# STUDIES ON SOME COMPOUNDS OF MEDICINAL INTEREST

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IN
THE FACULTY OF SCIENCE (CHEMISTRY)
BY


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UNDER THE GUIDANCE
OF

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

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

***(Dipen H. Vyas)***

Dt. 11.05.2004
Place : Rajkot.

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

Date : 11-05-2004
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DEDICATED TO
MY GRAND MOTHER
&
BELOVED MY PARENTS

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*Dipen H. Vyas*

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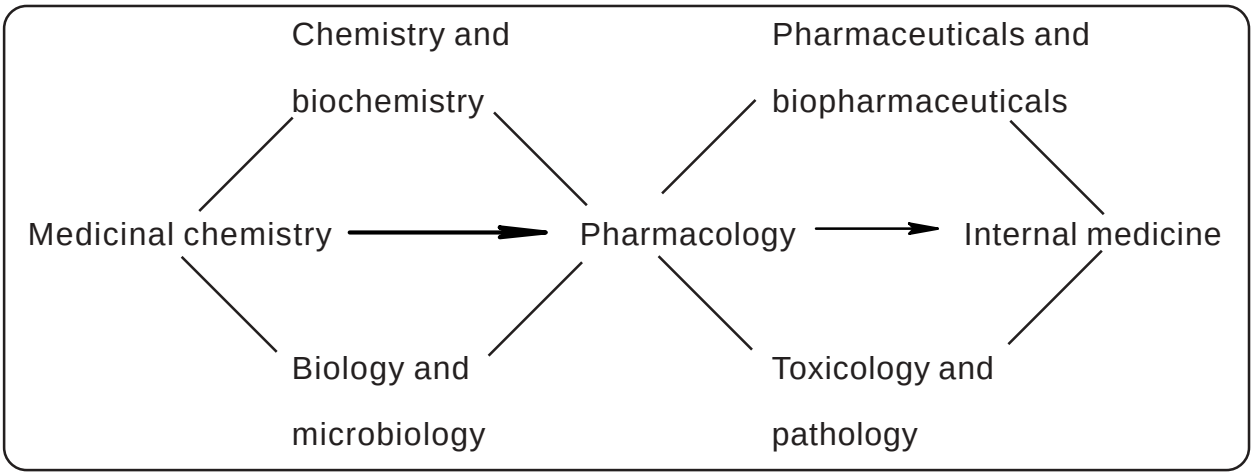
## General Introduction

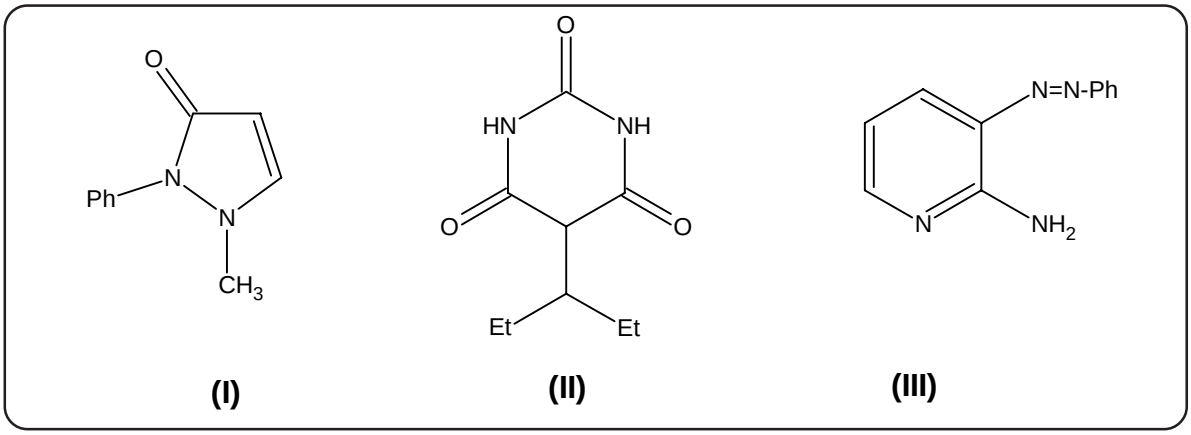
Research in the field of pharmaceuticals has its most important task in the development of new and better drugs and their successful introduction in to clinical practice. The word 'drug' is derived from the French word ‘drogue’, which means a dry herb. Ingeneral word a drug may be defined as a substance used in the prevention, diagnosis, treatment or cure of disease in man or other animal. According to WHO, a drug may be as any substance or product which is used or intended to be used for modifying or exploring physiological systems or pathological states for the benefit of the recipient.

Organic chemistry and medicinal chemistry share a remarcable common history. The relationship of medicinal chemistry to other disciplines has been indicated by the following diagram




The basis of understanding in the medicinal chemistry like in an awareness of the relationships between the chemistry of a particular compound or group of compounds and their interactions with the body, which is known as structure activity relationship, and the mechanism by which the compound influences the biological system, which is known as its mode of action.

The contribution of organic chemistry to be development of scientific medicine in the 19th century came mainly form acyclic and carbocyclic compounds, although the pyrazolone antipyrin (I) was introduced as an antipyretic and analgesic in 1984 and the first barbiturate barbitone (veranol) (II) in 1903. Guttmann treated, malaria with methylene blue in 1891, with slight success, and in 1912 he introduced acriflavin as trypancide, it has proved to be move valuable as an antiseptic, phenazopyridin (pyridium) (III) was introduced for the same purpose in 1926, and although it is relatively in effective it has continued to be used since it has some analgesic action.




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

The chemistry of the heterocyclic compounds is as logical as that of aliphatic or aromatic compounds. A heterocyclic compound is one, which possess acyclic structure with at least two different kinds of atoms in the ring. Heterocyclic compounds have great applicability in pharmaceutics because they have specific chemical reactivity and provides false synthon in biosynthetic process or block the normal functioning of biological receptors. Among large number of heterocycles found in nature, heterocycles containing nitrogen are most abundant than those containing oxygen or sulphur owing to their wide distribution in nucleic acid instance and involvement in almost every physiological process of plant and animals.

Most of the alkaloids which are nitrogenous bases occuring in plants and many antibiotic including penicillin and streptomycin also contain heterocyclic ring system. Many natural pigments such as indigo, haemoglobin and anthocyanin are heterocycles.

Most of the sugars and their derivatives including vitamin C, for instance, exist largely in the form of five membered (furanoside str.) or six membered (pyranoside str.) ring containing one oxygen atom. Vitamin B6 (Pyridoxine) is a derivative of pyridine essential in amino acid metabolism, important drugs, poisons and medicines (both natural and synthetic) such as sulphatiazole, pyrethrin, rotennone, strychnine, reserpine, certain of the antihistaminics, the ergof alkaloids, caffeine, cocaine, barbiturates etc. are heterocyclic.

Natural products containing heterocyclic compound such as alkaloids and glycosides have been used since old age, as remedial agents. Febrical alkaloid from ancient chinese drug chang shan, reserpine from Indian rouwolfia, curen alkaloid from arrow poison codeiene, tropine and strychnine are all examples of heterocyclic compounds. Many antibiotics like penicillin, cephalosporin, norfloxacin etc., veterinary products like atrazine and simazine are well known examples of some compounds of medicinal interest.

During the period 1930-1950, a large number of important drugs have been introduced and this period is regarded as "Golden Period" of now drug discovery. Thus starting from 1933 the first antibacterial drug prontosil leading to various sulfa drugs; 1940- penicillin; 1945- chloroguine, an antimalarial; 1950-mothyldopa, antidiabetic; 1958-coronary vasodilator; 1960-semisynthetic penicillin, antibacterial; 1965-trimethoprin-antimicrobial; 1967-captopril, antihypertensive. These are some of the specific examples representing new therapeutics.

Taking in to consideration the applicability of heterocyclic compounds, the placement of variety of substituted in these nuclei has been designed in order to evaluate the synthesized products for their better pharmaceutical profile.

## AIM AND OBJECTIVES

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

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

1. To synthesize therapeutically active compounds like pyrazolines, isoxazoles, cyanopyridines, cyanopyrans, cyano pyridones, cyano piperidones, cyano pyrimidines, pyranones and Indazole bearing 3,5-dibrimo-4-methoxy acetophenone moiety.
2. To generate several intermediates, like chalcones, cyclohexenones bearing 3,5-dibrimo-4-methoxy acetophenone moiety.
3. To characterize these products for structure elucidation using several spectroscopic techniques like IR, PMR and Mass spectral studies.
4. To assess the reaction and purity of the compounds were done by TLC.
5. To evaluate these products for better drug potential against different strains of bacteria and fungi.
6. All the compounds have been sent to TAACF, southern research institute, and USA; for antitubercular testing.

"**STUDIEIS ON SOME COMPOUNDS OF MEDICINAL INTEREST**"

A comprehensive summary of the work to be incorporated in the thesis entitled "**STUDIEIS ON SOME COMPOUNDS OF MEDICINAL INTEREST**" is described as follow

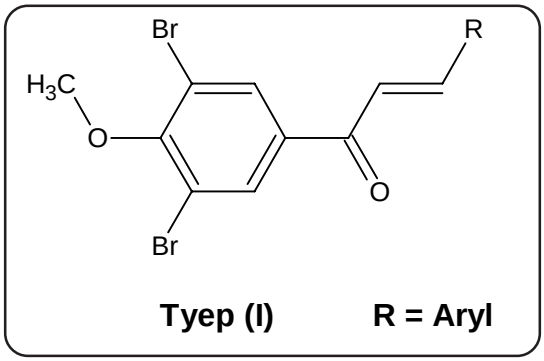
## STUDIEIS ON CHALCONE DERIVATIVES

The chemistry of chalcones containing an active keto-ethylenic linkage has assumed importance because of their versatility in the synthesis of many heterocyclic compounds. Furthermore, they are also associated with wide spectrum of pharmacological activities and industrial applications. The chalcones are reported to possess antibacterial, antiviral, agrochemical and diuretic activities. They have been found to be applicable for photosensitive materials, polymerization catalysts fluorescents brightening agents, pigments etc. With a view to supplement these valid observations, it was contemplated to synthesize some new chalcone derivatives using 3,5-dibromo-4-methoxy acetophenone with better biological activities which have been described as under.

## PART - I : STUDIEIS ON ISOXAZOLES

Isoxazole derivatives represent one of the modest class of compound possessing wide range of therapeutic activities, such as antidepressant, skeleton muscle relaxant, antidiabetic, anti-inflammatory, analgesic etc. With a view to mapping better medicinal value and to evaluate its pharmacological profile, we have synthesized some new isoxazole derivatives, which have been described as under.

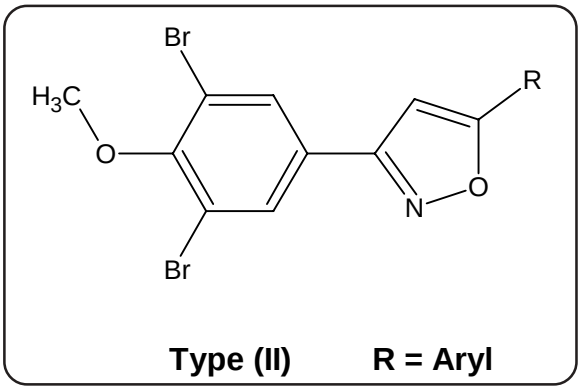
**SECTION-I : Synthesis and biological screening of (2E)-1-(3,5-Dibromo-4-methoxyphenyl)-3-(aryl)-prop-2-en-1-ones.**




**Tyep (I)** **R = Aryl**

The chalcones of Type - (I) have been synthesized by the condensation of 3,5- dibromo-4-methoxy acetophenone with various aromatic aldehydes.

**SECTION-II : Synthesis and biological screening of 3-(3,5-Dibromo-4-methoxyphenyl)-5-aryl isoxazoles.**



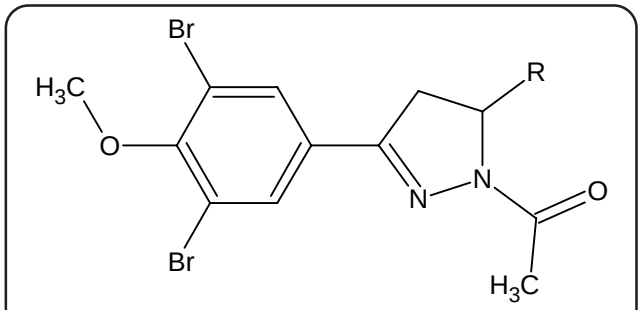

**Type (II)** **R = Aryl**

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

## PART- II : STUDIES ON PYRAZOLINES

Literature survey reveals that pyrazolines are well known for their biological activities. These have been reported to be active as anticancer, anticonvulsant, insecticidal, antitubercular, antibacterial and antipyretic. In order to achieving better drug potential, we have synthesis some new pyrazoline derivatives, which have been described as under.

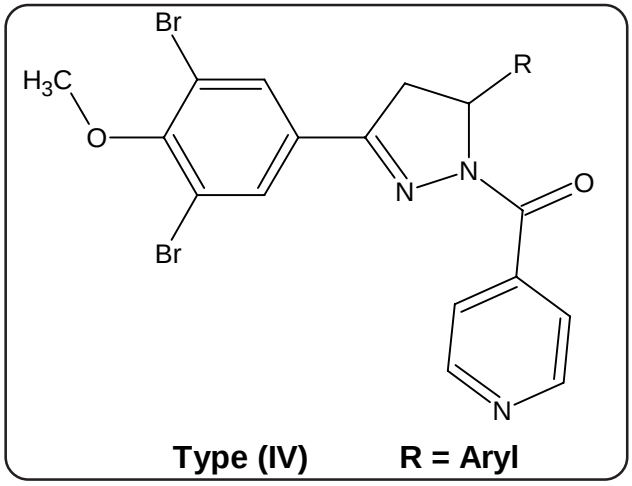
**SECTION-I : Synthesis and biological screening of 1-Acetyl-3-(3,5-dibromo-4-methoxy phenyl)-5-aryl-4,5-dihydro-1H-pyrazoles.**




**Type (III) R = Aryl**

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

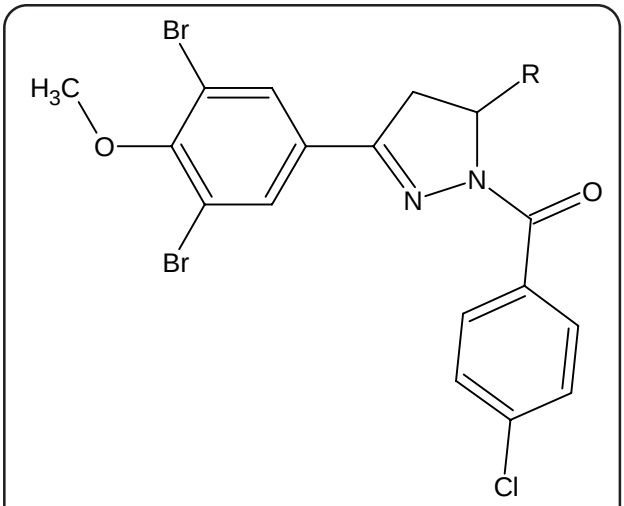
**SECTION-II : Synthesis and biological screening of 4-{[ 3-(3,5-Dibromo-4-methoxyphenyl)-5-aryl-4,5-dihydro-1H-pyrazol-1-yl]caronyl} pyridines.**




**Type (IV) R = Aryl**

Pyrazoline derivatives of Type - (IV) have been synthesized by the condensation of the chalcones of Type - (I) with isonicotinic hydrazide in presence of glacial acetic acid.

**SECTION-III : Synthesis and biological screening of 1-(4-Chlorobenzoyl)-3-(3,5-dibromo-4-methoxyphenyl)-5-aryl-4,5-dihydro-1H-pyrazoles.**



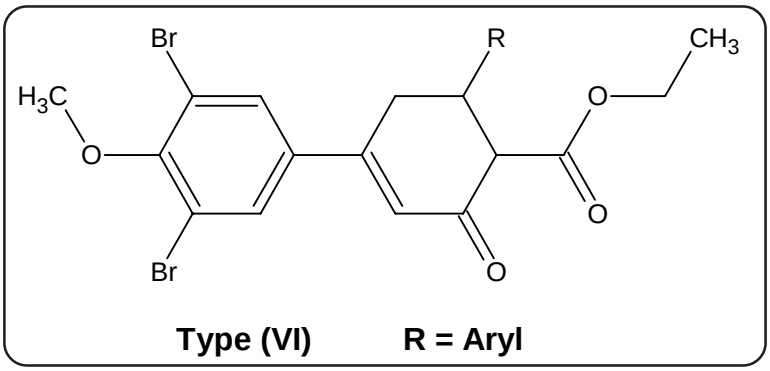

**Type (V)** **R = Aryl**

Pyrazoline derivatives of Type - (V) have been synthesized by the condensation of the chalcones of Type - (I) with para chlorobenzoyl hydrazide in presence of glacial acetic acid.

## PART-III : STUDIES ON INDAZOLES

Indazole derivatives have attracted considerable attention in view of their great therapeutic importance as anticancer, antibacterial, antifungial, antitubercular agents. To approach this goal, synthesis of some novel indazole has been described as under.

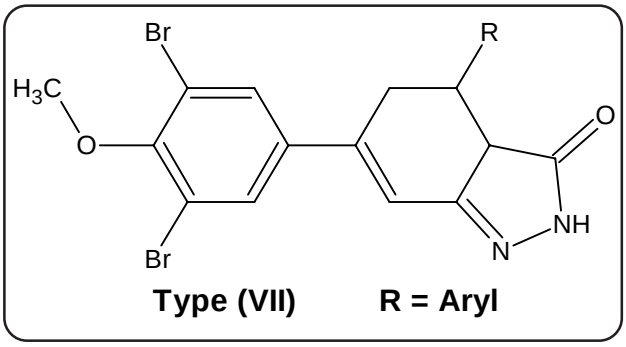
**SECTION-I : Synthesis and biological screening of Ethyl 4-(3,5-dibromo-4-methoxy phenyl)-6-aryl- 2- oxocyclohex-3-ene-1-carboxylates.**




**Type (VI)  R = Aryl**

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

**SECTION-II:Synthesis and biological screening of 6-(3,5-Dibromo-4-methoxyphenyl)-4-aryl- 2,3a,4,5-tetrahydro-3H-indazol-3-ones.**



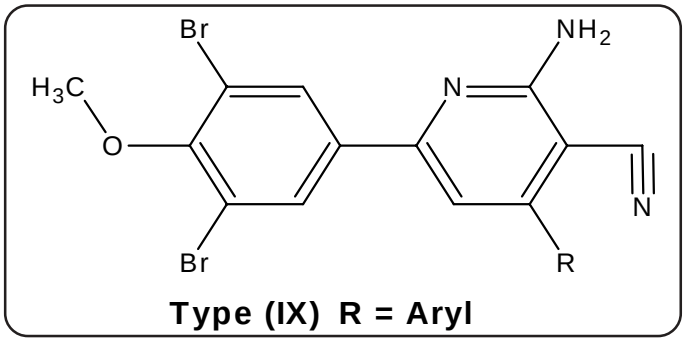

**Type (VII)  R = Aryl**

Indazole derivatives of Type - (VII) have been synthesized by the cyclocondensation of the cyclohexenoes of Type - (VI) with hydrazine hydrate.

## PART-IV: STUDIES ON CYANO PYRIDINES

Biological importance of cyanopyridine derivatives is well known. They have been reported to be active as an anticonvulsant, antibacterial, antitubercular, antiinflammatory, herbicidal and antitumor. In order to develop medicinally importnat compounds, it was considered of interest to synthesise some new cyano pyridines shown as under.

**SECTION-I : Synthesis and biological screening of 2-Amino-3-cyano-6-(3,5-dibromo-4-methoxyphenyl)-4-aryl-pyridines.**



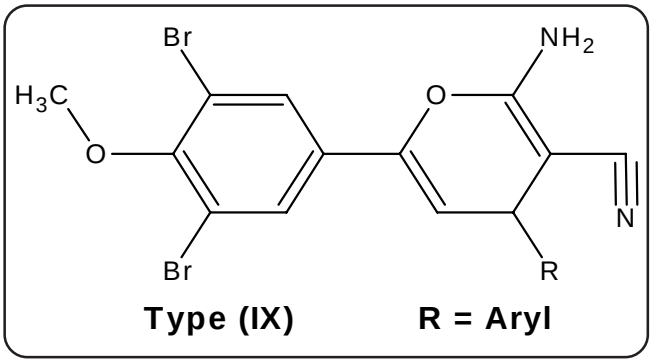

**Type (IX) R = Aryl**

Cyano pyridine derivatives of Type - (VIII) have been synthesized by the condensation of the chalcones of Type - (I) with malanonitrile and ammonium acetate.

## PART-V : STUDIES ON CYANO PYRANS

Cyano pyran derivatives have attracted considerable attention in view of their great therapeutic importance as anticonvulsant,. Antiintective, antimalerial, cardiotonic, tranquilizer, antidiarrheal etc. Keeping this in view, it was considered of interest to synthesize some novel cyano pyrans, which have been described as under.

**SECTION-I : Synthesis and biological screening of 2-Amino-3-cyano-6-(3,5-dibromo-4-methoxyphenyl)-4-aryl-pyrans.**



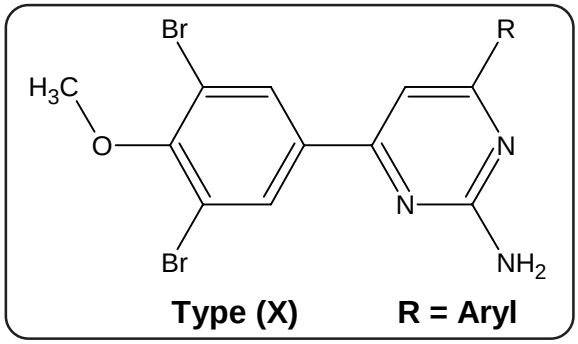

**Type (IX) R = Aryl**

Cyano pyran derivatives of Type- (IX) have been synthesized by the reaction of the chalcones of Type - (I) with malanonitrile and pyridine.

## PART - VI : STUDIES ON PYRIMIDINES

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, antitubercular, antibacterial, herbicidal etc. This valid observation led us to synthesise some new pyrimidines in search of agents having more medicinally activities, which have been described as under.

### SECTION-I : Synthesis and biological screening of 4-(3,5-Dibromo-4-methoxyphenyl)-6-aryl-pyrimidine-2-amines.



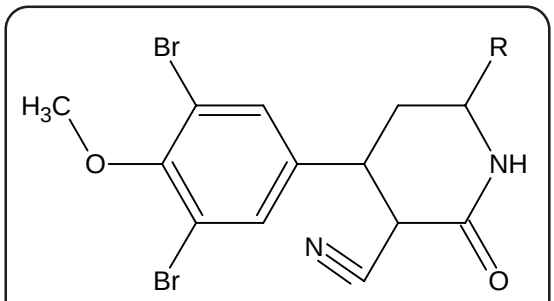

**Type (X)** **R = Aryl**

Pyrimidine derivative of Type - (X) have been prepared by the reaction of the chalcones of Type - (I) with guanidine hydrochloride in presence of sodium ethoxide.

## PART - VII : STUDIES ON PIPERIDINONES

Piperidinone derivatives are the important class of therapeutic agents, which have been deeply studied during search on new potential agents. They have been found to be active as anticoagulant, antitumor, analgesic, antiinflammatory, herbicidal and antimicrobial agent. In light of these findings, synthesis of some new piperidinone derivatives has been described as under.

**SECTION-I : Synthesis and biological screening of 3-Cyano-4-(3,5-dibromo-4-methoxyphenyl)-6-aryl-2-oxopiperidines**.



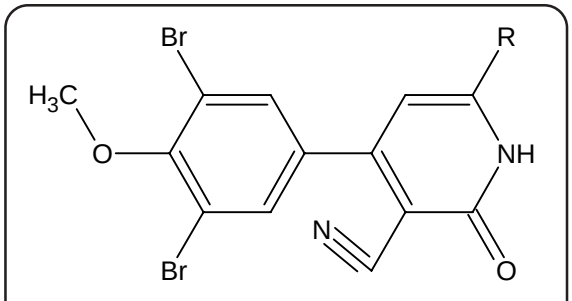

**Type (XI)** **R = Aryl**

Piperidinone derivatives of Type - (XI) have been prepared by the reaction of the chalcones of Type - (I) with cyano acetamide in presence of sodium ethoxide.

## PART-VIII: STUDIES ON CYANO PYRIDONES

In view of powerful biological activities shown by cyano pyridones, like antitumor, antimicrobial, analgesics, anti-inflammatory, herbicidal and antitubercular, it was worthwhile to synthesized some novel cyano pyridone derivatives possessing better biological active value with least side effect, which have been described as under.

**SECTION-I : Synthesis and biological screening of 3-Cyano-4-(3,5-dibromo-4-methoxyphenyl)-6-aryl-2-oxo-1,2-dihydropyridines.**



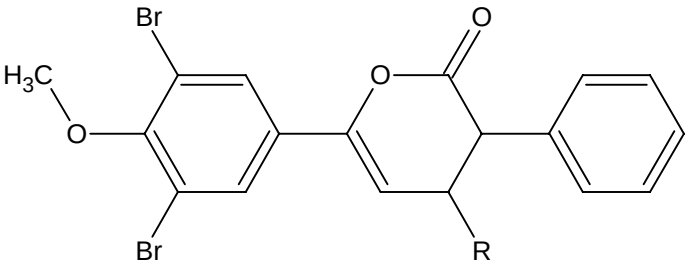

**Type (XII)** **R = Aryl**

Cyano pyridones derivatives of Type - (XII) have been prepared by the reaction of the chalcones of Type - (I) with ethyl cyano acetate and ammonium acetate.

## PART - IX: STUDIES ON PYRANONES

Pyranone nucleus has been the subject of several investigators in the realm of potential therapeutic activities like antibacterial, antitubercular, antiinflammatory, herbicidal and antitumor. In order to explore the activities associated with this nucleus, we have synthesized some new pyranones, which have been described as under.

### SECTION-I: Synthesis and biological screening of 6-(3,5-Dibromo-4-methoxyphenyl)-4-aryl-3-phenyl-3,4-dihydro-2H-pyran-2-ones.




**Type (XIII)** **R = Aryl**

Pyranones derivatives of Type - (XIII) have been prepared by the reaction of the chalcones of Type-(I) with ethyl phenyl acetate in presence of sodium ethoxide.

The structure elucidation of the 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. The purity of the compounds synthesized was checked by TLC.

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

The products 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 1.25 ug/ml using Rifampin as a standard drug.

Signature of Guide

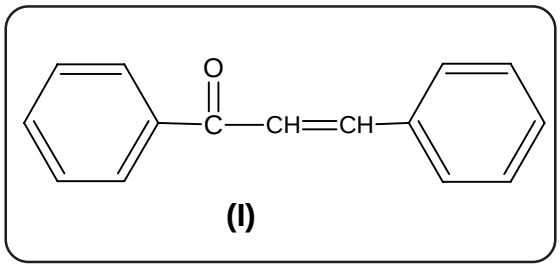
[Dr. H. S. JOSHI]

Signature of Students

[DEPEN H. VYAS]

## INTRODUCTION

The growing potent literatures of recent years demonstrate that chalcone, being a very active synthon, variety of novel heterocycles with good pharmacological profile can be designed. The presence of keto ethylenic linkage in general, gives the compound a great synthetic importance.

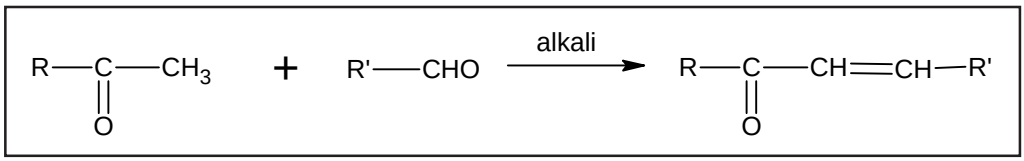



**(I)**

The term "Chalcone" was first coined by Kostanecki and Tambor[1], who did pioneering work in the synthesis of natural colouring compounds. This is well illustrated by benzal acetonphenone or phenyl styryl ketone or β-phenyl acrylophenone, γ-oxo-α, γ-diphenyl-α-propylene and α-phenyl-β-benzoyl-ethylene[2].

## SYNTHETIC ASPECT

The most convenient method for the preparation of chalcone consists is condensing an appropriate aryl methyl ketone with an aromatic aldehyde in presence of alcoholic KOH[3,4] that involves the Claisen-Schmidt condensation.




The other condensing agent employed in several cases and sometimes with advantages are hydrogen chloride[5,6] anhydrous aluminium chloride[7], weak bases like piperidine[8], boron trifluoride[9], aminoacids[10], organocadmium compounds[11], phosphorous oxychloride[12], borax[13], perchloric acid[14]and zinc chloride and acetic anhydride[15].

Chalcones can also be synthesised by condensing several other reagents instead of an aldehyde and ketone.

1. Nencki reaction with cinnamic acid on an aromatic compounds[16].
2. Di azo coupling of phenyl diazonium chloride with benzoyl acrylic acid[17].
3. Friedel craft's cinnamoylation[18].
4. Fries rearrangement of aryl cinnamates[19].

## REACTION MECHANISM

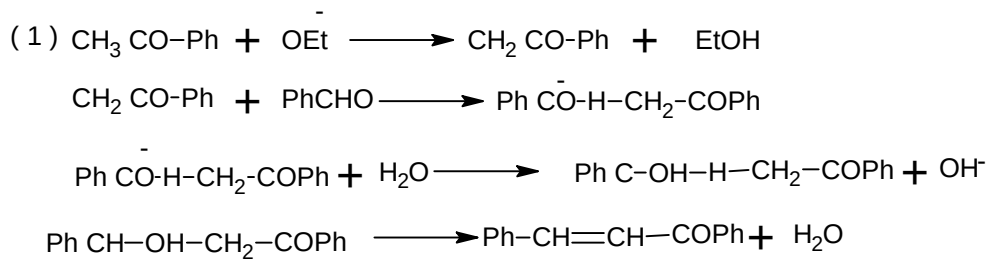
The following two mechanisms have been suggested for the synthesis of chalcones.

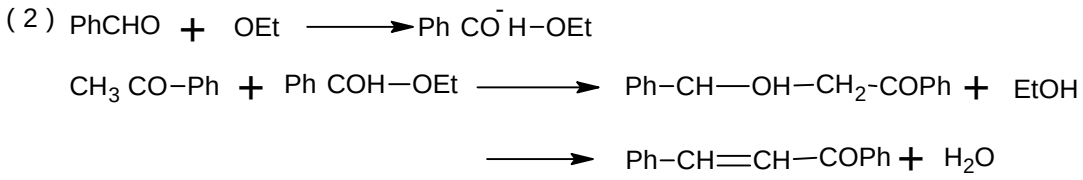
(A)Base catalysed[20]

(B) Acid catalysed[21]

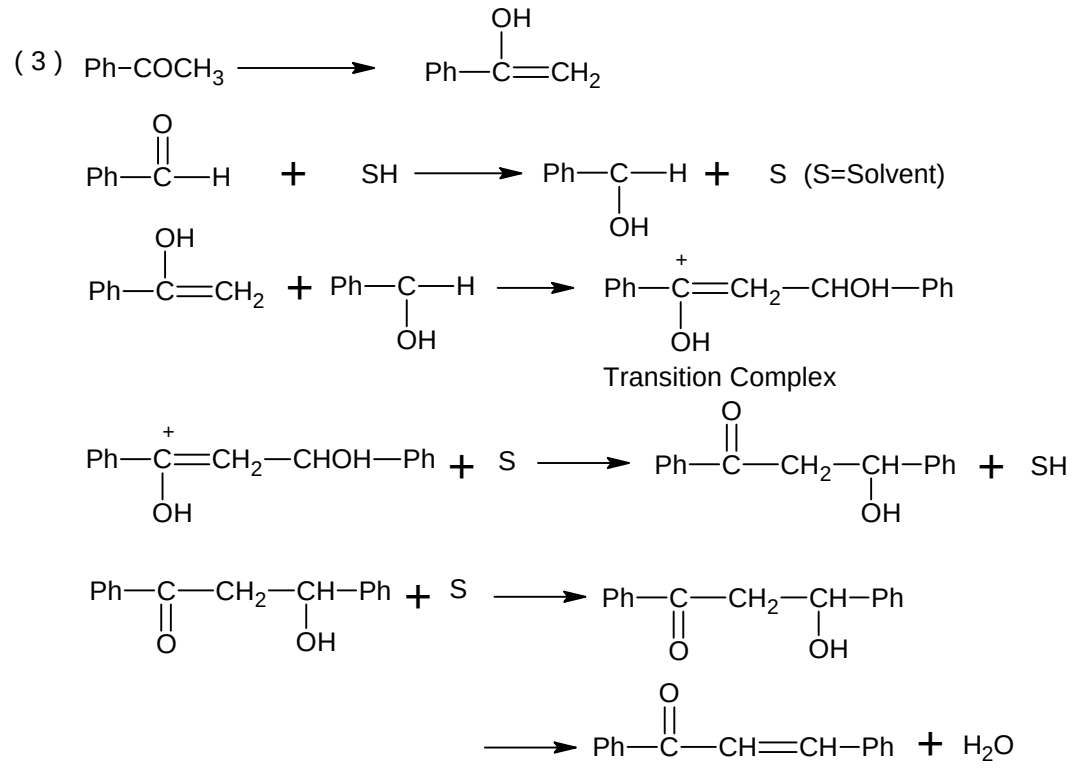
(A) Base catalysed :

Two alternative mechanisms were advanced for the reaction of benzaldenyde with acetophenone in the presence of a basic catalyst.





(B) Acid catalysed:



## IMPORTANCE OF CHALCONES

The chemistry of chalcones has assumed importance because of their versatility in the synthesis of many heterocyclic compounds furthermore, they are also associated with wide spectrum of pharmacological activities and industrial applications.

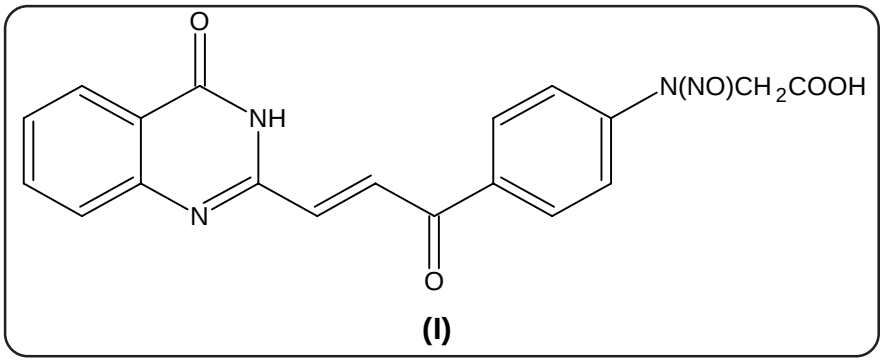
1. Chalcones bearing an active keto-ethylenic linkage and therefore, are reactive towards a number of reagents, yielding various heterocyclic compounds exhibiting significant biological activities viz. pyrimidines[22,23,24] cyano pyridines[25], cyano pyrans[26], Indazolines[27], pyrazolines[28], Isoxazole[29], piperidinone[30], cyano pyridone[31], pyranone[32] etc.
2. Chalcones are intermediate compounds for the synthesis of some naturally occuring haterocyclic compounds like flavones, flavanols, dihydroflavanols, benzal couumarinones, anthocyanins, etc.
3. They have been useful in providing the structure of some natural products like cyano maclurin[33], eriodictoyl[34], hemlock tannin[35], narighenin[36], phloretin[37], etc.
4. The chalcones are natural biocides[38-40] and are well-known key intermediate in the synthesis of heterocyclic compounds possessing biodynamic behavior [41-44].
5. The structure of some naturally occurring pigments like chrysin, galangin, kaempferol and quercetrol were established by their synthesis from suitable substituted chalcones [45].
6. Chalcones and their derivatives are also found to be applicable as light stabilizing agent[46], sweetening agent[47], organic brightening agent, photosensitive material, polymerisation. catalyst, scintillators as well as fluorescent whitening agent.
7. Chalcones are also useful for the detection of Fe(II)[48] and Ca(II)[49] ions in presence of Ba and Sr, as it reacts with a number of metal ions. Trihydroxy chalcones was used as an analytical reagent for amperometric estimation of copper[50] and for spectrophotometric study of the germanium[51].

## THERAPEUTIC IMPORTANCE

Chalcone derivatives have been found to possess wide range of therapeutic activities as shown below

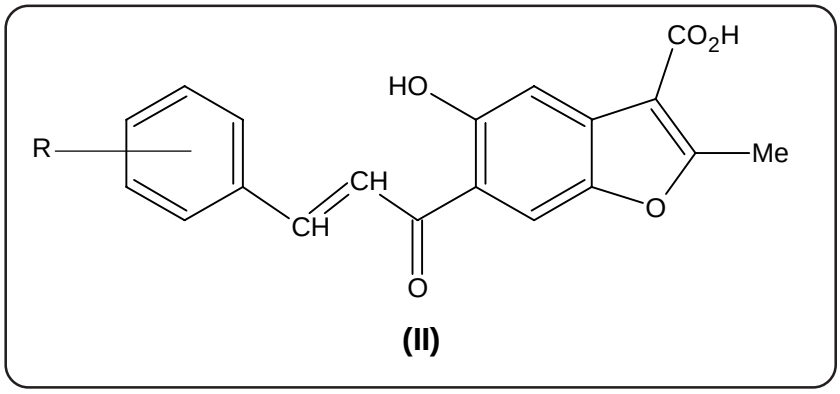
1. Anticancer[52,53]
2. Antiallergic[54]
3. Antimalarial[55,56]
4. Antiinflammatory[57,58]
5. Antiviral[59]
6. Antitubercular[60,61]
7. Antispasmodic[62]
8. Antitumor[63,64]
9. Anthelmintic[65,66]
10. Antiulcer[67,68]
11. Bactericidal[69,70]
12. Cardiovascular[71]
13. Fungicidal[72-74]
14. Germicidal[75]
15. Herbicidal[76]
16. Insecticidal[77-79]

Moreover Bekhit Adnan A. et al.[80] have prepared some chalcones (I) from 4(3H)-quinazolinone derivatives which possess significant antimicrobial activity.




**(I)**

Zawadowski Teodor et al.[81] have synthesised a series of substituted 2-methyl-5-hydroxy-6-acetyl-3-benzofuran carboxylic acid derivatives (II) as antibacterial and spasmolytic agents.

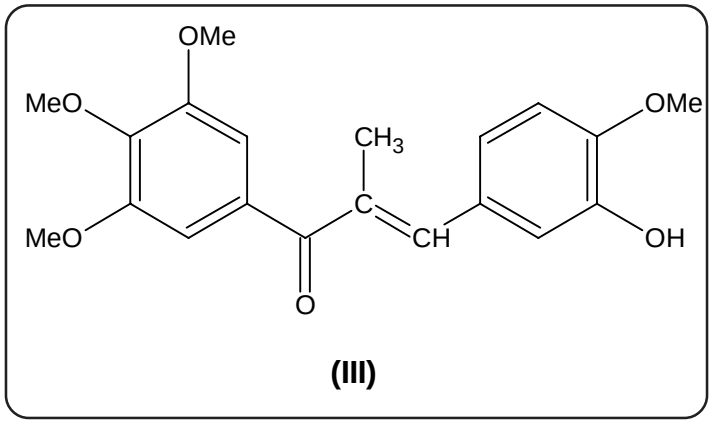



**(II)**

Bromidge, steven marks et al.[82] have prepared some indoline chalcones as useful antagonists, anxiolytics and antidepressants. Dela Torre et al.[83] have synthesised novel [60] fullerene-flavonoid chalcones.

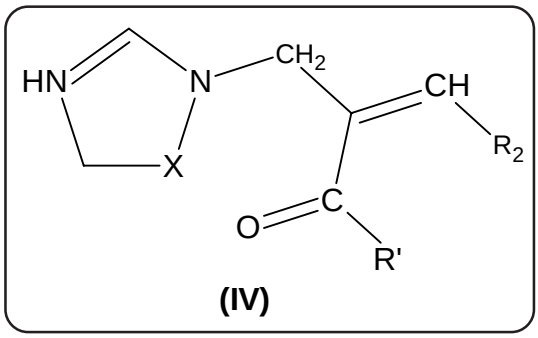
Moreover V. V. Mulund et al.[84] have prepared some chalcones from coumarin derivatives which possess significant antimicrobial activity. K. Bowden et al.[85] have prepared a series of substituted 3-(4-phenyl benzoyl)-chalcone/2-hydroxy chalcone α-bromo chalcones as potential antibacterial agents. B. V. Badani and co-workers[86] have reported some new chalcone derivatives as antifungal agent.

Some of the chalcones have been patented for their use as antifungal[87] antimicrobial[88,89] and anticancer[90] agents. Aldose reductase inhibitor activity of chalcones derivatives has been reported by Okayama et al.[91] Duck sylvie[92] have synthesised chalcone derivatives (III) possessing cytotoxic activity against the K-562 human leukemia cell lines.




**(III)**

Synthesis and insecticidal property of aryl-ω-(methyl-1,2,4-triazolimidazol-1-yl) chalcones (IV) have been document by R. seele et al.[93].




**(IV)**

Ezio and co-workers[94] have been reported chalcones having a valuable antiproliferation activity both on sensitive cancerous cell and on cell which are resistant to common chemotherapeutic drugs. Denny, William Alexander et al.[95] have prepared chalcones for use in antibody directed enzyme pro-drug therapy and gene directed enzyme pro-drug therapy.

Furthermore, Tanaka, Masayuki et al.[96] have prepared α,β-unsaturated quinolinyl-ketones as inhibitor of inter-leukinone production. Sreenivasulu. Sharma[97] have reported dichalcones with 100% antifeedant activity. Bradsher et al.[98] and T. Drikura[99] synthesised chalcones, which have been suggested as remedy for cancer.

Chalcones have been proved to be an important intermediate for the synthesis of many heterocyclic compounds in organic chemistry. These facts prompted us to synthesise some novel chalcones derivatives bearing 3,5-dibromo-4-methoxy acetophenone moiety, in order to achieving better therapeutic agents, this study is described in the following parts.

**PART-I : STUDIES ON ISOXAZOLES**

**PART-II : STUDIES ON PYRAZOLINES**

**PART-III : STUDIES ON INDAZOLES**

**PART-IV : STUDIES ON CYANOPYRIDINES**

**PART-V : STUDIES ON CYANOPYRANS**

**PART-VI : STUDIES ON PYRIMIDINES**

**PART-VII : STUDIES ON PIPERIDINONES**

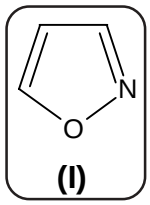
**PART-VIII : STUDIES ON CYANOPYRIDONES**

**PART-IX : STUDIES ON PYRANONES**

## INTRODUCTION

The five membered heterocyclic compounds containing nitrogen and oxygen atoms have so far been synthesised for their potentials in exhibiting some kind of activities and also for correlating it with its structure. The structural moieties such as Isoxazoles have been found to be responsible for their various physiological, biological and agricultural activities.

The structure of an isoxazole was first constructed by claisen in 1988, from the reaction of 1,3-diketone with hydroxylamine[100].



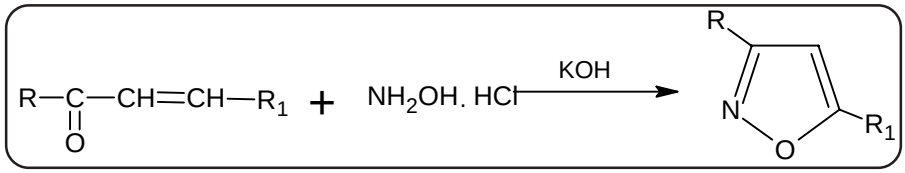

**(I)**

Subsequently, Quilico have developed the isoxazole chemistry by reaction of isoxazole[101] from nitrile-N oxides and unsaturated compounds.

## SYNTHETIC ASPECT

Isoxazoles can be prepared by various methods which are described as under.

1. Fanshave and crawely[102] prepared isoxazole from α,β-unsaturated carbonyl compounds, hydroxylamine hydrochloride and KOH in methanol.



2. It may be prepared by the reaction between α,β-diketones and hydroxylamine hydrochloride[103].
3. Schmidt and widmann[104] synthesized diethyl-α-methyl isoxazole-β,γ-dicarbonate by adding diethyl-β-diacetyl succinate to red fuming $HNO_3$ at 0- 5$^oC$.
4. Dawood, Kamal et al.[105] prepared isoxazole derivatives from enamino nitriles.
5. It may also be prepared by the reaction of dibromo chalocone with hydroxylamine hydrochloride[106].
6. It has been reported that cycloaddition reaction of the nitril-oxide one performed with simple stereogenic propargylic ethers, to give isoxazoles[107].
7. Tayde, V. B. et al.[108] synthesized some new 3,5-diaryl isoxazoles by the reaction of 2-aryl actophenones with hydroxylamine hydrochloride in presence of alkali.
8. J. F. Hansen and S. A. Strong[109] isolated isoxazoles from α,β-unsaturated ketones and N-bromosuccinamide.

Recently, Beatrice et al.[110] prepared isoxazoles by the one pot reaction under microwave irradiation. S. Balaic et al.[111] have been reported the reaction of 1,3-diketones with hydroxylamine hydrochloride on silicagel under microwave irradiation to generate isoxazole derivatives.

## THERAPEUTIC IMPORTANCE

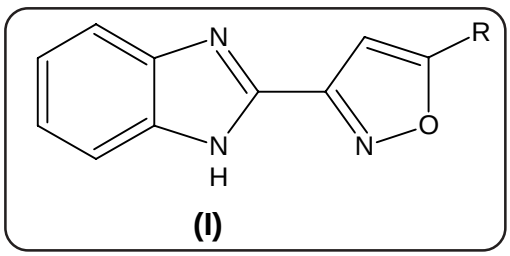
Isoxazole derivatives exhibit various biological and physiological activities such as

1. Antimicrobial[112]
2. Antiviral[113]

3. Antibacterial[114,115]
4. Anthelmintic[116]
5. Antiinflammatory[117,118]
6. Anticonvalsant[119,120]
7. Anticholestermic[121]
8. Adenosine antagonist[122]
9. Fungicidal[123,124]
10. Insectisidal[125]
11. Herbicidal[126,127]
12. Hypoglycergic[128]
13. Musscle relaxant[129]

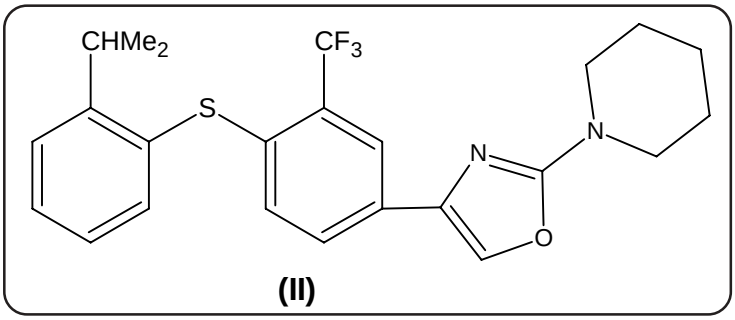
Moreover, antiinfilammatory activity of some newly synthesized isoxazole have been reported by A. Ando[130]. Teley Hand co-workers[131] and Mishra et al.[132] synthesized isoxazole and reported their analgesic and anti-inflammatory activities. Inai, Masato Shi et al.[133] also synthesized isoxazole derivatives possessing analgesic activity.

Vekariya, N. A. et al.[134] synthesised isoxazoles (I) and tested their anticancer activity. Burk Robert M. et al.[135] have prepared isoxazoles as prostaglandin $F_2\alpha$ antagonists.



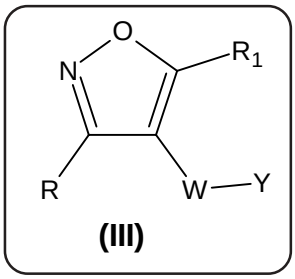

**(I)**

Wang, Gary, T. et al.[136] synthesised aryl phenyl heterocycle sulfide derivatives (II) as cell adhesion inhabiting, anti-inflammatory and immunosuppressive activity.



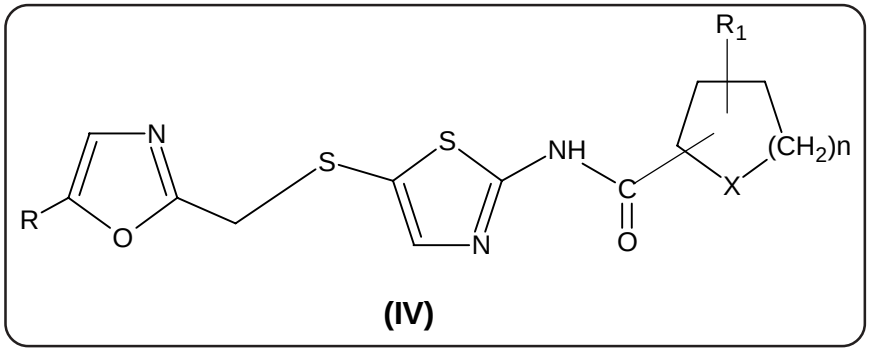

**(II)**

Dyke, Hazel Joun et al.[137] have prepared quinazolinedione derivatives as inosine 5'-monophosphate dehydrogenase (IMPDH) inhibitors for use in pharmaceutical compositions. Momose, Yu; Mackawa et al.[138] reported isoxazoles derivatives (III) for prevention and treatment of diabetes.



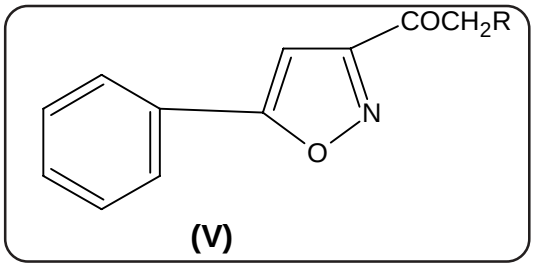

**(III)**

Diana, Guy D. et al.[139] documented some isoxazole derivatives as antipicor-navirus as agents. Misra, Raj, N et al.[140] prepared isoxazoles (IV) as inhibitors of cyclin dependent kinases.




**(IV)**

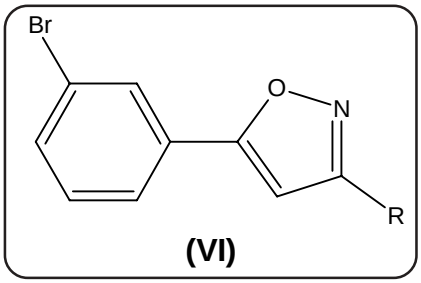
Shionogi et al.[141] synthesised and tested isoxazole derivatives (V) as antipyretic, analgesic, antiinflammatory and anticough activity.




**(V)**

G. Daidone, D. Roffa et al.[142] synthesized some novel 3-(isoxazol-3-yl)-quinozalin-4-(3H)-one derivatives and tested for their analgesic and antiinflammatory activities as wel as for their acute toxicity and ulcerogenic effect. Joshi et al.[143] synthesized some isoxazole (VI) derivatives as antitubercular and antimicrobial agents.

Antitumor activitity[144,145]of isoxazole derivatives have been reported by S. Rung and M. Scobie.




**(VI)**

Aicher Thomas D. et al.[146] reported isoxazoles as hypoglycemic agents. Kim Sujeone et al.[147] demonstrated isozazoles linkage for replacement of nucliotide phophodiester. Nyitrai et al.[148] reported isoxazole have remarkable anxiolytic and antihy pertensive effect.

Sezer Ozkhan et al.[149] have prepared isoxazoles and tested their insecticidal activity. Some potent herbicidal activity of isoxazoles found by Reddy et al.[150] Gudhadhe et al.[151] reported antimicrobial activity of isoxazole derivative. Parikh et al.[152] have been synthesized isoxazole and evaluated for their antimicrobial activity. Some isoxazole derivatives have been patented for their use as herbicides and fungicides [153] for the treatment of prophylaxis of autoimmune or inflammatory disease[154] and estrogen receptor modulators[155].

With an intention of preparing the compounds possessing better therapeutic activity, we have undertaken the synthesis of isoxazoles bearing 3,5-dibromo-4-methoxy acetophenone moiety which have been described in Section-II.

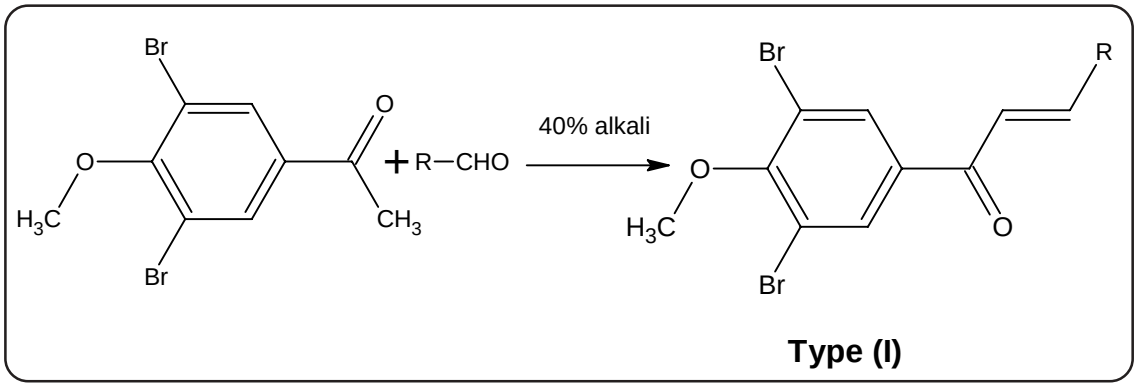
**SECTION-I : SYNTHESIS AND BIOLOGICAL EVALUTION OF (2E)-1-(3,5-DIBROMO-4-METHOXYPHENYL)-3-ARYL-PROP-2-EN-1-ONES.**

**SECTION-II : SYNTHESIS AND BIOLOGICAL EVALUTION OF 3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-ISOXAZOLES**

# SECTION - I

## SYNTHESIS AND BIOLOGICAL SCREENING OF (2E)-1-(3,5-DIBROMO-4-METHOXYPHENYL)-3-ARYL-PROP-2-EN-1-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 types (I) have been carried out by condensation of 3,5-dibromo-4-methoxy acetophenone with various aldehydes.




**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 40µg/ml. The biological activities of synthesized compounds were compared with standard drugs.

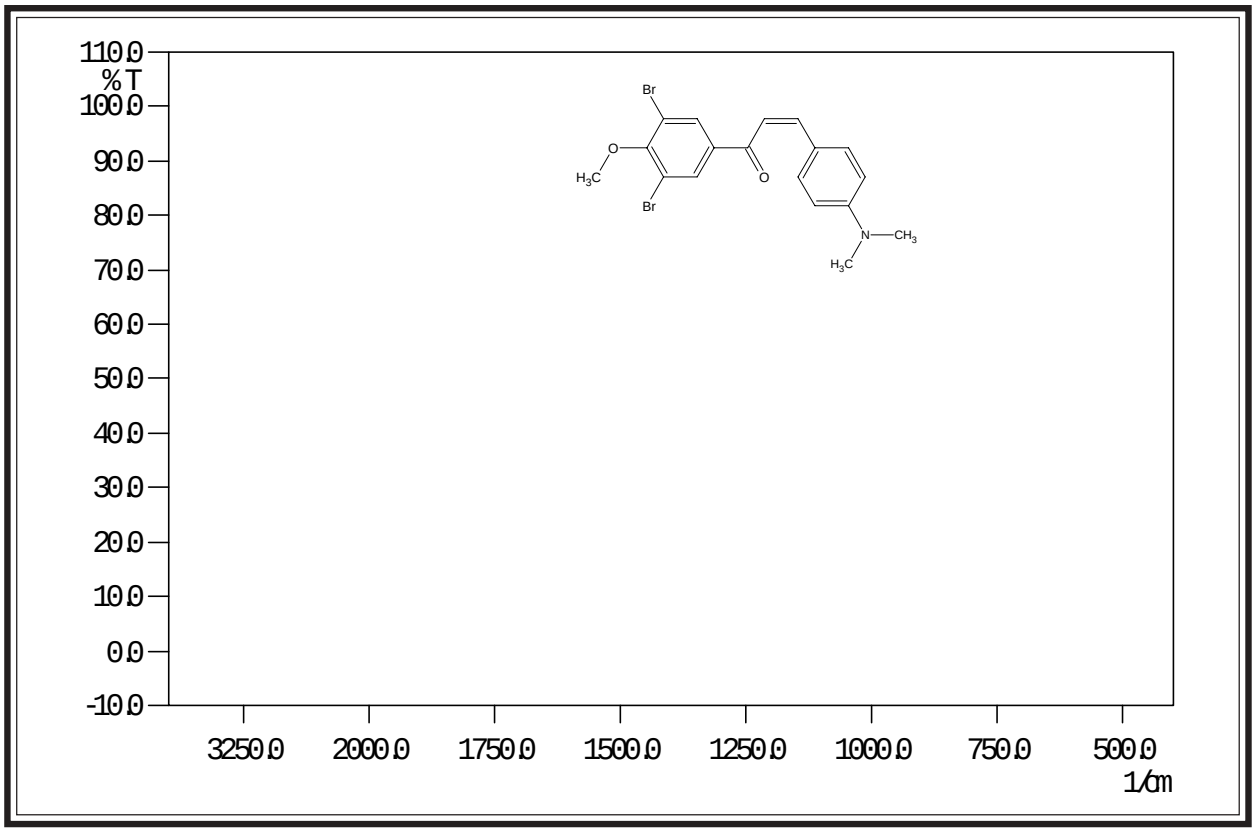
## MICROBIOLOGICAL EVALUATION

**Antimicrobial activity :**

| | | |
|---|---|---|
| Method | : | Cup-Plate[158,159] |
| Gram positive bacteria | : | *Bacillus megaterium* |
| | | *Bacillus subtillis* |
| Gram negative bacteria | : | *Escherichia coli* |
| | | *Proteus vulgaris* |
| Fungi | : | *Aspergillus niger* |
| Concentration | : | 40 μg/ ml |
| Sovent | : | Dimethyl formamide |
| Standard drugs | : | Amoxicillin, Benzyl penicillin, |
| | | Ampicillin, Norfloxacin, |
| | | Griseofulvin |

The results of antibacterial screening were 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.

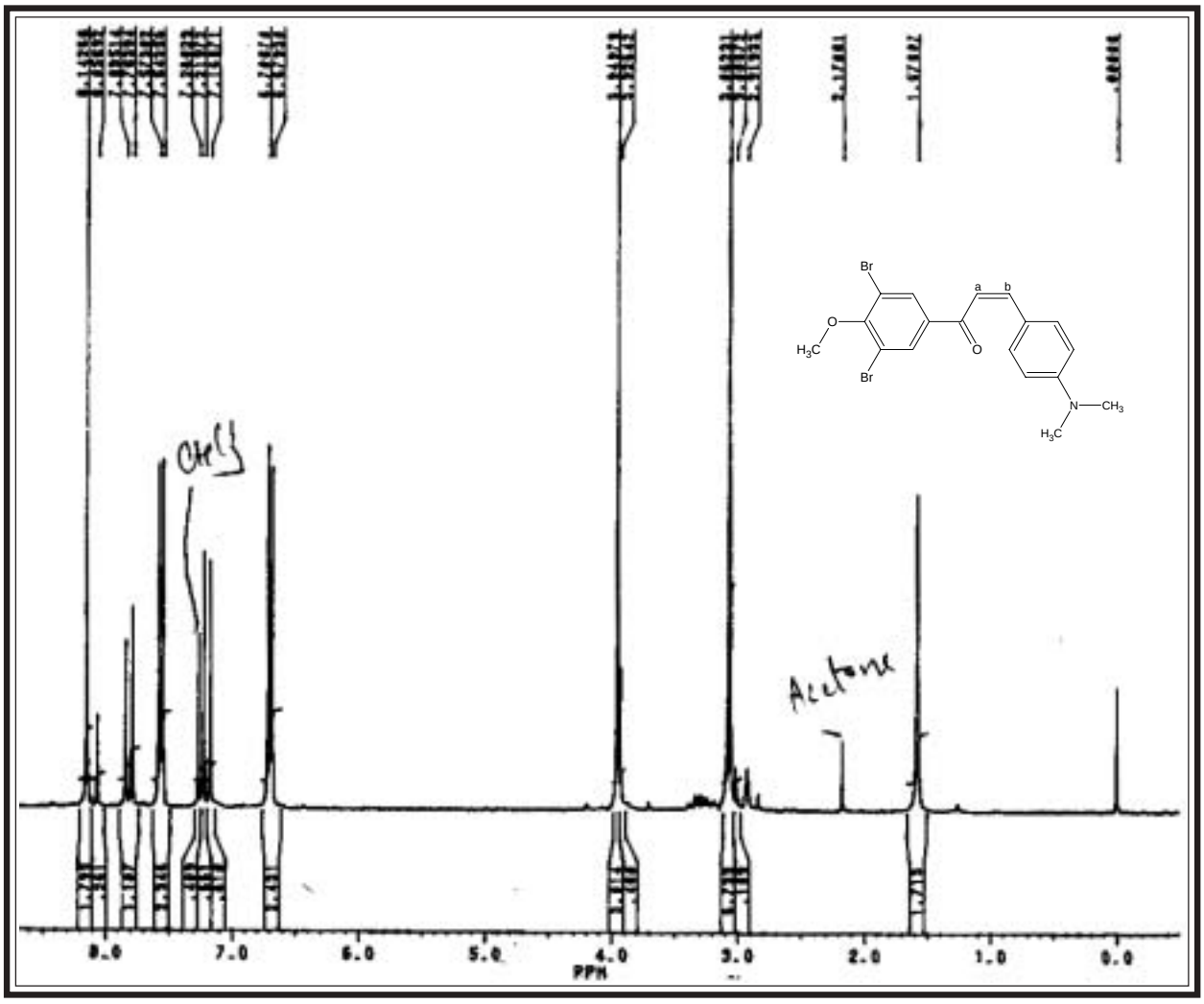
**IR spectral studies of (2E)-1-(3,5-dibromo-4-methoxyphenyl)-3-(4-N,N-di methylaminophenyl)-prop-2-en-1-one**




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

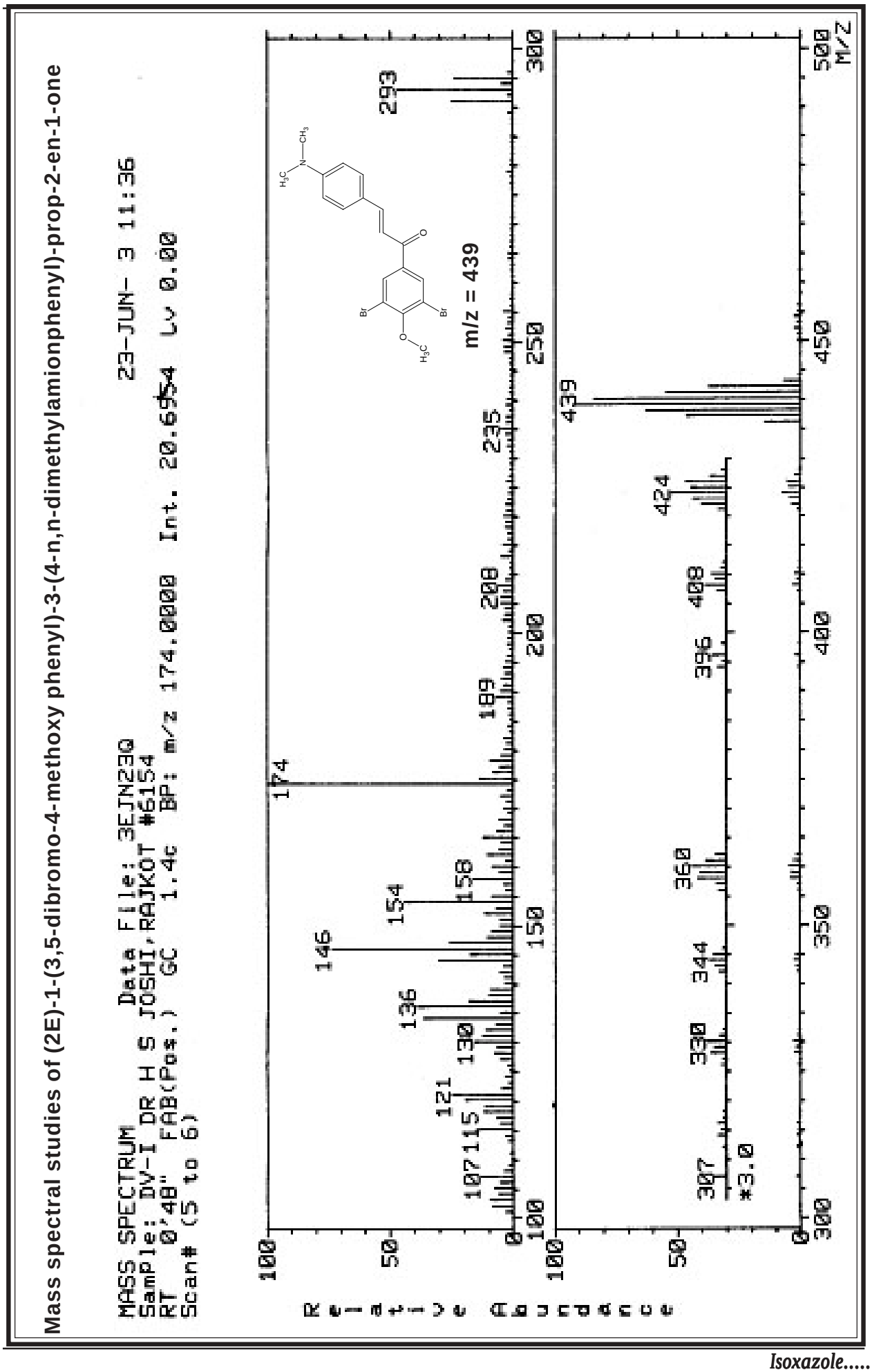
| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2925 | 2975-2950 | 156 |
| $-CH_3$ | C-H str.(sym.) | 2819 | 2880-2860 | " |
| | C-H def.(asym.) | 1467 | 1470-1435 | " |
| | C-H def.(sym.) | 1365 | 1390-1370 | " |
| Aromatic | C-H str. | 3060 | 3090-3030 | 157 |
| | C=C str. | 1467 | 1540-1480 | " |
| | | 1166 | 1125-1090 | " |
| | | 1053 | 1070-1000 | " |
| Halide | C-Br str. | 646 | 600-500 | 156 |
| Ether | C-O-C str.(sym) | 1215 | 1275-1200 | " |
| | | 1053 | 1075-1020 | " |
| Vinyl | CH=CH- str. | 3411 | 3050-3000 | " |
| Chalcone | C=C str. | 1569 | 1580-1550 | 157 |
| | C=O str. | 1651 | 1672-1652 | " |

## NMR SPECTRAL STUDIES OF (2E)-1-(3,5-DIBROMO-4-METHOXYPHENYL)-3-(4-N,N-DIMETHYLAMINOPHENYL)-PROP-2-EN-1-ONE




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

| Signal No. | Signal Position (δ ppm) | Relative No. of Proton | Multiplicity | Inference |
|---|---|---|---|---|
| 1. | 3.06 | 6H | singlet | N-$(CH_3)_2$ |
| 2. | 3.94 | 3H | singlet | Ar-$OCH_3$ |
| 3. | 7.17-7.22 | 1H | doublet | -CHa |
| 4. | 7.78-7.83 | 1H | doublet | -CHb |
| 5. | 6.67-8.14 | 6H | multiplet | Ar-H |


Mass spectral studies of (2E)-1-(3,5-dibromo-4-methoxy phenyl)-3-(4-n,n-dimethylamionphenyl)-prop-2-en-1-one
MASS SPECTRUM Data File: 3EJN230
Sample: DV-I DR H S JOSHI,RAJKOT #6154
RT 0'48" FAB(Pos.) GC 1.4c BP: m/z 174.0000 Int. 20.6954 Lv 0.00
Scan# (5 to 6)
23-JUN- 3 11:36
m/z = 439
Relative Abundance
M/Z
*3.0

# EXPERIMENTAL

## SYNTHESIS AND BIOLOGICAL SCREENING OF (2E)-1-(3,5-DIBROMO-4-METHOXYPHENYL)-3-ARYL-PROP-2-EN-1-ONES

### (A) Synthesis of 3,5-Dibromo-4-hydroxy acetophenone

4-Hydroxy acetophenone (1.36gm, 0.01mol) dissolved in glacial acetic acid and water(75ml) then it was stirred at room temerature to make a homogeneous solution. Then bromine(1.6gm, 0.01mol) in gacial aceticc acid was added drop wise to a solution and stirred for 1hr at room tempature. The resuting solution was then poured over crushed ice. The seperated solid was filtered and crystallized from methanol Yield 80%, m. p. $181^0$C, Anal. Calcd. for $C_8H_6Br_2O_2$ : Require: C, 32.69, H, 2.06; Found: C, 32.75, H, 2.12%.

### (B) Synthesis of 3,5-Dibromo-4-methoxy acetophenone

To a solution of 3,5-dibromo-4-hydroxy acetophenone (2.93gm, 0.01 mol) in a25ml methanol, dimethyl sulfate (2.5gm, 0.02 mol) was added dropwise.The resulting mixture was stirred for 1hr at room temprature. Then the content was poured on to crushed ice, this the solid seprated was filterated and crystallized from ethanol Yield 70%, m. p. $90^0$C, Anal. Calcd. for $C_9H_8Br_2O_2$ Require : C, 35.10, H, 2.62; Found: C, 32.20, H, 2.72%.

### (C) Synthesis of (2E)-1-(3,5-Dibromo-4-methoxyphenyl)-3-(4-N,N-dimethyl aminophenyl)-prop-2-en-1-one

Dissolve 3,5-dibromo-4-methoxy acetophenone (3.07gm, 0.01mol) in (25 ml methanol) to this add 4-N,N-dimethylamino benzaldehyde (1.49gm, 0.01mol)in (25 ml methanol) and was stirred at room temperature for 24hrs. in prasence of catalytical amount of 40% KOH. The resulting solution was poured on crushed ice, thus the solid seprated was filterated and crystallized from ethanol, Yield 65%, m. p. 145$^0$C, Anal. Calcd. for $C_{18}H_{17}Br_2NO_2$ Require : C, 49.23, H, 3.90, N, 3.19 ; Found: C, 49.35, H, 3.96, N, 3.17%.

Similarly, other compound were prepared. The physical data are recorded in Table No. 1

## (D) Biological screening of (2E)-1-(3,5-dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones

### (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 magaterium, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa in separate conical flasks at 40-50$^0$C and mixed well by gentle shaking. About25 ml content of the flask was poured and evenly spreaded in a petridish (13 cm diameter) and allowed to set for 2 hrs. The cups (10 mm diameter) were formed by the help of borer in agar medium and filled with 0.04ml (40mg) solution of sample in DMF.

