
SECTION - I : Preparation and biological evaluation of 2,4-Diamino-5-cyano-6-aryl-1,6-dihydro pyrimidines.



(I) **R = Aryl**

Pyrimidines (I) have been synthesized by the condensation of different aromatic aldehydes, guanidine hydrochloride and malononitrile.

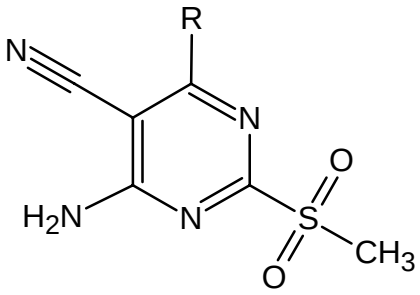
SECTION – II : Preparation and biological evaluation of 2-Mercapto Methyl-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines.



(II) **R = Aryl**

2-Mercaptomethyl pyrimidines (II) have been synthesized by the condensation of 2-mercapto-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines with dimethyl sulphate in presence of the base.

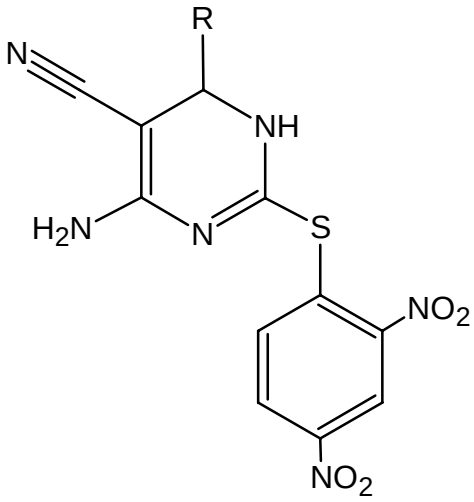
SECTION - III : Preparation and biological evaluation of 2-Methyl sulphonyl-4-amino-5-cyano-6-aryl pyrimidines.



(III) **R = Aryl**

2-Methylsulphonyl-4-amino-5-cyano-6-aryl pyrimidines (III) have been synthesized by the reaction of 2-mercaptomethyl-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines with hydrogen peroxide.

SECTION - IV : Preparation and biological evaluation of 2-[(2',4'-Dinitro phenyl)thio]-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines.



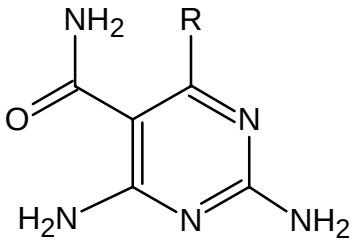
(IV) **R = Aryl**

Pyrimidines (IV) have been synthesized by the condensation of 2-mercapto-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines with 2,4-dinitro chlorobenzene in presence of the base.

PART - II : STUDIES ON CARBOXAMIDO PYRIMIDINES

The growing potent literature of recent years demonstrates that the carboxamido pyrimidines are used as better cardiovascular, antihypertensive, antitumor, anticonvulsant agents. Prompted by the above facts, some newer carboxamido pyrimidines have been synthesized as under.

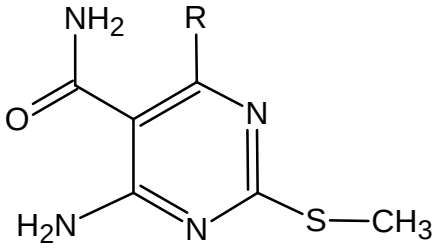
SECTION - I : Preparation and biological evaluation of 2,4-Diamino-5-carboxamido-6-aryl pyrimidines.



(V) **R = Aryl**

2,4-Diamino-5-carboxamido-6-aryl pyrimidines (V) have been synthesized by the reaction of 2,4-diamino-5-cyano-6-aryl-1,6-dihydro pyrimidines with concentrated sulfuric acid at 0^0C.

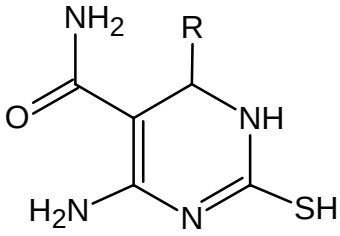
SECTION - II : Preparation and biological evaluation of 2-Mercapto methyl-4-amino-5-carboxamido-6-aryl pyrimidines.



(VI) **R = Aryl**

2-Mercaptomethyl-4-amino-5-carboxamido-6-aryl pyrimidines (VI) have been synthesized by the reaction of 2-mercaptomethyl-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines with concentrated sulfuric acid at 0^{o} C.

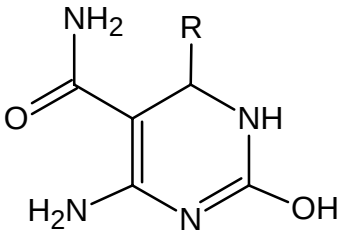
SECTION - III : Preparation and biological evaluation of 2-Mercapto-4-amino-5-carboxamido-6-(2'-chloro substituted quinolin-3'-yl)-1,6-dihydro pyrimidines.



(VII) **R = 2-Chloro substituted quinolin-3-yl**

Pyrimidines (VII) have been synthesized by condensation of different substituted 3-(2'-chloro quinolin-3'-yl)-2-cyanoacrylamides with thiourea.

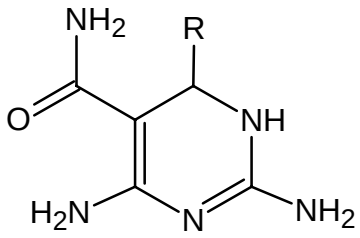
SECTION - IV : Preparation and biological evaluation of 2-Hydroxy-4-amino- 5-carboxamido-6-(2'-chloro substituted quinolin-3'-yl)-1,6-dihydro pyrimidines.



(VIII) **R = 2-Chloro substituted quinolin-3-yl**

Pyrimidines (VIII) have been synthesized by condensation of different substituted 3-(2'-chloro quinolin-3'-yl)-2-cyanoacrylamides with urea.

SECTION - V : Preparation and biological evaluation of 2,4- Diamino-5-carboxamido-6-(2'-chloro substituted quinolin-3'-yl)-1,6-dihydro pyrimidines.



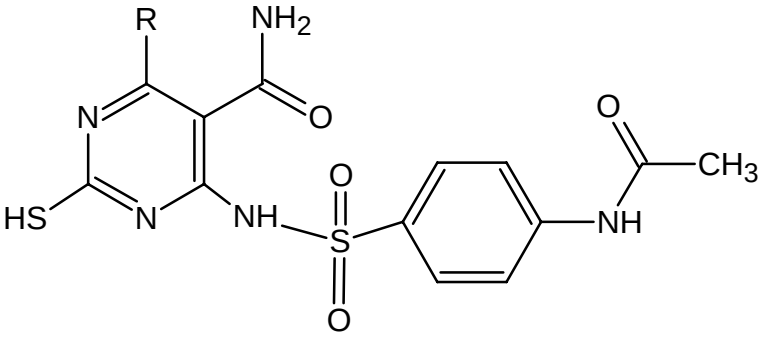
(IX) **R = 2-Chloro substituted quinolin-3-yl**

Pyrimidines (IX) have been synthesized by condensation of different substituted 3-(2'-chloro quinolin-3'-yl)-2-cyanoacrylamides with guanidine hydrochloride.

PART - III : STUDIES ON PYRIMIDINYL SULPHONAMIDES

The study of sulphonamides has revealed valuable drugs for the disease like cancer, tuberculosis, diabetics, malaria, leprosy and epilepsy. These valid observations lead us to synthesize some novel sulphonamides, which have been described as under.

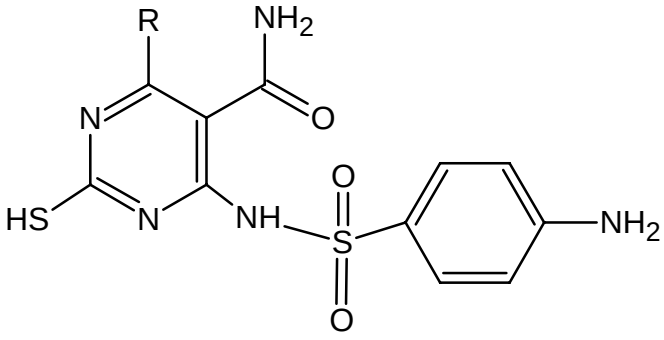
SECTION - I : Preparation and biological evaluation of 2-Mercapto-4-(*p*-acetamidophenyl sulphonylamino)-5-carboxamido-6-aryl pyrimidines.



(X) **R = Aryl**

4-Pyrimidyl-sulphonamides (X) have been synthesized by the condensation of 2-mercapto-4-amino-5-carboxamido-6-aryl pyrimidines with *p*-acetamidophenyl sulphonyl chloride in presence of pyridine.

SECTION - II : Preparation and biological evaluation of 2-Mercapto-4-(*p*-amino phenyl sulphonylamino)-5-carboxamido-6-aryl pyrimidines.



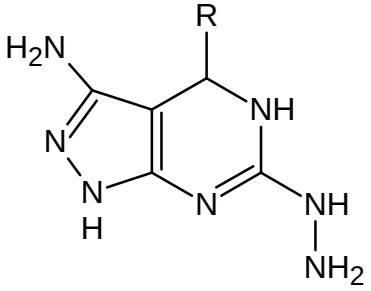
(XI) **R = Aryl**

2-Mercapto-4-(*p*-aminophenyl sulphonylamino)-5-carboxamido-6-aryl pyrimidines (XI) have been synthesized by the hydrolysis of 2-mercapto-4-(*p*-acetamidophenyl sulphonylamino)-5-carboxamido-6-aryl pyrimidines with hydrochloric acid.

PART - IV : STUDIES ON PYRAZOLO[3,4-d]PYRIMIDINES

Pyrazolo[3,4-d] pyrimidines are one of the most active class of compounds possessing diverse biological activities viz. anticancer, antitumor, diuretic, antipyretic and antimicrobial. Prompted by the above facts some new pyrazolo [3,4-d]pyrimidines have been prepared as under.

SECTION - I : Preparation and biological evaluation of 3-Amino-4-aryl-4,5-dihydro-6-hydrazino-1H-pyrazolo[3,4-d]pyrimidines.



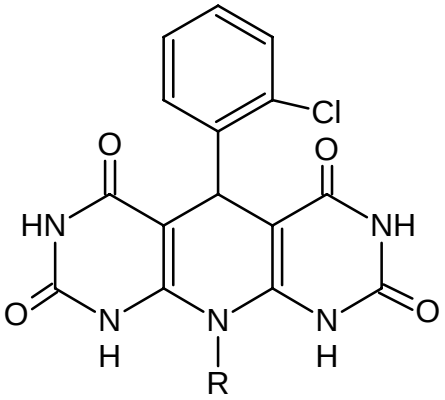
(XII) **R = Aryl**

Pyrazolo[3,4-d]pyrimidines (XII) have been synthesized by the condensation of 2-mercaptomethyl-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines with hydrazine hydrate.

(B) STUDIES ON PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINES

Pyrido[2,3-d : 6,5-d']dipyrimidines represent one of the most active classes of compounds possessing a wide spectrum of biological activities viz. anticancer, antihypertensive, antitubercular. Keeping in association of pyrido [2,3-d : 6,5-d']dipyrimidines with varied activities, it was worthwhile to synthesize some newer pyrido[2,3-d : 6,5-d']dipyrimidines which can be summarized as under.

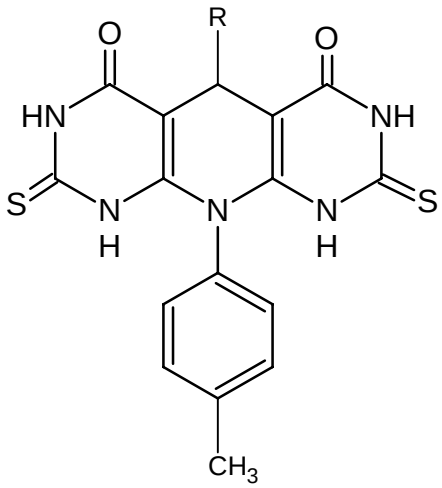
SECTION - I : Preparation and biological evaluation of 1,2,3,4,6,7,8,9-octahydro-10-aryl-5-(*o*-chlorophenyl)-2,4,6,8-tetraoxo-5H,10H-pyrido[2,3-d : 6,5-d']dipyrimidines.



(XIII) **R = Aryl**

Pyrido[2,3-d : 6,5-d']dipyrimidines (XIII) have been synthesized by the condensation of 2-chlorobenzaldehyde with barbituric acid and different aromatic amines.

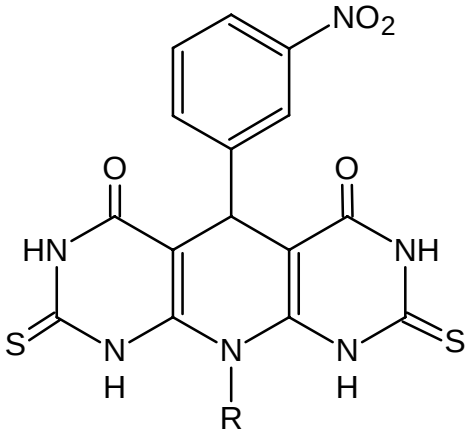
SECTION - II : Preparation and biological evaluation of 1,2,3,4,6,7,8,9-octahydro-10-(*p*-methylphenyl)-5-aryl-2,8-dimercapto-4,6-dioxo-5H,10H-pyrido[2,3-d : 6,5-d']dipyrimidines.



(XIV) **R = Aryl**

Pyrido[2,3-d : 6,5-d']dipyrimidines (XIV) have been synthesized by the condensation of different aromatic aldehydes with thiobarbituric acid and p-toluidine.

SECTION - III : Preparation and biological evaluation of 1,2,3,4,6,7,8,9-octahydro-10-aryl-5-(*m*-nitrophenyl)-2,8-dimercapto-4,6-dioxo-5H,10H-pyrido[2,3-d : 6,5-d']dipyrimidines.



(XV) **R = Aryl**

Pyrido[2,3-d : 6,5-d']dipyrimidines (XV) have been synthesized by the condensation of 3-nitrobenzaldehyde with thiobarbituric acid and different aromatic amines.

The constitutions of the products have been characterized by using elemental analyses, IR, PMR, and mass spectrometry.

The compounds have been screened for their *in vitro* therapeutic assay like antibacterial activities towards ***S. pyogens MTCC-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of synthesized compounds have been compared with standard drugs.

STUDIES ON COMPOUNDS OF MEDICINAL INTEREST

STUDIES ON COMPOUNDS OF MEDICINAL INTEREST

(A) Drug

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

(B) Pharmacology

Pharmacology is the science of drugs. In a broad sense, it deals with interaction of exogenously administered chemical molecules (drugs) with living system. It encompasses all aspects of knowledge about drugs, but most importantly those that are relevant to effective and safe use for medicinal purposes. For thousands of years most drugs were crude natural products of unknown composition and limited efficiency. Only the overt 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 include physiological and biochemical effects of drugs and their mechanism of action at macro molecular / sub cellular organ system.

(b) **Pharmacokinetics :** It is derived from the Greek word Kinesis means

movement. What the body does to the drug ? This refers to movements of the drug in and alternation of the drug by the body; includes absorption, distribution, binding / localization / storage, biotransformation and excretion of the drug.

Some other important aspects of pharmacology are given as under :

* ***Pharmacotherapecutics*** **:** It is the application of pharmaco-dynamic information together with knowledge of the disease for its prevention, mitigation or cure.
* ***Clinical Pharmacology :*** It is the scientific study of drug in man. It includes pharmacodynamic and pharmacokinetic investigation in healthy volunteers and in patients; evaluation of efficiency and safety of drugs and comparative trials with other forms of treatments; surveillance of patterns of drug uses, adverse effects, etc.
* ***Chemotherapy :*** It is the treatment of systemic infection / malignancy with specific drugs that have selective toxicity for the infecting organism / malignant cell with less effect on the host cells.

Drugs in general, can thus be divided into :

* ***Pharmacodynamic agents :*** These are designed to have pharmaco-dynamic effect in the recipient.
* ***Chemotherapeutic agents :*** These are designed to inhibit / kill invading parasites / malignant cells and have no minimal pharmacodynamic effects in the recipient.

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

It has been realized that only a handful of drugs out of the multitude

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

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

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

(III) Its choice should depend upon pattern of prevalent diseases; availability 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 properties and local facilities for manufacture and storage.

(VI) Most essential drug should be single compounds. Fixed ratio combination 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, epidemiological 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 practice for combating 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 extracts form or in pure form became 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. Strichinine stimulates the action of heart and aspirin still 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 activity of various chemicals for bacterial and human cells, this important factor prompted the Florey and Chain in 1939 to investigate penicillin which was discovered ten years earlier by Alexander Fleming. The spectular 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 1960. 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 – an antimalarial ; 1950 – Methyldopa – antidiabetic; 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 - calcium antagonist ‘1972 -; 1981 - captopril - antihypertensive; There are some specific examples representing new therapeutics.

(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. Efforts in the numerous laboratories 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 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 showed to possess useful medicinal properties.

The process of drug design is extensively driven by the instinct, intution and experience of pharmaceutical research scientists. It is often instructive to attempt to “capture” these experiences by analyzing the historical record that is successful drug design projects of past. From this analysis the inferences drawn to play an important role in shaping our on 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 as under.

(a) Anticancer drug

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

(b) Hepatoprotective drugs

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

(c) Antimalarial drugs

Drugs, which kills the plasmodium causing malaria are called antimalarial drug. Combination of sulphamethoxazole with pyrimethamine is a novel antimalarial drug.

(d) Drug for meningitis

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

(e) Drug for typhoid

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

(f) Antidiabetic drug

Drug, which converts the excess glucose of blood into glycogen are termed as antidiabetic drugs. Novel antidiabetic drugs are melformin, 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,

amlodopine and niphadipine.

(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 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 is called NSAID. Novel NSAID are pyroxicam, meloxicam and nimesulide.

Different kind of drugs generally used as designed as anaesthetic, antituberculostatic, antihypertensive, anticonvulsant, anthelmintic, antiinflammatory, sedative and hypnotics which prompted us to synthesise drugs having pyrimidine, quinoline, pyrazolo[3,4-d]pyrimidine, pyrido[2,3-d : 6,5-d'] dipyrimidine moieties as a better therapeutic activity.

Aims and objectives of the present investigation are,

(ai) To generate several biologically active moieties such as pyrimidines, carboxamido pyrimidines, pyrimidinyl sulphonamides, pyrazolo[3,4-d] pyrimidines, and pyrido[2,3-d : 6,5-d']dipyrimidines.

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

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

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

(A) Studies on pyrimidine derivatives

(B) Studies on pyrido[2,3-d : 6,5-d']dipyrimidines

(A)
STUDIES ON PYRIMIDINE DERIVATIVES

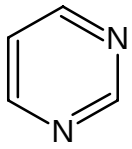
PART - I
STUDIES ON PYRIMIDINES

[A] STUDIES ON PYRIMIDINE DERIVATIVES

PART - I
STUDIES ON PYRIMIDINES

INTRODUCTION

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



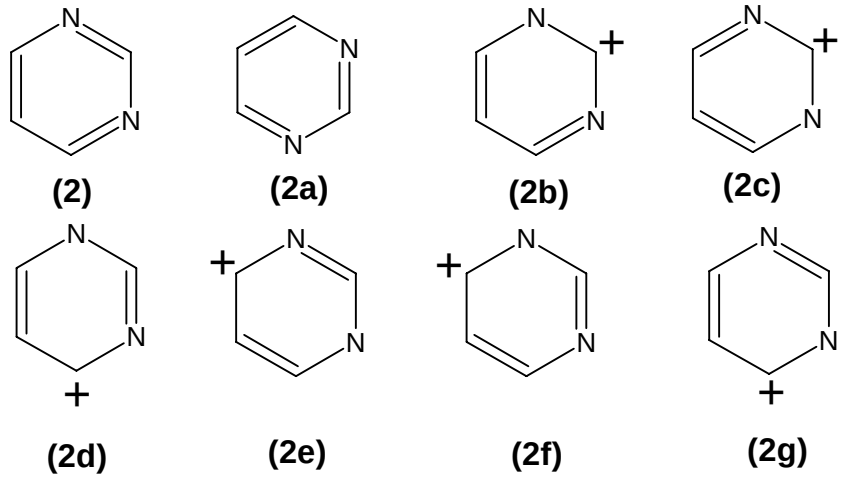
(1)
pyrimidine

Generally pyrimidine derivatives such as 2-hydroxy pyrimidine, 2-mercapto pyrimidine and 2-amino 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 analogs 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[1]. There are several other important groups of pyrimidines with medicinal uses.

Pyrimidine ring carrying various subtituents may be built up from two or three aliphatic fragments by the principle synthesis or by a variety of other synthesis, which are complimentary rather than alternative to it. A second type of synthesis is the isomerisation or break down of another heterocycles such as an hydration of purine but such roots are frequently used. Pyrimidine is best considered as a resonance hybrid to which the uncharged equivalent Kekule structures 2 and 2a and charged structures 2b and 2g contribute. 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[2]. Despite considerable localization of π (pi) electrons at nitrogen atoms of pyrimidines the ring system is still sufficiently aromatic to possess substantial stability. This is great advantage in the primary synthesis of pyrimidines.



(2) **(2a)** **(2b)** **(2c)**

(2d) **(2e)** **(2f)** **(2g)**

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[3-12]. It is also possible to prepare pyrimidines from other heterocyclic compounds such as pyrrole[13], imidazole[14], isoxazole and oxazole[15,16], pyridine[17], pyrazine[18], 1,3,5-triazine[19], oxazine[20], thiazine[21] by different processes.

SYNTHETIC ASPECTS

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[22].

(b) By the condensation of malonic ester and urea led to formation of pyrimidine[23].

(c) By the condensation of formamidine with phenylazomalononitrile led to formation of 4,5,6-triamino pyrimidine[24].

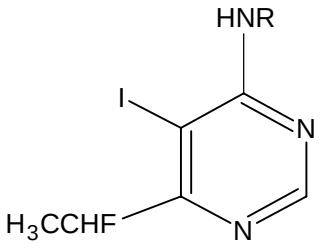
(d) By the condensation of aromatic aldehydes, ß-ketoester or substituted ß-ketoester with urea or thiourea led to formation of pyrimidines[25].

(e) By the condensation of thiourea and substituted ß-ketoester in presence of sodiumethoxide led to formation of 2-mercapto pyrimidines[26].

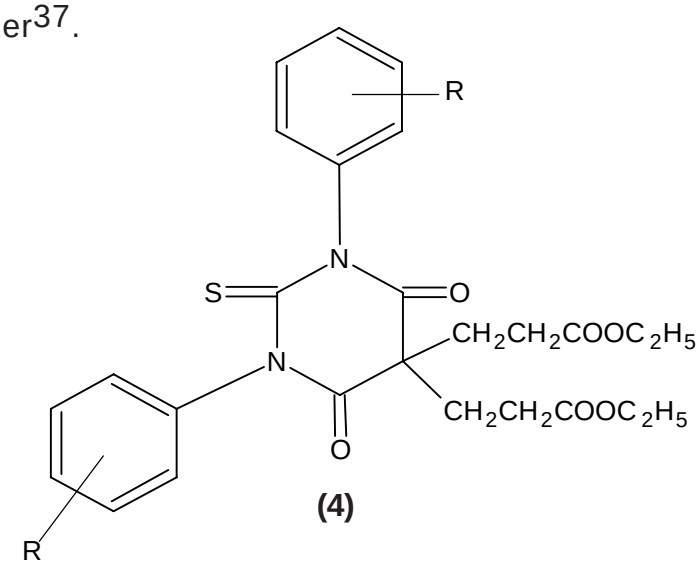
(f) By the condensation of chalcones with dicyandiamide in presence of piperidine led to formation of pyrimidines[27].

(g) By thermal or microwave irridiation of thiourea and substituted ß-ketoester in presence of dimethylformamide led to formation of substituted tetra hydro pyrimidines[28].

Pyrimidines found their applications as herbicidal[29], pesticidal[30,31] agents. Yoshida et al.,[32] have synthesized 4-amino-5-formyl-2-mercapto pyrimidines as agrochemical intermediates. C. Srivastava et al.,[33] have synthesized new substituted pyrimidines **(3)** at C_5- position of pyrimidine as potential insecticides. N. Yasushi et al.,[34] synthesized 6-(1-fluoro ethyl)-5-iodo-4-alkylamino pyrimidines **(4)** as pesticides for agriculture and horticulture. Besides such a great pharmacological importance of pyrimidines, they also contribute to an important class of dye viz. trichloro pyrimidine[35] dye which is a reactive dye. Pyrimidines also have applications in liquid crystal composition[36]. Many synthetic members of pyrimidines are important as vulcanizing accelerator agents and photography stabilizer[37].



(3) **R = Alkyl/Aryl**

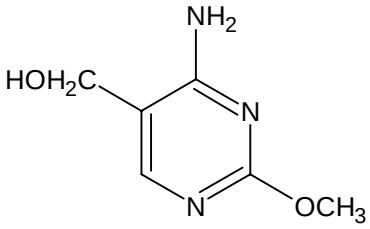


(4)

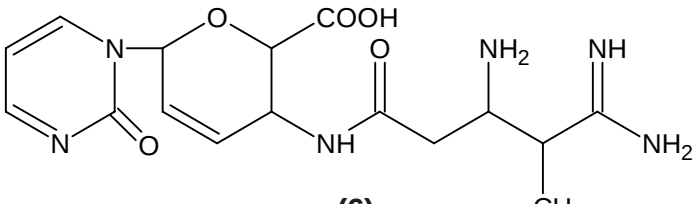
PHARMACOLOGICAL IMPORTANCE

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,

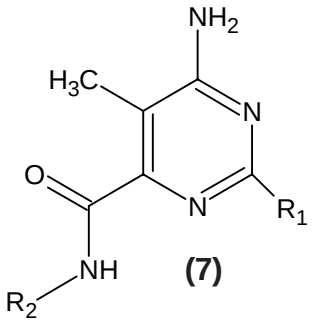
chroticacid, willardiline, tetradotoxine, becimethrian **(5)**, blasticidine **(6)**, cougerotin, amicetin, bamicetin and plicacetin, phleomicine, blemycin and related families **(7)**.



(5)



(6)



(7)

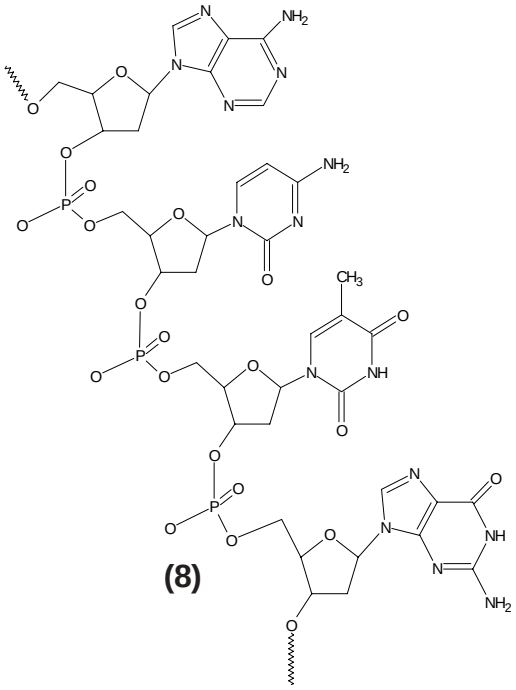
Pyrimidine derivatives have wide varieties of usages. Pyrimidine ring system is also present in Vitamin B_2 and folic acid. Pyrimidine ring system having a mercapto group occupy a unique position in medicinal chemistry[38]. These types of derivatives play a vital role in biological processes[39-41] as well as synthetic drugs[42].

The core of any rational drug discovery program is 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 no more than four years. Consequently, the scope of medicinal chemistry has recently expanded enormously, but the biological data of support conclusions about synthetic strategies are only beginning to emerge.

Modifications in the base, sugar and phosphate moeities of oligonucleotides have been reported. The subjects of medicinal chemical programs 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, cellular uptake and distribution and *in vivo* tissue distribution, metabolism and clearance.

Oligonucleotide Medicinal Chemistry Program

Desired Characteristics
" Increased stability
" Increased cellular uptake
" Optimal hybridisation
" Duplex recognition
" Catalytic cleaving finction
" Ease of synthesis
" Patentability



(8)

ISIS Design Strategy
" Exploit current oligo modifications
" Functionality placement
" Novel backbone modifications
" Heterocycle modifications
" Acid/base catalyzing functional groups
" 2'-substitution
" α-oligonucleotides
" Amphipathic group

Figure **(8)** shows the structure of an oligonucleotide, a number of design features and various design strategies that have been implemented at other laboratories. With regard to this class of molecules, as with all others. Increase potency and selectivity by improving pharmacokinetic and pharmacodynamic properties.

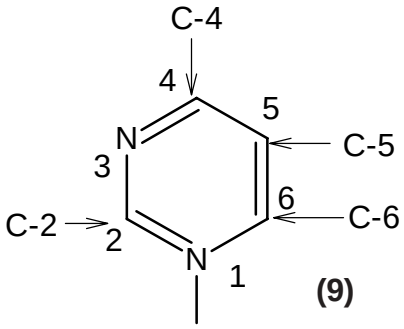
Although substantial progress in the medicinal chemistry oligonucleotides has been made in the past three years, it is not yet possible to reach conclusions about the therapeutic ability of the novel modifications. Preliminary data on effects on nuclease stability and hybridization properties and for a few modifications, activity in vitro suggest that the next generation of oligonucleotides may display substantially improved potencies and selectivity.

PYRIMIDINE MODIFICATIONS

A selectivity large number of modified pyrimidines have been synthesized and now evaluated in oligonucleotides. The principle sites of modification are C-2, C-4, C-5 and C-6. **(Fig. 9)**. These and other nucleoside analogs have

recently been thoroughly reviewed[43]. Consequently, a very brief summary of the analogs that displayed interesting properties is incorporated here.

Sites of pyrimidine Modification



(9)

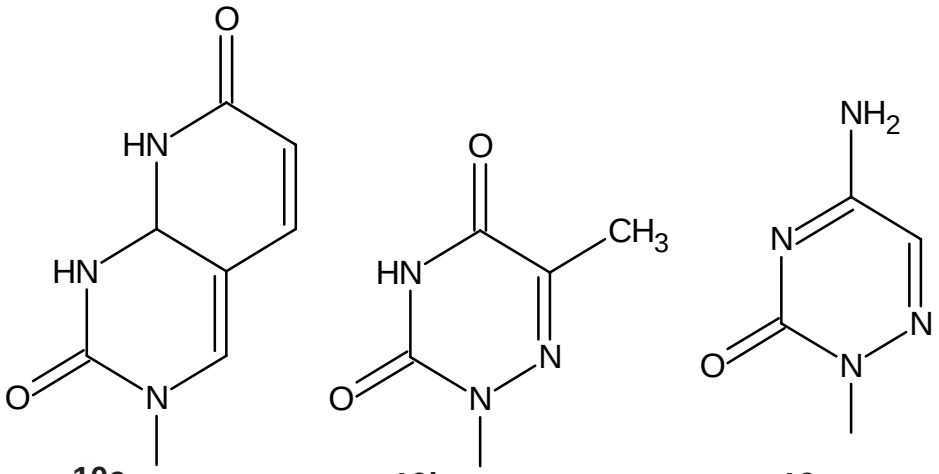
In as much as the C-5 position is involved in Watson-Crick hybridization, C-2 modified pyrimidine containing oligonucleotides have shown unattractive hybridization properties. An oligonucleotide containing 2-thiothymidine was found to hybridize well to DNA and in fact, the *Tm* increased by approximately 0-5 °C per modification[44] .

In contrast , several modifications in the 4-position that have interesting properties have been reported. 4-thio pyrimidines have been incorporated into oligonucleotides with no significant negative effect on hybridization[45]. Finally, a fluorescent base **(10a)** has been incorporated into oligonucleotides and shown to enhance duplex stability[46].

A large number of modifications at the C-5 position have also been reported including halogenated nucleosides. (Although the stability of duplexes may be enhanced by incorporating 5-halogenated nucleosides, the occasional mispairing with G and the potential that the oligonucleotide might degrade may cause the release of toxic nucleosides analogs[43].

In general, as expected, modifications in the C-6 position of pyrimidines are highly duplex destabilizing[47]. Oligonucleotides containing 6-aza pyrimidines **(10b,10c)** have been shown to reduce *Tm* by 1-2 ± C per modification, but to enhance the nuclease stability of oligonucleotides and to support RNase H induced degradation of RNA targets[43].

Pyrimidine Modifications

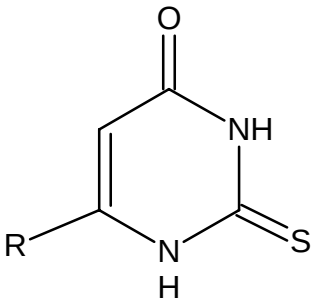


10a **10b** **10c**

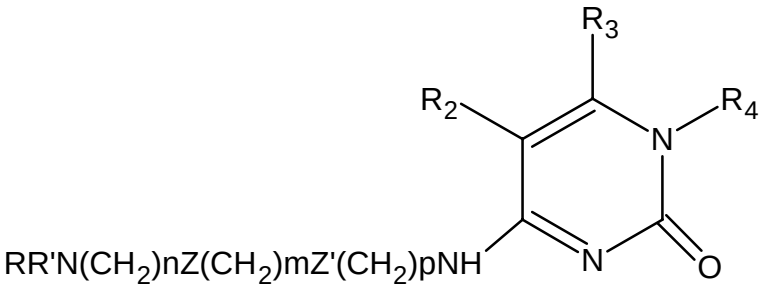
Some of the therapeutic activity of pyrimidine derivatives can be summarized as follows.

(a) Antithyroid[48]
(b) Antitumer[49]
(c) Antihypertensive[50-52]
(d) Antiinflammatory[53,54]
(e) Diuretic[55]
(f) Antimalarial[56-58]
(g) Antispasmodic[59]
(h) Anticonvulsant[60]
(i) Antineoplastic[61]
(j) Anthelmintic[62]
(k) Antimicrobial[63-88]
(l) Cardiovascular[89-91]
(m) Antiviral[92-94]
(n) Platelet aggregation inhibitor[95,96]
(o) Antihistamine[97]
(p) AntiHIV[98]

As a thyroid drug[99] known as some thiouracil **(11)** derivatives have been demonstrated recently. Propyl thiouracil is widely used probably because it has fewer side effects than the others. Smith kline[100] has synthesized **(12)** Cytosine derivatives as histamine antagonist.

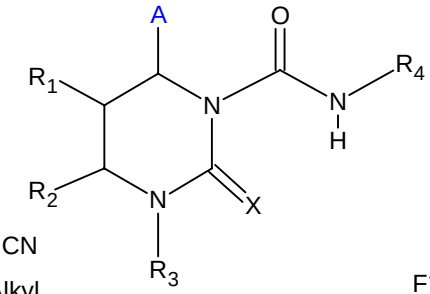


(11)



(12)

N. Dhanapalan et al.,[101] have been undertaken the preparation of **(13)** as selective melanin concentrating hormone-1 (mch-1) receptor antagonists. W. Gerd et al.,[102] have synthesized pyridinyl pyrimidine **(14)** and tested for their ability to inhibit the release of tumor necrosis factor-α (TNF-α) and interleukin-1β from peripheral blood mononuclear cells (PBMC) and human whole blood. In the pyrimidine series, structure activity relationship similar to those of the imidazole series were found, although generally pyrimidine comps. were less potent modification of the substituent at the 2-position of the pyrimidine led to the most active comps.



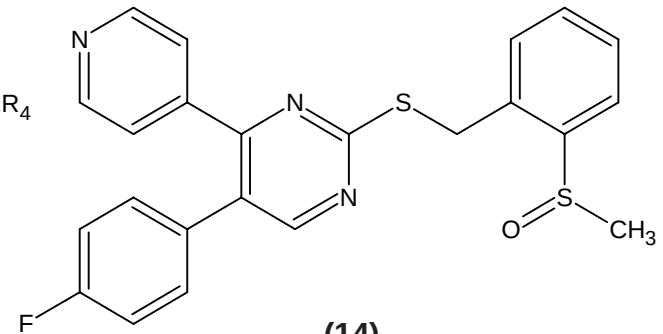
R_1=H,NO_2,CN

R_2=H,OH,Alkyl

R_3=H,Fluoro alkyl, alkenyl

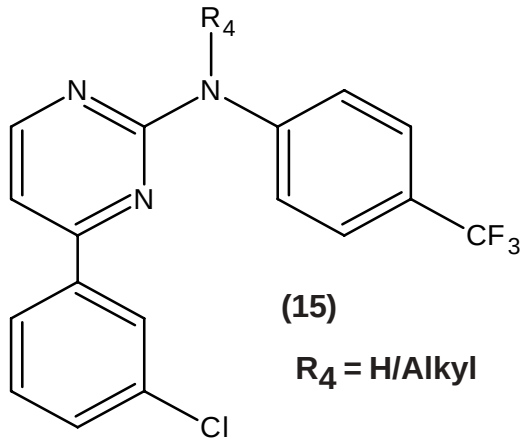
R_4=alkyl-Pipreidinyl, alkyl-tetrahydro pyridinyl

(13)



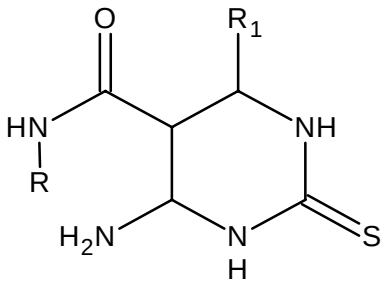
(14)

W. Max et al.,[103] have prepared **(15)** and their used in therapy of IgE-synthesis-mediated diseases, autoimmune diseases, gastrointestinal diseases and inflammatory diseases. M. K. Jani et al.,[104] have synthesized 5-N-aryl carbamoyl pyrimidine-2-thiones **(16)** and tested for antibacterial and antitubercular activities.



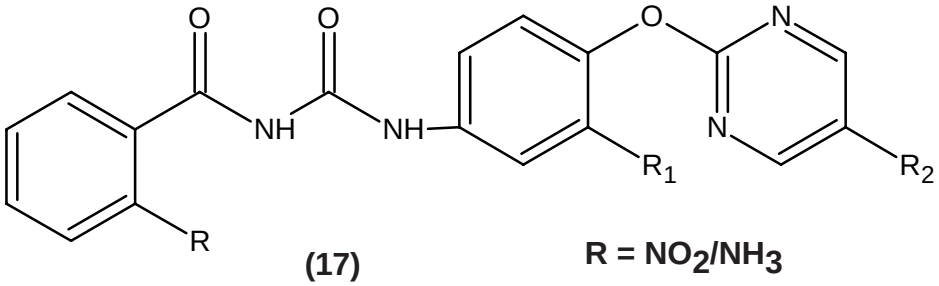
(15)

R_4 = H/Alkyl



(16) **R,R_1 = Aryl**

Okada et al.,[105] have synthesized pyrimidines **(17)** and their antitumor activity were examined *in vivo* against P_{388} Leukemia. Some of the compounds were highly soluble in water and shown good antitumor activity.

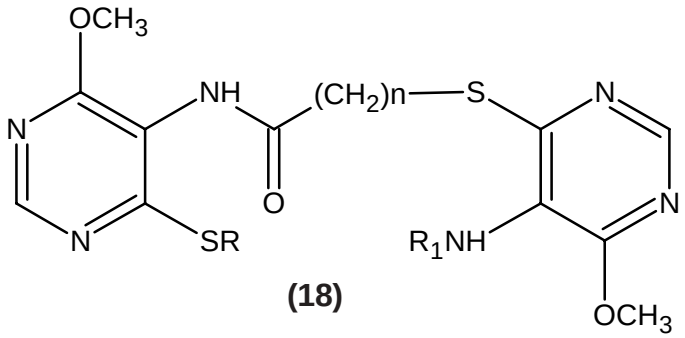


(17)

R = NO_2/NH_3

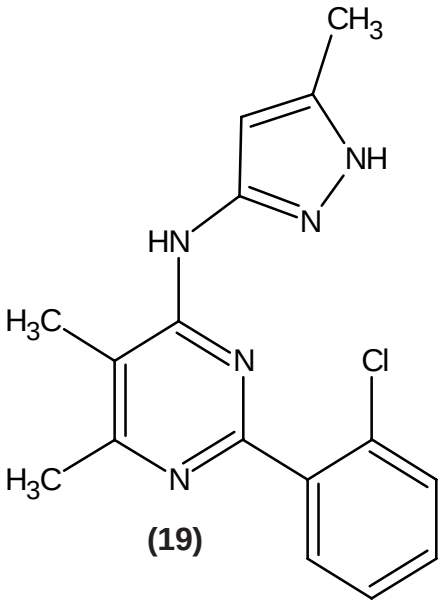
R_1,R_2=Cl/Br/Me

Safonova et al.,[106] have synthesized pyrimidine derivatives **(18)** as potent antitumor agents.

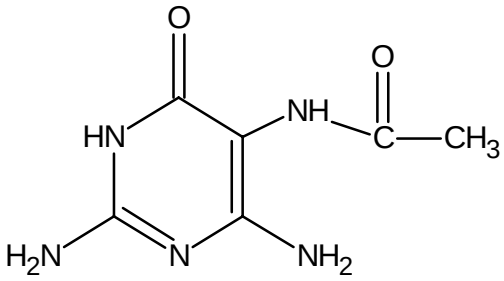


(18)

Recently, C. Jean-Damien et al.,[107] have synthesized pyrazolyl pyrimidine **(19)** as protein kinase inhibitors for treatment of cancer, diabetes and Alzheimer's disease. G. Khalili et al.[108] have synthesized **(20)** as antiviral agent gancyclovir.

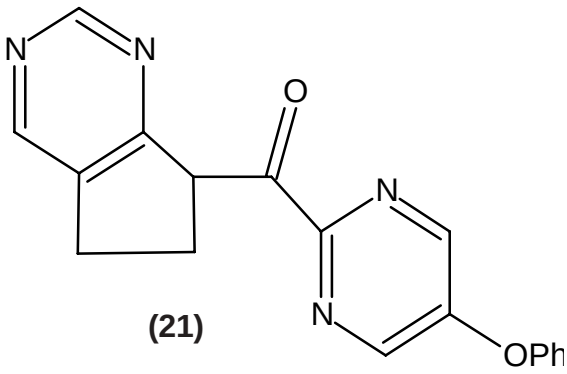


(19)



(20)

K. Noriyuki et al.,[109] have synthesized pyrimidine derivatives **(21)** as antiHIV integrase inhibitory activity.



(21)

In view of procuring highly potent biodynamic agents and after reviewing recent literature survey on 2-mercapto/amino pyrimidines for their various methods of synthesis and different pharmacological activities, synthesis of pyrimidines have been undertaken which can be summarized in the following sections as under :

SECTION - I : PREPARATION AND BIOLOGICAL EVALUATION OF 2,4-DIAMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES.

SECTION - II : PREPARATION AND BIOLOGICAL EVALUATION OF 2-MERCAPTOMETHYL-4-AMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES.

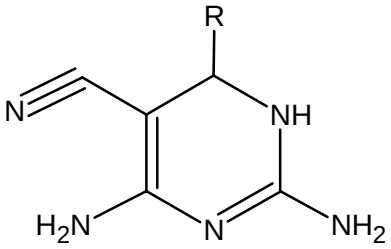
SECTION - III : PREPARATION AND BIOLOGICAL EVALUATION OF 2-METHYLSULPHONYL-4-AMINO-5-CYANO-6-ARYL PYRIMIDINES.

SECTION - IV : PREPARATION AND BIOLOGICAL EVALUATION OF 2-[(2',4'-DINITROPHENYL)THIO]-4-AMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES.

SECTION - I

PREPARATION AND EVALUATION OF 2,4-DIAMINO-5-CYANO-6-ARYL1,6-DIHYDRO PYRIMIDINES

Due to other properties[29-37] and biodynamic activities[48-104] of pyrimidines and with a view to have potent therapeutic agents, the synthesis of 2,4-diamino-5-cyano-6-aryl-1,6-dihydro pyrimidines (Ia-j) have been undertaken by the condensation of different aromatic aldehydes with malononitrile and guanidine hydrochloride.

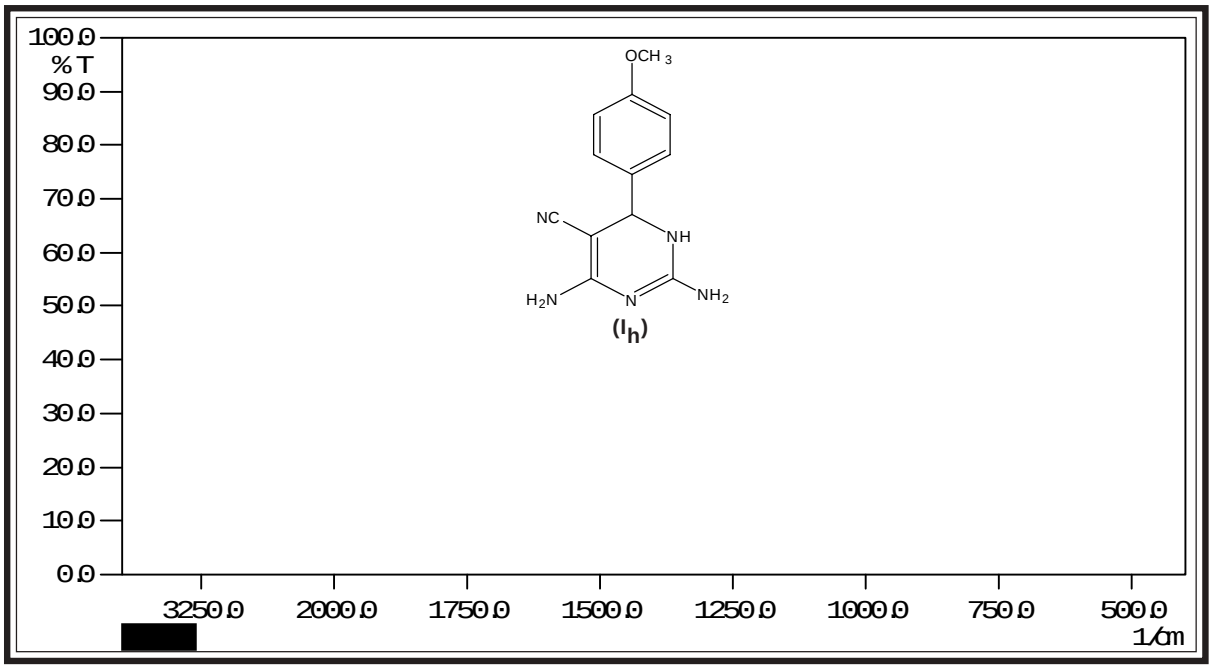


I_{a-j} **R=Aryl**

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

The products (I_{a-j}) were assayed for their *in vitro* biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

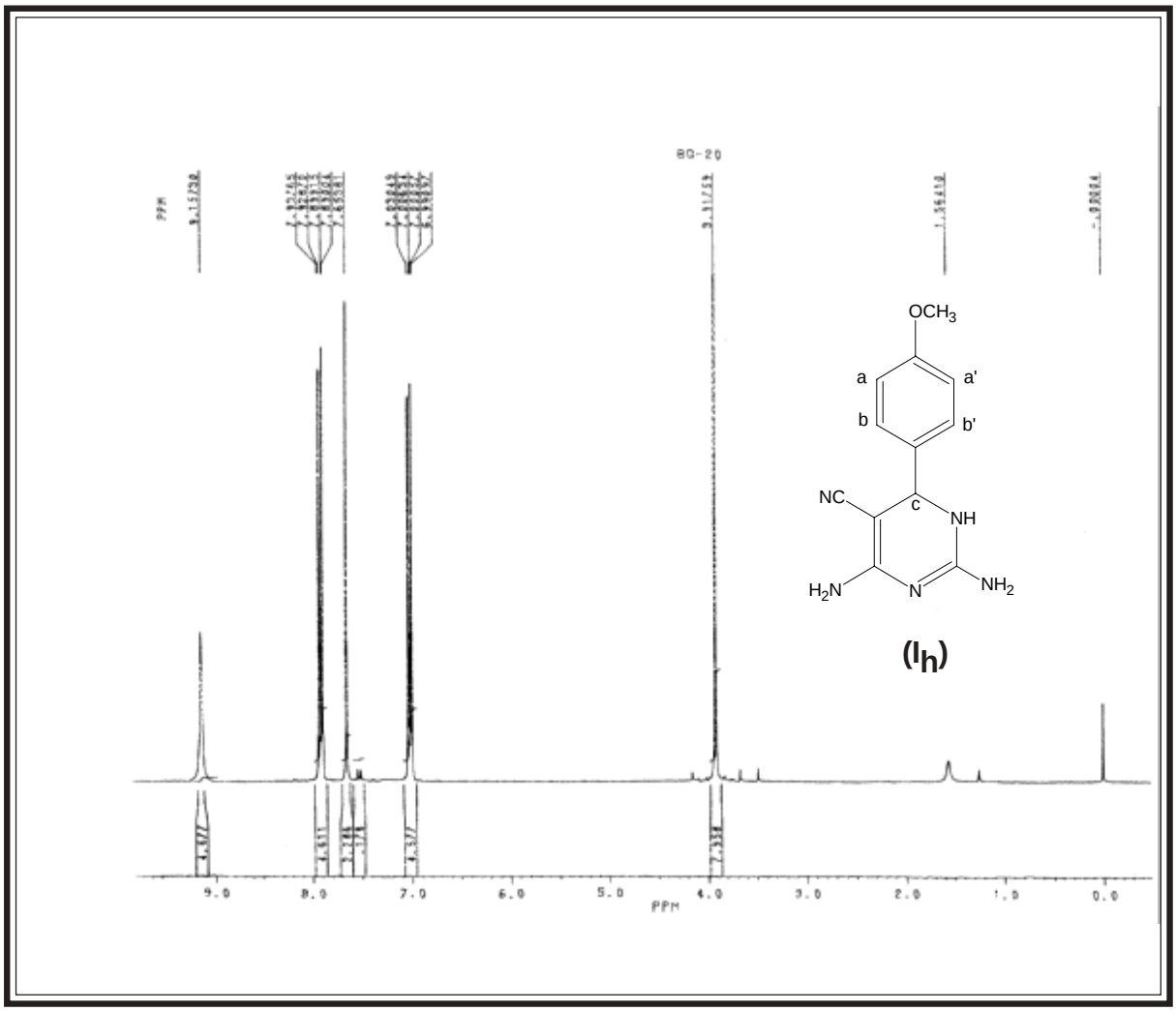
IR SPECTRAL STUDY OF 2,4-DIAMINO-5-CYANO-6-(*p*-METHOXY PHENYL)-1,6-DIHYDRO PYRIMIDINE (I_h)



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.(asym.)	2923.9	2975-2950	343
CH_3	C-H str.(sym.)	2852.5.	2880-2860	,,
	C-H def.(asym.)	1465.8	1460-1435	,,
	C-H def.(sym.)	1379.6	1385-1300	,,
Aromatic and	C=C + C=N and ring	1494.7	1520-1480	345
Pyrimidine moiety	skeletal vibration	1552.6	1580-1520	,,
	C-H str.	3087.8	3080-3030	,,
	C-H i.p. def.	1093.6	1125-1090	,,
	C-H o.o.p. def.	825.5	840-810	,,
Ether	C-O-C str. (asym.)	1255.6	1275-1200	346
	C-O-C str. (sym.)	1074.3	1075-1050	,,
Amine (Primary)	N-H str.	3350.1	3500-3300	343
	N-H def.	1645.2	1650-1580	,,
Nitrile	C=N str.	2208.3	2260-2190	345

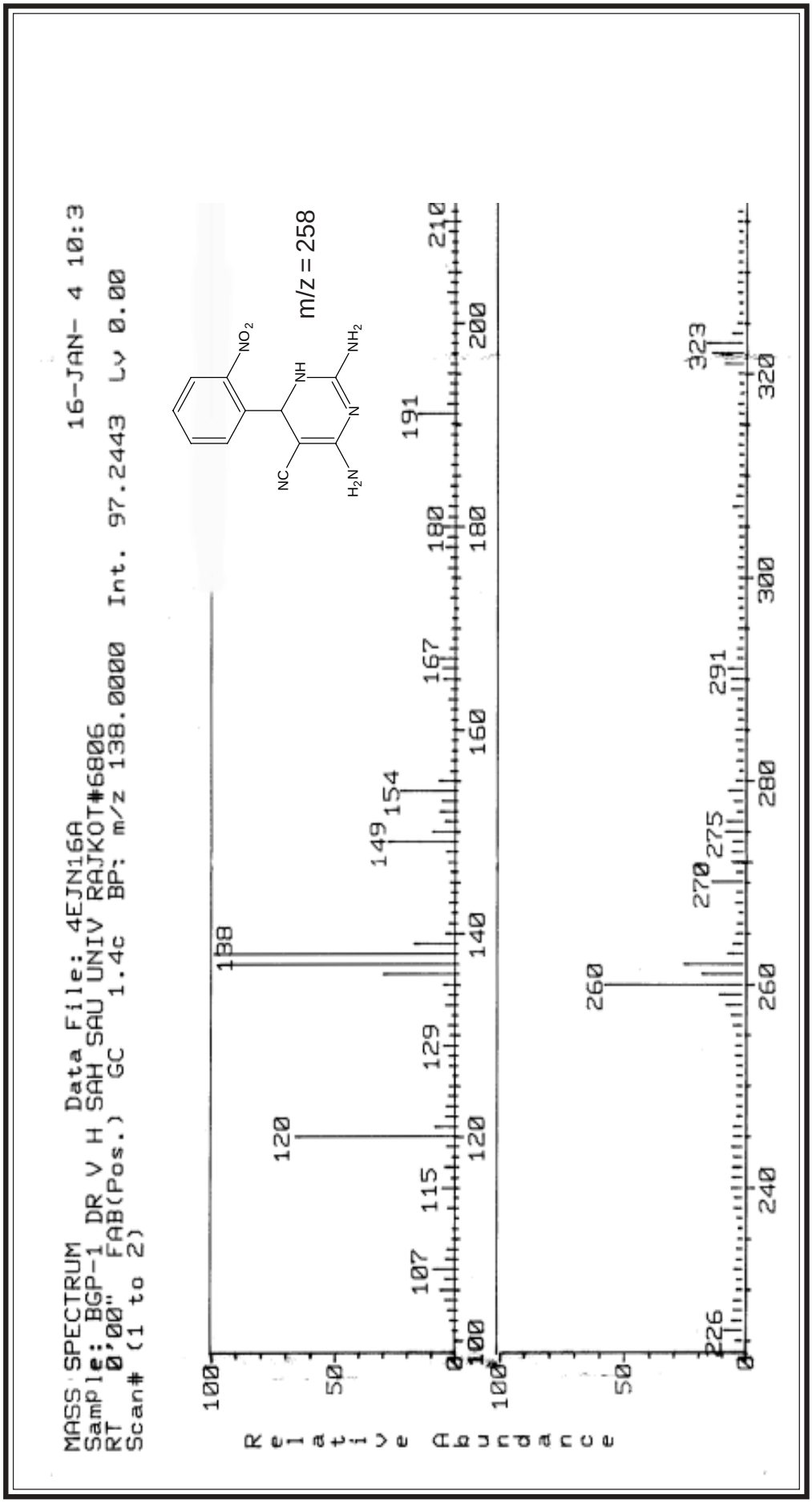
PMR SPECTRAL STUDY OF 2,4-DIAMINO-5-CYANO-6-(*p*-METHOXY PHENYL)-1,6-DIHYDRO PYRIMIDINE (I_h)

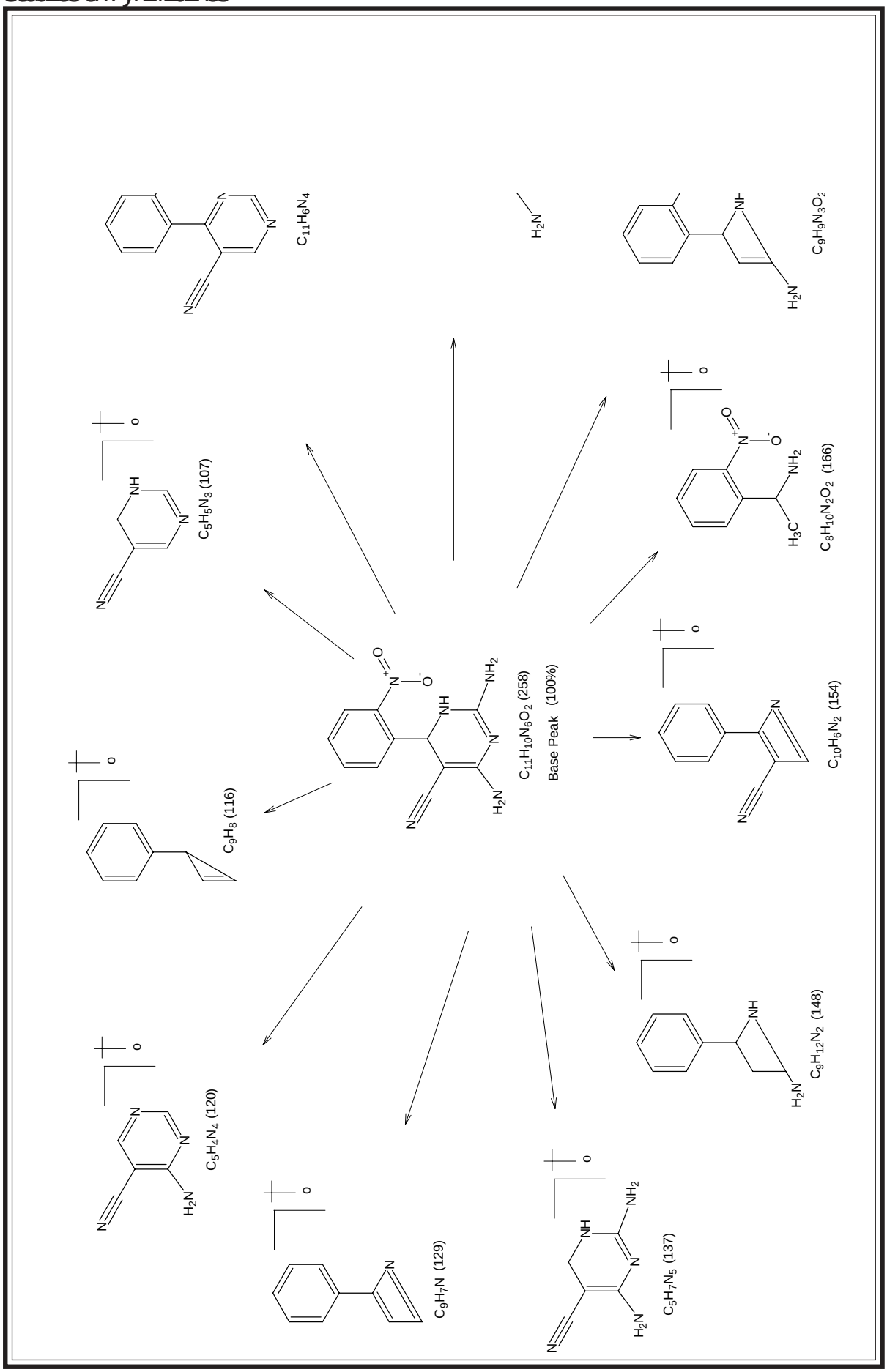


Internal Standard : TMS ; Solvent ; $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

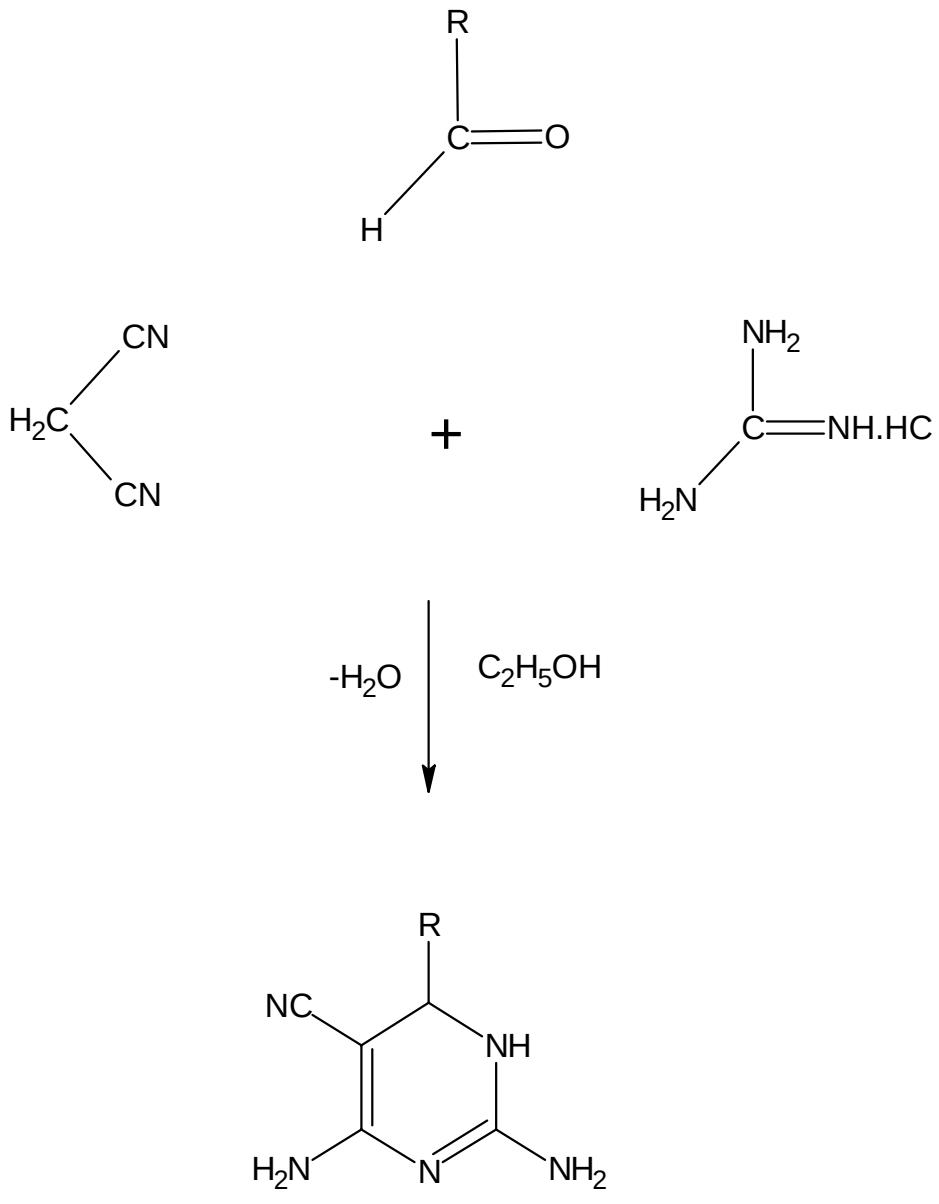
Signal No.	Signal Position (d ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.918	3H	singlet	$-OCH_3$
2.	7.001-7.030	2H	doublet	Ar-$H_{a,a'}$ (J=8.97)
3.	7.654	1H	singlet	Ar-Hc
4.	7.899-7.929	2H	doublet	Ar-$H_{b,b'}$ (J=8.86)
5.	9.157	2H	singlet	$-NH_2$

MASS SPECTRAL OF 2,4-DIAMINO-5-CYANO-6-(*o*-NITROPHENYL)-1,6-DIHYDRO PYRIMIDINE (If)




C11H6N4
H2N
C9H9N3O2
C5H5N3 (107)
C8H10N2O2 (166)
C11H10N6O2 (258)
Base Peak (100%)
C10H6N2 (154)
C9H8 (116)
C9H12N2 (148)
C5H4N4 (120)
C9H7N (129)
C5H7N5 (137)

REACTION SCHEME



(I_{a-j}) **R = Aryl**

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 2,4-DIAMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES

(A) Preparation of 2,4-Diamino-5-cyano-6-(*p*-methoxyphenyl)-1,6-dihydro pyrimidine (I_h).

A mixture of *p*-methoxybenzaldehyde (1.36 ml, 0.01 M), malononitrile (0.66 ml, 0.01 M) and guanidine hydrochloride (0.96 gm, 0.01 M) in ethanol (30 ml) was heated under refluxed condition for three hrs. Then the reaction mixture was kept at room temperature for two hrs. The yellow crystalline product was obtained. The product was isolated and recrystallized from ethanol. Yield : 48%, M.P. : 95°C, R_f : 0.68 (Required : C, 59.26%; H, 5.35%; N, 28.81% for $C_{12}H_{13}N_5O$, Found : C, 59.20%; H, 5.30%; N, 28.75%).

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

(B) Antimicrobial activity of 2,4-Diamino-5-cyano-6-aryl-1,6-dihydro pyrimidines (I_{a-j}).

Antimicrobial activity testing was carried out by using cup-plate method[110], which has been described as under.

* **Antibacterial activity**

S. pyogens MTCC-442 and ***S. aureus MTCC-96*** (Gram positive bacteria) were grown in nutrient broth and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative bacteria) in Peptone water (PW, 1% bacteriological peptone and 0.5% NaCl) for 24 hrs., this gave an optimum growth of the test bacteria. Each purified compound was dissolved in DMF sterilized by filtration by using sintered glass filter and stored at 4°C. Each agent was then added to molten nutrient agar in the following concentrations (µg/ml) : 0 (control), 5, 10, 25,

50, 100, 200, 500 and poured into sterile petri dished. The pH of the media was maintained at 7.2 -7.4. The inoculum consisted of an overnight grown broth culture of a bacterium diluted in such a manner that a 2 mm (internal diameter) loopful of the culture contain 10^5 colony-forming unit (CFU). These were then spot inoculated on nutrient agar plates containing increasing amount of a compound, incubated at 37°C up to 24 hrs. for determination of the minimum inhibitory concentration[111,112] (MIC). Which are recorded in zones of inhibition in mm for bacterias.

* **Antifungal activity**

C. albicans MTCC-227 and ***A. niger MTCC-282*** was employed for testing antifungal activity using cup-plate method. The culture was maintained on Sabouraud's agar for 72 hrs., this gave an optimum growth of the test fungal spores. Each purified compound was dissolved in DMF sterilized by filtration by using sintered glass filter and stored. Each agent was then added to Sabouraud's agar in the following concentrations (µg/ml): 0 (control), 5, 10, 25, 50, 100, 200, 500 and poured into sterile petri dished. The inoculum consisted of an overnight grown broth culture of a bacterium diluted in such a manner than a 2 mm (internal diameter) loopful of the culture contain 105 colony-forming unit (CFU). These were then spot inoculated on Sabouraud's agar plates containing increasing amount of a compound, incubated at 37°C up to 48 hrs. for determination of the minimum inhibitory concentration (MIC)[111,112]. The MIC values of test solutions are recorded in Table No. 1a, 1b & 1c . Which are recorded in zones of inhibition in mm for fungii.

TABLE NO. 1 : PHYSICAL CONSTANTS OF 2,4-DIAMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES (I_{a-j})

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. °C 5	Yield % 6	R_f Value 7	% of Nitrogen	
							Required 8	Found 9
Ia	C_6H_5	$C_{11}H_{11}N_5$	213.0	68	73	0.64	32.86	32.81
Ib	2-OH-C_6H_4	$C_{11}H_{11}N_5O$	229.0	118	74	0.59	30.57	30.52
Ic	4-OH-C_6H_4	$C_{11}H_{11}N_5O$	229.0	157	66	0.61	30.57	30.53
Id	2-Cl-C_6H_4	$C_{11}H_{10}N_5Cl$	247.5	90	62	0.54	28.28	28.23
Ie	4-Cl-C_6H_4	$C_{11}H_{10}N_5Cl$	247.5	146	58	0.59	28.28	28.24
If	2-NO_2-C_6H_4	$C_{11}H_{10}N_6O_2$	258.0	80	52	0.62	32.56	32.51
Ig	3-NO_2-C_6H_4	$C_{11}H_{10}N_6O_2$	258.0	133	56	0.63	32.56	32.52
Ih	4-CH_3O-C_6H_4	$C_{12}H_{13}N_5O$	243.0	95	48	0.68	28.81	28.75
Ii	C_6H_5-CH=CH-	$C_{13}H_{13}N_5$	239.0	112	62	0.71	29.29	29.26
Ij	$C_{14}H_9$	$C_{19}H_{15}N_5$	313.0	86	76	0.63	22.36	22.33

TLC solvent system ; Ethyl acetate : Cyclohexane = 2 : 8

TABLE NO. 1a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2,4-DIAMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES I_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442 5	10	25	50	100	250	500	S. aureus MTCC-96 5	10	25	50	100	250	500
Ia	C_6H_5	-	-	10	12	14	16	18	-	-	13	14	16	18	19
Ib	2-OH-C_6H_4	-	-	11	13	15	17	18	-	-	13	15	15	16	18
Ic	4-OH-C_6H_4	-	-	12	13	16	17	17	-	-	12	14	18	18	19
Id	2-Cl-C_6H_4	-	-	10	11	14	15	16	-	-	12	12	16	17	18
Ie	4-Cl-C_6H_4	-	-	10	12	14	14	15	-	-	12	13	15	16	17
If	2-NO_2-C_6H_4	-	-	10	12	14	15	16	-	-	13	14	16	17	18
Ig	3-NO_2-C_6H_4	-	-	10	12	15	16	18	-	-	12	13	15	17	17
Ih	4-OCH_3-C_6H_4	-	-	11	13	14	15	17	-	-	12	13	15	17	18
Ii	-CH=CH-C_6H_4	-	-	12	14	15	15	17	-	-	11	13	15	16	17
Ij	$C_{14}H_9$	-	-	10	12	14	14	15	-	-	11	12	15	17	17

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

Standard drug	Antibacterial activity														
											Ia Ib If	Ia Ib Ic If	Ia Ib Id If	Ia Ic	
Ampicillin	11	13	14	16	18	19	20	10	12	13	14	16	18	21	
Chloramphenicol	10	12	13	19	20	20	22	12	13	14	19	20	21	22	
Ciprofloxacin	16	18	19	21	21	22	22	17	18	19	21	22	22	23	
Norfloxacin	18	18	19	20	21	21	23	19	20	22	25	26	28	28	

N.B.(-): No Activity

TABLE NO. 1b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2,4-DIAMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES I_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)													
		E. Coli MTCC-443							B. subtillis MTCC-441						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
Ia	C_6H_5	-	-	11	13	17	17	16	-	-	14	16	15	15	17
Ib	2-OH-C_6H_4	-	-	14	15	16	18	19	-	-	16	17	18	19	14
Ic	4-OH-C_6H_4	-	-	12	13	15	17	18	-	-	14	15	17	19	19
Id	2-Cl-C_6H_4	-	-	13	14	15	16	19	-	-	15	17	18	19	19
Ie	4-Cl-C_6H_4	-	-	14	15	17	18	19	-	-	15	17	19	20	22
If	2-NO_2-C_6H_4	-	-	11	15	16	17	19	-	-	12	16	18	19	20
Ig	3-NO_2-C_6H_4	-	-	14	15	17	18	19	-	-	16	17	19	20	20
Ih	4-OCH_3-C_6H_4	-	-	14	15	17	18	19	-	-	15	17	18	19	20
Ii	-CH=CH-C_6H_4	-	-	14	15	17	18	20	-	-	15	17	19	19	19
Ij	$C_{14}H_9$	-	-	11	13	17	17	18	-	-	13	15	15	19	20

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

Standard drug	Antibacterial activity														
											Ib Ig				
Ampicillin	14	14	15	16	19	20	22	12	16	18	19	20	21	23
Chloramphenicol	14	15	17	23	23	23	23	12	14	16	19	22	23	23
Ciprofloxacin	20	21	23	28	28	28	28	16	17	19	22	22	23	23
Norfloxacin	22	23	25	26	27	29	29	19	20	22	23	24	25	28

N.B.(-): No Activity

TABLE NO. 1c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2,4-DIAMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES I_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antifungal activity (Zones of inhibition in mm)													
		C. albicans MTCC-227							A. niger MTCC-282						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
Ia	C_6H_5	-	-	16	17	20	21	22	-	-	18	18	21	22	22
Ib	2-OH-C_6H_4	-	-	17	18	20	21	22	-	-	18	18	22	23	24
Ic	4-OH-C_6H_4	-	-	17	18	20	20	22	-	-	16	19	22	22	24
Id	2-Cl-C_6H_4	-	-	17	18	20	20	22	-	-	18	20	23	22	24
Ie	4-Cl-C_6H_4	-	-	14	18	20	21	21	-	-	18	19	21	23	24
If	2-NO_2-C_6H_4	-	-	15	18	19	20	22	-	-	18	19	21	23	24
Ig	3-NO_2-C_6H_4	-	-	17	17	20	22	23	-	-	19	18	22	23	24
Ih	4-OCH_3-C_6H_4	-	-	17	18	20	21	22	-	-	18	19	20	22	24
Ii	-CH=CH-C_6H_4	-	-	17	18	20	21	22	-	-	18	19	22	22	24
Ij	$C_{14}H_9$	-	-	15	17	20	21	23	-	-	18	19	21	23	24

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

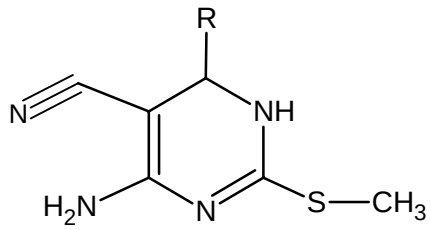
Standard drug	Antifungal activity													
													Ib Ic Id Ig Ii	
Griseofulvin	19	22	23	25	25	28	28	18	19	21	22	22	24	26

N.B.(-): No Activity

SECTION - II

PREPARATION AND EVALUATION OF 2-MERCAPTOMETHYL-4-AMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES

Looking to other properties[29-37] and biodynamic activities[48-104] of pyrimidines and with a view to have potent therapeutic agents, the synthesis of 2-mercaptomethyl-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines (II_{a-j}) have been undertaken by the condensation of 2-mercapto-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines with dimethyl sulphate in the presence of base.

