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SYNTHESIS, SPECTRAL STUDIES AND THERAPEUTIC ACTIVITY OF SOME HETEROCYCLIC COMPOUNDS

A THESIS
SUBMITTED TO
SAURASHTRA UNIVERSITY
FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN
THE FACULTY OF SCIENCE (CHEMISTRY)
BY

PARESH J. KATHIRIYA

UNDER THE GUIDANCE
OF

Dr. D. M. PUROHIT

SHREE M. & N. VIRANI SCIENCE COLLEGE
DEPARTMENT OF CHEMISTRY
KALAWAD ROAD, RAJKOT-360005
(GUJARAT) INDIA

2010

Dr. D. M. Purohit,
Department of Chemistry,
Shree M. & N. Virani Science College,
Rajkot-360005
Gujarat(INDIA)

Dr. D. M. Purohit,
B-149, "Shandilya",
Shastrinagar,
Nana mova road, Rajkot-5
Gujarat(INDIA)

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

The work included in the thesis is my own work under the supervision of **Dr. D. M. Purohit** and leads to some contribution in chemistry subsidised by a number of reference.

Date : - -2010 **Paresh J. Kathiriya**
Place : **Rajkot.**

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

Date : - -2010
Place : **Rajkot.**

Dr. D. M. Purohit
Shree M. & N. Virani Science College
Department of Chemistry
Kalawad Road, Rajkot-360005.

DEDICATED

TO

MY BELOVED PARENTS

ACKNOWLEDGEMENTS

"Shree Aai Khodiyar Maa"

Hats off to the Omnipresent, Omniscient and Almighty God, the glorious fountain and continuous source of inspirations ! I offer salutations to him and my head bows with rapturous dedication from within my heart, to the Omnipotent Lord

"Shree Aai Khodiyar Maa"

An endeavor such as a Ph.D. is impossible to accomplish without the generous help and support of my family, friends and colleagues. I would like to take this opportunity to thank those whom I was fortunate to know, work, and form friendship with over the past three years.

First I would like to express my deep appreciation and gratitude to my co-traveler and guide **Dr. D. M. Purohit** Lecturer, Department of Chemistry, Shree M. & N.Virani Science College, Rajkot. His dedication to science, unwavering demand for excellence from him has set up a high standard for his students to look up to and to follow. I appreciated the freedom he allowed, which permitted me to develop scientific thoughts and experimental skills independently, lofty research methodology and the motivation as well as them highly punctual, affectionate.

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Who in this world can entirely and adequately thank the parents who have given us everything that we possess in this life ? The life it self is their gift to us, so I am at loss of words in which to own my most esteemed father late. **Shri Jasubhai** and my loving mother **Smt. Bhanuben**. I would be remised if I failed to express my special gratitude to my elder brother **Hiren & his wife Nidhi.** Through the stress and strain of this study, my wife **Archana** has encouraged me to reach my destination.

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Paresh J. Kathiriya

SYNTHESIS, SPECTRAL STUDIES AND THERAPEUTIC ACTIVITY OF SOME HETEROCYCLIC COMPOUNDS

CONTENTS

SYNTHESIS, SPECTRAL STUDIES AND THERAPEUTIC ACTIVITY OF SOME HETEROCYCLIC COMPOUNDS.

SYNOPSIS

SYNTHESIS, SPECTRAL STUDIES AND THERAPEUTIC ACTIVITY OF SOME HETEROCYCLIC COMPOUNDS.

The research work presented in the thesis with the title, "SYNTHESIS, SPECTRAL STUDIES AND THERAPEUTIC ACTIVITY OF SOME HETEROCYCLIC COMPOUNDS" has been described as under.

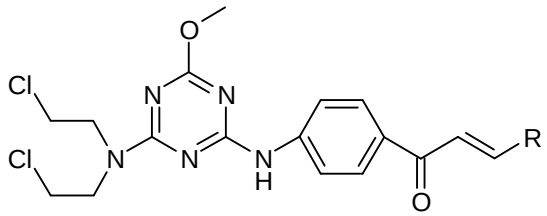
The aim of research is to be develop new bioactive entitles, especially with biological activities bearing heterocyclic ring system namely Bis (2-Chloroethyl) amine 1, 3, 5-triazine molecules. Numerous heterocyclic compounds like chalcones, isoxazoles, pyrazolines, pyrimidines, cyanopyridines, cyanopyrans, quinoxalines, barbitones and thiosemicarbazides, triazoles have been synthesized.

1, 3, 5-triazine and Bis (2-Chloroethyl) amine represent one of the most class of compounds possessing a wide spectrum of bactericidal, fungicidal, anticancer, antiviral, anti-inflammatory activities etc. With a view of to synthesize some new s-triazine, 2, 2-dichloro diethylamine derivatives which have been described as under.

PART - I : STUDIES ON CHALCONES

Chalcones are Phenyl styrylketones containing reactive keto ethylenic group (-CO-CH=CH-). Liturature serve reveals that chalcones derivatives possess antibacterial, antiviral, antifungal activities. Hence, it was thought worth while to synthesis chalcones derivatives of which have been described as under.

Section-I : Synthesis and Antimicrobial activity of 2-{4'-[(3"-Aryl)-2"-Propene-1"- one]-phenylamino}-6-[Bis(2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine.



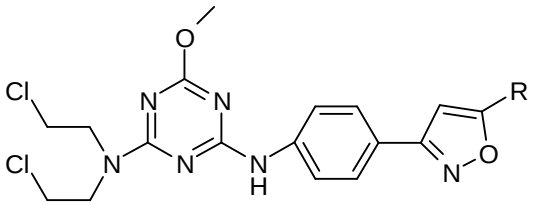
(Type-I) R = Aryl

The chalcones of Type-(I) have been synthesized by the condensation of 2-[(4'- acetyl) phenyl amino]-6-[Bis (2"-chloro ethyl)] amino-4-methoxy-1,3,5-triazine with aromatic aldehyde in presence of aqueous NaOH.

PART - II : STUDIES ON ISOXAZOLES

Isoxazole derivatives are the potent biological activities, these have been reported to be active as antidepressants, antibacterial, antifungal, antiviral, antiinflamatory, analgesics and Bis (2-chloroethyl) amine possess anticancer, anti-HIV activities. In order to achieving better potency to synthesize isoxazole derivatives which are described as under

Section-1 : Synthesis and Antimicrobial activity of 2-{4'-[(5"-aryl)-Isoxazole-3"-yl]- phenylamino}-6-[Bis(2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine.



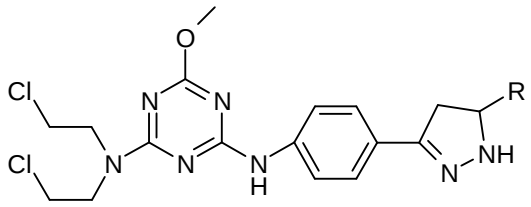
(Type-II) R = Aryl

Isoxazole of Type-(II)-have been syntesized by chemoselective cyclisation between chalcones of Type-(I) with hydroxyl amine hydrochloride.

PART - III : STUDIES ON PYRAZOLINES

Pyrazoline derivatives possess broad spectrum of pharmacological activities which are reflected by their use as analgesic, anticonvulsant, antimicrobial, antipyratics etc. The main moiety Bis (2-chloroethyl) amine, 1,3, 5-triazine nucleus have been reported to be active as antineoplastic agents with a view of above facts. Some new pyrazolines have been synthesized which have been described as under.

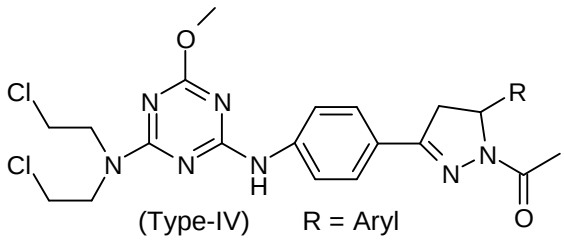
Section-I : Synthesis and Antimicrobial activity of 2-{4'-[(5"-Aryl) 4", 5"-dihydro-1"-(H)-Pyrazol-3"-yl]-phenylamino} –6-[Bis (2"'-chloroethyl) amino] – 4 - methoxy-1,3,5 - triazine.



(Type-III) R = Aryl

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

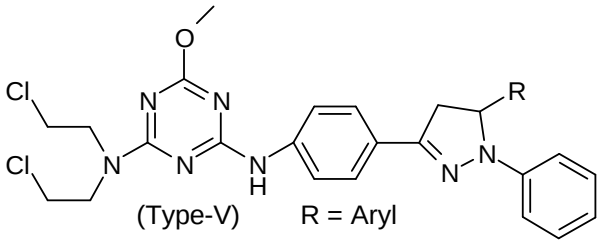
Section-II : Synthesis and Antimicrobial activity of 2-{4'-[(5"-aryl)-4", 5"-dihydro 1"-acetyl Pyrazol-3"-yl]-phenylamino} – 6 - [Bis (2"-chloroethyl) amino]-4-methoxy-1,3,5-triazine.



(Type-IV) R = Aryl

Acetyl pyrazolines derivatives of Type (IV) have been synthesized by the condensation of chalcones of Type-(I) with hydrazine hydrate and glacial acetic acid.

Section-III: Synthesis and Antimicrobial activity of 2-{4'-[(5"-Aryl)-4", 5"-dihydro-1"-Phenyl Pyrazole-3"-yl]-phenylamino} – 6 - [Bis (2"-chloroethyl) amino] – 4 – methoxy - 1,3,5 - triazine.



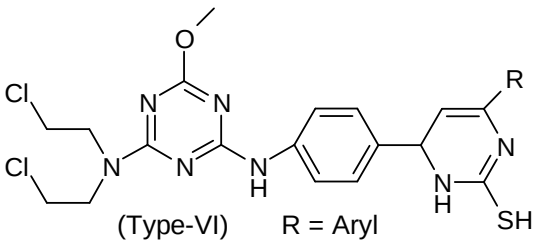
(Type-V) R = Aryl

Phenyl Pyrazoline derivatives of Type-(V) have been synthesized by the condesation of chalcones of Type-(I) with phenyl hydrazine.

PART-IV : STUDIES ON PYRIMIDINES

Pyrimidine nucleus possess remarkable pharmaceutical and biological activities. Pyrimidine derivatives are associated with various biological activities like antibacterial, antifungal, antitubercular, antimalarial, antitumor, antihypertensive etc. This valid observation led us to synthesize some new medicinally active compounds which have been described as under.

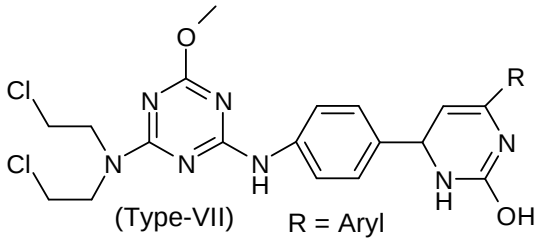
Section-I: Synthesis and Antimicrobial activity of 2-{4'-[(6"-Aryl)-2"-mercapto-3", 4"- dihydro- pyrimidine-4"-yl] -phenylamino} – 6 - [Bis (2"'- chloroethyl) amino] – 4 – methoxy - 1,3,5 - triazine.



(Type-VI) R = Aryl

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

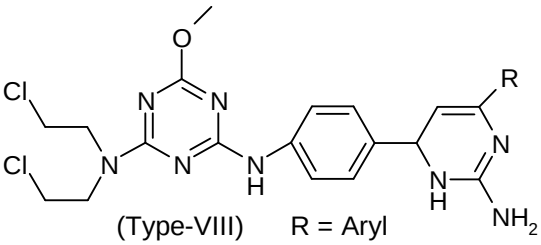
Section-II : Synthesis and Antimicrobial activity of 2-{4'-[(6"-Aryl)-2"-hydroxy-3", 4" – dihydro – pyrimidine - 4" - yl] - phenylamino} – 6 - [Bis (2"' - chloroethyl) amino] – 4 – methoxy - 1,3,5-triazine.



(Type-VII) R = Aryl

Pyrimidine derivatives of Type-(VII) have been synthesized by the reaction of chalcones of Type-(I) with urea.

Section-III : Synthesis and Antimicrobial activity of 2-{4'-[(6"-Aryl)-2"-amino-3", 4" – dihydro – pyrimidine - 4" – yl] – phenylamino } – 6 - [Bis(2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine.



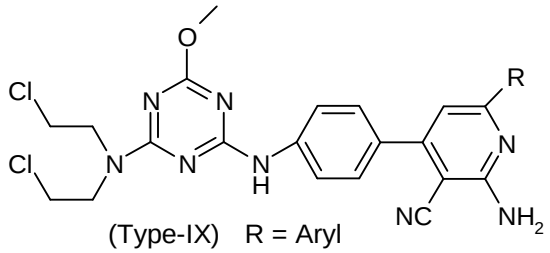
(Type-VIII) R = Aryl

Primidine derivatives of Type-(VIII) have been synthesized by the reaction of chalocnes of Type-(I) with guanidine hydrochloride.

PART-V : STUDIES ON CYANOPYRIDINES

In recent years, much interest have been focused of cyano pyridine derivatives showed wide range of application in the field of pharmaceutical. Cyano pyridine derivative have been reported to be active as antibacterial, antimalarial, antihypertensive, antineoplastic, antifungal, anticonvulsant etc. Considering these facts we thought it is worth while to syntesize some new cyanopyridine derivatives in association with s-triazine nucleus in search of better potential drugs. Which have been describe as under.

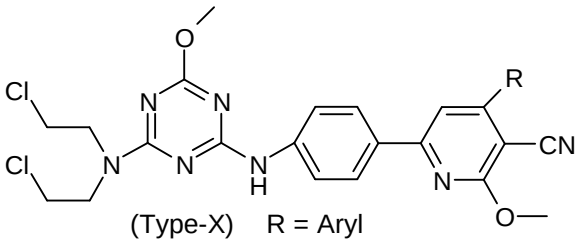
Section-I : Synthesis and Antimicrobial activity of 2-{4'-[(6"-Aryl)-2"-amino-3"-cyanopyridine-4"-yl]-phenylamino}-6-[Bis(2"'-chloroethyl) amino]-4-methoxy-1,3,5- trizine.



(Type-IX) R = Aryl

Pyridine derivatives of Type-(IX) have been synthesized by the reaction of the chalcones of Type-(I) with malono nitile in presence of ammonium acetate.

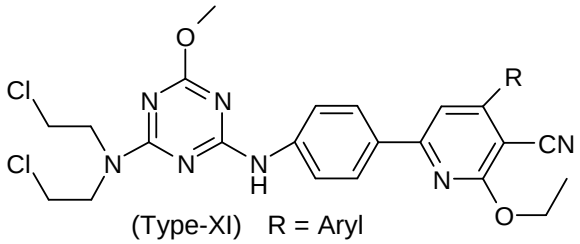
Section-II : Synthesis and Antimicrobial activity of 2-{4'-[(4"-Aryl)-3"-cyano-2"-methoxy-pyridine-6"-yl]-phenylamino}-6-[Bis(2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine.



(Type-X) R = Aryl

Pyridine derivatives of Type-(X) have been synthesized by the reaction of the chalcones of Type-(I) with malono nitrile in presence of sodium methoxide.

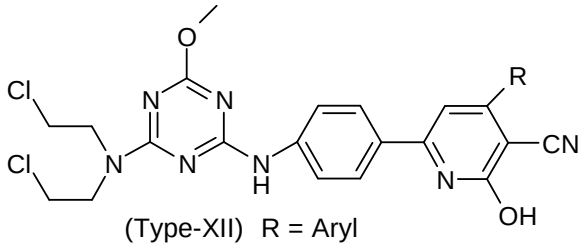
Section-III : Synthesis and Antimicrobial activity of 2-{4'-[(4"-Aryl)-3"-cyano-2"-ethoxypyridine-6"-yl]-phenylamino}-6-[Bis(2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine.



(Type-XI) R = Aryl

Pyridine derivatives of Type-(XI) have been synthesized by the reaction of chalcones of Type-(I) with malonoitrile in presence of sodium ethoxide.

Section-IV : Synthesis and Antimicrobial activity of 2-{4'-[(4"-Aryl)-3"-cyano-2"-hydroxypyridin-6"-yl] - phenylamino } - 6 - [Bis (2"'-chloroethyl) amino] – 4 - methoxy-1,3,5-triazine.



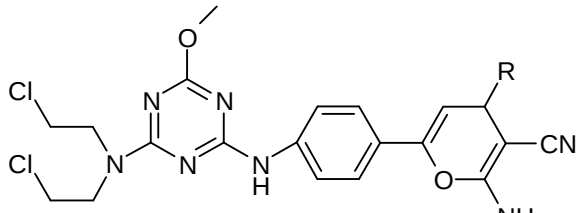
(Type-XII) R = Aryl

Pyridine derivatives of Type-(XII) have been synthesized by the reaction of the chalcones of Type-(I) with ehtyl cyano acetate in presence of ammonium acetate.

PART-VI : STUDIES ON CYANOPYRANS

Cyanpoyran derivatives have been reported to various pharmacological activities like antibacterial, antiviral, antifungal etc. In order to develop better pharmacologically important compounds, it was considered of interest to synthesize some new cyanopyran derivatives shown as under.

Section-I : Synthesis and Antimicrobial activity of 2-{4'-[(2"-Amino-4"-Aryl-4"-(H) – Pyran – 3 - carbonitrile) - 6" - yl] - phenylamino} – 6 - [Bis (2"' -chloroethyl) amino]-4-methoxy-1,3,5-triazine.



(Type-XIII) R = Aryl

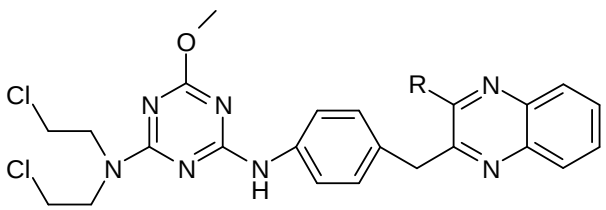
Cyanopyran derivatives of Type-(XIII) have been synthesized by the reaction of chalcones of Type-(I) with malononitrile in pyridine.

PART-VII : STUDIES ON QUINOXALINES

Quinoxalines have been found to possess wide range of therapeutic activities and industrial importance. These significant biological properties have aroused considerable interest to design the compounds in which Bis (2-chloroethyl) amine, 1,3,5-triazine nucleus in incorporated with a view to getting compounds with better potential drug.

Synthesis of quinoxalines of Type-(XIV) have been undertaken by the cyclocondensation of dibromo derivatives of chalcones of Type (I) with o-phenylenediamine as under.

Section-I : Synthesis and Antimicrobial activity of [2"-Aryl-(quinoxaline)3-yl]-(methylene phenylamino)-6-[Bis(2"'-chloroethyl) amino]-4-methoxy - 1,3,5 - triazine.



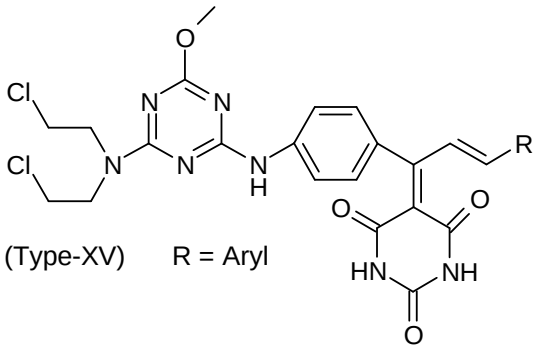
(Type-XIV) R = Aryl

Quinoxaline derivatives of Type-(XIV) have been synthesized by the reaction of chalcones of Type-(I) with bromine in glacial acetic acid and O-phenylene diamine.

PART-VIII : STUDIES ON BARBITONES

Barbituric acid derivatives are a wide spectrum of biological activites. Bis (2-chloroethyl) amine, 1,3,5-triazine molecules possess diversified anticancer, anti-HIV, and other therapeutic activities, considering all the above facts, it was though that barbituric acid group could be introduced to moiety, which have been described as under.

Section-I : Synthesis and Antimicrobial activity of 2-{4'-[(3"-Aryl)-2"-Propene-1"- barbituric acid]-phenylamino}-6-[Bis(2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine.



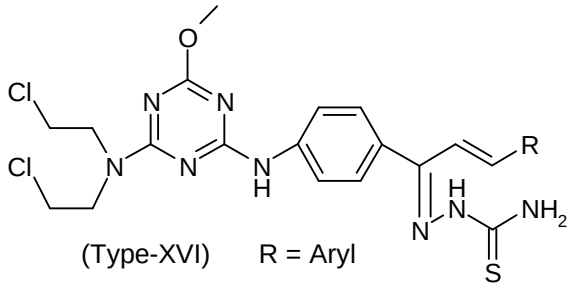
(Type-XV) R = Aryl

Barbituric acid derivatives of Type-(XV) have been synthesized by the reaction of chalcones fo Type-(I) with Barbituric acid in galcial acetic acid.

PART-IX : STUDIES ON THIOSEMICARBOXIMIDES

Thiosemicarboximes derivatives possess broad spectrum of therapeutic activity and antidiabetic, bactericidal, anticonvulsant, antipyretic etc, with a view of above facts to synthesize various thiosemicarboximes derivatives are represented as under.

Section-I : Synthesis and Antimicrobial activity of 2-{4'-[(3"-Aryl)-2"-Propene-1"- thiosemicarboximes] - phenylamino} – 6 - [Bis(2"'-chloroethyl) amino]-4-methoxy-1,3,5- triazine.



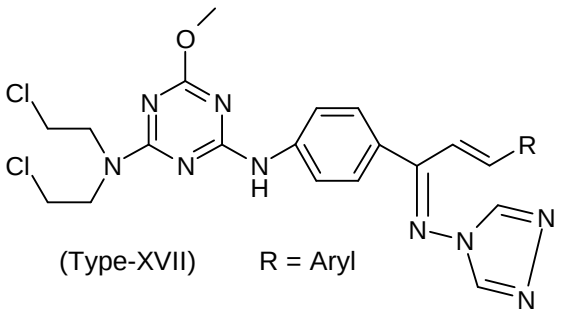
(Type-XVI) R = Aryl

Thiosemicarboximes derivatives of Type-(XVI) have been syntheszied by the reaction of chalcones of Type-(I) with Thiosemicarbazide in alcohol.

PART-X : STUDIES ON TRIAZOLES

Triazole derivatives possess wide spectrum of biological activity considering above facts, it was thought that triazole group could be introduced to moiety which have been described as under.

Section-I : Synthesis and Antimicrobial activity of 2-{4'-[(3"-Aryl)-2"-Propene-1"-N-(1,2,4-triazole)amino]} – 6 - [Bis (2"' - chloroethyl) amino]-4-methoxy - 1,3,5-triazine.



(Type-XVII) R = Aryl

Triazole derivatives of Type-(XVII) have been synthesized by the reaction of chalcones of Type-(I) with 4-amino-1,2,4-triazole in alcohol.

The structure elucidation of the synthesized compounds have been done on the basis of elemental analysis, IR and ^{1}H NMR spectroscopy and further supported by mass spectroscopy. The purity of the synthesized compounds checked by TLC.

All the compounds have been also evaluated for their antibacterial activity towards Gram +ve and Gram -ve bacteria and also evaluated antifunal activity at a concentration of 50µg/ml. The antimicrobial activity of the synthesized compounds have been compared with known standard drugs.

SYNTHESIS, SPECTRAL STUDIES AND THERAPEUTIC ACTIVITY OF SOME HETEROCYCLIC COMPOUNDS

SYNTHESIS, SPECTRAL STUDIES AND THERAPEUTIC ACTIVITY OF SOME HETEROCYCLIC COMPOUNDS

INTRODUCTION

Heterocyclic chemistry has been unparalled progress owing to their wide natural occurrence, specific chemical reactivity and broad spectrum utility.

Hetrocyclic compounds have great applicability in pharmaceutical, because they have specific chemical reactivity and provides false synthons in biosynthetic process.

Some heterocyclic compounds must ideally have a broad spectrum of activity with a rapid bactericidal action. We must always continue search new heterocyclic moleculer and identify its respective drugs activity. To take the care for synthesis new hetercyclic moleculer a lower toxicity, a partial or total absence of undesirable side effects, more neutritive value, improved stability, a decrease in production cost and check the qualitative or quantitative improvement in activity with standard drugs. Bis dichloro ethyl amine and s-triazene derivatives have been reported as a valuable medicine chemistry point of view e.g. anticancer, anthelmintic, antihistamine, Anti-HIV, antimalarial, antiviral, antifungal etc. s-triazine, substitutents serves as nucleus to a host of compound which are associated with wide spectrum of therapeutic activity.

Heterocyclic compounds have great biological significance properties.

(1) They have a specific chemical reactivity.

(2) They resemble essential metabolism and can also provide false synthons in biosynthetic process.

(3) They fit receptors and block their normal working.

(4) They provide convenient building blockers to which biologically active substituent's can be attached.

The interesting biological activities of heterocycles have stimulated considerable research work in recent years including to the synthetic utility.

Heterocyclic compounds can be synthesised by cyclization reactions (accompanied by elimination of small molecules) addition reactions; (adduct formation), ring transformation reactions or replacement involving groups. Formation of heterocycle from acylic compounds alters the reactivity.

AMIMS AND OBJECTIVES

Population of our country is skyrocketing number of diseases are uncoured e.g. cancer, Aids etc.

In the pharmaceutical field, there is a need for new and novel chemical inhibitors of biological functions. Our efforts are focused on the introduction of chemical diversity in the molecular frame work in order to synthesizing pharmacologically interesting heterocyclic compounds of widely different composition. During the course of research work looking to the applications of heterocyclic compounds, several entities, have been designed, generated and characterized using spectral studies. The aims and objectives of the work carried out are as under.

(1) To synthesise pharmacologically active entities like chalcones, isoxazoles, pyrazolines, pyrimidines derivatives, cyanopyrans, quinoxalines, barbitonees, thiosemicarboximides triazoles bearing Bis-(2-chloro ethyl) amine and S-triazine moiety.

(2) To characterize these products for structural elucidation using spectroscopic technique like IR, ^{1}H NMR and Mass spectral studies.

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

(4) To evaluate these new products for better drug potential against different strain of bacteria and fungi. Activity of synthesized compounds compared with known standard drugs.

(5) Some compounds selected for anticancer activity.

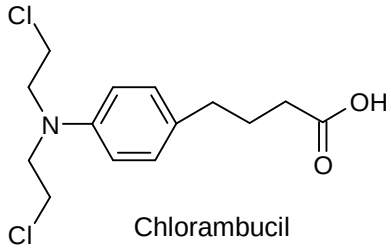
The research work is presented as studies on Bis (2-chloro ethyl) amine and S-triazine molecules included in our moiety.

SUBJECT INTRODUCTION

Bis(2-chloro ethyl) amine :

Literacher surve reveals that Bis (2-chloro ethyl) amine derivatives shows antineoplastic activity which are described as under.

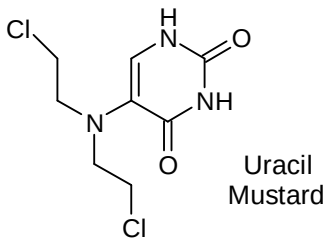
(i) 4-[Bis (2-chloroethyl) amino] Benzene butanoic acid "chorambicil" was reported as a antineoplastic agent.



Chlorambucil

[Ref. US 304301 [Boroughs well come (24-1-1962)]

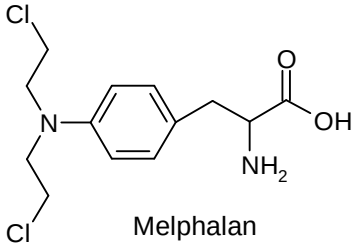
(ii) 5-[Bis (2-chloroethyl) amino]-2, 4-(1H, 3H) pyrimidinedione "Uracil mustard" or "uramustine" was reported antineoplastic agent.



Uracil Mustard

[Ref. US 2969364 (Upjohn) (24-1-1961)]

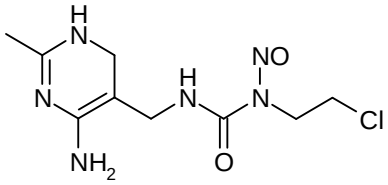
(iii) 4-[Bis (2-chloroethyl) amino] - 2- amino propanoic acid "Melphalan" was reported antineoplastic agent.



Melphalan

[Ref. US : 3032585 (Nat. Res. De V. crop) (1-5-1962)]

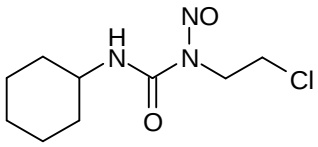
(iv) "Nimustine" N-[(4-Amino 2-methyl-5-pyrimidinly) methyl)-N-(2-chloro ethyl)-N-nitroso urea was reported as a antineoplastic agent.



Nimustine

[Ref : US 4003901 Sankyo (18-1-1977)]

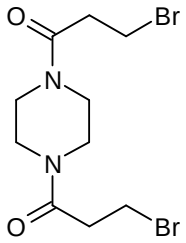
(v) T. P. Johnston et. al. have been synthesised "Lomustine" as a antineoplastic agent.



Lomustine

[Ref : J. Med. Chem. (JMCMAR) 9, 892 (1966)]

(vi) "Pipobroman", 1, 4-bis (3-bromo-1-oxo propyl) piperazine was reported as a antineoplastic agent.



Pipobroman

[Ref : DE 113878 (Abbott : Appl, 10-10-1960)

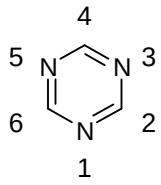
Bis (2-chloroethyl) amine derivatives procuring better therapeutic activity. Looking at their versatile therapeutic importance introduced this group in our moiety.

S-Triazine :

S-Triazine nucleus has been extensively explored for their applications in the field of medicine, agriculture and industrial chemisty. Although many substituted S-

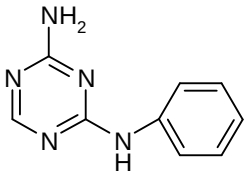
triazine compounds like other hetero cyclic compounds are synthesised with their functional group present froma cyclic compounds.

S-Trizine is a six membered heterocyclic ring having three nitrogen atom present at 1, 3, 5-position.



S-Triazine derivatives possoss wide range of biological activities like herbicidal, anticancer, antibacterial, antifungal etc., with a view of getting to introduced this molecules in our moiety.

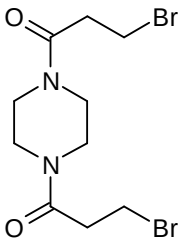
(i) Shapiro et. al. have been reported N-Phenyl - 1, 3, 5-triazine-2, 4 diamine "Amanozine" as a diuretic drug.



Amanozine

[Ref : Shapiro, J. Am. Chem. Soc. **76**, 93 (1954)]

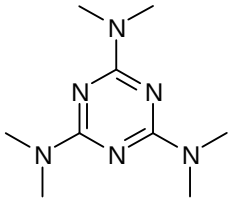
(ii) A. E. Johnson reported 2, 6-di (isopropyl amine)-4-methoxy-S-triazine "Prometon" as a herbicidal.



Pipobroman

[Ref : A. E. Johnson Am. J. Vet. Res. **33**, 1433 (1972)

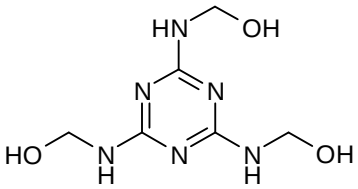
(iii) M. D. Incalci et al. have been synthesised 2, 4, 6-tris (dimethyl amino)-S-triazine. "Altretamine" and reported as a antineoplastic agent.



Altretamine

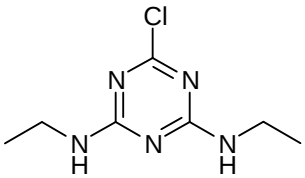
[Ref. M. D. In calci, Brit. J. Cancer, **41**, 630 (1980).]

(iv) Eichler, staib have been synthesised 2, 4, 6-tris (methylolamino)-1,3,5-triazine and reported it was a antineoplastic agent.



Tri methylol melamine

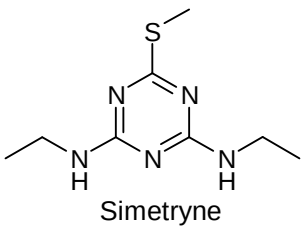
(v) Thurston et. al. have synthesised 2-chloro-4, 6-Bis (ethyl amino)-s-triazine "Simazine" and reported its herbicidal activity.



Simazine

[Ref. Thurston, ibid. 73, 2981 (1951)]

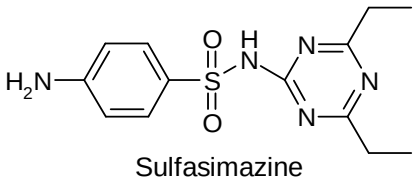
(vi) Kniisli have been synthesised 2, 4-bis-(ethyl amino)-6-(methlythio)-s-triazine "simetryne" represent herbicidal activity.



Simetryne

[Ref. Kniisli, C.A., 57, 14226 (1962)]

(vii) Taft et. al. have been synthesised 4-maino-N-(4, 6-diethyl-1,3,5-triazin-2-yl) benzene sulfonamide "Sulfasymazine" and reported as a antibacterial.



Sulfasimazine

[Ref : Taft et al. J. Med. Chem. 8, 784 (1965)]

Thus the important role displayed by Bis (2-chloro ethyl) amine; S-Triazine and its deivatives shows various therapeutic and biological activity prompted us to synthesis some chalcones, pyrazoles, cyanopyridines, isoxazoles, pyrimidines, cyano pyrans, quinoxalines, barbitones, triazoles derivatives bearing in Bis (2-chloro ethyl) amine-S-triazine moiety in order to active compounds having better biological activities as described in the following parts.

PART - I STUDIES ON CHALCONES

PART - II STUDIES ON ISOXAZOLES

PART - III STUDIES ON PYRAZOLINES

PART - IV STUDIES ON PYRIMIDINES

PART - V STUDIES ON CYANOPYRIDINES

PART - VI STUDIES ON CYANOPYRANS

PART - VII STUDIES ON QUINOXALINES

PART - VIII STUDIES ON BARBITONES

PART - IX STUDIES ON THIOSEMICARBOXIMIDES

PART - X STUDIES ON TRIAZOLES

PART – I

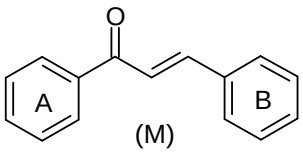
STUDIES ON CHALCONES

STUDIES ON CHALCONES

INTRODUCTION

The chemistry of chalcones (M) have generated intensive scientific studies through out the world specially interesting are their biological and industrial applications. Chalcones are coloured compounds because of the presence of the chromophore, auxochromes. They are known as benzalacetophenones or benzylidene acetophenones. S. V. Kostanecki and J. Tambor[1] have gave the name chalcone".

Chalcone are characterised by their possession of a structure in which two aromatic rings A and B are linked by an aliphatic three carbon chain.



(M)

The alternative names given to chlacones are pheny1 styry1 ketones, benzalacetophenones. β-pheny1 acry1phenone, γ-oxo-α–γ-dipheny1-α-propy1-ene and α-pheny1-β-benzoethylene.

SYNTHTIC ASPECT :

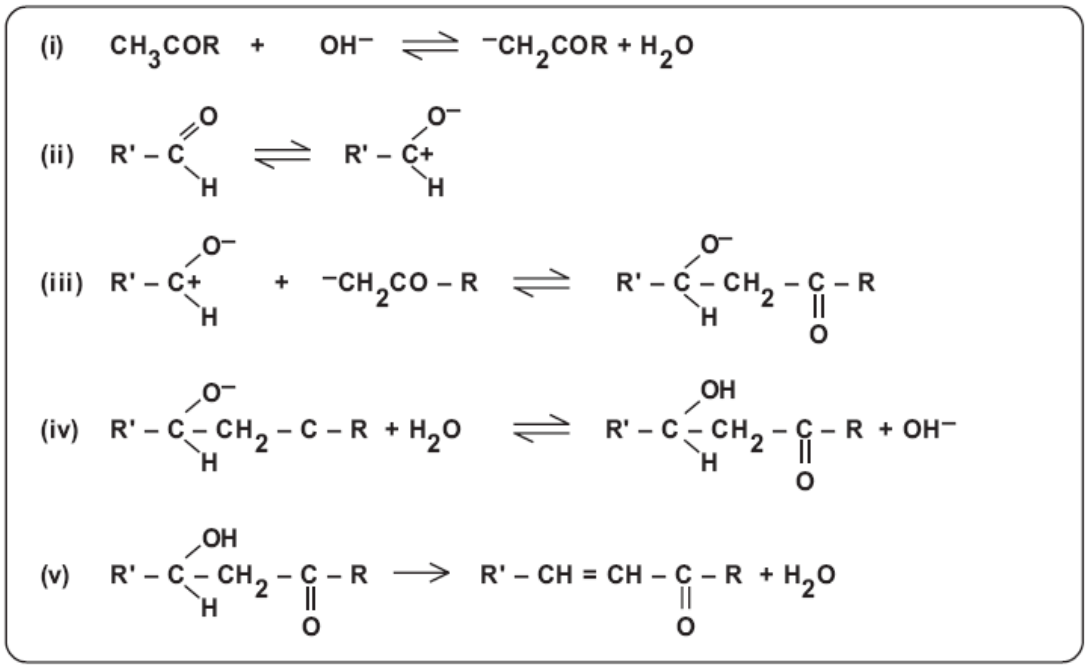
A considerable variety of methods are available for the synthesis of chalcones. The most convenient method is one that involves the Claisen-Schmidt condensation of equimolar quantities of an ary1 methy1 ketones with ary1 a1dehyde in presence of alcoholic alkali.[2]

Several condensing agents used are alkali of different strength[3-4], hydrogen chloride[5,6], Phosphorous oxychloride[7], Piperidine[8], anhydrous Aluminium choride[9],

Boron trifluoride[10], aqueous solution of borax[11], amino acid[12] and perchloric acid[13] etc.

MECHANISM :

Chalcone formation proceeds through aldol type of condensation and the process is catalysed by the presence of alkali[14], following steps of the reaction mechanism are as under.



The intermediate Aldol type of products formed readily undergoes dehydration even under mild condition, particularly when R and R' are aryl groups.

REACTIVITY OF CHALCONES :

The chalcone have been found to be useful for the synthesis of variety of heterocyclic compounds are as under.

(a) Pyrazolines[15] and its derivatives can be prepared by the condensation of chalcones with hydrazine hydrate and acetic acid.

(b) Chalcones on condensation with malononitrile and ammonium acetate yields 2-amino-3-cyano pyridines[16].

(c) Isoxazoles[17] can be prepared by the treatment of chalcones with hydroxylamine hydrochloride and sodium acetate.

(d) Chalcone on condensation with malononitrile in pyridine forms 2-amino 3-cyanopyrans.[18]

(e) Chalcones on treatment with urea in presence of alkali to affords 2-oxo Pyrimidines[19].

(f) Chalcones on reaction with thiourea in presence of alkali/acid yields 2-thio pyrimidines.[20]

(g) Chalcones on treatment with guanidine hydrochloride in presence of alkali to affords 2-amino pyrimidines.[21]

(h) Chalcones reacts with P_2S_5 yielding 2-isothiazolines.[22]

(i) Chalcones with sodium nitrile in presence of glacial acetic acid in ethanol produces 2-(H)-pyrimidines.[23]

(j) Chalcones with monoethanolamine in ethanol gives, 1, 4-oxazipines.[24]

(k) Chalcones with 2-amino thiophenol in acetic acid produces 1, 5-thiazepines.[25]

(l) Chalcones on reaction with semicarbazide hydrochloride in ethanol affords l-caroxamide pyrazolines.[26]

(m) Chalcones on reaction with 2-aminopyrimidine in glacial acetic acid affords pyrido pyrimidines.[27]

(n) Oxiran[28] can be prepared by the reaction of chalcone with H_2O_2 in basic media.

(o) Cyanopyridone[29] derivatives can be prepared by the condensation of Chalcone with ethyl cyanoacetate.

(p) Chalcones gives imine derivatives with amine in presence of sulphuric acid as a catalyst.[30]

(q) Chalcone on reaction with barbituric acid gave barbitone derivatives.[31]

THERAPEUTIC INTEREST :

Chalcones are potential bioactive in nature, some naturally occuring antibiotics and amino chalcones probably own their biological activity to the presence of α,β-unsturated carbonyl group.

(a) Insecticidal[32,33]

(b) Antiulcer[34]

(c) Antiinflammatory[35,36]

(d) Bactericidal[37,38]

(e) Fungicidal[39,40]

(f) Antiviral[41]

(g) Anthelmintics[42]

(h) Antiallergic[43]

(i) Carboxygenase inhibitor[44]

(j) Antitumor[45,46]

(k) Antimalarial[47]

(l) Anticancer[48]

(m) Antileishmanial[49]

Moreover, synthesis and antibacterial activity of substituted chalcone derivatives have been reported by S. R. Modi et al.[50] and A. Attia[51], V. R. Mudalir et al[52] have prepared phenoxy chalcones and observed their insecticidal activity. Kammei et al[53]. have been synthesised phenoxychalcones and observed their

insecticidal activity. R. De vincenzo et al[54]. and Han et al.[55] have chalcone derviatives for their anti-inflammatory activity. Okuyana et al[56]. have been reported chalcone derivatives reductase inhibitor activity. Antitumor and antifungal activity as reported by A. Tsotitus and co-worker[57]. Antifeedant activity of chalcones have been observed by P. N. sharma and Sreenivasulu[58].

Ezio Bombardelli et al[59]. have demonstrated that chalcone possess a valuable antiproliferation activity both on sensitive cancereous cell and on cell which are resistant to common chemotherapeutic drugs. S. Elichi et al. have been patented chalcones for their use for treatment of glaucoma[60]. B. B. Kalashnikov et al.[61] and S. Satoshi et al[62] showed antifungal activity, P. Walavalker et al.[63] showed aldose reductase inhibitor. O. tory et al[64] evaluated anticancer activity. J. R. Dimmock. et al.[65] and T. M. Abdel, Rahman[66] evaluated antimicrobial activity.

Recently, Ni Liming et al.[67] have synhesised chalcones and screened for their antiinflammatory and cardiovascular activity. Kumar Srinivas et al[68]. have synthesised chalcones as a antitumor agent. Ko Horng Huey et al[69]. have prepared chalcones as antiinflammatory agent. Nakahara Kazuhiko et al[70]. have synthesised chalcones as carcinogen inhibitors and antitubercular agents.

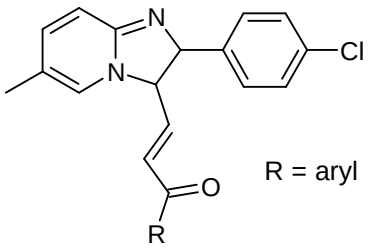
Lin Yah meei et al[71] have synthesis chalcones derivatives. B. R. Das et al[72]. have found that chalcones possesses larvicidal properties. Kirm Min Young et al[73]. have synthesised chalcones and tested for their matrixmetalloproteinase inhibitor activity.

Liu Mei et al[74]. have been prepared chalcones and evaluated antimalarial activity. O. veronika et al[75] have synthesised chalcones and screened as cardiovascular agent.

Moreover, it has been found that chalcone derivatives possesses nitric oxide inhibitor[76,77] and anti-HIV[78] activities.

Contribution in our laboratory :

D. M. Purohit et al[79] have been synthesised 2-(4'-chlorophenyl)-6-methyl-3-[1"aryl-2"-propene-1"-ones-3-yl]-imidazo (1, 2-a] pyridine and evaluated their antimicrobial activity.



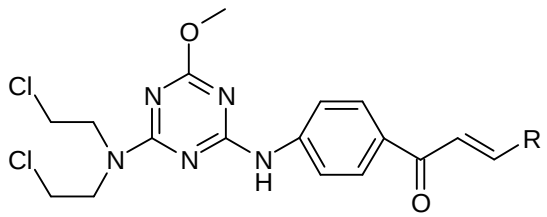
Chalcones bearing a very good synthon, variety of novel heterocycles with good pharmacological profile can be designed. These valid observation led us to explore chalcones chemistry by synthesising several derivatives like isoxazoles, pyrazolines, pyrimidines, cyanopyrans etc bearing different heterocyclic ring systems for medicine value, in order to achieving bettter therapeutic agents, these study described as under.

SECTION-1 SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(3"-ARYL)-2"'-PROPENE-1"-ONE]- PHENYLAMINO}-6-[BIS-(2"-CHLOROETHYL) AMINO] -4-METHOXY-1, 3, 5-TRIAZINE.

SECTION-I

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(3"-ARYL)-2"-PROPENE-1"-ONE]-PHENYLAMINO}-6-[BIS-(2"-CHLOROETHYL)AMINO]-4-METHOXY-1, 3, 5-TRIAZINE.

Recently much interest has been focoused on the synthesis and biodynamic activities of chalcones and it is a good synton for various heterocyclic rings, with a view to obtained compounds having better therapeutic activity of 2-{4'[(3"-aryl)-2"-propene-1"-one]-phenyl amino}-6-[Bis(2"-chloroethyl)amino]-4-methoxy-1, 3, 5-triazine of type- (I) have been synthesised by the condensation of 2-[(4'-acetyl)phenyl amino]-6-[Bis-(2"-chloroethyl)amino]-4-methoxy-1,3,5-triazine with aromatic aldehyde in presence of aq. NaOH. 2-(4'-acetyl phenyl amino)-4,6-dichloro-S-triazine have been synthesis by the condensation of cyanyric chloride with 4-amino acetophenone at 0° c temp. in the presence of aq. NaOH. 2-(4'-acetyl phenylamino)-6-chloro-4-methoxy-S-triazane have been synthesised by the condensation of 2-(4'-acetyl phenyl amino)-4-6-dichloro-S-triazine with sodium methoxide at room temp. in methanol. The 2-[(4'-acetyl phenyl) amino]-6-[Bis-(2"-chloro ethyl)amino]-4-methoxy-1,3,5-triazine have been synthesized by the condensation of 2-(4'-acetyl phenyl amino)-6-chloro-4-methoxy-S-triazine with 2,2'-dichloro diethyl amine hydrochloride in the presence of aq. NaOH and dioxane at 110° c temp.

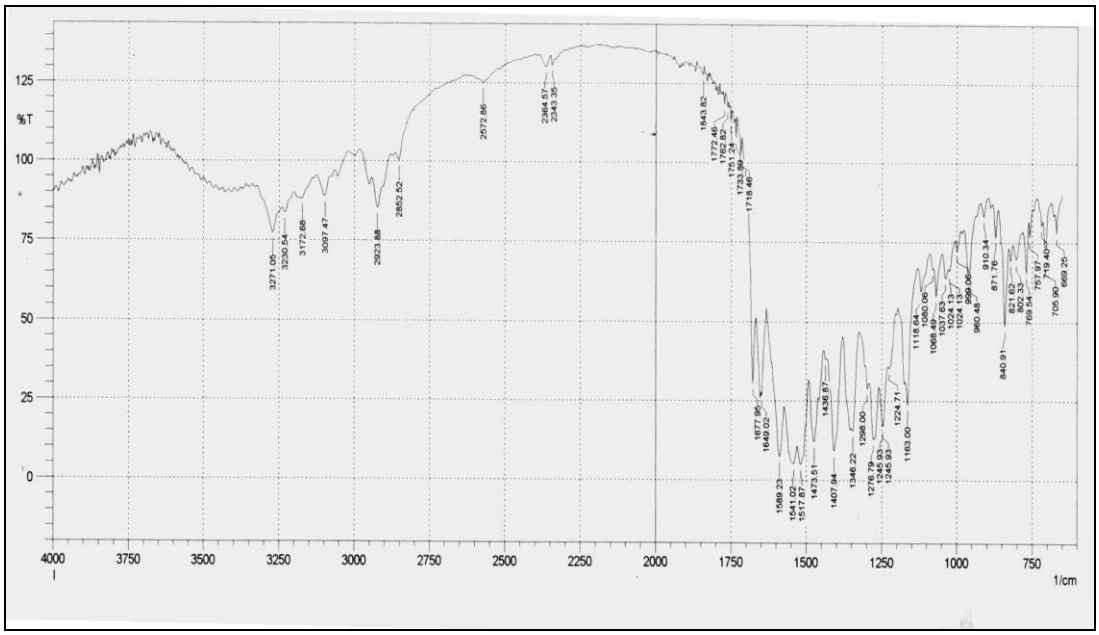


(Type-I) R = Aryl

The constitution of the synthesis products have been characterized by elemental analysis, IR, ^{1}HNMR and mass spectral study. The product were screened

for antimicrobial activity at a concentraion of 50 μg/ml. The details have been cited in the part-I section-I, Page no. 39-41.

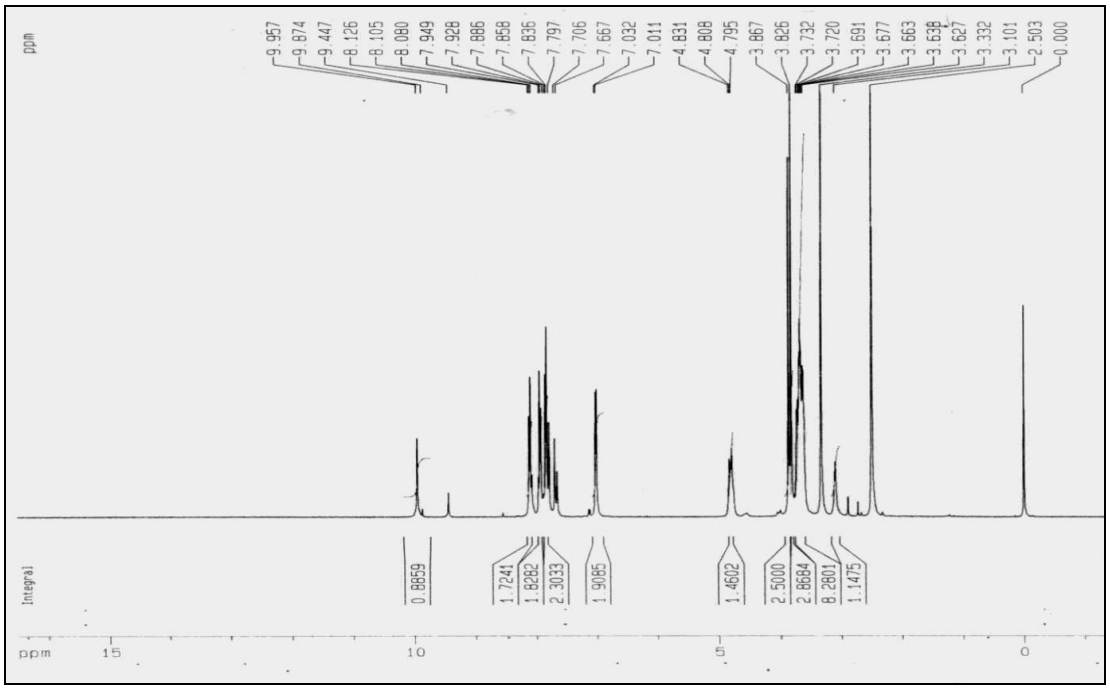
IR SPECTRAL STUDY OF 2-{4'-[3"-(4"'-METHOXY PHENYL)-2"-PROPENE-1"-ONE]-PHENYLAMINO-6-[BIS(2"-CHLOROETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE



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

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	reported	
Alkane	C-H Str.(Asym)	2923	2990-2850	422 – 423
	C-H Str.(asym)	2852	2880-2860	”
	C-H Str.(Asym)	1436	1470-1435	”
	C-H Str.(asym)	1371	1390-1360	”
Aromatic	C-H Str.	3097	3090-3030	”
	C-H i.p. def	1276	1300-1100	”
	C-H o.o.p. def	821	832-800	”
	C=C Str.	1517	1600-1450	”
Ketone	C=O Str.	1677	1700-1640	”
S-triazine	C-N Str.	1118	1220-1020	”
	C=N Str.	1589	1630-1590	”
Amine	N-H Str.	3311	3500-3310	”
	N-H Bending	1649	1650-1550	”
Vinyl	CH=CH	3045	3050-3000	”
Ether	C-O-C Str.(asym)	1245	1260-1220	”
	C-O-C Str.(sym)	1037	1075-1020	”
Halide	C-Cl Str.	768	800-600	”

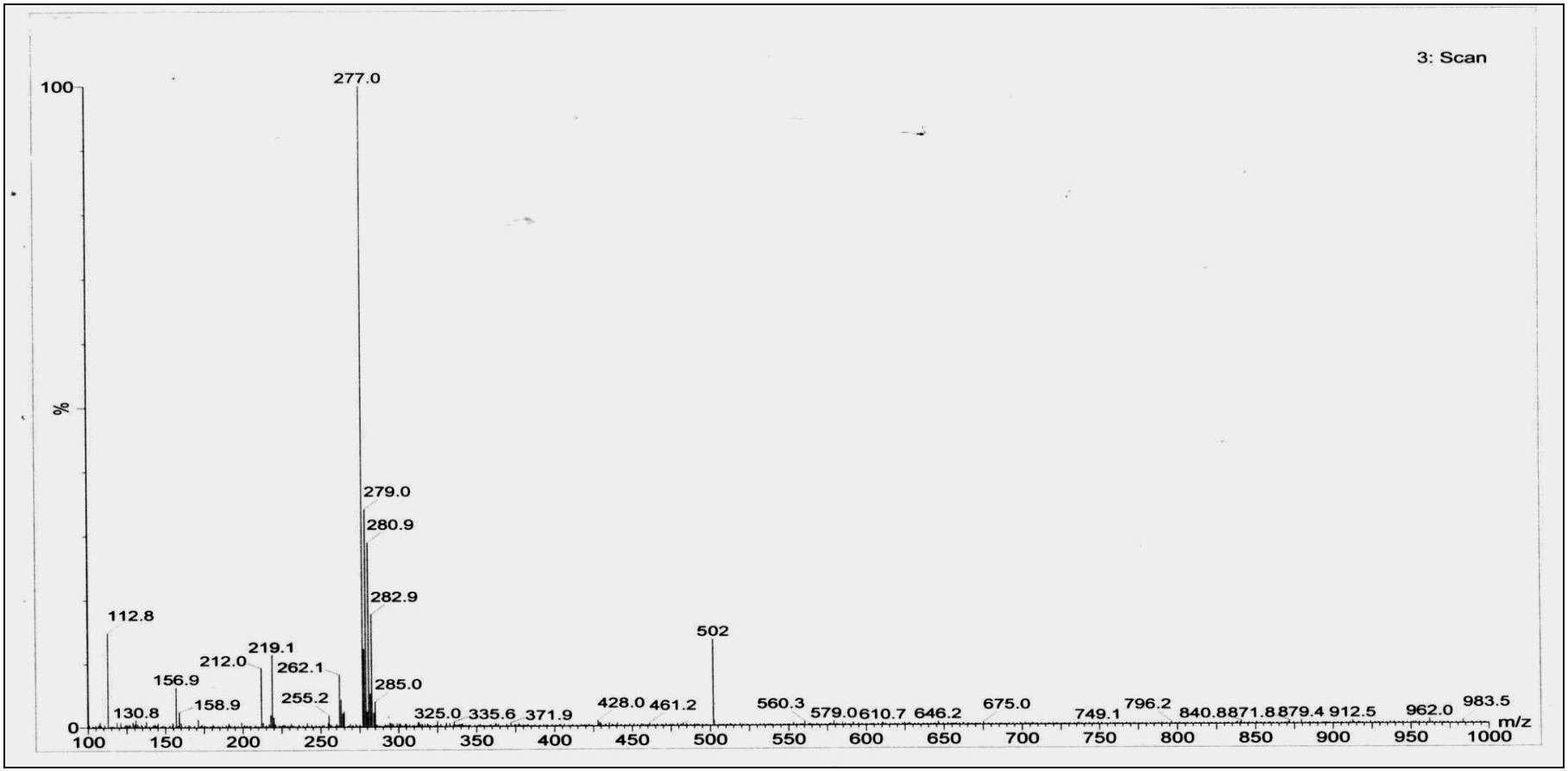
NMR SPECTRAL STUDY OF 2-{4'-[3"-(4"'-METHOXY PHENYL)-2"-PROPENE-1"-ONE]-PHENYLAMINO]-6-[BIS-(2"-CHLOROETHYL)AMINO] - 4 -METHOXY - 1, 3, 5-TRIAZINE.



Internal standard : TMS , Solvent : $CDCl_3$ Instrument : BRUKER Spectrometer (300 mhz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.62-3.86	6 H	Singlet	Ar-OCH_3
2	7.01-7.03	4 H	D. Doublet	Ar-H_b
3	8.08-8.12	4 H	D. Doublet	Ar-H_c
4	4.79-4.80	4 H	Triplet	-CH_2-Cl
5	2.50-2.51	4 H	Triplet	-N-CH_2-
6	9.95	1 H	Singlet	-NH_f
7	4.80-4.83	2 H	Doublet	-CH=CH_g-

MASS SPECTRAL STUDY OF 2-{4'-[3"-(4"'-METHOXY PHENYL)-2"-PROPENE-1"-ONE]-PHENYL AMINO]-6-[BIS-(2"-CHLOROETHYL)AMINO] - 4 -METHOXY - 1, 3, 5-TRIAZINE. (M.W. : 502)



Antimicrobial Activity:

Conclution :

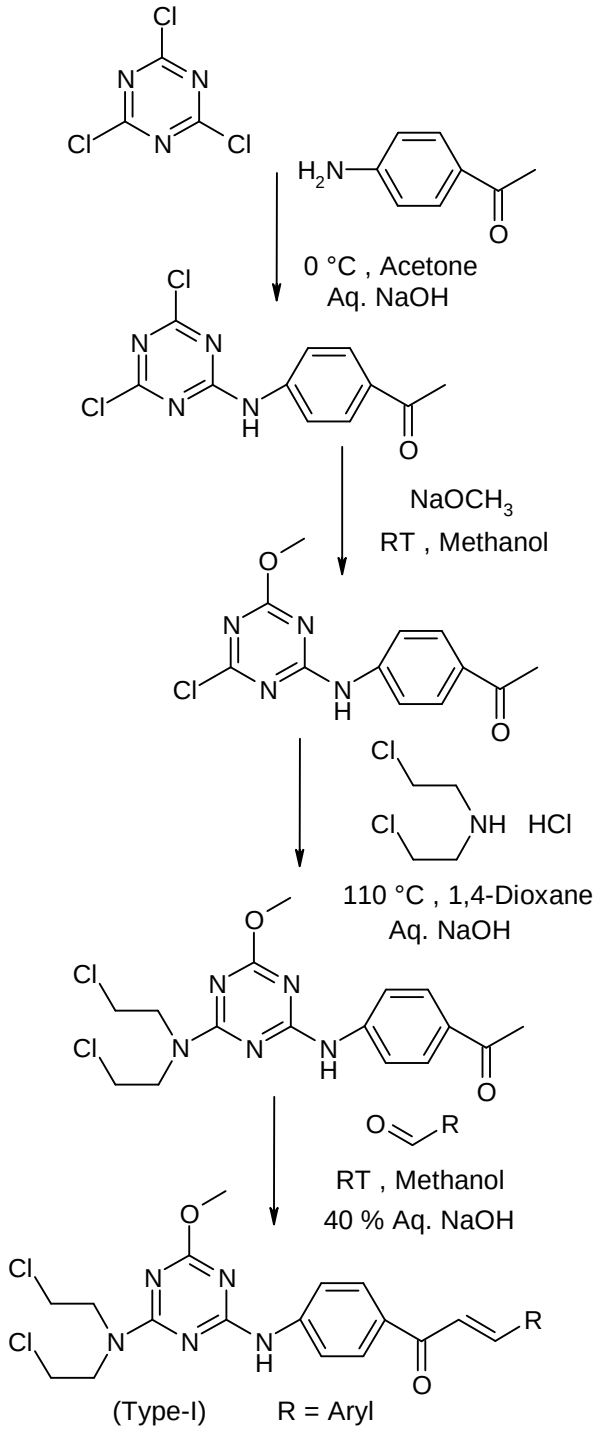
Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.				**Antifungal activity Zone of inhibition in m.m.**
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	4 Br. C_6H_4-(21)	3-OH C_6H_4-(19)	C_6H_5-(18)	4-OH C_6H_4-((21)	2-OH C_6H_4-(22)
	4-NO_2 C_6H_4 (21)	4-$OCH_3C_6H_4$(18)	4-OH C_6H_4-(20)	4-NO_2 C_6H_4-(22)	3-OH C_6H_4-(21)
		4-N,N-$(CH_3)_2C_6H_4$(18)	4-Br C_6H_4-(21)		4-OH C_6H_4-(23)
			4-NO_2 C_6H_4-(20)		4-Br C_6H_4-(20)

Comparable activity with known standard drugs

Ampicilin (50µg/ml.)	23	18	17	27	-
Chloramphenicol "	24	19	25	26	-
Norfloxacin "	24	19	25	26	-
Greseofulvin "	-	-	-	-	23

Reaction Scheme



(Type-I) R = Aryl

EXPERIMENTAL

SYNTHESIS OF 2-{4'-(3"-ARYL) -2"-PROPENE-1"-ONE]-PHENYL AMINO]-6-[BIS-(2"'-CHLOROETHYL)AMINO] - 4 -METHOXY - 1, 3, 5-TRIAZINE.