The plates were incubated at 37$^0$C for 24 hrs. and the control was also maintained with 0.04ml 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**

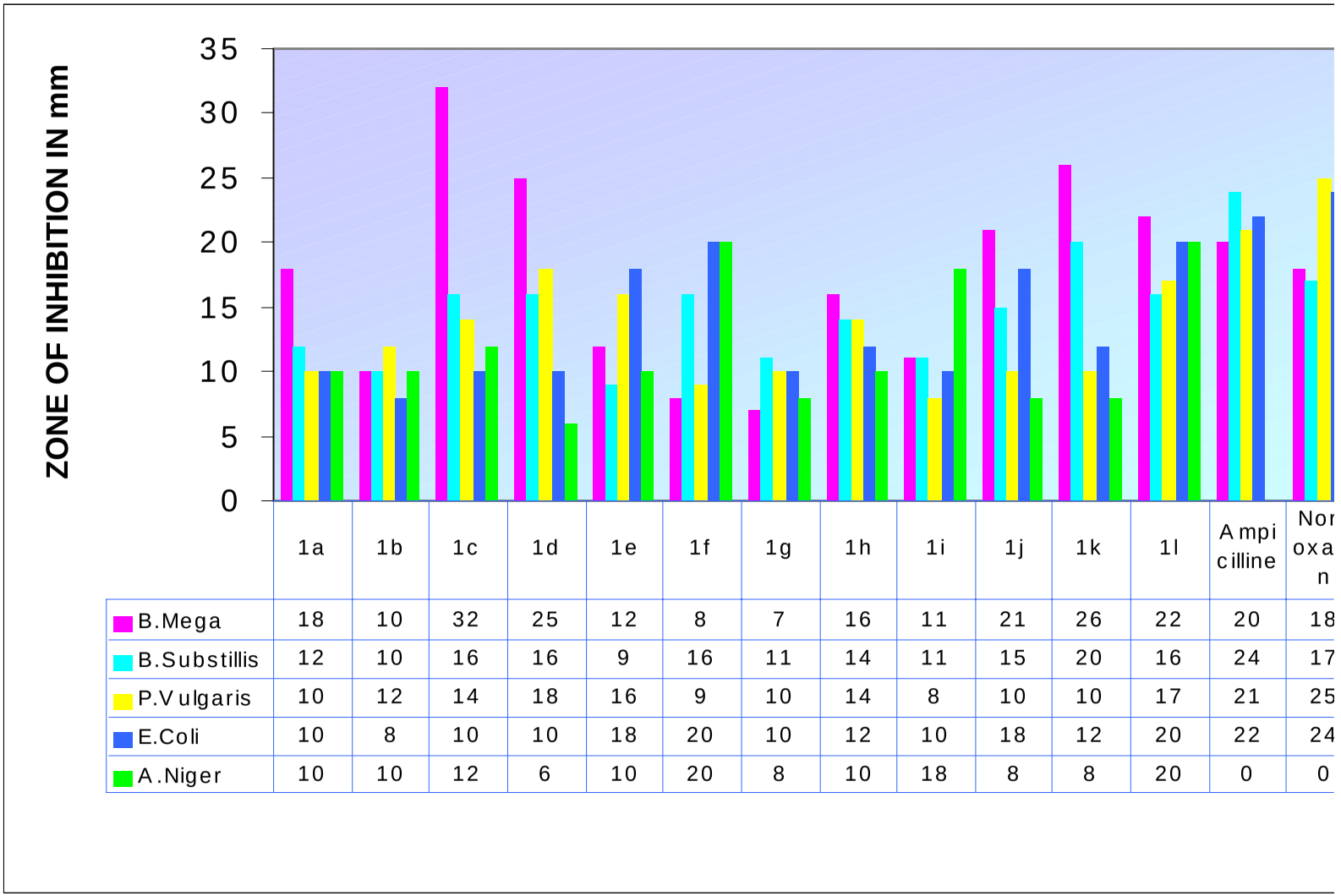
A. niger was employed for testing antifungal activity using cup-plate agar diffusion method. The culture was maintained on sabourauds agar slants sterilized sabourauds agar medium was inoculated with 72 hrs. old 0.5ml suspension of fungal spores in a separate flask. About 25ml of the inoculated medium was evenly spreaded in a petridish (13cm diameter) and allowed to set for 2 hrs. the cups (10mm diameter) were punched. The plates were incubated at $30^0$C for 48 hrs. After the completion of incubation period, the zone of inhibition of growth n the form of diameter in mm was measure. Along the test solution 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 CONSTNTS OF (2E)-1-(3,5-DIBROMO-4-METHOXY PHENYL)-3-ARYL-PROP-2-EN-1-ONES.**

| Sr. No. | R | Molecular Fromula | Molecular Weight | M.P. °C | Yield % | % of Nitrogen Calcd. | % of Nitrogen Found | Rf Value | Solvent System |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 1a | $C_6H_5$- | $C_{16}H_{12}Br_2O_2$ | 396 | 120 | 68 | - | - | 0.52 | S1 |
| 1b | 3-Br-$C_6H_4$- | $C_{16}H_{11}Br_3O_2$ | 474 | 148 | 72 | - | - | 0.54 | S1 |
| 1c | 2-Cl-$C_6H_4$- | $C_{16}H_{11}Br_2ClO_2$ | 430 | 118 | 66 | - | - | 0.58 | S1 |
| 1d | 4-Cl-$C_6H_4$- | $C_{16}H_{11}Br_2ClO_2$ | 430 | 125 | 70 | - | - | 0.65 | S1 |
| 1e | 4-$N(CH_3)_2$-$C_6H_4$- | $C_{18}H_{17}Br_2NO_2$ | 439 | 145 | 65 | 3.19 | 3.17 | 0.62 | S2 |
| 1f | 4-$OCH_3$-$C_6H_4$- | $C_{17}H_{14}Br_2O_3$ | 426 | 125 | 60 | - | - | 0.55 | S1 |
| 1g | 3,4-$(OCH_3)_2$-$C_6H_3$- | $C_{18}H_{16}Br_2O_4$ | 456 | 145 | 65 | 3.18 | 3.16 | 0.48 | S2 |
| 1h | 2-$NO_2$-$C_6H_4$- | $C_{16}H_{11}Br_2NO_4$ | 441 | 110 | 55 | 3.18 | 3.15 | 0.65 | S2 |
| 1i | 3-$NO_2$-$C_6H_4$- | $C_{16}H_{11}Br_2NO_4$ | 441 | 90 | 63 | - | - | 0.66 | S2 |
| 1j | 3-$OC_6H_5$-$C_6H_4$- | $C_{22}H_{16}Br_2O_3$ | 488 | 288 | 58 | - | - | 0.56 | S2 |
| 1k | 2-OH-$C_6H_4$- | $C_{16}H_{12}Br_2O_3$ | 412 | 220 | 58 | - | - | 0.46 | S2 |
| 1l | 4-OH-$C_6H_4$- | $C_{16}H_{12}Br_2O_3$ | 412 | 277 | 55 | - | - | 0.59 | S2 |

S1 Benzene: Ethylacetate (9:2) S2 Benzene: Ethylacetate (8.5:1.5)

## GRAPHICAL CHART NO. 1 : (2E)-1-(3,5-DIBROMO-4-METHOXY PHENYL)-3-ARYL-PROP-2-EN-1-ONES.

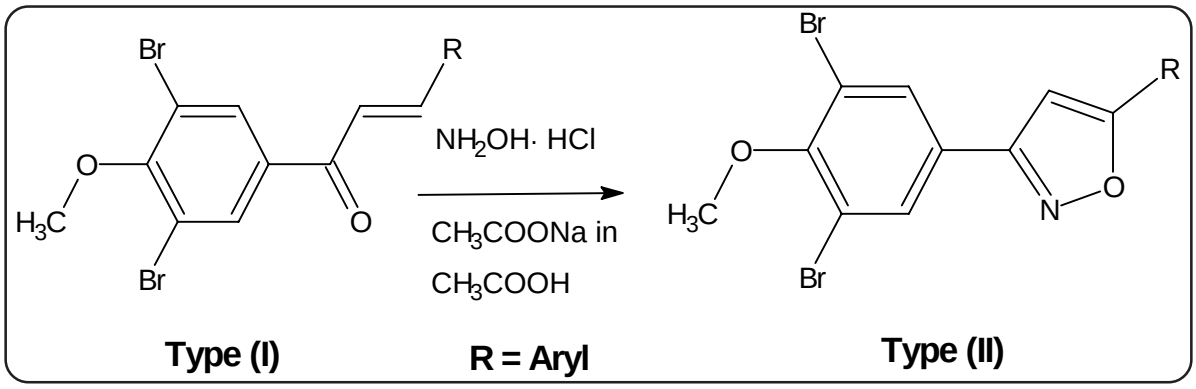



| | 1a | 1b | 1c | 1d | 1e | 1f | 1g | 1h | 1i | 1j | 1k | 1l | Ampicilline | Noroxan |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B.Mega | 18 | 10 | 32 | 25 | 12 | 8 | 7 | 16 | 11 | 21 | 26 | 22 | 20 | 18 |
| B.Substillis | 12 | 10 | 16 | 16 | 9 | 16 | 11 | 14 | 11 | 15 | 20 | 16 | 24 | 17 |
| P.Vulgaris | 10 | 12 | 14 | 18 | 16 | 9 | 10 | 14 | 8 | 10 | 10 | 17 | 21 | 25 |
| E.Coli | 10 | 8 | 10 | 10 | 18 | 20 | 10 | 12 | 10 | 18 | 12 | 20 | 22 | 24 |
| A.Niger | 10 | 10 | 12 | 6 | 10 | 20 | 8 | 10 | 18 | 8 | 8 | 20 | 0 | 0 |

# SECTION II

## SYNTHESIS AND BIOLOGICAL SCREENING OF 3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-ISOXAZOLES

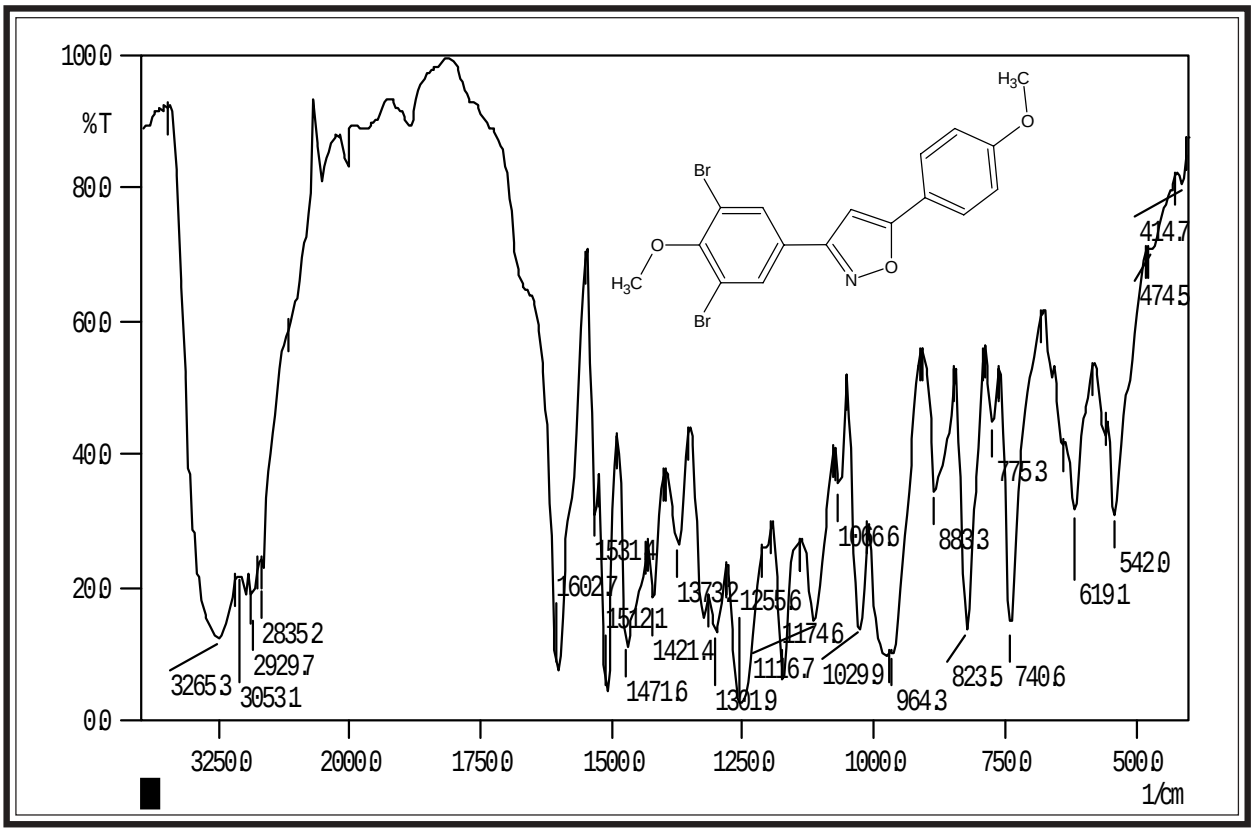
Isoxazole have been reported to have various pharmacological activities like antibacterial, antifungal, insecticidal etc. In order to achieving better drug potency. We have prepared isoxazole derivatives of type (II) by the cyclocondensation of (2E)-1-(3-5-dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones of type(I) with hydroxylamine hydrochloride in presence of sodium acetate in glacial aletic acid.




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 ***invitro*** 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.

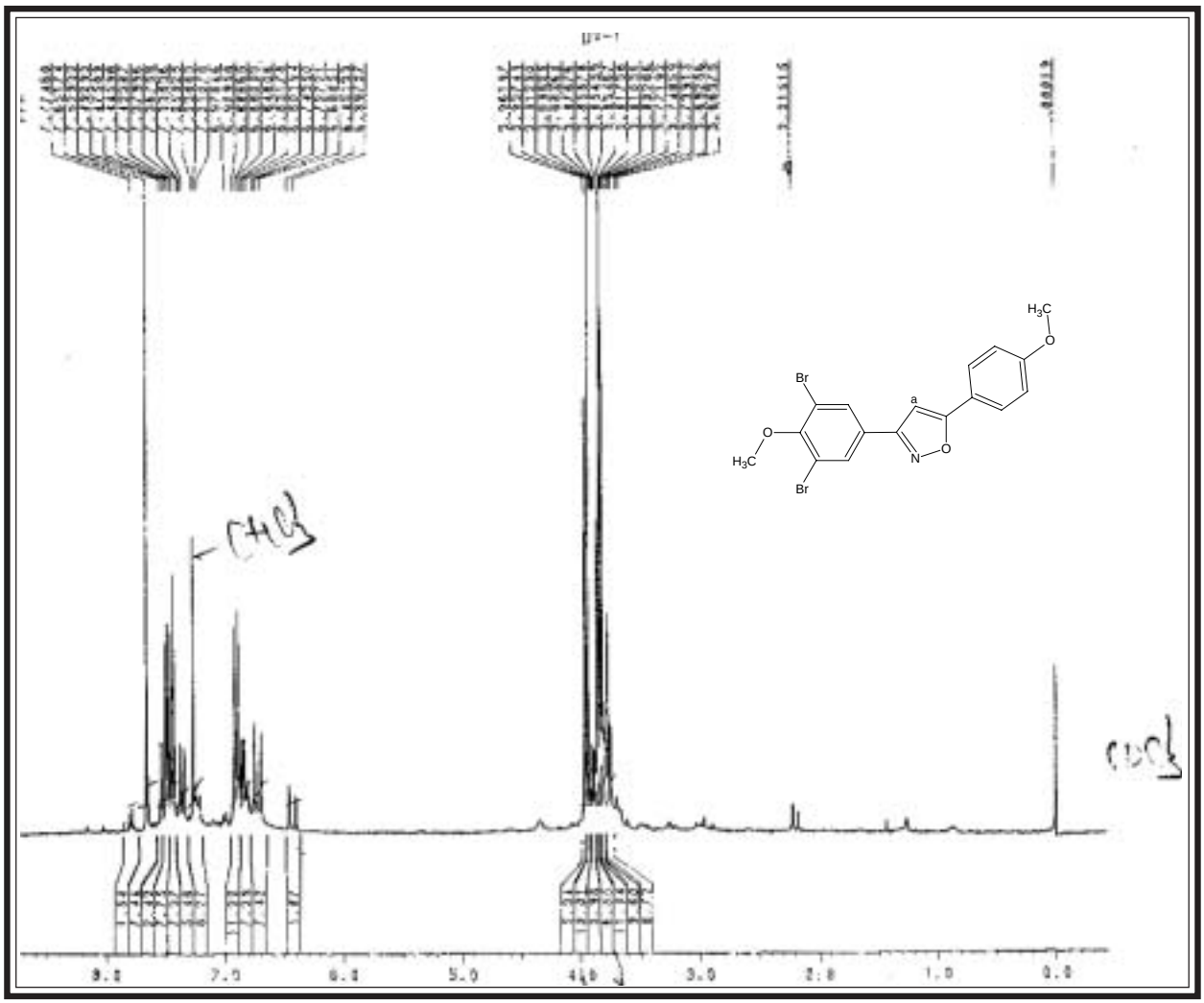
**IR spectral studies of 3-(3,5-Dibromo-4-methoxy phenyl)-5-(4-methoxy phenyl)isoxazole**




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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2929 | 2975-2950 | 156 |
| $-CH_3$ | C-H str.(sym.) | 2835 | 2880-2860 | " |
| | C-H def.(asym.) | 1421 | 1470-1435 | " |
| | C-H def.(sym.) | 1373 | 1390-1370 | " |
| Aromatic | C-H str. | 3053 | 3090-3030 | 157 |
| | C=C str. | 1521 | 1540-1480 | " |
| | | 1116 | 1125-1090 | " |
| Halide | C-Br str. | 619 | 600-500 | 156 |
| Ether | C-O-C str.(sym) | 1255 | 1275-1200 | " |
| | | 1029 | 1075-1020 | " |
| Isoxazole | C=C str. | 1531 | 1580-1550 | 157 |
| | C=N str. | 1471 | 1470-1460 | " |
| | N-O str. | 883 | 810-850 | " |

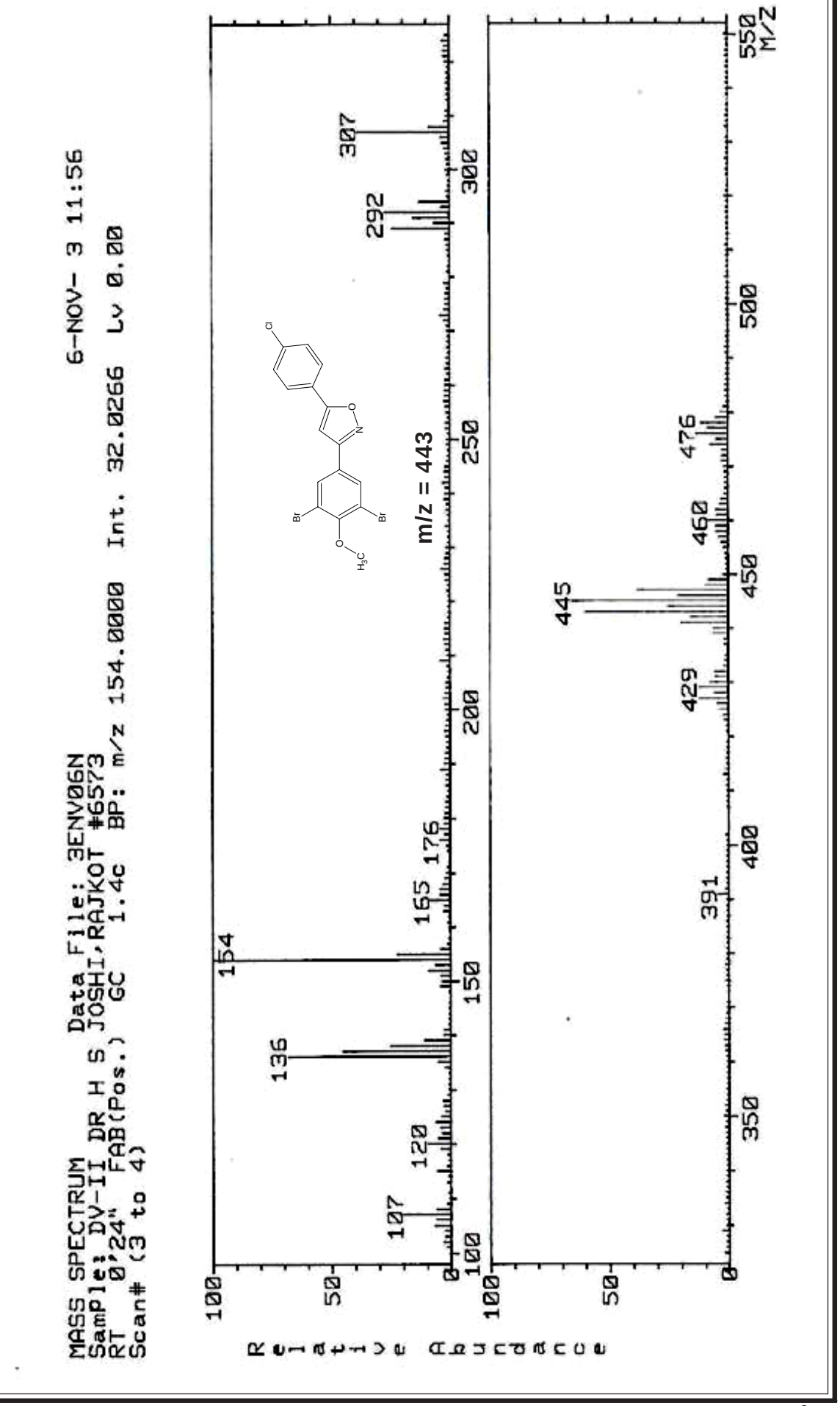
## NMR SPECTRAL STUDIES OF 3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-(4-METHOXYPHENYL)ISOXAZOLE




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

| Signal No. | Signal Position (δ ppm) | Relative No. of Proton | Multiplicity | Inference |
|---|---|---|---|---|
| 1. | 3.83 | 3H | singlet | Ar-$OCH_3$ |
| 2. | 3.94 | 3H | singlet | Ar-$OCH_3$ |
| 3. | 7.52 | 1H | singlet | Isox-CHa |
| 4. | 6.88-7.65 | 6H | multiplet | Ar-H |

**MASS spectral studies of 3-(3,5-Dibromo-4-methoxy phenyl)-5-(4-chlorophenyl)-isoxazole**



# EXPERIMENTAL

## SYNTHESIS AND BIOLOGICAL OF 3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-ISOXAZOLES

### (A) Synthesis of (2E)-1-(3,5-Dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones

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

### (B) Synthesis of 3-(3,5-Dibromo-4-methoxyphenyl)-5-(4-methoxyphenyl)-isoxazole

(2E)-1-(3-5-Dibromo-4-methoxyphenyl)-3-(4-methoxyphenyl)-prop-2-en-1-one (4.39 gm, 0.01 mol) in ethanol (25 ml) and anhydrous sodium acetate (0.739gm, 0.01 mol) dissolved in minimum amount of acetic acid. Mix this two solution and add hydroxylamine hydrochloride(0.59 gm, 0.01 mol). The reaction mixture was refluxed on oilbath for 7-8 hrs. The products was isolated and crystallized from ethanol. Yield 65 %, m.p. $115^0$C Anal. Calcd. For $C_{17}H_{13}Br_2NO_3$ Requires ; C, 46.50; H, 2.98; N, 3.19; Found C, 46.55, H, 3.03; N, 3.17%.

Similarly, other 3-(3,5-dibromo-4-methoxyphenyl)-5-aryl-isoxazoles were prepared. The physical data are recorded in Table No.3.

### (C) Biological screening of 3-(3,5-dibromo-4-methoxyphenyl)-5-aryl-Isoxazoles

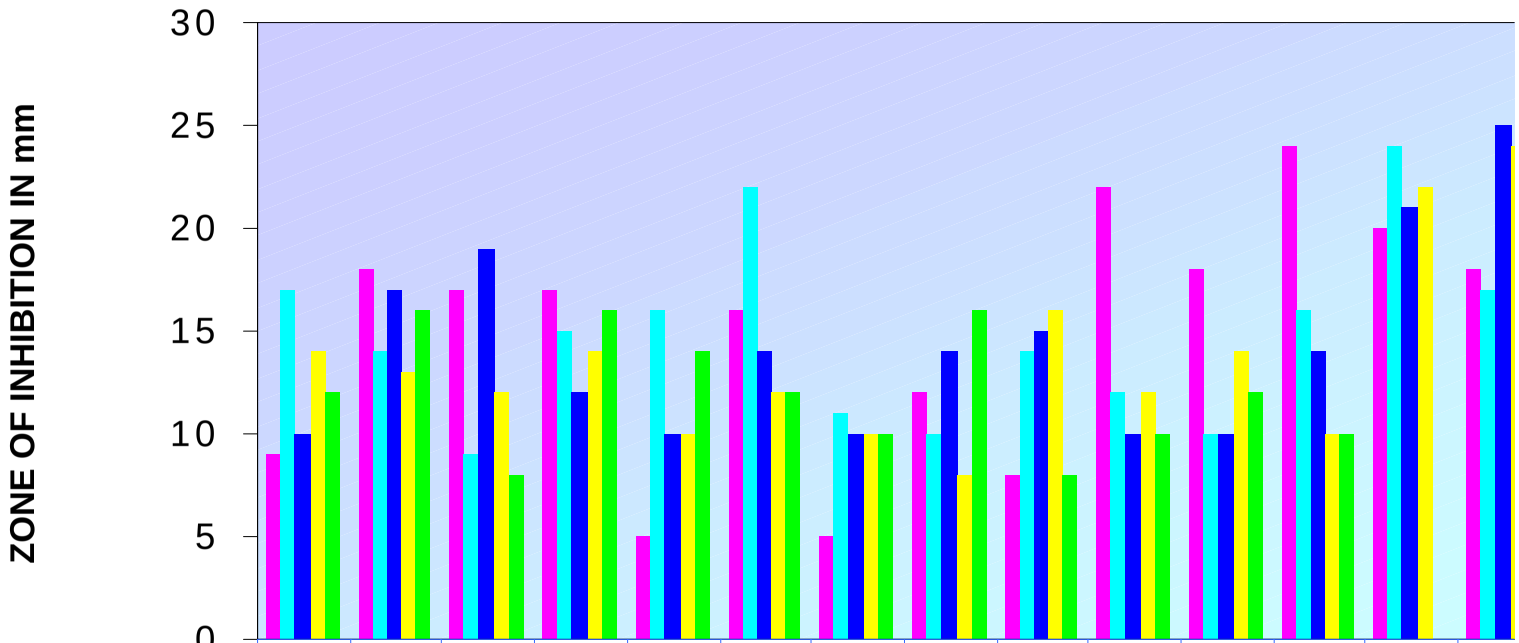
Antimicrobial testing were carried out as described in Part-I Section-1 (D). The zones of inhibition of test solution are reported in Graphical Chart No 3.

## TABLE-2: PHYSICAL CONSTANTS OF 3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-ISOXAZOLES.

| Sr. No. | R | Molecular Fromula | Molecular Weight | M.P. °C | Yield % | % of Nitrogen Calcd. | % of Nitrogen Found | Rf Value | Solvent System |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 2a | $C_6H_5$- | $C_{16}H_{11}Br_2NO_2$ | 409 | 105 | 70 | 3.42 | 3.40 | 0.57 | S1 |
| 2b | 3-Br-$C_6H_4$- | $C_{16}H_{10}Br_3NO_2$ | 487 | 113 | 68 | 2.87 | 2.88 | 0.63 | S1 |
| 2c | 2-Cl-$C_6H_4$- | $C_{16}H_{10}Br_2ClNO_2$ | 443 | 108 | 72 | 3.16 | 3.18 | 0.50 | S1 |
| 2d | 4-Cl-$C_6H_4$- | $C_{16}H_{10}Br_2ClNO_2$ | 443 | 110 | 66 | 3.16 | 3.15 | 0.61 | S1 |
| 2e | 4-$N(CH_3)_2$-$C_6H_4$- | $C_{18}H_{16}Br_2N_2O_2$ | 452 | 112 | 68 | 6.20 | 6.18 | 0.64 | S1 |
| 2f | 4-$OCH_3$-$C_6H_4$- | $C_{17}H_{13}Br_2NO_3$ | 439 | 115 | 65 | 3.19 | 3.17 | 0.57 | S1 |
| 2g | 2-$NO_2$-$C_6H_4$- | $C_{16}H_{10}Br_2N_2O_4$ | 454 | 101 | 58 | 6.17 | 6.15 | 0.36 | S1 |
| 2h | 3-$NO_2$-$C_6H_4$- | $C_{16}H_{10}Br_2N_2O_4$ | 454 | 125 | 60 | 6.17 | 6.16 | 0.38 | S1 |
| 2i | 3-$OC_6H_5$-$C_6H_4$ | $C_{22}H_{15}Br_2NO_3$ | 501 | 80 | 58 | 2.79 | 2.81 | 0.64 | S1 |
| 2j | 2-OH-$C_6H_4$- | $C_{16}H_{11}Br_2NO_3$ | 425 | 164 | 59 | 3.30 | 3.28 | 0.66 | S1 |
| 2k | 4-OH-$C_6H_4$- | $C_{16}H_{11}Br_2NO_3$ | 425 | 155 | 55 | 3.30 | 3.32 | 0.30 | S1 |
| 2l | -$C_4H_3O$ | $C_{14}H_9Br_2NO_3$ | 399 | 112 | 62 | 3.51 | 3.49 | 0.40 | S1 |

S1 hexane : Ethylacetate (7 : 3)

## GRAPHICAL CHART NO. 2 : 3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-ISOXAZOLES.




| | 2a | 2b | 2c | 2d | 2e | 2f | 2g | 2h | 2i | 2j | 2k | 2l | Ampicillin | Noroxan |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B.Mega | 9 | 18 | 17 | 17 | 5 | 16 | 5 | 12 | 8 | 22 | 18 | 24 | 20 | 18 |
| B.Substillis | 17 | 14 | 9 | 15 | 16 | 22 | 11 | 10 | 14 | 12 | 10 | 16 | 24 | 17 |
| P.Vulgaris | 10 | 17 | 19 | 12 | 10 | 14 | 10 | 14 | 15 | 10 | 10 | 14 | 21 | 25 |
| E.Coli | 14 | 13 | 12 | 14 | 10 | 12 | 10 | 8 | 16 | 12 | 14 | 10 | 22 | 24 |
| A.Niger | 12 | 16 | 8 | 16 | 14 | 12 | 10 | 16 | 8 | 10 | 12 | 10 | 0 | 0 |

## REFERENCES


1. S. V. Kostanecki and J. Tambor; *Chem. Ber.,* **32**, 1921 (1899)
2. F. Beilstelin; *Hondbuch der. Orgaischen Chemie*, 4th ed. Vol.**7**,p.428 (1926).
3. B. S. Holla and S. Y. Ambekar ; *J. Indian Chem. Soc.,* **50**, 673 (1973); *Chem. Abstr.,* **80**, 132961 (1974)
4. T. Szell; *Chem. Ber.,* **92**, 1672 (1959); *Chem. Abstr.,* **53**, 21913 (1959).
5. S. A. Hermes ; *Chem. Abstr.,* **70**, 98422 (1969).
6. R. E. Lyle and L. P. Paradis; *J. American Chem.Soc.,* **77**, 6667 (1955); *Chem. Abstr.,* **50**, 10057 (1956)
7. C. Kurodo and T. Matsukuma; *Sci. Papers Inst. Phys. Chem. Res. (Tokyo),* **18**, 51 (1932); *Chem. Abstr.,* **26**, 2442 (1932).
8. P. L. Cheng, P. Fournari and J. Tirouflet; *Bull. Soc. Chim. France,* 102248 (1963); *Chem. Abstr.,* **60**, 1683(1964).
9. D. S. Breslow and C. R. Houser ; *J. American Chem.Soc.,* **62**, 2385 (1940); *Chem.Abstr.,* **34,** 7875 (1940)
10. L. Reichel; *Naturwissenschallen* **32**, 215 (1944); *Chem.Abstr.,* **10**, 2441 (1946)
11. M. A. B. Linke and D. E. Ereleigh; *Z. naturtosch,* **308**, 606 (1975).
12. A. A. Rawal and N. M. Shah; *Indian J. Chem.,* **21,** 234 (1962)
13. G. V. Jadav and V. G. Kulkarni ; *Curr. Sci.* (1944).
14. V. M. Vlasov ;*Izu. Sib. Otd, Akad. Nauk. SSSR Ser. Khim. Nauk.* **2,** 96 (1971); *Chem.Abstr.,* **76,** 140411d (1972).
15. Claisen and Claparede; *Chem.Ber.,* **14,** 2460 (1881).
16. Bergellini and Morantonic Atti; Alad, Linli, 1968[4] 17, ii, 119-25; *Brit. Chem.Abstr.,* **8**, (i) 801(1908).
17. Mehra and Mathur; *J. Indian Chem.Soc.,* **32**, 465 (1955).
18. Stockhousen and gattermann; *Ber.,* **25**, 525 (1892); Shinodu and Sato; *J. Pharm. Soc. Japan,* **49**, 797 (1929); *Chem. Abstr.,* **24,** 604 (1930).
19. Christian and Amin; *J.Sci. Ind. Research* **14B**, 421 (1955)
20. M. Dzurilla and P. Kristian; *Chem. Abstr.,* **72**, 66551 (1970).
21. D. S. Noyte, W. A. Pryor and A. H. Bottini ; *J. American. Chem.Soc.*, **77**, 140z (1955).
22. N. Latif, N. Mishriky nand N. S. Girgis; *Indian Journal of Chemistry,* **20B**, 147-149 (1981).
23. H. G. Garg and P. P. Singh; *J. Med. Chem.* **11,** 1104 (1968).
24. B. S. Hastak and B. J. Ghiya; *Indian Journal of Heterocyclic Chemistry,* **2**, 135-136 (1992).
25. A. Sakari and H. Midorikawa; *Bull.Soc. Japan* **41**, 430 (1968); *Chem.Abstr.*, **69**,18985 (1968).

26. A. Samour, Y. Akjnoukh and H. Jahine (Pal.Sci.Ain Sharm Uni.Cario UAK) *J. Chem.* 1970 pub. (1971) 13(4), 421-37 (Eng.); *Chem. Abstr.,* **77**, 101348 (1977).
27. A. C. Jain, A. Mehta and P. Arya; *Indian Journal of Chemistry,* **26B**, 150-153 (1987).
28. A. M. Fahmy, M. Hussan, A. A. Khalt; R. A. Ahmedi; *Rev. Roum-Chim.,* **33(7)**, 755-61 (1988). *Chem.Abstr.,* **111,** 77898 (1989).
29. S. B. Lohiya and B. J. Ghiya; *Indian J. Chem.,* 279-82 (1986).
30. B. Shiva kumar and L. V. G. Nargund, *I. J. H. C.* **8**, 27-30(1998).
31. K. Folkers, S. A., Harris; *J. Am. Chem. Soc.,* **61,** 1245 (1939).
32. Yousuf. A. Al; Farkh, Parouck H; Al-Hajjar; *J. Heterocyclic Chem.,* **16,** 1(1979).
33. Arito, et al.;Japan P. 1956, 294,; *Chem. Abstr.,* **51,** 4054 (1957).
34. Shinoda and Sato; *J. Pharm. Soc. Japan;* **49**, 64 (1929); *Chem. Abstr.,* **23,** 4210 (1929).
35. Prafulchandra Mitter and Shrishkumar Shah; *J. Indian Chem. Soc.,* **11**, 257 (1934).
36. Shinoda and Sato; *J. Pharm. Soc. Japan,* **48,** 933 (1928); *Chem. Abstr.,* **23**, 2956 (1929).
37. Shinoda Sato and Kawagoe; *J. Pharm. Soc. Japan,* **49**, 548 (1929); *Chem. Abstr.,* **24**, 604 (1930).
38. W. B. Gifer and J. E. Com; *J. Ame.Chem. Soc.,* **67***,* 112 (1945).
39. D. H. Marian, P. B. russel and A. R. Todd; *J. Chem. Soc.,* 1419 (1947)
40. D. N. Dhar, Chemistry of Chalcones; Wiley, New York, (1981)
41. S. S. Misra and B. Nath; *Indian J. Appl. Chem.,* **34**,260(1971).
42. R. Kahn and H. R. Hensei; *Cme. Ber.* **86**, 1333 (1953).
43. S. S. Misra; *J. Indian Chem. Soc.,* **50**, 355 (1973).
44. R. Aries; *Ger. Pat.* **2,** 341 514 (1979); 146152 (1974)

45a. Kostancki et. al., *Ber.,* **39** 625 (1904)

45b. Hutchins and Wheeler; *J. Chem. Soc.,* **91** (1939).

46. Arita et al., *Japan, p.* 1956, 294; *Chem. Abstr.* **51**, 4054, (1957)
47. Krbeckek; *J.Agr. Food. Chem.,* **16,** 108 (1968).
48. K. Shyama Sundar; *Proc. Indian Acad. Sci.,* **59A,** 241 (1964)
49. Magyar Kimiai Folyoirat, **60,** 373 (1954); *Hung. Tech. Abstr.,* **3,** 7 (1955).
50. K. Shyam Sundar; *Proc. Indian Acad. Sci.* **67**, 259 (1964).
51. K. Shyam Sundar; *Proc. Indian Acad. Sci.* **67**, 90 (1968).
52. Guo. Zongru,han Ruj; CN 1,13, 909; *Chem.Abstr.,* **125,** 103768 (1996)
53. De. Vincenzo, R. Seamble G. Panicl,P.Benedess; Remelletti F.O.; *Anti Cancer Drug Des.,* **10(6),** 481-90 (1995); *Chem abstr.,* **124**, 247r (1996)
54. E.T. Ogensyna et.al.; *Khim.Form. Zh.* **25(8),** 18 (1991), *Chem. Abstr.,* **115,** 247497n (1991).
55. B Prescott : *Int. J. Clin.Pharmocol, Bio Pharm.,* **11(4)**, 332 (1975); *Chem. Abstr.,* **83,** 126292d (1975).

56. Li.Rongshi, Chem. Xiaowa; Gong baougang, Dominguez, Jose N. et.al.; *J. Med. Chem.* **38(26).** 5031-7 (1995); *Chem.Abstr.,* **124**, 232f (1996).

57. Hsieh, Hasin, Kaw; Lee-Tai-Hua Wang, Jih-pyang.Wang.et.al.; *Chem. Abstr.,* **128,** 225684n (1998).

58. A. E. Vanstone, G. K. Maile and L. K. Nalbantoglu; *Ger. Offen.* DE 3,537, 207 (Cl.07 c 65/40), (1986); *Chem. Abstr.,* **106,** 49778f (1987).

59. D. Binder, C. R. Noe. W. Holzer and B. Rosenwirth; *Arch. Pharm.* **318(1)**,48 (1975); *Chem.Abstr.,* **102,**149025u (1985).

60. A. S. Tomcufak, R. G. Wilkson and R. G. Child; *German Patent* **2**, 502, 490 (1975); *Chem. Abstr.,* **83**, 179067 (1975)

61. A. K. Bhatt, R. P. Bhamaria, Mrs. M. R. Patel, R. A. Bellare and C. V. Deliwiala; *Indian Chem.* **10(7),** 694 (1972); *Chem.Abstr.,* **78,** 119650n (1973).

62. A. C. Grosscurt, H. R. Van and K. Wellinga; *J. Agric. Food Chem.,* **27(2),** 406 (1979); *Chem. Abstr.,* **91,** 15132x (1979).

63. Kamei, Hideo, Koide, Tatsurou; Hashimoto Yoki, Kojima et al., *Chem. Abstr.,* **126,** 258666v (1997).

64. Tsotitus Andreas,Kalosoroulou Theodaran et al. PCT *Int. Apl.,* WO 99,54,278 (1999); *Chem. Abstr.,* **131,** 28260z (1999).

65. M.R. Bell : *US Appl*. 637,931 (1984); *Chem.Abstr.,***113,**211828t (1990).

66. L.Real, C. David and B. Francois; Can. *J.Pharm.Sci.,* **2,** 37(1967); *Chem. Abstr.*, **67**,98 058f (1967).

67. Tashio Pharmaceutical Co.Ltd.; *Japan, Kokai Tokkyo Koho Jp.* **51,**12,094 (CIA 61 K 31/215); *Chem. Abstr.,* **101,** 54722j (1984).

68. K. Kyogoku et.al.; *Chem. Pharm Bull,* **27(12),**2943(1979); *Chem. Abstr.,* **93,** 26047r (1980).

69. Y. Inamori et al.; *Chem.Pharm.Bull,* **39(6),**1604 (1991); *Chem. Abstr.,***115,**105547c (1991)

70. K. Bowden; P.A. Dal and C.K. Shah; *J. Chem. Res. Synop.,* **12,** 2801(1990); *Chem. Abstr.,* **114,**160570m(1991)

71. E. Marmo,A. P. Caputi and S. Cataldi; *Farmaco Ed. Prat*. **28(3),**132(1973); *Chem.Abstr.,* **79,**13501v (1973).

72. V. M. Gaurav and D. B. langle; *Indian J.Chem.* **25(8),** 868 (1986); *Chem. Abstr.,***17,**39321h (1987).

73. A. K. Pedersen and G. A. FitzGerald; *J. Pharm. Sci.,* **74(2),**188(1985); *Chem. Abstr.,***103,** 87592m (1985).

74. Kalashnikow B. B. Kalashnikova J. P.; *Russ. J. Ger. Che.,* 1998; *Chem. Abstr.,***130,** 296596n (1999).

75. S. S. Mishra and S. C. Kushwaha; *J. Indian Chem. Soc.,* **64,** 640 (1977).

76. Parmar Virinder S; Jain Subhash C; et al. *Indian J.Chem.,*Sect.B., *Org. Chem. Incl. Med. Chem.* **37B(7),** 628-643(1998), (Eng.),CSIR, *Chem. Abstr.,* **129,**289910m (1998).

77. S. R. Modi and H. B. Naik; *Orient J. Chem.,* **10(1),**85-6(1994); *Chem. Abstr.,***122,** 81186c (1995).

78. Nissan Chemical Industries Ltd.,*Japan Kokai Tokkyo Koho Japan* **38,**08,035,(1983), *Chem.Abstr.,* **98,** 178947 q (1983).

79. A. C. Gross Curt, H. R. Van and K. Wellinga; *J. Agric. Food. Chem.* **27(2),**406 (1979); *Chem. Abstr.,* **91,** 15132x (1979).

80. Bekhit Adnan A.: Hubib, Nargues S ; *Bollcttino Chimico Farmaceutico* **140(5)**, 297-301(2001) *Chem. Abstr.,* **136,** 294792g (2002).

81. Zawadowsi, Teodor; Rechowicz, brzemyslaw; *Chem. Abstr.* **95,**427902z (1981) .

82. Bromidge Steven, Marks; lovell, Peter, John; *Chem. Abstr.***136(12),** 183704b (2002).

83. Dela, Torre; Maria D. L.; Marcorin, Gian L ; *Chem. Abstr.,***137(2),** 20236g (2002).

84. V. V. Mulund, R. D. Bhagat; *I. J. H. C.* **7,** 245 (1998).

85. K. Bowden, P. A. Dal and C. K. Shahi *J. Chem. Res. Synop;* **12,** 2801 (1990); *Chem. abstr.,* **114,** 160570m (1991).

86. B. V. Badani and Chandrashekhar K. Hosamani; *I.J.H.C.,* **7,**245,(1998).

87. Walavalkar P.B. Pednekar Suhas; *J. Heterocylic Chem.*(1999): *Chem. Abstr.* **131**, 257517p (1999).

88. Abdel Rahman T. M. ; *Bull. Chim. Farm,* 1998; *Chem. Abstr.,* **132**,93276h (2000).

89. Patil S. D. Gudadhe S. K. Ukesh C. S. Jamode V. S.; *Asian J.Chem.*2000; *Chem. Abstr.,* **132**,180518x (2000).

90. Dimmock Jonathan R., Manavathu Eliask; U.S. US 6,017,933; *Chem.Abstr.,***132,** 107880n (2000).

91. Okayama Toru, Okada Yoshihito,Shibatashpji; *Jpn.Kokai, Tokkyo Koho JP* **11**,349,521; *Chem. Abstr.,* **132**,22752t (2000).

92. Duck Sylvie,Forrest Richard, Hadfield.John A.; et al.; *Bio.Org.Med.Chem.Lett.,* **8(9),**1051-56 (1998); *Chem.Abstr.,* **129,** 81558v (1998).

93. R. Seele et al.; *Eur. Pat. Appl. EP* **337,** 198 (C1. C07 D 249/08), (1989); *Chem. Abstr.,* **113,**178990s (1990).

94. Bombardeli Ezio, Valent Piero; *PCT Int.Appl.* WO 98, 58,913; *Chem.Abstr.,***130,** 95382 (1999).

95. Denny Wiliam Alexander, Tercel Moana, Alwell Graham, John, Milbank Javed; *PCT Int.Appl.* WO 98, 25, 898; *G.B. Appl.* **96,**25,913,39 pp (1996).

96. Tanaka Masayuki, Okita Makoto, Miyamoto Mitsuaki, Kaneko Toshihiko et al.*Jpn. Kokai Tokya Koho JP* **09**,309,879 (1995); *Jp. Apll.* **96,** 148, 569116p.

97. Sharma P.N. Sreenivasulu B.; *J. Indian Chem. Soc.,* **74(8),** 644-645 (1997); *Chem.Abstr.,* **128,** 88799n (1998).

98. C.K. Bradsher, F.C. Brown and W.B. Blue; *J. Amer.Chem. Soc.,* **71** 3570 (1949).

99. T. Drikura, Y.Hassegawa,H.Kawasaki and T. Toyata; *Chem.Abstr.,* **75,** 35746 (1971).

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

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

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

103. A. Quilico; (Five and six membered compounds with Nitrogen and Oxygen) ed. R.H. Wiley, Interscience, New York, 6, 1962.

104. J. Schimidt and K. Widmann ; Lab Pure and Pharm., Lem. Royal Techn. Hochschule, Stultgart; *Ber.* **41,** 1252-60 (May 9); *Chem. Abstr.,* **2**, 2249 (1908).

105. Dawood, Kamal M., Kundeel, Zaghku E; Faraq Ahmed M; *J. Chem. Res. Synp.* (4), 208-209 (1998); *Chem.Abstr.,* **129,** 67759e (1998).

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

107. Baskaran Subramaniam, Baskuran Chitra and Trivedi Girish K.; *J. Chem. Res. Synop.,* **11,** 394-395 (1997); *Chem.Abstr.,* **128,** 3632e (1998).

108. Tayde V.B. Jamode V.S.; *Asian J. Chem.,* **9(4),** 866-68 (1997); *Chem.Abstr.,* **128**, 88824s (1998).

109. John F. Hansen adn Scott A. Strong; *J. Heterocyclic Chem.,* **14,** 1289 (1977).
S. B. Lohiya and B. J. Ghiya; Indian J. Chem., 279-82 (1986).

110 Touux, Bea trice; Texier-Bouilet; Francoise; Hamelin Jack; *Hetero at. Chem.,* **9(3),** 351-354 (1998); *Chem.Abstr.,* **129**, 4600a (1998).

111. S. Balaic, A. Shariti and B. Ahganganian; *Indian J. Heterocycl. Chem.,* **10,** 149-150 (2000).

112. Akhil H. Bhatt, H.H. Parekh and A.R. Partikh; *Jur. Of Heterocylic Communication,* **4,**4 (1998).

113. G. D. Diana and C. P. Michel; *S. African Z A* 81 03, 105 (1981); *Chem.Abstr.,* **98,** 16671 (1983).

114. G. P. Reddy, E. Rajendra and A. K. Murthy; *Indian J. Heterocycl*. **3,** 233 (1994); *Chem.Abstr.,* **122,** 15724e (1995).

115. Naik, S. M. and Naik, H. B.; *Orient J. Chem.,* **14(1),** 167-168 (1998).

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

117. Vamanouchi Pharm. Co. Ltd., *Jpn Kokai Tokkyo Koho JP* **58,** 148, 858,(1982) (CI C 07D 207/335) (1983) Appl. 82/30045 (1982); *Chem.Abstr.,* **100,** 34538 (1984).

118. P.T. Gallagher, T.A. Hicka and G.W. Mullier (Lilly Ind. Ltd.); *Eur. Pat. EP* **2,** 57 882 (1988); *Chem.Abstr.,* **103,** 12339m (1985).

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

120. T. Tochiro, K. Shrji, I. Shinji, M. Hiroshi, S. Akira and V. Hiroshi; *Ger. Offen DE* **3,** 237, 149 (CI. C07 A 261/14); (1983); *Chem.Abstr.,* **99,** 88188 (1984).

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

122. I.A. Shehata and R.A. Glanoh; *J. Heterocycl. Chem.,* **24,** 1291 (1987).

123. M.D. Mackie, H.S. Anthony, W.J.R. Howe, S.P. John and W.S. Marry; *Brit; UK Pat. Apl.* GB **2,** 265, 371 (CI C07 D 261/06); *Chem.Abstr.,* **120,** 1641532 (1994).

124. Masui, Moriyusu, Hasegwa Yushi, *PCT Int. Apl. WO* **97** 43, 248 (CI. C 07, 25/50); *Chem. Abstr.,* **128,** 14605z (1998).

125. Sezer Ozkan, Debak Kudir, Anac Okay, Akar Ahmet; *Heterocycl. Commun.,* 1999; *Chem.Abstr.,* **131,** 5221f (1999).

126. Reddy Kusbakohtlu Venkat, Subita G. Rao; A.V. Subba; *Indian J. Chem.,* **37B(7),** 677-699 (1988); *Chem. Abstr.,* **129,** 260397p (1998).

127. M. Tibor, P.S. Neil and S.P. Henry Gount; *PCT Int. Apl.* WO 9414, 782 (CI. C 07 D 261/08); *Chem. Abstr.,* **121,** 255784t (1994).

128. Rajeev Jain, D.d. Agarwal and Damodharan; *J. Ind. Chem. Soc.* **72,** 825-27 (1995).

129. T. Taate, K. Nafira and H. Fukhola; *Chem. Pharm. Bull.* **35(9),** 37769 (1987); *Chem.Abstr.,* **108,** 186621e (1988).

130. A. Ando and R.W. Stevens; *PCT Int. Apl.* WO 94, 12, 481 (CI. C 07D 261/04); *Chem. Abstr.,* **122,** 56037x (1995).

131. Teley John J; Sikorski, James A.; Bruneto et.al., *PCT Int. Apl. WO* 96, 38, 418 (CI. C 07D 231/12), 5 Dec. 1996. *US Appl.* 458-54, 2 Jun, 1995, 134 pp (Eng.).

132. Mishra Ashutosh, Jain Sanmati K.; Ashthana j.; *Orient J. Chem.,* **14(1),** 151-152 (1998); *Chem.Abstr.,* **128,** 21 6538m (1998).

133. Inai, Masatoshi; Tanaka, Akie; Goto, Kyoto; *Jpn Kokai Tokkyo Koho* JP **07,** 215, 952 (95, 215, 952) (1995) *JP. Appl.* 93

134. Vekariya N. A.; Khunt M. D.; Parikh A. R.; *Indian J of Chem.,* **42B(2),** 421-424 (2003); *Chem. Abstr.,* **139,** 22184d (2003).

135. Burk, Robert M.; Donde, Yari V.; Garst, Michael E. *PCT Int. Appl* WO **02** 22,621 (Cl. CO7D493/08), 21 Mar 2002, US Appl. 661,771, 17 Sep. (2000); 33 pp; *Chem. Abstr.,* **136,** 263023u (2002).

136. Wang, Gary T.; Wang Shelden; Gentles, Robert; *PCT Int. Appl. WO* **02** 02, 539 (Cl. CO7D263/48), 10 Jan 2002, *US Appl.* 606,717, 29 Jun 2000; 135 pp; *Chem. Abstr.,* **136,** 102394a (2002).

137. Dyke, Hazel Joun; Richard, Marianna Dilani; Haughan, Alan Findlay; Sharpe, Andrew PCT *Int. Appl.* WO 03 53, 958 (Cl. CO7D413/04), 3 Jul 2003, GB Appl. 2002/4,137, 22 Feb 2002; 77 pp; *Chem. Abstr.,* **139,** 85370g (2003).

138. Momose, Yu; Mackawa, Tsuyoshi; Asakawa, Tomoko; Sakai, Nozomu *PCT Int. Appl* WO **02** 40,458 (Cl. Co7D 261/08), 23 May 2002, *Jp. Appl.* 2000/350, 869, 17 Nov. 2000; 270 pp.; *Chem. Abstr.,* **136,** 401786y, (2002).

139. Diana, Guy D. ; Mc Kinlay, M. A. Brisson C. J.; Zalay, E. S.; Miralles , J.Y.; Salvador; V. J. *J. Med. Chem.,* 1985, **28(6),** 748-52; *Chem. Abstr.,* **103,** 141870r (1987).

140. Misra, Raj N. ; Xiao, Hai-Xan (Bristol-Mayer Squibb Company, USA) *PCT Int. Appl.* WO **02** 10, 16z (Cl. Co7D 417/12), 7 Feb 2002, *US Appl.* 746,060,22 Dec. 2000; 60 pp (Eng.).

141. Shionogi and Co. Ltd., *Neth. Appl.* 6,408,694 (Cl. CO7a), Feb. 1.1965; *japan Appl.Jully* 7pp 31, 1963; *Chem. Abstra.,* **63,** 7015, (1965) .

142. G. Daidone, D. Roffa, B. Maggio, F. Plescia; VMC Cutuli; *Archiv Der Pharmazie,* **332(2),** 50-54 (1999).

143. H. S. Joshi et al. *J. Ind. Chem. Soc.,* **80**, 707-708 (2003)

144. S. Rung and D. Dus; *Pharmazie,* **49,** 727 (1994); *Chem. Abstr.,* **122,** 559344 (1995).

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

146. Aicher Thomas D., Balkam Bark, Bell Philip A; Brand Leonard J. et al.; *J. Med. Chem.* **41(23),** 4556-66(1998); *Chem. Abstr.,* **129,** 343429b(1998).

147. Kim Sujeone, Lee Ju Young and Kim Byeang Hyean; *Bioorg. Med.Chem.Lett.;* **8(11),** 1313-1316(1998); *Chem. Abstr.,* **129,**14168a (1998).

148. Nyitrai Jozsef, Nagg Jozsef, Simig Gyala et al.; *Chem. Abstr.,* **128,** 29477h (1998).

149. Sezer Ozkhan, Debak Kadir, Anac Okay and Akar Ahmet; *Heterocyclic commun.* (1999), *Chem. Abstr.,* **131,** 216538m (1998).

150. Reddy Kusbakahtla Venkat, Sabita G. Rao and A. V. Subba; *Indian J. Chem.,* **37B(7),** 677-699 (1998); *Chem. Abstr.,* **129,** 260397 (1998).

151. Gudhadhe S., K., Patil S. D. and Ukesh Jamode; *Orient J. Chem.,* **15(1),** 133-136(1998); *Chem. Abstr.,* **132,** 222481r (2000).

152. Ranjan C. Khunt, Neela J. Datta, Fatema M. Bharmal, G. P. Mankad and A. R. Parikh; *Indian J. Hetrocyclic Chem.,* **10,** 9-11(2000).

153. Tayade V. B. and Jamode V. S. ; *Asian J. Chem.,* **9(4),** 866-868(1997); *Chem. Abstr.,* **128**, 88824s (1998).

154. Nakatsuka Masushi, Ueno Yoshihide et al., *PCT Int. Appl.* WO **98** 47, 880(Cl. C 07 D 261/14)(1998); *Chem. Abstr.,* **129,** 330722s(1998).

155. Huebner Verena D., Lim Xiaoding, James lan , Chen Liya and Desai Manoj *PCT Int. Appl.* WO 00 08,001 (2001) .

156. Introduction of Infrared and Raman spectroscopy by Norman B. Colthup, Lowrence H. Daly and Stephen E. Wiberluy, Academic press(1975).

157. Spectrometric Identification of Organic Compounds 6th Edition by Robert M. Silverstein and Francis X. Webster(1997).

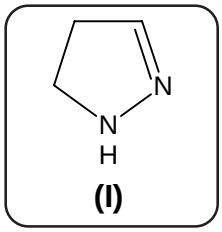
158. A. L. Barry; The Antimicrobial Suceptibility test; Principal and Practices, illusled and Febiger, Philadelphia 180-93 (1976); *Bio. Abstr.,* **64,**25783 (1976).

159. F. Simoncini, R, Rangane and C. Calani; *Farrmoco Ed. Part,* **23(10),** 559-70 (1968).*Chem. Abstr.,* **69** 109851 d (1968).

## INTRODUCTION

2- Pyrazoline consist a unique class of nitrogen containing five member heterocycle. Pyrozolines have attracted attention of medicinal chemists for both with regard to heterocyclic chemistry and the pharmacological activities associated with them. Pyrazoline have been studied extensively because of ready accessibility, diverse chemical reactivity, broad spectrum of biological activity[1] and varieties of industrial applications[2].

The chemistry of pyrazoline was reviewed by Jarobe in 1967.

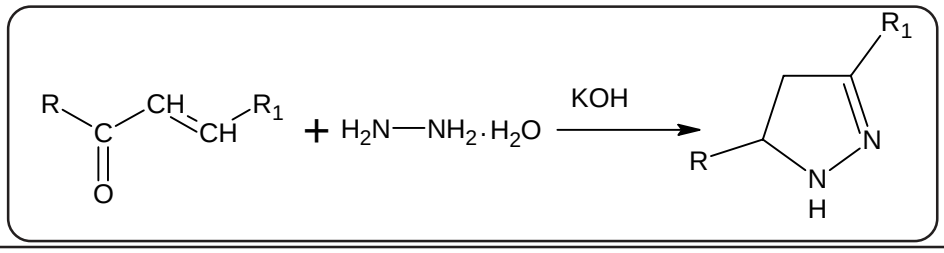



**(I)**

## SYNTHETIC ASPECT

Different methods available in literature for the preparation of pyrazolines are as under.

1. 2- Pyrazolines can be constructed by the cyclocondensation of chalcones with hydrazine hydrate[3].

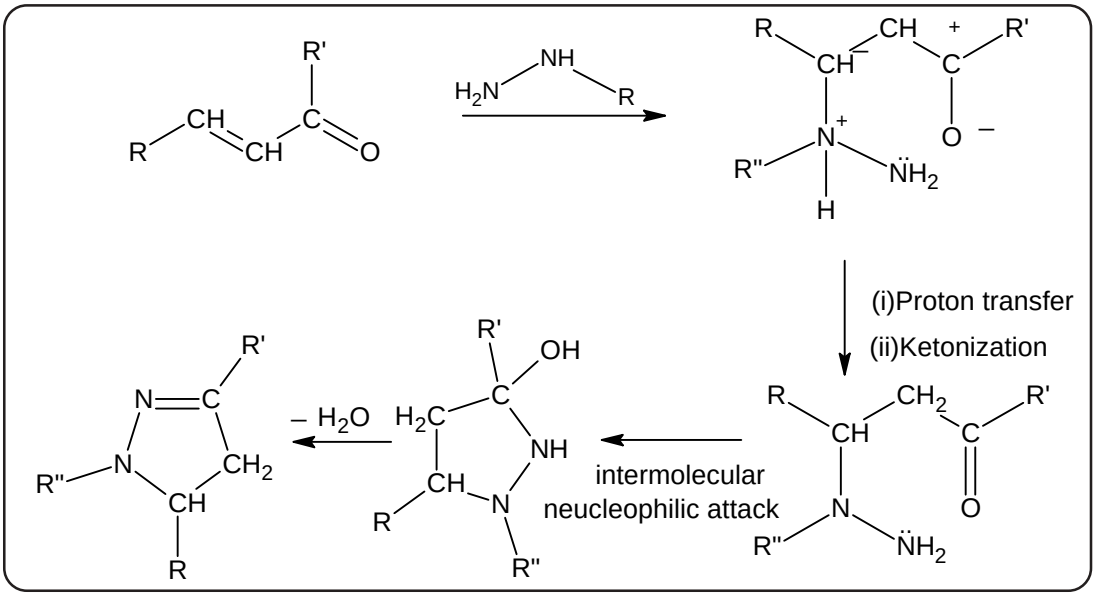


2. Epoxydation of chalcones gave epoxy ketones which on reaction with pyrazoline or phenyl pyrazoline to give substituted pyrazolines derivatives[4].
3. 2-Pyrazolines can also be synthesised by the reaction of chalcone dibromide with hydrazine hydrate[5].
4. Dipolar cycloaddition of nitrilamines to dimethyl 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].

Recently, 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 of chalcones with hydrazine hydrate[10]




## THERAPEUTIC IMPORTANCE

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

(1) Analgesic[11]

(2) Antiallergic[12]

(3) Anticonvulsant[13]

(4) Antidiabetic[14]

(5) Antiimplantation[15]

(6) Antiinflammatory[16]

(7) Antitumor[17]

(8) Antineoplastic[18]

(9) Bactericidal[19]

(10) Cardiovascular[20]

(11) Diuretic[21]

(12) Fungicidal[22]

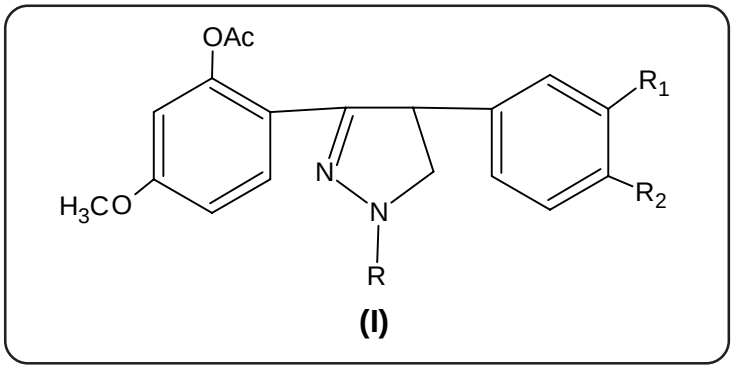
(13) Herbicidal[23]

(14) Hypoglycemic[24]

(15) Insecticidal[25]

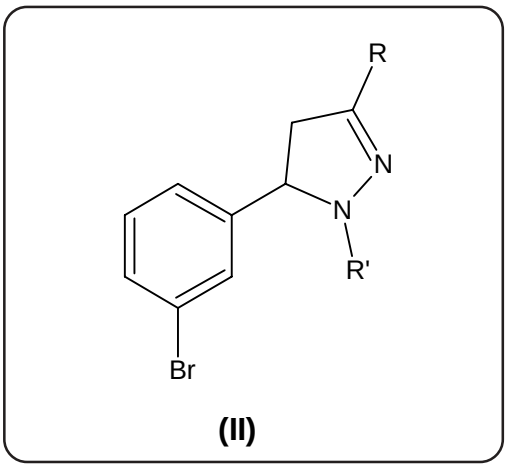
(16) Tranquillizing[26]

Sonave S. S. et al.[27] have synthesised 3-(2'-acetoxy-4'-methoxyphenyl)-5-(substituted phenyl)-pyrazolines (I) and tested their antimicrobial activity.



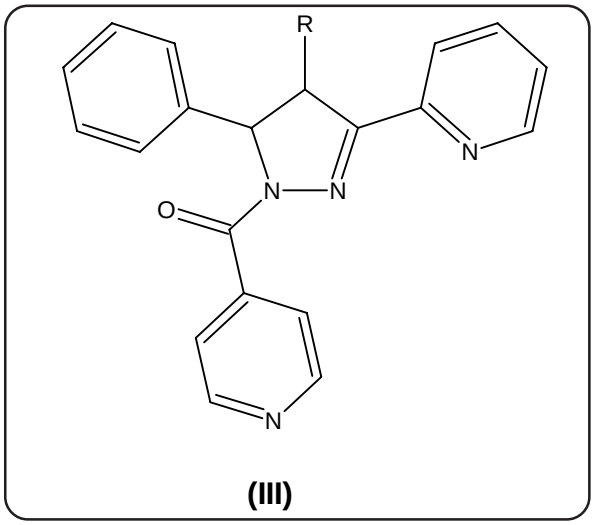

**(I)**

H. S. Joshi, et al.[28] synthesised 1-substituted -3-aryl-5-(3'-bromophynel)-pyrazoline(II) as anticancer, antitubercular and antimicrobial activity.



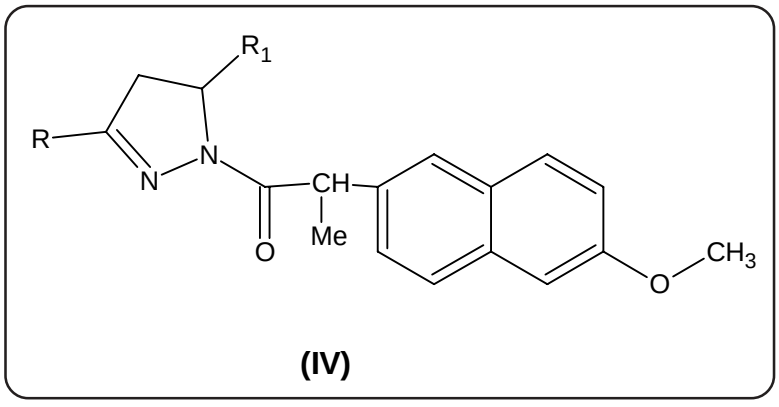

**(II)**

Grazia Momolo M. et al.[29] have synthesised 5-aryl-1-isonicotinoyl-3-(pyridin-2-yl)-4,5-dihydro-1H-pyrazoline derivatives (III) and reported as antimicrobial and antituberculosis agent.



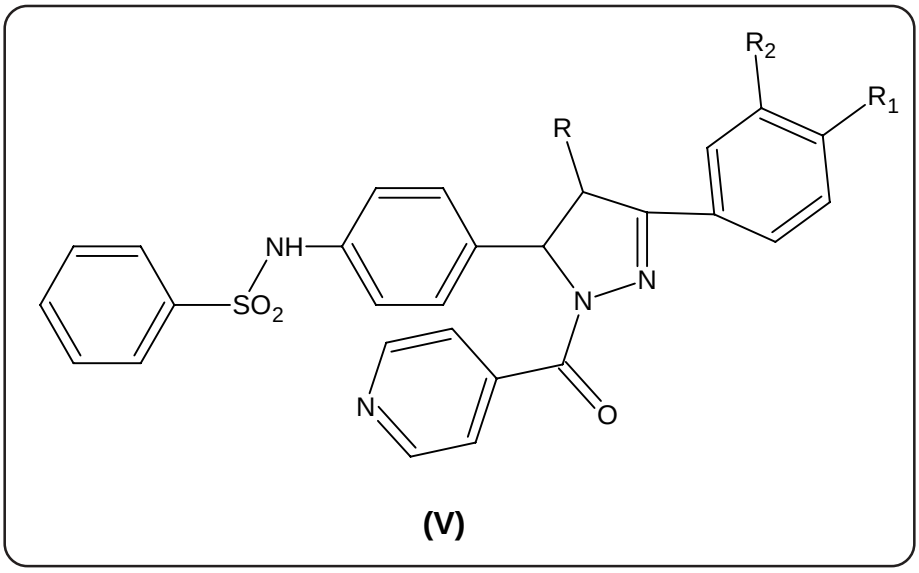

**(III)**

R. H. Udapi et al.[30] have sysnthesised 2-(6-methoxynaphthyl)-propionic acid (Neeproxen)(IV) and reported as antimicrobial and antiinflammatory activity.



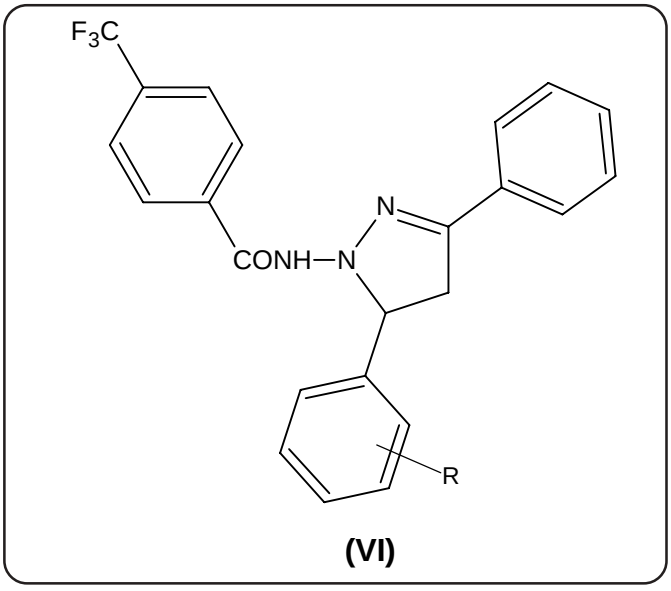

**(IV)**

V. S. Jamode et al.[31] have prepared and screened their antimicrobial activity of 1- isonicotinoyl carboxamido-2-pyrazolines (V).




**(V)**

Further more, Tsuboi et al.[32] have reported some new (phenyl amino carbonyl)-pyrazoline (VI) as an insecticides and at 40% concentration shows 100% mortality of spodostera litura larve after seven days.




**(VI)**

Parekh H. H. et al.[33] have also synthesised some new pyrazolines derivatives as an antimicrobial agent.

Sharan and co-workers[34] have reported antibacterial and antiinflammatory activities of pyrazolines. Bala Krishana Kaluraya and co-workers[35] have documented new pyrazolines as antifungal agent.

Stevenson et al.[36] have synthesised pyrazolines as selective insecticides. Simsek, Rahime et al.[37] prepared acetyl pyrazoline and reported as antifungal and antimicrobial agents.

Ehen- DMT et al.[38] have described N-substituted pyrazoline type insecticides. Tanka Katsiuhori[39] have patented pyrazoline derivatives as herbicides. Uhlendrot Jouchim and co-workers[40] synthesised pyrazolines as an antiinflammatory and allergy inhibitors. Some novel pyrazoline containing bisphosphonate ester was sythesised and reported as antiinflamatory and antiarithritic agents by Nugent Richard A. et al.[41]

B. Shivarama et al.[42] have synthesis phenyl pyrazolines as antibacterial activity. Gineinah et al.[43] have synthesised of phenyl pyrazolines as anticonvulsant agents. Gevariya. Harsukh et al.[44] have synthesised of some novel unsymmetrical pyrazolines as antitubercular agent.

Thus, significant biological properties associated with pyrazoline derivatives have aroused considerable interest to design the compounds with better drug potentials and to study their pharmacological profile, the synthesis and therapeutics evaluation of them, have been described as under.

**SECTION : 1** **PREPARATION AND BIOLOGICAL SCREENING OF 1-ACETYL-3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-4,5-DIHYDRO-1H-PYRAZOLES.**

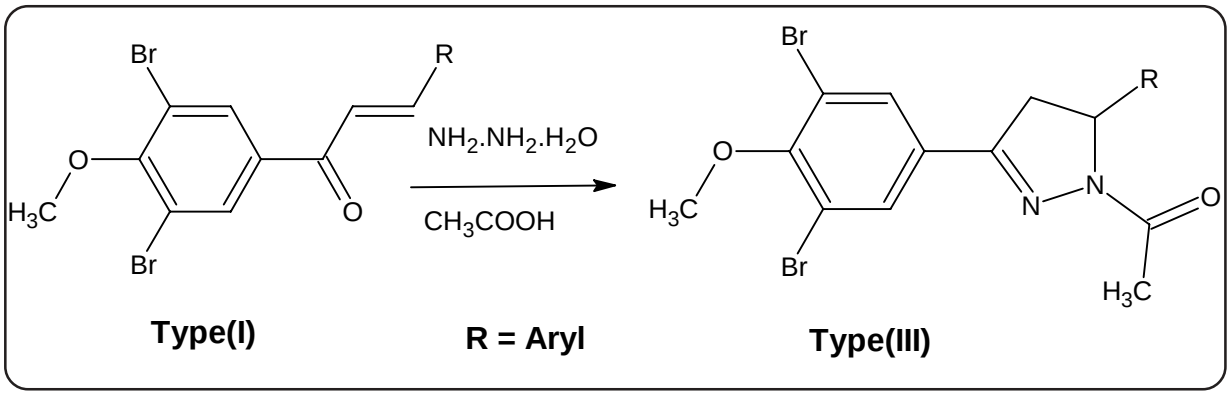
**SECTION : 2** **PREPARATION AND BIOLOGICAL SCREENING OF 4-{[3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-4,5-DIHYDRO-1H-PYRAZOL-1-YL]CARBONYL}PYRIDINES.**

**SECTION : 3** **PREPARATION AND BIOLOGICAL SCREENING OF 1-(4-CHLOROBENZOYL)-3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-4,5-DIHYDRO-1H-PYRAZOLES.**

## SECTION : I

## SYNTHSIS AND BIOLOGICAL SCREENING OF 1-ACETYL-3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-4,5-DIHYDRO-1H-PYRAZOLES

The broad spectrums of pharmacological properties have been demonstrate by the pyrazoline nucleus. Inspired by these facts, novel pyrazoline derivatives of Type (III) have been investigated. The (2E)-1-(3,5-dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones of type (I) when treated with hydrazine hydrate in acetic acid yielded 1-acetyl-3-(3,5-dibromo-4-methoxyphenyl)-5-aryl-4,5,dihydiro-1H pyrazoles, derivatives of type (III).