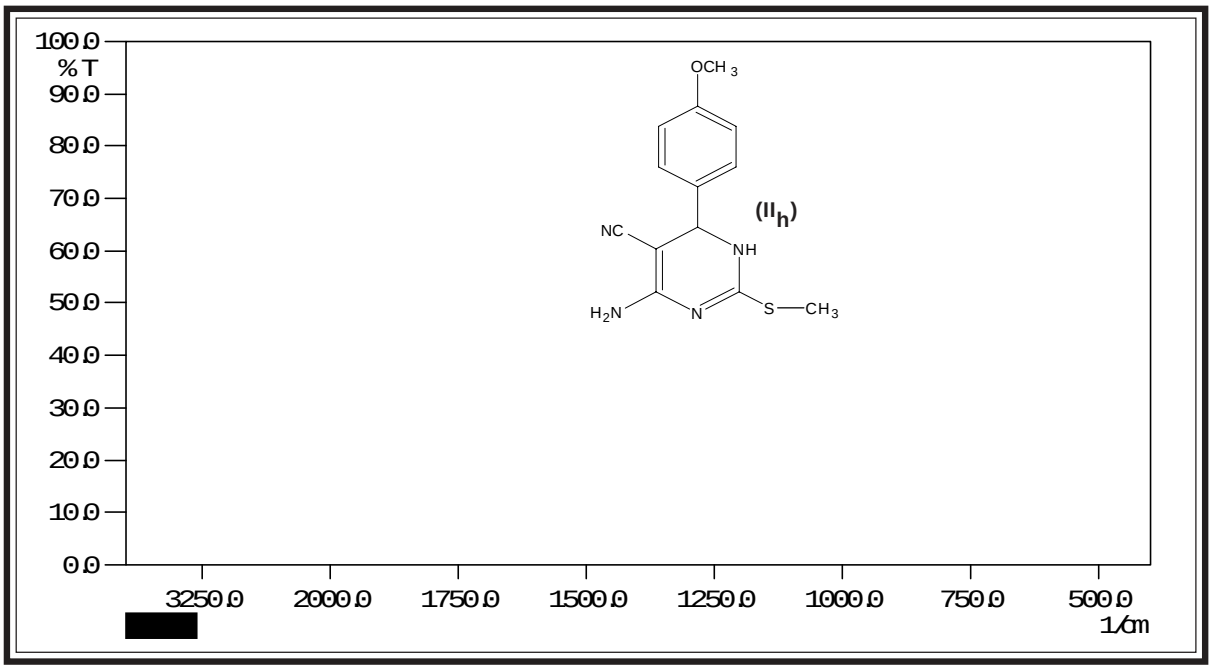


II_{a-j} **R=Aryl**

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

The products (II_{a-j}) were assayed for their *in vitro* biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

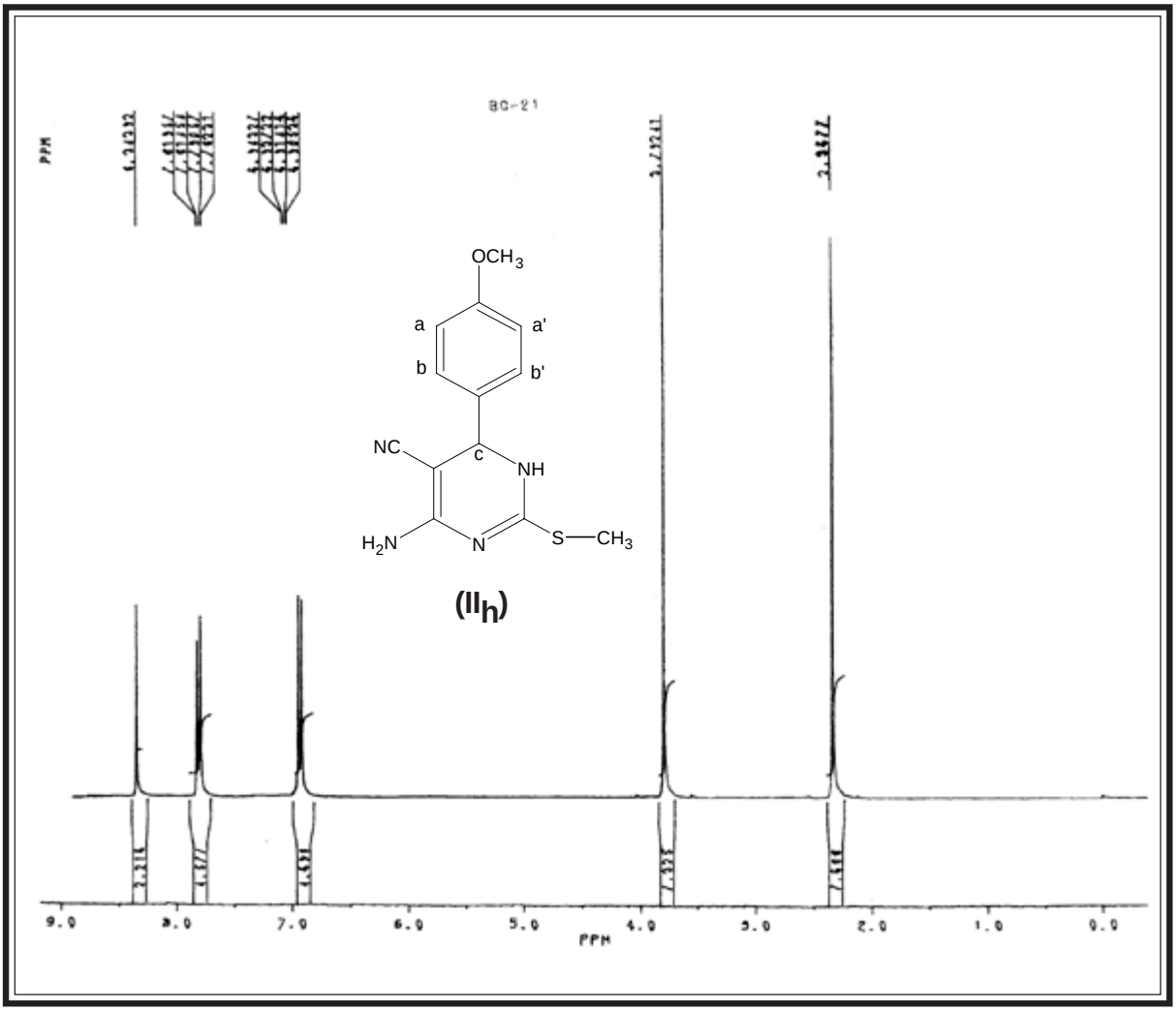
IR SPECTRAL STUDY OF 2-MERCAPTOMETHYL-4-AMINO-5-CYANO-6- (*p*-METHOXYPHENYL)-1,6-DIHYDRO PYRIMIDINE (II_h)



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.(asym.)	2922.0	2975-2950	343
CH_3	C-H str.(sym.)	2846 .7	2880-2860	,,
	C-H def.(asym.)	1458.1	1460-1435	,,
	C-H def.(sym.)	1355.9	1385-1300	,,
Aromatic and	C=C + C=N and ring	1514.0	1520-1480	345
Pyrimidine moiety	skeletal vibration	1568.0	1580-1520	,,
	C-H str.	3193.9	3080-3030	,,
	C-H i.p. def.	1112.8	1125-1090	,,
	C-H o.o.p. def.	833.2	840-810	,,
Ether	C-O-C str. (asym.)	1263.3	1275-1200	346
	C-O-C str. (sym.)	1055.0	1075-1050	,,
Amine (Primary)	N-H str.	3398.3	3500-3300	343
	N-H def.	1656.7	1650-1580	,,
Nitrile	C=N str.	2208.3	2260-2190	345
S-CH_3	C-S-C	634.5	700-600	343

PMR SPECTRAL STUDY OF 2-MERCAPTOMETHYL-4-AMINO-5-CYANO-6-(*p*-METHOXYPHENYL)-1,6-DIHYDRO PYRIMIDINE (II_h)

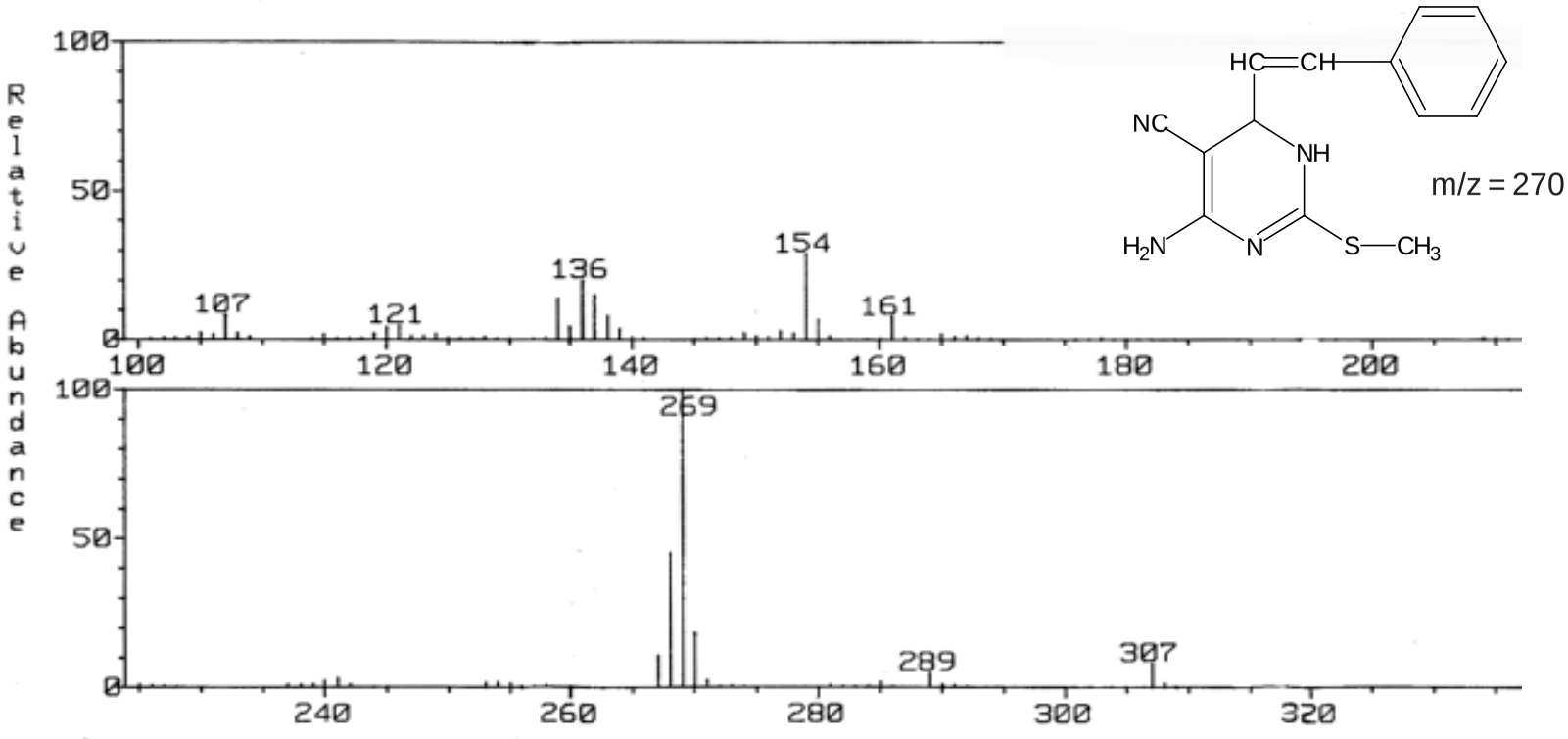


(II_h)

Internal Standard : TMS ; Solvent ; $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

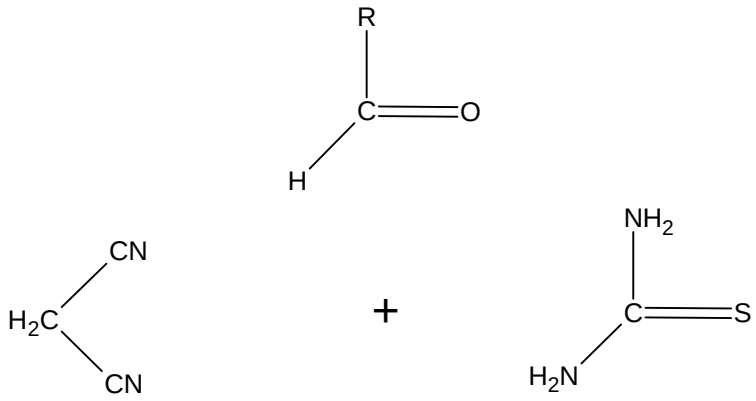
Signal No.	Signal Position (d ppm)	Relative No. of Proton	Multiplicity	Inference
1.	2.368	3H	singlet	$-SCH_3$
2.	3.792	3H	singlet	$-OCH_3$
3.	6.914-6.943	2H	doublet	Ar-$H_{a,a'}$(J=8.7)
4.	7.791-7820	2H	doublet	Ar-$H_{b,b'}$(J=8.7)
5.	8.344	1H	singlet	Ar-H_c

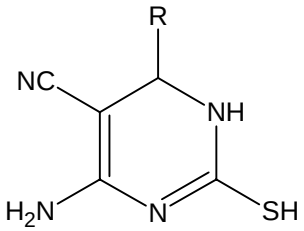
MASS SPECTRAL OF 2-MERCAPTOMETHYL-4-AMINO-5-CYANO-6-(VINYLPHENYL)-1,6-DIHYDRO PYRIMIDINE (II_j)



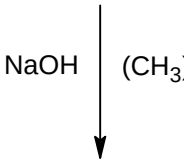
C14H14N4S (270)
Base Peak (100%)
C6H15N3S (161)
C5H5N3 (107)
C6H7N3 (136)
C6H8N
C5H6N4S (154

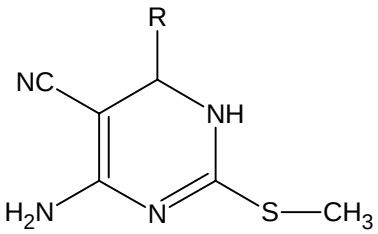
REACTION SCHEME





(1_{a-j})





(II_{a-j}) **R = Aryl**

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 2-MERCAPTOMETHYL-4-AMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES

(A) Preparation of 2-Mercapto-4-amino-5-cyano-6-(*p*-methoxyphenyl)-1,6-dihydro pyrimidine (1_h).

A mixture of *p*-methoxybenzaldehyde (1.36 ml, 0.01 M), malononitrile (0.66 ml, 0.01 M) and thiourea (0.76 gm, 0.01 M) in ethanol (30 ml) was heated under refluxed condition for three hrs. Then the reaction mixture was kept at room temperature for two hrs. The yellow crystalline product was obtained. The product was isolated and recrystallized from ethanol. Yield : 51%, M.P. : 120°C, R_f : 0.62 (Required : C, 55.38%; H, 4.62%; N, 21.54% for $C_{12}H_{12}N_4OS$, Found : C, 55.32% ; H, 4.58%; N, 21.48%).

Similarly, other compounds (1_{a-j}) were synthesized. The physical data are recorded in Table No. 2.

(B) Preparation of 2-Mercaptomethyl-4-amino-5-cyano-6-(*p*-methoxy phenyl)-1,6-dihydro pyrimidine (II_h).

A mixture of 2-mercapto-4-amino-5-cyano-6-(*p*-methoxyphenyl)-1,6-dihydro pyrimidine (2.60 gm, 0.01 M) and dimethyl sulphate (1.26 ml, 0.01 M) in ethanol (30 ml) and 40% aqueous sodium hydroxide was stirred for 12 hrs. at room temperature. The content was poured into ice cold water and filtered. The product was isolated and crystallized from ethanol. Yield : 62%, M.P. : 101°C; R_f : 0.72, (Required : C, 56.93%; H, 5.11%; N, 20.44% for $C_{13}H_{14}N_4OS$, Found : C, 56.88%; H, 5.06%; N, 20.40%).

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

(C) Antimicrobial activity of 2-Mercaptomethyl-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines (II_{a-j})

Antimicrobial activity testing was carried out as described in part-1, section-I, page No. 35. The MIC values of test solution are recorded in Table No. 3a, 3b & 3c.

TABLE NO. 2 : PHYSICAL CONSTANTS OF 2-MERCAPTO-4-AMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES (1_{a-j})

Comp. No.	R	Molecular Formula	M.W.	M.P. °C	Yield %	R_f Value	% of Nitrogen	
							Required	Found
1	2	3	4	5	6	7	8	9
1a	C_6H_5	$C_{11}H_{10}N_4S$	230.0	152	68	0.48	24.35	24.30
1b	2-OH-C_6H_4	$C_{11}H_{10}N_4OS$	246.0	88	74	0.57	22.76	22.70
1c	4-OH-C_6H_4	$C_{11}H_{10}N_4OS$	246.0	141	56	0.54	22.76	22.71
1d	2-Cl-C_6H_4	$C_{11}H_9N_4SCl$	264.5	148	72	0.51	21.17	21.12
1e	4-Cl-C_6H_4	$C_{11}H_9N_4SCl$	264.5	123	55	0.53	21.17	21.12
1f	2-NO_2-C_6H_4	$C_{11}H_9N_5O_2S$	275.0	172	49	0.59	25.45	25.41
1g	3-NO_2-C_6H_4	$C_{11}H_9N_5O_2S$	275.0	131	43	0.61	25.45	25.40
1h	4-CH_3O-C_6H_4	$C_{12}H_{12}N_4OS$	260.0	120	51	0.62	21.54	21.48
1i	C_6H_5-CH=CH-	$C_{13}H_{12}N_4S$	256.0	118	64	0.60	21.88	21.82
1j	$C_{14}H_9$	$C_{19}H_{14}N_4S$	330.0	127	68	0.63	16.97	16.93

TLC solvent system ; Acetone : Benzene = 1 : 9

TABLE NO. 3 : PHYSICAL CONSTANTS OF 2-MERCAPTOMETHYL-4-AMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES (II_{a-j})

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. ^oC 5	Yield % 6	R_f Value 7	% of Nitrogen	
							Required 8	Found 9
IIa	C_6H_5	$C_{12}H_{12}N_4S$	244.0	50	66	0.61	22.95	22.90
IIb	2-OH-C_6H_4	$C_{12}H_{12}N_4OS$	260.0	112	62	0.52	21.54	21.50
IIc	4-OH-C_6H_4	$C_{12}H_{12}N_4OS$	260.0	164	58	0.65	21.54	21.48
IId	2-Cl-C_6H_4	$C_{12}H_{11}N_4SCl$	278.0	82	61	0.67	20.11	20.09
IIe	4-Cl-C_6H_4	$C_{12}H_{11}N_4SCl$	278.0	>260	68	0.58	20.11	20.07
IIf	2-NO_2-C_6H_4	$C_{12}H_{11}N_5O_2S$	289.0	124	56	0.54	24.22	24.19
IIg	3-NO_2-C_6H_4	$C_{12}H_{11}N_5O_2S$	289.0	165	52	0.65	24.22	24.18
IIh	4-CH_3O-C_6H_4	$C_{13}H_{14}N_4OS$	274.0	101	62	0.72	20.44	20.40
IIh	C_6H_5-CH=CH-	$C_{14}H_{14}N_4S$	270.0	158	68	0.63	20.74	20.70
IIj	$C_{14}H_9$	$C_{20}H_{16}N_4S$	344.0	148	72	0.67	16.28	16.22

i TLC solvent system ; Ethyl acetate : Cyclohexane = 1 : 9

TABLE NO. 3a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-MERCAPTOMETHYL-4-AMINO-5-CYANO-6-ARYL-1,6- DIHYDRO PYRIMIDINES II_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442							S. aureus MTCC-96						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
IIa	C_6H_5	-	-	-	12	13	15	16	-	-	11	12	14	16	17
IIb	2-OH-C_6H_4	-	-	11	12	14	14	15	-	-	12	13	15	16	17
IIc	4-OH-C_6H_4	-	-	12	12	13	14	15	-	-	11	14	15	16	17
IId	2-Cl-C_6H_4	-	-	10	12	13	15	16	-	-	11	14	15	16	17
IIe	4-Cl-C_6H_4	-	-	12	12	14	15	15	-	-	10	11	15	17	18
IIf	2-NO_2-C_6H_4	-	-	10	12	12	14	14	-	-	11	12	13	16	16
IIg	3-NO_2-C_6H_4	-	-	11	12	13	15	15	-	-	10	11	15	16	17
IIh	4-OCH_3-C_6H_4	-	-	10	11	13	14	15	-	-	12	12	11	13	16
IIi	-CH=CH-C_6H_4	-	-	12	12	13	14	15	-	-	11	14	15	16	17
IIj	$C_{14}H_9$	-	-	11	11	12	13	15	-	-	13	14	14	15	16

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

Standard drug	Antibacterial activity														
											IIj	IIc IId IIi IIj			
Ampicillin	11	13	14	16	18	19	20	10	12	13	14	16	18	21
Chloramphenicol	10	12	13	19	20	20	22	12	13	14	19	20	21	22
Ciprofloxacin	16	18	19	21	21	22	22	17	18	19	21	22	22	23
Norfloxacin	18	18	19	20	21	21	23	19	20	22	25	26	28	28

N.B.(-): No Activity

TABLE NO. 3b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-MERCAPTOMETHYL-4-AMINO-5-CYANO-6-ARYL-1,6- DIHYDRO PYRIMIDINES II_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)													
		E. Coli MTCC-443							B. subtillis MTCC-441						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
IIa	C_6H_5	-	-	15	16	18	19	20	-	-	17	18	19	19	20
IIb	2-OH-C_6H_4	-	-	14	15	16	17	18	-	-	15	17	18	19	19
IIc	4-OH-C_6H_4	-	-	14	15	16	18	19	-	-	15	17	18	19	20
IId	2-Cl-C_6H_4	-	-	13	15	18	18	19	-	-	14	17	19	19	19
IIe	4-Cl-C_6H_4	-	-	14	15	17	18	18	-	-	15	16	18	19	19
IIf	2-NO_2-C_6H_4	-	-	13	14	15	17	18	-	-	15	16	18	19	19
IIg	3-NO_2-C_6H_4	-	-	12	14	16	18	18	-	-	14	16	18	19	19
IIh	4-OCH_3-C_6H_4	-	-	13	14	15	16	18	-	-	15	16	17	18	19
IIi	-CH=CH-C_6H_4	-	-	13	15	16	17	18	-	-	15	18	19	19	19
IIj	$C_{14}H_9$	-	-	14	15	16	16	18	-	-	16	17	17	18	19

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

Standard drug	Antibacterial activity														
			IIa	IIa						IIa IIj					
Ampicillin	14	14	15	16	19	20	22	12	16	18	19	20	21	23
Chloramphenicol	14	15	17	23	23	23	23	12	14	16	19	22	23	23
Ciprofloxacin	20	21	23	28	28	28	28	16	17	19	22	22	23	23
Norfloxacin	22	23	25	26	27	29	29	19	20	22	23	24	25	28

N.B.(-): No Activity

TABLE NO. 3c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-MERCAPTOMETHYL-4-AMINO-5-CYANO-6-ARYL-1,6- DIHYDRO PYRIMIDINES II_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antifungal activity (Zones of inhibition in mm) C. albicans MTCC-227							A. niger MTCC-282						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
IIa	C_6H_5	-	-	15	18	20	20	21	-	-	18	19	20	22	23
IIb	2-OH-C_6H_4	-	-	17	18	19	20	21	-	-	18	18	20	22	22
IIc	4-OH-C_6H_4	-	-	17	18	20	21	21	-	-	18	19	21	22	23
IId	2-Cl-C_6H_4	-	-	17	17	20	21	21	-	-	18	19	21	22	23
IIe	4-Cl-C_6H_4	-	-	17	18	20	21	22	-	-	18	19	21	23	24
IIf	2-NO_2-C_6H_4	-	-	17	18	20	20	21	-	-	18	19	22	22	22
IIg	3-NO_2-C_6H_4	-	-	17	17	19	20	20	-	-	18	19	21	21	22
IIh	4-OCH_3-C_6H_4	-	-	17	18	20	20	21	-	-	18	19	20	21	22
IIi	-CH=CH-C_6H_4	-	-	17	18	20	20	21	-	-	18	20	21	22	23
IIj	$C_{14}H_9$	-	-	17	17	19	20	21	-	-	18	18	20	21	23

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

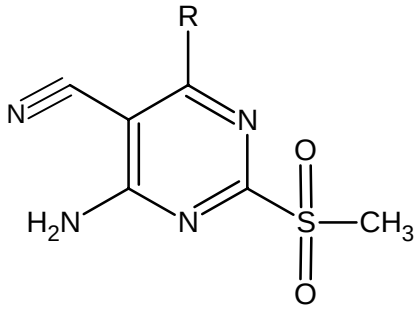
Standard drug	Antifungal activity													
													IIf	
Griseofulvin	19	22	23	25	25	28	28	18	19	21	22	22	24	26

N.B.(-): No Activity

SECTION - III

PREPARATION AND BIOLOGICAL EVALUATION OF 2-METHYL SULPHONYL-4-AMINO-5-CYANO-6-ARYL PYRIMIDINES

In view of various biodynamic activities[48-104] and other properties[29-37] of pyrimidines and in order to have highly potent therapeutic agents, the synthesis of 2-methylsulphonyl-4-amino-5-cyano-6-aryl pyrimidines (III_{a-j}) have been undertaken by the reaction of 2-mercaptomethyl-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines with hydrogen peroxide.

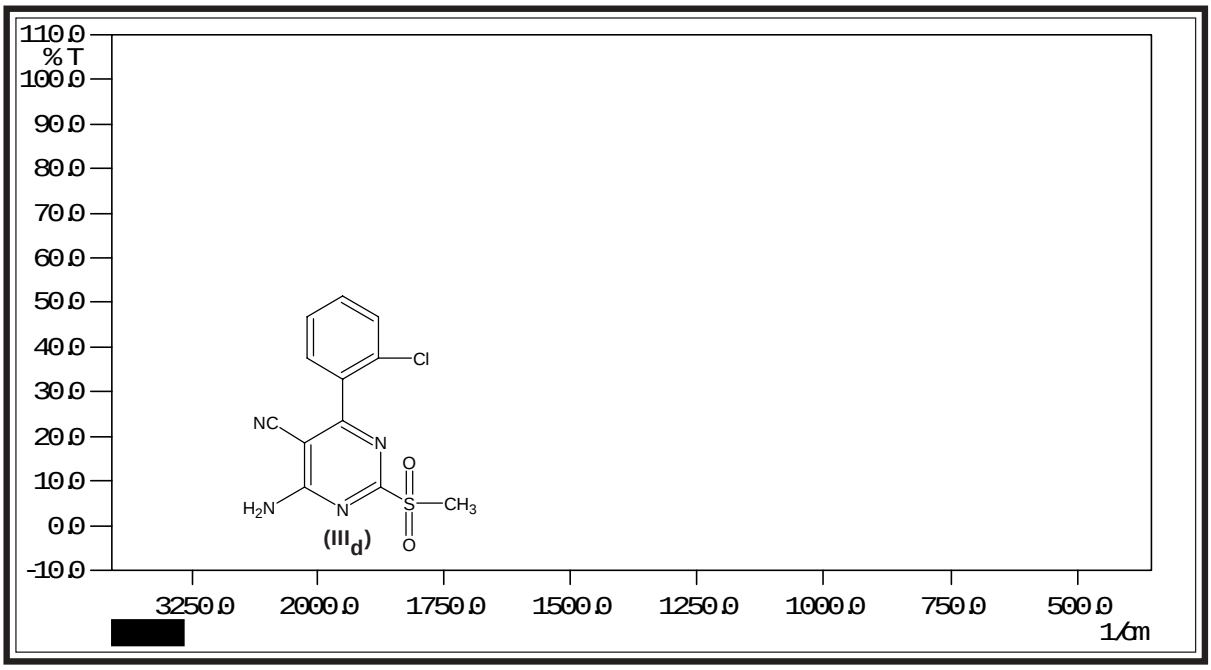


III_{a-j} **R=Aryl**

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

The products (III_{a-j}) were assayed for their *in vitro* biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

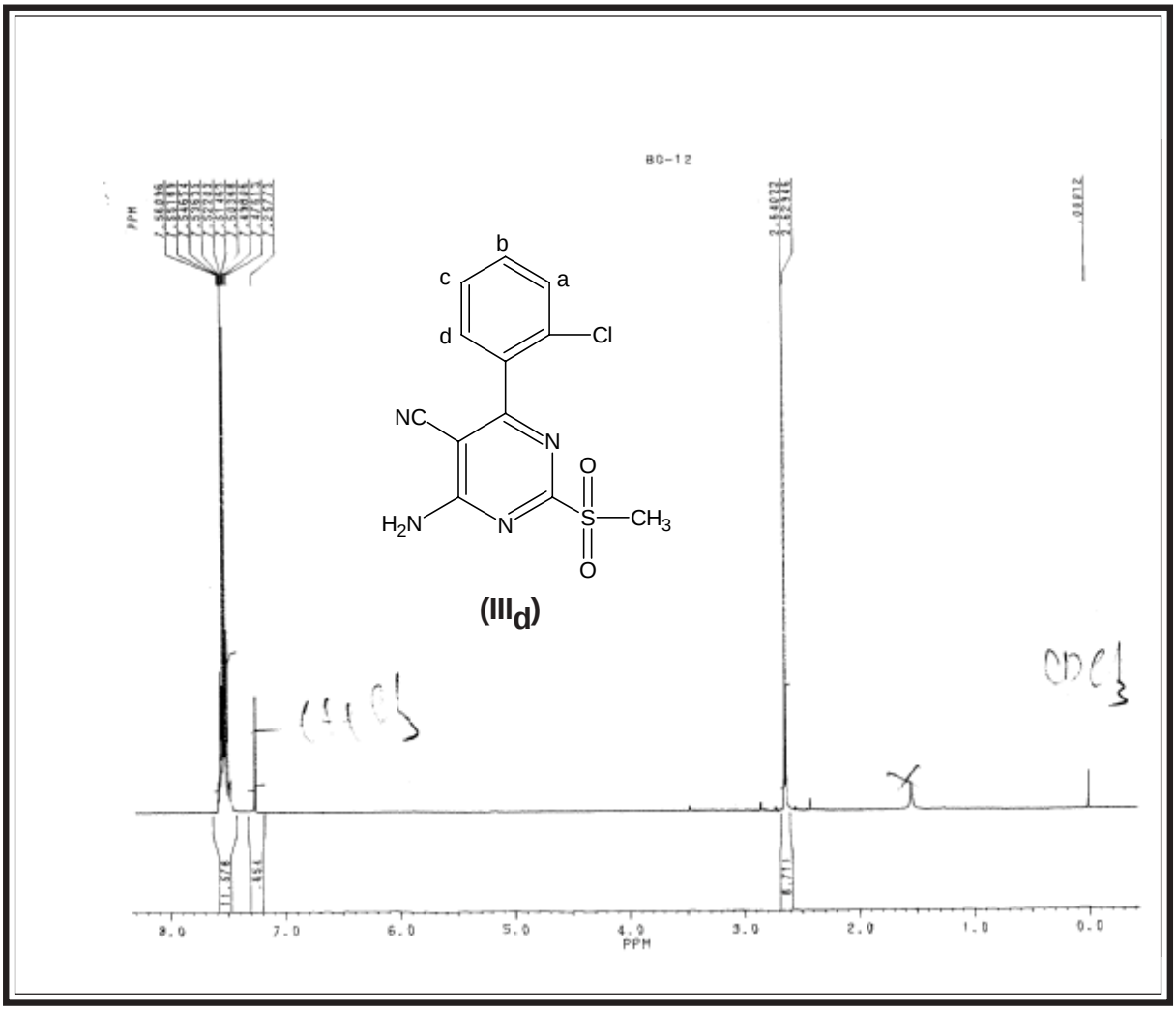
IR SPECTRAL STUDY OF 2-METHYLSULPHONYL-4-AMINO-5-CYANO-6-(*p*-CHLOROPHENYL) PYRIMIDINE (III_d)



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.(asym.)	2925.8	2975-2950	343
CH_3	C-H str.(sym.)	2854.5	2880-2860	,,
	C-H def.(asym.)	1477.4	1460-1435	,,
	C-H def.(sym.)	1386.7	1385-1300	,,
Aromatic and	C=C + C=N and ring	1512.1	1520-1480	345
Pyrimidine moiety	skeletal vibration	1541.0	1580-1520	,,
	C-H str.	3082.0	3080-3030	,,
	C-H i.p. def.	1139.9	1125-1090	,,
	C-H o.o.p. def.	829.3	840-810	,,
Amine (Primary)	N-H str.	3400.0	3500-3300	343
	N-H def.	1651.0	1650-1580	,,
Nitrile	C=N str.	2218.0	2260-2190	345
Halogen	C-Cl	773.4	800-600	343
SO_2-CH_3	S=O str. (asym)	1346.2	1380-1300	344
	S=O str. (sym)	1168.8	1180-1140	,,

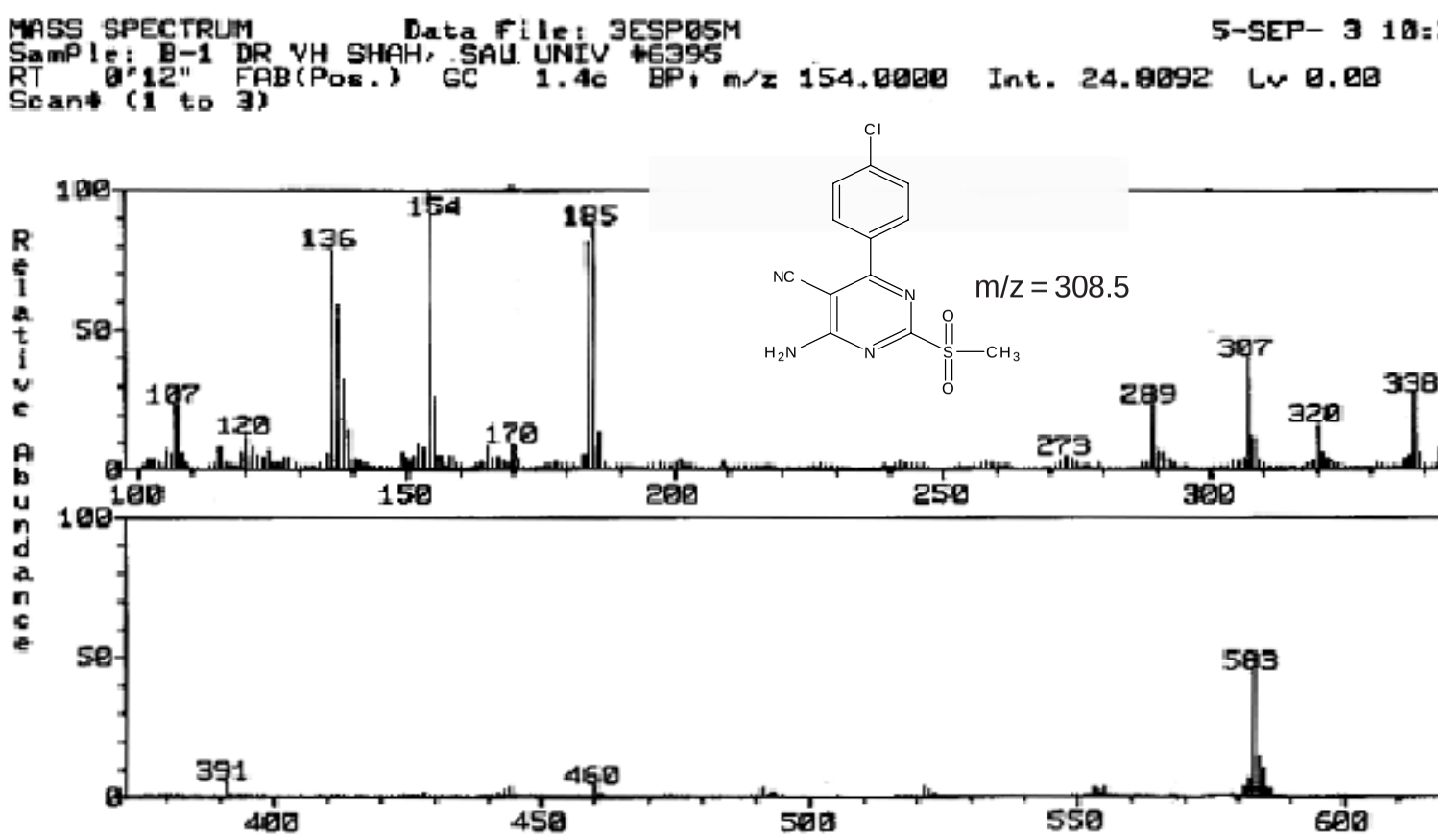
PMR SPECTRAL STUDY OF 2-METHYLSULPHONYL-4-AMINO-5-CYANO-6-(*p*-CHLOROPHENYL) PYRIMIDINE (III_d)



Internal Standard : TMS ; Solvent ; $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

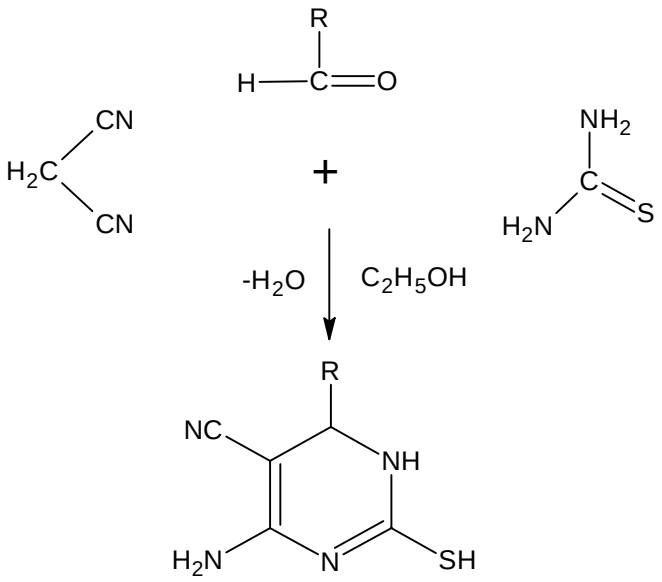
Signal No.	Signal Position (d ppm)	Relative No. of Proton	Multiplicity	Inference
1.	2.640	3H	singlet	$-SO_2CH_3$
2.	7.498-7.561	4H	multiplet	Ar-H_a , Ar-H_b , Ar-H_c , Ar-H_d

MASS SPECTRAL OF 2-METHYLSULPHONYL-4-AMINO-5-CYANO-6-(*p*-CHLOROPHENYL) PYRIMIDINE (III_e)

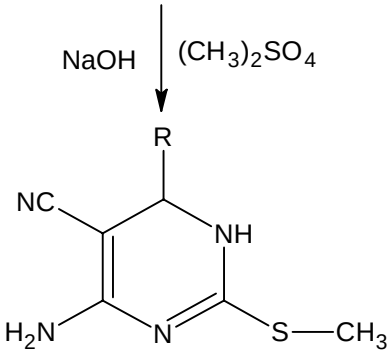


C6H7N3O2S (1
Base Peak (1
C12H9N4O2SCl (308.5)
C5H4N4 (120)
C12H10N4O2S (274)
C5H5N3 (107)

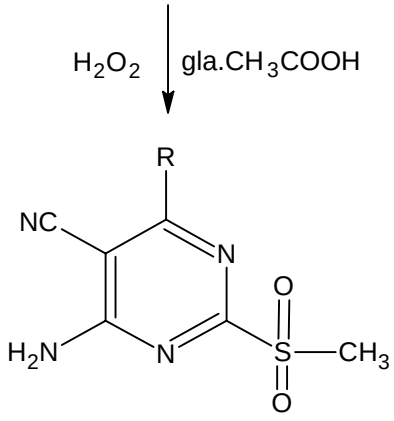
REACTION SCHEME



(1_{a-j})



(II_{a-j})



(III_{a-j}) **R = Aryl**

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 2-METHYL SULPHONYL-4-AMINO-5-CYANO-6-ARYL PYRIMIDINES

(A) Preparation of 2-Mercaptomethyl-4-amino-5-cyano-6-(*o*-chloro phenyl)-1,6-dihydro pyrimidine (II_d).

For preparation refer Part-I, Section-II, Page No. 47.

(B) Preparation of 2-Methylsulphonyl-4-amino-5-cyano-6-(*o*-chloro phenyl) pyrimidine (III_d).

2-mercaptomethyl-4-amino-5-cyano-6-(*o*-chlorophenyl)-1,6-dihydro pyrimidine (2.785 gm, 0.01M) was dissolved in 20ml of glacial acetic acid and add 12 ml of hydrogen peroxide and then kept for 48 hrs. at room temperature. The content was poured into ice cold water and filtered. The product was isolated and crystallized from ethanol. Yield : 56%, M.P. : 54°C, R_f : 0.63, (Required : C, 46.68%; H, 2.92%; N, 18.15% for $C_{12}H_9N_4O_2SCl$, Found : C, 46.62 %; H, 2.89%; N, 18.12%).

Similarly, other compounds (III_{a-j}) were synthesized. The physical data are recorded in Table No. 4.

(C) Antimicrobial activity of 2-Methylsulphonyl-4-amino-5-cyano-6-aryl pyrimidines (III_{a-j}).

Antimicrobial activity testing was carried out as described in part-1, section-I, page No. 35. The MIC values of test solution are recorded in Table No. 4a, 4b & 4c.

TABLE NO. 4 : PHYSICAL CONSTANTS OF 2-METHYLSULPHONYL-4-AMINO-5-CYANO-6-ARYL PYRIMIDINES (III_{a-j})

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. ^oC 5	Yield % 6	R_f Value 7	% of Nitrogen	
							Required 8	Found 9
IIIa	C_6H_5	$C_{12}H_{10}N_4O_2S$	274.0	80	62	0.72	20.44	20.40
IIIb	2-OH-C_6H_4	$C_{12}H_{10}N_4O_3S$	290.0	122	58	0.68	19.31	19.26
IIIc	4-OH-C_6H_4	$C_{12}H_{10}N_4O_3S$	290.0	185	64	0.62	19.31	19.27
IIId	2-Cl-C_6H_4	$C_{12}H_9N_4O_2SCl$	308.5	54	56	0.63	18.15	18.12
IIIe	4-Cl-C_6H_4	$C_{12}H_9N_4O_2SCl$	308.5	136	58	0.58	18.15	18.10
IIIf	2-NO_2-C_6H_4	$C_{12}H_9N_5O_4S$	319.0	142	54	0.60	21.94	21.90
IIIg	3-NO_2-C_6H_4	$C_{12}H_9N_5O_4S$	319.0	65	51	0.55	21.94	21.89
IIIh	4-CH_3O-C_6H_4	$C_{13}H_{12}N_4O_3S$	304.0	94	60	0.67	18.42	18.40
IIIi	C_6H_5-CH=CH-	$C_{14}H_{12}N_4O_2S$	300.0	103	58	0.69	18.67	18.63
IIIj	$C_{14}H_9$	$C_{20}H_{14}N_4O_2S$	374.0	112	66	0.63	14.97	14.92

TLC solvent system ; Ethyl acetate : Cyclohexane = 1 : 9

TABLE NO. 4a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-METHYLSULPHONYL-4-AMINO-5-CYANO-6-ARYL PYRIMIDINES III_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442							S. aureus MTCC-96						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
IIIa	C_6H_5	-	-	10	12	13	14	15	-	-	12	13	15	16	16
IIIb	2-OH-C_6H_4	-	-	10	11	12	14	14	-	-	12	13	14	16	16
IIIc	4-OH-C_6H_4	-	-	10	11	13	15	15	-	-	11	12	15	17	17
IIId	2-Cl-C_6H_4	-	-	12	12	14	15	15	-	-	14	15	16	17	17
IIIe	4-Cl-C_6H_4	-	-	11	12	12	14	15	-	-	12	12	14	15	16
IIIf	2-NO_2-C_6H_4	-	-	11	11	13	14	15	-	-	13	14	15	15	17
IIIg	3-NO_2-C_6H_4	-	-	10	11	13	14	14	-	-	11	13	15	16	17
IIIh	4-OCH_3-C_6H_4	-	-	12	12	14	14	14	-	-	14	14	15	16	16
IIIi	-CH=CH-C_6H_4	-	-	11	11	12	14	14	-	-	12	13	14	16	16
IIIj	$C_{14}H_9$	-	-	12	12	14	15	15	-	-	14	14	16	16	17

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

Standard drug	Antibacterial activity														
											IIId IIIf IIIh IIIj	IIId IIIf IIIh IIIj	IIId IIIj		
Ampicillin	11	13	14	16	18	19	20	10	12	13	14	16	18	21	
Chloramphenicol	10	12	13	19	20	20	22	12	13	14	19	20	21	22	
Ciprofloxacin	16	18	19	21	21	22	22	17	18	19	21	22	22	23	
Norfloxacin	18	18	19	20	21	21	23	19	20	22	25	26	28	28	

N.B.(-): No Activity

TABLE NO. 4b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-METHYLSULPHONYL-4-AMINO-5-CYANO-6-ARYL PYRIMIDINES III_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)													
		E. Coli MTCC-443							B. subtillis MTCC-441						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
IIIa	C_6H_5	-	-	13	13	14	16	18	-	-	15	16	18	19	19
IIIb	2-OH-C_6H_4	-	-	13	14	15	16	18	-	-	14	16	17	18	19
IIIc	4-OH-C_6H_4	-	-	13	15	16	18	18	-	-	14	16	18	18	19
IIId	2-Cl-C_6H_4	-	-	13	14	17	18	19	-	-	15	17	18	19	19
IIIe	4-Cl-C_6H_4	-	-	14	14	16	17	18	-	-	15	16	17	18	19
IIIf	2-NO_2-C_6H_4	-	-	14	15	17	18	18	-	-	16	17	19	20	20
IIIg	3-NO_2-C_6H_4	-	-	13	14	16	18	18	-	-	14	16	18	19	20
IIIh	4-OCH_3-C_6H_4	-	-	13	15	15	17	18	-	-	15	17	18	19	19
IIIi	-CH=CH-C_6H_4	-	-	14	15	16	17	18	-	-	15	17	17	19	19
IIIj	$C_{14}H_9$	-	-	15	16	17	18	18	-	-	17	17	17	18	19

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

Standard drug	Antibacterial activity													
			IIIj	IIIj						IIIf IIIj				
Ampicillin	14	14	15	16	19	20	22	12	16	18	19	20	21	23
Chloramphenicol	14	15	17	23	23	23	23	12	14	16	19	22	23	23
Ciprofloxacin	20	21	23	28	28	28	28	16	17	19	22	22	23	23
Norfloxacin	22	23	25	26	27	29	29	19	20	22	23	24	25	28

N.B.(-): No Activity

TABLE NO. 4c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-METHYLSULPHONYL-4-AMINO-5-CYANO-6-ARYL PYRIMIDINES III_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antifungal activity (Zones of inhibition in mm) C. albicans MTCC-227							A. niger MTCC-282						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
IIIa	C_6H_5	-	-	17	18	19	20	21	-	-	18	19	21	22	22
IIIb	2-OH-C_6H_4	-	-	16	17	19	20	21	-	-	18	18	20	21	23
IIIc	4-OH-C_6H_4	-	-	17	17	19	20	22	-	-	18	19	20	21	24
IIId	2-Cl-C_6H_4	-	-	17	18	20	21	22	-	-	18	18	20	22	24
IIIe	4-Cl-C_6H_4	-	-	17	18	19	20	21	-	-	19	19	20	21	22
IIIf	2-NO_2-C_6H_4	-	-	18	18	20	21	22	-	-	19	19	22	22	23
IIIg	3-NO_2-C_6H_4	-	-	16	17	19	20	21	-	-	18	18	20	22	24
IIIh	4-OCH_3-C_6H_4	-	-	17	18	20	20	21	-	-	18	19	21	22	23
IIIi	-CH=CH-C_6H_4	-	-	17	18	19	20	21	-	-	18	19	20	21	23
IIIj	$C_{14}H_9$	-	-	17	18	19	20	21	-	-	18	19	20	21	23

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

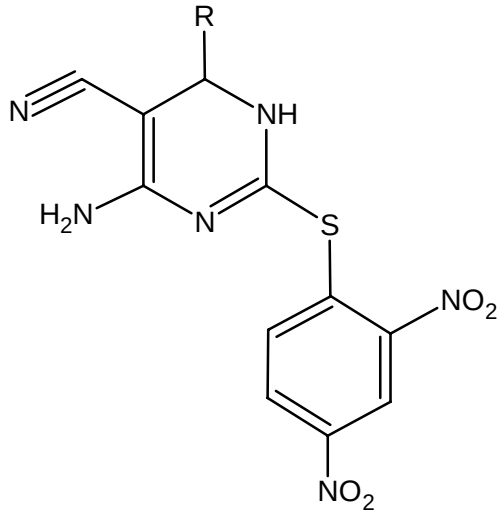
Standard drug	Antifungal activity													
													IIIf	
Griseofulvin	19	22	23	25	25	28	28	18	19	21	22	22	24	26

N.B.(-): No Activity

SECTION -IV

PREPARATION AND BIOLOGICAL EVALUATION OF 2-[(2',4'-DINITRO PHENYL)THIO]-4-AMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES

Due to enormous biodynamic activities[48-104] and other properties[29-37] of pyrimidines and with a view to have potent therapeutic agents, the synthesis of 2-[(2',4'-dinitrophenyl)thio]-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines (IV_{a-j}) have been undertaken by the condensation of 2-mercapto-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines with 2,4-dinitro chlorobenzene in presence of the base.

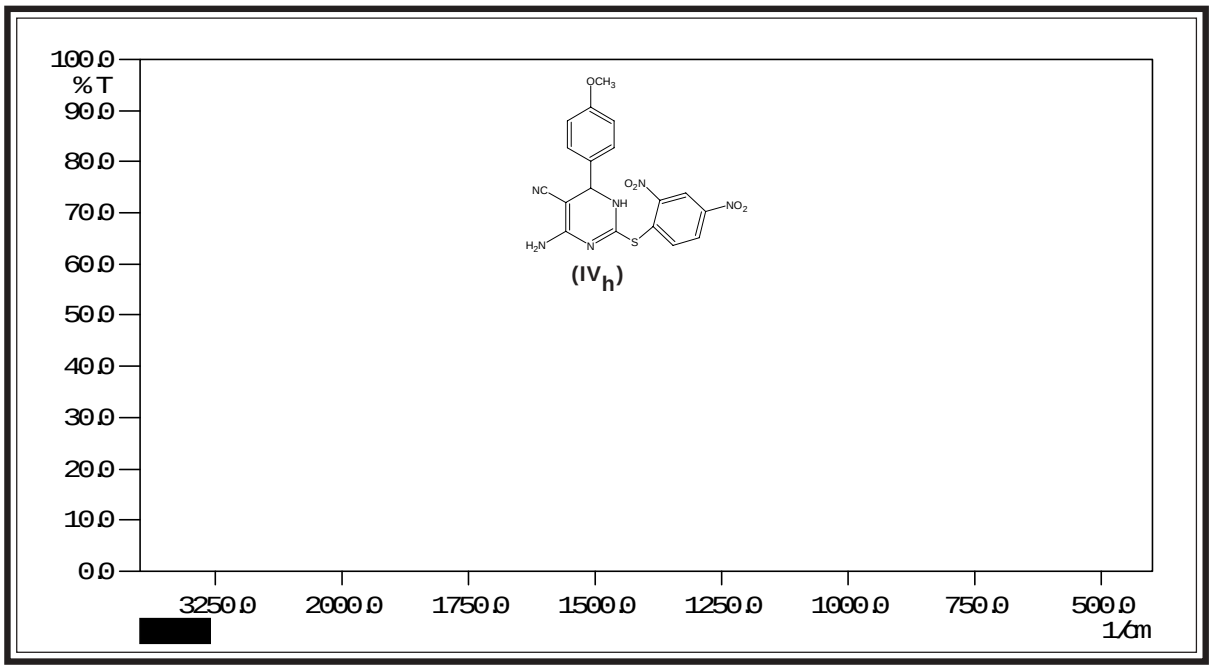


IV_{a-j} R=Aryl

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-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

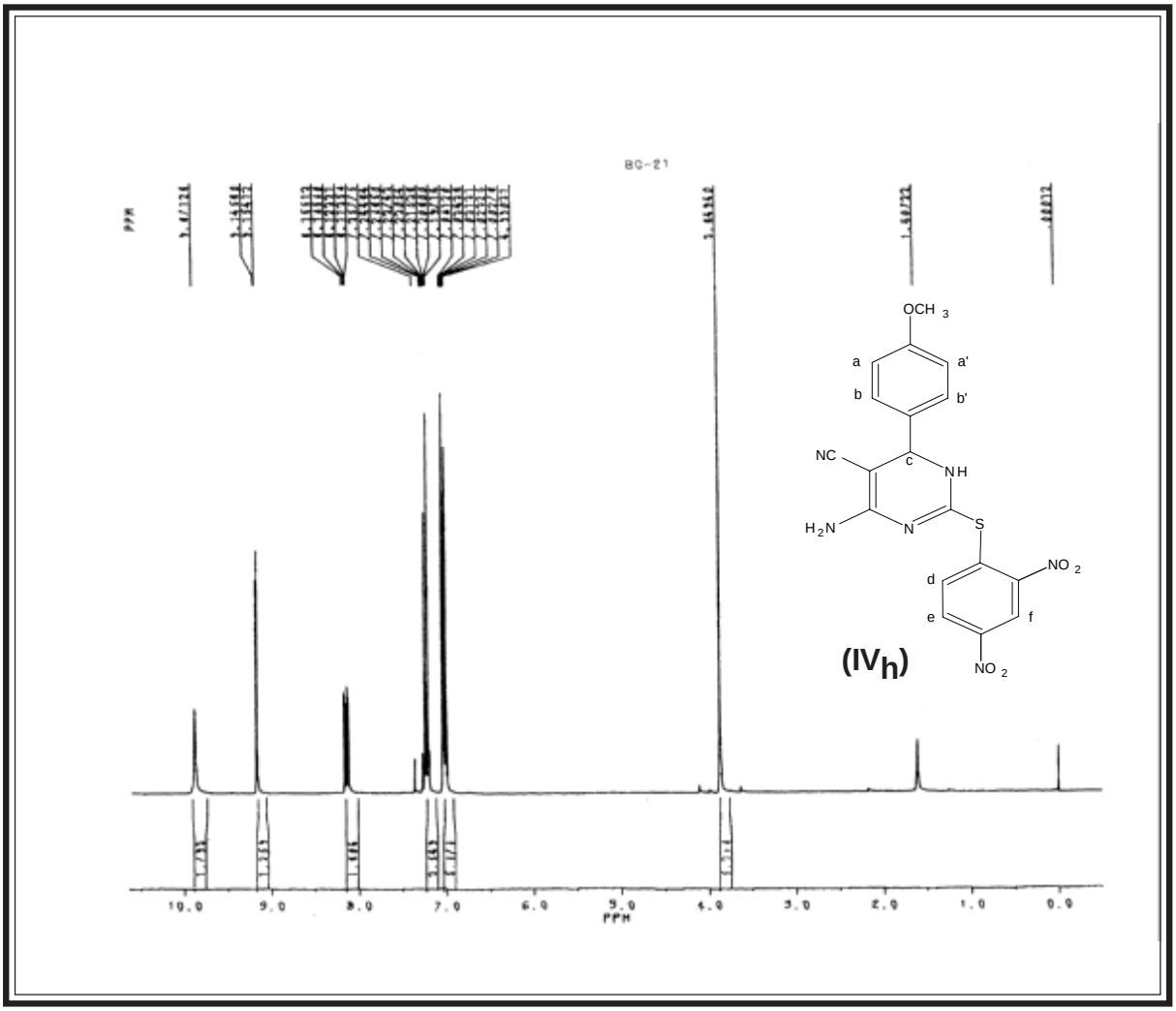
IR SPECTRAL STUDY OF 2-[(2',4'-DINITROPHENYL)THIO]-4-AMINO-5-CYANO-6-(*p*-METHOXYPHENYL)-1,6-DIHYDRO PYRIMINE (IV_h)



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.(asym.)	2923.9	2975-2950	343
CH_3	C-H str.(sym.)	2850.6	2880-2860	,,
	C-H def.(asym.)	1465.8	1460-1435	,,
	C-H def.(sym.)	1392.5	1385-1300	,,
Aromatic and	C=C + C=N and ring	1490.9	1520-1480	345
Pyrimidine moiety	skeletal vibration	1554.5	1580-1520	,,
	C-H str.	3060.8	3080-3030	,,
	C-H i.p. def.	1105.1	1125-1090	,,
	C-H o.o.p. def.	821.6	840-810	,,
Ether	C-O-C str. (asym.)	1257.5	1275-1200	346
	C-O-C str. (sym.)	1074.3	1075-1050	,,
Amine (Primary)	N-H str.	3348.2	3500-3300	343
	N-H def.	1645.2	1650-1580	,,
Nitrile	C=N str.	2206.4	2260-2190	345

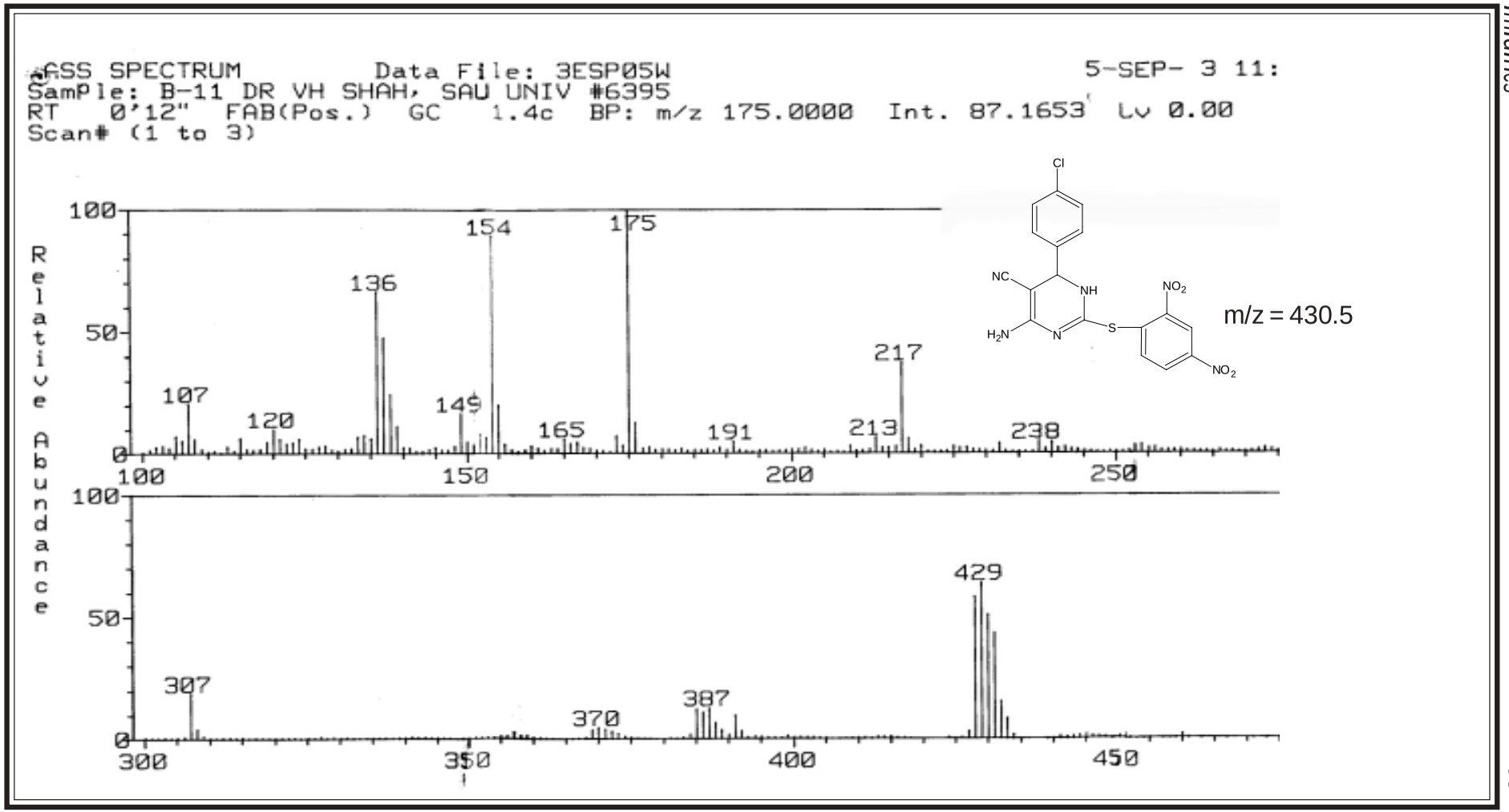
PMR SPECTRAL STUDY OF 2-[(2',4'-DINITROPHENYL)THIO]-4-AMINO-5-CYANO-6-(*p*-METHOXYPHENYL)-1,6-DIHYDRO PYRIMINE (IV_h)

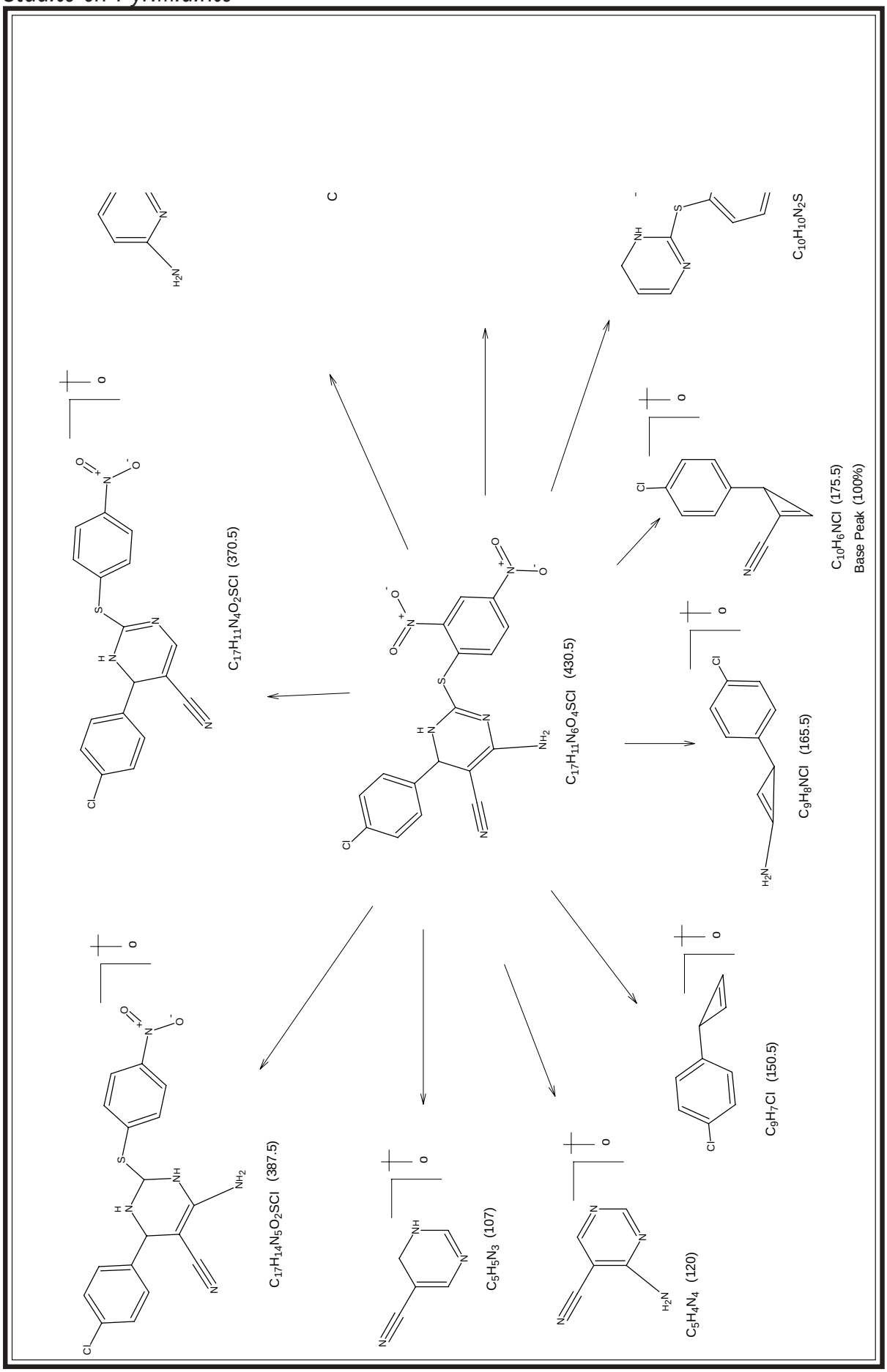


Internal Standard : TMS ; Solvent ; $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

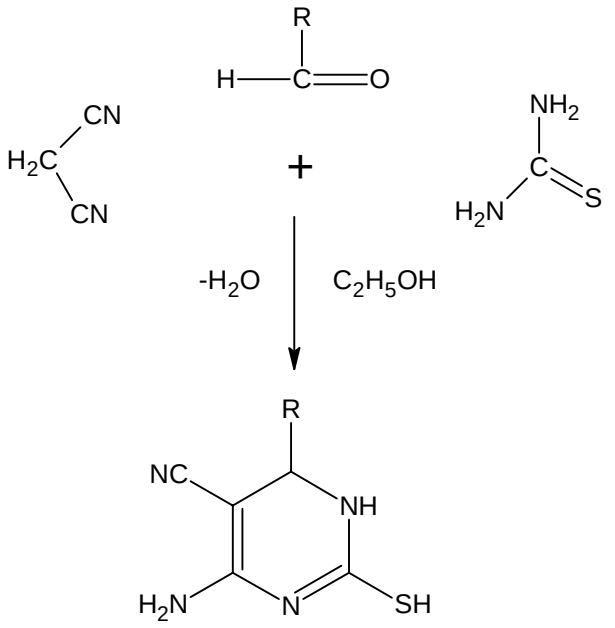
Signal No.	Signal Position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.870	3H	singlet	$-OCH_3$
2.	6.990-7.041	4H	multiplet	$Ar-H_{a,a'}$(J=8.5); $Ar-H_d$ (J=9.8); $Ar-H_c$
3.	7.208-7.238	2H	doublet	$Ar-H_{b,b'}$ (J=8.5)
4.	8.114-8.155	1H	double doublet	$Ar-H_e$
5.	9.156-9.166	1H	doublet	$Ar-H_f$
6.	9.871	1H	singlet	-N-H

MASS SPECTRAL OF 2-[(2',4'-DINITROPHENYL)THIO]-4-AMINO-5-CYANO-6-(*p*-CHLOROPHENYL)-1,6-DIHYDRO PYRIMIDINE (IV_e)

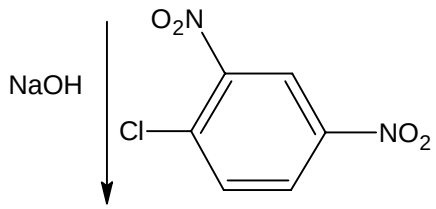


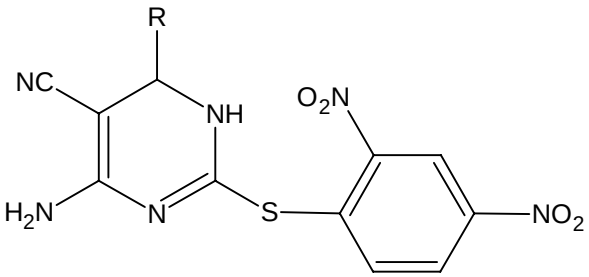

C
C17H11N6O4SCl (430.5)
C17H11N4O2SCl (370.5)
C17H14N5O2SCl (387.5)
C10H6NCl (175.5)
Base Peak (100%)
C9H8NCl (165.5)
C9H7Cl (150.5)
C10H10N2S
C5H5N3 (107)
C5H4N4 (120)

REACTION SCHEME



(1_{a-j})





(IV_{a-j}) **R = Aryl**

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 2-[(2',4'-DINITRO PHENYL)THIO]-4-AMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES

(A) Preparation of 2-Mercapto-4-amino-5-cyano-6-(*p*-methoxyPhenyl)-1,6-dihydro pyrimidine (1_h).

For preparation refer Part-I, Section-II, Page No.47.

(B) Preparation of 2-[(2',4'-Dinitrophenyl)thio]-4-amino-5-cyano-6-(*p*-methoxyphenyl)-1,6-dihydro pyrimidine (IV_h).

A mixture of 2-mercapto-4-amino-5-cyano-6-(*p*-methoxyphenyl)-1,6-dihydro pyrimidine (2.60 gm, 0.01 M) and 2,4-dinitro chlorobenzene (2.02 gm, 0.01 M) in ethanol (30 ml) and add 2 ml of 10% aqueous sodium hydroxide was heated under refluxed condition for three hrs. The content was poured into ice cold water and filtered. The product was isolated and crystallized from ethanol. Yield : 65%, M.P. : 124°C, R_f : 0.64, (Required : C, 50.70%; H, 3.29%; N, 19.72% for $C_{18}H_{14}N_6O_5S$, Found : C, 50.65%; H, 3.25%; N, 19.66%).

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

(C) Antimicrobial activity of 2-[(2',4'-Dinitrophenyl)thio]-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines (IV_{a-j}).

Antimicrobial activity testing was carried out as described in part-1, section-I, page No. 35. The MIC values of test solution are recorded in Table No. 5a, 5b & 5c.

TABLE NO. 5 : PHYSICAL CONSTANTS OF 2-[(2',4'-DINITROPHENYL)THIO]-4-AMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES (IV_{a-j})

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. °C 5	Yield % 6	R_f Value 7	% of Nitrogen	
							Required 8	Found 9
IVa	C_6H_5	$C_{17}H_{12}N_6O_4S$	396.0	146	67	0.65	21.21	21.15
IVb	2-OH-C_6H_4	$C_{17}H_{12}N_6O_5S$	412.0	115	72	0.68	20.39	20.35
IVc	4-OH-C_6H_4	$C_{17}H_{12}N_6O_5S$	412.0	138	63	0.64	20.39	20.36
IVd	2-Cl-C_6H_4	$C_{17}H_{11}N_6O_4SCl$	430.5	260	61	0.58	19.51	19.50
IVe	4-Cl-C_6H_4	$C_{17}H_{11}N_6O_4SCl$	430.5	233	56	0.52	19.51	19.48
IVf	2-NO_2-C_6H_4	$C_{17}H_{11}N_7O_6S$	441.0	156	59	0.59	22.22	22.18
IVg	3-NO_2-C_6H_4	$C_{17}H_{11}N_7O_6S$	441.0	172	53	0.63	22.22	22.19
IVh	4-CH_3O-C_6H_4	$C_{18}H_{14}N_6O_5S$	426.0	124	65	0.64	19.72	19.66
IVi	C_6H_5-CH=CH-	$C_{19}H_{14}N_6O_4S$	422.0	184	68	0.67	19.91	19.88
IVj	$C_{14}H_9$	$C_{25}H_{16}N_6O_4S$	496.0	162	71	0.59	16.94	16.90

i TLC solvent system ; Ethyl acetate : Cyclohexane = 2 : 8

TABLE NO. 5a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-[(2',4'-DINITROPHENYL)THIO]-4-AMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES IV_{a-j} (Minimum inhibition Concentration inμg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442							S. aureus MTCC-96						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
IVa	C_6H_5	-	-	12	12	14	15	15	-	-	14	14	16	16	17
IVb	2-OH-C_6H_4	-	-	10	11	12	14	14	-	-	12	12	14	16	16
IVc	4-OH-C_6H_4	-	-	11	11	13	14	14	-	-	12	13	14	16	16
IVd	2-Cl-C_6H_4	-	-	12	12	14	14	15	-	-	13	14	15	16	16
IVe	4-Cl-C_6H_4	-	-	10	11	13	14	14	-	-	12	12	14	16	16
IVf	2-NO_2-C_6H_4	-	-	10	11	12	14	14	-	-	11	13	13	16	16
IVg	3-NO_2-C_6H_4	-	-	12	12	13	14	14	-	-	14	14	15	16	17
IVh	4-OCH_3-C_6H_4	-	-	11	11	12	13	13	-	-	13	13	14	14	15
IVi	-CH=CH-C_6H_4	-	-	11	11	13	13	14	-	-	12	13	15	15	15
IVj	$C_{14}H_9$	-	-	12	12	14	14	15	-	-	14	15	16	16	17

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

Standard drug	Antibacterial activity														
											IVa IVg IVj	IVa IVd IVg IVj	IVa IVj		
Ampicillin	11	13	14	16	18	19	20	10	12	13	14	16	18	21	
Chloramphenicol	10	12	13	19	20	20	22	12	13	14	19	20	21	22	
Ciprofloxacin	16	18	19	21	21	22	22	17	18	19	21	22	22	23	
Norfloxacin	18	18	19	20	21	21	23	19	20	22	25	26	28	28	

N.B.(-): No Activity

TABLE NO. 5b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-[(2',4'-DINITROPHENYL)THIO]-4-AMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES IV_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)													
		E. Coli MTCC-443							B. subtillis MTCC-441						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
IVa	C_6H_5	-	-	15	16	17	18	18	-	-	17	17	17	18	19
IVb	2-OH-C_6H_4	-	-	13	14	15	17	18	-	-	15	16	17	18	19
IVc	4-OH-C_6H_4	-	-	14	14	16	17	18	-	-	15	16	18	19	19
IVd	2-Cl-C_6H_4	-	-	15	15	17	17	18	-	-	17	17	18	19	19
IVe	4-Cl-C_6H_4	-	-	13	14	16	18	18	-	-	15	15	17	19	19
IVf	2-NO_2-C_6H_4	-	-	12	14	15	17	18	-	-	14	16	17	18	18
IVg	3-NO_2-C_6H_4	-	-	15	16	16	18	18	-	-	16	17	18	19	19
IVh	4-OCH_3-C_6H_4	-	-	14	15	15	16	17	-	-	16	17	17	18	18
IVi	-CH=CH-C_6H_4	-	-	14	14	15	16	17	-	-	15	17	17	18	19
IVj	$C_{14}H_9$	-	-	15	16	17	18	18	-	-	15	16	19	19	19
Comparative activity of (IV_{a-j}) with known choosen standard drugs															
Standard drug		**Antibacterial activity**													
				IVa IVd IVg IVj	IVa IVg IVj						IVa IVd IVg IVh				
Ampicillin		14	14	15	16	19	20	22	12	16	18	19	20	21	23
Chloramphenicol		14	15	17	23	23	23	23	12	14	16	19	22	23	23
Ciprofloxacin		20	21	23	28	28	28	28	16	17	19	22	22	23	23
Norfloxacin		22	23	25	26	27	29	29	19	20	22	23	24	25	28

N.B.(-): No Activity

TABLE NO. 5c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-[(2',4'-DINITROPHENYL)THIO]-4-AMINO-5-CYANO-6-ARYL-1,6-DIHYDRO PYRIMIDINES IV_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antifungal activity (Zones of inhibition in mm) C. albicans MTCC-227							A. niger MTCC-282						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
IVa	C_6H_5	-	-	17	18	19	20	21	-	-	18	19	20	21	23
IVb	2-OH-C_6H_4	-	-	17	17	19	20	21	-	-	18	18	20	21	23
IVc	4-OH-C_6H_4	-	-	17	17	19	20	21	-	-	18	19	20	22	24
IVd	2-Cl-C_6H_4	-	-	17	18	19	20	21	-	-	18	19	21	21	23
IVe	4-Cl-C_6H_4	-	-	17	17	19	20	21	-	-	18	19	20	22	22
IVf	2-NO_2-C_6H_4	-	-	17	17	19	20	20	-	-	18	19	20	21	22
IVg	3-NO_2-C_6H_4	-	-	17	17	19	20	21	-	-	18	19	20	22	22
IVh	4-OCH_3-C_6H_4	-	-	17	18	19	20	21	-	-	18	18	20	21	24
IVi	-CH=CH-C_6H_4	-	-	17	18	19	20	21	-	-	18	19	20	21	23
IVj	$C_{14}H_9$	-	-	17	17	20	20	21	-	-	18	18	20	22	23
Comparative activity of (IV_{a-j}) with known choosen standard drugs															
Standard drug		**Antifungal activity**													
Griseofulvin		19	22	23	25	25	28	28	18	19	21	22	22	24	26

N.B.(-): No Activity

REFERENCES

1. Mc Gavack, T.H.J. Chevalley, S. Keni-gsberg, and S. Pearsib; *Bull N. Y. Med. Coll.,* **16,** 58 (1953).
2. Miller, Lykos and Schmeising, *J. Am. Chem. Soc.* **84,** 4623 (1962).
3. I.J. Rinkes; *Recl. Trav. Cairn Pays-Bas.,* 46268(1927).
4. G.A. Howard, B. Lythgoe and A.R. Todd; *J. Chem. Soc.,* 476 (1944).
5. C.W. Whitehead and J.J. Traversol; *J. Am. Chem. Soc.,* **80,** 2185 (1958).
6. H. Bredereck, F. Effenberger And H.J. Treiber; *Chem. Ber.,* **96,** 1505 (1963).
7. D. J. Brown; *Chem. Heterocycl. Compd.,* **16-51,** 20, (1970).
8. S. Inoue, A.J. Saggimoto and E.A. Nodiff; *J. Org. Chem.,* **26,** 4504 (1961).
9. J.A. Van Allan; *Org. Synth.,* **32,** 45 (1952).
10. E.C. Taylor and R.W. Morriosn. Jr.; *J. Org. Chem.,* **32,** 2379 (1967).
11. P.B. Russell and G.H. Hitchings; *J. Am. Chem. Soc.,* **74,** 3443 (1952).
12. P. Krohnke, E. Schmidt and W. Zoecher; *Chem. Ber.,* **97,** 1163 (1964).
13. T. Ajello; Gazz. *Chem. Ital.,* **70,** 504 (1940).
14. H K. Mitchell and J.F. Nyo; J. Am. Chem. Soc., **69,** 674 (1947).
15. G. Shaw and G. Saugowdz; *J. Chem. Soc.,* 665 (1954).
16. A. Dorhow and J. Hell; *Chem. Ber.,* **93,** 1998 (1960).
17. J.W. Streef and H.J. Denhertog; *Rec. Trav. Chem. Pays-Bas;* **88,** 1391(1969).
18. W.D. Crow and C. Wentrup; *Tetrahedron Lett.,* **7,** 3115 (1969).
19. F.C. Schaefer, K.R. Huffman and G.A. Peters; *J. Org. Chem.,* **27,** 548 (1962).
20. F. Eiden and B.S. Nagar; *Naturwissen Schaften,* **50,** 403(1963).
21. R.N. Warrer and E.N. Cairn; *Aust. J. Chem.* **24,** 785 (1971).
22. Acheson,*"An Introduction to the chemistry of Heterocyclic compounds", Inter Science* (1969).
23. A.I. Vogel, *"Vogel's Text book of Practical Organic Chemistry",* 5th Ed.(1994)
24. Badger *"Chemistry of Heterocyclic Compounds", Academic Press* (1961).
25. Biginelli, *Gazz Chem. Ital* **23,** 360 (1983); *Atti. Accad. Lincei,* **(5)3,** 195 (1894).
26. Y.M. Elkholy, A.H. Elassar and M.H. Elnagdi; *Hetero. Commun.,* **3 (2),**151 (1997).
27. P. Sharma, K.F. Hussain, S. Sukhwal, S. Kothari; *Ind. J. Chem.* **35(B),** 966-968 (1999).
28. B. Kumar, B. Kaur, J. Kaur, A. Parmar, R.D. Anand, H. Kumar; *Ind. J.Chem.* **41(B),** 1526-1530(2002).
29. A. Kreutzberger and J. Gillessen; *J. Fluorine Chem.* **29(4),** 385-97 (Ger.) 1985; *Chem Abstr.,* **105,** 133828j (1986).

