DISCOVERING THE NEW HETEROCYCLES OF THERAPEUTIC INTEREST

A THESIS
SUBMITTED TO THE
SAURASHTRA UNIVERSITY
FOR THE DEGREE OF

Doctor of Philosophy

IN
THE FACULTY OF SCIENCE (CHEMISTRY)

BY

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UNDER THE GUIDANCE
OF

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

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

Date : - 02- 2004 ***(Acharya Hitarth H.)***

Place : Rajkot

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

Date : - 02- 2004

Place : Rajkot

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ACKNOWLEDGEMENTS

It is with great pleasure and proud priviledge that I wish to express from the deepest core of my heart, the feelings of reverence and indebtedness to my learned Guide and Esteemed teacher Dr.H.H.Parekh, Prof. and Head, Department of Chemistry, Saurashtra University, for her faith in me, her conviction, inspiration, diligencee and ever viligant guidence without which the aims and objectives of the present work could not have been achieved.

I owe a great deal to Dr. A.R.Parikh, Rtd. Professor and Head, Department of Chemistry, Saurashtra University, who always showed deep concern and was always approachable in time to show the silver lining in every dark cloud that came across and his contribution continues to be the high spot of excellence.

I wish to thank Dr. N.A.Chauhan, for his constant guidance and moral support during the course of my research work.

Above all, needless to say "Thanks" is insufficient gratitude for my mother, Devangnaben for her unsurpassable devotion to the family, my father, Harshendubhai for his uncompromising principles which are guiding my life and my Grandmother Lt.Jivantikaben, who backed me all through the course of my study with her blessings. I would be remissed if I failed to express my special gratitude to my younger brother, Yatin whose unstopping flow of love helped me to reach the goal.

As with the completion of this task, I find myself in difficult position on attempting to express my deep indebtedness to Dr. Ranjan, Dr. Neela and Dr. Fatema. I wish to thank Ashish for his most willing co-operation and comprehensive exchange of ideas during the course of my research work.

I feel lucky and very proud to have intimate friends like Bharat, Mukesh, Rajendra, Parag, Mayur and Milan who have been always participating with my problems and disappointments and rebuilt my confidence at appropriate stages.

I offer my heartfull gratitude to Prafull, Dinesh, Snehal, Siddharth, Ashok, Kanji, Harshad, Ravi and all my seniors for their support and constructive criticism at various stages. I also like to thank my juniors who proved at all times a valiant comrade-at-arms.

I am very grateful to Mr. Devendra Goswami, who shepherded this thesis from manuscrtipts to finished pages.

I am thankful to the authorities of CDRI Lucknow, CIL Chandigarh, Dr. V. K. Kansal, Vice President, R & D Department, Alembic Ltd., Baroda for allowing us to use his library facility which is highly benifited and to the authoroties of Saurashtra University for providing all the necessary facilities and Junior Research Felloship during my research work.

My heart felt thanks are due to the esteemed organisation Tuberculosis Antimicrobial Acquisition and Co-ordinating Facilities, Alabama U.S.A. for kind cooperation extended by them for biological screening.

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

Acharya Hitarth H.

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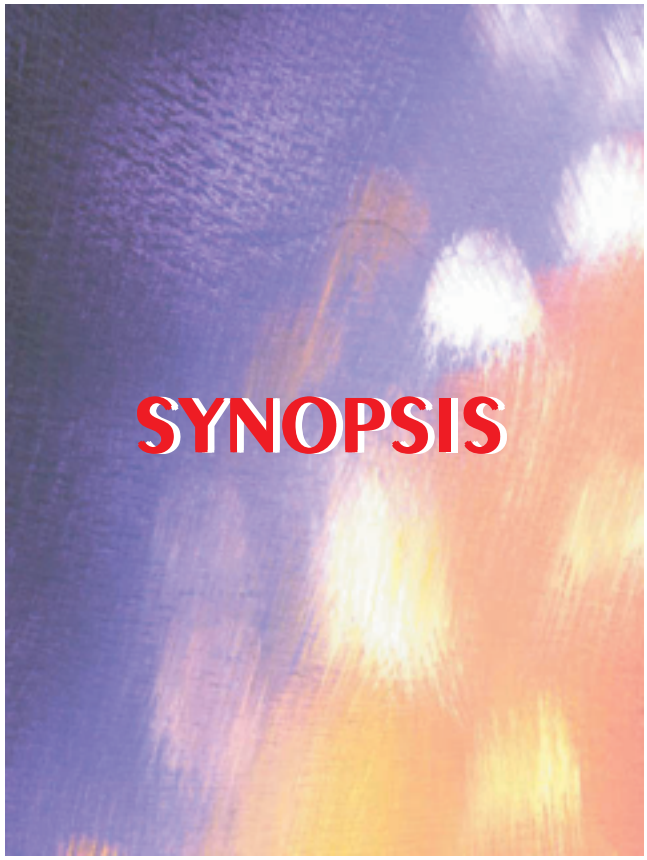
SYNOPSIS

Synopsis

DISCOVERING THE NEW HETEROCYCLES OF THERAPEUTIC INTEREST

Acharya Hitarth H.

September - 2003

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

Faculty	:	Science
Subject	:	Chemistry
Title	:	"**DISCOVERING THE NEW HETEROCYCLES OF THERAPEUTIC INTEREST**"
Name of the Candidate	:	**Acharya Hitarth H.**
Registration number	:	2634
Date of Registration	:	28th September 2001
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Submitted to	:	Saurashtra University

Place of Work

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(GUJARAT STATE - INDIA)

A brief summary of the work to be presented in the thesis entitled "DISCOVERING THE NEW HETEROCYCLES OF THERAPEUTIC INTEREST" has been described as under.

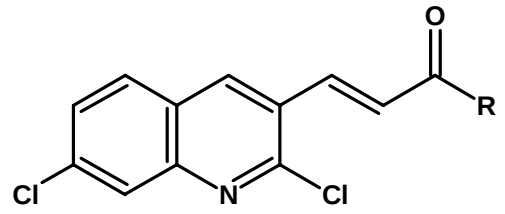
[A] STUDIES ON QUINOLINE DERIVATIVES

The group of the compounds containing quinoline moiety are a prominent structural feature in a variety of natural products like echipsine, quinine and cinchonine as well as in other compounds of medicinal interest and have attracted attention for their biological activities viz. CNS depressant, hypnotic, sedatives, antimalarial, antiinflammatory, fungicidal, analgesic, antitumor, antiulcer, anticonvulsant, antidiabetic, antiarrhythmic, antitumor, antagonist and antidepressant. Taking in view of the applicability of heterocyclic compounds, we have undertaken the synthesis of heterocycles like pyrazolines, isoxazoles, imidazolines, cyanopyridines, cyanopyridones, pyrimidinones, arylidines, barbitones and nitriles bearing 2,7-dichloroquinoline-3-carboxaldehyde nucleus. Our efforts are focused on the introduction of chemical diversity in the molecular frame work in order to synthesise pharmacologically interesting compounds of widely different composition.

PART - I : STUDIES ON PYRAZOLINES

Pyrazolines have been found to possess bactericidal, fungicidal, antiviral and other pharmacological properties like tuberculostatic, local anaesthetic, CNS depressant, anticonvulsant, antiinflammatory, analgesic, antipyretic, antidepressant and antifertile activities. Hence it was thought worthwhile to synthesise pyrazoline derivatives for better drug potential, which have been described in following sections.

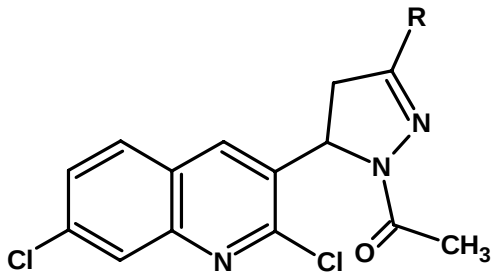
SECTION - I : Synthesis, characterisation and therapeutic evaluation of 1-Aryl-3-(2',7'-dichloroquinolin-3'-yl)-2-propene-1-ones



Type (I) **R = Aryl**

The chalcones of type (I) have been synthesised by the condensation of 2,7-dichloroquinoline-3-carboxaldehyde with various aromatic ketones.

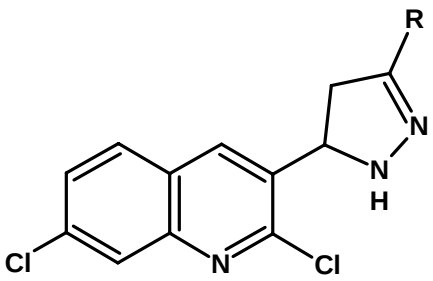
SECTION - II : Synthesis, characterisation and therapeutic evaluation of 1-Acetyl-3-aryl-5-(2',7'-dichloroquinolin-3'-yl)-pyrazolines



Type (II) **R = Aryl**

Pyrazolines of type (II) have been prepared by the condensation of the chalcones of type (I) with hydrazine hydrate and acetic acid.

SECTION - III : Synthesis, characterisation and therapeutic evaluation of 1H-3-Aryl-5-(2',7'-dichloroquinolin-3'-yl)-pyrazolines



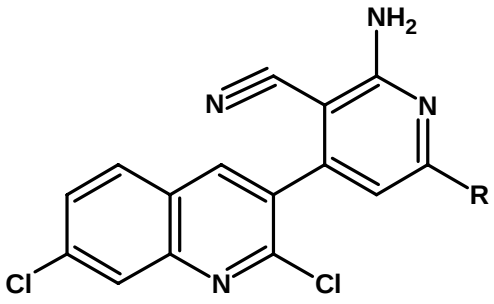
Type (III) **R = Aryl**

Pyrazoline derivatives of type (III) have been prepared by the condensation of the chalcones of type (I) with hydrazine hydrate.

PART - II : STUDIES ON CYANOPYRIDINES

Like other heterocyclic compounds, pyridine with different functional groups exhibit wide range of applications in the field of pharmaceutical and agriculture. Some cyanopyridine derivatives have been found to be associated with pharmacological activities such as antifungal, antidiabetic, anticholestemic and antihypertensive. They have been also used for dyes for cotton and polyester fabrics. On the basis of these results, we have synthesised new derivatives which have been described as under.

SECTION - I : Synthesis and therapeutic evaluation of 2-Amino-3-cyano-4-(2',7'-dichloroquinolin-3'-yl)-6-aryl pyridines



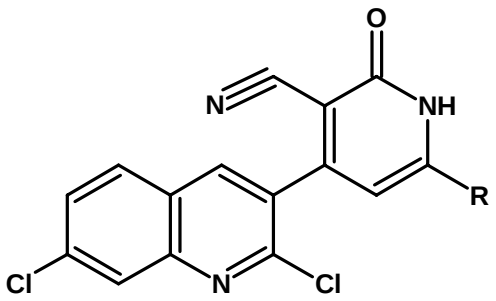
Type (IV) **R = Aryl**

2-Amino-3-cyanopyridine derivatives of type (IV) have been synthesised by the condensation of chalcones of type (I) with ammonium acetate and malononitrile.

PART - III : STUDIES ON CYANOPYRIDONES

Recently substituted cyanopyridone derivatives have drawn considerable attention due to their good pharmacological activities like anticonvulsant, antibacterial, antiinfective and antimalarial. These observations prompted us to combine this nucleus into well known pharmaceutical properties of 2,7-dichloroquinoline-3-carboxaldehyde moiety, so as to enhance the overall activities of resulting moiety, which have been described as under.

SECTION - I : Synthesis and therapeutic evaluation of 1,2-Dihydro-3-cyano-4-(2',7'-dichloroquinolin-3'-yl)-6-aryl-2-pyridones



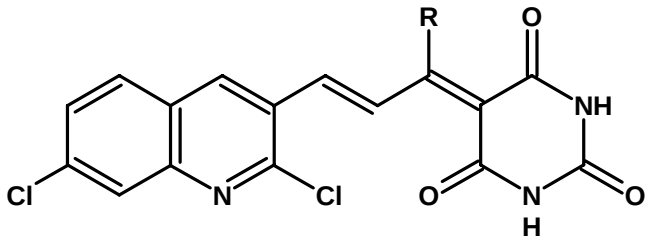
Type (V) **R = Aryl**

Cyanopyridone derivatives of type (V) have been synthesised by the condensation of chalcones of type (I) with ammonium acetate and ethyl cyano acetate.

PART - IV : STUDIES ON BARBITONES

The group of compounds containing the barbituric acid ring system have a prominent feature in medicinal chemistry and possess biological activities such as hypnotic, herbicidal and anticonvulsant. In view of these valid observations it was contemplated to synthesise some new barbitones possessing higher biological activity which have been described has under.

SECTION - I : Synthesis and therapeutic evaluation of [1-Aryl-3-(2',7'-dichloroquinolin-3'-yl)-2-propenylidine]-5-barbituric acids



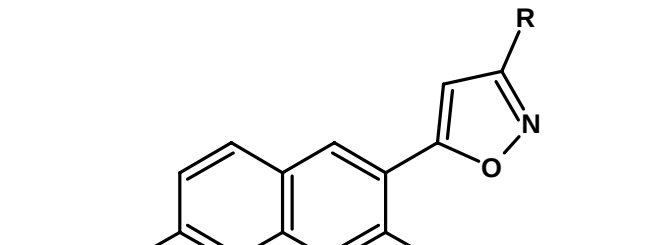
Type (VI) **R = Aryl**

Barbitone derivatives of type (VI) have been synthesised by the condensation of chalcones with barbituric acid.

PART - V : STUDIES ON ISOXAZOLES

Isoxazole derivatives represent one of the modest class of compounds possessing wide range of therapeutic activities such as antidepressant, skeleton muscle relaxant, analgesic and sedative. Keeping this in view, it was considered of interest to synthesise some novel isoxazole derivatives as under.

SECTION - I : Synthesis and therapeutic evaluation of 3-Aryl-5-(2',7'-dichloroquinolin-3'-yl)-isoxazoles



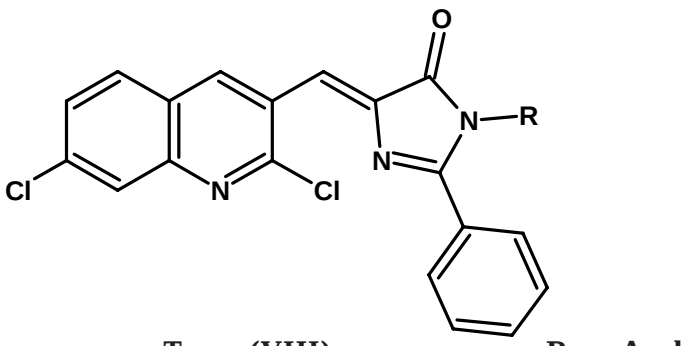
Type (VII) **R = Aryl**

Isoxazole derivatives of type (VII) have been synthesised by the condensation of the chalcones of type (I) with hydroxylamine hydrochloride.

PART - VI : STUDIES ON IMIDAZOLINES

5-Oxo imidazoline derivatives have been reported to be active as antiinflammatory, potent CNS depressant, sedatives, hypnotics, anticancer agent and mono amino oxidase (MAO) inhibitor. Thus significant biological properties associated with imidazolinone derivatives have aroused considerable interest to design the compounds in which 2,7-dichloroquinoline-3-carboxaldehyde nucleus is incorporated with a view to getting compounds with better drug potential, which have been described as under.

SECTION - I : Synthesis and therapeutic evaluation of 1N-Aryl-2-phenyl-4-(2',7'-dichloroquinolin-3'-methinyl)-5-imidazolinones



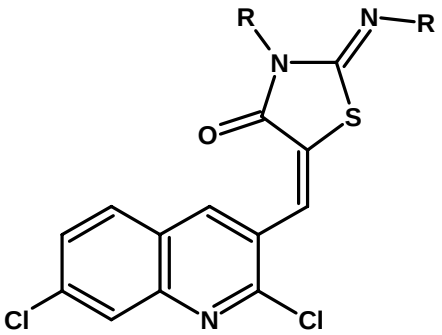
Type (VIII) **R = Aryl**

The compounds of type (VIII) have been prepared by the condensation of different amines with azalactones of 2,7-dichloroquinolin-3-carboxaldehyde, which in turn were prepared by well known Erlenmeyer azalactone synthesis.

PART - VII : STUDIES ON 5-ARYLIDENE-4-THIAZOLIDINONES

The interesting biological activities of a novel heterocycle like thiazolidinone have stimulated considerable research work in recent years leading to the synthetic utility of the derivatives of this ring system. In order to achieve compounds having better drug potential, we have combine 2,7-dichloroquinoline-3-carboxaldehyde with different substituted thiazolidinones. The pharmacological profile of the synthesised compounds have been studied and described as under.

SECTION - I : Synthesis and therapeutic evaluation of 2-Arylimino-3N-aryl-5-(2',7'-dichloroquinolin-3'-methinyl)-4-thiazolidinones



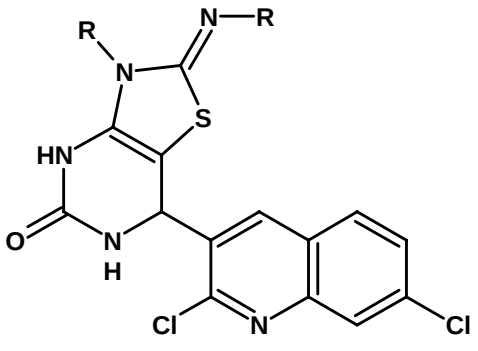
Type (IX) **R = Aryl**

The compounds of type (IX) have been prepared by the condensation of 2,7-dichloroquinoline-3-carboxaldehyde with different 4-thiazolidinone derivatives.

PART - VIII : STUDIES ON THIAZOLIDINOPYRIMIDINONES

Thiazolidinopyrimidinone derivatives represent one of the most active class of compounds possessing a wide spectrum of biological activity such as significant ***invitro*** activity against unrelated DNA and RNA viruses, antimalarial, diuretic, antibacterial and spermicidal. Led by these considerations, some new thiazolidinopyrimidinone derivatives were prepared, which have been described as under.

SECTION - I : Synthesis and therapeutic evaluation of 7-(2',7'-Dichloroquinolin-3'-yl)-2-arylimino-3-aryl-thiazolidino[4,5 -d]-pyrimidine-4,5,6,7-tetrahydro-5-ones



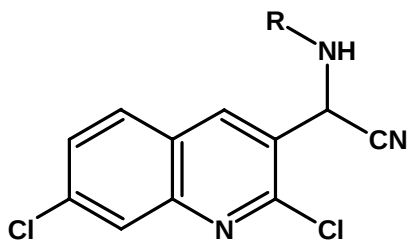
Type (X) **R = Aryl**

The compounds of type (X) have been prepared by the reaction of 2,7-dichloroquinoline-3-carboxaldehyde with urea, conc HCl and different 4-thiazolidinones.

PART - IX : STUDIES ON α-ARYLAMINONITRILES

The growing potent literature of recent years demonstrates that the nitrile derivatives are used as better herbicidal, antifungal and antibacterial agents. Prompted by above facts some newer nitriles have been synthesised which have been described as under.

SECTION - I : Synthesis and therapeutic evaluation of α-Aryl-amino-α-2,7-dichloroquinolin-3-yl-acetonitriles.



Type (XI) **R = Aryl**

The compounds of type (XI) have been synthesised by the condensation of 2,7-dichloroquinolin-3-carboxaldehyde with potassium cyanide and various aromatic amines.

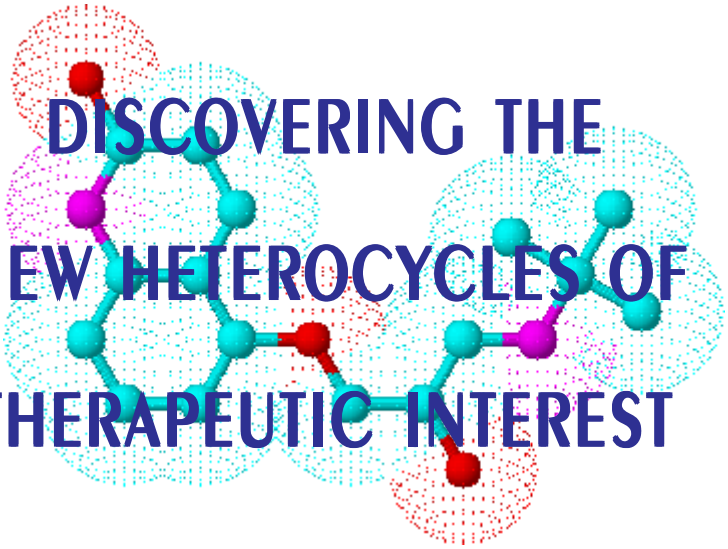
The constitution of the newly synthesised products have been characterised using elemental analysis, Infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry. Purity of all the compounds has been checked by thin layer chromatography.

In vitro study on multiple biological activites:

(i) All the compounds have been evaluated for their antibacterial activity towards Gram positive and Gram nagative bacterial strain and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg/ml. The biological activity of the synthesised compounds have been compared with standard drug.

(ii) Selected compounds have been evaluated for their ***invitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis H 37 Rv*** at a cocentration of 6.25 μg/ml using Rifampin as a standard drug, which have been tested by Tuberculosis Antimicrobial Acquisition Co-ordinating Facility (TAACF), Alabama U.S.A.

DISCOVERING THE NEW HETEROCYCLES OF THERAPEUTIC INTEREST



INTRODUCTION

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 numerous laboratories focused on the introduction of chemical diversity have been recently reviewed and pharmacologically interesting compounds have been identified from libraries of widely different composition.

Today our world increasingly is conceived of as being molecular. An ever widening range of phenomena are described logically in terms of molecular properties and molecular interactions. The majority of known molecules are heterocyclic and heterocycles dominate the fields of biochemistry, medicinal chemistry, dye stuffs, photographic science and are of increasing importance in many others, including polymers, adhesive and molecular engineering.

Heterocycles, containing nitrogen are most abundant in nature than those containing oxygen or sulfur. Considerable diversy in the ring system is possible. The number of atoms in the heterocyclic ring can range from three to many. The smallest ring possible is three membered, i.e. ethylene oxide, but very large rings are possible in the case of crown ethers.

Most of the alkaloids, which are nitrogenous bases occurring in plants and many antibiotics including penicillin and streptomycin also contain heterocyclic ring system. Many natural pigments such as indigo, heamoglobin and anthocyanin are heterocycles. Most of the sugars, their derivatives including vitamin C for instance, exist largely in the form of five membered or six membered ring containing nitrogen. Life saving drugs, poisons and medicines (both natural and synthetic) such as sulfathiazole, pyrethrin, ratennone, strychnine, reserprine, the ergot alkaloids caeffine, cocaine, barbiturates etc. are heterocyclic.

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

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

The "Golden Period" of new drug discovery was 1930 to 1960, a very large number of important drugs had been introduced during that period, such as:

NAME OF DRUGS	YEAR	USAGES
Sulfa drugs	1933	First antibacterial drug
Penicillin	1940	Antibiotic
Chloroquine	1945	Antimalarial
Methyl Dopa	1950	Antihypertensive

Chlorthiazide	1957	Diuretic
Adrenergic beta blockers	1958	Coronary Vasodilatory
Semi synthetic penicillin	1960	Antibacterial
Trimethoprim	1965	Antimicrobial
Disodium chromoglycoate	1970	Antiallergic

AIMS AND OBJECTIVES

In the pharmaceutical field, these have always been and will continue to be a need for new and novel chemical inhibitors of biological function. Our efforts are focused on the introduction of chemical diversity in the molecular frame work in order to synthesizing pharmacologically interesting compounds of widely different composition.

During the course of research work, looking to the application of heterocyclic compounds, several entities of heterocyclic compounds have been designed, generated and characterised using spectral studies. The details are as under.

(i) To generate several derivatives like chalcones, pyrazolines, isoxazoles, cyanopyridones, pyrimidinones, imidazolones bearing quinoline ring system.

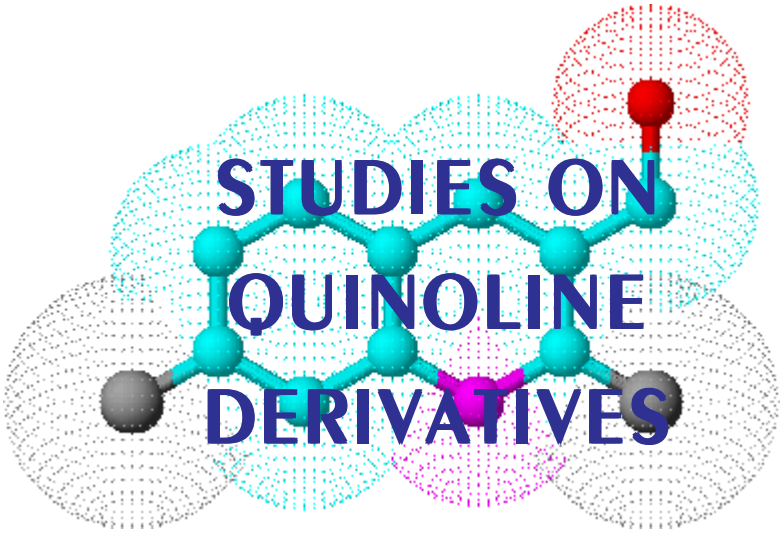
(ii) To synthesise arylidenes, cyanopyridines, barbitones, nitriles bearing quinoline moiety.

(iii) To characterise these product for structure elucidation using spectroscopic techniques like IR, PMR and mass spectral studies.

(iv) To check the purity of all compounds using thin layer chromatography.

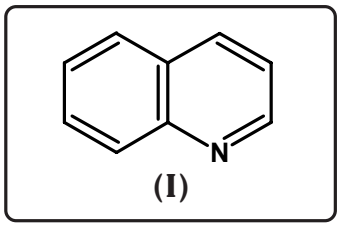
(v) To evaluate these new products for better drug potential against different strains of bacteria and fungi.

Taking in view of the applicability of heterocyclic compounds, the construction of new heterocycles of therapeutic importance, bearing quinoline nucleus have been investigated in following parts.


STUDIES ON
QUINOLINE
DERIVATIVES

INTRODUCTION

The quinoline contains a phenyl ring fused to pyridine ring, and also known as benzopyridine (I).



(I)

Quinoline is a very important heterocyclic compound as it is featured in a variety of natural products, as well as in other compounds of medicinal interest and have attracted attention for their biological activities. The chemistry of quinoline and its derivatives, has been the centre of attention for long time. R. H. Manske[1] and F. W. Bergstrom[2] has done excellent work on quinoline and its derivatives.

SYNTHETIC ASPECT

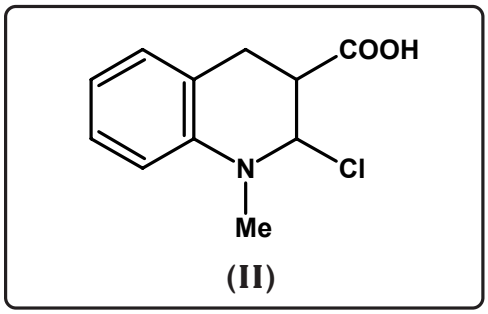
Different methods for the synthesis of quinoline derivatives are as follows:

(1) J. A. Moore et al. have synthesised 6-hydroxyquinoline by the oxidation of hydroxyquinolines by means of ferricyanide[3].

(2) T. Kametani et al.[4] have synthesised quinoline derivatives by deoxygenation with the help of triphenylphosphite.

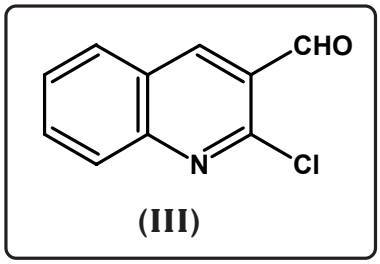
(3) o-Nitrocinnamaldehyde was reduced to quinoline by potassiumtetra carbonylhydrido ferrate was demonstrated by C. K. Bradsher and T. G. Wallis.[5]

(4) M. Lancaster and D. J. H. Smith[6] have prepared tetrahydroquinoline derivatives of type (II).



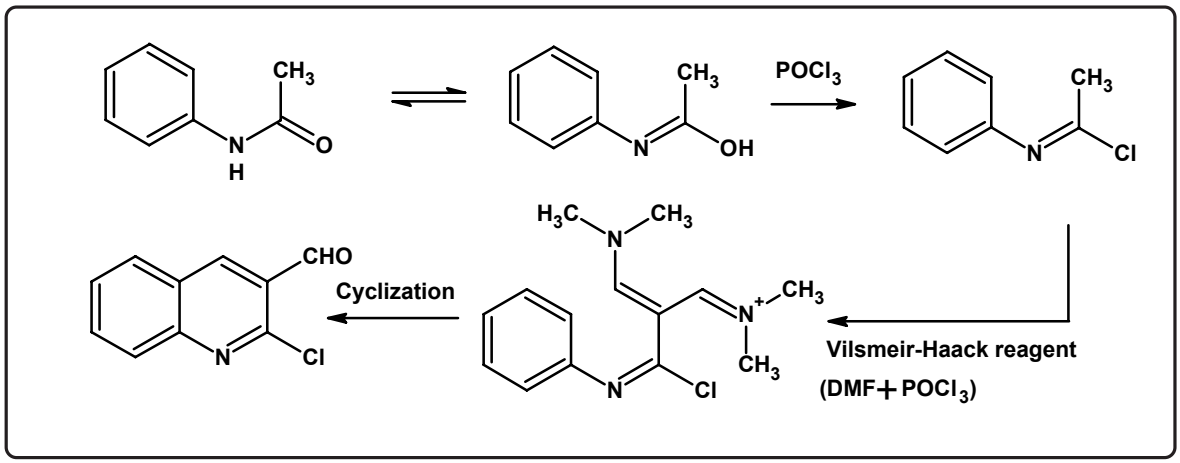
(II)

(5) Meth-Cohn and co-workers[7] have shown that treatment of acetanilides with the Vilsmeir Haack reagent with $POCl_3$ as solvent allows the preparation of quinoline derivative of type (III).



(III)

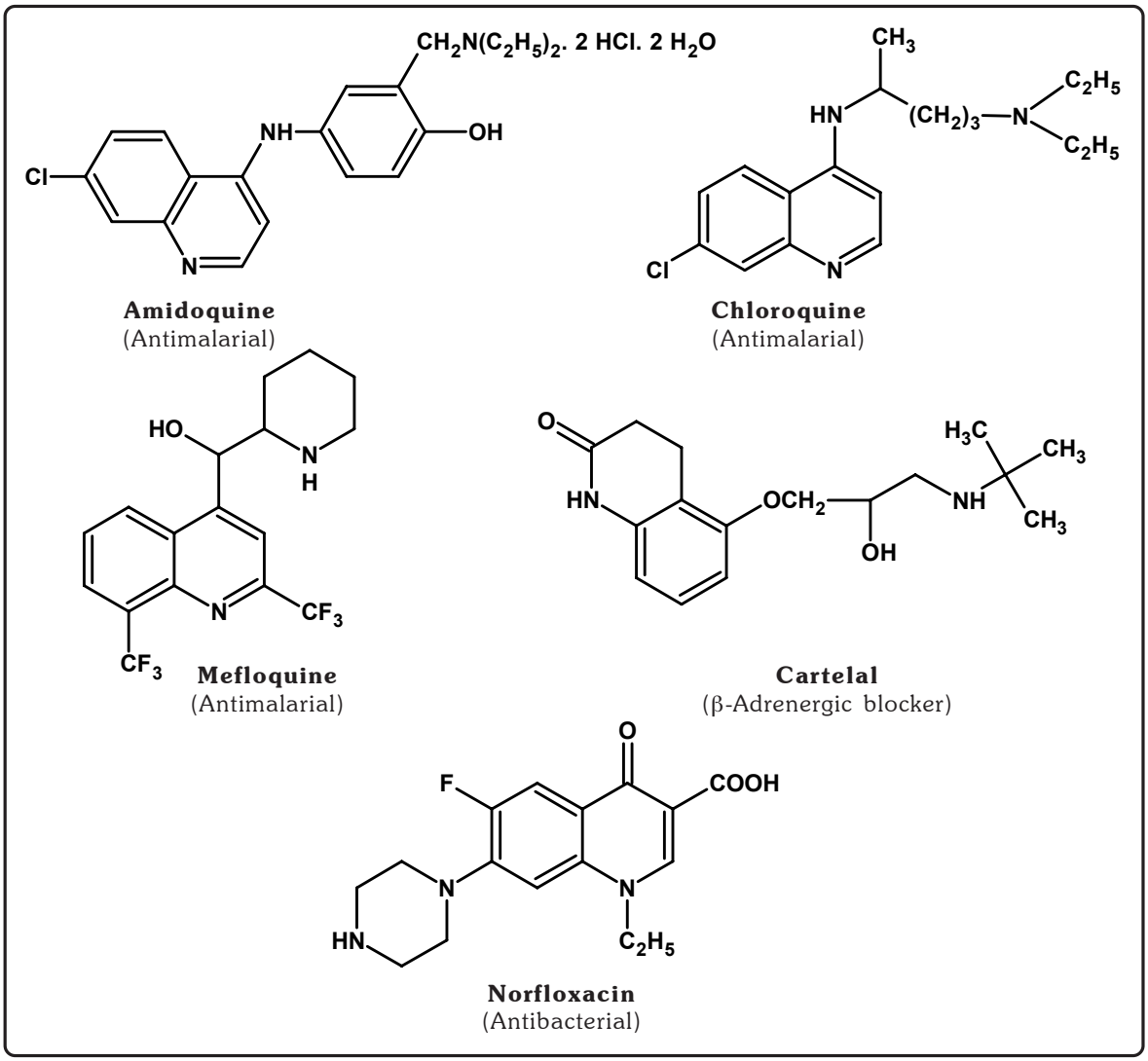
MECHANISM



In the first step hydroxy group is replaced by chlorine, which is possible by lone pair of electron of halogen atom. In the second step Vilsmeir - Haack reagent attacks on nucleophile and forms quaternarry ammonium ion as an intermediate. This intermediate on treatment by $POCl_3$ leads to the quinoline molecule.

THERAPEUTIC IMPORTANCE

Following are some quinoline derivatives reported to possess pharmacological activity :

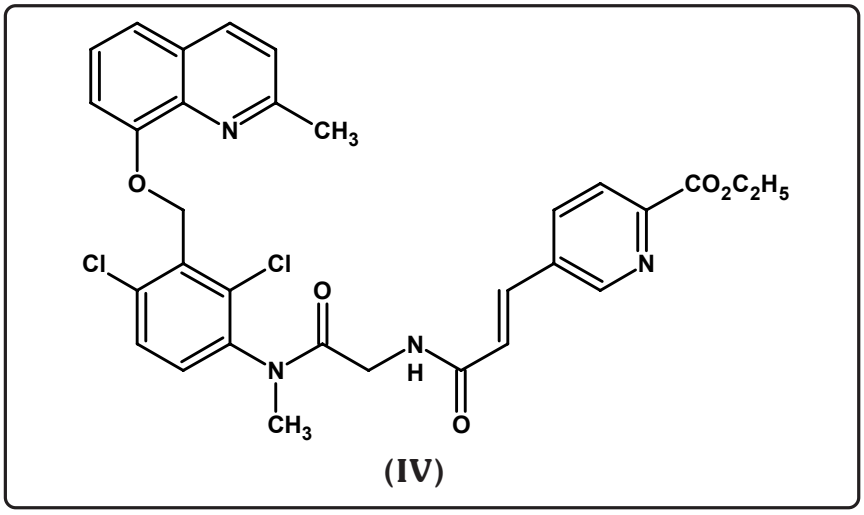


Quinoline and its annelated substrates occupy a unique place in the field of medicinal chemistry due to their wide spectrum of therapeutic activities which can be listed as under.

1. Antiinflammatory[8-12]
2. Antidepressant[13]
3. Antiallergic[14,15]
4. Antihypertensive[16]
5. Antiviral[17,18]
6. Antitumor[19,20]
7. Antiulcer[21]
8. Anticonvulsant[22]

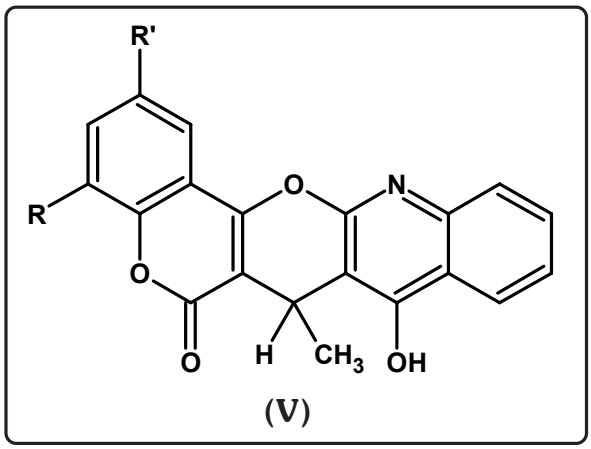
9. Analgesic[23,24]
10. Antimicrobial[25-27]
11. Antiarrythmic[28]
12. Antitubercular[29,30]
13. Antithrombotic[31]
14. Antiplatlet[32-34]
15. Antimalarial[35]
16. Antithyroid[36]

O. Teruo et al.[37] have prepared some new quinoline derivatives (IV) and documented them as bradykinin antagonists.



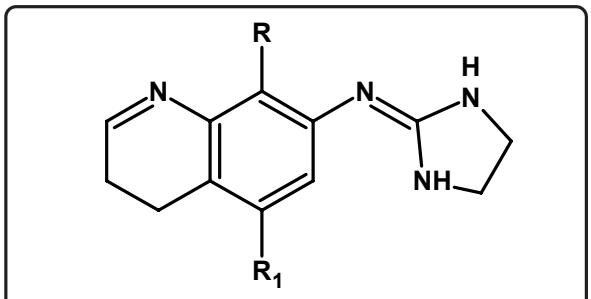
(IV)

Desai P. K. and co-workers[38] reported some new quinoline derivatives as antitubercular agent. Balasubramanian C. and co-workers[39] synthesised some novel benzopyranopyranoquinoline derivatives (V) and tested their antibacterial activity.



(V)

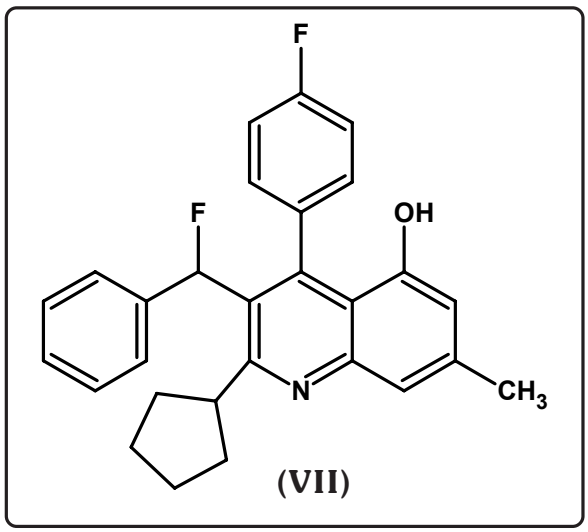
K. Seiichiro et al.[40] synthesised quinoline sulfide derivatives as selective antibacterial agents. D. H. Joan and co-workers[41] prepared quinoline sulfonamides and described them as tumor necrosis factor (TNF) inhibitors. C. T. Lee et al.[42] synthesised some new imidazolinyl quinolines (VI) and documented them as alpha-2-adrenoceptor agonists.



(VI)

Klein E. S. et al.[43] prepared some new quinoline derivatives and reported them as retinoid receptor antogonists. C. S. Hoon and co-workers[44] reported antitumor activity of some new 2-quinolone derivatives. Multidrug resistance modulating activity of a new series of tetrahydroquinolines was documented by H. Romana and co-workers.[45]

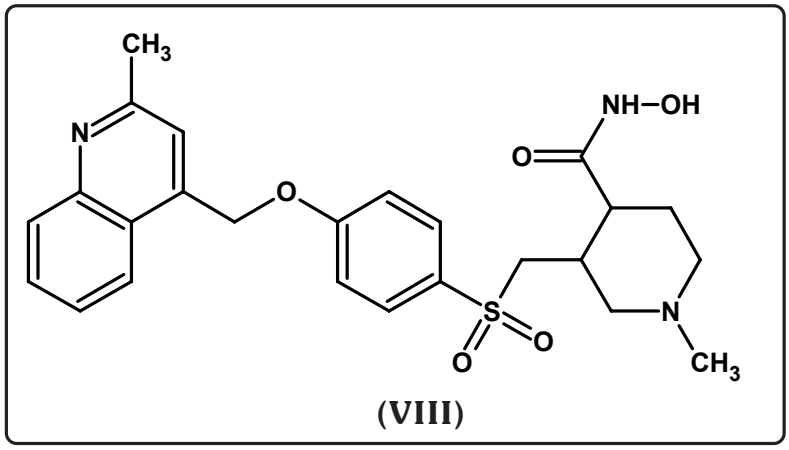
S. Yoshida and co-workers[46] prepared some new quinolone derivatives and reported their antiulcer activity. 4-Oxoquinoline derivatives are reported as antibacterial agents by Sarvanan J. et al.[47] Some quinolines of type-(VIII) have been prepared by M. G. Matthias and co-workers[48] and reported as antiarterioscierotics.



(VII)

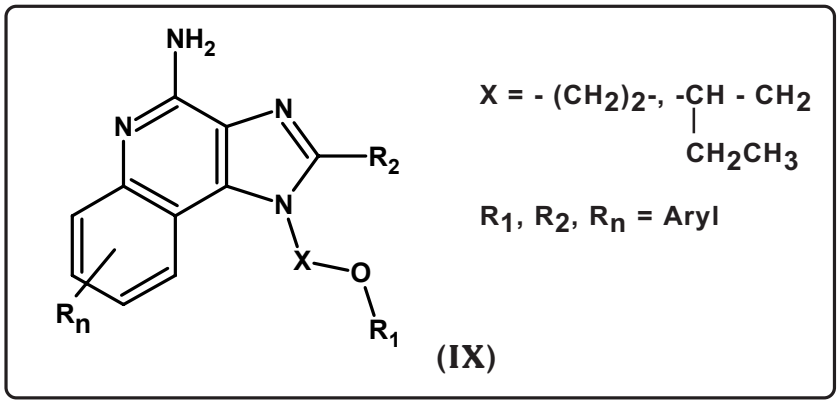
Antimalarial activity of some new 4-aminoquinolines was reported by Raynes K. J. and co-warkers.[49] B. T. Richard et al.[50] synthesised some new piperazinyl methyl quinolines and documented them as antipsychotics. Anticancer activity of 8-hydroxyquinolines was reported by Shen and co-workers.[51]

Quinoline derivatives of type (VIII) have been described by Xue C. B. and co-workers[52] and documented them as TNF inhibitors.



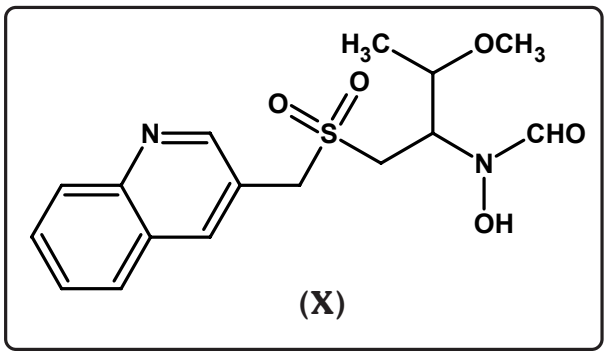
(VIII)

G. Qingchun et al.[53] described some new fluoroquinoline derivatives and tested their antibacterial activity. S. Sudahira and co-workers[54] synthesised some new quinoline carboxylic acid derivatives and reported them as bactericidal. Wackernagel and co-workers[55] studied some new quinoline derivatives and reported them as insecticidals. M. Jigna[56] synthesised some new arylquinolinyl pyrimidinones and screened for their antibacterial activity. Crooks S. L. et al.[57] prepared some new amidoether substituted quinolines (IX) as immune response modifiers.



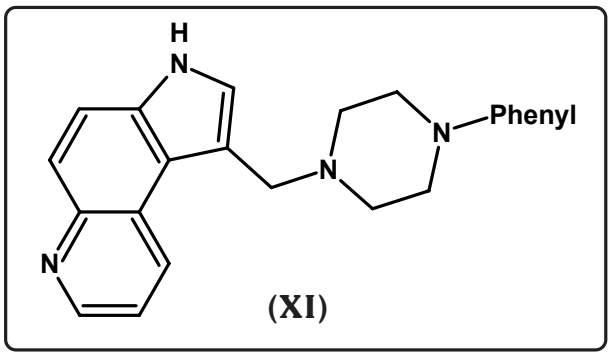
(IX)

M. Jansen and co-workers[58] reported some new quinolones and documented them as antagonists. Antibacterial activity of some new quinoline-2-one heterocycles was reported by Suchetak et al.[59] Use of quinolinylmethylsulfonyl butyl formamides (X) in the treatment of autoimmune disease and allergies were shown by B. D. John and co-woerkers.[60]



(X)

P. Uwe and co-workers[61] have described some new pyrolidinyl quinolones and reported them as antibacterial agents and food additives. Desouza N. J. et al.[62] investigated some new quinolone carboxaldehyde derivatives and reported their effect against multidrug resistance bacteria. F. M. Grazia and co-workers[63] studied some pyrazoloquinolines (XI) and documented their vasorelaxing effect.



(XI)

The universal template approach to drug design foresees that quinolines can be modified in such a way to afford better therapeutic agents, we have designed chalcones, pyrazolines, cyanopyridines, cyanopyridones, barbitones, isoxazoles, imidazolines arylidienes, pyrimidinones and nitriles bearing 2,7-dichloroquinoline-3-carboxaldehyde moiety, which is described in the following parts.

STUDIES ON QUINOLINE DERIVATIVES

PART-I : STUDIES ON PYRAZOLINES

PART-II : STUDIES ON CYANOPYRIDINES

PART-III : STUDIES ON CYANOPYRIDONES

PART-IV : STUDIES ON BARBITONES

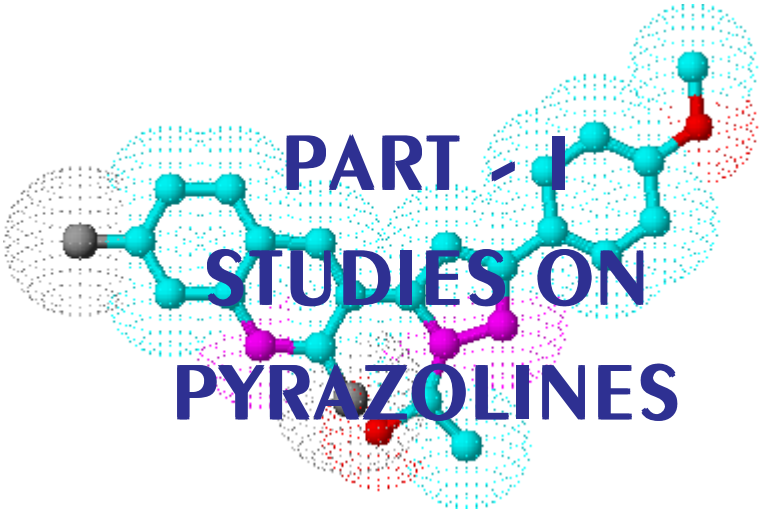
PART-V : STUDIES ON ISOXAZOLES

PART-VI : STUDIES ON IMIDAZOLINONES

PART-VII : STUDIES ON 5-ARYLIDENE-4-THIAZOLIDINONES

PART-VIII : STUDIES ON THIAZOLIDINOPYRIMIDINONES

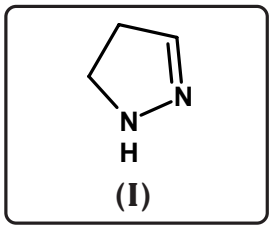
PART-IX : STUDIES ON α-ARYLMINONITRILES



PART - I
STUDIES ON PYRAZOLINES

INTRODUCTION

Pyrazolines are known to be among those heterocycles which find their utility in various fields of life. The significance of this moiety has increased due to its biocompability. The chemistry of pyrazoline was reviewed by Jarboe in 1967, which have been studied extensively for their biodynamic behaviour[64], and industrial applications[65].

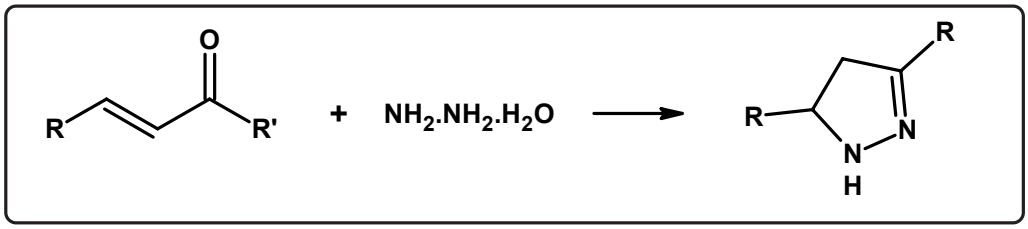


(I)

SYNTHETIC ASPECT

Different methods are available in literatures for the preparation of 2-pyrazolines. The popular methods are:

1. The most common procedure for the synthesis of 2-pyrazolines is the cyclocondensation of chalcones with hydrazine hydrate[66].

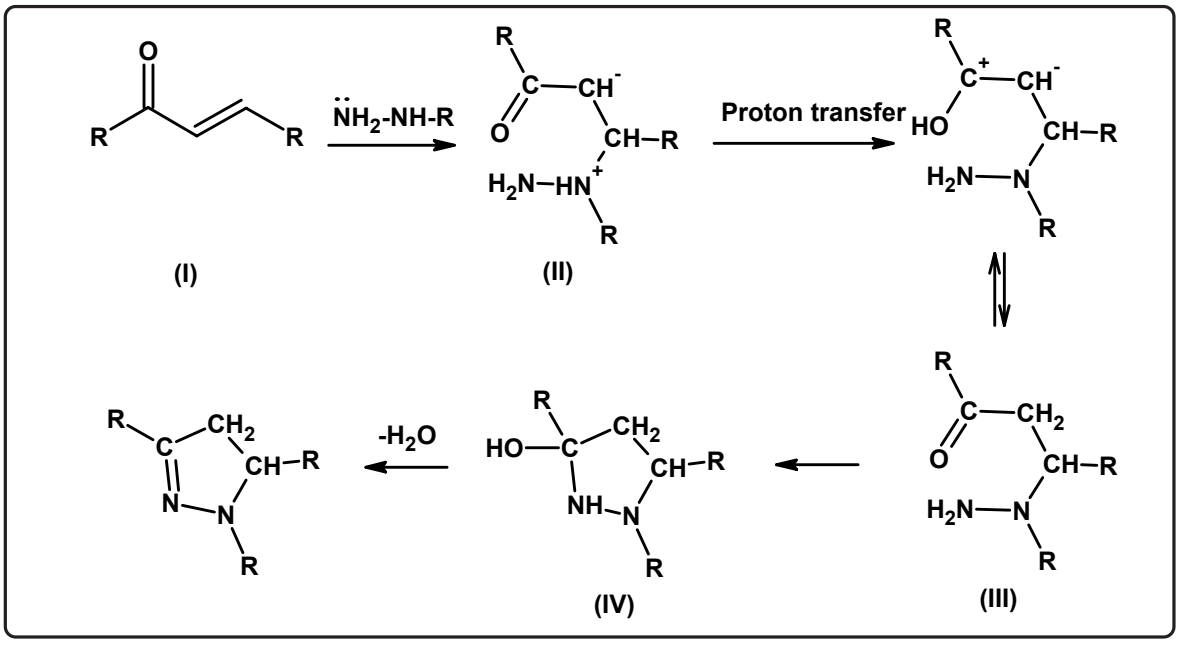


2. 2-Pyrazolines can be also prepared by the condensation of di-bromo derivative of chalcone with hydrazine hydrates[67].
3. 2-Pyrazolines can be constructed by the cycloaddition of diazomethane to substituted chalcones[68].

4. A number of diarylidene cycloalkanones on reaction with hydrazine hydrate produce pyrazolines[69].
5. Epoxidation of chalcones gave epoxy ketones which reacted with hydrazine hydrate and phenyl hydrazine to give pyrazolines[70].

REACTION MECHANISM

The following mechanism seems to be operable for the condensation of chalcones with hydrazine hydrate[71].



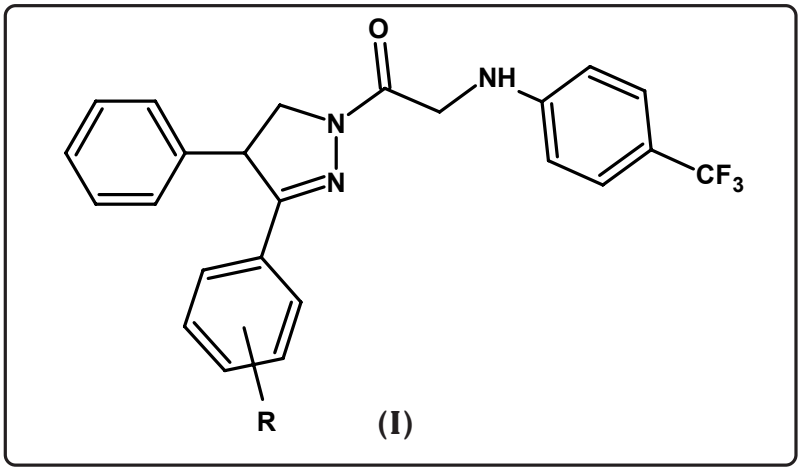
Nucleophillic attack by hydrazine at the β-carbon of the α,β-unsaturated carbonyl system forms species (II), in which the negative charge is mainly accommodated by the electronegative oxygen atom. Proton transfer from the nitrogen to oxygen produces an intermediate end which simultaneously ketonises to ketoamine (III). Another intramolecular nucleophillic attack by the primary amino group of ketoamine on its carbonyl carbon followed by proton transfer from nitrogen to oxygen leads ultimately to hydroxyl amine (IV). The later with a hydroxy group and amine group on the same carbon lose water easily to yield the pyrazolines.

THERAPEUTIC IMPORTANCE

From the literature survey, it was revealed that 2-pyrazoline derivatives are better therapeutic agents.

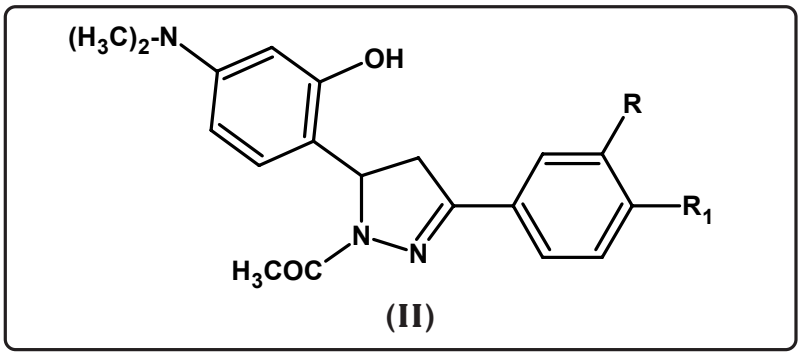
1. Insecticidal[72]
2. Diuretic[73]
3. Fungicidal[74]
4. Herbicidal[75]
5. Hypoglycemic[76]
6. Antiallergic[77]
7. Anticonvulsant[78]
8. Antidiabetic[79]
9. Antiinflammatory[80]
10. Antitumor[81]
11. Cardiovascular[82]
12. Analgesic[83]
13. Antineoplastic[84]
14. Bactericidal[85]
15. Tranquilizing[86]

T. S. Katshaki *et al.*[87] have synthesised some new (phenylcarbonyl) pyrazoline (I) as an insecticide which at 40% concentration shows 100% mortality of spodopeira litura lurve after seven days.



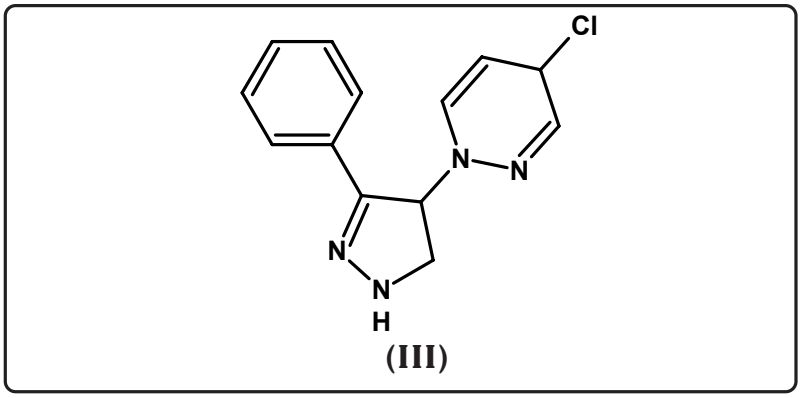
(I)

F. Manna and co-workers[88] have described 1-acetyl-5-(2'-bromophenyl)-4,5-dihydro-3-(2'-hydroxyphenyl)-1H-pyrazolines (II) and its derivatives which acts as potent antiinflammatory, analgesic and antipyretic agents.



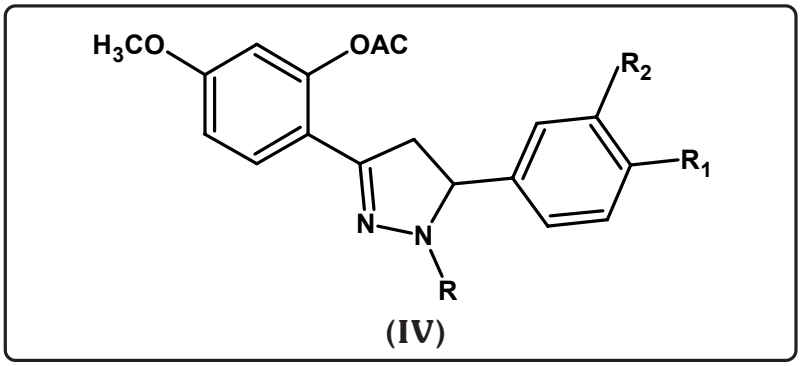
(II)

Fuche Rainer *et al.*[89] have prepared some new 1H-pyrazoline derivatives (III) and reported them as pesticides.



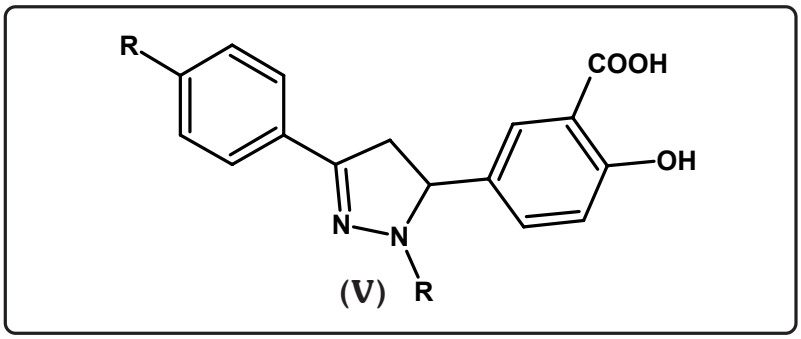
(III)

Moreover Ismil *et al.*[90] have prepared pyrazoline derivatives bearing sulfonamide moiety and tested their antimicrobial activity. Sarhan and co-workers[91] have synthesised pyrazolines derivatives and reported their antibacterial, analgesic and antiinflammatory activities. S S. Sonarc *et al.*[92] have studied 3-(2-acetoxy-4-methoxyphenyl)-5-(substituted phenyl)-pyrazolines (IV) for their antimicrobial activity.



(IV)

G. N. Mishirika et al.[93] have also prepared 2-pyrazolines derivatives of salicylic acid (V) possessing antimicrobial properties.



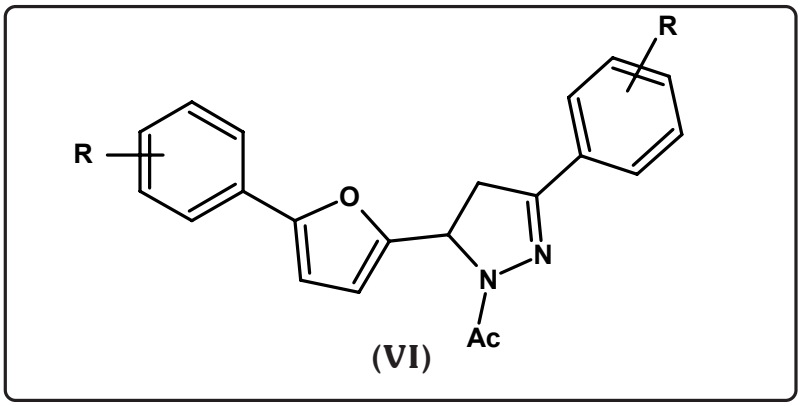
(V)

Further more, T.M. Stavenson et al.[94] have also investigated N-substituted pyrazoline type insecticides. Tanka Katsohori[95] have patented pyrazoline derivatives as herbicides.

CONTRIBUTION FROM OUR LABORATORY

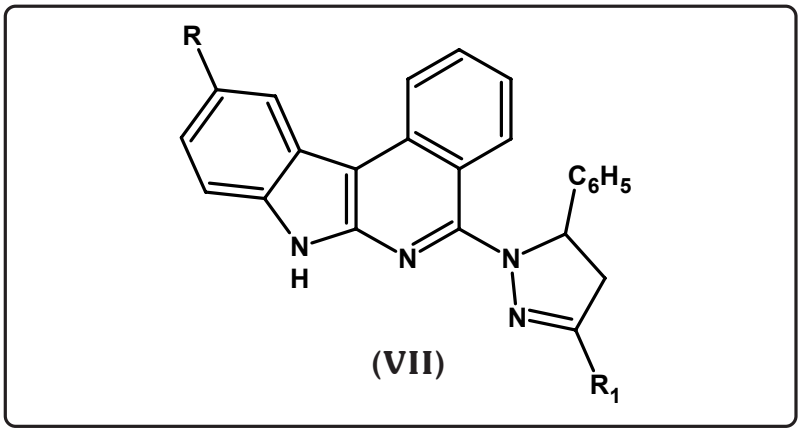
Jatin Upadhyay et al.[96] have prepared 1-acetyl-4,5-dihydro-5-(4-hydroxy-3-methoxyphenyl)-3-(4-phenyl-sulfonylaminophenyl)-1H-pyrazole and other derivatives which possess antimicrobial activity. Synthesis of some novel pyrazolines as biologically potent agents bearing quinazolone nucleus has been reported by Oza H. et al.[97] Parikh et al.[98] have synthesised m,m'-bis(5-aryl-1-phenyl)-pyrazolin-3-yl-p-phenyl-amino sulfonyl benzophenones and screened for their antimicrobial activity. Antimicrobial activity of pyrazolines have been documented by H. H. Parekh and co-workers.[99]

Shivananda M.K. and co-workers[100] have prepared pyrazolines and reported their antibacterial activity. B. Shivarama Holla et al.[101] have synthesised pyrazolines (VI) and reported their antibacterial activity.



(VI)

E. Palaska et al.[102] have prepared 3,5-diphenyl-2-pyrazoline derivatives and studied their antidepressant activity. S.P. Hiremath and co-workers[103] have reported analgesic, antiinflammatory and antimicrobial activity of 3,5-disubstituted pyrazolines (VII).



(VII)

Thus interesting biological activities of a novel heterocycles like pyrazolines have stimulated considerable research work in recent years leading to the synthetic utility of the derivatives of this ring system. In our search for new potential antimicrobial compounds, the reaction series of chalcones with hydrazine hydrate under different conditions has been investigated and the pharmacological profile of the compounds have been studied and described as under.

SECTION I : SYNTHESIS AND THERAPEUTIC EVALUATION OF 1-ARYL-3-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-PROPENE-1-ONES

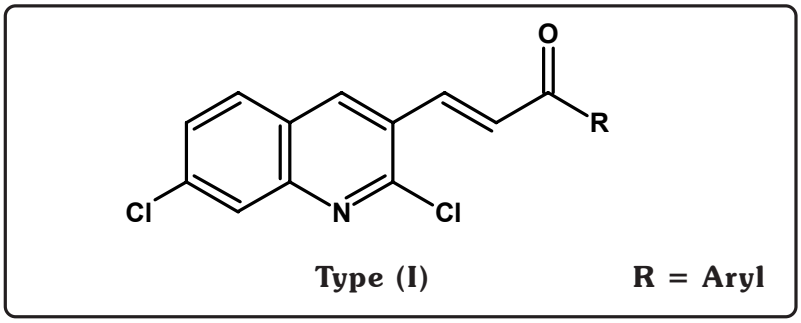
SECTION II : SYNTHESIS AND THERAPEUTIC EVALUATION OF 1-ACETYL-3-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-PYRAZOLINES

SECTION III : SYNTHESIS AND THERAPEUTIC EVALUATION OF 1H-3-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-YL) PYRAZOLINES

SECTION - I

SYNTHESIS AND THERAPEUTIC EVALUATION OF 1-ARYL-3-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-PROPENE-1-ONES

During the past years, considerable evidence has been accumulated to demonstrate the efficiency of chalcones in including variety of therapeutic activities. To further assess the potential of such a class of compounds as antibacterial and antifungal agents, a series of chalcones of type (I) have been synthesised by the condensation of 2,7-dichloroquinoline-3-carboxaldehyde with various aromatic ketones.

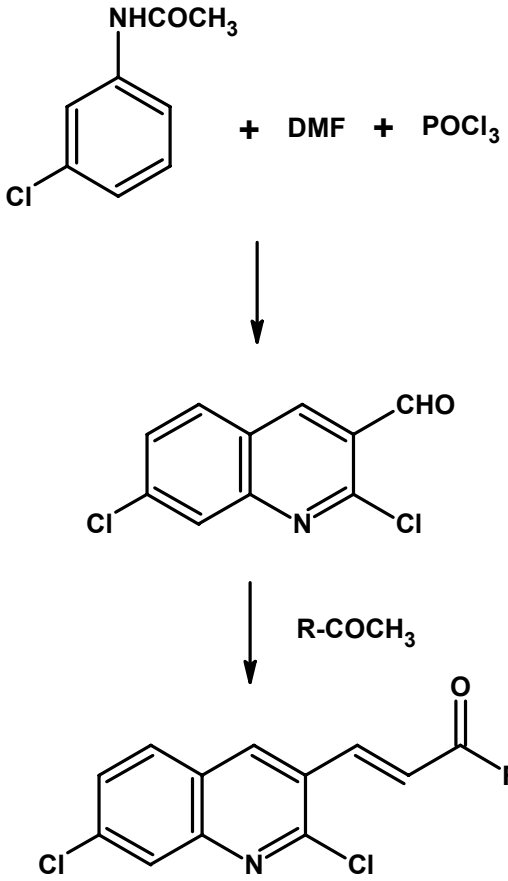


Type (I) **R = Aryl**

The constitution of the synthesised products has been characterised using elemental analyses, infra red and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass-spectrometry.

