

**SYNTHESIS OF ORGANIC COMPOUNDS OF POSSIBLE
THERAPEUTIC VALUE**

**THESIS SUBMITTED
UNIVERSITY OF BOMBAY**

**FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
IN
ORGANIC CHEMISTRY**

**SUBMITTED BY
ANUP R. BARDE**

**UNDER THE GUIDANCE OF
DR. B.G. KHADSE**

**HAFFKINE INSTITUTE FOR TRAINING, RESEARCH & TESTING
BOMBAY**

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Mr Anup R. Barde

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***Synthesis of
Organic Compounds of Possible
Therapeutic Value***

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

***By
Anup R. Barde
M.Sc.***

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STATEMENT

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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.

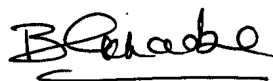
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Statement - I : The work embodied in the thesis to be submitted is original, based on the discovery of new facts, viz the syntheses and characterization of new and hitherto unknown compounds of possible chemotherapeutic value. Also included in the thesis, are new relation 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.



Anup R. Barde

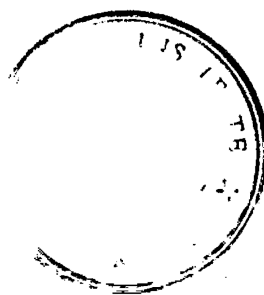
Research Student.

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PART I A

INTRODUCTION,
REVIEW OF LITERATURE



INTRODUCTION AND REVIEW OF LITERATURE

"Medicinal chemistry remains a challenging science 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."

ALFRED BURGER¹

In the prospective sense medicinal chemistry relates to the design and production of compounds those can be used in medicine for the prevention, treatment or cure of human and animal diseases. An early definition of Medicinal Chemistry was given by a IUPAC specialized commission "Medicinal chemistry concerns the discovery, the development, the identification and the interpretation of the mode of action of biologically active compounds at the molecular level. Emphasis is put on drugs but the interests of medicinal chemistry are not only restricted to drugs but also include bioactive compounds in general."

Medicinal chemistry can be said to have taken birth with the advent of man on earth, probably, precisely at the moment he realized he had been afflicted by certain abnormal feelings (now termed as diseases/ ailments) which he had to counteract for his normal being. Since then he has been testing himself with herbs, berries and various other substances gathered from his environment. Ever since the use of natural medicine elaborated and proliferated and it has been documented in the records of various civilizations.

For many centuries the search for chemotherapeutic substances focused on the investigation of herbs. In the nineteenth century the advent of analytical and synthetic chemistry triggered important changes when alkaloids were isolated in pure forms and simple molecules such as acetyl salicylic acid were synthesized.

However the true era of medicinal chemistry really began in the 1930's with the preparation and use of antibacterial sulfonamide drugs. From that time 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 disturbed mental, cardiovascular, gastrointestinal conditions. To boast, it can be claimed that certain forms of cancers can be cured by chemotherapy.

The work presented in this thesis is yet another humble effort in the field of medicinal chemistry though very minute even to be regarded as a small step in offering a practical solution to the innumerable problems, nevertheless, a devoted effort to sincerely contribute to a healthier and happier human life. The work deals with some of the commonest ailments viz. helminthiasis, tuberculosis, other bacterial and fungal infections though not considered fatal by and large. But even today these irritate physicians at times, when coupled with other chronic conditions and also due to the resistance offered by infecting organisms to various forms of therapy

HELMINTHIASIS

Since prehistoric times, helminthiasis - a disease caused by worms (helminths) has posed severe hazards to man and animals. It is a problem of considerable importance, both to the medical practitioner and the veterinary surgeon. The helminths as parasites of human and livestock, constitute the single most important group of infections, although many separate species are involved.

Dr. Stoll's estimate of global parasitism in 1947 ^{2a} appears to have altered little till the middle of the last decade ^{2b}. The various forms of helminth infections merely seem to have grown in proportion with respect to the growth of the human population (Table 1).

Table 1: Global intestinal helminth prevalence

	1947 <u>(in million)</u>	1989 <u>(in billion)</u>
Ascariasis	650	1.26
Hookworm	450	932
Trichuris	350	687

All helminths infections 4.5 billion.

The wide prevalence of parasitic diseases are essentially due to distinctive climatic conditions, poor environmental sanitation, low socioeconomic status, lack of health education and other related factors.

Types of infections

Among the various helminth parasites which infect man, livestock and poultry, the intestinal helminths pose the most serious threat. The hookworm is considered to be an important intestinal nematode whose presence causes severe disorders in the body functions. It is responsible for continued blood loss and the vitality of the patient is seriously impaired long before the diseases diagnosed. Infections due to two species of hookworm, *Ancylostoma duodenale* and *Necator americanus* continue to be major causes of iron deficiency anaemia and associated ill-health.

Filariasis or elephantiasis (a common term describing its final stage) is a group of infections that causes disability and severe disfigurement of the legs. It is transmitted by the bite of a mosquito. The filariae migrate to the lymphatic system wherein they mature. The pathology is caused essentially by continuous blockade of lymph flow, the resultant damming up of this fluid stretches and distorts the tissue into horrendous disfigurement.

Among soil-transmitted parasitic infections, ascariasis is a major public health problem in the developing world, primarily affecting children. It contributes significantly to the widespread menace of malnutrition and remains undiminished.

Strongyloides stercoralis has a direct effect in causing intractable diarrhoea. Heavy infections of trichuriasis causes colitis and diarrhoea that can be sufficiently severe so as to cause rectal prolapse. Schistosomiasis is another serious malady which causes liver, gut, and bladder fibrosis from schistosome eggs, deposited by worms.

Agents effective against Helminth Infections

Halogenated hydrocarbons

The anthelmintic activity of halogenated hydrocarbons have been known for quite some time now ^{3,4}. Several chlorinated hydrocarbons such as carbon tetrachloride, ethyl chloride, n-butyl chloride and 2-chlorobutane are reported to possess varying degrees of antihookworm activity. However, very few of these compounds find use in human clinical treatment due to adverse side effects caused.

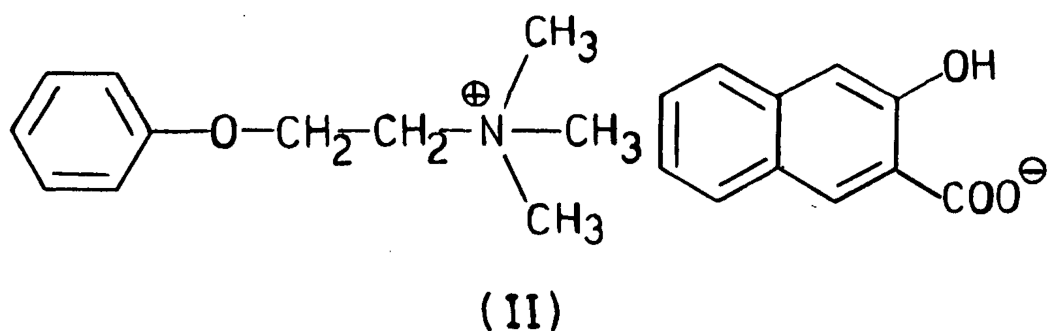
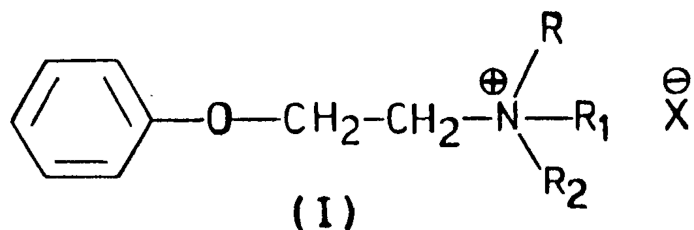
Tetrachloroethylene ($\text{Cl}_2\text{C} = \text{CCl}_2$) has been used since 1925 as an anthelmintic agent and probably still finds use in some quarters. It is reported to induce nausea, vomiting, headache, dizziness and abdominal cramps. Patients with severe anaemia have been known to collapse during therapy.

At a dose of 2 ml/adult, carbon tetrachloride (CCl_4) is capable of eliminating hookworms. However, prolonged use may lead to jaundice and cirrhosis and thus it was replaced by the more active tetrachloroethylene.

Chloroform (CHCl_3) too has been used in the treatment of human hookworm infections⁵ and have shown good response against *N. americanus* and *A. duodenale*. Nevertheless the drug should be given under strict medical supervision while children and pregnant women are recommended to abstain.

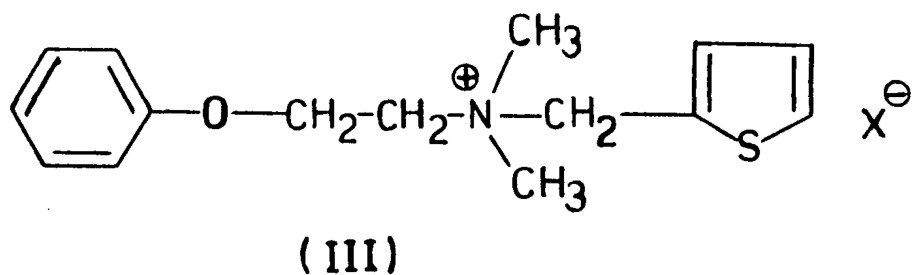
Quarterly ammonium compounds

Copp and his co-workers at Wellcome Laboratories reported in 1958, the potent anthelmintic activity associated with phenoxyethylammonium salts (I) of which bephenium hydroxynaphthoate (II) (Alcopar[®]) had the highest activity.