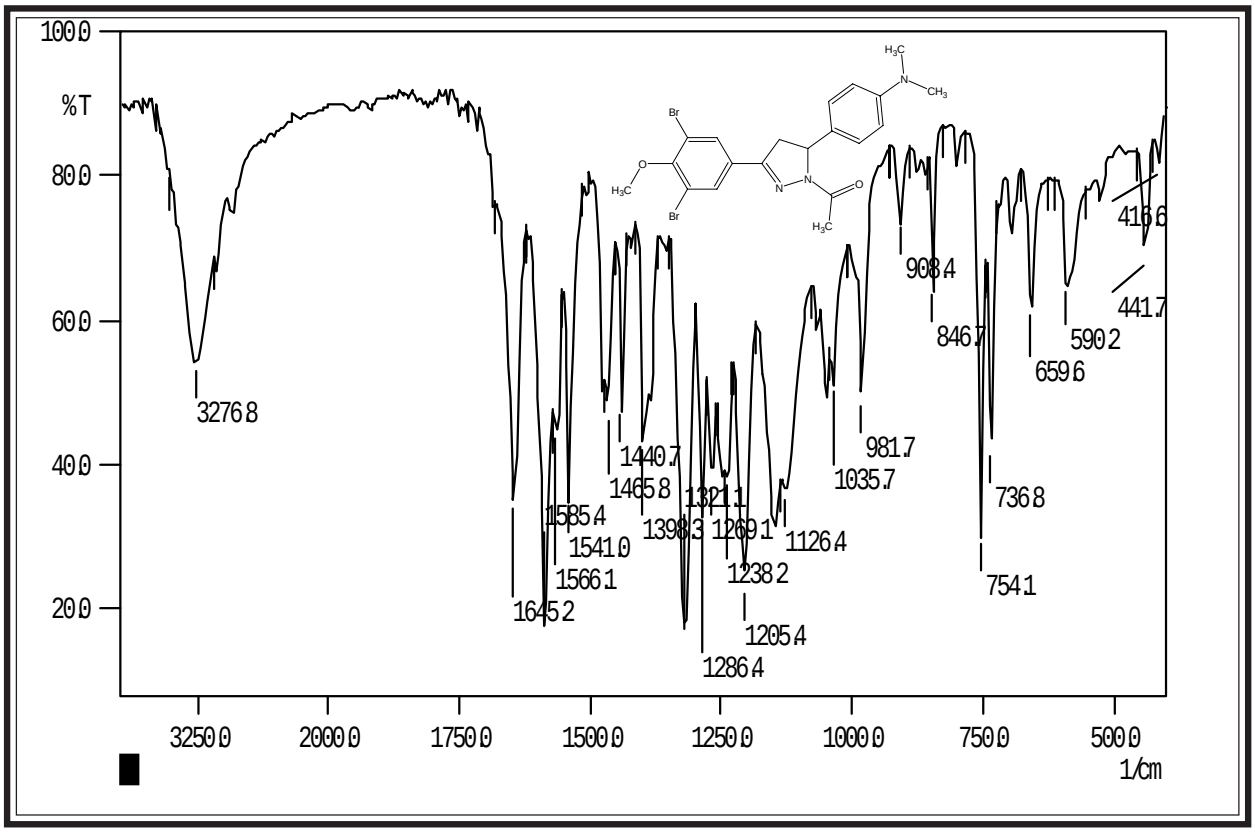



**Type(I)** **R = Aryl** **Type(III)**

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.

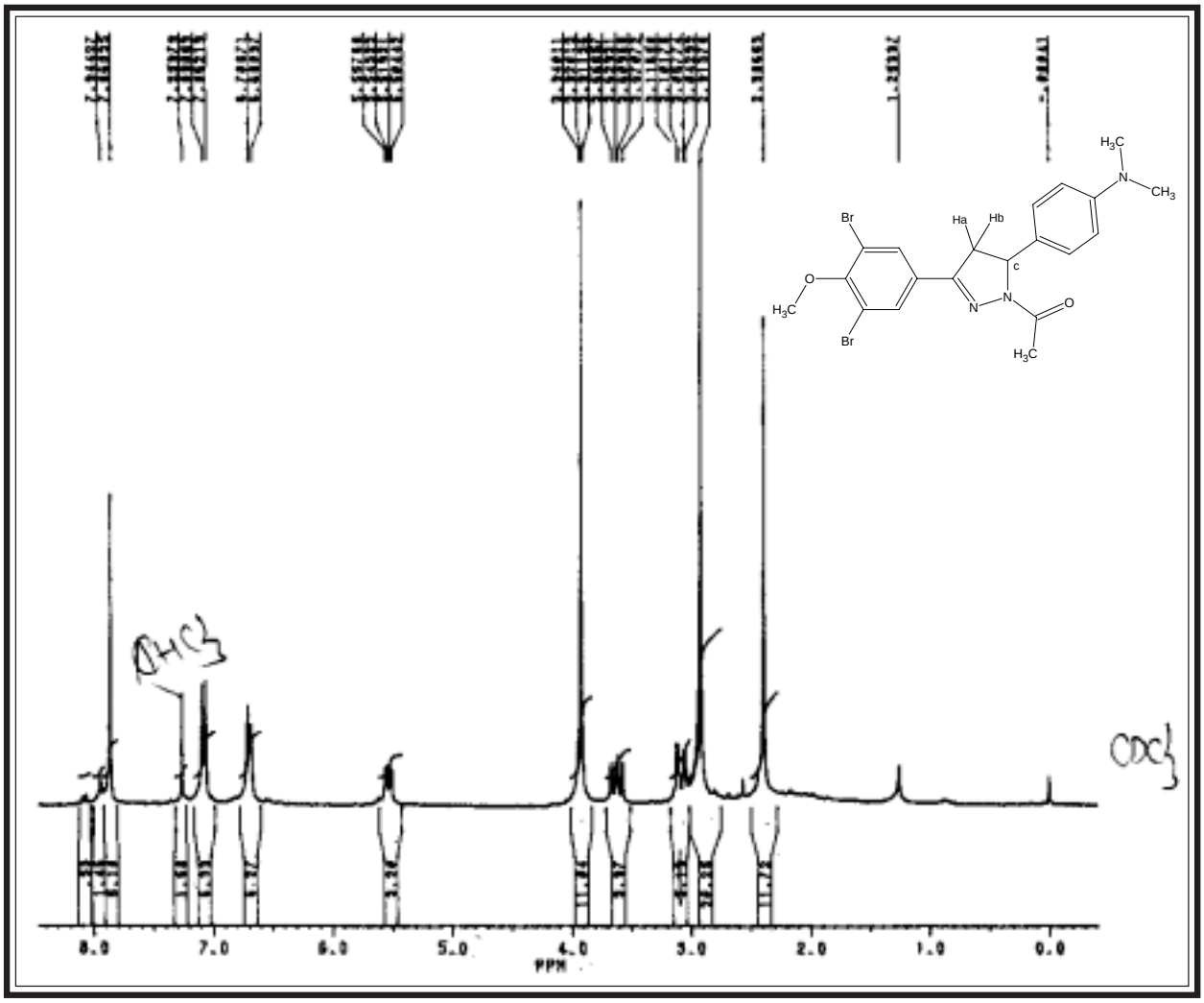
**IR spectral studies of 1-Acetyl-3-(3,5-dibromo-4-methoxy phenyl)-5-(4-N,N-dimethylaminophenyl)-4,5-dihydro-1H-pyrazole**




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

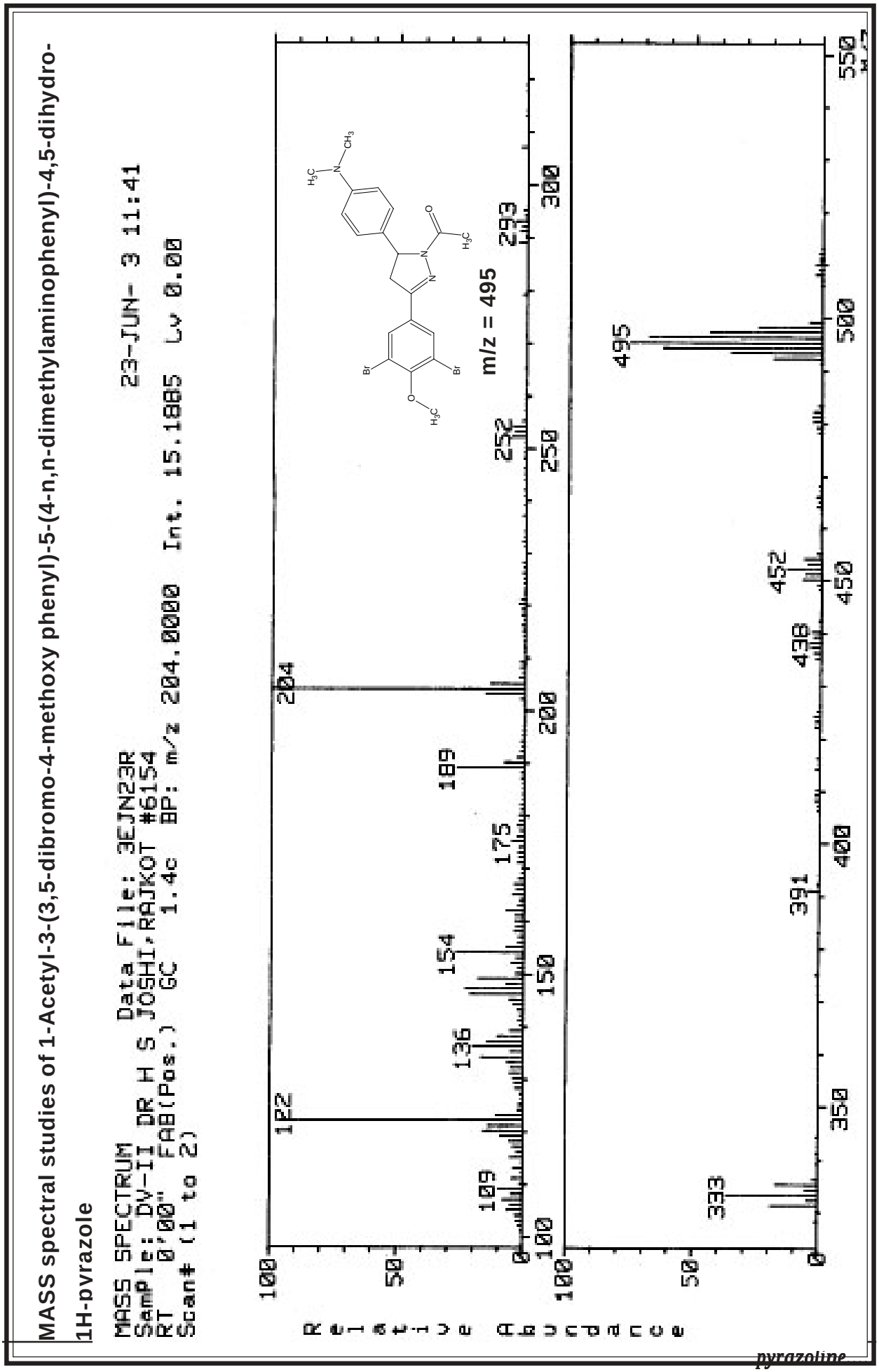
| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2970 | 2975-2950 | 45 |
| -$CH_3$ | C-H str.(sym.) | 2860 | 2880-2860 | " |
| | C-H def.(asym.) | 1440 | 1470-1435 | " |
| | C-H def.(sym.) | 1398 | 1390-1370 | " |
| Aromatic | C-H str. | 3070 | 3090-3030 | 46 |
| | C=C str. | 1566 | 1540-1480 | " |
| | | 1126 | 1125-1090 | " |
| | | 1035 | 1070-1000 | " |
| Halide | C-Br str. | 590 | 600-500 | 45 |
| Ether | C-O-C str.(sym) | 1269 | 1275-1200 | " |
| | | 1045 | 1075-1020 | " |
| Carbonyl | C=O str. | 1645 | 1680-1652 | 46 |
| Pyrazoline | C=N str. | 1585 | 1627-1580 | " |

## NMR SPECTRAL STUDIES OF 1-ACETYL-3-(3,5-DIBROMO-4-METHOXY PHENYL)-5-(4-N,N-DIMETHYLAMINOPHENYL)-4,5-DIHDRO-1H-PARAZOLE




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

| Signal No. | Signal Position (δ ppm) | Relative No. of Proton | Multiplicity | Inference |
|---|---|---|---|---|
| 1. | 2.83 | 3H | singlet | $-COCH_3$ |
| 2. | 2.91 | 6H | singlet | $-N(CH_3)_2$ |
| 3. | 3.04-3.12 | 1H | double-doublet | -CHa |
| 4. | 3.57-3.66 | 1H | double-doublet | -CHb |
| 5. | 3.92 | 3H | singlet | $Ar-OCH_3$ |
| 6. | 5.50-5.56 | 1H | double-doublet | -CHc |
| 7. | 6.68-7.86 | 6H | multiplet | Ar-H |


MASS spectral studies of 1-Acetyl-3-(3,5-dibromo-4-methoxy phenyl)-5-(4-n,n-dimethylaminophenyl)-4,5-dihydro-1H-pyrazole
MASS SPECTRUM Data File: 3EJN23R
Sample: DV-II DR H S JOSHI,RAJKOT #6154
RT 0'00" FAB(Pos.) GC 1.4c BP: m/z 204.0000 Int. 15.1885 Lv 0.00
Scan# (1 to 2)
23-JUN- 3 11:41
m/z = 495
Relative Abundance
pyrazoline

# EXPERIMENTAL

## SYNTHESIS AND BIOLOGICAL SCREENING OF 1-ACETYL-3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-4,5-DIHYDRO-1H-PYRAZOLES

### (A) Synthesis of (2E)-1-(3,5-Dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones

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

### (B) Synthesis of 1-Acetyl-3-(3,5-dibromo-4-methoxyphenyl)-5-(4-N,N-dimethylaminophenyl)-4,5-dihydro-1H-pyrazole

A mixture of (2E)-1-(3,5-Dibromo-4-methoxyphenyl)-3-(4-N,N-dimethyl aminophenyl)-prop-2-en-1-one. (4.39 gm, 0.01 mol) in methanol (25 ml) and hydrazine hydrate (0.5gm, 0.01 mol) was refluxed for 8 hrs. The product was isolated and crystallized from ethanol. Yield 68%, m.p. 178$^0$C, Anal. Calcd. for $C_{20}H_{21}Br_2N_3O_3$; Requires: C, 48. 51; H, 4.27; N, 8.49 %; Found: C, 48.55; H, 4.32; N, 8.47 %.

Similarly, other 1-Acetyl-3-(3,5-dibromo-4-methoxyphenyl)-5-aryl-4,5-dihydro-1H-pyrazoles were prepared. The physical data and recorded in Table No.3

### (C) Biological screening of 1-Acetyl-3-(3,5-dibromo-4-methoxyphenyl)-5-aryl-4,5-dihydro-1H-pyrazoles

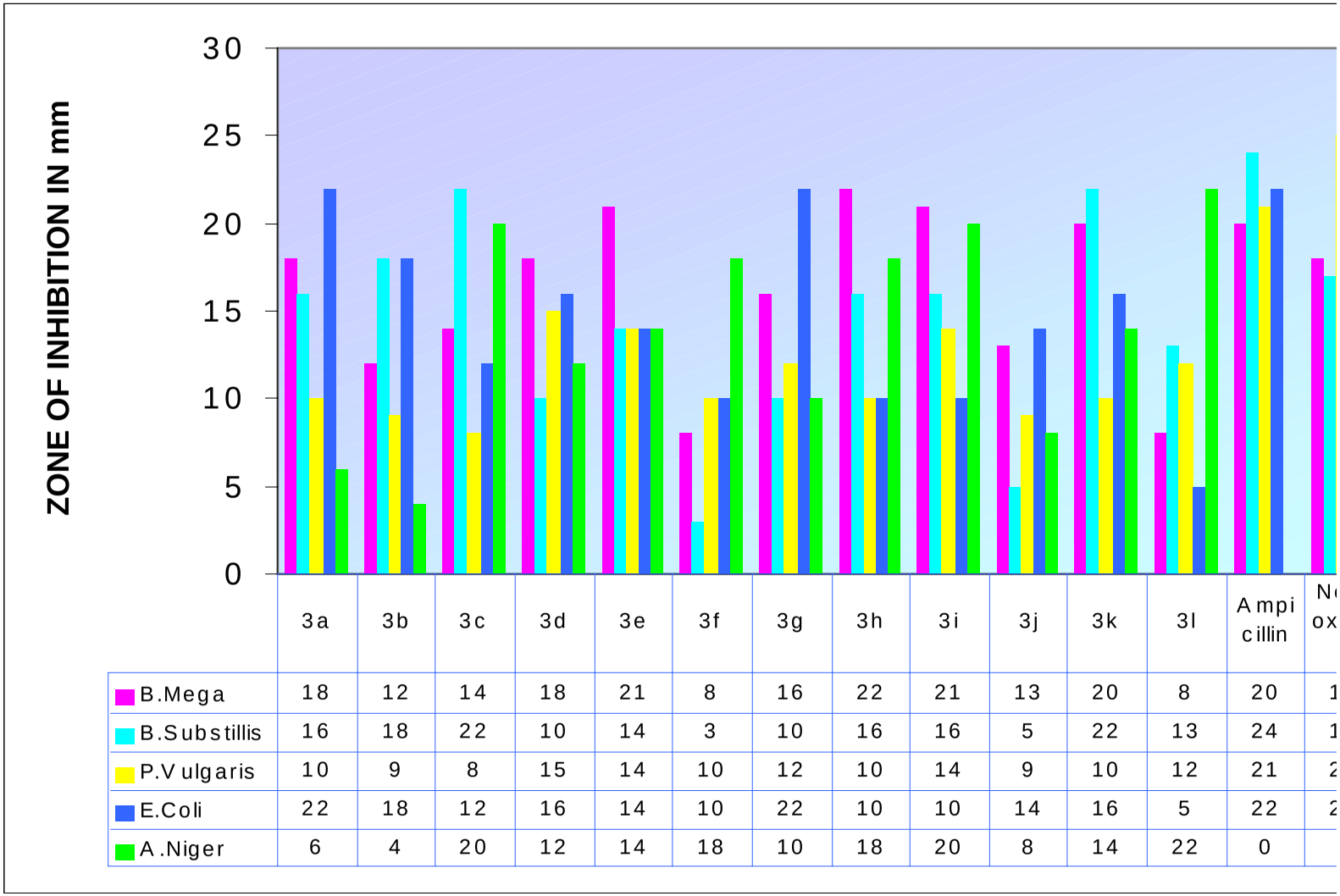
Antimicrobial testing were carried out as described in Part-I Section-I(D). The zones of inhibition of test solutions are recorded in Graphical Chart No.3

**TABLE-3: PHYSICAL CONSTANTS OF 1-ACETYL-3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-4,5-DIHDRO-1H-PARAZOLES.**

| Sr. No. | R | Molecular Fromula | Molecular Weight | M.P. °C | Yield % | % of Nitrogen Calcd. | % of Nitrogen Found | Rf Value | Solvent System |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 3a | $C_6H_5$- | $C_{18}H_{18}Br_2N_2O_2$ | 452.1 | 170 | 65 | 6.20 | 6.18 | 0.62 | S1 |
| 3b | 3-Br-$C_6H_4$- | $C18H_{15}Br_3N_2O_2$ | 531.0 | 158 | 69 | 5.28 | 5.26 | 0.55 | S1 |
| 3c | 2-Cl-$C_6H_4$- | $C_{18}H_{15}Br_3ClN_2O_2$ | 486.6 | 100 | 58 | 5.76 | 5.78 | 0.54 | S1 |
| 3d | 4-Cl-$C_6H_4$- | $C_{18}H_{15}Br_3ClN_2O_2$ | 486.6 | 110 | 55 | 5.76 | 5.75 | 0.63 | S1 |
| 3e | 4-N$(CH_3)_2$-$C_6H_4$- | $C_{20}H_{21}Br_2N_3O_3$ | 495.2 | 178 | 68 | 8.49 | 8.47 | 0.47 | S1 |
| 3f | 4-$OCH_3$-$C_6H_4$- | $C_{19}H_{18}Br_2N_2O_3$ | 482.2 | 75 | 68 | 5.81 | 5.79 | 0.65 | S1 |
| 3g | 3,4-$(OCH_3)_2$-$C_6H_3$- | $C_{20}H_{20}Br_2N_2O_4$ | 512.2 | 104 | 70 | 5.47 | 5.45 | 0.38 | S1 |
| 3h | 2-$NO_2$-$C_6H_4$- | $C_{18}H_{15}Br_2N_3O_4$ | 497.1 | 122 | 58 | 8.45 | 8.43 | 0.45 | S1 |
| 3i | 3-$NO_2$-$C_6H_4$- | $C_{18}H_{15}Br_2N_3O_4$ | 497.1 | 258 | 65 | 8.45 | 8.46 | 0.50 | S1 |
| 3j | 3-$OC_6H_5$-$C_6H_4$- | $C_{24}H_{20}Br_2N_2O_3$ | 544.2 | 158 | 55 | 5.15 | 5.13 | 0.48 | S1 |
| 3k | 2-OH-$C_6H_4$- | $C_{18}H_{16}Br_2N_2O_3$ | 468.1 | 148 | 58 | 5.98 | 5.97 | 0.46 | S1 |
| 3l | 4-OH-$C_6H_4$- | $C_{18}H_{16}Br_2N_2O_3$ | 468.1 | 240 | 60 | 5.98 | 6.00 | 0.68 | S1 |

S1 Benzene: Ethylacetate(9:1)

**GRAPHICAL CHART NO. 3 : 1-ACETYL-3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-4,5-DIHDRO-1H-PYRAZOLES.**

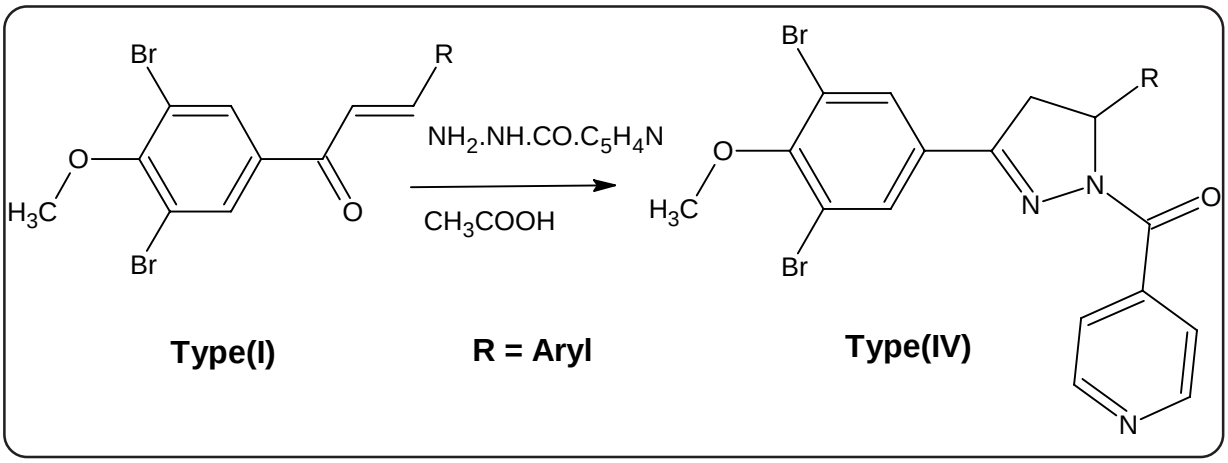



| | 3a | 3b | 3c | 3d | 3e | 3f | 3g | 3h | 3i | 3j | 3k | 3l | Ampicillin | Nox |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B.Mega | 18 | 12 | 14 | 18 | 21 | 8 | 16 | 22 | 21 | 13 | 20 | 8 | 20 | 1 |
| B.Substillis | 16 | 18 | 22 | 10 | 14 | 3 | 10 | 16 | 16 | 5 | 22 | 13 | 24 | 1 |
| P.Vulgaris | 10 | 9 | 8 | 15 | 14 | 10 | 12 | 10 | 14 | 9 | 10 | 12 | 21 | 2 |
| E.Coli | 22 | 18 | 12 | 16 | 14 | 10 | 22 | 10 | 10 | 14 | 16 | 5 | 22 | 2 |
| A.Niger | 6 | 4 | 20 | 12 | 14 | 18 | 10 | 18 | 20 | 8 | 14 | 22 | 0 | |

## SECTION - II

## SYNTHESIS AND BIOLOGICAL SCREENING OF 4-{[3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-4,5-DIHYDRO-1H-PYRAZOL-1-YL] CARBONYL} PYRIDINES

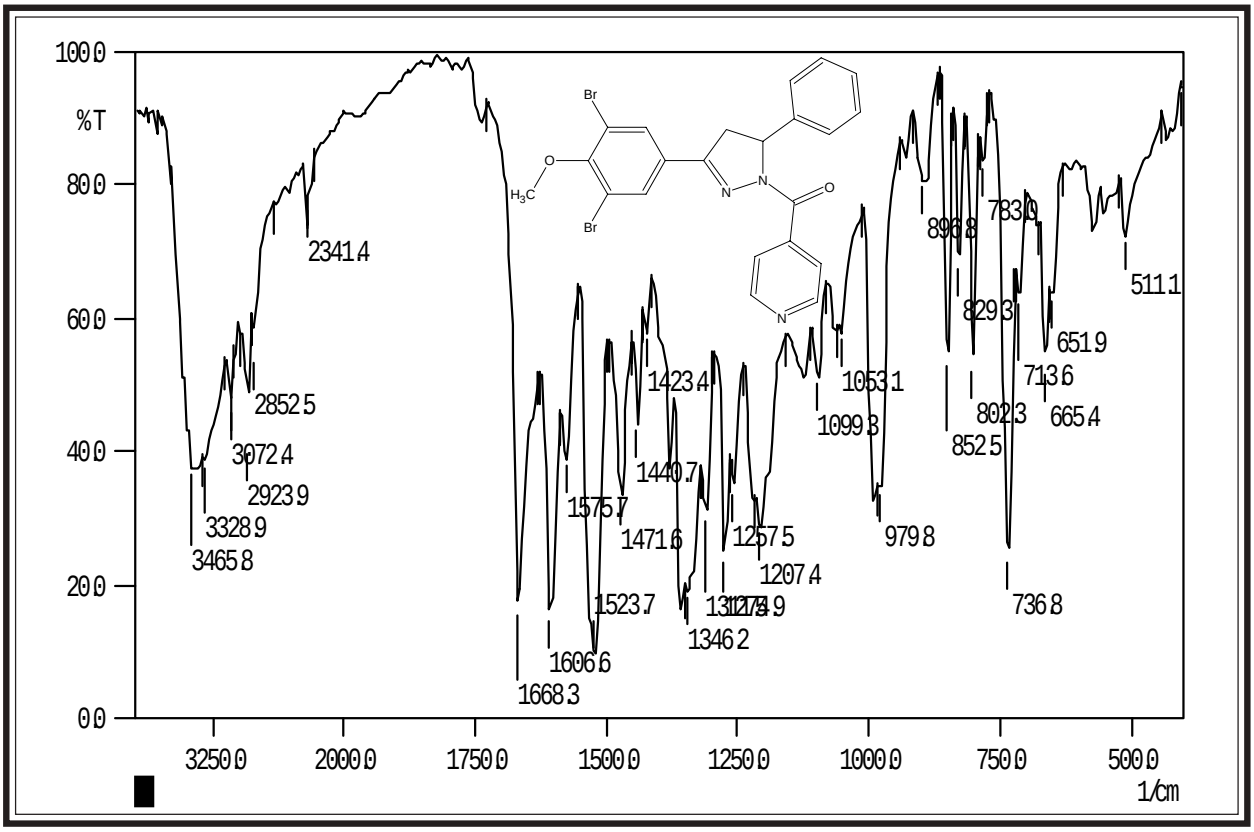
Pyrazoline have been found to be associated with broad spectrum of biological activities. Hence, it was thought of interest to synthesized 4-{[3-(3,5-dibromo-4-methoxyphenyl)-5-aryl-4,5-dihydro-1H-pyrazol-1-yl]carbonyl}pyridines of type-(IV) from (2E)-1-(3,5-dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones of type-(I) by the cyclo condensation with isoniazide 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.

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.

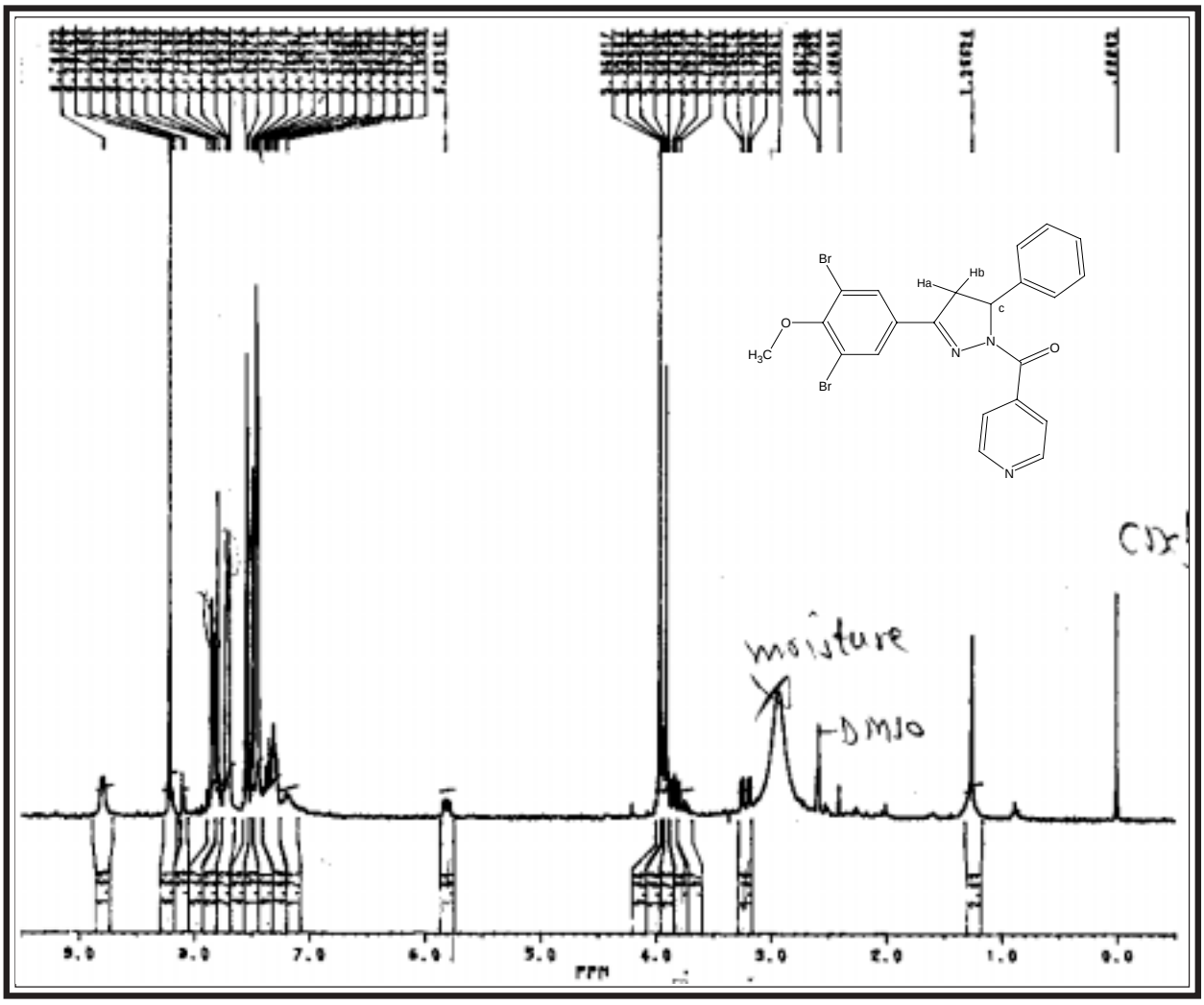
**IR spectral studies of 4-{[3-(3,5-Dibromo-4-methoxy phenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl]carbonyl}-pyridine**




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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2923 | 2975-2950 | 45 |
| $-CH_3$ | C-H str.(sym.) | 2852 | 2880-2860 | " |
| | C-H def.(asym.) | 1440 | 1470-1435 | " |
| | C-H def.(sym.) | 1346 | 1390-1370 | " |
| Aromatic | C-H str. | 3072 | 3090-3030 | 46 |
| | C=C str. | 1523 | 1540-1480 | " |
| | | 1099 | 1125-1090 | " |
| | | 1053 | 1070-1000 | " |
| Halide | C-Br str. | 651 | 600-500 | 45 |
| Ether | C-O-C str.(sym) | 1257 | 1275-1200 | " |
| | | 1053 | 1075-1020 | " |
| Carbonyl | C=O str. | 1668 | 1680-1652 | 46 |
| Pyrazoline | C=N str. | 1606 | 1627-1580 | " |

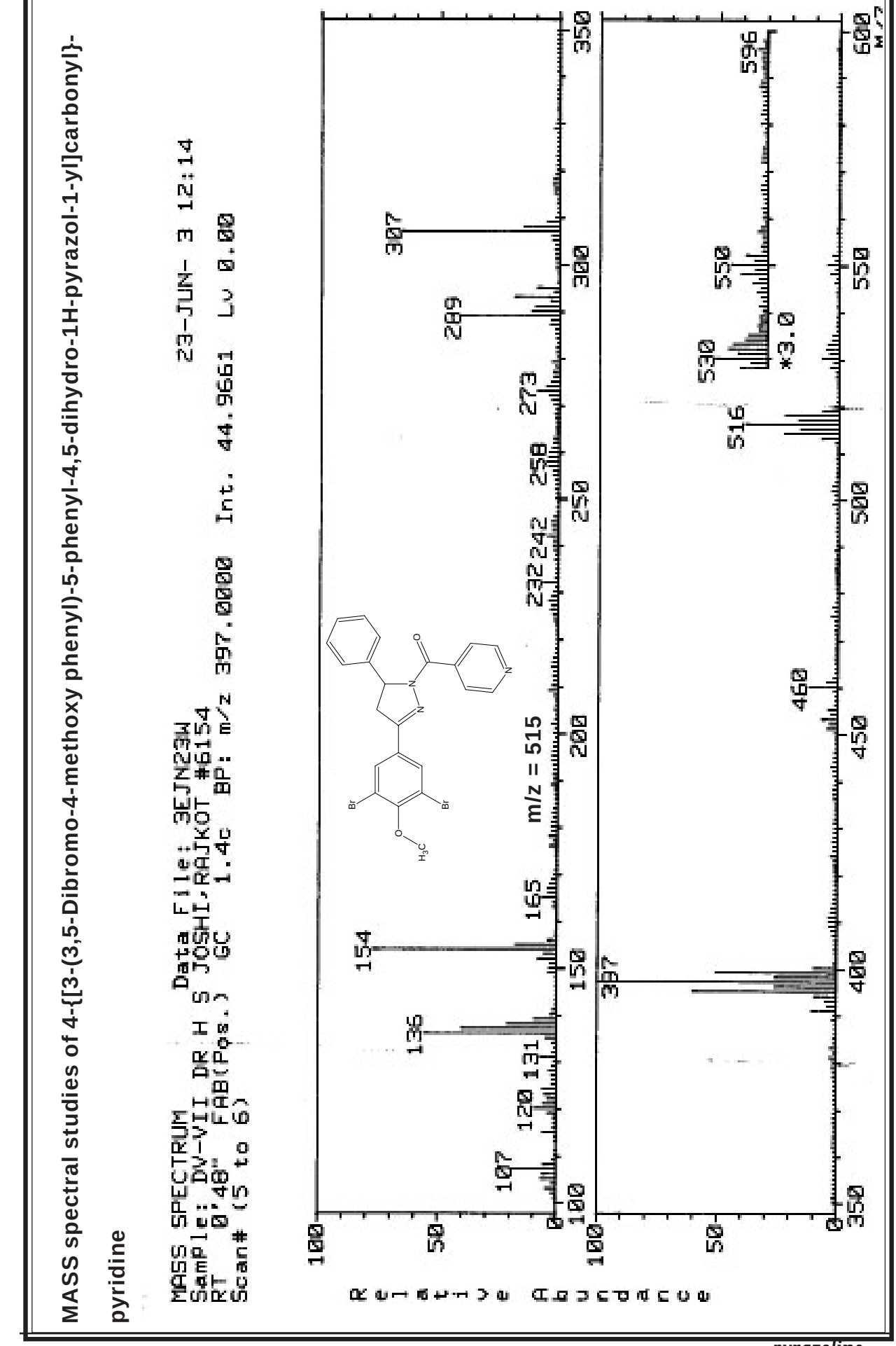
## NMR SPECTRAL STUDIES OF 4-{[3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-PHENYL-4,5-DIHYDRO-1H-PYRAZOL-1-YL]CARBONYL}PYRIDINE




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

| Signal No. | Signal Position (δ ppm) | Relative No. of Proton | Multiplicity | Inference |
|---|---|---|---|---|
| 1. | 3.17-3.23 | 1H | double-doublet | -CHa |
| 2. | 3.82-3.90 | 1H | double-doublet | -CHb |
| 3. | 3.96 | 3H | singlet | Ar-$OCH_3$ |
| 4. | 5.82 | 1H | double-doublet | -CHc |
| 5. | 7.74-8.82 | 11H | multiplet | Ar-H |

**MASS spectral studies of 4-{[3-(3,5-Dibromo-4-methoxy phenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl]carbonyl}-pyridine**



# EXPERIMENTAL

## SYNTHESIS AND BIOLOGICAL SCREENING OF 4-{[3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-4,5-DIHYDRO-1H-PYRAZOL-1-YL]CARBONYL} PYRIDINES

### (A) Synthesis of (2E)-1-(3,5-Dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones

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

### (B) Synthesis of 4-{[3-(3,5-Dibromo-4-methoxyphenyl)-5-phenyl-4,5-dihydro-1H-pyrazol-1-yl]carbonyl}pyridine

A mixture of (2E)-1-(3,5-Dibromo-4-methoxyphenyl)-3-phenyl-prop-2-en-1-one. (3.96gm, 0.01 mol) in a 25 ml of glacial acetic acid and isoniazide (1.47gm, 0.01 mol) was refluxed for 8 hrs. The resulting content was poured on to crushed ice. The product was isolated and crystallized from ethanol. Yield 70%, m.p. $139^0$C, Anal. Calcd. for $C_{22}H_{17}Br_2N_3O_3$; requires: C, 51.29; H, 3.33; N, 8.16; Found: C, 51.35; H , 3.42; N, 8.14 %.

Similarly, other 4-{[3-(3,5-dibromo-4-methoxyphenyl)-5-aryl-4,5-dihydro-1H-pyrazol-1-yl]carbonyl}pyridines were prepared. The physical data and recorded in Table No.4

### (C) Biological screening of 4-{[3-(3,5-Dibromo-4-methoxyphenyl)-5-ar yl-4,5-dihydro-1H-pyrazol-1-yl]carbonyl}pyridines

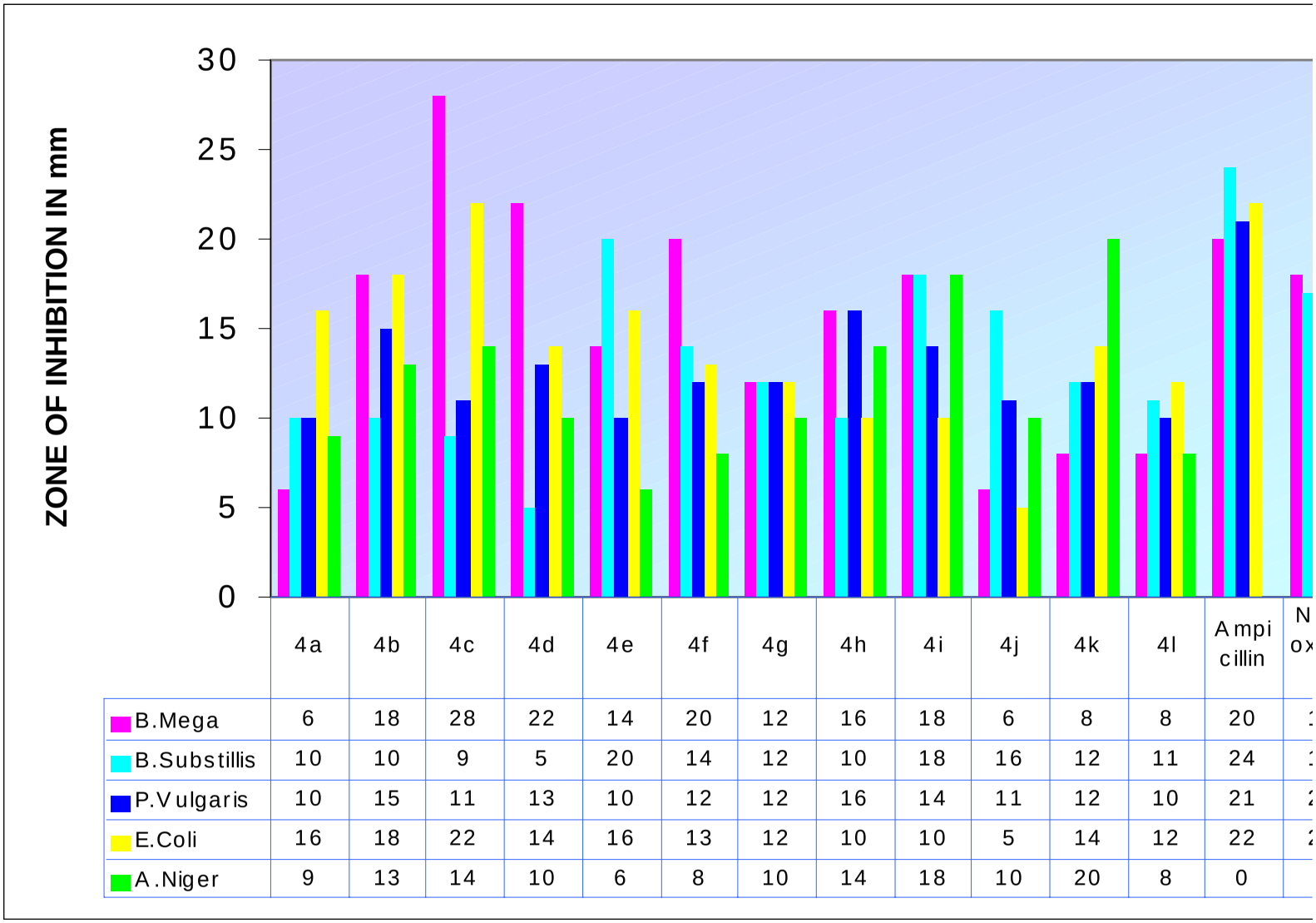
Antimicrobial testing were carried out as described in Part-I Section-I(D). The zones of inhibition of test solution are recorded in Graphical Chart No.4

**TABLE-4: PHYSICAL CONSTNTS OF 4-{[3-(3,5-DIBROMO-4-METHOXY PHENYL)-5-ARYL-4,5-DIHYDRO-1H-PYRAZOL-1-YL]CARBONYL}PYRIDINES.**

| Sr. No. | R | Molecular Fromula | Molecular Weight | M.P. °C | Yield % | % of Nitrogen Calcd. | % of Nitrogen Found | Rf Value | Solvent System |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 4a | $C_6H_5$- | $C_{22}H_{17}Br_2N_3O_2$ | 515.2 | 139 | 70 | 8.16 | 8.14 | 0.58 | S1 |
| 4b | 3-Br-$C_6H_4$- | $C22H_{16}Br_3N_3O_2$ | 594.1 | 120 | 65 | 7.07 | 7.11 | 0.57 | S1 |
| 4c | 2-Cl-$C_6H_4$- | $C_{22}H_{16}Br_2ClN_3O_2$ | 549.6 | 133 | 68 | 7.65 | 7.60 | 0.56 | S1 |
| 4d | 4-Cl-$C_6H_4$- | $C_{22}H_{16}Br_2ClN_3O_2$ | 549.1 | 145 | 60 | 7.65 | 7.58 | 0.55 | S1 |
| 4e | 4-$N(CH_3)_2$-$C_6H_4$- | $C_{24}H_{22}Br_2N_4O_2$ | 558.3 | 137 | 65 | 10.04 | 10.09 | 0.60 | S2 |
| 4f | 4-$OCH_3$-$C_6H_4$- | $C_{23}H_{19}Br_2N_3O_3$ | 545.2 | 124 | 66 | 7.71 | 7.76 | 0.58 | S1 |
| 4g | 3,4-$(OCH_3)_2$-$C_6H_3$- | $C_{24}H_{21}Br_2N_3O_4$ | 575.3 | 118 | 68 | 7.30 | 7.37 | 0.58 | S2 |
| 4h | 2-$NO_2$-$C_6H_4$- | $C_{22}H_{16}Br_2N_4O_4$ | 560.2 | 115 | 58 | 10.00 | 10.06 | 0.67 | S2 |
| 4i | 3-$NO_2$-$C_6H_4$- | $C_{22}H_{16}Br_2N_4O_4$ | 560.2 | 135 | 55 | 10.00 | 10.07 | 0.62 | S2 |
| 4j | 3-$OC_6H_5$-$C_6H_4$- | $C_{28}H_{21}Br_2N_3O_3$ | 607.2 | 90 | 72 | 6.92 | 7.00 | 0.57 | S2 |
| 4k | $C_4H_3O$- | $C_{20}H_{15}Br_2N_3O_3$ | 505.1 | 105 | 75 | 8.32 | 8.40 | 0.63 | S2 |

S1 Benzene: Ethylacetate (9:2)  S2 Benzene: Ethylacetate (8.5:1.5)

## GRAPHICAL CHART NO. 4 : 4-{[3-(3,5-DIBROMO-4-METHOXY PHENYL)-5-ARYL-4,5-DIHYDRO-1H-PYRAZOL-1-YL]CARBONYL}PYRIDINES.

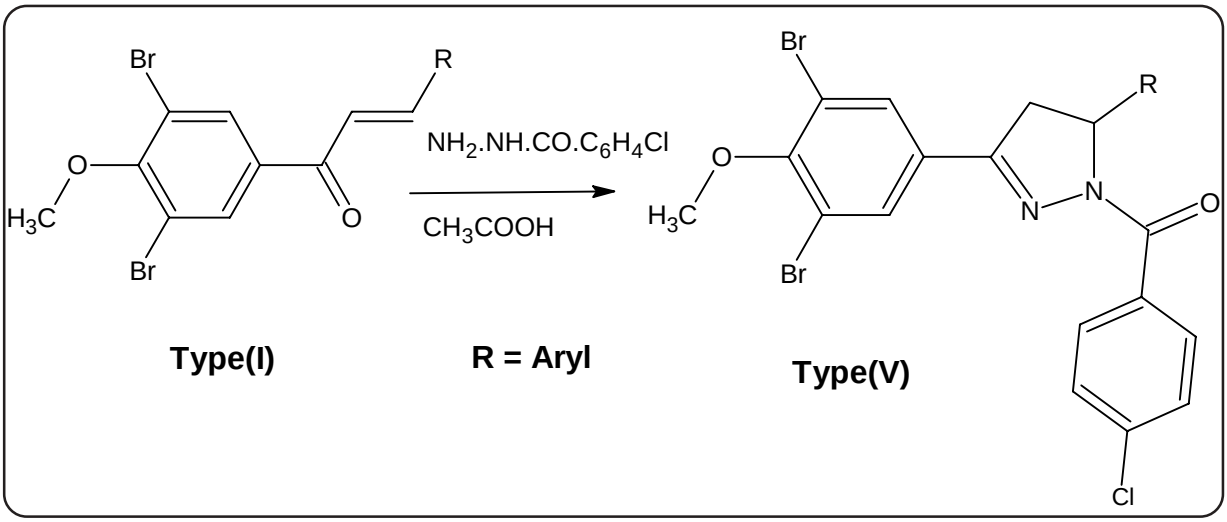



| | 4a | 4b | 4c | 4d | 4e | 4f | 4g | 4h | 4i | 4j | 4k | 4l | Ampicillin | Nox |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B.Mega | 6 | 18 | 28 | 22 | 14 | 20 | 12 | 16 | 18 | 6 | 8 | 8 | 20 | 1 |
| B.Substillis | 10 | 10 | 9 | 5 | 20 | 14 | 12 | 10 | 18 | 16 | 12 | 11 | 24 | 1 |
| P.Vulgaris | 10 | 15 | 11 | 13 | 10 | 12 | 12 | 16 | 14 | 11 | 12 | 10 | 21 | 2 |
| E.Coli | 16 | 18 | 22 | 14 | 16 | 13 | 12 | 10 | 10 | 5 | 14 | 12 | 22 | 2 |
| A.Niger | 9 | 13 | 14 | 10 | 6 | 8 | 10 | 14 | 18 | 10 | 20 | 8 | 0 | |

## SECTION - III

## SYTHESIS AND BIOLOGICAL SCREENING OF 1-(4-CHLOROBENZOYL)-3 -(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-4,5-DIHYDRO-1H-PYRAZOLES

Much interest have been focused around pyrazoline derivatives because of their wide variety of pharmacological properties and industrial application. In view of above findings and to achieve better drug potency, we have synthesized 1-(4-chlorobenzoyl)-3-(3,5-dibromo-4-methoxyphenyl)-5-aryl-4,5-dihydro-1H-pyrazoles of type-(V) by the condensation of 4-chlorobenzoyl hydrazine hydrate with chalcones of type-(I).

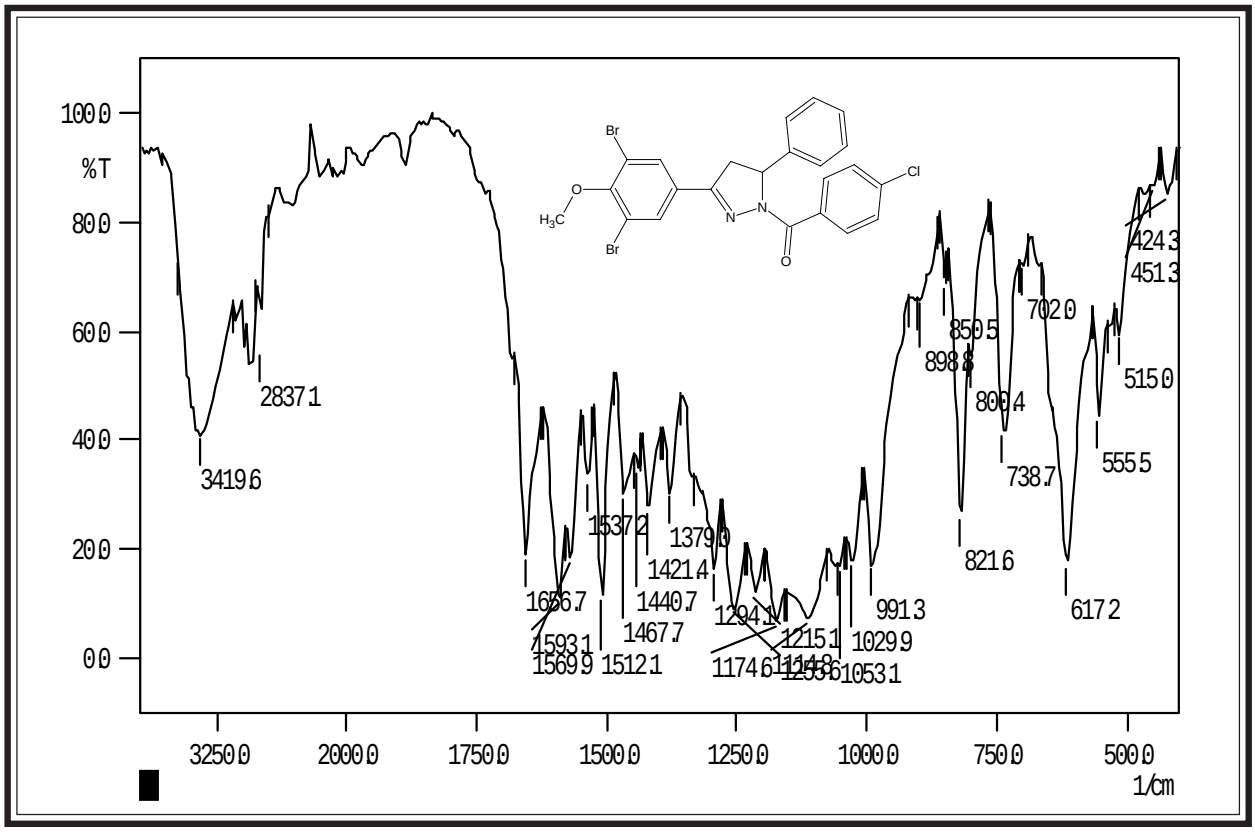



**Type(I)** **R = Aryl** **Type(V)**

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.

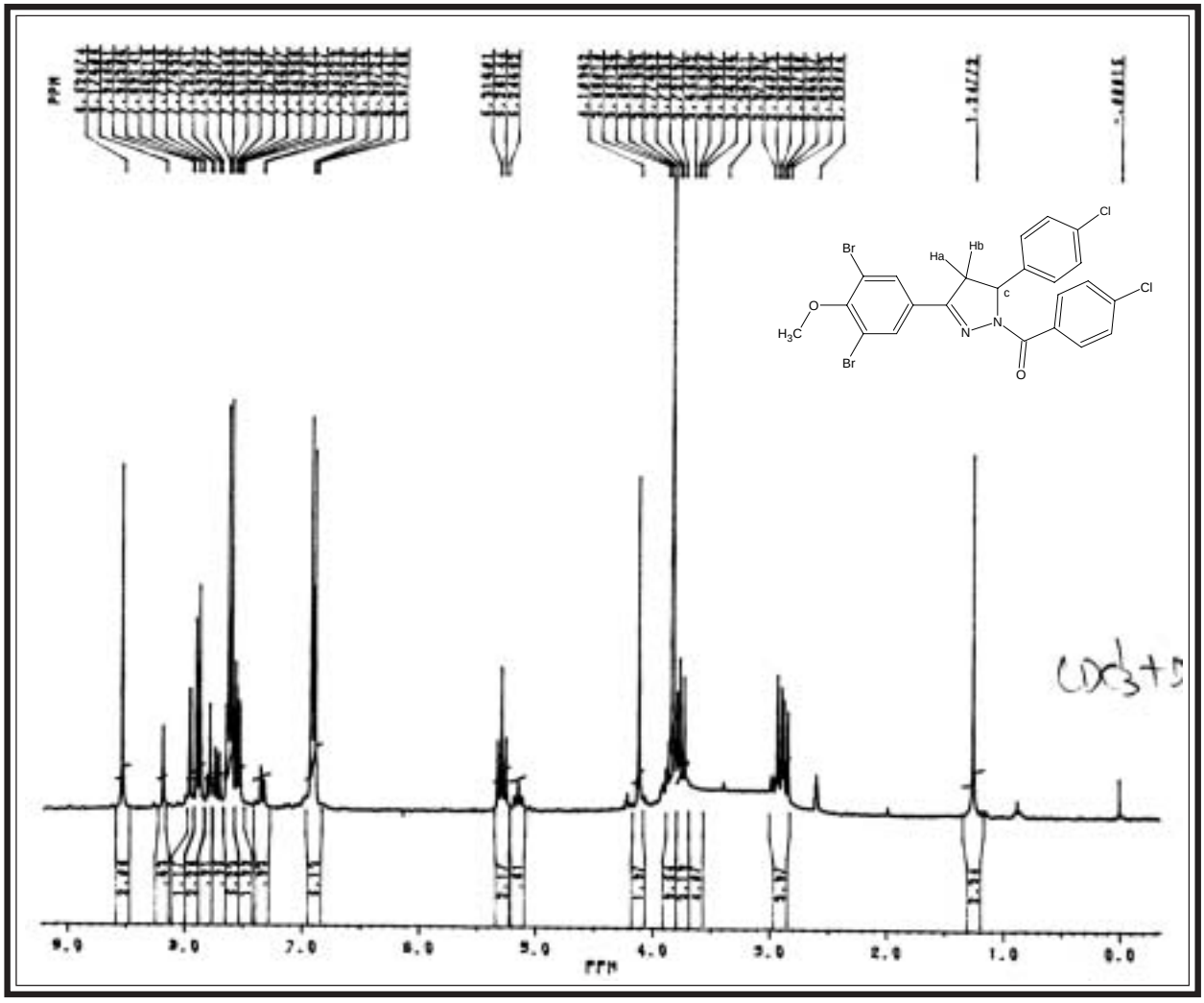
**IR spectral studies of 1-(4-Chlorobenzoyl)-3-(3,5-dibromo-4-methoxy phenyl)-5-phenyl-4,5-dihydro-1H-pyrazole**




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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2950 | 2975-2950 | 45 |
| $-CH_3$ | C-H str.(sym.) | 2837 | 2880-2860 | " |
| | C-H def.(asym.) | 1467 | 1470-1435 | " |
| | C-H def.(sym.) | 1379 | 1390-1370 | " |
| Aromatic | C-H str. | 3045 | 3090-3030 | 46 |
| | C=C str. | 1512 | 1540-1480 | " |
| | | 1148 | 1125-1090 | " |
| | | 1053 | 1070-1000 | " |
| Ether | C-O-C str.(sym) | 1215 | 1275-1200 | 45 |
| | | 1029 | 1075-1020 | " |
| Halide | C-Br str. | 555 | 600-500 | " |
| | C-Cl str. | 617 | 600-800 | " |
| Carbonyl | C=O str. | 1656 | 1680-1652 | 46 |
| Pyrazoline | C=N str. | 1569 | 1627-1580 | " |

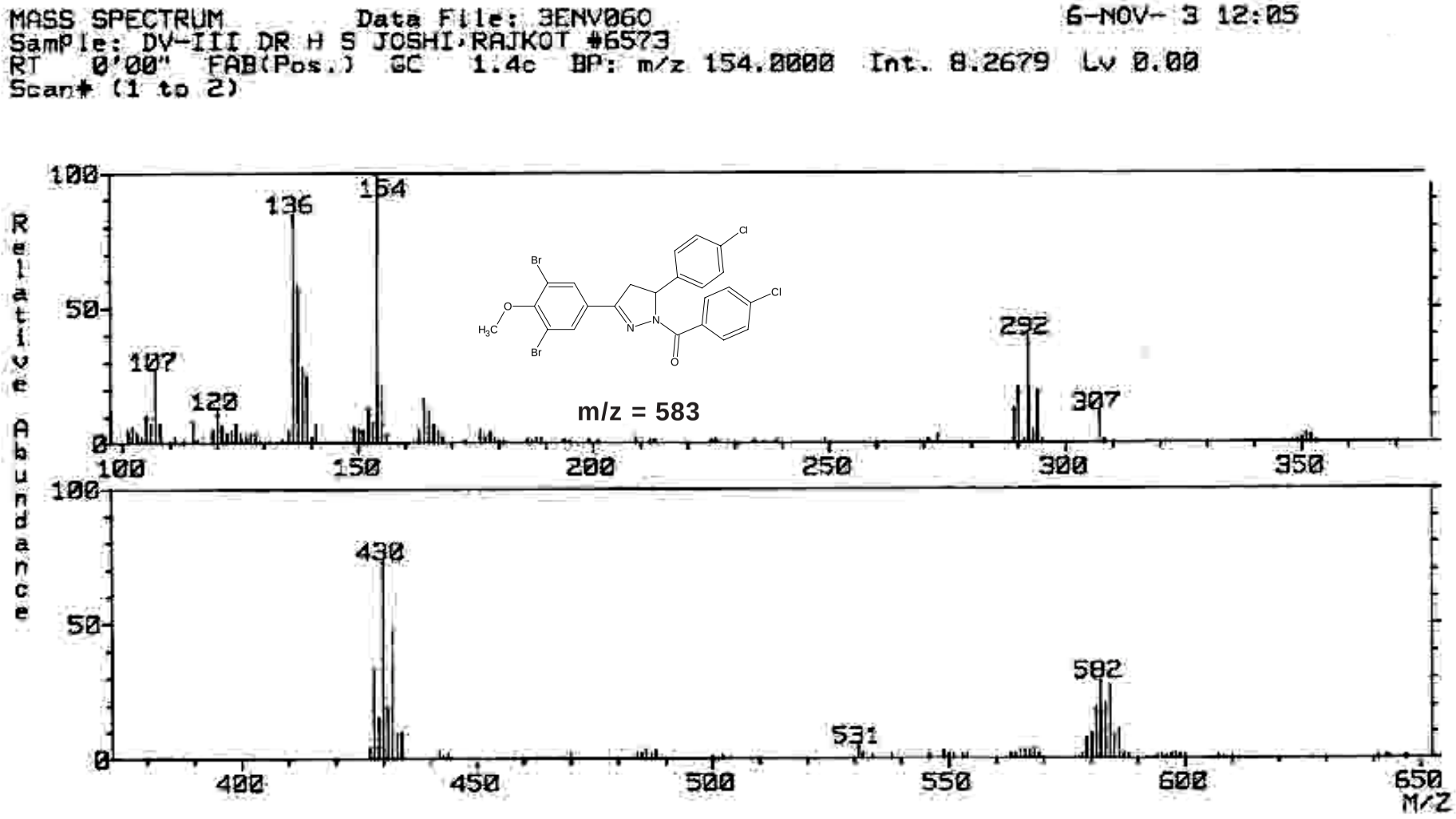
## NMR SPECTRAL STUDIES OF 1-(4-CHLOROBENZOYL)-3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-(4-CHLOROPHENYL)-4,5-DIHDRO-1H-PARAZOLES




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

| Signal No. | Signal Position (δ ppm) | Relative No. of Proton | Multiplicity | Inference |
|---|---|---|---|---|
| 1. | 3.17-3.23 | 1H | double-doublet | -CHa |
| 2. | 3.82-3.90 | 1H | double-doublet | -CHb |
| 3. | 3.96 | 3H | singlet | Ar-$OCH_3$ |
| 4. | 5.82 | 1H | double-doublet | -CHc |
| 5. | 7.74-8.82 | 10H | multiplet | Ar-H |

**MASS spectral studies of 1-(4-Chlorobenzoyl)-3-(3,5-dibromo-4-methoxy phenyl)-5-(4-chlorophenyl)-4,5-dihydro-1H-pyrazole**



# EXPERIMENTAL

## SYNTHESIS AND BIOLOGICAL SCREENING OF 1-(4-CHLOROBENZOYL)-3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-4,5-DIHYDRO-1H-PYRAZOLES

### (A) Synthesis of (2E)-1-(3,5-Dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones

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

### (B) Synthesis of 1-(4-Chlorobenzoyl)-3-(3,5-dibromo-4-methoxyphenyl)-5-(4-chlorophenyl)-4,5-dihdro-1H-pyrazole

A mixture of (2E)-1-(3,5-dibromo-4-methoxyphenyl)-3-(4-chlorophenyl)-prop-2-en-1-one. (4.39gm, 0.01 mol) in a 25 ml of glacial acetic acid and 4-chlorobenzoyl hydrazine hydrate (1.58gm, 0.01 mol) was refluxed for 10 hrs. The resulting mixture was poured on to crushed ice. The product was isolated and crystallized from ethanol. Yield 72%, m.p. $105^0$C, Anal. Calcd. for $C_{23}H_{16}Br_2Cl_2N_2O_2$; Requires: C, 47.38; H2.77; N, 4.80; Found: C, 47.45; H , 2.87; N, 4.75 %.

Similarly, other 1-(4-chlorobenzoyl)-3-(3,5-dibromo-4-methoxyphenyl)-5-aryl-4,5-dihydro-1H-pyrazoles.

### (C) Biological screening of 1-(4-Chlorobenzoyl)-3-(3,5-dibromo-4-methoxy phenyl)-5-aryl-4,5-dihdro-1H-pyrazoles

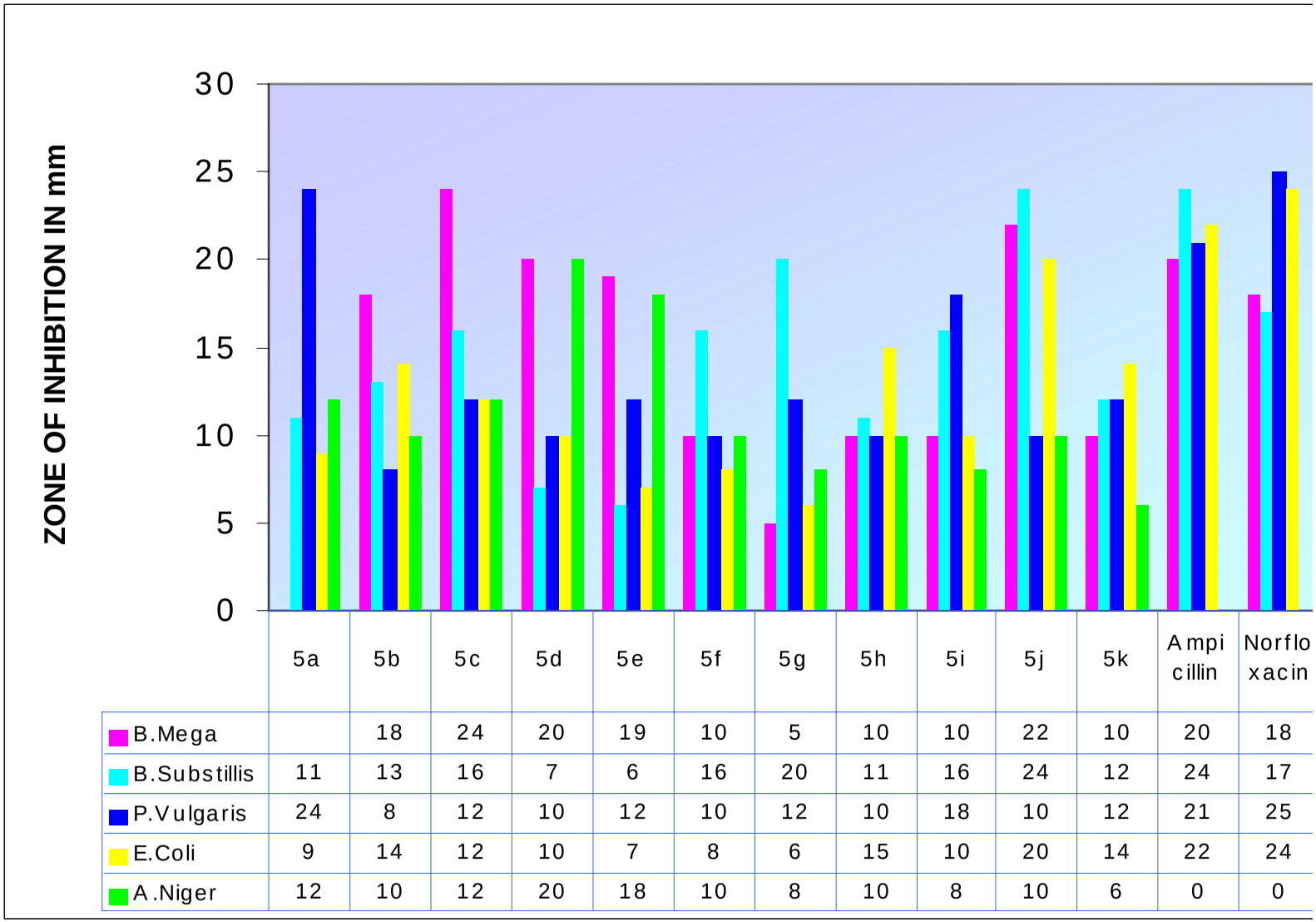
Antimicrobial testing were carried out as described in Part-I Section-I(D). The zones of inhibition of test solution are recorded in Graphical Chart No 5.

**TABLE-5 : PHYSICAL CONSTANTS OF 1-(4-CHLOROBENZOYL)-3-(3,5-DIBROMO-4-METHOXYPHENYL) -5-ARYL-4,5-DIHDRO-1H-PARAZOLES.**

| Sr. No. | R | Molecular Fromula | Molecular Weight | M.P. °C | Yield % | % of Nitrogen Calcd. | % of Nitrogen Found | Rf Value | Solvent System |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 5a | $C_6H_5$- | $C_{23}H_{17}Br_2ClN_2O_2$ | 548.6 | 98 | 65 | 5.11 | 5.17 | 0.64 | S1 |
| 5b | 3-Br-$C_6H_4$- | $C_{23}H_{16}Br_3ClN_2O_2$ | 627.5 | 125 | 68 | 4.46 | 4.40 | 0.54 | S2 |
| 5c | 2-Cl-$C_6H_4$- | $C_{23}H_{16}Br_2Cl_2N_2O_2$ | 583.0 | 138 | 70 | 4.80 | 4.84 | 0.52 | S2 |
| 5d | 4-Cl-$C_6H_4$- | $C_{23}H1_{16}Br_2Cl_2N_2O_2$ | 583.0 | 105 | 72 | 4.80 | 4.75 | 0.50 | S1 |
| 5e | 4-$N(CH_3)_2$-$C_6H_3$- | $C_{25}H_{22}Br_2ClN_3O_2$ | 591.7 | 140 | 66 | 7.10 | 7.50 | 0.39 | S2 |
| 5f | 4-$OCH_3$-$C_6H_4$- | $C_{24}H_{19}Br_2ClN_2O_3$ | 578.7 | 120 | 64 | 4.84 | 4.92 | 0.38 | S1 |
| 5g | 2-$NO_2$-$C_6H_4$- | $C_{23}H_{16}Br_2ClN_3O_4$ | 593.7 | 70 | 68 | 7.08 | 7.02 | 0.43 | S1 |
| 5h | 3-$NO_2$-$C_6H_4$- | $C_{23}H_{16}Br_2ClN_3O_4$ | 593.7 | 115 | 60 | 7.08 | 7.12 | 0.50 | S1 |
| 5i | 2-OH-$C_6H_4$- | $C_{23}H_{17}Br_2ClN_2O_3$ | 564.7 | 102 | 63 | 4.96 | 5.02 | 0.60 | S1 |
| 5j | 2-OH-$C_6H_4$- | $C_{23}H_{17}Br_2ClN_2O_3$ | 564.7 | 77 | 62 | 4.96 | 5.00 | 0.42 | S2 |
| 5k | $C_4H_3O$- | $C_{21}H_{15}Br_2ClN_2O_3$ | 538.6 | 240 | 65 | 4.56 | 4.61 | 0.45 | S2 |

S1 Hexane: Ethylacetate (9.5:0.5) S2 Hexane (10)

**GRAPHICAL CHART NO. 5 : 1-(4-CHLOROBENZOYL)-3-(3,5-DIBROMO-4-METHOXYPHENYL)-5-ARYL-4,5-DIHDRO-1H-PARAZOLES.**




| | 5a | 5b | 5c | 5d | 5e | 5f | 5g | 5h | 5i | 5j | 5k | Ampicillin | Norfloxacin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B.Mega | | 18 | 24 | 20 | 19 | 10 | 5 | 10 | 10 | 22 | 10 | 20 | 18 |
| B.Substillis | 11 | 13 | 16 | 7 | 6 | 16 | 20 | 11 | 16 | 24 | 12 | 24 | 17 |
| P.Vulgaris | 24 | 8 | 12 | 10 | 12 | 10 | 12 | 10 | 18 | 10 | 12 | 21 | 25 |
| E.Coli | 9 | 14 | 12 | 10 | 7 | 8 | 6 | 15 | 10 | 20 | 14 | 22 | 24 |
| A.Niger | 12 | 10 | 12 | 20 | 18 | 10 | 8 | 10 | 8 | 10 | 6 | 0 | 0 |

## REFERANCES


1. J. Elguero; In “comprehensive heterocyclic chemistry” eds. AR Katrizky and C.W. reis. Vol.5 Ch 4.04.
2. R.S. Theobald in : Rodd;s Chemistry of carbon compounds, Ed. M.F. Ansell, Vol.IV, Part C, Ch. 16, 2nd Edition, (Elsenier Science Publishers B.V., Amsterdam) (1998),
3. A. M. Fahmy, M. Hassan, A. A. Khalf, R. A. Ahmed; *Rev. Roum.Chim.,* **33(7)**, 755-61 (1988) (Eng.); *Chem.Abstr.,* **111,**77898 (1989).
4. M. A. El ., Hashash;M.EJ--Kady; m. A. Saiyed; A. A. Elsawy; Egypt; *J. chem.* **27(6),** 715-21(1985); [Eng.] *Chem. Abstr.,* 20868u(1986).
5. Padhy, Arun Ku., Jaggi K., Lakshminarayana V.; Pande, C. S., *J. Indian Chem. Soc.,* **75(2),** 1998 (104-105).
6. Hassaneen Hamdi M;Wad Hamad A; Mousa Hiyam A. H. Sulfur; 4. M.A. EL Hashash;M. EJ-Kady; M. A. Saiyed; A. A. Saiyed; A. A. Elsway; *Egypt. J.Chem.* **27(6)** 715-21 (1985); [Eng.] *Chem.Abstr.,***105** 20868u (1986).
7. Gohamukkala V. Subbaraju, A. Ranga Naykula and D. Parmeswara; *Indian J.of Hetero. Chem.,* **4,** 87-92 (1994).
8. S. Paul, R. Gupta; *Indian J. Chem.,* **37(B),** (12), 1279-1282 (1998).
9. Dandia Anshu, Taneja Harshitia, Sharma C. S.; *Indian J. Heterocylic Chem.,* 1999; *Chem.Abstr.,* **132,** 265161d (2000).
10. Reda. A. Kabli; Ali. A. Khalaf; M. T. Zimaltu; A. M. Khalil; A. M. Kaddah and H. A. AL. Rifuie; *J. Indian Chem. Soc.,* **68,** 47-51 (1991).
11. Delay Francois (Fermenich S.A.) Patentschrift (Switz); *Chem. Abstr.,* **117,** 90276f (1992).
12. B. Roman; *Pharmazle*, **45**, 214 (1990).
13. Z. Brozozowsk E. Pomarnacka; *Acta. Pol.Pharm.* **37(4),** 1378, 80 (1980); *Chem.Abstr.,* **25,** 80807 (1981).
14. H. G. Garg and P. P.Singh; *J. Chem.Abstr.,* **81,** 105494r (1974).
15. D. B. Reddy, T. Senshuma and M. V. Ramana Reddy; *Indian J. Chem.* **30(B),** 46 (1991).
16. A. Kumar, R. S. Verma and B. P. Jagu; *J. Ind. Chem. Soc.,* **67,** 120 (1990).