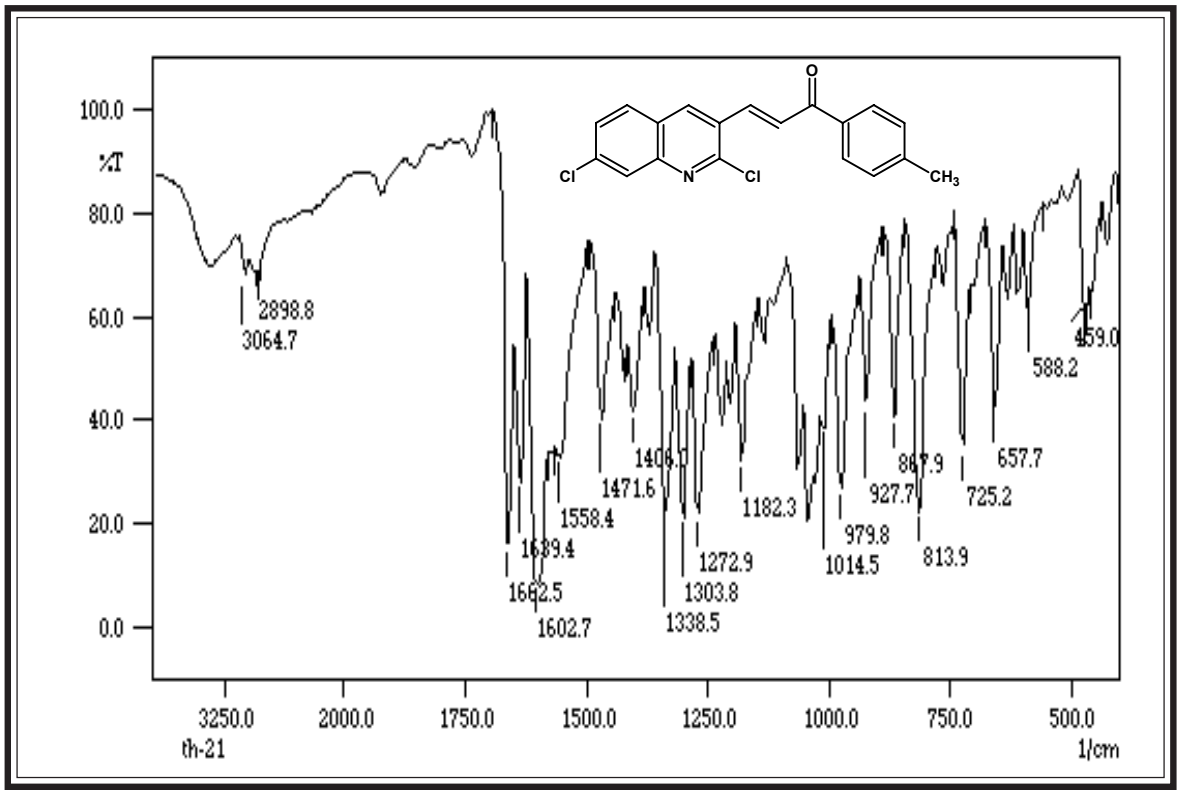
The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg. The biological activities of the synthesised compounds have been compared with standard drugs. The details have been cited in Part-I Section-I (D). The antimycobacterial activity was carried out towards ***Mycobacterium tuberculosis*** at 6.25 μg concentration using Rifampin as a standard drug.

REACTION



Type (I) **R = Aryl**

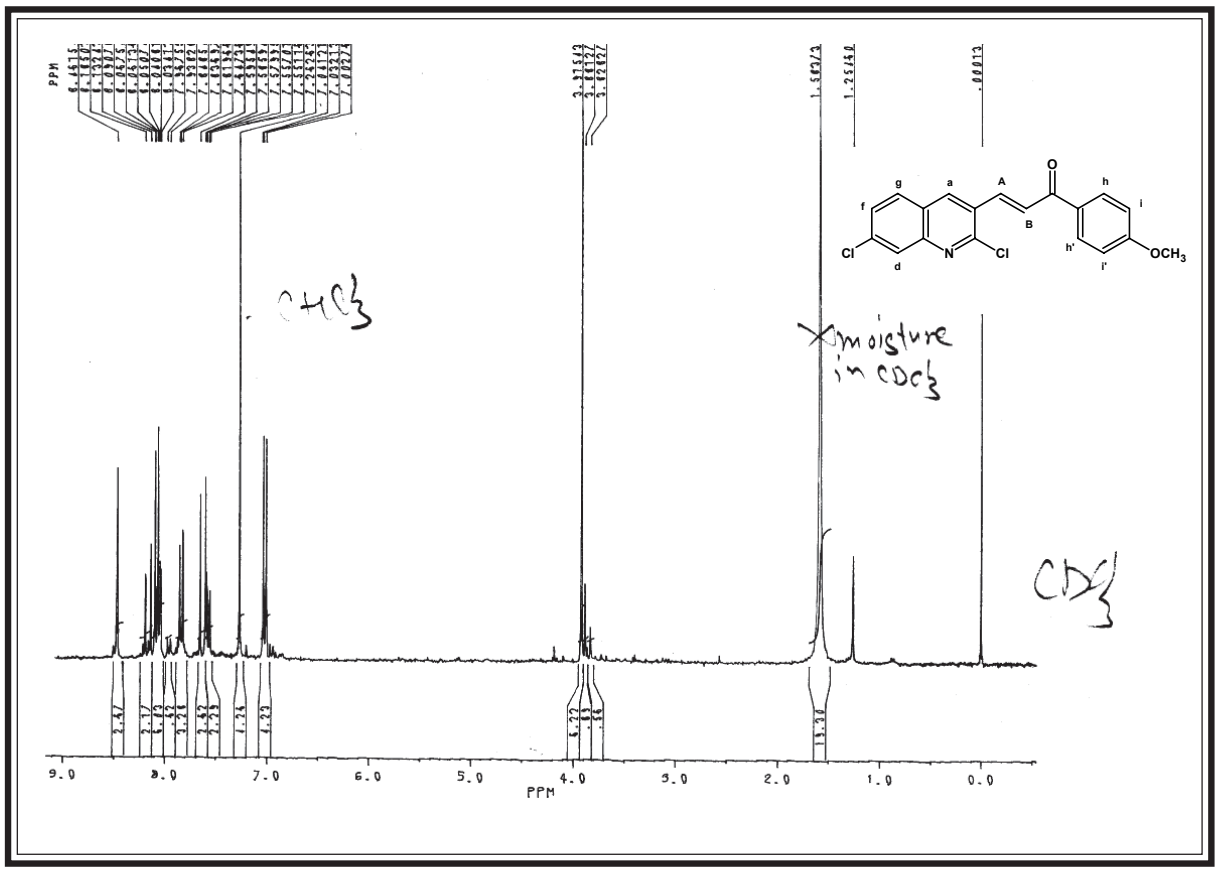
IR SPECTRAL STUDY OF 1-p-TOLYL-3-(2'-7'-DICHLORO-QUINOLIN-3'-YL)-2-PROPENE-1-ONE



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

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.	2998	2975-2850	419
	C – H def.	1471	1470-1435	"
Aromatic	C– H str.	3064	3090-3030	"
	C = C str.	1471	1520-1480	"
	C – H def.	1014	1070-1000	420
		813	835-810	"
Quinoline moiety	C = N str.	1602	1610-1590	419
	C = C str.	1602	1610-1590	"
	C – Cl str.	725.2	750-700	"
Chalcone	C = O str.	1662	1690-1665	"
Vinyl	CH = CH	3064	3050-3000	"

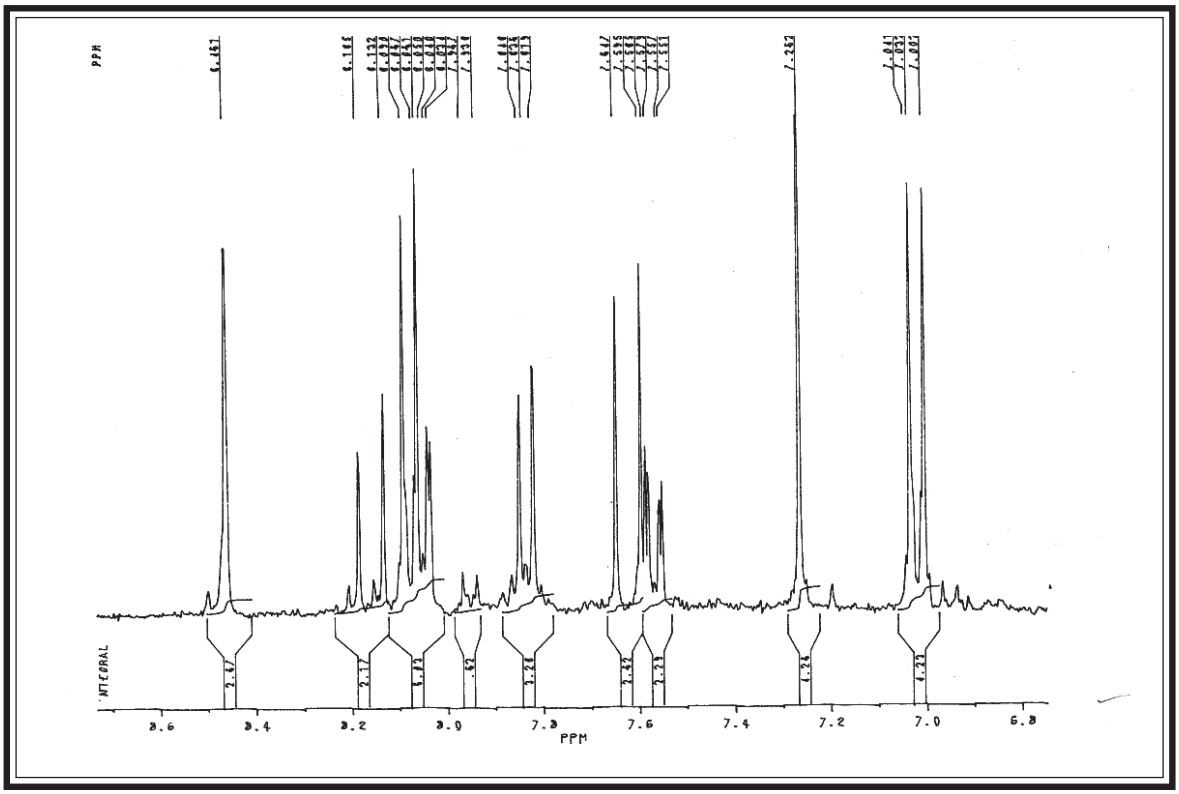
PMR SPECTRAL STUDY OF 1-(p-ANISYL)-3-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-PROPENE-1-ONES



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

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	J. Value in Hz		Inference
1	3.97	3H	singlet	-		Ar-OCH_3
2.	7.00-7.03	2H	doublet	Jih	8.81	Ar-Hi,i'
3.	7.55-7.59	1H	double doublet	Jfg	8.67	Ar-Hf
				Jfd	1.8	
4.	7.60-7.65	1H	doublet	JBA	15.56	$=CH_B$
5.	7.82-7.85	1H	doublet	Jgf	8.64	Ar-Hg
6.	8.03-8.04	1H	doublet	Jdf	2.00	Ar-Hd
7.	8.06-8.09	2H	doublet	Jhi	8.83	Ar-Hh,h'
8.	8.13-8.19	1H	doublet	JAB	15.86	$=CH_A$
9.	8.46	1H	singlet	-		Ar-Ha

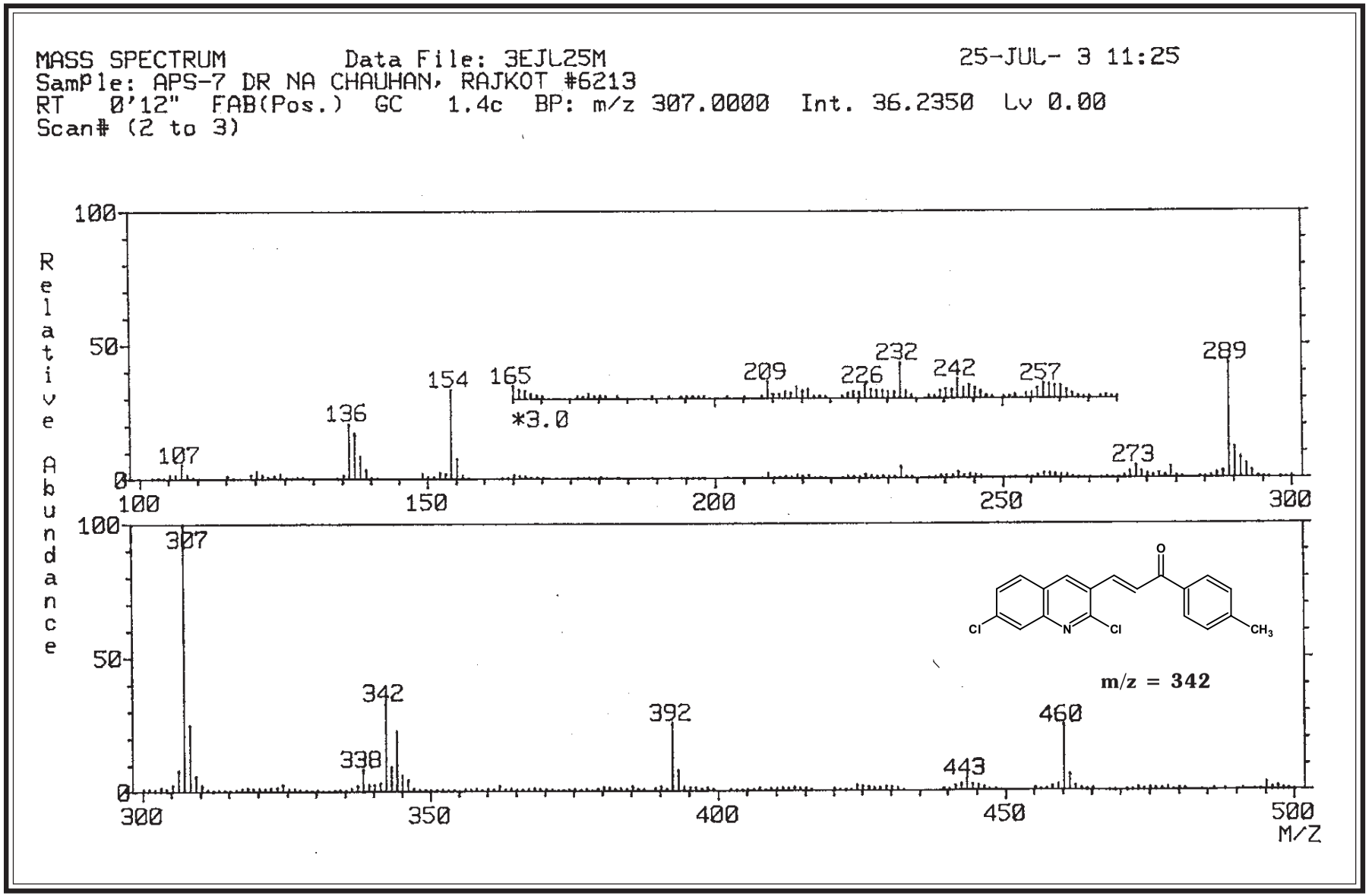
EXPANDED AROMATIC REGION



IR SPECTRAL DATA OF 1-ARYL-3-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-PROPENE-1-ONES

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

Sr. No.	R	C=O str. Chalcone
1a	C_6H_5	1658
1b	3-NH_2-C_6H_4	1660
1c	4-NH_2-C_6H_4	1662
1d	4-Br-C_6H_4	1658
1e	4-Cl-C_6H_4	1656
1f	2,6-$(OH)_2$-C_6H_3	1660
1g	4-F-C_6H_4	1662
1h	C_4H_3O	1658
1i	2-OH-C_6H_4	1632
1j	4-OH-C_6H_4	1660
1k	4-OCH_3-C_6H_4	1658
1l	4-CH_3-C_6H_4	1662
1m	3-NO_2-C_6H_4	1660
1n	4-NO_2-C_6H_4	1660


MASS SPECTRUM Data File: 3EJL25M 25-JUL- 3 11:25
Sample: APS-7 DR NA CHAUHAN, RAJKOT #6213
RT 0'12" FAB(Pos.) GC 1.4c BP: m/z 307.0000 Int. 36.2350 Lv 0.00
Scan# (2 to 3)
Relative Abundance
M/Z
107
136
154
165
*3.0
209
226
232
242
257
273
289
307
338
342
392
443
460
m/z = 342

ANTIMICROBIAL ACTIVITY

Method	:	Cup Plate
Gram positive bacteria	:	***B. megaterium., S.aureus***
Gram negative bacteria	:	***E. coli., P. vulgaris***
Fungi	:	***Aspergillus niger***
Concentration	:	40 μg.
Solvent	:	Dimethyl formamide
Standard drug	:	ampicillin, amoxicillin, ciprofloxacin, norfloxacin

The antimicrobial activity was compared with standard drugs viz. ampicillin, amoxicillin, ciprofloxacin, erythromycin and antifungal activity was compared with viz. greseofulvin zones of inhibition have been measured in mm.

Antitubercular activity

The antitubercular evaluation of the compounds was carried out at Tuberculous Antimicrobial Acquisition and Co-ordinating Facility (TAACF) U.S.A.

Method	:	BACTEC 460 Radiometric System
Bacteria	:	*Mycobacterium tuberculosis* H_{37} *Rv*
Concentration	:	6.25 μg/ml
Standard drug	:	Rifampin.

EXPERIMENTAL

SYNTHESIS AND THERAPEUTIC EVALUATION OF 1-ARYL-3-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-PROPENE 1-ONES

[A] Synthesis of 3-Chloroacetanilide

m-Chloroaniline (12.7 ml) was cooled to 15° to 20°C in 50 ml water. Acetic anhydride (12.7 ml) was added with stirring and the reaction mixture was heated under reflux for 2 and half hrs. The reaction mixture was poured into ice-water. The product was isolated and crystallised from methanol. yield 95%; m.p. 78°C.

[B] Synthesis of 2,7-Dichloroquinolin-3-carboxaldehyde.

Dimethyl formamide (9.13 g, 9.6 ml, 0.125 mol) was cooled to 0°C in a flask equipped with drying tube and phosphorous oxychloride (53.7 g, 32.2 ml, 0.35 mol) was added dropwise with stirring. To this solution was added m-chloroacetanilide (8.5 g, 0.05 mol) and after 5 min. the solution was heated under refluxed for 6 and half hrs. The reaction mixture was poured into ice-water and stirred for 30 min. at 0-10°C. The product was isolated and crystalised from ethyl acetale yield 54%; m.p. 120°C. Anal calcd. for $C_{10}H_5NCl_2O$ required : C, 53.13%; H, 2.23%; N, 6.20%; found: C, 5.9%; H, 1.85%; N, 6.30%

[C] Synthesis of 1-Aryl-3-(2',7'-dichloroquinolin-3'-yl)-2-propene-1-ones

A solution of 4-tolyl acetophenone (2.64 ml, 0.02 mol) in minimum quantity of ethanol (5 ml) was added to a mixture of 2,7-dichloro quinoline-3-carboxaldehyde (4.52 g, 0.02 mol) in ethanol (20 ml) and 40% NaOH was added to make it slightly alkaline. The reaction mixture was then stirred for 24 hrs. at room temperature. The product was isolated and crystallised from ethanol. yield 63%, m.p. 160°C Anal. calcd. for $C_{19}H_{13}NCl_2O$ required; C, 66.68%; H, 3.83%; N, 4.10% found C, 66.34%; H, 3.68%; N, 4.09%

TLC solvent system: Acetone: Benzene (2.5:7.5) visualizing agent : Iodine

Similarly other 1-Aryl-3-(2'-7'-dichloroquinolin-3'-yl)-2-propene-1-ones were prepared. The physical constants along with infra red spectral data are recorded in Table No.1a

[D] Therapeutic evaluation of 1-Aryl-3-(2',7'-dichloroquinolin-3'-yl)-2-propene-1-ones

All the products have been evaluated for their antimicrobial activity as described under.

(a) Antimicrobial activity[104]

It was carried out using cup-plate agar diffusion method which has been described as under.

(i) Antibacterial activity

The purified products were screened for their antibacterial activity. The nutrient agar broth prepared by usual method was inoculated aseptically with 0.5 ml of 24 hrs. old subculture of ***B. megaterium. S. aureus, E. coli and P. vulgaris*** in separate conical flask at 40-50°C and mixed well by gentle shaking. About 25 ml of the content of the flask were poured and evenly spreaded in a petridish (13 cm in diameter) and allowed to set for two hrs. The cups (10 mm in diameter) were formed by the help of borer in agar medium and filled with 0.04 ml (40 μg) solution of sample in DMF.

The plates were incubated at 37°C for 24 hrs and the control was also maintained with 0.04 ml of DMF in similar manner and the zones of inhibition of the bacterial growth were measured in millimeters and are recorded in Graphical Chart No.1

(ii) Antifungal activity

A. niger was employed for testing antifungal activity using cup-plate method. The culture was mainted on Sabouraud's agar slants. Sterilised Sabouraud's agar medium was inoculated with 72 hrs old 0.5 ml suspension of fungal spores in a separate flask. About 25 ml of the inoculated medium was evenly spreaded in a petridish and allowed to set for two hrs. The cups (10 mm in diameter) were punched in petridish and loaded with 0.04 ml (40 μg) of solution of sample in DMF. The plates were incubated at 30°C for 48 hrs. After the completion of incubation period, the zones of inhibition of growth in the form of diameter in mm was measured. Along the test solution in each petridish one cup was filled up with solvent which act as control. The zones of inhibition are recorded in Graphical Chart No. I.

(iii) Antitubercular activity

The antituberclar evaluation of the compouds was carried out at Tuberculosis Antimicrobial Acequisition and Coordination Facility (TAACF), U.S.A. Primary screening of the compounds for antitubercular activity have been conducted at 6.25 mg/ml towards *Mycobacterium Tuberculosis* H_{37} Rv in BACTEC 12B medium using the BACTEC 460 radiometric system. The compounds demonstrating atleast > 90% inhibition in the primary screen have been retested at lower concentration towards *Mycobacterium Tuberculosis* H_{37}Rv to determine the actual minimum inhibitory concentration (MIC) in the BACTEC 460.

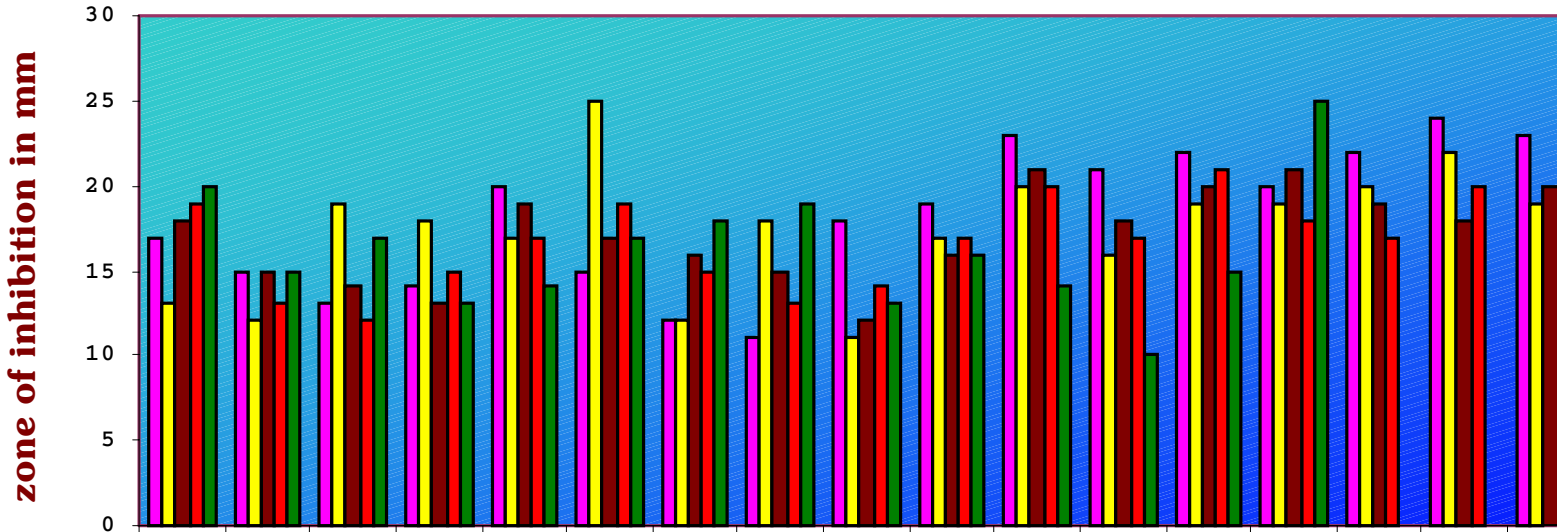
The antitubercular activity data have been compared with standard drug Rifampin at 6.25 μg/ml concentration and it showed 98% inhibition the data for % inhibition are recorded in Table No. 1b.

TABLE NO. 1a : PHYSICAL CONSTANTS OF 1-ARYL-3-(2',7'-ARYL-3-(2',7'-DICHOROQUINOLIN-3'-YL)-2-PROPENE-1-ONES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. ^{o}C 5	Rf Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
1a	C_6H_5-	$C_{18}H_{11}NCl_2O$	328	160	0.589	66	4.23	4.27
1b	3-NH_2-C_6H_4-	$C_{18}H_{12}N_2Cl_2O$	343	196	0.604	72	8.15	8.16
1c	4-NH_2-C_6H_4-	$C_{18}H_{12}N_2Cl_2O$	343	146	0.595	61	8.19	8.16
1d	4-Br-C_6H_4-	$C_{18}H_{10}NBrCl_2O$	407	160	0.499	68	3.47	3.44
1e	4-Cl-C_6H_4-	$C_{18}H_{10}NCl_3O$	361.5	120	0.569	56	3.85	3.86
1f	2,6-$(OH)_2$-C_6H_3-	$C_{18}H_{11}NCl_2O_3$	360	144	0.575	49	3.92	3.89
1g	4-F-C_6H_4-	$C_{18}H_{10}NCl_2FO$	346	148	0.583	62	4.01	4.05
1h	C_4H_3O-	$C_{16}H_9NCl_2O_2$	318	186	0.541	65	4.42	4.40
1i	2-OH-C_6H_4-	$C_{18}H_{11}NCl_2O_2$	344	158	0.589	56	4.08	4.07
1j	4-OH-C_6H_4-	$C_{18}H_{11}NCl_2O_2$	344	142	0.607	60	4.04	4.07
1k	4-OCH_3-C_6H_4-	$C_{19}H_{13}NCl_2O_2$	358	270	0.501	75	3.88	3.91
1l	4-CH_3-C_6H_4-	$C_{19}H_{13}NCl_2O$	342	160	0.484	63	4.10	4.09
1m	3-NO_2-C_6H_4-	$C_{18}H_{10}N_2Cl_2O_3$	373	140	0.551	50	7.55	7.51
1n	4-NO_2-C_6H_4-	$C_{18}H_{10}N_2Cl_2O_3$	373	210	0.493	58	7.49	7.51

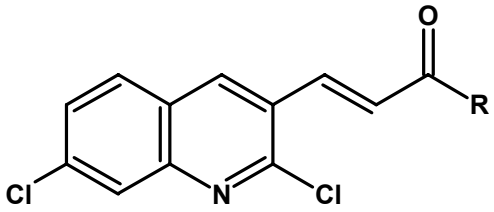
TLC Solvent System : Acetone : Benzene (2.5 : 7.5).

GRAPHICAL CHART NO. 1 : 1-ARYL-3-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-PROPENE-1-ONES



	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l	1m	1n	Ampicillin	Amoxycillin	Noxici
B.mega	17	15	13	14	20	15	12	11	18	19	23	21	22	20	22	24	23
s.aureus	13	12	19	18	17	25	12	18	11	17	20	16	19	19	20	22	19
E.coli	18	15	14	13	19	17	16	15	12	16	21	18	20	21	19	18	20
P.vulgaris	19	13	12	15	17	19	15	13	14	17	20	17	21	18	17	20	21
A.niger	20	15	17	13	14	17	18	19	13	16	14	10	15	25	0	0	0

TABLE NO. 1b : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



TAACF, Southern Research Institute
Primary Assay Summary Report

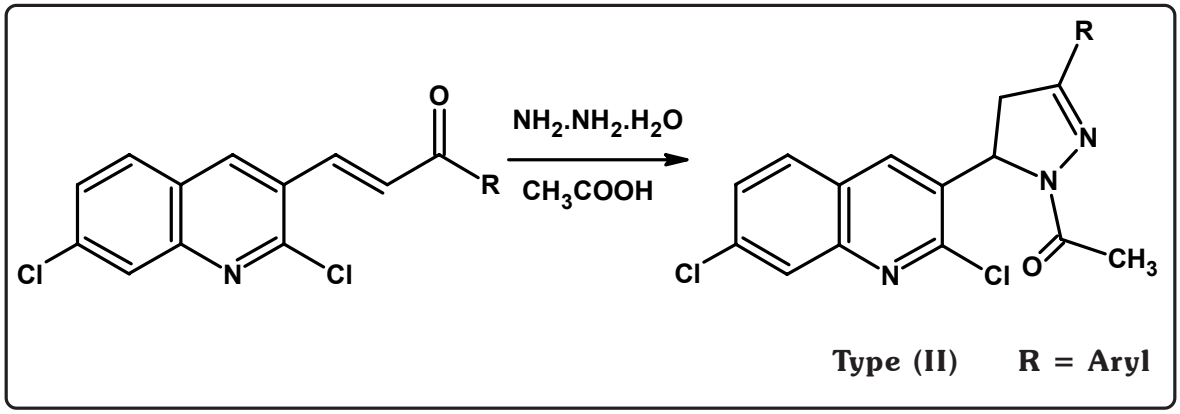
Dr. A. R. Parikh
Saurashtra University

Sample ID	*Corp ID*	*Where, R =*	*Supplier*	*Assay*	*MTb Strain*	*MIC*	*% Inhib*	*Comment*
162062	AP-10	4-NH_2-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	97	MIC Rifampin=0.25µg/ml @98% inhibition
162058	AP-6	4-OH-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	69	MIC Rifampin=0.25µg/ml @98% inhibition
162056	AP-4	4-Cl-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	64	MIC Rifampin=0.25µg/ml @98% inhibition
162060	AP-8	4-F-C_6H_4-	Saurashtra University	Alamar	H37Rv	>6.25	64	MIC Rifampin=0.25µg/ml @98% inhibition
162053	AP-1	C_6H_5	Saurashtra University	Alamar	H37Rv	>6.25	59	MIC Rifampin=0.25µg/ml @98% inhibition
162055	AP-3	4-OCH_3-C_6H_5	Saurashtra University	Alamar	H37Rv	>6.25	53	MIC Rifampin=0.25µg/ml @98% inhibition
162057	AP-5	4-Br-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	49	MIC Rifampin=0.25µg/ml @98% inhibition
162054	AP-2	4-CH_3-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	46	MIC Rifampin=0.25µg/ml @98% inhibition
162061	AP-9	C_4H_3O	Saurashtra University	Alamar	H37Rv	>6.25	31	MIC Rifampin=0.25µg/ml @98% inhibition
162059	AP-7	4-NO_2-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	23	MIC Rifampin=0.25µg/ml @98% inhibition

SECTION - II

SYNTHESIS AND THERAPEUTIC EVALUATION OF 1-ACETYL-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-3-ARYL-PYRAZOLINES

1-Acetyl pyrazolines have been found to be associated with diverse biological activities. These finding prompted us to prepare some new pyrazoline derivatives of type (II) possessing better biological activity, which have been prepared by the condensation of chalcones of type (I) with hydrazine hydrate in acetic acid.

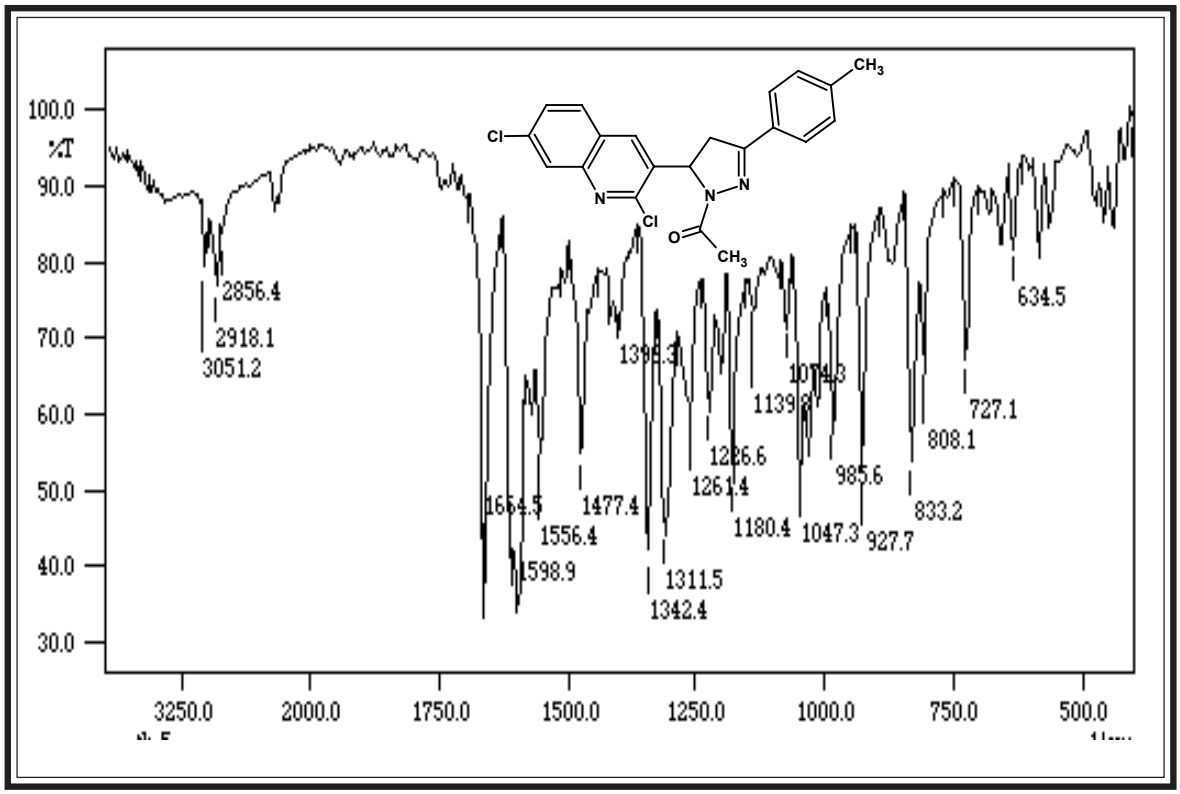


Type (II) R = Aryl

The constitution of the synthesised product has been characterised using elemental analyses, infra red and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg. The biological activities of the synthesised compounds have been compared with standard drugs. The details have been cited in Part-I, Section- I (D), antitubercular activity was carried out against *Mycobacterium Tuberculosis* $H_{37}Rv$ at a concentration of 6.25 μg using Rifampin as a standard drug.

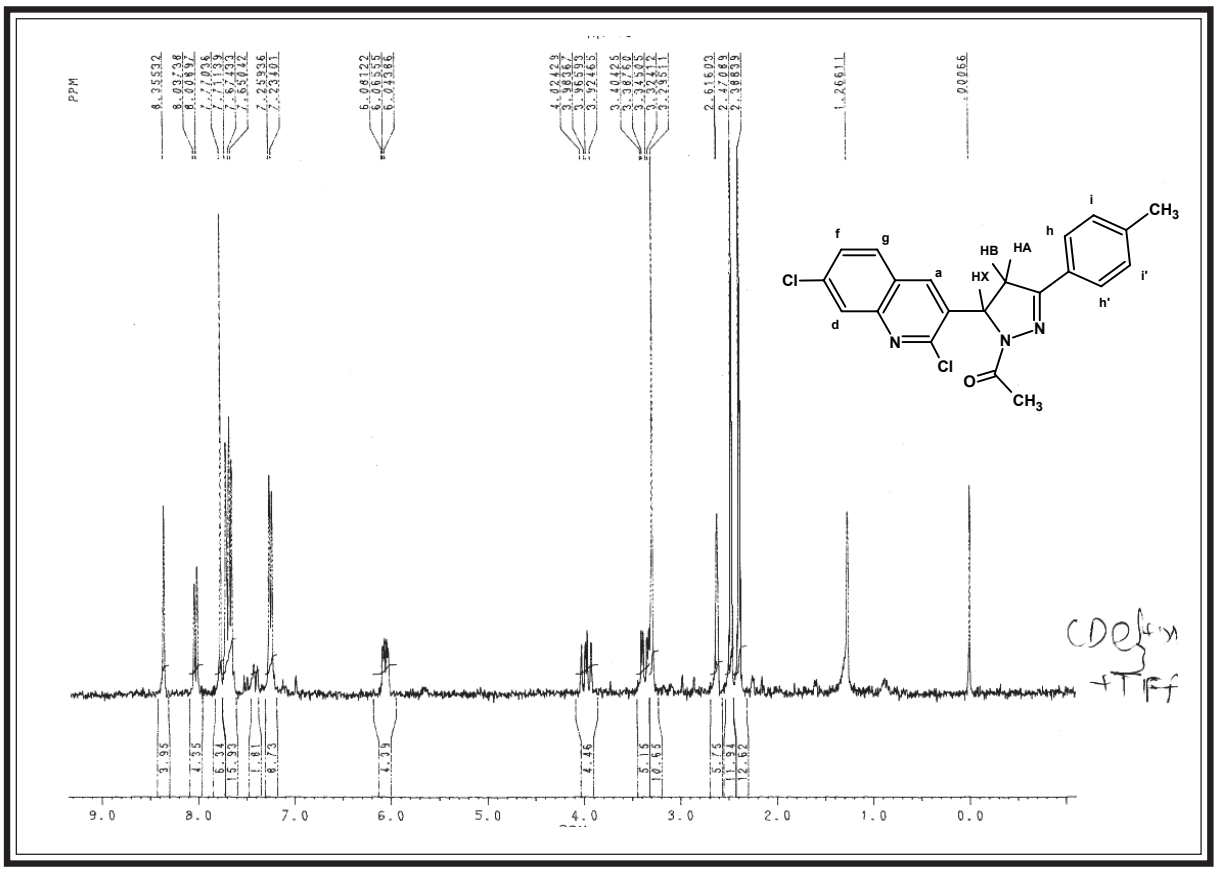
IR SPECTRAL STUDY OF 1-ACETYL-3-ρ-TOLYL-5-(2'-7'-DICHLOROQUINOLIN-3'-YL)-PYRAZOLINE



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

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.	2918	2975-2850	419
	C – H def.	1477	1470-1435	"
Aromatic	C– H str.	3051	3080-3030	"
	C = C str.	1596	1585-1570	"
		1477	1520-1480	"
	C – H def.	833	835-810	420
Quinoline moiety	C = N str.	1598	1612-1593	419
	C – Cl str.	727	750-700	"
Pyrazoline	C = N str.	1598	1627-1580	418
	N–C–CH_3- str. (‖ O)	1664	1660	"

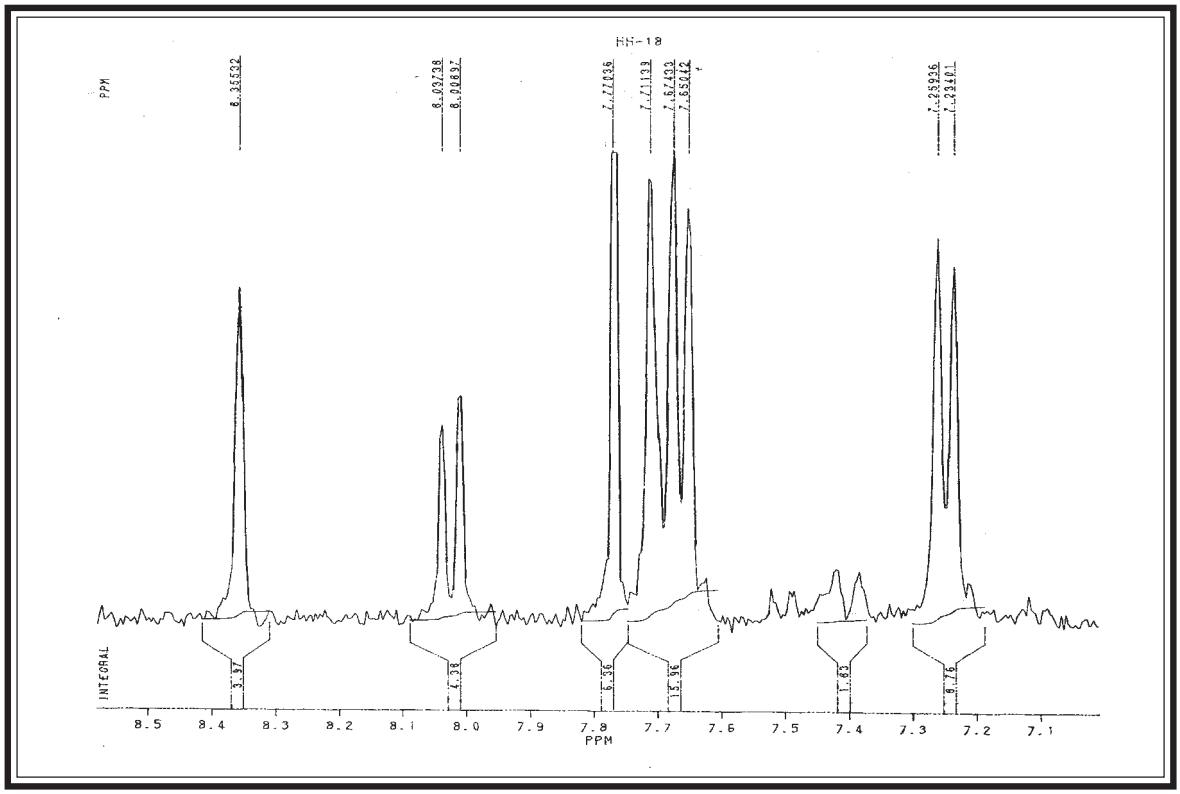
PMR SPECTRAL STUDY OF 1-ACETYL-3-(p-TOLYL)-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-PYRAZOLINES



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

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	J. Value in Hz	Inference
1	2.39	3H	singlet	-	$-COCH_3$
2.	2.47	3H	singlet	-	$-Ar-CH_3$
3.	3.32-3.40	1H	double doublet	J_{AX}=5.00 J_{AB}=17.76	$-CH_A$
4.	3.92-4.02	1H	double doublet	J_{BX}=12.19 J_{BA}=17.71	$-CH_B$
5.	6.04-6.08	1H	double doublet	J_{XB}=11.21 J_{XA}=4.70	$-CH_X$
6.	7.23-7.26	2H	doublet	Jhi 7.61	Ar-H'hh'
7.	7.65-7.71	4H	multiplate	-	Ar-H'ii Ar-Hf Ar-Hd
8.	8.01-8.04	1H	doublet	Jgf 8.52	Ar-Hg
9.	8.36	1H	singlet	-	Ar-Ha

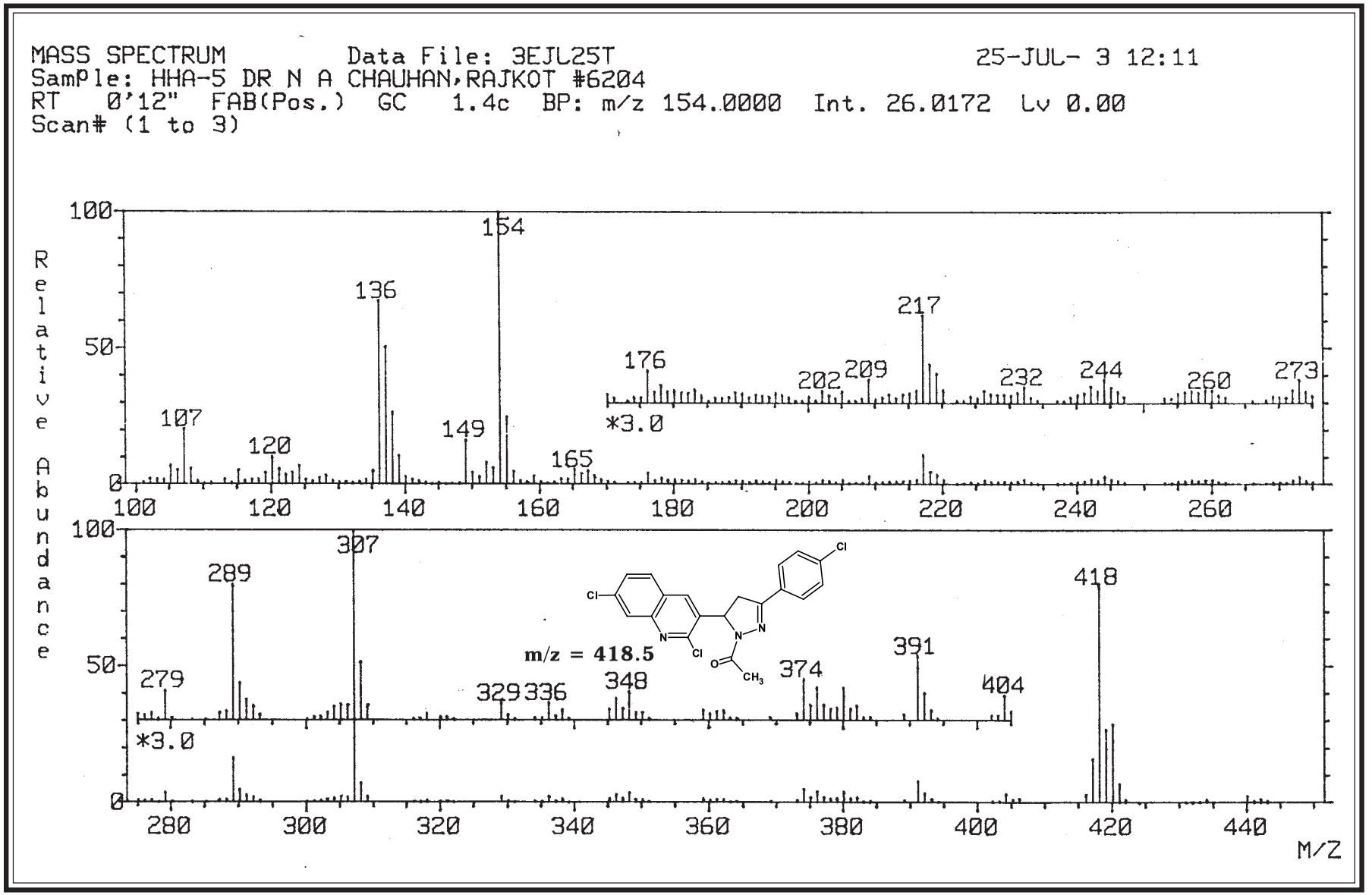
EXPANDED AROMATIC REGION



IR SPECTRAL DATA OF 1-ACETYL-3-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-PYRAZOLINES

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

Sr. No.	R	C=O str.
2a	C_6H_5	1656
2b	4-NH_2-C_6H_4	1658
2c	4-Br-C_6H_4	1658
2d	4-Cl-C_6H_4	1656
2e	4-F-C_6H_4	1658
2f	C_4H_3O	1658
2g	2-OH-C_6H_4	1659
2h	4-OH-C_6H_4	1660
2i	4-OCH_3-C_6H_4	1656
2j	4-CH_3-C_6H_4	1660
2k	3-NO_2-C_6H_4	1660
2l	4-NO_2-C_6H_4	1658


MASS SPECTRUM Data File: 3EJL25T 25-JUL- 3 12:11
SamPle: HHA-5 DR N A CHAUHAN,RAJKOT #6204
RT 0'12" FAB(Pos.) GC 1.4c BP: m/z 154.0000 Int. 26.0172 Lv 0.00
Scan# (1 to 3)
Relative Abundance
M/Z
m/z = 418.5
*3.0
*3.0

EXPERIMENTAL

SYNTHESIS AND THERAPEUTIC EVALUATION OF 1-ACETYL-3-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-PYRAZOLINES

[A] Synthesis of 1-Aryl-3-(2',7'-dichloroquinolin-3'-yl)-2-propene-1-ones

See part - I, Section-I (C)

[B] Synthesis of 1-Acetyl-3-aryl-5-(2',7'-dichloroquinolin-3'-yl)-pyrazolines

A mixture of 1-ρ-tolyl-3-(2',7'-dichloroquinolin-3'-yl)-2-propene-1-one (3.43 g, 0.01 mol) in 20 ml acetic acid and hydrazine hydrate (0.59, 0.01 mol) was refluxed for 10 hrs. The contents were poured onto ice & product was isolated, crystallised from ethanol yield 56%, m.p. 204°C. Anal. calcd. for $C_{21}H_{17}N_3Cl_2O$ required: C, 63.33%; H, 4.3%; N, 10.55%; found: C, 63.20%; H, 4.15%; N, 10.43%.

TLC solvent system: Acetone : Benzene (2:8) visualizing agent : Iodine

Similarly other chalcones were condensed with hydrazine hydrate. The physical data along with infra red spectral data are recorded in Table Ic.

[C] Therapeutic evaluation of 1-Acetyl-3-aryl-5-(2',7',-dichloroquinolin-3'-yl)-pyrazolines

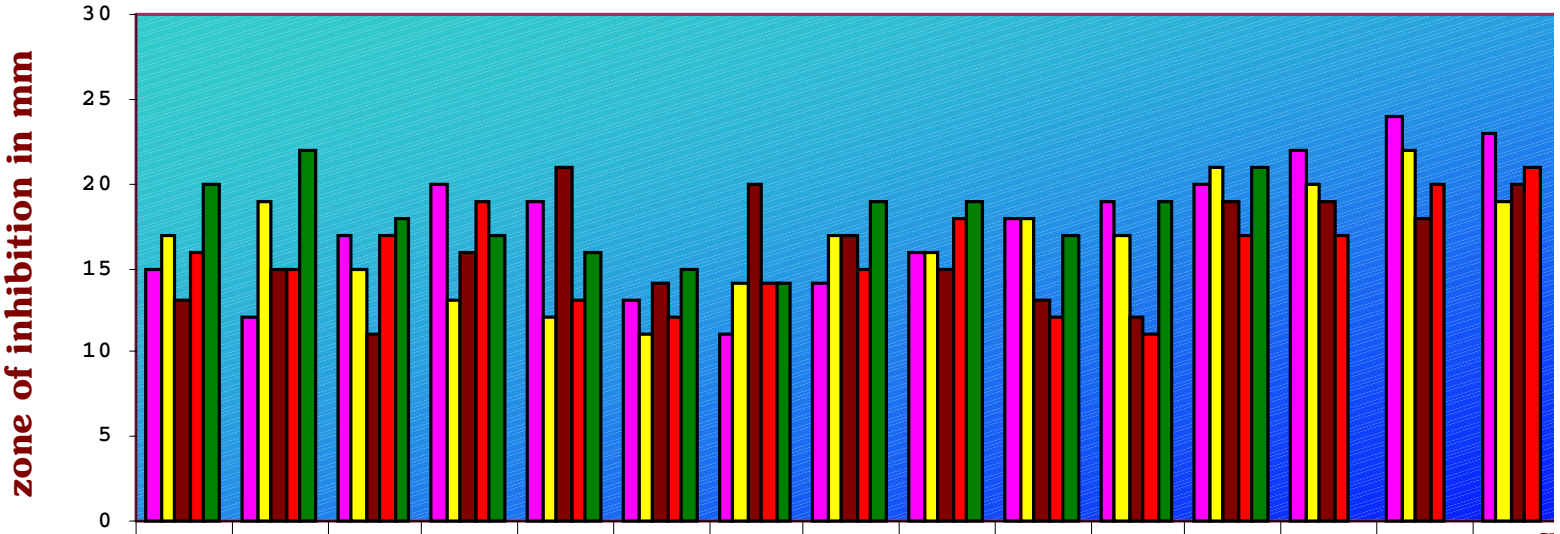
Antimicrobial testing was carried out as described in Part-I, Section-1 (D). The zone of inhibition of the test solution are recorded in Graphical Chart No. 2. The antitubercular activity data have been compared with standard drug rifampin at 6.25 μg/ml concentration and the data for % inhibition are recorded in Table No. 1d.

TABLE NO. 1c: PHYSICAL CONSTANTS OF 1-ACETYL-3-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-PYRAZOLINES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
2a	C_6H_5-	$C_{20}H_{13}N_3Cl_2O$	384	90	0.496	56	10.94	10.80
2b	4-NH_2-C_6H_4-	$C_{20}H_{16}N_4Cl_2O$	399	212	0.550	68	14.03	14.30
2c	4-Br-C_6H_4-	$C_{20}H_{14}N_3BrCl_2O$	463	288	0.568	72	9.07	9.29
2d	4-Cl-C_6H_4-	$C_{20}H_{13}N_3Cl_3O$	418.5	160	0.801	70	10.04	10.40
2e	4-F-C_6H_4-	$C_{20}H_{14}N_3Cl_2FO$	402	218	0.471	64	10.45	10.30
2f	C_4H_3O-	$C_{18}H_{13}N_3Cl_2O_2$	374	98	0.425	69	11.23	11.62
2g	2-OH-C_6H_4-	$C_{20}H_{15}N_3Cl_2O_2$	400	158	0.569	59	10.50	10.24
2h	4-OH-C_6H_4-	$C_{20}H_{15}N_3Cl_2O_2$	400	116	0.511	71	10.50	10.27
2i	4-OCH_3-C_6H_4-	$C_{21}H_{17}N_3Cl_2O_2$	414	222	0.623	70	10.14	10.32
2j	4-CH_3-C_6H_4-	$C_{21}H_{17}N_3Cl_2O$	398	204	0.571	56	10.55	10.43
2k	3-NO_2-C_6H_4-	$C_{20}H_{14}N_4Cl_2O_3$	429	192	0.614	64	13.05	13.29
2l	4-NO_2-C_6H_4-	$C_{20}H_{14}N_4Cl_2O_3$	429	144	0.509	63	13.05	13.38

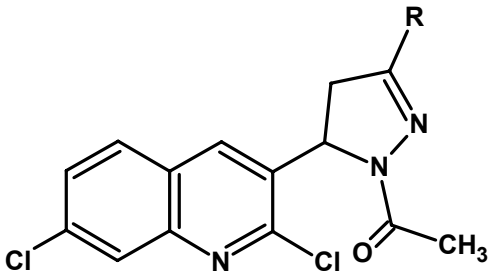
TLC Solvent System : Acetone : Benzene (2 : 8).

GRAPHICAL CHART NO. 2 : 1-ACETYL-3-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-PYRAZOLINES



	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l	Ampicillin	Amoxycillin	Norfloxacin
B.mega	15	12	17	20	19	13	11	14	16	18	19	20	22	24	23
s.aureus	17	19	15	13	12	11	14	17	16	18	17	21	20	22	19
E.coli	13	15	11	16	21	14	20	17	15	13	12	19	19	18	20
P.vulgaris	16	15	17	19	13	12	14	15	18	12	11	17	17	20	21
A.niger	20	22	18	17	16	15	14	19	19	17	19	21	0	0	0

TABLE NO. 1c : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



TAACF, Southern Research Institute
Primary Assay Summary Report

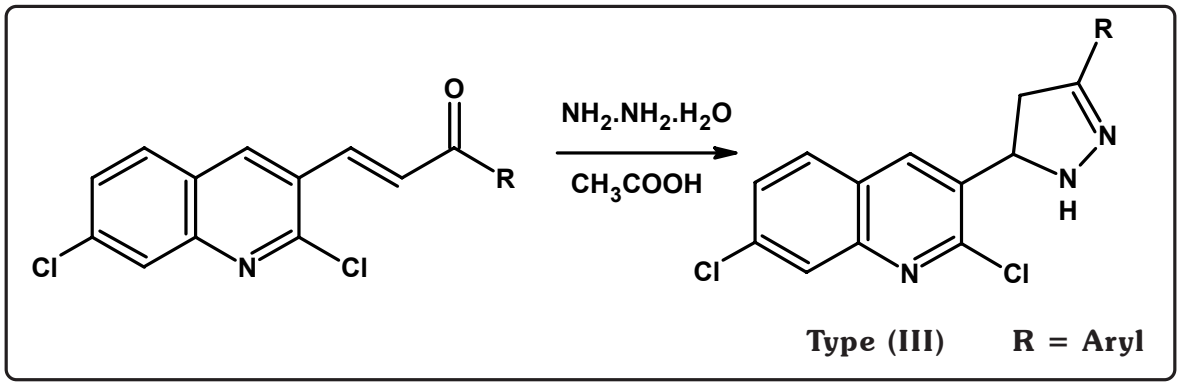
Dr. A. R. Parikh
Saurashtra University

Sample ID	*Corp ID*	*Where, R =*	*Supplier*	*Assay*	*MTb Strain*	*MIC*	*% Inhib*	*Comment*
162090	AP-38	4-F-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	54	MIC Rifampin=0.25µg/ml @98% inhibition
162083	AP-31	C_6H_5	Saurashtra University	Alamar	H37Rv	>6.25	39	MIC Rifampin=0.25µg/ml @98% inhibition
16092	AP-40	4-NH_2-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	24	MIC Rifampin=0.25µg/ml @98% inhibition
162084	AP-32	4-CH_3-C_6H_4-	Saurashtra University	Alamar	H37Rv	>6.25	23	MIC Rifampin=0.25µg/ml @98% inhibition
162089	AP-37	4-NO_2-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	21	MIC Rifampin=0.25µg/ml @98% inhibition
162086	AP-34	4-Cl-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	20	MIC Rifampin=0.25µg/ml @98% inhibition
162085	AP-33	4-OCH_3-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	14	MIC Rifampin=0.25µg/ml @98% inhibition
162088	AP-36	4-OH-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	10	MIC Rifampin=0.25µg/ml @98% inhibition
162091	AP-39	C_4H_3O	Saurashtra University	Alamar	H37Rv	>6.25	5	MIC Rifampin=0.25µg/ml @98% inhibition
162093	AP-41	2-OH-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	0	MIC Rifampin=0.25µg/ml @98% inhibition

SECTION-III

SYNTHESIS AND THERAPEUTIC EVALUATION OF 1H-3-ARYL-5-(2',7'-DICHLOROQUINOLIN-3-YL)-PYRAZOLINES

Pyrazoline derivatives are associated with diversified biological properties. Hence, it was thought of interest that a pyrazoline ring, if coupled to a 2,7-dichloroquinolin-3-carboxaldehyde nucleus, the resulting compounds may possess significant biological potency. Hence the synthesis of 1H-3-aryl-5-(2',7'-dichloroquinolin-3'-yl)-pyrazolines of type (III) have been undertaken by the cyclo-condensation of chalcones of the type (I) with hydrazine hydrate.

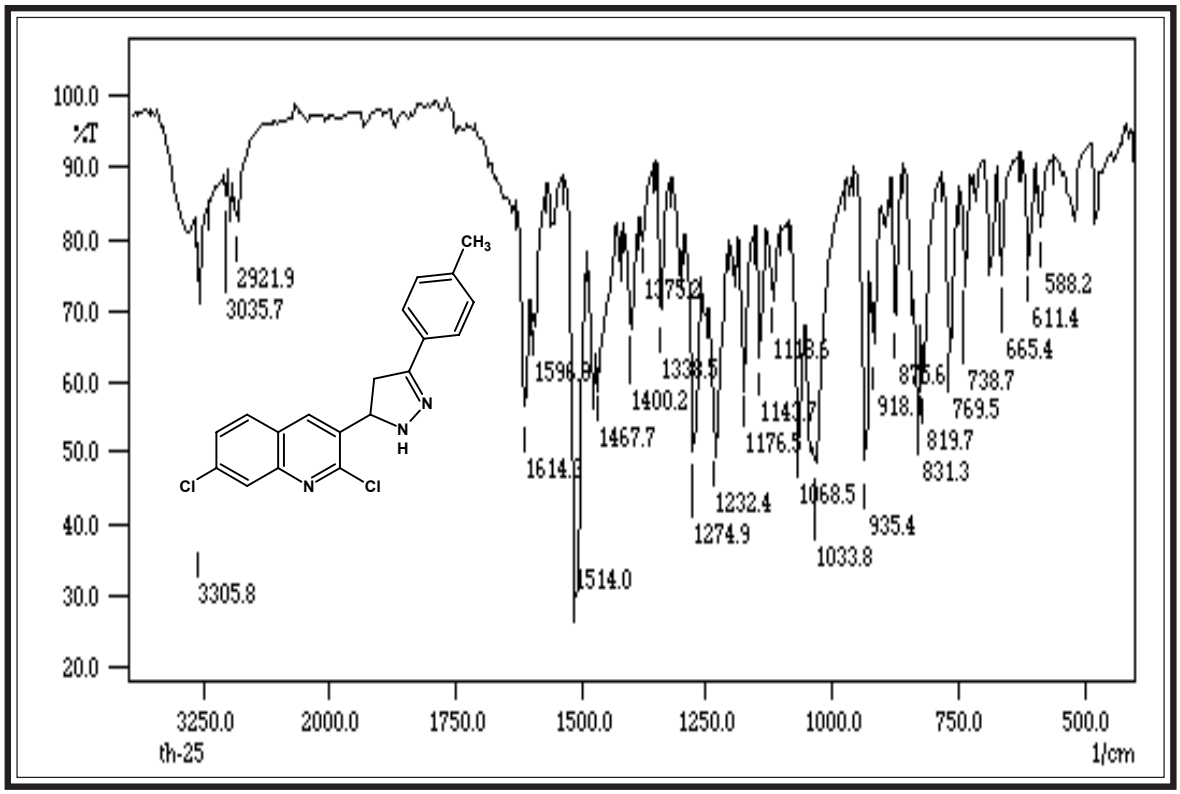


Type (III) R = Aryl

The constitution of the synthesised products have been characterised by using elemental analyses, infra red and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg The biological activities of the synthesised compounds have been compared with standard drugs. The details have been cited in Part-I, Section-I (D).

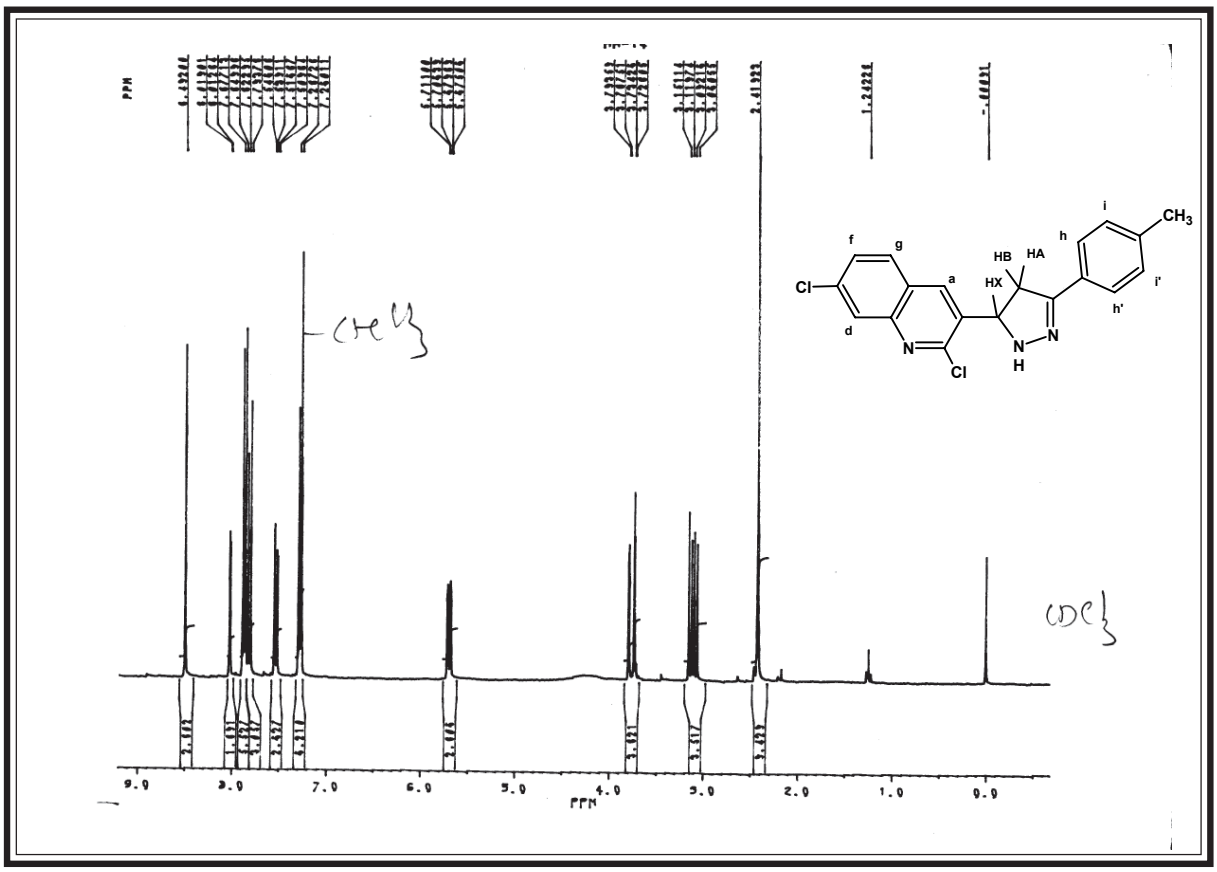
IR SPECTRAL STUDY OF 1H-3-p-TOLYL-5-(2'-7'-DICHLOROQUINOLIN-3'-YL)-PYRAZOLINE



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

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.	2921	2975-2850	419
	C – H def.	1467	1470-1435	"
Aromatic	C– H str.	3035	3080-3030	"
	C = C str.	1596	1585-1570	"
		1514	1520-1480	"
	C – H def.	1068	1070-1000	420
		831	835-810	"
Quinoline	C = N str.	1596	1612-1593	419
moiety	C – Cl str.	738	750-700	"
Pyrazoline	C = N str.	1614	1627-1580	"
	N–H str.	3305	3200-3400	"

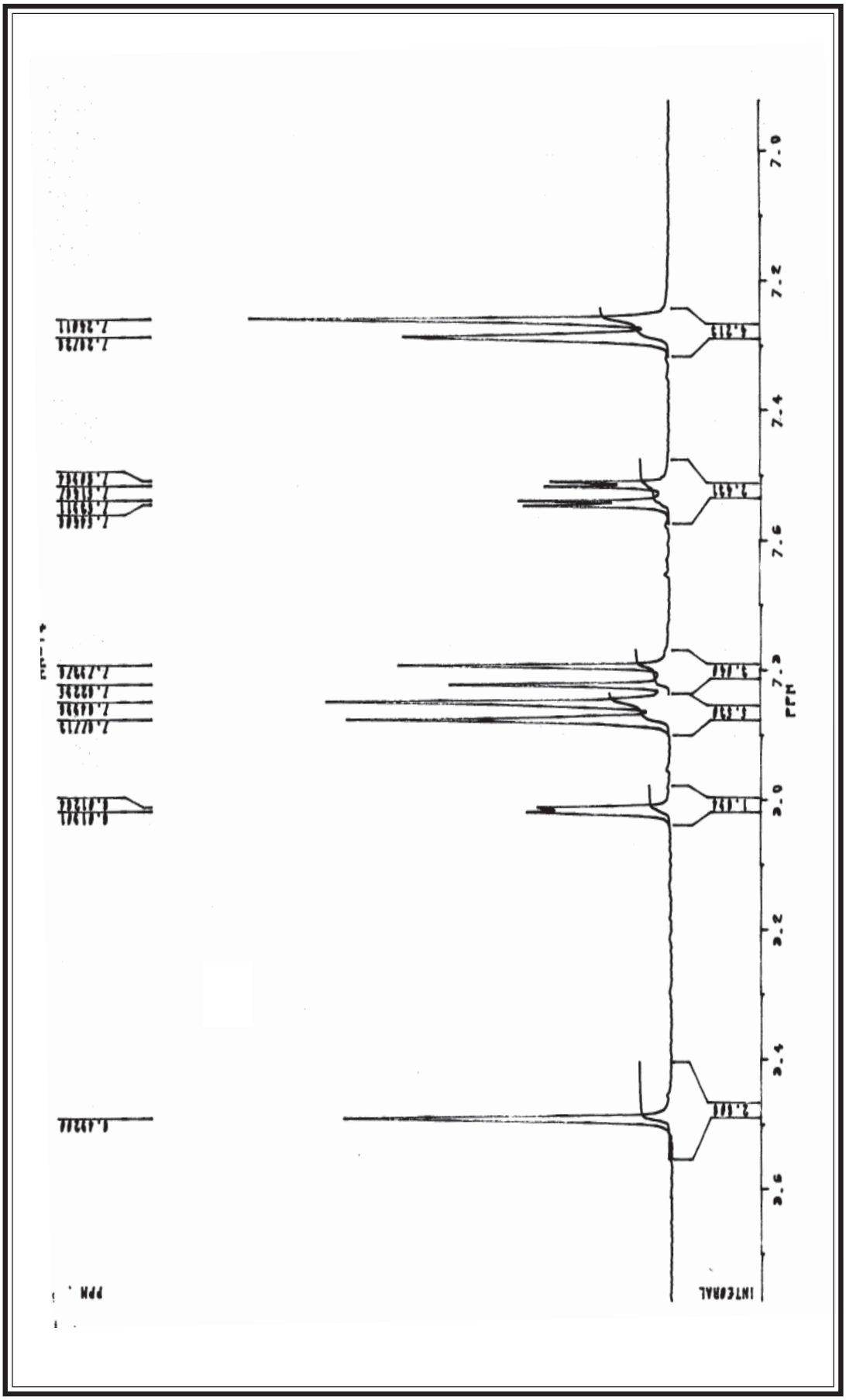
PMR SPECTRAL STUDY OF 1H-3-(ρ-TOLYL)-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-PYRAZOLINES

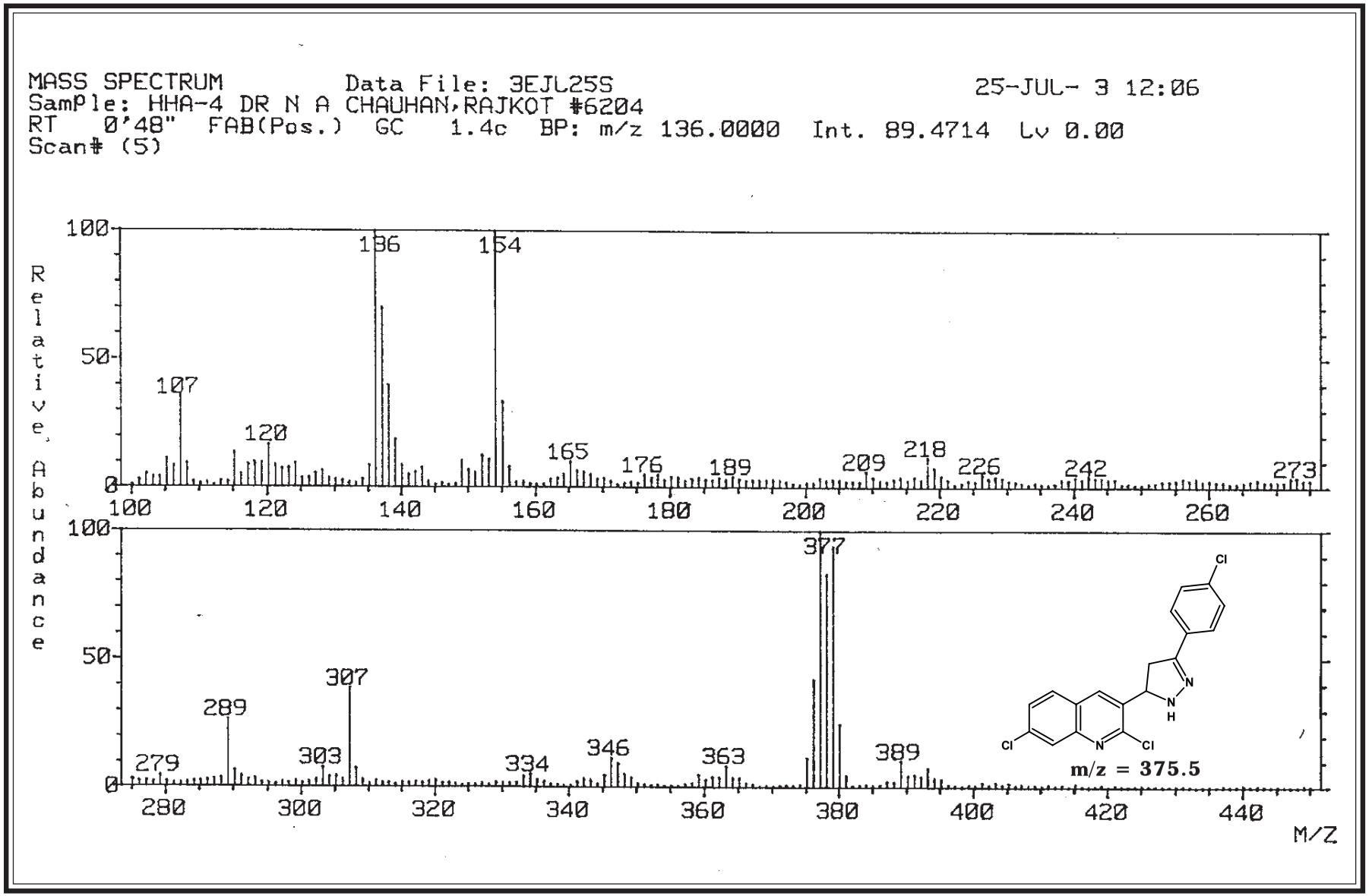


Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	J. Value in Hz	Inference
1.	2.41	3H	singlet	-	Ar-CH_3
2.	3.06-3.15	1H	double doublet	J_{AB}=17.76 J_{AX}=9.42	-CH_A
3.	3.72-3.79	1H	double doublet	J_{BA}=17.80 J_{BX}=1.82	-CH_B
4.	5.68-5.71	1H	double doublet	J_{XA}=9.40 J_{XB}=1.45	-CHX
5.	7.26-7.55	2H	doublet	Jhi 8.15	Ar-H h'h'
6.	7.51-7.55	1H	double doublet	Jfg 8.76 Jfd 2.09	Ar-Hf
7.	7.79-7.82	1H	doublet	Jgf 8.75	Ar-Hg
8.	7.85-7.88	2H	doublet	Jhi 8.14	Ar-H j'j
9.	8.01-8.02	1H	doublet	Jdf 2.09	Ar-Hd
10	8.49	1H	singlet	-	Ar-Ha

EXPANDED AROMATIC REGION




MASS SPECTRUM Data File: 3EJL25S 25-JUL- 3 12:06
SamPle: HHA-4 DR N A CHAUHAN,RAJKOT #6204
RT 0'48" FAB(Pos.) GC 1.4c BP: m/z 136.0000 Int. 89.4714 Lv 0.00
Scan# (5)
Relative Abundance
M/Z
m/z = 375.5

EXPERIMENTAL

SYNTHESIS AND THERAPEUTIC EVALUATION OF 1H-3-ARYL-5-(2',7'-DICHLOROQUIOLIN-3'-YL)-PYRAZOLINES

[A] Synthesis of 1-Aryl-3-(2',7'-dichloroquinolin-3'-yl)-2-propene-1-ones

See Part-I, Section I (C).