30. B. Schulze, S. Groksch, L. Weber and M. Muehistuedt; *Ger. D.D.* 244, 342, *Chem. Abstr.,* **107,** 19835q (1987).
31. S. Kawamura, J. Sato, T. Hamada, M. Sakaki and Sanemitsn; *J. Agri. Food.Chem.* **41,** 288 (1993).
32. Yoshida, Hiroshi, Saito, Koiji, Watanable Masayuki; *Jpn. Kokai Tokkyo Koho, Chem. Abstr.,* **105,** 208917y (1986).
33. C. Srivastava, V.K. Ahluwalia, B. Goyal, U. Das, R. Aggarwal; *Ind. J.Chem.* **35(B)** 976-979 (1996).
34. N. Yasushi, F. Katsutoshi; (Takeda Chemical Industries, Ltd., Japan) *PCT Int. Appl.* **WO 02** 38,550 (Cl. C07D239/26), 2002, *Chem. Abstra.,***137,** 169543n (2002).
35. G.R. Chatwal, *"Synthetic Organic Chernistry",* 272 (1990).
36. Nobumass K., Tesuye. Yashito F. and Naoyki Y.; *Chiso Corp. Jap. Pat.,* 47466914, (1984); *Chem. Abstr.* **105,** 162377s (1986).
37. J. Williams and V. Vandernberghe; *Chem. Abstr.,* **54,** 22657 (1960).
38 S.C. Nigam, G.S. Saharia, H.R. Sharma; *Ind. Chem. Soc.,* **60,** 583 (1983).
39. J. Baddiley, B. Lythgoe and A.R. Todd; *J. Chem. Soc.,* 318 (1944).
40. G.W. Kenner, B.Lythgoe and A.R. Todd; *J. Chem. Soc.,* 652 (1944).
41. J. Baddiley. G.W. Kenner, B.Lythgoe and A.R. Todd.; *J. Chem. Soc.,* 657 (1944).
42. A.P. Centolella, J.W. Nelson and H.G. Kolloff ; *J. Am. Chem. Soc.,* **65,** 209 (1943).
43. Y.S. Sanghvi, in *Antisense Research and Applications*, S.T. Crooke and B. Lebleu, Eds., CRC Press, Boca Raton, Fla, 1993, p.273.
44. T. Ishikawa, F. Yoneda, et al., *Biorg. & Med. Chem. Letts.*, **1,** 523 (1991).
45. T. T. Nikiforov and B.A. Connolly, *Tet. Letts.*, **32,** 3851 (1991).
46. H. Inoue and E. Ohtsuka, *Nucleic Acids Res.*, **13,** 7119 (1985).
47. Y.S. Sanghvi, G.D. Hoke, S.M. Freier, M.C. Zounes, C. Gonzalez, L. Cummins, H. Sasmor, and P.D. Cook, *Nucleic Acids Res.*, **21,** 3197 (1993).
48. D.S. Matteson, M.S. Bleenbaum, R.A. Bechtold, R.J. Willsek; *J. Org. Chem.,* **43,** 950 (1978).
49. C.C. Heidelberger, N.C. Chaudhari, P. Dannberg, D. Mooren, L. Griesgach, R.Duchinsky, R.I. Schnitzer, E. Pleven; *Scheiner Nature* 179, 663 (1957).
50 L. Vio and M.G. Mamolo Farmaco; *Ed. Sce.,* **38(4),** 255-64, (1983); *Chem. Abstr.,* **99,** 88139e (1983).
51. J.B. Press and R.K. Rushell; *U.S. Pat*. **4,** 670, 560, (1987), *Chem. Abstr.,* **107,** 115604v (1987).
52. R.K. Rushell, J.B. Press, R.A. Rampnlla, J.J. Mancnally, R. Falotiko; *J.Med. Chem.,* **31,** 1786 (1988).
53 W. Hepworth, T.W. Thompson; *Chem Abstr.,* **69,** 7724 (1968).

54. O. Nakaguti, N. Shimazaki, M. Shimazaki and M. Nakatuka; *Eur. Pat. Appl.,* **Ep-168,** 005 (1986); *Chem. Abstr.,* **105.** 191118p (1986).
55. V. Papesch, E.F. Schroeder; *US Pat.* 2724559 (1956), *Chem. Abstr.,* **50,** 1370 (1956).
56. N. Tokutake; *Brit. Pat.* 146836B *Chem. Abstr.,* **87,** 102370j (1977).
57. P. Steilbuck, R. Baltzly and H.M. Hood; *J. Org. Chem.,* **28,** 1983 (1963).
58. H.M. Hood; *Brit. Pat.* 957, 797 (1964); *Chem. Abstr.,* **61,** 3122 (1964).
59. C.J. Chappel and C. VanSeemann; *Prog. Med. Chem,,* **3,** 89 (1963).
60. K.P. Gupta, R.C. Gupta and K.P. Bhargava ; *Eur. J. Med. Chem., Chem.Ther.,* **17(5),** 448-52 (1982); *Chem. Abstr,* **98,** 72040j (1983).
61. R. Kotva and J. Krepelka; *Cellect. Czech. Chem. Commun.,* **48(I),** 1, 137-43, 299-303, 304-311 (1983); *Chem. Abstr.,* **98,** 160668a-670v (1983).
62. B. De'Souza and J.J. Galay; *Eur. Pat.* **105,** 029 (1984); *Chem. Abstr.,* **101,** 72748b (1984).
63. G.W. Anderson, IF.Halverstadt, WH, Miller RO, Rohlin; *J. Am. Chem.Soc.,* **67,** 2197 (1945).
64. Calas, Michele, Pages, Cecile and Barhier, Alain; *Eur. J. Med. Chem. Chim. Ther.,* **18(1)** (Fr.) (1983); *Chem. Abstr.,* **99,** 53686d (1983).
65. Guo, Huiyan, Yu. Zhili and Su. Shengmao; *Yzoxue Xuebao* **18(3),** 185-90 (Ch.); *Chem. Abstr.,* **99,** 70673r (1983).
66. A. Stuart, T. Paterson and B. Roth; *J. Med. Chem.,* **26(5),** 667-73 (1983); *Chem. Abstr.,* **98,** 16066y (1983).
67. R. Kotva, J. Krepelka; *Czech. C.S.,* **224,** 239 (1984); *Chem. Abstr.,* **102,** 45974m (1985).
68. V.K. Ahuwalia, H.R. Sharma and R. Tyagi; *Ind. J. Chem.* **26-B(7),** 697-699 (1987); *Chem. Abstr.,* **109,** 6474y (1988).
69. J.M. Parmar, J.J. Modha, A.R. Parikh; *Ind. J. Chem.* **38-B,** 440-444(1999).
70. O.A. Fathlla; *Ind. J. Chem.,* **40(B),** 37-42 (2001).
71. L.R. Patil, V.S. Ingle, S.P. Bondge, V.E. Bhingolikar; *Ind. J. Het. Chem.,* **11,** 131-134 (2001).
72. J.M. Parmar, J.J. Modha, A.R. Parikh; *J. Inst. Chemist (India);* **Vol.73,** Part-1, 38 (2001).
73. D.N. Nagar, K.H. Sikotra and V.H. Shah; *J. Inst. Chemist (India);* **Vol.73,** Part-3, 93 (2001).
74. D.N. Nagar, K.H. Sikotra and V.H. Shah; *J. Inst. Chemist (India);* **Vol.73,** Part-4, 132 (2001).
75. H.S. Patel, V.K. Patel, B.C. Dixit; *Oriental J. Chem.,* **17(3),** 411-414 (2001).
76. N.J. Datta, R.C. Khunt and A.R. Parikh; *Oriental J. Chem.,* **18(1),** 131-134 (2001).

77. C.S. Andotra, S. Kaur and J. Khajuria; *Ind. J. Het. Chem.,* **12(1),** 77-78 (2002).
78. E.S. Devi, E.O. Prakash, J.T. Rao; *J. Inst. Chemist (India);* **Vol.74,** Part-5, 167-168 (2002).
79. B. Kaspar, G.P. Sorana, I. Khalid; *Chem. Abstra.,***136,** 151176q (2002).
80. H.M.F. Madkour, M.A.I. Salem, E.A. Soliman, N.F.H. Mahmoud; *Phosphorus Sulfur and Silicon and the Related Elements* **170,** 15-27 (2002). *Chem. Abstra.,***136,** 183780y (2002).
81. S. Tsuneyuki, H. Toshihide, M. Toru, K. Tsutomu, H. Shinsuke; Ono Pharmaceutic Co. Ltd., *Japan PCT Int. Appl.* **WO 02** 51, 815, (Cl.C07D239/47) (2002); *Chem.Abstra.,* **137,** 78963h (2002).
82. E. Martin, Z. Hugo, C. Fredrik, A. Peter; *Syngenta participations A. G.;Switz. PCT Int. Appl.* **WO 02** 53, 560 (Cl. C07D401/04), (2002);*Chem. Abstra.,***137,** 169533j (2002).
83. Z. Chengxin, L. Zheng-Yu, W. George, B. Neal, L. Serge; *Motorina, Irina (usa) U.S. Pat.* **US 114,** 445 (2003); *Chem. Abstra.,***137,** 53032g (2003).
84. L.R. Patil, P.N. Mandhare, S.P. Bondge, S.B. Munde, R.A. Mane; *Ind. J. Het. Chem.,* **12(3),** 245-248 (2003).
85. B.K. Karale, C.H. Gill, M.S. Shinagare; *Ind. J. Het. Chem.,* **12(3),** 267-270 (2003).
86. S.N. Swamy, A.K. Murthy, E. Rajanendar; *Ind. J. Het. Chem.,* **12(4),** 357-360 (2003).
87. A. Kumar, P. Sharma, R. Sharma, P. Mohan; *Ind. J. Chem.,* **42-B,** 416-420 (2003).
88. A.K. Padhy; *Ind. J. Chem.,* **42-B,** 910-915 (2003).
89. M. Kurono; **Jp 62,** 267, 272 (1987); *Chem. Abstr.,* **109,** 37382t (1988).
90. K. Atwal; *U.S.* **US 4,** 769, 371 (1988); *Chem. Abstr.,* **110,** 114853a (1989).
91. Chotto and A. Mizuno ; *Eur. Pat.* **Ep. 195,** 374 (1988); *Chem. Abstr.,* **110,** 231653w (1989).
92. A. Kreutzberger and M. Sellheim; *Che. Zig.* **108** (7-8), 253-5, (1984); *Chem. Abstr.,* **102,** 24572p (1985).
93. Jaen, Ju an C; *Tularik Inc. usa PCT Int. Appl.* **WO 02** 64, 096 (Cl. A61K) 2002; *Chem. Abstr.,* **137,** 185498g (2002).
94. S.D. Chamberlain, K.Gudmundsson, B.A. Johns; *Chem. Abstr.,* **137,** 33316h (2002).
95. B. Narr and E. Woitun; *Ger. Offen* **2,** 200, 764 (1973); *Chem. Abstr.,* **79,** 922, 798 (1973).
96. K. Kikugawa and M. Ichino; *Chem. Pharm. Bull.,* **21,** 1151 (1973).
97. F.E. Janssens, L.E.J. Kennis, J.E. Hens, J.L.G. Torremans and G.S.M. Van; *Eur Pat.Appl.* **Ep. 151,** 826 (1985); *Chem. Abstr.,* **104,** 68861c (1986).
98. Okabe M., Sun, R.C. and Zenehoff G.B.; *J. Org. Chem.,* **56,** 4393 (1991).
99. A.R. Katritzky, C.W. Rees; *'Comprehensive Heterocyclic Chemistry'* **Vol.3,** 152 (1982).
100. Smith Kline and French Lab. Ltd.; *Chem. Abstr.,* **103,** 22613z (1985).

101. N. Dhanapalan, L. Bharat, W. John, M. Mohammad, D. John, G. Charles, N. Stewart; *Synaptic Pharmaceutical Corporation, usa; PCT Int. Appl.* **WO 02** 06, 245 (Cl. C07D239/32) 2002; *Chem. Abstr.,* **136,** 134773q (2002).

102. W. Gerd, L. Stefan; *Journal of Medicinal Chemistry,* **45(B),** 2733-2740 (2002); *Chem. Abstr.,* **137,** 140494m (2002).

103. W. Max, B. Murty, E. Peter, W. Klaur; *Novartis Pharma., Switz; PCT Int.* **WO 03** 63, 871 (Cl.A61K31/505) 2003; *Chem. Abstr.,* **139,** 164802c (2003).

104. M.K. Jani. B.R. Shah. N.K. Undavia, P.B. Trivedi; *Chem. Abstr.,* **121,** 35513p (1994).

105. Okada,Hirochi, Kato, Masanari, Koyanagi; *Chem. Pharm. Bull.,* 1999, **47(3),** 430-33 (Eng); *Chem. Abstr.,* **130,** 352240f (1999).

106. T.V. Safonova, A.F. Keremov, Yu. A. Ershova; *Khim. Farm. Zn.* 1998, **32(12),** 11-13 (Eng); *Chem. Abstr.,* **131,** 18975e (1999).

107. C. Jean-Damien, B. David, K. Ronald, G. Julian, Li Pan, D. Robert; *Vertex Pharmaceuticals Incorporated, usa; PCT Int. Appl.* **WO 02** 22, 608 (Cl. C07D403/12) 2002; *Chem. Abstr.,* **136,** 247584x (2002).

108. G. Khalili, R. Shariri; *Ind. J. Chem.,* **41-B,** 1526-1530 (2002).

109. K. Noriyuki, M. Hitoshi; Shionogi & Co. Ltd., *Japan PCT Int. Appl.* **WO 03** 47, 564 (Cl. A61K31/343) 2002; *Chem. Abstr.,* **139,** 36532c (2003).

110. A.L. Barry ; *The antimicrobic susceptibility test, Principle and Practices* {ELBS 4th Edition), 180-193.

111. Masmi Kawase, Bharat Varu, Anamik Shah, Noboru Motohashi, Satoru Tani, Satsuo Saito et al., *Arzneim.-Forsch./Drug Res.*, **61(1),** 67-71 (2001).

112. Dastidar, S.G., Chaudhary, A., Annadurai, S. et al., In vitro and in vivo antimicrobial action of fluphenazine., *J. Chem. - other.* **7**, 201 (1995).

PART - II
STUDIES ON 5-CARBOXAMIDO PYRIMIDINES

PART - II
STUDIES ON CARBOXAMIDO PYRIMIDINES

INTRODUCTION

Carboxamides are the substituted product of ammonia and acid. The characteristic group present in the simple carboxylic amide is $-CONH_2$. Many natural products are amides, urea, diamides of carbonic acid. Peptides and proteins are the linear structures of cyclic polyamides. Alkaloids of pepper, piperine and chavicine are N-substituted amides of unsaturated acid. N-isobutyl amides of certain highly unsaturated aliphatic acids occur in plants and show insecticidal activity[113]. Amides derived from polyacetylenic acids have been isolated from certain fungi[114]. Herbicidal and insecticidal activities[115,116] are well documented in literature.

SYNTHETIC ASPECTS

Several methods for the preparation of Carboxamides have been described as under :

(a) By the reaction of 2-amino-4,6-dimehtyl pyrimidine and 2,5-dimethyl pyrrole with $CISO_2CNO$ led to the formation of carboxamido pyrimidine[117].

(b) By the acylation of the amino acid with *p*-chlorobenzoylchloride, then converting the acid into the cyclohexylamide via lactam, lactone or anhydride to yield 2,4-dihydroxy-5-(*p*-chlorobenzamido)-6-cyclohexyl aminocarbonyl) pyrimidine[118].

(c) By the cyclization of 2-cyano-3-aryl acrylamide with thiourea led to the formation of carboxamido pyrimidines[119].

(d) By the condensation of 2-thiobarbituric acid with phenyl isocyanate led to the formation of carboxamido pyrimidines[120].

(e) By the reaction of 2-trifluoro methyl-5-methylsulphonyl-1,3,4-triazole and 4-hydroxyaniline with hexahydro-2,4,6-trioxo-5-pyrimidine carboxylate led to the formation of carboxamido pyrimidines[121].

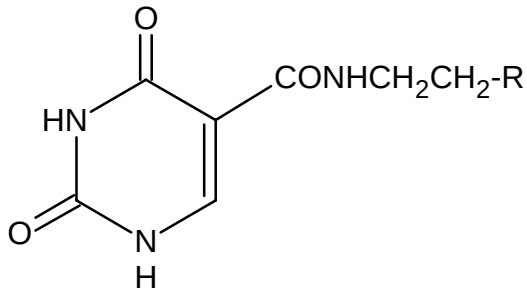
(f) By the cyclocondensation of 1,2-dibromo-1-carboxyl-2-ethanal with chlorinated product aminated by p-fluoroaniline which on further oxidation led to the formation of carboxamido pyrimidines[122].

THERAPEUTIC IMPORTANCE

Carboxamide pyrimidines have been widely used as pharmacologically useful entities. Several biological activities have been reported as under.

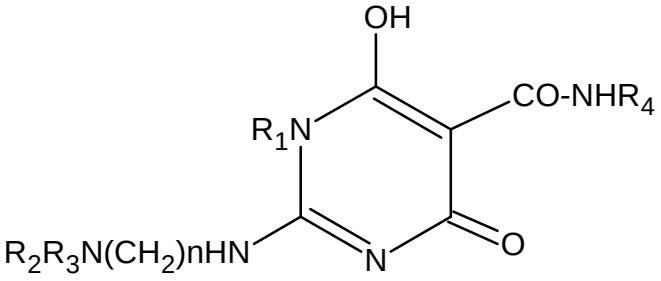
(a) Antipyretic[123]
(b) Analgesic[124]
(c) Anticancer[125]
(d) Anticonvulsant[126,127]
(e) Anthelmintic[128]
(f) Hypoglycemics[129]
(g) Antiallergic[130]
(h) Antiulcer[131]
(i) Tranquilizer[132]
(j) Cardiovascular[133,134]
(k) CNS-depressant[135]
(l) Diuretic[136]
(m) Psychotropic[137]
(n) Antimicrobial[138-144]
(o) Antagonist[145-147]
(p) Antithrombic[148]
(q) Antiamoebic[149]
(r) Antiarrhythmic[150]
(s) Antitumor[151]

H.E. Weidermann et al.,[152] have synthesized pyrimidine carboxamides **(22)** which reduces blood sugar in rats by 19% at 5mg/kg.



(22) **R=sub sulphonamido piperidyl**

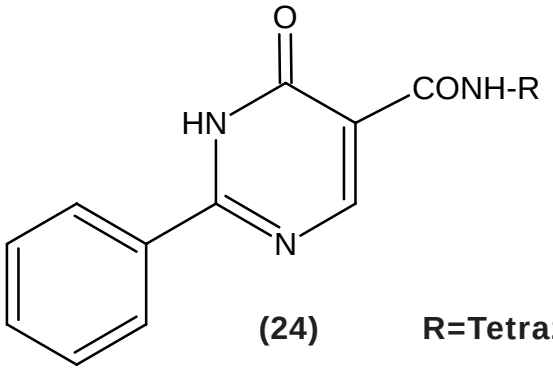
U. Herzog et al.,[153] have synthesized pyrimidine carboxamides **(23)** as promising amoebicides and protozoacides.



(23)

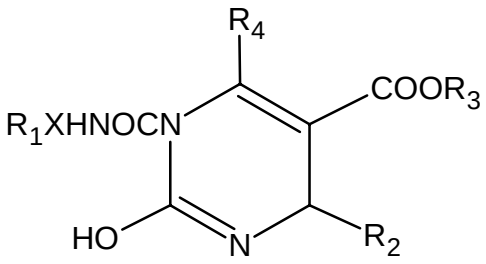
R_1=H/napthyl/alkyl; **R_2,R_3=H/alkyl;**
NR_2R_3=heterocyclic; **R_4=napthyl/alkyl;**

P.F. Juby et al.,[154] have prepared pyrimidine-5(N)-(1H-tetrazol-5-yl) carboxamides **(24)** which showed antiallergic activity.



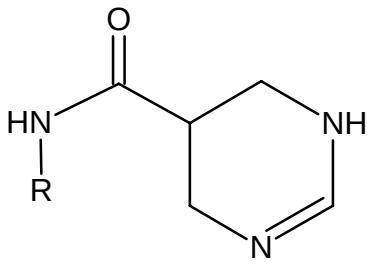
(24) **R=Tetrazolyl**

K. Atwal et al.,[155] have synthesized 5-pyrimidine carboxylic acids **(25)** and found to be active as antihypertensives.

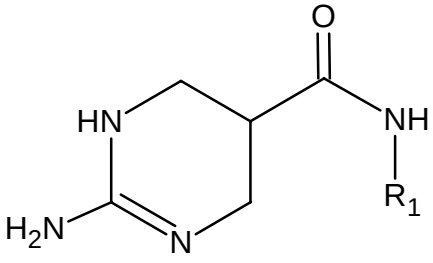


(25) **R_1,R_3=H/halogen/aryl; R_2=H/alkenyl; R_4=Aryl**

B. Ojo et al.,[156] have synthesized 1,4,5,6-tetrahydro pyrimidine 5-carboxamides **(26, 27)** and their salts, having binding affinities and agonist activity at muscarinic receptor in the CNS.

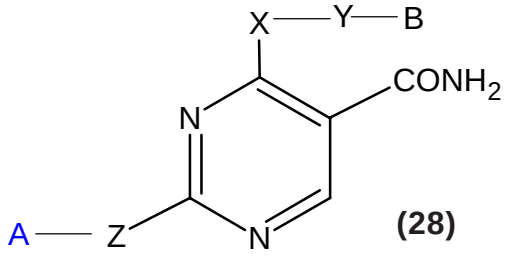


(26)



(27)

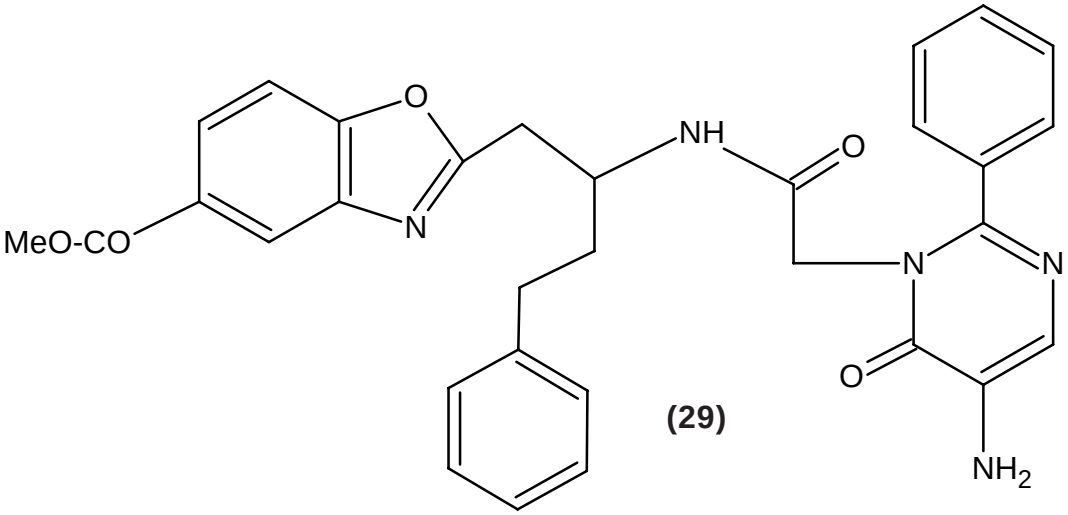
H. Hisamichi et al.,[157] have synthesized pyrimidine-5-carboxamido derivatives **(28)** as effective tyrosinase inhibitor useful as 5-HT antagonist and antiallergic.



(28)

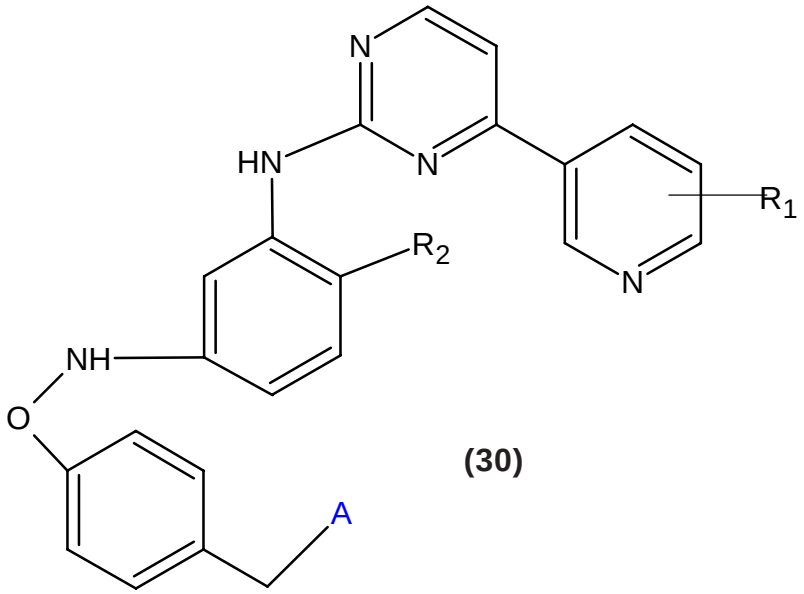
X=O/S/NR1/CO/CONR1; Y=lower alkylene-optionally subs. by OR or NHR1; Z=O, NR2, A=H, B=Optically subs. aryl / heteroaryl; R1,R2= H

F. Kobayashi et al.,[158] have prepared (1,6-dihydro-6-oxo-1-pyrimidinyl-1-pyridinyl) acetamide derivatives **(29)** as antibody production inhibitors are useful as preventives or remedies for bronchial asthma, allergic dermatitis etc.



(29)

U. Pfaar et al.,[159] have prepared carboxamido pyrimidine derivatives **(30)** and reported for their antitumor activity.



(30)

R_1=OH; R_2=H/alkyl/hydroxyalkyl; A=NR_3R_4/CR_3R_4/OR_3R_4; R_3R_4=alkylene/oxaalkylene/azaalkylene

In view of procuring highly potent biodynamic agents and after reviewing literature survey on carboxamide pyrimidine for their various methods of synthesis and different biological activities, synthesis of carboxamide pyrimidines have been undertaken which can be summarized in the following sections as under.

SECTION – I : PREPARATION AND BIOLOGICAL EVALUATION OF 2,4-DIAMINO-5-CARBOXAMIDO-6-ARYL PYRIMIDINES

SECTION – II : PREPARATION AND BIOLOGICAL EVALUATION OF 2-MERCAPTOMETHYL-4-AMINO-5-CARBOXAMIDO-6-ARYL PYRIMIDINES

SECTION – III : PREPARATION AND BIOLOGICAL EVALUATION OF 2-MERCAPTO-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES

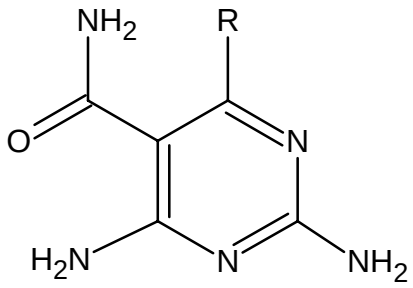
SECTION - IV : PREPARATION AND BIOLOGICAL EVALUATION OF 2-HYDROXY-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES

SECTION - V : PREPARATION AND BIOLOGICAL EVALUATION OF 2,4-DIAMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES

SECTION - I

PREPARATION AND BIOLOGICAL EVALUATION OF 2,4-DIAMINO-5-CARBOXAMIDO-6-ARYL PYRIMIDINES

Looking to the biodynamic profile[123-159] and the other properties[113-116] of carboxamido pyrimidines and in view to have potent therapeutic agents, the synthesis of 2,4-diamino-5-carboxamido-6-aryl pyrimidines (V_{a-j}) have been undertaken by the reaction of 2,4-diamino-5-cyano-6-aryl-1,6-dihydro pyrimidines with concentrated sulphuric acid.

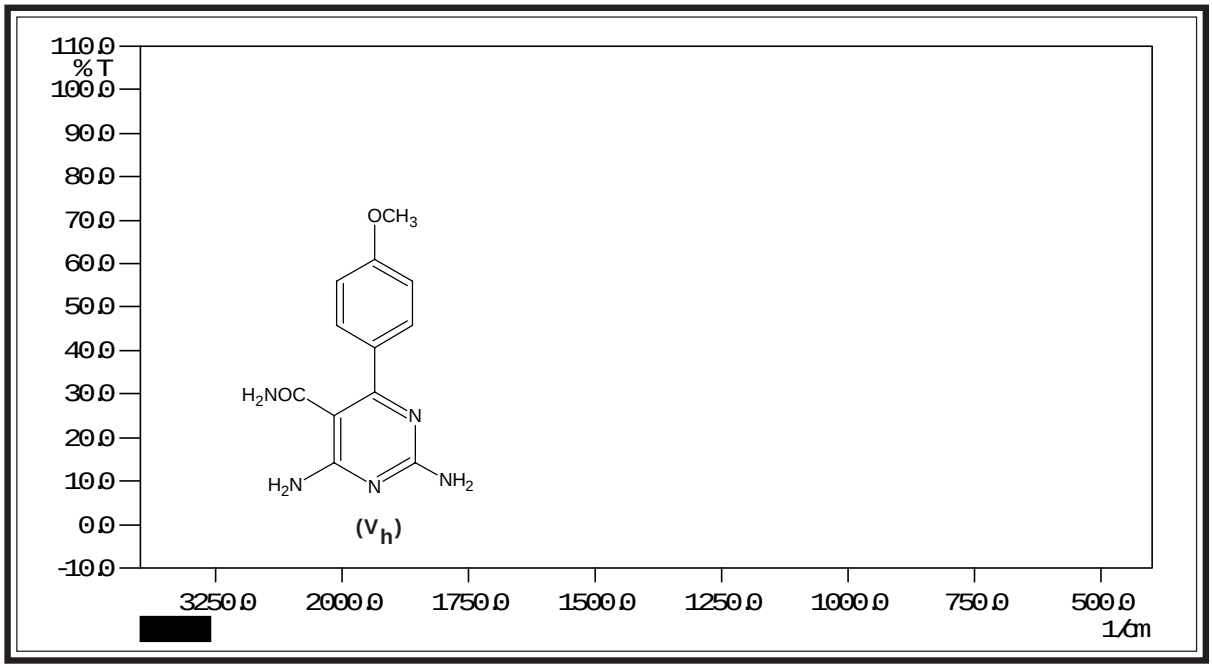


V_{a-j} **R=Aryl**

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

The products (V_{a-j}) were assayed for their *in vitro* biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

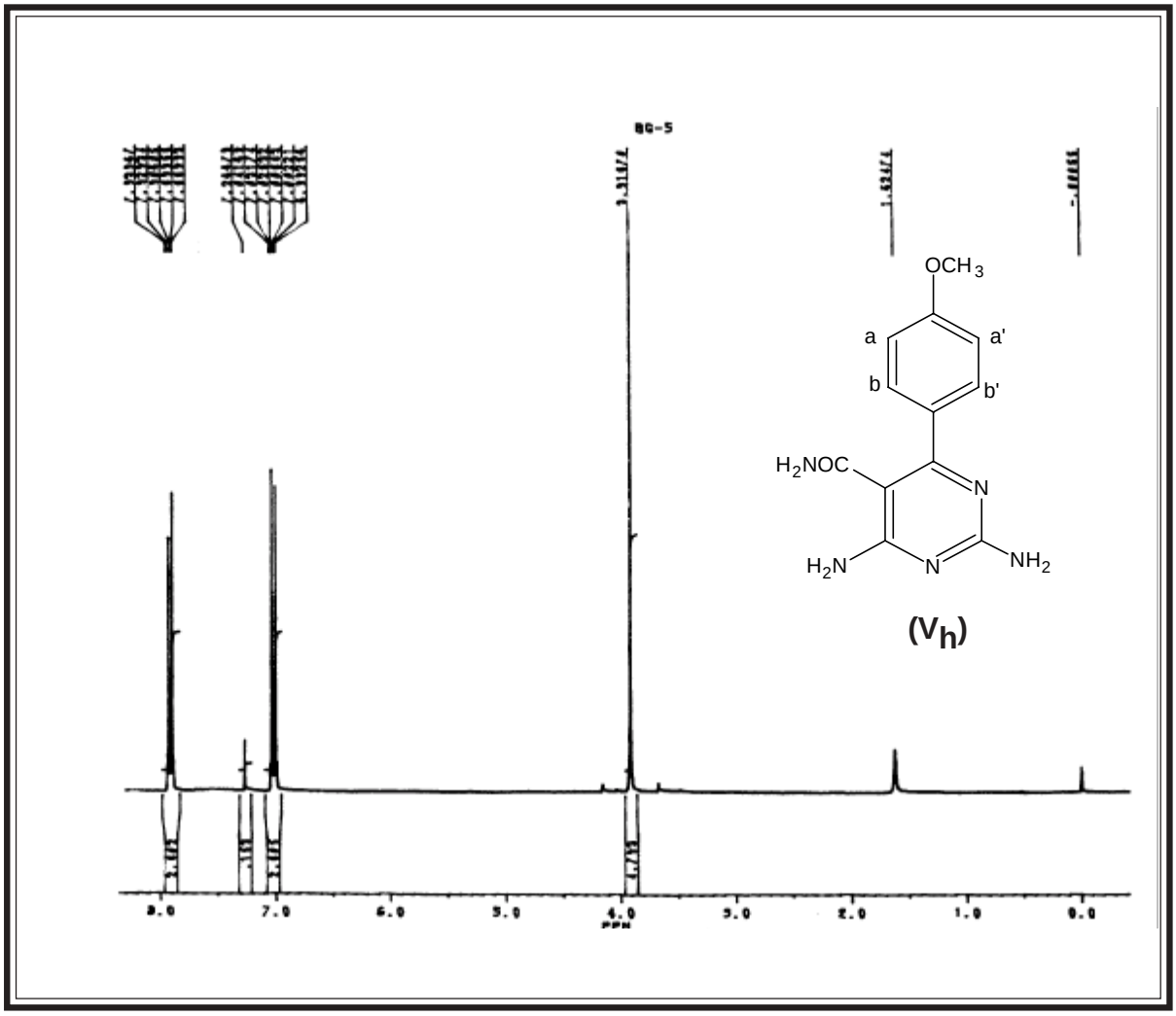
IR SPECTRAL STUDY OF 2,4-DIAMINO-5-CARBOXAMIDO-6-(*p*-METHOXY PHENYL) PYRIMIDINE (V_h)



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.(asym.)	2922.0	2975-2950	343
CH_3	C-H str.(sym.)	2862.2	2880-2860	,,
	C-H def.(asym.)	1454.2	1460-1435	,,
	C-H def.(sym.)	1363.6	1385-1300	,,
Aromatic and	C=C + C=N and ring	1519.8	1520-1480	345
Pyrimidine moiety	skeletal vibration	1573.8	1580-1520	,,
	C-H str.	3064.7	3080-3030	,,
	C-H i.p. def.	1103.2	1125-1090	,,
	C-H o.o.p. def.	825.5	840-810	,,
Ether	C-O-C str. (asym.)	1226.6	1275-1200	346
	C-O-C str. (sym.)	1056.9	1075-1050	,,
Amine (Primary)	N-H str.	3400.3	3500-3300	343
	N-H def.	1598.9	1650-1580	,,
Amide	N-H str.	3400.3	3500-3300	345
	C=O str.	1672.2	1710-1650	,,

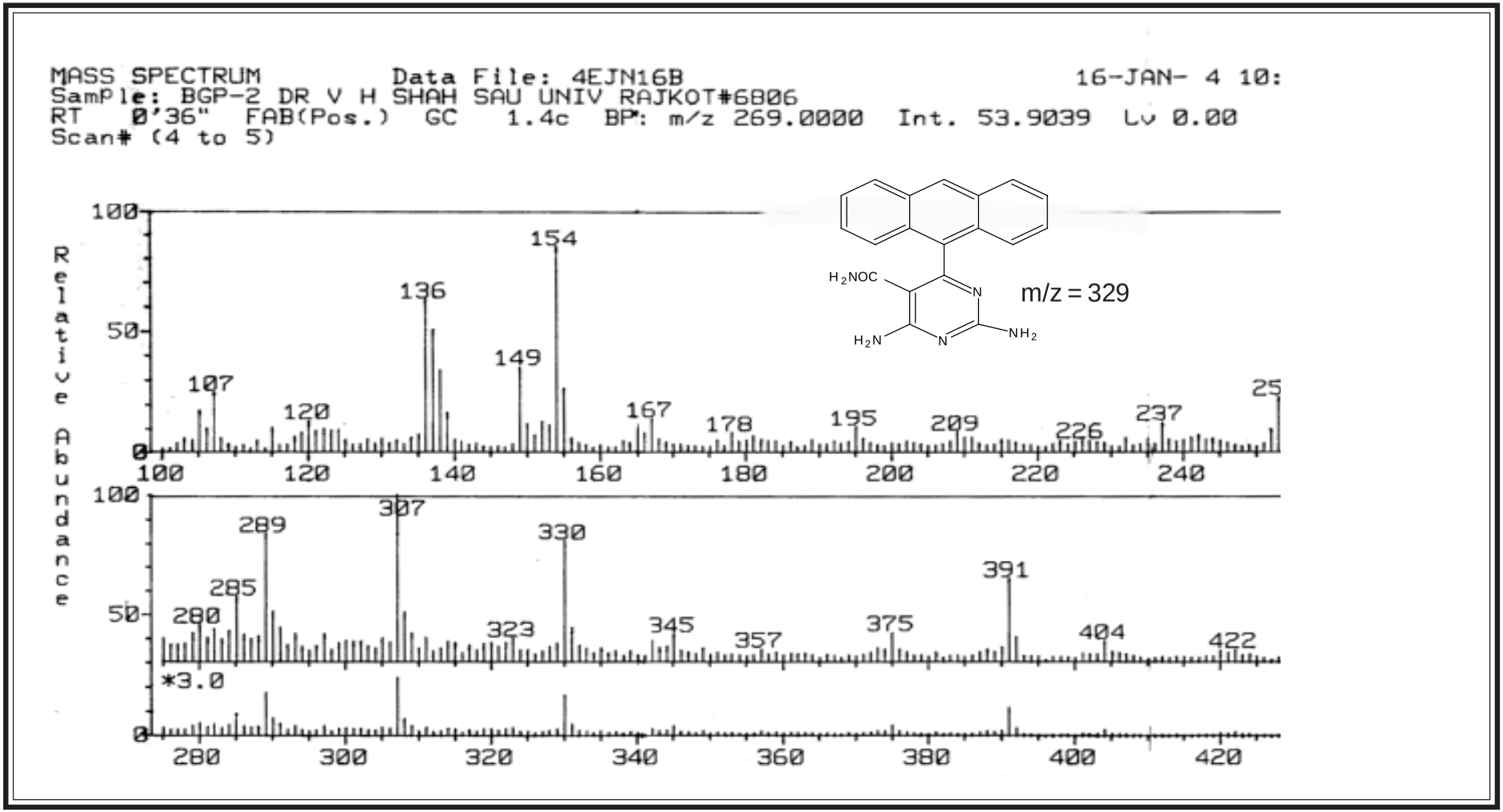
PMR SPECTRAL STUDY OF 2,4-DIAMINO-5-CARBOXAMIDO-6-(*p*-METHOXY PHENYL) PYRIMIDINE (V_h)

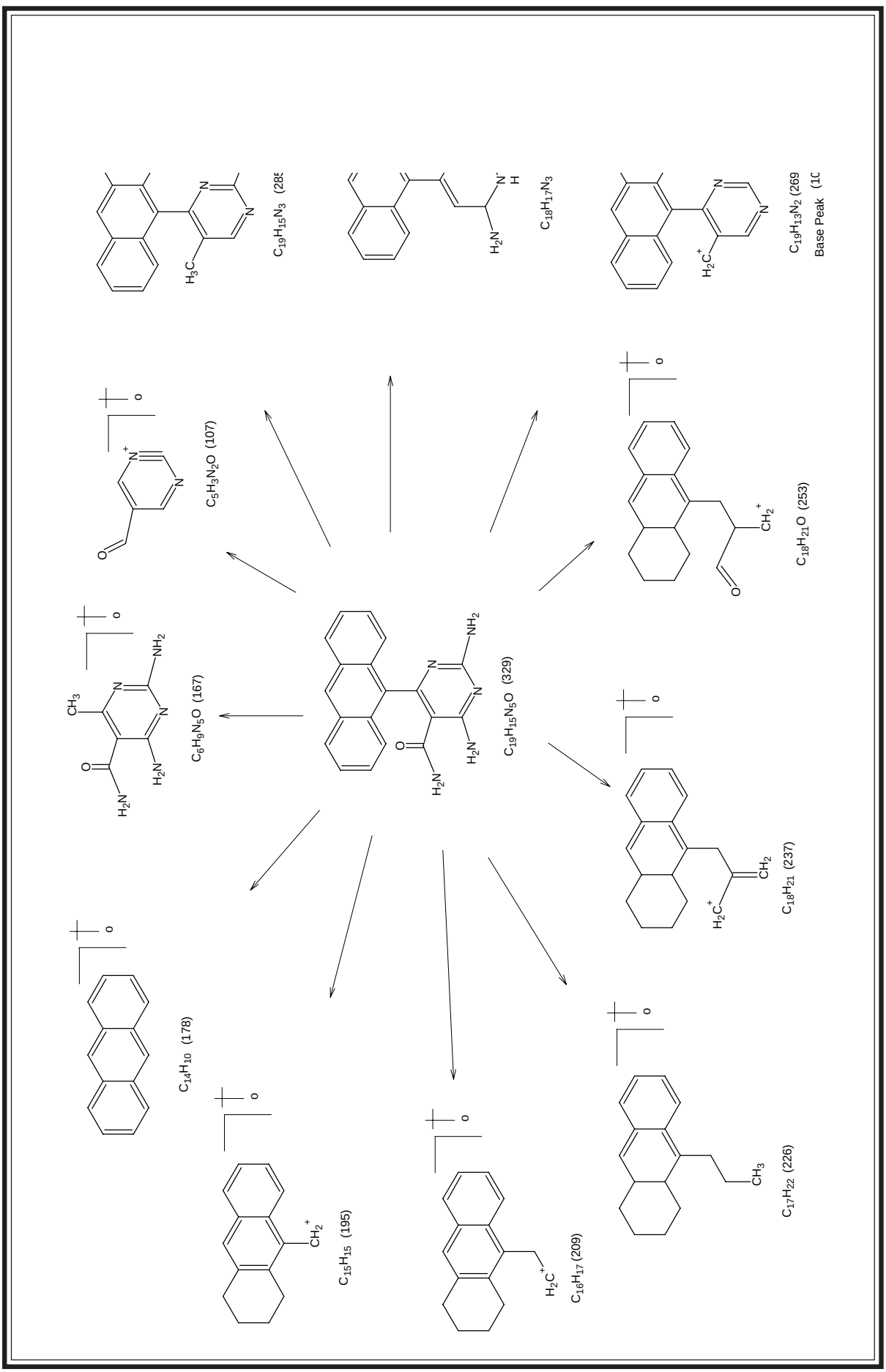


Internal Standard : TMS ; Solvent ; $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

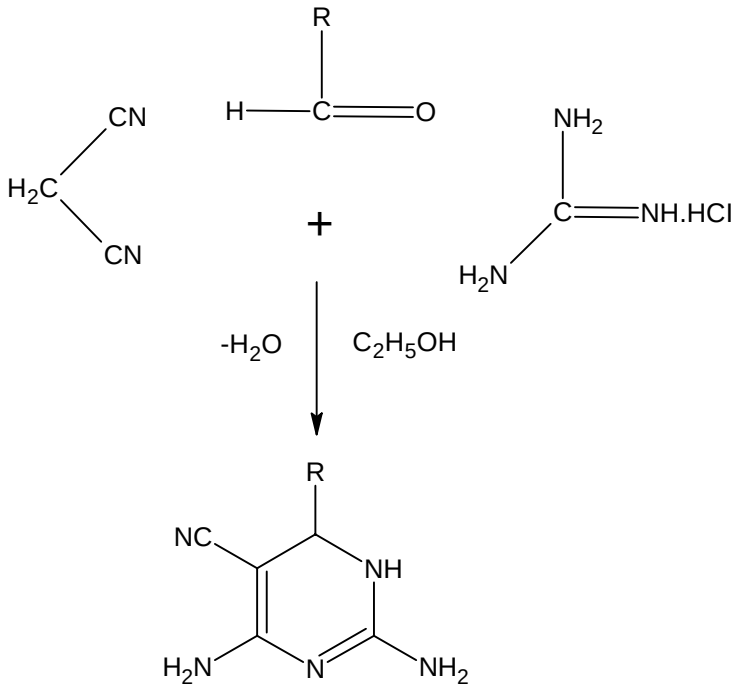
Signal No.	Signal Position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.919	3H	singlet	$-OCH_3$
2.	7.002-7.032	2H	doublet	Ar-$H_{a,a'}$ (J=8.86)
3.	7.900-7.930	2H	doublet	Ar-$H_{b,b'}$ (J=8.93)

MASS SPECTRAL OF 2,4-DIAMINO-5-CARBOXAMIDO-6-(ANTHRA-9'-YL) PYRIMIDINE (V_j)

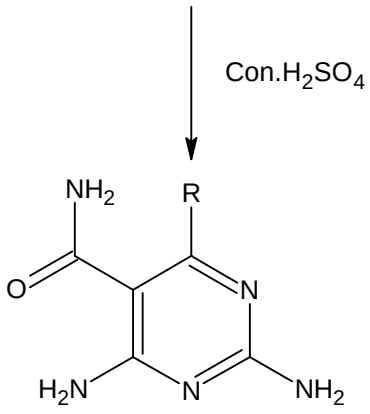



C19H15N3 (28
C18H17N3
C19H13N2 (269
Base Peak (1C
C5H3N2O (107)
C18H21O (253)
C6H9N5O (167)
C19H15N5O (329)
C14H10 (178)
C18H21 (237)
C15H15 (195)
C16H17 (209)
C17H22 (226)

REACTION SCHAME



(I_{a-j})



(V_{a-j}) **R = Aryl**

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 2,4-DIAMINO-5-CARBOXAMIDO-6-ARYL PYRIMIDINES

(A) Preparation of 2,4-Diamino-5-cyano-6-(*p*-methoxyphenyl)-1,6-dihydro pyrimidine (I_h).

For preparation refer Part-I, Section-I, Page No. 35.

(B) Preparation of 2,4-Diamino-5-carboxamido-6-(*p*-methoxyphenyl) pyrimidine (V_h).

2,4-Diamino-5-cyano-6-(*p*-methoxyphenyl)-1,6-dihydro pyrimidine (2.43 gm, 0.01M) was dissolved in concentrated sulphuric acid (20ml) below 5 ^oC and kept for 48 hrs. at room temperature. The content was poured into ice cold water and filtered. The product was isolated and crystallized from ethanol. Yield : 53%, M.P. : 147°C, R_f : 0.58, (Required : C, 55.60%; H, 5.02%; N, 27.03% for $C_{12}H_{13}N_5O_2$, Found : C, 55.55%; H, 4.98%; N, 27.00%).

Similarly, other compounds (V_{a-j}) were synthesized. The physical data are recorded in Table No. 6.

(C) Antimicrobial activity of 2,4-Diamino-5-carboxamido-6-aryl pyrimidines (V_{a-j}).

Antimicrobial activity testing was carried out as described in part-1, section-I, page No. 35. The MIC values of test solution are recorded in Table No. 6a, 6b & 6c.

TABLE NO. 6 : PHYSICAL CONSTANTS OF 2,4-DIAMINO-5-CARBOXAMIDO-6-ARYL PYRIMIDINES (V_{a-j})

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. °C 5	Yield % 6	R_f Value 7	% of Nitrogen	
							Required 8	Found 9
Va	C_6H_5	$C_{11}H_{11}N_5O$	229.0	115	52	0.48	30.57	30.52
Vb	2-OH-C_6H_4	$C_{11}H_{11}N_5O_2$	245.0	169	49	0.52	28.57	28.52
Vc	4-OH-C_6H_4	$C_{11}H_{11}N_5O_2$	245.0	220	54	0.54	28.57	28.53
Vd	2-Cl-C_6H_4	$C_{11}H_{10}N_5OCl$	263.5	156	51	0.49	26.57	26.51
Ve	4-Cl-C_6H_4	$C_{11}H_{10}N_5OCl$	263.5	210	58	0.54	26.57	26.53
Vf	2-NO_2-C_6H_4	$C_{11}H_{10}N_6O_3$	274.0	112	54	0.56	30.66	30.62
Vg	3-NO_2-C_6H_4	$C_{11}H_{10}N_6O_3$	274.0	143	57	0.53	30.66	30.61
Vh	4-CH_3O-C_6H_4	$C_{12}H_{13}N_5O_2$	259.0	147	53	0.58	27.03	27.00
Vi	C_6H_5-CH=CH-	$C_{13}H_{13}N_5O$	255.0	88	56	0.57	27.45	27.40
Vj	$C_{14}H_9$	$C_{19}H_{15}N_5O$	329.0	78	68	0.46	21.28	21.21

☐ **TLC solvent system ; Acetone : Benzene = 1.5 : 8.5**

TABLE NO. 6a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2,4-DIAMINO-5-CARBOXAMIDO-6-ARYL PYRIMIDINES V_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442 5	10	25	50	100	250	500	S. aureus MTCC-96 5	10	25	50	100	250	500
Va	C_6H_5	-	-	10	10	12	14	14	-	-	12	12	14	15	16
Vb	2-OH-C_6H_4	-	-	10	11	13	14	14	-	-	11	13	15	16	17
Vc	4-OH-C_6H_4	-	-	12	12	14	14	15	-	-	14	15	16	17	17
Vd	2-Cl-C_6H_4	-	-	11	11	13	13	14	-	-	12	12	14	15	16
Ve	4-Cl-C_6H_4	-	-	12	12	14	14	15	-	-	14	14	15	16	17
Vf	2-NO_2-C_6H_4	-	-	10	10	12	14	15	-	-	11	12	14	14	16
Vg	3-NO_2-C_6H_4	-	-	10	11	12	13	13	-	-	11	12	14	14	15
Vh	4-OCH_3-C_6H_4	-	-	12	12	13	14	14	-	-	14	14	15	16	17
Vi	-CH=CH-C_6H_4	-	-	11	11	13	14	14	-	-	12	13	15	15	16
Vj	$C_{14}H_9$	-	-	11	11	12	14	14	-	-	13	13	14	16	16

Comparative activity of (Va-j) with known choosen standard drugs

Standard drug	Antibacterial activity									Vc Ve Vh Vj	Vc Ve Vh	Vc			
Ampicillin	11	13	14	16	18	19	20	10	12	13	14	16	18	21
Chloramphenicol	10	12	13	19	20	20	22	12	13	14	19	20	21	22
Ciprofloxacin	16	18	19	21	21	22	22	17	18	19	21	22	22	23
Norfloxacin	18	18	19	20	21	21	23	19	20	22	25	26	28	28

N.B.(-): No Activity

TABLE NO. 6b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2,4-DIAMINO-5-CARBOXAMIDO-6-ARYL PYRIMIDINES V_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)													
		E. Coli MTCC-443							B. subtillis MTCC-441						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
Va	C_6H_5	-	-	13	14	15	17	17	-	-	15	16	17	18	19
Vb	2-OH-C_6H_4	-	-	12	13	14	16	17	-	-	14	15	17	18	19
Vc	4-OH-C_6H_4	-	-	15	16	17	17	18	-	-	15	15	16	18	19
Vd	2-Cl-C_6H_4	-	-	14	15	16	17	17	-	-	16	17	17	18	19
Ve	4-Cl-C_6H_4	-	-	15	16	17	17	18	-	-	15	17	17	18	18
Vf	2-NO_2-C_6H_4	-	-	13	13	15	16	18	-	-	15	15	17	18	18
Vg	3-NO_2-C_6H_4	-	-	13	14	15	16	16	-	-	14	16	18	17	18
Vh	4-OCH_3-C_6H_4	-	-	15	16	17	18	18	-	-	17	17	18	19	19
Vi	-CH=CH-C_6H_4	-	-	14	14	16	17	18	-	-	14	16	18	18	19
Vj	$C_{14}H_9$	-	-	14	15	16	17	18	-	-	16	16	17	19	19

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

Standard drug	Antibacterial activity													
			Vc Ve Vh	Vc Ve Vh						Vd Vh Vj				
Ampicillin	14	14	15	16	19	20	22	12	16	18	19	20	21	23
Chloramphenicol	14	15	17	23	23	23	23	12	14	16	19	22	23	23
Ciprofloxacin	20	21	23	28	28	28	28	16	17	19	22	22	23	23
Norfloxacin	22	23	25	26	27	29	29	19	20	22	23	24	25	28

N.B.(-): No Activity

TABLE NO. 6c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2,4-DIAMINO-5-CARBOXAMIDO-6-ARYL PYRIMIDINES V_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antifungal activity (Zones of inhibition in mm) C. albicans MTCC-227 5	10	25	50	100	250	500	A. niger MTCC-282 5	10	25	50	100	250	500
Va	C_6H_5	-	-	17	18	19	20	22	-	-	18	19	20	21	24
Vb	2-OH-C_6H_4	-	-	16	17	18	19	20	-	-	18	19	20	21	22
Vc	4-OH-C_6H_4	-	-	17	18	19	20	21	-	-	18	19	20	20	22
Vd	2-Cl-C_6H_4	-	-	17	17	19	19	20	-	-	18	19	21	22	22
Ve	4-Cl-C_6H_4	-	-	17	17	19	20	20	-	-	18	19	20	21	22
Vf	2-NO_2-C_6H_4	-	-	17	18	18	19	20	-	-	18	19	20	21	22
Vg	3-NO_2-C_6H_4	-	-	17	18	19	20	20	-	-	19	19	21	21	23
Vh	4-OCH_3-C_6H_4	-	-	17	18	20	21	22	-	-	19	19	21	23	22
Vi	-CH=CH-C_6H_4	-	-	17	17	19	20	21	-	-	18	19	21	21	24
Vj	$C_{14}H_9$	-	-	17	18	19	19	20	-	-	19	19	20	22	22

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

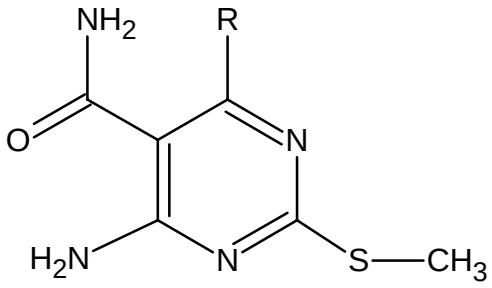
Standard drug	Antifungal activity													
Griseofulvin	19	22	23	25	25	28	28	18	19	21	22	22	24	26

N.B.(-): No Activity

SECTION - II

PREPARATION AND BIOLOGICAL EVALUATION OF 2-MERCAPTO METHYL-4-AMINO-5-CARBOXAMIDO-6-ARYL PYRIMIDINES

Looking to the biodynamic profile[123-159] and the other properties[113-116] of carboxamido pyrimidines and with a view to have potent therapeutic agents, the synthesis of 2-mercaptomethyl-4-amino-5-carboxamido-6-aryl pyrimidines (VI_{a-j}) have been undertaken by the reaction of 2-mercaptomethyl-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines with concentrated sulphuric acid.

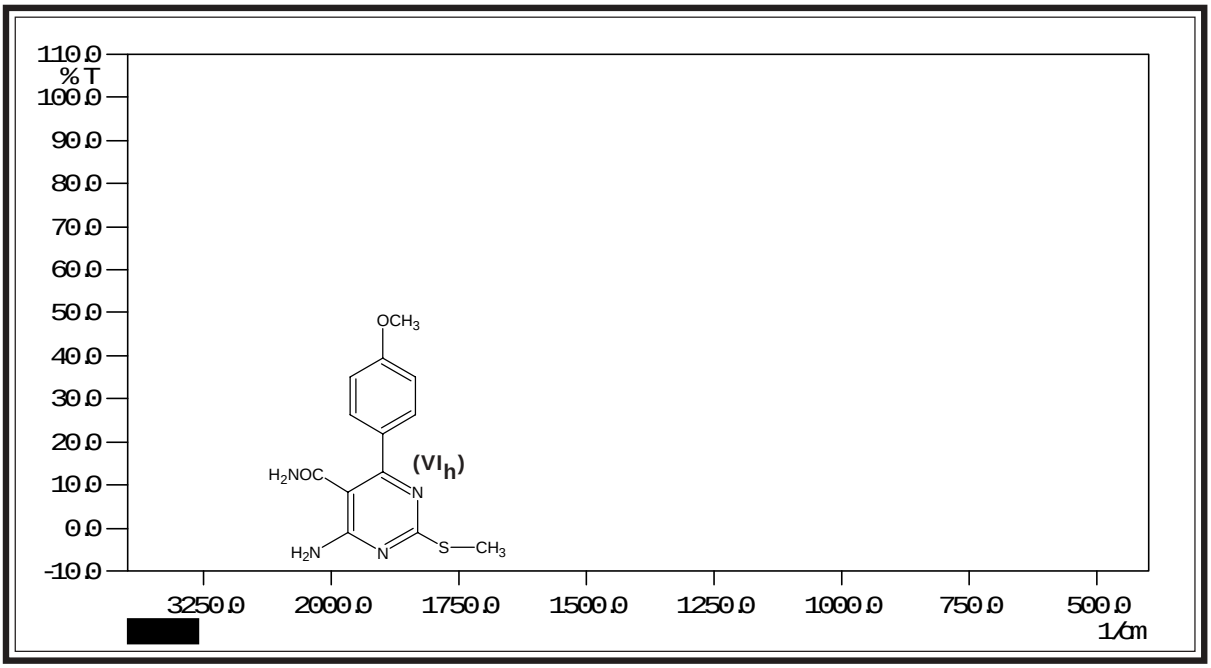


VI_{a-j} **R=Aryl**

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

The products (VI_{a-j}) were assayed for their *in vitro* biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

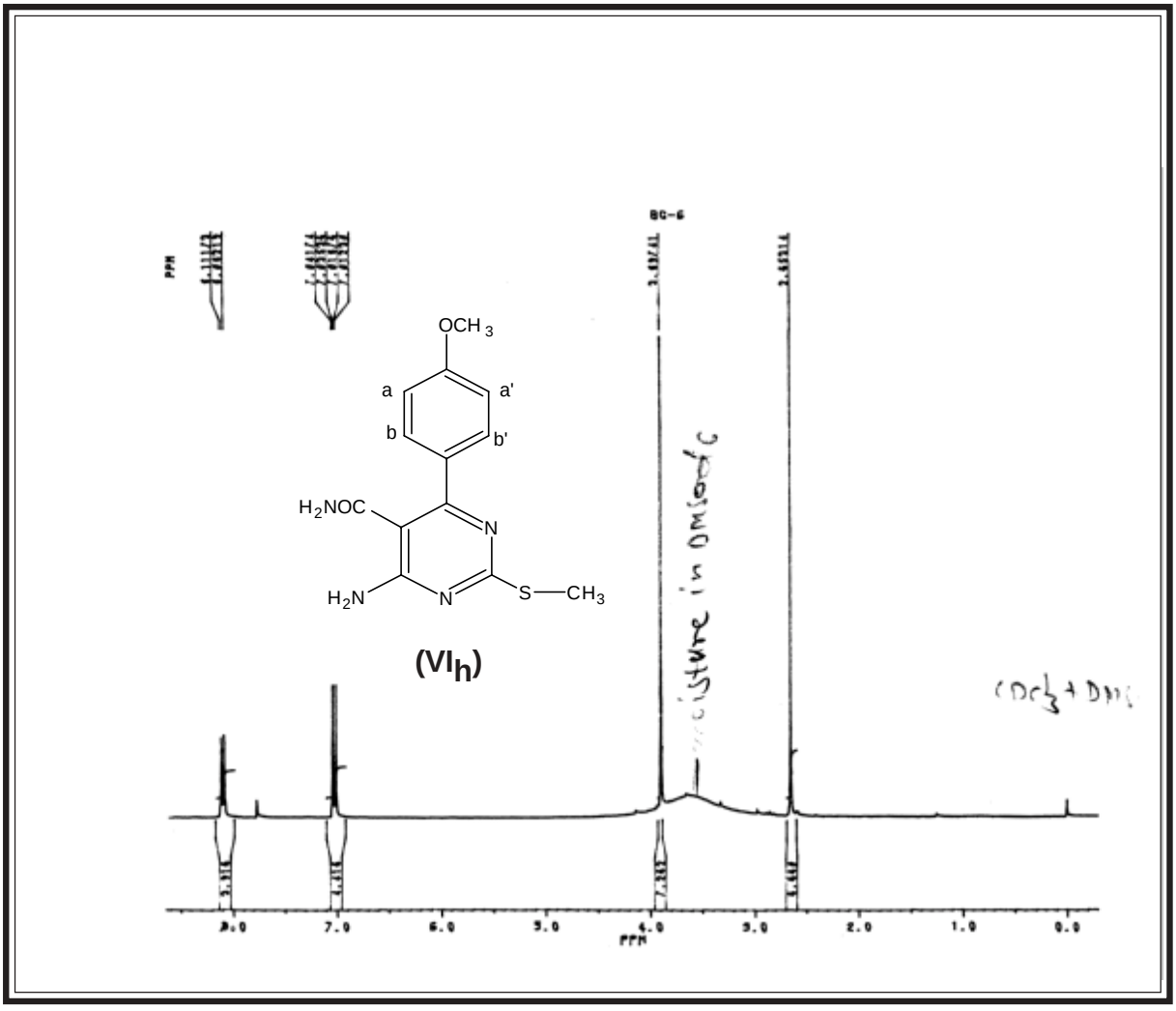
IR SPECTRAL STUDY OF 2-MERCAPTOMETHYL-4-AMINO-5-CARBOXAMIDO-6-(*p*-METHOXYPHENYL) PYRIMIDINE (VI_h)



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.(asym.)	2933.5	2975-2950	343
CH_3	C-H str.(sym.)	2837.1	2880-2860	,,
	C-H def.(asym.)	1458.1	1460-1435	,,
	C-H def.(sym.)	1367.4	1385-1300	,,
Aromatic and	C=C + C=N and ring	1508.2	1520-1480	345
Pyrimidine moiety	skeletal vibration	1546.8	1580-1520	,,
	C-H str.	3030.3	3080-3030	,,
	C-H i.p. def.	1112.8	1125-1090	,,
	C-H o.o.p. def.	825.5	840-810	,,
Ether	C-O-C str. (asym.)	1242.1	1275-1200	346
	C-O-C str. (sym.)	1064.6	1075-1050	,,
Amine (Primary)	N-H str.	3328.9	3500-3300	343
	N-H def.	1602.7	1650-1580	,,
Amide	N-H str.	3328.9	3500-3300	345
	C=O str.	1668.3	1710-1650	,,
$S-CH_3$	C-S-C	692.4	700-600	343

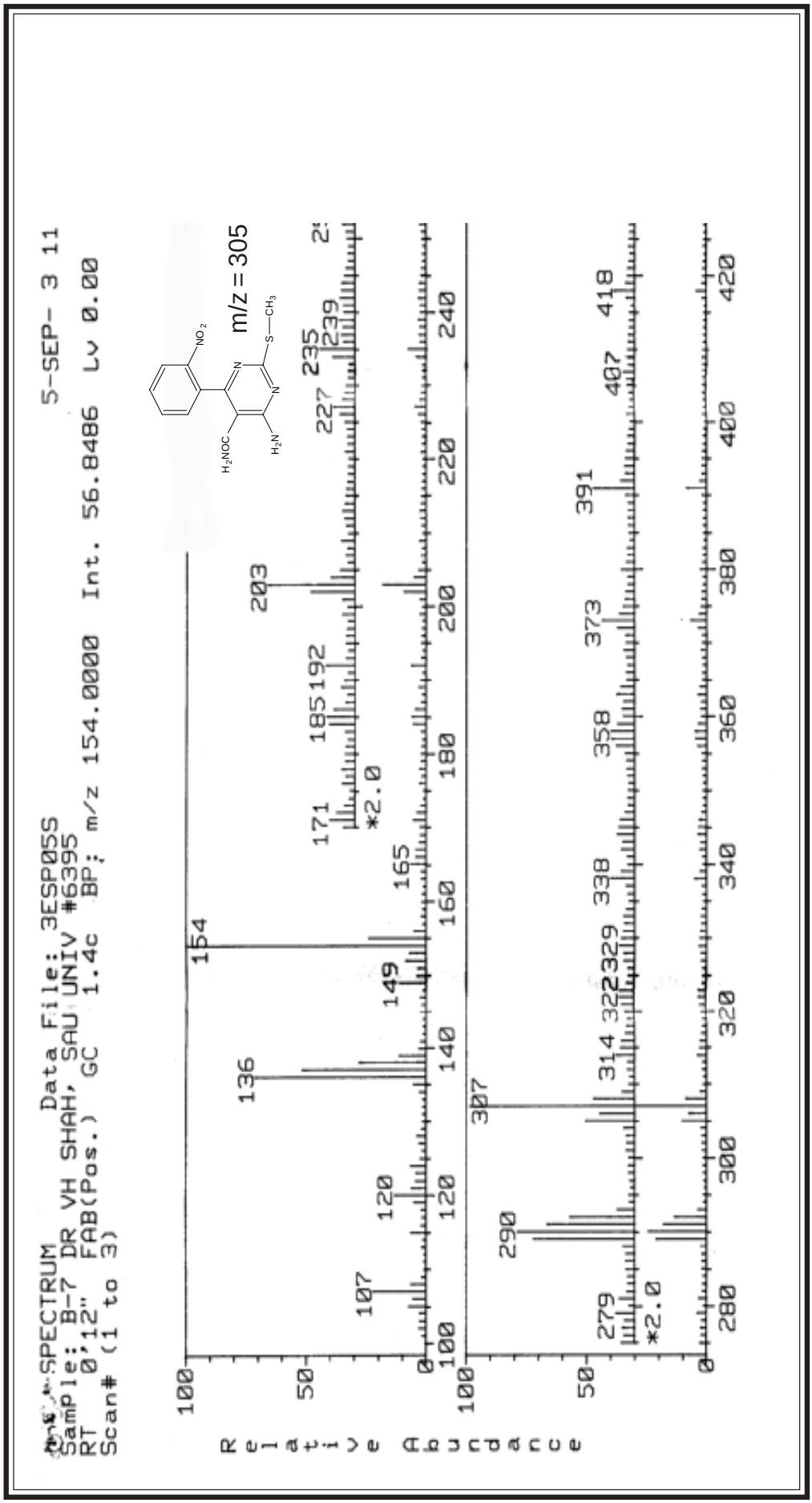
PMR SPECTRAL STUDY OF 2-MERCAPTOMETHYL-4-AMINO-5-CARBOXAMIDO-6-(*p*-METHOXYPHENYL) PYRIMIDINE (VI_h)

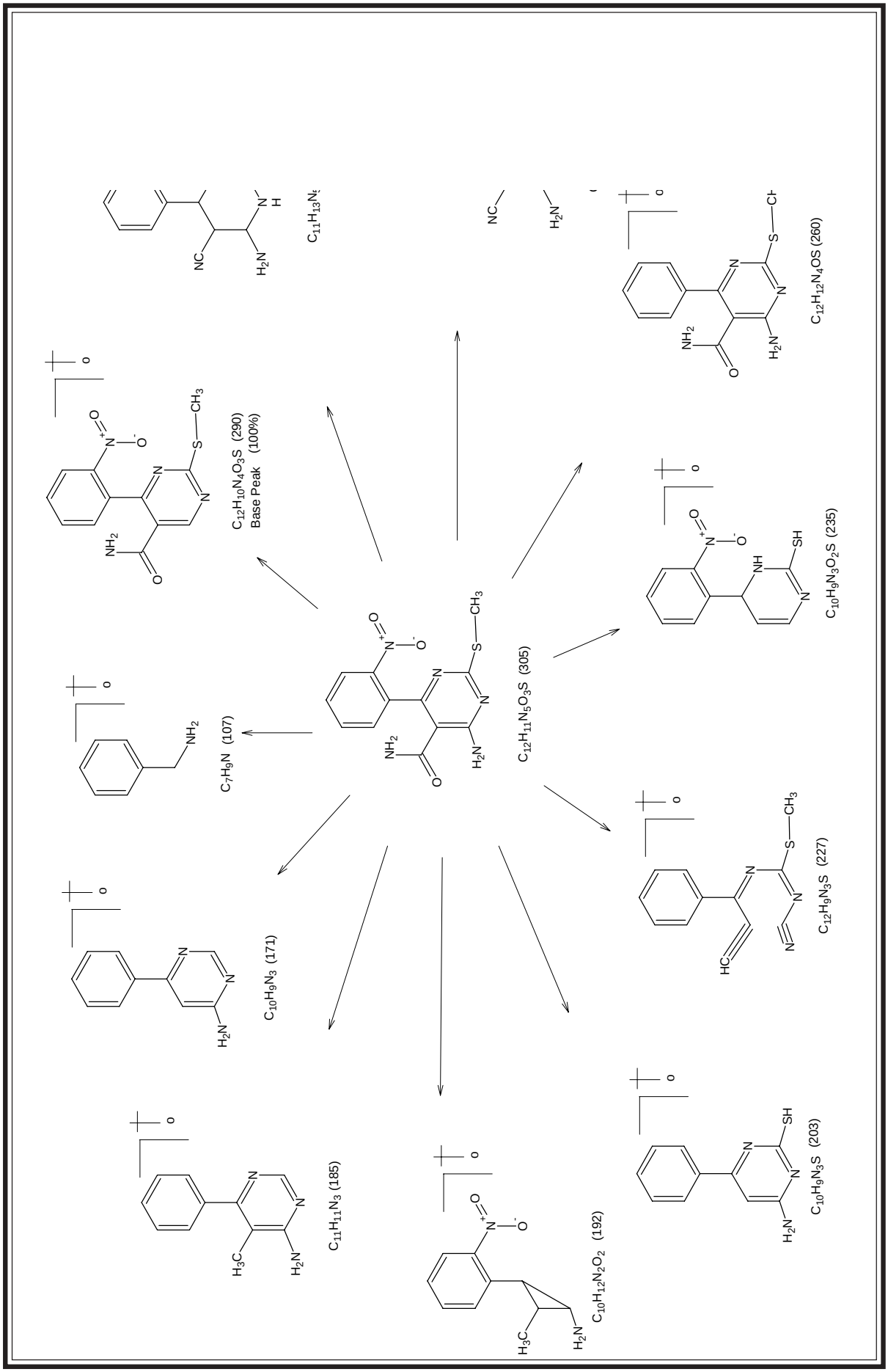


Internal Standard : TMS ; Solvent ; $CDCl_3$+$DMSOd_6$; Instrument : BRUKER Spectrometer (300 MHz)

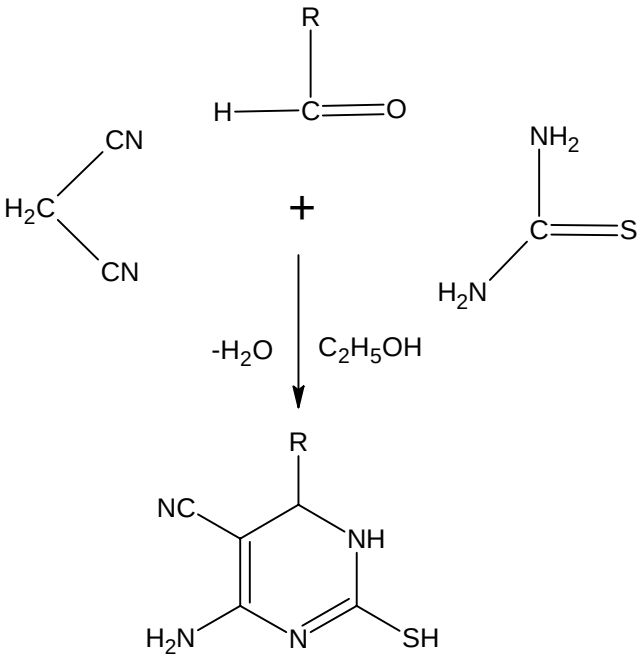
Signal No.	Signal Position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	2.653	3H	singlet	S-CH_3
2.	3.897	3H	singlet	-OCH_3
3.	7.012-7.042	2H	doublet	Ar-$H_{a,a'}$ (J=8.83)
4.	8.082-8.112	2H	doublet	Ar-$H_{b,b'}$ (J=8.86)

MASS SPECTRAL OF 2-MERCAPTOMETHYL-4-AMINO-5-CARBOXAMIDO-6-(*o*-NITROPHENYL) PYRIMIDINE (VI_f)

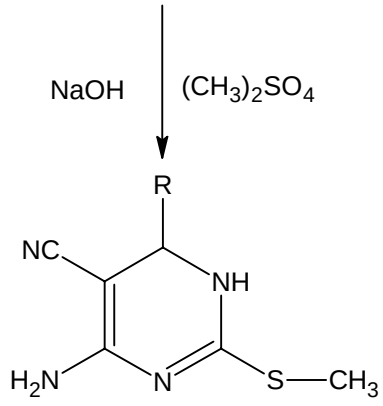



C12H11N5O3S (305)
C12H10N4O3S (290)
Base Peak (100%)
C7H9N (107)
C10H9N3 (171)
C11H11N3 (185)
C10H12N2O2 (192)
C10H9N3S (203)
C12H9N3S (227)
C10H9N3O2S (235)
C12H12N4OS (260)

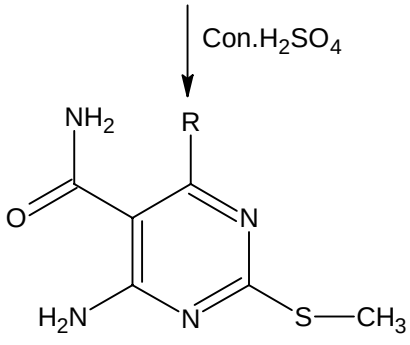
REACTION SCHAME



(1_{a-j})



(II_{a-j})



(VI_{a-j})

R = Aryl

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 2-MERCAPTOMETHYL-4-AMINO-5-CARBOXAMIDO-6-ARYL PYRIMIDINES

(A) Preparation of 2-Mercaptomethyl-4-amino-5-cyano-6-(*p*-methoxy phenyl)-1,6-dihidro pyrimidine (II_h).

For preparation refer Part-I, Section-II, Page No. 47.

(B) Preparation of 2-Mercaptomethyl-4-amino-5-carboxamido-6-(*p*-methoxyphenyl) pyrimidine (VI_h).

2-Mercaptomethyl-4-amino-5-cyano-6-(*p*-methoxyphenyl)-1,6-dihydro pyrimidine (2.74 gm, 0.01M) was dissolved in concentrated sulphuric acid (20ml) below 5 ^oC and kept for 48 hrs. at room temperature. The content was poured in to ice cold water and filtered. The product was isolated and crystallized from ethanol. Yield : 56%, M.P. : 185°C, R_f : 0.61, (Required : C, 53.79%; H, 4.83%; N, 19.31% for $C_{13}H_{14}N_4O_2S$, Found : C, 53.73%; H, 4.80%; N, 19.25%).

.

Similarly, other compounds (VI_{a-j}) were synthesized. The physical data are recorded in Table No. 7.

(C) Antimicrobial activity of 2-Mercaptomethyl-4-amino-5-carboxamido -6-aryl pyrimidines (VI_{a-j}).

Antimicrobial activity testing was carried out as described in part-1, section-I, page No. 35. The MIC values of test solution are recorded in Table No. 7a, 7b & 7c.