17. Woiln Ronald L., Afonso Adriano; U.S. USS,597, 821 (Cl 514-232-8 A 61K31 l 535) 28 Jan., 1997, *Appl.* 356, 826, 15, Dec., 1994, 14pp [Eng.] *Chem. Abstr.,* **126,** 181346f (1997).

18. H. M. Mokhtar, H. M. Faidallah; *Pharmazie,* **42,** 481 (1987).

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

20. Yamashita, Hiroyuti,Odala Mocoto,Lizuka Hajime, Kawazura Hirashi, et al.; *Eur. Pat. Appl.* EP 295695 (Cl C07D 401/6) (1988); *J.P. Appl.* 87/148919 (1987). *Chem. Abstr.,* **111,** 23510 (1989).

21. Zalgislaw, K. Zbigneiw and A. Settan : *Acta. Pol. Pharm.* **36(6),** 645(1979); *Chem. Abstr.,* **93,** 204525e (1980).

22 S. S. Nayal, C. P. Singh; *Asian Journal of Chemistry,* **11,** 1, 207-212 (1999).

23 Wellinga Kobus, Eussen Jacobus H.H.; *Eur.Appl. EP* 269 141 (Cl C07D 231/06) (1988); *Chem. Abstr.,* **110,** 8204 (1989).

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

25. D. Bhaskar Raddy, T. Senshama, B. Seenhaiha & M. V. Ramma Reddy; *Indian J. Chem.,* **30(B),** 46 (1991).

26. B. Hans. R. Rolf and R. Rudoff; *US. Pat.* 3, 822,283 (1974); *Chem. Abstr.,* **81,** 105494r (1974).

27. Sonare S. S. Asian *J. Chem. Abstr.,* **10(3),** 591-593 (1998) *Chem.Abstr.,* **129,** 633, 54317j (1998).

28. H. S. Joshi, et al.; *Indian Journal of Heterocyclic Chemistry,* Vol. 12, Jan-Mar 225-228 (2003).

29. Grazia, Momolo, M. ; Zampieri; D. ; *Chem. Abstr.,* **136,** 200135m (2002).

30. Udapi R. H. ; kushnoor, A. S.; *Chem. Abstr.,* **130,** 81450i (2001).

31. V. S. Jamode; H. S. Chandak; *Indian J. Heterocycl. Chem.* **12,** 323-326 ,(2002).

32. Tsuboi-Shinichiwada, Katshaki et al.; *Eur. Pat. Appl.* EP 537-580 (Cl C 07D 401/64) (1993); *J.P. Appl.* 91/297,772 (1991); *Chem. Abstr.,* **119,** 139220r (1993).

33. Fernandes V. J., H. H. Parekh; *J. Indian Chem.Soc.,* **74(3),** 238 (1997).(Eng.); *Indian Chemi cal Society*.

34. Sharan El-Taher Z., Mohammed Shaidia A. and Mikhae Anwar N.; *Alexandria J. Pharma Sci.,* **7(1)** 41-44 (1993); *Chem. Abstr.,* **122,** 81233r 91995).

35. Balakrishna Kaluraya, Alphonsus D'souza and Arun M. Isloor; *indian J. Heterocyclic Chem.,* **8,** 309-314 ( 1999).

36. Stevenson Thomas M., Annis Gary D. Et al.; *Acs. Sympo. Ser.,* 584(Synthesis and chem istry of agrochemicals IV), 291-299 (1995).

37. Simsek Rahime, Safac Lihat, Abbasoglu Ufuc, Ozclik Berrin; *int. J. Chem.,* **7(2),** 89-98 (1996); *Chem. Abstr.,* **128,** 61452g (1998).

38. DMT-Cham, T. M. Stavenson, D. W. Piotrowski, MAH Fahmy, R. L.Lowe, K. l. Monaco; *Chem. Abstr., American Chemical Society,* **217,** MAR Part I, 29 AGRO (1999).

39. Tanka Katsiuhori, Adachi Hiroyuki, Koyuchi Masumi; PCT *Int Appl.* WO **98**, 56, 760; *Chem. Abstr.,* **130,** 66492w (1999).

40. Uhlendrot Jouchim, Kuhl Peter Leyck Sigard; *Ger. Offen.* DE 3, 075, 933 (Cl. 07D 417/ 04)(1998); *Chem. Abstr.,* **110,** 38987e (1989).

41. Nugent Richard A., Murphy Megan et al.; *J. Med. Chem.,* 134-139 (1993). *Chem. Abstr.,* **118,**191847u (1993).

42. B. Shivarama; Shivarnanda N. K. ; *Indian Jouranal of Heterocyclic Chemistry,* **10(4)**, 305-306 (20001)*Chem. Abstr.,* **136,** 15110k (2002)

43. Gineinah, Mugdy, Mohamed M.; *Scientia Pharmaceutical* **69(1),** 53-61 (2001)*; Chem. Abstr.,* **136,** 102345k (2002).

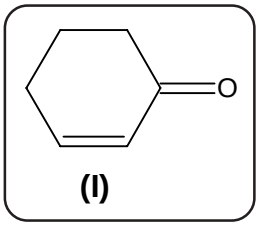
44. Gevariya, Harsukh; *Heterocyclic Communications* **7(5),** 481-484 (2001),*Chem. Abstr.,* **136,** 340625w (2002).

45. A. Hand book of Spectroscopic data by B. D. Mishtry, Ist ed. ABDPress Jaiptt 11-36 (2000); "Absorption Spectroscopy data of Organic Compounds" by V. M. Parikh, Addition Wesley Pub.Co.,London, 243-258 (1978).

46. Introduction to Infrared and Ramann Spectroscopy by Norman B. Colhap, Lowerence H. Daly and Stephene E. Wilberluy, Academic Press (1975).

## INTRODUCTION

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

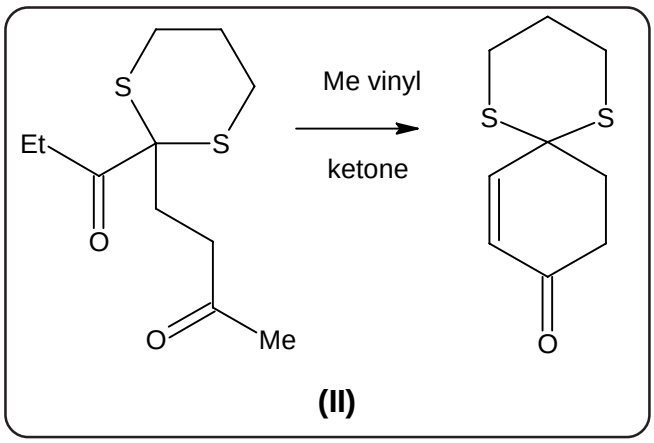



**(I)**

## SYNTHETIC ASPECT

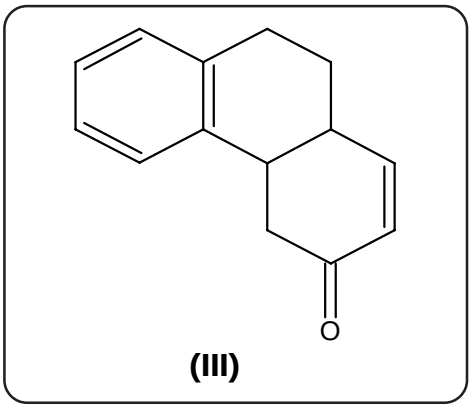
Different methods for the preparation of cyclohexenone derivatives have been described in literature[1-14].

(I) Page Philip C. and co-workers[15] have been prepared ethyl substituted cyclohexenone derivative (II).



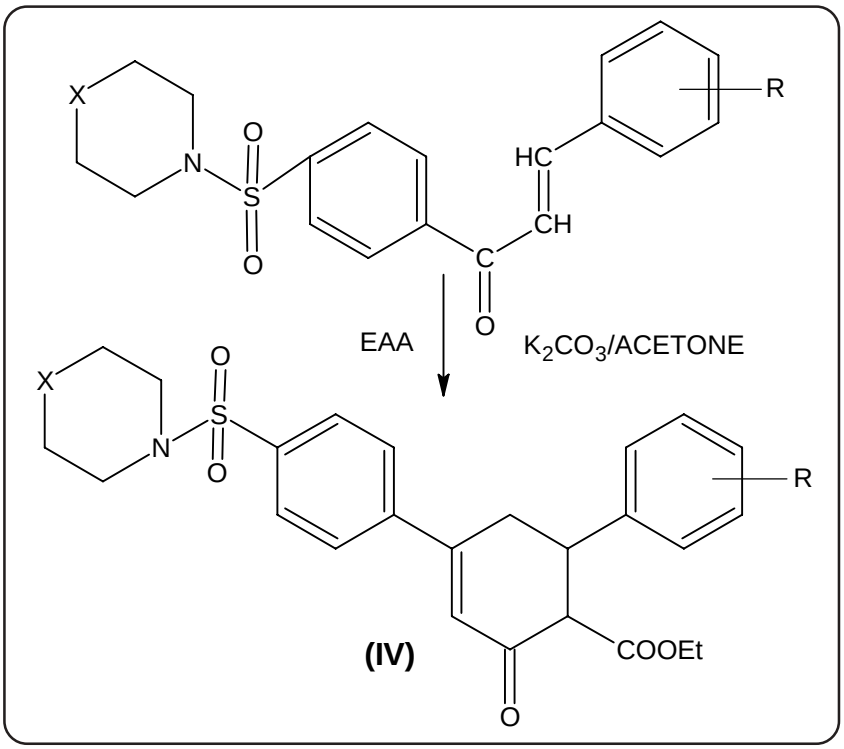

**(II)**

(II) A review of the earlier literature by Gerald et al.[16] describes representative synthetic procedure of cyclohexenone derivative (III).




**(III)**

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



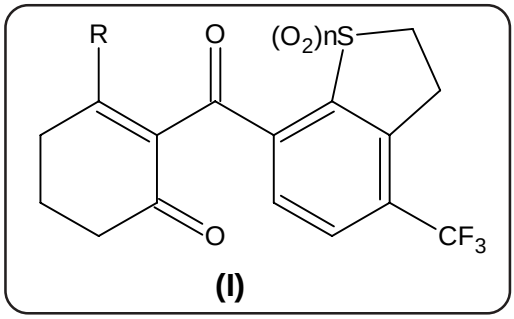

**(IV)**

## THERAPEUTIC IMPORTANCE

Cyclohexenones have various medicinal applications such as anthelmintic, hypoglycemic, nematocidal, antibacterial, antifungal, antiviral, analgesic etc. Antiarhythmic activity[18] of some cyclohexenone derivatives have been investigated.

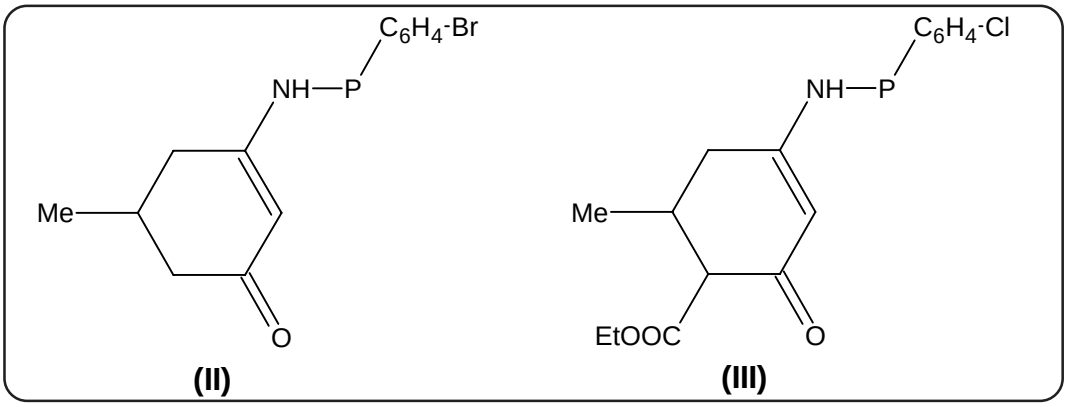
Cyclohexenone possess cardiovascular, osteoporosis, menpausal symptoms, estrogen dependent and cancers activities, which was reported by Jacobsen Poul et al.[19].

De Mesmaeker et al.[20] prepared cyclohexenone carbonyl benzo thiophene (I) as herbicides.




**(I)**

Eddington, et al.[21] synthesised and evaluted anticonvulsant activity of Ethyl 4-[(substituted phenyl) amino ]-6-methyl-2-oxo-cyclohex-3-ene-1-carboxylates (II) and their corresponding 5-methyl cyclohex-2-enone (III).




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

Cyclohexenone and its derivatives have been prepared and reported as broad spectrum of physiological properties viz. antibiotic[22,23], bactericidal[24], herbicidal[25], antimicrobial[26], anticonvulsant[27]. Alekseeva L.M. and co-workers[28] have synthesised cyclohexenone derivatives which are useful in neurotropic activity. Toshiyuki et al.[29] have prepared some novel cyclohexenones and screened for allergy inhibitor, antithrombitic platelet aggregation inhibitors and fibrinogen antagonist activity.

Collis David J. et al.[30] have documented cyclohexenone derivatives which possess estrogenic activity. V. K. Ahluwalia et al.[31] have reported some new cyclohexenone as anti HIV-I, gastric secretion inhibitors and pesticidal activity. Nagarajan and shenoy[32] have prepared substituted cyclohexenones which shown to possess marked antiinflammatory activity. Nagao et al.[33] have reported antiarhythmics activity of cyclohexenones. Inverse agonist for GABA activity[34a] of some derivatives have been investigated.

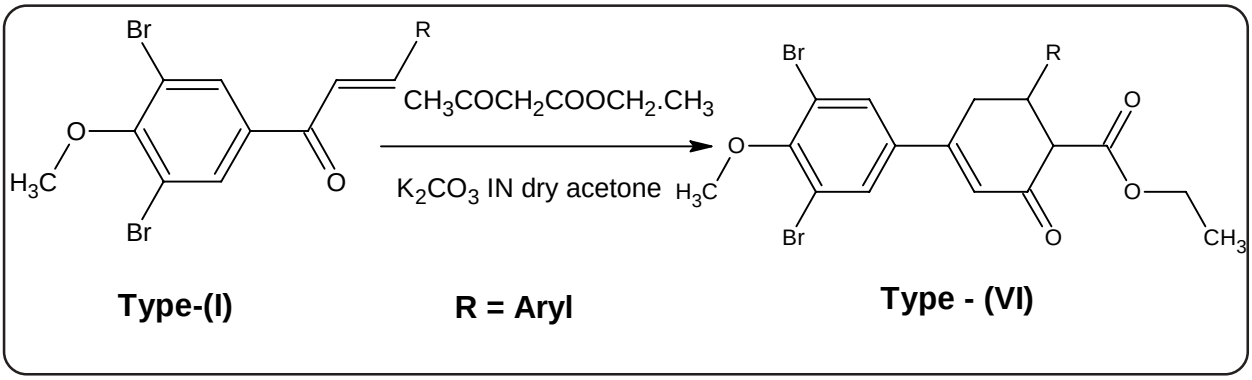
Antimicrobial activity have been studied by Salamu and Atshikh.[34b] Cyclohexenone possess neutropeptide-γ-receptor antagonist activity which was reported by Takehiro and co-workers[35]. Broughton Howard[36] have demonstrated cyclohexenone as GABA α5 receptor ligands for enhancing cognition properties. Cyclohexenone possess inhibitory activity against the growth of lettuce seedling found by kimura and co-workers[37]. Parekh and co-workers[38] synthesised new cyclohexenones as antimicrobial agents. Shklyaev Yu. et al.[39] have prepared cyclohexenones as potent biological agents. Cragoe et al.[40] have synthesize some cyclohexenone derivatives which was useful in the treatment of brain injury.

These valid observations prompted as to combine this nucleus into well known pharmaceutical properties of 3,5-dibromo-4-methoxy acetophenone nucleus so as to enhance the overall activities of resulting moiety, which have been described as under.

# SECTION - I

## SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL 4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-2-OXOCYCLOHEX-3-ENE-1-CARBOXYLATES

Therapeutic importance of cyclohexenones aroused considerable interest to synthesis ethyl 4-(3,5-dibromo-4-methoxyphenyl)-6-aryl-2-oxocyclohex-3-ene-1-caboxylates of the type (VI) by the cyclocondensation of (2E)-1-(3,5-dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones with ethylacetoacetate in the presence of anhydrous $K_2CO_3$ in order to study their biodynamic behavior.

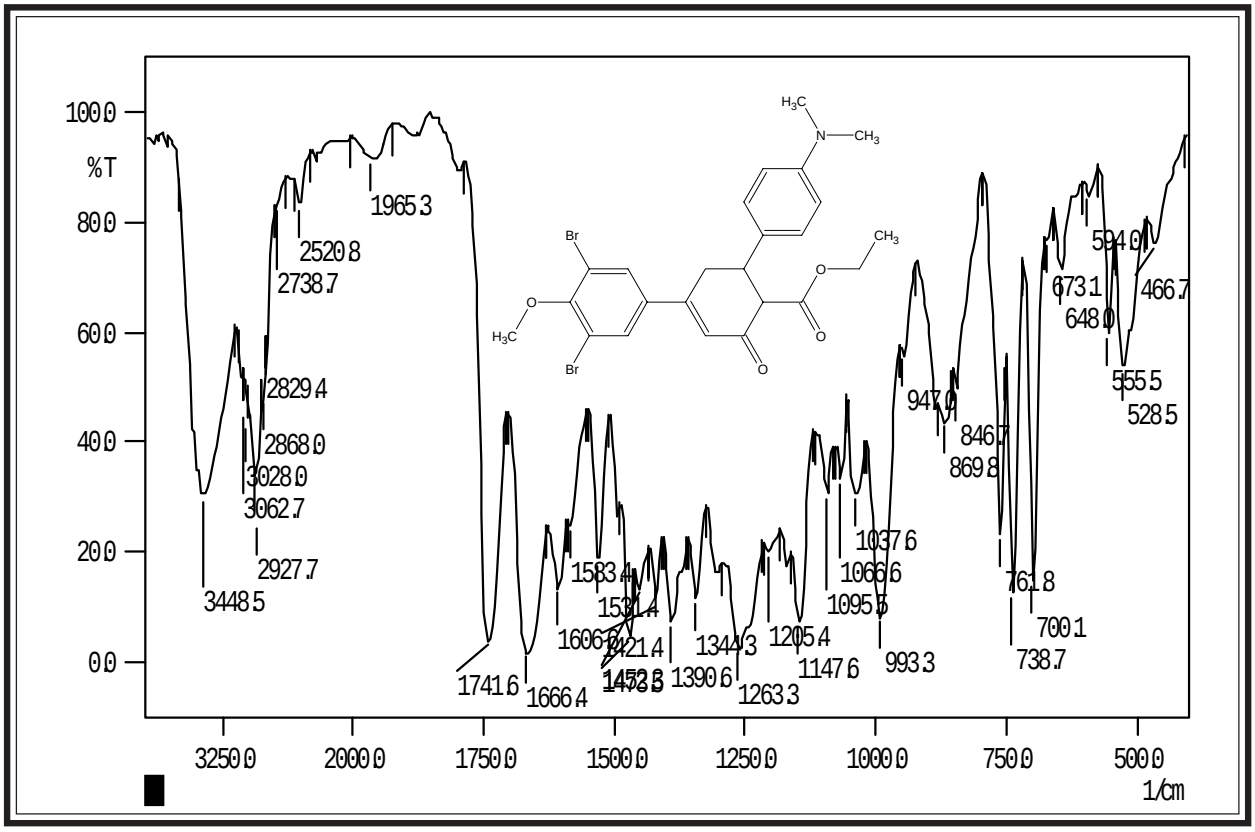



**Type-(I)** **R = Aryl** **Type - (VI)**

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.

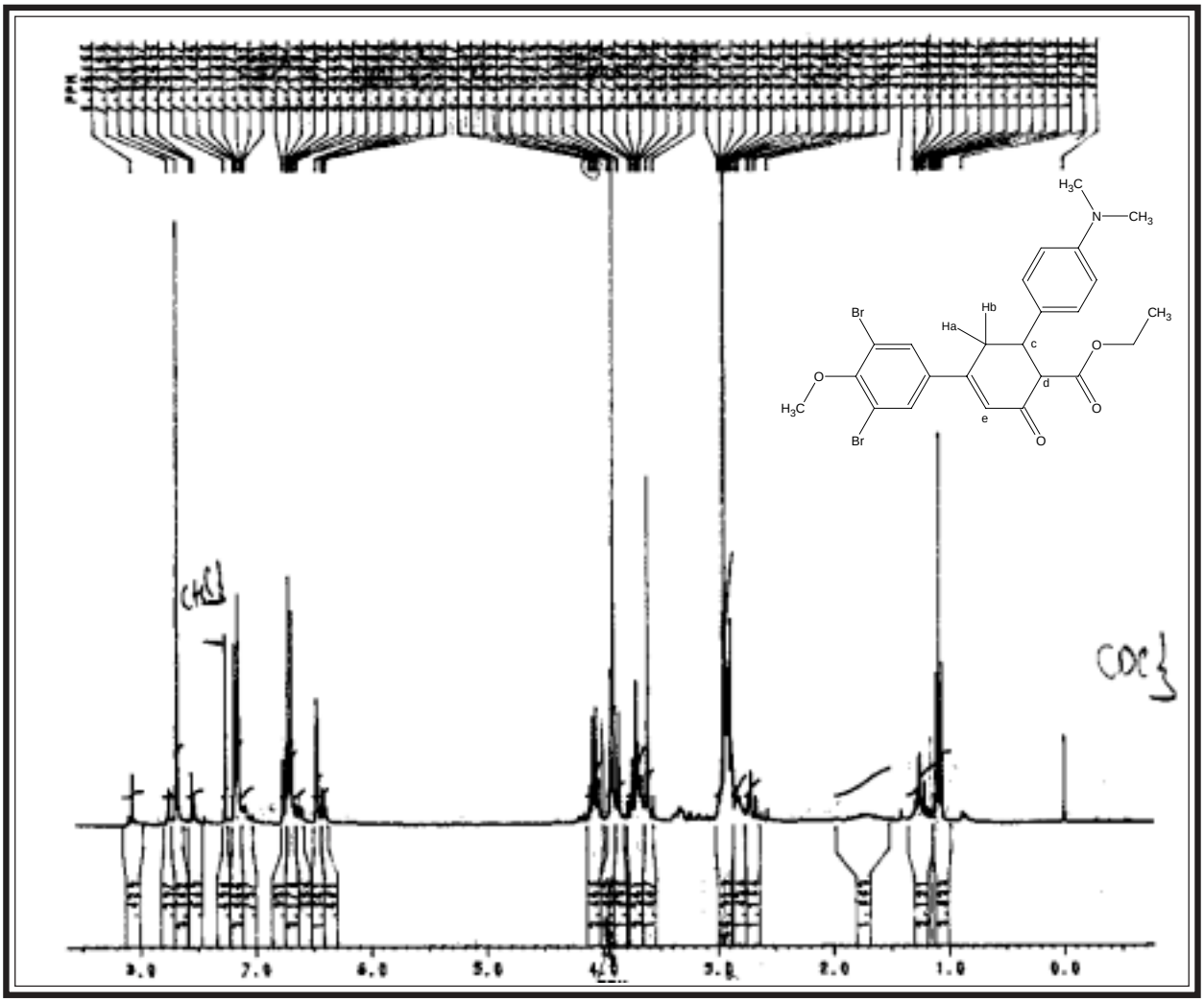
**IR spectral studies of Ethyl 4-(3,5-dibromo-4-methoxy phenyl)-6-(4-N,N-di methyl aminophenyl)-2-oxocyclohex-3-ene-1-carboxylate**




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

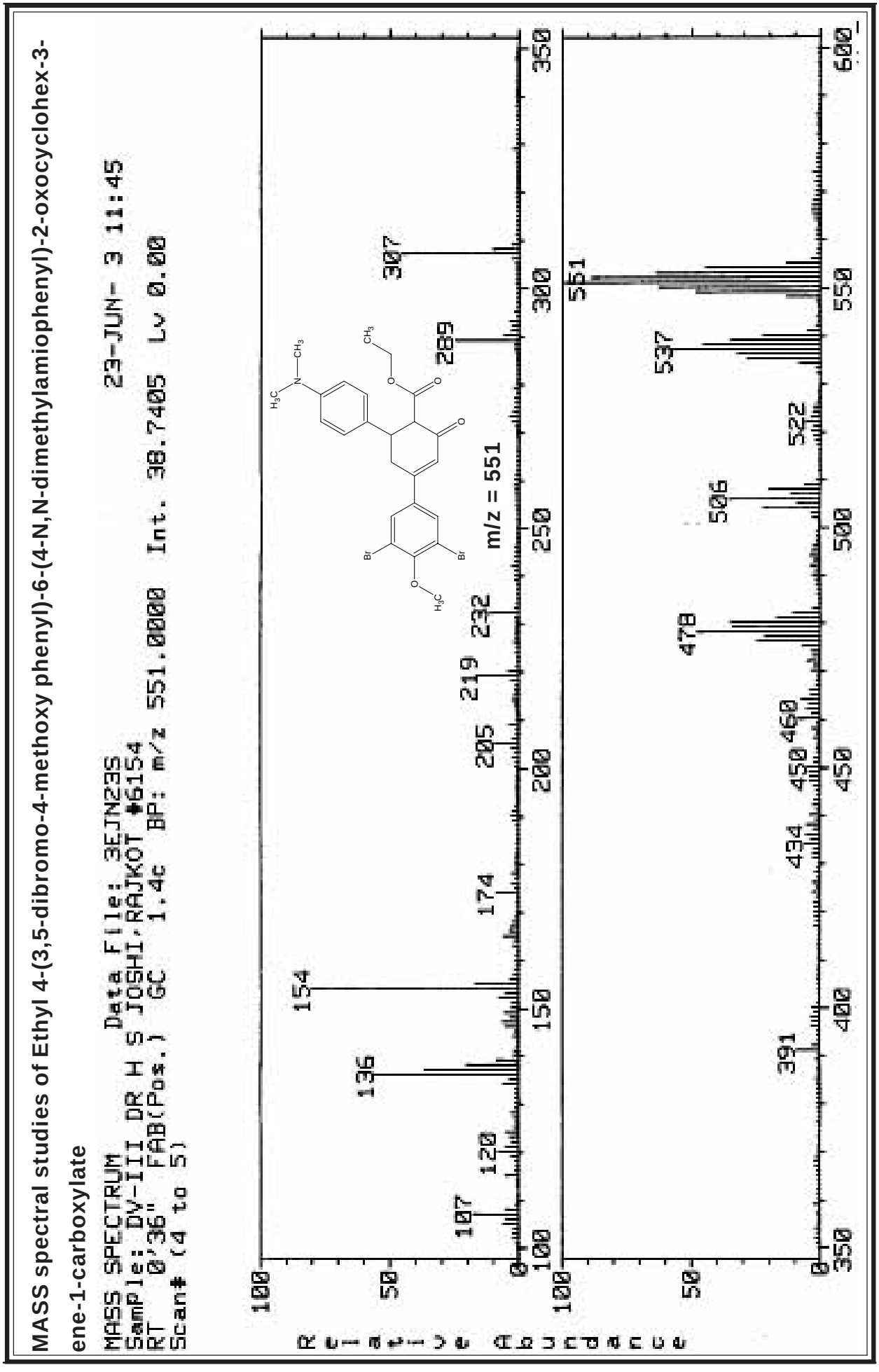
| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2927 | 2975-2950 | 86 |
| $-CH_3$ | C-H str.(sym.) | 2868 | 2880-2860 | " |
| | C-H def.(asym.) | 1452 | 1470-1435 | " |
| | C-H def.(sym.) | 1390 | 1390-1370 | " |
| Aromatic | C-H str. | 3062 | 3090-3030 | 87 |
| | C=C str. | 1531 | 1540-1480 | " |
| | | 1095 | 1125-1090 | " |
| | | 1066 | 1070-1000 | " |
| Halide | C-Br str. | 555 | 600-500 | 86 |
| Ether | C-O-C str.(sym) | 1263 | 1275-1200 | " |
| | | 1066 | 1075-1020 | " |
| Carbonyl | C=O str. | 1741 | 1735-1717 | 87 |
| Cyclohex. | C=O str. | 1666 | 1685-1665 | " |

**NMR SPECTRAL STUDIES OF ETHYL 4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-(4-N,N-DIMETHYLAMINOPHENYL)-2-OXOCYCLOHEX-3-ENE-1-CARBOXYLATE**




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

| Signal No. | Signal Position (δ ppm) | Relative No. of Proton | Multiplicity | Inference |
|---|---|---|---|---|
| 1. | 1.21-1.25 | 3H | triplet | $-CH_2-CH_3$ |
| 2. | 2.95 | 6H | singlet | $-N-(CH_3)_2$ |
| 3. | 3.90 | 3H | singlet | $Ar-OCH_3$ |
| 4. | 2.67 | 1H | double-doublet | -Ha |
| 5. | 2.83 | 1H | double-doublet | -Hb |
| 6. | 4.02-4.10 | 2H | quartet | $-CH_2-$ |
| 7. | 6.46 | 1H | singlet | -Hd |
| 8. | 7.26 | 1H | singlet | -Hc |
| 9. | 7.55 | 1H | singlet | -He |
| 10. | 6.68-7.67 | 6H | multiplet | Ar-H |


MASS spectral studies of Ethyl 4-(3,5-dibromo-4-methoxy phenyl)-6-(4-N,N-dimethylamiophenyl)-2-oxocyclohex-3-ene-1-carboxylate
MASS SPECTRUM Data File: 3EJN23S
Sample: DV-III DR H S JOSHI,RAJKOT #6154
RT 0'36" FAB(Pos.) GC 1.4c BP: m/z 551.0000 Int. 38.7405 Lv 0.00
Scan# (4 to 5)
23-JUN- 3 11:45
Relative Abundance
m/z = 551
107
120
135
154
174
205
219
232
289
307
391
434
450
460
478
505
522
537
551

# EXPERIMENTAL

## SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL 4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-2-OXOCYCLOHEX-3-ENE-1-CARBOXYLATES

### (A) Preparation of (2E) -1-(3,5- Dibromo-4-methoxy phenyl)-3-aryl-prop-2-en-1-ones

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

### (B) Preparation of Ethyl 4- (3,5-Dibromo-4-methoxyphenyl)-6-(4-N,N-dimethylaminophenyl)-2-oxocylohex-3-ene-1-carboxylate

To a solution of (2E)-1-(3,5-dibromo-4-methoxy phenyl)-3-(4-N,N-dimethylamino phenyl)-prop-2-en-1-one (4.39gm, 0.01 mol) in dry acetone, anhydrous $K_2CO_3$ (5.42gm, 0.04 mol) and ethyl acetoacetate(2.60gm, 0.02 mol) was added and the reaction mixture was stirred at room temperature overnight and was filtered. The solvent from the filtrate on evaporation gave a solid, which was crystallized from methanol. Yield 62%, m.p. $120^0$C, Anal.Calcd. for $C_{24}H_{25}Br_2NO_4$; Requires: C, 52.29; H, 4.57; N, 2.54; Found : C, 52.36; H, 4.61; N, 2.50 %.

Similarly, other Ethyl 4-(3,5-dibromo-4-methoxyphenyl)-6-aryl-2-oxocyclohex-3-ene-1-carboxylates were prepared. The physical data and recorded in Table No.6

### (C) Biological screening of Ethyl-4-(3,5-dibromo-4-methoxyphenyl)-6-aryl-2-oxocyclohex-3-ene-1-carboxylates

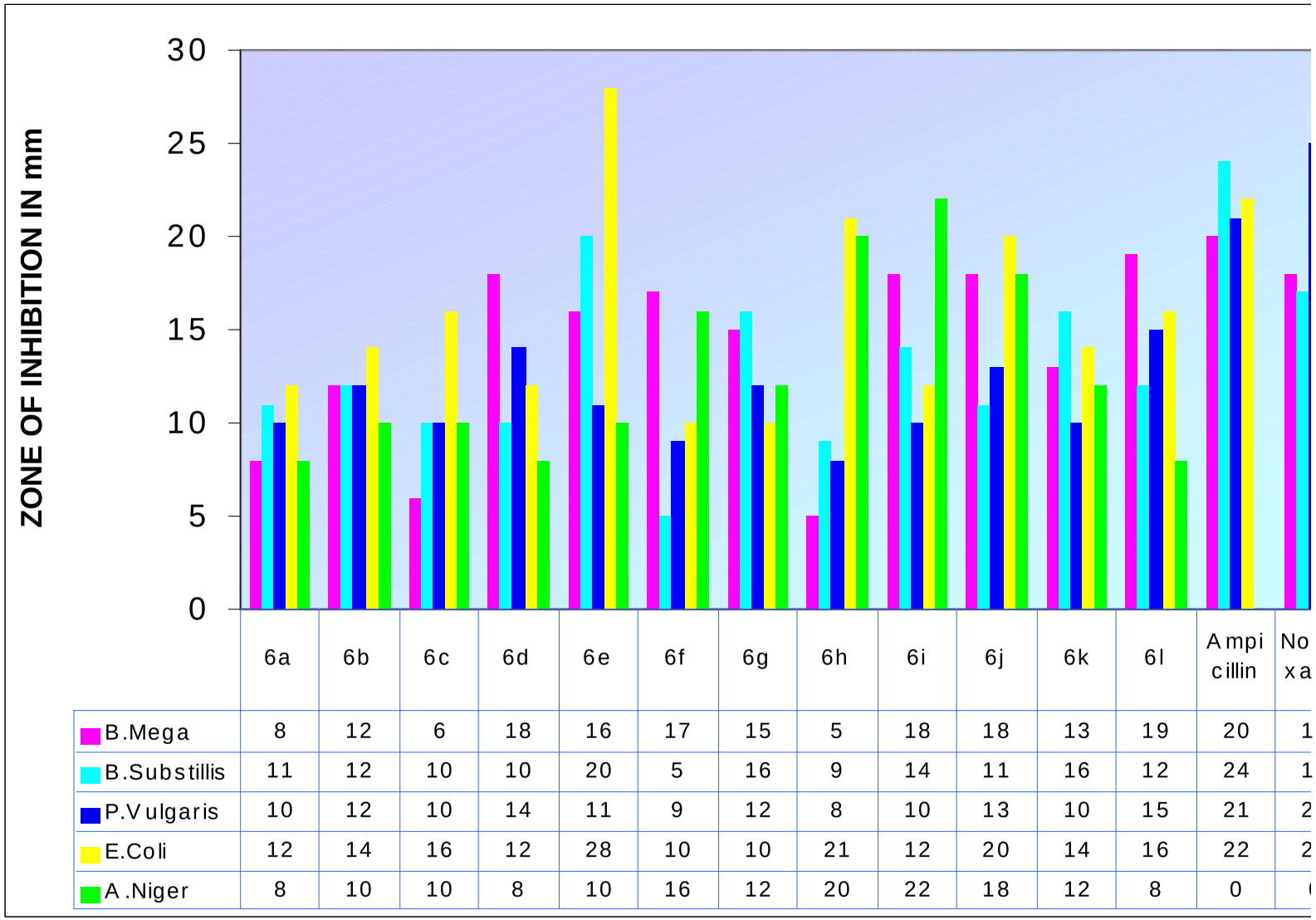
Antimicrobial testing were carried out as described in Part-I, Section (D). The zones of inhibition of test solutions are recorded in Graphical Chart No.6

**TABLE-6 : PHYSICAL CONSTANTS OF ETHYL 4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-2-OXO CYCLOHEX-3-ENE-1-CARBOXYLATES.**

| Sr. No. | R | Molecular Fromula | Molecular Weight | M.P. °C | Yield % | % of Nitrogen Calcd. | % of Nitrogen Found | Rf Value | Solvent System |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 6a | $C_6H_5$- | $C_{22}H_{20}Br_2O_4$ | 508.0 | 115 | 68 | - | - | 0.50 | S1 |
| 6b | 3-Br-$C_6H_4$- | $C_{22}H_{19}Br_3O_4$ | 587.1 | 300 | 70 | - | - | 0.49 | S2 |
| 6c | 2-Cl-$C_6H_4$- | $C22H_{19}Br_2ClO_4$ | 542.7 | 80 | 66 | - | - | 0.48 | S1 |
| 6d | 4-Cl-$C_6H_4$- | $C_{22}H_{19}Br_2ClO_4$ | 542.7 | 100 | 68 | - | - | 0.43 | S1 |
| 6e | 4-$N(CH_3)_2$-$C_6H_4$- | $C_{24}H_{25}Br_2NO_4$ | 551.3 | 120 | 62 | 2.54 | 2.50 | 0.50 | S2 |
| 6f | 4-$OCH_3$-$C_6H_4$- | $C_{23}H_{22}Br_2O_5$ | 538.2 | 124 | 60 | - | - | 0.54 | S2 |
| 6g | 3,4-$(OCH_3)_2$-$C_6H_3$- | $C_{24}H_{24}Br_2O_4$ | 568.3 | 222 | 58 | - | - | 0.46 | S2 |
| 6h | 2-$NO_2$-$C_6H_4$- | $C_{22}H_{19}Br_2{}^2NO_6$ | 553.2 | 168 | 55 | 2.53 | 2.59 | 0.57 | S2 |
| 6i | 3-$NO_2$-$C_6H_4$- | $C_{22}H_{19}Br_2NO_6$ | 553.2 | 134 | 60 | 2.53 | 2.49 | 0.45 | S1 |
| 6j | 3-$OC_6H_5$-$C_6H_4$- | $C_{28}H_{24}Br_2O_5$ | 600.3 | 130 | 63 | - | - | 0.46 | S1 |
| 6k | 4-OH-C6H4- | $C_{22}H_{20}Br2O_5$ | 524.2 | 50 | 60 | - | - | 0.52 | S2 |
| 6l | $C_4H_3O$- | $C_{26}H_{22}Br2O_5$ | 574.3 | 60 | 63 | - | - | 0.43 | S2 |

S1 Hexane: Ethylacetate (7:3) S2 Hexane: Ethylacetate (8:2)

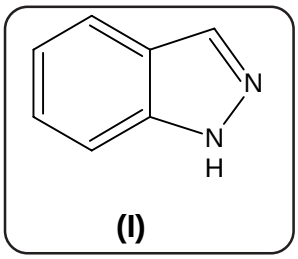
## GRAPHICAL CHART NO. 6 : ETHYL 4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-2-OXOCYCLOHEX-3-ENE-1-CARBOXYLATES.




| | 6a | 6b | 6c | 6d | 6e | 6f | 6g | 6h | 6i | 6j | 6k | 6l | Ampicillin | Noxa |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B.Mega | 8 | 12 | 6 | 18 | 16 | 17 | 15 | 5 | 18 | 18 | 13 | 19 | 20 | 1 |
| B.Substillis | 11 | 12 | 10 | 10 | 20 | 5 | 16 | 9 | 14 | 11 | 16 | 12 | 24 | 1 |
| P.Vulgaris | 10 | 12 | 10 | 14 | 11 | 9 | 12 | 8 | 10 | 13 | 10 | 15 | 21 | 2 |
| E.Coli | 12 | 14 | 16 | 12 | 28 | 10 | 10 | 21 | 12 | 20 | 14 | 16 | 22 | 2 |
| A.Niger | 8 | 10 | 10 | 8 | 10 | 16 | 12 | 20 | 22 | 18 | 12 | 8 | 0 | |

## INTRODUCTION

Heterocyclic compounds bearing a 1,2-diazole ring system i.e. pyrazole ring system, attached to benzene ring system are known as benzo pyrazoles or indazoles (I). Buchner first described Indazole in 1869.



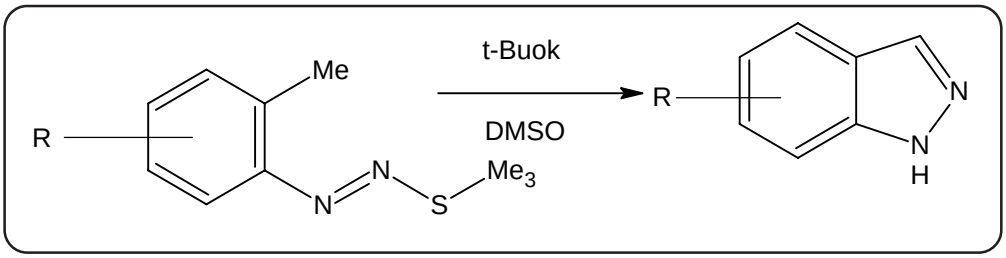

**(I)**

The compounds of medicinal interest in this group so far have been non-steroidal antiinflammatory agents or analgesics.

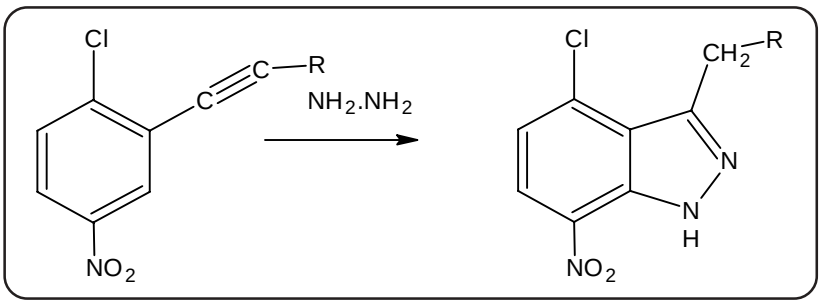
## SYNTHETIC ASPECT

Various method[41-47] for the preparation of indazoles have been described in the literature among the popular are

1. Indazoles can be synthesized by condensing[48,49] hydrazine hydrate with cyclohexenone derivatives.
2. Reaction of substituted azo sulfides with potassium-t-butoxide in DMSO lead to the corresponding 1-H indazole derivatives[50].

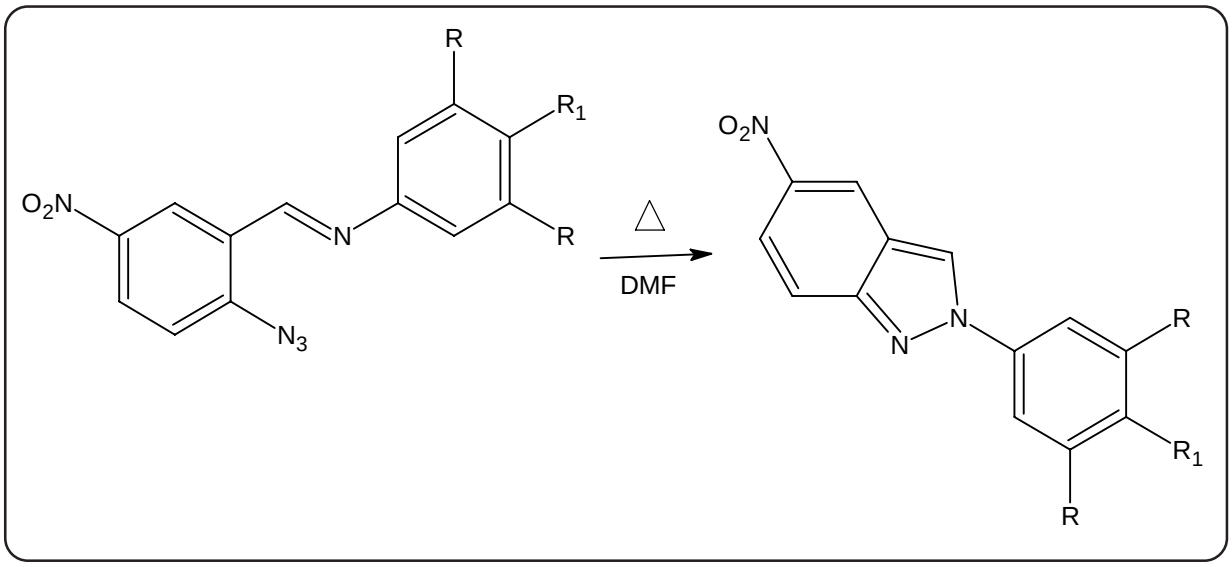


3. Cyclocondensation of activated acetylene with hydrazine afforded indazole derivatives[51].

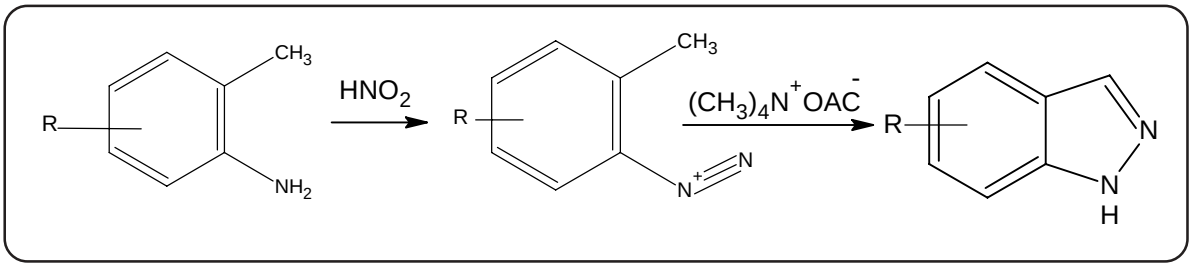



4. Indazoles[52] can be prepared by the cyclization of 2,6-dialkoxy or hydroxyl acetophenone hydrazones in presence of PPA.

5. Synthesis of some indazole derivatives[53] by heating benzylidene aniline derivatives in DMF was reported by Okhim L-Yu et al.




6. Indazole ring system[54] can also be designed by the diazotization of substituted anilines eg o-toludine.



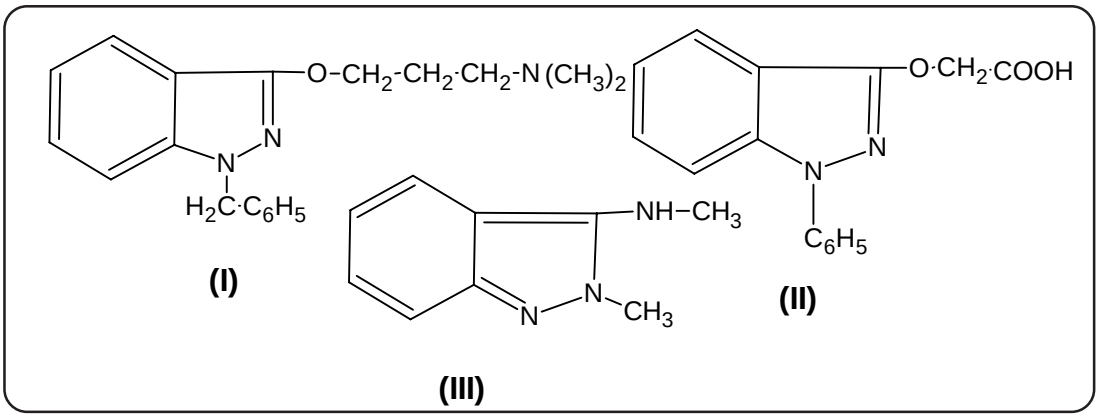

7. Carbon Stephan and co-workers[55] have described that the condensation of 2-acyl aryl mesylates with hydrazines affords corresponding indazole derivatives.

## THERAPEUTIC IMPORTANCE

Indazole derivatives are biologically interesting class of compounds. They are associated various pharmacological properties such as,

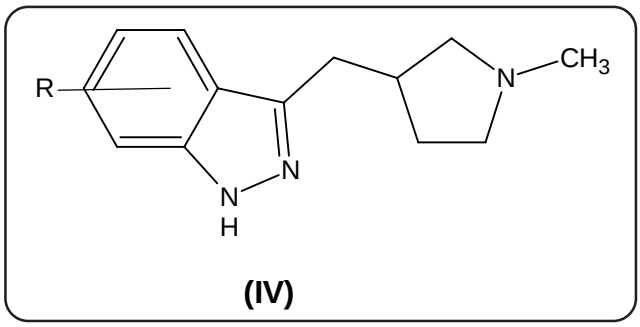
1. Antitumor[56,57]
2. Antiallergic[58]
3. Antipsychotics[59]
4. Antiinflammatory[60]
5. Antipyretic[61]
6. Antineoplastic[62]
7. Antiviral[63]
8. Antihypertensive[64]
9. Cytotoxic[65]
10. Sedative[66]
11. Herbicidal[67]
12. Enzyme inhibitors[68]
13. Fungicidal[69]
14. Pesticidal[70]

As reported earlier, indazoles are non-steroidal antiinflammatory agents or analgesics, the prototype is benzydamine (I)[71], a fairly potent nonsteroidal antiinflammatory agent with significant antipyretic and analgesic properties.The other examples are bendazac (II)[72] and tetrydamine (III)[73].



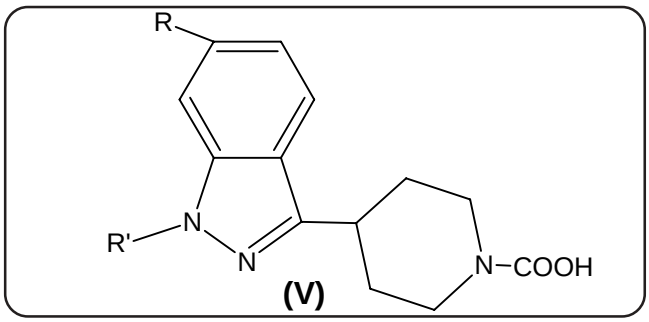
More over Yamaguchi Masahisa et al.[74] prepared some indazole derivatives as novel anti asthametic agents with dual activities of thromboxane $A_2$ synthetase inhibitor and bronchodialations. Ooe Taknori et al.[75] reported some indazoles as hematinics, immuno stimulants and antitumor agents. Some indazole derivatives[76] showed activity for enhancing macrophage phagocytosis, improving immunity and antitumor activity.

Lavielle Gilbert et al.[77] documented the [(pyrrolidinyl) methyl]-indazoles(IV) as 5-HT, like agonists and remedy for the treatment of migrains and schizoprenia[78].



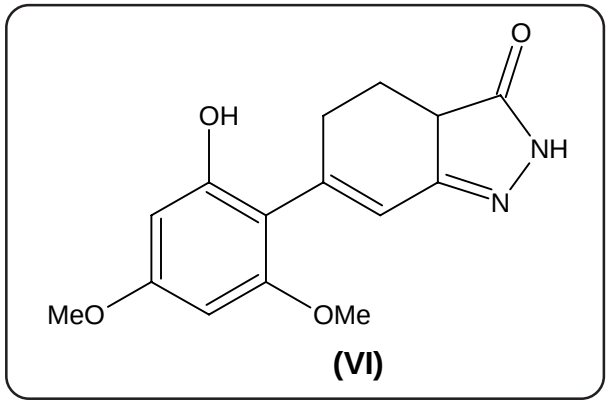

**(IV)**

Mewshaw Richard Eric et al.[79] have synthesized 4-amino ethoxy indazoles useful as dopamine D2 agonists. Allan David and co-workers[80] have synthesised some indazole derivatives (V) and postulated them as fibrinogen antagonist.



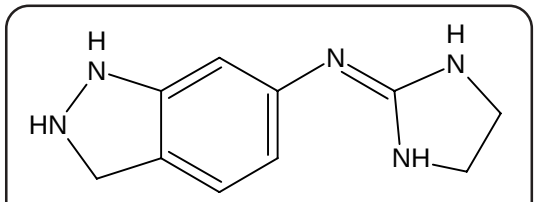

**(V)**

Jain A.C. et al.[81] have described the synthesis, separation of tautomers and biological activities of 4,6-diaryl-3-oxo-2,3a,4,5-tetrahydro-2H-indazoles (VI).




**(VI)**

Thomas Lee and co-workers[82] demonstrated the preparation and formulation of 6-(imidazolinyl amino) indazoles (VII) as α-2 adreno-receptor agonists.




**(VII)**

Several co-workers have patented indazole derivatives useful as hypolipidemic or hypocholersterolemic[83] and cardiovascular[84], agents Effland Richard Charles et al.[85] constructed 3-(pyridyl amino) indazoles and reported their use as antidepressants and anxiolytics.

A wide variety of pharmacological properties have been encountered with indazole systems. Keeping the above in mind some novel indazole derivative have been synthesised which have been described as under.

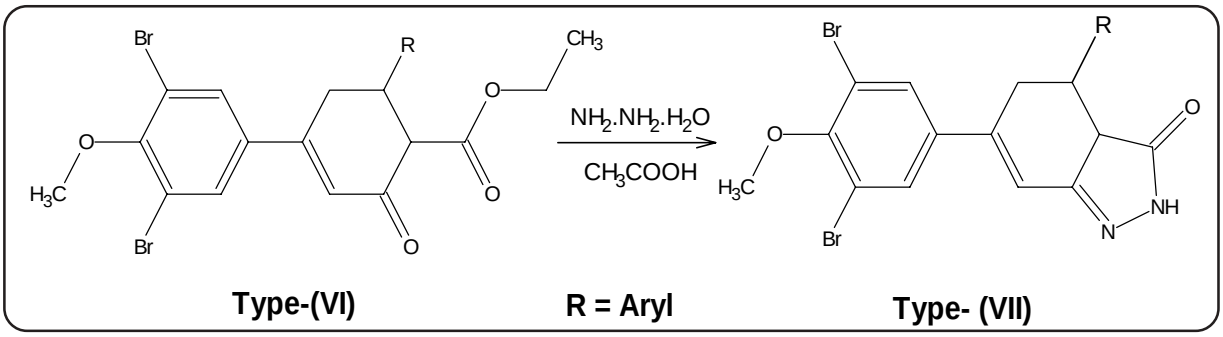
**SECTION-I: SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL 4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-2-OXO-CYCLOHEX-3-ENE-1-CARBOXYLATES**

**SECTION-II: SYNTHESIS AND BIOLOGICAL SCREENING 6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-2,3a,4,5-TETRAHYDRO-2H-INDAZOLES**

# SECTION - II

## SYNTHESIS AND BIOLOGICAL SCREENING OF 6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-2,3a,4,5-TETRAHYDRO-2H-INDAZOL-3-ONES

The synthesis of indazole has attracted the attention of chemists because of their potential pharmcodynamic properties. Looking to the interesting properties of indazoles, it appeared interest to synthesise a series of 6-(3,5-dibromo-4-methoxyphenyl)-4-aryl-2,3a,4,5-tetrahydro-2H-indazol-3-ones of type (VII) for obtaining biologically potent agents, which were prepared by reacting ethyl 4-(3,5-dibromo-4-methoxyphenyl)-6-aryl-2-oxocyclochex-3-ene-1-carboxylates of type (VI) with hydrazine hydrate in presence of glacial acetic acid.

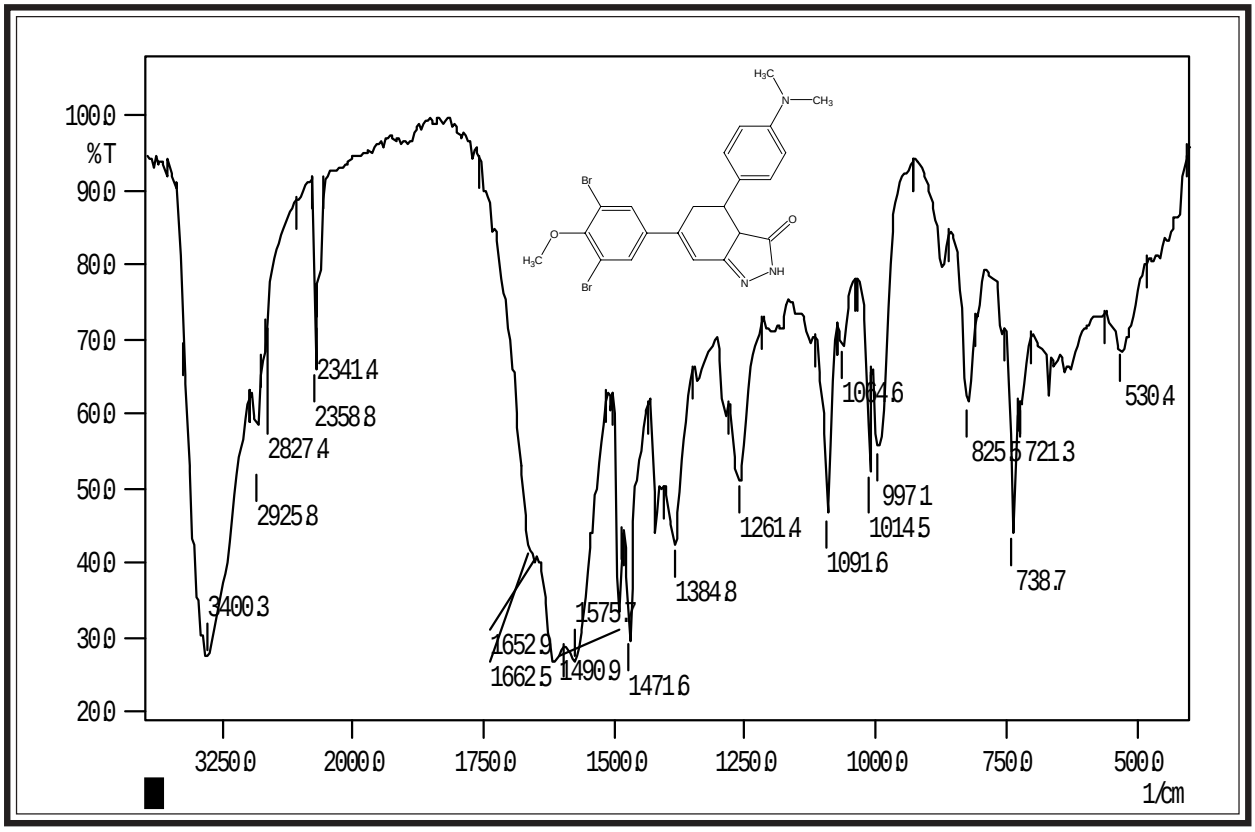



**Type-(VI)** **R = Aryl** **Type- (VII)**

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.

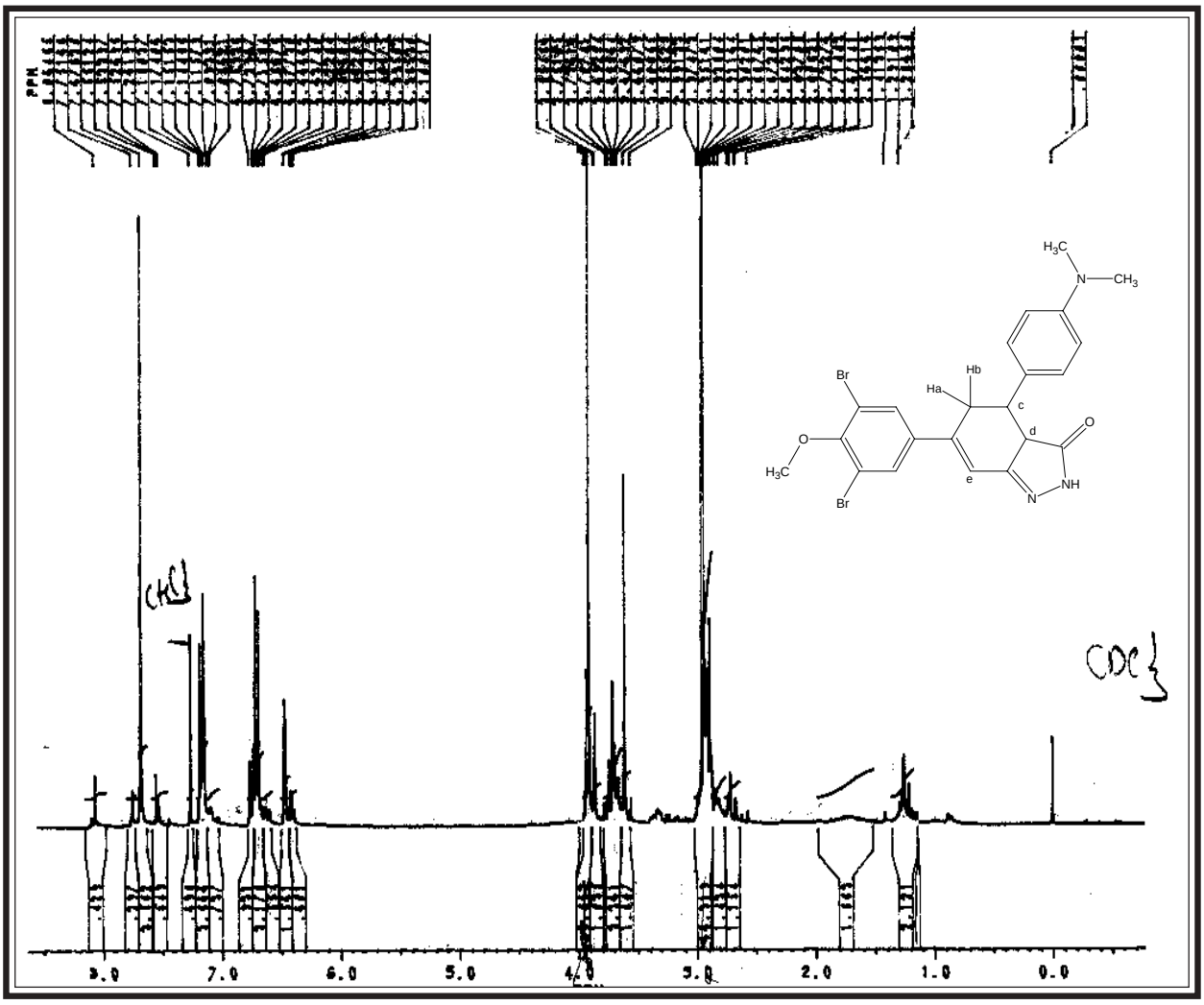
**IR spectral studies of 6-(3,5-Dibromo-4-methoxy phenyl)-4-(4-N,N-dimethyl aminophenyl)-2,3a,4,5-tetrahydro-3H-indazol-3-one**




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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2925 | 2975-2950 | 86 |
| $-CH_3$ | C-H str.(sym.) | 2827 | 2880-2860 | " |
| | C-H def.(asym.) | 1471 | 1470-1435 | " |
| | C-H def.(sym.) | 1384 | 1390-1370 | " |
| Aromatic | C-H str. | 3050 | 3090-3030 | 87 |
| | C=C str. | 1490 | 1540-1480 | " |
| | | 1091 | 1125-1090 | " |
| | | 1064 | 1070-1000 | " |
| Halide | C-Br str. | 530 | 600-500 | 86 |
| Ether | C-O-C str.(sym) | 1261 | 1275-1200 | " |
| Amide | NH-(C=O)- str. | 1662 | 1680-1636 | 87 |
| Indazole | C=N str. | 1652 | 1645-1630 | " |
| | C=O str. | 1652 | 1672-1652 | " |

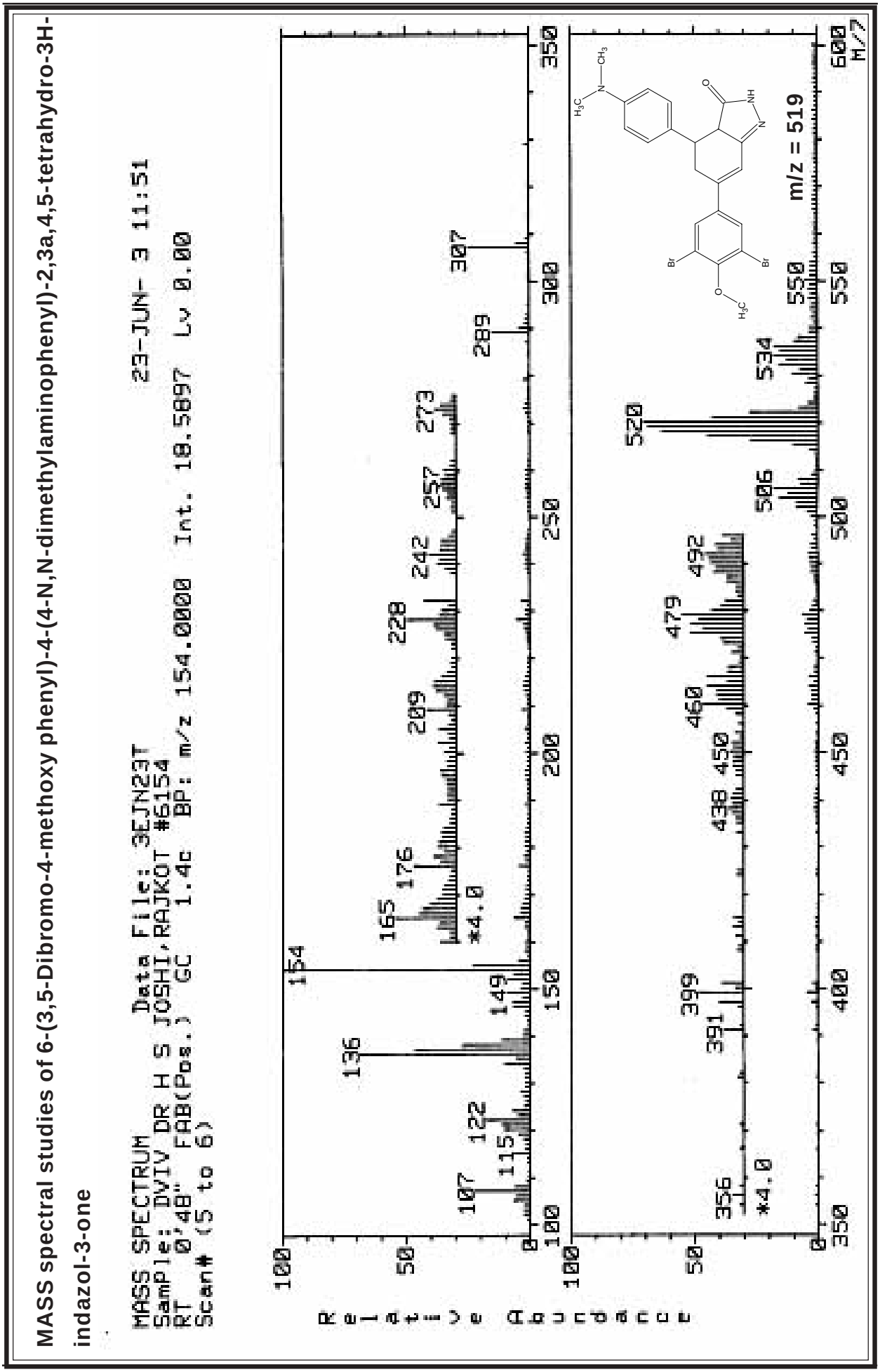
**NMR SPECTRAL STUDIES OF 6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-(4-N,N-DIMETHYLAMINOPHENYL)-2,3a,4,5-TETRAHYDRO-3H-INDAZOL-3-ONE**




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

| Signal No. | Signal Position (δ ppm) | Relative No. of Proton | Multiplicity | Inference |
|---|---|---|---|---|
| 1. | 2.95 | 6H | singlet | -N-$(CH_3)_2$ |
| 2. | 3.95 | 3H | singlet | Ar-$OCH_3$ |
| 3. | 2.65 | 1H | double-doublet | -Ha |
| 4. | 2.85 | 1H | double-doublet | -Hb |
| 5. | 6.96 | 1H | singlet | -Hd |
| 6. | 7.35 | 1H | singlet | -Hc |
| 7. | 7.14-7.67 | 7H | multiplet | Ar-H + He |
| 8. | 6.5 | 1H | singlet | -NH |

**MASS spectral studies of 6-(3,5-Dibromo-4-methoxy phenyl)-4-(4-N,N-dimethylaminophenyl)-2,3a,4,5-tetrahydro-3H-indazol-3-one**



# EXEPERIMENTAL

## SYNTHESIS AND BIOLOGICAL SCREENING OF 6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-2,3a,4,5-TETRAHYDRO-2H-INDAZOL-3-ONES

### (A) Preparation of (2E) -1-(3,5- Dibromo-4-methoxyphenyl)-3-prop-2-en-1-ones

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

### (B) Preparation of Ethyl 4-(3,5-dibromo-4-methoxyphenyl)-6-(4-N,N-dimethylaminophenyl)-2-oxocyclohex-3-ene-1-carboxylate

See Part-III, Section-I(A).

### (C) Preparation of 6- (3,5-Dibromo-4-methoxyphenyl)-4-(4-N,N-dimethyl aminopheyl)-2,3a,4,5-tetrahydro-2H-indazol-3-one

A mixture of ethyl 4-(3,5-dibromo-4-methoxyphenyl)-6-(4-N,N-dimethylamino phenyl)-2-oxocyclohex-3-ene-1-carboxylate (5.65gm, 0.01mol) in ethanol (20 ml), hydrazine hydrate (0.5gm 0.01 mol) and acetic acid (2 ml) was refluxed at 80 $^0$C for 4 hr on water bath. The residue obtained after cooling was filtered and isolated and crystallized from methanol. Yield 58 %, m. p. 148 $^0$C. Anal. Calcd. for $C_{22}H_{21}Br_2N_3O_2$ Requires C, 50.89; H, 4.08; N, 8.09% Found C, 50.95; H, 4.12; N, 8.01%.

Similarly other, 6- (3,5-dibromo-4-methoxyphenyl)-4-aryl-2,3a,4,5-tetrahydro-2H-indazol-3-ones were prepared. The physical data were recorded in Table No. 7.