[B] Synthesis of 1H-3-Aryl-5-(2',7'-dichloroquinolin-3'-yl)-pyrazolines

A mixture of 1-tolyl-3-(2',7'-dichloroquinolin-3'-yl)-2-propene-1-one (3.43 g, 0.01 mol) in 25 ml ethanol, hydrazine hydrate (0.5 g, 0.01 mol) and 2-3 drops of acetic acid was refluxed for 12 hrs. The resulting mixture was poured into ice and neutralised with ammonia solution. The product was isolated and crystallised from ethanol. Yield 64%, m.p. 176^{o}C Anal. Calcd. for $C_{19}H_{15}N_3Cl_2$ required: C, 64.06%; H, 4.24%; N, 11.80%; found: C, 63.86%; H, 3.99%; N, 11.57%.

TLC solvent system: Acetone: Benzene (1.5 : 8.5) Visualizing agent : Iodine

Similarly other 1H-3-Aryl-5-(2',7'-dichloro quinolin-3-yl)-pyrazolines were prepared. The physical data along with infra red spectral data are recorded in Table Ie.

[C] Therapeutic evaluation of 1H-3-Aryl-5-(2',7'-dichloroquinolin-3-yl)-pyrazolines

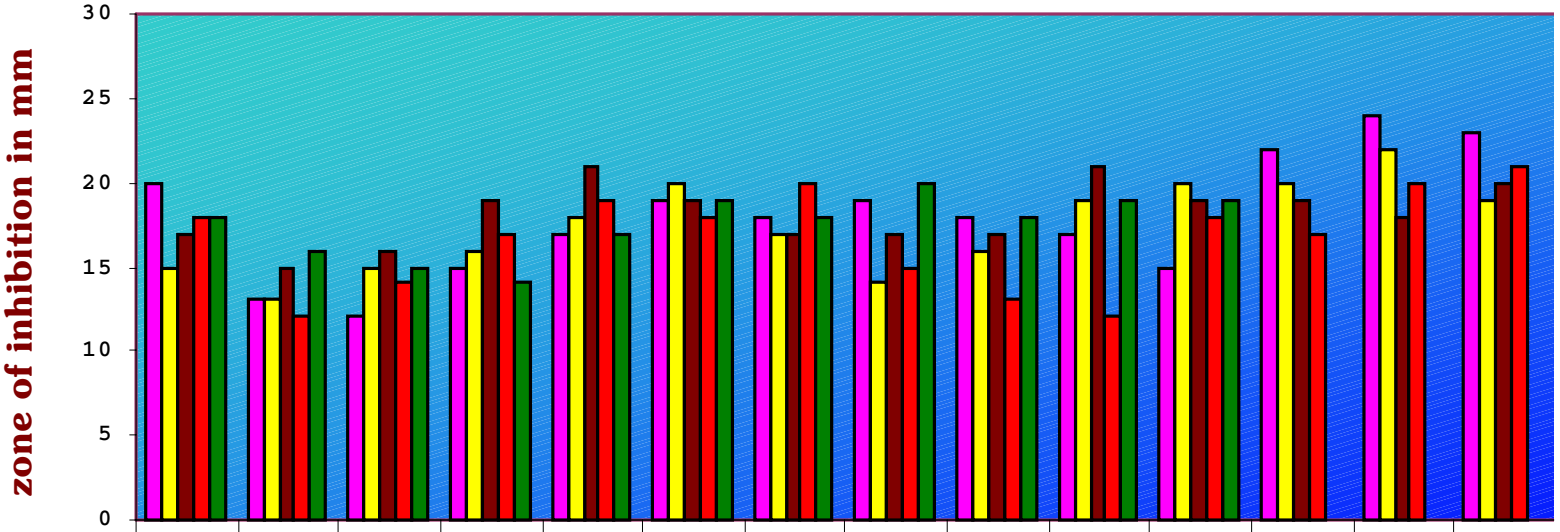
Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zones of inhibition of the test solution are recorded in Graphical Chart No. 3.

TABLE NO. 1e: PHYSICAL CONSTANTS OF 1-H-3-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-PYRAZOLINES

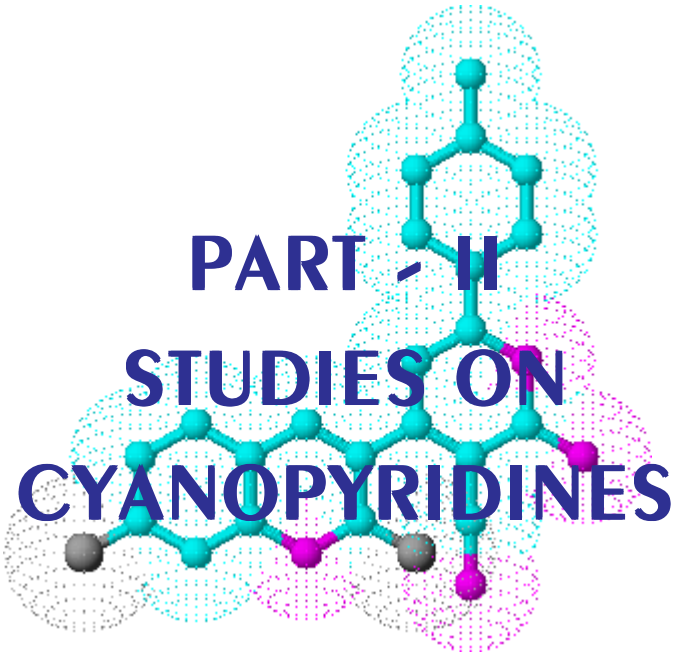
Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
3a	C_6H_5-	$C_{18}H_{13}N_3Cl_2$	342	186	0.485	53	12.28	12.08
3b	4-NH_2-C_6H_4-	$C_{18}H_{14}N_4Cl_2$	357	210	0.450	59	15.68	15.46
3c	4-Br-C_6H_4-	$C_{18}H_{12}N_3BrCl_2$	421	>300	0.568	58	9.98	9.65
3d	4-Cl-C_6H_4-	$C_{18}H_{12}N_3Cl_3$	375.5	240	0.612	60	11.16	11.55
3e	4-F-C_6H_4-	$C_{18}H_{12}N_3Cl_2F$	360	172	0.520	62	11.67	10.27
3f	2-OH-C_6H_4-	$C_{18}H_{13}N_3Cl_2O$	358	236	0.741	57	11.73	11.99
3g	4-OH-C_6H_4-	$C_{18}H_{13}N_3Cl_2O$	358	160	0.639	66	11.73	11.58
3h	4-OCH_3-C_6H_4-	$C_{19}H_{15}N_3Cl_2O$	372	184	0.580	69	11.29	11.65
3i	4-CH_3-C_6H_4-	$C_{19}H_{15}N_3Cl_2$	356	176	0.565	64	11.80	11.57
3j	3-NO_2-C_6H_4-	$C_{18}H_{12}N_4Cl_2O_2$	387	136	0.419	70	14.47	14.95
3k	4-NO_2-C_6H_4-	$C_{18}H_{12}N_4Cl_2O_2$	387	216	0.678	55	14.47	14.05

TLC Solvent System : Acetone : Benzene (1.5 : 8.5).

GRAPHICAL CHART NO. 3 : 1H-3-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-PYRAZOLINES



	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k	Ampicillin	Amoxycillin	Norfloxacin
B.mega	20	13	12	15	17	19	18	19	18	17	15	22	24	23
s.aureus	15	13	15	16	18	20	17	14	16	19	20	20	22	19
E.coli	17	15	16	19	21	19	17	17	17	21	19	19	18	20
P.vulgaris	18	12	14	17	19	18	20	15	13	12	18	17	20	21
A.niger	18	16	15	14	17	19	18	20	18	19	19	0	0	0

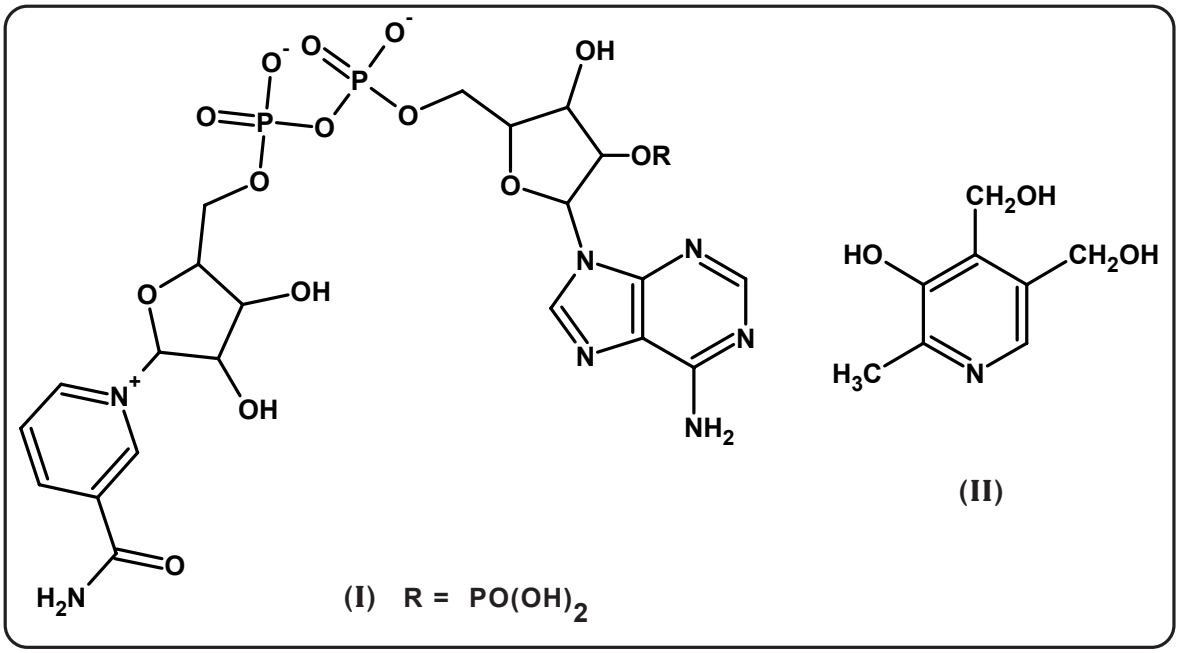


PART - II

STUDIES ON CYANOPYRIDINES

INTRODUCTION

*H*istorically, a wide range of biological activities have been attributed to pyridine derivatives. Pyridine-3-carboxamide occurs as a component of the structure of the important coenzymes NADP + (I), one of the B_2 complex of vitamins, occurs in red blood carpuscles and participates in biochemical redox reaction. Pyridoxal (Vitamin B6) (II), occurs in yeast and wheatgerm is an important food additive.

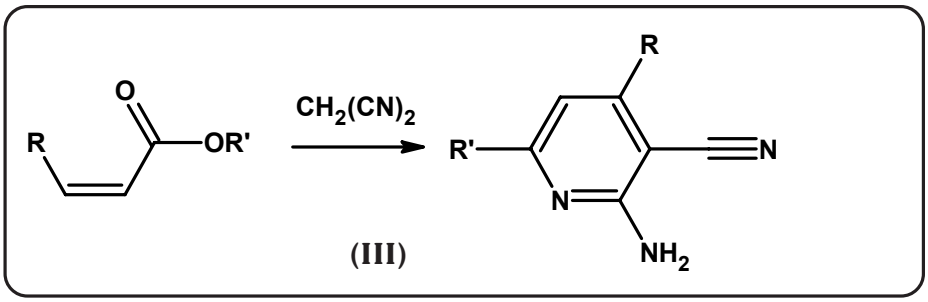


The availability of 3-cyanopyridine, nicotinamide and nicotinic acid make possible their use as synthetic intermediates.

SYNTHETIC ASPECT

Different methods for the preparation of 3-cyanopyridines are available in literature[105-111]. The well known method is:

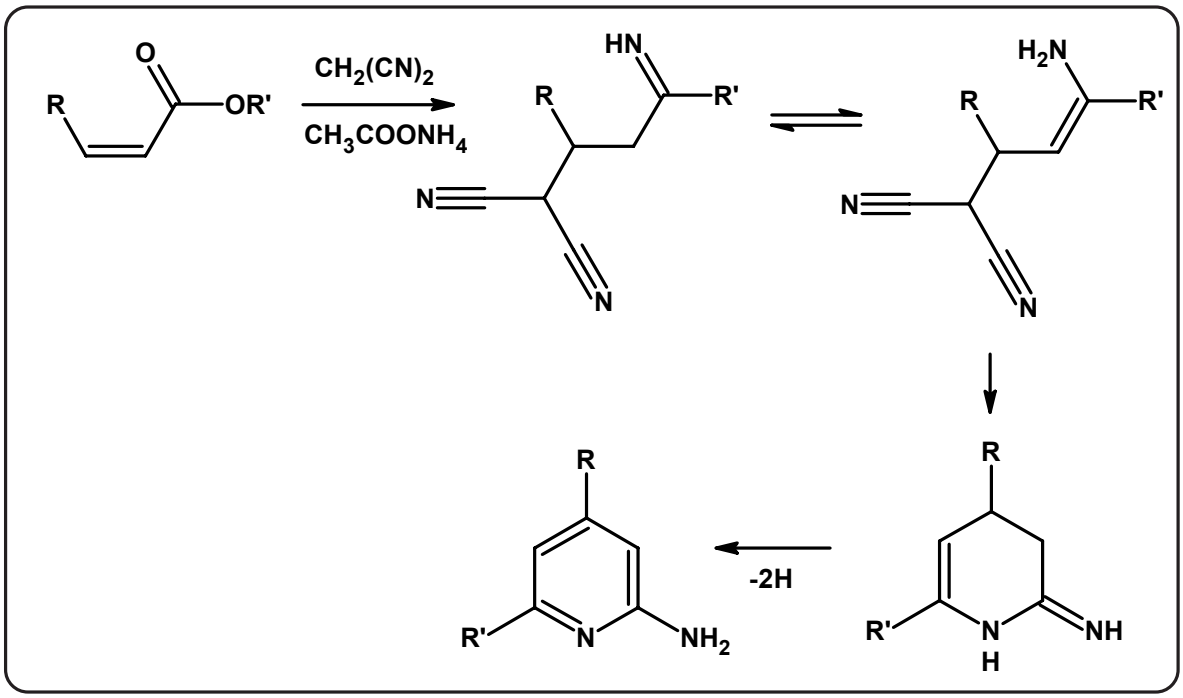
Sakurai and Midorikwa[112,113] have reported that malononitrile reacts with α,β unsaturated ketones to give 2-amino-3-cyano-4,6-disubstituted pyridines (III).



(III)

MECHANISM:

The reaction proceeds through conjugated addition of active methylene compounds to the α,β-unsaturated system as shown below.



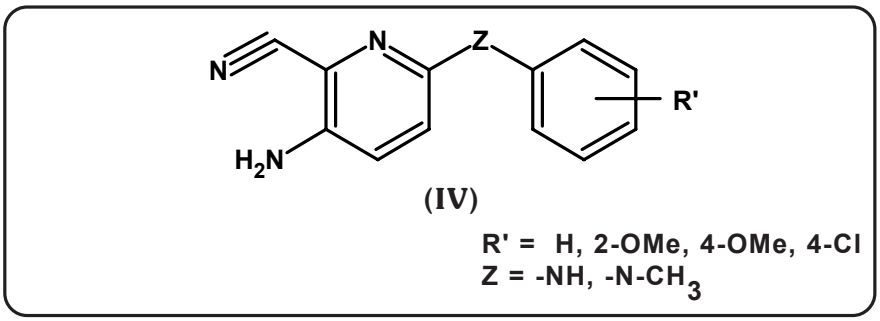
THERAPEUTIC IMPORTANCE

The cyanopyridine derivatives are extensively used in medicine, due to its antidiabetic, antihypertensive, anticholestemic, antifungal and antibacterial properties. Various cyanopyridines are known to exhibit a broad spectrum of biological activities such as,

1. Anti HIV[114]
2. Antitubercular[115]
3. Analgesic[116]
4. Insecticidal[117]
5. Antisoriasis[118]

6. Antihypertensive[119]
7. Antifungal[120]
8. Antiepileptic[121]
9. Anticonvulsant[122]
10. Antibacterial[123,124]
11. Antiinflammatory[125]

Gangjee et al.[126] have synthesised some novel cyanopyridine derivatives of type-(IV) as potent antitumor agents.



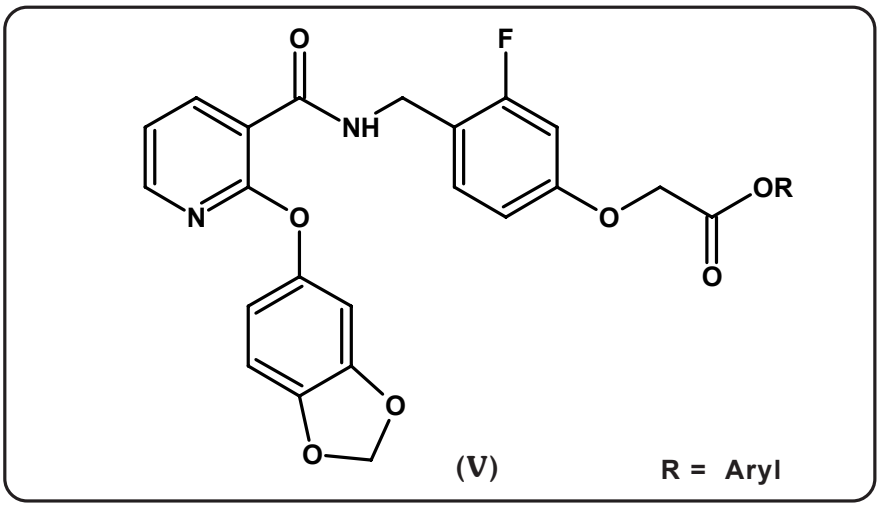
(IV)

R' = H, 2-OMe, 4-OMe, 4-Cl
Z = -NH, -N-CH_3

The insecticidal activity of cyanopyridines has been screened by Y. Sasaki et al.[127] Umed Ten et al.[128] have prepared cyanopyridines as agrochemical fungicides. The oxide activator bleaching activity of cyanopyridine has been proved by Rees M.[129] Oshida Mario[130] prepared cyanopyridine derivatives which inhibit cerebral edema and delayed neuron death. Hence, they are useful as cerebral edema inhibitors as cerebrovascular disorder remedies.

Several co-workers have prepared some novel cyanopyridine derivatives and reported their cholinesterase inhibitors[131], antihistaminic and antiallergic[132], adernegic[133], herbicidal[134], antiinflammatory[135], and insecticidal[136] activities.

Chambers et al.[137] have synthesised new carbonyl substituted pyridine derivatives (V) and prooved that they are inhibitors of phosphodiestercy (IV) isozymes.



Some new 3-cyanopyridine derivatives have been prepared by Hammama A. and co-workers[138] showing anticancer and anti HIV-I activity.

CONTRIBUTION FROM OUR LABORATORY

H. Parekh *et al.*[139-141] have synthesised the series of cyanopyridines and postulated them as antimicrobial agents. A. R. Parikh *et al.*[142] have prepared some new cyanopyridines and studied their antimicrobial activity. H. H. Parekh *et al.*[143] have synthesised 3-cyanopyridines bearing quinoline nucleus and tested their antimicrobial and antitubercular activity.

Abdallah N. *et al.*[144] have prepared cyanopyridine derivatives which showed analgesic and antiinflammatory activity. Ladouceur Getan H. *et al.*[145] have synthesised some new pyridine derivatives behaving as glucagon antagonist. Caroline Charlie and co-worker[146] have prepared pyridine derivatives having antiinflammatory activity. Antimicrobial activity of 3-cyanopyridine derivatives have been studied by Mona Komel *et al.*[147]

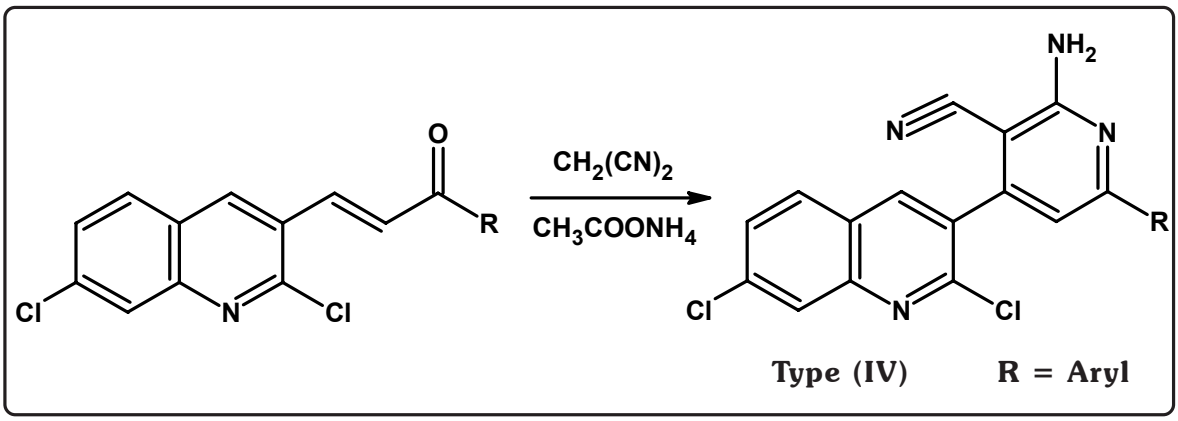
In view of the above observations, the synthesis of new 3-cyanopyridine derivatives bearing 2,7-dichloroquinoline moiety, were aimed at investigating biological activities of these compounds.

SECTION - I : SYNTHESIS AND THERAPEUTIC EVALUATION OF 2-AMINO-3-CYANO-4-(2',7'-DICHLOROQUINOLIN-3'-YL)-6-ARYL PYRIDINES

SECTION - I

SYNTHESIS AND THERAPEUTIC EVALUATION OF 2-AMINO-3-CYANO-4-(2',7'-DICHLOROQUINOLIN-3'-YL)-6-ARYL PYRIDINES

A perusal of the literature has revealed manifold implications of cyanopyridines, viz. antibacterial, antifungal, and antiallergic etc. The cyanopyridine derivatives are endowed with variety of pharmacological activities. In view of these findings, it was contemplated to synthesise some new cyanopyridine derivatives bearing 2,7-dichloroquinolin-3-carboxaldehyde moiety and assess their biopotential. The synthesis was carried out by the condensation of chalcones of type (I) with malononitrile and ammonium acetate.

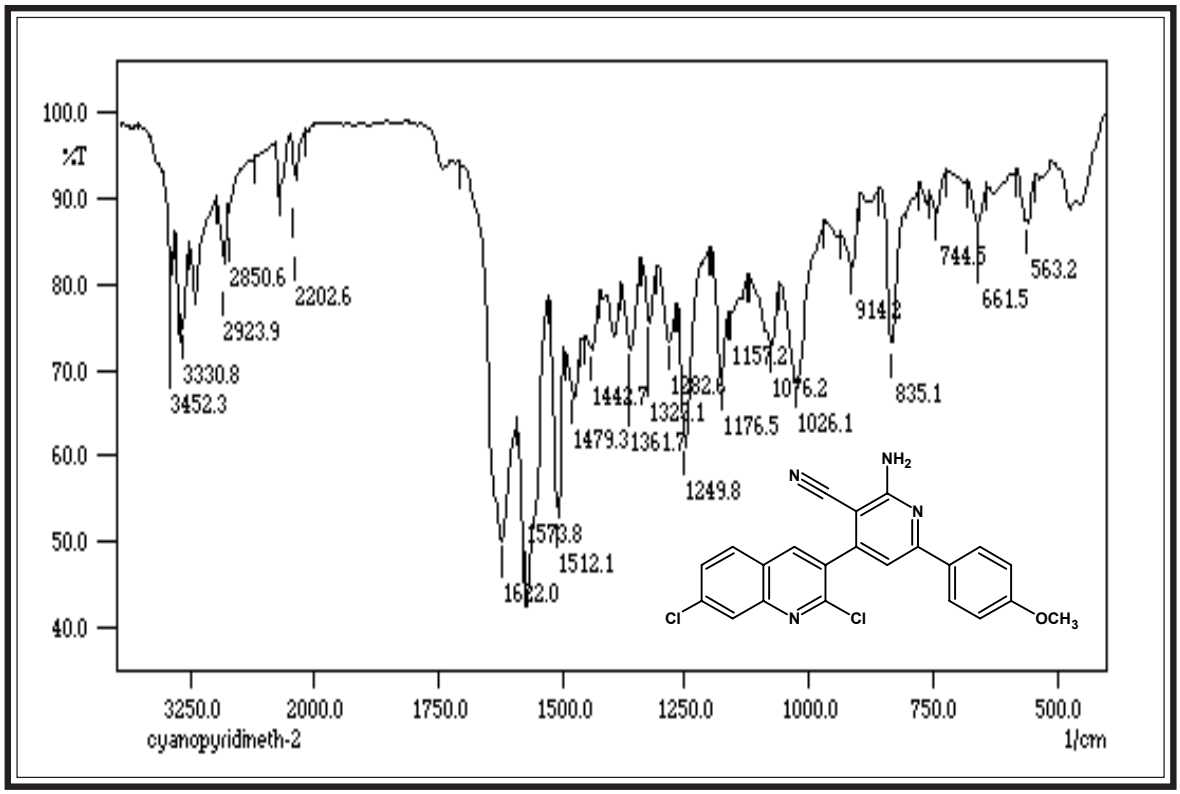


Type (IV) **R = Aryl**

The constitution of the synthesised products have been characterised using elemental analyses, infra red and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass-spectrometry.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg/ml. The biological activities of the synthesised compounds have been compared with standard drugs. The details have been cited in Part-I, Section-I (D).

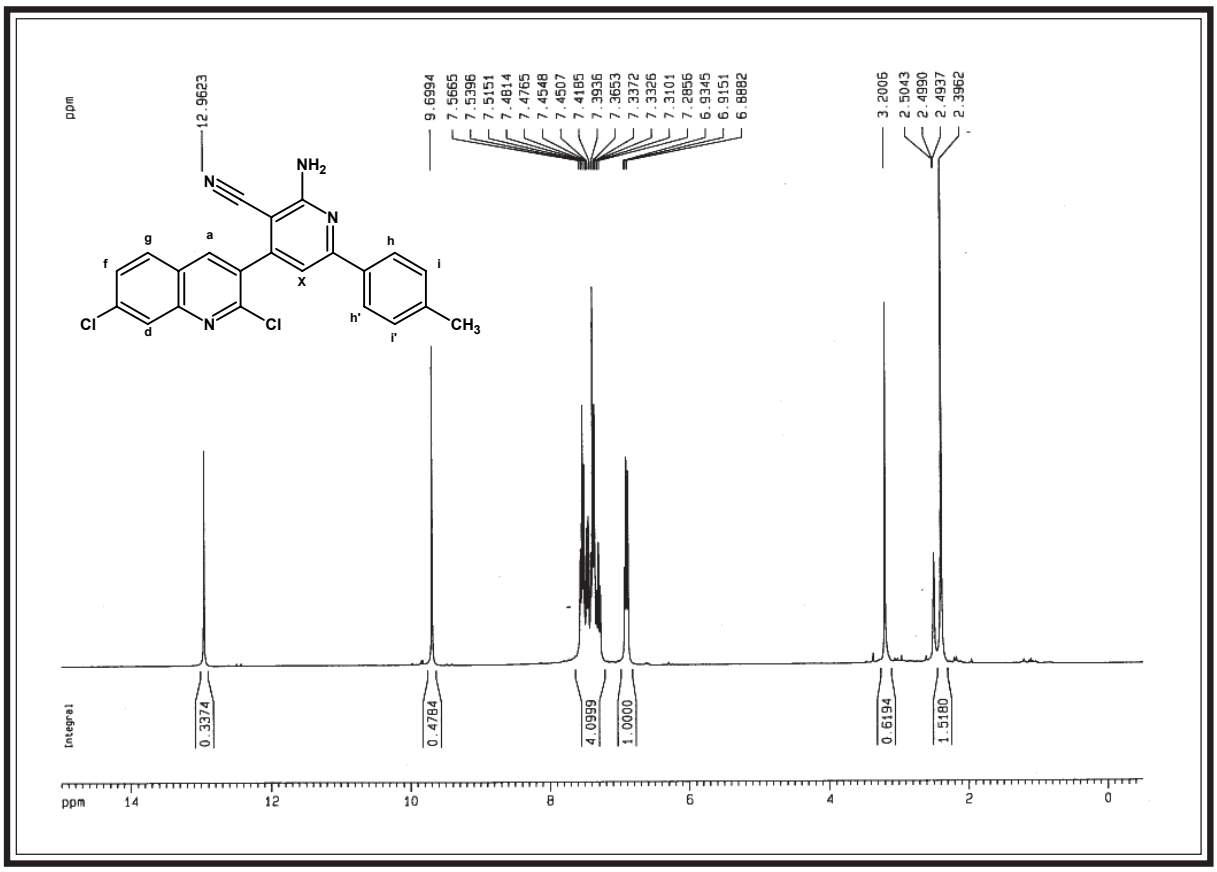
IR SPECTRAL STUDY OF 2-AMINO-3-CYANO-4-(2',7'-DICHLOROQUINOLIN-3'-YL)-6-p-ANISYL PYRIDINE



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

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane $-CH_3$	C – H str. (asym)	2923	2975-2950	419
	C – H str. (sym)	2850	2880-2860	"
	C – H def. (asym)	1442	1470-1435	"
	C – H def. (sym)	1361	1385-1370	"
Aromatic	C– H str.	3088	3080-3030	"
	C = C str.	1576	1585-1570	"
		1512	1520-1480	"
	C – H i.p.def.	1076	1125-1090	420
		1026	1070-1000	"
	C – H. o.o.p. def.	835	835-810	"
Quinoline moiety	C = N str.	1622	1612-1593	419
	C – Cl str.	744	750-700	"
Pyridine	C = H str.	3088	3080-3030	"
	C = C str.	1622 (overlaped)	1650-1520	"
	C = N str.	1573 (overlaped)	1580-1550	"
Nitrile	C ≡ N str.	2202	2240-2220	"
Ether	C – O – C str.	1249	1275-1200	418
	N-H str.	3330	3400-3250	419

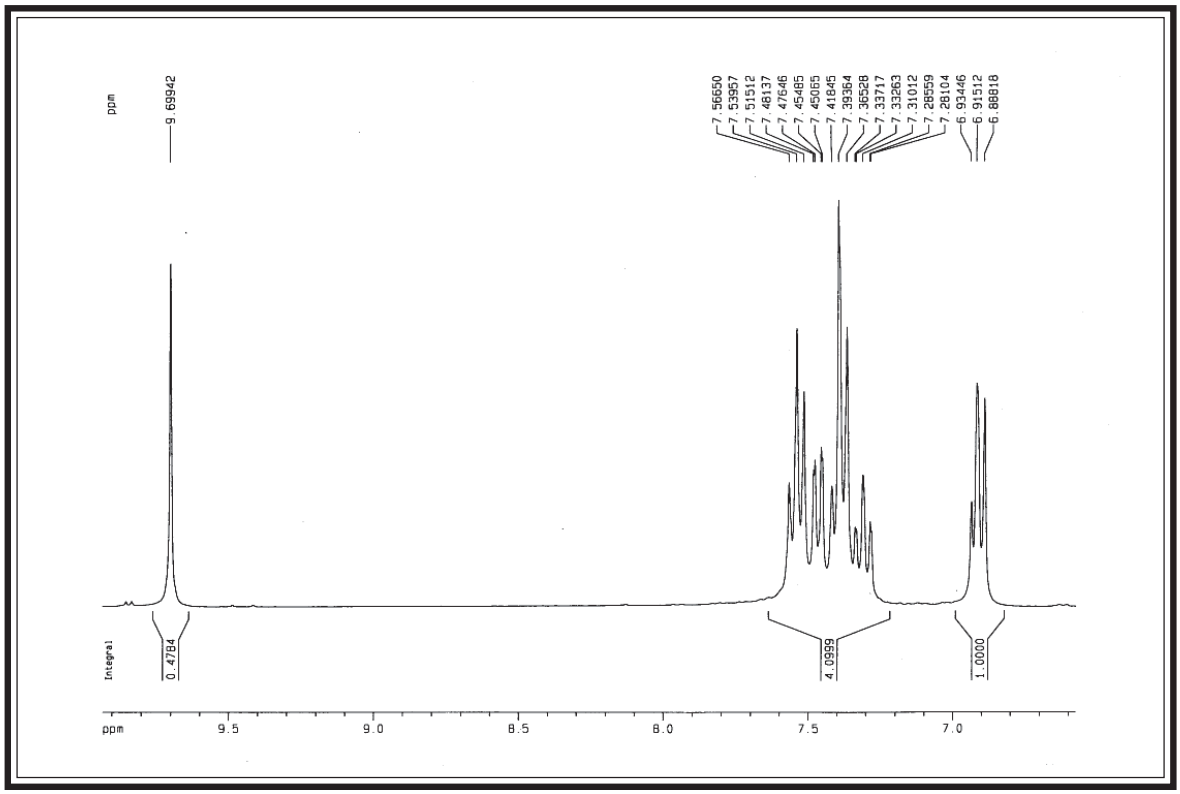
PMR SPECTRAL STUDY OF 2-AMINO-3-CYANO-4-(2',7'-DICHLOROQUINOLIN-3'-YL)-6-(p-TOLYL)-PYRIDINES



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

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	J. Value in Hz		Inference
1.	2.4	3H	singlet	-		Ar-CH_3
2.	6.89-6.92	2H	doublet	Jih	8.08	Ar-H i,i'
3.	7.28-7.29	1H	doublet	Jdf	1.37	Ar-Hd
4.	7.31	1H	singlet	-		Ar-HX
5.	7.39-7.42	2H	doublet	Jhi	8.51	Ar-H h,h'
6.	7.45-7.46	1H	double doublet	Jfg	7.96	Ar-Hf
				Jfd	1.47	
7.	7.51-7.54	1H	doublet	Jgf	7.34	Ar-Hg
8.	9.70	1H	singlet	-		Ar-Ha

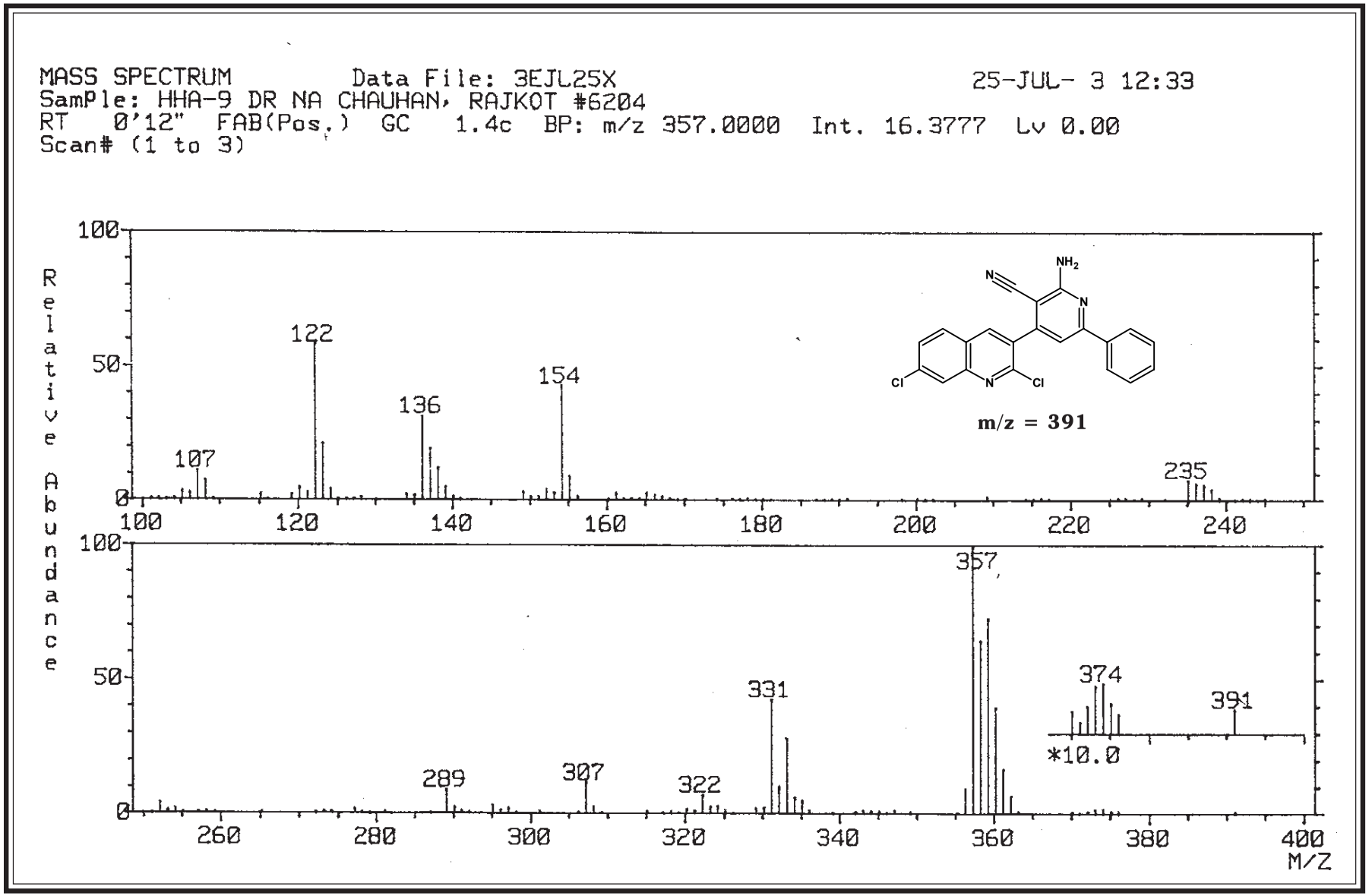
EXPANDED AROMATIC REGION



IR SPECTRAL DATA OF 2-AMINO-3-CYANO-4-(2',7'-DICHLOROQUINOLIN-3'-YL)-6-ARYL PYRIDINES

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

Sr. No.	R	C≡N str.
4a	C_6H_5	2200
4b	4-NH_2-C_6H_4	2198
4c	4-Br-C_6H_4	2202
4d	4-Cl-C_6H_4	2210
4e	4-F-C_6H_4	2198
4f	C_4H_3O	2196
4g	2-OH-C_6H_4	2198
4h	4-OH-C_6H_4	2200
4i	4-OCH_3-C_6H_4	2202
4j	4-CH_3-C_6H_4	2202
4k	3-NO_2-C_6H_4	2204
4l	4-NO_2-C_6H_4	2202


MASS SPECTRUM Data File: 3EJL25X 25-JUL- 3 12:33
SamPle: HHA-9 DR NA CHAUHAN, RAJKOT #6204
RT 0'12" FAB(Pos.) GC 1.4c BP: m/z 357.0000 Int. 16.3777 Lv 0.00
Scan# (1 to 3)
Relative Abundance
M/Z
m/z = 391
*10.0

EXPERIMENTAL

SYNTHESIS AND THERAPEUTIC EVALUATION OF 2-AMINO-3-CYANO-4-(2',7'-DICHLOROQUINOLIN-3'-YL)-6-ARYL-PYRIDINES

[A] Synthesis of 1-Aryl-3-(2',7'-dichloroquinolin-3'-yl)-2-propene-1-ones.

See part (I) Section - I (C).

[B] Synthesis of 2-Amino-3-cyano-4-(2',7'-dichloroquinoline-3'-yl)-6-aryl-pyridines

A mixture of 1-p-tolyl-3-(2',7'-dichloroquinolin-3'-yl)-2-propene-1-one (342 g, 0.01 mol), malononitrile (1.29 g, 0.01 mol) and ammonium acetate (9.24 g. 0.12 mol) dissolved in absolute alcohol (50 ml) were heated under reflux for 12 hrs., cooled and poured into crushed ice. The product separated was filtered and recrystallised from ethanol. Yield 52%, m.p 162^{O}C; Anal. Calcd. for $C_{22}H_{14}N_4Cl_2$ required : C, 65.20%; H, 3.48%; N, 13.82%; found : C, 65.25%; H, 3.45%; N, 13.58%.

TLC Solvent System : Acetone : Benzene (10:0), Visualizing Agent : Iodine.

Similarly, other 2-amino-3-cyano-4-(2',7'-dichloroquinolin-3'-yl)-6-aryl-pyridines were prepared. The physical data along with infra red spectral data are recorded in Tabel No. 2a.

[C] Therapeutic evaluation of 2-Amino-3-cyano-4-(2',7'-dichloro quinolin-3'-yl)-6-aryl-pyridines

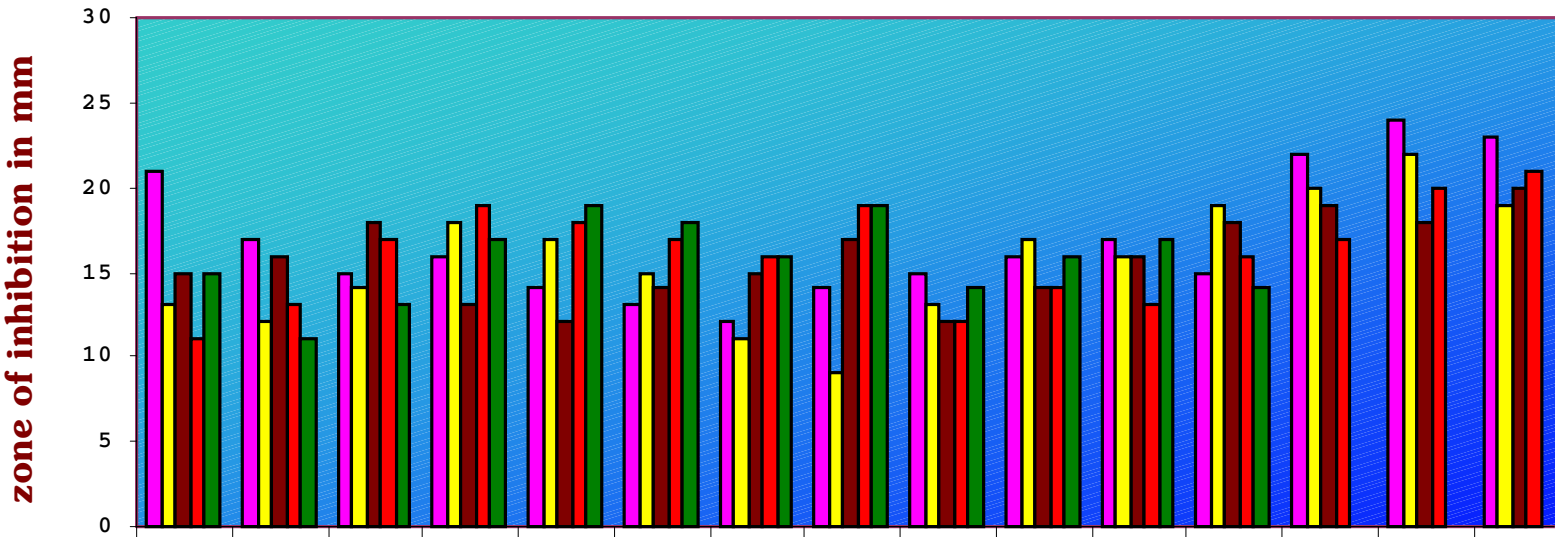
Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zone of inhibition of the test solution are recorded in Graphical Chart No. 4. The antitubercular activity data have been compared with standard drug rifampin at 6.25 μg/ml concentration and the data for % inhibition are recorded in Table No. 2b.

TABLE NO. 2a : PHYSICAL CONSTANTS OF 2-AMINO-3-CYANO-4-(2',7'-DICHLOROQUINOLIN-3'-YL)-6-ARYL-PYRIMIDINES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
4a	C_6H_5-	$C_{21}H_{12}N_4Cl_2$	391	192	0.413	63	14.32	14.67
4b	4-NH_2-C_6H_4-	$C_{21}H_{15}N_5Cl_2$	406	182	0.477	53	17.24	17.64
4c	4-Br-C_6H_4-	$C_{21}H_{11}N_4BrCl_2$	470	198	0.550	54	11.92	11.65
4d	4-Cl-C_6H_4-	$C_{21}H_{11}N_4Cl_3$	425.5	104	0.509	58	13.16	13.50
4e	4-F-C_6H_4-	$C_{21}H_{11}N_4Cl_2F$	409	162	0.635	56	13.69	13.93
4f	C_4H_3O-	$C_{19}H_{10}N_4Cl_2O$	381	202	0.521	59	13.70	14.88
4g	2-OH-C_6H_4-	$C_{21}H_{12}N_4Cl_2O$	407	184	0.487	61	13.76	13.99
4h	4-OH-C_6H_4-	$C_{21}H_{12}N_4Cl_2O$	407	166	0.620	63	13.76	13.51
4i	4-OCH_3-C_6H_4-	$C_{22}H_{14}N_4Cl_2O$	421	122	0.537	60	13.30	13.64
4j	4-CH_3-C_6H_4-	$C_{22}H_{14}N_4Cl_2$	405	162	0.566	52	13.82	13.58
4k	3-NO_2-C_6H_4-	$C_{21}H_{11}N_5Cl_2O_2$	436	152	0.498	51	16.50	16.77
4l	4-NO_2-C_6H_4-	$C_{21}H_{11}N_5Cl_2O_2$	436	>250	0.538	57	16.50	16.83

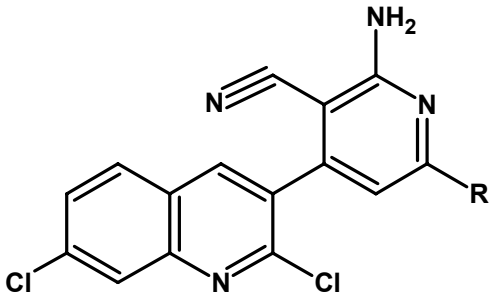
TLC Solvent System : Acetone : Benzene (10 : 0).

GRAPHICAL CHART NO. 4 : 2-AMINO-3-CYANO-4-(2',7'-DICHLOROQUINOLIN-3'-YL)-6-ARYL PYRIDINES



	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	4k	4l	Ampicillin	Amoxycillin	Norfloxacin
B.mega	21	17	15	16	14	13	12	14	15	16	17	15	22	24	23
s.aureus	13	12	14	18	17	15	11	9	13	17	16	19	20	22	19
E.coli	15	16	18	13	12	14	15	17	12	14	16	18	19	18	20
P.vulgaris	11	13	17	19	18	17	16	19	12	14	13	16	17	20	21
A.niger	15	11	13	17	19	18	16	19	14	16	17	14	0	0	0

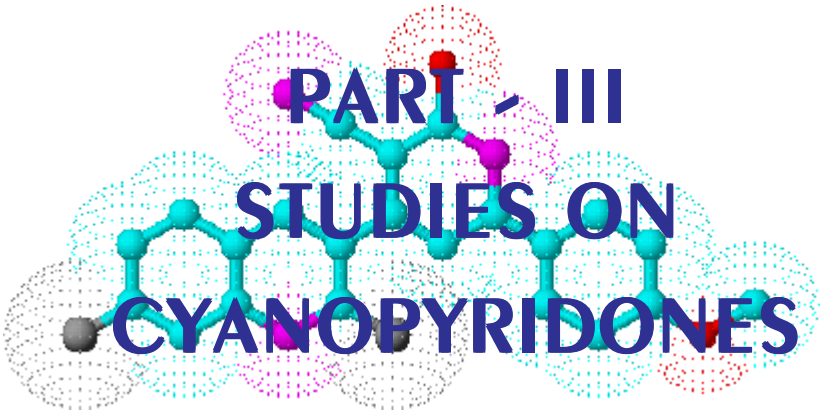
TABLE NO. 2a : PRIMARY ASSAY OF ANTITUBERCULAR ACTIVITY



TAACF, Southern Research Institute
Primary Assay Summary Report

Dr. A. R. Parikh
Saurashtra University

Sample ID	*Corp ID*	*Where, R =*	*Supplier*	*Assay*	*MTb Strain*	*MIC*	*% Inhib*	*Comment*
162100	AP-48	4-F-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	93	MIC Rifampin=0.25µg/ml @98% inhibition
162095	AP-43	4-CH_3-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	64	MIC Rifampin=0.25µg/ml @98% inhibition
162096	AP-44	4-OCH_3-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	57	MIC Rifampin=0.25µg/ml @98% inhibition
162098	AP-46	4-OH-C_6H_4-	Saurashtra University	Alamar	H37Rv	>6.25	44	MIC Rifampin=0.25µg/ml @98% inhibition
162099	AP-47	4-NO_2-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	32	MIC Rifampin=0.25µg/ml @98% inhibition
162097	AP-45	4-Br-C_6H_4	Saurashtra University	Alamar	H37Rv	>6.25	30	MIC Rifampin=0.25µg/ml @98% inhibition
162101	AP-49	C_4H_3O	Saurashtra University	Alamar	H37Rv	>6.25	25	MIC Rifampin=0.25µg/ml @98% inhibition

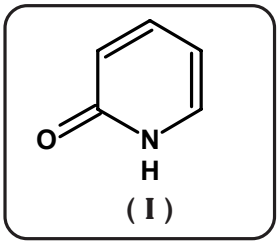


PART - III

STUDIES ON CYANOPYRIDONES

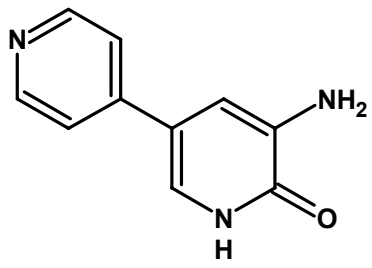
INTRODUCTION

Biosignificant pyridones form a component in a number of useful drugs and are associated with many biological, pharmaceutical and therapeutic activities. Pyridones, with a carbonyl group at position 2(I) have been subject of extensive study in the recent years. Numerous reports have appeared in the literature which highlight their chemistry and use.

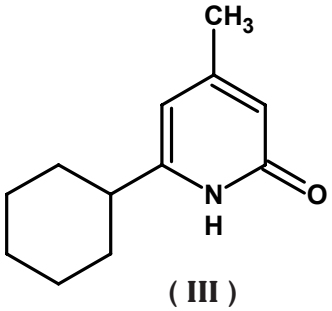


(I)

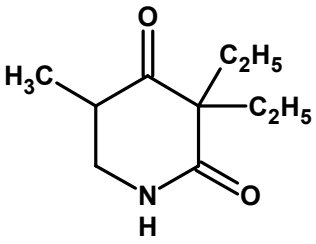
2-Pyridones are derivatives of pyridine with carbonyl group at 2-position(I), some 2-pyridones, which are pharmacologically important are as under: eg. amrinone(II), ciclopirox(III) and methylphylone (IV).



(II)



(III)



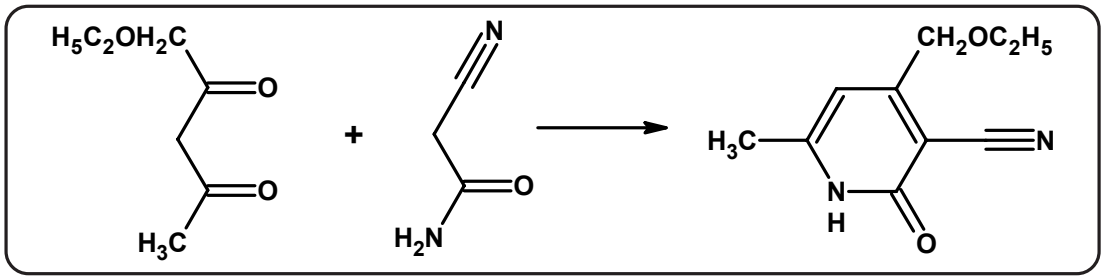
(IV)

Synthetic pyridone derivatives contribute much to the searchable literature of pyridone derivatives in huge libraries owing to their wide applicability in different fields.

SYNTHETIC ASPECT :

Different methods for the preparation of 2-pyridones are as under.

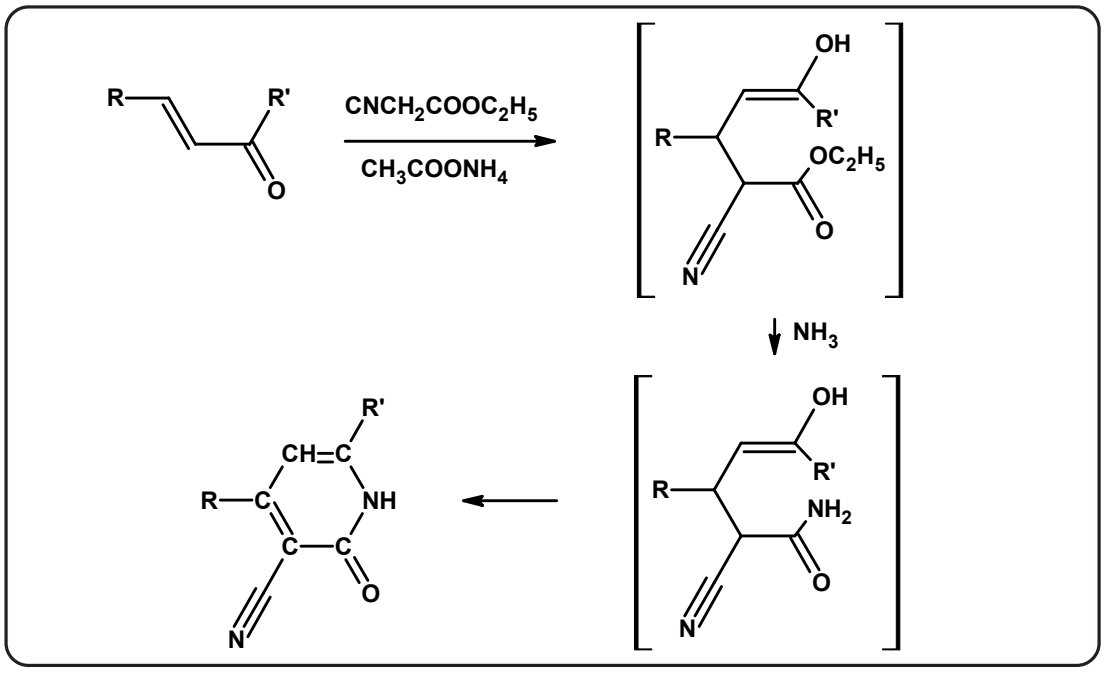
1. S. A. Harris and K. Falkers[148] have reported 3-cyano-2-pyridone by the condensation of cyanoacetamide with 1,3-diketone or β-ketoester.



2. M. A. Slwyter et al.[149] have prepared fused 2-pyridones.
3. G. Simchen and G. Entemann[150] have synthesised 2-pyridone in which the ring nitrogen comes from a nitrile group in acyclic precursor. Addition of HCl to the nitrile produces an imidoyl chloride which can cyclize.

MECHANISM

The addition reaction between ethylcyanoacetale and α,β-unsaturated ketone give cyanopyridone via Michael addition. Here, α,β–unsaturated compound is known as acceptor and active methylene group containing compound known as addender. It involves nucleophillic addition of carbanion to the C=C of the acceptor.

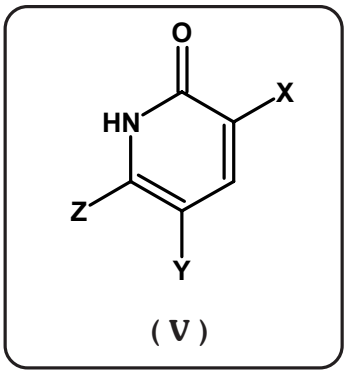


THERAPEUTIC IMPORTANCE

Literature survey reveals that various pyridones having potential of drugs are known to exhibit a broad spectrum of biological activities such as:

1. Anticancer[151]
2. Antimicrobial[152]
3. Pesticidal[153]
4. Angitensin II antagonistic[154]
5. Herbicidal[155]
6. Antiviral[156]
7. Antibacterial[157]

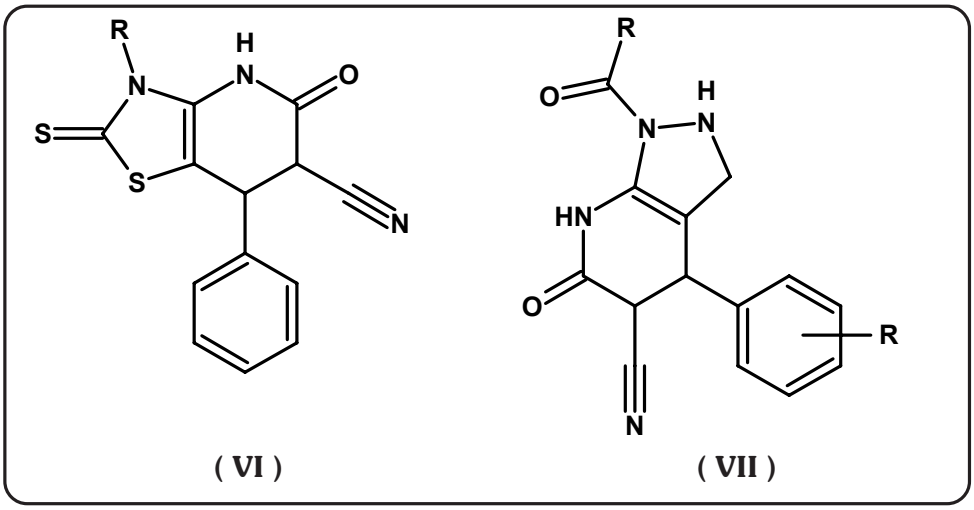
Peter et al.[158] have prepared pyridinylmethyl substituted pyridines and pyridones as angiotensin II antagonists. H. Poner[159] reported 2-pyridones as physiologically active compounds. Collins and co-workers[160] prepared heteroaryl pyridones as GABA α_2/α_3 ligands (V).



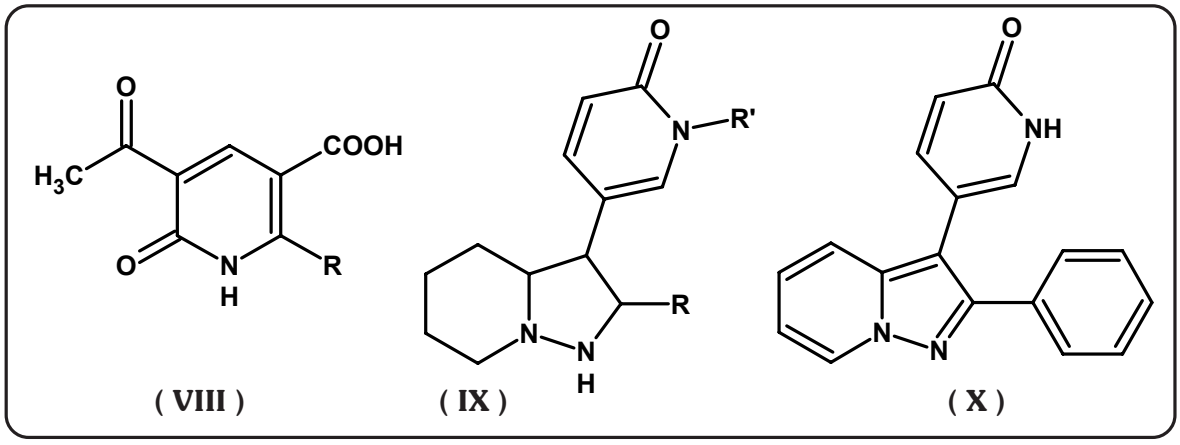
(V)

More over, several co-workers have pre-reported 2-pyridones as S_3 site of thrombin inhibitor[161], herbicidal[162], SH_2 domain inhibitor[163], antimicrobial[164], GABA-A reccptor[165] and antiiinflammatory[166].

Mukhta Hussain Khan and co-workers[167,168] have synthesised 2-pyridone derivatives (VI) and (VII) which possess insecticidal and pesticidal activity.



E. Amer[169] reported 3-cyano-2-pyridone derivatives, displaying high antimicrobial activity. Abou El-Fotooh *et al.*[170] have demonstrated pyridones as anticancer agent. F. Paala[171] synthesised 2-pyridone derivatives (VIII), showing good cardiotonic activity. Gulcan Ozturk *et al.*[172] described 1,2,5-substituted-4-pyridone derivatives having analgesic and antiinflammatory activity. Tanaka A. and co-workers [173] reported 2-pyridone derivatives (IX and X) which showed adenosine antagonist activity and anticatalepsy activity.



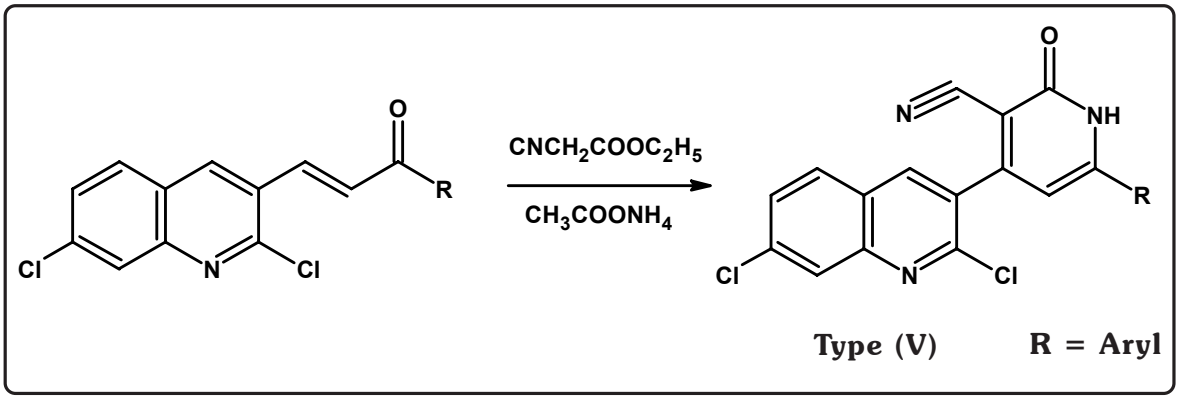
Thus, significant biological properties associated with pyridones, have aroused considerable interest to design the compounds with a view to get better drug potential, to study their pharmacological profile, which have been described as under.