Bephenium is effective against *N. americanus* and *A. duodenale* in man. It is also found to give 95-100% cure rates in dogs and cats carrying hookworms. The main side effects accompanying this compounds are nausea and vomiting.

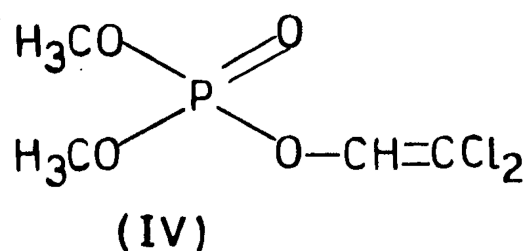
Thenium (III) (Canopar[®]) is a thiophene analog of bephenium used extensively to control canine and feline hookworm diseases due to its lesser property to cause vomiting than bephenium.



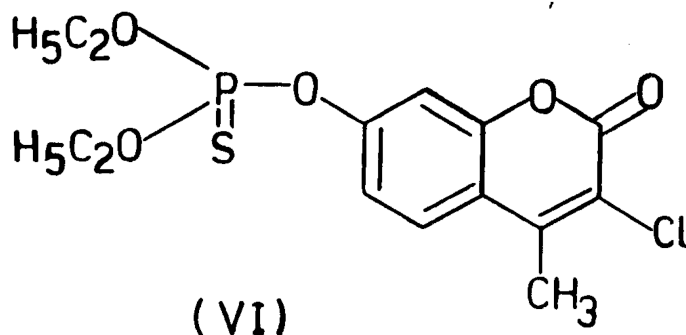
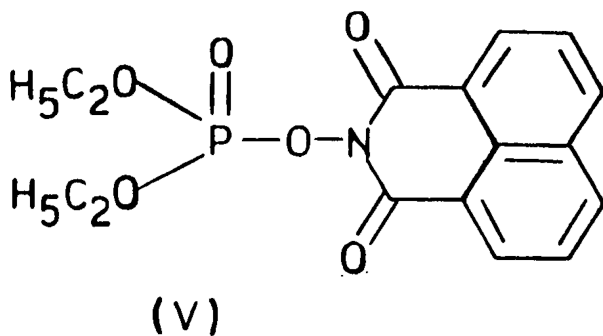
Organophosphates

A large number of organophosphates have been claimed to possess activity against different helminths, but few have found uses in human clinical treatment essentially due to their high toxicity and narrow margin of safety.

Largely due to its unique formulation, dichlorovos (IV) has a broader margin of safety and high efficiency compared to other organophosphates. It is given in polyvinyl chloride resin pellets which releases the drug slowly by evaporation, thus saving the patient from sudden toxicity of concentrated dose. The body detoxifies the low concentrations released from the pellets which are ultimately excreted in 2-3 days.



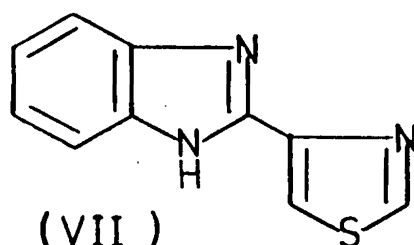
Naphthalophos (V) and coumaphos (VI) are other organophosphates which merit mention. The former is capable of removing 90-95 % of the hookworm at a dose of 50 mg/kg, while the latter clears *Bunostomum* in calves at a dose of 2 mg/kg.



Organophosphates are potent inhibitors of acetylcholinesterases and it is believed that they exert their toxic effects in the worms in a more or less similar fashion as they are toxic to insects and vertebrates.

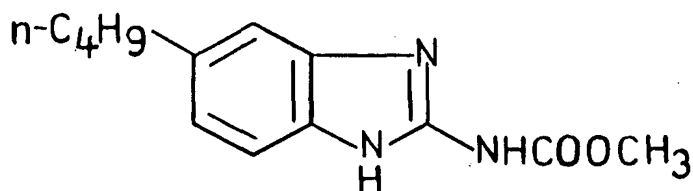
Benzimidazoles :

Modern parasitologic research has given birth to a series of benzimidazoles exhibiting marketed activity against different intestinal nematodes. Thiabendazole (VII), the first truly modern anthelmintic was introduced in 1961 by Merck ⁶. This was quickly followed by a generation of various benzimidazoles, several of which are currently used in the treatment of human helminth infections.



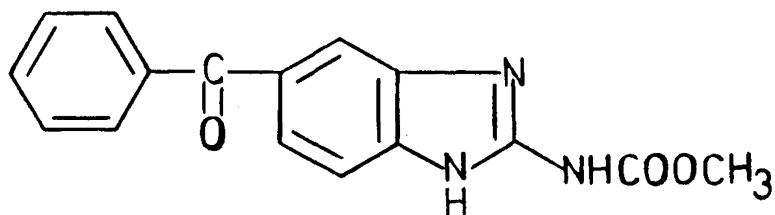
Thiabendazole is a very good agent for the treatment of hookworm infections and is most effective in multiple dose therapy achieving cure rates to the order of 75-83%. It also shows anti-inflammatory activity which may be advantageous in the treatment of human hookworm infections. However, it suffers a disadvantage of being readily deactivated in sheep due to hydroxylation at its 5-position ⁷.

Parbendazole (VIII) was introduced by Smith, Kline & French Laboratories which exhibited significant activity against different helminth parasites, although its action is rather limited against hookworms. It shows about 66-88 % clearance of *A. caninum* infection in dogs at an oral dose of 20 mg/kg.



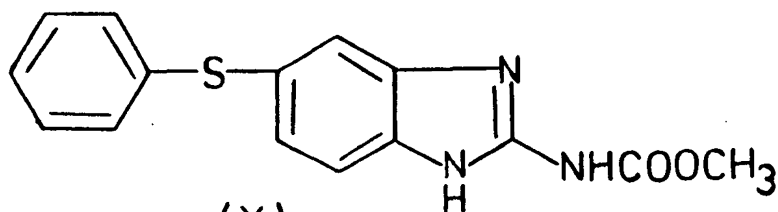
(VIII)

Parbendazole was soon followed by mebendazole (IX) , marketed by Janssen Pharmaceutica ⁸ which is a powerful anthelmintic agent possessing strong efficacy against different species of nematodes and cestodes. Mice infected with *N. brasiliensis* show 100 % clearance when treated with mebendazole which also shows high activity against *A. ceylanicum* in hamsters and *A. caninum* in dogs. It is also equally effective against human hookworm infections and shows about 95 % clearance of *N. americanus* at a dose of 100 mg/kg when given twice a day for three days ⁹.



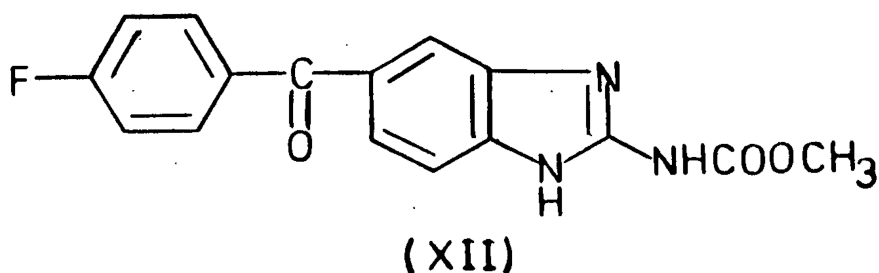
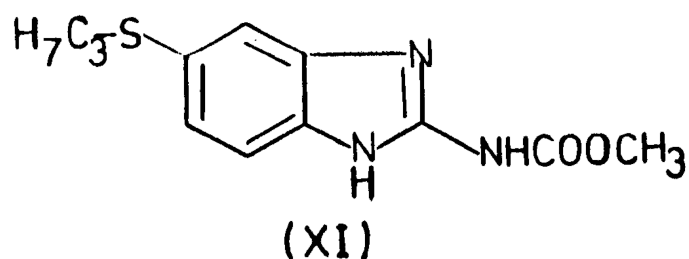
(IX)

Fenbendazole (X) was introduced by Hoechst which exhibits marketed activity against different species of lung worms and intestinal nematodes.



(X)

Two more compounds in this class were introduced by Janssen Pharmaceutica - Albendazole (XI) in 1976 and Flubendazole (XII) in 1978.



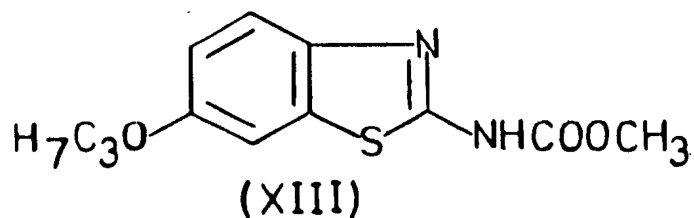
Albendazole exhibits high efficacy against *A. canium* in dogs at a dose of 50 mg/kg given for three days while it shows relatively weak activity if a single dose of 250 mg/kg is administered.

Flubendazole shows a high level of activity against a variety of nematode and cestode infections, either natural or induced in experimental animals. It exhibits excellent activity at a dose of 10 mg/kg against a number of intestinal nematodes.