TABLE NO. 7 : PHYSICAL CONSTANTS OF 2-MERCAPTOMETHYL-4-AMINO-5-CARBOXAMIDO-6-ARYL PYRIMIDINES (VI_{a-j})

Comp. No. 1	R 2	Molecular Formula 3	M. W. 4	M.P. ^oC 5	Yield % 6	R_f Value 7	% of Nitrogen	
							Required 8	Found 9
VIa	C_6H_5	$C_{12}H_{12}N_4OS$	260.0	73	48	0.54	21.54	21.50
VIb	2-OH-C_6H_4	$C_{12}H_{12}N_4O_2S$	276.0	130	46	0.50	20.29	20.25
VIc	4-OH-C_6H_4	$C_{12}H_{12}N_4O_2S$	276.0	152	51	0.49	20.29	20.24
VId	2-Cl-C_6H_4	$C_{12}H_{11}N_4OSCl$	294.5	137	48	0.51	19.02	18.98
VIe	4-Cl-C_6H_4	$C_{12}H_{11}N_4OSCl$	294.5	160	53	0.54	19.02	18.97
VIf	2-NO_2-C_6H_4	$C_{12}H_{11}N_5O_3S$	305.0	152	55	0.53	22.95	22.89
VIg	3-NO_2-C_6H_4	$C_{12}H_{11}N_5O_3S$	305.0	117	52	0.52	22.95	22.90
VIh	4-CH_3O-C_6H_4	$C_{13}H_{14}N_4O_2S$	290.0	185	56	0.61	19.31	19.25
VIi	C_6H_5-CH=CH-	$C_{14}H_{14}N_4OS$	286.0	124	59	0.58	19.58	19.52
VIj	$C_{14}H_9$	$C_{20}H_{16}N_4OS$	360.0	96	64	0.47	15.56	15.50

☐ **TLC solvent system ; Acetone : Benzene = 2 : 8**

TABLE NO. 7a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-MERCAPTOMETHYL-4-AMINO-5-CARBOXAMIDO-6-ARYL PYRIMIDINES VI_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442							S. aureus MTCC-96						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
VIa	C_6H_5	-	-	10	10	12	13	14	-	-	11	12	13	15	16
VIb	2-OH-C_6H_4	-	-	11	11	13	14	14	-	-	13	14	15	16	16
VIc	4-OH-C_6H_4	-	-	10	10	12	12	14	-	-	12	12	14	14	15
VId	2-Cl-C_6H_4	-	-	12	12	14	14	14	-	-	14	14	15	16	16
VIe	4-Cl-C_6H_4	-	-	11	11	12	13	13	-	-	12	13	14	15	15
VIf	2-NO_2-C_6H_4	-	-	12	12	14	14	14	-	-	14	14	16	16	17
VIg	3-NO_2-C_6H_4	-	-	10	10	12	12	14	-	-	12	13	15	15	16
VIh	4-OCH_3-C_6H_4	-	-	10	11	13	13	14	-	-	11	12	14	15	16
VIi	-CH=CH-C_6H_4	-	-	11	11	12	14	14	-	-	12	13	14	16	17
VIj	$C_{14}H_9$	-	-	12	12	14	14	14	-	-	13	14	16	16	17

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

Standard drug	Antibacterial activity														
											VIb VId VIf VIj	VIb VId VIf VIj	VIf VIj		
Ampicillin	11	13	14	16	18	19	20	10	12	13	14	16	18	21
Chloramphenicol	10	12	13	19	20	20	22	12	13	14	19	20	21	22
Ciprofloxacin	16	18	19	21	21	22	22	17	18	19	21	22	22	23
Norfloxacin	18	18	19	20	21	21	23	19	20	22	25	26	28	28

N.B.(-): No Activity

TABLE NO. 7b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-MERCAPTOMETHYL-4-AMINO-5-CARBOXAMIDO-6-ARYL PYRIMIDINES VI_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)													
		E. Coli MTCC-443							B. subtillis MTCC-441						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
VIa	C_6H_5	-	-	12	14	15	17	17	-	-	14	15	16	18	19
VIb	2-OH-C_6H_4	-	-	14	14	15	17	18	-	-	16	17	18	19	19
VIc	4-OH-C_6H_4	-	-	13	14	15	16	18	-	-	15	16	17	17	19
VId	2-Cl-C_6H_4	-	-	15	16	17	17	18	-	-	17	17	19	19	19
VIe	4-Cl-C_6H_4	-	-	14	14	16	16	17	-	-	14	15	16	18	19
VIf	2-NO_2-C_6H_4	-	-	15	16	17	18	18	-	-	17	18	18	19	19
VIg	3-NO_2-C_6H_4	-	-	13	15	16	17	18	-	-	15	16	18	18	19
VIh	4-OCH_3-C_6H_4	-	-	13	14	16	17	17	-	-	14	15	17	18	19
VIi	-CH=CH-C_6H_4	-	-	14	14	15	16	18	-	-	16	16	17	18	19
VIj	$C_{14}H_9$	-	-	15	16	17	18	19	-	-	15	16	18	19	19
Comparative activity of (VI_{a-j}) with known choosen standard drugs															
Standard drug		**Antibacterial activity**													
				VId VIf VIj	VId VIf VIj						VIb VId VIf VIi				
Ampicillin		14	14	15	16	19	20	22	12	16	18	19	20	21	23
Chloramphenicol		14	15	17	23	23	23	23	12	14	16	19	22	23	23
Ciprofloxacin		20	21	23	28	28	28	28	16	17	19	22	22	23	23
Norfloxacin		22	23	25	26	27	29	29	19	20	22	23	24	25	28

N.B.(-): No Activity

TABLE NO. 7c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-MERCAPTOMETHYL-4-AMINO-5-CARBOXAMIDO-6-ARYL PYRIMIDINES VI_{a-j} (Minimum inhibition Concentration in µg/ml)

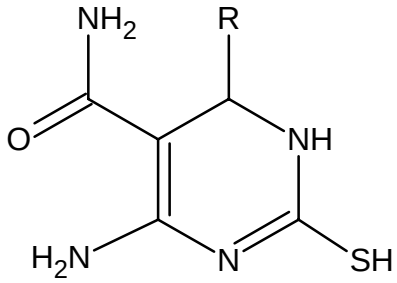
Compd No.	R	Antifungal activity (Zones of inhibition in mm)													
		C. albicans MTCC-227							A. niger MTCC-282						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
VIa	C_6H_5	-	-	16	17	19	20	20	-	-	18	18	20	21	22
VIb	2-OH-C_6H_4	-	-	17	18	19	20	21	-	-	18	19	21	22	22
VIc	4-OH-C_6H_4	-	-	16	17	18	19	20	-	-	18	18	20	20	22
VId	2-Cl-C_6H_4	-	-	18	18	20	20	21	-	-	18	19	21	22	24
VIe	4-Cl-C_6H_4	-	-	16	17	19	19	20	-	-	18	18	20	21	22
VIf	2-NO_2-C_6H_4	-	-	17	18	19	20	21	-	-	19	19	21	21	24
VIg	3-NO_2-C_6H_4	-	-	16	17	19	20	21	-	-	18	19	21	22	23
VIh	4-OCH_3-C_6H_4	-	-	16	17	18	20	21	-	-	18	18	20	20	23
VIi	-CH=CH-C_6H_4	-	-	17	17	20	19	20	-	-	18	19	20	22	22
VIj	$C_{14}H_9$	-	-	17	18	20	20	21	-	-	18	19	21	22	24
Comparative activity of (VI_{a-j}) with known choosen standard drugs															
Standard drug		**Antifungal activity**													
Griseofulvin		19	22	23	25	25	28	28	18	19	21	22	22	24	26

N.B.(-): No Activity

SECTION - III

PREPARATION AND BIOLOGICAL EVALUATION OF 2-MERCAPTO-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES

Due to wide range of biological activities[123-159], recent literature survey[117-122], other properties[113-116] and in view to have potent therapeutic agents, the synthesis of 2-mercapto-4-amino-5-carboxamido-6-(2'-chloro substituted quinolin-3'-yl)-1,6-dihydro pyrimidines (VII_{a-j}) have been undertaken by the reaction of 3-(2'-chloro substituted quinolin-3'-yl)-2-cyanoacrylamides with thiourea.

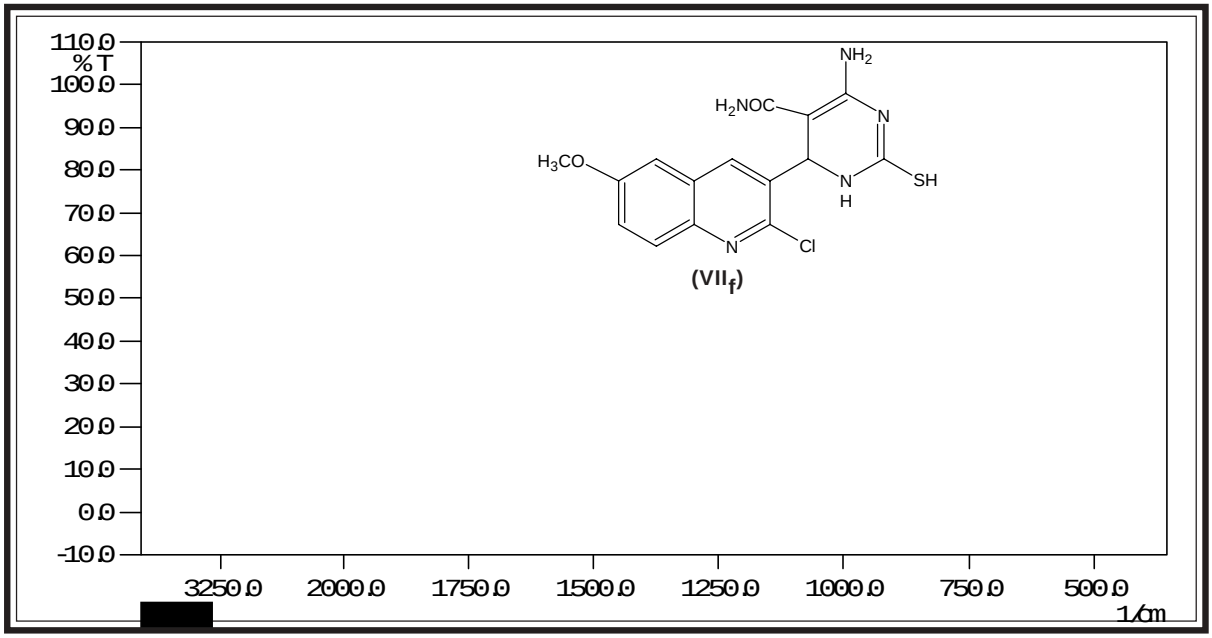


VII_{a-j} **R=2-Chloro substituted Quinolin-3-yl**

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

The products (VII_{a-j}) were assayed for their *in vitro* biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

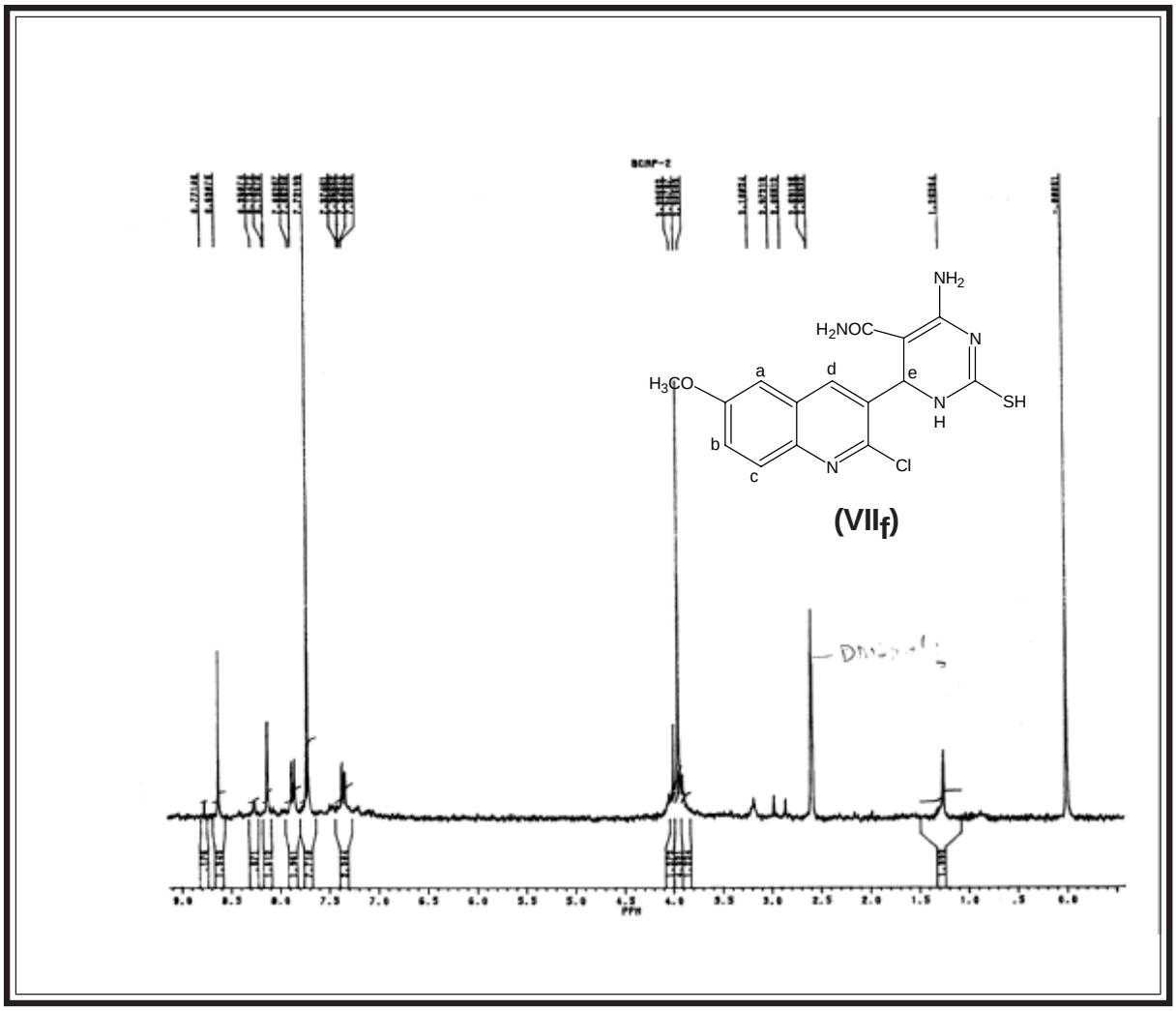
IR SPECTRAL STUDY OF 2-MERCAPTO-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO-6'-METHOXY QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINE (VII_f)



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.(asym.)	2923.9	2975-2950	343
CH_3	C-H str.(sym.)	2850.6	2880-2860	,,
	C-H def.(asym.)	1442.7	1460-1435	,,
	C-H def.(sym.)	1334.6	1385-1300	,,
Aromatic and	C=C + C=N and ring	1498.6	1520-1480	345
Pyrimidine moiety	skeletal vibration	1514.0	1580-1520	,,
	C-H str.	3093.6	3080-3030	,,
	C-H i.p. def.	1132.1	1125-1090	,,
	C-H o.o.p. def.	825.5	840-810	,,
Ether	C-O-C str. (asym.)	1269.1	1275-1200	346
	C-O-C str. (sym.)	1060.8	1075-1050	,,
Amine (Primary)	N-H str.	3313.5	3500-3300	343
	N-H def.	1616.2	1650-1580	,,
Amide	N-H str.	3313.5	3500-3300	345
	C=O str.	1672.2	1710-1650	,,
Quinoline	C-Cl str.	742.5	750-600	343
moiety	C=N str.	1585.4	1612-1593	,,
	C=C str.	1598.9	1612-1593	,,
Mercapto	S-H str.	2617.2	2600-2550	343

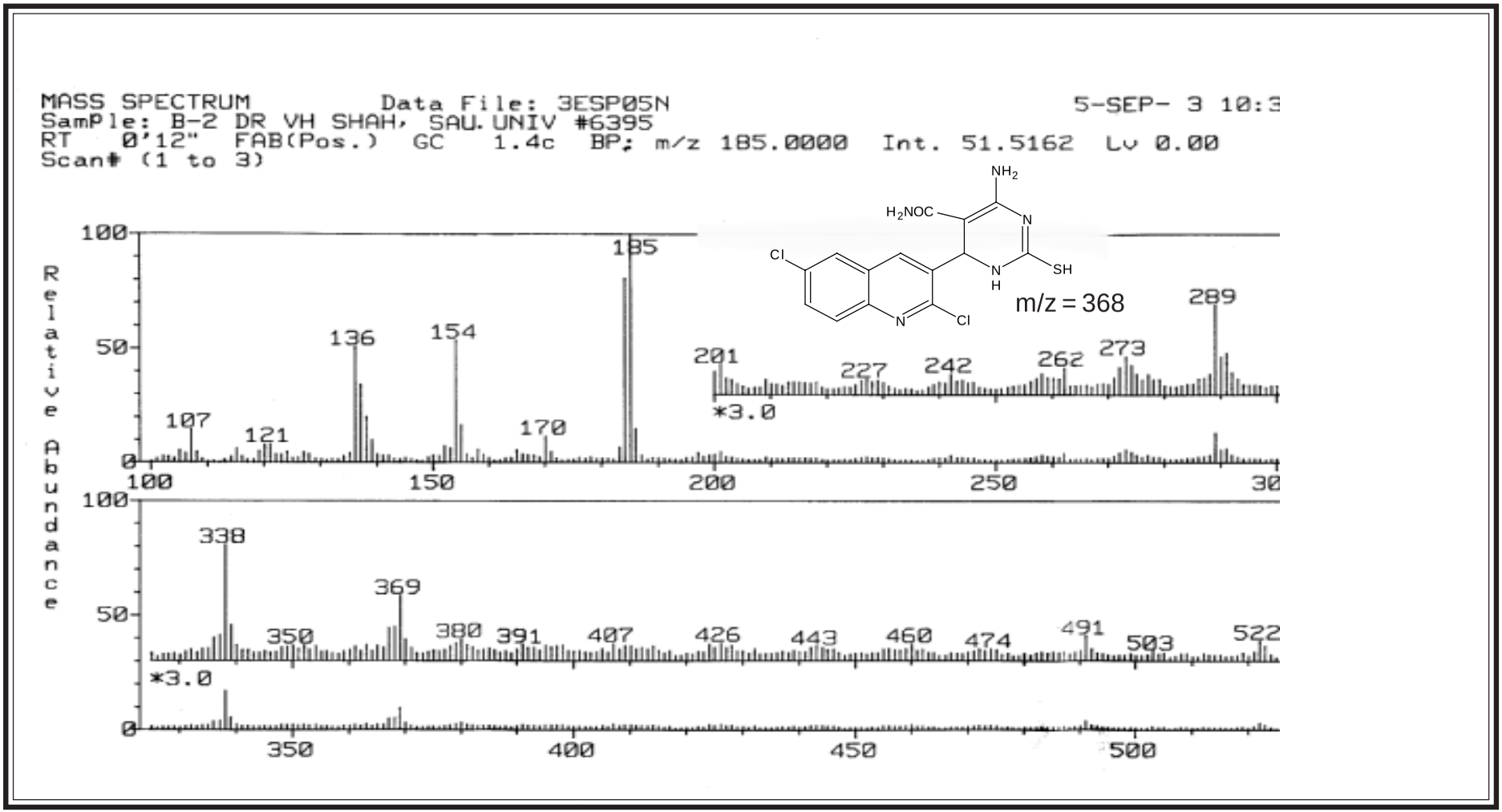
PMR SPECTRAL STUDY OF 2-MERCAPTO-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO-6'-METHOXY QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINE (VII_f)

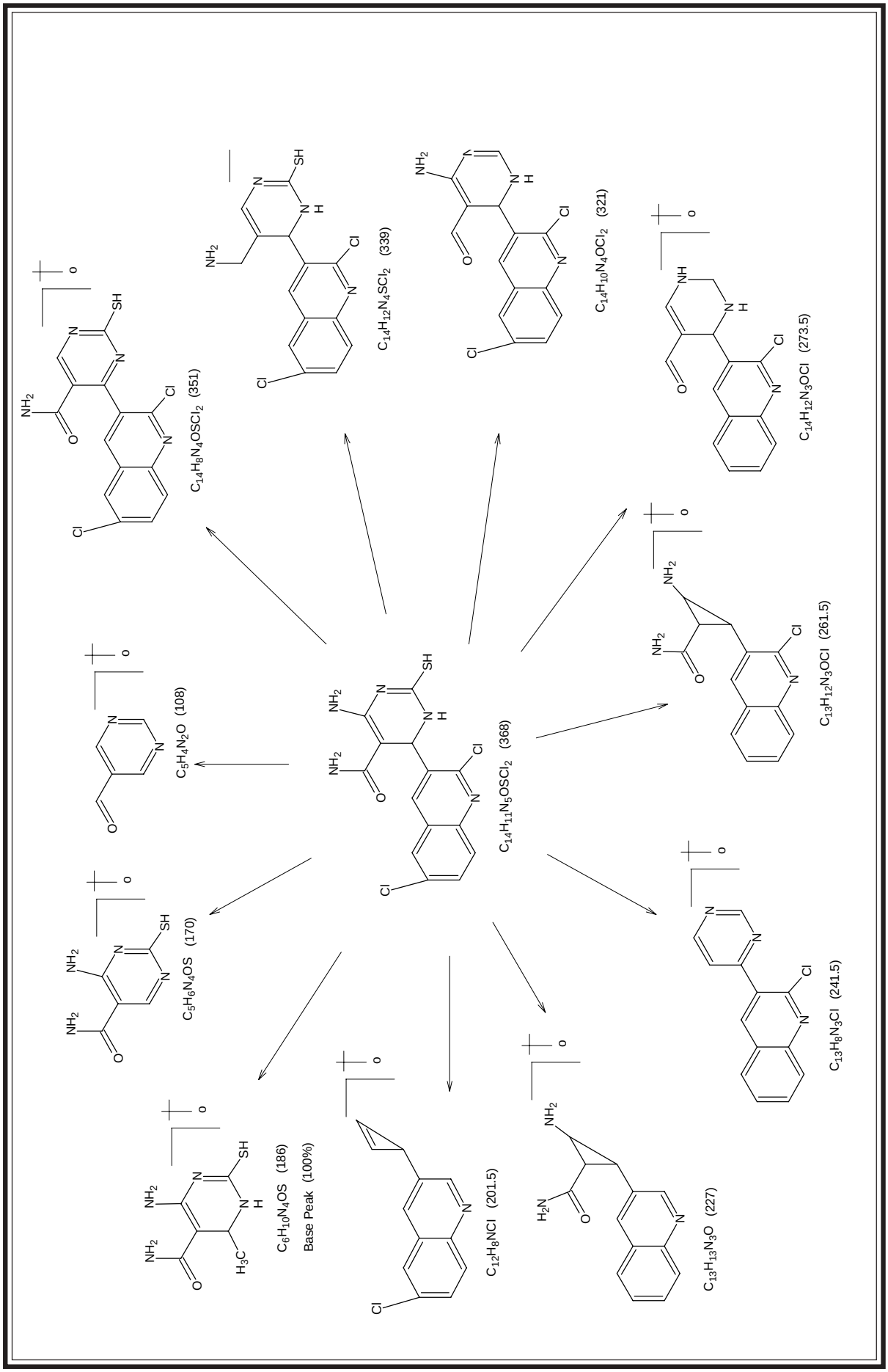


Internal Standard : TMS ; Solvent ; $CDCl_3$+$DMSOd_6$; Instrument : BRUKER Spectrometer (300 MHz)

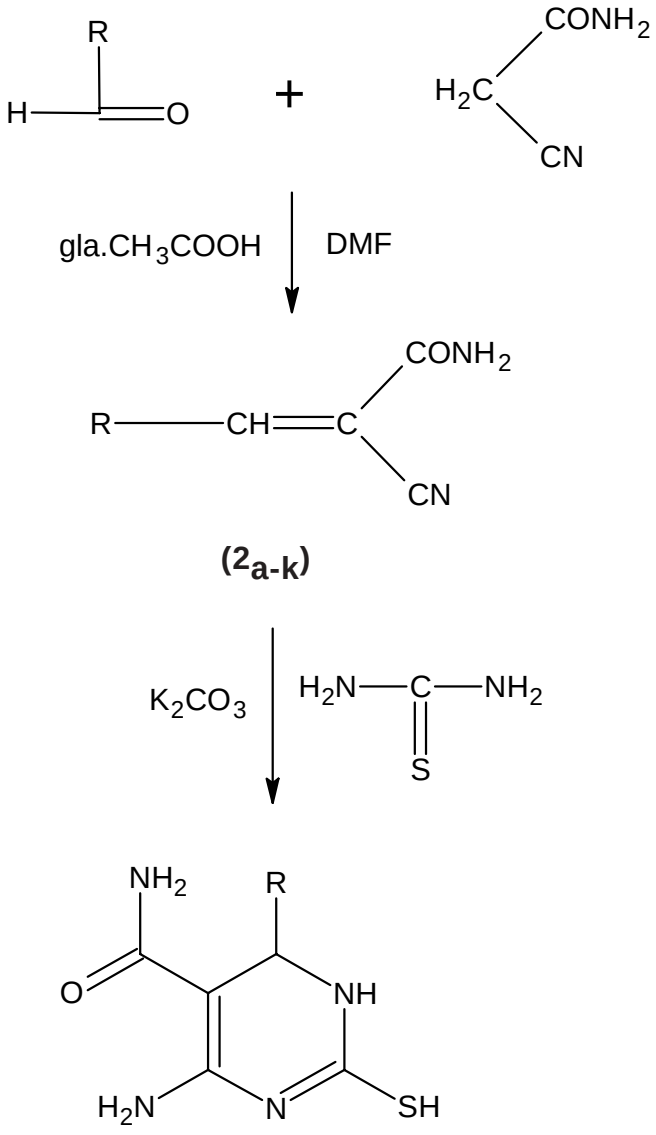
Signal No.	Signal Position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.948	3H	singlet	$-OCH_3$
2.	7.336-7.375	1H	double doublet	Ar-H_b
3.	7.722	4H	multiplet	Ar-H_e+ NH_2+ NH
4.	7.853-7.883	1H	doublet	Ar-H_c (J=9.02)
5.	8.127-8.135	1H	doublet	Ar-H_a (J=2.41)
6.	8.631	1H	singlet	Ar-H_d

MASS SPECTRAL OF 2-MERCAPTO-4-AMINO-5-CARBOXAMIDO-6-(2',6'-DICHLORO QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINE (VII_h)




C14H8N4OSCl2 (351)
C14H12N4SCl2 (339)
C14H10N4OCl2 (321)
C14H12N3OCl (273.5)
C5H4N2O (108)
C14H11N5OSCl2 (368)
C13H12N3OCl (261.5)
C5H6N4OS (170)
C13H8N3Cl (241.5)
C6H10N4OS (186)
Base Peak (100%)
C12H8NCl (201.5)
C13H13N3O (227)

REACTION SCHAME



(2_{a-k})

(VII_{a-j}) **R = 2-Chloro substituted Quinolin-3-yl**

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 2-MERCAPTO-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES

(A) Preparation of 3-(2'-chloro-6'-methoxy quinolin-3'-yl)-2-cyano acrylamide (2_f).

To the mixture of 2-chloro-6-methoxy quinolin-3-carboxaldehyde (2.22 gm, 0.01 M) and cyano acetamide (0.84 gm, 0.01 M) in DMF(30 ml), 8 ml of glacial acetic acid was added and the reaction mixture was stirred for 48 hrs. at room temperature . The content was poured into ice cold water and filtered. The product was isolated and crystallized from ethanol. Yield : 68%, M.P. : 127°C, R_f : 0.62, (Required : C, 58.43%; H, 3.48%; N, 14.61% for $C_{14}H_{10}N_3O_2Cl$, Found : C, 58.39%; H, 3.43%; N, 14.56%).

Similarly, other compounds (2_{a-k}) were synthesized. The physical data are recorded in Table No. 8.

(B) Preparation of 2-Mercapto-4-amino-5-carboxamido-6-(2'-chloro-6'-methoxy quinolin-3'-yl)-1,6-dihydro pyrimidine (VII_f).

A mixture of 3-(2'-chloro-6'-methoxy quinolin-3'-yl)-2-cyano acrylamide (2.88 gm, 0.01M) and thiourea (0.76 gm, 0.01M) in DMF (20 ml) was heated in an oil-bath at 130 ^oC for 8 hrs. in presence of potassium carbonate. The content was poured into ice cold water and neutralized with diluted hydrochloric acid and filtered. The product was isolated and crystallized from DMF. Yield : 62%, M.P. : 116°C, R_f : 0.59, (Required : C, 49.52%; H, 3.85%; N, 19.26 % for $C_{15}H_{14}N_5O_2SCl$; Found : C, 49.50%; H, 3.81%; N, 19.21%).

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

(C) Antimicrobial activity of 2-Mercapto-4-amino-5-carboxamido-6-(2'-chloro substituted quinolin-3'-yl)-1,6-dihydro pyrimidines (VIIa-j).

Antimicrobial activity testing was carried out as described in part-1, section-I, page No. 35. The MIC values of test solution are recorded in Table No. 9a, 9b & 9c.

TABLENO. 2 : PHYSICAL CONSTANTS OF 3-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-2-CYANO ACRYLAMIDES (2_{a-k})

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. ^{o}C 5	Yield % 6	R_f Value 7	% of Nitrogen	
							Required 8	Found 9
2a	2-Cl-C_9H_5N	$C_{13}H_8N_3OCl$	257.7	123	62	0.52	16.31	16.25
2b	2-Cl-8-CH_3-C_9H_4N	$C_{14}H_{10}N_3OCl$	271.7	157	65	0.56	15.47	15.42
2c	2-Cl-7-CH_3-C_9H_4N	$C_{14}H_{10}N_3OCl$	271.7	112	61	0.48	15.47	15.41
2d	2-Cl-6-CH_3-C_9H_4N	$C_{14}H_{10}N_3OCl$	271.7	174	58	0.54	15.47	15.42
2e	2-Cl-8-CH_3O-C_9H_4N	$C_{14}H_{10}N_3O_2Cl$	287.7	136	60	0.51	14.61	14.55
2f	2-Cl-6-CH_3O-C_9H_4N	$C_{14}H_{10}N_3O_2Cl$	287.7	142	55	0.46	14.61	14.56
2g	2,7-$(Cl)_2$-C_9H_4N	$C_{13}H_7N_3OCl_2$	292.1	102	57	0.49	14.38	14.31
2h	2,6-$(Cl)_2$-C_9H_4N	$C_{13}H_7N_3OCl_2$	292.1	180	53	0.47	14.38	14.32
2i	2-Cl-6-Br-C_9H_4N	$C_{13}H_7N_3OClBr$	336.5	168	59	0.52	12.50	12.45
2j	2,6,7-$(Cl)_3$-C_9H_3N	$C_{13}H_6N_3OCl_3$	326.5	192	62	0.49	12.86	12.80
2k	2-Cl-5,8-$(CH3O)_2$-C_9H_3N	$C_{15}H_{12}N_3O_3Cl$	317.7	137	64	0.47	13.23	13.19

i **TLC solvent system ; Ethyl acetate : Cyclohexane = 2 : 8**

TABLENO. 9 : PHYSICAL CONSTANTS OF 2-MERCAPTO-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES (VII_{a-j})

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. ^oC 5	Yield % 6	R_f Value 7	% of Nitrogen	
							Required 8	Found 9
VIIa	2-Cl-C_9H_5N	$C_{14}H_{12}N_5OSCl$	333.5	155	58	0.49	20.99	20.94
VIIb	2-Cl-8-CH_3-C_9H_4N	$C_{15}H_{14}N_5OSCl$	347.5	170	55	0.54	20.14	20.09
VIIc	2-Cl-7-CH_3-C_9H_4N	$C_{15}H_{14}N_5OSCl$	347.5	223	54	0.57	20.14	20.10
VIId	2-Cl-6-CH_3-C_9H_4N	$C_{15}H_{14}N_5OSCl$	347.5	128	58	0.51	20.14	20.08
VIIe	2-Cl-8-CH_3O-C_9H_4N	$C_{15}H_{14}N_5O_2SCl$	363.5	102	53	0.47	19.26	19.23
VIIf	2-Cl-6-CH_3O-C_9H_4N	$C_{15}H_{14}N_5O_2SCl$	363.5	116	62	0.59	19.26	19.21
VIIg	2,7-$(Cl)_2$-C_9H_4N	$C_{14}H_{11}N_5OSCl_2$	368.0	162	59	0.52	19.02	18.96
VIIh	2,6-$(Cl)_2$-C_9H_4N	$C_{14}H_{11}N_5OSCl_2$	368.0	>250	57	0.56	19.02	18.97
VIIi	2-Cl-6-Br-C_9H_4N	$C_{14}H_{11}N_5OSClBr$	412.0	124	61	0.48	16.99	16.94
VIIj	2,6,7-$(Cl)_3$-C_9H_3N	$C_{14}H_{10}N_5OSCl_3$	402.5	134	64	0.52	17.39	17.34

i **TLC solvent system ; Acetone :Benzene = 1 : 9**

TABLE NO. 9a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-MERCAPTO-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES VII_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)													
		S. pyogens MTCC-442							S. aureus MTCC-96						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
VIIa	C_6H_5	-	-	12	12	13	14	14	-	-	14	15	15	16	16
VIIb	2-OH-C_6H_4	-	-	10	10	12	13	14	-	-	12	13	15	15	16
VIIc	4-OH-C_6H_4	-	-	11	11	13	14	14	-	-	13	14	15	16	17
VIId	2-Cl-C_6H_4	-	-	10	10	12	13	14	-	-	11	12	14	15	15
VIIe	4-Cl-C_6H_4	-	-	12	12	13	13	14	-	-	14	15	15	16	16
VIIf	2-NO_2-C_6H_4	-	-	10	10	12	14	14	-	-	11	12	14	15	15
VIIg	3-NO_2-C_6H_4	-	-	11	11	12	14	14	-	-	12	13	15	16	16
VIIh	4-OCH_3-C_6H_4	-	-	11	11	13	13	14	-	-	12	13	15	16	16
VIIi	-CH=CH-C_6H_4	-	-	12	12	13	13	14	-	-	14	14	15	16	16
VIIj	$C_{14}H_9$	-	-	10	10	12	14	13	-	-	12	12	14	15	16

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

Standard drug	Antibacterial activity														
											VIIa VIIe VIIi	VIIa VIIc VIIe VIIi			
Ampicillin	11	13	14	16	18	19	20	10	12	13	14	16	18	21
Chloramphenicol	10	12	13	19	20	20	22	12	13	14	19	20	21	22
Ciprofloxacin	16	18	19	21	21	22	22	17	18	19	21	22	22	23
Norfloxacin	18	18	19	20	21	21	23	19	20	22	25	26	28	28

N.B.(-): No Activity

TABLE NO. 9b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-MERCAPTO-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES VII_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)													
		E. Coli MTCC-443							B. subtillis MTCC-441						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
VIIa	C_6H_5	-	-	15	15	16	18	18	-	-	17	17	18	19	19
VIIb	2-OH-C_6H_4	-	-	13	13	14	16	17	-	-	15	16	17	18	18
VIIc	4-OH-C_6H_4	-	-	15	15	16	17	17	-	-	16	17	18	19	19
VIId	2-Cl-C_6H_4	-	-	12	14	16	16	17	-	-	14	15	16	18	18
VIIe	4-Cl-C_6H_4	-	-	15	17	18	18	18	-	-	17	17	19	19	20
VIIf	2-NO_2-C_6H_4	-	-	14	14	15	17	17	-	-	15	16	17	17	18
VIIg	3-NO_2-C_6H_4	-	-	14	14	12	17	18	-	-	15	16	18	18	19
VIIh	4-OCH_3-C_6H_4	-	-	14	15	16	17	18	-	-	15	17	18	19	19
VIIi	-CH=CH-C_6H_4	-	-	15	16	16	17	18	-	-	17	17	18	19	19
VIIj	$C_{14}H_9$	-	-	13	14	15	16	17	-	-	14	15	17	18	19
Comparative activity of (VII_{a-j}) with known choosen standard drugs															
Standard drug		**Antibacterial activity**													
				VIIa VIIc VIIe VIIi	VIIe VIIi						VIIa VIIc VIIe VIIi				
Ampicillin		14	14	15	16	19	20	22	12	16	18	19	20	21	23
Chloramphenicol		14	15	17	23	23	23	23	12	14	16	19	22	23	23
Ciprofloxacin		20	21	23	28	28	28	28	16	17	19	22	22	23	23
Norfloxacin		22	23	25	26	27	29	29	19	20	22	23	24	25	28

N.B.(-): No Activity

TABLE NO. 9c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-MERCAPTO-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES VII_{a-j} (Minimum inhibition Concentration in µg/ml)

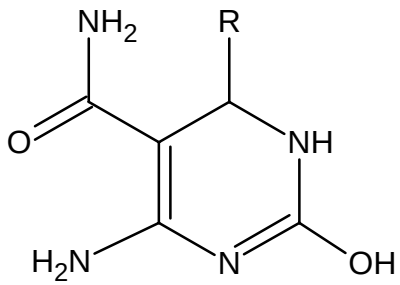
Compd No.	R	Antifungal activity (Zones of inhibition in mm) C. albicans MTCC-227							A. niger MTCC-282						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
VIIa	C_6H_5	-	-	17	18	19	20	21	-	-	19	19	21	22	23
VIIb	2-OH-C_6H_4	-	-	16	17	19	20	20	-	-	18	19	21	21	22
VIIc	4-OH-C_6H_4	-	-	17	18	18	20	20	-	-	18	19	20	22	23
VIId	2-Cl-C_6H_4	-	-	16	17	19	20	21	-	-	18	18	20	22	24
VIIe	4-Cl-C_6H_4	-	-	18	19	21	21	22	-	-	19	21	22	23	24
VIIf	2-NO_2-C_6H_4	-	-	17	18	19	20	21	-	-	19	19	21	21	23
VIIg	3-NO_2-C_6H_4	-	-	17	18	20	20	21	-	-	18	19	21	22	22
VIIh	4-OCH_3-C_6H_4	-	-	17	18	20	21	21	-	-	19	19	21	23	24
VIIi	-CH=CH-C_6H_4	-	-	17	18	19	20	20	-	-	18	19	20	22	23
VIIj	$C_{14}H_9$	-	-	16	17	19	20	20	-	-	18	18	20	22	23
Comparative activity of (VII_{a-j}) with known choosen standard drugs															
Standard drug		**Antifungal activity**													
													VIIe		
Griseofulvin		19	22	23	25	25	28	28	18	19	21	22	22	24	26

N.B.(-): No Activity

SECTION - IV

PREPARATION AND BIOLOGICAL EVALUATION OF 2-HYDROXY- 4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES

Due to wide range of biological activities[123-159], recent literature survey[117-122], other properties[113-116] and in view to have potent therapeutic agents, the synthesis of 2-hudroxy-4-amino-5-carboxamido-6-(2'-chloro substituted quinolin-3'-yl)-1,6-dihydro pyrimidines ($VIII_{a-j}$) have been undertaken by the reaction of 3-(2'-chloro substituted quinolin-3'-yl)-2- cyanoacrylamides with urea.

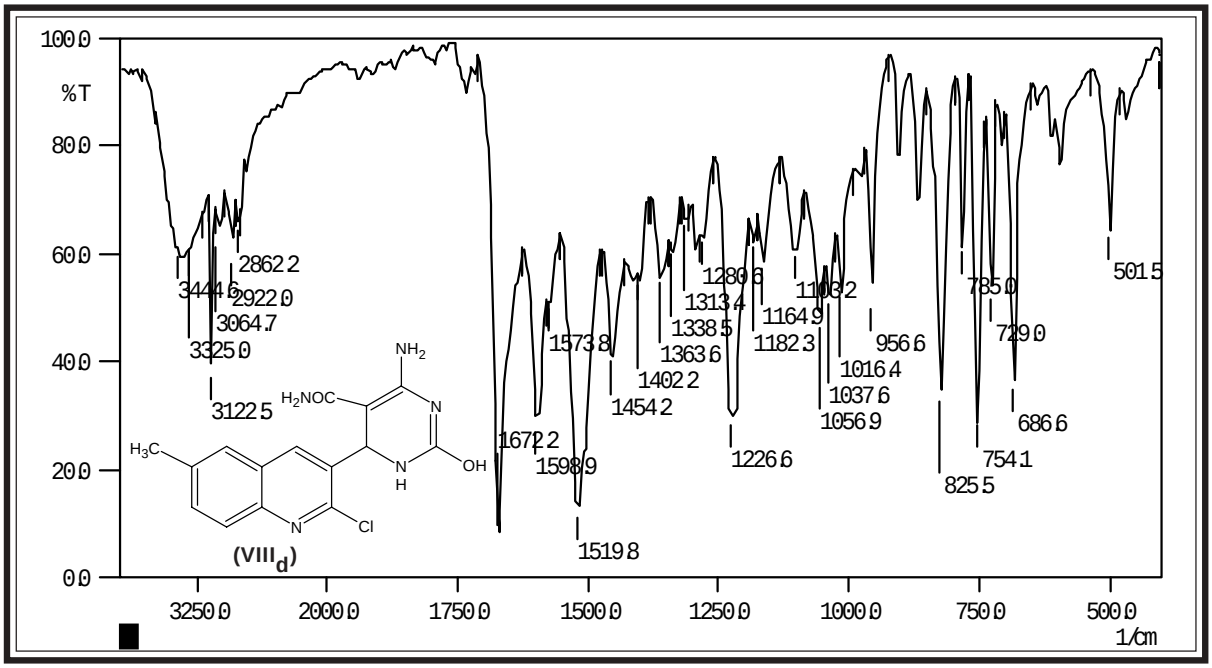


$VIII_{a-j}$ R=2-Chloro substituted Quinolin-3-yl

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

The products ($VIII_{a-j}$) were assayed for their *in vitro* biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

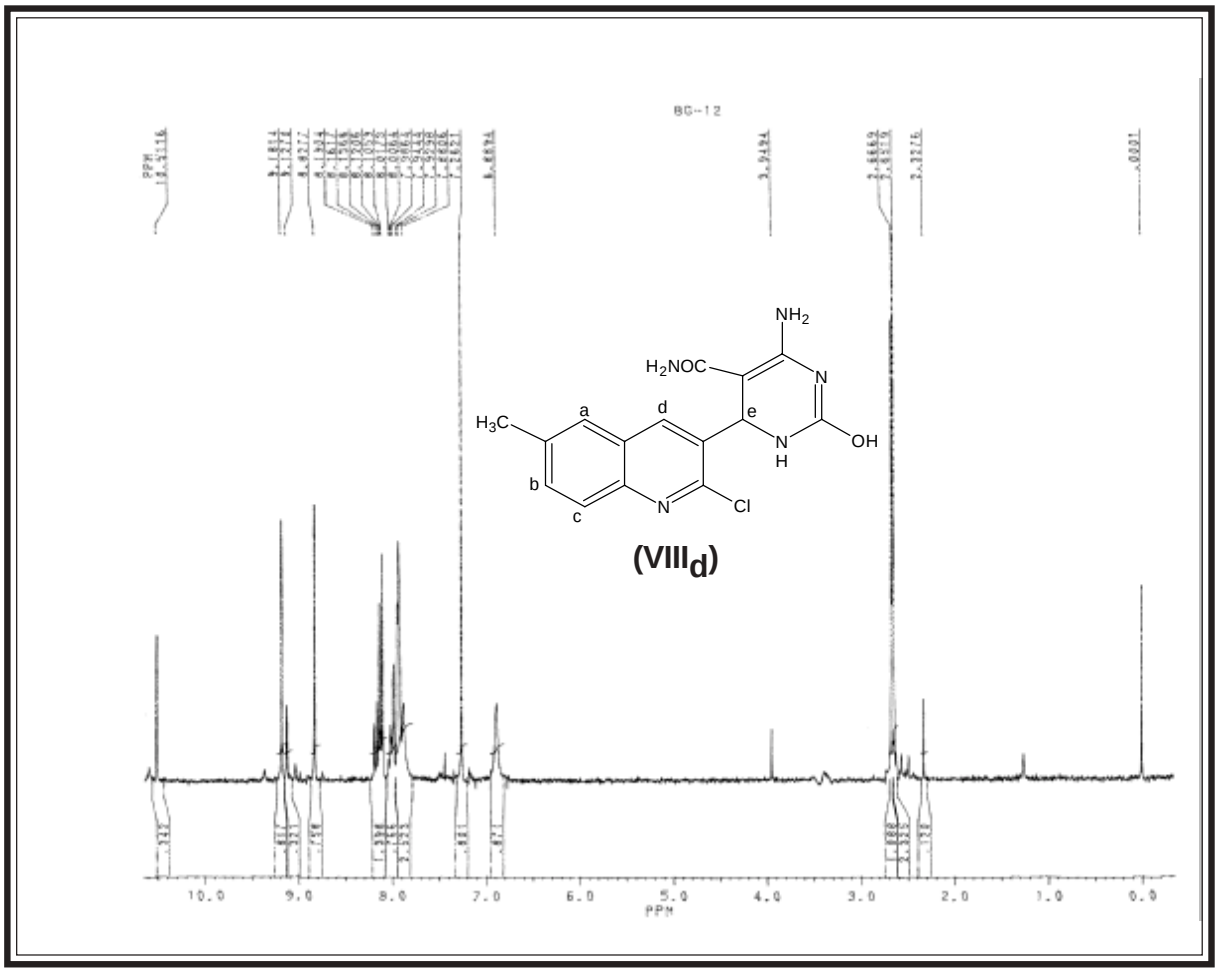
IR SPECTRAL STUDY OF 2-HYDROXY-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO-6'-METHYL QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINE ($VIII_d$)



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.(asym.)	2922.0	2975-2950	343
CH_3	C-H str.(sym.)	2862.2	2880-2860	,,
	C-H def.(asym.)	1454.2	1460-1435	,,
	C-H def.(sym.)	1363.6	1385-1300	,,
Aromatic and	C=C + C=N and ring	1519.8	1520-1480	345
Pyrimidine moiety	skeletal vibration	1573.8	1580-1520	,,
	C-H str.	3064.7	3080-3030	,,
	C-H i.p. def.	1108.2	1125-1090	,,
	C-H o.o.p. def.	825.5	840-810	,,
Hydroxy	-OH str.	3444.6	3500-3300	343
Amine (Primary)	N-H str.	3325.0	3500-3300	343
	N-H def.	1598.9	1650-1580	,,
Amide	N-H str.	3325.5	3500-3300	345
	C=O str.	1672.2	1710-1650	,,
Quinoline	C-Cl str.	754.1	750-600	343
moiety	C=N str.	1598.9	1612-1593	,,
	C=C str.	1598.9	1612-1593	,,

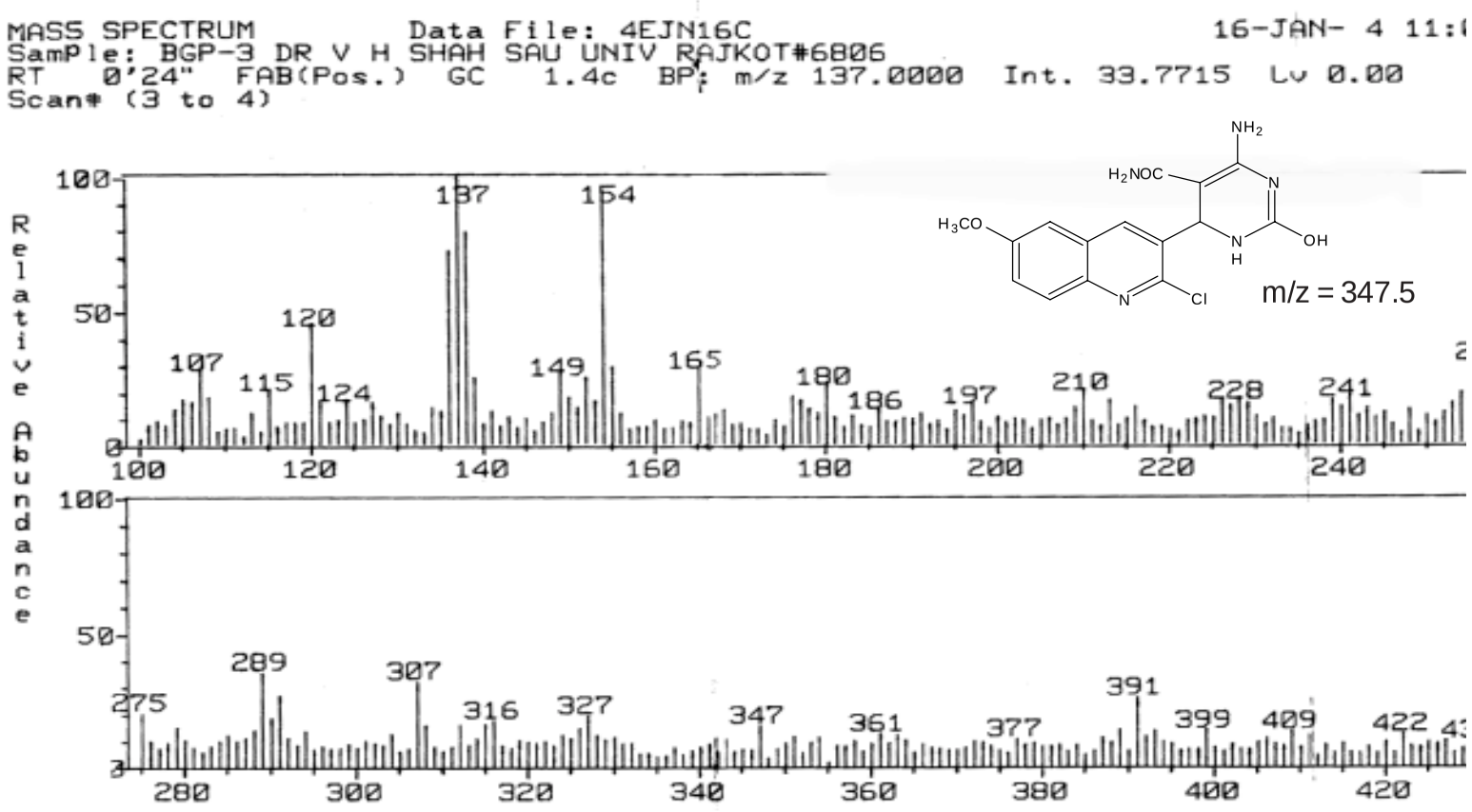
PMR SPECTRAL STUDY OF 2-HYDROXY-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO-6'-METHYL QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINE ($VIII_d$)

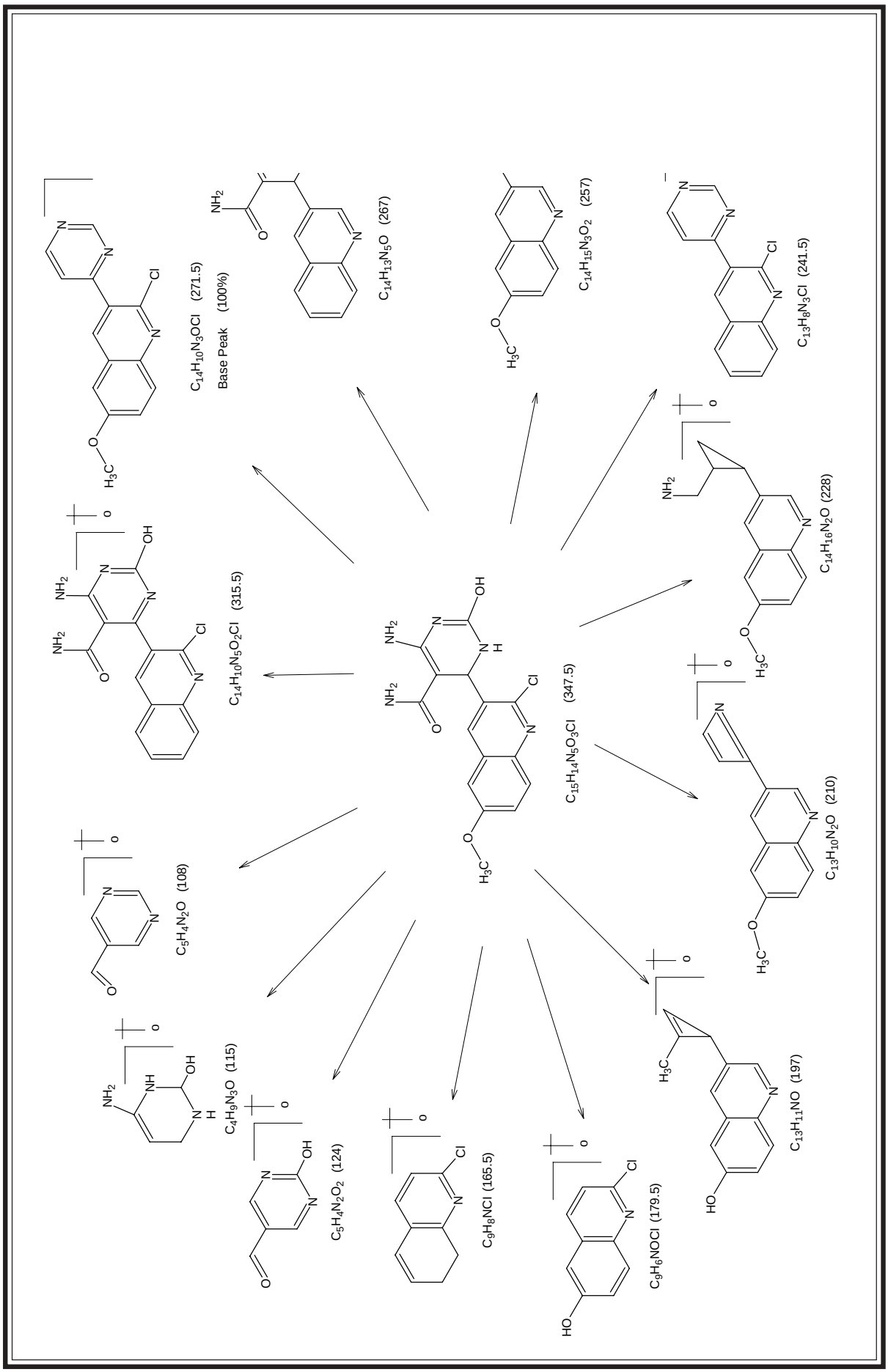


Internal Standard : TMS ; Solvent ; $CDCl_3$+TFA ; Instrument : BRUKER Spectrometer (300 MHz)

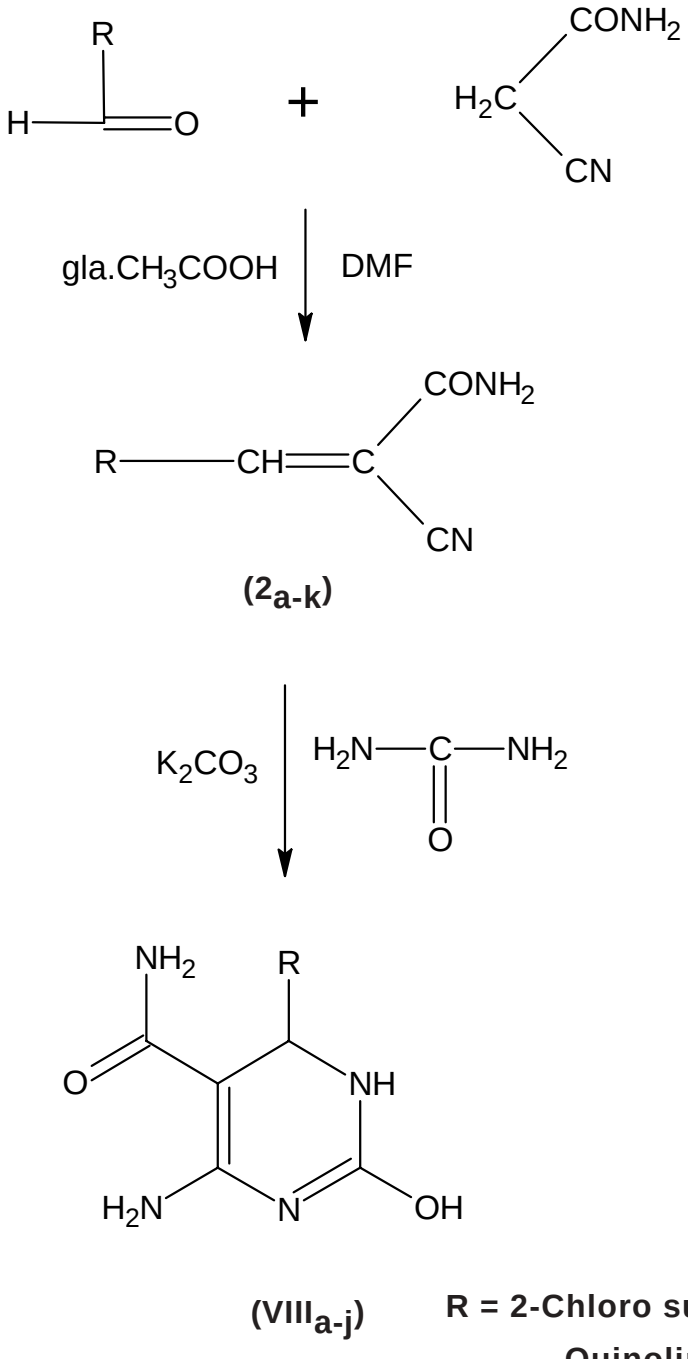
Signal No.	Signal Position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	2.652	3H	singlet	$-CH_3$
2.	7.881	2H	singlet	$-NH_2$
3.	7.930-7.944	1H	doublet	Ar-H_a
4.	7.986-8.017	1H	doublet	Ar-H_c
5.	8.106	1H	singlet	-NH
6.	8.162-8.190	1H	double doublet	Ar-H_b
7.	8.828	1H	singlet	Ar-H_e
8.	9.181	1H	singlet	Ar-H_d
9.	10.511	1H	singlet	-OH

MASS SPECTRAL OF 2-HYDROXY-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO-6'-METHOXY QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINE ($VIII_f$)




C14H10N3OCl (271.5)
Base Peak (100%)
C14H13N5O (267)
C14H15N3O2 (257)
C13H8N3Cl (241.5)
C14H16N2O (228)
C13H10N2O (210)
C13H11NO (197)
C9H6NOCl (179.5)
C9H8NCl (165.5)
C5H4N2O2 (124)
C4H9N3O (115)
C5H4N2O (108)
C14H10N5O2Cl (315.5)
C15H14N5O3Cl (347.5)

REACTION SCHAME



(2_{a-k})

($VIII_{a-j}$) **R = 2-Chloro substituted Quinolin-3-yl**

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 2-HYDROXY-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES

(A) Preparation of 3-(2'-chloro-6'-methyl quinolin-3'-yl)-2-cyano acrylamide (2_d).

For preparation refer Part-II, Section-III, Page No. 115.

(B) Preparation of 2-Hydroxy-4-amino-5-carboxamido-6-(2'- chloro-6'-methyl quinolin-3'-yl)-1,6-dihydro pyrimidine ($VIII_d$).

A mixture of 3-(2'-chloro-6'-methyl quinolin-3'-yl)-2-cyano acrylamide (2.72 gm, 0.01M) and urea (0.60 gm, 0.01 M) in DMF (20 ml) was heated in an oil-bath at 130 ^oC for 8 hrs. in presence of potassium carbonate. The content was poured into ice cold water and neutralized with diluted hydrochloric acid and filtered. The product was isolated and crystallized from DMF. Yield : 61%, M.P. : 178°C, R_f : 0.49, (Required : C, 54.30%; H, 4.22%; N, 21.12% for $C_{15}H_{14}N_5O_2Cl$; Found : C, 54.25%; H, 4.18%; N, 21.08%).

Similarly, other compounds ($VIII_{a-j}$) were synthesized. The physical data are recorded in Table No. 10.

(C) Antimicrobial activity of 2-Hydroxy-4-amino-5-carboxamido-6-(2'-chloro substituted quinolin-3'-yl)-1,6-dihydro pyrimidines ($VIII_{a-j}$).

Antimicrobial activity testing was carried out as described in part-1, section-I, page No. 35. The MIC values of test solution are recorded in Table No. 10a, 10b & 10c.

TABLENO. 10 : PHYSICAL CONSTANTS OF 2-HYDROXY-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES ($VIII_{a-j}$)

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. ^{o}C 5	Yield % 6	R_f Value 7	% of Nitrogen	
							Required 8	Found 9
VIIIa	2-Cl-C_9H_5N	$C_{14}H_{12}N_5O_2Cl$	317.5	162	62	0.53	22.05	22.00
VIIIb	2-Cl-8-CH_3-C_9H_4N	$C_{15}H_{14}N_5O_2Cl$	331.5	113	58	0.56	21.12	21.06
VIIIc	2-Cl-7-CH_3-C_9H_4N	$C_{15}H_{14}N_5O_2Cl$	331.5	98	56	0.51	21.12	21.07
VIIId	2-Cl-6-CH_3-C_9H_4N	$C_{15}H_{14}N_5O_2Cl$	331.5	178	61	0.49	21.12	21.08
VIIIe	2-Cl-8-CH_3O-C_9H_4N	$C_{15}H_{14}N_5O_3Cl$	347.5	143	59	0.57	20.14	20.09
VIIIf	2-Cl-6-CH_3O-C_9H_4N	$C_{15}H_{14}N_5O_3Cl$	347.5	167	63	0.45	20.14	20.10
VIIIg	2,7-$(Cl)_2$-C_9H_4N	$C_{14}H_{11}N_5O_2Cl_2$	352.0	218	58	0.54	19.89	19.83
VIIIh	2,6-$(Cl)_2$- C_9H_4N	$C_{14}H_{11}N_5O_2Cl_2$	352.0	148	57	0.58	19.89	19.84
VIIIi	2-Cl-6-Br-C_9H_4N	$C_{14}H_{11}N_5O_2ClBr$	396.0	130	61	0.49	17.68	17.63
VIIIj	2-Cl-5,8-$(CH_3O)_2$-C_9H_3N	$C_{16}H_{16}N_5O_4Cl$	377.5	106	64	0.53	18.54	18.50

i **TLC solvent system ; Acetone : Benzene = 1 : 9**

TABLE NO. 10a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-HYDROXY-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES $VIII_{a-j}$ (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442 5	10	25	50	100	250	500	S. aureus MTCC-96 5	10	25	50	100	250	500
VIIIa	C_6H_5	-	-	12	12	14	14	14	-	-	12	14	15	16	17
VIIIb	2-OH-C_6H_4	-	-	11	11	12	13	13	-	-	12	13	14	15	16
VIIIc	4-OH-C_6H_4	-	-	10	10	12	12	13	-	-	11	12	16	14	15
VIIId	2-Cl-C_6H_4	-	-	12	12	14	14	15	-	-	14	14	16	16	17
VIIIe	4-Cl-C_6H_4	-	-	11	11	13	13	14	-	-	12	12	14	15	15
VIIIf	2-NO_2-C_6H_4	-	-	10	10	12	13	14	-	-	12	13	13	15	16
VIIIg	3-NO_2-C_6H_4	-	-	11	11	13	14	14	-	-	13	13	14	15	16
VIIIh	4-OCH_3-C_6H_4	-	-	10	11	13	14	14	-	-	12	13	15	15	16
VIIIi	-CH=CH-C_6H_4	-	-	12	12	13	13	14	-	-	13	13	14	15	16
VIIIj	$C_{14}H_9$	-	-	11	11	13	14	14	-	-	12	12	14	16	16

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

Standard drug	Antibacterial activity									VIIId VIIIg VIIIi	VIIIa VIIId	VIIIc VIIId			
Ampicillin	11	13	14	16	18	19	20	10	12	13	14	16	18	21
Chloramphenicol	10	12	13	19	20	20	22	12	13	14	19	20	21	22
Ciprofloxacin	16	18	19	21	21	22	22	17	18	19	21	22	22	23
Norfloxacin	18	18	19	20	21	21	23	19	20	22	25	26	28	28

N.B.(-): No Activity

TABLE NO. 10b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-HYDROXY-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES $VIII_{a-j}$ (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)													
		E. Coli MTCC-443							B. subtillis MTCC-441						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
VIIIa	C_6H_5	-	-	14	15	17	17	19	-	-	15	17	18	19	19
VIIIb	2-OH-C_6H_4	-	-	14	14	14	16	17	-	-	15	16	17	18	19
VIIIc	4-OH-C_6H_4	-	-	12	14	15	15	17	-	-	14	15	17	18	18
VIIId	2-Cl-C_6H_4	-	-	15	16	17	17	18	-	-	16	17	19	19	19
VIIIe	4-Cl-C_6H_4	-	-	14	14	16	17	18	-	-	15	16	17	18	18
VIIIf	2-NO_2-C_6H_4	-	-	13	15	16	17	17	-	-	15	17	17	19	19
VIIIg	3-NO_2-C_6H_4	-	-	15	16	16	17	18	-	-	16	17	18	19	19
VIIIh	4-OCH_3-C_6H_4	-	-	13	13	14	16	17	-	-	15	16	17	18	19
VIIIi	-CH=CH-C_6H_4	-	-	15	16	16	17	18	-	-	16	17	17	18	19
VIIIj	$C_{14}H_9$	-	-	14	15	16	17	18	-	-	14	16	18	19	19
Comparative activity of ($VIII_{a-j}$) with known choosen standard drugs															
Standard drug		**Antibacterial activity**													
				VIIId VIIIg VIIIi	VIIId VIIIg VIIIi						VIIId VIIIg VIIIi				
Ampicillin		14	14	15	16	19	20	22	12	16	18	19	20	21	23
Chloramphenicol		14	15	17	23	23	23	23	12	14	16	19	22	23	23
Ciprofloxacin		20	21	23	28	28	28	28	16	17	19	22	22	23	23
Norfloxacin		22	23	25	26	27	29	29	19	20	22	23	24	25	28

N.B.(-): No Activity

TABLE NO. 10c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-HYDROXY-4-AMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES $VIII_{a-j}$ (Minimum inhibition Concentration in µg/ml)

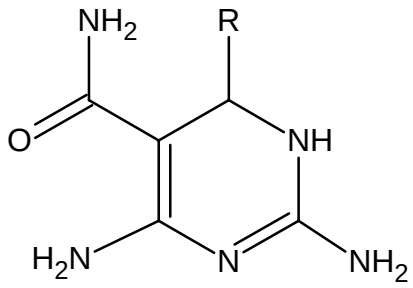
Compd No.	R	Antifungal activity (Zones of inhibition in mm)													
		C. albicans MTCC-227							A. niger MTCC-282						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
VIIIa	C_6H_5	-	-	17	17	18	20	21	-	-	19	19	21	21	24
VIIIb	2-OH-C_6H_4	-	-	17	18	19	20	20	-	-	19	19	21	21	22
VIIIc	4-OH-C_6H_4	-	-	16	17	19	20	20	-	-	18	18	20	21	22
VIIId	2-Cl-C_6H_4	-	-	18	18	20	20	21	-	-	19	19	22	22	22
VIIIe	4-Cl-C_6H_4	-	-	17	18	19	20	20	-	-	18	19	20	22	22
VIIIf	2-NO_2-C_6H_4	-	-	17	17	19	20	21	-	-	18	19	21	21	22
VIIIg	3-NO_2-C_6H_4	-	-	17	18	19	20	21	-	-	19	19	20	22	22
VIIIh	4-OCH_3-C_6H_4	-	-	16	17	19	20	22	-	-	18	18	20	21	24
VIIIi	-CH=CH-C_6H_4	-	-	17	18	19	20	21	-	-	19	19	21	21	22
VIIIj	$C_{14}H_9$	-	-	16	17	19	21	21	-	-	18	19	20	22	23
Comparative activity of ($VIII_{a-j}$) with known choosen standard drugs															
Standard drug		**Antifungal activity**													
													VIIId		
Griseofulvin		19	22	23	25	25	28	28	18	19	21	22	22	24	26

N.B.(-): No Activity

SECTION -V

PREPARATION AND BIOLOGICAL EVALUATION OF 2,4-DIAMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES

Due to wide range of biological activities[123-159], recent literature survey[117-122], other properties[113-116] and in view to have potent therapeutic agents, the synthesis of 2,4-diamino-5-carboxamido-6-(2'-chloro substituted quinolin-3'-yl)-1,6-dihydro pyrimidines (IX_{a-j}) have been undertaken by the reaction of 3-(2'-chloro substituted quinolin-3'-yl)-2-cyanoacrylamides with guanidine hydrochloride.