SECTION-I : SYNTHESIS AND THERAPEUTIC EVALUATION OF 1,2-DIHYDRO-3-CYANO-4-(2',7'-DICHLOROQUINOLIN-3'-YL)-6-ARYL-2-PYRIDONES

SECTION - I

SYNTHESIS AND THERAPEUTIC EVALUATION OF 1,2-DIHYDRO-3-CYANO-4-(2',7'-DICHLOROQUNOLIN-3'-YL)-6-ARYL-2-PYRIDONES

During the last few years, interest in the use of cyanopyridone derivatives in medicine and agriculture has greatly increased. To further assess the potential of such a class of compounds as antimicrobial agents, a series of cyanopyridone of type (V) have been synthesised by the condensation of chalcones of type(I) with ethyl cyanoacetale in presence of ammonium acetate as under.

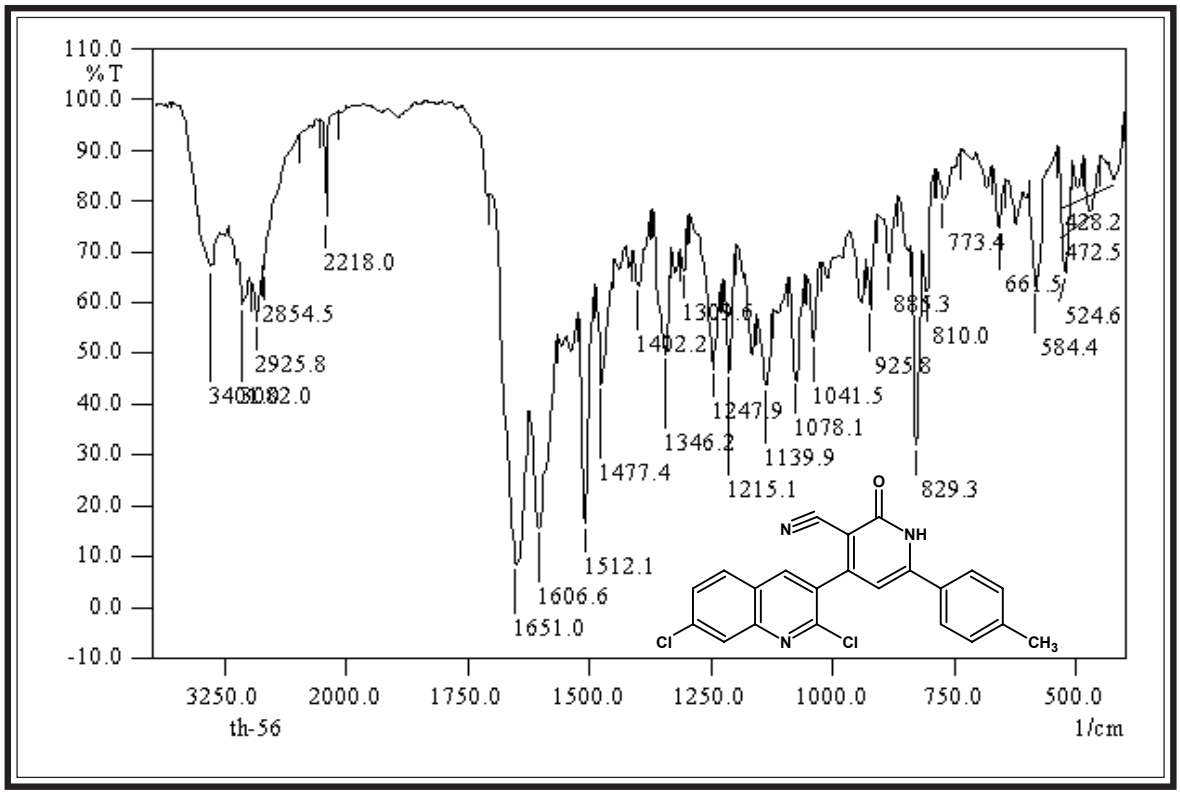


Type (V) **R = Aryl**

The constitution of the synthesised products have been characterised using elemental analyses, infra red and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass-spectrometry.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg. The biological activities of the synthesised compounds have been compared with standard drugs. The details have been cited in Part-I, Section-I (D).

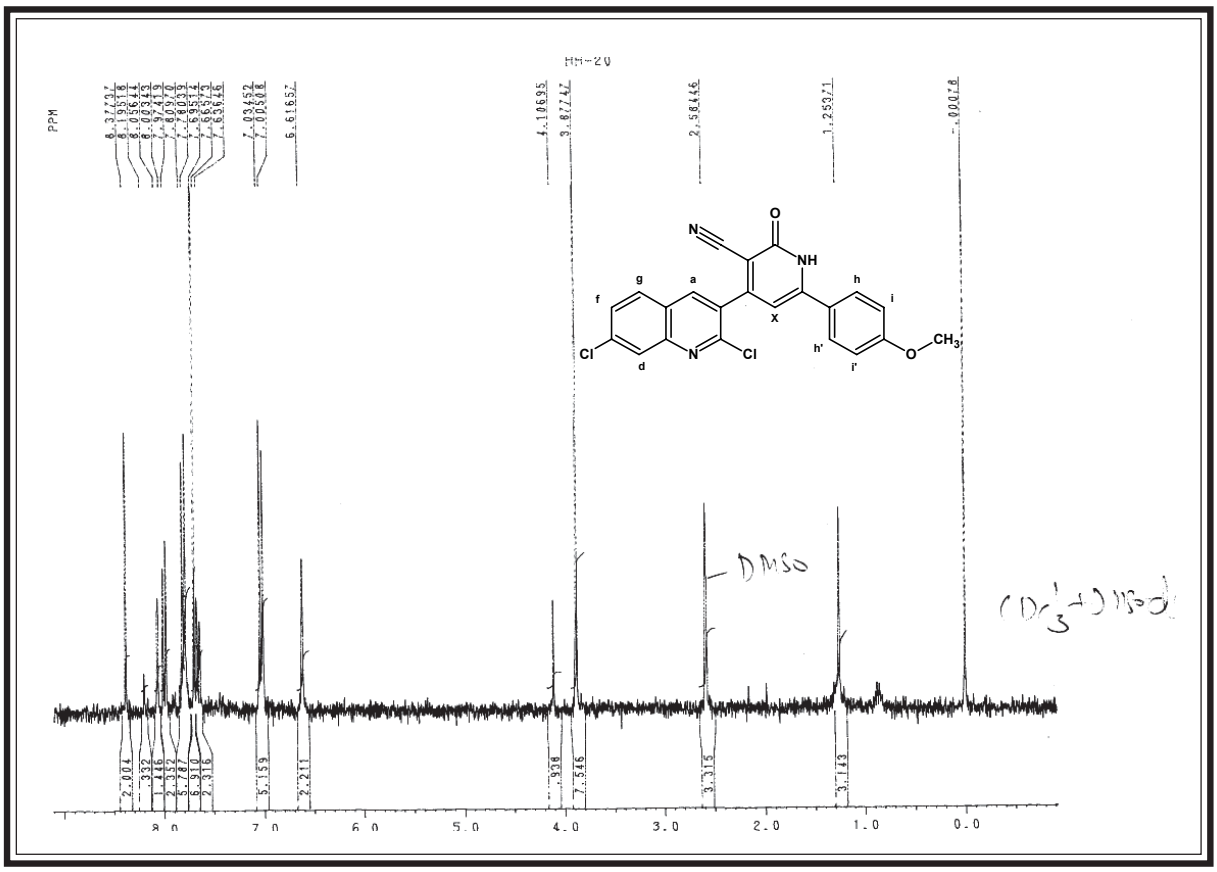
IR SPECTRAL STUDY OF 1,2-DIHYDRO-3-CYANO-4-(2',7'-DICHLOROQUINOLIN-3'-YL)-6-p-TOLYL-2-PYRIDONE



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

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.	2925	2975-2950	419
$-CH_3$	C – H def. (asym)	1477	1470-1435	"
Aromatic	C– H str.	3082	3090-3030	"
	C = C str.	1512	1550-1480	"
	C – H.i.p. def.	1139	1125-1090	420
	C – H. o.o.p. def.	829	835-810	"
Quinoline	C = N str.	1606	1612-1593	419
moiety	C – Cl str.	773	750-700	"
Pyridone	N – H str.	3401	3400-3250	"
ring	C ≡ N str.	2218	2250-2120	"
	C = O str	1651	1780-1655	"

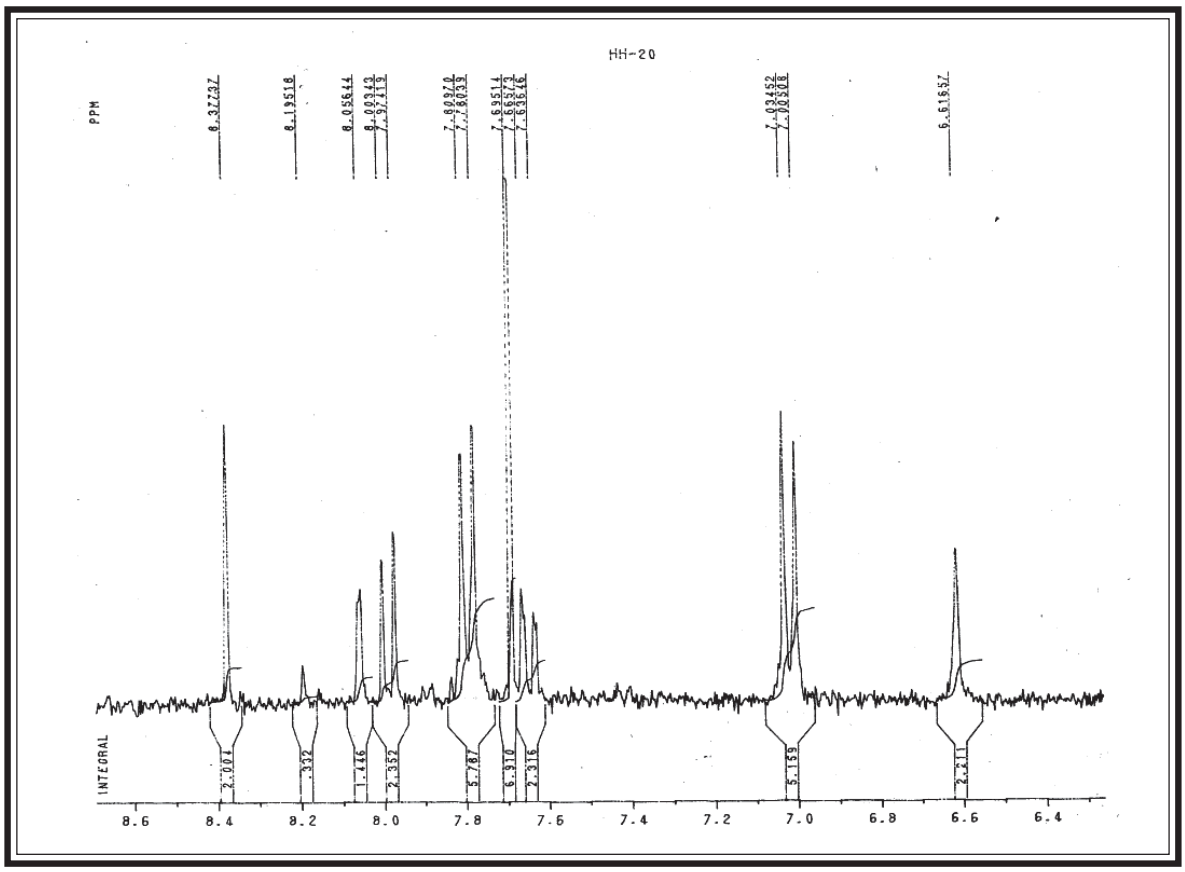
PMR SPECTRAL STUDY OF 1,2-DIHYDRO-3-CYANO-4-(2',7'-DICHLOROQUINOLIN-3'-YL)-6-(p-METHOXYPHENYL)-2-PYRIDONES



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

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	J. Value in Hz		Inference
1.	3.88	3H	singlet	-		Ar-OCH_3
2.	6.62	1H	singlet	-`		Ar-HX
3.	7.00-7.03	2H	doublet	Jin	8.83	Ar-Hi,i'
4.	7.64-7.67	1H	doublet doublet	Jfg	8.78	Ar-Hf
5.	7.78-7.81	2H	doublet	Jhi	8.79	Ar-Hh,h'
6.	7.97-8.00	1H	doublet	Jgf	8.77	Ar-Hg
7.	8.05	1H	singlet	-		Ar-Hd
8.	8.37	1H	singlet	-		Ar-Ha

EXPANDED AROMATIC REGION

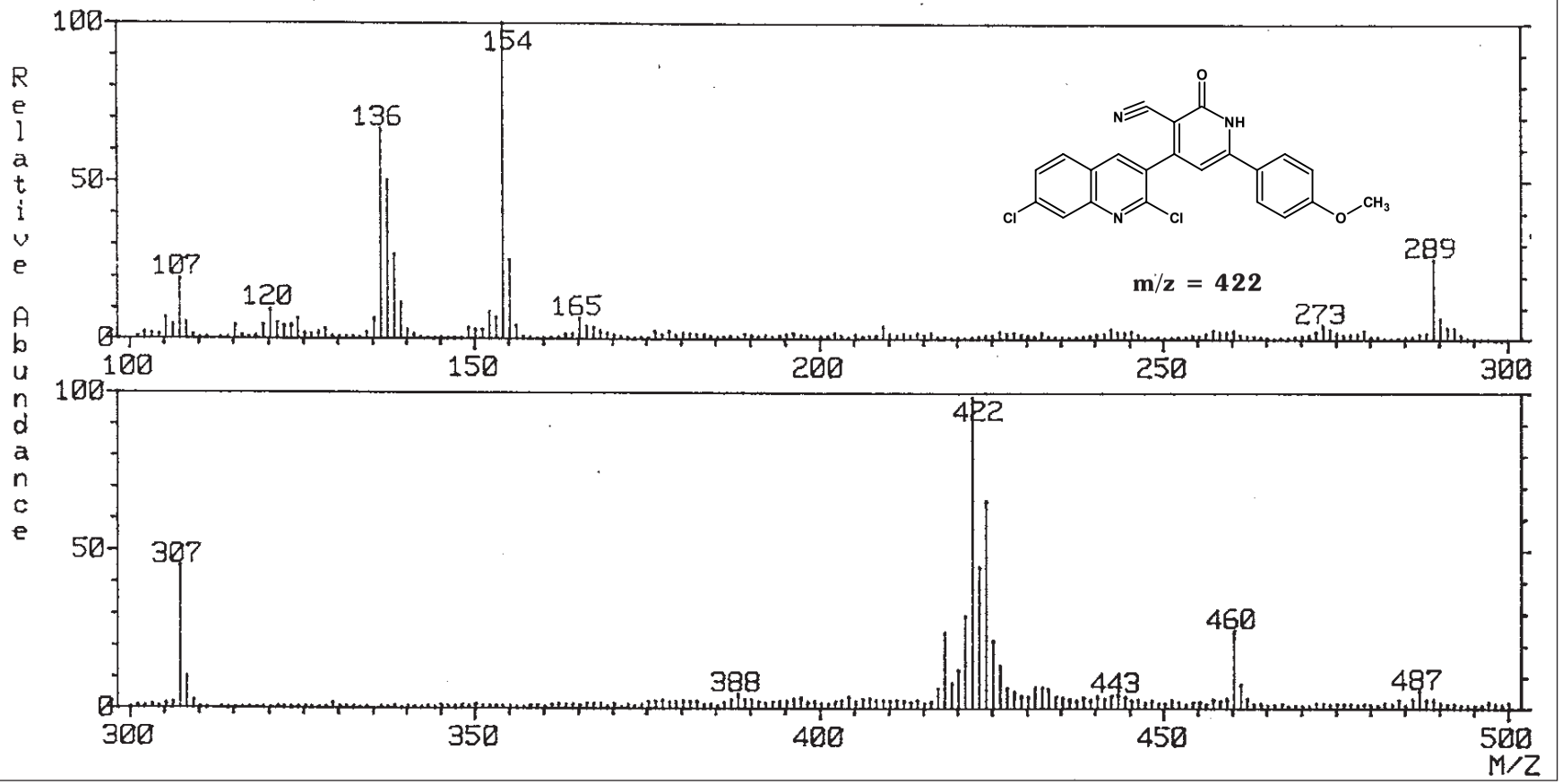


IR SPECTRAL DATA OF 1,2-DIHYDRO-3-CYANO-4-(2',7'-DICHLOROQUINOLIN-3'-YL)-6-ARYL-2-PYRIDONES

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

Sr. No.	R	–C≡N	C=O
5a	C_6H_5	2218	1649
5b	3-NH_2-C_6H_4	2218	1651
5c	4-NH_2-C_6H_4	2210	1649
5d	4-Br-C_6H_4	2216	1649
5e	4-Cl-C_6H_4	2220	1649
5f	2,6-$(OH)_2$-C_6H_3	2218	1651
5g	4-F-C_6H_4	2218	1651
5h	2-OH-C_6H_4	2216	1651
5i	4-OH-C_6H_4	2218	1649
5j	4-OCH_3-C_6H_4	2210	1649
5k	3-CH_3-C_6H_4	2218	1651
5l	3-NO_2-C_6H_4	2210	1649
5m	4-NO_2-C_6H_4	2215	1652

MASS SPECTRUM Data File: 3EJL25W 25-JUL- 3 12:29
SamPle: HHA-8 DR NA CHAUHAN, RAJKOT #6204
RT 0'24" FAB(Pos.) GC 1.4c BP: m/z 154.0000 Int. 38.1446 Lv. 0.00
Scan# (3 to 4)



EXPERIMENTAL

SYNTHESIS AND THERAPEUTIC EVALUATION OF 1,2-DIHYDRO-3-CYANO-4-(2',7'-DICHLOROQUINOLIN-3'-YL)-6-ARYL-2-PYRIDONES

[A] Synthesis of 1-Aryl-3-(2',7'-dichloroquinolin-3'-yl)-2-propene-1-ones

See Part (I), Section-I(C).

[B] Synthesis of 1,2-Dihydro-3-cyno-4-(2',7'-dichloroquinolin-3-yl)-6-aryl-2-pyridones

1-p-Tolyl-3-(2',7'-dichloroquinolin-3'-yl)-2-propene-1-one (3.42g 0.01mol) was dissolved in ethanol (50 ml). Add ethylcyanoacetate (1.13g. 0.01mol) and ammonium acetate (9.24g. 0.12 mol) to it. The mixture was then heated under reflux for 8 hrs. The product separated was filtered and recrystallised from methanol. Yield. 57%, m.p. 224°C; Anal. calcd for $C_{22}H_{13}N_3Cl_2O$: C, 65.04%; H, 3.23%; N, 10.34%; Found : C, 65.07%; H, 3.25%; N, 9.93%.
TLC solvent system: Acetone: Benzene (0.5: 9.5) Visulizing Agent : Iodine.

Similarly, other 1,2-Dihydro-3-cyano-4-(2',7'-dichloroquinolin-3'-yl)-6-aryl-2-pyridones were prepared. The physical data along with infra red spectral data are recorded in Table No. 3

[C] Therapeutic evaluation of 1,2-Dihydro-3-cyano-4-(2',7'-dichloro quinolin-3'-yl)-6-aryl-2-pyridones

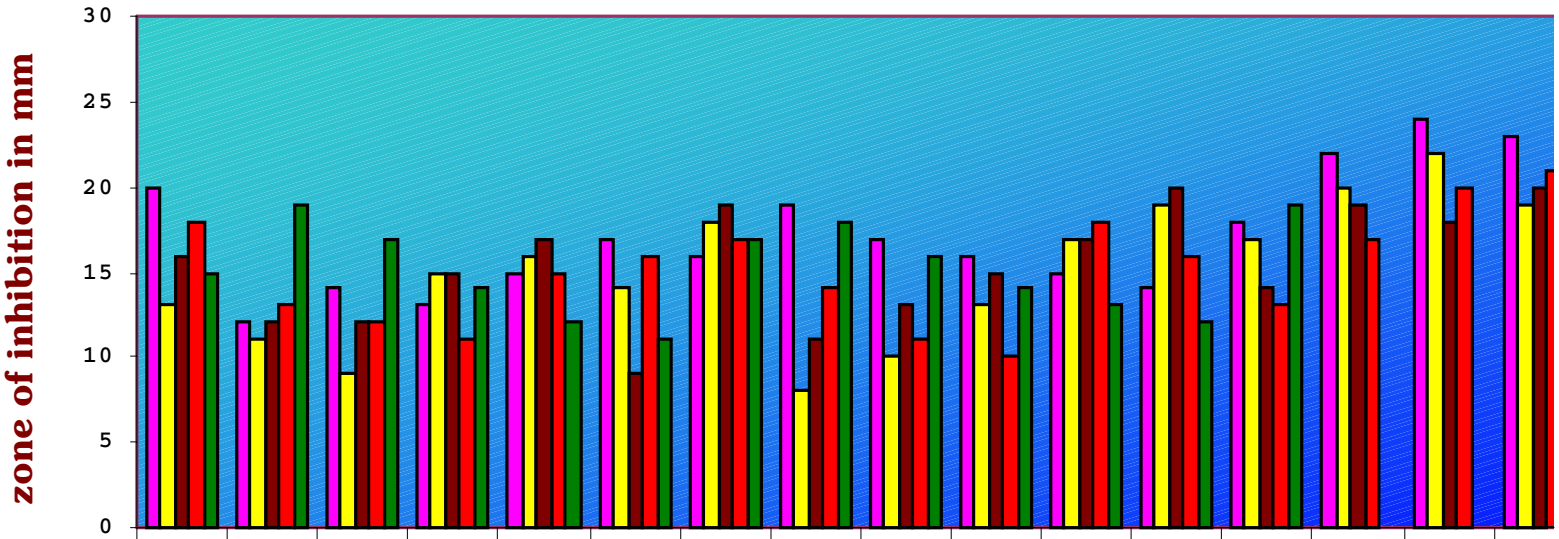
Antimicrobial testing was carried out as described in Part-I, Section-I(D). The zones of inhibition of the felt solution are recorded in Graphical Chart No. 5.

TABLE NO. 3 : PHYSICAL CONSTANTS OF 1,2-DIHYDRO-3-CYANO-4-(2',7'-DICHLOROQUINOLIN-3'-YL)-6-ARYL-2-PYRIDONES

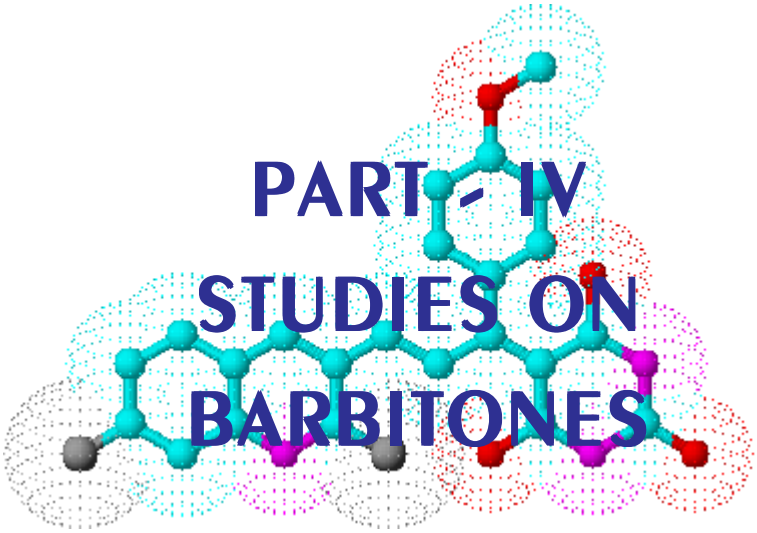
Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
5a	C_6H_5-	$C_{21}H_{11}N_3Cl_2O$	392	124	0.534	63	10.71	10.29
5b	3-NH_2-C_6H_4-	$C_{21}H_{12}N_4Cl_2O$	407	158	0.405	61	13.76	13.35
5c	4-NH_2-C_6H_4-	$C_{21}H_{12}N_4Cl_2O$	407	204	0.435	59	13.76	13.99
5d	4-Br-C_6H_4-	$C_{21}H_{10}N_3BrCl_2O$	471	172	0.585	58	8.92	8.54
5e	4-Cl-C_6H_4-	$C_{21}H_{10}N_3Cl_3O$	426.5	170	0.609	59	9.85	9.57
5f	2,6-$(OH)_2$-C_6H_3-	$C_{21}H_{11}N_3Cl_2O_3$	424	168	0.659	60	9.90	9.63
5g	4-F-C_6H_4-	$C_{21}H_{10}N_3Cl_2FO$	410	148	0.714	55	10.24	10.51
5h	2-OH-C_6H_4-	$C_{21}H_{11}N_3Cl_2O_2$	408	202	0.650	54	10.29	10.59
5i	4-OH-C_6H_4-	$C_{22}H_{11}N_3Cl_2O_2$	408	150	0.473	56	10.29	10.05
5j	4-OCH_3-C_6H_4-	$C_{22}H_{13}N_3Cl_2O_2$	422	176	0.512	58	9.95	9.69
5k	4-CH_3-C_6H_4-	$C_{22}H_{13}N_3Cl_2O$	406	224	0.591	57	10.34	9.93
5l	3-NO_2-C_6H_4-	$C_{21}H_{10}N_4Cl_2O_3$	437	184	0.481	60	12.81	12.69
5m	4-NO_2-C_6H_4-	$C_{21}H_{10}N_4Cl_2O_3$	437	196	0.541	62	12.81	12.97

TLC Solvent System : Acetone : Benzene (0.5 : 9.5).

GRAPHICAL CHART NO. 5 : 1,2-DIHYDRO-3-CYANO-4-(2',7'-DICHLOROQUINOLIN-3'-YL)-6-ARYL-2-PYRIDONES



	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	5k	5l	5m	Ampicillin	Amoxycillin	Nor lox cir
B.mega	20	12	14	13	15	17	16	19	17	16	15	14	18	22	24	23
s.aureus	13	11	9	15	16	14	18	8	10	13	17	19	17	20	22	19
E.coli	16	12	12	15	17	9	19	11	13	15	17	20	14	19	18	20
P.vulgaris	18	13	12	11	15	16	17	14	11	10	18	16	13	17	20	21
A.niger	15	19	17	14	12	11	17	18	16	14	13	12	19	0	0	0



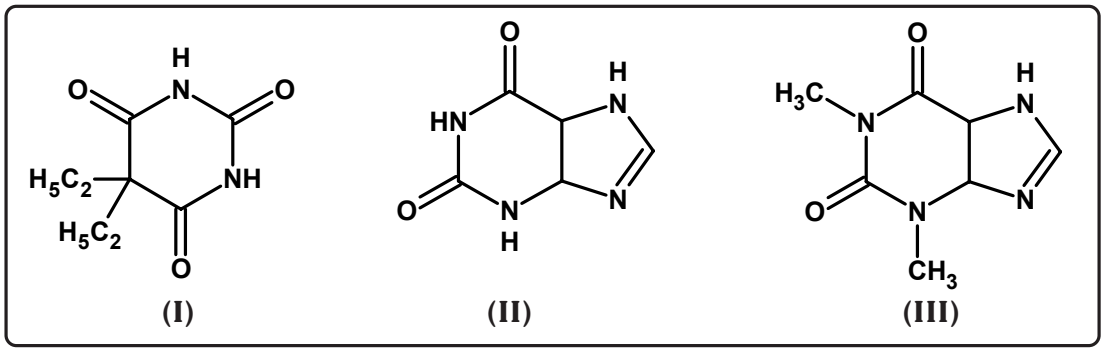
PART - IV

STUDIES ON BARBITONES

INTRODUCTION

Barbituric acid derivatives have gained prominance because of their potential pharmaceutical values. Many barbituric acid derivatives play vital role in many physiological action. Most important is the effect of barbiturates on the central nervous system. There are more than 40 synthetic drugs bearing barbituric acid, in use recently. They possess diverse type of biological properties including hypnotic, sedatives, anticonvulsant, cardiovascular etc. The first member of hypnotic drugs series was barbital (I).

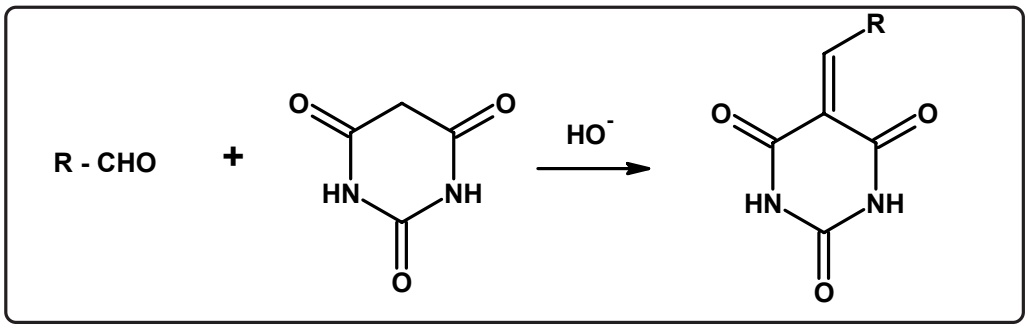
Barbituric acid ring system has been found in many natural products like alkaloids, which includes Xanthine (II) and Theophyline (III) are constituents of tea leaves. Theobromine is found in cocoa beans.



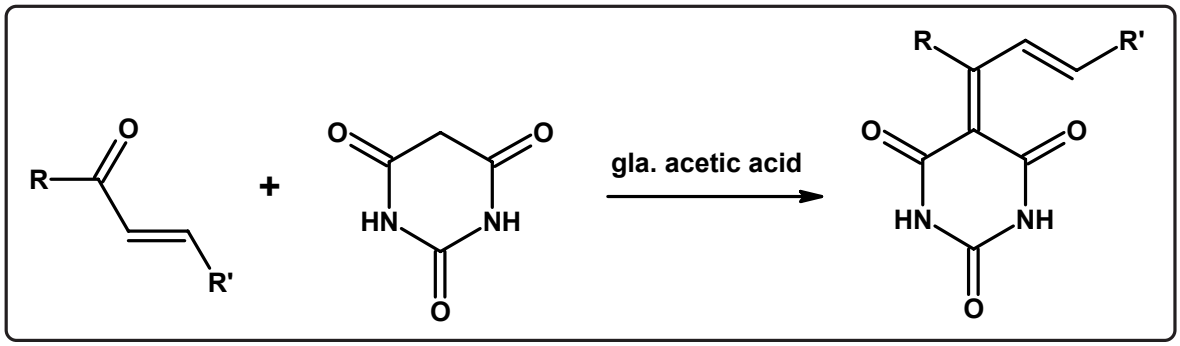
SYNTHETIC ASPECT

Different methods are used for the preparation of barbitones in literature[174,175].

1. Cao-Yun Weu et al.[176] have prepared barbituric acid derivatives by the reaction of different aldehydes with barbituric acid in basic media.



2. M. R. Mahmoud *et al.*[177] have synthesised barbituric acid derivatives from chalcone.

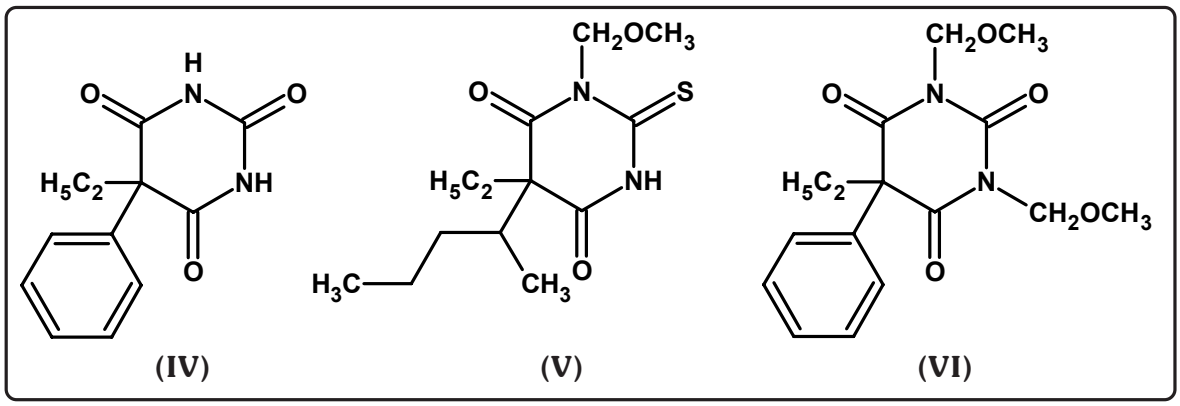


3. Ogus Funda *et al.*[178] have synthesised barbiturates by the reaction between acetone and barbituric acid.

THERAPEUTIC IMPORTANCE

Barbituric acid derivatives demonstrate a very broad spectrum of biological activity, because of their structural relationship with nucleic acids, viz. uracil, thymine and cytosine. Perhaps barbituric acid derivatives are most widely used pyrimidines in medicinal chemistry.

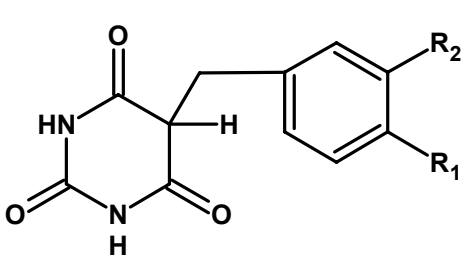
Phenobarbitone (IV) possess sedative and hypnotic activities, thiopentone (V) is a useful local anaesthetic while Eterobarb (VI) is an anticonvulsant drug.



(IV) **(V)** **(VI)**

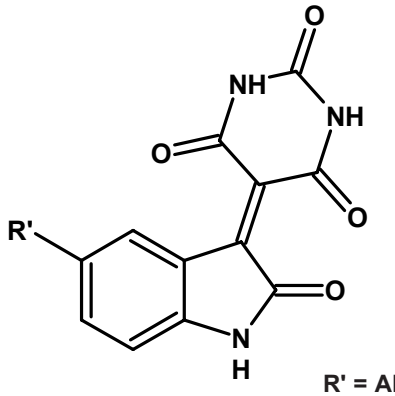
Carbubarb[179] is a barbituric acid derivative, which is used as a veternary anaesthetics. Some isoxazole pyrimidine derivatives have been studied because of their potential as as pesticidal[180,181] activity. Some barbiturates showing cardiovascular[182-184] and analgesic and antiinflammatory activities[185] have been reported.

Ulf Wellmar et al.[186] have synthesised some uracil derivatives and screened for antiviral activity[187,188]. Raymond et al.[189] investigated some barbiturates (VII), showing anticancer activity while Mahmoud et al.[190] reported their antimicrobial activity.



(VII)

R_1, R_2 = H
R_1 = OCH_3
R_2 = H



R' = Alkyl / X / H

(VIII)

Some isoxazolo pyrimidine derivatives have been extensively studied and reported as antagonist[191] and antitumor[192] agents. Agricultural activity of 5-(3-benzylthiazolidine-2-ylidene)-1,3-dimethyl hexahydro pyrimidine-2,4,6-trione was reported by Wolf-Gang et al.[193] Harbicidal and insecticidal activity of barbiturates was documented by Andre Roland and co-workers[194]. Omar M. T.[195] have showed barbitone derivatives demonstrating antimicrobial activity. Sakai and co-workers[196] has synthesised some new barbitones which are assessed for bone and cartilage diseases. R. T. Pardasani and co-workers[197] have described some new isatylidene barbitones (VIII) and tested their antibacterial activity.

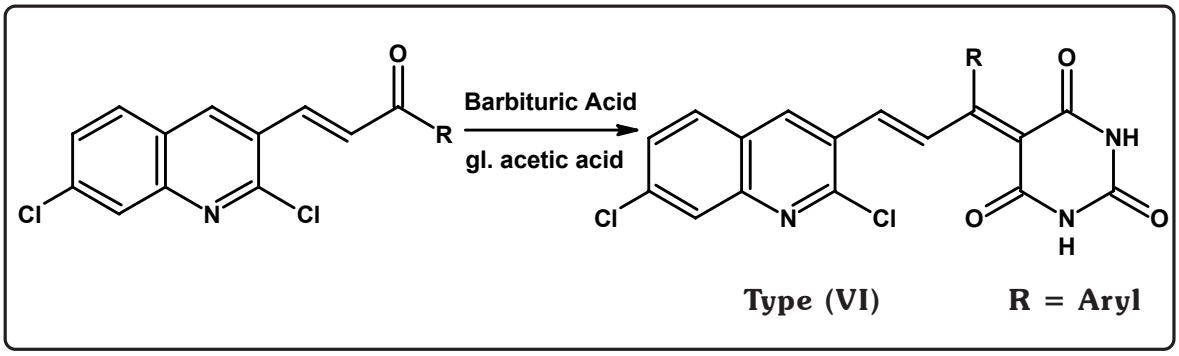
Vital contribution of barbituric acid ring system to the medicinal chemistry as an active constituent of hypnotics and sedatives made chemists to explore for its other derivatives as therapeutic agents. Accordingly several derivatives of barbituric acid have been designed as under.

SECTION - I : SYNTHESIS AND THERAPEUTIC EVALUATION OF [1-ARYL-3-(2',7'-DICHLOROQUINOLIN-3'-YL]-2-PROPENYLIDENE]-5-BARBITURIC ACIDS

SECTION - I

SYNTHESIS AND THERAPEUTIC EVALUATION OF [1-ARYL-3-(2',7'-DICHLOROQUINOLIN-3'-YL]-2-PROPENYLIDENE]-5-BARBITURIC ACIDS

Barbiturates are known to play an important role in medicinal chemistry because of their effect on central nervous system. The first member of hypnotic drugs series was barbital. Considering this background, some new barbituric acid derivatives of type (VI) were prepared by the condensation of compounds of type (I) with barbituric acid in glacial acetic acid.

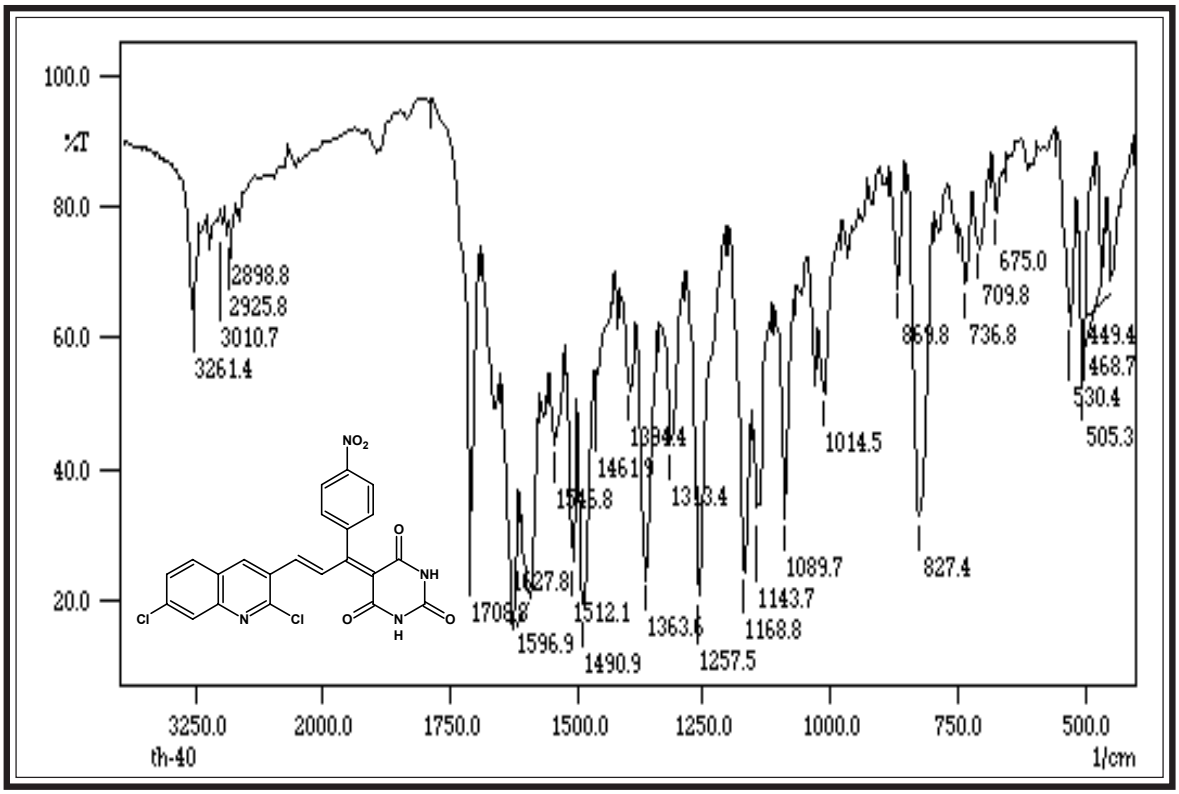


Type (VI) **R = Aryl**

The constitution of the synthesised products have been characterised using elemental analyses, infra red and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg. The biological activities of the synthesised compounds have been compared with standard drugs. The details have been cited in Part-I, Section-I (D).

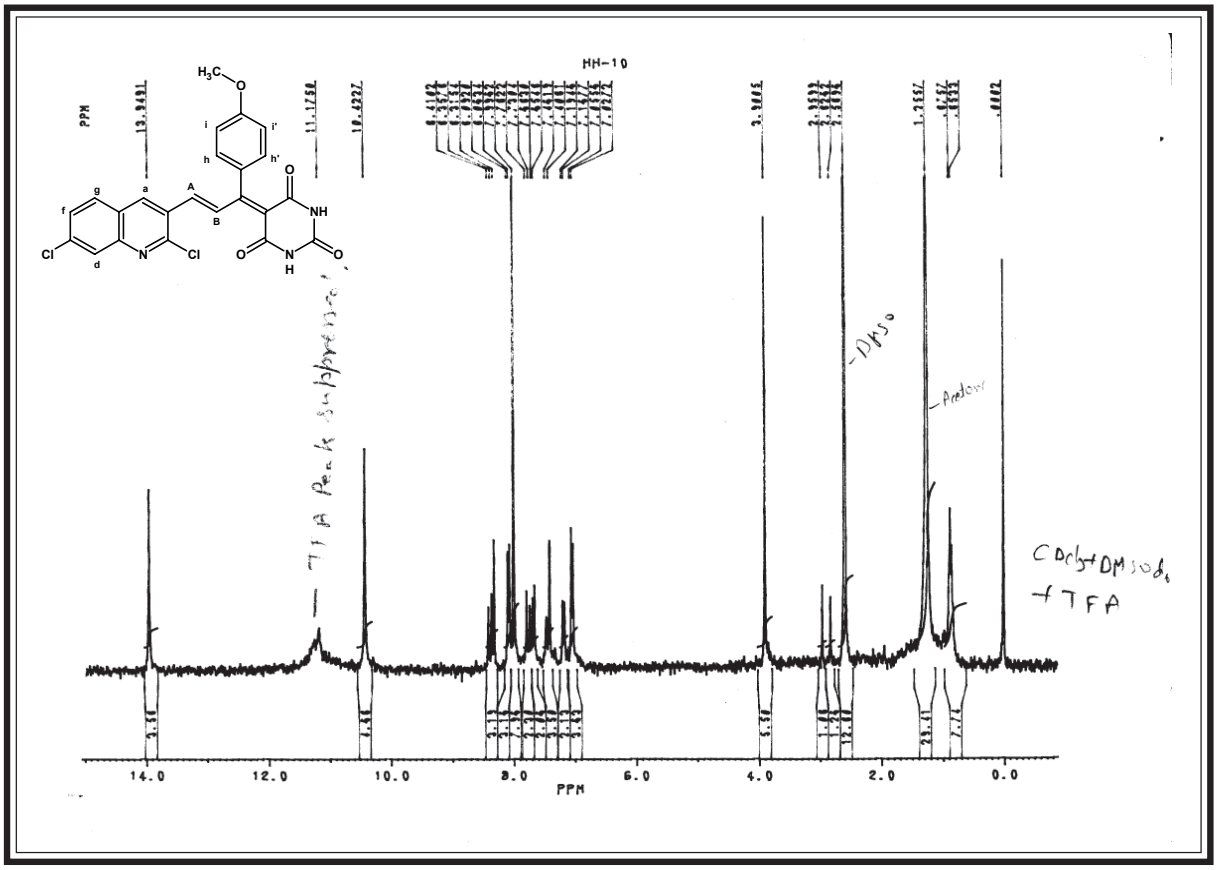
IR SPECTRAL STUDY OF [1-p-NITROPHENYL-3-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-PROPENYLIDENE]-5-BARBITURIC ACID



Instrument : SHIMADZU-FT-IR 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	2975-2950	419
$-CH_3$	C – H def. (sym)	1490	1470-1435	"
Aromatic	C– H str.	3010	3080-3030	"
	C = C str.	1512	1520-1480	"
	C – H.i.p. def.	1143	1150-1090	420
	C – H. o.o.p. def.	827	835-810	"
Quinoline moiety	C = N str.	1627	1650-1590	419
	C – Cl str.	736	750-700	"
Barbitone	N – H str.	3261	3350-3140	422
	C = O str.	1708	1750-1700	"
Vinyl	HC= CH str.	3010	3050-3000	"
	N – O str.	827	850-810	"

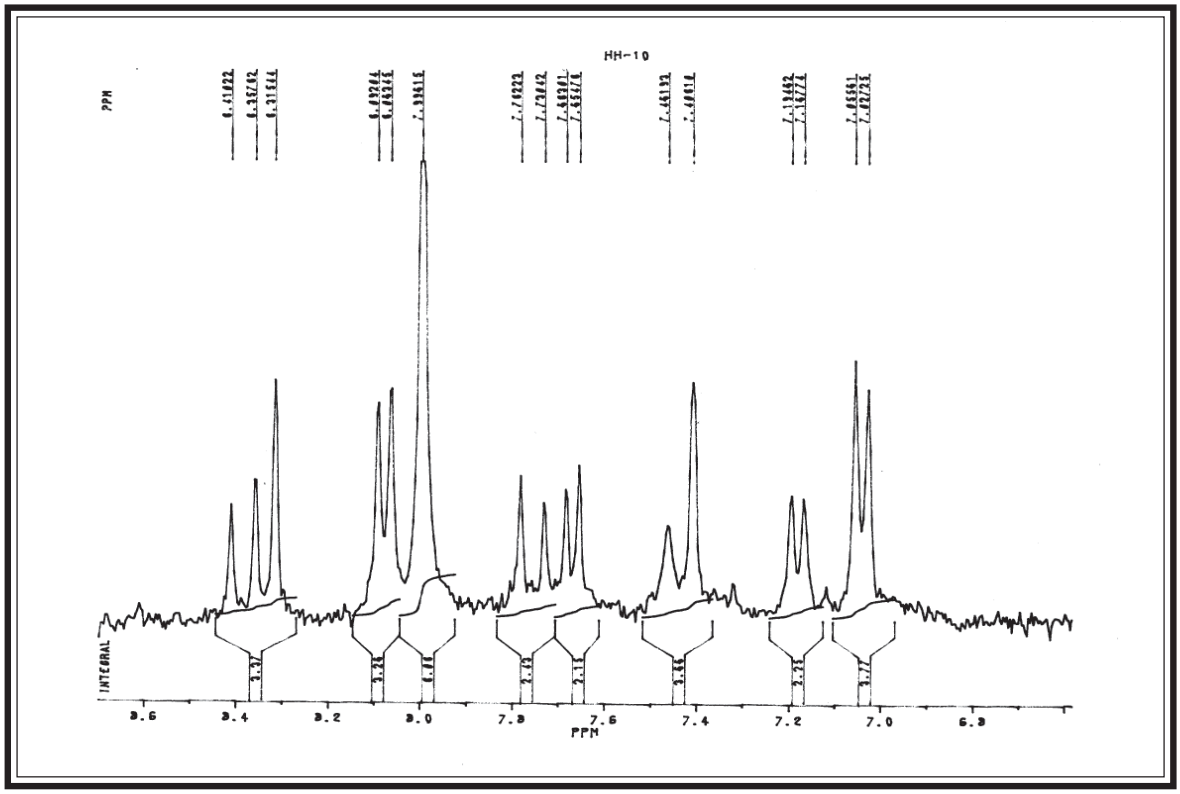
PMR SPECTRAL STUDY OF [1-(p-ANISYL)-3-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-PROPENYLIDINE]-5-BARBITURIC ACID



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

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	J. Value in Hz	Inference
1.	3.9	3H	singlet	-	Ar-OCH_3
2.	7.03-7.06	2H	doublet	Jih 8.51	Ar-H i,i'
3.	7.17-7.20	1H	doublet	Jfg 8.06	Ar-Hf
4.	7.40	1H	singlet	-	Ar-Hd
5.	7.65-7.68	1H	doublet	Jgf 8.47	Ar-Hg
6.	7.74-7.78	1H	doublet	JBA 13.14	-CH_B
7.	8.06-8.09	2H	doublet	Jhi 8.58	Ar-H h,h'
8.	8.32-8.36	1H	doublet	JAB 12.71	-CH_A
9.	8.41	1H	singlet	-	Ar-Ha

EXPANDED AROMATIC REGION

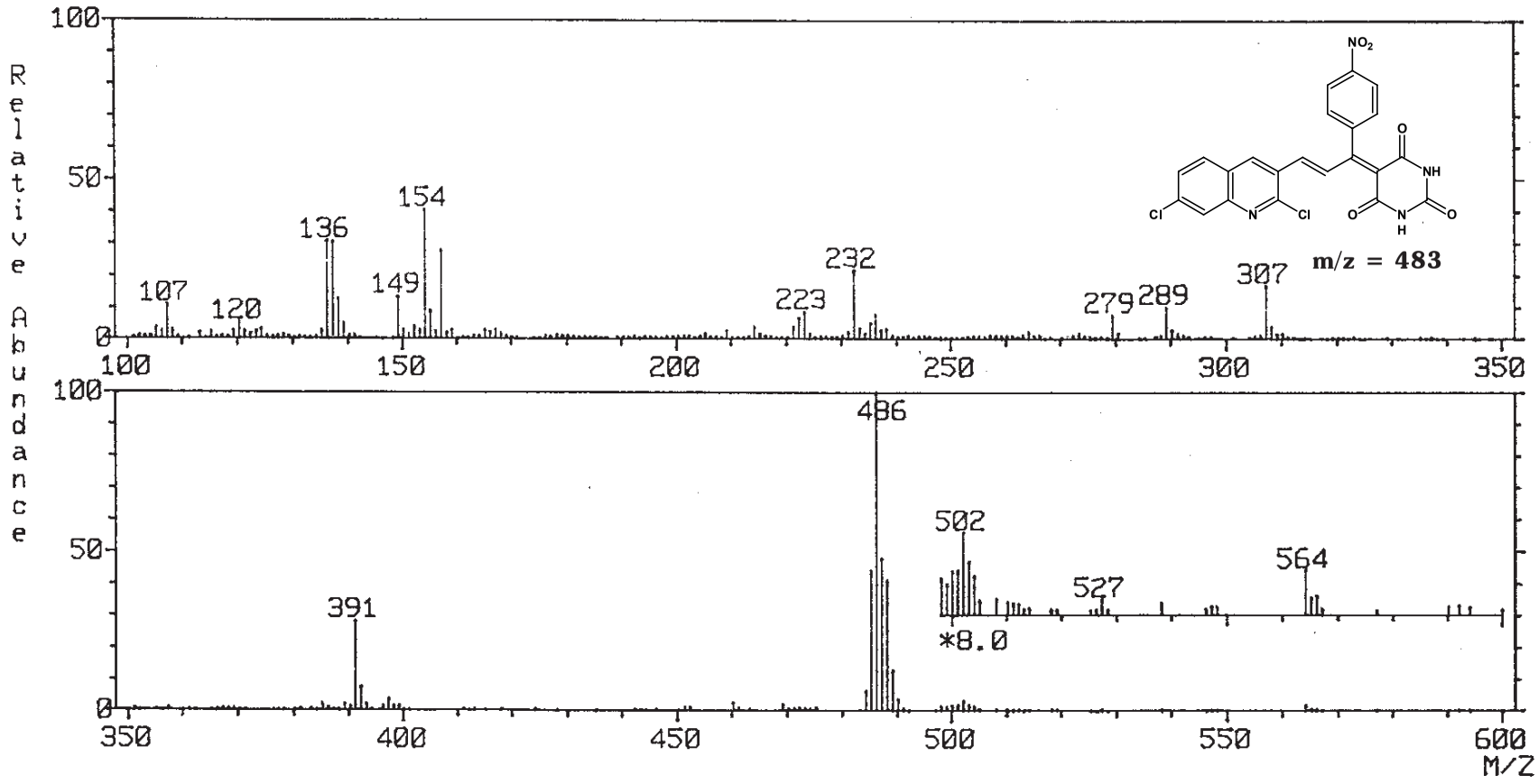


IR SPECTRAL DATA OF [1-ARYL-3-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-PROPENYLIDENE]-5-BARBITURIC ACIDS

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

Sr. No.	R	C=O str.
6a	C_6H_5	1706
6b	3-NH_2-C_6H_4	1708
6c	4-NH_2-C_6H_4	1710
6d	4-Br-C_6H_4	1706
6e	4-Cl-C_6H_4	1710
6f	2,6-$(OH)_2$-C_6H_3	1700
6g	4-F-C_6H_4	1710
6h	2-OH-C_6H_4	1708
6i	4-OH-C_6H_4	1706
6j	4-OCH_3-C_6H_4	1710
6k	4-CH_3-C_6H_4	1708
6l	4-NO_2-C_6H_4	1710
6m	4-NO_2-C_6H_4	1708

MASS SPECTRUM Data File: 3EJL25Y 25-JUL- 3 12:37
Sample: HHA-10 DR NA CHAUHAN, RAJKOT #6204
RT 0'24" FAB(Pos.) GC 1.4c BP: m/z 486.0000 Int. 43.0831 Lv 0.00
Scan# (3 to 4)



EXPERIMENTAL

SYNTHESIS AND THERAPEUTIC EVALUATION OF [1-ARYL-3-(2',7'-DICHLOROQUINOLIN-3'-YL]-2-PROPENYLIDENE]-5-BARBITURIC ACIDS

[A] Synthesis of 1-Aryl-3-(2',7'-dichloroquinolin-3'-yl)-2-propene-1-ones

See Part - (I), Section - I (C).

[B] Synthesis of [1-Aryl-3-(2',7'-dichloroquinolin-3'-yl)-2-propenylidine] -5-barbituric acids

A mixture of 1-p-tolyl-3-(2',7'-dichloroquinolin-3'-yl)-2-propene-1-ones (3.42g. 0.01 mol) and barbituric acid (1.28 g., 0.01 mol) in glacial acetic acid was refluxed for 12 hrs. The contents were poured into ice and product was isolated, crystallised from ethanol. Yield 54%, m.p. 270°C, Anal. Calcd for $C_{23}H_{15}N_3Cl_2O_3$ required : C, 60.81%; H, 3.77%; N, 9.25%; found : C, 60.85%; H, 3.75%; N, 9.53%.

TLC Solvent system : Acetone : Benzene (1:9) visulising Agent : Iodine.

Similarly, other [1-Aryl-3-(2',7'-dichloroquinolin-3'-yl)-2-propenylidine]-5-barbituric acids were prepared. The physical data along with infra red spectral data are recorded in Table No. 4.

[C] Therapeutic evaluation of [1-Aryl-3-(2',7'-dichloroquinolin-3'-yl)-2-propenylidine]-5-barbituric acids

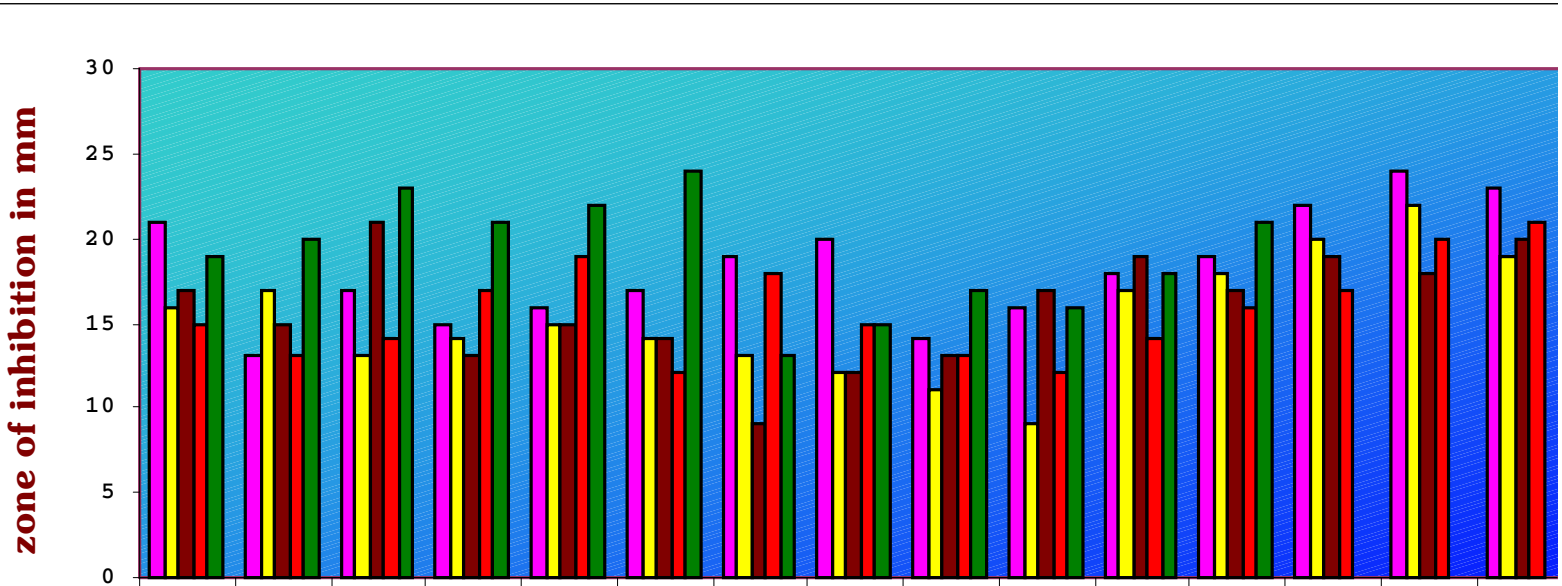
Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zones of inhibition of the test solutions are recorded in Graphical Chart No. 6.

TABLE NO. 4 : PHYSICAL CONSTANTS OF [1-ARYL-3-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-PROPENYLIDENE]-5-BARBITURIC ACIDS

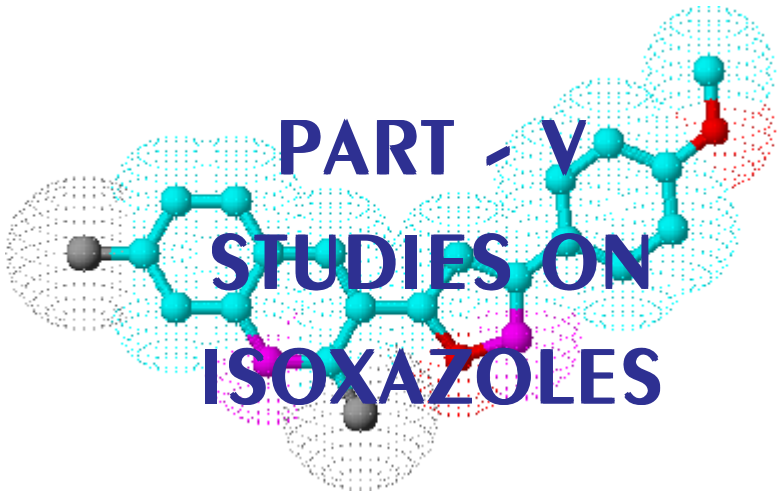
Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
6a	C_6H_5-	$C_{22}H_{13}N_3Cl_2O_3$	438	212	0.686	53	9.54	9.19
6b	3-NH_2-C_6H_4-	$C_{22}H_{14}N_4Cl_2O_3$	453	234	0.652	51	12.31	12.59
6c	4-NH_2-C_6H_4-	$C_{22}H_{14}N_4Cl_2O_3$	453	214	0.565	54	12.31	11.98
6d	4-Br-C_6H_4-	$C_{22}H_{12}N_3BrCl_2O_3$	517	298	0.489	56	8.09	8.23
6e	4-Cl-C_6H_4-	$C_{22}H_{12}N_3Cl_3O_3$	472.5	286	0.580	57	8.85	8.57
6f	2,6-$(OH)_2$-C_6H_3-	$C_{22}H_{13}N_3Cl_2O_5$	470	280	0.691	56	8.90	8.64
6g	4-F-C_6H_4-	$C_{22}H_{12}N_3Cl_2FO_3$	456	276	0.666	55	9.17	9.43
6f	2-OH-C_6H_4-	$C_{22}H_{13}N_3Cl_2O_4$	454	274	0.613	59	9.21	9.39
6h	4-OH-C_6H_4-	$C_{22}H_{13}N_3Cl_2O_4$	454	266	0.602	57	9.21	9.51
6j	4-OCH_3-C_6H_4-	$C_{23}H_{15}N_3Cl_2O_4$	468	288	0.549	58	8.93	8.69
6k	4-CH_3-C_6H_4-	$C_{23}H_{15}N_3Cl_2O_3$	452	270	0.586	54	9.25	9.53
6l	3-NO_2-C_6H_4-	$C_{22}H_{12}N_4Cl_2O_5$	483	296	0.494	53	11.55	11.80
6m	4-NO_2-C_6H_4-	$C_{22}H_{12}N_4Cl_2O_5$	483	290	0.439	52	11.55	11.83

TLC Solvent System : Acetone : Benzene (1 : 9).

GRAPHICAL CHART NO. 6 : [1-ARYL-3-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-PROPENYLIDENE]-5-BARBITURIC ACIDS



	6a	6b	6c	6d	6e	6f	6g	6h	6i	6j	6k	6l	Ampicillin	Amoxycillin	Norfloxacin
B.mega	21	13	17	15	16	17	19	20	14	16	18	19	22	24	23
s.aureus	16	17	13	14	15	14	13	12	11	9	17	18	20	22	19
E.coli	17	15	21	13	15	14	9	12	13	17	19	17	19	18	20
P.vulgaris	15	13	14	17	19	12	18	15	13	12	14	16	17	20	21
A.niger	19	20	23	21	22	24	13	15	17	16	18	21	0	0	0

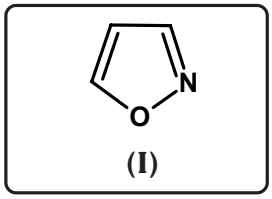


PART - V

STUDIES ON ISOXAZOLES

INTRODUCTION

Isoxazoles offer a wide range of applications in medicinal field, as they are associated with a broad spectrum of biological activity. The investigation of isoxazole was made in 1888, by Claisen, who named isoxazole (I) for a product obtained by the reaction of 1,3-diketone with hydroxylamine[198]. There after, Claisen and his students form a strong foundation for the chemistry of isoxazoles. Isoxazole possess typical properties of an aromatic system but under certain reaction conditions, particularly in reducing or basic media, it becomes highly labile.



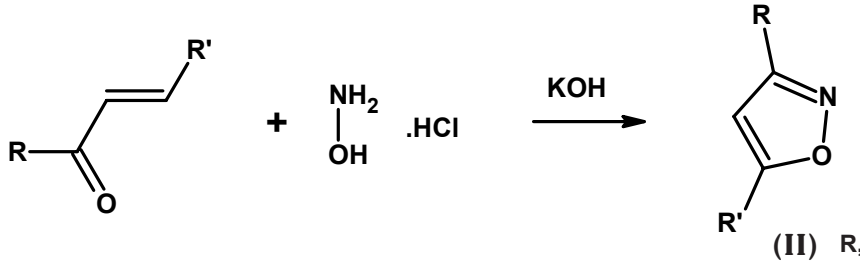
(I)

A huge role in the chemistry of isoxazoles was played by Quelico in 1946, when he began to study the formation of isoxazoles from nitrile N-oxides and unsaturated compounds[199].

SYNTHETIC ASPECT

The construction of isoxazole ring was carried out by the reaction of hydroxylamine with α,β-unsaturated carbonyl compounds, which results in an oxime, which later on undergo cyclisation.

(1) Fanshawe and Crawley[200] prepared isoxazoles (II) from chalcones.



(II) R, R' = Aryl

(2) Substituted isoxazoles were prepared by the reaction between hydroxylamine hydrochloride and chalcone dibromides[201].

(3) J. F. Hansen and S. A. Strong[202] isolated isoxazoles from α,β-unsaturated ketones and N-bromosuccinamide.

(4) D'Alcontres and G. Ae Gamco[203] synthesised isoxazoles from benzonitrile N-oxide and unsaturated aldehydes.

THERAPEUTIC IMPORTANCE

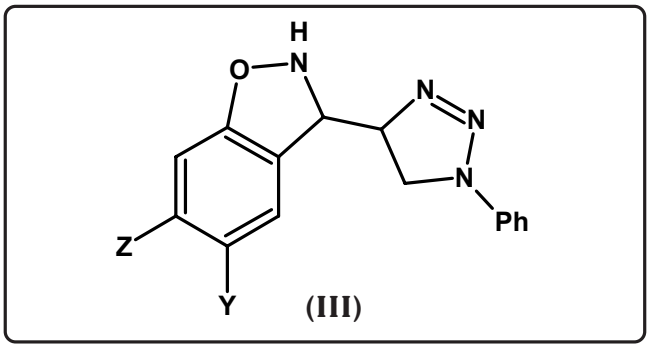
Isoxazoles have various medicinal applications such as:

(1) Antiinflammatory[204-207]
(2) Anticonvulsant[208,209]
(3) Muscle Relaxant[210,211]
(4) Antipyretic[212]
(5) Anticholestermic[213]
(6) Antibacterial[214-216]
(7) Antidiabetic[217]
(8) Nematocidal[218]
(9) Fungicidal[219,220]
(10) Antiviral[221]
(11) Herbicidal[222, 223]
(12) Anthelmintics[224]
(13) Antileukemic[225]
(14) Antitumor[226]
(15) Hypoglycemic[227]
(16) Analgesic[228]

Isoxazoles bearing quinazolone moiety were prepared by Maggio et al.[229] and tested for their analgesic and antiinflammatory activities. Some of them had a very low ulcerogenic effect. C. B. Xue and co-worker[230] reported the replacement of the benzamide in XUO57 (potent inhibitor) with an isoxazole carboxamide resulted in significant improvement ***in vitro*** potency. Isoxazoles

having pesticidal activity have been synthesised by Masui *et al.*[231] Some excellent herbicidal results are obtained by Reddy and co-workers[232]. Nyitrai *et al.*[233] have reported remarkable anxiolytic and antihypertensive effect of some new isoxazole derivatives. Mishra and co-workers[234] have synthesised and reported isoxazoles as useful agents for analgesic and antiinflammatory activities.

Sezer Ozkan *et al.*[235] have prepared 3-(1-phenyl-1,2,3-triazol-4-yl)-benzisoxazoles (III) and studied their insecticidal activity.



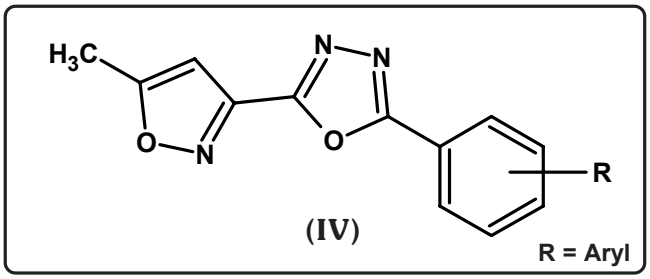
(III)

Some isoxazoles are found to possess herbicidal[236,237], potential antiinflammatory[238,239] antimicrobial,[240,241] estrogen receptor modulators[242] and inhibitor of p38 MAP kinase activities[243]. R. Ulrich *et al.*[244] have synthesised some new isoxazole derivatives and reported their adrenergic antagonist activity.