(A) Synthesis of 2-(4'-Acetyl phenyl amino)-4, 6-dichloro-1, 3, 5-triazine.

A mixture of 2, 4, 6-trichloro-s-triazine (1.845 gm, 0.01M), 4-amino acetophenone (1.35 g, 0.01M) in acetone (25 ml.). and aq. NaOH solution till solution basic. The reaction mixture was stirring at 0^0c temp. for 5 hrs. The content was poured into crushed ice, filtered and washed with water. The isolated product was crystallised from dioxane yield : 82% mp. 112ºC.

(found : C : 46.61;, H : 2.79; N : 19.75; $C_{11}H_8N_4OCl_2$, required C: 46.64, H: 2.82; N : 19.79%)

(B) Synthesis of 2-(4'-Acetyl phenyl amino)-6-chloro - 4- methoxy-1, 3, 5-traiazine.

A mixture of 2-(4'-acetyl phenyl amino) - 4, 6-dichloro-1,3,5 trizine (2.83 gm, 0.01 M); sodium methoxide (0.56 gm, 0.01 M) in methanol. The reaction mixture was strrring at room temp. for 7 hrs. The content was poured into crashed ice, filtered and wash with water. The isolated product was crystallised from dioxane. Yield : 86%, M.P. 178º c.

(found C: 51.65; H : 3.91; N : 20.09 $C_{12}H_{11}N_4O_2Cl$ required C : 51.70; H : 3.94; N : 20.10%)

(C) Synthesis of 2-(4'-Acetyl phenyl amino)-6-[Bis(2"-chloro ethyl)amino]-4-methoxy-1,3,5-triazine.

A mixture of 2-(4'-acetyl phenyl amino)-6-chloro-4- methoxy-1,3,5-triazine (2.78g., 0.01 M.) 2,2'-di chloro diethyl amine hydrochloride (1.43 gm, 0.01M); dioxane (25 ml) and aq. NaOH. The reaction mixture was refluxed at 110º C for 6 hrs. The content was cooled and poured into crushed ice, filtered and washed with water. The isolated product was crystallised from dixoane. Yield 79% ; mp 249º C.

(Found : C : 49.88, H : 4.91. N : 18.19 $C_{16}H_{19}N_5O_2Cl_2$ reqired C : 50.00; H : 4.94; N : 18.22%)

(D) Synthesis of 2-{4'-[3"-(4"''-Methoxy phenyl) -2"-propene - 1" - one] phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.

A mixture of 2-(4'-acetyl phenyl amino) - 6- [Bis (2" - chloro ethyl) amino]-4 - methoxy - 1, 3, 5-triazine (3.84 gm, 0.01M); 4-methoxy benzaldehyde (1.36 gm, 0.01M), methanol (25 ml.) add 40% NaOH solution till becomes basic medium. The reaction mixture was stirring 24 hrs. at room temp. The contents were poured into crushed ice, acidified filtered and crystallized from dioxane. Yield : 79%, M.P : 198ºC. (Found: C : 57.31; H : 4.90; N : 13.91; $C_{24}H_{25}O_3N_5Cl_2$ C : 57.37; H : 4.98; N : 13.94%)

Simillarly other chalcones were prepared and their physical data are recorded in Table No. 1

(E) Antimicrobial activity of 2-{4'-[(3"-Aryl) - 2" - Propene - 1"-one] phenylamino}-6-[Bis (2'"-chloroethyl) amino]-4-methoxy - 1, 3, 5 triazine.

The antimicrobial testing was carried out as described in Part : I, Section : I, Page No. 39-41.

The zone of inhibition of the test solution are recorded in Table No. 2.

(F) **Antimicrobail activity of 2-(4'-Acetyl phenyl)-6-[Bis(2"-chloroethyl)amino]4-methoxy-1,3,5-triazine.**

Method : It was carried out using the cup-plate method which has been described as under.

Antibacterial activity :[80]

The Purified products were screened for their antibacterial activity. The neutrient agarbroth prepared by the usual method, was inoculated specially with 0.5 ml for 24 hours, old subsclture of *B. megaterium Bacillus subtillis Escherichia coli, pseudonomus fluorescens,* in separate concial flasks at 40-50^{0}C and mixed well by gentle shaking. About 25 ml of the contents of the flask were poured and evenly spread in a petridish (13 cm in diameter) and allowed to set for 2 hrs. The cups (10 mm in diameter) were formed by the help of borer in a agar medium and filled with 0.10 ml (1.0 μg/ml) solution of sample in dimethyl formamide.

The plates were incubated at 32^{0}C for 24 hrs. and the control was also maintained with 0.1 ml of DMF in similar manner and the zone of inhibition of the bacterial growth are measured in mm, diameter are recorded in Table No. A.

Antifungal activity[81]

Aspergillus awamori was employed for testing fungicidal activity using cup-plate method the cultures were maintained on subouraud's agar slants. Purified compounds were used for testing the fungicidal activity, sterlised subouraud's agar medium was inoculated with 72 hours old 0.5 ml suspension of fungal spores in a sterilised sepearate flask. About 25 ml of the inoculated medium was evntly spreaded in a petridish and allowed to set for 2 hrs. The cups (10 mm in a diameter) were punched in petridish and loded with 0.1 ml (1.0 mg/ml) of solution of a sample in DMF.

The plate were incubated at room temp. 37^0 C for 48 hrs. After the completion of incubation period. The zone of inhibition or growth in the form of diameter in mm

was measured. Along the test solution in each petridish one cup was filled up with solvent acts as control. The zone of inhibition are recorded in Table No.A

ANTIMICROBIAL ACTIVITY

Product	:	**2-[(4'-acetyl phenyl) amino]-6-[Bis(2'-chloro ethyl) amino]-4-methoxy-1,3,5 triazine**
Method	:	**Cup plate**
Gram Positive Bacteria	:	***Bacillus megaterium***
		Bacillus subtillis
Gram Negative Bacteria	:	***Escherichia Coli***
		Psenudonomus Fluorescens
Fungi	:	***Aspergilus awamori***
Concentration	:	50 µg
Solvent	:	**Dimethyl formamide**
Standard Drugs	:	**Ampicillin, chloramphenicol, Norfloxacin, Greseofulvin**

The antibacterial activity was compared with standard drugs viz. ampicillin, chloramphenicol, norfloxacin and antifungal activity was compared with standard drug viz. greseofulvin. The Zones of inhibition were measured in mm. The Zones of inhibition that displayed by standard drugs are recorded in Part-I, Page No. 41.

TABLE NO. A : ANTIMICROBIAL ACTIVITY; ZONE OF INHIBITION FOR STANDARD DRUGS

Sr. No.	Standard Drugs	Antibacterial activity Zone of inhibition in mm.			Antifungal activity Zone of inhibition in mm.	
		B. mega.	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	Ampicilin (50 µg)	23	18	17	27	-
2	Chloramphenicol (50 µg)	24	19	25	26	-
3	Norfloxacin (50 µg)	24	19	25	26	-
4	Greseofulvin (50 µg)	-	-	-	-	23

TABLE NO. : 1 PHYSICAL CONSTANT OF 2-{4'-[(3"-ARYL)-2"-PROPENE-1"-ONE] PHENYLAMINO}-6-[BIS(2"-CHLORO ETHYL)-AMINO]-4- METHOXY-1, 3, 5-TRIAZINE

Sr. No.	R	Molecular Formula	M.P. .c	Yield %	% of Nitrogen	
					Calcd	Found
1.	$C_6H_5^-$	$C_{23}H_{23}Cl_2N_5O_2$	218	70	14.83	14.80
2.	2-OH $C_6H_4^-$	$C_{23}H_{23}\ Cl_2N_5O_3$	224	82	14.34	14.31
3.	3-OH $C_6H_4^-$	$C_{23}H_{23}Cl_2N_5O_3$	230	85	14.34	14.32
4.	4-OH $C_5H_4^-$	$C_{23}H_{23}Cl_2N_5O_3$	220	81	14.34	14.29
5.	4-OCH_3 C_6H_{4-}	$C_{24}H_{25}Cl_2N_5O_3$	198	79	13.94	13.91
6.	4-OH, 3-OCH_3 C_6H_{3-}	$C_{24}H_{25}Cl_2N_5O_4$	231	83	13.51	13.49
7.	4-Br. C_6H_{4-}	$C_{23}H_{22}Br\ Cl_2N_5O_2$	172	86	12.70	12.69
8.	3-NO_2 C_6H_{4-}	$C_{23}H_{22}Cl_2N_6O_4$	222	89	16.24	16.22
9.	4-NO_2 C_6H_{4-}	$C_{23}H_{22}Cl_2N_6O_4$	175	81	16.24	16.21
10	4-N, N-$(CH_3)_2$ C_6H_{4-}	$C_{25}H_{28}Cl_2N_6O_2$	226	78	16.30	16.25
11.	C_4 H_3O (Furfuryl)	$C_{21}H_{21}Cl_2N_5O_3$	238	83	15.15	15.10

TABLE NO. 2 : ANTIMICROBIAL ACTIVITY OF 2-{4'-[(3"-ARYL)-2"-PROPENE-1"-ONE] PHENYLAMINO}-6-[BIS(2"-CHLORO ETHYL)-AMINO]-4- METHOXY-1, 3, 5-TRIAZINE

Sr. No.	R	Antibacterial activity Zone of inhibition in mm.				Antifungal activity Zone of inhibition in mm.
		B. mega.	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5	16	13	18	19	17
2	2-OH C_6H_4	17	15	17	18	22
3	3-OH C_6H_4	19	19	16	19	21
4	4-OH C_5H_4	20	17	20	21	23
5	4-OCH_3 C_6H_4	15	18	18	17	16
6	4-OH, 3-OCH_3 C_6H_3	18	14	16	22	18
7	4-Br. C_5H_4	21	19	21	18	20
8	3-NO_2 C_6H_4	17	16	18	19	17
9	4-NO_2 C_6H_4	21	17	20	22	19
10	4-NN-$(CH_3)_2$ C_6H_4	15	18	17	17	18
11	C_4 H_3O (Furfuryl)	14	15	16	19	17

PART - II

STUDIES ON ISOXAZOLES

STUDIES ON ISOXAZOLES

INTRODUCTION

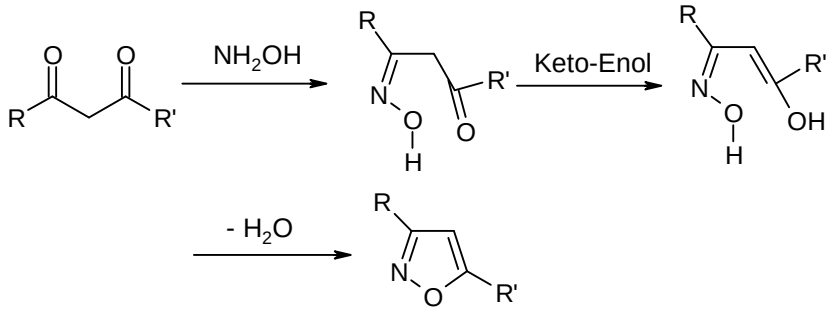
Isoxazoles.(N) are a group of heterocyclic compounds containing two hereo atoms : oxygen and nitrogen.

(N)

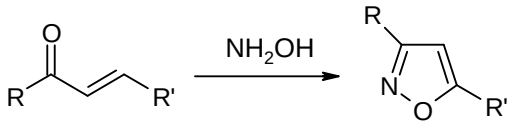
In 1888 claisen first suggest in isoxazoles (N) for a product from the reaction of 1, 3 diketone with hydroxylamine[82] subsequently a solid foundation for the chemistry of isoxazoles was laid down by claisen and his students. It was shown to possess typical properties of an aromatic system but under certain reaction conditions, particularly in reducing or basic media, it becomes very highly labile. The next important contribution to the chemistry of isoxazoles was made by Quelico in 1946 when he began to study the formation of isoxazoles from nitrile N-oxides and unsaturated compounds.[83]

SYNTHETIC ASPECT :

Isoxazole may be prepared by the reaction between hydroxylamine and -unsaturated compounds the reaction proceeds Via the formation of an oxime. Which possibly undergoes cylization.



Isoxazole can be prepared by various methods which are described as under. L. S. Crawley[84] prepared isoxazole from chalcones hydroxylamine hydrocloride and KOH in methanol.



THERAPEUTIC IMPORTANCE

Isoxazole possess wide therapeutic activites which are as under.

(a) Antiinflammatory[85,86,87,88]

(b) Antivonvulsant[89,90]

(c) Muscle relaxant[91,92]

(d) Antipyretic[93]

(e) Anticholestemic[94]

(f) Antibacterial[95,96,97]

(g) Diabetic[98]

(h) Nematocidal[99]

(i) Fungicidal[100,101]

(j) Antiviral[102]

(k) Herbicidal[103,104,105]

(l) Anthelmintics[106]

(m) Antileukemia[107]

(n) Antitumor[108]

(o) Hypoglycemic[109]

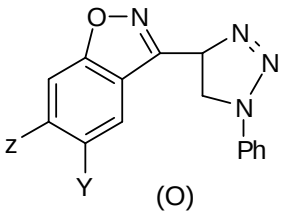
(p) Analgesic[110]

B. Maggio et al[111] synthesised novel 3-(isoxazol-3-yl)-quinazolin-4-(3H)- one derivatives and tested for their analgesic and antiinflammatory activities, as well as for their actual toxicity and ulcerogenic effect. Some of them had a very low ulcerogenic effect.

C. B. Xue et al[112] reported the replacement of the benzamide in XUO57 (potent inhibitor) with an isoxazole carboxamide resulted in significant improverment in vitro potency. More importanty the analogue XXUO65 showed on excellent oral antiplatelet effect in dogs.

M. Masui et al.[113] have prepared isoxazoles having pesticidal activity. Some excellent herbicidal results obtained by K. V. Reddy et al.[114] Moreover isoxazoles found to possess remarkable anixolytic and antihypertensive effect, reported by J. Nyitrai et al.[115], A. Mishra et. al.[116] have synthesised and reported isoxazoles as useful agents for analgesic and antiinflammatory activities. T. D. Aicher et al.[117] reported some isoxazole derivatives possessing hypoglycemic agents.

S.Ozkan et al.[118] have prepared 3-(1-phenyl-1,2,3-triazol-4-yl) benziscreazoles (O) and studied their insecticidal acitvity.



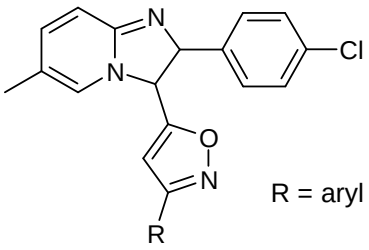
(O)

M. Dauria[119] studied photochemical behaviour of isoxazole derviatives. Y. N. Manohara et at.[120] ivestigated thermal decomposition kinetics of Co (II) and Ni (II) complexes of substituted isoxazole and their antibacterial activity. A. R. Parikh and co

worker[121] have prepared isoxazole derivatives and documented antitubercular activity. Some isoxazoles are found to possess herbicidal[122-124] Potential anti-inflammatory[125,126] and antimicrobial agents[127,128] estrogen receptor modulators[129] and inhibior of P38 MAP kinose activities.[130]

Contribution in our Laborartoy :

D. M. Purohit et al[131] have been synthesised 2-(4'-chloro phenyl)-6-methyl-3-[3"-arylisoxazol-5"-yl)-imidazo[1,2,-a] pyridine



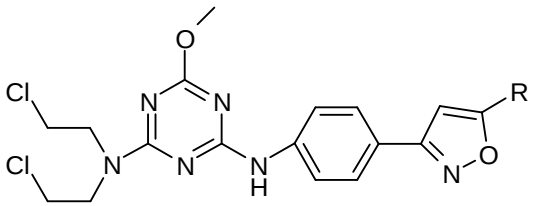
When an intension of the compounds possessing better therapeutic activity we have undertaken the synthesised of isoxazoles bearing Bis (2-chloro ethyl) amine, S-triazine molecules included in our moiety which have been described as under.

SECTION-I : SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(5"-ARYL)-ISOXAZOLE-3"-YL]-PHENYLAMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

SECTION : I

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(5"-ARYL) – ISOXAZOLE – 3" – YL] - PHENYLAMINO} – 6 - [BIS (2"' - CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Isoxazole derivatives reported to potent biological activities, taking into consideration of wide therapeutic activity of isoxazole derivatives. The synthesis of 2-{4'-[(5"-aryl)-isoxazole-3"-yl]-phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine have been sythesised by the condensation of 2-{4'-[(3"-aryl)2"-Propene-1"-one]-pheyl amino}-6-[Bis-(2"'-chloro ethyl) amino]-4- methoxy-1,3,5- triazine with hydroxyl amine hydrochloride.

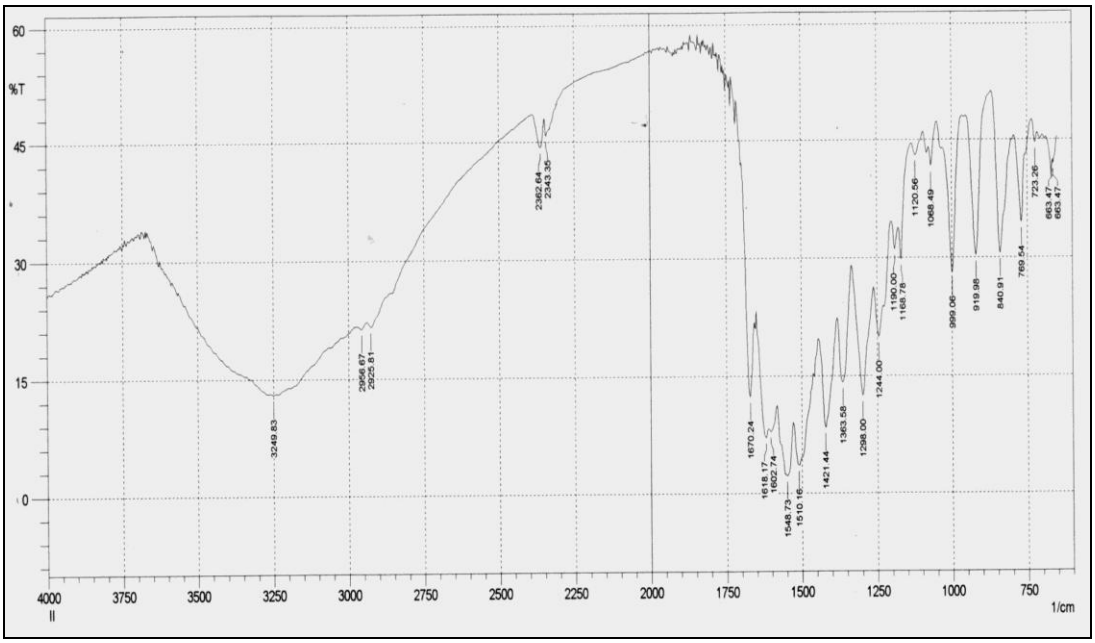


(Type-II) R = Aryl

The constitution of the products have been characterised by elemental analyses, IR, ^{1}H NMR and Mass spectral study. The product were screened for antimicrobial activity at a concentration of 50 µg.

The details have been cited in the part : I, section : I, Page No. 39-41.

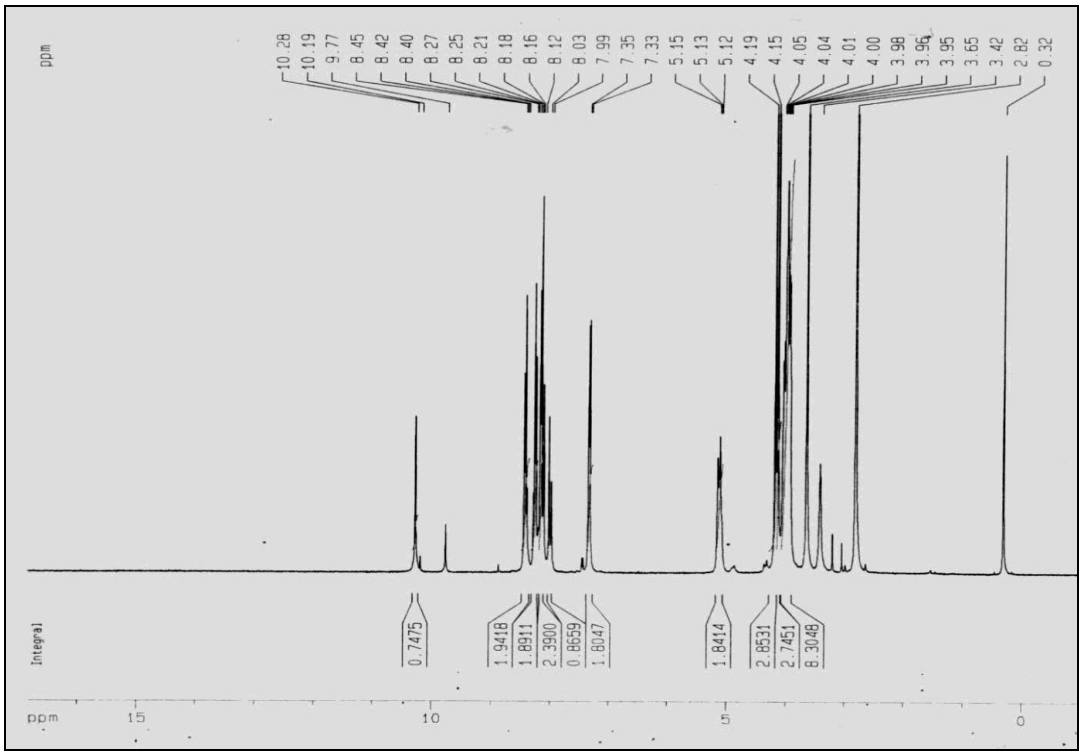
IR SPECTRAL STUDY OF 2-{4'-[(5"-(4""-METHOXYPHENYL)-ISOXAZOLE-3"-YL]-PHENYLAMINO}-6-[BIS(2"'-(CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Instrument : SHIMADZU-FT-IR-8400, Spectrophoto meter frequency range : 4000-400cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	reported	
Alkane	C-H Str.(asym)	2956	2990-2850	422 – 423
	C-H Str.(sym)	2875	2880-2860	”
	C-H def.(asym)	1421	1470-1435	”
	C-H def.(sym)	1363	1390-1360	”
Aromatic	C-H Str.	3060	3090-3030	”
	C-H i.p. def	1168	1300-1100	”
	C-H o.o.p. def	840	832-800	”
	C=C Str.	1510	1600-1450	”
S-triazine	C-N Str.	1120	1220-1020	”
	C=N Str.	1602	1630-1590	”
Amine	N-H Str.	3348	3500-3310	”
	N-H Bending	1618	1650-1550	”
Ether	C-O-C Str.(asym)	1244	1260-1220	”
	C-O-C Str.(sym)	1068	1075-1020	”
Halide	C-Cl Str.	769	800-600	”
Isoxazole	C-N Str.	1190	1230-1020	”
	C=N Str.	1602	1650-1550	”
	N-O Str.	840	850-810	”

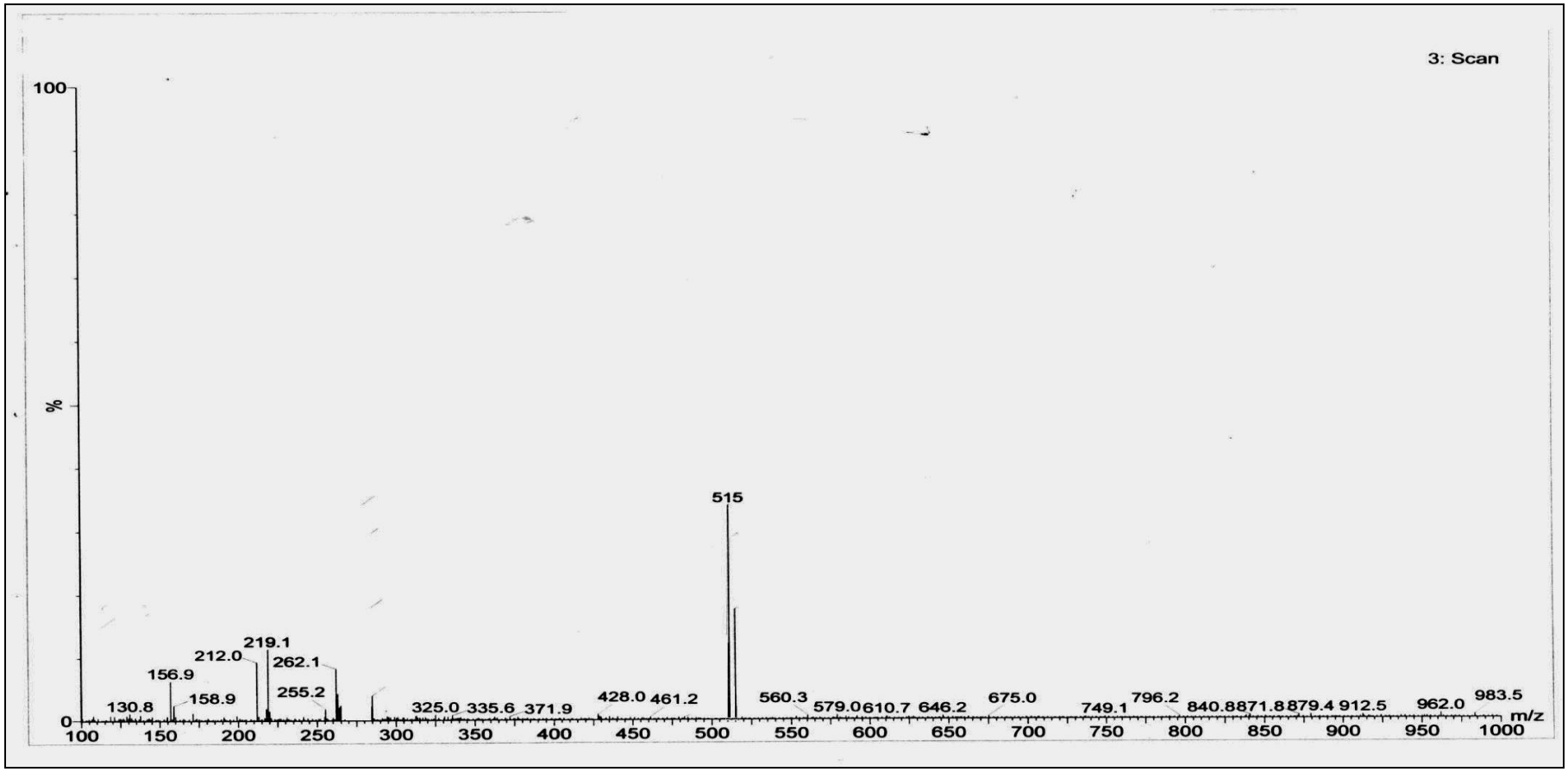
NMR SPECTRAL STUDY OF 2-{5"-[(4""-METHOXYPHENYL)-ISOXAZOLE-3"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Internal standard : TMS , Solvent : $CDCl_3$, Instrument : BRUKER spectrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.42-3.98	6 H	Singlet	Ar-OCH_3
2	7.35-7.99	4 H	D Doublet	Ar-H_b
3	8.12-8.40	4 H	D Doublet	Ar-H_c
4	4.05-4.19	4 H	Triplet	-CH_2-Cl
5	2.82-2.84	4 H	Triplet	-N-CH_2-
6	10.19-10.28	1 H	Singlet	Ar-NH_f
7	8.12-8.16	1 H	Singlet	Ar-H_g

MASS SPECTRAL STUDY OF 2-{4'-[(5"-(4""METHOXY PHENYL)-ISOXAZOLE-3"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE. (M.W. : 515)



Antimicrobial Activity :

Conclution :

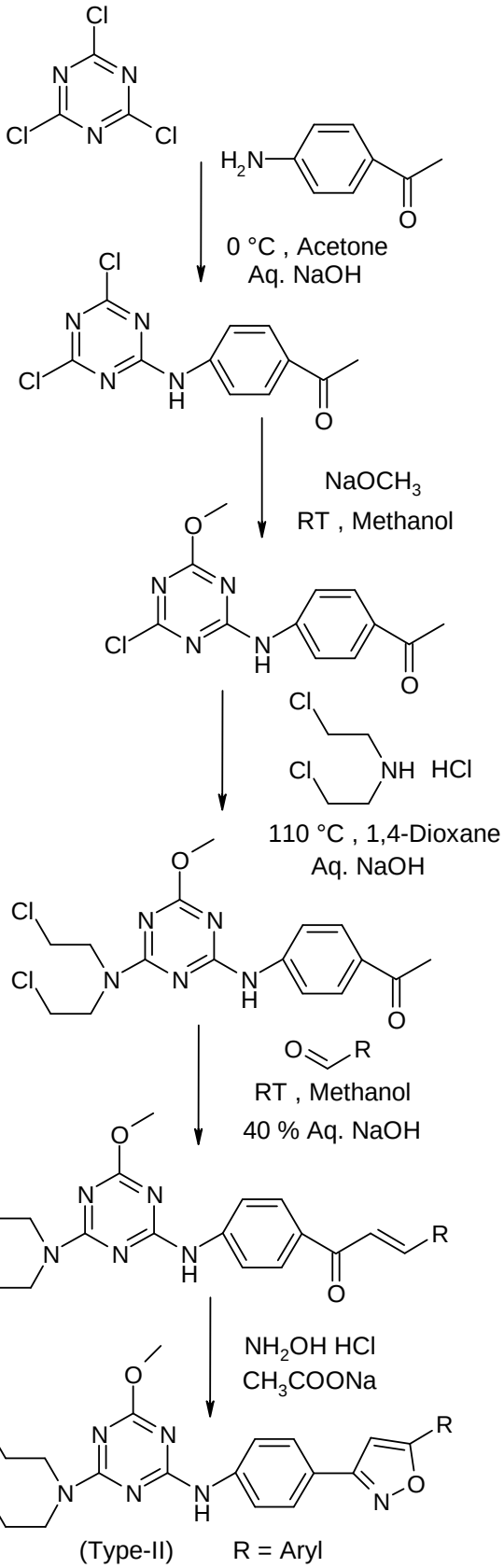
Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.				**Antifungal activity Zone of inhibition in m.m.**
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	4-OH C_6H_4-(22)	3-OH C_6H_4 (20)	3-OH C_6H_4 (21)	2-OH C_6H_4 (22)	4-OH C_6H_4 (22)
	4-Br. C_6H_4 (22)	4-OH C_6H_4 (21)	4-OH C_6H_4 (22)	4-OH C_6H_4 (21)	4-OH C_6H_4 (21)
		4-NO_2 C_6H_4 (22)	4OH, 3OCH_3 C_6H_3 (20)	4-OCH_3 C_6H_4 (23)	4-Br C_6H_4 (23)
			4-NO_2 C_6H_4 (21)	4-NO_2 C_6H_4 (24)	4-NO_2 C_6H_4 (20)

Comparable activity with known standard drugs

Ampicilin 50 µg.	23	18	17	27	-
Chloramphenicol ”	24	19	25	26	-
Norfloxacin ”	24	19	25	26	-
Greseofulvin ”	-	-	-	-	23

REACTION SCHEME



(Type-II) R = Aryl

EXPERIMENTAL

SYNTHESIS OF 2-{4'-[(5"-ARYL)-ISOXAZOLE-3"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

(A) **Synthesis of 2-(4'-Acetyl Phenyl amino)-4,6-dichloro-1,3,5-triazine.**

For synthesis sec Part-I, Section-I, Page no. 36-38.

(B) **Synthesis fo 2-(4'-Acetyl phenyl amino)-6-chloro-4-methoxy-1,3,5-triazine**

For synthesis see Part-I, Section-I, Page no. 36-38.

(C) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-[Bis(2"- chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis see Part-I, Section-I, Page no. : 36-38.

(D) **Synthesis of 2-{4'-[3"-(4-'"'-Methoxy phenyl)-2"-propene-1"-one] phenyl amino}-6-[Bis (2"'- chloro ethyl) amino]-4-methoxy-1,3,5 trizine.**

For synthesis see Part-I, Section-I, Page no. 36-38.

(E) **Synthesis of 2-{4'-[5"-(4""-Methoxy phenyl)-isoxazole-3"-yl]-phenyl amino}-6-[Bis (2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

A mixture of 2-{4'-[3"-(4""-methoxy phenyl)-2"-propene-1"-one] phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triaizine. (5.02 gm, 0.01 M) hydroxy amine hydrochloride (0.69 gms., 0.01 M) and ethanol (20 ml). The reaction mixture was reflux at 120^{o} C. for 6 hrs. The reaction mixture was cooled, poured into crushed ice, filtered, dried. The isolated products was

crystallised from methanol. Yield 73% ; mp. 118º C. (Found : C : 55.89; H : 4.61; N : 16.28, $C_{24}H_{24}O_3N_6Cl_2$, required : C : 55.92; H : 4.66, N : 16.31%)

Simillary other isoxazols were synthesised and their physical data recorded in Table no. 3

(F) **Antimicrobial activity of 2-{4'-[5"-aryl)-isoxazole-3"-yl]-Phenyl amino}-6-[Bis-(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

Antimicrobial testing was carried out as described in Part-I, Section-I, Page no. 39-41.

The zone of inhibition of the test solutions are recorded in Table no. 4

TABLE NO. : 3 PHYSICAL CONSTANT OF 2-{4'-[(5"-ARYL)-ISOXAZOLE-3"-YL]-PHENYL AMINO}-6-[BIS(2"-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Molecular Formula	M.P. °C	Yield %	% of Nitrogen	
					Calcd	Found
1.	C_6H_5	$C_{23}H_{22}Cl_2N_6O_2$	219	69	17.31	17.29
2.	2-OH C_6H_4	$C_{23}H_{22}Cl_2N_6O_3$	225	72	16.76	16.70
3.	3-OH C_6H_4	$C_{23}H_{22}Cl_2N_6O_3$	265	75	16.76	16.17
4.	4-OH C_6H_4	$C_{23}H_{22}Cl_2N_6O_3$	198	77	16.76	16.70
5.	4-OCH_3 C_6H_4	$C_{24}H_{24}Cl_2N_6O_3$	118	73	16.31	16.28
6.	4-OH, 3-OCH_3 C_6H_3	$C_{24}H_{24}Cl_2N_6O_4$	210	82	15.81	15.79
7.	4-Br C_6H_4	$C_{23}H_{21}BrCl_2N_6O_2$	209	87	14.89	14.83
8.	3-NO_2 C_6H_4	$C_{23}H_{21}Cl_2N_7O_4$	264	81	18.49	18.47
9.	4-NO_2 C_6H_4	$C_{23}H_{21}Cl_2N_7O_4$	202	83	18.49	18.45
10	4-N,N-$(CH_3)_2$ C_6H_3	$C_{25}H_{27}Cl_2N_7O_2$	173	79	18.55	18.51
11.	C_4H_3O (Furfuryl)	$C_{21}H_{20}Cl_2N_6O_2$	234	86	17.68	17.62

TABLE NO. 4 : ANTIMICROBIAL ACTIVITY OF 2-{4'-[(5"-ARYL)-2"-ISOXAZOLE-3"-YL]PHENYLAMINO}-6-[BIS(2"-CHLORO ETHYL)-AMINO]-4- METHOXY-1, 3, 5-TRIAZINE

Sr. No.	***R***	**Antibacterial activity Zone of inhibition in mm.**				**Antifungal activity Zone of inhibition in mm.**
		B. mega.	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5-	19	15	17	20	17
2	2-OH C_6H_4-	17	17	18	22	19
3	3-OH C_6H_4-	20	20	21	19	18
4	4-OH C_6H_4-	22	21	22	21	22
5	4-OCH_3 C_6H_4-	18	19	19	23	21
6	4-OH, 3-OCH_3 C_6H_3-	19	18	20	18	16
7	4-Br C_6H_4-	23	16	18	17	23
8	3-NO_2 C_6H_4-	16	17	19	16	17
9	4-NO_2 C_6H_4-	18	22	21	24	20
10	4-N,N-$(CH_3)_2$ C_6H_3-	17	18	21	18	19
11	C_4H_3O (Furfuryl)	19	17	18	16	15

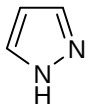
PART - III

STUDIES ON PYRAZOLINES

STUDIES ON PYRAZOLINES

INTRODUCTION

Amongst nitrogen containing five membered heterocycles, pyrazolines (Q) have proved to be the most useful frame work for biological activities, pyrazolines have attracted attention of medicinal chemistry for both with regard to hererocyclic chemistry and the pharmacological activities associated with them in 1967. Jarobe reviewed the chemistry of pyrazolines, which have been studied extensively for their[132-133] and industrial applications.

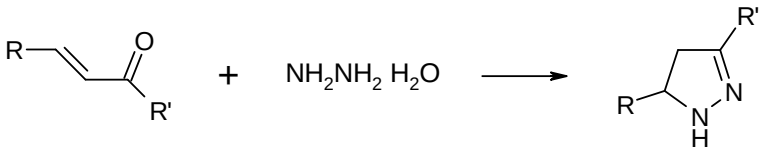


(Q)

SYNTHETIC ASPECT :

Different methods for the preparation of 2-pyrazoline derivatives documented in literature are as follows.

(1) 2-pyrazolines can be constructed by the cyclocondensantion of chalcones with hydrazine hydrate.[134]



(2) 2-Pyrazoline can also be prepared by the condensation of chalcone dibromide with hydrazines.[135]

(3) 2-Pyrazolines can be synthesised by the cycloaddition of diazomethane to substituted chalcone.[136]

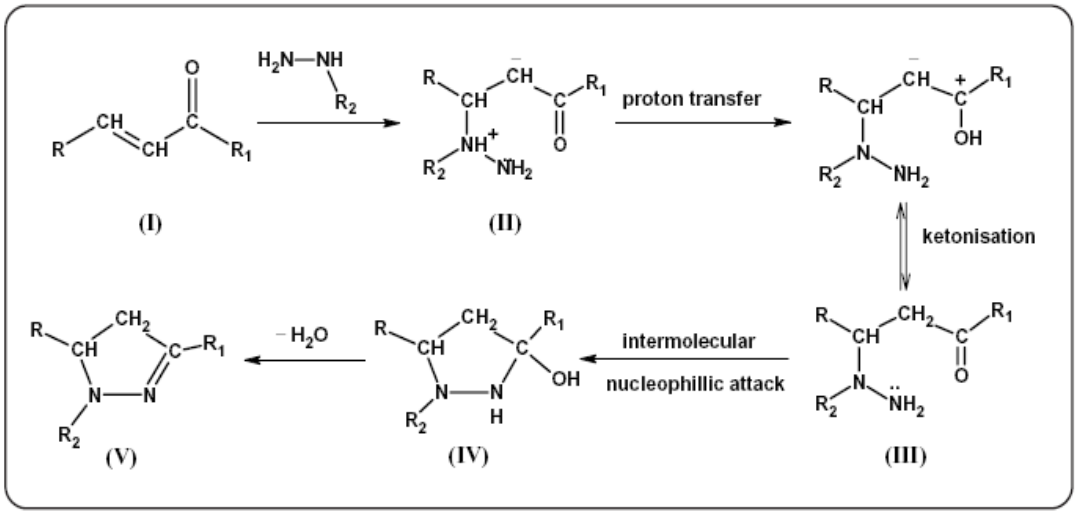
(4) Dipolar cycloaddition of intrilimines of dimethyl fumarate fumaronitrile and the N-aryl maleimides yields the corresponding pyrazolines.[137]

(5) Epoxidation of chalcones have epoxy ketones which reacted with hydrazine and phenyl hydrazine to give pyrazolines.[138]

Further more, B. Gyassi et al.[139] investigated the one pot synthesis of some pyrazolines in dry media under microwave irradiation. S. Paul et. al.[140] A. Dandia et. al.[141] have also described the microwave synthesis of 2-pyrazolines.

MECHANISM :

The following mechanism seems to be operable for the condensation of chalcones with hydrazine hydrate.[142]



Nucleophilic attack by hydrazine at the β-carbon of the $\alpha-\beta$ unsaturated carbonyl system forms species (II) in which the-ve charge is mainly accomodated by the electro nagative oxygen atom.

Proton transfer from the nitrogen to -ve oxygen produces an intermediate enol which simultaniously ketonise to ketoamine (III). Another intramolecular nucleophilic attack

by the primary amino group of ketoamine on its carbonyl carbon followed by proton transfer from nitrogen to oxygen leads ultimately to amine (IV). The later with by hydroxy group and amino group on the carbon lose water moleculer to yield the pyrazolines.

THERAPEUTIC IMPORTANCE :

From the literature survey, it was reveled that 2-pyrazolines are better therapeutic agents,

(a) Analgesic[143,144]

(b) Bactericidal[145,146]

(c) Cardiovascular[147]

(d) Diuretic[148]

(e) Fungicidal[149]

(f) Herbicidal[150]

(g) Hypoglycemic[151]

(h) Insecticidial[152]

(i) Tranquilizer[153]

(j) Antiallergic[154]

(k) Anticonvalsant[155-156]

(i) Antidiabetic[157]

(m) Antiimplantation[158]

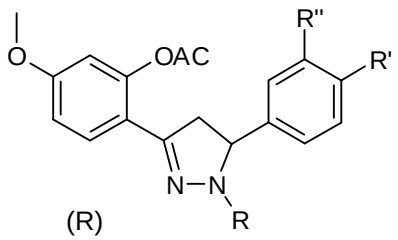
(n) Antiinflamatory[159]

(o) Antitumor[160]

(p) Antineoplastic[161]

(q) Antimicrobial[162]

S. S. Sonarc et al.[163] have synthesized 3-(2-acetoxy-4-methoxy phenyl)- 5-(substituted phenyl)-pyrazolines(R) and tested their antimicrobial activity.



(R)

Moreover, T. M. Stivenson et al.[164] have also investigated N-substituted pyrazoline type insecticides. Katsuhori[165] have patented pyrazoline derivatives as herbicides and K. Johannes, et. al.[166] reported insecticides. Z. Moritaz and S. Hadol[167] to investigated a semiemperial molecular orbital study on the reaction of aminopyrazolinyl azo dye with singlet molecular oxygen.

M. K. Shivnanda and co-worker[168] have prepared pyrazolines and reported their antibacterial activity. B. Shivarama Holla et. al.[169-170] have synthesised pyrazolines as antibacterial agent. S. P. Hiremath et al.[171] have synthesised pyrazolines as analgesic, antiinflammatory and antimicrobial agent. V. Malhotra et. al.[172] have synthesised new pyrazolines as a cardiovascular agent.

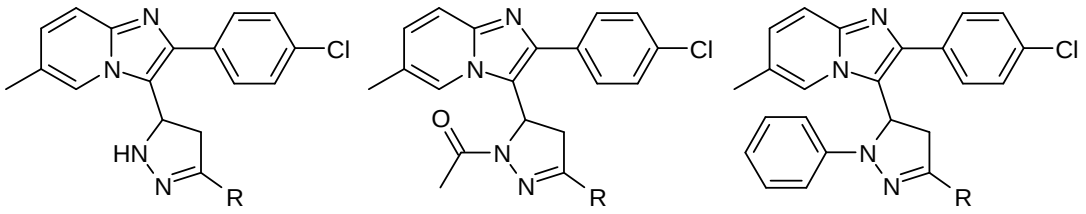
Ji-In Kim Almstead et. al.[173] have prepared pyrazolines as vascularization agent. Guniz kucukguzel et. al.[174] have synthesised pyrazolines as a antimicrobial and anticonvulsant agents.

T. Z. Gulhan and co-workers[175] have prepared pyrazolines as a hypogxycemic agent. S. Sharma et. al.[176] have synthesised pyrazolines and tested their

antiinflamatory activity. Ashok Kumar et. al.[177] have synthesised pyrazolines as anticonvulsant agent.

Contribution in our Laboratory :

D. M. Purohit et. al.[131] have synthesised 2-(4'-chloro phenyl)-6-methyl-3-(3"-aryl-4", 5"-dihydro-1"-H-pyrazole-5"-yl)-imidazo [1, 2-a] pyridine.



R = aryl

SECTION-I : SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-(5"ARYL)4", 5"-DIHYDRO-1"-(H) PYRAZOL-3"-YL] PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.

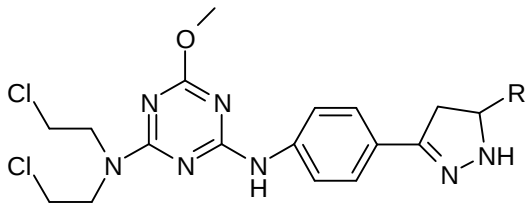
SECTION-II : SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(5"-ARYL)-4", 5"-DIHYDRO-1"-ACETYL PYRAZOL-3"-YL]-PHENYLAMINO}-6-[BIS. (2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.

SECTION-III : SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[5"-ARYL]-4"-5"-DIHYDRO-1"-PHENYL PYRAZOL-3"-YL]-PHENYL AMINO}-6-[BIS. (2"'-CHLORO ETHYL) AMINO]-4- METHOXY-1,3, 5- TRIAZINE.

SECTION : 1

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-(5"-ARYL)4", 5"-DIHYDRO-1"-(H) PYRAZOL-3"-YL] PHENYL AMINO}-6-[BIS (2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Pyrazoline derivatives possess broad spectrum of pharmacological activities which are reflacted by their use as analgesic, anticonvulsant, antimicrobial, antipyratics agents. Prompted by above facts 2-{4'-(5"-aryl)4", 5"-dihydro-1"-(H) pyrazol-3"-yl] phenyl amino}-6-[Bis (2"'-chloroethyl) amino]-4-methoxy- 1,3,5-triazine Type-(III) have been synthesised by the condensation of 2-{4'-[(3"-aryl)-2"-propene-1". one]-phenyl amino}-6-[Bis 2"'-chloroethyl) amino]-4-methoxy-1,3,5-trazine with hydrazine hydrate.

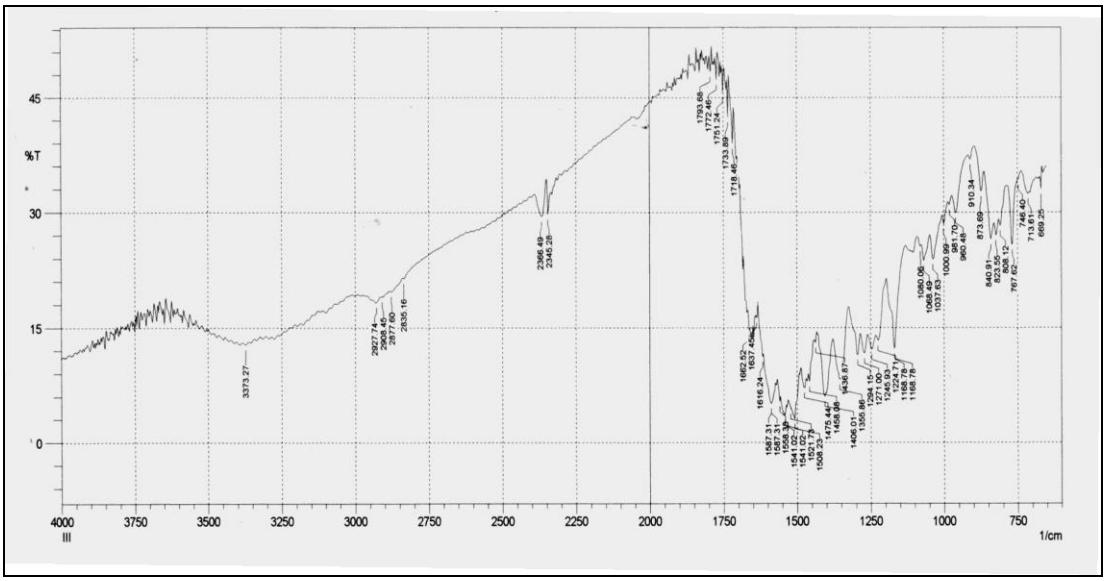


(Type-III) R = Aryl

The constitution of the synthesized products were supported by IR, ^{1}H, NMR and Mass spectral study. The products were screened for their antimicrobial activity at a concentration of 50 µg.

The details have been cited in the Part : I, Section : I, Page No. 39-41.

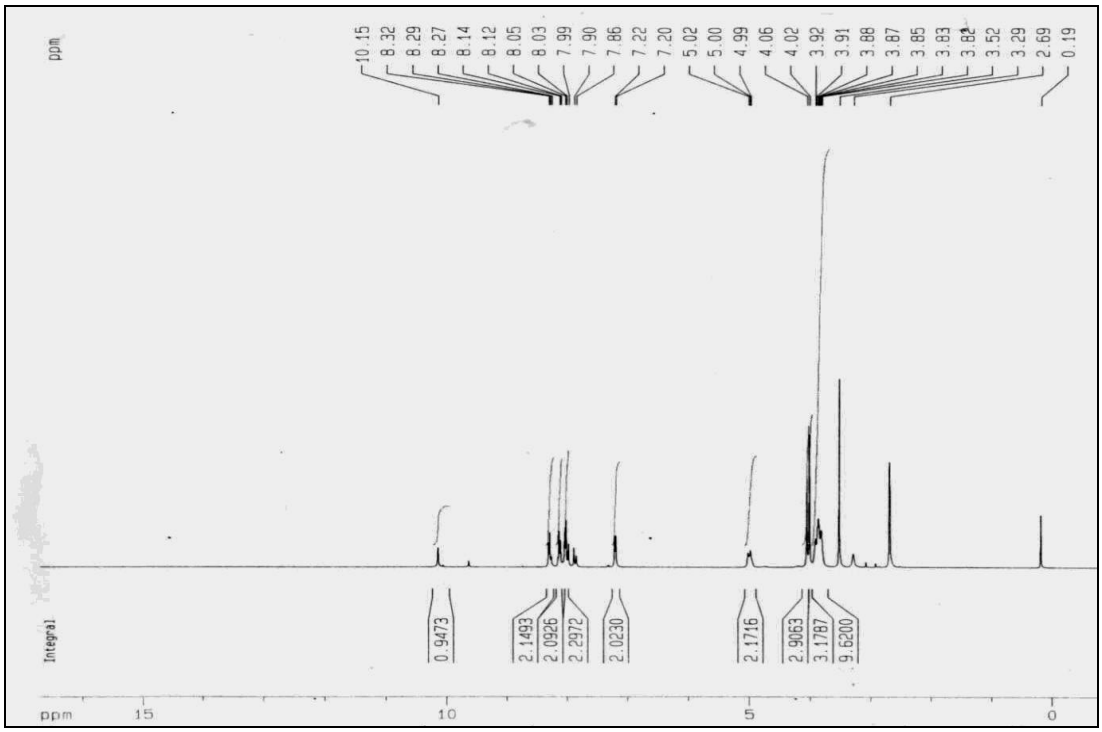
IR SPECTRAL STUDY OF 2-{4'-(5"-(4""-METHOXYPHENYL)4", 5"-DIHYDRO-1"-(H) PYRAZOL-3"-YL] PHENYL AMINO}-6-[BIS (2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Instrument : SHIMADZU-FT-IR-8400, Spectrophoto meter frequency range : 4000-400cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	reported	
Alkane	C-H Str.(asym)	2908	2990-2850	422 – 423
	C-H Str.(sym)	2877	2880-2860	”
	C-H def.(asym)	1458	1470-1435	”
	C-H def.(sym)	1361	1390-1360	”
Aromatic	C-H Str.	3072	3090-3030	”
	C-H i.p. def	1294	1300-1100	”
	C-H o.o.p. def	823	832-800	”
	C=C Str.	1458	1600-1450	”
S-triazine	C-N Str.	1168	1220-1020	”
	C=N Str.	1616	1630-1590	”
Amine	N-H Str.	3373	3500-3310	”
Ether	C-O-C Str.(asym)	1245	1260-1220	”
	C-O-C Str.(sym)	1037	1075-1020	”
Halide	C-Cl Str.	767	800-600	”
Pyrazoline	C=O Str.	1662	1705-1650	”
	C=N Str.	1667	1650-1550	”
	CH-CH_2 Str.	2366	2850-1790	”
	N-H Str.	3303	3520-3140	”

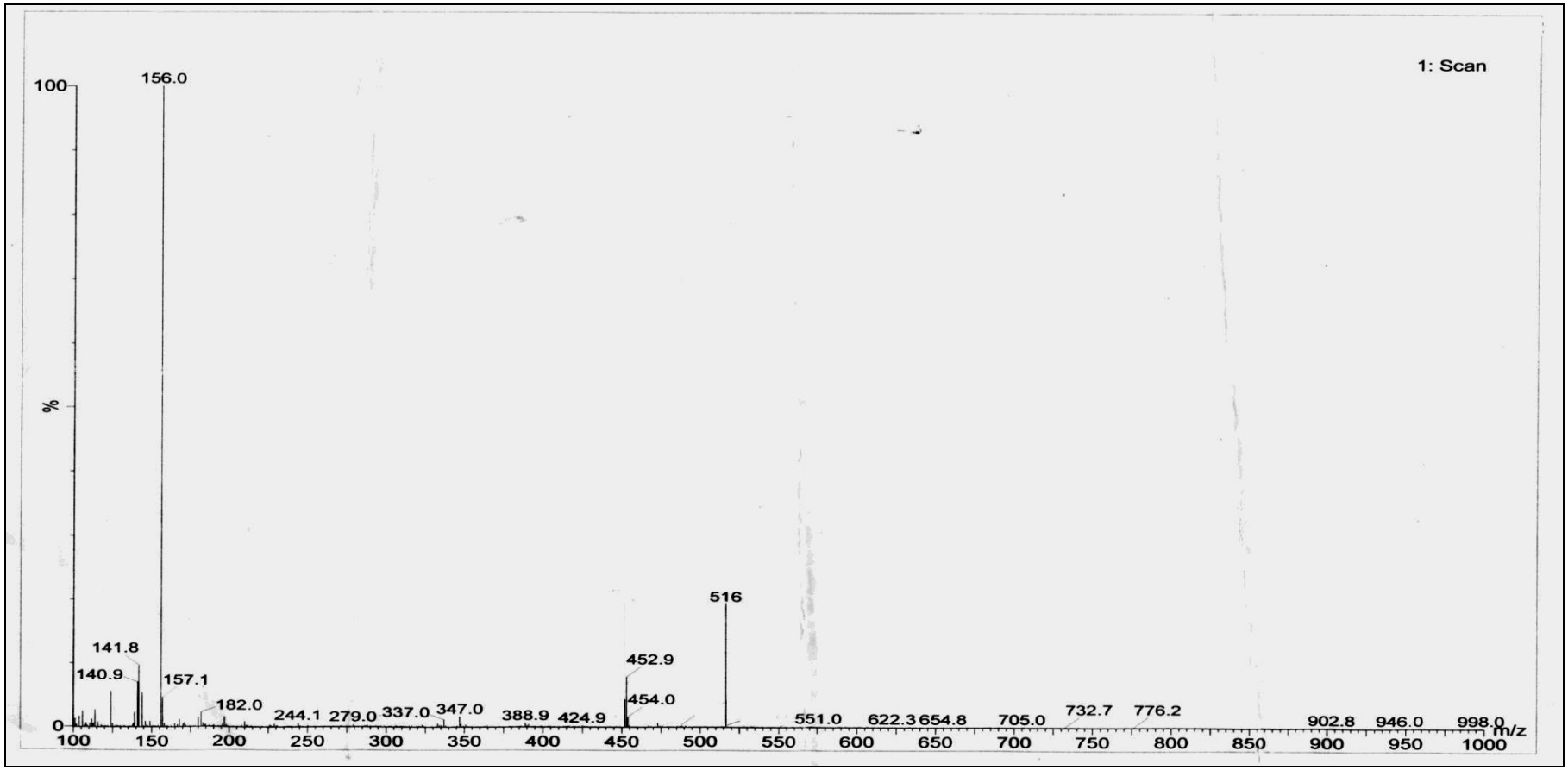
NMR SPECTRAL STUDY OF 2-{4'-(5"-(4""-METHOXYPHENYL)4", 5"-DIHYDRO-1"-(H) PYRAZOL-3"-YL] PHENYL AMINO}-6-[BIS (2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Internal standard : TMS, Solvent : $CDCl_3$, Instrument : DPX-200 Spectrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.83-3.92	6 H	Singlet	Ar-OCH_3
2	7.20-7.22	4 H	D. Doublet	Ar-H_b
3	8.12-8.32	4 H	D. Doublet	Ar-H_c
4	4.02-4.06	4 H	Triplet	-CH_2-Cl
5	2.69-3.29	4 H	Triplet	-N-CH_2-
6	10.15	2 H	Singlet	Ar-NH_f
7	3.52-3.82	2 H	Singlet	-$CH_{2\,h}$

MASS SPECTRAL STUDY OF 2-{4'-(5"-(4""-METHOXYPHENYL)4", 5"-DIHYDRO-1"-(H) PYRAZOL-3"-YL] PHENYL AMINO}-6-[BIS (2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE. (M.W. : 516)



Antimicrobial Activity :

Conclution :

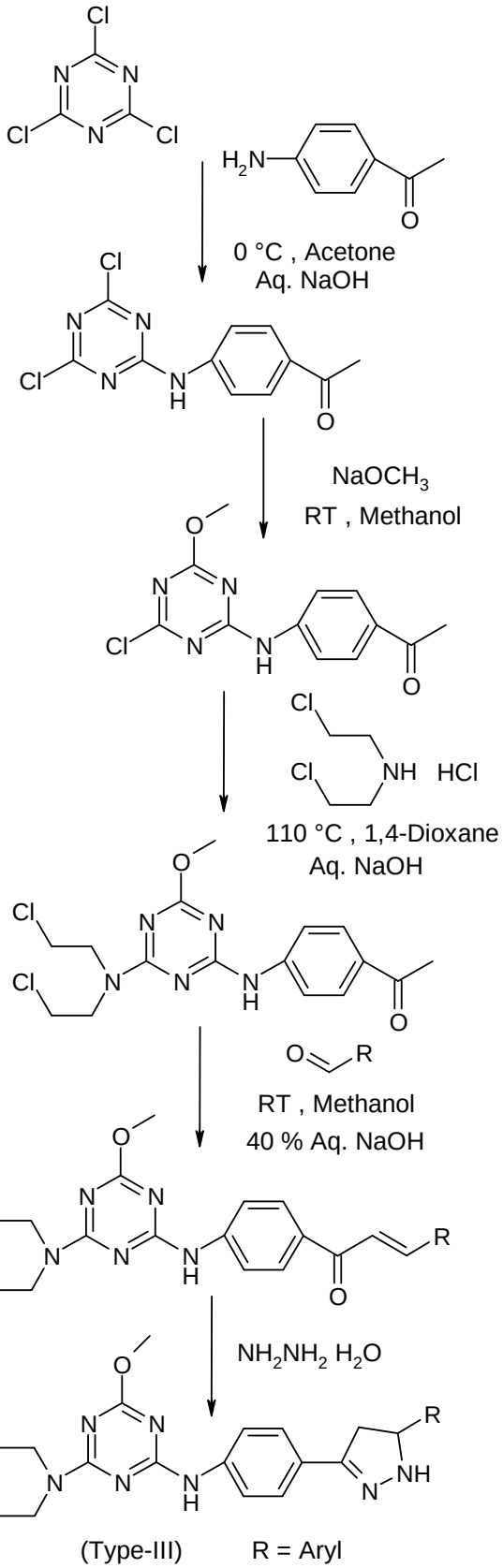
Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.				**Antifungal activity Zone of inhibition in m.m.**
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R.***
	2-OH C_6H_4 (21)	3-OH C_6H_4 (18)	3-OH C_6H_4 (21)	2-OH C_6H_4 (21)	C_6H_4 (21)
	4-OH C_6H_4 (23)	4-OH C_6H_4 (19)	4-OH C_6H_4 (20)	4-OH C_6H_4 (23)	3-OH C_6H_4 (22)
	4-Br C_6H_4 (22)	4-OH 3-OCH_3 C_6H_3 (18)	4-Br. C_6H_4 (23)	4-OH, 3OCH_3 C_6H_3 (22)	4-OCH_3 C_6H_4 (23)
		4-N,N $(CH_3)_2$ C_6H_4 (21)	4-NO_2 C_6H_4 (20)	4-Br. C_6H_4 (22)	4-Br. C_6H_4 (21)

Comparable activity with known standard drugs

Ampicilin (50 µg.)	23	18	17	27	-
Chloramphenicol "	24	19	25	26	-
Norfloxacin "	24	19	25	26	-
Greseofulvin "	-		-	-	23

REACTION SCHEME



(Type-III) R = Aryl

EXPERIMENTAL

SYNTHESIS OF 2-{4'-(5"-ARYL)4", 5"-DIHYDRO-1"-(H) PYRAZOL-3"-YL] PHENYL AMINO}-6-[BIS (2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.