### (C) Biological screening of 6- (3,5-Dibromo-4-methoxyphenyl)-4-aryl-2,3a,4,5-tetrahydro-2H-indazol-3-ones

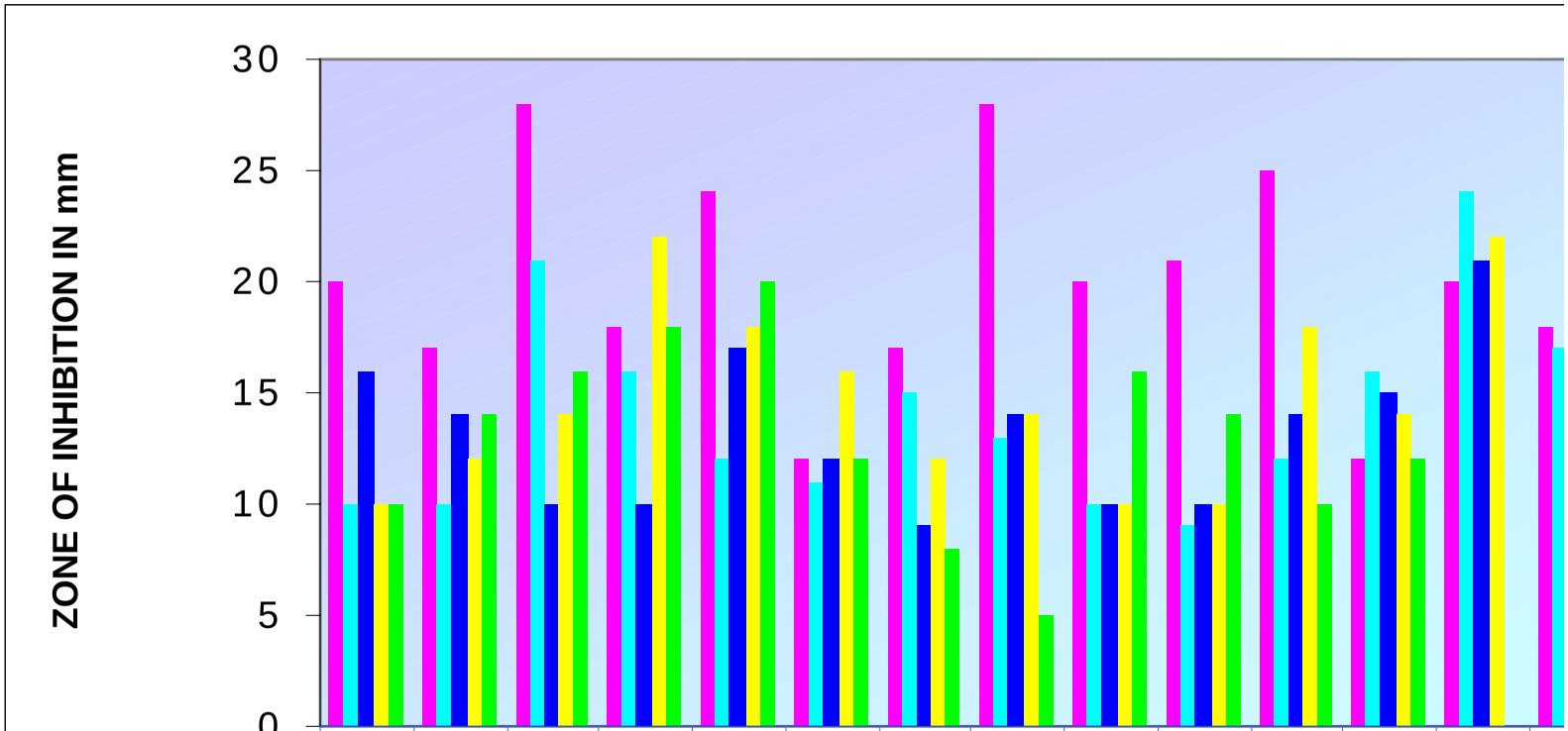
Antimicrobial testing were carried out as described in Part-I, Section (D). The zones of inhibition of test solutions are recorded in Graphical Chart No.7

**TABLE-7 : PHYSICAL CONSTANTS OF 6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-2,3a,4,5-TETRA HYDRO-3H-INDAZOL-3-ONES.**

| Sr. No. | R | Molecular Fromula | Molecular Weight | M.P. °C | Yield % | % of Nitrogen Calcd. | % of Nitrogen Found | Rf Value | Solvent System |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 7a | $C_6H_5$- | $C_{20}H_{16}Br_2N_2O_2$ | 476.2 | 220 | 60 | 5.88 | 5.80 | 0.56 | S2 |
| 7b | 3-Br-$C_6H_4$- | $C_{20}H_{15}Br_3N_2O_2$ | 555.0 | 186 | 65 | 5.05 | 4.98 | 0.65 | S2 |
| 7c | 2-Cl-$C_6H_4$- | $C_{20}H_{15}Br_2ClN_2O_2$ | 510.6 | 184 | 68 | 5.49 | 5.42 | 0.48 | S2 |
| 7d | 4-Cl-$C_6H_4$- | $C_{20}H_{15}Br_2ClN_2O_2$ | 510.6 | 190 | 62 | 5.49 | 5.45 | 0.52 | S2 |
| 7e | 4-$N(CH_3)_2$-$C_6H_4$- | $C_{22}H_{21}Br_2N_3O_2$ | 519.2 | 148 | 58 | 8.09 | 8.01 | 0.44 | S1 |
| 7f | 4-$OCH_3$-$C_6H_4$- | $C_{21}H_{18}Br_2N_2O_3$ | 506.2 | 150 | 60 | 5.53 | 5.59 | 0.66 | S1 |
| 7g | 3,4-$(OCH_3)_2$-$C_6H_3$- | $C_{22}H_{20}Br_2N_2O_4$ | 536.2 | 120 | 62 | 5.22 | 5.15 | 0.52 | S1 |
| 7h | 2-$NO_2$-$C_6H_4$- | $C_{20}H_{15}Br_2N_3O_4$ | 521.2 | 133 | 57 | 8.06 | 8.12 | 0.65 | S1 |
| 7i | 3-$NO_2$-$C_6H_4$- | $C_{20}H_{15}Br_2N_3O_4$ | 521.2 | 165 | 55 | 8.06 | 8.14 | 0.68 | S1 |
| 7j | 3-$OC_6H_5$-$C_6H_4$- | $C_{26}H_{20}Br_2N_2O_3$ | 568.3 | 98 | 58 | 4.93 | 4.87 | 0.60 | S1 |
| 7k | 4-OH-$C_6H_4$- | $C_{20}H_{16}Br_2N_2O_3$ | 492.2 | 248 | 56 | 5.69 | 5.47 | 0.48 | S2 |
| 7l | $C_4H_3O$- | $C_{18}H_{14}Br_2N_2O_3$ | 466.1 | 70 | 65 | 6.01 | 5.95 | 0.58 | S1 |

S1 Acetone: Benzene (2:8) S2 Acetone: Benzene (1:9)

## GRAPHICAL CHART NO. 7 : 6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-2,3a,4,5-TETRAHYDRO-3H-INDAZOLE-3-ONES.




| | 7a | 7b | 7c | 7d | 7e | 7f | 7g | 7h | 7i | 7j | 7k | 7l | Ampicillin | Nox |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B.Mega | 20 | 17 | 28 | 18 | 24 | 12 | 17 | 28 | 20 | 21 | 25 | 12 | 20 | 1 |
| B.Substillis | 10 | 10 | 21 | 16 | 12 | 11 | 15 | 13 | 10 | 9 | 12 | 16 | 24 | 1 |
| P.Vulgaris | 16 | 14 | 10 | 10 | 17 | 12 | 9 | 14 | 10 | 10 | 14 | 15 | 21 | 2 |
| E.Coli | 10 | 12 | 14 | 22 | 18 | 16 | 12 | 14 | 10 | 10 | 18 | 14 | 22 | 2 |
| A.Niger | 10 | 14 | 16 | 18 | 20 | 12 | 8 | 5 | 16 | 14 | 10 | 12 | 0 | |

## REFERENCES


1. Gao Dawel, Jia-jinli Zhang Yumin, Hua Shiving Chen Hiaodong; *Jilin Daxue Ziran Kexue Xuebao* (1997), *Chem. Abstr.*,**128**, 114845W (1998).
2. Carteno M. Carmen, Parez Gonazalez, ManuaRibogordaa Maria, Houk K.N. *J. Org. Chem.* 1998; *Chem. Abstr.,* **129,** 54166j (1998).
3. Newman Christopher Paul, Aggarwal Varinder Kumar, Vennale Graham Patrick; Eur. Pat. Appl. Ep. 854, 143; *Chem. Abstr.,* **129,** 148908e(1998).
4. Kobayash Yukiwto, Takeshi, Ogita Yoshihiri, Nishimura Kazuaki; *Jpn. Kokai Tokkyo Koho JP* **10,** 87, 664; *Chem. Abstr.,* **128,** 230234v (1998).
5. Estenban Gemma, Lopez-Sanchez Mighel A., Martinez Maria Engenia, Plemet Joaquin; *Tetrahedron*, 1998; *Chem. Abstr.,* **128,** 114765v (1998)
6. Barlier Daniel, Benhda Rachid, Vazeux Michael; Phosphorus, sulpur silicon relat. Elem. 1993; *Chem. Abstr.,* **120,** 322734v (1998).
7. Kim in O. Lee Sang Gee; *Brit. UK Pat. Apl*GB 2,21,410; *Chem. Abstr.,* **120,** 322784n (1994).
8. Miura Tooru, Wada Masaru, Faruya masauki, Nagata Teruyuki; *Jpn. Kokai Tokkyo Koho* JP **01,** 160932; *Chem. Abstr.,* **112,** 35332t (1990).
9. Ito Nabuhiko, Hasebe Alio Takesuki; *Jpn. Kokai Tokkyo Koho* JP **10,**237,008; *Chem. Abstr.,* **129,** 244945k (1998).
10. E.M. Hammouda ., Sadek E. G., Khajil A. M.; *Inidan J. Heterocyclic Chem.,* 1998; *Chem. Abstr.,* **130,** 81476n (1999)
11. Taber Douglass F., Kanai Kazuo, Jiang Qin, Bui Gina; *J.Am. Chem. Soc.*,2000;*Chem. Abstr.,* **133,** 176965x (2000).
12. Tateishi Keiichi, Yanagihara Naoto; *Jpn. Kokai Tokkyo Koho* JP **04,** 870,247;*Chem. Abstr.,* **118,** 101554t (1993).
13. Matsuoka Rikitaro, Watanabe Kiyoshi; *Jpn. Kokai Tokkyo Koho* JP **01,** 316,565; *Chem. Abstr.,* **118,** 14749b (1993).
14 Grenhill John V., Chaaban Ibrahim, Steel Pater *; I. J. Hetrocyctic Chem.,* 1992; *Chem. Abstr.,* **118,** 169-70k(1993).
15. Page Phillip C. Marchington allan P. Graham Lisa J. Harkin Shaun A. Wood William, *Tetrahedron,* 1993; *Chem. Abstr.,* **120,** 244801d (1994).
16. Duker Girald, Frundt Pater, Markwitz Hardu, Henkel Gerald; *J. Org. Chem.* 1998.
17. Emam H. A. Hassan S. M., EL-Maghaby A. A. ; *J. Serb. Chem. Soc.*1997; *Chem. Abstr.,* **127,**190698v(1997).
18. Ahmad Sallem, Stein Phillip D., Ferram Rancis N., Atwal Karnil s.; *PTC Int. Appl. WO,* **98** 36, 749; *US Appl.* **36**,317 (1997).

19. Jacobsen Poul, Trappendhi Svend, Bury Paul Stanley, Kanstrup Anders, Christiansen Lise Brown; PCT *int.Appl*.WO98 18,777;*Chem. Abstr.,* **128,** 321562s (1998).

20. De Mesmaeker, Alain; Schaetzer; Juergen; *Chem. Abstr.,* **136,** (2002).

21. Eddington, Watalie, O.; Cox; Donna S.; *Chem. Abstr.,* **139,** 36284y (2003).

22. Alcaraz lilian, Tamaj, Anzik Borut Kuzman Tadeja, Mesar Tamaj, Koczan Darko; *Chem. Commun.* 1998; *Chem. Abstr.,* **129** 95339m (1998).

23. Copar Auton, Salmajer Tomaj, Anzik Borut Kuzman Tadeja, Messar Tomaj, Koczan Darko; *Eur. Pat. Appl. EP* 854,143,*Chem. Abstr.,***129** 148908e (1998).

24. Assy M.G., Hataba A. A.; *J. Indian Chem. Soc.*1997; *Chem. Abstr.,* **127** 5060v (1997).

25. Gilkerson Terence, Shaw Robert William; *Eur. Pat. Appl. EP*.**310**,186; *Chem. Abstr.*, **111**,231259x(1989).

26. Tvanov E. I.,Konupl .P. Konup L. A. Stepanov D. E.,Grishchat V., *Khim-Farm* Zh. 1993; *Chem. Abstr.,* **121** 35462w (1994).

27. Scott Keneth R., Nicholson Jesse M., Edafiogho Ivan O. *PCT Int. Appl. WO* **93** 17,678; *Chem. Abstr.,* **120** 133914u (1994).

28. Krichevnshkii E. S., Alekseeva L. M., Anisimova O. S., Parshin V. A., Ashina V. V.,Granik V. G.; *Khim. Farm*, Zh 1997; *Chem. Abstr.,* **128,**244027s (1998).

29. Shimazaki Toshiyuki. Toshiyuki Yamashita, Hiroyasi; *Jpn. Kokai Tokyo Koho JP* **09** 118,653; 1997; *Chem. Abstr.,* **127,**3410j (1997).

30. Collins David J., Cullen John D., Stone Graant M. ; *Aust. J. Chem,* 1999; *Chem. Abstr.,* **110,**94655g (1989).

31. V. K. Ahluwalia Poja Sharma, Bindu Goyal; *I. J. Chem.* Vol. **36B**, 1997.

32. Nagarajan K., Shenoy S.J.; *Indian J. Chem.* **Sec.B**. 1987; *Chem. Abstr.,* **108***,* 150224p (1988).

33. Albaugh Pamela, Liu Grang, Hutchison Alan, Nagao Suhara; U.S. IS 5, 723,462 (1998); *Chem. Abstr.,* **128,** 204804m (1998).

34a. Salama M. A., Atshikh M. A.; *Egypt. J. Pharm. Sci.* 1997; *Chem. Abstr.,* **130,** 81478q (1999).

34b. Salama M. A., Atshikh M. A.; *Egypt. J. Pharm. Sci.* 1997; *Chem. Abstr.,* **130,** 81478q (1999).

35. Fukami Takehiro, Fukuroda Takahiro, Kanatani Akiolhara; *PCT Int. Appl. WO*.**99** 15,516; *Chem. Abstr.,* **130,** 237476a (1999).

36. Broughton Howard Braff, Bryant. Helen Jane, Chambers Mark Stuart, Curtis Neil Roy; *PCT Int. Appl. WO*.**99** 62,889; *Chem. Abstr.,* **132,**12259y (2000).

37. Kimura Yasuo, Mizano Takashi, Kowano Tsuyoshi, Shimada Aslami; Z. Naturforsc. B. *Chem. Sci.* 1999. *Chem. Abstr.,* **132** 35551b(2000).

38. Vasavada, Jalaji A. ; Parekh H. H.; *Chem. Abstr.,* **139,** 221662z (2003).
39. Shklyaer, Yu , ; V. J. Nifontov, Yu, V; *Chem. Abstr.,* **139,** 36429z (2003).
40. Cragoc, Edward D., Jr. Maltersdorfotto W.; *Chem. Abstr.,* **107,**70619g (1987).
41. Strukovsk, A.; Strakova 1; Petrova, M.; *Latu. Kim. Z.* 1995 **(5-6),** 96-100; *Chem.Abstr.,* **126,** 838 (1997).
42. Watabe, Yoshihisa ; Kondo, Terryuki; Akazomi, Motohiro : *Jpn. Kokai Tokkyo Koho Jp.,* **04,**282, 372 (Cl. C07D231/56); 07 Oct. 1992, Appl. 91/43, 583, 08 Mar, 1991, 7pp.,*Chem. Abstr.,* **118** (1993).
43. Chuanmin, Wang Xiaoyuan, Beijing Shifan Daxue Xuebao, *Ziren Kexueban;* **32(4),**524-528c (1996), *Chem. Abstr.,* **127,** 81393w (1997).
44. Lylbchankaya, Valeriy M.; Alekseeva, Lyudulila M.; Granik, Vladimir G.; *Tetrahedron.,* 1997, **53 (44)**, 15005-15110. *Chem.Abstr.,***128,** 22855w (1998).
45. W.A.F. Gladstone, R.O.C. Norman; *J.Chem. Soc.,* 5177-82, 1965 ; *Chem.Abstr.,* **63,** 16336d (1965).
46. Welch. Willard M., Hanav, Catherine E., Whalon, William M.; *Synthesis.,* **10,** 937-9 (1992); *Chem.Abstr.,* **118,** 6910y (1943).
47. Manouchehr Satjoughiun and Kenneth Turnbull; *J. Heterocyclic Chem.,* **25,** 1817 (1988).
48. A.C. Jain, A. Mehtia and P.Arya; *Indian Journal of Chemistry,* **Vol. 26B** February 1987, pp.150-153. *Chem.Abstr.,* **107,** 236591x (1987).
49. Chandreshekar K. Hosamani and Bharti V. Badami; *I. J. H. C.,* **vol. 7,** 245, (1998).
50. Dell Erbacarlo ; Novi Marino;Petrillo,Giovanni et.al., *Tetrahedron,*1994, **50(11),**3529-36. *Chem.Abstr.,* **121,** 83159z (1994).
51. Vasilevsky, Sergey F.; Prikhodiko, Tafyana A.; *Mendeleev common.,* **(3),** 98-99, (1996). *Chem.Abstr.,* **125,** 114539n (1996).
52. Qui Guo-Fu ; Qui-Yu-Zhu; Zhang Zheng : Hu Hong Wen : *Yougi Huaxne,* **19(2),** 162-65 (1999).
53. Okhim L-Yu; Orlove,G.1; Lideman,S.V.; et.al.; *Izv. Akad. Nauk, Ser, Khimp,* **(6),** 1095-7 (1994); *Chem.Abstr.,* **122,** 160538x (1995).
54. V.R. Vasileva et.al.; *Zh.Obsch Khim,* **31,**1501(1961).
55. Carbon Stephane and Vazquez Enrique; *Synthesis,* **(4),** 588-92 (1994), *Chem. Abstr.,* **131,** 5226m (1999).
56. V. G. Beylin; N. Y. Colbry; A. B. Giordani et al.; *J. Heterocyclic. Chem.*,**28,** 517 (1991).
57. C.Bailly and M.J. Waring; *Bio chemistry,* **32,** 5985 (1993).
58. B.Roman; *Pharmazie,* **45,** 214 (1990).
59. Sasaki Toshro; Nakatani, Juko; Hiranuma, Tayoichi et.al.;*Jpn Kokai Tokkyo Koho JP* **07** 33, 744 (Cl. C07D 231/56) (1995) Appl. 93/204, 612 (1993).;*Chem.Abstr.,* **123,** 55870x (1995).

60. Bodran Mohga M.; Ismail Mohamed A. Hamid; Yousset Khairia A.et al.; *Alexandria J. Pharm. Sci.,* **13(1),** 73-79 (1999); *Chem.Abstr.,* **131,** 18990f (1999).

61. Kim. Byung-Chal, Kim Jin li, Jhang Y. Umgdong; *Bull Korean Chem.Soc.,* **15(2),** 97-8 (1994). *Chem.Abstr.,* **121,** 50097z (1994).

62. H.M. Mokhtar, H.M. Faidallah; *Pharmazie,* **42,**481 (1987).

63. De.Lucca, George V., Kim. U.T., Liang Jing et.al.; *J. Med. Chem.,* **41(13),** 2411-2423 (1998); *Chem.Abstr.,***129,** (1998).

64. Butera, John A.: Antane Schugler A.; U.S. US 5, 179, 118 (Cl. C07 D 231/16) (1995); *Chem.Abstr.,* **123,** 256703u (1995).

65. Aran Viicente J.; Flores Maria; Munor, Pilar et al.; *Liebigs Ann.,* **(5),**817-24 (1995); *Chem.Abstr.,* **123,** 285914u (1996).

66. A. Hofmann and F. Troxler : *French Patent,* **1,** 434, 479 (1966); *J. Heterocylic Chem.,* **7,** 117 (1970).

67. Heistracher, Elisabeth, Rueb Lothur, Hamprecht Gerhard et.al.; *PCT Int.Appl.,* **96,** 06,830 (Cl. C07 D 231/56) (1996); D E Appl. 4,430,257 (1994); *Chem.Abstr.,* **125,** 86636w (1998).

68. Bigham Eric.Reinhard John Fredric J. et.al.; *PCT Inti Apl.* WO **94** 14, 780 (cl. C07 D 239/48) (1994); *Chem.Abstr.,* **122,** 160666n (1995).

69. Kyomura, Mobuo Okui, Shuko; Suzuki Shigeru et al.; *Eur.pat.Appl.*EP 726, 266 (cl. C07D 401/12) (1996); *Chem.Abstr.,* **125,** 195645u (1996).

70. Fuchs Rainer, Erdelen, Christoph et al.; *Ger.Offen.* DE **4,**336, 307 (Cl. C07 D 231/16) (1995); *Chem.Abstr.,* **123,** 256703u (1995).

71. G. Palazzo, G. Corsi, L. Baiocchi and R. Silvosterini : *J. Med. Chem.,* **9,** 38 (1966).

72. G. Palazzo, U.S. Patent 3, 470, 194 (1969); *Chem. Abstr.,* **72,** 110, 697n (1970).

73. G. Musserilli, L. Del Corona and G. Signorelli ; *Bull. Cheim. Farm.,* **108,** 706 (1969).

74. Yamaguchi,Masashisa : Maruyama, Narikki ; Koga Takki; Kamei Kenshi : *Chem. Pharm. Bull;* **43(2),** 332-334 (1995); *Chem.Abstr.,* **123,** 94191 (1995).

75. Ooe Takanori ; Konayushi, Haruhito ; Lke Zuwa, Ryuhei; *Jpn. Kokai Tokkyo Koho* JP **06,** 206, 872, (CI, C07 D 231/56), Jul. 1994; JP Appl. 92/93, 894 Oct.1992 12pp.*Chem.Abstr.,* **122,** 187576v (1995).

76. Ooe Takanori, Sueoka, Hiroyuka ; Chiba Kenji et al.; *Jpn Kokai Tokkyo Koho* JP 07 02, 786 (CI C07 D 231/56) (1956); JpAppl. 93/81, 438 (1993), *Chem. Abstr.,***122,** 239697g (1995).

77. Lavielle, Gilbert ; Maillos, Philippe ; Muller, Olivier et al.; *Eur. Pat. Appl.* EP 610, 134 (CI C07 D 403/06) ; (1994), FR Appl. 93/1054 (1993); *Chem. Abstr.,* **121,** 255804z (1994).

78. Lavoelle. Gobert ; Muller, Olyvier, et al., *Eur. Pat. Appl.* EP 747, 379 (1996), FR Appl. 95/6663 (1995). *Chem. Abstr.,* **126,** 89354j (1997).

79. Mewshaw Richard Eric, Vervoijs, Anthonie Johan; U.S. US 5, 872, 144 (CI, 514-403 ; A61 k 31/415) (1999); Appl. 24, 660 (1998); *Chem. Abstr.,* **130,** 182462k (1999).

80. Allan David, George, Elderd Colin, David Mitchell, William Lionard. ; *PCT. Int. Appl.* WO **96** 20,192 (CI. C07D 401/14) (1996); G.B. Appl. 94/26 231.(1994); *Chem. Abstr.,***125,** 167980f (1996).

81. Jain A. C. Mehta A., Mrs. Arya P.: *Indian J. Chem.,* **Sect. B.** (1987) **26B(2),** 150-3 (Eng.); *Chem.Abstr.,* **107,** 236591x (1997).

82. Cupps, Thomas Lee; Bogdun, Sophle Evai; Henry, Raymond Todd. et al.*PCT Int.Appl.*WO 98, 28, 609 US Appl. 31, 740 (1996); 53 pp; *Chem. Abstr.,* **129,** 4113u (1998).

83. Conoly Peter J. Wachter, Micheal P., U.S. US 5, 387, 639 (CI. C07 D 231/54) (1995); US Appl. 742, 788,(1991);*Chem. Abstr.,*265369w (1995).

84. Kaiwa, Fumiko ; Shoji, Musutaki ; Yoshimoto Ryota ; *Jpn. Kokai Tokkyo Koho* JP **05,** 255, 308. (CI C07 D 401/04), 05 Oct. (1993). Appl. 92/52, 696, 11 March 1992, *Chem. Abstr.,* **120,** 245090d (1994).

85. Efflard, Richard Charles; Klein, Joseph Thomas; Martin Lawrence Leo.; *Eur. Pat. Appl. EP* **509,** 402 (CI. C07 D 401/12). 21 Oct. 1992. US Appl. 688, 964, 17 Apr. 1991 ; 43 pp.

86. A. Hand book of Spectroscopic data by B. D. Mishtry, Ist ed. ABDPress Jaiptt 11-36 (2000); "Absorption Spectroscopy data of Organic Compounds" by V. M. Parikh, Addition Wesley Pub.Co.,London, 243-258 (1978).

87. Introduction to Infrared and Ramann Spectroscopy by Norman B. Colhap, Lowerence H. Daly and Stephene E. Wilberluy, Academic Press (1975).

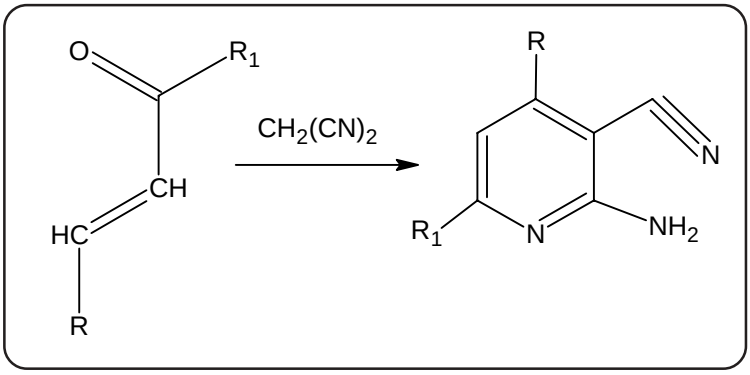
## INTRODUCTION

Pyridines are of considerable chemical and biological importance, as the pyridine derivatives have displayed diverse pharmacological activities[1] The simple pyridine compounds are synthesised by the cyclisation of aliphatic raw materials, while various polysubstituted pyridine compounds prepared from acyclic compounds in a manner similar to chemistry of the benzenoid chemistry.

## SYNTHETIC ASPECT

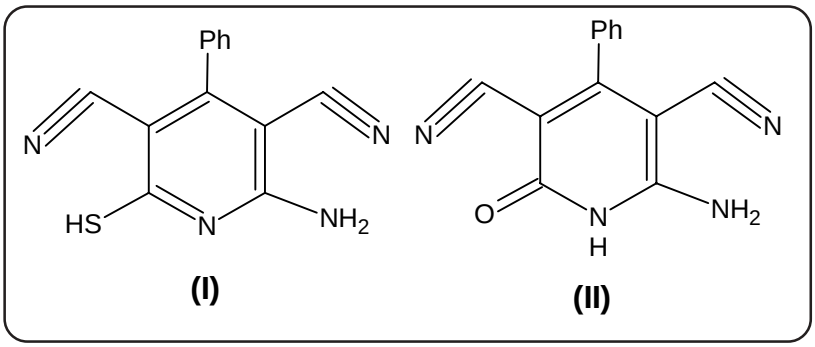
A variety of methods are available for the preparation of 3-cyano pyridines in literature [2-8]. Some of them are as follows.

1. A. Sakuri and Midorikawa have reported that malononitrile reacts with α,β-unsaturated ketones to give 2-amino-3-cyano-4,6-disubstituted pyridines[9,10]




2. Samour and co-workers[11,12] prepared substituted cyano pyridines by the condensation of chalcones with ethyl acetoacetate and malononitrile in presence of ammonium acetate.

3. Cyano pyridine derivatives (I) are obtained by the reaction of R-CO-$CH_3$ with 2-cyanothioacetamid in presence of N-methyl morpholine, which have been prepared by Dayachenko V.D.[13] Cyano pyridine derivatives (II) have also reported by Metwalla Nadia et al.[14]

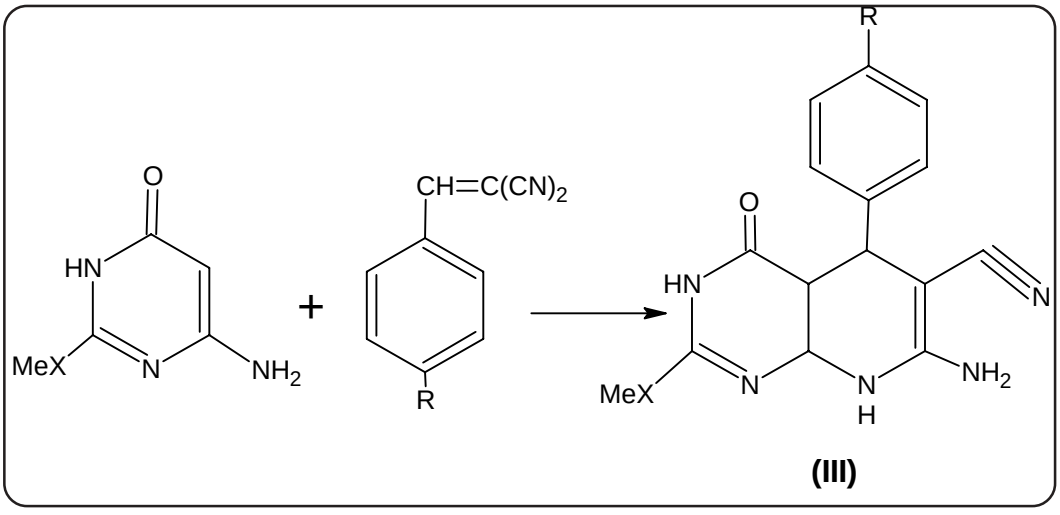



4. Substituted cyanopyridine derivatives were also prepared from 3-substituted phenyl pyrazolone derivatives with malononitrile.[15]

5. G. Ege and co-workers and H. Kurithara et al. have prepared 2-amino 3-cyano pyridine derivatives by using arylidene, malononitrile, lithiumisopropylamide and DMF dichloride.[16,17]

6. J. M. Babbit et al.[18] synthesized 3-cyano pyridines by the cyclo condensation of cyano acetamide with ethyl acetoacetate in presence of alkali.

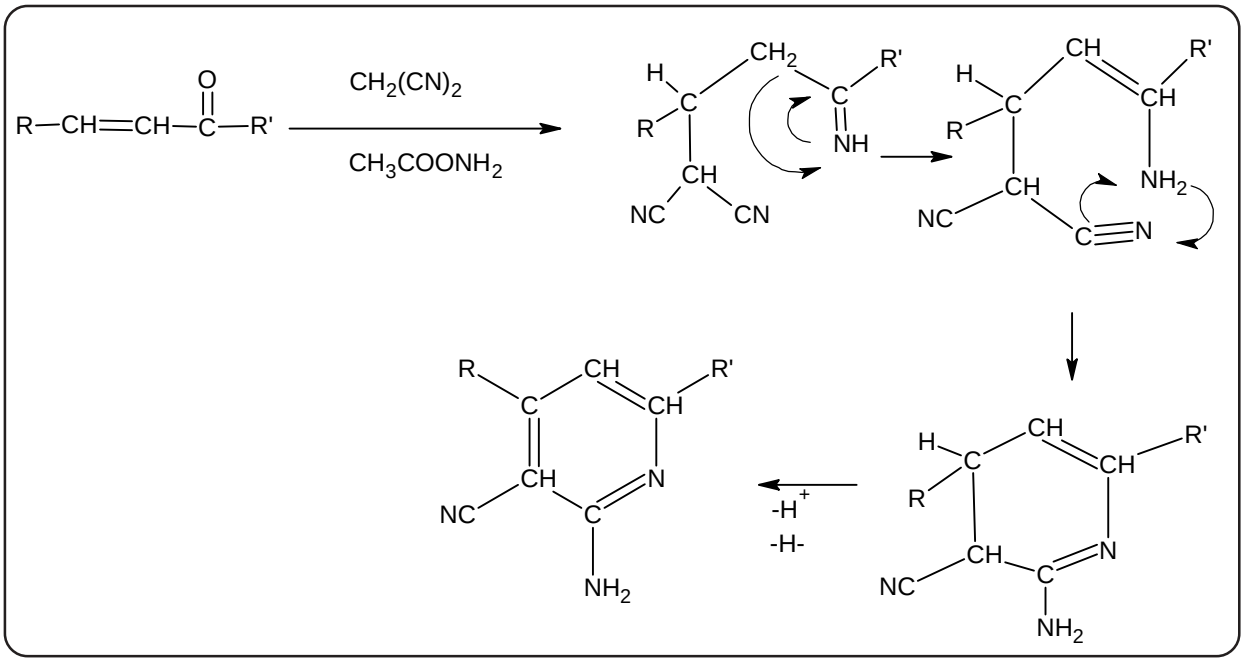
7. Quiroya Jairo and co-workers[19] have synthesized pyrido-[2,3-d]-pyrimidine-4-[3 H]-ones (III) from 6-amino-2-pyrimidinones and arylidene malononitrile.




8. Aromatic nitrile can be prepared from the corresponding primary carboxylic acid amide in presence of $TiCl_4$ and a base like $Et_3$ N at $^0$C.

## REACTION MECHANISM

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

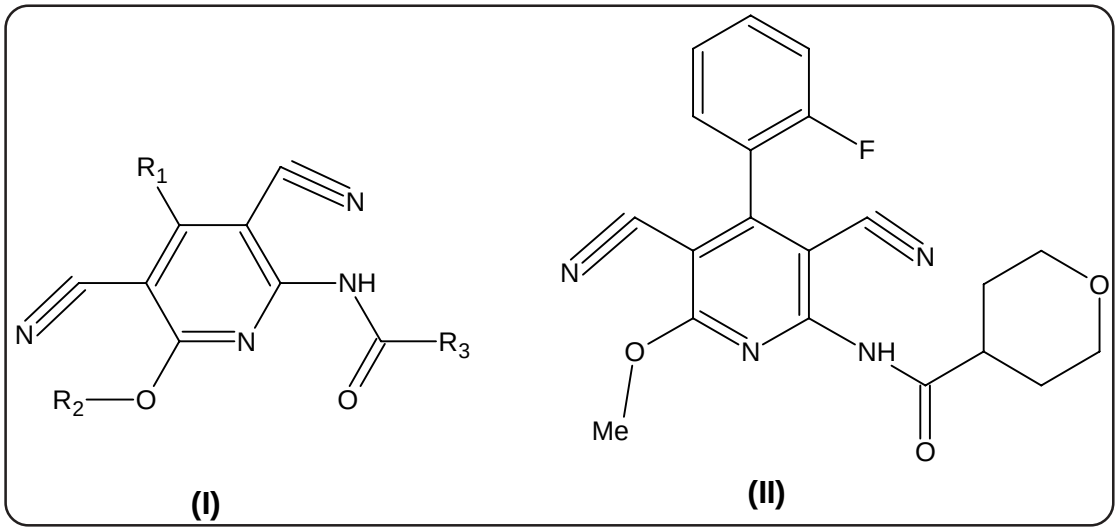



## THERAPEUTIC IMPORTANCE

Cyanopyridine derivatives have been found to posses wide range of therapeutic activities shown as under.

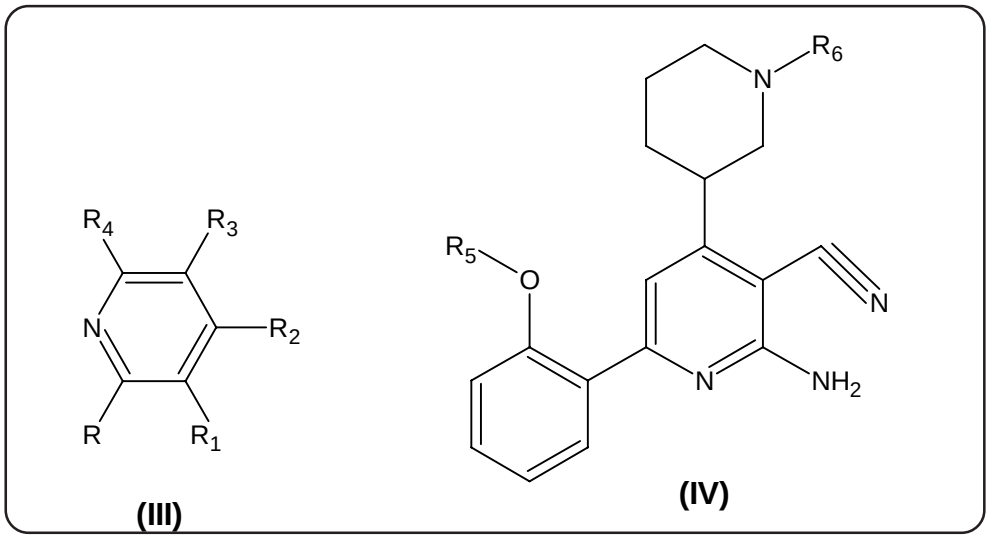
1. Antimicrobial[20]
2. Antitubercular [21]
3. Analgesic [22]
4. Antiallergic [23]
5. Anticonvulsant [24,25]
6. Antihypertensive [26]
7. Adrenergic [27]
8. Antifungal [28]
9. Antiepileptic [29]
10. Antisoriasis [30]
11. Herbicidal [31,32]

Harda, Hiroki; et al.[33] have prepared 2-acylamino-3,5-dicyanopyridine derivatives as high conductance type calicium sensitivity K channel openings drugs. (I),(II).



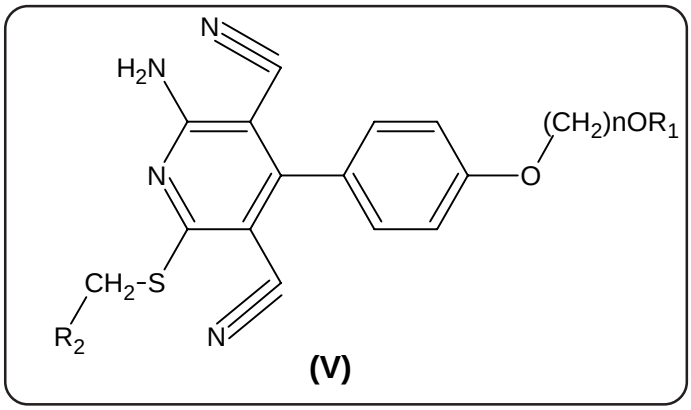

**(I)** **(II)**

Villhauer, et al.[34] synthesised cyano pyridine as antihyper glycemic agent are. Timothy B. et al.[35] prepared hydroxy aryl pyridines (III)(IV), which used for asthama and ischemia, in addition to compounds are show antitumor and immuno suppressant activity.




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

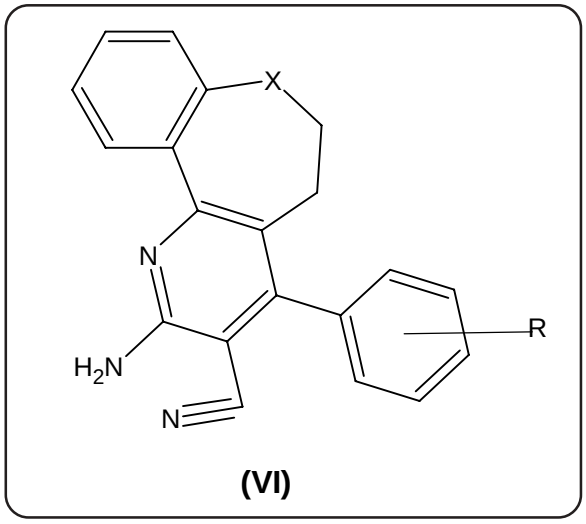
Resentreter et al.[36] prepared 2-thio-3,5-dicyano-4-phenyl-6-amino pyridines (V) as adenosine Al receptor agoinsts in the treatment of cardiacorurogential disease, cancer, inflammation, neurodegenerative disease and in pain.




**(V)**

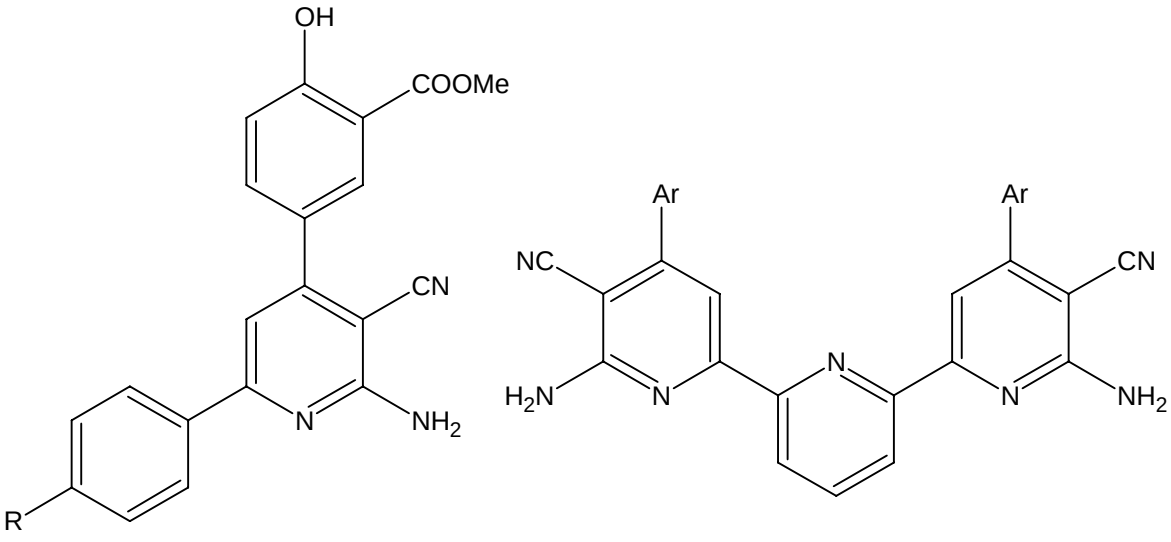
El-Nabawia and co-workers [37] have prepared cyano pyridine and studied their antimicrobial activity, Parekh el al.[38,39] have synthesised the series of cyano pyridies and reported their antimicrobial activities.

Hammama Abou and co-workers [40] synthesised 3-cyano pyridine derivatives (VI) and reported as anticancer and anti HIV agents.




**(VI)**

More ever, Grant N and co-workers[41] synthesized some cyano pyridines (VII) and reported as a antibacterial agents. Abd EL-Galil and E-Amr[42] prepared cyanopyridine derivatives (VIII) and screened for their antimicrobial activity.




**(VII)** **(VIII)**

Mann Padele and co-workers[43] have reported some 3-cyano pyridines as anti inflammatory agents. Villalobas Anabella et al.[44] have prepared some new 3-cyano pyridines and reported them as choline-steurase inhibitors.

Bhatt and co-workers[45] have synthesised 3-cyano pyridines and postulated them as inmuno suppressive agents. Prancis and coworkers[46] have studied the effect of some substituted pyridines on the growth of the walker carcino sarcome-256 in tissue culture.

The insecticidal[47-48] fungicidal[49] and other pesticidal activities[50] have documented in the literature by several workers.

Furthermore cycnopyridines are also found applicable in the dyeing of polyester and acrylic fiber[51,52]. The oxidie activator bleaching activity of cyano pyridine has been proved by Rees Wayne M.[53]

Moreover Oshidu murio[54] have constructed some new cyano pyridine derivatives which inhibitertceberal edema and delayed neuron death. Hence they are useful as caberal eduma inhibitor or cerebrovascular disorder remedies.

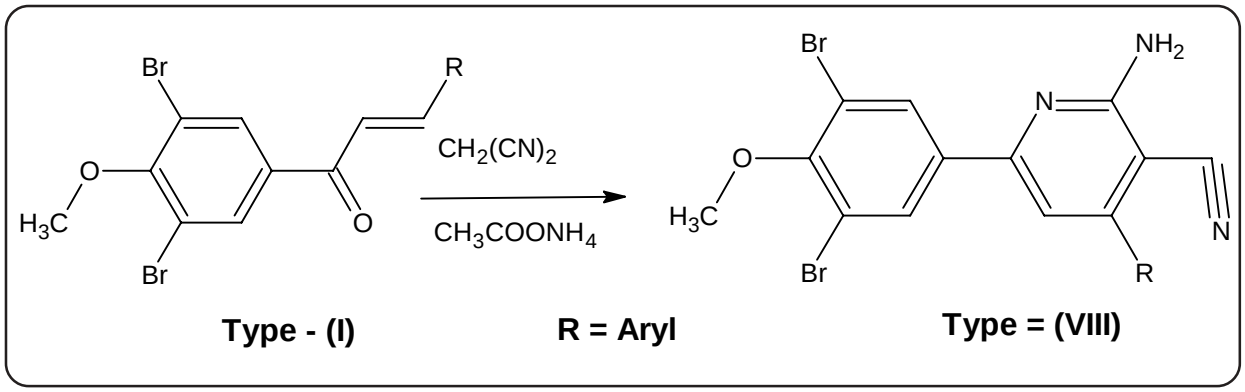
Thus, diverse biological activities have been encountered in compounds containing cyano pyridine ring system. Therefore it was considered worth while to synthesise cyano pyridine derivatives which have been described as under.

**SECTION - I SYNTHESIS AND BIOLOGICAL OF 2-AMINO-3-CYANO-6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-PYRIDINES**

## SECTION - I

## SYNTHESIS AND BIOLOGICAL SCREENING OF 2-AMINO-3-CYANO-6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-PYRIDINES

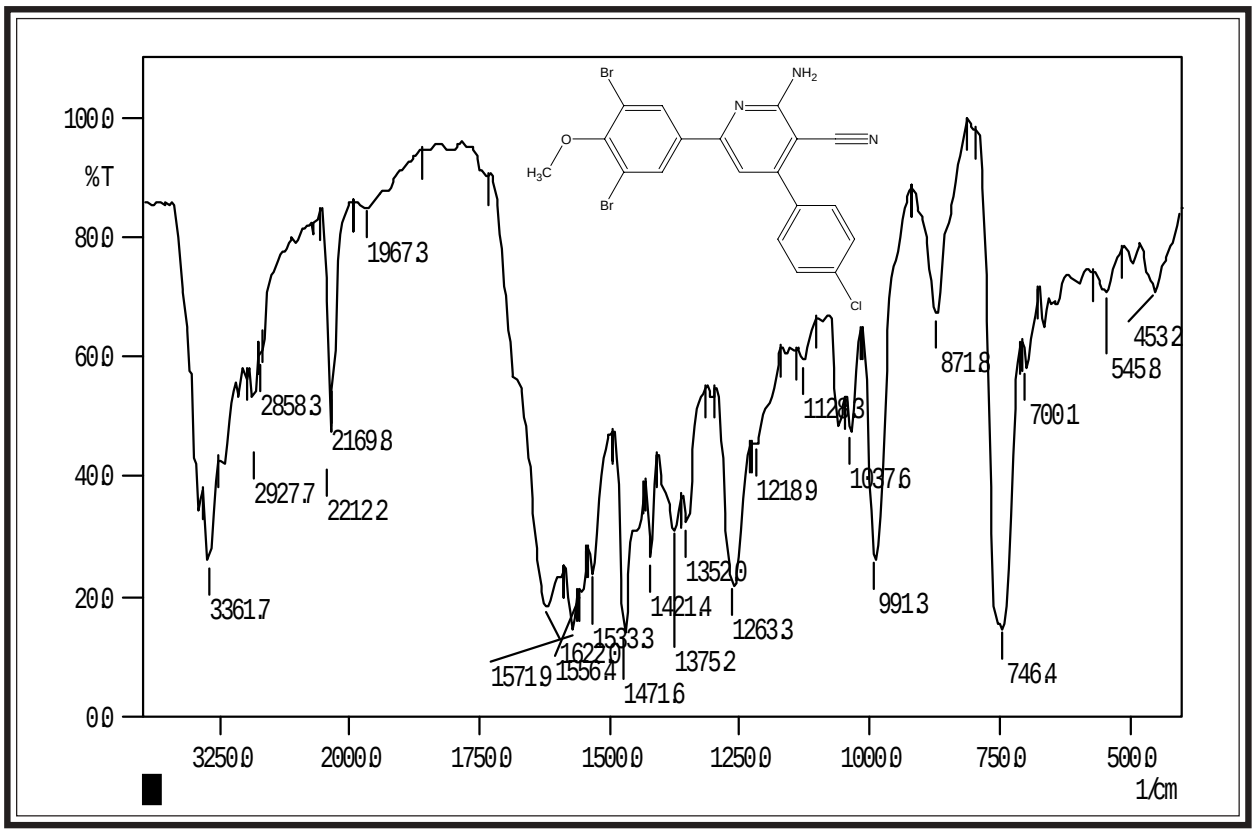
Cyanopyridines play a vital role owing to their range of biological and physiological activites. In the light of these biological activities and variety of industrial applications, some new 2-amino-3-cyano-6-(3,5-dibromo-4-methoxyphenyl)-4-aryl-pyridine derivatives of type (VIII) have been prepared, by the condensation of (2E)-1-(3,5-dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones of type (I) with malononitrile in presence of ammonium acetate.




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 ***invitro*** 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.

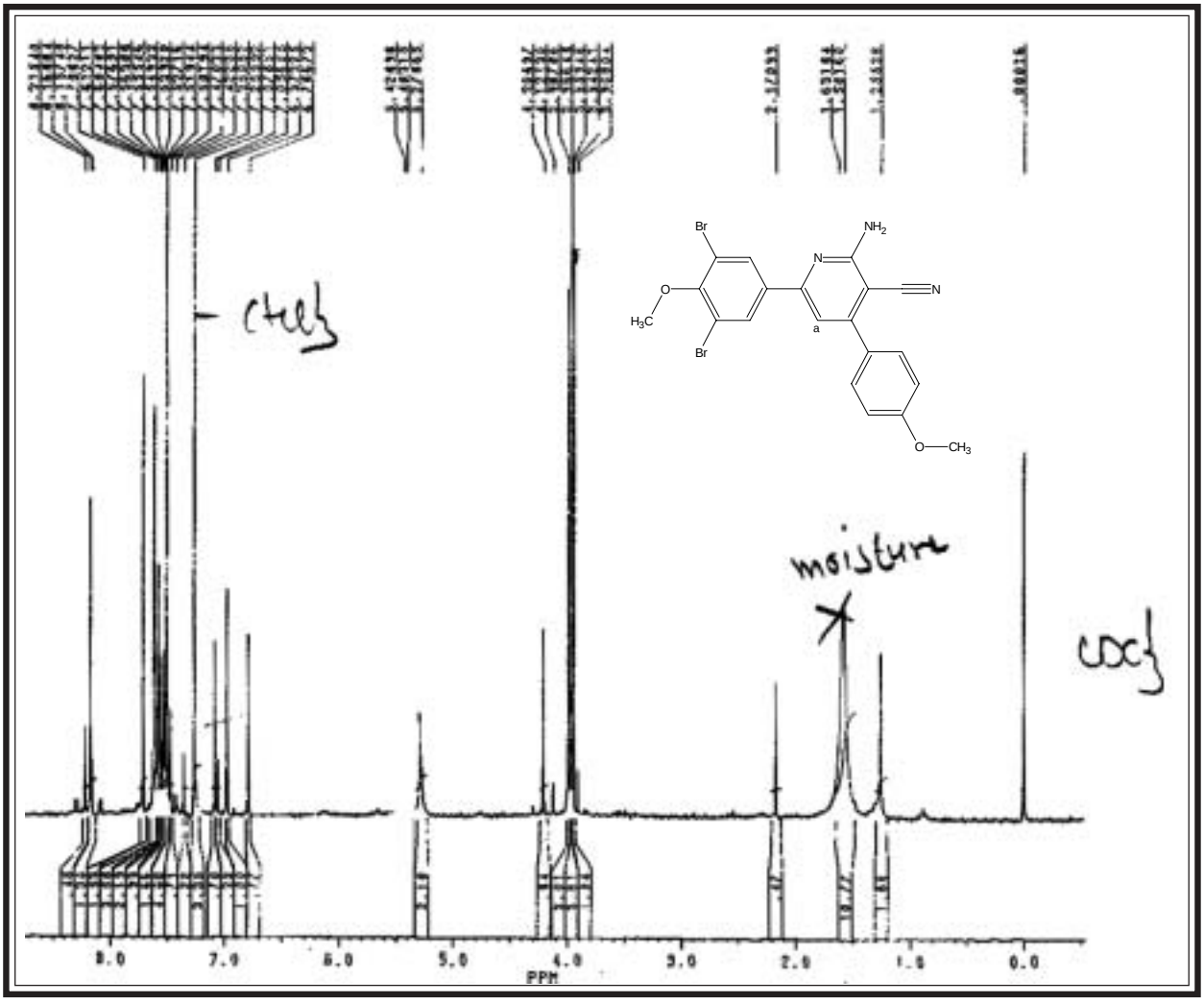
**IR spectral studies of 2-Amino-3-cyano-6-(3,5-dibromo-4-methoxy phenyl)-4-(4-chorophenyl)-pyridine**




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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2927 | 2975-2950 | 55 |
| $-CH_3$ | C-H str.(sym.) | 2858 | 2880-2860 | " |
| | C-H def.(asym.) | 1471 | 1470-1435 | " |
| | C-H def.(sym.) | 1352 | 1390-1370 | " |
| Aromatic | C-H str. | 3060 | 3090-3030 | 56 |
| | C=C str. | 1533 | 1540-1480 | " |
| | | 1129 | 1125-1090 | " |
| Halide | C-Br str. | 545 | 600-500 | 55 |
| Ether | C-O-C str.(sym) | 1263 | 1275-1200 | " |
| Pyridine | C=C str. | 1622 | 1650-1520 | 56 |
| | C=N str. | 1571 | 1580-1550 | " |
| Nitrile | C=N str. | 2212 | 2240-2120 | " |
| Amine | N-H str. | 3361 | 3380-3350 | " |

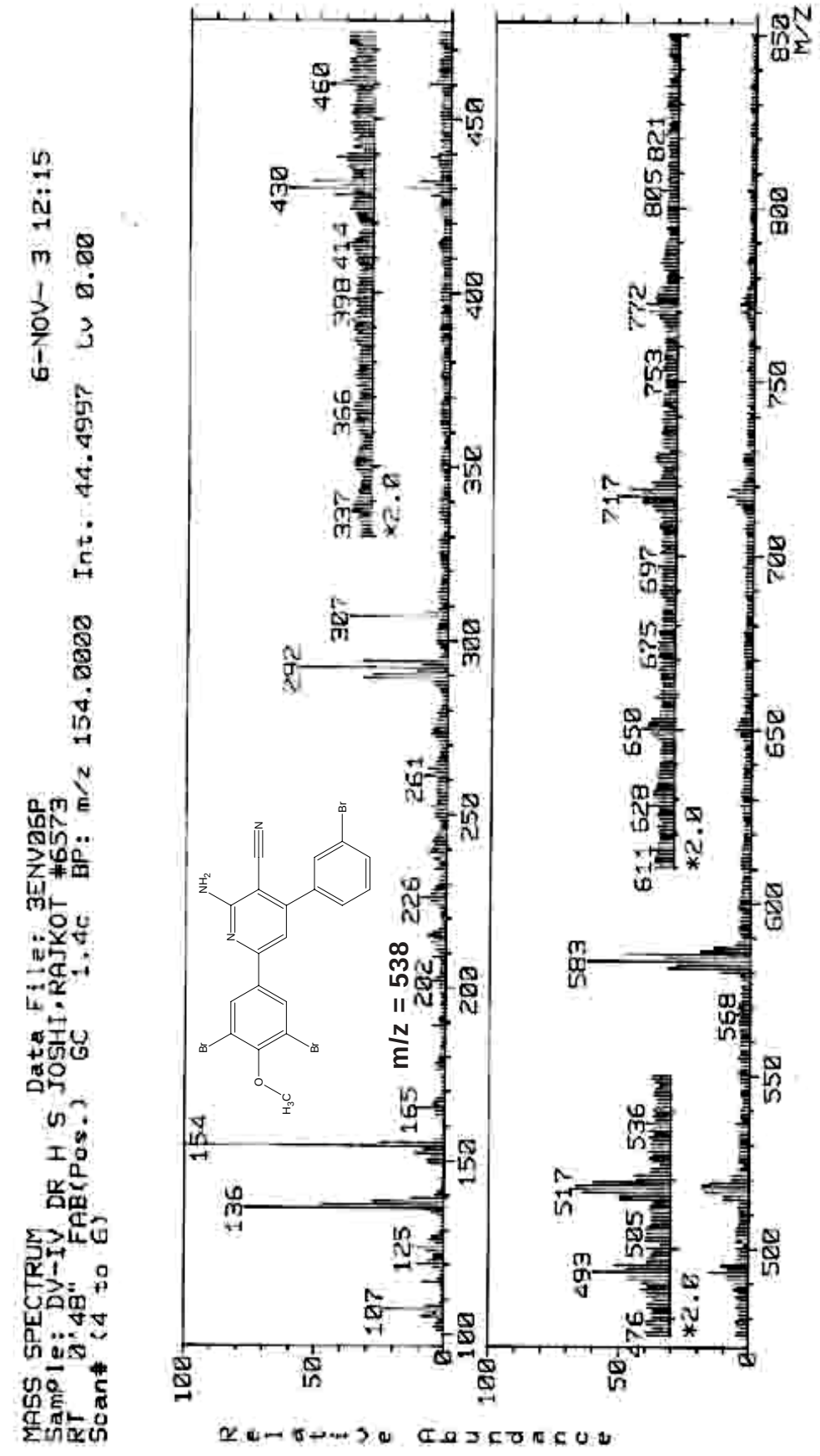
## NMR SPECTRAL STUDIES OF 2-AMINO-3-CYAN0-6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-(4-METHOXYPHENYL)-PYRIDINE




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

| Signal No. | Signal Position (δ ppm) | Relative No. of Proton | Multiplicity | Inference |
|---|---|---|---|---|
| 1. | 3.96 | 3H | singlet | Ar-$OCH_3$ |
| 2. | 3.98 | 3H | singlet | Ar-$OCH_3$ |
| 3. | 5.27 | 2H | singlet | -$NH_2$ |
| 4. | 6.97 | 1H | singlet | -Ha |
| 5. | 7.50-7.70 | 6H | multiplet | Ar-H |

MASS spectral studies of 2-Amino-3-cyano-6-(3,5-dibromo-4-methoxy phenyl)-4-(3-bromophenyl)-pyridine



# EXPERIMENTAL

## SYNTHESIS AND BIOLOGICAL OF 2-AMINO-3-CYANO-6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-PYRIDINES.

### (A) Synthesis of (2E)-1-(3,5-Dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones.

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

### (B) Synthesis of 2-Amino-3-cyano-6-(3,5-dibromo-4-methoxyphenyl)-4-chlorophenyl-pyridines

A mixture of (2E)-1-(3,5-dibromo-4-methoxyphenyl)-3-(4-chlorophenyl)-prop-2-en-1-one (4.3 gm, 0.01 mol), malononitrile (0.60gm, 0.01 mol) and ammonium acetate (6.6gm, 0.08 mol) dissolved in ethanol (20ml), the content was heated under reflux for 12 hrs. The product was isolated and crystallized from ethanol. Yield 70%, m. p. 170 $^0$C, Anal. Calcd. for $C_{19}H_{12}Br_2ClN_3O$; Requires: C,46.23; H,2.45; N,8.18; Found: C,46.28 ; H,2;55; N,8.14 %.

Similarly, other 2-Amino-3-cyano-6-(3,5-dibromo-4-methoxyphenyl)-4-aryl-pyridines

### (C) Biological screening of 2-Amino-3-cyano-6-(3,5-dibromo-4-methoxy phenyl)-4-aryl-pyridines

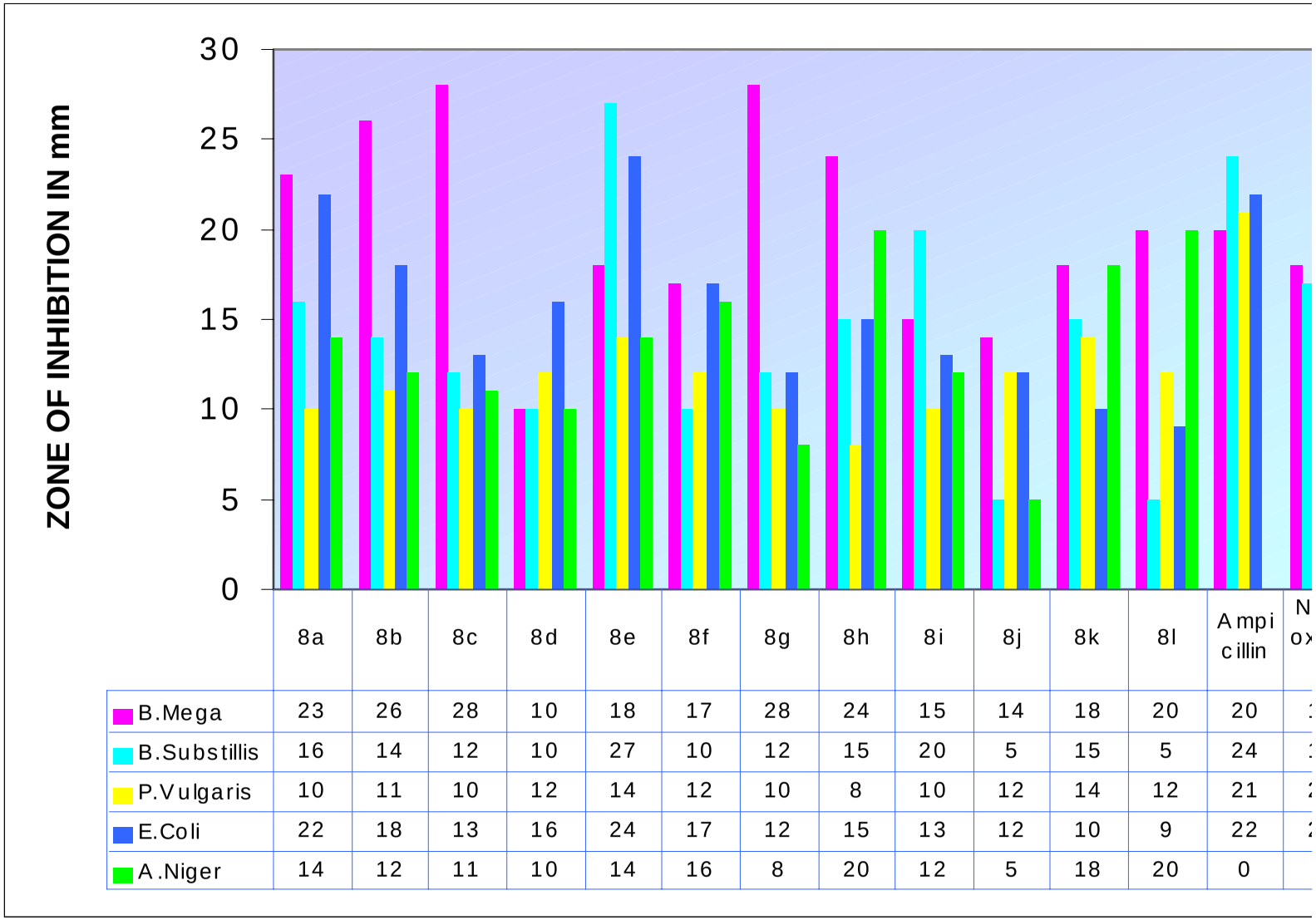
Antimicrobial testing were carried out as described in Part-I Section-1 (D). The zones of inhabition of test solution are recorded in Graphical Chart No 8.

## TABLE-8 : PHYSICAL CONSTANTS OF 2-AMINO-3-CYANO-6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-PYRIDINES.

| Sr. No. | R | Molecular Fromula | Molecular Weight | M.P. °C | Yield % | % of Nitrogen Calcd. | % of Nitrogen Found | Rf Value | Solvent System |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 8a | $C_6H_5$- | $C_{19}H_{13}Br_2N_3O$ | 459.1 | 172 | 65 | 9.15 | 9.09 | 0.65 | S2 |
| 8b | 3-Br-$C_6H_4$- | $C_{19}H_{12}Br_3N_3O$ | 538.0 | 126 | 60 | 7.81 | 7.75 | 0.68 | S1 |
| 8c | 2-Cl-$C_6H_4$- | $C_{19}H_{12}Br_2ClN_3O$ | 493.6 | 132 | 58 | 7.18 | 7.10 | 0.40 | S3 |
| 8d | 4-Cl-$C_6H_4$- | $C_{19}H_{12}Br_2ClN3O$ | 493.6 | 170 | 70 | 7.18 | 7.14 | 0.66 | S1 |
| 8e | 4-$N(CH_3)_2$-$C_6H_4$- | $C_{21}H_{18}Br_2N_4O$ | 502.2 | 98 | 72 | 11.16 | 11.10 | 0.48 | S1 |
| 8f | 4-$OCH_3$-$C_6H_4$- | $C_{20}H_{15}Br_2N_3O_2$ | 489.3 | 140 | 65 | 8.56 | 8.51 | 0.60 | S2 |
| 8g | 3,4-$(OCH_3)_2$-$C_6H_3$- | $C_{21}H_{17}Br_2N_3O_3$ | 519.2 | 210 | 68 | 8.09 | 8.16 | 0.58 | S3 |
| 8h | 2-$NO_2$-$C_6H_4$- | $C_{19}H_{12}Br_2N_4O_3$ | 504.1 | 134 | 58 | 11.11 | 11.15 | 0.69 | S2 |
| 8i | 3-$NO_2$-$C_6H_4$- | $C_{19}H_{12}Br_2N_4O_3$ | 504.1 | 129 | 55 | 11.11 | 11.01 | 0.55 | S3 |
| 8j | 3-$OC_6H_5$-$C_6H_4$- | $C_{25}H_{17}Br_2N_3O_2$ | 551.2 | 52 | 60 | 7.62 | 7.54 | 0.62 | S1 |
| 8k | 2-OH-$C_6H_4$- | $C_{19}H_{13}Br_2N_3O_2$ | 475.1 | 87 | 56 | 8.84 | 8.76 | 0.44 | S2 |
| 8l | 4-OH-$C_6H_4$- | $C_{19}H_{13}Br_2N_3O_2$ | 475.1 | 101 | 58 | 8.84 | 8.92 | 0.56 | S3 |

S1=Ethyl acetate: Hexane (2.5:7.5), S2=Ethyl acetate: Hexane (2:8), S3=Acetone: Benzene (2.5:7.5)

## GRAPHICAL CHART NO. 8 : 2-AMINO-3-CYANO-6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-PYRIDINES.




| | 8a | 8b | 8c | 8d | 8e | 8f | 8g | 8h | 8i | 8j | 8k | 8l | Ampicillin | No |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B.Mega | 23 | 26 | 28 | 10 | 18 | 17 | 28 | 24 | 15 | 14 | 18 | 20 | 20 | 1 |
| B.Substillis | 16 | 14 | 12 | 10 | 27 | 10 | 12 | 15 | 20 | 5 | 15 | 5 | 24 | 1 |
| P.Vulgaris | 10 | 11 | 10 | 12 | 14 | 12 | 10 | 8 | 10 | 12 | 14 | 12 | 21 | 2 |
| E.Coli | 22 | 18 | 13 | 16 | 24 | 17 | 12 | 15 | 13 | 12 | 10 | 9 | 22 | 2 |
| A.Niger | 14 | 12 | 11 | 10 | 14 | 16 | 8 | 20 | 12 | 5 | 18 | 20 | 0 | |

## REFERANCES

1. Attia, A. ; Michael, M. (Lab. Appl. Org. Chem. nat.Res. Cent. Cairo. Egypt ) *Altachim. hung.,* **112(1)**, 89-98 (1983); *Chem. abstr.,* **99,** 88006j(1983) .
2. E. C. Taylor and A. J. Crovetti; *J. Org. Chem.,* **19,** 1633-40 (1954); *Chem. Abstr.* **132,** 137287m (2000).
3. Tsukube Hiroshi, Shinoda Satoshi, Venish Junichi, Hireroka Tako; *J. Org. Chem.* (1998); *Chem. Abstr.* **129,** 16096d (1998).
4. Kazoe Takashi; Wong Shuzhong; PCT *Int. Appl.* WO 00, 06, 547 *Chem. Abstr.* **132,** 137287m (2000).
5. Dayochenko U. P. Russ. *J. Org. Chem.* 1998; *Chem. Abstr*. **130,** 223222c (1999).
6. Krivokolysko S. G.; *Chem. Heterocycl. Compd.* (N.Y.) 1999.
7. Kanded Ez-el-din M.; *Chin. Pharm, J.* 1999, *Chem. Abstr.* **132,** 3217844y (2000).
8. J. V. Saidi, A. F. Muschette and G. Mayarnick; US 2, 680, 742 (1954); *Chem. Abstr.* **49,** 6316d (1955).
9. A. Sakurai and N. Midorikawa; *Bull Chem. Soc. Japan,* **40,** 1680 (1967).
10. A. Sakurai and N. Midorikawa; *Bull Chem. Soc. Japan,* **41,** 430 (1968).
11. A. Samour, Y. Akhnookh and H. Jahine; *Egypt i. Chem.,* **13,** 420 (1970).
12. A. Samour, M. B. I. Sleim and M. S. Abdiel Hatim; *Egupt J. Chem.,* **15,** 23, (1972).
13. Dayachenko V. D., Litvinov V. P. Russ; *J. Org. Chem.,* 1998; *Chem. Abstr.,* **130,** 223222c (1999).
14. Metwalla Nadia H., Abdelrazek Fathy Mohmmed.*Prakt. Chem.,* (1998); *Chem. Abstr.,* **130,** 13960r (1999).
15. Sayed G. H., Kassab R. R.; *Bull. Fac. Pharm.,* 1998; *Chem. Abstr.,* **137,** 15727p (1999).
16. G. Ege, H. O. Frey and E. Schuck; *Synthesis.,* 376 (1976).
17. H. Kurihara and H. Mishima; *J. Heterocycl. Chem.,* **14,** 1077 (1977).
18. J. M. Babbit and D. A. Scola; *J. Org. Chem.,* **25,** 560 (1960).
19. Quiroay Jairo, Alvarado Mario, Insuasty Braudio, Nogeras; *J. Heterocycl. Chem.* (1998).
20. Patel V. B., Sorathiya S. D., Parikeh A. R.; *Indian J.Chem.,* Sec.**B**.*Org. Chem. Ind. Med. Chem.,* **36 B (9),** 822-825 (1997).
21. W. L. Hoefling, D. Elhancer and G. Rackling; VEB Leuna-Werke, "Welter Ulbrichat"Ger. 1, 193, 506 (CIC07D) May 26 (1965); *Chem. Abstr.,* **63,** 6979 (1965).
22. Abdallah Nevine A; *Acta Pharm., (Zegrab),* 1999; *Chem. Abstr.,* **132,** 137287n (2000).
23. Yoshida Hiroshi, Omori Kiyoshi, Yoneda Yasuyuki, Fase Kensaku; *Jpn. Kokai Tokkyo Koho JP.,* **10,** 120, 677; *Chem. Abstr.,* **129,** 160629 (1948).
24. Masered Bernard, Wouters Johan, Pochet Lionel, lambert Didier;*J. Med. Chem.,* **41(17),** 3235-3244 (1998); *Chem. Abstr.,* **129,** 202846y (1998).

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

26. V. Scott and Joseph ; *Ger. Pat.,* 2803 592 (1979); *Chem. Abstr.,* **92,** 82428 (1980).

27. Devries Keith Michael, Daw Robert Lee, Wright Stephen Wayne; PCT *Int. Appl.* WO **98,** 21, ` 184 *Chem. Abstr.* **129,** 27896r (1998).

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

29. W. Von Behenburg, J. Engel, Heese and K. Thiele; *Ger. Offen , D. E.* **3,** 593 (CI C07D 213/ 72) 1984; *Chem. Abstr.,* **101,**130595n(1984)

30. V. Scott and E. Joseph; *Jap. Pat.,* **7** 99 8 338 (1979); *Chem.Abstr.,* **92,** 82428 (1980).

31. Nebel, Kurt, Brunner, Hans-Geary, Schurfer Rolf; *PCT Int. Apl.* WO, **98,** 21, 1998; *Chem.Abstr.,* **129,** 27898t (1998).

32. Baltruschat Helmat Siegried, Mater Thomas, Scheiblich Stefan; *Eur. Por. App. EP,* **820,** 996; *Chem.Abstr.,* **128,** 154018k (1998).

33. Harada, Hiroki; *Chem. Abstr.,* **139,** 69158p (2003).

34. Villhauer, Edwin B.; *Chem. Abstr.,* **139,** 133417b (2003).

35. Lowinger, Timothy B.; *Chem. Abstr.,* **136,** 279345m (2002).

36. Rosontreter, Ulricn; *Chem. Abstr.,* **139,** 36452b (2003).

37. El-Nabawia El-Said Goda; Fatma; Alexandria; *J. Pharm. Sci.,* **13(2),** 145-148 (1999); *Chem.Abstr.,* **132,** 151650g (2000).