CONTRIBUTION FROM OUR LABORATORY

A. R. Parikh *et al.*[245] have prepared some new isoxazoles and documented them as antimicrobial agent. H. Parekh and co-workers[246] have synthesised new isoxazole derivatives and reported their antitubercular activity.

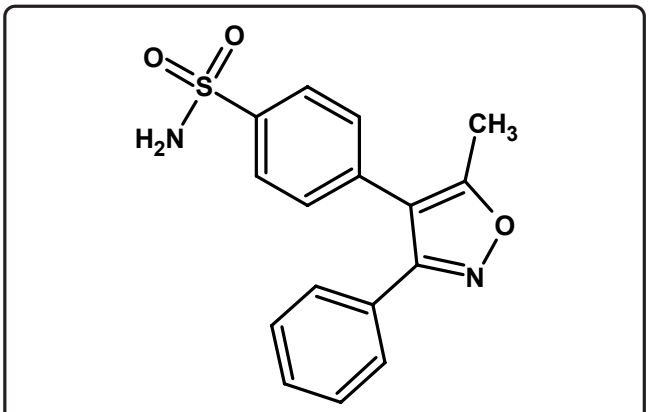
Xin-Ping Hui *et al.*[247] prepared isoxazole derivatives of type (IV) and tested their antibacterial activity.



(IV)

R = Aryl

W. Chengde and co-workers[248] have synthesised isoxazole derivatives and reported them as endothelin modulators. Herbicidal activity of isoxazole derivatives have been documented by Q. Chuanmin et al.[249] F. Gallemi and co-workers[250] described isoxazoles as antitumor agent. Caroline C. et al.[251] prepared isoxazoles of type (V), which have been evaluated for clinical trials for asthama.



(V)

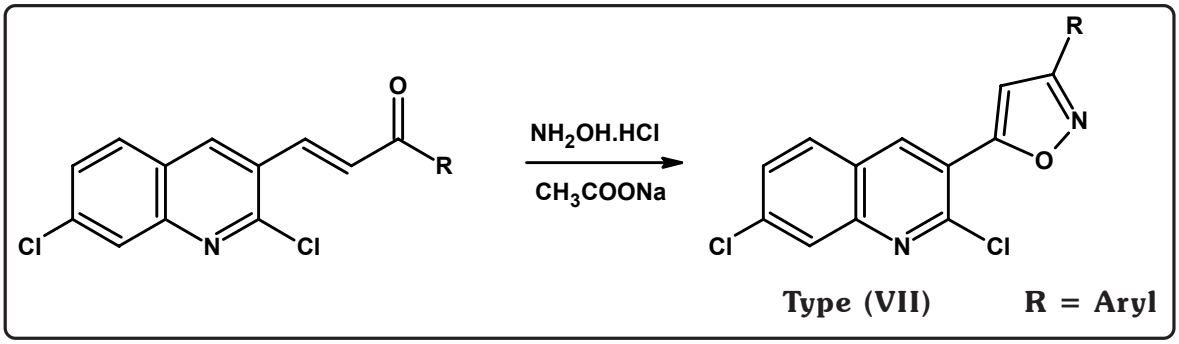
With a view to getting better therapeutic value, it was contemplated to synthesise isoxazole derivatives incorporating quinoline as parent molecule, to enhance the overall activity of resulting compounds which have been described as under.

SECTION - I : SYNTHESIS AND THERAPEUTIC EVALUATION OF 3-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-ISOXAZOLES

SECTION - I

SYNTHESIS AND THERAPEUTIC EVALUATION OF 3-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-ISOXAZOLES.

Isoxazole derivatives are well known for their valid pharmacological activities. Therefore, it was planned to synthesise some new isoxazoles of type (VII), bearing 2,7-dichloroquinoline-3-carboxaldehyde nucleus which have been described as under.

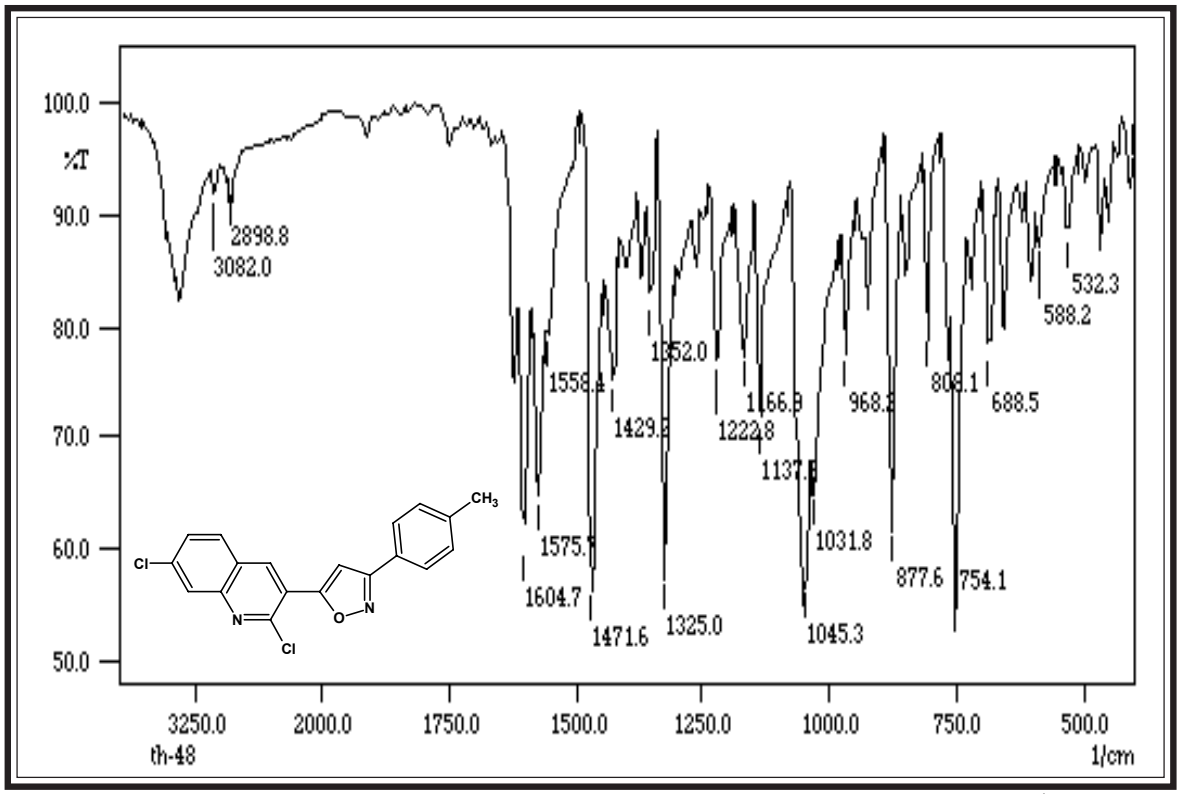


Type (VII) **R = Aryl**

The constitution of the synthesised products have been characterised using elemental analyses, infra red and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg. The biological activities of the synthesised compounds have been compared with standard drugs. The details have been cited in Part-I, Section-I (D).

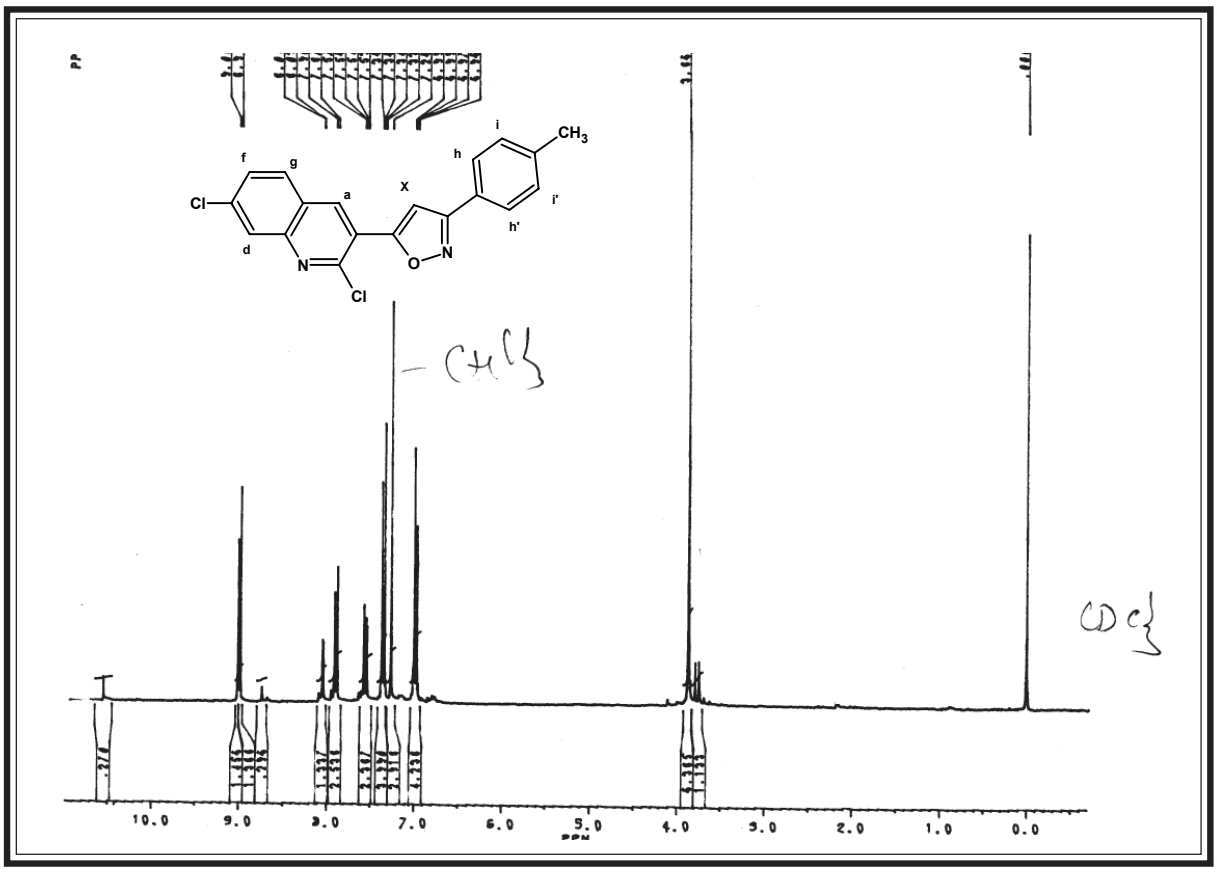
IR SPECTRAL STUDY OF 3-TOLYL-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-ISOXAZOLE



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

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.	2898	2975-2950	419
	C – H. def.	1471	1470-1435	"
Aromatic	C– H str.	3082	3080-3030	"
	C = C str.	1575	1585-1570	"
	C – H. def.	1137	1125-1090	420
		808	835-810	"
Quinoline moiety	C = N str.	1604	1612-1693	419
	C – Cl str.	754	750-700	"
Isoxazole	C = C str.	1575	1580-1550	"
	C = N str.	1471	1470-1460	"
	N – O str.	808 (overlaped)	850-810	"

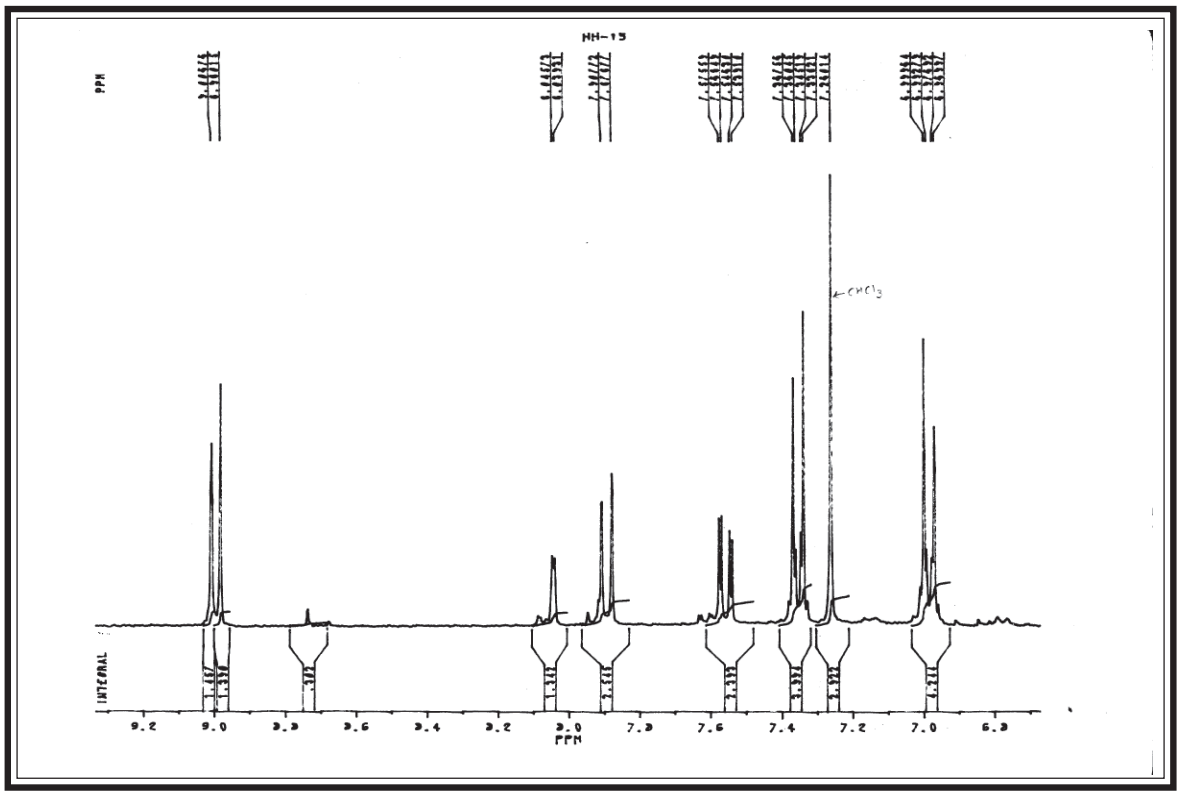
PMR SPECTRAL STUDY OF 3-(p-ANISYL)-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-ISOXAZOLE

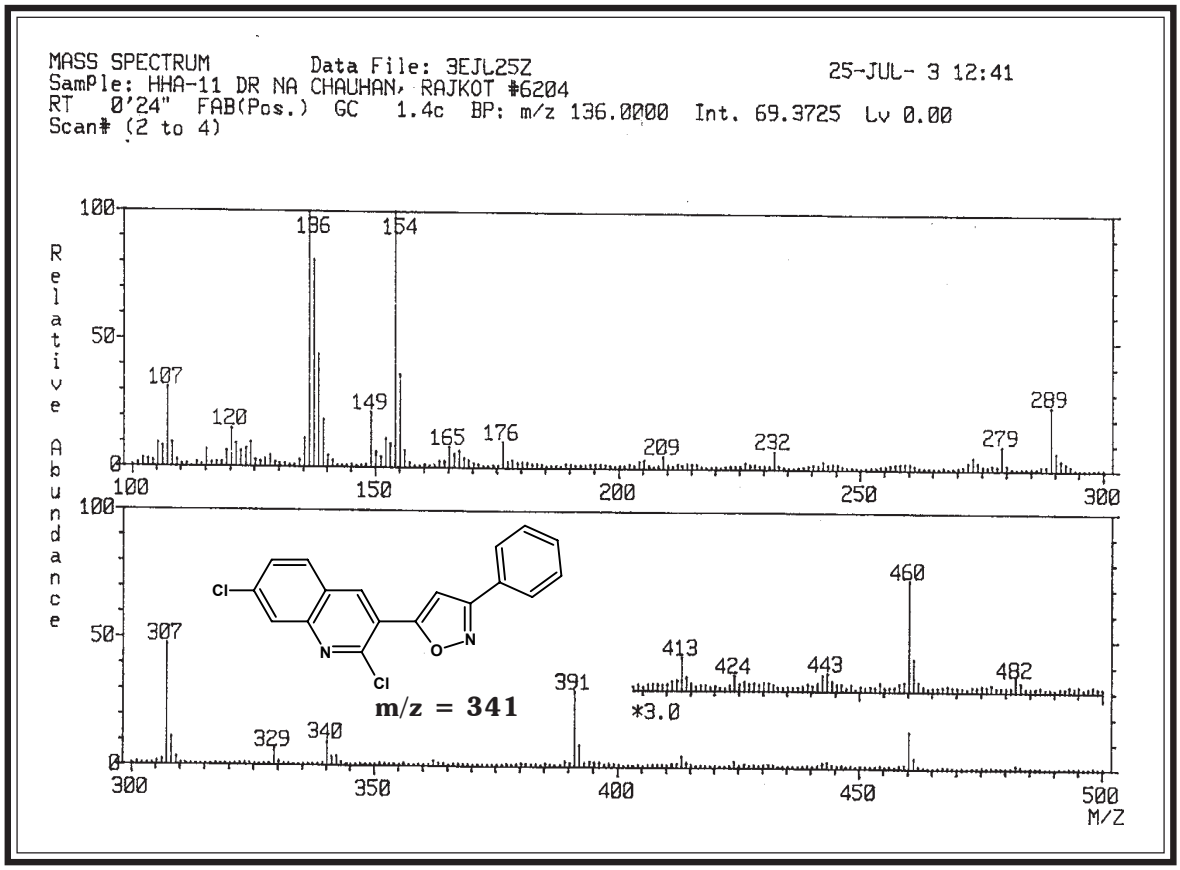


Internal Standard : TMS; Solvent : $CDCl_3$; Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	J. Value in Hz		Inference
1.	3.87	3H	singlet	-		Ar-OCH_3
2.	6.97-7.00	2H	doublet	Jih	8.9	Ar-H i,i'
3.	7.34-7.37	2H	doublet	Jhi	8.81	Ar-H h,h'
4.	7.54-7.58	1H	double doublet	Jfg	8.79	Ar-Hf
				Jfd	2.13	
5.	7.88-7.91	1H	doublet	Jgf	8.68	Ar-Hg
6.	8.04-8.05	1H	doublet	Jdf	1.93	Ar-Hd
7.	8.98	1H	singlet	-		Ar-Ha
8.	9.0	1H	singlet	-		Ar-HX

EXPANDED AROMATIC REGION





EXPERIMENTAL

SYNTHESIS AND THERAPEUTIC EVALUATION OF 3-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-ISOXAZOLES.

[A] Synthesis of 1-Aryl-3-(2',7'-dichloroquinolin-3'-yl)-2-propene-1-ones

See Part (I), Section - 1 (C).

[B] Synthesis of 3-Aryl-5-(2',7'-dichloroquinolin-3'-yl)-isoxazoles

Anhydrous sodium acetate (1.46g, 0.02 mol) dissolved in a minimum amount of hot acetic acid was added to a solution of hydroxylamine hydrochloride (1.4 g, 0.02 mol) in ethanol (20 ml). This solution was added to a solution of 1-p-tolyl-3-(2',7'-dichloroquinolin-3'-yl)-2-propene-1-one (3.42 g, 0.01 mol) in ethanol (25 ml). The mixture was heated under reflux on waterbath for 12 hrs. The product was isolated and recrystallised from ethanol. Yield 64%, m.p. 174^{o}C. Anal. Calcd. for $C_{19}H_{12}N_2Cl_2O$ required : C , 64.24%; H, 3.41%; N, 7.89%; Found : C, 64.20%; H, 3.44%; N, 7.69%.

TLC Solvent system : Acetone : Benzene : (3 : 7) Visulising Agent : Iodine

Similarly other 3-Aryl-5-(2',7'-dichloroquinolin-3'-yl)-isoxazoles were prepared. The physical data along with infra red spectral data are recorded in Table No. 5.

[C] Therapeutic evaluation 3-Aryl-5-(2',7'-dichloroquinolin-3'-yl)-isoxazoles

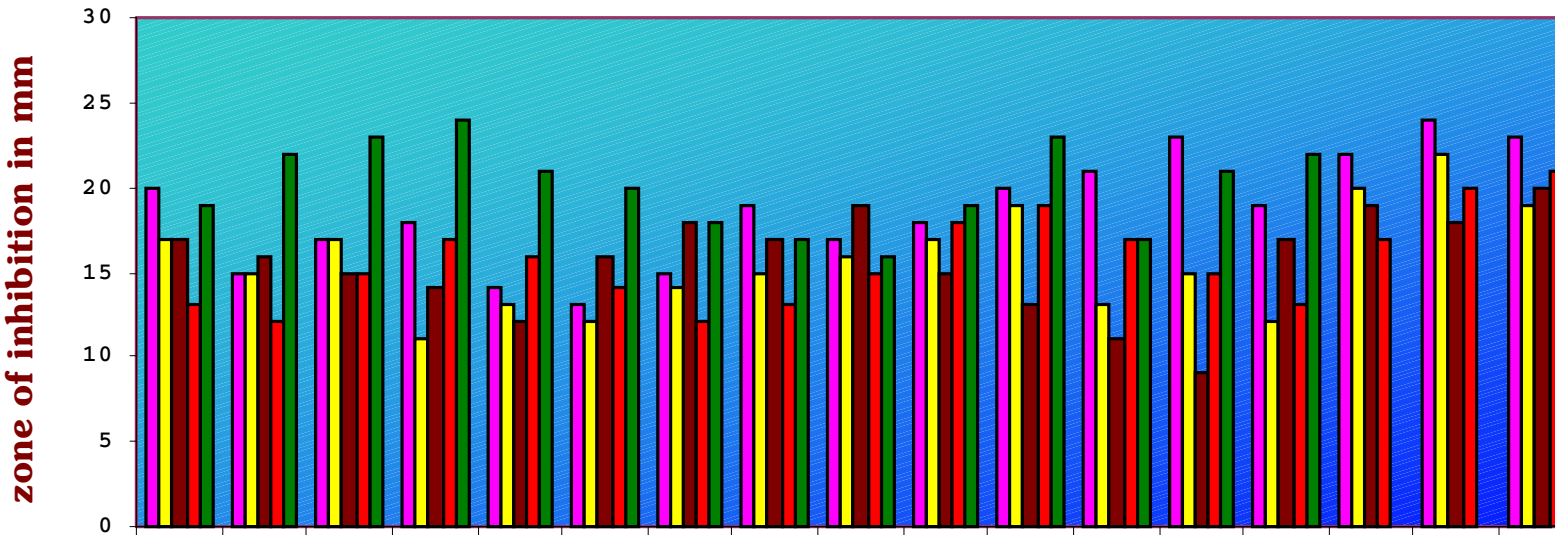
Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zones of inhibition of the test solutions are recorded Graphical Chart No. 7.

TABLE NO. 5 : PHYSICAL CONSTANTS OF 3-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-ISOXAZOLES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
7a	C_6H_5-	$C_{18}H_{10}N_2Cl_2O$	341	238	0.682	64	8.21	8.49
7b	3-NH_2-C_6H_4-	$C_{18}H_{11}N_3Cl_2O$	356	248	0.520	66	11.80	11.55
7c	4-NH_2-C_6H_4-	$C_{18}H_{11}N_3Cl_2O$	356	210	0.469	68	11.80	12.05
7d	4-Br-C_6H_4-	$C_{18}H_9N_2BrCl_2O$	420	260	0.652	69	6.67	6.95
7e	4-Cl-C_6H_4-	$C_{18}H_9N_2Cl_3O$	375.5	186	0.534	70	7.46	7.69
7f	2,6-$(OH)_2$-C_6H_3-	$C_{18}H_{10}N_2Cl_2O_3$	373	196	0.554	71	7.51	7.57
7g	4-F-C_6H_4-	$C_{18}H_9N_2Cl_2FO$	359	210	0.480	75	7.80	7.23
7h	C_4H_3O-	$C_{16}H_8N_2Cl_2O_2$	331	224	0.587	67	8.46	8.63
7i	2-OH-C_6H_4-	$C_{18}H_{10}N_2Cl_2O_2$	357	164	0.643	68	7.84	7.59
7j	4-OH-C_6H_4-	$C_{18}H_{10}N_2Cl_2O_2$	357	216	0.687	69	7.84	7.22
7k	4-OCH_3-C_6H_4-	$C_{19}H_{12}N_2Cl_2O_2$	371	212	0.667	74	7.55	7.55
7l	4-CH_3-C_6H_4-	$C_{19}H_{12}N_2Cl_2O$	355	174	0.713	64	7.89	7.69
7m	3-NO_2-C_6H_4-	$C_{18}H_9N_3Cl_2O_3$	386	252	0.728	62	10.88	10.62
7n	4-NO_2-C_6H_4-	$C_{18}H_9N_3Cl_2O_3$	386	128	0.678	69	10.88	10.82

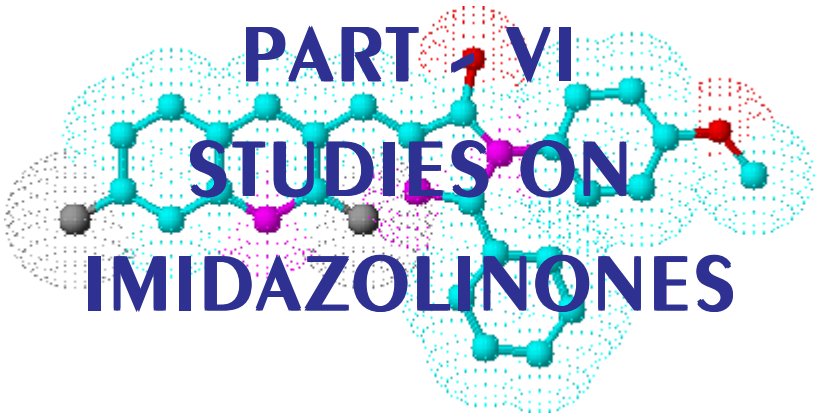
TLC Solvent System : Acetone : Benzene (3 : 7).

GRAPHICAL CHART NO. 7 : 3-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-YL)-ISOXAZOLES



	7a	7b	7c	7d	7e	7f	7g	7h	7i	7j	7k	7l	7m	7n	Ampicillin	Amoxycillin	Nor lox cin
B.mega	20	15	17	18	14	13	15	19	17	18	20	21	23	19	22	24	23
s.aureus	17	15	17	11	13	12	14	15	16	17	19	13	15	12	20	22	19
E.coli	17	16	15	14	12	16	18	17	19	15	13	11	9	17	19	18	20
P.vulgaris	13	12	15	17	16	14	12	13	15	18	19	17	15	13	17	20	21
A.niger	19	22	23	24	21	20	18	17	16	19	23	17	21	22	0	0	0

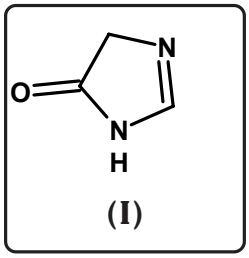
PART - VI



STUDIES ON IMIDAZOLINONES

INTRODUCTION

Imidazolinone (I) is a five membered ring containing 2-nitrogen atoms at the 1- and 3-positions and a carbonyl group at 5- position.



(I)

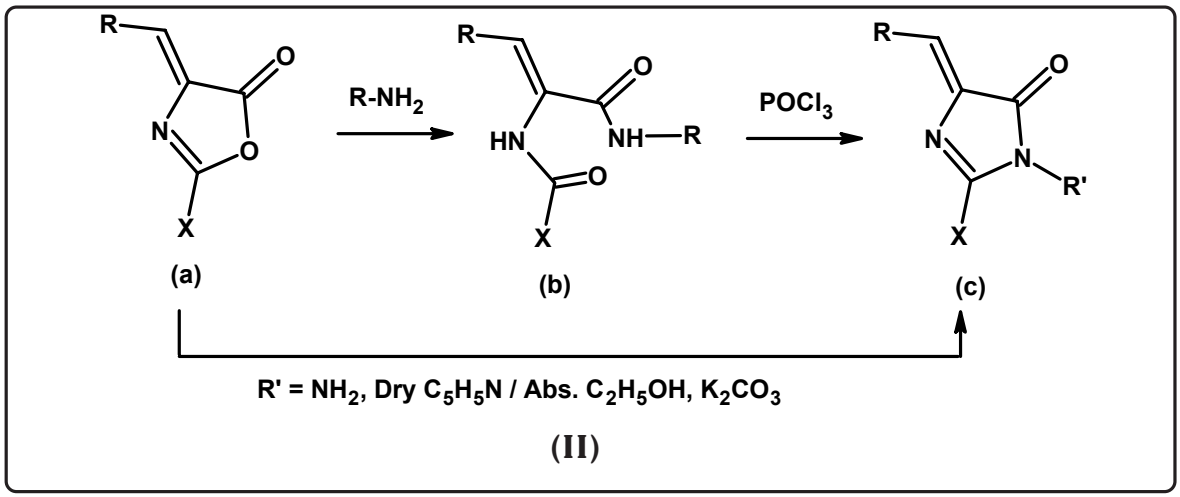
2-Substituted-5-oxoimidazoline was discovered a century back in 1888 by A. W. Hoffmann[252], when he prepared 2-methyl-2-imidazoline (lysidine) by heating N'-diacetylethylenediamine in a steam of dry hydrogen chloride. A. Ladenburg[253] prepared the same compound by fusing two equivalents of sodium acetate with one equivalent of ethylenediamine dihydrochloride.

SYNTHETIC ASPECT

Different methods have been documented for the synthesis of imidazolines in literature[254-257]. Accordingly, imidazolones can be prepared by the condensation of substituted azalactones and primary amine under anhydrous condition. Formation of imidazolones by the aminolysis of oxazalone with amine has been mentioned in the literature[258].

MECHANISM

Azalactone (a) forms amides (b) of α-acylamino acrylic acid by reaction with different amines. The amide on ring closure reaction is converted into imidazolinone derivative (c).



(II)

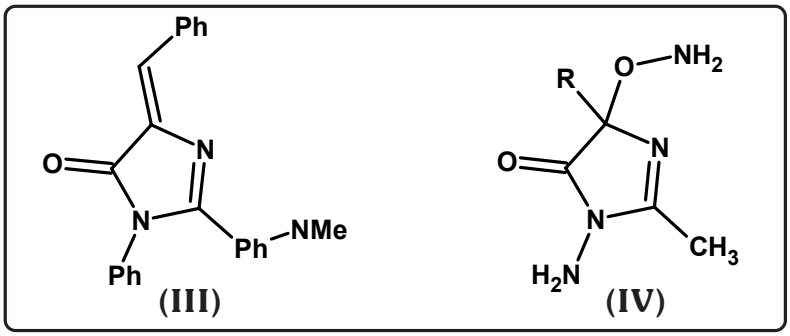
The ring closure can be afforded under a variety of conditions, substituted anilides have been converted into imidazolinone derivatives by the action of phosphorous oxy-chloride. Scheme (II).

THERAPEUTIC IMPORTANCE

Historically, a wide range of biological activities have been attributed to imidazolinone derivatives. A number of imidazolinones have resulted in many potential drugs and are known to possess a broad spectrum of biological activity such as:

1. Antihistamine[259]
2. Antiinflammatory[260]
3. Potent CNS depressant[261]
4. Antipyretics and analgesic[262]
5. Anthelmintic[263]
6. Hypertensive[264]
7. Local anaesthetic[265]
8. Monoamine oxidase (MAO) inhibitor[266]
9. Antiparkinsonian activity[267]
10. Bactericidal[268]
11. Anticonvulsant[269]

Ding M. et al.[270] (III) and Pilkington B. et al.[271] have reported a new series of biologically active analogues of 5-oxo-imidazolines.

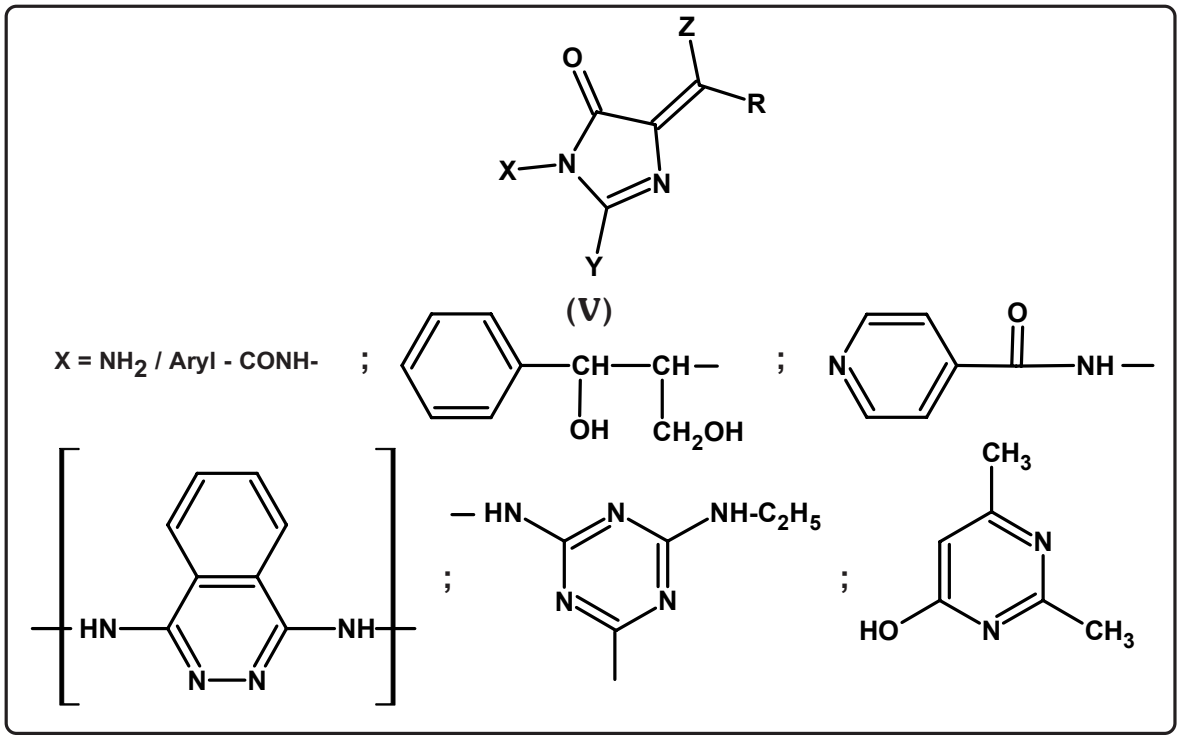


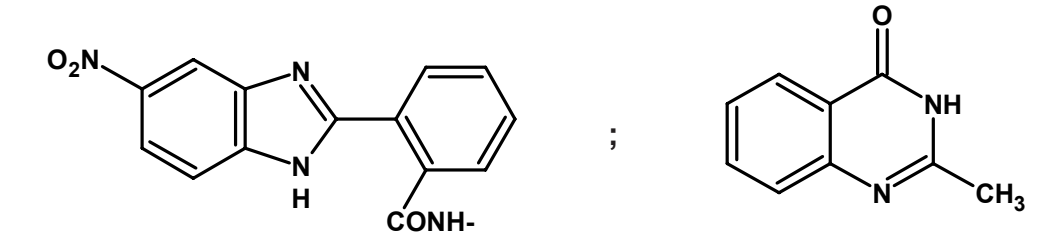
Yokohama Shuichi et al.[272] prepared some new imidazolinone derivatives having calmodulin inhibitors activity. Jagham Samir et al.[273] have documented imidazolinone derivatives (IV) as histaminergic H_3 receptors.

CONTRIBUTION FROM OUR LABORATORY

H. H. Parekh and co-workers have assessed imidazolinones containing isoniazide[274], and s-triazine[275] moieties which were demonstrated as potent antimicrobial agents. A. R. Parikh et al. have synthesised imidazolinones bearing phthalazine[276] and chloramphenicol[277] moiety at one position which were evaluated for their antimicrobial activity.

General structure for above references are as under.

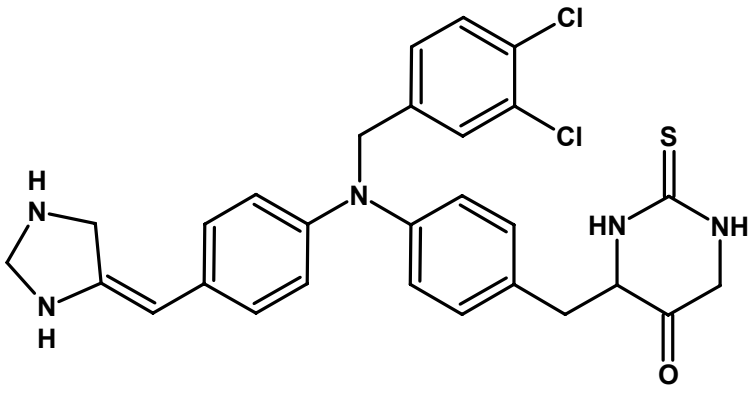




Y = CH_3 / C_6H_5, Z = H, R = Aryl

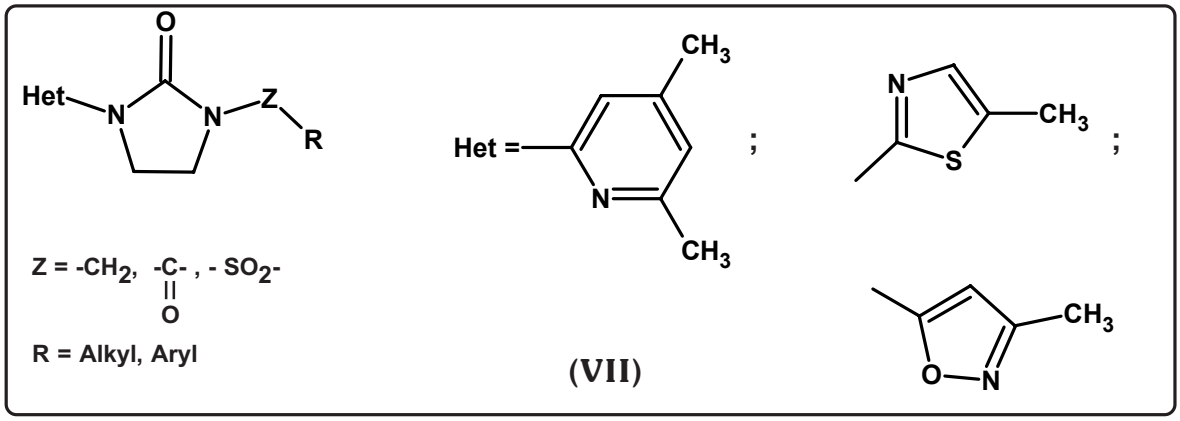
Dharti Joshi *et al.*[278] have reported several novel imidazolinones bearing benzimidazole moiety which were evaluated for their ability to potentiate antimicrobial activity. Akhil Bhatt *et al.*[279] have reported 4-(4'-arylidene-2'-phenyl-5'-oxo-imidazoline-1'-yl)-benzophenones which were screened for their antimicrobial activity. K. Parikh and co-workers[280] have synthesised imidazolinone derivatives and described them as antimicrobial agents. H. H. Parekh *et al.*[281] have prepared imidazolinone derivatives and reported their antimicrobial activity.

Stefan A. L. *et al.*[282] have prepared imidazolinones and tested for the treatment of cyatokine release. Battistina and co-workers[283] have demonstrated some novel imidazolinones to possess insecticidal activity. Anti-HIV activity of imidazolinone derivatives have been reported by Arthur and co-workers[284]. M. Daisuke and co-workers[285] prepared 4-oxo-2-thioxoimidazolidine derivatives (III), which behave as telomerase inhibitors and antitumor agents.



(VI)

Irene and co-workers[286] synthesised some new imidazole derivatives showing antireteroviral activity. Jin-Michel H. et al.[287] constructed 2-oxo-tetrahydro imidazole derivatives (VII) possessing antileishmanial activity. Biological activity of some new imidazolinone derivatives have been reported by C. Hamdouchi et al.[288]



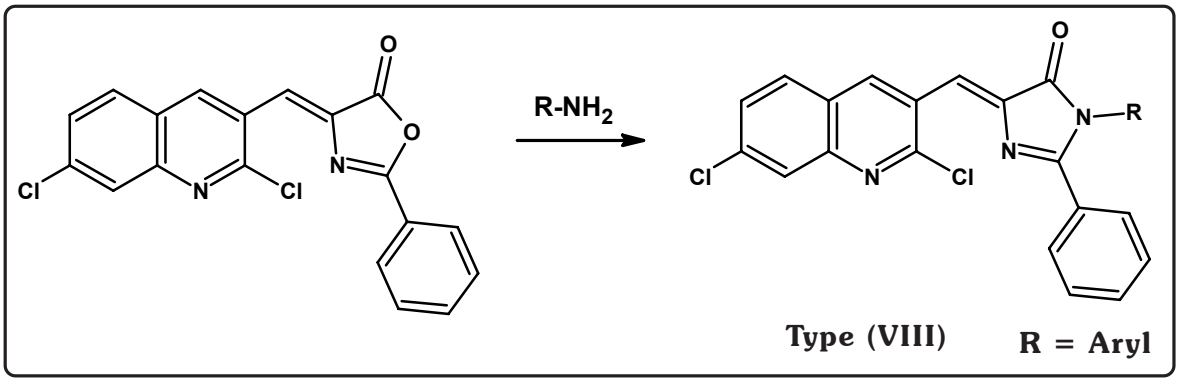
In pursuing the work on the systems incorporating pharmaceutically active molecules, 4-imidazolinone derivatives bearing 2,7-dichloroquinoline nucleus have been synthesised which have been described as under:

SECTION - I : SYNTHESIS AND THERAPEUTIC EVALUATION OF 1N-ARYL-2-PHENYL-4-(2',7'-DICHLOROQUINOLIN-3'-METHINYL)-5-IMIDAZOLINONES

SECTION - I

SYNTHESIS AND THERAPEUTIC EVALUATION OF 1N-ARYL-2-PHENYL-4-(2',7'-DICHLOROQUINOLIN-3'-METHINYL)-5-IMIDAZOLINONES

Imidazolinone derivatives possess varieties of biological and pharmacological properties. Here, we report the synthesis of some new 5-Imidazolinones of type (VIII). The strategy employed for the synthesis of desired compounds involved the reaction of 2-phenyl-4-(2',7'-dichloroquinolin-3'-methinyl)-5-oxazolones with different amines.

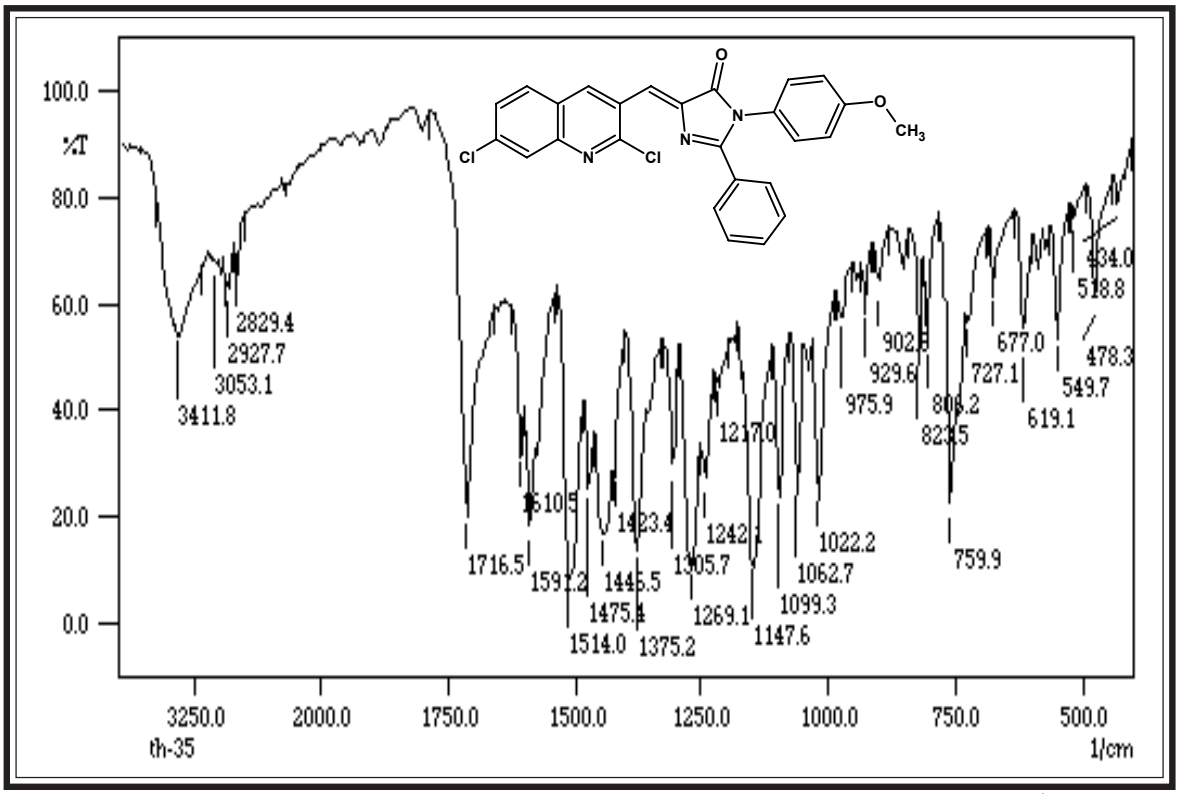


Type (VIII) **R = Aryl**

The constitution of the synthesised products have been characterised using elemental analyses, infra red and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg. The biological activities of the synthesised compounds have been compared with standard drugs. The details have been cited in Part-I, Section-I (D).

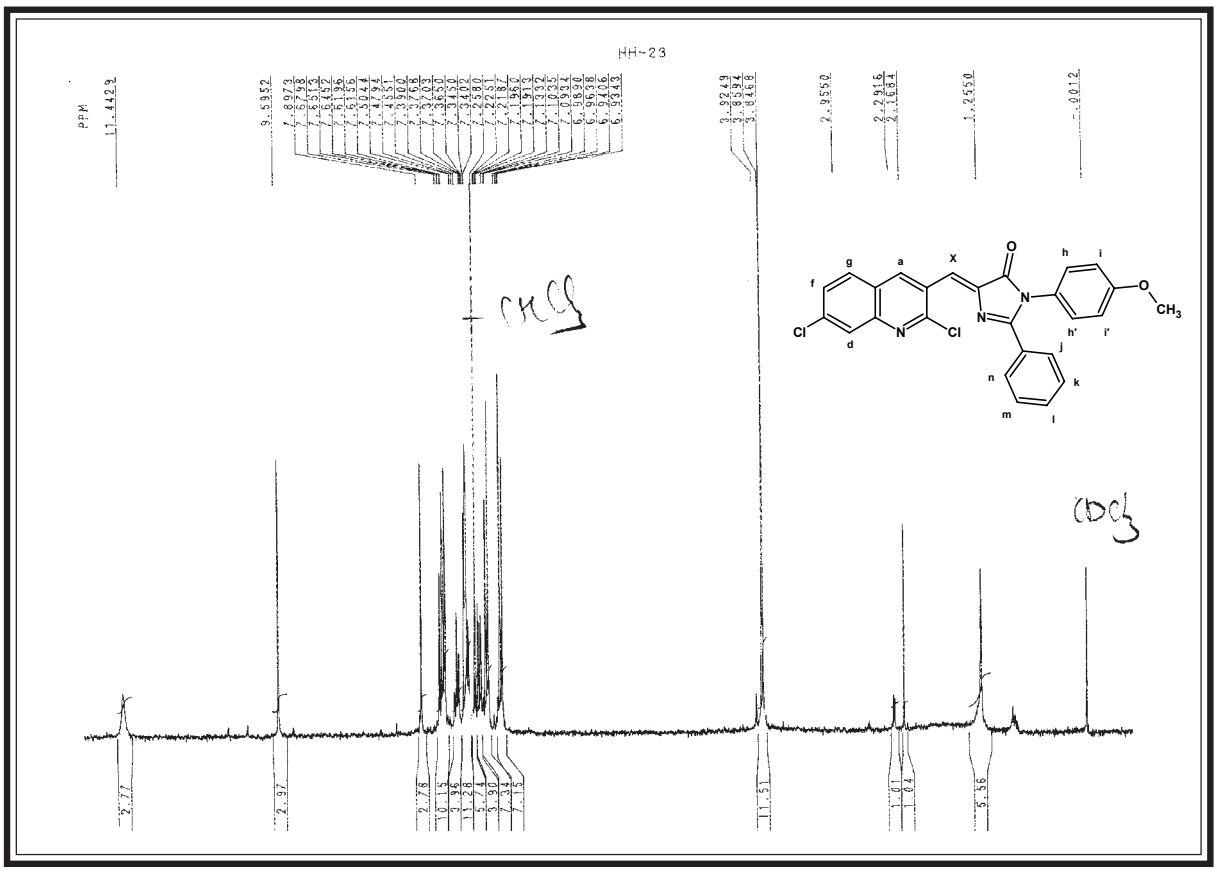
IR SPECTRAL STUDY OF 1N-ANISYL-2-PHENYL-4-(2',7'-DICHLOROQUINOLIN-3'-METHINYL)-3-IMIDAZOLINONE



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

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane –CH_3	C – H str. (asym)	2927	2975-2950	419
	C – H str. (sym)	2829	2880-2860	"
	C – H def. (asym)	1446	1470-1435	"
	C – H def. (sym)	1375	1385-1370	"
Aromatic	C– H str.	3053	3080-3030	"
		1591	1585-1570	"
	C – H. i.p. def.	1099	1125-1090	420
	C – H. o.o.p. def.	823	835-810	"
Quinoline moiety	C = N str.	1610	1612-1693	419
	C – Cl str.	759	750-700	"
Imidazole	C = O str.	1716	1760-1665	"
	C – N – C str.	1147	1146-1132	"
Ether	C – O – C	1242	1275-1200	418

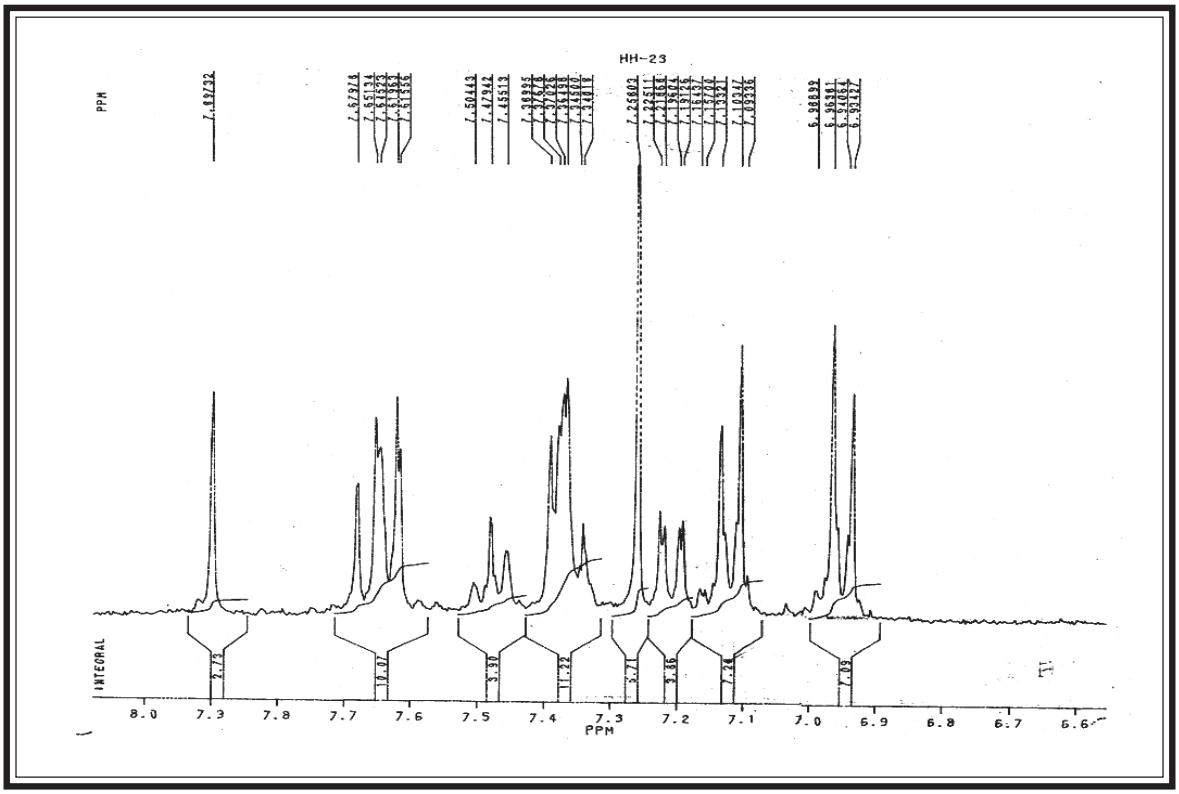
PMR SPECTRAL STUDY OF 1N-(p-ANISYL)-2-PHENYL-4-(2',7'-DICHLOROQUINOLIN-3'-METHINYL)-5-IMIDAZOLINONE



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

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	J. Value in Hz		Inference
1.	3.85	3H	singlet	-		Ar-OCH_3
2.	6.93-6.96	2H	doublet	Jih	8.86	Ar-Hi,i'
3.	7.10-7.13	2H	doublet	Jhi	8.92	Ar-Hh,h'
4.	7.19-7.23	1H	double doublet	Jfg	8.72	Ar-Hf
				Jfd	1.93	
5.	7.34-7.40	3H	multiplate	-		Ar-Hg,j,n
6.	7.46-7.50	1H	triplet	-		Ar-Hi
7.	7.62-7.68	3H	multiplate	-		Ar-Hd,k,m
8.	7.89	1H	singlet	-		Ar-Ha
9.	9.60	1H	singlet	-		Ar-HX

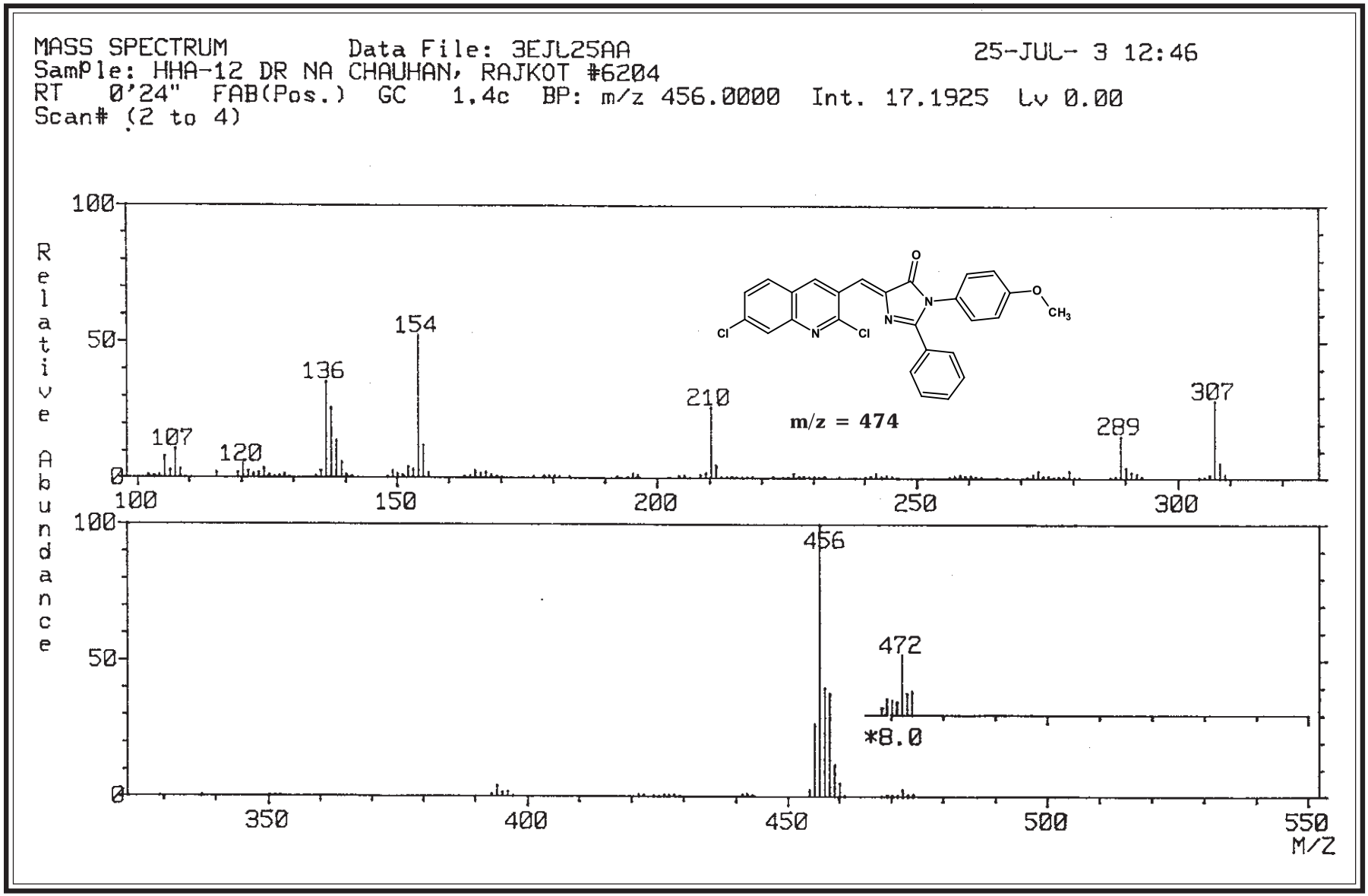
EXPANDED AROMATIC REGION



IR SPECTRAL DATA OF 1N-ARYL-2-PHENYL-4-(2',7'-DICHLOROQUINOLIN-3'-METHINYL)-5-IMIDAZOLINONES

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

Sr. No.	R	C=O str.
8a	C_6H_5	1716
8b	2-Cl-C_6H_4	1716
8c	3-Cl-C_6H_4	1726
8d	4-Cl-C_6H_4	1716
8e	2,5-$(Cl)_2$-C_6H_3	1720
8f	3,4-$(Cl)_2$-C_6H_3	1710
8g	3-Cl,4-F-C_6H_3	1714
8h	2-OCH_3-C_6H_4	1714
8i	4-OCH_3-C_6H_4	1716
8j	2-CH_3-C_6H_4	1716
8k	4-CH_3-C_6H_4	1712
8l	2-NO_2-C_6H_4	1718
8m	3-NO_2-C_6H_4	1710
8n	4-NO_2-C_6H_4	1712


MASS SPECTRUM Data File: 3EJL25AA 25-JUL- 3 12:46
Sample: HHA-12 DR NA CHAUHAN, RAJKOT #6204
RT 0'24" FAB(Pos.) GC 1.4c BP: m/z 456.0000 Int. 17.1925 Lv 0.00
Scan# (2 to 4)
Relative Abundance
100
50
0
107
120
136
154
210
289
307
m/z = 474
100
150
200
250
300
456
472
*8.0
350
400
450
500
550
M/Z

EXPERIMENTAL

SYNTHESIS AND THERAPEUTIC EVALUATION OF 1N-ARYL-2-PHENYL-4-(2',7'-DICHLOROQUINOLIN-3'-METHINYL)-5-IMIDAZOLINONES

[A] Synthesis of 2-Phenyl-4-(2',7'-dichloroquinolin-3'-methinyl)-5-oxazolone

This was prepared by the condensation of 2,7-dichloroquinolin-3-carboxaldehyde with benzoyl glycine in presence of sodium acetate and acetic anhydride as described by Vogel.[289]

[B] Synthesis of 1N-Aryl-2-phenyl-4-(2',7'-dichloroquinolin-3'-methinyl)-5-imidazolinones

To a mixture of 2-phenyl-4-(2',7'-dichloroquinolin-3'-methinyl)-5-oxazolone (3.69 g, 0.01 mol) and ρ-anisidine (1.23 g, 0.01 mol), 20 ml of dry pyridine was added and contents were refluxed for 9 hrs. Resulting mass was poured onto crushed ice and neutralised with HCl, filtered and the product was crystallised from ethanol. Yield 57% m.p. 226°C, Anal. Calcd. for $C_{26}H_{17}N_3Cl_2O_2$ required : C, 65.83%; H, 3.61%; N, 8.86%; found : C, 65.85%; H, 3.66%; N, 8.60%. TLC Solvent System : Acetone : Benzene (1.4:8.6) Visulising Agent : Iodine.

Similarly other 1N-Aryl-2-phenyl-4-(2',7'-dichloroquinoline-3'-methiyl)-5-imidazolinones were prepared. The physical data along with infra red spectral data are recorded in Table No. 6.

[C] Therapeutic evaluation of 1N-Aryl-2-phenyl-4-(2',7'-dichloroquinolin-3-methinyl)-5-imidazolinones

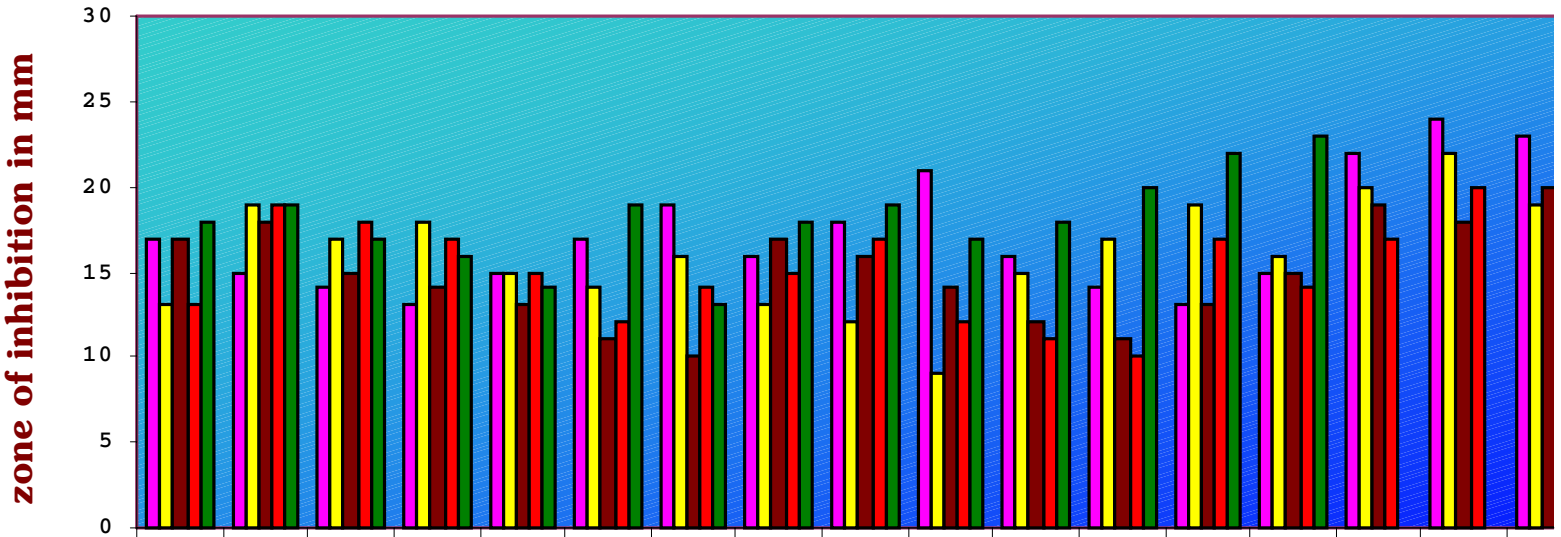
Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zone of inhibition of the test solutions are recorded in Graphical Chart No. 8.

TABLE NO. 6 : PHYSICAL CONSTANTS OF 1N-ARYL-2-PHENYL-4-(2',7'-DICHLOROQUINOLIN-3'-METHINYL)-5-IMIDAZOLINONES

Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. ^{o}C 5	Rf Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
8a	C_6H_5-	$C_{25}H_{15}N_3Cl_2O$	444	216	0.744	57	9.46	9.24
8b	2-Cl-C_6H_4-	$C_{25}H_{14}N_3Cl_3O$	478.5	>300	0.674	56	8.78	8.59
8c	3-Cl-C_6H_4-	$C_{25}H_{14}N_3Cl_3O$	478.5	178	0.542	59	8.78	8.25
8d	4-Cl-C_6H_4-	$C_{25}H_{14}N_3Cl_3O$	478.5	186	0.771	51	8.78	8.58
8e	2,5-$(Cl)_2$-C_6H_3-	$C_{25}H_{13}N_3Cl_4O$	513	220	0.681	53	8.19	8.39
8f	3,4-$(Cl)_2$-C_6H_3-	$C_{25}H_{13}N_3Cl_4O$	513	110	0.742	60	8.19	8.44
8g	3-Cl,4-F-C_6H_3-	$C_{25}H_{13}N_3Cl_3FO$	496.5	182	0.648	65	8.46	8.29
8h	2-OCH_3-C_6H_4-	$C_{26}H_{17}N_3Cl_2O_2$	474	178	0.694	55	8.86	8.58
8i	4-OCH_3-C_6H_4-	$C_{26}H_{17}N_3Cl_2O_2$	474	226	0.744	57	8.86	8.60
8j	2-CH_3-C_6H_4-	$C_{26}H_{17}N_3Cl_2O$	458	212	0.548	58	9.17	9.37
8k	4-CH_3-C_6H_4-	$C_{26}H_{17}N_3Cl_2O$	458	172	0.624	54	9.17	9.40
8l	2-NO_2-C_6H_4-	$C_{25}H_{14}N_4Cl_2O_3$	489	192	0.621	51	11.45	11.23
8m	3-NO_2-C_6H_4-	$C_{25}H_{14}N_4Cl_2O_3$	489	208	0.634	56	11.45	11.67
8n	4-NO_2-C_6H_4-	$C_{25}H_{14}N_4Cl_2O_3$	489	222	0.567	59	11.45	11.18

TLC Solvent System : Acetone : Benzene (1.4 : 8.6).

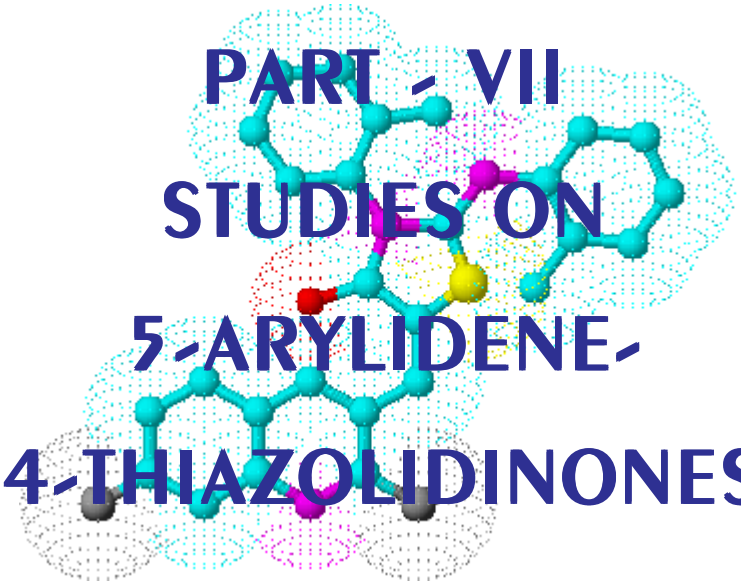
GRAPHICAL CHART NO. 8 : 1N-ARYL-2-PHENYL-4-(2',7'-DICHLOROQUINOLIN-3'-METHINYL)-5-IMIDAZOLINONES



	8a	8b	8c	8d	8e	8f	8g	8h	8i	8j	8k	8l	8m	8n	Ampicillin	Amoxycillin	Nolox ci
B.mega	17	15	14	13	15	17	19	16	18	21	16	14	13	15	22	24	2
s.aureus	13	19	17	18	15	14	16	13	12	9	15	17	19	16	20	22	1
E.coli	17	18	15	14	13	11	10	17	16	14	12	11	13	15	19	18	2
P.vulgaris	13	19	18	17	15	12	14	15	17	12	11	10	17	14	17	20	2
A.niger	18	19	17	16	14	19	13	18	19	17	18	20	22	23	0	0	0

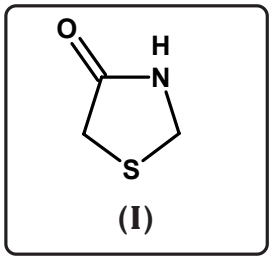
PART - VII

STUDIES ON 5-ARYLIDENE-4-THIAZOLIDINONES



INTRODUCTION

In the family of heterocyclic compounds, thiazolidinones are presumably important. Thiazolidinones are reported to possess a broad spectrum of biological activity. 4-Thiazolidinones are derivatives of thiazolidine with a carbonyl group at 4-position (I). Numerous reports have been appeared in the literature which highlight their chemistry and use.



