

SYNTHESIS OF NOVEL 2, 3-DISUBSTITUTED 5-
NITROQUINAZOLINONE AND ALLIED COMPOUNDS
AS ANTIBACTERIAL AGENTS

THESIS SUBMITTED
UNIVERSITY OF MUMBAI

FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
ORGANIC CHEMISTRY

SUBMITTED BY
MUKTA BHORA

UNDER THE GUIDANCE OF
DR. B. G. KHADSE

DEPARTMENT OF CHEMOTHERAPY
HAFFKINE INSTITUTE FOR TRAINING, RESEARCH & TESTING
MUMBAI

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SYNTHESIS OF NOVEL 2,3-DISUBSTITUTED-5-NITROQUINAZOLINONE AND ALLIED COMPOUNDS AS ANTIBACTERIAL AGENTS

**A
Thesis Submitted
To The
University Of Mumbai
For The Degree of
Doctor of Philosophy
In
The Faculty of Science
(Organic Chemistry)**

**By
Ms. Mukta Bohra
M.Sc.**

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2001

In
Loving Memory
of My
Beloved Brother

Acknowledgement

It is with immense pleasure and gratitude that I look upon this part acknowledgement. It gives me an opportunity to express my gratitude towards all those who have involved themselves in making my work a success. I express my immense sense of gratitude to my guide, respected Dr. B.G. Khadse Ex-director Haffkine institute, whose valuable guidance and encouragement made me carry out my research work.

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Above all I thank almighty God for providing me the strength to get through the difficult moments of my life.

Mukta

STATEMENT

Statement submitted under rule 0.770

For the Thesis, which I intend to submit, no degree or diploma or distinction has been conferred on me before, either in this or any other University.

Statement submitted under rule 0.771

Statement I :

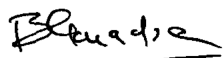
The work embodied in the Thesis to be submitted is original, based on the discovery of new facts, viz. the synthesis and characterization of new and unknown compounds of possible chemotherapeutic value. Also included in the Thesis, are new relations of facts, observed on the basis of in vitro testing.

The assessment of the compounds has been made at the Department of Microbiology and Department of Chemotherapy, Haffkine Institute, Mumbai 400 – 012.

Statement II :

During the study, all available information of related nature published in scientific journals by previous workers in allied fields, has been used as a source of information, as indicated in the "**References**".

The entire work has been planned and carried out by the candidate.



Dr. B. G. Khadse
Research Guide



Mukta Bohra
Research Student

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*Introduction
and
Review of Literature*

Introduction and Review of Literature

“Medicinal chemistry remains a challenging field which provides profound satisfaction to its practitioners. It intrigues those of us who like to solve problems posed by nature. It verges increasingly on biochemistry and on all the physical, genetic and chemical riddles in animal physiology, which bear on medicine. Medicinal chemists have a chance to participate in the fundamentals of prevention, therapy and understanding of diseases, and thereby to contribute to a healthier and happier life. For many centuries, the search for chemotherapeutic substances focussed on the investigation of natural products. In the nineteenth century, the advent of analytical and synthetic chemistry triggered important changes when alkaloids were isolated in pure forms. Molecules such as acetyl salicylic acid were synthesized. However, the true era of medicinal chemistry really began in the 1930s with the preparation and use of antibacterial sulfonamide drugs.

From that time, on the history of medicine was dominated by medicinal therapeutics.

Today, a large number of diseases are cured, or at least controlled by drug therapy. The fight against bacterial and fungal infections has been largely won and significant progress has been made in treating mental, cardiovascular and gastrointestinal conditions. The work presented in this thesis is yet another humble effort in the field of medicinal chemistry, though very minute to be regarded as a small step in offering a practical solution to the innumerable problems. The work deals with some of the commonest ailments, viz. tuberculosis, other bacterial and fungal infections which are not considered fatal by and large. But even today these create problems, when coupled with other chronic conditions, and also due to the resistance offered by infecting organisms to various forms of therapy.

TUBERCULOSIS

Tuberculosis, a disease largely caused by *Mycobacterium tuberculosis*, an ‘acid-fast’ bacilli, is known to mankind since Vedic times. It occurs throughout the world and is a significant contributor to the morbidity and mortality in several developing countries. Approximately one-third of the world population is infected by *M. tuberculosis*. It is estimated¹ that in 1995 alone, 8.8 million people were infected, out of which 3 million died. While it has been largely contained in the industrialized

countries, TB has reemerged among patients infected, with the human immunodeficiency virus (HIV)².

In India, as per reports, nearly 5,00,000 persons die of tuberculosis annually. The number of patients at any given time has been estimated to be atleast 9-10 million, of which one-fourth (2-2.5 million) are likely to bear the infectious type³.

Apart from *M. tuberculosis*, which is the principle mycobacteria responsible for causing tuberculosis, other causative mycobacteria include *M. bovis* and *M. africanum*. While *M. tuberculosis* is generally transmitted through airborne droplets dispersed by patients with infectious pulmonary or laryngeal disease, *M. bovis* is transmitted through milk from diseased cows.

Mycobacterial and other common bacterial infections differ in their host-parasite relationship. The common bacteria multiply rapidly and induce a quick, defensive response from the host. If the defence mechanism of the host is adequate to deal with the invasion, then the bacteria are eliminated, and if not, then the bacteria emerge victorious by overwhelming the host. In either case, the process is usually of short duration and the outcome of the contest is decided in a short time.

Mycobacterial infections such as tuberculosis, are chronic diseases which do not elicit a rapid response from the host. After initial infection and multiplication the bacilli may lie dormant for a long time without giving rise to any of the clinical symptoms. Often, however, the bacilli may be reactivated due to malnutrition, immunosuppressive drugs and diseases, including HIV infection. As the human system is endowed with a relatively high resistance through years of natural selection, particularly in our urban communities, the effect of this invasion by a slow growing, but persistent organism, is to prolong the struggle, thus making the disease chronic.

Tuberculosis is characterized by the formation of nodular bodies or tubercles in the tissues, from which the disease derives its name. In most cases, the primary area of infection is the lungs, but other vulnerable areas include lymph nodes, kidneys, bones, the genital tract, the brain and the meninges. In case of infections of the

lungs, the lesions often liquify and drain into the bronchial tree, giving rise to a persistent cough accompanied by sputum.

Tuberculosis causes extensive tissue destruction and virulent bacilli reside in the cavities and debris of the tissue, thus being relatively immune to any drug action. The tubercle formation, even though serving a useful purpose of walling off the infection and preventing them from spreading, also protects walled off colonies from chemotherapeutic attack.

Also, tubercle bacilli are vulnerable to bactericidal drugs only when they are metabolically active and replicating. Here, the problem lies in the fact that a small subpopulation of bacilli can remain dormant indefinitely, except for short periods when they become transiently active, thus evading chemotherapeutic agents. Another difficulty is in the existence of drug resistant mutants in populations of bacilli hitherto unexposed to antibiotics.

A truly effective drug should, therefore, be capable of penetrating the tubercle and the debris, enter the phagocytes within which the bacilli are growing and finally destroy them. It should possess potent bactericidal/sterilizing activity against metabolically active and semidormant bacilli while also preventing the emergence of resistant strains throughout the normally prolonged period of treatment.

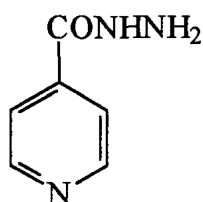
There is no known drug individually self-sufficient, possessing all the listed properties in its entirety. Hence, a combination of two or more drugs is used for the treatment, which may stretch to several months before a reasonable cure is effected.

Five drugs are currently considered essential in the control of tuberculosis – Isoniazid, Rifampicin, Streptomycin, Ethambutol and Pyrazinamide. Thiacetazone too is used widely to supplement Isoniazid in many developing countries due to its low cost. Other drugs of value in treating patients with multiple-drug-resistant disease include p-amino salicylic acid (PAS), Kanamycin, Cycloserine, Capreomycin, Viomycin and Ethionamide, but generally they are more toxic and expensive.

A review of all the known antitubercular agents would be voluminous and are in any case well recorded in other sources of information. Hence, a brief description of the essential drugs used for the control of the disease would be within the scope of this work.

Isoniazid (INH)

Isoniazid (I), the hydrazide of isonicotinic acid, was first described in 1912 but its action against the tubercle bacilli was only discovered in 1952. It is unrivalled in its bactericidal action and ensures the destruction of the bacilli within a few days of starting treatment. It is highly active against replicating tubercle bacilli but does not affect the semidormant species⁴ which resume multiplication after removal of contact with the drug.



(I)

INH is rapidly absorbed when administered either orally or parenterally and diffuses readily into all fluids and tissues. INH is a member of all antitubercular chemotherapeutic combinations currently recommended by the World Health Organisation (W.H.O.)

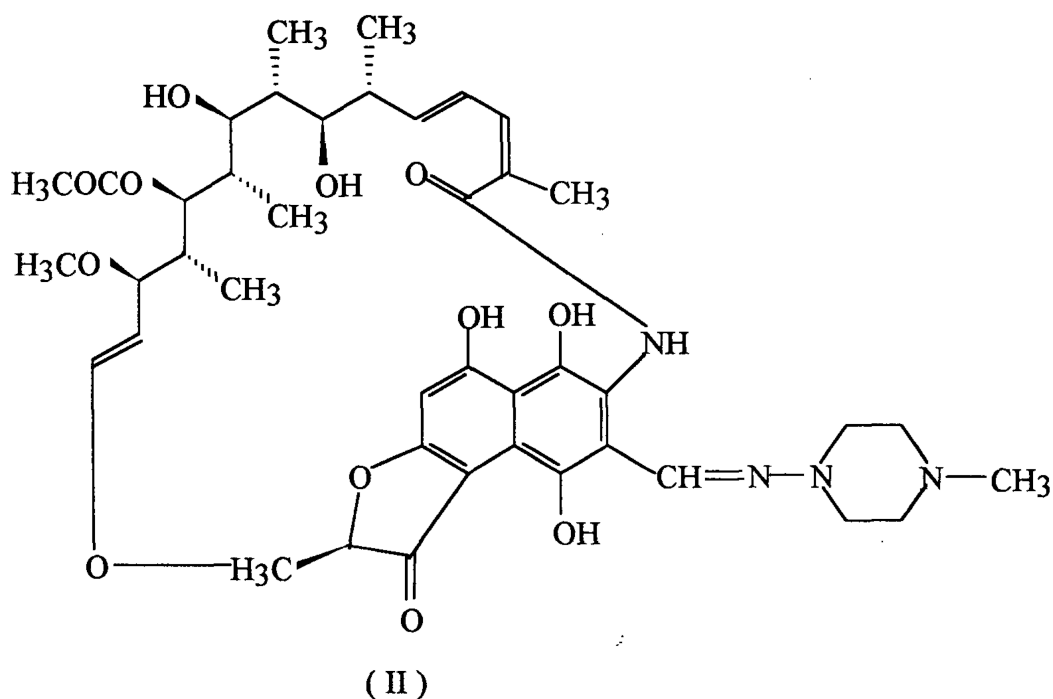
INH is generally well tolerated at the recommended dose, which is approximately 5 mg/kg (maximum 300mg) daily, for adults and children. The most important side effect of the drug is related to its toxicity, especially to the peripheral and central nervous system. Peripheral neuritis is the most common reaction and is said to occur in 17% of the patients receiving 6mg/kg of Isoniazid daily. This can be prevented by administering 100mg of Pyridoxine, a naturally occurring form of Vitamin B₆.

Hepatitis is a not so common, but nevertheless a serious side effect associated with INH therapy. This is mostly prevented by a prompt withdrawal of treatment. A sharp rise in the serum concentrations of hepatic transaminases at the onset of treatment is usually not clinically significant. If the enzyme levels normalise on suspension of

dosage then there is less chance of them rising once again when treatment is resumed.

Rifampicin

It is a semi-synthetic derivative of Rifamycin, a complex antibiotic which inhibits the synthesis of ribonucleic acid (RNA) in a broad range of microbial pathogens. It exhibits potent bactericidal and sterilizing action against tubercle bacilli, in both cellular and extra-cellular locations.



The effectiveness of Rifampicin(II) in the treatment of patients with drug-resistant tuberculosis was considered 'extraordinary' when it was first introduced⁵.

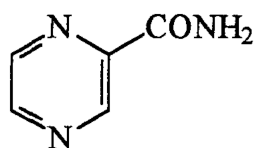
Rifampicin is believed to inhibit the synthesis of RNA by inactivating the deoxyribonucleic acid (DNA) dependent RNA polymerase, thus terminating the process of bacterial gene expression. Since Resistance to Rifampicin develops rapidly, it is always administered in combination with other effective antimycobacterial agents.

As absorption of the drug is reduced when taken with food, it is preferably given about 30 minutes before meals at a dosage of 10 mg/kg (max. 600 mg) daily in both adults and children. It is usually well tolerated at recommended doses, although

there are reports of severe gastrointestinal disturbances. Other adverse effects include skin rashes, fever and influenza-like syndrome.

Pyrazinamide

Pyrazinamide (III) is a synthetic Pyrazine analogue of Nicotinamide and was successfully used against human tuberculosis in 1952⁶. It is only weakly bactericidal against *M. tuberculosis* but has a potent sterilizing activity on organisms that exhibit slow growth owing to an acidic pH of the environment, such as inside macrophages. Thus, it is able to destroy tubercle bacilli which is otherwise left relatively untouched by other drugs. It is highly effective during the first two months of treatment and is administered at a dosage of 30 mg/kg daily, in both adults and children.

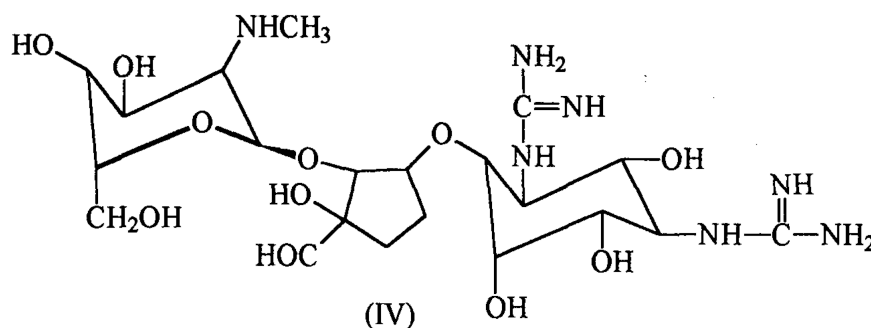


(III)

It is usually well tolerated but there have been complaints of slight flushing of the skin. An excessive exposure of the skin to sunshine may occasionally cause a reddish brown colouration of the exposed areas resembling sunburn. Other adverse effects are pain in the joints and sometimes attacks of gout necessitating treatment.

Streptomycin

The antitubercular action of Streptomycin (IV), an antibiotic isolated from a culture of *Streptomyces griseus*, was first demonstrated by Schatz and Waksman in 1944. It is not absorbed from the intestinal tract, but after intramuscular administration it diffuses readily into most body tissues and attains bactericidal concentrations in tuberculous cavities. This drug is of particular use when primary resistance to other drugs is suspected.



Hypersensitivity reactions due to the use of Streptomycin are common and include severe vestibular damage. This was a high risk factor earlier but is uncommon with the currently recommended dosages. If there are complaints of headache, vomiting or vertigo, the dosage is reduced.

Ethambutol (V) has been classified as a bacteriostatic drug⁷. It has been developed as a synthetic congener of related ethanediamines and is bactericidal against *M. tuberculosis*, *M. bovis* and some non-specific mycobacteria. It is used in combination with other antitubercular drugs to prevent or delay the emergence of resistant strains. Approximately 75 % of the strains of the human type are sensitive to Ethambutol at a concentration of 1 µg/ml. Bacterial resistance to the drug develops *in vivo* when it is given alone.



Ethambutol can bring about dose-dependent optic neuritis, readily resulting in impairment of visual acuity and color vision. If detected early, this effect is usually reversible, but blindness can occur if treatment is not discontinued promptly. Patients

who are too young or who are otherwise unable to comprehend early should not receive this drug.

OTHER BACTERIAL INFECTIONS

The development of resistance to current antibacterial therapy continues to drive the search for more effective agents. Bacteria are commonly responsible for many diseases, which were considered until recently to be resistant to chemotherapy. The bacteria were thought to be primitive in structure and so could be influenced by chemicals which are not highly toxic to the host. Many attempts have been made to combat bacterial infections in animals by the use of drugs, but most of them have met with little or no success, with the exception of Morgenroth and Levy's partial success in the year 1911, in combating bacterial infections of the blood stream. They found that ethyldihydrocuprein (Ophocin), a quinine derivative, would cure *Pneumococcal* infection in mice. Heidelberger and Jacobs, coupled diazotised p-amino benzene sulphonamide with dihydrocuprien and found that the resultant compound had only mild activity and was not further investigated.

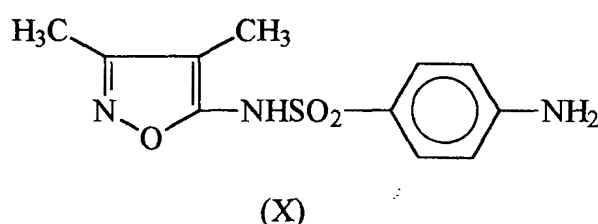
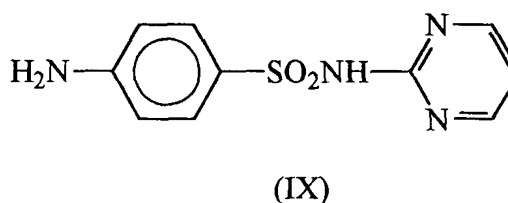
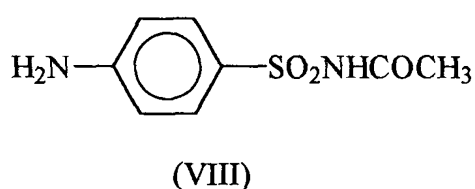
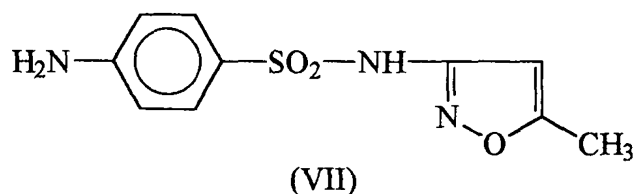
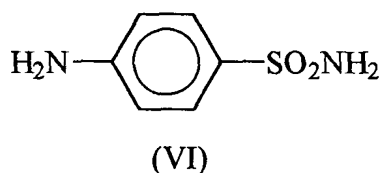
However, in 1935, Dogmagk⁸ Mietzsch and Klarer⁹ first dispelled the failure of earlier scientists by discovering Prontosil, and reported that this compound cures *Streptococcal* infections in mice and *Staphylococcal* infections in rabbits. This period was considered to be a brilliant era in the chemotherapy of microbial infections.

The history of antibacterials has thus been dynamic, characterized by the constant emergence of new challenges followed by investigation, discovery and the production of new drugs. A complete review of the various agents employed as antibacterials would be beyond the scope of this work and hence, is not attempted. The following pages present a brief summary of the important classes of compounds used for this purpose.

Sulfonamides :

The term sulfonamide is usually employed as a generic name for derivatives of p-aminobenzene-sulfonamide. These drugs were the first synthetic chemotherapeutic agents employed to prevent and cure bacterial infections in man, and were quite effective in bringing about a sharp decline in the morbidity and mortality figures for

the treatable infectious diseases. The important members of this class include Sulfanilamide (VI), Sulfamethoxazole (VII), Sulfacetamide (VIII), Sulfadiazine (IX) and Sulfisoxazole (X).



The sulfonamides have a wide range of antibacterial activity against both gram-positive and gram-negative bacteria. They are usually rapidly absorbed from the gastrointestinal tract, except in the bowel. Approximately about 70-100% of an oral dose is absorbed and finally eliminated from the body, partly as metabolic products; the largest fraction being excreted in the urine.

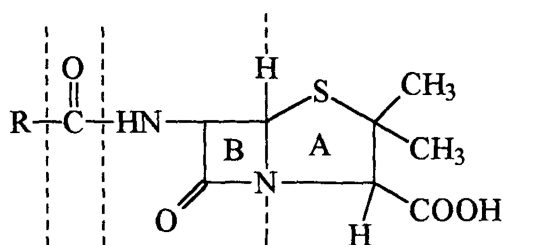
Resistant strains of bacteria to the sulfonamides have become common during recent years. Also, the advent of Penicillins and other broad spectrum antibiotics has diminished the role of sulfonamides as antibacterial agents. However, the introduction of the combination of Trimethoprim and Sulfamethoxazole, known popularly as Cotrimoxazole, has resulted in the increased use of Sulfonamides for the treatment of specific bacterial infections.

Penicillins and Cephalosporins :

Since Alexander Fleming's serendipitous discovery of Penicillin in 1928, Penicillins have remained one of the most important group of antibiotics. Despite the discovery

of several other bacterial agents, the Penicillins are widely used with new derivatives being produced every year. Due to their unique advantages, members of this group of antibiotics are presently the drugs of choice for the treatment of a large number of infectious diseases.

The basic structure of Penicillin (XI) consists of a thiazolidine ring (A) connected to a β -lactam ring (B), which is attached to a side chain(R) through an amide carbonyl. The Penicillin nucleus is an important requirement for biological activity, alteration of which causes loss of all significant activity. Many of the bacterial and pharmacological characteristics of Penicillins are determined by its side chain, which can also alter the susceptibility of the resultant compounds to inactivating enzymes (β -lactamases).



(XI)

The Penicillins are classified according to their spectrum of antibacterial activity. While the pharmacological properties of the individual drug in the various classes would constitute a lengthy discussion, certain generalisations can, however, be made. Following absorption, Penicillins are widely distributed throughout the body. The therapeutic concentrations of these agents are quite rapidly achieved in tissues, but comparatively much lower levels are found in brain tissues and intra-ocular fluids.

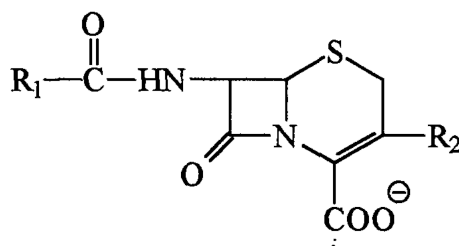
The Penicillins do not penetrate the living phagocytic cells to a great extent. This class of compounds is quite rapidly eliminated, particularly by glomerular filtration and renal tubular filtration, as a result of which high concentrations of the drug are found in the urine. Therefore, they exhibit short half-lives of approximately 30-60 minutes.

No sooner was the fact established that Penicillins are capable of eradicating microorganisms, than it was practically administered in every situation where there

was a risk of bacterial infection. But after the investigations of prophylaxis under controlled conditions, it is now understood that Penicillin is highly efficient in some situations, quite the contrary in others and of questionable value in still others.

The commonly cited adverse effects in the usage of Penicillins, which are probably the most common causes of drug allergy, have been the hypersensitivity reactions. Such reactions could occur with any dosage form of Penicillin, but as the drug is rapidly eliminated, the allergic reactions usually subside. In some cases the symptoms may persist for one to two weeks after withdrawal of treatment, while in other cases, the reaction is mild and disappears during therapy with the drug. At the worst of circumstances, an extreme allergic reaction may even result in death of the patient.

The Cephalosporins (XII) have shown tremendous growth over the past decade and are usually classified by the 'generations' system, which is based on the general features of antibacterial activity.



(XII)

The first generation Cephalosporins exhibit good activity against gram-positive organisms and relatively lower activity against gram-negative bacteria. The second generation Cephalosporins exhibit better activity against gram-negative microorganisms, but are inferior to the third generation Cephalosporins. The third generation Cephalosporins are generally less active against gram-positive bacteria as compared to first generation agents, but are much more active against β -lactamase producing strains.

The Cephalosporins are widely used as antibiotics, and perhaps overused for conditions where much less expensive antibiotic could not provide relief. Nevertheless they are indeed useful as alternatives to Penicillins for a variety of infections in patients who suffer allergic reactions to Penicillins.

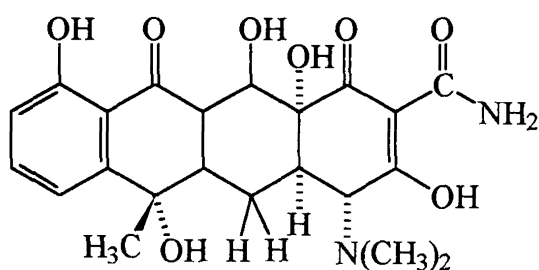
The Cephalosporins also find wide use in prophylaxis during and after surgery, wherein the first generation agents have been shown to be safe and effective. A few of the third generation Cephalosporins are the drugs of choice for meningitis, and in some cases are superior to the combination of Ampicillin and Chloramphenicol.

The β -lactam antibiotics (Penicillins and Cephalosporins) suffer bacterial resistance due to a variety of factors. It may be caused by the inability of the agents to enter the site of action¹⁰. Also, it is possible for a sensitive strain to acquire resistance by mutation and has been described for gram-positive cocci¹¹.

Bacteria can also destroy the β -lactam antibiotics enzymatically. β -lactamases are capable of inactivating certain of these antibiotics and is the major term of this enzyme although different microorganisms synthesise a number of distinct β -lactamases. Depending on substrate specifications, these are often described as either Penicillinases or Cephalosporinases. Individual Penicillins and Cephalosporins vary in their susceptibility to these enzymes.

Tetracyclines :

Tetracyclines (XIII) exhibit a wide range of activity against gram-positive and gram-negative bacteria. In general, gram-positive bacteria are affected by lower concentrations of Tetracycline than the gram-negative species. However, they are rarely recommended for infections caused by gram-positive bacteria due to problems of resistance and availability of superior antibacterial agents.



(XIII)

Microorganisms that have become resistant to one Tetracycline frequently exhibit resistance to other members of the family. The bacterial species possibly exhibit resistance only after exposure to the drug. The Tetracyclines were initially useful for the treatment of infections with aerobic gram-negative bacteria, but most species are

now relatively resistant. Nevertheless, more than 90% strains of *Haemophilus influenzae* may still be sensitive to either Tetracycline or Doxycycline.

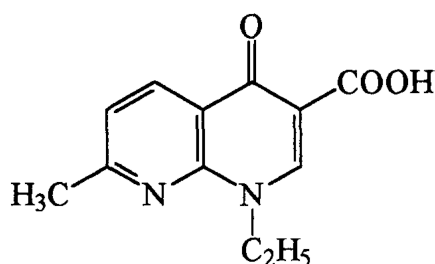
All Tetracyclines produce gastrointestinal irritation to varying degrees in some individuals, and this is more common after oral administration. Diarrhoea may also be a side effect which, though frequent and fluid, does not contain blood or leukocytes. Doxycycline, and to a lesser extent other derivatives, may produce mild to severe reactions in the skin of treated individuals exposed to sunlight.

Other important antibacterial agents include Chloramphenicol and furan derivatives such as Nitrofurantoin, Nitrofurazones, Furazolidone etc. Several of these drugs are active against various species of gram-positive and gram-negative microorganisms besides mycobacteria.

Quinolones :

The quinolone carboxylic acids, or 4-quinolones, are a group of synthetic antibacterial agents structurally related to Nalidixic acid (XIV). Nalidixic acid is active against gram-negative bacteria but has little activity against *Pseudomonas* and gram-positive organisms, because of which their bactericidal use has generally been limited to the treatment of urinary tract infections.

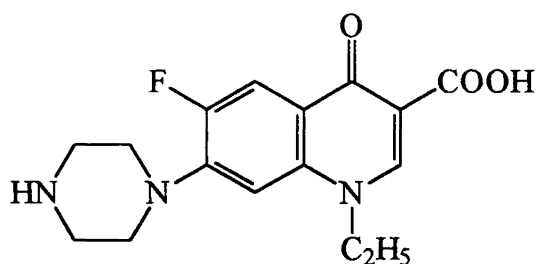
Modifications in the structure of Nalidixic acid have produced related antibacterial agents such as oxolinic acid, piromidic acid, cinoxacin and acrosoxacin. None has been considered to represent a significant clinical advance over nalidixic acid.



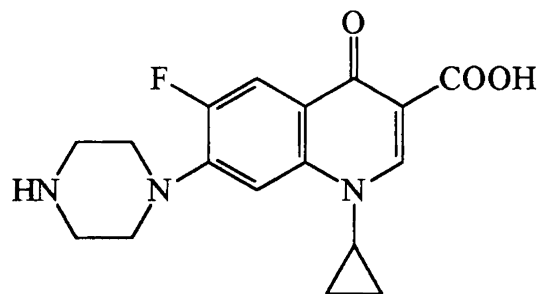
(XIV)

Addition of the 7-piperazinyl group and a fluorine atom at 6-position of the quinolone has produced a group of fluoroquinolones with spectrum of activity broader than that of nalidixic acid, and they are found to be more useful for the treatment of systemic infections. They include Norfloxacin (XV), Ciprofloxacin (XVI), Enoxacin (XVII), Ofloxacin (XVIII) and Lomefloxacin (XIX). One disadvantage of all the quinolone

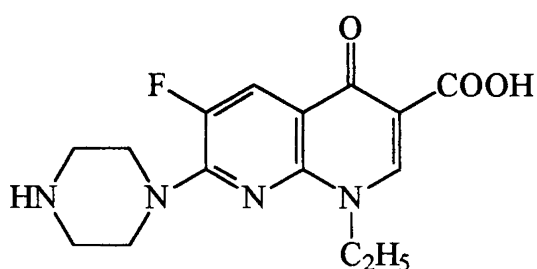
antibacterial agents is that they are generally not recommended for use in children, adolescent, pregnant and breast feeding women, because of their propensity to cause joint erosions in immature animals.



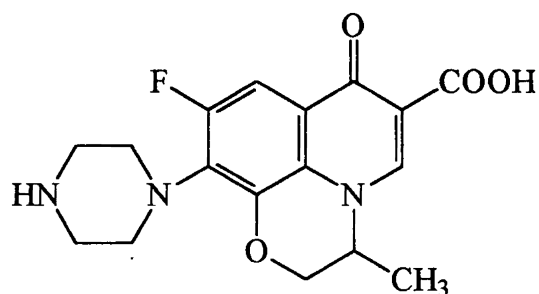
(XV)



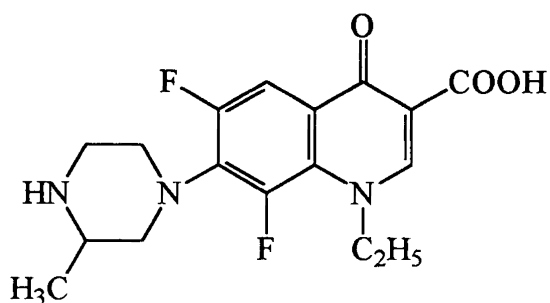
(XVI)



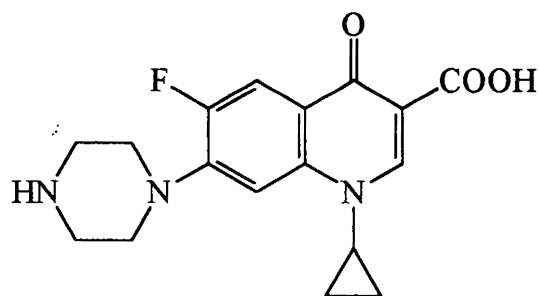
(XVII)



(XVIII)



(XIX)

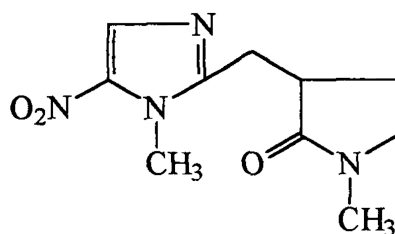


(XX)

Tefloxacin (XX) was demonstrated by J. L. Chen *et al*¹² to possess activity against Penicillin resistant *Staphylococcus*, *Streptococcus* and *Haemophilus* species. It was itself a β -lactamase inhibitor and displayed synergy with Ampicillin.

Miscellaneous :

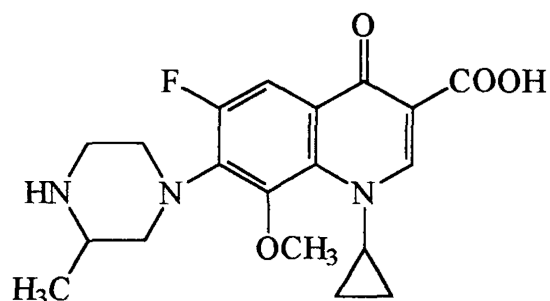
A series of 2-substituted-5-nitroimidazoles was reported to active against anaerobic organisms. Compound (XXI) was unique in this series, and was found to be more potent both *in vitro* and *in vivo* as compared to Metronidazole.



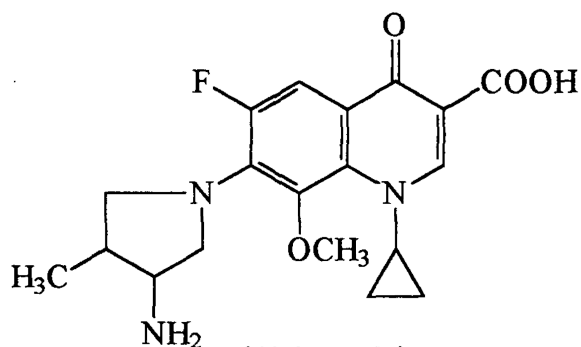
(XXI)

Quinolones :

The use of N-cyclopropyl and C-8 hetero atom substituents on quinolone nucleus continued to provide potent antibacterial agents. AM – 1155 and AM – 1174, new quinolones bearing 8-methoxy group, outperformed Ciprofloxacin against anaerobes and a range of gram-positive bacterial with potency upto 16 to 62 – fold greater than Ciprofloxacin¹³.

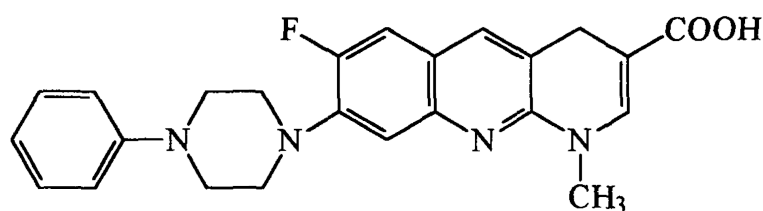


(AM - 1155)



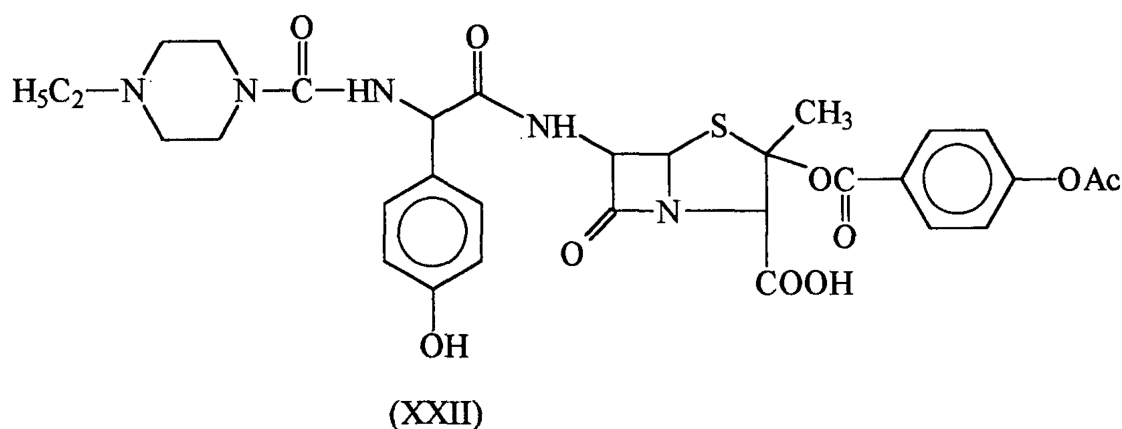
(AM - 1174)

RU –67829 (a compound in benzonaphthyridine series) was found to be more active against gram-positive organisms than Ciprofloxacin¹⁴.

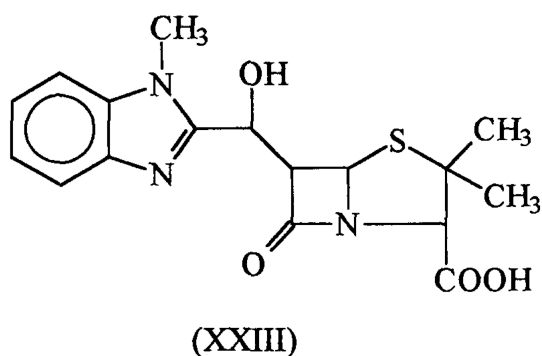


(Ru - 67829)

In Penicillins, the catechol containing compounds (XXII) had outstanding activity against *Pseudomonas*, and stability to gram-negative β -lactamases, but not to the lactamases of *S. aureus*¹⁵.

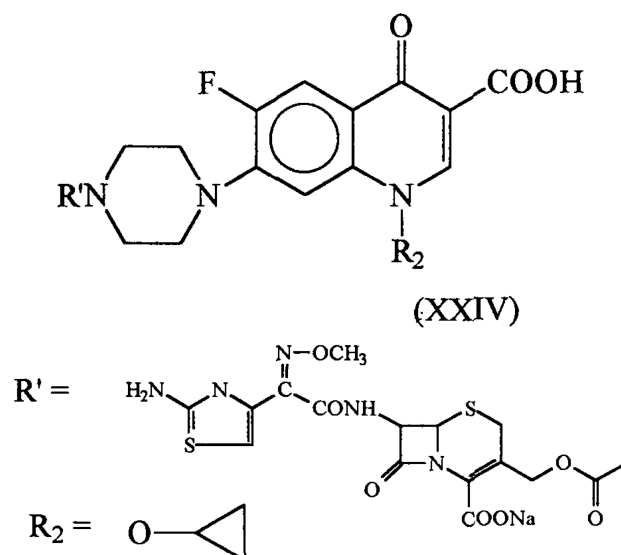


The stability to gram-positive β -lactamases could be achieved through the use of a (benzimidazole-2-yl)-hydroxymethyl group at the R-position (XXIII).



AM – 1174 exhibited activity 128-fold that of Ciprofloxacin against Ciprofloxacin-resistant strains of *S. aureus*¹⁶.

Recently, new β -lactum quinolone hybrids have been reported. The carbamate linked R0-24-4383 (XXIV) showed a broad spectrum of activity and exhibited aqueous solubility much greater than that of the quinolone component alone¹⁷.



FUNGAL INFECTIONS

Fungi, like the human host, are eukaryotic organisms, and thus the number of suitable targets for therapeutic attack are limited. Nonetheless considerable progress in treating fungal infections has been achieved through better application of established antifungal agents and the development of promising new investigational agents. This ever expanding battery of antifungal agents exhibits a wide variety of pharmacokinetic profiles, mechanisms of action and toxicities.

The incidence of systemic mycoses continues to rise steadily. This increase is due in part to improved recognition and diagnosis of fungal infections, but also to the prolonged survival of patients with global defects in their host defense mechanism including patients with neoplastic diseases, organ-transplant recipients, diabetics and patients with AIDS. These patients are susceptible to an ever growing list of opportunistic fungi. From the data collected by Centre for Disease Control, it is known that among the 1 and 2 million healthy Americans who have already been infected with AIDS, a significant number of these cases are associated with various fungal infections¹³⁵. One yeast-like fungus, *Cryptococcus neoformans*, is reported to be the common reason for debilitating and life-threatening infections in AIDS patients¹⁸.

The agents which are currently in use as antifungals are classified and listed below:

Allylamines

Naftifine
Terbinafine

Triazoles

Fluconazole
Itraconazole
Terconazole

Imidazoles

Bifconazole
Butaconazole
Chlorimidazole
Clotrimazole
Econazole
Enilconazole
Fenticonazole
Isoconazole
Ketoconazole
Niconazole
Oxiconazole
Sulconazole
Tioconazole

Polyene macrolides

Amphotericin
Candididin
Hachimycin
Kanamycin
Nystatin
Pentamycin

Most of the antifungals given above are applied in the treatment of infections of hair mucous membranes, nails and skin caused by *Candida dermatophytes*, fungi including *Epidermophyton*, *Microsporum*, *Trichophyton* and *Malassezia furfur*. The main agents, which are used in treating these infections, are listed below.

Superficial Fungal Infection

Candida infections
Tinea
Pityriasis versicolor

Main topical antifungal agents

Azoles, Polyene antifungals
Olamine, Haloprogin, Tolnaftate, Azoles, Ciclopirox,
Azoles, Ciclopirox, Olamine, Haloprogin, Tolnaftate

Systemic fungal infections tend to occur in immuno-compromised patients and include infections due to *Aspergillus*, *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus*, *Histoplasma*. The common drugs used in such infections are listed below.

Systemic fungal infections

Aspergillosis
Blastomycosis

Main antifungal agents

Amphotericin
Amphotericin, Ketoconazole

Candidal infections:

Oesophageal
Disseminated
Coccidioidomycosis
Cryptococcosis
Histoplasmosis
Paracoccidioidomycosis

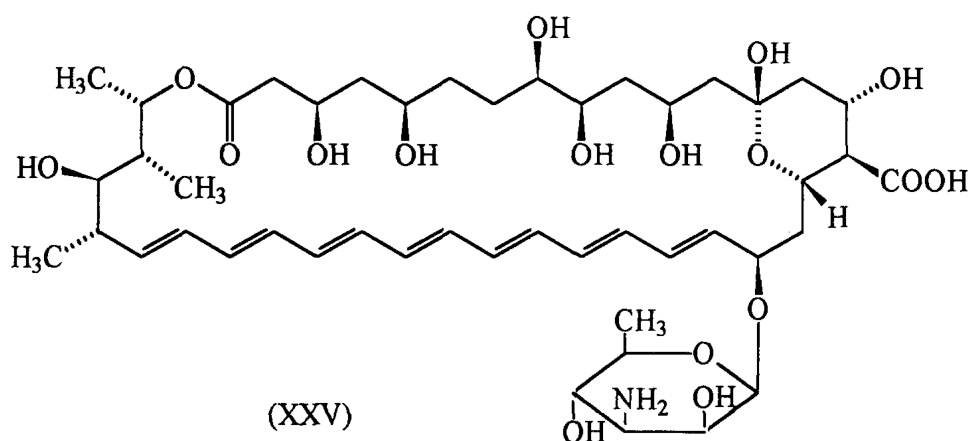
Fluconazole, Ketoconazole
Amphotericin, with or without Flucytosine
Amphotericin, Ketoconazole
Amphotericin, with or without Flucytosine, Fluconazole
Amphotericin, Ketoconazole
Amphotericin, Ketoconazole

A brief description about major drugs used in treating fungal infections is presented in the following pages.