38. Y. J. Fernandes and Hansa Parekh; *J. Inst. Of Chem.,* **63,** 69 (1991).

39. Pankaj Patel, S. Kjoregaokar, M. Shah and H. Parekh; *IL Pharmaco.,* **51(1),** 59-63 (1996).

40. Hammama Abou, Elfatoon G.; El-hafeza Naglu A., Abd, Miduras Wandan; Z. Naturforch B. *Chem. Sci.* (2000).

41. Grant N., Mishriky, Nawar, Assad F. M. and Awzy N. G.; *Pharmazie,* **53(8),** 543-47 (1998).

42. Abd El-Galil. E. Amr.; *Indian J. Heterocyclic. Chem.,* **10,** 49-58 (2000).

43. Mann Padele, Chnmenti Franco, Bolaso Adrino, Bizzari Bruna, Filippeli Walter; Feillipelli Amella: *Eur. J. Meid. Chem.,* 1999; *Chem.Abstr.,* **130,** 352178s (1999).

44. Villalobas Anabella, Negel Arthur A., Chem. Yuhpyng L.; U.G. US 5, 750, 542; *Chem.Abstr.,* **129,** 4661w (1998).

45. Bhatt Douglas G., Petraitis Joseph J., Sherk Susan R., Copeland Robert A.; *Bio. Org. Med. Chem., Lett.* **8(13),** 1715-1750 (1998).

46. Prancis E. Reinhart, J. H. Gray and Wiliam G. Batt; *J. Franklin Inst.,* **261,** 669-70 (1966); *Chem.Abstr.,* **50,** 10930c (1956).

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

48. Umed Ten, Kusunoki, Masoyuki Takuro, Maechara Shinya Kutsuma Seikhi; *Jpn Kokai Tokkyo Koho JP* **09,** 95, 489 (1997); *Chem.Abstr.,* **127,** 17699y (1997).

49. Khan Mukhtar Hussain, Haque Ruzial, Sufi Ahmed, Nizamuddin; *Indian J. Chem.,* **Sect. B**. *Org. Chem. Ind. Med. Chem.,* (1998); *Chem.Abstr.,* **130,** 23754h (1999).

50. Rigiterink ; Raymond H. (Don Chemical Co.) ;US 3, 899, 205 (CE 260-294-8) 27 Auyg (1968); *Chem. Abstr.,* **69,** 96483h (1968).

51. E. Fleckenstein; *Ger. Pat.* **2,** 339, 713 (1975); *Chem. Abstr.,* **84,** 61161j (1976).

52. J. Dehnert and G. Lahm; *Ger. Pat.* **2,** 352, 831 (1975); *Chem. Abstr.,* **83,** 99180g (1975).

53. Rees Wayne M. (S. C. Johnson and Son lme. USA); *PCT Int. Apl.* WO 97 42295 (CI. C11 D5 /13 Nov. 1997). US Appl. 643, 811, 6 May 1996, 24 pp; *Chem. Abstr.,* **128,** 4928t (1998).

54. Oshidiu Murio, Mimaki Yogi, Satoh Hiroaki and Yokoyama Shinji; *PCT Int. Apl.* WO **98,** 22, 439; *Chem. Abstr.,* **129,** 4582w (1998).

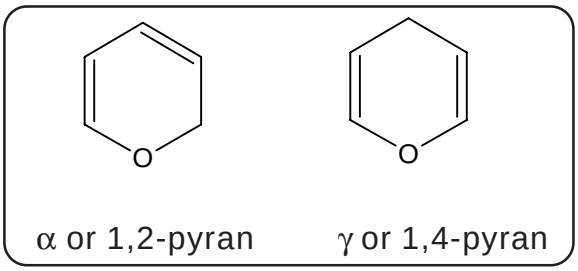
55. A Handbook of Spectroscopic data by B.D.Mishtry; 1st ed. ABD press Jaipur 11-36(2000)., "Absorption Spectroscopy of Organic Compounds", by V.M.Parikh, *addision-Wesley Pub. co., London*, 243-258(1978).

56. Introduction to Infrared and Raman Spectroscopy by Nurmav B. Colthup, Lowrence H-Daly and Stephene E. Wiberluy, *Academic Press*(1975).

## INTRODUCTION

Pyran derivatives constitute a class of interesting compounds finding versatile applications in various fields viz. pharmaceuticals, dyes, agrochemicals and sweet smelling substances. They are also present in some natural products like vitamin E, cloves, certain alkaloids and some natural coloured compounds.

Pyrans are six membered doubly unsaturated compounds containing one oxygen atom in the ring. The two double bonds may be conjugated or isolated known as α or 1,2-pyran and γ or 1,4- pyran respectively.




A high degree of stabilization of the pyran nucleus is achieved by substituting phenyl group in the 2 and 4-preferably and also in the 6-position.

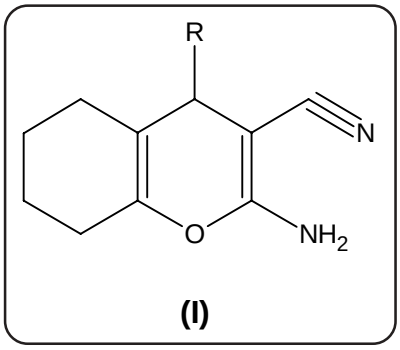
## SYNTHETIC ASPECT

Different methods are available in literature [1-10] for the preparation of pyran derivatives.

The popular methods are

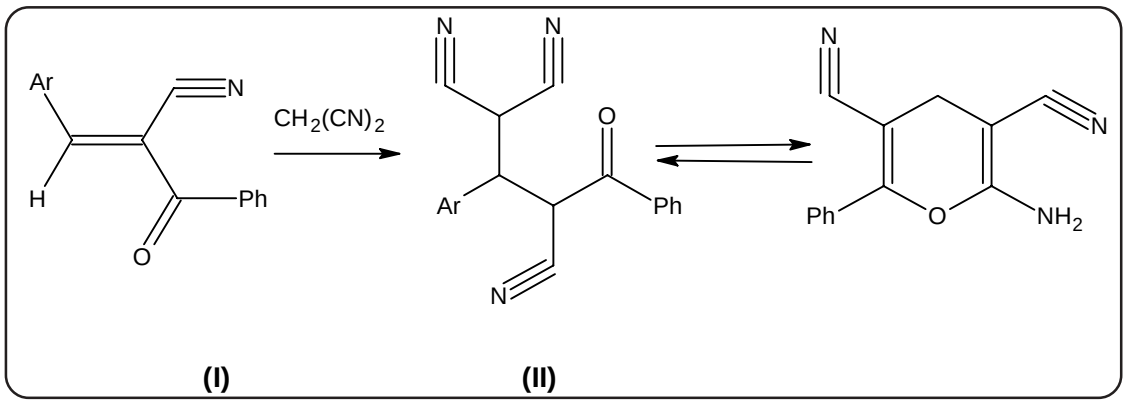
1. Reaction between α, β- unsaturated carbonyl system with $(CH_2CN)_2$ led to corresponding 2-amino-3-cyano-4H-pyrans[11]

2. Fabrizi et al.[12] have reported the synthesis of dihydro pyrans via pd-catalysed cyclisation of 2-alkyl-1,3-dicarbonyl compounds and vinylic triflates or halides.
3. Some alkylidene 2-H-pyrans were synthesized[13] by thermal electrolyting ring closure of divinyl alkenyl.
4. Reaction of cyclohexenone with cinnamonitriles, gave substituted pyran derivatives[14].



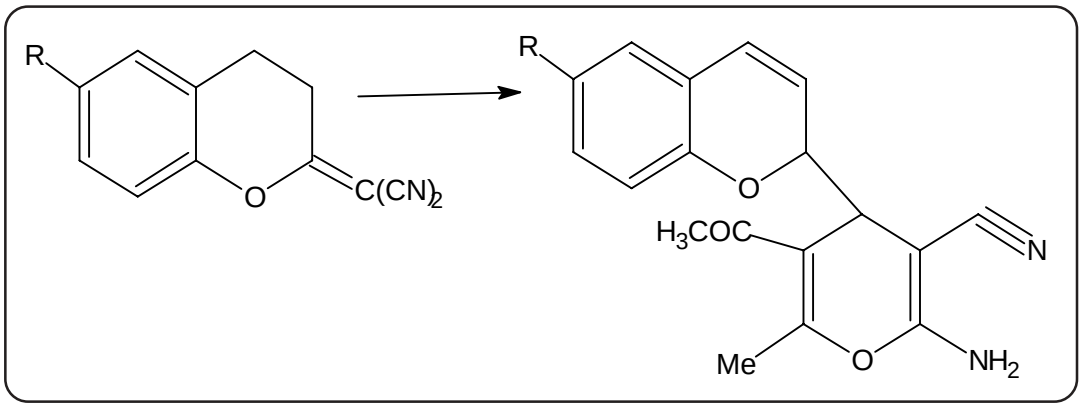

**(I)**

5. N. M. Abed and co-workers[15] have synthesized pyran derivatives, exist in equilibrium with (II) in solution.



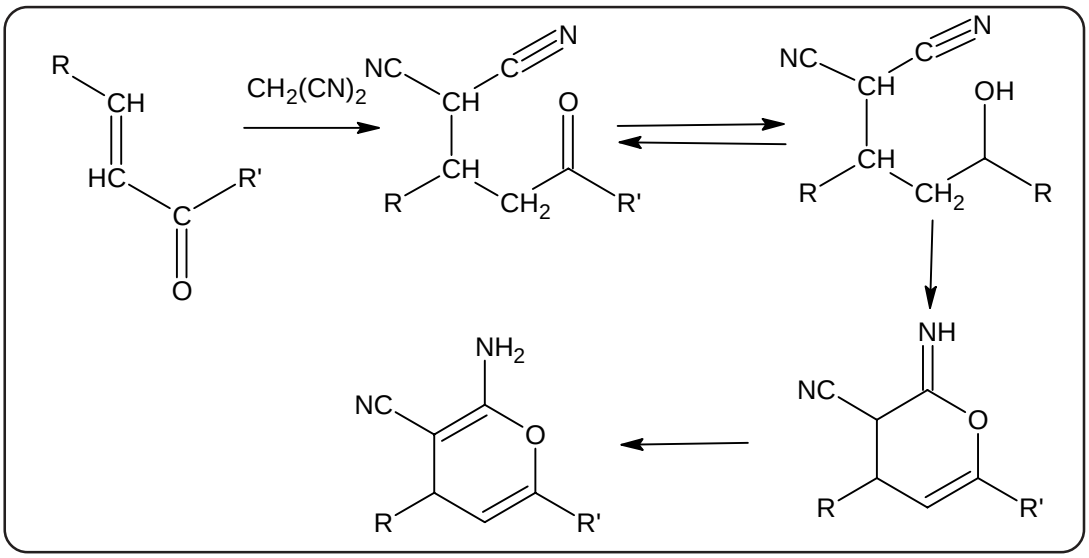

**(I)** **(II)**

6. Abdel Ghany H. et al.[16] have prepared some new pyran derivatives by condensing 2-coumarylidene malononitrile with active methylene containing compounds.




## MECHANISM

The reaction mechanism for the formation of pyran derivative proceeds through Michael addition of an active methylene of malononitrile to the β- carbon atom of chalcone.



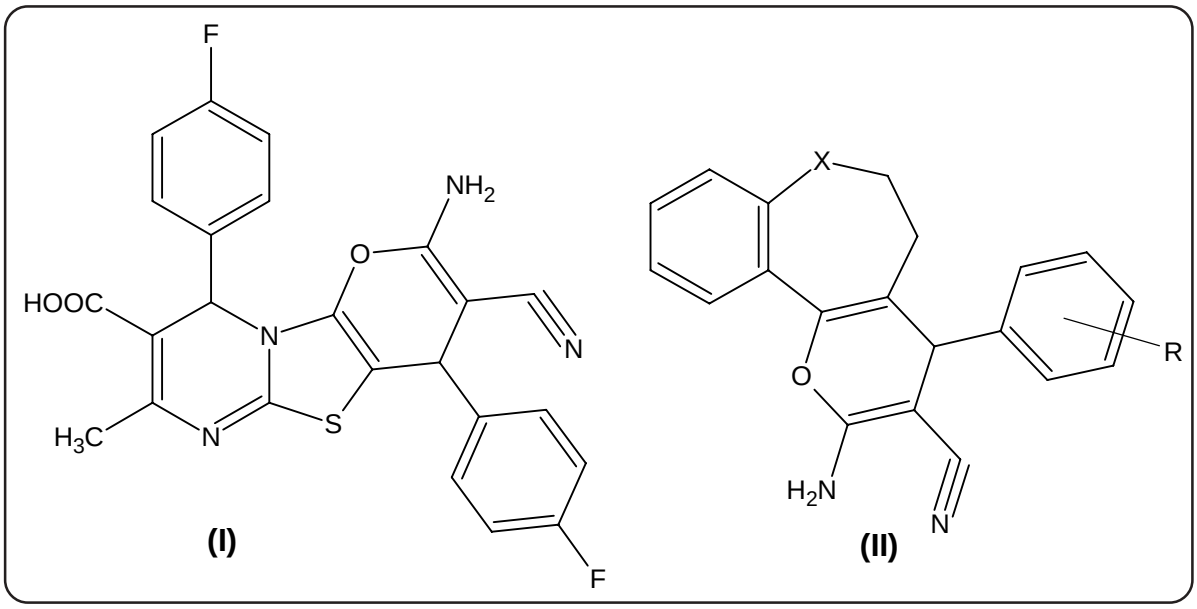

## THERAPEUTIC IMPORTANCE

Functionally substituted pyran derivatives show varied biological and pharmacological properties.

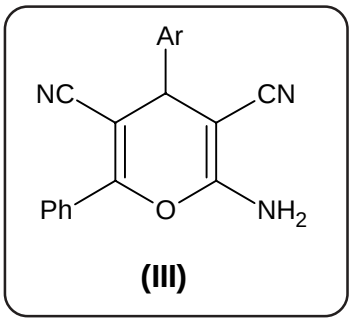
1. Antiallergic[17]
2. Antitumor[18]
3. Antifungal[19]
4. AntiHIV[20]
5. Antagonist[21,22]

6. Analgesic[23]
7. Antiinvasine[24]
8. Antiasthmatic[25]
9. Antimicrobial[26]
10. CNS active agent[27]
11. Antipyretic[28]

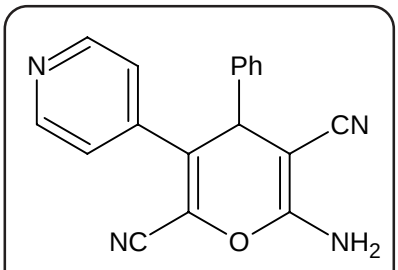
El Gaby Mohamed S. and co-workers[29] described the synthesis and anticancer activity of pyran containing fluorine (I) and (II), to enhance the anticancer and anti HIV activity.




Elassar A.Z. et al.[30] have prepared some new cyanopyran derivatives (III) exhibiting *in vitro* antifungal and antibacterial activity.




Krauze A. et al[31] have prepared 2-amino -4-H pyran (IV) exhibiting cardiotonic activity.




**(IV)**

More ever, sonker R. M.[32] have synthesized some new 2-amino-3-cyano pyran derivatives, possessing antibacterial and antifungal activity containing coumarin heterocycles. Fathy F. Alddet hatif et al.[33] and Piao-minz-zhu et al.[34] have reported the synthesis of pyran derivatives and studied their biological activity.

Tomich faul et al.[35] have also reported the anti HIV activity of some pyran derivativeds.Antitumor activity of some pyran derivative was reported by Nobble stuart A.[36] Long teans[37] have prepared some cyano pyran derivative as gastric acid secretion inhibitors. Adrinolytic activity was described by kossakowshi zery et al.[38]

Further more, some of the pyran derivatives have been patented for their use as inhibitors of cell proliferation[39], anti hypertensive[40], antitumor[41], antagonists[42], [43] and antiviral[44] agents.

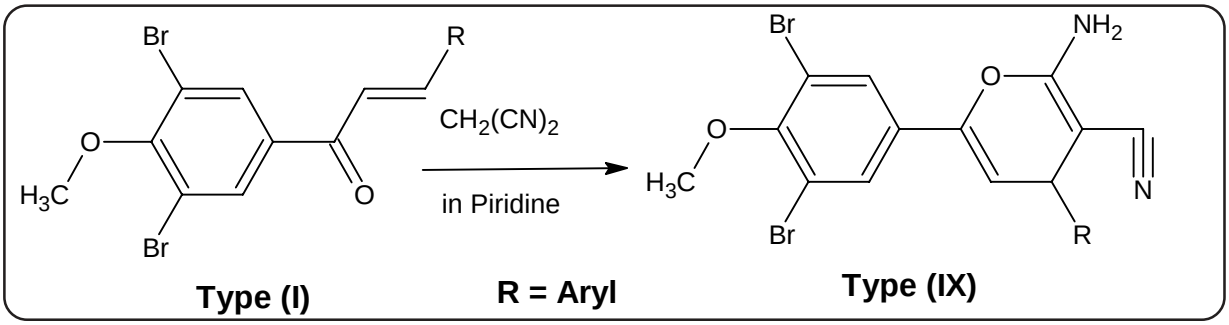
These observations prompted us to combine this nucleus into 4-methoxy-3,5-dibromo acetophenone so as to enhance the overall activities of resulting moiety, which have been described as under

## SECTION - I SYNTHEIS AND BIOLOGICAL SCREENING OF 2-AMINO-3-CYANO-6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-PYRANS.

# SECTION - I

## SYNTHESIS AND BIOLOGICAL SCREENING OF 2-AMINO-3-CYANO-6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-PYRANS

Cyano pyran derivatives have been found to be associated with various pharmacological activities. These findings encouraged us to synthesise, some novel 2-amino-3-cyano-6-(3,5-dibromo-4-methoxyphenyl)-4-aryl-pyrans derivatives of type (IX) by the cyclocondensation of (2E)-1-(3,5- dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones of type-(I), with malononitrile in pyridine.

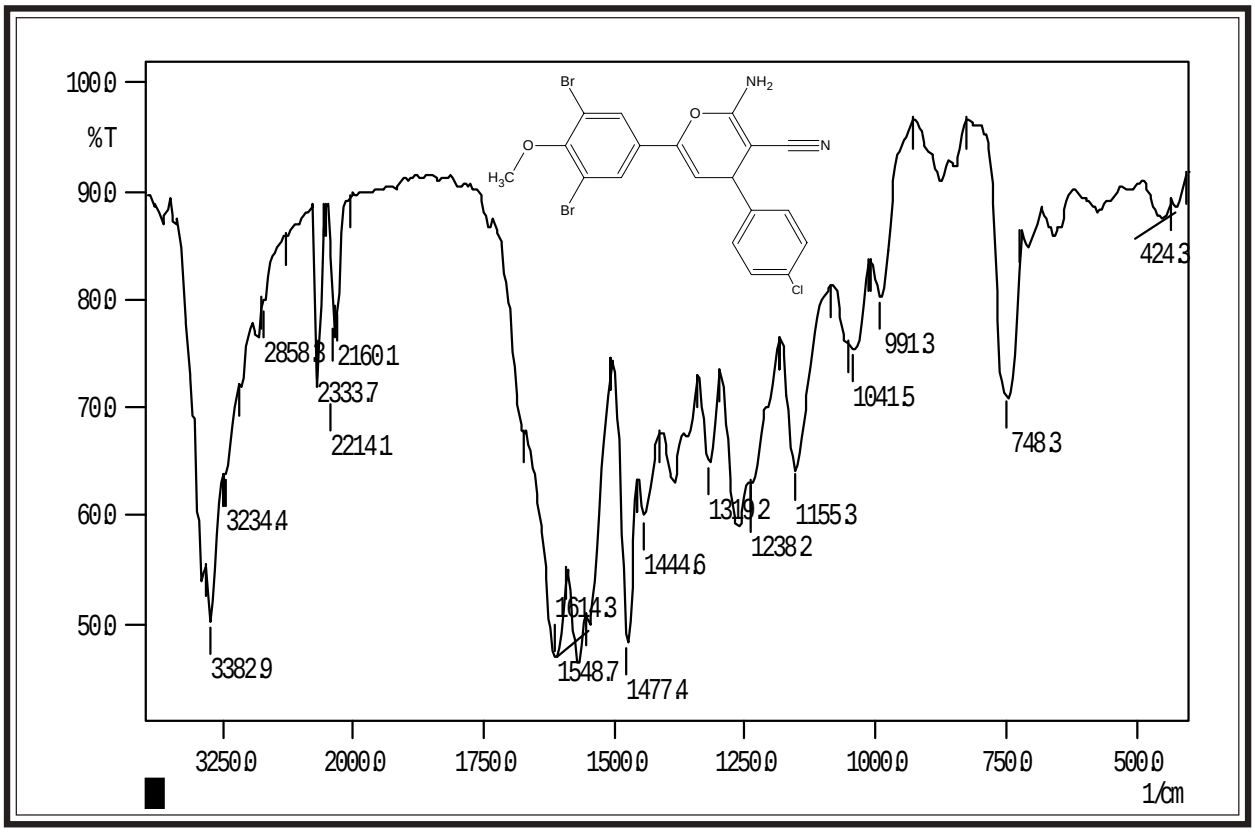



**Type (I)** **R = Aryl** **Type (IX)**

The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and $^1H$ nuclear magnetic resonance spectroscopy and farther 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.

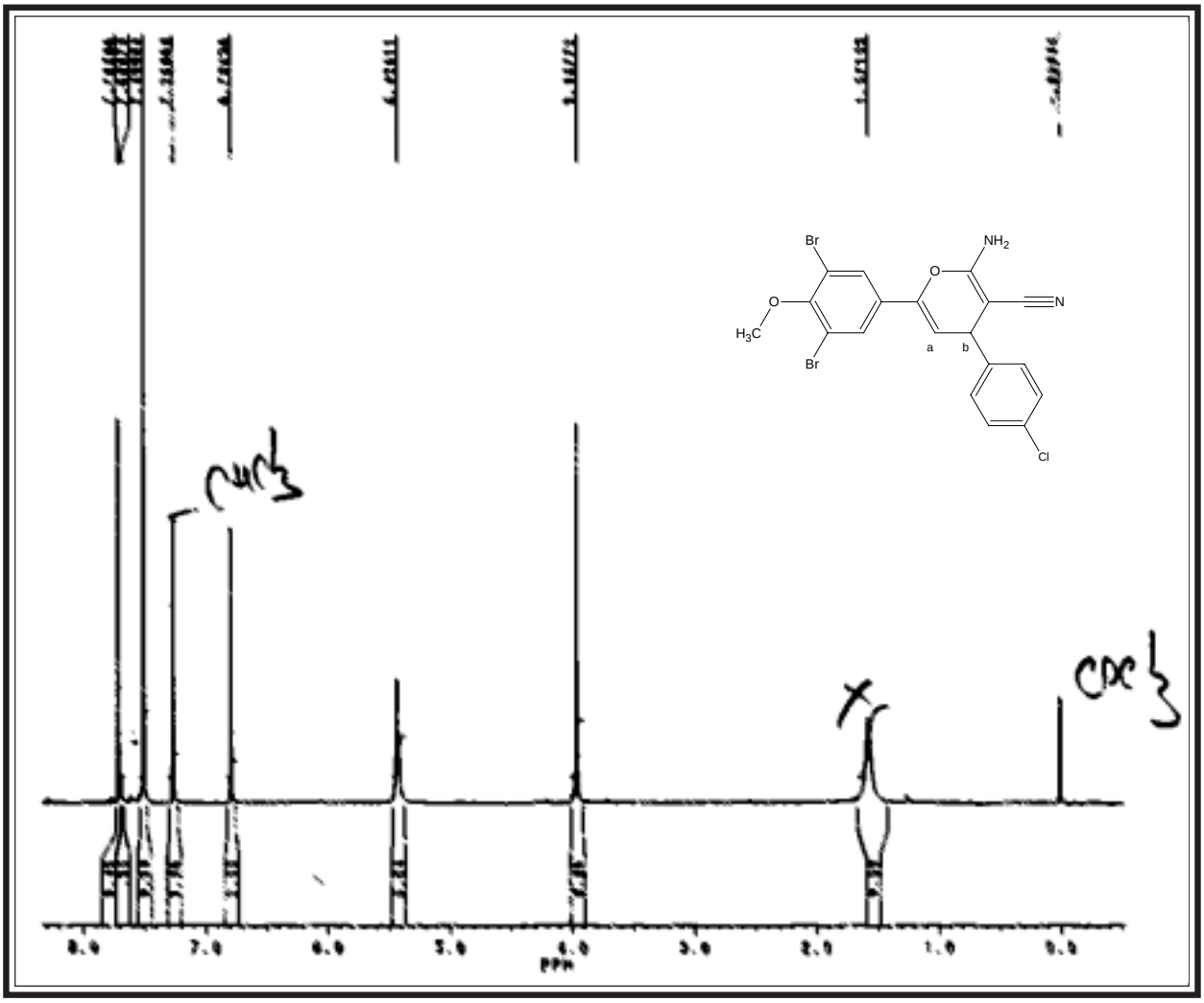
**IR spectral studies of 2-Amino-3-cyano-6-(3,5-dibromo-4-methoxyphenyl)-4-(4-chorophenyl)-pyran**




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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2930 | 2975-2950 | 44 |
| $-CH_3$ | C-H str.(sym.) | 2858 | 2880-2860 | " |
| | C-H def.(asym.) | 1440 | 1470-1435 | " |
| | C-H def.(sym.) | 1360 | 1390-1370 | " |
| Aromatic | C-H str. | 3060 | 3090-3030 | 45 |
| | C=C str. | 1477 | 1540-1480 | " |
| | | 1155 | 1125-1090 | " |
| Halide | C-Br str. | 550 | 600-500 | 44 |
| Ether | C-O-C str.(sym) | 1238 | 1275-1200 | " |
| Pyran | C=C str. | 1614 | 1650-1520 | 45 |
| Nitrile | C=N str. | 2214 | 2240-2120 | " |
| Amine | N-H str. | 3382 | 3380-3350 | " |

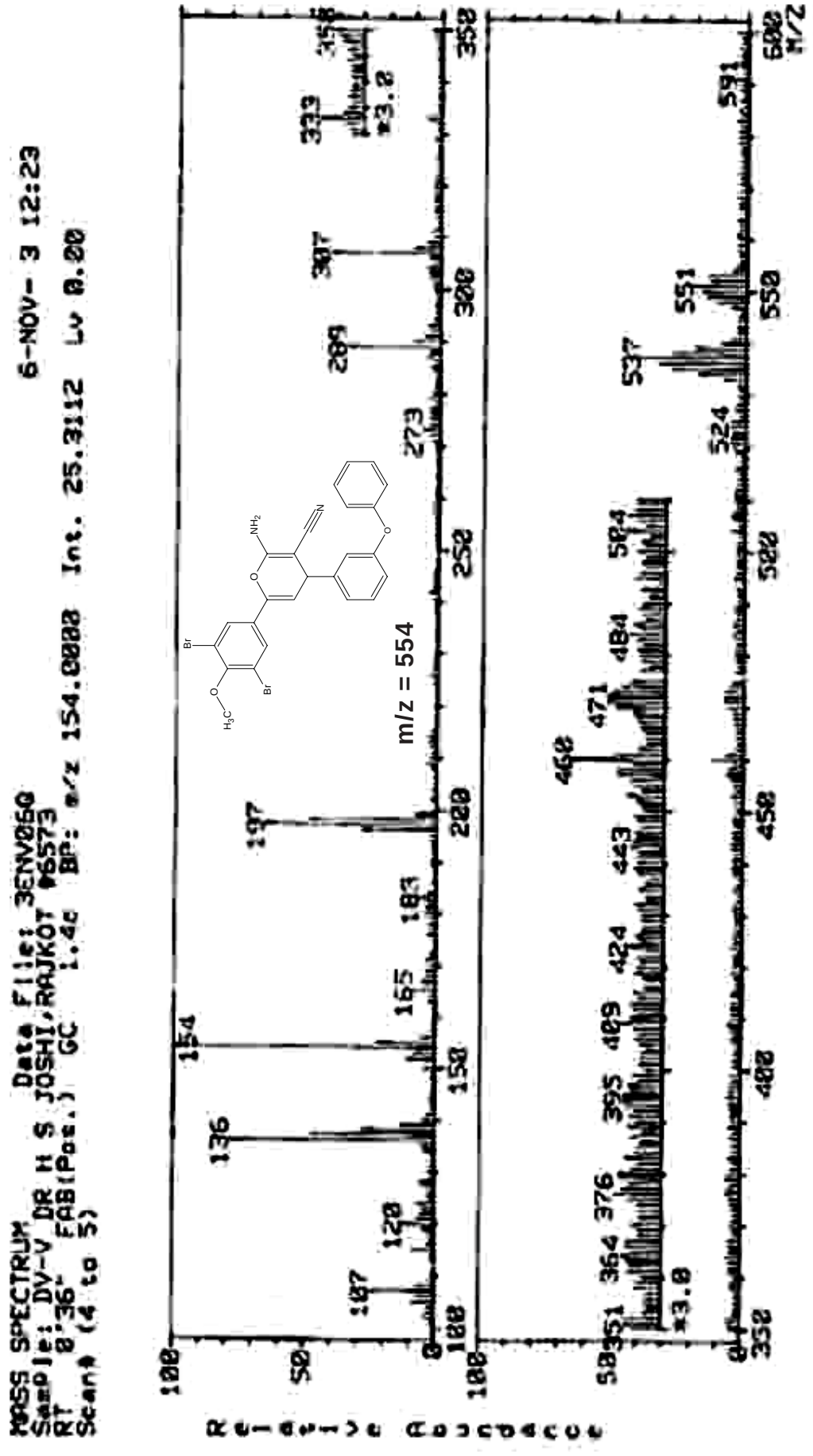
## NMR SPECRAL STUDIES OF 2-AMINO-3-CYANO-6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-(4-CHOROPHENYL)-PYRAN




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

| Signal No. | Signal Position (δ ppm) | Relative No. of Proton | Multiplicity | Inference |
|---|---|---|---|---|
| 1. | 3.95 | 3H | singlet | Ar-$OCH_3$ |
| 2. | 5.42 | 2H | singlet | -$NH_2$ |
| 3. | 6.75-6.78 | 1H | doublet | -Hb |
| 4. | 7.25-7.28 | 1H | doublet | -Ha |
| 5. | 6.81-7.70 | 6H | multiplet | Ar-H |

MASS spectral studies of 2-Amino-3-cyano-6-(3,5-dibromo-4-methoxyphenyl)-4-(3-phenoxyphenyl)-pyran



## EXPERIMENTAL

### SYNTHESIS AND BIOLOGICAL SCREINING OF 2-AMINO-3-CYANO-6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-PYRANS

**(A) Synthesis of (2E)-1-(3,5-dibromo-4-methoxy phenyl)-3-aryl-prop-2-en-1-ones**

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

**(B) Synthesis of 2-Amino-3-cyano-6-(3,5-dibromo-4-methoxyphenyl)-4-(4-chorophenyl)-pyran**

A mixture of (2E)-1-(3,5-dibromo-4-methoxyphenyl)-3-(4-chlorophenyl)-prop -2-en-1-one (4.30gm, 0.01 mol) and malononitrile (0.66gm, 0.01 mol) dissolved in pyridine (20 ml) was heated under reflux for 10 hrs. on oilbath. The reaction mixture was cooled and poured on to crushed ice. The residue was neutralized with 20% HCl, where upon a solid separated out, which was filtered and crystallized from ethanol. Yield 70%, m.p.130 $^{o}$C Anal. Calcd. for $C_{19}H_{13}Br_2ClN_2O_2$; Requires: C,45.96; H, 2.64; N, 5.64 %; Found: C, 45.98; H,2.71; N, 5.58%.

Similarly, other 2-amino-3-cyano-6-(3,5-dibromo-4-methoxyphenyl)-4-aryl-pyrans were prepared. The physical data and recorded in Table No.9

**(C) Biological screening of 2-Amino-3-cyano-6-(3,5-dibromo-4-methoxy phenyl)-4-aryl-pyrans**

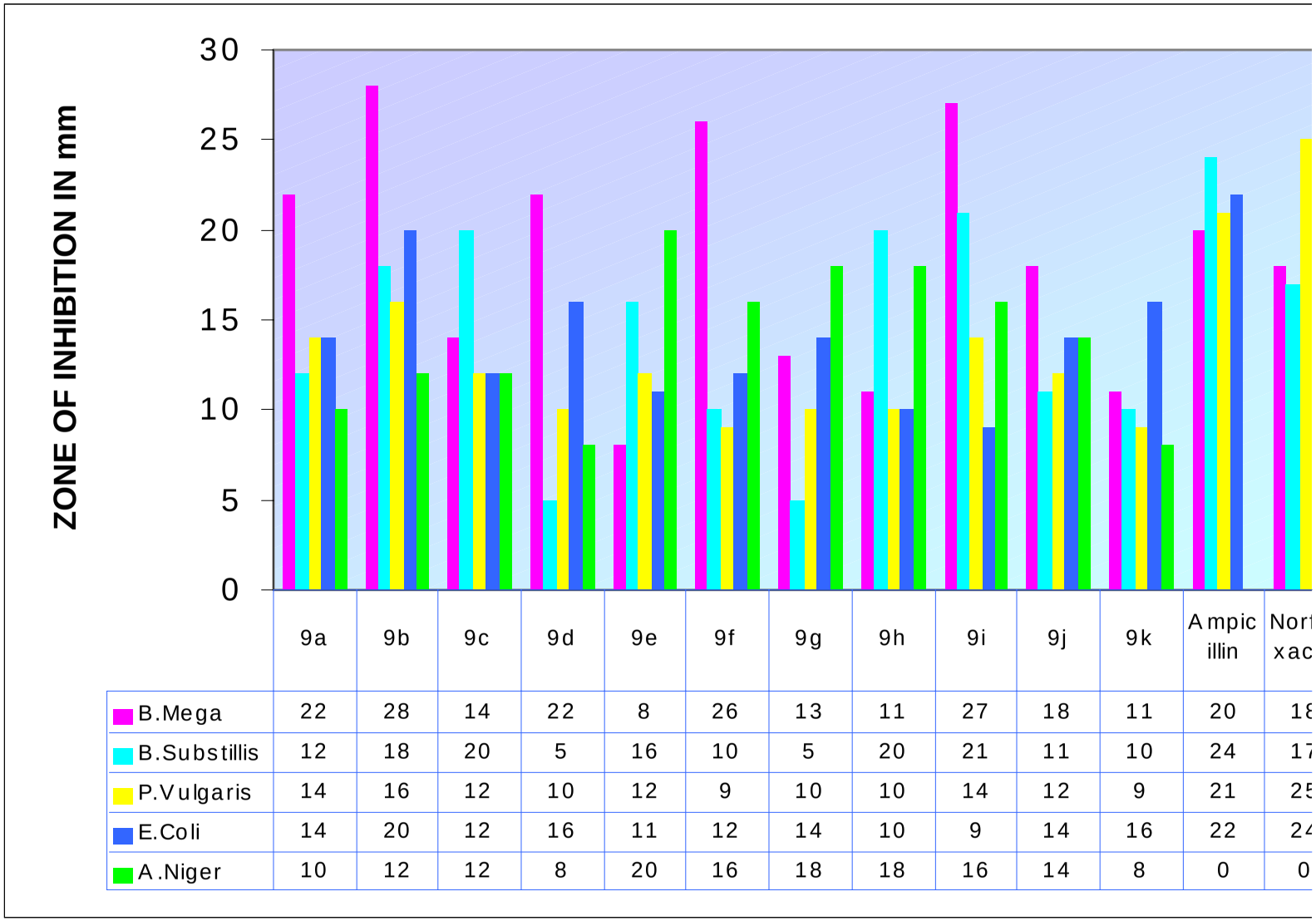
Antimicrobial testing were carried out as described in Part-I, Section-I(D). The zones of inhibition or test solution are recorded in Graphical Chart No.9

**TABLE-9 : PHYSICAL CONSTANTS OF 2-AMINO-3-CYANO-6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-PYRANS.**

| Sr. No. | R | Molecular Fromula | Molecular Weight | M.P. °C | Yield % | % of Nitrogen Calcd. | % of Nitrogen Found | Rf Value | Solvent System |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 9a | $C_6H_5$- | $C_{19}H_{14}Br_2N_2O_2$ | 462.1 | 150 | 62 | 6.06 | 6.00 | 0.52 | S1 |
| 9b | 3-Br-$C_6H_4$- | $C_{19}H_{13}Br3N_2O_2$ | 541.0 | 154 | 65 | 5.18 | 5.09 | 0.67 | S1 |
| 9c | 2-Cl-$C_6H_4$- | $C_{19}H_{13}Br_2ClN_2O_2$ | 496.6 | 152 | 68 | 5.64 | 5.69 | 0.49 | S1 |
| 9d | 4-Cl-$C_6H_4$- | $C_{19}H_{13}Br_2ClN_2O_2$ | 496.6 | 130 | 70 | 5.64 | 5.55 | 0.54 | S1 |
| 9e | 4-$N(CH_3)_2$-$C_6H_4$- | $C_{21}H_{19}Br_2N_3O_2$ | 505.2 | 102 | 64 | 8.32 | 8.25 | 0.43 | S2 |
| 9f | 4-$OCH_3$-$C_6H_4$- | $C_{20}H_{16}Br_2N_2O_3$ | 496.2 | 144 | 65 | 5.69 | 5.62 | 0.65 | S1 |
| 9g | 3,4-$(OCH_3)_2$-$C_6H_3$- | $C_{21}H_{18}Br_2N_2O_4$ | 522.2 | 230 | 70 | 5.32 | 5.40 | 0.50 | S2 |
| 9h | 2-$NO_2$-$C_6H_4$- | $C_{19}H_{13}Br_2N_3O_4$ | 507.1 | 300 | 55 | 8.29 | 8.22 | 0.62 | S2 |
| 9i | 3-$NO_2$-$C_6H_4$- | $C_{19}H_{13}Br_2N_3O_4$ | 507.1 | 100 | 58 | 8.29 | 8.35 | 0.64 | S2 |
| 9j | 3-$OC_6H_5$-$C_6H_4$- | $C_{25}H_{18}Br_2N_2O_3$ | 554.2 | 60 | 60 | 5.05 | 5.10 | 0.51 | S2 |
| 9k | $C_4H_3O$- | $C_{17}H_{12}Br_2N_2O_3$ | 452.1 | 224 | 65 | 6.20 | 6.12 | 0.44 | S2 |

S1 =Acetone: Benzene (2:8), S2= Acetone: Benzene (2.5:7.5)

## GRAPHICAL CHART NO. 9 : 2-AMINO-3-CYANO-6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-PYRANS.




| | 9a | 9b | 9c | 9d | 9e | 9f | 9g | 9h | 9i | 9j | 9k | Ampicillin | Norfxac |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B.Mega | 22 | 28 | 14 | 22 | 8 | 26 | 13 | 11 | 27 | 18 | 11 | 20 | 18 |
| B.Substillis | 12 | 18 | 20 | 5 | 16 | 10 | 5 | 20 | 21 | 11 | 10 | 24 | 17 |
| P.Vulgaris | 14 | 16 | 12 | 10 | 12 | 9 | 10 | 10 | 14 | 12 | 9 | 21 | 25 |
| E.Coli | 14 | 20 | 12 | 16 | 11 | 12 | 14 | 10 | 9 | 14 | 16 | 22 | 24 |
| A.Niger | 10 | 12 | 12 | 8 | 20 | 16 | 18 | 18 | 16 | 14 | 8 | 0 | 0 |

## REFERANCES


1. Augustin M., Jeschke P.; *J. Prakt. Chem.* (1987); *Chem.Abstr.,* **111**, 7246d (1989).
2. Piao Minz Zhu, Imatuku Kimiaki; *Tetrahedron lett.,* **38(30),** 5301-62 (1997); *Chem.Abstr.,* **127,** 19659h (1997).
3. Selim Mohmed R.; Al-Azhar Bull. Sci. (1997); *Chem.Abstr.,* **130,** 110131d (1999).
4. A. Chan Seng. H. Brimble Margaret; *Aust. J. Chem.* (1998); *Chem.Abstr.,* **129,** 16105f (1998).
5. Hallet Michael R; Painteir James E.; Quayle Pter, Rickelts Deans; *Tetrahedron lett.* (1998); *Chem.Abstr.,* **129,** 16083f (1998).
6. El-Sayed Ahmed Mohmmad, Mohmed Mournir et al.; Gaz Chima Ital. (1997); *Chem.Abstr.,* **129,** 4604c (1998).
7. Hassanien A.A., Zahran M.D., El-Gaby M.S.A. Ghorab M.M.; *J. Indian Chem. Soc.,* (1999); *Chem.Abstr.,* **131,** 214249k (1999).
8. Shesto Palov Antoliy M.; Niazimbetova Zukuira l; et al.; *Heterocycles* (1999); *Chem.Abstr.,* **131,** 44172m (2000).
9. Hsung Richard P., Zificsak, Craig A., Wei-Lin Li; et al.; *J. Org. Chem.* (1999); *Chem.Abstr.,* **132,** 46557t (2000).
10. Kiokol G.V., Kalvokolysko S.G., Dya Chenko V.D., Litvinov V.P.; *Chem. Heterocycl. Compd.* (N.Y.) (1999); *Chem.Abstr.,* **133,** 43477t (2000).
11. Emorsy S.S., Habib O.M. Mutwally M.A.; An. Quim 83 (7-8), 711-13 (1993); *Chem.Abstr.,* **121,** 108724v (1994).
12. Cacchi, Sandro, Fabrizi et al.; Synlett (8), 888-890 (1998); *Chem.Abstr.,* **129,** 275811t (1998).
13. De Lero Angel R., Torrado Alicia, Rey Jose, Loper Susana; *Tetrahedron Lett.,* **38(42),** 7421-24 (1997); *Chem.Abstr.,* **128,** 13179b (1998).
14. Assay M.G., Hussanier M.M., Zaki S.A.; *Pol. J. Chem.* **69(3),** 371-375 (1995); *Chem.Abstr.,* ***123,*** 32875p (1995).
15. N. M. Abed, N. S. Ibrahim and M. H. Elnagdi; *Z. Naturforsch.,* **416** (1986), 925 *IJHC* **3,** 15-18(1993).
16. Abdel-Ghany H., Moustafa H.M., Khodairy A.; *Syth-Commun.,* **28(18),** 3431-41 (1998); *Chem.Abstr.,* **129,** 260360w (1998).

17. D.B. Shinde, M.S. Singare; *Indian J. Chem.,* **30B,** 450 (1991).

18. Wang Wori, Li Tiechou, Mibbum Robert, Yares J., Attardo Giorgio et al.; *Bio. Org. Med., Chem. Lett.* 1998; *Chem.Abstr.,* **129,** 20833s (1998).

19. Macritchie Jacqueline Anne, O'Mahony Mary Josephine, Linde Stephen Derid.; PCT *Int. Apl.* WO 98, 27, 080; *Chem. Abstr.,* **129,** 20833s (1998).

20. Boyer Frederick Earl. Jr., Domagala John Micheal. et al., *Chem.Abstr.,* **129,** 16055q (1998).

21. Galgun Ayhankicigil and Rahmiye Ertan; *J. Heterocycl. Chem.,* **35,** 1485 (1998).

22. Sahoyya Ozbey and Engin Kendi; *J. Heterocycl. Chem.,* **35,** 1485 (1998).

23. Puidgellivol Pere, Godry Elisa; *Spain ES* 511, 501.

24. Virendra S., Parmar, Subhash C. Jain, Amitabh Jha et al., *Indian J. of Chem.,* **36B,** 8762-879 (1997).

25. Zwagstra Mariel E., Korthouwer Ronald E.M. Timmerman Henk, Zhung Ming-Quinng; *Eur. J. Med. Chem.* (1998); *Chem.Abstr.,* **129,** 16039n (1998).

26. Anshu Dandio, Virender Sehgal and Pahup Singh; *Indian J. of Chem.,* **32B,** 1288-91 (1993).

27. Kulkarni Y.D., Srivastavav D., Bishnoi Ana, Dua P.R.; *J. Indian Chem. Soc.,* **73(45),** *Chem. Abstr.,* **125,** 86440c (1996).

28. Hodu E, Wiwani, Hend E, Shawawi et al., *Indian J. of Chem.,* **34(B),** 273, (1995).

29. El Gaby Mohamed S., Abd El-Aal, Abdel-Hamide Sanai G.; Ghorab Moustafa H.; *Acta. Pharm. (Zagreb)* 1999; *Chem.Abstr.,* **132,** 93278d (2000).

30. Elassar A.Z. and Abdelzaher A.; *Pharmazie,* **53(4),** 223-27 (1998); *Chem.Abstr.,* **129,** 4562q (1998).

31. Krauze, A.; Duburs. G. ; *Chemistry of Heterocyclic Compounds* **38(2),** 251-252 (2002) *Chem. Abstr.,* **137,** 352873j (2002).

32. Sonker R.M.; *Pharmizie,* **51(3),** (1996); *Chem.Abstr.,* **125,** 10762p (1996).

33. Fathy F-Alddet-Latif, Rafat M. Shaker and Nagdaa S. Abdel-Aziz; *Heterocyclic Communica tion,* **3,** 245-252 (1997).

34. Pio Minz Zhu, Imafaka Kimaki; *Chem.Abstr.,* **127,** 19065h (1997).

35. Tomichfaul Kasta, Bohanon Micheal Turner, Stevan Ronald, David Dohn et al.; *Eur. Pat. Appl.* WO 807, 629; *Chem.Abstr.,* **128,** 34684c (1998).

36. Nobble Stuart A; Attardo Giorgio; *Bio. Org. Med. Chem. Lett.* (1998); *Chem.Abstr.,* **129,** 202833s (1998).

37. Long teans J. Chem., gerlach Vwe, Hropt max; *Eur. Pat. Appl*. EP 807, 629; *Chem.Abstr.,* **128,** 34684c (1998).

38. Kossakowshi Zerzy, Zawadowski Teodar, Suski Slawomir; *Acta Pol. Pharm.* 1998; *Chem.Abstr.,* **129,** 230614q (1998).

39. Dell Colin Peter, Williams Andrew Carwyn; *Eur. Pat. Appl.* EP 599, 514; *Chem.Abstr.,* 168765j (1994).

40. Milcy Jehan A.A.; Sharaf hammonda H.; *Indian J. Chem. Soc. B. Org. Chem. Incl. Med. Chem.* (1998); *Chem.Abstr.,* **129,** 95421g (1998).

41. Alkama Tsutomu, Veno Kiminisha; Synthesis (1997); *Chem.Abstr.,* **128,** 14002e (1998).

42. Fujimoto Katsuel; Mikoshifa Ishama, Tanaka Matsuki, Iwano Yaji; Isima; *Jpn Kokai Tokkyo Koho* JP 09, 301, 915, *Chem.Abstr.,* **128,** 131479 (1998).

43. Jacobson Kenneth A.; Jiang Ji-long, Kim Young Chai et al.; *PCT Int. Apl.* WO 97, 27,177 (1996); *Chem. Abstr.,* **127,** 19065y (1997).

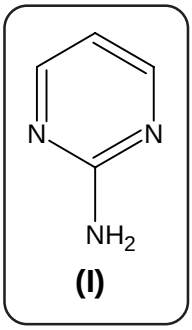
44. Jo Jue Chon, Kum Sung Jin, Morikawo Kazuwi; *PCT Int. Apl.* WO 98 23, 916 *Chem. Abstr.,* **129,** 81667q (1998).

45. A Handbook of Spectroscopic data by B.D.Mishtry; $^{1}$st ed. ABD press Jaipur 11-36(2000)., "Absorption Spectroscopy of Organic Compounds", by V.M.Parikh, *addision-Wesley Pub. co., London*, 243-258(1978).

46. Introduction to Infrared and Raman Spectroscopy by Nurmav B. Colthup, Lowrence H-Daly and Stephene E. Wiberluy, *Academic Press*(1975).

## INTRODUCTION

2-Amino pyrimidine is the most important member of all the diazines, as the ring system occurs widely in living organisms. Gabriel and colman first isolated pyrimidine in 1899. 2-Amino pyrimidine and its derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activities.




**(I)**

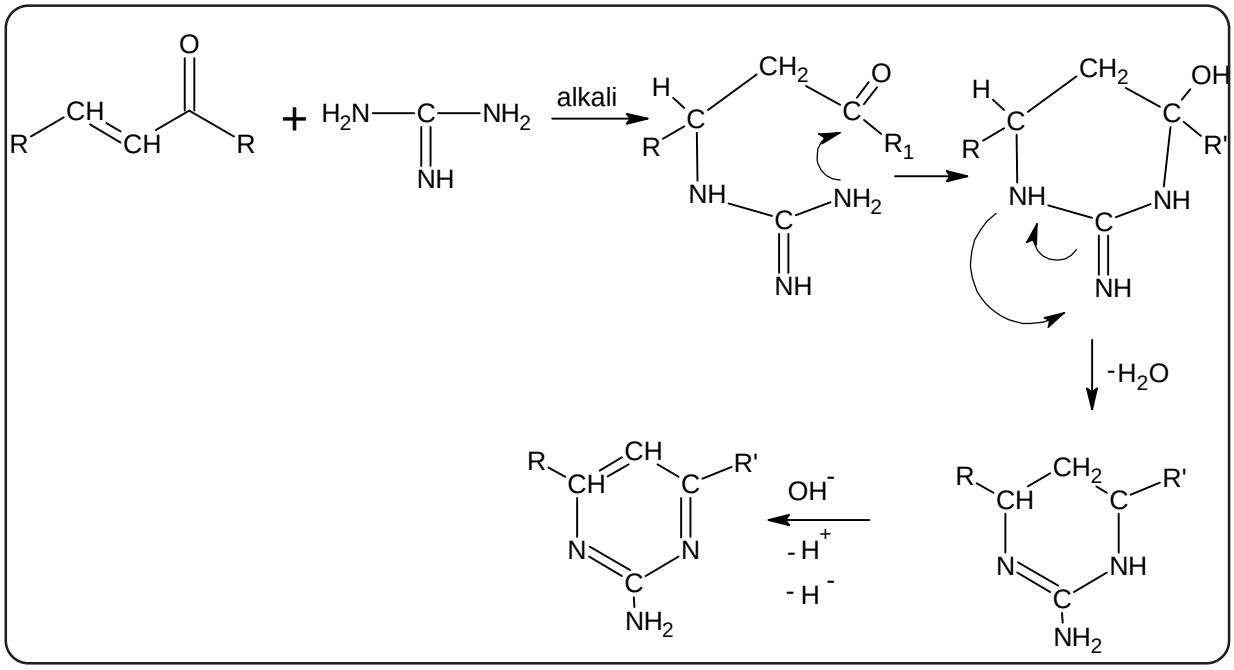
## SYNTHETIC ASPECT

Synthesis of 2-amino pyrimidines have been described in literature[1-3] some of them are as under.

1. Abd-El-Galil E. Amr[4] synthesised amino pyrimidine by the reaction of chalcone with guanidine hydrochloride in presence of sodium hydroxide.
2. Rasaki Abayomi Osisany[5] synthesised 2-amino pyrimidines by the reaction of chalcone epoxide with guanidine carbonate in xylene.
3. B. K. Karale et al.[6] have prepared 2-amino pyrimidines from schiff bases of 3-formyl chromones.
4. Taylor, Edward C. et al.[7] have reported an expenditions synthesis of 2-amino-4-(3H)-oxo-5H-pyrrolo-[3,a-d]pyrimidine(g-duaza guanine)

## REACTION MECHENISM

The following mechanism seems to be operable for the condensation of chalcones with guanidine hydrochloride in presence of alkali.

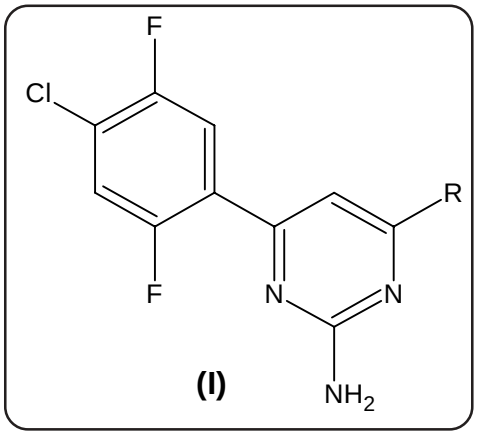



## THERAPEUTIC IMPORTANCE

2-Amino pyridines are associated with different biological activities[8-12].

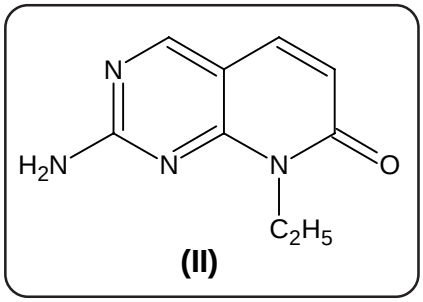
1. Antimalarial[13]
2. Antimicrobial[14]
3. Antibacterial[15]
4. Antidiabetic and Antitumor[16]
5. Analgesic[17]
6. Musscle relaxant[18]
7. Fungicidal[19]
8. Tranquilizing[20]

Moreover Devi. F. Sree and co-workers[21] have synthesised, pyrimidine derivatives (I) which is useful as active antibacterial compound.



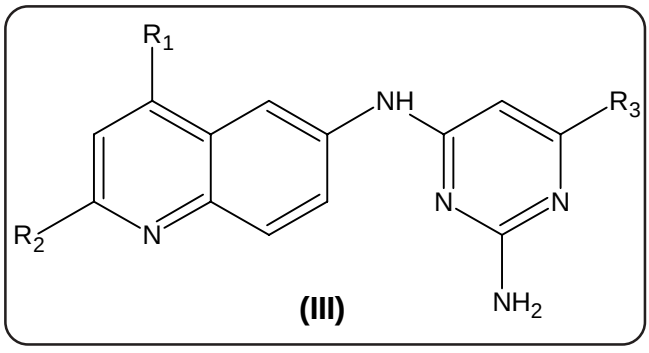

**(I)**

Zimmermann Juerg[22] synthesised some amino pyrimidine derivatives and reported their use in therapy of tumoral diseases. Boschelli Diane harries et al.[23] have documented some amino pyrimidine derivatives (II) as inhibitor of cellular proliferation.



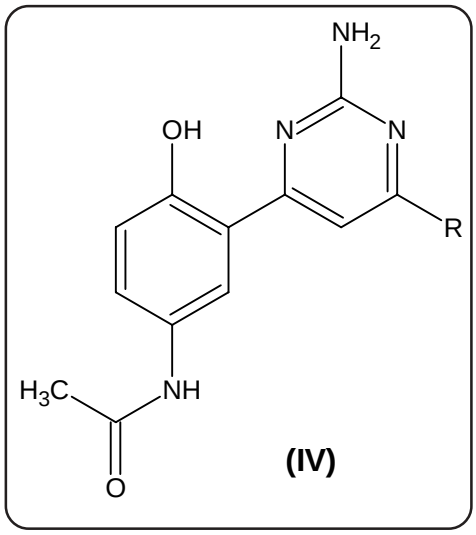

**(II)**

Chaudhari and co-workers[24] have prepared N-6-(2-amino pyrimidin-4-yl)-quinoline-4,6-diamines. (III) as N-type calcium channel antagonists for treatment of pain.



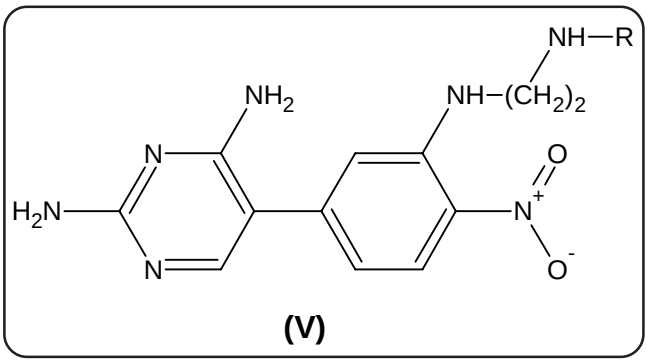

**(III)**

Patil L. R. and co-workers[25] synthesised some new pyrimidines bearing paracetamol and imidazolyl moieties (IV).




**(IV)**

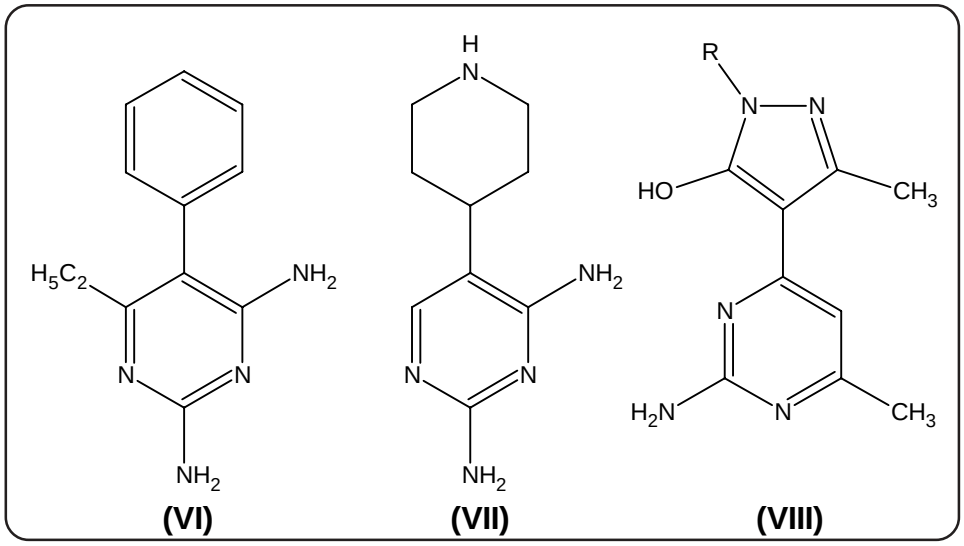
Robson, clative et al.[26] have prepared amino pyrimidine derivatives (V) as novel fluorescent, antifolate agent, pap and MRP-over expressing tumor cell lines.




**(V)**

Henrie, Robert N. and co-workers[27] have synthesised amino pyrimidines, useful as active ingredients in insecticidal and acaricidal compounds, Hisaki Masakatsu and co-workers[28] have prepared some amino pyrimidines as antirota viral agent, useful for the prophylaxis and in infant diarrhea. Jean-Paul et al.[29] have reported some amino pyrimidine derivatives as dopamine D4 - antagonists.

As described earlier, so many drug constitute an amino pyrimidine ring system, some well known drugs are Minoxidil[30] (VI) is an effective hypotensive agent, Ormetraprim (VII) is an antibacterial agent, Pyrimethamine and Trimethoprim[31] are antimalarial agents




**(VI)** **(VII)** **(VIII)**

Further more, Shir P. Shingh et al.[32] have reported the antimicrobial activity of 4-(4-pyrazoly)-2-aminopyrimidine derivatives (VIII). Kothari Seema[33] have synthesised some amino pyrimidines and tested their antibacterial and herbicidal activity.

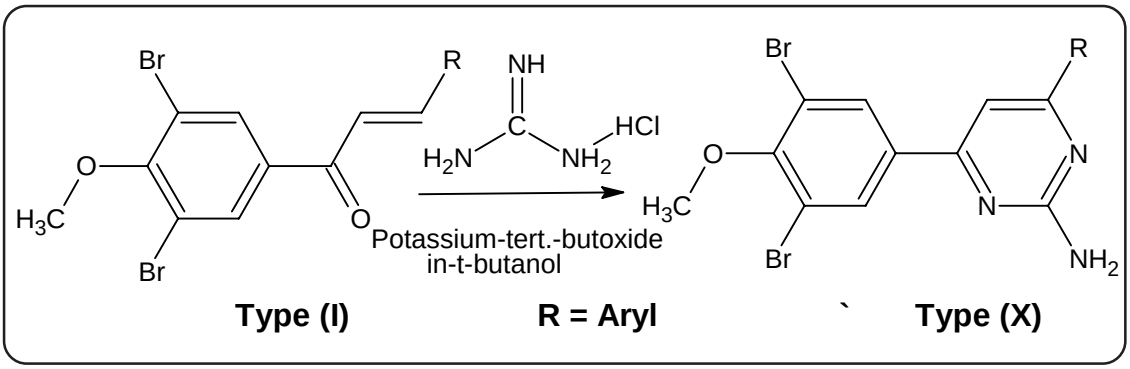
Amino pyrimidine derivatives show varied biological and pharmacological properties. Therefore, in view of this interesting finding, the synthesis of 2-amino pyrimidine has been under taken as described as under.

## SECTION - I SYNTHESIS AND BIOLOGICAL SCREENING OF 4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-PYRIMIDINE-2-AMINES

# SECTION I

## SYNTHESIS AND BIOLOGICAL SCREENING OF 4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-PYRIMIDINE-2-AMINES

Compounds containing pyrimidine ring are widely distributed in nature. Many amino pyrimidine derivatives are reported to possess different biological activities. In view of these report; it was considered, worthwhile to synthesize some new 4-(3,5-dibromo-4-methoxyphenyl)-6-aryl-pyrimidine-2-amines of type- (X) to study their biological activities. Amino pyrimidine derivatives have been prepared by the reaction of the chalcones of type- (I) with guanidine hydrochloride in presence of potassium tertiary-butoxide in tertiary-butanol shown as under.

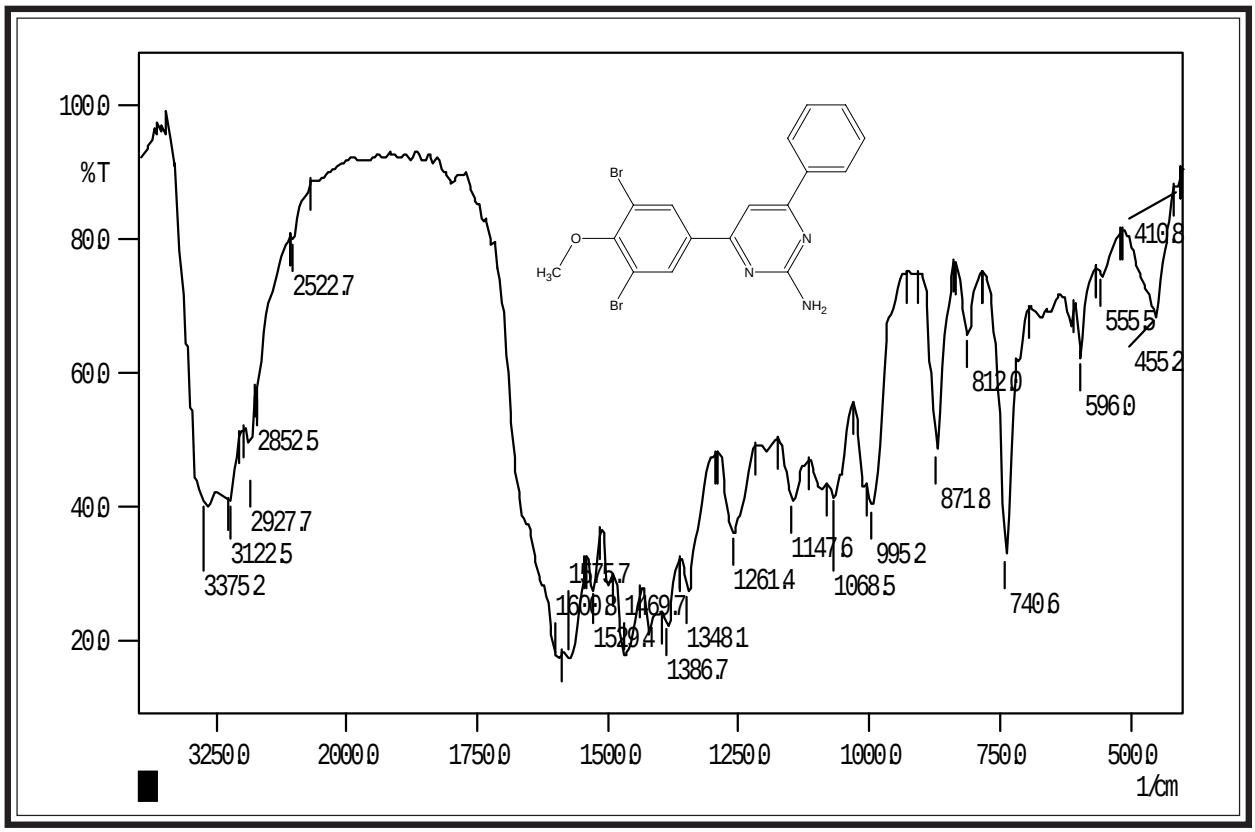



**Type (I)** **R = Aryl** **Type (X)**

The structure elucidation of synthesized compounds has 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.

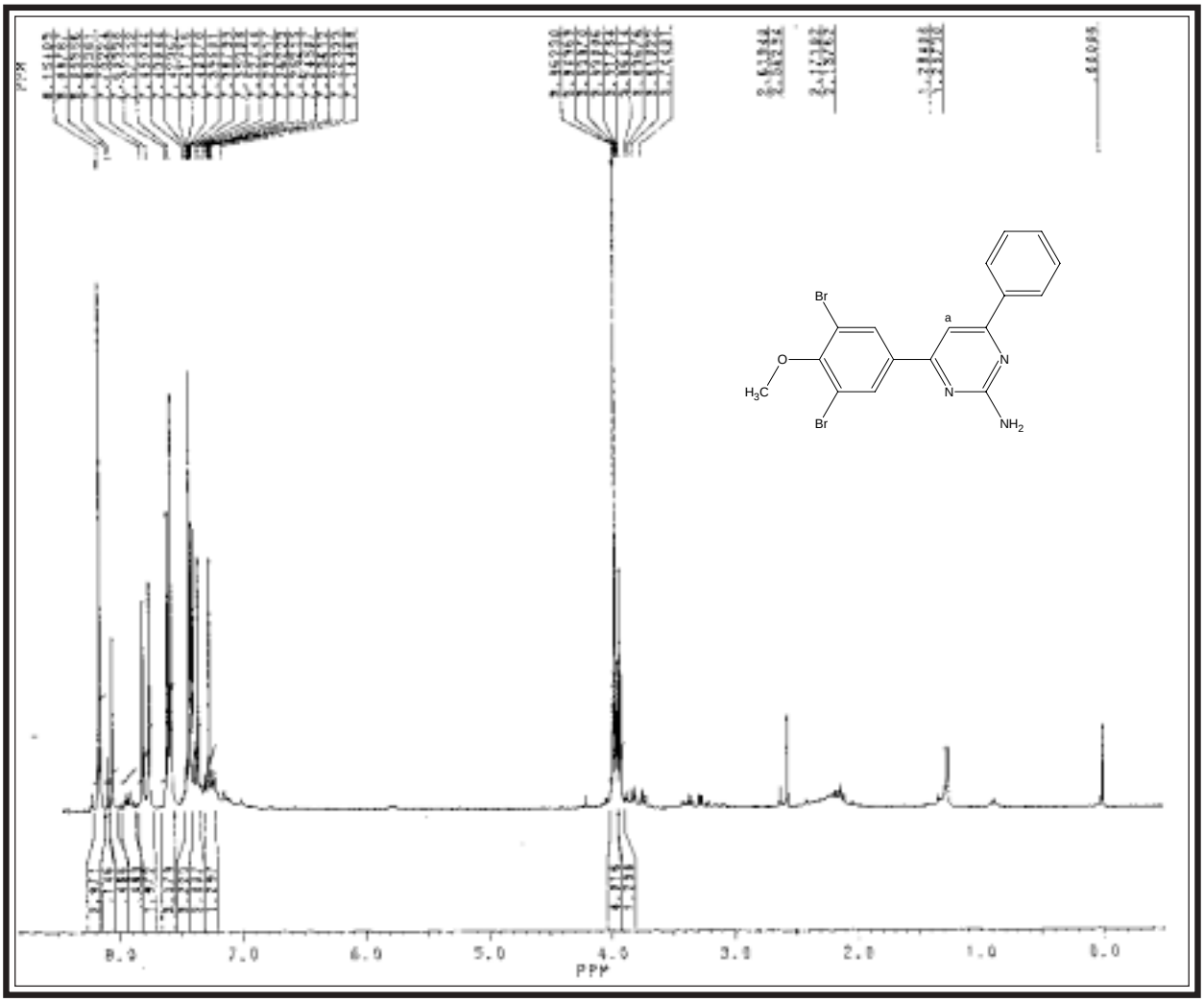
**IR spectral studies of 4-(3,5-Dibromo-4-methoxy phenyl)-6-phenyl pyrimidine-2-amine**




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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2927 | 2975-2950 | 34 |
| $-CH_3$ | C-H str.(sym.) | 2852 | 2880-2860 | " |
| | C-H def.(asym.) | 1469 | 1470-1435 | " |
| | C-H def.(sym.) | 1386 | 1390-1370 | " |
| Aromatic | C-H str. | 3122 | 3090-3030 | 35 |
| | C=C str. | 1529 | 1540-1480 | " |
| | | 1147 | 1125-1090 | " |
| Ether | C-O-C str.(sym) | 1261 | 1275-1200 | 34 |
| Amine | $NH_2$- str. | 3375 | 3559-3350 | " |
| Pyrimidine | C=N str. | 1575 | 1580-1520 | 35 |
| Halide | C-Br str. | 596 | 600-500 | " |
| | C-Cl str. | 740 | 600-800 | " |

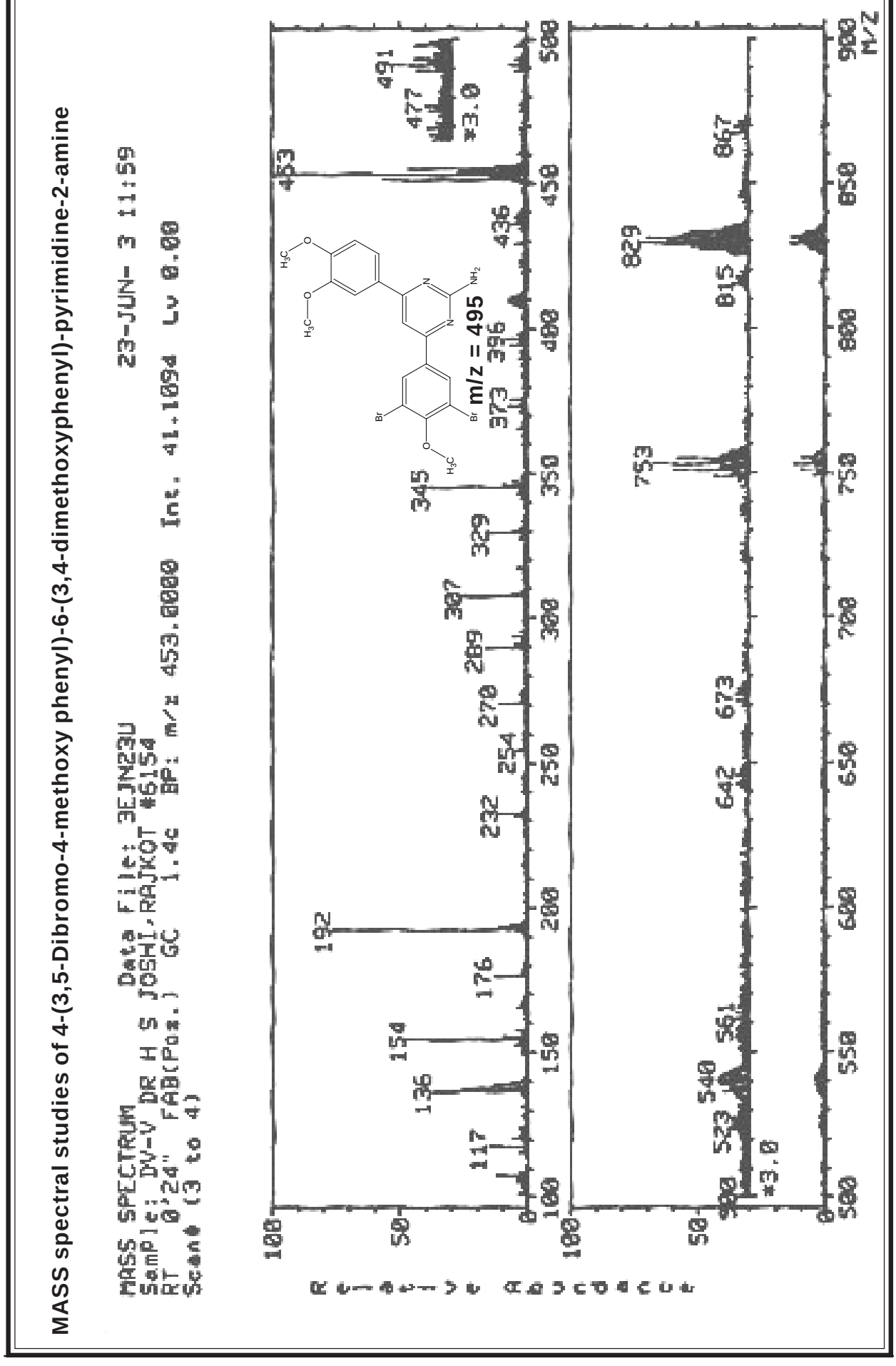
## NMR SPECTRAL STUDIES OF 4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-PHENYL-PYRIMIDINE-2-AMINE




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

| Signal No. | Signal Position (δ ppm) | Relative No. of Proton | Multiplicity | Inference |
|---|---|---|---|---|
| 1. | 3.96 | 3H | singlet | Ar-$OCH_3$ |
| 2. | 7.14 | 1H | singlet | -Ha |
| 3. | 7.22-7.52 | 7H | multiplet | Ar-H |
| 4. | 8.15 | 1H | singlet | -$NH_2$ |

**MASS spectral studies of 4-(3,5-Dibromo-4-methoxy phenyl)-6-(3,4-dimethoxyphenyl)-pyrimidine-2-amine**



# EXPERIMENTAL

## SYNTHESIS AND BIOLOGICAL SCREENING OF 4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-PIRIMIDINE-2-AMINES

### (A) Synthesis of (2E)-1-(3,5-Dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones

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

### (B) Synthesis of 4-(3,5-Dibromo-4-methoxy phenyl)-6-(4-chlorophenyl)-pyrimidine-2-amine

A mixture of (2E)-1-(3,5-Dibromo-4-methoxyphenyl)-3-(4-chlorophenyl)-pyrimidine-2-amine (4.3 gm 0.01 mol) and guanidine hydrochloride (1.10gm, 0.01 mol) was refluxed in potassium-t-butoxide (11.2gm, 0.01 mol) in t-butanol (20ml) on a water bath for 4-5 hours. The solvent was evaporated and the residue was neutralized with 20% HCl, the separated solid was filtered out and crystallized from ethanol. Yield 62%, m.p. $156^0$C, Anal. Calcd. for $C_{17}H_{12}Br_2ClN_3O$; C, 43.48; H, 2.58; N, 8.95; Found: C, 43.55; H, 2.50; N, 8.89 %.