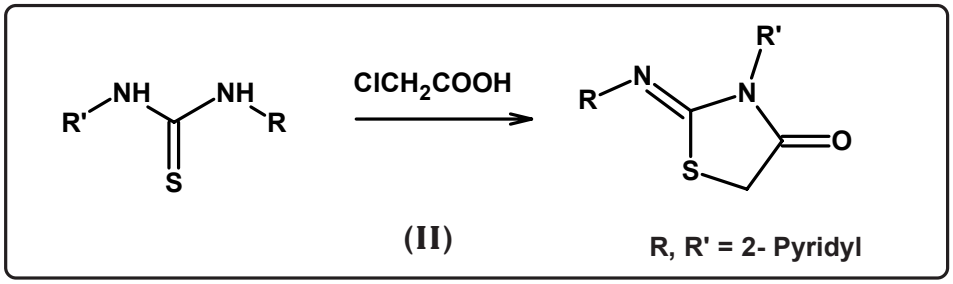
(I)

The cyclic structure was assigned after recognisation of mercaptoacetic acid as a primary product of hydrolysis of 3-phenyl-2-phenylimino-4-thiazolidinones[290].

SYNTHETIC ASPECT

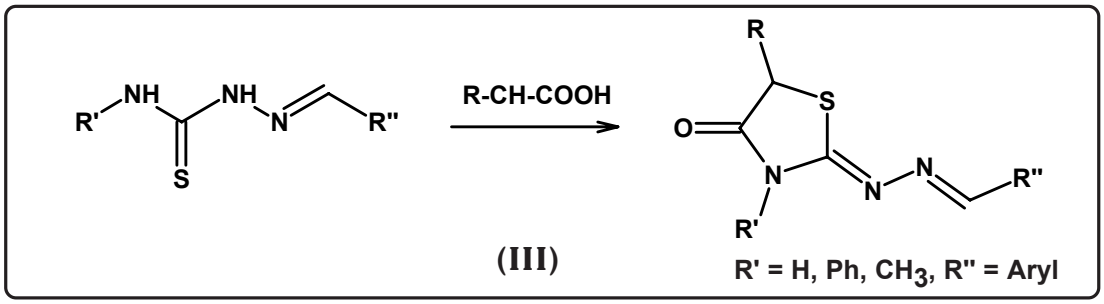
Several methods for the preparation of 4-thiazolidinones are narratted in literature[291-299].

1. R. Nath and K. Shanker[300] have prepared 4-thiazolidinone by cyclization of N-aryl-N'-(2'-pyridyl)-thiocarbamide with chloroacetic acid.



(II) R, R' = 2- Pyridyl

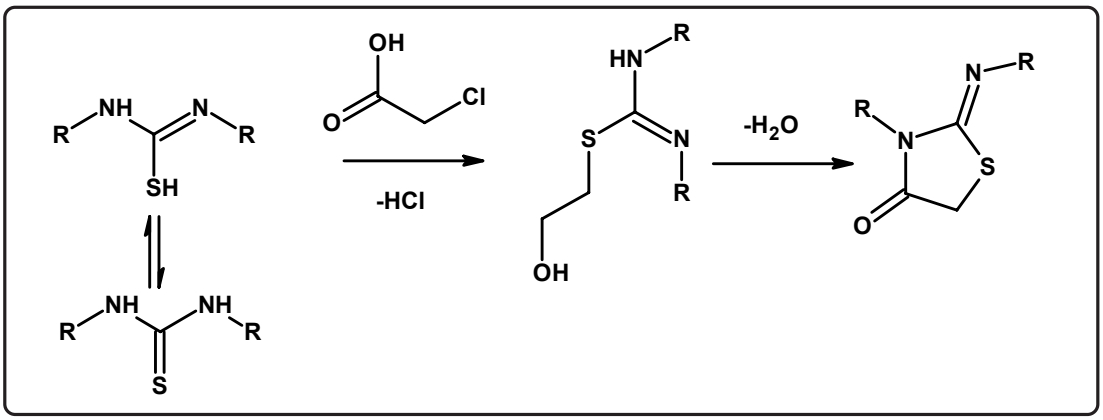
2. I. D. Shah and J. P. Trivedi[301] synthesised thiazolidinones from the 4-aryl thiosemecarbazones by condensing them with chloroacetic acid, α-bromopropionic acid and α-bromophenyl acetic acid.



3. M. Seada and co-workers[302] synthesised some new thiazolidinones from N-thiurea derivatives and chloroacetic acid.

MECHANISM

The reaction proceeds with the tautomerisation of bis-thiourea derivative which on reaction with chloroacetic acid gives thioether derivative. The later on cyclodehydration gives 4-thiazolidinones derivative.



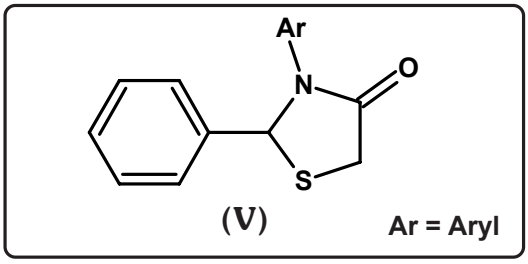
THERAPEUTIC IMPORTANCE

Thiazolidinone, being a biologically active molecule, has attracted many scientist to investigate therapeutic values of thiazolidinone derivatives. 2,3-Disubstituted thiazolidinones are reported to demonstrate a wide spectrum of biological activity.

1. Antimicrobial[303,304]
2. Thrombin inhibitors[305]
3. Bactericidal[306, 307]
4. Antidiabetic[308]
5. Antifungal[309,310]
6. Antipsychotic[311]

7. CNS effect[312]
8. Antihypertensive[313]
9. Antiinflammatory[314]
10. Anthelmintics[315]
11. Anticonvulsant[316]
12. Plant Growth Inhibitor[317,318]
13. H1-histamine antagonists[319]
14. Antitubercular[320]
15. Antioxidant[321]

R. S. Lodhi and co-workers[322] have synthesised 4-thiazolidinone derivatives, which demonstrate antimicrobial, antiinflammatory and analgesic activities. V. S. Ingle et al.[323] have prepared some novel 4-thiazolidinones and documented as potent antimicrobial agent. Sharma R. C. and co-workers[324] have synthesised some new thiazolidin-4-one derivatives (V) as possible antimicrobial agents.



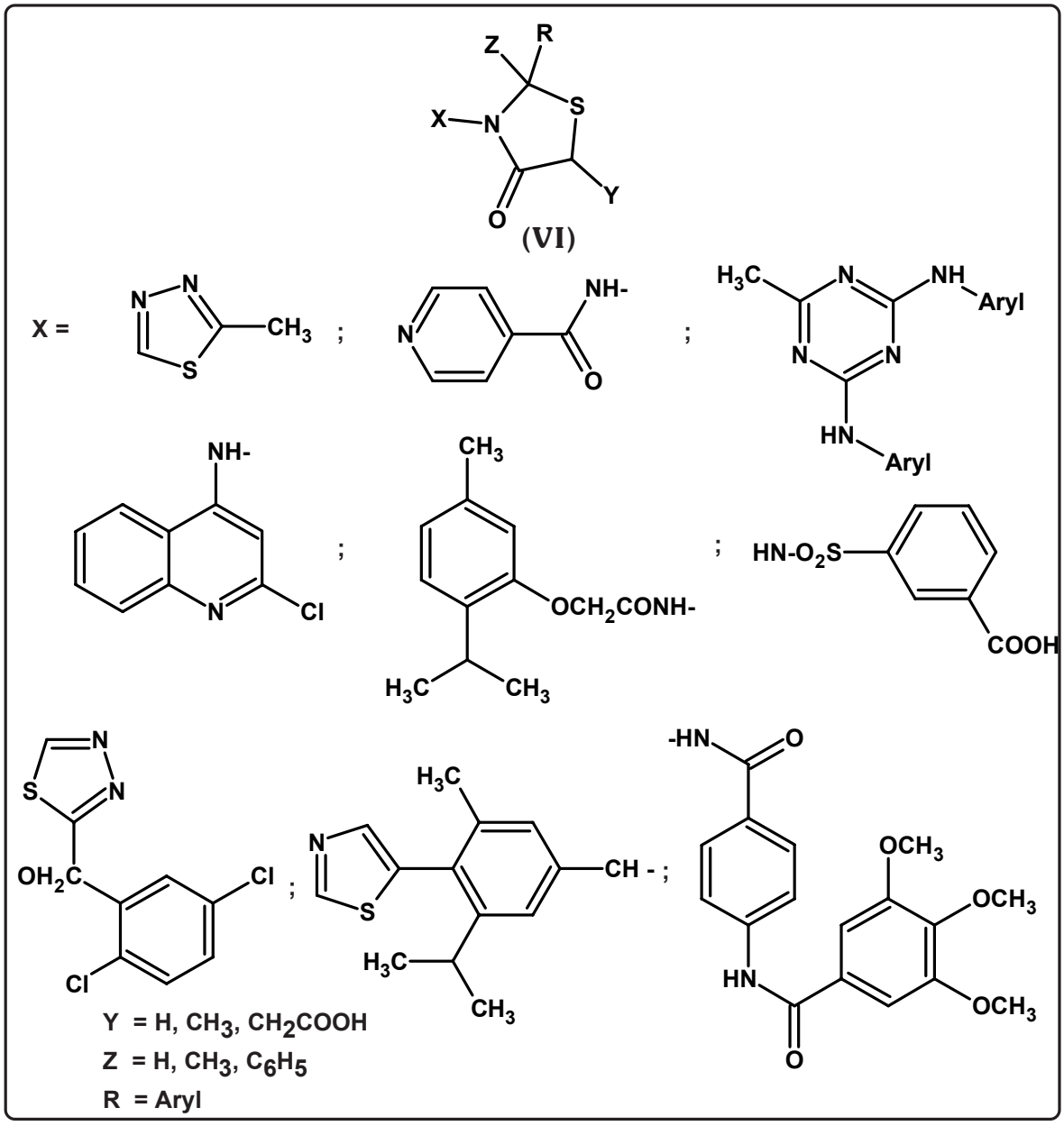
(V) Ar = Aryl

CONTRIBUTION FROM OUR LABORATORY

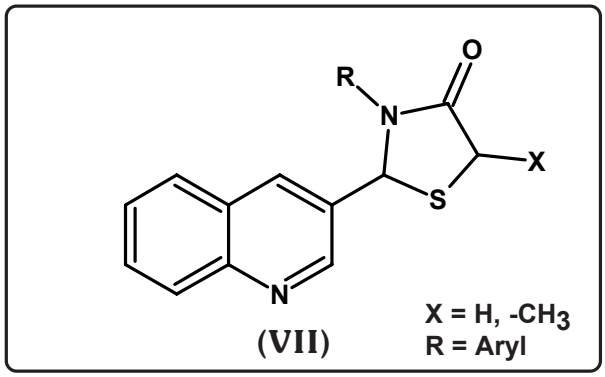
4-Thiazolidinones (VI) bearing s-triazine[325,326], acridin-9-yl[327], dapson[328,329], 6-hydroxypyrimidine[330], thymoloxy acetamido[331] have been synthesised by H. H. Parekh et al. and documented as potent antimicrobial agent.

Parikh et al. have synthesised variety of 4-thiazolidinone derivatives bearing arsenilic acid[332], 2-aryl-1,3,4-thiadiazol[333], γ-picolinylamino[334], s-triazine[335], benzoylamino acetamido[336], sulphonamido-benzoylamino[337], substituted aryl[338], substituted quinoline[339] moieties and reported as potent antimicrobial agent.

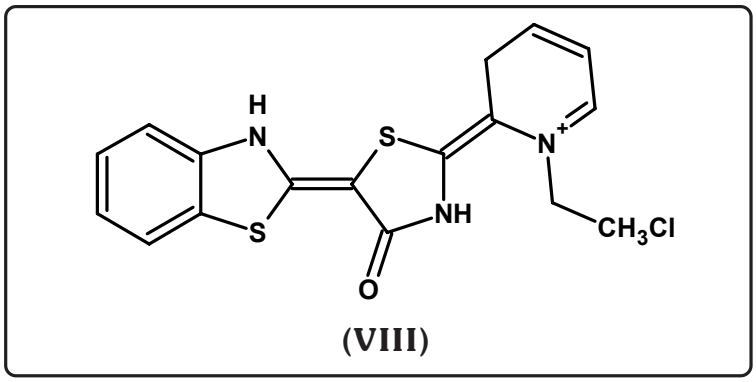
General structure for above references are as under.



A. R. Parikh and co-workers[340] have prepared 4-thiazolidinones bearing quinoline moiety (VIII) and reported their antibacterial activity.

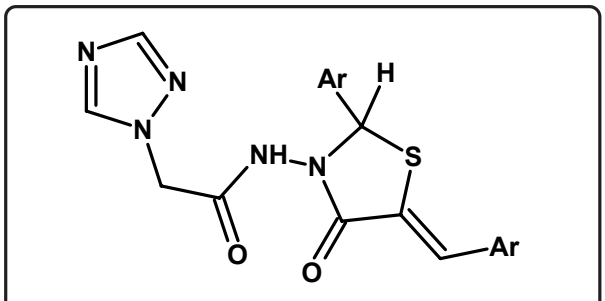


4-Thiazolidinones incorporating benzthiazole nucleus with good antimalarial activity have been synthesised by Takasu *et al.*[341] Abdel-Megid and co-worker[342] have prepared some new bis-4-thiazolidinone derivatives and reported their antifungal activity. A. Tsutomu and co-workers[343] have synthesised some novel thiazolidine-diones and described them as telomerase inhibitors. S. G. Kucukguzel *et al.*[344] have reported antimicrobial and antitumor activity of some novel 4-thiazolidinones (VIII).



(VIII)

S. K. Srivastava *et al.*[345] have described some new 5-arylidene-4-thiazolidinone derivatives (IX) and documented their antimicrobial, analgesic and diuretic activities.



(IX) Ar = Aryl

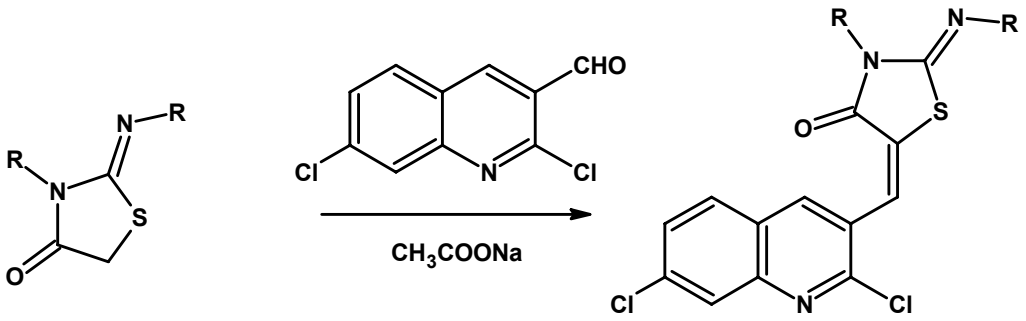
In view of the above observations, the synthesis of novel 4-thiazolidinone derivatives starting from different amines were aimed at investigating therapeutic importance of these compounds, which has been described as under:

SECTION - I : SYNTHESIS AND THERAPEUTIC EVALUATION OF 2-ARYLIMINO-3N-ARYL-5-(2',7'-DICHLORO-QUINOLIN-3'-METHINYL)-4-THIAZOLIDINONES

SECTION - I

SYNTHESIS AND THERAPEUTIC EVALUATION OF 2-ARYLIMINO-3N-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-METHINYL)-4-THIAZOLIDINONES

Thiazolidinone derivatives are known to be among those heterocycles which find their utility in various fields of life. The significance of this moiety has increased due to its biocompatibility, which inspired us to synthesis some new thiazolidinones of type (IX).

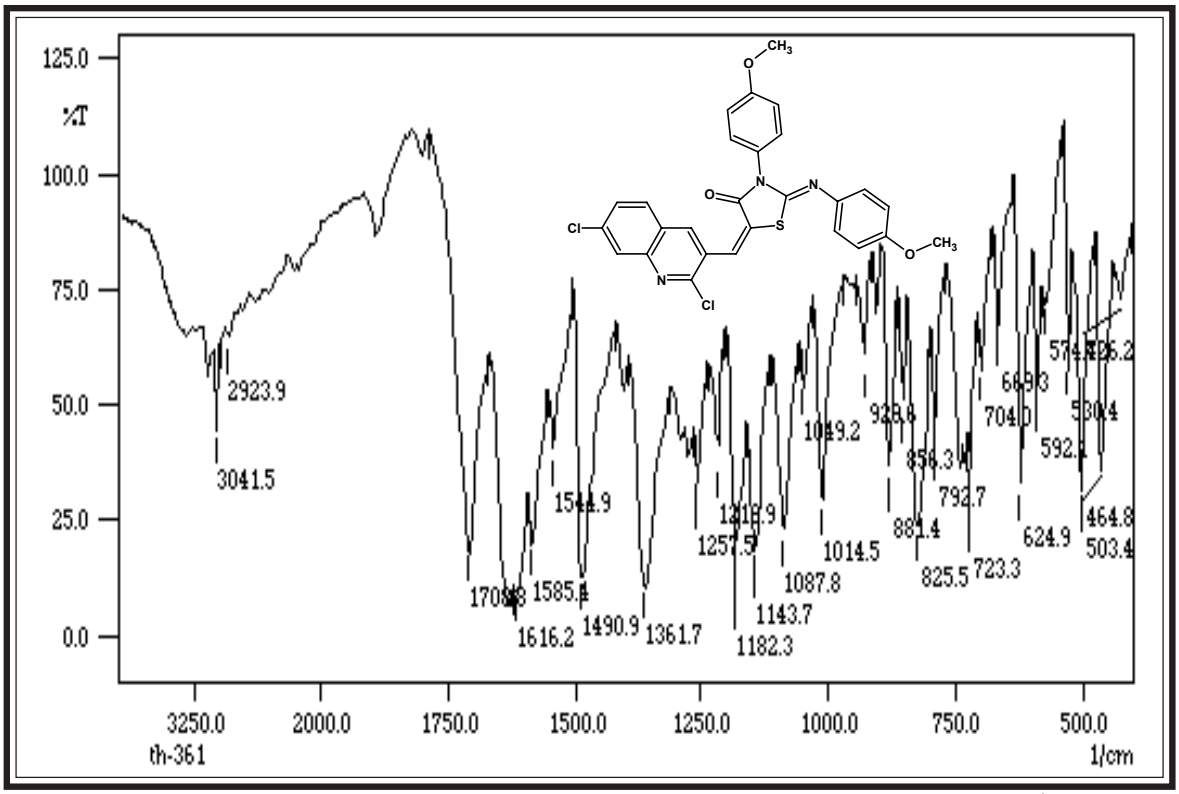


Type (IX) **R = Aryl**

The constitution of the synthesised products have been characterised using elemental analyses, infra red and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg. The biological activities of the synthesised compounds have been compared with standard drugs. The details have been cited in Part-I, Section-I (D).

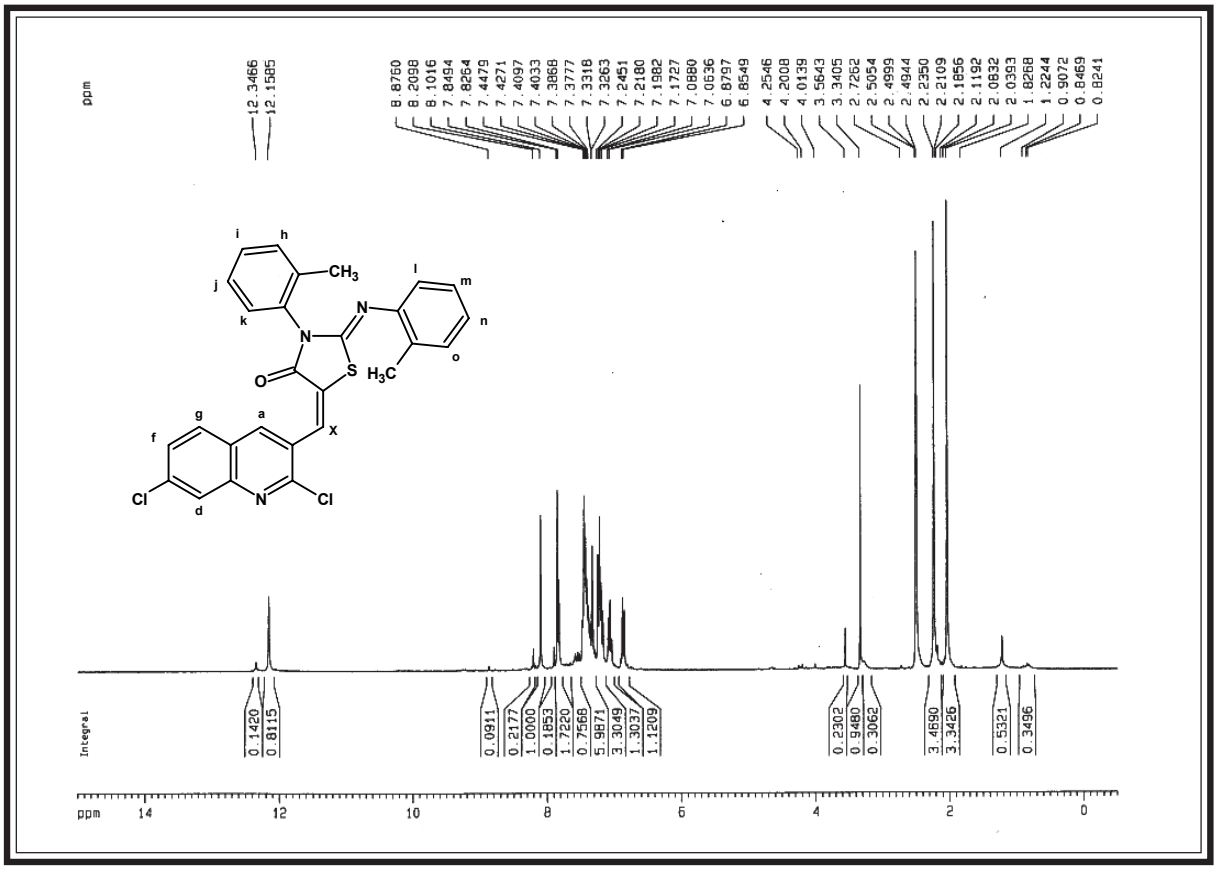
IR SPECTRAL STUDY OF 2-ANISYLIMINO-3N-ANISYL-5-(2'-7'-DICHLORO-QUINOLIN-3'-METHINYL)-4-THIAZOLIDINONE



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

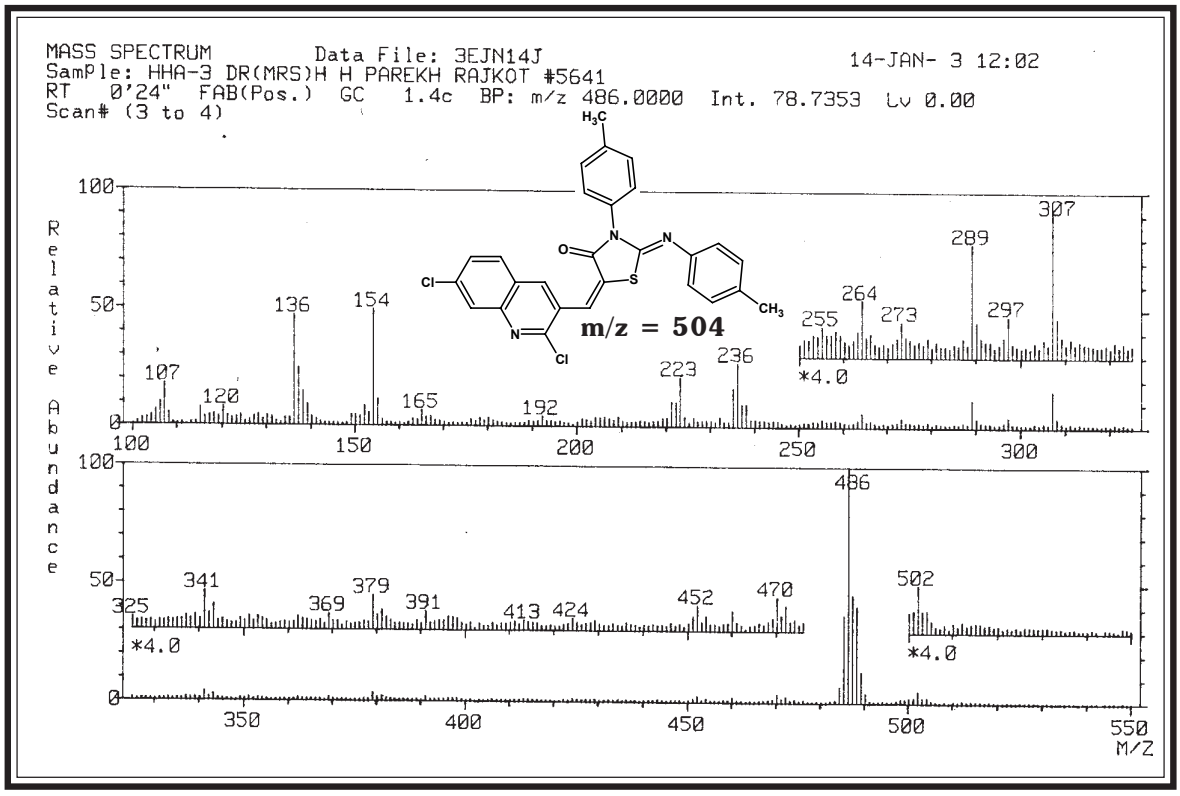
Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.	2923	2975-2850	419
	C – H def.	1361	1385-1370	"
Aromatic	C– H str.	3041	3080-3030	"
	C = C str.	1585	1585-1570	"
	C – H. def.	1087	1125-1090	420
		825	835-810	"
Quinoline moiety	C = N str.	1616	1612-1593	419
	C – Cl str.	723	750-700	"
Ether	C – O – C	1257	1275-1200	"
Thiazolidinone	C = O str.	1708	1760-1655	418
	C – N str.	1218	1220-1020	"
	C – S – C str.	624	700-600	"

PMR SPECTRAL STUDY OF 2-(o-TOLYL)-IMINO-3N-(o-TOLYL)-5-(2',7'-DICHLORO-QUINOLIN-3'-METHINYL)-4-THIAZOLIDINONE



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

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	J. Value in Hz		Inference
1.	2.03	3H	singlet	-		Ar-CH_3
2.	2.23	3H	singlet	-		Ar-CH_3
3.	6.73-6.76	1H	doublet	Jim	6.62	Ar-Hi
4.	7.06-7.09	1H	doublet	Jhi	7.31	Ar-Hh
5.	7.17-7.25	3H	multiplate	-		Ar-H f,k,o
6.	7.32-7.48	5H	multiplate	-		Ar-H d,i,j,m,n
7.	7.83-7.86	2H	doublet	Jef	6.89	Ar-H $g,_X$
8.	8.1	1H	singlet	-		Ar-Ha



IR SPECTRAL DATA OF 2-ARYLIMINO-3N-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-METHINYL)-4-THIAZOLIDIONES

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

Sr. No.	R	C=O str.
9a	C_6H_5	1703
9b	4-Cl-C_6H_4	1707
9c	3,4-$(Cl)_2$-C_6H_3	1708
9d	4-F-C_6H_4	1710
9e	2-OCH_3-C_6H_4	1712
9f	4-OCH_3-C_6H_4	1708
9g	2-CH_3-C_6H_4	1703
9h	3-CH_3-C_6H_4	1703
9i	4-CH_3-C_6H_4	1710
9j	2-NO_2-C_6H_4	1714
9k	3-NO_2-C_6H_4	1715
9l	4-NO_2-C_6H_4	1710

EXPERIMENTAL

SYNTHESIS AND THERAPEUTIC EVALUATION OF 2-ARYLIMINO-3N-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-METHINYL)-4-THIAZOLIDINONES

[A] Synthesis of Bis-thiourea derivatives

A solution of ρ-anisidine (1.23g, 0.01 mol) in methanol and carbon disulfide was refluxed for 4 hrs., poured into ice water to afford the desired product. Excess of CS_2 was removed by placing the reaction mixture at room temp. for 2 hrs. The crude product was isolated and crystallised in methanol. Yield 80% m.p. 196^{o}C. Anal Calcd. : C, 63.50%; H, 5.55%; N, 9.72%; Found : C, 62.48%; H, 5.53%; N, 9.70%.

Similarly other bisthiourea derivatives have been prepared.

[B] Synthesis of 2-Arylimino-3N-aryl-4-thiazolidinone

A solution of 1,3-dianisyl thiourea (2.88 g. 0.01 mol) and chloroacetic acid in glacial acetic acid (20 ml) was refluxed with fused sodium acetate (1.25 g. 0.015 mol.) for 10 hrs. The reaction mixture was poured into ice water and glacial acetic acid was neutralised by sodium bicarbonate and crude product was isolated and crystallised from methanol. Yield 72% m. p. 98^{o}C. Anal Calcd. C, 62.19%; H, 4.87%; N, 8.53%; Found : C, 62.20%; H, 4.90%; N, 8.51%.

Similarly, other 2-arylimino-3N-aryl-4-thiazolidinones were prepared.

[C] Synthesis of 2-Arylimino-3N-aryl-5-(2',7'-dichloroquinolin-3'-methinyl)-4-thiazolidinones

A mixture of 1-anisylimino-3-anisyl-5H-4-thaizolidinone (3.28 g., 0.01 mol), 2,7-dichloroquinolin-3-carboxaldehyde (2.26g. 0.01 mol) and fused sodium acetate (1.25 g. 0.01 mol) were refluxed in glacial acetic acid (25 ml) for 12 hrs. The reaction mixture was then poured into ice water. The crude mass was isolated and treated with sodium bisulfide. The solid thus obtained was filtered, washed,

dried and crystallised from DMF. Yield 72%, m.p. 284°C. Anal Calcd. for $C_{27}H_{19}N_3Cl_2O_3S$: C, 60.45%; H, 3.57%; N, 7.83%; Found : C, 60.43%; H, 3.58%; N, 7.55%.

TLC Solvent System: Acetone : Benzene (4:6), Visulizing Agent : Iodine.

Similarly other 4-thiazolidinone derivatives were prepared. The physical data along with infra red and spectral data are recorded in Table No. 7.

[D] Therapeutic evaluation of 1-Arylimino-3-aryl-5-(2',7'-dichloro quinolin-3'-methinyl)-4-thiazolidinones

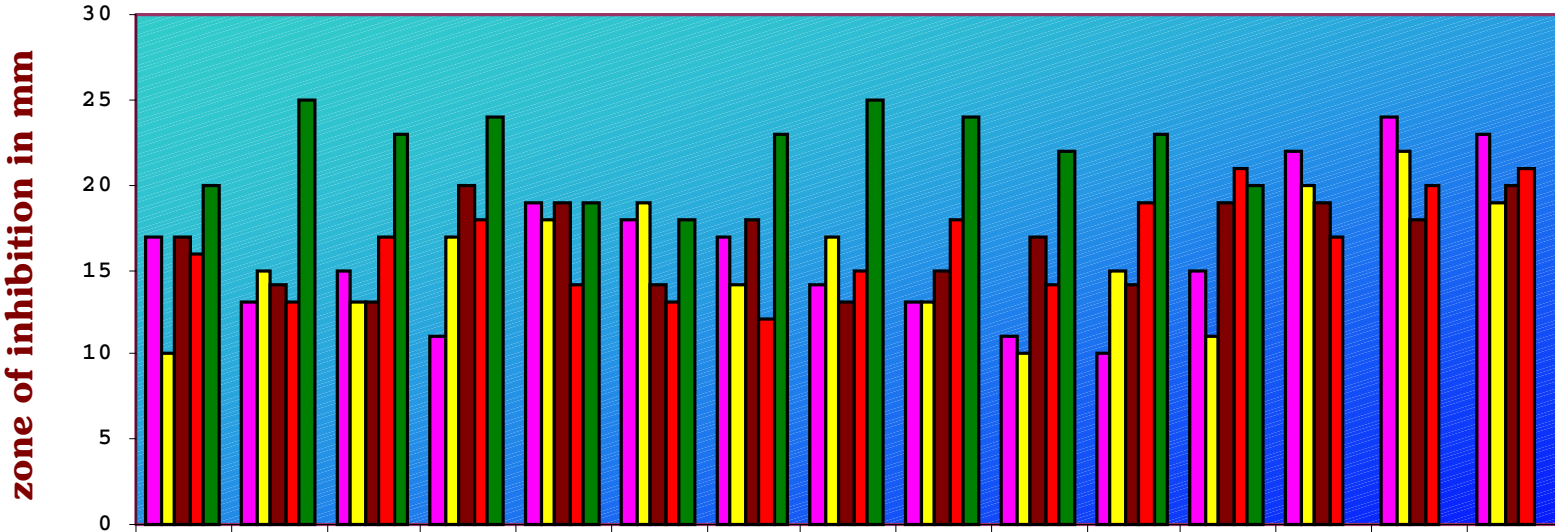
Antimicrobial testing was carried out as described in Part - I, Section-I (D). The zones of inhibition of the test solutions are recorded in Graphical Chart No. 9.

TABLE NO. 7 : PHYSICAL CONSTANTS OF 2-ARYLIMINO-3N-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-METHINYL)-4-THIAZOLIDINONES

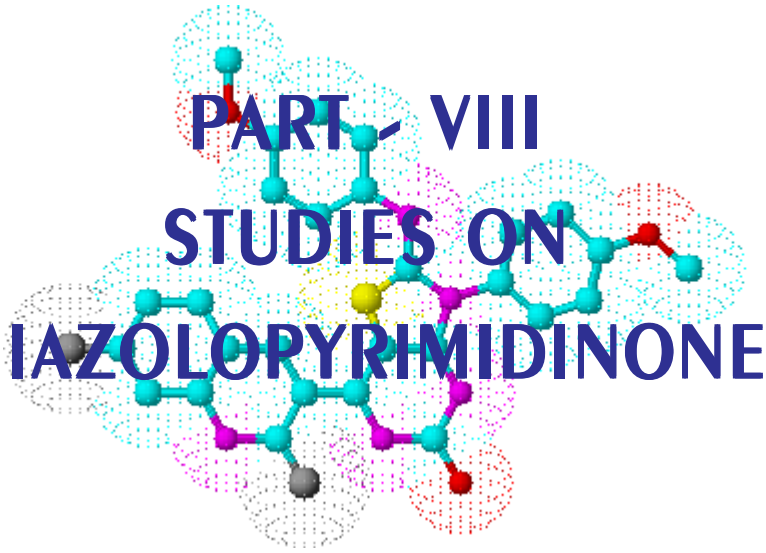
Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. ^{o}C 5	Rf Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
9a	C_6H_5-	$C_{25}H_{15}N_3Cl_2OS$	476	272	0.878	59	8.82	8.55
9b	4-Cl-C_6H_4-	$C_{25}H_{13}N_3Cl_4OS$	545	264	0.495	63	7.71	7.57
9c	3,4-$(Cl)_2$-C_6H_3-	$C_{25}H_{11}N_3Cl_6OS$	614	258	0.485	67	6.84	6.59
9d	4-F-C_6H_4-	$C_{25}H_{13}N_3Cl_2F_2OS$	512	254	0.675	68	8.20	8.47
9e	2-OCH_3-C_6H_4-	$C_{27}H_{19}N_3Cl_2O_3S$	536	288	0.625	69	7.83	7.60
9f	4-OCH_3-C_6H_4-	$C_{27}H_{19}N_3Cl_2O_3S$	536	284	0.523	72	7.83	7.55
9g	2-CH_3-C_6H_4-	$C_{27}H_{19}N_3Cl_2OS$	504	294	0.439	70	8.33	8.65
9h	3-CH_3-C_6H_4-	$C_{27}H_{19}N_3Cl_2OS$	504	242	0.760	66	8.33	8.08
9i	4-CH_3-C_6H_4-	$C_{27}H_{19}N_3Cl_2OS$	504	234	0.563	69	8.33	8.19
9j	2-NO_2-C_6H_4-	$C_{25}H_{13}Cl_2N_5O_5S$	566	256	0.614	73	12.37	12.59
9k	3-NO_2-C_6H_4-	$C_{25}H_{13}Cl_2N_5O_5S$	566	280	0.512	75	12.37	12.62
9l	4-NO_2-C_6H_4-	$C_{25}H_{13}Cl_2N_5O_5S$	566	276	0.496	72	12.37	12.08

TLC Solvent System : Acetone : Benzene (4 : 6).

GRAPHICAL CHART NO. 9 : 2-ARYLIMINO-3N-ARYL-5-(2',7'-DICHLOROQUINOLIN-3'-METHINYL)-4-THIAZOLIDINONES



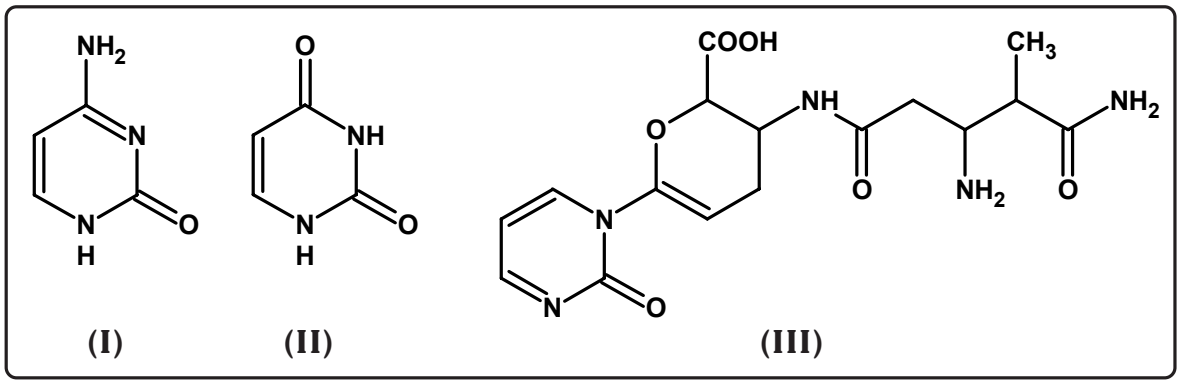
	9a	9b	9c	9d	9e	9f	9g	9h	9i	9j	9k	9l	Ampicillin	Amoxycillin	Norfloxacin
B.mega	17	13	15	11	19	18	17	14	13	11	10	15	22	24	23
s.aureus	10	15	13	17	18	19	14	17	13	10	15	11	20	22	19
E.coli	17	14	13	20	19	14	18	13	15	17	14	19	19	18	20
P.vulgaris	16	13	17	18	14	13	12	15	18	14	19	21	17	20	21
A.niger	20	25	23	24	19	18	23	25	24	22	23	20	0	0	0



PART - VIII
STUDIES ON THIAZOLOPYRIMIDINONES

INTRODUCTION

Pyrimidinones is very interesting class of heterocyclic compounds having wide range of applications in medicine and synthetic chemistry. Pyrimidine derivatives like cytosine (I), urecil (II) and blasticidin (III) occur widely in nature, have remarkable pharmaceutical importance bacause of their diverse physiological action. Several analogs of nucleic acids have been used as compounds that interfere with the synthesis and functioning of nucleic acids, an example is fluorouracil which has been used in cancer treatment.

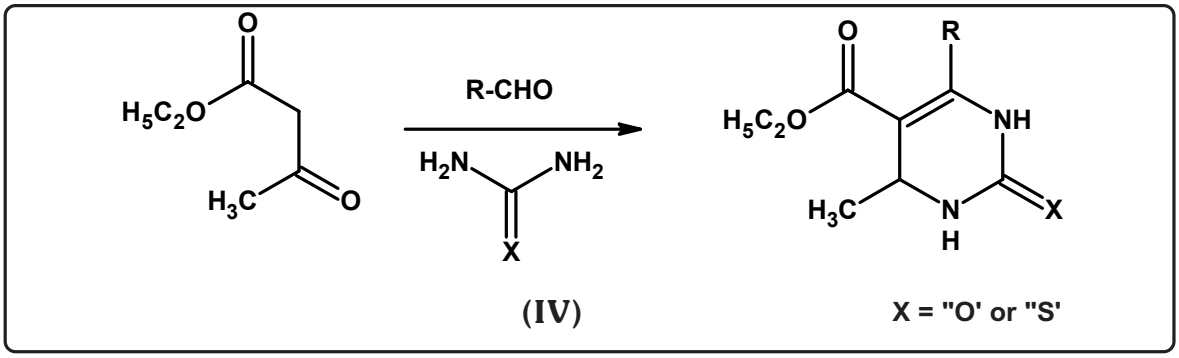


Despite considerable localization of -π-electrons at the nitrogen atom of pyrimidinone, the ring system is still sufficiently aromatic to possess substantial stability. This has great advantage in the primary synthesis of pyrimidinones.

SYNTHETIC ASPECT

Various methods for the synthesis of pyrimidinones have been cited in the literature[346-349].

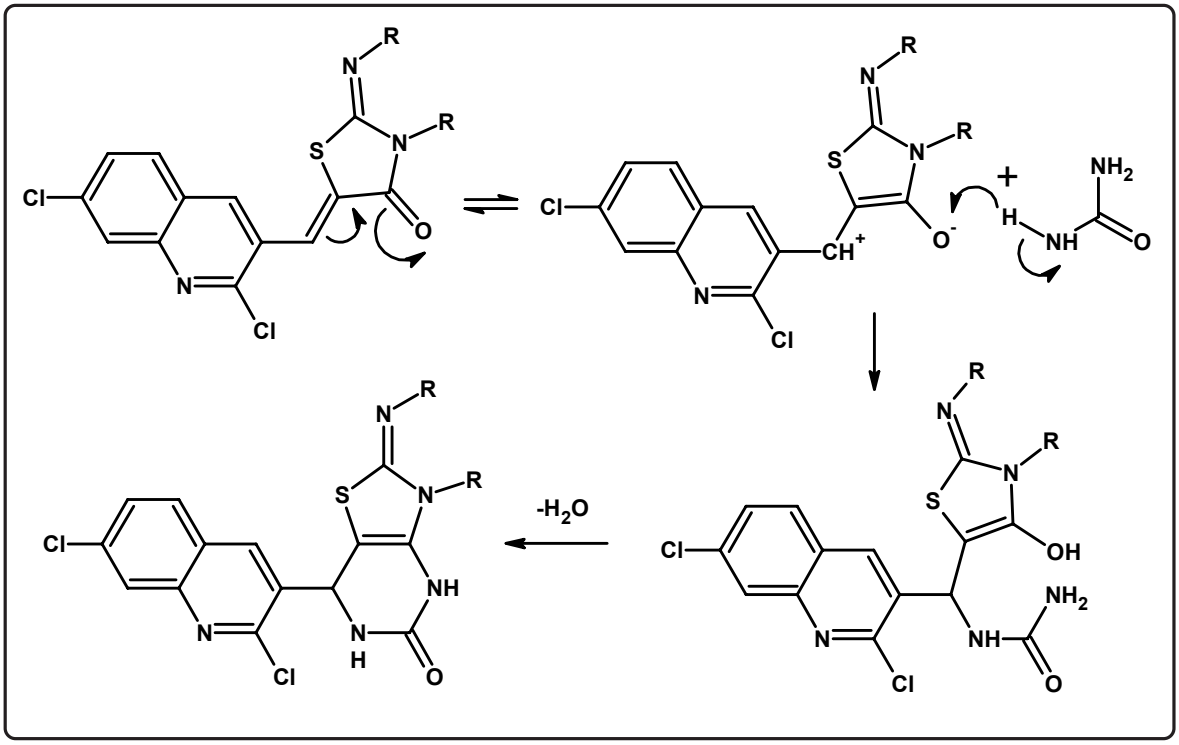
1. Rajiv Gupta and co-workers[350] improved synthesis of 4-aryl-6-methyl-1,2,3,4-tetrahydro-pyrimidine-2-one/thione-5-carboxaldehyde by microwave irradiation.
2. Biginelli[351] investigated the reaction of an aromatic aldehyde with β-ketoester and urea or thiourea which yielded pyrimidine derivative (IV).



MECHANISM

Pyrimidinone derivatives are formed through cycloaddition process. The reaction proceeds through conjugated addition of urea to the α,β,-unsaturated system. Here bond formation take place between N-atom of urea and C-atom of arylidene.

In the first step migration of electron takes place due to the more electronegativity of O-atom than C-atom. So carbon has positive charge while nitrogen atom looses proton so it aquires negative charge, with simultaneous removal of water.

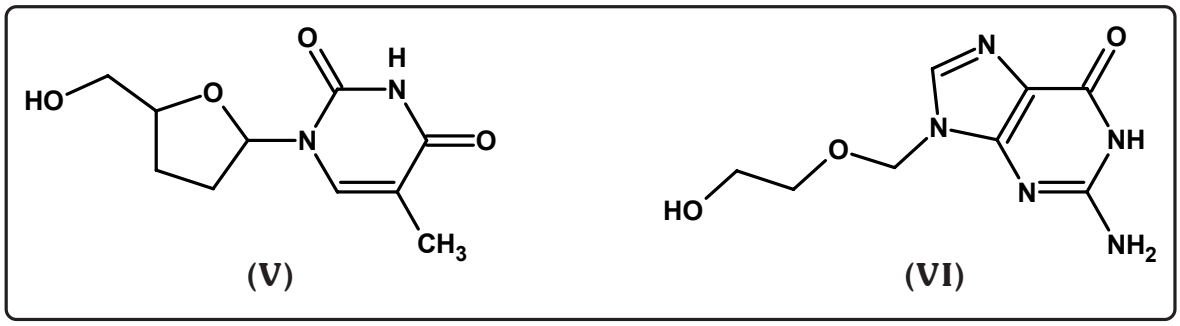


THERAPEUTIC IMPORTANCE

The pyrimidinone derivatives have been prooven to be of great importance in exhibiting and enhancing the biological activities. The important biological activities shown by the pyrimidinones are as under:

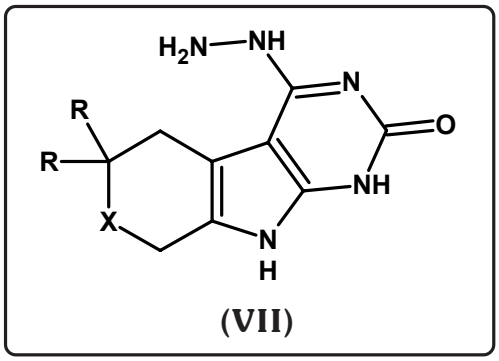
1. Anticonvulsant[352]
2. Anthelmintics[353]
3. Cardiovascular[354,355]
4. Anti HIV[356,357]
5. Antihypertensive[358,359]
6. Antiviral[360,361]
7. Antitumor[363,363]
8. Antibiotic[364]
9. Analgesic[365]
10. Antagonist[366-368]
11. Antiinflammatory[369]

Azaryan and co-workers[370] synthesised pyrimidine dione as antitumor agent. Some important drugs of this type have been produced such as zidovudine (AZT) (V) used in the treatment of AIDS is a close analogue of thymidine. A very highly useful drug for herpes virus infection is acyclovir (ACV) (VI) because of its high selectivity.



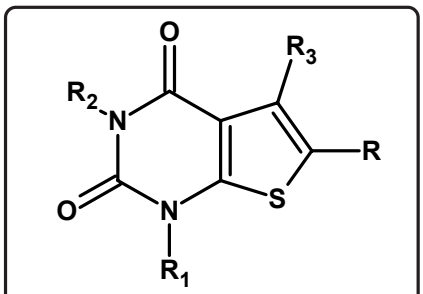
(V) (VI)

Anti HIV activity of pyrimidinone molecule has been reported by Watanabe and Harado[371]. Paronikyan E.G. and co-workers[372] have prepared some new pyrimidinones of type (VII) and tested their biological activities.



(VII)

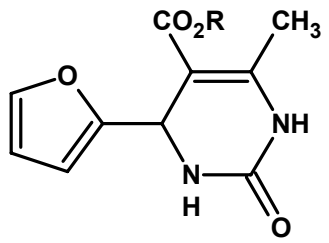
Antiviral, antifungal and insecticidal activity of pyrimidones was documented by M. M. Heravi and co-workers[373]. Sidler and Larson[374] have reported pyrimidone derivatives useful as an α/A adrenergic receptor antagonists. Antiinflamatory agent bearing parent molecule pyrimidone has been documented by Modica and co-worker[375]. Cho et al.[376] have prepared pyrimidinone derivative and reported their antiviral activity. Bantick J. and co-workers[377] synthesised thienopyrimidinediones (VIII) and reported their antiasthamatic activity.



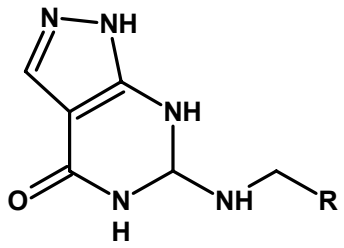
(VIII)

Baldev Kumar and co-workers[378] have prepared a new series of substituted tetrahydropyrimidines and reported as calcium channel blockers. Antiinflammatory activity of some fused pyrimidinones have been reporeted by A. E. Galil et al.[379] S. Raffaele and co-workers[380] have synthesised some new pyrimidones and documented their anti HIV activity.

Hu Chun et al.[381] prepared some new tetrahydropyrimidone derivatives (IX) and reported them as calcium antagonist. A. Ali et al.[382] have synthesised pyrazolo pyrimidone derivatives (X) and documented their antimicrobial activity.



(IX)



(X) R = Aryl

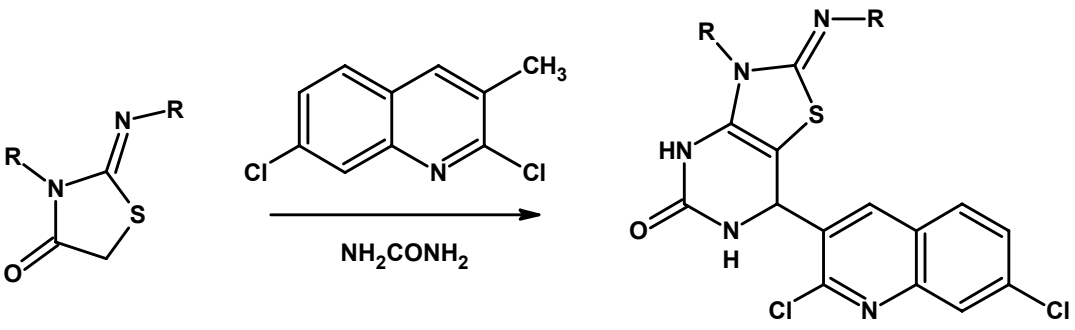
In view of the above observations, it was thought worth while to synthesise some new pyrimidones bearing 2,7-dichloroquinolin-3-carboxaldehyde nucleus, which has been described in the following section.

SECTION - I : SYNTHESIS AND THERAPEUTIC EVALUATION OF OF 7-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-ARYLIMINO-3N-ARYLTHIAZOLIDINO[4,5-d]-PYRIMIDINE-4,5,6,7-TETRAHYDRO-5-ONES

SECTION - I

SYNTHESIS AND THERAPEUTIC EVALUATION OF 7-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-ARYLIMINO-3N-ARYLTHIAZOLIDINO [4,5-d]-PYRIMIDIN-4,5,6,7-TETRAHYDRO-5-ONES

Pyrimidinones are found to have antimicrobial, anti-tumor, CNS depressant, cardiovascular activities. Keeping this in view, we planned to synthesise some new pyrimidinones of type (X). The desired pyrimidinones were synthesised using substituted 4-thiazolidinone with 2,7-dichloroquinolin-3-carboxaldehyde and urea.

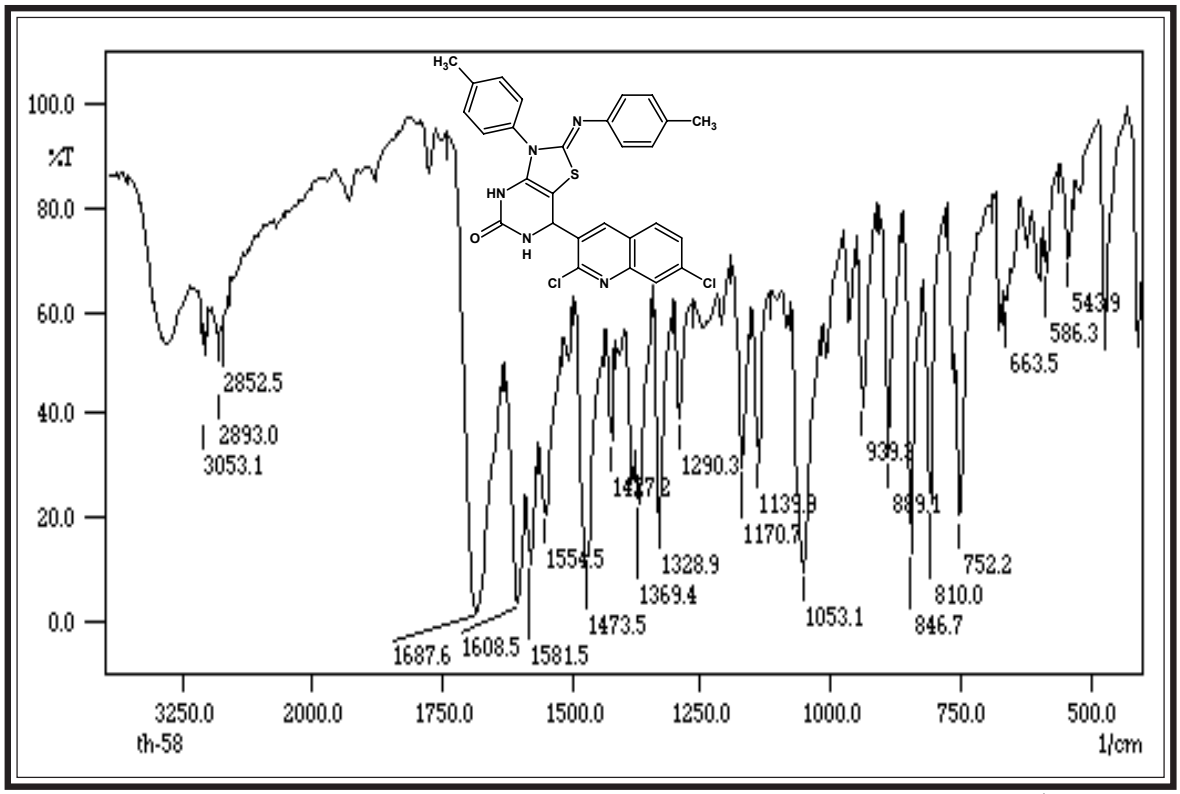


Type (X) **R = Aryl**

The constitution of the synthesised products have been characterised using elemental analyses, infra red and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg. The biological activities of the synthesised compounds have been compared with standard drugs. The details have been cited in Part-I Section-I (D).

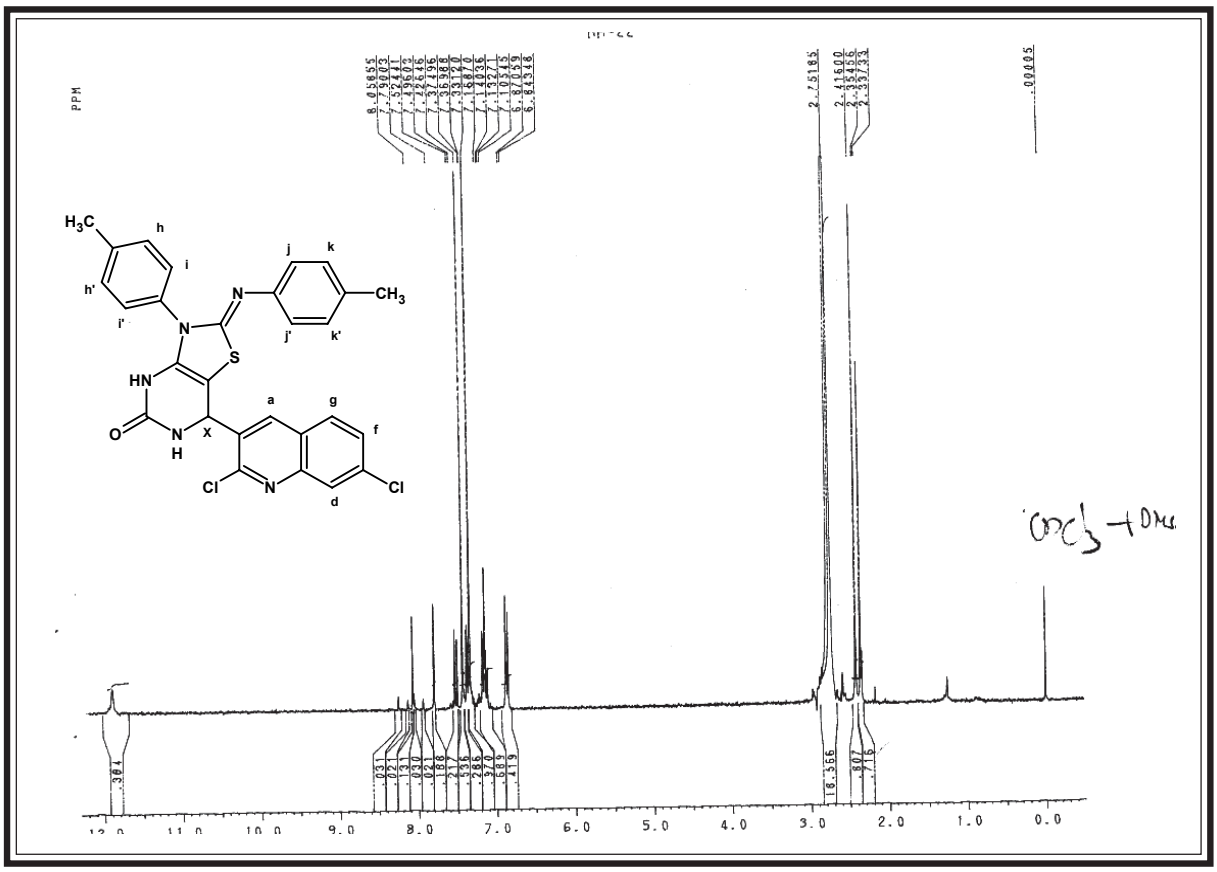
IR SPECTRAL STUDY OF 7-(2'-7'-DICHLOROQUINOLIN-3'-YL)-2-TOLYLIMINO-3N-TOLYLTHIAZOLIDINO-[4,5-d]-PYRIMIDINE-4,5,6,7-TETRAHYDRO-5-ONE



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

Type	Vibration mode	Frequency in cm^{-1}		Ref.
		Observed	Reported	
Alkane	C – H str.	2893	2975-2850	419
	C – H def.	1369	1385-1370	"
Aromatic	C– H str.	3053	3080-3030	"
	C = C str.	1581	1585-1570	"
		1473	1520-1480	"
	C – H. def.	1053	1070-1000	420
		810	835-810	"
Quinoline moiety	C = N str.	1608	1612-1593	419
	C – Cl str.	752	750-700	"
Thiazolidine	C – N str.	1170	1220-1020	418
	C – S – C str.	663	700-600	"
Pyrimidinone	C = O str.	1687	1690-1630	"

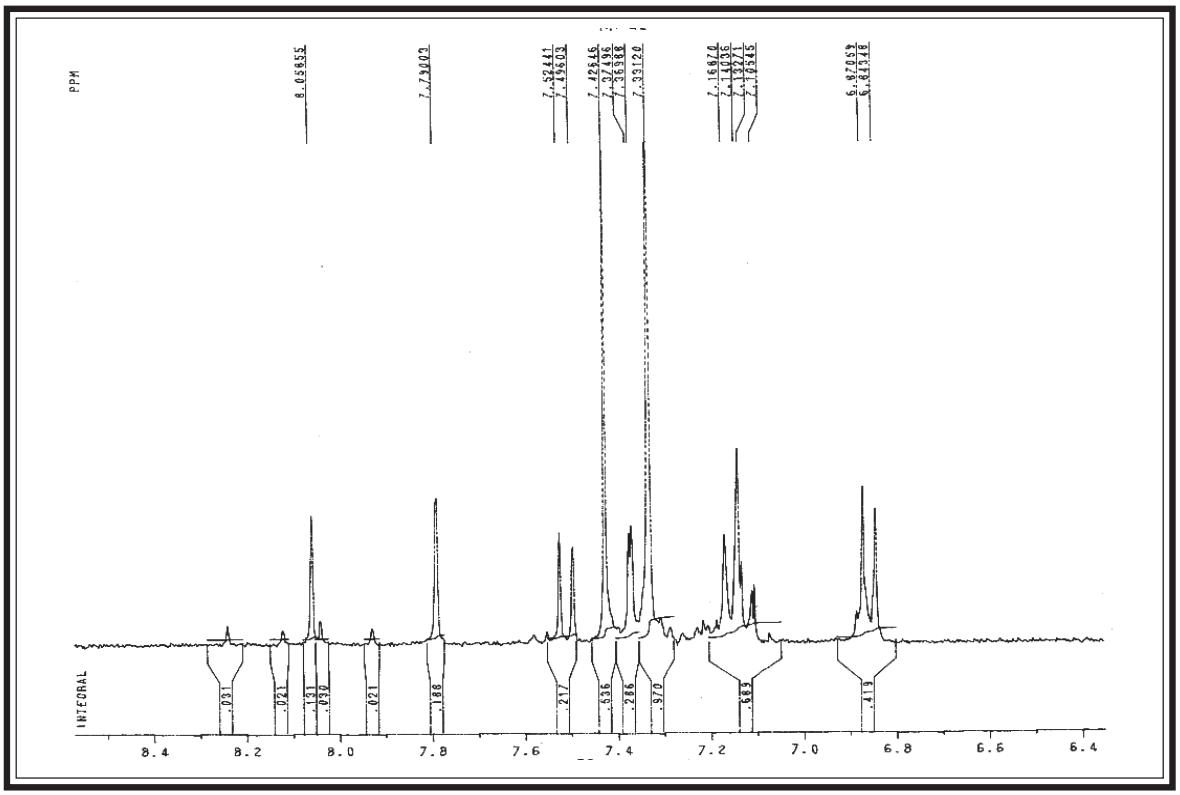
PMR SPECTRAL STUDY OF 7-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-(p-TOLYL)-IMINO-3N-(p-TOLYL)-THIAZOLIDINO-[4,5-d]-PYRIMIDINE-4,5,6,7-TETRAHYDRO-5-ONE



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

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	J. Value in Hz		Inference
1.	2.35	3H	singlet	-		Ar-CH_3
2.	2.41	3H	singlet	-		Ar-CH_3
3.	6.84-6.87	2H	singlet	Jhi	8.13	Ar-H h,h'
4.	7.11-7.17	3H	multiplate	-		Ar-H i,i',f
5.	7.33	4H	singlet	-		Ar-H j,j',k,k'
6.	7.37-7.38	1H	doublet	Jdf	1.52	Ar-Hd
7.	7.49-7.52	1H	doublet	Jgf	8.51	Ar-Ha
8.	7.79	1H	singlet	-		Ar-Ha
9.	8.06	1H	singlet	-		Ar-HX

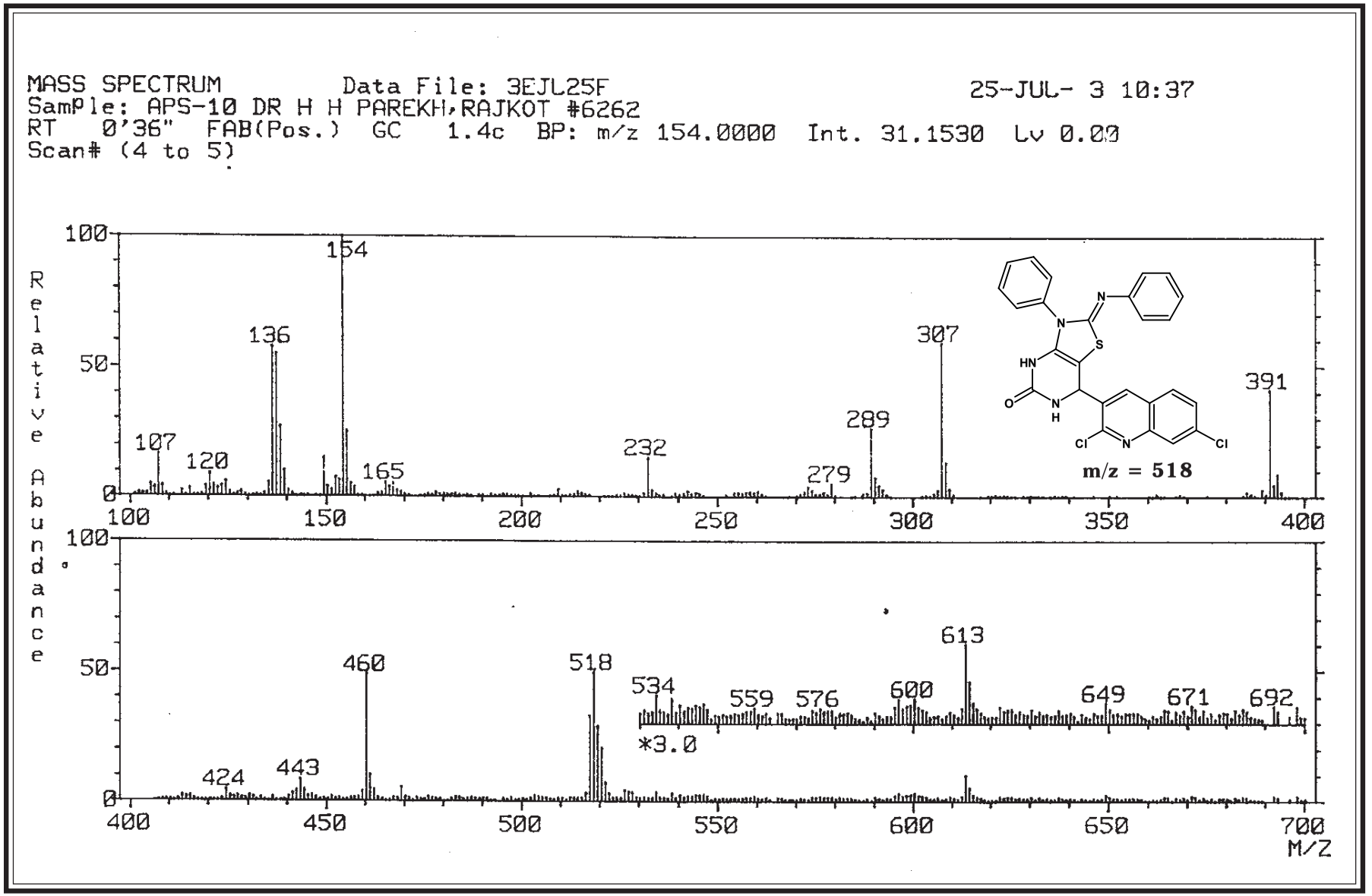
EXPANDED AROMATIC REGION



IR SPECTRAL DATA OF 7-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-ARYLIMINO-3N-ARYL THIAZOLIDINO [4,5,d]-PYRIMIDINE-4,5,6,7-TETRAHYDRO-5-ONES

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

Sr. No.	R	C=O str.
10a	C_6H_5	1687
10b	4-Cl-C_6H_4	1689
10c	3,4-$(Cl)_2$-C_6H_3	1690
10d	4-F-C_6H_4	1691
10e	2-OCH_3-C_6H_4	1689
10f	4-OCH_3-C_6H_4	1689
10g	2-CH_3-C_6H_4	1689
10h	3-CH_3-C_6H_4	1689
10i	4-CH_3-C_6H_4	1687
10j	2-NO_2-C_6H_4	1691
10k	3-NO_2-C_6H_4	1696
10l	4-NO_2-C_6H_4	1680


MASS SPECTRUM Data File: 3EJL25F 25-JUL- 3 10:37
Sample: APS-10 DR H H PAREKH,RAJKOT #6262
RT 0'36" FAB(Pos.) GC 1.4c BP: m/z 154.0000 Int. 31.1530 Lv 0.00
Scan# (4 to 5)
Relative Abundance
M/Z
m/z = 518
*3.0

EXPERIMENTAL

SYNTHESIS AND THERAPEUTIC EVALUATION OF 7-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-ARYLIMINO-3N-ARYLTHIAZOLIDINO [4,5-d]-PYRIMIDINE-4,5,6,7-TETRAHYDRO-5-ONES

[A] Synthesis of Bis-thiourea derivatives

See Part - VII, Section - I (A)

[B] Synthesis of 2-Arylimino-3-aryl-5H-4-thiozolidinones

See Part - VII, Section I (B)

[C] Synthesis of 7-(2',7'-Dichloroquinolin-3'-yl)-2-arylimino-3N-aryl thiazolidino [4,5 d]-pyrimidin-4,5,6,7-tetrahydro-5-ones

A mixture of 2-anisylimino-3-anisyl-5H-4-thiazolidinone (3.28g, 0.01mol), 2,7-dichloroquinolin-3-carboxaldehyde (2.26g, 0.01 mol) and urea (0.56g, 0.01 mol) in methanol was added a few drops of conc. HCl and heated under reflux for 4 hrs. The product isolated was filtered and crystallised from DMF. Yield 61%, m.p. 274°C Anal Calcd. for $C_{28}H_{21}N_5Cl_2O_3S$ required : C, 56.57%, H, 3.56%, N, 12.11%; found : C, 56.59%, H, 3.59% N, 12.44%.
TLC Solvent System : Acetone : Benzene (1.2 :8.8), Visulizing Agent : Iodine.