Amphotericin B

It was the first commercially available systemic antifungal drug, it was first isolated in the 1950s from *Streptomyces nodosus*. It is a polyene macrolide that consists of seven conjugated double bonds, an internal ester, a free carboxylic group and a glycoside chain with a primary amino group(XXV). It is amphoteric in nature, forming soluble salts in both basic and acidic environments.

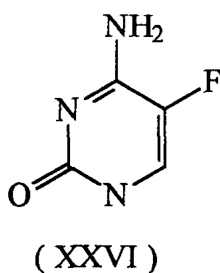
The primary mechanism of action of the polyenes in general, and Amphotericin B in particular, is binding to ergosterol, the principal sterol present in the cell membrane of sensitive fungi¹⁹.



The most significant adverse effect is nephrotoxicity. In spite of the adverse effects, it is still the drug of choice for treating most deeply invasive mycoses, including both endemic mycoses and opportunistic mycoses.

Flucytosine

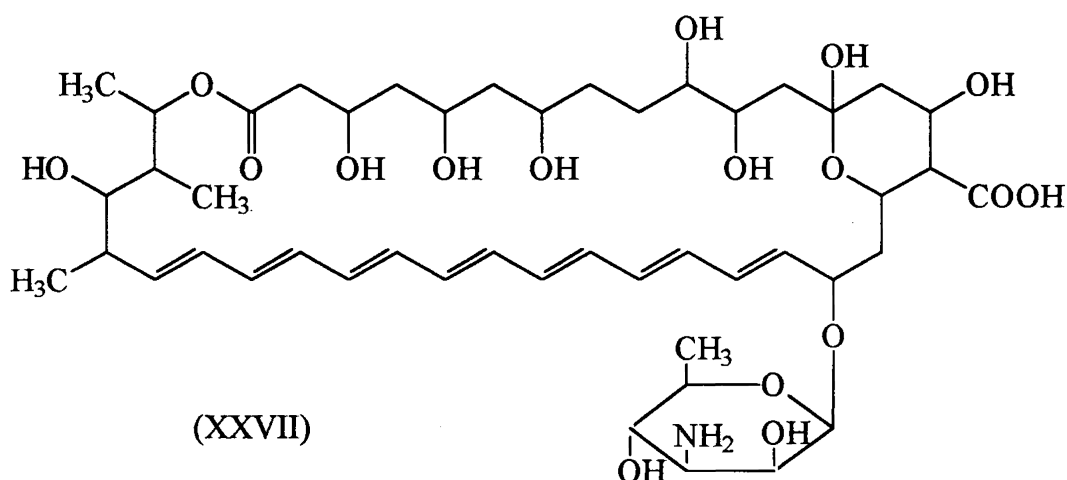
It is a fluorine analogue of Cytosine (XXVI). It was found to have in vitro and *in vivo* antifungal activity²⁰. It is increasingly being used as an adjunct to Amphotericin B therapy.



The mechanism of action of Flucytosine is the disruption of protein synthesis by inhibition of DNA synthesis, and alteration of the amino acid pool by inhibition of RNA synthesis. It is used for treating infections caused by *Candida albicans*, *Cryptococcus neoformans* and *Torulopsis glabrata*.

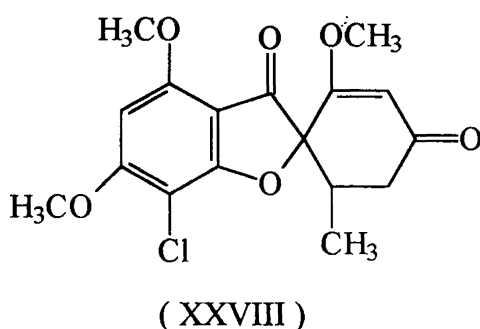
Nystatin

Nystatin(XXIV) is produced by *Streptomyces noursei*. It was discovered by Hazen and Brown²¹ and possesses food antifungal activity. The toxicity after parenteral administration to animals has led to its use only topically or orally. The MIC of this drug for *Candida* species and *Cryptococcus neoformans* is in the range of 1.56-12.6 µg/ml.



Griseofulvin

Griseofulvin (XVIII) was discovered by Oxford *et al* in 1939 as a metabolic product of *Penicillium griseofulvum*. Grove predicted its chemical structure in 1950²².



As a "cell-wall antibiotic" particularly active on *Dermatophytes*, *Griseofulvin* interferes with biosynthesis of the chitinous elements of the hyphal wall. No resistant strains are observed among *Dermatophytes* during the treatment with this drug.

The synthetic antifungal agents

Metal containing molecules

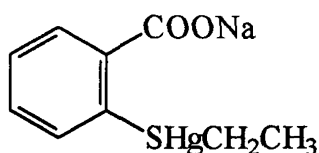
Heavy metal ions such as Ag^+ , Hg^{2+} , Cu^{2+} and Zn^{2+} have long been used as fungitoxicants in agriculture and also in topical ointments for dermatophytoses. A combination of a heavy metal atom with an organic molecule increases the activity, but a more important aspect is the selective toxicity of the metal.

Example of antifungal compounds that are metal complexes are given below:

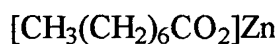
Zinc dimethyldithiocarbamate (XXIX), metal complex of 5-chloro-7-iodo-8-hydroxyquinoline(XXX), sodium ethyl mercurithio salicylate(XXXI), Zinc caprylate (XXXII) and pyriothione (XXXIII).



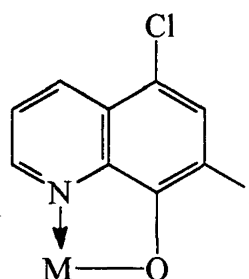
(XXIX)



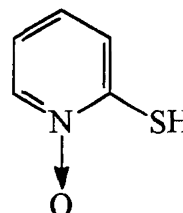
(XXXI)



(XXXII)



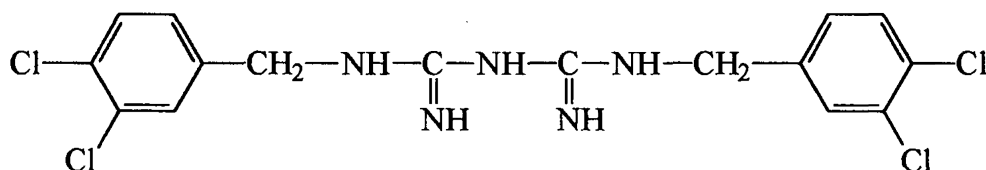
(XXX)



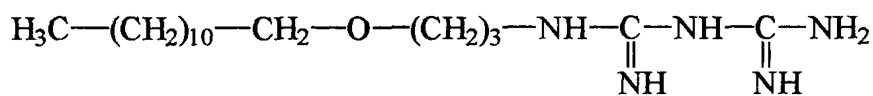
(XXXIII)

Chelating agents

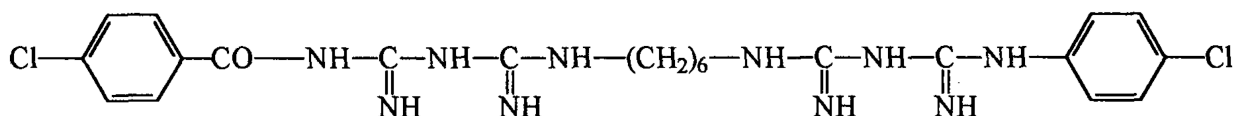
Among chelating agents with considerable *in vitro* antifungal potency, are substituted biguanides like N^1 , N^5 -bis-(3,4-dichlorobenzyl) biguanide(XXXIV), N^1 -Y lauroxypropyl biguanide(XXXV), 1,6-bis-(5-chlorophenyl biguanidine) hexane(XXXVI)²³ etc.



(XXXIV)



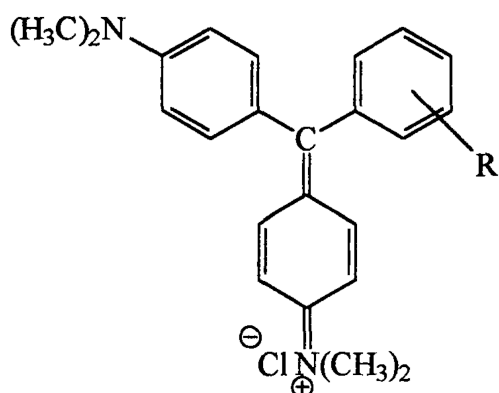
(XXXV)



(XXXVI)

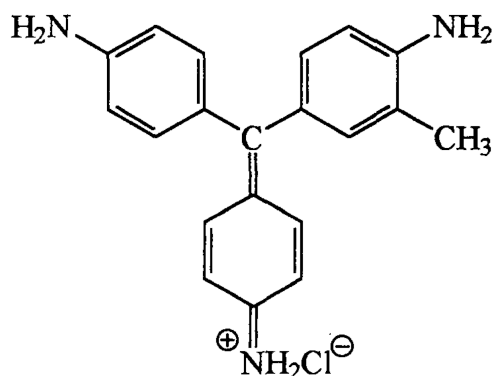
Aniline Dyes

Aniline dyes, such as malachite green(XXXVII), gentian violet(XXXVIII), methyl rosaniline chloride (XXXIX) have been employed in topical therapy of dermatophytoses as well as Candidiasis of skin and mucous membranes.



(XXXVII) R = H

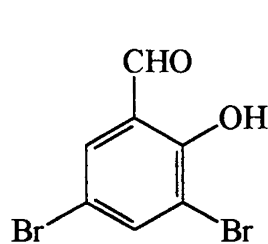
(XXXVIII) R = N(CH₃)₂



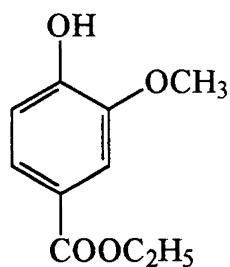
(XXXIX)

Phenolics and Diamides

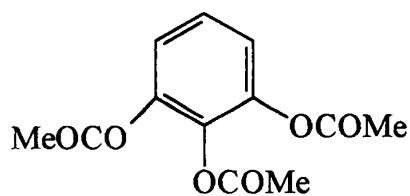
Phenolic compounds are known for their antifungal potency. Among the numerous phenolic compounds that have been used externally for mycotic infections are phenol, phenyl mercuric nitrate, cresol, m-cresyl acetate, benzoic acid, 4-hydroxybenzoic acid, salicylic acid, salicylanilide, 3,5-dibromo salicylaldehyde (XXXX), ethyl vanillate(XXXXI), pyrogallol triacetate(XXXXII), 3-iodo-2-propynyl-2',4',5'-trichlorophenyl ether(XXXXIII), Haloprogin 1,8-hydroxyanthranol (XXXXIV) and tetrachlorobenzoquinone(XXXXV).



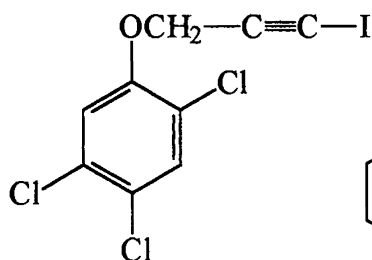
(XXXX)



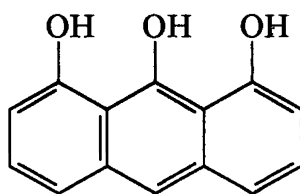
(XXXXI)



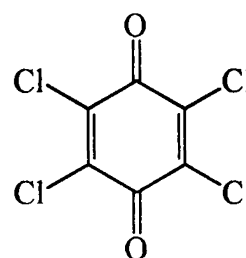
(XXXXII)



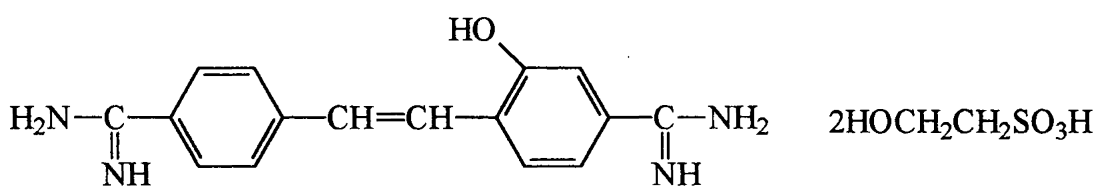
(XXXXIII)



(XXXXIV)



(XXXXVI)



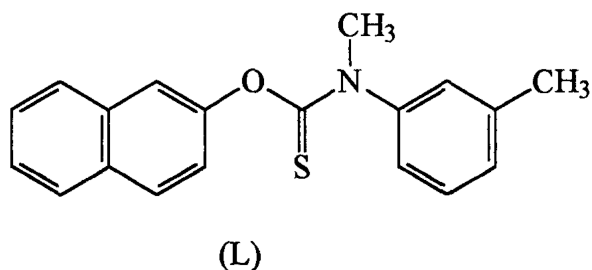
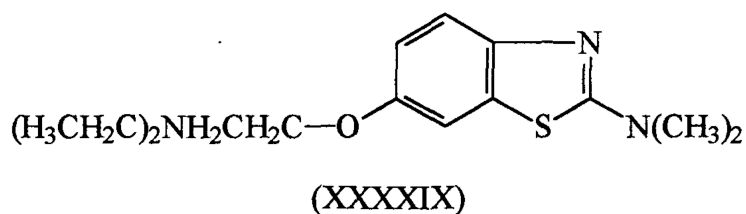
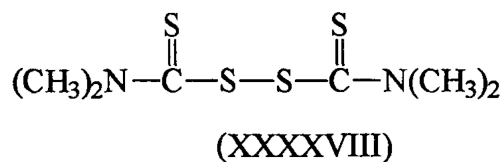
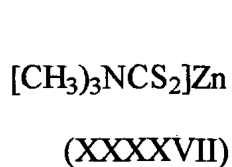
(XXXXV)



Several biamidines (e.g. stibamidine, propamidine, pentamidine) are antifungal *in vitro*. 2-hydroxystilbimidine diisothionate (XXXIII) has been successfully employed in patients with blastomycosis. It is less toxic than Amphotericin B²⁴.

Sulfur-containing molecules as antifungal agents

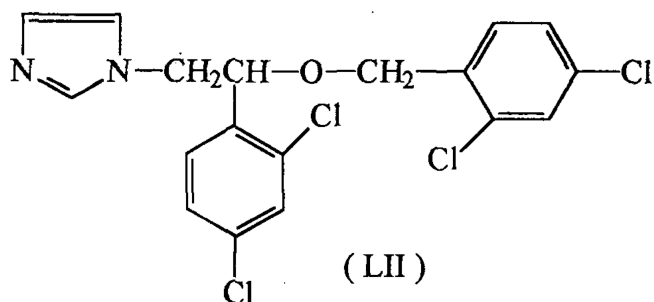
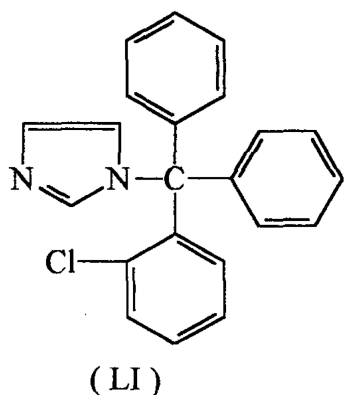
A variety of organic compounds, which contain divalent sulfur attached to carbon atom have *in vitro* fungistatic action, and many of these have been employed in topical therapy of dermatophytoses. Among these are dithiocarbamates (XXXXVII), tetraethylthiuram disulfide (XXXXVIII) and benzothiazoles such as 6-(diethylaminoethoxy)-2-dimethyl amino derivatives (XXXXIX)^{25,26}.



A widely used compound with unusually high *in vitro* and *in vivo* activity against the dermatophytes is o-2-naphthyl ester of m-N-dimethylthiocarbanilic acid (L) (Tolnaftate). It is also effective against candidal lesions²⁷.

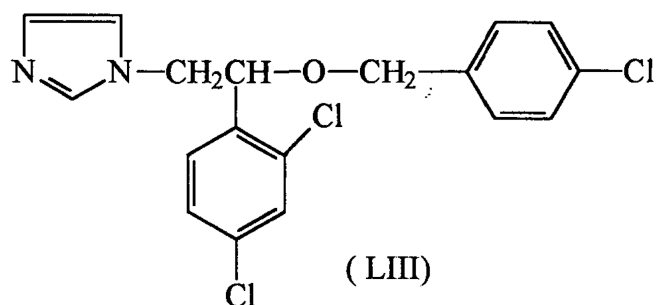
Imidazole antifungals

Among all the imidazole compounds, three distinct compounds are actually therapeutic antifungals with very wide spectra against yeast and filamentous fungi. They are Clotrimazole(LI), Miconazole(LII) and Econazole (LIII).



Clotrimazole was developed by investigators at the Bayer Laboratories in 1969, and is utilized topically in superficial mycoses, or orally in clinical trials in deep mycoses^{28b}.

Miconazole²⁸ is a well known antifungal drug developed by the investigators at Janssen Pharmaceutica in 1969. It is utilized in superficial mycoses and by oral / intravenous routes in deep mycoses, in clinical experimental trials.

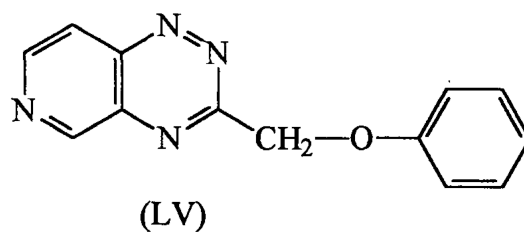
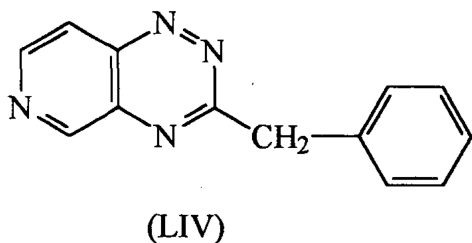


Econazole is a phenethyl imidazole derivative. Like Miconazole, it is utilized as a topical agent in superficial mycoses and as a systemic antifungal, by oral or intravenous routes, in deep mycoses²⁹.

The mode of action studied by Preusser⁴⁵ on *Candida albicans* and *Trichophyton rubrum* shows that at a concentration as low as 1.1×10^{-7} M, alterations on the cellular membranes and lysis of the intracytoplasmic organelles occurred with decomposition of ribosomes.

Miscellaneous

Some pyridotriazines, Triafungin (LIV) and oxyfungin (LV) have been described as antifungal agents by Wright^{30,31}.



Triazoles

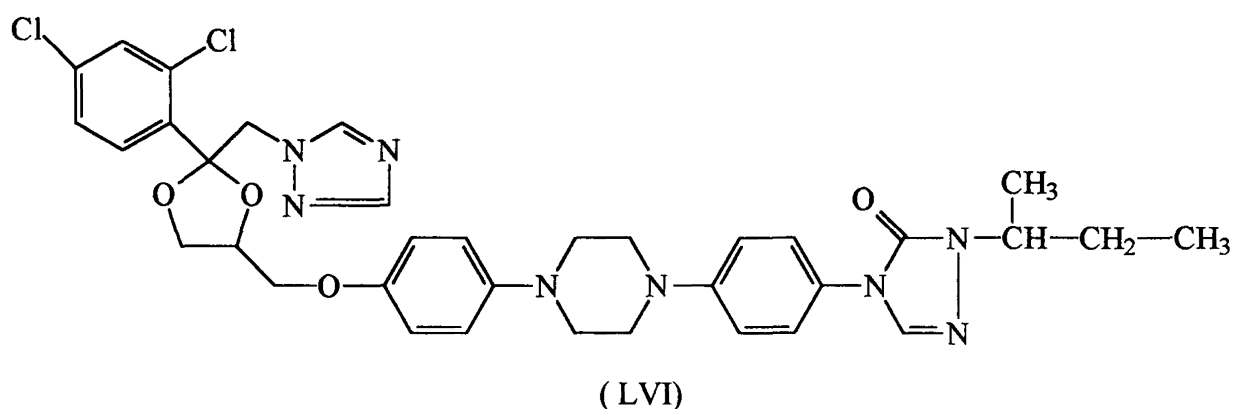
The replacement of imidazole ring with the triazole offers many advantages to these newer azoles³².

- 1) It allows for greater polarity, which may improve solubility and reduce protein binding.
- 2) The triazole ring is less nucleophilic and more resistant to metabolic attack.

There are a number of these compounds that have recently been licensed, or are currently being developed and tested.

Itraconazole

Itraconazole (LVI) is a water-soluble, lipophilic triazole analogue that exhibits excellent activity against most fungal pathogens.

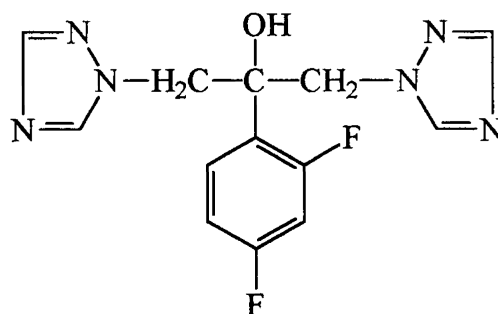


When compared with Ketoconazole, its potential advantages include a broader spectrum of activity (including *Aspergillus* spp.), a more desirable pharmacokinetic profile and less toxicity³³.

Most of the adverse reactions reported are transient and include gastrointestinal disturbance, dizziness, headache, depressed libido (with normal testosterone levels) and leucopenia³⁴.

Fluconazole

Fluconazole (LVII) is a water-soluble fluorine substituted bis-triazole that has been shown to be effective against a variety of fungal infections in immunocompetent and immunocompromised hosts. Fluconazole has complete activity similar to that of Ketoconazole and the mechanism of action is inhibition of fungal C-14 demethylase.



(LVI)

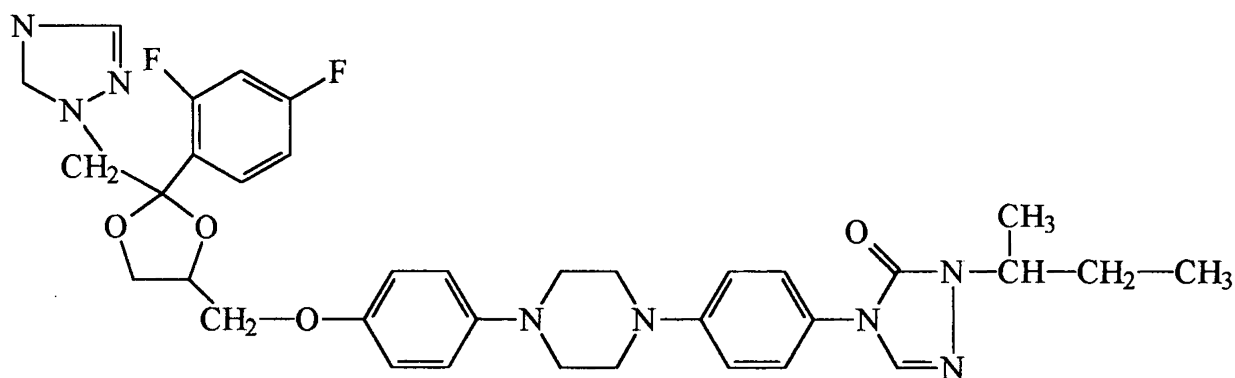
A major point of confusion during the development of this drug, however, has been its relatively low activity *in vitro* compared to its high *in vivo* activity.

It possesses pharmacokinetic properties that are distinct from the previously discussed azole derivatives. It has been well tolerated, with very few dose limiting side effects. Nausea, other GI symptoms and elevation in hepatic transaminases have been reported in 5% of the patients receiving the drug. Fluconazole is also a potential candidate for prevention and early treatment of disseminated candidiasis in granulocytopenic patients³⁵.

Finally, Fluconazole is also currently being studied for primary treatment of histoplasmosis and sporotrichosis.

Saperconazole

Saperconazole (LVIII) is a water-soluble, lipophilic fluorinated triazole with a chemical structure similar to Itraconazole except that the two chlorine atoms are replaced by fluorine.



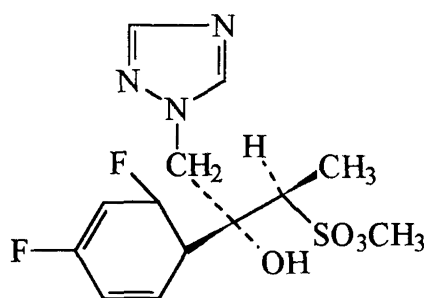
(LVIII)

It has a broad spectrum of antifungal activity including the dimorphic fungi, phacohyphomycetes, *Cryptococcus* spp and *Aspergillus* spp³⁶.

OTHER AZOLES

SCH 39304

SCH 39304 (LIX) is a N-substituted triazole with a broad spectrum of antifungal activity. It is active orally, parenterally and topically.

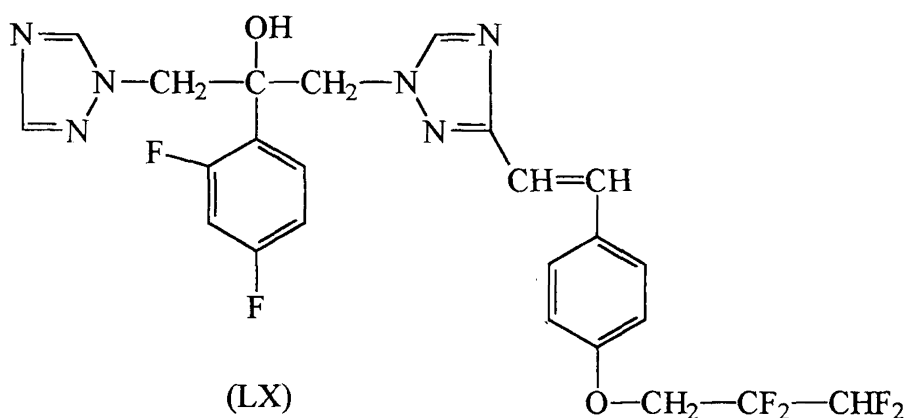


(LIX)

The potent broad spectrum *in vivo* activity of SCH 39304 against *Candida*, *Aspergillus*, *Cryptococcus*, *Blastomyces*, *Coccidioides* and *dematiaceous* moulds hold exceptional promise as a valuable agent. SCH 39304 has been shown to cause hepatocellular carcinoma in animals, and probably became an orphan drug only available to patients who fail to respond to all other antifungal drugs.

ICI 195739

ICI 195739 (LX) is an orally active bis-triazole with a broad spectrum of antifungal activity³⁷.



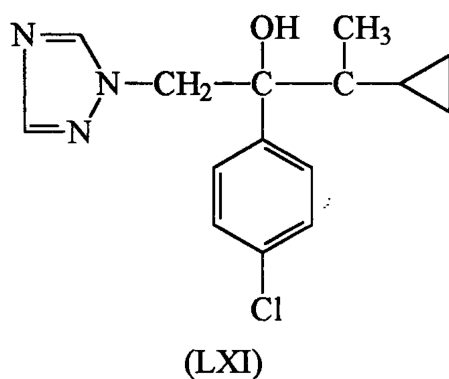
(LX)

Like other antifungal azoles, it is a potent inhibitor of fungal C-14 sterol demethylation. However, ICI 195739 is more freely permeable than Ketoconazole

and fluconazole, and therefore, organisms that are resistant due to reduced azole uptake are more sensitive to this drug³⁸.

SDZ 89-845

SDZ 89-845 (LXI) is a triazole antifungal agent that has shown activity in a number of animal models against of superficial and systemic fungal infections³⁹⁻⁴².



Plan of Work

PLAN OF WORK

Successive discoveries in the field of medicinal chemistry have added to the list of infections which can be cured or curbed by chemotherapy. Still some of the drugs which are necessary to use, are far from being ideal, either because of toxicity or unsatisfactory pharmacological properties. Also, some forms of treatment are consequently less often successful than others. Moreover, microbial resistance remains a constant threat to the future usefulness of almost any drug. All successful chemotherapeutic agents should have certain properties in common :

- 1) They must exert an antimicrobial action, whether inhibitory or lethal, in high dilutions and in the complex chemical environment, which they encounter in the body.
- 2) Also, since they are brought into contact with every tissue in the body, they must possibly act without any disrupting or harmful effect on the normal function of any organ.

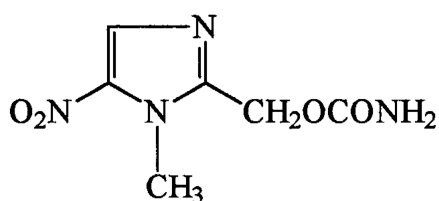
To these two essential qualities may be added the others viz. stability, free solubility, a slow rate of excretion, diffusibility into remote areas etc.

Subsequently, there has been immense progress in the knowledge of the anatomy, chemical composition and metabolism of various microbial cells. This new knowledge has been helpful in understanding what drugs do to the infecting organisms. Discoveries have continued to result only from random trials, purely in the field of chemotherapy, although sometimes based on reasonable theoretical expectations.

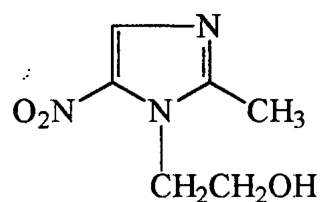
A line of advance other than the discovery of new drugs is the adaptation of old ones. An outstanding example of what can be achieved in this way is presented by the sulfamides. Similar efforts in the field of antibiotics have given fruitful and encouraging results. Most of these changes are produced by additions to the drug molecule. But it is observed that modifications in the essential structure of the drug molecule alters its antimicrobial-properties usually for the worse, and rarely to an advantage. The logic supporting the work presented in this thesis was formulated,

bearing in mind the biological activities of known moieties and attempting certain structural modifications or adaptations, in the light of the recent trends in drug research and incorporating newly emerged pharmacophores on existing moieties.

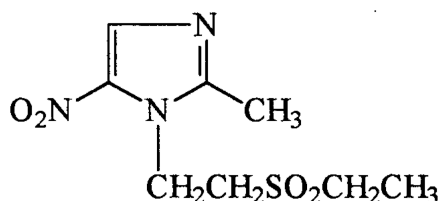
The Nitroheterocyclic compounds have been studied extensively in literature for various types of biological activities. This led to the development of very important molecules, such as Ronidazole(I), Metronidazole(II) Tinidazole(III), Nitrofurantoin(IV), Secnidazole(V) etc.



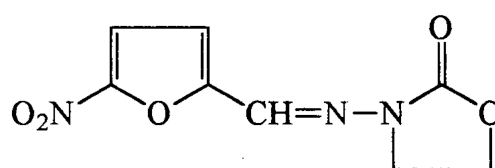
(I)



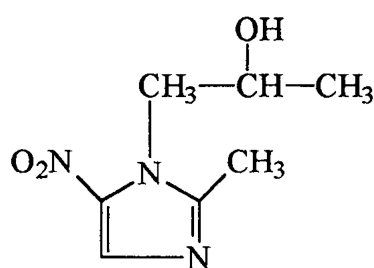
(II)



(III)

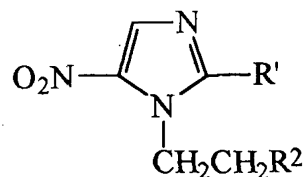
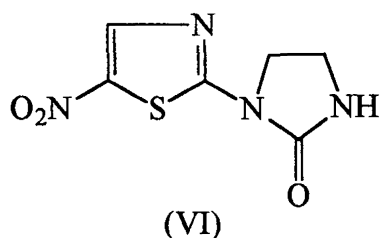


(IV)



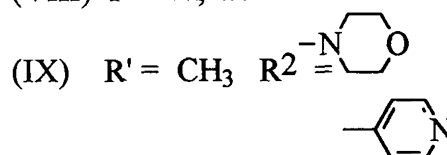
(V)

In 1964, Ciba Laboratories(Basel) announced⁴³⁻⁴⁴ the discovery of a novel schistosomicide, Niridazole (VI)⁴⁵ Niridazole was synthesized as a part of systemic investigations of heterocyclic nitro compounds as antiparasitic agents. One requirement for activity in all Niridazole congeners appeared to be the presence of the 5-nitro group⁴⁶.

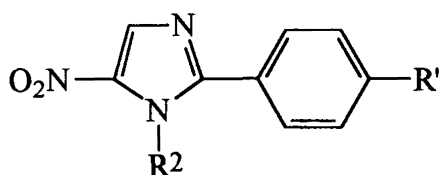


(VII) $R' = \text{CH}_3$, $R^2 = \text{SO}_2\text{CH}_2\text{CH}_3$

(VIII) $R' = \text{H}$, $R^2 =$



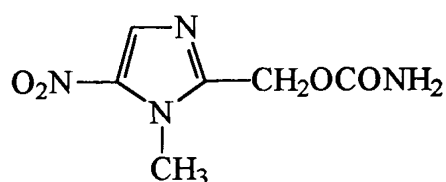
Amongst the nitroimidazoles, Metronidazole (II) is established as a drug of choice in the treatment of all forms of amoebiasis⁴⁸⁻⁵². An attempt to improve trichomonocidal activity and metabolic stability led to the discovery of Tinidazole(VII), Nimarazole(VIII), Panidazole (IX), with retention of the nitro group at the fifth position. Most interesting nitro Imidazoles include Flunidazole (X), nitro imidazole (XI), ACA-nitro imidazole (XII), Ronidazole (XIII), etc.



(X) $R' = \text{F}$, $R^2 = \text{CH}_2\text{CH}_2\text{OH}$

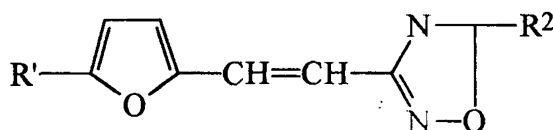
(XI) $R' = \text{F}$, $R^2 = \text{CH}_3$

(XII) $R' = \text{CONH}_2$, $R^2 = \text{CH}_3$



(XIII)

Newer more interesting experimental compounds include oxadiazole derivatives(SQ 18506)⁵³⁻⁵⁵.



(XIV) $R' = \text{NO}_2$, $R^2 = \text{NH}_2$

This was consistently active at high dose levels against *S. mansoni* and *S. japonicum* in mice and monkeys. The non-nitrated compounds lacked activity.

Nitropyrroles⁵⁶ and nitropyridines^{57,58} have been investigated for their antiamoebic properties.

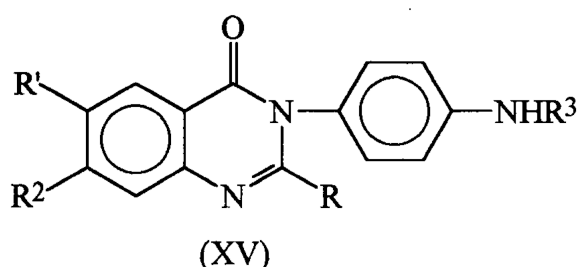
Because of the wide variety of biological activities possessed by the nitroheterocycles such as schistosomicidal, trichomonocidal and amoebicidal activities, it was proposed to synthesize nitro heterocyclic molecules for this research project.

Quinazolinone derivatives have drawn considerable attention due to the various types of biological activities exhibited by them⁵⁹.

Quinazolinone derivatives play a vital role in many biological processes and as synthetic drugs⁶⁰. Substituted quinazoline-4(3H)-ones have been reported to possess various biological activities⁶¹.

Many fused Quinazolinones have been reported to have remarkable pharmacological activities⁶². Rossman Abdel *et al* have reported that 2,4 dioxo-1,2,3,4-tetrahydro quinazoline derivatives are found to exhibit antibacterial activity comparable to Tetracycline HCl⁶³.

Some new 2-substituted 3-[4-N'-aryl-sulfonyl biguanide] phenyl] quinazolin-4-one hydrochlorides (XV) are reported to have potential anthelmintic activity⁶⁴.

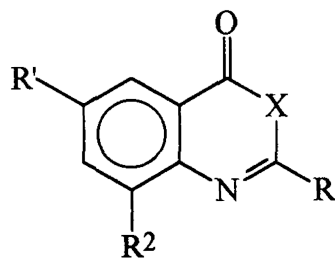


$R = H, S-Cl(NO_2)C_6H_3$

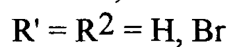
$R' = R^2 = H, Br$

$R^3 = C(: NH)NH(: NH)NHSO_2Ph$

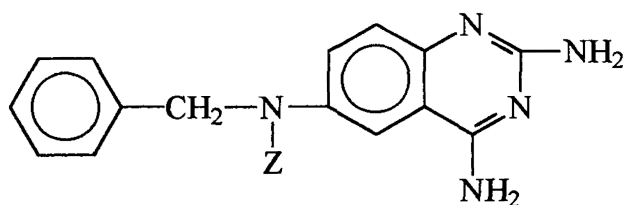
2'-alkyl / aryl-6',8'-substituted quinazolinon-3'-ylamino acetyl)- N³-aryl ureas (XVI)⁶⁵ are found to be active against coecal amoebiasis of rats (*in vivo*).



(XVI)



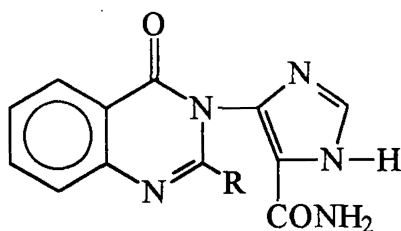
Similarly 2,4-diamino-6-N: N²-disubstituted hydrazinoquinazolin(XVII) derivatives show good antimalarial activity⁶⁶.



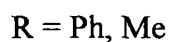
(XVII)



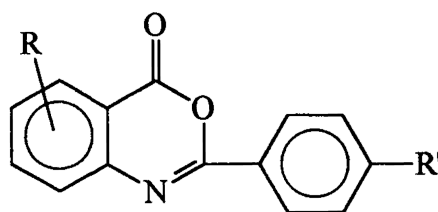
Saxena A.K. *et al*⁶⁷ have reported some quinazolinone derivatives (XVIII) which are tested as guanine deaminase inhibitors, to be helpful in the chemotherapy of cancers.



(XVIII)



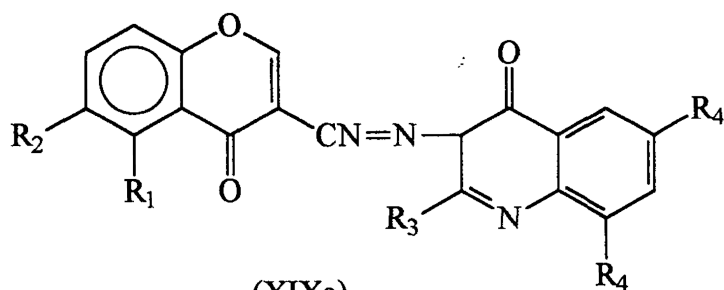
5-fluoro -4(3H)- benzoxazine-4-ones (XIX) are useful as herbicides⁶⁸.



(XIX)

R = F, R' = H, halogen alkyl etc

Quinazolinone derivatives of following types(XIXa) are reported to have good bactericidal activity⁶⁹.



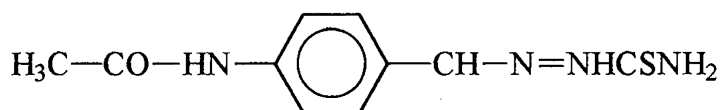
(XIXa)

Also, literature survey revealed that very less work has been carried out on nitroquinazolinones. Considering the various biological activities exhibited by quinazolinone derivatives, and keeping in mind the importance of nitroheterocycles, it was decided to synthesize some nitroquinazolinone derivatives, i.e. 3-amino-2-methyl-5/6-nitro-4(3H) quinazolinone derivatives in a hope to achieve good antimicrobial activity.

Synthesis of 2- methyl – 5 nitro-3-[(substituted phenyl/heterocycle)methylene amino] quinazoline-4 (3H)one :

The presence of an azomethine linkage in compounds has been known to decrease their toxicity considerably⁷⁰. Schiff bases of 5-chlorosalicylaldehyde, 5-bromosalicylaldehyde and 4-N, N-dimethyl amino benzaldehyde have shown encouraging antitubercular activity *in vitro*⁷¹.

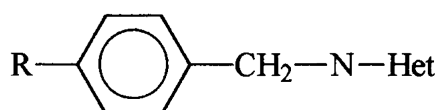
The thiosemicarbazone of 4-acetamido benzaldehyde, Thiacetazone(XX), was introduced for the treatment of tuberculosis in 1950^{72,73,74}.



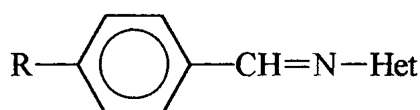
(XX)

This was the first synthesized drug that approached the activity of Streptomycin in experimental infection in animals⁷², and it contains an azomethine linkage.

Recently, R. Firavanti *et al* have reported antimicrobial properties of some new heteroaryl benzyl amines (XXI, XXII) and their Schiff bases⁷⁵.



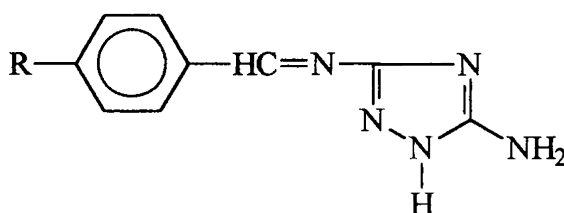
(XXI)



(XXII)

R = H, CH₃, Br etc

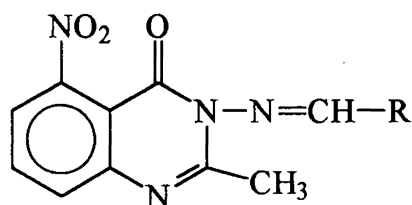
The azomethine linkage is known to impart biological activity due to various heterocyclic moieties e.g. Straukas T. *et al* have reported antiinflammatory activity of triazole(XXIII) Schiff bases⁷⁶.



