STUDIES
ON
HETEROCYCLIC COMPOUNDS

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 elaborated in this thesis is my own work, which is carried out under the supervision of ***Dr. H. S.* Joshi.** The thesis adds many useful information in the field of organic chemistry. The work is supported by relevant references.

Date : 26 - 02 -2004
Place : Rajkot

(Mr. Mayur R. Patel)

This is to certify that the work submitted by ***Mr. Mayur R. Patel*** for the Ph. D. Degree of Saurashtra University is his own work, which may lead to the advancement in the field of **Organic Chemistry**. The thesis has been built up under my supervision.

Date : 26 - 02 -2004
Place : Rajkot

Dr. H. S. Joshi
Associate Professor,
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Acknowledgements

It is a matter of immense pleasure and proud privilege to me to express my heartful gratitude to all those personality who have been helping me in diversified ways.

In the first place I offer salutations and adorations upto the Universal Being, who is Supreme source of all inspirations. I bow my head in most utter humility and complete dedication to the God Almighty.

Words are insufficient to record my deep sense of gratitude to my esteemed teacher, mentor and guide ***Dr. H. S. Joshi****, Associate Professor, Department of Chemistry, Saurashtra University, Rajkot-5 as his constant inspiration with keen interest and ever vigilant guidance without which this task could not have been achieved. He has not only guided me but also acted as co-traveler too, throughout my research work and ensured that I reach destination. The only way to thank him would be perhaps to strive to work similarly in years ahead, and continue the chain succession.*

My gratitudes are also due to ***Dr. H. H. Parekh****, Prof. and Head, Department of Chemistry, Saurashtra University, Rajkot for her fruitful suggestions, constructive and comprehensive exchange of ideas throughout the course of my work.*

I am beholden to entire Chemistry Fraternity for their ungrunding co-operation, however special mention is ***Dr. A. R. Parikh****, Retired Prof. and Head for his affection, moral support and inspiration rendered to me during my course of study.*

I extend my cordial thanks to all the professors of department for their kind co-operation, moral support and warm encouragement during the course of my study.

As with the completion of this task, I find myself in a difficult position of attempting to express my deep indebtedness to my never failing friends ***Ashish, Hitarth, Sunil, Dipen, Tapan, Dinesh, Paresh, Praful, Dushyant, Ragin, Kena, Sarika, Anjana****, and* ***Priti*** *all other seniors and juniors for the stimulating companionship and timely assistance. I am highly thankful to* ***Dr. Ranjan*** *for her kind cooperation and invaluable help during research work.*

My vocabulary fails to express my feelings in acknowledging the tremendous debt that I owe to my father ***Ramnikbhai****, mother* ***Urmilaben****, grand father* ***Popatbhai****. It is only because of their blessings, continuous encouragement and inspiration that I have been able to steer through the stresses and strains of this study. My thanks are also due to kind and affectionate inspiration and amiability from my younger brother* ***Rushikesh****. However I assure them to be worthy of whatever they have done for me.*

I am thankful to authorities of CDRI Lucknow, CIL Chandigarh and Professor and Head, Department of Chemistry, Saurashtra University, Rajkot for providing facilities for spectral studies.

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

And finally I express my grateful acknowledgements to the authorities of Saurashtra University for providing me research facilities.

Mayur R. Patel

CONTENTS

“STUDIES ON HETEROCYCLIC COMPOUNDS”

A comprehensive summary of the work to be incorporated in the thesis entitled “**STUDIES ON HETEROCYCLIC COMPOUNDS”** included investigations pertaining to **CINNOLINE** and its derivatives.

The aim of research is to be develop a new bioactive entities, especially with antimicrobial and antitubercular activities bearing a heterocyclic ring system namely cinnoline.

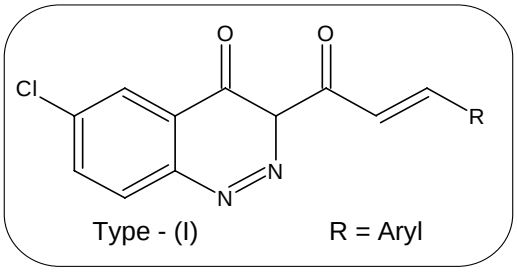
Our strategy is based on literature precedents that the combination of fused bicyclic system with pharmacologically active heterocyclic entities in molecular frame work, which may result in compounds with better drug potential. Bicyclic compounds with heteroatoms have a wide range of physiological activities including bactericidal, fungicidal, antitubercular, psychotropic, antitumor, spasmolytic, vasodilator etc. Among their vast number of synthesized heterocyclic compounds, derivatives of cinnoline were found to have the most promising tuberculostatic activity.

Keeping in association with cinnoline of various activities, it was thought worthwhile to synthesize some novel heterocycles, which have been described as under.

PART-I : STUDIES ON ISOXAZOLES

Isoxazole derivatives represents one of the modest classes of compounds possessing wide range of therapeutic activities such as antidepressants, muscle relaxant, antidiabetic, antiinflammatory, analgesic etc. With a view to getting better therapeutic agent and to evaluate its pharmacological profile, different type of isoxazole have been designed and synthesized, which have been described as under.

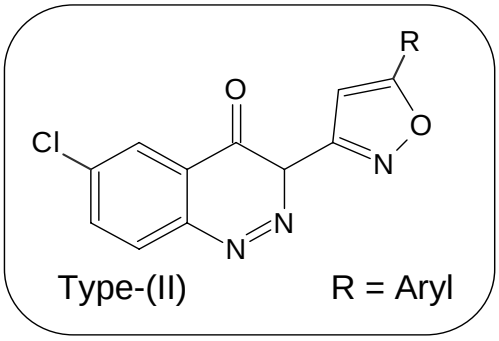
SECTION-I: Synthesis and biological screening of 6-Chloro-3-[(2E)-3-arylprop-2-enoyl]cinnolin-4(3H)-one



The chalcones of Type-(I) have been synthesized by the condensation of 3-acetyl-6-chlorocinnolin-4(3H)-one with various aldehydes.

SECTION-II : Synthesis and biological screening of 6-Chloro-3-(5-aryl isoxazol-3-yl)-cinnolin-4(3H)-one

Isoxazole derivatives of Type-(II) have been synthesized by the condensation of the chalcones of Type-(I) with hydroxylamine hydrochloride in presence of sodium acetate in acetic acid.

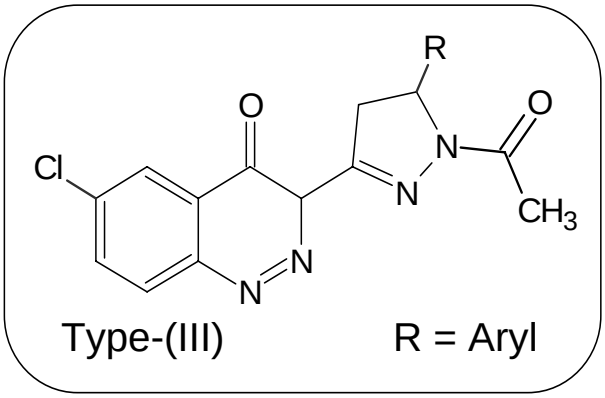


PART-II : STUDIES ON PYRAZOLINES

Pyrazolines as a class of heterocyclic compounds have been studied extensively for the past several years. They are associated with broad spectrum of biological activities like anticancer, anticonvulsant, insecticidal, antipyratic etc. Keeping in view of these diversified biological activities, we have undertaken the synthesis of some new pyrazoline derivatives possessing better biological activity which

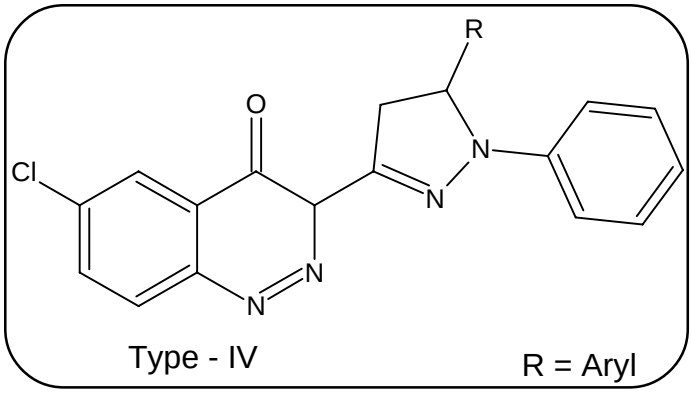
have been described as under.

SECTION-I : Synthesis and biological screening of 3-(1-Acetyl-5-aryl-4,5-dihydro-1H-pyrazol-3-yl)-cinnolin-4(3H)-one



Pyrazoline derivatives of Type-(III) have been synthesized by the condensation of the chalcones of Type-(I) with hydrazine hydrate in glacial acetic acid.

SECTION-II : Synthesis and biological screening of 6-Chloro-3-(1-Phenyl-5-aryl-4,5-dihydro-1H-pyrazol-3-yl)-cinnolin-4(3H)-one



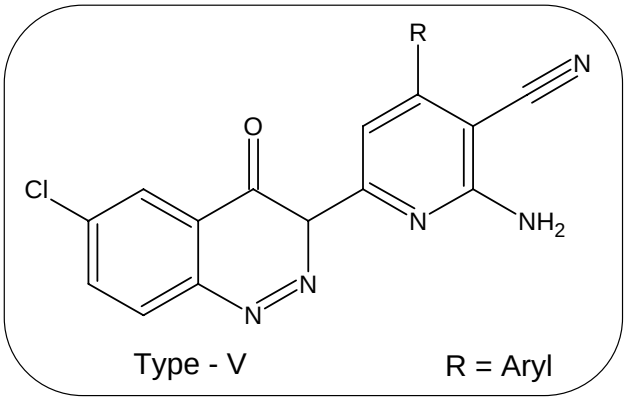
Pyrazoline derivatives of Type-(IV) have been prepared by the condensation of the chalcones of Type-(I) with phenyl hydrazine.

PART-III: STUDIES ON CYANOPYRIDINE

In recent years, much interest has been focused on the synthesis of pyridines as the pyridine ring system is associated with valuable pharmacological activity like

antibacterial, antimalarial, antihypertensive, antifungal, anticonvulsant etc. Consideraing these facts we thought it is worthwhile to synthesize some novel derivatives in association with cinnoline nucleus in search of better potential drugs.

SECTION-I: Synthesis and biological screening of 2-Amino-4-aryl-6-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)nicotinonitrile



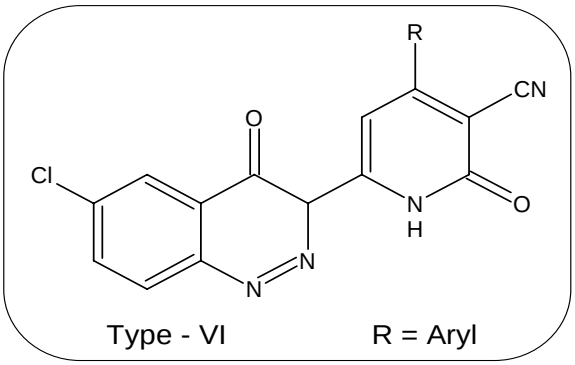
Cyanopyridine derivatives of Type-(V) have been synthesized by the reaction of the chalcones of the Type-(I) with malononitrile in presence of ammonium acetate.

Part-IV: STUDIES ON NICOTINONITRILE

Nicotinonitrile derivatives have been reported to have various biological activities like antibacterial, antifungal, antihypertensive, antiviral, antiinflammtory, etc. From the above facts led us to prepared better therapeutic agents which have been described as under.

SECTION-I: Synthesis and biological screening of 4-Aryl-6-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile

Nicotinonitrile derivatives of Type-(VI) have been synthesis of the chalcones of the Type-(I) with ethyl cyanoacetate in presence of ammonium acetate.

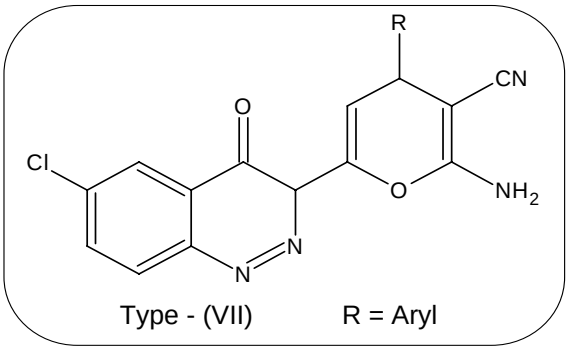


Type - VI R = Aryl

PART- V: STUDIES ON CYANOPYRAN

Cyanopyran derivatives have been reported to have various pharmacological activities like antibacterial, antisecretary, antiviral, antifungal etc. In order to develope better medicinally important compounds, it was considered of interest to synthesize some cyanopyran derivatives shown as under.

SECTION-I: Synthesis and biological screening of 2-Amino-4-chloro-6-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-4H-pyran-3-carbonitrile



Type - (VII) R = Aryl

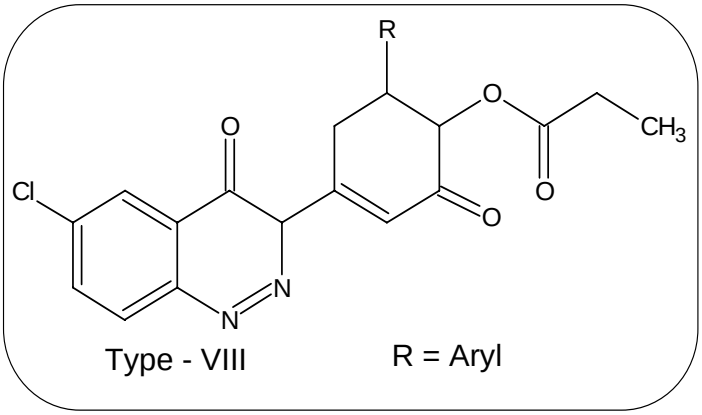
Cyanopyran derivatives of Type-(VII) have been synthesized by the reaction of the chalcones of Type-(I) with malononitrile in pyridine.

PART-VI: STUDIES ON INDAZOLES

Various derivatives of indazole exhibit interesting biological properties like

anticancer, antiinflammatory, anticonvulsant, antipyretic etc. With a view to prepare more potential drugvalue compounds we have carried out the synthesis of indazole derivatives, which have been briefed as under.

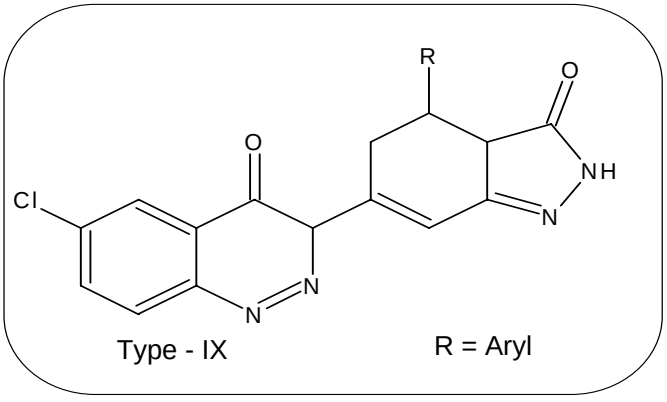
SECTION-I: Synthesis and biological screening of Ethyl-6-aryl-4 -(6-chloro-4-oxo-3,4-dihydrocinnoline-3-yl)-2-oxocyclohex-3-ene-1-carboxylate



Type - VIII R = Aryl

Cyclohexenone derivatives of Type-(VIII) have been synthesized by the cyclocondensation of the chalcones of Type-(I) with ethyl acetoacetate in presence of sodium ethoxide.

SECTION-II: Synthesis and biological screening of 6-Chloro-3-(4-Aryl-3-oxo-3,3a,4,5-tetrahydro-2H-indazol-6-yl)-cinnolin-4(3H)-one



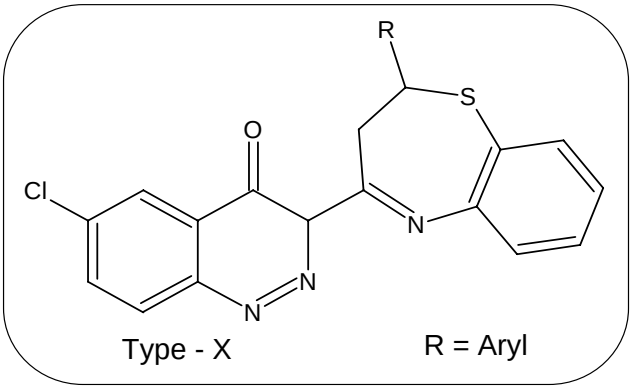
Type - IX R = Aryl

Indazole derivatives of Type-(IX) have been prepared by the condensation of cyclohexenone derivatives of Type-(VII) with hydrazine hydrate.

PART-VII: STUDIES ON BENZOTHIAZEPINE DERIVATIVES

Various types of benzothiazepine derivatives shows wide range of biological activity such as anticancer, antifungal, antimicrobial, antitubercular, antidiabetic etc. With a view to get better therapeutic agents, we have synthesized different types of benzothiazepine derivatives which have been described as under.

SECTION-I: Synthesis and biological screening 6-Chloro-3-(2-aryl-2,3 -dihydro-1,5-benzothiazepine-4-yl)cinnolin-4(3H)-one



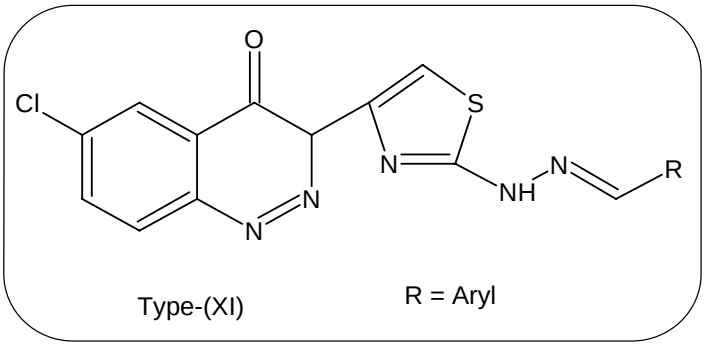
Type - X R = Aryl

Benzothiazepine derivatives of Type-(X) have been prepared by condensation of chalcones of Type-(I) and 2-amino thiophenol in presence of piperidine.

PART-VIII: STUDIES ON THIAZOLE DERIVATIVES

Thiazole and its derivatives endowed with wide range of therapeutic activities like antimicrobial, antitubercular, anticancer, antidiabetic, antiinflammatory etc. In order to prepare compounds possesing better biological activities, it was considered worthwhile to synthesize thiazole derivatives shown as under.

SECTION-I Synthesis and biological screening of (1E)-Aryl-[4-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-1,3-thiazol-2-yl]hydrazone



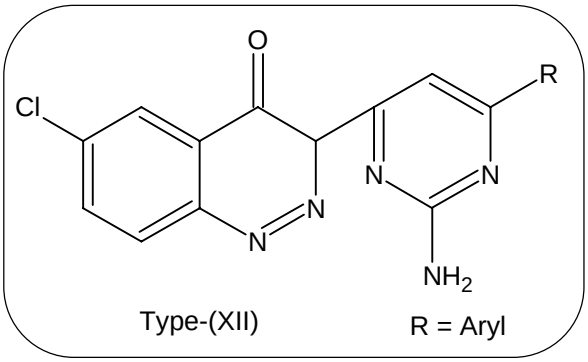
Type-(XI) R = Aryl

Thiazole derivatives of Type-(XI) have been prepared by condensation of bromo acetyl cinnoline and different types of thiosemicarbazones, which was prepared by condensation of aryl aldehyde and thiosemicarbazide.

PART-IX: STUDIES ON PYRIMIDINE DERIVATIVES

Pyrimidine derivatives are biologically important products and their synthesis and chemistry have received remarkable attention. It has been reported that pyrimidine derivatives are associated with various biological activities like antifungal, anti tubercular, antibacterial, herbicidal etc. These valid observations prompted us to synthesize some pyrimidine derivatives with the hope that they might be important therapeutic nucleus of choice, which have been described as under.

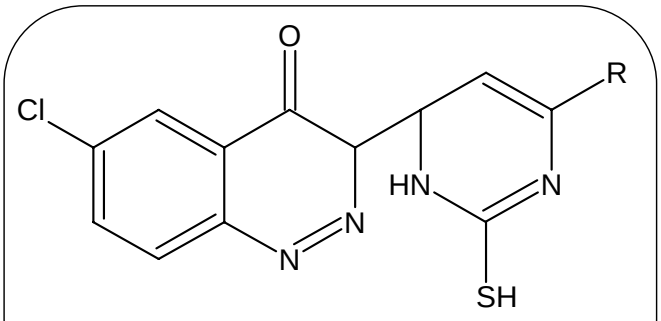
SECTION-I: Preparation and biological screening of 3-(2-Amino-6--arylpyrimidin-4-yl)-6-chlorocinnolin-4(3H)-one



Type-(XII) R = Aryl

Pyrimidine derivatives of Type-(XII) have been prepared by the reaction of the chalcones of Type-(I) with guanidine hydrochloride in presence of alcoholic potassium hydroxide.

SECTION-II: Preparation and microbial evaluation of 6-Chloro-3-(6-aryl-2-mercapto-3,4-dihydropyrimidin-4-yl)cinnolin-4(3H)-one



Type-(XIII) R = Aryl

Pyrimidine derivatives of Type-(XIII) have been synthesized by the reaction of the chalcones of Type-(I) with thiourea in presence of alcoholic potassium hydroxide.

The constitution of all above products has been supported by elemental analyses and spectral studies like IR, ^{1}H NMR and Mass spectroscopy. The purity of the compounds synthesized was checked by TLC.

***In vitro* study on multiple biological activities:**

- All the compounds have been evaluated for their antibacterial activity towards Gram +ve and Gram -ve bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration 40 mg/ml. The biological activities of the synthesized compounds have been compared with standard drugs.

- Some of the selected compounds have been sent to Tuberculosis Antimicro bial Acqistion Coordinating Facility (TAACF) Alabama, USA, for antimicro-

bial data of synthesized compound. The compounds have been screened for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis $H_{37}Rv$*** at a concentration of 6.25 mg/ml using Rifampin as a standard drug.

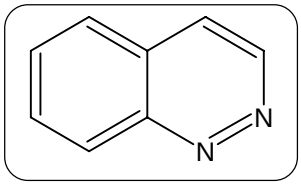
Date:

Signature of Guide Signature of Student

(Dr. H. S. Joshi) (Patel Mayur R.)

INTRODUCTION

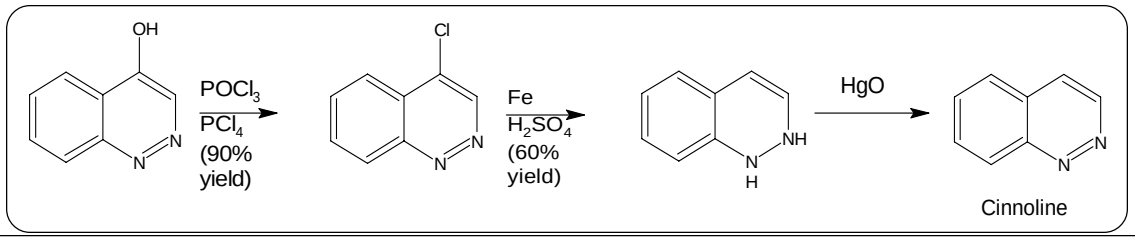
The discovery of cinnoline or 1,2-diazanaphthalene or benzo[c]pyridazine dates from, but the compound and its derivatives have not received the attention accord related heterocyclic nitrogen compounds. The first synthesis of cinnoline was reported in 1883 by von Richter[1]. A number of substituted cinnolines have been described as dyes[2-6].



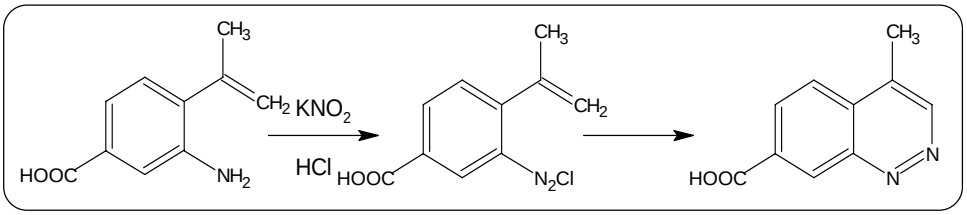
SYNTHETIC ASPECTS

The diazonium chloride obtained from o-amino phenylpropiolic acid was heated in water solution at 70^0C. Cooling caused the separation of 4-hydroxycinnoline-3-carboxylic acid in quantitative yield. When this acid was heated above its melting point, carbon dioxide was liberated and 4-hydroxy cinnoline was formed in nearly theoretical yield. Distillation of 4-hydroxy cinnoline with zinc dust furnished a small amount of basic oil, which was assumed to be cinnoline.

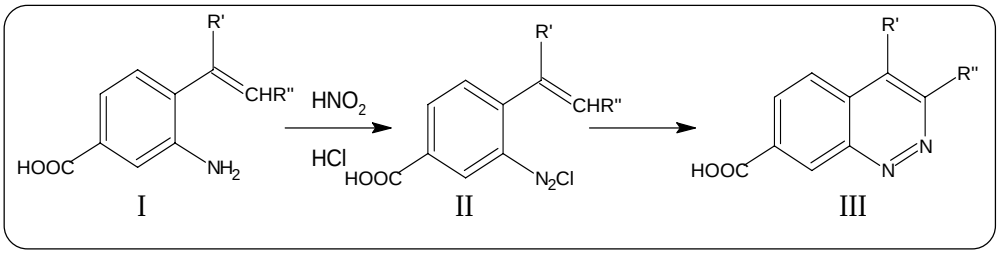
Busch and Rast[7] converted the 4-hydroxy cinnoline successfully to cinnoline via the 4-chloro compound.



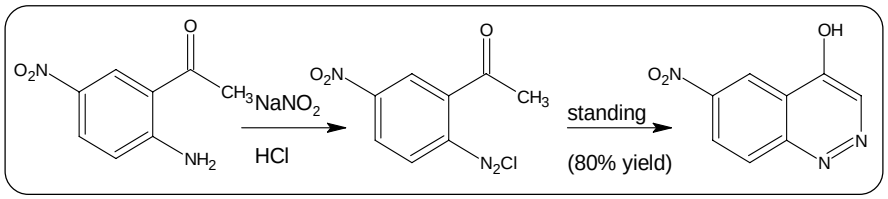
When diazonium salts prepared from certain o-aminophenylethylenes are allowed to stand, cinnolines are formed. When diazotized 3-amino-4-isopropenylbenzoic acid was allowed to stand at room temperature it undergo to ring closure to 4-methylcinnoline-7-carboxylic acid was found by Widman[8,9].



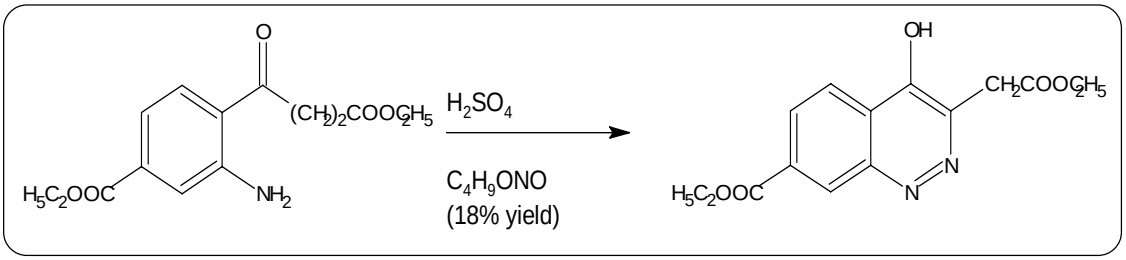
Stoermer, Gaus and Fincke[10,11], extended this method. Diazotization of the substituted o-aminophenylethylene was followed by cyclisation, which usually occurred spontaneously at room temperature in nearly quantitative yield.



Borsche and Herbert[12] diazotized 2-amino-5-nitroacetophenone and allowed the diazonium salt solution to stand at room temperature. The product, 4-hydroxy-6-nitrocinnoline, separated in 80 % yield.

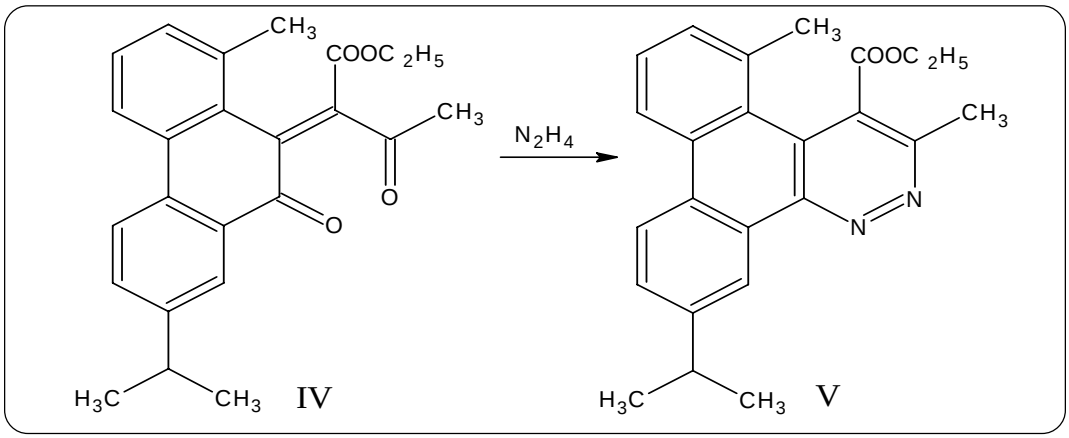


Koelsch[13] carried out a similar diazotization and ring closure.

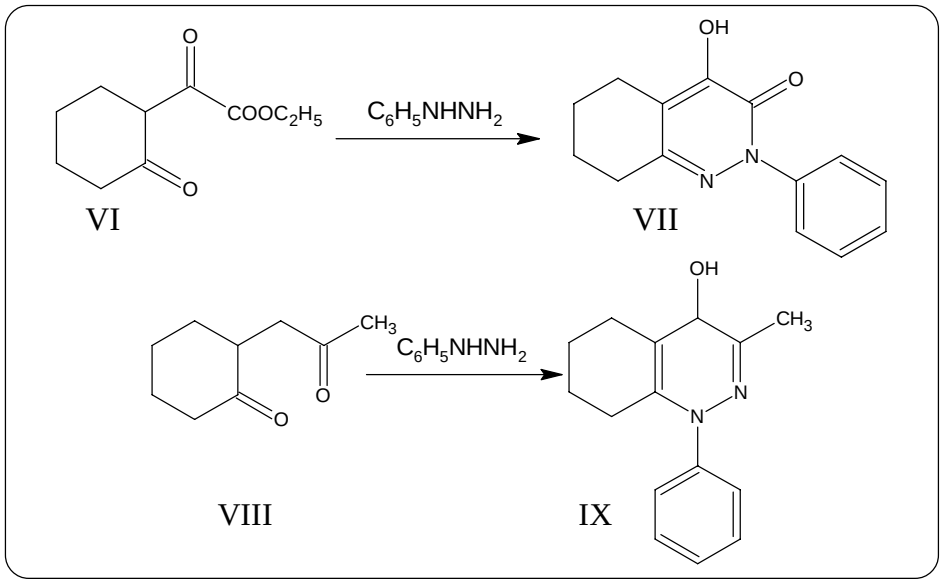


The reaction of a dicarbonyl compound with hydrazine to form an azines is well known. This reaction has been used to advantage by a number of workers for the prepa

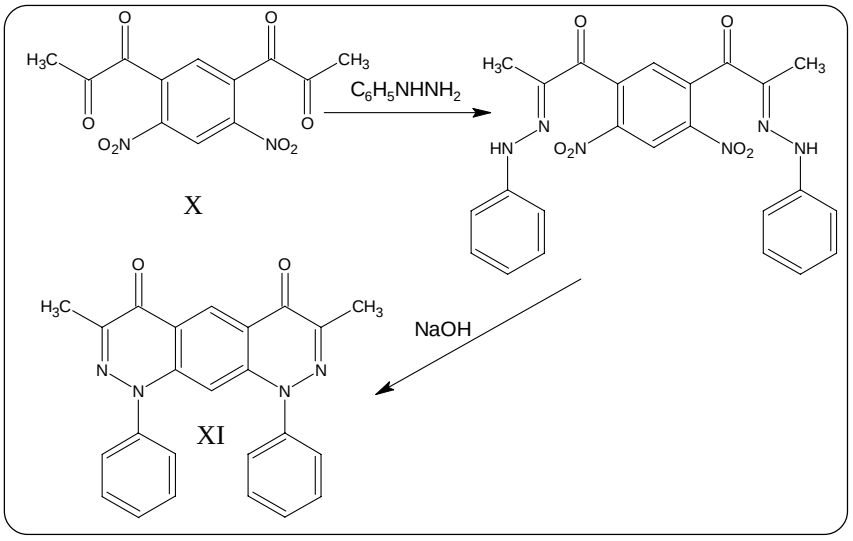
ration of cinnolines from certain 1,4-dicarbonyl compounds. An example is provided by Heiduschka and Khudadad[14], who synthesized ethyl 1,5-dimethyl-11-isopropyldibenzo [f, h] cinnoline-4-carboxylate (V) by the condensation of “retoxyleneaceto acetic ester” (IV) with hydrazine.



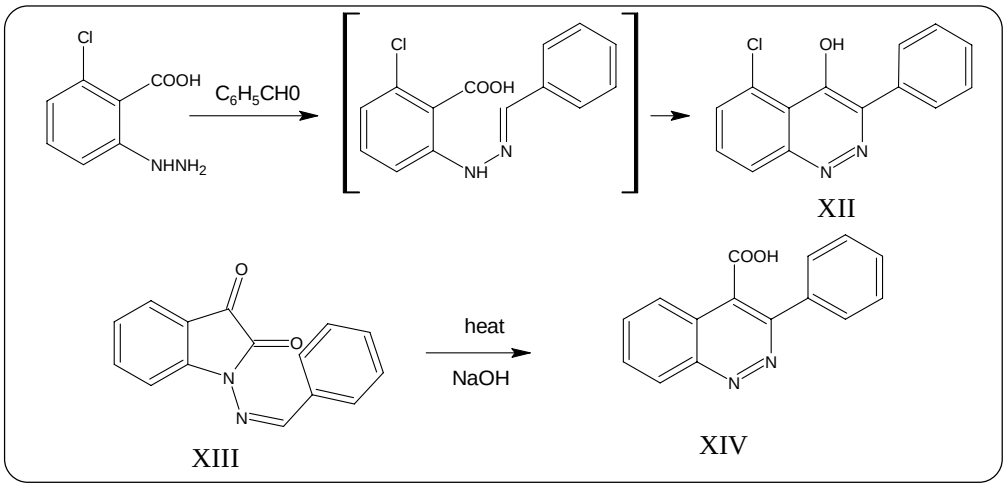
Reaction of phenyl hydrazine with ethyl cyclohexanoxalate gave 5, 6, 7, 8-tetrahydro-4-hydroxy-2-phenyl-3(2)-cinnoline (VII)[15,16]. Reaction of phenyl hydrazine with acetonyl cyclohexanone (VIII) furnished 1, 4, 5, 6, 7, 8-hexahdro-3-methyl-1-phenyl cinnoline (IX).



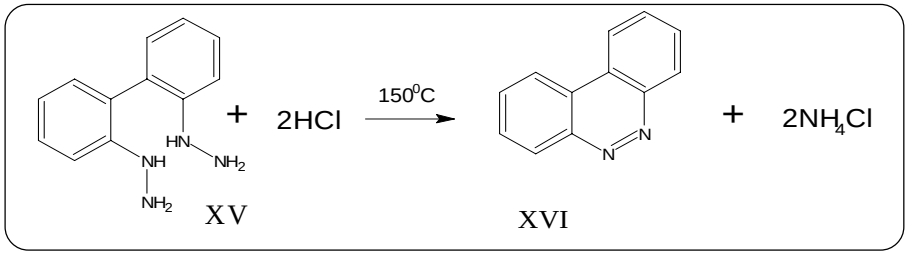
Closely related to these reactions with phenyl hydrazine is the synthesis of 3, 7-dimethyl-1, 9-diphenyl pyridazo [4, 3 - g] cinnoline-4, 6 (1, 9)-dione (XI) by Ruggi and Straub[17].



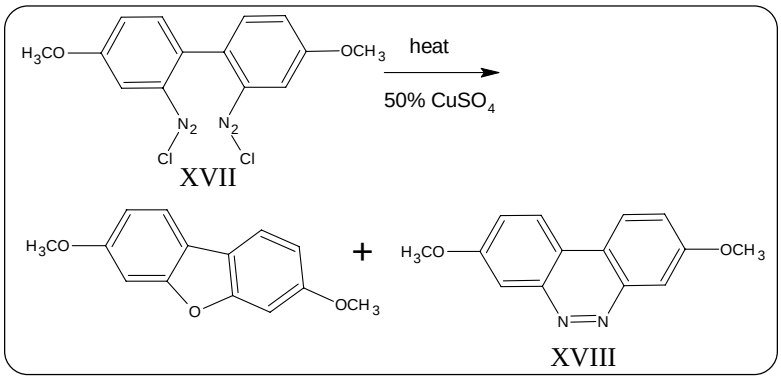
5-Chloro-4-hydroxy-3-phenyl cinnoline (XII) was obtained in low yield by Pfannstiel and Janecke[18], and 3-phenyl-cinnoline-4-carboxylic acid (XIV) was considered to be the product obtained by Stolle and Becker[19] in the following reactions.



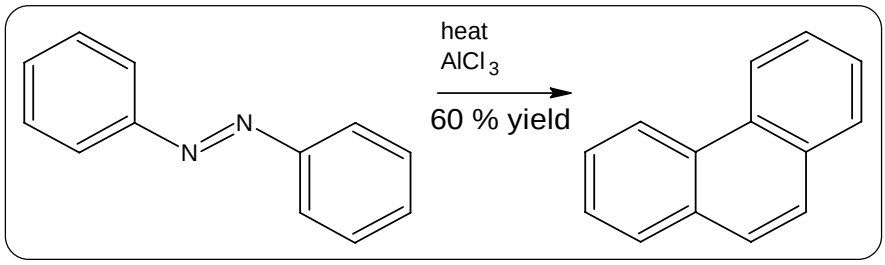
A dihydrazino compound has also been used for the preparation of a cinnoline. When 2,2'-dihydrazinobiphenyl (XV) was heated with hydrochloric acid under pressure, Tauber[20] was able to obtain benzo[c]cinnoline (XVI) in quantitative yield. Tauber likewise obtain benzo[c] cinnoline by heating diacetyl derivative of (XV).



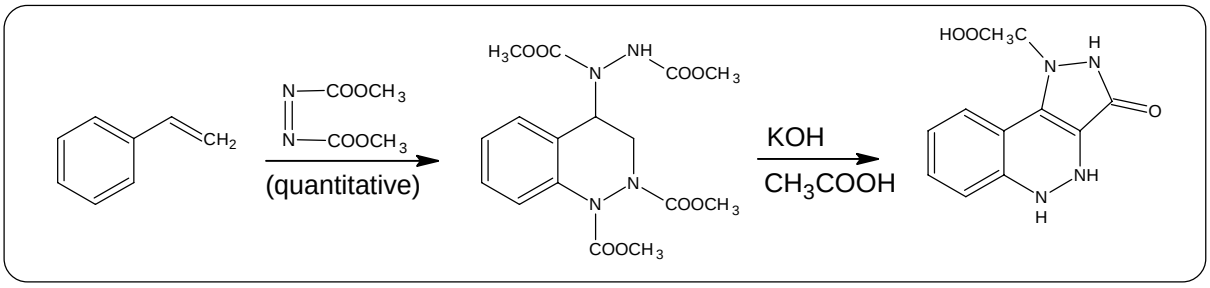
In 1935, Hata, Tatematsu and Kubota[21] obtained 3,8-dimethoxybenzo[c]cinnoline (XVIII) as a by product in their synthesis of 2,7-dimethoxydiphenylene oxide by treatment of tetraazotized 2,2'-diamino-4,4'-dimethoxy biphenyl (XVII) with copper sulphate.



The conversion of a few azo compounds to cinnolines has been reported. The preparation of benzo[c]cinnoline has been described in a patent[1] which calls for the fusion of azobenzene with aluminium chloride and sodium chloride at 120^{0}C. 3,8-dimethyl benzo[c]cinnoline was similarly prepared from m.m'-diazobistoluene at 100^{0}C in 25 % yield; 3,8-tetramethyldiaminobenzo[c]cinnoline, from m,m'-azobisdimethylaniline at 100^{0}C in 40 % yield.



The addition of dimethyl azodicarboxylate to styrene provides the only examples of cinnoline formation by means of a Diels-Alder reaction[22]. Methylstyrene, propenylbenzene, and stillbene failed to give cinnoline type compounds when treated with dimethyl azodicarboxylate.



REACTION MECHANISM

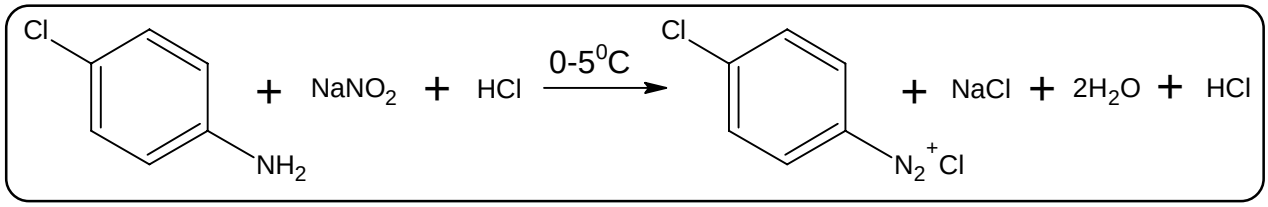
Mechanism of cinnoline nucleus can be explain on the basis of following three steps which is given as below.

(i) Diazotization,

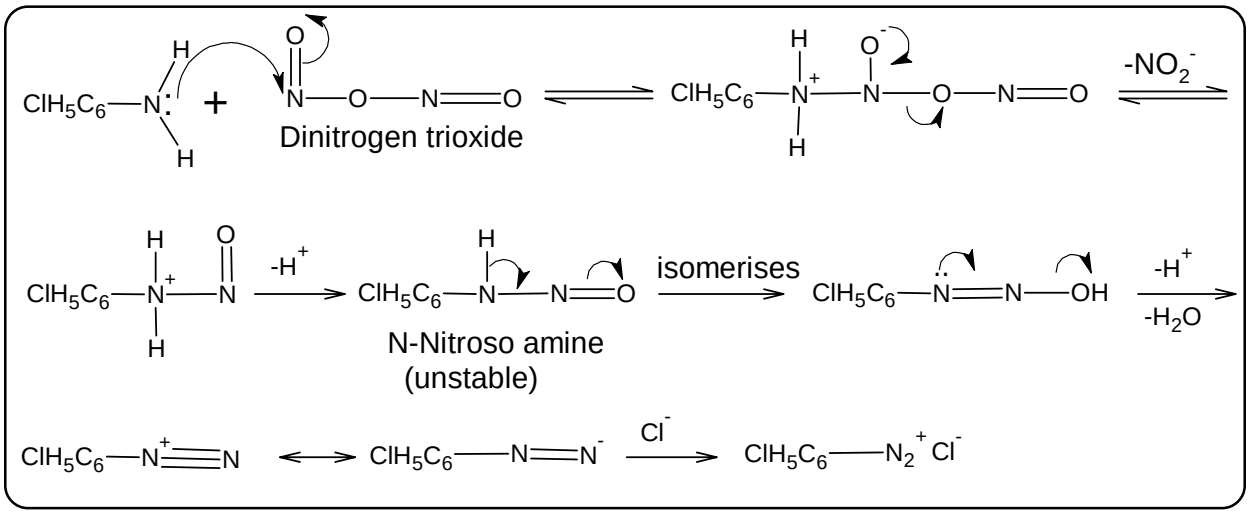
(ii) Coupling and

(iii) Cyclization.

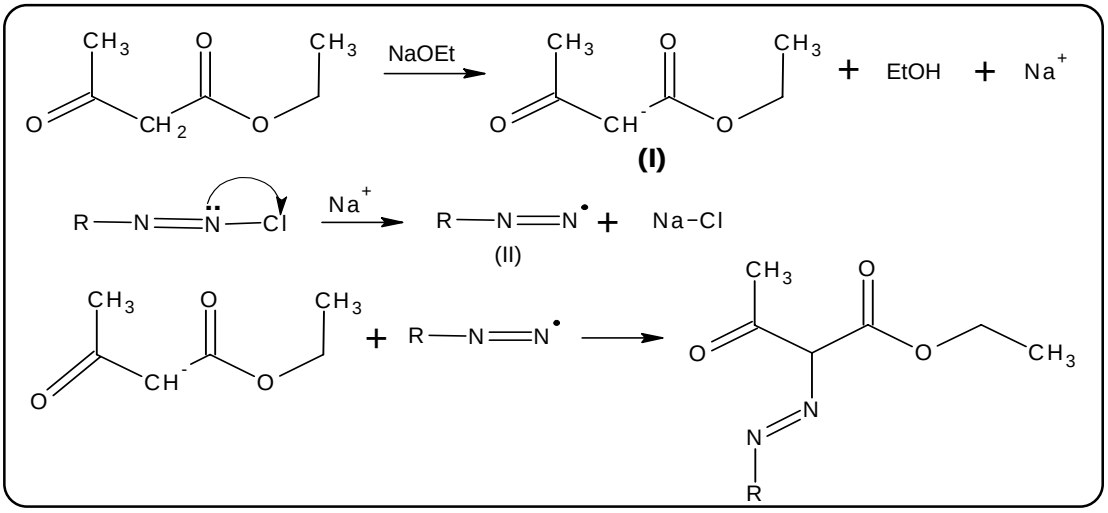
(i) Amine react with nitrous acid to yield diazonium salts via a number of intermediate species. This reaction is called *Diazo reaction*. Since it was discovered by Johan Peter Griess (1858) it is referred to as Griess Diazo reaction[23,24].



The various steps involved in the diazo reaction are as under:

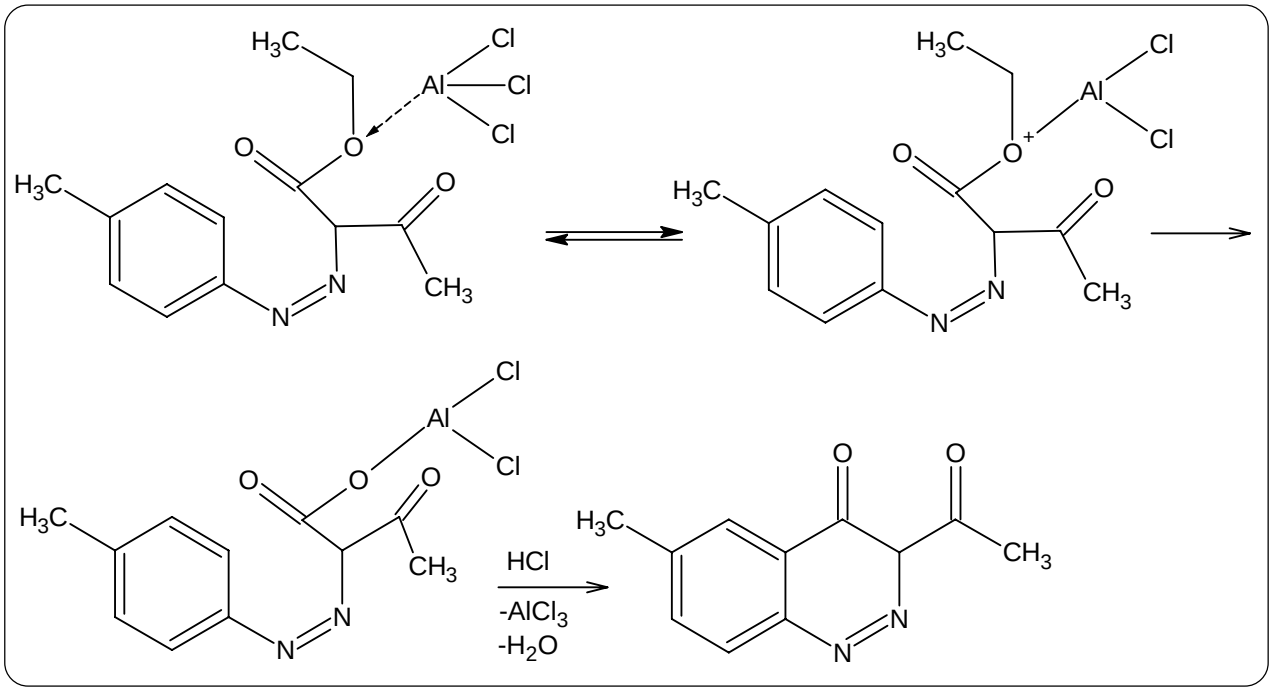


(ii) Diazonium salts reacts with aromatic amines, phenols and active mathylene group to give azo compounds having the general formula ArN=NAr . The reaction is known as coupling reaction. The coupling reaction is electrophilic substitution involving the diazonim ion, which reacts at the position of greatest electron avail ability.



Ethoxide ion attacks on active methylene group and takeup proton and forms carbonion (I). In another way sodium ion attacks on diazonium salt and forms cation (II), which on reaction with carbonion of ester to forms diazo derivatives.

(iii) In third step of cyclization, aluminium chloride withdraw electron from the acyl-oxygen bond and facilitates the initial heterolysis. The resulting cation then at tack on the ring of anion at the avalible ortho position.



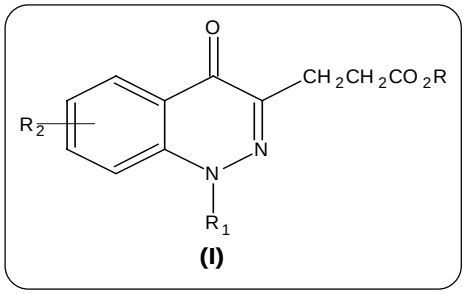
THERAPEUTIC IMPORTANCE

Heterocyclic annelated pyridazines attract considerable attention, which mainly arises from the large variety of interesting pharmacological activities observed with pyridazine derivatives[25]. The modern discovery[26] of a natural antifungal, antibiotics, containing this heteroarene system, most probably will stimulate even broader interest in 1,2-diazine chemistry. On the other hand, derivatives of cinnolines and their benzo and heterocyclic analogs exhibit biological activity in various areas, including antihypertensive, antithrombotic, antitumor, antisecretory and bactericidal activities[27-30]. 4-Amino-cinnolines became of recent importance due to their antimicrobial, antihistamine and insecticide properties[31], its derivatives have been extensively utilized as intermediate for the synthesis of fused cinnolines of potential biological activity[32-35]. A. M. Amer[36] et al. have reported the synthesis and potential biological activity of cinnoline.

Cinnoline derivatives have been found to possess anumber of therapeutic activities like,

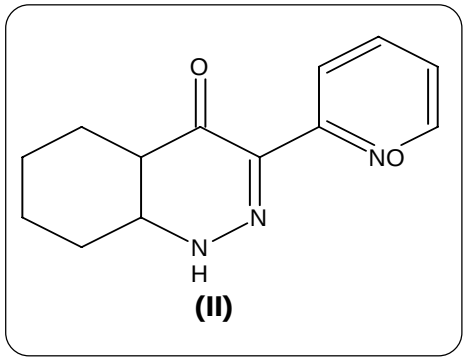
1. Immunosuppressants[37],
2. Antiallergic[38],
3. Herbicides[39],
4. Antimicrobial[40, 41],
5. Antiinflmmatory[42],
6. Antibacterial[43],
7. Antimicrobial[44],
8. Anti-anxiety[45],
9. Herbicides[46],

Furthermore, Jones Geraint[47] have synthesized 1,4-dihydro-4-oxo-3-cinnolinyl propionates (I) and tested as immunosuppressants. Stanczak A. et al.[48] have also synthesized and checked the action on the central nervous system of N^2-substituted cinnoline derivatives.



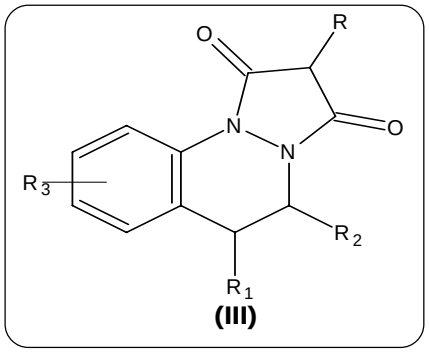
(I)

Garcia and co-workers[49] have reported hypotensive activity of 3-hydrazinethieno(2,3-h)cinnoline. Holland D. and co-workers[50] have prepared cinnoline-3-propionic acids as an orally active antiallergic substances. 3-(2-pyridinyl)-4(1H)-cinnoline-N-oxide (II) are reported as the antisecretory agents[51].



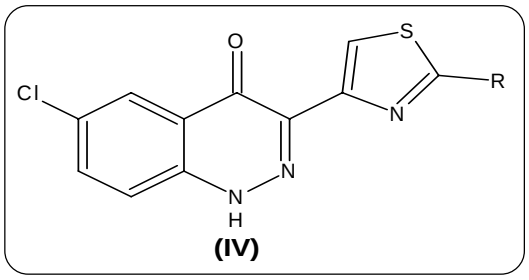
(II)

Moreover, Barraja et al.[52] and Cirrincion[53] have synthesized indolo[3,2-c]cinnolines and reported them as an antiproliferative, antifungal, antibacterial and antileukemic agents. 1,2-Malonyl-1,2dihydro cinnoline (III) reported as antiinflammatory, antianalgesic and antipyraric agents by Siegfried A. G. et al.[54].



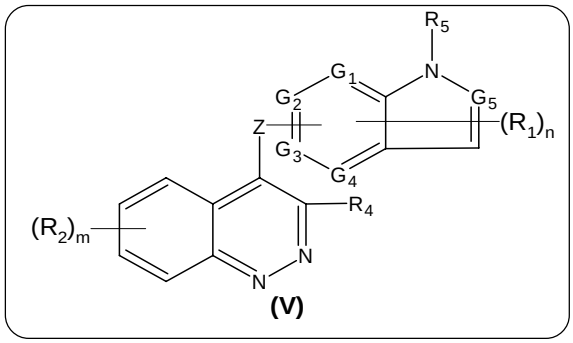
(III)

Yu Y. et al.[55] have synthesized substituted dibenzo[c,h]cinnolines and reported them as topoisomerase I-targeting anticancer agents. Moreover, Brzezinska E. et al.[56] prepared 4-amino-3-cinnoline carbixylic acid derivatives and tested for antibacterial properties, while Vingkar et al.[57] reported (6-chloro-cinnolinyl)thiazoles (IV) as anti-microbial agents.



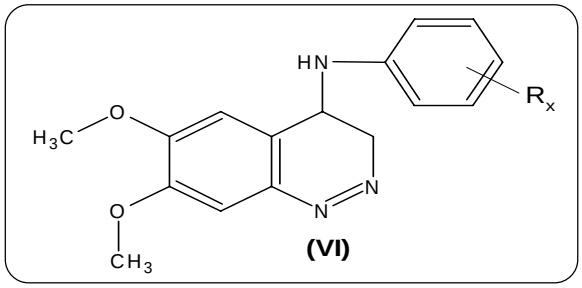
(IV)

Hennequin Laurent et al.[58] prepared cinnoline compounds (V) having antiangiogenic and vascular activity. Nakao, Toyoo et al.[59] also prepared cinnoline derivatives having antiinflammatory and antiallergic activity.Lunt E. et al.[60] synthesized 4-amino cinnolines as antiprotozoal agents.



(V)

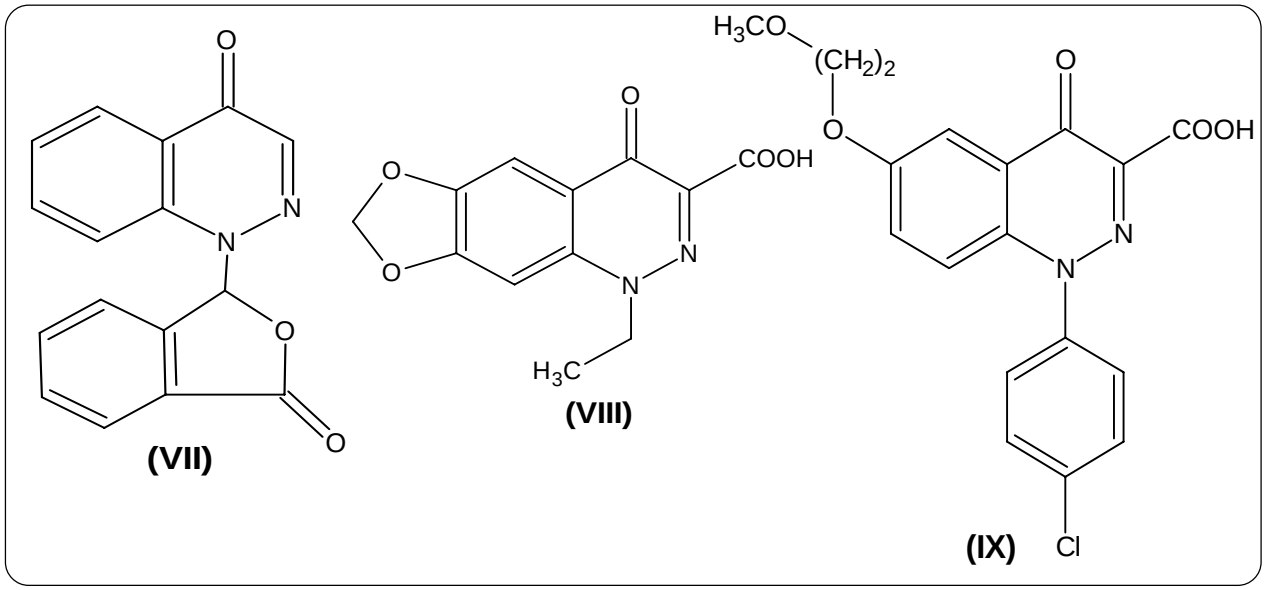
Nargund L. V. et al.[61] synthesized substituted 4-arylaminopyrimido[5,4-c] cinnoline as antibacterial agent. Stanczak A. et al.[62] noted that some 4-amino-3-cinnoline carboxylic acid derivatives and dioxo-1,2,3,4-tetrahydropyrimido[5,4-c]cinnolines possessed some important biological activity. Yarnal S. M. et al.[63] studies on aryl amino cinnolines (VI) and demonstrat as antihistaminic, antiinflammatory and antiarthritic agents.



(VI)

Marshall P. A. et al.[64] have studied cinnolinyl isobenzofuranes (VII) for central nervous system. Schenker F. et al.[65] have reported the antihypertensive action of bicyclic 3-hydrazinocinnoline. Pandey Anjali et al.[66] noted that 4-quinazolinyl-1-piperazinecarboxamides useful as kinase inhibitors for treatment of proliferative diseases.

Some cinnoline derivatives are used as a drugs such as 1-ethyl-1,4-dihydro-4-oxo[1,3]-dioxolo[4,5-g]cinnoline-3-carboxylic acid (VIII), known as ***Cinoxacin*** and used as antibiotics. Some other derivatives of cinnolines are used as pesticide such as ***Sinofem*** 1-(4-chlorophenyl)-1,4-dihydro-5-(2-methoxy)-4-oxo-cinnoline-3-carboxylic acid (IX) used as plant growth regulators.



Summarize some of the studies in this area, and indicate that in preparing potentially useful biologically active agents of all classes, cinnoline rings may replace pyridazine, naphthalene or quinoline rings to produce active compounds, which may be less toxic, have different psychological disposition and/or different modes of metabolism or detoxification, and thus impart desirable properties.

Literature survey revels that the novel cinnoline derivatives have the unique electronic properties of the cinnoline ring system are often utilized to manipulate the elect

ronic and optical properties of various materials including dyes, light emitting diodes and molecular devices. They possess drug potential activities. Looking to the diversified pharmacological activity, it appeared of interest to synthesized some isoxazole, pyrazoline, cyanopyridine, cyclohexenone, indazole, thiazole, thiazepine, thiopyrimidine etc. bearing 3-acetyl-6-chloro-cinnolin-4(3H)-one moiety in order to achieving compounds having better therapeutic activity. These studies are described in the following parts.

Studies on cinnoline derivatives

PART-I : Synthesis and biological screening of isoxazole derivatives

PART-II : Synthesis and biological screening of pyrazoline derivatives

PART-III : Synthesis and biological screening of cyanopyridine derivatives

PART-IV : Synthesis and biological screening of nicotinonitrile derivatives

PART-V : Synthesis and biological screening of cyanopyran derivatives

PART-VI : Synthesis and biological screening of indazole derivatives

PART-VII : Synthesis and biological screening of benzothiazepine derivatives

PART-VIII : Synthesis and biological screening of thiazole derivatives

PART-IX : Synthesis and biological screening of pyrimidine derivatives

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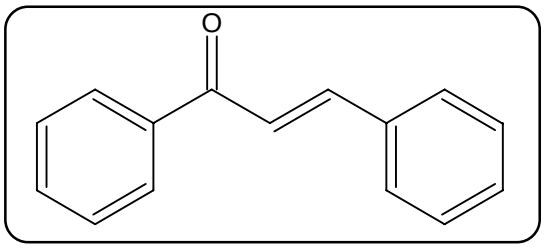
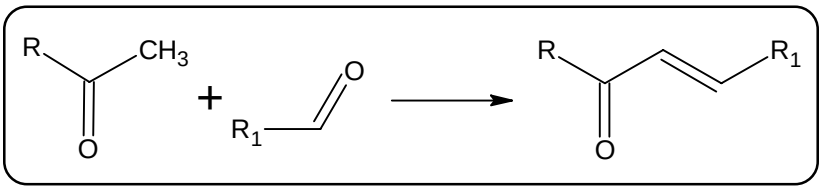
INTRODUCTION

The growing potent literature of recent years demonstrate that chalcone, being a very active intermediate through which novel heterocycles with good medicinal profile can be designed. The presence of keto-ehtylenic linkage in general, gives the compound a great synthetic importance. This is well illustrated by benzalacetophenone or phenyl styryl ketone or phenyl acrylophenone names as chalcone first coined by Kotanecki and Tumbor[1].



SYNTHETIC ASPECT

A considerable variety of methods are available for the preparation of chalcones. The most convenient method for the preparation of chalcone consist is condensing an appropriate aryl methyl ketone with an appropriate aromatic aldehyde using a suitable condensing agent.



The other condensing agents employed in several cases and sometimes advantages are Hydrogen chloride[2,3], Zinc chloride and Acetic anhydride[4], Phosphorus oxychloride[5], Borax solution[6], Boron trifluoride[7], weak bases like Piperidine[8], Amino

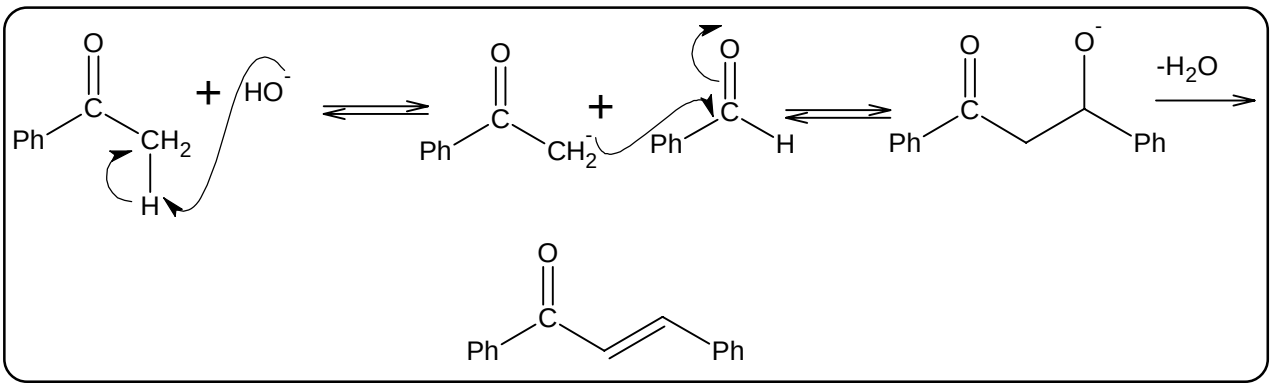
acid[9] and Organocadmimum compounds[10].

Besides the condensation of an aldehyde with ketone, the other methods used are,

1. Fries rearrangement of aryl cinnamates[11],
2. Friedel craft's cinnamoylation[12],
3. Nencki reaction with cinnamic acid on an aromatic compounds[13],
4. Diazo coupling of phenyl diazonium chloride with benzoyl acrylic acid[14].

REACTION MECHANISM

Chalcone proceeds through Clasien-Schmidt condensation[15,16] and the process is catalysed in the presence of relatively strong base to form α, β-unsaturated aldehyde or a ketone.



IMPORTANCE OF CHALCONE

In recent years an increasing number of groups have become interested in chalcone and related compounds since they are finding extensive use in several medicinal and industrial fields.

1. The chalcones are natural biocides[17-19] and are well known key intermediates in the synthesis of heterocyclic compounds exhibiting biological activities[20-23].
2. The chemical reactivity of α, β-unsaturated carbonyl system [24,25] present in chal cone is utilized to prepare various heterocyclic systems of medicinal values like

pyrazolines[26], isoxazoles[27], cyanopyridines[28], cyanopyrans[29], nicotinonitriles[30], indazoles[31], pyrimidines[32-34], thiazepines[35], pyranones[36], piperidone[37] etc.

3. The chalcones are used as starting compounds to synthesize naturally occurring flavanones, flavenes, flavanols[38,39] etc.
4. The chalcones have also been found to be useful in arriving at the structure of several naturally occurring products like hemlock tannins[40], phloretin[41] and cyanomalcurin[42].
5. The structure of some naturally occurring pigments like chrysin, galangin, kaempferol and quercetrol were established by their synthesis from suitably sub stituted chalcones[43].
6. Chalcone and their derivatives also have been found applicable as stabilizers photosensitive materials, polymerization catalyst, fluorescent whitening agents and organic brightening agents e.g. methyl chalcones and 4-chloro chalcone are patented as light stabilizing agent for polivinylidine[44].
7. Chalcones react with a number of metal ions this reaction has been reported for the detection of Fe(II)[42] in presence of Sr and Ba ions. Trihydroxy chalcone was used as an analytical reagent for amperometric estimation of copper[45] and spectrophotometric study of germanium[46].

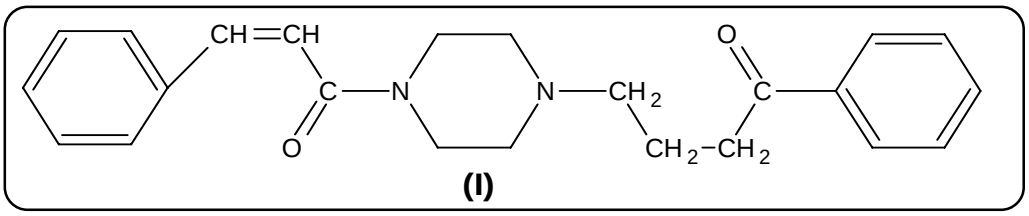
THERAPEUTIC IMPORTANCE

Chalcone derivatives also exhibits several agrochemical and pharmacological activities like,

1. Herbicidal[47],
2. Germicidal[48,49],
3. Insecticidal[50],
4. Bactericidal[51,52],
5. Antimalarial[53,54],

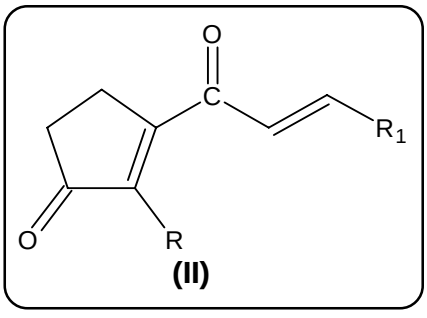
6. Antiviral[55],
7. Antispasomodic[56],
8. Antiulcer[57,58],
9. Anthelmintic[59,60],
10. Antitubercular[61,62],

Kumar S. K. et al.[63] have prepared novel boronic chalcone derivatives as antitumor agents. Some derivatives of chalcones as antimicrobial agents were reported by Bekhit, Adnan A. et al.[64]. Cinnamoyl piperidinobutyrophenone (I) reported by Carr, A. A. et al.[65] as antipsycotic agents.



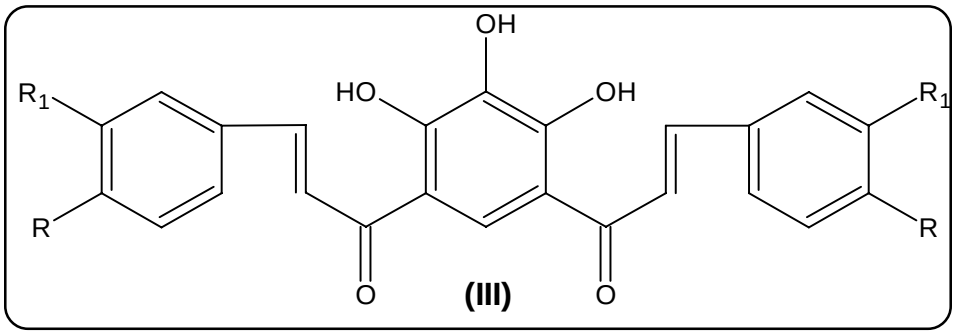
(I)

Chalcones are potential biocides, because some naturally occurring antibiotics[66] and aminochalcones[67,68] probably owe their biological activity in the presence of the α, β-unsaturated carbonyl group. Nelson, G. L. et al.[69] synthesized the analogs of prostaglandin (II).



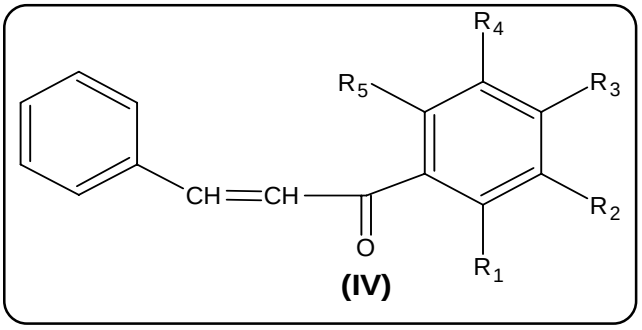
(II)

Some dihydrochalcones are well known for their sweetening property[70,71] and appear to be non-nutritive sweeteners. A dihydrochalcone 'Uvaretin' from Uvaria acuminata has shown antitumor activity[72] in lymphocytic leukemia test. V. K. Ahluvalia et al.[73] have noted that 5-cinnamoylchalcones (III) have good for antibacterial activity.