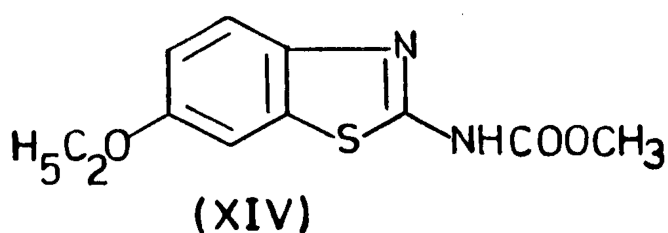
Thus it can be seen that benzimidazoles represent the only class of truly broad spectrum anthelmintics. However, poor drug absorption and lack of water solubility are problems that are characteristic of these compounds which limit their usage.

Benzothiazoles and related compounds :

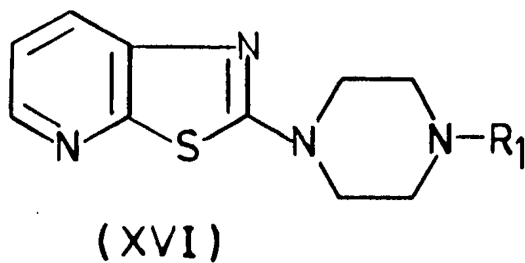
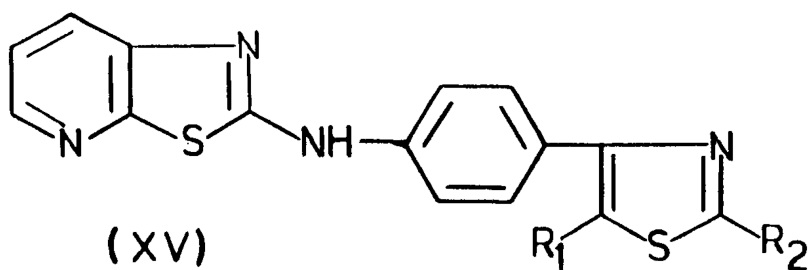
Attempts to extend the functional characteristics of the benzothiazole class of compounds to the benzothiazoles with a view to develop possible anthelmintics have met with some success. Several substituted benzothiazoles have been synthesized of which methyl 6-propoxy benzothiazole-2-carbamate (XIII) (Tioxidiazole) has emerged as a potent anthelmintic compound for intestinal worms ¹⁰. At a dose of 50 mg/kg for five days it shows excellent activity against *N. dubius* in mice.

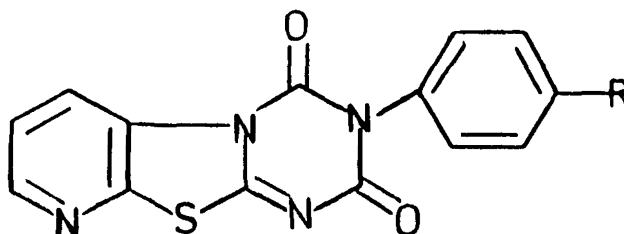


Another benzothiazole of similar structure, ethyl 6-ethoxybenzothiazole-2-carbamate (XIV) exhibits over 90 % clearance of *H. contortus* and *B. trigonocephalum* in lambs at a dose of 200 mg/kg¹⁰.



A few pyridothiazoles (XV - XVII) have been reported to possess anthelmintic activity¹¹⁻¹³ of which caused 90 % mortality of adult *N. dubius* worms at a dose of 1 mg/kg. The other two compounds (XVI) and (XVII), exhibited moderate activity against *N. dubius* in mice.

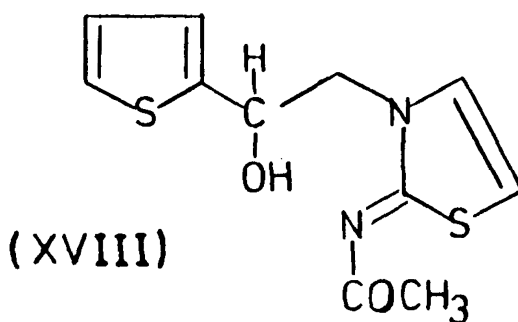




(XVII)

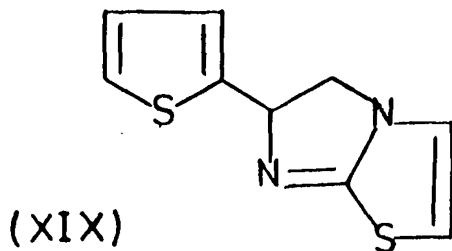
Imidazothiazoles

In the 1960's, Janssen Pharmaceutica while engaged in the search for a broad spectrum anthelmintic discovered that thiazothienol (XVIII) showed promising activity in chickens ¹⁴.



(XVIII)

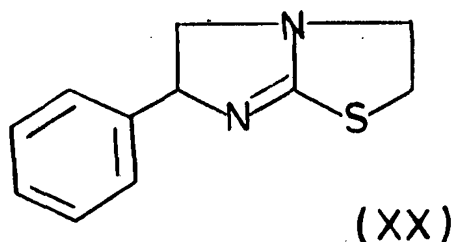
While (XVIII) also exhibited activity against sheep nematodes, it was ineffective in rats or mice suggesting that the active principle was probably a metabolite. Thereafter, chickens were dosed with (XVIII) and thiazothielite (XIX) (among other metabolites) was isolated from the faeces. (XIX) was far more potent than its precursor and is also active in both mice and rats ¹⁴.



(XIX)

With the imidazothiazole as the lead compound, other such molecules were synthesized of which Tetramisole (XX) represents a broad spectrum anthelmintic. It is actually a racemic mixture of R- and S- 2,3,4,6-tetrahydro-6-phenylimidazo(2,1-b)thiazole which have been resolved and their absolute configurations established. The anthelmintic activity is only due to its S(-) isomer, termed Levamisole.

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Tetramisole is also used for veterinary purposes and exhibits high activity against various gastrointestinal nematodes of sheep, dogs, fowl, cattle and horses. In humans it gives a 27-75 % cure rates against hookworm infections at a single dose of 2.5-5 mg/kg given for a period of three days.

Several other structural analogs of Tetramisole have been synthesized but none have matched the potency of the parent drug.

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 worlds population is infected by *M. Tuberculosis*. It is estimated^{15a} that in 1995 alone 8.8 million people were infected out of which 3 million died and 3.1 million ill. While it has been largely contained in the industrialized countries, it has reemerged among patients infected with the human immunodeficiency virus (HIV) ^{15b}.

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 type ¹⁶.

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 in airborne droplets dispersed by patients

with infectious pulmonary or laryngeal disease, *M. bovis* is transmitted in milk from diseased cows.

Mycobacterial and 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 the victor 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 genetic 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, thus 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 small subpopulations 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.

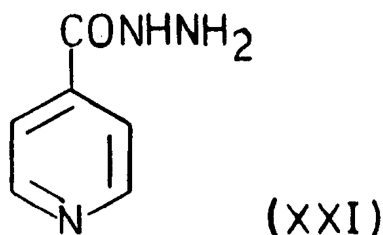
There is no known drug individually self-sufficient, possessing all the listed properties in its entirety. Hence a combination of two or more drugs are used for the treatment which may stretch to several months before a reasonable cure is effected.

Five drugs are currently considered essential in the control of tuberculosis - isoniazide, rifampicin, streptomycin, ethambutol and pyrazinamide. Thiacetazone too is widely used to supplement isoniazide 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.

Isoniazide(INH)

Isoniazide (XXI), the hydrazide of isonicotinic acid was first described in 1912, but its action against the tubercle bacillus was only discovered in 1952. It is unrivaled in its bactericidal action and ensures the destruction of the bacilli within a few days of starting treatment. It is highly effective against replicating tubercle bacilli but does not affect the semidormant species ¹⁷ which resume multiplication after removal of contact with the drug.



INH is rapidly absorbed and diffuses readily into all fluids and tissues. It is a component of all antitubercular chemotherapeutic regimens currently recommended by the World Health Organisation (WHO). It is normally taken orally but may also administered intramuscularly in case of critically ill patients.

INH is generally well tolerated at recommended doses which is approximately 5 mg/kg (max. 300 mg) daily for adults and children. The most common toxic manifestation of INH therapy is peripheral neuropathy which if left untreated may cause distress to the patient. This can be prevented by daily supplements of pyridoxine, the naturally occurring form of vitamin B₆.

Hepatitis is not a 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 of clinical significance. If the enzyme levels normalise on suspension of dosage then there is a less likelihood of them rising once again when treatment is resumed.

Rifampicin

It is a semisynthetic 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.

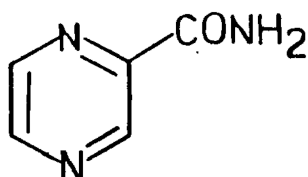
The effectiveness of rifampicin in the treatment of patients with drug-resistant tuberculosis was considered 'extraordinary' when it was first introduced ¹⁸.

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 (XXII) is a synthetic pyrazine analogue of nicotinamide and was successfully used against human tuberculosis in 1952¹⁹. 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.



(XXII)

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

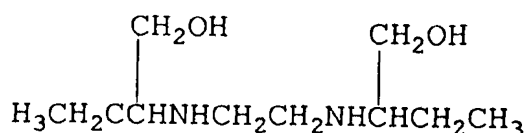
The antitubercular action of streptomycin, an antibiotic isolated from a culture of *Streptomyces griseus* was first demonstrated by Schatz and Waksman in 1944. It is not absorbed from the intestinal tract but after intramuscular administration, it diffuses readily into most body tissues and attains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

The normal dosage for adults and children are 15 mg/kg daily while in patients over 60 years of age it should be used with caution. In case of children too it is preferably avoided since the injections are painful and may also lead to irreversible auditory nerve damage. It also should not be used in pregnancy as it crosses the placenta thus causing the same effect in the foetus.