(XXIII)

R = 2-Cl, 4-F, 4-OMe etc

Taking into account the importance of azomethine linkage that imparts antimicrobial activity, Schiff bases of 3-amino-2-methyl-5-nitro 4(3H) quinazolinone were synthesized, which have the following structure (XXIV) :



(XXIV)

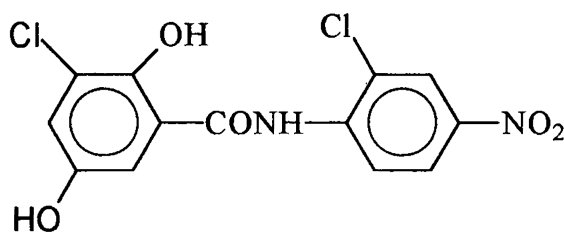
where R = substituted phenyl,
heterocycle

They were tested for antifungal, antibacterial and antitubercular activity.

Synthesis of 3-(substituted acetamido)-2-methyl-6-nitroquinazoline-4-(3H)one:

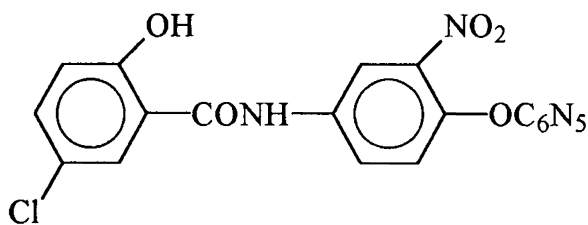
Moderate activity was claimed for 5-chloro salicylanilide⁷⁷ derivatives as anthelmintic and antibacterial agents. The acid amido linkage was found to be responsible for various kinds of activity as seen from the following examples.

Niclosamide⁷⁸ (XXV), a 5-chloro-salicylanilide derivative, is a drug of choice in the treatment of cestodes.



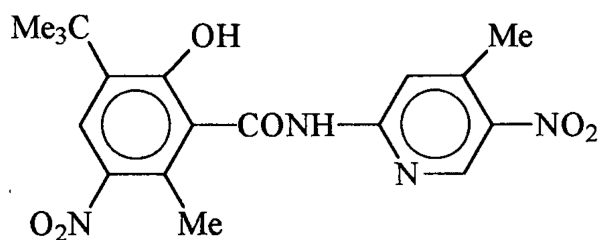
(XXV)

Another salicylanilide derivative was found to be effective against Penicillin-resistant *S. aureus*, at a minimum dose of 0.00609 $\mu\text{g/ml}$ ^{78a}.



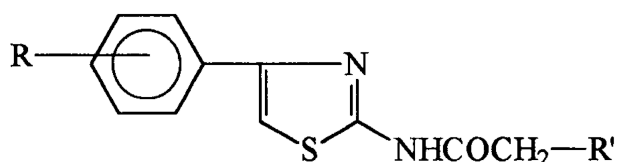
(XXVI)

Substituted pyridylamide (XXVII) showed activity against *F. hepatica*⁷⁹.



(XXVII)

Bhargava *et al* have synthesized a series of 2-(N-substituted glylcylamino)-4-substituted phenyl thiazoles (XXVIII), useful as local anesthetics⁸⁰.

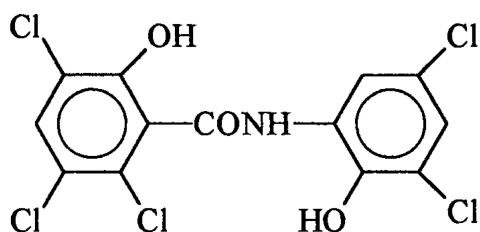


(XXVIII)

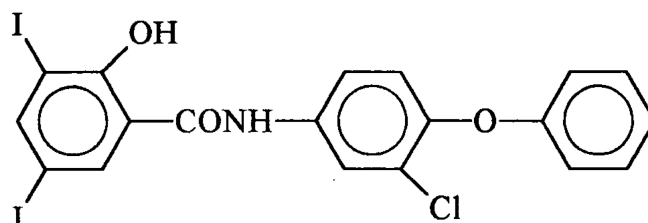
R = 4-Cl, 4-Br, 3-NO₂, 4-CH₃

R' = morpholino, piperidino, piperazino etc.

Niclosamide^{81,82} (XXV), Oxyclozanide⁸³ (XXIX), Rafoxanide⁸⁴ (XXX) etc. are the drugs which owe their activity to the amide linkage.

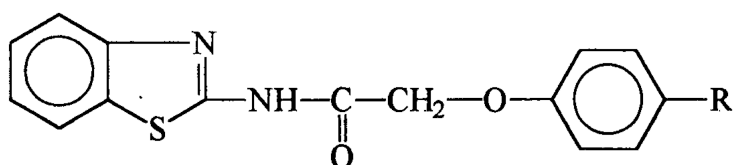


(XXIX)



(XXX)

Lacova M *et al*⁸⁵ have reported the compounds of following type (XXXI) with good antimicrobial activity.

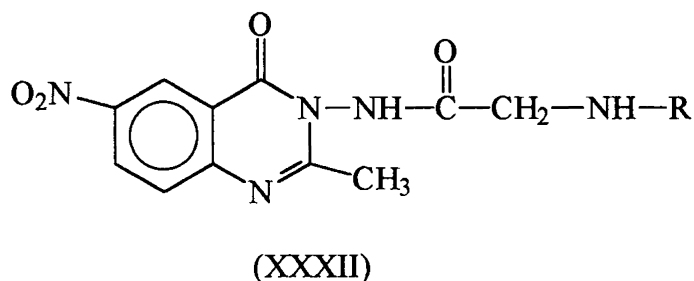


(XXXI)

R = H, Cl

The acetamido group in the molecule was responsible for its activity. Also substitution at 3-position of the quinazolinone ring system was found to increase the activity of the parent moiety.

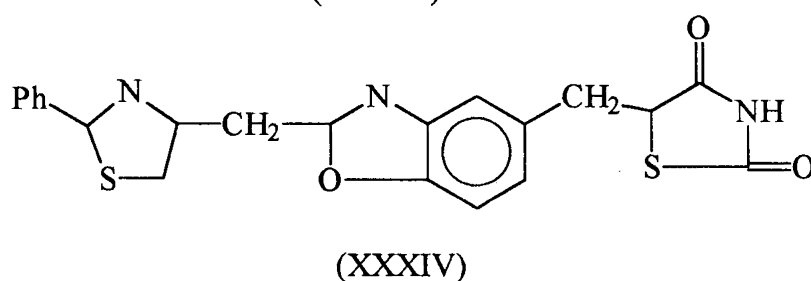
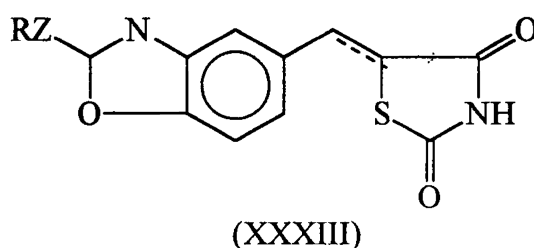
Considering these facts, we planned to synthesize 3-(substituted acetamido)-2-methyl-6-nitro quinazoline-4-(3H) one derivatives (XXXII) in the hope of achieving antimicrobial activity.



R = morpholine, piperazine, fluoroaniline etc.

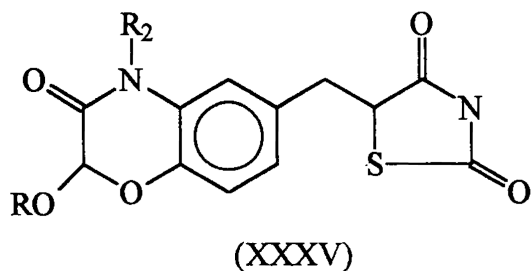
Synthesis of 3- [2-methyl -6- nitro -4(3H) -one- 3 - quinazolinyl] - 2-(substituted phenyl / heterocycle)-4-thiazolidinones :

The presence of thiazolidine ring in Penicillin and related derivatives was the first recognition of its occurrence in nature⁸⁶. This led to extensive structure activity studies on thiazolidine 2,4-diones and related thioxo analogues⁸⁷. Many of the thiazolidinone derivatives exhibit a wide variety of biological activities⁸⁸, such as antimicrobial, antiinflammatory, antihistaminic, antidiabetic, etc⁸⁹.



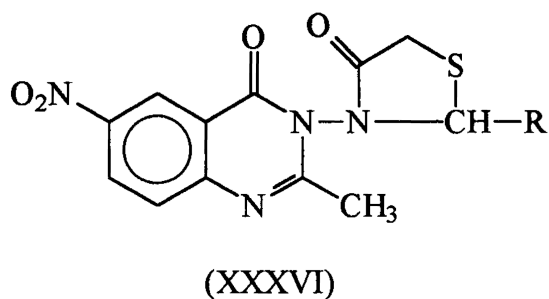
3-[benzoxazolyl methyl/methylene]-2,4-thiazolidinone derivatives, (XXXIII), (XXXIV) are reported to have bactericidal and antidiabetic activities⁹⁰.

Thiazolidinyl derivatives of benzoxazine 3(4H)-one⁹¹ (XXXV) are reported to have antimicrobial activity.



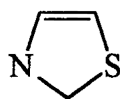
3-aryl-2-allyl-imino-4-thiazolidinones derived from N-aryl-N'-allyl thioureas are reported to have fungicidal activity against *Alternaria solani* at 10 ppm⁹².

Considering the importance of thiazolidinone ring and various types of activities shown by this moiety, it was decided to synthesize thiazolidinone derivatives, viz. 3-[2-methyl-4(3H)-oxo-3-quinazolinyl] - 2-(substituted phenyl / heterocycle)-4-thiazolidinone. The general structure (XXXVI) of these derivatives is as follows :



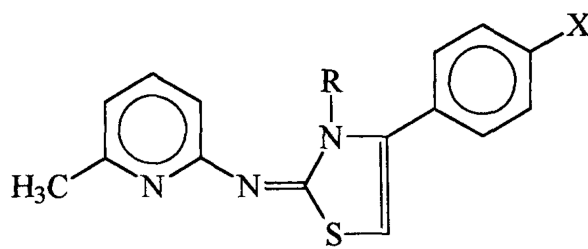
R = substituted aryl / heteroaryl

Synthesis of 2-methyl-6-nitro-(3-phenyl-4-substituted 2,3-dihydrothiazole-2-ylidene amino-4-(3H)quinazolinone.



(XXXVII)

Thiazoline (XXVII) and its derivatives are found to exhibit a wide variety of biological activities⁹³ such as antimicrobial, anti-inflammatory, antihistaminic, etc. Hasan *et al*⁹⁴ observed moderate antimicrobial activity of compounds bearing a thiazoline ring on the parent pyridine moiety (XXXVIII).

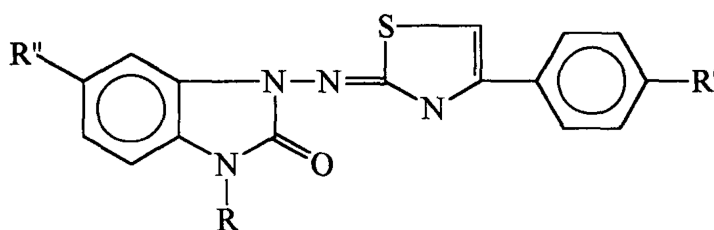


(XXVIII)

X = Br, Cl, OCH₃

R = CH₃, C₂H₅, C₆H₅ etc

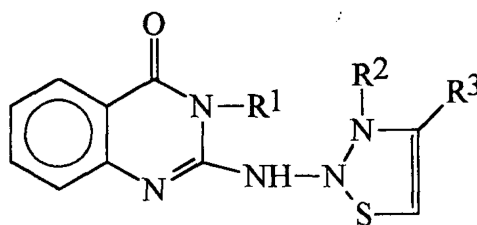
Karali *et al*⁹⁵ synthesized derivatives of 3-[3,4-disubstituted-4-thiazolin-2-ylidene) hydrazono-] -1-4-2-indolinones (XXXIX), as potent antitubercular agents having MIC < 12.5 µg/ml against H₃₇R_v strain of *M. tuberculosis*.



(XXXIX)

R = H, R' = H, Br, R'' = CH₃, C₂H₅

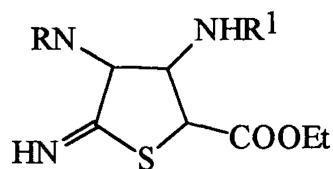
Thiazoline ring prepared by the cyclization of thiourea was found to impart antimicrobial activity to the compounds⁹⁶.



(XXXX)

In the above structure, the activity of the parent quinazolinone (XXXX) was enhanced on converting it to its thiazoline derivative, which exhibited significant *in vitro* antibacterial activity against Gram-positive organisms. This activity of the products was found to be equivalent to that of Penicillin.

Some Ureidothiazoline (XXXXI) derivatives are reported to have fungicidal activity against *Aspergillus niger* at 0.1 ppm⁹⁷.

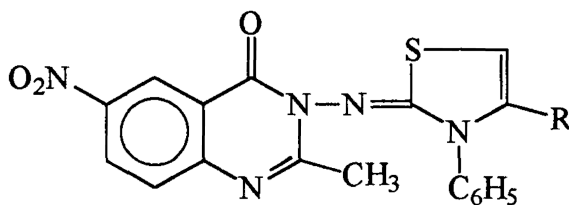


(XXXXI)

- I) $R^1 = C(S)NHR^2$
 II) $R_1 = H$
 $R = BrC_6H_4$
 $PhCH_2CH_2, C_6H_4Br$

It is proved that 4-(3H)-quinazolinone derivatives possessing a thiazolyl or benzothiazolyl moiety at 3-position exhibit antibacterial and antifungal activity⁹⁸.

Hence, it was decided to introduce a benzothiazolyl moiety at 3-position of the quinazolinone. The general structure (XXXXII) of the compounds synthesized in this series is as follows



(XXXXII)

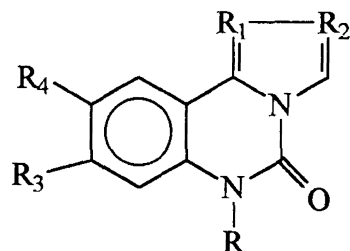
R = substituted phenyl

Synthesis of 3-N-(substituted phenyl)aminomethylene pyrazolo [5,1-b]-7-nitro-quinazolin-9(1H)one.

Pyrazole was first described by Buchner⁹⁹ who obtained it by pyrazole 3,4,5 tricarboxylic acid.

A number of pyrazolyl pyrimidines¹⁰⁰ have shown interesting biological activity in diverse fields Interesting anticancer, antitubercular and antiinflammatory properties of these compounds have been reported from time to time.

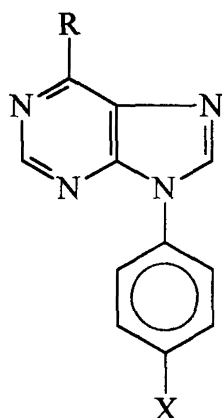
Pyrazole [1,5-C] quinazoline¹⁰¹ (XXXIII) derivatives are reported to have antiallergic activity.



(XXXXIII)

R = H, alkyl, PhCH₂ etc
 R₁ = R₂ = H, alkyl, halo etc
 R₄ = R₅ = H, alkyl, alkoxy

1-H pyrazolo [3,4-d] pyrimidine (XXXXIV)¹⁰² derivatives are reported to have anticancer activity.



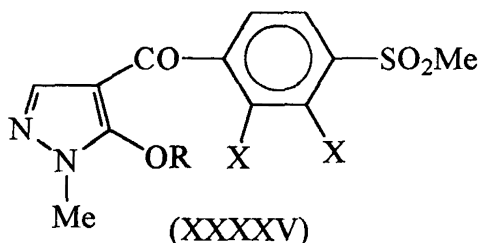
(XXXXIV)

R = cyano, X = Cl, F
 R = NH(CH₂)_nCOOH
 X = Cl, F, n = 1-5

The LD₅₀ of these compounds was found to be 169 mg/kg against – L517754 tumor cells.

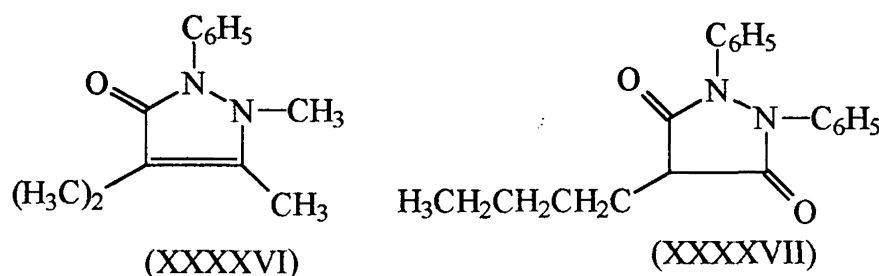
The condensation of 4-bromo-2-pyrazolin-5-one with mercapto-3-aryl-4-quinazolones yielded the quinazolone derivatives having potential fungicidal activity¹⁰³. They are fungitoxic against rice blast pathogen *Pyricularia oryzae*, and brown spot leaf pathogen, *Helminthosporium oryzae*.

4-benzoyl-1-methyl-5-hydroxy pyrazoles (XXXXV) are reported to have herbicidal¹⁰⁴ activity. These derivatives gave 90% control of *Echinochloa oryzae* and *Cyperus exculentus*.

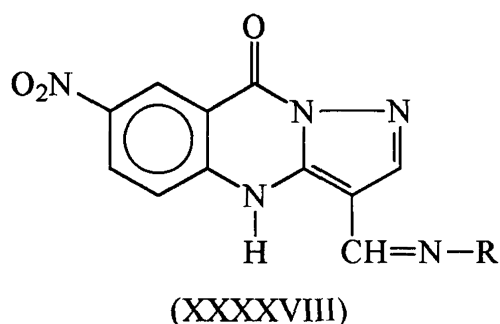


(XXXXV)

In the chemotherapy of diseases of connective tissue, pyrazolyl type of compounds perform various roles the most important being aminopyrine¹⁰⁵, and phenyl butazone¹⁰⁶.



Taking into the consideration the various types of biological activities exhibited by pyrazole derivatives, a series of compounds having pyrazole ring system was designed. The general structure (XXXXVIII) of the various derivatives can be shown as :

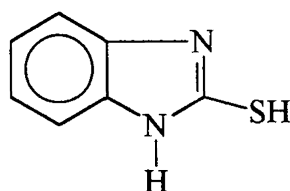


R = substituted phenyl

Synthesis of 5/5,6-substituted -2-thio(isopropyl sulfonyl)benzimidazoles / benzoxazoles :

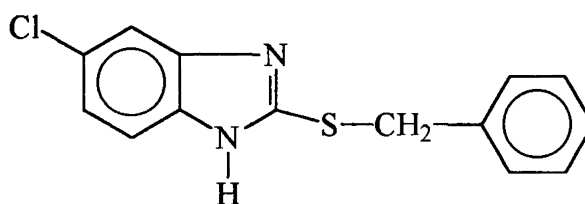
The pharmacological history of several thousands of imidazole derivatives has been established over 30 years, after the discovery of the antibacterial and antifungal activity of benzimidazole by Wolley¹⁰⁷, which later led to the synthesis of benzimidazole derivatives with strong antiprotozoal and anthelmintic properties. The discovery of new antibacterials (Azomycin), trichomonocides (Metronidazole) and anthelmintic agents (Thiabendazole and Carbendazole), which contain prominent imidazole nucleus, has added impetus to investigations in these areas, with particular emphasis on the synthesis of newer benzimidazole derivatives with pharmacological activity.

A number of 2-mercapto benzimidazole (XXXXIX) derivatives have demonstrated a broad spectrum of significant biological activity¹⁰⁹⁻¹¹⁰, i.e. plant growth inhibition, bactericidal, fungicidal and virucidal activities.



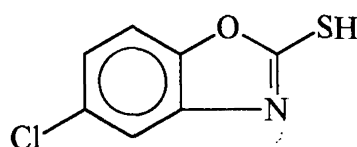
(XXXXIX)

During the literature survey, it was found that 2-mercapto benzimidazole derivatives, namely 5-chloro-2-(benzylthio) benzimidazole¹¹¹ (L), possess antifungal activity against *Trichophyton interdigitale* at a dilution of 3.4 µg/ml. Similarly, bactericidal activity¹¹² was also reported for 2-mercaptobenzimidazole against *Staphylococcus aureus*.



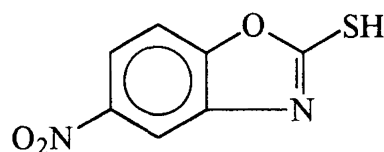
(L)

Literature survey revealed that 5-chloro-2-mercaptobenzoxazole (LI) shows good antimicrobial activity^{112a}.



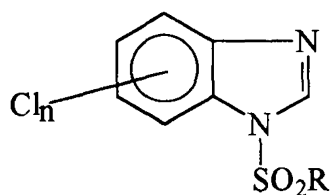
(LI)

6-nitro-2-mercapto benzoxazole (LII) was also found to be active as an antimicrobial agent¹¹³.



(LII)

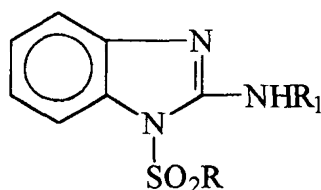
In literature, 5-alkyl and sulphone linkages introduced on the parent moiety, were found to enhance the antitubercular activity¹¹⁴ of the derivatives thus formed. Alkyl sulfonyl benzimidazoles (LIII) are active against *Eimeria tenella* infection in chick¹¹⁵.



(LIII)

R = 6-alkyl, n = 2-4

1-sulfonyl-5,6 substituted benzimidazoles (LIV) are found to be useful as antiviral agents¹¹⁶.

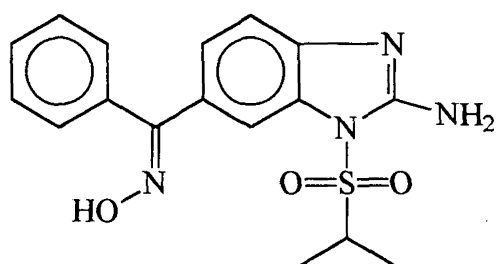


R₁ = H,
R = 1-4 alkyl

(LIV)

These derivatives showed activity at 15 µg/ml (100% inhibition) against Polio I virus growth *in vitro*.

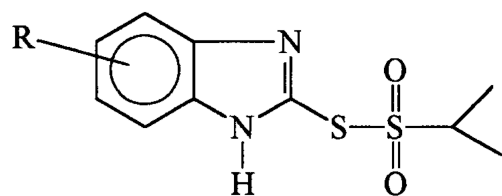
Enviroxime¹¹⁷ (LV), an established molecule with activity against Rhinovirus multiplication, contains isopropyl sulphonyl group, which is responsible for its activity.



(LV)

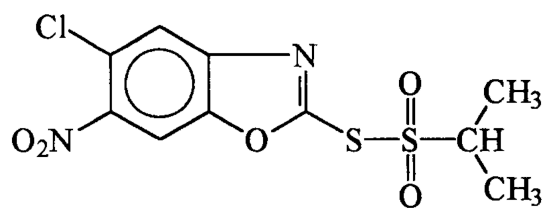
These facts prompted us to synthesize compounds having benzimidazole / benzoxazole derivatives, having disulphide linkage.

These derivatives can be shown by the general structure (LVI, LVII)



(LVI)

R = Cl, OCH₃, NO₂ etc

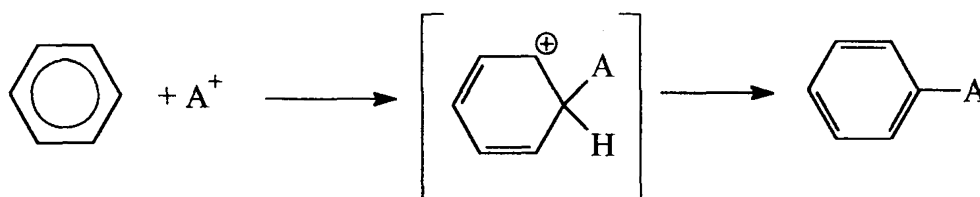


(LVII)

Chemistry

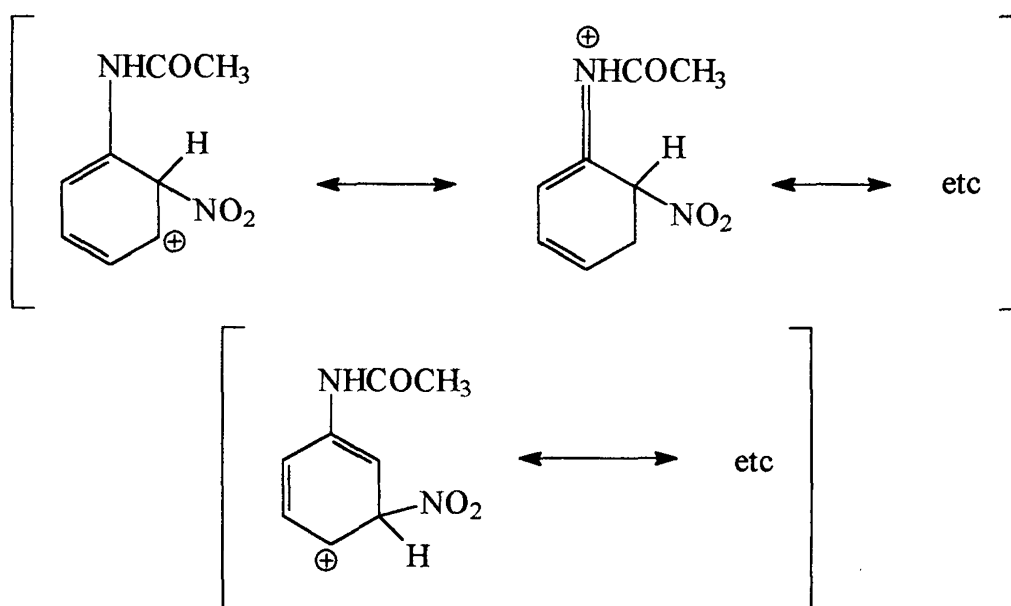
CHEMISTRY OF NITRATION

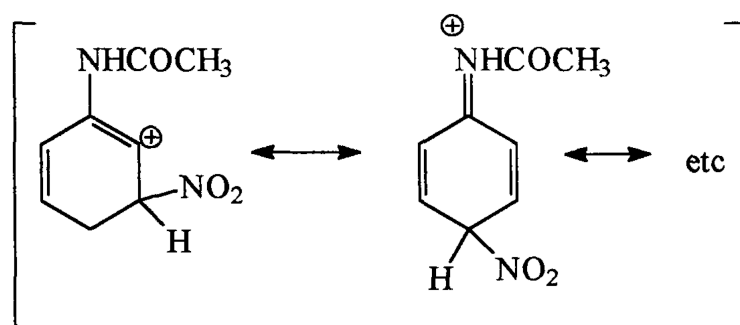
Of the various types of electrophilic substitution reaction, nitration is most widely studied. The attacking electrophile in these reaction is often, though not always, the nitronium ion No_2^+ . In great majority if such reactions the reaction then requires the breakage of a rather strong C-H bond with aromatic substrates, however, there is one important circumstances that ferrous electrophilic substitution the attacking electrophile may form a new bond before the old bond breaks, and the energy that becomes available when the new bond forms may be used to help bring (about the breakage of the old bond). It might than be anticipated that the attack on an aromatic system by an electrophile on an aromatic system. By an electrophile A^+ will pass through an intermediate of the type X, in which both the attacking species and leaving group bound to the substrate.



Nitration of acetanilide

Representative structure for each of the possible action intermediate are shown as follows^{118d}.

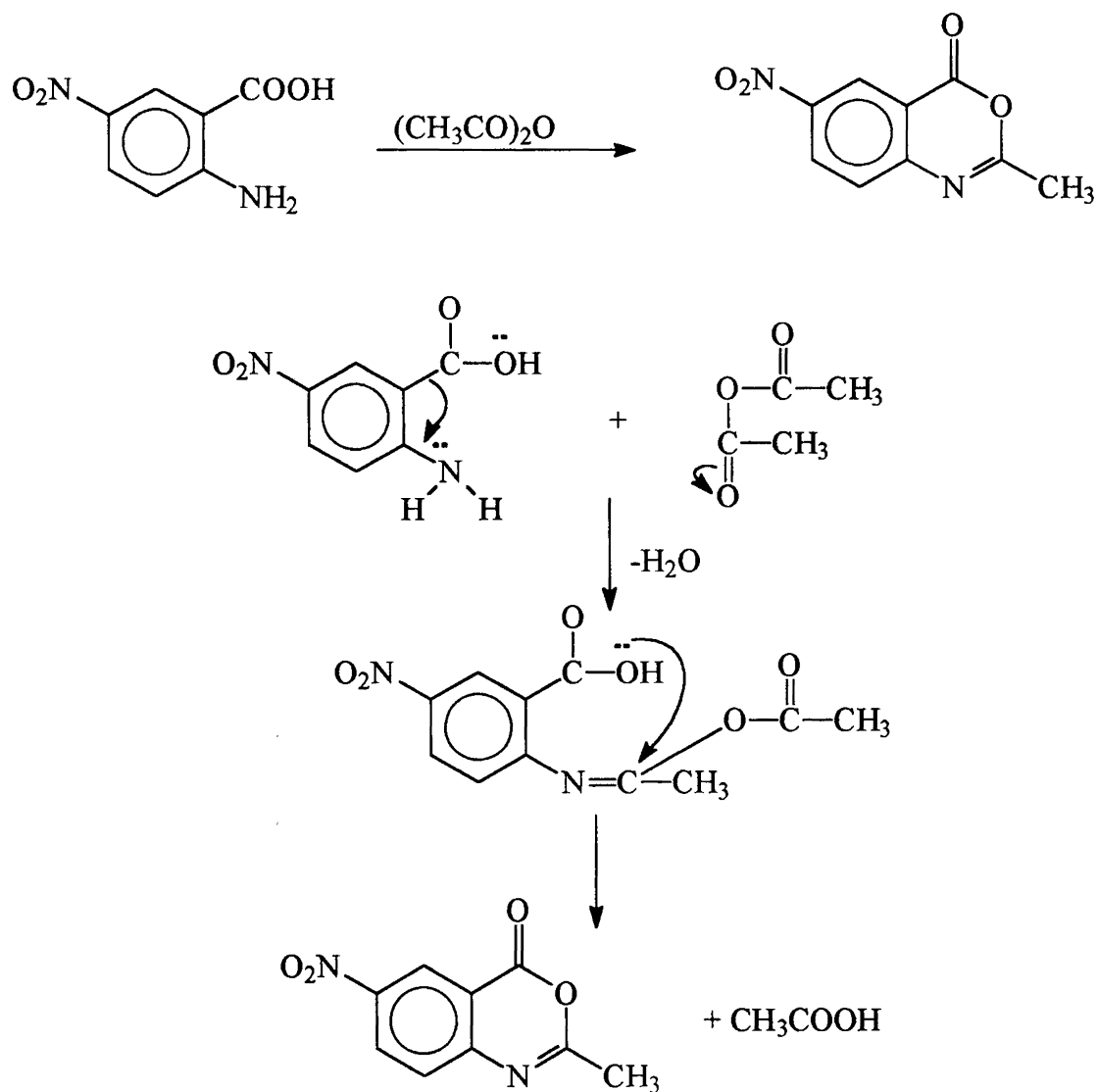




in the immediate for meta attack the + charge carried in by the NO_2^+ ion must remain on the benzene ring until the proton departs. Completing the substitution reaction on the other hand with ortho or para attack π electron density drifts from the electron rich nitrogen atom into the ring, dispersing the positive charge and lowering the energy both of the intermediate and the transition state leading to it, it is thus concluded that in the nitration of acetanilide, ortho and para positions are readily attacked than meta position, although it can not be said which of the two position is more reactive in case of acetanilide, nitrogen bound to ring has one unshared available pair of electron and in each case electrodensity from this pair drifts into ring to help disperse the positive charge carried by the electrophile attacking either at the ortho or the para position. If the para position of the acetanilide is blocked ortho substituted isomer is obtained.

CHEMISTRY OF 3,1-BENZOXAZIN-(4H)ONE

For the preparation of 3,1 benzoxazin-(4H)one we referred to the procedure reported in literature^{118b}. According to the procedure we have cyclised 5-nitro anthranilic acid in the presence of acetic anhydride.



CHEMISTRY OF SCHIFF BASES

Schiff bases are prepared by the condensation of amine and carbonyl group of aldehyde¹¹⁹.



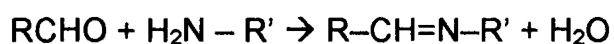
Schiff for the first time reported condensation of this kind, and hence the condensation products are referred to as Schiff bases. Many procedures have been described in literature for the synthesis of Schiff bases. The important methods are listed below:-

- 1) The simplest method appears to be the one in which equimolar quantities of an amine and an aldehyde are condensed by boiling them in methanol or ethanol.
- 2) In 1946, Tipson and Dapp¹²⁰ obtained Schiff bases by refluxing the amine and aldehyde in toluene, with a few drops of Piperidine. The water formed during the course of the reaction was removed by employing a Dean stark trap.
- 3) In 1950, Hayes¹²¹ *et al* prepared Schiff bases by heating a mixture of an aldehyde and an amine in benzene and removing the water formed during the reaction using Dean stark apparatus.
- 4) In 1953, Giovambettista¹²² and Rabassa suggested acetic acid as a catalyst for the synthesis of Schiff bases in good yield.
- 5) In 1971, condensation of hydrazine and an aldehyde using glacial acetic acid as a solvent, has been described.

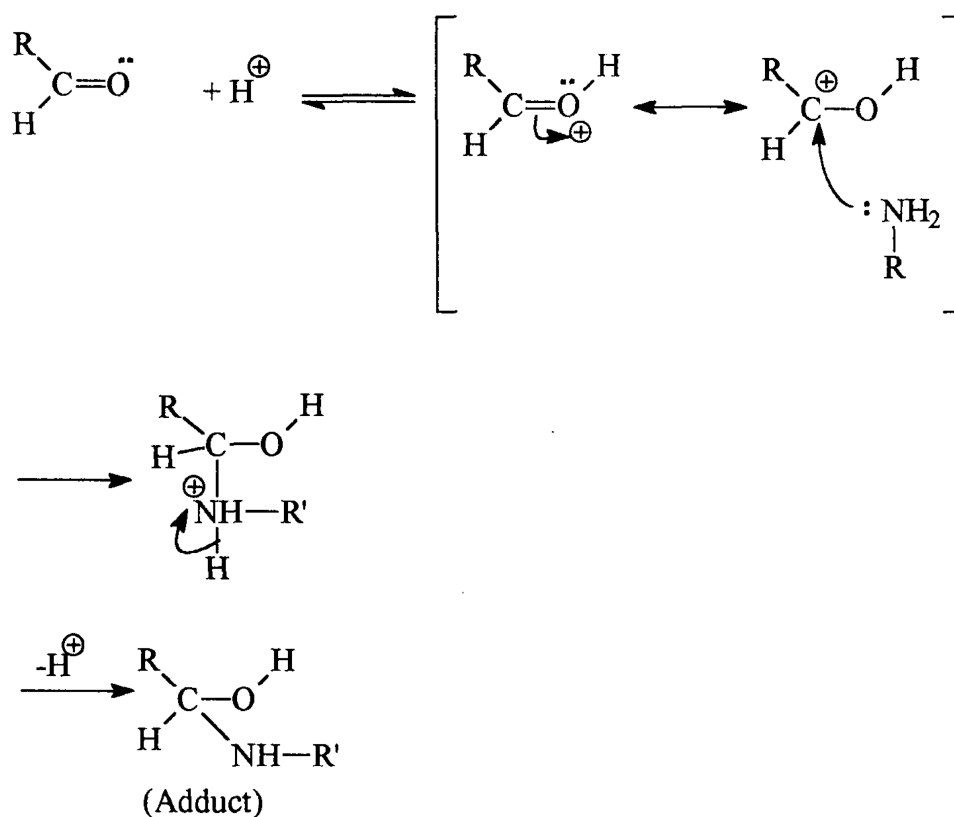
As the first method was found to give good yield, it was followed initially. Addition of few drops of acetic acid improved the yield. Later on, during the course of investigation, the last method, using acetic acid as a solvent, was found to be the best for the following reasons.

1. Simple apparatus and no need for Dean stark trap.
2. Good yield
3. Time course of the reaction was reduced

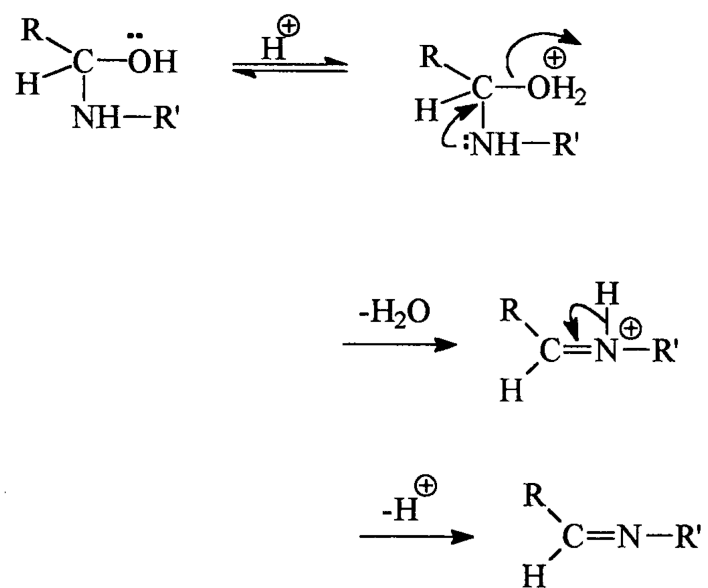
Reaction Mechanism :



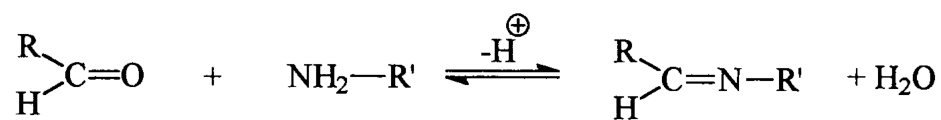
When an amine and an aldehyde are heated in the presence of an acid, the acid protonates carbonyl oxygen and promotes the attack of nucleophilic amino group.



The adduct thus formed undergoes a further reaction to eliminate water and forms a carbon-nitrogen double bond.



The overall reaction :



CHEMISTRY OF ACID CHLORIDES

Acid chlorides are used primarily as intermediates in synthesis. They are fairly reactive compounds and are usually liquids. Acid chlorides are obtained from acids through the replacement of the hydroxyl group with chloride. This exchange may be accomplished by the use of a number of inorganic chlorine compounds. Among these, thionyl chloride, phosphorous pentachloride, sulphuryl chloride and phosgene are the most important.

Phosphorous pentachloride is a highly reactive compound and its use offers a general method for the preparation of acid chlorides. The products of the reaction are phosphorous oxychloride and hydrogen chloride, in addition to the acid chloride.



The use of thionyl chloride¹²³ for the preparation of acid chlorides presents many advantages in a large number of cases. The reaction results in the formation of sulphur dioxide and hydrogen chloride in addition to the acid chloride, and the isolation of the chloride, is for this reason, a simple matter.



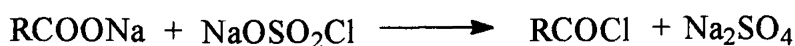
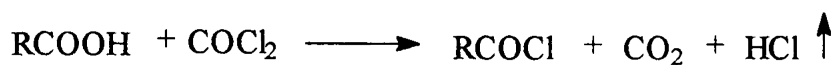
The thionyl chloride must be pure, as the impure product has been known to cause somewhat explosive decomposition in some instances. The procedure consists of mixing the chlorinating agent with acid and heating the mixture, if necessary. The product may be isolated by fractional distillation, or if solid, by crystallization.

Phosphorous oxychloride, reacts with the sodium salt of carboxylic acid to give acid chloride. This method is of importance for acids, which undergo decomposition with other chlorides of phosphorous.



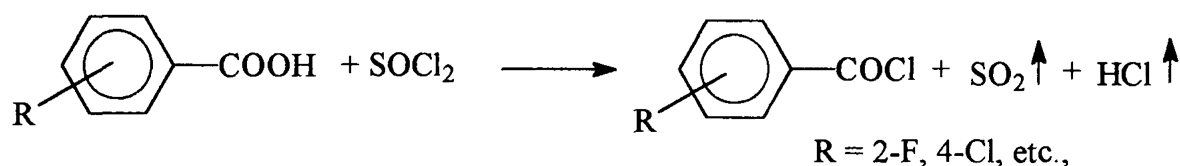
The reaction of phosgene¹²⁴ with carboxylic acids, and p-toluene sulphonyl chloride or of sodium chlorosulphonate with salts of carboxylic acids are also used for the

preparation of acid chlorides.

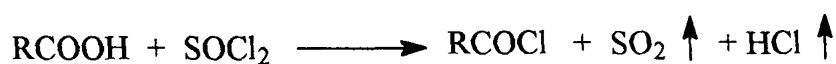


The acid chlorides are obtained readily through the reaction of sulfuryl chlorides with anhydrous salts of organic acids. The reagents are well mixed and subjected to distillation.

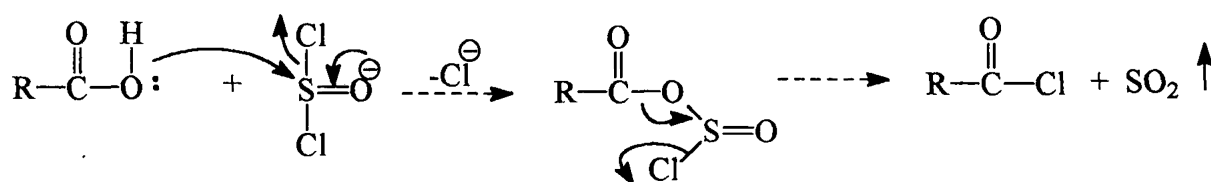
In the present work, all the acid chlorides were prepared by reacting thionyl chloride with corresponding acids.