Similarly other pyrimidinones were prepared. The physical data along with infra red spectral data are reported in Table No. 8.

[D] Therapeutic evaluation of 7-(2',7'-Dichloroquinolin-3'-yl)-2-arylimino-3N-arylthiozolidino [4,5 d]-pyrimidin-4,5,6,7-tetrahydro-5-ones

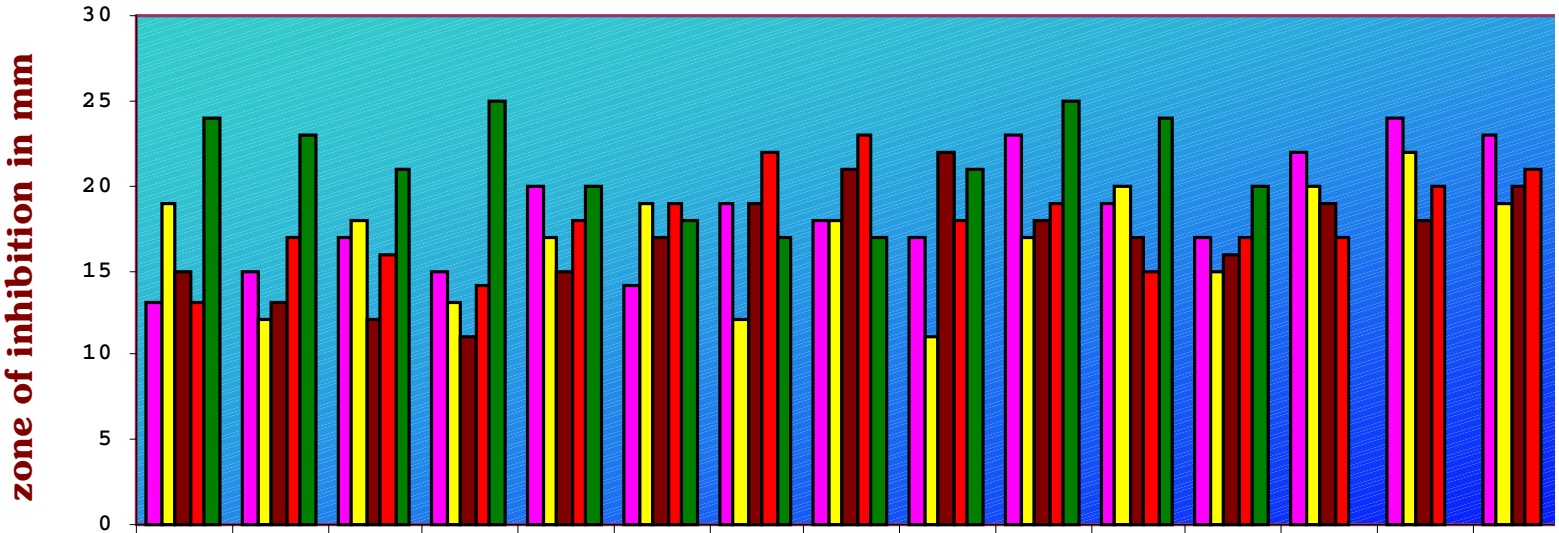
Antimicrobial testing was carried out as described in Part-I, Section-I (D). The zones of inhibition of the test solutions are recorded in Graphical Chart No. 10.

TABLE NO. 8 : PHYSICAL CONSTANTS OF 7-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-ARYLIMINO-3N-ARYL THIAZOLIDINO [4,5-d]-PYRIMIDINE-4,5,6,7-TETRAHYDRO-5-ONES

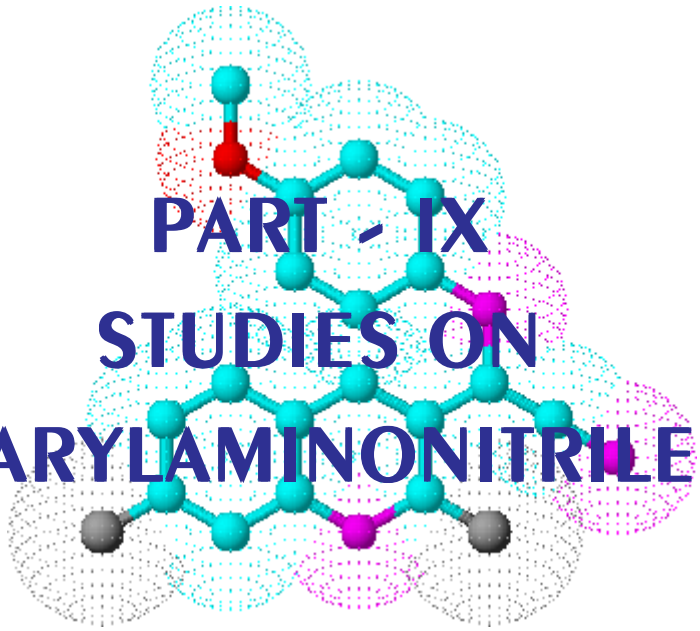
Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
10a	C_6H_5-	$C_{26}H_{17}N_5Cl_2OS$	318	176	0.540	68	13.51	13.80
10b	4-Cl-C_6H_4-	$C_{26}H_{15}N_5Cl_4OS$	587	208	0.629	60	11.92	11.63
10c	3,4-$(Cl)_2$-C_6H_3-	$C_{26}H_{13}N_5Cl_6OS$	656	240	0.551	63	10.67	10.87
10d	4-F-C_6H_4-	$C_{26}H_{15}N_5Cl_2F_2OS$	554	252	0.721	65	12.63	12.57
10e	2-OCH_3-C_6H_4-	$C_{28}H_{21}N_5Cl_2O_3S$	578	268	0.650	62	12.11	11.88
10f	4-OCH_3-C_6H_4-	$C_{28}H_{21}N_5Cl_2O_3S$	578	274	0.658	61	12.11	12.44
10g	2-CH_3-C_6H_4-	$C_{28}H_{21}N_5Cl_2OS$	546	256	0.545	60	12.82	12.53
10h	3-CH_3-C_6H_4-	$C_{28}H_{21}N_5Cl_2OS$	546	260	0.591	65	12.82	12.99
10i	4-CH_3-C_6H_4-	$C_{28}H_{21}N_5Cl_2OS$	546	262	0.623	69	12.82	12.67
10j	2-NO_2-C_6H_4-	$C_{26}H_{15}N_7Cl_2O_5S$	608	276	0.680	70	16.12	16.33
10k	3-NO_2-C_6H_4-	$C_{26}H_{15}N_7Cl_2O_5S$	608	284	0.730	76	16.12	16.49
10l	4-NO_2-C_6H_4-	$C_{26}H_{15}N_7Cl_2O_5S$	608	242	0.494	72	16.12	15.87

TLC Solvent System : Acetone : Benzene (1.2 : 8.8).

GRAPHICAL CHART NO. 10 : 7-(2',7'-DICHLOROQUINOLIN-3'-YL)-2-ARYLIMINO-3N-ARYL-THIAZOLIDINO[4,5-d] PYRIMIDINE-4,5,6,7-TETRAHYDRO-5-ONES



	10a	10b	10c	10d	10e	10f	10g	10h	10i	10j	10k	10l	Ampicillin	Amoxycillin	Norfloxacin
B.mega	13	15	17	15	20	14	19	18	17	23	19	17	22	24	23
s.aureus	19	12	18	13	17	19	12	18	11	17	20	15	20	22	19
E.coli	15	13	12	11	15	17	19	21	22	18	17	16	19	18	20
P.vulgaris	13	17	16	14	18	19	22	23	18	19	15	17	17	20	21
A.niger	24	23	21	25	20	18	17	17	21	25	24	20	0	0	0



PART - IX
STUDIES ON
α-ARYLAMINONITRILES

INTRODUCTION

The nitrile derivatives possess wide range of therapeutic activities such as antipyretic, analgesic, antiseptic, antimalarial, anticonvulsant and antimicrobial etc. The first synthesis of nitriles has been reported in 1832 by Wohler and Liebig[383,384] and in 1834 by Pelouce[385]. Because of their high toxicity, nitriles are much used in agricultural field. The nitriles are very useful intermediate for various products such as acrylonitrile for plastics, synthetic rubber, fibers and phthalonitriles for a dye stuff.

SYNTHETIC ASPECT

A numerous methods for the preparation of nitriles have been reviewed by David Mowry[386]. Some current methods are as under:

(i) From halides using NaCN, Al_2O_3[387]

(ii) From alkyl halides using KCN, tetraalkylammonium salt and water in trace[388]

(iii) Preparation of metathesis[389]

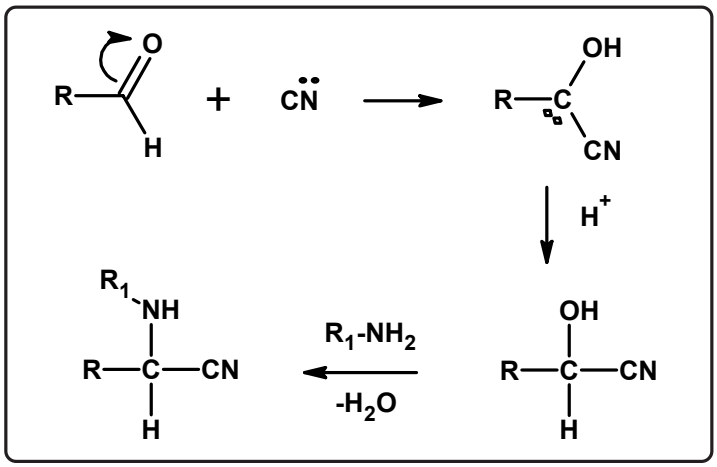
(iv) Dehydrating amides using $POCl_3$[390]

(v) The pyrolysis of Schiff's base[391]

(vi) A practical method for the preparation of nitriles from primary amines under microwave irradiation, has been reported[392-394]

MECHANISM

The mechanism of nitrile is shown as under.



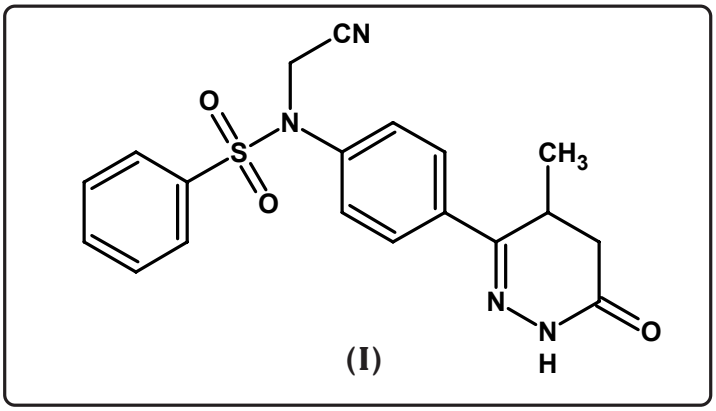
Reaction between $C\ddot{N}$ and aldehyde is a type of nucleophilic substitution reaction. From the above reaction, it can be seen that a nucleophile ($C\ddot{N}$) attacks on the carbonyl carbon of aldehyde and yields cyanohydrin which reacts with amine to yield nitrile derivatives.

THERAPEUTIC IMPORTANCE

Nitrile shows various biological activities such as

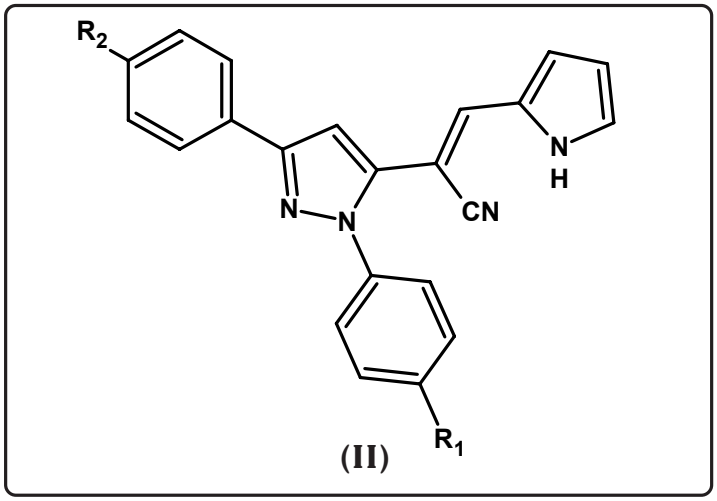
1. Herbicidal and Viricidal[395]
2. Central nervous stimulants[396]
3. Antihypotoxic[397]
4. Antiinflammatory[398]
5. Antihypertensive[399]
6. Fungicidal[400]
7. Antimicrobial[401]
8. Pesticidal[402]
9. Antiarrhythymic[403]

Nitriles with fused pyridine ring were reported as ulcer inhibitor[404]. The 3'-cyanophenyl alkanoamines were found to be sympathomimetic drugs[405] Cardenolide nitriles demonstrated moderate biological activity in rats (Cather Method)[406]. The benzylidene derivatives of maleic acid dinitriles showed 98% effectiveness against tetranychus urticase[407]. Sabani et al.[408] have reported nitriles as a refrigeration lubricating oil. Nobuyuki and co-workers[409] have described some new nitriles (I) as tumor necrosis factor(TNF) production inhibitors.



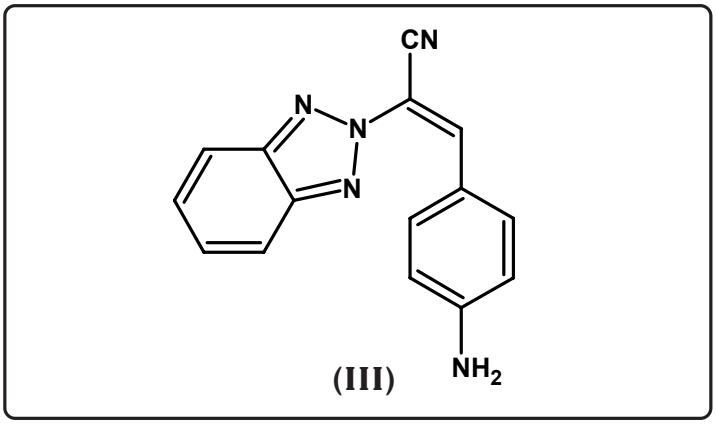
(I)

Kobayashi *et al.*[410] have synthesised new derivatives of nitrile. Peterson I. A. and co-workers[411] have studied antiapoptotic activity of some new amino nitriles. A series of nitriles (II) as novel antioxidants was synthesised by Parmar V. S. and co-workers[412].



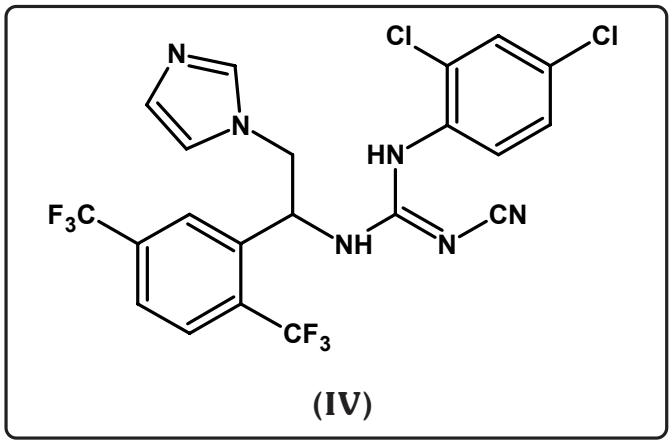
(II)

Parikh *et al.*[413] prepared acetonitrile derivatives and documented as bactericidal and fungicidal. Parlo S. and co-workers[414] prepared some new acrylonitrile derivatives (III) and tested their antitubercular activity.



(III)

Nosyruva *et al.*[415] have synthesised nitrile derivatives and tested their antimicrobial activity. Catherine M. and co-workers[416] synthesised some new iminonitriles and reported as thromboxane receptor antagonist. Cyanoguanidine derivative (IV) has been synthesised and reported as inhibitors of mitochondrial F, FO, ATPase by A. Karnails *et al.*[417]



(IV)

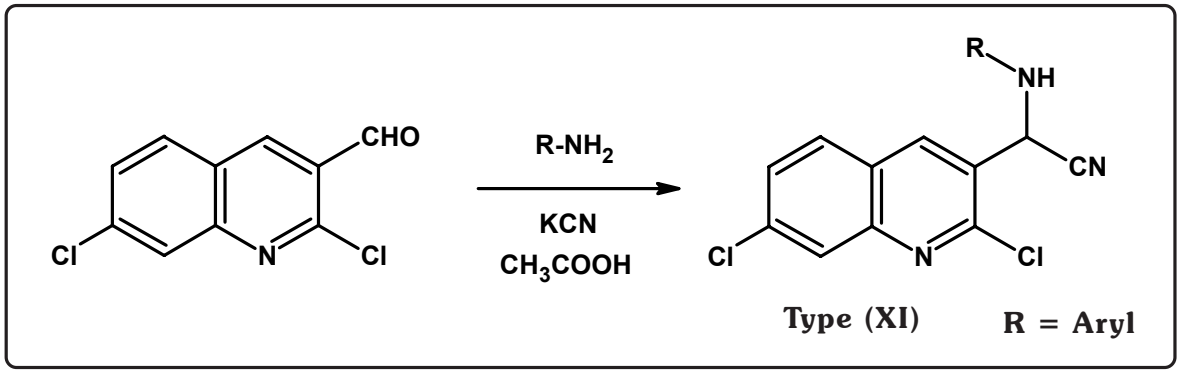
The synthesis of nitriles is of current interest owing to their enormous occurrence in biologically active derivatives. Hence, considerable attention has been focused on the study of pharmaceutically important nitriles bearing quinoline moiety as described below.

SECTION - I : SYNTHESIS AND THERAPEUTIC EVALUATION OF α-ARYLAMINO-α-2,7-DICHLOROQUINOLIN-3-YL-ACETONITRILES

SECTION - I

SYNTHESIS AND THERAPEUTIC EVALUATION OF α-ARYLAMINO-α-2,7-DICHLOROQUINOLIN-3-YL-ACETONITRILES

Nitrile derivatives have received considerable attention in recent years due to their wide spectrum of biological activities. Led by these considerations, we have designed some nitriles of type (XI). The technique applied to get the desired compounds involved the condensation of different amines with 2,7-dichloroquinolin-3-carboxaldehyde using KCN in presence of glacial acetic acid.

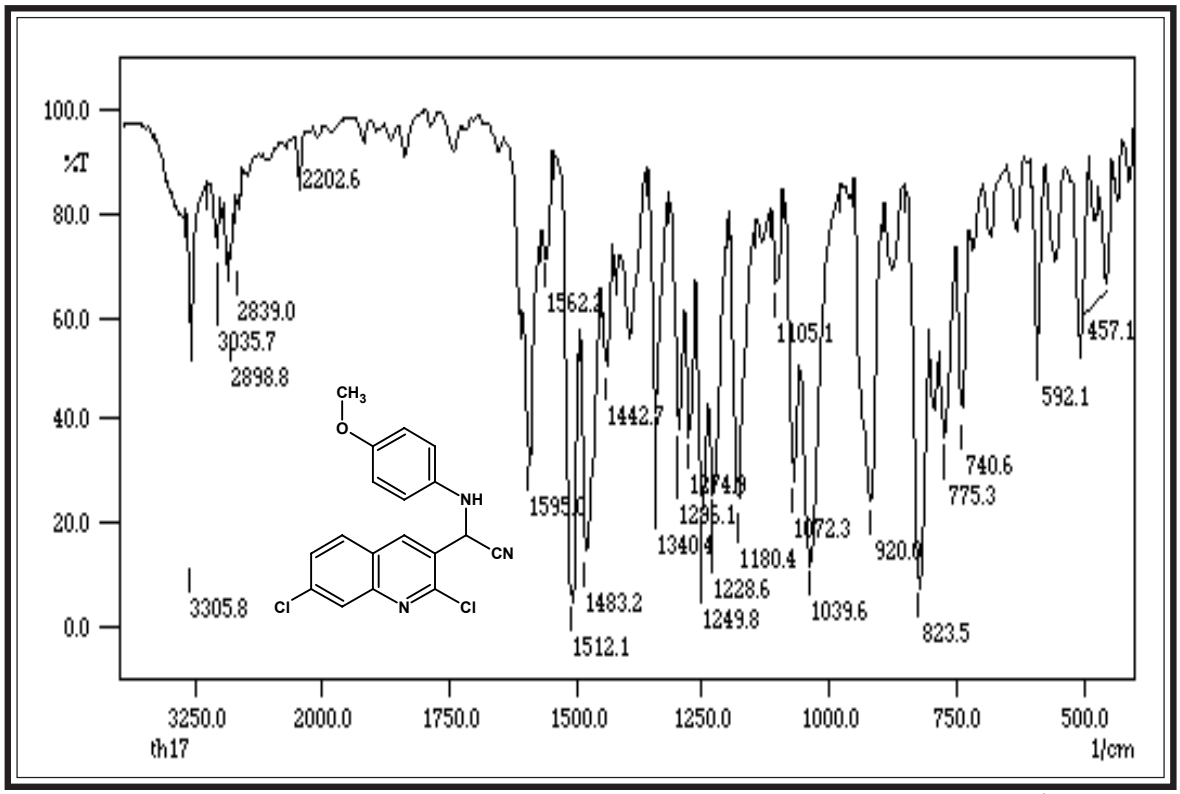


Type (XI) **R = Aryl**

The constitution of the synthesised products have been characterised using elemental analyses, infra red and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

The products have been screened for their ***in vitro*** biological assay like antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg. The biological activities of the synthesised compounds have been compared with standard drugs. The details have been cited in Part-I, Section-I (D).

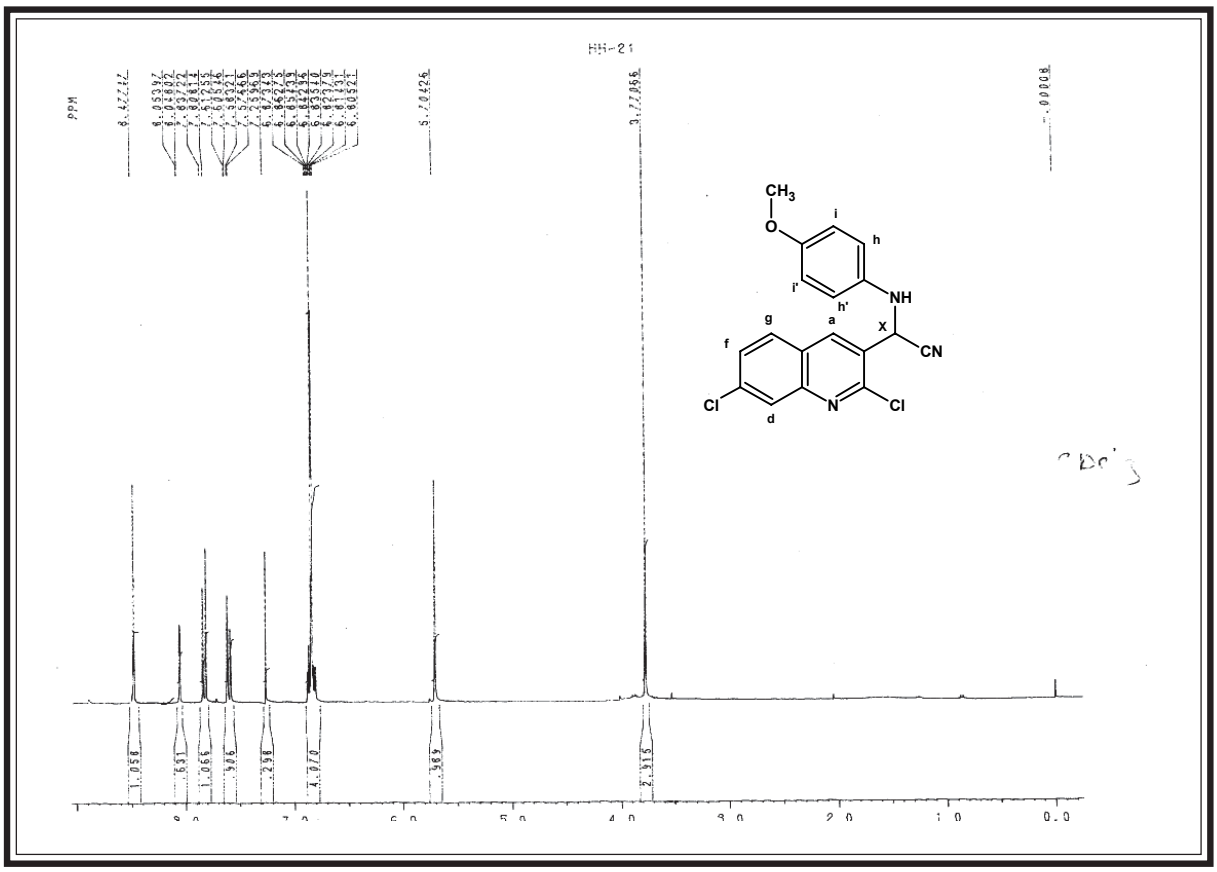
IR SPECTRAL STUDY OF α-p-ANISYLAMINO-α-2'-7'-DICHLOROQUINOLIN-3-YL-ACETONITRILE



Instrument : SHIMADZU-FT-IR 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	2975-2950	419
$-CH_3$	C – H str. (sym)	2880	2880-2850	"
	C – H def. (asym)	1442	1475-1450	"
	C – H def. (sym)	1340	1385-1370	"
Aromatic	C– H str.	3010	3080-3030	"
	C = C str.	1562	1585-1570	"
	C – H.i.p. def.	1105	1125-1090	420
	.	1072	1070-1000	"
	C – H. o.o.p def.	823	835-810	"
	N – H str.	3305	3400-3200	"
Quinoline	C = N str.	1595	1612-1593	419
moiety	C – Cl str.	740	750-700	"
Nitrile	C ≡ N str.	2202	2260-2200	421
Ether	C – O – C str.	1228	1275-1200	"

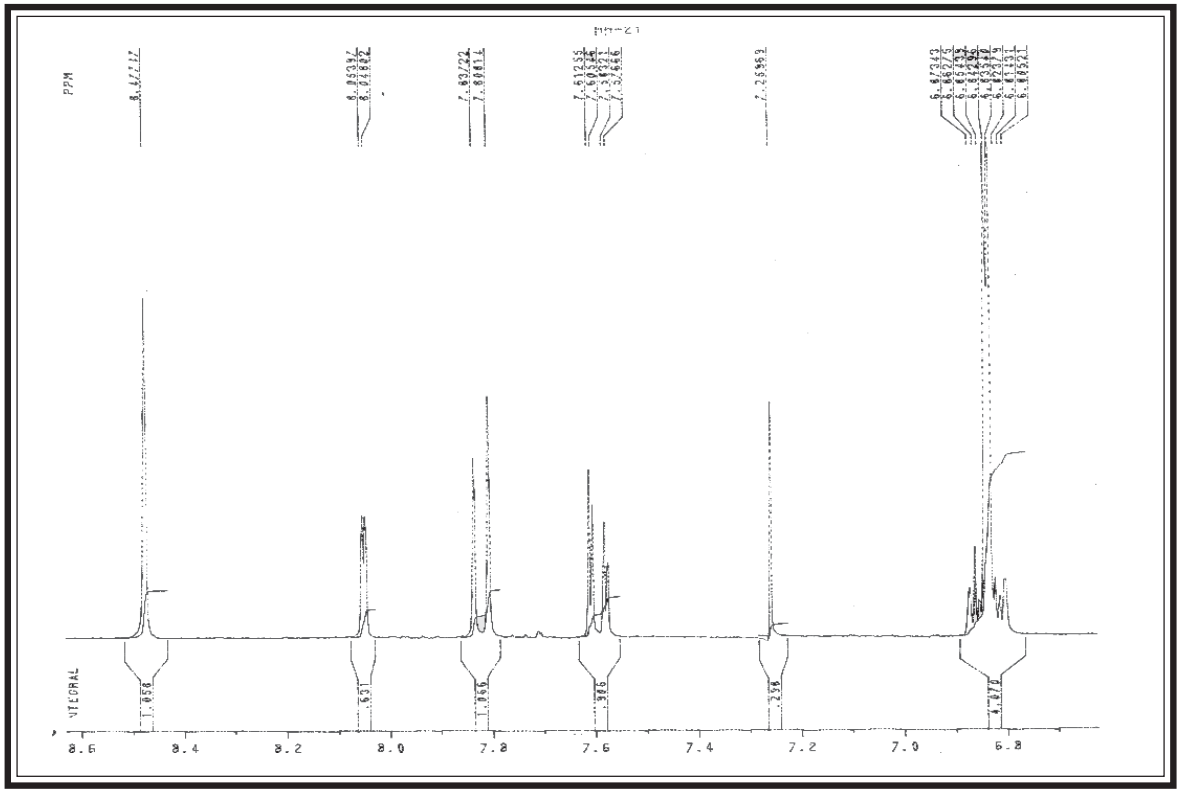
PMR SPECTRAL STUDY OF α-p-ANISYLAMINO-α-2,7-DICHLOROQUINOLIN-3-YL-ACETONITRILE



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

Signal No.	Signal Position (δ ppm)	Relative No. of Protons	Multiplicity	J. Value in Hz		Inference
1.	3.77	3H	singlet	-		Ar-OCH_3
2.	5.70	1H	singlet	-		-CHX
3.	6.81-6.87	4H	multiplate	-		Ar-H h,h',i,i'
4.	7.58-7.61	1H	double doublet	Jfg	8.64	Ar-Hf
				Jfd	1.97	
5.	7.81-7.84	1H	doublet	Jgf	8.72	Ar-Hg
6.	8.48-7.54	1H	doublet	Jdf	1.79	Ar-Hd
7.	8.48	1H	singlet	-		Ar-Ha

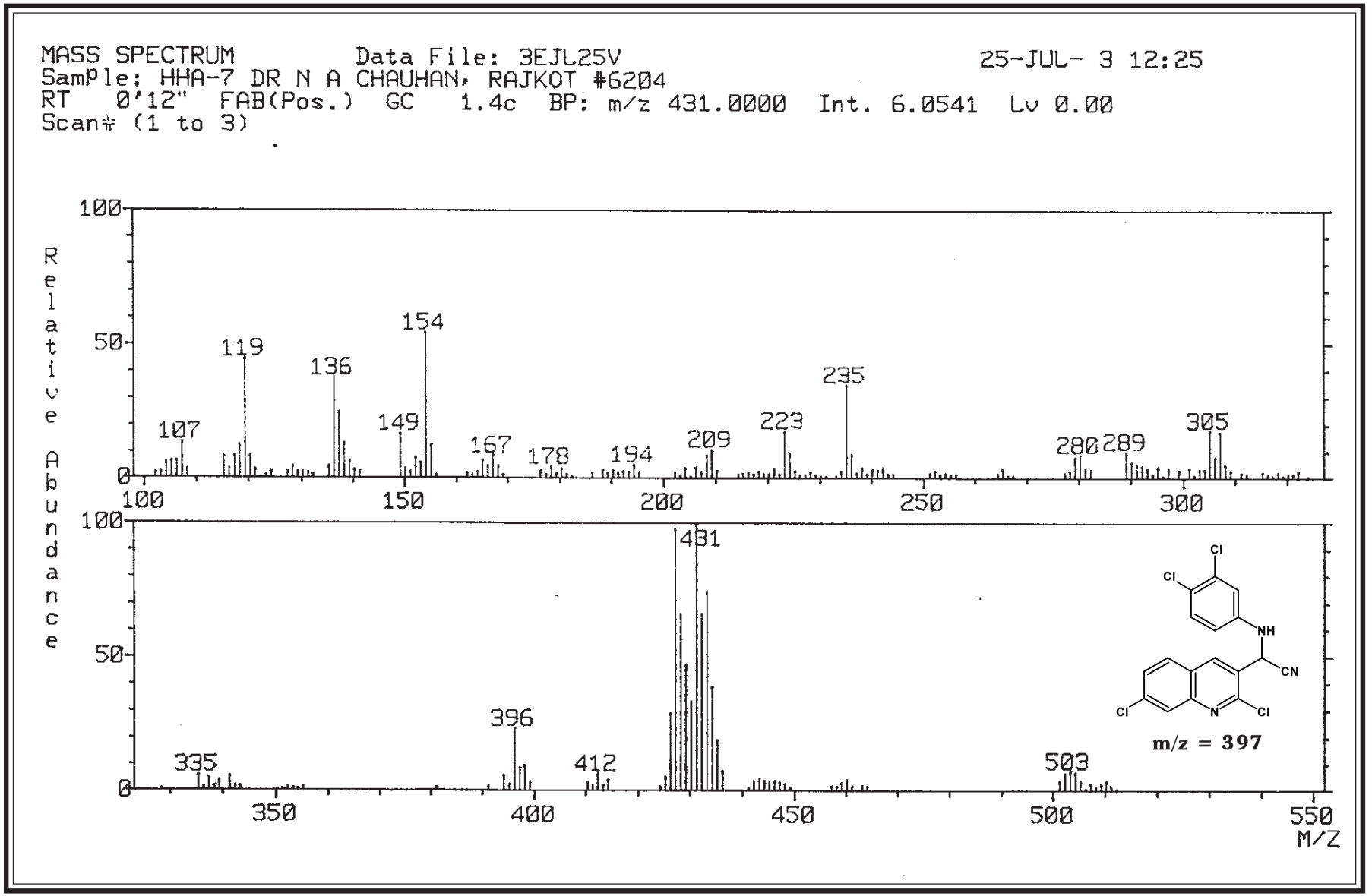
EXPANDED AROMATIC REGION



IR SPECTRAL DATA OF α-ARYLAMINO-α-2,7-DICHLOROQUINOLIN-3-YL-ACETONITRILES

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

Sr. No.	R	C≡N str.
11a	C_6H_5	2198
11b	2-Cl-C_6H_4	2196
11c	3-Cl-C_6H_4	2200
11d	4-Cl-C_6H_4	2002
11e	2,6-$(Cl)_2$-C_6H_3	2202
11f	3,4-$(Cl)_2$-C_6H_3	2210
11g	3-Cl,4-F-C_6H_4	2203
11h	4-F-C_6H_4	2200
11i	2-OCH_3-C_6H_4	2202
11j	4-OCH_3-C_6H_4	2202
11k	2-CH_3-C_6H_4	2202
11l	4-CH_3-C_6H_4	2200
11m	2-NO_2-C_6H_4	2201
11n	3-NO_2-C_6H_4	2200
11o	4-NO_2-C_6H_4	2200


MASS SPECTRUM Data File: 3EJL25V 25-JUL- 3 12:25
Sample: HHA-7 DR N A CHAUHAN, RAJKOT #6204
RT 0'12" FAB(Pos.) GC 1.4c BP: m/z 431.0000 Int. 6.0541 Lv 0.00
Scan# (1 to 3)
Relative Abundance
M/Z
m/z = 397

EXPERIMENTAL

SYNTHESIS AND THERAPEUTIC EVALUATION OF α-ARYLAMINO-α-2,7-DICHLOROQUINOLIN-3-YL-ACETONITRILES

[A] Synthesis of 2,7-Dichloroquinolin-3-carboxaldehydes

See, Part - I, Section - I (B).

[B] Synthesis of α-Arylamino-α-2,7-dichloroquinolin-3-yl-acetonitriles

2,7-Dichloroquinolin-3-carboxaldehyde (2.26 g, 0.01 mol) dissolved in ethanol (10 ml) was added to potassium cyanide (6.4 g, 0.1 mol) dissolved in water (8 ml.) followed by glacial acetic acid (12 ml). The contents were then stirred for 5 mins. to form aldehyde cyanohydrine and kept at 0°C. ρ-Anisidine (1.23 g, 0.01 mol) in ethanol (10 ml) was added to the reaction mixture, contents were kept at room temperature for 24 hrs. and poured into ice. The resulting solid was crystallised from ethanol. Yield 50%, m.p. 126°C. Anal Calcd. for $C_{18}H_{13}N_3Cl_2O$ required : C, 60.35%; H, 3.66%; N, 11.73%; found : C, 60.38%; H, 3.63%; N, 11.71%.

TLC Solvent system : Acetone : Benzene (2.8 : 7.2), Visulizing Agent : Iodine.

Similarly other **α**-arylamino-**α**-2,7-dichloroquinolin-3-yl-acetonitriles were prepared. The physical data along with infra red spectral data are reported in Table No. 9.

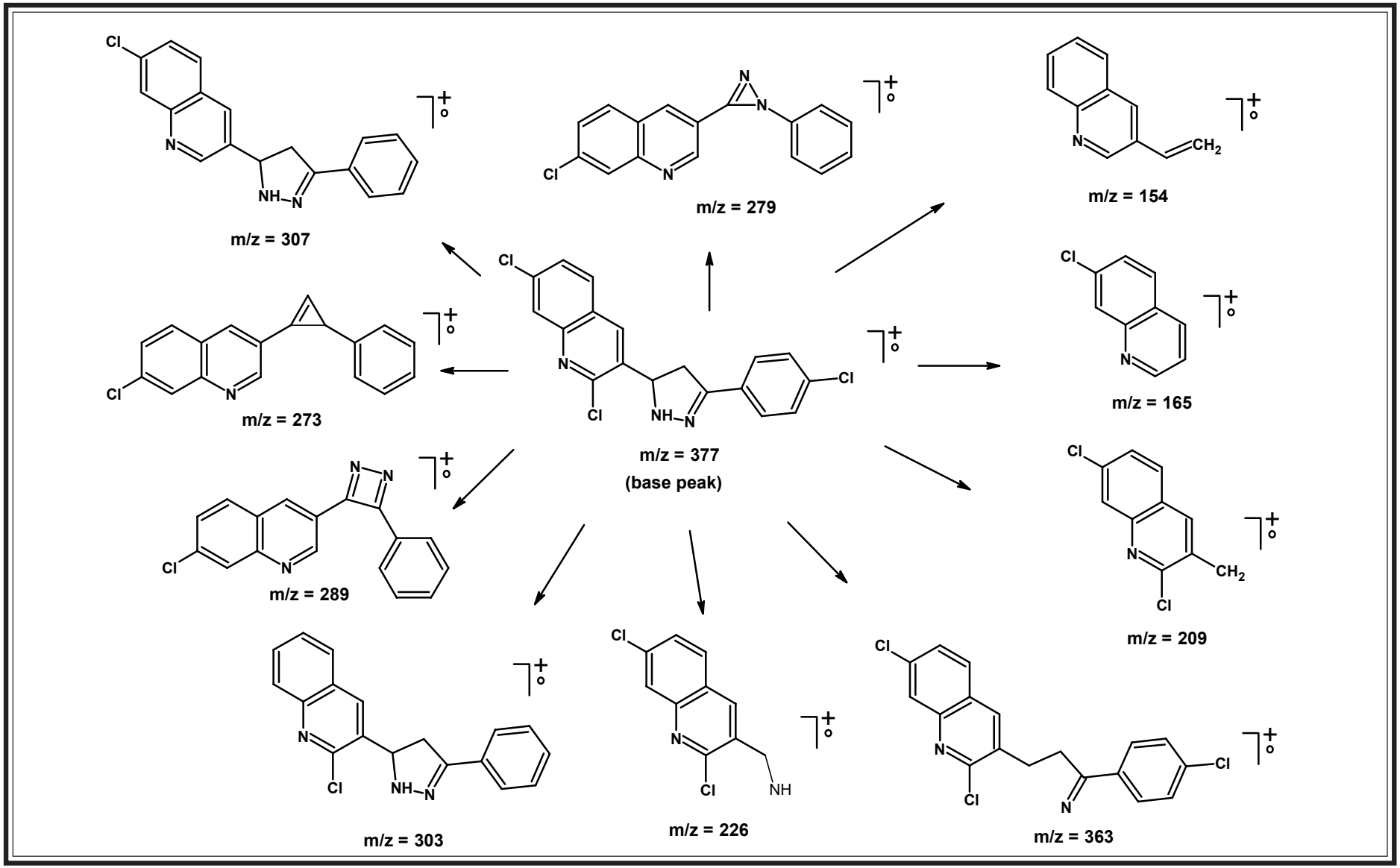
[C] Therapeutic evaluation of α-Arylamino-α-2,7-dichloroquinolin-3-yl-acetonitriles

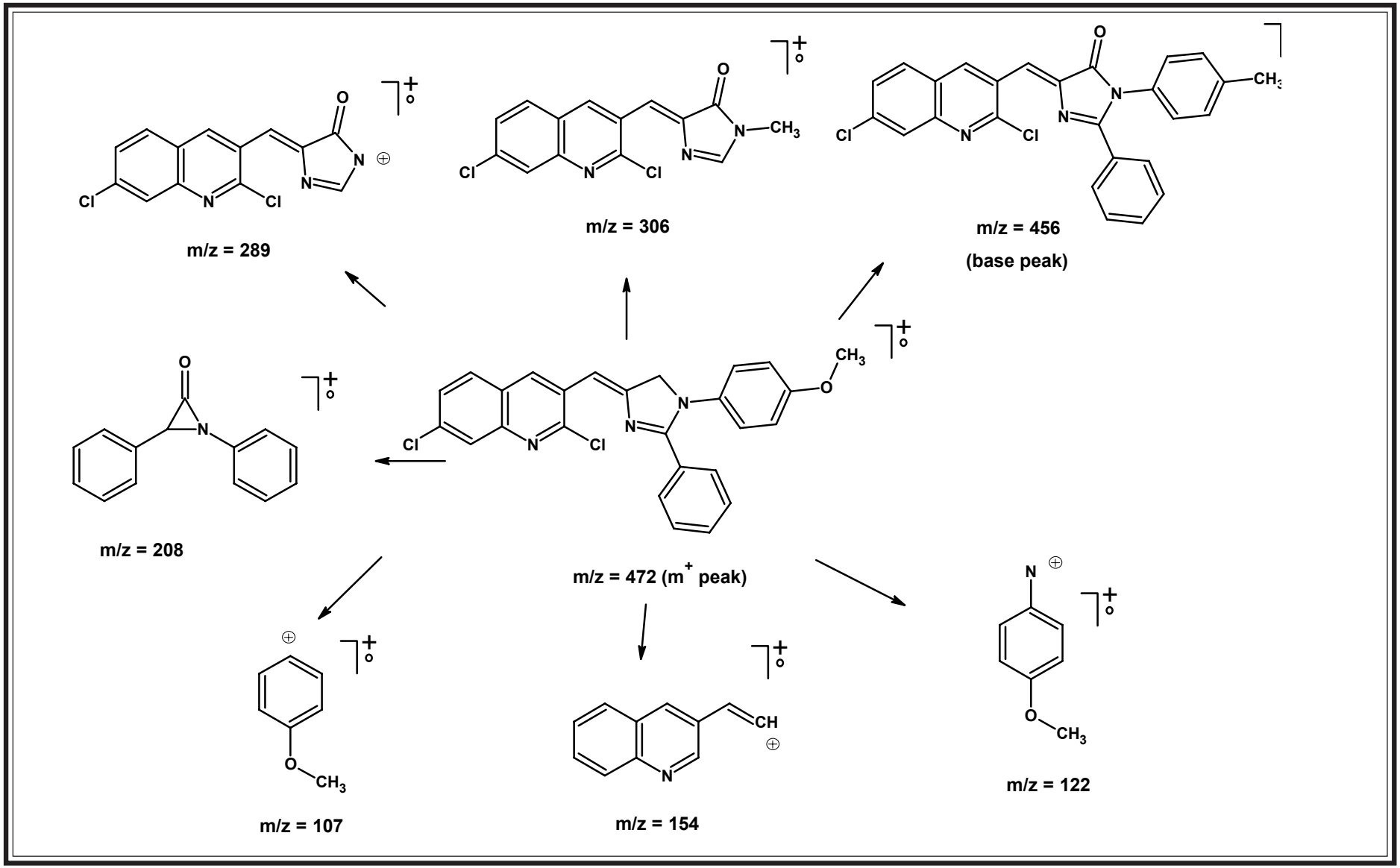
Antimicrobial testing was carried out as described in Part - I, Section - I (D). The zones of inhibition of the test solutions are recorded in Graphical Chart No. 11.

TABLE NO. 9 : PHYSICAL CONSTANTS OF α-ARYLAMINO-α-2,7-DICHLOROQUINOLIN-3-YL-ACETONITRILES

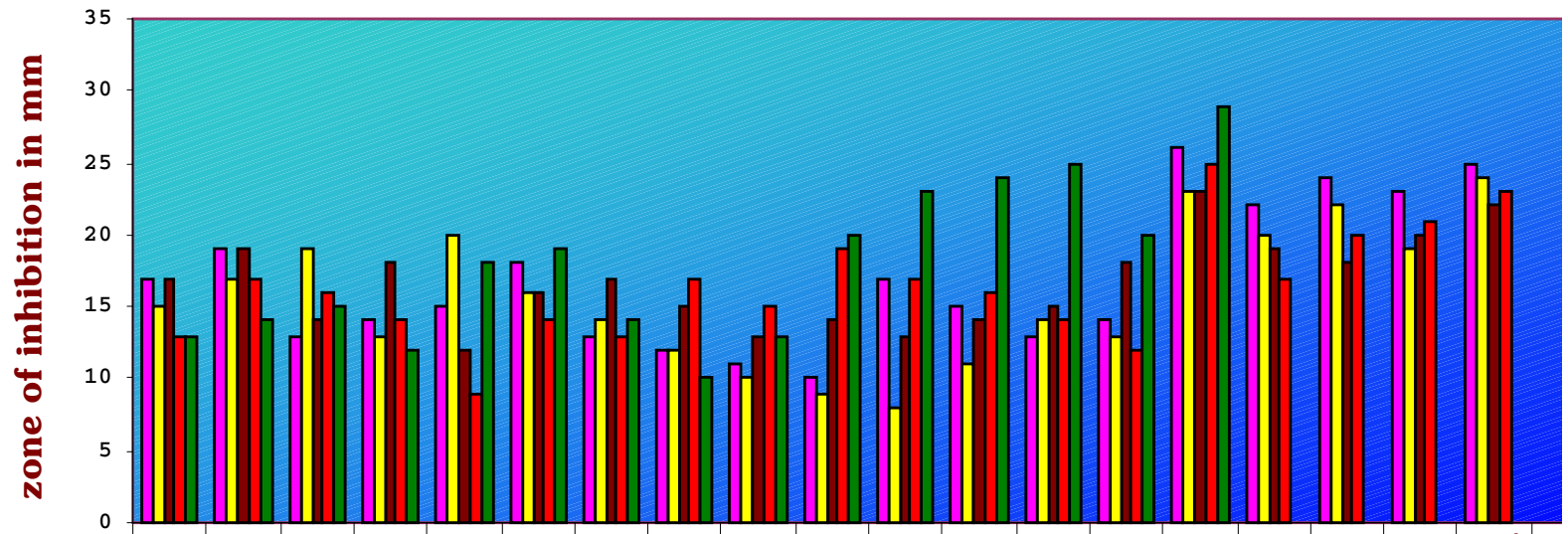
Sr. No. 1	R 2	Molecular Formula 3	Molecular Weight 4	M.P. °C 5	Rf Value 6	Yield % 7	% of Nitrogen Calcd. 8	% of Nitrogen Found 9
12a	C_6H_5-	$C_{17}H_{11}N_3Cl_2$	328	110	0.562	58	12.28	12.50
12b	2-Cl-C_6H_4-	$C_{17}H_{10}N_3Cl_3$	362.5	162	0.489	64	11.59	11.75
12c	3-Cl-C_6H_4-	$C_{17}H_{10}N_3Cl_3$	362.5	120	0.595	63	11.59	11.33
12d	4-Cl-C_6H_4-	$C_{17}H_{10}N_3Cl_3$	362.5	176	0.632	61	11.59	11.40
12e	2,6-$(Cl)_2$-C_6H_3-	$C_{17}H_9N_3Cl_4$	397	138	0.658	66	10.58	10.77
12f	3,4-$(Cl)_2$-C_6H_3-	$C_{17}H_9N_3Cl_4$	397	140	0.767	72	10.58	10.82
12g	3-Cl,4-F-C_6H_3-	$C_{17}H_9N_3Cl_3F$	379.5	118	0.684	79	11.07	11.23
12h	4-F-C_6H_4-	$C_{17}H_{10}N_3Cl_2F$	346	162	0.639	57	12.14	12.45
12i	2-OCH_3-C_6H_4-	$C_{18}H_{13}N_3Cl_2O$	358	152	0.527	55	11.73	11.98
12j	4-OCH_3-C_6H_4-	$C_{18}H_{13}N_3Cl_2O$	358	126	0.510	50	11.73	11.51
12k	2-CH_3-C_6H_4-	$C_{18}H_{13}N_3Cl_2$	342	162	0.687	45	12.28	12.49
12l	4-CH_3-C_6H_4-	$C_{18}H_{13}N_3Cl_2$	342	160	0.676	43	12.28	12.53
12m	2-NO_2-C_6H_4-	$C_{17}H_{10}N_4Cl_2O_2$	373	142	0.662	58	15.01	15.24
12n	3-NO_2-C_6H_4-	$C_{17}H_{10}N_4Cl_2O_2$	373	140	0.537	59	15.01	14.68
12o	4-NO_2-C_6H_4-	$C_{17}H_{10}N_4Cl_2O_2$	373	158	0.428	64	15.01	14.79

TLC Solvent System : Acetone : Benzene (2.8 : 7.2).


m/z = 307
m/z = 279
m/z = 154
m/z = 273
m/z = 165
m/z = 377
(base peak)
m/z = 289
m/z = 209
m/z = 303
m/z = 226
m/z = 363


m/z = 289
m/z = 306
m/z = 456
(base peak)
m/z = 208
m/z = 472 (m+ peak)
m/z = 107
m/z = 154
m/z = 122

GRAPHICAL CHART NO. 11 : α-ARYLAMINO-α-2,7-DICHLOROQUINOLIN-3-YL-ACETONITRILES



	11a	11b	11c	11d	11e	11f	11g	11h	11i	11j	11k	11l	11m	11n	11o	Ampicillin	Amoxycillin	Norfloxacin	Penicillin	G se u
B.mega	17	19	13	14	15	18	13	12	11	10	17	15	13	14	26	22	24	23	25	
s.aureus	15	17	19	13	20	16	14	12	10	9	8	11	14	13	23	20	22	19	24	
E.coli	17	19	14	18	12	16	17	15	13	14	13	14	15	18	23	19	18	20	22	
P.vulgaris	13	17	16	14	9	14	13	17	15	19	17	16	14	12	25	17	20	21	23	
A.niger	13	14	15	12	18	19	14	10	13	20	23	24	25	20	29	0	0	0	0	2

REFERENCES

1. R. H. Manske;
Chem Review, **30,** 113 (1942).
2. F. W. Bergstrom;
Chem Review, **35,** 150 (1944).
3. J. A. Moore and E. C. Capaldi;
J. Org. Chem., **29,** 2860 (1964).
4. T. Kametani, K. Nyu and T. Yamanaku;
Chem Pharma Bull., **19,** 1321 (1971).
5. C. K. Bradsher and T. G. Wallis;
J. Org. Chem., **43,** 3817, (1978).
6. M. Lancaster and D. J. H. Smith;
J. Chem., Soc. Chem. Commun., **43,** 3817 (1980).
7. O. Meth- Cohn, B. Narine and B. Taronwski;
J. Chem., Soc., Perkin Trans, **1,** 1520 (1981).
8. Kreft Anthony Frank, Keep Kenneth Lewis, Musser John Henry, Pattison Thomas Woolford, Bicksler, James Jacob;
Brit. UK Pat. Appl., GB, **2,** 181, 135; *Chem Abstr.,* **107,** 96605c (1987).
9. El- Sayed Ola A., El-Semary Mona, Kehalil Mounira;
Alexandria J. Pharma Sci., **10(1),** 43-46 (1996); *Chem. Abstr.,* **125,** 33571q (1996).
10. Gupta Rajiv, Gupta Avinash K., Pauli Satya, Kachroo P. L.;
Indian J. Chem., **37(B),** 1211-1213 (1998).
11. Amir Mohd., Agrawal Rajesh;
Indian J. Heterocycl Chem., **7(3),** 225-228 (1998).
12. Griesgraber Gerorge W., Heppner Phillip D., Manske Karl J., Mickelson John W., Rice Michel J.;
PCT Inst. Appl. WO **02** 46, 193 (Cl. CO7D 471104), (2002); *Chem Abstr.,* **137,** 33299e (2002).
13. Anchibald John, Leheup Ward, Terence James;
Brit. UK Pat. Appl. GB **2,** 182, 935; *Chem. Abstr.,* **107,** 198110e (1987).
14. Takagaki Hidetsugu, Yamaguchi Shinobu, Abe Masayoshi, Sakai Mitsuru, Misumi Osomu;
Eur Pat Appl. EP **927,** 718 (Cl. CO7D 215/38) (1997); *Chem. Abstr.,* **131,** 73569a (1999).
15. Takagaki Hidetsugu, Nakanishi Shigenori, Kimura Nobuyuki, Yomaguchi Shinobu, Akoi Yasuo;
Eur. Pat. Appl. EP. **933,** 378 (Cl. C07H 17/02) (1999); *Chem. Abstr.,* **131,** 116454d (1999).
16. Skrzypek L., Folwarczna J., Janiec W., Kacrmarczyksedlak I., Masalankiewicz A., Pyllikm.;
Pol. J. Chem., **72(6),** 1127-30 (1998); *Chem. Abstr.,* **129,** 108974s (1998).
17. Afonso Adrian, Kelly Joseph M., Chuckalamannil Samvel;
U. S. US **5,** 306, 236 (Cl. A61K 31/435) (1996); *Chem. Abstr.,* **125,** (1996).
18. Tucker John Alan, Vaillancout Valerie A, Strohbach Joseph Walter, Romines Kaen Rene, Schnute Marke., Cuddhy Michele M., Thlisrivongs Suvit, Turner Steven R.;
PCT Int. Appl. Wo **99** 32, 450, (Cl. C07D 215/56) (1998); *Chem. Abstr.,* **131,** 73568z (1999).
19. Lee Kuo-Hsiung, Kuo Sheng-Chu, Wu, Tian-Shung, Wang Hvi- Kang, Li Leping;
PCT Int Appl WO **96** 10, 563 (Cl. CO7D 215/38) (1996); *Chem. Abstr.,* **125,** 114507a (1996).
20. El- Hamovly W. S.;
Egypt J. Chem., **38(4),** 393-402 (1995); *Chem. Abstr.,* **125,** 142520t (1996).

21. Uchida Minoru, Komatsu makoto, Morita Seiji, Nakagawa Kazuyuki;
Chem. Abstr., **104,** 88454a (1986).

22. Simiand, Jacques, Boigegrain, Robert Keane, Peter, Eugene, Verniers, Jean Claude;
Fr Demande FR **2** 593, 811 (Cl. CO7D 215/56); *Chem. Abstr.,* **108,** 94413k (1988).

23. Mehrotra Suman, Barthwl J. P., Gupta T. K., Bhargava K. P.;
Indian J. Physiol Pharmacol., **26(3),** 253-257 (1982); *Chem. Abstr.,* **98,** 143248w (1983).

24. Clemence Francoise, Fortine michel, Le Martret Odile, Delevallee Francoise;
Fr, Demande FR **2** S92, 879 (Cl CO7D 401/09); *Chem. Abstr.,* **109,** 22848d (1989).

25. Kim Dae Young, Jung Inchang, Lee Jae Wook, Yoon, Geal Jang;
J. Karean Chem. Soc., **42(1),** 102-104 (1998); *Chem. Abstr.,* **128,** 230273g (1998).

26. Al-Maosudi, Najim A., Al-Sound Yaseon A., Ehrmann Michel, De dercq;
Eric. Nucleosides Nucleotides, **17(12),** 2255-2266 (1998); *Chem. Abstr.,* **130,** 110531; (1999).

27. Kamel M. M., Omar M. T., Kassem E. M. M., Khalifa N. M.;
Egypt J. Phrm. Sci., **38(13),** 61-69 (1997); *Chem. Abstr.,* **130,** 81382d (1999).

28. Renault Christian, Mestremichel;
Cur. Pat. Appl. Ep. **155,** 888 (Cl. CO7D 401/06); *Chem. Abstr.,* **104,** 6875a (19860.

29. Desai Pratibha, Patel Dinesh, Naik Jiten, Kesai C. M.;
Asian J. Chem., **10(2),** 370-372 (1998); *Chem. Abstr.,* **128,** 243930u (1998).

30. Desai P. K. Desai Pratibha, Machhi Dilip, Desai C. M., Patel Dinesh;
Indian J. Chem., **35(B),** 871-73 (1996).

31. Heckel Armin, Soyka Rainer, Grell Wolygang, Hgaksma Eric, Binder Klaus, Zimmermann Rainer;
Ger. Offen De **19** 727, 117 (Cl. CO7D 215/12) (1999); *Chem. Abstr.,* **130,** 110166u (1999).

32. Hsich Ming-Chieh, Huang Li-Jiau, Wu Tian-Shung, Lee Kuo-Hsing, Teng Cheming, Kuo Sheng-Chu;
Chin Pharm J., **50(5),** 277-288 (1998); *Chem. Abstr.,* **130,** 182429e (1999).

33. Wang Tai-Chi, Chen Yeh-Long, Tzeng Cherng-Chyi, Liou Shorong-Shii, Chang Ya-Ling, Teng Che-Ming;
Heiv Chem Acta., **79(6),** 1620-1626 (1996); *Chem. Abstr.,* **125,** 275458a (1996).

34. Wang Tai-Chi, Chen Yeh-Long, Tzeng Cherng-Chyi, Liou Shorong-Shii, Tzeng Weng-Ferg, Chang ya-Ling, Teng Che-Ming;
Helv Chem Acta., **81(6),** 1038-1047 (1998); *Chem. Abstr.,* **129,** 136085w (1998).

35. Talesara G. L. Suresh K. S.;
Asian J. Chem., **9(4),** 635-639 (1997); *Chem. Abstr.,* **128,** 188768b (1998).

36. Ukrainets I. V., taran S. G., Gorokhova O. V., Marusenko N. A., Turov A. V.;
Chem Heterocycl Compd., **33(5),** 600-604 (1997); *Chem. Abstr.,* **128,** 102030p (1998).

37. Oku Teruo, Kayakiri Hiroshi, Satoh Shigexi, Abe Yashito, Sawada Yuki, Inove Takayuki, Tanaka Hirokazv;
PCT Int. Appl. WO **96,** 13, 13, 485 (Cl. CO7D215/16) (1996); *Chem. Abstr.,* **125,** 142578t (1996).

38. Desai P. K., Desia Pratibha, Machhi Dilip, Desai, C. M., Patel Dinesh;
Indian J. Chem., **35(B),** 871-73 (1996).

39. Balasubramanian C., Sekar M., Mohan P. S.;
Indian J. Cehm., **35(B),** 1125-1227 (1996).

40. Kawashima Seiichiro, terada, Sumio, Saito Ken-ichi, Suzuki Toshiaki, Sasahara Hiroya, Kanda, Toshihisa, Inoue Tsuneo;
PCT Int. Appl. WO **98** 04,529 (Cl. CO7D 215/36) (1998); *Chem. Abstr.,* **128,** 167860r (1998).

41. Dyke Hazal Joan, Montana Johan Gary;
PCT Int. Appl. WO **97** 44,322 (Cl. CO7D 215/36) (1998); *Chem. Abstr.,* **128,** 48150n (1999).

42. Cupps Thomas Lee, Bogdan Sophie E., Henry Raymond T., Shldon Russell James;
U.S. US **5,** 916, 900 (Cl. 514-312; A61K31/47) (1995); *Chem. Abstr.,* **131,** 58765t (1999).

43. Klein Elbiot S., Johnson Alan T., Standeven Andrew M., Beard Richard L., Gillet Samuel J., Duong Tien T., Nagpal Sunil, Vuligonda Vidyasagar, teng Min, Chandraratna Roshantha A.;
PCT Int. Appl. WO **99** 33, 821 (Cl. CO7D 355/06) (1997); *Chem. Abstr.,* **131,** 87727n (1999).

44. Cheon Seung Hoon, Lee Joon Yeol, Chung Byung-Ho, Chol Bo-Gil, Cho Won-Jea, Kim Tae-Sung;
Arch Pharmacal Res., **22(2),** 179-83 (1999); *Chem. Abstr.,* **131,** 102424g (1999).

45. Hiessboeck Romana, Wolf Christian, Richter Elisabeth, Hitzler Manuela, Chiba Peter, Kratzel Martin, Ecker Gerhard;
J. Med. Chem., **42(11),** 1921-26 (1999); *Chem. Abstr.,* **131,** 87799n (1999).

46. SadaYoshida, Adegawa, Shigeru Mogi Kinichi Honda Haruyoshi Eto Hiromichi, Morimoto Shinichi, Okawa janiji, Umehara Norimitsu, Sato Susumu;
Eur. Pat Appl. EP. **900,** 789 (Cl. CO7D 215/44) (1999); *Chem. Abstr.,* **130,** 196582m (1999).

47. Sarvanan J.m Murthy S. Narsimha, Manjunath K. S.;
Indian Drugs, **36(3),** 192-195 (1999); *Chem. Abstr.,* **131,** 228632s (1999).

48. Myeller Gliemann Matthias, Anger bauer Rolf, Brandes Arndt, Loeyers, Michael, Schmeck Corsten, Schmidt Delf;
Gen. Offen DE **19,** 709, 125 (Cl. CO7D 215/20) (1998); *Chem. Abstr.,* **129,** 230650y (1998).

49. Raynes Kaylene J., Stocks Paul A., O'Neill Paul M., Park B. Kevin, Ward Stephen A.;
J. Med Chem., **42(15),** 2747-2751 (1999); *Chem. Abstr.,* **131,** 1848534h (1999).

50. Belliotti Thomas Richard, Blankley Clifton John, Kesten Suzanne Ross, Wise Lawrence David, Wustrow David Juergen;
U.S. US **5,** 945, 421 (1999); *Chem. Abstr.,* **131,** 199708r (1999);

51. Shen Ai-Yu, Wu Sheng-Nani, Chiv Chin-Tsao;
J. Pharm. Pharmacol., **51(5),** 543-548 (1999); *Chem. Abstr.,* **131,** 271795j (1999).

52. Xue Chu-Biao, Decicco Carl P., He Xiaohua;
PCT Int. Appl. WO **02** 55, 491 (Cl. CO7D) (2002); *Chem. Abstr.,* **137,** 93692n (2002).

53. Guo Qingchun, Yang Yuan, Wang Jiaming, Lin Fotain, Zhang Zhiping;
Faming Zhuanli Shenquing Gongkai Shuomingshu CN **1,** 306, 001 (Cl. CO7D 405/06) (2001); *Chem. Abstr.,* **137,** 154944v (2002).

54. Shimizu Sadahira, Makino Toru, Kino Toshiaki, Nagasawa Hiroshi, Ota Naoki, Akiba Toshifumi;
Jpn Kokiai Tokkyo Koho Jp 201, 191 (Cl. CO7D 401/04) (2002); *Chem. Abstr.,* **137,** 93736e (2002).

55. Wackernagel, Michael;
PCT Int. Appl. WO **02** 46, 163 (Cl. CO7D 215/22) (2002); *Chem. Abstr.,* **137,** 33225c (2002).

56. Machhi Jigna, Patel Dinesh, Desai C. M., Desai Pratibha, joshi H. D.,
J. Insti. Of Chem., **73(4),** 140-42 (2001); *Chem. Abstr.,* **137,** 63219w (2002).

57. Crooks Stephen L., Griesgraber George W., heppner PhilipD., Merrill Bryon A.;
PCT Int. Appl. WO **02 46,** 188 (Cl. CO7D 47/04) (2002); *Chem. Abstr.,* **137,** 33295a (2002).

58. Michaela jansen, Gerd Dannhardt;
Eur. J. Med Chem., **38,** 661-70 (2003).

59. Suchetak and Rao B.;
Heterocycl Commun., **8(6),** 569-572 (2002); *Chem. Abstr.,* **139,** 22197k (2003).

60. Best Desmond John, Bruton Gordong, Orlek Barry Sidneyl
PCT Int. Appl. WO 03 45, **922** (Cl. CO7D 215/12) (2003); *Chem. Abstr.,* **139,** 22116h (2003).

61. Peterson Uwe, Schenke Thomas, Krebs Andreas, Grohe Klaus, Schriewer Michael, Haller Ingo, Metzger Kurl G., Endermann Rainer, Zeiler hans Joachim;
U.S. US **5,** 607, 942 (Cl. 546-200; A61k31/47) (1997); *Chem. Abstr.,* **138,** 14019t (2003).

62. Desouza Noel S., Patel Mahesh V., Deshpande Preasad K., Agarwal Shivkumar, Kandepu Sreenivas, Nair Sheela C., Chugh Yati, Shukla Milind C.,
PCT Int. Appl. WO **03** 50,107 (Cl. CO7D 401/04) (2003); *Chem. Abstr.,* **139,** 52893b (2003).

63. Ferlin Maria Grazia, Chiarelotto Gianfranco, Antonucci Francesca, Caparotta, Laura, Froldi Guglielmina;
Eur. J. Med Chem., **37(5)**, 427-434 (2002); *Chem. Abstr.,* **138,** 14021n (2003).

64. J. Elguero, A. R. Katritzky and C. W. Res.;
Comprehensive Heterocyclic Chemistry, **Vol 5,** *Ch.* 404, (1957).

65. R. S. Theobald;
Rodd's Chemistry of Carbon Compounds, Ed. M. F. Ansell, **Vol. IV**, Part C, Ch. 16 2nd Edition, (Elsenier Science Publishers B. V., Amsterdam) 59 (1998).

66. A. M. Fahmy, M. Hassan, A. A. Khalf, R. A. Ahmed;
Rev. Roum. Chim. **33(7),** 755-61 (1998); *Chem. Abstr.,* **111,** 77898 (1989).

67. A. K. Padya, K. Jaggi, V. Lakshminarayana, C. S. Pande;
J. Indian Chem. Soc., **75(2),** 104-105 (1998).

68. V. Gohanmukkala, A. Subbaraju, R. Naykula and D. Parmeswara,
Indian J. Heterocyclic Chem., **4**, 87-92 (1994).

69. R. A. Kabli, A. H. Kaddah, A. M. Khalil, A. A. Khalof;
Indian J. Chem., **25(B),** (2), 152-6 (1986); *Chem. Abstr.,* **106,** 119756 (1987).