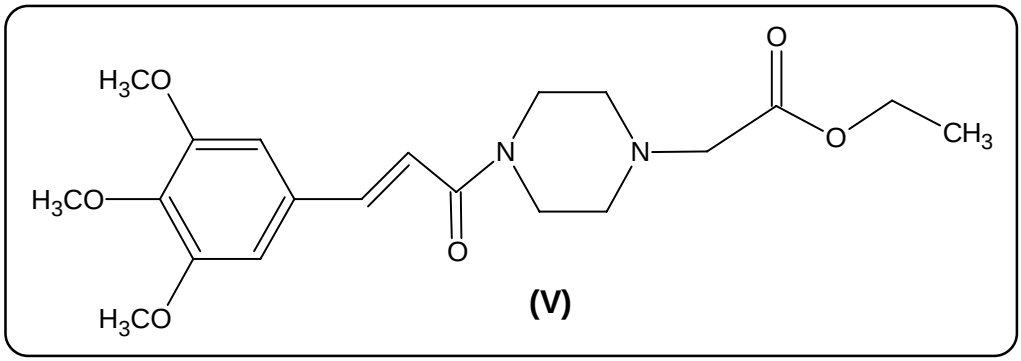
(III)

Moreover, Zwagstra, M. E. et al.[74] synthesized chalcone (IV) and reported as antiallergic agent. Anti invasine and herbicidal activity of 1,3-diaryl propenones has been reported by Parmar, V. S. et al.[75]. Ezio et al.[76] have been reported chalcones having a valuable antiproliferation activity both on sensitive cancerous cell and on cell which are resistant to common.

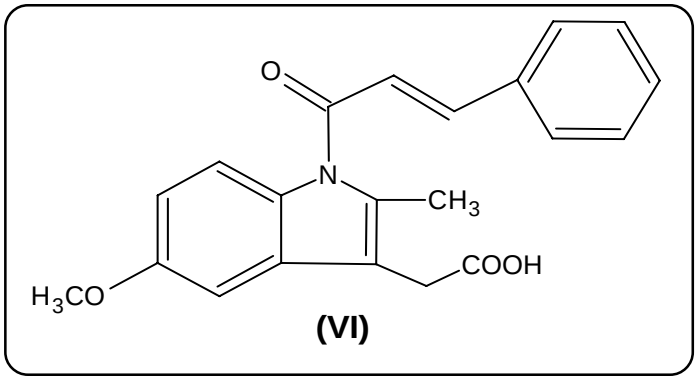


(IV)

The compound 4-[1-oxo-3-(3,4,5-trimethoxyphenyl)-2-propenyl]-1-piperazine acetic acid ethyl ester (V) has been marketed under the name of '***Cinepazet***' used as vasodilator. The other 5-methoxy-2-methyl-1-(1-oxo-7-phenyl)-1H-indole-3-acetic acid (VI) has been marketed under the name of '***Cinmetacin***' and useful as antiinflammatory.



(V)



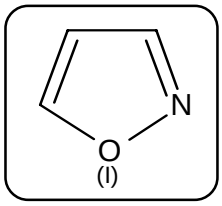
(VI)

Chalcones have served as starting material for several synthetic manipulations and a versatile synthon in organic synthesis. Furthermore, it is well documented in literature that the majority of cinnoline derivatives possess pharmacologically proven therapeutic potential. Though extensive research work has been reported on acetyl cinnoline derivatives, relatively very known so far, about cinnoline derivatives. This enthused us to synthesize the chalcone derivatives presuming that these chemical entity with 6-chloro-3-acetyl-cinnolin-4(3H)-one in conjugation with unsaturated carbonyl system may have a good therapeutic importance, that's why we have been described in following section.

SECTION-I : Synthesis and biological screening of 6-Chloro-3-[(2E)-3-arylprop-2-enoyl]cinnolin-4(3H)-one

INTRODUCTION

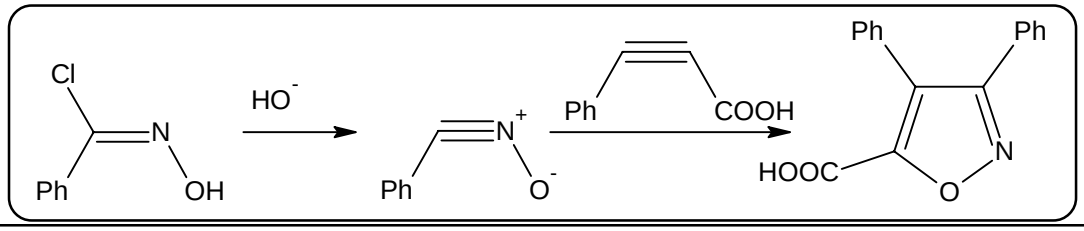
In 1888, Clasien suggested an isoxazole structure (I), a product from the reaction of 1,3-diketone with hydroxylamine[77]. Subsequently Clasien and his students laid down a solid foundation for the chemistry of isoxazole. Isoxazoles are a group of heterocyclic compounds containing two heteroatoms in five membered ring: Nitrogen and Oxygen.



(I)

It was shown to possess the typical properties of an aromatic system but under certain reaction conditions, particularly in reducing or basic media , it becomes highly labile. Isoxazoles when substituted in the 3,5-positions are stable to alkali but when 3-position is vacant, the ring is opened in the presence of cold alkaline media to give ketonitriles and when 5-position is vacant, the ring is opened in the presence of hot alkaline media to give nitriles and carboxylic acids.

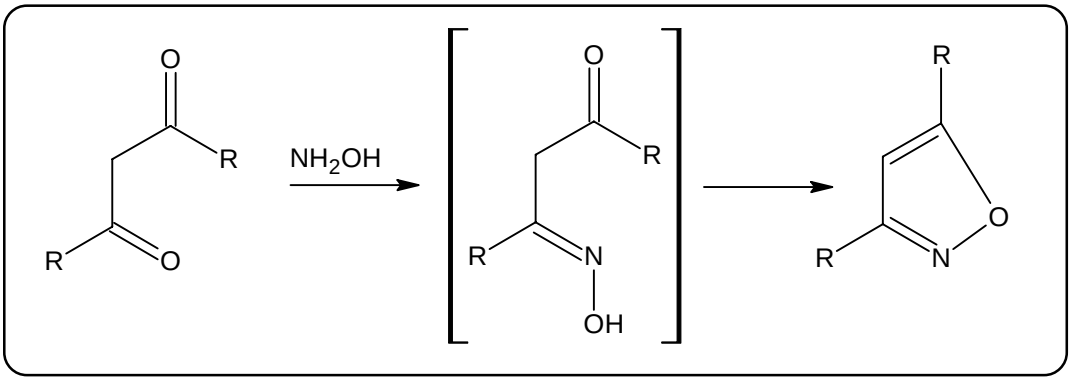
Quilico[78] made the most important contribution to the chemistry of isoxazoles in 1946, when he began to study the formation of isoxazoles from nitriles N-oxides and unsaturated compounds[79].



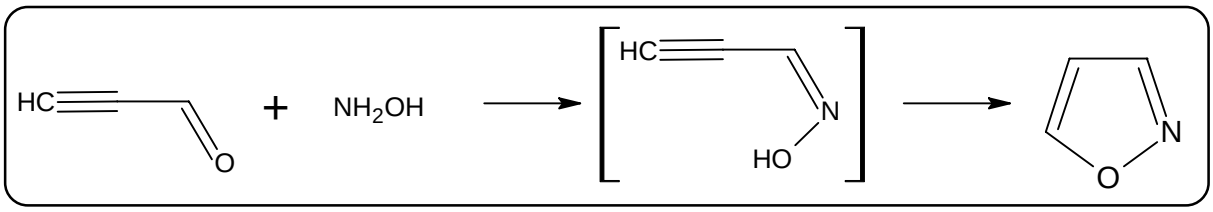
Well known sulpha drug, sulphamethoxazole and antibiotic oxamycin or cycloserain is D4-amino-3-isoxazolidinone both contains isoxazole type of nucleus suggesting isoxazoles and its derivatives have better therapeutic values in the field of medicinal chemistry.

SYNTHETIC ASPECT

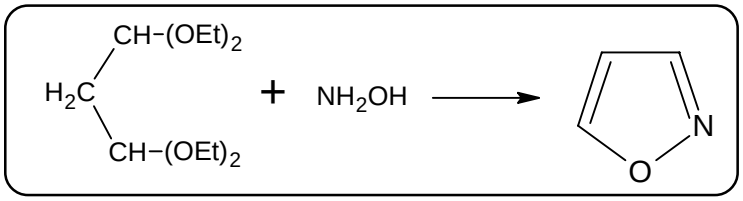
Isoxazole ring system have the pair of heteroatoms adjacent. The most useful route to prepare is start with a 1,3-dicarbonyl[80] compound and bring about cyclization with a reagent to N-O bond; this is hydroxylamine for isoxazoles.



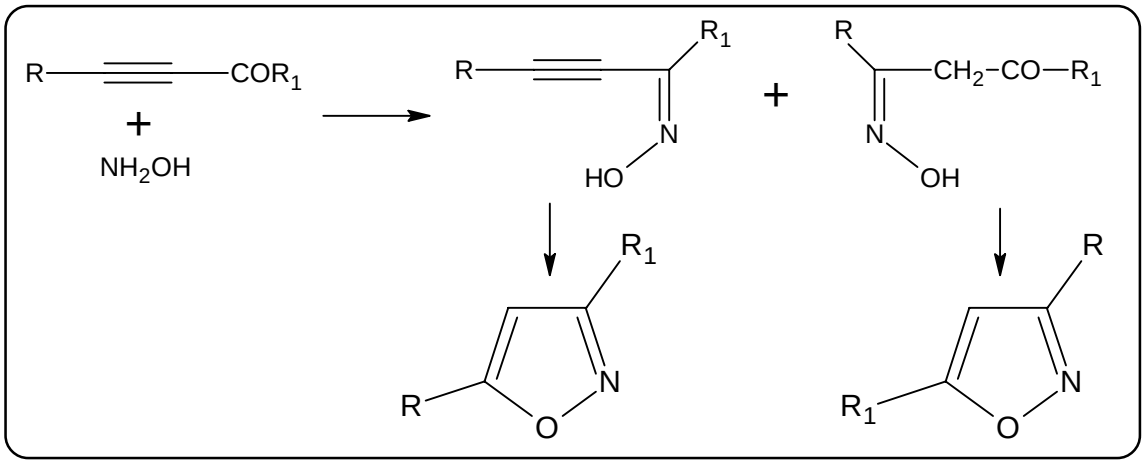
Isoxazole[81] itself may be prepared by the action of hydroxylamine on propargylaldehyde.



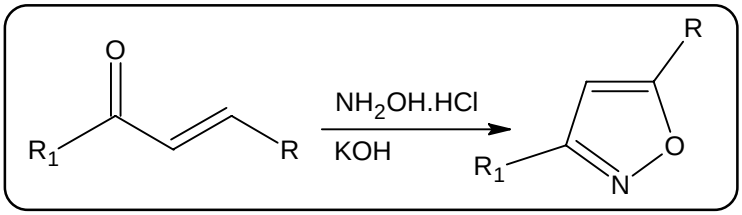
The most convenient preparation [82] is the reaction between 1,1,3,3-tetraethoxy propane and hydroxylamine hydrochloride.



Isoxazole is also synthesized the condensation of acetylenic carbonyl[83] compounds with hydroxylamine hydrochloride.



Fanshave and Crawley[84] prepared by isoxazole from α, β-unsaturated carbonyl compounds, hydroxylamine hydrochloride and KOH in methanol.



Recently, Beatrice et al.[85] prepared isoxazoles by one pot reaction under microwave irradiation. S. Balaic et al.[86] have been reported the reaction of 1,3-diketones with hydroxylamine hydrochloride on silica gel under microwave irradiation to generate isoxazole derivatives.

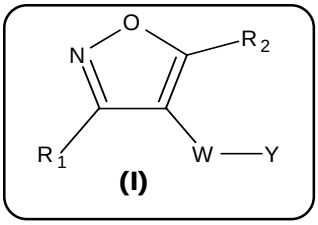
THERAPEUTIC INTEREST

Isoxazole derivatives associated with wide spectrum of biological activities.

1. Antiviral[87],
2. Analgesic[88],
3. Antitumor[89],
4. Hypoglycemic[90],

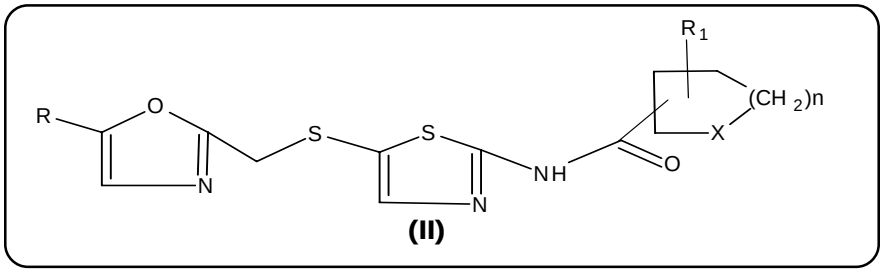
5. Antileukemic[91],
6. Antipyratic[92],
7. Anticonvulsant[93],
8. Diabetic[94]

A few pharmacological active isoxazoles are known. Momose, Yu et al.[95] have prepared the isoxazole derivatives (I) which were used for prevention and treatment of diabetes.



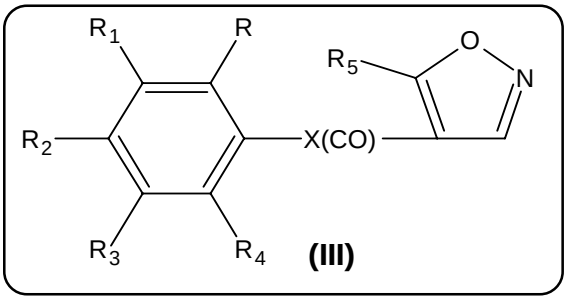
(I)

Moreover, Shiongogi and Co. Ltd.[96] reported as antipyratic, analgesic antiinflammatory, and anticough properties. Misra R. N. et al.[97] prepared N-[5-[[[5-alkyl-2-oxazolyl]methyl]thio]-2-thiazolyl]carboxamides (II) as an inhibitors of cyclin dependent kinase.



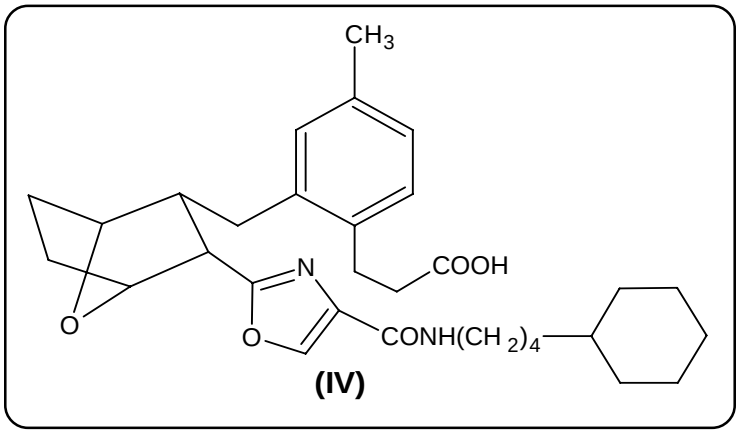
(II)

Allen, Larry et al.[98] reported that (αS,5S)- 4-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid was used to inhibit g-glutamyl transpeptidase from human pancreatic carcinema cell. Vekariya, N. A. et al.[99] synthesize the isoxazole derivatives and reported it as potential anticancer agents. Hanifin, J. W. et al.[100] was used isoxazole carboxylic acid phenyl esters (III) in pharmaceutical composition which was used as an antiarthritic drugs.



(III)

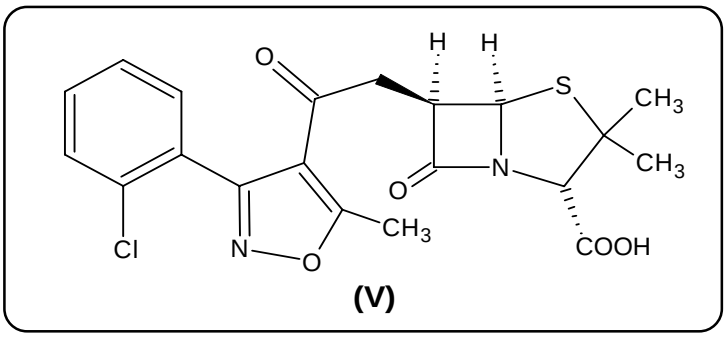
Recently, Hashimoto, H. et al[101] prepared 4-(4-cycloalkyl/aryl-oxazol-5-yl)benzenesulfonamides for the treatment of rheumatoid arthritis, ostevathritis and acute pain. Burk, R. M. et al[102] have synthesized interphenylene-7-oxabicyclic[2.2.1]heptane oxazoles (IV) as prostaglandine $F_2\alpha$ antagonists.



(IV)

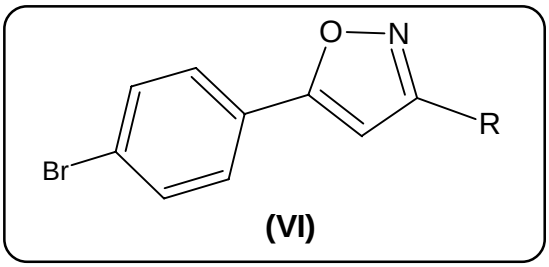
Over and above various workers have reported isoxazoles as hypoglycemic[103], linkage for replacement of nucleotide phosphodiester[104] and insecticidal agent[105]. Some potent herbicidal activity of isoxazoles found by Reddy et al.[106]. Some isoxazole derivatives have been patented for their use as herbicides and fungicides[107], for the treatment of prophylaxis of antoimmune or for the treatment inflammatory diseases[108], estrogen receptor modulators[109].

The compound [2S-(2α, 5α, 6β)]-6-[[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (V) was marketed under the name '***Cloxacilin***' and used as antibacterial drug.



(V)

In very recent study Joshi et al.[110]. synthesized some isoxazole (VI) derivatives as antitubercular and antimicrobial agents.



(VI)

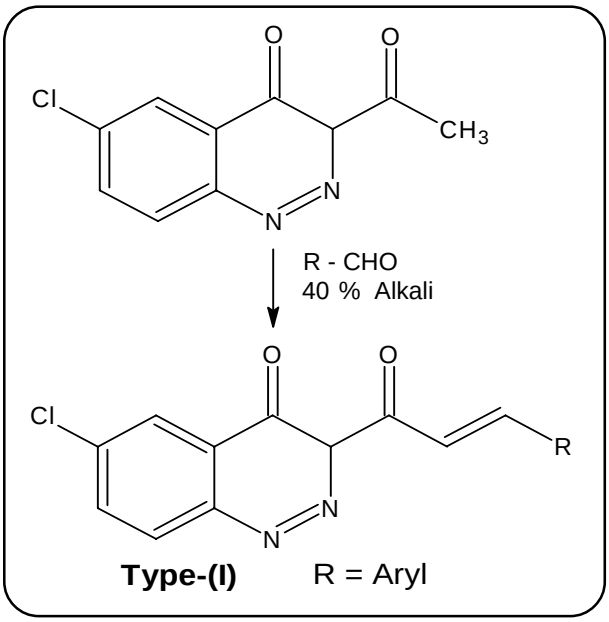
As an extension of this study, we wish to report herein a convenient synthesis of the new isoxazole derivatives bearing 6-chloro cinnolin-4(3H)one moiety which have been described as under.

SECTION-II: Synthesis and biological screening of 6-chloro-3-(5-aryl isoxazol-3-yl)-cinnolin-4(3H)-one

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-CHLORO-3-[(2E)-3-ARYL PRPO-2-ENOYL]CINNOLIN-4(3H)-ONES.

Chalcone derivatives occupy a unique place in the field of medicinal chemistry due to wide range of biological activities exhibited by them, prompted by these facts, the preparation of chalcones of Type (I) have been carried out by condensation of 3-acetyl-6-chloro cinnolin-4(3H)-one with various aldehydes.



Type-(I) R = Aryl

The structure elucidation of synthesized compounds have been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated 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 synthesized compounds were compared with standard drugs.

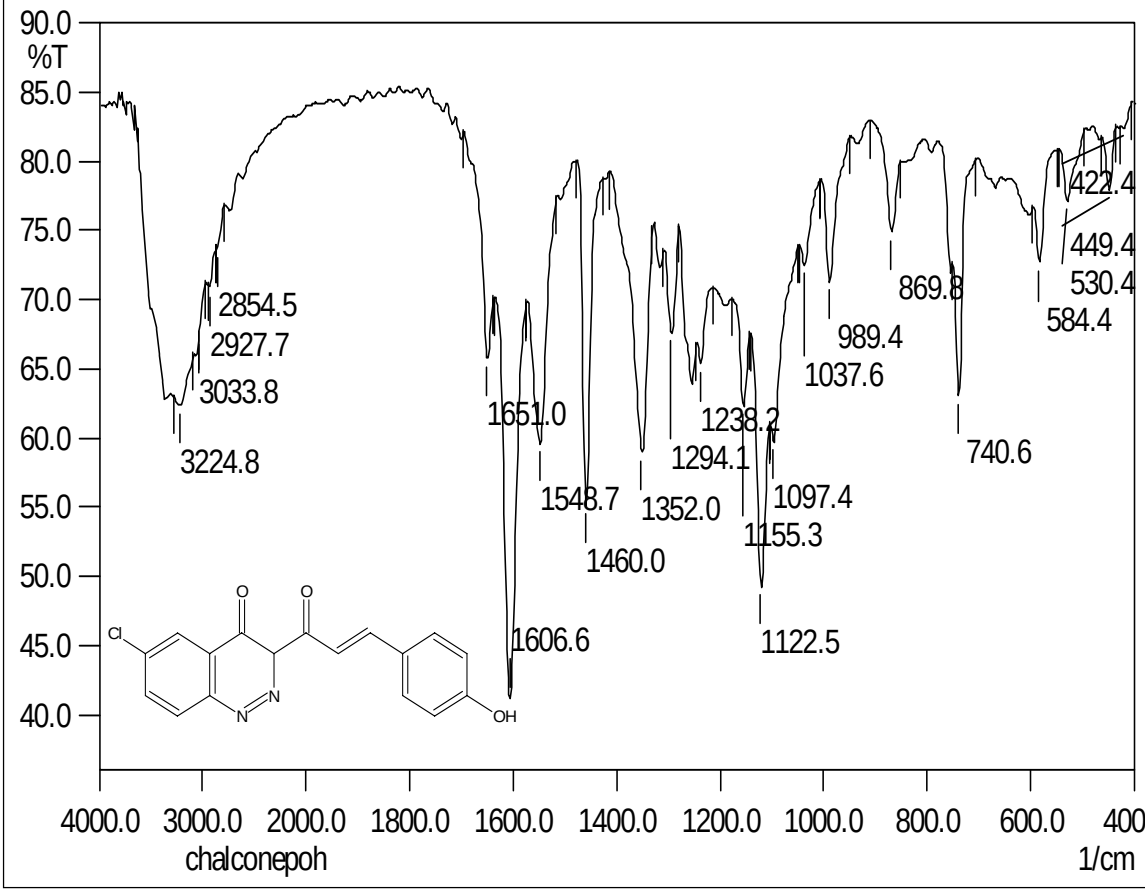
MICROBIOLOGICAL EVALUATION

Antimicrobial activity :

Method	:	Cup-plate[111]
Gram positive bacteria	:	*Bacillus megaterium* *Bacillus subtillis*
Gram negative bacteria	:	*Escherichia coli* *Proteus vulgaris*
Fungi	:	*Aspergillus niger*
Concentration	:	40 μg/ml
Solvent	:	Dimethyl formamide
Standard drugs	:	Amoxicillin, Benzyl penicillin, Ampicillin, Norfloxacin, Griseofulvin

The results of antibacterial screening was compared with standard drugs viz. Amoxicillin, Benzyl penicillin, Ampicillin, Norfloxacin and the results of antifungal testing was compared with Griseofulvin. The zones of inhibition have been measured in mm.

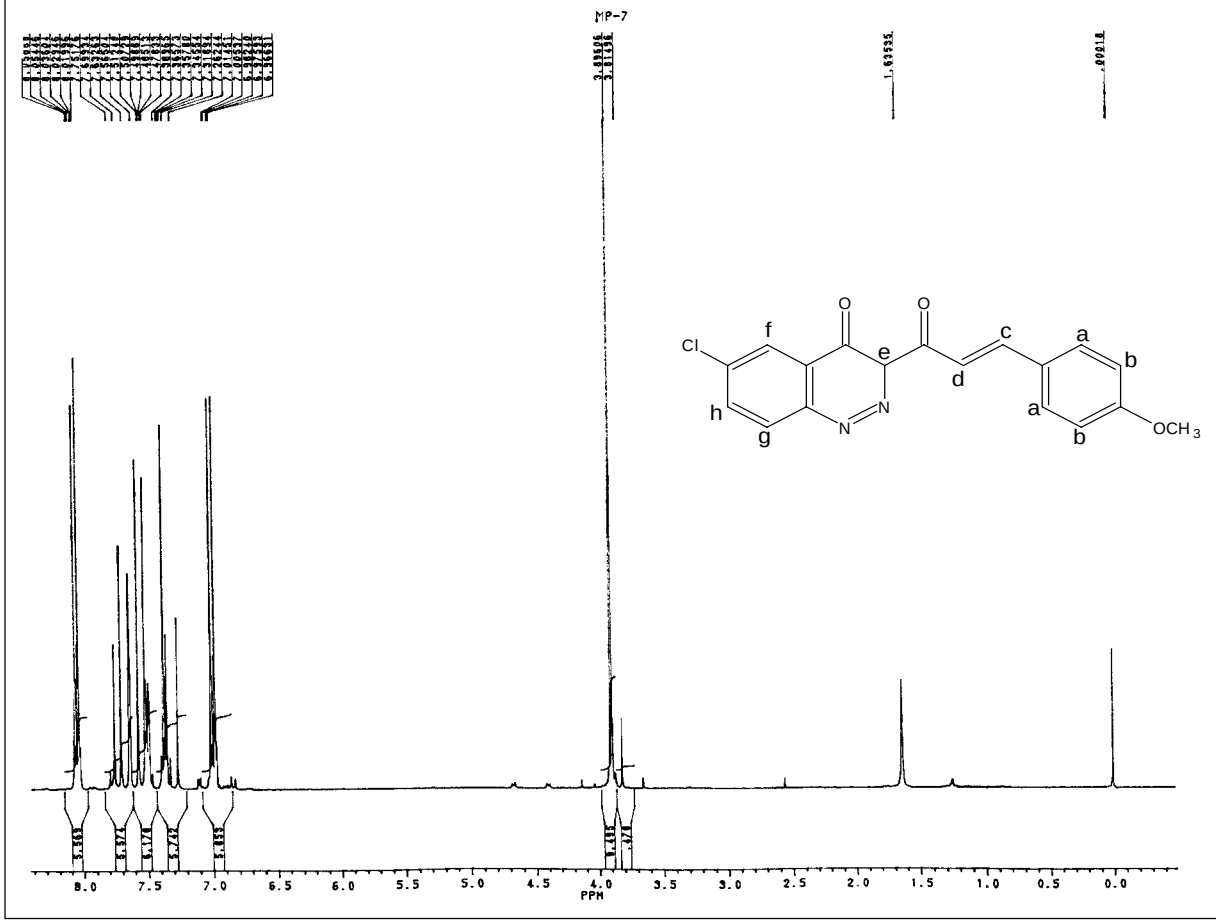
IR SPECTRAL STUDY OF 6-CHLORO-3[(2E)-3-(p-HYDROXY PHENYL) PROP-2-ENOYL]CINNOLIN-4(3H)-ONE



Frequency range: 4000-400cm^{-1} (KBr disc) Instrument : Shimadzu-8400 FTIR

Type	Vibration mode	Frequency in cm^{-1} Observed	Reported	References
Alkane	C-H str. (asym.)	2927	2975-2950	112
-CH_3	C-H str. (sym.)	2854	2880-2860	"
	C-H def. (asym.)	1460	1470-1435	"
	C-H def. (sym.)	1352	1385-1370	"
Aromatic	C-H str.	3033	3080-3030	113
	C=C str.	1548	1620-1430	"
	C-H i.p. def	1238	1269-1013	"
	C-H o.o.p. def.	869	833-660	"
Ether	C-O-C str.	1238	1275-1200	112
Carbonyl	C=O	1661	1690-1665	"
Vinyl	CH=CH str.	3033	3050-3000	113
Halide	C-Cl str.	740	750-700	112

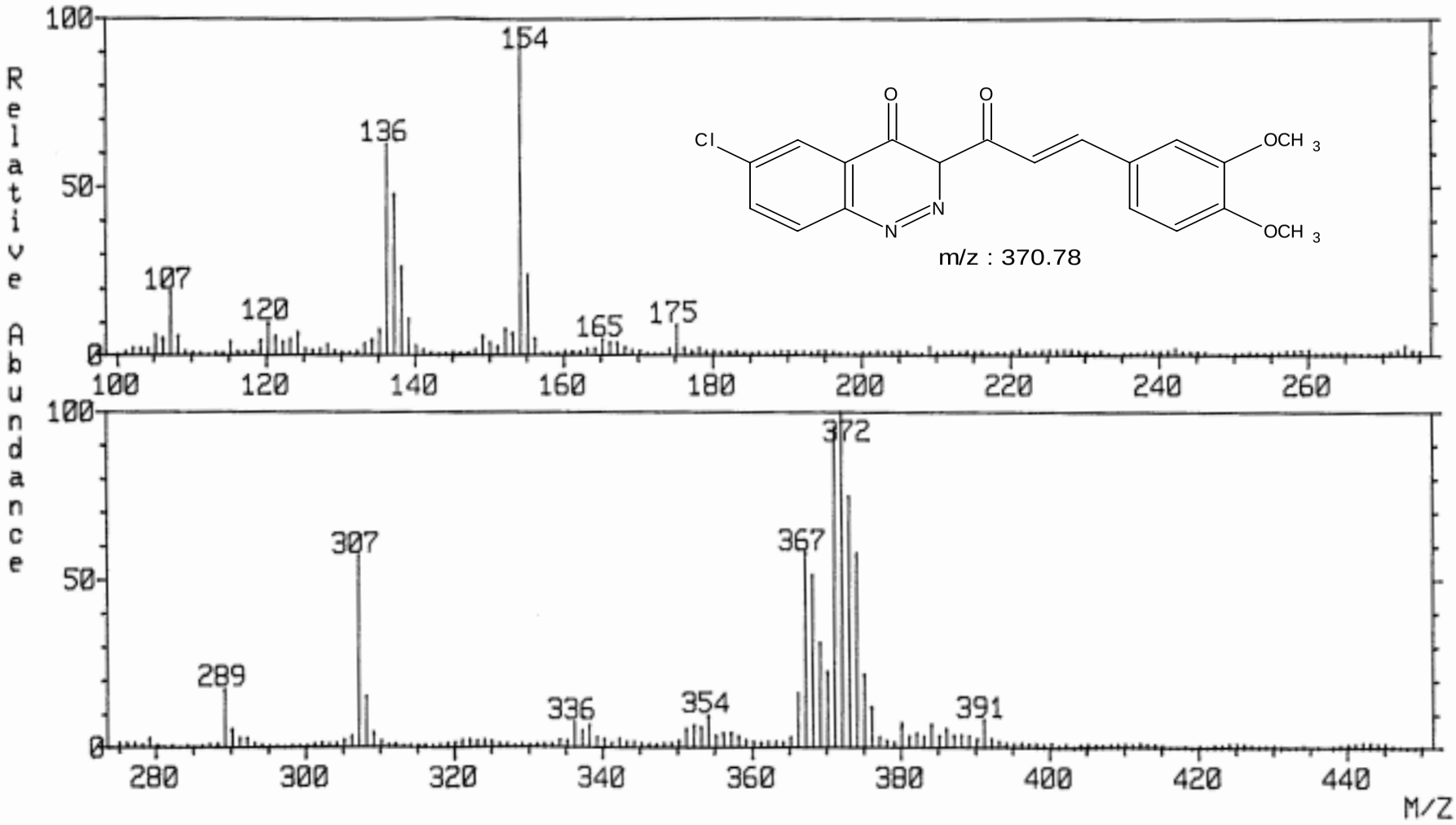
PMR SPECTRAL STUDIES OF 6-CHLORO-3[(2E)-3-(p-METHOXY PHENYL) PROP-2-ENOYL]CINNOLIN-4(3H)-ONE



Internal reference: TMS; Solvent: $CDCl_3$; Instrument: BRUKER spectrometer(300 MHz)

Signal No.	Signal position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.86	3H	singlet	Ar-OCH_3
2.	6.99	2H	double	Ar-H_a (p-disubstitution)
3.	7.26	1H	double	Vinylic -CH_c=CH_d-
4.	7.30	1H	double doublet	Ar-H_e
5.	7.49	1H	double doublet	Ar-Hg
6.	7.50	1H	doublet	Ar-H_h
7.	7.53	1H	singlet	Ar-H_f
8.	7.79	1H	doublet	Vinylic -CH_c=CH_d-
9.	8.04	2H	double doublet	Ar-H_b (p-sub.)

MASS SPECTRUM Data File: 3EJL25J 25-JUL- 3 11:04
SamPle: PM-4 DR H S JOSHI,RAJKOT #6213
RT 0'24" FAB(Pos.) GC 1.4c BP: m/z 372.0000 Int. 48.5893 Lv 0.00
Scan# (3 to 4)



m/z : 370.78

Experimental

SYNTHESIS AND BIOLOGICAL SCREENING 6-CHLORO-3-[(2E)-3-ARYLPROP-2-ENOYL]CINNOLIN-4(3H)-ONES.

(A) Synthesis of Ethyl 2-[(E)-(4-chlorophenyl)diazenyl]-3-oxobutaroate

4-Chloro aniline (1.28g, 0.01 mol) dissolved in a mixture of con. HCl (15 ml) and water (15 ml) and cooled to 0 - 5 ^{0}C in an ice bath. To this, a cold saturated solution of sodium nitrite (1.02g, 0.015 mol) was added with constant stirring. The diazonium salt thus formed was filtered into a cooled solution of ethyl acetoacetate (1.3g, 0.01 mol) in ethanol (15 ml) and sodium acetate (16.2g, 0.2 mol) in water (250 ml). The solid was collected and recrystallized from methanol. Yield 74%, m.p. 94 ^{0}C. Anal. Calcd. for $C_{12}H_{13}ClN_2O_3$ Requires: C, 53.64; H, 4.88; N, 10.43 % Found: C, 53.61; H, 4.87; N, 10.41 %.

(B) Synthesis of 3-Acetyl-6-chlorocinnolin-4(3H)-one

To ethyl 2-[(E)-(4-chlorophenyl)diazenyl]-3-oxobutaroate (3.0g, 0.0112 mol), anhydrous $AlCl_3$ (2.98g, 0.023 mol) and chlorobenzene (30 ml) was added in order to dissolve the solids. The mixture was refluxed for 12 hr. Cooled and dilute HCl (25 ml) was added to it, then heated on a waterbath. After cooling the product was separated filtered, washed twice with dilute NaOH solution. The product was recrystallized from methanol. Yield 59 %, m.p. 201 ^{0}C. Anal. Calcd. for $C_{10}H_7ClN_2O_3$ Requires: C, 53.95; H, 3.17; N, 12.58 % Found: C, 53.91; H, 3.15; N, 12.55 %.

(C) Synthesis of 6-Chloro-3[(2E)-3-(4-methoxyphenyl)prop-2-enoyl]cinnolin-4-one

Dissolve 3-acetyl-6-chlorocinnolin-4(3H)-one (2.23 g, 0.01 mole) and

anisaldehyde (1.36 g, 0.01 mol) in dimethyl formamide (30 ml) and was stirred at room temperature for 24 hr in presence catalytic amount of 40% KOH . The resulting solution was then poured over crushed ice, the seperated solid was filtered and crystallized from 1,4-dioxane. Yield 68%, m.p. 190 ^{0}C. Anal. Calcd. for $C_{18}H_{13}ClN_2O_3$ Requires: C, 63.44; H, 3.85; N, 8.22 % Found: C, 63.42; H, 3.84; N, 8.20 %.

Similarly, other compounds were prepared. The physical data are recorded in Table no. 1.

(D) Biological Screening of 6-Chloro-3[(2E)-3-arylprop-2-enoyl]cinnolin-4-one.

(a) Antibacterial activity

The purified products were screened for their antibacterial activity using cup-plate agar diffusion method. The nutrient agar broth prepared by the usual method was inoculated aseptically with 0.5 ml of 24 hrs. old subcultures of *Bacillus megaterium, Bacillus subtillis, Escherichia coli, Proteus vulgaris* in separate conical flask at 40-50 ^{0}C and mixed well by gentle shaking. About 25 ml content of the flask were poured and evenly spreaded in a petridish (13 cm diameter) and allowed to set for 2 hrs. The cups (8mm 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 ^{0}C for 24 hrs. and the control was also maintained with 0.04 ml of DMF in a similar manner and the zone of inhibition of the bacterial growth were measured in millimeter and recorded in Graphical Chart No. 1.

(b) Antifungal activity

A. niger was employed for testing antifungal activity using cup-plate agar diffusion method. The culture was maintained on sabourauds agar slants sterilized

sabourauds 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 (13 cm diameter) and allowed to set for 2 hrs. The cups (8 mm diameter) were punched. The plates were incubated at 30 ^{0}C for 48 hrs. After the completion of incubation period, the zone of inhibition in each petridish one cup was filled up with solvent which acts as control. The zone of inhibition of test solution are recorded in Graphical Chart No. 1.

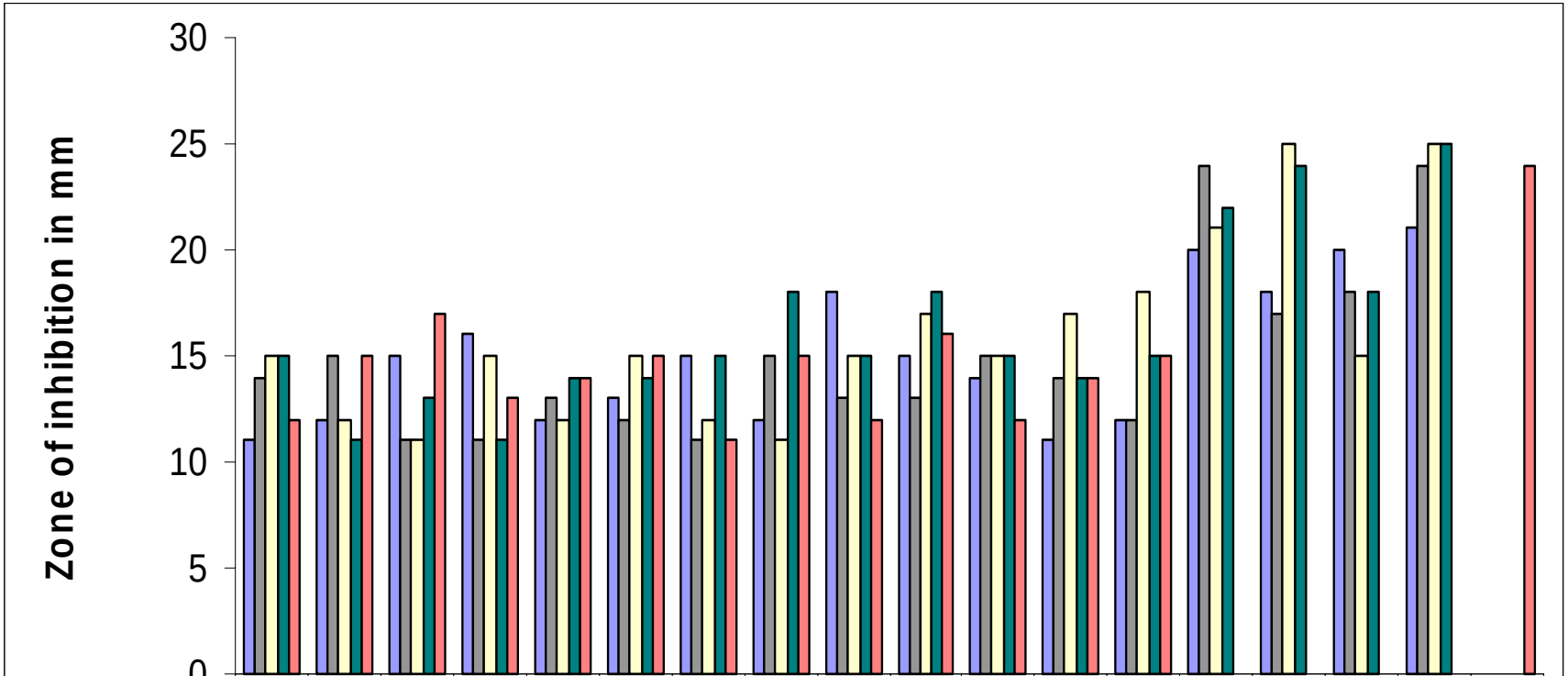
TABLE-1: PHYSICAL CONSTANTS OF 6-CHLORO3-[(2E)-3-ARYLPROP-2-ENOYL]CINNOLIN-4(3H)-ONE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	R_f Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
1a	C_6H_5-	$C_{17}H_{11}ClN_2O_2$	310.73	210	0.563	S_1	74	9.02	9.02
1b	3-Br-C_6H_4-	$C_{17}H_{10}BrClN_2O_2$	389.63	198	0.527	S_1	71	7.19	7.15
1c	2-Cl-C_6H_4-	$C_{17}H_{10}Cl_2N_2O_2$	345.18	220	0.366	S_2	72	8.12	8.11
1d	3-Cl-C_6H_4-	$C_{17}H_{10}Cl_2N_2O_2$	345.18	174	0.542	S_2	65	8.12	8.06
1e	4-Cl-C_6H_4-	$C_{17}H_{10}Cl_2N_2O_2$	345.18	170	0.538	S_2	59	8.12	8.08
1f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{19}H_{15}ClN_2O_4$	370.78	178	0.543	S_1	64	7.56	7.54
1g	4-OCH_3-C_6H_4-	$C_{18}H_{13}ClN_2O_3$	340.76	190	0.465	S_2	68	8.22	8.20
1h	4-SCH_3-C_6H_4-	$C_{18}H_{13}ClN_2O_2S$	356.83	204	0.450	S_2	54	7.85	7.83
1i	3-NO_2-C_6H_4-	$C_{17}H_{10}ClN_3O_4$	355.73	206	0.556	S_2	72	11.81	11.80
1j	2-OH-C_6H_4-	$C_{17}H_{11}ClN_2O_3$	326.73	212	0.500	S_2	75	8.57	8.54
1k	4-OH-C_6H_4-	$C_{17}H_{11}ClN_2O_3S$	326.73	228	0.497	S_1	63	8.57	8.52
1l	3-C_6H_5-O-C_6H_4-	$C_{23}H_{15}ClN_2O_3$	402.83	181	0.488	S_1	60	6.95	6.94
1m	4-$N(CH_3)_2$-C_6H_4-	$C_{19}H_{16}ClN_3O_2$	353.80	194	0.528	S_1	50	11.88	11.84

S_1 = Ethyl acetate : Hexane (3 : 7)

S_2 = Ethyl acetate : Hexane(2.5 : 7.5)

Graphical Chart No. 1 : Antimicrobial activity of 6-Chloro-3-[(2E)-3-arylprop-2-enoyl]cinnolin-4(3H)-one

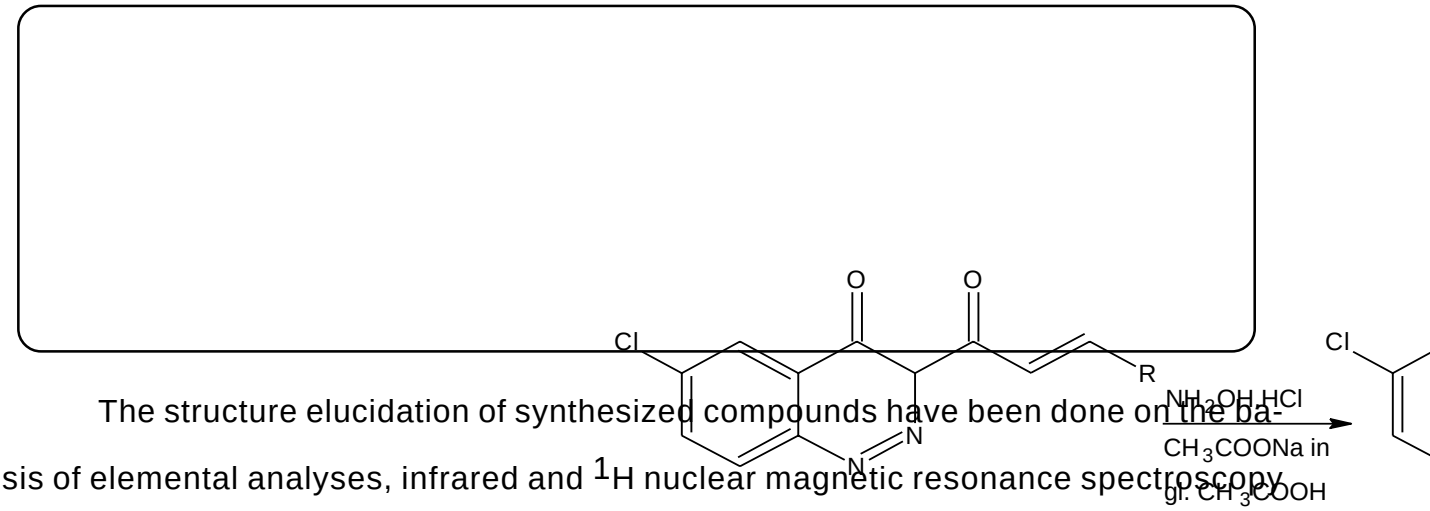


	1a	1b	1c	1d	1e	1f	1g	1h	1i	1j	1k	1l	1m	Ampicillin	Norfloxacin	Benzyl penici	Amoxicillin	Griseofulvin
B.mega	11	12	15	16	12	13	15	12	18	15	14	11	12	20	18	20	21	
B.substilis	14	15	11	11	13	12	11	15	13	13	15	14	12	24	17	18	24	
P.vulgaris	15	12	11	15	12	15	12	11	15	17	15	17	18	21	25	15	25	
E.coli	15	11	13	11	14	14	15	18	15	18	15	14	15	22	24	18	25	
A.niger	12	15	17	13	14	15	11	15	12	16	12	14	15					24

SECTION-II

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-CHLORO-3-(5-ARYLISOXAZOL-3-YL)-CINNOLIN-4(3H)-ONE.

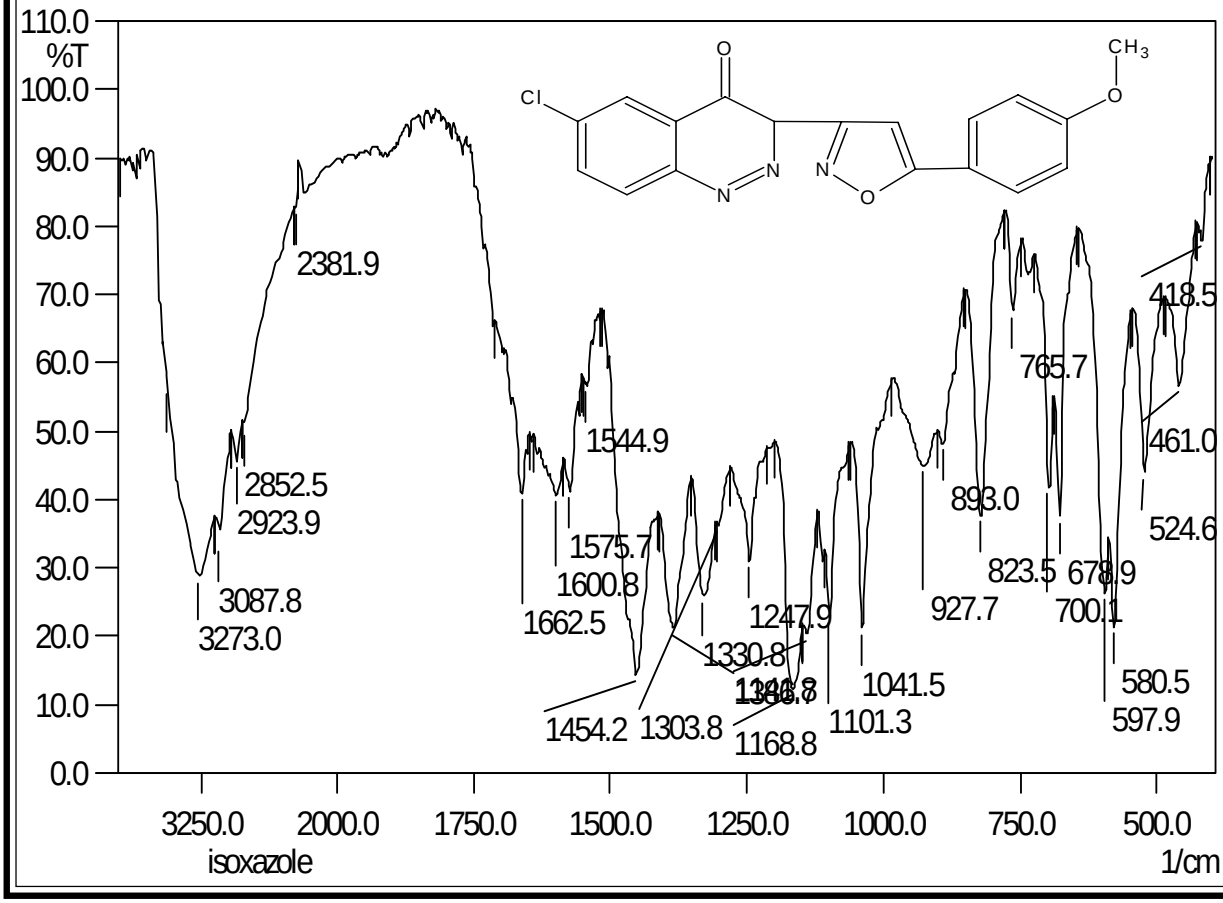
Isoxazole have been reported to have various pharmacological activities like antibacterial, antifungal, insecticidal etc. In order to achieving better drug potency, we have prepared isoxazole derivatives of Type-(II) by the cyclo condensation of 6-chloro-3-[(2E)-3-arylprop-2-enoyl]cinnolin-4(3H)-one of Type-(I) with hydroxylamine hydrochloride in presence of sodium acetate in glacial acetic acid.



The structure elucidation of synthesized compounds have been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated 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 synthesized compounds were compared with standard drugs.

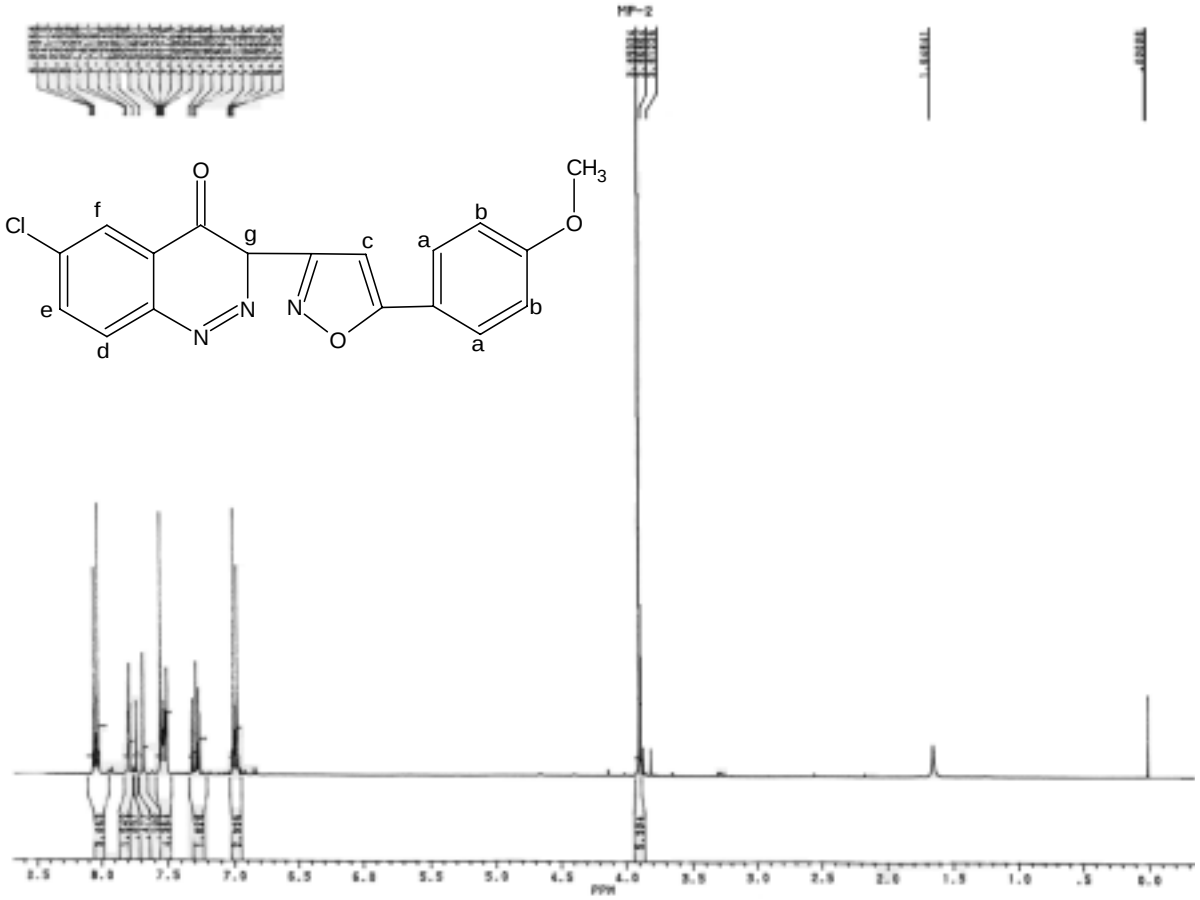
IR SPECTRAL STUDY OF 6-CHLORO-3-(5-(p-METHOXY PHENYL) ISOXAZOL-3-YL)-CINNOLIN-4(3H)-ONE



Frequency range: 4000-400cm^{-1} (KBr disc) Instrument : Shimadzu-8400 FTIR

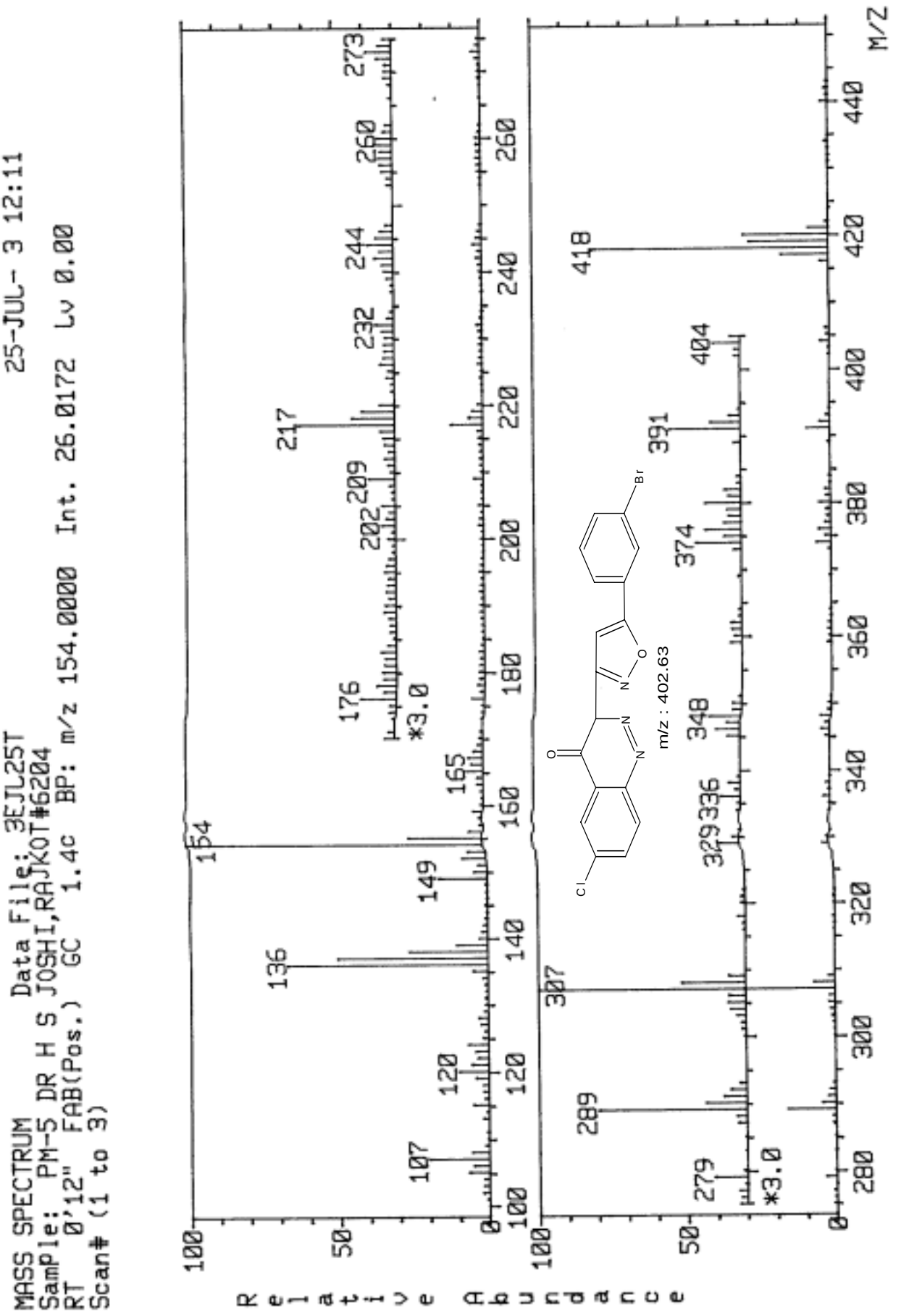
Type	Vibration mode	Frequency in cm^{-1} Observed	Reported	References
Alkane	C-H str. (asym.)	2923	2975-2950	112
-OCH_3	C-H str. (sym.)	2840	2880-2860	"
	C-H def. (asym.)	1454	1470-1435	"
	C-H def. (sym.)	1381	1385-1370	"
Aromatic	C-H str.	3087	3080-3030	113
	C=C str.	1544-1454	1620-1430	"
	C-H i.p. def	1247	1269-1013	"
	C-H o.o.p. def.	678	833-660	"
Isoxazole	C=C str.	1575	1580-1500	112
	C=N str.	1454	1470-1460	"
	N-O str.	823	850-810	"
Ether	C-O-C	1247	1260-1200	113
		1041	1075-1020	"
Halide	C-Cl str.	740	750-700	112

PMR SPECTRAL STUDIES OF 6-CHLORO-3-(5-(p-METHOXY PHENYL) ISOXAZOL-3-YL)-CINNOLIN-4(3H)-ONE



Internal reference: TMS; Solvent: $CDCl_3$; Instrument: BRUKER spectrometer(300 MHz)

Signal No.	Signal position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.88	3H	singlet	Ar-OCH_3
2.	6.98	2H	double	Ar-H_a (p-disubstitution)
3.	7.30	1H	double doublet	Ar-H_d
4.	7.51	1H	singlet	Ar-H_g
5.	7.53	1H	doublet	Ar-He
6.	7.68	1H	singlet	Ar-H_f
7.	7.79	1H	singlet	Ar-H_c (isoxazole ring)
8.	8.04	2H	double doublet	Ar-H_b (p-sub.)


MASS SPECTRUM
SamPle: PM-5 DR H S JOSHI,RAJKOT#6204
RT 0'12" FAB(Pos.) GC 1.4c BP: m/z 154.0000 Int. 26.0172 Lv 0.00
Data File: 3EJL25T
25-JUL- 3 12:11
Relative Abundance
M/Z
m/z : 402.63
*3.0
*3.0

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-CHLORO-3-(5-ARYLISOXAZOL-3-YL)-CINNOLIN-4(3H)-ONE

(A) Synthesis of 6-Chloro-3-[(2E)-3-aryl-prop-2-enoyl]cinnolin-4(3H)-one.

See Part-I, Section-I(C)

(B) Synthesis of 6-Chloro-3-(5-(4-methoxyphenyl)isoxazol-3-yl)-cinnolin-4(3H)-one

6-Chloro-3-[(2E)-3-(4-methoxyphenyl)-prop-2-enoyl]cinnolin-4(3H)-one (3.4 gm, 0.01 mol) in dioxane and anhydrous sodium acetate (0.73gm, 0.01 mol) dissolved in minimum amount of acetic acid was added to a solution of hydroxylamine hydrochloride. The reaction mixture was refluxed on oil bath for 10-12 hrs. The product was isolated and crystallized from ethanol. Yield 51 %, m.p. 200 ^{0}C Anal. Calcd. for $C_{18}H_{12}ClN_3O_3$ Requires: C, 61.11; H, 3.42; N, 11.88 % Found: C, 61.10; H, 3.40, N, 11.84 %.

Similarly, other 6-chloro-3-(5-arylisoxazol-3-yl)cinnolin-4(3H)-ones. The physical data are recorded in Table No. 2.

(C) Biological screening of 6-Chloro-3-[5-arylisoxazol-3-yl]cinnolin-4(3H)-one

Antimicrobial testing were carried out as described in Part-I, Section-I(D). The zones of inhibition of test solution are reported in Graphical Chart No. 2.

TABLE-2: PHYSICAL CONSTANTS OF 6-CHLORO-3-(5-ARYLISOXAZOLE-3-YL)-CINNOLIN-4(3H)-ONE

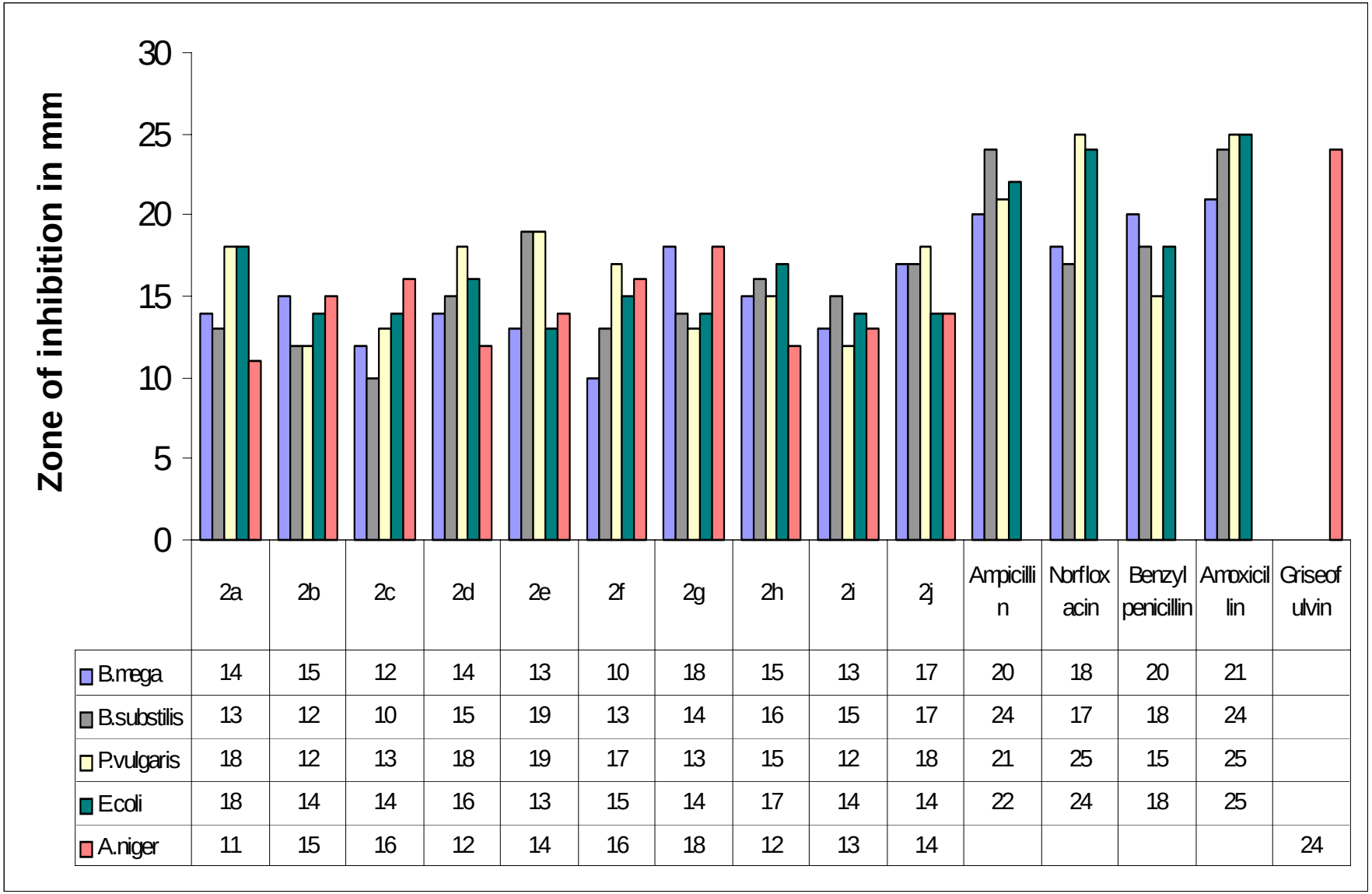
Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^0C	R_f Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
2a	C_6H_5-	$C_{17}H_{10}ClN_3O_2$	323.73	166	0.462	S_1	54	12.98	12.94
2b	3-Br-C_6H_4-	$C_{17}H_9BrClN_3O_2$	402.63	210	0.483	S_1	56	10.44	1042
2c	2-Cl-C_6H_4-	$C_{17}H_9Cl_2N_3O_2$	358.18	190	0.405	S_2	51	11.73	11.72
2d	3-Cl-C_6H_4-	$C_{17}H_9Cl_2N_3O_2$	358.18	182	0.467	S_1	62	11.73	11.63
2e	4-Cl-C_6H_4-	$C_{17}H_9Cl_2N_3O_2$	358.18	214	0.453	S_1	63	11.73	11.70
2f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{19}H_{14}ClN_3O_4$	383.79	176	0.437	S_1	59	10.95	10.92
2g	4-OCH_3-C_6H_4-	$C_{18}H_{12}ClN_3O_3$	353.76	200	0.478	S_3	51	11.88	11.84
2h	4-SCH_3-C_6H_4-	$C_{18}H_{12}ClN_3O_2S$	369.83	210	0.405	S_3	54	8.67	8.62
2i	3-C_6H_5-O-C_6H_4-	$C_{23}H_{14}ClN_3O_3$	415.83	160	0.413	S_1	50	10.11	10.10
2j	4-$N(CH_3)_2$-C_6H_4-	$C_{19}H_{15}ClN_4O_2$	366.80	218	0.368	S_1	62	15.27	15.24

S_1 = Ethyl acetate : Hexane (1.4:8.6)

S_2 = Ethyl acetate : Hexane (3:7)

S_3 = Ethyla acetate : Hexane (2.5:7.5)

Graphical Chart No. 2 : Antimicrobial activity of 6-Chloro-3-(5-aryl isoxazol-3-yl)-cinnolin-4(3H)-one



	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	Ampicillin	Norfloxacin	Benzyl penicillin	Amoxicillin	Griseofulvin
B.mega	14	15	12	14	13	10	18	15	13	17	20	18	20	21	
B.substilis	13	12	10	15	19	13	14	16	15	17	24	17	18	24	
P.vulgaris	18	12	13	18	19	17	13	15	12	18	21	25	15	25	
E.coli	18	14	14	16	13	15	14	17	14	14	22	24	18	25	
A.niger	11	15	16	12	14	16	18	12	13	14					24

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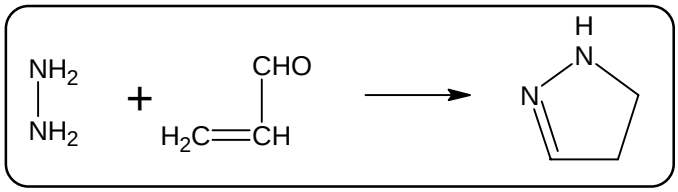
INTRODUCTION

The chemistry of pyrazoline was reviewed by Jarobe in 1967. Pyrazoline has three possible tautomeric structures, but the structure shown is the most stable, which can be prepared by the reaction of hydrazine hydrate with acrolein.

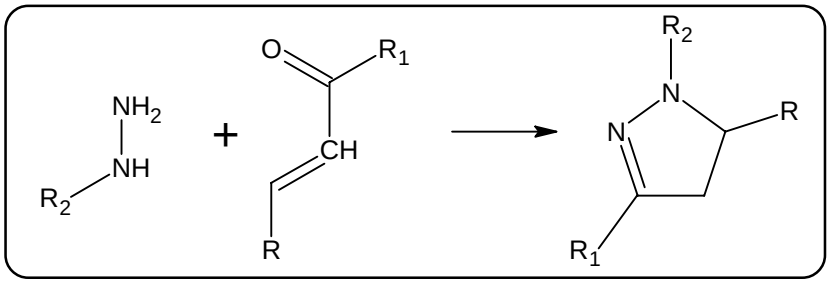


2-Pyrazoline consist a unique class of five membered nitrogen heterocycle. During the past years considerable evidence has been accumulated to demonstrate the importance of 2-pyrazoline derivatives. There has been considerable interest in the pyrazoline ring system both with regard to heterocyclic chemistry and the pharmacological activities of several of its derivatives.

SYNTHETIC ASPECT

Different methods are available in literature for the preparation of 2-pyrazoline. The popular methods are:

1. Among the methods employed in synthesis of pyrazolines, condensation of a variety of substituted chalcones with hydrazine and its derivatives is commonly used[1,2,3].
2. 2-Pyrazolines can also synthesized by the reaction of chalconedibromide with hydrazine hydate[4].