Reaction mechanism :

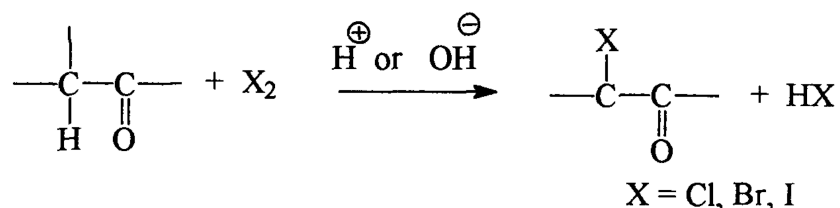


Acids and their salts are the only common starting materials for the synthesis of acid chlorides, and several reagents are utilized as a source of nucleophilic chloride. All the reagents form reactive intermediate (I), so that the leaving group in the substitution is not hydroxyl group.



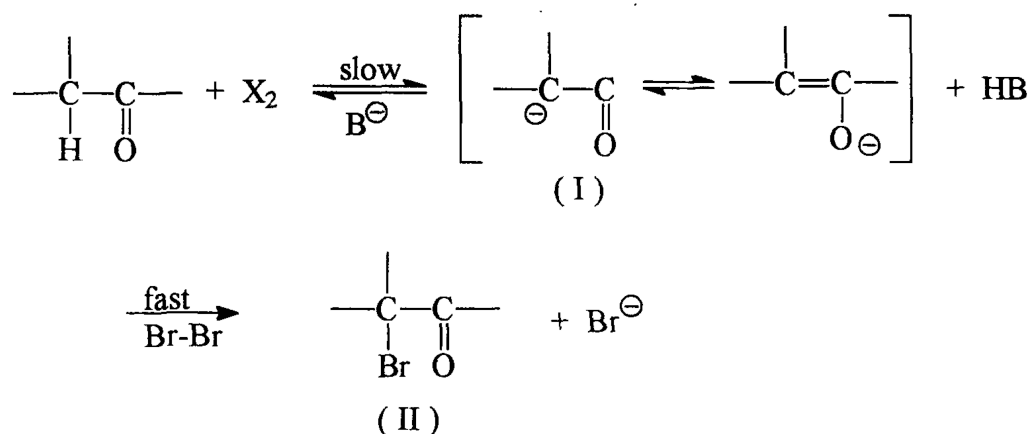
CHEMISTRY OF HALOGENATION OF KETONES

Ketones that have an α -hydrogen can be readily halogenated with bromine, chlorine or iodine in an acidic as well as basic medium.



Base-promoted halogenation of ketones

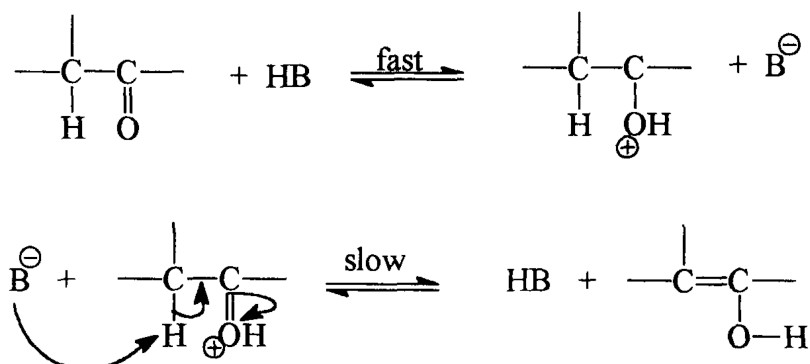
When basic catalysts are used, they slowly abstract a proton from the ketone to give a carbanion (I), which then rapidly reacts with bromine to yield the bromoketone (II).

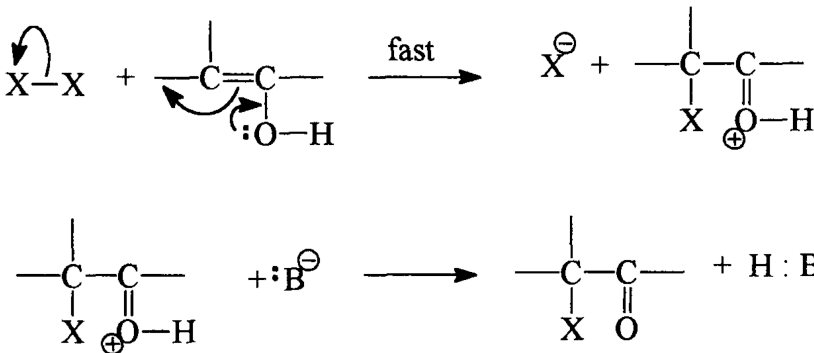


Since the rate of generation of carbanion determines the overall rate of the reaction it is the rate determining step. The carbanions react with the bromine molecule as soon as they are formed.

Acid-catalysed halogenation of ketones

Acids, like bases, speed up the halogenation of ketones. Since the acids are not consumed, the reaction may be called as acid-catalysed halogenation of ketones.





The rate determining reaction here is the formation of the enol, which involves two steps: rapid reversible protonation step (I) of the carbonyl oxygen, followed by the slow loss of an α -hydrogen step (II). Once formed, the enol reacts rapidly with the halogen to give the haloketone.

Solvents like chloroform, carbon tetrachloride, diethyl ether can be used conveniently and with better results. When diethyl ether is used as a solvent, aluminium chloride is often added to prompt enolization.

It is observed during bromination that the presence of sunlight, or slight heating during the initial stages, facilitates the initiation of the reaction. Heat or light may help bromine molecule to get polarised to the Br radical, which would favour the attack of polarised Br₂ molecule or Br⁺ on the enol form of the ketone.

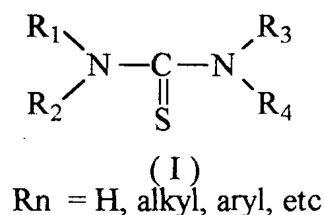
Cupric halides have been used occasionally to halogenate aromatic ketones, particularly if the use of free halogen causes nuclear halogenation, e.g. with phenolic ketones. The copper (II) halide presumably catalyses enol formation and transfers the halogen to the enol, giving α -haloketone.

CHEMISTRY OF THIOUREA

Since the first synthesis of thiourea and its derivatives was made in about 1870, a vast literature on these compounds has accumulated. In fact an extensive knowledge of the properties and principles of synthesis and reactivity of thioureas was available at a relatively early stage in the history of thiocarbonyl chemistry. A main reason for this situation is that thioureas, in general, are well defined, crystalline compounds of high stability and being further more easily accessible by relatively simple synthetic procedures.

Thioureas have found wide application as pharmaceuticals, insecticides, preservatives, rodenticides and otherwise are of commercial use in dyes, photographic films, plastics, textiles etc.

Thioureas in common practice are represented by the structure (I).

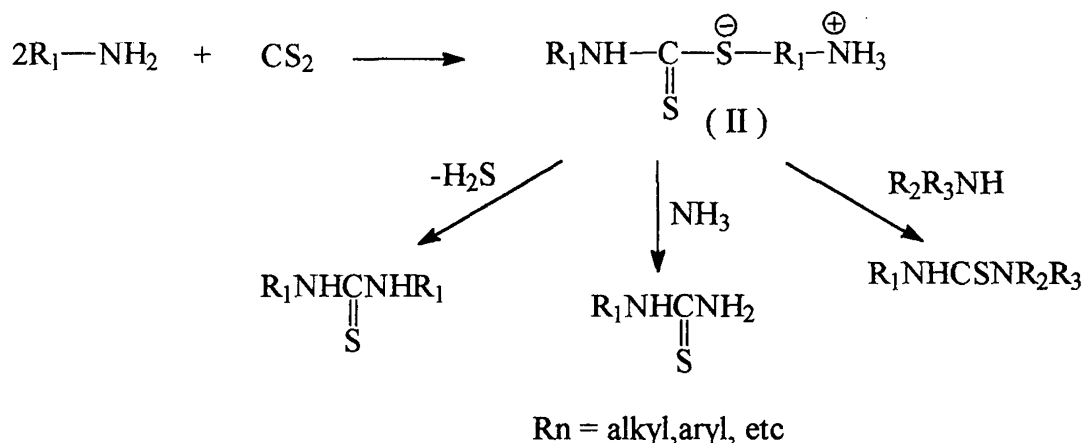


Summary of general synthetic methods

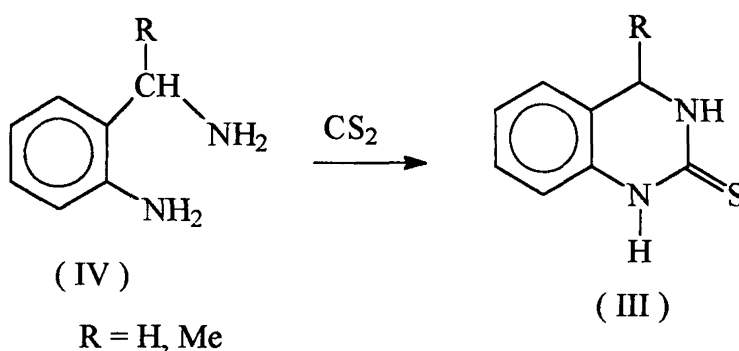
As a synthetic route to thioureas, the direct thionation of the carbonyl group of ureas by means of phosphorous pentasulfide is of minor significance. Apparently, it applies to the synthesis of tetra substituted thioureas and certain heterocycles having an incorporated thiourea moiety^{125,126}.

However, several other well established methods are available for the synthesis of thioureas. One of the cheapest methods for preparing symmetrical thioureas is based on the reaction of primary amines (I) with carbon disulfide¹²⁷.

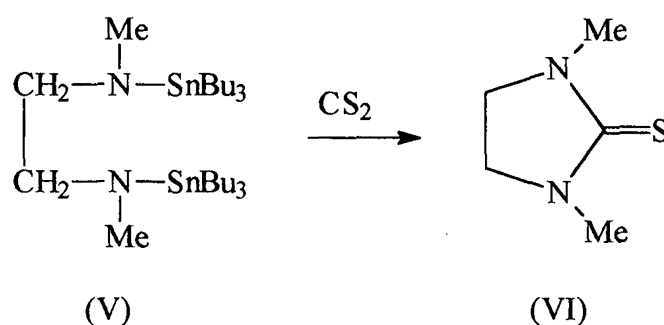
The mechanism of this is not quite clear, but apparently an intermediate ammonium dithiocarbamate (II) is involved in the reaction, when carried out in the presence of ammonia or another amine, afforded by products derived from the latter.



The reaction is influenced by catalysts such as elemental sulfur, hydrogen peroxide, hydroxide ions, iodine and pyridine, and is also applicable to the synthesis of cyclic thioureas, as exemplified by the preparation of (III) from (IV)¹²⁸.



An interesting variation involves the reaction of the tributyltin-substituted ethylene diamine (V) with carbon disulfide, affording the cyclic thiourea (VI)¹²⁹.



Perhaps the most important methods of synthesizing thiourea is based on the reaction of alkyl and aryl isothiocyanates with ammonia or amines¹³⁰. By this reaction monosubstituted, 1,3-disubstituted, and 1,1,3-tri substituted thioureas can be obtained.



$R_1, R_2, R_3 = H, \text{ alkyl, aryl, etc}$

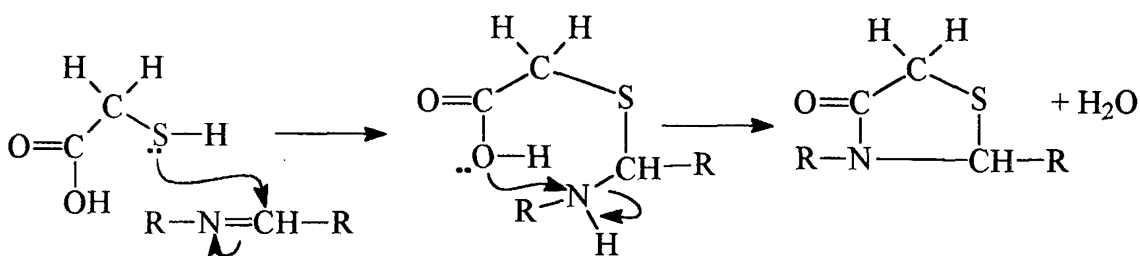
The broad scope of the reaction is most clearly demonstrated by the large variety of thioureas that have been synthesized on the basis of active participation of aliphatic, aromatic, open chain and cyclic amines, as well as amine derivatives such as ketimines, hydroxylamines, imino esters and amidines^{125,126,127}.

CHEMISTRY OF THIAZOLIDINONE

For the method of the preparation of thiazolidinone derivatives of quinazolinone moiety, we referred the procedure described by Kumar P. *et al.*¹³¹

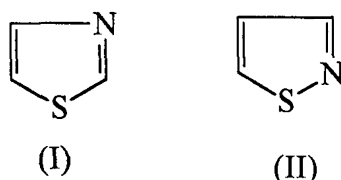
We have cyclised Schiff bases of 3-amino-2-methyl-6-nitro-quinazolinone in the presence of thioglycolic acid, using dry DMF and catalytic amounts of ZnCl_2 , to obtain 3-[2-methyl-4(3H)-oxo-3-quinazolinyl]-2-aryl-4-thiazolidinone.

Reaction mechanism :



CHEMISTRY OF THIAZOLES

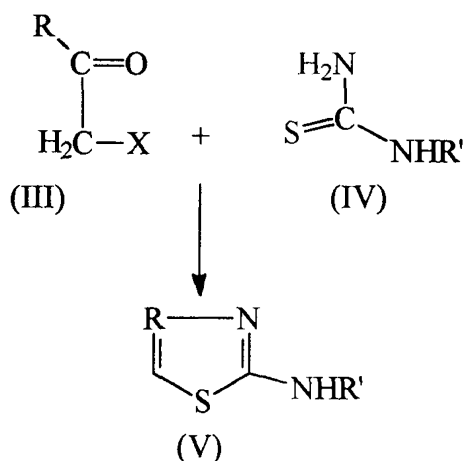
The thiazoled heterocycles(I) was first delineated by Hantzsch and Webber¹³², further they described it as the pyrroline of the thiohene series. The thiazole moiety exists in two different configurations, as thiazole(I) and isothiazole(II), respectively.



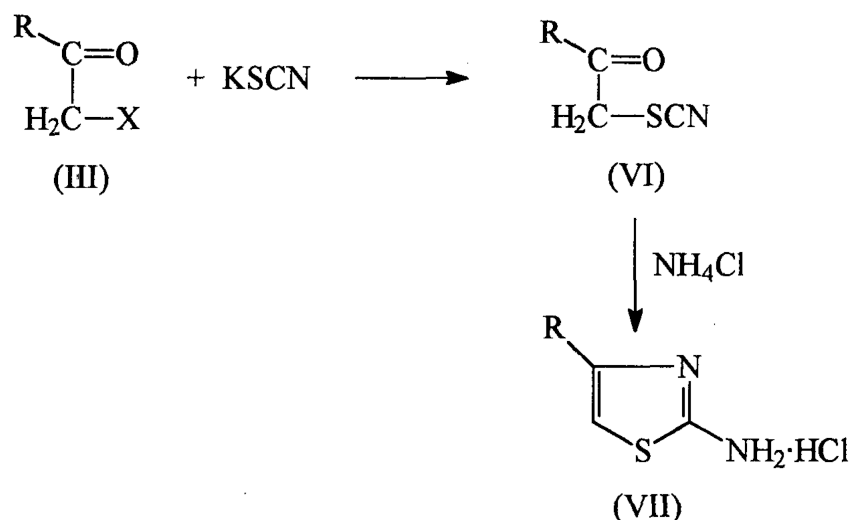
The thiazole derivatives have been more extensively studied as compared to the isothiazole derivatives, since they form a part of the important structural requirements in innumerable, naturally occurring compounds possessing diverse properties. Many fungicides, pesticides and bactericides are derivatives of 2-amino thiazole. Other thiazole derivatives possess mitodepressive and mitostatic properties¹³³. The high reactivity of the thiazole molecule is due to the group attached to the carbon between sulfur and nitrogen.

Methods of preparation of amino thiazole

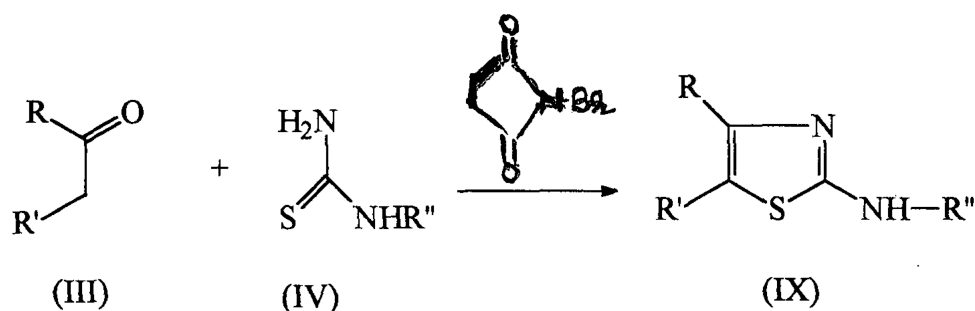
- I) The most common method employed for the synthesis of substituted thiazole, has been the one described by Hantzsch¹³⁴. The reaction between halocarbonyl compounds (III), and thiourea / substituted thiourea(IV) yields the respective 2-amino thiazole, or its derivatives (V).



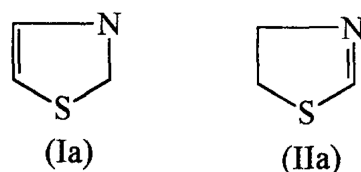
- II) Potassium thiocyanate reacts with α -halo-carbonyl compounds (III) to yield α -thiocyano ketones (VI) which on treatment with ammonium chloride yield the hydrochloride of 2-amino thiazole (VII).



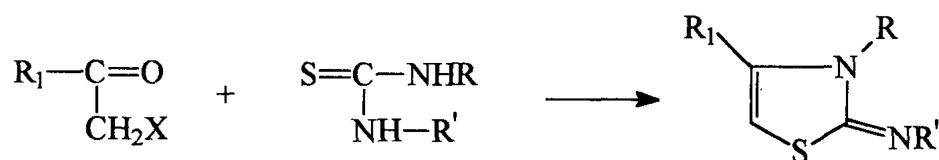
III) The reaction of substituted thiourea (IV) with ketones (III) in the presence of N-bromosuccinimide furnishes the 2-amino thiazole derivatives^{134a}(IX).



Thiazoline, another thiazole derivative, is present as 4,5 dihydrothiazole(Ia) and 2,3-dihydro thiazole(Iia)

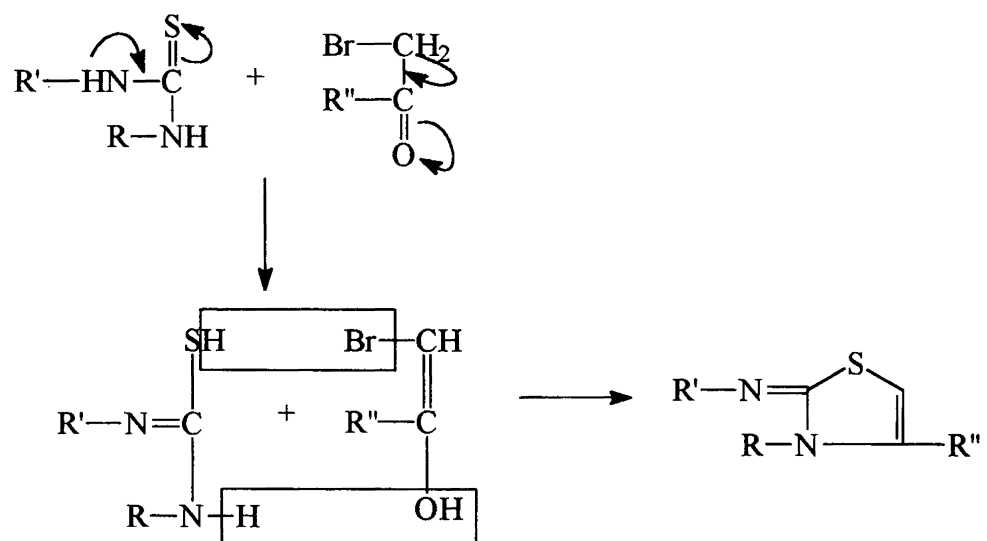


The symmetric and unsymmetrical disubstituted thiourea do not give thiazole ring, but give thiazoline ring which is derived from the tautomeric form of the 2-aminothiazole¹³⁵. Mechanism of formation of thiazoline ring is



In the present work compounds have been synthesized by reaction of thiourea with various substituted phenacyl bromides in dry alcohol.

Mechanism :



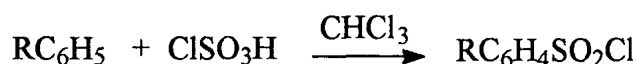
CHEMISTRY OF SULFONYL CHLORIDES

The sulfonyl chlorides are prepared by various methods

- 1) Sulfonyl chloride is made by reacting sodium sulfonate with PCl_5 or POCl_3 at 180°C ^{135a}. In this reaction, benzene sulfonate reacts with the PCl_5 or POCl_3 to yield benzene sulfonyl chloride.



Chlorosulfonic acid is utilized for the conversion of aromatic hydrocarbons to sulfonyl derivatives and can be used in the characterization of unknown hydrocarbons¹³⁶. In this, chlorosulfonyl chloride is used to provide the sulfonyl chloride ($-\text{SO}_2\text{Cl}$) group to the aromatic hydrocarbon. Thus, the sulfonyl chloride group is introduced to the aromatic nucleus by treatment with an excess of chlorosulfonic acid in chloroform¹³⁷.

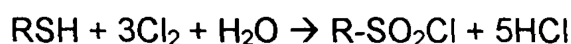


Sulfonyl chlorides have also been prepared by the reaction of Grignard reagent first with SO_2 , and then with chlorine gas¹³⁸.

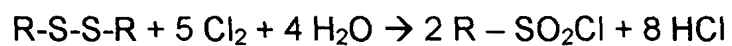


Aliphatic hydrocarbons can also be chlorosulfonated with sulfonyl chloride derivatives¹³⁹ e.g. 2,3 – dimethyl butane yields 20 % of 2,3–dimethyl butane-1-sulfonyl chloride. More recently, photolytic chlorosulfonation of alkane has been reported to yield alkane sulfonyl halide^{140,141}. In this mixture, C_{10-20} alkane sulfonyl chloride were prepared by photolytic chlorosulfonation of a paraffin mixture with chlorine and a large excess of SO_2 . The advantage of this method is that it minimizes the chlorination and degradation of sulfonyl chloride to give a yield.

Mercaptans or disulfides on reaction with chlorine in aqueous hydrochloric acid can be converted to sulfonyl chloride^{142,143}. Thus, methyl mercaptan is converted into methane sulfonyl chloride by simultaneous hydrolysis and chlorination at $40-70^\circ\text{C}$ in saturated HCl .



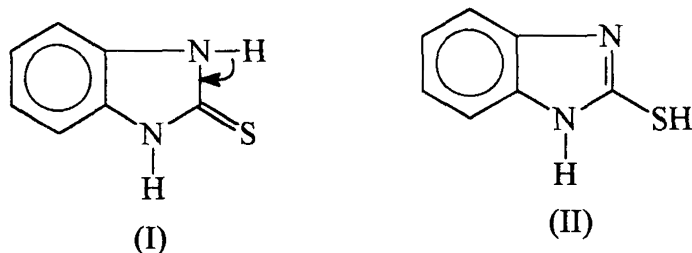
Disulfide can also be converted to sulfonyl chloride by simultaneous hydrolysis and chlorination.



There are relatively few heterocyclic sulfonamides in which the sulfur atom is joined directly to the carbon of a heterocyclic ring. In such a case, sulfonyl chlorides are usually prepared by chlorosulfonation or conversion to sulfonic acid and acid chloride.

CHEMISTRY OF 2-MERCAPTO BENZIMIDAZOLE

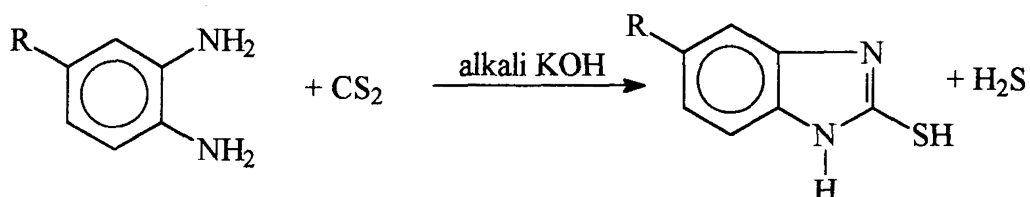
2-(3H) benzimidazole thione (I) and 2-mercapto benzimidazole (II) are tautomeric substances analogous to 2 (3H) benzimidazolone, and 2-hydroxy benzimidazole.



Different methods of preparation of 2- mercapto benzimidazole are :

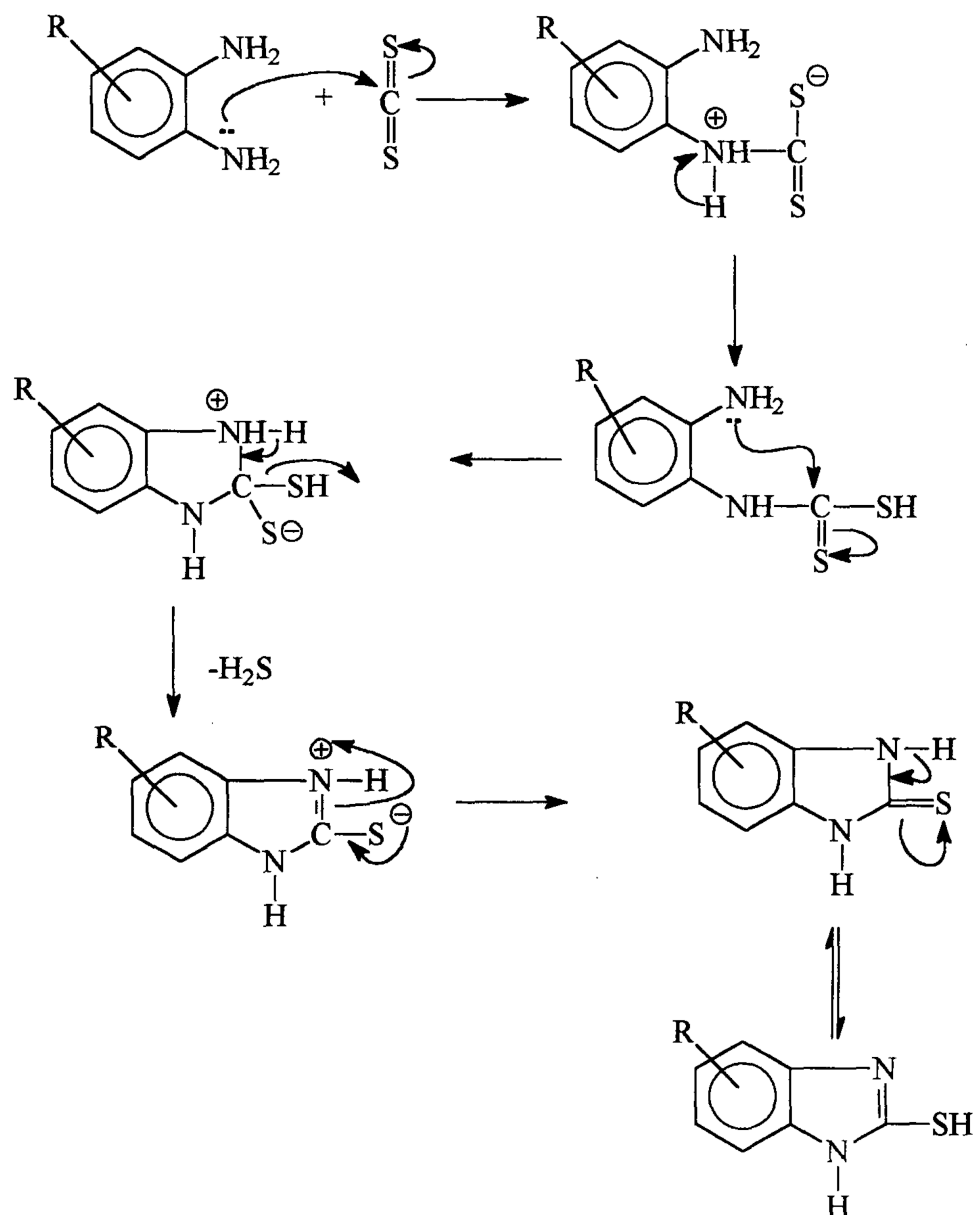
a) Synthesis from o-phenylene diamine and carbon disulfide

2- mercapto benzimidazole, in general, may be prepared very conveniently by this method. The reaction is carried out usually by heating the reactant in alcoholic solution with or without the addition of alkali to the reaction mixture 2-mercapto benzimidazole itself has been prepared by this method^{144,145}.



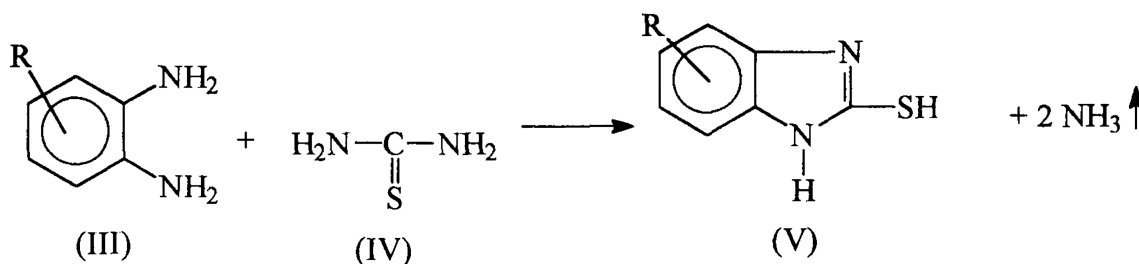
o-phenylene diamines containing substituents on the phenyl ring have been used, including those containing alkyl¹⁴⁶, halogen¹⁴⁷, phenyl¹⁴⁸, aniline¹⁴⁹ and sulphonamido¹⁵⁰ group.

Probable reaction mechanism :



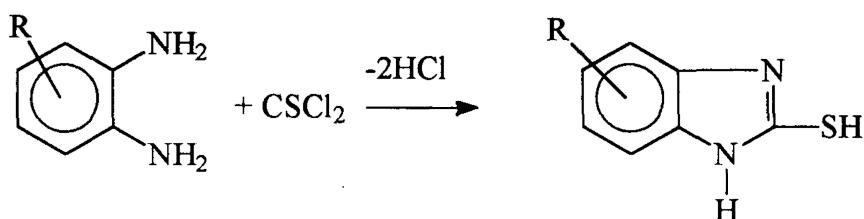
b) Synthesis from o-phenylene diamine and thiourea

This reaction is analogous to the preparation of 2-hydroxy benzimidazole from o-phenylene diamine and urea. Substituted-2-mercapto benzimidazoles (V) may be prepared by this method by heating substituted o-phenylene diamine dihydrochloride (III) and thiourea (IV) to 170-180°C¹⁵¹. Excellent yields have been obtained by carrying out the reaction in amyl alcohol and heating under reflux, until the evolution of ammonia becomes negligible.



c) Synthesis from-o-phenylene diamine and thiophosgene

Billeter and Steiner¹⁵² obtained 2-mercapto benzimidazole and 5-methyl-2-mercapto benzimidazole by action of thiophosgene on phenylenediamine and 3,4-diamino benzene arsenic acid and thiophosgene gave 78% yield of 2-mercapto-5-arsenic acid benzimidazole¹⁵³



d) Miscellaneous methods

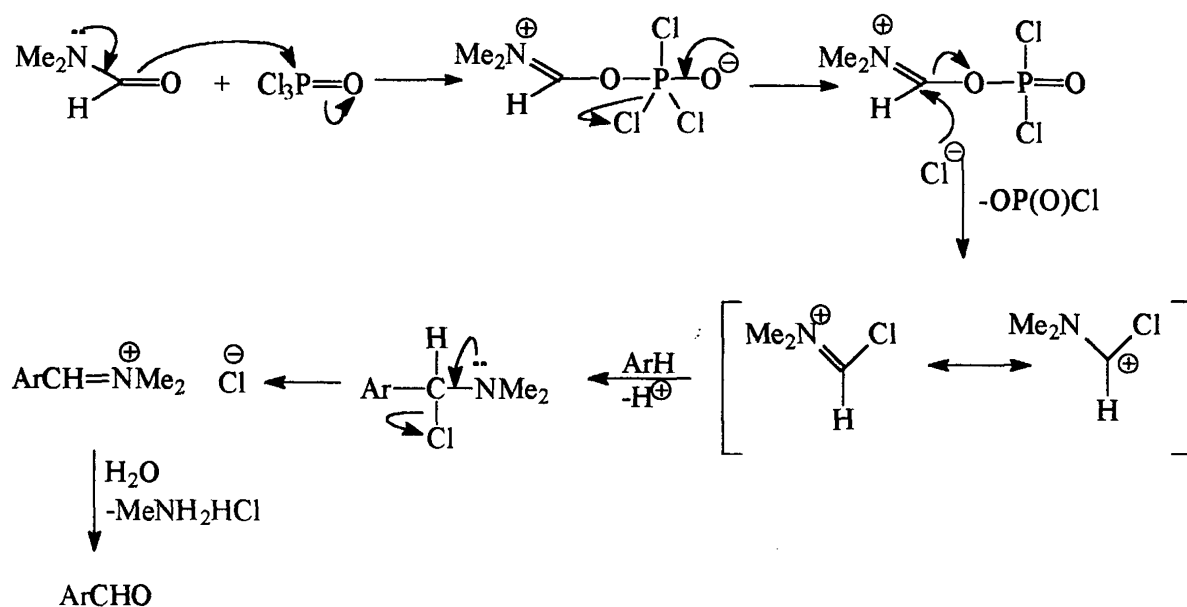
2-Mercapto benzimidazole can be prepared in 84-85% yield by the action of potassium ethyl xanthate on o-phenylene diamine¹⁵⁴. 2-Mercaptobenzimidazoles have also been reported from o-phenylene diamine hydrochloride and ammonium thiocyanate. A solution of the two substances is usually evaporated to dryness on a steam bath and then heated for a short time. By this method 2-mercapto benzimidazole¹⁵⁵ and its 5-chloro¹⁵⁶, 4-methyl¹⁵⁷ etc derivatives have been prepared.

CHEMISTRY OF VILSMEIER HACK REACTION :

Aromatic aldehydes may be obtained by passing a mixture of carbon monoxide and hydrogen chloride into the aromatic hydrocarbon in the presence of a mixture of copper (I) chloride and aluminium chloride, which acts as a catalyst.

Certain reactive aromatic hydrocarbons are formylated by dimethyleformamide in the presence of phosphorus oxychloride¹⁵⁸, i.e. Vilsmeier reaction. This method can also be used with advantage for the formylation of π excessive heteroaromatic systems, e.g. preparation of 2-formyl thiophene.

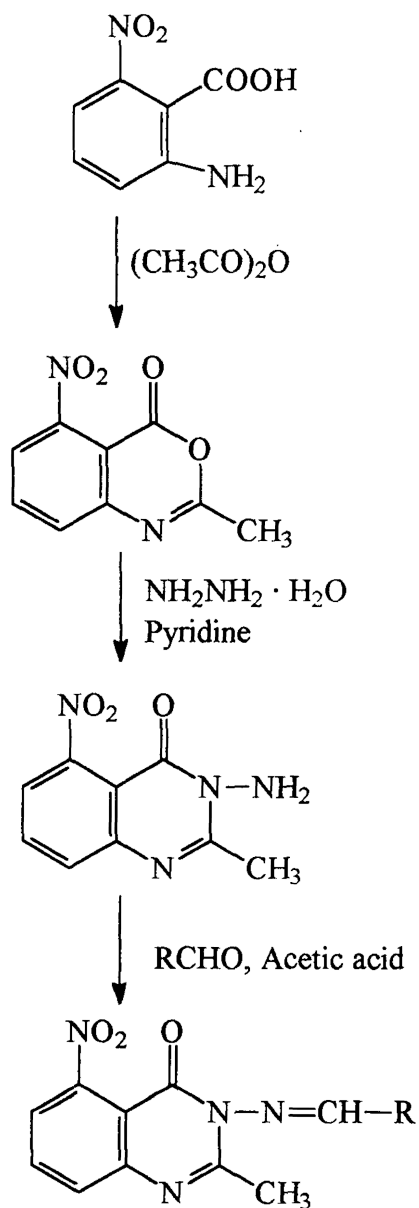
The mechanism of action is as follows :



Schematic Representation

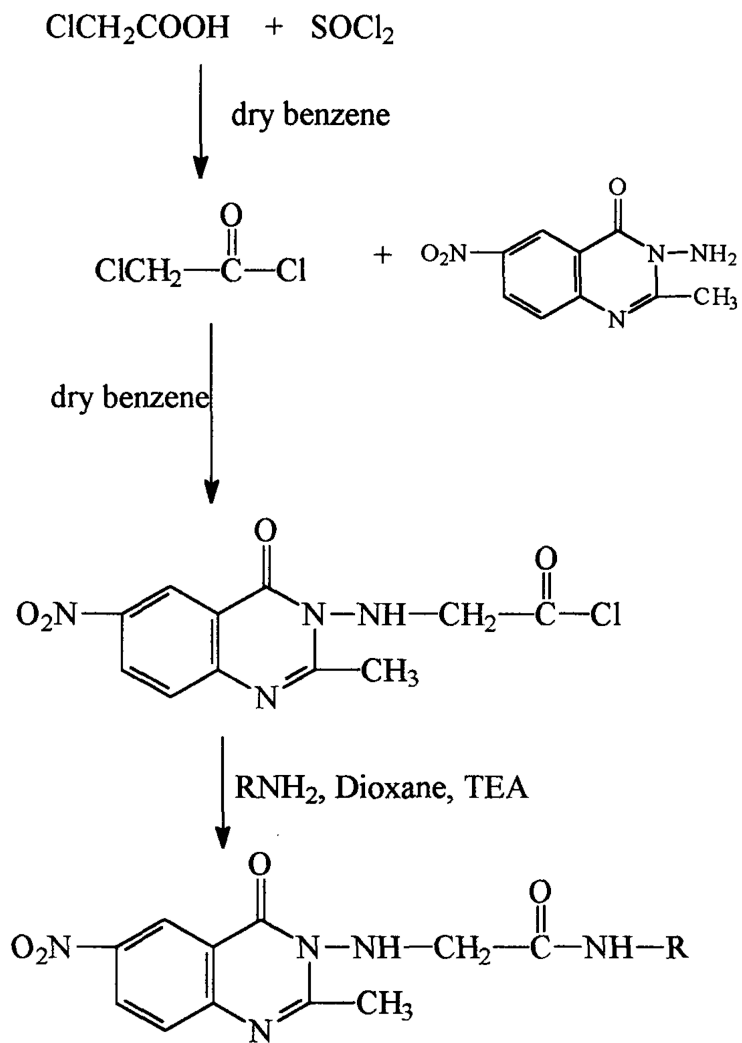
SCHEMATIC REPRESENTATIONS

Scheme 1
Synthesis of 2-methyl-5-nitro-3-[(substituted phenyl / heterocycle)methyleneaminoquinazoline -4-(3H)one.



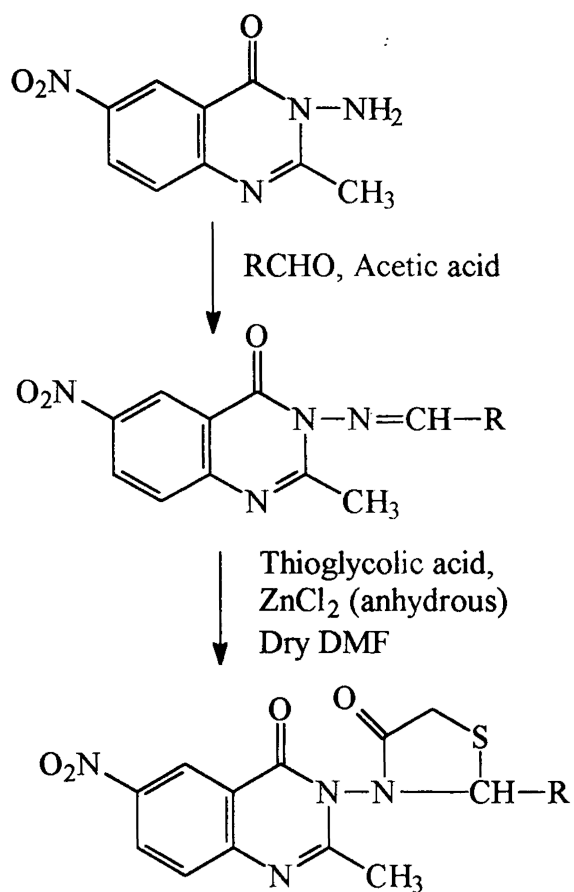
R = substituted aryl

Scheme 2
Synthesis of 3-(substituted acetamide)-2-methyl-6-nitro-quinazoline-4-(3H)one.