Hypersensitivity reactions due to the use of streptomycin are common and can be severe. Vestibular damage, earlier considered a high risk factor is uncommon with currently recommended dosages. If there are complaints of headache, vomiting or vertigo, then the dosage is reduced.

Ethambutol

Ethambutol (XXIII) has been classified as a bacteriostatic drug²⁰. It has been developed as a synthetic congener of related ethanediamines 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 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.



(XXIII)

It is administered orally and is readily absorbed from the gastrointestinal tract. The normal dosage for adults and children ranges from 15-25 mg/kg daily to 40 mg/kg three times weekly. The dosage is carefully calculated on a weight basis to avoid toxicity and is reduced in patients with impaired renal function.

Ethambutol can bring about dose-dependent optic neuritis readily resulting in impairment of visual acuity and color vision. If detected early, then 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 this effect on vision, 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 to be influence 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 (Opthocin) a quinine derivative, would cure pneumonococcal infections in mice. Heidelberger and Jacobs, coupled diazotised *p*-amino benzene sulphonamide with dihydrocuprein and found that the resultant compound had only mild activity and was not further investigated.

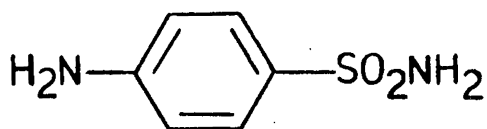
However, Dogmagk ²¹, Mietzsch and Klarer ²² in 1935 first dispelled the failure of earlier scientists by discovering prontosil, and reported that this compound cures streptococcal infections in mice and staphylococcal infections in rabbits. This period was considered to be a brilliant era in chemotherapy 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.

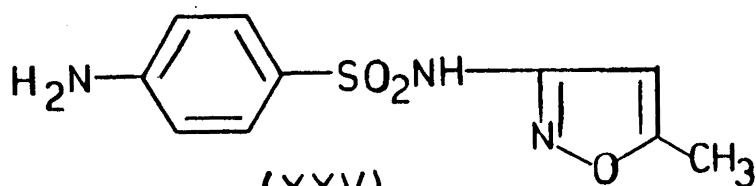
Sulfonamides

The term 'sulfonamide' is usually employed as a generic name for derivatives of *p* -amino benzenesulfonamide (sulfanilamide). These drugs were the first, systemic chemotherapeutic agents employed to prevent and cure bacterial infections in man and

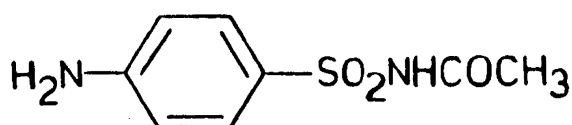
were quite effective in bringing about a sharp decline in the morbidity and mortality figures for the treatable infections diseases. Important members of this class include Sulfanilamide (XXIV), Sulfamethoxazole (XXV), sulfacetamide (XXVI), sulfadiazine (XXVII) and sulfisoxazole (XXVIII).



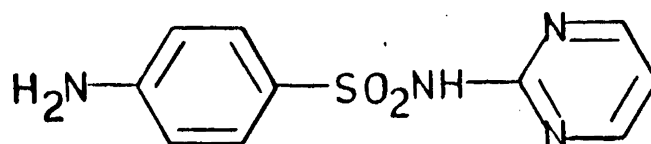
(XXIV)



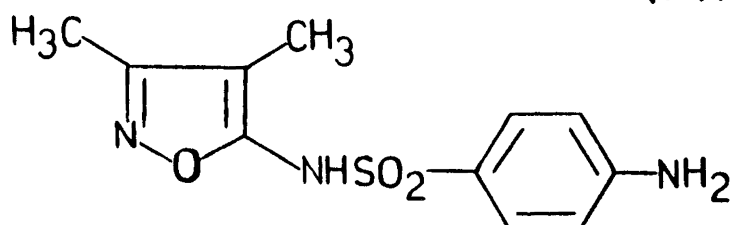
(XXV)



(XXVI)



(XXVII)



(XXVIII)

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 are finally eliminated from the body partly as the unchanged drug and partly as metabolic products, the largest fraction being excreted in the urine.

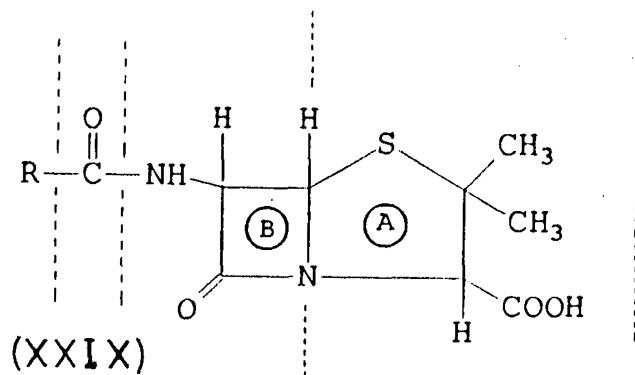
Resistant strains of bacteria to the sulfonamide have become common during recent years. Also the advent of penicillins and other antibiotics has diminished the role of sulfonamides as antibacterial agents. However, the introduction of the combination

of trimethoprim and sulfamethoxazole, known popularly as cotrimoxazole, has resulted in increased use of sulfonamides for the treatment of specific bacterial infections.

Penicillins and Cephalosporins

Since Alexander Fleming's serendipitous discovery of penicillin in 1928 it has remained one of the most important group of antibiotics. Despite the discovery of several other antibacterial 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 treatment of large number of infections diseases.

The basic structures of penicillin (XXIX) consists of thiazolidine ring (A) connected to a β -lactum ring (B) which is attached to a side chain (R) through 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).



The penicillins are classified according to their spectrum of antibacterial activity. While the pharmacological properties of the individual drugs in the various classes would constitute a lengthy discussion, certain generalizations can however be made. Following absorption, penicillins are widely distributed throughout the body. Therapeutic concentrations of these agents are quite rapidly achieved in tissues but comparatively much lower levels are found in parasitic secretions brain tissues and intraocular fluid.

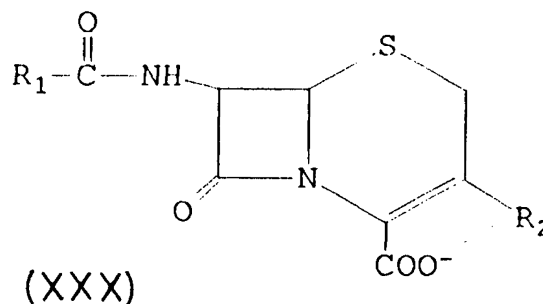
The penicillins do not penetrate the living phagocytic cells to a great extent. This class of compounds are quite rapidly eliminated particularly by glomerular filtration

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, 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 investigation 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 cause of drug allergy, has 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 (XXX) 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.



The first generation cephalosporins exhibit good activity against Gram-positive and relatively lower activity against Gram-negative bacteria. The second generation cephalosporins exhibit better activity against Gram-negative microorganism 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 antibiotics ,perhaps over used for conditions, where much less expensive antibiotics could provide relief. Nevertheless they are indeed useful as alternatives to penicillins for a variety of infections in patients who suffer allergic reactions to penicillins.

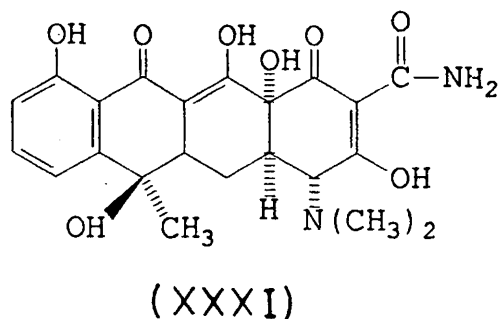
The cephalosporins also find wide use in prophylaxis during and after surgery, wherein the first generation agents have been shown to be safe and effective. A few of the third generation cephalosporins are the drug of choice for meningitis and in some cases superior to a combination of ampicillin and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

The β -lactum antibiotics (penicillins and cephalosporins) suffer bacterial resistance due to variety of factors. It may be caused by the inability of the agents to enter the site of action ²³. Also it is possible for a sensitive strain to acquire resistance by mutation and has been described for Gram-positive cocci ²⁴.

Bacteria can also destroy the β -lactum antibiotics enzymatically. β -lactamases are capable of inactivating certain of these antibiotics and is the major form of this enzyme although different microorganisms synthesize a number of distinct β -lactamases. Depending on substrate specificities these are often described as either penicillinases or cephalosporinases. Individual penicillins and cephalosporins vary in their susceptibility to these enzymes.

Tetracyclines

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



Microorganisms that have become resistant to one type of tetracycline frequently exhibit resistance to the other members of the family. The bacterial species possibly exhibit resistance only after exposure to the drug. The tetracyclines were initially useful for treatment of infections with aerobic Gram-negative bacteria but most species are now relatively resistant. Nevertheless, more than 90% of strains of *Haemophilus influenzae* may still be sensitive to either tetracycline or doxycycline.