(A) **Synthesis of 2-(4'-Acetyl phenyl amino)-4, 6-dichloro-1,3,5-triazine**

For synthesis see Part-I, Section-I, Page no. 36-38.

(B) **Synthesis of 2-(4'-Acetyl phenyl amino)-6- chloro-4-methoxy-1,3,5-triazine.**

For synthesis see Part-I, Section-I, Page no. 36-38.

(C) **Synthesis of 2-(4'-Acetyl Phenyl amino)-6-[Bis-(2"-chloroethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis see Part-I, Section-I, Page no. 36-38.

(D) **Synthesis of 2-{4'-[3"-(4"'-methoxy phenyl)- 2"-propene-1"-one] phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4- methoxy-1,3,5-triazine.**

For synthesis see Part-I, Section-I, Pagen no. 36-38.

(E) **Synthesis of 2-{4'-[5-'"(4""-methxoxy phenyl) 4", 5"-dihydro-1"-(H) -pyrazol - 3"-yl] phyenyl amino}-6-[Bis (2"'-chloroethyl) amino]-4-methoxy-1,3,5- triazine.**

A mixture of 2-{4'-[3"-(4""-methoxyphenyl)-2"-propene-1"-one] phenyl amino}-6-[Bis (2"'-chloroethyl) amino]-4-methxoxy-1,3,5-triazine

(5.02 gm, 0.01 M) hydrazine hydrate (1.0 ml) in methanol (15 ml) was refluxed for 12 hrs. The product was poured into crushed ice filtered, washed with water and crystallised from dixoane yield : 82%, M.P. 280° C. (Found : C : 55.80, H : 5.21, N : 18.97, $C_{24}H_{27}O_2N_7Cl_2$; C : 55.81, H : 5.23, N : 18.99%) Simillarly other pyrazoleo derivatives have been synthesisded and their physical data are recorded in Table no. 5

(F) **Antimicrobial activity of 2-{4'-[(5''-aryl) 4", 5" - dihydro-1"-(H)-pyrazol-3"-yl]-phenyl amino}-6-[Bis. (2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine**

The antimicrobial testing was carried out as described in Part-I, Secton-I, Page no. 39-41.

The zone of inhibition of the test solution are recorded in Table no. 6.

TABLE NO : 5 PHYSICAL CONSTANTS OF 2-{4'-(5"-ARYL)4", 5"-DIHYDRO-1"-(H) PYRAZOL-3"-YL] PHENYL AMINO}-6-[BIS (2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Molecular Formula	M.P. .c	Yield %	% of Nitrogen	
					Calcd	Found
1.	C_6H_5	$C_{23}H_{25}Cl_2N_7O$	207	70	20.16	20.11
2.	2-OH C_6H_4	$C_{23}H_{25}Cl_2N_7O_2$	249	72	19.52	19.50
3.	3-OH C_6H_4	$C_{23}H_{25}Cl_2N_7O_2$	225	75	19.52	19.51
4.	4-OH C_6H_4	$C_{23}H_{25}Cl_2N_7O_2$	198	79	19.52	19.48
5.	4-OCH_3 C_6H_4	$C_{24}H_{27}Cl_2N_7O_2$	280	82	18.99	18.97
6.	4-OH, 3-OCH_3 C_6H_3	$C_{24}H_{27}Cl_2N_7O_3$	268	81	18.41	18.40
7.	4-Br C_6H_4	$C_{23}H_{24}$ Br Cl_2N_7O	205	69	17.34	17.32
8.	3-NO_2 C_6H_4	$C_{23}H_{24}Cl_2N_8O_3$	242	83	21.09	21.08
9.	4-NO_2 C_6H_4	$C_{23}H_{24}Cl_2N_8O_3$	188	89	21.09	21.05
10	4-N,N$(CH_3)_2$ C_6H_4	$C_{25}H_{30}Cl_2N_8O$	216	71	21.16	21.12
11.	C_4H_3O (Furfuryl)	$C_{21}H_{23}Cl_2N_7O_2$	298(d)	77	20.58	20.57

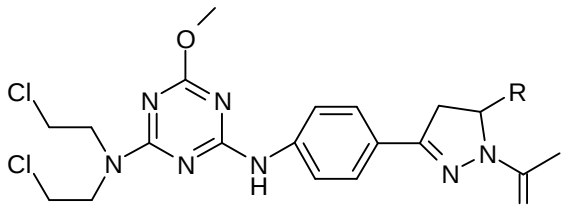
TABLE NO : 6 ANTIMICROBIAL ACTIVITY OF 2-{4'-(5"-ARYL)4", 5"-DIHYDRO-1"-(H) PYRAZOL-3"-YL] PHENYL AMINO}-6-[BIS (2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	**R**	**Antibacterial activity Zone of inhibition in mm.**				**Antifungal activity Zone of inhibition in mm.**
		B. mega.	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5	19	15	17	18	21
2	2-OH C_6H_4	21	14	19	21	19
3	3-OH C_6H_4	20	18	21	20	22
4	4-OH C_6H_4	23	19	20	23	20
5	4-OCH_3 C_6H_4	18	16	22	19	23
6	4-OH, 3-OCH_3 C_6H_3	17	18	18	22	18
7	4-Br C_6H_4	22	20	23	22	21
8	3-NO_2 C_6H_4	20	15	17	19	17
9	4-NO_2 C_6H_4	18	17	20	18	20
10	4-N, $N(CH_3)_2$ C_6H_4	19	21	17	20	19
11	C_4H_3O (Furfuryl)	17	16	18	19	20

SECTION : II

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(5"-ARYL)-4", 5"-DIHYDRO-1"-ACETYL PYRAZOL-3"-YL]-PHENYLAMINO}-6-[BIS. (2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Acetyl pyrazoline dervatives procuring better therapeutic and antimicrobial activity looking at their better therapeutic importance and with an aim to getting better drug, it was considered worth while to synthesis some new pyrazoline. The synthesis of 2-{4'-[(5"-Aryl)-4", 5"-dihydro-1"-acetyl pyrazol-3"-yl]-phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy -1,3,5-triazine of Type (IV) have been synthesised by the cyclocondensation of chalcones of Type (I) with hydrazine hydrate and glacial acetic acid.

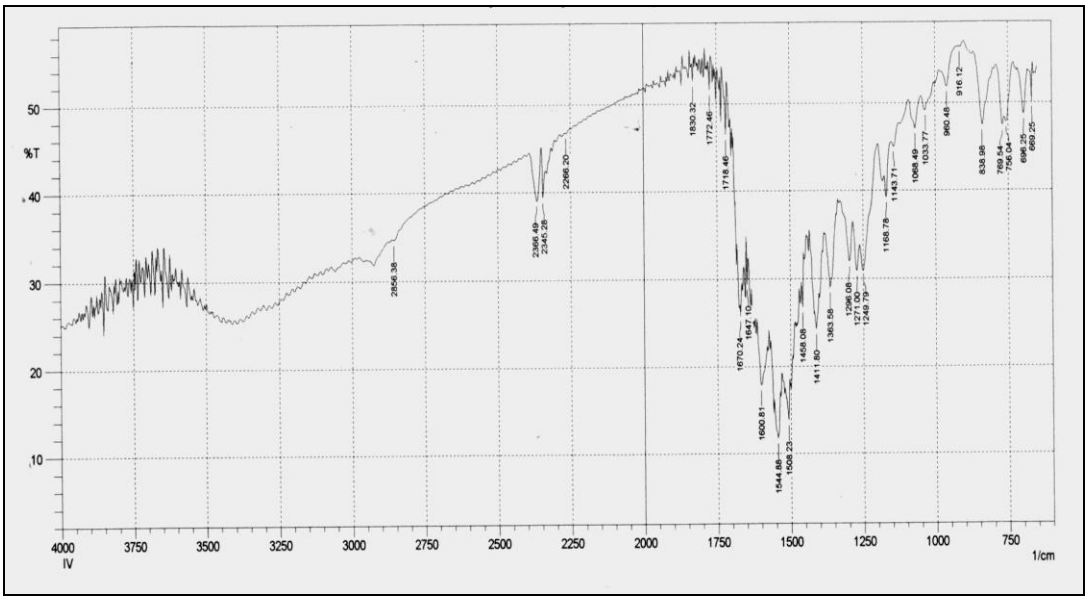


(Type-IV) R = Aryl

The constitution of the products have been characterised by elemental analyses IR, ^{1}H NMR and Mass spectral study. The products were screened for their antimicrobial activity at a concentration of 50 µg.

The details have been in the Part : I, Section I, Page No. 39-41.

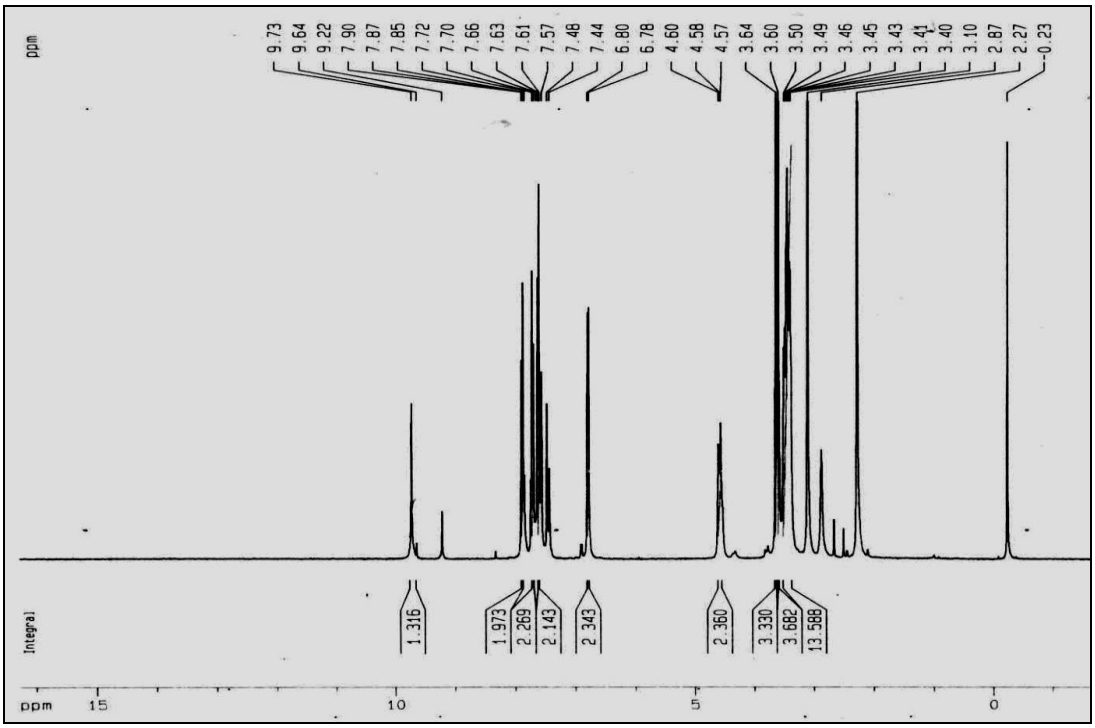
IR SPECTRAL STUDY OF 2-{4'-[(5"-(4""-METHOXYPHENYL)-4", 5"-DIHYDRO-1"-ACETYL PYRAZOL-3"-YL]-PHENYLAMINO}-6-[BIS. (2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Instrument : SHIMADZU-IR-8400, Spectrophoto meter frequency range : 4000-400 cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	reported	
Alkane	C-H Str.(asym)	2856	2990-2850	422 – 423
	C-H Str.(sym)	2878	2880-2860	”
	C-H def.(asym)	1458	1470-1435	”
	C-H def.(sym)	1363	1390-1360	”
Aromatic	C-H Str.	3055	3090-3030	”
	C-H i.p. def	1249	1300-1100	”
	C-H o.o.p. def	838	832-800	”
	C=C Str.	1458	1600-1450	”
S-triazine	C-N Str.	1068	1220-1020	”
	C=N Str.	1600	1630-1590	”
Amine	N-H Str.	3452	3500-3310	”
	N-H Bending	1647	1650-1550	”
Ether	C-O-C Str.(asym)	1271	1260-1220	”
	C-O-C Str.(sym)	1033	1075-1020	”
Halide	C-Cl Str.	769	800-600	”
Pyrazoline	C=O Str.	1670	1705-1650	”
	C=N Str.	1600	1650-1550	”
	CH-CH_2 Str.	1830	2850-1790	”

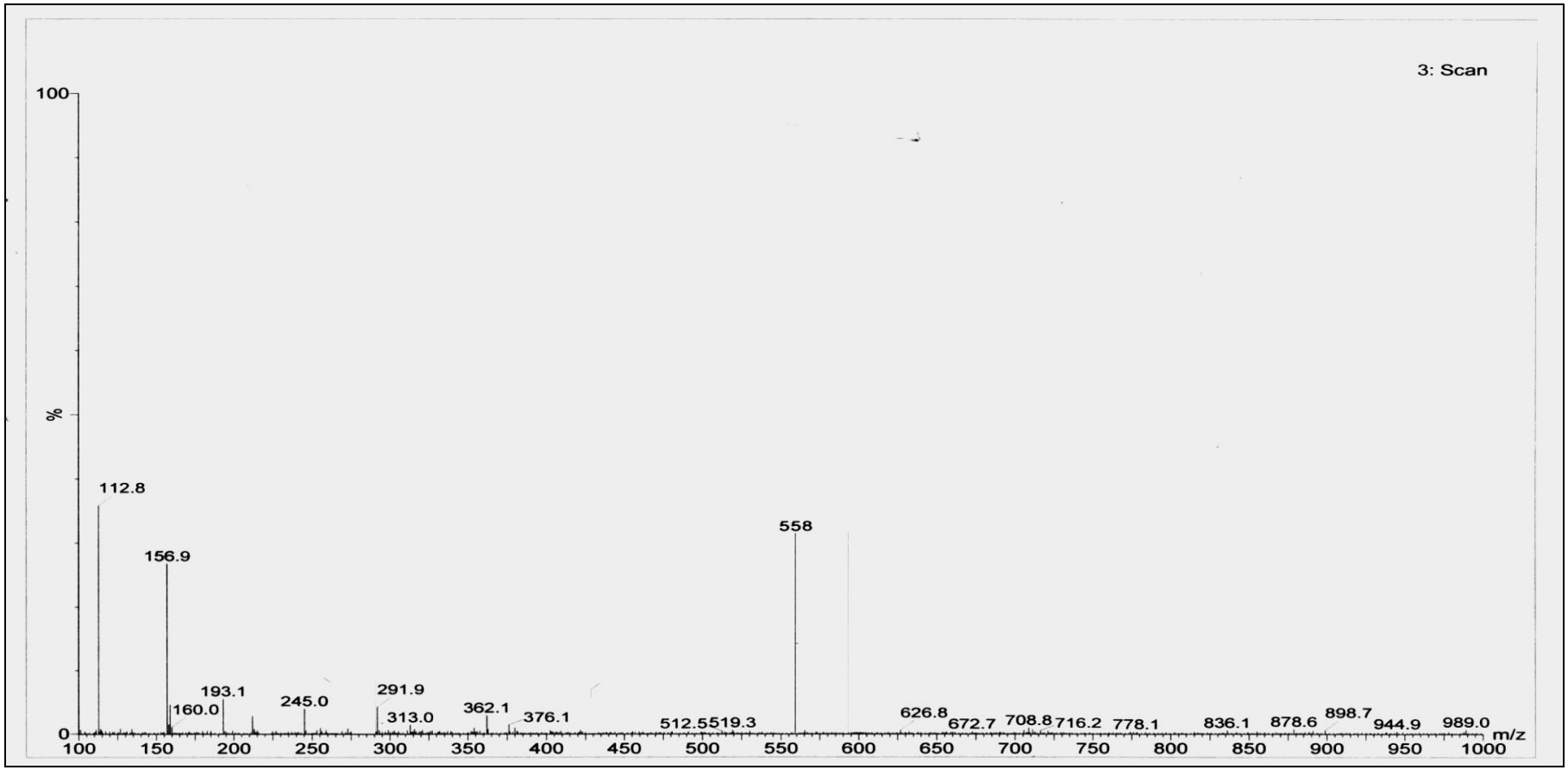
NMR SPECTRAL STUDY OF 2-{4'[(5"-(4""-METHOXYPHENYL)-4", 5"-DIHYDRO-1"-ACETYL PYRAZOL-3"-YL]-PHENYLAMINO}-6-[BIS. (2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Internal standard : TMS ; solvent : DMSO ; Instrument : BRUKER Sepctrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.60-3.64	6 H	Singlet	Ar-OCH_3
2	7.44-7.72	4 H	D Doublet	Ar-H_b
3	7.85-9.90	4 H	D Doublet	Ar-H_c
4	4.57-4.60	4 H	Triplet	-CH_2-Cl
5	2.27-2.87	4 H	Triplet	-N-CH_2-
6	9.73	1 H	Singlet	Ar-NH_f
7	3.10-3.40	2 H	Singlet	-$CH_{2\,h}$
8	2.87	3 H	Singlet	-$COCH_3$

MASS SPECTRAL STUDY OF 2-{4'-[(5"-(4""-METHOXYPHENYL)-4", 5"-DIHYDRO-1"-ACETYL PYRAZOL-3"-YL]-PHENYLAMINO}-6-[BIS (2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE. (M.W. : 558)



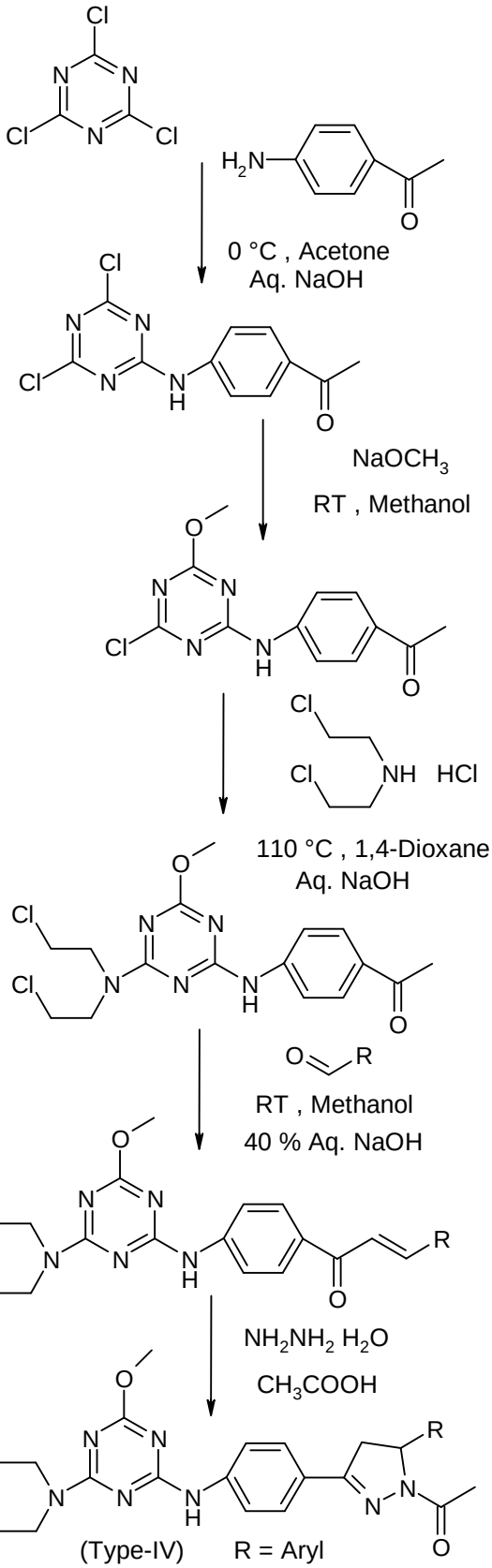
Antimicrobial Activity :

Conclution :

Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.				**Antifungal activity Zone of inhibition in m.m.**
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	4-OH C_6H_4 (22)	2-OH C_6H_4 (28)	3-OH C_6H_4 (20)	2-OH C_6H_4 (21)	3-OH C_6H_4 (20)
	4-OCH_3 C_6H_4 (21)	3-OH C_6H_4 (19)	4-OH C_6H_4 (23)	4-OH C_6H_4 (23)	4-OH C_6H_4 (21)
	4-OCH_3, 3-OCH_3	4-OH C_6H_4 (21)	4-OCH_3 C_6H_4 (22)	4-OH, 3-OCH_3–C_6H_3 (21)	4-Br C_6H_4 (22)
	C_6H_3 (23)	4-Br C_6H_4 (22)	4-Br C_6H_4 (20)		-
	4-Br C_6H_4 (22)	4-NO_2 C_6H_4 (21)	-	C_4H_3O-(21)	-
	4-N,N$(CH_3)_2$ C_6H_4 (23)	C_4H_3O (20)			
Comparable activity with known standard drugs					
Ampicilin (50 μg)	23	18	17	27	-
Chloramphenicol "	24	19	25	26	-
Norfloxacin "	24	19	25	26	-
Greseofulvin "	-	-	-	-	23

REACTION SCHEME



(Type-IV) R = Aryl

EXPERIMENTAL

SYNTHESIS AND ANTIMICROBIAL ACTIVITYOF 2-{4'-[(5"-ARYL)-4", 5"-DIHYDRO-1"-ACETYL PYRAZOL-3"-YL]-PHENYLAMINO}-6-[BIS. (2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.

(A) **Synthesis of 2-(4'-Acetylphenyl amino)-4, 5-dichloro-1,3,5-triazine.**
For synthesis Part-I, Section-I, Page no. 36-38.

(B) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-chloro-4-methoxy-1,3,5-triazine.**
For synthesis Part-I, Section-I, Page no. 36-38.

(C) **Synthesis of 2-(4'-Acetyl phenyl amino)-6- [Bis (2"-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**
For synthesis Part-I, Section-I, Page no. 36-38.

(D) **Syntesis of 2-{4'-[3"-(4""-methoxyphenyl)-2"-propene-1"-one] phenyl amino}-6-[Bis (2"'-chloroethyl) amino]-4-methoxy 1,3,5-triazine.**
For synthesis, Part-I, SectionI, Page No. 36-38.

(E) **Synthesis of 2-{4'-[5"-(4""-methoxyphenyl)-4", 5"- dihydro-1"-(H)-pyrazol-3"-yl]-phenylamino}-6-[Bis(2"'-chloro ethyl amino]-4-methoxy-1,3,5-triazine.**

A mixture of 2-{4'-[3"-(4""methoxyphenyl)-2" propene-1"-one] phenyl amino-6-[Bis (2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine (5.02 gm, 0.01M); hydrazine hydrate (1.0 ml), glacial aceticacid (2.0 ml.)and methanol (20 ml) was refluxed for 12 hrs. The reaction mixture is poured into crushed ice, filtered, dried and crystallised from dioxane. Yield : 80%, M.P.: 168^{o} C, (Found C : 55.90, H : 5.17; N : 17.54; $C_{29}H_{29}O_3Cl_2N_7$ required C : 55.91; H : 5.19, N : 17.56%)

Simillarly other acetyl pyrazoline have been synthesised and their physical constant are recorded in Table No.7)

(F) **Antimicrobial activity of 2-{4'-[(5"-Aryl)-4", 5"- dihydro 1"-acetyl pyrazol-3"-yl]-phenyl amino}-6- [bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5- triazine.**

The antimicrobial testing was carried out as described in Part : I, Section : , Page No. : 39-41.

The zone of inhibition of the test solution are recorded in Table No. : 8

TABLE NO : 7 PHYSICAL CONSTANTS OF 2-{4'-[(5"-ARYL)-4", 5"-DIHYDRO-1"-ACETYL PYRAZOL-3"-YL]-PHENYLAMINO}-6-[BIS (2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Molecular Formula	M.P. .c	Yield %	% of Nitrogen	
					Calcd	Found
1.	C_6H_5	$C_{25}H_{27}Cl_2N_7O_2$	171	78	18.55	18.52
2.	2-OH C_6H_4	$C_{25}H_{27}Cl_2N_7O_3$	215	71	18.01	18.00
3.	3-OH C_6H_4	$C_{25}H_{27}Cl_2N_7O_3$	272	75	18.01	18.01
4.	4-OH C_6H_4	$C_{25}H_{27}Cl_2N_7O_3$	186	81	18.01	17.99
5.	4-OCH_3 C_6H_4	$C_{26}H_{29}Cl_2N_7O_3$	168	80	17.56	17.54
6.	4-OH 3-OCH_3 C_6H_3	$C_{26}H_{29}Cl_2N_7O_4$	235	79	17.07	17.05
7.	4-Br C_6H_4	$C_{25}H_{26}BrCl_2N_7O_2$	227	82	16.14	16.12
8.	3-NO_2 C_6H_4	$C_{25}H_{26}Cl_2N_8O_4$	280	84	19.54	19.50
9.	4-NO_2 C_6H_4	$C_{25}H_{26}Cl_2N_8O_4$	256	87	19.54	19.51
10	4-N,N$(CH_3)_2$ C_6H_4	$C_{27}H_{32}Cl_2N_8O_2$	279	73	19.61	19.60
11.	C_4H_3O (furfuryl)	$C_{23}H_{25}Cl_2N_7O_3$	194	77	18.91	18.89

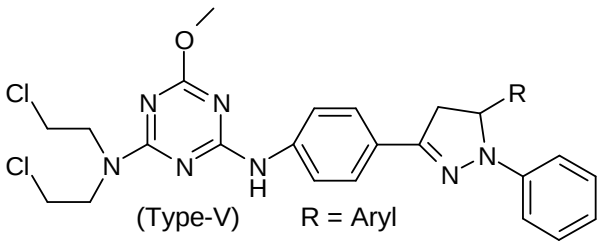
TABLE NO : 8 ANTIMICROBIAL ACTIVITY OF 2-{4'-[(5"-ARYL)-4", 5"-DIHYDRO-1"-ACETYL PYRAZOL-3"-YL]-PHENYLAMINO}-6-[BIS(2"'-CHLORO ETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	**Antibacterial activity Zone of inhibition in m.m.**				**Antifungal activity Zone of inhibition in m.m.**
	B. mega.	***B. subtillis***	***E. coli.***	***P. fluorescens.***	***A. awamori.***
C_6H_5	18	16	18	15	18
2-OH C_6H_4	19	18	17	21	17
3-OH C_6H_4	17	19	20	19	20
4-OH C_6H_4	22	21	23	23	21
4-OCH_3 C_6H_4	21	17	22	20	16
4-OH 3-OCH_3 C_6H_3	23	16	19	22	18
4-Br C_6H_4	22	22	20	23	22
3-NO2 C_6H_4	16	18	18	19	16
4-NO_2 C_6H_4	19	21	19	20	19
4-N,N$(CH_3)_2$ C_6H_4	23	17	20	18	19
C_4H_3O (furfuryl)	18	20	19	21	18

SECTION-III

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(5"-ARYL)-4"-5"-DIHYDRO-1"-PHENYL PYRAZOL-3"-YL]-PHENYL AMINO}-6-[BIS. (2"'-CHLORO ETHYL) AMINO]-4- METHOXY-1,3, 5- TRIAZINE.

Phenyl pyrazoline derivatives showes good therapeutic activities, it was considered worth while to synthesis compounds bearing 2-{4'-[(5"-aryl)-4", 5"-dihydro-1"-phenyl pyrazol-3"-yl]-phenyl amino}-6-[Bis (2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine of Type-(v) have been synthesised by the condensation of 2-{4'-[(3"-aryl)-2"-propene-1"-one]-phenyl amino}-6-[Bis(2"'-chloroethyl) amino -4-methoxy - 1,3,5-triazine of Type-(I) with phenyl hydrazine.

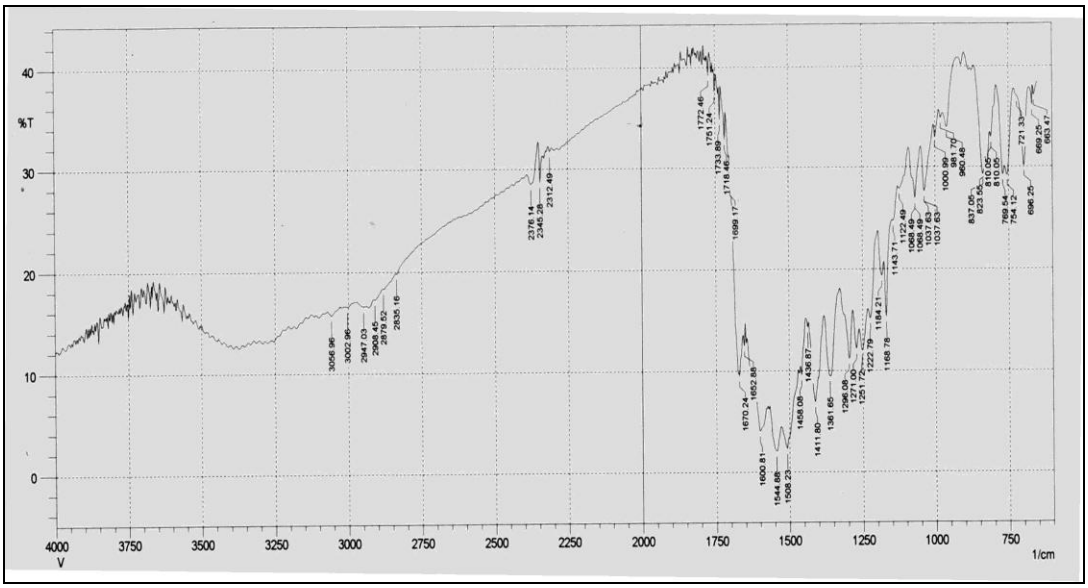


(Type-V) R = Aryl

The constitution of the products have been characterised by elemental analysis IR, ^{1}H NMR, Mass spectral study. The products were screened for their antimicrobial activity at a concentration of 50 µg.

The details have been cited in the Part-I, Section-I, Page no. 39-41.

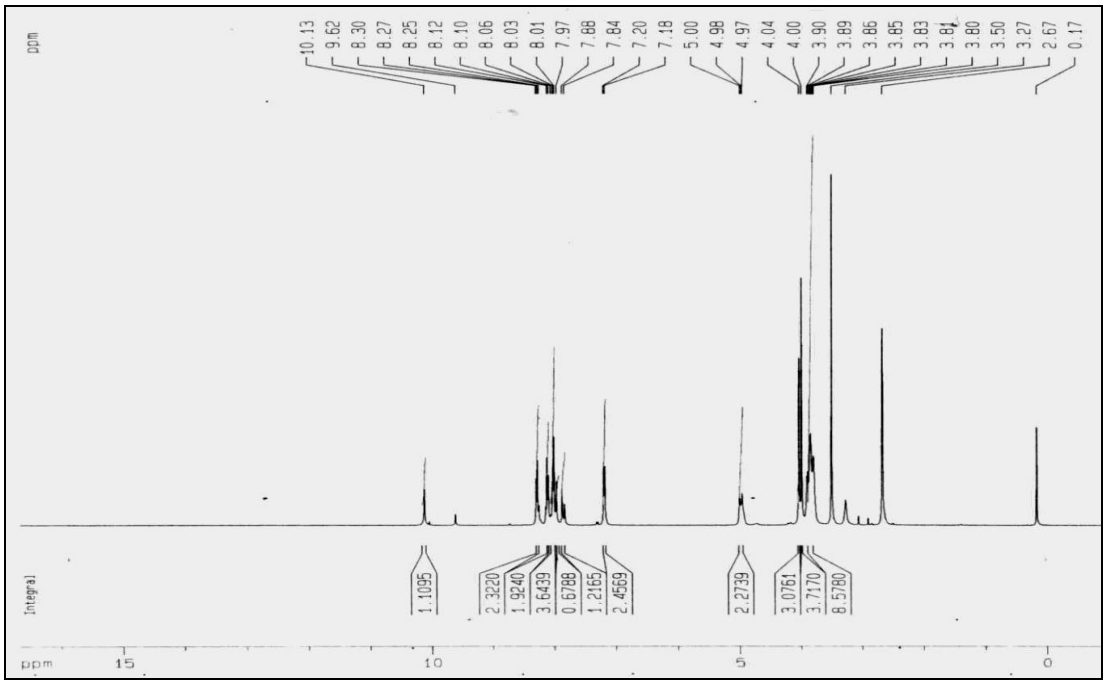
IR SPECTRAL STUDY OF 2-{4'-[5"-(4""-METHOXYPHENYL]-4"-5"-DIHYDRO-1"-PHENYL PYRAZOL-3"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLORO ETHYL) AMINO]-4- METHOXY-1,3, 5- TRIAZINE.



Instrument : SHIMADZU-IR-8400, Spectrophoto meter frequency range : 4000-400 cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	reported	
Alkane	C-H Str.(asym)	2808	2990-2850	422 – 423
	C-H Str.(sym)	2879	2880-2860	,,
	C-H def.(asym)	1436	1470-1435	
	C-H def.(sym)	1361	1390-1360	,,
Aromatic	C-H Str.	3056	3090-3030	
	C-H i.p. def	1168	1300-1100	,,
	C-H o.o.p. def	823	832-800	
	C=C Str.	1458	1600-1450	,,
S-triazine	C-N Str.	1037	1220-1020	,,
	C=N Str.	1600	1630-1590	
Amine	N-H Str.	3396	3500-3310	,,
	N-H Bending	1600	1650-1550	
Ether	C-O-C Str.(asym)	1251	1260-1220	,,
	C-O-C Str.(sym)	1068	1075-1020	
Halide	C-Cl Str.	769	800-600	,,
Pyrazoline	C-N Str.	1068	1705-1650	,,
	C=N Str.	1601	1650-1550	
	CH-CH_2 Str.	2345	2850-1790	,,

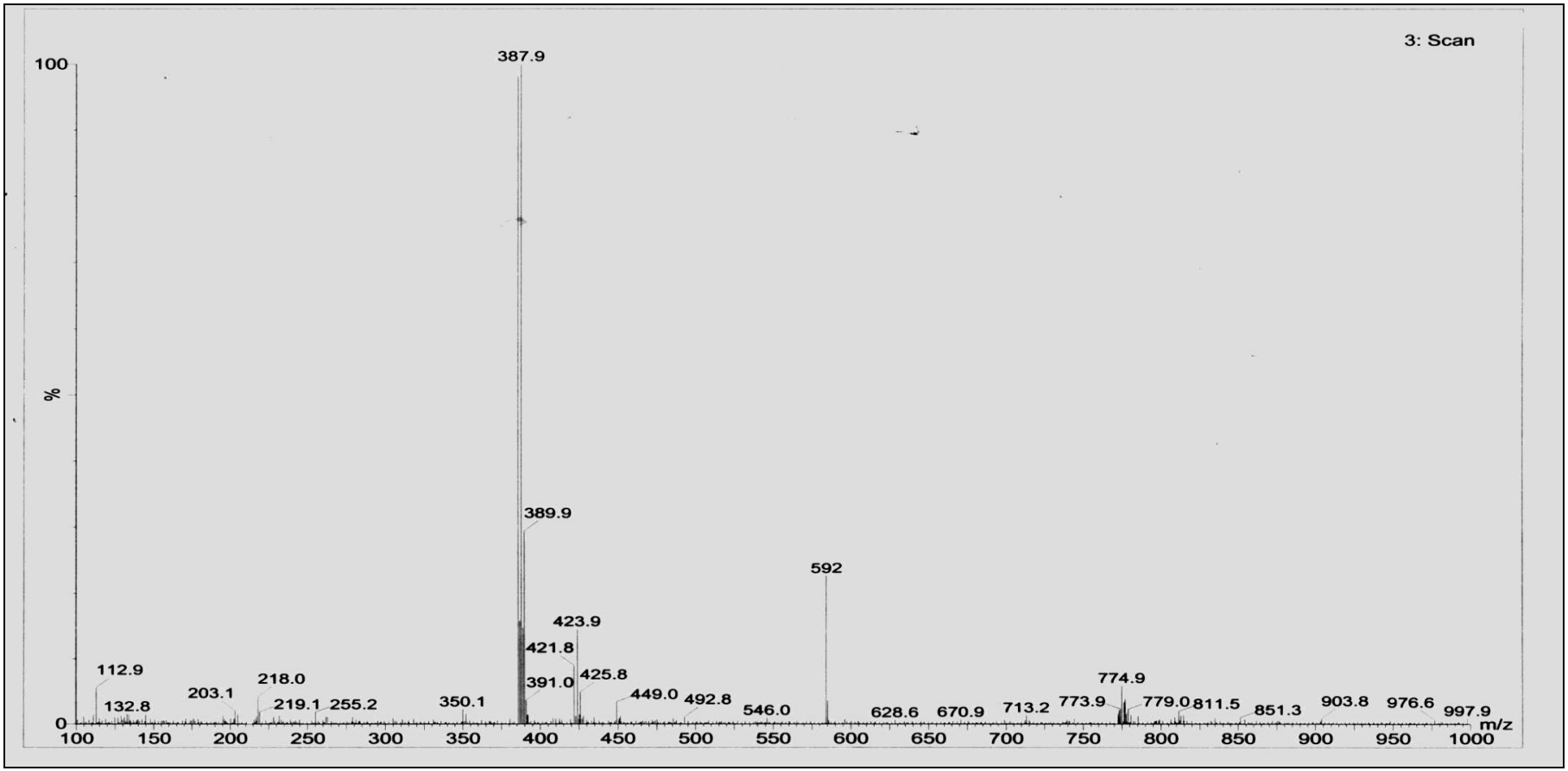
NMR SPECTRAL STUDY OF 2-{4'-[5"-(4""-METHOXYPHENYL]-4"-5"-DIHYDRO-1"-PHENYL PYRAZOL-3"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLORO ETHYL) AMINO]-4- METHOXY-1,3, 5- TRIAZINE.



Internal standard : TMS ; solvent : $CDCl_3$; Instrument : BRUKER spectrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.80-3.90	6 H	Singlet	Ar-OCH_3
2	7.18-7.88	4 H	D. Doublet	Ar-H_b
3	7.97-8.25	4 H	D. Doublet	Ar-H_c
4	4.02-4.04	4 H	Triplet	-CH_2-Cl
5	2.67-3.27	4 H	Triplet	-N-CH_2-
6	10.13	1 H	Singlet	Ar-NH_f
7	7.97-8.12	5 H	Multiplate	ArH_g
8	3.50	2 H	Singlet	-$CH_{2\,h}$

MASS SPECTRAL STUDY OF 2-{4'--[5"-(4""-METHOXYPHENYL]-4"-5"-DIHYDRO-1"-PHENYL PYRAZOL-3"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4- METHOXY-1,3, 5- TRIAZINE. (M.W. : 592)



Antimicrobial Activity :

Conclution :

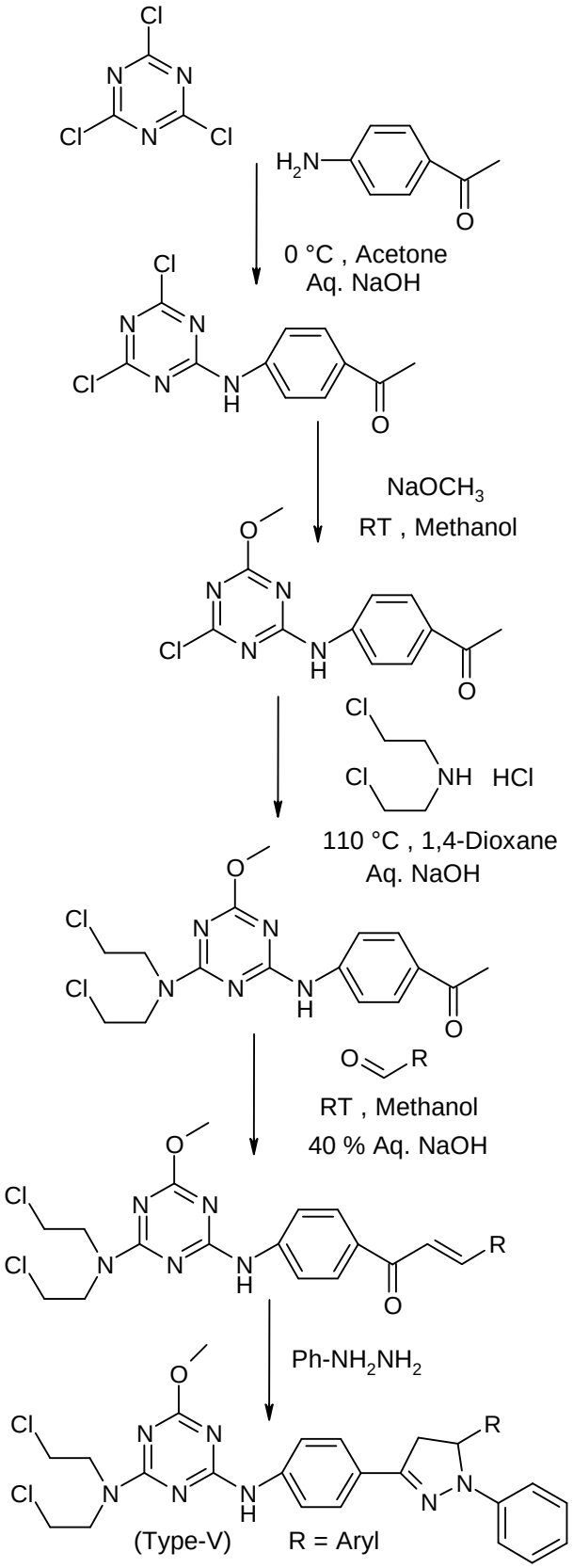
Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.				**Antifungal activity Zone of inhibition in m.m.**
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	4-OH C_6H_4(21)	3-OH C_6H_4(18)	4-OH C_6H_4(21)	3-OH C_6H_4(22)	C_6H_4(23)
	4-OCH_3 C_6H_4(20)	4-OH C_6H_4(19)	4-Br. C_6H_4(22)	4-OH C_6H_4(23)	4-OH C_6H_4(24)
	4-Br. C_6H_4(22)	4-OH, 3-OCH_3 C_6H_4(18)	3-NO_2 C_6H_4(20)	4-Br C_6H_4(24)	3-NO_2 C_6H_4(21)
	4-NO_2 C_6H_4(21)	4-Br C_6H_4(19)	4-NO_2 C_6H_4(22)	4-NO_2 C_6H_4(23)	4-NO_2 C_6H_4(22)
		4-NO_2 C_6H_4(20)		4-N,N $(CH_3)_2$ C_6H_4(21)	

Comparable activity with known standard drugs

Ampicilin 50 μg	23	18	17	27	-
Chloramphenicol ”	24	19	25	26	-
Norfloxacin ”	24	19	25	26	-
Greseofulvin ”	-	-	-	-	23

REACTION SCHEME



(Type-V) R = Aryl

EXPERIMENTAL

SYNTHESIS OF 2-{4'-[5"-ARYL]-4"-5"-DIHYDRO-1"-PHENYL PYRAZOL-3"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3, 5- TRIAZINE.

(A) **Synthesis of 2-(4'-Acetyl pheyl amino)-4, 6-dichloro-1,3,5-triazine.**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(B) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-chloro-4-methoxy-1,3,5-triazine.**

For synthesis Part-I, Section-I, Page no. 36-38.

(C) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-[Bis (2"-chloro ethyl) amino]-4-methoxy-1,3,5-triazine**

For synthesis see Part-I, Section-I, Page no. 36-38.

(D) **Synthesis of 2-{4'-[3"-(4""-Methoxy phenyl)-2"-propene-1"-one] phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-trizine**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(E) **Synthesis of 2-{4'-[5"-(4""-Methoxyphenyl)-4", 5"- dihydro-1"-phenyl pyrazole-3"-yl]-phenyl amino} -6- [Bis (2"'-chloro ethyl) amino]-4-methoxy-1,3,5- triazine.**

A mixture of 2-{4'-[3"-(4""-methoxy phenyl)-2"-propene-1"-one] phenyl amino}-6-[Bis (2"'-chloro ethyl) amino]-4- methoxy-1,3,5-triazine (5.02 gm, 0.01M) phenyl hydrazine hydrate (1.0 ml) and methanol (20 ml) was refluxed

for 12 hrs. The reaction mixture was poured into crushed ice, filtered, washed with water and crystallised from dioxane. Yield : 78%, M.P. : 183° C. (Found C : 60.79, H : 5.21, N : 16.54, $C_{30}H_{31}O_2N_7Cl_2$ required C : 60.81, H : 5.23; N : 16.55%)

Simillarly other phenylpyrazolines have been synthesised and their physical data are reocrded in Table No.9

(F) **Antimicrobial activity of 2-{4'[(5"-aryl)-4", 5"- dihydro-1" phenyl pyrazole - 3" - yl]-phenyl amino}-6-[Bis. (2"'-chloro ethyl) amino]-4-methoxy- 1,3,5- trizine.**

The antimicrobied testing was carried out as described in Part-I, Section-I, Page no. 39-41.

The zone of inhibition of the test solution are recorded in Table No. 10

TABLE NO : 9 PHYSICAL CONSTANTS OF 2-{4'-[(5"-ARYL)-4"-5"-DIHYDRO-1"-PHENYL PYRAZOL-3"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLORO ETHYL) AMINO]-4- METHOXY-1,3, 5- TRIAZINE.

Sr. No.	R	Molecular Formula	M.P. °C	Yield %	% of Nitrogen	
					Calcd	Found
1.	C_6H_5	$C_{29}H_{29}Cl_2N_7O$	218	78	17.43	17.41
2.	2-OH C_6H_4	$C_{29}H_{29}Cl_2N_7O_2$	249	81	16.95	16.92
3.	3-OH C_6H_4	$C_{29}H_{29}Cl_2N_7O_2$	258	76	16.95	16.91
4.	4-OH C_6H_4	$C_{29}H_{29}Cl_2N_7O_2$	197	83	16.95	19.93
5.	4-OCH_3 C_6H_4	$C_{30}H_{31}Cl_2N_7O_2$	183	78	16.55	16.54
6.	4-OH, 3-OCH_3 C_6H_3	$C_{30}H_{31}Cl_2N_7O_3$	205	79	16.11	16.09
7.	4-Br. C_6H_4	$C_{29}H_{28}BrCl_2N_7O$	210	84	15.29	15.23
8.	3-NO_2 C_6H_4	$C_{29}H_{28}Cl_2N_8O_3$	256	81	18.44	18.41
9.	4-NO_2 C_6H_4	$C_{29}H_{28}Cl_2N_8O_3$	211	78	18.44	18.42
10	4-N,N-$(CH_3)_2$ C_6H_4	$C_{31}H_{34}Cl_2N_8O$	278	85	18.50	18.48
11.	C_4H_3O (Furfuryl)	$C_{27}H_{27}Cl_2N_7O_2$	191	88	17.75	17.71

TABLE NO : 10 ANTIMICROBIAL ACTIVITY OF 2-{4'-[(5"-ARYL)-4"-5"-DIHYDRO-1"-PHENYL PYRAZOL-3"-YL]-PHENYL AMINO}-6-[BIS. (2"'-CHLORO ETHYL) AMINO]-4- METHOXY-1,3, 5- TRIAZINE.

Sr. No.	***R***	**Antibacterial activity Zone of inhibition in mm.**				**Antifungal activity Zone of inhibition in mm.**
		B. mega.	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5	18	14	16	17	19
2	2-OH C_6H_4	17	12	18	19	23
3	3-OH C_6H_4	19	18	19	22	21
4	4-OH C_6H_4	21	19	21	23	24
5	4-OCH_3 C_6H_4	20	16	20	21	19
6	4-OH, 3-OCH_3 C_6H_3	16	18	19	20	17
7	4-Br. C_6H_4	22	19	22	24	19
8	3-NO_2 C_6H_4	18	17	20	21	21
9	4-NO_2 C_6H_4	21	20	22	23	22
10	4-N,N-$(CH_3)_2$ C_6H_4	17	16	18	21	19
11	C_4H_3O (Furfuryl)	19	15	18	20	17

PART - IV

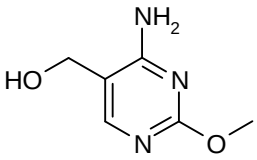
STUDIES ON PYRIMIDINES

STUDIES ON PYRIMIDINES

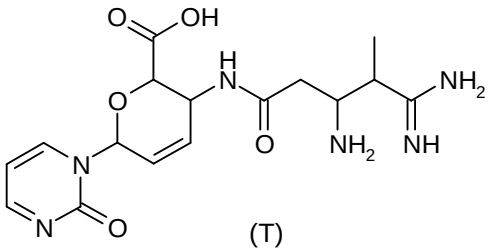
INTRODUCTION

Pyrimidine derivatives occur in natural products[179] like nucleic acid and vitamin-B have remarkable pharmaceutical importance because of their biological[180-183] several analogs of nucleic acids have been used as compound that interfere with the synthesis and functioning of uncleic acids, and example is fluorouracil which has been used in cancer treatment. Pyrimidines are among those molecules that make life possible as being same of the building blocker of DNA and RNA.

Some pyrimidines of physiologically as well as pharmacologically importance are as under : e.g. cytosine, beclmeihrin(S), blasticidin(T).



(S)



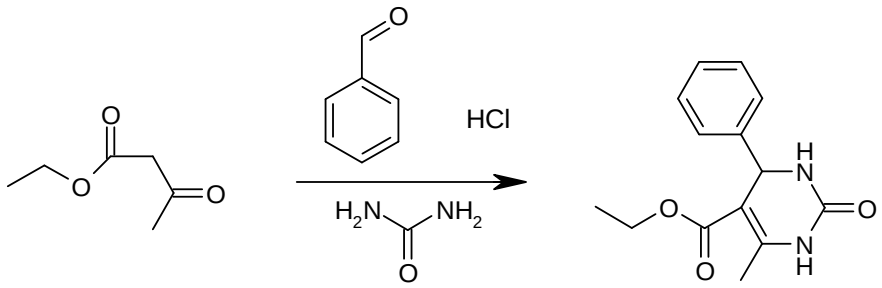
(T)

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

SYNTHETIC ASPECT :

Different methods for the synthesis of pyrimidine have been cited in the literature.[184]

1. F. Bigi and co-worker[185] have synthesised as shown below under solvent free condition.



REACTION MECHANISM :

The reaction of α,β-unsaturated system with urea to the formation of 4-oxo-pyrimidine by 1, 2 and 1, 4 michal addition.

THERAPEUTIC IMPORTANCE

Pyrimidine derivatives have proven to be of great importance in exhibiting and enhancing the biological activities such as.

(a) Antitumor[186]

(b) Carcinostatic[187]

(c) antiinflammatory and anticonvulsant[188-189]

(d) Antimalarial[190]

(e) Antithyroid[191]

(f) Anthelmintic[192]

(g) Anti-HIV[193-194]

(h) Antilishmenial[195]

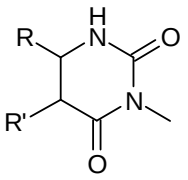
(i) Antiviral[196]

(j) Antimicrobial[197]

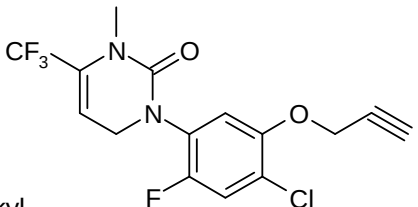
(k) Herbicidal[198-204]

(l) Antagonists[205-209]

Moreover, L. V. Azarayan et al.[210] have synthesised pyrimidine diones as antitumor agent. V. P. Krivongov and co-worker[211] have synthesised pyrimidinone derivatives possessing immunotropic and antiinflammatory activity. M. Refai and co-worker[212] have prepared some new pyrimidine derivatives showed moderate activity against the growth of *Bacillus substilis, staphylococus aureus* and *Aspergillus niger.* A. Kofies et. al.[213] have seggested that pyrimidinone (U)(V) as herbicidal and plant growth regulators.



(U)



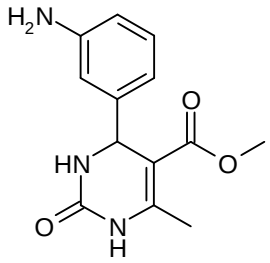
R = alkyl
R' = H, halogen

(V)

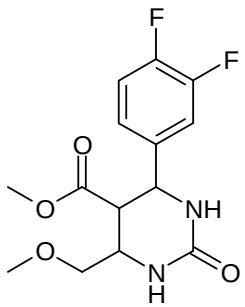
K. Mogilaiash[214] have prepared spiro pyrimidinones as antibacterial. M. wilhelm[215] have synthesised pyrimidinones as herbicidal agents.

C. D. Timothy and co-worker[216] have suggested imidazolyl pyrimidinones as antiviral T. Nagamatsu et. al.[217] have prepared some new triazolo [3,4-c] pyrimidine as xanthin oxidase inhibitors. A. Roland et. al.[218] have prepared oxazolyl uracil as herbicidal and insecticidal. M. M. Yari and co-worker[219] have investigated the pyrimidinone derivatives which possess caclcium antagonist activity.

M. A. Bruce and co-worker[220] prepared the dihydro pyrimidinones as NPY antagonist.

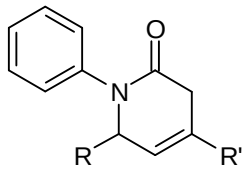


D. R. Sidler[221] have reported pyrimidinone derivatives, useful as an α-adrenergic receptor antagonist.



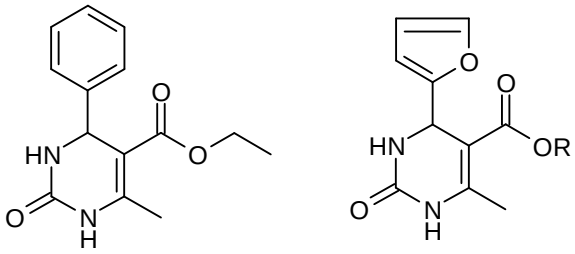
Mona Mahram and co-worker[222] have synthesied pyrimidine derivatives as potent antimicrobial and antitumor agents.

K. A. Gupta and co-worker[223] have prepared 2,6-disubstituted pyrimidinones as CNS agent.

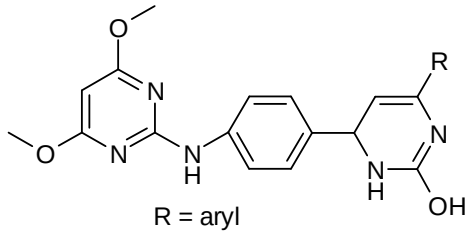


R = alkyl, aryl
R' = alkyl, aryl

Pyrimidinone derivatives[224-225] have found to be calcium channel blocker. M. M. Barbuliene et. al.[226] have synthesised pyrimidione as antiinflammatary agent.



Recently. Amjad Ali et. al.[227] have synthesised new fused pyrimidinones as antimicrobial agents. Abd El-Galil et. al.[228] have synthesised pyrimidine as androgenic, anabolic and antiinflammatory agents. Martin Bolli et. al.[229] have synthesised pyrimidines as endothelin receptor antagonists. G. Z. Hang et. al.[230] have synthesised and screened for their leukocyte functions inhibitor activity. Yam amoto et al.[231] have synthesised pyrimidines and tested their hyderproliferative disorder activity. V. N. Patolia et al.[232] have been synthesised 2-{4'[6"(aryl)-2-"hydroxy,3",4"dihydro pyrimidine-4"-yl]-phenyl amino}-4,6-dimethoxy pyrimidines and screened their antimicrobial acivity.



R = aryl

The synthesis of pyrimidines derivatives described as under.

SECTION : I SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(6"-ARYL-2"-MERCAPTO,3"-4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYLAMNIO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

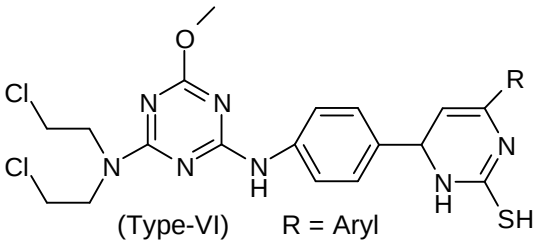
SECTION : II SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4-[(6"-ARYL-2"-HYDROXY-3",4"-DIHYDRO)-PYRIMIDNE-4"-YL]-PHENYLAMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

SECTION: III SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[6"-ARYL-2"-AMINO-3", 4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYLAMINO}-6-[BIS(2"'-CHLOROETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.

SECTION-I

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(6"-ARYL-2"-MERCAPTO-3",4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Pyrimidine nucleus possess remarkable pharmaceutical and biological activites. This valid observation lead us to synthesised 2-{4'-[(6"-aryl-2"-mercapto-3", 4"-dihydro)-pyrimidine-4"-yl]-phenyl amino}-6-[Bis (2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine of Type-(VI) have been condensation by the reaction of chalcones of Type-(I) with thiourea in the presence of alcoholic potassium hydroxide.