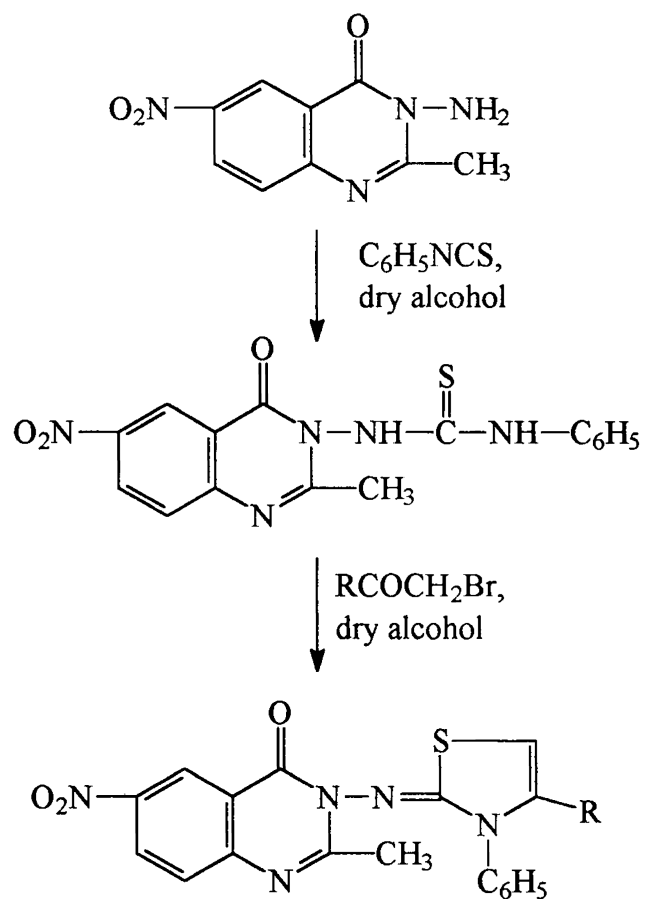
R = substituted aryl / heterocycle

Scheme 3
Synthesis of 3-[2-methyl-6-nitro-4(3H)-oxo-3-quinazolinyl]-2-(substituted phenyl / heterocycle) - 4-thiazolidinones



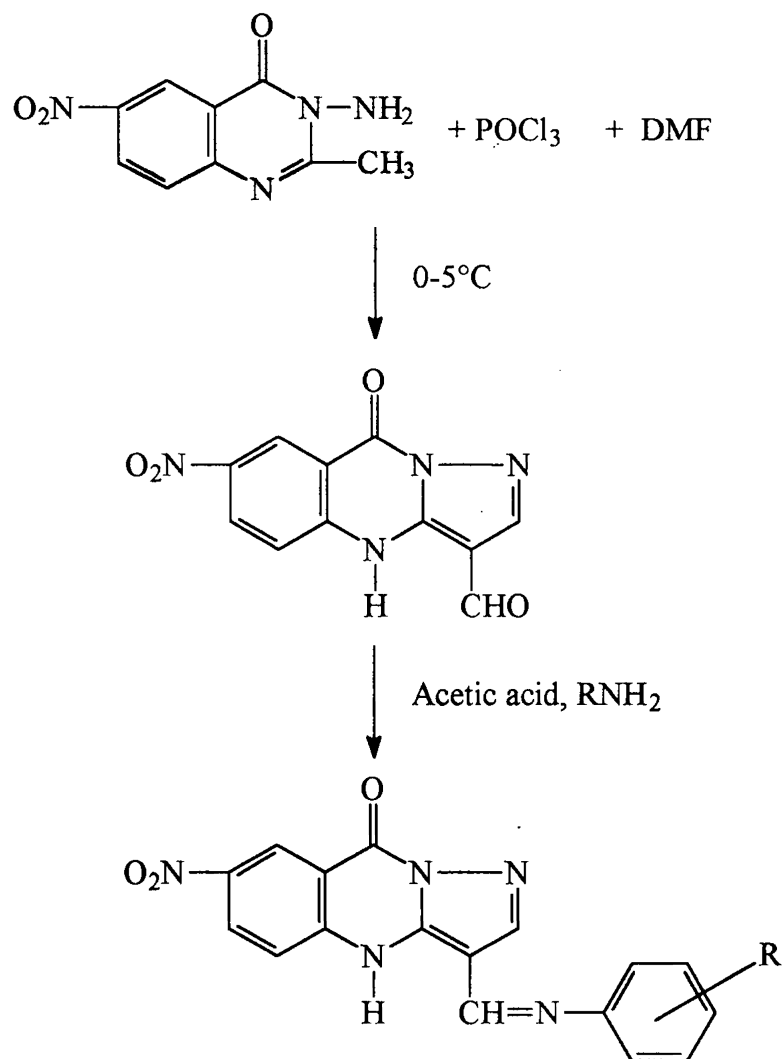
R = substituted aryl / heterocycle

Scheme 4
Synthesis of 2-methyl-6-nitro (3-phenyl-4-substituted-2,3-dihydrothiazole-2-ylideneamino-4-(3H)quinazolinone



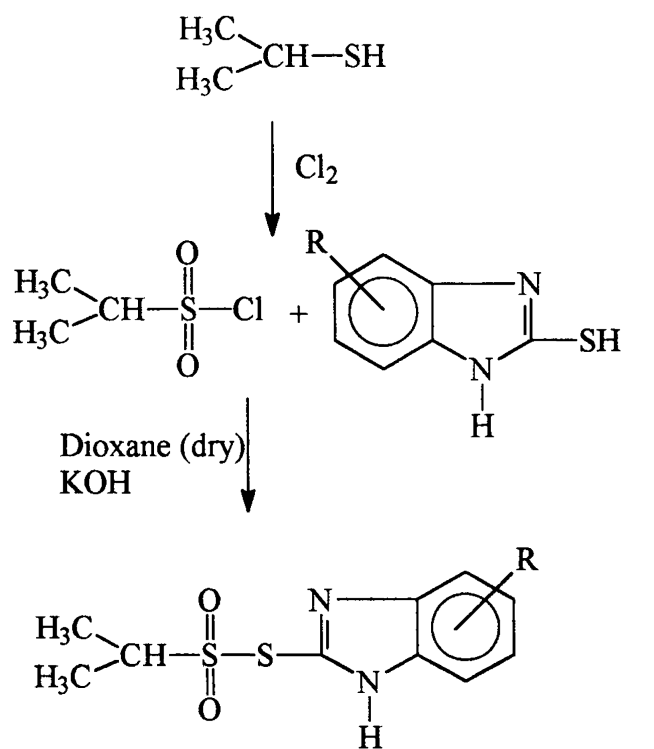
R = substituted aryl / heterocycles

Scheme 5
Synthesis of 3-N-(substituted phenyl)amino methylene pyrazolo [5,1-b]-7-nitroquinazoline-9(1H)one



R = substituted aryl / heterocycles

Scheme 6
Synthesis of 5/5,6 substituted-2-thio-(isopropyl sulfonyl)benzimidazoles / benzoxazoles



R = Cl, F, NO₂ etc.

Experimental

Part II

Synthesis of 2-methyl-5-nitro-3-[(substituted phenyl / heterocycle) methylene amino] quinazoline-4-(3H)one

Experimental

Synthesis of 2-methyl 5-nitro 3,1-benzoxazin 4(H)one.

In a 100 ml round bottomed flask, 6-nitro anthranilic acid (5 gm., 0.027 M) was dissolved in 25 ml. of acetic anhydride. The reaction mixture was refluxed for 5 hours. The excess of solvent was removed under reduced pressure and the solid product thus obtained was recrystallised from ethanol.

M.P. – 195 – 196°C

Yield – 80%.

Elemental analysis – $C_9H_6N_2O_4$

	Carbon	Hydrogen	Nitrogen
Calculated	52.42	2.91	13.59
Found	52.79	2.63	13.88

Synthesis of 3-amino – 2-methyl – 5-nitro quinazoline 4- (3H) one.

In a 100 ml round bottomed flask fitted with a reflux condenser 2-methyl-5-nitro-3,1 benzoxazine 4(H)-one (5gm, 0.02 M) was taken and was dissolved in 15 ml of pyridine. Hydrazine hydrate (1.00 gm, 0.97 M, 0.2 M) was added to it and the reaction mixture was refluxed for 7 hours. It was cooled and dumped in ice cold water. It was neutralized with dil HCl. The solid product separated out was filtered, washed with water and dried.

M.P. : 220°C

Yield : 65.66%

Elemental analysis – C₉H₈N₄O₃

	Carbon	Hydrogen	Nitrogen
Calculated	49.09	2.72	25.45
Found	49.28	2.89	25.83

Synthesis of 2 methyl 5-nitro -3-[(substituted phenyl (heterocycle) methylene amino]-quinazolin-4-(3H)one.

In a 50ml round bottomed flask fitted with a reflux condenser was taken 2-methyl -3-amino-5-nitro-4(3H)-quinazolinone (2.2 gm. 0.1 M) in 15 ml. glacial acetic acid. To this was added 2-methoxy benzaldehyde (1.36 gm 0.1 M) in 5 ml glacial acetic acid. The mixture was refluxed for 8 hrs. and then poured on to crushed ice. The solid thus separated out was filtered and recrystallised from ethanol. All the other derivatives have been prepared in a similar manner and their physical constants have been recorded in Table 1.

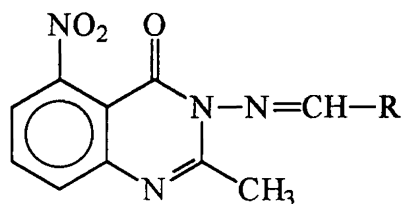
M.P. : 226-228°C

Yield : 49.65%

Elemental analysis – C₁₇H₁₄N₄O₄

	Carbon	Hydrogen	Nitrogen
Calculated	60.35	4.14	16.56
Found	60.09	4.00	16.88

Table No. 1 : 2-methyl (-5-nitro-3-[substituted phenyl / heterocycle] methylene amino quinazoline-4-(3H)ones



Sr No	R	Molecular formula	Mol. weight	MP (°C)	Yield (%)	Elemental Analysis (%)					
						Calculated			Found		
						C	H	N	C	H	N
1	3-chloro phenyl	C ₁₆ H ₁₁ N ₄ O ₃ Cl	342.5	257-59	55.92	56.05	3.21	16.35	56.24	3.56	15.95
2	2,4-dichloro phenyl	C ₁₆ H ₁₀ N ₄ O ₃ Cl ₂	377	235-36	50.10	50.92	2.65	14.85	50.57	2.63	15.12
3	2,6-dichloro phenyl	C ₁₆ H ₁₀ N ₄ O ₃ Cl	377	230-32	54.23	50.92	2.65	14.85	50.86	2.60	15.25
4	2-fluoro phenyl	C ₁₆ H ₁₁ N ₄ O ₃ F	326	255-56	49.78	58.89	3.37	17.17	58.56	3.46	17.57
5	4-fluoro phenyl	C ₁₆ H ₁₁ N ₄ O ₃ F	326	251-52	45.66	58.89	3.37	17.17	59.19	3.57	16.95
6	3,4-dichloro phenyl	C ₁₆ H ₁₀ N ₄ O ₃ Cl ₂	377	185-87	50.02	50.92	2.65	14.85	51.23	2.61	15.12
7	4-chloro phenyl	C ₁₆ H ₁₁ N ₄ O ₃ Cl	342.5	250-52	51.37	56.05	3.21	16.35	56.44	3.15	16.07
8	3-fluoro phenyl	C ₁₆ H ₁₁ N ₄ O ₃ F	326	225-26	53.55	58.59	3.37	17.17	58.39	3.11	17.53
9	2-methoxy phenyl	C ₁₇ H ₁₄ N ₄ O ₄	338	226-28	49.65	60.35	4.14	16.56	60.09	4.00	16.88

Spectral studies of 2-methyl-5-nitro-3-[(4-chloro phenyl methylene amino)]-quinazoline-4-(3H)-one. Table no 1, Comp. No. 7.

IR (KBr) cm^{-1}

Wave number	Assignment
2921.6	CH_3
1681.0	$\text{C}=\text{O}$
1331, 1531	NO_2
1631.72	$\text{CH}=\text{N}$

PMR (DMSO - d_6) δ :

2.8	(s, 3H, $-\text{CH}_3$)
6.3	(s, 1H, $-\text{N}=\text{CH}-$)
7.8-8.7	(m, 8H, ArH)

Spectral studies of 2-methyl-5-nitro-3-[(2,4-dichloro phenyl methylene amino)]-quinazoline-4-(3H)-one. Table no 1, Comp. No. 2.

IR (KBr) cm^{-1}

Wave number	Assignment
2959.1	CH_3
1700.7	$\text{C}=\text{O}$
1349.96, 1531.69	NO_2
1638.08	$\text{CH}=\text{N}$

File # 1 = AZOFL

Mode= 2 (Mid-IR)

11/5/98 4:05 PM

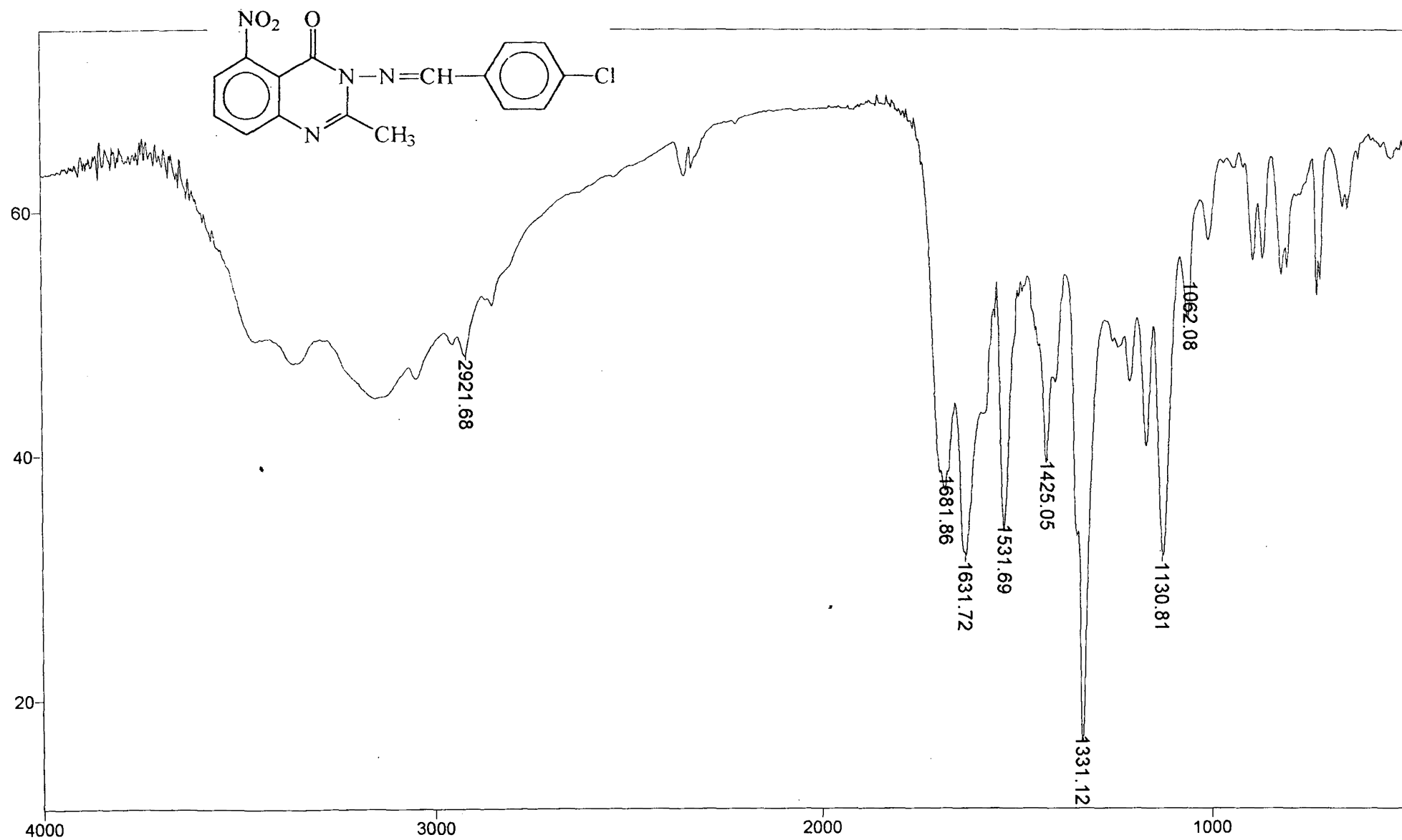
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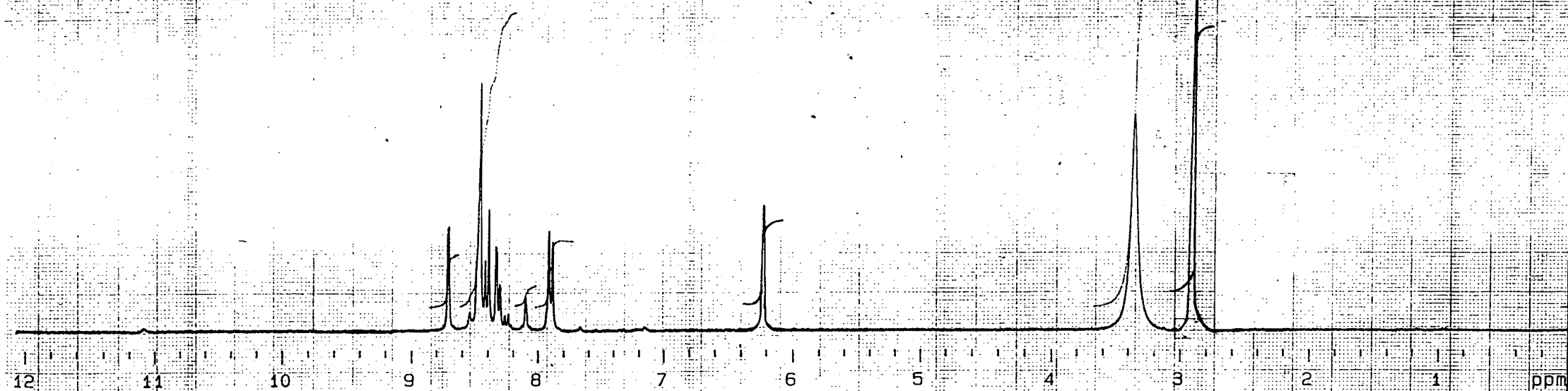
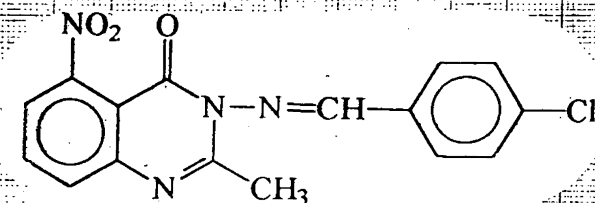
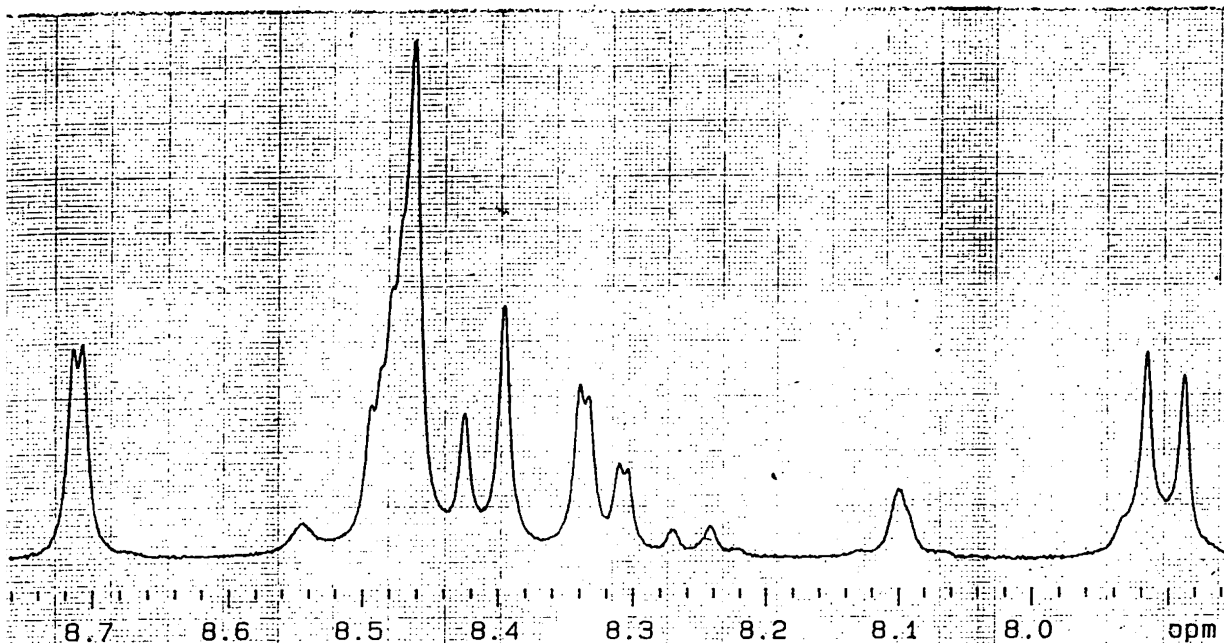
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Res=4 cm-1

Apod= Cosine

Zero Filling= 1 x





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 Pulse Width 10.0 usec

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 Offset 1200.0 Hz
 Delay 0 sec
 Transmits 216

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 Nucleus C
 Value 17.5

FN not used
 LB 0.100 not used
 Width 3664.2 Hz
 Reference -17.8 ppm

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 Solvent DMSO

SAMPLE
 M5

Number
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 Date Mar 17 99
 VPRO 300

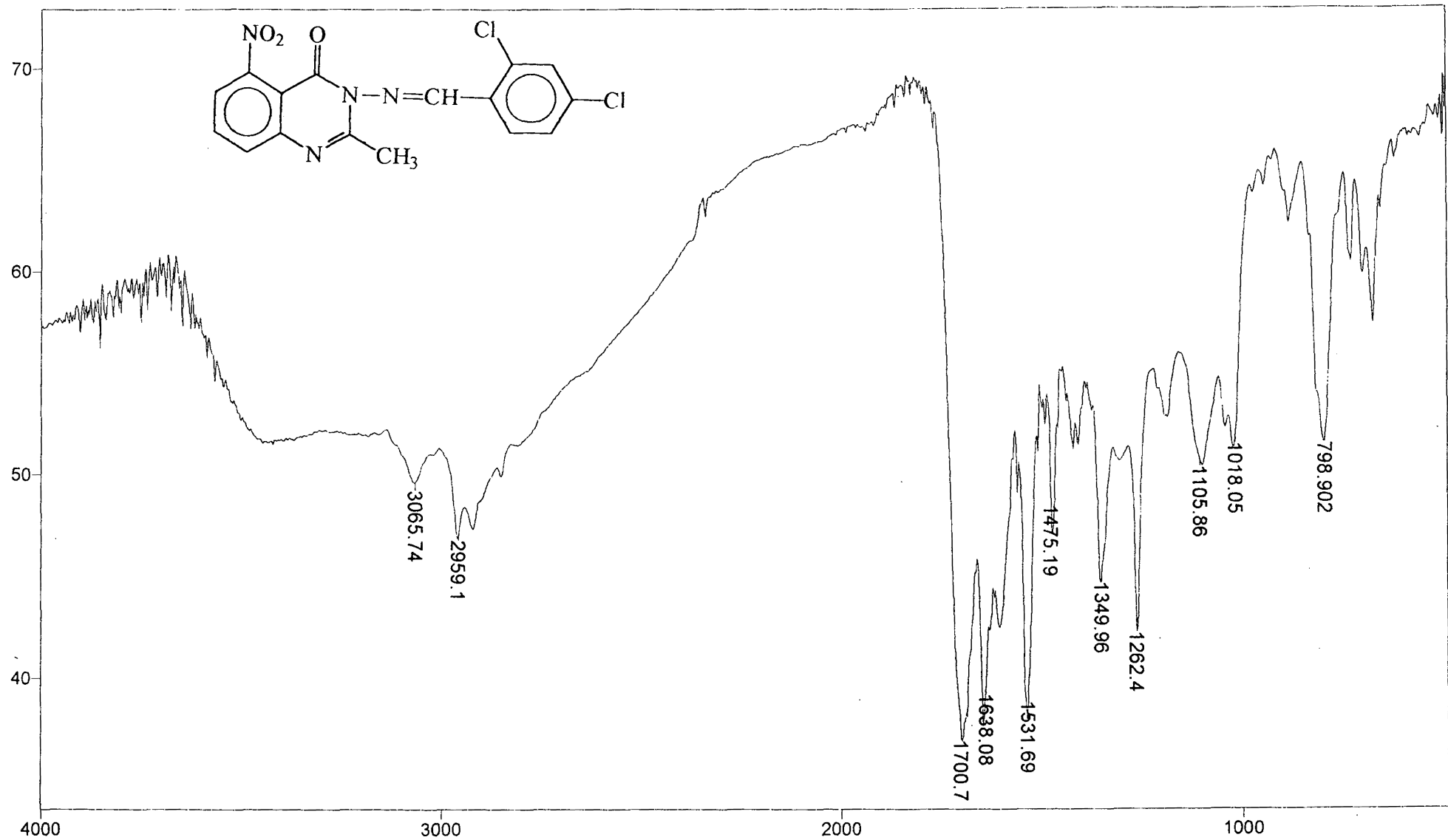
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Res=4 cm-1

Apod= Cosine

Zero Filling= 1 x



Part III

***Synthesis of 3-
(substituted acetamido)-
2-methyl-6-
nitroquinazoline-4-
(3H)one***

Synthesis of chloro acetyl chloride

In a 100 ml round bottomed flask was taken a solution of dry benzene (15 ml) and mono chloroacetic acid (5 gm, 0.05 M). Thionylchloride. (6.3 ml., 0.08 M) was added to it. The reaction mixture was refluxed for 6 hours under anhydrous conditions. The excess Benzene and thionyl chloride was distilled off and the product was washed with dry benzene 3 times. The benzene was distilled off and the fraction which distills at 105°C was collected.

B.P. : 105°C, lit. 105°C¹⁵⁹

Yield : 78.84 %

Synthesis of 3 –chloroacetamide –2-methyl-6-nitro- 4-(3H)quinazolinone

To a cold solution of 3-amino-2-methyl-6-nitro-quinazolinone (2.2 gm, 0.02M) in dry benzene (18 ml.), chloroacetyl chloride (1.59 ml. 0.004 M) was added slowly with stirring. The reaction mixture was refluxed for 8 hours. The solvent was then distilled off and the resultant solid was recrystallized from benzene.

M.P. : 170°C

Yield : 66.5 %

Elemental analysis – C₁₁H₉N₄O₄Cl

	Carbon	Hydrogen	Nitrogen
Calculated	44.51	3.03	18.88
Found	44.89	3.25	19.99

Synthesis of 3-(substituted acetamido)-2-methyl-5-nitro-4-(3H)quinazolinone

3-chloroacetamido-2-methyl-6-nitro-4- (3H) quinazolinone (1 gm, 0.042M) and 2-chloroaniline (0.35 ml, 0.042 M) were dissolved in dry 1,4-dioxane (10 ml.) containing triethylamine (0.45 ml, 0.042M). The reaction mixture was refluxed for 7 hours and poured onto crushed ice, where upon a solid separated out, which was filtered, washed thoroughly with water and recrystallised from methanol. All the other derivatives have been prepared in a similar manner and their physical constants have been recorded in Table no. 2.

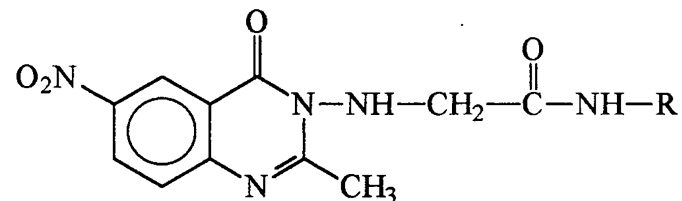
M.P. : 219-220 °C

Yield : 49.77 %

Elemental analysis – C₁₇H₁₄N₅O₄Cl

	Carbon	Hydrogen	Nitrogen
Calculated	52.64	3.61	18.06
Found	52.37	3.76	17.84

Table No. 2 : 3-(substituted acetamide)-2-methyl-6-nitro quinazoline-4-(3H)-one



Sr No	R	Molecular formula	Mol. weight	MP (°C)	Yield (%)	Elemental Analysis (%)					
						Calculated			Found		
						C	H	N	C	H	N
1	2-chlorophenyl	C ₁₇ H ₁₄ N ₅ O ₄ Cl	387.5	219-20	49-77	52.64	3.61	18.06	52.37	3.76	17.84
2	2,6-dimethyl piperidiny	C ₁₉ H ₂₁ N ₅ O ₄	383	257	48.23	59.53	5.48	18.27	59.80	5.77	18.58
3	2-aminopyridine	C ₁₆ H ₁₄ N ₆ O ₄	354	250-52	55.59	54.23	3.95	23.72	54.62	4.2	24.08
4	2,6-dimethyl phenyl	C ₁₉ H ₁₉ N ₅ O ₄	381	244	57.32	59.84	4.98	18.37	59.61	5.11	18.73
5	2,5-dimethoxy phenyl	C ₁₉ H ₁₉ N ₅ O ₆	413	233-35	59.11	55.20	4.60	16.94	54.80	4.72	47.73
6	3-amino quinoliny	C ₂₀ H ₁₆ N ₅ O ₄	390	220-22	54.55	61.53	4.10	17.94	61.74	4.5	17.66
7	5-amino-4,6-dimethyl pyrimidiny	C ₁₇ H ₁₇ N ₇ O ₄	383	141-43	51.03	53.26	4.43	21.93	53.07	4.54	22.3
8	Piperaziny	C ₁₅ H ₁₈ N ₆ O ₄	346	220-21	50.05	52.02	5.20	24.27	51.90	5.37	24.63
9	N-methyl piperaziny	C ₁₆ H ₂₀ N ₆ O ₄	360	205-07	50.55	53.33	5.55	23.33	53.68	5.82	23.73
10	2-amino pyrimidiny	C ₁₅ H ₁₃ N ₇ O ₄	355	225-27	59.12	50.70	3.60	27.60	50.90	3.89	27.38

Spectral studies of 3-(2-chlorophenyl acetamide)-2-methyl-6-nitro quinazoline-4-(3H)one. Table no 2, Comp. No. 1

IR (KBr) cm^{-1}

Wave number	Assignment
2959.1	CH_3
3316.2	NH stretch
1681.86	NH-C=O
1349.96	NO_2

PMR (DMSO - d_6) δ :

2.6	(s, 3H, CH_3)
1.8	(d, 2H, CH_2)
5.63	(t, 1H, NH)
4.4	(s, 1H, NH)
6.4-7.8	(m, 7H, Ar-H)

le # 1 = BZO

Mode= 2 (Mid-IR)

6/8/98 9:09 AM

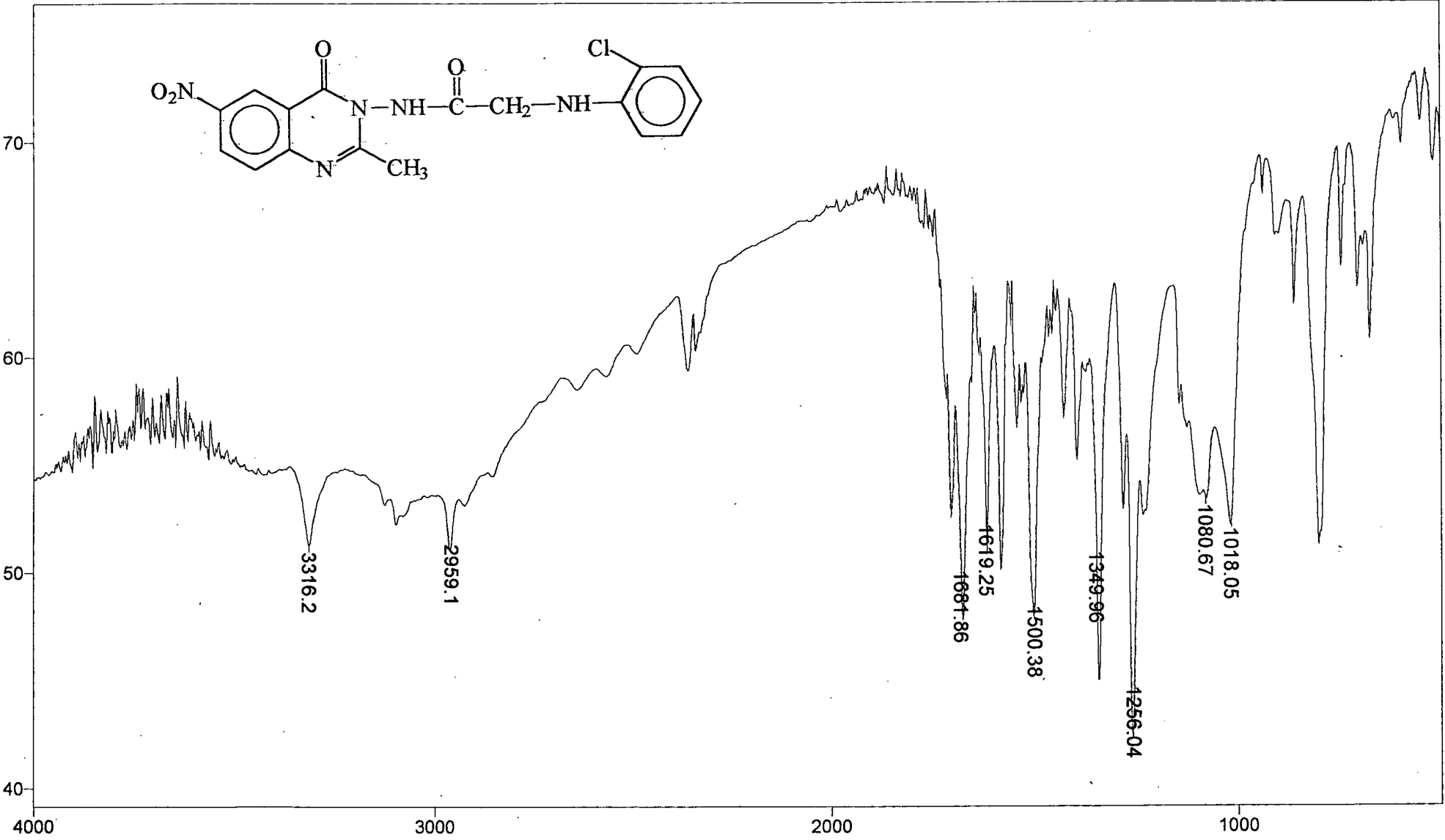
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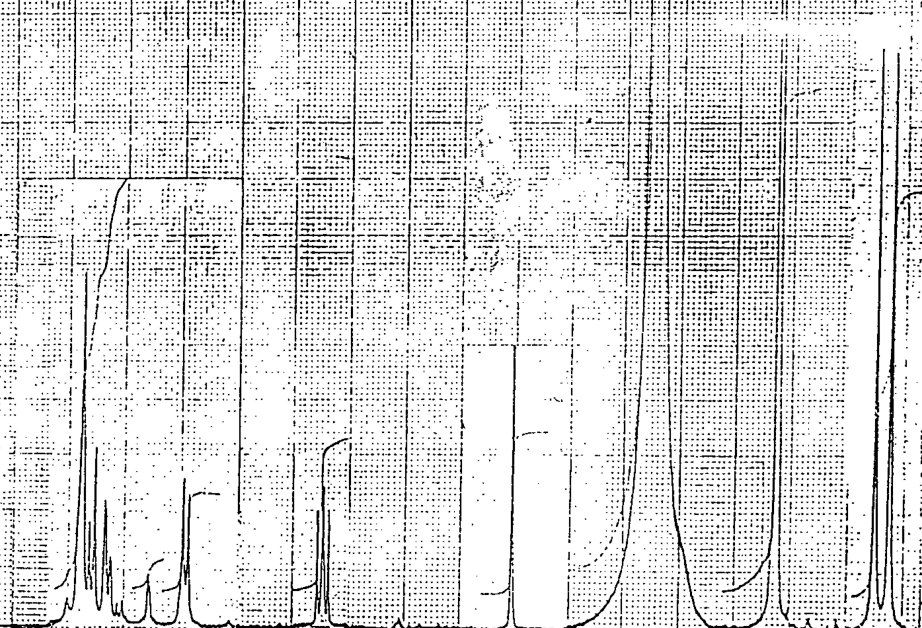
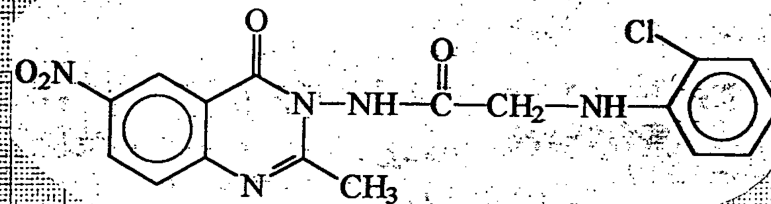
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Res=4 cm-1

Apod= Cosine

Zero Filling= 1 x





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 Pulse Width 10.000 Transients 304

Nucleus H1 Offset 315.0 Hz
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 Modulation Mode C Freq 200 Hz
 Pulse Width 17.5 sec Power Mode NOT USED

PLOT/PROCESSING
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 LB 0.100 sec not used sec CD sec
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 Reference _____

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SAMPLE
 MB 2+4

Number _____
 File exp
 Date Dec 30 99
 VOP 300

Part IV

Synthesis of 3- [2- methyl -6-nitro-4(3H)- one-3 - quinazolinyl]-2- (substituted phenyl / heterocycle)-4- thiazolidinones

Synthesis of 3-[2-methyl-6-nitro-4(3H)-oxo-3-quinazolinyl]-2-(methoxy phenyl) - 4-thiazolidinones

2-methyl-6-nitro 3[(2-methoxy phenyl) methylene amino] quinazolinone (0.67 gm, 0.002 M) was refluxed in dry DMF (10 ml.) containing a pinch of anhydrous ZnCl_2 and thioglycolic acid (0.13 gm. 0.002M) for 9 hrs. The reaction mixture was cooled and poured on ice. The solid product separated out was filtered, washed with water and recrystallised from DMF : water (8:2). All other derivatives have been prepared in a similar manner and their physical constants have been recorded in Table No. 3.