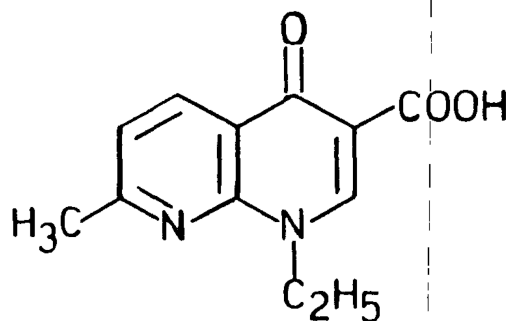
All the tetracyclines produce gastrointestinal irritation to varying degrees in some individuals and is more common after oral administration. Diarrhoea may also be a side effect, which though frequent and fluid, does not contain blood or leukocytes. Doxycycline and to a lesser extent other derivatives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

Other important antibacterial agents include chloramphenicol and the furan derivatives such as nitrofurantoin, nitrofurazone, furalidone etc. Several of the drugs active against *M. tuberculosis* discussed earlier are also active against various species of Gram-positive and Gram-negative microorganisms besides mycobacteria.

Quinolones

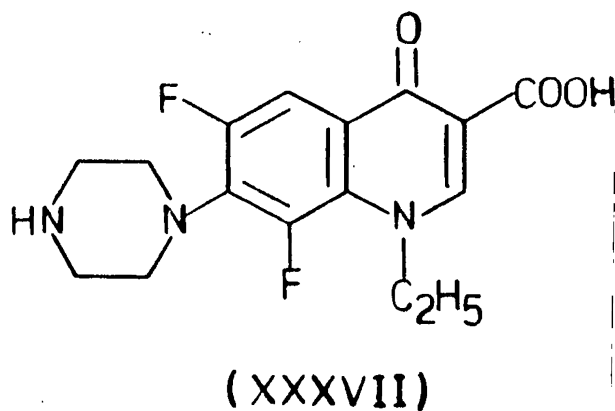
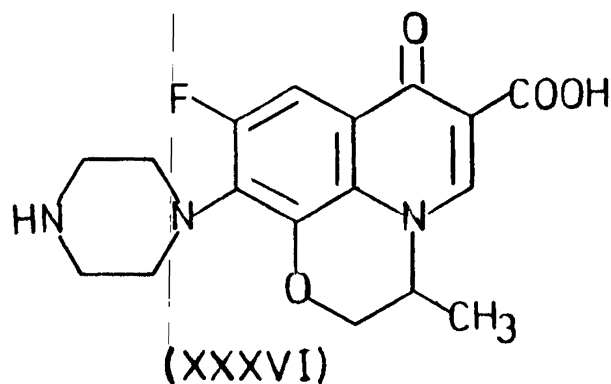
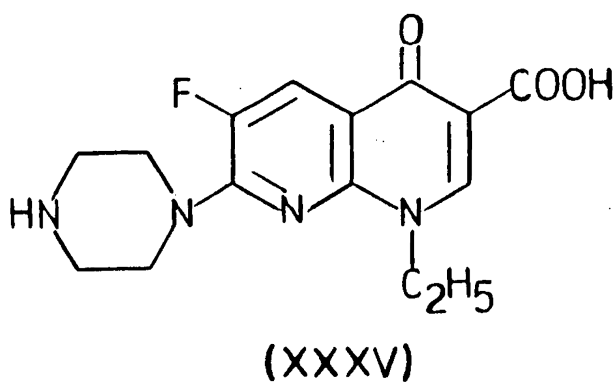
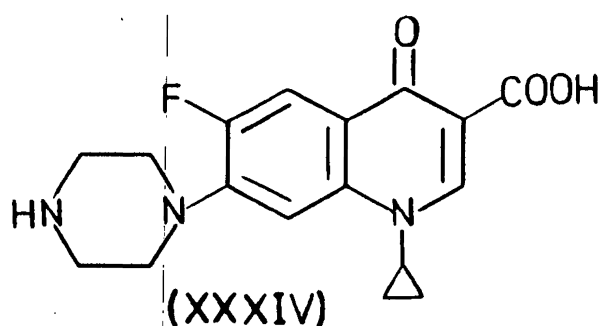
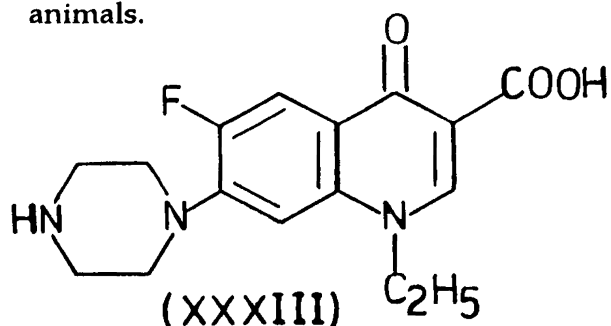
The quinolone carboxylic acids, or 4-quinolones are a group of synthetic antibacterial agents structurally related to nalidixic acid (XXXII). Nalidixic acid is active against Gram-negative bacteria but has little activity against pseudomonas and Gram-positive organisms, because of which bactericidal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

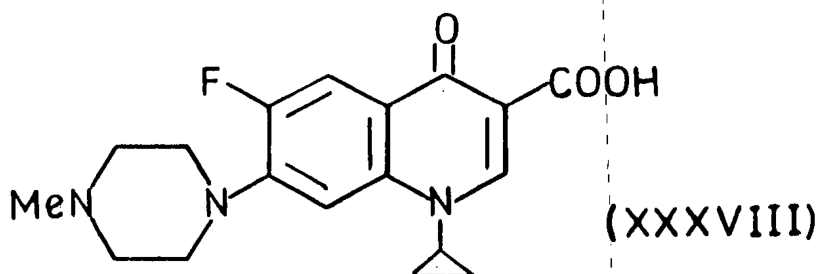
Modification of the structure of nalidixic acid has produced related antibacterial agents such as oxolinic acid, piromidic acid, cinoxacin, and acrosoxacin. None has been considered to represent a significant clinical advance over nalidixic acid.



(XXXII)

Addition of the 7-piperazinyl group and a fluorine atom at position 6 has produced a group of fluoroquinolones with a broad spectrum of activity than nalidixic acid, and are more useful for the treatment of systemic infections. They include norfloxacin (XXXIII), ciprofloxacin (XXXIV), Enoxacin (XXXV), ofloxacin (XXXVI) and lomefloxacin (XXXVII). 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 erosion in immature animals.

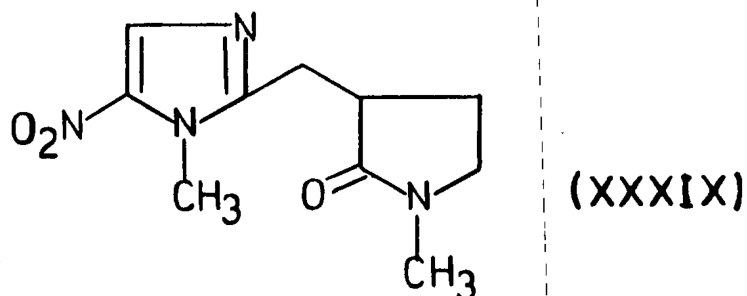




Tefloxacin (XXXVIII) was demonstrated by Y L Chen *et al*²⁵ for activity versus penicillin-resistant staphylococcus, streptococcus and haemophilus. It was itself a β -lactamase inhibitor and displayed synergy with ampicillin.

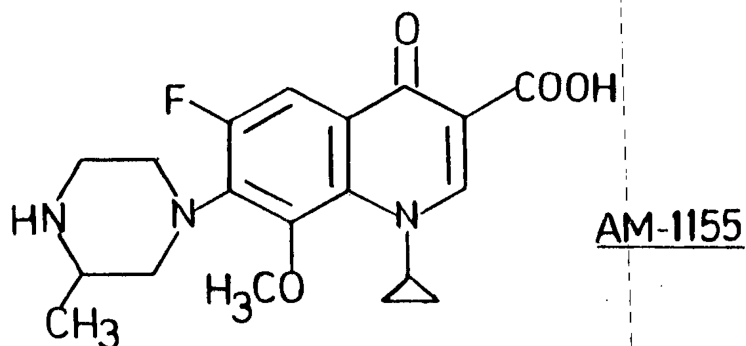
Miscellaneous

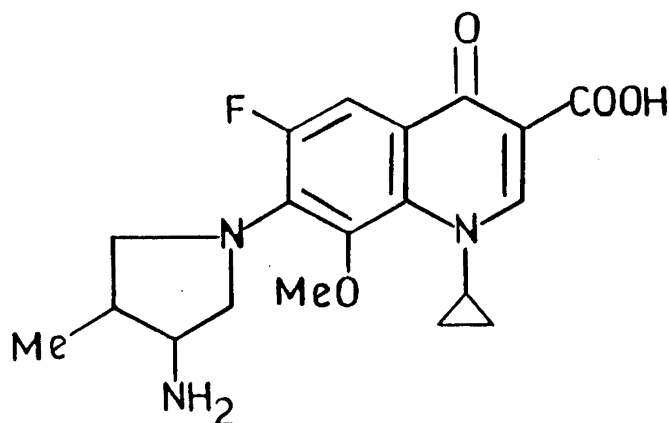
Activity against anaerobic organisms was reported for a series of 2-substituted 5-nitroimidazoles. Compound (XXXIX) was unique in this series, and was found to be more potent both *in vitro* and *in vivo* than metronidazole.