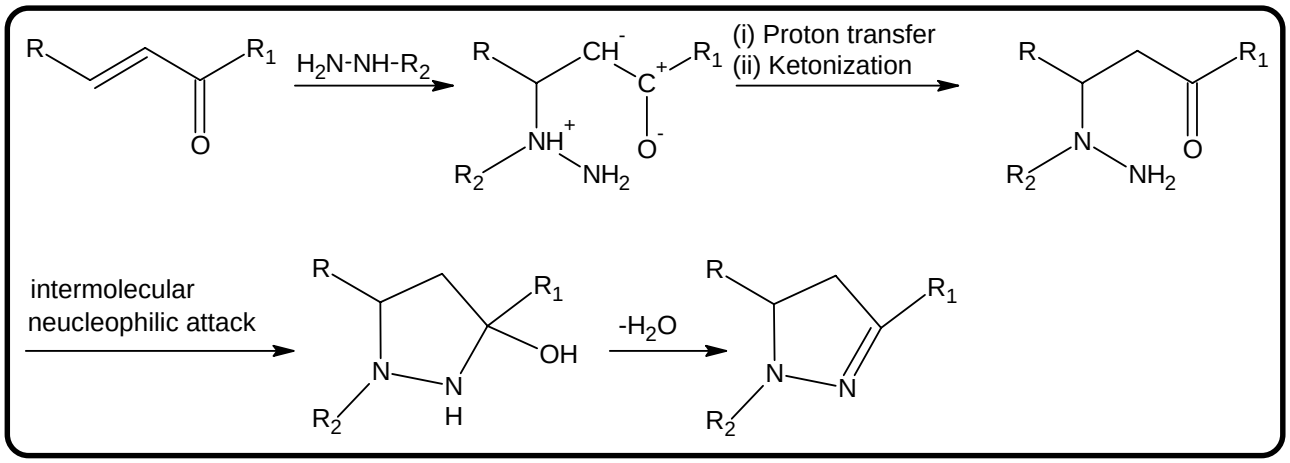


3. Epoxydation of chalcones gave epoxy ketones which on reaction with pyrazoline or phenyl pyrazoline to give substituted pyrazoline derivatives[5].
4. Dipolar cycloaddition of nitrilamines to dimethyl fumarate, fumaro nitrile and the N-aryl maleimides yields the corresponding pyrazolines[6].
5. 2-Pyrazolines can also be obtained through cycloaddition of diazomethane to appropriately substituted chalcones[7].

   Recenlty, microwave assisted synthesis of 2-pyrazolines described by S. Paul et al.[8] and Dandia Anshu et al.[9].

REACTION MECHANISM

The following mechanism seems to be operable for the condensation for the chalcone with hydrazine derivative[10].



THERAPEUTIC IMPORTANCE

Pyrazoline derivatives have been found to possess a number of therapeutic activities like

1. Analgesic[11],

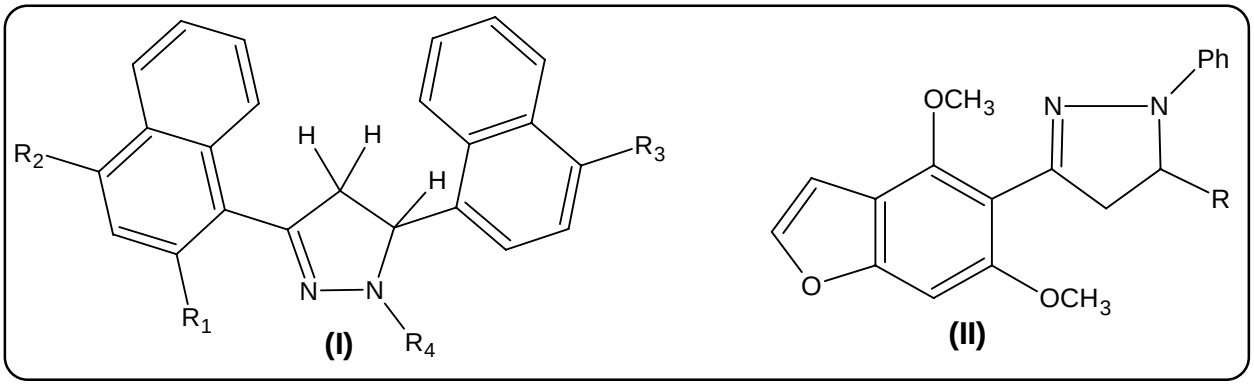
2. Bactericidal[12],
3. Cardiovascular[13],
4. Diuretic[14],
5. Fungicidal[15],
6. Herbicidal[16],
7. Hypoglycemic[17],
8. Insecticidal[18],
9. Tranquillizing[19],
10. Antiallergic[20]

An interesting activity of various substituted pyrazolines as biological agents have attracted considerable attention. The pharmaceutical importance of these compounds lies in the fact that they can be effectively utilized as antibacterial, antifungal, antiviral, antiparasitic, antitubercular, incecticidal[21-26] agent. Some of these compounds have also antiinflammatory, antidiabetic, anesthetic and analgesic properties[27-30]. In addition,pyrazolines have played a crucial part in the development of theory in heterocyclic chemistry and also used extensively in organic synthesis[31-35].

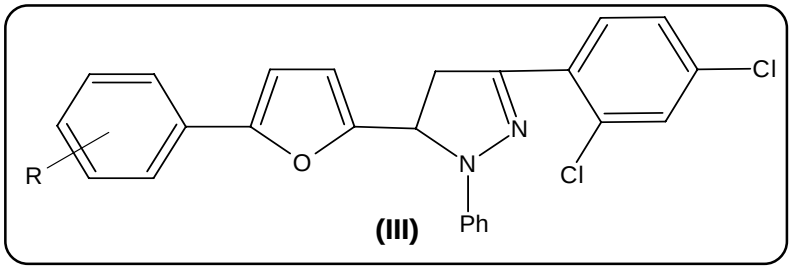
Davood azarifar[36] have synthesized some new 3,5-dinaphthyl substituted 2-pyrazolines (I) and studied their antimicrobial activity. Dashi and Kadu[37] have recently reported the synthesis and antimicrobial activity of naphthyl substituted 2-pyrazoline. Clinton, R. O. et al.[38] also synthesized some pyrazoline derivatives as bacteriostatic, fungicidal and anticancer agents.

Recently O. M. Abdel Hafez et al.[39] have prepared some potentially bioactive pyrazoline derivatives (II) from visnaginone. Nauduri D et al.[40] synthesized 2-pyrazoline derivatives and tested for antibacterials and antimycotics activity. Palaska E et al.[41]

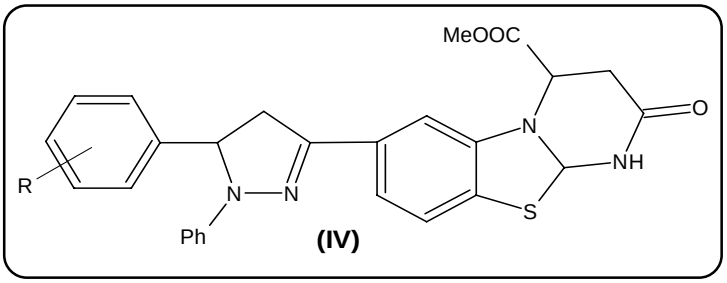
have synthesised and reported some 3,4-diphenyl-2-pyrazolines as antidepressant agents.



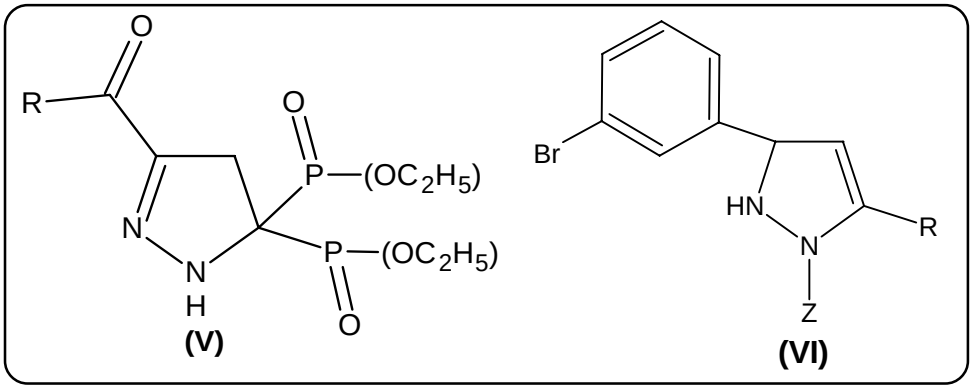
Srivastava et al.[42] have synthesized 1-acetyl-5-arylidenyl-3-(2'-oxo/ thiobarbiturinyl)-2-pyrazolines and reported it as anticonvulsant agents. Holla, B et al.[43] prepared some fluorine containing arylfuryl-N-phenylpyrazolines (III) for antibacterial activity. Chan-DMT et al.[44] have described N-substituted pyrazoline type insecticides. Tanka Katsuhori[45] have patented pyrazoline as herbicides.



Furthermore, Sonare S. S. et al.[46] have synthesized 3-(2'-acetixy-4'-methoxyphenyl)-5-(substituted phenyl)-pyrazoline and tested their antimicrobial activity. Balakrishana Kalluraya and co-workers[47] have reported 1-aryl acetyl-3-(5'-nitro-2'-thienyl)-5-aryl-5-hydroxy pyrazoline as antifungal agent. Gieninah, Magdy et al.[48] prepared 6-,7-and 8-(5-aryl-1-phenyl-2-pyrazolin-3-yl) imidazo and pyrimidi[2,1-b]benzothiazoles (IV) as anticonvulsant agents.



Some novel pyrazoline containing bisphosphonate ester (V) was synthesized and reported as antiinflammatory and antiarithritic agents by Nugent Richard A et al.[49]. In continuation of our work on pyrazoline derivatives (VI) Joshi et al.[50] prepared some anticancer, antitubercular and antimicrobial agents.



(V) **(VI)**

Therefore,as a part of our program focused on 2-pyrazolines with biological activity, and in connection with our interest in the chemistry of arylated pyrazolines,in this part we report the synthesis and antimicrobial properties of some new 2-pyrazolines containing 6-chloro cinnolin-4(3H)-one moiety. The synthesis and therapeutic evaluation of them, have been described as under.

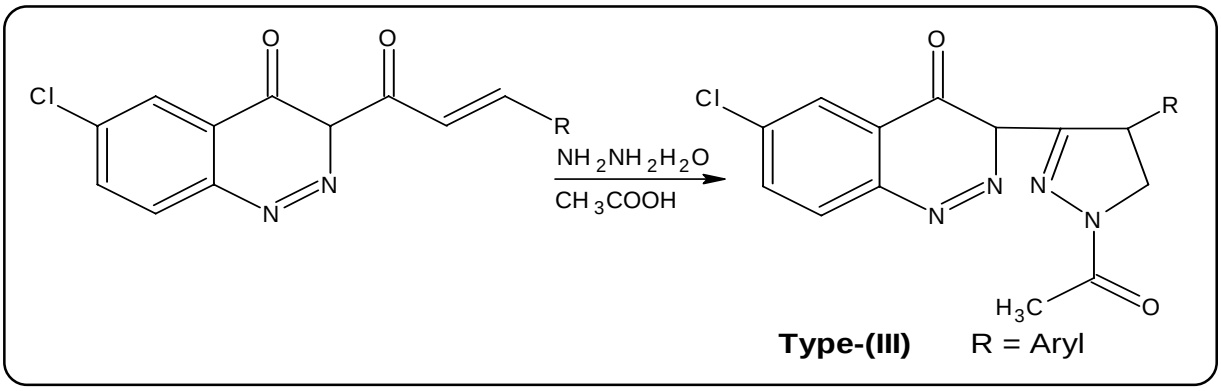
SECTION-I: Synthesis and biological screening of 3-(1-Acetyl-5-aryl-4,5-dihydro-1H-pyrazol-3-yl)cinnolin-4(3H)-one

SECTION-II: Synthesis and biological screening of 6-Chloro-3-(1-phenyl-5-aryl-4,5-dihydro-1H-pyrazol-3-yl)cinnolin-4(3H)-one

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-[1-ACETYL-5-ARYL-4,5-DIHYDRO-1*H*-PYRAZOL-3-YL]-6-CHLOROCINNOLIN-4(3*H*)-ONE

Pyrazolines as a class of heterocyclic compounds have been studied extensively for the past several years. They are associated with broad spectrum of biological activities like anticancer, anticonvulsant, insecticidal, antipyratic etc. Keeping in view of these diversified biological activities, we have undertaken the synthesis of some new pyrazoline derivatives possessing better biological activity which have been described as under. We have synthesized 3-[1-acetyl-5-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-3-yl]-6-chlorocinnolin-4(3H)-one of Type-(III) by the condensation of hydrazine hydrate with chalcones of Type-(I).

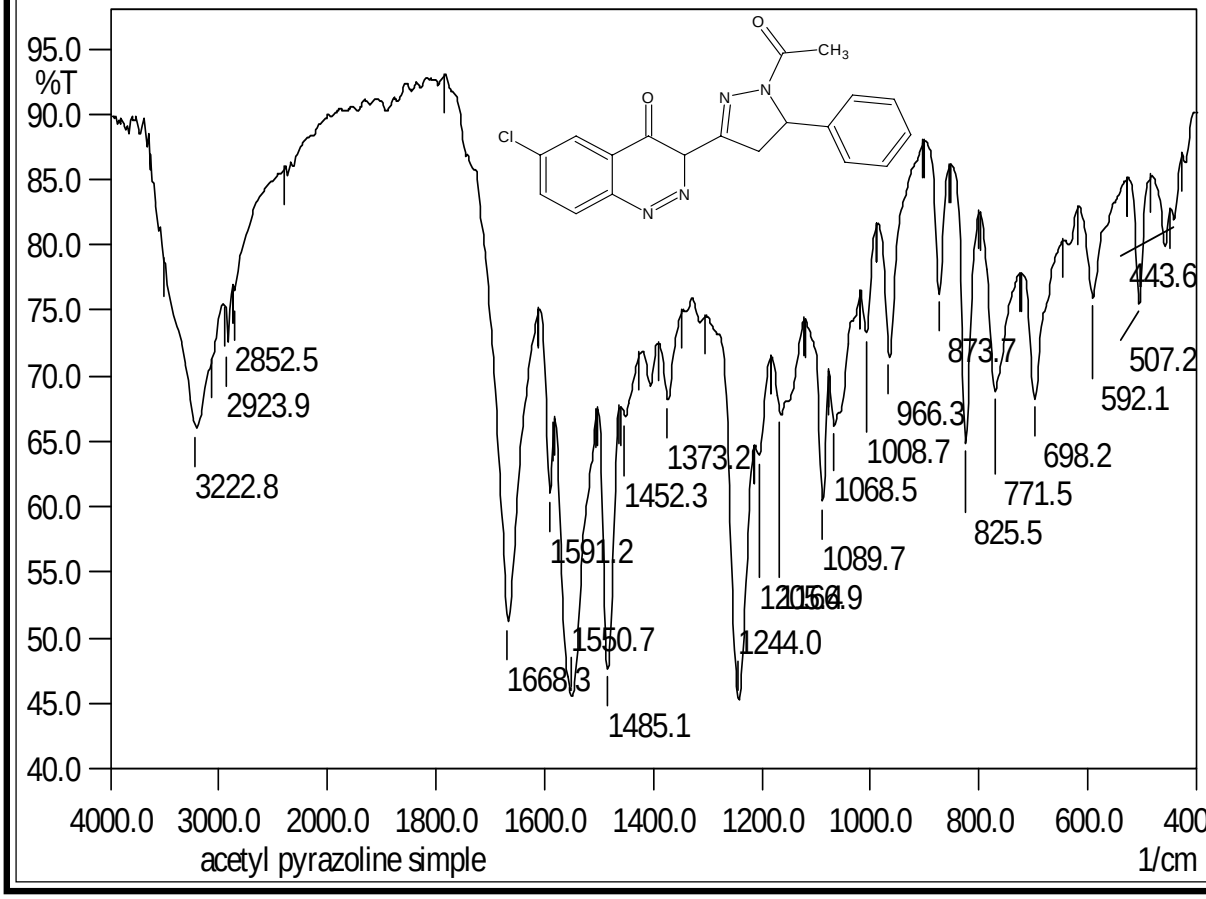


Type-(III) R = Aryl

The structure elucidation of synthesized compounds have been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated 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 synthesized compounds were compared with standard drugs.

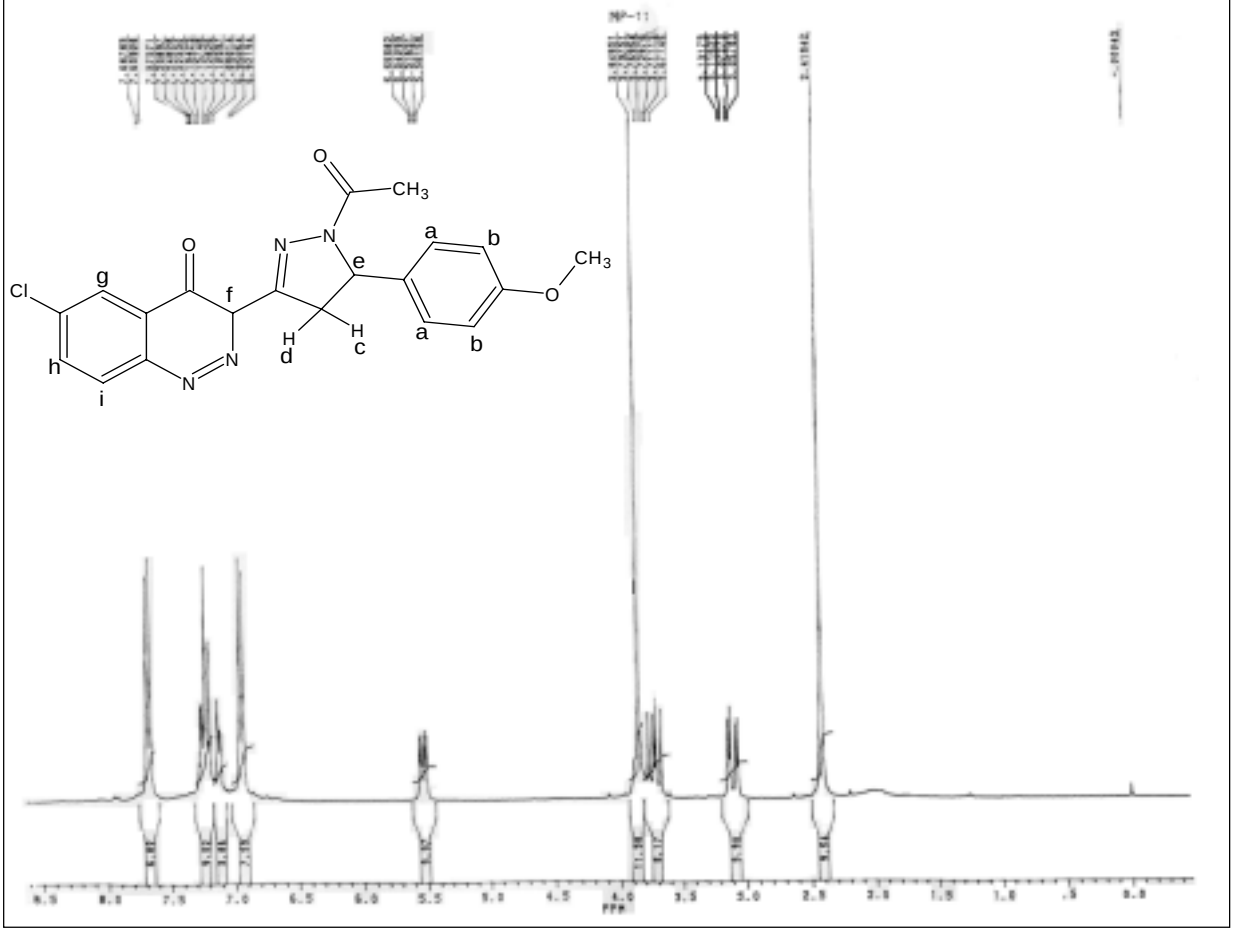
IR SPECTRAL STUDY OF 3-[1-ACETYL-5-PHENYL-4,5-DIHYDRO-1*H*-PYRAZOL-3-YL]-6-CHLORO CINNOLIN-4(3*H*)-ONE



Frequency range: 4000-400cm^{-1} (KBr disc) Instrument : Shimadzu-8400 FTIR

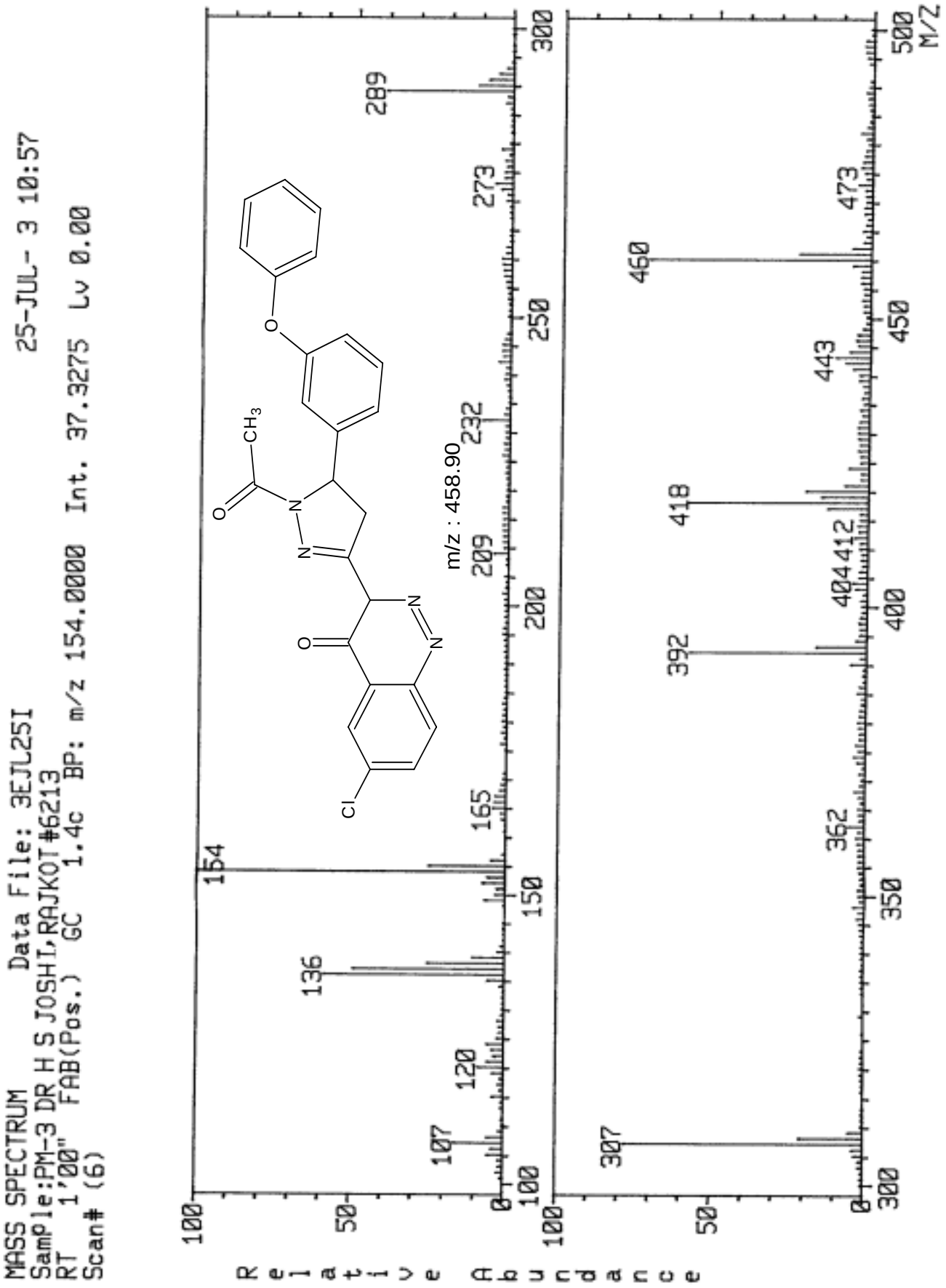
Type	Vibration mode	Frequency in cm^{-1} Observed	Reported	References
Alkane	C-H str. (asym.)	2923	2975-2950	51
-CH_3	C-H str. (sym.)	2852	2880-2860	"
	C-H def. (asym.)	1452	1470-1435	"
	C-H def. (sym.)	1373	1385-1370	"
Aromatic	C-H str.	3060	3080-3030	52
	C=C str.	1485	1620-1430	"
	C-H i.p. def	1068	1269-1013	"
	C-H o.o.p. def.	873	833-660	"
Ether	C-O-C str.	1244	1275-1200	51
Pyrazoline	C=O	1668	1690-1665	"
	C=N str.	3033	3050-3000	52
Halide	C-Cl str.	771	750-700	51

PMR SPECTRAL STUDIES OF 3-[1-ACETYL-5-(4-METHOXY PHENYL)-4,5-DIHYDRO-1*H*-PYRAZOL-3-YL]-6-CHLORO CINNOLIN-4(3*H*)-ONE



Internal reference: TMS; Solvent: $CDCl_3$; Instrument: BRUKER spectrometer(300 MHz)

Signal No.	Signal position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	2.4	3H	singlet	-C(=O)CH_3
2.	3.01	1H	double doublet	-C-H_c
3.	3.72	1H	double duoblet	-CH_d
4.	3.84	3H	singlet	Ar-OCH_3
5.	5.54	1H	double doublet	-CH_e
6.	6.9	2H	doublet	Ar-H_a (p-sub.)
7.	7.11	1H	singlet	Ar-H_f
8.	7.18	1H	doublet	Ar-H_i
9.	7.22	1H	singlet	Ar-H_g
10.	7.26	1H	double doublet	Ar-H_h
11.	7.68	2H	doublet	Ar-H_b (p-sub.)


MASS SPECTRUM Data File: 3EJL2SI
Sample:PM-3 DR H S JOSHI,RAJKOT#6213
RT 1'00" FAB(Pos.) GC 1.4c BP: m/z 154.0000 Int. 37.3275 Lv 0.00
Scan# (6)
25-JUL- 3 10:57
m/z : 458.90
Relative Abundance
M/Z

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-[1-ACETYL-5-ARYL-4,5-DIHYDRO-1*H*-PYRAZOL-3-YL]-6-CHLOROCINNOLIN -4-(3*H*)-ONE

(A) Synthesis of 6-Chloro-3-[(2E)-3-aryl-prop-2-enoyl]cinnolin-4-(3H)-one.

See Part-I, Section-I(C)

(B) Synthesis of 3-[1-Acetyl-5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]-6-chlorocinnolin-4(3H)-one

A mixture of 6-chloro-3-[(2E)-3-(4-methoxyphenyl)-prop-2-enoyl]cinnolin-4(3H)-one (3.4 gm, 0.01 mol) in glacial acetic acid (25 ml) and hydrazine hydrate (0.5gm, 0.01 mol) was refluxed for 8 hrs. The resulting mixture was poured onto crushed ice. The product was isolated and crystallized from ethanol. Yield 53 % m. p. 186^{0}C, Anal. Calcd. for $C_{20}H_{17}ClN_4O_3$ Requires: C, 60.53; H, 4.32; N, 14.12 % Found: C, 60.50; H, 4.31; N, 14.11 %.

Similarly, other 3-[1-acetyl-5-aryl-4,5-dihydro-1H-pyrazol-3-yl]-6-chlorocinnolin-4(3H)-ones were prepared. The physical data are recorded in Table No. 3.

(C) Biological screening of 3-[1-Acetyl-5-aryl-4,5-dihydro-1H-pyrazol-3-yl]-6-chlorocinnolin-4(3*H*)-one

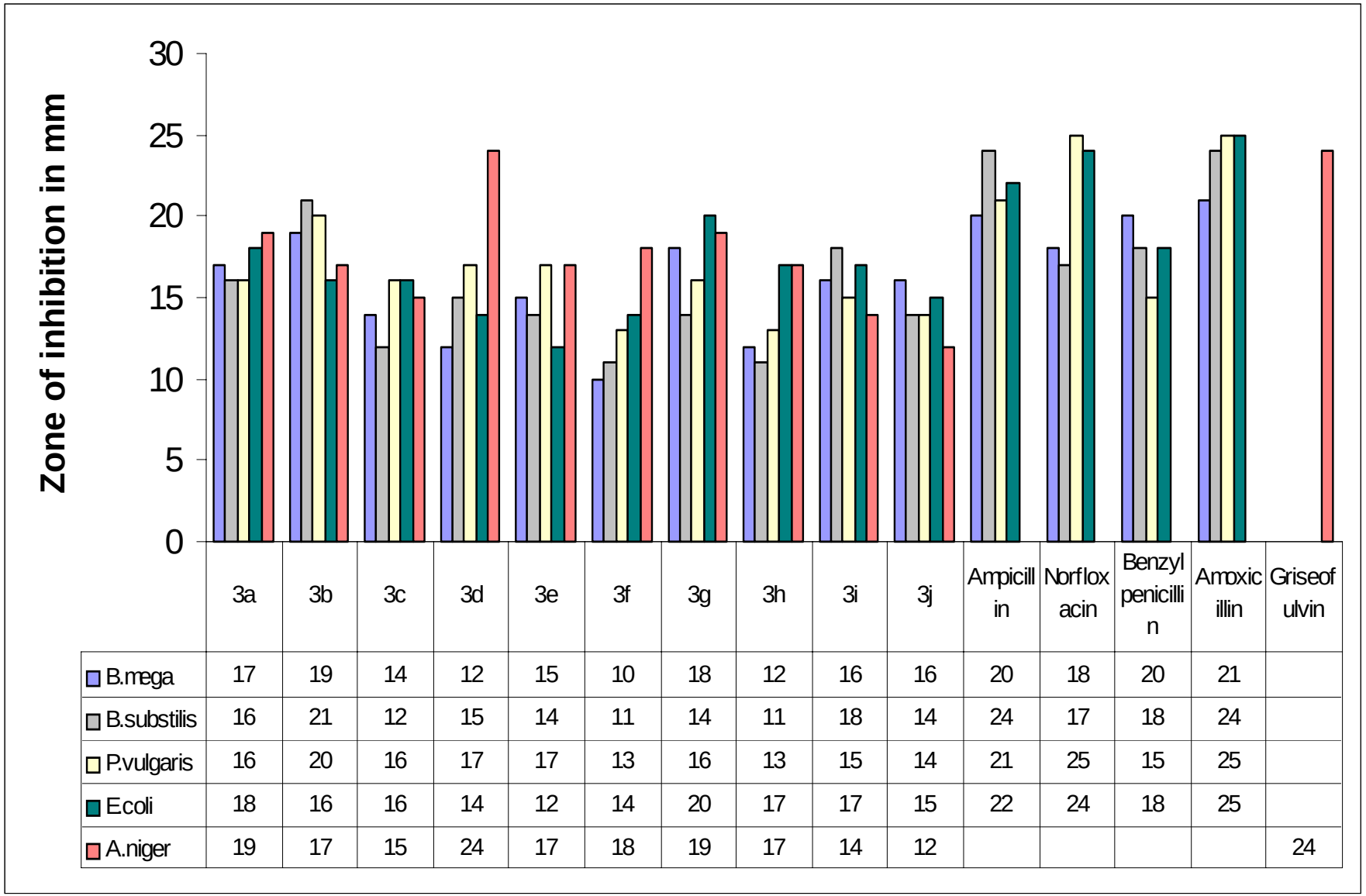
Antimicrobial testing were carried out as described in Part-I, Section-I(D). The zones of inhibition of test solution are reported in Graphical Chart No. 3.

TABLE-3: PHYSICAL CONSTANTS OF 6-CHLORO-3-(1-ACETYL-5-ARYL-4,5-DIHYDRO-1H-PYRAZOL-3-YL)-CINNOLIN-4(3H)-ONE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^0C	R_f Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
3a	C_6H_5-	$C_{19}H_{15}ClN_4O_2$	366.80	164	0.587	S_1	55	15.27	15.25
3b	3-Br-C_6H_4-	$C_{19}H_{14}BrClN_4O_2$	445.70	158	0.529	S_1	58	12.57	12.54
3c	2-Cl-C_6H_4-	$C_{19}H_{14}Cl_2N_4O_2$	401.25	170	0.619	S_1	59	13.96	13.95
3d	3-Cl-C_6H_4-	$C_{19}H_{14}Cl_2N_4O_2$	401.25	184	0.492	S_1	54	13.96	13.94
3e	4-Cl-C_6H_4-	$C_{19}H_{14}Cl_2N_4O_2$	401.25	164	0.604	S_1	61	13.96	13.96
3f	3,4-$(OCH_3)_2$-C_6H_3-	$C_{21}H_{19}ClN_4O_4$	426.85	202	0.514	S_1	64	13.13	13.12
3g	4-OCH_3-C_6H_4-	$C_{20}H_{17}ClN_4O_3$	396.83	186	0.565	S_1	53	14.12	14.11
3h	4-SCH_3-C_6H_4-	$C_{20}H_{17}ClN_4O_2S$	412.89	188	0.551	S_1	57	13.57	13.55
3i	3-NO_2-C_6H_4-	$C_{19}H_{14}ClN_5O_4$	411.80	168	0.456	S_1	62	17.01	17.00
3j	2-OH-C_6H_4-	$C_{19}H_{15}ClN_4O_3$	382.78	244	0.412	S_1	50	14.64	14.63
3k	4-OH-C_6H_4-	$C_{19}H_{15}ClN_4O_3$	382.78	258	0.467	S_1	54	14.64	14.62
3l	3-C_6H_5-O-C_6H_4-	$C_{25}H_{19}ClN_4O_3$	458.90	229	0.421	S_1	51	12.21	12.20
3m	4-$N(CH_3)_2$-C_6H_4-	$C_{21}H_{20}ClN_5O_2$	409.87	226	0.442	S_1	50	17.09	17.05

S_1 = Ethyl acetate : Hexane (3 : 7)

Graphical Chart No. 3 : Antimicrobial activity of 3-(1-Acetyl-5-aryl-4,5-dihydro-1H-pyrazol-3-yl)-cinnolin-4(3H)-one

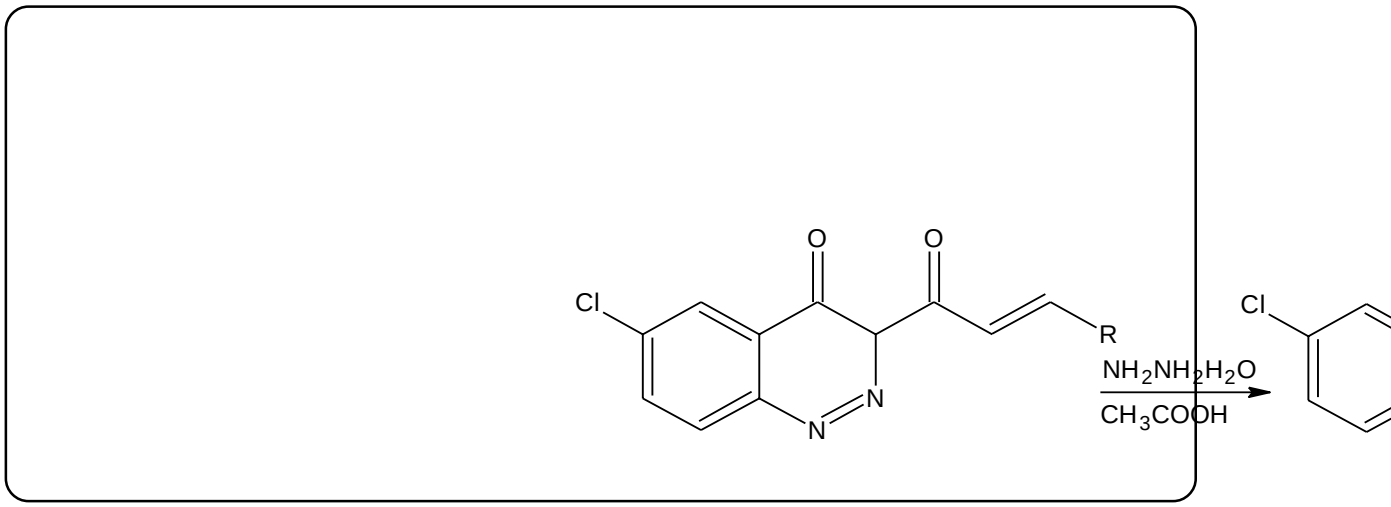


	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	Ampicillin	Norfloxacin	Benzylpenicillin	Amoxicillin	Griseofulvin
B.mega	17	19	14	12	15	10	18	12	16	16	20	18	20	21	
B.substilis	16	21	12	15	14	11	14	11	18	14	24	17	18	24	
P.vulgaris	16	20	16	17	17	13	16	13	15	14	21	25	15	25	
E.coli	18	16	16	14	12	14	20	17	17	15	22	24	18	25	
A.niger	19	17	15	24	17	18	19	17	14	12					24

SECTION-II

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-CHLORO-3-[5-ARYL-1-PHENYL-4,5-DIHYDRO-1H-PYRAZOL-3-YL]CINNOLIN-4(3H)-ONE

Pyrazolines have been found to be associated with broad spectrum of biological activities. Hence, it was thought of interest to synthesize 6-chloro-3-[5-aryl-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl]cinnolin-4(3H)-ones of Type (IV) from 6-chloro-3-[(2E)-3-aryl-prop-2-enoyl]cinnolin-4(3H)-ones of Type (I) by the cyclocondensation with phenyl hydrazine shown as under.

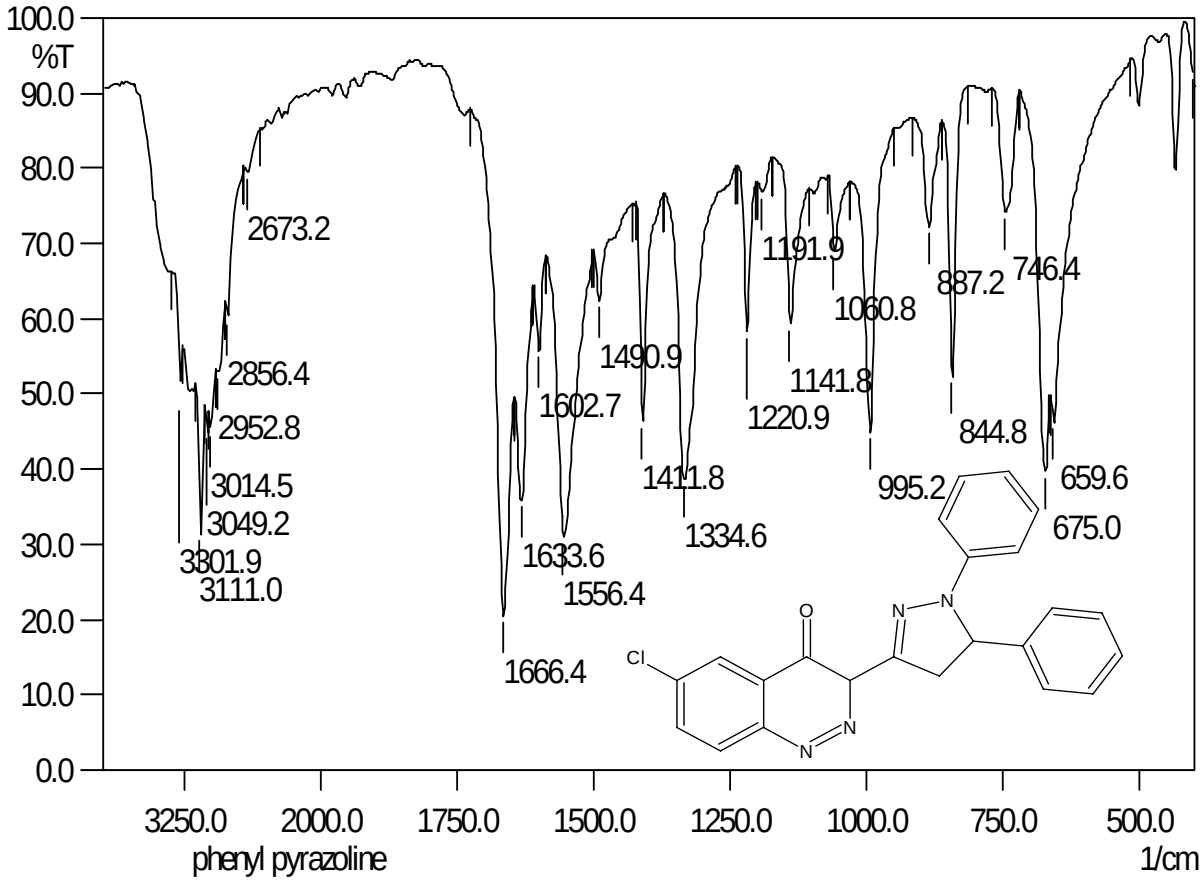


The structure elucidation of synthesized compounds have been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

Ty

All the compounds have been evaluated 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 synthesized compounds were compared with standard drugs.

IR SPECTRAL STUDY OF 6-CHLORO-3-[1,5-DIPHENYL-4,5-DIHYDRO-1H-PYRAZOL-3-YL]CINNOLIN-4(3H)-ONE



Frequency range: 4000-400cm^{-1} (KBr disc) Instrument : Shimadzu-8400 FTIR

Type	Vibration mode	Frequency in cm^{-1} Observed	Reported	References
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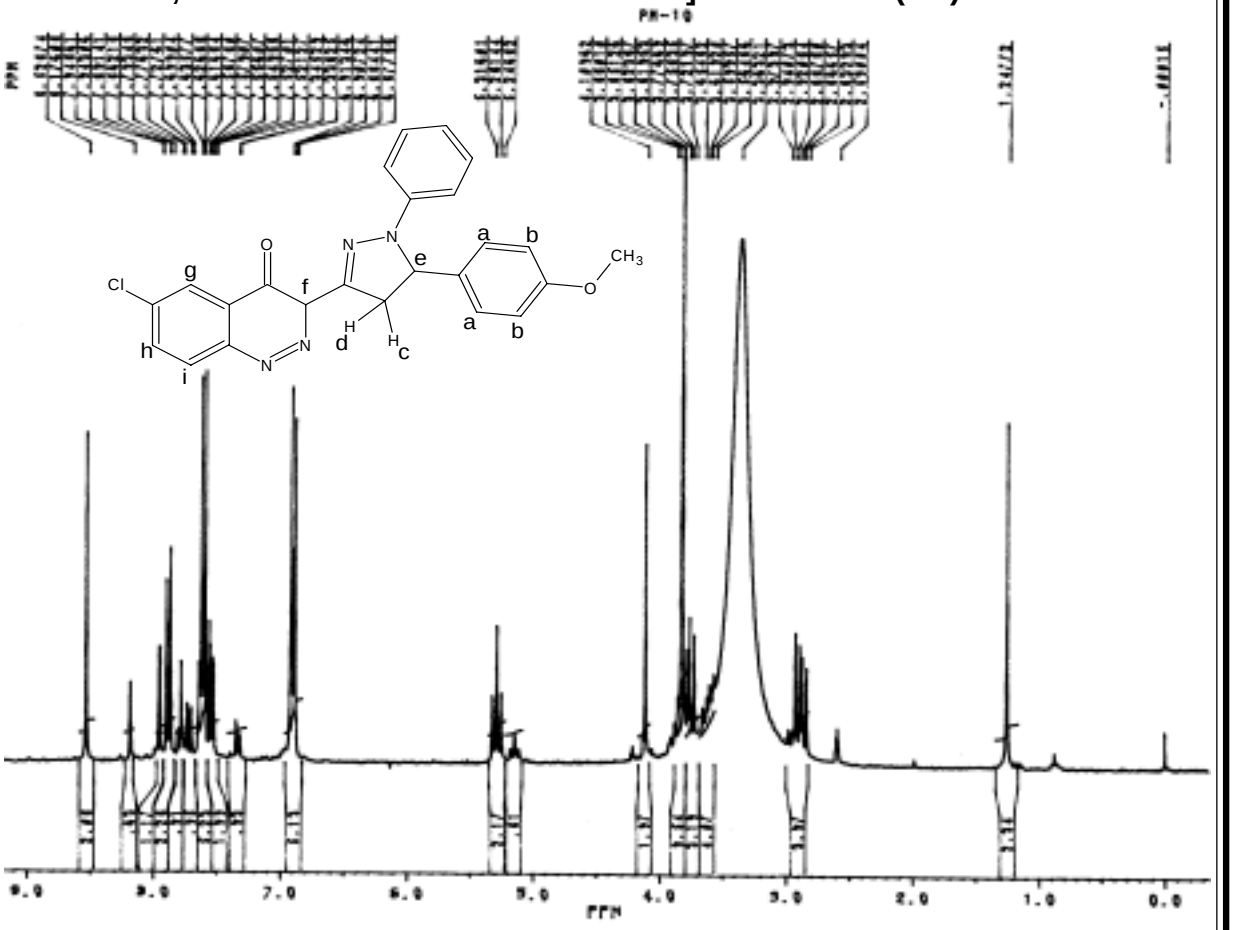
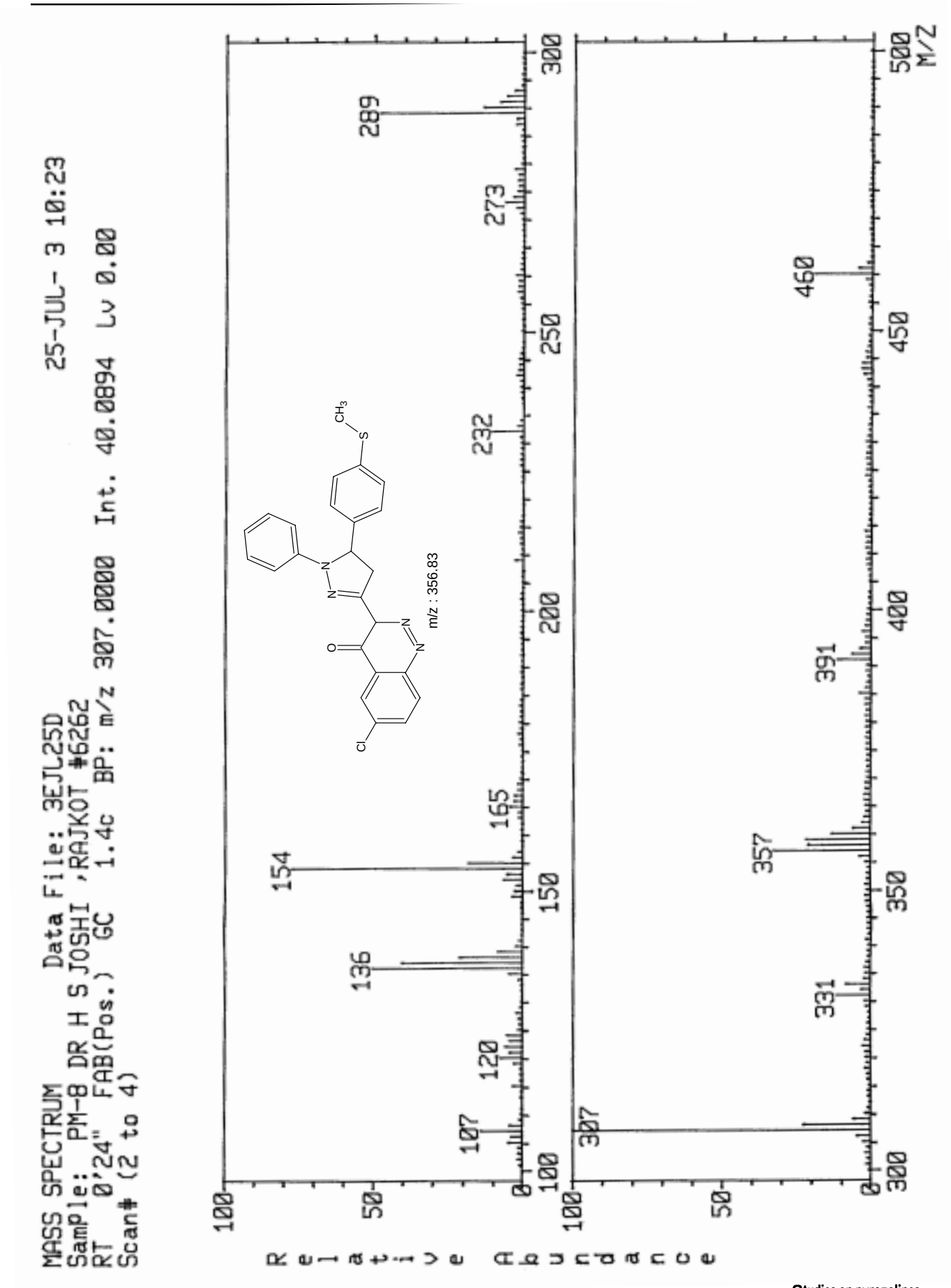
-CH_3	C-H str. (sym.)	2856	2880-2860	"
	C-H def. (asym.)	1411	1470-1435	"
	C-H def. (sym.)	1334	1385-1370	"
Aromatic	C-H str.	3049	3080-3030	51
	C=C str.	1490	1620-1430	"
	C-H i.p. def	1060	1269-1013	"
	C-H o.o.p. def.	844	833-660	"
	C=O	1660	1725-1650	50
Pyrazoline	C=N str.	1633	1627-158	51
Halide	C-Cl str.	746	750-700	50

PMR SPECTRAL STUDIES OF 6-CHLORO-3-[5-(4-METHOXYPHENYL)-1-PHENYL-4,5-DIHYDRO-1H-PYRAZOL-3-YL]CINNOLIN-4(3H)-ONE



Internal reference: TMS; Solvent: $CDCl_3$; Instrument: BRUKER spectrometer(300 MHz)

Signal No.	Signal position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	2.97	1H	double doublet	-C-H_c
3.	3.72	1H	double duoblet	-CH_d
4.	3.81	3H	singlet	Ar-OCH_3
5.	5.21	1H	double doublet	-CH_e
6.	6.93	2H	doublet	Ar-H_a (p-sub.)
7.	7.11	1H	singlet	Ar-H_f
8.	7.18	1H	doublet	Ar-H_i
9.	7.22	1H	singlet	Ar-H_g
10.	7.26	2H	doublet	Ar-H_h
11.	7.63	2H	doublet	Ar-H_b (p-sub.)
12.	7.52-7.62	5H	multiplet	Ar-H


MASS SPECTRUM Data File: 3EJL25D
SamPle: PM-8 DR H S JOSHI ,RAJKOT #6262
RT 0'24" FAB(Pos.) GC 1.4c BP: m/z 307.0000 Int. 40.0894 Lv 0.00
Scan# (2 to 4)
25-JUL- 3 10:23
m/z : 356.83
Relative Abundance
M/Z

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-CHLORO-3-[5-ARYL-1-PHENYL-4,5-DIHYDRO-1H-PYRAZOL-3-YL]CINNOLIN - 4(3H)-ONE

(A) Synthesis of 6-Chloro-3-[(2E)-3-aryl-prop-2-enoyl]cinnolin-4(3H)-one.

See Part-I, Section-I(C)

(B) Synthesis of 6-Chloro-3-[5-(4-methoxyphenyl)-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl]cinnolin-4(3H)-one

A mixture of 6-chloro-3-[(2E)-3-(4-methoxyphenyl)-prop-2-enoyl]cinnolin-4(3H)-one (3.4 gm, 0.01 mol) in alcohol (25 ml) and phenyl hydrazine (0.92gm, 0.01 mol) was refluxed for 8 hrs. The resulting mixture was poured on crushed ice. The product was isolated and crystallized from ethanol. Yield 60 % m. p. 140^0C, Anal. Calcd. for $C_{18}H_{13}ClN_2O_3$ Requires: C, 66.90; H, 4.44; N, 13.00 % Found: C, 66.87; H, 4.43; N, 12.98 %.

Similarly, other 6-chloro-3-[5-aryl-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl]cinnolin-4(3H)-one were prepared. The physical data are recorded in Table No. 3.

(C) Biological screening of 6-Chloro-3-[5-aryl-1-phenyl-4,5-dihydro-1H-pyrazol-3-yl]cinnolin-4(3H)-one

Antimicrobial testing were carried out as described in Part-I, Section-I(D). The zones of inhibition of test solution are reported in Graphical Chart No. 4.

TABLE-4: PHYSICAL CONSTANTS OF 6-CHLORO-3-(1-PHENYL-5-ARYL-4,5-DIHYDRO-1H-PYRAZOL-3-YL)-CINNOLIN-4(3H)-ONE

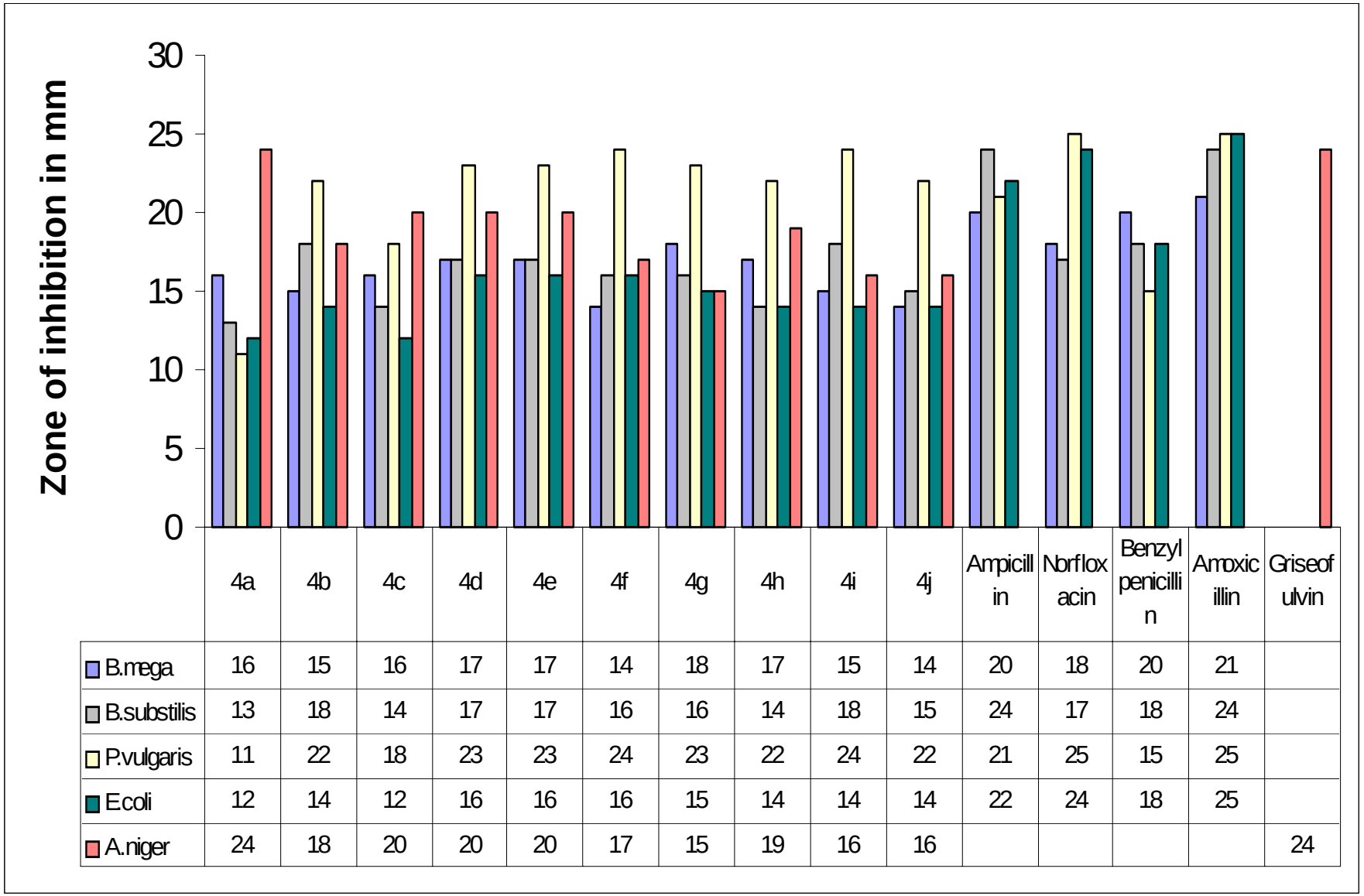
Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^0C	R_f Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
4a	C_6H_5-	$C_{23}H_{17}ClN_4O$	400.86	158	0.701	S_1	65	13.98	13.94
4b	3-Br-C_6H_4-	$C_{23}H_{16}BrClN_4O$	479.76	150	0.524	S_1	62	11.68	11.64
4c	2-Cl-C_6H_4-	$C_{23}H_{16}Cl_2N_4O$	435.31	144	0.574	S_2	54	12.87	12.85
4d	3-Cl-C_6H_4-	$C_{23}H_{16}Cl_2N_4O$	435.31	122	0.594	S_1	53	12.87	12.86
4e	4-Cl-C_6H_4-	$C_{23}H_{16}Cl_2N_4O$	435.31	124	0.452	S_3	48	12.87	12.85
4f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{25}H_{21}ClN_4O_3$	460.91	124	0.486	S_3	45	12.16	12.15
4g	4-OCH_3-C_6H_4-	$C_{24}H_{19}ClN_4O_2$	430.89	140	0.553	S_2	60	13.00	12.98
4h	4-SCH_3-C_6H_4-	$C_{24}H_{19}ClN_4OS$	446.96	110	0.508	S_1	55	12.54	12.52
4i	3-C_6H_5-O-C_6H_4-	$C_{29}H_{21}ClN_4O_2$	49296	118	0.534	S_1	51	11.37	11.34
4j	4-$N(CH_3)_2$-C_6H_4-	$C_{25}H_{22}ClN_5O$	443.93	164	0.614	S_3	50	15.78	15.74

S_1 = Benzene : Acetone (9 : 1)

S_2 = Benzene : Acetone (8 : 2)

S_3 = Ethyla acetate : Hexane (2.5:7.5)

Graphical Chart No. 4 : Antimicrobial activity of 6-Chloro-3-(1-phenyl-5-aryl-4,5-dihydro-1H-pyrazol-3-yl)cinnolin-4(3H)-one



	4a	4b	4c	4d	4e	4f	4g	4h	4i	4j	Ampicillin	Norfloxacin	Benzylpenicillin	Amoxicillin	Griseofulvin
B.mega	16	15	16	17	17	14	18	17	15	14	20	18	20	21	
B.substilis	13	18	14	17	17	16	16	14	18	15	24	17	18	24	
P.vulgaris	11	22	18	23	23	24	23	22	24	22	21	25	15	25	
E.coli	12	14	12	16	16	16	15	14	14	14	22	24	18	25	
A.niger	24	18	20	20	20	17	15	19	16	16					24

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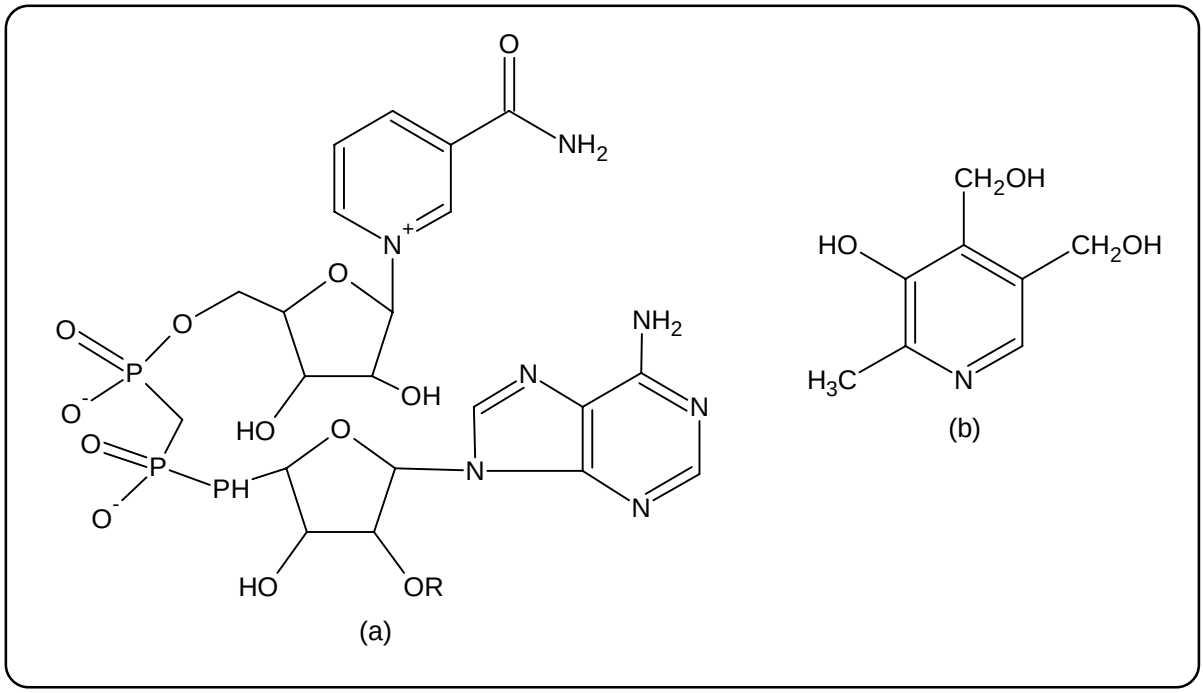
Introduction

Pyridine, which belong to an important group of heterocyclic compounds has been explored extensively for their applications in the field of medicine[1], agriculture and industrial chemistry. Pyridine-3-carboxamide occurs as a component of the structure of the important coenzymes NADP+(a), one of the B_2 complex of Vitamins, occurs in red blood corpuscles and participates in biochemical redox reaction. Pyridoxol (Vitamin B_6)(b), occurs in yeast and wheatgerm is an important food additive.

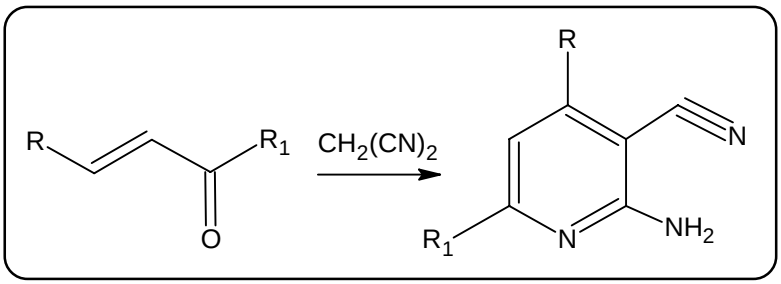


The availability of 3-cyano pyridine, nicotinamide and nicotic acid make possible their use as synthetic intermediates.

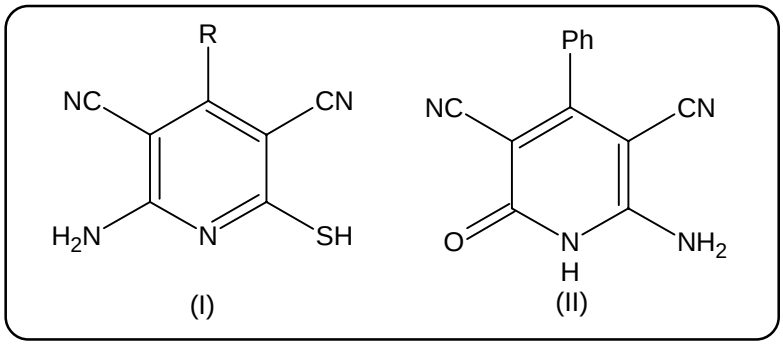
SYNTHETIC ASPECT

Different methods for preparation of 3-cyanopyridines documented in literature some of them are as follows:

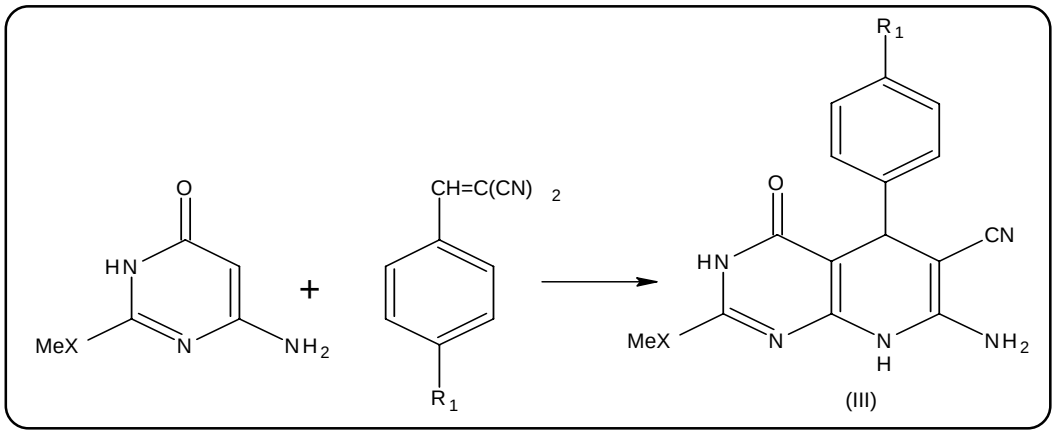
1. 3-Cyanopyridine can be prepared by the vapour phase air oxidation of nicotine over V_2O_5[2] or alkenyl substituted pyridines in presence of ammonia[3].
2. Oxley and co-workers[4] synthesized pyridine benzenesulphonate by heating nicotinic acid, benzenesulphonate and $PhSO_2NH_2$ at 230^0 for 40 minutes.
3. Samour and co-workers prepared substituted cyanopyridines by the condensation of chalcone with ethyl cyanoacetate and malononitrile in presence of ammonium acetate[5,6].
4. A. Sakuri and Midorikawa have reported that malononitrile reacts with α,β-unsaturated ketones to give 2-amino-3-cyano-4,6-disubstituted pyridines[7,8].



5. Cyanopyridine derivatives (I) are obtained by reaction of R-CO-CH_3 with 2-cyanothioacetamide in presence of N-methyl morpholine, have been reported by Dayachenko V. D.[9], and cyanopyridine derivatives (II) reported by Metwally Nadia et al.[10].



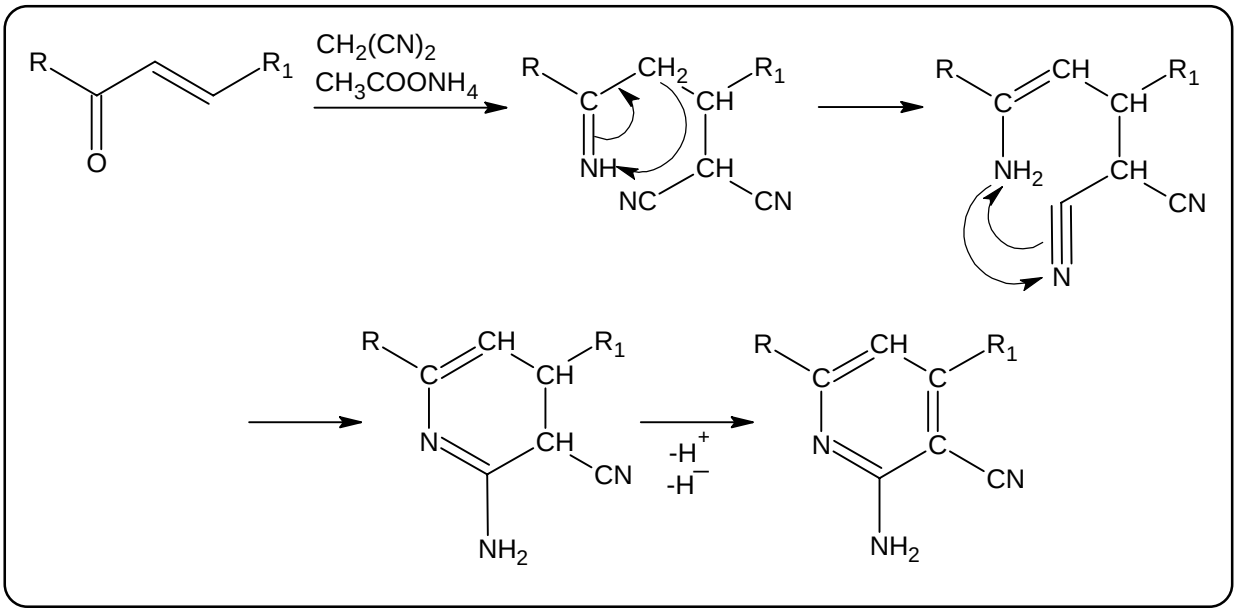
6. Quiroya Jairo and co-workers have synthesized pyrido-[2,3-d]-pyrimidin-4(3H)-one (III) from 6-amino-2-pyrimidinones and arylidene malononitrile[11].



7. Dornow and Neuse[12] synthesized substituted 3-cyano-pyridine by boiling ethyl cyanoacetate and ethyl acetoacetate with ammonia.

REACTION MECHANISM

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



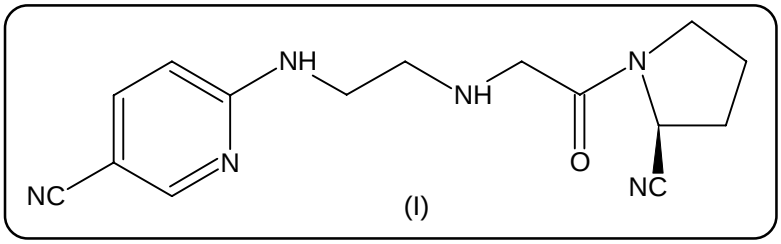
THERAPEUTIC INTEREST

Cyano pyridine derivatives have been found to posses range of therapeutic activities as shown below.