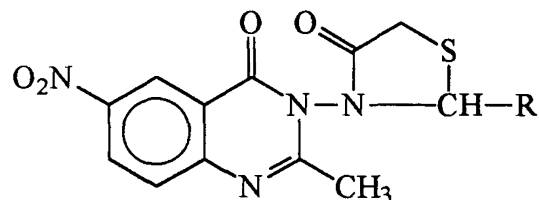
M.P. : 210-211°C

Yield. : 49.70%

Elemental analysis – $\text{C}_{19}\text{H}_{13}\text{N}_4\text{O}_4\text{SF}_3$

	Carbon	Hydrogen	Nitrogen
Calculated	50.66	2.88	12.44
Found	50.89	3.01	12.75

**Table No. 3 : 3-[2-methyl-6-nitro-4(3H)-one-3-quinazolinyl]-2-(substituted phenyl / heterocycle)
-4-thiazolidinones**



Sr No	R	Molecular formula	Mol. weight	MP (°C)	Yield (%)	Elemental Analysis (%)					
						Calculated			Found		
						C	H	N	C	H	N
1	2-methoxy phenyl	C ₁₉ H ₁₆ N ₄ O ₅ S	412	130-32	50.12	55.33	3.88	13.59	55.56	3.53	13.91
2	2-pyridyl	C ₁₇ H ₁₃ N ₅ O ₄ S	383	185	55.78	53.26	3.39	18.27	53.04	3.48	18.64
3	N-methyl pyrrolyl	C ₁₇ H ₁₅ N ₅ O ₄ S	385	202-204	50.70	52.98	3.89	18.18	53.33	4.21	18.58
4	2-thienyl	C ₁₆ H ₁₂ N ₄ O ₄ S ₂	388	200	48.90	49.48	3.09	14.43	49.85	3.30	14.78
5	5-bromo thienyl	C ₁₆ H ₁₁ N ₄ O ₄ S ₂ Br	467	274-75	52.90	41.11	2.35	11.99	40.96	2.55	12.20
6	3-methyl thienyl	C ₁₇ H ₁₄ N ₄ O ₄ S ₂	402	196-98	45.85	50.74	3.48	13.93	50.95	3.26	14.24
7	2-trifluoromethyl phenyl	C ₁₉ H ₁₃ N ₄ O ₄ SF ₃	450	210-11	49.70	50.66	2.88	12.44	50.89	3.01	12.75
8	4-trifluoromethyl phenyl	C ₁₉ H ₁₃ N ₄ O ₄ SF ₃	450	156-57	55.59	50.66	2.88	12.44	50.97	3.03	12.25
9	4-chlorophenyl	C ₁₈ H ₁₃ N ₄ O ₄ SCl	416.5	215-17	57.20	51.86	3.12	13.44	52.09	3.28	13.08

Spectral studies of 3-(2-methyl-6-nitro-4-(3H)-one-3-quinazolinyl]-2-(4-chlorophenyl)
4-thizolidinones. Table no 3, Comp. No. 9

IR (KBr) cm^{-1}

Wave number	Assignment
1681	C=O
2959.1	CH_3
3000	CH_2
1349.96, 1500	NO_2
1619	C=N

PMR (DMSO - d_6) δ :

1.8	(s, 1H, -CH)
2.2	(s, 2H, CH_2)
2.4-2.6	(s, 3H, CH_3)
6.8-8.8	(m, 7H, Ar-H)

Mass spectra m/z 388 compound no. 4, table no. 3

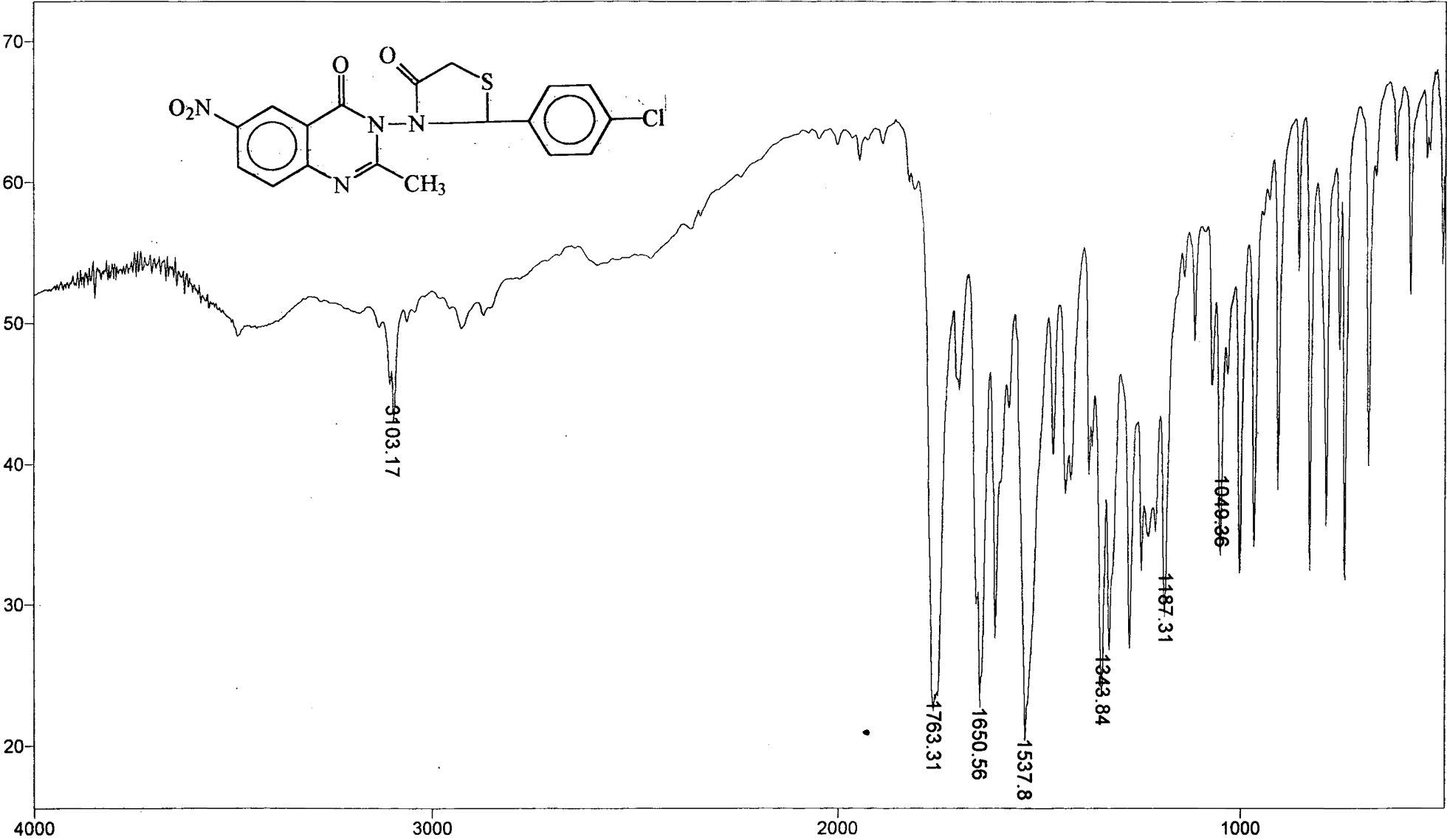
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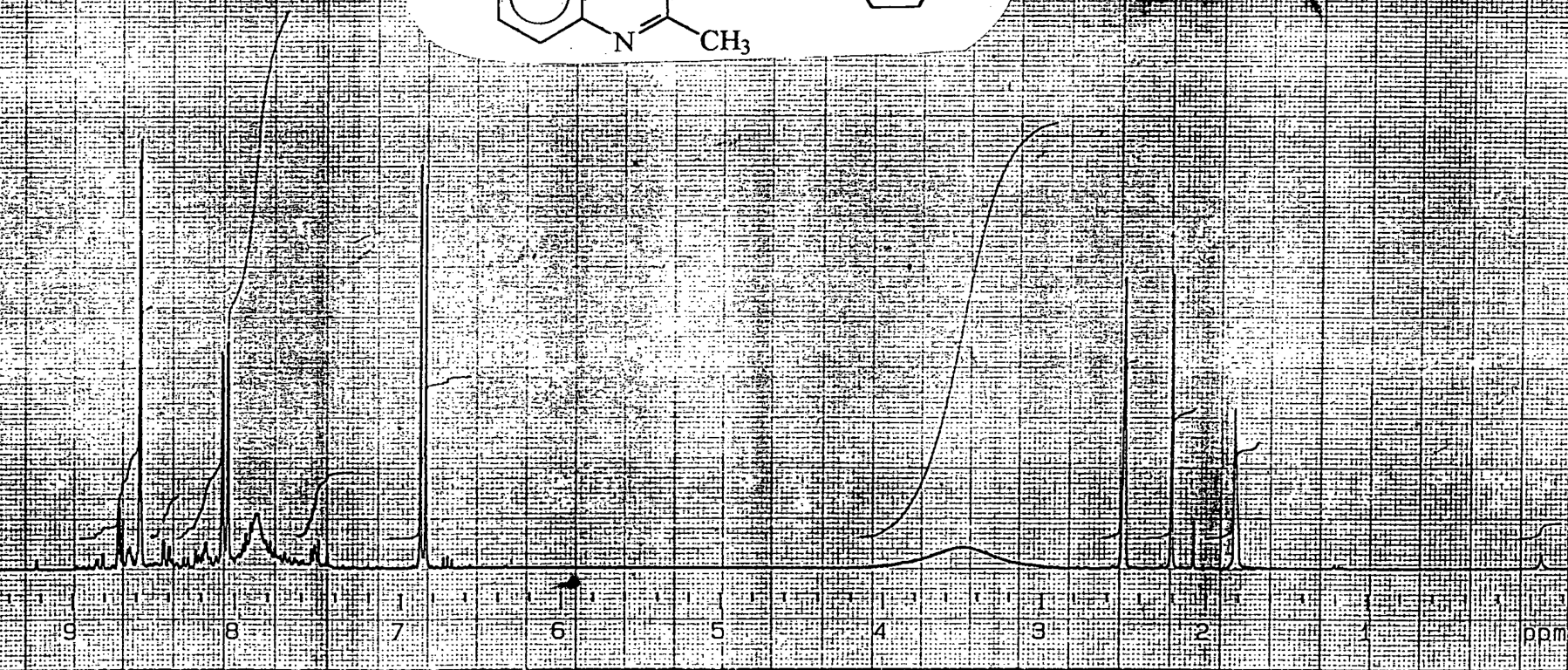
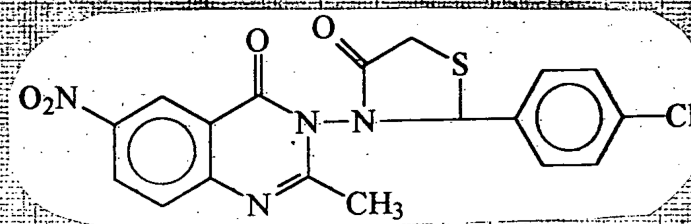
Scans= 10 Slow

Res=4 cm-1

Apod= Cosine

Zero Filling= 1 x





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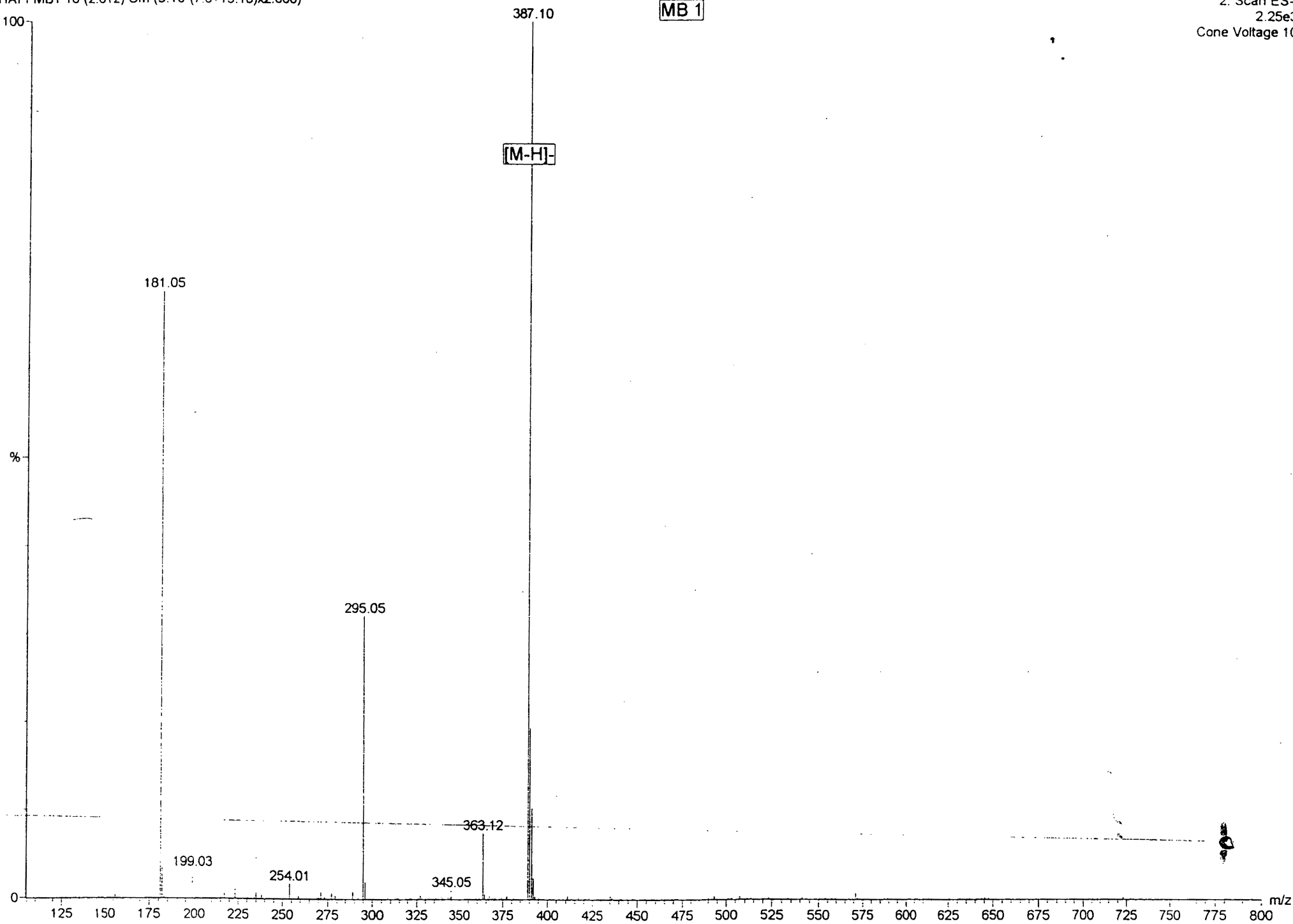
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27/12/00

Part V

Synthesis of 2-methyl-6-nitro-(3-phenyl-4-substituted 2,3-dihydrothiazole-2-ylidene amino-4-(3H)quinazolinone

Synthesis of 4-chloro-phenacyl bromide

4-chloroacetophenone (6.662g, 0.042 M) was dissolved in 21 ml of dry chloroform. This solution was transferred to a three necked round bottomed flask, fitted with efficient mechanical stirrer, a dropping funnel and a water condenser with guard tube (anhydrous CaCl_2). The reaction mixture was exposed to 200 watt light and warmed to 50°C . 1.075 ml. (3.30g, 0.042M) of bromine dissolved in 20 ml of dry chloroform was then added dropwise to the well stirred reaction mixture. It was stirred at 50°C for half an hour. A stream of air was then passed through the reaction mixture to sweep out the HBr. The reaction mixture was then diluted with petroleum ether ($40 - 60^\circ\text{C}$) and refluxed to dissolve the syrupy mass. The clear petroleum ether solution was treated with charcoal, filtered and concentrated to get crystalline 4-chloro-phenacyl bromide.

All other substituted phenacyl bromides used in the reactions have been synthesized in a similar manner and obtained from the laboratory.

MP. (lit.¹⁶⁰) 91°C

M.P. : $90-91^\circ\text{C}$.

Synthesis of 2-methyl-3-(phenyl)-thiocarbamoylamino-4(3H)quinazolinone

To a solution of 3-amino-2-methyl 6-nitro-quinazolin 4-(3H)-one (2.2 gm, 0.02M) in dry ethanol (25 ml.) was added phenyl isothiocyanate. (2gm, 2.3ml, 0.02M) in 5 ml of dry ethanol. The reaction mixture was heated under reflux for 12 hours, partially concentrated and cooled. The separated solid was filtered and recrystallised from ethanol.

M.P. : 183 – 185°C

Yield. : 72.75%

Elemental analysis – C₁₆H₁₃N₅O₃S

	Carbon	Hydrogen	Nitrogen
Calculated	54.08	3.66	19.71
Found	54.39	3.89	19.90

Synthesis of 2-methyl-6-nitro (3-phenyl-4-substituted) –2,3 dihydro thiazole-2-ylidene, amino-4-(3H)quinazolinone

To a hot solution of 2 methyl-3-(phenyl) thiocarbomoyl amino-4(3H) quinazolinone (1gm, 0.00028M) in absolute ethanol (20 ml.) was added 4-chlorophenacyl bromide (0.65g, 0.0028M) and sodium acetate (0.22g, 0.0028 M). The reaction mixture was heated under reflux for 12 hours filtered and partially concentrated and left over night. The separated product was filtered and recrystallised from ethanol.

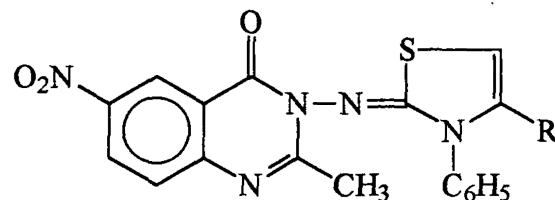
M.P. : 219.-221°C

Yield. : 44.44%

Elemental analysis – C₂₄H₁₆N₅O₃SCI

	Carbon	Hydrogen	Nitrogen
Calculated	58.83	3.26	14.30
Found	58.46	3.50	13.98

Table No. 4 : 2-methyl-6-nitro-(3-phenyl-4-substituted 2,3-dihydrothiazole-2-ylidene amino-4-(3H)-quinazolinone



Sr No	R	Molecular formula	Mol. Wt.	MP (°C)	Yield (%)	Elemental Analysis (%)					
						Calculated			Found		
						C	H	N	C	H	N
1	4-fluorophenyl	C ₂₄ H ₁₆ N ₅ O ₃ SF	473	200-02	42.98	60.88	3.38	14.79	60.97	3.46	14.59
2	2-fluorophenyl	C ₁₄ H ₁₆ N ₅ O ₃ SF	473	195-97	51.01	60.88	3.38	14.79	61.11	3.11	15.15
3	3-fluorophenyl	C ₂₄ H ₁₆ N ₅ O ₃ SF	473	192	45.35	60.88	3.38	14.79	60.83	3.13	15.17
4	3-trifluoromethyl phenyl	C ₂₅ H ₁₆ N ₅ O ₃ SF ₃	523	240-42	55.33	57.36	3.05	13.38	57.76	2.84	13.77
5	2,4dichloro-5-fluoro phenyl	C ₂₄ H ₁₄ N ₅ O ₃ SCl ₂ F	542	140-42	54.75	53.13	2.58	12.91	53.26	2.22	12.74
6	4-chlorophenyl	C ₂₄ H ₁₆ N ₅ O ₃ SCl	489.5	219-21	44.44	58.83	3.26	14.30	58.46	3.50	13.98
7	2-hydroxy-4-methoxyphenyl	C ₂₅ H ₁₉ N ₅ O ₅ S	501	225	49.26	59.88	3.79	13.97	60.25	4.00	14.26
8	2,3,4-trimethoxy phenyl	C ₂₇ H ₂₃ N ₅ O ₆ S	545	222-24	58.18	59.44	4.22	12.84	59.74	4.45	13.16
9	2,5-dihydroxy phenyl	C ₂₄ H ₁₇ N ₅ O ₅ S	487	180-81	53.82	59.13	3.49	14.37	59.27	3.30	14.68
10	3-nitrophenyl	C ₂₄ H ₁₆ N ₆ O ₅ S	500	193-95	53.88	51.60	3.2	16.80	51.75	3.45	16.51
11	4-methoxy phenyl	C ₂₅ H ₁₉ N ₅ O ₄ S	485	217-18	43.62	61.85	3.91	14.43	61.70	4.18	14.72
12	Cyclopropyl	C ₂₁ H ₁₇ N ₅ O ₃ S	419	202-03	47.25	60.14	4.05	16.70	60.31	4.14	17.02
13	3,4-dichlorophenyl	C ₂₄ H ₁₅ N ₅ O ₃ ClS	524	247-49	61.38	54.96	2.86	13.35	55.19	3.05	13.66
14	3-chlorophenyl	C ₂₄ H ₁₆ N ₅ O ₃ SCl	489.5	253-55	60.55	58.83	3.26	14.30	59.10	3.51	14.52
15	2,3-dichlorophenyl	C ₂₄ H ₁₅ N ₅ O ₃ Cl ₂ S	524	189-91	59.68	54.73	2.86	13.35	54.73	2.66	13.06
16	2,4-dichlorophenyl	C ₂₄ H ₁₅ N ₅ O ₃ Cl ₂ S	524	207-09	62.26	54.96	2.86	13.35	54.65	2.69	13.52

Spectral studies of 2-methyl-6-nitro-(3-phenyl)-4-(4-chlorophenyl)-2,3-dihydrothiazole-2-ylidene amino-4-(3H)quinazolinone. Table no 4, Comp. No. 6

IR (KBr) cm^{-1}

Wave number	Assignment
2959.1	CH_3
1694.34	C=O
1650	C=N
1356.32, 1531.69	NO_2

PMR (DMSO - d_6) δ :

2.68	(s, 3H, $-\text{CH}_3$)
6.8-9.2	(m, 11H (10H, Ar-H), (1H, thiazole))

Spectral studies of 2-methyl-6-nitro-(3-phenyl)-4-(3,4-dichlorophenyl)-2,3-dihydrothiazole-2-ylidene amino-4-(3H)-quinazolinone. Table no 4, Comp. No. 15

IR (KBr) cm^{-1}

Wave number	Assignment
2900	CH_3
1675.5	C=O
1638	C=N
1531, 1349.96	NO_2

PMR (DMSO - d_6) δ :

2.4-2.6	(s, 3H, $-\text{CH}_3$)
6.48	(s, 1H, thiazole)
6.8-8.6	(m, Ar-H)

Mass spectra m/z 419 of compound 12, table no. 4

File # 1 = MB2

Mode= 2 (Mid-IR)

11/13/98 9:49 AM

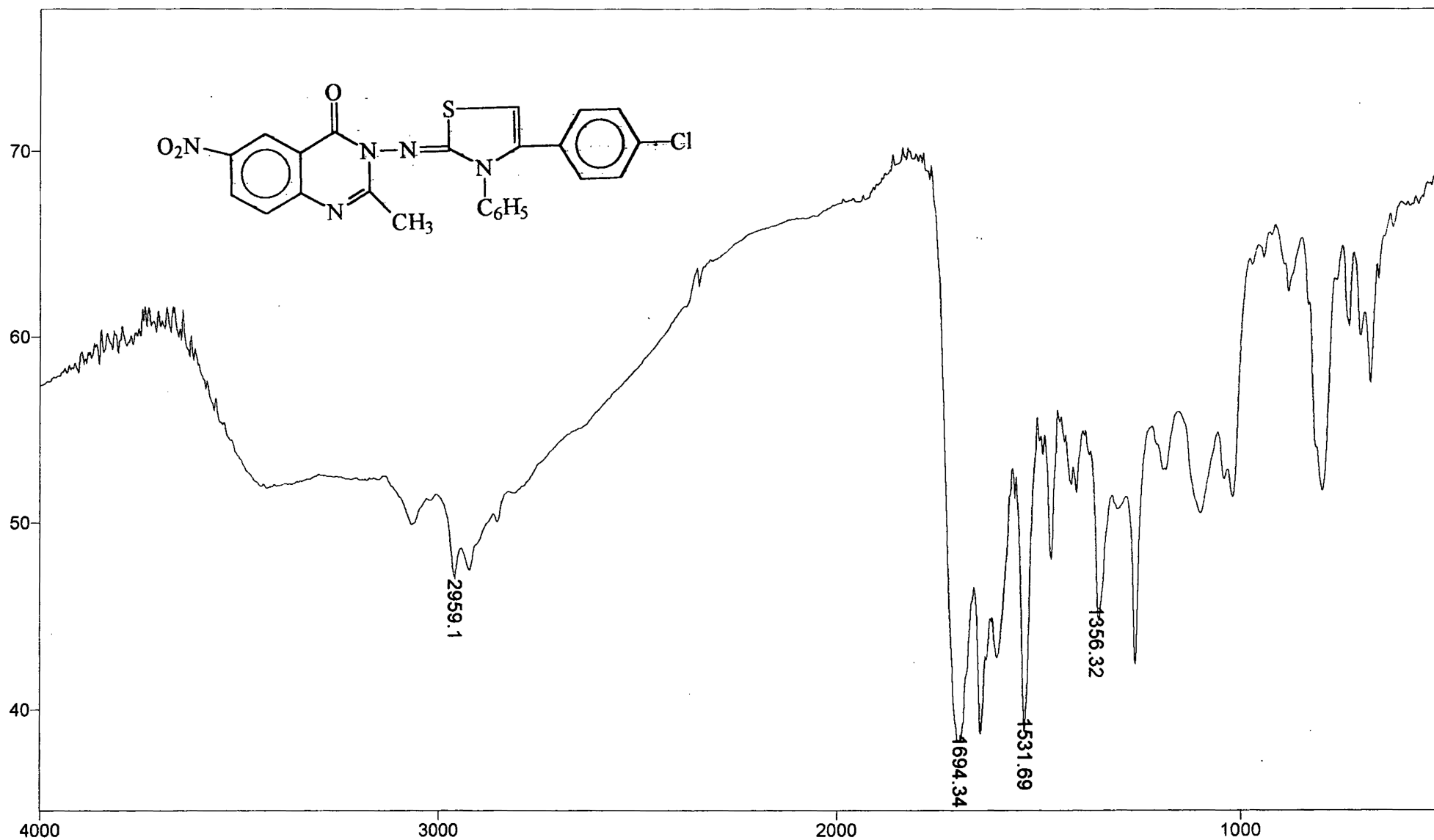
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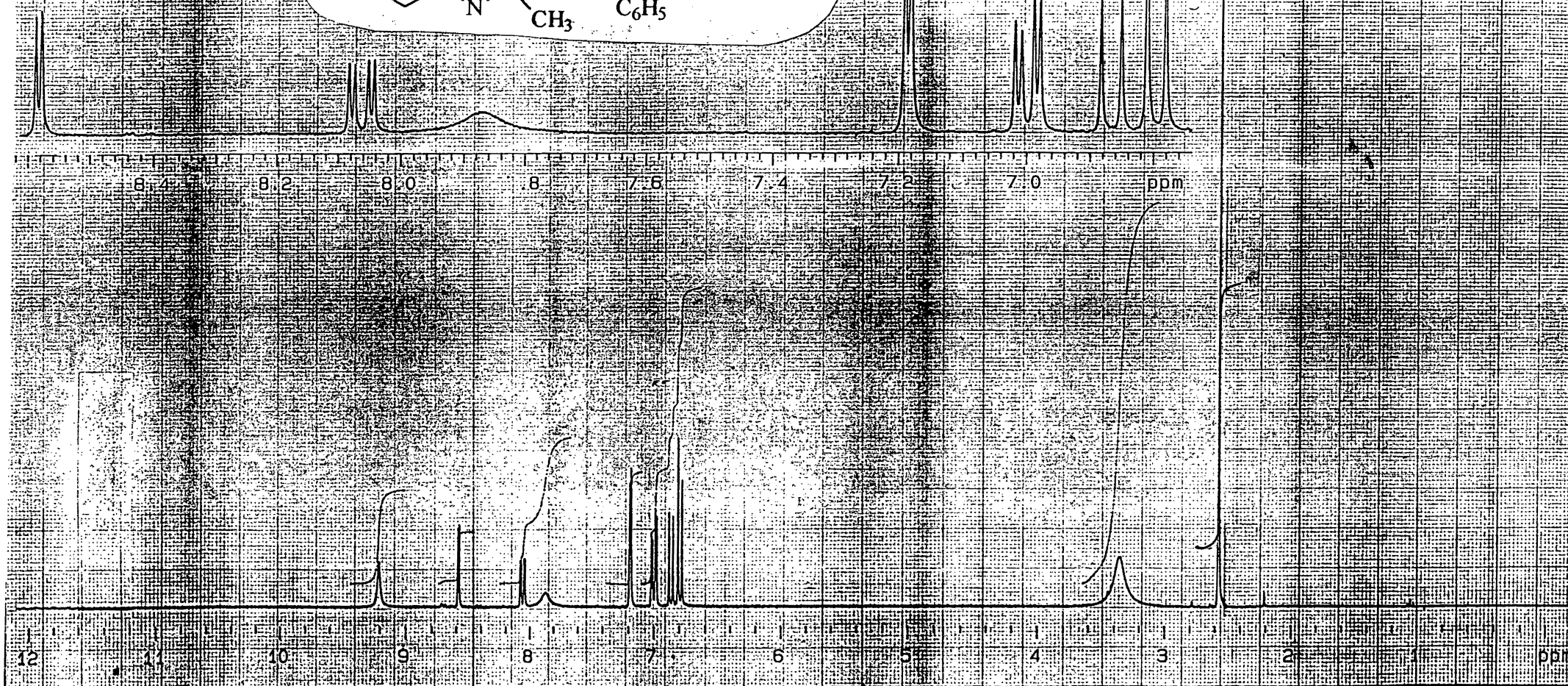
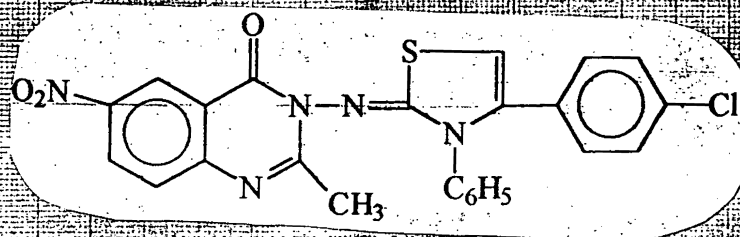
Scans= 10 Slow

Res=4 cm-1

Apod= Cosine

Zero Filling= 1 x





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	Spec Width	5998.8 Hz	Offset	1200.0 Hz		Mode	n	Power	20 dB	LR	0.100	not used		cm	Tube O.D.			mm	43	File	M3.fid
	Acq. Time	4.00 sec	Delay	0 sec		Multiscan Mode	1	C	Freq	200 Hz	Waltz	3733.1 Hz		Start	87.0 Hz		Temp	25.0°C	Date	Mar 17 99	
	Pulse Width	10.0 sec	Transmit	1.72		Pulse Width	17.5 sec	Power Mode	not used	Reference		Solvent		DMSO	YXRO		300				

File # 1 = AZOMB1

Mode= 2 (Mid-IR)

10/15/98 9:50 AM

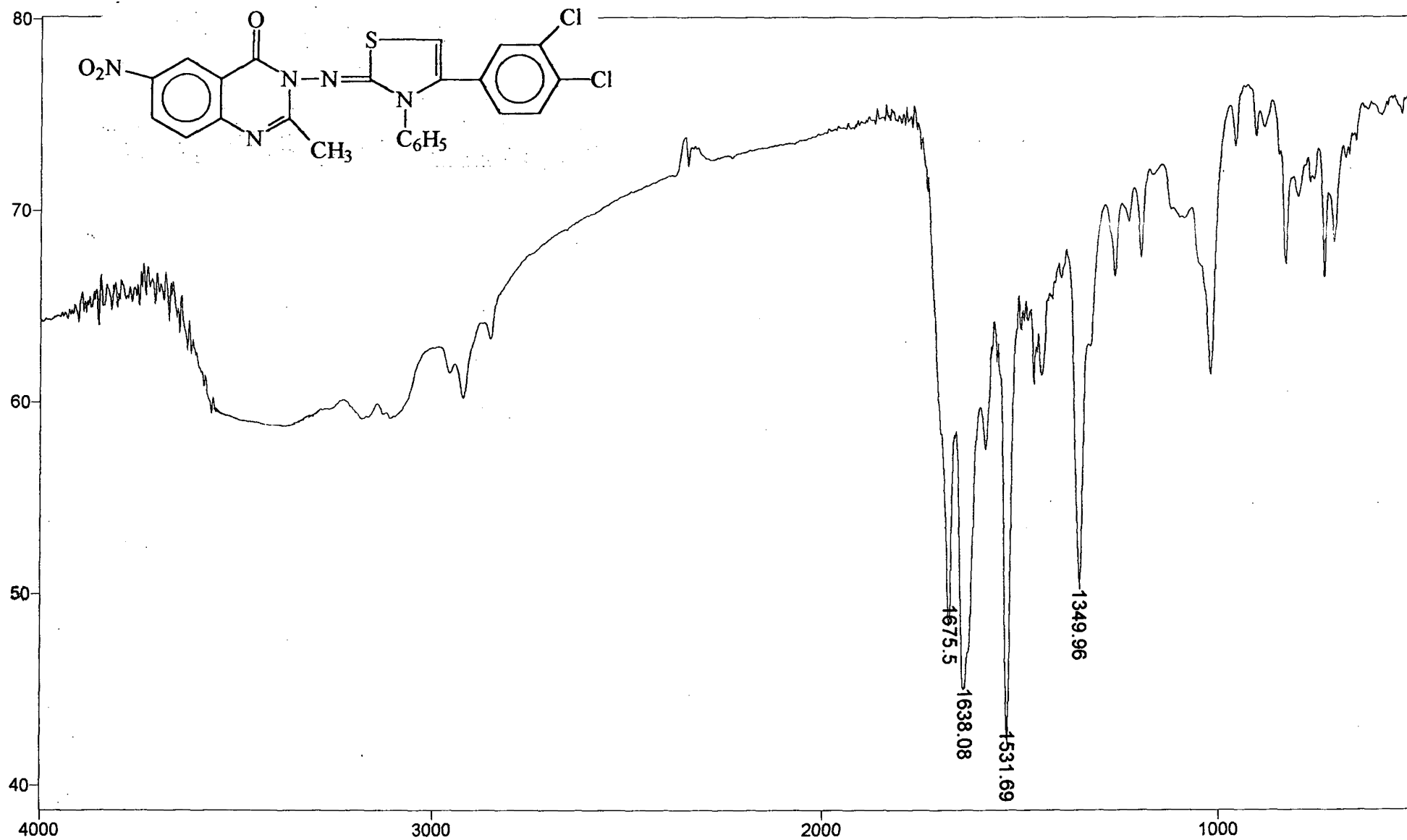
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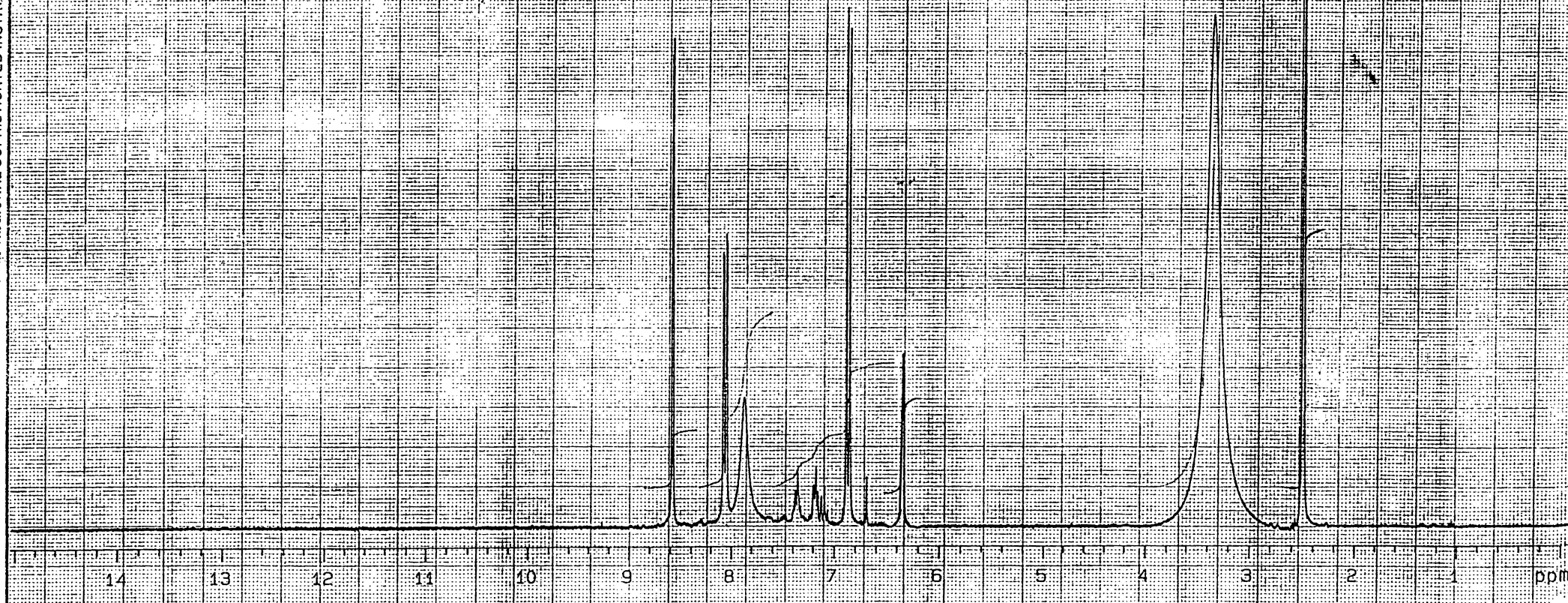
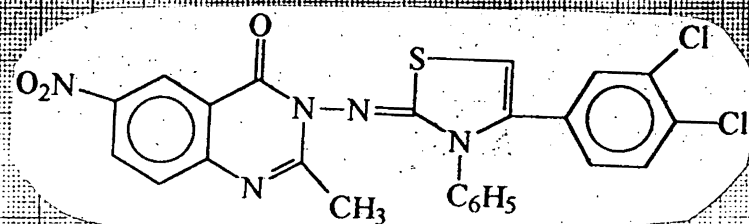
Scans= 10 Slow

Res=4 cm⁻¹

Apod= Cosine

Zero Filling= 1 x





OBSERVE
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Spec. Width 5998.8 Hz Offset 1200.0 Hz
Acq. Time 4.00 sec Delay 0 sec
Pulse Width 10.0 sec Transients 144

DECOUPLE
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Mode n Power 20 dB
Modulation Mode c Freq. 200 Hz
Pulse Width 17.5 sec Power Mode not used

PLOT/PROCESSING
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LB 0.100 Hz AT used sec CD sec
Width 4562.2 Hz/ppm Start -52.4 Hz/ppm
Reference sec

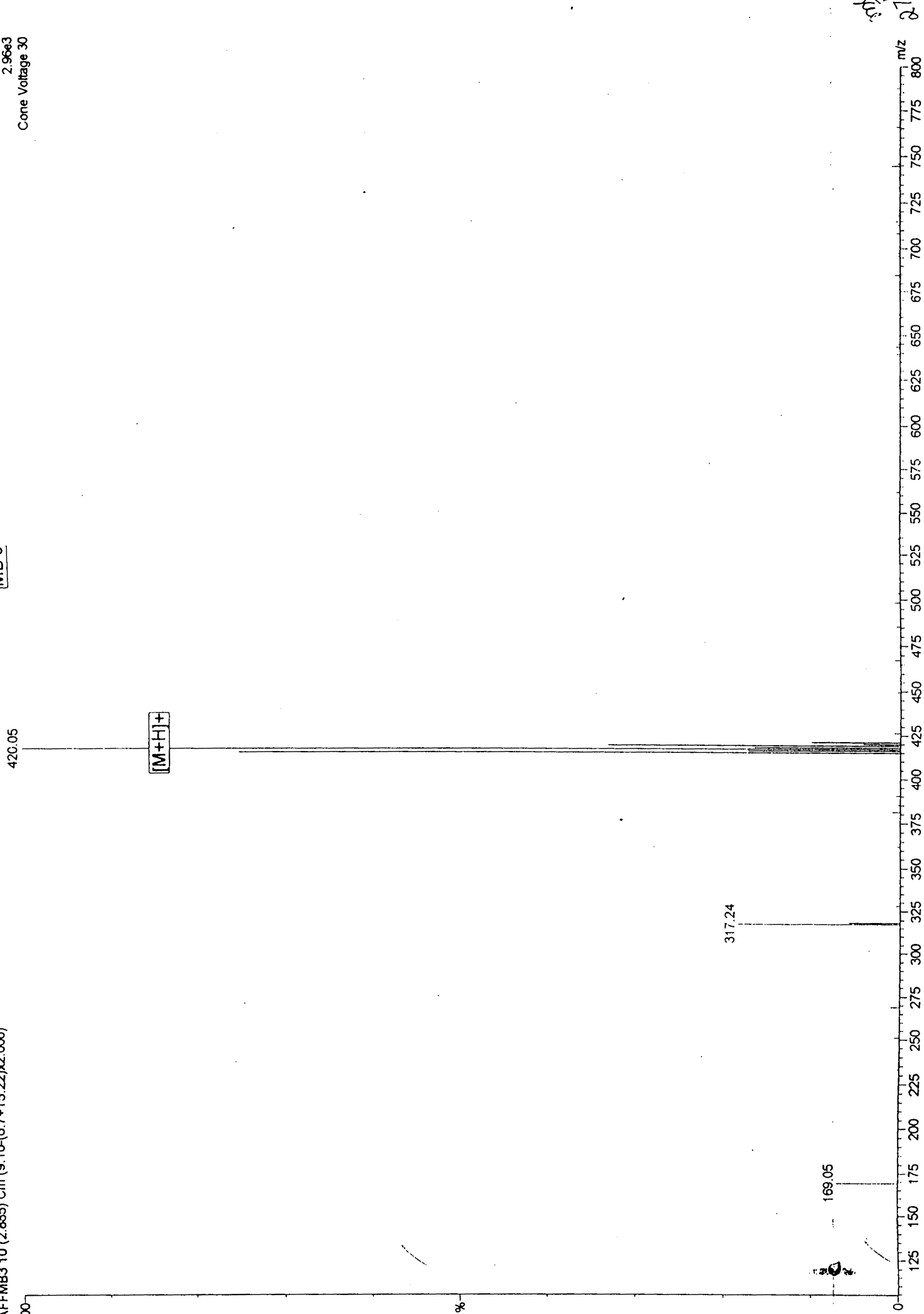
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Tube O.D. mm NB 4+6
Temp. 25.0 °C
Solvent DMSO

Number sec
File exp
Date Dec 30 99
VXR0 300

3: Scan ES+
2.96e3
Cone Voltage 30

MB 3

27-Dec-2000 13:39:01
HAFFMB3 10 (2.895) Cm (9.10-(6:7+15:22)x2.000)



27/11/00
MB 3

Part VI

***Synthesis of 3-N-
(substituted
phenyl)aminomethylene
pyrazolo [5,1-b]-7-nitro-
quinazolin-9(1H)one***

Synthesis of 3-formyl pyrazolo [5,1-b] quinazolin-9 (1H)one

In a 100 ml three necked round bottomed flask fitted with a reflux condenser and dropping funnel, 1.8 ml (0.023 M) of DMF (dry) was taken. Phosphorus oxychloride 1.39 ml (0.025 M) was taken in the dropping funnel. Anhydrous conditions maintained and the temperature was maintained between 0-5°C. POCl₃ was added to dry DMF slowly (with stirring) while maintaining temperature. After the addition of phosphorous oxychloride, reaction mixture was kept in cold condition with stirring for half an hour. 3-amino-2-methyl-6-nitro-quinazoline-4-(3H)one (2 gm, 0.009M) was dissolved in 10 ml of dry DMF. This solution was added to Vilsmeier reagent (POCl₃ + DMF) drop wise, while maintaining the temperature between 0-5°C. After the addition the reaction mixture was kept for stirring in cold condition for 2 hours. After this the reaction mixture was heated on water bath for 2 hrs, cooled and brought to room temperature. Sodium acetate (cold aqueous solution) (9 gm of sodium acetate + 15.75 ml water) was added to the reaction mixture and stirred at 0°C for 2 hrs. A crystalline product separated out, which was filtered and dried.

M.P. : 235-36°C

Yield : 50%

Elemental analysis – C₁₁H₆N₄O₄

	Carbon	Hydrogen	Nitrogen
Calculated	51.16	2.32	21.70
Found	50.79	2.17	21.99

Synthesis of 3-N- (substituted phenyl) amino methylene pyrazolo [5,1-b]- 7-nitro quinazolin-9 (1 H)one.

3-formylpyrazolo-[5,1-b]-7-nitro-quinazolin-9(1H)-one [1 gm, 0.0038M] was dissolved in 9 ml of acetic acid in a 50 ml round bottomed flask 2,4 dichloroaniline (0.62 gm, 0.0038M) was added to it and the reaction mixture was refluxed for 10 hours. It was then poured on crushed ice, the solid product separated out was filtered, dried and recrystallised from ethanol.

Other derivatives have been prepared in a similar manner and their physical data has been recorded in Table 5.