Similarly, other 4-(3,5-dibromo-4-methoxyphenyl)-6-aryl-pyrimidine-2-amines were prepared. The physical data are recorded in Table No.10

### (C) Biological screening of 4-(3,5-dibromo-4-methoxyphenyl)-6-aryl-pyrimidine-2-amines

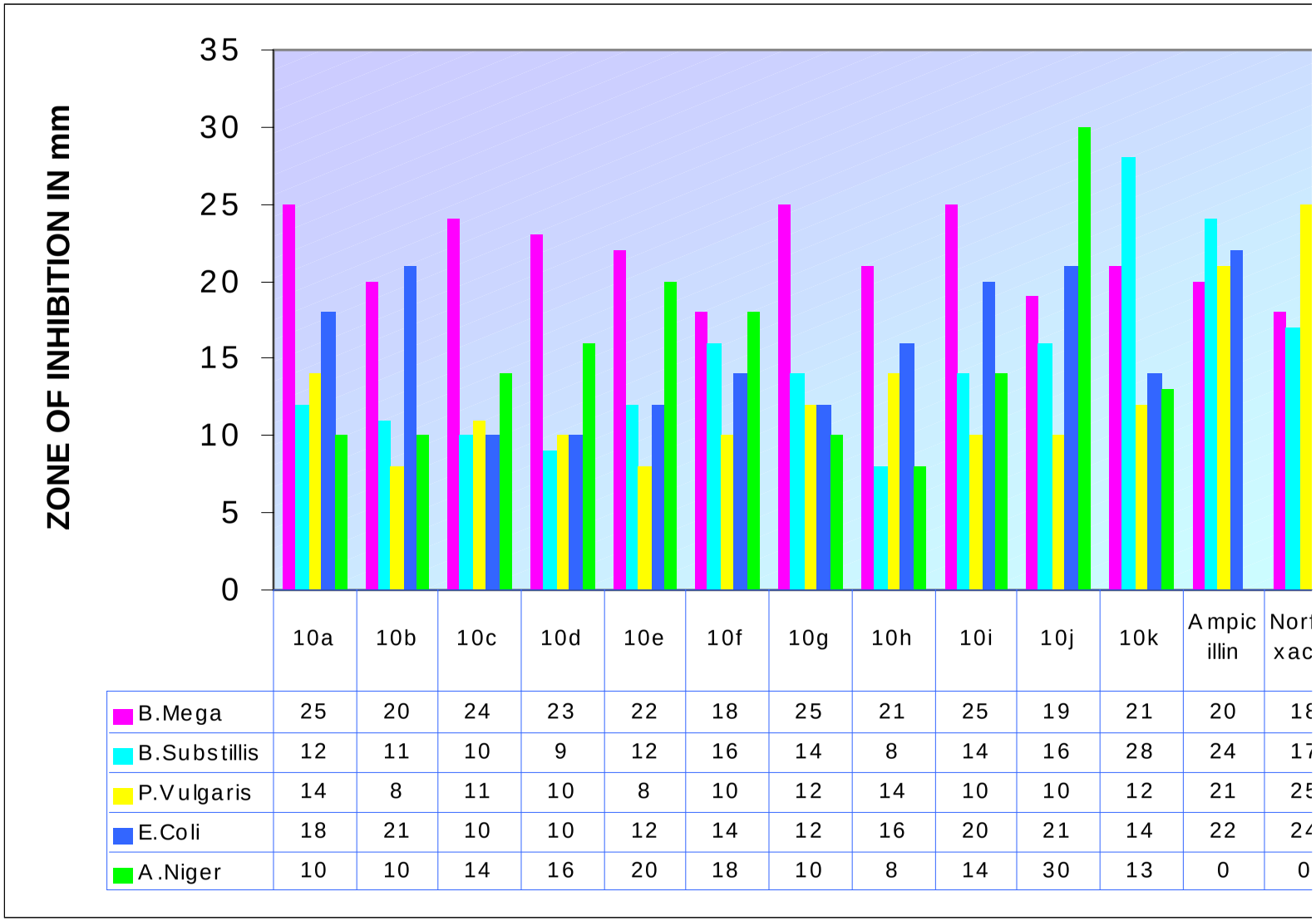
Antimicrobial testing were carried out as described in Part-I Section-1 (D). The zones of inhibition of test solution are recorded in Graphical Chart No.10

## TABLE-10 : PHYSICAL CONSTANTS OF 4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-PYRIMIDINE-2-AMINES.

| Sr. No. | R | Molecular Fromula | Molecular Weight | M.P. °C | Yield % | % of Nitrogen Calcd. | % of Nitrogen Found | Rf Value | Solvent System |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 10a | $C_6H_5$- | $C_{17}H_{13}Br_2N_3O$ | 435.1 | 164 | 58 | 9.66 | 9.57 | 0.50 | S2 |
| 10b | 3-Br-$C_6H_4$- | $C_{17}H_{12}Br_3N3O$ | 514.0 | 198 | 60 | 8.17 | 8.25 | 0.47 | S2 |
| 10c | 2-Cl-$C_6H_4$- | $C_{17}H_{12}Br_2ClN_3O$ | 469.6 | 300> | 65 | 8.95 | 8.88 | 0.51 | S1 |
| 10d | 4-Cl-$C_6H_4$- | $C_{17}H_{12}Br_2ClN_3O$ | 469.6 | 156 | 62 | 8.95 | 8.89 | 0.52 | S1 |
| 10e | 4-$N(CH_3)_2$-$C_6H_4$- | $C_{19}H_{18}Br_2N_4O$ | 478.2 | 195 | 64 | 11.72 | 11.67 | 0.44 | S1 |
| 10f | 4-$OCH_3$-$C_6H_4$- | $C_{18}H_{15}Br_2N_3O_2$ | 465.1 | 300> | 61 | 9.03 | 8.95 | 0.56 | S2 |
| 10g | 3,4-$(OCH_3)_2$-$C_6H_3$- | $C_{19}H_{17}Br_2N_3O_3$ | 495.1 | 80 | 65 | 8.49 | 8.55 | 0.48 | S1 |
| 10h | 2-$NO_2$-$C_6H_4$- | $C_{17}H_{12}Br_2N_4O_3$ | 480.1 | 98 | 60 | 11.67 | 11.72 | 0.55 | S1 |
| 10i | 3-$NO_2$-$C_6H_4$- | $C_{17}H_{12}Br_2N_4O_3$ | 480.1 | 104 | 58 | 11.67 | 11.60 | 0.44 | S2 |
| 10k | 3-OC6H5-$C_6H_4$- | $C_{23}H_{17}Br_2N_3O_2$ | 527.2 | 212 | 58 | 7.97 | 8.02 | 0.39 | S1 |
| 10l | $C_4H_3O$- | $C_{15}H_{11}Br_2N_3O_2$ | 425.0 | 280 | 70 | 9.89 | 9.80 | 0.51 | S2 |

S1=Ethyl acetate: Hexane(2:8) S2=Ethyl acetate: Hexane(3:7)

**GRAPHICAL CHART NO. 9 : 4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-PYRIMIDINE-2-AMINES.**




| | 10a | 10b | 10c | 10d | 10e | 10f | 10g | 10h | 10i | 10j | 10k | Ampicillin | Norf xac |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B.Mega | 25 | 20 | 24 | 23 | 22 | 18 | 25 | 21 | 25 | 19 | 21 | 20 | 18 |
| B.Substillis | 12 | 11 | 10 | 9 | 12 | 16 | 14 | 8 | 14 | 16 | 28 | 24 | 17 |
| P.Vulgaris | 14 | 8 | 11 | 10 | 8 | 10 | 12 | 14 | 10 | 10 | 12 | 21 | 25 |
| E.Coli | 18 | 21 | 10 | 10 | 12 | 14 | 12 | 16 | 20 | 21 | 14 | 22 | 24 |
| A.Niger | 10 | 10 | 14 | 16 | 20 | 18 | 10 | 8 | 14 | 30 | 13 | 0 | 0 |

## REFERANCES


1. Y. L. N. Murthy and G. Jagmohan; *Indian J. Heterocylic Chem.,* **8,** 277-80 (1999).
2. Tominago, Yoshinori; Matsuoka, Yoshiki; Kohra, Shinyo; Hosomi, Akira; *Heterocyles* **26(3),** 615-16 (1987). *Chem. Abstr.,* **107,** 236648w (1987).
3. Mehta P. A. Naik H. B., *Asian J. Chem.,* **10(4),** 1017-1018 (1998); *Chem. Abstr.,***129,**330803n (1998).
4. Abd-EL-Galil E., Amr.; *Indian J. Heterocyclic Chem.,* **10,** 49-58 (1999).
5. Rasaki Abayomi Osisany and James Olabisi Oluwadiya; *J. Heterocyclic Chem.,* **26,** 947 (1989).
6.. B.K. Karale; M.S. Shangare and C.H. Gill; *Indian J. Heterocylic Chem.,* **10,** 31-36 (2000)
7. Taylor, Edward C.,; Young, Wendy B.; *Tetrahedron, Lett,* **34(29)** 4595-8 (1993); *Chem.Abstr.,***120,**8551x (1994).
8. D. Lednicer and L.A. Mitscher; *Organic Chem. Of Drug Synthesis, Ny,* V 1-3 (1977). *Indian J. Heterocyclic Chem.,* **34,**509, (1997).
9. A.G. Sarolla and A. Bendich; *J.Ame.Chem. Soc.;* **80,** 5744 (1958).
10. A. Kreutzberger; J.Fluorine Chem.,29,385(1985).
11. I.I.Gerus; S.I.Vdovenko; M.G. Gorbunova and V.P. Kukhar; *Chem. Helerocyclic Compounds,* 398 (1992).
12. Jerzyl, Moksosz and Andrzej J.Bojaraski ; *J.Heterocyclic Chem.,***33,**1207 (1996).
13. D.C. Martin and J.D. Arnold, *J.Am. Med. Chem. Association,* **203,** 476 (1968).
14. Kadu V. B.; Doshi A. G.; *Res. J.Chem.Environ.,* **2(1),** 67-71 (1998).
15. Barot Vijay M,; *Asian J. Chem.,* **8(4),** 802-04 (1996).
16. M. Habert-Habart; K. Takogi and R. Rover; *Chim. Ther.,* **197,** 2(1967), *Indian J.Heterocyclic chem.,***13,**165,170(1994).
17. Tanaka Masaaki; Murakami, Yukitoshi; et al; *Jpn.Kokai Tokkyo Koho JP* **662,**123,177 (C1 C07 D 239/30), Appl.85/263, 483,12 Nov 1985;7pp*. Chem.Abstr.,* **107,** 236727w (1987).
18. V.Karbanow, L.P. Prikarchikova, V.Boldirev, I.A. Nasyr et.al.; *Chem.Abstr.,* **94,** 15741 (1981).
19. Obatokio, Fujii; Katsu, Toshi; Narita, Isami et.al.; *Jpn. Tokkyo Koho JP* **08,** 269, 021 (1995); *Chem.Abstr.,***126,** 74864b (1997).
20. G.B. Bennet, R.B. Nason, L.J. Alden and J.B. Roach; *J.Med. Chem.,* **21,** 623 (1978).
21. Devi. F. Sree; Prakash E. Om.; *Journal of the Institution of Chemists* **74(5),** 167-168(2002); *Chem. Abstr.,* **139,** 180031f (2003).
22. Zimmermann Jureg; U.S. 5, 521, 184 (Cl. 514-252; Co7D239/92), CH Appl. 92/1,083 (1992). *Chem. Abstr.,* **125,** 114681c (1996).
23. Boschelli Diane Narris, Dobrusin Ellen Myra, Doherty Annette Marian et.al.; *PCT Int. Appl. WO* **98** 33,798; *Chem.Abstr.,* **129,** 3700a (1998).

24. Chaudhari, Bipinchandra;*PCT Int Appl. WO* **02,** 36, 586(Cl CO7D 401/12), 56pp, (2002) *Chem. Abstr.,* **136,** 369729u(2002).

25. Patil, L. R. ; Tngle, G. S. and *Chem. Abstr.,* **137,** 337890f; *Indian Journal of Chemistry* **11(2)**,131-134 (2001).

26. Robson Clative, Wright Karenk, Twentymen Pater R., Lambert Pater et.al.; *Biochim,Pharmcol,* **56(7),** 807-16 (1998); *Chem.Abstr.,* **129,** 330701j (1998).

27. Henrie, Robert N. II, Beake Clinton J., Yleager Walter H. et.al.; *PCT Int. Appl. WO* **98,**20, 878, Appl. 96/17, 748 (1996), *Chem.Abstr.,***129,** 161365 (1998).

28. Hisaki Masakatsu, Ohta Yochiro, Kawanishi Kenji et.al.; *Eur. Pat. Appl. EP* **97** 806,418, JP Appl. 96/115,147; *Chem. Abstr.,* **128,** 22917t (1998).

29. Bosmas Jean Paul, Rene Marie Andre, Love Christopher John et.al.; *PCT Int. Appl. WO* **97** 43,279; EP Appl. 96/115,147;*Chem.Abstr.,* **128,** 34778m (1998).

30. W.C. Anthony and J. J. Ursprang; *U.S. Patent* **3,** 461, 461 (1969); *Chem. Abstr.,* **52,** 20212a (1958).

31 P. Stenback and H.M. Hood; *U.S. Patent* **3,** 049, 544 (1962).

32. Shiv P.Shingh and Hitesh Batra; *Indian J. Heterocyclic Chem.,* **9,** 73-74 (1999).

33. Kothari, seema Vyas, Rajesh; *Indian J. Heterocylc. Chem.,* **8(a)**,285-288 (1999).

34. A Handbook of Spectroscopic data by B.D.Mishtry; 1st ed. ABD press Jaipur 11-36(2000)., "Absorption Spectroscopy of Organic Compounds", by V.M.Parikh, *addision-Wesley Pub. co., London*, 243-258(1978).

35. Introduction to Infrared and Raman Spectroscopy by Nurmav B. Colthup, Lowrence H-Daly and Stephene E. Wiberluy, *Academic Press*(1975).

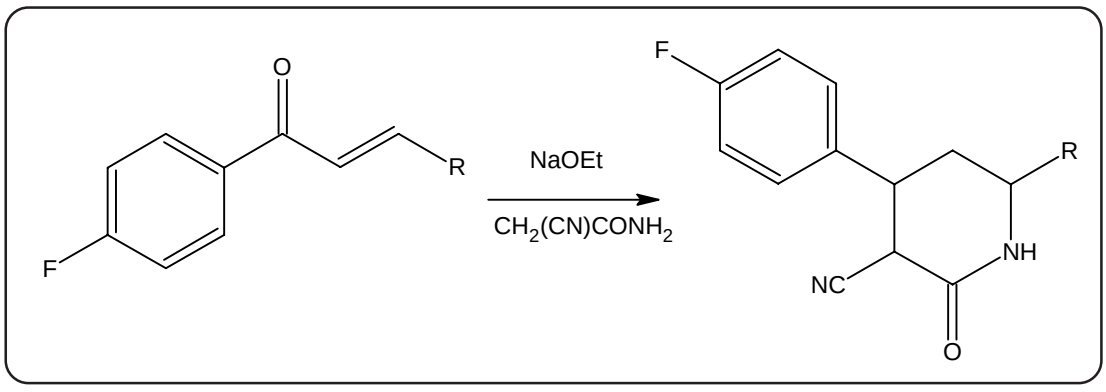
## INTRODUCTION

Piperidinones are well known for their antibacterial and antiinflammatory properties. It plays an important role as intermediate in the synthesis of drug. It enhances the biological activity, when attached with other compounds.

## SYNTHETIC ASPECT

Different methods have been documented for the synthesis of piperidinones in litrature[1-14]

1. B. shrivakumar et al.[15] have synthesized cyano piperidones by reaction of chalcones with cyano acetamide in presence of sodium ethoxide.



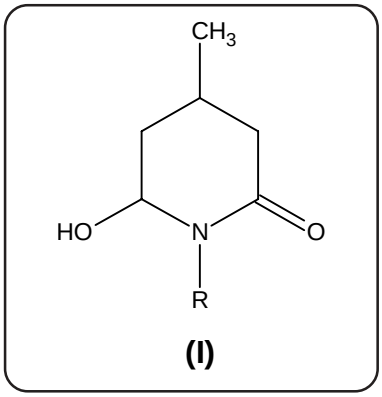

2. Hamed, A. A. et al.[16] have synthesised piperidones by reaction of chalcones with cyano acetamide in presence of sodium ethoxide
3. Nelson, Richard V. et al.[17] have prepared piperidones by reaction of $BrCH_2(OH)MeCH_2CH_2COOEt$ with hydroxylamine sulfate in aques NaOH

## THERAPEUTIC IMPORTNACE

Piperidinoes are reported to exhibit a wide varieties of theraputic activities such as

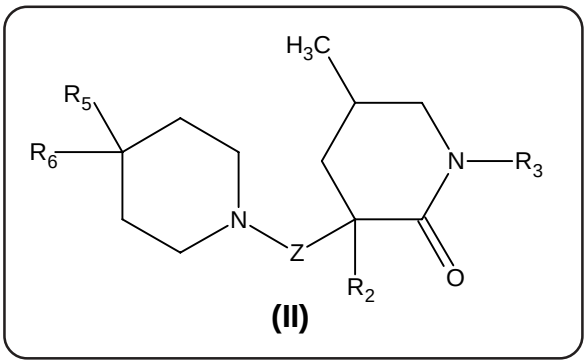
1. ACE and NEP activity[18]
2. Anesthetic[19]
3. Antiarrythmetic and antifubrillatory[20]
4. Anticonvalsnt[21]
5. CNS antidepressant[22]
6. Antimicrobial[23]
7. Antiinflammatory[24]
8. NK3 receptor antagonist[25]
9. Herbicidal[26]
10. Cardiotonic[27]
11. Fungitoxic[28,29,30]

Kobuyashi et al.[31] have synthesised piperidinones (I) as drug intermediate for biological active compounds.



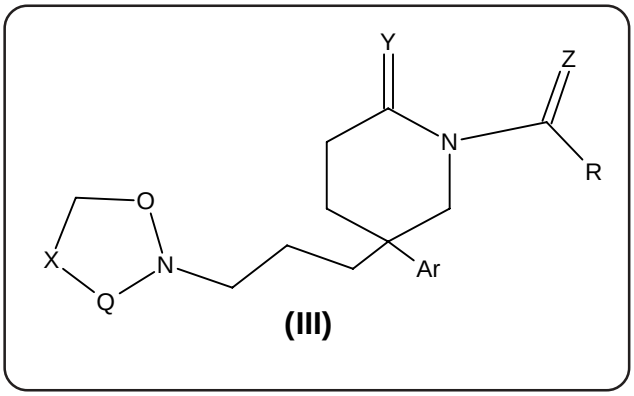

**(I)**

Chabert, Nathalic et al.[32] have synthesised 2-piperidino alkyl-2-piperidinones (II) and reported as $NK_3$ receptor antagonists activity.




**(II)**

Maccoss, Malcom et al.[33] have prepared pipridinones (III) as modulators of chemokine receptor activity




**(III)**

More over, Timothy, J. et al.[34] reported 2-piperidinones as analogous fashion by employing $(DHQD)_2$ AQN in the intial Ad reactivity Micovic. Ivan U. et al.[35] synthesised 2-piperidinones and reported their analgesic activity. Robl, Jeffrey et al.[36] reported 2-piperidinones as hemarable inhibitor of ACE and NEP activity. Laker, Tim., et al.[37] sytnhesized 2-piperidinone derivatives and their biological activity.

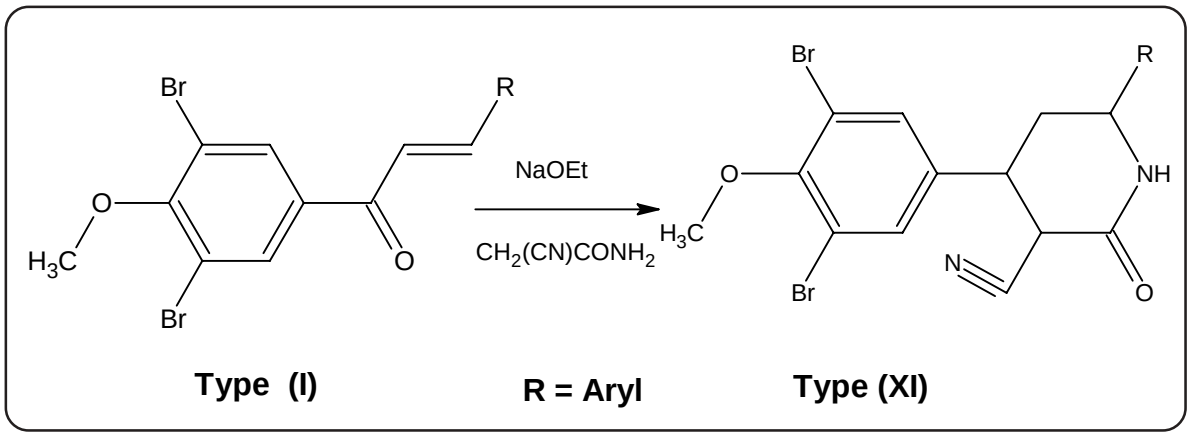
With an intention of preparing the compounds possesing better therapeutic activity, we have undertaken the synthesis of cyanopiperidinones bearing 3,5-dibromo-4-methoxy acetophenone moity which have been discribed under.

## SECTION - I SYNTHESIS AND BIOLOGICAL SCREENING OF 3-CYANO-4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-2-OXOPIPERIDINES

# SECTION-I

## SYNTHESIS AND BIOLOGICAL SCREENING OF 3-CYANO-4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-2-OXOPIPERIDINES

Piperidinones have been reported to have various pharmacological activities like anticancer, anticonvulsant etc. In order to achieving better drug potency, we have prepared piperidinone derivatives of type -(XI) by the cyclo condensation of (2E)-1-(3,5-dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones of type(I) with cyanoacetamide in presence of sodium ethoxide in ethanol.

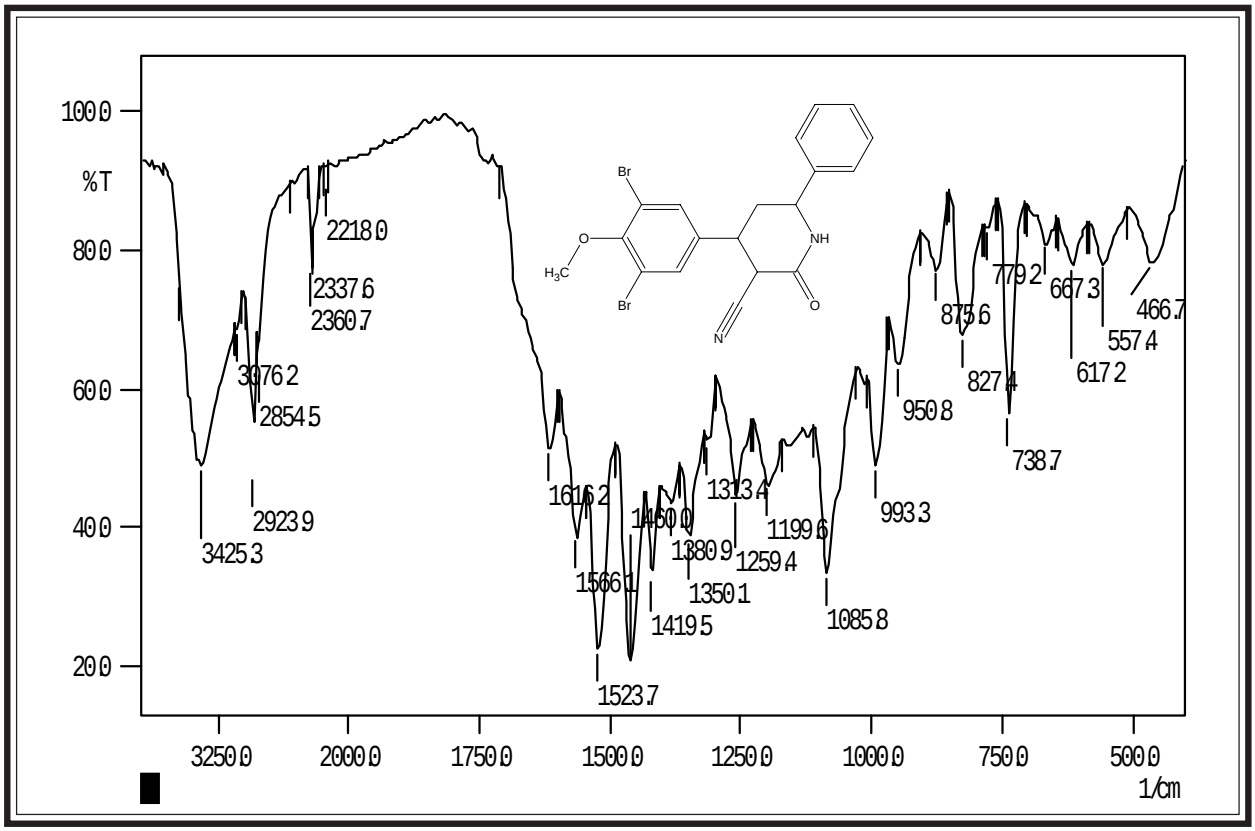



**Type (I)** **R = Aryl** **Type (XI)**

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

All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards from 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.

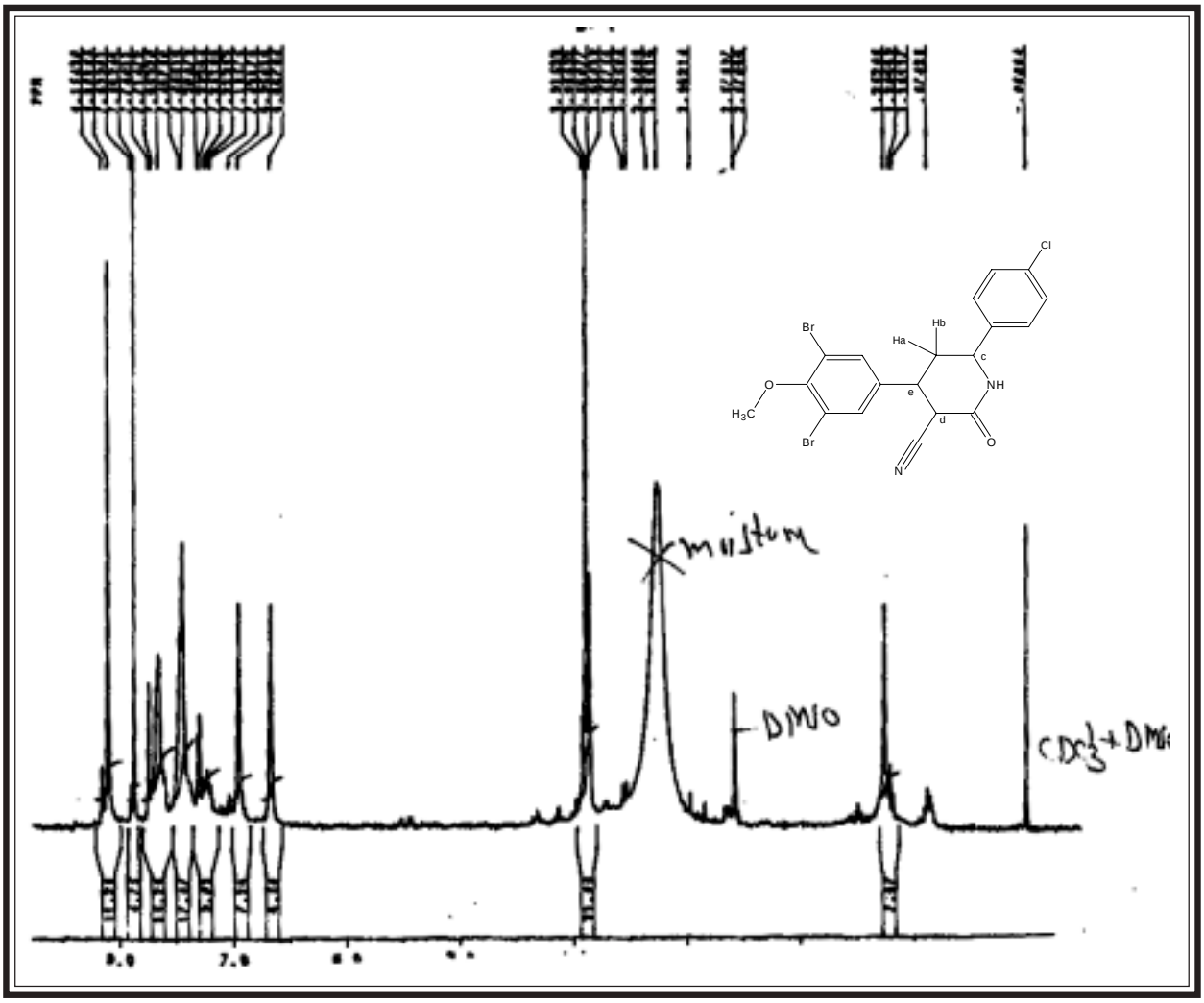
**IR spectral studies of 3-Cyano-4-(3,5-dibromo-4-methoxyphenyl)-6-phenyl -2-oxo-piperidine**




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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2923 | 2975-2950 | 38 |
| $-CH_3$ | C-H str.(sym.) | 2854 | 2880-2860 | " |
| | C-H def.(asym.) | 1460 | 1470-1435 | " |
| | C-H def.(sym.) | 1380 | 1390-1370 | " |
| Aromatic | C-H str. | 3076 | 3090-3030 | 39 |
| | C=C str. | 1566 | 1540-1480 | " |
| | | 1085 | 1125-1090 | " |
| Halide | C-Br str. | 557 | 600-500 | 38 |
| Ether | C-O-C str.(sym) | 1199 | 1275-1200 | |
| Piperidinone | C=N str. | 2218 | 2240-2120 | 39 |
| | C=O str. | 1651 | 1760-1655 | " |
| | N-H str. | 3425 | 3450-3250 | " |
| | N-H def. | 1566 | 1650-1580 | " |

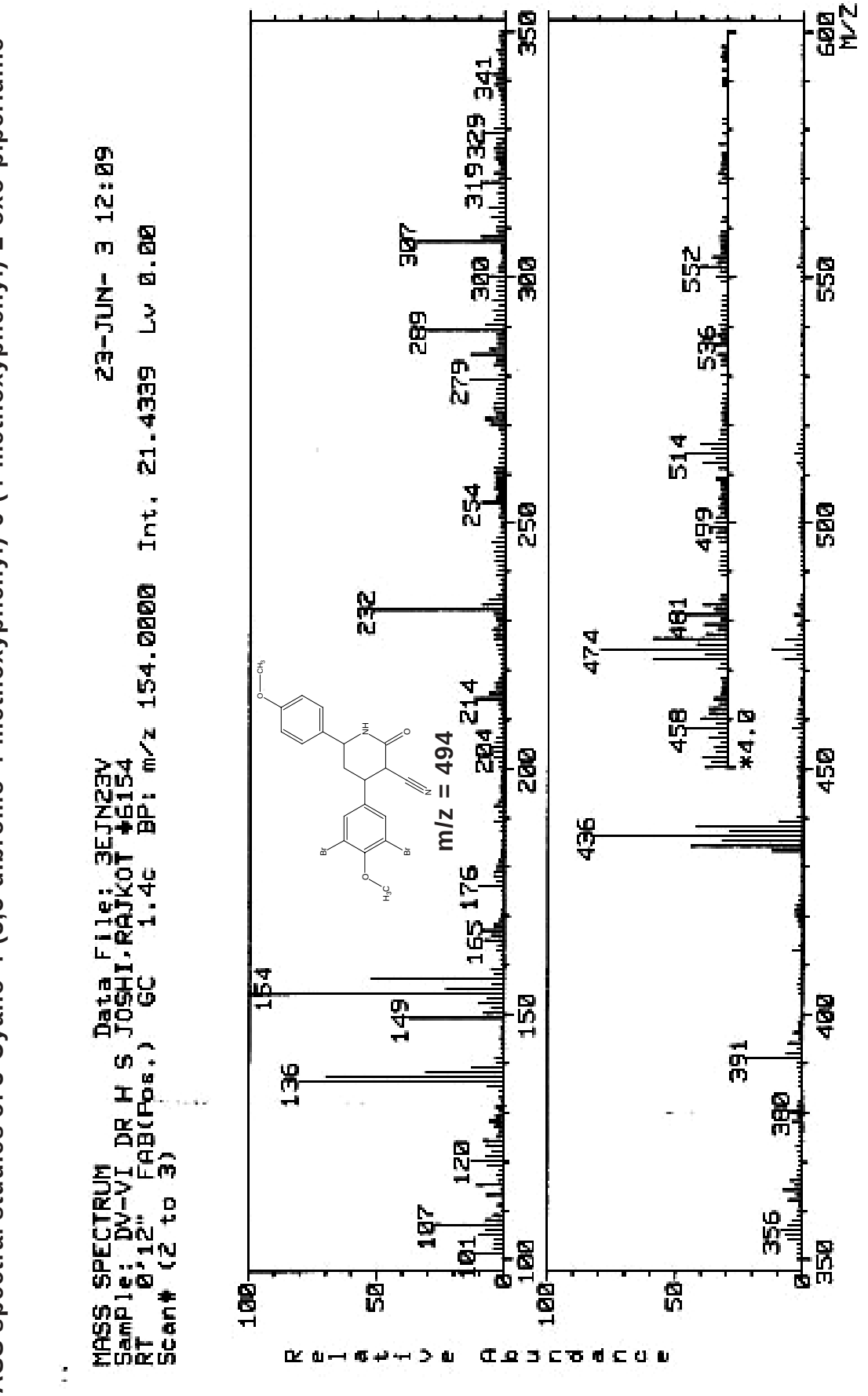
## NMR SPECTRAL STUDIES OF 3-CYANO-4-(3,5-DIBROMO-4-METHOXYPHENYL) -6-(4-CHLOROPHENYL)-2-OXO-1,2-DIHYDROPYRIDINE




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

| Signal No. | Signal Position (δ ppm) | Relative No. of Proton | Multiplicity | Inference |
|---|---|---|---|---|
| 1. | 3.95 | 3H | singlet | Ar-$OCH_3$ |
| 2. | 4.2 | 2H | triplet | -Ha,Hb |
| 3. | 5.65 | 2H | dublet | -Hc |
| 4. | 5.65-8.3 | 7H | multiplet | Ar-H + He,Hd |

**MASS spectral studies of 3-Cyano-4-(3,5-dibromo-4-methoxyphenyl)-6-(4-methoxyphenyl)-2-oxo-piperidine**



# EXPERIMENTAL

## SYNTHESIS AND BIOLOGICAL SCREENING OF 3-CYANO-4-(3,5-DIBROMO-4-METHOXY PHENYL)-6-ARYL-2-OXOPIPERIDINES

### (A) Synthesis of (2E)-1-(3,5-Dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones

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

### (B) Synthesis of 3-Cyano-4-(3,5-dibromo-4-methoxyphenyl)-6-phenyl-2-oxopiperidine

(2E)-1-(3,5-Dibromo-4-methoxyphenyl)-3-phenyl-1-prop-2-en-1-one (3.96gm, 0.01 mol) in (25ml) ethanol and sodium salt of cyano acetamide (1.0gm, 0.012 mol) was refluxed for 8 hrs. on a waterbath. The reaction mixture was concentrated and poured in to cold dil. HCl. The product was isolated and crystalised from methanol Yield 60%; m.p. 278 $^{o}$C ; Anal. Calcd. for $C_{19}H_{16}Br_2N_2O_2$ Requires:C,49.17; H,3.47; N, 6.04% Found: C,49.25; H,3.55; N, 5.99 %.

Similarly, other 3-Cyano-4-(3,5-dibromo-4-methoxyphenyl)-6-aryl-2-oxopiperidines were prepared. The physical data are recorded in Table No.11

### (C) Biological screening of 3-Cyano-4-(3,5-dibromo-4-methoxyphenyl)-6-aryl-2-oxopiperidines

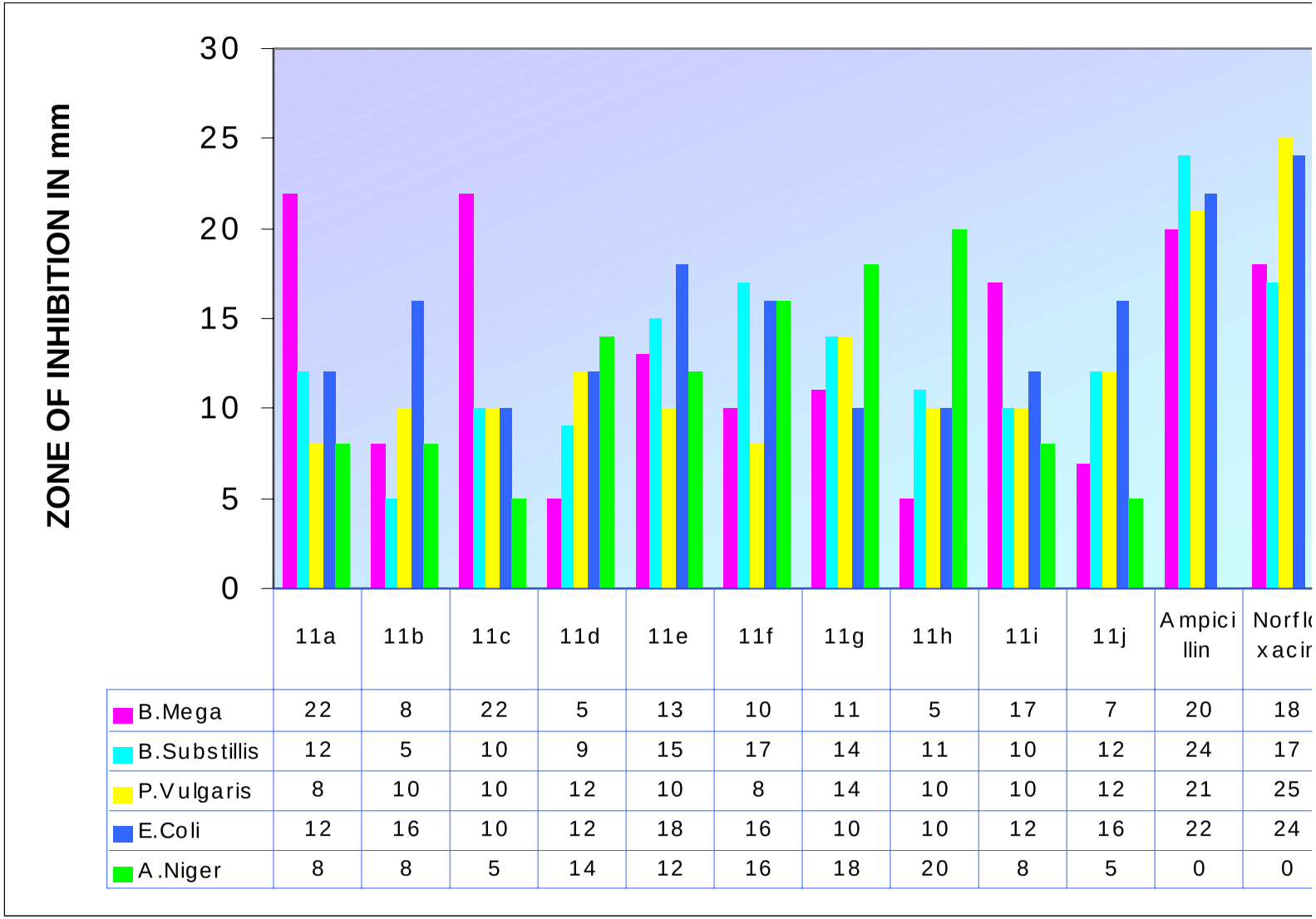
Antimicrobial testing were carried out as described in Part-I Section-1(D). The zones of inhibition of test solutions are recorded in Graphical Chart No.11

**TABLE-11 : PHYSICAL CONSTANTS OF 3-CYANO-4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-2-OXO PIPERIDINES.**

| Sr. No. | R | Molecular Fromula | Molecular Weight | M.P. °C | Yield % | % of Nitrogen Calcd. | % of Nitrogen Found | Rf Value | Solvent System |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 11a | $C_6H_5$- | $C_{19}H_{16}Br_2N_2O_2$ | 464.2 | 278 | 60 | 6.04 | 5.99 | 0.55 | S1 |
| 11b | 3-Br-$C_6H_4$- | $C_{19}H_{15}Br_3N_2O_2$ | 543.0 | 198 | 65 | 5.19 | 5.25 | 0.53 | S1 |
| 11c | 2-Cl-$C_6H_4$- | $C_{19}H_{15}Br_2ClN_2O_2$ | 498.6 | 180 | 68 | 5.62 | 5.68 | 0.46 | S1 |
| 11d | 4-Cl-$C_6H_4$- | $C_{19}H_{15}Br_2ClN_2O_2$ | 498.6 | 165 | 70 | 5.62 | 5.55 | 0.44 | S1 |
| 11e | 4-N$(CH_3)_2$-$C_6H_4$- | $C_{21}H_{21}Br_2N_3O_2$ | 507.2 | 106 | 68 | 8.28 | 8.21 | 0.41 | S2 |
| 11f | 4-$OCH_3$-$C_6H_4$- | $C_{20}H_{18}Br_2N_2O_3$ | 494.2 | 300> | 70 | 5.67 | 5.75 | 0.53 | S1 |
| 11g | 2-$NO_2$-$C_6H_4$- | $C_{19}H_{15}Br_2N_3O4$ | 509.2 | 224 | 55 | 8.25 | 8.19 | 0.56 | S2 |
| 11h | 3-$NO_2$-$C_6H_4$- | $C_{19}H_{15}Br_2N_3O4$ | 509.2 | 108 | 58 | 8.25 | 8.32 | 0.45 | S2 |
| 11i | 3-OC6H5-$C_6H_4$- | $C_{25}H_{20}Br_2N_2O_3$ | 556.3 | 70 | 60 | 5.04 | 5.12 | 0.51 | S2 |
| 11j | -$C_4H_3O$ | $C_{17}H_{14}Br_2N_2O_3$ | 454.1 | 300> | 62 | 6.17 | 6.11 | 0.53 | S2 |

S1=Ethyl acetate : Benzene(2:8) S2=Ethyl acetate : Benzene(1:9)

## GRAPHICAL CHART NO. 11 : 3-CYANO-4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-2-OXO-1,2-DIHYDROPYRIDINES.




| | 11a | 11b | 11c | 11d | 11e | 11f | 11g | 11h | 11i | 11j | Ampicillin | Norfloxacin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B.Mega | 22 | 8 | 22 | 5 | 13 | 10 | 11 | 5 | 17 | 7 | 20 | 18 |
| B.Substillis | 12 | 5 | 10 | 9 | 15 | 17 | 14 | 11 | 10 | 12 | 24 | 17 |
| P.Vulgaris | 8 | 10 | 10 | 12 | 10 | 8 | 14 | 10 | 10 | 12 | 21 | 25 |
| E.Coli | 12 | 16 | 10 | 12 | 18 | 16 | 10 | 10 | 12 | 16 | 22 | 24 |
| A.Niger | 8 | 8 | 5 | 14 | 12 | 16 | 18 | 20 | 8 | 5 | 0 | 0 |

**REFERANCES**


1. Fischer, E. et al., *Ber.,* **42,** 4878 (1909).
2. Fischer, E. et al., Annalen, **96**, 398 (1909).
3. Donaruma, L. G. et al., *J. O. C.,* **21,**965 (1956).
4. Smeykal, K. et al., *J. Parakt. Chem.,* **30,** 126 (1965).
5. Sheehan, J. C. et al, *J. O. C.* **39,** 2264(1974).
6. Williamson, K. L. et al, *J. A. C. S.,* **98,** 5082 (1976).
7. Nelson, Richard V. ; Stephen, John F. (ICI Americs, Int.) U. S. US4, 104, 664 (Cl 546-243; Co7D 211/40). 12 March 1985. *Chem. Abstr.* **103,** 6233v (1985)
8. Chi; Lin, Jen Hom; Wu, Shihn, Sheng. *Chem. Abstr.* **103,** 215127c (1985).
9. Kobayashi, Kaoru; Kusudu Shinya (Ono Pharmaceutical Co. Japan) *Chem. Abstr.***131,** 129904a
10. Mills, Catherine E; Heightman. Thomas D.; *Tetrahedron Lett.* **39(9),** 1025- 1028 (1998).
11. Julius, Manfred; *Chem. Abstr.* **128,** 16, 192559v (1998).
12. Hichour. Mohammed, Blache yves; Charignon, Oliver *Chem. Abstr.,* **128,** 18, 217257k(1998).
13. Fisyuk, Alexenders; Poenduew. Nicolou V.; *Chem. Abstr.* **128,** 18, 230215g.
14. Chen. Ling Ching, Wong Eng, Chi, *Chem. Abstr.,* **103,**215187c (1986).
15. B. Shriva kumar and L. V. G. Nargund, *I. J. H. C.* **8**, 27-30(1998).
16. Hamed, A. A., Madkour, H. F.; *Egyt. abstr.,* **108,** 167258z (1988).
17. Nelsone, Rischard, V., Stephen, John F. U. S. US4, 104, 664 (Cl. 546-243;Co 7D211/40), 12 March 1985 Appl. 496,580 20 May, 5 (1983).
18. Robl, Jeffrey A.; Sun, Chong-Qing Eur. Pat. Appl. EP 743,319 (Cl Co7k5/06) *Chem. Abstr.* **126(6),** 1497 (1997).
19. Kobayashi, Kaoru; Kusudu Shinya (Ono Pharmaceutical Co. Japan) *Chem. Abstr.***131,** 129904a
20. Kobayashi, Kaoru; Kusudu Shinya (Ono Pharmaceutical Co. Japan) *Chem. Abstr.* **131,** 129904a
21. Matthew W. Hill, Reddy P. A, Covera D. F; J. Pharmacol Exp. **285(3),** 1303-9 (1998).

22. Matthew W. Hill, Reddy P. A, Covera D. F; *British Journal of Pharmacology.,* **129,**283-290(2000).

23. B. Shiva kumar and L. V. G. Nargund, *I. J. H. C.* **8**, 27-30(1998).

24. B. Shiva kumar and L. V. G. Nargund, *I. J. H. C.* **8**, 27-30(1998).

25. Chabert, Nathlie; Ducoux Jeanpliliope, *Chem. Abstr.,* **129,** 1, (1998) .

26. Adachi, Hiroyuki, Sagae, Talcaniro, Koguchi, Musumi; *Chem. Abstr.,* **129,** 9, (1998)

27. Lesher, Beorge Yohe, Singh, Balder, Carbateas; *Chem. Abstr.,* **101,** 151757g (1984).

28. B. H. Toshima, K. Maru M. Saito and A. Ichihara, *Teterahedron Lett,* **40,** 939-942 (1999).

29. B. H. Toshima, K. Maru M. Saito and A. Ichihara, *Teterahedron Lett,* **40,** 939-942 (1999).

30. H. Toshima, K. Maru M. Saito and A. Ichihara, *Teterahedron Lett,* **55,** 5793-5808 (1999).

31. Kobuyashi, Kaoru; Kusudu Shinya (Ono Pharmaceutical Co. Japan) *Chem. Abstr.***131,** 129904a

32. Chabert, Nathlie; Ducoux Jeanpliliope, *Chem. Abstr.,* **129,** 1, (1998) .

33. Maccoss,Malcom; Mills, Sander G; *PTC Int. App. WO* **98** 31, 364(cl Abl K/3144)(1998) *Chem. Abstr.,* **129(11),** 3106098c (1998).

34. Hodgin son, Timothy. J. Shipman, Micheal Synthesis, 8, 1141-1144 (1998). *Chem. Abstr.,* **129,** 260326q (1998).

35. Micovic, Ivan U. Roglie Goran M.; J. Serb. Chem. Soc. 61(10), 849-857(1996).

36. Robl, Jeffrey A.; Sun, Chong-Qing Eur. Pat. Appl. EP 743,319 (Cl Co7k5/06) *Chem. Abstr.* **126(6),** 1497 (1997).

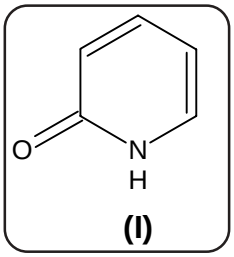
37. Laker Tim, et al *Tetrahedron,***37(45),** 8257-8260 (1996) *Chem. Abstr.,* **126(4),** 43 (1997).

38. A Handbook of Spectroscopic data by B.D.Mishtry; $^{1}$st ed. ABD press Jaipur 11-36(2000)., "Absorption Spectroscopy of Organic Compounds", by V.M.Parikh, *addision-Wesley Pub. co., London*, 243-258(1978).

39. Introduction to Infrared and Raman Spectroscopy by Nurmav B. Colthup, Lowrence H-Daly and Stephene E. Wiberluy, *Academic Press*(1975).

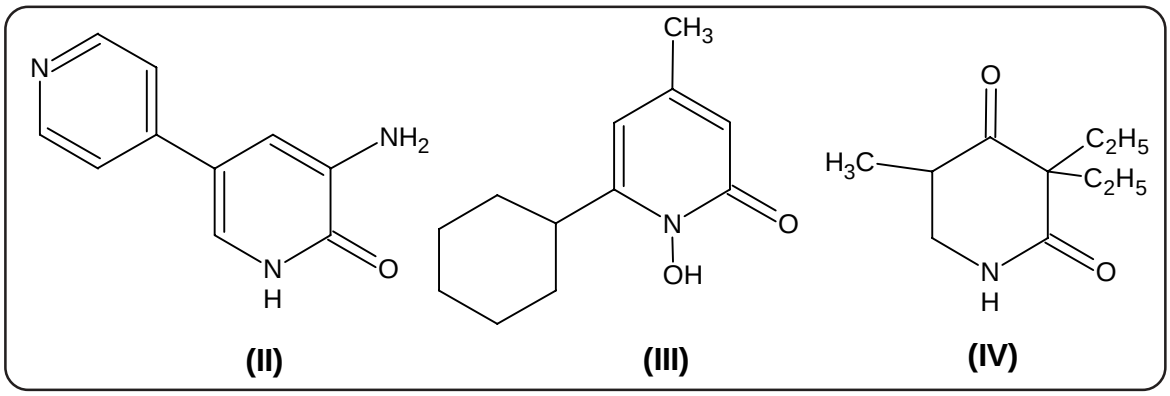
## INTORDUCTION

Pyridones, which belong to important group of heterocylic compound have been extensively explore for their applications in the field of medicine. Pyridine with a carbonyl group at position-2 (I) have been subjected of extensive study in recent past. Numerous reports have appeared in the literature, which highlight, their chemistry and use.




**(I)**

2-Pyridones are derivatives of pyrimidine with carbonyl group at 2-position (I) Some 2-pyridones are physiologically as well as pharmacologically important which are as under: eg. Amrinone (II), Ciclopirox (III) and Menthylprylon (IV).



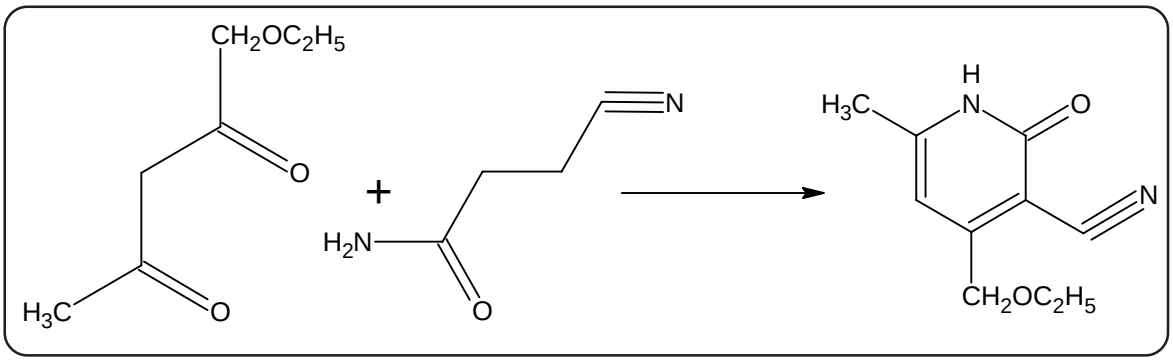

**(II)** **(III)** **(IV)**

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

## SYNTHETIC ASPECT

Different methods for the preparation of 2-pyridones are as follows

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



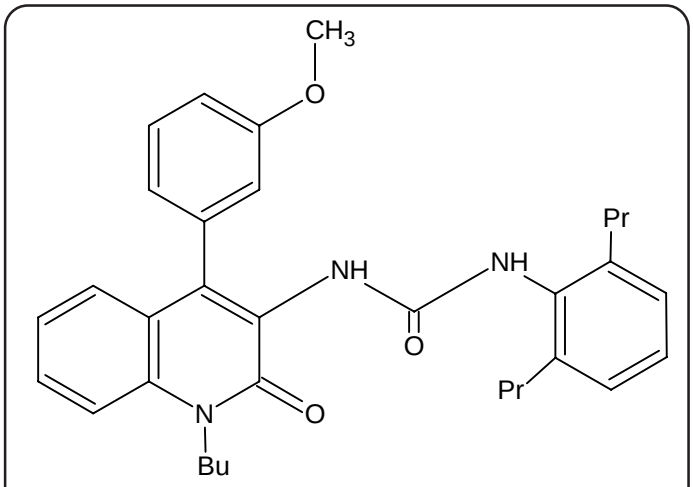

2. G. Simchen and G.Enremmann[2] have synthesised 2-pyridone in which the ring nitrogen comes from a nitrile group in a cyclic precursor.
3. M. A. Sluyter and co-worker[3] have prepared fused 2-pyridones.

## THERAPEUTIC IMPORTANCE

Pyridon derivatives have been found to possess variety of therapeutic activities as shown below.

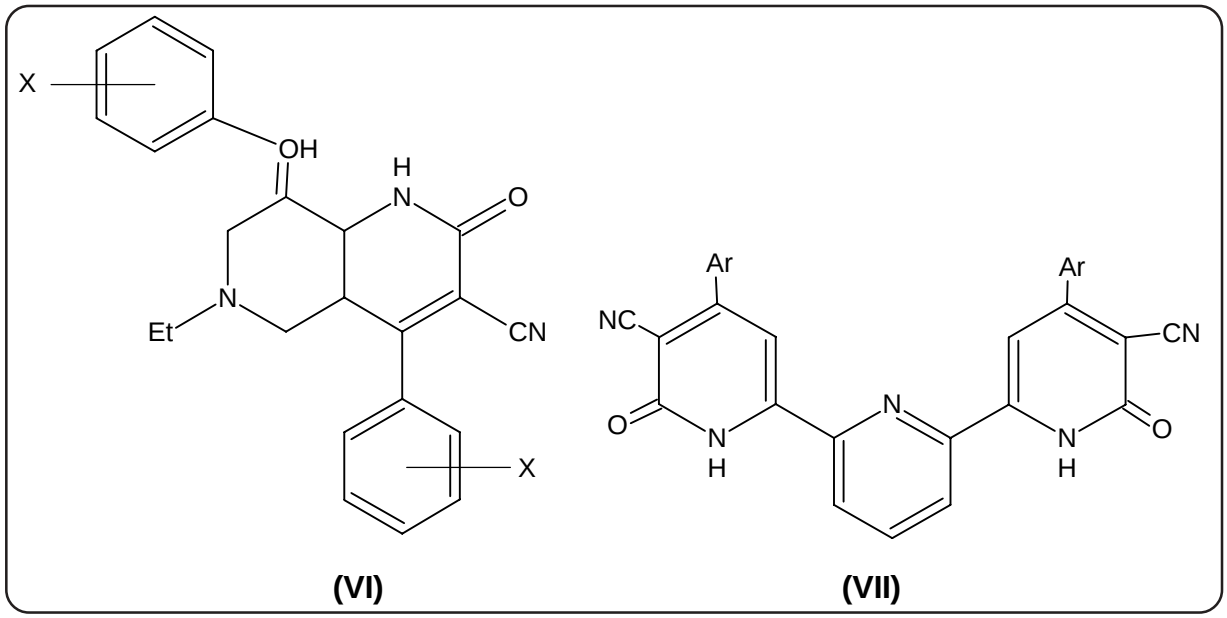
1. Anticancer[4]
2. Pesticidal[5,6]
3. Herbicidal[7]
4. Antimicrobial[8]
5. Angitensin II antagonist[9-10]
6. Antiviral[11]
7. Anti HIV[12]

Morishita koji et al.[13] have synthesised m-(2-oxo-1,2-dihydropyridyl) derivatives (V) possessing cholesterol acyltransterase (ACAT) inhibitory activity and are useful for the treatment of hyperlipidemia and arteriosclerosis.



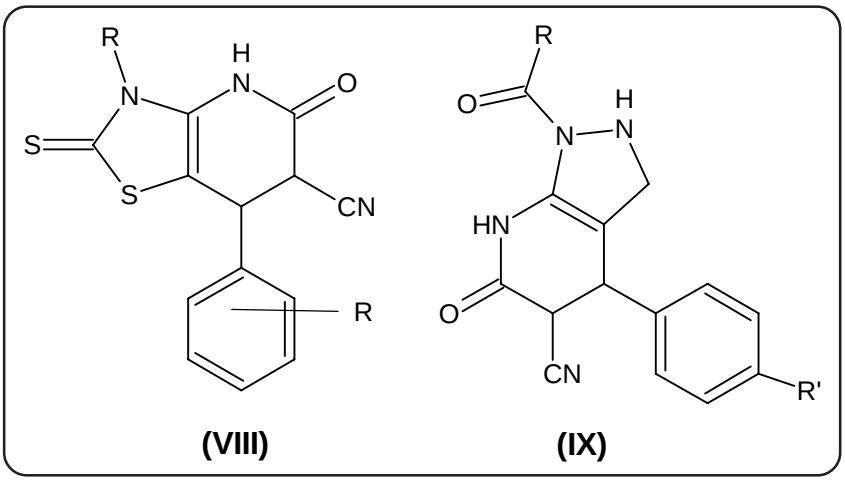

**(V)**

Abou EL Fotooh and co-worker[14] have demonstrated pyridones (VI) as anticancer agent. E. Amer[15] prepared 3-cyano 2-pyridone derivatives (VII) displaying high antimicrobial activity.

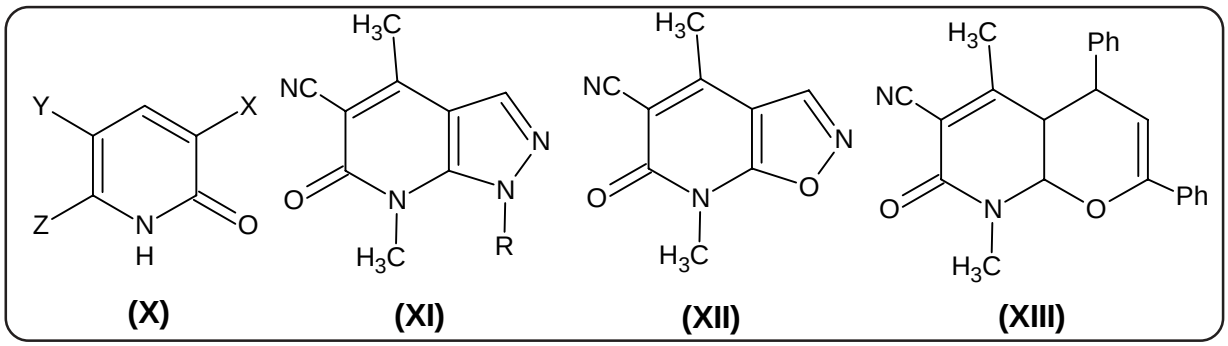



**(VI)** **(VII)**

Mukhtar Hussain Khan and co-worker[16,17] have prepared 2-pyridone derivatives (VIII) and (IX) which possess insecticidal and pesticidal activity.

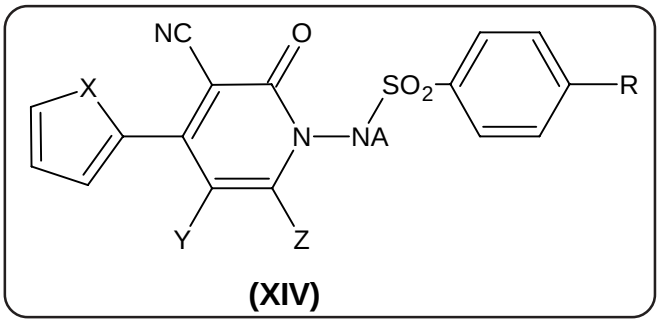



H. Posnes[18] synthesised 2-pyridones and 2-pyrones as physiologically active compounds. Peter and co-workers[19] have prepared pyridinylmethyl substituted pyridines and tested as angiotesin II antagonists. Collins et al.[20] prepared heteroaryl pyridones as GABA $\alpha_2/\alpha_3$ ligands (X). Pednekar[21] synthesised fused 2-pyridone derivatives (XI),(XII) and (XIII) as useful heterocyclic moieties as they possess a broad spectrum of biological activity such as antiviral, CNS depressant, bactericidal and ulcer inhibitor.




M. G. Nizamuddin et al.[22] have prepared cyano pyridone derivatives (XIV) and documented their antifungal activity.

Davi. F. Sree ; et al.[23] have prepared cyano pyridone derivative (XIV) and documented their antibacterial activity.




**(XIV)**

Azama yutaka et al.[24] and Devadas et al.[25] have prepared cyano pyridone derivative for medicinally important compounds.

Moreover several co-workers have prepared 2-pyridones as $S_3$ site of throbin inhibitor[26], herbicidal[27], $SH_2$ domain inhibitor[28], antimicrobial[29], GABA-$\alpha$ receptor[30] and antiinflammatory[31]activity.

Upadhyay and co-worker[32] have synthesised cyano pyridone derivatives which showed antifungal and antileishmanial activeties.

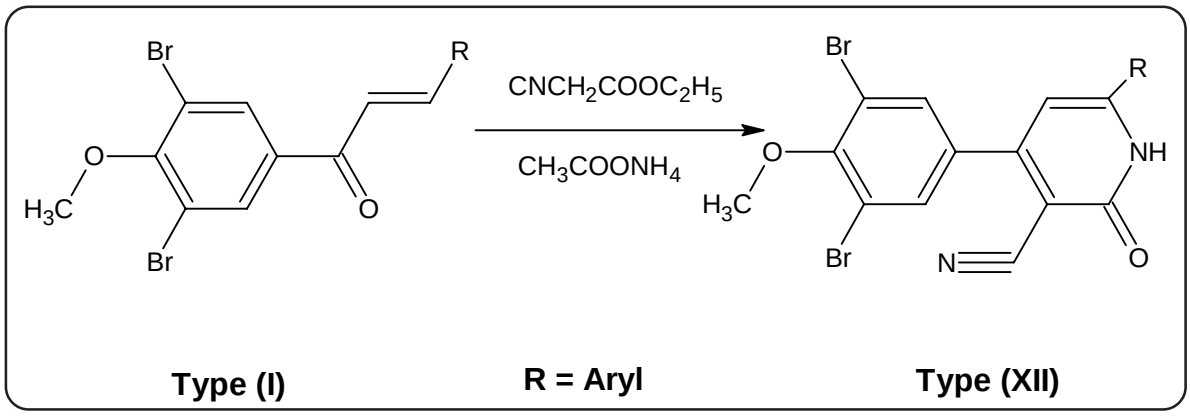
Looking to the interesting properties of pyridones, we have synthesised some new pyridone derivatives, which have been described as under

## SECTION - I : SYNTHESIS AND BIOLOGICAL SCREENING OF 3-CYANO-4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-2-OXO-1,2-DIHYDROPYRIDINES

# SECTION-I

## SYNTHESIS AND BIOLOGICAL SCREENING OF 3-CYANO-4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-2-OXO-1,2-DIHYDROPYRIDINES

In view of powerful biological activities shown by cyano pyridones, like antimicrobial and antitubercular, it was worthwhile to synthesized some novel cyano pyridone derivatives possessing better biological activity. Synthesis of some new 3-cyano-4-(3,5-dibromo-4-methoxyphenyl)-6-aryl-2-oxo-1,2-dihydropyridines of type(XII) carried out by condensation of chalcones of type(I) with ethylcyanoacetate in presence of ammonium acetate as under.

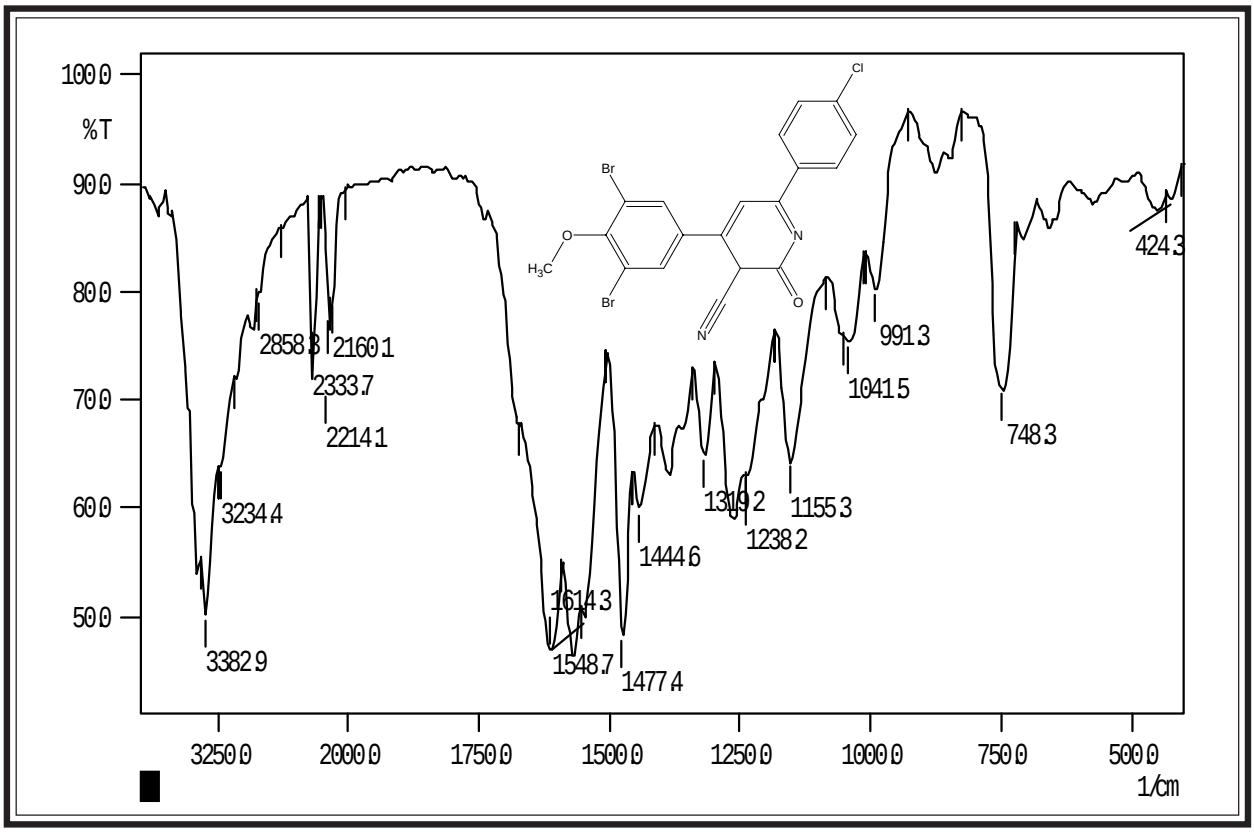



**Type (I)** **R = Aryl** **Type (XII)**

The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and $^{1}H$ nuclear magnetic resonance spectroscopy and farther 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.