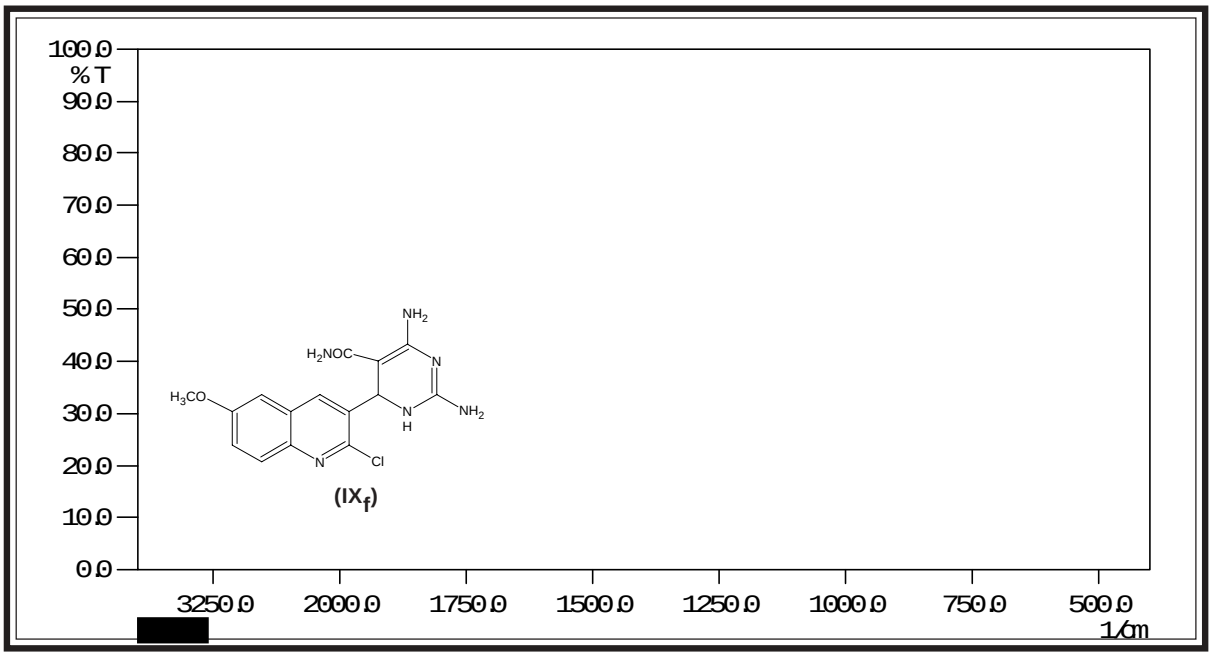


IX_{a-j} **R=2-Chloro substituted Quinolin-3-yl**

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

The products (IX_{a-j}) were assayed for their *in vitro* biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

IR SPECTRAL STUDY OF 2,4-DIAMINO-5-CARBOXAMIDO-6-(2'-CHLORO -6'-METHOXY QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINE (IX_f)

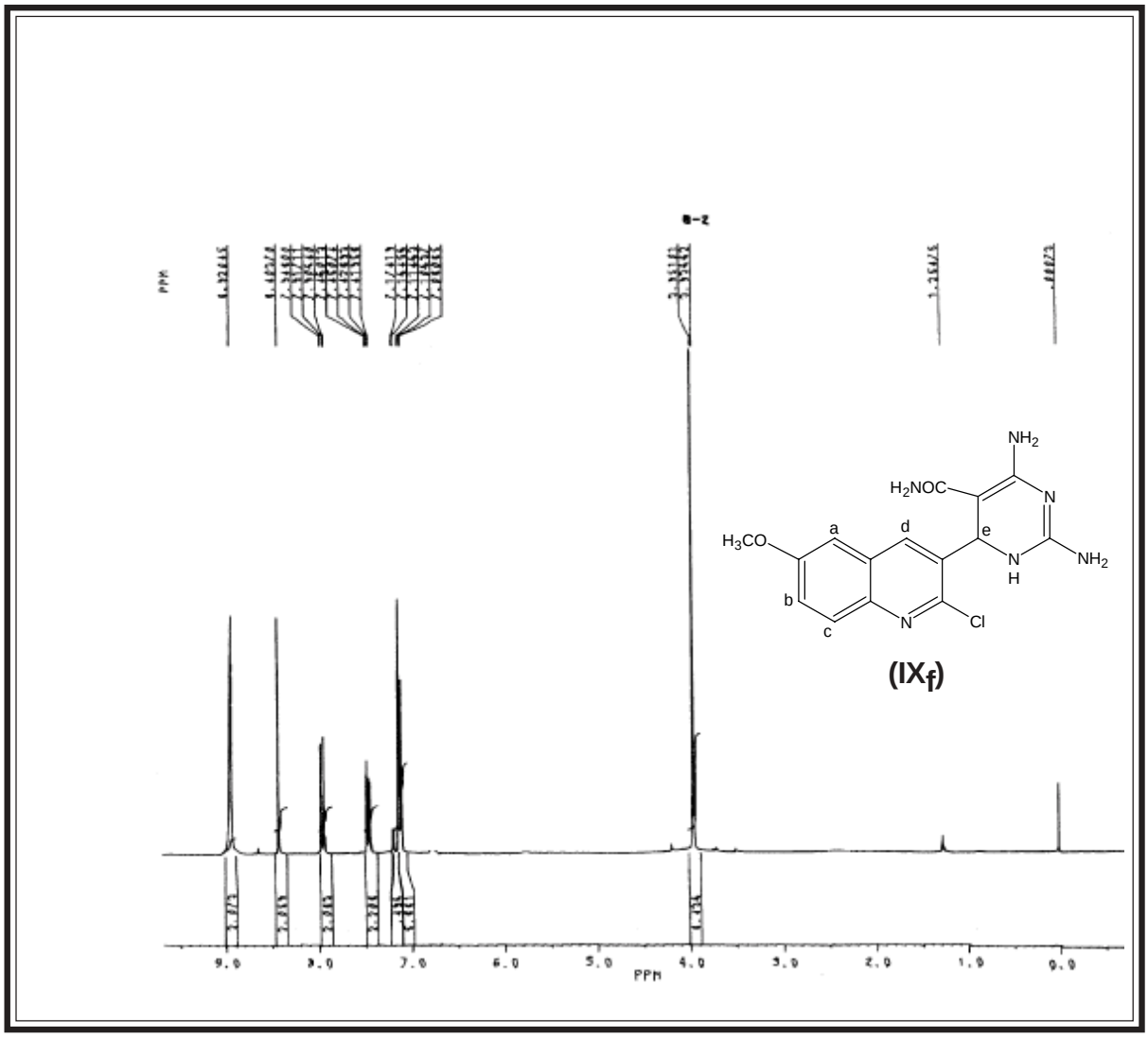


(IX_f)

Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.(asym.)	3030.0	2975-2950	343
CH_3	C-H str.(sym.)	2837.1	2880-2860	,,
	C-H def.(asym.)	1454.2	1460-1435	,,
	C-H def.(sym.)	1357.8	1385-1300	,,
Aromatic and	C=C + C=N and ring	1454.2	1520-1480	345
Pyrimidine moiety	skeletal vibration	1523.7	1580-1520	,,
	C-H str.	3124.5	3080-3030	,,
	C-H i.p. def.	1097.4	1125-1090	,,
	C-H o.o.p. def.	842.8	840-810	,,
Ether	C-O-C str. (asym.)	1226.6	1275-1200	346
	C-O-C str. (sym.)	1056.9	1075-1050	,,
Amine (Primary)	N-H str.	3377.1	3500-3300	343
	N-H def.	1598.9	1650-1580	,,
Amide	N-H str.	3377.1	3500-3300	345
	C=O str.	1672.5	1710-1650	,,
Quinoline	C-Cl str.	732.9	750-600	343
moiety	C=N str.	1598.9	1612-1593	,,
	C=C str.	1598.9	1612-1593	,,

PMR SPECTRAL STUDY OF 2,4-DIAMINO-5-CARBOXAMIDO-6-(2'-CHLORO -6'-METHOXY QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINE (IX_f)

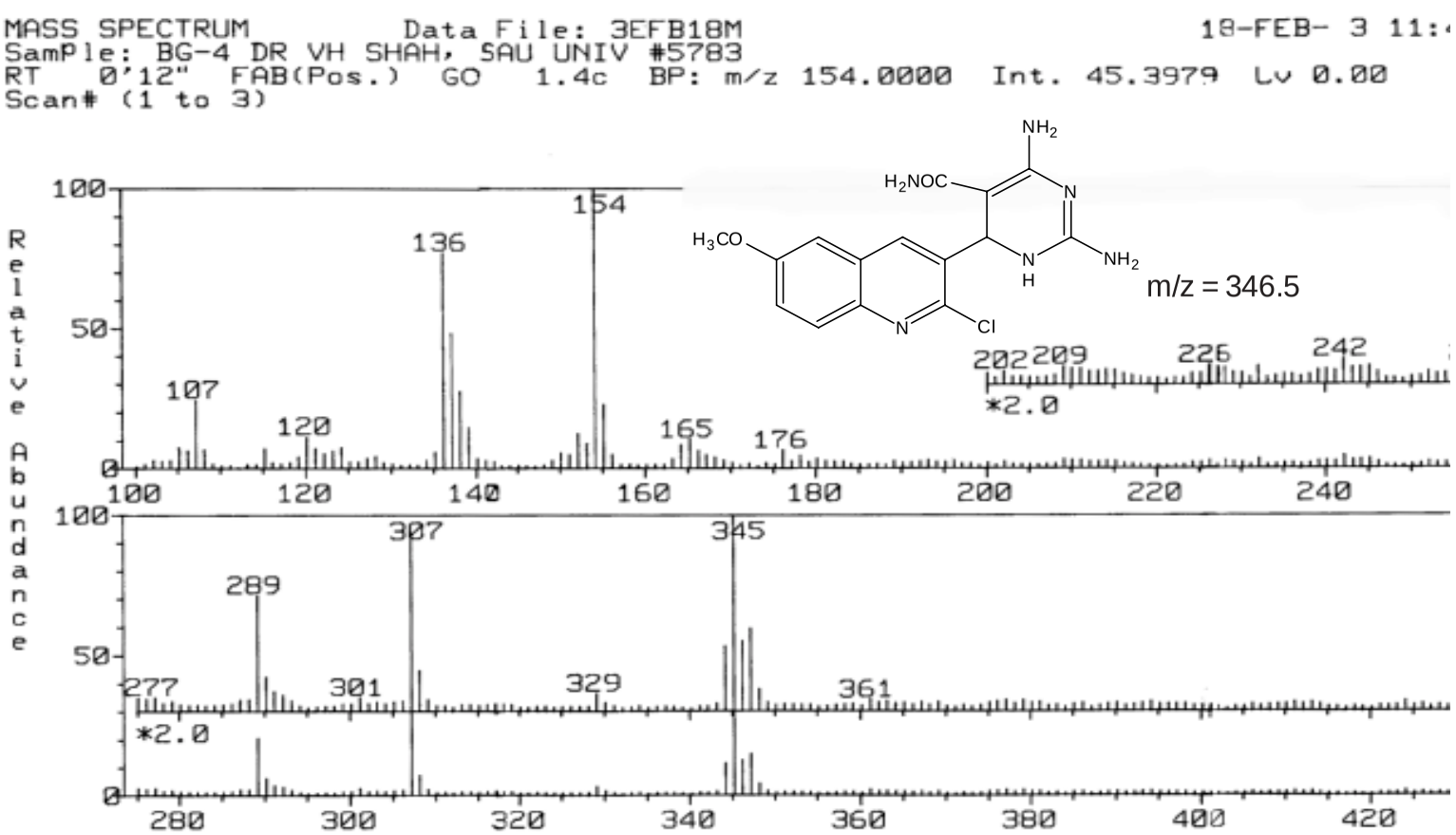


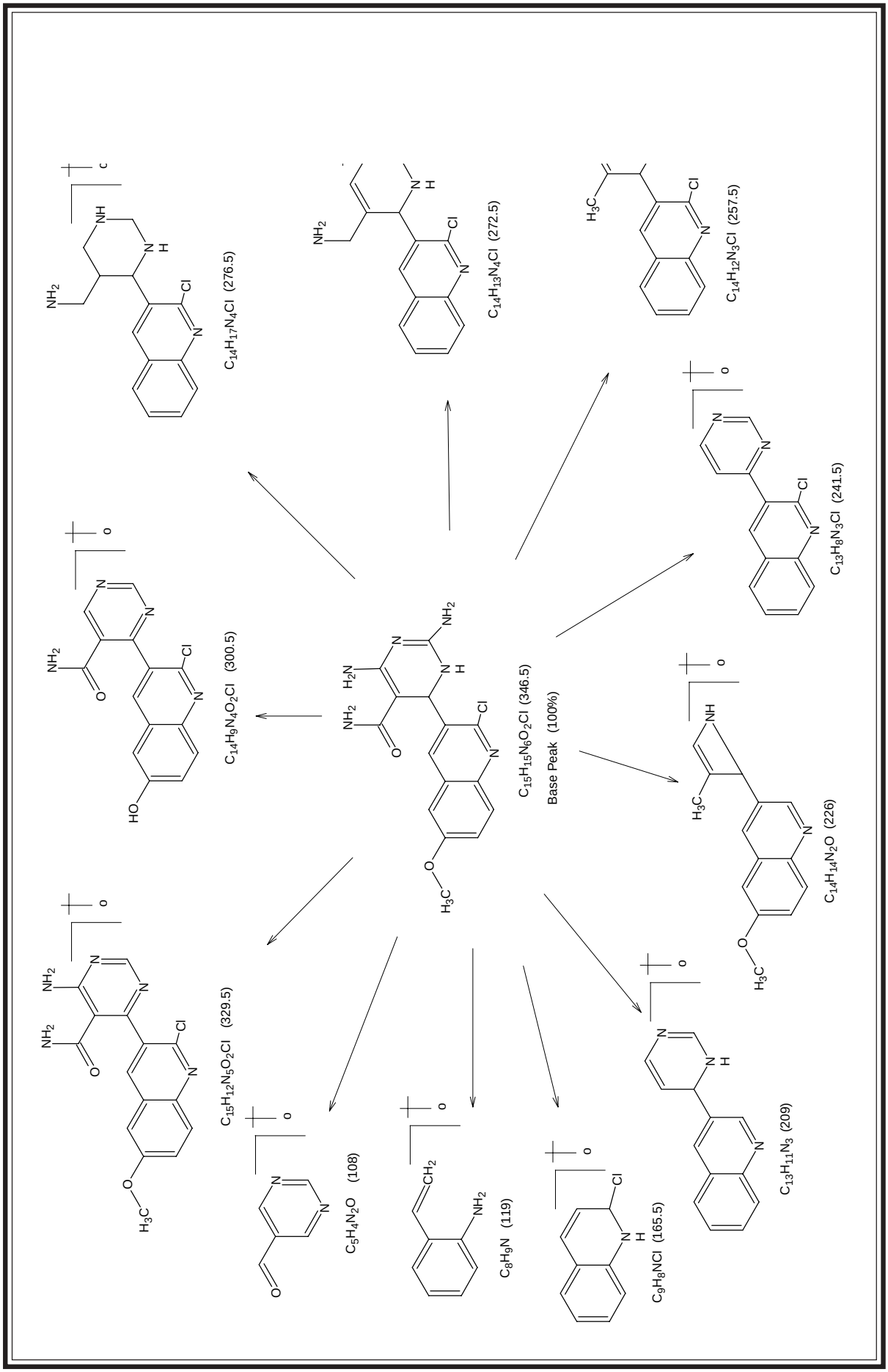
(IX_f)

Internal Standard : TMS ; Solvent ; $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

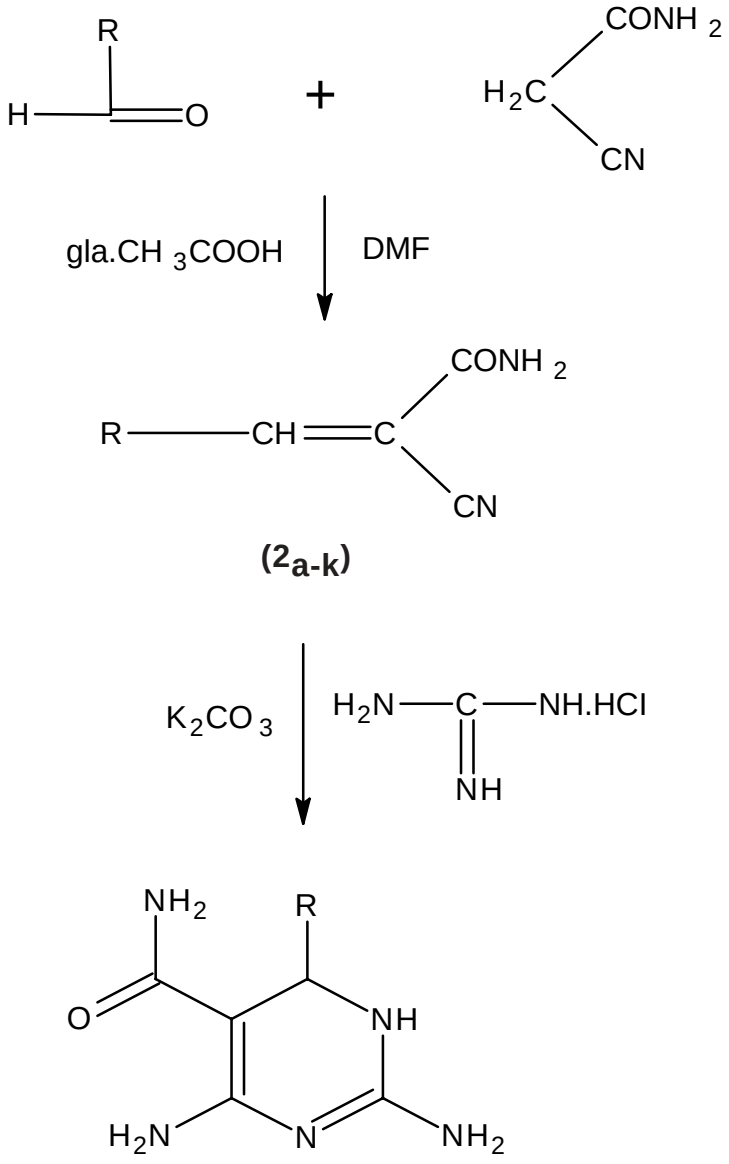
Signal No.	Signal Position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.951	3H	singlet	$-OCH_3$
2.	7.081	2H	singlet	$-NH_2$
3.	7.106-7.115	1H	doublet	Ar-H_a (J=2.379)
4.	7.420-7.460	1H	double doublet	Ar-H_b
5.	7.917-7.948	1H	doublet	Ar-H_c (J=9.2)
6.	8.404	1H	singlet	Ar-H_e
7.	8.920	1H	singlet	Ar-H_d

MASS SPECTRAL OF 2,4-DIAMINO-5-CARBOXAMIDO-6-(2'-CHLORO-6'-METHOXY QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINE (IX_f)




C15H15N6O2Cl (346.5)
Base Peak (100%)
C14H17N4Cl (276.5)
C14H13N4Cl (272.5)
C14H12N3Cl (257.5)
C14H9N4O2Cl (300.5)
C13H8N3Cl (241.5)
C14H14N2O (226)
C15H12N5O2Cl (329.5)
C5H4N2O (108)
C8H9N (119)
C9H8NCl (165.5)
C13H11N3 (209)

REACTION SCHAME



(2_{a-k})

(XI_{a-j}) **R = 2-Chloro substituted Quinolin-3-yl**

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 2,4-DIAMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES

(A) Preparation of 3-(2'-chloro-6'-methoxy quinolin-3'-yl)-2-cyano acrylamide (2_f).

For preparation refer Part-II, Section-III, Page No. 115.

(B) Preparation of 2,4-Diamino-5-carboxamido-6-(2'-chloro-6'-methoxy quinolin-3'-yl)-1,6-dihydro pyrimidine (IX_f).

A mixture of 3-(2'-chloro-6'-methoxy quinolin-3'-yl)-2-cyano acrylamide (2.88 gm, 0.01M) and guanidine hydrochloride (0.96 gm, 0.01) in DMF (20 ml) was heated in an oil-bath at 130 ^oC for 8 hrs. in presence of potassium carbonate. The content was poured into ice cold water and neutralized with diluted hydrochloric acid and filtered. The product was isolated and crystallized from DMF. Yield : 64%, M.P. : 108°C, R_f : 0.59, (Required : C, 51.95%; H, 4.33%; N, 24.24% for $C_{15}H_{15}N_6O_2Cl$; Found : C, 51.90%; H, 4.30%; N, 24.19%).

Similarly, other compounds (IX_{a-j}) were synthesized. The physical data are recorded in Table No. 11.

(C) Antimicrobial activity of 2,4-Diamino-5-carboxamido-6-(2'- chloro substituted quinolin-3'-yl)-1,6-dihydro pyrimidines (IX_{a-j}).

Antimicrobial activity testing was carried out as described in part-1, section-I, page No. 35. The MIC values of test solution are recorded in Table No. 11a, 11b & 11c.

TABLE NO. 11 : PHYSICAL CONSTANTS OF 2,4-DIAMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES (IX_{a-j})

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. °C 5	Yield % 6	R_f Value 7	% of Nitrogen	
							Required 8	Found 9
IXa	2-Cl-C_9H_5N	$C_{14}H_{13}N_6OCl$	316.5	188	65	0.50	26.54	26.50
IXb	2-Cl-8-CH_3-C_9H_4N	$C_{15}H_{15}N_6OCl$	330.5	130	59	0.53	25.42	25.37
IXc	2-Cl-7-CH_3-C_9H_4N	$C_{15}H_{15}N_6OCl$	330.5	115	57	0.54	25.42	25.35
IXd	2-Cl-6-CH_3-C_9H_4N	$C_{15}H_{15}N_6OCl$	330.5	98	61	0.48	25.42	25.36
IXe	2-Cl-8-CH_3O-C_9H_4N	$C_{15}H_{15}N_6O_2Cl$	346.5	123	58	0.51	24.24	24.20
IXf	2-Cl-6-CH_3O-C_9H_4N	$C_{15}H_{15}N_6O_2Cl$	346.5	108	64	0.47	24.24	24.19
IXg	2,7-$(Cl)_2$-C_9H_4N	$C_{14}H_{12}N_6OCl_2$	351.0	134	59	0.60	23.93	23.86
IXh	2,6-$(Cl)_2$-C_9H_4N	$C_{14}H_{12}N_6OCl_2$	351.0	142	56	0.55	23.93	23.87
IXi	2-Cl-5,8-$(CH_3O)_2$-C_9H_3N	$C_{16}H_{17}N_6O_3Cl$	376.5	146	63	0.52	22.31	22.26
IXj	2,6,7-$(Cl)_3$- C_9H_3N	$C_{14}H_{11}N_6OCl_3$	385.5	138	62	0.58	21.79	21.72

i TLC solvent system ; Acetone : Benzene = 0.5 : 9.5

TABLE NO. 11a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2,4-DIAMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES IX_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442 5	10	25	50	100	250	500	S. aureus MTCC-96 5	10	25	50	100	250	500
IXa	C_6H_5	-	-	10	11	13	14	14	-	-	11	12	13	14	16
IXb	2-OH-C_6H_4	-	-	11	11	13	13	14	-	-	13	13	15	15	16
IXc	4-OH-C_6H_4	-	-	12	12	12	14	14	-	-	14	15	16	16	17
IXd	2-Cl-C_6H_4	-	-	10	11	13	14	14	-	-	11	12	14	15	16
IXe	4-Cl-C_6H_4	-	-	12	12	13	14	14	-	-	14	14	15	16	16
IXf	2-NO_2-C_6H_4	-	-	11	11	13	13	14	-	-	12	13	15	16	17
IXg	3-NO_2-C_6H_4	-	-	10	10	12	14	14	-	-	12	12	14	15	15
IXh	4-OCH_3-C_6H_4	-	-	10	11	13	14	14	-	-	11	12	14	14	15
IXi	-CH=CH-C_6H_4	-	-	12	12	13	13	14	-	-	13	14	14	15	16
IXj	$C_{14}H_9$	-	-	11	11	13	14	14	-	-	12	14	15	15	16
Comparative activity of (IX_{a-j}) with known choosen standard drugs															
Standard drug		**Antibacterial activity**													
											IXb IXc IXe IXi	IXc IXe IXi IXj	IXc		
Ampicillin		11	13	14	16	18	19	20	10	12	13	14	16	18	21
Chloramphenicol		10	12	13	19	20	20	22	12	13	14	19	20	21	22
Ciprofloxacin		16	18	19	21	21	22	22	17	18	19	21	22	22	23
Norfloxacin		18	18	19	20	21	21	23	19	20	22	25	26	28	28

N.B.(-): No Activity

TABLE NO. 11b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2,4-DIAMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES IX_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)												
		E. Coli MTCC-443							B. subtillis MTCC-441					
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
IXa	C_6H_5	-	-	13	14	15	16	17	-	-	14	16	17	18	19
IXb	2-OH-C_6H_4	-	-	14	15	16	17	18	-	-	16	16	18	18	19
IXc	4-OH-C_6H_4	-	-	15	16	18	18	19	-	-	17	17	19	19	19
IXd	2-Cl-C_6H_4	-	-	13	15	17	17	18	-	-	15	16	18	18	18
IXe	4-Cl-C_6H_4	-	-	15	16	18	18	19	-	-	17	17	18	19	19
IXf	2-NO_2-C_6H_4	-	-	14	15	15	17	18	-	-	15	15	17	19	19
IXg	3-NO_2-C_6H_4	-	-	13	14	15	16	17	-	-	14	15	17	18	19
IXh	4-OCH_3-C_6H_4	-	-	14	14	16	17	18	-	-	15	16	17	18	19
IXi	-CH=CH-C_6H_4	-	-	15	16	17	17	17	-	-	17	17	17	18	19
IXj	$C_{14}H_9$	-	-	14	15	17	18	18	-	-	15	16	18	19	19

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

Standard drug	Antibacterial activity													
			IXc IXe IXi	IXc IXe IXi						IXb IXc IXe IXi				
Ampicillin	14	14	15	16	19	20	22	12	16	18	19	20	21	23
Chloramphenicol	14	15	17	23	23	23	23	12	14	16	19	22	23	23
Ciprofloxacin	20	21	23	28	28	28	28	16	17	19	22	22	23	23
Norfloxacin	22	23	25	26	27	29	29	19	20	22	23	24	25	28

N.B.(-): No Activity

TABLE NO. 11c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2,4-DIAMINO-5-CARBOXAMIDO-6-(2'-CHLORO SUBSTITUTED QUINOLIN-3'-YL)-1,6-DIHYDRO PYRIMIDINES IX_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antifungal activity (Zones of inhibition in mm)													
		C. albicans MTCC-227							A. niger MTCC-282						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
IXa	C_6H_5	-	-	16	18	19	20	21	-	-	18	19	20	22	22
IXb	2-OH-C_6H_4	-	-	18	18	20	20	22	-	-	19	18	21	22	23
IXc	4-OH-C_6H_4	-	-	17	18	20	21	23	-	-	19	19	21	22	24
IXd	2-Cl-C_6H_4	-	-	16	18	20	21	21	-	-	18	19	21	21	23
IXe	4-Cl-C_6H_4	-	-	17	18	20	20	21	-	-	19	19	21	22	24
IXf	2-NO_2-C_6H_4	-	-	16	17	19	20	20	-	-	18	18	20	22	24
IXg	3-NO_2-C_6H_4	-	-	16	17	19	20	21	-	-	18	18	21	22	23
IXh	4-OCH_3-C_6H_4	-	-	17	17	19	20	22	-	-	18	19	20	21	23
IXi	-CH=CH-C_6H_4	-	-	17	18	19	20	21	-	-	19	19	21	22	24
IXj	$C_{14}H_9$	-	-	17	18	20	20	21	-	-	18	18	21	22	22
Comparative activity of (IX_{a-j}) with known choosen standard drugs															
Standard drug		**Antifungal activity**													
Griseofulvin		19	22	23	25	25	28	28	18	19	21	22	22	24	26

N.B.(-): No Activity

REFERENCES

113. F.D. Gunstone; *Progr. Org. Chem.,* **4,** 1-30 (1958); *Chem. Abstr.,* **52,** 9940 (1958).

114. W.E. Burge; *A.M.J. Physiol.,* **48,** 133 (1919); *Chem. Abstr.,* **13,** 1860 (1920).

115. R. Romida, B. Patricia; *U.S.* **4,** 885, 027; *Chem. Abstr.,***112,** 231316C (1990).

116. Tada Isao, Takahashi Nobuyoshi, Murakami Mitsuyuki; *Jpn. Kokai Tokkyo Koho* **Jp** 2000, **26,** 432; *Chem. Abstr.,* **132,** 93215b (2000).

117. Budzinski, John C.;Levitt, George; *U.S.* **US 4,** 368, 067 (Cl. 71-92; A01N43/02), 1983; *Chem. Abstr.,* **98,** 143461k (1983).

118. Machon, Zdzislaw, Jasztold, Wilimowski, Marian; *Chem. Abstr.,* **101,** 110945y (1984).

119. Lorente, Antonio, Garcia, Navio, Jose L., Lopez P. ; *Chem. Abstr.,* **103,** 104910h (1985).

120. Minaelelli, John A., Brewer, Arthur D., *Ger. Offen* **DE 3,** 446, 371 (Cl. CO7D239/22); *Chem. Abstr.,* **104,** 19602k (1985).

121. Sturm, Elmar, Galley, Jeaques, Kristinsson; *Eur. Pat. Appl.* **Ep. 192,** 180 Cl. CO7D 403/12); *Chem. Abstr.,* **105,** 226636k (1986).

122. Wetterich, Frank, Hill, Regina, Luise, Gisela; *(BASE A.-G., Germany) Ger. Offen.* **DE 19,** 622, 270 (Cl. CO7D 239/38); *Chem. Abstr.,* **128,** 48238x (1998).

123. R.S. Andrews, G. Margetts; *Brit. Pat.* **2,** 051, 043 (1981).

124. G.B. Singh, A. Jetley; *Indian J. Chem.*, **20-B (1),** 76 (1981).

125. Makio Kitazawa, Masuo Akahane, Vasusni Nakano; *Chem. Abstr.,* **112,** 35803x (1990).

126. E.E. Beedle, D.W. Robertson; *Eur. Pat. Appl.* **279,** 633 (1958); *Chem. Abstr.,* **110,** 7875n (1986).

127. P.J. Blackburn, R.E. Buckingham, W.M. Chan; *Org. Med. Chem. Lett.* **5(11),** 1163-6 (1995); *Chem. Abstr.,* **124,** 86760m (1996).

128. V. Zikan, J. Sluka, J. Denek; *Czech CS,* **254,** 544 (1988); *Chem. Abstr.,* **110,** 231666c (1989).

129. Chugai Pharmaceutical Co. Ltd., *Jpn. Kokai Tokkyo Koho* **Jp 58,** 67, 657 (1983); *Chem. Abstr.,* **99,** 55390c (1983).

130. D.T. Connor, M.D. Mullican; *U.S.* **4,** 764, 525 (1988); *Chem. Abstr.,* **109,** 2110636c (1988).

131. D. Nisato, S. Boveri, A. Bianchetti, R. Roncucci, P. Carrninati; *Eur. Pat. Appl.* **Ep. 69,** 664 (1983); *Chem. Abstr.,* **99,** 382314 (1983).

132. Goesta Florall and Coworkers; *Eur. Pat. Appl.* **Ep. 60,** 235 (1982); *Chem. Abstr*., **98,** 33687j (1983).

133. K. Sakakibara, N. Yoneshina, T. Osawa; *Jpn. Kokai Tokkyo Koho* **Jp 62,** 158, 252 (1987); *Chem. Abstr.,* **108,** 112238p (1988).

134. A. A. Alexandri, M. Safta, T. Bafeu; *Chem. Abstr.,* **114,** 59017e (1991).

135. R. Agrawal, M.K. Shukla, R.K. Satsangi; *Indian J. Pharmacol.,* **14(2),** 177-82 (1982); *Chem. Abstr.,* **100,** 174780c (1984).

136. Kuniyasu Masuzawa and Co-workers; *Jpn Kokai Tokkyo Koho* **Jp 62,** 255, 479 (1987); *Chem. Abstr.,* **108,** 18632q (1988).

137. Epuram Jean; *Fr. Demande Fr.* **2,** 578, 538 (19860; *Chem. Abstr.,* **107,** 1758772w (1987).

138. Y.D. Kulkarni, Ali S, Mohd., S. Rowhani; *Indian Drugs* **25(12),** 505-7 (1988); *Chem. Abstr.,* **110,** 114786f (1989).

139. J.M. Parmar, H.H. Bhatt, B.C. Merja. A.R. Parikh; *J. Inst. Chemist (India)*; **Vol.72,** Part-6, pg. 214 (2000).

140. J.M. Parmar, H.H. Bhatt, A.R. Parikh; *J. Inst. Chemist (India);* **Vol.73,** Part-1, pg. 35 (2001).

141. K.H. Sikotra , D.N. Nagar, V.H. Shah; *J. Inst. Chemist (India);* **Vol.73,** Part-3, pg. 111(2001).

142. J.J. Modha, N.J. Dutta, J.M. Parmar, H.H. Parekh; *Oriental J. Chem.,* **18(1),** 81-84(2002).

143. D.N. Nagar, T.S. Mehta, V.H. Shah; *J. Inst. Chemist (India);* **Vol.74,** Part-4, pg.125 (2002).

144. D.N. Nagar, T.S. Mehta, V.H. Shah; *J. Inst. Chemist (India);* **Vol.74,** Part-4, pg.127 (2002).

145. A.G. Mehta, G.C. Desai, P.B. Desai; *J. Inst. Chem.,* **65(5),** 163-64 (1993); *Chem. Abstr.,* **122,** 31295s (1995).

146. Chang An-Chih, Takimori Akira E., Portoghese Philips; *Chem. Abstr.,* **121,** 9076d (1994).

147. A. Orjaies, L. Alonsocires, L. Iabeaga, A. Inneranty; *Eur.J.Med.Chem.,* **30(7-8),** 651-4 (1995); *Chem. Abstr.,* **124,** 55498c (1996).

148. Masters John Joseph , Mehdel David, Milot Guy, Sawyer Jason Scott; *PCT Int. Appl.* **WO 99,** 00, 127; *Chem. Abstr.,* **130,** 95393v (1999).

149. F. Benazet et al.; *Compt. Rend. Ser. D.,* 263 **(3),** (1966); *Chem. Abstr.,* **65,** 17171c (1966).

150. Clude A.B., Christin Codamine; *J. med. Chem.,* **26,** 451-55 (1983).

151. Noguchi Kazahuru, Wadika Motoji, Suzuki Kenji, Yamado; *PCT Int. Appl.* **WO 00,** 01, 672; *Chem. Abstr.,* **132,** 93221e (2000).

152. Weidermann, Hans E. (Pfizer Inc), *U.S.* **3,** 998, 828 (Cl.260-256.5 R; C07D 401/12) 1976; *Chem. Abstr.,* **86,** 155689q (1977).

153. Ursula, Herzog Reinshagen; *Swiss* 614, 944 (Cl. CO7D 239/46) 28 Dec. 1979; *Chem. Abstr.,* **93,** 82041c (1980).

154. Juby, Peter F.; *U.S.* **US 4,** 209, 623 (Cl. 544-319 ; A61K 31/505) 24 Jun 1980; *Chem. Abstr.,* **94,** 15766u (1981).

155. Atwal, Karnail; *Ger. Offen* **DE 3,** 840, 380 (Cl. CO7D 239/22) 08 Jun 1989; *Chem. Abstr.,* **112,** 21008c (1990).

156. Ojo, Babatue, Dunbar, Philip G.; *U.S.* **US 5,** 618, 818 (Cl. 514-256 ; A61K 31/505), *Chem. Abstr.,* **126,** 317389g (1997).

157. Hisamichi, Hiroyuki, Natio, Ryo, Kawazone, Suichirou, Toyoshima; *PCT Int. Appl.* **WO 99,** 31, 073 (Cl. C07D 239/48), 1999; *Chem. Abstr.,* **131,** 44844f (1999).

158. F. Kobayashi, S. Kawahara; *PCT Int. Appl.* **WO 99,** 45, 928 (Cl. A61K 31/505), 16 Sep. 1999, *JP Appl.* 1998/100, 361,27 Mar. 1998; 6 pp., *Chem. Abstr.,* **131,** 214297z (1999).

159. U. Pfaar, B. K. Olf; E. Peter; G. Gerhard; (Novartis Ag; Novartis Pharma Gmbh, swits.) *PCT Int. Appl.* **WO 03,** 62,220 (Cl. C07D401/04), 2003; *Chem. Abstr.,* **139,** 149642g (2003).

PART - III
STUDIES ON 4-PYRIMIDINYL SULPHONAMIDE

PART - III
STUDIES ON PYRIMIDINYL SULPHONAMIDES

INTODUCTION

The discovery of sulphonamides marked the beginning of chemotherapeutic era by making possible, a direct attack on microbial infections [160]. Sulphonamide antibacterial continued to be used because they are effective, inexpensive and free of super infection problems of the broad spectrum antibiotics[161].

General formula of sulphonamides - R-SO2-N-R'-R"
R=Organic radicals, R'and R"= hydrogen or organic radical.

Depending upon the nature of R, the sulphonamides are classified as aliphatic, aromatic and heterocyclic. The aliphatic sulphonamides have not yet become important. Aromatic and heterocyclic sulphonamides have achieved great commercial significance as their applications in bacterial chemotherapy is well known. Considerable interest has been shown in the chemistry of sulphonamides due to their use as antibacterial, anticancer, antimalarial, antifungal, antiplasmodic, anticonvulsant, herbicidal, pesticidal, antiinflammatory and analytical preparation.

SYNTHETIC ASPECT

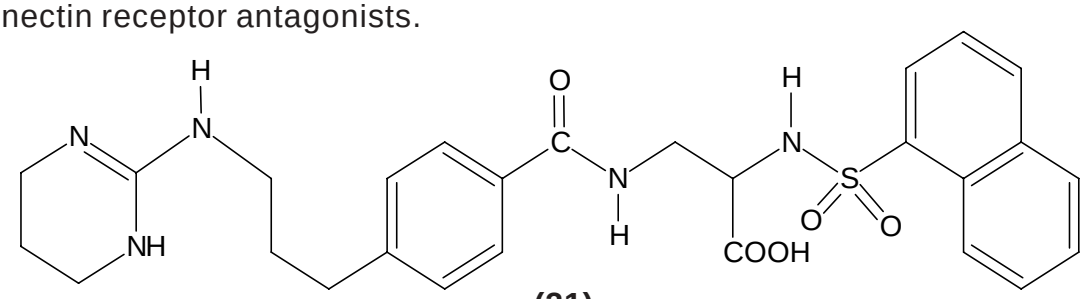
The synthesis of sulphonamides have been reported in the literature[162-164].

BIOLOGICAL IMPORTANCE

Considerable research has been undertaken to extend the activity and reduce toxicity of sulpha drugs. Monogram and review[165,166] surveying various aspects of sulpha drugs have been published. The specific biological activities have been represented as under.

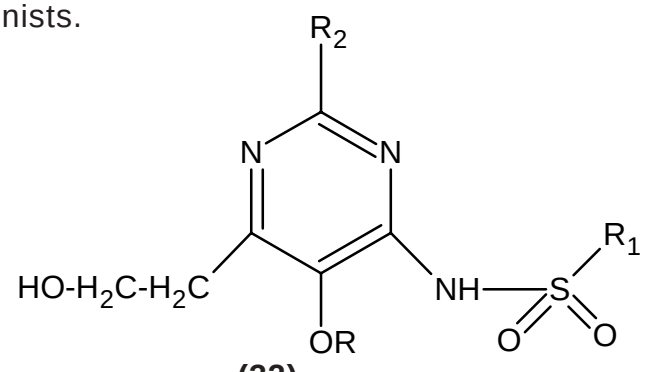
(a) Antihypertensive[167]
(b) Diuretic[168-170]
(c) Anticonvulsant[171]
(d) Antitumor[172,173]
(e) Herbicidal[174,175]
(f) Antiviral[176]
(g) Antimalarial[177]
(h) Antimicrobial[178-183]
(i) Hypoglycemic[184,185]
(j) Cardiovascular[186]
(k) Hypotensive[187,188]
(l) Anti conversant[189]
(m) AntiHIV activity[190,191]
(n) Antineoplastic activity[192]
(o) Antidiabetic activity[193]
(p) Aspartyl protease inhibitor[194]

Recently, H. Peyman et al.,[195] have reported aryl sulphonamides **(31)** as vitronectin receptor antagonists.



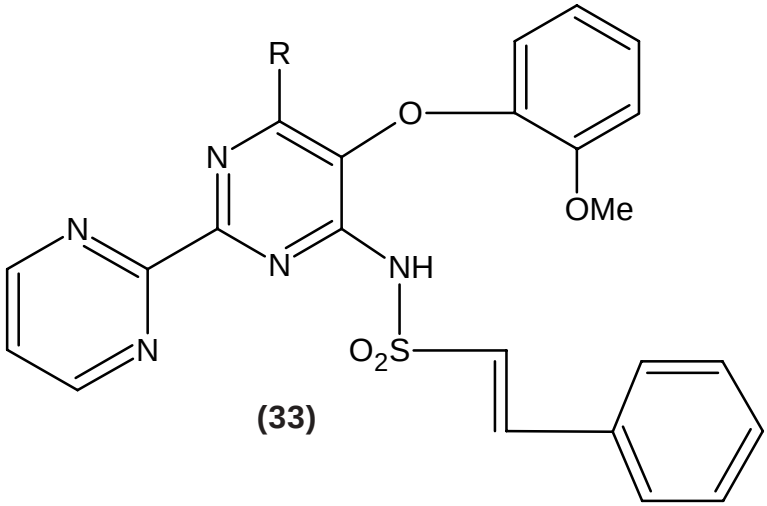
(31)

B. Volker et al.,[196] have prepared heteroaromatic sulphonamides **(32)** as endothelin antagonists.



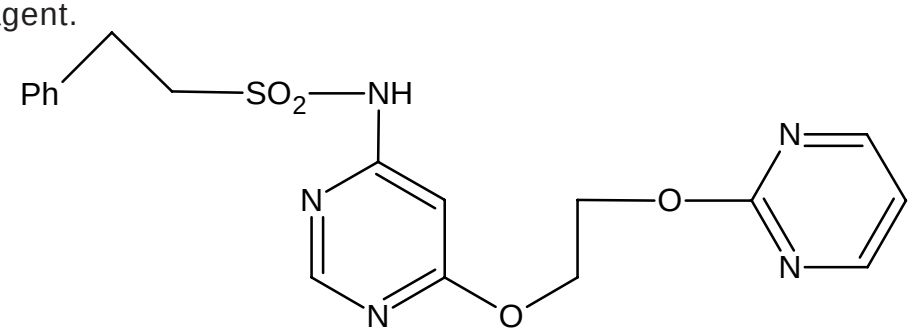
(32)

Y. Isao et al.,[197] have synthesized pyrimidinyl sulphonamides **(33)** as endothelin receptor antagonists.



(33)

F. Walter et al.,[194] have demonstrated pyrimidinyl sulphonamide **(34)** as antagonists agent.



(34)

In view of procuring highly potent biodynamic agents and after reviewing literature survey on sulphonamides for their various method of synthesis and different pharmacological activities, synthesis of pyrimidinyl sulphonamides have been undertaken which can be summarized as under.

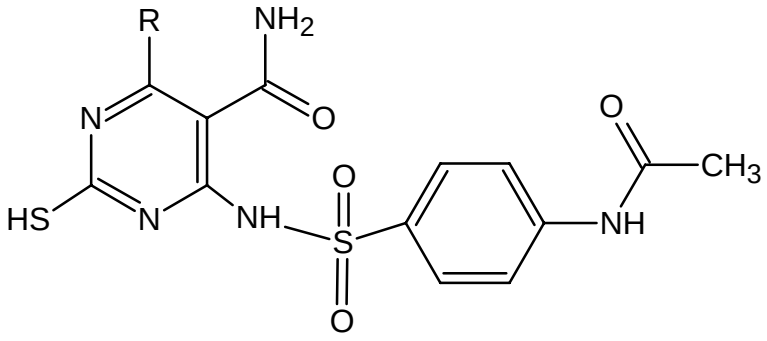
SECTION - I : PREPARATION AND BIOLOGICAL EVALUATION OF 2-MERCAPTO-4-(*P*-ACETAMIDOPHENYL SULPHONYLAMINO)-5-CARBOXMIDO-6-ARYL PYRIMIDINES.

SECTION - II : PREPARATION AND BIOLOGICAL EVALUATION OF 2-MERCAPTO-4-(*P*-AMINOPHENYL SULPHONYLAMINO)-5-CARBOXMIDO-6-ARYL PYRIMIDINES.

SECTION - I

PREPARATION AND BIOLOGICAL EVALUATION OF 2-MERCAPTO-4-(*P*-ACETAMIDOPHENYL SULPHONYLAMINO)-5-CARBOXAMIDO-6-ARYL PYRIMIDINES

Keeping in view the interesting properties[160-164] and pharmacological activities[165-198] sulphonamides, it has been revealed that sulphonamides are valuable drugs for various diseases and for viral diseases. These observation led us to synthesis of some novel 2-mercapto-4-(*p*-acetamidophenyl sulphonylamino)-5-carboxamido-6-aryl pyrimidines (X_{a-j}) by condensation of 2-mercapto-4-amino-5-carboxamido-6-aryl pyrimidines with *p*-acetamidophenyl sulphonylchloride.

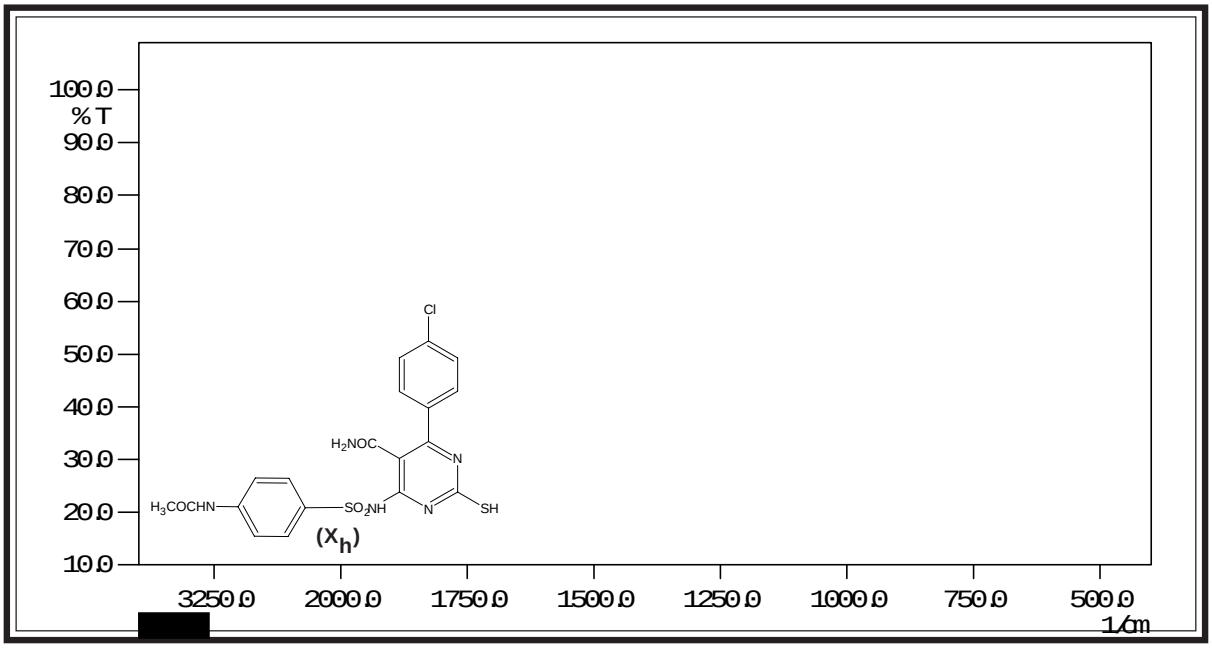


X_{a-j} **R=Aryl**

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

The products (X_{a-j}) were assayed for their *in vitro* biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

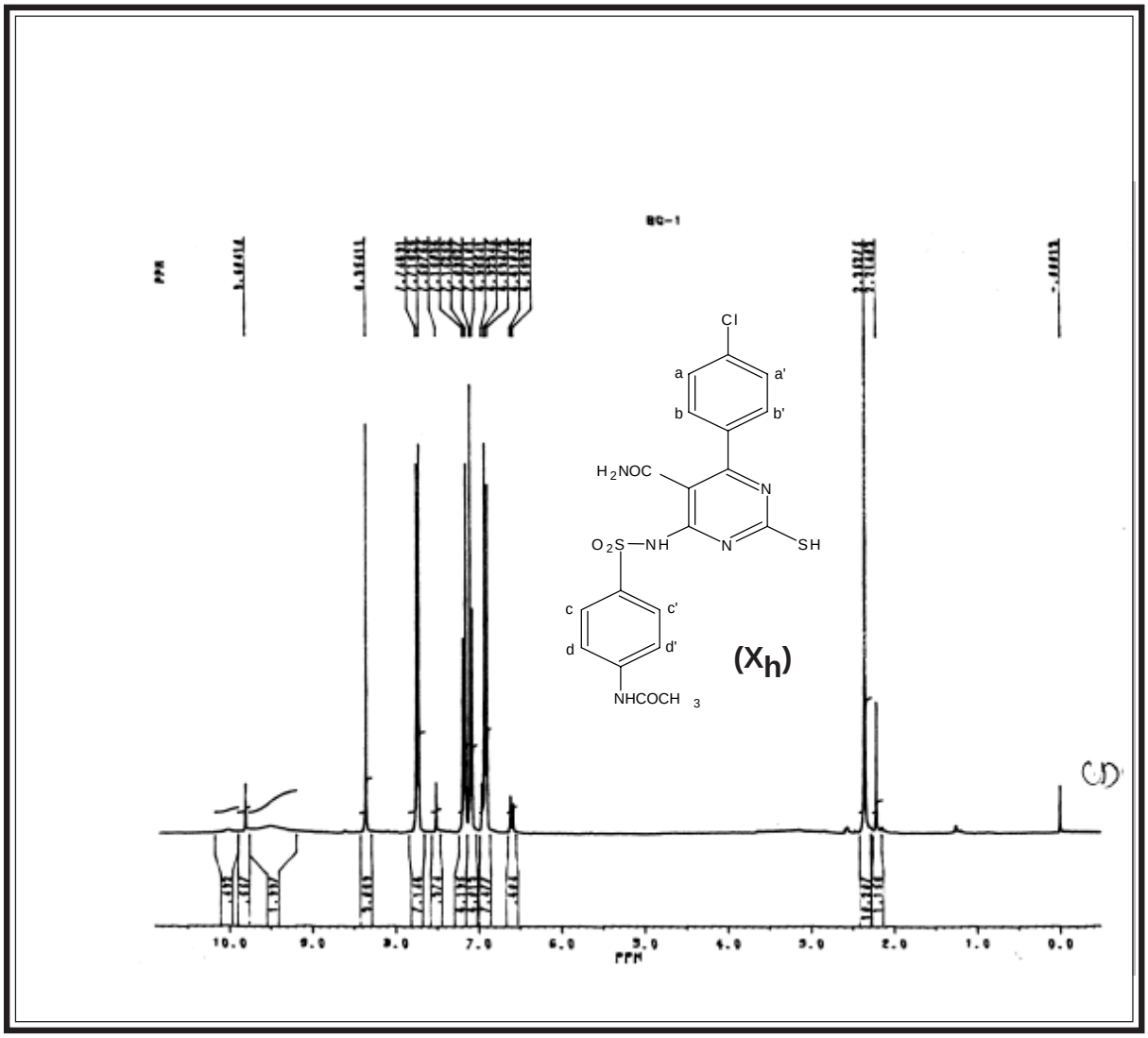
IR SPECTRAL STUDY OF 2-MERCAPTO-4-(*p*-ACETAMIDOPHENYL SULPHONYLAMINO)-5-CARBOXAMIDO-6-(*p*-CHLOROPHENYL) PYRIMIDINE (X_h)



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.(asym.)	2958.6	2975-2950	343
CH_3	C-H str.(sym.)	2868.0	2880-2860	,,
	C-H def.(asym.)	1469.7	1460-1435	,,
	C-H def.(sym.)	1384.8	1385-1300	,,
Aromatic and	C=C + C=N and ring	1488.9	1520-1480	345
Pyrimidine moiety	skeletal vibration	1585.4	1580-1520	,,
	C-H str.	3064.7	3080-3030	,,
	C-H i.p. def.	1101.3	1125-1090	,,
	C-H o.o.p. def.	819.7	840-810	,,
Amide	N-H str.	3321.2	3500-3300	343
	C=O str.	1681.8	1710-1650	,,
Sulphonamide	N-H def.	1176.5	1180-1140	344
	S=O str. (asym)	1311.5	1380-1300	,,
	S=O str. (sym)	1176.5	1180-1140	,,
	C=O str.	1662.5	1710-1650	,,
Halogen	C-Cl str.	773.4	800-600	343

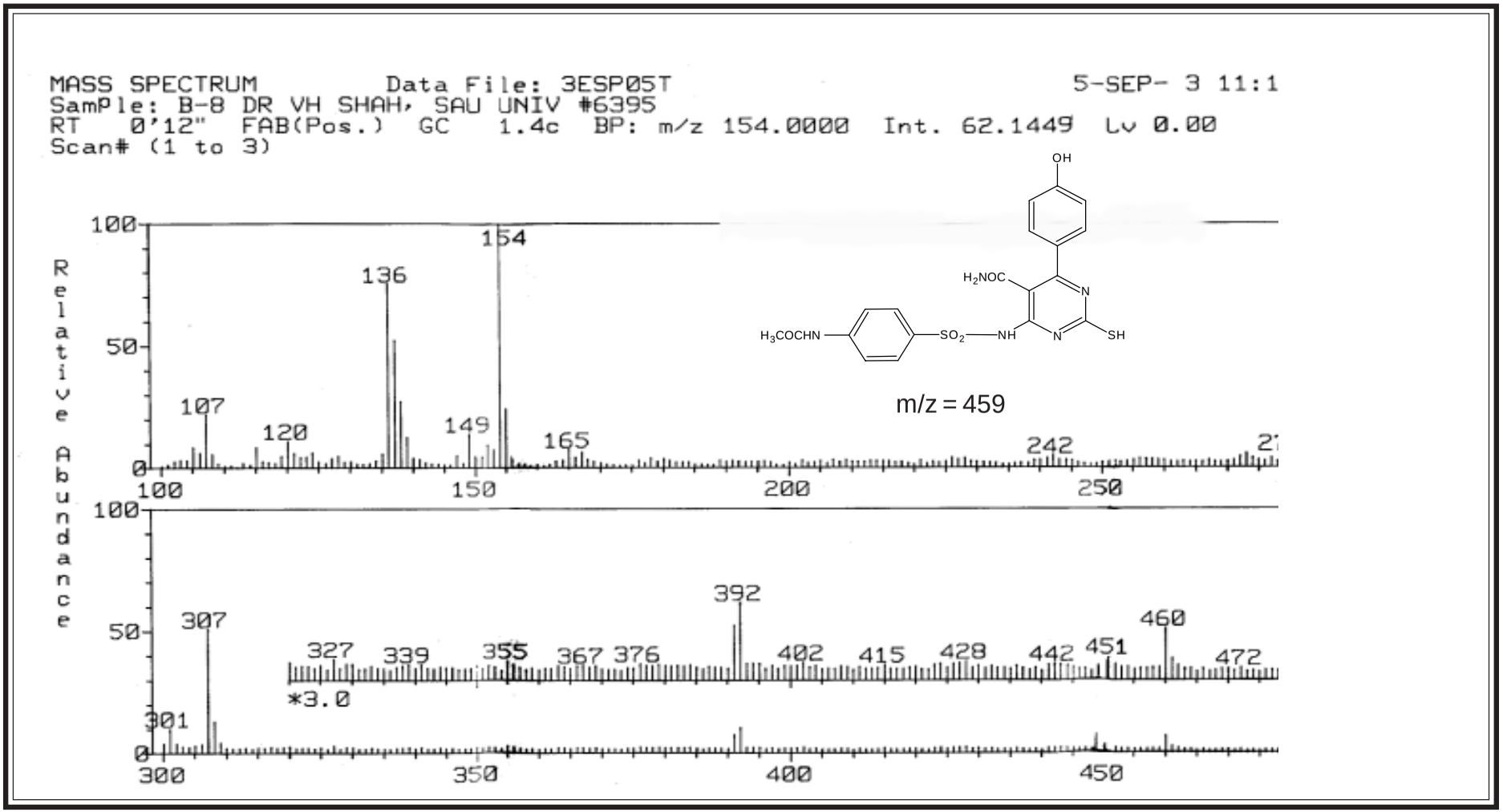
PMR SPECTRAL STUDY OF 2-MERCAPTO-4-(*p*-ACETAMIDOPHENYL SULPHONYLAMINO)-5-CARBOXAMIDO-6-(*p*-CHLOROPHENYL) PYRIMIDINE (X_h)

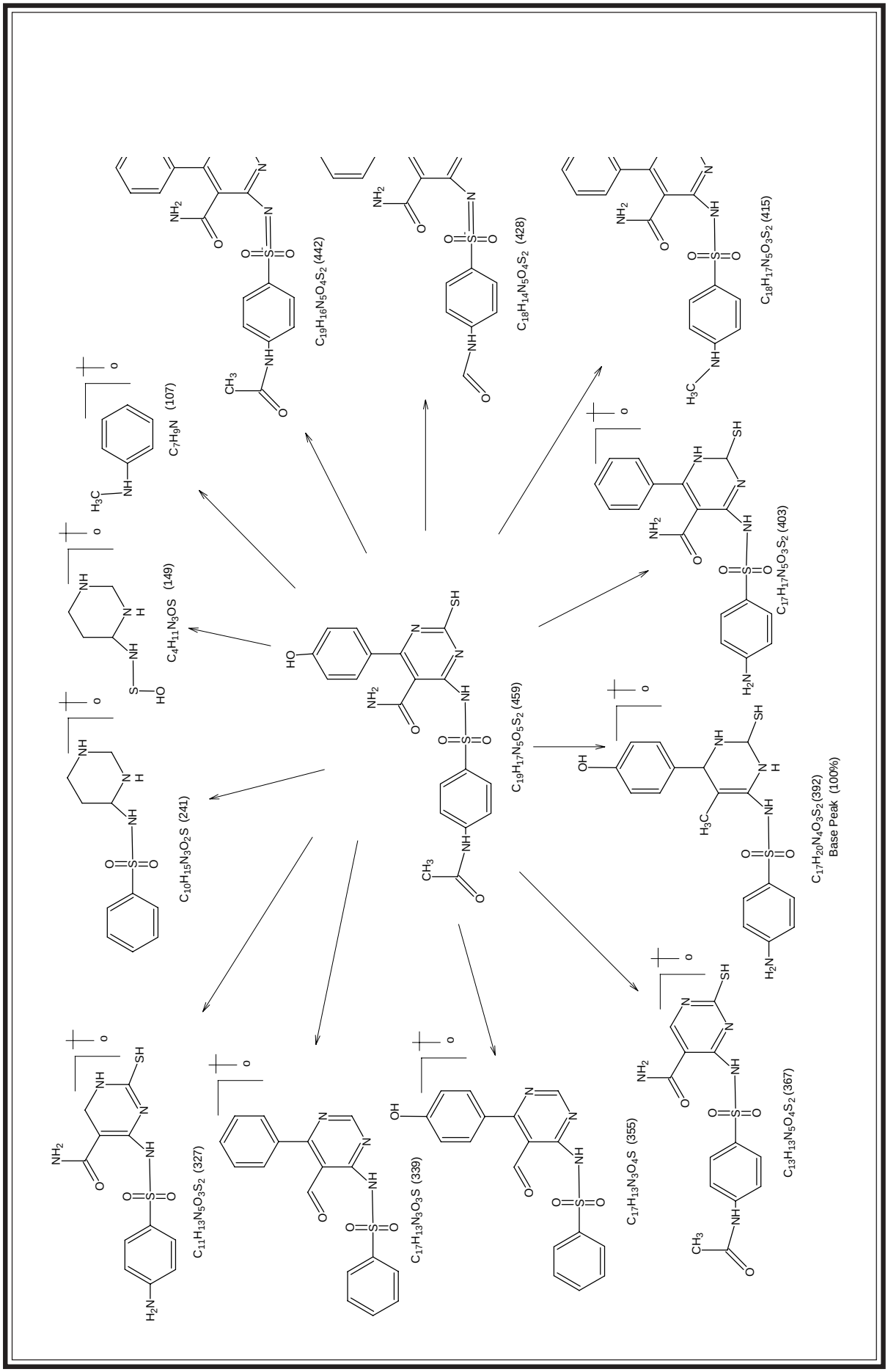


Internal Standard : TMS ; Solvent ; $CDCl_3$+TFA ; Instrument : BRUKER Spectrometer (300 MHz)

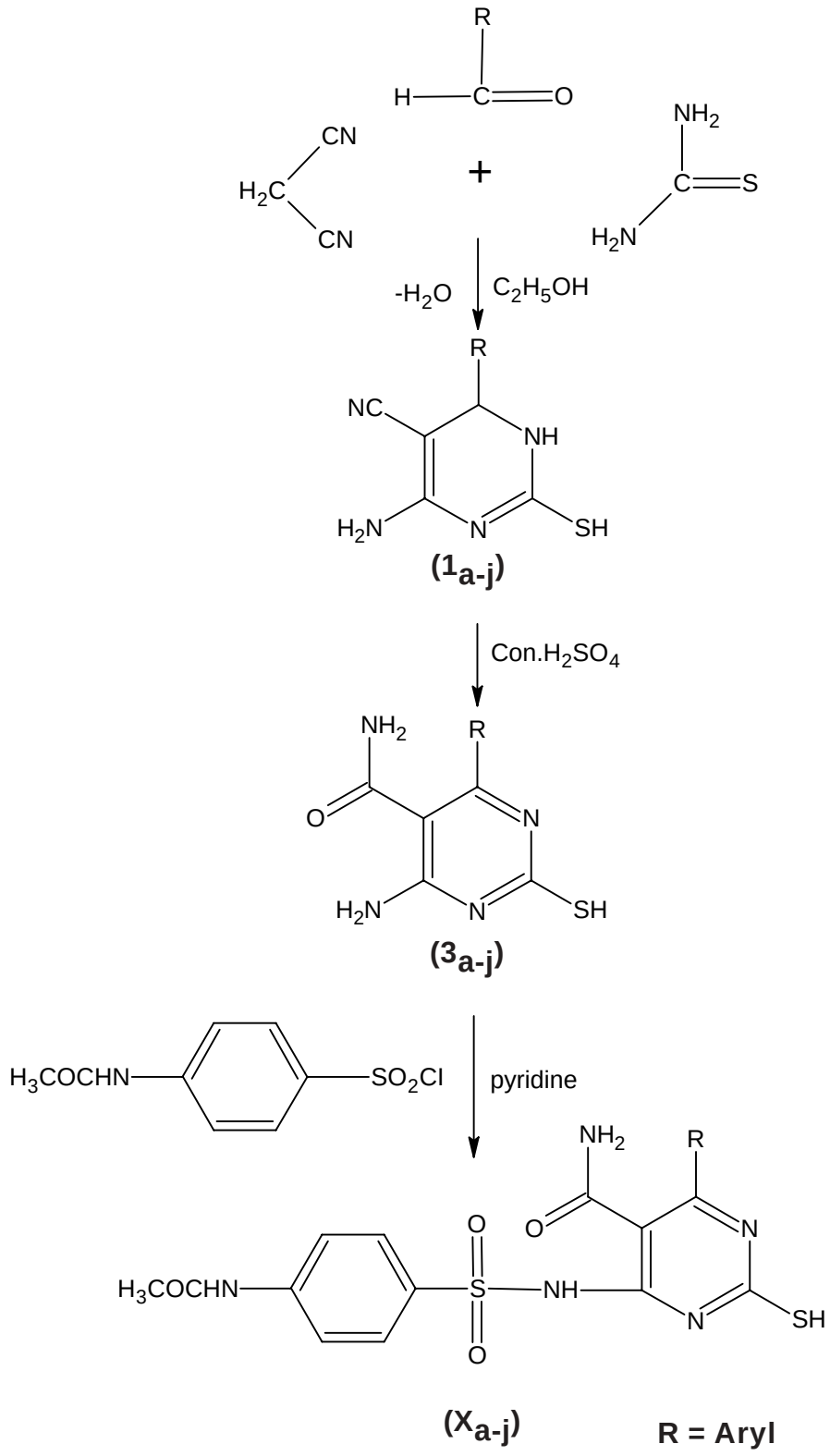
Signal No.	Signal Position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	2.353	3H	singlet	-$NHCOCH_3$
2.	6.895-6.923	2H	doublet	Ar-$H_{d,d'}$ (J=8.62)
3.	7.071-7.098	2H	doublet	Ar-$H_{a,a'}$ (J=8.18)
4.	7.152-7.180	2H	doublet	Ar-$H_{b,b'}$ (J=8.26)
5.	7.718-7.747	2H	doublet	Ar-$H_{c,c'}$ (J=8.61)
6.	8.354	1H	singlet	-NH

MASS SPECTRAL OF 2-MERCAPTO-4-(*p*-ACETAMIDOPHENYL SULPHONILAMINO)-5-CARBOXAMIDO-6-(*p*-HYDROXYPHENYL) PYRIMIDINE (X_C)




C19H16N5O4S2 (442)
C18H14N5O4S2 (428)
C18H17N5O3S2 (415)
C7H9N (107)
C19H17N5O5S2 (459)
C17H17N5O3S2 (403)
C4H11N3OS (149)
C10H15N3O2S (241)
C17H20N4O3S2 (392)
Base Peak (100%)
C11H13N5O3S2 (327)
C17H13N3O3S (339)
C17H13N3O4S (355)
C13H13N5O4S2 (367)

REACTION SCHEME



EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 2-MERCAPTO-4-(*p*-ACETAMIDOPHENYL SULPHONYLAMINO)-5-CARBOXAMIDO-6-ARYL PYRIMIDINES

(A) Preparation of 2-Mercapto-4-amino-5-cyano-6-(*p*-chlorophenyl)-1,6-dihydro pyrimidine (1_e).

For preparation refer Part-I, Section-II (A), Page No. 47.

(B) Preparation of 2-Mercapto-4-amino-5-carboxamido-6-(*p*-chloro phenyl) pyrimidine (3_e).

2-Mercapto-4-amino-5-cyano-6-(*p*-chlorophenyl)-1,6-dihydro pyrimidine (2.65 gm, 0.01 M) was dissolved in concentrated sulphuric acid (20ml) below 5 ^oC and kept for 48 hrs. at room temperature. The content was poured into ice cold water and filtered. The product was isolated and crystallized from ethanol. Yield : 51%; M.P. : 147°C, R_f : 0.54, (Required : C, 47.06%; H, 3.21%; N, 19.96% for $C_{11}H_9N_4OSCl$, Found : C, 47.02%; H, 3.16%; N, 19.89%).
.

Similarly, other compounds (3_{a-j}) were synthesized. The physical data are recorded in Table No. 12.

(C) Preparation of 2-Mercapto-4-(*p*-acetamidophenyl sulphonyl amino)-5-carboxamido-6-(*p*-chlorophenyl) pyrimidine (X_e).

A mixture of 2-mercapto-4-amino-5-carboxamido-6-(*p*-chlorophenyl) pyrimidine (2.81gm, 0.01M) and *p*-acetamidophenyl sulphonylchloride (2.33 gm, 0.01M) in pyridine (15 ml) was heated under reflux condition for five hrs. The content was poured into crushed ice. Filtered the product and recrystallized from ethanol. Yield : 59%, M.P. : 185°C, R_f : 0.64, (Required : C, 47.75%; H, 3.35%; N, 14.66% for $C_{19}H_{16}N_5O_4S_2Cl$, Found : C, 47.70%; H, 3.30 %; N, 14.60%).

Similarly, other compounds (X_{a-j}) were synthesized. The physical data are recorded in Table No. 13.

(D) Antimicrobial activity of 2-Mercapto-4-(*p*-acetamidophenyl sulphonylamino)-5-carboxamido-6-aryl pyrimidines (X_{a-j}).

Antimicrobial activity testing was carried out as described in part-1, section-I, page No. 35. The MIC values of test solution are recorded in Table No. 13a, 13b & 13c.

TABLE NO. 12 : PHYSICAL CONSTANTS OF 2-MERCAPTO-4-AMINO-5-CARBOXAMIDO-6-ARYL PYRIMIDINES (3_{a-j})

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. °C 5	Yield % 6	R_f Value 7	% of Nitrogen	
							Required 8	Found 9
3a	C_6H_5	$C_{11}H_{10}N_4OS$	246.0	170	47	0.49	22.76	22.70
3b	2-OH-C_6H_4	$C_{11}H_{10}N_4O_2S$	262.0	121	53	0.59	21.37	21.34
3c	4-OH-C_6H_4	$C_{11}H_{10}N_4O_2S$	262.0	153	60	0.51	21.37	21.33
3d	2-Cl-C_6H_4	$C_{11}H_9N_4OSCl$	280.5	168	49	0.52	19.96	19.90
3e	4-Cl-C_6H_4	$C_{11}H_9N_4OSCl$	280.5	147	51	0.54	19.96	19.89
3f	2-NO_2-C_6H_4	$C_{11}H_9N_5O_3S$	291.0	208	54	0.55	24.05	23.99
3g	3-NO_2-C_6H_4	$C_{11}H_9N_5O_3S$	291.0	152	51	0.59	24.05	23.98
3h	4-CH_3O-C_6H_4	$C_{12}H_{12}N_4O_2S$	276.0	140	48	0.58	20.29	20.25
3i	C_6H_5-CH=CH-	$C_{13}H_{12}N_4OS$	272.0	139	61	0.53	20.59	20.54
3j	$C_{14}H_9$	$C_{19}H_{14}N_4OS$	346.0	184	66	0.56	16.19	16.15

i **TLC solvent system ; Acetone : Benzene = 1 : 9**

TABLE NO. 13 : PHYSICAL CONSTANTS OF 2-MERCAPTO-4-(*p*-ACETAMIDOPHENYL SULPHONILAMINO)-5-CARBOXAMIDO-6-ARYL PYRIMIDINES (X_{a-j})

Comp. No. 1	R 2	Molecular Formula 3	M. W. 4	M.P. °C 5	Yield % 6	R_f Value 7	% of Nitrogen	
							Required 8	Found 9
Xa	C_6H_5	$C_{19}H_{17}N_5O_4S_2$	443.0	156	63	0.58	15.80	15.75
Xb	2-OH-C_6H_4	$C_{19}H_{17}N_5O_5S_2$	459.0	>260	61	0.52	15.25	15.19
Xc	4-OH-C_6H_4	$C_{19}H_{17}N_5O_5S_2$	459.0	233	58	0.61	15.25	15.20
Xd	2-Cl-C_6H_4	$C_{19}H_{16}N_5O_4S_2Cl$	477.5	146	56	0.56	14.66	14.59
Xe	4-Cl-C_6H_4	$C_{19}H_{16}N_5O_4S_2Cl$	477.5	185	59	0.64	14.66	14.60
Xf	2-NO_2-C_6H_4	$C_{19}H_{16}N_5O_6S_2$	488.0	208	60	0.55	17.21	17.15
Xg	3-NO_2-C_6H_4	$C_{19}H_{16}N_5O_6S_2$	488.0	120	57	0.53	17.21	17.16
Xh	4-CH_3O-C_6H_4	$C_{20}H_{19}N_5O_5S_2$	473.0	218	53	0.62	14.80	14.75
Xi	C_6H_5-CH=CH-	$C_{21}H_{19}N_5O_4S_2$	469.0	193	58	0.57	14.93	14.86
Xj	$C_{14}H_9$	$C_{27}H_{21}N_5O_4S_2$	543.0	>260	64	0.54	12.89	12.84

i **TLC solvent system ; Acetone : Benzene = 0.5 : 9.5**

TABLE NO. 13a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-MERCAPTO-4-(*p*-AETAMIDOPHENYL SULPHONILAMINO)-5-CARBOXAMIDO-6-ARYL PYRIMIDINES X_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442							S. aureus MTCC-96						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
Xa	C_6H_5	-	-	12	12	14	14	14	-	-	14	14	15	16	16
Xb	2-OH-C_6H_4	-	-	10	11	13	15	15	-	-	11	13	15	16	16
Xc	4-OH-C_6H_4	-	-	10	12	12	13	14	-	-	12	13	15	16	18
Xd	2-Cl-C_6H_4	-	-	12	12	14	14	14	-	-	14	15	16	16	17
Xe	4-Cl-C_6H_4	-	-	11	12	14	14	14	-	-	12	13	15	15	16
Xf	2-NO_2-C_6H_4	-	-	10	11	12	13	13	-	-	11	12	14	15	15
Xg	3-NO_2-C_6H_4	-	-	11	11	12	14	14	-	-	13	13	14	16	17
Xh	4-OCH_3-C_6H_4	-	-	12	12	14	14	14	-	-	13	14	15	16	16
Xi	-CH=CH-C_6H_4	-	-	10	11	13	13	14	-	-	12	12	14	15	16
Xj	$C_{14}H_9$	-	-	11	11	12	13	13	-	-	13	14	14	15	16

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

Standard drug	Antibacterial activity														
											Xa Xd	Xa Xd Xh Xj	Xd		
Ampicillin	11	13	14	16	18	19	20	10	12	13	14	16	18	21
Chloramphenicol	10	12	13	19	20	20	22	12	13	14	19	20	21	22
Ciprofloxacin	16	18	19	21	21	22	22	17	18	19	21	22	22	23
Norfloxacin	18	18	19	20	21	21	23	19	20	22	25	26	28	28

N.B.(-): No Activity

TABLE NO. 13b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-MERCAPTO-4-(*p*-AETAMIDOPHENYL SULPHONILAMINO)-5-CARBOXAMIDO-6-ARYL PYRIMIDINES X_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)													
		E. Coli MTCC-443							B. subtillis MTCC-441						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
Xa	C_6H_5	-	-	15	16	16	18	18	-	-	16	17	18	19	19
Xb	2-OH-C_6H_4	-	-	13	14	14	17	17	-	-	15	16	17	18	19
Xc	4-OH-C_6H_4	-	-	13	15	16	17	19	-	-	14	14	17	19	19
Xd	2-Cl-C_6H_4	-	-	15	16	17	18	19	-	-	17	18	19	19	19
Xe	4-Cl-C_6H_4	-	-	14	14	16	18	18	-	-	15	16	16	17	18
Xf	2-NO_2-C_6H_4	-	-	13	15	15	16	17	-	-	14	15	17	17	18
Xg	3-NO_2-C_6H_4	-	-	15	15	16	18	18	-	-	16	17	18	18	19
Xh	4-OCH_3-C_6H_4	-	-	15	15	17	18	18	-	-	16	17	18	18	19
Xi	-CH=CH-C_6H_4	-	-	13	14	16	18	18	-	-	15	16	17	19	19
Xj	$C_{14}H_9$	-	-	14	15	16	17	17	-	-	15	15	17	19	19
Comparative activity of (X_{a-j}) with known choosen standard drugs															
Standard drug		**Antibacterial activity**													
				Xa Xd Xg Xh	Xa Xd						Xa Xd Xg Xh				
Ampicillin		14	14	15	16	19	20	22	12	16	18	19	20	21	23
Chloramphenicol		14	15	17	23	23	23	23	12	14	16	19	22	23	23
Ciprofloxacin		20	21	23	28	28	28	28	16	17	19	22	22	23	23
Norfloxacin		22	23	25	26	27	29	29	19	20	22	23	24	25	28

N.B.(-): No Activity

TABLE NO. 13c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-MERCAPTO-4-(*p*-AETAMIDOPHENYL SULPHONILAMINO)-5-CARBOXAMIDO-6-ARYL PYRIMIDINES X_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antifungal activity (Zones of inhibition in mm) C. albicans MTCC-227							A. niger MTCC-282						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
Xa	C_6H_5	-	-	18	18	20	20	21	-	-	19	19	22	22	24
Xb	2-OH-C_6H_4	-	-	17	18	20	20	22	-	-	18	19	21	22	23
Xc	4-OH-C_6H_4	-	-	16	17	19	20	21	-	-	18	18	20	22	22
Xd	2-Cl-C_6H_4	-	-	17	18	20	22	22	-	-	19	19	21	23	23
Xe	4-Cl-C_6H_4	-	-	16	17	18	20	20	-	-	18	18	20	21	22
Xf	2-NO_2-C_6H_4	-	-	16	17	19	20	22	-	-	19	19	20	21	23
Xg	3-NO_2-C_6H_4	-	-	17	18	20	20	21	-	-	19	19	21	22	22
Xh	4-OCH_3-C_6H_4	-	-	18	18	20	21	21	-	-	19	19	22	22	23
Xi	-CH=CH-C_6H_4	-	-	16	18	19	20	20	-	-	18	19	20	22	23
Xj	$C_{14}H_9$	-	-	17	18	19	20	21	-	-	18	19	21	22	22

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

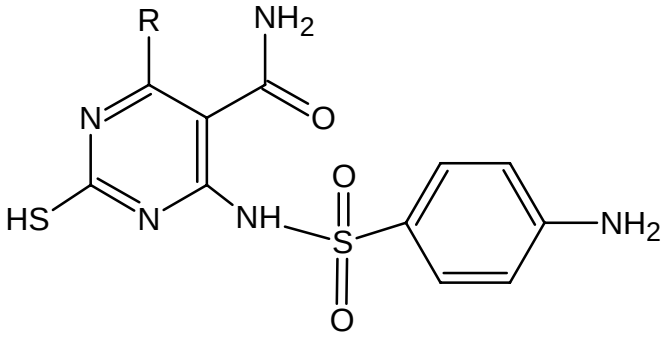
Standard drug	Antifungal activity													
													Xa Xh	
Griseofulvin	19	22	23	25	25	28	28	18	19	21	22	22	24	26

N.B.(-): No Activity

SECTION - II

PREPARATION AND BIOLOGICAL EVALUATION OF 2-MERCAPTO-4-(*P*-AMINOPHENYL SULPHONYLAMINO)-5-CARBOXAMIDO-6-ARYL PYRIMIDINES

Looking to the biodynamic activities[165-198] and the other properties[160-164] of sulphonamides and in order to have highly potent therapeutic agents, the synthesis of 2-mercapto-4-(*p*-aminophenyl sulphonylamino)-5-carboxamido-6-aryl pyrimidines (XI_{a-j}) have been undertaken by the hydrolysis of 2-mercapto-4-(*p*-acetamidophenyl sulphonylamino)-5-carboxamido-6-aryl pyrimidines with hydrochloric acid.