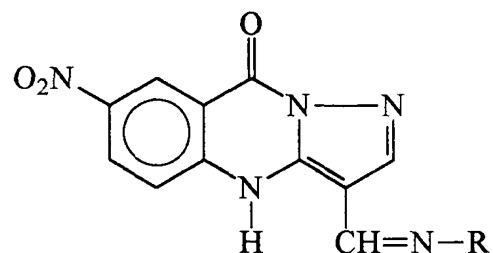
M.P. : 140-142°C

Yield : 55.26 %

Elemental analysis – C₁₇H₉N₅O₃Cl₂

	Carbon	Hydrogen	Nitrogen
Calculated	50.74	2.23	17.41
Found	51.11	1.83	17.11

Table No. 5 : 3-N-(substituted phenyl) amino methylene pyrazolo [5,1-b]-7-nitro-quinazoline-9(1H)one



Sr No	R	Molecular formula	Mol. weight	MP (°C)	Yield (%)	Elemental Analysis (%)					
						Calculated			Found		
						C	H	N	C	H	N
1	2-fluorophenyl	C ₁₇ H ₁₀ N ₅ O ₃ F	351	135-36	43.92	58.11	2.84	19.94	57.87	2.69	20.07
2	2,4-dichlorophenyl	C ₁₇ H ₉ N ₅ O ₃ Cl ₂	402	142-44	55.26	50.74	2.23	17.41	51.11	1.83	17.11
3	2,6-dimethyl phenyl	C ₁₉ H ₁₅ N ₅ O ₃	361	140-43	59.88	63.15	4.15	19.39	63.39	3.91	18.97
4	4-nitro-2-fluoro phenyl	C ₁₇ H ₉ N ₆ O ₅ F	396	140-42	41.75	51.51	2.70	21.21	51.75	2.68	21.55
5	4-chloro-5-fluoro phenyl	C ₁₇ H ₉ N ₅ O ₃ ClF	385.5	226-28	48.11	52.91	2.33	18.15	53.22	2.46	18.32
6	3,4-dichlorophenyl	C ₁₇ H ₉ N ₅ O ₃ Cl ₂	402	210-12	53.28	50.74	2.23	17.41	51.05	1.99	17.66
7	2,6-dichloro-4-nitro	C ₁₇ H ₈ N ₆ O ₅ Cl ₂	447	185-86	47.66	45.63	1.78	18.79	44.86	2.01	18.57
8	2-Chlorophenyl	C ₁₇ H ₁₀ N ₅ O ₃ Cl	351	179-81	51.51	58.11	2.84	19.94	57.93	2.65	19.03

Spectral studies of 3-N-(2-chlorophenyl)-amino methylene pyrazolo [5,1b]-7-nitro-quinazolinone-9-(1H)one. Table no 8, Comp. No. 5

IR (KBr) cm^{-1}

Wave number	Assignment
3422.6	NH
2947.6	CH_3
1681.86	C=O
1630	CH=N

PMR (DMSO - d_6) δ :

6.3	(s, 1H, -N=CH-)
7.2-8.0	(m, 8H, Ar-H)

Spectral studies of 3-N-(2,4-dichlorophenyl)-amino methylene pyrazolo [5,1b]-7-nitro-quinazolinone-9-(1H)-one. Table no 5, Comp. No. 8

IR (KBr) cm^{-1}

Wave number	Assignment
3423.4	NH-
2927.8	CH_3
1676	C=O
1641.4	C=N
1350.74	NO_2

PMR (DMSO - d_6) δ :

6.4	(s, 1H, -N=CH-)
7.2-8.0	(m, Ar-H)

Mass spectra m/z 385.5 of compound 5, table no. 5

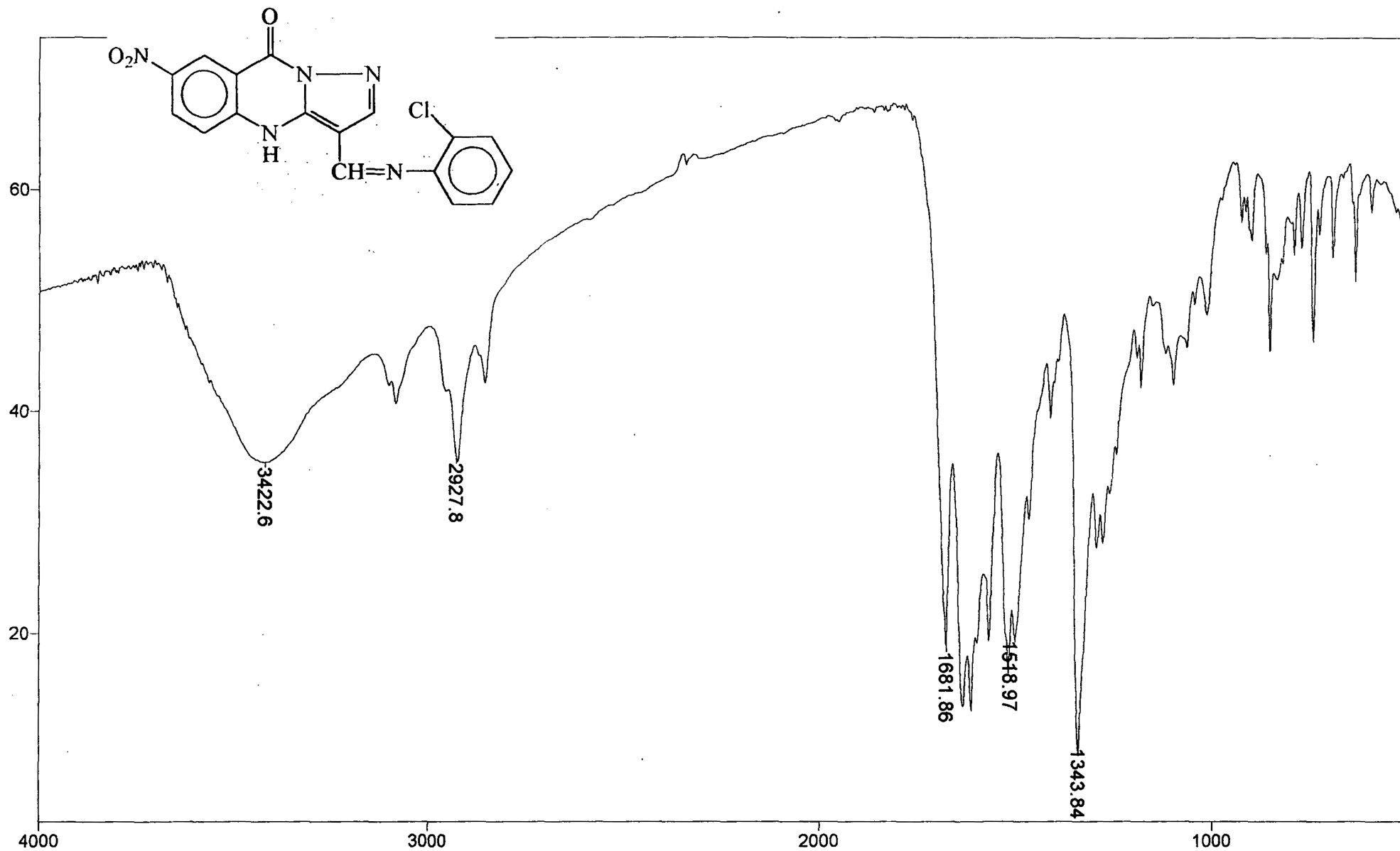
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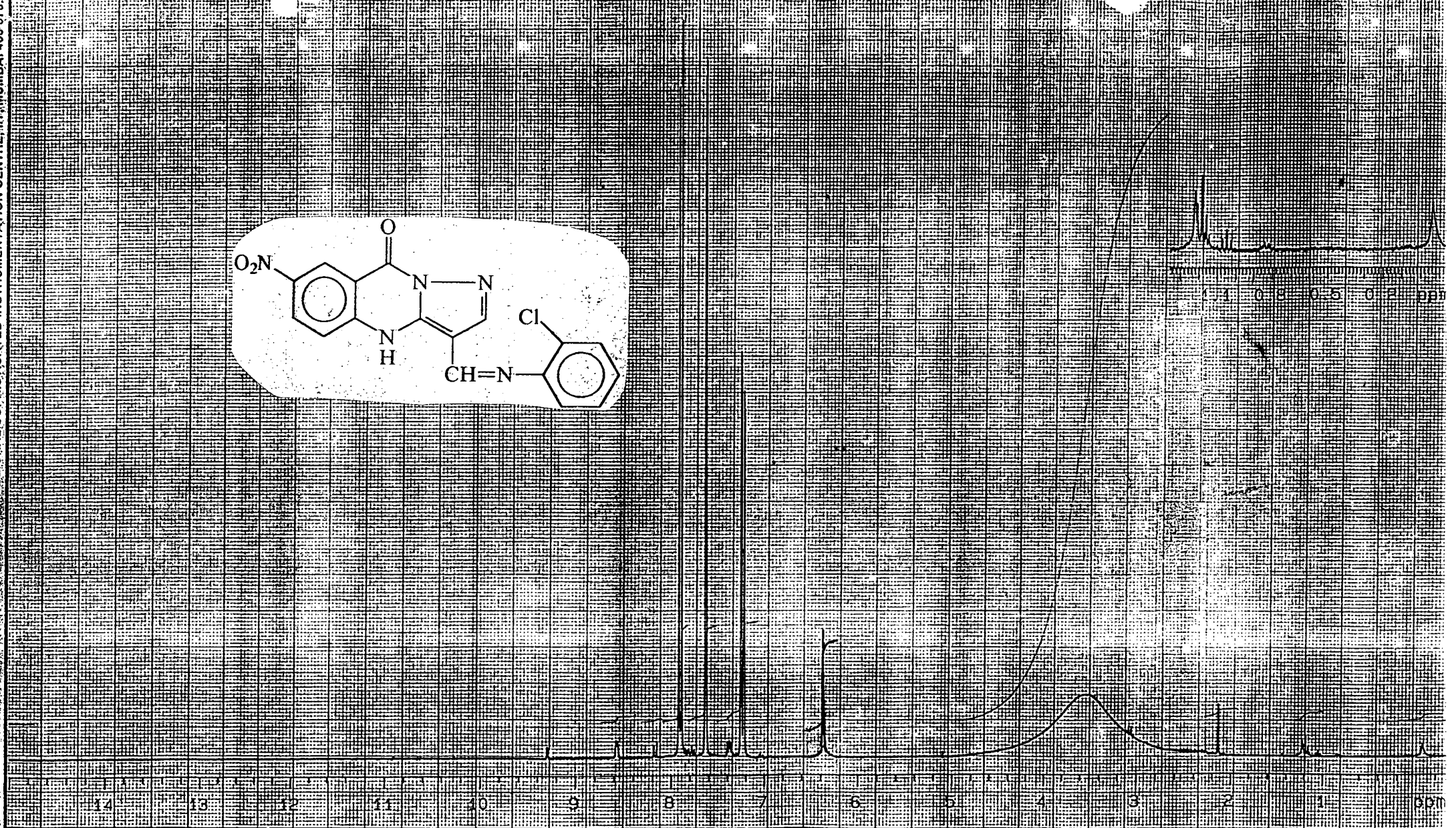
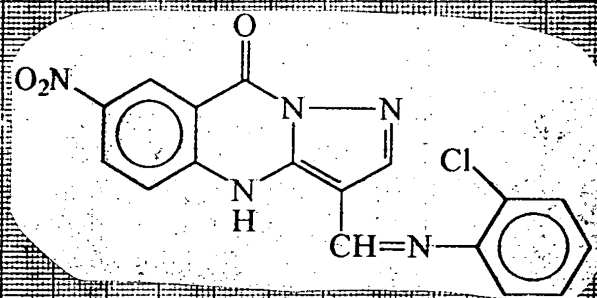
Scans= 10 Slow

Res=4 cm-1

Apod= Cosine

Zero Filling= 1 x





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	Acq. Time	<u>4.00</u> sec	Delay	<u>0</u> sec		Modulation Mode	<u>c</u>	Freq	<u>200</u> Hz		Width	<u>4519.7</u> Hz/ppm	Start	<u>-119.2</u> Hz/ppm	Temp	<u>25.0</u> °C		Date	<u>Dec 30 99</u>			
	Pulse Width	<u>10.0</u> sec	Transients	<u>344</u>		Pulse Width	<u>17.5</u> sec	Power Mode	<u>not used</u>		Reference	<u> </u>	Solvent	<u>DMSO</u>	VXRO	<u>300</u>						

File # 1 = AZO4

Mode= 2 (Mid-IR)

10/13/98 1:45 PM

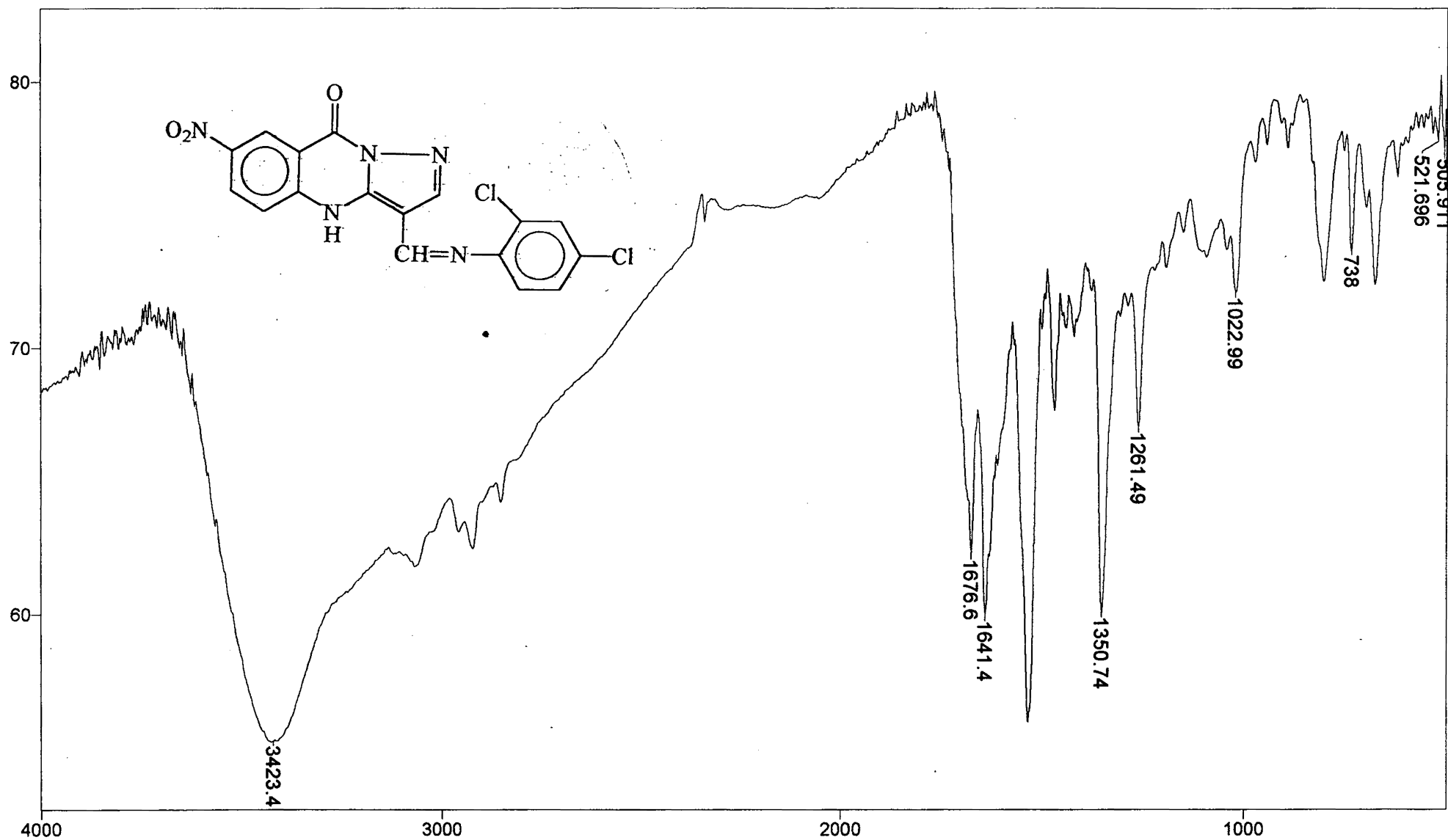
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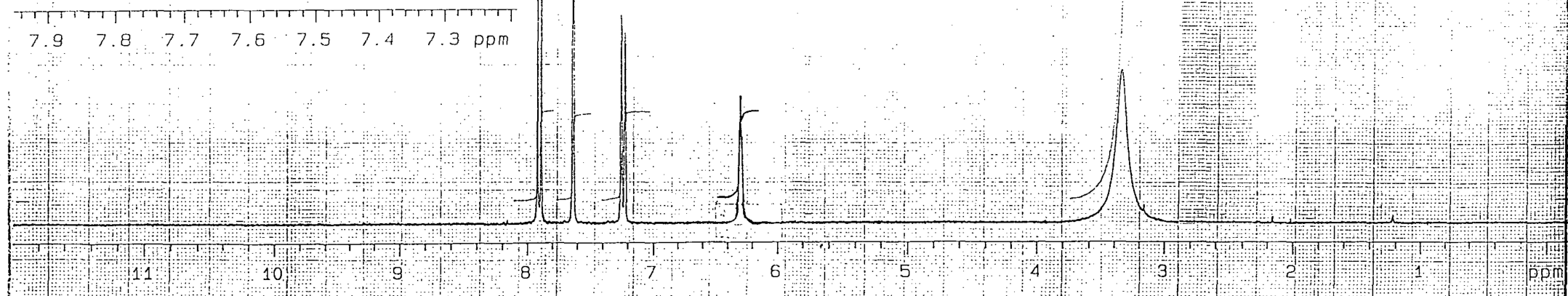
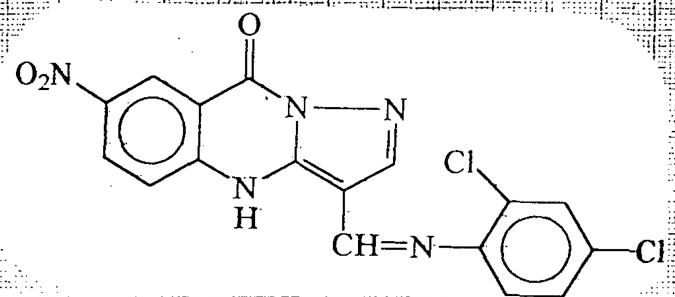
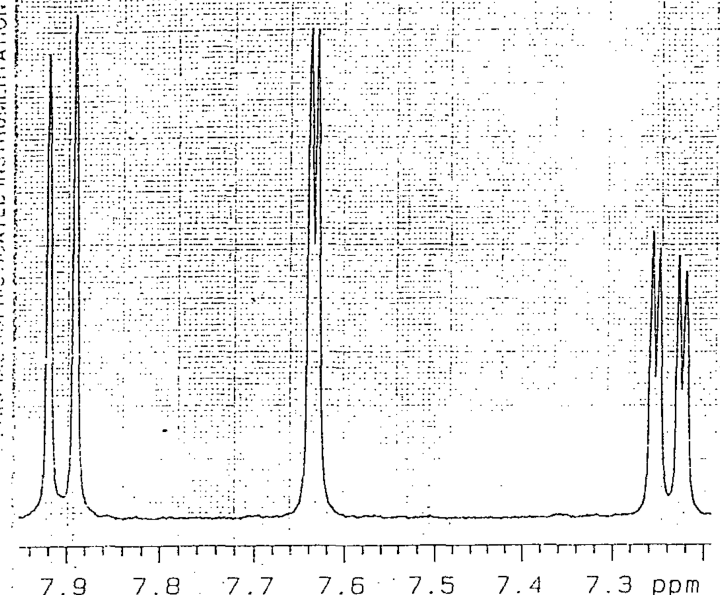
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Res=4 cm-1

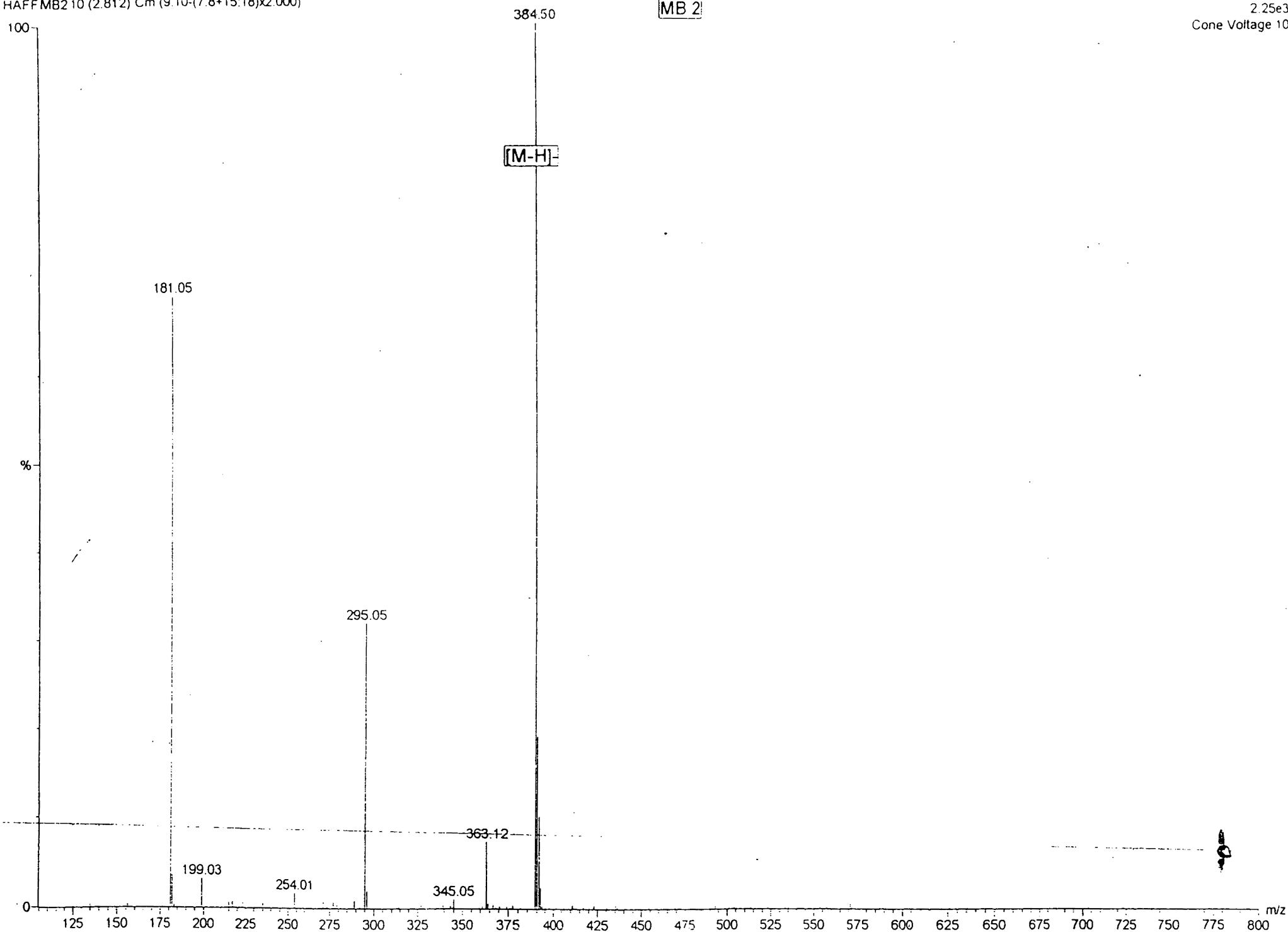
Apod= Cosine

Zero Filling= 1 x





OBSERVE Nucleus: <u>H1</u> Spec. Width: <u>6998.814</u> Acq. Time: <u>4:00:13</u> Pulse Width: <u>10.0</u>	Freq: <u>299.9486</u> MHz Offset: <u>1200.0</u> Hz Delay: <u>0</u> sec Transmits: <u>248</u>	DECOUPLE Nucleus: <u>H1</u> Mode: <u>n</u> Multiscale: <u>c</u> Pulse Width: <u>17.5</u> sec	Offset: <u>-1769.8</u> Power: <u>20.0</u> Relax: <u>200.0</u> Power Mode: <u>not used</u>	PROB/PROCESSING CP: <u>not used</u> US: <u>0.100</u> not used WDW: <u>3654.314</u> ppm Ref: <u>-57.314</u> ppm	EXPERIMENT Time Sequence: <u>s2pu1</u> Tube ID: <u>nm</u> Temp: <u>25.0</u> °C Solvent: <u>DMSO</u>	SAMPLE File: <u>M4.fid</u> Date: <u>Mar 17 99</u> VXRO: <u>300</u>	Number: <u></u>
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Part VII

Synthesis of 5/5,6- substituted -2- thio(isopropyl sulfonyl) benzimidazoles / benzoxazoles

Preparation of Isopropyl sulfonyl chloride

In a 100 ml three-necked round bottom flask equipped with air condenser, gas inlet tube and stopper, was taken 60 ml of 4N HCl. The flask was placed in an ice bath. 10 ml of 2 propanethiol was added to the flask and chlorine was bubbled through the mixture while stirring for 3 to 4 hours at 5-8°C. Isopropyl sulfonyl chloride accumulated at the bottom of the flask. The whole mixture was transferred to a separating funnel and the heavy layer of isopropyl sulfonyl chloride was separated out. It was subjected to distillation and pure isopropyl sulfonyl chloride was collected at 74-75°C/19 mm of Hg.

Yield : 52%

Lit B.P. 75°C 19 mm of Hg¹⁶⁵

B.P. 74-75°C at 19 mm of Hg

Preparation of 5-chloro-2-mercaptobenzimidazoles

In a 100 ml round-bottomed flask equipped with water condenser was placed 7.125 g (0.05 M) of 4-chloro-1,2 phenylenediamine. It was dissolved in 40 ml of ethanol. To this was added 3.1g (0.055 M) of KOH and 4.18g (3.3 ml., 0.055M) of CS₂. The reaction mixture was refluxed on a water bath for 4 to 5 hours and the excess ethanol was removed under reduced pressure. The residue obtained was dumped in cold water and acidified with dil HCl. The solid separated out was filtered and dried.

Yield : 67.2%

M.P. : 290°C

Reported M.P. = 290-292°C¹⁶⁶

Synthesis of 5/5, 6-disubstituted-2-thio-(isopropyl sulfonyl)benzimidazoles / benzoxazole

5-chloro-2-mercapto-benzimidazole (1 gm, 0.034 M) was dissolved in 10 ml of ethyl alcohol, potassium hydroxide (1.904 gm, 0.034 M) was added to it. Refluxed for 4 hrs., potassium salt of 5-chloro-2-mercapto-benzimidazole starts separating out, it is filtered and dried. The potassium salt of 5-chloro-2-mercapto benzimidazole (1 gm, 0.004 M) was dissolved in 7ml of dry 1,4-dioxane. Isopropyl sulfonyl chloride (0.004 mole, 0.57 gm, 0.447 ml) is added to this dropwise, while stirring the reaction mixture. The reaction mixture was refluxed for 8 hours, cooled and filtered. It was then dumped in ice-cold water. The solid product separated out was filtered and dried. It was recrystallised from methanol.

M.P. : 200-202°C

Yield : 55.12%

Elemental analysis – C₁₀H₁₁N₂O₂S₂Cl

	Carbon	Hydrogen	Nitrogen
Calculated	41.30	3.78	9.63
Found	41.63	4.03	9.79

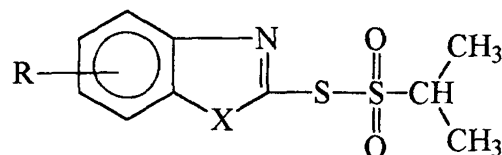
Synthesis of 4-chloro-5-nitro-2-mercapto benzoxazoles

4-chloro-5-nitro-2-aminophenol (0.5gm, 0.002M) was dissolved in alcohol (8 ml). Potassium hydroxide (0.112 gm, 0.002 M) was dissolved in water (1 ml). This aqueous solution of potassium hydroxide was added to the alcoholic solution of 4-chloro-5-nitro-2-amino phenol. Carbon disulfide (2 ml) was added to it and reaction mixture was refluxed on water bath for eight hours. Reaction was monitored on TLC, when the reaction was complete reaction mixture was filtered, It was concentrated to evaporate alcohol and residue was dumped into ice cold water. This was neutralized by dilute hydrochloric acid. Solid product separates out at acidic pH. This was filtered and washed with water.

M.P. : 220-222°C

Yield : 72.44%

Table No. 6 : 5/5,6-disubstituted-2-thio-(isopropyl sulfonyl)benzimidazoles / benzoxazole



Sr No	R	X	Molecular formula	Mol. weight	MP (°C)	Yield (%)	Elemental Analysis (%)					
							Calculated			Found		
							C	H	N	C	H	N
1	5,6 dichloro	NH	C ₁₀ H ₁₀ N ₂ O ₂ S ₂ Cl ₂	325	220-21	60.88	36.92	3.076	8.61	37.23	3.09	8.84
2	5-nitro	NH	C ₁₀ H ₁₁ N ₃ O ₄ S ₂	301	279-80	47.53	39.85	3.65	13.95	40.17	3.60	14.20
3	5-propoxy	NH	C ₁₁ H ₁₄ N ₂ O ₃ S ₂	286	215-17	41.81	46.15	4.89	9.79	46.39	5.10	10.19
4	5-fluoro	NH	C ₁₀ H ₁₁ N ₂ O ₂ F	210	268-69	35.11	57.14	5.23	13.33	57.43	5.5	13.72
5	5-chloro,6-nitro	O	C ₁₀ H ₉ N ₂ O ₅ S ₂ Cl	336.5	210-12	49.50	35.66	2.67	8.32	35.38	2.88	7.97
6	5-chloro	NH	C ₁₀ H ₁₁ N ₂ O ₂ S ₂ Cl	290.5	200-02	58.58	41.30	3.78	9.63	41.63	4.03	9.79

Spectral studies of 5-chloro-2-thio-(isopropyl sulfonyl)benzimidazole. Table no 6

Comp. No. 6

IR (KBr) cm^{-1}

Wave number	Assignment
3436.28	NH
2853.43, 2924.55, 2961.5	$\text{H}_3\text{C}-\text{CH}-\text{CH}_3$
1336.27	SO_2

PMR (DMSO - d_6) δ :

1	(d, 3H, CH_3)
2-2.2	(d, 3H, CH_3)
4-4.4	(m, 1H, CH)
5.4-5.6	(s, 1H, NH)
6.4-8.6	(m, Ar-H)

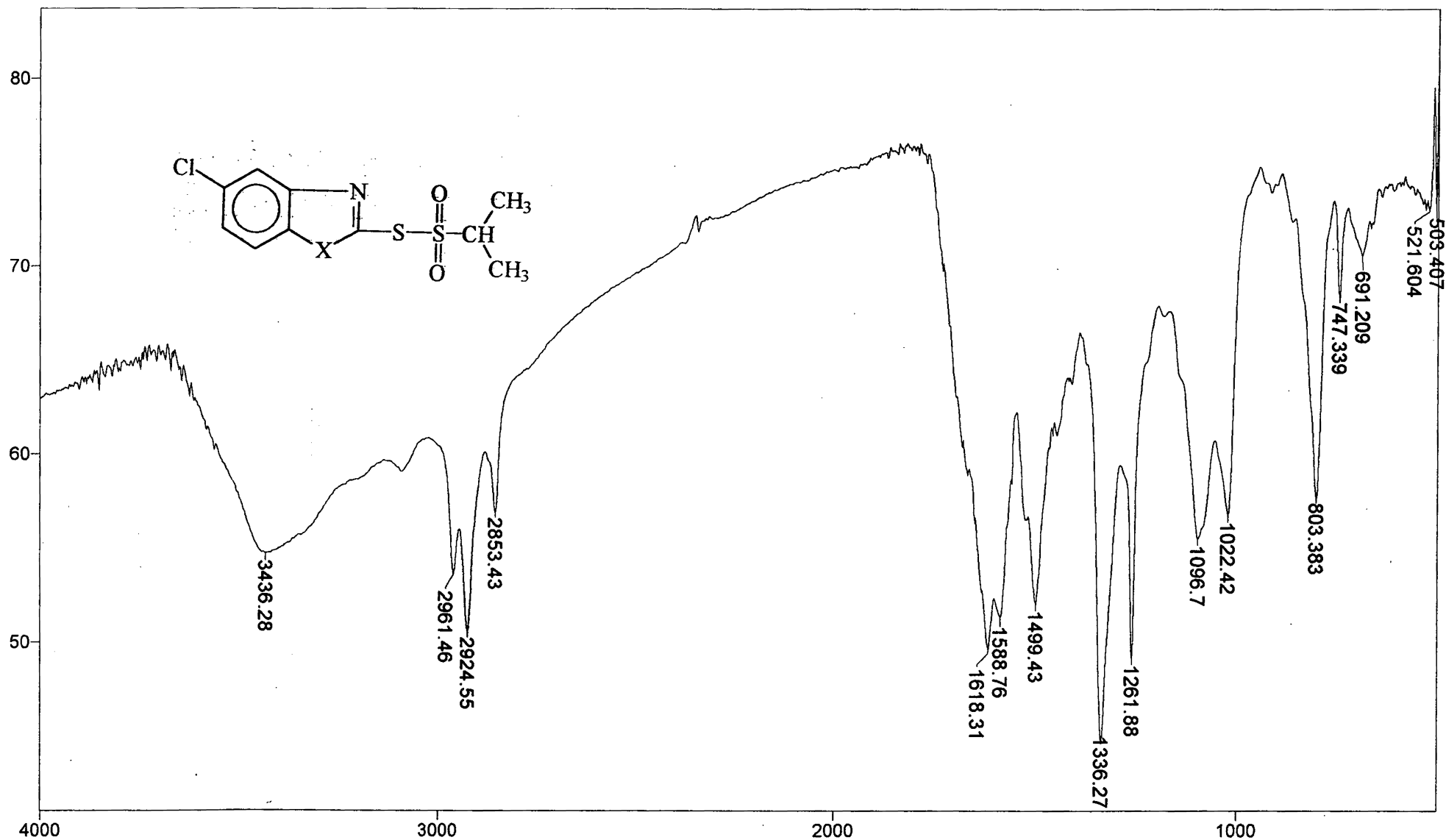
Sample Description:

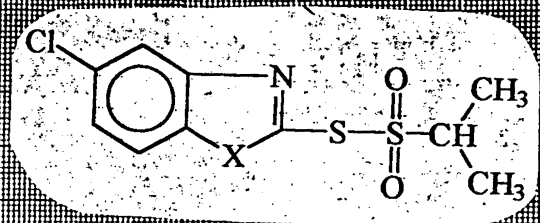
Scans= 10 Slow

Res=4 cm⁻¹

Apod= Cosine

Zero Filling= 1 x





OBSERVE				DECOUPLE				PLOT/PROCESSING				EXPERIMENT				SAMPLE															
Nucleus	H1	Freq.	299.9486	MHz	Nucleus	H1	Offset	1328.6	Hz	FN	not used	K	RE	sec	CD	sec	Pulse Sequence	32pu1	Tube O.D.	mm	Temp.	25.0	°C	Solvent	DMSO	File	exp	Date	Jul 6 98	VCR	300
Spec. Width	5998.8	Hz	Offset	1200.0	Hz	Mode	n	Power	20	dB	LB	0.100	Hz	RF	not used	CCD															
Acq. Time	4.001	sec	Delay	0	sec	Modulation Mode	c	Freq.	200	Hz	Width	4583.1	Hz/ppm	Start	78.2	Hz/ppm															
Pulse Width	10.0	μsec	Transients	168		Pulse Width		Power Mode	not used		Reference																				

Part VIII

***Biological Screening,
Results and Conclusion***

BIOLOGICAL SCREENING

The compounds synthesized in the present work have been subjected to various biological screening programs.

The various screening programs carried out include the *in vitro* study against H₃₇RV strain of *Mycobacterium tuberculosis*, *in vitro* study against Gram-positive and Gram-negative bacteria viz. *Staphylococcus aureus* ATCC 3750 and *Salmonella typhi* NCTC 786 and also *in vitro* study against various fungal strains, viz. *Candida albicans*, *Trichophyton mentagrophytes* and *Trichophyton rubrum*. The methodology adopted for the various biological screening programs undertaken in this study has been described in the following section.

The test compounds (10 mg) were dissolved in suitable solvent (10 ml) such as dimethylformamide, ethanol, dil HCl as the case may be, so as to prepare drug stock solution 1000 µg/ml. From this stock solution following final drug concentrations were made 200, 100, 40, 20 µg/ml. For lower final drug concentrations, the drug stock solution was diluted to prepare various stock solutions such as 50 µg/ml, 2.5 µg/ml etc.

Controls

- 1) Media control : Sterilized medium was kept as control so as to assure sterility of medium. If this control shows growth, medium is not properly sterilized and in that case results are not valid.
- 2) Organism control : It contains sterilized medium and organism. Organism should grow in the medium. If no growth is observed, it can be concluded that medium is unable to support the growth.
- 3) Solvent Control : This includes sterilized medium, solvent (used to dissolve the drug) and culture. Organism should be able to grow in the quantity of solvent used in testing. If no growth is observed, it can be concluded that solvent inhibits the growth of organism and in that case results of the test are not valid.

ANTITUBERCULAR SCREENING :

The test compounds have been subjected to *in vitro* screening by tube dilution technique employing the human virulent H₃₇RV strain of *M. tuberculosis*. In this method, Kirchner's medium containing tween -80 as described by Rake *et al*¹⁷⁵ was used.

Kirchner's medium (sterilized) was dispensed in each borosilicate tube and to this 0.5 ml of sterile horse serum was added. The drug solution was added in each tube so as to attain final drug concentrations as 200, 100, 40, 20, 10, 5, 2, 1, 0.5, 0.25 µg/ml. Finally, the inoculum of standard suspension i.e. 0.1 ml of *M. tuberculosis* (H₃₇R_V strain) 10⁶ bacilli per ml was added. The tubes were incubated at 37°C for ten days and then examined for the presence or absence of growth of the test organism. The lowest concentration which showed no visible growth was taken as the end point. i.e. Minimum Inhibitory Concentration. Isoniazid was used as a standard drug and was also subjected to same screening pattern. Minimum Inhibitory concentration of isoniazid is 0.04 µg/ml

ANTIBACTERIAL SCREENING :

The test compounds have been subjected to *in vitro* screening by the tube dilution technique against Gram-positive and Gram-negative bacteria viz. *S. aureus* and *S. typhi* using Mueller Hinton broth as the culture medium.

Mueller Hinton broth (sterilized) was dispensed in each borosilicate test tube (150 x 20 mm). The drug solution was added in order to attain final drug concentrations as 200, 100, 40, 20, 10, 5, 2, 1, 0.5, 0.25 etc. µg/ml

At the end, inoculum of standard suspension, 0.1ml of the desired bacterial strain (*S. aureus* or *S. typhi*) containing 10⁶ bacilli / ml was added. The tubes were incubated at 37°C for 48 hours and then examined for the presence or absence of growth of the test organisms.

The lowest concentration which showed no visible growth was taken as an end point (MIC).

Ampicillin and Trimethoprim were used as standard drugs against Gram-positive and Gram-negative bacteria respectively and were subjected to similar screening programs.

MIC of ampicillin is 0.01 μg / ml against *S. aureus* and that of trimethoprim is 1 μg /ml against *S. typhi*.

ANTIFUNGAL SCREENING :

The organisms employed in the test were

1) *Candida albicans* 2) *Trichophyton mentagrophytes* and 3) *Trichophyton rubrum*.

These organisms were maintained on Sabouraud's agar slants by regular subculturing *C. albicans* was cultured every week and the rest of the organism at the interval of 12 days.

Serafataller medium was employed for the testing and pH of medium was adjusted to 5.2. The medium (sterilized) was dispensed in each borosilicate tube. The drug solution was added in order to attain final drug concentrations as 200, 100, 40, 20, 10, 5, 2, 1, 0.5 μg /ml.

The tubes were incubated at room temperature (28-30°C) in a dark place.

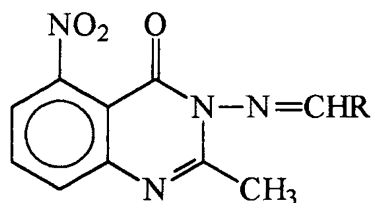
Incubation period for *C. albicans* is 7 days whereas that of *T. mentagrophytes* and *T. rubrum* is 14 days.

The presence or absence of growth was noted visually. The lowest concentration, which showed no visible growth was taken as end point (MIC).

Miconazole was used as a standard drug and was subjected to same screening pattern.

MIC of miconazole is 6.25 μg /ml for *C. albicans* and 1.56 μg /ml for *T. mentagrophytes* and *T. rubrum*.