1. Antisoriasis[13],

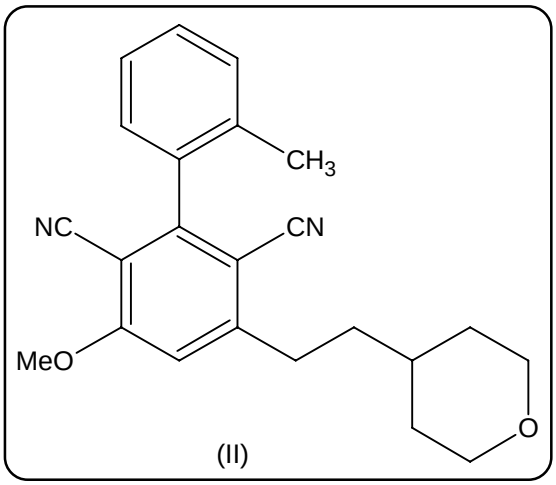
2. Antiepileptic[14],
3. Adrenergic[15],
4. Anticonvulsant[16],
5. Antitubercular[17],
6. Antihypertensive[18],
7. Analgesic[19],
8. Antiallergic[20],
9. Antifungal[21],
10. Herbicidal[22,23],
11. Antiviral[24]

Recently, Villhauer, Edwin B. et.al.[25] reported the derivatives of cyano pyridine (I) as antihyperglycemic agent. K. Kadlec and Hanslian[26] showed that 2-methyl-3-nitro-4-methoxy-5-cyano-6-chloropyridines caused occupational eczema in Vitamin-B6 factoty workers. Rigternik and Raymond[27] studied the pesticidal activity of 3-cyano-pyridine derivatives. W. Hoefling and co-workers[28] prepared 3- and 4-cyanopyridines, which possess tuberculosis arresting properties.



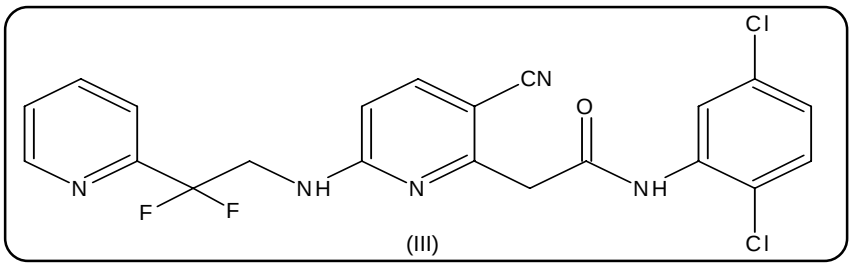
(I)

Moreover, Harada, Hiroki et al.[29] synthesized 2-acylamino-3,5-dicyanopyridine derivatives (II) as high conductance type calcium sensitivity K channel opening drugs. Barton et al.[30] prepared 2-substituted-3-cyano-5-nitropyridines which possess fungicidal and insecticidal properties. Kurt et al.[31] studied the antiphlogistic and analgesic properties of substituted 3-cyanopyridines.



(II)

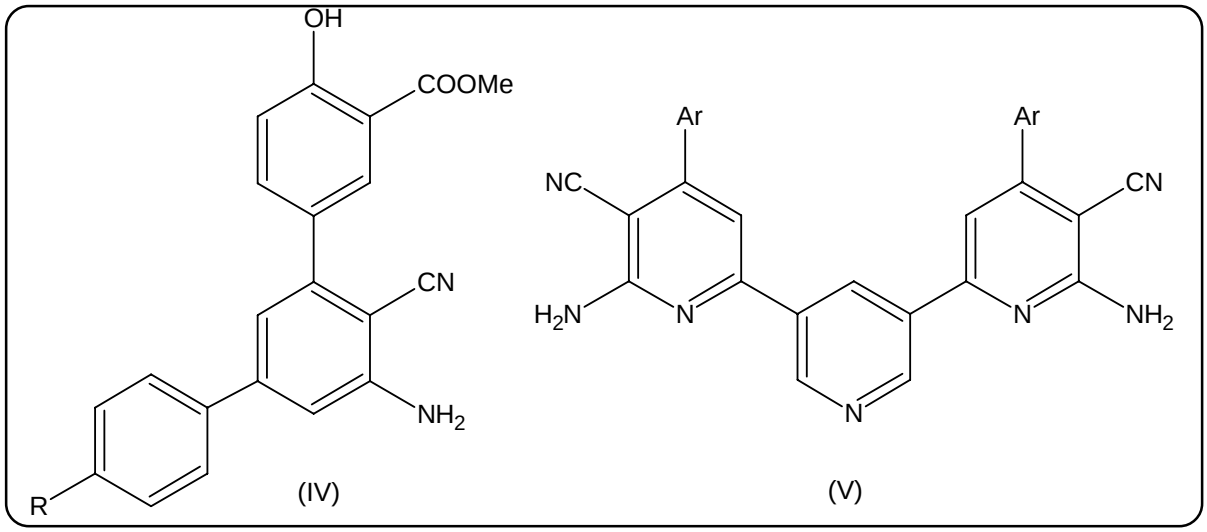
Furthermore, Nantermet, Philippe G. et al.[32] also prepared pyridinyl aminoamides (III) as thrombin inhibitors. Manna Fedele and co-workers[33] have reported some 3-cyano pyridines as antiinflammatiry agents. Villa lobas Anabella et al.[34] have prepared some new 3-cyanopyridines and reported them as choline-stearase inhibitors.



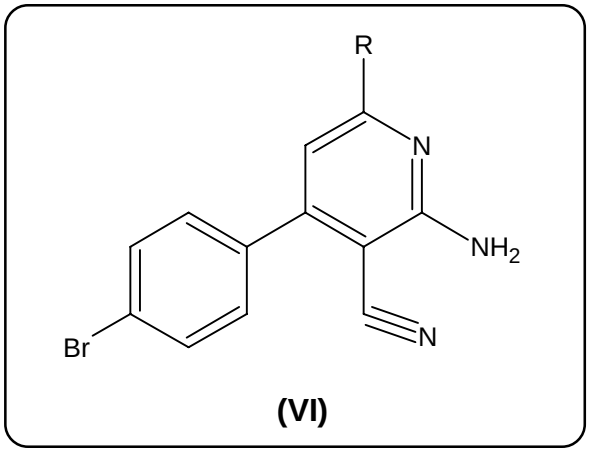
(III)

Abd El-Galil and E. Amr[35] prepared cyanopyridine derivatives (V) and screened for their antimicrobial activity. Umed-Ten and co-workers[36] prepared cyanopyridines as potent fungicides. Some novel cyanopyridines synthesized and reported as fungcidal[37], insecticidal[38] and herbicidal[39]. Some investigator have studied as antimicrobial agent[40] and studied bacteriostatic effect[41,42,43].

Furthermore cyanopyridines are also found applicable in the dying of polyester and acrylic fiber[44]. The oxide activator bleaching activity of cyanopyridine has been proved by Rees Wayne M.[45].Moreover, Oshida Mario[46] have constructed some new cyanopyridine derivatives which inhibit ceberal edema and delayed neuron death. Hence, they are useful as ceberal edama inhibitor or cerebrovascular disorder remedies.



Joshi et al[47]. recently have synthesized some new cyano pyridine (VI) derivatives as anticancer and antimicrobial agents.



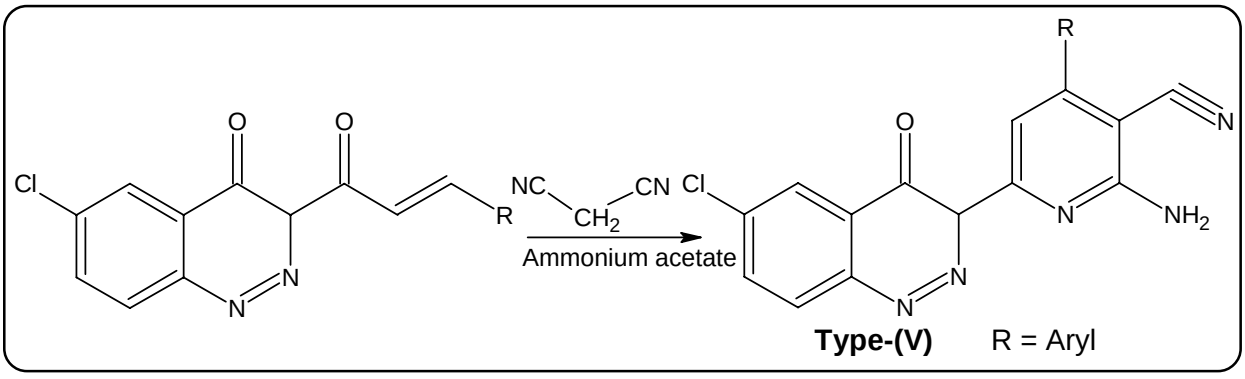
Keeping these observations in view and in continuation of our work on the synthesis of cyanopyridine heterocyclec, it was contemplated to synthesize a new series of cyanopyridine containing 6-chloro cinnolin-4(3H)-one moiety.

SECTION-I : Synthesis and biological screening of 2-Amino-4-aryl-6-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)nicotinonitrile

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-AMINO-4-ARYL-6-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)NICOTINONITRILE.

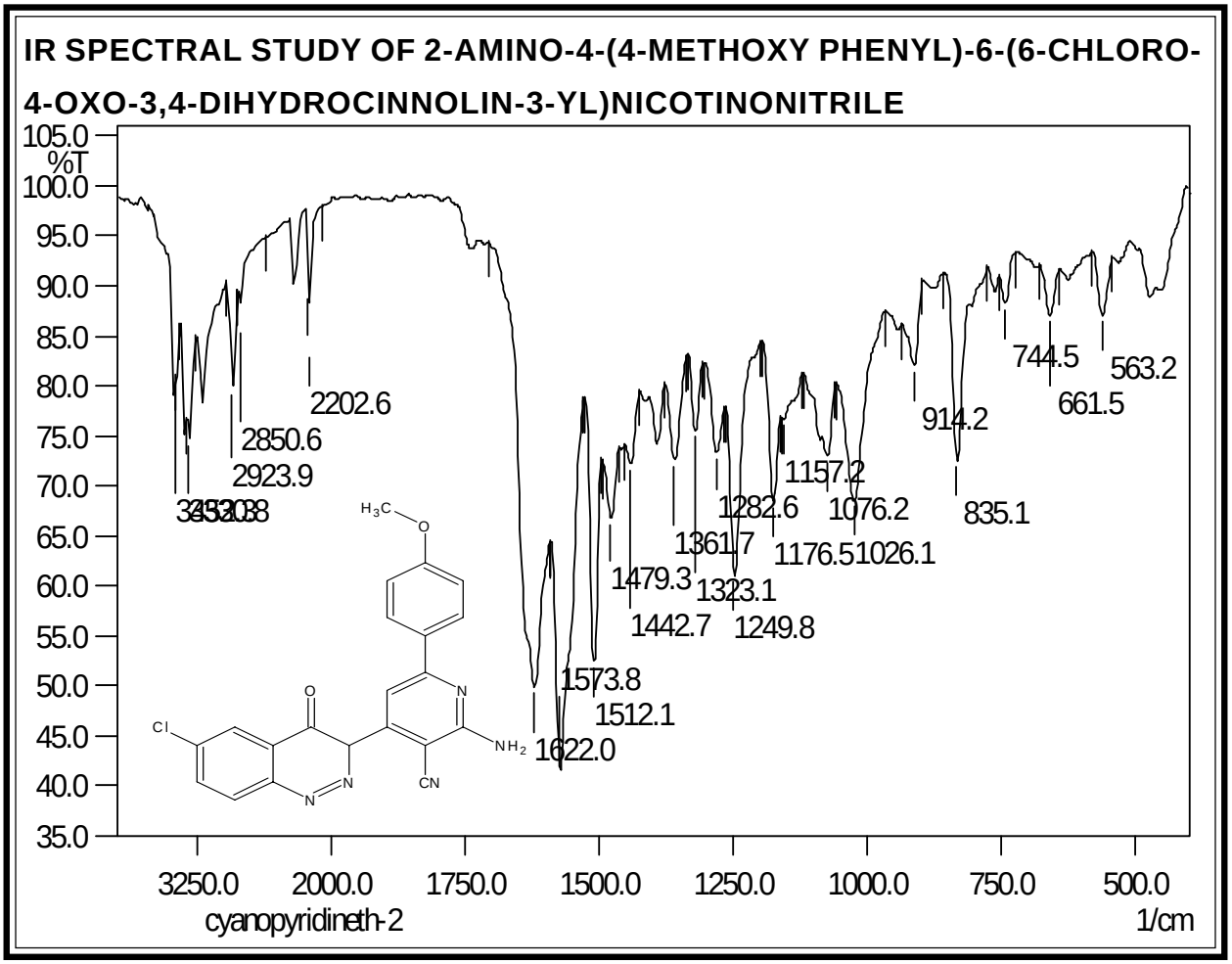
In recent years, much interest has been focused on the synthesis of pyridines as the pyridine ring system is associated with valuable pharmacological activity like antibacterial, antimalarial, antihypertensive, antifungal, anticonvulsant etc. Considering these facts we thought it is worthwhile to synthesize some novel derivatives in association with cinnoline nucleus in search of better potential drugs. Cyanopyridine derivatives of Type-(V) have been synthesized by the reaction of the chalcones of the Type-(I) with malononitrile in presence of ammonium acetate.



Type-(V) R = Aryl

The structure elucidation of synthesized compounds have been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

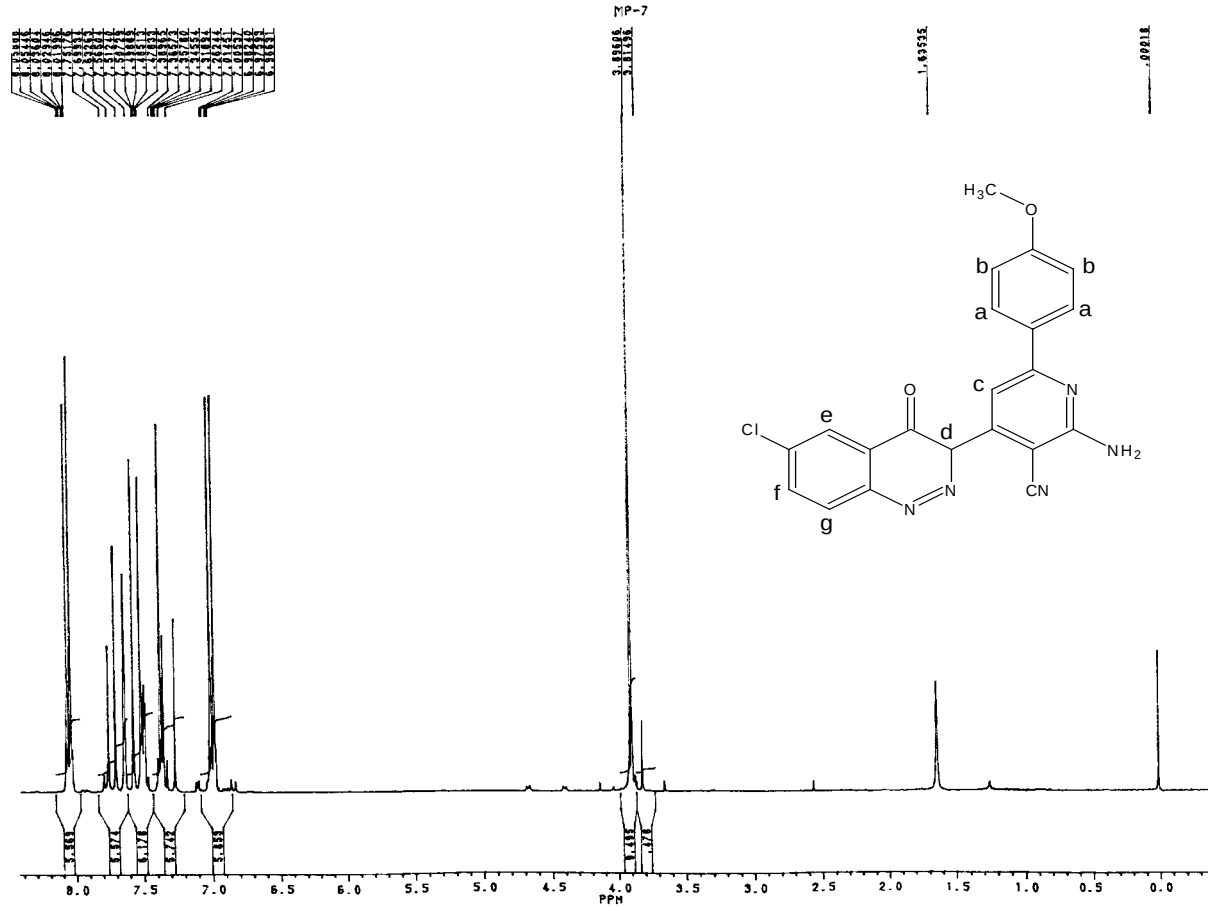
All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards gram positive and gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40 μg/ml. The biological activities of synthesized compounds were compared with standard drugs.



Frequency range: 4000-400cm^{-1} (KBr disc) Instrument : Shimadzu-8400 FTIR

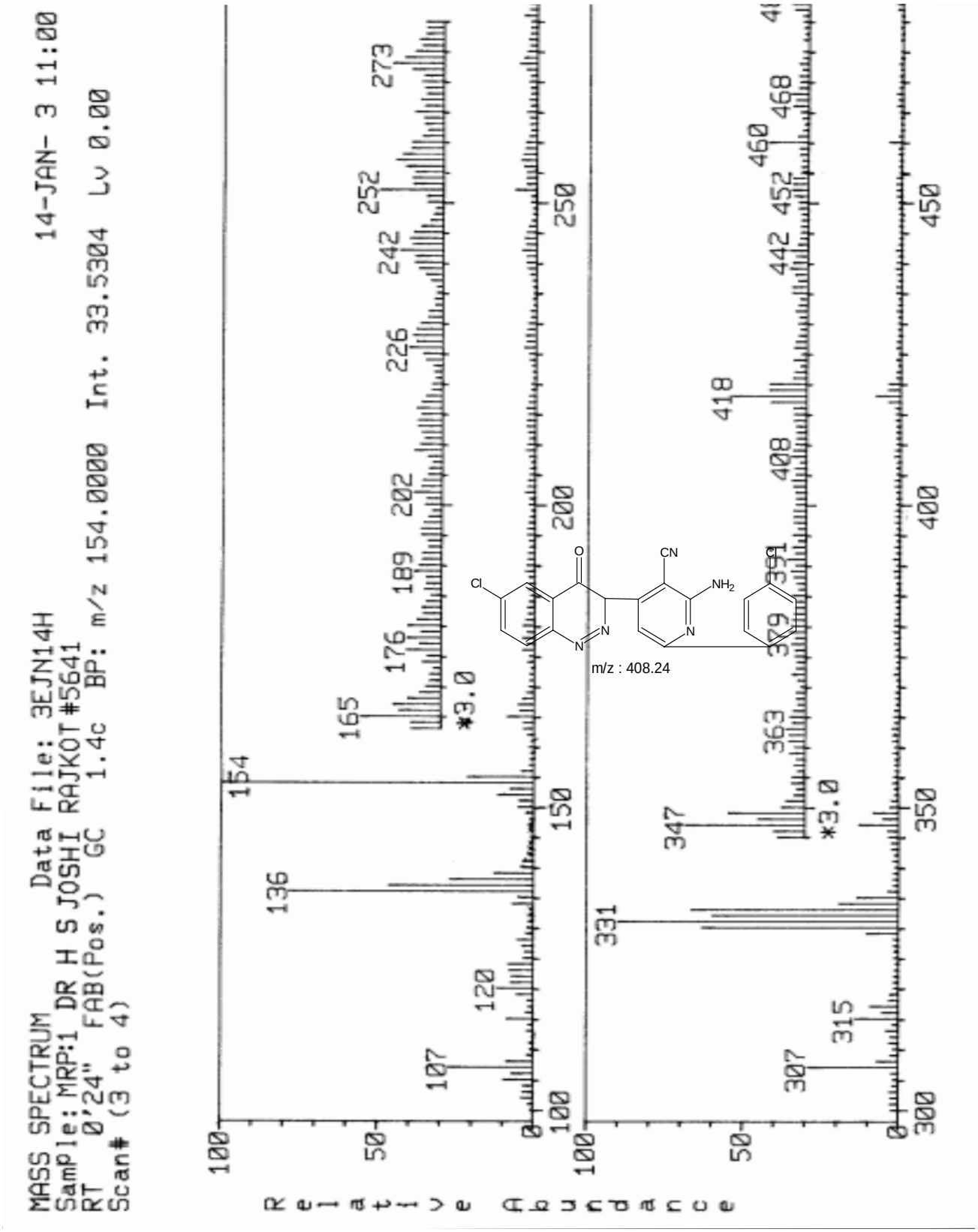
Type	Vibration mode	Frequency in cm^{-1} Observed	Reported	References
Alkane	C-H str. (asym.)	2923	2975-2950	48
-CH_3	C-H str. (sym.)	2850	2880-2860	"
	C-H def. (asym.)	1442	1470-1435	"
	C-H def. (sym.)	1361	1385-1370	"
Aromatic	C-H str.	3033	3080-3030	49
	C=C str.	1479	1620-1430	"
	C-H i.p. def	1282	1269-1013	"
	C-H o.o.p. def.	835	833-660	"
Ether	C-O-C str.	1249	1275-1200	48
Pyridine	C=C str.	1622	1650-1520	49
	C=N str.	1573	1580-1550	"
Nitrile	C=N str.	2202	2240-2120	"
Halide	C-Cl str.	744	750-700	48
Amino	NH_2- str.	3452, 3330	3550-3250	49
		1573	1650-1550	"

PMR SPECTRAL STUDIES OF 2-AMINO-4-ARYL-6-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)NICOTINONITRILE



Internal reference: TMS; Solvent: $CDCl_3$; Instrument: BRUKER spectrometer(300 MHz)

Signal No.	Signal position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.87	3H	singlet	Ar-OCH_3
2.	6.98	2H	doublet	Ar-H_a (p-sub.)
3.	7.31	1H	singlet	Ar-H_d
4.	7.36	1H	duoblet	Ar-H_f
5.	7.56	1H	singlet	Ar-H_e
6.	7.63	1H	doublet	Ar-H_g
7.	7.75	1H	singlet	Ar-H_c (pyridine)
8.	8.03	2H	doublet	Ar-H_b (p-sub.)


MASS SPECTRUM Data File: 3EJN14H
SamPle: MRP:1 DR H S JOSHI RAJKOT #5641
RT 0'24" FAB(Pos.) GC 1.4c BP: m/z 154.0000 Int. 33.5304 Lv 0.00
Scan# (3 to 4)
14-JAN- 3 11:00
Relative Abundance
m/z : 408.24
*3.0
*3.0

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 2-AMINO-4-ARYL-6-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)NICOTINONITRILE

(A) Synthesis of 6-Chloro-3-[(2E)-3-aryl-prop-2-enoyl]cinnolin-4(3H)-one.

See Part-I, Section-I(C)

(B) Synthesis of 2-Amino-4-(4-methoxyphenyl)-6-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)nicotinonitrile.

To a solution of 6-chloro-3-[(2E)-3-(4-methoxyphenyl)-prop-2-enoyl]cinnolin-4(3H)-one (3.4 gm, 0.01 mol) in dioxane, malononitrile (1.29g, 0.01 mol) and ammonium acetate (9.24 g, 0.12 mol) was added and refluxed on oil bath for 12 hr. The reaction mixture was cooled and poured over crushed ice. The product was isolated and crystallized from toluene. Yield 53 %, m.p. 206 ^{0}C Anal. Calcd. for $C_{21}H_{14}ClN_5O_2$ Requires: C, 62.46; H, 3.49; N, 17.34 % Found: C, 62.43; H, 3.47, N, 17.33 %.

Similarly, other 2-amino-4-aryl-6-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)nicotinonitrile. The physical data are recorded in Table No. 5.

(C) Biological screening of 2-Amino-4-aryl-6-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)nicotinonitrile

Antimicrobial testing were carried out as described in Part-I, Section-I(D). The zones of inhibition of test solution are reported in Graphical Chart No. 5.

TABLE-5: PHYSICAL CONSTANTS OF 2-AMINO-4-ARYL-6-(6-CHLORO-4-OXO-3,4-DIHYDRO CINNOLIN-3-YL)NICOTINONITRILE

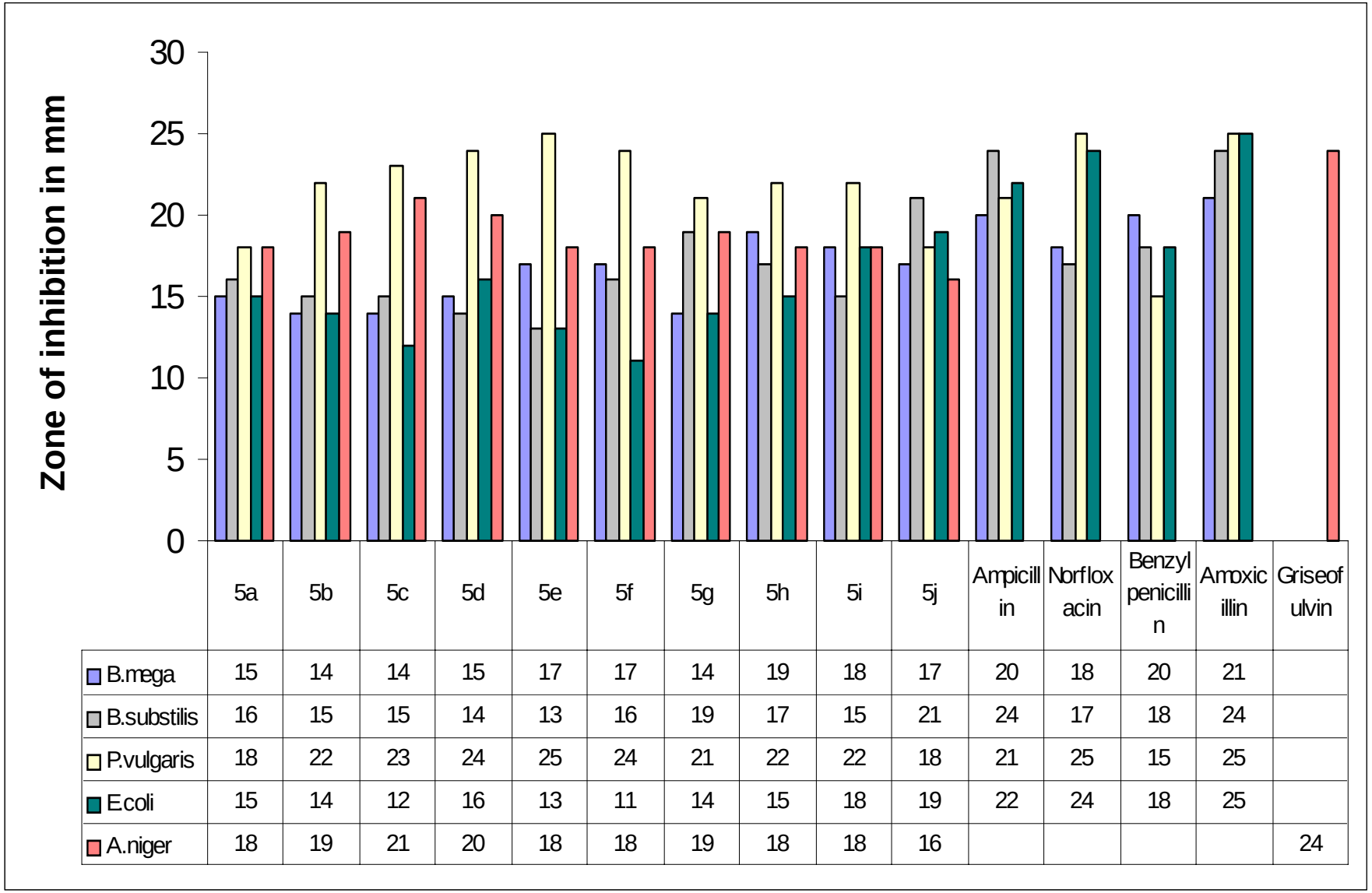
Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	R_f Value	Solvent System	Yield %	% of Nitrogen Calcd	% of Nitrogen Found
1	2	3	4	5	6	7	8	9	10
5a	C_6H_5-	$C_{20}H_{12}ClN_5O$	373.79	118	0.57	S1	55	18.74	18.72
5b	3-Br-C_6H_4-	$C_{20}H_{11}BrClN_5O$	452.69	196	0.51	S2	56	15.47	15.45
5c	2-Cl-C_6H_4-	$C_{20}H_{11}Cl_2N_5O$	408.24	164	0.38	S2	42	17.16	17.15
5d	3-Cl-C_6H_4-	$C_{20}H_{11}Cl_2N_5O$	408.24	210	0.69	S1	46	17.16	17.13
5e	4-Cl-C_6H_4-	$C_{20}H_{11}Cl_2N_5O$	408.24	220	0.69	S3	49	17.16	17.15
5f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{22}H_{16}ClN_5O_3$	433.85	230D	0.65	S3	54	16.14	16.13
5g	4-OCH_3-C_6H_4-	$C_{21}H_{14}ClN_5O_2$	403.82	206	0.50	S2	53	17.34	17.33
5h	4-SCH_3-C_6H_4-	$C_{21}H_{14}ClN_5OS$	419.88	198	0.39	S2	61	16.68	16.64
5i	3-C_6H_5-O-C_6H_4-	$C_{26}H_{17}ClN_5O_2$	465.89	118	0.67	S3	48	15.03	15.02
5j	4-$N(CH_3)_2$-C_6H_4-	$C_{22}H_{17}ClN_6O$	416.86	238	0.58	S1	45	20.16	20.15

S1 = Benzene : Acetone (5 :5)

S2 = Benzene : Mrthanol (7 : 3)

S3 = Benzene : Acetone (3 : 7)

Graphical Chart No. 5 : Antimicrobial activity of 2-Amino-4-aryl-6-(6-achloro-4-oxo-3,4-dihydro cinnolin-3-yl)nicotinonitrile



	5a	5b	5c	5d	5e	5f	5g	5h	5i	5j	Ampicillin	Nbrfloxacin	Benzylpenicillin	Amoxicillin	Griseofulvin
B.mega	15	14	14	15	17	17	14	19	18	17	20	18	20	21	
B.substilis	16	15	15	14	13	16	19	17	15	21	24	17	18	24	
P.vulgaris	18	22	23	24	25	24	21	22	22	18	21	25	15	25	
E.coli	15	14	12	16	13	11	14	15	18	19	22	24	18	25	
A.niger	18	19	21	20	18	18	19	18	18	16					24

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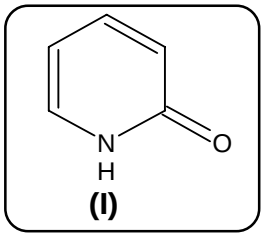
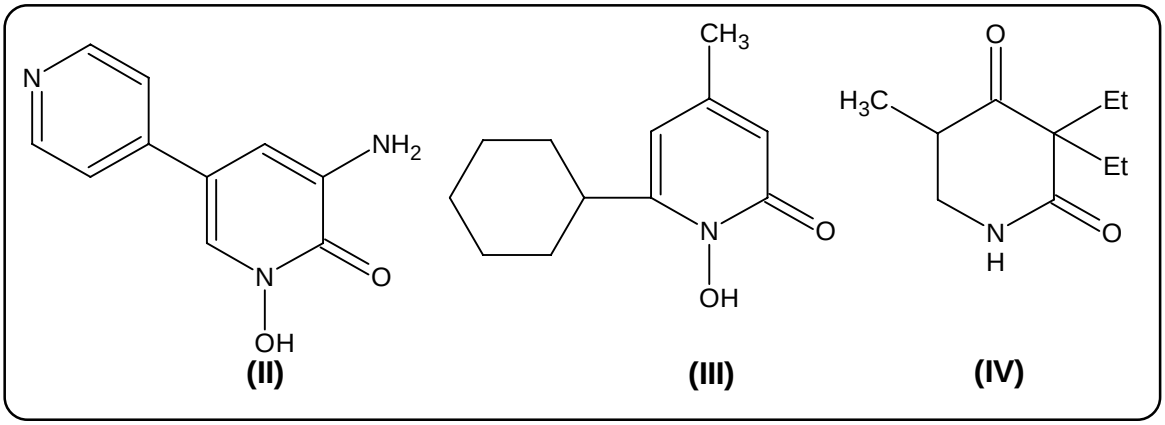
INTRODUCTION

Pyridones, which belongs to an group of nitrogen containing heterocyclic compounds have been extensively explored for their application in the field of medicine. In recent years, pyridones with a carbonyl group at position 2 (I), have attracted considerable attention as they are endowed with wide range of activities. Numerous reports have appeared in the literature which focused their chemistry and applications.



(I)

Some 2-pyridones are physiologically as well as pharmacologically important which are as under: amrinone (II), ciclopirox (III) and mathylprylon (IV).

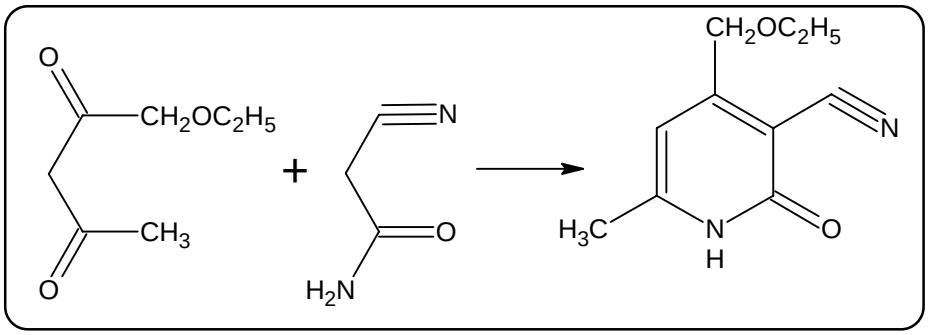


(II) **(III)** **(IV)**

SYNTHETIC ASPECT

Various methods are documented in literature for preparation of 2-pyridones, which are as under.

(i) S. A. harris and K. Folkers[1] have prepared 3-cyano-2-pyridone by the condensation of cyanoacetamide with 1,3-diketone or β-keto ester.

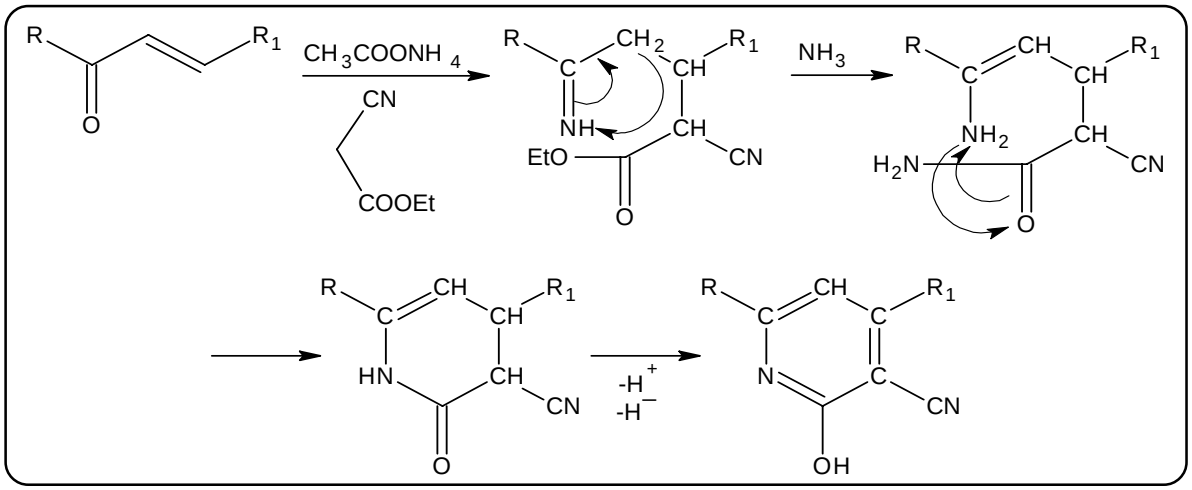


(ii) M. A. Sluyter et al.[2] have prepared fused 2-pyridones.

(iii) G. Simchen and G. Entemmann[3] have synthesized 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.

REACTION MECHANISM

The addition reaction between ethyl cyano acetate and α,β-unsaturated ketone give cyano pyridone via Michael addition. Here α,β-unsaturated compound is known as acceptors and active –CH group containing compound known as addendam. It involves nucleophilic addition of carbanion to the C=C of the acceptor.

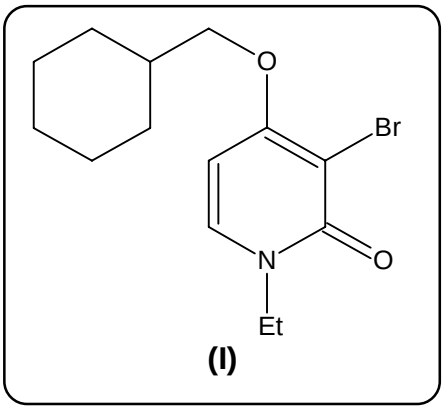


THERAPEUTIC IMPORTANCE

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

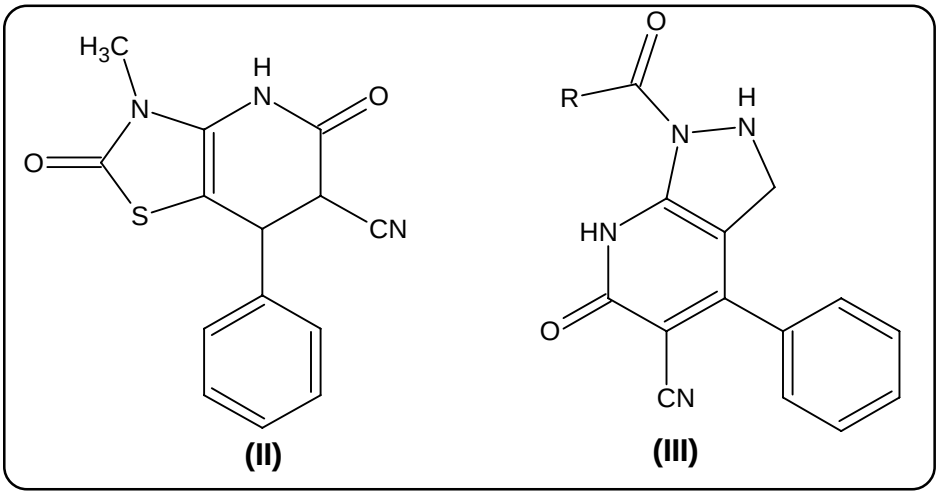
1. Anticancer[4],
2. Antimicrobial[5],
3. Pesticidal[6],
4. Angitensin II antagonistic[7],
5. Herbicidal[8],
6. Antiviral[9],
7. Antibacterial[10],
8. Antiinflammatory[11],
9. Molluscicidal activity[12],
10. Anti-HIV[13],

Moreover, several co-workers have pre reported 2-pyridones as S_3 site of thrombin inhibitors[14], herbicidal[15], SH_2 domain inhibitor[16] and GABA-A receptor[17]. Peter et al.[18] have prepared pyridinyl methyl substituted pyridines and pyridones as angiotensin II antagonists. H. Posnes[19] reported 2-pyridones as physiologically active compounds. Devdas, Balekudru et al.[20] prepared substituted as pyridinones (I) as modulators of P^{38} NAP kinase.



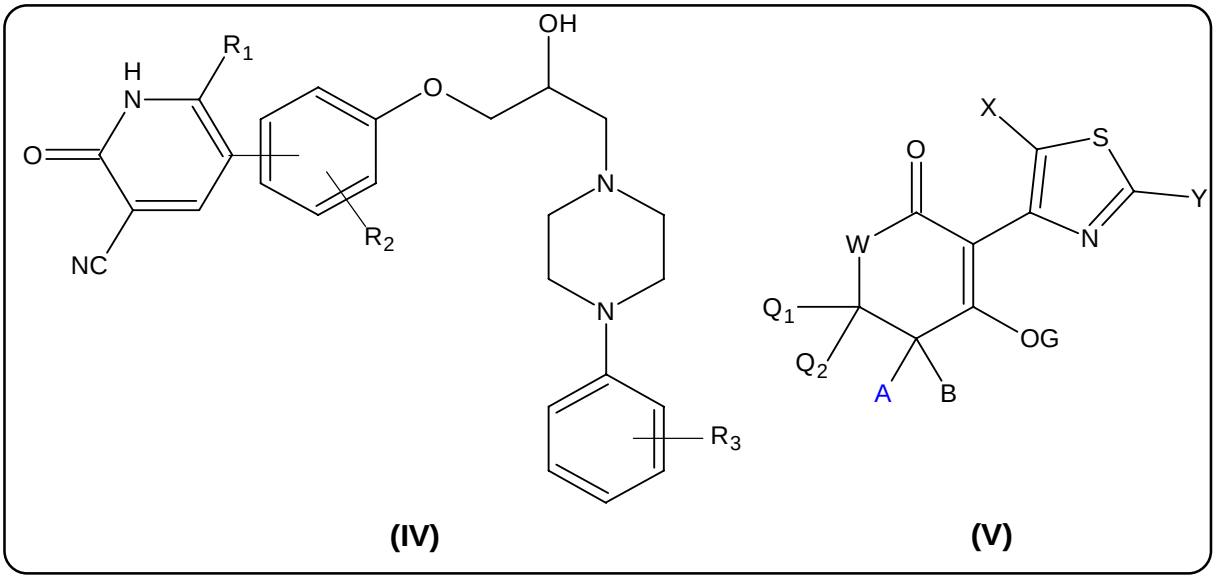
(I)

Mukhtar Hussain Khan and co-workers[21-22] have synthesized 2-pyridone derivatives (II) and (III) which possess insecticidal and pesticidal activity. E. Amer[23] prepared 3-cyano-2-pyridone derivatives displaying high antimicrobial activity. Abou El-Fotooh et al.[24] have demonstrated pyridones as anticancer agents. F. Paila[25] synthesized 2-pyridone derivatives showing good cardiotonic activity.



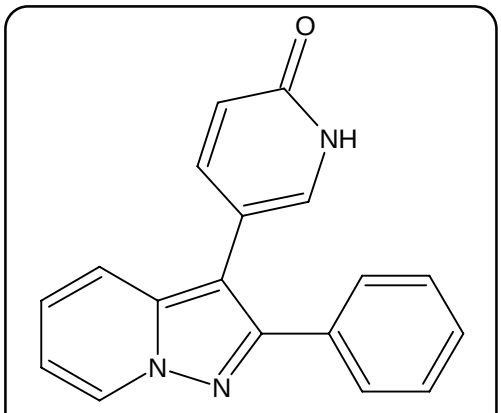
(II) **(III)**

Furthermore, Stenzel, Wolfgang et al.[26] reported some pyridone derivatives (IV) as cardiotonic, hypnotics, antiasthematics and antithrombotic. Fischer Reiner et al.[27] prepared (thiazolyl) dihydro-1H-pyridinones (V) as pesticides and herbicides.



(IV) **(V)**

Gulcan Ozturk et al.[28] prepared 1,2,5-substituted-4-pyridone derivatives having analgesic and antiinflammatory activity. Tanaka A. and co-workers[29] prepared 2-pyridone derivatives, which showed adenosine antagonist activity and anticatalepsy activity.



(VI)

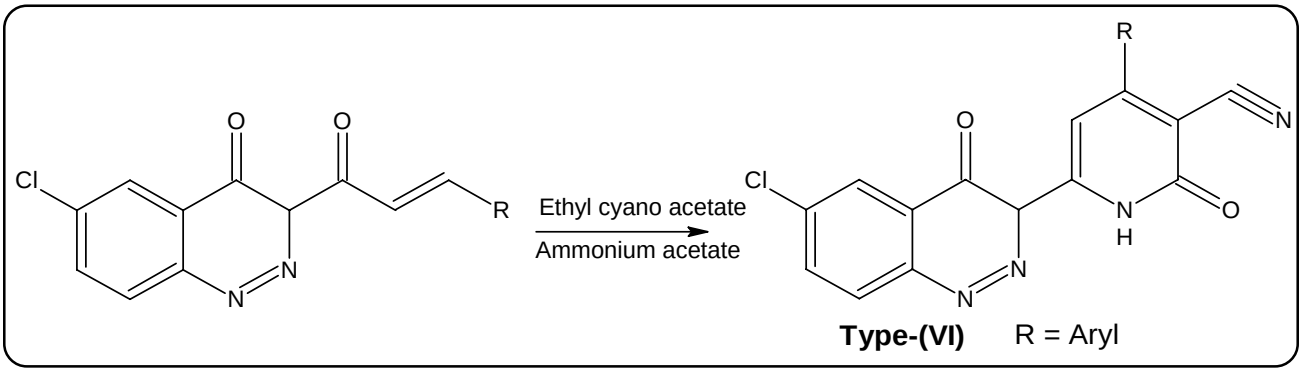
Thus, significant biological properties associated with pyridones have aroused considerable interest to design the compounds with a view to get better drug potential to study their pharmacological profile, which have been described as under.

SECTION-I: Synthesis and biological screening of 4-Aryl-6-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonotrile

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 4-ARYL-6-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-2-OXO-1,2-DIHYDROPYRIDINE-3-CARBONITRILE.

Compounds containing pyridine ring are widely distributed in nature. Many pyridone derivatives are reported to associated with valuable pharmacological activity like antibacterial, antimalarial, antihypertensive, antifungal, anticonvulsant etc. Considering these facts we thought it is worthwhile to synthesize some novel derivatives in association with cinnoline nucleus in search of better potential drugs. Nicotinonitrile derivatives of Type-(VI) have been synthesis of the chalcones of the Type-(I) with ethyl cyanoacetate in presence of ammonium acetate.

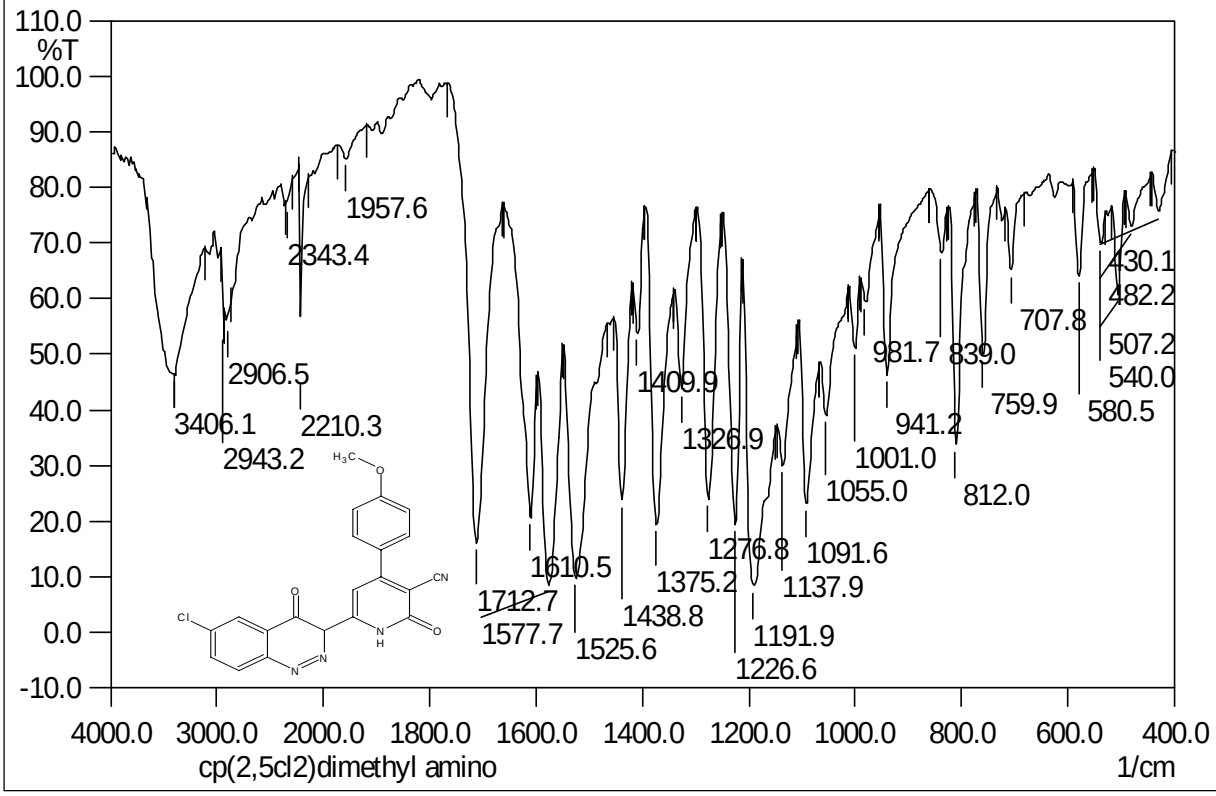


Type-(VI) R = Aryl

The structure elucidation of synthesized compounds have been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated 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 concen tration of 40 µg/ml. The biological activities of synthesized compounds were compared with standard drugs.

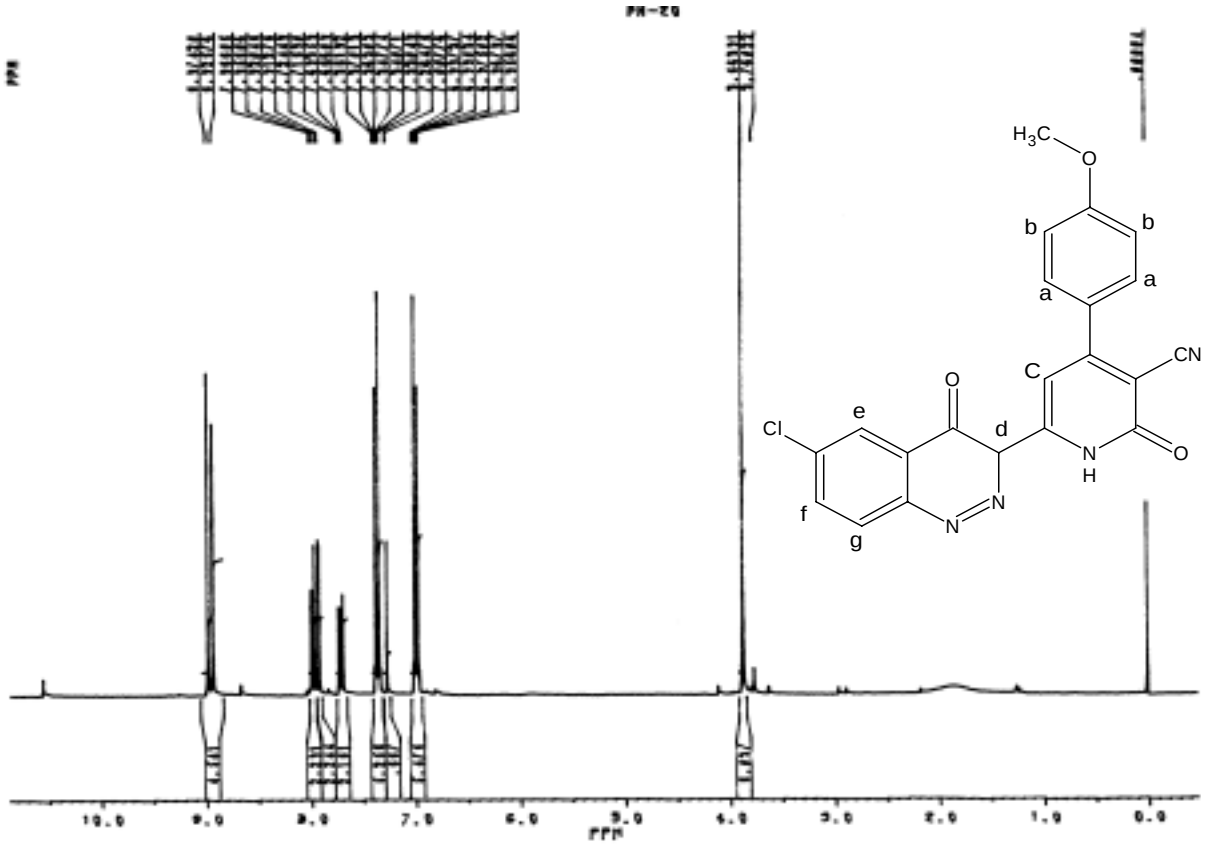
IR SPECTRAL STUDY OF 4-(4-METHOXY PHENYL)-6-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-2-OXO-1,2-DIHYDROPYRIDINE-3-CARBONITRILE



Frequency range: 4000-400cm^{-1} (KBr disc) Instrument : Shimadzu-8400 FTIR

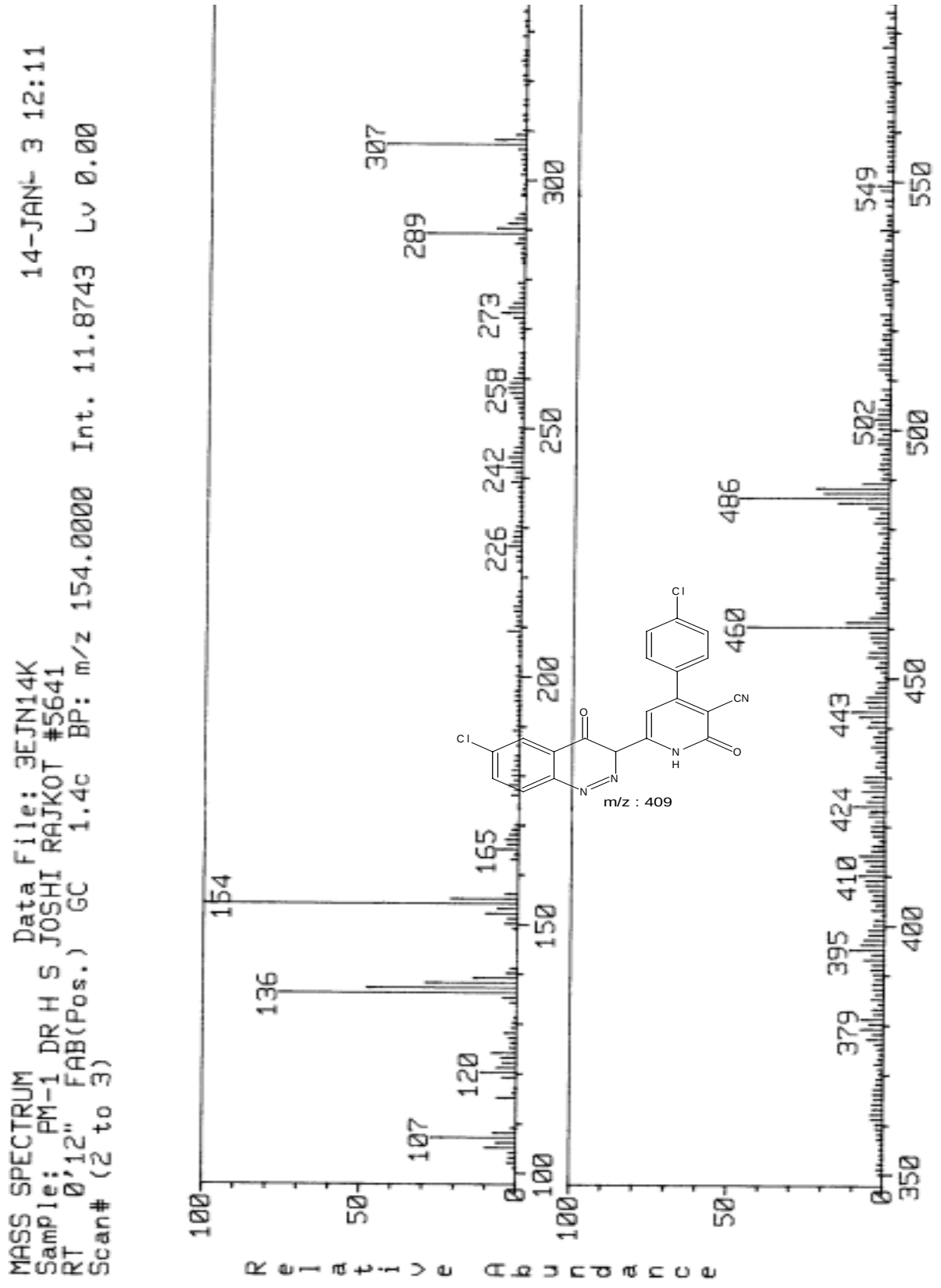
Type	Vibration mode	Frequency in cm^{-1} Observed	Reported	References
Alkane	C-H str. (asym.)	2943	2975-2950	47
-CH_3	C-H str. (sym.)	2906	2880-2860	"
	C-H def. (asym.)	1438	1470-1435	"
	C-H def. (sym.)	1375	1385-1370	"
Aromatic	C-H str.	3033	3080-3030	48
	C=C str.	1479	1620-1430	"
	C-H i.p. def	1276	1269-1013	"
	C-H o.o.p. def.	839	833-660	"
Ether	C-O-C str.	1226	1275-1200	47
Pyridone	C=O str.	1712	1650-1520	48
Nitrile	C=N str.	2210	2240-2120	"
	N - H str.	3406	3450-3200	"
	N-H str.	1610	1650-1580	"
Halide	C-Cl str.	744	750-700	47

PMR SPECTRAL STUDIES OF 4-(4-METHOXY PHENYL)-6-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-2-OXO-1,2-DIHYDROPYRIDINE-3-CARBONITRILE



Internal reference: TMS; Solvent: $CDCl_3$; Instrument: BRUKER spectrometer(300 MHz)

Signal No.	Signal position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.86	3H	singlet	Ar-OCH_3
2.	6.99	2H	doublet	Ar-H_a (p-sub.)
3.	7.34	1H	singlet	Ar-H_d
4.	7.69	1H	singlet	Ar-H_c
5.	7.91	1H	singlet	Ar-H_e
6.	7.96	1H	doublet	Ar-H_f
7.	8.92	2H	doublet	Ar-H_b (p-sub.)


MASS SPECTRUM
Sample: PM-1 DR H S JOSHI RAJKOT #5641
RT 0'12" FAB(Pos.) GC 1.4c BP: m/z 154.0000 Int. 11.8743 Lv 0.00
Scan# (2 to 3)
Data File: 3EJN14K
14-JAN- 3 12:11
Relative Abundance
m/z : 409

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 4-ARYL-6-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-2-OXO-1,2-DIHYDROPYRIDINE-3-CARBONITRILE

(A) Synthesis of 6-Chloro-3-[(2E)-3-aryl-prop-2-enoyl]cinnolin-4(3H)-one.

See Part-I, Section-I(C)

(B) Synthesis of 4-(Methoxy phenyl)-6-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonotrile.

A mixture of 6-chloro-3-[(2E)-3-(4-methoxyphenyl)-prop-2-enoyl]cinnolin-4(3H)-one (3.4 gm, 0.01 mol), ethyl cyanoacetate (1.13 g, 0.01 mol) in presence of ammonium acetate (9.24 g, 0.12 mol) dissolve in dioxane was refluxed on oil bath for 12 hrs. The reaction mixture was cooled and poured over crushed ice. The product was isolated and crystallized from toluene. Yield 55 %, m.p. 180 ^{0}C Anal. Calcd. for $C_{18}H_{12}ClN_3O_3$ Requires: C, 62.31; H, 3.24; N, 13.84 % Found: C, 62.30; H, 3.21, N, 13.81 %.

Similarly, other 4-Aryl-6-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonotrile. The physical data are recorded in Table No. 6.

(C) Biological screening of 4-Aryl-6-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonotrile

Antimicrobial testing were carried out as described in Part-I, Section-I(D). The zones of inhibition of test solution are reported in Graphical Chart No. 6.

TABLE-6: PHYSICAL CONSTANTS OF 4-ARYL-6-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-2-OXO-1,2-DIHYDROPYRIDINE-3-CARBONITRILE

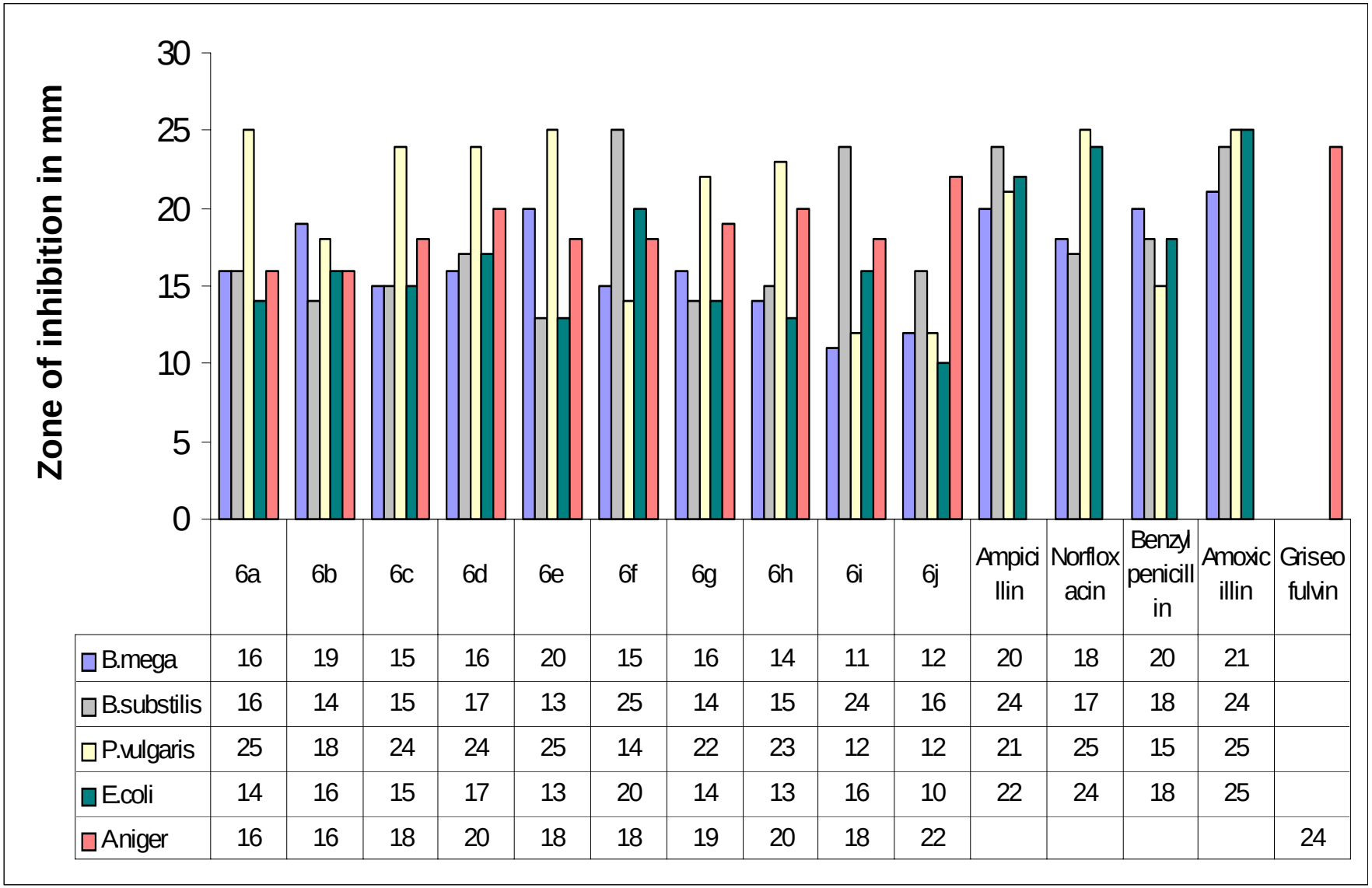
Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	R_f Value	Solvent System	Yield %	% of Nitrogen Calcd	% of Nitrogen Found
1	2	3	4	5	6	7	8	9	10
6a	C_6H_5-	$C_{20}H_{11}ClN_4O_2$	374.78	176	0.35	S_1	51	14.95	14.62
6b	3-Br-C_6H_4-	$C_{20}H_{10}BrClN_4O_2$	453.68	162	0.46	S_2	53	12.35	12.34
6c	2-Cl-C_6H_4-	$C_{20}H_{10}Cl_2N_4O_2$	409.23	154	0.54	S_3	58	13.69	13.65
6d	3-Cl-C_6H_4-	$C_{20}H_{10}Cl_2N_4O_2$	409.23	180	0.48	S_1	46	13.69	13.66
6e	4-Cl-C_6H_4-	$C_{20}H_{10}Cl_2N_4O_2$	409.23	186	0.38	S_2	59	13.69	13.65
6f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{22}H_{15}ClN_4O_4$	434.83	172	0.48	S_2	51	12.88	12.84
6g	4-OCH_3-C_6H_4-	$C_{21}H_{13}ClN_4O_3$	404.81	180	0.49	S_3	55	13.84	13.81
6h	4-SCH_3-C_6H_4-	$C_{21}H_{13}ClN_4O_2S$	420.87	198	0.55	S_1	48	13.31	13.25
6i	3-C_6H_5-O-C_6H_4-	$C_{26}H_{15}ClN_4O_3$	466.88	128	0.52	S_3	49	12.00	11.97
6j	4-$N(CH_3)_2$-C_6H_4-	$C_{22}H_{16}ClN_5O_2$	417.85	158	0.31	S_3	52	16.76	16.74

S_1 = Ethyl acetate : Hexane (1 : 9)

S2 = Ethyl acetate : Hexane (2 : 8)

S3 = Acetone : Benzene (1.5 : 8.5)

Graphical Chart No. 6 : Antimicrobial activity of 4-Aryl-6-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile



	6a	6b	6c	6d	6e	6f	6g	6h	6i	6j	Ampicillin	Norfloxacin	Benzylpenicillin	Amoxicillin	Griseofulvin
B.mega	16	19	15	16	20	15	16	14	11	12	20	18	20	21	
B.substilis	16	14	15	17	13	25	14	15	24	16	24	17	18	24	
P.vulgaris	25	18	24	24	25	14	22	23	12	12	21	25	15	25	
E.coli	14	16	15	17	13	20	14	13	16	10	22	24	18	25	
A.niger	16	16	18	20	18	18	19	20	18	22					24

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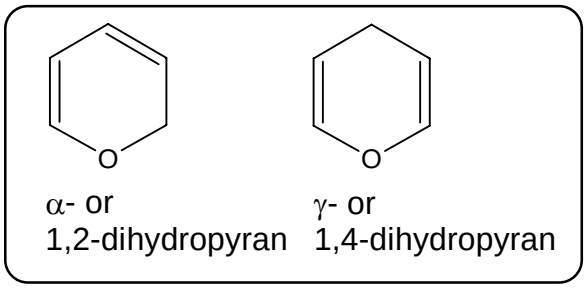
INTRODUCTION

Pyran derivatives are associated with wide range of applications in various fields like pharmaceutical, dyes, insecticides and sweet smelling substances. Pyran ring system also occurs in nature abundantly such as in large number of natural coloured compounds, in vitamine E, in cloves, in fish poisons, in certain alkaloids and other substances.

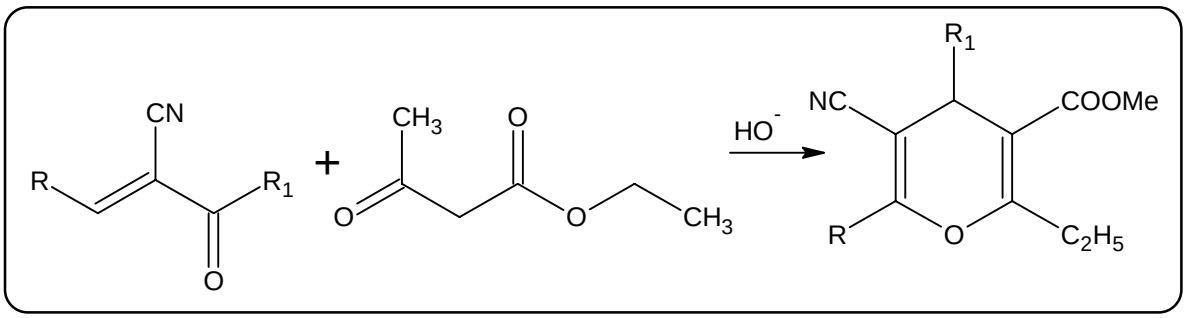
Pyran are six member doubly unsaturated compounds containing one oxygen atom in the ring. The double bonds may be conjugated known as α- or 1,2-pyran or it may be isolated known as γ-or 1,4-pyran.



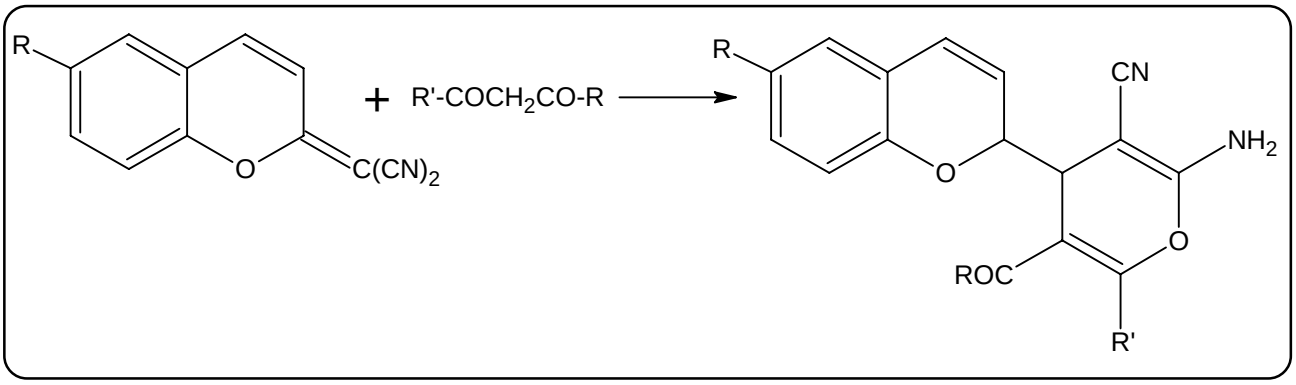
SYNTHETIC ASPECT

Various methods for the preparation of pyran derivatives have been cited in the literature[1-10].

1. Reaction between α,β- unsaturated carbonyl system with malononitrile led to correspnding 2-amino-3-cyano-4H-pyran[11].
2. Elssar A. Z. et al[12] prepared 3-cyano-pyran derivatives by the reaction of α-cyano chalcone derivatives with $C_2H_5COCH_2COOCH_3$ in basic medium.

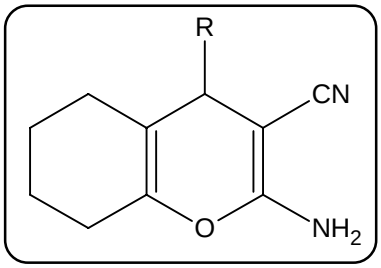


3. Abdel-Ghany H. et al.[13] have been synthesized cyano derivatives by the reaction of 2-coumariylidene malononitrile with active methylene containing compounds.