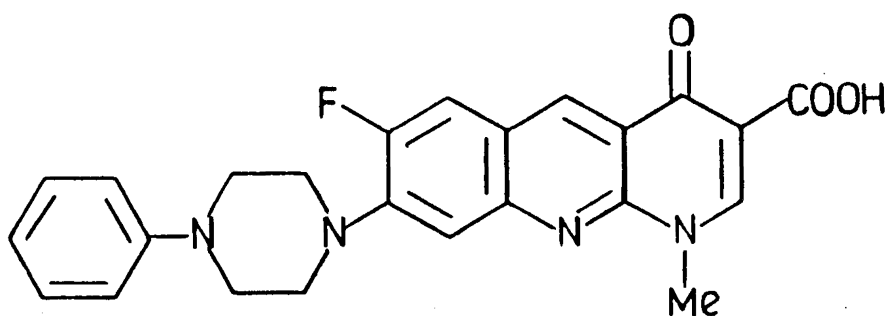
Quinolones

Use of N-cyclopropyl and C-8 heteroatom substituents continued to provide potent antibacterial agents. AM-1155 and AM-1174, new quinolones bearing an 8-methoxy group, outperformed ciprofloxacin against anaerobes and range of Gram-positive bacteria with potency upto 16-62 fold greater than ciprofloxacin²⁶.

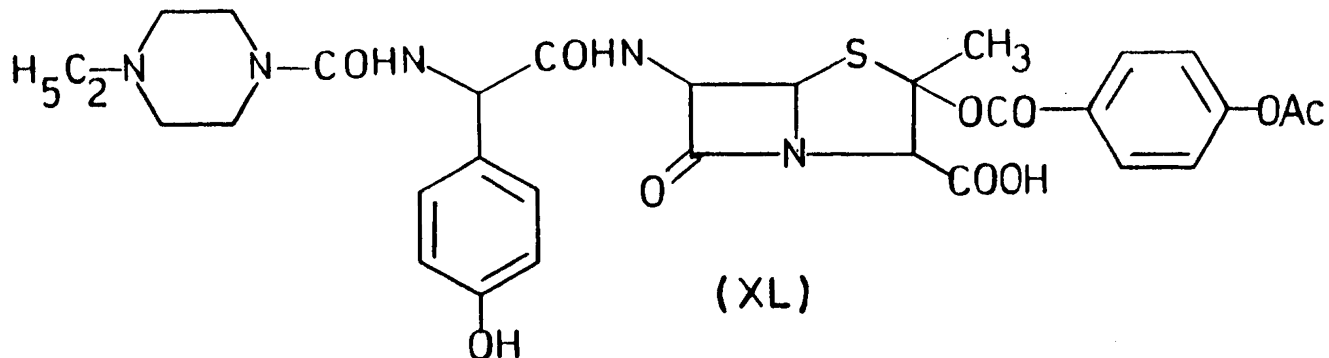


AM-1174

Ru-67829 (a compound in benzonaphthyridine series) was found to be more active against Gram-positive organisms than ciprofloxacin ²⁷.

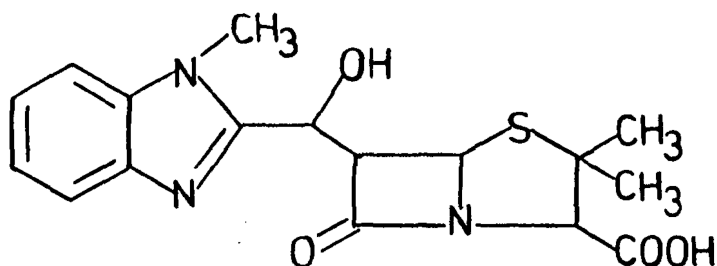
Ru-67829

In penicillins, the catechol-containing compound (XL) had outstanding activity against *Pseudomonas*, and stability to Gram-negative β -lactamases, but not to the lactamases of *S. aureus* ²⁸.



(XL)

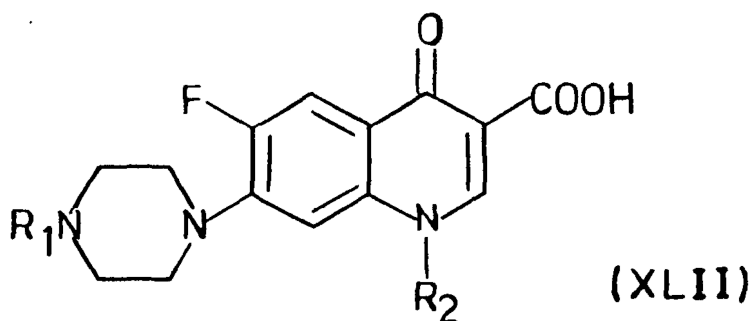
The stability to Gram-positive β -lactamases could be achieved through the use of a (benzimidazol-2-yl)-hydroxy methyl group at the R-position (XLI).



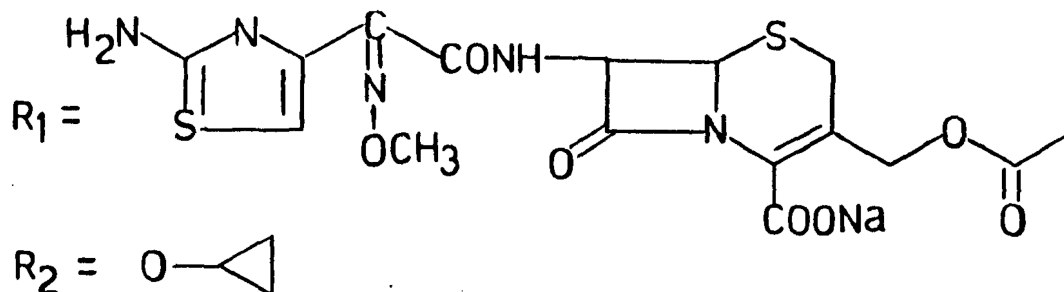
(XLI)

AM-1174 exhibited activity 128 fold that of ciprofloxacin against ciprofloxacin-resistant strains of *S. aureus* ²⁹.

New β -lactum-quinolone hybrids have been reported. The carbamate-linked Ro 24-4383 (XLII) showed broad spectrum activity and exhibited aqueous solubility much greater than that of the quinolone component alone ³⁰.



(XLII)



FUNGAL INFECTIONS

Fungi, like the human host, are eukaryotic organisms, and thus the number of suitable targets for therapeutic attacks 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 profile 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 fungi. Infections, but also to the prolonged survival of patients with global defects in their host defence 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 infections³¹. One yeast-like fungus, *Cryptococcus neoformans*, is reported to be the common of debilitating and life-threatening infections in AIDS patients ³².

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

Allylamine	Triazoles
Naftisine	Fluconazole
Terbinafine	Itraconazole
	Terconazole

Imidazoles	Polyene macrolides
Bifconazole	Amphotericin
Butoconazole	Candididin
Chlormidazole	Hachimycin
Clotrimazole	Hamycin
Econazole	Klatamycin
Enilconazole	Nystatin
Fenticonazole	Pentamycin
Isoconazole	
Ketoconazole	
Miconazole	
Oxiconazole	
Sulconazole	
Tioconazole	

Most of the antifungal agents in the Table are applied topically in the treatment of infections of hair, mucous membranes, nails and skin by *Candida* (Candidiasis), dermatophyte fungi including *Epidermophyton*, *Microsporum*, *Trichophyton* (tinea, ringworm) and *Malassezia furfur*. The main agents which are used in treating these infections are listed below :

Superfacial Fungal Infections	Main Topical antifungal Agents
Candid infections	Azoles, Polyene antifungals
Tinea	Azoles, Ciclopirox, Olamine haloprogin, Tolnaftate
Pityriasis versicolor	Azoles, Ciclopirox, Olamine haloprogin, Tolnaftate

Systemic fungal infections tend to occur in immunocompromised patients and include infections due to *Aspergillus*, *Blastomyces*, *Candida*, *Coccidioides*, *Cryptococcus*, *Histoplasma*. The principal drugs which are used in such infections are listed below :

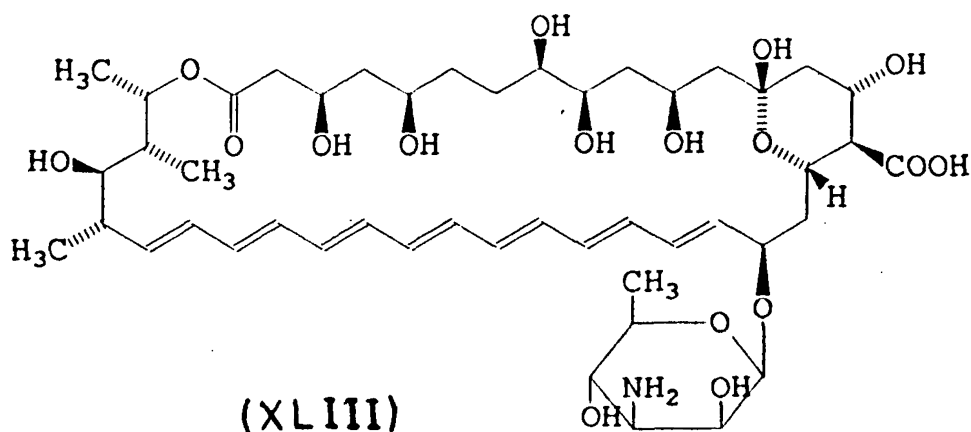
Systemic Fungal Infections	Main antifungal agents
Aspergillosis	Amphotericin
Blastomycosis	Amphotericin, Ketoconazole
<u>Candidal infections :</u>	
Oesophageal	Fluconazole, Ketoconazole
disseminated	Amphotericin with or without Flucytosine
Coccidioidomycosis	Amphotericin, Ketoconazole
Cryptococcosis	Amphotericin with or without Flucytosine, Fluconazole.
Histoplasmosis	Amphotericin, Ketoconazole
Paracoccidioidomycosis	Amphotericin, Ketoconazole

The following pages represent a brief description about major principal drugs which are used in treating fungal infections.