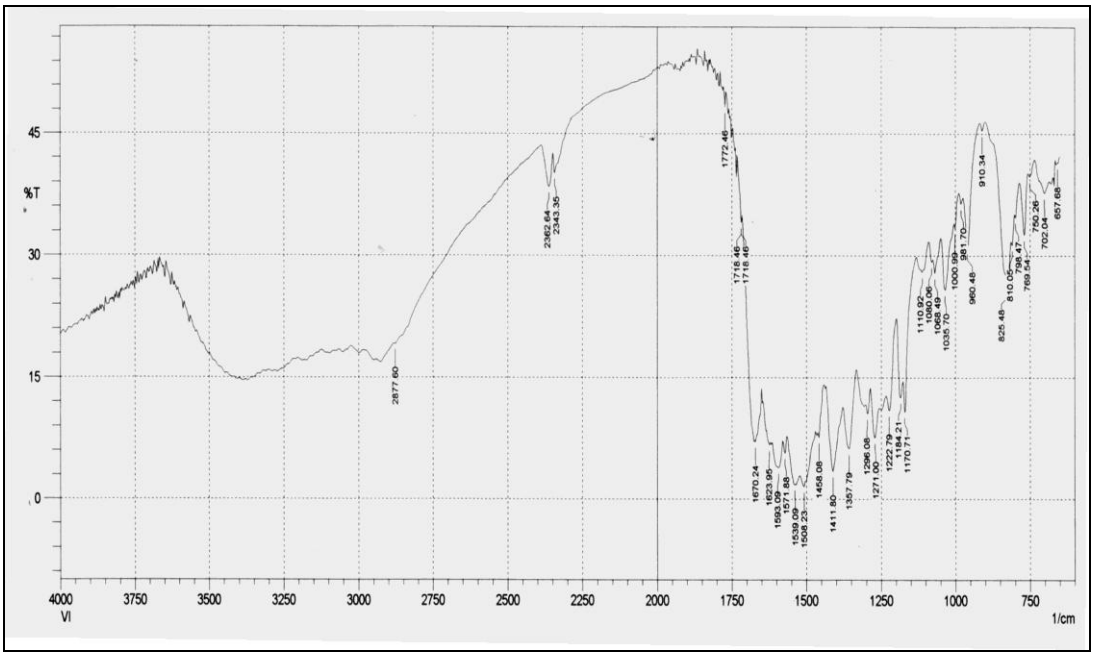


(Type-VI) R = Aryl

The constitution of the products have been characterised by elemental analyses IR, ^{1}H NMR, Mass spectral study. The products were screened for antimicrobial activity at a concentration of 50 µg.

The details have been cited in the part : I, section : I, page no. 39-41.

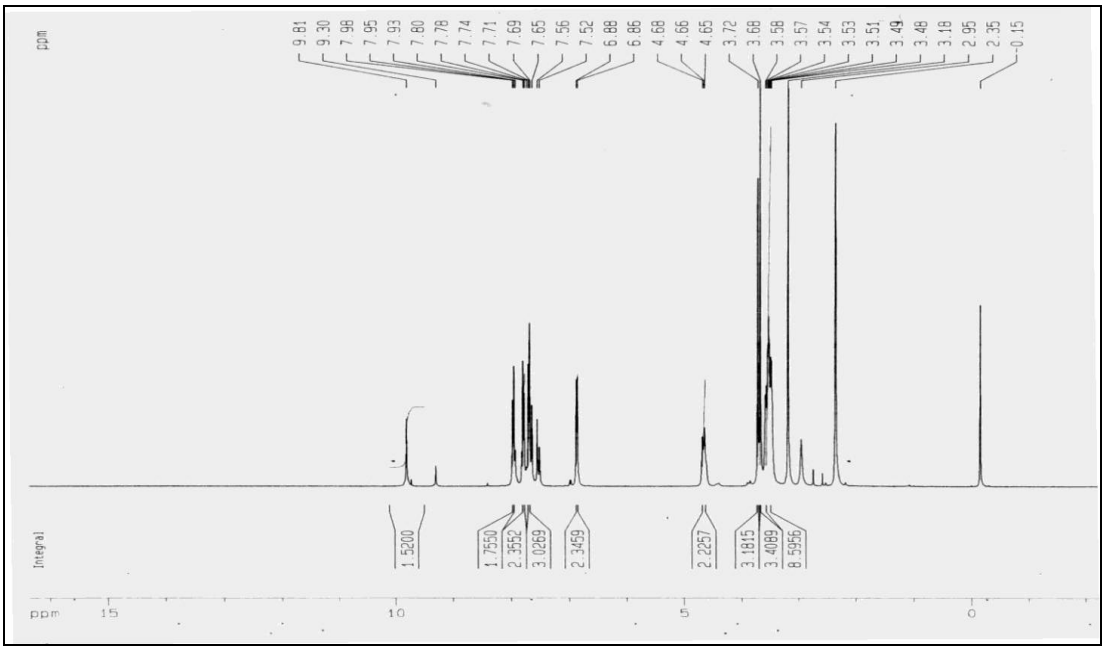
IR SPECTRAL STUDY OF 2-{4'-[6"-(4""-METHOXYPHENYL-2"-MERCAPTO-3",4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Instrument : SHIMADZU-FT-IR-8400, Spectrophoto meter frequency range : 4000-400 cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	reported	
Alkane	C-H Str.(asym)	2905	2990-2850	422 – 423
	C-H Str.(sym)	2877	2880-2860	,,
	C-H def.(asym)	1458	1470-1435	
	C-H def.(sym)	1357	1390-1360	,,
Aromatic	C-H Str.	3031	3090-3030	
	C-H i.p. def	1170	1300-1100	,,
	C-H o.o.p. def	810	832-800	
	C=C Str.	1508	1600-1450	,,
S-triazine	C-N Str.	1035	1220-1020	,,
	C=N Str.	1539	1630-1590	
Amine	N-H Str.	3350	3500-3310	,,
	N-H Bending	1539	1650-1550	
Ether	C-O-C Str.(asym)	1222	1260-1220	,,
	C-O-C Str.(sym)	1068	1075-1020	
Halide	C-Cl Str.	769	800-600	,,
Thio Pyrimidine	C=S Str.	1571	1590-1550	

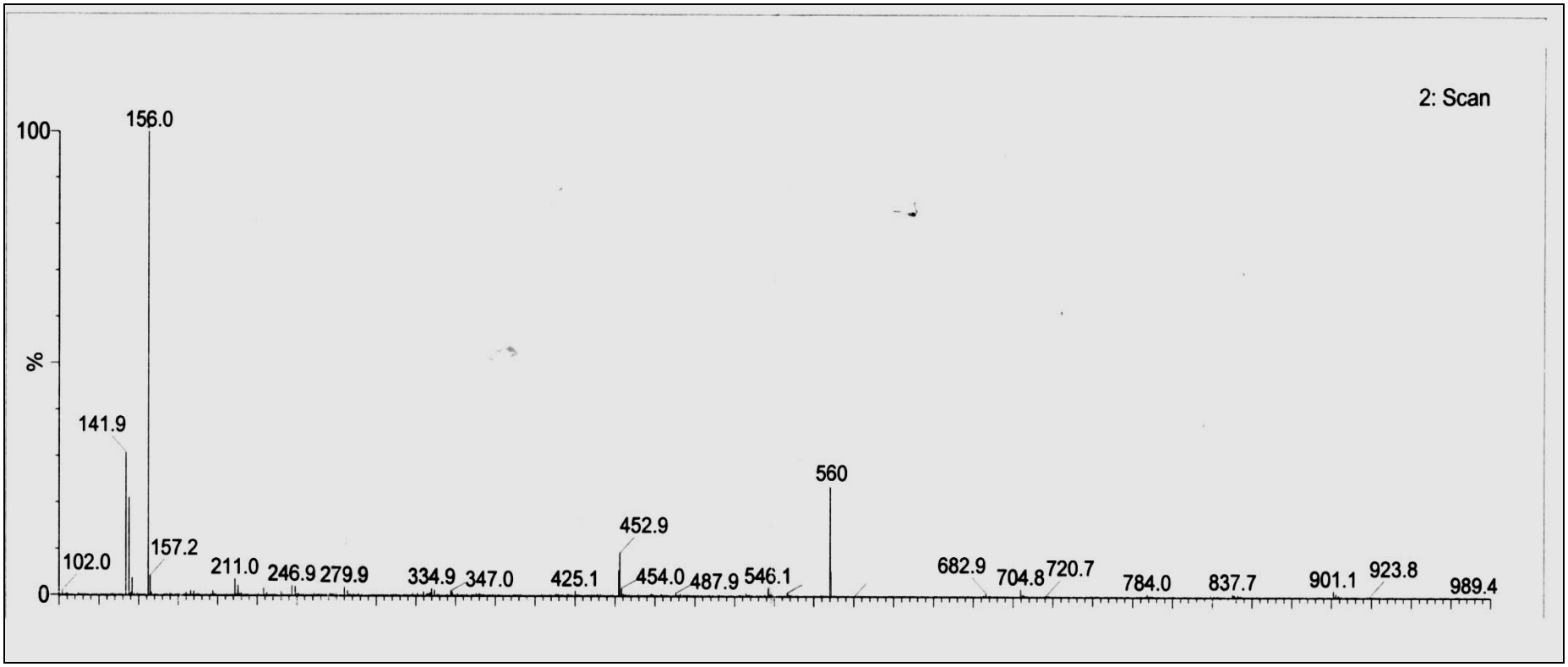
NMR SPECTRAL STUDY OF 2-{4'-[6"-(4""-METHOXYPHENYL-2"-MERCAPTO-3",4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Internal standard : TMS; solvent : $CDCl_3$; Instrument : BRUKER spectrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.54-3.72	6 H	Singlet	Ar-OCH_3
2	7.52-7.78	4 H	D. Doublet	Ar-H_b
3	7.80-7.95	4 H	D. Doublet	Ar-H_c
4	4.65-4.68	4 H	Triplet	-CH_2-Cl
5	2.95-3.18	4 H	Triplet	-N-CH_2-
6	9.81	2 H	Singlet	Ar-NH_f
7	2.35	1 H	Singlet	$ArSH_g$
8	7.71-7.74	1 H	Singlet	-Ar_h

MASS SPECTRAL STUDY OF 2-{4'-[6"- [(4""-METHOXYPHENYL-2"-MERCAPTO-3"-4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMNIO}-6-[BIS (2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE. (M.W. : 560)



Antimicrobial Activity :

Conclution :

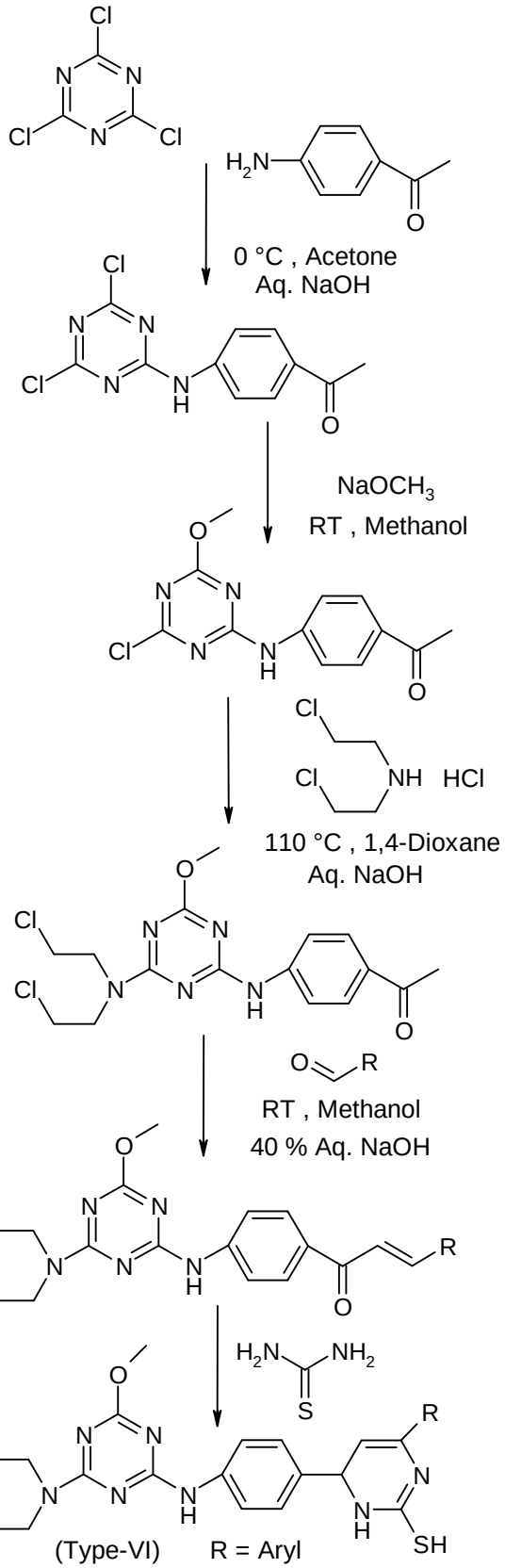
Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.				**Antifungal activity Zone of inhibition in m.m.**
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	3-OH C_6H_4 (23)	3-OH C_6H_4 (18)	4-OH C_6H_4 (24)	C_6H_5 (23)	3-OH C_6H_4 (23)
	4-OH C_6H_4 (23)	4-OH C_6H_4 (19)	4-OH, 3-OCH_3	3-OH C_6H_4 (24)	4-Br C_6H_4 (21)
	4-Br. C_6H_4 (22)	4-Br. C_6H_4 (20)	C_6H_3 (22)	4-OH C_6H_4 (24)	4-NO_2 C_6H_4 (22)
	3-NO_2 C_6H_4 (24)	4-NO_2 C_6H_4 (19)	4-Br C_6H_4 (23)	4-Br. C_6H_4 (23)	
		C_4H_3O (20)	4-NO_2 C_6H_4 (21)		

Comparable activity with known standard drugs

Ampicilin 50 μg	23	18	17	27	-
Chloramphenicol "	24	19	25	26	-
Norfloxacin "	24	19	25	26	-
Greseofulvin "	-	-	-	-	23

REACTION SCHEME



(Type-VI) R = Aryl

EXPERIMENTAL

SYNTHESIS OF 2-{4'-[(6"-ARYL-2"-MERCAPTO-3",4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

(A) **Synthesis of 2-(4'-Acetyl phenyl amino)-4, 6-dichloro - 1, 3, 5-triazine.**

For synthesis Part-I, Section-I, Page no. 36-38.

(B) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-chloro-4-methoxy-1,3,5-triazine**

For syntesis Part-I, Section-I, Page no. 36-38.

(C) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-[Bis (2"-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis Part-I, Section-I, Pagen no. 36-38.

(D) **Synthesis of 2-{4'-[3"-(4""-methoxy phenyl)-2"-propene-1"-one] phenyl amino}-6-[Bis (2"'-chloro ethyl) amino]-4- methoxy-1,3,5-triazine.**

For synthesis Part-I, Section-I Page no. 36-38.

(E) **Synthesis of 2-{4'-[6"-(4""-methoxy phenyl)-2"-mercapto- 3", 4"-dihydro-Pyrimidine-4"-yl]-phenyl amino}-6-[Bis (2"'-chloro ethyl) amino]-4-methoxy - 1, 3, 5, triazine.**

A mixture of 2-{4'-[3"-(4""-methoxy phenyl)-2"- propene-1"-one] phenyl amino}-6-[Bis (2"'-chloro ethyl) amino} -4- methoxy-1,3,5-triazine (5.02 gm,

0.01 M); and thiourea (0.66 gm, 0.01 M) was refluxed at 90° C for 13 hrs. in the presence of basic medium like alcoholic KOH and methanol. The reaction mixture was poured into crushed ice, filtered and dried. The product was isolated and crystallised from dioxane yield : 70%. m.p. : 171° C. (Found C : 53.54; H : 4.81; N : 17.45; $C_{25}H_{27}O_2N_7Cl_2S$ required C: 55.57, H : 4.82, N : 17.49%)

Simillarely other compounds were prepared and their physical data are recorded in Table No. 11

(F) **Antimicrobial activity of 2-{4'-[(6"-aryl-2"-mercapto-3", 4"-dihydro)-pyrimidine-4"-yl]-phenyl amino}-6-[Bis. (2"'-chloro ethyl) amino]-4-methoxy-1,3,5- triazine.**

The antimicrobial testing was carried out as described in Part-I, Section-I, Page no. 39-41.

The zone of inhibition of the test solution are recorded in Table no. 12.

TABLE NO : 11 : PHYSICAL CONSTANTS OF 2-{4'-[(6"-ARYL-2"-MERCAPTO, 3"-4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Molecular Formula	M.P. .c	Yield %	% of Nitrogen	
					Calcd	Found
1.	C_6H_5	$C_{24}H_{25}Cl_2N_7OS$	218	77	18.48	18.41
2.	2-OH C_6H_4	$C_{24}H_{25}Cl_2N_7O_2S$	180	81	16.09	16.07
3.	3-OH C_6H_4	$C_{24}H_{25}Cl_2N_7O_2S$	138	83	16.09	16.05
4.	4-OH C_6H_4	$C_{24}H_{25}Cl_2N_7O_2S$	265	78	16.09	16.01
5.	4-OCH_3 C_6H_4	$C_{25}H_{27}Cl_2N_7O_2S$	171	70	17.49	17.45
6.	4-OH, 3-OCH_3 C_6H_3	$C_{25}H_{27}Cl_2N_7O_3S$	228	73	17.01	17.00
7.	4-Br C_6H_4	$C_{24}H_{24}BrCl_2N_7OS$	272	82	16.09	16.02
8.	3-NO_2 C_6H_4	$C_{24}H_{24}Cl_2N_8O_3S$	236	85	19.47	19.42
9.	4-NO_2 C_6H_4	$C_{24}H_{24}Cl_2N_8O_3S$	157	87	19.47	19.44
10.	4-N,N$(CH_3)_2$ C_6H_4	$C_{26}H_{23}Cl_2N_8OS$	183	79	19.54	19.50
11.	C_4H_3O (Furfuryl)	$C_{22}H_{23}Cl_2N_7O_2S$	226	76	18.48	18.43

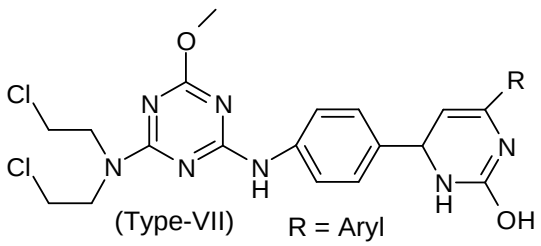
TABLE NO : 12 ANTIMICROBIAL ACTIVITY OF 2-{4'-[6"-(ARYL-2"-MERCAPTO-3"4"-DIHYDRO)PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLORO ETHYL) AMINO]-4- METHOXY-1,3, 5- TRIAZINE.

Sr. No.		**Antibacterial activity Zone of inhibition in mm.**				**Antifungal activity Zone of inhibition in mm.**
	R	***B. mega.***	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5	21	14	18	23	17
2	2-OH C_6H_4	20	13	19	22	19
3	3-OH C_6H_4	23	18	20	24	23
4	4-OH C_6H_4	23	19	24	24	20
5	4-OCH_3 C_6H_4	19	16	17	20	18
6	4-OH, 3-OCH_3 C_6H_3	17	15	22	19	16
7	4-Br C_6H_4	22	20	23	23	21
8	3-NO_2 C_6H_4	24	18	18	19	19
9	4-NO_2 C_6H_4	21	19	21	21	22
10	4-N, $N(CH_3)_2$ C_6H_4	20	18	20	19	18
11	C_4H_3O (Furfuryl)	19	20	18	16	17

SECTION : II

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(6"-ARYL)2"-HYDROXY-3",4"-DIHYDRO-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Pyrimidine derviatives showed wide range of application in the field of pharmaceutical, it was considered worth while to synthesis compounds bearing S-triazine, Bis (2-chloro ethyl) amine nucleus linked to pyrimidine nucleus. 2-{4'-[(6"-aryl-2"-hydroxy-3", 4"-dihydro)-pyrimidine-4"-yl]-phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy -1,3,5-triazine of type(VII) have been synthesised by the condensation of 2-{4'-[(3"-aryl)-2"- propene-1"-one]-phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine of Type-(I) with urea in presence of catalytic amount of conc. HCl

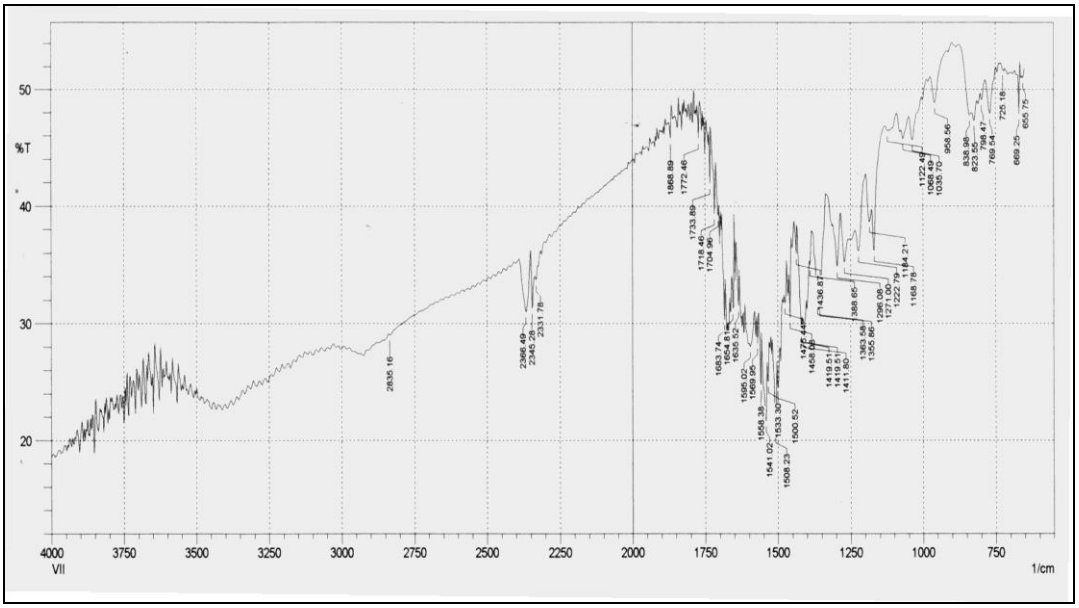


(Type-VII) R = Aryl

The constituion of the products have been characterised by elemental analyses IR, ^{1}H NMR, Mass spectral study. The products were screened for antimicrobial activity at a concentration of 50 µg.

The details have been cited in the part : I, Section I, Page NO. 39-41.

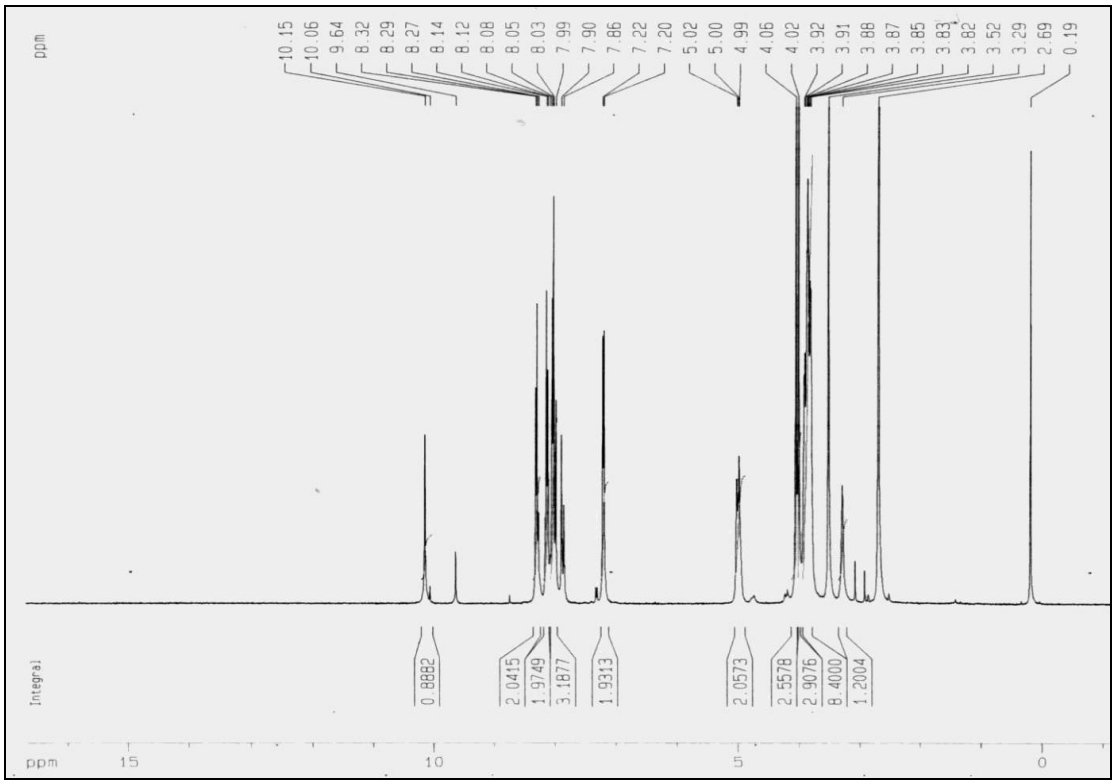
IR SPECTRAL STUDY OF 2-{4'-[6"-(4'''-METHOXYPHENYL)-2"-HYDROXY-3",4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Instrument : SHIMADZU-FT-IR-8400, Spectrophotometer; frequency range : 4000-400 cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	Reported	
Alkane	C-H Str.(asym)	2835	2990-2850	422 – 423
	C-H Str.(sym)	2880	2880-2860	,,
	C-H def.(asym)	1458	1470-1435	
	C-H def.(sym)	1363	1390-1360	,,
Aromatic	C-H Str.	3036	3090-3030	
	C-H i.p. def	1168	1300-1100	,,
	C-H o.o.p. def	823	832-800	
	C=C Str.	1458	1600-1450	,,
S-triazine	C-N Str.	1122	1220-1020	,,
	C=N Str.	1595	1630-1590	
Amine	N-H Str.	3368	3500-3310	,,
	N-H Bending	1635	1650-1550	
Ether	C-O-C Str.(asym)	1222	1260-1220	,,
	C-O-C Str.(sym)	1068	1075-1020	
Halide	C-Cl Str.	769	800-600	,,
Oxy Pyrimidine	C=O Str.	1654	1650-1550	

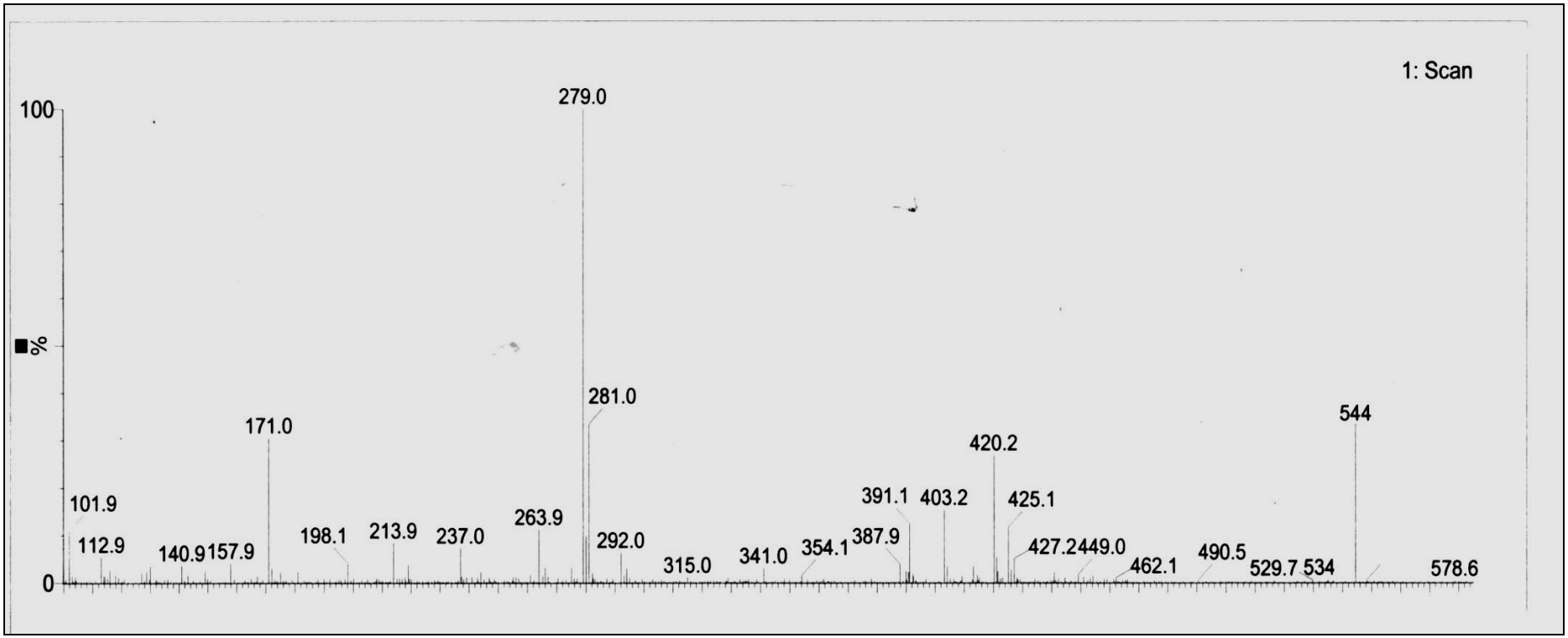
NMR SPECTRAL STUDY OF 2-{4'-[6"-(4'''-METHOXYPHENYL)-2"-HYDROXY-3",4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE



Internal standard : TMS; solvent : DMSO ; Instrument : DPX-200 spectrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.82-3.92	6 H	Singlet	Ar-OCH_3
2	7.22-7.99	4 H	D Doublet	Ar-H_b
3	8.03-8.32	4 H	D Doublet	Ar-H_c
4	4.02-4.06	4 H	Triplet	-CH_2-Cl
5	2.69	4 H	Triplet	-N-CH_2-
6	10.06-10.15	2 H	Singlet	Ar-NH_f
7	9.64	1 H	Singlet	Ar-OH_g
8	7.99	1 H	Singlet	-Ar $_h$

MASS SPECTRAL STUDY OF 2-{4'-[6"-(4'''-METHOXYPHENYL)-2"-HYDROXY-3",4"-DIHYDRO)-PYRIMIDNE-4"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE. (M.W. : 544)



Antimicrobial Activity :

Conclution :

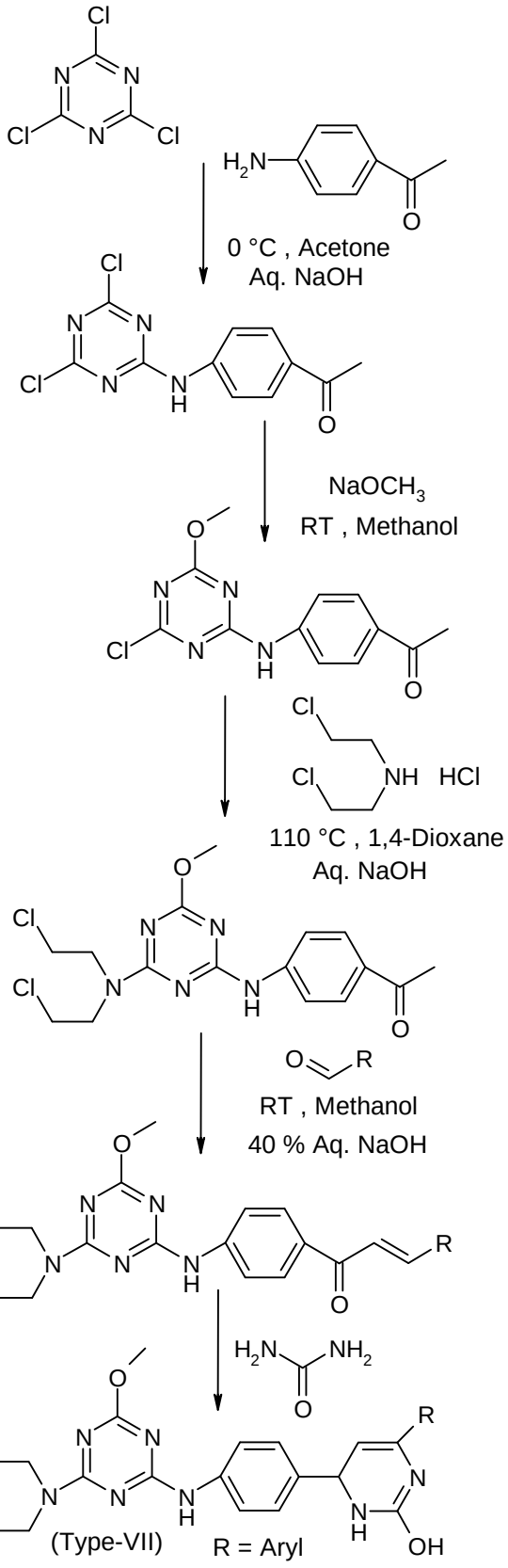
Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.				**Antifungal activity Zone of inhibition in m.m.**
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	2-OH C_6H_4(23)	3-OH C_6H_4(18)	C_6H_5(18)	3-OH C_6H_4(23)	2-OH C_6H_4(20)
	4-OH C_6H_4(24)	4-OH C_6H_4(19)	3-OH C_6H_4(19)	4-OH C_6H_4(23)	4-OH C_6H_4(22)
	4-Br C_6H_4(22)	4-OCH_3 C_6H_4(18)	4-OH C_6H_4(22)	4-Br C_6H_4(22)	3-NO_2 C_6H_4(21)
	4-NO_2 C_6H_4(23)	4-NO_2 C_6H_4(19)	3-NO_2 C_6H_4(20)	4-NO_2 C_6H_4(24)	
		4-N,N$(CH_3)_2$ C_6H_4(20)			

Comparable activity with known standard drugs

Ampicilin 50 µg	23	18	17	27	-
Chloramphenicol "	24	19	25	26	-
Norfloxacin "	24	19	25	26	-
Greseofulvin "	-	-	-	-	23

REACTION SCHEME



EXPRIMENTAL

SYNTHESIS OF 2-{4'-[(6"-ARYL-2"-HYDROXY-3",4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE

(A) **Synthesis of 2-(4'-Acetyl phenyl amino)-4, 6-dichloro-1,3,5-triazine.**

For synthesis see Part-I, Section-I, Page no. 36-38.

(B) **Synthesis of 2-(4'-Acetyl phenyl amino)-6- chloro-4-methoxy-1,3,5-triazine.**

For synthesis see Part-I, Section-I, Page no. 36-38.

(C) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-[Bis. (2"chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For syntheis see Part-I, Section-I, Page no. 36-38.

(D) **Syntheis of 2-{4'-[3" -(4"'-Methoxy phenyl)-2"-propene-1"-one]phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-riazine.**

For synthesis see Part-I, Section-I, Page no. 36-38.

(E) **Synthesis of 2-{4'-[6"-(4""-Methoxy phenyl)-2"-hydroxy-3", 4"-dihydro)-pyrimidine-4"-yl]-phenyl amino}-6-[Bis.(2"'-chloroethyl) amino]-4-methoxy-1,3,5- triazine.**

A mixture of 2-{4'-[3"-(4"'-methoxy phenyl)-2"-Propene-1"-one] phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine (5.02 gm, 0.01 M) and urea (0.60 g, 0.01 M) was refluxed at 90º C. for 12 hrs. in presence of acid catalyst like HCl in methanol the reaction mixture was poured into crushed ice, filtered and dried the product was isolated, crystallised from dioxane. Yield : 78%. M.P. 110º C. (Found : C : 55.11; H : 4.95; N : 17.99; $C_{25}H_{27}O_3N_7Cl_2$ required C : 55.14; H : 4.96; N : 18.01%)

Simillarly other pyrimidine derivatives have been synthesised and their physical data are recorded in Table no. 13.

(F) **Antimicrobial activity of 2-{4'[(6"-Aryl-2"-hydroxy, 3", 4"-dihydro)-Pyrimidine - 4"-yl] phenyl amino}-6-[Bis.(2"'-chloro ethyl) amino]-4-methoxy-1,3,5 triazine.**

The antimicrobial testing was carried out as described in Part-I, Section-I, Page no. 39-41.

The zone of inhibition of the test solutions are recorded in Table no. 14.

TABLE NO : 13 : PHYSICAL CONSTANTS OF 2-{4'-[(6"-ARYL-2"-HYDROXY-3",4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE

Sr. No.	R	Molecular Formula	M.P. .c	Yield %	% of Nitrogen	
					Calcd	Found
1.	C_6H_5	$C_{24}H_{25}Cl_2N_7O_2$	180	81	19.06	19.03
2.	2-OH C_6H_4	$C_{24}H_{25}Cl_2N_7O_3$	228	79	18.48	18.41
3.	3-OH C_6H_4	$C_{24}H_{25}Cl_2N_7O_3$	262	83	18.48	18.43
4.	4-OH C_6H_4	$C_{24}H_{25}Cl_2N_7O_3$	280	85	18.48	18.47
5.	4-OCH_3 C_6H_4	$C_{25}H_{27}Cl_2N_7O_3$	110	78	18.01	17.99
6.	4-OH, 3-OCH_3 C_6H_4	$C_{25}H_{27}Cl_2N_7O_4$	192	76	17.49	17.43
7.	4-Br. C_6H_4	$C_{24}H_{24}BrCl_2N_7O_2$	224	79	16.53	16.51
8.	3-NO_2 C_6H_4	$C_{24}H_{24}Cl_2N_8O_4$	265	81	20.03	20.01
9.	4-NO_2 C_6H_4	$C_{24}H_{24}Cl_2N_8O_4$	249	84	20.03	20.02
10	4-N,N$(CH_3)_2$ C_6H_4	$C_{26}H_{30}Cl_2N_8O_2$	213	79	20.10	20.08
11.	C_4H_3O (Furfuryl)	$C_{22}H_{23}Cl_2N_7O_3$	211	83	19.44	19.41

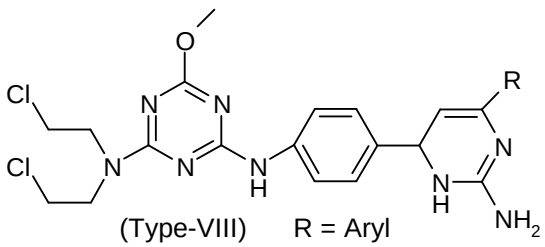
TABLE NO : 14 : ANTIMICROBIAL ACTIVITY OF 2-{4'-[(6"-ARYL-2"-HYDROXY-3",4"-DIHYDRO)-PYRIMIDNE-4"-YL]-PHENYL AMINO}-6-[BIS (2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE

Sr. No.		**Antibacterial activity Zone of inhibition in mm.**				**Antifungal activity Zone of inhibition in mm.**
	R	***B. mega.***	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5	20	12	18	15	19
2	2-OH C_6H_4	23	14	17	19	20
3	3-OH C_6H_4	21	18	19	23	19
4	4-OH C_6H_4	24	19	22	23	22
5	4-OCH_3 C_6H_4	19	18	16	20	18
6	4-OH, 3-OCH_3 C_6H_4	17	16	15	18	17
7	4-Br. C_6H_4	22	15	17	22	19
8	3-NO_2 C_6H_4	18	17	20	21	21
9	4-NO_2 C_6H_4	23	19	16	24	20
10	4-$N_1N(CH_3)_2$ C_6H_4	19	20	17	16	16
11	C_4H_3O (Furfuryl)	17	16	14	21	18

SECTION : III

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[6"-ARYL-2"-AMINO-3",4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYLAMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Looking to the interesting pharmacological and agricultral activity of pyrimidine ring system it was considered worth while to synthesis compound being Bis (2-chloro ethyl) amine and S-triazine nucleus linked to the pyrimidime nucleus 2-{4'-[6"-Aryl-2"-amino-3", 4"-dihydro)-pyrimidine-4"-yl] phenyl amino]-6-[Bis(2"'-chloroethyl) amino]-4- methoxy-1,3,5-triazine of Type (VIII) have been synthesised by the condensation of 2-{4'-[(3"-aryl)--2"-propene - 1" - one]- phenyl amino}-6-[Bis (2"'-chloroethyl) amino-4-methoxy-1,3,5-triazine of Type (I) with guanidine hydrochloride in the presence of alcoholic potassium hydroxide.

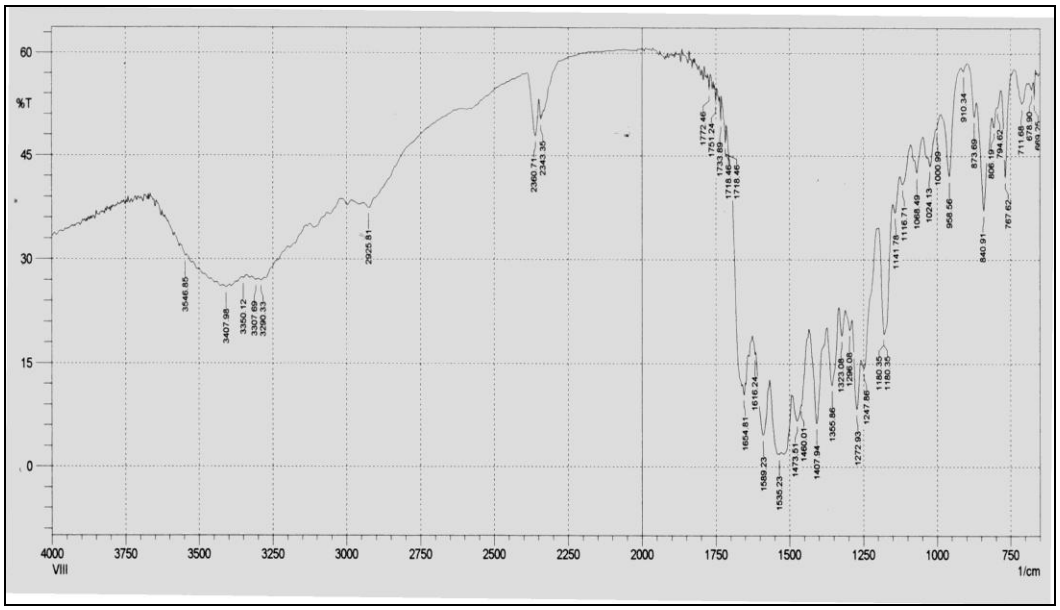


(Type-VIII) R = Aryl

The constitution of the products have been characterised by elemental analysis IR, ^{1}H NMR, Mass spectral study. The products were screened for antimicrobial acivity at a concentration of 50 µg.

The details have been cited in the Part : I, Section : I, Page No. 39-41.

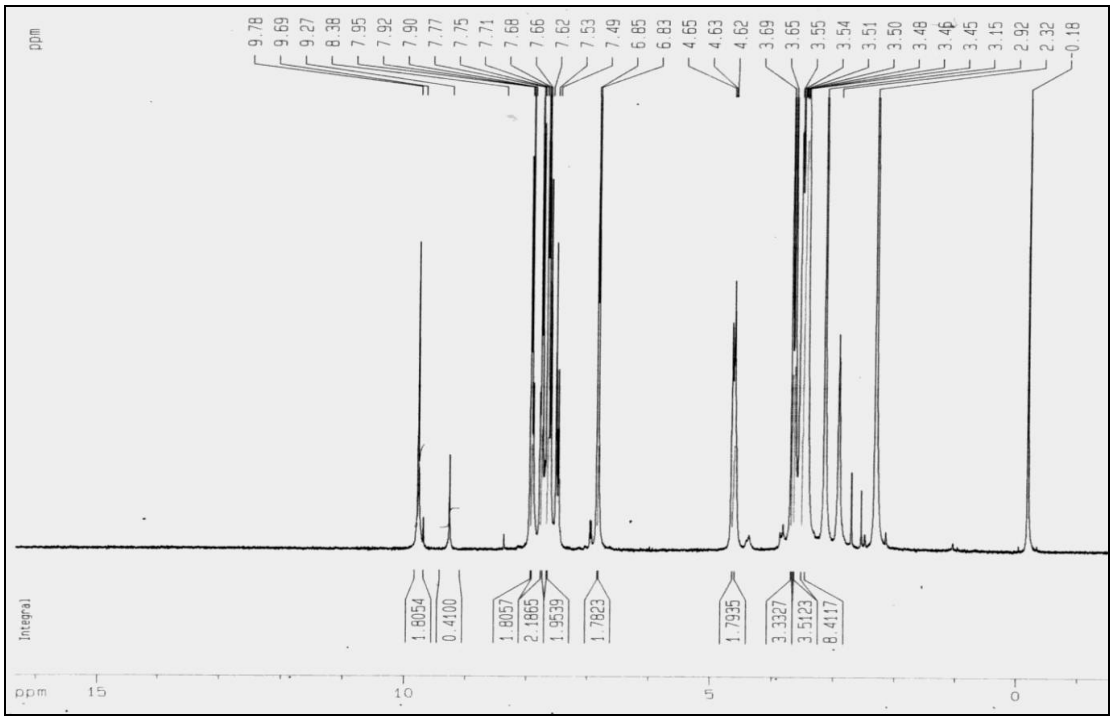
IR SPECTRAL STUDY OF 2-{4'-[6"-(4'''-METHOXYPHENYL)-2"-AMINO-3", 4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Instrument : SHIMADZU-FT-IR-8400, Spectrophotometer; frequency range : 4000-400 cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	Reported	
Alkane	C-H Str.(asym)	2925	2990-2850	422 – 423
	C-H Str.(sym)	2876	2880-2860	,,
	C-H def.(asym)	1460	1470-1435	
	C-H def.(sym)	1355	1390-1360	,,
Aromatic	C-H Str.	3081	3090-3030	
	C-H i.p. def	1180	1300-1100	,,
	C-H o.o.p. def	806	832-800	
	C=C Str.	1473	1600-1450	,,
S-triazine	C-N Str.	1141	1220-1020	,,
	C=N Str.	1589	1630-1590	
Amine	N-H Str.	3407	3500-3310	,,
	N-H Bending	1589	1650-1550	
Ether	C-O-C Str.(asym)	1247	1260-1220	,,
	C-O-C Str.(sym)	1068	1075-1020	
Halide	C-Cl Str.	767	800-600	,,
Amino Pyrimidine	N-H Str.	3350	3350-3250	,,
	C=N Str.	1616	1612-1550	
	C-N Str.	1116	1220-1020	

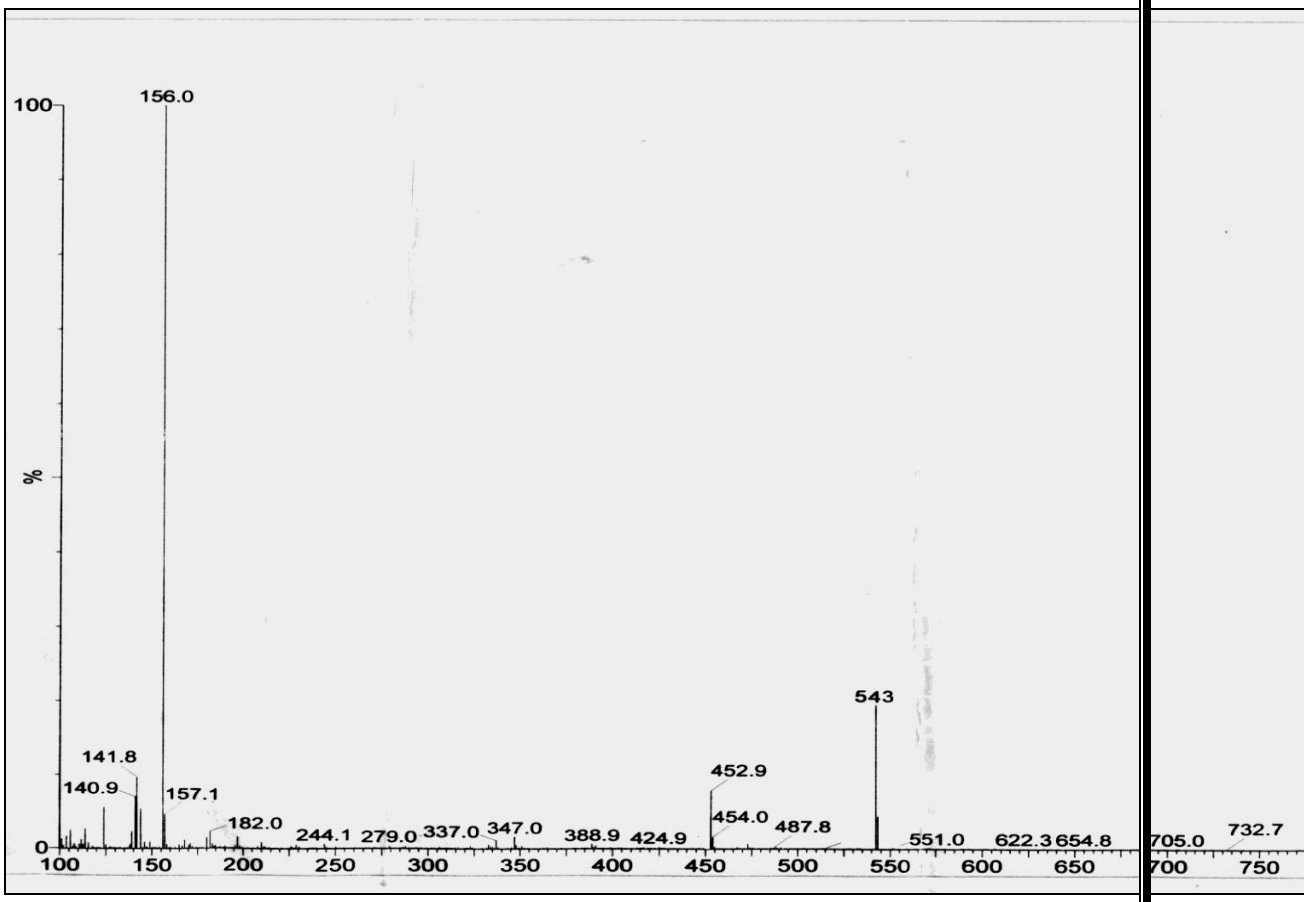
NMR SPECTRAL STUDY OF 2-{4'-[6"- [4'''-METHOXYPHENYL)-2"-AMINO-3", 4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.



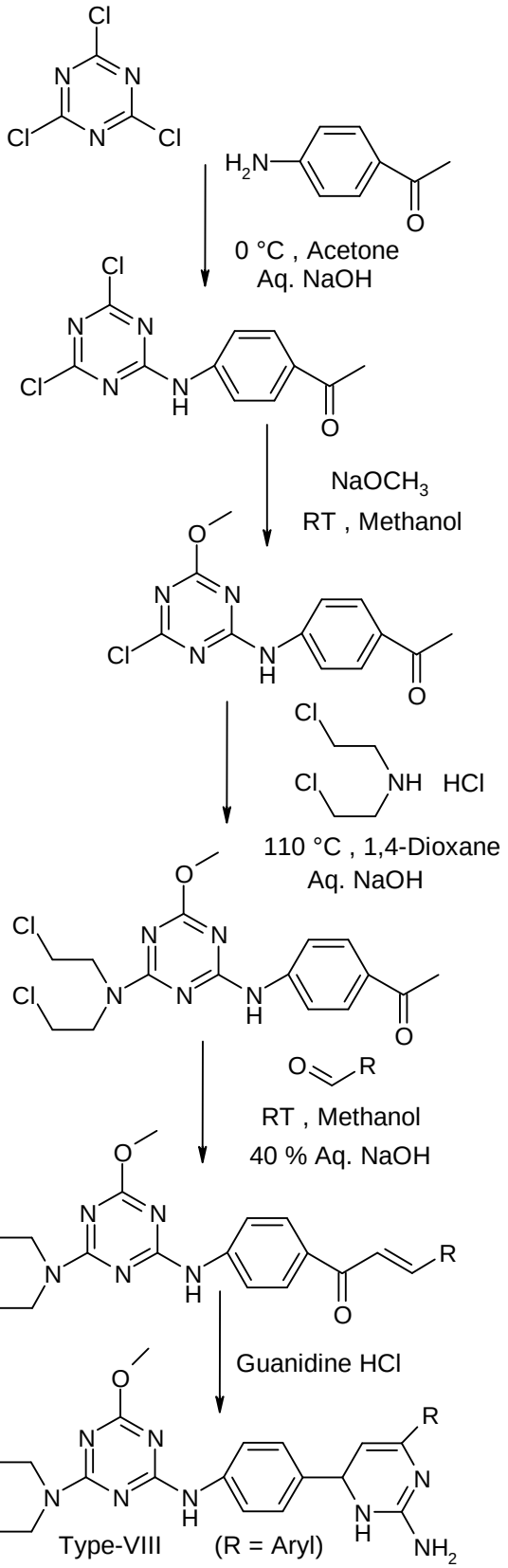
Internal standard : TMS; solvent : DMSO : Instrument : DPX-200 spectrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.50-3.69	6 H	Singlet	Ar-OCH_3
2	7.49-7.90	4 H	D. Doublet	Ar-H_b
3	7.92-9.27	4 H	D. Doublet	Ar-H_c
4	4.62-4.65	4 H	Triplet	-CH_2-Cl
5	2.32-2.92	4 H	Triplet	-N-CH_2-
6	9.69	2 H	Singlet	Ar-NH_f
7	9.78	2 H	Singlet	Ar-$NH_{2\ g}$
8	7.49-7.52	1 H	Singlet	-Ar_h

MASS SPECTRAL STUDY OF 2-{4'-[6"- (4'''-METHOXYPHENYL)-2"-AMINO-3", 4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE. (M.W. : 543)



REACTION SCHEME



Type-VIII (R = Aryl)

Antimicrobial Activity :

Conclution :

Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.				**Antifungal activity Zone of inhibition in m.m.**
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	4-OH C_6H_4-(24)	3-OH C_6H_4-(19)	3-OH C_6H_4-(21)	2-OH C_6H_4-(24)	4-OCH_3 C_6H_4-(20)
	4-NO_2 C_6H_4-(23)	4-OH C_6H_4-(20)	4-OCH_3 C_6H_4-(20)	4-OH C_6H_4-(23)	4-Br C_6H_4-(22)
	4-N,N $(CH_3)_2$	4-NO_2 C_6H_4-(22)	4-Br C_6H_4-(22)	4-NO_2 C_6H_4-(22)	4-NO_2 C_6H_4-(21)
	C_6H_4-(21)		4-N,N$(CH_3)_2$ C_6H_4-(23)	4-N,N$(CH_3)_2$ C_6H_4-(23)	4-N,N $(CH_3)_2$ C_6H_4-(20)
					C_4H_3O(22)

Comparable activity with known standard drugs

Ampicilin 50 µg.	23	18	17	27	-
Chloramphenicol ”	24	19	25	26	-
Norfloxacin ”	24	19	25	26	-
Greseofulvin ”	-	-	-	-	23

EXPERIMENTAL

SYNTHESIS OF 2-{4'-[(6"-ARYL-2"-AMINO-3", 4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

(A) **Syntesis of 2-(4'-Acetyl phenyl amino)-4,6'-dichloro-1,3,5-triazine.**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(B) **Synthesis of 2-(4"-Acetyl phenyl amino)-6-chloro-4-methoxy-1,3,5-triazine.**

For synthesis, See Part-I, Section-I, Page No. 36-38.

(C) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-[Bis(2"- chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(D) **Synthesis of 2-{4'-(3"-(4"'-Methoxy phenyl)-2"-propene-1"-one] phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis, See Part-I, Section-I, Page no. 36-38.

(E) **Synthesis of 2-{4'-[6"-(4""-Methoxy phenyl)-2"-amino-3",4", dihydro-pyrimidine-4"-yl]-phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

A mixture of 2-{4'-[3"-(4"'-methoxyphenyl)-2"-propene-1"-one]phenyl amino}-6-[Bis. (2"'-chloroethyl) amino]-4- methoxy-1,3,5-triazine (5.02 gm., 0.01 M) and guanidine hydrochloride (0.95 g, 0.01M) was refluxed at 110º C for 12 hrs. in presence of alcoholic KOH in methanol. The reaction mixture was poured into crushed ice filtered, dried and crystallised from dioxne. Yield : 80%. M.P. : 153º C (Found : C : 55.21; H : 5.13; N : 20.61; $C_{25}H_{28}O_2N_8Cl_2$, required C: 55.24; H : 5.15; N : 20.62%).

Simillarly other pyrimidines were synthesised and their physical data are recorded in Table no. 15

(F) **Antimicrobial activity of 2-{4'-[(6"-aryl - 2"-amino-3", 4"-dihydro)-pyrimidine-4"-yl]-phenyl amino}-6-[Bis-(2"'-chloroethyl) amino]-4-methoxy-1,3, 5,-triazine.**

Antimicrobial testing was carried out as described in part : I, section : I, Page no. 39-41.

The zone of inhibition of the test solutions are recordeds in Table No. 16

TABLE NO : 15 : PHYSICAL CONSTANTS OF 2-{4'-[(6"-ARYL-2"-AMINO-3", 4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Molecular Formula	M.P. .c	Yield %	% of Nitrogen	
					Calcd	Found
1.	C_6H_5	$C_{24}H_{26}C_{l2}N_8O$	189	78	21.82	21.80
2.	2-OH C_6H_4	$C_{24}H_{26}Cl_2N_9O_2$	180	81	21.16	21.14
3.	3-OH C_6H_4	$C_{24}H_{26}Cl_2N_8O_2$	212	69	21.16	21.15
4.	4-OH C_6H_4	$C_{24}H_{26}Cl_2N_8O_2$	239	73	21.16	21.13
5.	4-OCH_3 C_6H_4	$C_{25}H_{28}Cl_2N_8O_2$	153	80	20.62	20.61
6.	4-OH, 3-OCH_3 C_6H_3	$C_{25}H_{28}Cl_2N_8O_3$	149	72	20.03	20.01
7.	4-Br. C_6H_4	$C_{24}H_{25}BrCl_2N_8O$	264	79	18.92	18.99
8.	3-NO_2 C_6H_4	$C_{24}H_{25}Cl_2N_9O_3$	253	81	22.57	22.56
9.	4-NO_2 C_6H_4	$C_{24}H_{25}Cl_2N_9O_3$	211	83	22.57	22.55
10	4-$N_1N(CH_3)_2$ C_6H_4	$C_{26}H_{31}Cl_2N_9O$	236	78	22.65	22.62
11.	C_4H_3O (Furfurl)	$C_{22}H_{24}Cl_2N_8O_2$	197	77	22.26	22.21

TABLE NO : 16 :ANTIMICROBIAL ACTIVITY OF 2-{4'-[(6"-ARYL-2"-AMINO-3", 4"-DIHYDRO)-PYRIMIDINE-4"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	**R**	**Antibacterial activity Zone of inhibition in mm.**			**Antifungal activity Zone of inhibition in mm.**	
		B. mega.	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5	20	12	18	21	15
2	2-OH C_6H_4	22	14	17	24	14
3	3-OH C_6H_4	18	19	21	20	18
4	4-OH C_6H_4	24	20	19	23	19
5	4-OCH_3 C_6H_4	18	15	20	18	20
6	4-OH, 3-OCH_3 C_6H_3	17	17	16	17	17
7	4-Br. C_6H_4	19	16	22	19	22
8	3-NO_2 C_6H_4	20	18	19	16	18
9	4-NO_2 C_6H_4	23	22	18	22	21
10	4-N,N$(CH_3)_2$ C_6H_4	21	18	23	23	20
11	C_4H_3O (Furfuryl)	16	17	19	16	22

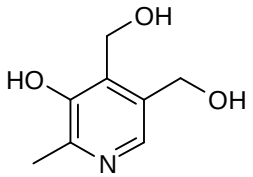
PART - V

STUDIES ON CYANOPYRIDINES

STUDIES ON CYANOPYRIDINES

INTRODUCTION

Pyridine and its derivatives represent one of the most active class of compounds possessing a wide spectrum of biological activities in the field of medicine, agriculture and industrial chemistry. Pyridine-3-carboxamide occurs as a component of the structure of the important coenzymes NADP +, one of the B_{12} complex of vitamins, occurs in red blood corpuscles and participates in biochemical redox reaction. Pyridoxol (Vitimin B_6) (I) Occurs in yeast and wheatgerm is an important food additive.



(I)

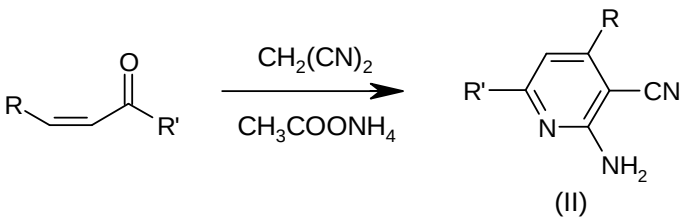
The availability of 3-cyanopyridine, nicotinamide and nicotinic acid make possible their use as synthetic intermediates.