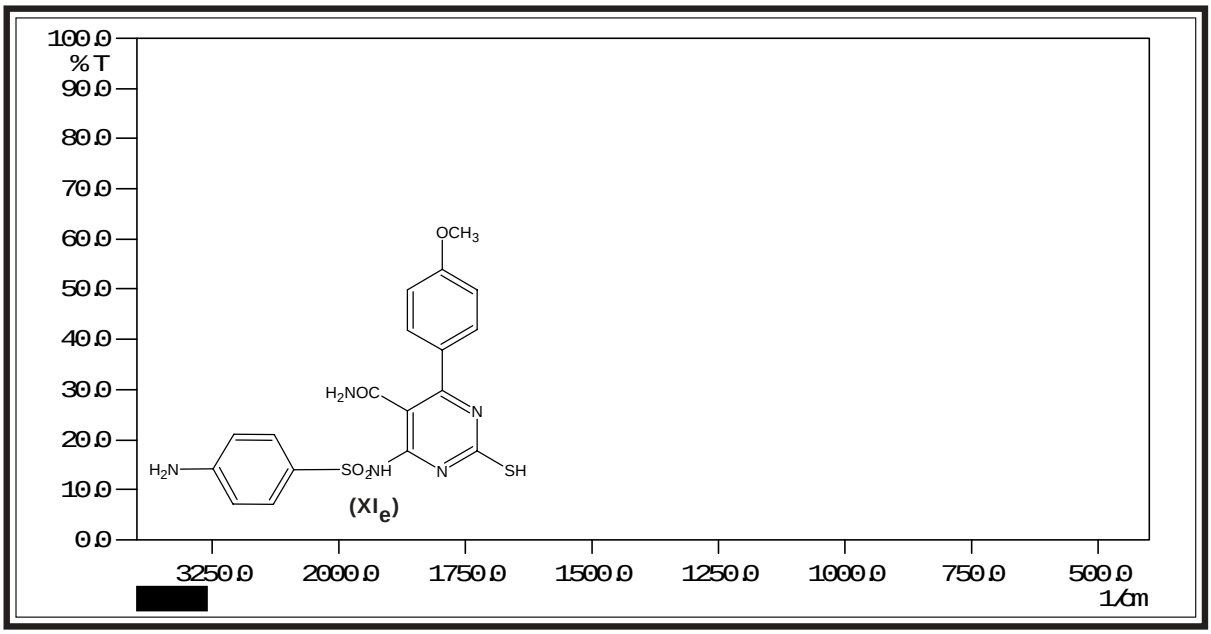


XI_{a-j} **R=Aryl**

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

The products (XI_{a-j}) were assayed for their *in vitro* biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

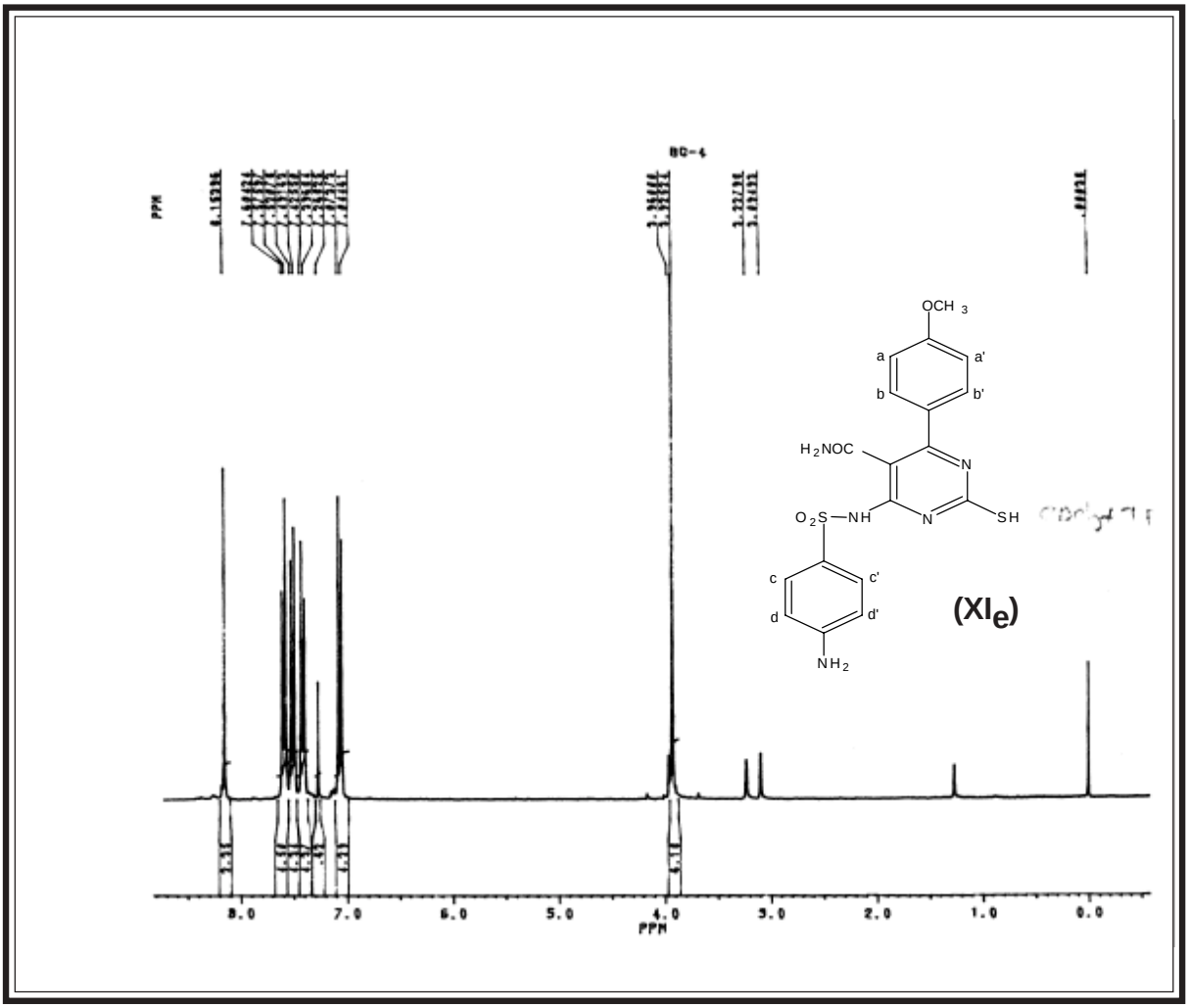
IR SPECTRAL STUDY OF 2-MERCAPTO-4-(*p*-AMINOPHENYL SULPHONYLAMINO)-5-CARBOXAMIDO-6-(*p*-METHOXYPHENYL) PYRIMIDINE (XI_e)



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.(asym.)	2923.9	2975-2950	343
CH_3	C-H str.(sym.)	2852.5	2880-2860	,,
	C-H def.(asym.)	1446.5	1460-1435	,,
	C-H def.(sym.)	1357.8	1385-1300	,,
Aromatic and	C=C + C=N and ring	1502.4	1520-1480	345
Pyrimidine moiety	skeletal vibration	1541.0	1580-1520	,,
	C-H str.	3070.5	3080-3030	,,
	C-H i.p. def.	1097.4	1125-1090	,,
	C-H o.o.p. def.	842.8	840-810	,,
Ether	C-O-C str. (asym.)	1222.8	1275-1200	346
	C-O-C str. (sym.)	1097.4	1075-1050	,,
Amine (Primary)	N-H str.	3423.4	3500-3300	343
	N-H def.	1618.2	1650-1580	,,
Amide	N-H str.	3423.4	3500-3300	345
	C=O str.	1668.3	1710-1650	,,
Sulphonamide	N-H def.	1155.3	1180-1140	344
	S=O str. (asym)	1313.4	1380-1300	,,
	S=O str. (sym)	1155.3	1180-1140	,,

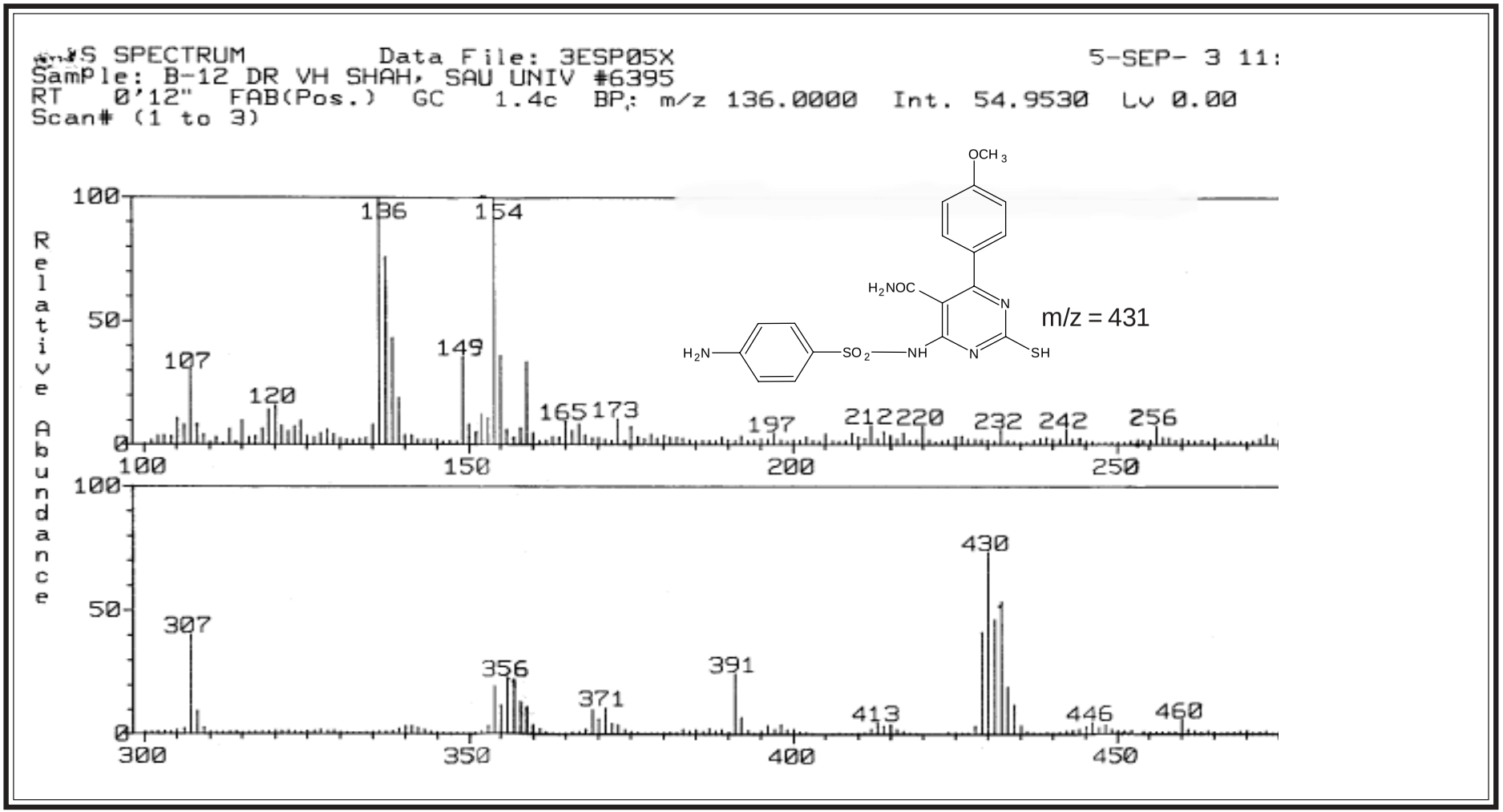
PMR SPECTRAL STUDY OF 2-MERCAPTO-4-(*p*-AMINOPHENYL SULPHONYLAMINO)-5-CARBOXAMIDO-6-(*p*-METHOXYPHENYL) PYRIMIDINE (XI_e)

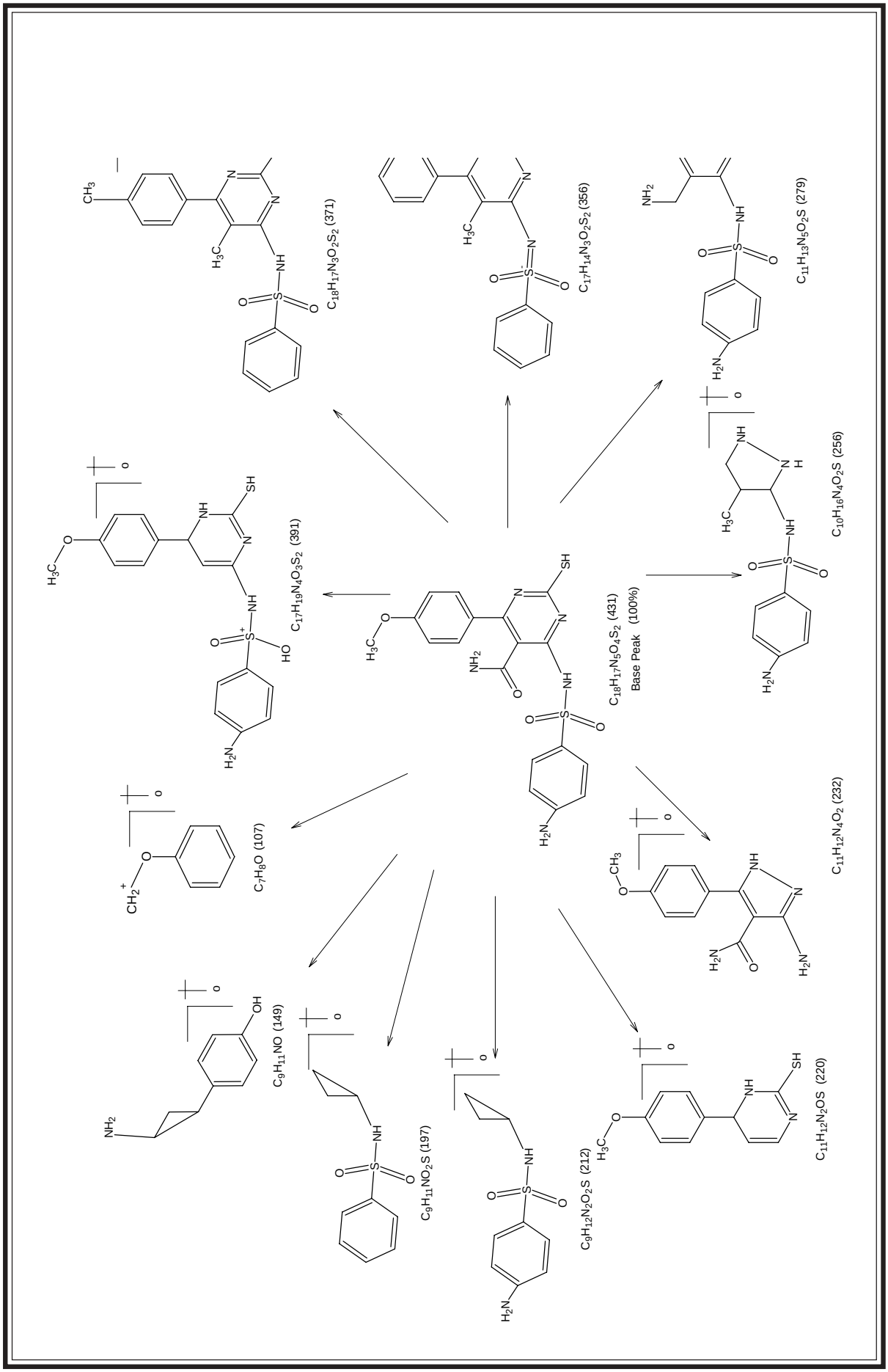


Internal Standard : TMS ; Solvent ; $CDCl_3$+TFA ; Instrument : BRUKER Spectrometer (300 MHz)

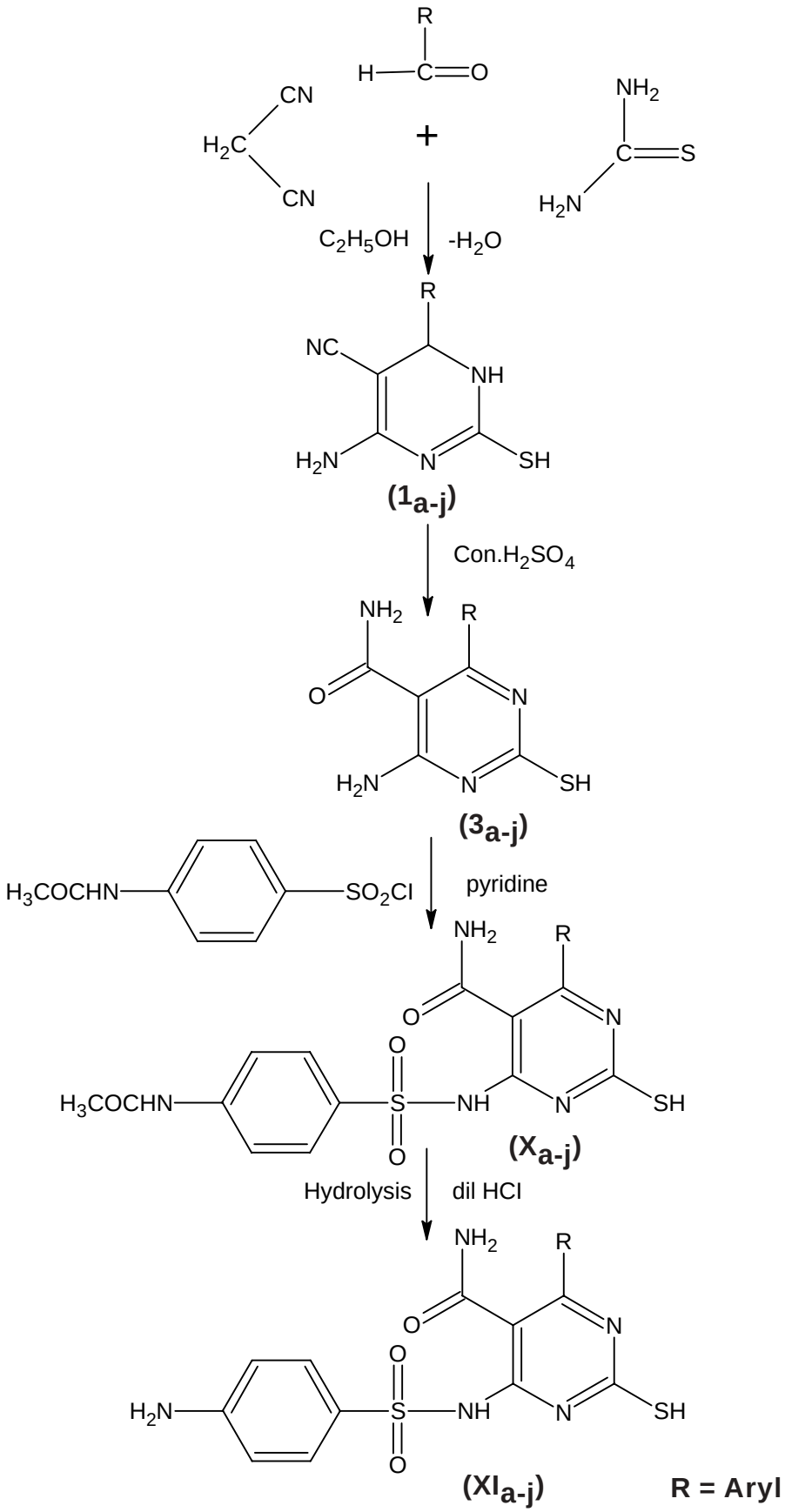
Signal No.	Signal Position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.925	3H	singlet	$-OCH_3$
2.	7.045-7.074	2H	doublet	Ar-$H_{d,d'}$ (J=8.74)
3.	7.397-7.426	2H	doublet	Ar-$H_{a,a'}$ (J=8.59)
4.	7.492-7.521	2H	doublet	Ar-$H_{c,c'}$ (J=8.75)
5.	7.576-7.604	2H	doublet	Ar-$H_{b,b'}$ (J=8.48)
6.	8.154	1H	singlet	-NH

MASS SPECTRAL OF 2-MERCAPTO-4-(*p*-AMINOPHENYL SULPHONILAMINO)-5-CARBOXAMIDO-6-(*p*-METHOXYPHENYL) PYRIMIDINE (XI_h)




C18H17N3O2S2 (371)
C17H14N3O2S2 (356)
C11H13N5O2S (279)
C17H19N4O3S2 (391)
C18H17N5O4S2 (431)
Base Peak (100%)
C10H16N4O2S (256)
C7H8O (107)
C11H12N4O2 (232)
C9H11NO (149)
C9H11NO2S (197)
C9H12N2O2S (212)
C11H12N2OS (220)

REACTION SCHEME



EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 2-MERCAPTO-4-(*p*-AMINOPHENYL SULPHONYLAMINO)-5-CARBOXAMIDO-6-ARYL PYRIMIDINES

(A) Preparation of 2-Mercapto-4-(*p*-acetamidophenyl sulphonylamino)--5-carboxamido-6-(*p*-methoxyphenyl) pyrimidine (X_h).

For preparation refer Part-III, Section-I, Page No. 156.

(B) Preparation of 2-Mercapto-4-(*p*-aminophenyl sulphonylamino-5-carboxamido-6-(*p*-methoxyphenyl) pyrimidine (XI_h).

A mixture of 2-mercapto-4-(*p*-acetamidophenyl sulphonylamino)-5-carboxamido-6-(*p*-methoxyphenyl) pyrimidine (4.73gm, 0.01M) was dissolved in concentrated hydrochloric acid (20ml) and heated under reflux condition for five hrs. The content was poured into ice cold water and filtered. The product was isolated and crystallized from ethanol. Yield : 58%, M.P. : 105°C, R_f : 0.64, (Required : C, 52.90%; H, 3.94%; N, 16.24% for $C_{19}H_{17}N_5O_4S_2$, Found : C, 52.85%; H, 3.90% ; N, 16.20%).

.

Similarly, other compounds (XI_{a-j}) were synthesized. The physical data are recorded in Table No. 14.

(C) Antimicrobial activity of 2-Mercapto-4-(*p*-aminophenyl sulphonyl amino)-5-carboxamido-6-aryl pyrimidines (XI_{a-j}).

Antimicrobial activity testing was carried out as described in part-1, section-I, page No. 35. The MIC values of test solution are recorded in Table No. 14a, 14b & 14c.

TABLE NO. 14 : PHYSICAL CONSTANTS OF 2-MERCAPTO-4-(*p*-AMINOPHENYL SULPHONILAMINO)-5-CARBOXAMIDO-6-ARYL PYRIMIDINES (XI_{a-j})

Comp. No. 1	R 2	Molecular Formula 3	M.W. 4	M.P. °C 5	Yield % 6	R_f Value 7	% of Nitrogen Required 8	% of Nitrogen Found 9
XIa	C_6H_5	$C_{17}H_{15}N_5O_3S_2$	401.0	91	66	0.54	17.46	17.41
XIb	2-OH-C_6H_4	$C_{17}H_{15}N_5O_4S_2$	417.0	165	61	0.59	16.79	16.75
XIc	4-OH-C_6H_4	$C_{17}H_{15}N_5O_4S_2$	417.0	>260	62	0.57	16.79	16.76
XId	2-Cl-C_6H_4	$C_{17}H_{14}N_5O_3S_2Cl$	435.5	132	59	0.60	16.07	16.01
XIe	4-Cl-C_6H_4	$C_{17}H_{14}N_5O_3S_2Cl$	435.5	118	62	0.58	16.07	16.02
XIf	2-NO_2-C_6H_4	$C_{17}H_{14}N_6O_5S_2$	446.0	153	65	0.63	18.83	18.79
XIg	3-NO_2-C_6H_4	$C_{17}H_{14}N_6O_5S_2$	446.0	147	63	0.61	18.83	18.80
XIh	4-CH_3O-C_6H_4	$C_{18}H_{17}N_5O_4S_2$	431.0	105	58	0.64	16.24	16.20
XIi	C_6H_5-CH=CH-	$C_{19}H_{17}N_5O_3S_2$	427.0	217	54	0.56	16.39	16.33
XIj	$C_{14}H_9$	$C_{25}H_{19}N_5O_3S_2$	501.0	209	68	0.59	13.97	13.92

TLC solvent system ; Acetone : Benzene = 0.5 : 9.5

TABLE NO. 14a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-MERCAPTO-4-(*p*-AMINOPHENYL SULPHONILAMINO)-5-CARBOXAMIDO-6-ARYL PYRIMIDINES XI_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442							S. aureus MTCC-96						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
XIa	C_6H_5	-	-	11	12	13	13	14	-	-	12	13	13	14	17
XIb	2-OH-C_6H_4	-	-	12	12	13	14	14	-	-	14	14	15	16	16
XIc	4-OH-C_6H_4	-	-	10	10	12	12	13	-	-	11	12	14	14	15
XId	2-Cl-C_6H_4	-	-	10	11	13	13	14	-	-	12	12	14	14	15
XIe	4-Cl-C_6H_4	-	-	12	12	13	14	14	-	-	13	13	14	15	16
XIf	2-NO_2-C_6H_4	-	-	11	11	13	13	14	-	-	12	13	15	15	16
XIg	3-NO_2-C_6H_4	-	-	10	10	12	13	14	-	-	11	11	13	13	16
XIh	4-OCH_3-C_6H_4	-	-	11	12	12	13	14	-	-	13	13	14	15	15
XIi	-CH=CH-C_6H_4	-	-	10	10	12	13	13	-	-	12	12	14	15	15
XIj	$C_{14}H_9$	-	-	12	12	12	14	14	-	-	13	14	14	15	15

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

Standard drug	Antibacterial activity														
											XIb	XIb XIj			
Ampicillin	11	13	14	16	18	19	20	10	12	13	14	16	18	21
Chloramphenicol	10	12	13	19	20	20	22	12	13	14	19	20	21	22
Ciprofloxacin	16	18	19	21	21	22	22	17	18	19	21	22	22	23
Norfloxacin	18	18	19	20	21	21	23	19	20	22	25	26	28	28

N.B.(-): No Activity

TABLE NO. 14b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-MERCAPTO-4-(*p*-AMINOPHENYL SULPHONILAMINO)-5-CARBOXAMIDO-6-ARYL PYRIMIDINES XI_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)													
		E. Coli MTCC-443							B. subtillis MTCC-441						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
XIa	C_6H_5	-	-	14	15	17	17	18	-	-	15	17	19	19	19
XIb	2-OH-C_6H_4	-	-	15	16	17	17	18	-	-	16	17	19	19	19
XIc	4-OH-C_6H_4	-	-	13	13	15	16	16	-	-	15	16	16	17	18
XId	2-Cl-C_6H_4	-	-	13	14	16	17	17	-	-	15	15	17	18	19
XIe	4-Cl-C_6H_4	-	-	15	16	16	17	17	-	-	16	17	17	18	19
XIf	2-NO_2-C_6H_4	-	-	14	14	15	16	18	-	-	15	16	16	18	19
XIg	3-NO_2-C_6H_4	-	-	13	14	15	16	17	-	-	14	15	15	17	18
XIh	4-OCH_3-C_6H_4	-	-	14	15	15	17	18	-	-	16	17	18	18	19
XIi	-CH=CH-C_6H_4	-	-	14	15	16	16	17	-	-	15	15	15	17	19
XIj	$C_{14}H_9$	-	-	15	15	16	17	17	-	-	16	16	17	17	18

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

Standard drug	Antibacterial activity														
			XIb XIe XIj	XIb XIe						XIb XIe XIh XIj					
Ampicillin	14	14	15	16	19	20	22	12	16	18	19	20	21	23
Chloramphenicol	14	15	17	23	23	23	23	12	14	16	19	22	23	23
Ciprofloxacin	20	21	23	28	28	28	28	16	17	19	22	22	23	23
Norfloxacin	22	23	25	26	27	29	29	19	20	22	23	24	25	28

N.B.(-): No Activity

TABLE NO. 14c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 2-MERCAPTO-4-(*p*-AMINOPHENYL SULPHONILAMINO)-5-CARBOXAMIDO-6-ARYL PYRIMIDINES XI_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antifungal activity (Zones of inhibition in mm) C. albicans MTCC-227 5	10	25	50	100	250	500	A. niger MTCC-282 5	10	25	50	100	250	500
XIa	C_6H_5	-	-	17	18	20	21	22	-	-	18	19	21	22	23
XIb	2-OH-C_6H_4	-	-	18	18	20	20	21	-	-	19	19	20	22	23
XIc	4-OH-C_6H_4	-	-	16	17	18	19	20	-	-	18	18	20	20	22
XId	2-Cl-C_6H_4	-	-	17	18	19	20	20	-	-	19	19	21	22	22
XIe	4-Cl-C_6H_4	-	-	18	18	19	20	21	-	-	19	20	20	21	22
XIf	2-NO_2-C_6H_4	-	-	17	18	19	20	21	-	-	19	19	20	22	24
XIg	3-NO_2-C_6H_4	-	-	17	17	19	20	20	-	-	18	19	20	22	23
XIh	4-OCH_3-C_6H_4	-	-	18	18	19	20	20	-	-	19	19	21	21	22
XIi	-CH=CH-C_6H_4	-	-	17	18	19	20	21	-	-	18	19	20	22	23
XIj	$C_{14}H_9$	-	-	18	18	19	20	20	-	-	19	19	21	21	22
Comparative activity of (XI_{a-j}) with known choosen standard drugs															
Standard drug		**Antifungal activity**													
Griseofulvin		19	22	23	25	25	28	28	18	19	21	22	22	24	26

N.B.(-): No Activity

REFERENCES

160. Shepherd, R.G.; *Sulphanilamides and other g-amino benzoic acid antagonists in medicinal chemistry,* **Vol. 1,** edited by A. Burger (Wiley Interscience Toronto), p. 255 (1949).

161. Krupp M.A. and Chalton M.J.; *Current medicinal diagnosis and treatment* (1980).

162. Willms, Lothar; (Hoechst A.-G.) *Ger. Offen.* **DE 3,** 330, 603 (Cl. C07D239/47), 21Mar 1985, Appl. 25 Aug 1983; 17 pp, *Chem. Abstr.,* **103,** 54094x (1985).

163. N. Alois, C. Jindrich, B. Jana, K. Jiri, H. Vladislava; Czech. CS 254, 541 (Cl. C07D239/49), 15 sep 1988, Appl. 86/3,198, 4 May 1986; 3pp, *Chem. Abstr.,* **111,** 23530x (1989).

164. M. Drewes, R.F. Gesing, J.R. Jansen, K. Mueller, H. Riebel, M. Dollinger, H. Santel; (Bayer A.-G., Germany) *Ger.Offen.* **DE 19,** 504, 281(Cl. C07D239/52), 14Aug 1996, Appl. **19,** 504, 281, 9 Feb 1995, 9pp, *Chem. Abstr.,* **125,** 195684f (1996).

165. F.L. Rose; *Chem. Ind.* (London), **21,** 658-65 (1964); *Chem. Abstr.,* **61,** 2901b (1964).

166. R.S. Mc Cutcheon; *Pharm. Index.,* 7, **4A,** 4-8 (1984).

167. P.O. Wester; *Acta Med. Scand.,* **196(6),** 489-94 (1974); *Chem. Abstr.,* **82,** 93324g (1975).

168. Feit P. Worner, O.B.T. Neilsen and H. Bruun; *Brit.,* **1,** 523, 631 (1978); *Chem. Abstr.,* **91,** 56629h (1979).

169. Cribb A.E., Lee Belle L.; (Merck Research Laboratories) West Paint P.A., USA, *Advance drug react Toxicol. Rev.* 1996, *US* Cl. 9-50 (Eng), *Chem. Abstr.,* **126,** 220193a (1997).

170. E. Selvaag, Thune P.; *Chem. Abstr.,* **128,** 347c (1998).

171. V. Hagen, E. Morgenstern and E. Georges; *Pharmazie*, **35(3),** 183-5 (1980); *Chem. Abstr.,* **93,** 106817g (1980).

172. J.J. Howbert, A.C. Thomas, F.K. Kenneth and V.T. Eddie; *J. Med. Chem.,* **33(9),** 2393-407 (1990); *Chem. Abstr.,* **113,** 114771j (1990).

173. Hiroshi Yoshino, Norihiri Ueda, Nil Jima, Jan, Toru, Kotake, Yoshimalsa, Kentaro, Tsukahara, Naoko, Watanabe, Tatsuo Haneda; *PCT Int. Appl.* ***WO*** **95,** 03, 279 (1995); *Chem. Abstr.,* **122,** 314588c (1995).

174. Tobler Hans; *PCT Int. Appl.* ***WO*** **93,** 16, 079 (1993); *Chem. Abstr.,***120,** 54559d (1994).

175. A. Go, S. Kudo, J. Jakashashi and R. Higare; *Jpn. Kokai Tokkyo Koho* **Jp 06,** 172, 323 (1994); *Chem. Abstr.,***122,** 1332079 (1995).

176. Abe Takaaki, Akiyoshi Yuji et al.; *Eur. Pat. App.* **Ep.** 567, 014, 27 Oct. (1993); *Chem. Abstr.,* **121**, 83357n (1994).

177. K. Henry Sobolewski and Dionizy Skwafski; *nn. Acta Pol. Pharm.* **46(3),** 232-6 (1989); *Chem. Abstr.,* **114,** 6421 (1991).

178. K. Joachim Seydel, Helmut Pieper and Albrecht Jung; *Ger. Offen.* **DE. 3,** 919, 214;

Chem. Abstr., **114,** 185536t (1991).

179. Yoshio Katahashi, Toyohik Okume, Akihiko Yanagi, Ikuro Honder and Hashisho Honda; *Jpn. Kokai Tokkyo Koho* **Jp 02,** 286, 674; *Chem. Abstr.,* **114,** 164225 (1991).
180. K.H. Patel and K.R. Desai; *Proc. Nat. Acad. Sci., India, Sect. A* **60(1),** 7 (1990); *Chem. Abstr.,* **114,** 164164E (1991).
181. K.H. Sikotra, D.N. Nagar, V.H. Shah; *J. Inst. Chemist (India);* **Vol.73,** Part-3, pg.111 (2001); *Chem. Abstr.,* **136,** 401723a (2002).
182. J.M. Parmar, J.J. Modha, R.C. Khunt, A.R. Parikh; *J. Inst. Chemist (India);* **Vol.73,** Part-3, pg.114 (2001); *Chem. Abstr.,* **137,** 63221r (2002).
183. J.J. Modha, N.J. Dutta, J.M. Parmar, A.R. Parikh; *J. Inst. Chemist (India);* **Vol.73,** Part-6, pg.206 (2001).
184. J. Bartroli, M. Anquita, J. Belloe, E. Carcellor and C. Atmanza; *US*, **5,** 360, 813 (1994); *Chem. Abstr.,***122,** 4984g (1995).
185. K. Rama Rao, Y.V.D. Nageswar, T.N. Srinivasan and P.B. Sattur; *Indian J. Chem.,* **29B,** 1041 (1990).
186. J.C. Henquin; *Diabotologia* 60(1), 904-12 (1992); *Chem. Abstr.,***118,** 87p (1993).
187. L. Anderson, M. Kangasaho and H. Nikander; *PCT Int. Appl.* **WO 88,** 07, 991 (1988); *Chem. Abstr.,* **110,** 135085s (1989).
188. Yoshikawa Yashinavi, Saito Hidesi and Oochi Yutake; *Jpn. Kokai Tokkyo* **Jp 04,** 174, 782 (1992); *Chem. Abstr.,* **118,** 38917 (1993).
189. W.I. Yasaka and P. Braz; *PIBR* 9201, 786 (1993); *Chem. Abstr.,* **122,** 25918f (1995).
190. M.L. Vazquez and Co-workers ; *Pat. Int. Appl.* **WO 94,** 04, 493 (1994); *Chem. Abstr.,* **122,** 55727k (1995).
191. M.I. Reider, R. Krause, I.R. Bird and G.A. Debakan; *J. Acquired Immune Defic, Syndr. Hum. Retroviro.* 8(2), 134 (1995); *Chem. Abstr.,* **122,** 230194n (1995).
192. William Loh, Lucille A. Cosby and Alan C. Sartorelli; *J. Med. Chem.,* **23,** 630 (1980).
193. M.A. Kaldrikyan, V.A. Geboyan and A.R. Avoyani; *Arm. Khim. Zh.,* **33(3),** 242-6 (1980); *Chem. Abstr.,* **93,** 114216q (1980).
194. Tung Roger, D. Mureko Mark A. Bhiselti, Govinda R.; 87 pp Cont. in of U.S. Ser. No. 941-982 abandones (Eng); *Chem. Abstr.,* **128,** 144117m (1998).
195. Peyman Helmut and co-workers; *PCT Int. Appl.* **WO 99,** 37, 621 (1999); *Chem. Abstr.,* **128,** 489, 23 (1998).
196. Breu, Volker; *US Appl.* 676, 313 (1996); *Chem. Abstr.,* **130,** 13993d (1999).
197. Y.I. Isao, H. Hironari, K. Jun-Ichi , W. Susumu, T. Ryuji, S. Katsumi; *Chemical & pharmaceutical Bulletin* 2001, 49 (12), 1593-1603 (Eng), *pharmaceutical society of Japan*, *Chem. Abstr.,* **136,** 263139m (2002).
198. F. Walter; W. Thomas; B. Martin; B. Christoph; C. Martine; Actelion *pharmaceutical Ltd. switz , PCT Int. Appl.* **WO 02,** 24, 665. *Chem. Abstr.,* **136,** 263176w (2002).

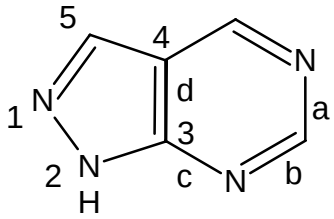
PART -IV
STUDIES ON PYRAZOLO[3,4-d] PYRIMIDINES

PART - IV

STUDIES ON PYRAZOLO[3,4-d]PYRIMIDINES

INTRODUCTION

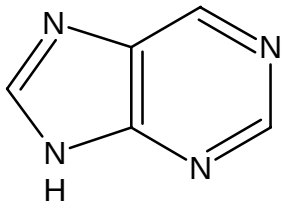
Pyrazolo[3,4-d]pyrimidine **(35)** is a fused heterocyclic compound in which pyrimidine with its d-position is fused at 3,4-position of pyrazole ring system.



(35)

Pyrazolo[3,4-d]pyrimidine

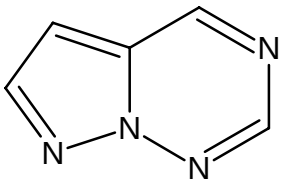
R. Justoni et al.,[199] have synthesized 1H-pyrazolo[3,4-d]pyrimidine 4(5H)-ones-6-methyl-1,3-diphenyl in 1938. Pyrazolo[3,4-d]pyrimidine ring system is isomeric with the purine **(36)** ring system and therefore, is of interest as a model for biologically active compounds. Pyrazolo[3,4-d]pyrimidine is also known as allopurine.



(36)

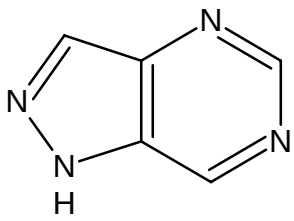
Purine ring system

There are other two possible isomers of pyrazolo[3,4-d]pyrimidines, which are fused at different positions represented as under.



(37)

Pyrazolo[1,5-a]pyrimidine



(38)

Pyrazolo[4,3-d]pyrimidine

SYNTHETIC ASPECTS

Extensive studies have been made in the field of synthesis of pyrazolo [3,4-d]pyrimidines. Various methods for the preparation of pyrazolo[3,4-d] pyrimidines have been described as under:

(a) By the condensation of 5-amino-4-cyano-pyrazole with 5-nitro-2-furonitrile led to formation of 4-amino-6-(5'-nitro-2'-furyl)-1H-pyrazolo [3,4-d] pyrimidines[200].

(b) By the cyclocondensation of 4,6-dichloro-5-formylpyrimidine with hydrazine hydrate led to formation of 1H-pyrazolo[3,4-d]pyrimidines[201].

(c) 1,3-dimethyl-6-hydrazino uracil is fused at 150°C with dimethyl formamide dimethylacetal (DMFDMA) led to formation of 2-alkyl-5,7-dimethyl pyrazolo [3,4-d]pyrimidine-4,6(5H, 7H)-diones[202].

(d) By the fusion of 5-arylazo-6-arylidene-hydrazino-1,3-dimethyl uracils at 200°C led to formation of 2-benzyl-5,7-dimethyl-3-phenyl pyrazolo[3,4-d] pyrimidines-4,6(5H,7H)-diones[203].

(e) By the cyclocondensation of 5-amino-4-cyano pyrazole with guanidine carbonate led to formation of 4,6-diamino pyrazolo[3,4-d]pyrimidines[204].

(f) By the cyclocondensation of arylidene derivative of 1,3-diphenyl uracil with hydrazine hydrate led to the formation of pyrazolo[3,4-d]pyrimidines[205].

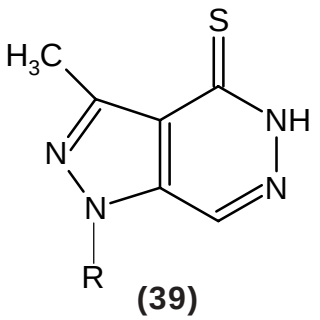
(g) By the cyclocondensation of 4-carboxamido-5-amino-1,2,3-trihydro pyrazole with formamide led to the formation of pyrazolo[3,4-d] pyrimidines[206].

(h) By the cyclocondensation of 3,4-dicyano-5-amino-1-N-substitied pyrazole with trichloro acetonitrile led to formation of pyrazolo[3,4-d] pyrimidines[207].

(i) By the cyclocondensation of 3-aryl-2-arylamino-5-cyano-6-methyl-sulphonyl pyrimidine-4-one with hydrazine hydrate led to formation of pyrazolo [3,4-d]pyrimidines[208].

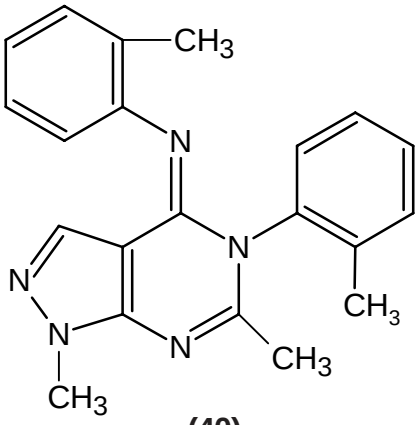
(j) By the cyclization of 2-chloro-6-methoxy quinolin-3-carboxaldehyde and 3-methyl-1-N-phenyl-5-pyrazolone with thiourea led to formation of pyrazolo[3,4-d]pyrimidines[209].

Pyrazolo[3,4-d]pyrimidines were found to possess remarkable fungicidal [210] **(39)**, pesticidal [211,212] **(40)** and herbicidal [213] **(41)** activities.

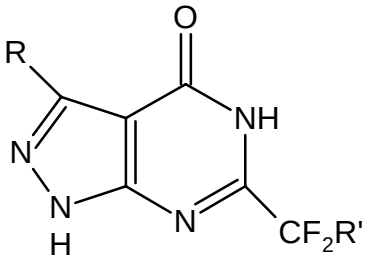


(39)

R=ph/4-Cl-C_6H_4



(40)



(41)

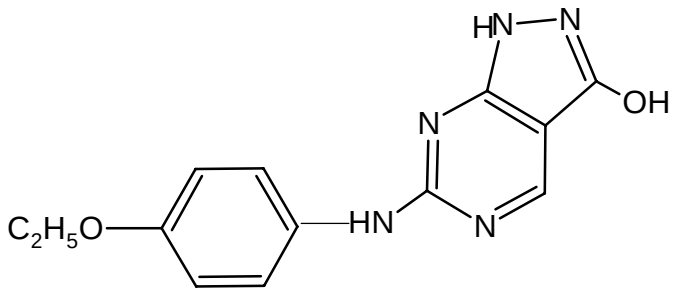
BIOLOGICAL IMPORTANCE

Considerable research has been undertaken to extend the activity and reduce toxicity of Pyrazolo[3,4-d]pyrimidine. The specific biological activities have been represented as under.

(a) Hyperuricemia[214,215]
(b) Protozoacidal[216]
(c) Hypoglycemic[217]
(d) Antimalarial[218]
(e) Anticancer[219-222]
(f) Analgesic, antipyretic, antiinflammatory[223-226]
(g) Antimycotic agent[227]
(h) Xanthine oxidase inhibitor[228,229]
(i) Antitumor[230-232]
(j) AntiHIV[233]

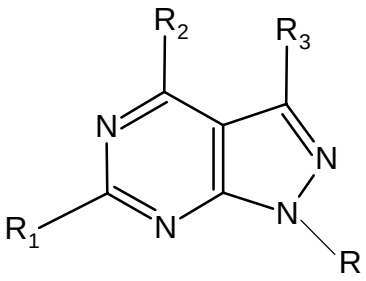
(k) Anxiolytic agent[234]
(l) Cardiovascular[235,236]
(m) Antileishmanial[237-239]
(n) Tranquilizer[240]
(o) Blood sugar lower agent[241]
(p) Antiparasitic[242]
(q) Antianaphylactic agent[243]
(r) Coccidiostatic agent[244]
(s) Anticonvulsant[245]
(t) Antiviral[246]
(u) Antiallergic[247]

F. Robert et al.,[248] have conducted the studies of pyrazolo[3,4-d]pyrimidine as a chemotherapeutic agent against neurospora. The family of 4-amino pyrazolo[3,4-d]pyrimidines linked at 3 and 1 position by pyridoxine and pyridoxamine which are involved in a thiamine metabolism and which are linked by series of related compounds adenine, thiamine, caffeine and some vitamins can exhibit neurospora growth. E. Harward et al.,[249] tested 4-amino pyrazolo [3,4-d]pyrimidines and its methyl derivative as significant growth inhibitor of adrenocarcinoma 755 in mice. Machon et al.,[250] have synthesized pyrazolo [3,4-d]pyrimidines **(42)** which possess carcinostatic activity at 50 mg/kg gave 71 to 76% inhibitor respective of Ehrlich Carcinoma in mice.



(42)

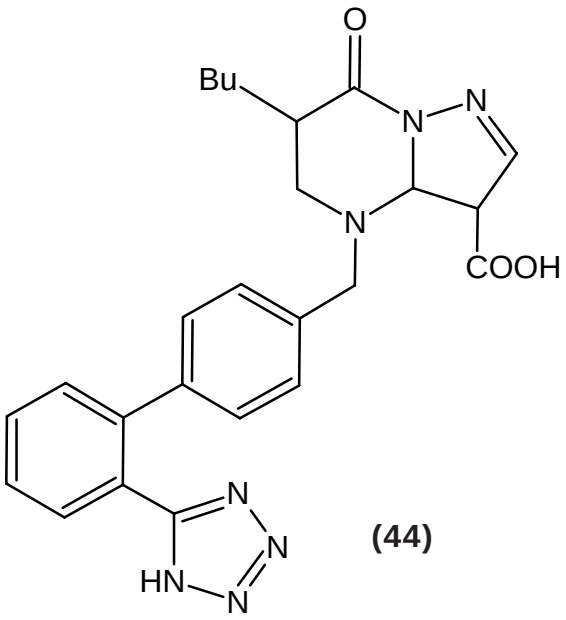
Dobrynine et al.,[251] have tested 3,4-disubstituted-6-(methylmercapto) pyrazolo[3,4-d]pyrimidines **(43)** for cytotoxic activity on a human overiancarcinoma cell and antiviral activity against Herpes and Pox infection in chicken fibroblasts.



(43)

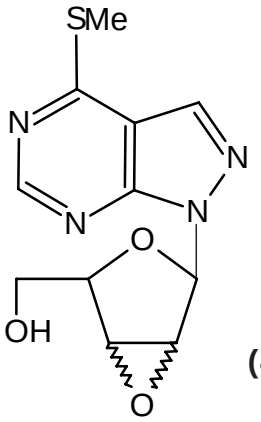
R=H, R_1=SMe, R_2,R_3=SH/SMe/OCH_3

Fusishita et al.,[252] have synthesized pyrazolo[3,4-d]pyrimidines **(44)** as angiotensin (II) antagonists.



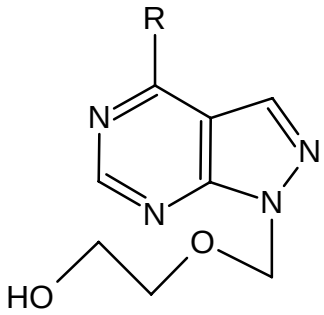
(44)

R. P. Tripathi et al.,[253] have synthesized 2',2'-anhydro nucleosides of pyrazolo[3,4-d]pyrimidines **(45)** as antiviral agents.



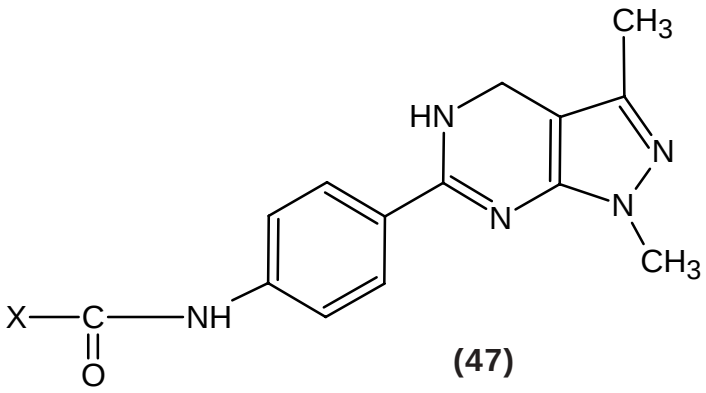
(45)

M.L. Taha et al.,[254] have synthesized 1-(2-hydroxy ethoxymethyl) pyrazolo[3,4-d]pyrimidines **(46)** as antiHIV agents.



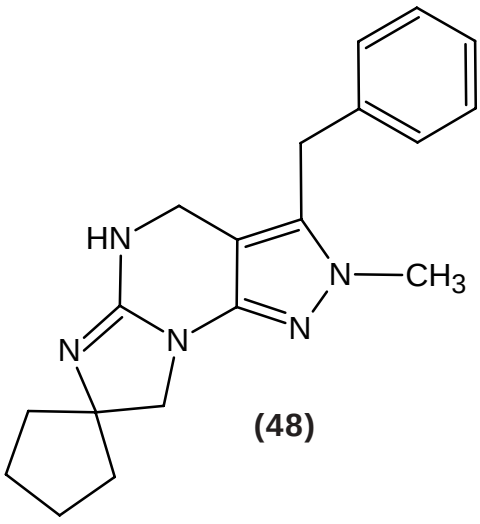
(46)

Oocta et al., [255] have prepared 1H-pyrazolo[]3,4-d]pyrimidines **(47)** as potent antihypertensive and cardiovascular agent.



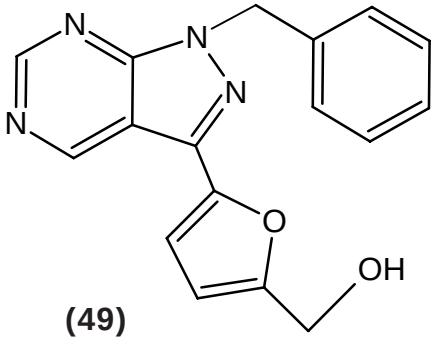
(47)

Y. Xia et al.,[256] have synthesized polycyclic pyrazolo[3,4-d]pyrimidines **(48)** and evaluated as PDE-1, PDE-5, CGMF-phosphodiesterase inhibitor. This compound was also good orally active antihypertensive in laboratory.



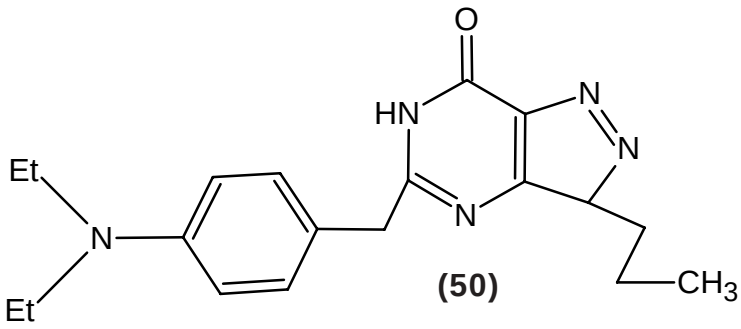
(48)

A. Straub et al.,[257] have synthesized pyrazolo[3,4-d]pyrimidines **(49)** with better cardiovascular agents.



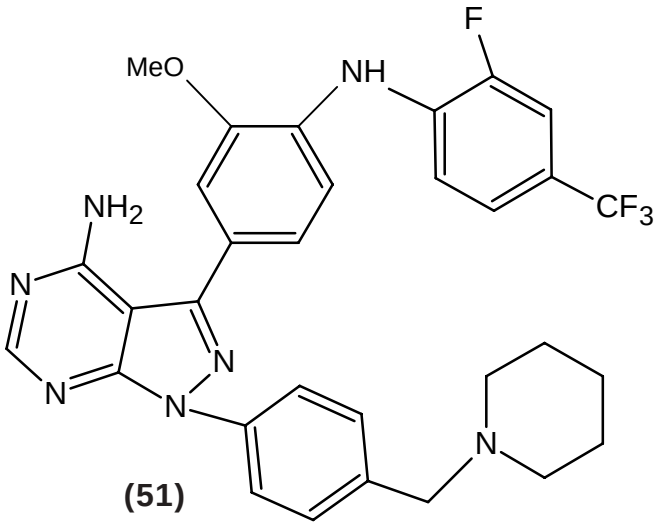
(49)

Recently, A.S. Bell et al.,[258] have prepared pyrazolo[3,4-d]pyrimidines **(50**) are useful for treatment of memory enhancement, hypertension, congestive heart failure and female sexual dysfunction.



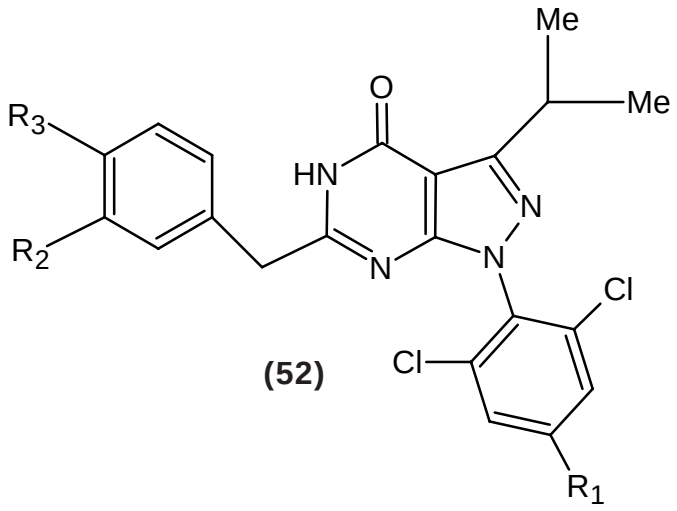
(50)

M. Friedman et al.,[259] have prepared 3-(azo hetero)aryl-1H- pyrazolo [3,4-d]pyrimidine-3-amines **(51)** as protein kinase inhibitors with antiangiogenic properties.



(51)

J. Markwalder et al.,[260] have synthesized 6-substitited pyrazolo[3,4-d] pyrimidin-4-ones **(52)** useful as cyclin dependent Kinase (cdk) inhibitors for treating cancer and proliferative diseases.



(52)

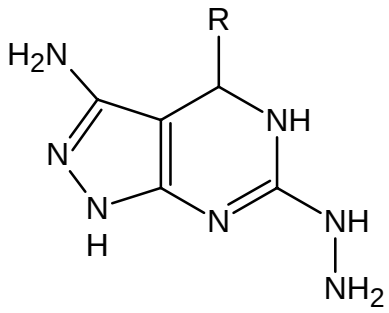
In view of procuring highly potent biodynamic agents and after reviewing literature survey on pyrazolo[3,4-d]pyrimidines for their various methods of synthesis and different pharmacological activities, synthesis of pyrazolo [3,4-d]pyrimidines have been undertaken which can be summarized in the following section as under.

SECTION - 1 : PREPARATION AND BIOLOGICAL EVALUATION OF 3-AMINO-4-ARYL-4,5-DIHYDRO-6-HYDRZINO-1H-PYRAZOLO[3,4-d] PYRIMIDINES.

SECTION - I

PREPARATION AND BIOLOGICAL EVALUATION OF 3-AMINO-4-ARYL-4,5-DIHYDRO-6-HYDRAZINO-1H-PYRAZOLO[3,4-d]PYRIMIDINES

In view of various biodynamic activities[214-260], other properties[199-213] of pyrazolo[3,4-d]pyrimidines and in order to have highly potent therapeutic agents, the synthesis of 3-amino-4-aryl-4,5-dihydro-6-hydrazino-1H-pyrazolo [3,4-d]pyrimidines (XII_{a-j}) have been undertaken by the condensation of 2-mercaptomethyl-4-amino-5-cyano-6-aryl-1,6-dihydro pyrimidines with hydrazine hydrate.

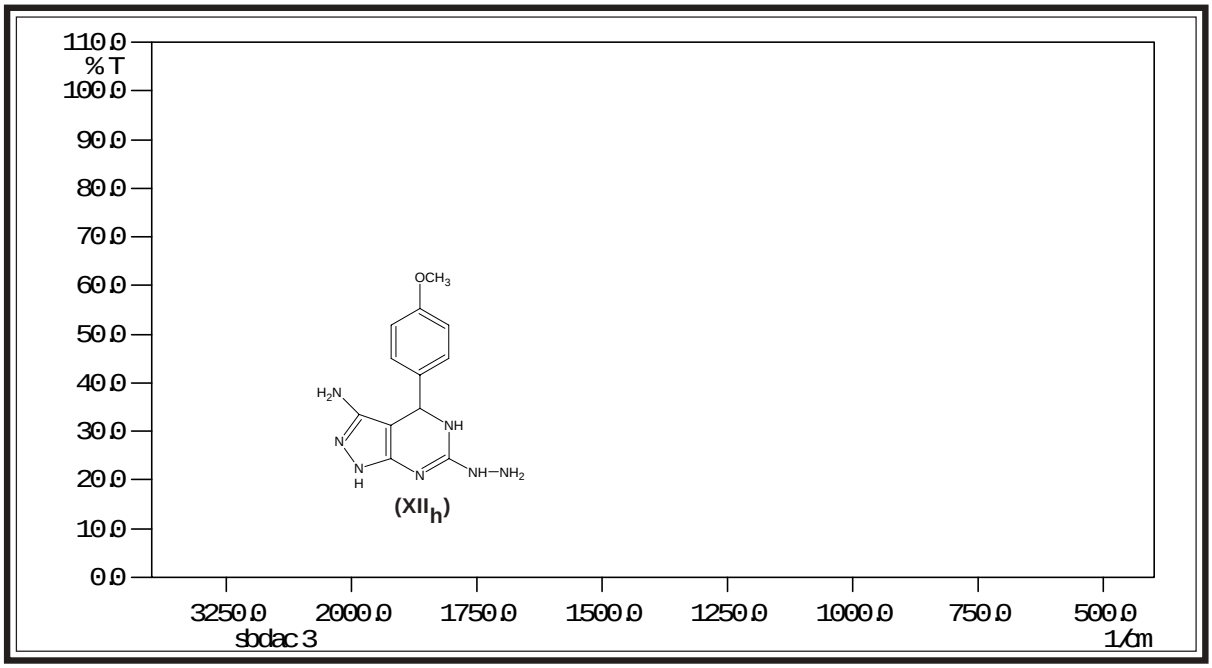


XII_{a-j} **R=Aryl**

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

The products (XII_{a-j}) were assayed for their *in vitro* biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

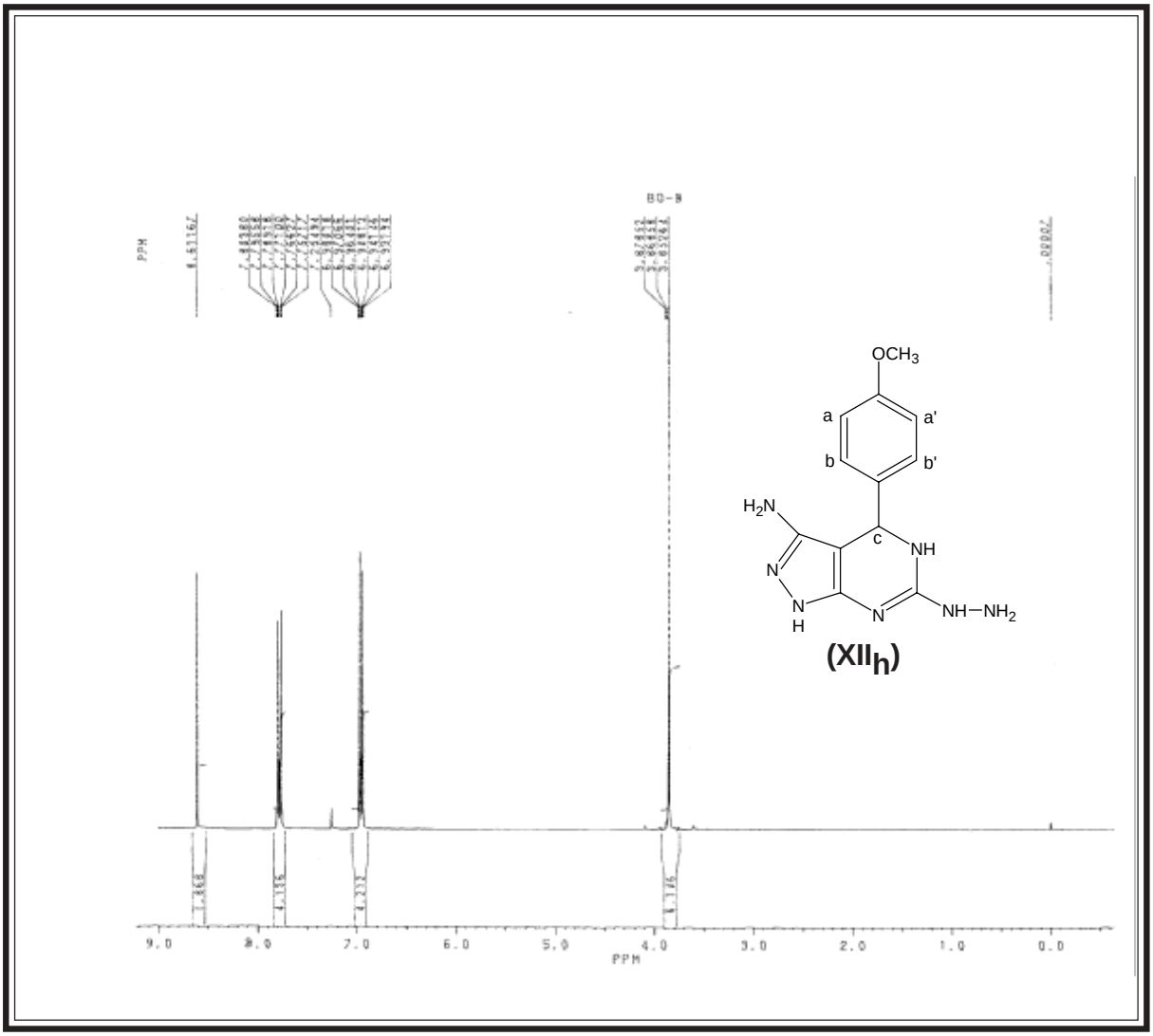
IR SPECTRAL STUDY OF 3-AMINO-4-(*p*-METHOXYPHENYL)-4,5-DIHYDRO-6-HYDRAZINO-1H-PYRAZOLO[3,4-d]PYRIMIDINE (XII_h)



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.(asym.)	2937.4	2975-2950	343
CH_3	C-H str.(sym.)	2858.3	2880-2860	,,
	C-H def.(asym.)	1444.6	1460-1435	,,
	C-H def.(sym.)	1352.0	1385-1300	,,
Aromatic and	C=C + C=N and ring	1568.0	1520-1480	345
Pyrimidine moiety	skeletal vibration	1406.0	1580-1520	,,
	C-H str.	3026.1	3080-3030	,,
	C-H i.p. def.	1083.9	1125-1090	,,
	C-H o.o.p. def.	823.5	840-810	,,
Ether	C-O-C str. (asym.)	1259.4	1275-1200	346
	C-O-C str. (sym.)	1010.6	1075-1050	,,
Amine (Primary)	N-H str.	3411.8	3500-3300	343
	N-H def.	1589.2	1650-1580	,,
Pyrazole	C=N str.	1589.2	1650-1580	344
	N-N str.	1627.8	1650-1580	,,
	C-N str.	1166.9	1220-1020	,,

PMR SPECTRAL STUDY OF 3-AMINO-4-(*p*-METHOXYPHENYL)-4,5-DIHYDRO-6-HYDRAZINO-1H-PYRAZOLO[3,4-d]PYRIMIDINE (XII_h)

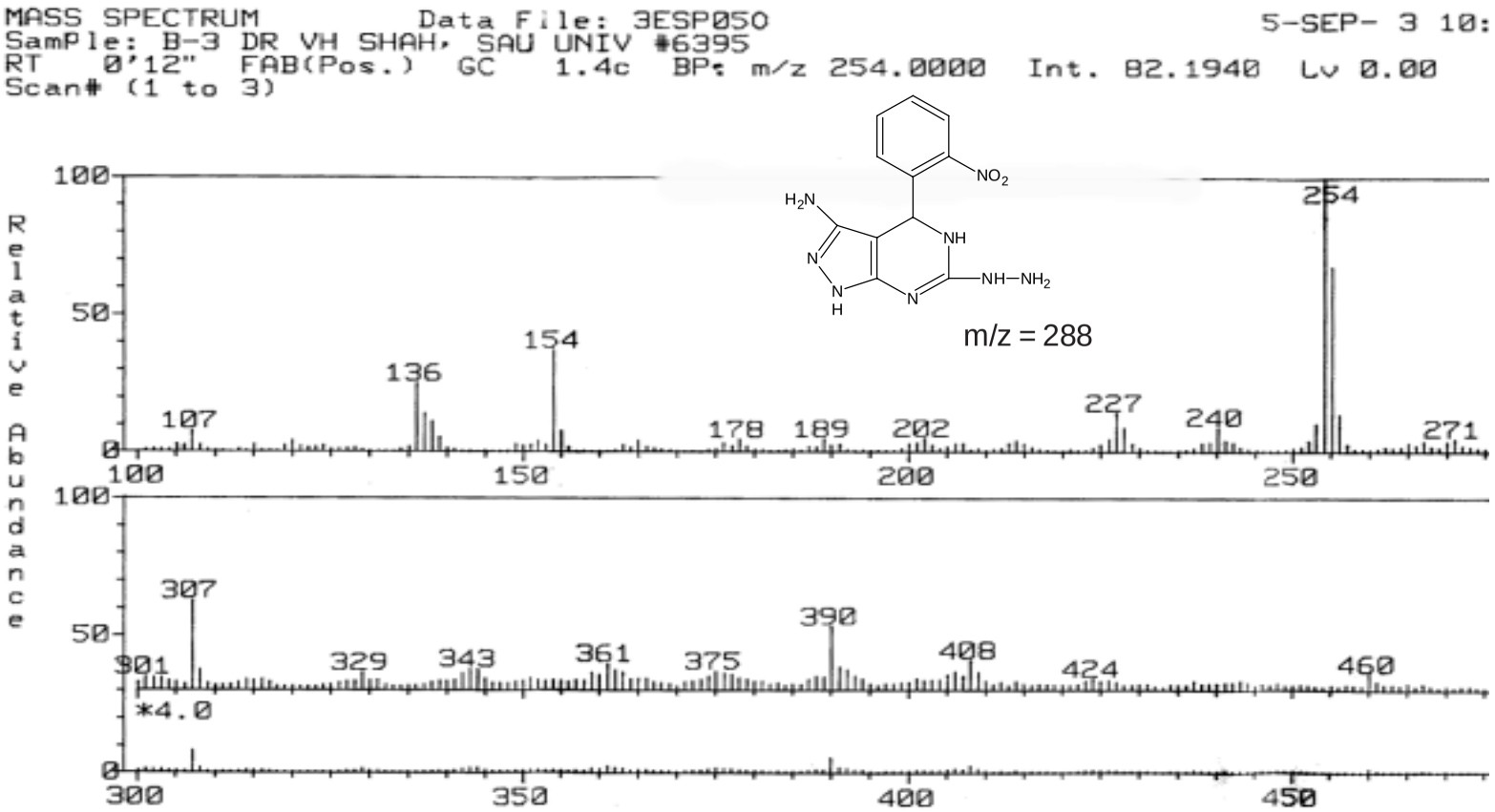


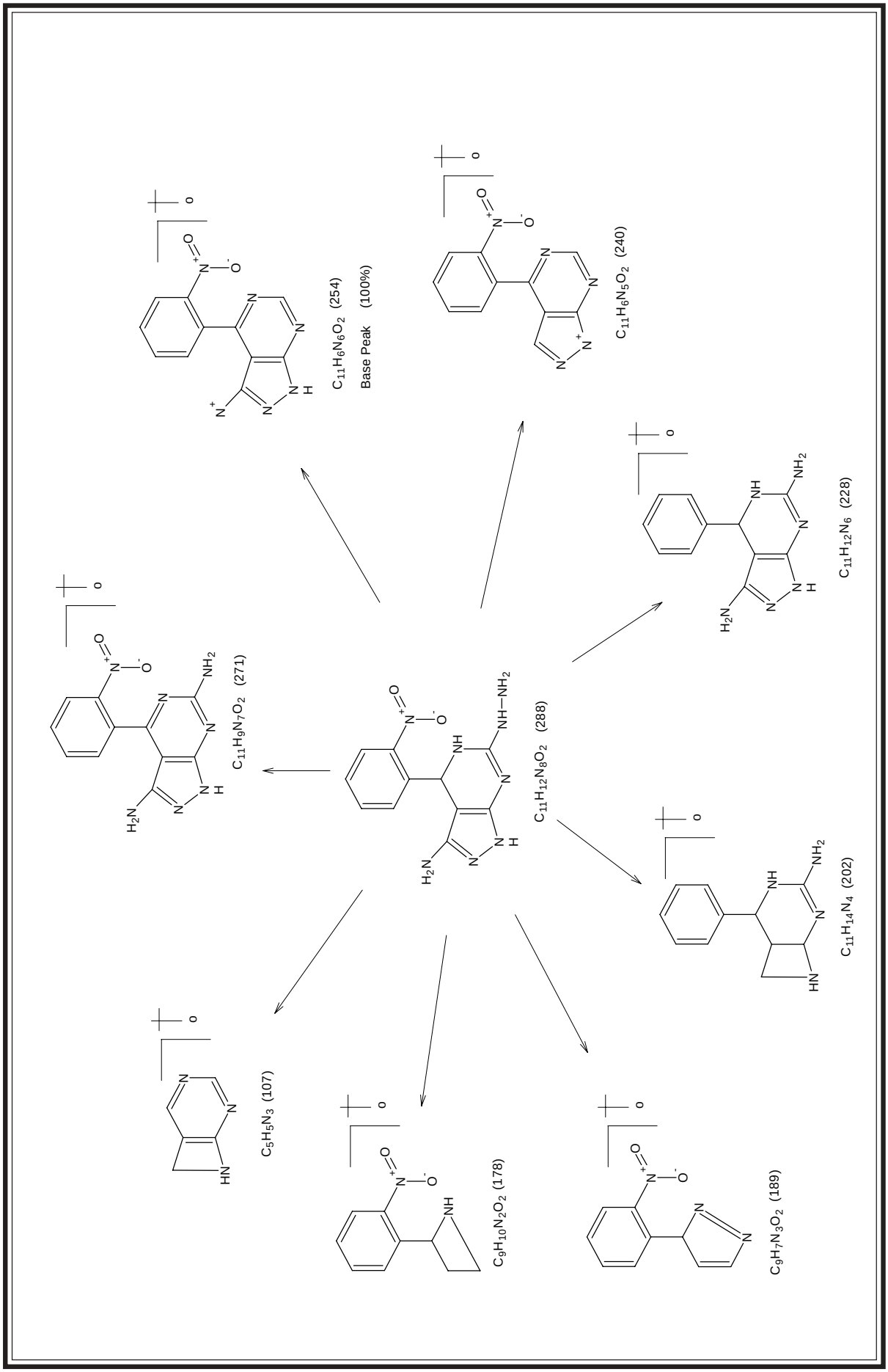
(XII_h)

Internal Standard : TMS ; Solvent ; $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

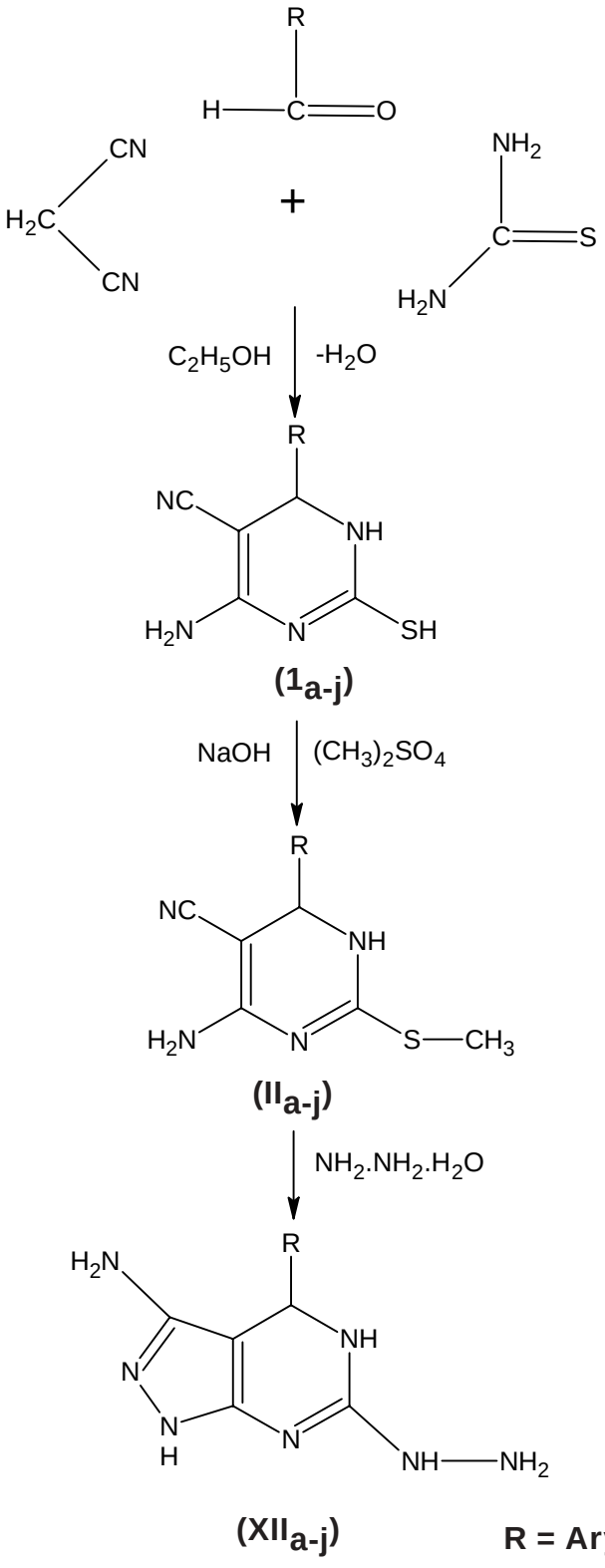
Signal No.	Signal Position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.853	3H	singlet	$-OCH_3$
2.	6.932-6.980	2H	doublet	Ar-$H_{a,a'}$ (J=8.76)
3.	7.757-7.804	2H	doublet	Ar-$H_{b,b'}$ (J=8.79)
4.	8.612	1H	singlet	Ar-H_c

MASS SPECTRAL OF 3-AMINO-4-(*o*-NITROPHENYL)-4,5-DIHYDRO-6-HYDRAZINO-1H-PYRAZOLO[3,4-d]PYRIMIDINE (XII_f)




C11H6N6O2 (254)
Base Peak (100%)
C11H6N5O2 (240)
C11H12N6 (228)
C11H9N7O2 (271)
C11H12N8O2 (288)
C11H14N4 (202)
C5H5N3 (107)
C9H10N2O2 (178)
C9H7N3O2 (189)

REACTION SCHEME



EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 3-AMINO-4-ARYL-4,5-DIHYDRO-6-HYDRAZINO-1H-PYRAZOLO[3,4-d]PYRIMIDINES

(A) Preparation of 2-Mercaptomethyl-4-amino-5-cyano-6-(*p*-methoxy phenyl)-1,6-dihydro pyrimidine (II_h).

For preparation refer Part-I, Section-II, Page No. 47.

(B) Preparation of 3-Amino-4-(*p*-methoxyphenyl)-4,5-dihydro-6-hydrazino-1H-pyrazolo[3,4-d]pyrimidine (XII_h).

A mixture of 2-mercaptomethyl-4-amino-5-cyano-6-(*p*-methoxyphenyl)-1,6-dihydro pyrimidine (2.74 gm, 0.01 M) and hydrazine hydrate (1.0 ml, 0.02M) in ethanol (30 ml) was heated under reflux condition for five hrs. The content was poured into ice cold water and filtered. The product was isolated and crystallized from ethanol. Yield : 62%, M.P. : 143°C, R_f : 0.63, (Required : C, 52.75%; H, 5.49%; N, 35.90% for $C_{12}H_{15}N_7O$, Found : C, 52.70%; H, 5.45%; N, 35.85%).

Similarly, other compounds (XII_{a-j}) were synthesized. The physical data are recorded in Table No. 15.

(C) Antimicrobial activity of 3-Amino-4-(*p*-methoxyphenyl)-4,5-dihydro -6-hydrazino-1H-pyrazolo[3,4-d]pyrimidines (XII_{a-j}).

Antimicrobial activity testing was carried out as described in part-1, section-I, page No. 35. The MIC values of test solution are recorded in Table No. 15a, 15b & 15c.

TABLE NO. 15 : PHYSICAL CONSTANTS OF 3-AMINO-4-ARYL-4,5-DIHYDRO-6-HYDRAZINO-1H-PYRAZOLO[3,4-d]PYRIMIDINES (XII_{a-j})

Comp. No. 1	R 2	Molecular Formula 3	M. W. 4	M.P. ^{o}C 5	Yield % 6	R_f Value 7	% of Nitrogen	
							Required 8	Found 9
XIIa	C_6H_5	$C_{11}H_{13}N_7$	243.0	128	65	0.62	40.33	40.30
XIIb	2-OH-C_6H_4	$C_{11}H_{13}N_7O$	259.0	153	58	0.58	37.84	37.80
XIIc	4-OH-C_6H_4	$C_{11}H_{13}N_7O$	259.0	>260	59	0.55	37.84	37.81
XIId	2-Cl-C_6H_4	$C_{11}H_{12}N_7Cl$	277.5	120	61	0.56	35.32	35.28
XIIe	4-Cl-C_6H_4	$C_{11}H_{12}N_7Cl$	277.5	170	63	0.54	35.32	35.27
XIIf	2-NO_2-C_6H_4	$C_{11}H_{12}N_8O_2$	288.0	192	66	0.61	38.89	38.82
XIIg	3-NO_2-C_6H_4	$C_{11}H_{12}N_8O_2$	288.0	>260	64	0.64	38.89	38.83
XIIh	4-CH_3O-C_6H_4	$C_{12}H_{15}N_7O$	273.0	143	62	0.63	35.90	35.85
XIIi	C_6H_5-CH=CH-	$C_{13}H_{15}N_7$	269.0	187	61	0.59	36.43	36.40
XIIj	$C_{14}H_9$	$C_{19}H_{17}N_7$	343.0	107	63	0.62	28.57	28.51

□ **TLC solvent system ; Ethyl acetate : Cyclohexane = 1 : 9**

TABLE NO. 15a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 3-AMINO-4-ARYL-4,5-DIHYDRO-6-HYDRAZINO-1H-PYRAZOLO[3,4-d]PYRIMIDINES XII_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442							S. aureus MTCC-96						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
XIIa	C_6H_5	-	-	12	12	13	13	14	-	-	13	14	16	16	16
XIIb	2-OH-C_6H_4	-	-	10	11	12	13	14	-	-	12	12	14	15	17
XIIc	4-OH-C_6H_4	-	-	11	11	12	14	14	-	-	13	13	14	15	16
XIId	2-Cl-C_6H_4	-	-	12	12	14	14	14	-	-	14	14	15	16	17
XIIe	4-Cl-C_6H_4	-	-	11	11	13	13	14	-	-	12	13	15	15	16
XIIf	2-NO_2-C_6H_4	-	-	10	10	12	12	13	-	-	12	12	14	15	17
XIIg	3-NO_2-C_6H_4	-	-	12	12	12	14	14	-	-	14	14	15	15	16
XIIh	4-OCH_3-C_6H_4	-	-	11	11	13	13	14	-	-	12	12	14	14	16
XIIi	-CH=CH-C_6H_4	-	-	12	12	12	13	13	-	-	13	13	14	15	15
XIIj	$C_{14}H_9$	-	-	10	10	12	13	14	-	-	12	12	14	15	15

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

Standard drug	Antibacterial activity														
											XIIb XIIg	XIIa XIId XIIg	XIIa		
Ampicillin	11	13	14	16	18	19	20	10	12	13	14	16	18	21
Chloramphenicol	10	12	13	19	20	20	22	12	13	14	19	20	21	22
Ciprofloxacin	16	18	19	21	21	22	22	17	18	19	21	22	22	23
Norfloxacin	18	18	19	20	21	21	23	19	20	22	25	26	28	28

N.B.(-): No Activity

TABLE NO. 15b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 3-AMINO-4-ARYL-4,5-DIHYDRO-6-HYDRAZINO-1H-PYRAZOLO[3,4-d]PYRIMIDINES XII_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) E. Coli MTCC-443							B. subtillis MTCC-441						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
XIIa	C_6H_5	-	-	14	15	17	17	18	-	-	16	17	18	19	19
XIIb	2-OH-C_6H_4	-	-	12	14	14	16	17	-	-	14	15	16	18	19
XIIc	4-OH-C_6H_4	-	-	15	16	16	18	18	-	-	16	17	17	18	19
XIId	2-Cl-C_6H_4	-	-	15	16	17	17	17	-	-	17	17	17	18	19
XIIe	4-Cl-C_6H_4	-	-	14	14	16	17	18	-	-	16	16	17	18	19
XIIf	2-NO_2-C_6H_4	-	-	13	14	15	17	18	-	-	15	15	17	18	18
XIIg	3-NO_2-C_6H_4	-	-	15	16	16	17	18	-	-	17	17	18	19	19
XIIh	4-OCH_3-C_6H_4	-	-	14	15	15	16	17	-	-	15	15	16	18	19
XIIi	-CH=CH-C_6H_4	-	-	15	16	16	18	18	-	-	16	16	17	17	19
XIIj	$C_{14}H_9$	-	-	13	14	15	17	17	-	-	15	15	17	17	18
Comparative activity of (XII_{a-j}) with known choosen standard drugs															
Standard drug		**Antibacterial activity**													
				XIIc XIId XIIg XIIi	XIIc XIId XIIg XIIi						XIId XIIg				
Ampicillin		14	14	15	16	19	20	22	12	16	18	19	20	21	23
Chloramphenicol		14	15	17	23	23	23	23	12	14	16	19	22	23	23
Ciprofloxacin		20	21	23	28	28	28	28	16	17	19	22	22	23	23
Norfloxacin		22	23	25	26	27	29	29	19	20	22	23	24	25	28

N.B.(-): No Activity

TABLE NO. 15c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 3-AMINO-4-ARYL-4,5-DIHYDRO-6-HYDRAZINO-1H-PYRAZOLO[3,4-d]PYRIMIDINES XII_{a-j} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antifungal activity (Zones of inhibition in mm) C. albicans MTCC-227							A. niger MTCC-282						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
XIIa	C_6H_5	-	-	18	19	20	20	21	-	-	19	20	21	22	24
XIIb	2-OH-C_6H_4	-	-	16	17	19	20	20	-	-	18	18	20	21	22
XIIc	4-OH-C_6H_4	-	-	17	18	19	20	22	-	-	19	19	21	21	24
XIId	2-Cl-C_6H_4	-	-	18	18	19	21	21	-	-	19	19	20	22	23
XIIe	4-Cl-C_6H_4	-	-	17	18	20	20	21	-	-	19	19	21	22	24
XIIf	2-NO_2-C_6H_4	-	-	17	18	20	20	21	-	-	18	18	21	22	23
XIIg	3-NO_2-C_6H_4	-	-	18	19	20	20	21	-	-	19	20	21	21	23
XIIh	4-OCH_3-C_6H_4	-	-	17	17	19	20	21	-	-	18	19	20	22	24
XIIi	-CH=CH-C_6H_4	-	-	18	18	19	20	21	-	-	19	19	21	22	23
XIIj	$C_{14}H_9$	-	-	17	18	19	20	20	-	-	18	19	20	21	22
Comparative activity of (XII_{a-j}) with known choosen standard drugs															
Standard drug		**Antifungal activity**													
Griseofulvin		19	22	23	25	25	28	28	18	19	21	22	22	24	26

N.B.(-): No Activity

REFERENCES

199. Romco Justoni, Raffaello, *Fusco Ibid.,* 59-76, *Chem. Abstr.,* **32,** 62449 (1938).

200. Homer A. Bureh; *J. med. Chem*. **11,** 81-83 (1968).

201. Clarke, Anthony Graham R. (Delmar chemical Ltd.) *Brit* **1,** 284, 084 (Cl. C07d, A61k) 02 Aug 1972, *Appl* 19, 684/69, 17 Mar 1969, 9 pp. *Chem. Abstr.,* **77,** 152213f (1972).