Amphotericin B

It is the first commercially available systemic antifungal drugs, and remains the cornerstone for therapy in critically ill patients with systemic fungal infections. It was first isolated in the 1950's 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 (XLIII). It is amphoteric, forming, soluble salts in both basic and acidic environments.

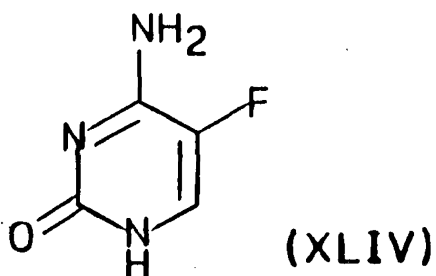
The primary mechanism of action of the polyenes in general and amphotericin B in particular, is due to binding to ergosterol, the principal sterol present in the cell membrane of sensitive fungi ³³.



The formidable effectiveness of amphotericin B is tempered by the variety and frequency of adverse effects. 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

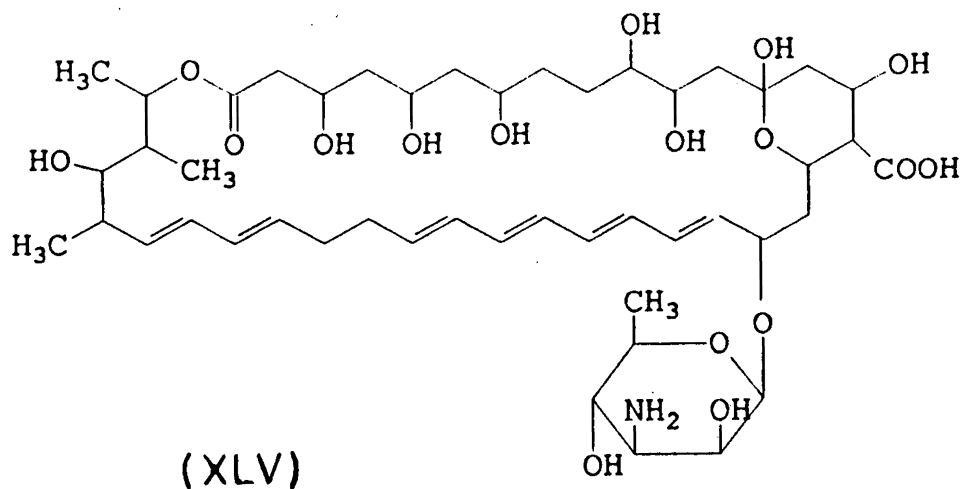
It is a fluorine analogue of cytosine (XLIV), was synthesized in the 1950's as a potential antineoplastic agent. It was found to have *in vitro* and *in vivo* antifungal activity ³⁴. It has been increasing in usage as an adjunct to amphotericin B therapy.



The mechanism of action of Flucytosine are the disruption of protein synthesis by inhibition of DNA synthesis, and alteration of the amino acid pool by inhibition of RNA synthesis. It combines with amphotericin B to exhibit synergistic action in both *in vitro* and *in vivo* systems. It has few side effects. However, it is still in use for treating the infections caused by *Candida albicans*, *Cryptococcus neoformans* and *Torulopsis glabrata*.

Nystatin

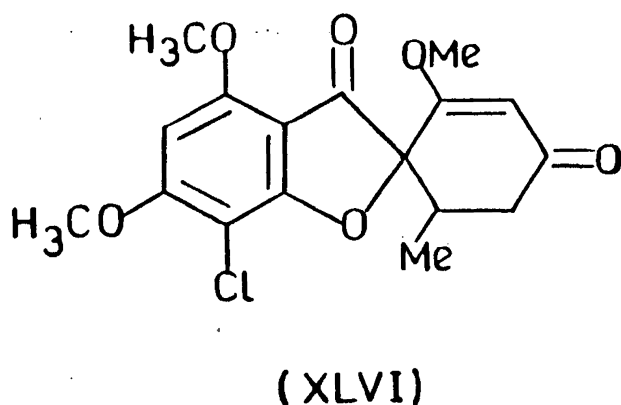
Nystatin (XLV) is produced by *Streptomyces noursei*. It was discovered by Hazen and Brown ³⁵ and possesses good antifungal activity. Toxicity after parental administration to animals has led to its use only topically or orally.



The minimum inhibitory concentration of this drug for *Candida* species, *Cryptococcus neoformans* and the dimorphic fungi causing systemic mucoses is in the range of 1.56- 12.6 µg/mL.

Griseofulvin

Griseofulvin (XLVI) was discovered by Oxford et al in 1939 as a metabolic product of penicillin griseofulvin. Grove predicted its chemical structure in 1950 ³⁶.



As a "cell-wall antibiotic" particularly active on dermatophytes, griseofulvin interferes with biosynthesis of the chitinous elements of the hyphal wall. It has no activity against bacteria, yeasts or actinomycetes and its activity against the fermentous fungi is selective and particularly limited to all species of dermatophytes. No resistant strains are observed among dermatophytes during the treatment with this drug.

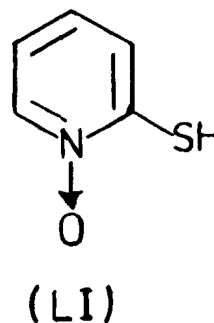
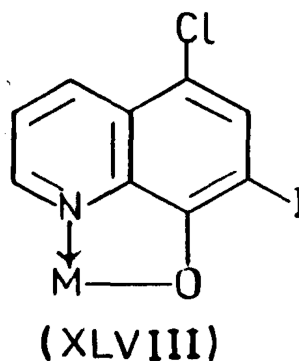
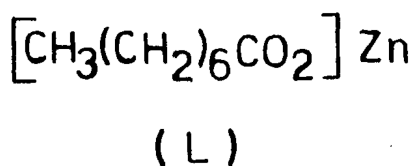
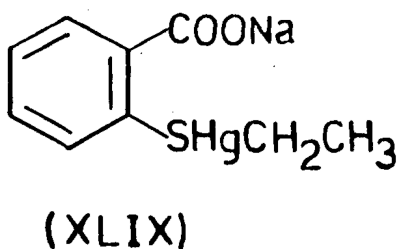
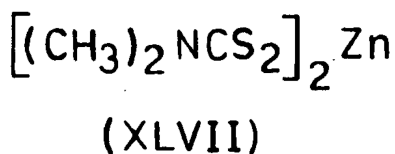
The synthetic antifungal agents

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 and more important is the selective toxicity of the metal.

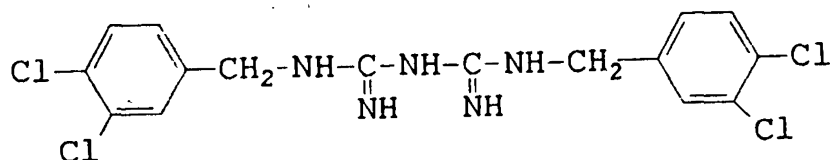
Examples of antifungal compounds that are metal complexes are given below:

Zinc dimethyldithiocarbamate (XLVII), metal complex of 5-chloro -7-iodo-8-hydroxyquinoline (XLVIII), sodium ethyl mercurithio salicylate (XLIX), Zinc caprylate (L) and pyrithione (LI)

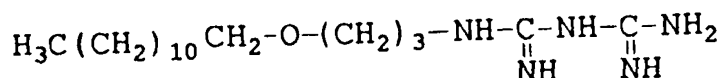


Chelating agents

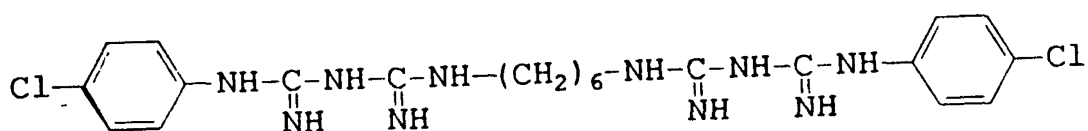
Among chelating agents with considerable in vitro antifungal potency are substituted biguanides as N^1 , N^5 -bis-(3,4-dichlorobenzyl) biguanide (LII) N^1 - γ -lauroxypropyl biguanide (LIII), 1,6-bis-(5-p-chlorophenyl biguanidine) hexane (LIV) ³⁷.