Most derivatives are prepared by manipulation of pyridine and its simple homologues in a manner similar to chemistry of the benzenoid chemistry. However the simple pyridine compounds are prepared by the cyclisation of aliphatic raw material.

SYNTHETIC ASPECTS

Preparation of 3-cyanopyridines have been cited in literature [233-237] with different methods. The well known method is :

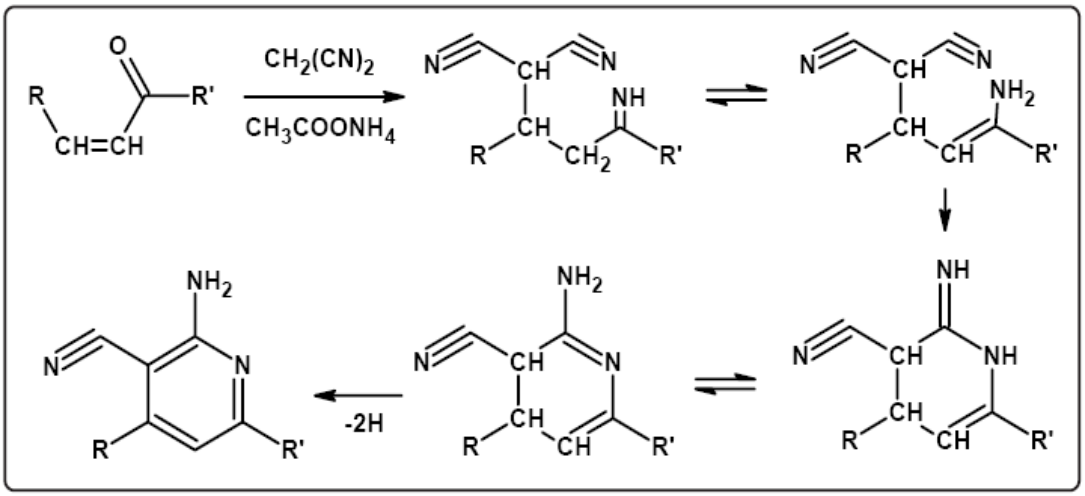
1. A.Samour and co-workers[238] have prepared substituted cyanopyridines by the condensation of chalcones with malononitrile in presence of ammonium acetate.



(II)

MECHANISM

The mechanism for the condensation of chalcones with malononitrile is shown as under.



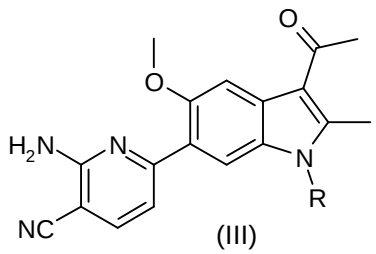
The reaction proceeds through conjugated addition of active methylene compounds to the α,β unsaturated system. The α,β-unsturated compound is known as acceptors and active methylene compound are known as following therapeutic activity.

THERAPEUTIC IMPORTANCE

Cyanopyridines possess wide therapeutic activities listed as under.

1. Antihypertensive[239]
2. Antisoriasis[240]
3. Antiepileptic[241]
4. Anticonvulsant[242]
5. Antifungal[243]
6. Antibacterial[244]
7. Herbicidal[245]
8. Antiinflammatory[246]
9. Anti HIV[247]

S. S. Verma et al.[248] have synthesised 2-amino-3-cyano-2, 6-disubstituted pyridines and studied their biological activities. The insecticidal activity of cyanopyridines has been investigated by Y. Sosaki[249], I. Teu and coworkers[250] have shown cyanopyridines as agrochemical fungicides. M. Hussans and co-workers[251] have prepared 3-cyanopyridines and reported their pharmacological activity. S. Guru evaluated[252] cyanopyridine derivatives (III) have been documented for their multiple biological activities.

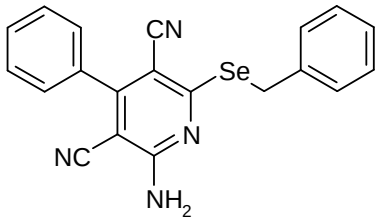


(III)

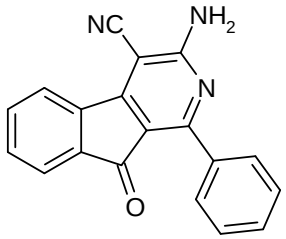
F. Manna and co-workers[253] have reported the antiinflammatory activity of 3-cyanopyridines. Some new 3-cyanopyridine derivatives have been found to show anticancer and anti HIV activity.[254] A. R. Parikh et al.[255-256] have prepared some new cyanopyridines and studied their antimicrobial activity.

U. D. Pyachenko and co-workers[257] have synthesised some cyanopyridine derivatives (IV) which are useful in the treatment of retroviral diseases.

Cyanopyridine derivatives (V) showing significant biological activity are described[258].



(IV)



(V)

H. H. Parekh et al.[259] have prepared new cyanopyridines and all products have been evaluated for their in vitro growth inhibitory activity against different microbes. T. B. Lowinger et al.[260] have prepared some new cyanopyridines and postulated them as vitro and cellular activities.

Moreover, H. Hiroki et al.[261] synthesised 2-acylamino-3, 5-dicyanopyridine derivatives useful as calcium channel opening drugs. Antimicrobial activity of cyanopyridine derivatives have reported by M. M. Komal[262], E. B. Villhauer et al.[263] have prepared novel cyanopyridines which has been found to be bioactive dipeptidyl peptidase inhibitors.

The synthesis of cyanopyridines is of current interest owing to their bi dynamic occurence in biologically active derivatives. Hence, considerable attention has been focused on the study of efficient and pharmaceutically important cyanopyridines bearing Bis (2-chloroethyl) amine and s-triazine molecules included in our moiety which are described as under.

SECTION : I **SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(6"-ARYL)-2"-AMINO-3"-CYANOPYRIDINE-4"-YL]-PHENYLAMINO}-6-[BIS-(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE**

SECTION : II **SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(4"-ARYL)-3"-CYANO-2"-METHOXY-PYRIDINE-6"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.**

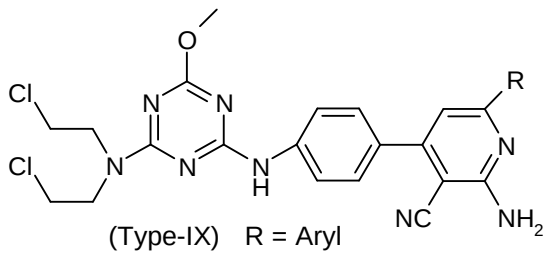
SECTION : III **SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(4"-ARYL)-3"-CYANO-2"-ETHOXY PYRIDINE -6"-YL]-PHENYL AMiNO}-6-[BIS-(2"'-CHLOROETHYL) AMINO]-4-METHOXY - 1, 3, 5-TRIAZINE.**

SECTION : IV **SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(4"-ARYL)-3"-CYANO-2"-HYDROXY PYRIDINE-6"-YL]-PHENYL AMINO}-6-[BIS-(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE**

SECTION : I

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(6"-ARYL-2"-AMINO-3"-CYANOPYRIDINE-4"-YL]-PHENYLAMINO}-6-[BIS-(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE

Pyridine nucleus plays in important role in medicine agriculture and industrial chemistry. To further assess the potential of such a classes of compounds, cyano pyridine derivative of 2-{4'-[(6"-Aryl-2"-amino-3"-cyano pyridine-4"-yl] phenyl amino}-6-[Bis(2"-chloroehtyl) amino]-4-methoxy-1,3,5-triazine of Type(IX) have been synthesised by the condensation of 2-{4'-[(3"-aryl)-2"-propene-1"-one]-phenyl amino}-6-[Bis (2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine, chalcones of Type(I) with malononitirle in presence of ammonium acetate.

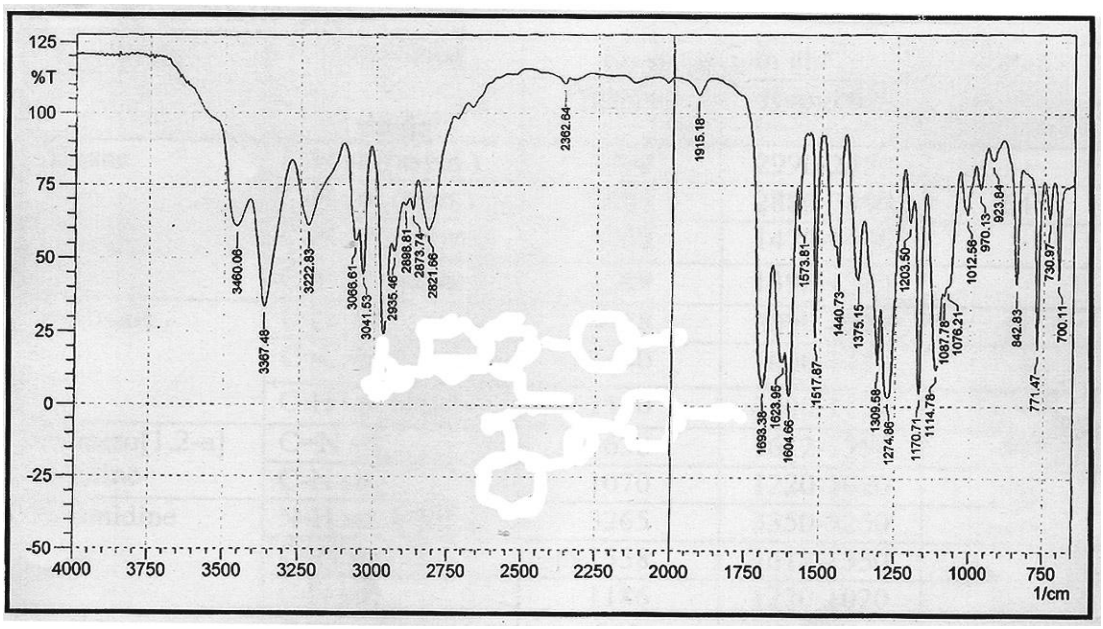


(Type-IX) R = Aryl

The constitution of the products have been characterised by elemental analyses IR, ^{1}H NMR, Mass spectral study. The products were screened for antimicrobial activity at a concentration of 50 μg.

The details have been cited in the part : I, section : I, Page no. 39-41.

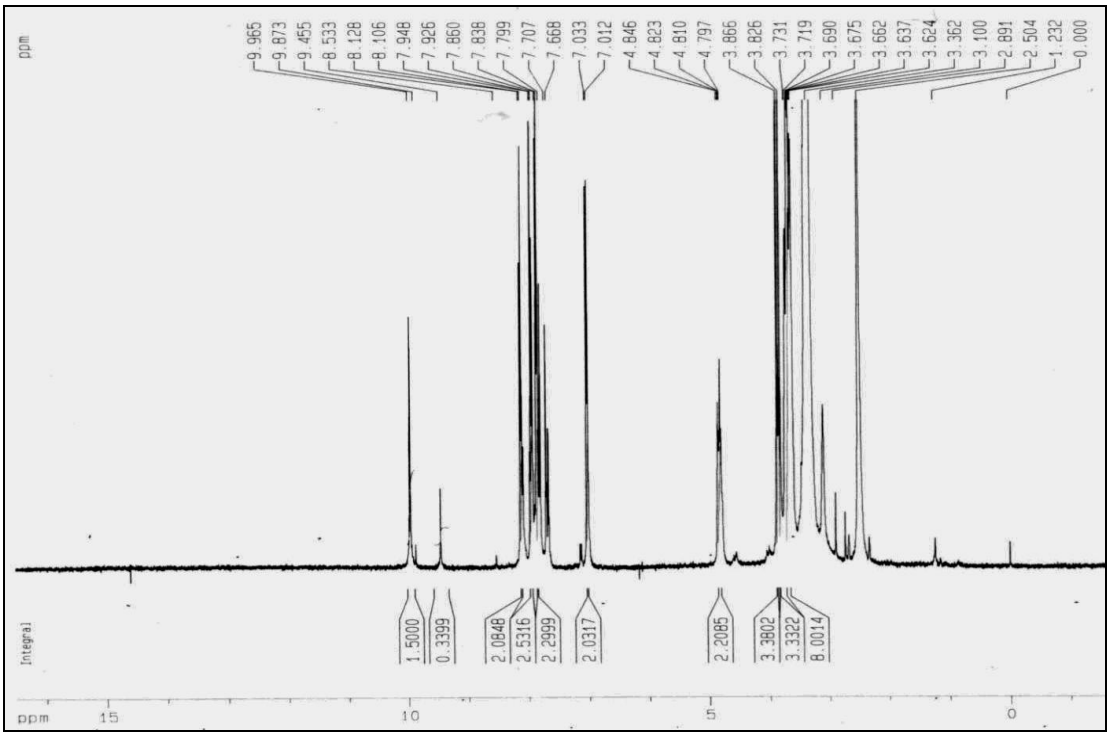
IR SPECTRAL STUDY OF 2-{4'-[6"-(4""-METHOXYPHENYL)-2"-AMINO-3"-CYANOPYRIDINE-4"-YL]-PHENYLAMINO}-6-[BIS-(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE



Instrument : SHIMADZU-FT-IR-8400, Spectrophotometer, frequency range : 4000-400 cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	reported	
Alkane	C-H Str.(asym)	2890	2990-2850	422 – 423
	C-H Str.(sym)	2873	2880-2860	,,
	C-H def.(asym)	1440	1470-1435	
	C-H def.(sym)	1375	1390-1360	,,
Aromatic	C-H Str.	3041	3090-3030	
	C-H i.p. def	1274	1300-1100	,,
	C-H o.o.p. def	842	832-800	
	C=C Str.	1517	1600-1450	,,
S-triazine	C-N Str.	1170	1220-1020	,,
	C=N Str.	1623	1630-1590	
Amine	N-H Str.	3460	3500-3310	,,
	N-H Bending	1604	1650-1550	
Ether	C-O-C Str.(asym)	1274	1260-1220	,,
	C-O-C Str.(sym)	1076	1075-1020	
Halide	C-Cl Str.	771	800-600	,,
Pyridine Nitrile	N-H Str. (-NH_2)	3350	3350-3250	,,
	C=N Str.	1604	1612-1550	
	C-N Str.	1087	1220-1020	

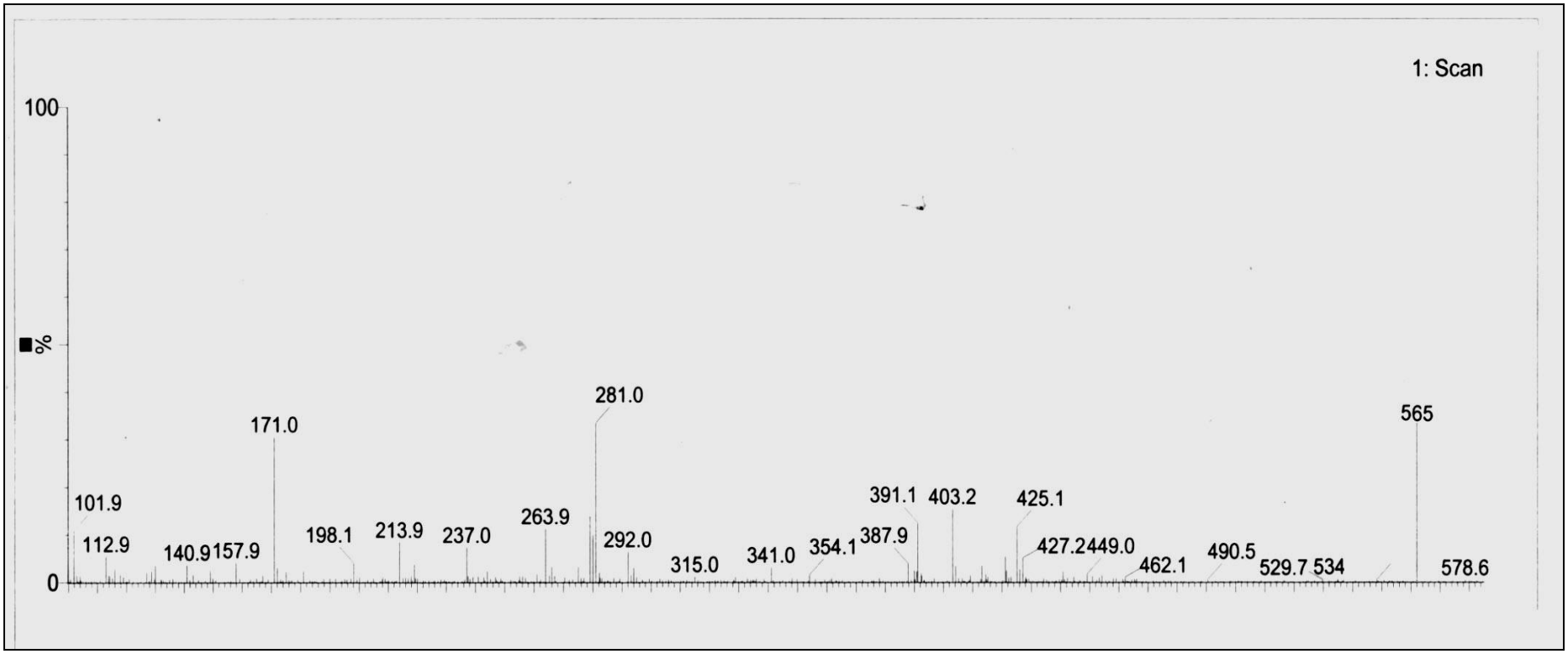
NMR SPECTRAL STUDY OF 2-{4'-[6"-(4""-METHOXYPHENYL)-2"-AMINO-3"-CYANOPYRIDINE-4"-YL]-PHENYLAMINO}-6-[BIS-(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE



Internal standard : TMS; solvent : DMSO : Instrument : DPX-200 spectrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.66-3.86	6 H	Singlet	Ar-OCH_3
2	7.66-7.86	4 H	D. Doublet	Ar-H_b
3	8.10-8.53	4 H	D. Doublet	Ar-H_c
4	4.79-4.81	4 H	Triplet	-CH_2-Cl
5	2.50-2.89	4 H	Triplet	-N-CH_2-
6	9.45	1 H	Singlet	Ar-NH_f
7	9.87-9.96	2 H	Singlet	Ar-$NH_{2\ g}$
8	7.01-7.03	1 H	Singlet	-Ar_h

MASS SPECTRAL STUDY OF 2-{4'-[6"-(4""-METHOXYPHENYL)-2"-AMINO-3"-CYANOPYRIDINE-4"-YL]-PHENYLAMINO}-6-[BIS-(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE. (M.W. : 565)



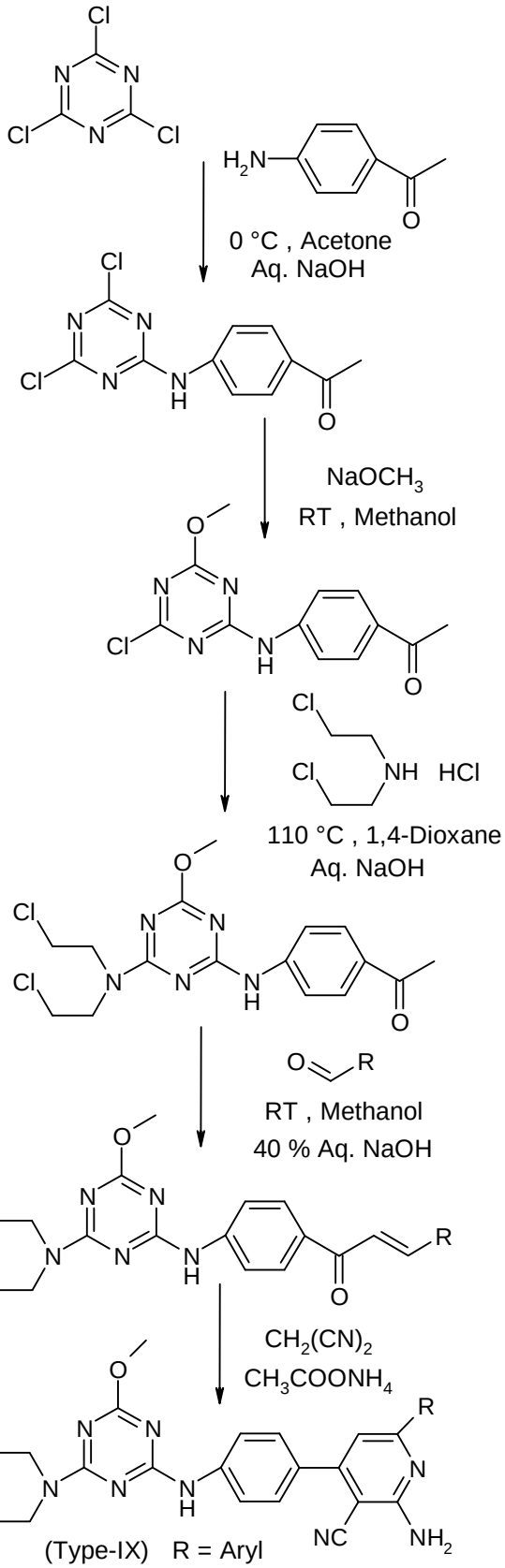
Antimicrobial Activity :

Conclution :

Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.				**Antifungal activity Zone of inhibition in m.m.**
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	4-OH C_6H_4 (21)	3-OH C_6H_4 (18)	4-OH C_6H_4 (21)	3-OH C_6H_4 (20)	C_6H_5 (20)
	4-Br. C_6H_4 (22)	4-OH C_6H_4 (20)	4-Br. C_6H_4 (20)	4-OH C_6H_4 (22)	4-OH C_6H_4 (23)
	4-NO_2 C_6H_4 (21)	4-Br. C_6H_4 (18)	4-NO_2 C_6H_4 (22)	4-NO_2 C_6H_4 (21)	3-NO_2 C_6H_4 (21)
		3-NO_2 C_6H_4 (19)		4-$N,N(CH_3)_2$	4-NO_2 C_6H_4 (22)
				C_6H_4 (20)	
Comparable activity with known standard drugs					
Ampicilin 50 µg	23	18	17	27	-
Chloramphenicol "	24	19	25	26	-
Norfloxacin "	24	19	25	26	-
Greseofulvin "	-	-	-	-	23

REACTION SCHEME



(Type-IX) R = Aryl

EXPERIMENTAL

SYNTHESIS OF 2-{4'-[(6"-ARYL)-2"-AMINO-3"-CYANOPYRIDINE-4"-YL]-PHENYLAMINO}-6-[BIS-(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE

(A) **Synthesis of 2-(4'-Acetyl phenyl amino)-4, 6-dichloro-1,3,5-triazine**

For synthesis, Part-I, Section-I, Page no. 36-38.

(B) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-chloro-4-methoxy-1,3,5-triazine.**

For synthesis Part-I, Section-I, Page no. 36-38.

(C) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-[Bis (2"-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis Part-I, Section-I, Page no. 36-38.

(D) **Synthesis of 2-{4'-[3"(4""-Methoxy phenyl)-2"-propene-1"-one]- phenyl amino}-6-[Bis. (2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis Part-1, Section-I, Page No. 36-38.

(E) **Synthesis of 2-{4'-[(6”-(4""-Methoxy phenyl)-2"-amino - 3"-cyano pyridine-4"-yl]-phenyl amino}-6-[Bis (2"-chloroethyl) amino]-4-methoxy-1,3,5-triazine.**

A mixture of 2-{4'-[3"(4""-methoxy phenyl)-2"-propene-1"-one] phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine (5.02 gm, 0.01 M); malononitrile (0.66 g, 0.01M) and ammonium acetate (0.77 gm, 0.01 M) and dioxane (25 ml.) The reaction mixture was refluxed 10 hrs. at 120º C., The reaction mixture was poured into crushed ice, filtered, dried, crystallised from dioxane, yield : 70%. M.P. : 228º C. (Found : C : 57.31; H : 4.59; N : 19.81; $C_{27}H_{26}O_2N_8Cl_2$ required C : 57.34; H : 4.60; N : 19.82%)

Simillarly other compounds were synthesised and their physical data are recorded in Table No. 17.

(F) **Antimicrobial activity of 2-{4'-(6"-Aryl) - 2"-amino-3"-cyano pyridine-4"-yl]-Phenyl amino}-6-[Bis. (2"'-chloro ethyl) amino]-4- methoxy-1,3,5-triazine.**

The antimicrobial testing was carried out as described in Part-I, Section-I, Page No. 39-41.

The zone of inhibition of the test solutions are recorded in Table No. 18.

TABLE NO : 17 : PHYSICAL CONSTANTS OF 2-{4'-[(6"-ARYL)-2"-AMINO-3"-CYANOPYRIDINE-4"-YL]-PHENYLAMINO}-6-[BIS-(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE

Sr. No.	R	Molecular Formula	M.P. .c	Yield %	% of Nitrogen	
					Calcd	Found
1.	C_6H_5	$C_{26}H_{24}Cl_2N_8O$	199	76	20.93	20.91
2.	2-OH C_6H_4	$C_{26}H_{29}Cl_2N_8O_2$	215	69	18.24	18.21
3.	3-OH C_6H_4	$C_{26}H_{24}Cl_2N_8O_2$	139	72	18.24	18.20
4.	4-OH C_6H_4	$C_{26}H_{24}Cl_2N_8O_2$	206	82	18.24	18.19
5.	4-OCH_3 C_6H_4	$C_{27}H_{26}Cl_2N_8O_2$	228	70	19.82	19.81
6.	4-OH, 3-OCH_3 C_6H_3	$C_{27}H_{26}Cl_2N_8O_3$	236	73	19.27	19.23
7.	4-Br. C_6H_4	$C_{26}H_{23}Br\ Cl_2N_8O$	219	67	18.24	18.22
8.	3-NO_2 C_6H_4	$C_{26}H_{23}Cl_2N_9O_3$	207	71	21.72	21.70
9.	4-NO_2 C_6H_4	$C_{26}H_{23}Cl_2N_9O_3$	206	79	21.72	21.72
10	4-N,N$(CH_3)_2$ C_6H_4	$C_{28}H_{29}Cl_2N_9O$	225	85	21.79	21.75
11.	C_4H_3O (Fufuryl)	$C_{24}H_{22}Cl_2N_8O_2$	186	87	21.33	21.28

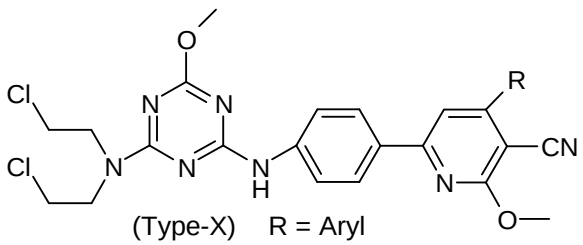
TABLE NO : 18 : ANTIMICROBIAL ACTIVITY OF 2-{4'-[(6"-ARYL)-2"-AMINO-3"-CYANOPYRIDINE-4"-YL]-PHENYLAMINO}-6-[BIS-(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE

Sr. No.	**R**	**Antibacterial activity Zone of inhibition in mm.**				**Antifungal activity Zone of inhibition in mm.**
		B. mega.	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5	15	14	16	18	20
2	2-OH C_6H_4	14	16	15	19	18
3	3-OH C_6H_4	17	18	19	20	19
4	4-OH C_6H_4	21	20	21	22	23
5	4-OCH_3 C_6H_4	19	17	16	17	19
6	4-OH, 3-OCH_3 C_6H_3	18	15	15	16	18
7	4-Br. C_6H_4	22	18	20	15	13
8	3-NO_2 C_6H_4	20	19	18	18	21
9	4-NO_2 C_6H_4	21	17	22	21	22
10	4-N,N$(CH_3)_2$ C_6H_4	18	15	17	20	16
11	C_4H_3O (Fufuryl)	16	14	19	16	15

SECTION - II

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(4"-ARYL)-3"-CYANO-2"-METHOXY-PYRIDINE-6"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

In recent years, much interest have been foucused of cyanopyridine derivatives showed wide range of application in the field of pharmaceutical. In view of getting 2-{4'-[(4"-Aryl)-3"-cyano-2"-methoxy-pyridine-6"yl]phenylamino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine of Type(X) have been synthesised by the condensation of 2-{4'-[(3"-aryl)-2"-propene-1"-one]-phenyl amino}-6-[Bis (2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine with malono nitrile in the presence of sodium methoxide.

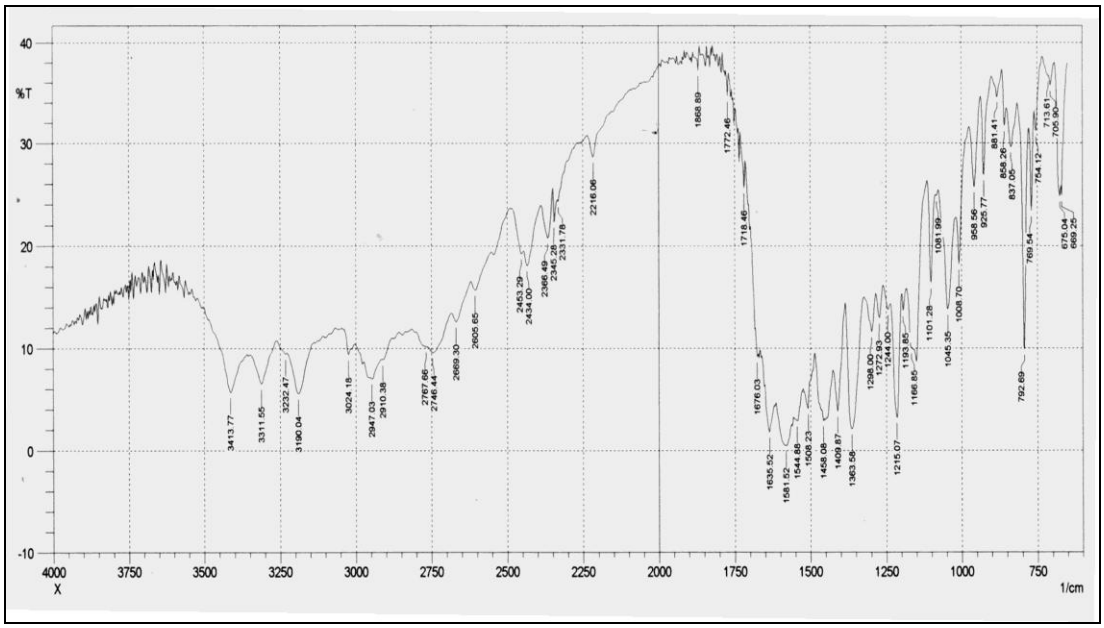


(Type-X) R = Aryl

The constitution of the products have been characterised by elemental analysis IR, ^{1}H NMR, Mass spectral study. The products were screened for antimicrobial activity at a concentration of 50 µg.

The details have been cited in the part : I, Section : I, Page no. 39-41.

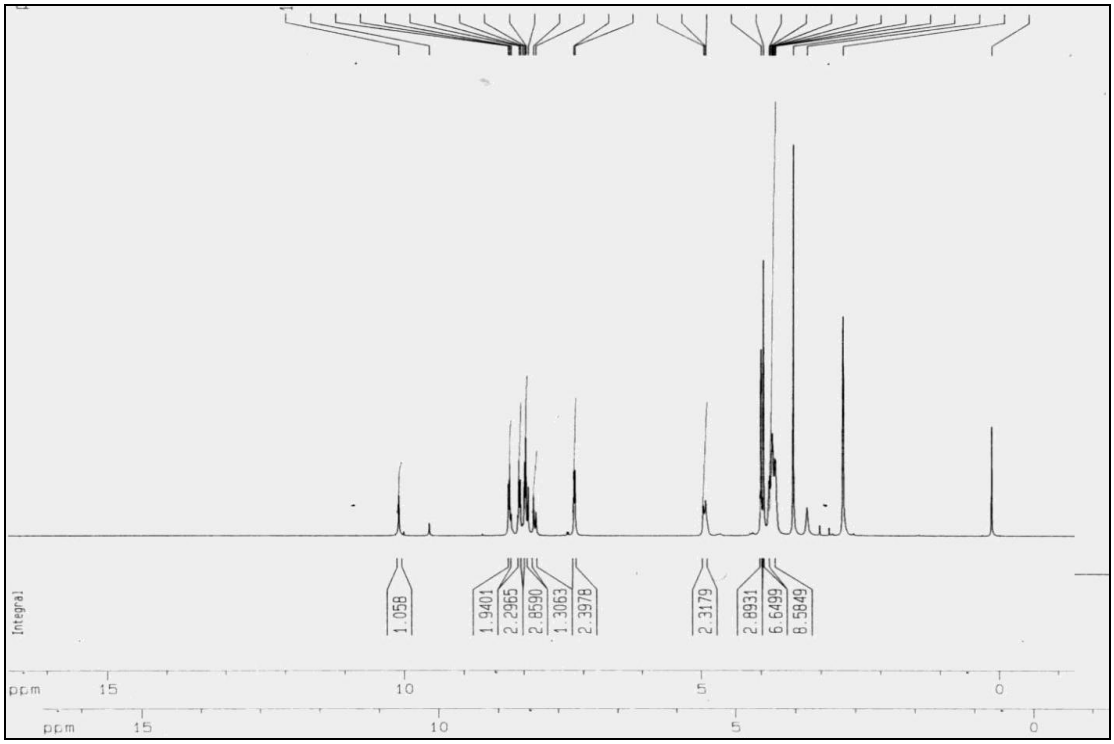
IR SPECTRAL STUDY OF 2-{4'-[4"-(4""-METHOXYPHENYL)-3"-CYANO-2"-METHOXY)-PYRIDINE-6"-YL]-PHENYLAMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Instrument : SHIMADZU-FT-IR-8400, Spectrophoto meter frequency range : 4000-400 cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	Reported	
Alkane	C-H Str.(asym)	2910	2990-2850	422 – 423
	C-H Str.(sym)	2876	2880-2860	,,
	C-H def.(asym)	1458	1470-1435	
	C-H def.(sym)	1363	1390-1360	,,
Aromatic	C-H Str.	3024	3090-3030	
	C-H i.p. def	1298	1300-1100	,,
	C-H o.o.p. def	837	832-800	
	C=C Str.	1458	1600-1450	,,
S-triazine	C-N Str.	1215	1220-1020	,,
	C=N Str.	1593	1630-1590	
Amine	N-H Str.	3413	3500-3310	,,
	N-H Bending	1635	1650-1550	
Ether	C-O-C Str.(asym)	1244	1260-1220	,,
	C-O-C Str.(sym)	1045	1075-1020	
Halide	C-Cl Str.	792	800-600	,,
Pyridine Nitrile	C=N Str.	2216	2240-2120	,,
	C-N Str.	1581	1650-1520	

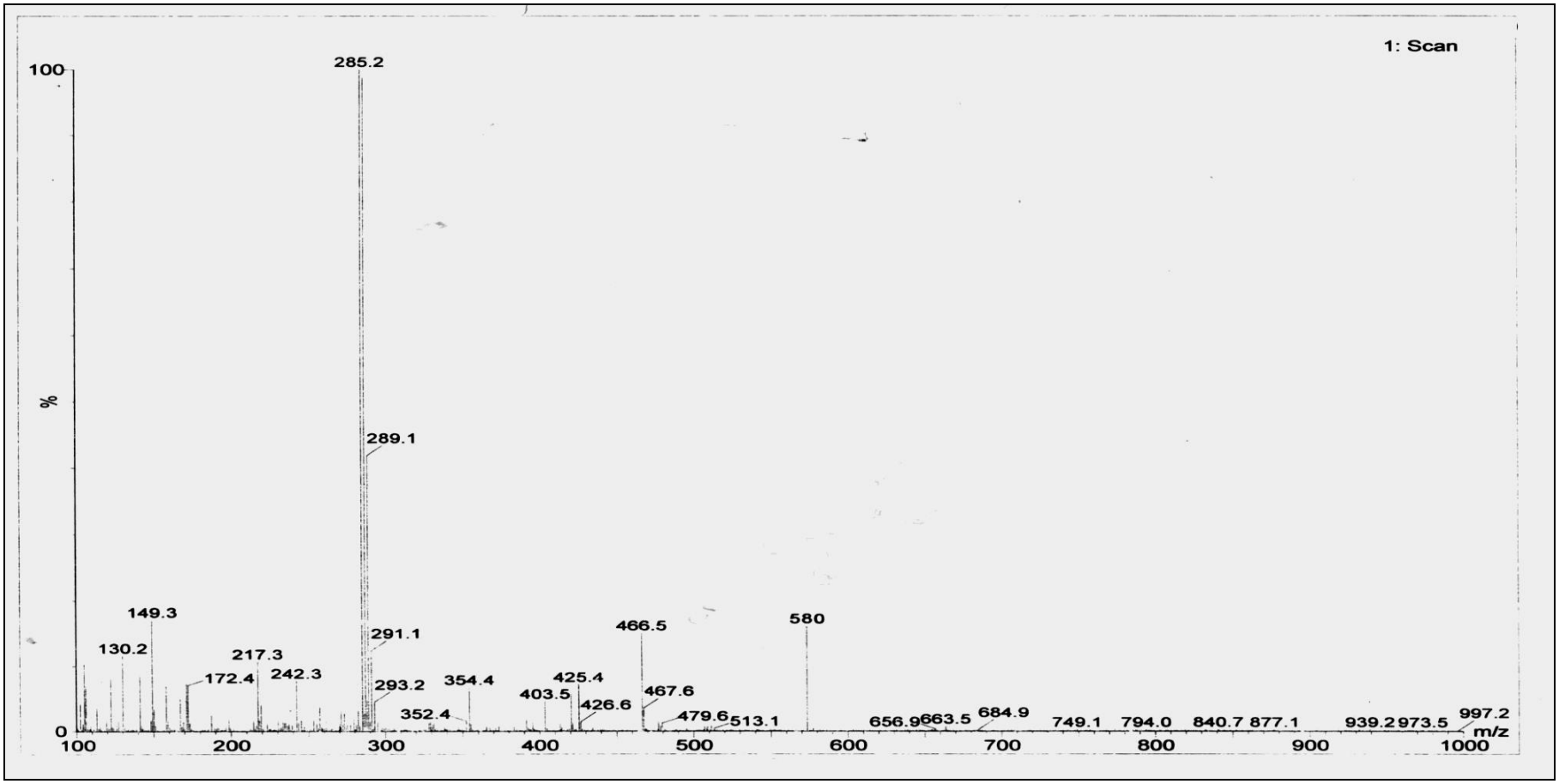
NMR SPECTRAL STUDY OF 2-{4'-[4"-(4""-METHOXYPHENYL)-3"-CYANO-2"-METHOXY)-PYRIDINE-6"-YL]-PHENYLAMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Internal standard : TMS; solvent : $CDCl_3$; Instrument : BRUKER spectrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.76-3.96	9 H	Singlet	Ar-OCH_3
2	7.41-7.84	4 H	D. Doublet	Ar-H_b
3	7.93-8.24	4 H	D. Doublet	Ar-H_c
4	4.00-4.96	4 H	Triplet	-CH_2-Cl
5	2.63-3.23	4 H	Triplet	-N-CH_2-
6	10.09	1 H	Singlet	Ar-NH_f
7	7.97	1 H	Singlet	Ar-$NH_{2\ g}$

MASS SPECTRAL STUDY OF 2-{4'-[4"-(4""-METHOXYPHENYL)-3"-CYANO-2"-METHOXY)-PYRIDINE-6"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE. (M.W. : 580)



Antimicrobial Activity :

Conclution :

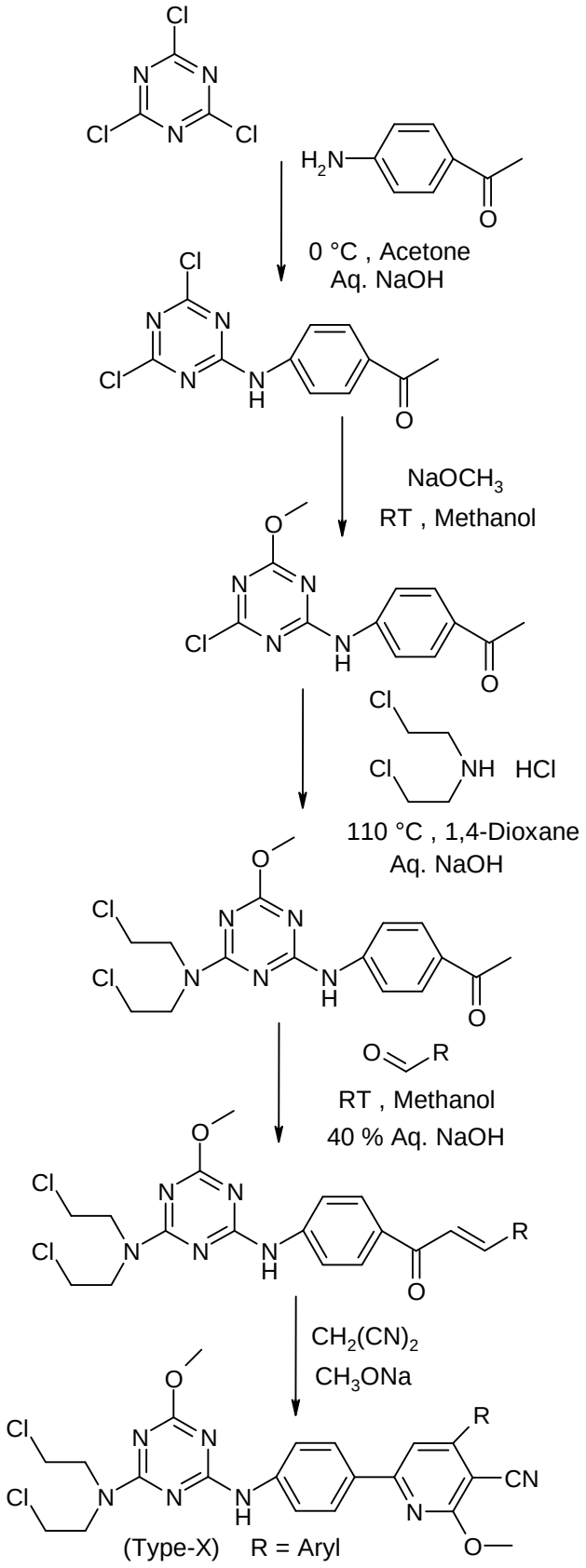
Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.				**Antifungal activity Zone of inhibition in m.m.**
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	4-OH, 3-OCH_3	4-OH C_6H_4(17)	4-Br. C_6H_4(21)	3-OH C_6H_4(20)	3-OH C_6H_4(23)
	C_6H_3 (20)	4-Br. C_6H_4(19)	4-NO_2 C_6H_4(20)	4-OH C_6H_4(21)	4-OH C_6H_4(21)
	4-NO_2 C_6H_4(19)	4-NO_2 C_6H_4(20)		4-Br. C_6H_4(22)	4-NO_2 C_6H_4(20)
	C_4H_3O (19)			4-NO_2 C_6H_4(20)	

Comparable activity with known standard drugs

Ampicilin 50 µg	23	18	17	27	-
Chloramphenicol "	24	19	25	26	-
Norfloxacin "	24	19	25	26	-
Greseofulvin "	-	-	-	-	23

REACTION SCHEME



EXPERIMENTAL

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(4"-ARYL)-3"-CYANO-2"-METHOXY)-PYRIDINE-6"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

(A) **Synthesis of 2-(4'-Acetylphenyl amino)-4, 6-dichloro-1,3,5-triazine.**

For synthesis Part-I, Section-I, Page no. 36-38.

(B) **Synthesis of 2-(4'-Acetylphenyl amino) -6-chloro-4-methoxy-1,3,5-triazine.**

For synthesis Part-I, Section-I, Page no. 36-38.

(C) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-[Bis- (2"-chloroethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis Part-I, Section-I, Page No. 36-38.

(D) **Synthesis of 2-{4'-[3"-(4""-Methoxyphenyl)-2"-propene-1"-one]phenyl amino}-6-[Bis. (2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis Part-I, Section-I, Page no. 36-38.

(E) **Synthesis of 2-{4'-[4"-(4""-Methoxyphenyl)-3"-cyano-2"-methoxy-pyridine-6"-yl]-phenyl amino}-6-[Bis. (2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

A mixture of 2-{4'-[3"-(4""-methoxyphenyl)-2"-propene-1"-one]phenyl amino}-6-[Bis(2"'-chloro ethyl)-amino]-4-methoxy-1,3,5,- triazine (5.02 gm,

0.01M) methanol (25 ml) malono nitrile (0.66 gm, 0.01 M); sodium methoxide, (0.44 g., 0.01M) The reaction mixture was refluxed 10 hrs. at 170º C. in dioxane. The product was poured into crushed ice, filtered and dried, crystallised from dioxane, yield : 78%, M.P. : 188º C. (Found : C : 5780; H : 4.69; N : 16.81; $C_{28}H_{27}O_3N_7Cl_2$ required C : 57.83; H : 4.71 ; N : 16.89%)

Simillarly other compounds were synthesised and their physical data are recorded in Table no. 19.

(F) **Antimicrobial activity of 2-{4'[(4"-Aryl-3"-cyano-2", methoxy)-pyridine-6"-yl]-phenyl amino}-6-[Bis. (2"'-chloro ethyl) amino]-4- methoxy-1,3,5-triazine.**

The antimicrobial testing was carried out as described in Part-I, Section-I, Page no. 39-41.

The Zone of inhibition of the test solution are recorded in Table no. 20.

TABLE NO : 19 : PHYSICAL CONSTANTS OF 2-{4'-[(4"-ARYL)-3"-CYANO-2"-METHOXY-PYRIDINE-6"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Molecular Formula	M.P. .c	Yield %	% of Nitrogen	
					Calcd	Found
1.	C_6H_5	$C_{27}H_{25}Cl_2N_7O_2$	201	64	17.81	17.80
2.	2-OH C_6H_4	$C_{27}H_{25}Cl_2N_7O_3$	212	68	17.31	17.30
3.	3-OH C_6H_4	$C_{27}H_{25}Cl_2N_7O_3$	179	72	17.31	17.29
4.	4-OH C_6H_4	$C_{27}H_{25}Cl_2N_7O_3$	153	75	17.31	17.27
5.	4-OCH_3 C_6H_4	$C_{28}H_{27}Cl_2N_7O_3$	188	78	16.89	16.81
6.	4-OH, 3-OCH_3 C_6H_3	$C_{28}H_{27}Cl_2N_7O_4$	176	80	16.44	16.42
7.	4-Br. C_6H_4	$C_{27}H_{24}BrCl_2N_7O_2$	205	85	15.58	15.53
8.	3-NO_2 C_6H_4	$C_{27}H_{24}Cl_2N_8O_4$	164	79	18.82	18.81
9.	4-NO_2 C_6H_4	$C_{27}H_{24}Cl_2N_8O_4$	179	78	18.82	18.80
10	4-N,N$(CH_3)_2$ C_6H_4	$C_{29}H_{30}Cl_2N_8O_2$	171	81	18.88	18.83
11.	C_4H_3O (Furfuryl)	$C_{25}H_{23}Cl_2N_7O_3$	119	85	18.14	18.09

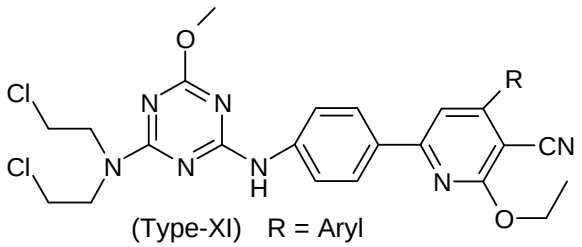
TABLE NO : 20 : ANTIMICROBIAL ACTIVITY OF 2-{4'-[(4"-ARYL)-3"-CYANO-2"-METHOXY-PYRIDINE-6"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Antibacterial activity Zone of inhibition in mm.				Antifungal activity Zone of inhibition in mm.
		B. mega	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5	13	12	14	16	17
2	2-OH C_6H_4	14	13	16	19	19
3	3-OH C_6H_4	17	14	18	20	23
4	4-OH C_6H_4	18	17	18	21	21
5	4-OCH_3 C_6H_4	15	13	16	17	18
6	4-OH, 3-OCH_3 C_6H_3	20	14	14	15	15
7	4-Br. C_6H_4	16	19	21	22	16
8	3-NO_2 C_6H_4	17	18	18	18	17
9	4-NO_2 C_6H_4	19	20	20	20	20
10	4-N,N$(CH_3)_2$ C_6H_4	15	18	16	17	14
11	C_4H_3O (Furfuryl)	19	17	17	19	18

SECTION : III

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(4"-ARYL)-3"-CYANO-2"-ETHOXY PYRIDINE -6"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY - 1, 3, 5-TRIAZINE.

Pyridine derivatives have been reported to have various pharmacological activities like antibacterial, antiviral, antifungal etc. With a view of getting better therapeutic activity 2-{4'-[(4"-aryl)-3"-cyano-2"-ethoxy-pyridine-6"-yl]-phenyl amino}-6-[Bis (2"-chloroethyl) amino]-4-methoxy-1,3,5-triazine of Type-(XI) have been synthesised by the condensation of 2-{4'-[(3"-aryl)-2"-propene-1"-one]-phenyl amino}-6-[Bis (2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine chalcones of Type(I) with malononitrile in the presence of sodium ethoxide.

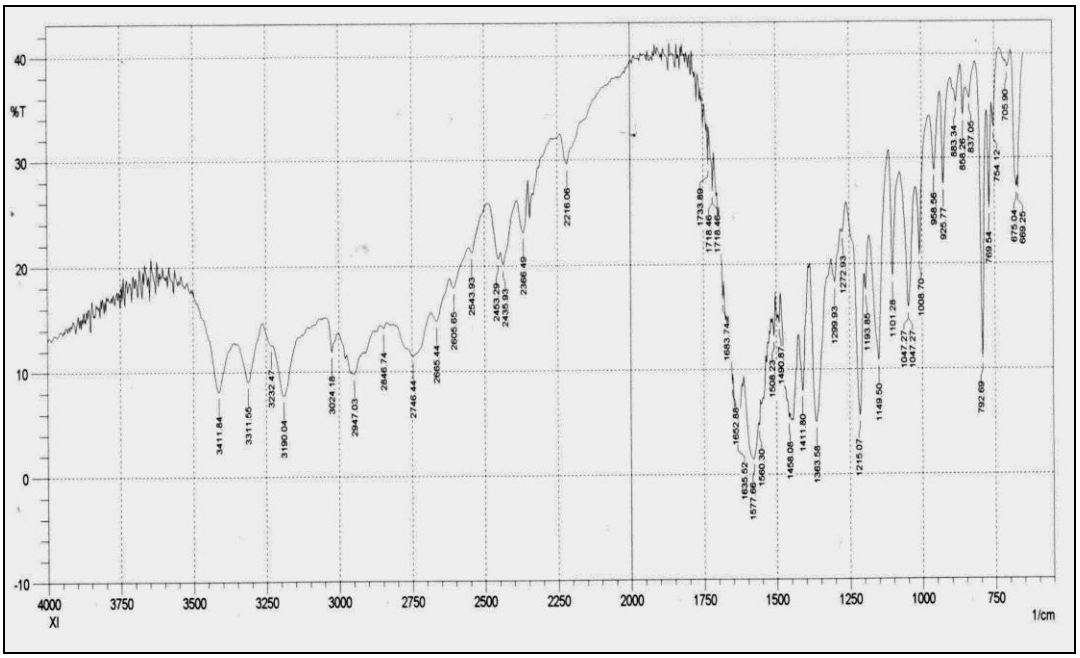


(Type-XI) R = Aryl

The constitution of the products have been characterised by elemental analysis IR, ^{1}H NMR, Mass spectral study. The products were screened for antimicrobial activity at a concentration of 50 µg.

The details have been cited in the Part P I, Section : I, Page No. 39-41.

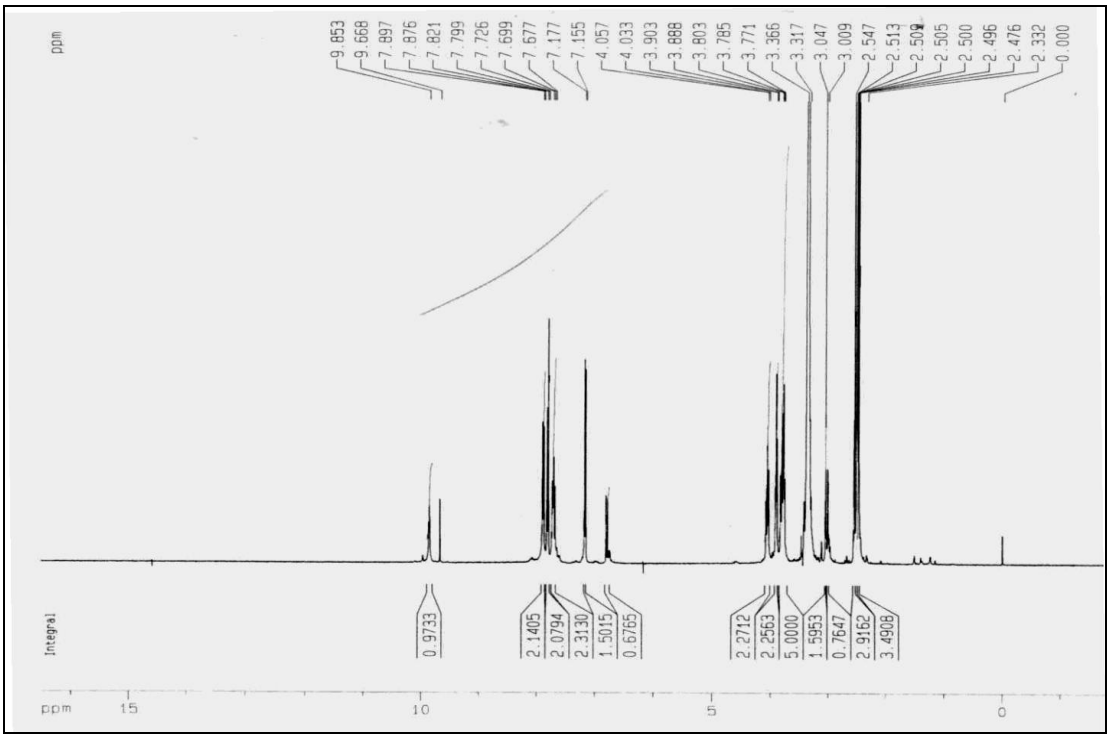
IR SPECTRAL STUDY OF 2-{4'-[4"- (4""-METHOXYPHENYL)-3"-CYANO-2"-ETHOXY PYRIDINE -6"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY - 1, 3, 5-TRIAZINE.



Instrument : SHIMADZU-FT-IR-8400, Spectrophoto meter frequency range : 4000-400 cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	reported	
Alkane	C-H Str.(asym)	2947	2990-2850	422 – 423
	C-H Str.(sym)	2875	2880-2860	,,
	C-H def.(asym)	1458	1470-1435	
	C-H def.(sym)	1363	1390-1360	,,
Aromatic	C-H Str.	3024	3090-3030	
	C-H i.p. def	1149	1300-1100	,,
	C-H o.o.p. def	837	832-800	
	C=C Str.	1458	1600-1450	,,
S-triazine	C-N Str.	1215	1220-1020	,,
	C=N Str.	1593	1630-1590	
Amine	N-H Str.	3411	3500-3310	,,
	N-H Bending	1577	1650-1550	
Ether	C-O-C Str.(asym)	1215	1260-1220	,,
	C-O-C Str.(sym)	1047	1075-1020	
Halide	C-Cl Str.	792	800-600	,,
Pyridine Nitrile	C=N Str.	2216	2240-2120	,,
	C-N Str.	1577	1650-1520	

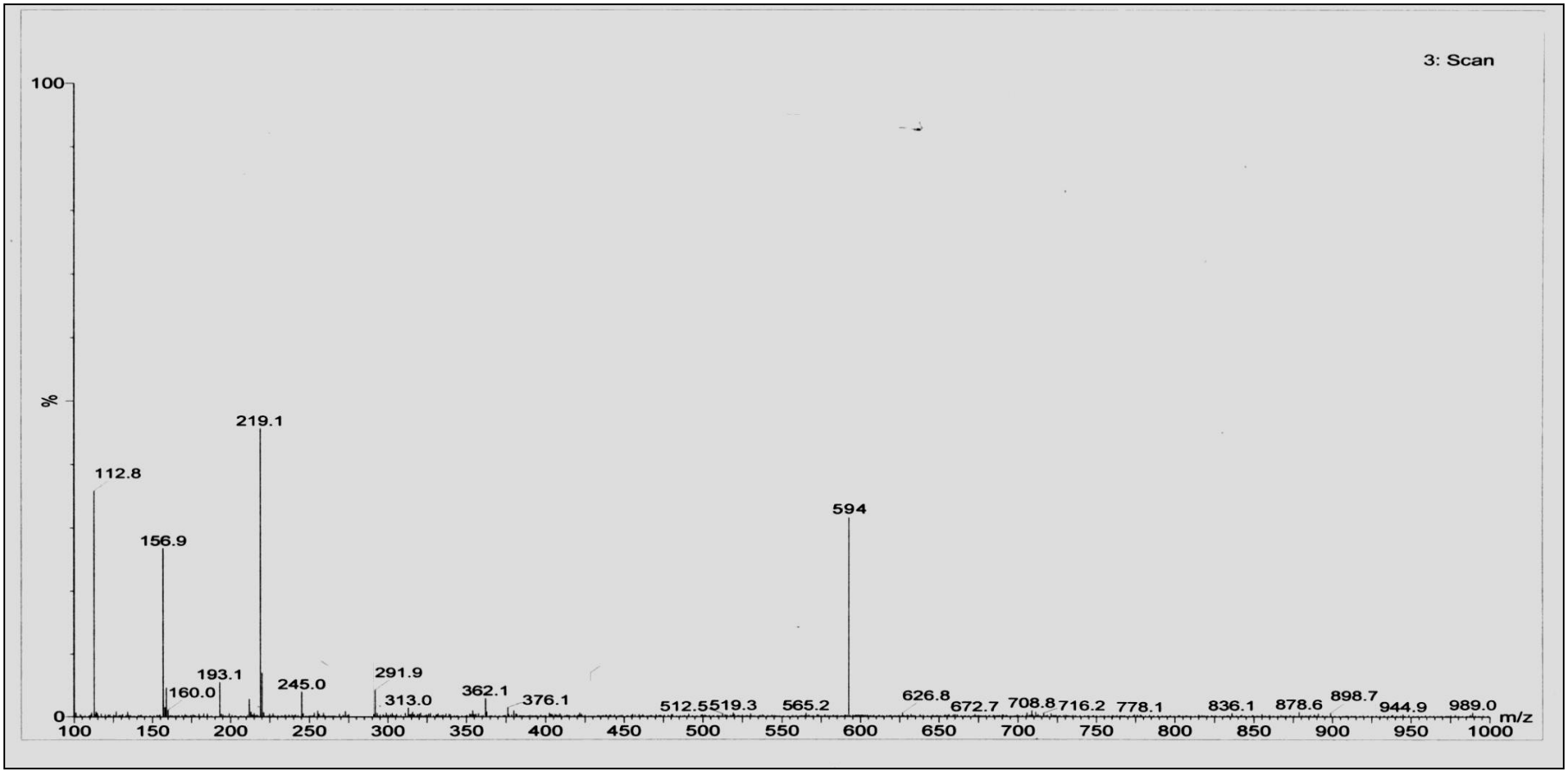
NMR SPECTRAL STUDY OF 2-{4'-[4"- (4""-METHOXYPHENYL)-3"-CYANO-2"-ETHOXY PYRIDINE -6"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY - 1, 3, 5-TRIAZINE.