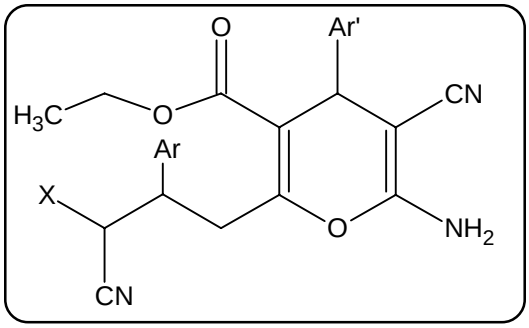
4. β–Siloxy acrylonitrile were reacted with chalcones to furnish the respective 3-cyano-4H-pyran derivatives[14].

5. Assay M. G. et al.[15] have synthesized some cyanopyran derivatives by the reaction of cyclohexenone with cinnamon nitriles.



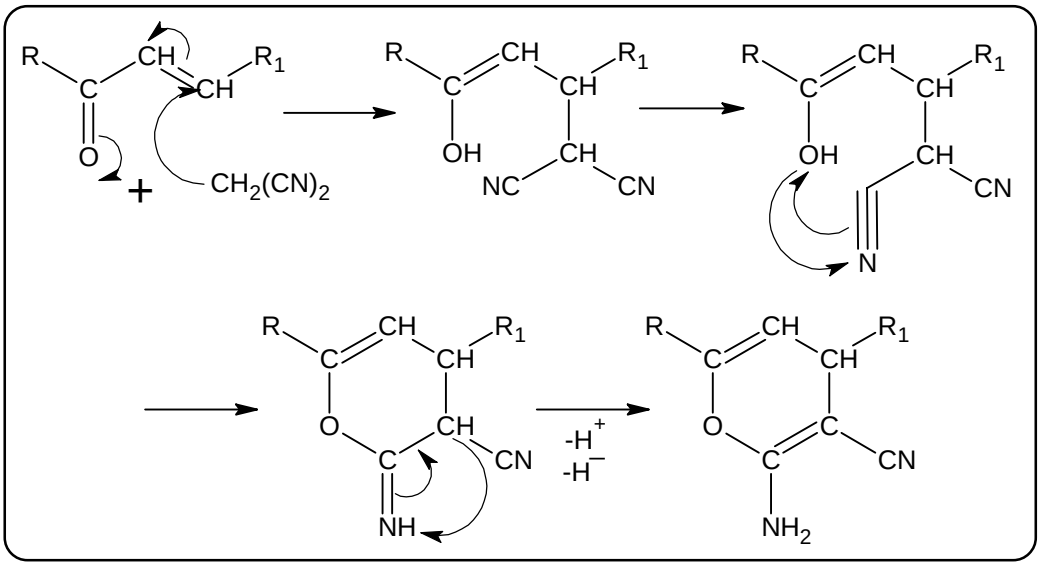
6. De Lera Angel R. and co-workers[16] synthesized pyran derivatives by thermal electrolutic ring closure of divinylallenals.

7. In recent, A. M. Hussein and et al.[17] prepared some novel derivatives of cyanopyran.



REACTION MECHANISM

The reaction mechanism for the formation of pyran derivatives proceeds through Micheal addition of active methylene group of malononitrile to the β–carbon atom of chalcone described as under.



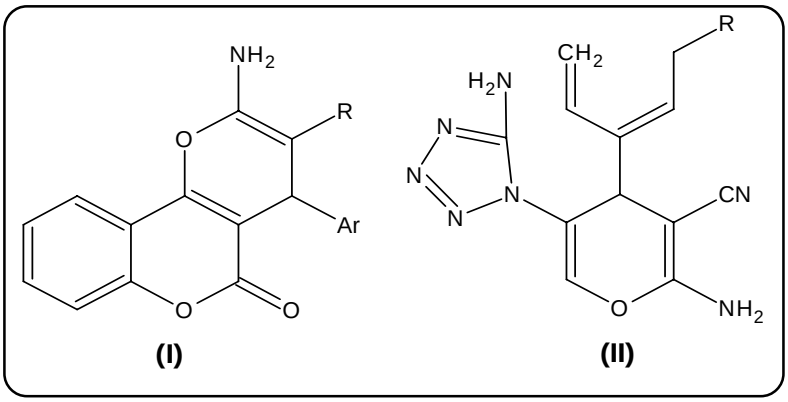
THERAPEUTIC IMPORTANCE

Polysubstituted pyran derivatives are biologically interesting class of compounds[18,19]. They are associated with various pharmaceutical properties like

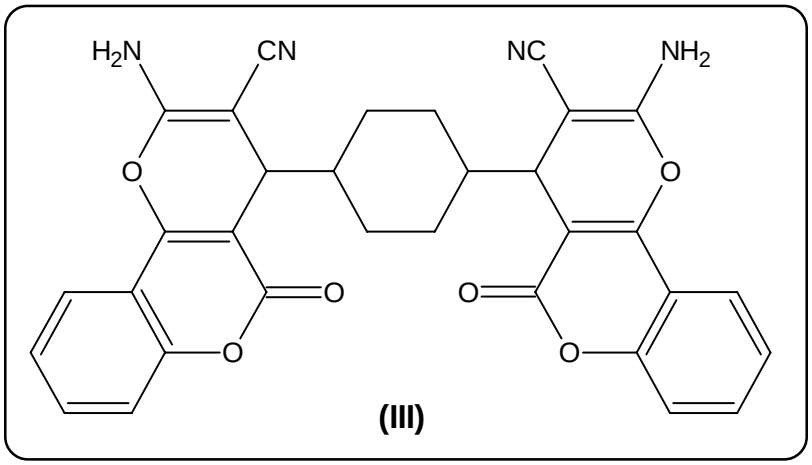
1. Anticancer[20],
2. Antiinvasive[21],
3. Anti-HIV[22,23],
4. Antiallergic[24],
5. Antifungal[25,26],
6. Cytotoxic[27],

7. Antitumor[28],
8. Antiviral[29],
9. Antipyratic[30],
10. Analgesic[31]

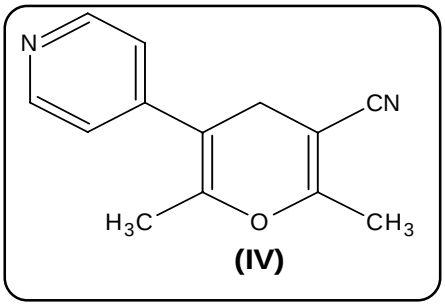
M. A. Al-Haiza and co-workers[32] prepared some cyanopyran derivatives (I) and tested their antibacterial and antifungal activities. Samet A. V. [33] et al. aynthesized 2-amino-5-azolyl-3-cyano-4H-pyrans (II) and evaluated for biological activity. Elassar A. Z. et al.[34] reported that cyanopyran exhibited in vitro antifungal and antibacterial activities.



Moreover, Shaker R. M.[35] have prepared some coumarin ring containing 2-amino-3-cyanopyran (III) derivatives and studied their antimicrobial activity. Kulkarni Y. D. and co-workers[36] synthesized some pyran derivatives as CNS active agents. A. A. Hassainien et al.[37] prepared 2-amino-3-cyano-7,7-dimethyl-4-substitutedphenyl-5-oxo-4,5-6,8-tetrahydro-pyran and tested for their biological activities.

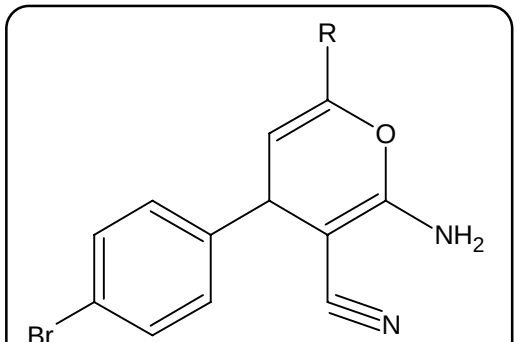


Furthermore, Krauze, A. et al.[38] synthesized 5-(4-pyridyl)derivatives of 2-amino-4H-pyran (IV) for antimicrobial activity. Fowzia S. Al-Saleh[39] and coworkers synthesized some new cyanopyran derivatives and reported them as antimicrobial agents. Some pyran derivatives have been pantented for their use as gastric acid secretion inhibitors[40], inhibitors of cell proliferation[41], antihypertensive[42], antitumor[43], antagonists[44,45] and antiviral agents[46].



(IV)

Joshi et al[47]. recently have synthesized some new cyano pyridine (V) derivatives as anticancer and antimicrobial agents.



(V)

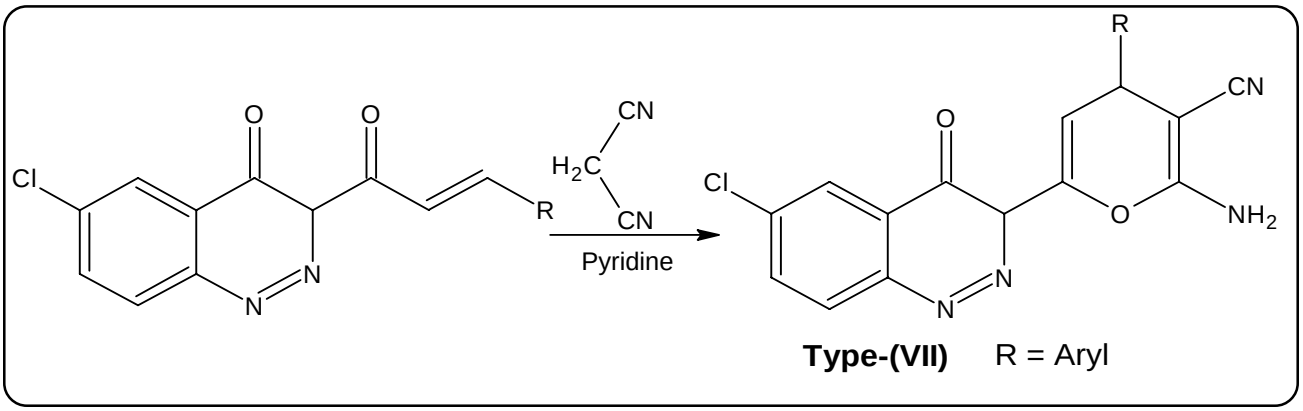
Thus with an effort to capitalize the biological potential of the heterocyclic system and to synthesize interesting compounds having better biological potential, the titled compounds have been investigated, which have been described as under.

SECTION-I: Synthesis and biological screening of 2-Amino-4-chloro-6-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-4H-pyran-3-carbonitrile

SECTION-I

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-4-ARYL-6-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-4H-PYRAN-3-CARBONITRILE

Cyanopyran derivatives have been reported to have various pharmacological activities like antibacterial, antisecreatary, antiviral, antifungal etc. In order to develope better medicinaly important compounds, it was considered of interest to synthesize some cyanopyran derivatives shown as under. Cyanopyran derivatives of Type-(VII) have been synthesized by the reaction of the chalcones of Type-(I) with malononitrile in pyridine.

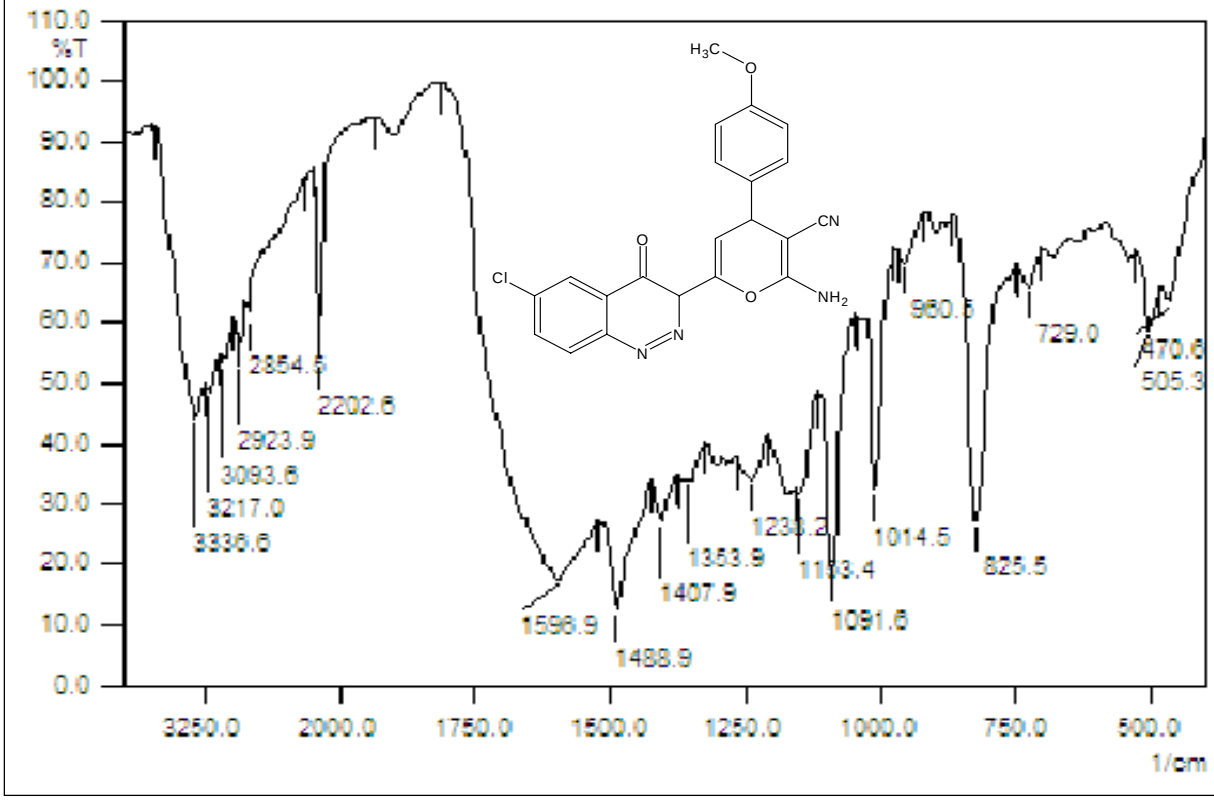


Type-(VII) R = Aryl

The structure elucidation of synthesized compounds have been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activitytowards gram positive and gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concen tration of 40 μg/ml. The biological activities of synthesized compounds were compared with standard drugs.

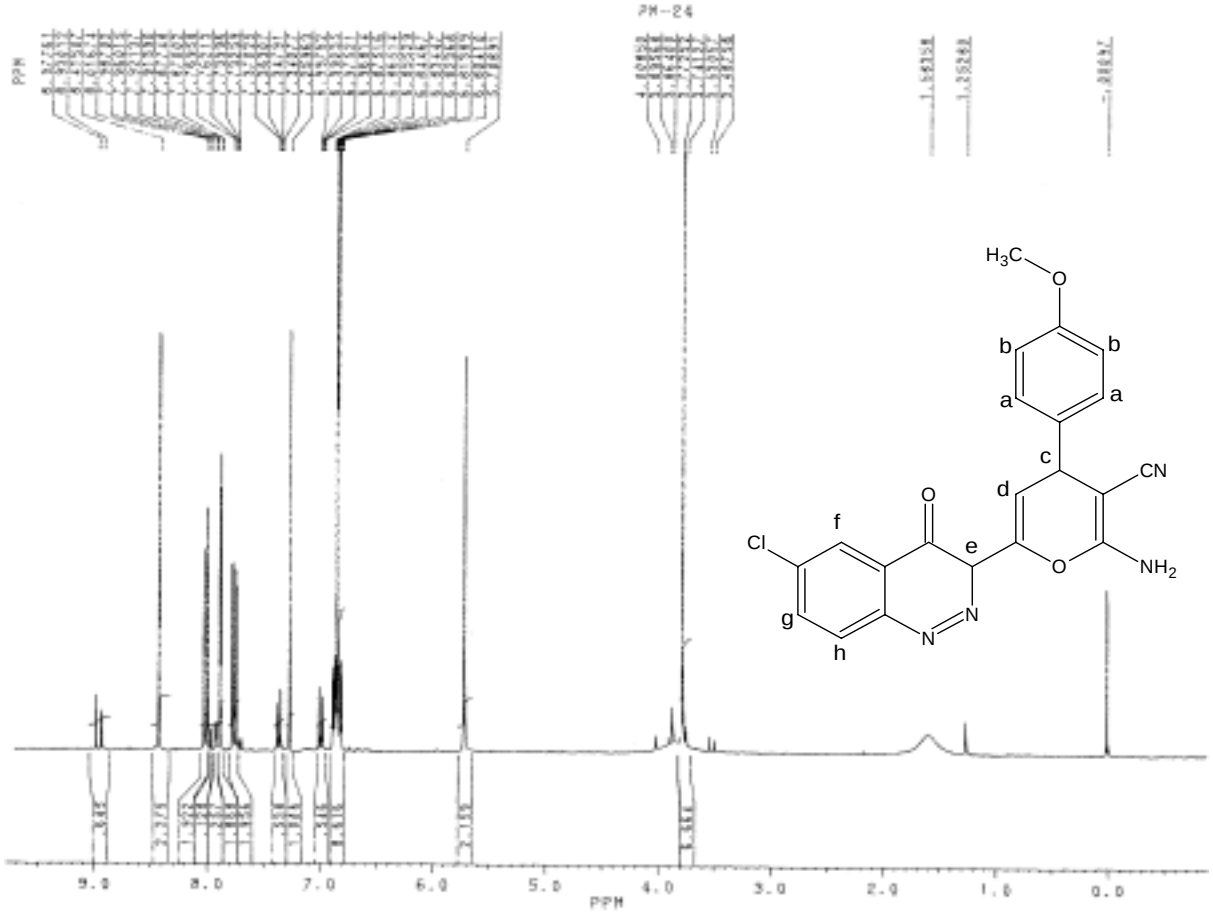
IR SPECTRAL STUDY OF 2-AMINO-4-(4-METHOXY PHENYL)-6-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-4H-PYRAN-3-CARBONITRILE



Frequency range: 4000-400cm^{-1} (KBr disc) Instrument : Shimadzu-8400 FTIR

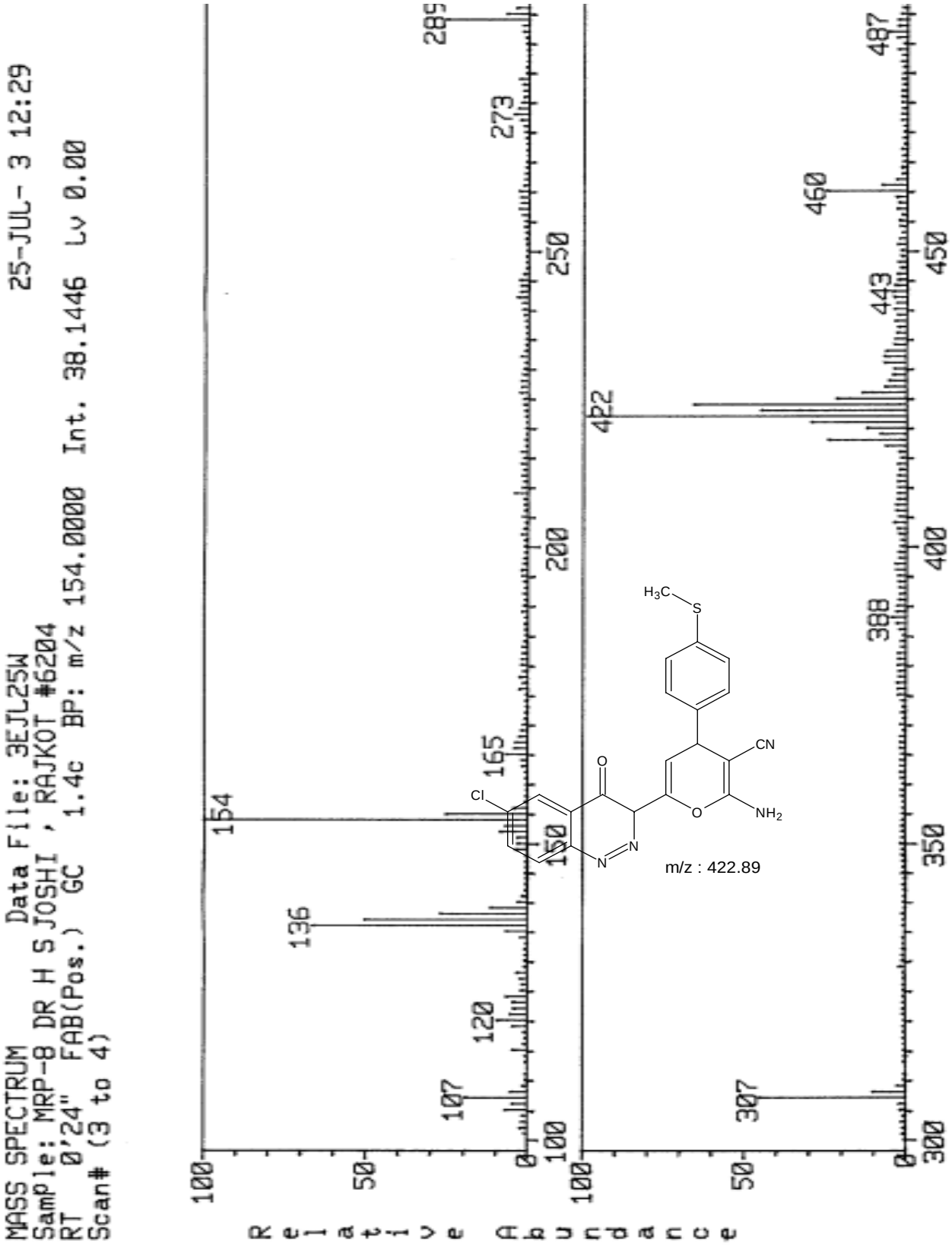
Type	Vibration mode	Frequency in cm^{-1} Observed	Reported	References
Alkane	C-H str. (asym.)	2923	2975-2950	48
-CH_3	C-H str. (sym.)	2854	2880-2860	"
	C-H def. (asym.)	1488	1470-1435	"
	C-H def. (sym.)	1353	1385-1370	"
Aromatic	C-H str.	3093	3080-3030	49
	C=C str.	1596	1620-1430	"
	C-H i.p. def	1233	1269-1013	"
	C-H o.o.p. def.	825	833-660	"
Ether	C-O-C str.	1249	1275-1200	48
Pyran	C=C str.	1622	1650-1520	49
Nitrile	C=N str.	2202	2240-2120	"
Halide	C-Cl str.	729	750-700	48
Amino	NH_2- str.	3336	3550-3250	49

PMR SPECTRAL STUDIES OF 2-AMINO-4-CHLORO-6-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-4H-PYRAN-3-CARBONITRILE



Internal reference: TMS; Solvent: $CDCl_3$; Instrument: BRUKER spectrometer(300 MHz)

Signal No.	Signal position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.77	3H	singlet	Ar-OCH_3
2.	5.70	1H	doublet	Ar-H_c (pyran ring)
3.	7.73	2H	double duoblet	Ar-H_a (p-sub.)
4.	7.76	1H	duoblet	Ar-H_d
5.	7.56	1H	singlet	Ar-H_f
6.	7.63	1H	doublet	Ar-H_g
7.	7.96	1H	doublet	Ar-H_b (p-sub.)
8.	8.01	2H	singlet	Ar-H_e


MASS SPECTRUM Data File: 3EJL25W
Sample: MRP-8 DR H S JOSHI , 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)
25-JUL- 3 12:29
Relative Abundance
m/z : 422.89

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL EVALUATION OF 2-AMINO-4-ARYL-6-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-4H-PYRAN-3-CARBONITRILE.

(A) Synthesis of 6-Chloro-3-[(2E)-3-aryl-prop-2-enoyl]cinnolin-4(3H)-one.

See Part-I, Section-I(C)

(B) Synthesis of 2-amino-4-(4-methoxy phenyl)-6-(6-chloro-4-oxo-3,4-dihydro cinnolin-3-yl)-4H-pyran-3-carbonitrile

A mixture of 6-chloro-3-[(2E)-3-(4-methoxyphenyl)-prop-2-enoyl]cinnolin-4(3H)-one (3.4 gm, 0.01 mol) and malononitrile (1.29g, 0.01 mol) dissolved in pyridine was refluxed on oil bath for 10 hr. The reaction mixture was cooled and poured onto crushed ice. The residue was neutralize with 20% HCl, where upon a solid separated out which was filtered and crystallized from toluene. Yield 53 %, m.p. 220 ^{0}C Anal. Calcd. for $C_{18}H_{12}ClN_3O_3$ Requires: C, 62.00; H, 3.72; N, 13.77 % Found: C, 61.97; H, 3.71, N, 13.74 %.

Similarly, other 2-amino-4-aryl-6-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-4H-carbonitrile. The physical data are recorded in Table No. 7.

(C) Biological screening of 2-Amino-4-aryl-6-(6-chloro-4-oxo-3,4-dihydro cinnolin-3-yl)-4H-pyran-3-carbonitrile

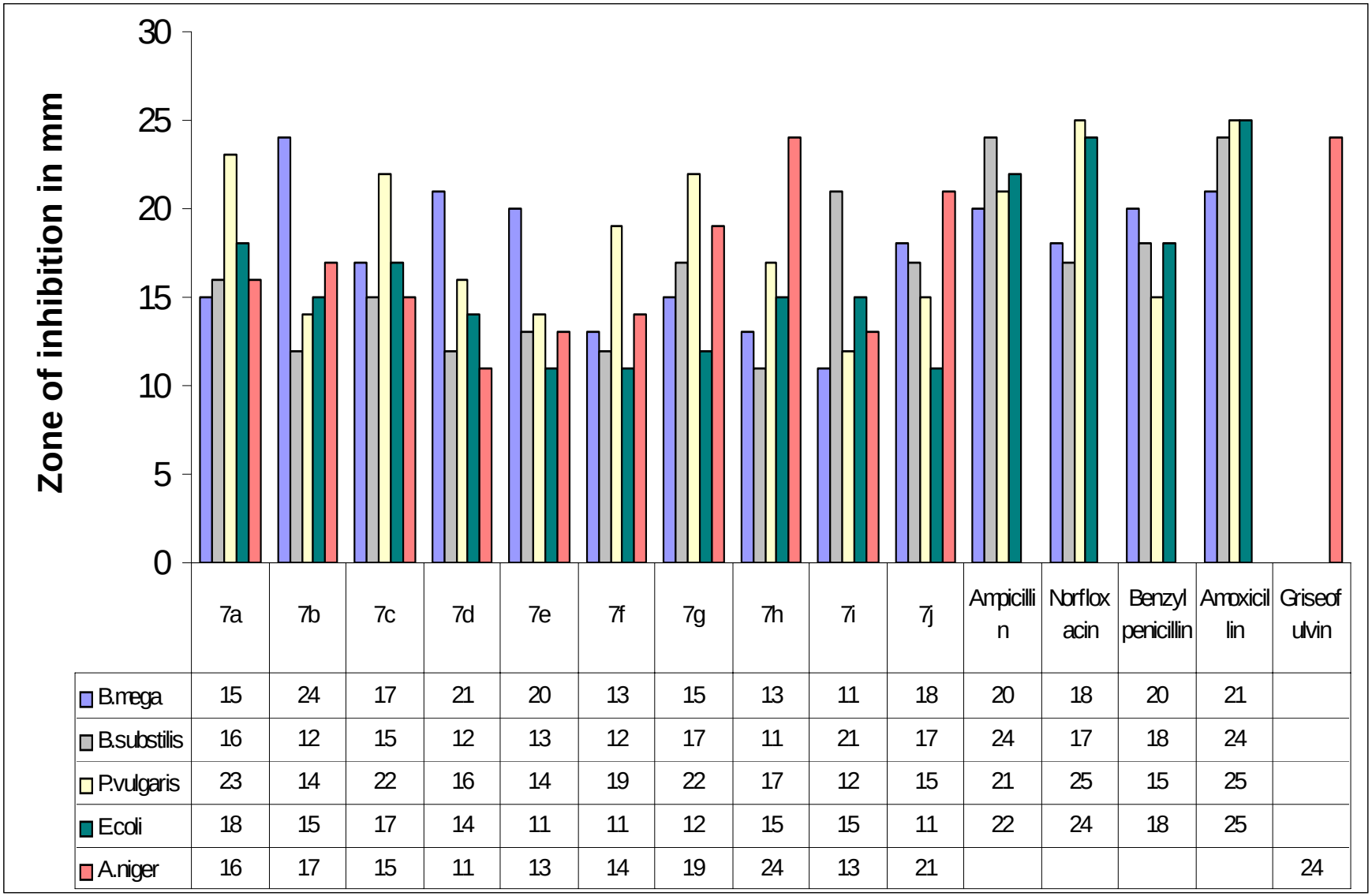
Antimicrobial testing were carried out as described in Part-I, Section-I(D). The zones of inhibition of test solution are reported in Graphical Chart No. 2.

TABLE-7: PHYSICAL CONSTANTS OF 2-AMINO-4-ARYL-6-(6-CHLORO-4-OXO-3,4-DIHYDRO CINNOLIN-3-YL)-4H-PYRAN-3-CARBONITRILE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	R_f Value	Solvent System	Yield %	% of Nitrogen Calcd	% of Nitrogen Found
1	2	3	4	5	6	7	8	9	10
7a	C_6H_5-	$C_{20}H_{13}ClN_4O_2$	376.79	186	0.35	S_1	54	14.87	14.85
7b	3-Br-C_6H_4-	$C_{20}H_{12}BrClN_4O_2$	455.69	198	0.45	S_2	54	12.29	12.27
7c	2-Cl-C_6H_4-	$C_{20}H_{12}Cl_2N_4O_2$	411.24	265	0.42	S_1	52	13.62	13.61
7d	3-Cl-C_6H_4-	$C_{20}H_{12}Cl_2N_4O_2$	411.24	226	0.52	S_1	55	13.62	13.60
7e	4-Cl-C_6H_4-	$C_{20}H_{12}Cl_2N_4O_2$	411.24	270	0.57	S_2	54	13.62	13.62
7f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{22}H_{17}ClN_4O_4$	436.85	>300	0.38	S_3	52	12.83	12.81
7g	4-OCH_3-C_6H_4-	$C_{21}H_{15}ClN_4O_3$	406.82	220	0.55	S_2	53	13.77	13.74
7h	4-SCH_3-C_6H_4-	$C_{21}H_{15}ClN_4O_2S$	422.89	285D	0.49	S_2	51	13.25	13.24
7i	3-C_6H_5-O-C_6H_4-	$C_{26}H_{17}ClN_4O_3$	468.89	189	0.51	S_2	54	11.95	11.94
7k	4-$N(CH_3)_2$-C_6H_4-	$C_{22}H_{18}ClN_5O_2$	419.86	>300	0.63	S_1	56	16.68	16.64

S_1 = Ethyl acetate : Hexane (1:9), S_2 = Ethyl acetate : Hexane (2.5 : 7:5), S_3 = Acetone : Benzene (2 : 8)

Graphical Chart No. 7 : Antimicrobial activity of 2-Amino-4-chloro-6-(6-chloro-4-oxo-3,4- dihydro cinnolin-3-yl-4H-pyran-3-carbonitrile



	7a	7b	7c	7d	7e	7f	7g	7h	7i	7j	Ampicillin	Norfloxacin	Benzyl penicillin	Amoxicillin	Griseofulvin
B.mega	15	24	17	21	20	13	15	13	11	18	20	18	20	21	
B.substilis	16	12	15	12	13	12	17	11	21	17	24	17	18	24	
P.vulgaris	23	14	22	16	14	19	22	17	12	15	21	25	15	25	
E.coli	18	15	17	14	11	11	12	15	15	11	22	24	18	25	
A.niger	16	17	15	11	13	14	19	24	13	21					24

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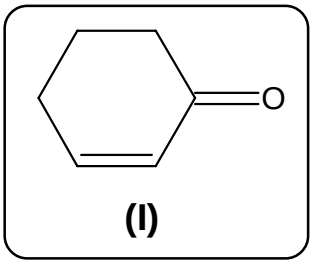
INTRODUCTION

Cyclohexenones are derivatives of cyclohexane with carbonyl grooup at position -1 and double bond at position -2 (I). There are different types of cyclohexenone derivatives but the greatest difference in structure and properties is exerted by the groups attached to carbon atom.

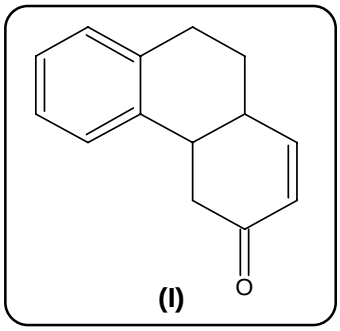


(I)

SYNTHETIC ASPECT

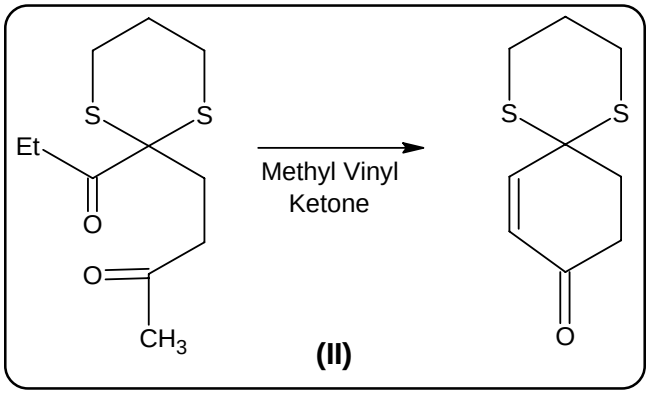
Different methods for the preparation of cyclohexenone derivatives have been described in literature[1-14].

(I) A review of the earlier literature by Gerald et al.[15] described representative synthetic procedure of cyclohexenone derivative (I).



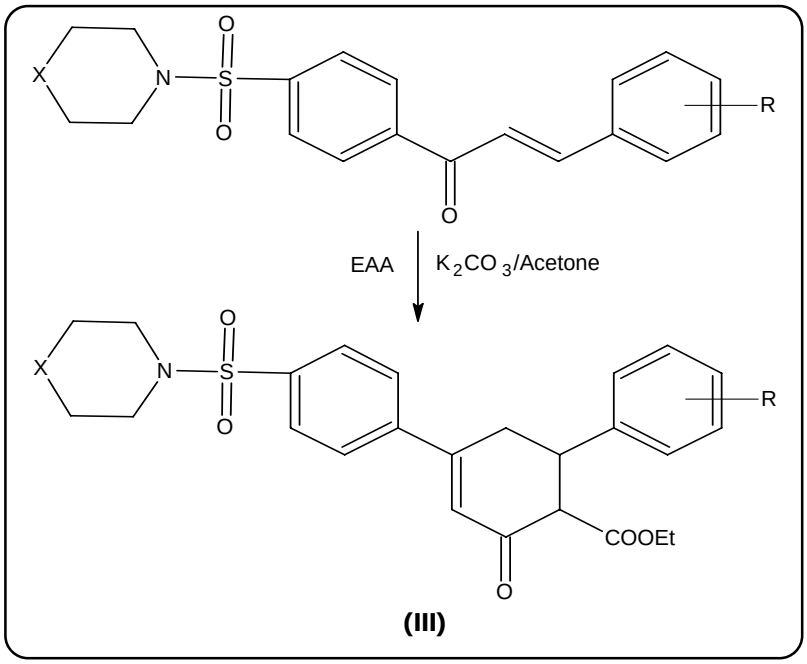
(I)

(II) Page Philip C. and co-workers[16] have been prepared substituted cyclohexenone derivatives (II).



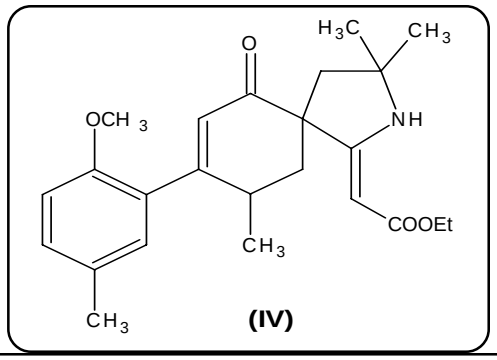
(II)

(III) Eman H. A. et al.[17] have been prepared cyclohexenone derivatives (III) from chalcone.



(III)

(IV) Shklyaev A. S. et al.[18] have been synthesized 1-substituted (R,S)-8-(2-methoxy-5-methylphenyl)-3,3,9-trimethyl-2-azaspiro[4,5]deca-1,7-dien-6-ones (IV).



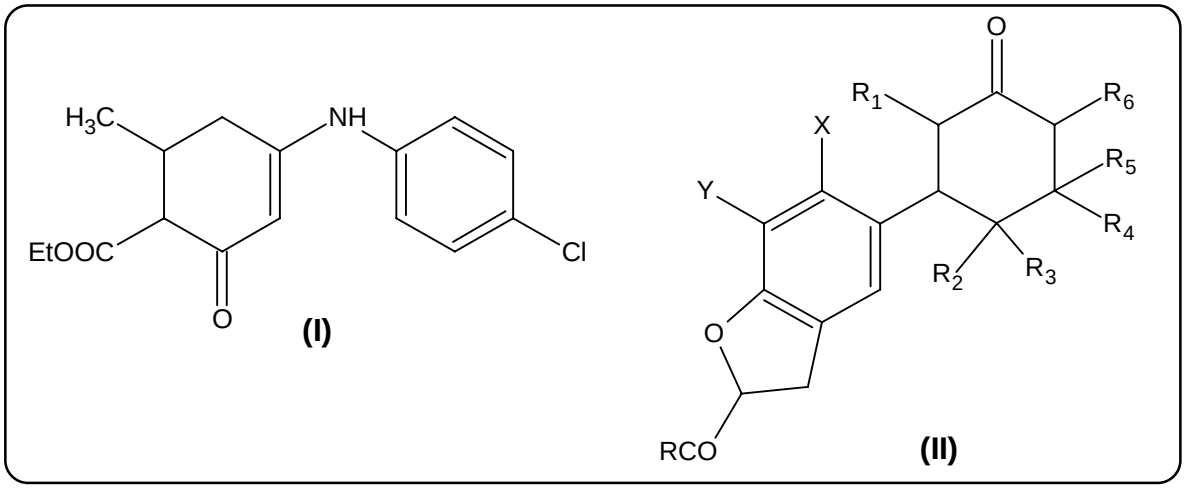
(IV)

THERAPEUTIC IMPORTANCE

Cyclohexenone have various medicinal applications such as anthelmintic, hypoglycemic, nematocidal, antibacterial, antifungal, antiviral, analgesic etc. Antiarhythmic activity[19] of some cyclohexenone derivatives have been investigated. Cyclohexenone possess cardiovascular, osteoporosis, menpausal symptoms, estro

gen dependent, cancer activities, which was reported by Jacobsen Poul et al.[20].

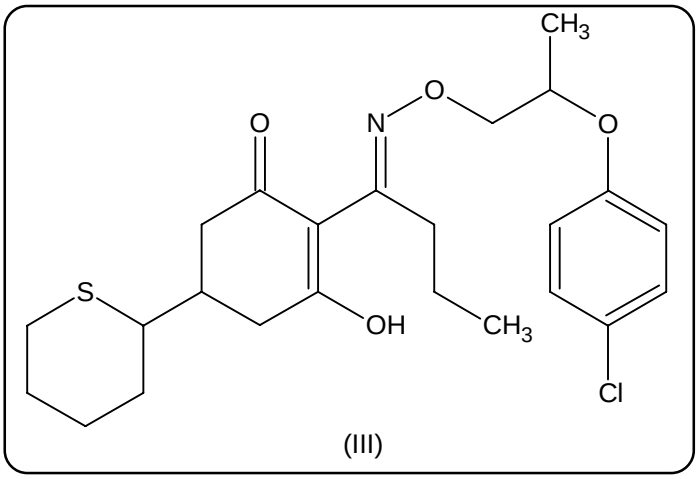
Eddington N. D. et al.[21] synthesize ethyl 4-[(substituted phenyl)amino]-6-methyl-2-oxocyclohex-3-ene-1-carboxylates (I) and screened their anticonvulsant activity. Cragoe, Edward J. et al.[22] also prepared 2,3-dihydro-5-(3-oxo-2-cyclohexen-1-yl)-2-benzofurancarboxylic acids (II) and their salts which are used in the treatment of brain injury.



Cyclohexenone and its derivatives have been prepared and reported as broad spectrum of physiological properties viz., antibiotics[23,24], bactericidal[25], herbicidal[26], antimicrobial[27], anticonvulsant[28] etc. Alekseeva L. M. and co-workers[29] have synthesized cyclohexenone derivatives which are as useful as neurotropic activity. Toshiyuki et al.[30] have prepared some novel cyclohexenone and screened for allergy inhibitor, antithrombotic platelet aggregation inhibitors and fibrinogen antagonist activity.

Recently, antimicrobial activity have been studied by Salama and Atshikh[31]. Cyclohexenone possess neutropeptide γ-receptor antagonist activity which was reported by Takehiro and co-workers[32]. Broughton Howard[33] have demonstrated cyclohexenone as GABA α5 receptor ligands for enhancing coagulating properties. Cyclohexenone possess inhibitory activity against the growth of lettuce seeding found by Kimura and co-workers[34].

The presence of pesticidal activity among cyclohexenone derivatives is well documented. The compound 2-{(E,Z)-1-[(2R,S)-2-(4-chlorophenoxy)propoxy imino]butyl}-3-hydroxy-5-thian-3-yl)cyclohex-2-en)-one (III) has been marketed under the name of ***'Profoxydim'*** as an herbicides.



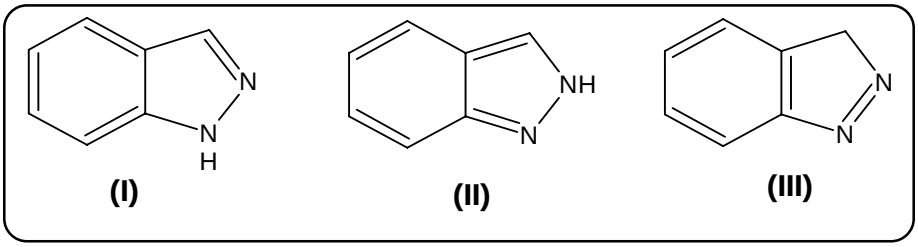
(III)

These valid observation led us to synthesize new cyclohexenone derivatives bearing cinnoline nucleus in search of agent having better therapeutic potential which have been described as under.

SECTION-I: Synthesis and biological screening of Ethyl-6-aryl-4 -(6-chloro-4-oxo-3,4-dihydrocinnoline-3-yl)-2-oxocyclohex-3-ene-1-carboxylate

INTRODUCTION

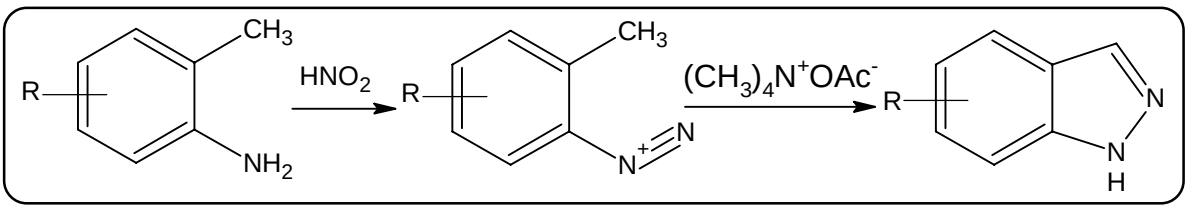
Indazole or benzopyrazoles a heterocyclic ring system in which a benzene ring is fused to two carbon atoms of a pyrazole ring , is capable of existing in three tautomeric forms (I, II, III)[35]. Although the chemistry of indazoles has been extensively studied, they have not been found in natural products and are at the present time of little commercial use. It was first described by Buchner in 1869.



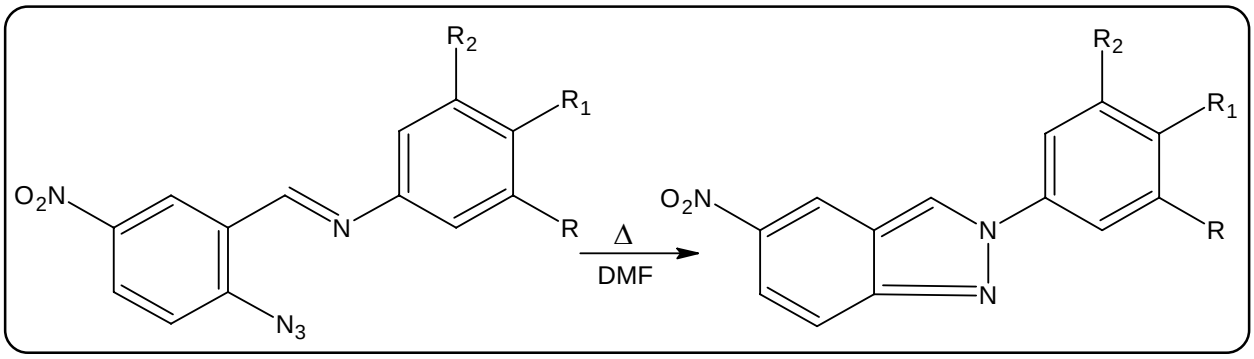
SYNTHETIC ASPECT

Several methods[36-41] are available for the preparation of indazoles. Some of these are as under,

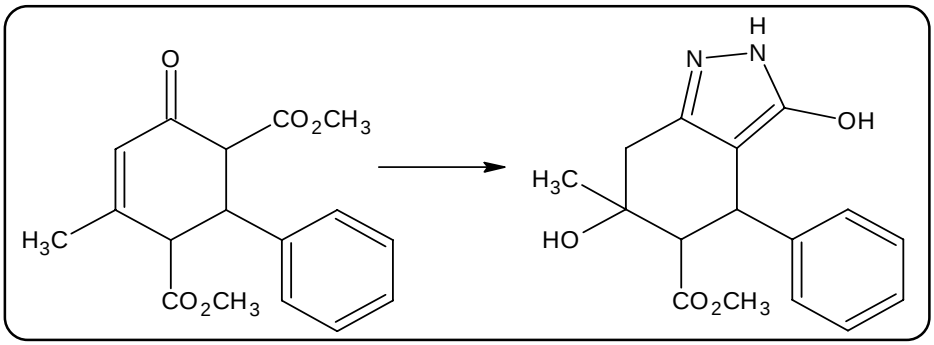
(I) The most frequently used route for synthesis of indazole ring system consists of the diazotization of substituted anilines, e.g. o-toludine leds to the parent indazoles[42].



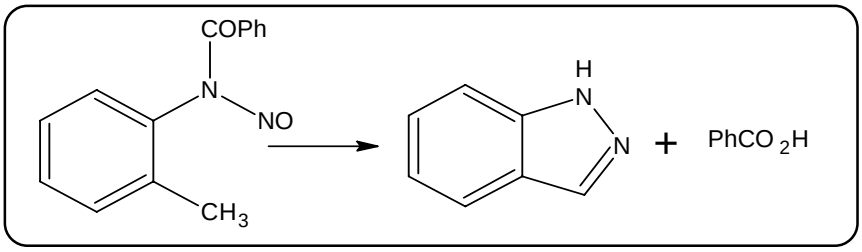
(II) Okhim L. Yu et al.[43] synthesized some indazole derivatives by heating benzylidene aniline derivatives in DMF.



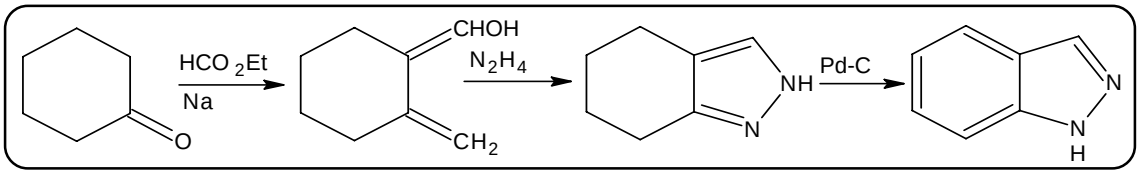
(III) Shri Niwas and co-workers[44] have synthesized few indazole derivatives from cyclohexenone intermediates.



(IV) Indazoles may conveniently be prepared by heating o-nitroso-N-benzoltoluidine in benzene solution.



(V) Another synthesis is that due to Ainsworth (1957).



(VI) Qui-Guo Fu et al.[45] have reported that in presence of PPA 2,6-dialkoxyl or hydroxyl acetophenone hydrazones were cyclized to indazoles.

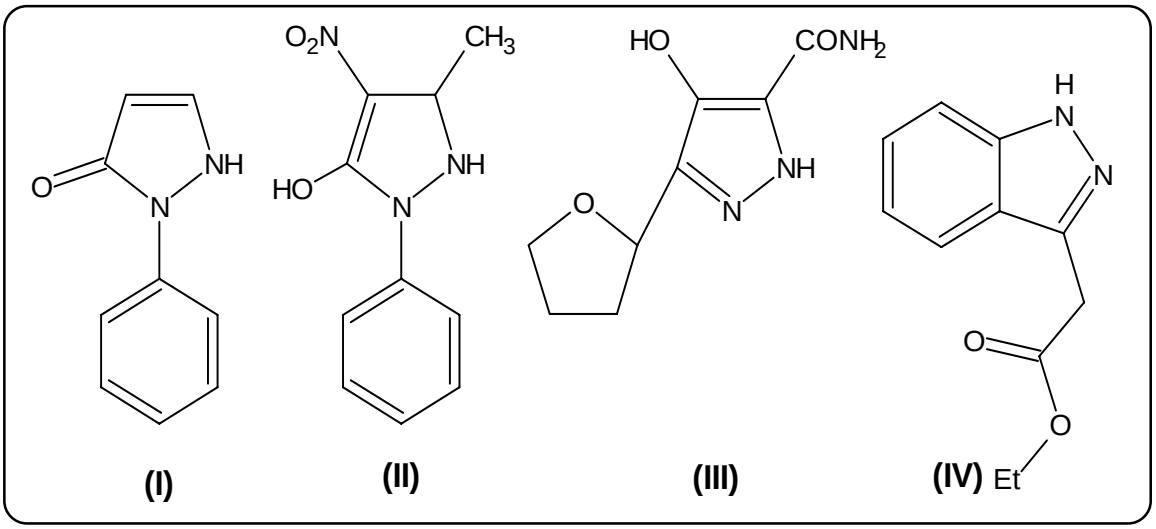
(VII) Recently, a facile synthesis of substituted indazoles from 2-acyl aryl mesylates and hydrazine is described by Carom Stephane et al.[46].

THERAPEUTIC IMPORTANCE

A wide range of pharmacological properties have been encountered with indazole derivatives like,

1. Antiallergic[47],
2. Antibacterical[48,49],
3. Antidepressant[50],
4. Antiinflammatory[51],
5. Antineoplastic[52],
6. Antipsychotic[53,54],
7. Antitumor[55,
8. Antiviral[56,57],
9. Fungicidal[58],
10. Herbicidal[59,60],

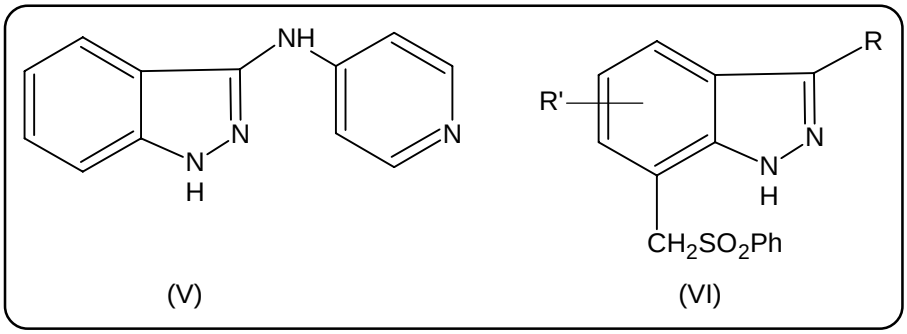
The indazoles has attracted considerable attention in the last 25 years, because of several commercially useful drugs contain pyrazole ring system. For example Antipyrine (I) has potent antipyretic activity. Similarly ***Butazolidine*** (II) has proved a powerful antiinflammatory drug used for rheumatic patients. ***Pyrazofurin*** (III) shows activity against a number of viruses. Moreover, ***Ethylchlozate*** (IV) is used as a plant growth regulators.



(I) **(II)** **(III)** **(IV)**

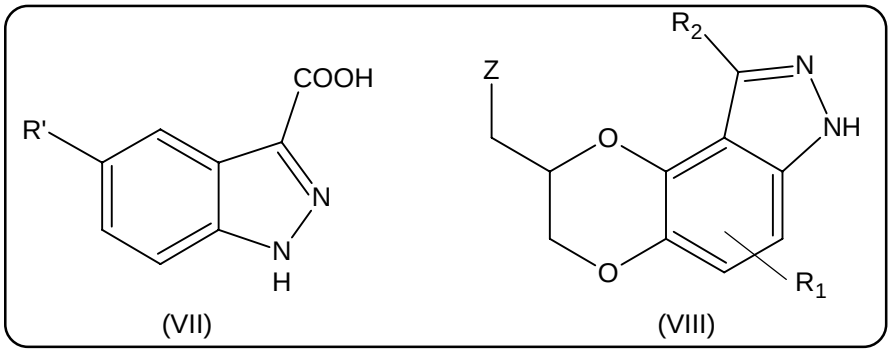
Ooe Takanon et al.[61] synthesized some indazole derivatives which showed activity for enhansing macrophage phagocytosis, improving immunity and antitumor activity. Yamaguchi Masahisa et al.[62] prepared some indazole derivatives as novel antiasthametic agents with dual activities of thromboxane A_2 synthetase inhibitors and bronchodialtion. The remarkable cytotoxic activity of indazole derivatives have been reported by Aran Vincente J et al.[63].

Moreover, Effland Richard Charles et al.[64] synthesized 3-(pyridylamino)-indazoles(V) and reported their use as antidepressants and anxiolytics. Some sulfonyl indazoles (VI) synthesized by Duzinska Usarewicz et al[65] have been found to possess antiinflammtory activity. Butera John et al.[66] prepared some indazole derivatives which are useful as potassium channel activators.



(V) (VI)

Recently, Nishino, Shigehide et al.[67] prepared 3-carboxy-5-(1-carboxy ethyl) indazole (VII) which was used as intermediate for the preparation pesticides. Stack, Gary Paul and co-workers[68] prepared antipsychotic aminomethyl derivatives of 7,8-dihydro-3H-6,9-dioxa-2,5-diaza-cyclopenta[a]naphthalene (VIII).



(VII) (VIII)

Furthermore, Fukunaga K et al.[69] reported that DY-97603, 3-[2-[4-(3-chloro-2-methylphenyl)-1-piperazinyl]ethyl]-5,6-dimethoxy-1-(4-imidazolylmethyl)-1H-indazole dihydrochloride, a novel calmodulin antagonist, possesses neuroprotective activity. Mosti L. et al.[70] synthesize novel N-substituted 1-amino-3-[1-methyl(phenyl)-1H-indazol-4-yloxy]-propan-2-ols as potential antiarrhythamic, local anaesthetic and analgesic agents. Lee F Y and co-workers[71] synthesized 1-benzyl-3-(5'hydroxymethyl-2'-furyl)indazole analogues as novel antiplatelet agents. Pinna G A et al.[72] have synthesized bis benzo[g]indazol-3-carboxamides and related dimers and checked their antiproliferative activity.

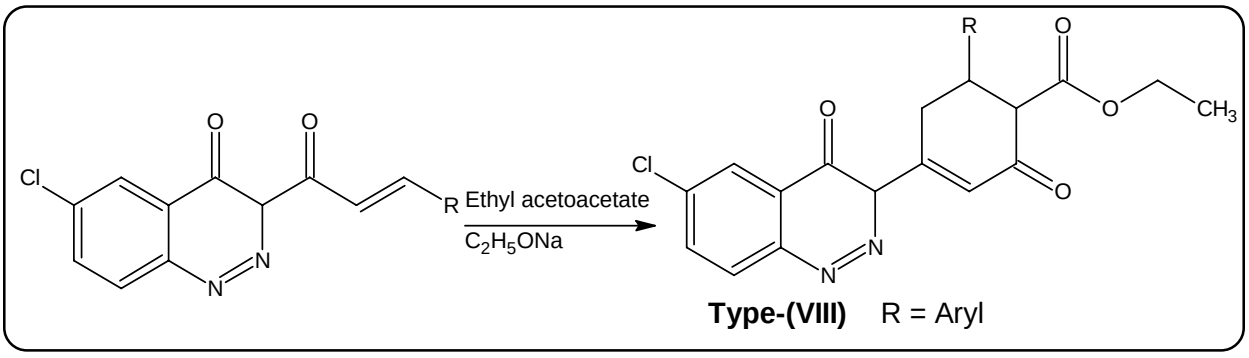
In light of wide varieties of biological activities exhibited by indazoles, it appeared of interest to synthesize indazole derivatives, in order to achieving compounds having better therapeutic activity described as under.

SECTION-II: Synthesis and biological screening of 6-Chloro-3-(4-aryl-3-oxo-3,3a,4,5-tetrahydro-2H-indazol-6-yl)-cinnolin-4(3H)-one

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-6-ARYL-4-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLINE-3-YL)-2-OXOCYCLOHEX-3-ENE-1-CARBOXY-LATE

Cyclohexenone derivatives have considerable attention in view of their potential pharmacological properties such as antimicrobial, anticonvulsant anticancer, etc. Led by these considerations, the preparation of cyclohexenone derivatives of Type-(VIII) has been undertaken. The synthesis was carried out by the condensation of 6-chloro-3-[(2E)-3-arylprop-2-enoyl]connolin-4(3H)-ones of Type-(I)with ethyl acetoactate shown as under.

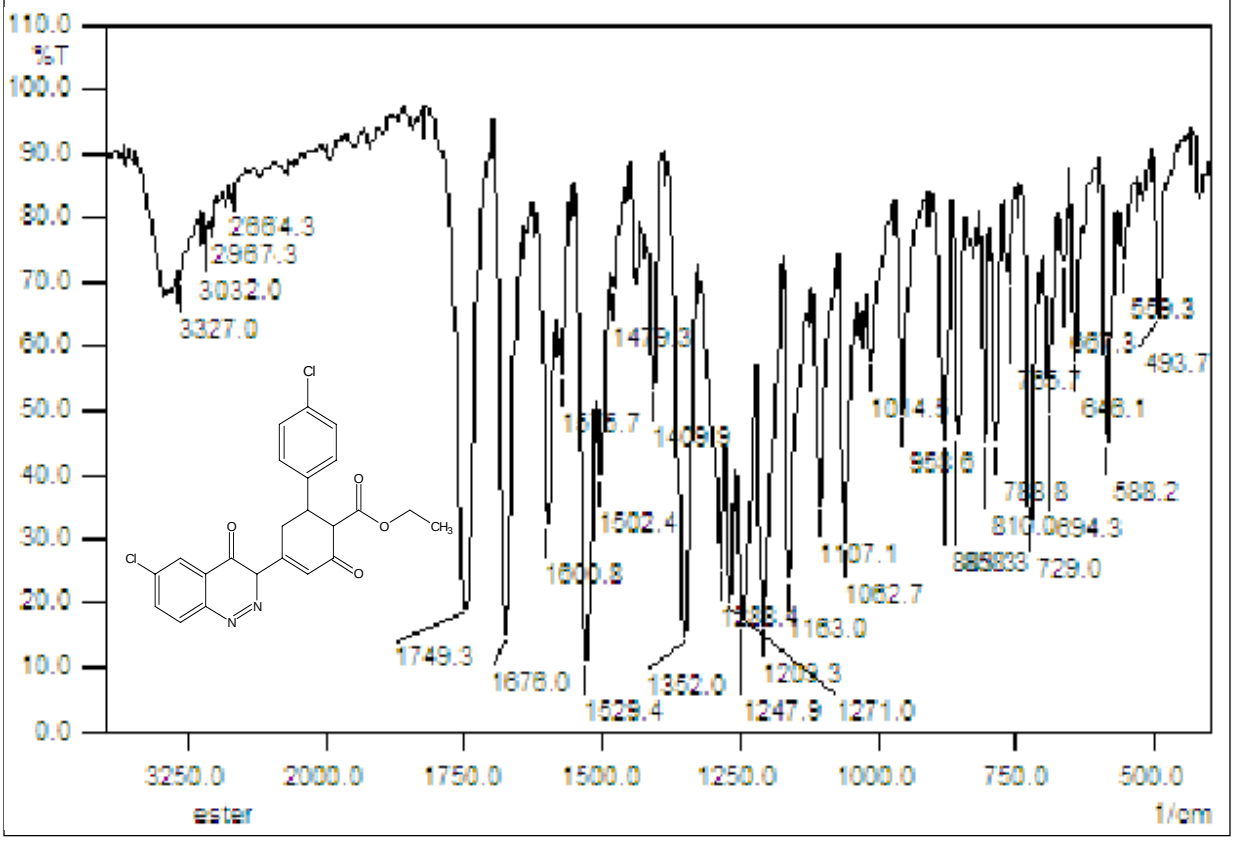


Type-(VIII) R = Aryl

The structure elucidation of synthesized compounds have been done on the basis of elemental analyses, infrared and ^1H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

All the compounds have been evaluated 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 synthesized compounds were compared with standard drugs.

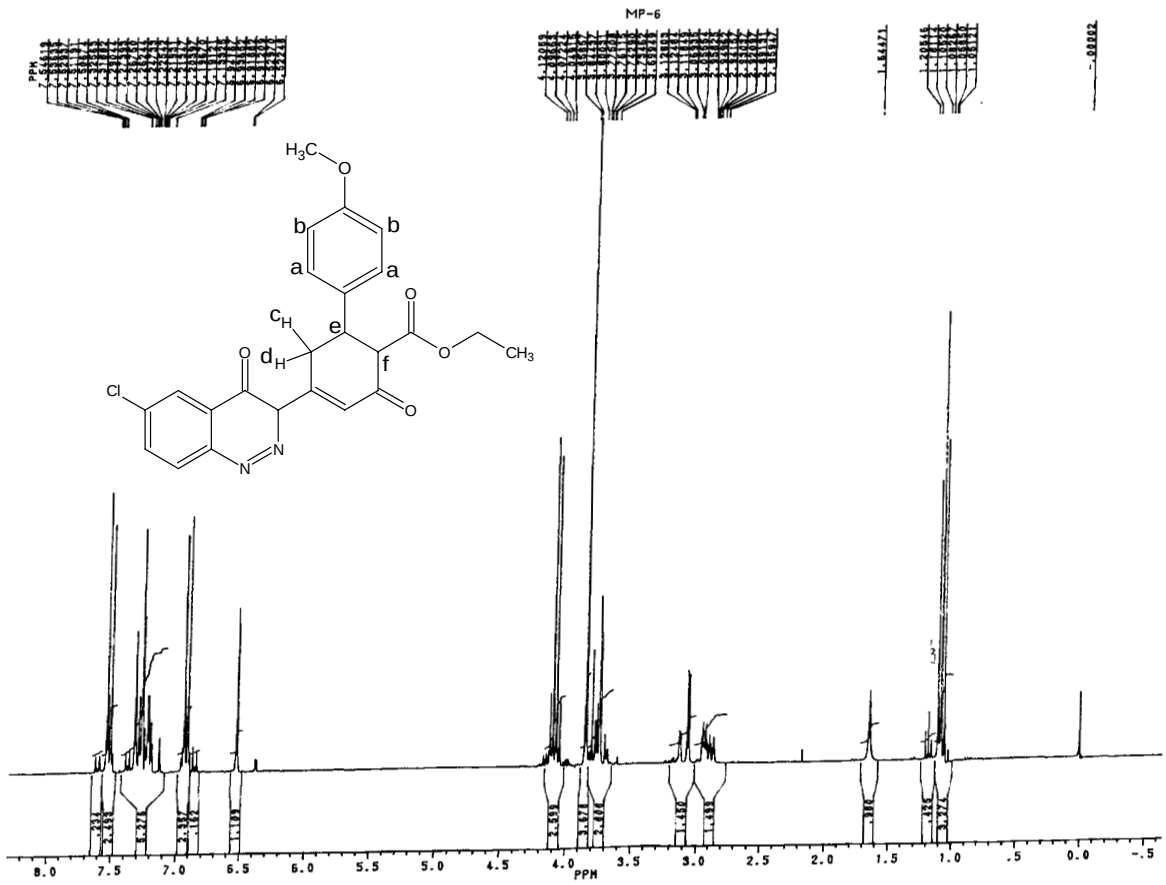
IR SPECTRAL STUDY OF ETHYL-6-(4-CHLORO PHENYL)-6-(6-CHLORO-4-OXO-3.4-DIHYDROCINNOLIN-3-YL)-2-OXO-CYCLOHEXE-3-ENE-1-CARBOXYLATE



Frequency range: 4000-400cm^{-1} (KBr disc) Instrument : Shimadzu-8400 FTIR

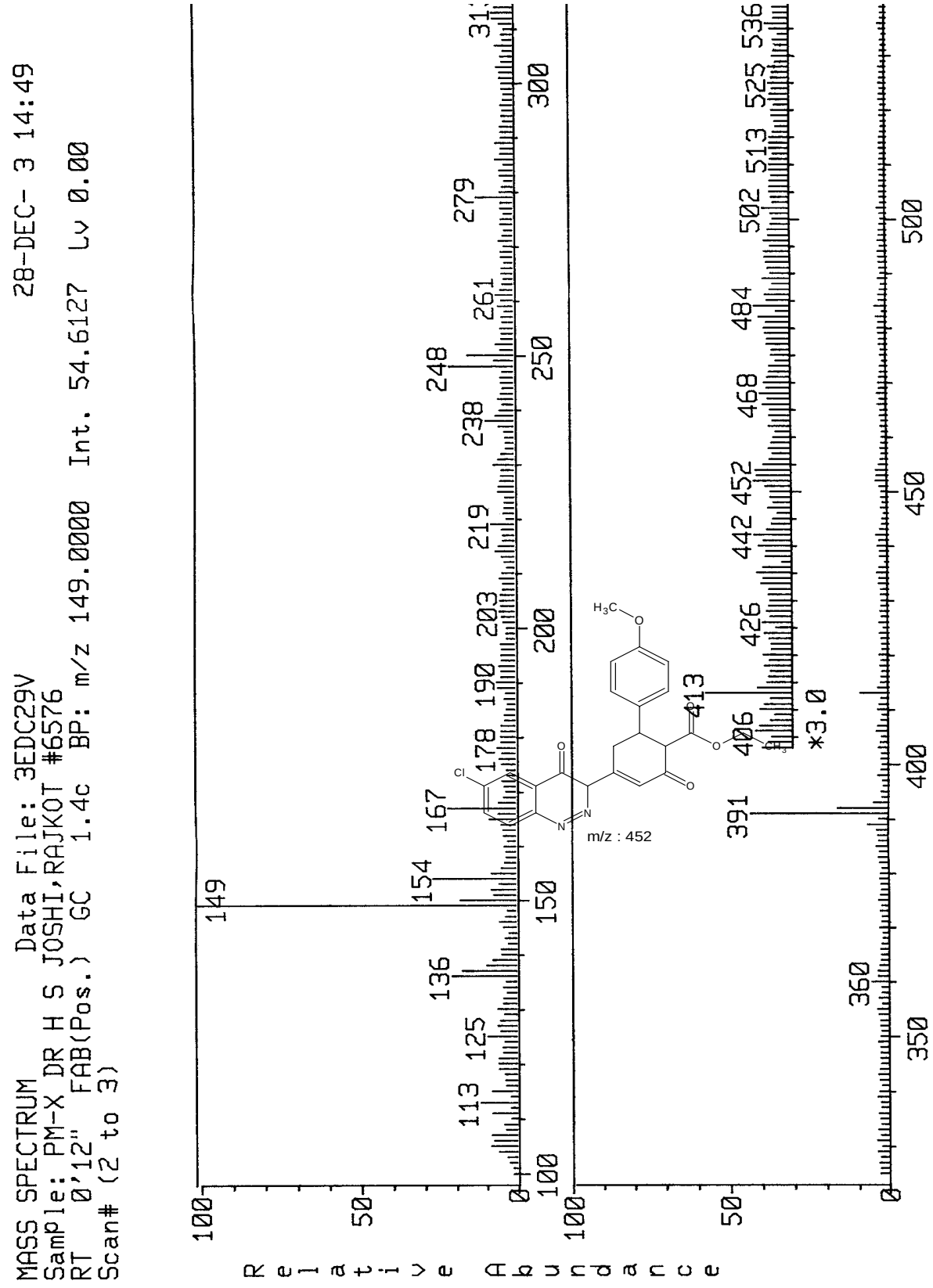
Type	Vibration mode	Frequency in cm^{-1} Observed	Reported	References
Alkane	C-H str. (asym.)	2967	2975-2950	73
-CH_3	C-H str. (sym.)	2884	2880-2860	"
	C-H def. (asym.)	1479	1470-1435	"
	C-H def. (sym.)	1362	1385-1370	"
Aromatic	C-H str.	3032	3080-3030	74
	C=C str.	1567	1620-1430	"
	C-H i.p. def	1247	1269-1013	"
	C-H o.o.p. def.	833	833-660	"
Ether	C-O-C str.	1209	1275-1200	73
Carbonyl	C=O	1676	1690-1665	"
Ester	C(=O)OCH_2CH_3	1749	1750-1717	74
Halide	C-Cl str.	765	750-700	73

PMR SPECTRAL STUDIES OF ETHYL-6-(4-METHOXY PHENYL)-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLINE-3-YL)-2-OXO-CYCLOHEX-3-ENE-1-CARBOXY-LATE



Internal reference: TMS; Solvent: $CDCl_3$; Instrument: BRUKER spectrometer(300 MHz)

Signal No.	Signal position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	1.08	3H	triplet	$-CH_2-CH_3$
2.	2.94	1H	double doublet	$-CH_c$
3.	3.05	1H	double doublet	$-CH_d$
4.	3.77	1H	multiplate	$-CH_e$
5.	3.80	1H	singlet	-CHg
6.	3.84	1H	singlet	$Ar-OCH_3$
7.	4.09	2H	quateret	$-CH_2-CH_3$
8.	6.52	1H	doublet	$-CH_f$
9.	6.92	2H	doublet	$Ar-H_a$ (p-sub.)
10.	7.20-7.40	4H	multiplet	Ar-H
11.	7.52	2H	doublet	$Ar-H_b$ (p-sub.)