202. Keitaro Senga, Yukako Kanamori, Hashine Kanazawa; *J. Het. Chem*. **15,** 359 (1978).

203. Sadao Nishigaki, Misuzu Ichiba, Kiyoko Fukami; *J. Het. Chem*., **19,** 769 (1982).

204. Peter Scheiner, Sara arwin, Manes Eliacin, James Tu (USA); *J. Het. Chem.,* **22,** 1435 (1985).

205. Das, Prabhat K., Behera, G.B.; Sahay, A.K.; *Ind. J. Chem*. 1985, **24B (4),** 437-39, (Eng). *Chem. Abstr*. **104,** 148823g (1985).

206. L. Dee Nord, Ganapathi. R. Revankar, Roland K. Robins (USA), *J. Het*. *Chem*. **27,** 439 (1990).

207. Samira A. Swelam, Osama I. Abdel Salam anel magdi E.A. Zaki, *Ind. J. Het*. *Chem*., **8,** 257-62 (1999.)

208. C.J. Shishoo, T. Ravikumar, K.S. Jain, I.S. Rathod, T.P. Gandhi, M.C. Satia, *Ind. J. Chem*., **38B,** 1075-85 (1999)

209. S.D. Nakum; V.H. Shah; *J. Inst. Chemist (India);* **Vol.73,** Part-3, pg. 125(2002). *Chem. Abstr*. **137,** 63220q (2002).

210. S B S Biotech Corp*. Jpn. Kokai Tokkyo Koho* **Jp 60,** 100, 581 (Cl. C07D487/04), 04 Jun 1985, Appl. 831207, 583, 07Nov. 1983; 17pp *Chem. Abstr.,* **103,** 10534a (1985).

211. Finlander, Peter; Nielsen, Soeren, V; Pedersen, *Erik* B.; *Chem. Scr*. 1983, **22(4),** 1716 (Eng). *Chem. Abstr.,* **100,** 34489q (1984).

212. Benoit, Remy; Grote Thomas; Bayer, Herbert (BASF A.-G.) *PCT Int. Appl* **WO 96,** 35, 690 (Cl. C07D 487/04) 14 Nov. 1996, **DE** *Appl*. **19,** 602, 072, 20 Jan 1996; 115 pp. (Eng) *Chem. Abstr*., **126,** 59966t (1997)

213. Doming, Beryl In. (*Pfi 3er Inc*.) can 1, 007, 229 (Cl. 260-242.2), 22 Mar. 1977, Appl. 193, 855, 01 Mar 1974, 22pp. *Chem. Abstr*., **87,** 53367c (1977).

214. Hitchings, George H.; Talco, Elvira A. (Burroughs. Wellcome and Co.) *U.S*. **3,** 519, 716 (Cl. 424-251; A 61K), 07 Jul 1970, *Brit, Appl*. 23 May 1962-23 Aug 1962, 2pp. *Chem. Abstr*., **73,** 98991a (1970).

215. Podesva, Citral; Musil, Vaclav; Scott, William; (Delmar Chemical Ltd.) *Ger*. *Offen.* **2,** 018, 345 (Cl. Co7d), 19 Nov. 1970, *Brit. Appl*. 17 Apr. 1969; 35 pp. *Chem. Abstr*. **74,** 22888q (1971).

216. Kranf, Eckart; Bock, Marianne; (Farbenfabriken Bayer, A-G.). *Ger. Offen.* **2,** 058, 500 (Cl.C07d) 31 May 1972, *Chem. Abstr*., **77,** 88523w (1972)

217. Bruener, Hermann; Schulze, Ernst: Treuner, Uwe, (Chemisclie Fabrik Vonugden, A.-G.) *Ger. Offen*. **2,** 136, 950 (Cl. Co7d). *Chem. Abstr.,* **76,** 140860f (1972).

218. Howarth, Grahum; Gainer, James; (Ciba Geigry A.-G.). *Ger. Offen*. **2,** 218, 717 (Cl. C07D) 16 Nov. 1972, *Brit. Appl*. 11, 492, 171, 27 Apr 1971; 48 pp. *Chem*. *Abstr.,* **78,** 43514y (1973).

219. Griengl, H.; Guenfl, F. (Austrica); *J. Het. Chem*. **21(2),** 505- (1984)

220. Lion Corp; *Jpn Kokai Tokkyo. Koho* **Jp 58,** 208, 293 (83, 208, 293) (Cl. C07D 487/04), *Chem. Abstr*., **100,** 139140x (195).

221. Hayashi, Eisaku; Higashine, Takeo; Sufuki, Shinichi (Lion- Dentifrice Co.) *Jpn. Kokai Tokkyo Koho* **17,** 127, 493, (Cl. C07D 487/04) 07 Nov. 1978, Appl. 77/42, 434 9 pp. *Chem. Abstr*., **90,** 121632f (1979).

222. Shibutani, Naotaka, Koji, Yasuo; Okamura Takashi, (Otsuka Pharm. Co. Ltd. Japan) *Jpn. Kokai Tokkyo Koho* **Jp 10,** 237, 074 (98, 237, 074) (Cl. C07D 487/04). *Chem. Abstr*., **129,** 260469p (1998).

223. Inoue, Makoto; Okamura, Takashi; Shoji Yasuo; Hashimoto Kinji (Otsuka Pharm. Factory Inc. Japan), *PCT Int. Appl.* **WO 96,** 32, 394 (Cl. CO7D 487/04), 17 Oct. 1996, **Jp** *Appl.* **95,** 236, 427, 14 Sep. 1995 ; 61 pp. *Chem. Abstr.,* **126,** 18885x (1997).

224. Granik, V.G., Sochneva, E.O., Soloneva, N.P., Shvarts, G. Ya., Sjubaw, R.D., Mashkovskii, M.D., (USSR) *Khim. Farm. Zn.* 1980, **14(6),** 36-40 (Russ), *Chem. Abstr.,* **93,** 220653 (1980).

225. Treuner, Uwe D., Breuer, Hermann, *U.S.* **4,** 124, 764 (Cl. 544-251; A61K 31/505), 07 Nov. 1978, *Appl.* 678, 832, 21 Apr. 1976, 5 pp., *Chem. Abstr.,* **90,** 87508b (1979).

226. Furukawa, Yoshiyasu, Maki, Yoshitaka, *Eur. Pat. Appl.* **Ep.** 166, 054 (Cl. C07D 487/04), *Chem. Abstr.,* **105,** 60525e (1986).

227. Kreutzberger, Alfred; Burgcuitz, Klemens (Berlin), *Arch. Pharm. (Weinheim, Ger.)* 1983, 313(**11**), *Chem. Abstr.,* **94,** 139746g (1981).

228. Senga, Keitaro, Robins, Roland K.; *J. Het. Chem.* **19(6)**, 1567-7, 1982; *Chem. Abstr.,* **98,** 160667z (1983).

229. Shaw, Gorden; Lees, Peter; *Ger. Offen* **1,** 814, 082 (Cl. CO7D), 25 Jul. 1970, *Appl.* 11 Dec. 1968; 21 pp., *Chem. Abstr.,* **73,** 66626x (1970).

230. Schwartz, Pauline M. ; Dunigan, Janis M. ; Maroh, John C. ; Handschumacher, Robert E. (USA), *Cancer Res.* 1980, **40(6)**, 1885-9 (Eng.); *Chem. Abstr.,* **93**, 88657y (1980).

231. Yoshinori Tominaga, Yasumasa Honkawa, Mayumi Hara, Akira Hosomi, Olagasaki, (Japan), *J. Het. Chem.*, **27,** 765 (1990).

232. J. Sudhakar, Rao; Ojwang, Joshua O.; Marshall, Helene B.; Revankar, Ganapathi R.; *J. Het. Chem.,* **34(1),** 257-62 (1997).

233. Lak S. Jeong, J. Warren Beach, Chung K. Chu; *J. Het. Chem.,* **30,** 1445 (1993).

234. Dusza, John P. ; Albright, Jay D.; *U.S.* **4,** 281, 000 (Cl. 424-251; A61K31/505), 28 Jul 1981, *App.* 55, 941, 09 Jul 1974; 12 pp. *Chem. Abstr.,* **95,** 187293z (1981).

235. Regnier, Gilbert; Canevari, Roger; Poignunt, Jean Claude (Science Union et Cie – Societe – Francaise de Recherche Medicale), *Ger. Offen.* **2,** 651, 789, *Chem. Abstr.,* **87,** 168097g (1977).

236. Boyer, Serge H.; Erion, Mark D.; Ugarkar, Bheemarao G.;(Gensia Inc. USA), *U.S.* **US 5,** 674, 998 (Cl. 538-27. 13 ; C07H19/044), *Chem. Abstr.,* **127,** 293561z (1998).

237. Y.S. Prabhakar, V.J. Ram; *Ind. J. Pharm. Sci.,* **59(6),** 286-91 (1997).

238. Ram Vishnu J.; Haque (Med. Chem. Div. Central drug research Inst. Lucknow, India), *Ind. J. Chem. Sec-B, Org. Chem. Incl. Med. Chem.,* **34B(6),** 521-9, 1995 ; *Chem. Abstr.,* **123,** 256664g (1995).

239. Hasan, A.; Tripathi, R.P.; Pratap, Ram; Bhakuni, D.S.; Pal R.; Mishra A.; Guru P.Y.; *Ind. J. Chem.* **28B (5),** 1989, 403-9 (Eng); *Chem. Abstr.,* **112,** 56530a (1990).

240. Shibutani, Naotaka; Koji, Yasuo; (Otsuka Pharmaceutical Co. Ltd. Japan), *Jpn. Kokai Tokkyo Koho* **Jp 10,** 273, 074 [98 237, 074] (Cl. C07D 487/04); *Chem. Abstr.,* **129,** 1260469p (1998).

241. Breuer, Hermann; Schulze, Ernst, (Chemische Fabrik Von Heyden A.-G.), *Ger. Offen.* **2,** 140, 986 (Cl. C07d), 09 Mar. 1972, *US Appl.* **69,** 172, 02 Sep. 1970 ; 15 pp., *Chem. Abstr.,* **77,** 34565t (1972).

242. Hoyle, William; Howarth Graham A.; Gainer, James (Ciba Geigy A.-.G..) *Swiss*, 545, 315 (Cl. C07d), 31 Jan. 1974, *Appl.* 14, 968/70, 12 Oct. 1970; 3 pp, *Chem. Abstr.,* **81,** 25693p (1973).

243. Broughton, Barbara J.; Large, Bryan J.; Marshall, Stuart Malcolm; *Ger. Offen.* **2,** 428, 486 (Cl. C07d), 09 Jan. 1975; *Brit. Appl.* **27,** 920/73, 12 Jun. 1973; 34 pp., *Chem. Abstr.,* **82,** 171076b (1975).

244. Wellcome Foundation Ltd., *Jpn. Kokai Tokkyo Koho* **Jp 79,** 22, 393 (Cl. C07D 487/04), 20 Feb. 1979, *Brit. Appl.* 7/30, 380, 20 Jul. 1977; 21 pp. *Chem. Abstr.,* **90,** 204158a (1979).

245. Ege, Guenter; Pross, Michael; *Ger. Offen.* **DE 4,** 333, 705 (Cl. C07D 487/04) 06 Apr. 1995, *Appl.* 02 Oct. 1993 ; 11 pp, *Chem. Abstr.,* **123,** 33098z (1995).

246. Richard J. Goebel, Alexander D. Adams, Patricia A.; *J. Med. Chem.,* **25,** 1334 (1982).

247. Takamizawa, Akira (Shionogi and Co. Ltd.) Japan 71 31, 228 (Cl. C07c, A61K), 10 Sep. 1971, *Appl.* 27 Jan. 1967; 2pp, *Chem. Abstr.,* **76,** 3887z (1972).

248. Robert Fuerst, Carolyn E. Somers, T.C. Hsu (Univ. of Texas, Houston), *J. Bacteriol.,* 72, 387-93 (1956); *Chem. Abstr.,* **50,** 16974c (1956).

249. Howard E. Skipper, Roland K. Robino, J. Richard Thomson, (Kettering-Meyer Lab., Bir mingham, Ala), *Proc. Soc. Exptl. Bio. Med.* **89,** 549-6 (1955); *Chem. Abstr.,* **50,** 483b (1956).

250. Machon, Zdzislaw; (Inst. Chem. Technol. Drugs, Med. Acad., Wroclaw, Pol.), *Pol. J. Pharmacol. Pharm.,* 1976, **28(5),** 511-20 (Eng.), *Chem. Abstr.,* **87,** 5906f (1977).

251. Dobrynin, Ya; Bektemirov, T.A.; Ivanova, T.P.; Chekunova, E.V.; Andzhaparidze, O.G.; (USSR) *Khim. Farm. Zn.* 1980, **14(5),** 10-15 (Russ), *Chem. Abstr.,* **93,** 88460d (1979).

252. Fusishita, Toshio; Kyama, Ryuichi; Fujimoto, Masabumi, Hara, Mariko; *Jpn. Kokai Tokkyo Koho* **Jp 06,** 329, 616 [94 329, 676] (Cl. C07D 487/04), 29 Nov. 1994, *JP Appl.* 93/62, 207, 22 Mar. 1993; 8 pp, *Chem. Abstr.,* **122,** 214095a (1995).

253. Tripathi, R.P.; Mishra, Anil; Pratap, Ram; Bhakuni, D.S. (Medicinal Chem. Div., C.D.R.I., Lucknow, India); *Ind. J. Chem. Sec-B Org. Chem. Incl. Med. Chem.,* 1996, **35B (5),** 441-5 (Eng.), *Chem. Abstr.,* **125,** 34025b (1996).

254. Taha, M.L.; Lazrek, H.B.; Barascut, J.L.; Imbach, J.L. (Laboratoriese Chimie Bio-organique, Univ. Ibnou Zohr. Fr.), *Bull. Soc. Chim. Belg.,* 1996, **105 (5),** 279-285 (Eng.), *Chem. Abstr.,* **125,** 248292k (1996).

255. Oota, Tomoki; Taguchi, Minoru; Kawashima, Yutaka; Hatayama (Taisho Pharmaceutical Co. Ltd. Japan) (Cl. C07D 487/04), 10 Oct. 1996, **Jp 95,** 16, 986, 20 Jan. 1995; 13 pp , *Chem. Abstr.,* **126,** 31225b (1997).

256. Xia, Yan; Chackalamannil, Samuel; Hsinejan; *J. Med. Chem.* 1997, **40 (26),** 4372-4377 (Eng.); *Chem. Abstr.,* **128,** 127977r (1998).

257. Straub, Alexander; Robyr, Chemta; Jaetsch, Thomas; Feurer, Achim (Bayer A.-G., Germany), *Ger. Offen.* **DE 19,** 649, 460 (Cl. C07D 484/4) 28 May 1998, Appl. **19,** 649, 460, 26 Nov. 1996; 14 pp, *(Ger.) Chem. Abstr.,* **129,** 27956k (1998).

258. Bell, Andrew Simon; Terrett, Nicholas Kenneth; *Eur. Pat. Appl.* **Ep** 911, 333 (Cl. C07D 487/04); *Chem. Abstr.,* **130,** 73574c (1999).

259. Friedman, Michael M; Arnold, Lee D; Hirst, Gavin C; *(Abboh G.m.b.h. & Co. KG, Germany) PCT Int. Appl.* **WO 02,** 76, 986 (Cl. CO7D 487/04), 3 Oct. 2002, *Chem. Abstr.,* **137,** 263056c (2002).

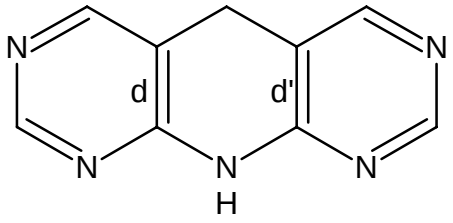
260. J. Markwalder; S. Seitz; S. Sherk; *(Bristol-Mayers Squibb Pharma Company, USA) PCT Int. Appl.* **WO 03,** 63,764 (Cl. A61K), 7Aug. 2003, *Chem. Abstr.,* **139,** 164800a (2003).

(B)
STUDIES ON PYRIDO[2,3-d : 6,5-d’] DIPYRIMIDINES

[B] STUDIES ON PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINES

INTRODUCTION

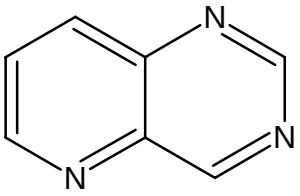
Pyrido[2,3-d : 6,5-d']dipyrimidine **(53)** is a fused heterocyclic compound in which two pyrimidines with their d-position are fused at 2,3 and 6,5 positions of pyridine ring system.



(53)

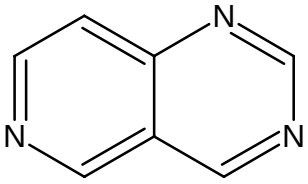
Pyrido[2,3-d : 6,5-d']dipyrimidine

K.R. Roland et al.,[261] have synthesized 4 and 2,4-disubstituted pyrido [2,3-d]pyrimidines in 1959. There are other three possible isomers of pyrido pyrimidines which are fused at different position and four isomers represented under.



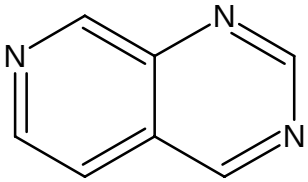
(54)

Pyrido[3,2-d]pyrimidine



(55)

Pyrido[4,3-d]pyrimidine



(56)

Pyrido[3,4-d]pyrimidine

SYNTHETIC ASPECTS

Extensive studies have been made in the field of synthesis of pyrido [2,3-d]pyrimidines, Various methods have been reported in the literature which can be described as under.

(a) By the cyclocondensation of pyrimidine carboxaldehyde with N-substituted 2-cyano acetamide[262].

(b) By the cyclocondensation of 4-amino pyrimidine with ethoxydiethyl methylene malonate led to the formation of 5-oxo-2-(4/3-pyrimidinyl) pyrido[2,3-d]pyrimidine-6-carboxyllic acid[263].

(c) By the reaction of 2-(*m*-nitroaniline)-3-carbethoxy pyridine with N-carb ethoxyaminomethane led to formation of pyridopyrimidinediones[264].

(d) By the cyclocondensation of 2-pyrido thione derivatives with benzoyliso thiocyanate or malononitrile led to the formation of pyrido[2,3-d] pyrimidine[265].

(e) By the cyclocondensation of 2-amino-pyridine-3-carboxyllic acid with urea led to formation of 2,4-dioxo pyrido[2,3-d]pyrimidines[266].

(f) By the hydrolysis of 2-amino-3-cyano-4,6-disubstituted pyridines to 2-amino-3-carboxamido-4,6-disubstituted pyridines followed by the treatment with aryl isocyanate led to the formation of 3,5,7-tri substituted pyrido[2,3-d]pyrimidines[267].

(g) By the cyclization of 3-cyano-1,4-dimethyl-5-ureidomethylene-1H,5H-pyridin-2,6-dione in presence of phosphorous pentoxide led to formation of pyrido[2,3-d]pyrimidines[268].

(h) By the condensation of 4-amino-2-methoxypyrimidine-5-carboxaldehyde with diethyl malonate led to the formation of pyrido[2,3-d]pyrimidines[269].

(i) By the cyclocondensation of 6-amino-2-methoxy-3,4-dihydro-4-pyrimidine with arylidene derivatives of malononitrile led to the formation of pyrido [2,3-d]pyrimidines[270].

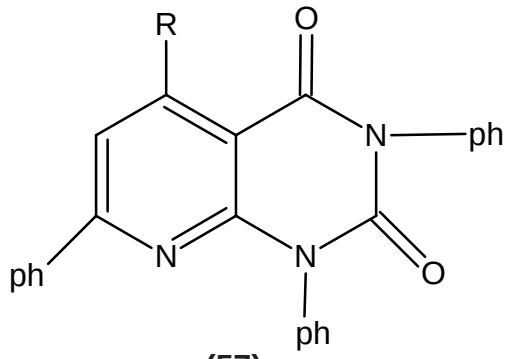
(j) By the reaction of 5-formyl-4-amino-2-oxopyrimidine with ethylcyano acetate led to formation of pyrido[2,3-d]pyrimidines[271].

(k) By the cyclocondensation reaction of aromatic aldehyde with 2 moles of thiobarbituric acid and aromatic amines[272].

(l) By the cyclocondensation reaction of 6-[(dimethylamino)methylene]-amino-1,3-dimethyluracil and Benzalacetone led to formation of pyrido[2,3-d] pyrimidines[273].

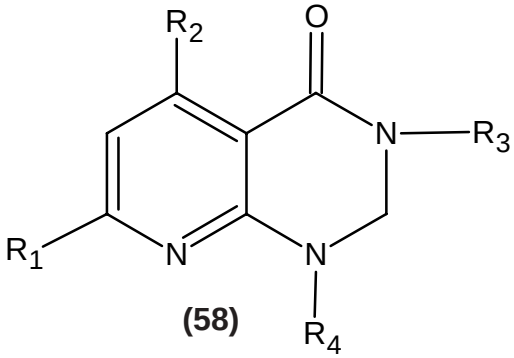
(m) By the reaction of 1,3-diaryl-2-thiobarbituricacid with thiophene-2-carbaldehyde and aniline led to formation of pyrido[2,3-d]pyrimidines[274].

Pyrido[2,3-d]pyrimidine have been found to possess remarkable insecticidal[275] **(57)** and herbicidal[276] **(58)** activities.



(57)

R=4-Cl-C_6H_4 / 4-CH_3-C_6H_4



(58)

R_1=sub. phenyl, R_2=H, R_3=H, R_4=H / Alkyl

Pyrido[2,3-d]pyrimidine derivatives from a class of fused heterocyclic compound which have interesting pharmacological and biological activities, particularly the oxo and amino derivatives of pyrido[2,3-d]pyrimidines standout for their antitumor[277] and antiviral[278] activities.

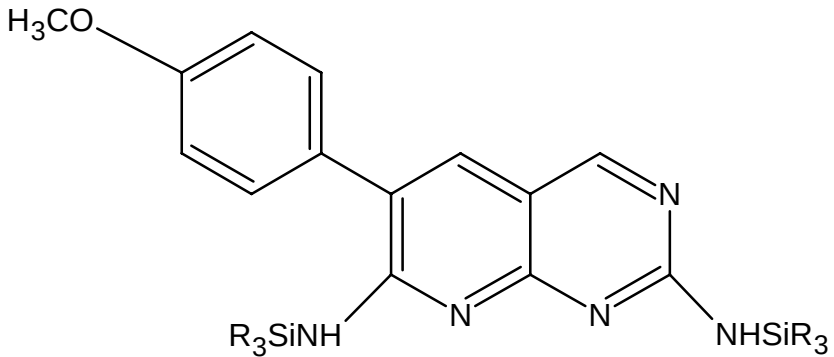
BILOGICAL IMPORTANCE

The extensive use of pyrido[2,3-d : 6,5-d']dipyrimidines in medicine is due to its vast biological activities, which are summarized as below.

(a) Antibacterial[279-284]
(b) Anticancer[285,286]
(c) Diuretic[287-291]
(d) Anticonvulsant[292-294]
(e) Antitumor[295-301]
(f) Antiallergic agent[302,303]
(g) Antiphlogistic[304]
(h) CNS depressant[305-311]
(i) Antitussive[312]
(j) Coronary vasodilator[313]
(k) Antihypertensive[314-316]
(l) Antiarrythmic agent[317]
(m) Immunossuppressing agent[318]

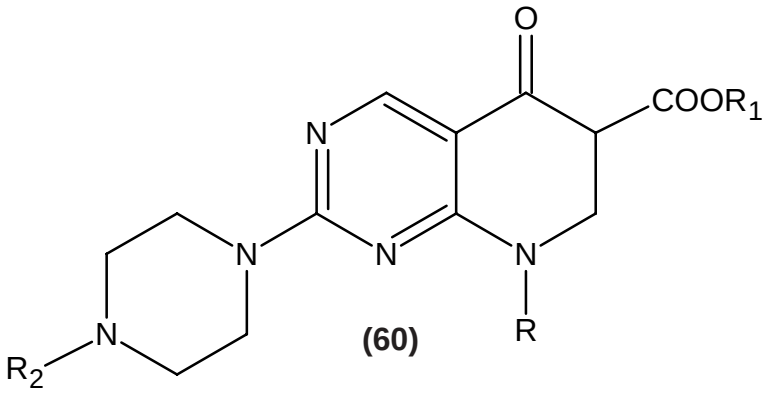
(n) Antispasmodic[319]
(o) Cardiovascular[320]
(p) Antiepileptic[321,322]
(q) Antiprotoxoal[323]
(r) Anxiolyticagent[324,325]
(s) Antiasthamintics[326]
(t) Antitubercular[327]
(u) AntiHIV[328,329]

R.F. Meyer et al.,[330] have synthesized 6-aryl-2,7-bis[(trialkylsilyl)amino] pyrido[2,3-d]pyrimidines **(59)** and were administered orally to fasting rats at 2 mg/kg and 20 mg/kg and was effective as diuretic.

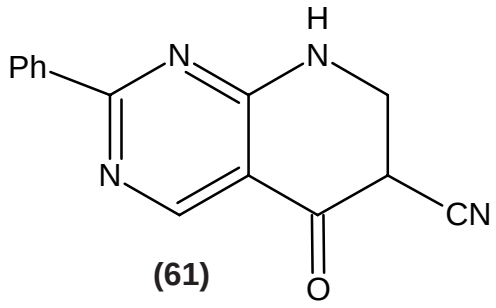


(59)

S. Minami et al.,[331] have synthesized pyrido[2,3-d]pyrimidines **(60)** and tested for antibacterial ED50 i.p. in mice against *pseudomonas aurigenous* 6.3 gm and *salmonella typhimurium* 15.5 mg/kg and an i.v. LD50>500 mg.kg. A. Santilli et al.,[332] have synthesized 5,6,7,8-tetrahydro-5-oxo-pyrido [2,3-d]pyrimidines-6-carbonitrile **(61)** and tested as central nervous system depressants in mice at 12.7 to 40mg/kg i.p.

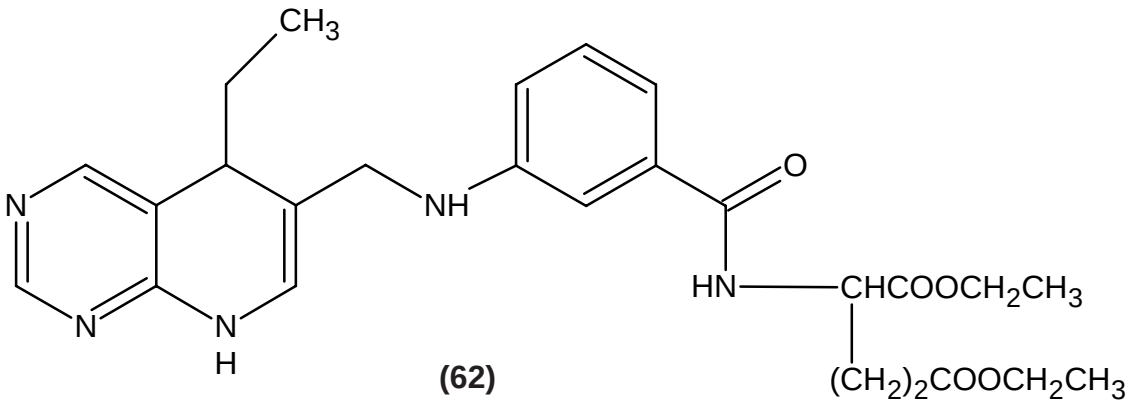


(60)



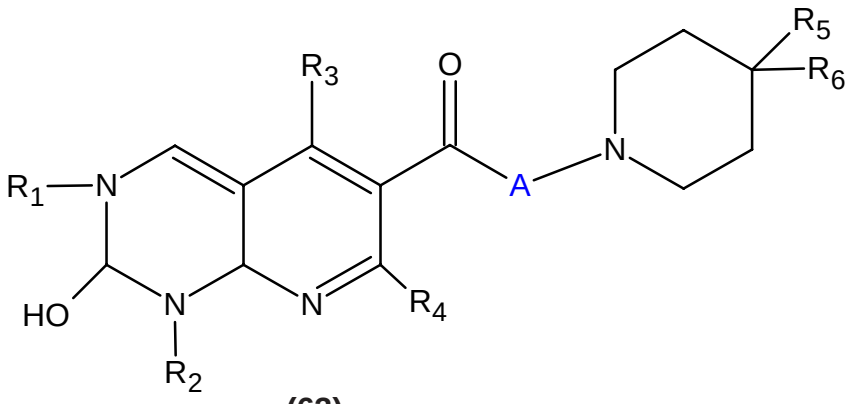
(61)

R.P. James et al.,[333] have synthesized pyrido[2,3-d]pyrimidines **(62)** as greater antifolate selectivity for antitumor over normal proliferative tissue.

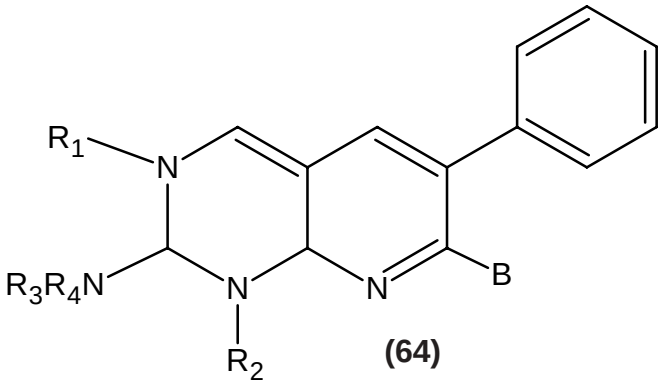


(62)

T. Bear et al.,[334] have synthesized pyrido[2,3-d]pyrimidines **(63)** as potent antitumor agent. C.J. Blankyel et al.,[335] have synthesized 6-aryl-pyrido [2,3-d]pyrimidines **(64)** and found useful as inhibitors of protein tyrosine kinase and thus useful in treating atherosclerosis, restenosis, psoriasis as well as bacterial infection.



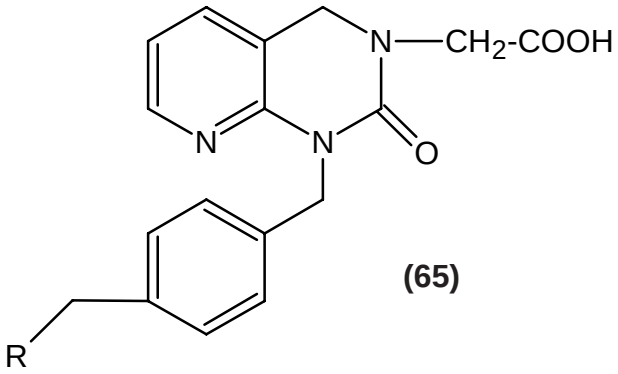
(63)



(64)

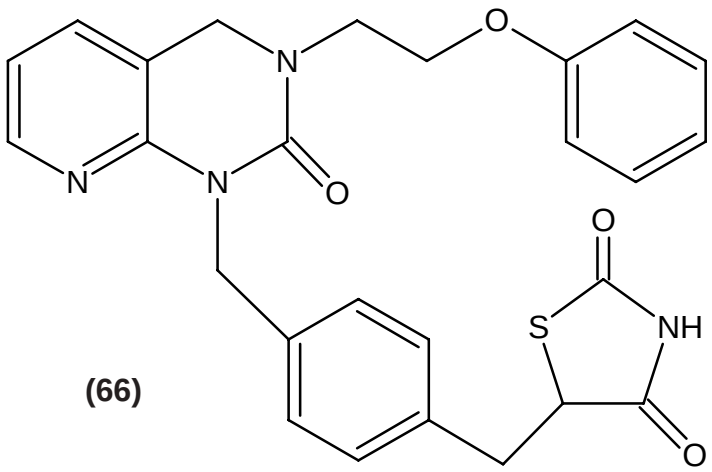
R_1, R_2, NR_3R_4 = H / C_{1-8}alkyl / C_{2-8}alkyl;
B = Halogen

H. Sato et al.,[336] have synthesized pyrido[2.3-d]pyrimidines **(65)** as aldose reducatase inhibitors.



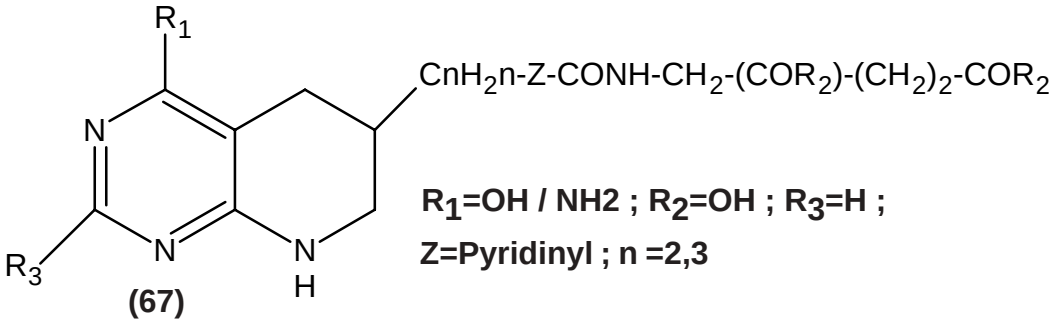
(65)

Y. Yonezawa et al.,[337] have synthesized pyrido[2,3-d]pyrimidines **(66)** as hypoglycemics and aldose reductase inhibitors.



(66)

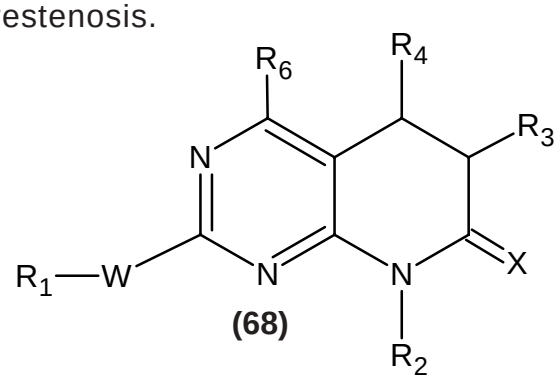
E.C. Tyloret al.,[338] have synthesized glutamic acid 5,6,7,8-tetrahydro pyrido[2,3-d]pyrimidines **(67)** as antineoplastic agent.



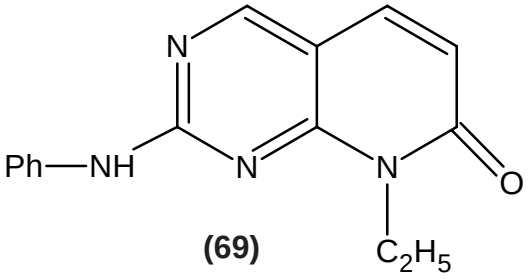
(67)

R_1=OH / NH2 ; R_2=OH ; R_3=H ;
Z=Pyridinyl ; n =2,3

D.H. Boshelli et al.,[339] have synthesized pyrido[2,3-d]pyrimidines **(68)**,**(69)** and found useful in the treatment of cell proliferatives disorders such as cancer and restenosis.



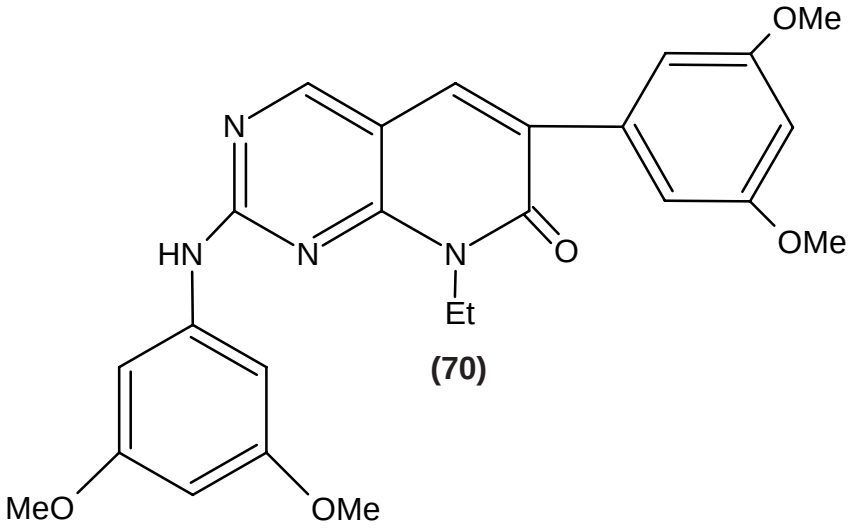
(68)



(69)

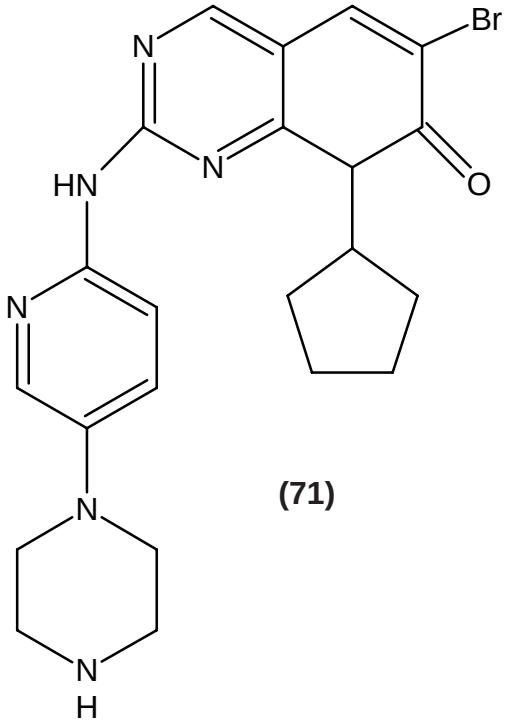
R_1=R_2=H ; R_3=H / alkyl ; R_4=R_5=H ;
W=NH / S ; X=O / NH

J.B. Kramer et al.,[340] have synthesized 2-(4-pyridyl)amino-6-dialkoxy-phenyl-pyrido[2,3-d]pyrimidin-7-ones **(70)** as novel antiangiogenic agents and useful for the treatment of diseases associated with abserrant blood vessel proliferation.



(70)

H. Zhou et al.,[341] have synthesized pyrido[2,3-d]pyrimidin-7-ones **(71)** as useful for treating cell proliferative disorders, such as cancer, atherosclerosis and restenosis.



(71)

In view to get potent therapeutic agents, the synthesis of pyrido[2,3-d : 6,5-d] dipyrimidine derivatives have been undertaken which can be described as under.

SECTION - I : PREPARATION AND BIOLOGICAL EVALUATION OF 1,2,3,4, 6,7,8,9-OCTAHYDRO-10-ARYL-5-(*o*-CHLOROPHENYL)-2,4,6,8-TETRAOXO-5H,10H-PYRIDO[2,3-d : 6,5-d'] DIPYRIMIDINES

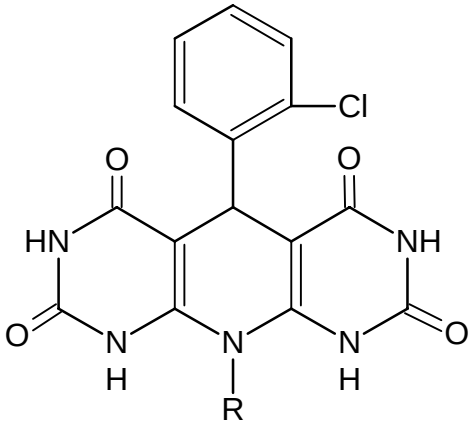
SECTION - II : PREPARATION AND BIOLOGICAL EVALUATION OF 1,2,3,4, 6,7,8,9-OCTAHYDRO-10-(*p*-METHYLPHENYL)-5- ARYL-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d'] DIPYRIMIDINES

SECTION - III : PREPARATION AND BIOLOGICAL EVALUATION OF 1,2,3,4, 6,7,8,9-OCTAHYDRO-10-ARYL-5-(*m*-NITROPHENYL)-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d'] PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINES

SECTION - I

PREPARATION AND BIOLOGICAL EVALUATION OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-ARYL-5-(*o*-CHLOROPHENYL)-2,4,6,8-TETRAOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINES

In view of various biodynamic activities[279-329], other properties[275,276], literature survey[330-341] and in order to have potent therapeutic agents, synthesis of 1,2,3,4,6,7,8,9-octahydro-10-aryl-5-(*o*-chlorophenyl)-2,4,6,8-tetraoxo-5H,10H-pyrido[2,3-d : 6,5-d']dipyrimidines ($XIII_{a-n}$) have been under taken by the cyclocondensation of different aromatic amines with two moles of barbituric acid and *o*-chlorobenzaldehyde in ethanol.

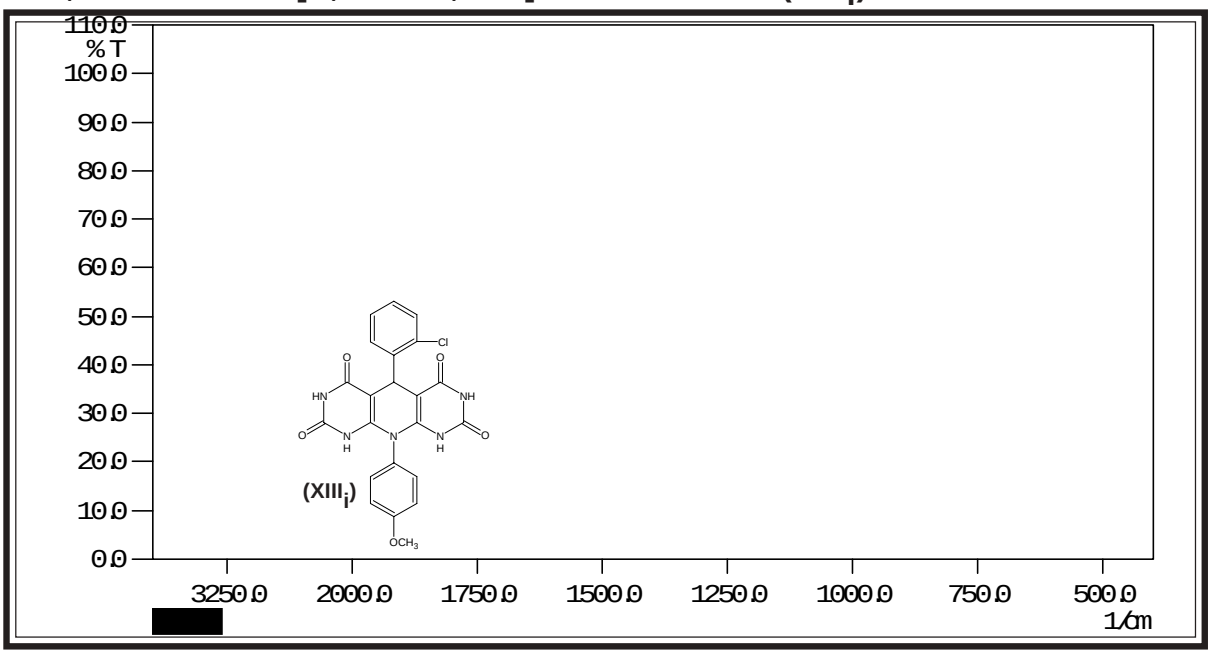


$XIII_{a-n}$ **R=Aryl**

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

The products ($XIII_{a-j}$) were assayed for their *in vitro* biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

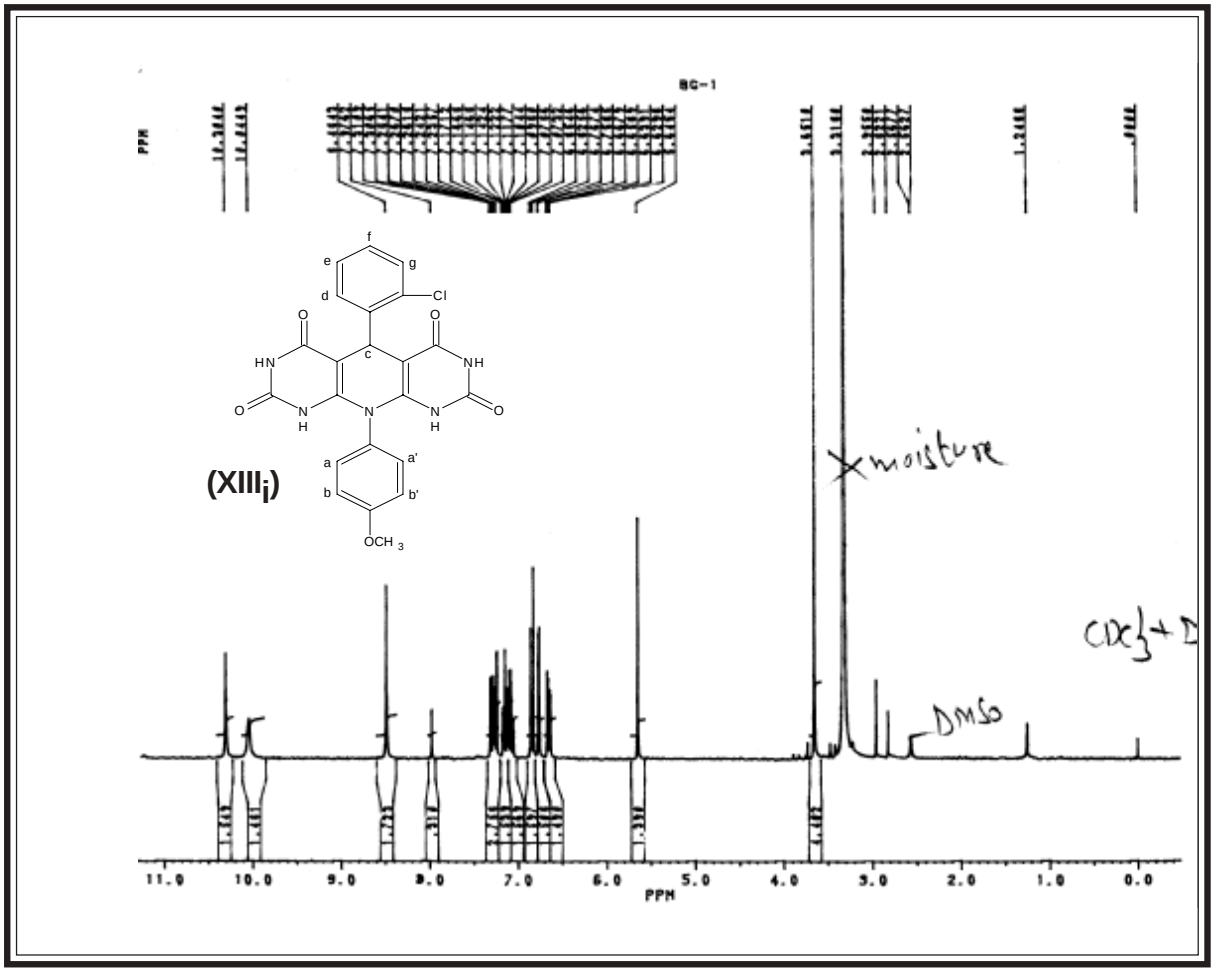
IR SPECTRAL STUDY OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-(*p*-METHOXYPHENYL)-5-(*o*-CHLOROPHENYL)-2,4,6,8-TETRAOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINE (XIII$_i$)



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.(asym.)	2958.6	2975-2950	343
CH_3	C-H str.(sym.)	2833.2	2880-2860	,,
	C-H def.(asym.)	1440.7	1460-1435	,,
	C-H def.(sym.)	1375.2	1385-1300	,,
Aromatic and	C=C + C=N and ring	1560.3	1520-1480	345
Pyrimidine moiety	skeletal vibration	1440.7	1580-1520	,,
	C-H str.	3024.2	3080-3030	,,
	C=C str.	1506.3	1520-1490	,,
	C-H i.p. def.	1103.2	1125-1090	,,
	C-H o.o.p. def.	827.4	840-810	,,
Ether	C-O-C str. (asym.)	1242.1	1275-1200	346
	C-O-C str. (sym.)	1028.0	1075-1050	,,
Amine (Sec.)	N-H str.	3411.8	3500-3300	343
	N-H def.	1604.7	1650-1580	,,
Pyridine ring	C=N str.	1639.4	1650-1580	344
	C-N str.	1166.9	1200-1020	,,
Carbonyl	C=O str.	1710.7	1720-1665	,,
Halogen	C-Cl str.	827.4	800-600	343

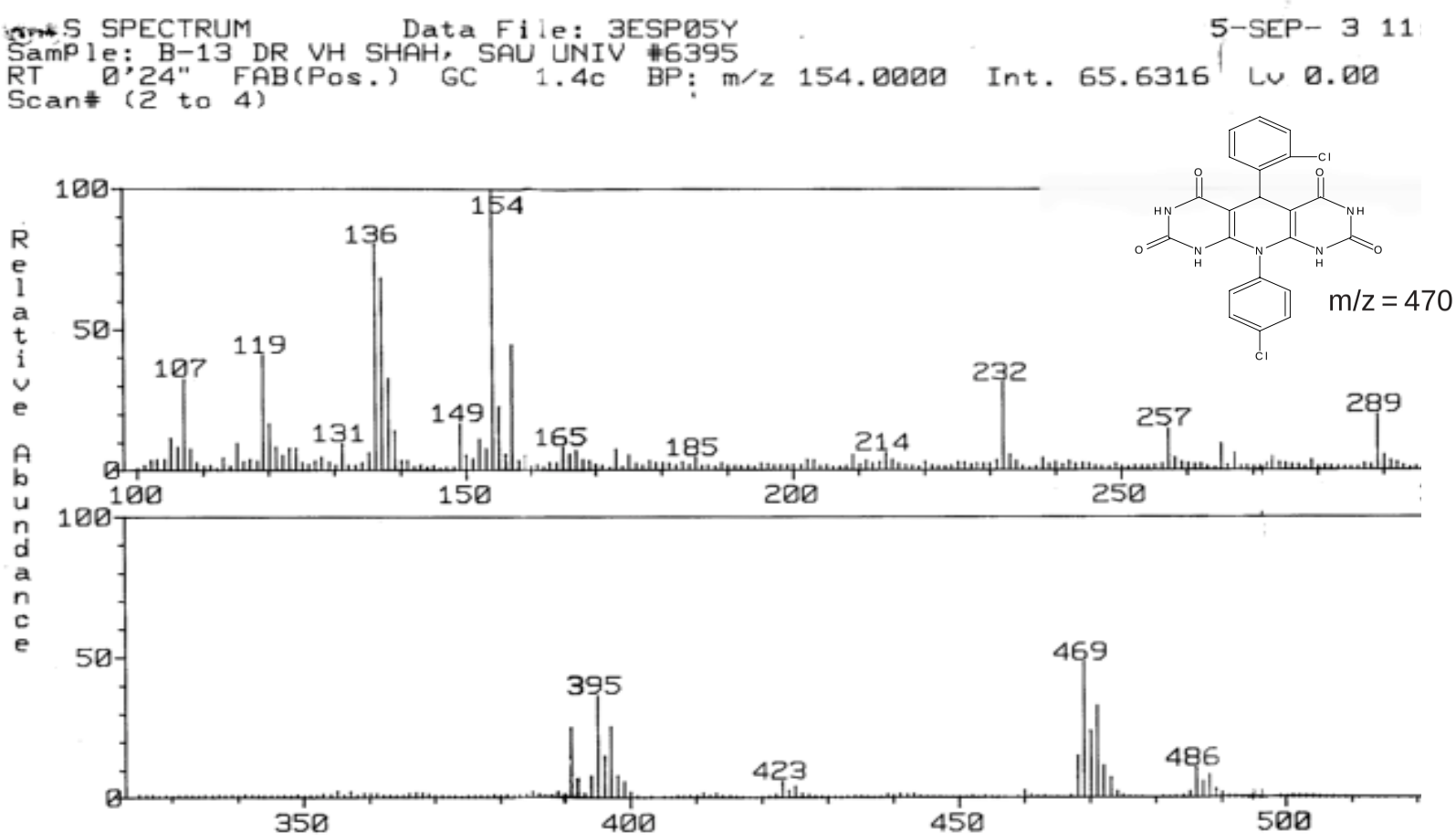
PMR SPECTRAL STUDY OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-(*p*-METHOXYPHENYL)-5-(*o*-CHLOROPHENYL)-2,4,6,8-TETRAOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINE ($XIII_i$)

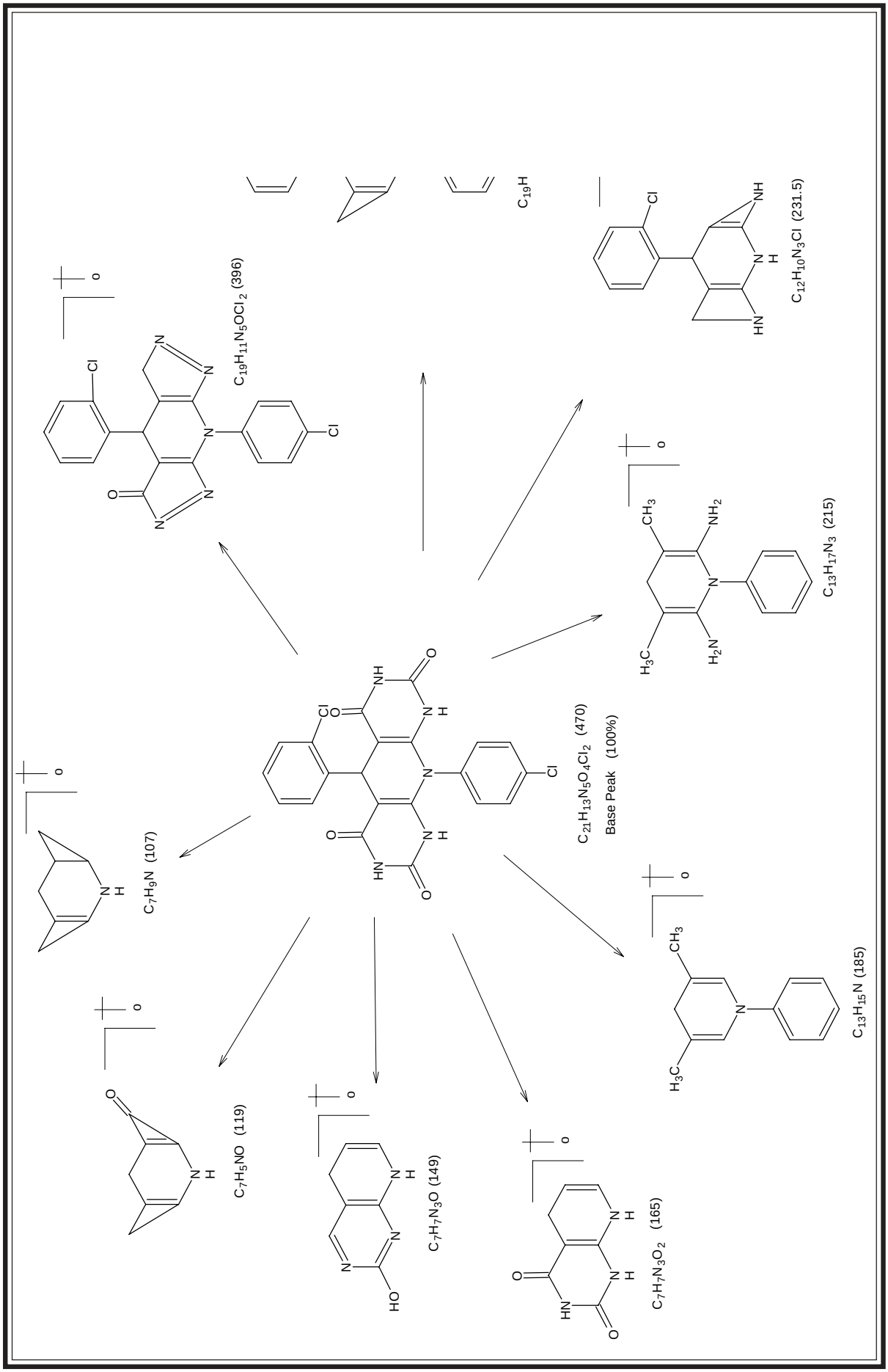


Internal Standard : TMS ; Solvent ; $CDCl_3$+$DMSOd_6$; Instrument : BRUKER Spectrometer (300 MHz)

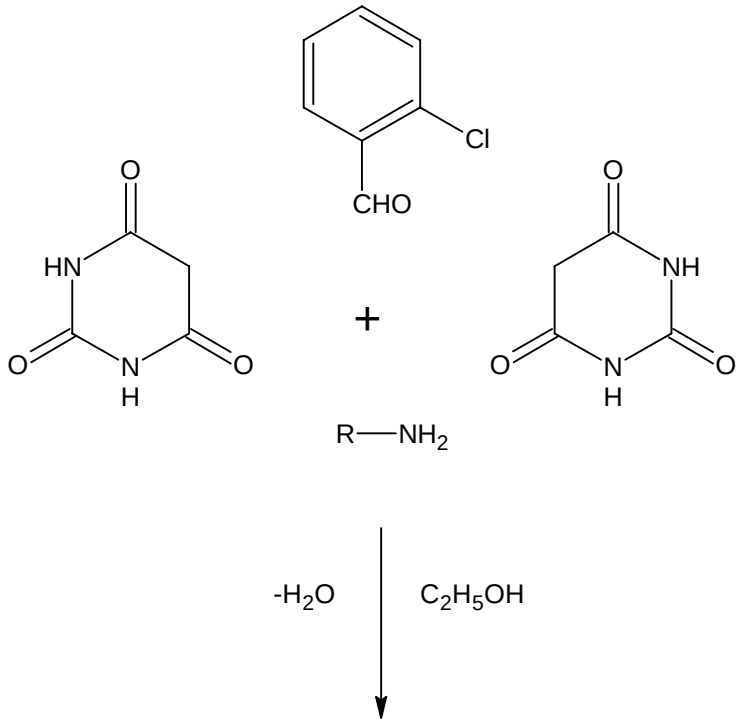
Signal No.	Signal Position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.651	3H	singlet	$-OCH_3$
2.	5.645	1H	singlet	Ar-H_c
3.	6.630-6.668	2H	doublet	Ar-$H_{b,b'}$
4.	6.758-6.767	1H	doublet	Ar-H_d
5.	6.826-6.855	2H	doublet	Ar-$H_{a,a'}$
6.	7.049-7.104	1H	multiplet	Ar-H_e
7.	7.118-7.171	1H	multiplet	Ar-H_f
8.	7.236-7.311	1H	multiplet	Ar-H_g
9.	8.484	1H	singlet	-NH
10	10.045	1H	singlet	-NH
11.	10.304	1H	singlet	-NH

MASS SPECTRAL OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-(*p*-CHLOROPHENYL)-5-(*o*-CHLOROPHENYL)- 2,4,6,8-TETRAOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINE ($XIII_d$)




C19H
C12H10N3Cl (231.5)
C19H11N5OCl2 (396)
C13H17N3 (215)
C21H13N5O4Cl2 (470)
Base Peak (100%)
C7H9N (107)
C13H15N (185)
C7H5NO (119)
C7H7N3O (149)
C7H7N3O2 (165)

REACTION SCHEME



(XIII$_{a-n}$) **R = Aryl**

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-ARYL-5-(*o*-CHLOROPHENYL)-2,4,6,8-TETRAOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINES

(A) Preparation of 1,2,3,4,6,7,8,9-Octahydro-10-(*p*-methoxyphenyl)-5-(*o*-chlorophenyl)-2,4,6,8-tetra-oxo-5H,10H-pyrido[2,3-d : 6,5- d'] dipyrimidine ($XIII_i$).

A mixture of *o*-chlorobenzaldehyde (1.41 ml, 0.01 M), barbituric acid (2.60 gm, 0.02 M) and *p*-anisidine (1.23 gm, 0.01 M) in ethanol (30 ml) was heated under refluxed condition for six hrs. The content was poured into ice cold water. The separated solid was filtered and crystallized from DME:methanol (2:1). Yield : 79%, M.P. : 196°C, R_f : 0.46, (Required : C, 56.71%; H, 3.44%; N, 15.04% for $C_{22}H_{16}N_5O_5Cl$, Found : C, 56.65%; H, 3.40%; N, 14.99%).

Similarly, other compounds ($XIII_{a-n}$) were synthesized. The physical data are recorded in Table No. 16.

(B) Antimicrobial activity of 1,2,3,4,6,7,8,9-Octahydro-10-aryl-5-(*o*-chloro phenyl)-2,4,6,8-tetraoxo-5H,10H-pyrido[2,3-d : 6,5-d'] dipyrimidines ($XIII_{a-n}$).

Antimicrobial activity testing was carried out as described in part-1, section-I, page No. 35. The MIC values of test solution are recorded in Table No. 16a, 16b & 16c.

TABLE NO. 16 : PHYSICAL CONSTANTS OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-ARYL-5-(*o*-CHLOROPHENYL) -2,4,6,8-TETRAOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINES ($XIII_{a-n}$)

Comp. No. 1	R 2	Molecular Formula 3	M. W. 4	M.P. °C 5	Yield % 6	R_f Value 7	% of Nitrogen Required 8	% of Nitrogen Found 9
XIIIa	C_6H_5	$C_{21}H_{14}N_5O_4Cl$	435.5	158	75	0.52	16.07	16.02
XIIIb	2-Cl-C_6H_4	$C_{21}H_{13}N_5O_4Cl_2$	470.0	187	71	0.49	14.89	14.85
XIIIc	3-Cl-C_6H_4	$C_{21}H_{13}N_5O_4Cl_2$	470.0	210	73	0.53	14.89	14.84
XIIId	4-Cl-C_6H_4	$C_{21}H_{13}N_5O_4Cl_2$	470.0	196	68	0.55	14.89	14.83
XIIIe	2-CH_3-C_6H_4	$C_{22}H_{16}N_5O_4Cl$	449.5	260	72	0.54	15.57	15.52
XIIIf	3-CH_3-C_6H_4	$C_{22}H_{16}N_5O_4Cl$	449.5	212	76	0.49	15.57	15.51
XIIIg	4-CH_3-C_6H_4	$C_{22}H_{16}N_5O_4Cl$	449.5	180	77	0.45	15.57	15.53
XIIIh	2-CH_3O-C_6H_4	$C_{22}H_{16}N_5O_5Cl$	465.5	166	66	0.44	15.04	15.00
XIIIi	4-CH_3O-C_6H_4	$C_{22}H_{16}N_5O_5Cl$	465.5	196	79	0.46	15.04	14.99
XIIIj	2-NO_2-C_6H_4	$C_{21}H_{13}N_6O_6Cl$	480.5	234	76	0.52	17.48	17.41
XIIIk	3-NO_2-C_6H_4	$C_{21}H_{13}N_6O_6Cl$	480.5	207	78	0.49	17.48	17.42
XIIIl	4-NO_2-C_6H_4	$C_{21}H_{13}N_6O_6Cl$	480.5	191	81	0.46	17.48	17.43
XIIIm	2,5-$(Cl)_2$-C_6H_3	$C_{21}H_{12}N_5O_4Cl_3$	504.5	187	68	0.53	13.88	13.82
XIIIn	3,4-$(Cl)_2$-C_6H_3	$C_{21}H_{12}N_5O_4Cl_3$	504.5	236	65	0.51	13.88	13.83

TLC solvent system ; Acetone : Benzene = 1.5 : 8.5

TABLE NO. 16a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-ARYL-5-(*o*-CHLOROPHENYL)-2,4,6,8-TETRAOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']PYRIMIDINES XIII$_{a-n}$ (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442							S. aureus MTCC-96						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
XIIIa	C_6H_5	-	-	11	11	12	12	14	-	-	13	13	14	14	16
XIIIb	2-Cl-C_6H_4	-	-	11	11	12	13	14	-	-	12	12	13	14	16
XIIIc	3-Cl-C_6H_4	-	-	12	12	14	14	14	-	-	14	14	15	16	16
XIIId	4-Cl-C_6H_4	-	-	10	10	12	14	14	-	-	11	11	14	16	17
XIIIe	2-CH_3-C_6H_4	-	-	12	12	13	13	14	-	-	14	11	16	16	17
XIIIf	3-CH_3-C_6H_4	-	-	11	11	12	14	14	-	-	13	13	15	15	16
XIIIg	4-CH_3-C_6H_4	-	-	11	12	12	13	14	-	-	12	13	13	15	16
XIIIh	2-OCH_3-C_6H_4	-	-	10	10	12	12	13	-	-	12	12	14	14	16
XIIIi	4-OCH_3-C_6H_4	-	-	12	12	12	14	14	-	-	14	14	15	16	17
XIIIj	2-NO_2-C_6H_4	-	-	10	11	11	12	13	-	-	11	12	12	14	15
XIIIk	3-NO_2-C_6H_4	-	-	12	12	13	13	14	-	-	13	13	14	15	16
XIIIl	4-NO_2-C_6H_4	-	-	11	11	12	12	14	-	-	12	13	14	16	16
XIIIm	2,5-Cl_2-C_6H_3	-	-	12	12	12	14	14	-	-	13	14	16	16	17
XIIIn	3,4-Cl_2-C_6H_3	-	-	10	10	12	12	13	-	-	12	12	14	15	17

Comparative activity of (XIII$_{a-n}$) with known choosen standard drugs

Standard drug	Antibacterial activity														
											XIIIc XIIIe XIIIi	XIIIc XIIIi XIIIm	XIIIe XIIIm		
Ampicillin	11	13	14	16	18	19	20	10	12	13	14	16	18	21
Chloramphenicol	10	12	13	19	20	20	22	12	13	14	19	20	21	22
Ciprofloxacin	16	18	19	21	21	22	22	17	18	19	21	22	22	23
Norfloxacin	18	18	19	20	21	21	23	19	20	22	25	26	28	28

N.B.(-): No Activity

TABLE NO. 16b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-ARYL-5-(*o*-CHLOROPHENYL)-2,4,6,8-TETRAOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']PYRIMIDINES $XIII_{a-n}$ (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) E. Coli MTCC-443							B. subtillis MTCC-441						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
XIIIa	C_6H_5	-	-	14	15	16	17	18	-	-	16	16	17	18	19
XIIIb	2-Cl-C_6H_4	-	-	13	14	15	15	18	-	-	15	15	16	16	19
XIIIc	3-Cl-C_6H_4	-	-	16	16	17	17	18	-	-	17	18	18	18	19
XIIId	4-Cl-C_6H_4	-	-	13	14	14	15	17	-	-	15	15	16	17	18
XIIIe	2-CH_3-C_6H_4	-	-	15	15	17	18	18	-	-	16	17	18	19	19
XIIIf	3-CH_3-C_6H_4	-	-	14	15	15	16	17	-	-	15	15	16	18	19
XIIIg	4-CH_3-C_6H_4	-	-	14	15	16	16	17	-	-	16	16	17	17	19
XIIIh	2-OCH_3-C_6H_4	-	-	13	14	15	16	17	-	-	15	15	17	18	19
XIIIi	4-OCH_3-C_6H_4	-	-	15	16	17	17	18	-	-	17	17	18	18	18
XIIIj	2-NO_2-C_6H_4	-	-	13	13	14	16	17	-	-	14	15	15	17	19
XIIIk	3-NO_2-C_6H_4	-	-	14	15	15	17	18	-	-	16	17	17	18	18
XIIIl	4-NO_2-C_6H_4	-	-	14	14	16	17	18	-	-	15	16	17	18	18
XIIIm	2,5-Cl_2-C_6H_3	-	-	15	15	16	17	18	-	-	16	17	18	19	19
XIIIn	3,4-Cl_2-C_6H_3	-	-	13	14	15	15	17	-	-	15	15	17	18	19

Comparative activity of ($XIII_{a-n}$) with known choosen standard drugs

Standard drug	Antibacterial activity													
			XIIIc XIIIe XIIIi	XIIIc XIIIi						XIIIc XIIIi				
Ampicillin	14	14	15	16	19	20	22	12	16	18	19	20	21	23
Chloramphenicol	14	15	17	23	23	23	23	12	14	16	19	22	23	23
Ciprofloxacin	20	21	23	28	28	28	28	16	17	19	22	22	23	23
Norfloxacin	22	23	25	26	27	29	29	19	20	22	23	24	25	28

N.B.(-): No Activity

TABLE NO. 16c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-ARYL-5-(*o*-CHLOROPHENYL)-2,4,6,8-TETRAOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']PYRIMIDINES XIII$_{a-n}$ (Minimum inhibition Concentration in µg/ml)

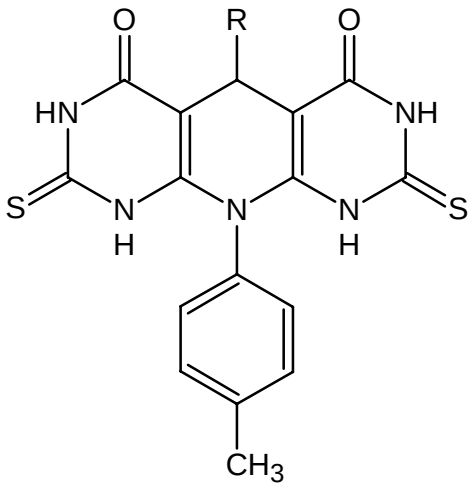
Compd No.	R	Antifungal activity (Zones of inhibition in mm) C. albicans MTCC-227							A. niger MTCC-282						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
XIIIa	C_6H_5	-	-	17	18	19	20	21	-	-	19	19	20	22	22
XIIIb	2-Cl-C_6H_4	-	-	17	18	19	20	21	-	-	18	19	20	20	23
XIIIc	3-Cl-C_6H_4	-	-	18	18	20	20	21	-	-	19	19	21	22	24
XIIId	4-Cl-C_6H_4	-	-	17	18	19	20	20	-	-	19	19	21	21	22
XIIIe	2-CH_3-C_6H_4	-	-	18	18	20	20	22	-	-	19	19	21	22	24
XIIIf	3-CH_3-C_6H_4	-	-	17	17	19	20	20	-	-	18	18	20	22	22
XIIIg	4-CH_3-C_6H_4	-	-	17	18	20	20	21	-	-	18	19	21	22	24
XIIIh	2-OCH_3-C_6H_4	-	-	17	17	18	20	22	-	-	19	19	20	21	24
XIIIi	4-OCH_3-C_6H_4	-	-	18	19	20	21	22	-	-	19	20	22	22	23
XIIIj	2-NO_2-C_6H_4	-	-	17	17	18	20	20	-	-	18	18	20	21	22
XIIIk	3-NO_2-C_6H_4	-	-	18	18	20	20	21	-	-	19	19	20	21	23
XIIIl	4-NO_2-C_6H_4	-	-	17	17	19	20	21	-	-	18	19	20	22	24
XIIIm	2,5-Cl_2-C_6H_3	-	-	18	18	20	20	21	-	-	19	19	21	22	23
XIIIn	3,4-Cl_2-C_6H_3	-	-	17	18	19	20	22	-	-	18	19	20	22	24
Comparative activity of (XIII$_{a-n}$) with known choosen standard drugs															
Standard drug		**Antifungal activity**													
													XIIIi		
Griseofulvin		19	22	23	25	25	28	28	18	19	21	22	22	24	26

N.B.(-): No Activity

SECTION - II

PREPARATION AND BIOLOGICAL EVALUATION OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-(*p*-METHYLPHENYL)-5-ARYL-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINES

In view of various biodynamic activities[279-329], other properties[275,276], literature survey[330-341] and in order to have potent therapeutic agents, synthesis of 1,2,3,4,6,7,8,9-octahydro-10-(*p*-methylphenyl)-5-aryl-2,8-dimercapto-4,6-dioxo-5H,10H-pyrido[2,3-d : 6,5-d']dipyrimidines (XIV_{a-k}) have been under taken by the cyclocondensation of different aromatic aldehydes with two moles of thiobarbituric acid and *p*-toluidine in ethanol.