Internal standard : TMS; solvent : $CDCl_3$; Instrument : BRUKER spectrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.77-3.90	6 H	Singlet	Ar-OCH_3
2	7.15-7.17	4 H	D. Doublet	Ar-H_b
3	7.67-7.89	4 H	D. Doublet	Ar-H_c
4	4.03-4.05	4 H	Triplet	-CH_2-Cl
5	2.33-2.54	4 H	Triplet	-N-CH_2-
6	9.85	1 H	Singlet	Ar-NH_f
7	3.30	2 H	Quartate	-$OCH_{2\ g}$
8	2.33	3 H	Triplet	-CH_2-$CH_{3\ h}$

MASS SPECTRAL STUDY OF 2-{4'-[4"- (4""-METHOXYPHENYL)-3"-CYANO-2"-ETHOXY PYRIDINE -6"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY - 1, 3, 5-TRIAZINE. (M.W. : 594)



Antimicrobial Activity :

Conclution :

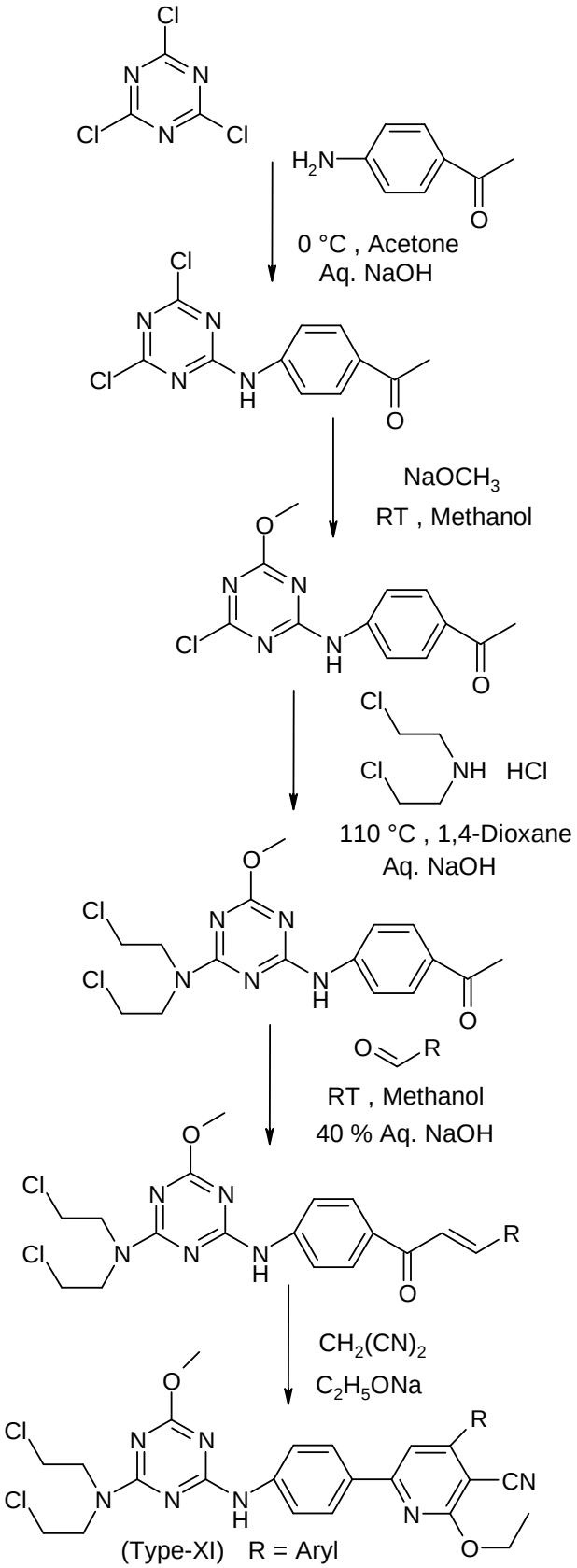
Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.				**Antifungal activity Zone of inhibition in m.m.**
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	3-OH C_6H_4 (22)	2-OH C_6H_4 (17)	3-OH C_6H_4 (21)	3-OH C_6H_4 (23)	C_6H_5 (20)
		3-OH C_6H_4 (19)	4-OH C_6H_4 (22)	4-OH C_6H_4 (24)	4-OH C_6H_4 (21)
		4-OH C_6H_4 (20)	3-NO_2 C_6H_4 (21)	3-NO_2 C_6H_4 (23)	4-NO_2 C_6H_4 (23)
		4-Br C_6H_4 (18)	4-NO_2 C_6H_4 (23)	4-NO_2 C_6H_4 (22)	
		4-NO_2 C_6H_4 (19)			

Comparable activity with known standard drugs

Ampicilin 50 µg	23	18	17	27	-
Chloramphenicol "	24	19	25	26	-
Norfloxacin "	24	19	25	26	-
Greseofulvin "	-	-	-	-	23

REACTION SCHEME



(Type-XI) R = Aryl

EXPERIMENTAL

SYNTHESIS OF 2-{4'[(4"-ARYL)-3"-CYANO-2"-ETHOXY PYRIDINE -6"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY - 1, 3, 5-TRIAZINE.

(A) **Synthesis of 2-(4'-Acetyl phenyl amino) 4, 6-dichloro-1,3,5-triazine.**

For synthesis Part-I, Section-I, Page no. 36-38.

(B) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-chloro-4-methoxy-1,3,5-triazine.**

For synthesis Part-I, Section-I, Page no. 36-38.

(C) **Synthesis of 2-(4'- Acetyl Phenyl amino)-6-[Bis(2"-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis Part-I, Section-I, Page no. 36-38.

(D) **Synthesis of 2-{4'-[3"-(4""-Methoxyphenyl)-2"-propene-1"-one] phenyl amino}-6-[Bis. (2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis Part-I, Section-I, Page no. 36-38.

(E) **Synthesis of 2-{4'-[4"-(4""-Methoxy phenyl)-3"-cyano-2"-ethoxy-pyridine-6"-yl]-phenyl amino}-6- [Bis (2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triaine.**

A mixture of 2-{4'[3"-(4""-methoxyphenyl)-2"-Propene-1"-one] phenyl amino}-6-[Bis.(2"'-chloro ethyl) amino]-4- methoxy-1,3,5-triazine (5.02 gm, 0.01M) and malnonitrile (0.66 gm, 0.01M); sodium ethoxide (0.68 gm, 0.01M) and ethanol (15 ml) : The reaction mixture was refuxed for 12 hrs. at 100º C temp. The reaction mixture was poured into crushed ice, filtered, dried and crystallised from ethanol. Yield : 65%, M.P.: 248º C. (Found : C : 58.55; H; 4.85; N : 16.48; $C_{29}H_{29}O_3N_7Cl_2$ required C : 58.58; H : 4.88; N : 16.49%).

Simillarly other compounds were synthesised and their physical data recorded in Table no. 21.

(F) **Antimicrobial activity of 2-{4'-[4" -(Aryl)-3"-cyano-2"-ethoxypyridine-6"-yl]-phenyl amino}-6-[Bis. (2"'- chloro ethyl) amino]-4- methoxy-1, 3, 5-triazine.**

The antimicrobial testing was carried out as described in Part-I, Section-I, Page No. 39-41.

The zone of inhibition of the test solution are recorded in Table no. 22.

TABLE NO : 21 : PHYSICAL CONSTANTS OF 2-{4'-[(4"-ARYL)-3"-CYANO-2"-ETHOXY PYRIDINE -6"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLOROETHYL) AMINO]-4-METHOXY - 1, 3, 5-TRIAZINE.

Sr. No.	R	Molecular Formula	M.P. .c	Yield %	% of Nitrogen	
					Calcd	Found
1.	C_6H_5	$C_{28}H_{27}Cl_2N_7O_2$	215	27	17.37	17.31
2.	2-OH C_6H_4	$C_{28}H_{27}Cl_2N_7O_3$	193	52	16.89	16.82
3.	3-OH C_6H_4	$C_{28}H_{27}Cl_2N_7O_3$	252	60	16.89	16.85
4.	4-OH C_6H_4	$C_{28}H_{27}Cl_2N_7O_3$	279	62	16.89	16.88
5.	4-OCH_3 C_6H_4	$C_{29}H_{29}Cl_2N_7O_2$	248	65	16.49	16.48
6.	4-OH, 3-OCH_3 C_6H_3	$C_{29}H_{29}Cl_2N_7O_4$	195	58	16.06	16.05
7.	4-Br. C_6H_4	$C_{29}H_{26}BrCl_2N_7O_2$	180	70	15.24	15.21
8.	3-NO_2 C_6H_4	$C_{28}H_{26}Cl_2N_8O_4$	279	73	18.39	18.38
9.	4-NO_2 C_6H_4	$C_{28}H_{26}Cl_2N_8O_4$	183	75	18.39	18.32
10	4-N,N$(CH_3)_2$ C_6H_4	$C_{30}H_{32}Cl_2N_8O_2$	218	57	18.44	18.41
11.	C_4H_3O (Furfuryl)	$C_{26}H_{25}Cl_2N_7O_3$	187	58	17.68	17.66

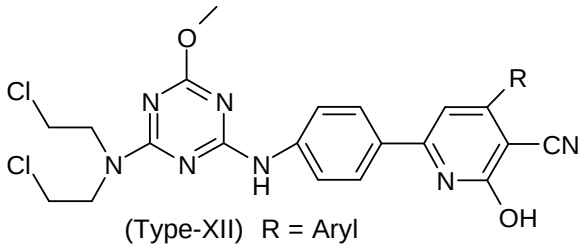
TABLE NO : 22 : ANTIMICROBIAL ACTIVITY OF 2-{4'-[(4"-ARYL)-3"-CYANO-2"-ETHOXY-PYRIDINE-6"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Antibacterial activity Zone of inhibition in mm.				Antifungal activity Zone of inhibition in mm.
		B. mega.	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5	18	17	17	20	20
2	2-OH C_6H_4	13	17	20	21	16
3	3-OH C_6H_4	22	19	21	23	18
4	4-OH C_6H_4	19	20	22	24	21
5	4-OCH_3 C_6H_4	19	15	17	18	17
6	4-OH, 3-OCH_3 C_6H_3	15	16	18	17	19
7	4-Br. C_6H_4	14	18	19	19	18
8	3-NO_2 C_6H_4	16	17	21	23	20
9	4-NO_2 C_6H_4	18	19	23	22	23
10	4-N,N$(CH_3)_2$ C_6H_4	16	12	18	16	17
11	C_4H_3O (Furfuryl)	14	13	18	19	18

SECTION : IV

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(4"-ARYL)-3"-CYANO-2", HYDROXY-PYRIMIDINE-6"-YL]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Pyridine derivatives have been found to possess wide range of therapeutic activities and industrial importance with a view of getting 2-{4'-[(4"-aryl)- 3"-cyano-2"-hydroxy pyridine-6"-yl] phenyl amino}-6-[Bis (2"'-chloroethyl) amino] -4-methoxy-1,3,5-triazine of Type-(XII) have been synthesised by the condensation of 2-{4'-[(3"-aryl)-2"-propene-1"-one]-phenyl amino}-6- [Bis (2"'- chloroethyl) amino]-4-methoxy-1,3,5-triazine with ethyl cyano acetate in the presence of ammonium acetate.

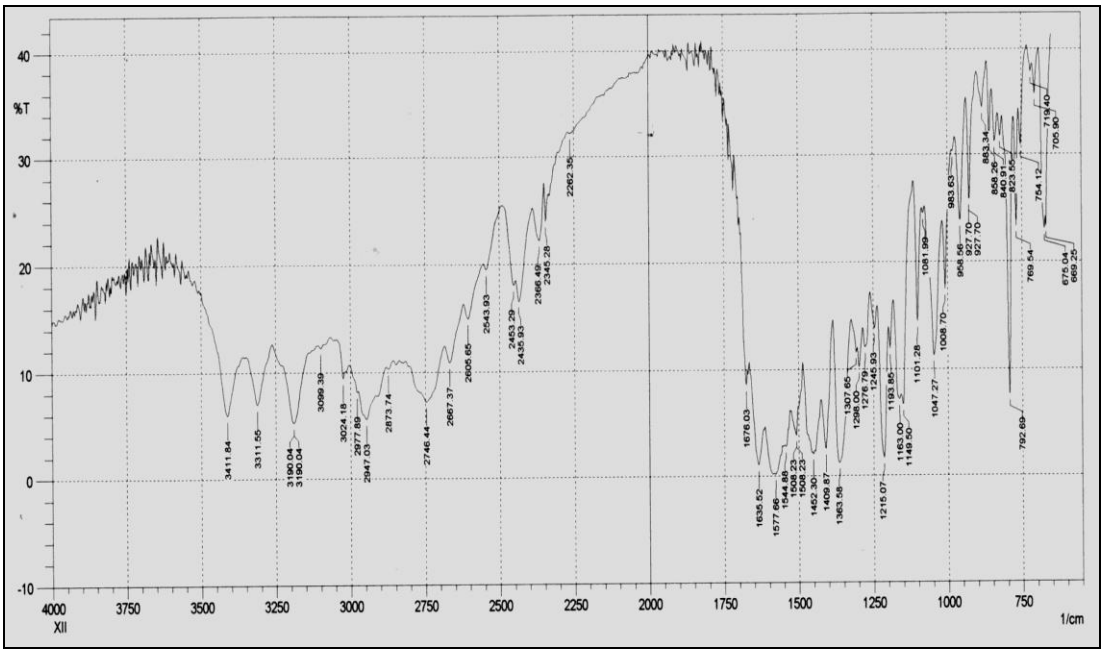


(Type-XII) R = Aryl

The constitution of the synthesised products have been characterised by elemental analysis IR, ^{1}H NMR, Mass spectral study. The products were screened for their antimicrobial activity at a concentration of 50 µg

The details have been cited in the part : I, Section : I, Page no. 39-41.

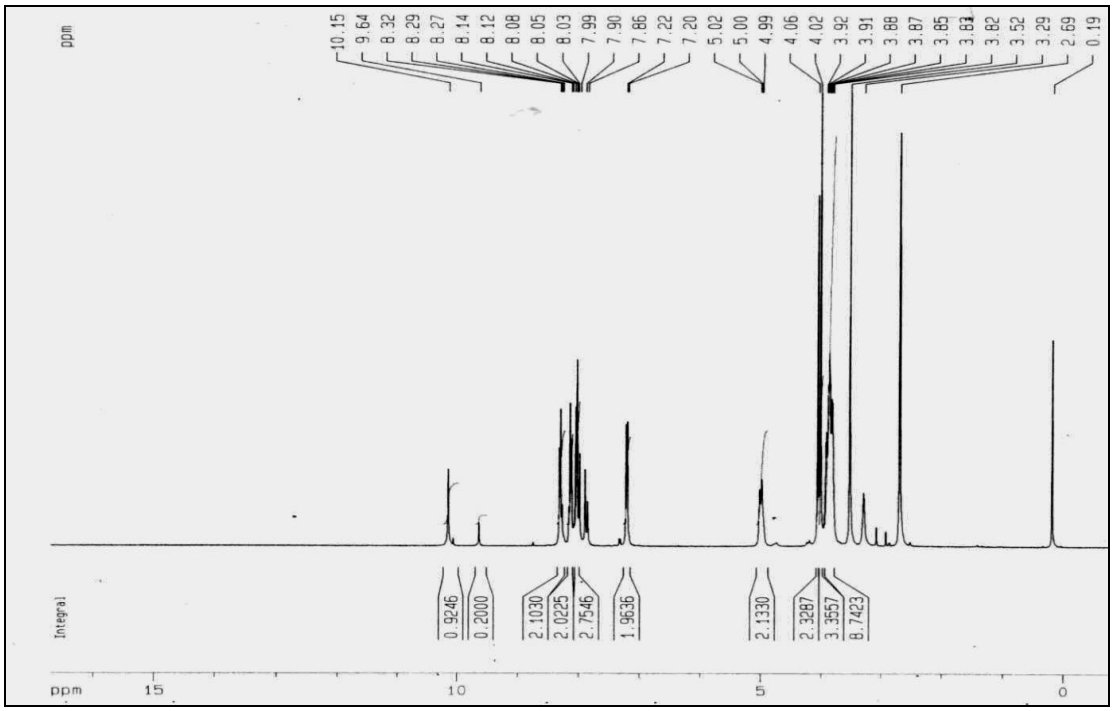
IR SPECTRAL STUDY OF 2-{4'-[4"-(4""METHOXY PHENYL)-3"-CYANO-2"-HYDROXY-PYRIDINE-6"YL] PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Instrument : SHIMADZU-FT-IR-8400, Spectrophoto meter frequency range : 4000-400 cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	reported	
Alkane	C-H Str.(asym)	2903	2990-2850	422 – 423
	C-H Str.(sym)	2873	2880-2860	
	C-H def.(asym)	1452	1470-1435	,,
	C-H def.(sym)	1363	1390-1360	,,
Aromatic	C-H Str.	3090	3090-3030	
	C-H i.p. def	1215	1300-1100	,,
	C-H o.o.p. def	823	832-800	
	C=C Str.	1452	1600-1450	,,
S-triazine	C-N Str.	1081	1220-1020	
	C=N Str.	1593	1630-1590	,,
Amine	N-H Str.	3311	3500-3310	,,
	N-H Bending	1635	1650-1550	
Ether	C-O-C Str.(asym)	1245	1260-1220	,,
	C-O-C Str.(sym)	1047	1075-1020	
Halide	C-Cl Str.	792	800-600	,,
Pyridine Nitrile	C=N Str.	2240	2240-2120	
	C-N Str.	1577	1650-1520	

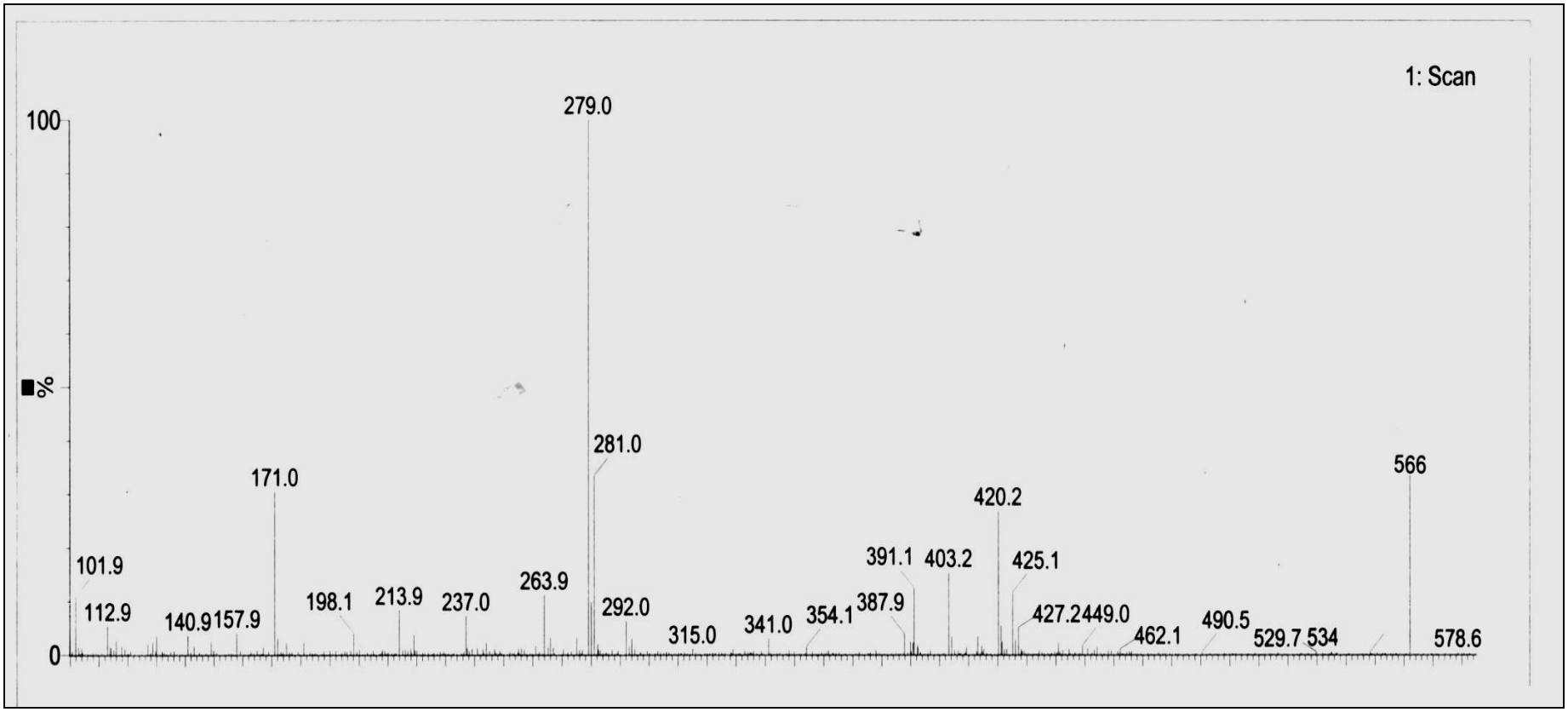
NMR SPECTRAL STUDY OF 2-{4'-[4"-(4""-METHOXY PHENYL)-3"-CYANO-2"-HYDROXY-PYRIDINE-6"YL]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Internal standard : TMS; solvent : DMSO ; Instrument : BRUKER spectrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.82-3.92	6 H	Singlet	Ar-OCH_3
2	7.20-7.90	4 H	D. Doublet	Ar-H_b
3	7.99-8.32	4 H	D. Doublet	Ar-H_c
4	4.99-5.02	4 H	Triplet	-CH_2-Cl
5	2.69-3.29	4 H	Triplet	-N-CH_2-
6	10.15	1 H	Singlet	Ar-NH_f
7	9.64	1 H	Singlet	Ar-OH_g
8	7.99-8.03	1 H	Singlet	Ar-OH_i

MASS SPECTRAL STUDY OF 2-{4'-[4"-(4""-METHOXY PHENYL-3"-CYANO-2"-HYDROXY-PYRIDINE-6"YL]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE. (M.W. : 566)



Antimicrobial Activity :

Conclution :

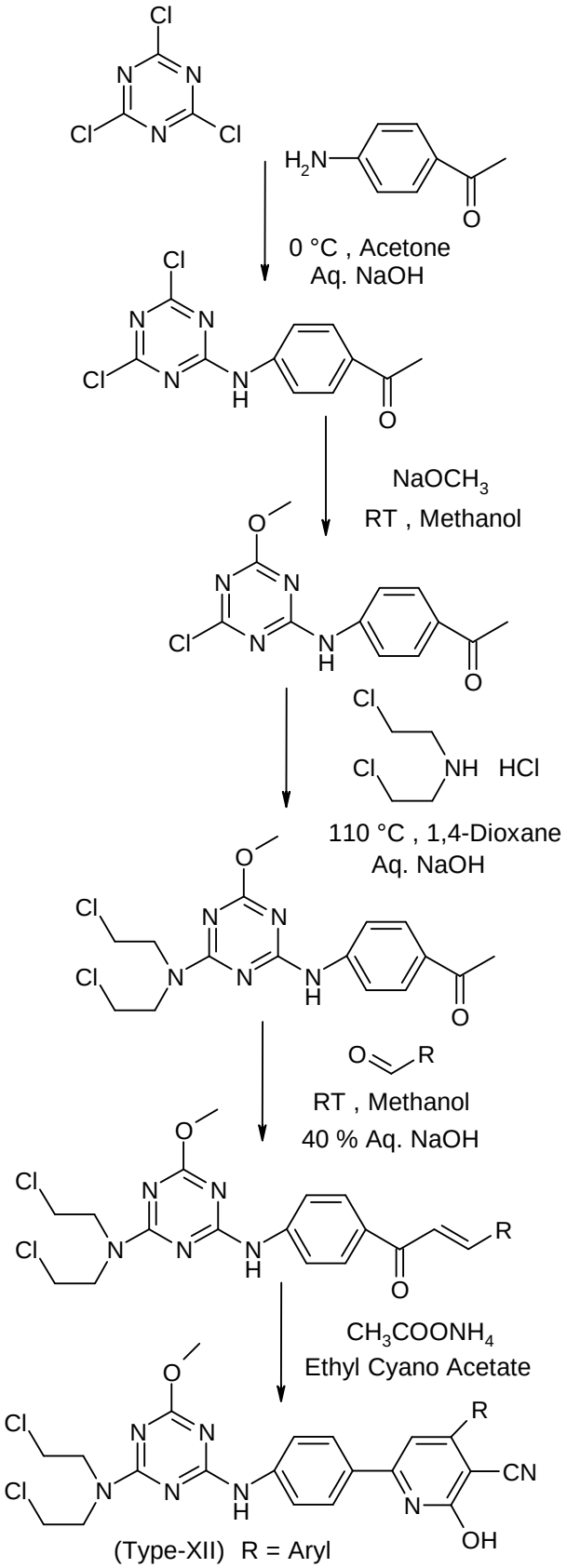
Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.			**Antifungal activity Zone of inhibition in m.m.**	
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	4-OH C_6H_4 (20)	4-OH C_6H_4 (19)	3-OH C_6H_4 (19)	4-OH C_6H_4 (23)	C_6H_5 (20)
	4-Br. C_6H_4 (23)	3-NO_2 C_6H_4 (20)	4-OH C_6H_4 (22)	4-Br. C_6H_4 (23)	4-OH C_6H_4 (21)
		4-NO_2 C_6H_4 (21)	4-OH, 3-OCH_3		4-Br C_6H_4 (23)
			C_6H_4 (19)		4-NO_2 C_6H_4 (22)
			4-NO_2 C_6H_4 (21)		

Comparable activity with known standard drugs

Ampicilin 50 µg.	23	18	17	27	-
Chloramphenicol "	24	19	25	26	-
Norfloxacin "	24	19	25	26	-
Greseofulvin "	-	-	-	-	23

RECATION SCHEME



(Type-XII) R = Aryl

EXPERIMENTAL

SYNTHESIS OF 2-{4'-[(4"-ARYL)-3"-CYANO-2"-HYDROXY-PYRIDIN-6"-YL]PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

(A) **Synthesis of 2-(4'-Acetyl phenyl amino)-4, 6-dichloro-1,3,5-triazine**

For synthesis see Part-I, Section-I, Page no. 36-38.

(B) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-chloro-4-methoxy-1,3,5-triazine.**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(C) **Synthesis of 2-(4'-Acetyl Phenyl amino)-6-[Bis (2"-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(D) **Synthesis of 2-{4'-[3"-(4""-Methoxy phenyl)-2"-propene-1"-one]phenyl amino}-6-[Bis (2"'-chloro ethylamino]-4- methoxy-1,3,5-triazine**

For synthesis, see Part-I, Section I, Page no. 36-38.

(E) **Synthesis of 2-{4'-[4"-(4""-Methoxy phenyl)-3"-cyano-2"-hydroxy) pyridine-6"-yl]-phenyl amino}-6-[Bis (2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine**

A mixture of 2-{4'-[3"-(4""-methoxyphenyl) -2"-propene-1"-one]phenyl amino}-6-[Bis. (2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine (5.02 gm,

0.01 M); ethyl cyano acetate (1.13 ml; 0.01M) and methanol (10 ml). The reaction mixtrue was refluxed for 10 hrs. at 100º C in presence of ammonium acetate. The reaction mixture was poured into crushed ice, filtered, dried and crystallised from dioxame, Yield : 65%, M.P. : 191º C. (Found : C : 57.21; H : 4.39; N : 17.30; $C_{27}H_{25}O_3N_7Cl_2$, required C : 57.24; H : 4.41; N : 17.31%)

Simillarly other compounds were synthesised and their physical data are recorded in Table no. 23.

(F) **Antimicrobial activity of 2-{4'-[(4"-Aryl)-3"-cyano -2"-hydroxypyridine-6"-yl]-phenyl amino}-6- [Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

The antimicrboial testing was carried out as described in Part-I, Section-I, Page NO. 39-41.

The zone of inhibition of the test solution are recorded in Table no. 24.

TABLE No : 23 : PHYSICAL CONSTANTS OF 2-{4'-[(4"-ARYL)-3"-CYANO -2"-HYDROXYPYRIDINE-6"-YL] -PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Molecular Formula	M.P. .c	Yield %	% of Nitrogen	
					Calcd	Found
1.	C_6H_5	$C_{26}H_{23}Cl_2N_7O_2$	235	63	18.28	18.28
2.	2-OH C_6H_4	$C_{26}H_{23}Cl_2N_7O_3$	230	51	17.75	17.70
3.	3-OH C_6H_4	$C_{26}H_{23}Cl_2N_7O_3$	228	57	17.75	17.71
4.	4-OH C_6H_4	$C_{26}H_{23}Cl_2N_7O_3$	238	65	17.75	17.72
5.	4-OCH_3 C_6H_4	$C_{27}H_{25}Cl_2N_7O_3$	191	65	17.31	17.30
6.	4-OH, 3-OCH_3 C_6H_3	$C_{27}H_{25}Cl_2N_7O_4$	232	68	16.83	16.82
7.	4-Br. C_6H_4	$C_{26}H_{22}BrCl_2N_7O_2$	192	63	15.93	15.91
8.	3-NO_2 C_6H_4	$C_{26}H_{22}Cl_2N_8O_4$	202	71	19.27	19.26
9.	4-NO_2 C_6H_4	$C_{26}H_{22}Cl_2N_8O_4$	118	53	19.27	19.25
10	4-N,N$(CH_3)_2$ C_6H_4	$C_{28}H_{28}Cl_2N_8O_2$	143	59	19.34	19.31
11.	C_4H_3O (Furfuryl)	$C_{24}H_{21}Cl_2N_7O_3$	235	64	18.83	18.82

TABLE NO : 24 : ANTIMICROBIAL ACTIVITY OF 2-{4'-[(4''-ARYL)-3''-CYANO-2''''-HYDROXY PYRIDIN-6''YL]- AMINO}-6-[BIS(2'''-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Antibacterial activity Zone of inhibition in mm.				Antifungal activity Zone of inhibition in mm.
		B. mega.	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5	13	16	14	16	20
2	2-OH C_6H_4	17	17	15	19	18
3	3-OH C_6H_4	19	16	19	18	17
4	4-OH C_6H_4	20	19	22	23	21
5	4-OCH_3 C_6H_4	18	15	18	20	19
6	4-OH, 3-OCH_3 C_6H_3	17	14	19	21	16
7	4-Br. C_6H_4	23	16	15	23	23
8	3-NO_2 C_6H_4	17	20	17	20	19
9	4-NO_2 C_6H_4	19	21	21	19	22
10	4-N,N$(CH_3)_2$ C_6H_4	14	14	15	16	18
11	C_4H_3O (Furfuryl)	17	12	18	15	19

PART - VI

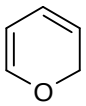
STUDIES ON CYANOPYRANS

STUDIES ON CYANOPYRANS

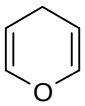
INTRODUCTION

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

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



1,2-dihydropyran



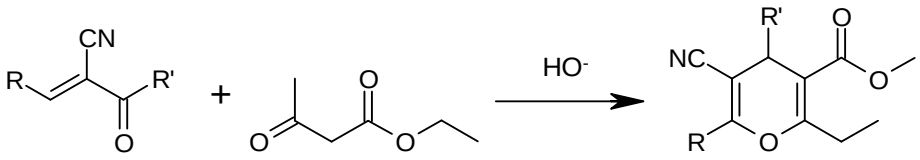
1,4-dihydropyran

SYNTHETIC ASPECT

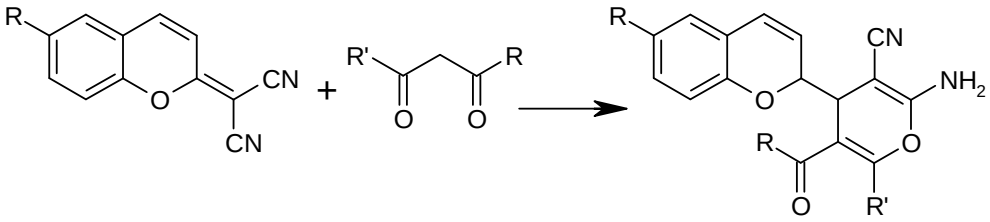
Various methods for the preparation of pyran derivatives have been cited in the literature[264-273]

1. Reaction between α,β-unsaturated carbonyl system with malononitrile led to correspnding 2-amino-3-cyano-4H-pyran[274]

2. A. Z. Elssar et al.[275] prepared 3-cyano-pyran derivatives by the reaction of α-cyano chalcone derivative with $C_2H_5COCH_2COOCH_3$ in basic medium.

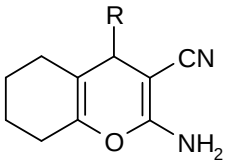


3. H. Abdel - Ghyan et. al.[276] have been synthesized cyano derivatives by the reaction of 2-coumariylidene malononitrile with active methylene containing compounds.



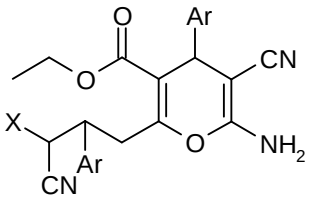
4. β-Siloxy acrylonitrile were reacted with chalcones to furnish the respective cyano-4H-pyran derivatives[277]

5. M. G. Assay et al.[278] have synthesized some cyanopyran derivatives by the reaction of cyclohexane with cinnamon nitriles.



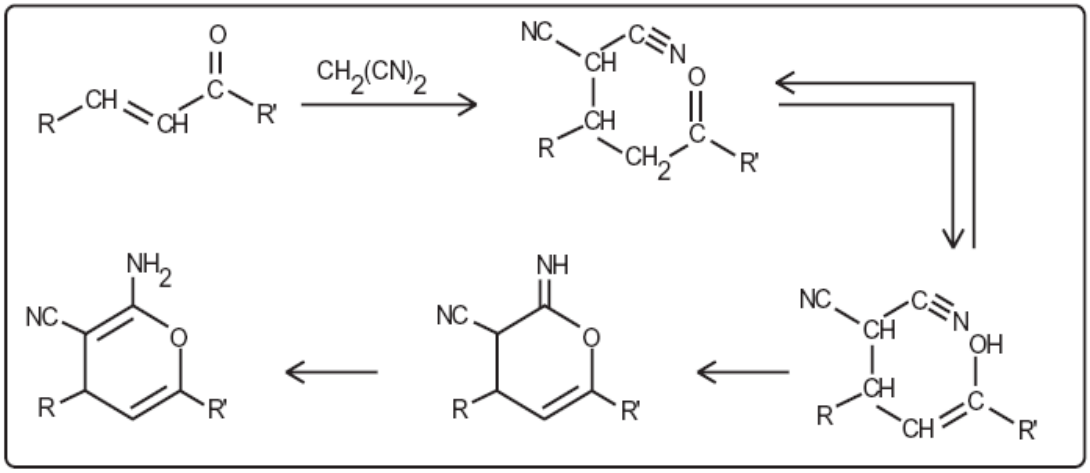
6. R. De Lera Angel and co-workers[279] synthesized pyran derivatives by thermal electrolytic ring closure of divinylallenals.

7. In recent, A. M. Hussein and et al.[280] prepared some novel derivatives of cyanopyran.



REACTION MECHANISM

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

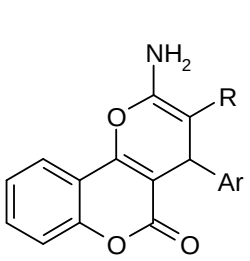


THERAPEUTIC IMPORTANCE

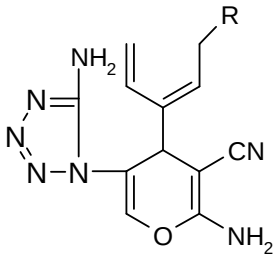
Polysubstituted pyran derivatives are biologically interesting class of compounds[281-282] They are associated with various pharmaceutical properties like.

1. Anticancer[283]
2. Antiinvasive[284]
3. Anti-HIV[285,286]
4. Antiallergic[287]
5. Antifungal[288,289]
6. Cytotoxic[290]
7. Antitumor[291]
8. Antiviral[292]
9. Antipyratic[293]
10. Analgesic[294]

M. A. AI-Haiza and co-workers[295] prepared some cyanopyran derivatives (I) and tested their antibacterial and antifungal activities. A. V. Samet[296] et al. synthesized 2-amino-5-azolyl-3-cyano-4H-pyrans (II) and evaluated for biological activity. A. Z. Elassar et al.[297] reported that cyanopyran exhibited in vitro antifungal and antibacterial activities.

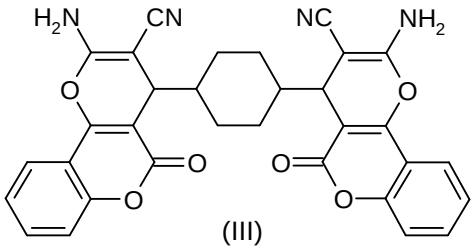


(I)



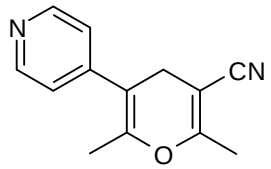
(II)

Moreover, R. M. Shaker.[298] have prepared some coumarin ring containing 2-amino-3-cyanopyran (III) derivatives and studied their antimicrobial activity. Y. D. Kulkarni and co-workers[299] synthesized some pyran derivatives as CNS active agents. A. A. Hassainien et al.[300] prepared 2-amino-3-cyano-7, 7-dimethyl-4-substituted phenyl-5-oxo-4,5,6,8-tetrahydropyran and tested for their biological activities.



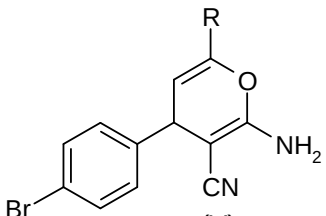
(III)

Further more, A. Krauze et al.[301] synthesized 5-(4-pyridyl) derivatives of 2-amino-4H-pyran (IV) for antimicrobial activity. S. Fowzia, Al-Saleh[302] and coworkers synthesized some new cyanopyran derivatives and reported as antimicrobial agents. Some pyran derivatives have been pantented for their use as gastric acid secretion inhibitors[303] inhibitors of cell proliferation[304] antihypertensive[305] antitumor[306] antagonists[307-308] and antiviral agents[309]



(IV)

H. S. Joshi et al.[310] and co-workers recently have synthesized some new cyano pyran (V) derivatives as anticancer and antimicrobial agents.



(V)

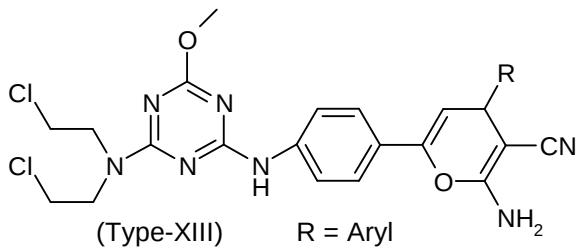
Thus with an effort to capitalize the biological potential of the heterocyclic system and to synthesize interesting compounds having better biological potential, the titled compounds have been investigated which have been described as under.

SECTION : I : SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(2"- AMINO-4"-ARYL-4"-(H)-PYRAN-3-(CARBONITRILE)-6"-YL]-PHENYLAMINO}-6-[BIS (2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE.

SECTION : I

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(2"- AMINO-4"-ARYL-4"-(H)-PYRAN-3-(CARBONITRILE)-6"-YL]-PHENYLAMINO}-6-[BIS (2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Cyanopyran derivatives have been reported to have various pharmalogical activities like antibacterial, antiviral, antifungal etc. In order to develop better medicinally important componds. It was considered of interest to synthesised some cyanopyran derivatives shown as under. Cyanopyran derivatives of 2-{4'[(2"-amino-4"-(H)-pyran-3-carbonitrile)-6"-yl]-phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine of Type (XIII) have been synthesised by the reaction of chalcones of Type (I) with malononitrile in pyridine.

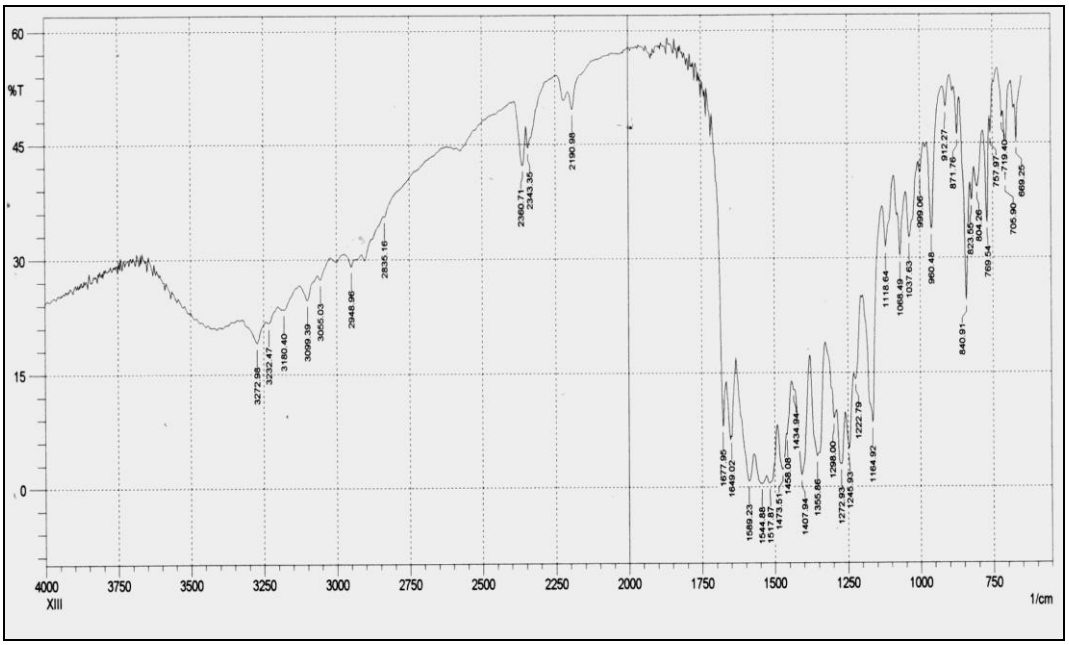


(Type-XIII) R = Aryl

The constitution of the products have been characterised by elemental analysis IR, ^{1}H NMR, Mass spectral study. The products were screened for antimicrobial activity at concentration of 50 µg.

The details have been cited in the Part : I, Section I, Page No. 39-41.

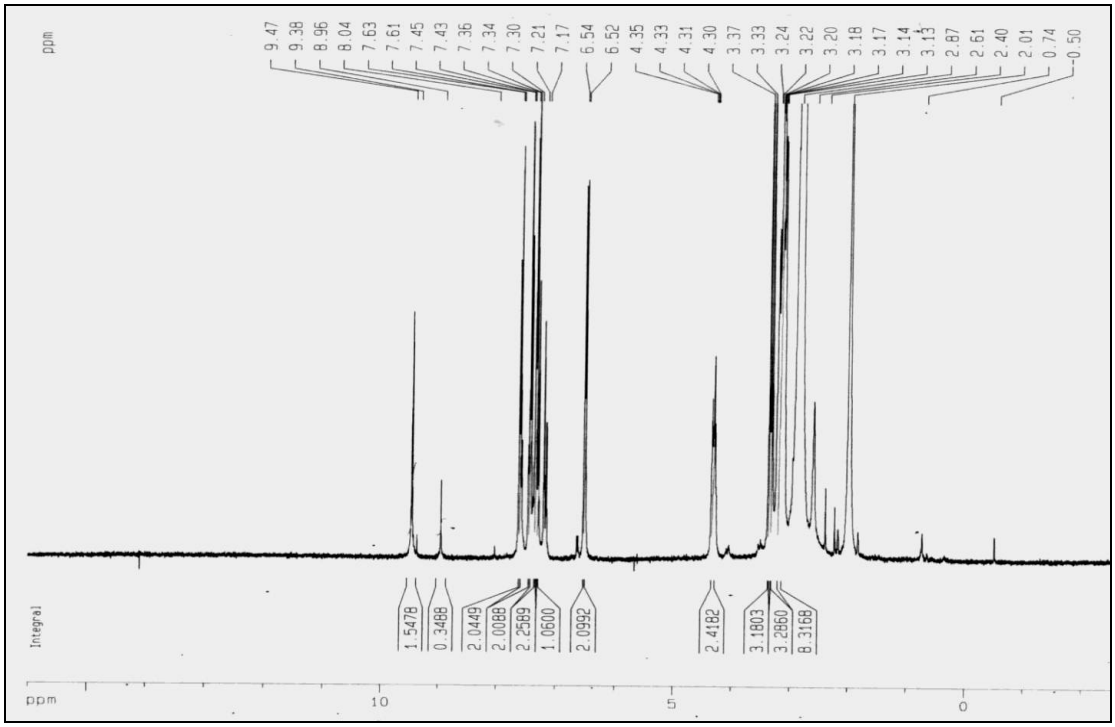
IR SPECTRAL STUDY OF 2-{4'-[2"- AMINO-4"-(4""-METHOXYPHENYL) -4"-(H)-PYRAN-3-(CARBONITRILE-6"-YL]-PHENYLAMINO}-6-[BIS(2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Instrument : SHIMADZU-FT-IR-8400, Spectrophotometer frequency; range : 4000-400 cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	reported	
Alkane	C-H Str.(asym)	2948	2990-2850	422 – 423
	C-H Str.(sym)	2889	2880-2860	,,
	C-H def.(asym)	1458	1470-1435	
	C-H def.(sym)	1355	1390-1360	,,
Aromatic	C-H Str.	3055	3090-3030	
	C-H i.p. def	1164	1300-1100	,,
	C-H o.o.p. def	823	832-800	
	C=C Str.	1458	1600-1450	,,
S-triazine	C-N Str.	1068	1220-1020	,,
	C=N Str.	1593	1630-1590	
Amine	N-H Str.	3405	3500-3310	,,
	N-H Bending	1649	1650-1550	
Ether	C-O-C Str.(asym)	1245	1260-1220	,,
	C-O-C Str.(sym)	1068	1075-1020	
Halide	C-Cl Str.	769	800-600	,,
Pyran Nitrile	N=N Str.	3272	3350-3250	,,
	C=N Str.	2190	2240-2120	
	C-N Str.	1589	1650-1520	

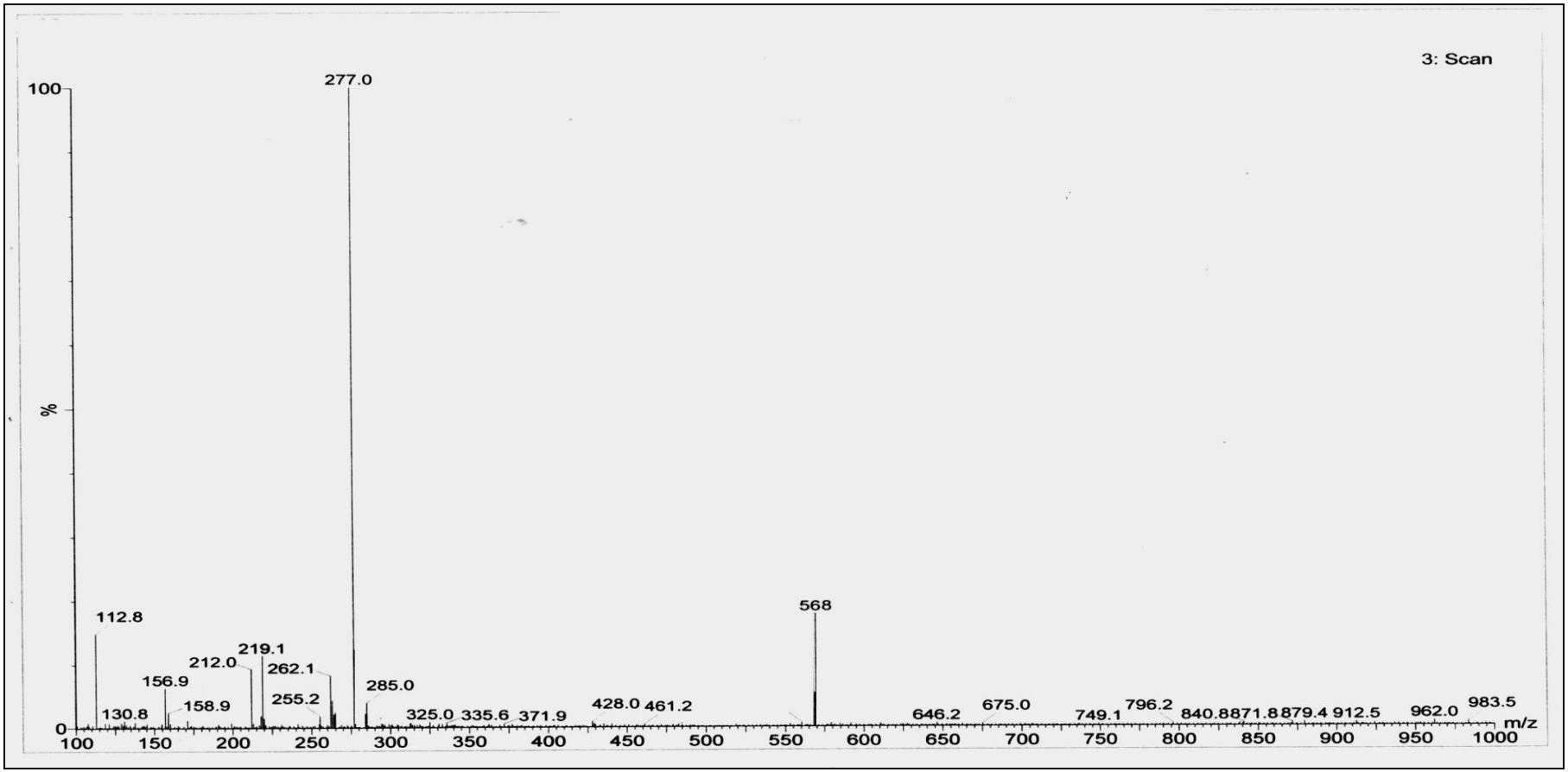
NMR SPECTRAL STUDY OF 2-{4'-[(2"- AMINO- 4" - (4"" - METHOXYPHENYL) - 4" - (H) – PYRAN – 3 - (CARBONITRILE - 6" – YL] -PHENYLAMINO}-6-[BIS-(2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Internal standard : TMS; solvent : DMSO ; Instrument : BRUKER spectrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.33-3.37	6 H	Singlet	Ar-OCH_3
2	7.17-7.63	4 H	D. Doublet	Ar-H_b
3	8.04-8.96	4 H	D. Doublet	Ar-H_c
4	4.30-4.35	4 H	Triplet	-CH_2-Cl
5	2.40-2.87	4 H	Triplet	-N-CH_2-
6	8.96	1 H	Singlet	Ar-NH_f
7	9.38-9.47	2 H	Singlet	Ar-$NH_{2\ g}$
8	6.52-6.54	1 H	Singlet	Ar-H_i

MASS SPETRAL STUDY OF 2-{4'-[2"- AMINO- 4" - (4"" -METHOXYPHENYL) - 4" - (H) – PYRAN – 3 - (CARBONITRILE -6"-YL]-PHENYLAMINO}-6-[BIS (2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE. (M.W. : 568)



Antimicrobial Activity :

Conclution :

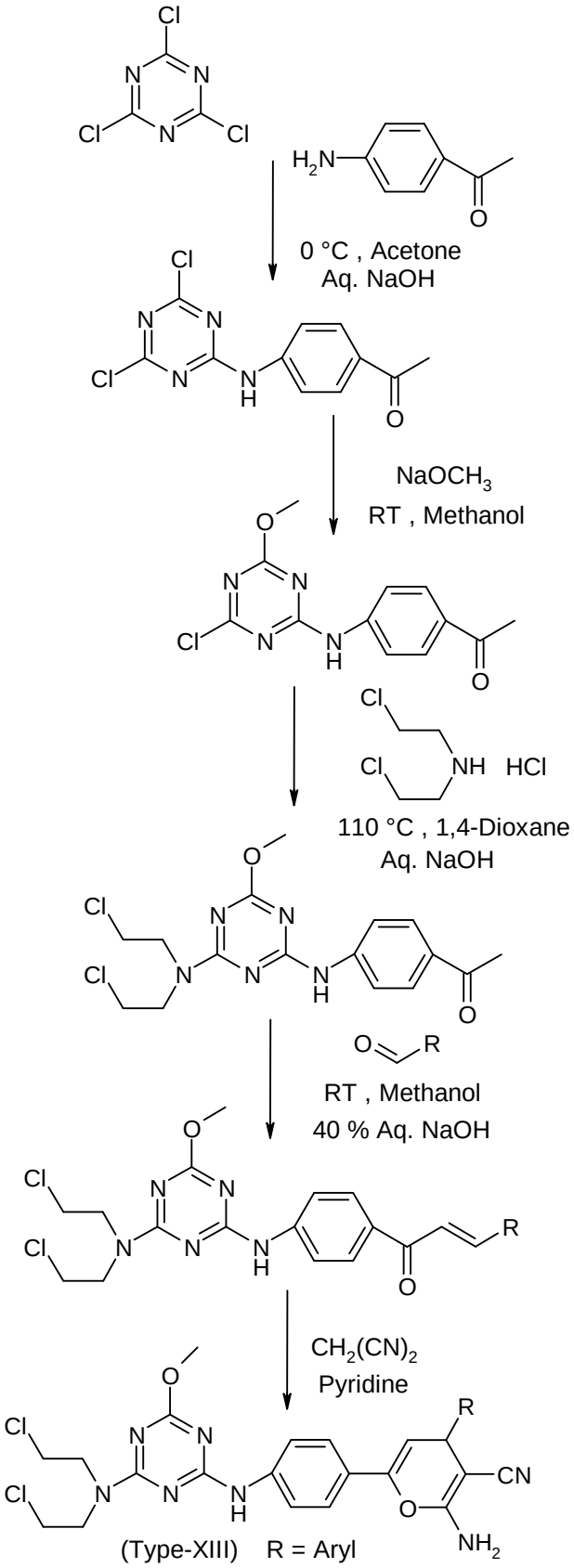
Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.				**Antifungal activity Zone of inhibition in m.m.**
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	C_6H_5 (21)	4-OH C_6H_4(18)	3-OH C_6H_4(20)	3-OH C_6H_4(23)	4-OH C_6H_4(21)
	4-OH C_6H_4(20)	3-NO_2 C_6H_4(18)	4-OH C_6H_4(21)	4-OH C_6H_4(24)	4-Br C_6H_4(22)
	4-NO_2 C_6H_4(21)	4-NO_2 C_6H_4(20)	4-NO_2 C_6H_4(22)	4-Br C_6H_4(22)	
				C_4H_3O(23)	

Comparable activity with known standard drugs

Ampicilin	50 µg	23	18	17	27	-
Chloramphenicol	"	24	19	25	26	-
Norfloxacin	"	24	19	25	26	-
Greseofulvin	"	-	-	-	-	23

REACTION SCHEME



(Type-XIII) R = Aryl

EXPERIMENTAL

SYNTHESIS OF 2-{4'-[(2"- AMINO-4"-ARYL-4"-(H)-PYRAN-3-CARBO NITRILE)-6"-YL]-PHENYLAMINO}-6-[BIS (2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE.

(A) **Synthesis of 2-(4'-Acetyl phenyl amino)-4, 6-dichloro-1,3,5-traizine.**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(B) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-chloro-4-methoxy-1,3,5-trazine.**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(C) **Synthesis of 2-(4'-Acetyl phenyl amino-6-[Bis(2"-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(D) **Synthesis of 2-{4'-[3"-(4""-Methoxy phenyl)-2"-propene-1"-one] phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4- methoxy-1,3,5-triazine.**

For synthesis, see Part-I, Section-1, Page no. 36-38.

(E) **Synthesis of 2-{4'-[2"-Amino-4"-(4""-methoxy phenyl)-4"-(H)-pyran-3-carbonitrile-6"-yl]-phenyl amino}-6-[Bis - (2"'-chloro ethyl) amino]-4-methoxy-1,3,5 - triazine.**

A mixture of 2-{4'-[3"-(4""-methoxy phenyl)-2"- propene-1"-one] phenyl amino}-6-[Bis- (2"'-chloroethyl) amino]-4-methoxy-1,3,5- triazine (5.02 gm,

0.01M) and malonontirile (0.66 gm, 0.01 M) in Pyridine (10 ml). The reaction mixture was reluxed for 12 hrs. at 120º C. The reaction mixture was poured into crushed ice, filtered, dried and crystallised from dixoane, yield : 67%, M. P. : 101º C. (Found : C : 57.01; H : 4.72; N : 17.21; $C_{27}H_{27}O_3N_7Cl_2$ required C : 57.04; H : 4.75; N : 17.25%)

Simillarly other compounds were synthesised and their physical data are recorded in Table no. 25.

(F) **Antimicrobial activity of 2-{4'-[(2"-Amino-4"-aryl-4"-(H)-pyran-3-carbo nitrile)-6"-yl]-phenyl amino}-6-[Bis (2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

The antimicrobial testing was carried out as described in Part-I, Section-I, Page No. 39-41.

The zone of inhibition of the test solution are recorded in Table no. 26.

TABLE NO : 25 : PHYSICAL CONSTANTS OF 2-{4'-[(2"- AMINO-4"-ARYL-4"-(H)-PYRAN-3-CARBONITRILE)-6"-YL]-PHENYLAMINO}-6-[BIS (2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Molecular Formula	M.P. .c	Yield %	% of Nitrogen	
					Calcd	Found
1.	C_6H_5	$C_{26}H_{25}Cl_2N_7O_2$	157	58	18.21	18.20
2.	2-OH C_6H_4	$C_{26}H_{25}Cl_2N_7O_3$	198	62	17.68	17.66
3.	3-OH C_6H_4	$C_{26}H_{25}Cl_2N_7O_3$	205	65	17.68	17.67
4.	4-OH C_6H_4	$C_{26}H_{25}Cl_2N_7O_3$	192	70	17.68	17.52
5.	4-OCH_3 C_6H_4	$C_{27}H_{27}Cl_2N_7O_3$	101	97	17.25	17.21
6.	4-OH, 3-OCH_3 C_6H_3	$C_{27}H_{27}Cl_2N_7O_4$	117	68	16.78	16.75
7.	4-Br. C_6H_4	$C_{26}H_{24}BrCl_2N_7O_2$	205	81	15.88	15.83
8.	3-NO_2 C_6H_4	$C_{26}H_{24}Cl_2N_8O_4$	215	83	19.21	19.19
9.	4-NO_2 C_6H_4	$C_{26}H_{24}Cl_2N_8O_4$	229	79	19.21	19.18
10	4-N,N$(CH_3)_2$ C_6H_4	$C_{28}H_{30}Cl_2N_8O_2$	112	73	19.27	19.23
11.	C_4H_3O (Furfuryl)	$C_{24}H_{23}Cl_2N_7O_3$	145	83	18.56	18.53

TABLE NO : 26 : ANTIMICROBIAL ACTIVITY OF 2-{4'-[(2"- AMINO-4"-ARYL-4"-(H)-PYRAN-3-CARBONITRILE)-6"-YL]-PHENYLAMINO}-6-[BIS (2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	**R**	**Antibacterial activity Zone of inhibition in mm.**			**Antifungal activity Zone of inhibition in mm.**	
		B. mega.	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5	21	14	17	20	17
2	2-OH C_6H_4	18	13	15	21	18
3	3-OH C_6H_4	19	16	20	23	19
4	4-OH C_6H_4	20	18	21	24	21
5	4-OCH_3 C_6H_4	11	14	19	18	18
6	4-OH, 3-OCH_3 C_6H_3	17	16	17	17	17
7	4-Br. C_6H_4	15	15	18	22	22
8	3-NO_2 C_6H_4	16	18	19	17	15
9	4-NO_2 C_6H_4	21	20	22	19	16
10	4-N,N$(CH_3)_2$ C_6H_4	15	12	18	18	16
11	C_4H_3O (Furfuryl)	12	13	17	23	18

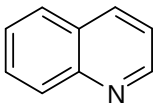
PART - VII

STUDIES ON QUINOXALINES

STUDIES ON QUINOXALINES

INTRODUCTION

The quinoxaline or benzopyrazine (I) are the product formed by spontaneous condensation of o-phenylene diamine with 1, 2-dicarbonyl compounds.