70. M. A. El. Hashah, M., El-Kady, M. A. Saiyed, A. A. Elsawy;
Egypt. J. Chem., **27(6)**, 715-21 (1985); *Chem. Abstr.*, **105**, 208684 (1986).

71. A. K. Reda, A. A. Khalaf, M. T. Zimaltu, A. M. Khalil, A. M. Kaddah and H. A. Al-Rifuie;
J. Indian Chem. Soc., **68,** 47-51 (1991).

72. D. Bhaskar Reddy, T. Senshama, B. Seehaina and M.V. Ramma Reddy;
Indian J. Chem., **30(B)**, 46, (1991).

73. K. Zalgislaw, and A. Seffan ;
Acta. Pol. Pharm., **36(6)**, 645 (1979); *Chem. Abstr.*, **93**, 204525e (1980).

74. S.S. Nayal and C.P. Singh;
Asian J. Chem., **11,** 1, 207-212 (1999).

75. K. Wellinga, H. H. Eussen Jacobus;
Eur. Pat. EP., **269** 141 (C1C07D 231/06) (1988); *Chem. Abstr.,* **110,** 8204 (1989).

76. K. Trena and Zolzislaw;
Acta. Pol. Pharm., 36 (3), 227 (1979); *Chem. Abstr.,* **93,** 4650r (1980).

77. B. Roman;
Pharmazie, **45,** 214 (1990).

78. Z. Brozozowsk, E. Pormarnacka;
Acta. Pol. Pharm., **37(4),** 1378, 80 (1980); *Chem. Abstr.,* **25,** 80807 (1981).

79. H. G. Garg and P. P. Singh;
J. Chem. Soc., **2,** 1141 (1936).

80. Ashok Kumar, R. S. Verma and B. P. Jagu;
J. Ind. Chem. Soc., **67,** 120 (1990).

81. W. I. Ronald, A. Adriano;
Chem. Abstr., **126**, 181346f (1997).

82. Y. Hiroyuti, O. Mocoto, et al.;
Eur. Pat. Appl. EP. **295695** (C1. C07D 40/16) (1988); *Chem. Abstr.,* **111,** 23510 (1989).

83. Delay Francois (Fermenich S. A.) Patent Schrift (Switz);
Chem. Abstr., **117,** 90276f (1992).

84. H. M. Mokhtar, H. M. Faidallah;
Pharmazie, **42,** 482 (1987).

85. P. Desaea; A. Nunrich; M. Carderny and G. Devaux;
Eur. J. Med. Chem., **25,** 285 (1990).

86. B. Hans, R. Rolf and R. Rudolf;
Us. Pat. **3,** 822, 283 (1974); *Chem. Abstr.,* **81,** 105494r (1974).

87. Tsuboi-Shinichiwada, Katshaki et. al.;
Eur. Pat. Appl. EP. 537-580 (C1 C07D 401/64) (1993); JP Appl. 91/297; 772 (1991); *Chem. Abstr.,* **119,** 139220r (1993).

88. F. Manna, F. Chiments, A. Belasco, Cenicola M. L., Amico;
Chem. Abstr., **118,** 80902r (1993).

89. F. Rainer, E. Christoph;
Ger. Offen. DE **4,** 336, 307 (Cl. C07D 231/16) (1995); *Chem. Abstr.,* **123,** 256703u (1995).

90. Ismil, Mohamed Mohsen, El-Gendy, Adel A., Abdou, Madia A., El-Falaha, Bhogat M. A., Alexandria;
J. Pharm. Sci., **8(2),** 141-4 (1994); *Chem. Abstr.,* **122,** 239607c (1995).

91. Sarhan, El-Taher Z., Mohammed, Shadia A., Mikhael, Anwar N., Alexandria;
J. Pharm. Sci., **7(1),** 41-4 (1993); *Chem. Abstr.,* **122**, 81233r (1995).

92. S. S. Sonarc;
Asian J. Chem., **10(3),** 591-593 (1998); *Chem. Abstr.,* **129,** 54317j (1998).

93. N. Mishrika, N. Assod, F. M. Fawzy;
Pharmazie, **53 (8),** 543-547 (1998); *Chem. Abstr.,* **129,** 26038o (1998).

94. T. M. Stavenson, D. W. Piotrowski, M. A. H. Fahmy, R. L. Lowe, K. L. Monaco;
American Chemical Society, **217,** MAR Part - I, 29 AGRO (1999).

95. T. Katsohori, A. Hiroyuki, K. Masumij;
PCT Int. Appl. WO **98,** 56, 760; *Chem. Abstr.,* **130,** 66492w (1999).

96. Jatin Upadhyay, Utpal Dave and Hansa Parekh;
Chem. Abstr., **116**, 128768n (1992).

97. H. Parekh, H. Oza and D. Joshi;
Heterocyclic Communication, **Vol. - 3, 3** (1997).

98. A. H. Bhatt, H. H. Parekh and A. R. Parikh;
Heterocyclic Communication, **Vol. 4-4** (1998).

99. Fatema Bharmal, Devendra Kaneriya and Hansa Parekh;
Indian J. Heterocyclic Chem., **12,** 21-24 (2002).

100. M. K. Shivananda, P. M. Akberali, B. Holla, Shivarama, M. Shenoy, Shalini;
Indian J. Chem. **Sec. 13** *Org. Chem. Incl. Med. Chem.* **39B(6),** 440-447 (Eng.); *Chem. Abstr.,* **134,** 86195n (2000).

101. B. Shivarama Holla, M. K. Shivananda, B. Veerendra;
J. Heterocyclic Chem., **12,** 135-138 (2002).

102. E. Palaska, M. Aytemin, I. T. Uzboy, D. Erol;
Europian Journal of Medicinal Chemistry, **36(6),** 539-543 (Eng), 2001; *Chem. Abstr.,* **136,** 18374v (2002).

103. S. P. Hiremath, K. Rudresh and A. R. Saundane;
Indian J. Chem., **41(B),** 394-399 (2002).

104. A. L. Barry;
The antimicrobial susceptibility tests, Principle and practices, Illus. lea and Fehiger; Philadelphia, pa U.S.A. 108-93 (1976).

105. M. L. Crossley, V. L. King, L. H. Northey, T. E. Scholz;
U.S. US 02 **491,** 253 (1949); *Chem. Abstr.,* **45,** 4746 (1961)

106. A. Samour, Y. Akhnookh and H. Jahine;
J. Chem., **13(4),** 421-37 (1971); *Chem. Abstr.,* **77,** 101348 (1972)

107. S. G. Krivokolysko;
Chem. Heterocycl. Compd., (N.Y.) (1999)

108. U. P. Dayochenko;
Russ. J. Org. Chem., **34(4),** 554-56 (1998); *Chem. Abstr.,* **130,** 223222c (1999)

109. G. H. Sayed, R. R. Kassab;
Chem. Abstr., **131,** 15727p (1999).

110. Okazoe Takashi;
PCT Int. Appl. WO **00** 06, 347; *Chem. Abstr.,* **132,** 321784y (2000).

111. M. Kanded Ez-El-Din;
Chin. Pharm. J. (1999); *Chem. Abstr.,* **132**, 321784y (2000).

112. A. Sakuri and H. Midorikwa;
Bull. Chem. Soc. Japan, **40**, 1680 (1967); *Chem. Abstr*; **69**, 18985 (1968)

113. A. Sakuri and H. Midorikaw.
Bull. Chem. Soc. Japan, **41 (2)**, 430 (1968); *Chem. Abstr*; **69**, 1898s (1968)

114. Al-Omran, Fatima, Elassar, Abdel, El-Khair, Abdel-A.;
PCT Int. Appl. WO **04,** 29, 679 (Cl. C07D 408/09); *Chem. Abstr.,* **136,** 309834q (2002).

115. W. L. Hoefling, D. Elahaner and G. Recking;
VEB Leuna-Werke "Watter Ulbricht" Ger., **1,** 193, 506 (1965); *Chem. Abstr.,* **63,** 6979 (1965).

116. Thiele Kurt, Von be Benburg, Walter E;
S. African., **6**, 905-06 (1970).

117. B. John ED, Freeman and Peter F. M.;
Ger. Offen., **2,** 029, 079 (Cl. A 01 N007d) (1971); *Brist. Appl.* (1969); *Chem. Abstr.,* **74**, 99891d, (1971).

118. V. Scott and E. Joseph;
Jap. Pat., **2,** 803, 592 (1979); *Chem. Abstr.,* **92,** 47216 (1980).

119. J. J. Baldwin, A. Scrialrine, G. S. Ponticeello, E. L. Engelhardt and C. S. Sweeti;
J. Heterocycl. Chem., **17(3),** 425 (1980); *Chem. Abstr.,* **93,** 186222x (1980).

120. N. Latif, N. Mishry and N. S. Girgis;
Indian J. Chem., **20 (B)**, 147-149 (1981)

121. W. Von Behenburg, J. Engel, J. Heese and K. Thiele;
Ger. Offen., D. E., **3,** 337**,** 593 (C1C 07D 213/72) 1984; *Chem. Abstr.,* **101,** 130595n (1984)

122. M. R. Pavia, C. P. Taylor, F. M. Hershenon and S. J. Lobbestael;
J. Med. Chem., **30,** 1210 (1987)

123. C. Castedo, J. M. Quintela, and R. Riguers;
Eur. J. Med. Chem. Chim. Ther., **19(5),** 555 (1984); *Chem. Abstr.,* **103,** 37337 (1985).

124. Promilla S., Garg S.;
Chem. Abstr., **135,** 41634f (2001)

125. Urich Rosentreter, Rolf Henning, Marcus Bausex;
Chem. Abstr., **134,** 295744e (2001)

126. Gangjee Alam, Zhu Yunning, F. Sherry;
J. Med. Chem., **41,** 4539 (1998)

127. Y. Sasaki, J. Takuro, M. Ooishi, M. Sekine and S. Imaki, J. Takuma;
Jpn. Kokai Tokkyo Koho J.P., **06,** 315, 390 (1994); *Chem. Abstr.,* **122,** 131184y (1995)

128. Umed Ten, Kusunoki, M. Takuro, M. Shinya;
Jpn. Kokai Tokkyo Koho JP, **09,** 95, 489 (1997); *Chem. Abstr.,* **127,** 17699y (1997).

129. Rees Waynee M. (S. C. Johnson and Son Ime, USA);
PCT Int. Appl. WO **97,** 42, 295 (1997); *Chem. Abstr.,* **128,** 4928t (1998).

130. Oshida Mario, M. Yogi, S. Hiroaki, Y. Shinji;
PCT Int. Appl. WO **98,** 22, 439; *Chem. Abstr.,* **129,** 4582w (1998).

131. Villalobos Anabella, N. Arthur, C. Yuppyng L.;
UG. US **5,** 750, 592; *Chem. Abstr.,* **129,** 4661w (1998)

132. Yoshida Hiroshi, O. Kiyoshi, Y. Yasujuki, F. Kensaku;
Jpn. Kokai Tokkyo Koho JP **10**, 120, 677; *Chem. Abstr.,* **129**, 16062q (1998)

133. Devries Keith Michael, D. R. Lee, W. S. Wayne;
PCT Int Appl. WO **98,** 21, 184; *Chem. Abstr.,* **129,** 27896r (1998)

134. Nebel, Kurt, Brunner, H-Geary, S. Rolf;
PCT Int. Appl. WO **98,** 21, 199; *Chem. Abstr.,* **129,** 27898t (1998).

135. Manna Fedele, C. Franco, B. Adriana, B. Bruna, F. Walter, F. Amelia;
Eur. J. Med. Chem., **34(3)**, 245-254 (1999); *Chem. Abstr.,* **131**, 352178s (1999).

136. K. M. Hussain, H. Ruzial, S. Ahmed, Nizamuddin;
Indian J. Chem., **37(B),** 1069-1074, (1999); *Chem. Abstr.,* **131,** 237504h (1999).

137. Chambers, Robert James, Magee Thomas Victor, Marfat Anthony;
PCT Int. Appl. WO **02** 60, 896; *Chem. Abstr.,* **137,** 154859w, (2002).

138. Hammama Abou Elfatoon G.; El-Hafeza N. A.; M. Wandall; Z. Naturforsch B.;
Chem. Sci., (2000).

139. Rajeev Doshi, Preeti Kagthara, H. H. Parekh;
Indian J. of Chem. **38(B)**, 348-352, (1999).

140. Manish Shah, P. Patel, S. Koregaokar and H. Parekh;
Indian J. Chem., **35(B)**, 1282-1286 (1996).

141. Y. J. Fernandes & Hansa Parekh;
J. Inst. Chem., **63,** 69-70 (1991).

142. Akhil Bhatt, H. H. Parekh, K. Parikh, & A. R. Parikh;
Indian J. Chem., **40(B)**, 57-58, (2001).

143. A. V. Dobaria, J. R. Patel, H. H. Parekh;
J. Indian Chem. Soc., **79,** 772-773, (2002).

144. Abdallah Nevine A., Zakimagdi E. A.;
Acta Pharm (Zagreb) 1999; *Chem. Abstr.,* **132**, 137287n (2000).

145. Ladouceur Getan H., Cook James H., Doherthy Elizabeth M., Giebel Dierk, Schoen William R.;
Tetrahedron Letters, **43(25),** 4455-4458, (2002).

146. Caroline Charlier, Catherin Michaux;
Eur. J. Med. Chem., **38,** 645-659, (2003).

147. Mona M. Komel, Manal M. M. Hussain;
Indian J. Chem., **42(B),** 2136-2141, (2003).

148. S. A. Harris and K. Folkers;
J. Amer. Chem. Soc., **61**, 1245 (1939).

149. M. A. Sluyter, U. K. Pandit, W. N. Speckamp and H. O. Huisman;
Tetranedron Lett., **87** (1966).

150. G. Simchen and G. Entenmann;
Angew. Chem. Int. Edn Engl., **12**, 119 (1973).

151. Hu Zhiyong, Wang Huicai;
Chem. Abstr., **119**, 72465d (1993).

152. Erol D. D., Yulung N. and Ankara Turk;
Eur. J. Med. Chem., **29(11)**, 893-7 (1994); *Chem. Abstr.,* **122**, 13650a (1995).

153. Hartann R. W., Reichert N. and Gozhring S.;
Eur. J. Med. Chem., **29(11)**, 807-17 (1994); *Chem. Abstr.,* **122**, 239500n (1995).

154. Peter Fey, Han Ko Rudolf Huebsch Walter and Kraemer Thomas;
Eur. Pat. Appl. Ep. **62**, 3611, (Cl. C07D 401/14); *Chem. Abstr.,* **122**, 55897r (1995).

155. Uekawa Toru, Takemura Susumu, Enomato Masayuki and Sakaki Ma Saharu;
Eur. Pat. Appl. EP. **4** 88, 220 (Cl. C07D 413/04) (1992); *Chem. Abstr.,* **118**, 80944d (1993).

156. Rosenstock Bernd, Peyman Anu Schirwan, Ruppert Dieter, Riess Guenther;
PCT. Int. Appl. WO **96** 30, 342 (Cl. C07D 213/89); *Chem. Abstr.,* **126**, 7993e (1997).

157. D. D. Erol, N. Yulung and A. Turk;
Eur. J. Med. Chem., **29(11),** 8937 (1994). *Chem. Abstr.,* **122,** 13650a (1995).

158. Peter Fey, Dressel Juergem, Hanko Rudolf, Huebsch Walter and Kraemer Thomas;
Eur. Pat. Appl. EP. **62** 3611 (Cl. C07D 401/14); *Chem. Abstr.,* **122**, 55897r (1995).

159. H. Gary Posnes;
Org. Synth. **177** (1994); *Chem. Abstr.,* **123**, 167349g (1996).

160. Collins Ivan James, Lesson Paul David and Moger Christopher Richard;
PCT Int. Appl. WO **98** 55, 480 (1998); *Chem. Abstr.,* **130**, 38376t (1999).

161. Reiner Jonn E., Lim-Wilby, Margeu Rita S., Brunck Terence K. and Ha-Vong Theresa;
Chem. Lett., **9(6)**, 895-900 (1999); *Chem. Abstr.,* **131**, 286379a (1999).

162. Yamagudi Mikio, Ito Voshiniro Shibaytama Atsushi, Yomaji. Mitsuhiro and Hanai Rgo;
Jpn. Kokai Tokkyo Koho JP **11** 140, 054 (Cl. C07D 213/64); *Chem. Abstr.,* **131**, 44738a (1999).

163. Betageri Rajashekhar, Beaulieu, Llinas Brunet, Pierrel ;
PCT Int. Appl. WO **99** 31, 066 (Cl. C07D213/75); *Chem. Abstr.,* **131**, 59136a (1999).

164. Solman Asmaa, Said Salem;
Pharmazie, **54(3)**, 178-183 (1993); *Chem. Abstr.,* **130**, 281907k (1999).

165. Harison Timothy, Moyes Christopher Richard laewis Richard Thomas;
PCT Int. Appl. WO **98** 10, 384 (Cl. C07D 471/14); *Chem. Abstr.,* **130**, 13918h (1999).

166. Shivakumar B. and Nargund L. G. ;
Indian J. Heterocyclic Chem., **8(1)**, 27-36 (1998); *Chem. Abstr.,* **130**, 66428e (1999).

167. Mukhtar Hussain Khan, Raizul Haque and Nizamuddin;
Indian J. Chem., **37(B)**, 1069 (1998).

168. Mukhtar Hussain Khan, Raizul Haque, Taruna Agrawal and Nizamuddin;
Indian J. Chem., **38(B)**, 452-456 (1999).

169. Abd El-Galil and E. Amer;
Indian J. Heterocyclic Chem., **10**, 49 (2000).

170. Abou El-Fotooh, G. Hammam, Mohie A. Sharaf and Nagalaa A. Abd El-Hafeza;
Indian J. Chem., **40(B)**, 213-221 (2001).

171. Fossa Palola; Most Lusia; menozzi Giulia, manetti Faprizio; Dorigo Padoa, Floreuni Maura;
Med. Chem. Research,, **11(3),** 137-152, (2002), *Chem. Abstr.,* **137,** 369943e, (2002).

172. Gulcan Ozturk, Dilek Demir Eral, Mutlu Diisiz Aytermir, Joyfun uzbay;
Eur. J. Med Chem., **37,** 829-834, (2002).

173. Tanaka Akira; Minagawa Malatoshi, Akahane Atsushi;
Chem. Abstr., **139,** 22210j (2003).

174. A. R. Grey and J. B. Dickey;
Org. Syn. Coll., **2**, 60 (1943).

175. C. B. Reese and S. R. James;
Tetrahedron Lett., **2915** (1975).

176. Chai Xian Dong, Cao-Yun Wei, Jiang Yue-Shan;
Gaodeng Xuexiao Huaxue Xuebao, **16(2),** 225-229 (1995); *Chem. Abstr.,* **123,** 33021u (1995).

177. M. R. Mahmoud, Awatef E.F. Ebrahim, M. S. Abd El-Halim. and A. M. Rodwan;
Indian J. Heterocyclic Chem., **4,** 131-36 (1994).

178. Ogus Funda and Dogan Llknur;
Chem. Abstr., **129,** 16097e (1998).

179. Malcom Daniels and Alec Grimison;
U.S. Pat. **13,** 150, 137 (1964); *Chem. Abstr.,* **59,** 7539c (1963).

180. J. M. Cox, C. D. Snowling and M. C. Shepard;
Ger. Offer, **2,** 812,367 (1978); *Chem. Abstr.,* **90,** 82129u (1978).

181. Z. H. Khalil, A. I. M. Karaiem and R. M. Abu-El-Hameed;
J. Chem. Technol. Biotechnol., **36,** 473 (1986).

182. Y. K. Gupta, K. P. Bhargava, K. Shanker and J. C. Agarwal;
Indian J. Chem., **20(B),** 714 (1981).

183. J. C. Agarwal, Y. K. Gupta, P. Kumar, C. Nath, K. P. Bhargava and K. Shanker;
Indian J. Chem., **22(B),** 955 (1981).

184. G. P. Gupta, Sharda Singh and K. Shanker;
Indian J. Chem., **24(B),** 1094 (1985).

185. Y. Furukawa;
Eur. Pat. Appl. Ep., **88,** 413 (1983); *Chem. Abstr.,* **100,** 22688 (1983).

186. Ulf Wellmar, Anna-Britta Hornfield and Salo Gromowite;
J. Heterocyclic Chem., **32,** 1159 (1995).

187. D. Peters, A. B. Hornfield and S. Gromowitz;
J. Heterocyclic Chem., **27,** 2165 (1990).

188. R. A. M. Herdwijin;
Antiviral Chem. Chemother., **5,** 131 (1994); *J. Heterocyclic Chem.,* **32,** 1159 (1995).

189. Raymond P., Diane L., Dan-Chang Wei, Wang;
J. Heterocyclic Chem., **30,** 1399 (1993).

190. M. R. Mahmoud, M. S. Abd, El-Halim and A. M. Radwan;
Indian J. Heterocyclic Chem., **4,** 131-136 (1994).

191. R. F. Burns;
Biochim. Pharmacol., **30**, 325 (1981); *J. Heterocyclic Chem.,* **33,** 1025 (1996).

192. A. G. Manukyam, R. G. Malik and B. T. Guri bdz hanyan;
Khim-Pharm Zh., **19,** 685 (1985); *Chem. Abstr.,* **104,** 207622s (1996).

193. Wolf-gang, Hanefold and Helge Hurms;
Indian J. Heterocyclic Chem., **34,** 509 (1997).

194. Andre Roland, Dollinger Markus and Erdeten Christopher;
Ger. Offen. DE **19,** 715**,** 017 (Cl. C07D 401/12), (1998); *Chem. Abstr.,* **129,** 302655d (1998).

195. Omar M. T.;
Egypt J. Pharma. Sci., **38** (4-6), 281-89 (1997); *Chem. Abstr.,* **131**, 257514k (1999).

196. Sakai, Kunikazu, Satoh, Yusuke;
PCT. Int. Appl. WO **99** 50, 252(Cl. C07D 239/62); *Chem. Abstr.,* **131,** 243286a (1999).

197. R. T. Pardasani, S. K. Jain, S. K. Yadav and I. Sharma;
Indian J. Heterocyclic Chem., **12**, 179-80, (2002).

198. L. Claisen and O. Lowmann ;
Chem. Ber., **21**, 1149 (1888).

199. A. Quelico ;
Chem. Heterocycl.Compd. **17**, 1 (1962).

200. L. S. Crawley and W.J. Fanshawe ;
J. Heterocycl. Chem., **14**, 531 (1977).

201. M. A. Krishna Rao, K. S. R. Krishna Mohan and Rao N. V. Subba ;
Indian J. Chem., **6(2)**, 66-8 (1968).

202. John F. Hansen and Scott A. Strong ;
J. of Heterocycl. Chem., **14**, 1289 (1977).

203. G. S. D'Alcontres and G. De Gamco;
Chem. Abstr., **54,** 19646 (1960).

204. Vamanauchi Pharm. Co. Ltd.;
Jpn Kokai Koho JP **58,** 148, 858 (Cl. CO7D 207/333) (1982); *Chem. Abstr.,* **100,** 34538 (1984).

205. P. T. Gallagher, T. A. Hicka and G. W. Mullier;
Eur. Pat. Ep **2** 57, 882 (1988); *Chem. Abstr.,* **108,** 6499K (1988).

206. A. Ando and R. W. Stevens ;
PCT Int. Appl. WO **94**, 12, 481 (Cl. C07 D 261/04); *Chem. Abstr.*, **122**, 56037x (1995).

207. W. Wells, A. Michele, H. Todd;
Chem. Abstr., **136,** 340680j (2002).

208. T. Tochiro, K. Shrji, I. Shinji, M. Hiroshi, S. Akira, V. Hiroshi;
Gen. Offen. DE **3,** 237,149 (Cl. CO7A 261114) (1983); *Chem. Abstr.,* **99,** 88188 (1984).

209. T. U. Quazi ;
Pak. J. Sci. Ind. Res., **27**, 326 (1984); *Chem. Abstr.*,**103**, 12339m (1985).

210. Nippon Chemiphar Co. Ltd.;
Jpn. Kokai Koho JP **58,** 46,077 (Cl. CO7A 261/14) (1983); *Chem. Abstr.,* **99,** 17574 (1984).

211. T. Taate, K. Natira and H. Fukhola;
Chem. Pharm. Buld., **35(9),** 37769 (1987); *Chem. Abstr.,* **108,** 186621e (1988).

212. B. Victor, J. Safir and Sidney R.;
Chem. Abstr., **72,** 79017d (1970).

213. R. Major, B. Eisele, P. Mutler and H. Grube;
Ger. Offen. DE 3621372 (1988); *Chem. Abstr.,* **108,** 67456r (1988).

214. S. Suzuki, K. Ueno and K. Mori;
Yakugaku Kenkua, **34,** 224-31 (1962); *Chem. Abstr.,* **57,** 16754 (1962).

215. G. P. Reddy, E. Rajendra and A. K. Murthy ;
Indian J. Heterocycl. **3**, 233 (1994); *Chem. Abstr.*, **122**, 105724e (1995).

216. B. Victor, J. Safir and R. Sidney;
Chem. Abstr., **72,** 79017d (1970).

217. K. Hass Duane, B. Carr John;
U.S. US **3** 879,532 (Cl. A61K 242/72) (1975); *Chem. Abstr.,* **83,** 108626m (1975).

218. D. J. David, D. B. Allon and E. A. Frederick;
Ger. Offen., **2,** 723,688 (Cl. A01N 9/28) (1977); *Chem. Abstr.,* **88,** 132015k (1978).

219. M. D. Mackie, H. S. Anthony, W. J. R. Howe, S. P. John and W. S. Marry; Brit.;
UK Pat. Appl. GB **2**, 265, 371 (Cl. C07 D 261/06); *Chem. Abstr.*, **120**, 164153z (1994).

220. G. D. Diana and C. P. Michel;
S. African ZA, **81,** 03, 105 (1981); *Chem. Abstr.,* **98,** 1667, (1983).

221. C. P. Alfred, C. David, Herman, D. Nancy, B. Daniel;
PCT Int. Appl. WO **95,** 22, 9103 (1995); *Chem. Abstr.,* **124,** 3055m (1996).

222. A. K. Banerjee;
Arzneim Forsch., **44**, 863 (1994); *Chem. Abstr.*, **122**, 160522n (1995).

223. H. Katsumasa, N. Shigehide, H. Kenji;
Chem. Abstr., **136,** 340672j (2002).

224. S. Rung and D. Dus;
Pharmazie, **49,** 727 (1994); *Chem. Abstr.,* **122,** 55934h (1995).

225. M. Scobie and M. D. Threadojill ;
J. Org. Chem., **59**, 7008 (1994); *Chem. Abstr.*, **122**, 10090f (1995).

226. R. Jain, D. D. Agrawal and Damodharan;
J. Ind. Chem. Soc., **72**, 825-827 (1995).

227. Inai, Masatoshi, Tanaka, Akie, Goto, Kyoto;
Jpn Kokai Tokkyo Koho JP **07**, 215, 952 (95, 215, 952) (1995); *Chem. Abstr.,* **124**, 86995s (1996).

228. Inai, Masatoshi, Tanaka, Akie, Goto, Kyoto;
Jpn Kokai Tokkyo Koho JP **07**, 215, 952 (95, 215, 952) (1995); *Chem. Abstr.,* **124**, 86995s (1996).

229. B. Maggio, G. Daidone, D. Raffa, F. Plescia, V. M. C. Cutuli;
Archiv. Der Parmazie, **332(2),** 50-54 (1999).

230. C. B. Xue, J. Roderick, S. Mousa, R. E. Olason, W. F. Degrado;
Bio org. Med. Chem. Lett., **8(24)b**, 3499-3504 (1998).

231. M. Masui, H. Yasushi;
Chem. Abstr. **128,** 13256z (1998).

232. K. V. Reddy, S.G. Rao, A. V. Subba;
Indian J. Chemistry, **37(B)**, 677-99 (1998); *Chem. Abstr.,* **129,** 260397p (1998).

233. J. Niyitrai, N. Josheph, S. Gyala;
Chem. Abstr., **128,** 294778h (1998).

234. A. Mishra, J. K. Sanmati, J. Asthana;
Orient. J. Chem., **14(1),** 151-52 (1998); *Chem. Abstr.,* **128,** 216538m (1998).

235. S. Ozkan, D. Kadir, A. Okay, A. Ahmet;
Chem. Abstr., **131,** 5221f (1999).

236. D. Mesmacker, A. Schaetzer, J. Kunzwalter;
PCT Int. Appl. WO **9,** 51, 583 (1999); *Chem. Abstr.,* **131**, 2718272g (1999).

237. A. Hiroyuki, S. Takahiro, A. Toshio;
PCT Int. Appl. WO **99** 64, 404; *Chem. Abstr.,* **132,** 12313m (2000).

238. M. Mauro, S. Enzo;
Farmaco **54(7),** 452-460 (1999); *Chem. Abstr.,* **131,** 299393a (1999).

239. D. A. Jacob, M. A. John, C. L. Stanley;
PCT Int. Appl. WO **00,** (Cl. C07D 00/477); *Chem. Abst.,* **132,** 64256r (2000).

240. S. K. Gudadhe, S. D. Patil, U.S. Jamode;
Orient J. Chem., **15(1),** 133-136 (1999); *Chem. Abstr.,* **132,** 222481r (2000).

241. Hui-Xin-Ping, Zhang Lin-Mei, Zhang Zi-Yi;
Chem. Abstr., **132,** 207803c (2000).

242. V. D. Huebner, Lin Xiaodong, James Ian, C. Liya, M. Desai;
Chem. Abstr., **132,** 222486w (2000).

243. M. Nobugoshi, S. Michitaka, H. Kokhi;
Jpn Kokai Tokkyo Koho JP **86,** 657 (2000); *Chem. Abstr.,* **132,** 251139r (2000).

244. R. Ulrich, H. Rolf;
Chem. Abstr., **134,** 311203k (2001).

245. B. P. Kansagra, H. H. Bhatt and A. R. Parikh;
Heterocycl. Commun., **4(4),** (1998).

246. A. H. Bhatt, H. H. Parekh, A. R. Parikh;
Heterocyclic Commun., **4(4)**, (1998).

247. Xin-Ping Hui, Chang-Hu Chu, Zi-Yi Zhang;
Indian J. Chem., **41(B),** 2176-79 (2002).

248. Wu Chengde, Raju Bore Gowda, Kogan Timothy, Blok Natalie;
U.S. US **6,** 420, 567 (Cl. C07D 261/04) (2002); *Chem. Abstr.,* **137,** 93741c (2002).

249. Qi Chuanmin, Wang Yunfeng, Zhang Guanxin, Feng Shujuan;
Beijing Shifan Daxue Xuebao Ziram Kexueban, **37(6),** 787-89 (2001); *Chem. Abstr.,* **137,** 370004f (2002).

250. Farrerons Gallemi Carles, Lagunas Arnal, Miquel Bono;
PCT Int. Appl. WO **03** (Cl. C07D 261/08) (2003); *Chem. Abstr.,* **138,** 137295n (2003).

251. Caraline Charlier and Catherin Michaux;
Eur. J. Med. Chem., **38,** 645-659 (2003).

252. A. W. Hoffman;
Ber., **21**, 2332 (1880).

253. A. Ladenburg;
Ber., **27**, 2952 (1894).

254. Zednikova, Gabriela, Nalepa Karel;
Acta Univ. Palacki Olumuc., Fac. Rerum Nat. Chem., **37,** 69-71 (1998); *Chem. Abstr.,* **131**, 116188v (1999).

255. Isidor Greenwala;
J. Amer. Chem. Soc., **47**, 1443-7 (1925).

256. S. C. Granacher and G. Gulbas;
Helv. Chem. Acta., **10**, 819-26 (1927).

257. Abdel Hamid, Harbash Kassal and Elbanmi;
Indian J. Chem., **9**, 789-93 (1971).

258. C. Granacher and M. Mahler;
Helv. Chem. Acta., **90**, 819-826 (1927); *Chem. Abstr.,* **21**, 1813 (1928).

259. R. Agarwal, C. Chaudhary and V. S. Misra;
Indian J. Chem., **22(B)**, 308 (1983).

260. S. M. Sethna and R. C. Shah;
J. Indian Chem. Soc., **1459** (1993).

261. E. Bousquet, G. Romeo, N. A. Snatagati, T. Lancetta, A. Caruso and V. Leone, A. Felice;
Farmaco., **44(9),** 851-853 (1989); *Chem. Abstr.,* **112,** 191378t (1990).

262. M. I. Husain and Vinay Kumar;
J. Indian Chem. Soc., **68,** 102 (1991).

263. Thomas I. Kalman;
PCT Int. Appl. WO **94** 21, 658 (1994); *Chem. Abstr.,* **122,** 315045k (1995).

264. Hussieny Hamed Moharram, R. Samiya El-Amin and Ahmed El-Dawany;
J. Serb. Chem. Soc., **54(7)**, 335-42 (1989); *Chem. Abstr.,* **114**, 101822x (1991).

265. U. Niedballa dn I. Boettcher;
Ger. Offen., **2,** 856,909 (Cl. C07D 233/84); *Chem. Abstr.,* **94,** 15732e (1981).

266. P. Kumar, C. Nath and K. Shanker;
Pharmazie, **40(H)**, 267 (1985).

267. P. K. Naithani, V. K. Srivastava, J. P. Barthawal, A. K. Saxena, T. K. Gupta and K. Shanker;
Indian J. Chem., **28(B),** 990-92 (1989).

268. K. C. Mathur and R. Sahay;
J. Indian Chem. Soc., **67,** 856 (1990).

269. A. Sudhir and P. C. Dandiya;
Proc. Dec. Conf. Ind. Pharmacol. Soc. Abs No. **88 (**1977).

270. Ding, Ming WO; Tu, Hai-Yang, Liu, Zhao-Jie, Zhuang, Nong-Bo.;
Gaodeng Xuexiau Huaxue Xuebao, **19(6)**, 895-898 (1998); *Chem. Abstr.,* **129,** 122615h (1998).

271. Pilkington, Brian Leslie, Russell, Sally Elizabeth, Whittle, Alan John, Mound, William Roderick;
Brit. UK Pat. Appl. GB., **2,** 329, 180 (Cl. C07D 233/80) (1999); *Chem. Abstr.,* **129,** 58826r (1999).

272. Yokohama Shuichi, Takeda Yasuyuki, Kawakoshi Keiichi, Yamamoto Kenjiro;
Jpn. Kokai Tokkyo Koho JP, **11 279,** 156 (99 219 156); *Chem. Abstr.,* **131,** 271875k (1999).

273. Jagham Samir, Saady Mourad, Yaiche Philippe and Horter Laurence;
PCT Int. Appl. WO **99** 31, 089; *Chem. Abstr.,* **131,** 44821w (1999).

274. P. S. Upadhyay, A C. Pandya and H. H. Parekh;
J. Indian Chem. Soc., **68,** 296-98 (1991).

275. N. Joshi, A. Bapodara and H. H. Parekh;
Indian J. Chem., **33(B)**, 662 (1994).

276. P. S. Upadhyay, H. D. Joshi, A. J. Baxi and A. R. Parikh;
Indian J. Hetero. Chem., **1,** 71 (1991); *Chem. Abstr.,* **117,** 48407z (1992).

277. V. C. Soni and A. R. Parikh;
Indian J. Pharm. Sci., **53**, 185 (1991); *Chem. Abstr.,* **116**, 151653, (1992).

278. Dharti G. Joshi, Haresh B. Oza and H. H. Parekh;
Heterocyclic Communications, **3(2),** 169 (1997).

279. Akhil H. Bhatt, Khyati A. Parikh and A. R. Parikh;
Indian J. Chem., **38(B),** 628-631 (1999).

280. Khyati Parikh, Paresh Oza and A. R. Parikh;
J. Inst. Chem., **71(3),** 83-87 (1999); *Chem. Abstr.,* **133,** 308291r (2000).

281. S. B. Hirpara, K. A. Parikh, B. C. Merja and H. H. Parekh;
Indian J. Chem., **42(B),** 1172-75 (2003).

282. Stefan A. Lauter, Hans Gunther, Gerd Wagner;
J. Med. Chem., **45,** 4695-4705 (2002).

283. Battistina Aspromi, Anedeo Pau, Mauro Bitti;
J. Med. Chem., **45,** 4655 (2002).

284. Declerca Arthur, Herdeciln Piet;
PCT Int Appl. WO **68,** 395 (Cl. CO7D 235/84) (2002); *Chem. Abstr.,* **137,** 201308c (2002).

285. Machil Daisuke, Hagihara Kaji, Asai Akira, Arai Hitoshi, Yamashita Yoshinori, Chin Allison C., Piatyszek Mieczslaw A.;
Chem. Abstr., **137,** 93750e (2002).

286. Irene M. Lagoja, Christopher Pannecouque, Arthur Van Aerschat, Myriam Witurouw, Zeger Debyser, Jan Balzarimi, Piet Herdewijin and Erik De Clercq;
J. Med. Chem., **46(8),** 1546-53 (2003).

287. Jean-Michel H., Robert Carolin Subourin, Nidja Alvorez, Sylvie Robert-Piessard, Guilloume Le Baut, Patrice Le Pape;
Eur. J. Med. Chem., **38,** 711-718 (2003).

288. Chafiq Hamdouchi, Concha Sanchez, Joseph Gruber and Mirimdel Prado;
J. Med. Chem., **46,** 4333-4341 (2003).

289. A. I. Vogel;
Practical Organic Chemistry, ELBS and Longman Ltd., 909-10 (1971).

290. C. Liberman and A. Lange ;
Ann., **207**, 121 (1881).

291. A. Mystafa, W. Asker, A. F. A. Shalaby and M. E. E. Shobby;
J. Org. Chem., **23,** 1992 (1958).

292. W. Davies;
J. Chem. Soc., **2633** (1949); *Chem. Abstr.,* **44,** 2977 (1953).

293. A. R. Surry;
J. Amer. Chem. Soc., **74,** 3450 (1952); *Chem. Abstr.,* **48,** 3348s (1954).

294. H. Erlenmeyers;
Helv. Chem. Acta., **39,** 1156 (1956); *Chem. Abstr.,* **51,** 1148d (1957).

295. A. R. A. Raouf, M. T. Omar and M. M. El-Attal;
Acta. Chim. Acad. Sci. Hung, **87,** 187 (1975); *Chem. Abstr.,* **84,** 74185 (1976).

296. D. R. Patel, P. S. Satpanthi, P. B. Patel, J. J. Trivedi;
J. Inst. Chem., **48,** 305 (1976).

297. E. Fisher, I. Hartmann and H. Priebs;
Z. Chem., **15,** 480 (1975); *Chem. Abstr.,* **84,** 155534 (1976).

298. J. Rogere and M. Audibert;
Bull. Soc. Chim. Fr., **4021** (1972).

299. A. R. Astik, G. B. Joshi and K. A. Thaker;
J. Indian Chem. Soc., **52,** 1071 (1975).

300. R. Nath, K. Shanker, R. C. Gupta and K. Kishor;
J. Indian Chem. Soc., **55,** 832-834 (1978).

301. I. D. Shah and J. P. Trivedi;
J. Indian Chem. Soc., **40,** 889-893 (1963).

302. M. Seada, M. Abdel-Megid and I. M. El-Deen;
Indian J. Heterocyclic Chem., **3,** 81-86 (1993).

303. Daulatabad C. D., Bhatt G. G.;
Indian J. Heterocyclic Chem., **7(3),** 209-212 (1998); *Chem. Abstr.,* **129,** 54311c (1998).

304. E. Piscopo, M. V. Diurno, R. Gagliardi, O. Mazzoni, C. Parill, and G. Veneruso;
Boll Soc. Ital. Biol. Sper., **65(2),** 131-6 (1989); *Chem. Abstr.,* **111,** 170938q (1989).

305. S. Grasso, A. Chimirri, P. Monforte, G. French, M. Zappala and A. M. Monforte;
Farmaco Ed. Sci., **43(10)**, 851-6 (1988) ; *Chem. Abstr.*, **110,** 50734c (1989).

306. Hassan Hoda V., El-Koussi Nawal A., Farghaly Zeinab S.;
Chem. Pharm. Bull., **46(5),** 863-66 (1998); *Chem. Abstr.,* **129,** 95436r (1998).

307. Sun Xiao-Weng Liang Hong-Tao, Zhang Zi-Yi, Wang Quin, Wang Fang;
Indian J. Chem., **38(B),** 679-683 (1999); *Chem. Abstr.,* **131,** 336976r (1999).

308. Kamiya Shoji, Kasai Masayasa, Yoshimi Akihisa Sirahase, Hiroaki Malsui Hiroshi;
PCT Int. Appl. WO **99** 24, 429 (Cl. C07D 417/12) (1999); *Chem. Abstr.,* **131,** 338105j (1999).

309. Kidwai M., Bhushan K. R.
Chem. Par., **53(2)**, 114-117 (1999).

310. Mohd. Siddique, Mohd. Idress A. G. Doshi;
Asian. J. of Chem., **14(1)**, 181-184 (2002); *Chem. Abstr.,* **130,** 168288b (1999).

311. Kolla Suresh and Bhatt R. R.;
J. Inst. Chem., **70(4),** 146-8 (1998); *Chem. Abstr.,* **133,** 168288b (1999).

312. Goel Bhawna, Tyagi Ritu, Bansal Ekta, Sinha N. J.;
Eur. J. Med. Chem., **34(3)**, 256-59 (1999); *Chem. Abstr.*, **131(7)**, 87859g (1999).

313. El-Subbagh, Hussein I.;
Saudi Pharm. J., **7(1-2)**, 14-21 (1999); *Chem. Abstr.,* **131,** 212875h (1999).

314. Ram Tilak, Tyagi Ritu, Goel Bhawna, Saxena K. K., Srivastava V. K., Kumar Ashok;
Indian Drugs, **35(4),** 216-221 (1998); *Chem. Abstr.,* **129,** 338104i (1998).

315. Lee Byung H., Dutton Fred E., Cholpier Michael F., Bowncan Jerry W., Davis John P., Johnson Sandra S., Thomas Eilein H., Zantello Mayori;
Bioorg. Med. Chem. Lett., **9(12),** 1727-32 (1999); *Chem. Abstr.,* **131,** 157734r (1999).

316. Liu Jun, Hu Xing Hing, Xu Han Sheng;
Chin. Chem. Lett., **10(3),** 199-200 (1999); *Chem. Abstr.,* **131,** 199659y (1999).

317. Wang Xi-Chun, Yu Tian-Zhi, Li Zheng, Chen Ji-Chuo, Wang Xiu-Chun;
Gaodeng Xuexiao Huaxue Xuebao, **20(10),** 1581-1583 (1999); *Chem. Abstr.,* **131,** 322591z (1999).

318. Guido Mayer, VLF Misslitc;
PCT Int. Appl. WO **02** 48**,** 140 (Cl. C07D 413/06); *Chem. Abstr.,* **137,** 33290v (2002).

319. Diurno, M. Vittoria;
Farmaco, **54(9)**, 579-583 (1999); *Chem. Abstr.,* **132,** 35644j (2000).

320. Tatsuta Nariaki, Ukai Toshinao, Kanakanmi Masayuki;
J. Med. Chem., **40(20),** 3153 (1997).

321. Kato Tatsuya, Ozaki Tomokazu;
Organic Process, Research and Development, **5,** 122-26, (2001).

322. Lodhi R. S., Srivastava S. D. and Srivastava S. K.;
Indian J. Chem., **37(B),** 899-903 (1998); *Chem. Abstr.,* **130,** 110190x (1999).

323. V. S. Ingle, A. R. Sawale, R. D. Ingle and R. A. Mane;
Indian J. Chem., **40(B),** 124-28 (2001).

324. Sharma R. C. and Kumar Devendra;
J. Indian Chem. Soc., **77(10),** 492-3 (2000); *Chem. Abstr.,* **134,** 115886w (2001).

325. L. Mehta and H. Parekh;
J. Indian Chem. Soc., **65,** 574 (1988).

326. C. L. Patel and H. Parekh;
J. Indian Chem. Soc., **65,** 574 (1988).

327. C. L. Patel and H. Parekh;
J. Indian Chem. Soc., **65,** 282 (1988).

328. R. N. Vansdadia, K. P. Roda and H. Parekh;
J. Indian Chem. Soc., **66,** 113 (1989).

329. U. Dave, K. Ladva and H. Parekh;
J. Inst. Chem., **64,** 74 (1992).

330. K. Ladva, U. Dave and H. Parekh;
J. Indian Chem. Soc., **68,** 370-71 (1991).

331. K. P. Roda, R. N. Vansdadia and H. Parekh;
J. Inst. Chem., **64,** 109 (1992).

332. G. C. Kamdar, D. J. Bhatt and A. R. Parikh;
Acta Ciencia Indica **90(2),** 65 (1983); *Chem. Abstr.,* **101,** 151971 (1984).

333. S. B. Kalaiya and A. R. Parikh;
J. Inst. Chem. Soc., **62,** 255 (1985); *Chem. Abstr.,* **104,** 109527u (1986).

334. R. R. Shah, R. D. Mehta and A. R. Parikh;
J. Indian Chem. Soc., **62,** 255 (1985); *Chem. Abstr.,* **105,** 78865s (1986).

335. G. C. Kamdar, A. C. Chawda and A. R. Parikh;
J. Indian Chem. Soc., **64,** 298 (1987).

336. P. M. Parashrya and A. R. Parikh;
J. Inst Chem., **63,** 63 (1991); *Chem. Abstr.,* **115,** 256035s (1991).

337. V. L. Pachhamia and A. R. Parikh;
Acta Ciencia Indica, **17C(1)**, 67 (1991); *Chem. Abstr.,* **117,** 26399w (1992).

338. J. M. Parmar and A. R. Parikh;
Indian J. Chem., **38(B),** 440-444 (1999).

339. Neela J. Datta, Fatema Bharmal and A. R. Parikh;
J. Inst. Chem., **78,** 47 (2001).

340. Neela J. Datta, Ranjan C. Khunt and A. R. Parikh;
Indian J. Chem., **41(B),** 433 (2002).

341. Takasu Kiyosei, Inoue Hiroshi, Suzuki Makoto;
J. Med. Chem., **45,** 995 (2002).

342. Abdel-Megid M., Awas M. A. A.;
Heterocyclic Communications, **8(2),** 161-68 (2002); *Chem. Abstr.,* **137,** 370017n (2002).

343. Akama Tsutomu, Hel comb Ryan, Tolman Richard L.;
PCT Int. Appl. WO **02,** 51,409 (Cl. A6/K 31/425) (2000); *Chem. Abstr.,* **137,** 63244a (2002).

344. S. Guniz Kucukguzel, E. Elein Oruc, Sevin Rollas, Fikrettin Sahin, Ahmet Ozbek;
Eur. J. Med. Chem., **37,** 197-206 (2002).

345. Srivastava S. K., Soumya Srivastava and Srivastava S. D.;
Indian J. Chem., **41(B),** 1937-1945 (2002); *Chem. Abstr.,* **138,** 153485e (2003).

346. Y. S. Sadananda, M. M. Shetty, P. V. Diwan;
J. Med. Chem., **27,** 87-92 (1992).

347. S. Inoue, A. J. Saggimoto, E. A. Modifit;
J. Org. Chem., **26,** 4504 (1961).

348. D. J. Brown, P. Waring;
Aust. J. Chem., **30,** 621 (1977).

349. A. Takamizawa and K. Hirani;
Chem. Pharm. Bull., **12,** 393 (1964).

350. Rajiv Gupta, A. K. Gupta, S. Paul and P. L. Kachroo;
Indian J. Chem., **34(B),** 151-152 (1995).

351. Beginelli;
Gazz. Chim., **23,** 360 (1983); *Atti Accad Licei.,* **3(5),** 195 (1984).

352. K. P. Gupta, R. C. Gupta and K. P. Bhargava;
Eur. J. Med. Chem., Chim. Ther., **17(5),** 448-52 (1982); *Chem. Abstr.,* **98,** 72040j (1983).

353. Atwal Kornial;
U. S. US 4, 769, 371 (Cl. 514-275; CO7D 239/42) (1988); *Chem. Abstr.,* **110**, 114853a (1989).

354. Cho H., Mizuno A. and S. Keiyu;
Eur. Pat. Appl. Ep., **195,** 374 (1988); *Chem. Abstr.,* **110,** 231653w (1989).

355. Martin J. A., Bushnel D. J., Duncan;
J. Med. Chem., **33,** 2137 (1990).

356. Watanabe K. A., Hurado K., Zeidler J.;
J. Med. Chem., **33,** 2145 (1990).

357. Ram V. J., Haque N., Guru P. Y.;
Eur. J. Med. Chem., **27,** 851 (1992).

358. L. Vio and M. G. Mamolo;
Chem. Abstr., **99,** 88139e (1983).

359. Schnell, Barbaru Strauss, Verdinopetra;
Chem., Abstr., **133,** 135285q (2000).

360. Akimoto H., Miwa and Otsuk;
Indian J. Chem., **37(B),** 517 (1998).

361. A. Kreutz berger and M. Sellheim;
Chem. Abstr., **102,** 24572p (1985).

362. Bear Thomas;
PCT. Int. Appl. No. **94** 18,809 (Cl. CO7D 401/04) (1994); *Chem. Abstr.,* **122,** 290877 (1995).

363. Kajima, Eiji, Miyawaki, Soichi, Fujii, Yuji, Murakami;
Jpn. Kokai Tokkyo Koho JP 09 **286,** 786 (Cl. CO7D 403/14); *Chem. Abstr.,* **128**, 3701b (1998).

364. Omer M. T. Fahmy H. H., Mohamad H. S.;
Egypt J. Pharm Sci., **37** (1-6), 609-620 (1996).

365. Machon. Z., Witkiewicz and Krystyna;
Acta. Pol. Chem., **42(b)** 516 (1985); *Chem. Abstr.,* **106,** 138388 (1986).

366. Patane Michael A., Bock Mark G. Senick Harold G.;
PCT Int. Appl. WO **98** 57,64 (Cl. A61K31/445) (1998); *Chem. Abstr.,* **130,** 81520x (1999).

367. Kindon, Nicholas, Meghani Premji, Thom Stephan;
PCT Int. Appl. WO **98,** 54, 180 (Cl. CO7D417/06) (1998); *Chem. Abstr.,* **130,** 38394x (1999).

368. Hu, Chun, Ding, Licheng, Xing, Xin, Vatian;
Zhongguo Yaowu Huaxue Zazhi, **11(5),** 255-58 (2001). *Chem. Abstr.,* **137,** 169475s (2002).

369. Adams Jerryl., Bower Michael J., Hau Ralph F., Don E., Underwood David C.;
Chem. Abstr., **135,** 19649w (2001).

370. Azaryan L. V., Avetisyan S. A., Chachoyan A. A., Bugukyan N. S., Garibdzhanyan B. T.;
Khim. Farm. Zh., **31(6),** 8-10 (1997); *Chem. Abstr.,* **127,** 262648d (1997).

371. Watanabe K. A., Harado Zeidler J.;
J. Med. Chem., **33,** 2145, (1990).

372. Paronikyan E. G., Noravyan A. S.;
Chem. Abstr., **126,** 789332 (1997).

373. M. M. Heravi, M. M. Mojahedi and S. M. Bolourtchian;
Indian J. Chem., **38(B),** 210 (1999).

374. Sidler Daniel R., Larson R. D., Chartrain M., Ikemato N. and Roberge C. M.;
PCT Int. Appl. WO **99** 07, 695 (Cl. CO7D 401/00) (1999); *Chem. Abstr.,* **130,** 182478v (1999).

375. Modica M., Santagati M., Santagati A., Cutul V., Mangano N., Caruso A.;
Pharmazie, **55(7)**, 500-02 (2000); *Chem. Abstr.,* **133,** 252354q (2000).

376. Cho, Eui-Hwan, Chung, Sun, Gan, Lee;
PCT Int. Appl. WO **00** 61, 564 (Cl. CO7D 239/54); *Chem. Abstr.,* **133,** 296448c (2000).

377. Bantick John, Ingall Anthony, Perry Mathew, Reynolds Rachel;
PCT Int. Appl. WO **01** 83, 439 (Cl. CO7D 495/04) (2001); *Chem. Abstr.,* **135,** 357940x (2001).

378. Baldev Kumar, Balbir Kaur and Jatinder Kaur;
Indian J. Chem., **41(B),** 1526-1530. (2002).

379. Abd. El-Galil, E. Arr and M. M. Abdulla;
Indian J. Heterocyclic Chem., **12,** 129-34 (2002).

380. Saladino Reffaele, Ciambecchini Umberto, Mega Giovanni, Mastromarino Paola, Conti Cinzia, Botta Maurizio;
Bioorganic and Medicinal Chem., **10(7),** 2143-53 (2002). *Chem. Abstr.,* **137,** 169362c (2002).

381. Hu Chun, Ding Licheng, Xing Guging, Xin Yutian, Wang Shengfu;
Zhorgguo Yaowu Huaxue Zazhi, **11(5),** 255-58 (2002); *Chem. Abstr.,* **137,** 169475a (2002).

382. Amjad Ali, Gayle E. Taylor, Ken Ellsworth, Georgiana Harris, Ronald Painfer, Lynn L. Silver and Katherine Young ;
J. Med. Chem., **46(10),** 1824-30 (2003).

383. Wohler F. and Liebig;
J. Ann., **3,** 249-267 (1832).

384. Fehling Anon;
Ber., **18,** 1814 (1885).

385. Pelouze;
J. Ann., **10,** 1814 (1834).

386. Moury D. T.;
Chem. Rev., **2,** 189 (1948).

387. Hsiu Shih Mei, Ting Lin Kwang;
Chem. Abstr., **103,** 141038a (1985).

388. Bram G., Loupy A., Pedouassant M.;
Bull. Soc. Chim. Fr., **1,** 124-8 (1986); *Chem. Abstr.,* **105,** 190460g (1986).

389. Nicodemus O.;
German Patent, **463,** 123 (1928).

390. Takabe Akinisa;
Chem. Abstr., **109,** 54333y (1988).

391. Maible A. and Goden F.;
De Compt Rend, **165,** 557(1917); 166,215 (1918), *nn. Chim.* **13,** (1919), *Bull. Sci. Chim.,* **4,** 23, 18 (1918); 25, 588 (1919), 27, 229 (1920).

392. Sibhash D. Bose, B. Jayalakshmi;
J. Org. Chem., **64(5),** 1713-1714 (1999); *Chem. Abstr.,* **230,** 237105d (1999).

393. Verma R. S., Naicker Kannan P.;
Chem. Abstr., **129,** 67576t (1998).

394. Feng Jun-Cai, Liu Bin, Li Dai;
Synth. Commun., **28(20),** 3785-3786 (1998); *Chem. Abstr.,* **129,** 330520i (1998).

395. Sato Hiroshi, Hirose Kench;
Chem. Abstr., **108,** 55670 (1988).

396. Voigl Hans;
Chem. Abstr., **58,** 1412b (1963).

397. Stezhko T. V., Granik V. G., Glushokov R. G., Roshehina L. F., Polezhaeva A. I., Mashkovskii M. O.;
KimFarm Zh., **18(3),** 296-7 (1984); *Chem. Abstr.,* **101,** 90704p (1984).

398. Uhlendorf Jochim, Leyck Sigurd, Nattermann A.;
Chem. Abstr., **100,** 68161s (1984).

399. Bormann Gerhard;
Chem. Abstr., **100,** 68184 b (1984).

400. Lai Hoi Kiong, Davis Robert Allan, Relyea Douglas Irving;
Chem. Abstr., **131,** 170273q (1999).

401. Bimber Russell M.;
Chem. Abstr., **74,** 87655s (1971).

402. Tanaka Masato, Sakakura Toshi Yasu;
Chem. Abstr., **104,** 88317h (1986).

403. Bermanis G. Kolvins, Acena I., Lukeuics E., Veveris M., Kauss V., Trapenster P., Liering E.;
Chem. Abstr., **103,** 59761 (1985).

404. Shepard R. G.;
U.S. US 727149; *Chem. Abstr.,* **111,** 97104h (1998).

405. Pratesi P., Grana E., Villa L.;
Farmaco Ed. Sci., **28 (10),** 753-65 (1973); *Chem. Abstr.,* **80,** 26892u (1974).

406. Makarenich I. F., Mokrou M. V., Topchif L., Kovalev I. P., Sokolova V. E., Gubin Y. I., Bublik N. P., Polyalov V. A.;
Khim. Prir. Soedin, **(5),** 608-12 (1983); *Chem. Abstr.,* **100,** 156894r (1984).

407. Heidenreich Holger, Becker Benedikt;
Chem. Abstr., **100,** 78304u (1988).

408. Sabani Mahmood;
U.S. US, **683,** 618 (Cl. 252-68; 09k5/04) (1997); *Chem. Abstr.,* **128,** 14605z (1998).

409. F. Nobuyuki, K. Hidetoshi, Ooka Hisayoshi;
Chem. Abstr., **131,** 299454w (1999).

410. Kobayashi, Shigco, Tsuchida, Hiroyuki, Yinno, Atusushi;
JPN Kokai Tokkyo Koho JP, **10,** 30035 (98 30, 035). (Cl. C082 13/001) (1998); *Chem. Abstr.,* **128,** 155352b (1998).

411. Peterson I. A., Duck L. E., Davis B. A.;
PCT Int. Appl. WO **48,** 858 (1999); *Chem. Abstr.,* **131,** 243589b (1999).

412. Parmar V. S., Kumar A.;
Bioorg. Med. Chem., **7 (7),** 1425-36 (1999); *Chem. Abstr.,* **131,** 243214q (1999).

413. Rajan C. Khunt, Neela J. Datta and A. R. Parikh;
J. Inst. Chem., **72,** 3 (2000).

414. Parlo Sanna, Antonio Carta, Mohamma E., Rahbar Nikookar;
Eur. J. Med. Chem., **35,** 535-43 (2000).

415. Nosyruva V. V., Trotimov B. A.;
PCT Int. Appl. WO **49,** 148 (Cl. C07D 87422); *Chem. Abstr.,* **136,** 216684a (2002).

416. Catherine Michaux, Jean-Michael Dogne, Stephanie Rolin, Bernard Masereel, John Wouters, Francois Durant;
Eur. J. Med. Chem., **38,** 703-10, (2003).

417. Atwal Karnails, Grover Gary J., Ding Charles C., Stein Philip P., Woyd John, Ahmed Saleem, Hamann Lawrence G., Green David, Ferrara Francis N.;
PCT Int. Appl. WO **03** 50, 261 (Cl. C12N); *Chem. Abstr.,* **139,** 53018g (2003).

418. F. V. Loffe;
Khim. Geterokeikl Soedin, **6** 1089 (1968); *Chem. Abstr.,* **70,** 72338 (1968).

419. V. M. Parikh;
"*Absorption Spectroscopy of Organic Molecules*" Addision-Wesley Pub. Co. London, 243-258 (1978).

420. C. N. R. Rao;
"*Chemical Applications of Infra-red Spectroscopy*" Academic Press, New York, 157-194 (1963).

421. A. R. Kartizky and R. Alan Jones;
J. Chem. Soc., 2942 (1960).

422. "*Strukturaufklarang Organischer Verbindungen*" Mit Spektroskopis chem methoden zweite, uberarbeitete and erganzie Autlage (Springer-Veriag, Bertin Heidelberg, New York-1981).

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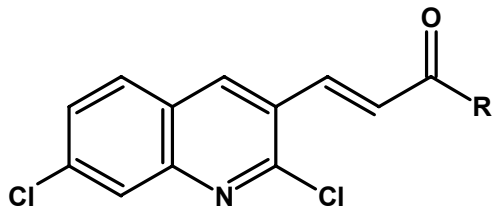

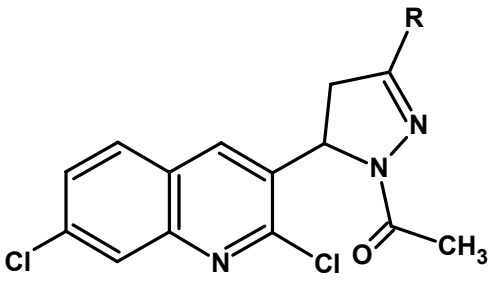

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4-NH_2-C_6H_4	4-Br-C_6H_4
4-Br-C_6H_4	4-Cl-C_6H_4
4-Cl-C_6H_4	4-F-C_6H_4
2,6-$(OH)_2$-C_6H_3	C_4H_3O
4-F-C_6H_4	2-OH-C_6H_4
C_4H_3O	4-OH-C_6H_4
2-OH-C_6H_4	4-OCH_3-C_6H_4
4-OH-C_6H_4	4-CH_3-C_6H_4
4-OCH_3-C_6H_4	3-NO_2-C_6H_4
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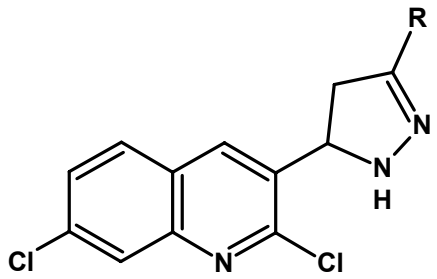

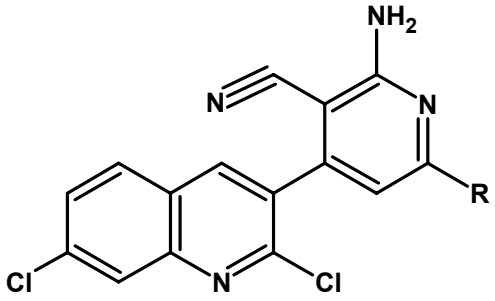

R	R
C_6H_5	C_6H_5
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4-Br-C_6H_4	4-Br-C_6H_4
4-Cl-C_6H_4	4-Cl-C_6H_4
4-F-C_6H_4	4-F-C_6H_4
2-OH-C_6H_4	C_4H_3O
4-OH-C_6H_4	2-OH-C_6H_4
4-OCH_3-C_6H_4	4-OH-C_6H_4
4-CH_3-C_6H_4	4-OCH_3-C_6H_4
3-NO_2-C_6H_4	4-CH_3-C_6H_4
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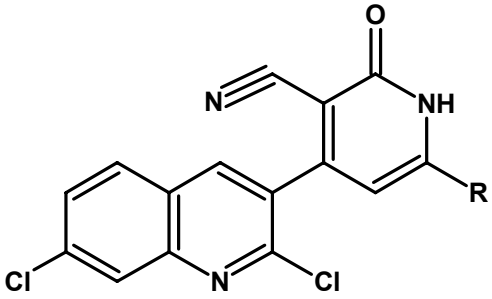
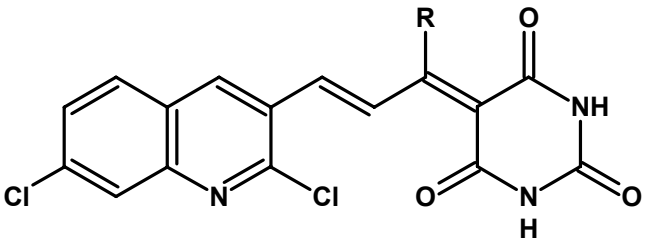
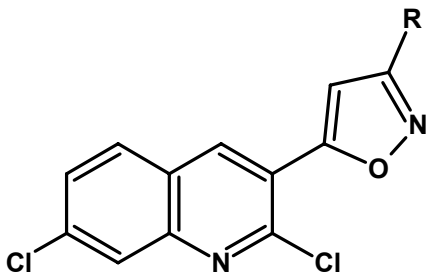
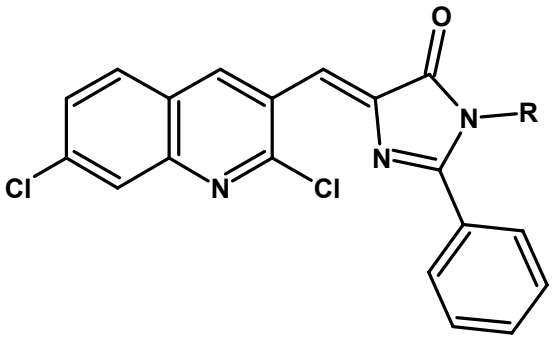




R	R
C_6H_5	C_6H_5
3-NH_2-C_6H_4	3-NH_2-C_6H_4
4-NH_2-C_6H_4	4-NH_2-C_6H_4
4-Br-C_6H_4	4-Br-C_6H_4
4-Cl-C_6H_4	4-Cl-C_6H_4
2,6-$(OH)_2$-C_6H_3	2,6-$(OH)_2$-C_6H_3
4-F-C_6H_4	4-F-C_6H_4
2-OH-C_6H_4	2-OH-C_6H_4
4-OH-C_6H_4	4-OH-C_6H_4
4-OCH_3-C_6H_4	4-OCH_3-C_6H_4
4-CH_3-C_6H_4	4-CH_3-C_6H_4
3-NO_2-C_6H_4	3-NO_2-C_6H_4
4-NO_2-C_6H_4	4-NO_2-C_6H_4





R	R
C_6H_5	C_6H_5
3-NH_2-C_6H_4	2-Cl-C_6H_4
4-NH_2-C_6H_4	3-Cl-C_6H_4
4-Br-C_6H_4	4-Cl-C_6H_4
4-Cl-C_6H_4	2,5-$(Cl)_2$-C_6H_3
2,6-$(OH)_2$-C_6H_3	3,4-$(Cl)_2$-C_6H_3
4-F-C_6H_4	3-Cl,4-F-C_6H_3
C_4H_3O	2-OCH_3-C_6H_4
2-OH-C_6H_4	4-OCH_3-C_6H_4
4-OH-C_6H_4	2-CH_3-C_6H_4
4-OCH_3-C_6H_4	4-CH_3-C_6H_4
4-CH_3-C_6H_4	2-NO_2-C_6H_4
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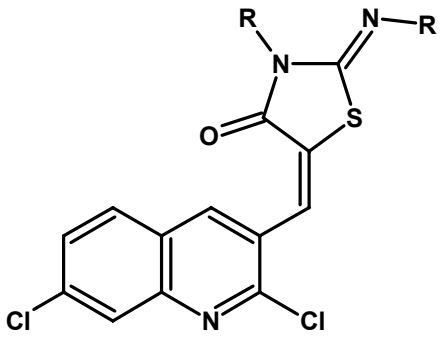
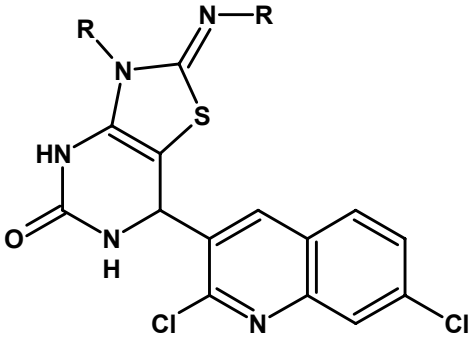
4-NO_2-C_6H_4	4-NO_2-C_6H_4





R	R
C_6H_5	C_6H_5
4-Cl-C_6H_4	4-Cl-C_6H_4
3,4-$(Cl)_2$-C_6H_3	3,4-$(Cl)_2$-C_6H_3
4-F-C_6H_4	4-F-C_6H_5
2-OCH_3-C_6H_4	2-OCH_3-C_6H_4
4-OCH_3-C_6H_4	4-OCH_3-C_6H_4
2-CH_3-C_6H_4	2-CH_3-C_6H_4
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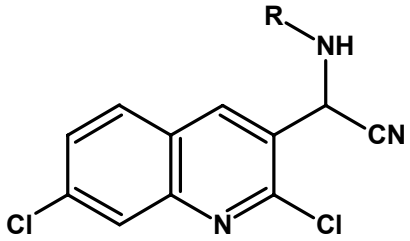

R
C_6H_5
2-Cl-C_6H_4
3-Cl-C_6H_4
4-Cl-C_6H_4
2,6-$(Cl)_2$-C_6H_3
3,4-$(Cl)_2$-C_6H_3
3-Cl, 4-F-C_6H_3
4-F-C_6H_4
2-OCH_3-C_6H_4
4-OCH_3-C_6H_4
2-CH_3-C_6H_4
4-CH_3-C_6H_4
2-NO_2-C_6H_4
3-NO_2-C_6H_4
4-NO_2-C_6H_4