MASS SPECTRUM Data File: 3EDC29V
Sample: PM-X DR H S JOSHI,RAJKOT #6576
RT 0'12" FAB(Pos.) GC 1.4c BP: m/z 149.0000 Int. 54.6127 Lv 0.00
Scan# (2 to 3)
28-DEC- 3 14:49
Relative Abundance
m/z : 452
*3.0

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-6-ARYL-4-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-2-OXO-CYCLOHEX-3-ENE-1-CARBOXYLATE

(A) Synthesis of 6-Chloro-3-[(2E)-3-aryl prop-2-enoyl]cinnolin-4(3H)-one.

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

(B) Synthesis of Ethyl-6-(4-methoxyphenyl)-4-(6-chloro-4-oxo-3,4-dihydro cinnolin-3-yl)-2-oxo-cyclohex-3-ene-1-carboxylate.

To a solution of 6-chloro-3-[(2E)-3-(4-methoxyphenyl)-prop-2-enoyl]cinnolin-4(3H)-one (3.4 gm, 0.01 mol) in dioxane (30 ml), sodium ethoxide (0.15 mol) and ethyl acetoacetate (2.60 gm, 0.02 mol) was added and the reaction mixture was refluxed on oil bath for 12 hrs. The reaction mixture was cooled and poured over crushed ice. The product was isolated and crystallized from toluene. Yield 58 %, m.p. 206 ^{0}C Anal. Calcd. for $C_{25}H_{23}ClN_2O_6$ Requires: C, 63.65; H, 4.67; N, 6.19 % Found: C, 63.63; H, 4.64, N, 6.17 %.

Similarly, other ethyl-6-aryl-4-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-2-oxo-cyclohex-3-ene-1-carboxylate. The physical data are recorded in Table No. 8.

(C) Biological screening of Ethyl-6-aryl-4-(6-chloro-4-oxo-3,4-dihydro cinnolin-3-yl)-2-oxo-cyclohex-3-ene-1-carboxylate.

Antimicrobial testing were carried out as described in Part-I, Section-I(D). The zones of inhibition of test solution are reported in Graphical Chart No. 8.

TABLE-8: PHYSICAL CONSTANTS OF ETHYL-6-ARYL-4-(6-CHLORO-4-OXO-3,4-DIHYDRO CINNOLIN-3-YL)-2-OXO-CYCLOHEX-3-ENE-1-CARBOXYLATE

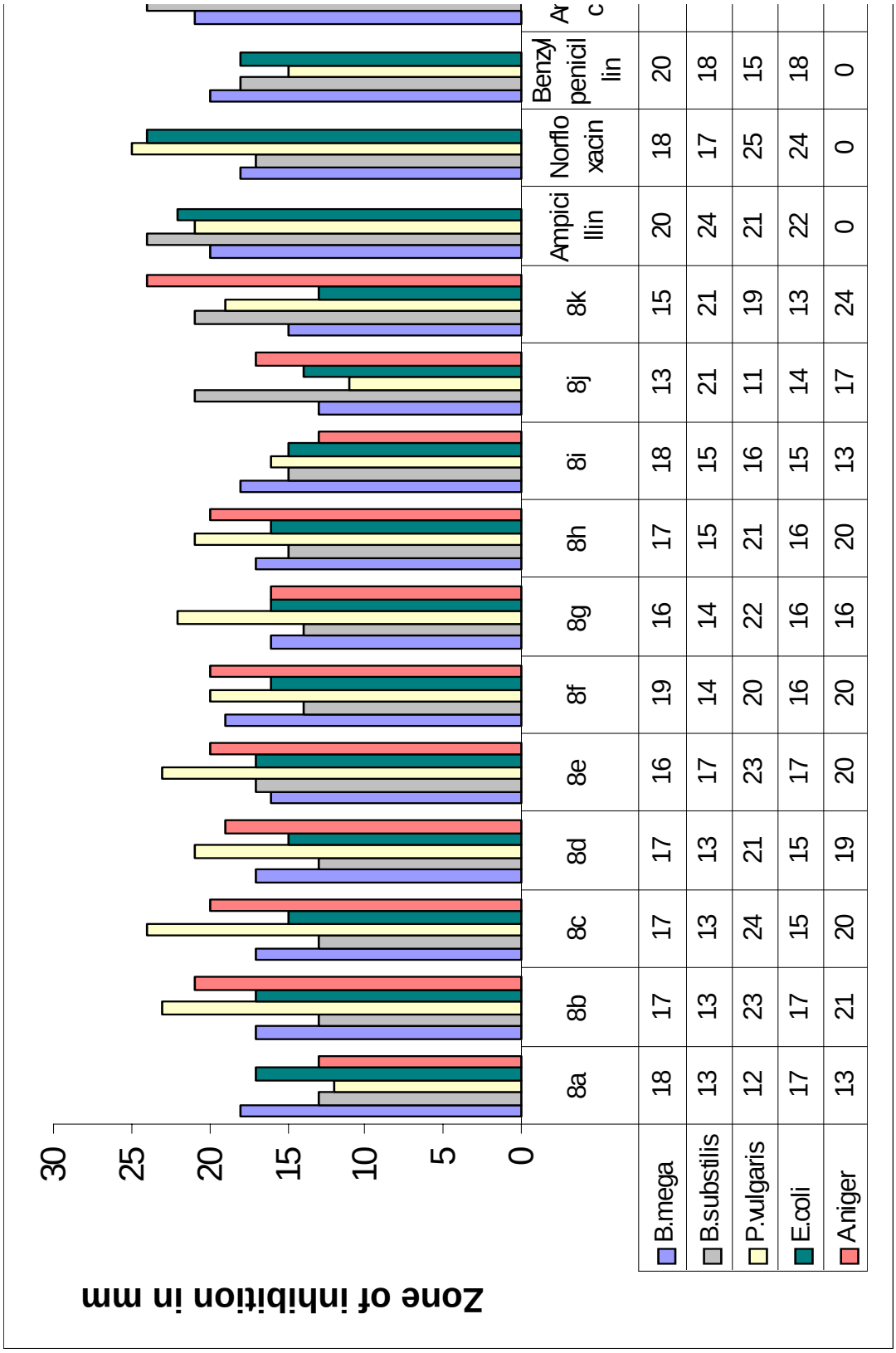
Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	Rf Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
8a	C_6H_5-	$C_{23}H_{19}ClN_2O_4$	422.86	212	0.46	S_1	57	6.62	6.61
8b	3-Br-C_6H_4-	$C_{23}H_{18}BrClN_2O_4$	501.76	224	0.41	S_1	58	5.58	5.54
8c	2-Cl-C_6H_4-	$C_{23}H_{18}Cl_2N_2O_4$	457.31	118	0.52	S_1	60	6.13	6.11
8d	3-Cl-C_6H_4-	$C_{23}H_{18}Cl_2N_2O_4$	457.31	186	0.37	S_1	54	6.13	6.12
8e	4-Cl-C_6H_4-	$C_{23}H_{18}Cl_2N_2O_4$	457.31	132	0.44	S_2	55	6.13	6.10
8f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{25}H_{23}ClN_2O_6$	482.91	238	0.56	S_2	54	5.80	5.79
8g	4-OCH_3-C_6H_4-	$C_{24}H_{21}ClN_2O_5$	452.89	146	0.34	S_2	58	6.19	6.17
8h	4-SCH_3-C_6H_4-	$C_{24}H_{21}ClN_2O_4S$	468.95	156	0.38	S_3	54	5.97	5.99
8i	3-C_6H_5-O-C_6H_4-	$C_{29}H_{23}ClN_2O_5$	514.96	164	0.42	S_3	55	5.44	5.43
8J	4-$N(CH_3)_2$-C_6H_4-	$C_{25}H_{24}ClN_3O_4$	465.93	142	0.49	S_1	54	9.02	9.01
8K	C_9H_6ClN	$C_{26}H_{19}Cl_2N_3O_4$	508.27	159	0.47	S_3	53	8.27	8.24

S_1 = Ethyl acetate : Hexane (2 : 8)

S_2= Ethyl acetate : Hexane (3 : 7)

S3= Acetone : Benzene (1 :9)

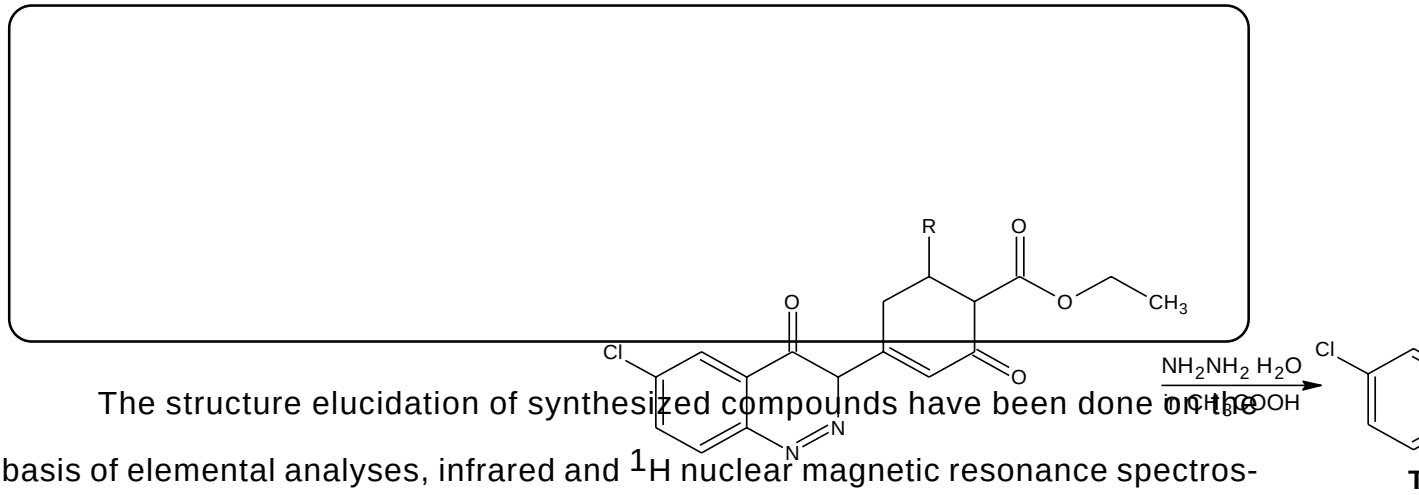
Graphical Chart No. 8 : Antimicrobial activity of Ethyl-6-aryl-4-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-2-oxo-cyclohex-3-ene-1-carboxylate



SECTION-II

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-CHLORO-3-(4-ARYL-3-OXO-3,3a,4,5-TETRAHYDRO-2H-INDAZOL-6-YL)-CINNOLIN-4(3H)-ONE

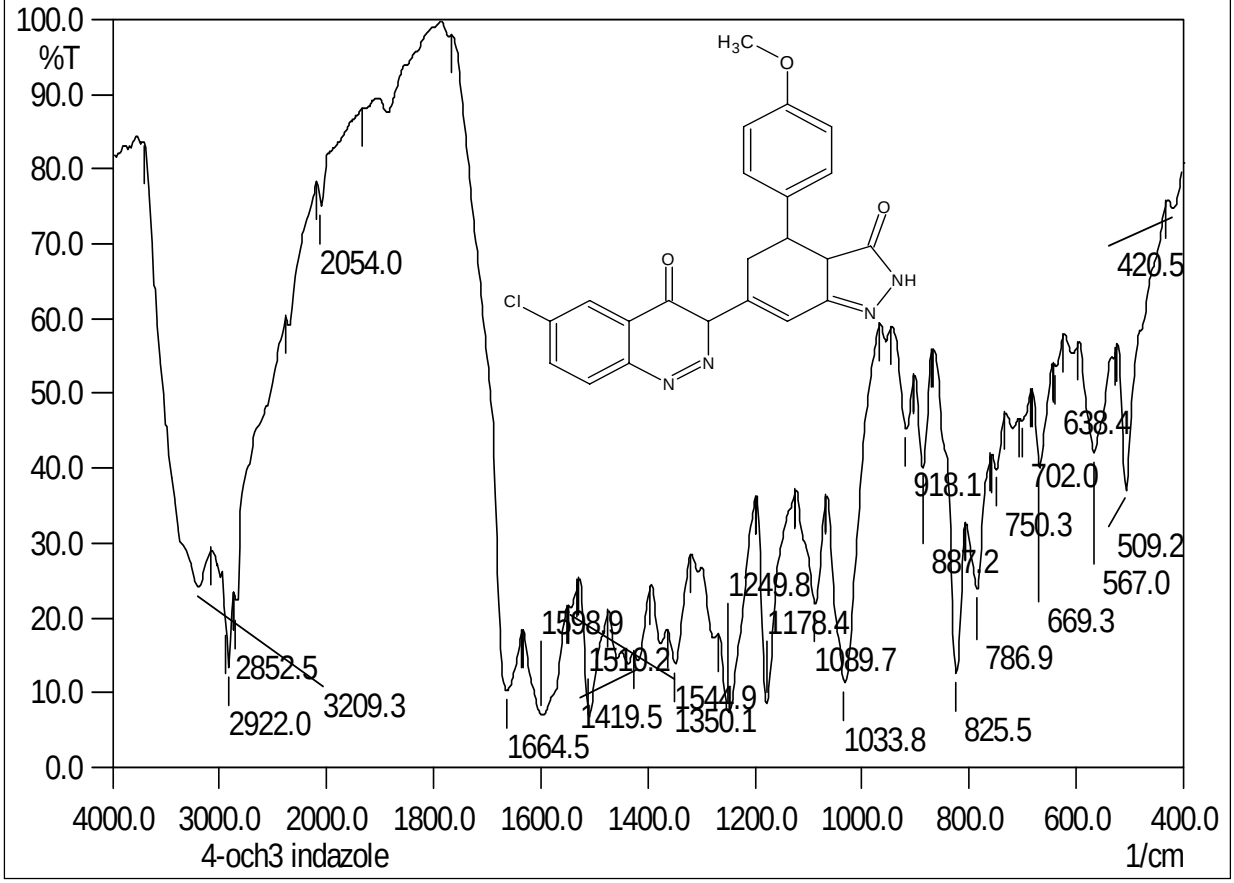
Various derivatives of indazole exhibit interesting biological properties like anticancer, antiinflammatory, anticonvulsant, antipyretic etc. With a view to prepare more potential drug value compounds we have carried out the synthesis of Indazole derivatives of Type-(IX) have been prepared by the condensation of cyclohexenone derivatives of Type-(VII) with hydrazine hydrate. derivatives, which have been briefed as under.



The structure elucidation of synthesized compounds have been done on the basis of elemental analyses, infrared and ^1H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

All the compounds have been evaluated 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 synthesized compounds were compared with standard drugs.

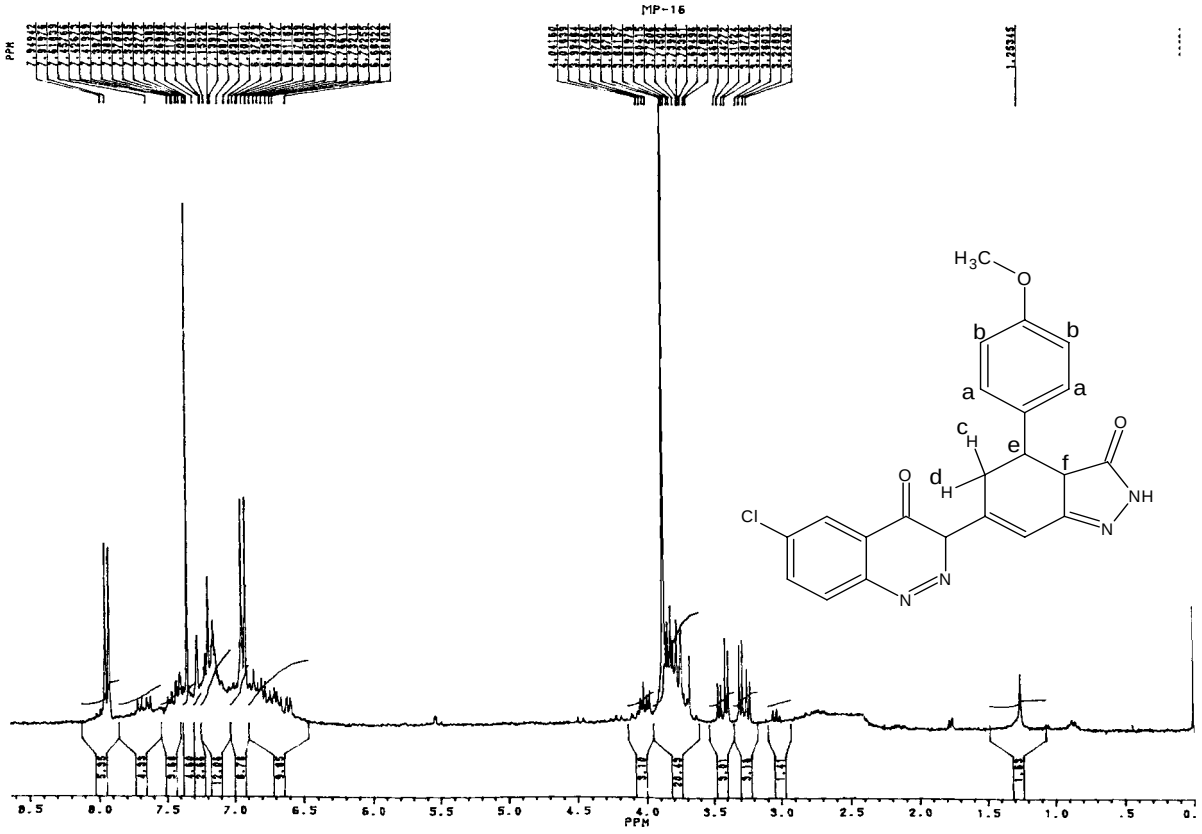
IR SPECTRAL STUDY OF 6-CHLORO-3-(4-ARYL-3-OXO-3,3a,4,5-TETRAHYDRO-2H-INDAZOL-6-YL)-CINNOLIN-4(3H)-ONE



Frequency range: 4000-400cm^{-1} (KBr disc) Instrument : Shimadzu-8400 FTIR

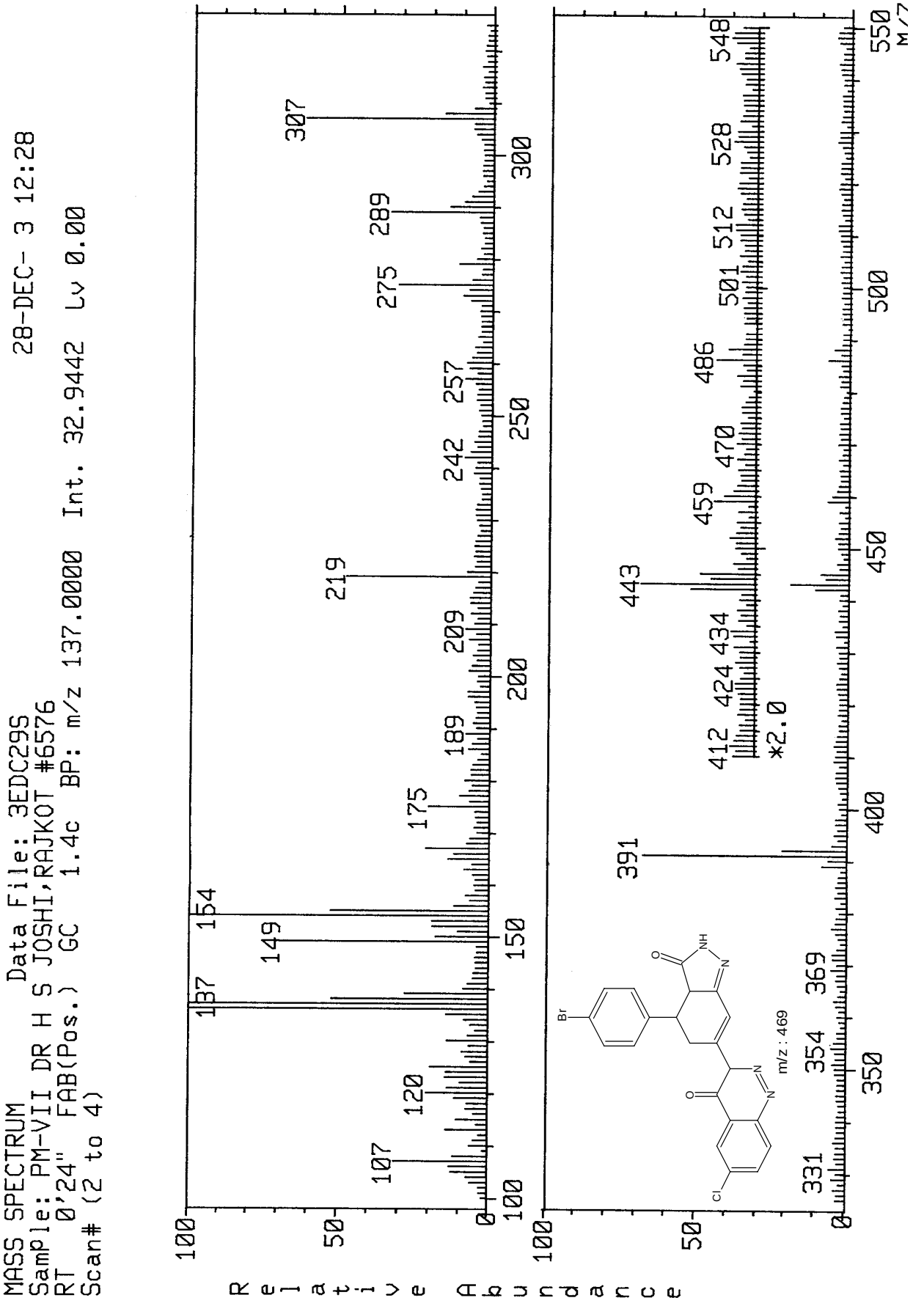
Type	Vibration mode	Frequency in cm^{-1} Observed	Reported	References
Alkane	C-H str. (asym.)	2922	2975-2950	73
-CH_3	C-H str. (sym.)	2852	2880-2860	"
	C-H def. (asym.)	1460	1470-1435	"
	C-H def. (sym.)	1350	1385-1370	"
Aromatic	C-H str.	3033	3080-3030	74
	C=C str.	1558	1620-1430	"
	C-H i.p. def	1174	1269-1013	"
	C-H o.o.p. def.	825	833-660	"
Amide	NHC(=O)- str.	1664	1680-1636	73
Indazole	C=N	1598	1660-1480	74
Ether	C-O-C str.	1249	1275-1200	73
Halide	C-Cl str.	750	750-700	"

PMR SPECTRAL STUDIES OF ETHYL-6-(4-METHOXY PHENYL)-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLINE-3-YL)-2-OXO-CYCLOHEX-3-ENE-1-CARBOXY-LATE



Internal reference: TMS; Solvent: $CDCl_3$; Instrument: BRUKER spectrometer(300 MHz)

Signal No.	Signal position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.24	1H	double doublet	$-CH_c$
2.	3.42	1H	double doublet	$-CH_d$
3.	3.80	1H	multiplate	$-CH_e$
4.	3.90	3H	singlet	$Ar-OCH_3$
5.	4.04	1H	doublet	$Ar-H_f$
6.	6.97	2H	doublet	$Ar-H_{a(p\text{-}sub.)}$
7.	7.1-7.5	4H	multiplet	Ar-H
8.	7.94	2H	doublet	$Ar-H_b$ (p-sub.)
9.	8.00	1H	singlet	-N-H


MASS SPECTRUM Data File: 3EDC29S
Sample: PM-VII DR H S JOSHI,RAJKOT #6576
RT 0'24" FAB(Pos.) GC 1.4c BP: m/z 137.0000 Int. 32.9442 Lv 0.00
Scan# (2 to 4)
28-DEC- 3 12:28
Relative Abundance
m/z
*2.0
m/z : 469

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-CHLORO-3-(4-ARYL-3-OXO-3,3a,4,5-TETRAHYDRO-2H-INDAZOL-6-YL)-CINNOLIN-4(3H)-ONE

(A) Synthesis of 6-Chloro-3-[(2E)-3-aryl-prop-2-oyl]cinnolin-4(3H)-one

See Part-I, Section-I (A)

(B) Synthesis of Ethyl-6-aryl-4-(6-chloro-4-oxo-3,4-dyhydro cinnolin-3-yl)-2-oxo-cyclohex-3-ene-1-carboxylate

See Part-VI, Section-I (B)

(C) Synthesis of 6-Chloro-3-[4-(4-methoxy phenyl)-3-oxo-3,3a,4,5-tetrahydro-2H-indazol-6-yl]-cinnolin-4(3H)-one

A mixture of Ethyl-6-(4-methoxyphenyl)-4-(6-chloro-4-oxo-3,4-dyhydro cinnolin-3-yl)-2-oxo-cyclohex-3-ene-1-carboxylate (gm, 0.01 mol) and hydrazine hydrate (0.05 gm, 0.01 mol) were refluxed in ethanol (50 ml) containing 1-3 ml gl. acetic acid, on a water bath for 5 hr. The residue obtains after cooling was filtered and crystallized from methanol. Yield 43%, m. p. 159^{0}C; Anal. Calcd. for $C_{22}H_{17}ClN_4O_3$: C, 62.79; H, 4.07; N, 13.31%, found: C, 62.77; H, 4.04; N, 13.30%.

Similarly other 6-chloro-3-(4-aryl-3-oxo-3,3a,4,5-tetrahydro- 2H-indazol-6-yl) -cinnolin-4(3H)-ones were prepared. The physical data are recorded in Table No. 9.

(D) Boiological evaluation of 6-Chloro-3-(4-aryl-3-oxo-3,3a,4,5-tetrahydro-2H-indazol-6-yl) -cinnolin-4(3H)-ones

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

TABLE-9: PHYSICAL CONSTANTS OF 6-CHLORO-3-(4-ARYL-3-OXO-3,3a,4,5-TETRAHYDRO-2H-INDAZOL-6-YL)-CINNOLIN-4(3H)-ONE

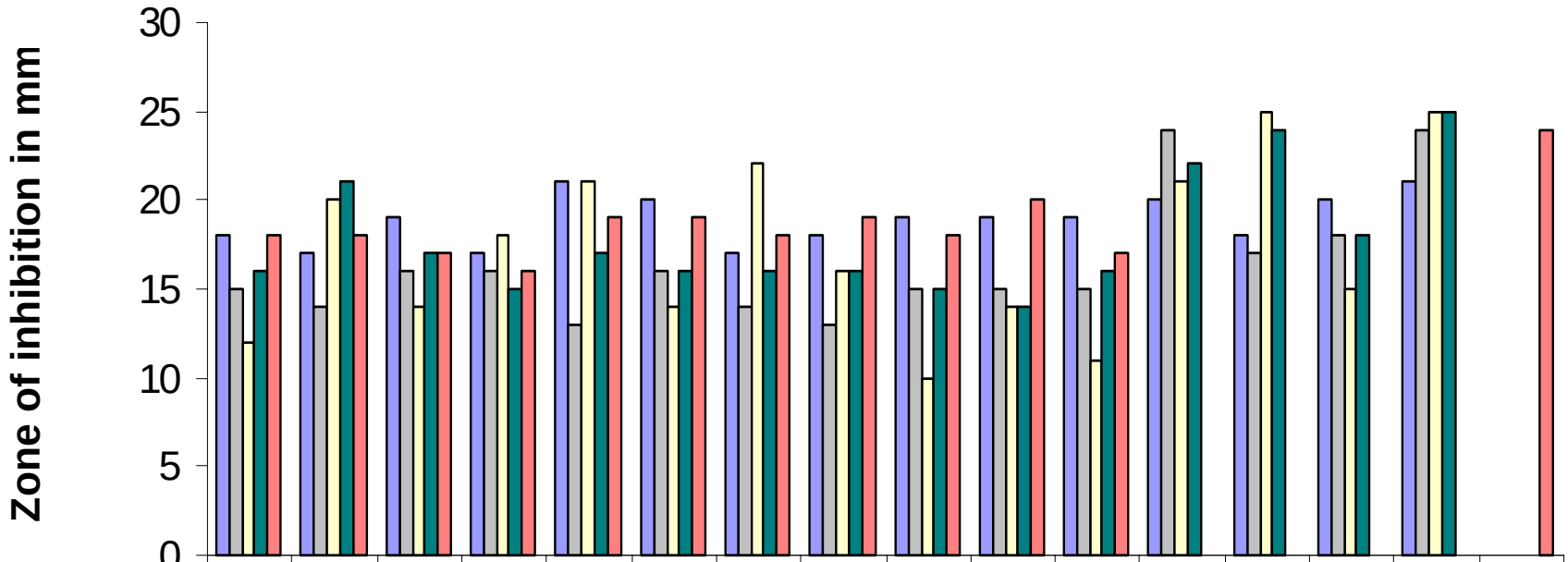
Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^0C	R_f Value	Solvent System	Yield %	% of Nitrogen Calcd	% of Nitrogen Found
1	2	3	4	5	6	7	8	9	10
9a	C_6H_5-	$C_{21}H_{15}ClN_4O_2$	390.82	210	0.48	S_1	45	14.34	14.33
9b	3-Br-C_6H_4-	$C_{21}H_{14}BrClN_4O_2$	469.72	198	0.54	S_1	43	11.93	11.90
9c	2-Cl-C_6H_4-	$C_{21}H_{14}Cl_2N_4O_2$	425.27	220	0.38	S_1	48	13.17	13.15
9d	3-Cl-C_6H_4-	$C_{21}H_{14}Cl_2N_4O_2$	425.27	174	0.36	S_2	46	13.17	13.14
9e	4-Cl-C_6H_4-	$C_{21}H_{14}Cl_2N_4O_2$	425.27	170	0.49	S_3	45	13.17	13.15
9f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{23}H_{19}ClN_4O_4$	450.87	178	0.55	S_2	42	12.43	12.44
9g	4-OCH_3-C_6H_4-	$C_{22}H_{17}ClN_4O_3$	420.85	159	0.54	S_1	43	13.31	13.30
9h	4-SCH_3-C_6H_4-	$C_{22}H_{17}ClN_4O_2S$	436.92	204	0.41	S_1	45	12.82	12.81
9i	3-C_6H_5-O-C_6H_4-	$C_{27}H_{19}ClN_4O_3$	482.92	181	0.59	S_3	42	11.60	11.59
9j	4-$N(CH_3)_2$-C_6H_4-	$C_{23}H_{20}ClN_5O_2$	433.89	194	0.51	S_3	49	16.14	16.13
9k	C9H6ClN	$C_{24}H_{15}Cl_2N_5O_2$	476.31	226	0.61	S_2	53	14.22	14.20

S_1 = Ethyl acetate : Hexane (1.4:8.6)

S_2 = Ethyl acetate : Hexane (3:7)

S_3 = Ethyla acetate : Hexane (2.5:7.5)

Graphical Chart No. 9 : Antimicrobial activity of 6-Chloro-3-(4-aryl-3-oxo-3,3a,4,5-tetrahydro-2H-indazol-6-yl)-cinnolin-4(3H)-one



	9a	9b	9c	9d	9e	9f	9g	9h	9i	9j	9k	Ampicillin	Norfloxacin	Benzylpenicillin	Amoxicillin	Griseofulvin
B.mega	18	17	19	17	21	20	17	18	19	19	19	20	18	20	21	
B.substilis	15	14	16	16	13	16	14	13	15	15	15	24	17	18	24	
P.vulgaris	12	20	14	18	21	14	22	16	10	14	11	21	25	15	25	
E.coli	16	21	17	15	17	16	16	16	15	14	16	22	24	18	25	
A.niger	18	18	17	16	19	19	18	19	18	20	17					24

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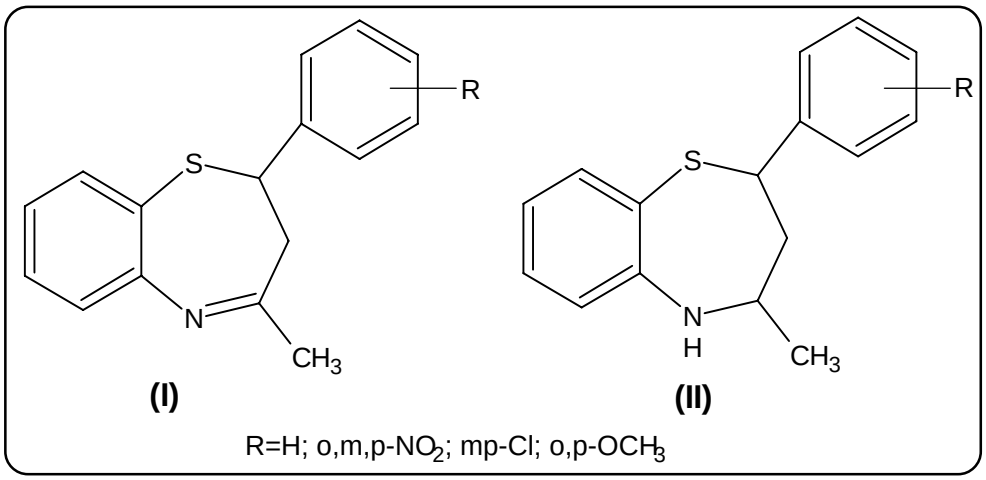
INTRODUCTION

Large number of derivatives of benzothiazepines have been found to exhibit a wide variety of biological activity. Many pharmacological compositions of benzothiazepines have been patented[1-4] and some of the popularly used drugs are Thiazesim, Diltiazem[5] and Clentienzem[6] etc.

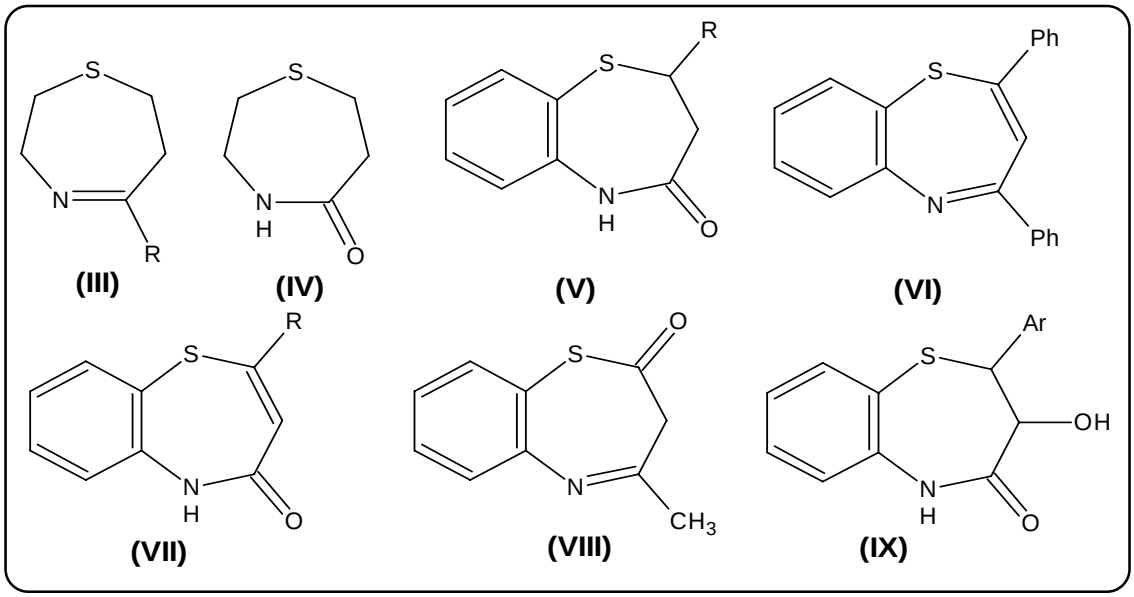
SYNTHETIC ASPECT

On account of their main fold implications, a plethora of 1,5-benzothiazepines have been synthesized and numerous strategies worked upon for the purpose. Reactions of 2-amino thiophenol with chalcones seems to be the most explored route for the synthesis of benzothiazepines.

Yang et al.[7] have reported cyclocondensation of $RC_6H_4CH{:}CHCOMe$ with 2-amino thiophenol to accomplish dihydrobenzothiazepines(I) which were reduced by $NaBH_4$ to tetrahydro benzothiazepines(II).

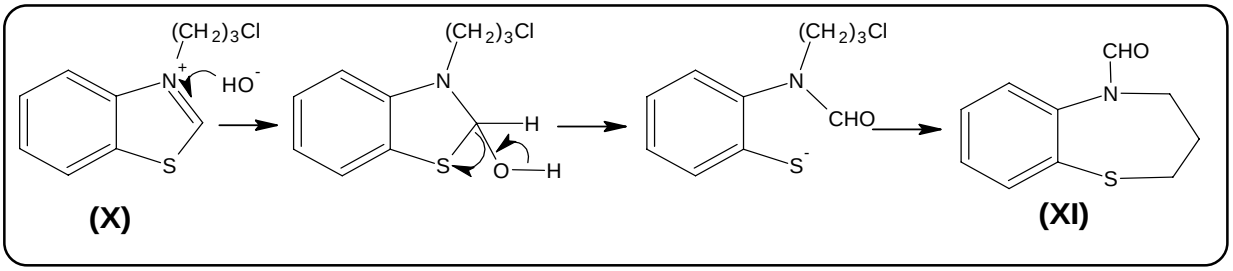


2-Amino thiophenol can be reacted with 1,3-biscarbon electrophiles to give variouss types of 1,5-benzothiazepine. Thus the benzo analogus of (III) and (IV), e.g., (V), are prepared by parallel routes, reaction with 1,3-diphenyl propynone gives (VI), reaction with β-ketoesters gives products of type (VII), reaction with diketene gives (VIII), and the reaction with methyl-3-arylglycidates gaves (IX) which could not be dehydrated.

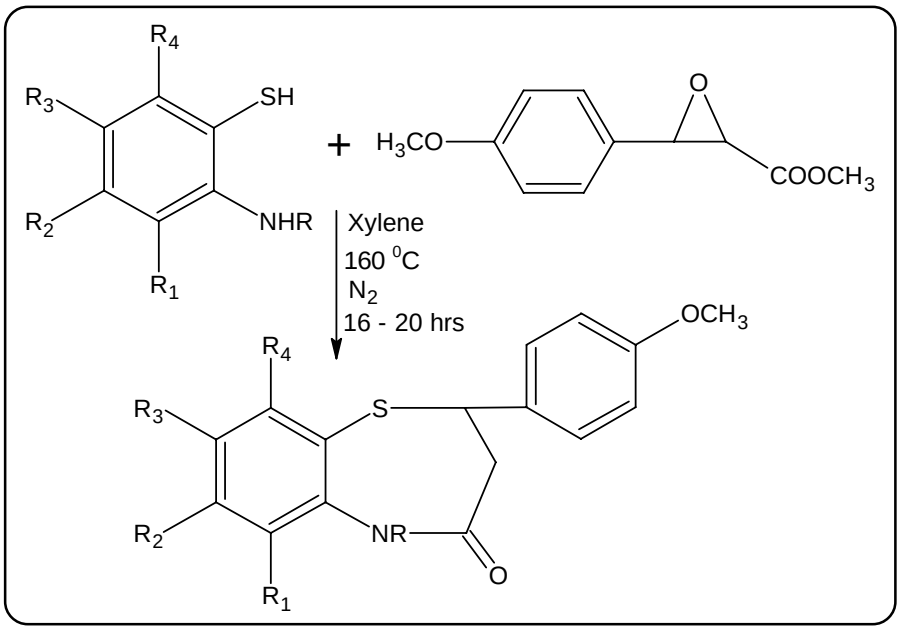


As with 1,4-oxazepines the Schmidt reaction of cyclic ketones and the Beckmann rearrangement of their oximes can be applied to the synthesis of monocyclic 1,4-thiazepines, 1,4- and 1,5-benzothiazepines and their 1-oxides and 1,1-dioxides[8].

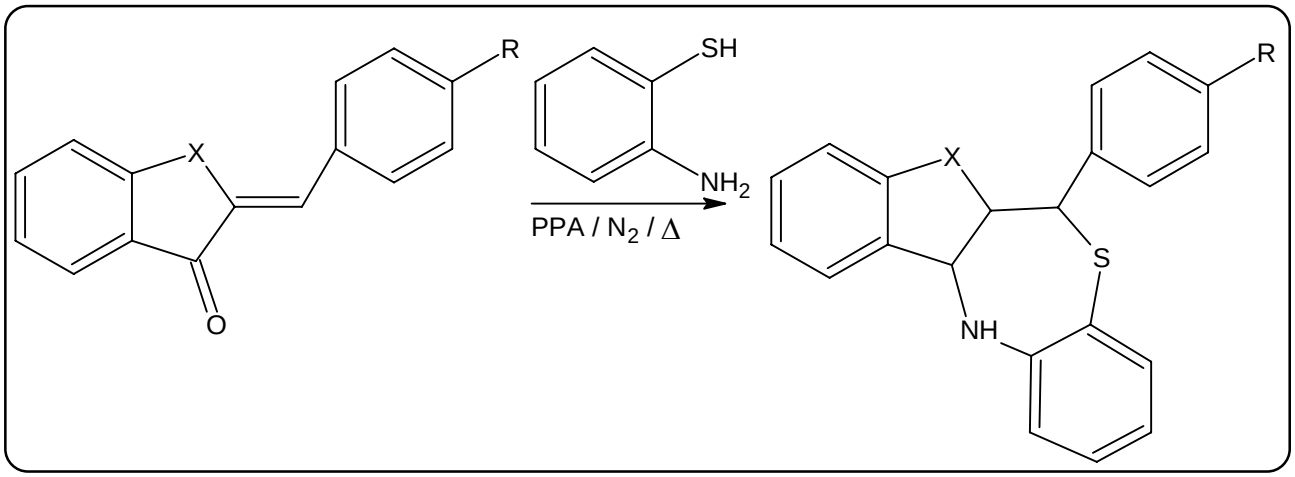
Thioxanthen-9-one, 10,10-dixides, on treatment with sodamide in liquid ammonia, undergo a novel ring expansion to give dibenzo[b,f][1,4]-thazepine-11-one-5,5-dioxides[9]. The thiazolium salt (X) undergoes base-induced ring expansion to give (XI)[10], a direct parallel of the conversion of analogues oxazolium salts to 1,4-benzoxazepines.



Moreover, A. K. Sharma and co-workers[11] have find out new method for the preparation of new 1,5-benzothiazepine, they prepared (+) cis-2-(4-methoxyphenyl)-3-hydroxy/methoxy-2,3-dihydro-1,5-benzothiazepine-4[5H/5-chloroacetyl/5-(4'-methylpiperazino-1')-acetyl]-ones by the condensation of 2-amino benzene thiols with methyl (+) trans-3-(4-methoxy phenyl)glycidate in xylene.

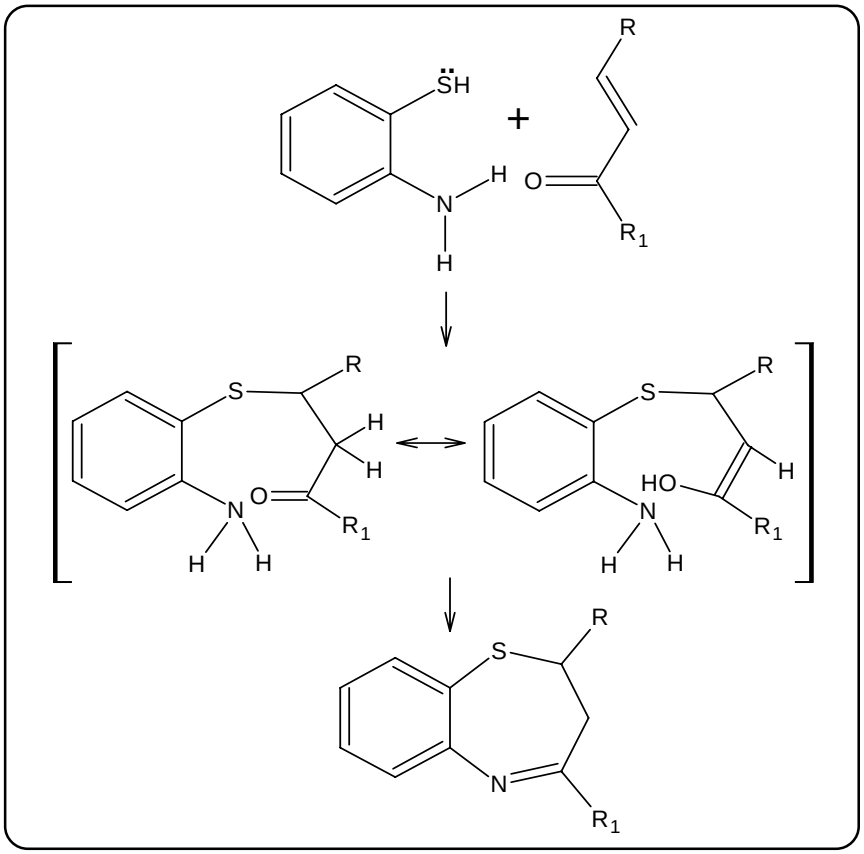


Recently, M.Wichers and K. Gorlitzer[12] synthesize the 6,12-dihydro benzofuro[2,3-c][1,5]-benzothiazepines by heating (Z)-2-benzylidene-3(2H)-benzofuranonesand (Z)-2-benzylidene benzo[b]thiophene-3(2H)-ones in polyphosphoric acid under nitrogen.



REACTION MECHANISM

Mechanism of reaction of chalcones with 2-aminothiophenol can be visualized as formulated below.



The reactions of 2-amino benzene thiols with the chalcone is initially a nucleophilic addition[13] to give a type of Michael adduct which is formed by the attack of the lone pair of sulphydryl electrons over the β-carbon of chalcone to give a ketoamine. The latter tautomerizes to the enolic form which on dehydrative cyclization results in the formation of the final product.

THERAPEUTIC INTEREST

The importance of the 1,5-benzothiazepine nucleus has large number of patents as chemotherapeutic agents, available on it. A number of biological activities have been associated with it, such as.

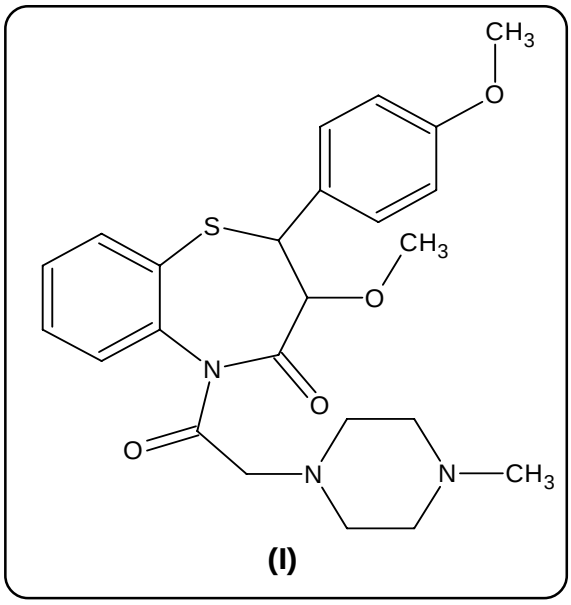
1. Antihypertensive[14,15],
2. Antiasthemic[15,16],
3. Analgesic[17],
4. Cardiovascular[18],
5. Platelate aggregation inhibitor[15],
6. Anticancer[19],
7. Anticonvulsant[20],
8. Antidepressant[21],
9. Coronary vasodilation[22],
10. Anti-HIV[23],
11. Antibacterial[24]

1,5-Benzothiazepine class of compounds have given calcium channel blockers of proven utility such as Diltiazem and those in which fused benzene ring is substituted at various positions have been found to have enhanced pharmacological properties.

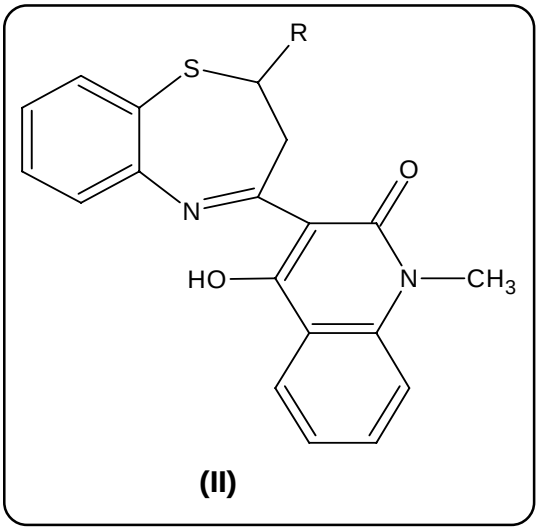
Moreover, A. K. Sharma[25] and other co-workers synthesize new derivatives of 1,5-benzothiazepine (I) as analogus of anticancer drugs. Micheli F., et al.[26] led to combinatorial approach to [1,5]-benzothiazpine derivatives as potential antibacterial agents. Shetgiri N. P. et al.[27] also derived some new derivatives of benzothiazepine as antimicrobial activities.

2,5-Disubstituted-3,4-dihydro-2H-benzo[b][1,4]thiazepine featured as potent and selective V(2) arginine vasopressin receptor antagonists by Urbanski M. J. and et al.[28]. Sucheta K. and et al.[29] synthesize some new 1,5-benzothiazepines containing 2H(1)-quinolin-2-one (II) and studied their pharmacological properties. Kurokawa J.

et al.[30] check the effects of a novel, potent benzothiazepine as Ca2+channel antagonist, DTZ-323 on guinea-pig ventricular myocytes.

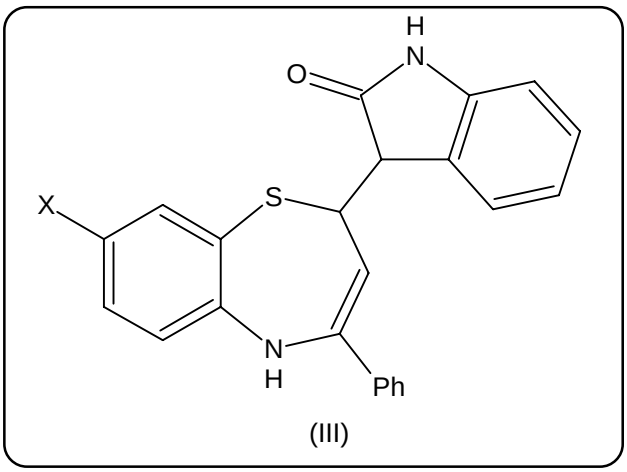


(I)



(II)

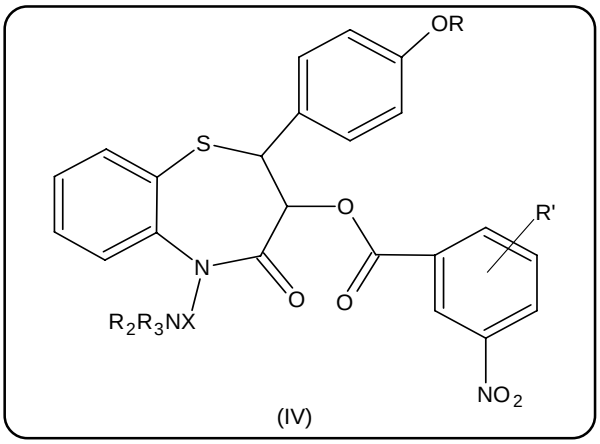
Furthermore, Dandia Anshu and et al.[31] prepared 8-substituted-2,5-dihydro-1,5-benzothiazepine-2-spiro-3'-3H-indol-2'(1H)-ones (III) by microwave irradiation and check their antifungal and antitubercular activities. Meiji, Seika[32] reported 1,5-benzothiazepine as pesticides. Press, Jeffery B. et al.[33] prepared 2-phenyl-3,4-dihydro-2H- and 3,4,5,6-tetrahydro-2H-1,5-benzothiazepine and investigated the prepared derivatives as centrl nervous systems activity.



(III)

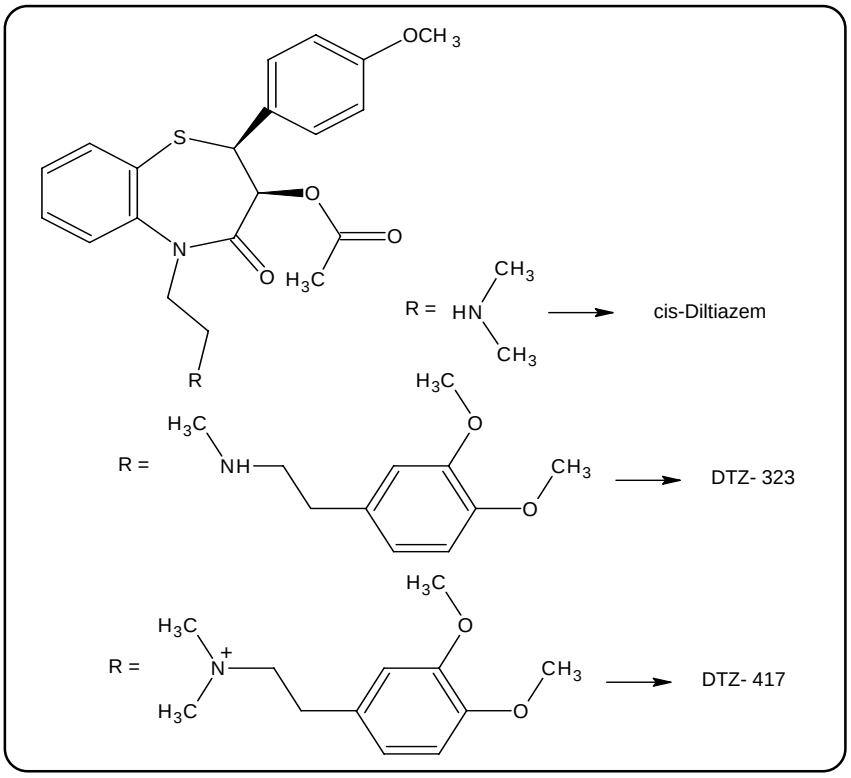
Sanwa, Kagaku Kenkyusho[34] prepared 1-phenyl-2,5-benzothiazepine derivatives which showed weaker analgesic activity. Ohishi, Tokuro and et al.[35] derived new

benzothiazepine derivatives (IV) which was useful as vasodilators, antithrombotics and calmodilin inhibitors. Slade, Joel and co-workers[36] synthesize hetero-benzothiazepine derivatives which at 10mg/kg orally in rat lowered blood pressure by ~35mm Hg.



(IV)

Some benzothiazepine derivatives are used as a drugs such as (2R,3R)-5-[2-(dimethylamino)ethyl]-2(4-methoxyphenyl)-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepin-3-ylacetate (V), known as ***cis-Diltiazem*** and used as calcium channel blockers.



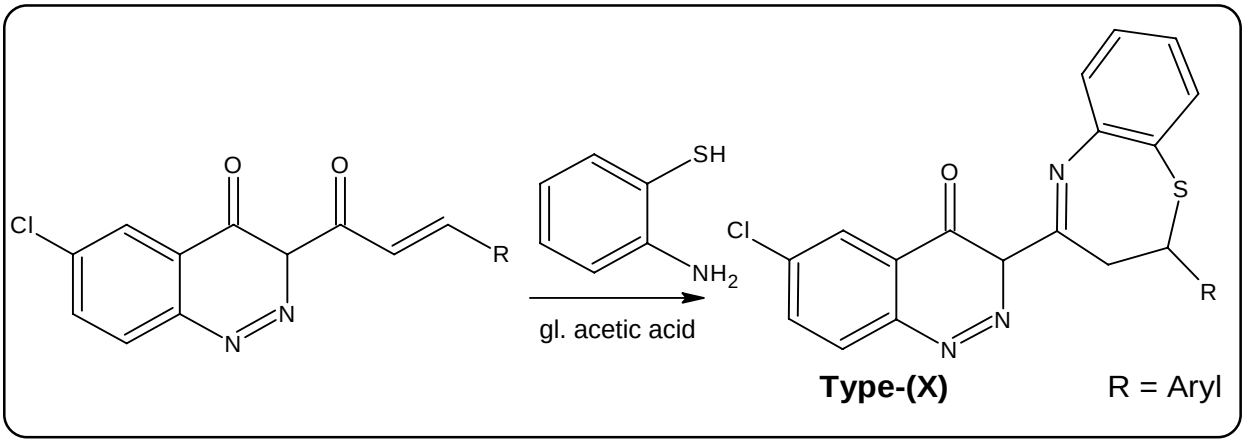
With this in mind, some new 1,5-benzothiazepine derivatives have been synthesized in search of better therapeutic agents, by a convenient single pot method, which is described as under.

SECTION-I : Synthesis and biological screening of 6-Chloro-3-(2-aryl-2,3-dihydro-1,5-benzothiazepine-4-yl)cinnolin-4(3H)-ones

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-CHLORO-3-(2-ARYL-2,3-DIHYDRO-1,5-BENZOTHIAZEPINE-4-YL)CINNOLIN-4(3H)-ONES.

Various types of benzothiazepine derivatives shows wide range of biological activity such as anticancer, antifungal, antimicrobial, antitubercular, antidiabetic etc. With a view to get better therapeutic agents, we have synthesized different types of benzothizepine derivatives of Type-(X) have been prepared by condensation of chalcones of Type-(I) and 2-amino thiophenol in presence of piperidine, which have been described as under.

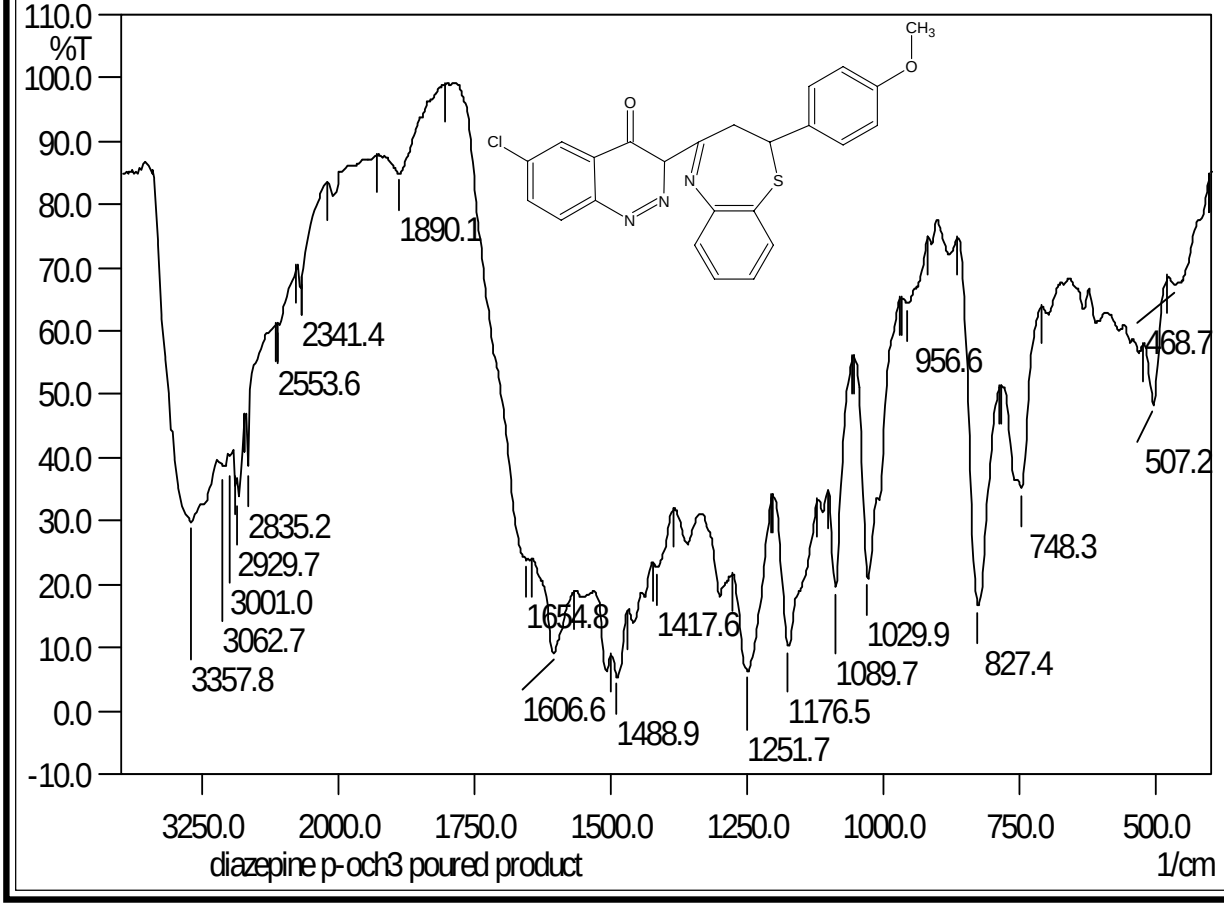


Type-(X) R = Aryl

The structure elucidation of synthesized compounds have been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

All the compounds have been evaluated 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 synthesized compounds were compared with standard drugs.

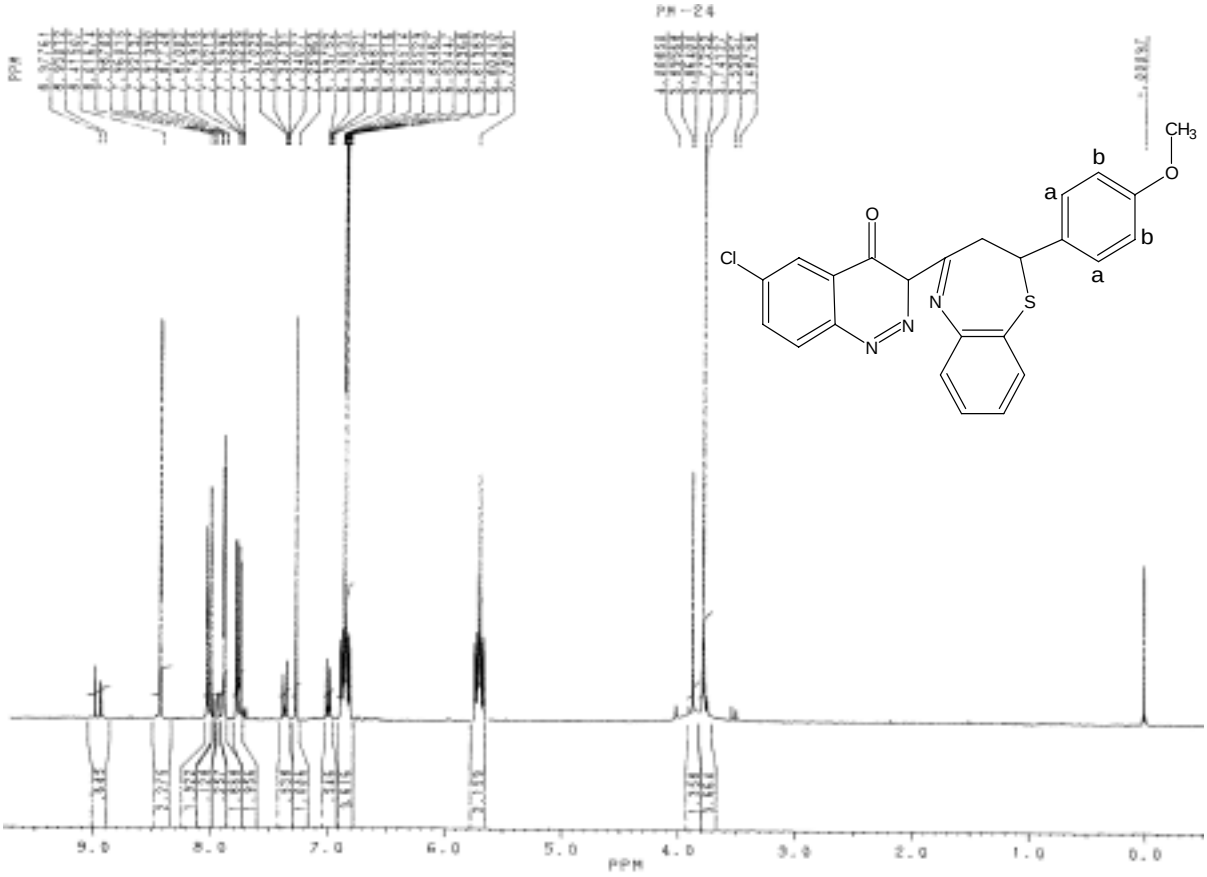
IR SPECTRAL STUDY OF 6-CHLORO-3-(2-(4-METHOXY PHEBYL)-2,3-DIHYDRO-1,5-BENZOTHIAZEPINE-4-YL)CINNOLIN-4(3H)-ONE



Frequency range: 4000-400cm^{-1} (KBr disc) Instrument : Shimadzu-8400 FTIR

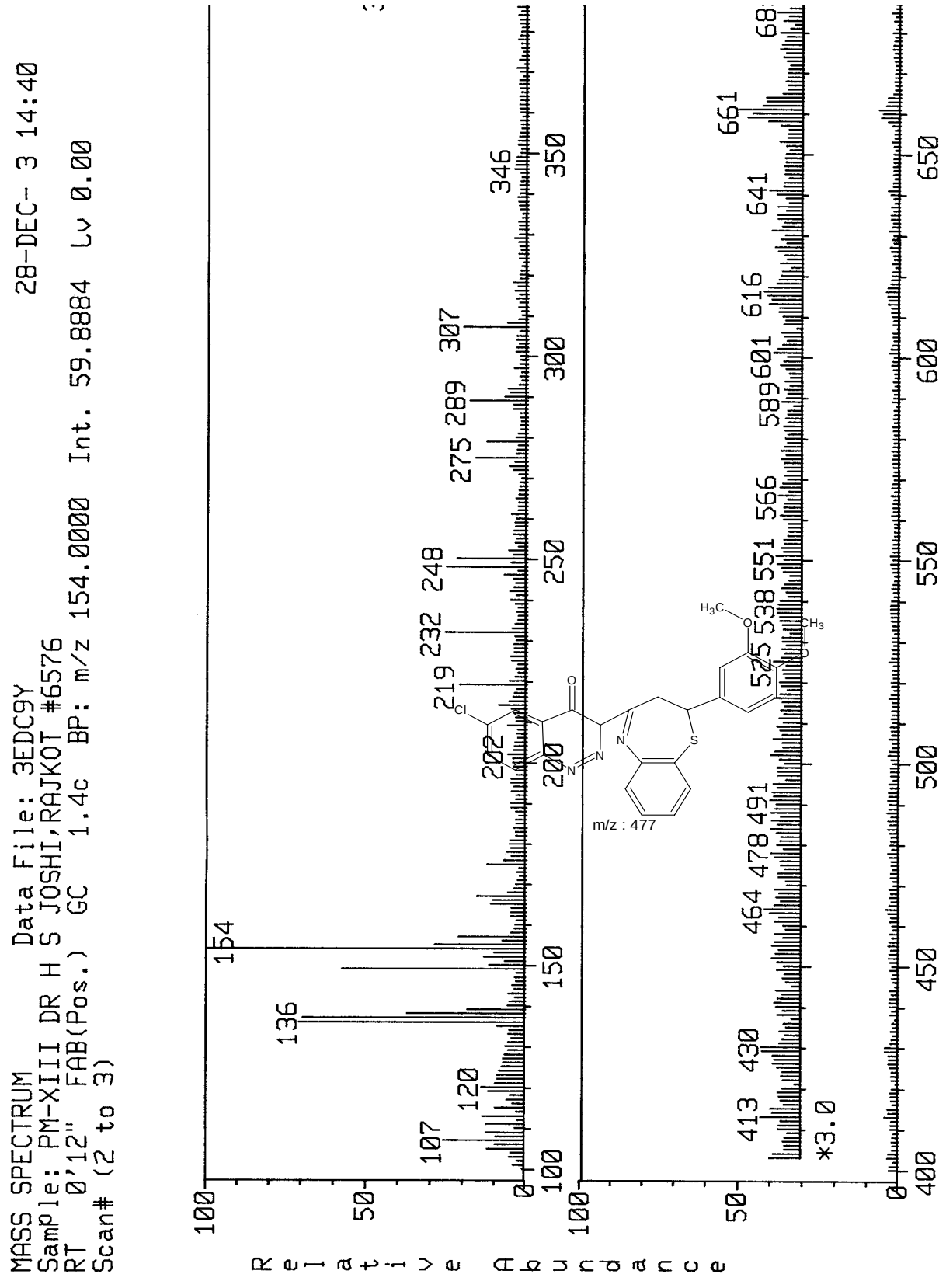
Type	Vibration mode	Frequency in cm^{-1} Observed	Reported	References
Alkane	C-H str. (asym.)	2927	2975-2950	37
-CH_3	C-H str. (sym.)	2854	2880-2860	"
	C-H def. (asym.)	1460	1470-1435	"
	C-H def. (sym.)	1352	1385-1370	"
Aromatic	C-H str.	3033	3080-3030	38
	C=C str.	1548	1620-1430	"
	C-H i.p. def	1238	1269-1013	"
	C-H o.o.p. def.	869	833-660	"
Ether	C-O-C str.	1238	1275-1200	37
Carbonyl	C=O	1661	1690-1665	"
Halide	C-Cl str.	740	750-700	"

PMR SPECTRAL STUDIES OF 6-CHLORO-3-(2-(4-METHOXY PHEBYL)-2,3-DIHYDRO-1,5-BENZOTHIAZEPINE-4-YL)CINNOLIN-4(3H)-ONE



Internal reference: TMS; Solvent: $CDCl_3$; Instrument: BRUKER spectrometer(300 MHz)

Signal No.	Signal position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.77	3H	singlet	Ar-OCH_3
2.	5.78	1H	multiplate	Ar-CH_2
3.	6.81	3H	multiplate	Ar-H (cinnoline ring)
4.	7.25	1H	singlet	Ar-H
5.	7.73	2H	doublet	Ar-H_a(p-sub.)
6.	7.87	1H	doublet	Ar-H
7.	7.96	2H	double	Ar-H_b (p-sub.)
8.	8.41	1H	singlet	Ar-NH


MASS SPECTRUM Data File: 3EDC9Y
Sample: PM-XIII DR H S JOSHI,RAJKOT #6576
RT 0'12" FAB(Pos.) GC 1.4c BP: m/z 154.0000 Int. 59.8884 Lv 0.00
Scan# (2 to 3)
28-DEC- 3 14:40
Relative Abundance
m/z : 477
*3.0

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-CHLORO-3-(2-ARYL-2,3-DIHYDRO-1,5-BENZOTHIAZEPINE-4-YL)CINNOLIN-4(3H)-ONES.