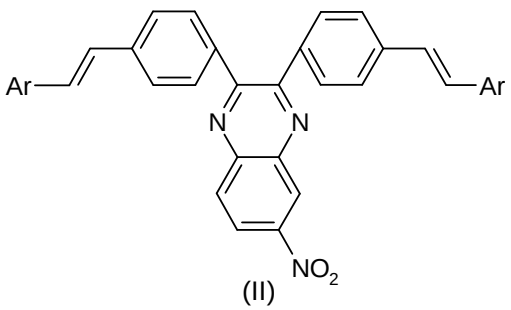
(I)

This reaction was discovered by Korner[311] and by Hinsberg[312] independently. Since quinoxalino are also obtained when $\alpha - \beta$ -dihalo ketones condensed with o-phenyliene diamine. The structure of these cyclic base are obvious from the mode of formatiora and analytical data. The ring structure was further confirmed by Gabriel. who demonstrated experimentally the relationship between the quinoxaline and the pyrazines by oxidizing quinoxaline to pyrazine-2, 3-dicarboxylic acid.

SYNTHETIC ASPECT

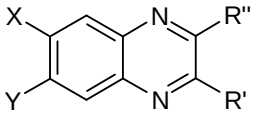
Different methods are available in literature[313-316] for the preparation of quinoxalines. The popular methods are :

(1) M. L. Keshtov and co-worker[317] have been prepared dimer type quinoxaline derivatives (II).



(II)

(2) Quinoxaline derivative[318] (III) are prepared by reaction of Nitrobenzene with NH_2OR in presence of Cu catalyst and reaction of nitroanilines and presence of hydrogenation catalyst.



(III)

(3) S K. Kanungo et. al.[319] have prepared 1, 3-Dimethylpyrrolo quinoxaline-2-ones from chloroacetic acid and o-phenylene diamine.

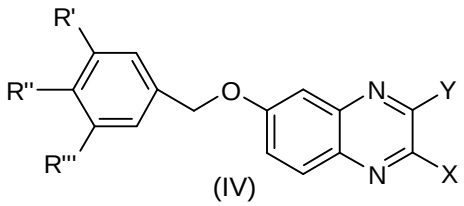
THERAPEUTIC IMPORTANCE

Quinoxaline derivatives have been found to possess wide range of terapeutic activities.

1. Inhibition of Candida albicans[320]
2. CNS depressant[321-322]
3. Antitubercular[323]
4. Antiulcer[324-325]
5. Analgesic[326]
6. Anxiolytic[327]
7. Antihypertensive[328]
8. Antitumor[329]
9. Cardiovascular[330]
10. Herbicidal[331]
11. Antifungal[332]

1-(Aminoalkyl)-3-quinoxaline-2-one derivatives were prepared as neuroprotective agents by K. Ehrenberger and F. Dominik[333]. A new series of sulphonamido quinoxaline were synthesised and assessed for various biological activity[334], antibiotics action of some novel quinoxaline derivative were studied by T. V. Alfreson[335] and co-workers.

V.Gabriella and co-workers[336] have formulated some new quinoxaline. derivative (IV) as in vitro anticancer activity.



(IV)

Recently, serveral co-workers have been prepared quinoxaline derivatives by different methods which possess AMPA receptor antagonist and antihistaminic [337-339], antagonist[340-341], human dopamine D4 receptor[342], antibacterial[343], antimicrobial[344-346], anticancer[347], and antitumor[348] activities.

More recently, B. Konig et al.[349] have synthesised quinoxaline derivatives which has activation of PPARa and PPAR gamma reduces triacyglycerol G. Sarodirick, T. G. Linker et al.[350] have prepared quinoxaline. derivatives having bactericidal, algecide, fungicide activity for agriculture use. Quinoxaline derivative used PDGE receptor and LCK tyrosine kinase inhibitors.

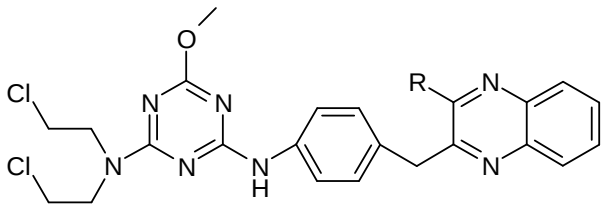
In order to achieve better therapeutic agent, the preparation of quinoxaline derivatives has been taken as under.

SECION : I : SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF [2"-ARYL(QUINOXALINE)-3-YL]-(METHYLENE PHENYL AMINO)-6-[BIS(2"'-CHLOROETHYL)AMINO]-4-METHOXY-1,3,5-TRIAZINE.

SECTION : I

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF [2"-ARYL(QUINOXALINE)-3-YL]-(METHYLENE PHENYL AMINO)-6-[BIS-(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Quinoxalines have been found to possess wide range of therapeutic activities and industrial importance. In view of getting [2"-aryl-(quinoxaline)-3-yl]-(methylene phenyl amino)-6-[Bis(2"'-chloroethyl-amino]-4-methoxy-1,3,5-triazine of Type-(XIV) have been synthesised by the condensation of 2-{4'-[(3"-aryl)-2"-propene-1"-one]-phenylamino}-6-[Bis(2"'- chloroethyl amino]-4-methoxy-1,3,5-triazine. of Type-(I) with bromine in glacial actetic acid and o-phenylenediamine.

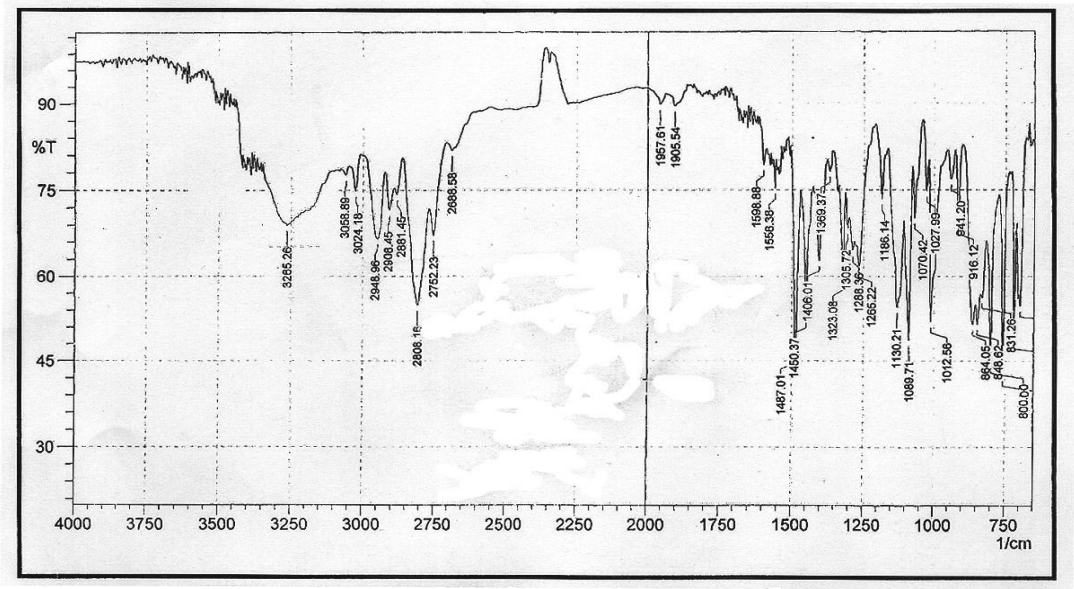


(Type-XIV) R = Aryl

The constitution of the products have been charactrised by elemental analysis IR, ^{1}H NMR, Mass spectral study. The products were screened for antimicrobial activity at a concentration of 50 µg.

The details have been cited in the Part : I, Section I, Page No. 39-41.

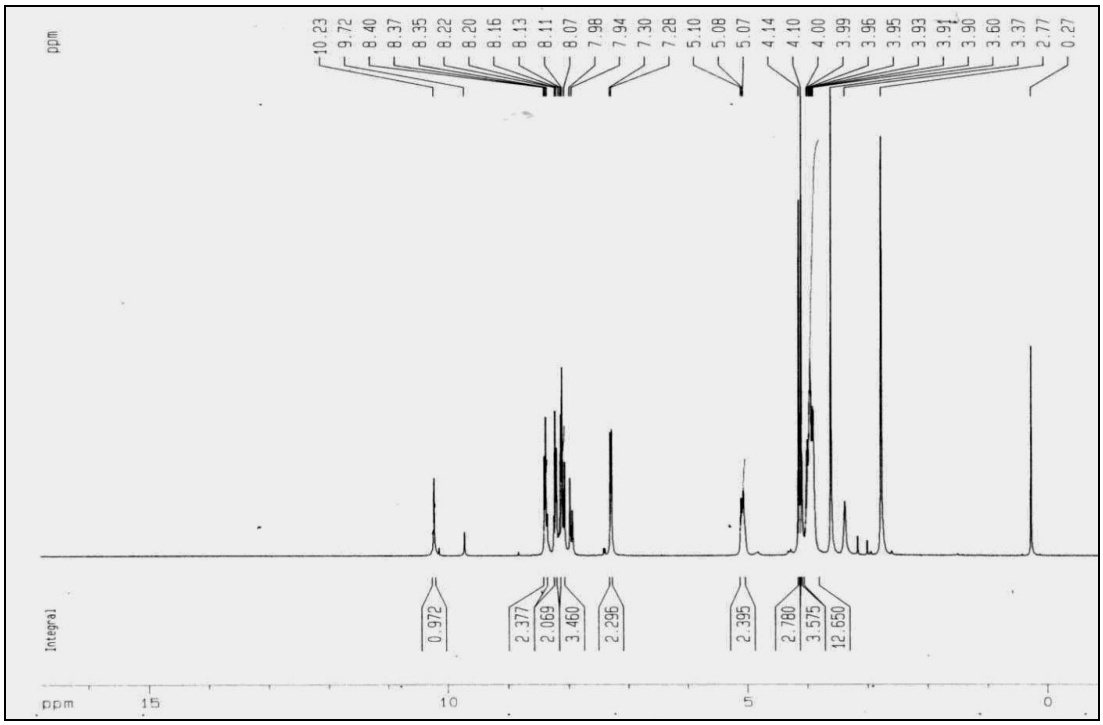
IR SPECTRAL STUDY OF [2"-(4""-METHOXYPHENYL) (QUINOXALINE)-3YL]-(METHYLENE PHENYL AMINO)-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Instrument : SHIMADZU-FT-8400, Spectrophoto meter frequency range : 4000-400 cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	reported	
Alkane	C-H Str.(sym)	2900	2990-2850	422 – 423
	C-H Str.(sym)	2881	2880-2860	,,
	C-H def.(sym)	1450	1470-1435	
	C-H def.(sym)	1369	1390-1360	,,
	$-CH_2$ Str.	1450	1485-1445	
Aromatic	C-H Str.	3058	3090-3030	,,
	C-H i.p. def	1265	1300-1100	
	C-H o.o.p. def	800	832-800	,,
	C=C Str.	1487	1600-1450	,,
S-triazine	C-N Str.	1070	1220-1020	
	C=N Str.	1598	1630-1590	,,
Amine	N-H Str.	3315	3500-3310	
	N-H Bending	1558	1650-1550	,,
Ether	C-O-C Str.(asym)	1265	1260-1220	
	C-O-C Str.(sym)	1070	1075-1020	,,
Halide	C-Cl Str.	800	800-600	,,
Quinoxalines	C=N Str.	1608	1630-1590	
	C-N Str.	1089	1220-1020	

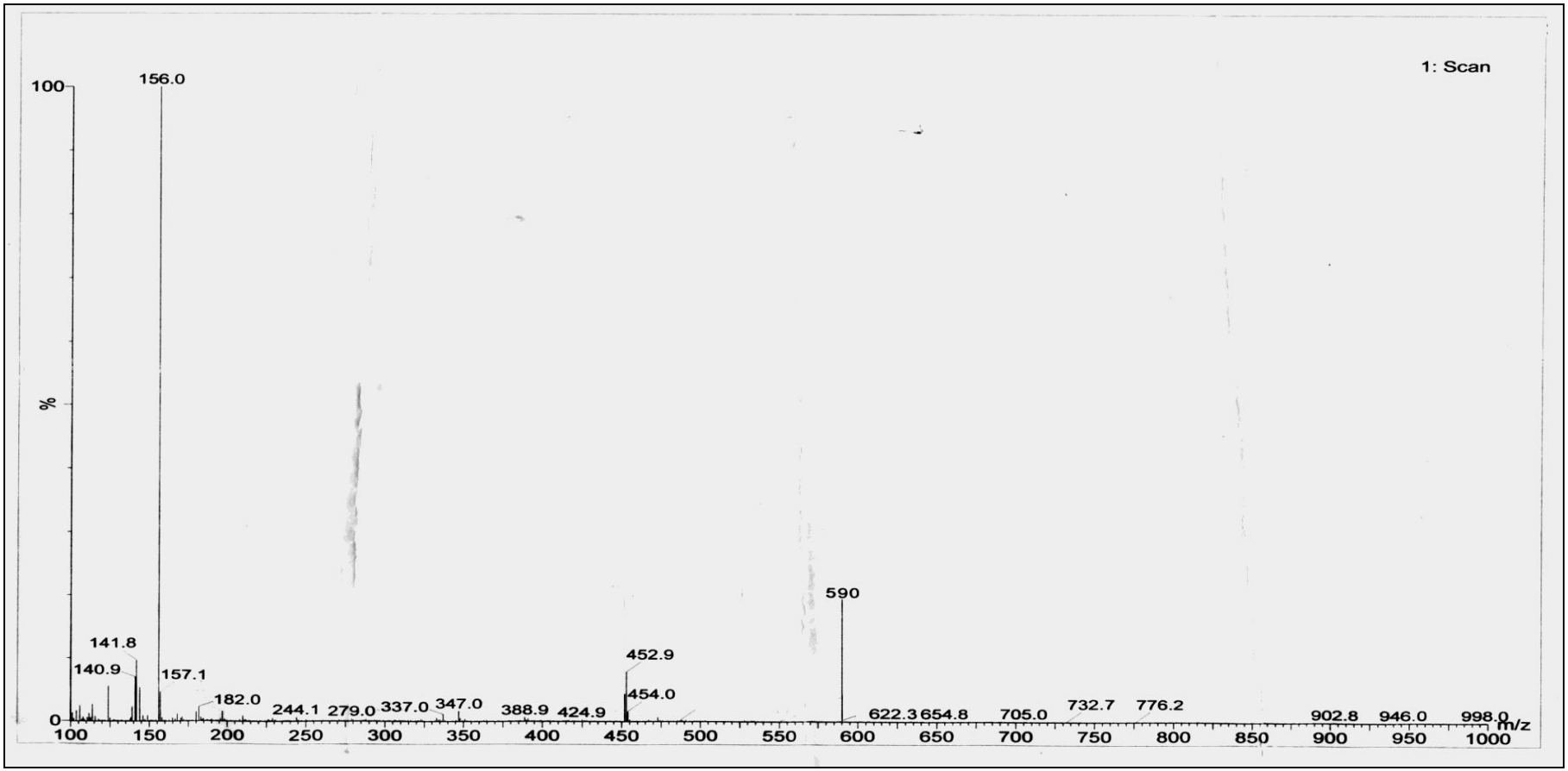
NMR SPECTRAL STUDY OF [2"-(4""-METHOXYPHENYL) (QUINOXALINE)-3YL]-(METHYLENE PHENYL AMINO)-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Internal standard : TMS; solvent : DMSO ; Instrument : DMSO spectrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.60-4.00	6 H	Singlet	Ar-OCH_3
2	7.94-7.98	4 H	D. Doublet	Ar-H_b
3	8.07-8.40	4 H	D. Doublet	Ar-H_c
4	4.10-4.14	4 H	Triplet	-CH_2-Cl
5	2.77	4 H	Triplet	-N-CH_2-
6	10.23	1 H	Singlet	Ar-NH_f
7	3.37	2 H	Singlet	Ar-H_g
8	7.28-8.07	4 H	Multiplate	Ar-H_i

MASS SPECTRAL STUDY OF [2"-"-(4""-METHOXYPHENYL) (QUINOXALINE)-3-YL]-(METHYLENE PHENYL AMINO)-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE. (M.W. : 590)



Antimicrobial Activity :

Conclution :

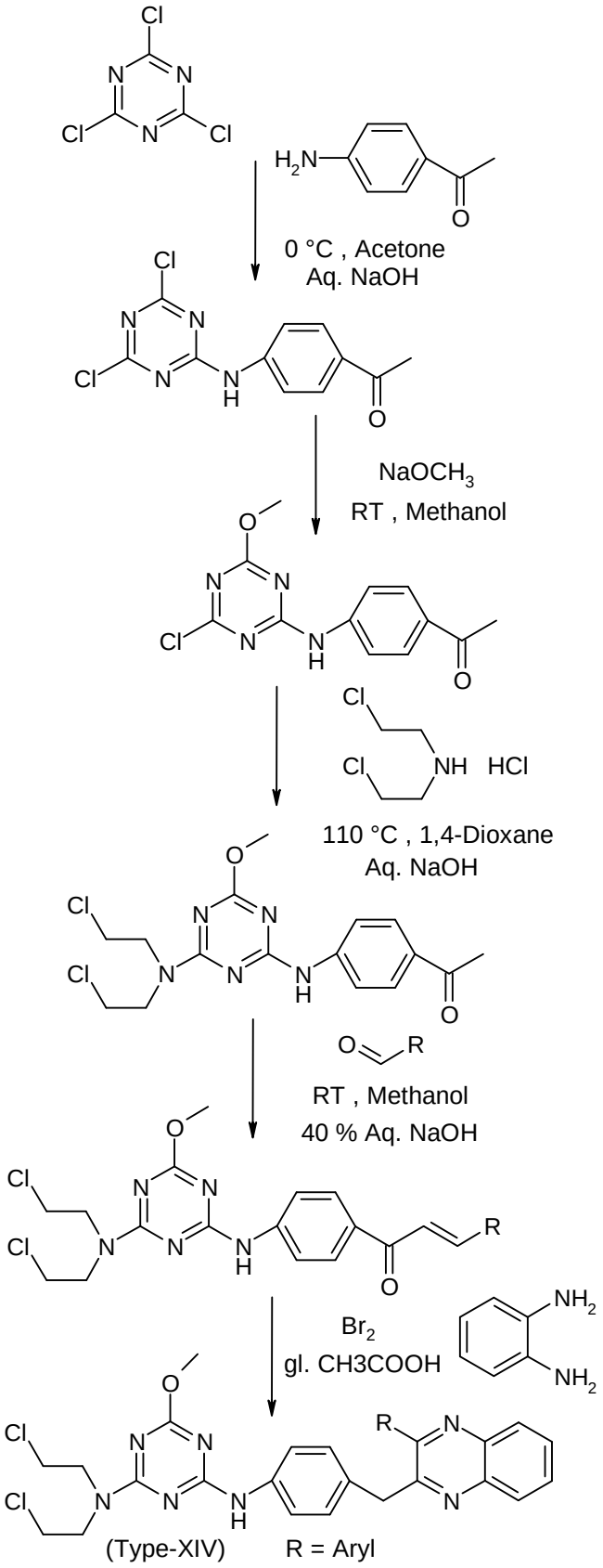
Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.			**Antifungal activity Zone of inhibition in m.m.**	
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	2-OH C_6H_4 (24)	C_6H_5 (19)	3-OH C_6H_4 (21)	4-OH C_6H_4 (22)	4-OH, $3OCH_3$ C_6H_4 (20)
	4-OH C_6H_4 (23)	4-OH C_6H_4 (21)	4-Br C_6H_4 (20)	4-OCH_3 C_6H_4 (23)	4-NO_2 C_6H_4 (23)
	4-NO_2 C_6H_4 (21)	$3NO_2$ C_6H_4 (19)	4-N,N $(CH_3)_2$	4-NO_2 C_6H_4 (21)	
		4-NO_2 C_6H_4 (21)	C_6H_4 (22)		

Comparable activity with known standard drugs

Ampicilin	50 µg	23	18	17	27	-
Chloramphenicol	"	24	19	25	26	-
Norfloxacin	"	24	19	25	26	-
Greseofulvin	"	-	-	-	-	23

REACTION SCHEME



(Type-XIV) R = Aryl

EXPERIMENTAL

SYNTHESIS OF [2"-ARYL(QUINOXALINE)-3YL]-(METHYLENE PHENYL AMINO)-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

(A) **Synthesis of 2-(4'-Acetylphenyl amino)-4, 6-dichloro-1,3,5-triazie.**

For synthesis, see Part-I, Section-I, Page No. 36-38.

(B) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-chloro-4-methoxy-1,3,5-triazine.**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(C) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-[Bis (2"-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For Synthesis, see Part-I, Section-I, Page no. 36-38.

(D) **Synthesis of 2-{4'-[3"-(4""-Methoxy phenyl)-2"- propene-1"-one] phenyl amino}-6-[Bis(2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis, see Part-I, Section-I, Page No. 36-38.

(E) **Synthesis of 2-{4'-[3"-(4""-Methoxy phenyl)-2", 3"-dibromo-1"-one] phenyl amino}-6-[Bis (2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

A chalcones of Type (I) 0.01 M was dissoved in acetic acid (30 ml) a bromine in acetic acid (1 ml) 10% was slowly added to it. The reaction mixture was stirred for 2 hrs. It was poured into water and crystallized from methanol. Yellow needles obtained.

(F) **Synthesis of [2"-(4""-Methoxy phenyl)-(quinoxaline)-3-yl]-(methylene phyenyl amino)-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

A mixture of 2-{4'-[3"-(4""-methoxy phenyl)2", 3"- dibromo-1"-one] phenyl amino}-6-[Bis(2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine (6.60 gm, 0.01 M) and o-phenylene diamine (1.08 gm, 0.01 M) taken in methanol (25 ml). A few drops of conc. H_2SO_4 was added. The reaction mixture was heated at 90º C. for 1 hr. in water bath. The reaction mixture poured into crushed ice, filtered, dried and crystallised from dioxane. Yield : 69%, M. P. 239º C (Found C : 61.00; H : 4.89; N : 16.58; $C_{30}H_{29}O_2N_7Cl_2$ required C : 61.01; H : 4.91; N : 16.60%).

Simillarly other compounds were prepared and their physical data recorded intable no.27

(F) Antimicrobial activity of [2"-Aryl (quinoxaline)-3-yl]-(methylene phenyl amino)-6-[Bis(2"'-chloroethyl) amino]-4- methoxy-1,3,5-triazine.

The antimicrobial testing was carried out as described in Part-I, Section-I, Page no. 39-41.

The zone of inhibition of the test solutions are recorded in Table no. 28.

TABLE NO : 27 : PHYSICAL CONSTANTS OF [2"-ARYL(QUINOXAINE)-3YL]-(METHYLENE PHENYL AMINO)-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Molecular Formula	M.P. .c	Yield %	% of Nitrogen	
					Calcd	Found
1.	C_6H_5	$C_{294}H_{27}Cl_2N_7O$	199	80	17.49	17.45
2.	2-OH C_6H_4	$C_{29}H_{27}Cl_2N_7O_2$	204	76	17.01	17.01
3.	3-OH C_6H_4	$C_{29}H_{27}Cl_2N_7O_2$	175	73	17.01	16.99
4.	4-OH C_6H_4	$C_{29}H_{27}Cl_2N_7O_2$	181	75	17.01	17.00
5.	4-OCH_3 C_6H_4	$C_{30}H_{29}Cl_2N_7O_2$	239	69	16.60	16.58
6.	4-OH, 3-OCH_3 C_6H_3	$C_{30}H_{29}Cl_2N_7O_3$	203	79	16.17	16.12
7.	4-Br. C_6H_4	$C_{29}H_{26}BrCl_2N_7O$	212	73	15.33	15.31
8.	3-NO_2 C_6H_4	$C_{29}H_{26}Cl_2N_8O_3$	159	78	18.51	18.49
9.	4-NO_2 C_6H_4	$C_{29}H_{26}Cl_2N_8O_3$	173	81	18.51	18.45
10	4-N,N$(CH_3)_2$ C_6H_4	$C_{31}H_{32}Cl_2N_8O$	198	70	18.57	18.56
11.	C_4H_3O (Furfuryl)	$C_{27}H_{25}Cl_2N_7O_2$	179	78	17.81	17.80

TABLE NO : 28 : ANTIMICROBIAL ACTIVITY OF [2"-ARYL(QUINOXALINE)-3YL]-(METHYLENE PHENYL AMINO)-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Antibacterial activity Zone of inhibition in mm.				Antifungal activity Zone of inhibition in mm.
		B. mega.	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5	15	19	16	20	15
2	2-OH C_6H_4	24	18	17	18	17
3	3-OH C_6H_4	20	17	21	19	16
4	4-OH C_6H_4	23	20	18	22	18
5	4-OCH_3 C_6H_4	12	16	17	23	19
6	4-OH, 3-OCH_3 C_6H_3	17	15	16	18	17
7	4-Br. C_6H_4	16	14	20	17	20
8	3-NO_2 C_6H_4	15	19	18	19	18
9	4-NO_2 C_6H_4	21	21	19	21	23
10	4-N,N$(CH_3)_2$ C_6H_4	20	17	22	15	18
11	C_4H_3O (Furfuryl)	18	15	15	17	19

PART - VIII

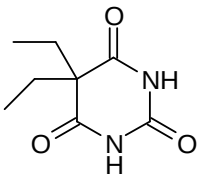
STUDIES ON BARBITONES

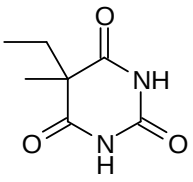
STUDIES ON BARBITONES

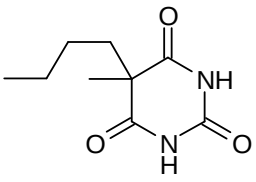
INTRODUCTION

The emerging role of barbitones in pharmaceutical chemistry as well as in biochemistry stimulated temendous interest in the synthesis of barbitones of therapetic interest. Most important is the effect of barbiturates on the central nervous system. Barbituric acid derivatives constitute an important class of compounds possessing diverse type of biological properties including hypnotic, sedative, anticonvulsant, cardiovascular etc.

Barbituric acid derivatives are perhaps the most widely used pyrimidines in medicine. Veronal (I) and Luminol (II) possess hypnotic activities, while pentothiol (III) is used as an anaesthetic.


(I)

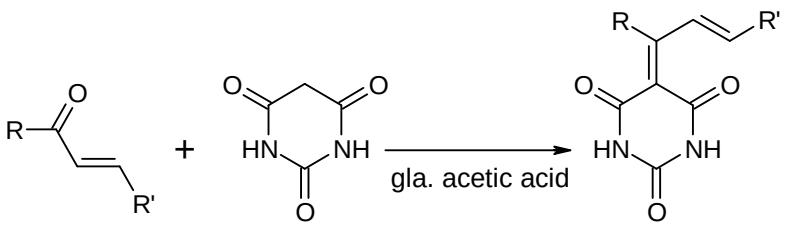

(II)


(III)

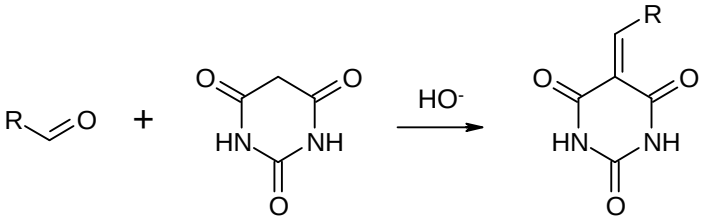
SYNTHETIC ASPECT

Different methods for the synthesis of barbitones have been described in literature[351-355]

1. M. R. Mahmoud et al.[356] have synthesized barbituric acid derivatives from chalcones.



2. Cao-Yun et al.[357] have prepared barbituric acid derivatives by the reaction of different aldehydes with barbituric acid in basic media.

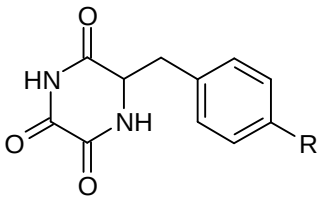


3. R. K. Roy et al.[358] have synthesised barbituric acid derivatives by the reaction of urea derivatives with malonic acid.

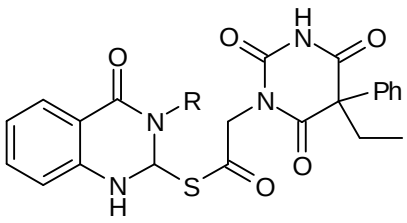
THERAPEUTIC IMPORTANCE :

At present time great interet is being taken in barbituric acid derivative because of its biological activity and their relation with nucleic acids, viz uracil, thymine and cytosine.

Some barbiturates showing cardiovascular[359-360] antiinflammatory[361] and pesticidal[362] activities have been reported. D. Peters et al[363] they have synthesised some uracil derivatives and screened for antiviral activity. R. Raymond et al[364] synthesised some barbiturates (IV) which showed anticancer activity.



(IV)



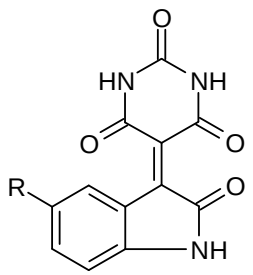
(V)

Several co-workers have synthesised barbitone derivatives and reported their antagonist[365], antitumor[366], anticonvulsant[367] and metalloproteinas inhibitor[368] activities. Abdel-Hamide and co-workers[369] have prepared barbituric acid derivatives (V) having anticonvulsant activity. A. N. Shivanyuk at al.[370] have demonstrated

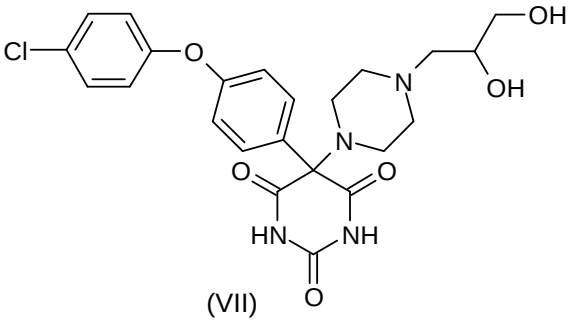
barbitone derivatives as porphyrin melamine calixarene receptor. Wolf-Gange et al.[371] have reported 5-(3-benzylthiazolidine-2-ylidene)- 1, 3-dimethyl hexahydro pyrimidine-2,4, 6-trione having agricultural activity. Some barbituric acid derivatives used as herbicides and insecticides have been demonstrated.[372]

M. T. Omar[373] has synthesised barbitone derivatives showing antimicrobial activity. Sakai et al.[374] have synthesised some new barbitones which were assessed for bone and cartilage disease. F. Grams and G. Zimmermantv[375] have prepared barbitones as metalloprotease inhibitors. Some barbitone derivatives have been studied for their antitumor activity[376].

Moreover, isotylidene barbiturates (VI) showing antibacterial activity have been synthesised[377]. D. Geppert and co-workers[378] have prepared new pyrimidine-2,4,6-triones (VII) as metalloproteinase inhibitors.



(VI)



(VII)

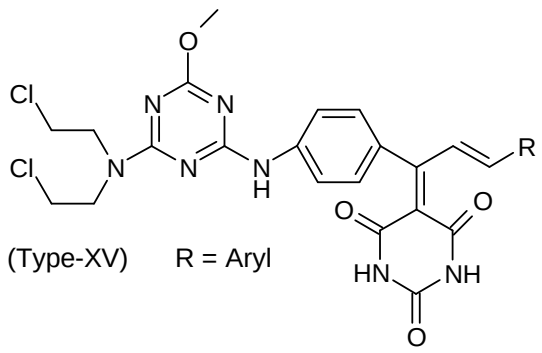
Keeping in view the important biological activities possessed by barbituric acid derivatives, we have tried to synthesise some new barbitones having better biological activities.

SECTION : I SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(3"-ARYL)-2"-PROPENE-1"-BARBITURIC ACID]-PHENYLAMINO} - 6 - [BIS (2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE.

SECTION : I

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(3"-ARYL)-2"-PROPENE-1"-BARBITURIC ACID]-PHENYLAMINO}-6-[BIS (2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Barbituric acid derivatives are wide spectrum of biological activities. Bis (2-chloroethyl) amine, 1,3,5-triazine molecules possess diversified anticancer, anti-HIV and other therapeutic activity with a view of 2-{4'-[(3"-Aryl)-2"-propene-1"-barbituric acid]-phenyl amino}-6-[Bis(2"'-chloroethyl) amino]-4-methoxy-1,3,5- triazine of Type (XV) have been synthesised by the reaction of 2-{4'-[(3"-aryl)-2"-propene-1"-one]-phenyl amino}-6-[Bis(2"'- chloroethyl) amino]-4-methoxy-1,3,5- triazine of Type-(I) with barbituric acid in glacial acetic acid.

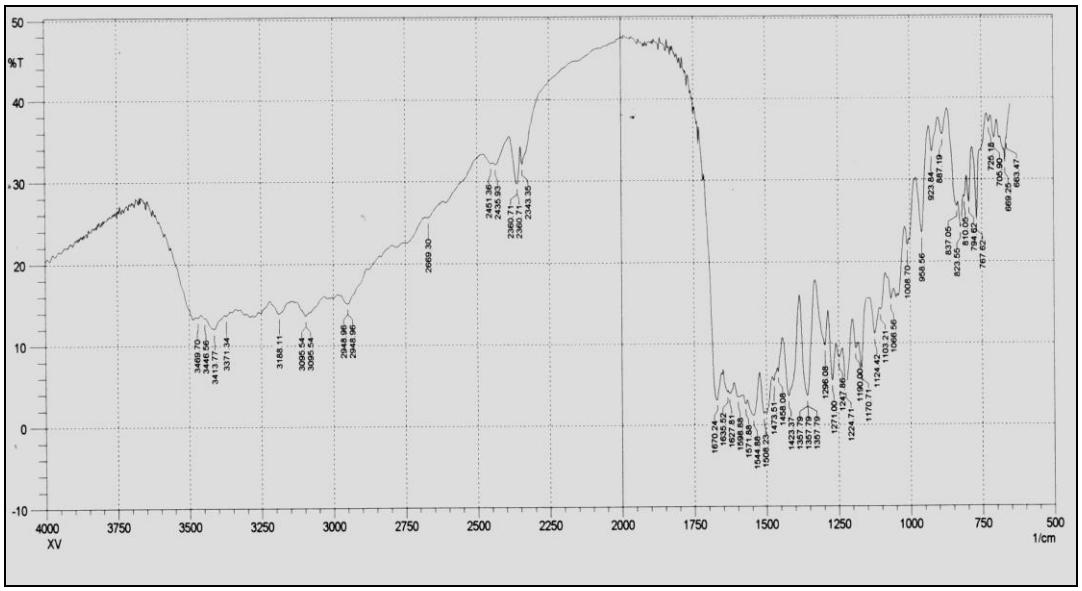


(Type-XV) R = Aryl

The constitution of the products have been characterised by elemental analysis IR, ^{1}H NMR, and Mass spectral study. The products were screened for antimicrobial activity at a concentration of 50 µg.

The details have been cited in the Part : I, Section : I, Page no. 39-41.

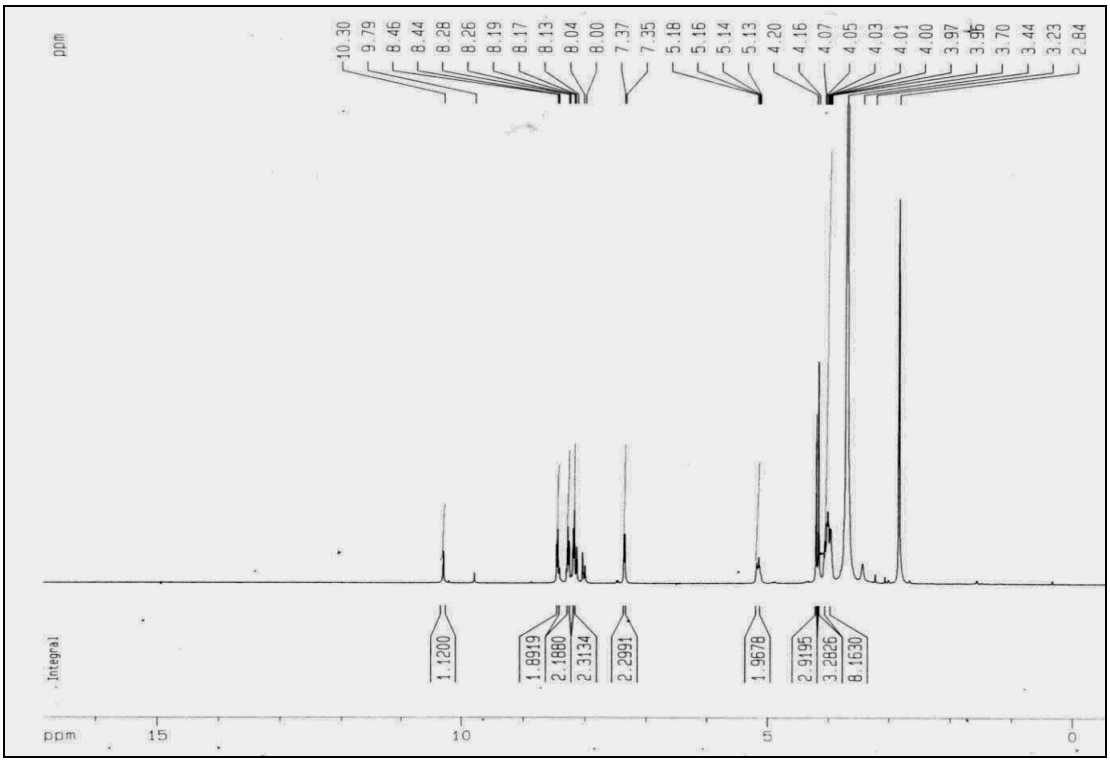
IR SPECTRAL STUDY OF 2-{4'-[(3"-4""-METHOXYPYENYL)-2"-PROPENE-1"-BARBITURIC ACID]-PHENYLAMINO}-6-[BIS (2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Instrument : SHIMADZU-FT-8400, Spectrophoto meter frequency range : 4000-400 cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	reported	
Alkane	C-H Str.(asym)	2948	2990-2850	422 – 423
	C-H Str.(sym)	2872	2880-2860	,,
	C-H def.(asym)	1458	1470-1435	
	C-H def.(sym)	1373	1390-1360	,,
	C-H Bending	1458	1470-1440	
Aromatic	C-H Str.	3095	3090-3030	,,
	C-H i.p. def	1224	1300-1100	
	C-H o.o.p. def	823	832-800	,,
	C=C Str.	1508	1600-1450	,,
S-triazine	C-N Str.	1124	1220-1020	
	C=N Str.	1598	1630-1590	,,
Amine	N-H Str.	3374	3500-3310	
	N-H Bending	1571	1650-1550	,,
Ether	C-O-C Str.(asym)	1214	1260-1220	
	C-O-C Str.(sym)	1068	1075-1020	,,
Halide	C-Cl Str.	767	800-600	,,
Barbitones	N-H Str.	3348	3350-3250	
	C=O Str.	1670	1750-1610	,,
	C=C Str.	1544	1600-1450	

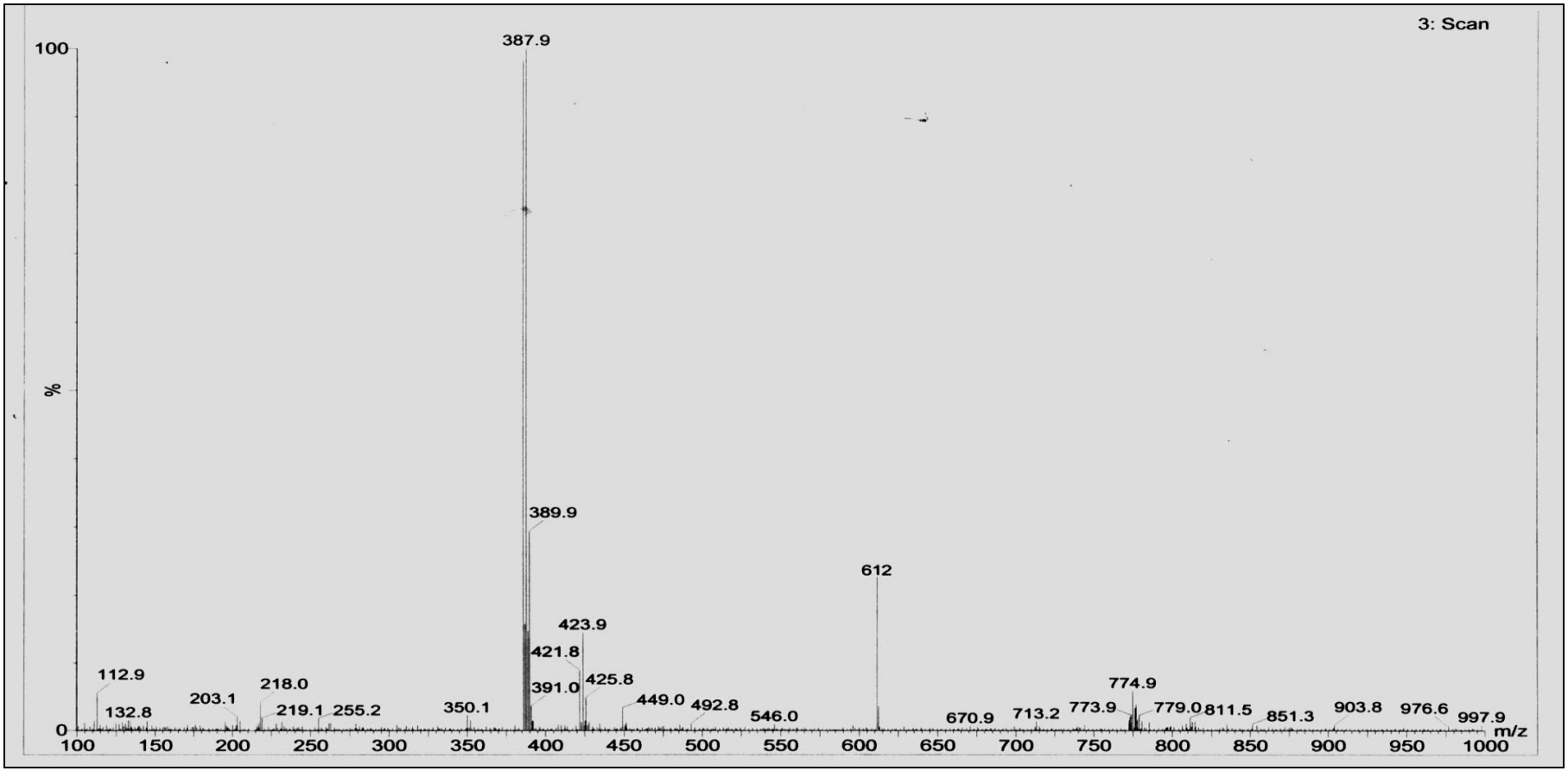
NMR SPECTRAL STUDY OF 2-{4'-[3"-(4""-METHOXYPHENYL) -2"-PROPENE-1"-BARBITURIC ACID]-PHENYLAMINO}-6-[BIS (2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE.



Internal standard : TMS; solvent : DMSO ; Instrument : DPX-200 spectrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.70-4.00	6 H	Singlet	Ar-OCH_3
2	7.35-7.37	4 H	D. Doublet	Ar-H_b
3	8.00-8.28	4 H	D. Doublet	Ar-H_c
4	4.05-4.20	4 H	Triplet	-CH_2-Cl
5	2.84	4 H	Triplet	-N-CH_2-
6	9.79-10.30	3 H	Singlet	Ar-NH_f
7	5.13-5.18	2 H	Doublet	-CH=CH_g

MASS SPECTRAL STUDY OF 2-{4'-[3"-(4""-METHOXYPHENYL) -2"-PROPENE-1"-BARBITURIC ACID]-PHENYLAMINO}-6-[BIS (2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE. (M.W. : 612)



Antimicrobial Activity :

Conclution :

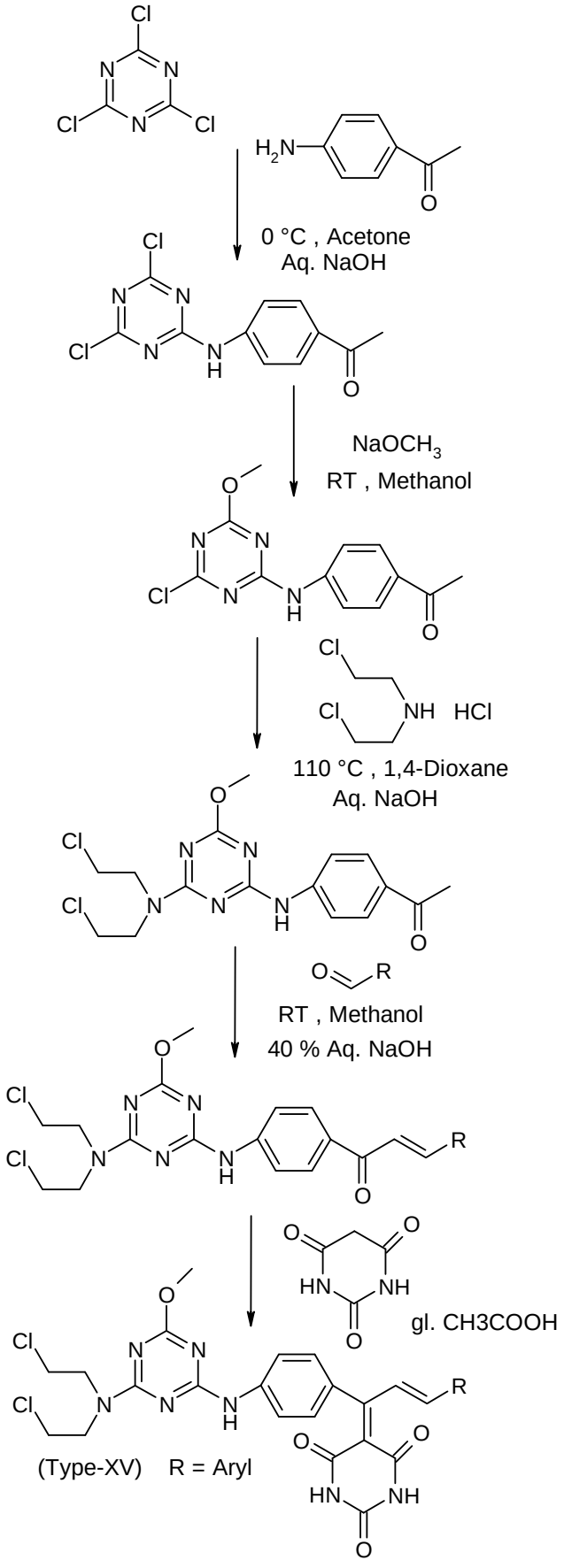
Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.				**Antifungal activity Zone of inhibition in m.m.**
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	2-OH C_6H_4(21)	4-OH C_6H_4(18)	2-OH C_6H_4(22)	4-OH C_6H_4(21)	C_6H_5(21)
	3-OH C_6H_4(23)	4-OCH_3 C_6H_4(19)	3-OH C_6H_4(25)	4-OH, 3OCH_3,	4-OH C_6H_4(22)
	4-Br C_6H_4(22)	4-NO_2 C_6H_4(18)	4-OCH_3 C_6H_4(21)	C_6H_3(22)	3-NO_2 C_6H_4(22)
			4-N,N$(CH_3)_2$		
			C_6H_4(23)		

Comparable activity with known standard drugs

Ampicilin	50 µg	23	18	17	27	-
ChlorAmphenicol	"	24	19	25	26	-
Norfloxacin	"	24	19	25	26	-
Greseofulvin	"	-	-	-	-	23

REACTION SCHEME



EXPERIMENTAL

SYNTHESIS OF 2-{4'-[(3"-ARYL)-2"-PROPENE-1"-BARBITURIC ACID]-PHENYLAMINO}-6-[BIS (2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE.

(A) **Synthesis of 2-(4'-Acetyl phenyl amino)-4, 6-dichloro-1,3,5-triazine.**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(B) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-chloro-4-methoxy-1,3, 5-triazine.**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(C) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-[Bis(2"chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis, see Part-I, Section-I, Pagen no. 36-38.

(D) **Synthesis of 2-{4'-[3"-(4""-Methoxyphenyl)-2"-propene-1"-one] phenyl amino}-6-Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For systhesis, see Part-I, Section-I, Page no. 36-38.

(E) **Synthesis of 2-{4'-[3"-(4""-Methoxy phenyl)-2"-propene-1"-barbituric acid]-phenyl amino}-6-[Bis-(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

A mixture of 2-{4'-[3"-(4""-methoxyphenyl)2"-propene-1"-one] phenyl amino}-6-[Bis(2'"-choroethyl) amino]-4-methoxy-1,3,5-triazine (5.02 gm, 0.01M); barbituric acid (1.28 gm, 0.01M) and gla. aceticacid in methanol, the reaction mixture was refluxed 12 hrs. at 100° C. temp. The content was poured into crushed ice, filtered, dried and crystallised from dioxane. Yield : 75%, M. P. 165 C (Found : C 54.89; H : 4.40; N : 16.00, $C_{28}H_{27}O_5N_7Cl_2$ required C:54.90; H:4.41; N:16.01 %)

similaraly other compound were synthesised and their physical data recorded in Table no. 29.

(F) **Antimicrobial activity of 2-{4'-[(3"-aryl)-3"-propene-1"-barbituricacid]-phenyl amino}-6-[Bis (2"-chloro ethyl-amino]-4- methoxy-1,3,5- triazine.**

The antimicrobial testing was carried out as described in Part : I, Section : I, Page No. 39-41.

The zone of inhibition of the test solution are recorded in Table No. 30.

TABLE NO : 29 : PHYSICAL CONSTANTS OF 2-{4'-[(3"-ARYL)-2"-PROPENE-1"-BARBITURIC ACID]-PHENYLAMNI}-6-[BIS (2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Molecular Formula	M.P. .c	Yield %	% of Nitrogen	
					Calcd	Found
1	2	3	4	5	6	7
1.	C_6H_5	$C_{27}H_{25}Cl_2N_7O_4$	201	58	16.83	16.80
2.	2-OH C_6H_4	$C_{27}H_{25}Cl_2N_7O_5$	238	60	16.38	16.35
3.	3-OH C_6H_4	$C_{27}H_{25}Cl_2N_7O_5$	265	65	16.38	16.32
4.	4-OH C_6H_4	$C_{27}H_{25}Cl_2N_7O_5$	222	70	16.38	16.30
5.	4-OCH_3 C_6H_4	$C_{28}H_{27}Cl_2N_7O_5$	165	75	16.01	16.00
6.	4-OH, 3-OCH_3 C_6H_3	$C_{28}H_{27}Cl_2N_7O_6$	201	72	15.60	15.55
7.	4-Br. C_6H_4	$C_{27}H_{24}BrCl_2N_7O_4$	125	76	14.83	15.81
8.	3-NO_2 C_6H_4	$C_{27}H_{24}Cl_2N_8O_6$	165	58	17.86	17.83
9.	4-NO_2 C_6H_4	$C_{27}H_{24}Cl_2N_8O_6$	117	81	17.86	17.82
10	4-N,N$(CH_3)_2$ C_6H_4	$C_{29}H_{30}Cl_2N_8O_4$	192	69	17.91	17.89
11.	C_4H_3O (Furfuryl)	$C_{25}H_{23}Cl_2N_7O_5$	185	73	17.13	17.09

TABLE NO : 30 : ANTIMICROBIAL ACTIVITY OF 2-{4'-[(3"-ARYL)-2"-PROPENE-1"-BARBITURIC ACID]-PHENYLAMNI}-6-[BIS (2"'-CHLOROETHYL)-AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	**R**	**Antibacterial activity Zone of inhibition in mm.**			**Antifungal activity Zone of inhibition in mm.**	
		B. mega	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5	20	12	19	18	21
2	2-OH C_6H_4	21	14	22	17	18
3	3-OH C_6H_4	23	15	25	16	19
4	4-OH C_6H_4	18	18	20	21	22
5	4-OCH_3 C_6H_4	17	19	21	19	16
6	4-OH, 3-OCH_3 C_6H_3	15	15	16	22	15
7	4-Br. C_6H_4	22	15	18	15	14
8	3-NO_2 C_6H_4	18	14	17	14	22
9	4-NO_2 C_6H_4	19	18	19	19	18
10	4-N,N$(CH_3)_2$ C_6H_4	16	13	23	20	19
11	C_4H_3O (Furfuryl)	15	12	18	18	20

PART-IX

STUDIES

ON

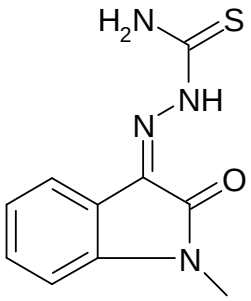
THIOSEMICARBOXIMIDES

STUDIES ON THIOSEMICARBOXIMIDES

INTRODUCTION

Thiosemicarbazone derivatives are of special importance because of their versatile biological and pharmacological activities. Thiosemicarbazone derivatives have found applications in drug development for the treatment of central nervous system disorders, of bacterial infections, as well as analgesic and antiallergic agent. They are potent intermediates for the synthesis of pharmaceutical and bioactive materials.

The clinically active drug methisazone and related compounds have shown activity against DNA viruses, principally the orthopoxviruses, both in vitro and in vivo.

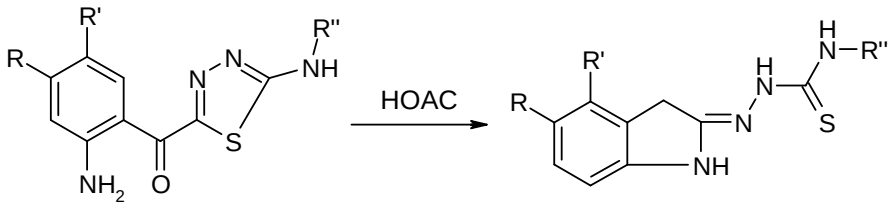


SYNTHETIC ASPECT

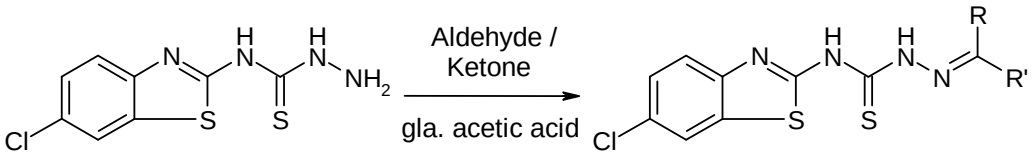
Nowadays reaction between thiosemicarbazide with ketones or aldehydes have attracted a great attention, because of their interesting nature of resulting compounds for their applications and biological activities.

Different methods are used for the synthesis of thiosemicarbazones which are described in literature[379-382].

1. A. B. Tomchin[383] has synthesised thiosemicarbazones by the recyclisation of 2-amino-5-(2-aminoaroyl)-1,3,4-thiadiazoles.



2. Y. Perumal and co-workers[384] have prepared thiosemicarbazones by the condensation of 6-chlorobenzothiazolyI-2-thiosemicarbazide with aldehydes or ketones.



THERAPEUTIC IMPORTANCE :

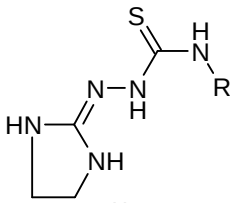
Thiosemicarbazones exhibit a wide variety of biological activities which are listed as under.

1. Antibacterial[385]
2. Anthelmintic[386]
3. Antifungal[387]
4. Anticonvulsant[388]
5. Antirheumatics[389]
6. Antiherpes[390]
7. Antimalarial[391]
8. Antitumor[392-393]
9. anticancer[394]

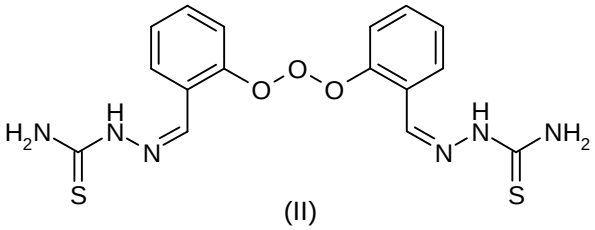
Antimicrobial activity of thiosemicarbazone derivatives have been reported [395-396], T. Siatra et al.[397] have synthesised some new thiosemicarbazones from 3-acetyl indole and reported its effect on DNA synthesis and cell proliferation. 5-chloro

salicyaldehydic thiosemicarbazone derivatives have been documented by Z. Quianawin et al.[398]

N-substituted thiosemicarbazones showing antitumor activity have been reported[399]. D. Wang et al.[400] patented thiosemicarbazones useful as sodium channel blockers. K. I. Zabella[401] has prepared thiosemicarbazones (I) from 1, 3-cyclic diamino and reported as anticancer agent. O. V. Fedorova et at.[402] synthesised some thiosemicarbazones (II) having potent in vitro tuberculostatic activity.



(I)



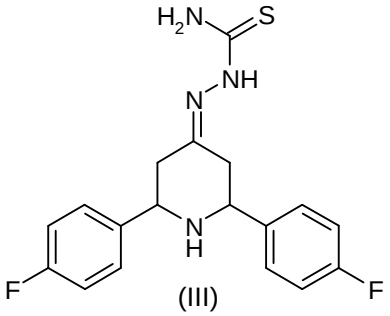
(II)

Some 3-aminopyrimidine 2-carboxaldehyde thiosemicarbazone derivatives are reported as novel prodrug forms of ribonucleotide reductase inhibitors 3-AP and 3-AMP by Li Jun et al.[407]

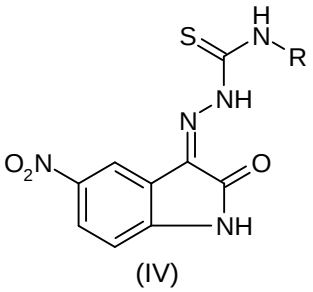
Some new thiosemicarbazone derivatives have been studied for their anticancer activity[404] D. Sharma et al.[405] have synthesised thiophene 2-carboxaldehyde thiosemicarbazones and evaluated their antimicrobial and antiviral activity. S.P.R. Rodiriguez and co-workers[406] have synthesised 4-substituted thiosemicarbazones and reported its antiproliferartive activity. Thiosemicarbazone derivatives as potent antiviral agents have been investigated G. E. Iniama et al[407]

Moreover, Jin Shuhui and co-workers[408] thiosemicarbazones and prepared thiosemicarbazones and reported them for antifungal activity. Thiosemicarbazones

(III) showing significant antimicrobial activity are described[409]. Nilgun K. [410] have synthesised some thiosemicarbazones (IV) bearing indol nucleus and evaluated their cytotoxicity.



(III)



(IV)

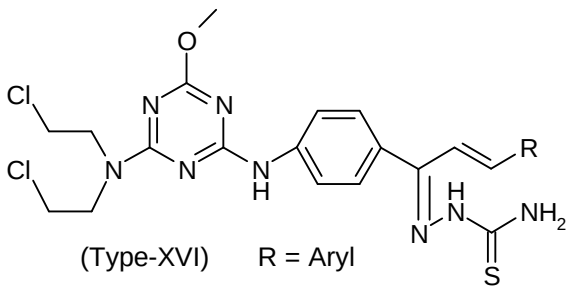
Due to the physiological and biological activities of thiosemicarbazones, it was contemplated to synthesis some new thiosemicarbazones with a hope that these compounds may have better pharmacological activities.

SECTION - I : SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(3"ARYL)-2"-PROPENE-1"-THIOSEMICARBOXIMIDE] -PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO] – 4 - METHOXY-1,3,5-TRIAZINE.

SECTION : I

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(3"-ARYL)-2"-PROPENE-1"-THIOSEMICARBOXIMIDE]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4- METHOXY-1,3,5-TRIAZINE.