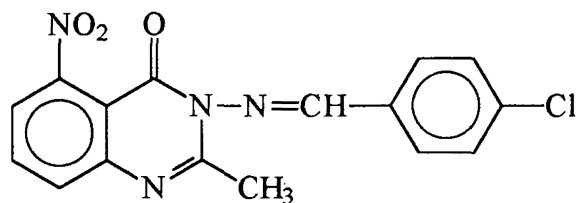
Table No. 7 : Antimicrobial activity of 2-methyl (-5-nitro-3-[substituted phenyl / heterocycle] methylene amino quinazoline-4-(3H)ones



Sr. No.	R	Activity in µg/ml					
		H ₃₇ Rv strain of <i>M. tuberculosis</i>	<i>S. aureus</i>	<i>S. typhi</i>	<i>C. albicans</i>	<i>T. mentagrophyte</i>	<i>T. rubrum</i>
1	3, chlorophenyl	100	100	100	-	200	100
2	2,4 dichlorophenyl	100	100	100	-	200	100
3	2,6 dichlorophenyl	100	10	40	200	200	200
4	2 fluorophenyl	40	25	40	200	-	-
5	4 fluorophenyl	40	40	40	-	200	200
6	3,4 dichlorophenyl	100	100	100	-	200	-
7	4 chlorophenyl	100	100	100	-	-	100
8	3 fluorophenyl	40	100	100	-	200	100
9	2-methoxyphenyl	200	100	100	-	100	40

'-' = Inactive at 200 µg/ml

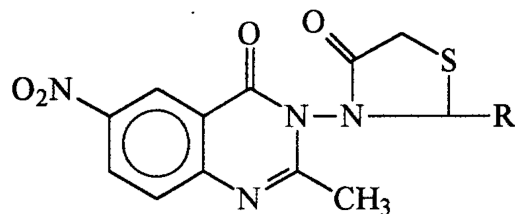
Table 8 : Antimicrobial activity of 3-(substituted acetamide)-2-methyl-6-nitro quinazoline-4-(3H)-one



Sr. No.	R	Activity in µg/ml					
		H ₃₇ Rv strain of <i>M. tuberculosis</i>	<i>S. aureus</i>	<i>S. typhi</i>	<i>C. albicans</i>	<i>T. mentagrophyte</i>	<i>T. rubrum</i>
1	2-chlorophenyl	40	100	100	40	40	40
2	2,6 dimethylmorpholino	25	100	100	-	-	-
3	3-aminoquinoliny	40	100	100	-	40	-
4	2-aminopyridyl	40	100	100	-	-	-
5	2,6dimethylphenyl	100	100	100	200	40	-
6	2,5 dimethoxyphenyl	100	100	100	-	40	-
7	2-amino-4,6dimethyl pyrimidynyl	100	100	100	200	-	200
8	piperaziny	100	100	100	40	200	200
9	N-methylpiperaziny	40	100	100	-	-	-
10	2-aminopyrimidinyl	100	100	100	25	-	-

'-' = Inactive at 200 µg/ml

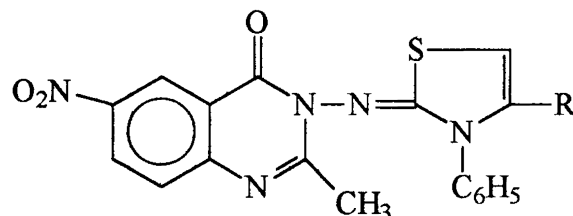
Table 9 : Antimicrobial activity of 3-[2-methyl-6-nitro-4(3H)-one-3-quinazolinyl]-2-(substituted phenyl / heterocycle)-4-thiazolidinones



Sr. No.	R	Activity in µg/ml					
		H ₃₇ Rv strain of <i>M. tuberculosis</i>	<i>S. aureus</i>	<i>S. typhi</i>	<i>C. albicans</i>	<i>T. mentagrophyte</i>	<i>T. rubrum</i>
1	2-methylphenyl	100	100	100	200	200	-
2	2-pyridyl	40	40	100	100	200	-
3	N-methyl pyrole	40	100	100	200	100	100
4	2-Thienyl	100	100	100	100	100	100
5	5-bromo thienyl	100	40	100	200	100	100
6	2-trifluoro methylphenyl	100	100	100	100	200	-
7	4-trifluoromethyl	40	40	100	100	200	200
8		40	40	100	200	200	200

'-' = Inactive at 200 µg/ml

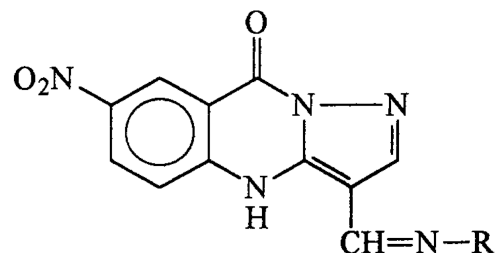
Table No. 10 : Antimicrobial activity of 2-methyl-6-nitro-(3-phenyl-4-substituted 2,3-dihydrothiazole-2-ylidene amino-4-(3H)-quinazolinone



Sr. No.	R	Activity in µg/ml					
		H ₃₇ Rv strain of <i>M. tuberculosis</i>	<i>S. aureus</i>	<i>S. typhi</i>	<i>C. albicans</i>	<i>T. mentagrophyte</i>	<i>T. rubrum</i>
1	4-fluorophenyl	100	100	100	-	100	40
2	2-fluorophenyl	40	100	100	-	200	100
3	3-fluorophenyl	40	100	100	-	200	200
4	3-trifluoromethylphenyl	40	100	100	-	100	-
5	2,4-dichloro-5-fluorophenyl	100	100	100	-	100	100
6	4-chlorophenyl	100	100	100	-	200	100
7	2-hydroxy 4-methoxyphenyl	100	100	100	-	100	100
8	2,3,4-trimethoxyphenyl	100	100	200	200	100	100
9	2,5-dihydroxy	100	100	200	-	100	-
10	3-nitrophenyl	100	200	200	200	200	-
11	4-methoxyphenyl	40	200	100	200	-	100

'-' = Inactive at 200 µg/ml

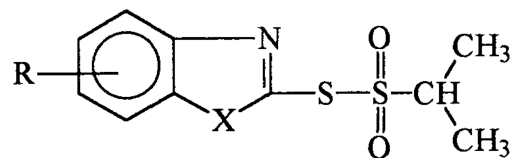
Table No. 12 : Antimicrobial activity of 3-N-(substituted phenyl) amino methylene pyrazolo [5,1-b]-7-nitro-quinazoline-9(1H)-one



Sr. No.	R	Activity in µg/ml					
		H ₃₇ Rv strain of <i>M. tuberculosis</i>	<i>S. aureus</i>	<i>S. typhi</i>	<i>C. albicans</i>	<i>T. mentagrophyte</i>	<i>T. rubrum</i>
1	4-fluorophenyl	40	40	40	200	100	200
2	2,4-dichlorophenyl	200	100	25	-	200	-
3	2,6-dimethyl	-	100	100	200	100	100
4	2-nitro-4-fluorophenyl	25	40	40	40	200	100
5	3-chloro-4-fluorophenyl	25	40	25	200	-	-
6	3,4-dichlorophenyl	100	100	100	100	200	100
7	2,6-dichloro-4-nitro	40	100	100	200	-	-
8	2-fluoro-phenyl	40	40	100	100	100	100

'-' = Inactive at 200 µg/ml

Table No. 13 : Antimicrobial activity of 5/5,6-disubstituted-2-thio-(isopropyl sulfonyl)benzimidazoles / benzoxazole



Sr. No.	R	X	Activity in µg/ml					
			H ₃₇ Rv strain of <i>M. tuberculosis</i>	<i>S. aureus</i>	<i>S. typhi</i>	<i>C. albicans</i>	<i>T. mentagrophyte</i>	<i>T. rubrum</i>
1	5,5-dichloro	NH	100	100	100	-	-	-
2	5-nitro	NH	100	100	100	-	-	-
3	3-propoxy	NH	100	100	100	-	-	-
4	5-fluoro	NH	100	100	100	-	-	-
5	5-chloro-6-nitro	O	100	100	100	-	-	-
6	5-chloro	NH	100	100	100	-	-	-

- = Inactive at 200 µg/ml

2-methyl-5-nitro-3-[(substituted phenyl) methylene amino] quinazoline-4-(3H)one

In this series (Table no. 7), 10 compounds have been synthesized. The screening results exhibited the minimum inhibitory concentration (MIC) against Gram positive bacteria in the range of 10-100 µg/ml. Most of the compounds have shown activity upto 100µg/ml. Only one compound has shown activity at 10µg/ml. Compound no. 4 and 5 have shown activity upto 25µg/ml respectively. Compound no. 3, 4 and 5 have shown activity against *S. typhi* at the concentration of 41µg/ml.

For antifungal screening data, it has been observed that most of the compounds are active in the range of 100-200 µg/ml. Only one compound, where the substitution is 2-methoxy phenyl has shown activity at the concentration of 40µg/ml against *T. rubrum*.

Out of the 10 compounds, three compounds have shown activity at the concentration of 40µg/ml against H₃₇Rv strain of *Mycobacterium tuberculosis*. Rest of the compounds showed activity at the concentration of 100µg/ml.

3-(substituted acetamido)-2-methyl-6-nitro quinazoline-4-(3H)one

In this series (Table no. 8), a total of 10 compounds were screened against the bacterial species of *S. typhi* and *S. aureus*. The results were not very encouraging as all the 10 compounds synthesized are active only at the concentration of 100µg/ml against *S. aureus* and *S. typhi*.

All these compounds were subjected for antifungal screening and only one compound no. 10 has shown activity at the concentration of 25µg/ml against *C. albicans*. Most of the compounds are inactive. Two compounds no. 1 and 8 have shown activity at 40µg/ml against *C. albicans*.

Compound nos. 1,3,5 and 6 have shown activity at concentration of 40µg/ml against *T. mentagrophyte* and compound no. 1 has shown activity at the concentration of 40µg/ml against *T. rubrum* also.

Out of 10 compounds, only one has shown activity at 25µg/ml against H₃₇Rv strain of *Mycobacterium tuberculosis*. Four compounds 1,3,4 and 9 have shown activity at the concentration of 40µg/ml. Rest of the compounds have shown activity at the concentration of 100µg/ml only.

2-methyl-6-nitro(-3-phenyl-4-substituted)-2,3dihydrothiazole-2-ylidene amino-4-(3H)quinazolinone

Total fifteen compounds have been synthesized in this series and screened for their *in vitro* antitubercular and antibacterial activity (Table no. 10) and the screening results exhibited the MIC against *S. aureus* in the range of 100-200 µg/ml where only one compound no. 12 showed activity at the concentration of 40µg/ml for *S. typhi*. The other results are in similar pattern.

For the antifungal screening, results are very discouraging, where all the compounds have shown activity in the range of 100-200 µg/ml and most of them are inactive against *C. albicans*.

The results obtained for antitubercular screening have somewhat been how better than antifungal and antimicrobial screening, where five compounds 2,3,4,11 and 12 showed activity at the concentration of 40µg/ml. Rest of the compounds showed activity at the concentration of 100µg/ml.

3-[2-methyl-6- nitro-4(3H)-oxo-3-quinazolinyl]-2-(substituted phenyl / heterocycle)-4-thiazolidinones

A total of 8 compounds have been synthesized in this series (Table No. 9). All the compounds showed moderate activity in the range of 100-200 µg/ml.

Four compounds 2,3,4 and 5 showed activity at 40µg/ml against *S. aureus*. All the synthesized compounds showed moderate activity against *S. typhi*.

The results of antitubercular screening are also not very encouraging. Only four compounds showed activity at the concentration of 40µg/ml.

3-N-(substituted phenyl) amino methylene pyrazolo [5,1-b]-7-nitro-quinazoline-9(1H)one.

Results of biological screening (Table no. 12) revealed that all the compounds showed moderate activity against *C. albicans*, *T. mentagrophytes* and *T. rubrum*. However, compounds with fluoro substituent shows MIC at 40 µg/ml and 25µg/ml against *S. aureus*, *S. typhi* and H37Rv strain (Compound no. 1,4,5 and 8).

5/5,6-disubstituted-2-thio-(isopropyl sulfonyl)benzemidazoles / benzoxazole

7 compounds have been synthesized in this series and all of them are inactive against *C. albicans*, *T. mentagrophytes* and *T. rubrum*. All the synthesized compounds show activity at 100µg/ml against *S. aureus*, *S. typhi* and H37Rv strain of *M. tuberculosis*.

Conclusion

The aim of this research project was to check the effect of a nitro group on the parent quinazolinone moiety and increase in biological activity was expected after taking into consideration the effect of –NO₂ groups in various established heterocycle molecule. However, inspite of introducing the –NO₂ groups on the quinazolinone, no significant effect on the biological activity has been observed. The introduction of various other heterocycles and halo substituent on the quinazolinone moiety has also been unsuccessful in obtaining a compound with significant biological activity.

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**A SYNOPSIS OF THE THESIS TO BE SUBMITTED TO THE UNIVERSITY OF
MUMBAI FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN THE
FACULTY OF SCIENCE (ORGANIC CHEMISTRY).**

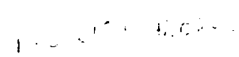
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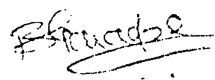
Name of the candidate : Ms. Mukta Bohra.

**Name and designation
Of the guide** : Dr. B.G.Khadse,
Director and Research Guide.
Haffkine Institute, Parel, Mumbai - 12.

Place of research : Haffkine Institute for Training, Research and
Testing, Parel, Mumbai - 12.

**Number and date of
Registration** : 38; May 5, 1998.

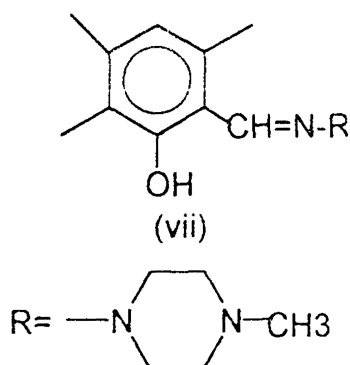
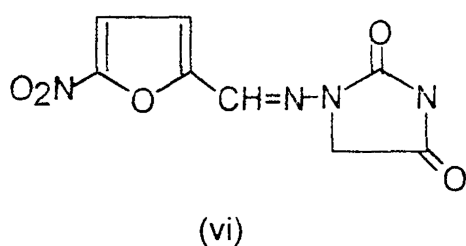
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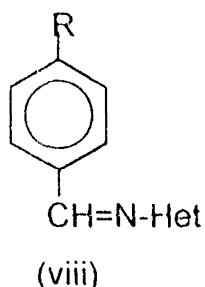
In all the above drugs the -NO₂ group is present at a specific position on the molecule and is responsible for the biological activity of the molecule⁸. It has also been proved experimentally that if the position of the nitro group in the molecule of a particular drug is changed, or the group is removed from the molecule, there is a decrease or total loss of biological activity⁹. Taking these facts into consideration, it was proposed to synthesize 3-amino-2-methyl-5/6-nitro-4-(3H)-quinazolinone, in search for new antimicrobial agents. It was thought worthwhile to incorporate some additional heterocyclic and aromatic moieties on the 3-amino-2-methyl-5/6-nitro-4-(3H)-quinazolinone and study the biological activity of the resulting compounds.

2) Synthesis of 2-methyl-5-nitro-3-[(substituted phenyl/heterocycle) methylene amino]-quinazoline-4-(3H)-one :

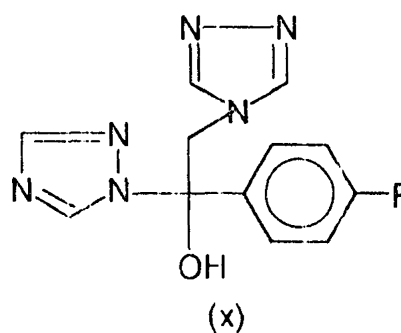
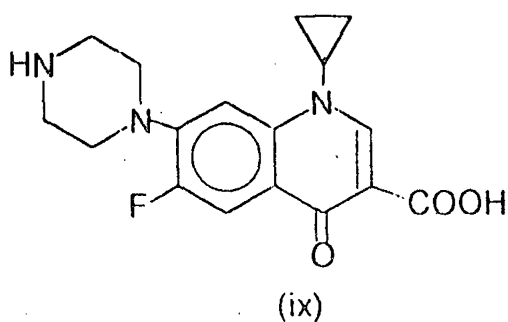
Schiff bases of 5-chlorosalicylaldehyde, 5-bromosalicylaldehyde and 4 -N,N-dimethyl aminobenzaldehyde have been reported to have encouraging tuberculostatic action¹⁰. The presence of azomethine linkage ($-N=C$) in the compounds has also been known to decrease the toxicity considerably¹¹. The presence of azomethine linkage in the variety of biologically active compounds such as Furazolidone (vi) and also in the field of antibiotics such as Rifampin(vii), has been proved to be very essential ¹².



Recently R. Fioravanti *et al*¹³ have reported the antimicrobial activity of some new heteroaryl benzyl amines and their Schiff bases (viii).

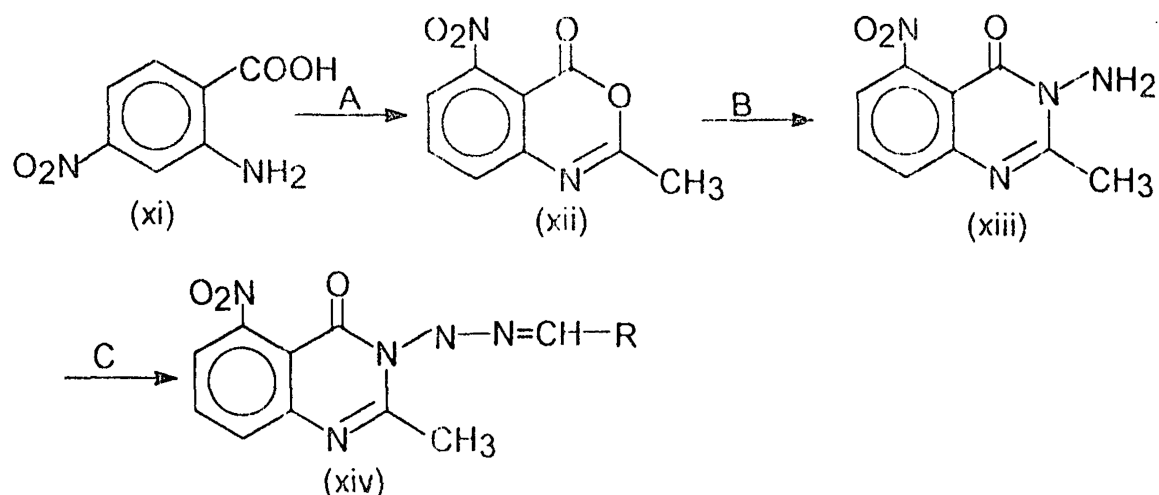


Fluorine containing drugs such as Ciprofloxacin (ix), Fluconazole(x) have been proved to be very specific drugs for the treatment of microbial diseases and they owe their activity to the presence of fluorine which increases lipophilicity of the molecule¹⁴.



Considering this special property of fluorinated compounds, Schiff bases of 3-amino-2-methyl-5-nitro quinazoline-4 -(3H) one were synthesized by condensation with various fluorinated and other aromatic aldehydes. A total of 10 compounds were synthesized and tested for their biological activity.

Scheme:-



R= methoxy, 2-fluoro, 2-trifluoromethyl etc.

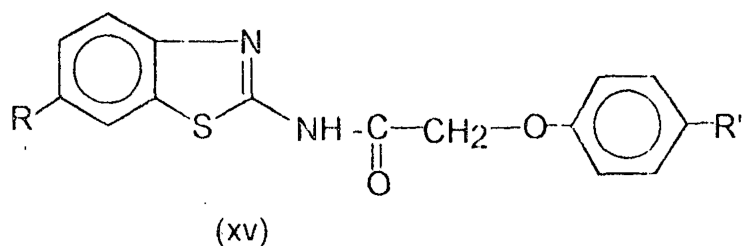
A=(CH₃CO)₂O

B=NH₂.NH₂.H₂O

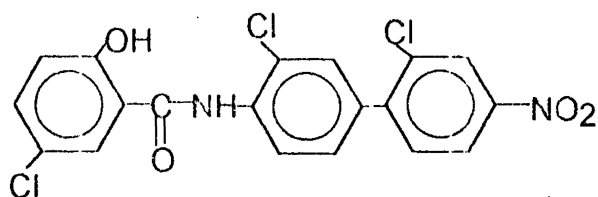
C=RCHO

3) Synthesis of 3-(substituted acetamido)-2-methyl-6-nitro-quinazoline-4-(3H)-one :

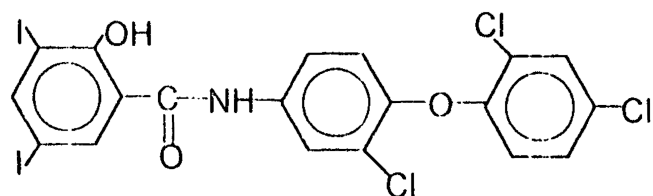
Lacova M *et al*¹⁵ have reported the compounds of the following type with good biological activity.



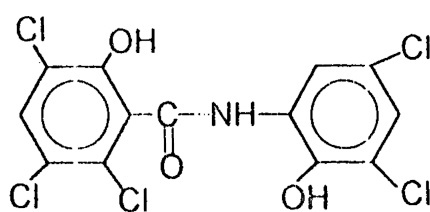
The acetamido group in the molecule was responsible for its activity. Aromatic amides have been proved to be useful in the field of medicinal chemistry. Niclosamide(xvi), Rafoxanide(xvii), Oxyclozanide(xviii) etc. are the drugs which owe their activity to the amide linkage.



(xvi)

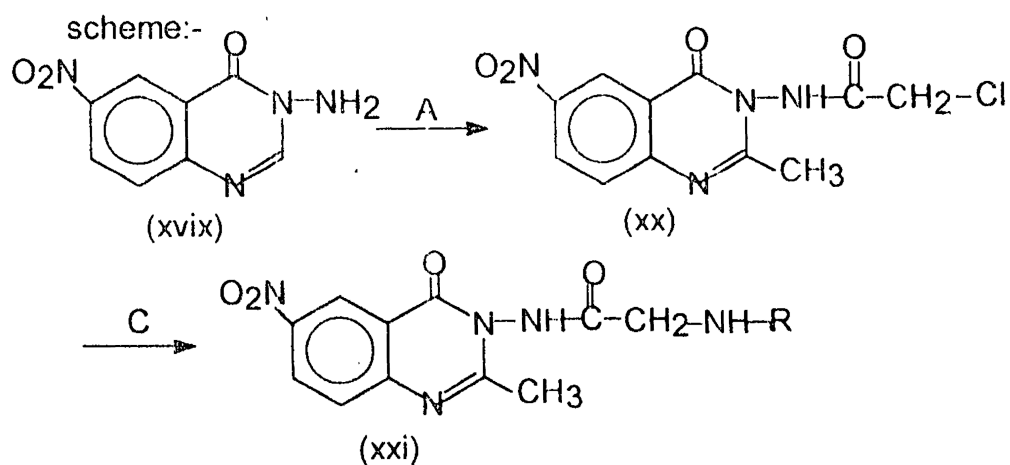


(xvii)



(xviii)

Also, substitution at 3- position of the quinazolinone ring was found to increase the activity of the parent moiety¹⁶. Hence, it was decided to introduce amide linkage on 3-amino-2-methyl-6-nitro-quinazolin-4-(3H)-one(xix), by reacting the amino group at 3-position with chloroacetylchloride. The -Cl group on the compound thus formed(xx), was reacted with different aromatic amines to obtain the title compounds (xxi).



where R=morpholine, Piperazine, fluoroanilic

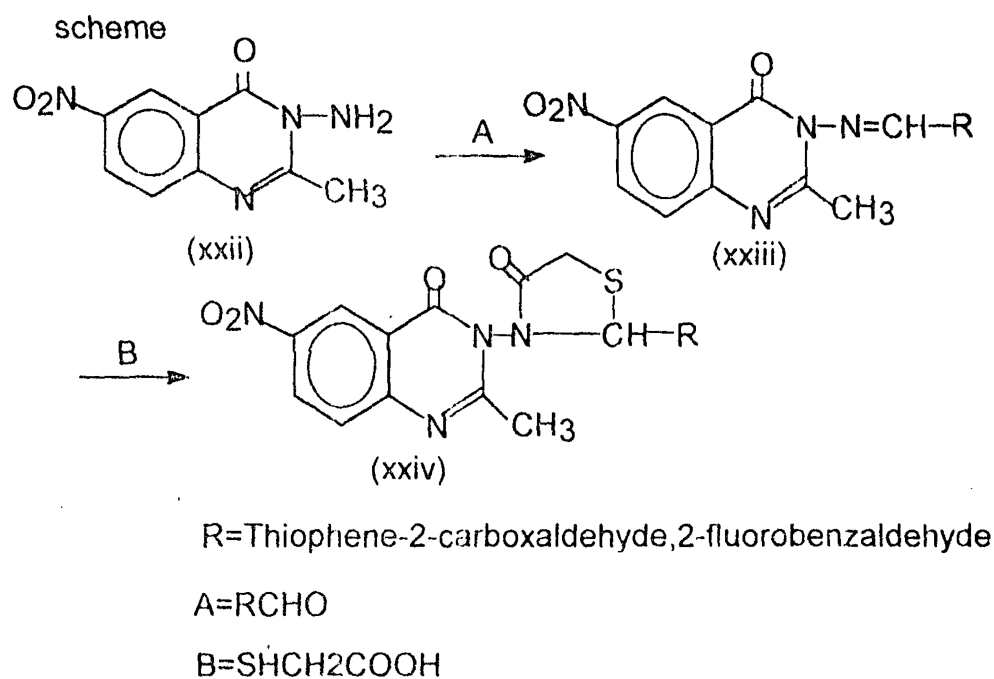
A= ClCOCH₂Cl

B=RNH₂

4) Synthesis of 3-[2-methyl-6-nitro-4-(3H)-oxo-3-quinazolinyl]-2-(substituted phenyl/heterocycle)-4-thiazolidinones:

The presence of thiazolidine ring in Penicillin and related derivatives was the first recognition of its occurrence in nature¹⁷. This led to extensive structure- activity studies on thiazolidine-2,4-diones and related thioxo analogues¹⁸. It has been established that the introduction of arylazo, sulfamoyl, phenylazo, moieties at different positions of thiazolidine ring enhances the antimicrobial activity of the parent molecule¹⁹⁻²⁰. Many of the thiazolidinone derivatives exhibit a wide variety of biological activities²¹ such as antimicrobial, anti-inflammatory, antihistaminic etc.

In the light of these findings, it was proposed to synthesize thiazolidinone derivatives of the lead molecule -the quinazolinone moiety -by treating it as follows:-

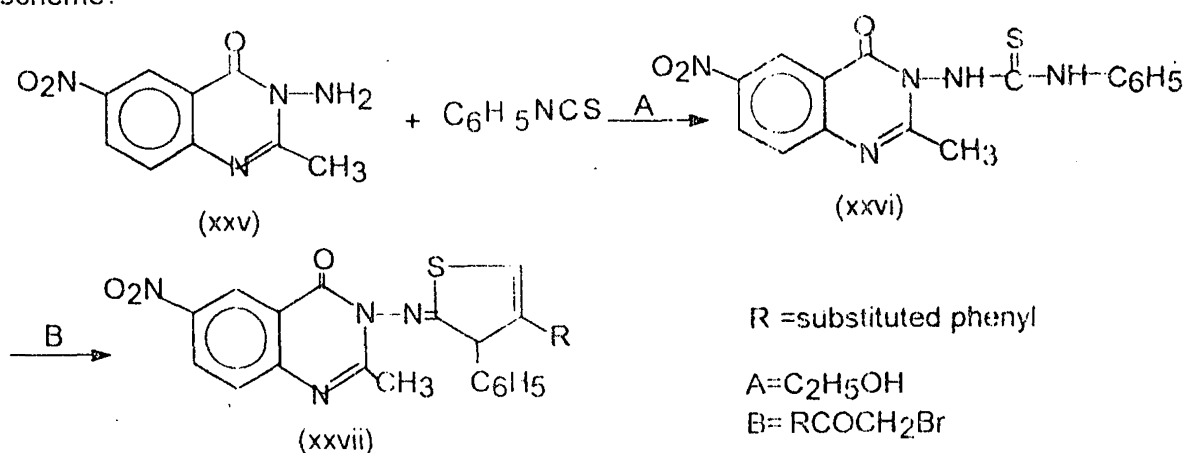


A total of 8 such compounds were obtained and screened for biological activity.

5) Synthesis of 2-methyl -6-nitro-(3-phenyl-4-substituted) -2,3-dihydrothiazol-2-ylidene amino-4-(3H)-quinazolinone:

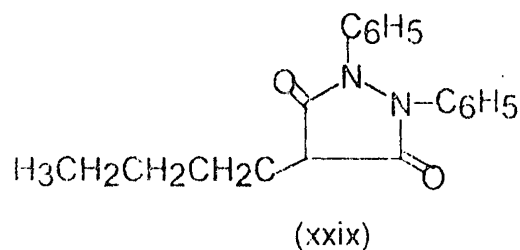
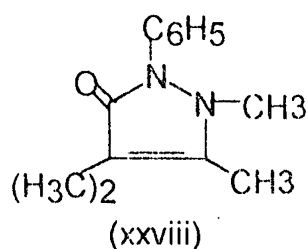
It is proved that 4-(3H)-quinazolinone derivatives possessing a thiazolyl, pyridyl or benzothiazolyl moiety at 3-position exhibit antibacterial and antifungal activity²². Hence, it was decided to introduce a benzothiazolyl moiety at 3-position of the quinazolinone. It is also reported that increase in number of carbon atoms at 4-position of the benzothiazolyl moiety enhances the biological activity²³. Thus, substitutions were carried out at the 4-position of the benzothiazolyl moiety on the quinazolinone in a hope to increase the antimicrobial activity. Also, since the presence of electron -withdrawing groups like -NO₂ enhances the activity of the molecule²⁴, it was decided to introduce a -NO₂ group at 6-position of the parent quinazolinone. All these substitutions led to the title compounds (xxv), which were then tested for antimicrobial activity.

scheme:-

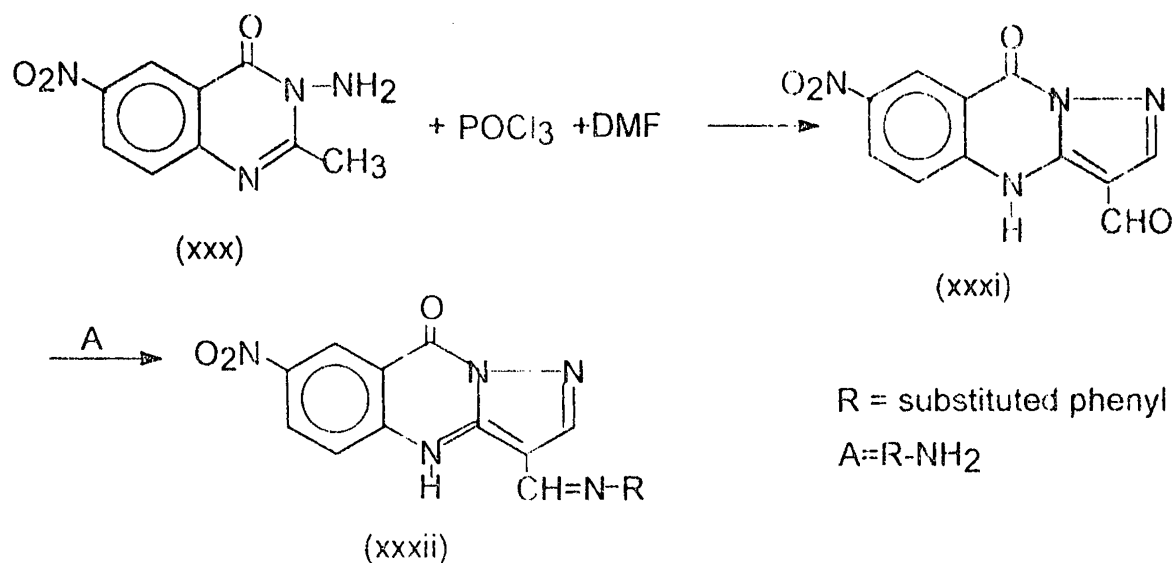


Synthesis of 3-N-(substituted phenyl) amino methylene pyrazolo [5,1-b]-7-nitro-quinazoline-9(1H)one:

A number of pyrazolylpyrimidines have shown interesting biological activity in diverse fields²⁵. Interesting anticancer, antitubercular and anti-inflammatory properties of these compounds have been reported from time to time. In the chemotherapy of disease of connective tissue, pyrazolyl type of compounds perform various roles, the most important being Aminopyrine(xxviii) and Phenylbutazone(xxix)²⁶.

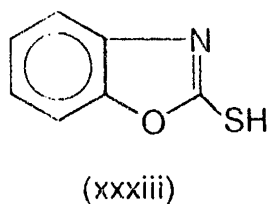


Considering the various biological activities exhibited by pyrazole ring it was proposed to synthesize pyrazolylquinazolinone derivatives. 8 such compounds were synthesized in the following manner.

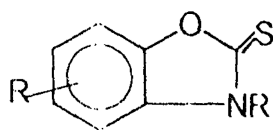


7) Synthesis of 5-chloro-6-nitro-2-thio-(substituted sulphonyl)- benzoxazole:-

El-Shaar *et al*²⁷ reported in 1997 the antimicrobial activity of a series of 2-substituted benzoxazoles. These compounds were synthesized using 2-mercaptobenzoxazole (xxxiii) as the starting material.



Also, Vematsu *et al*²⁸ reported the antifungal activity of benzoxazole derivatives(xxxiv) bearing the following structure.

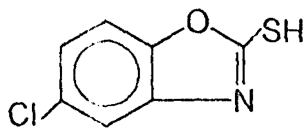


(xxxiv) R=CH₃, C₂H₅

R1=CH₃, Halogen

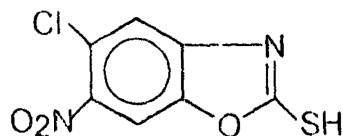
Similarly, antimycotic activity of 2-benzoxazolyl-N-methyl-N-(1-naphthyl) dithiocarbamate was reported by Wildfever *et al*²⁹. Considering these references it was decided to synthesize substituted 2-mercaptobenzoxazoles to test their activity as antimicrobial agents.

Denisova *et al*³⁰ reported the synthesis of 5-chloro-2-mercapto-benzoxazoles(xxxv) with good anti-microbial activity.



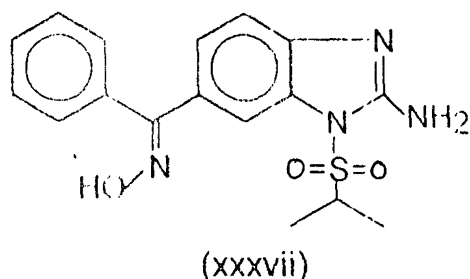
(xxxv)

They also found 6-nitro-2-mercapto-benzoxazole to be active as an antimicrobial agent. As discussed earlier, electron withdrawing groups like nitro, chloro etc. enhance the biological activity of the parent moiety. Hence, it was decided to synthesize 5-chloro-2-mercapto-6-nitro-benzoxazole(xxxvi), which would be used as the starting material for a new series of compounds.



(xxxvi)

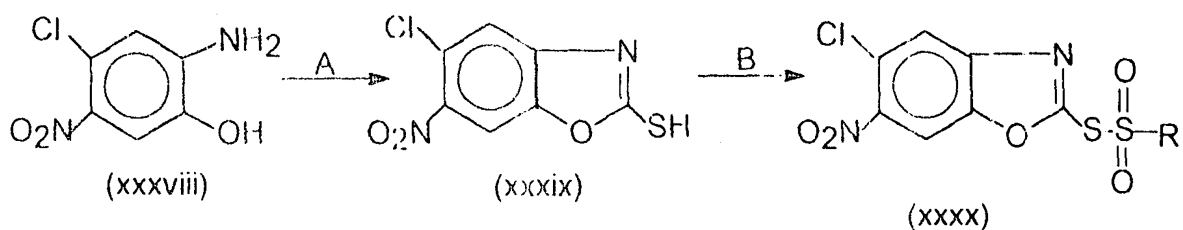
In literature, S-alkyl and sulphone linkage introduced on the parent moiety were found to enhance the antitubercular activity of the derivatives thus formed³¹.



Enviroxime(xxxvii), an established molecule with activity against Rhinovirus multiplication contains the isopropyl sulphonyl group, which is responsible for its activity¹². Considering the importance of such sulphonyl and s-linkages, it was decided to introduce these linkages on 5-chloro-2-mercapto-6-nitrobenzoxazole to obtain the title compounds.

4-chloro-5-nitro-2-aminophenol was cyclised using CS₂, KOH and methanol to obtain 5-chloro-2-mercapto-6-nitrobenzoxazole. The -SH group of this compound was treated with various substituted suphonyl chlorides to obtain the final compounds(xxxx).

SCHEME:-



R=substituted sulphonyl chloride

A=CS₂/KOH

B=R-SO₂Cl

8) Biological screening:

All the 50 compounds synthesized herein have been screened for their *in vitro* antitubercular, antibacterial and antifungal activities.

Antitubercular screening:- The *in vitro* antitubercular screening of the compounds was carried out by the tube dilution technique employing H37RV strain of *Mycobacterium tuberculosis*. This method uses Kirchner's medium containing Tween 80 as described by

Rake *et al*²⁷. The standard drug used was Isoniazid. The MIC of Isoniazid is 0.04 µg /ml against H37RV strain of *M. tuberculosis*.

Antibacterial screening:- The compounds synthesized were also subjected to *in vitro* test against *Staphylococcus aureus* and *Salmonella typhi* by using the tube dilution method. The culture medium employed in the screening was Mueller Hinton Broth. The standard drugs used were Ampicillin Sodium against *S.aureus* and Trimethoprim against *S. typhi*. The MIC of Ampicillin Sodium is 0.01 µg/ml and that of Trimethoprim is 0.1 µg /ml.

Antifungal screening:- The compounds have also been screened for their antifungal activity against strains *Candida albicans*, *Trichophyton mentagrophytes* and *Trichophyton rubrum*. The standard drug used was Miconazole. The MIC of Miconazole is 6.25 µg /ml against *C.albicans* and 1.56 µg /ml against *T.mentagrophytes* and *T. rubrum*.

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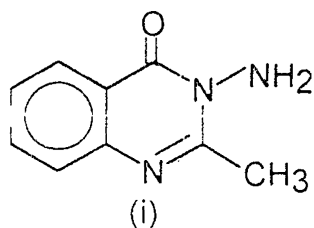
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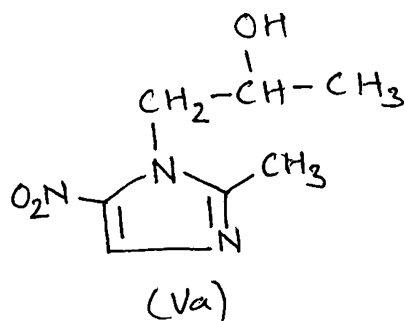
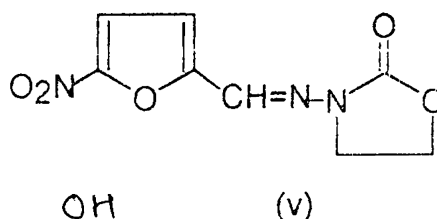
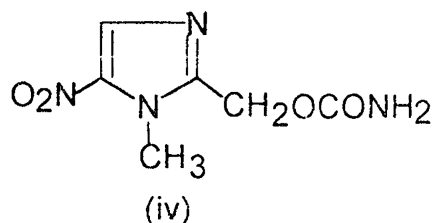
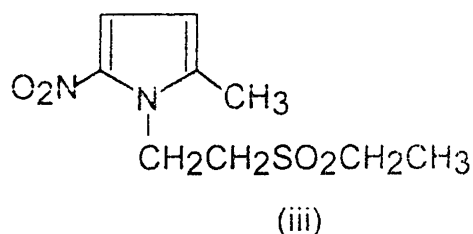
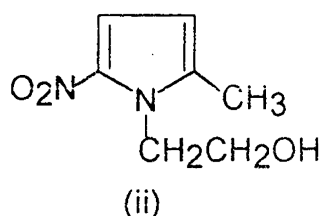
8. Biological screening and results.

The parent moiety selected for this research project is the quinazolinone(i) system.



Compounds bearing a quinazolinone moiety are endowed with a variety of biological activities¹⁻⁴. Several aminoquinazolinones have been found to be active on the CNS and also as antitubercular agents⁵. A number of diazo, hydrazide and hydrazine derivatives have been found to be good CNS- active and antibacterial agents⁶. Many fused quinazolinones are reported to exhibit remarkable pharmacological activity⁷. This justifies the selection of quinazolinone moiety, which was derivatised to obtain several analogues in the hope of achieving antimicrobial activity.

Nitroheterocycles have been proved in the field of medicinal chemistry to be very important group of biologically active compounds. The most promising compounds among them are Metronidazole(ii) Tinidazole(iii) Ronidazole(iv), Nitrofurantoin(v) etc., all of which contain a nitro in 5 position group.



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Appendix

APPENDIX

1. The Melting points have been determined in open capillaries in a Veego VMP-1 melting point apparatus, and are uncorrected.
2. The TLC of the compounds have been run on Eastman Kodak precoated Silica gel plates of type K301 R and E. Merck precoated silica gel plates of type 60 F 254.
3. The Infrared Spectra were recorded on BOMEM MB-104 Fourier Transform Infrared Spectrometer.
4. The PMR Spectras were recorded on Varian 300 MHz spectrometer using TMS as the internal reference, at RSIC, IIT, Powai.
5. Carbon, nitrogen and hydrogen analyses were carried out on Heraeus C, H, N, Elemental Analyzer at the Haffkine Institute.

Synopsis

Mankind has always been afflicted by diseases and ailments. It is evident from ancient literature that he has attempted to control these afflictions since time immortal. The struggle of man against microbes has been the struggle of life against death. The most dramatic and most heroic of all wars of the last millennium has been the relentless one waged by mankind against various diseases. It has been a constant battle to outwit shifty bacteria, lethal viruses and deadly parasites, and to find new ways of combating the infectious diseases with novel therapeutic agents. We have learnt to control, if not totally eradicate diseases. However, at the end of the millennium, we seem to have come to a full circle. Newer mutations of viruses and bacteria heckle at our doors. Thus, it seems that in the war against infectious diseases there are no permanent treaties - just pauses between battles. Ever-growing resistance towards current therapy continues the drive for the search of new agents. One aspect of medicinal chemistry deals with the incorporation of newly emerged pharmacophores on already existing biologically active moieties to produce newer molecules with higher efficacy. Based on this aspect, efforts have been made to synthesize molecules by incorporating heterocyclic and aromatic substituents on 3-amino-2-methyl-5/6-nitroquinazolinone. All the synthesized compounds have been characterized by TLC, FT-IR, NMR and elemental analyses. The melting points were recorded in open capillaries and are uncorrected.

The thesis will consist of the following eight parts:-

1. Introduction, review of literature and plan of work.
2. Synthesis of 2-methyl-5-nitro-3-[(substituted phenyl/heterocycle)methyleneamino]-quinazolin-4(3H)-one.
3. Synthesis of 3-(substituted acetamido)-2-methyl-6-nitroquinazolin-4(3H)-one.
4. Synthesis of 3-[2-methyl-6-nitro-4(3H)-oxo-3-quinazolinyl]-2-(substituted phenyl/heterocycle)-4-thiazolidinones.
5. Synthesis of 2-methyl-6-nitro-(3-phenyl-4-substituted)-2,3-dihydrothiazol-2-ylideneamino-4(3H)quinazolinone.
6. Synthesis of 3-N-(substituted phenyl)amino methylene pyrazolo [5,1-b]-7-nitroquinazolin-9(1H)-one.
7. Synthesis of 5-chloro-6-nitro-2-thio(substituted sulphonyl)benzoxazole.