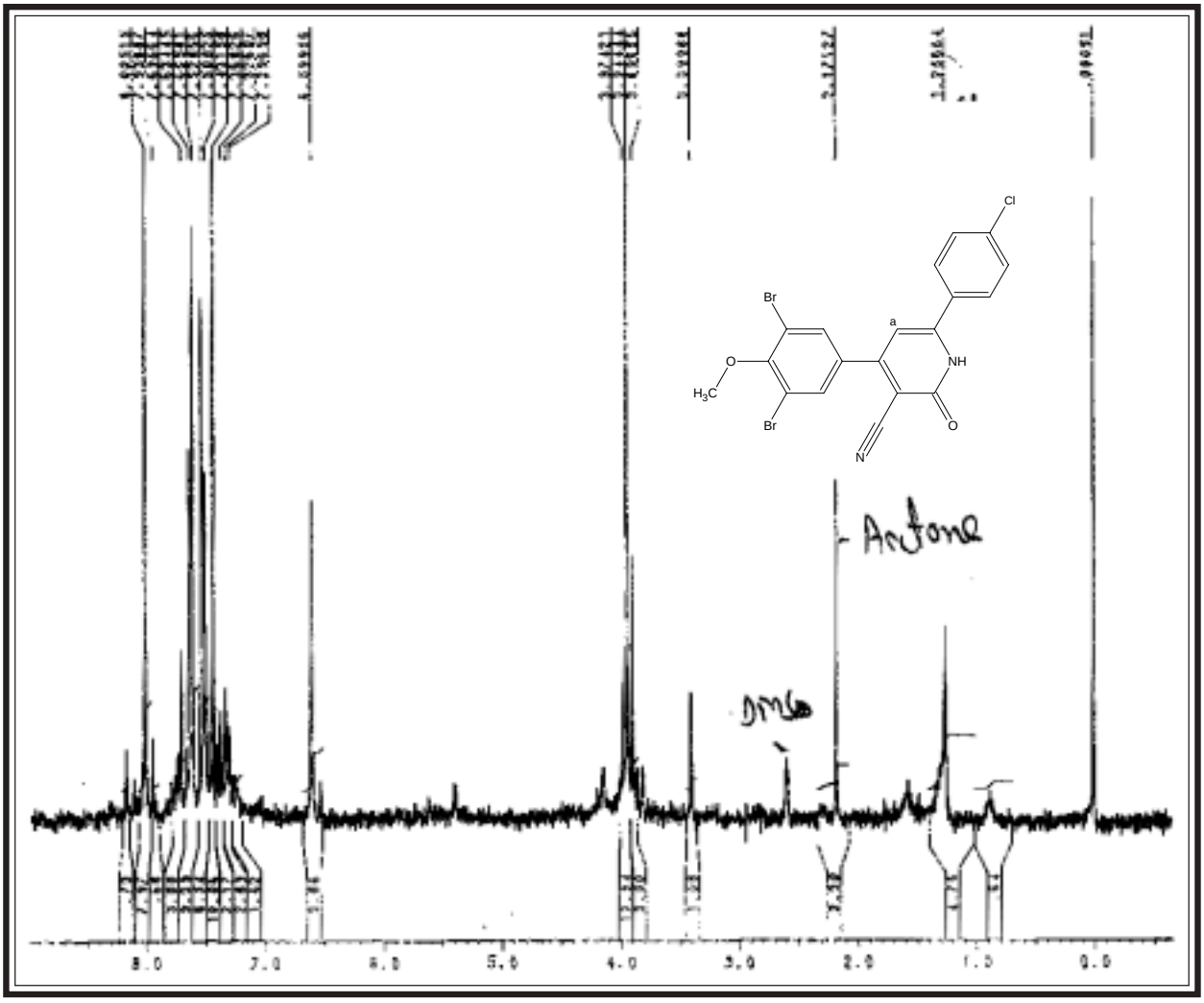
**IR spectral studies of 3-Cyano-4-(3,5-dibromo-4-methoxyphenyl)-6-(4-chlorophenyl)-2-oxo-1,2-dihydropyridine**




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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2956 | 2975-2950 | 33 |
| $-CH_3$ | C-H str.(sym.) | 2858 | 2880-2860 | " |
| | C-H def.(asym.) | 1444 | 1470-1435 | " |
| | C-H def.(sym.) | 1351 | 1390-1370 | " |
| Aromatic | C-H str. | 3060 | 3090-3030 | 34 |
| | C=C str. | 1548 | 1540-1480 | " |
| | | 1155 | 1125-1090 | " |
| Halide | C-Br str. | 540 | 600-500 | 33 |
| Ether | C-O-C str.(sym) | 1238 | 1275-1200 | " |
| Pyridone | C=N str. | 2214 | 2240-2120 | 34 |
| | C=O str. | 1734 | 1760-1655 | " |
| | N-H str. | 3382 | 3450-3250 | " |
| | N-H def. | 1641 | 1650-1580 | " |

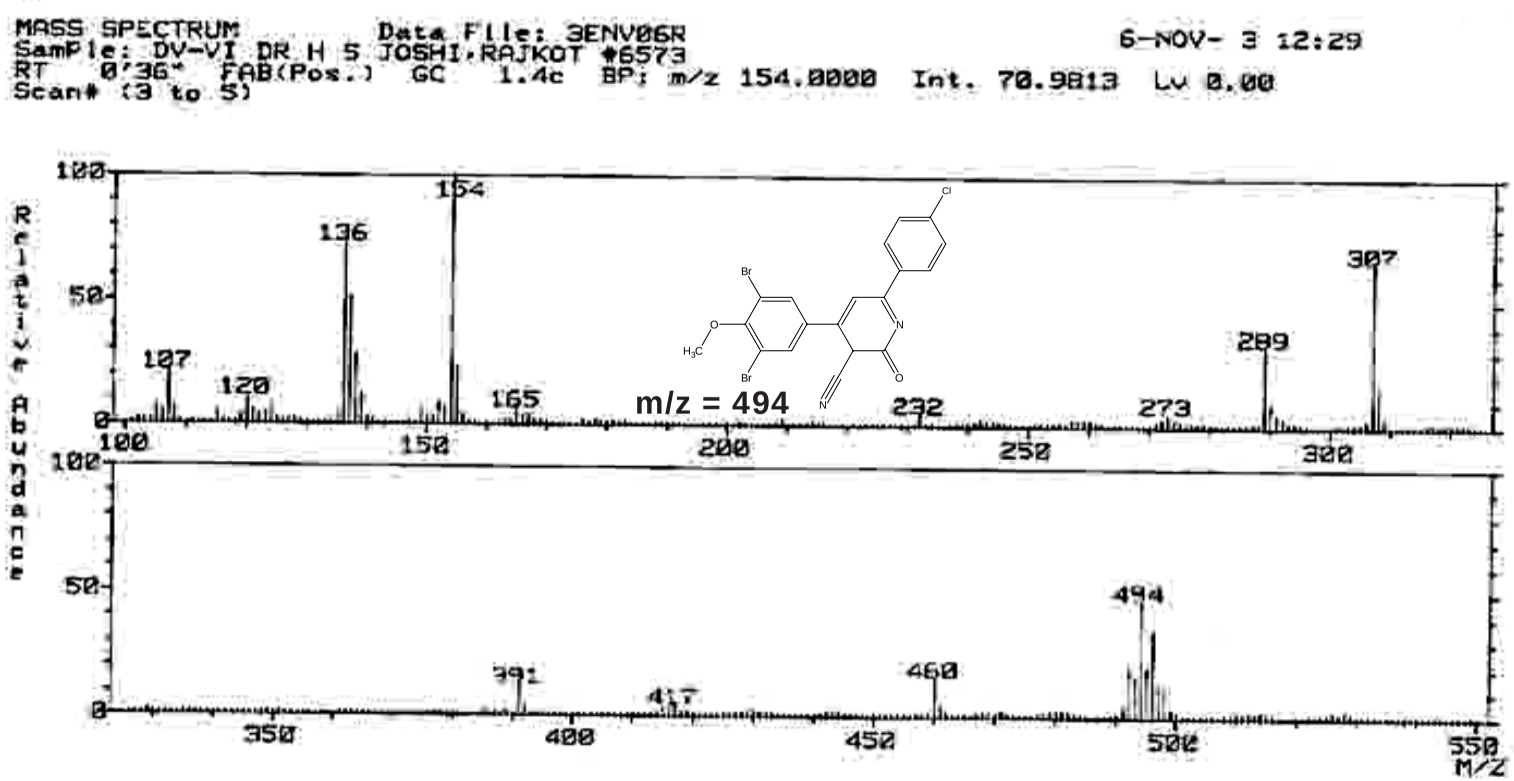
**NMR SPECTRAL STUDIES OF 3-CYANO-4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-(4-CHLOROPHENYL)-2-OXO-1,2-DIHYDROPYRIDINE**




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

| Signal No. | Signal Position (δ ppm) | Relative No. of Proton | Multiplicity | Inference |
|---|---|---|---|---|
| 1. | 3.94 | 3H | singlet | Ar-$OCH_3$ |
| 2. | 6.59 | 1H | singlet | -Ha |
| 3. | 7.43-7.60 | 6H | multiplet | -Ar-H |
| 4. | 8.00 | 1H | singlet | -NH |

**MASS spectral studies of 3-Cyano-4-(3,5-dibromo-4-methoxyphenyl)-6-(4-chlorophenyl)-2-oxo-1,2-dihydro pyridine**



# EXPERIMENTAL

## SYNTHESIS AND BIOLOGICAL SCREENING OF 3-CYANO-4-(3,5-DIBROMO-4-METHOXY PHENYL)-6-ARYL-2-OXO-1,2-DIHYDROPYRIDINES

### (A) Synthesis of (2E)-1-(3,5-Dibromo-4-methoxyphenyl)-3-aryl-prop-2-en-1-ones

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

### (B) Synthesis of 3-Cyano-4-(3,5-dibromo-4-methoxy phenyl)-6-(4-chloro-phenyl)-2-oxo-1,2-dihydropyridine

A mixture of (2E)-1-(3,5-dibromo-4-methoxyphenyl)-3-(4-chlorophenyl)-prop-2-en-1-one. (4.39gm, 0.01 mol), etylcyanoacetate (1.13gm, 0.01 mol) and ammonium acetate (5.92gm, 0.08mol) was refluxed for 8 hrs. The resulting mixture was poured on to crushed ice. The product was isolated and crystallized from ethanol. Yield 68%, m.p. $300^0$C, Anal. Calcd. for $C_{19}$ $H_{11}Br_2ClN_2O_2$; Requires: C, 46.14; H, 2.24; N, 5.66; Found: C, 46.20; H , 2.28; N, 5.60%.

Similarly, other 3-cyano-4-(3,5-dibromo-4-methoxy phenyl)-6-aryl-2-oxo-1,2-dihydropyridines.

### (C) Biological screening of 3-cyano-4-(3,5-Dibromo-4-methoxy phenyl)-6-aryl-2-oxo-1,2-dihydropyridine

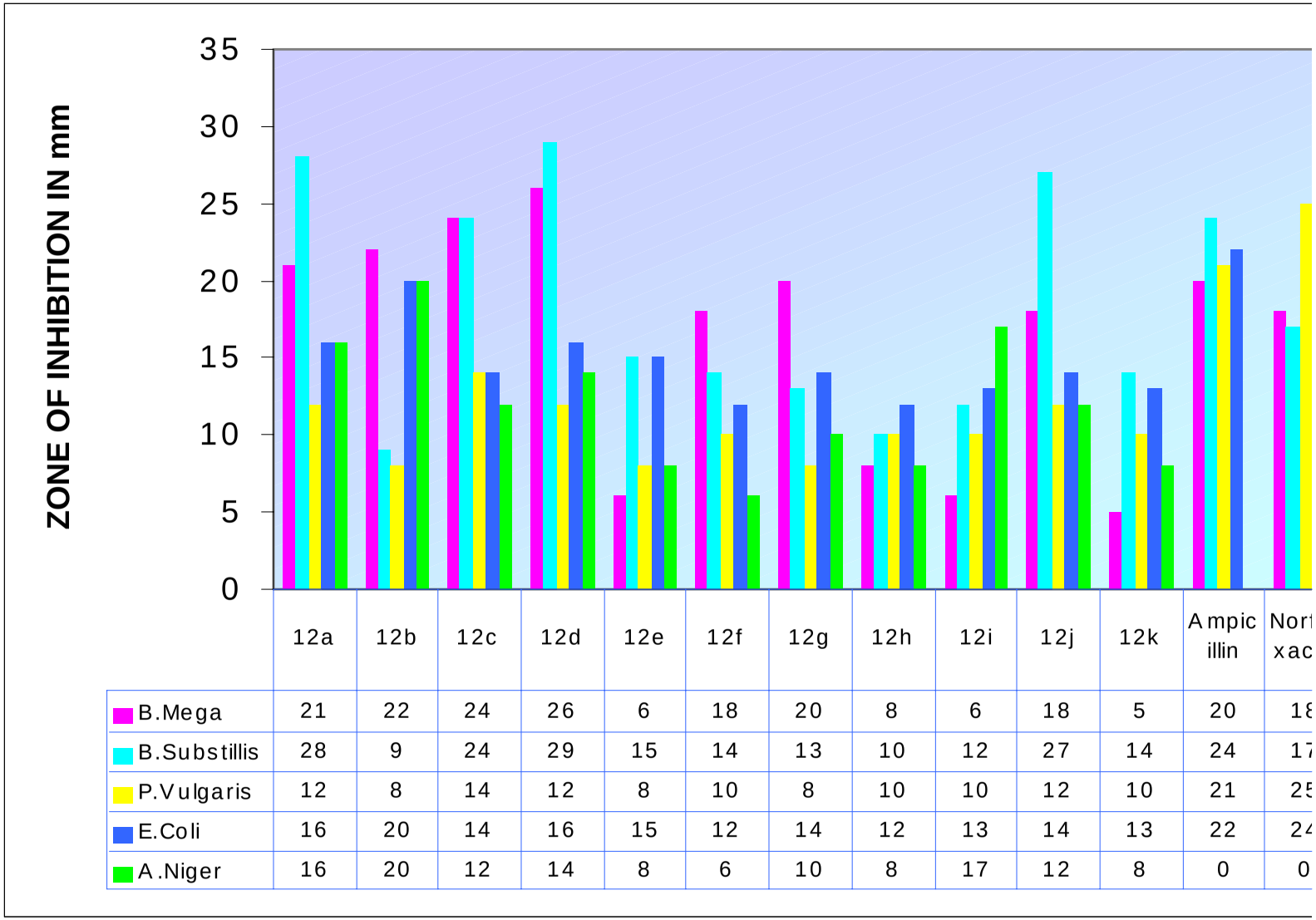
Antimicrobial testing were carried out as described in Part-I Section-I(D). The zones of inhibition of test solution are recorded in Graphical Chart No 12.

## TABLE-12 : PHYSICAL CONSTANTS OF 3-CYANO-4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-2-OXO-1,2-DIHYDROPYRIDINES.

| Sr. No. | R | Molecular Fromula | Molecular Weight | M.P. °C | Yield % | % of Nitrogen Calcd. | % of Nitrogen Found | Rf Value | Solvent System |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 12a | $C_6H_5$- | $C_{19}H_{12}Br_2N_2O_2$ | 460.0 | 300> | 70 | 6.09 | 6.15 | 0.57 | S2 |
| 12b | 3-Br-$C_6H_4$- | $C_{19}H_{11}Br_3N_2O_2$ | 539.0 | 90 | 68 | 5.20 | 5.12 | 0.42 | S1 |
| 12c | 2-Cl-$C_6H_4$- | $C_{19}H_{11}Br_2ClN_2O_2$ | 494.5 | 88 | 65 | 5.66 | 5.59 | 0.55 | S2 |
| 12d | 4-Cl-$C_6H_4$- | $C_{19}H_{11}Br_2ClN_2O_2$ | 494.5 | 300> | 68 | 5.66 | 5.70 | 0.48 | S1 |
| 12e | 4-$OCH_3$-$C_6H_4$- | $C_{19}H_{14}Br_2N_2O_3$ | 590.1 | 52 | 66 | 5.72 | 5.80 | 0.66 | S2 |
| 12f | 3,4-$(OCH_3)_2$-$C_6H_3$- | $C_{21}H_{16}Br_2N_2O_4$ | 520.0 | 118 | 65 | 5.39 | 5.32 | 0.67 | S1 |
| 12g | 2-$NO_2$-$C_6H_4$- | $C_{19}H_{11}Br_2N3O_4$ | 505.1 | 56 | 58 | 8.32 | 8.25 | 0.58 | S1 |
| 12h | 3-$NO_2$-$C_6H_4$- | $C_{19}H_{11}Br_2N3O_4$ | 505.1 | 175 | 60 | 8.32 | 8.36 | 0.60 | S1 |
| 12i | 2-OH-$C_6H_4$- | $C_{19}H_{12}Br_2N_2O_3$ | 476.1 | 300> | 56 | 5.88 | 5.94 | 0.45 | S2 |
| 12j | 4-OH-$C_6H_4$- | $C_{19}H_{12}Br_2N_2O_2$ | 476.1 | 235 | 58 | 5.88 | 5.80 | 0.42 | S2 |
| 12k | $C_4H_3O$- | $C_{17}H_{10}Br_2N_2O_3$ | 450.0 | 296 | 60 | 6.22 | 6.34 | 0.54 | S2 |

S1=Ethyl acetate : Benzene(1.5:8.5), S1=Ethyl acetate : Benzene(2.5:7.5)

## GRAPHICAL CHART NO. 12 : 3-CYANO-4-(3,5-DIBROMO-4-METHOXYPHENYL)-6-ARYL-2-OXO-1,2-DIHYDROPYRIDINES.




| | 12a | 12b | 12c | 12d | 12e | 12f | 12g | 12h | 12i | 12j | 12k | Ampicillin | Norfxac |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B.Mega | 21 | 22 | 24 | 26 | 6 | 18 | 20 | 8 | 6 | 18 | 5 | 20 | 18 |
| B.Substillis | 28 | 9 | 24 | 29 | 15 | 14 | 13 | 10 | 12 | 27 | 14 | 24 | 17 |
| P.Vulgaris | 12 | 8 | 14 | 12 | 8 | 10 | 8 | 10 | 10 | 12 | 10 | 21 | 25 |
| E.Coli | 16 | 20 | 14 | 16 | 15 | 12 | 14 | 12 | 13 | 14 | 13 | 22 | 24 |
| A.Niger | 16 | 20 | 12 | 14 | 8 | 6 | 10 | 8 | 17 | 12 | 8 | 0 | 0 |

## REFERENCES


1. K. Folkers. S.A. Harris; *J. Am. Chem. Soc.,* **61,** 1245 (1939).
2. G. Simchen and G. Enremmann; *Angew Chem. Int. Edn. Engl.,* **12,** 119 (1973).
3. M. A. Sluyter. U. K. Pandit. W. N. Speckamp and H. O. Huisman. *Tetranedron Letr.* **87,** (1966).
4. Hu Zhiyong Wang Huical; *Chem.Abstr.,* **119,** 72465d (1993).
5. R.W. Hartann. N. Reichert and S. Gozhring. *Eur. J. Med. Chem.,* **29(11),** 807-17 (1994), *Chem. Abstr.,* **122,** 239500n (1995).
6. K. Jonhannes, F. Rainer. J. R. Jansen and S. Nichael, *Ger. Offen DE* **4,** 309, 552 (CI C07/D 213 85) *Chem. Abstr.,* **122,** 9877m (1995).
7. U. Toru, T. Susumu. E. Masayuki and S. M. Saharu. *Eur. Pat. Appl. EP* **4,** 88, 220 (CI C07D 413 04) (1992). *Chem. Abstr.,* **118,** 80944d (1993).
8. D.D. Erol. N. Yulung and A. Turk; *Eur. J. Med. Chem.,* **29(11),** 893-7 (1994); *Chem.Abstr.,* **122,** 13650a (1995).
9. P. fey. H. K. Rudolf, H. Walter and K. Thomas: *Eur. Pat. Appl. Ep*. **62,** 3611, (CI. C07D 401/14); *Chem. Abstr.,* **122.** 55897r (1995).
10. H. Rudolf, H. Walter, D. Juergen and F. Peter; *Eur. Pat. Appl. Ep.* **5**, 57, 843 (CI. C07D401/12); *Chem. Abstr.,* **120**. 8478d (1994)
11. H. Michael. Haesslein Jean-luc and H. Bertrand ; *PCT Int. Appl.* WO 93 16, 149 (CI.C07D211/86) ; *Chem. Abstr.,* **120,** 10677w (1994)
12. R. Bernd. P. A. Schirwan. R. Dieter. R. Guenther; *PCT Int. Appl.* Wo 96 30. 342 (CI.C07D213/89) ; *Chem. Abstr.,* **126,** 7993e (1997).
13. M. K. Morishita, A. Nagisa and J. Masashi; *PCT Int. Appl.* WO **99** 43, 659 (CI. CO7D 213/72); *Chem. Abstr.,* **131,** 170353h (1999).
14. Abou El-Fotooh, G. Hammam, M. A. Sharaf and N. A. Abd EI-Hafeza;*Indian J. Chem.,* **40B**, 213-221 (2001).
15. Abd EI Galil and E. Amer; *Indian J. Heterocylic Chem.,* **10,** 49 (2000).
16. Mukhtar Hussain Khan, Raizul Haque and Nizamauddin; *Indian J Chem.,* **37B,** 1069 (1998).

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

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

19. F. Peter. D. Juergem, H Rudolf. H. Walter and K. Thomas; *Eur. Pat Appl. Ep* 62 3611, (CI . C07D 4011 14) ; *Chem. Abstr.,* **122,** 55897r (1995).

20. I. J. Collins, L. P. David and M C. Richard. *PCT Int. Appl* WO 98 55, 480 (1998) *Chem. Abstr.,* **130,** 38376t (1999).

21. Pedneker. *PCT Int. Appl* WO 98 30, 342 (1998); *Chem. Abstr.,* **130,** 48719t (1999).

22. M. G. Nizamuddin, K. S. Manoj; *Chem, Abstr.,* **136,** 279375x (2002).

23. Devi. F. Sree; Prakash, E. Om; *Journal of the Institution of Chemists* **74(5),** 167-168(2000) *Chem. Abstr.,* **139,** 1800 31f (2003).

24. Azama Yutaka ; Morone, Micko; Heterocycles 60(6), 1461-1468 (2003) *Chem. abstr.,* **139,** 197340 (2003).

25. Dev Das, Balclcudru; Walker, John; *PCT Int Appl.* WO03 68 230 (Cl A61K31/4412), 21 Aug 2003, US Appl. pv 436, 915, 30 Dec. 2002; 1052pp *Chem. Abstr.,* **139,** 197371g (2003).

26. J. E. Reiner. Lim Wilby. R. S. Marge. T. K. Brunck and Ha-Vong; *Chem. Lett.,***9(6),** 895-900 (1999); *Chem. Abstr.,* **131,** 286379a (1999).

27. Y. Mikio. I. Voshiniro, S. Atsushi, Y. Mitsuhiro and H. Rgo; *Jpn. Kokai Tokkyo Koho JP* 11 140. 054 CI . C07D 213 64: *Chem. Abstr.,* **131,** 44738a (1999).

28. R. betageri. L. Beaulieu. B Pierrel ; *PCT Int. Appl* WO 99 31, 066 (CI . C07D 213 75): *Chem. Abstr.,* **131** 59136a (1999).

29. S. Asmaa. S. Salem; *Pharmazie* **54(3),** 178-183 (1993); *Chem.Abstr.,* **130,** 13918h (1999).

30. H. Timothy, M. Christopher, R. iaewis, R. Thomas. *PCT Int. Appl.* WO 98 10, 384 (CI C07D 471/14); *Chem.Abstr.,* **130,** 13918h (1999).

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

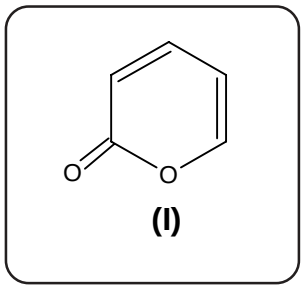
32. D. N. Upadhyay, V. J. Ram; *I. J. Chem.* Sec.(B) *Org. Chem. Abstr.,* **131,** (1999).

33. A Handbook of Spectroscopic data by B.D.Mishtry; 1st ed. ABD press Jaipur 11-36(2000)., "Absorption Spectroscopy of Organic Compounds", by V.M.Parikh, *addision-Wesley Pub. co., London*, 243-258(1978).

34. Introduction to Infrared and Raman Spectroscopy by Nurmav B. Colthup, Lowrence H-Daly and Stephene E. Wiberluy, *Academic Press*(1975).

## INTORDUCTION

2-Pyranone is a six membered oxygen containing heterocyclic compound having keto group at 2-position. It was discovered form 2-hydroxy succinic acid through Von pechmann synthesis. Then after the chemistry of 2-pyranones has aroused a great interest due to its medicinal interest.



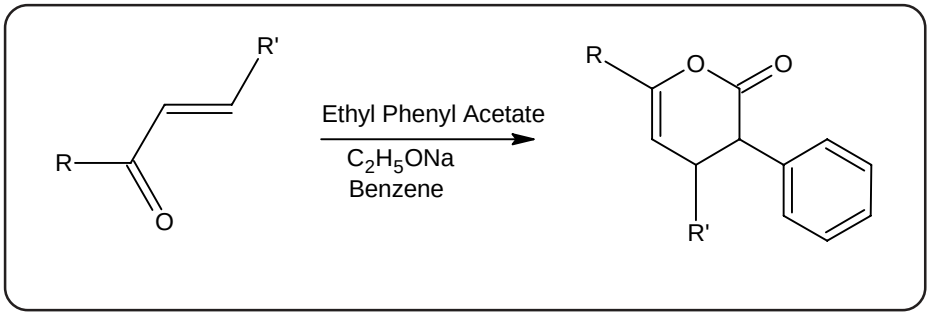

**(I)**

Biological importance of pyranone derivatives is well known. They have been reported to be active as an anticoagulants, HIV protease, serine proteases, herbicides, antialeish manid, anticancer, insecticidal, antibiotic etc.

## SYNTHETIC ASPECT

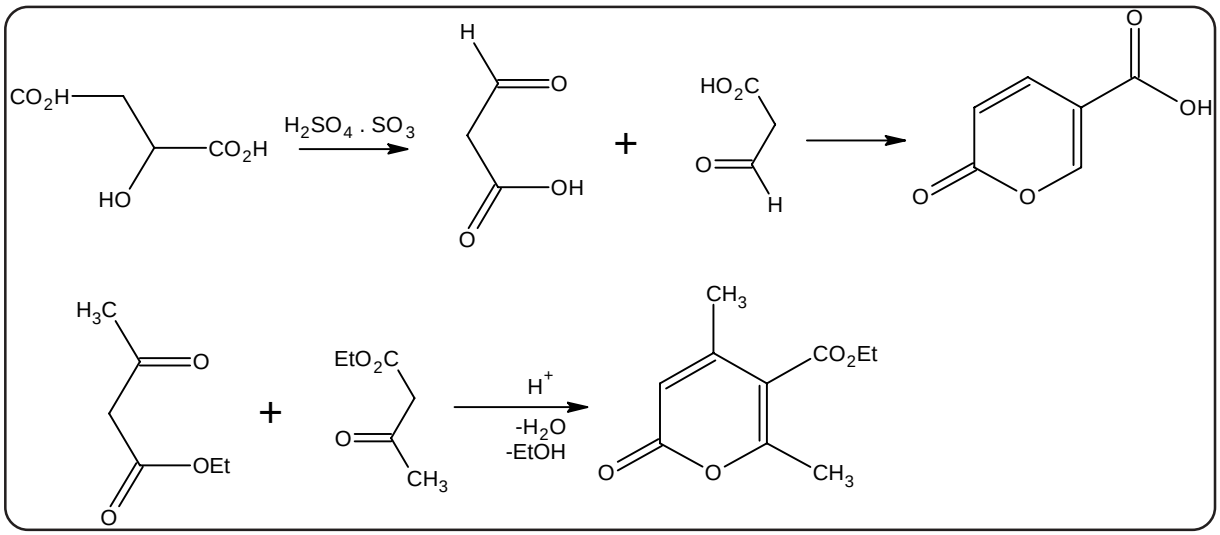
Different methods have been documented for the synthesis of pyranones in literature[1-23].

1. Yousuf A. Al; et al.[24] synthesised pyranone derivatives from 3-aryl-1-phenyl-2-prop-1-ones with ethylphenyl acetate.




## REACTION MECHANISM

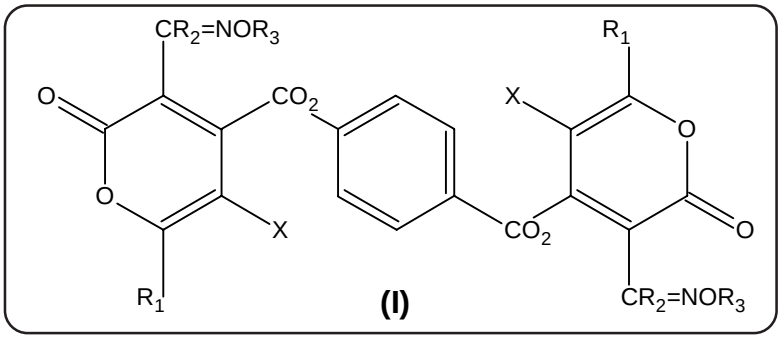
The probable reaction mechanism can be explaining on the basis of Pechmann synthesis as follow.




## THERAPEUTIC IMPORTANCE

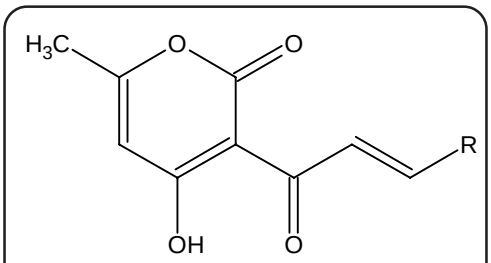
1. Antibiotic[25]
2. Insecticidal[26]
3. Anticancer[27]
4. Antialeish manid[28]
5. Serine propteases[29]
6. Anticoagulants[30]
7. Herbicidal[31]
8. HIV protease[32]
9. Induced liver injury in rats[33]

Nippon sodu co., Ltd.[34] synthesised 2-pyranone(I) as herbicidal agent.



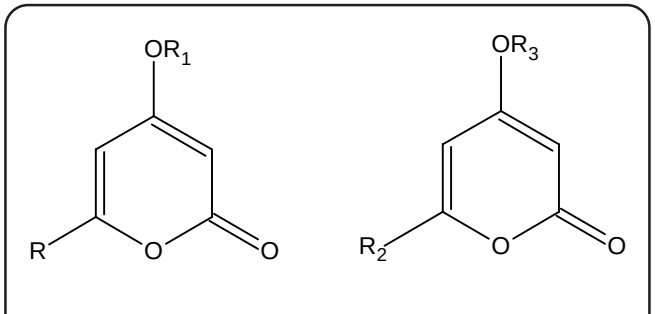

**(I)**

Rehse, Klaus et al.[35] prepared and evaluted 2-pyranone (II) as anticoagulants and their N-oxidase.



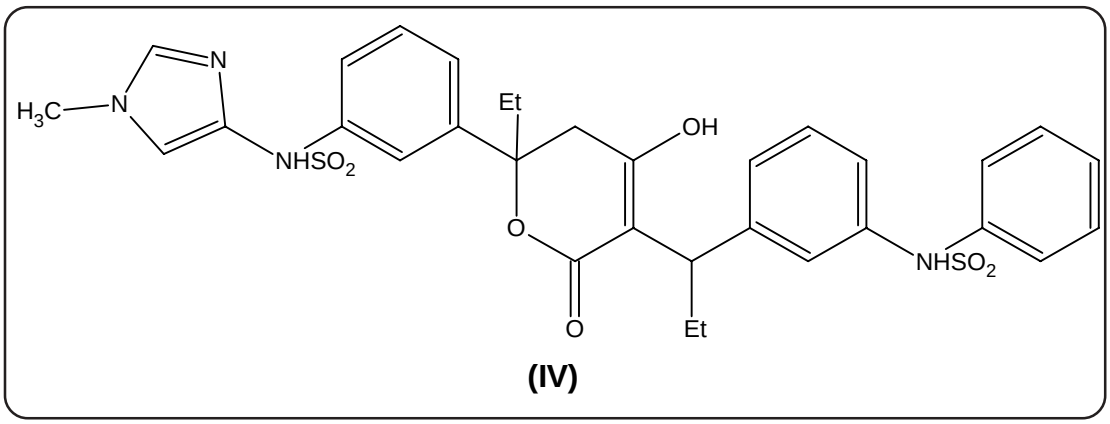

**(II)**

Groutas, william C. et al.[36] have prepared some 2-pyranone(III) derivatives and reported them as inhibitors of the serine proteases.




**(III)**

$C_2$-symmmetry based resin of bis-sulfonamide dihydropyrones (IV) is a non-peptidic HIV protease inhibitors was synthesized by Janakiraman et al.[37]




**(IV)**

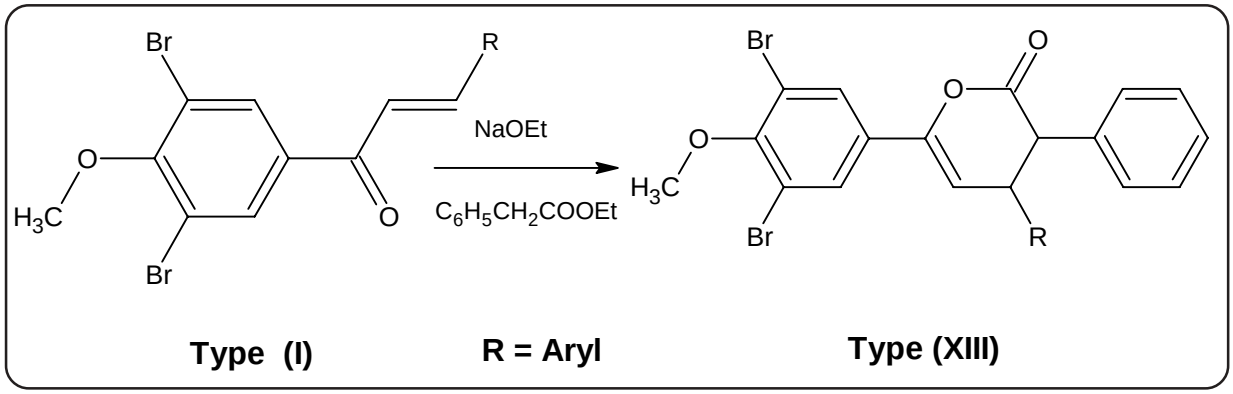
These valid observations prompted us to combine this nucleus with 4-methoxy-3,5-dibromo acetophenone so as to enhance the overall activities of resulting moiety, which have been described as under:

## SECTION - I SYNTHESIS AND BIOLOGICAL SCREENING OF 6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-3-PHENYL- 3,4-DIHYDRO-2H-PYRAN-2-ONES

# SECTION-I

## SYNTHESIS AND BIOLOGICAL SCREENING OF 6-(3,5-DIBROMO-4-METHOXY PHENYL)-4-ARYL-3,4-DIHYDRO-2H-PYRAN-2-ONE

Pyranones have been reported to have various pharmacological activities like anticancer, antibacterial etc. In order to achieving better drug potency, we have prepared pyranone derivatives of type -(XIII) by the cyclo condensation of (2E)-1-(3,5-dibromo-4-methoxy phenyl)-3-aryl-prop-2-en-1-ones of type-(I) with ethylphenyl acetate in presence of sodium ethoxide in benzene

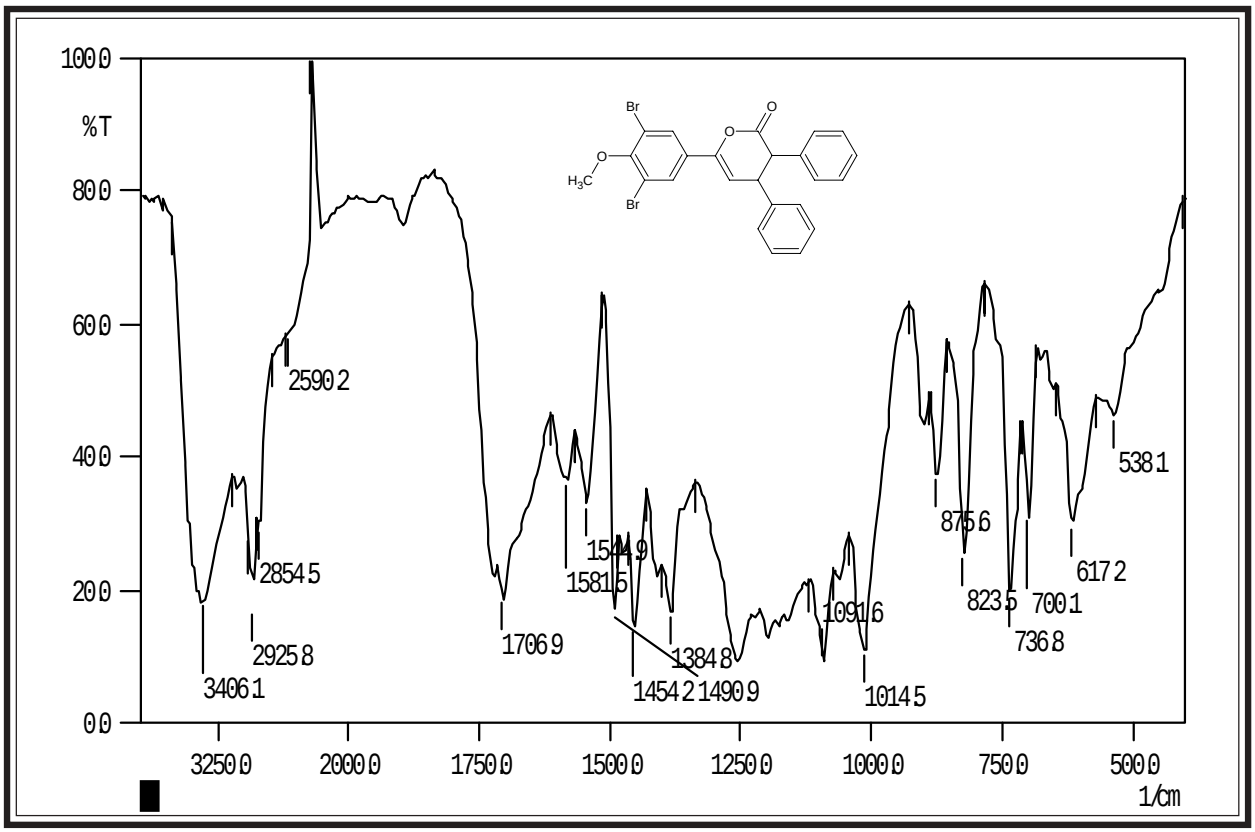



**Type (I)** **R = Aryl** **Type (XIII)**

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 spectroscopy.

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

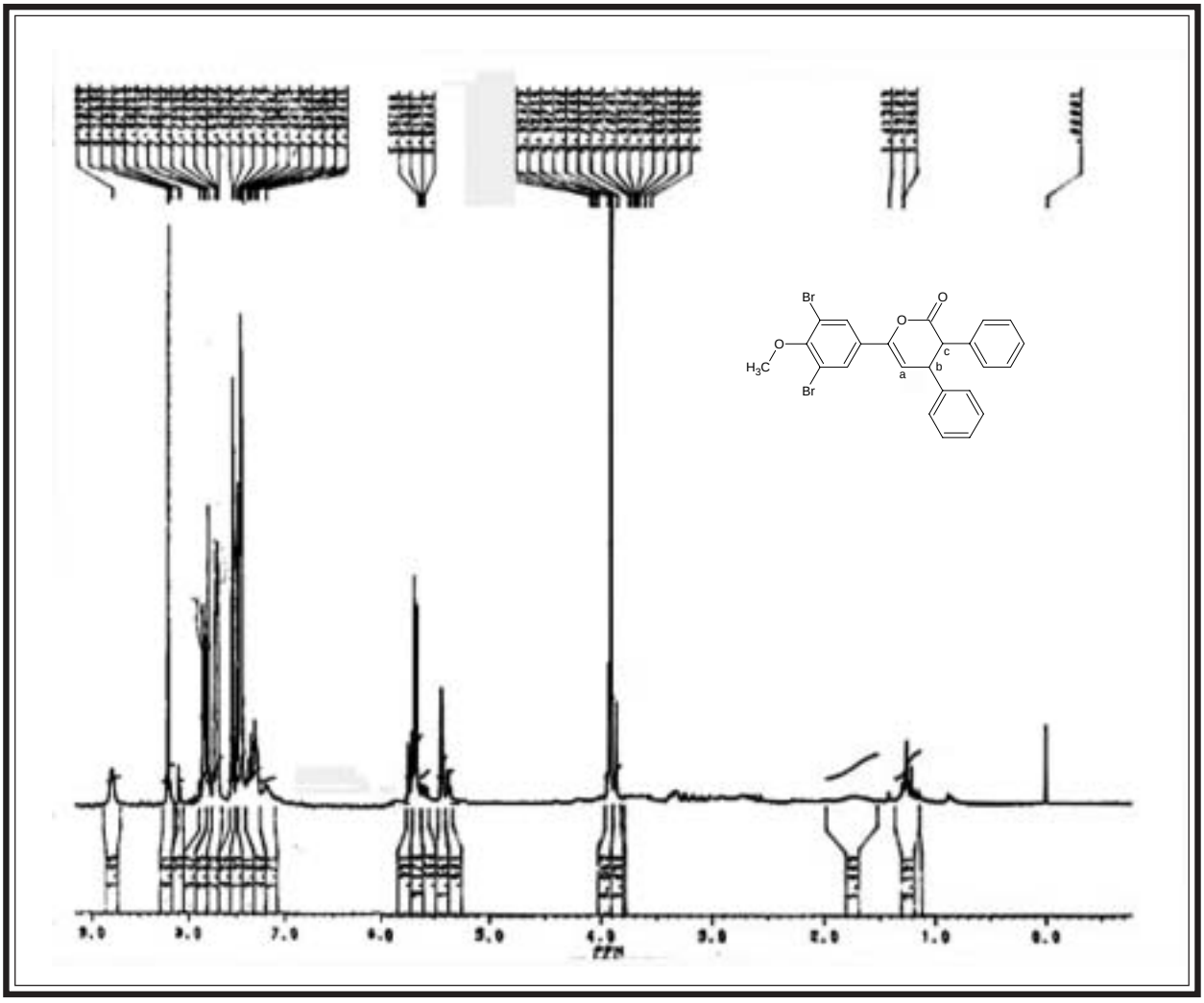
**IR spectral studies of 6-(3,5-Dibromo-4-methoxyphenyl)-4-phenyl-3-phenyl-3,4-dihydro-2H-pyran-2-one**




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

| Type | Vibration Mode | Frequency in $cm^{-1}$ | | Ref. |
|---|---|---|---|---|
| | | Observed | Reported | |
| Alkane | C-H str.(asym.) | 2925 | 2975-2950 | 38 |
| $-CH_3$ | C-H str.(sym.) | 2854 | 2880-2860 | " |
| | C-H def.(asym.) | 1454 | 1470-1435 | " |
| | C-H def.(sym.) | 1389 | 1390-1370 | " |
| Aromatic | C-H str. | 3060 | 3090-3030 | 39 |
| | C=C str. | 1544 | 1540-1480 | " |
| | | 1091 | 1125-1090 | " |
| Halide | C-Br str. | 538 | 600-500 | 38 |
| Ether | C-O-C str.(sym) | 1210 | 1275-1200 | " |
| Pyranone | C=O str. | 1706 | 1740-1700 | 39 |

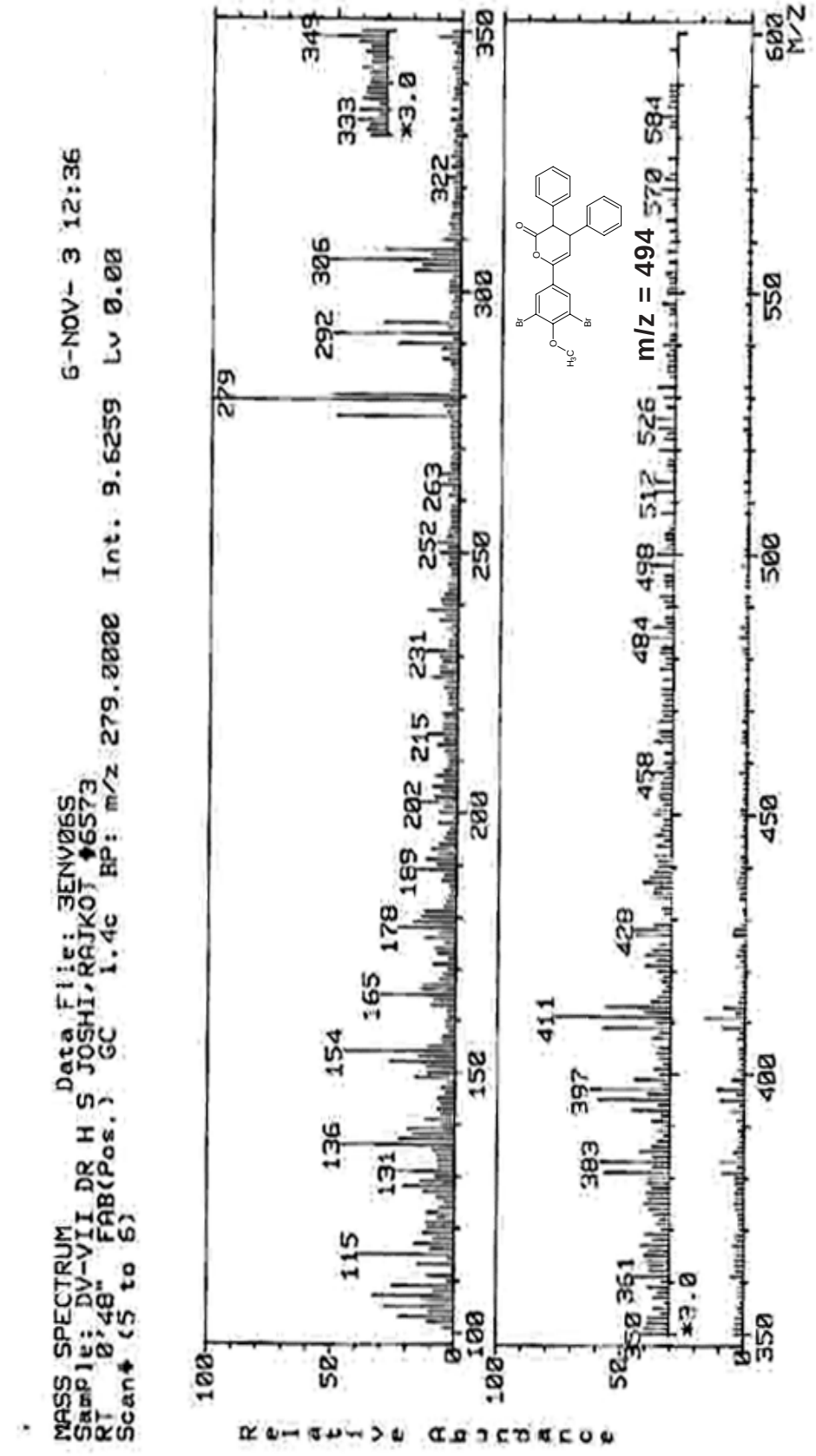
**NMR SPECRTRAL STUDIES OF 6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-PHENYL -3-PHENYL-3,4-DIHYDRO-2H-PYRAN-2-ONE**




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

| Signal No. | Signal Position (δ ppm) | Relative No. of Proton | Multiplicity | Inference |
|---|---|---|---|---|
| 1. | 3.95 | 3H | singlet | Ar-$OCH_3$ |
| 2. | 5.65 | 1H | triplet | -Hb |
| 3. | 5.35 | 1H | doublet | -Hc |
| 4. | 7.00-8.14 | 12H | multiplet | Ar-H |
| 5. | 8.15 | 1H | doublet | -Ha |

**MASS spectral studies of 6-(3,5-dibromo-4-methoxy phenyl)-4-phenyl-3-phenyl-3,4-dihydro-2H-pyran-2-one**



# EXPERIMENTAL

## SYNTHESIS AND BIOLOGICAL SCREENING OF 6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-3-PHENYL- 3,4-DIHYDRO-2H-PYRAN-2-ONES

### (A) Synthesis of (2E)-1-(3,5- Dibromo-4-methoxy phenyl)-3-aryl-prop-2-en-1-ones

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

### (B) Synthesis of 6-(3,5-Dibromo-4-methoxyphenyl)-4-phenyl-3-phenyl-3,4-dihydro-2H-pyran-1-one

(2E)-1-(3,5-dibromo-4-methoxyphenyl)-4-phenyl-3-phenyl-prop-2-en-1-one. (3.96gm, 0.01 mol) and ethyl phenyl acetate (1.64gm, 0.01 mol) were added successively to a suspension of sodium ethoxide (0.46gm, 0.01 mol) in dry benzene (50 ml). The reaction mixture was heated on a water-bath for 3 hrs. The reaction mixture was poured into cold dilute HCl (10%) and extracted with benzene. The benzene layer was washed with sodium bicarbonate solution, dried and evaporated. The residue was crystallized from methanol. Yield.60% ; $C_{24}H_{18}Br_2O_3$ m.p. $96^0$C Anal. Calcd. for Requires: C, 56.06; H, 3.53; Found: C, 56.16; H,3.59%

Similarly, other 6-(3,5-dibromo-4-methoxyphenyl)-4-aryl-3-phenyl-3,4-dihydro-2H-pyran-1-ones were prepared. The physical data are recorded in Table No. 13

### (C) Biological screening of 6-(3,5-Dibromo-4-methoxyphenyl)-4-aryl-3-phenyl-3,4-dihydro-2H-pyran-1-ones

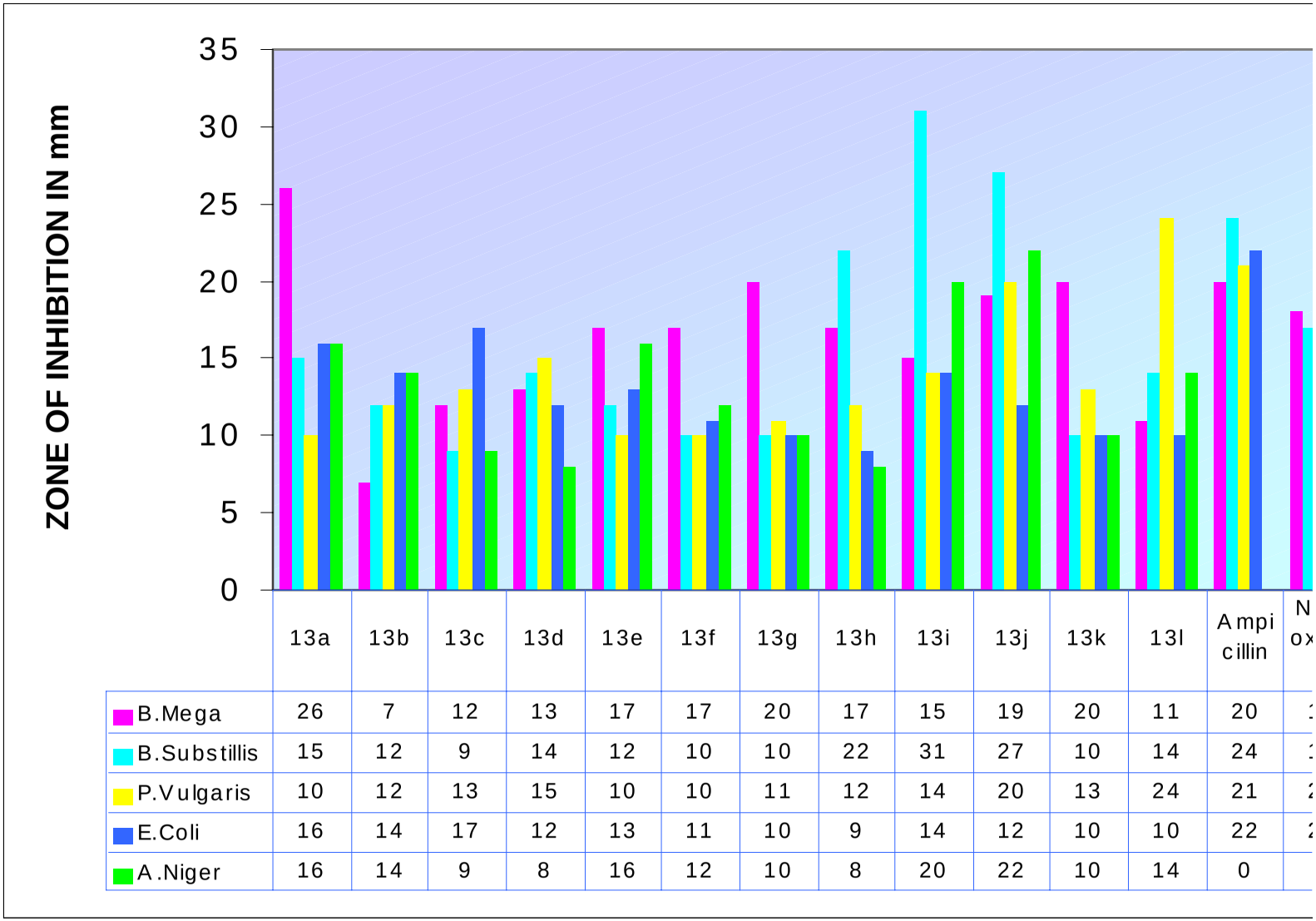
Antimicrobial testing were carried out as described in Part-I Section-1(D). The zones of inhibition of test solutions are recorded in Graphical Chart No. 13

## TABLE-13 : PHYSICAL CONSTANTS OF 6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-3-PHENYL-3,4-DIHYDRO-2H-PYRAN-2-ONES.

| Sr. No. | R | Molecular Fromula | Molecular Weight | M.P. °C | Yield % | % of Nitrogen Calcd. | % of Nitrogen Found | Rf Value | Solvent System |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| 13a | $C_6H_5$- | $C_{24}H_{18}Br_2O_3$ | 514.2 | 96 | 60 | - | - | 0.55 | S1 |
| 13b | 3-Br-$C_6H_4$- | $C_{24}H_{17}Br_3O_3$ | 593.1 | 65 | 58 | - | - | 0.48 | S2 |
| 13c | 2-Cl-$C_6H_4$- | $C_{24}H_{17}Br_2ClO_3$ | 548.7 | 102 | 62 | - | - | 0.50 | S1 |
| 13d | 4-Cl-$C_6H_4$- | $C_{24}H_{17}Br_2ClO_3$ | 548.7 | 106 | 55 | - | - | 0.45 | S1 |
| 13e | 4-$N(CH_3)_2$-$C_6H_4$- | $C_{26}H_{23}Br_2NO_3$ | 557.3 | 70 | 56 | 2.44 | 2.52 | 0.52 | S2 |
| 13f | 4-$OCH_3$-$C_6H_4$- | $C_{25}H_{20}Br_2O_4$ | 544.2 | 118 | 58 | - | - | 0.56 | S2 |
| 13g | 3,4-$(OCH_3)_2$-$C_6H_3$- | $C_{26}H_{22}Br_2O_5$ | 574.3 | 108 | 60 | - | - | 0.49 | S2 |
| 13h | 2-$NO_2$-$C_6H_4$- | $C_{24}H_{17}Br_2NO_4$ | 559.2 | 140 | 65 | 2.43 | 2.49 | 0.59 | S2 |
| 13i | 3-$NO_2$-$C_6H_4$- | $C_{22}H_{17}Br_2NO_4$ | 559.2 | 94 | 62 | 2.43 | 2.39 | 0.47 | S1 |
| 13j | 2-OH-$C_6H_4$- | $C_{24}H_{18}Br_2O_4$ | 530.2 | 78 | 60 | - | - | 0.44 | S1 |
| 13k | 4-OH-$C_6H_4$- | $C_{24}H_{18}Br_2O_4$ | 530.2 | 70 | 57 | - | - | 0.54 | S2 |
| 13l | $C_4H_3O$- | $C_{22}H_{16}Br_2O_4$ | 504.2 | 60 | 56 | - | - | 0.43 | S2 |

S1 Hexane:Ethyl acetate(5:5), S2 Hexane:Ethyl acetate(6:4)

## GRAPHICAL CHART NO.13 : 6-(3,5-DIBROMO-4-METHOXYPHENYL)-4-ARYL-3-PHENYL-3,4-DIHYDRO-2H-PYRAN-2-ONES.




| | 13a | 13b | 13c | 13d | 13e | 13f | 13g | 13h | 13i | 13j | 13k | 13l | Ampicillin | N ox |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B.Mega | 26 | 7 | 12 | 13 | 17 | 17 | 20 | 17 | 15 | 19 | 20 | 11 | 20 | 1 |
| B.Substillis | 15 | 12 | 9 | 14 | 12 | 10 | 10 | 22 | 31 | 27 | 10 | 14 | 24 | 1 |
| P.Vulgaris | 10 | 12 | 13 | 15 | 10 | 10 | 11 | 12 | 14 | 20 | 13 | 24 | 21 | 2 |
| E.Coli | 16 | 14 | 17 | 12 | 13 | 11 | 10 | 9 | 14 | 12 | 10 | 10 | 22 | 2 |
| A.Niger | 16 | 14 | 9 | 8 | 16 | 12 | 10 | 8 | 20 | 22 | 10 | 14 | 0 | |

**REFERANCES**


1. Yousuf. A. Al; Farkh, Parouck H.; Al-Hajjar: *J.Heterocylic chem.,***16,**1 (1979)
2. Alberto Bargagna(a), Fillppo, Evangelistic (b): *J.Heterocylic chem.,* **16,** 93 (1979)
3. B. K. Triputhi, S. Srivastava, R. Rastogi Peepak Rainu *J. med. Chem.,* **70,** 40 (23), (1997).
4. Trollient, Maurice; Longeray, Remi; *Bull. Soc. Chem. Fr.* ***7-8,pt-2,*** 1485-1486 (1974).
5. Tukeuchi, Yoshi C; Mukino, Yutaka; *Heterocycles,***14(2),**163-168(1980),*Chem. Abstr.,***81,** 105188(1974).
6 Agami Chemical Research center. *Jpn.Kakai Tokyo Kohu* **80,**162, 781 (Cl.Co7D309/32),18,Dec. 1980, Appl. 79/69, 978, 06 Jan 1979,6pp,*Chem. Abstr.,***95,** 807279(1981).
7. Bargagna, Alberto; Evanggelish, Fillppo, *J. Heterocyclic Chem.,* 111-116 (1981),*Chem. Abstr.,* **95,**80845d(1981)
8. Christi, Manfred; Lonzendoerfer, Ulrika; *Angew Chem.,* **95,** 686-687(1981) *Chem.Abstr.,* **95,**150608d(1981)
9. Weyerstohl, Peter; Marschall-weyer stahl, Helga; *Chem.Ber.,*(1986). *Chem.Abstr.,* **104,** 224808y(1986).
10. A. D. Argoudelis; J. F. Zieserl; *Tetrahydra. Letters.,* **18,** 1969-1973 (1966) *Chem. Abstr.,* **65,**2191e(1966).
11. Al-Fark, Yousut. A., Al-Hajjar, Furouk H.; *J. Heterocycl, Chem.,* **16(1),**1-6(1979) *Chem. Abstr.,* **90,**168403r(1979).
12. Shakhatani, H, K; Shiroyam, F, R; *Ame. Khim. Zh.* **31,** 857-861(1979) *Chem. Abstr.,* **90,** 152064r(1979).
13. Semet, Robert, Longeray, Remi, *Bull. Soc. Chem.Fr.,* **3-4, Pt-(2),** 185-192 (1978)*Chem. Abstr.,* **89,**197270e(1978).
14. Cervello, J; Gil, M; *Tetrahydra. Letters.,* **43(10),** 2381(1987) *Chem.Abstr.,* **107,**217437f(1987).
15. Mitra, R. B; Kulkarni, G, H; *Systh. Commun.,* **17(9),** 1089-1094,(1987) *Chem. Abstr.,* **107,** 217437f (1987).
16. Dimedone, Leyky, Pavel; Kronig, Peter; *fer. Pat. Appl. EP* **65,** 708 (Cl Co745160) , (1981) *Chem. Abstr.,* **98,** 106865z (1983).
17 Vanin, V. V, Krutskil, L. N. *Ch. Parikl, Kim.* **57(3),** 628-630(1984).*Chem. Abstr.,* **101,** 90718w (1984).

18. Midland, M. Mark, Graham, Richard; *J. Am. Chem.Soc.,* **101,** 90719x(1984) *Chem.Abstr.,* **101,** 90719w (1984).

19. El-Khely, Ibrahim, El-Sayed; *J. Heterocycli. Che.,* **19(6),** 1329-1334(1982) *Chem.Abstr.,* **99,** 5478h (1983).

20. Fieser and Fieser; Reagents for Oraganic *Systhesis,* Wiley, **1,** 970 (1967).

21. Evnin, A. B. et al. *J. A. C. S.* **89,** 952 (1967).

22. Nakagawa, M. et al. *Synthsis*., **39,** 1935 (1974).

23. Izumi, T. et al. *Bull. Chem. Soc. Jpn.,* **48,** 1673 (1975).

24. Yousuf. A. Al; Farkh, Parouck H.; Al-Hajjar: *J.Heterocylic chem.,***16,**1 (1979)

25. A. D. argoudelis, J. F. Zieserl. *Tetrahedron Letters* **18,** 1969-1973 (1996).

26. Mitra R. B.; Kulkarni G. H. Khanna. P. N. ; *Synth. Commun.* **17(9),**1089-94(1987).

27. Haa, Duy, H.; Perchellet, Jear-pierre. *Chem. Abstr.* **131**, 2432594 (1999).

28. Saeed, M.; Ilg. T.; Schick, M. N.; Abbas, M.; *Chem. Abstr.,* **136,** 69685w (2002).

29. Groutas, Wiliam e: Huang, Tiene; *Chem. Abstr.,* **131,** 2151196 (1999).

30. Rehse, Klaus; Brandt, Fried helm; *Chem. Abstr.,* **100,**68142 m (1983).

31. Nipponsodu co., Ltd.JPN, *Chem. Abstr*., **98,** 16579e (1983).

32. Domagala, Jom. Michacl; et al. *Chem. Abstr.,* **129,** 245043 b(1996).

33. B. K. Triputhi, S. Srivastava, R. Rastogi Peepak Rainu *J. med. Chem.,* **70,** 40 (23), 1997.

34. Nipponsodu co., Ltd.JPN, *Chem. Abstr*., **98,** 16579e (1983).

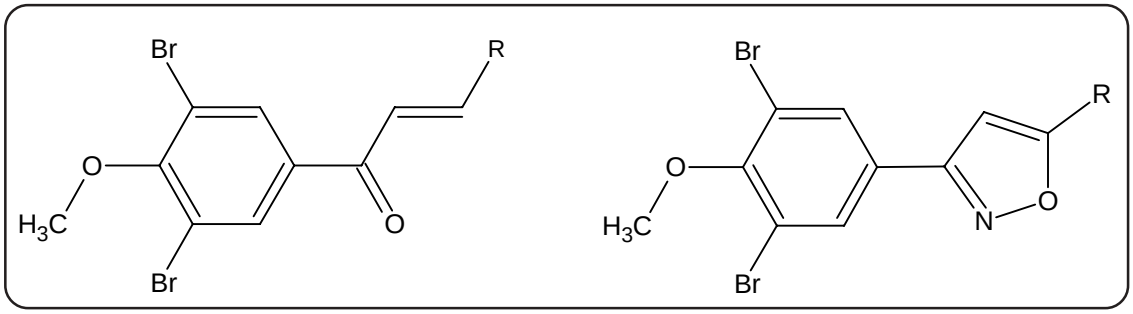
35. Rehse, Klaus; Brandt, Friedhelh, *Arch Pharma.,* **312(12),** 1630-1634 (1983) *Chem. Abstr*., **100,** 68142m (1984).

36. Groutas, William C.; Huang, Tiene; *Chem. Abstr.,* **131,** 2151196 (1999).

37. Jana kiraman ; Musiri N.; watenpaugh ; Keith D.; *Chem. Abstr.,* **129,** 214186(1998).

38. A Handbook of Spectroscopic data by B.D.Mishtry; 1sted. ABD press Jaipur 11-36(2000)., "Absorption Spectroscopy of Organic Compounds", by V.M.Parikh, *addision-Wesley Pub. co., London*, 243-258(1978).

39. Introduction to Infrared and Raman Spectroscopy by Nurmav B. Colthup, Lowrence H-Daly and Stephene E. Wiberluy, *Academic Press*(1975).

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T-4-$OCH_3$-$C_6H_4$
T-3,4$(OCH_3)2$-$C_6H_3$
T-2-$NO_2$-$C_6H_4$
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T-3-$C_6H_5$-O-$C_6H_4$
T-2-OH-$C_6H_4$
T-4-OH-$C_6H_4$

T-$C_6H_5$
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T-2-Cl-$C_6H_4$
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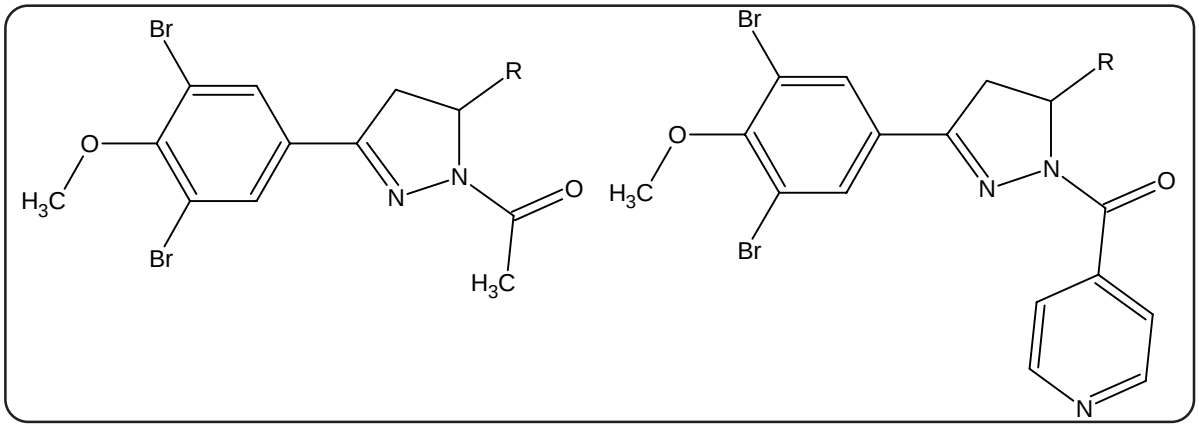
T-4-$OCH_3$-$C_6H_4$
T-2-$NO_2$-$C_6H_4$
T-3-$NO_2$-$C_6H_4$
T-3-$C_6H_5$-O-$C_6H_4$
T-4-OH-$C_6H_4$
T-2-OH-$C_6H_4$
T-$C_4H_3O$

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T-$C_6H_5$
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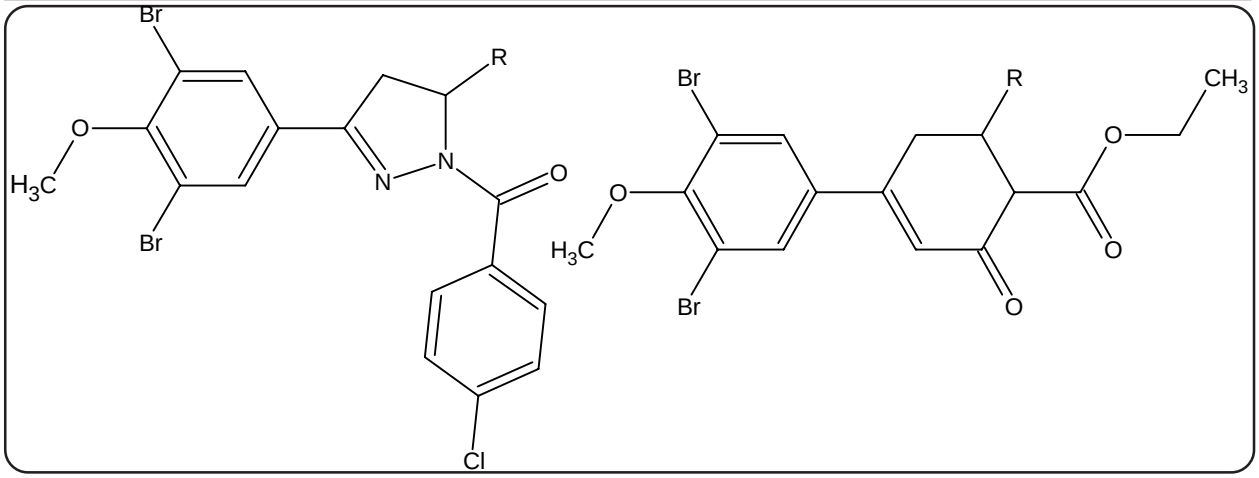


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T-2-OH-$C_6H_4$
T-$C_4H_3$ O

T-$C_6H_5$
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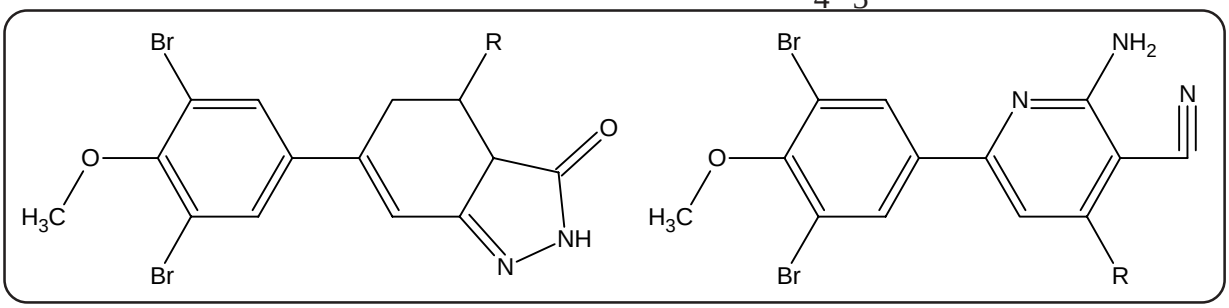


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T-3-$NO_2$-$C_6H_4$
T-3-$C_6H_5$-O-$C_6H_4$
T-4-OH-$C_6H_4$
T-$C_4H_3O$

T-$C_6H_5$
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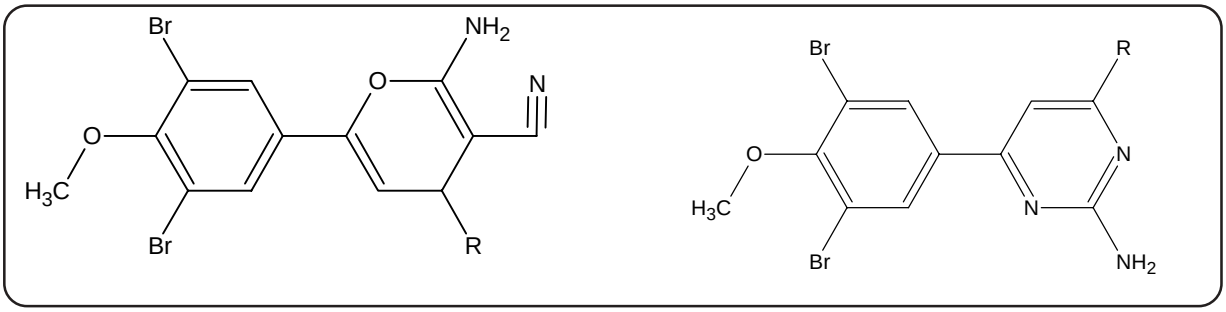


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T-$C_6H_5$
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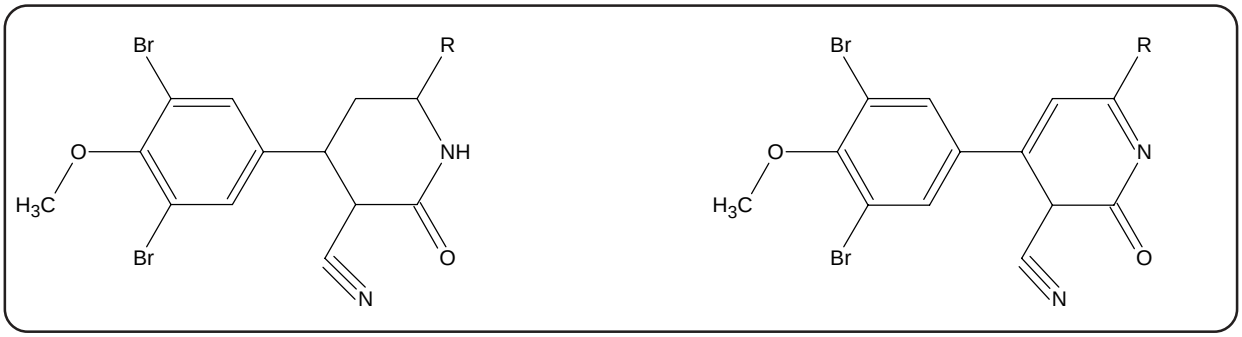


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T-4-$OCH_3$-$C_6H_4$
T-2-$NO_2$-$C_6H_4$
T-3-$NO_2$-$C_6H_4$
T-3-$C_6H_5$-O-$C_6H_4$
T-$C_4H_3O$

T-$C_6H_5$
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T-3,4-$(OCH_3)_3$-$C_6H_3$
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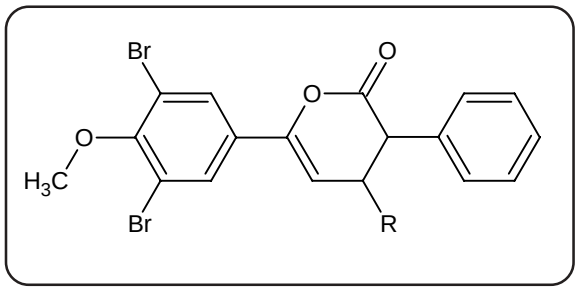


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T-4-Cl-$C_6H_4$
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T-3,4-$(OCH_3)_3$-$C_6H_3$
T-2-$NO_2$-$C_6H_4$
T-3-$NO_2$-$C_6H_4$
T-2-OH-$C_6H_4$
T-4-OH-$C_6H_4$
T-$C_4H_3O$

**T = Compounds selected by Tuberculosis Antimicrobial Acquisation Coordinating Facility (TAACF), Southern research institute, Alabama, U.S.A. for antitubercular activity.**