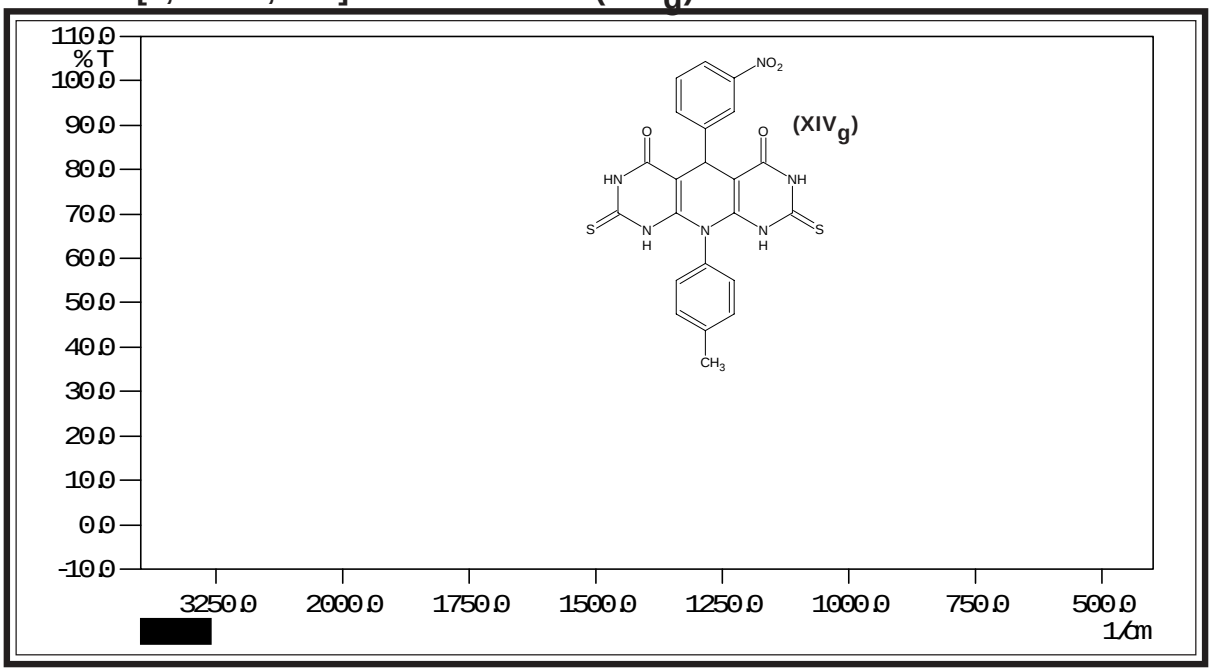


XIV_{a-k} **R=Aryl**

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

The products (XIV_{a-k}) were assayed for their *in vitro* biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

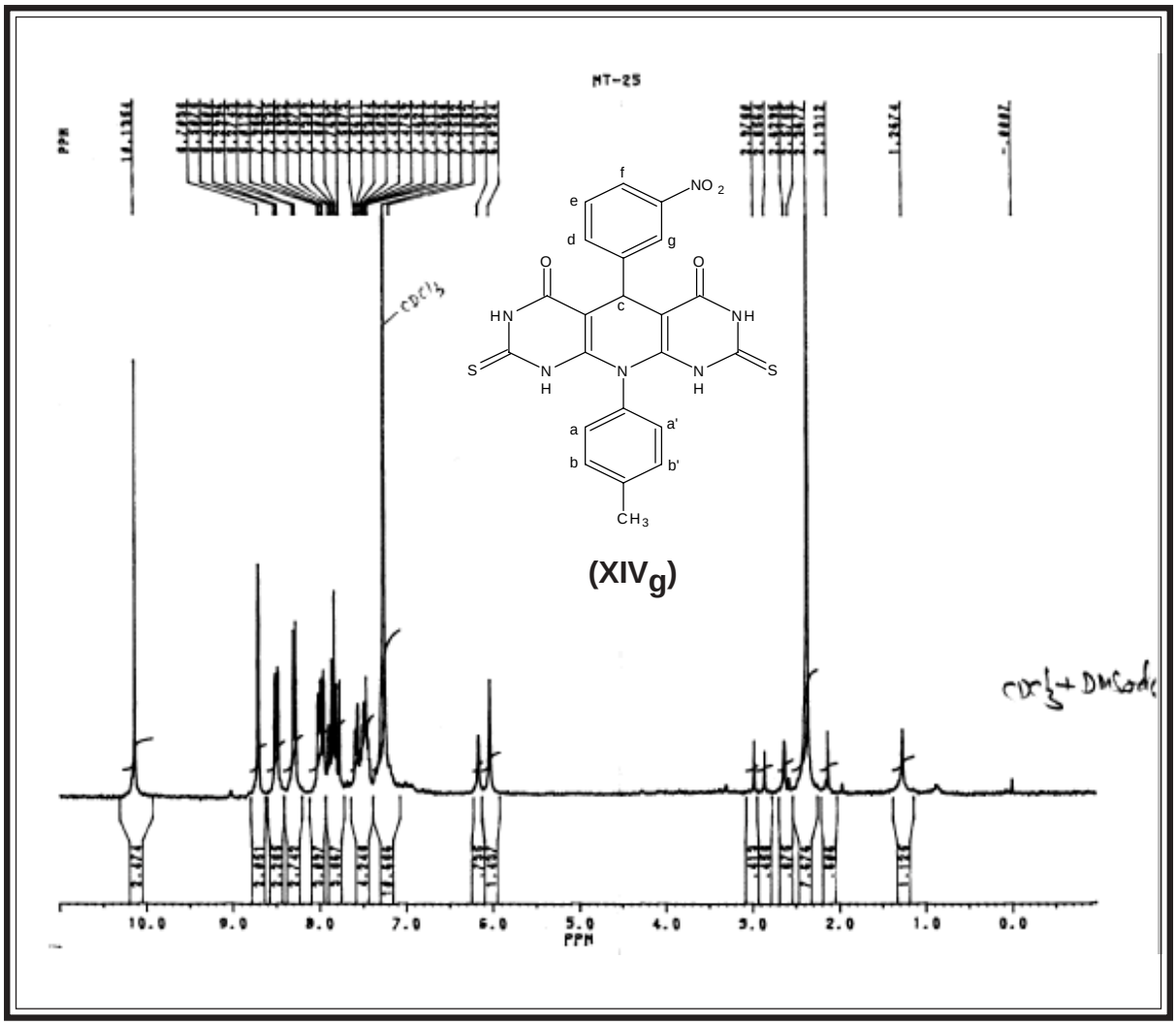
IR SPECTRAL STUDY OF 1,2,3,4, 6,7,8,9-OCTAHYDRO-10-(*p*-METHYL PHENYL)-5-(*m*-NITROPHENYL)-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINE (XIV_g)



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.(asym.)	2987.5	2975-2950	343
CH_3	C-H str.(sym.)	2873.7	2880-2860	,,
	C-H def.(asym.)	1475.4	1460-1435	,,
	C-H def.(sym.)	1361.7	1385-1300	,,
Aromatic and	C=C + C=N and ring	1527.5	1520-1480	345
Pyrimidine moiety	skeletal vibration	1448.4	1580-1520	,,
	C-H str.	3064.7	3080-3030	,,
	C=C str.	1508.2	1520-1490	,,
	C-H i.p. def.	1107.1	1125-1090	,,
	C-H o.o.p. def.	846.7	840-810	,,
	C=S str.	1596.9	1650-1580	,,
Amine (Sec.)	N-H str.	3330.8	3500-3300	343
	N-H def.	1596.9	1650-1580	,,
Pyridine ring	C=N str.	1658.7	1650-1580	344
	C-N str.	1176.5	1200-1020	,,
Carbonyl	C=O str.	1706.9	1720-1665	,,

PMR SPECTRAL STUDY OF 1,2,3,4, 6,7,8,9-OCTAHYDRO-10-(*p*-METHYL PHENYL)-5-(*m*-NITROPHENYL)-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINE (XIV_g)

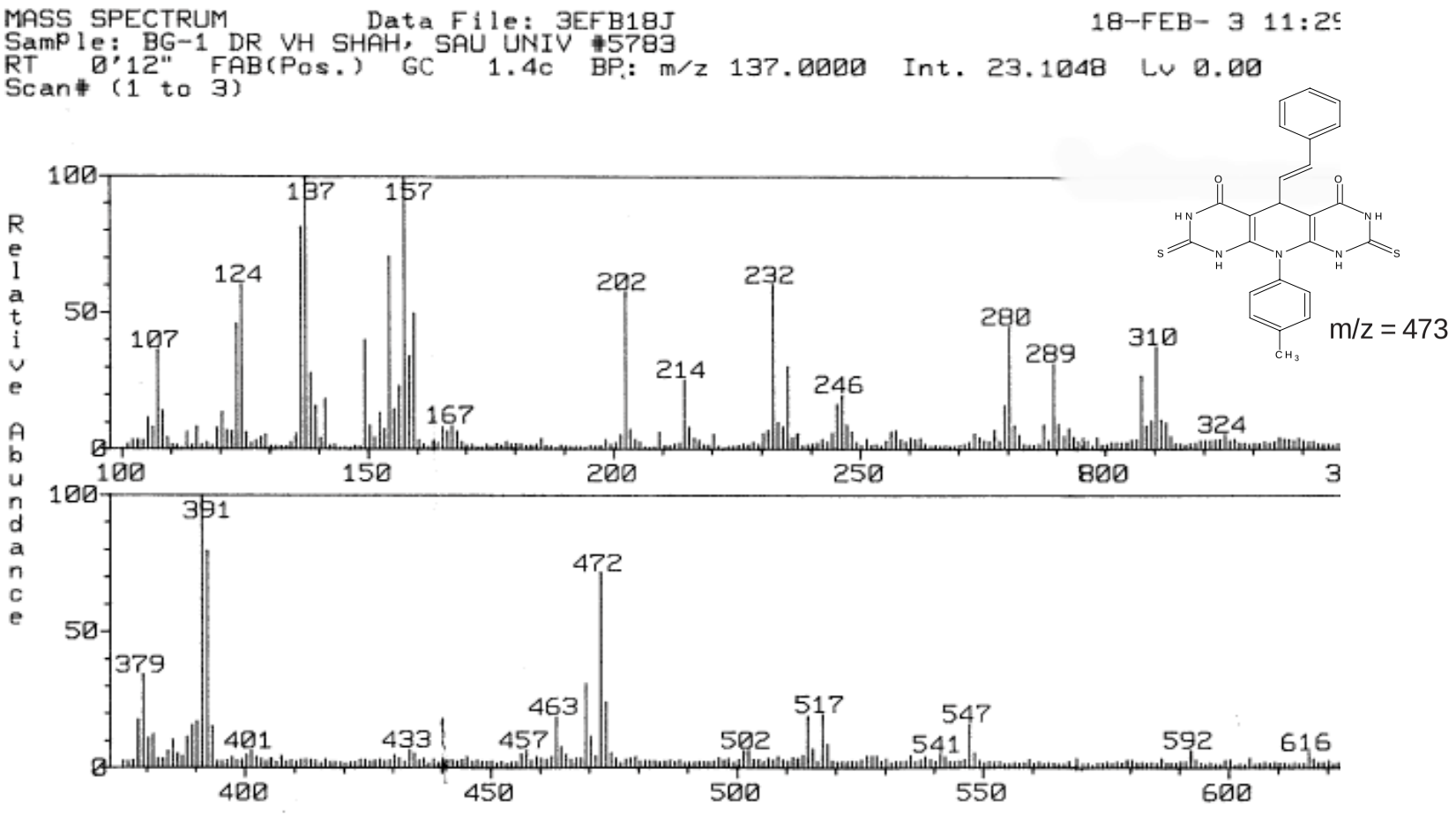


(XIV_g)

Internal Standard : TMS ; Solvent ; $CDCl_3$+$DMSOd_6$+TFA ; Instrument : BRUKER Spectrometer (300 MHz)

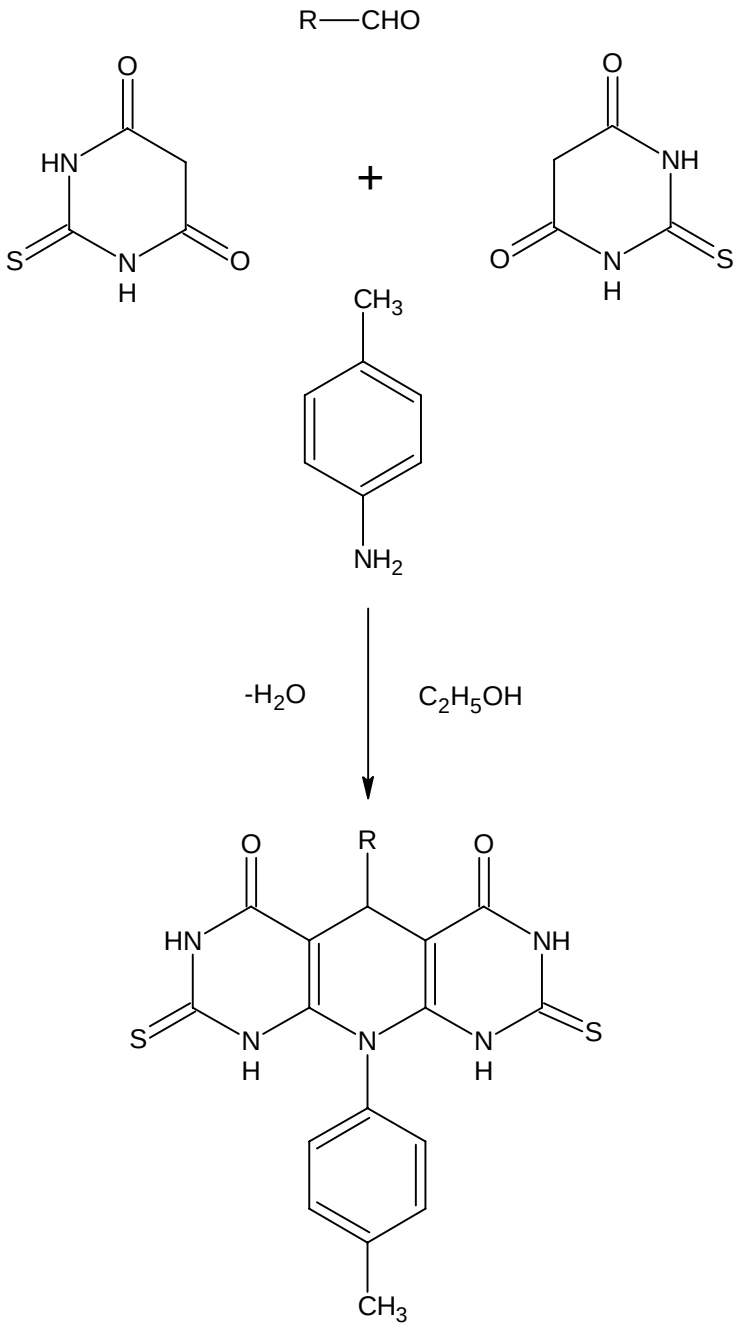
Signal No.	Signal Position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	2.368	3H	singlet	$-CH_3$
2.	6.032	1H	singlet	Ar-H_c
3.	7.437-7.587	2H	doublet	Ar-$H_{b,b'}$
4.	7.769-7.892	2H	doublet	Ar-$H_{a,a'}$
5.	7.831	1H	singlet	-NH
6.	7.953-8.013	1H	triplet	Ar-H_e
7.	8.274-8.300	1H	double doublet	Ar-H_f
8.	8.480-8.507	1H	double doublet	Ar-H_d
9.	8.704	1H	doublet	Ar-H_g

MASS SPECTRAL OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-(*p*-METHOXYPHENYL)-5-(VINYLPHENYL)-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d:6,5-d']DIPYRIMIDINE (XIV_i)



C24H19N5O2S2 (473)
C22H25N5S (391)
Base Peak (100%)
C16H13N5OS2 (355)
C16H14N4OS (310)
C15H12N4O2 (280)
C14H22N4 (246)
C11H12N4O2 (232)
C10H10N4O (202)
C15H19N (213)
C8H13N3O (167)
C7H12N2 (124)
C7H9N (107)

REACTION SCHEME



(XIV$_{a-k}$) **R = Aryl**

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 1,2,3,4, 6,7,8,9-OCTAHYDRO-10-(*p*-METHYLPHENYL)-5-ARYL-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINES

(A) Preparation of 1,2,3,4,6,7,8,9-Octahydro-10-(*p*-methylphenyl)-5-(*m*-nitrophenyl)-2,8-dimercapto-4,6-dioxo-5H,10H-pyrido [2,3-d : 6,5- d'] dipyrimidine (XIV_g).

A mixture of *m*-nitrobenzaldehyde (1.51 gm, 0.01 M), thiobarbituric acid (2.92 gm, 0.02 M) and *p*-toluidine (1.07gm, 0.01 M) in ethanol (30 ml) was heated under refluxed condition for six hrs. The content was poured into ice cold water. The separated solid was filtered and crystallized from DME:methanol (2:1). Yield : 77%, M.P. : 180°C, R_f : 0.49, (Required : C, 53.66%; H, 3.25%; N, 17.07%; for $C_{22}H_{16}N_6O_4S_2$, Found : C, 53.62%; H, 3.21%; N, 17.02%).

Similarly, other compounds (XIV_{a-k}) were synthesized. The physical data are recorded in Table No. 17.

(B) Antimicrobial activity of 1,2,3,4,6,7,8,9-Octahydro-10-(*p*-methyl phenyl)-5-aryl-2,8-dimercapto-4,6-dioxo-5H,10H-pyrido [2,3-d : 6,5-d'] dipyrimidines (XIV_{a-k}).

Antimicrobial activity testing was carried out as described in part-1, section-I, page No. 35. The MIC values of test solution are recorded in Table No. 17a, 17b & 17c.

TABLE NO. 17 : PHYSICAL CONSTANTS OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-(*p*-METHYLPHENYL)-5-ARYL-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINES (XIV_{a-k})

Comp. No. 1	R 2	Molecular Formula 3	M. W 4	M.P. °C 5	Yield % 6	R_f Value 7	% of Nitrogen	
							Required 8	Found 9
XIVa	C_6H_5	$C_{22}H_{17}N_5O_2S_2$	447.0	152	72	0.54	15.66	15.60
XIVb	2-OH-C_6H_4	$C_{22}H_{17}N_5O_3S_2$	463.0	87	76	0.51	15.12	15.08
XIVc	4-OH-C_6H_4	$C_{22}H_{17}N_5O_3S_2$	463.0	218	73	0.46	15.12	15.09
XIVd	2-Cl-C_6H_4	$C_{22}H_{16}N_5O_2S_2Cl$	481.5	123	78	0.47	14.54	14.50
XIVe	4-Cl-C_6H_4	$C_{22}H_{16}N_5O_2S_2Cl$	481.5	194	80	0.53	14.54	14.49
XIVf	2-NO_2-C_6H_4	$C_{22}H_{16}N_6O_4S_2$	492.0	64	79	0.57	17.07	17.01
XIVg	3-NO_2-C_6H_4	$C_{22}H_{16}N_6O_4S_2$	492.0	180	77	0.49	17.07	17.02
XIVh	4-CH_3O-C_6H_4	$C_{23}H_{19}N_5O_3S_2$	477.0	102	74	0.51	14.68	14.61
XIVi	C_6H_5-CH=CH-	$C_{24}H_{19}N_5O_2S_2$	473.0	140	72	0.58	14.80	14.75
XIVj	4-OH-3-CH_3O-C_6H_3	$C_{23}H_{19}N_5O_4S_2$	493.0	157	68	0.52	14.20	14.14
XIVk	4-N-$(CH_3)_2$-C_6H_4	$C_{24}H_{22}N_6O_2S_2$	490.0	172	71	0.54	17.14	17.10

TLC solvent system ; Acetone : Benzene = 1.5 : 8.5

TABLE NO. 17a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-(*p*-METHYL PHENYL)-5-ARYL-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']PYRIMIDINES XIV_{a-k} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442							S. aureus MTCC-96						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
XIVa	C_6H_5	-	-	10	11	13	13	14	-	-	11	14	14	14	16
XIVb	2-OH-C_6H_4	-	-	11	11	12	14	14	-	-	13	15	14	15	17
XIVc	4-OH-C_6H_4	-	-	12	12	14	14	14	-	-	13	14	15	15	17
XIVd	2-Cl-C_6H_4	-	-	11	12	12	13	13	-	-	14	12	16	16	17
XIVe	4-Cl-C_6H_4	-	-	10	10	12	12	13	-	-	12	13	14	14	15
XIVf	2-NO_2-C_6H_4	-	-	12	12	13	14	14	-	-	14	14	16	17	18
XIVg	3-NO_2-C_6H_4	-	-	10	10	11	13	13	-	-	11	14	13	15	16
XIVh	4-OCH_3-C_6H_4	-	-	11	11	13	13	14	-	-	13	13	14	15	15
XIVi	-CH=CH-C_6H_4	-	-	12	12	12	13	14	-	-	13	13	14	14	15
XIVj	4-OH,3-OCH_3-C_6H_3	-	-	10	10	12	14	14	-	-	11	12	14	14	15
XIVk	4-N-$(CH_3)_2$-C_6H_4	-	-	12	12	13	13	14	-	-	13	14	14	15	16

Comparative activity of (XIV_{a-k}) with known choosen standard drugs

Standard drug	Antibacterial activity														
											XIVd XIVf	XIVb	XIVd XIVf		
Ampicillin	11	13	14	16	18	19	20	10	12	13	14	16	18	21
Chloramphenicol	10	12	13	19	20	20	22	12	13	14	19	20	21	22
Ciprofloxacin	16	18	19	21	21	22	22	17	18	19	21	22	22	23
Norfloxacin	18	18	19	20	21	21	23	19	20	22	25	26	28	28

N.B.(-): No Activity

TABLE NO. 17b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-(*p*-METHYL PHENYL)-5-ARYL-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']PYRIMIDINES XIV_{a-k} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm)													
		E. Coli MTCC-443							B. subtillis MTCC-441						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
XIVa	C_6H_5	-	-	12	14	14	17	18	-	-	14	14	16	18	18
XIVb	2-OH-C_6H_4	-	-	14	14	16	17	19	-	-	16	16	17	17	18
XIVc	4-OH-C_6H_4	-	-	14	15	16	17	17	-	-	15	16	17	18	18
XIVd	2-Cl-C_6H_4	-	-	13	14	16	18	18	-	-	15	16	18	18	19
XIVe	4-Cl-C_6H_4	-	-	14	15	15	16	18	-	-	15	16	17	18	19
XIVf	2-NO_2-C_6H_4	-	-	15	16	16	18	18	-	-	17	17	18	18	19
XIVg	3-NO_2-C_6H_4	-	-	13	14	14	16	18	-	-	14	14	16	17	19
XIVh	4-OCH_3-C_6H_4	-	-	14	15	15	17	18	-	-	16	16	18	18	19
XIVi	-CH=CH-C_6H_4	-	-	15	16	16	17	17	-	-	14	16	17	19	19
XIVj	4-OH,3-OCH_3-C_6H_3	-	-	13	13	15	16	16	-	-	16	15	16	18	18
XIVk	4-N-$(CH_3)_2$-C_6H_4	-	-	15	16	16	18	18	-	-	16	16	17	19	19

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

Standard drug	Antibacterial activity														
			XIVf XIVi XIVk	XIVf XIVi XIVk				XIVf						
Ampicillin	14	14	15	16	19	20	22	12	16	18	19	20	21	23
Chloramphenicol	14	15	17	23	23	23	23	12	14	16	19	22	23	23
Ciprofloxacin	20	21	23	28	28	28	28	16	17	19	22	22	23	23
Norfloxacin	22	23	25	26	27	29	29	19	20	22	23	24	25	28

N.B.(-): No Activity

TABLE NO. 17c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-(*p*-METHYL PHENYL)-5-ARYL-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']PYRIMIDINES XIV_{a-k} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antifungal activity (Zones of inhibition in mm) C. albicans MTCC-227 5	10	25	50	100	250	500	A. niger MTCC-282 5	10	25	50	100	250	500
XIVa	C_6H_5	-	-	17	17	19	20	21	-	-	19	19	21	21	22
XIVb	2-OH-C_6H_4	-	-	18	18	19	20	20	-	-	19	19	20	21	22
XIVc	4-OH-C_6H_4	-	-	17	17	18	20	21	-	-	18	18	20	21	22
XIVd	2-Cl-C_6H_4	-	-	17	18	19	20	20	-	-	19	19	21	21	22
XIVe	4-Cl-C_6H_4	-	-	18	18	19	20	20	-	-	19	19	20	22	22
XIVf	2-NO_2-C_6H_4	-	-	18	18	20	20	21	-	-	19	19	20	22	22
XIVg	3-NO_2-C_6H_4	-	-	17	17	19	21	21	-	-	18	18	20	22	23
XIVh	4-OCH_3-C_6H_4	-	-	17	18	20	20	21	-	-	19	19	21	22	22
XIVi	-CH=CH-C_6H_4	-	-	17	18	19	20	21	-	-	19	19	21	22	23
XIVj	4-OH,3-OCH_3-C_6H_3	-	-	17	17	19	21	21	-	-	19	19	20	23	24
XIVk	4-N-$(CH_3)_2$-C_6H_4	-	-	18	18	19	21	21	-	-	19	19	21	22	23

Comparative activity of (XIV_{a-k}) with known choosen standard drugs

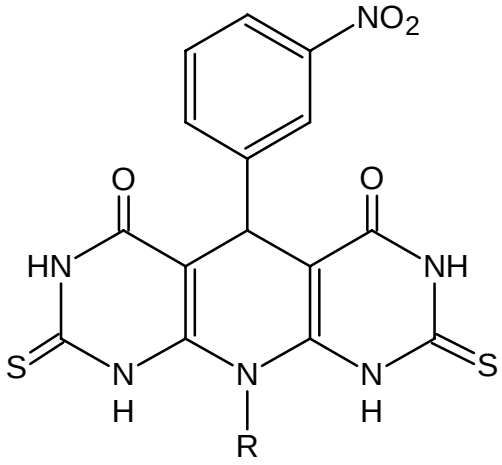
Standard drug	Antifungal activity													
Griseofulvin	19	22	23	25	25	28	28	18	19	21	22	22	24	26

N.B.(-): No Activity

SECTION - III

PREPARATION AND BIOLOGICAL EVALUATION OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-ARYL-5-(*m*-NITROPHENYL)-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINES

Due to wide range of pharmacodynamic activities[279-329], recent literature survey[330-341], other properties[275,276] and in view to have potent therapeutic agents, the synthesis of 1,2,3,4,6,7,8,9-octahydro-10-ayrl-5-(*m*-nitrophenyl)-2,8-dimercapto-4,6-dioxo-5H,10H-pyrido[2,3-d : 6,5-d'] dipyrimidines (XV_{a-n}) have been under taken by the cyclocondensation of different aromatic amines with two moles of thiobarbituric acid and *m*-nitrobenzaldehyde in ethanol.

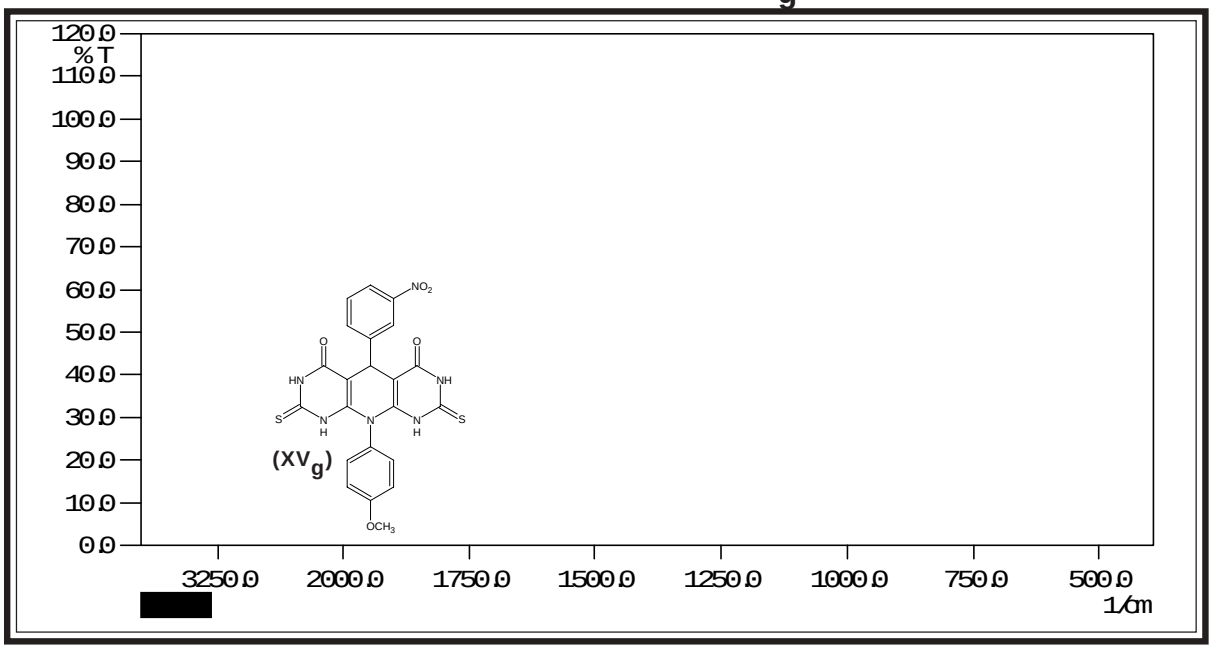


XV_{a-n} **R=Aryl**

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

The products (XV_{a-n}) were assayed for their *in vitro* biological assay like antibacterial activity towards ***S. pyogens MTCC-442*** and ***S. aureus MTCC-96*** (Gram positive) and ***E. coli MTCC-443*** and ***B. subtillis MTCC-441*** (Gram negative) bacterial strain and antifungal activity towards ***Aspergillus niger MTCC-282*** and ***Candida albicans MTCC-227*** at different concentrations (µg/ml) : 0 (control), 5, 10, 25, 50, 100, 200, 500 for their MIC (Minimum Inhibitory Concentration) values. The biological activities of the synthesized compounds were compared with standard drugs.

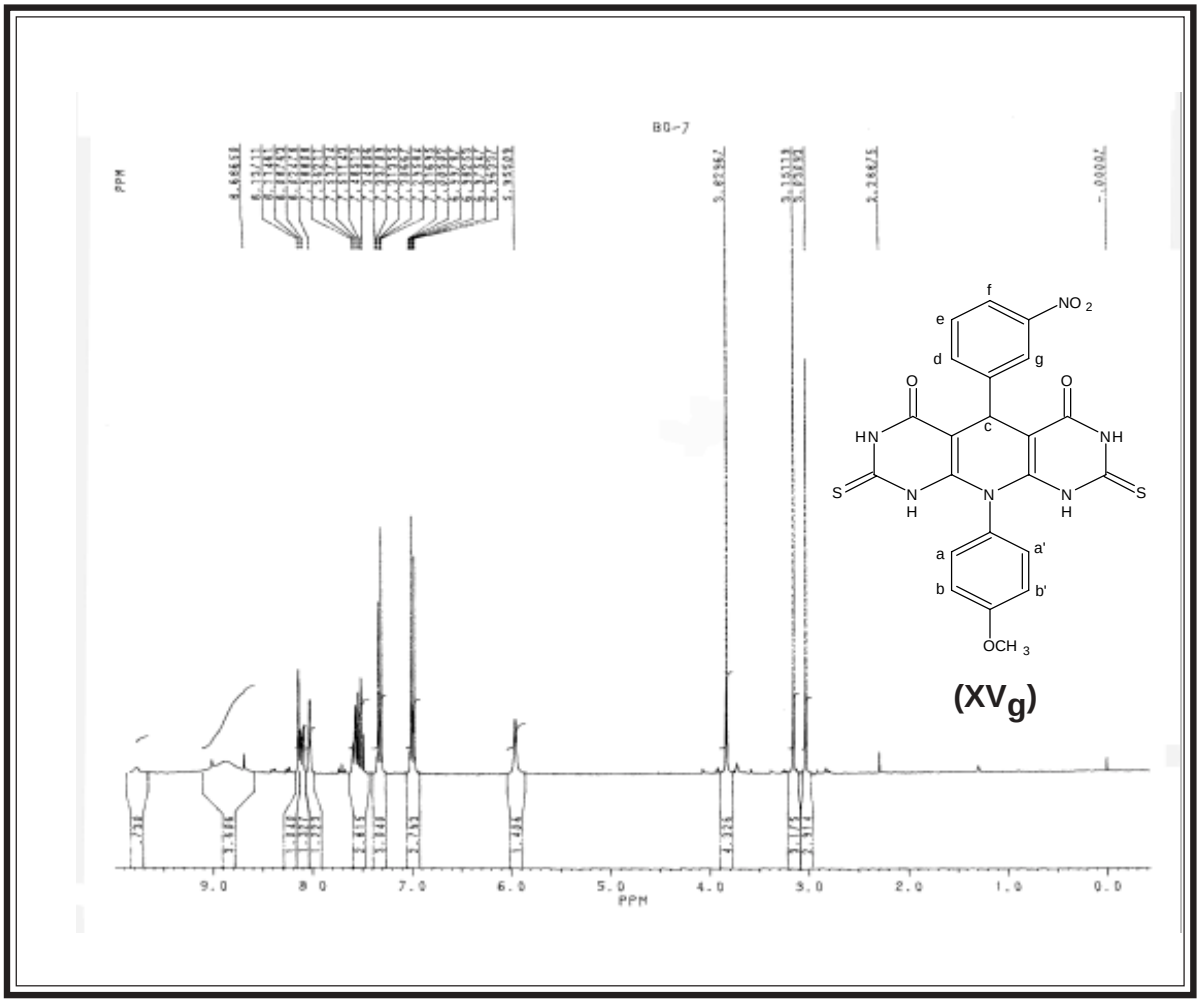
IR SPECTRAL STUDY OF 1,2,3,4, 6,7,8,9-OCTAHYDRO-10-(*p*-METHOXYPHENYL)-5-(*m*-NITROPHENYL)-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d:6,5-d']DIPYRIMIDINE (XV_g)



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C-H str.(asym.)	2956.7	2975-2950	343
CH_3	C-H str.(sym.)	2854.4	2880-2860	,,
	C-H def.(asym.)	1458.1	1460-1435	,,
	C-H def.(sym.)	1375.2	1385-1300	,,
Aromatic and	C=C + C=N and ring	1568.0	1520-1480	345
Pyrimidine moiety	skeletal vibration	1419.5	1580-1520	,,
	C-H str.	3022.2	3080-3030	,,
	C=C str.	1510.2	1520-1490	,,
	C-H i.p. def.	1105.1	1125-1090	,,
	C-H o.o.p. def.	827.4	840-810	,,
	C=S str.	1598.9	1650-1580	,,
Ether	C-O-C str. (asym.)	1257.5	1275-1200	346
	C-O-C str. (sym.)	1055.0	1075-1050	,,
Amine (Sec.)	N-H str.	3421.5	3500-3300	343
	N-H def.	1598.9	1650-1580	,,
Pyridine ring	C=N str.	1637.6	1650-1580	344
	C-N str.	1022.2	1200-1020	,,
Carbonyl	C=O str.	1714.6	1720-1665	,,

PMR SPECTRAL STUDY OF 1,2,3,4, 6,7,8,9-OCTAHYDRO-10-(*p*-METHOXYPHENYL)-5-(*m*-NITROPHENYL)-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d:6,5-d']DIPYRIMIDINE (XV_g)

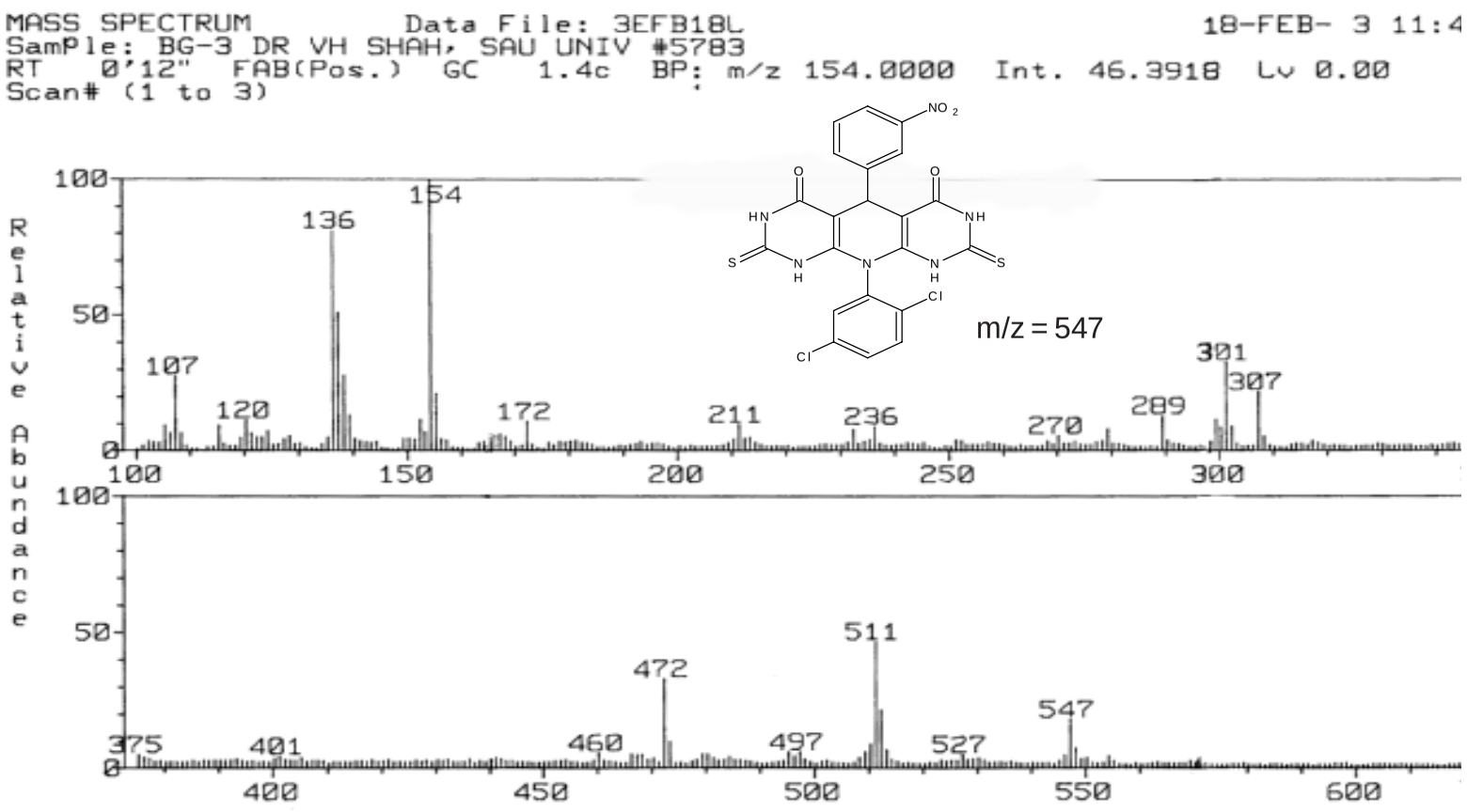


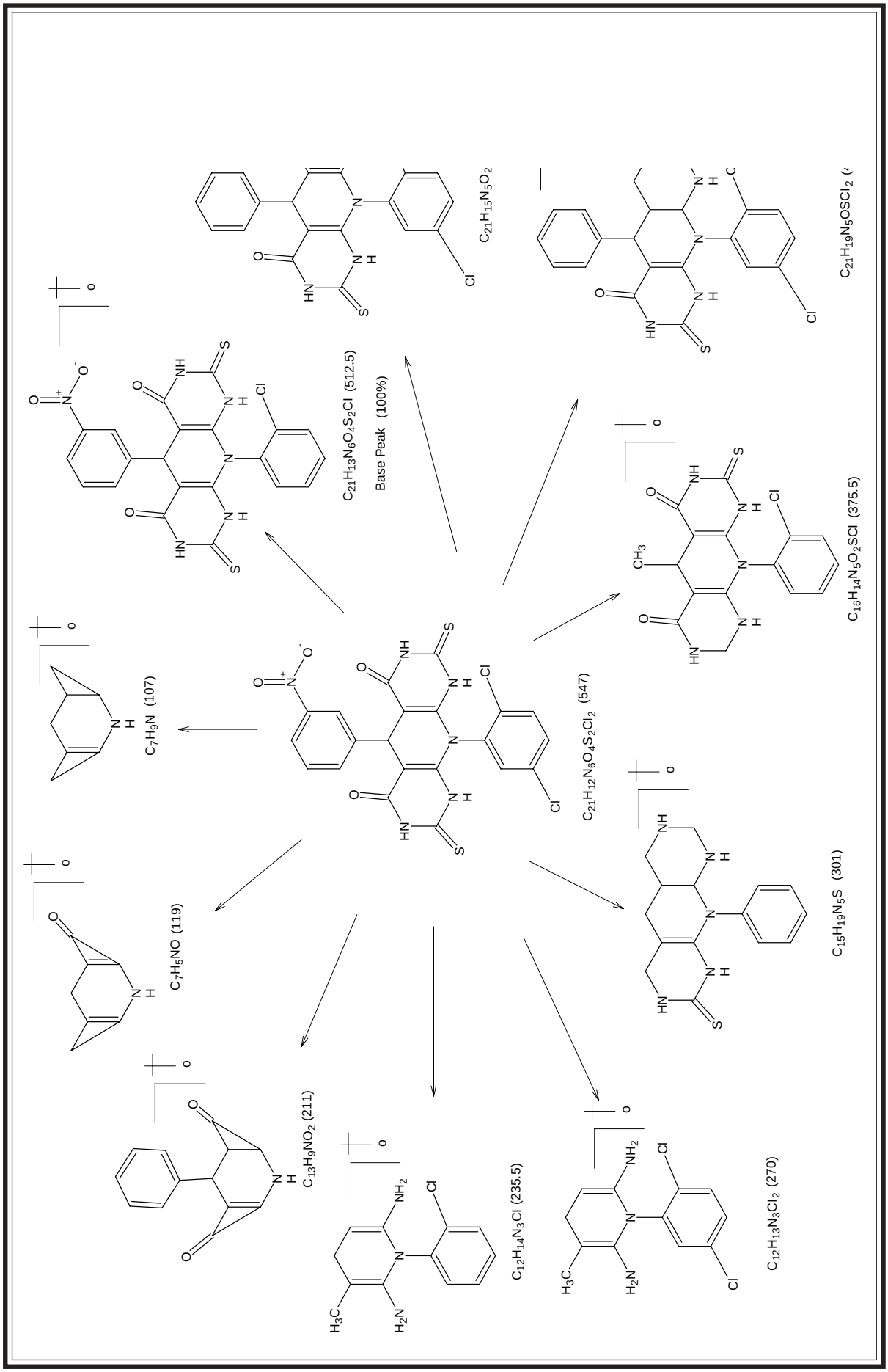
(XV_g)

Internal Standard : TMS ; Solvent ; $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

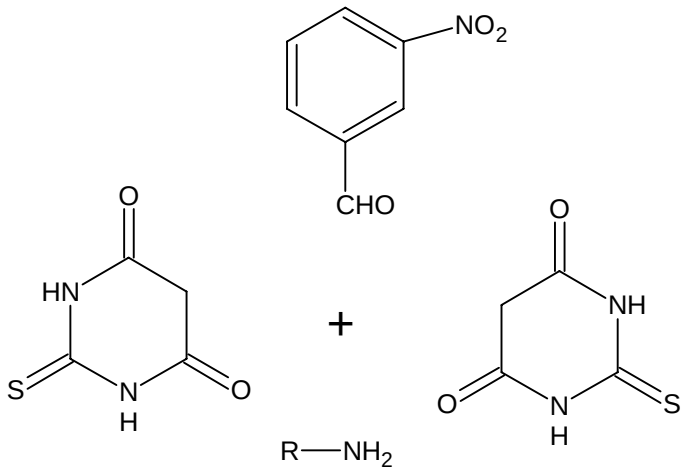
Signal No.	Signal Position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.830	3H	singlet	$-OCH_3$
2.	5.955	1H	singlet	Ar-H_c
3.	6.963-7.017	2H	doublet	Ar-$H_{b,b'}$
4.	7.296-7.348	2H	doublet	Ar-$H_{a,a'}$
5.	7.485-7.588	2H	multiplet	Ar-H_e ; Ar-H_d
6.	8.025	1H	doublet	Ar-H_g
7.	8.088-8.115	1H	double doublet	Ar-H_f

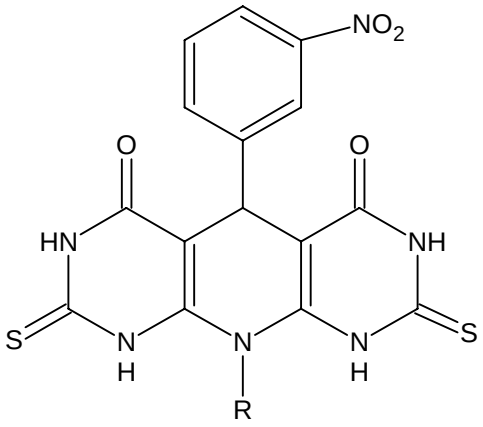
MASS SPECTRAL OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-(2',5'-DICHLOROPHENYL)-5-(*m*-NITROPHENYL)-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINE (XV_m)




C21H15N5O2
C21H19N5OSCl2
C21H13N6O4S2Cl (512.5)
Base Peak (100%)
C16H14N5O2SCl (375.5)
C21H12N6O4S2Cl2 (547)
C7H9N (107)
C15H19N5S (301)
C7H5NO (119)
C13H9NO2 (211)
C12H14N3Cl (235.5)
C12H13N3Cl2 (270)

REACTION SCHEME





(XV_{a-n}) **R = Aryl**

EXPERIMENTAL

PREPARATION AND BIOLOGICAL EVALUATION OF 1,2,3,4, 6,7,8,9-OCTAHYDRO-10-ARYL-5-(*m*-NITROPHENYL)-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d:6,5-d']DIPYRIMIDINES

(A) Preparation of 1,2,3,4,6,7,8,9-Octahydro-10-(*p*-methoxyphenyl) -5-(*m*-nitrophenyl)-2,8-dimercapto-4,6-dioxo-5H,10H-pyrido [2,3-d : 6,5- d']dipyrimidine (XV_i).

A mixture of *m*-nitrobenzaldehyde (1.51 gm, 0.01 M), thiobarbituric acid (2.92 gm, 0.02 M) and *p*-anisidine (1.23 gm, 0.01 M) in ethanol (30 ml) was heated under refluxed condition for six hrs. The content was poured into ice cold water. The separated solid was filtered and crystallized from DME:methanol (2:1). Yield : 79%, M.P. : 219°C, R_f : 0.53, (Required : C, 53.66%; H, 3.25%; N, 16.54% for $C_{22}H_{16}N_6O_5S_2$, Found : C, 53.60%; H, 3.20%; N, 16.49%).

Similarly, other compounds (XV_{a-n}) were synthesized. The physical data are recorded in Table No. 18.

(B) Antimicrobial activity of 1,2,3,4,6,7,8,9-Octahydro-10-aryl -5-(*m*-nitrophenyl)-2,8-dimercapto-4,6-dioxo-5H,10H-pyrido [2,3-d : 6,5- d']dipyrimidines (XV_{a-n}).

Antimicrobial activity testing was carried out as described in part-1, section-I, page No. 35. The MIC values of test solution are recorded in Table No. 18a, 18b & 18c. .

TABLE NO. 18 : PHYSICAL CONSTANTS OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-ARYL-5-(*m*-NITROPHENYL) -2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d']DIPYRIMIDINES (XV_{a-n})

Comp. No. 1	R 2	Molecular Formula 3	M. W. 4	M.P. °C 5	Yield % 6	R_f Value 7	% of Nitrogen	
							Required 8	Found 9
XVa	C_6H_5	$C_{21}H_{14}N_6O_4S_2$	478.0	187	73	0.48	17.57	17.51
XVb	2-Cl-C_6H_4	$C_{21}H_{13}N_6O_4S_2Cl$	512.5	195	70	0.51	16.39	16.34
XVc	3-Cl-C_6H_4	$C_{21}H_{13}N_6O_4S_2Cl$	512.5	219	68	0.46	16.39	16.35
XVd	4-Cl-C_6H_4	$C_{21}H_{13}N_6O_4S_2Cl$	512.5	>260	67	0.49	16.39	16.36
XVe	2-CH_3-C_6H_4	$C_{22}H_{16}N_6O_4S_2$	492.0	235	69	0.52	17.07	17.00
XVf	3-CH_3-C_6H_4	$C_{22}H_{16}N_6O_4S_2$	492.0	206	72	0.44	17.07	17.01
XVg	4-CH_3-C_6H_4	$C_{22}H_{16}N_6O_4S_2$	492.0	>260	75	0.51	17.07	17.02
XVh	2-CH_3O-C_6H_4	$C_{22}H_{16}N_6O_5S_2$	508.0	192	71	0.42	16.54	16.50
XVi	4-CH_3O-C_6H_4	$C_{22}H_{16}N_6O_5S_2$	508.0	219	79	0.53	16.54	16.49
XVj	2-NO_2-C_6H_4	$C_{21}H_{13}N_7O_6S_2$	523.0	235	76	0.47	18.74	18.70
XVk	3-NO_2-C_6H_4	$C_{21}H_{13}N_7O_6S_2$	523.0	172	72	0.49	18.74	18.69
XVl	4-NO_2-C_6H_4	$C_{21}H_{13}N_7O_6S_2$	523.0	>260	80	0.45	18.74	18.68
XVm	2,5-$(Cl)_2$-C_6H_3	$C_{21}H_{12}N_6O_4S_2Cl_3$	547.0	168	71	0.46	15.36	15.31
XVn	3,4-$(Cl)_2$-C_6H_3	$C_{21}H_{12}N_6O_4S_2Cl_3$	547.0	213	69	0.51	15.36	15.30

TLC solvent system ; Acetone : Benzene = 1.5 : 8.5

TABLE NO. 18a : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-ARYL-5-(*m*-NITROPHENYL)-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d'] DIPYRIMIDINES XV_{a-n} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) S. pyogens MTCC-442							S. aureus MTCC-96						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
XVa	C_6H_5	-	-	11	11	12	12	13	-	-	12	13	13	14	14
XVb	2-Cl-C_6H_4	-	-	12	12	13	14	14	-	-	14	14	15	17	17
XVc	3-Cl-C_6H_4	-	-	10	10	12	13	13	-	-	11	11	13	14	15
XVd	4-Cl-C_6H_4	-	-	11	11	12	14	14	-	-	12	12	13	15	15
XVe	2-CH_3-C_6H_4	-	-	10	11	12	13	13	-	-	12	13	14	15	15
XVf	3-CH_3-C_6H_4	-	-	10	10	11	13	13	-	-	12	12	14	15	15
XVg	4-CH_3-C_6H_4	-	-	12	12	12	14	14	-	-	13	13	15	15	16
XVh	2-OCH_3-C_6H_4	-	-	11	11	12	13	13	-	-	13	13	14	14	16
XVi	4-OCH_3-C_6H_4	-	-	12	12	13	13	14	-	-	14	14	15	16	17
XVj	2-NO_2-C_6H_4	-	-	10	10	12	12	14	-	-	12	12	14	15	17
XVk	3-NO_2-C_6H_4	-	-	10	11	12	13	14	-	-	11	12	14	16	16
XVl	4-NO_2-C_6H_4	-	-	11	11	12	13	14	-	-	13	13	14	15	17
XVm	2,5-Cl_2-C_6H_3	-	-	12	12	12	14	14	-	-	14	14	16	17	18
XVn	3,4-Cl_2-C_6H_3	-	-	10	10	12	12	13	-	-	11	11	14	15	17

Comparative activity of (XV_{a-n}) with known choosen standard drugs

Standard drug	Antibacterial activity														
											XVb XVi XVm	XVb XVi XVm	XVm		
Ampicillin	11	13	14	16	18	19	20	10	12	13	14	16	18	21	
Chloramphenicol	10	12	13	19	20	20	22	12	13	14	19	20	21	22	
Ciprofloxacin	16	18	19	21	21	22	22	17	18	19	21	22	22	23	
Norfloxacin	18	18	19	20	21	21	23	19	20	22	25	26	28	28	

N.B.(-): No Activity

TABLE NO. 18b : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-ARYL-5-(*m*-NITROPHENYL)-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d'] DIPYRIMIDINES XV_{a-n} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antibactrial activity (Zones of inhibition in mm) E. Coli MTCC-443							B. subtillis MTCC-441						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
XVa	C_6H_5	-	-	13	14	15	17	17	-	-	15	16	16	18	19
XVb	2-Cl-C_6H_4	-	-	15	15	16	16	18	-	-	17	18	18	19	19
XVc	3-Cl-C_6H_4	-	-	13	13	15	15	17	-	-	15	16	16	18	18
XVd	4-Cl-C_6H_4	-	-	14	15	15	17	17	-	-	16	16	17	19	19
XVe	2-CH_3-C_6H_4	-	-	13	14	15	16	17	-	-	14	15	16	17	18
XVf	3-CH_3-C_6H_4	-	-	14	14	16	16	18	-	-	15	16	17	17	19
XVg	4-CH_3-C_6H_4	-	-	14	14	16	16	17	-	-	16	17	18	18	19
XVh	2-OCH_3-C_6H_4	-	-	14	15	15	16	17	-	-	16	16	17	18	19
XVi	4-OCH_3-C_6H_4	-	-	14	15	17	17	18	-	-	16	16	18	18	19
XVj	2-NO_2-C_6H_4	-	-	13	13	15	17	18	-	-	15	15	16	17	19
XVk	3-NO_2-C_6H_4	-	-	13	14	14	15	17	-	-	14	14	16	17	19
XVl	4-NO_2-C_6H_4	-	-	14	15	15	17	18	-	-	16	16	18	18	19
XVm	2,5-Cl_2-C_6H_3	-	-	15	15	17	17	18	-	-	16	16	17	18	19
XVn	3,4-Cl_2-C_6H_3	-	-	12	14	15	17	17	-	-	14	15	17	18	19

Comparative activity of (XV_{a-n}) with known choosen standard drugs

Standard drug	Antibacterial activity														
			XVb XVm							XVb					
Ampicillin	14	14	15	16	19	20	22	12	16	18	19	20	21	23
Chloramphenicol	14	15	17	23	23	23	23	12	14	16	19	22	23	23
Ciprofloxacin	20	21	23	28	28	28	28	16	17	19	22	22	23	23
Norfloxacin	22	23	25	26	27	29	29	19	20	22	23	24	25	28

N.B.(-): No Activity

TABLE NO. 18c : COMPARATIVE ANTIMICROBIAL ACTIVITY OF 1,2,3,4,6,7,8,9-OCTAHYDRO-10-ARYL-5-(*m*-NITROPHENYL)-2,8-DIMERCAPTO-4,6-DIOXO-5H,10H-PYRIDO[2,3-d : 6,5-d'] DIPYRIMIDINES XV_{a-n} (Minimum inhibition Concentration in µg/ml)

Compd No.	R	Antifungal activity (Zones of inhibition in mm) C. albicans MTCC-227							A. niger MTCC-282						
		5	10	25	50	100	250	500	5	10	25	50	100	250	500
XVa	C_6H_5	-	-	17	18	20	20	22	-	-	19	19	21	22	23
XVb	2-Cl-C_6H_4	-	-	18	18	20	21	21	-	-	19	19	20	22	23
XVc	3-Cl-C_6H_4	-	-	17	18	19	20	21	-	-	18	19	21	22	24
XVd	4-Cl-C_6H_4	-	-	17	17	17	20	20	-	-	18	18	18	20	21
XVe	2-CH_3-C_6H_4	-	-	17	17	18	19	20	-	-	18	19	20	21	21
XVf	3-CH_3-C_6H_4	-	-	18	18	20	20	22	-	-	19	19	21	22	23
XVg	4-CH_3-C_6H_4	-	-	17	17	19	20	20	-	-	19	19	20	22	22
XVh	2-OCH_3-C_6H_4	-	-	18	18	20	21	21	-	-	19	19	21	22	23
XVi	4-OCH_3-C_6H_4	-	-	17	17	19	20	22	-	-	18	18	20	22	24
XVj	2-NO_2-C_6H_4	-	-	18	18	20	20	21	-	-	19	19	21	22	22
XVk	3-NO_2-C_6H_4	-	-	17	17	19	20	21	-	-	18	18	21	21	23
XVl	4-NO_2-C_6H_4	-	-	18	18	20	20	21	-	-	19	19	21	22	24
XVm	2,5-Cl_2-C_6H_3	-	-	18	18	19	20	21	-	-	19	19	20	22	23
XVn	3,4-Cl_2-C_6H_3	-	-	17	17	20	21	21	-	-	18	18	20	22	24
Comparative activity of (XV_{a-n}) with known choosen standard drugs															
Standard drug		**Antifungal activity**													
griseofulvin		19	22	23	25	25	28	28	18	19	21	22	22	24	26

N.B.(-): No Activity

REFERENCES

261. Roland K. Robins, Geo.H. Hitchigns (WellcomeResearch Labs.); *J.Am.Chem.Soc.,* **77,** 2256-60 (1955) ; *Chem. Abstr.,* **50,** 2604h (1956).

262. Santilli, Arthur A., Kim, Dong A. (American Home Products Corp.); *U.S.* **3,** 725, 405, (Cl. 260/2472; C04d), 3 Apr. 1973, Appl. **47,** 571, 18 Jun 1970; 4pp. *Chem. Abstr.,* **78,** 159651v (1973).

263. Lesher, George Y., Singh, Baldev (Sterling Drug, Inc.); *U.S.* **3,** 992, 380 (Cl. 260-256. 4F; C07D 487/04), 16 Nov. 1976, Appl. 555, 051, 03, Mar. 1975; *Chem. Abstr.,* **86,** 9874j (1977).

264. Hisamitsu Pharmaceutical Co.Inc.; *Jpn.Tokkyo Koho* **Jp 58,** 02 953 (Cl. C07D 471/04) (1983); *Chem. Abstr.,* **98,** 215613m (1983).

265. FahmyS.M., Mohreb R.M.(Egypt); Tetrahedron, **42(2),** 687-90 (1986); *Chem. Abstr.,* **106,** 32780c (1987).

266. J.Reish, C.O.Usifoh,; *J.Het.Chem.,* **27,** 287 (1990).

267. Yadav, Ashok K., Agrawal, Hemlata, Singh., Arpita,Prakash, Lalit; *Indian.J.Hetro. Chem.,* **6(3),** 237-238 (1997).

268. KrishnaA.Rao, Jaywant N.Gardre, Suhas Pendeker; *Indian.J.Chem.,* **36(B),** 410-13 (1997).

269. Francisco Peradones, Jose L-Soto; *J.Het.Chem.,* **35,** 413 (1998).

270. Jairo Quiroga, Mario Alvarado, Braulio Industyl; *J.Het.Chem.,* **35,** 1309 (1998).

271. M.B.Deshmukh, M.A.Shelar, M.Mittelbach, H.Junek; *Indian.J.Chem.,* **37(B),** 491-493 (1998).

272. P. Saikia, A. J. Thakur, D. Prajapati, J. S. Sandhu; *Indian.J.Chem.,* **41B (4),** 804-807 (2002); *Chem.Abstr.,* **137,** 185463s (2002).

273. R.N. Kumar, T. Suresh, P.S. Mohan; *Oriental J.Chem.,* **18(1),** 93-96 (2002); *Chem.Abstr.,* **137,** 279160t (2002).

274. Das A., Miss Shahu, K.Mishra, B.K. Behera G.B.; *Chem. Abstr.,* **104,** 148823g (1985).

275. Kihara, Noriaki, Ishida, Tatsuyoshi, Isayama, Shigera; *PCT Int. Appl.* **WO 86,** 01, 207 (Cl. C07D 471/04) (1986); *Chem.Abstr.,* **105,** 24277 (1986).

276. A.Gangjee, A.Vasudevan, F.Queener; *J.med.Chem.,* **38,** 1778 (1995); *Chem. Abstr.,* **125,** 33667a (1996).

277. E.M.Grivsky, S.Lee, C.W.Sigel, D.S.Duch, C.A.Nichol; *J.Med.Chem.,* **23,** 327(1987).

278. Franscisco Perandones, Jose L-Soto; *J.Het.Chem.,* **35,** 413 (1998).

279. Nisigaki, Sadao, Ogiwara, Kafuko; Senga, Keitatro; Fukafawa, Shinobu; *Aida.Chem.Pharm.Bull.,* **18(7),**1385-93 (1970); *Chem.Abstr.,* **73 ,** 66530m (1970).

280. Matsumoto, Junichi; Sekine, Yutaka; Takase, Yoshiyuki; (Dainippon. Pharmaceutical Co.) *Ger.Offen.,* **2,** 143, 369 (Cl. C07d), 09 Mar 1972, *Japan Appl.* 70 75,812,29,29 Aug 1970, 28pp.;*Chem.Abstr.,* **77,** 345594 (1972).

281. Matsumoto, Junichi; Miyamoto, Akiyuki; *Jpn.KokaiTokkyoKoho,* **80,** 36, 436 (Cl. C07D 471/04), 14 Mar, 1980 Appl. 78/110, 268, 07 Sep. 1976, 3pp.; *Chem. Abstr.,* **93,** 132509c (1980).

282. Daito-Koeki Co. Ltd., *Jpn. Kokai Tokkyo Koho.,* **81,** 97, 287(Cl. Co7D 471/04) 05 Aug 1981, Appl. 80/726, 3pp.; *Chem.Abstr.,* **95,** 203995n (1981).

283. M.Yu. Gavrilov, G.N. Rudometova, M.E. Korishin; Russ. **RU 2,** 148, 580 (Cl.C07 D471/14) 10May 2000, Appl. 99, 102, 459, 9Feb 1999, 5pp.; *Chem. Abstr.,* **136,** 247595b (2002).

284. F. Soliman, N.F. Abd Et-Ghafar, N.T. Dawood; *Al-Azhar Bulletin of science,* 2000, **11(2),** 147-154pp.(Eng).; *Chem. Abstr.,* **137,** 310879k (2002).

285. Duch. David S., Sigel, Carl W., Bowers, Seaton W., Edelstein, Mark P.; (USA); *Curr. Chemother.Infect.Dis.Proc.Inf.Congr.Chemother.,*11th (1979); Chem.Abstr., **93**, 88634p (1980).

286. Duch, David S.,Edelstein,Mark P.,Nichol,Charles A. (USA) ; *Mol.Pharmacol.,* **18(1),** 100-4 (Eng) (1980); *Chem.Abstr.,* **93,** 142916x (1980).

287. H.A. Parish, R.D. Gilliom, W.P. Purcell, R.K. Browne, R.F. Spirk, H.D. White ; *J.Med.Chem.,* **25,** 98 (1982).

288. A.Monge, V.Martinez, Merino E. Cenaruzalbeitia, B. Lasheras, E. Feranamdez, Alvarez; *Eur. J. med. Chem.,* **20,** 61 (1985).

289. Bornochein, Inga; Kraft, Regina; Pfeifer S.; *Pharmazie,* **34(11)**, 732-5 (Ger) (1979); *Chem.Abstr.,* **93,** 323c (1980).

290. Yuragi, Shoijiro, Kikuchi, Shintaro (Takeda Chemical Industries Ltd.); *Ger. Offen.,* **2,** 242, 162 (Cl. C07d, A61K), 08 Mar (1973); Japan Appl., **71,** 66, 03, 28 Aug; 18 pp (1971), *Chem.Abstr.,* **78,** 147993v (1973).

291. Mongenega, Antonio, Martinez Merino, Victor, Sanmartin Grijalba (Antibiotics Farma, S.A.); Span, **E 52,** 056, 742 (Cl. C07D 471/04), 01 Oct.(1994) , Appl. 9, 300, 358, 24 Feb 13 pp.(1993); *Chem.Abstr.,* **122,** 187601c (1995).

292. D.A. Vanden Berghe, A.J. Vlietinck; *J.Het.Chem.,* **25,** 217 (1988).

293. Gary L. Anderson; *J.Hetro.Chem.,* **22,** 1469 (1985).

294. Herold, Franciszek, Pyzemyk, Barbars, Szafranski, Bohdan; *Acta.Pol.Pharm.,* **49(3),** 85-91 (Pol) (1992); *Chem.Abstr.,* **120,** 244932t (1994).

295. Sladowska, H.Zawisza,; *Farmaco.Ed.Sci.,* **41(2),** 954-63 (Eng) (1986); *Chem.Abstr.,* **127,** 58917t (1987).

296. H. Akimoto, T. Miwa, K. Otsu; *Japan Patent,* **04,** 235, 986 (1992); *Chem.Abstr.,* **118,** 213101q (1993).

297. G.L. Anderson, J.L. Shim, A.D. Broom; *J.Org.Chem.,* **41,** 1095 (1976).

298. Syam K. Singh, John Hynes (USA); *J.Het.Chem.,* **28,** 977 (1991).

299. Maria Teresa Cocco, Cenzocongiu, Antonio Mccioni, Valentinaonnis; *J.Hetro.Chem.,* **30,** 253 (1993).

300. Taylor, Edward C; Lee, Koo (Dept. Chemistry, Princeton University, Princeton, NJ 08544, USA); *Heterocycles,* **45(11),** 2229-2237 (Eng) (1997); *Chem. Abstr. ,***128,** 48194e (1998).

301. Shih, Chuan, Gossett, Lynn S., Gill,William J., Taylor, Edward C., Metz, James T.; (Cl. 517-258; C07D 47/02) 28 Jul (1998); Appl. 708, 351, 4 Sep17 pp (Eng) (1996); *Chem.Abstr.,***129,** 149259t (1998).

302. Juby, Peter (Bristol-Myers Co.); *U.S.* **4,** 122, 274 (Cl. 544-282 ; C07D 471/04), 24 Oct. 1978); Appl. 800, 264, 25 May 19 pp (1971); *Chem. Abstr.,* **90,** 1039984 (1979).

303. Dave C.G., Shah P.R., Desai V.B., Srinivasan S.; *Indian.J.Pharm.Sci.,* **44(4),** 83-5 (Eng) (1982); *Chem.Abstr.,* **98,** 53822y (1983).

304. Hardtmann,Goetz E., Ott, Hans; *Ger.Offen.,* **1,** 961, 326 (Cl. C07D), 09 Jul 1970, *US* Appl.10 Dec36 pp.(1968); *Chem.Abstr.,* **73,** 77280t (1970).

305. Noda, Kanji, Nakagawa, Akira,Yamagata, Kenji,Yoshitake, Taddaki, Noguchi, (Hisamitsu Pharm. Co. Ltd.); Japan Kokai Tokkyo Koho, **76** 41, 394 (Cl.C07D47/04), 07 Apr. (1976); Appl.74/109, 121, 20 Sep.4 pp (1974); *Chem.Abstr.,* **86,** 29861t (1977).

306. Sato, Akeshi, Aikawa, Norio (Kanebo Ltd.); *Japan Kokai Tokkyo koho.,* **76** 54, 594 (Cl. C07D 471/04),13 May (1976); Appl. 74/116, 298, 2 pp 09 Oct.(1974); *Chem. Abstr.,* **86,** 43731g (1977).

307. Santilli, Arthur A., Kim, Dong H. (American Home Products Corp.) *U.S.* **3,** 795, 674 (Cl. 260-256 4N; C07d), 05 Mar.(1974); Appl. 47, 571, 18 Jun.3 pp (1970); Chem. Abstr., **80,** 120994q (1974).

308. Raddatz, Peter, Weber, Wolf Dietrich, Barber, Andrew, Wolf; *Ger.Offen.,* **DE 3,** 738, 844 (Cl. A61K 31/505) 24 May (1989), Appl. 16 Nov. (1988); 8 pp; *Chem.Abstr.,* **112,** 7502e (1990).

309. Hisamitsu Pharmaceutical Co.Inc.; *Jpn.Tokkyo Koho.* **Jp 57** 60, 352 [82 60, 352] (Cl. C07D 471/04); *Chem.Abstr.,* **98,** 198269j (1983).

310. Hisamitsu Pharmaceutical Ltd., *Jpn.Tokkyo Koho* **Jp 58** 00, 429 [83 00, 429] (Cl. C07D 471/04); *Chem.Abstr.,* **98,** 179411h (1983).

311. Bernier J.L., Henichart J.P.; Warin V., Bacart F.; *J.Pharm.Sci.*, **69(11),** 1343-5 (Eng) (1980); *Chem.Abstr.,* **94,** 139745f (1981).

312. T. Toshiaki, F. Hilomichi, T. Yoshio; *Jpn.Kokai Tokkyo Koho* **Jp** (Cl. CO7D 47/04); *Chem.Abstr.,* **107,** 39854j (1987).

313. Kleinochroth, Juergen , Satzinger, Gerhend, Mannhardt, Karl, Hartenstein, Osswald, Hartmut; *Ger.Offen.* **DE 3,** 438, 351 (Cl. C07D 471/04); *Chem.Abstr.,* **105,** 133903e (1986).

314. Yokoyama, Keiichi, Kato; Koji, Kitahara, Tamuki; Nishina, Takashi; Awaya, Kumakura; *Eur. Pat.* Appl. **Ep.** 188, 094 (Cl. C07D 471/04) 23 Jul. (1986); Appl. 84/263, 015, 235 pp; *Chem.Abstr.,* **105,** 208919a (1986).

315. C.John Blankley, Lawrence R. Bennett, Robert W. Fleming, Roland D. Smith; *J.Med.Chem.,* **26,** 403 (1983).

316. Nickl Josef; Mueller, Erich, Narr, Berthold, Roch, Josef (Thomae, Dr. Karl G. m. b. H.), *Ger.Offen.,* **2,** 117, 657 (Cl. C07D) 19 Oct(1972), Appl. P. 21 17 657.8, 10 Apr.(1971) 37; *Chem.Abstr.,* **78,** 29811m (1973).

317. Chornat Robert J., Prodam, Kathleen A., Adelstein, Gilbert W., Stamm, Margarete H., Frederick; *J.Med.Chem.,* **28(9),** 1285-91 (1985).

318. Yuki, Hiroshi, Naka, Yoichi (Yoshitomi Pharm. Industries Ltd.); Japan Kokai Tokkyo koho, **76,** 139, 633 (Cl. C07D 471/04), 02 Dec.(1976) ,Appl.75/63, 857,5 pp.; *Chem. Abstr.,* **87,** 23318v (1977).

319. Osselaere, J.P., Lapiere, C.L. (Inst. Pharm. Univ. Liege, Belg.); *Ann.Pharm.Fr.,* **32(11),** 575-9 (Fr.) (1974); *Chem.Abstr.,* **83,** 9970n (1975).

320. Fujita Hiroshi, Shimoji Yasuo, Kojima Shunshi, Nishino Hiroshi, Kamoshita (Sanyo Co.Ltd.Tokkyo Japan); Sankyo Kenkyusho Nempo 29, 75-98 (Eng) (1977), *Chem. Abstr.,* **89,** 43299j (1978).

321. W. Von Behenburg, J.Engel, J.Heese, Thiele; *Ger.Offen.* **DE 3,** 337, 593 (Cl. C07 D 213/72) (1984); *Chem.Abstr.,* **101,** 130595n (1984).

322. Uros Urleh, Branko Stainovkin, Miha Tisler; *J.Het.Chem.,* **27,** 643 (1990).

323. Minami Shinsaku, Matsumoto Junichi; *Japan Kokai Tokkyo koho .,* **74** 11, 720 (Cl. C07D, A61K), 19 Mar.(1974), Appl. **70** 127, 163, 26 Dec. 1970; 3 pp; *Chem.Abstr.,* **81,** 91550r (1974).

324. Kowalska Teresa, Kowalski Piotr, Rutkowski Kazimierz, Wozniak Marian; *Acta.Pol. Pharm.,* **51(2),** 143-8 (Eng)(1994); *Chem.Abstr.,* **122,** 187520x (1995).

325. Fujiwara Hiromichi, Sato Shogo, Takahashi Yashio, Tamura Toshiaki; *Jpn.Kokai Tokkyo Koho* **Jp 62,** 142, 171 [87 142, 171] (Cl. C07D 471/04); *Chem.Abstr.,* **107,** 236738a (1987).

326. Lowe John Adams; *Eur.Pat.* Appl.**Ep 260**, 817 (Cl. C07D 471/04) (1988); *Chem.Abstr.,* **109,** 22980r (1988).

327. WEB Leuna-Werke, “Waiter Ulbricht” (by WL Hoefling, D. Elhaner and G. Reckling); *Ger.Offen.,* **1,** 193, 506 (Cl. C07D) (1965); *Chem.Abstr.,* **63,** 6919 (1965).

328. Hammama Abou, Elfatoon G., Z. Naturforch B.; *Chem. Sci.* (2000).

329. Gangjee Aleem, Devraj Rajesh, Queena Sherry F.; *J.Med.Chem.,* **40(4),** 470-78 (Eng) (1997); *Chem.Abstr.,* **126,** 131431j (1998).

330. R.F. Meyer (Parke Davis and Co.), *U.S.* **3,** 639, 401 (Cl. 260-256.4 ; C07d) (1972); *Chem.Abstr.,* **76,** 113241s (1972).

331. S. Minami, M. Junichi, S. Masanao, TekaseYoshiyaki; *Ger. Offen.,* **2,** 362, 558 (Cl. C07d), 20 Jun. (1974), Japan Appl. 72 126, 968, 43, pp18 Dec.(1972); *Chem.Abstr.,* **81,** 1055621c (1974).

332. A. Santilli, K. Dong (American Home Products Corp.), *U.S.* **3,** 843, 645 (Cl. 260-247 2B; (C07d) (1974); *Chem.Abstr.,* **82,** 43455n (1975).

333. R .P. James, I.T. Joseph, C.P. Hiroaki; *Chem.Abstr.,* **106,** 501494h (1987).

334. T. Bear, W. Wrich, P. Zimmermann, H. Boss; PCT Int. Appl. **WO 94**, 14, 809 (Cl. C07D 471/04), 07 Jul. 1994; *Chem.Abstr.,* **122,** 290877t (1995).

335. C.J. Blankyel, A.M. Doherty, J.M. Hamby, R.L. Ranek, Schoeder Melconrad; PCT Int. Appl. **WO 96,** 15, 128 (Cl. C07D 471/04), 23 May 1996; US Appl.339,051,14 Nov.1994; 134 pp. (Eng); *Chem.Abstr.,***125,** 114688k (1996).

336. H. Sato, M. Sugizaki, S. Myaoka; *Jpn.Kokai Tokkyo Koho* **Jp 08,** 143, 568 [96, 143, 568] (Cl. C07D 471/04), 4 Jun. 1996, Appl. 94/287, 626, 22 Nov.1994; 24pp. (Japan); *Chem.Abstr.,* **125,** 168007f (1996).

337. Y. Yonezawa, H. Kasugawa; *Jpn.Kokai Tokkyo Koho* **Jp 09**, 295, 977 [97 295, 977] (Cl. C07D 471/04), 18 Nov. 1997, Appl. 96/109, 864, 30 Apr. 1996; 20 pp, (Japan); *Chem.Abstr.,* **128,** 48234t (1998).

338. E.C. Taylor, P. Gillespie (Trustees of Princeton Uni, USA); PCT Int.Appl. **WO 97,** 49, 705 (Cl. C07D 471/04), 31 Dec. 1997; US Appl. 20, 398, 25 Jun. 1996; 25pp. *Chem.Abstr.,***128,** 89102s (1998).

339. D.H. Boschelli, E.M. Dobrusin, A. Doherty (Cl. C07D 471/00), (1998) ; *U.S.* Appl.**69**, 743, ,170 pp (Eng) 16 Dec.(1997);*Chem.Abstr.,***129,** 161569q (1998).

340. J.B. Kramer, J.M. Hamby, S.Kramer; (Warner-Lambert Company, USA) PCT Int. Appl. **WO 02,** 12, 238; *Chem.Abstr.*,**136,** 183833t (2002).

341. H. Zhou, M.R. Barvian, R.J. Richard, J. Quin, J.T. Repine, D.J. Sheehan, P.L.Toogood, S.N. Vanderwel; (Warner-Lambert Company LIC, USA) PCT Int. Appl. **WO 03,** 62,236 (Cl. C07D471/04), 31 Jul 2003, US. Appl. PV 350, 877, 22Jan 2002; 146pp.(Eng). *Chem.Abstr.*,**139,**149646m (2003).

342. C.N. Rao; Chemical Application of Infra Red Spectroscopy, Academic Press, New Yorik, 317-333 (1963).

343. V.M. Parikh; Absorption Spectroscopy of Organic Molecules; Addission-Wesley Publishing Company, 243-58 (1978)

344. D.H. Williams and L. Fleming; “Spectroscopic Methods of Organic Chemistry”, 2nd Edition, London.

345. F.V. Loffe; *Khim. Geterokeikl. Soidin,* **6,** 1089 (1968).

346. N.B. Calthup, L.H. Paly and Stephen C. Wiberely, ” Introduction of IR and Raman Spectroscopy “ ; *Academic Press Inter Edu.* (1964).

NOTES

1. All the temperatures are expressed in degree **centigrade (^{0}C).**
2. All melting points are uncorrected and have been recorded by **open capillary method.**
3. Room temperature wherever mentioned, normally corresponds to **28-33 ^{0}C.**
4. Silica gel-G was used for preparing the plates for TLC using different solvent systems.
5. Infra red spectra were recorded on **SHIMADZU-FTIR-8400 Spectrophotometer** using KBr disc.
6. PMR Spectra were recorded on **BRUKER Spectrophotometer (300 MHz)** using TMS as a internal standard and $CDCl_3$, $DMSOd_6$ and TFA as solvents.
7. FAB mass spectra were recorded on **JEOL SX 102/DA-600-Mass Spectrometer.** The matrix peaks appear at m/z 136,137, 154,289,307 in the absence of any metal ions were not shown for mass fragmentations.