Thiosemicarboximaides derivatives possess broad spectrum of therapeutic activity e.g. antidiabectic, antimicrobial, anticonvulsant, antipyretic etc., with a view of above facts 2-{4'-[(3"-aryl)-2"-propene-1"-thiosemicarboximides]-phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine of Type. (XVI) have been synthesised by the reaction of 2-{4'-[(3"-aryl)-2"-propene-1"-one]-phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4- methoxy-1,3,5-triazine, chalcones of Type (I) with thiosemicarbazide in alcohol.

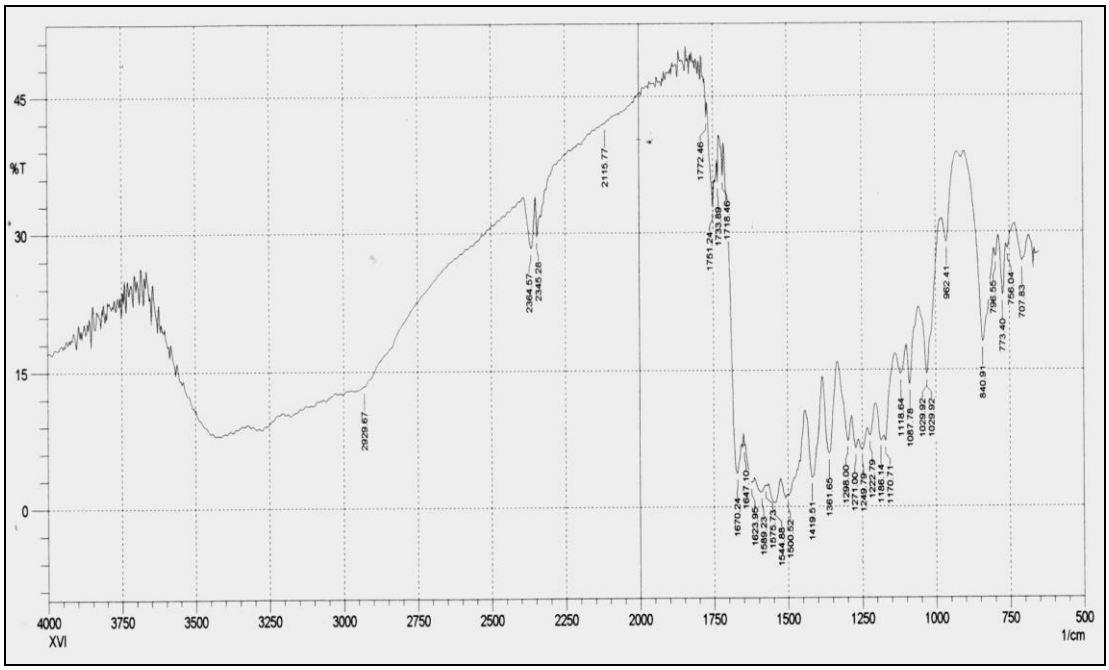


(Type-XVI) R = Aryl

The constitution of the products have been characterised by elemental analysis IR, ^{1}H NMR, and Mass spectral study. The products were screened for antimicrobial activity at a concentration of 50 µg.

The details have been cited in the part : I, Section : I, Page no. 39-41.

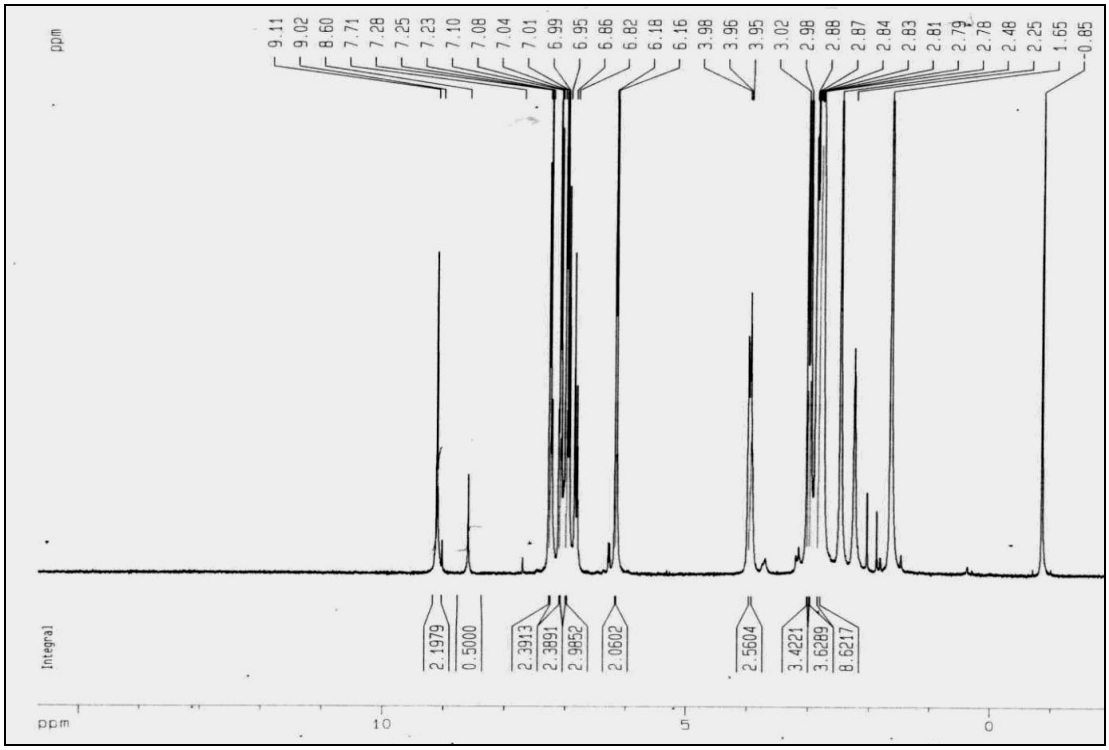
IR SPECTRAL STUDY OF 2-{4'-[(3"-(4""-METHOXYPHENYL)-2"-PROPENE-1"-THIOSEMICARBOXIMIDE]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4- METHOXY-1,3,5-TRIAZINE.



Instrument : SHIMADZU-FT-IR-8400, Spectrophoto meter frequency range : 4000-400 cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	Reported	
Alkane	C-H Str.(asym)	2929	2990-2850	422 – 423
	C-H Str.(sym)	2878	2880-2860	,,
	C-H def.(asym)	1465	1470-1435	
	C-H def.(sym)	1361	1390-1360	,,
Aromatic	C-H Str.	3073	3090-3030	
	C-H i.p. def	1170	1300-1100	,,
	C-H o.o.p. def	840	832-800	
	C=C Str.	1475	1600-1450	,,
S-triazine	C-N Str.	1029	1220-1020	,,
	C=N Str.	1623	1630-1590	
Amine	N-H Str.	3447	3500-3310	,,
	N-H Bending	1623	1650-1550	
Ether	C-O-C Str.(asym)	1249	1260-1220	,,
	C-O-C Str.(sym)	1029	1075-1020	
Halide	C-Cl Str.	773	800-600	,,
Thiosemi	C=N Str.	1647	1650-1630	,,
	C-N Str.	1361	1380-1332	
	C=S Str.	1575	1590-1550	

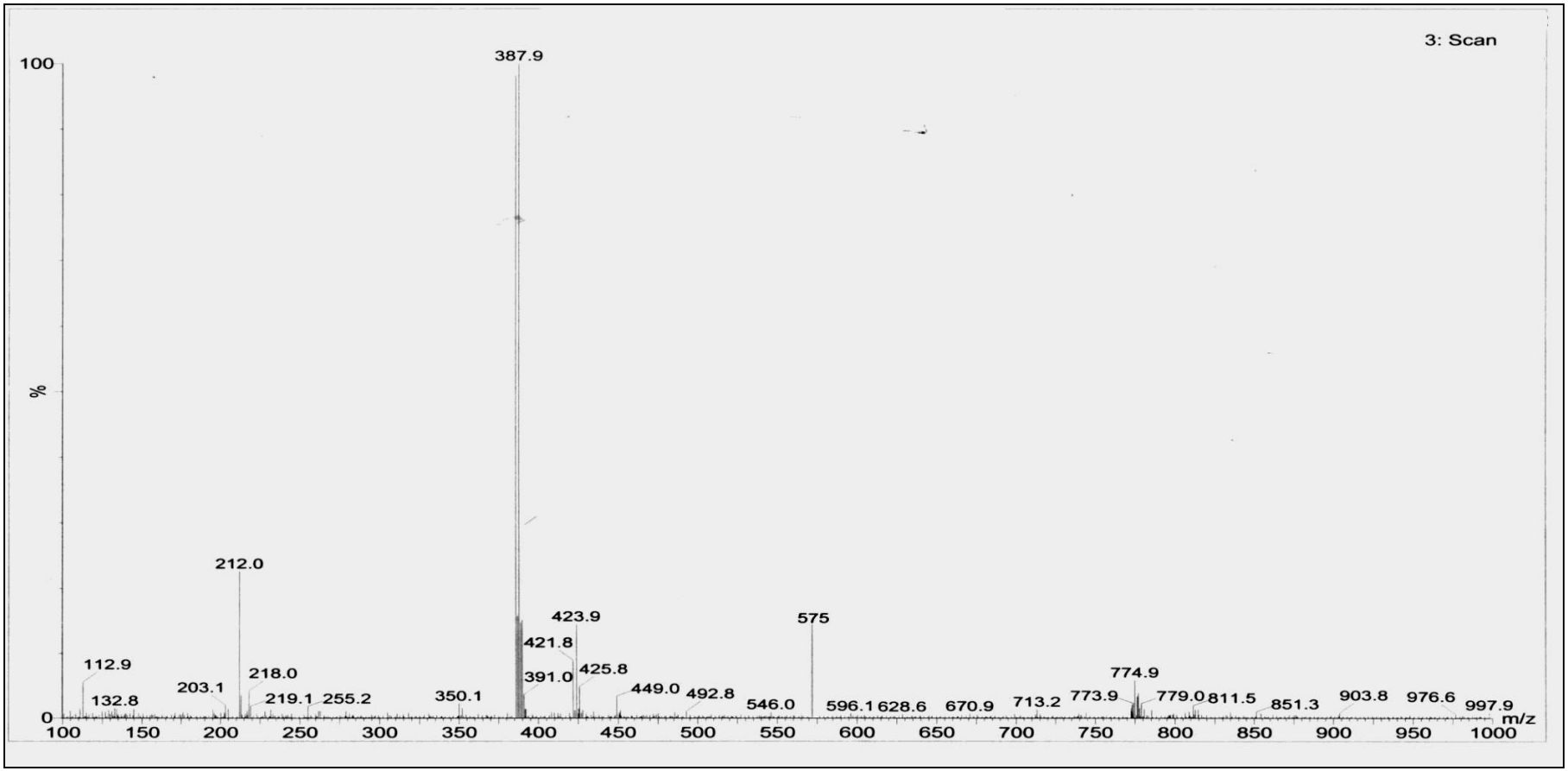
NMR SPECTRAL STUDY OF 2-{4'-[(3"-(4""-METHOXYPHENYL)-2"-PROPENE-1"-THIOSEMICARBOXIMIDE]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4- METHOXY-1,3,5-TRIAZINE.



Internal standard : TMS; solvent : DMSO ; Instrument : BRUKER spectrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.95-3.98	6 H	Singlet	Ar-OCH_3
2	7.23-7.71	4 H	D. Doublet	Ar-H_b
3	8.60	4 H	D. Doublet	Ar-H_c
4	3.96-3.98	4 H	Triplet	-CH_2-Cl
5	2.25-2.84	4 H	Triplet	-N-CH_2-
6	8.60	1 H	Singlet	Ar-NH_f
7	3.98	2 H	Doublet	-CH=CH_g
8	9.02	1 H	Singlet	-N-NH_h
9	9.11	2 H	Singlet	-$NH_{2\,i}$

MASS SPECTRAL STUDY OF 2-{4'-[3"-(4""-METHOXYPHENYL) -2"-PROPENE-1"-THIOSEMICARBOXIMIDE]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4- METHOXY-1,3,5-TRIAZINE. (M.W. : 575)



Antimicrobial Activity :

Conclution :

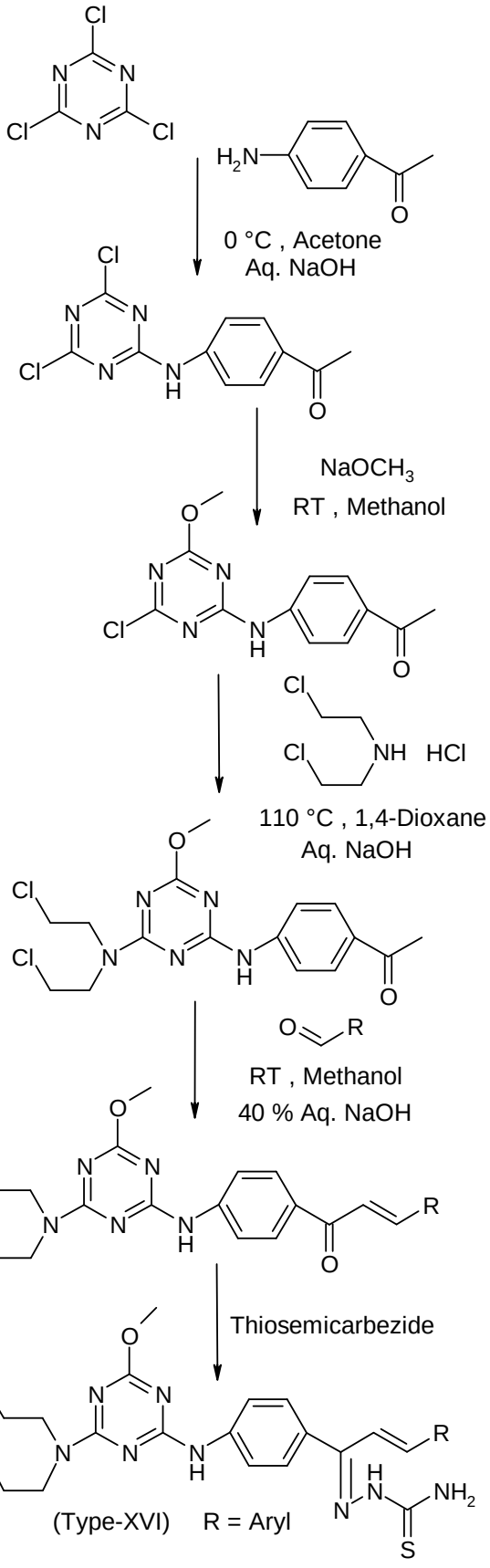
Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.				**Antifungal activity Zone of inhibition in m.m.**
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	4-OH C_6H_4(22)	4-OH C_6H_4(20)	3-OH C_6H_4(23)	C_6H_5(21)	3-OH C_6H_4(22)
	4-NO_2 C_6H_4(26)	3-NO_2 C_6H_4(23)	4-OH C_6H_4(20)	4-OH C_6H_4(20)	4-NO_2 C_6H_4(24)
			4-Br C_6H_4(22)	4-Br C_6H_4(22)	4-N,N $(CH_3)_2$ C_6H_4(23)

Comparable activity with known standard drugs

Ampicilin 50 µg.	23	18	17	27	-
ChlorAmphenicol ”	24	19	25	26	-
Norfloxacin ”	24	19	25	26	-
Greseofulvin ”	-	-	-	-	23

REACTION SCHEME



(Type-XVI) R = Aryl

EXPERIMENTAL

SYNTHESIS OF 2 - { 4' - [(3"-ARYL) - 2" – PROPENE - 1" – THIOSEMICARBOXIMIDE] - PHENYL AMINO} – 6 - [BIS (2"' - CHLORO ETHYL) AMINO] – 4 - METHOXY - 1, 3, 5 - TRIAZINE.

(A) **Synthesis of 2-(4'-Acetyl phenyl amino)-4, 6-dichloro-1,3,5-triazine.**

For synthesis, see Part : I, Section-I, Page no. 36-38.

(B) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-chloro-4-methoxy-1.3,5-triazine.**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(C) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-[Bis(2"-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis see Part-I, Section-I, Page no. 36-38.

(D) **Synthesis of 2-{4'-[3"-(4""-Methoxyphenyl)-2"-propene-1"-one]phenyl amino}-6- [Bis. (2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis See Part-I, Section-I, Page no. 36-38.

(E) **Synthesis of 2-{4'-[3"-(4""-Methoxy phenyl)-2"-propene-1"-thiosemicarboxamide]- phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5- triazine.**

A mixture of 2-{4'-[3"-(4""-Methoxy phenyl)-2"-propene-1"-one]phenyl amino}-6-[Bis(2"'-chloroethyl) amino]-4-methoxy-1,3,5, triazine (5.02 gm, 0.01 M); thioseimicarbazide (0.91 gm, 0.01 M) and alcoholic KOH, the reaction mixture was refluxed for 10 hrs. at 100º C. temp. The reaction mixture poured into crushed ice, filtered,dried, and crystallised from dioxane, yield : 76%, M.P. : 143º C. (Found : C : 52.70;, H : 4.83; N : 19.43; $C_{25}H_{28}O_2N_8Cl_2S$ required C : 52.17; H : 4.86; N : 19.47%)

Similarly other compounds were prepared and their physical data recorded in Table no.31.

(F) **Antimicrobial activity of 2-{4'-[(3"-aryl)-2"-propene-1"-thiosemicarboximide]-phenyl amino}-6-[Bis. (2'"-chloro ethyl)- amino]-4-methoxy-1,3,5-triazine,**

The antimicrobial testing was carried out as described in Part : I, Section : I, Page no. 39-41.

The zone of inhibition of the test solution are recorded in Table No. 32.

TABLE NO : 31 : PHYSICAL CONSTANTS OF 2-{4'-[(3"-ARYL)-2"-PROPENE-1"-THIOSEMICARBOXIMIDES]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4- METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Molecular Formula	M.P. .c	Yield %	% of Nitrogen	
					Calcd	Found
1.	C_6H_5	$C_{24}H_{26}Cl_2N_8O$ S	191	58	20.54	20.51
2.	2-OH C_6H_4	$C_{24}H_{26}Cl_2N_8O_2$ S	201	70	19.96	19.90
3.	3-OH C_6H_4	$C_{24}H_{26}Cl_2N_2O_2$ S	229	69	19.96	19.92
4.	4-OH C_6H_4	$C_{24}H_{26}Cl_2N_8O_2$ S	178	81	19.96	19.94
5.	4-OCH_3 C_6H_4	$C_{25}H_{28}Cl_2N_8O_2$ S	143	76	19.47	19.43
6.	4-OH, 3-OCH_3 C_6H_3	$C_{25}H_{28}Cl_2N_8O_3$ S	157	77	18.94	18.89
7.	4-Br. C_6H_4	$C_{24}H_{25}BrCl_2N_8O$ S	111	82	17.95	17.90
8.	3-NO_2 C_6H_4	$C_{24}H_{25}Cl_2N_9O_3$ S	135	68	21.35	21.31
9.	4-NO_2 C_6H_4	$C_{24}H_{25}Cl_2N_9O_3$ S	218	65	21.35	21.32
10	4-N,N$(CH_3)_2$ C_6H_4	$C_{26}H_{31}Cl_2N_9O$ S	203	71	21.42	21.41
11.	C_4H_3O (Furfuryl)	$C_{22}H_{24}Cl_2N_8O_2$ S	115	75	20.93	20.98

TABLE NO : 32 : ANTIMICROBIAL ACTIVITY OF 2-{4'-[(3"-ARYL)-2"-PROPENE-1"-THIOSEMICARBOXIMIDE]-PHENYL AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4- METHOXY-1,3,5-TRIAZINE.

Sr. No.	**R**	**Antibacterial activity Zone of inhibition in mm.**				**Antifungal activity Zone of inhibition in mm.**
		B. mega.	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5	15	17	14	21	19
2	2-OH C_6H_4	17	19	17	17	20
3	3-OH C_6H_4	18	14	23	19	22
4	4-OH C_6H_4	22	20	20	24	21
5	4-OCH_3 C_6H_4	18	12	18	19	19
6	4-OH, 3-OCH_3 C_6H_3	15	15	17	18	17
7	4-Br. C_6H_4	17	17	22	17	14
8	3-NO_2 C_6H_4	19	23	18	15	17
9	4-NO_2 C_6H_4	26	14	17	22	24
10	4-N,N$(CH_3)_2$ C_6H_4	15	15	15	16	23
11	C_4H_3O (Furfuryl)	13	17	14	15	16

PART - X

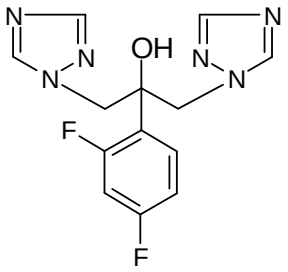
STUDIES ON TRIAZOLES

STUDIES ON TRIAZOLES

INTRODUCTION

Triazole derviatives are of special importance because of their versatile biological and pharacological activities. Triazole derivatives have been found plant growth regulator, herbicide, fungicide, analgesic and antiallergic agent. They are potent intermediates for the synthesis of pharmaceutical and bioactive materials.

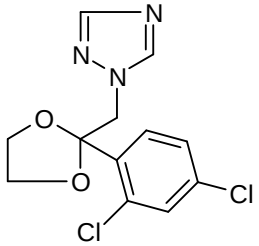
The clinically active drug Fluconazole[411] represent under :



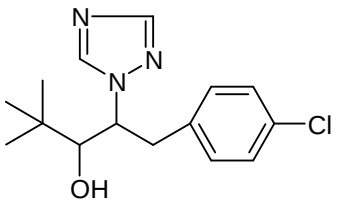
SYNTHETIC ASPECT :

Nowadays reaction between triazole with on their substituent to produce new biologically acitve compounds.

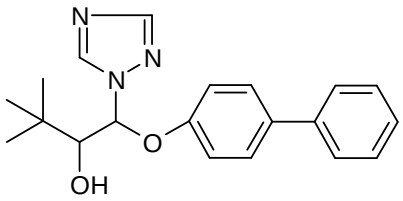
1. B. Buttler[412] have been synthesised 1-{[2-(2"-dicholrophenyl)-4-propyl-1,3-dioxo-2-yl] methyl]-1H-1,3,4-triazole "Propiconazole". as a antifungal agents.



2. Wiley et al.[413] have been reported 1-ter. butyl -2-(p-chloro benzyl)-2-(1,3,4-triazol-1-yl)-ethanol as a plant growth regulartor.



3. S. V. Overton et al.[414] have been reported 1-(biphenyl-4-yl oxy)-3,3-dimethyl-1-(1H-1,3,4-triazle-1-yl)-butan-2-ol "Bitertanol" as agricultural fungicide.



THERAPEUTIC IMPORTANCE :

Thriazole exhibit a wide range variety of biological acitvitiews which are listed as under.

1. Fungicide[415-416]
2. Antideprassant[417]
3. Coronary vasodilator[418]
4. Sedative, hypnofic[419]
5. anti viral[420]
6. antiallergic[421]

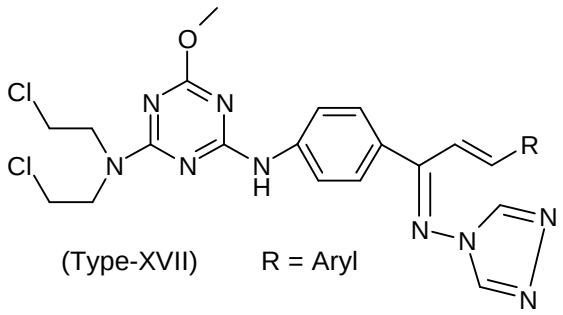
Due to the physiological and biological activities of possessed by triazoles derivatives, we have tried to synthesis some new triazoles having better biological activities.

SECTION - I : SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(3"-ARYL)-2"-PROPENE-1" – N - (1,2,4 - TRIAZOLE) AMINO]} – 6 - [BIS(2"'-CHLORO ETHYL) AMINO] – 4 –METHOXY - 1, 3, 5-TRIAZINE.

SECTION - I

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-{4'-[(3"-ARYL)-2"-PROPENE-1"-N-(1,2,4-TRIAZOLE) AMINO]}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1, 3, 5-TRIAZINE.

Triazole derivatives possess wide spectrum of therapeutic activity such as antifungal, anticonvalusant, antibacterial etc. In view of getting 2-{4'-[(3"-aryl)-2"-propene-1"-N-(1,2,4-triazole) amino]}-6-[Bis(2"'-chloro ethyl)] amino-4-methoxy-1,2,4-triazine of Type (XVII) have been synthesised by the reaction of 2-{4'-[(3"-aryl)-2"-propene-1"-one]-phenyl amino}-6-[Bis(2"'-chloroethyl)] amino -4- methoxy-1,3,5 - triazine with 4-amino -1,2,4 - triazole in alcohol.

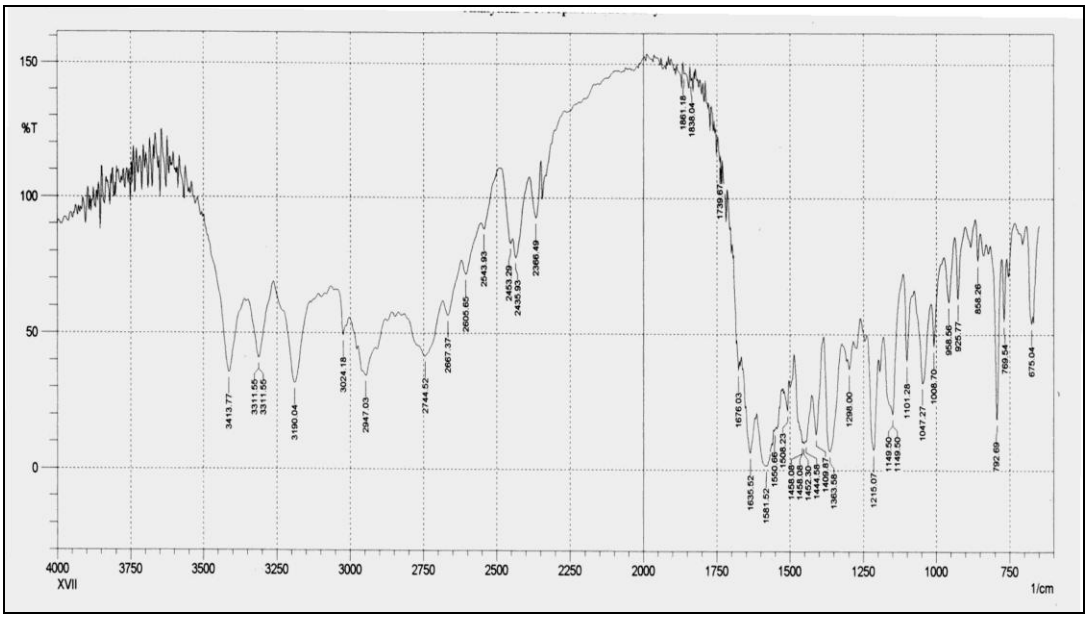


(Type-XVII) R = Aryl

The constitution of the products have been chaoracterised by elemental analysis. IR, ^{1}H NMR, and Mass spectral study. The products were screended for antimicrobial activity at a concentration of 50 µg.

The details have been cited in the Part-I, Section-I, Page no. 39-41.

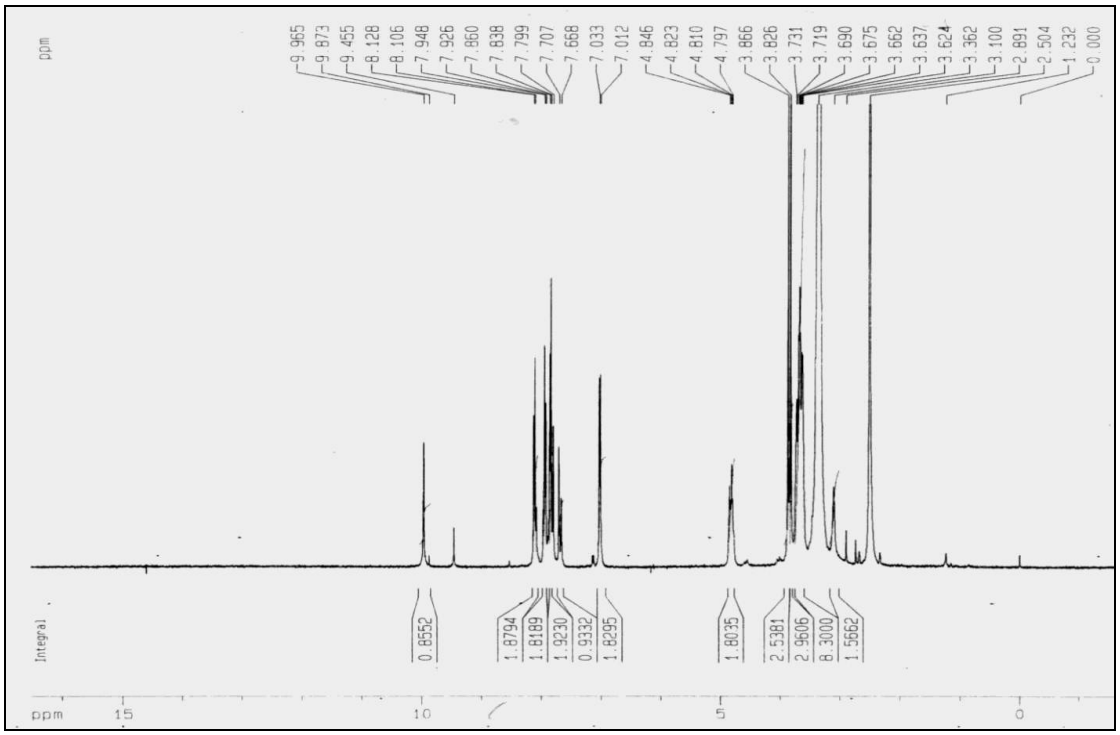
IR SPECTRAL STUDY OF 2-{4'-[3"-(4""-METHOXYPHENYL) -2"-PROPENE-1"-N-(1,2,4-TRIAZOLE) AMINO]}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1, 3, 5-TRIAZINE.



Instrument : SHIMADZU-FT-8400, Spectrophoto meter frequency range : 4000-400 cm^{-1} (KBrdisc)

Type	Vibration Mode	Frequency in cm^{-1}		Ref.
		observed	reported	
Alkane	C-H Str.(asym)	2947	2990-2850	422 – 423
	C-H Str.(sym)	2889	2880-2860	,,
	C-H def.(asym)	1444	1470-1435	
	C-H def.(sym)	1363	1390-1360	,,
Aromatic	C-H Str.	3024	3090-3030	
	C-H i.p. def	1101	1300-1100	,,
	C-H o.o.p. def	830	832-800	
	C=C Str.	1450	1600-1450	,,
S-triazine	C-N Str.	1149	1220-1020	,,
	C=N Str.	1581	1630-1590	
Amine	N-H Str.	3413	3500-3310	,,
	N-H Bending	1550	1650-1550	
Ether	C-O-C Str.(asym)	1215	1260-1220	,,
	C-O-C Str.(sym)	1047	1075-1020	
Halide	C-Cl Str.	792	800-600	,,
Triazole	C-N Str.	1676	1690-1640	,,
	N-N Str.	1581	1630-1575	
	C=N Str.	1598	1630-1593	,,
	C-N Bending	1298	1340-1250	

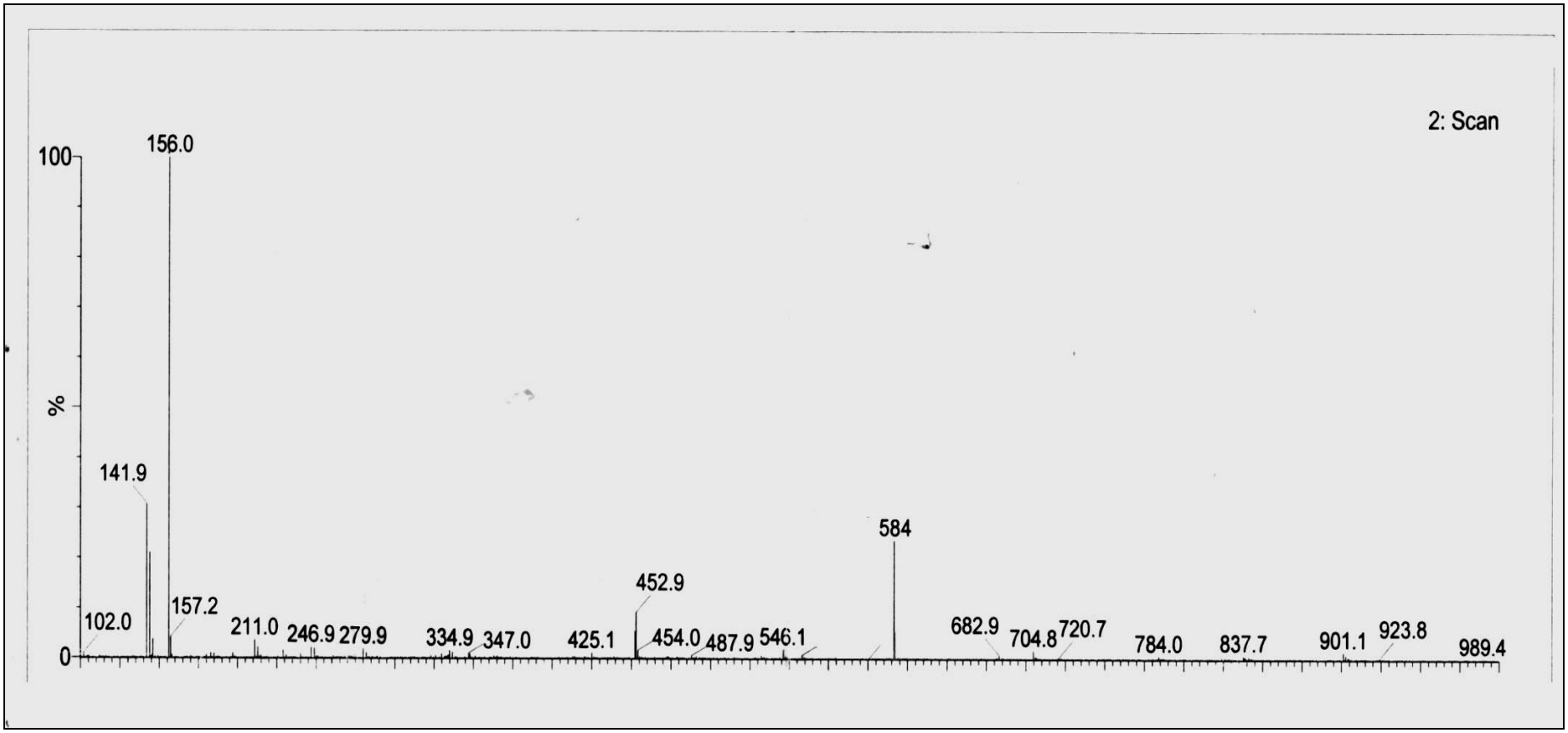
NMR SPECTRAL STUDY OF 2-{4'-[3"-(4""-METHOXYPHENYL) -2"-PROPENE-1"-N-(1,2,4-TRIAZOLE) AMINO]}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1, 3, 5-TRIAZINE.



Internal standard : TMS; solvent : DMSO ; Instrument : DPX-200 spectrometer (300 MHz)

Signal No.	Signal Position (ppm)	Relative no. of protons	Multiplicity	Inference
1	3.71-3.86	6 H	Singlet	Ar-OCH_3
2	7.66-7.79	4 H	D. Doublet	Ar-H_b
3	7.99-8.12	4 H	D. Doublet	Ar-H_c
4	4.79-4.84	4 H	Triplet	-CH_2-Cl
5	2.50-2.89	4 H	Triplet	-N-CH_2-
6	9.87-9.96	1 H	Singlet	Ar-NH_f
7	4.81-4.84	2 H	Doublet	-CH=CH_g
8	7.01-7.03	2 H	Singlet	Ar-H_h

MASS SPECTRAL STUDY OF 2-{4'-[(3"-(4""-METHOXYPHENYL) -2"-PROPENE-1"-N-(1,2,4-TRIAZOLE) AMINO]}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1, 3, 5-TRIAZINE. (M.W. : 584)



Antimicrobial Activity :

Conclution :

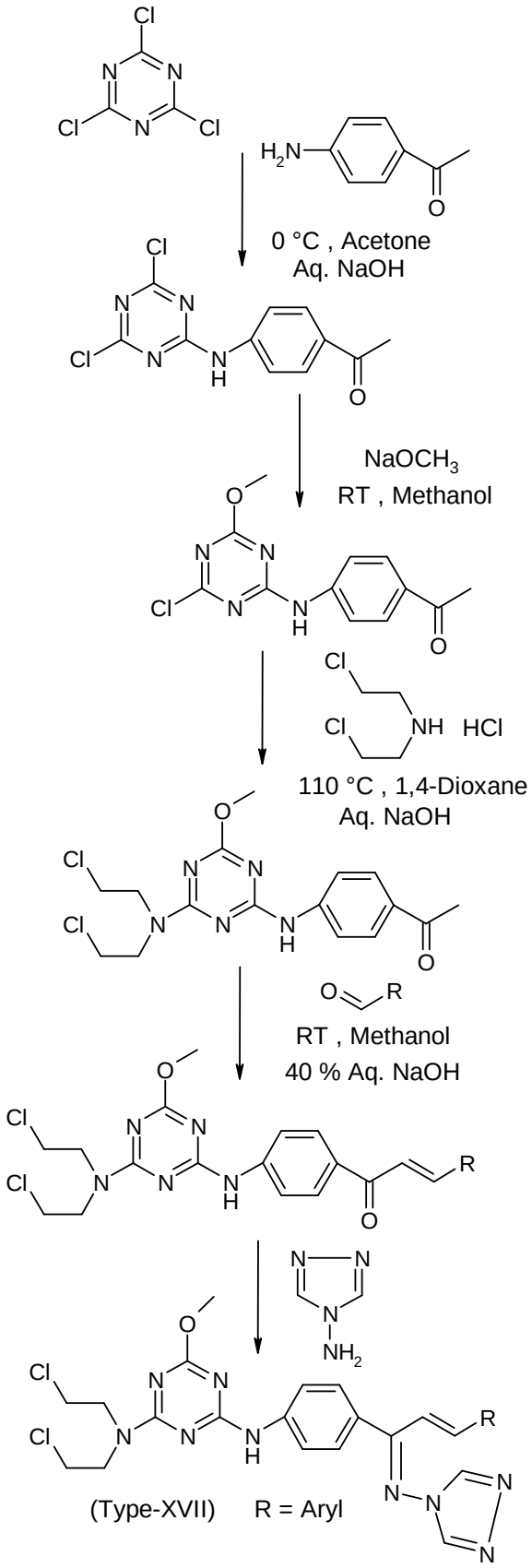
Maximum antimicrobial activity :

	Antibacterial activity Zone of inhibition in m.m.				**Antifungal activity Zone of inhibition in m.m.**
	B. mega. ***R***	***B. subtillis*** ***R***	***E. coli.*** ***R***	***P. fluorescens.*** ***R***	***A. awamori.*** ***R***
	3-OH C_6H_4 (20)	4-OH C_6H_4 (20)	3-OH C_6H_4 (23)	4-OH C_6H_4 (23)	C_6H_5 (20)
	4-OCH_3 C_6H_4 (19)	4-NO_2 C_6H_4 (21)	4-OH C_6H_4 (22)	4-NO_2 C_6H_4 (21)	3-OH C_6H_4 (21)
	4-OH, 3-OCH_3		4-OH, 3-OCH_3		3-NO_2 C_6H_4 (21)
	C_6H_4 (19)		C_6H_4 (18)		C_4H_3O (22)
	3-NO_2 C_6H_4 (23)				
	4-NO_2 C_6H_4 (24)				

Comparable activity with known standard drugs

Ampicilin	50 µg	23	18	17	27	-
Chloramphenicol	"	24	19	25	26	-
Norfloxacin	"	24	19	25	26	-
Greseofulvin	"	-	-	-	-	23

REACTION SCHEME



(Type-XVII) R = Aryl

EXPERIMENTAL

SYNTHESIS OF 2-{4'-[(3"-ARYL)-2"-PROPENE-1"-N-(1,2,4-TRIAZOLE) AMINO]}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1, 3, 5-TRIAZINE.

(A) **Synthesis of 2-(4'-Acetyl phenyl amino)-4, 6-dichloro-1,2,5-triazine**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(B) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-chloro-4-methoxy-1,3,5-triazine**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(C) **Synthesis of 2-(4'-Acetyl phenyl amino)-6-[Bis(2"-chloro ethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(D) **Synthesis of 2-{4'-[3"-(4""-methoxy phenyl)-2"-propene-1"-one) phenyl amino}-6-[Bis(2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine.**

For synthesis, see Part-I, Section-I, Page no. 36-38.

(E) **Synthesis of 2-{4'-[3"(4""-Methoxy phenyl)-2"-propene-1-N-(1,2,4-triazole) amino]}-6-[Bis(2"'-chloroethyl) amino]-4-methoxy-1,3,5-triazine.**

A mixture of 2-{4'-[3"-(4""-methoxy phenyl)-2"-propene-1"-one] phenyl amino}-6-[Bis(2"'-chloro ethyl) amino]-4-methoxy-1,3,5-triazine(5.02 gm,

0.01 M); 1-amino-1,3,4-triazole (0.76 gm; 0.01 M) and alcoholic KOH, the reaction mixture was refluxed fo 10 hrs. at 100º C. temp. The reaction mixture poured into crushed ice, filtered,dried and crystallised from dioxane, Yield : 79% ; M.P. 185º C. (Found : C : 54.90; H : 4.73; N : 22.15, $C_{26}H_{27}O_2N_9Cl_2$ required C : 54.92; H : 4.75; N : 22.18%).

Similarly other compounds were prepared and their physical data recorded in Table no. 33

(F) **Antimicrobial activity of 2-{4'-[3"-aryl)-2"-propene-1"-N-(1,2,4-triazole) amino]}-6-[Bis (2"'-chloro ethyl) amino]-4- methoxy-1,3,5-triazine.**

The antimicrobial testing was carried out as described in Part-I, Section-I, Page no. 39-41.

The zone of inhibition of the test solutions are recorded in Table no. 34.

TABLE NO : 33 : PHYSICAL CONSTANTS OF 2-{4'-[(3"-ARYL)-2"-PROPENE-1"-N-(1,2,4-TRIAZOLE) AMINO]}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1, 3, 5-TRIAZINE.

Sr. No.	R	Molecular Formula	M.P. .c	Yield %	% of Nitrogen	
					Calcd	Found
1.	C_6H_5	$C_{25}H_{25}Cl_2N_9O$	238	57	23.41	23.39
2.	2-OH C_6H_4	$C_{25}H_{25}Cl_2N_9O_2$	232	62	22.74	22.71
3.	3-OH C_6H_4	$C_{25}H_{25}Cl_2N_9O_2$	215	65	22.74	22.72
4.	4-OH C_6H_4	$C_{25}H_{25}Cl_2N_9O_2$	223	72	22.74	22.69
5.	4-OCH_3 C_6H_4	$C_{26}H_{27}Cl_2N_9O_2$	185	79	22.18	22.15
6.	4-OH, 3-OCH_3 C_6H_3	$C_{26}H_{27}Cl_2N_9O_3$	222	74	21.57	21.53
7.	4-Br. C_6H_4	$C_{25}H_{24}BrCl_2N_9O$	120	80	20.42	20.41
8.	3-NO_2 C_6H_4	$C_{25}H_{24}Cl_2N_{10}O_3$	182	83	24.01	24.00
9.	4-NO_2 C_6H_4	$C_{25}H_{24}Cl_2N_{10}O_3$	193	69	24.01	23.99
10	4-N,N$(CH_3)_2$ C_6H_4	$C_{27}H_{30}Cl_2N_{10}O$	169	72	24.09	24.05
11.	C_4H_3O (Furfuryl)	$C_{23}H_{23}Cl_2N_9O_2$	242	95	23.86	23.81

TABLE NO : 34 : ANTIMICROBIAL ACTIVITY OF 2-{4" [3"-ARYL)-2"-PROPENE-1"-N-(1, 2, 4 – TRIAZOLE) AMINO}-6-[BIS(2"'-CHLORO ETHYL) AMINO]-4-METHOXY-1,3,5-TRIAZINE.

Sr. No.	R	Antibacterial activity Zone of inhibition in mm.				Antifungal activity Zone of inhibition in mm.
		B. mega.	***B. subtillis***	***E. coli.***	***P. fluorescens***	***A. awamori***
1	C_6H_5	16	17	14	19	20
2	2-OH C_6H_4	15	19	17	20	17
3	3-OH C_6H_4	20	14	23	18	21
4	4-OH C_6H_4	18	20	22	23	19
5	4-OCH_3 C_6H_4	19	12	13	20	19
6	4-OH, 3-OCH_3 C_6H_3	19	15	18	18	16
7	4-Br. C_6H_4	16	14	17	17	14
8	3-NO_2 C_6H_4	23	17	15	19	21
9	4-NO_2 C_6H_4	24	21	14	21	16
10	4-N,N$(CH_3)_2$ C_6H_4	15	15	19	18	17
11	C_4H_3O (Furfuryl)	13	17	18	17	22

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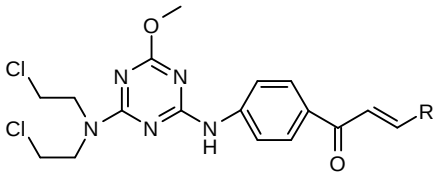
List of Papers Publication :

(1) Synthesis and Antimicrobial activity of 2-{4'-[(3"-Aryl)-2"-Propene-1"-one]-phenylamino}-6-[Bis(2"'-chloroethyl)amino]-4-methoxy-1,3,5-triazine.

P. J. Kathiriya, V. N. Patolia and D. M. Purohit*
Shree M. & N. Virani Science College, Kalawad Road, Rajkot-5, Gujarat(INDIA)

Chalcones are Phenyl styrylketones containing reactive keto ethylenic group (-CO-CH=CH-). Liturature serve reveals that chalcones derivatives possess antibacterial, antiviral, antifungal activities. Hence, it was thought worth while to synthesis chalcones (4a-4k) derivatives. The constitution of the products delinated by IR, ^{1}H NMR, Mass spectral studies and TLC. The products are evaluated their antimicrobial activity against Gram +ve bacteria, Gram –ve bacteria and fungi.



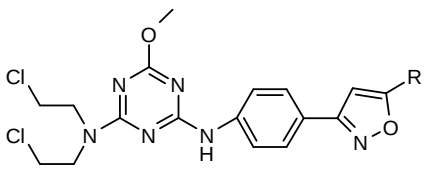
(4a-4k) R = Aryl

(An Indian Journal : Organic Chemistry)

(2) Synthesis and Antimicrobial activity of 2-{4'-[(5"-Aryl)-isoxazole-3"-yl]-phenylamino}-6-[Bis(2"'-chloroethyl)amino]-4-methoxy-1,3,5-triazine.

P. J. Kathiriya, V. N. Patolia and D. M. Purohit*
Shree M. & N. Virani Science College, Kalawad Road, Rajkot-5, Gujarat(INDIA)

Isoxazole derivatives are the potent biological activities, these have been reported to be active as antidepressants, antibacterial, antifungal, antiviral, antiinflamatory, analgesics and Bis (2-chloroethyl) amine possess anticancer, anti-HIV activities. In order to achieving better potency to synthesize isoxazoles (4a-4k) derivatives. The constitution of the products delinated by IR, ^{1}H NMR, Mass spectral studies and TLC. The products are evaluated their antimicrobial activity against Gram +ve bacteria, Gram –ve bacteria and fungi.



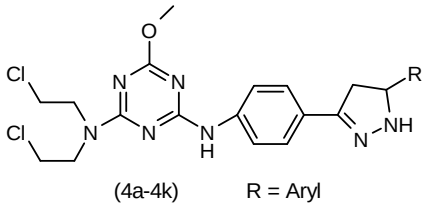
(4a-4k) R = Aryl

(Indian Journal of Heterocylclic Chemistry)

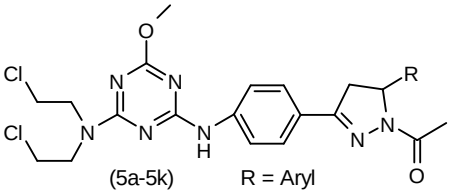
(3) Synthesis and Antimicrobial activity of 2-{4'-[(5"-Aryl) 4", 5"-dihydro-1"-(H)/acetyl-Pyrazol-3"-yl]-phenylamino} –6-[Bis (2"'-chloroethyl) amino] – 4 - methoxy-1,3,5 - triazine.

P. J. Kathiriya, V. N. Patolia and D. M. Purohit*
Shree M. & N. Virani Science College, Kalawad Road, Rajkot-5, Gujarat(INDIA)

Pyrazoline derivatives possess broad spectrum of pharmacological activities which are reflected by their use as analgesic, anticonvulsant, antimicrobial, antipyratics etc. The main moiety Bis (2-chloroethyl) amine, 1,3, 5-triazine nucleus have been reported to be active as antineoplastic agents with a view of above facts. Some new pyrazolines (4a-4k), (5a-5k) have been synthesized. The constitution of the products delinated by IR, ^{1}H NMR, Mass spectral studies and TLC. The products are evaluated their antimicrobial activity against Gram +ve bacteria, Gram –ve bacteria and fungi.



(4a-4k) R = Aryl



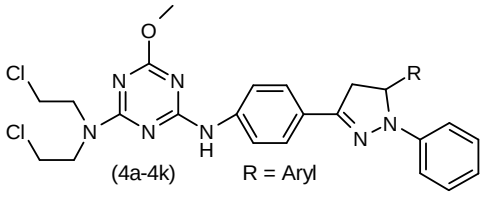
(5a-5k) R = Aryl

(Indian Journal of Chemistry, section-B)

(4) Synthesis and Antimicrobial activity of 2-{4'-[(5"-Aryl)-4", 5"- dihydro-1"-Phenyl Pyrazole-3"-yl]-phenylamino} – 6 - [Bis (2"- chloroethyl) amino] – 4 – methoxy - 1,3,5 - triazine.

P. J. Kathiriya, V. N. Patolia and D. M. Purohit*
Shree M. & N. Virani Science College, Kalawad Road, Rajkot-5, Gujarat(INDIA)

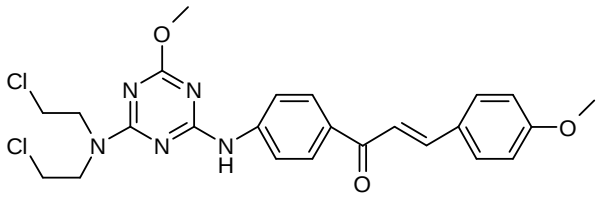
Pyrazoline derivatives possess broad spectrum of pharmacological activities which are reflected by their use as analgesic, anticonvulsant, antimicrobial, antipyratics etc. The main moiety Bis (2-chloroethyl) amine, 1,3, 5-triazine nucleus have been reported to be active as antineoplastic agents with a view of above facts, some new pyrazolines (4a-4k), have been synthesized. The constitution of the products delinated by IR, ^{1}H NMR, Mass spectral studies and TLC. The products are evaluated their antimicrobial activity against Gram +ve bacteria, Gram –ve bacteria and fungi.



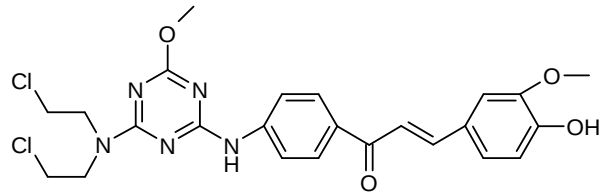
(4a-4k) R = Aryl

(Indian Journal of Heterocyclic Chemistry)

List of Compounds Selected for Anti Cancer And Anti-HIV Screening at NCI (USA)



Compound Code : PJK-005



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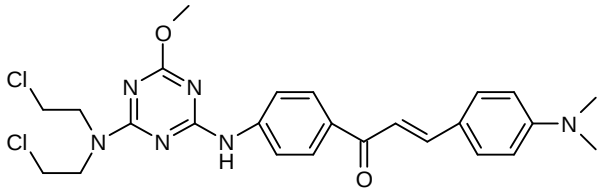

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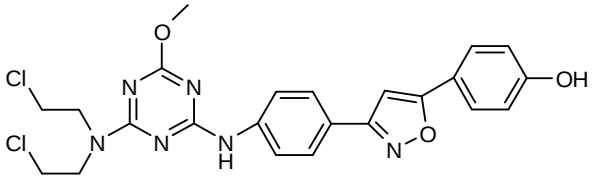

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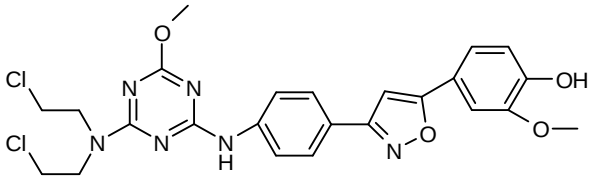

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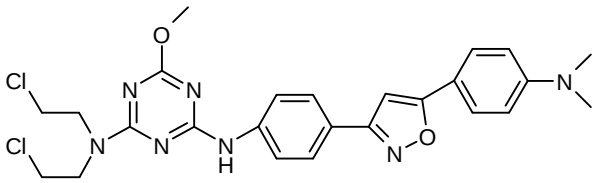

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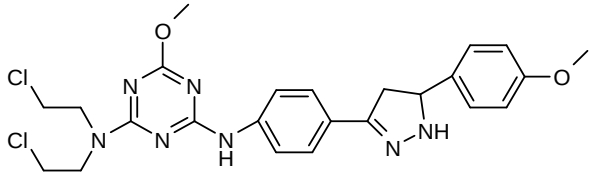

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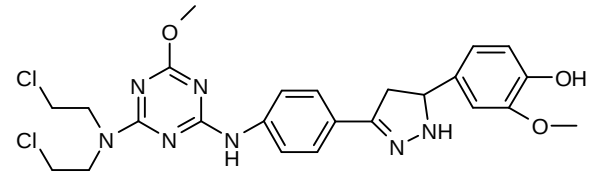

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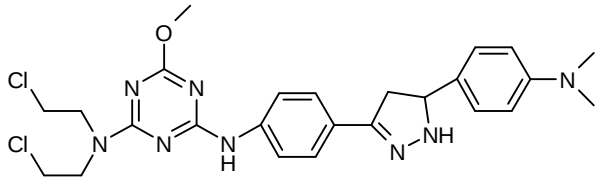

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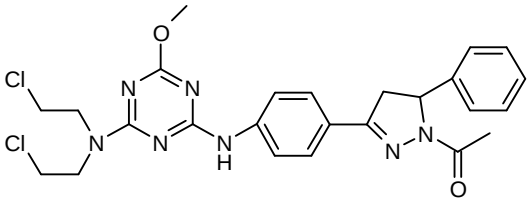

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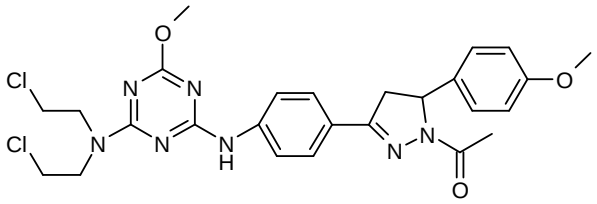

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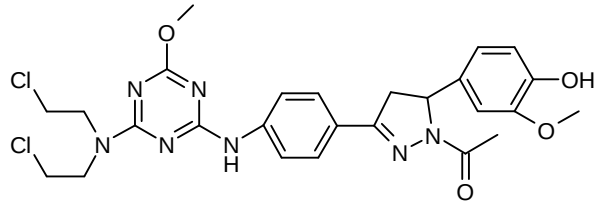

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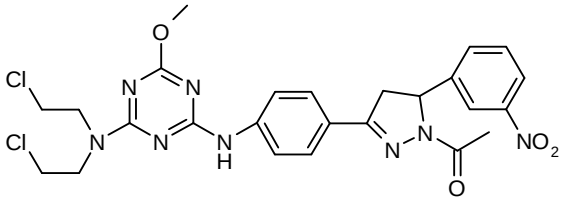

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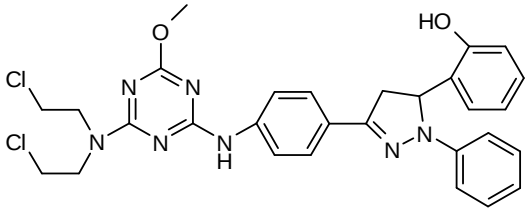

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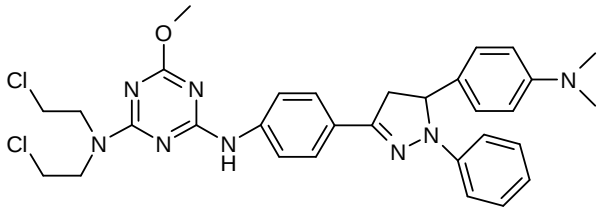

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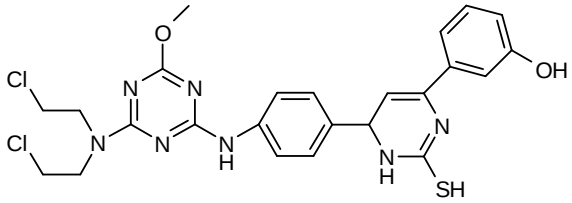

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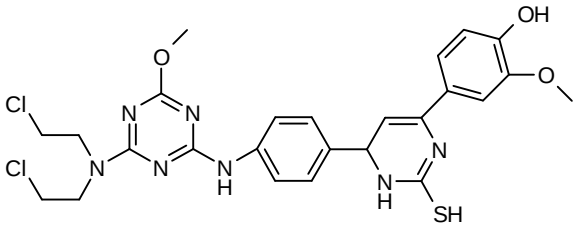

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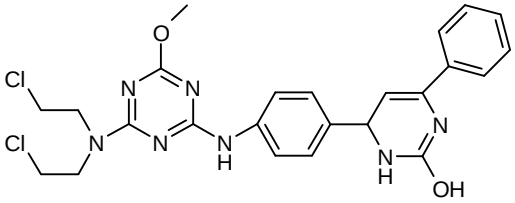

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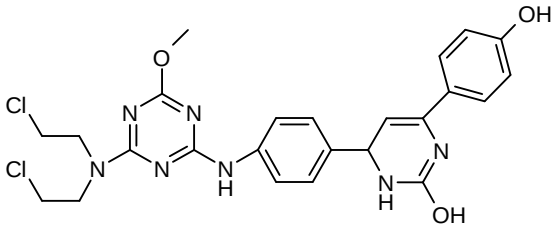

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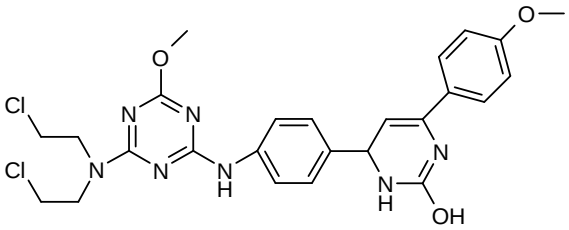

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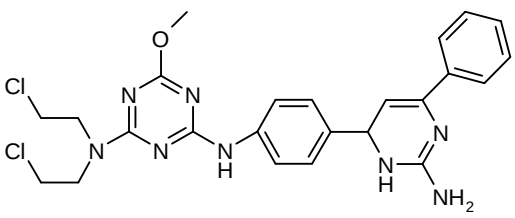
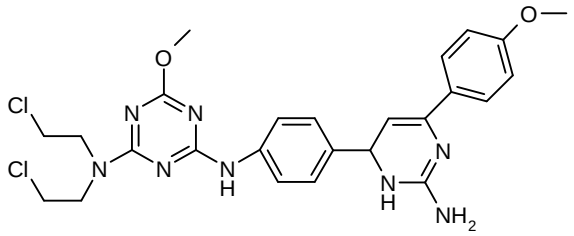


Compound Code : PJK-078



Compound Code : PJK-082