(A) Synthesis of 6-Chloro-3-[(2E)-3-aryl-prop-2-enoyl]cinnolin-4(3H)-one.

See Part-I, Section-I(C)

(B) Synthesis of 6-Chloro-3-[2-(4-mehtoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4-yl]cinnolin-4(3H)-one.

A mixture of 6-chloro-3-[(2E)-3-(4-methoxyphenyl)-prop-2-enoyl]cinnolin-4(3H)-one (3.4 gm, 0.01 mol), 2-amino thiophenol (0.68 gm, 0.01 mol) in ethanol containing gl. acetic acid was refluxed on oil bath for 4 hr. The reaction mixture was cooled and poured onto crushed ice. The product was isolated and crystallized from toluene. Yield 55 %, m.p. 117 ^{0}C. Anal. Calcd. for $C_{24}H_{18}ClN_3O_2S$Requires: C, 64.35; H, 3.42; N, 9.38 % found: C, 64.10; H, 3.40, N, 9.36 %.

Similarly, other 6-chloro-3-(2-aryl-2,3-dihydro-1,5-benzothiazepin-4-yl)cinnolin-4(3H)-one. The physical data are recorded in Table No. 10.

(C) Biological screening of 6-Chloro-3-[2-aryl-2,3-dihydro-1,5-benzothiazepin-4-yl]cinnolin-4(3H)-one.

Antimicrobial testing were carried out as described in Part-I, Section-I(D). The zones of inhibition of test solution are reported in Graphical Chart No. 10.

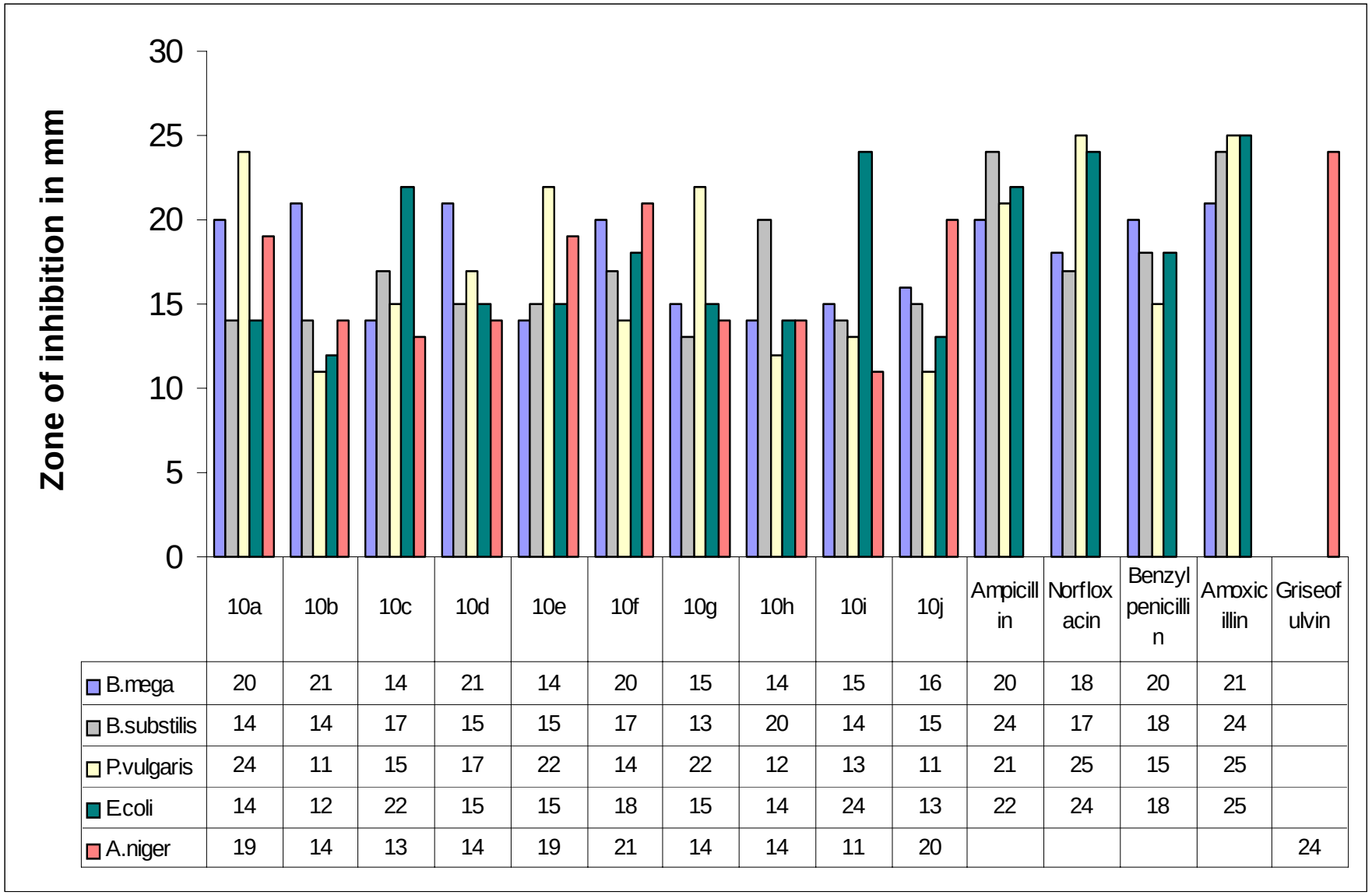
TABLE-10: PHYSICAL CONSTANTS OF 6-CHLORO-3-(2-ARYL-2,3-DIHYDRO-1,5-BENZOTHIAZEPIN-4-YL)-CIN(3H)-ONE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^0C	R_f Value	Solvent System	Yield %	% of Nitrogen Calcd	% of Nitrogen Found
1	2	3	4	5	6	7	8	9	10
10a	C_6H_5-	$C_{23}H_{16}ClN_3OS$	417.91	109	0.590	S_1	65	10.05	10.04
10b	3-Br-C_6H_4-	$C_{23}H_{15}BrClN_3OS$	496.81	140	0.546	S_2	66	8.46	8.44
10c	2-Cl-C_6H_4-	$C_{23}H_{15}Cl_2N_3OS$	452.36	130	0.482	S_1	59	9.29	9.25
10d	3-Cl-C_6H_4-	$C_{23}H_{15}Cl_2N_3OS$	452.36	125	0.637	S_1	52	9.29	9.24
10e	4-Cl-C_6H_4-	$C_{23}H_{15}Cl_2N_3OS$	452.36	125	0.593	S_1	54	9.29	9.26
10f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{25}H_{20}ClN_3O_3S$	477.96	115	0.545	S_2	57	8.79	8.75
10g	4-OCH_3-C_6H_4-	$C_{24}H_{18}ClN_3O_2S$	447.94	117	0.470	S_2	55	9.38	9.36
10h	4-SCH_3-C_6H_4-	$C_{24}H_{18}ClN_3OS_2$	464.00	110	0.567	S_1	53	9.06	9.04
10i	3-C_6H_5-O-C_6H_4-	$C_{29}H_{20}ClN_3O_2S$	510.01	100	0.518	S_1	64	8.24	8.21
10j	4-$N(CH_3)_2$-C_6H_4-	$C_{25}H_{21}ClN_4OS$	460.98	95	0.488	S_2	65	12.15	12.13

S_1 = Ethyl acetate : Hexane (1.5 : 8.5)

S_2 = Ethyl acetate : Hexane (2.4 : 7.6)

Graphical Chart No. 10 : Antimicrobial activity of 6-Chloro-3-(2-aryl-2,3-dihydro-1,5-benzothiazepine-4-yl)-cinnolin-4(3H)-one



	10a	10b	10c	10d	10e	10f	10g	10h	10i	10j	Ampicillin	Norfloxacin	Benzylpenicillin	Amoxicillin	Griseofulvin
B.mega	20	21	14	21	14	20	15	14	15	16	20	18	20	21	
B.substilis	14	14	17	15	15	17	13	20	14	15	24	17	18	24	
P.vulgaris	24	11	15	17	22	14	22	12	13	11	21	25	15	25	
E.coli	14	12	22	15	15	18	15	14	24	13	22	24	18	25	
A.niger	19	14	13	14	19	21	14	14	11	20					24

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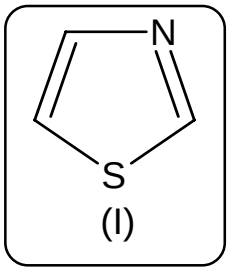
INTRODUCTION

Thiazole may be considered to be derived from benzene by replacing a CH group with a nitrogen atom and a CH=CH group, at position 3 and 4 of the corresponding pyridine with a sulfur atom. The chemistry of thiazole therefore shows similarities to those of pyridine and thiophene. Hence the thiazole ring (I) was first described by Hantzch and Weber[1] in 1987 as "the pyridine of the thiophene series".



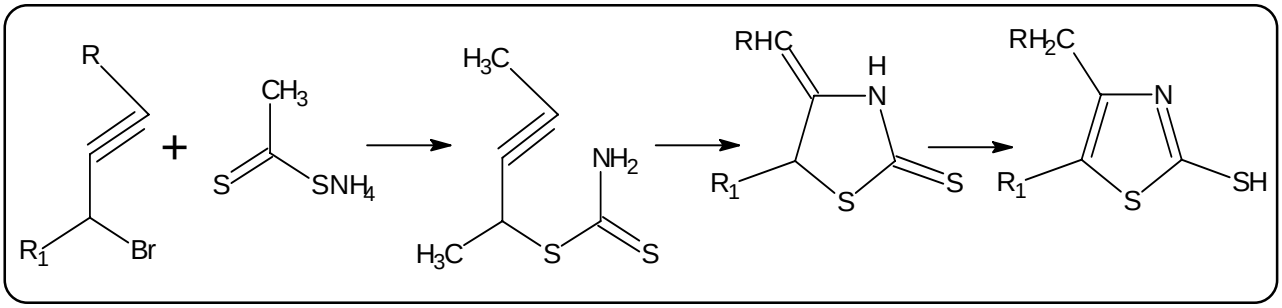
(I)

The groups of compound containing the thiazole moiety are a prominent structural feature in a variety of natural products, like Vitamin B, and penicillin as well as in other compounds of medicinal interest and have attracted attention for their biological activities. They constitute the skeleton of antibiotics such as Althomyccin[2] and Micrococcin[3] as do many metabolites of living organisms. Even first synthetic drug bearing thiazole moiety i. e., "***Sulphathiazole***" derived from 2-amino thiazole has many applications in pharmacology due to its bacteriostatic effect.

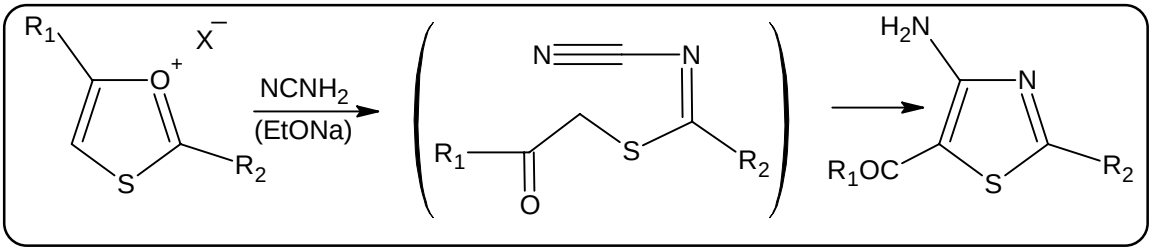
SYNTHETIC ASPECT

The thiazole ring was first described in 1987 by Hantzch, the cyclisation of α-halo carbonyl compounds by a great variety of reactants bearing the N-C-S fragment of the ring is still the most widely used method of synthesis of thiazoles.

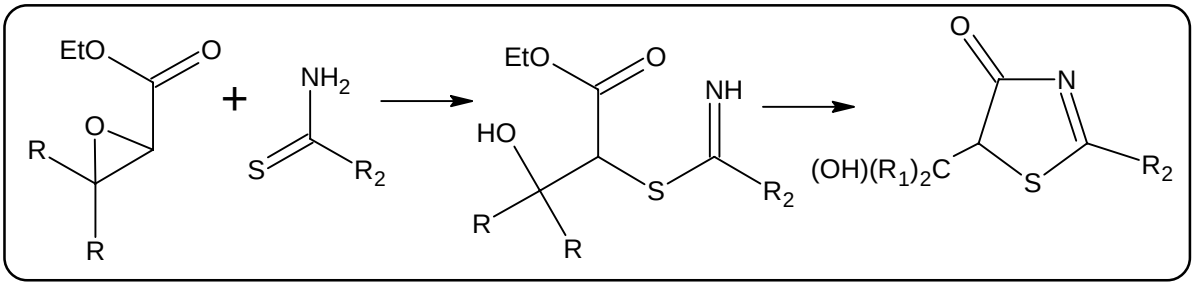
1. α-Bromo alkynes also give 2-mercaptothiazoles by condensation with ammonium dithiocarbamate in alcohol solution.



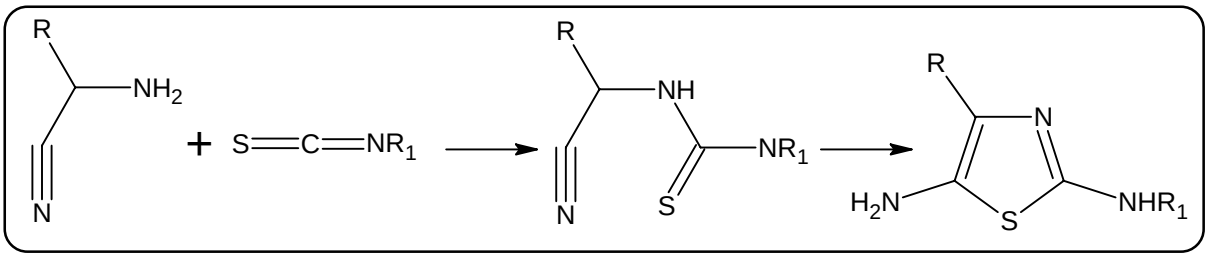
2. 1,3-Oxathiolylium salts condense with cyanamide in the presence of sodium ethoxide to give an open chain intermediate, which cyclizes to substituted 4-aminothiazoles[4].



3. Thiourea and phenyldithiocarbamate react with glycidic esters to give Δ²-thiazolin-4-ones[5].

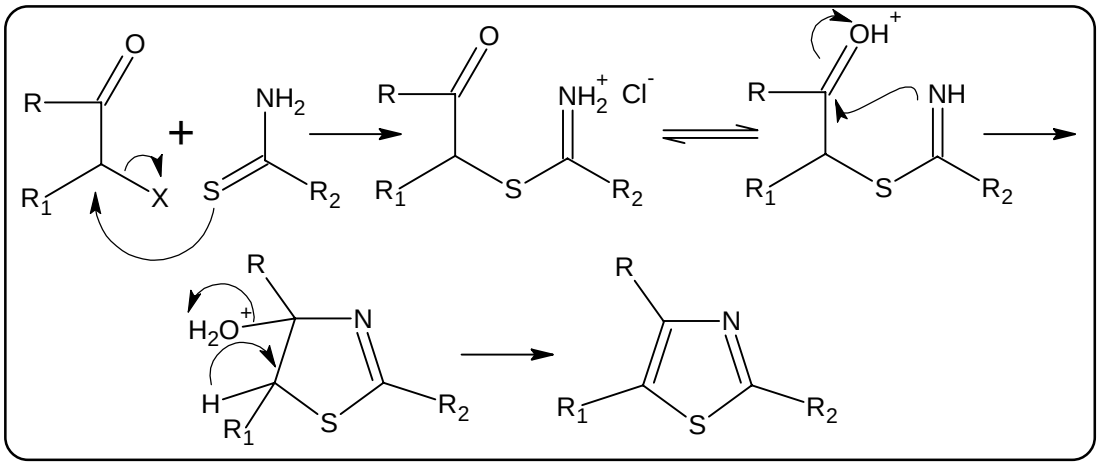


4. Isothiocyanate condense with α-aminonitriles affording 2-substituted-5-amino thiazoles through an acyclic intermediates. In some cases the 2,5-disubstituted amino thiazoles was isolated as a by product.



REACTION MECHANISM

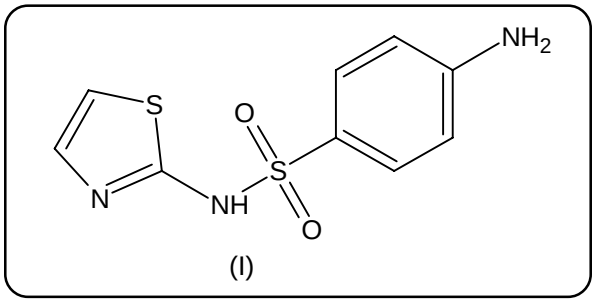
The mechanism of the Hantzch synthesis has been established and is shown in scheme. Substitution of the halogen atom of the α-haloketone by the sulfur atom of the thioamide occurs first to give an open chain a-thioketone, which under transprotonation proceeds to give a 4-hydroxy- Δ^2-thiazoline in aprotic solvents or a thiazole by acid catalyzed dehydration of the intermediate thiazolines in protic solvents.



THERAPEUTIC IMPORTANCE

2-Amino thiazole derivatives exhibit a variety of biological activities. One of the first synthetic drug bearing thiazole moiety as "***Sulphatiazole*** (I)", a simple sulphanomide antibiotic derived from 2-amino thiazole. It has bacteriostatic effects and other sulphadrugs derived from 2-amino thiazole. The succinyl sulphathiazole and

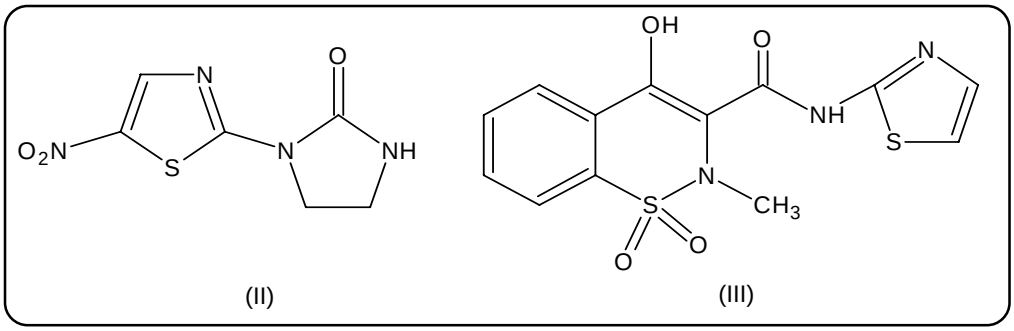
promizole, which are used in intestinal infections and for the treatment of leprosy respectively.



(I)

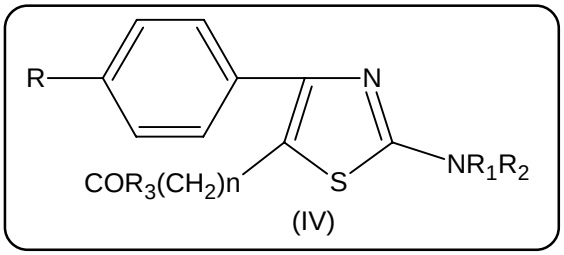
Aminitrozole i.e. 2-acetamido-5-nitrothiazole has been used for intestinal amobiasis in rats and dogs at well-tolerated doses[6]. From this conclusion it led to the synthesis of ***Niridazole***[7] [1-(5-nitro-2-thiazolyl)-2-imidazolidinone] (II), which showed the *in vitro* activity against *E.histolytica* at a concentration of 10 μg/ml. Many other activities were also exhibited such as antiamoebic and antischistosomal[8-10] by D. B. Capps and M. Avramoff.

Lombardino and wiseman have prepared sudoxucam (III), and reproted their potent antiinflammatory activity[11] at a concentration of 0.3 mg/kg doses.



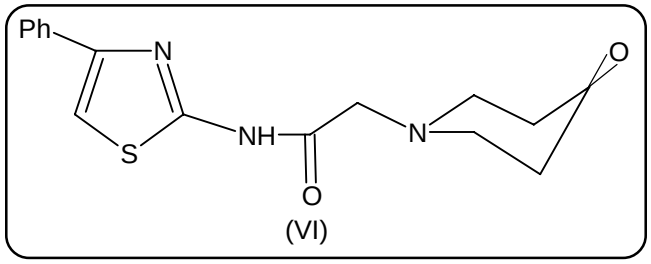
(II) (III)

2-Amino-4-aryl-5-thiazole carboxylic derivatives (IV) showed antiinflammatory, antipyretic, analgesic and antitumor activity[12] in mice at 560 mg/kg intraperitoneal (I. P.) and 200 mg/kg orally.



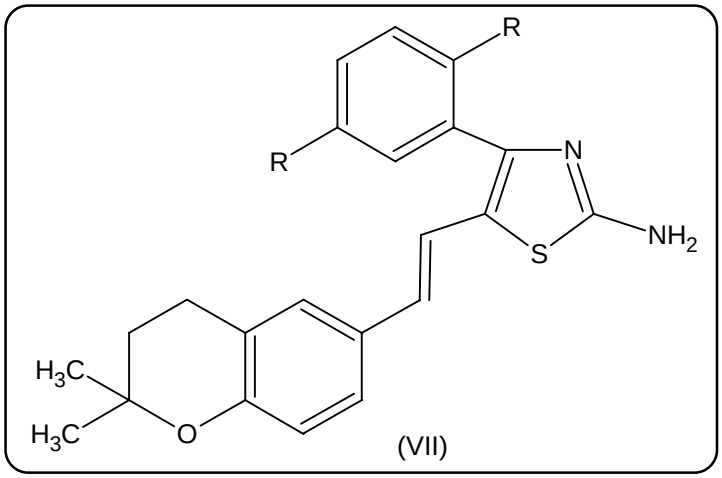
(IV)

N-Phenyl-N'-(2-thiazolyl)urea have displayed potential antiparkinson, anthelmintic and trichomodial activities[13,14]. Screening data of 4-(isoxazolyl)thiazol-2-oxamic acid derivatives revealed their antiarthritics, antiallergic and antianaphylactic activity[15,16]. P. N. Bhargava[17] have synthesized 2,6-diaryl-3-ethoxy carbonyl-4-piperidino acetyl-2'-amino-4'-phenyl thiazole (VI) as local anesthetic .



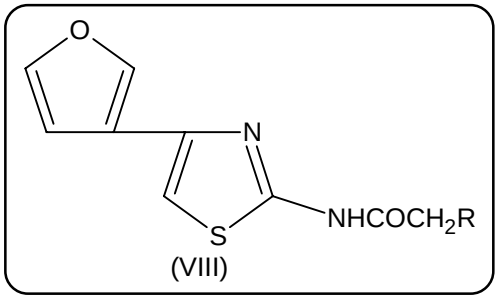
(VI)

Some new tetrahydropyrimidinyl substituted 2-amino thiazole derivatives showed *in vitro* activity against *Trichopyton mentagrophyts* and *Candida albicans*[18] at a concentration of 2-4 μg/ml. Hypoglycemic activity of 2-amino thiazole have been studied by Alfred et al.[19]. Kwang and co-workers[20] have prepared 2'-(2-amino ethyl)-2,4'-bithiazole-4-carboxylic acid which possess antitumor and antibiotic activity. Ahluwalia et al.[21] synthesized amino thiazole derivatives of type (VII) having antimicrobial activity against *S.aureus* and *E.coli* at 10-25 μg/ml.



(VII)

Saldabols and Medhe[22] have reported substituted amino thiazole derivatives (VIII) with furan ring at 4-position possessing bactericidal as well as virucidal activities.



(VIII)

Moreover compounds bearing thiazole moiety are reported to possess antiinflammatory[23,24], anticonvulsant[25], nematocide[26], antitubercular[27,28], antiviral[29], insecticidal[30], herbicidal[31,32], pesticidal[33], antifungal[34,35] and antibacterial[36,37] activities.

2-Substituted amino thiazole derivatives were prepared as antipsychotics agent by Rao[38], and N. Atsuo[39,40]. S. Masaru[41] and co workers have synthesized 2-amino-4,5-diphenyl derivatives and useful as inhibitors of blood platelet aggregation.

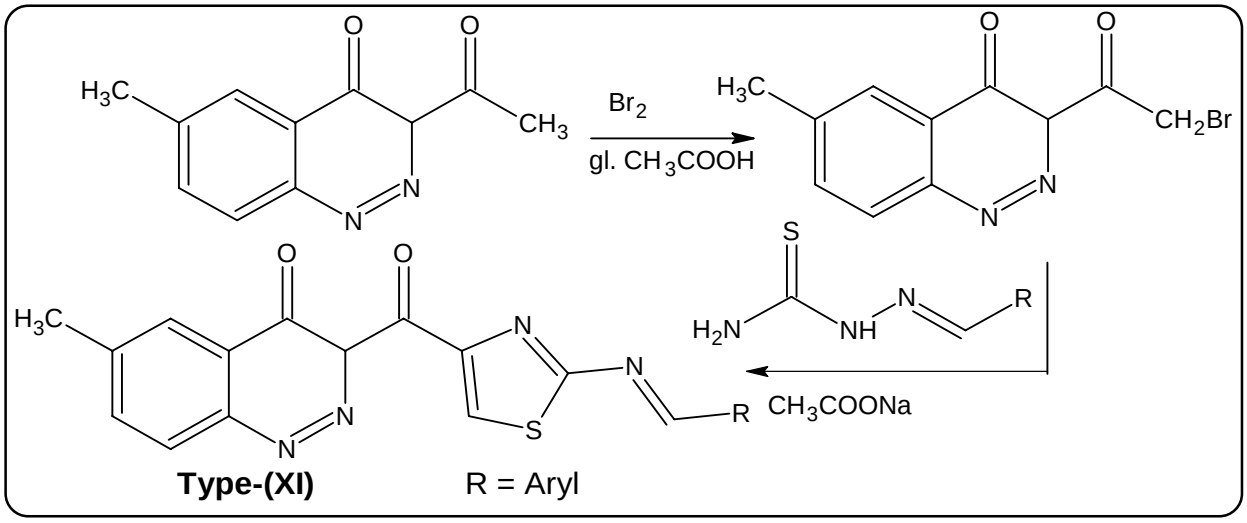
Very recently antiinflammatory activity[42] of substituted 2-amino-4-carboxy-5-thiazole acetic acid by Patil and co-workers have been described. Joshi et al.[43] have prepared 3'-(4-aryl-2-thiazolyl)-6'-aryl-imidazo(2,1-b)thiazole as apossible antibacterial agent. In vitro activity of some new and known members of cephalosporin antibiotics with amino thiazole moety are described by M. Valencie[44]. Thienyl thiazole derivatives as tested against Helicobacter phylori 8004[45] has a MIC of 0.2 μg/ml. Thus the important role displayed by thiazole moiety for various physiological activities prompted us to synthesized some thiazole derivatives bearing 6-chloro cinnolin-4(3H)-one moiety. This study is described in the following part.

SECTION-I: Synthesis and biological screening of (1E)-Aryl-[4-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-1,3-thiazol-2-yl]hydrazone

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF (1E)-ARYL-[4-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-1,3-THIAZOL-2-YL]HYDRAZONE.

Various types of thiazole derivatives shows wide range of biological activity such as anticancer, antifungal, antimicrobial, antitubercular, antidiabetic etc. With a view to get better therapeutic agents, we have synthesized different types of thiazole derivatives which have been described as under. Thiazole derivatives of Type-(XI) have been prepared by condensation of bromo acetyl cinnoline with different types of thiosemicarbazones, which was prepared by the condensation of aryl aldehyde and thiosemicarbazide.

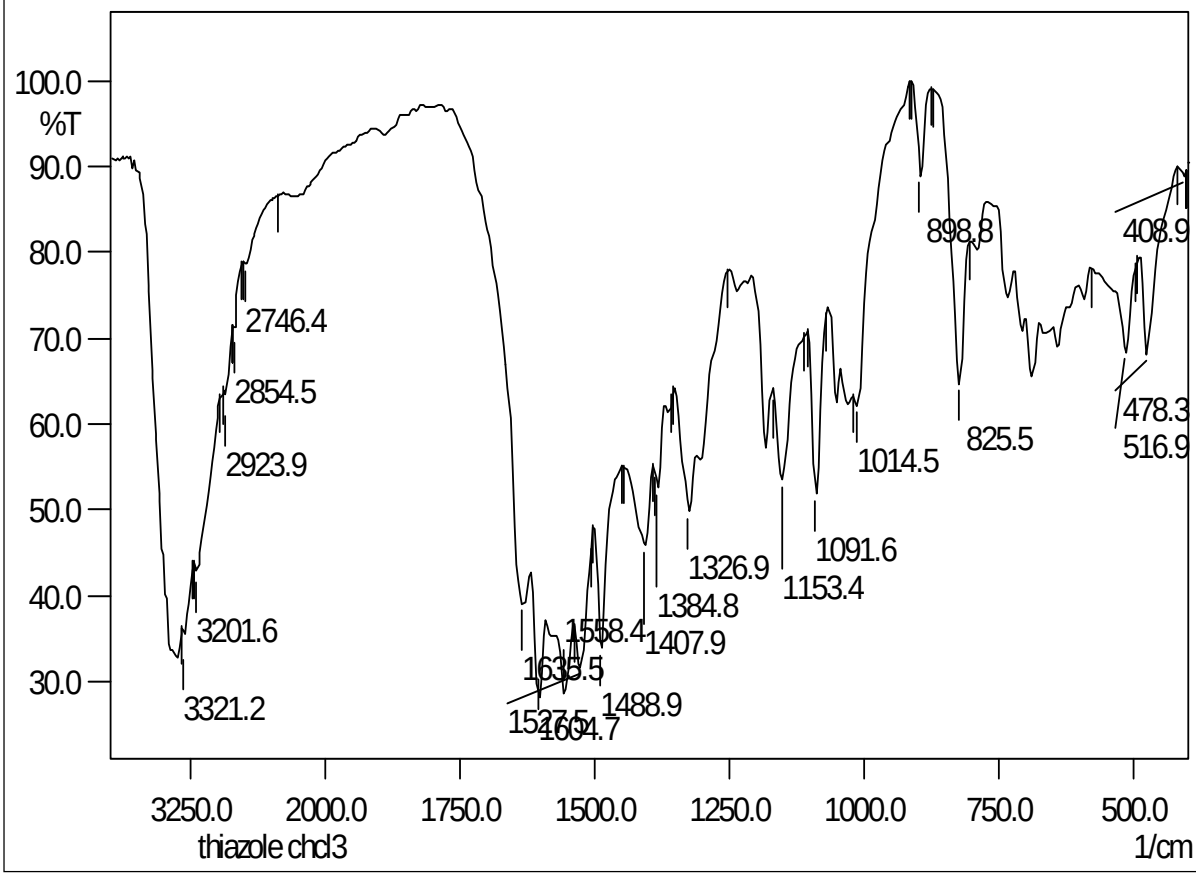


Type-(XI) R = Aryl

The structure elucidation of synthesized compounds have been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

All the compounds have been evaluated 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 synthesized compounds were compared with standard drugs.

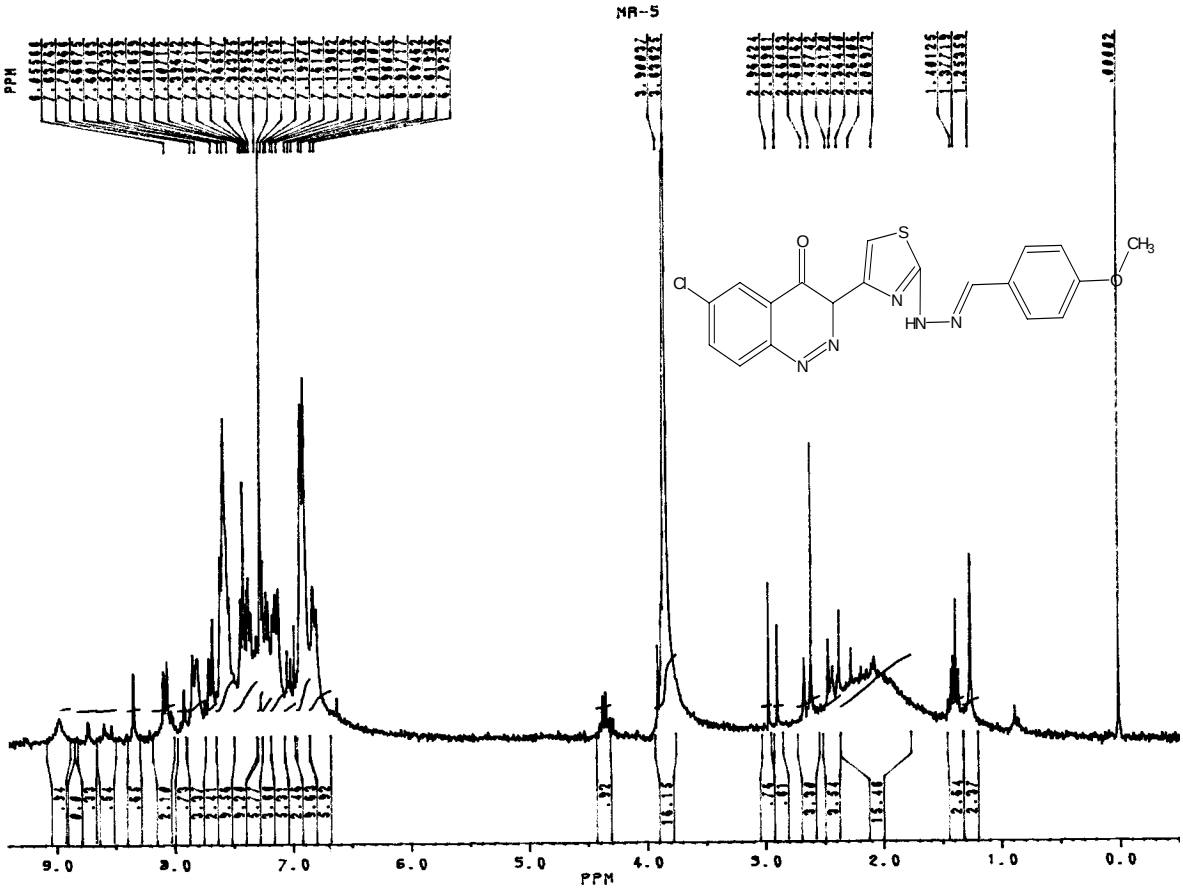
IR SPECTRAL STUDY OF (1E)-ARYL-[4-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-1,3-THIAZOL-2-YL]HYDRAZONE



Frequency range: 4000-400cm^{-1} (KBr disc) Instrument : Shimadzu-8400 FTIR

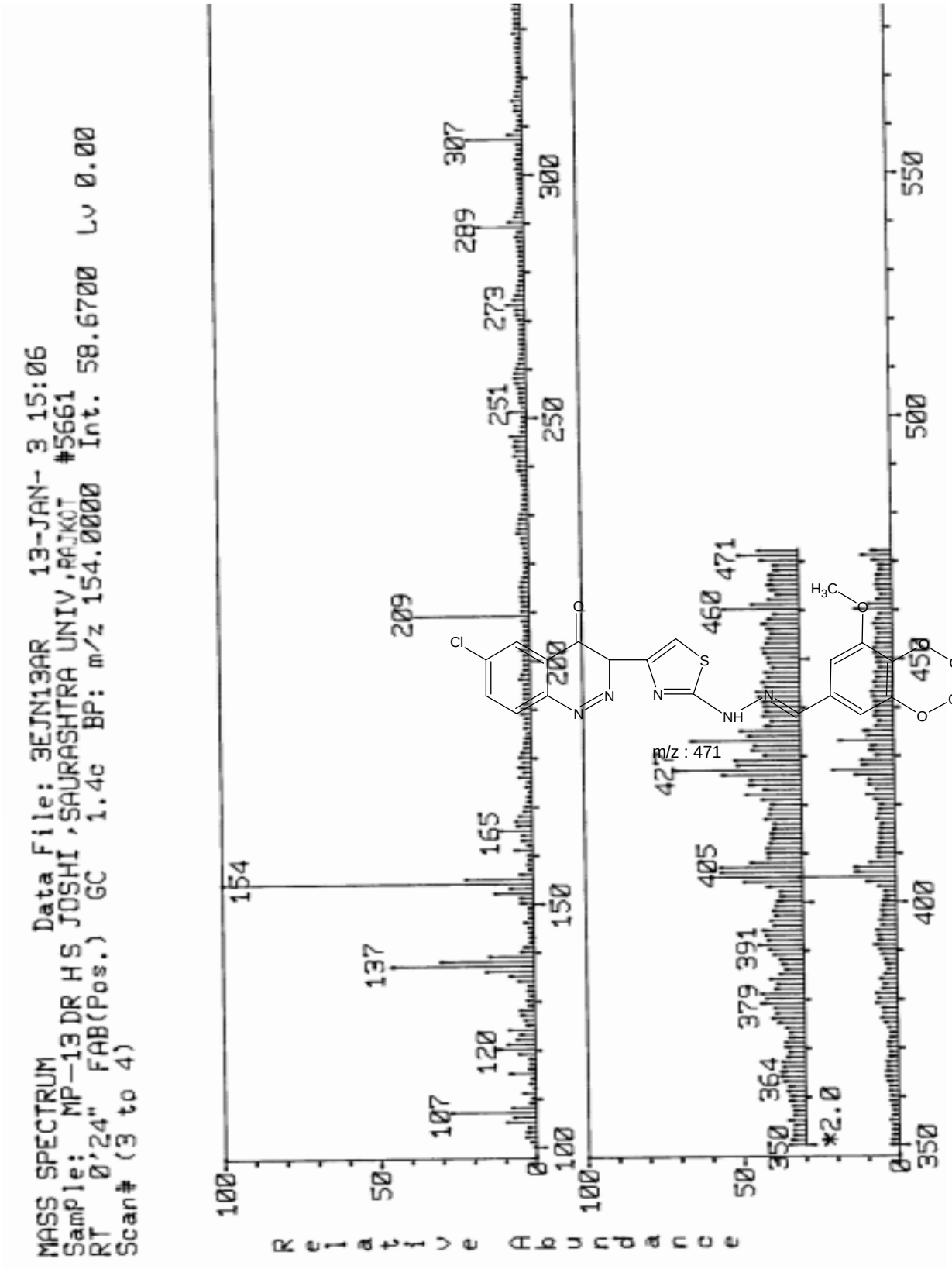
Type	Vibration mode	Frequency in cm-1 Observed	Reported	References
Alkane	C-H str. (asym.)	2923	2975-2950	46
-CH_3	C-H str. (sym.)	2854	2880-2860	"
	C-H def. (asym.)	1488	1470-1435	"
	C-H def. (sym.)	1384	1385-1370	"
Aromatic	C-H str.	3033	3080-3030	47
	C=C str.	1527	1620-1430	"
	C-H i.p. def	1238	1269-1013	"
	C-H o.o.p. def.	825	833-660	"
Amine	NH- str.	3321	3300-3450	"
Ether	C-O-C str.	1153	1275-1200	46
Halide	C-Cl str.	740	750-700	47

PMR SPECTRAL STUDIES OF 2-AMINO-4-ARYL-6-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)NICOTINONITRILE



Internal reference: TMS; Solvent: $CDCl_3$; Instrument: BRUKER spectrometer(300 MHz)

Signal No.	Signal position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.87	3H	singlet	Ar-OCH_3
2.	6.98	2H	doublet	Ar-H_a (p-sub.)
3.	7.31	1H	double duoblet	Ar-H_d
4.	7.36	1H	double duoblet	Ar-H_f
5.	7.56	1H	doublet	Ar-H_e
6.	7.63	1H	doublet	Ar-H_g
7.	7.75	1H	singlet	Ar-H_c (pyridine)
8.	8.03	2H	doublet	Ar-H_b (p-sub.)


MASS SPECTRUM Data File: 3EJN13AR 13-JAN- 3 15:06
Sample: MP-13 DR H S JOSHI,SAURASHTRA UNIV,RAJKOT #5661
RT 0'24" FAB(Pos.) GC 1.4c BP: m/z 154.0000 Int. 58.6700 Lv 0.00
Scan# (3 to 4)
Relative Abundance
m/z : 471
*2.0

EXPERIMENTAL

SYNTHESIS OF (1E)-ARYL-[4-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-1,3-THIAZOL-2-YL]HYDRAZONE

(A) Synthesis of 3-Bromoacetyl-6-chloro cinnolin-4(3H)-one.

Dissolve 3-acetyl-6-chlorocinnolin-4(3H)-one (2.22 gm, 0.01 mol) in 50 ml of dioxane. To this solution, 1.60 gm (0.01 mol) of bromine in dioxane, was added dropwise with continuous stirring. The contents were heated at 50 ^{0}C for one hr. After cooling the reaction mixture was poured into the ice cold water. The solid so separated was filtered, washed with cold water, dried and crystallized from ethanol. Yield 65 % m. p. 148 ^{0}C.

(B) Synthesis of 4-Methoxybenzaldehyde thiosemicarbazone.

To a solution of thiosemicarbazide (0.9 gm, 0.01 mol) in ethanol (40 ml), 4-methoxy benzaldehyde (1.36 gm, 0.01 mol) and sodium acetate (0.4 gm) was added and relfuxed it on water bath for 3-4 hr. The solid mass separated after cooling was filtered, washed with water, dried and recrystallized from ethanol. Yield 72 % m. p. 128 ^{0}C.

(C) Synthesis of 4-Methoxy benzaldehyde [4-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-1,3-thiazol-2-yl]-hydrazone.

A mixture of 3-bromoacetyl-6-chlorocinnolin-4(3H)-one (3.01 gm, 0.01mol) and 4-methoxybenzaldehyde thiosemicarbazone (2.09 gm, 0.01 mol) in 50 ml ethanol, was refluxed on a water bath for about 5 hr. The volume of the reaction mixture was then reduced to one fourth, after which it was cooled and added ammonia solution with stirring. The solid so obtained was foltered, washed with water and crystallized from aqueous ethanol. Yield 55 % m.p. 140 ^{0}C. Anal. Calcd. for $C_{19}H_{14}ClN_5O_2S$ Requires:

C, 55.41; H, 3.43; N, 17.00 % Found: C, 55.40; H, 3.40, N, 16.98 %.

Similarly, other (1E)-aryl [4-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-1,3-thiazol-2-yl]-hydrazone. The physical data are recorded in Table No. 11.

(D) Biological screening of (1E)-aryl [4-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-1,3-thiazol-2-yl]-hydrazone.

Antimicrobial testing were carried out as described in Part-I, Section-I(D). The zones of inhibition of test solution are reported in Graphical Chart No. 11.

TABLE-11: PHYSICAL CONSTANTS OF (1E)-ARYL-[4-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-1,3-THIAZOL-2-YL]HYDRAZONE

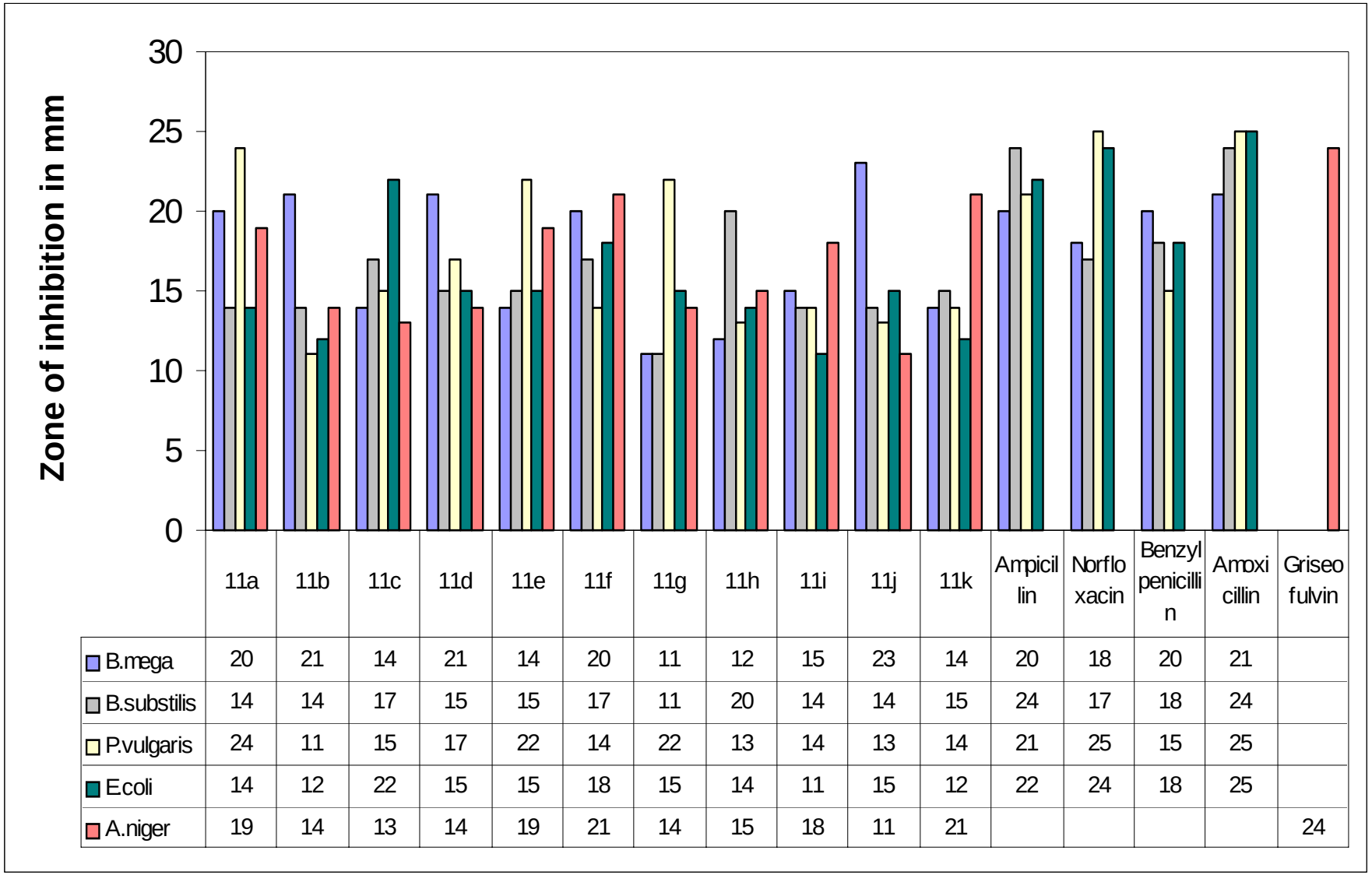
Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	Rf Value	Solvent System	Yield %	% of Nitrogen Calcd	% of Nitrogen Found
1	2	3	4	5	6	7	8	9	10
11a	C_6H_5-	$C_{18}H_{12}ClN_5OS$	381.84	168	0.373	S_2	64	18.34	18.33
11b	3-Br-C_6H_4-	$C_{18}H_{11}BrClN_5OS$	460.74	125	0.394	S_1	65	15.20	15.18
11c	2-Cl-C_6H_4-	$C_{18}H_{11}Cl_2N_5OS$	416.28	178	0.291	S_1	66	16.82	16.80
11d	3-Cl-C_6H_4-	$C_{18}H_{11}Cl_2N_5OS$	416.28	120	0.437	S_1	65	16.82	16.82
11e	4-Cl-C_6H_4-	$C_{18}H_{11}Cl_2N_5OS$	416.28	150	0.494	S_2	64	16.82	16.81
11f	3,4-$(OCH_3)_2$-C_6H_3-	$C_{20}H_{16}ClN_5O_3S$	441.89	130	0.444	S_3	59	15.85	15.846
11g	3,4,5-$(OCH_3)_3$-C_6H_2-	$C_{21}H_{18}ClN_5O_4S$	471.92	140	0.541	S_3	58	14.84	14.81
11h	4-OCH_3-C_6H_4-	$C_{19}H_{14}ClN_5O_2S$	411.87	140	0.423	S_1	55	16.37	16.35
11i	2-OH-C_6H_4-	$C_{18}H_{12}ClN_5O_2S$	397.84	190	0.535	S_1	57	17.00	16.98
11j	3-C_6H_5-O-C_6H_4-	$C_{24}H_{16}ClN_5O_2S$	473.94	118	0.425	S_2	59	14.78	14.77
11k	4-$N(CH_3)_2$-C_6H_4-	$C_{20}H_{17}ClN_6OS$	424.91	145	0.295	S_1	62	19.78	19.74

S_1 = Ethyl acetate : Hexane (2:8)

S_2 = Ethyl acetate : Hexane (0.5:9.5)

S_3 = Ethyl acetate : Hexane (1:9)

Graphical Chart No. 11 : Antimicrobial activity of (1E)-Aryl-[4-(6-chloro-4-oxo-3,4-dihydrocinnolin-3-yl)-1,3-thiazol-2-yl]hydrazone



	11a	11b	11c	11d	11e	11f	11g	11h	11i	11j	11k	Ampicillin	Norfloxacin	Benzylpenicillin	Amoxicillin	Griseofulvin
B.mega	20	21	14	21	14	20	11	12	15	23	14	20	18	20	21	
B.substilis	14	14	17	15	15	17	11	20	14	14	15	24	17	18	24	
P.vulgaris	24	11	15	17	22	14	22	13	14	13	14	21	25	15	25	
E.coli	14	12	22	15	15	18	15	14	11	15	12	22	24	18	25	
A.niger	19	14	13	14	19	21	14	15	18	11	21					24

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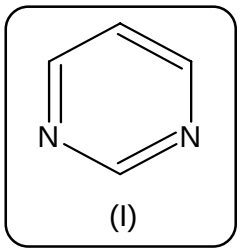
INTRODUCTION

In recent years much interest has been focused on the study of the pyrimidine ring system because of its potential pharmacological activities. Forstly pyrimidine was isolated by Garbial and Colman in 1899. Pyrimidine ring (I) system consists of two nitrogen atoms in a sis member heterocyclic ring at 1,3-position.



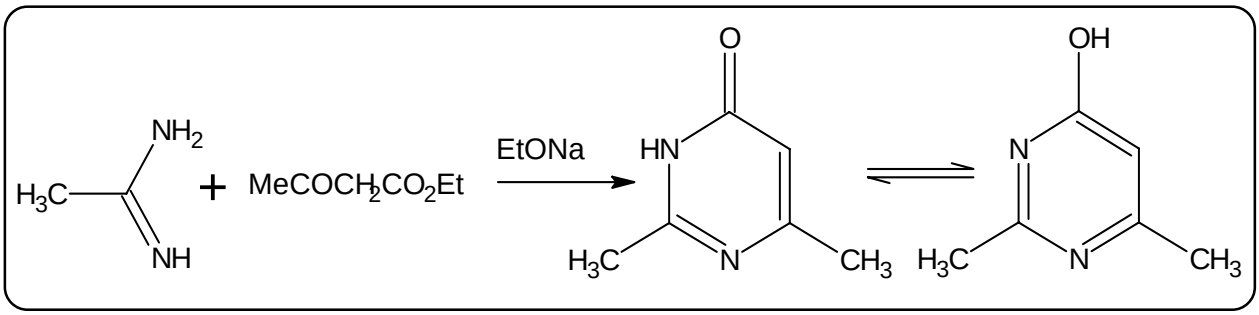
(I)

Purines, uric acid, alkoxan, barbituric acid and a mixture of antimalarial and antibacteial also contain the pyrimidine ring. The chemistry of pyrimidine has been widely studied by several co-workers.

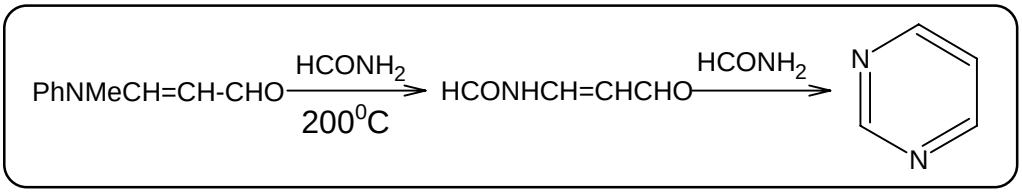
SYNTHETIC ASPECT

A very important general method for preparing pyrimidines is the condensation between a three carbon compounds of the type YCH_2Z, where Y and Z = COR, CO_2R, CN, and compounds having the amidine structure $R(C=NH)NH_2$, where R = R (an amidine), OH (urea), SH or SR (thiourea or its s-derivative), NH_2 (guanidine); the condensation is carried out in te presence of sodium hysroxide or sodium ethoxide. This general reaction may be illustrate by the condensation of acetamidine with ethyl

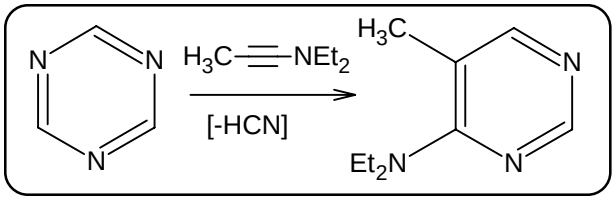
acetoacetate to form 4-hydroxy-2,6-dimethylpyrimidine.



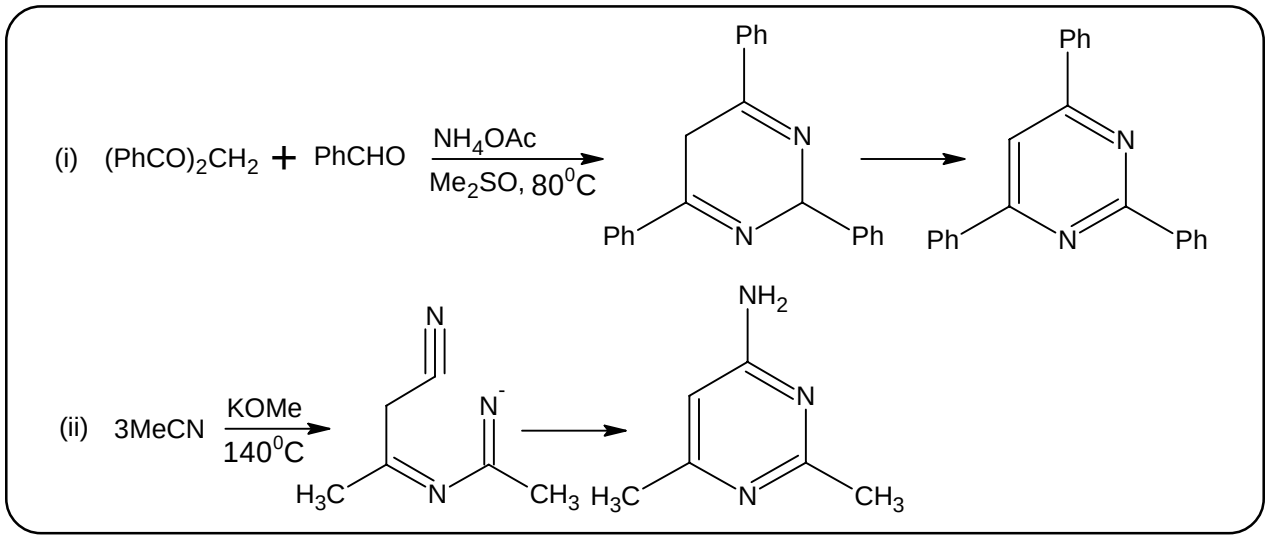
There are many other methods of pyrimidine ring synthesis which are of more limited scope. The reaction of 1,3-dicarbonyl compound or an equivalent reagent with formamide provides a route of several pyrimidine which are unsubstituted at the 2-position.



Pyrimidines can also be prepared by cycloaddition reaction of 1,3,5-triazines, which act as electron deficient dienes.

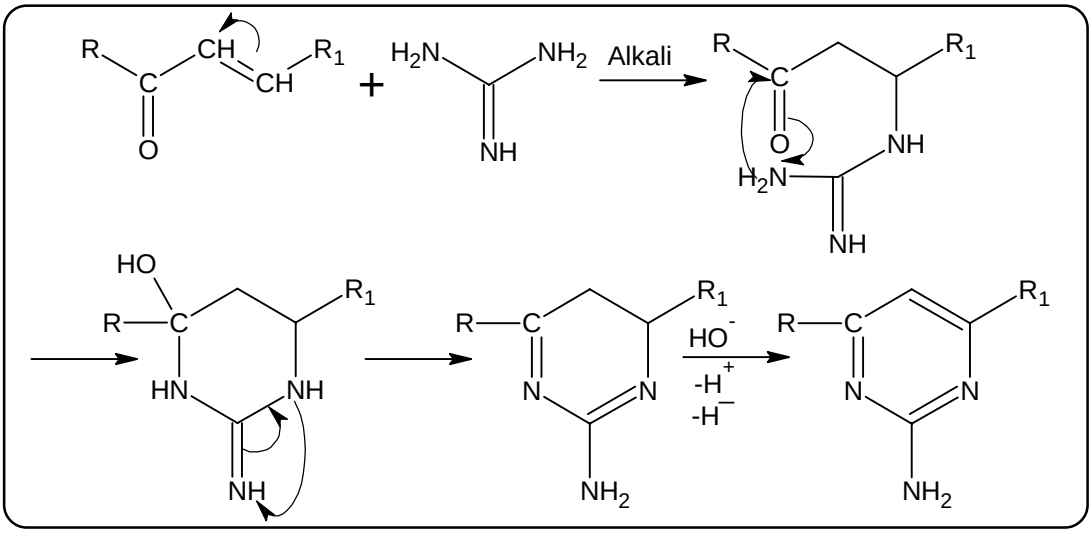


Some other examples of pyrimidine synthesis are as under.



REACTION MECHANISM

The reaction mechanism for the formation of pyrimidine derivatives described as under.



THERAPEUTIC IMPORTANCE

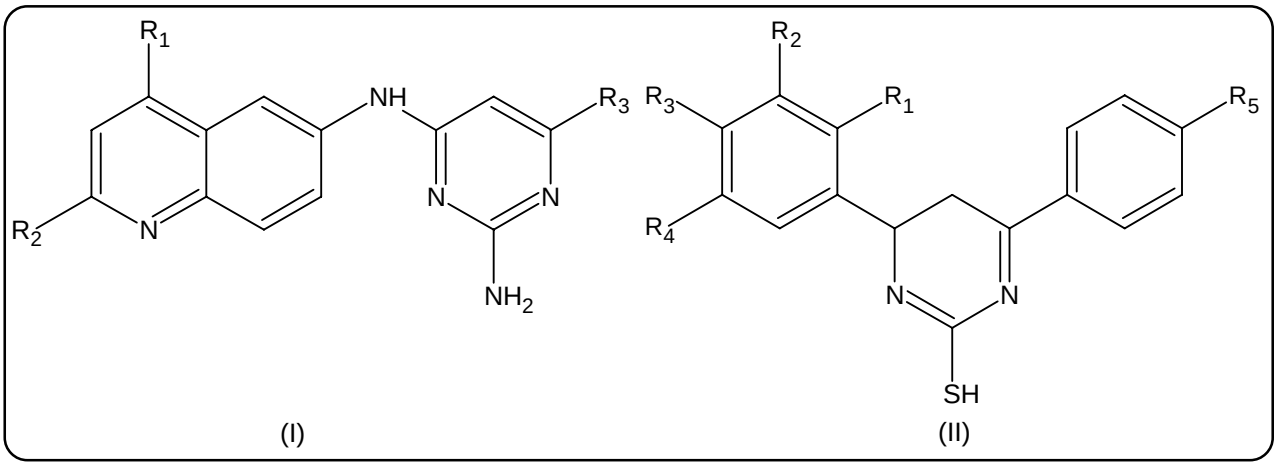
It is revealed from the literature survey that pyrimidine derivatives have been found possessing biological activities reported as under.

1. Antidiabetic[1],
2. Antihypertensive[2],
3. Analgesic[3],
4. Antibacterial[4],
5. Diuretic[5],
6. Fungicidal[6],
7. Insecticidal[7],
8. Anticonvulsant[8],
9. Antitubercular[9],
10. Tranquilizing[10],

Moreover, Chaudhari Bipinchandra and et al.[11] prepared N6-(2-aminopyrimidin-4-yl)-quinoline-4,6-diamine (I) as N-type calsium channel antagonists for the treatment of pain. Devi E. Sree and co-workers[12] prepared pyrimidine derivatives and tested for

antimicrobial activity. Kovalenko A. L.[13] synthesized and reported antifungal activity of pyrimidine derivatives. Shiv P. Singh and co-workers[14] synthesized 4-(4-pyrazolyl)-2-aminopyrimidines(H) and tested them for their antimicrobial activity.

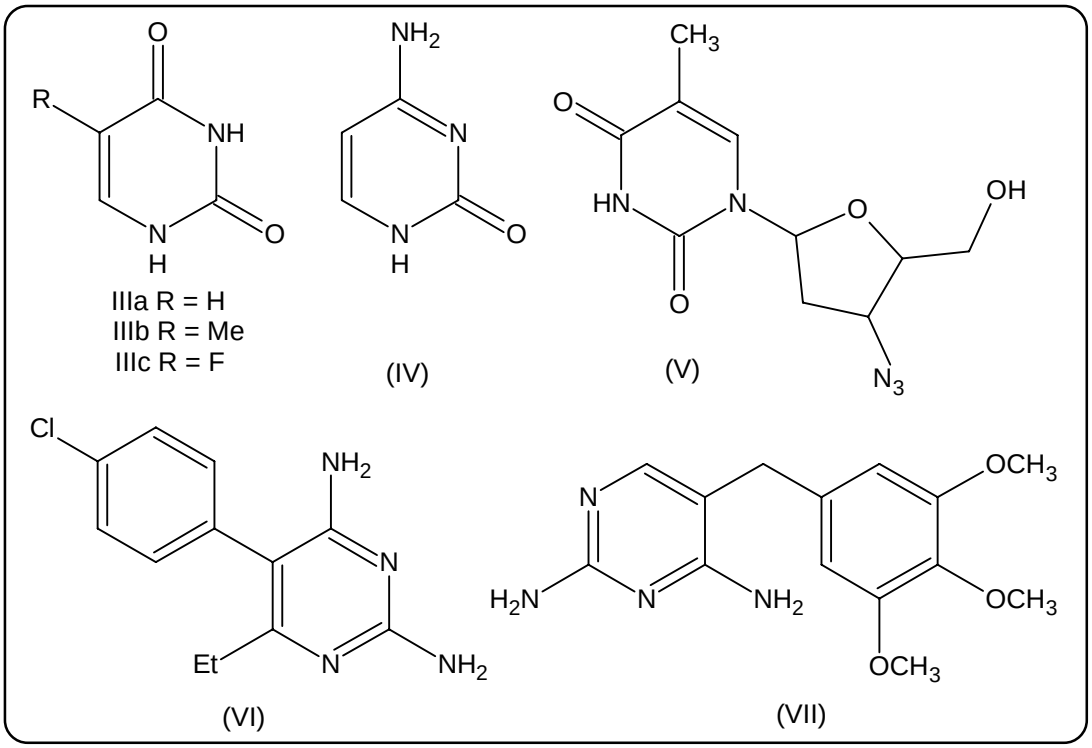
Patil, L. R. et al.[15] synthesize some new pyrimidines bearing paracetamol and imidazolyl moieties. B. J. Ghiya et al.[16] synthesized some mercapto pyrimidine derivatives (II) and screened for their anticancer, antitubercular and anti HIV activities. Kaplina N. V. and co-workers[17] exibited herpes inhibiting activity of some mercapto pyrimidine derivatives.

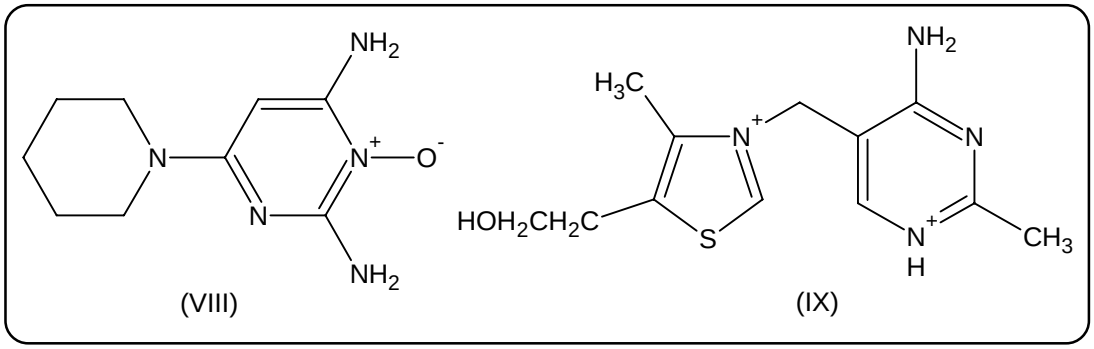


(I) (II)

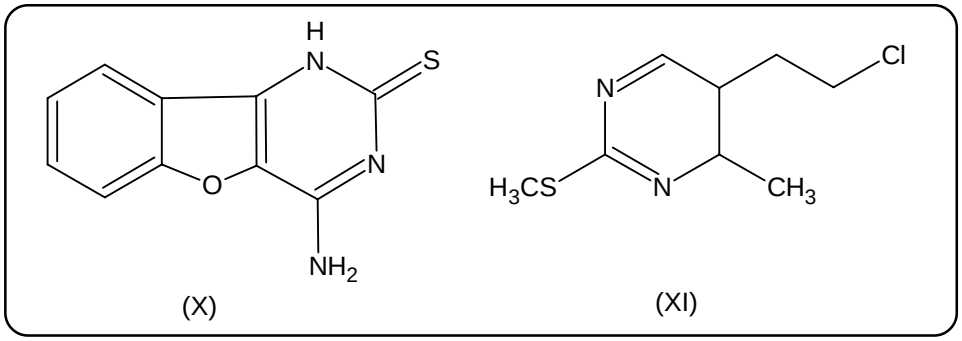
The pyrimidines uracil (IIIa), thyamine (IIIb) and cytosine (IV) occur very widely in nature since they are components of nucleic acids, in the form of N-substituted sugar derivatives. Several analogues have been used as compounds that interfere with the synthesis and functioning of nulic acids: example are fluorouracil (IIIc), and the anti-AIDS drug Zidovudine (AZT) (V). Some diaminopyrimidines , including pyrimethamine (VI) and trimethoprim (VII), are antimalarial agents; trimethoprim is also an effective antibacterial agent when used in combination with a sulphonamide. Minoxidil (VIII) is a vasodilator which has been used in the treatment of hypertension. Vitamine B_1(IX) is also a pyrimidine.

S. S. Sangapure and S. M. Mulagi18 have tested the antimicrobial activity of benzofuro[3,2-d]pyrimidine derivatives (X). El Sayed[19] and A. M. Badaway[20] have synthesized alkylated substituted mercapto pyrimidine derivatives (XI) and studied their





anticancer and antineoplastic activity. H. Y. Moustafa21 have prepared some pyrimidine derivatives and studied their biological activities.



Some pyrazolo thieno oyrimidine derivatives exhibit antiulcer activity[22]. Skolova A. S. and co-workers[23] have synthesized 5-amino-6-mercapto pyrimidine possessing antitumor and cytostatic activity. Hozein Zeinab et al.[24] and Khalafallah Ali Kamel[25] have prepared mercaptoderivatives and screened for their antibacterial and antifun-

gal activity.

In our study on therapeutically active molecules, we have undertaken synthesis of pyrimidine derivatives, which have been described in following section.

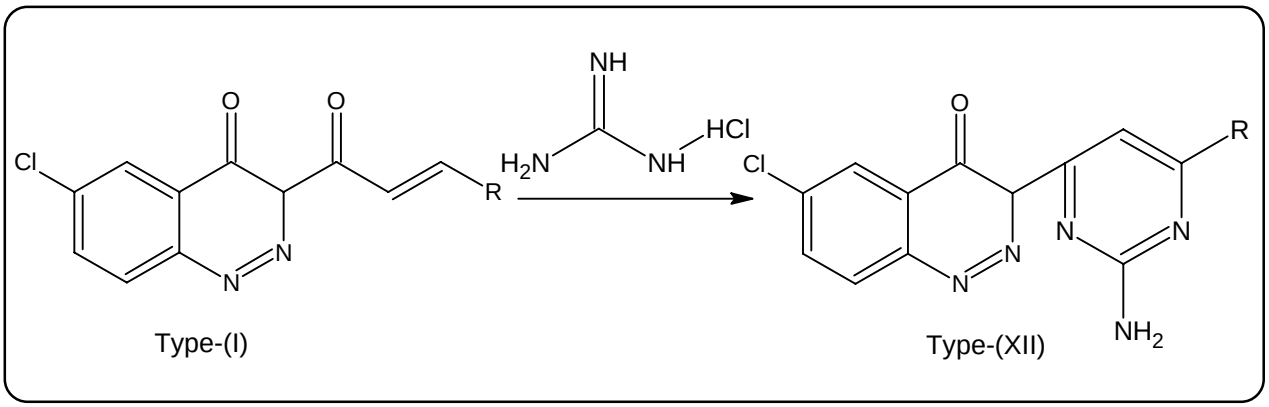
SECTION-I : Preparation and biological screening of 3-(2-Amino-6-aryl pyrimidin-4-yl)-6-chlorocinnolin-4(3H)-one

SECTION-II : Preparation and biological screening of 6-chloro-3-(6-aryl-2-mercapto-3,4-dihydropyrimidin-4-yl)-cinnolin-4(3H)-one

SECTION-I

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(2-AMINO-6-ARYL PYRIMIDIN-4-YL)-6-CHLOROCINNOLIN-4(3H)-ONE.

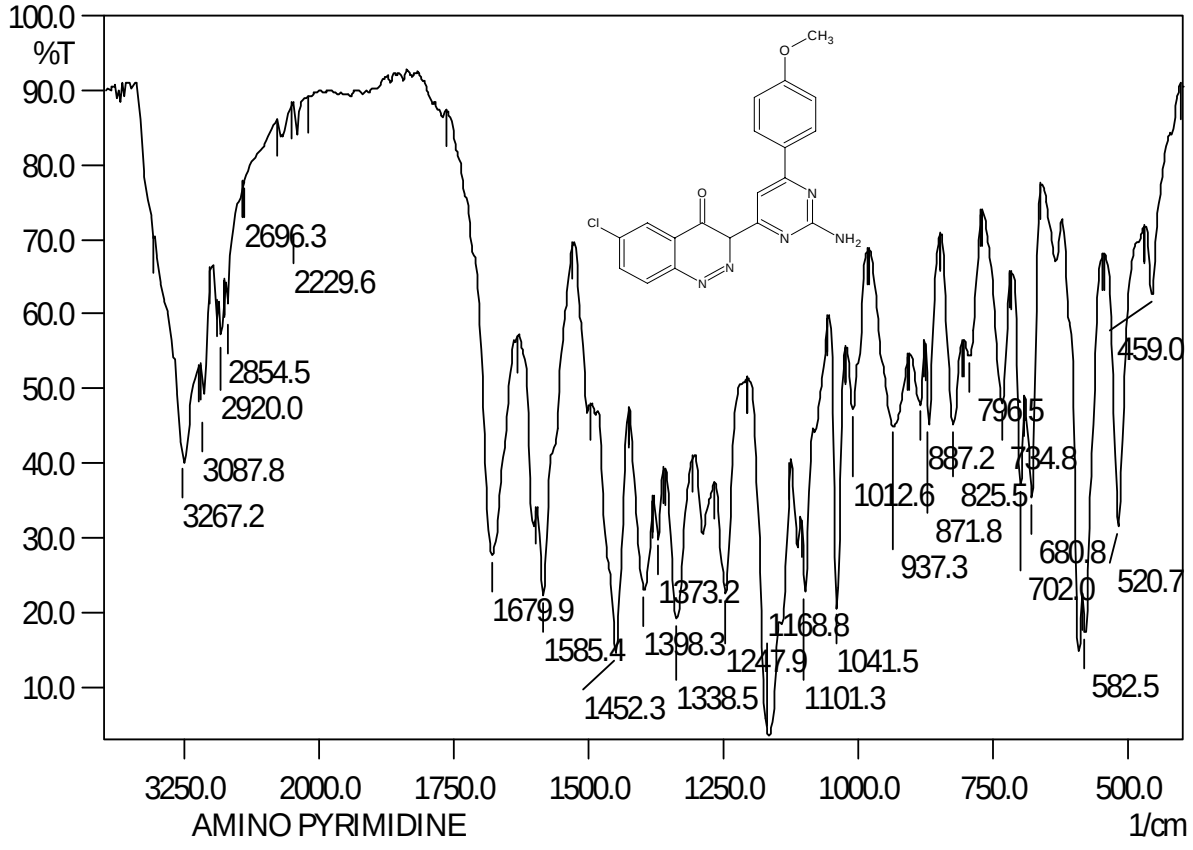
Pyrimidines receive an extra ordinary amount of attention by synthetic and medicinal chemists because of their unique role played by this hetero aromatic ring in biological systems. These results made it interesting to prepare 3-(2-amino-6-aryl pyrimidin-4-yl)-6-chlorocinnolin-4(3H)-one of type-(XII) by condensing 6-chloro-3-[(2E)-3-arylprop-2-enoyl]cinnolin-4(3H)-ones of type-(I) with guanidine hydro chloride in presence of alcoholic potassium hydroxide.



The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

All the compounds have been evaluated 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 synthesized compounds were compared with standard drugs.

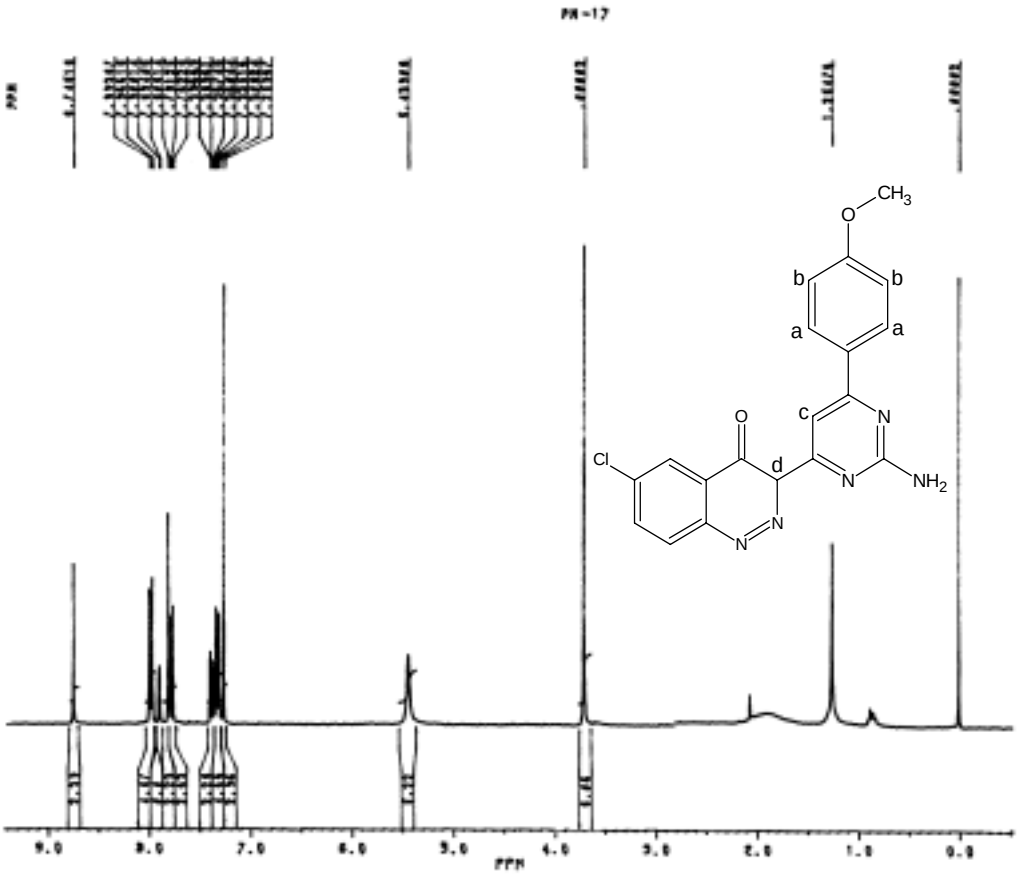
IR SPECTRAL STUDY OF 3-(2-AMINO-6-ARYLPYRIMIDIN-4-YL)-6-CHLOROCINNOLIN-4(3H)-ONE



Frequency range: 4000-400cm^{-1} (KBr disc) Instrument : Shimadzu-8400 FTIR

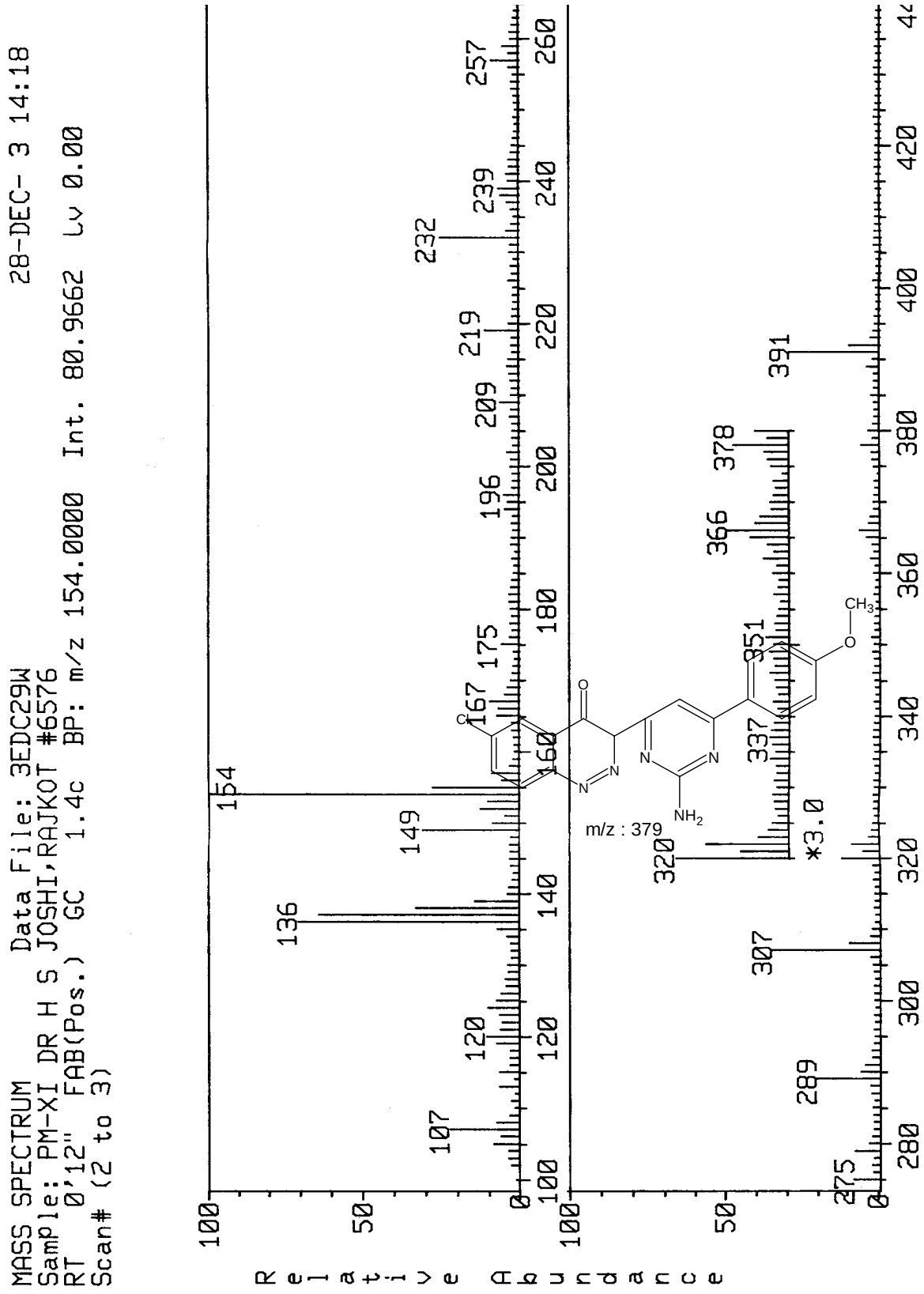
Type	Vibration mode	Frequency in cm^{-1} Observed	Reported	References
Alkane	C-H str. (asym.)	2920	2975-2950	25
-CH_3	C-H str. (sym.)	2854	2880-2860	"
	C-H def. (asym.)	1452	1470-1435	"
	C-H def. (sym.)	1373	1385-1370	"
Aromatic	C-H str.	3087	3080-3030	26
	C=C str.	1585	1620-1430	"
	C-H i.p. def	1247	1269-1013	"
	C-H o.o.p. def.	825	833-660	"
Amine	NH_2- str.	3267, 3355	3450-3300	"
Ether	C-O-C str.	1168	1275-1200	25
Carbonyl	C=O	1679	1690-1665	26
Halide	C-Cl str.	734	750-700	"

PMR SPECTRAL STUDIES OF 3-(2-AMINO-6-ARYLPYRIMIDIN-4-YL)-6-CHLOROCINNOLIN-4(3H)-ONE



Internal reference: TMS; Solvent: $CDCl_3$; Instrument: BRUKER spectrometer(300 MHz)

Signal No.	Signal position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.78	3H	singlet	Ar-OCH_3
2.	5.43	1H	singlet	Ar-CH_c
3.	7.25	1H	singlet	Ar-H (cinnoline ring)
4.	7.30	2H	doublet	Ar-H (p-sub.)
5.	7.36-7.90	3H	multiplate	Ar-H
6.	7.96	2H	double	Ar-H (p-sub.)
7.	8.74	2H	singlet	Ar-NH_2


MASS SPECTRUM Data File: 3EDC29W
Sample: PM-XI DR H S JOSHI,RAJKOT #6576
RT 0'12" FAB(Pos.) GC 1.4c BP: m/z 154.0000 Int. 80.9662 Lv 0.00
Scan# (2 to 3)
28-DEC- 3 14:18
Relative Abundance
m/z : 379
*3.0

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(2-AMINO-6-ARYLPYRIMIDIN-4-YL)-6-CHLOROCINNOLIN-4(3H)-ONE

(A) Synthesis of 6-Chloro-3-[(2E)-3-aryl-prop-2-enoyl]cinnolin-4(3H)-one.

See Part-I, Section-I(C)

(B) Synthesis of 3-[2-Amino-6-(4-methoxyphenyl)pyrimidin-4-yl]-6-chlorocinnolin-4(3H)-one.

A mixtureof 6-chloro-3-[(2E)-3-(4-methoxyphenyl)-prop-2-enoyl]cinnolin-4(3H)-one (3.4 gm, 0.01 mole) and guanidine hydrochloride (1.10g, 0.01 mol) was refluxed on a water-bath in presence of alcoholic KOH in dioxane for 8 hr. The solvent was evaporated and the residue was neutralized with 20 % HCl, the separated solid was filtered out and crystallized from ethanol. Yield 46 %, m.p. 304 ^{0}C Anal. Calcd. for $C_{19}H_{14}ClN_5O_2$ Requires: C, 60.09; H, 3.72; N, 18.44 % Found: C, 60.05; H, 3.70, N, 18.42 %.

Similarly, other 3-(2-Amino-6-arylpyrimidin-4-yl)-6-chlorocinnolin-4(3H)-ones. The physical data are recorded in Table No. 12.

(C) Biological screening of 3-(2-Amino-6-arylpyrimidin-4-yl)-6-chlorocinnolin-4(3H)-one

Antimicrobial testing were carried out as described in Part-I, Section-I(D). The zones of inhibition of test solution are reported in Graphical Chart No. 12.

TABLE-12: PHYSICAL CONSTANTS OF 3-(2-AMINO-6-ARYLPYRIMIDIN-4-YL)-6-CHLOROCINNOLIN-4(3H)-ONE

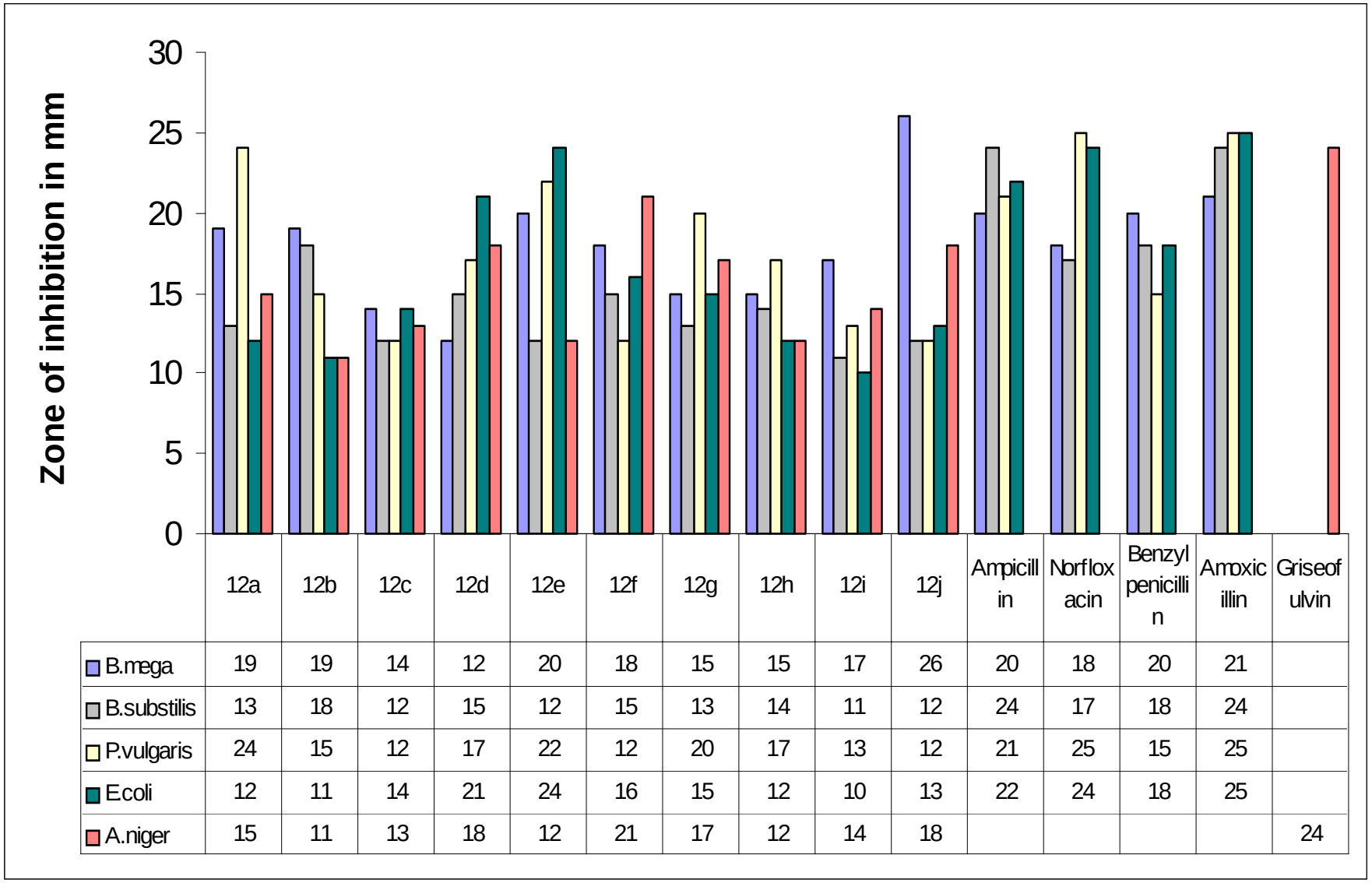
Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	Rf Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
12a	C_6H_5-	$C_{18}H_{12}ClN_5O$	349.77	245	0.69	S_1	56	20.02	20.01
12b	3-Br-C_6H_4-	$C_{18}H_{11}BrClN_5O$	428.67	230	0.54	S_2	54	16.34	16.32
12c	2-Cl-C_6H_4-	$C_{18}H_{11}Cl_2N_5O$	384.22	282	0.68	S_2	49	18.23	18.22
12d	3-Cl-C_6H_4-	$C_{18}H_{11}Cl_2N_5O$	384.22	180	0.56	S_1	48	18.23	18.21
12e	4-Cl-C_6H_4-	$C_{18}H_{11}Cl_2N_5O$	384.22	134	0.71	S_3	47	18.23	18.23
12f	C_4H_3-O-	$C_{16}H_{10}ClN_5O_2$	339.74	308	0.54	S_1	45	20.61	20.58
12g	4-OCH_3-C_6H_4-	$C_{19}H_{14}ClN_5O_2$	379.80	304	0.48	S_3	46	18.44	18.42
12h	4-SCH_3-C_6H_4-	$C_{19}H_{14}ClN_5OS$	395.80	260	0.62	S_2	48	17.69	17.66
12i	3-C_6H_5-O-C_6H_4-	$C_{24}H_{16}ClN_5O_2$	441.87	175	0.39	S_1	52	15.85	15.81
12j	4-$N(CH_3)_2$-C_6H_4-	$C_{20}H_{17}ClN_6O$	392.84	160	0.48	S_2	53	21.39	21.38

S_1 = Ethyl acetate : Hexane (1.5 : 8.5)

S_2 = Ethyl acetate : Hexane (2 : 8)

S_3 = Ethyl acetate : Hexane (3: 7)

Graphical Chart No. 12 : Antimicrobial activity of 3-(2-Amino-6-arylpyrimidin-4-yl)-6-chlorocinnolin-4(3H)-one

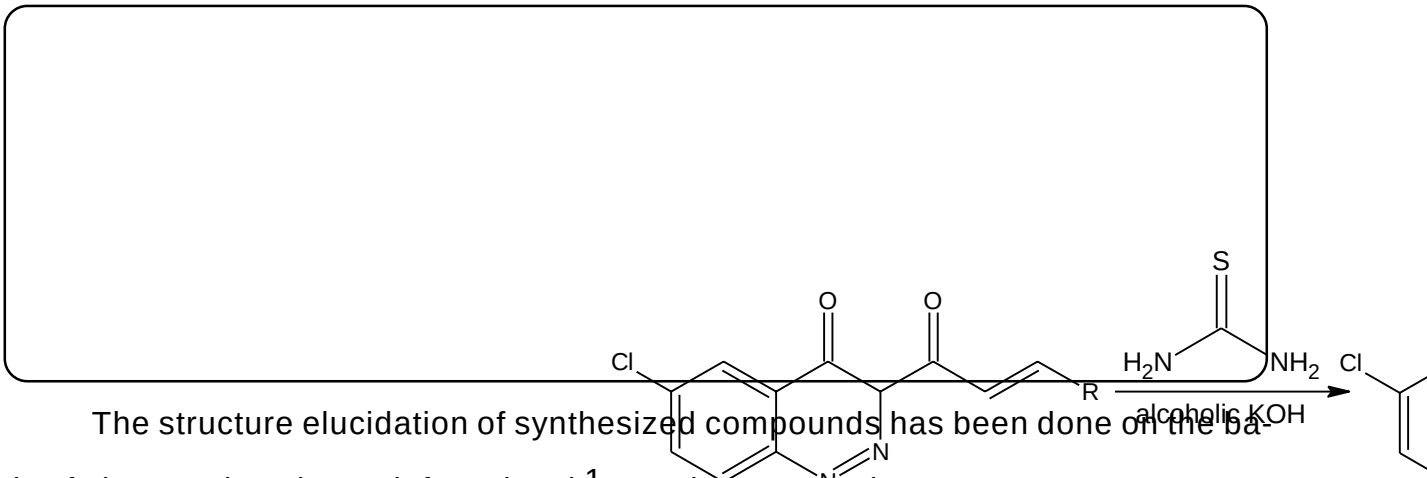


	12a	12b	12c	12d	12e	12f	12g	12h	12i	12j	Ampicillin	Norfloxacin	Benzylpenicillin	Amoxicillin	Griseofulvin
B.mega	19	19	14	12	20	18	15	15	17	26	20	18	20	21	
B.substilis	13	18	12	15	12	15	13	14	11	12	24	17	18	24	
P.vulgaris	24	15	12	17	22	12	20	17	13	12	21	25	15	25	
E.coli	12	11	14	21	24	16	15	12	10	13	22	24	18	25	
A.niger	15	11	13	18	12	21	17	12	14	18					24

SECTION-II

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-CHLORO-3-(6-ARYL-2-MERCAPTO-3,4-DIHYDROPYRIMIDIN-4-YL)CINNOLIN-4(3H)-ONES.

Pyrimidines have been studied extensively because of their ready accessibility, diverse chemical reactivity and broad spectrum of biological activities. Led by these considerations the synthesis of pyrimidine derivatives of type-(XIII) has been undertaken by the cyclocondensation of 6-chloro-3-[(2E)-3-arylprop-2-enoyl]cinnolin-4(3H)-ones of type-(I) with thiourea in presence of alcoholic KOH.

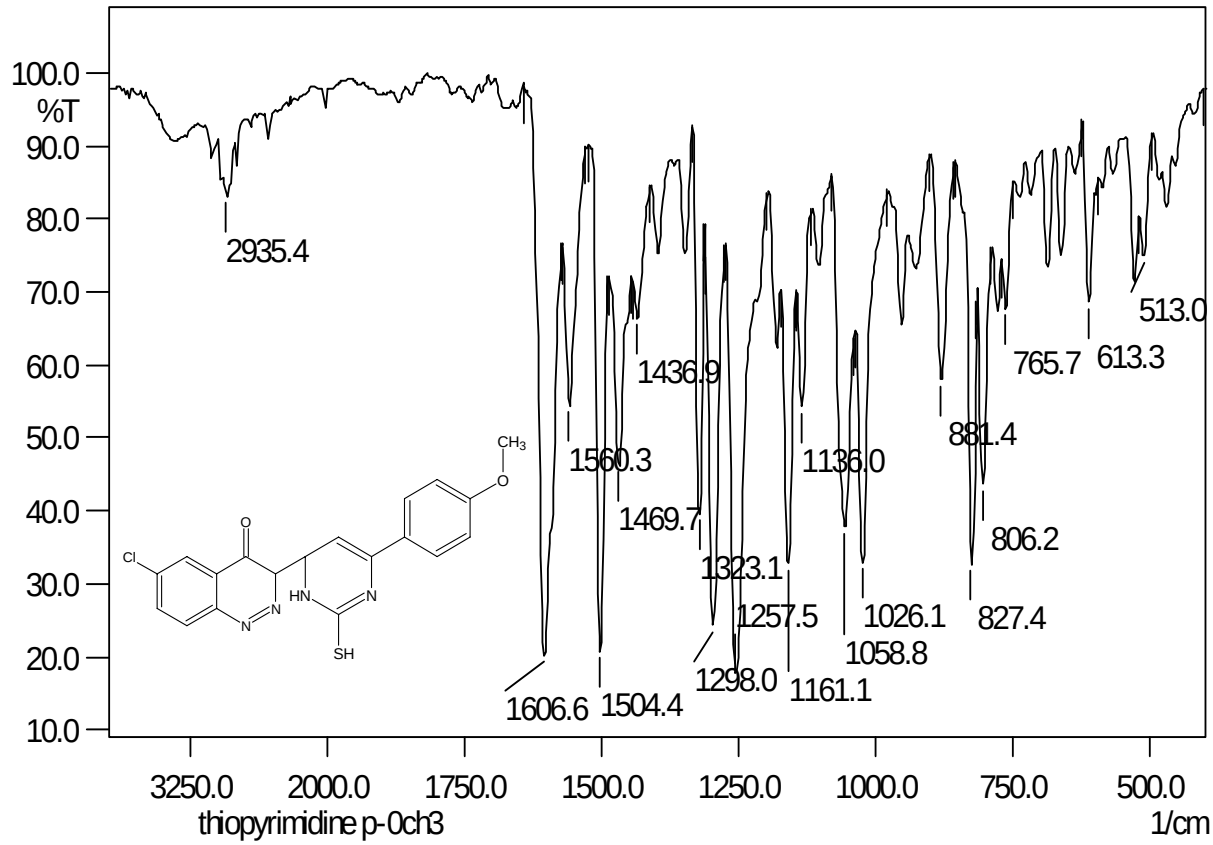


Type-(I)

The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by mass spectrometry.

All the compounds have been evaluated 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 synthesized compounds were compared with standard drugs.

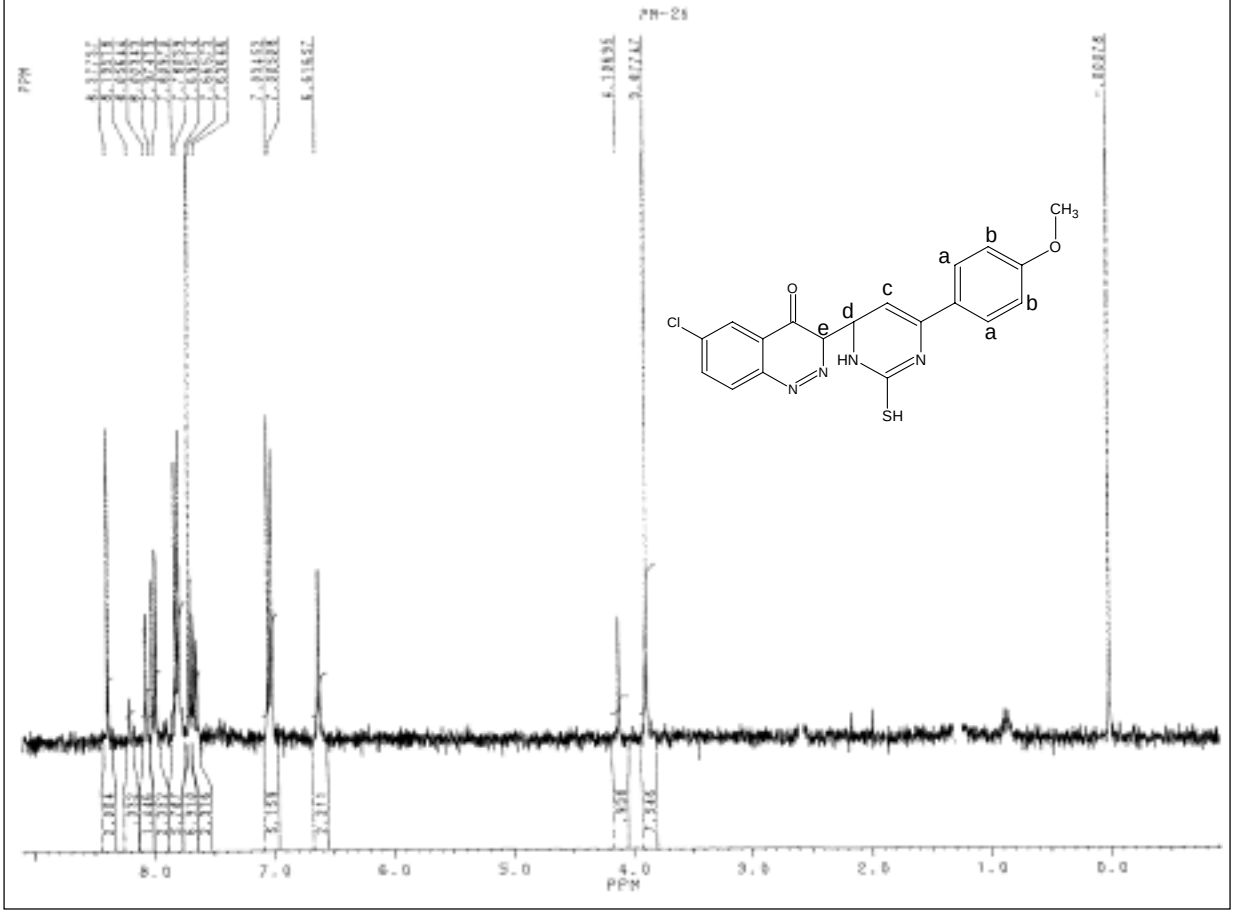
IR SPECTRAL STUDY OF 6-CHLORO-3-(6-ARYL-2-MERCAPTO-3,4-DIHYDROPYRIMIDIN-4-YL)CINNOLIN-4(3H)-ONES



Frequency range: 4000-400cm^{-1} (KBr disc) Instrument : Shimadzu-8400 FTIR

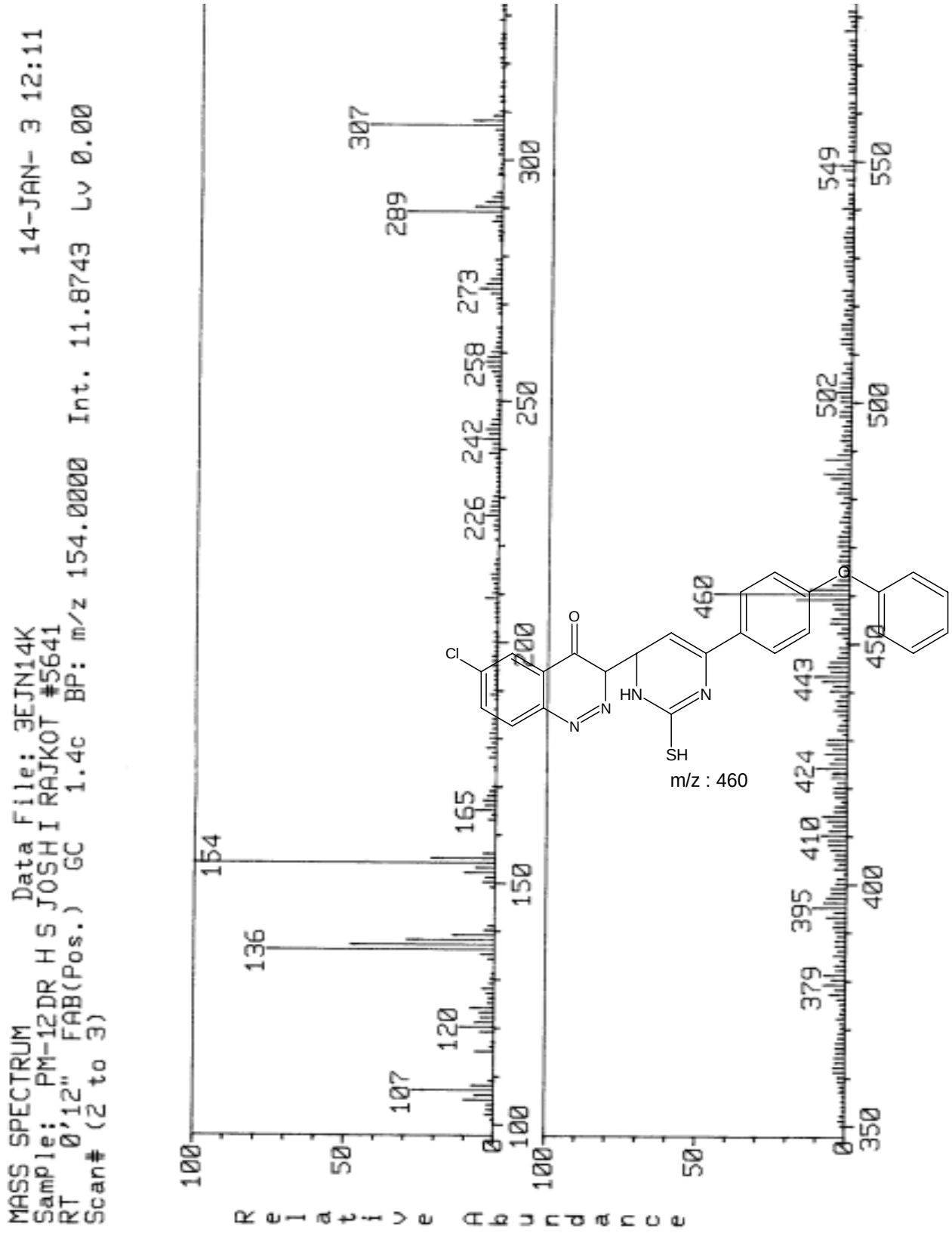
Type	Vibration mode	Frequency in cm^{-1} Observed	Reported	References
Alkane	C-H str. (asym.)	2935	2975-2950	25
-CH_3	C-H str. (sym.)	2854	2880-2860	"
	C-H def. (asym.)	1469	1470-1435	"
Aromatic	C-H str.	3033	3080-3030	26
	C=C str.	1560	1620-1430	"
	C-H i.p. def	1258	1269-1013	"
	C-H o.o.p. def.	827	833-660	"
Ether	C-O-C str.	1161	1275-1200	25
Halide	C-Cl str.	765	750-700	26

PMR SPECTRAL STUDIES OF 6-CHLORO-3-(6-(4-METHOXYPHENYL)-2-MERCAPTO-3,4-DIHYDROPYRIMIDIN-4-YL)CINNOLIN-4(3H)-ONES



Internal reference: TMS; Solvent: $CDCl_3$; Instrument: BRUKER spectrometer(300 MHz)

Signal No.	Signal position (δ ppm)	Relative No. of Proton	Multiplicity	Inference
1.	3.87	3H	singlet	Ar-OCH_3
2.	6.61	1H	doublet	Ar-CH_c
3.	7.00	3H	multiplate	Ar-H_a
4.	7.69	1H	singlet	Ar-H (cinnoline ring)
5.	7.78	2H	doublet	Ar-H (p-sub.)
6.	7.97	1H	doublet	Ar-H_d
7.	7.80	2H	doublet	Ar-H (p-sub.)
8.	8.41	1H	singlet	Ar-NH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RT 0'12" FAB(Pos.) GC 1.4c BP: m/z 154.0000 Int. 11.8743 Lv 0.00
Scan# (2 to 3)
14-JAN- 3 12:11
Relative Abundance
m/z : 460

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-CHLORO-3-(6-ARYL-2-MERCAPTO-3,4-DIHYDROPYRIMIDIN-4-YL)CINNOLIN-4(3H)-ONES.

(A) Synthesis of 6-Chloro-3-[(2E)-3-(4-methoxyphenyl)-prop-2-enoyl]cinnolin-4(3H)-one.

See Part-I, Section-I(C)

(B) Synthesis of 6-Chloro-3-[6-(4-methoxy phenyl)-2-mercapto-3,4-dihydropyrimidin-4-yl)cinnolin-4(3H)-one.

A mixtureof 6-chloro-3-[(2E)-3-(4-methoxyphenyl)-prop-2-enoyl]cinnolin-4(3H)-one (3.4 gm, 0.01 mole) and thiourea (0.78g, 0.01 mol) was refluxed on a water-bath in presence of alcoholic KOH in dioxane for 10 hr. The solvent was evaporated and the residue was neutralized with diluted HCl, the separated solid was filtered out and crystallized from ethanol. Yield 51 %, m.p. 200 ^{0}C Anal. Calcd. for $C_{18}H_{12}ClN_3O_3$ Requires: C, 61.11; H, 3.42; N, 11.88 % Found: C, 61.10; H, 3.40, N, 11.84 %.

Similarly, other 6-chloro-3-[6-aryl-2-mercapto-3,4-dihydropyrimidin-4-yl)cinnolin-4(3H)-ones The physical data are recorded in Table No. 13.

(C) Biological screening of 6-Chloro-3-[6-aryl-2-mercapto-3,4-dihydropyrimidin-4-yl)cinnolin-4(3H)-ones.

Antimicrobial testing were carried out as described in Part-I, Section-I(D). The zones of inhibition of test solution are reported in Graphical Chart No. 13.

TABLE-13: PHYSICAL CONSTANTS OF 6-CHLORO-3-(6-ARYL-2-MERCAPTO-3,4-DIHYDRO PYRINIDIN-4-YL)-4(3H)-ONE

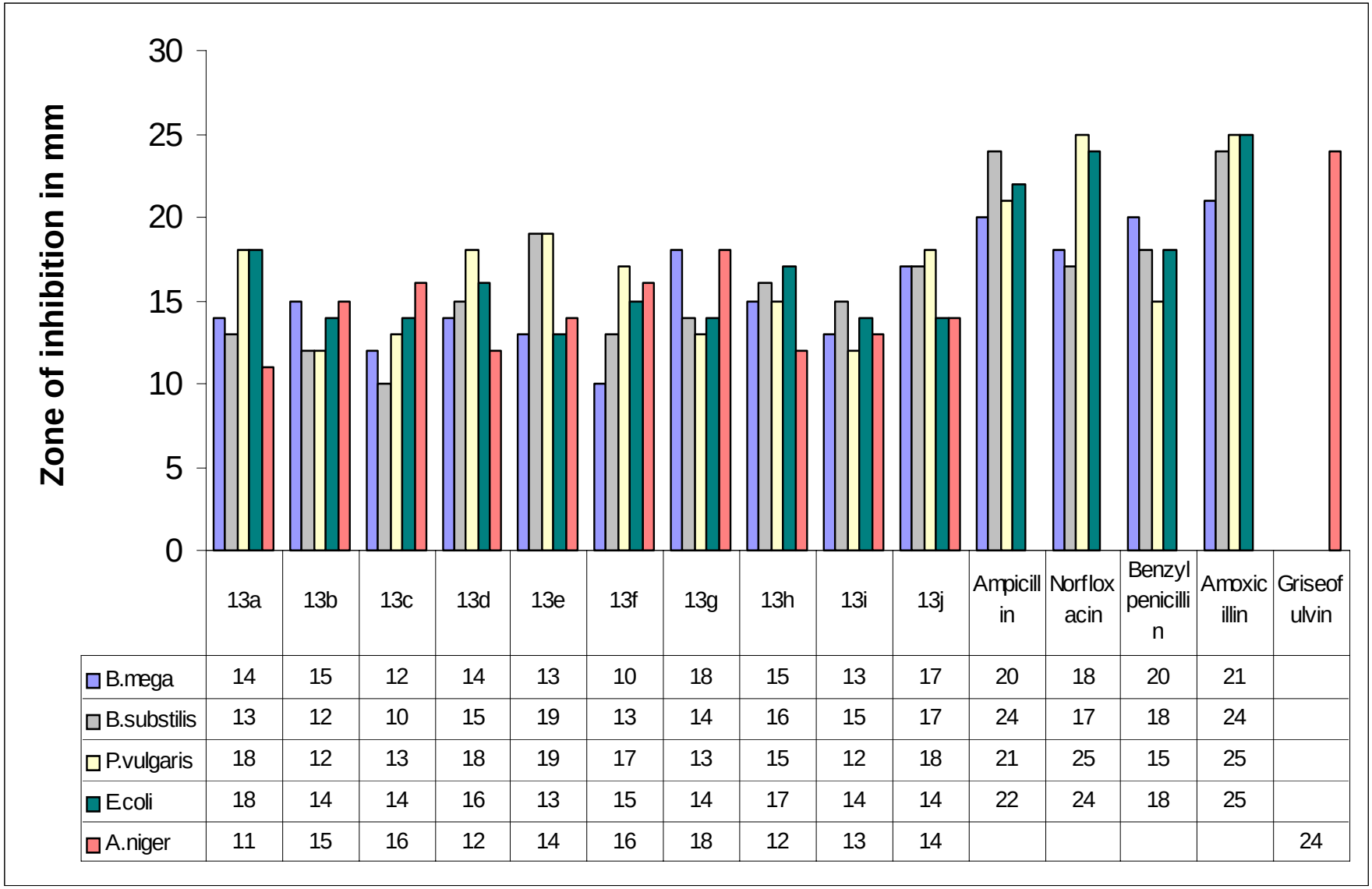
Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	Rf Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
13a	C_6H_5-	$C_{18}H_{13}ClN_4OS$	368.84	149	0.48	S_1	54	15.19	15.17
13b	3-Br-C_6H_4-	$C_{18}H_{12}BrClN_4OS$	447.74	108	0.69	S_1	54	12.51	12.50
13c	2-Cl-C_6H_4-	$C_{18}H_{12}Cl_2N_4OS$	403.89	156	0.52	S2	56	13.89	13.88
13d	3-Cl-C_6H_4-	$C_{18}H_{12}Cl_2N_4OS$	403.89	182	0.50	S_1	55	13.89	13.87
13e	4-Cl-C_6H_4-	$C_{18}H_{12}Cl_2N_4OS$	403.89	188	0.54	S_3	53	13.89	13.88
13f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{20}H_{17}ClN_4O_3S$	428.89	290	0.68	S_3	58	13.06	13.04
13g	4-OCH_3-C_6H_4-	$C_{19}H_{15}ClN_4O_2S$	398.87	178	0.63	S_1	49	14.05	14.03
13h	4-SCH_3-C_6H_4-	$C_{19}H_{15}ClN_4OS_2$	414.93	145	0.65	S_3	47	13.50	13.47
13i	4-OH-C_6H_4-	$C_{18}H_{13}ClN_4O_2S$	384.84	140	0.67	S_3	51	14.56	14.55
13j	3-C_6H_5-O-C_6H_4-	$C_{24}H_{17}ClN_4O_2S$	460.94	188	0.61	S_2	50	12.16	12.15
13k	4-$N(CH_3)_2$-C_6H_4-	$C_{20}H_{18}ClN_5OS$	411.91	164	0.57	S_2	54	17.00	12.98

S_1 = Ethyl acetate : Hexane (1.5 : 8.5)

S_2 = Ethyl acetate : Hexane (2 : 8)

S_3 = Ethyl acetate : Hexane (3: 7)

Graphical Chart No. 13 :Antimicrobial activity of 6-Chloro-3-(6-aryl-2-mercapto-3,4-dihydropyrimidin-4-yl)-2-cinnolin-4(3H)-one



	13a	13b	13c	13d	13e	13f	13g	13h	13i	13j	Ampicillin	Norfloxacin	Benzylpenicillin	Amoxicillin	Griseofulvin
B.mega	14	15	12	14	13	10	18	15	13	17	20	18	20	21	
B.substilis	13	12	10	15	19	13	14	16	15	17	24	17	18	24	
P.vulgaris	18	12	13	18	19	17	13	15	12	18	21	25	15	25	
E.coli	18	14	14	16	13	15	14	17	14	14	22	24	18	25	
A.niger	11	15	16	12	14	16	18	12	13	14					24

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TABLE-1: PHYSICAL CONSTANTS OF 6-CHLORO3-[(2E)-3-ARYLPROP-2-ENOYL]CINNOLIN-4(3H)-ONE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	Rf Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
1a	C_6H_5-	$C_{17}H_{11}ClN_2O_2$	310.73	210	0.563	S_1	74	9.02	9.02
1b	3-Br-C_6H_4-	$C_{17}H_{10}BrClN_2O_2$	389.63	198	0.527	S_1	71	7.19	7.15
1c	2-Cl-C_6H_4-	$C_{17}H_{10}Cl_2N_2O_2$	345.18	220	0.366	S_2	72	8.12	8.11
1d	3-Cl-C_6H_4-	$C_{17}H_{10}Cl_2N_2O_2$	345.18	174	0.542	S_2	65	8.12	8.06
1e	4-Cl-C_6H_4-	$C_{17}H_{10}Cl_2N_2O_2$	345.18	170	0.538	S_2	59	8.12	8.08
1f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{19}H_{15}ClN_2O_4$	370.78	178	0.543	S_1	64	7.56	7.54
1g	4-OCH_3-C_6H_4-	$C_{18}H_{13}ClN_2O_3$	340.76	190	0.465	S_2	68	8.22	8.20
1h	4-SCH_3-C_6H_4-	$C_{18}H_{13}ClN_2O_2S$	356.83	204	0.450	S_2	54	7.85	7.83
1i	3-NO_2-C_6H_4-	$C_{17}H_{10}ClN_3O_4$	355.73	206	0.556	S_2	72	11.81	11.80
1j	2-OH-C_6H_4-	$C_{17}H_{11}ClN_2O_3$	326.73	212	0.500	S_2	75	8.57	8.54
1k	4-OH-C_6H_4-	$C_{17}H_{11}ClN_2O_3S$	326.73	228	0.497	S_1	63	8.57	8.52
1l	3-C_6H_5-O-C_6H_4-	$C_{23}H_{15}ClN_2O_3$	402.83	181	0.488	S_1	60	6.95	6.94
1m	4-$N(CH_3)_2$-C_6H_4-	$C_{19}H_{16}ClN_3O_2$	353.80	194	0.528	S_1	50	11.88	11.84

S_1 = Ethyl acetate : Hexane (3 : 7) S_2 = Ethyl acetate : Hexane(2.5 : 7.5)

TABLE-2: PHYSICAL CONSTANTS OF 6-CHLORO-3-(5-ARYLISOXAZOLE-3-YL)-CINNOLIN-4(3H)-ONE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	Rf Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
2a	C_6H_5-	$C_{17}H_{10}ClN_3O_2$	323.73	166	0.462	S_1	54	12.98	12.94
2b	3-Br-C_6H_4-	$C_{17}H_9BrClN_3O_2$	402.63	210	0.483	S_1	56	10.44	1042
2c	2-Cl-C_6H_4-	$C_{17}H_9Cl_2N_3O_2$	358.18	190	0.405	S_2	51	11.73	11.72
2d	3-Cl-C_6H_4-	$C_{17}H_9Cl_2N_3O_2$	358.18	182	0.467	S_1	62	11.73	11.63
2e	4-Cl-C_6H_4-	$C_{17}H_9Cl_2N_3O_2$	358.18	214	0.453	S_1	63	11.73	11.70
2f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{19}H_{14}ClN_3O_4$	383.79	176	0.437	S_1	59	10.95	10.92
2g	4-OCH_3-C_6H_4-	$C_{18}H_{12}ClN_3O_3$	353.76	200	0.478	S_3	51	11.88	11.84
2h	4-SCH_3-C_6H_4-	$C_{18}H_{12}ClN_3O_2S$	369.83	210	0.405	S_3	54	8.67	8.62
2i	3-C_6H_5-O-C_6H_4-	$C_{23}H_{14}ClN_3O_3$	415.83	160	0.413	S_1	50	10.11	10.10
2j	4-$N(CH_3)_2$-C_6H_4-	$C_{19}H_{15}ClN_4O_2$	366.80	218	0.368	S_1	62	15.27	15.24

S_1 = Ethyl acetate : Hexane (1.4:8.6)

S_2 = Ethyl acetate : Hexane (3:7)

S_3 = Ethyla acetate : Hexane (2.5:7.5)

TABLE-3: PHYSICAL CONSTANTS OF 6-CHLORO-3-(1-ACETYL-5-ARYL-4,5-DIHYDRO-1H-PYRAZOL-3-YL)-CINNOLIN-4(3H)-ONE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	Rf Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
3a	C_6H_5-	$C_{19}H_{15}ClN_4O_2$	366.80	164	0.587	S_1	55	15.27	15.25
3b	3-Br-C_6H_4-	$C_{19}H_{14}BrClN_4O_2$	445.70	158	0.529	S_1	58	12.57	12.54
3c	2-Cl-C_6H_4-	$C_{19}H_{14}Cl_2N_4O_2$	401.25	170	0.619	S_1	59	13.96	13.95
3d	3-Cl-C_6H_4-	$C_{19}H_{14}Cl_2N_4O_2$	401.25	184	0.492	S_1	54	13.96	13.94
3e	4-Cl-C_6H_4-	$C_{19}H_{14}Cl_2N_4O_2$	401.25	164	0.604	S_1	61	13.96	13.96
3f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{21}H_{19}ClN_4O_4$	426.85	202	0.514	S_1	64	13.13	13.12
3g	4-OCH_3-C_6H_4-	$C_{20}H_{17}ClN_4O_3$	396.83	186	0.565	S_1	53	14.12	14.11
3h	4-SCH_3-C_6H_4-	$C_{20}H_{17}ClN_4O_2S$	412.89	188	0.551	S_1	57	13.57	13.55
3i	3-NO_2-C_6H_4-	$C_{19}H_{14}ClN_5O_4$	411.80	168	0.456	S_1	62	17.01	17.00
3j	2-OH-C_6H_4-	$C_{19}H_{15}ClN_4O_3$	382.78	244	0.412	S_1	50	14.64	14.63
3k	4-OH-C_6H_4-	$C_{19}H_{15}ClN_4O_3$	382.78	258	0.467	S_1	54	14.64	14.62
3l	3-C_6H_5-O-C_6H_4-	$C_{25}H_{19}ClN_4O_3$	458.90	229	0.421	S_1	51	12.21	12.20
3m	4-$N(CH_3)_2$-C_6H_4-	$C_{21}H_{20}ClN_5O_2$	409.87	226	0.442	S_1	50	17.09	17.05

S_1 = Ethyl acetate : Hexane (3 : 7)

TABLE-4: PHYSICAL CONSTANTS OF 6-CHLORO-3-(1-PHENYL-5-ARYL-4,5-DIHYDRO-1H-PYRAZOL-3-YL)-CINNOLIN-4(3H)-ONE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	Rf Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
4a	C_6H_5-	$C_{23}H_{17}ClN_4O$	400.86	158	0.701	S_1	65	13.98	13.94
4b	3-Br-C_6H_4-	$C_{23}H_{16}BrClN_4O$	479.76	150	0.524	S_1	62	11.68	11.64
4c	2-Cl-C_6H_4-	$C_{23}H_{16}Cl_2N_4O$	435.31	144	0.574	S_2	54	12.87	12.85
4d	3-Cl-C_6H_4-	$C_{23}H_{16}Cl_2N_4O$	435.31	122	0.594	S_1	53	12.87	12.86
4e	4-Cl-C_6H_4-	$C_{23}H_{16}Cl_2N_4O$	435.31	124	0.452	S_3	48	12.87	12.85
4f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{25}H_{21}ClN_4O_3$	460.91	124	0.486	S_3	45	12.16	12.15
4g	4-OCH_3-C_6H_4-	$C_{24}H_{19}ClN_4O_2$	430.89	140	0.553	S_2	60	13.00	12.98
4h	4-SCH_3-C_6H_4-	$C_{24}H_{19}ClN_4OS$	446.96	110	0.508	S_1	55	12.54	12.52
4i	3-C_6H_5-O-C_6H_4-	$C_{29}H_{21}ClN_4O_2$	49296	118	0.534	S_1	51	11.37	11.34
4j	4-$N(CH_3)_2$-C_6H_4-	$C_{25}H_{22}ClN_5O$	443.93	164	0.614	S_3	50	15.78	15.74

S_1 = Benzene : Acetone (9 : 1)

S_2 = Benzene : Acetone (8 : 2)

S_3 = Ethyla acetate : Hexane (2.5:7.5)

TABLE-5: PHYSICAL CONSTANTS OF 2-AMINO-4-ARYL-6-(6-CHLORO-4-OXO-3,4-DIHYDRO CINNOLIN-3-YL)NICOTINONITRILE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	R_f Value	Solvent System	Yield %	% of Nitrogen Calcd	% of Nitrogen Found
1	2	3	4	5	6	7	8	9	10
5a	C_6H_5-	$C_{20}H_{12}ClN_5O$	373.79	118	0.57	S1	55	18.74	18.72
5b	3-Br-C_6H_4-	$C_{20}H_{11}BrClN_5O$	452.69	196	0.51	S2	56	15.47	15.45
5c	2-Cl-C_6H_4-	$C_{20}H_{11}Cl_2N_5O$	408.24	164	0.38	S2	42	17.16	17.15
5d	3-Cl-C_6H_4-	$C_{20}H_{11}Cl_2N_5O$	408.24	210	0.69	S1	46	17.16	17.13
5e	4-Cl-C_6H_4-	$C_{20}H_{11}Cl_2N_5O$	408.24	220	0.69	S3	49	17.16	17.15
5f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{22}H_{16}ClN_5O_3$	433.85	230D	0.65	S3	54	16.14	16.13
5g	4-OCH_3-C_6H_4-	$C_{21}H_{14}ClN_5O_2$	403.82	206	0.50	S2	53	17.34	17.33
5h	4-SCH_3-C_6H_4-	$C_{21}H_{14}ClN_5OS$	419.88	198	0.39	S2	61	16.68	16.64
5i	3-C_6H_5-O-C_6H_4-	$C_{26}H_{17}ClN_5O_2$	465.89	118	0.67	S3	48	15.03	15.02
5j	4-$N(CH_3)_2$-C_6H_4-	$C_{22}H_{17}ClN_6O$	416.86	238	0.58	S1	45	20.16	20.15

S1 = Benzene : Acetone (5 :5)

S2 = Benzene : Mrthanol (7 : 3)

S3 = Benzene : Acetone (3 : 7)

TABLE-6: PHYSICAL CONSTANTS OF 4-ARYL-6-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-2-OXO-1,2-DIHYDROPYRIDINE-3-CARBONITRILE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	Rf Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
6a	C_6H_5-	$C_{20}H_{11}ClN_4O_2$	374.78	176	0.35	S_1	51	14.95	14.62
6b	3-Br-C_6H_4-	$C_{20}H_{10}BrClN_4O_2$	453.68	162	0.46	S_2	53	12.35	12.34
6c	2-Cl-C_6H_4-	$C_{20}H_{10}Cl_2N_4O_2$	409.23	154	0.54	S_3	58	13.69	13.65
6d	3-Cl-C_6H_4-	$C_{20}H_{10}Cl_2N_4O_2$	409.23	180	0.48	S_1	46	13.69	13.66
6e	4-Cl-C_6H_4-	$C_{20}H_{10}Cl_2N_4O_2$	409.23	186	0.38	S_2	59	13.69	13.65
6f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{22}H_{15}ClN_4O_4$	434.83	172	0.48	S_2	51	12.88	12.84
6g	4-OCH_3-C_6H_4-	$C_{21}H_{13}ClN_4O_3$	404.81	180	0.49	S_3	55	13.84	13.81
6h	4-SCH_3-C_6H_4-	$C_{21}H_{13}ClN_4O_2S$	420.87	198	0.55	S_1	48	13.31	13.25
6i	3-C_6H_5-O-C_6H_4-	$C_{26}H_{15}ClN_4O_3$	466.88	128	0.52	S_3	49	12.00	11.97
6j	4-$N(CH_3)_2$-C_6H_4-	$C_{22}H_{16}ClN_5O_2$	417.85	158	0.31	S_3	52	16.76	16.74

S_1 = Ethyl acetate : Hexane (1 : 9)

S2 = Ethyl acetate : Hexane (2 : 8)

S3 = Acetone : Benzene (1.5 : 8.5)

TABLE-7: PHYSICAL CONSTANTS OF 2-AMINO-4-ARYL-6-(6-CHLORO-4-OXO-3,4-DIHYDRO CINNOLIN-3-YL)-4H-PYRAN-3-CARBONITRILE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	Rf Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
7a	C_6H_5-	$C_{20}H_{13}ClN_4O_2$	376.79	186	0.35	S_1	54	14.87	14.85
7b	3-Br-C_6H_4-	$C_{20}H_{12}BrClN_4O_2$	455.69	198	0.45	S_2	54	12.29	12.27
7c	2-Cl-C_6H_4-	$C_{20}H_{12}Cl_2N_4O_2$	411.24	265	0.42	S_1	52	13.62	13.61
7d	3-Cl-C_6H_4-	$C_{20}H_{12}Cl_2N_4O_2$	411.24	226	0.52	S_1	55	13.62	13.60
7e	4-Cl-C_6H_4-	$C_{20}H_{12}Cl_2N_4O_2$	411.24	270	0.57	S_2	54	13.62	13.62
7f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{22}H_{17}ClN_4O_4$	436.85	>300	0.38	S_3	52	12.83	12.81
7g	4-OCH_3-C_6H_4-	$C_{21}H_{15}ClN_4O_3$	406.82	220	0.55	S_2	53	13.77	13.75
7h	4-SCH_3-C_6H_4-	$C_{21}H_{15}ClN_4O_2S$	422.89	285D	0.49	S_2	51	13.25	13.24
7i	3-C_6H_5-O-C_6H_4-	$C_{26}H_{17}ClN_4O_3$	468.89	189	0.51	S_2	54	11.95	11.94
7k	4-$N(CH_3)_2$-C_6H_4-	$C_{22}H_{18}ClN_5O_2$	419.86	>300	0.63	S_1	56	16.68	16.64

S_1 = Ethyl acetate : Hexane (1:9), S_2 = Ethyl acetate : Hexane (2.5 : 7:5), S_3 = Acetone : Benzene (2 : 8)

TABLE-8: PHYSICAL CONSTANTS OF ETHYL-6-ARYL-4-(6-CHLORO-4-OXO-3,4-DIHYDRO CINNOLIN-3-YL)-2-OXO-CYCLOHEX-3-ENE-1-CARBOXYLATE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	Rf Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
8a	C_6H_5-	$C_{23}H_{19}ClN_2O_4$	422.86	212	0.46	S_1	57	6.62	6.61
8b	3-Br-C_6H_4-	$C_{23}H_{18}BrClN_2O_4$	501.76	224	0.41	S_1	58	5.58	5.54
8c	2-Cl-C_6H_4-	$C_{23}H_{18}Cl_2N_2O_4$	457.31	118	0.52	S_1	60	6.13	6.11
8d	3-Cl-C_6H_4-	$C_{23}H_{18}Cl_2N_2O_4$	457.31	186	0.37	S_1	54	6.13	6.12
8e	4-Cl-C_6H_4-	$C_{23}H_{18}Cl_2N_2O_4$	457.31	132	0.44	S_2	55	6.13	6.10
8f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{25}H_{23}ClN_2O_6$	482.91	238	0.56	S_2	54	5.80	5.79
8g	4-OCH_3-C_6H_4-	$C_{24}H_{21}ClN_2O_5$	452.89	146	0.34	S_2	58	6.19	6.17
8h	4-SCH_3-C_6H_4-	$C_{24}H_{21}ClN_2O_4S$	468.95	156	0.38	S_3	54	5.97	5.99
8i	3-C_6H_5-O-C_6H_4-	$C_{29}H_{23}ClN_2O_5$	514.96	164	0.42	S_3	55	5.44	5.43
8J	4-$N(CH_3)_2$-C_6H_4-	$C_{25}H_{24}ClN_3O_4$	465.93	142	0.49	S_1	54	9.02	9.01
8K	C_9H_6ClN	$C_{26}H_{19}Cl_2N_3O_4$	508.27	159	0.47	S_3	53	8.27	8.24

S_1 = Ethyl acetate : Hexane (2 : 8)

S_2= Ethyl acetate : Hexane (3 : 7)

S3= Acetone : Benzene (1 :9)

TABLE-9: PHYSICAL CONSTANTS OF 6-CHLORO-3-(4-ARYL-3-OXO-3,3a,4,5-TETRAHYDRO-2H-INDAZOL-6-YL)-CINNOLIN-4(3H)-ONE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	R_f Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
9a	C_6H_5-	$C_{21}H_{15}ClN_4O_2$	390.82	210	0.48	S_1	45	14.34	14.33
9b	3-Br-C_6H_4-	$C_{21}H_{14}BrClN_4O_2$	469.72	198	0.54	S_1	43	11.93	11.90
9c	2-Cl-C_6H_4-	$C_{21}H_{14}Cl_2N_4O_2$	425.27	220	0.38	S_1	48	13.17	13.15
9d	3-Cl-C_6H_4-	$C_{21}H_{14}Cl_2N_4O_2$	425.27	174	0.36	S_2	46	13.17	13.14
9e	4-Cl-C_6H_4-	$C_{21}H_{14}Cl_2N_4O_2$	425.27	170	0.49	S_3	45	13.17	13.15
9f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{23}H_{19}ClN_4O_4$	450.87	178	0.55	S_2	42	12.43	12.44
9g	4-OCH_3-C_6H_4-	$C_{22}H_{17}ClN_4O_3$	420.85	159	0.54	S_1	43	13.31	13.30
9h	4-SCH_3-C_6H_4-	$C_{22}H_{17}ClN_4O_2S$	436.92	204	0.41	S_1	45	12.82	12.81
9i	3-C_6H_5-O-C_6H_4-	$C_{27}H_{19}ClN_4O_3$	482.92	181	0.59	S_3	42	11.60	11.59
9j	4-$N(CH_3)_2$-C_6H_4-	$C_{23}H_{20}ClN_5O_2$	433.89	194	0.51	S_3	49	16.14	16.13
9k	C9H6ClN	C24H15Cl2N5O2	476.31	226	0.61	S_2	53	14.22	14.20

S_1 = Ethyl acetate : Hexane (1.4:8.6)

S_2 = Ethyl acetate : Hexane (3:7)

S_3 = Ethyla acetate : Hexane (2.5:7.5)

TABLE-10: PHYSICAL CONSTANTS OF 6-CHLORO-3-(2-ARYL-2,3-DIHYDRO-1,5-BENZOTHIAZEPIN-4-YL)-CINNOLIN-4(3H)-ONE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	Rf Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
10a	C_6H_5-	$C_{23}H_{16}ClN_3OS$	417.91	109	0.590	S_1	65	10.05	10.04
10b	3-Br-C_6H_4-	$C_{23}H_{15}BrClN_3OS$	496.81	140	0.546	S_2	66	8.46	8.44
10c	2-Cl-C_6H_4-	$C_{23}H_{15}Cl_2N_3OS$	452.36	130	0.482	S_1	59	9.29	9.25
10d	3-Cl-C_6H_4-	$C_{23}H_{15}Cl_2N_3OS$	452.36	125	0.637	S_1	52	9.29	9.24
10e	4-Cl-C_6H_4-	$C_{23}H_{15}Cl_2N_3OS$	452.36	125	0.593	S_1	54	9.29	9.26
10f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{25}H_{20}ClN_3O_3S$	477.96	115	0.545	S_2	57	8.79	8.75
10g	4-OCH_3-C_6H_4-	$C_{24}H_{18}ClN_3O_2S$	447.94	117	0.470	S_2	55	9.38	9.36
10h	4-SCH_3-C_6H_4-	$C_{24}H_{18}ClN_3OS_2$	464.00	110	0.567	S_1	53	9.06	9.04
10i	3-C_6H_5-O-C_6H_4-	$C_{29}H_{20}ClN_3O_2S$	510.01	100	0.518	S_1	64	8.24	8.21
10j	4-$N(CH_3)_2$-C_6H_4-	$C_{25}H_{21}ClN_4OS$	460.98	95	0.488	S_2	65	12.15	12.13

S_1 = Ethyl acetate : Hexane (1.5 : 8.5)

S_2 = Ethyl acetate : Hexane (2.4 : 7.6)

TABLE-11: PHYSICAL CONSTANTS OF (1E)-ARYL-[4-(6-CHLORO-4-OXO-3,4-DIHYDROCINNOLIN-3-YL)-1,3-THIAZOL-2-YL]HYDRAZONE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^0C	Rf Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
11a	C_6H_5-	$C_{18}H_{12}ClN_5OS$	381.84	168	0.373	S_2	64	18.34	18.33
11b	3-Br-C_6H_4-	$C_{18}H_{11}BrClN_5OS$	460.74	125	0.394	S_1	65	15.20	15.18
11c	2-Cl-C_6H_4-	$C_{18}H_{11}Cl_2N_5OS$	416.28	178	0.291	S_1	66	16.82	16.80
11d	3-Cl-C_6H_4-	$C_{18}H_{11}Cl_2N_5OS$	416.28	120	0.437	S_1	65	16.82	16.82
11e	4-Cl-C_6H_4-	$C_{18}H_{11}Cl_2N_5OS$	416.28	150	0.494	S_2	64	16.82	16.81
11f	3,4-$(OCH_3)_2$-C_6H_3-	$C_{20}H_{16}ClN_5O_3S$	441.89	130	0.444	S_3	59	15.85	15.846
11g	3,4,5-$(OCH_3)_3$-C_6H_2-	$C_{21}H_{18}ClN_5O_4S$	471.92	140	0.541	S_3	58	14.84	14.81
11h	4-OCH_3-C_6H_4-	$C_{19}H_{14}ClN_5O_2S$	411.87	140	0.423	S_1	55	16.37	16.35
11i	2-OH-C_6H_4-	$C_{18}H_{12}ClN_5O_2S$	397.84	190	0.535	S_1	57	17.60	17.58
11j	3-C_6H_5-O-C_6H_4-	$C_{24}H_{16}ClN_5O_2S$	473.94	118	0.425	S_2	59	14.78	14.77
11k	4-$N(CH_3)_2$-C_6H_4-	$C_{20}H_{17}ClN_6OS$	424.91	145	0.295	S_1	62	19.78	19.74

S_1 = Ethyl acetate : Hexane (2:8)

S_2 = Ethyl acetate : Hexane (0.5:9.5)

S_3 = Ethyl acetate : Hexane (1:9)

TABLE-12: PHYSICAL CONSTANTS OF 3-(2-AMINO-6-ARYLPYRIMIDIN-4-YL)-6-CHLOROCINNOLIN-4(3H)-ONE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	Rf Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
12a	C_6H_5-	$C_{18}H_{12}ClN_5O$	349.77	245	0.69	S_1	56	20.02	20.01
12b	3-Br-C_6H_4-	$C_{18}H_{11}BrClN_5O$	428.67	230	0.54	S_2	54	16.34	16.32
12c	2-Cl-C_6H_4-	$C_{18}H_{11}Cl_2N_5O$	384.22	282	0.68	S_2	49	18.23	18.22
12d	3-Cl-C_6H_4-	$C_{18}H_{11}Cl_2N_5O$	384.22	180	0.56	S_1	48	18.23	18.21
12e	4-Cl-C_6H_4-	$C_{18}H_{11}Cl_2N_5O$	384.22	134	0.71	S_3	47	18.23	18.23
12f	C_4H_3-O-	$C_{16}H_{10}ClN_5O_2$	339.74	308	0.54	S_1	45	20.61	20.58
12g	4-OCH_3-C_6H_4-	$C_{19}H_{14}ClN_5O_2$	379.80	304	0.48	S_3	46	18.44	18.42
12h	4-SCH_3-C_6H_4-	$C_{19}H_{14}ClN_5OS$	395.80	260	0.62	S_2	48	17.69	17.66
12i	3-C_6H_5-O-C_6H_4-	$C_{24}H_{16}ClN_5O_2$	441.87	175	0.39	S_1	52	15.85	15.81
12j	4-$N(CH_3)_2$-C_6H_4-	$C_{20}H_{17}ClN_6O$	392.84	160	0.48	S_2	53	21.39	21.38

S_1 = Ethyl acetate : Hexane (1.5 : 8.5)

S_2 = Ethyl acetate : Hexane (2 : 8)

S_3 = Ethyl acetate : Hexane (3: 7)

TABLE-13: PHYSICAL CONSTANTS OF 6-CHLORO-3-(6-ARYL-2-MERCAPTO-3,4-DIHYDRO PYRINIDIN-4-YL)-4(3H)-ONE

Sr. No.	R-	Molecular Formula	Molecular Weight	M. P. ^{0}C	Rf Value	Solvent System	Yield %	% of nitrogen Calcd	% of nitrogen Found
1	2	3	4	5	6	7	8	9	10
13a	C_6H_5-	$C_{18}H_{13}ClN_4OS$	368.84	149	0.48	S_1	54	15.19	15.17
13b	3-Br-C_6H_4-	$C_{18}H_{12}BrClN_4OS$	447.74	108	0.69	S_1	54	12.51	12.50
13c	2-Cl-C_6H_4-	$C_{18}H_{12}Cl_2N_4OS$	403.89	156	0.52	S2	56	13.89	13.88
13d	3-Cl-C_6H_4-	$C_{18}H_{12}Cl_2N_4OS$	403.89	182	0.50	S_1	55	13.89	13.87
13e	4-Cl-C_6H_4-	$C_{18}H_{12}Cl_2N_4OS$	403.89	188	0.54	S_3	53	13.89	13.88
13f	3,4-$(OCH_3)_2$-C_6H_4-	$C_{20}H_{17}ClN_4O_3S$	428.89	290	0.68	S_3	58	13.06	13.04
13g	4-OCH_3-C_6H_4-	$C_{19}H_{15}ClN_4O_2S$	398.87	178	0.63	S_1	49	14.05	14.03
13h	4-SCH_3-C_6H_4-	$C_{19}H_{15}ClN_4OS_2$	414.93	145	0.65	S_3	47	13.50	13.47
13i	4-OH-C_6H_4-	$C_{18}H_{13}ClN_4O_2S$	384.84	140	0.67	S_3	51	14.56	14.55
13j	3-C_6H_5-O-C_6H_4-	$C_{24}H_{17}ClN_4O_2S$	460.94	188	0.61	S_2	50	12.16	12.15
13k	4-$N(CH_3)_2$-C_6H_4-	$C_{20}H_{18}ClN_5OS$	411.91	164	0.57	S_2	54	17.00	12.98

S_1 = Ethyl acetate : Hexane (1.5 : 8.5)

S_2 = Ethyl acetate : Hexane (2 : 8)

S_3 = Ethyl acetate : Hexane (3: 7)