(LII)



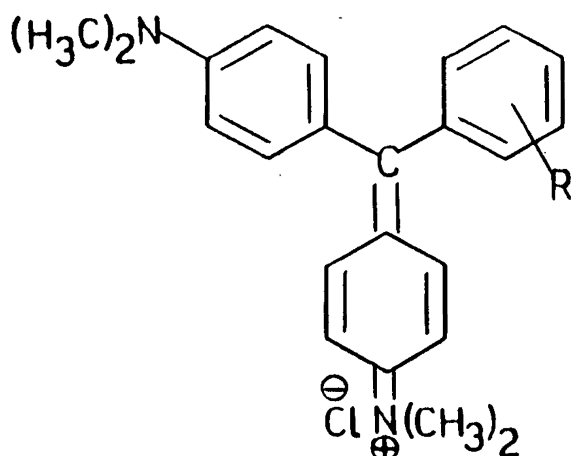
(LIII)



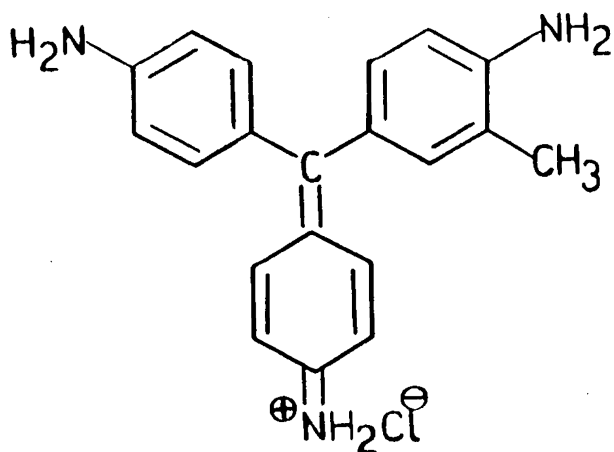
(LIV)

Aniline Dyes

Aniline dyes, such as malachite green (LV), gentian violet (LVI), methyl rosaniline chloride (LVII) have been employed in topical therapy of dermatophytes as well as of Candidiasis of skin and mucous membranes.



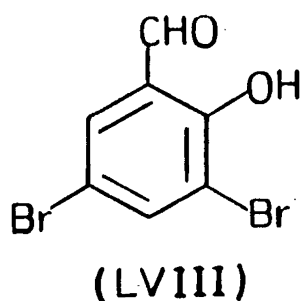
(LV) R = H

(LVI) R = N(CH₃)₂

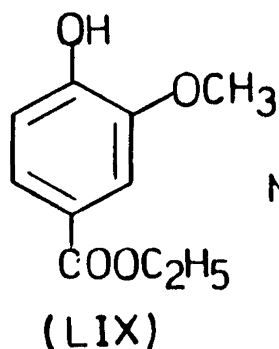
(LVII)

Phenolics and Diamides

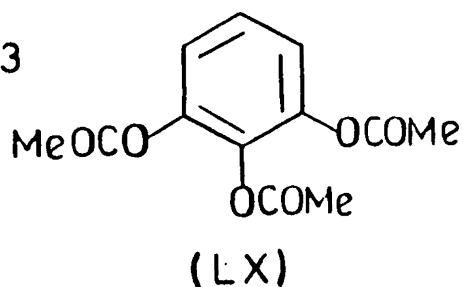
Phenolic compounds were known for their antifungal potency. Among the numerous phenolic compounds that have been used externally for mycotic infections are phenol, phenyl mercuric nitrate, cresol, m-cresyl acetate, benzoic acid, 4-hydroxybenzoic acid, salicylic acid, salicylanilide, 3,5-dibromo salicylaldehyde (LVIII), ethyl vanillate (LIX), pyrogallol triacetate (LX), 3-iodo-2-propynyl-2',4',5'-trichlorophenyl ether (LXI), Halorpogin 1,8-hydroxyanthranol (LXII) and tetrachlorobenzoquinone (LXIII).



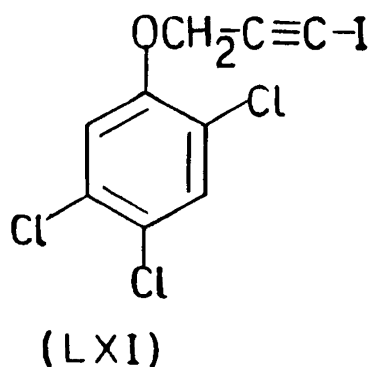
(LVIII)



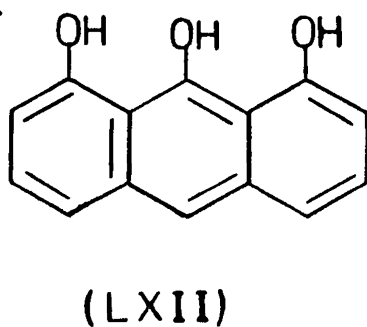
(LIX)



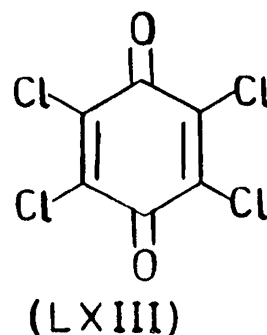
(LX)



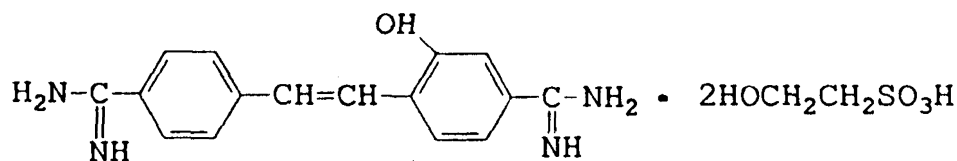
(LXI)



(LXII)



(LXIII)

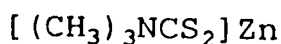


(LXIV)

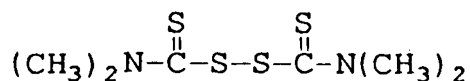
Several biamidines (e.g. stibamidine, propamidine, pentamidine) are antifungal *in vitro* . 2-Hydroxystilbimidine diisothionate (LXIV) has been successfully employed in patients with blastomycosis. It is less toxic than amphotericin B ³⁸.

Sulfur containing molecules as antifungal agents

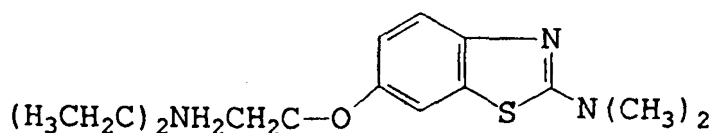
A variety of organic compounds that contain divalent sulfur attached to carbon atom have *in vitro* fungistatic action, and many of these have been employed in topical therapy of dermatophytoses. Among these, are dithiocarbamates (LXV), tetraethylthiuram disulfide (LXVI) and benzothiazoles such as 6-(*b*-diethylaminoethoxy)-2-dimethyl amino derivatives (LXVII) ^{39,40}.



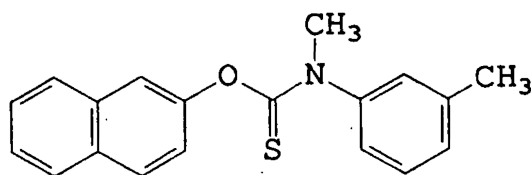
(LXV)



(LXVI)



(LXVII)

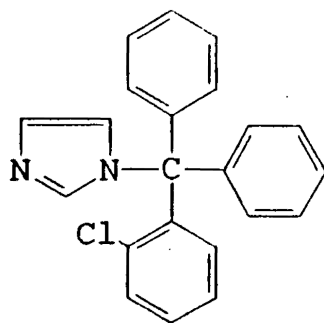


(LXVIII)

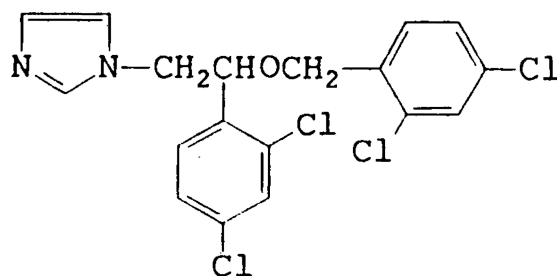
A widely used compounds with unusually high *in vitro* and *in vivo* activity against the dermatophytes is 0-2 naphthyl ester of *m*-N-dimethylthiocarbanilic acid (LXVIII) (Tolnaftate). It is also effective against candidal lesions ⁴¹.

Imidazole Antifungals

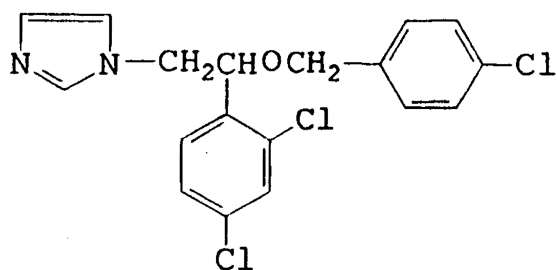
Among all the imidazole compounds, three distinct compounds are actually therapeutic antifungals with very wide spectra against yeast and filamentous fungi. They are clotrimazole (LXIX), Miconazole (LXX) and econazole (LXXI).



(LXIX)



(LXX)



(LXXI)

Clotrimazole (LXIX) was developed by investigators of the Bayer Laboratories in 1969, and is utilized topically in superficial mycoses or orally in clinical trials in deep mycoses⁴².

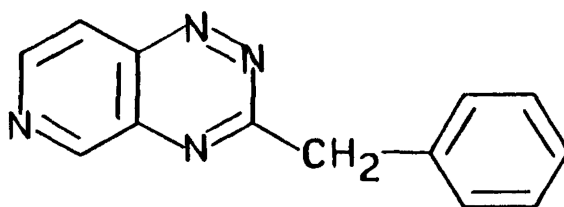
Miconazole⁴³ (LXX) is a well known antifungal drug developed by the investigators of Janssen Pharmaceuticals in 1969. It is utilized topically in superficial mycoses and by oral, intravenous routes in deep mycoses in clinical experimental trials .

Econazole (LXXI) is a phenethyl imidazole derivative. Like Miconazole, it is utilized as topical agent in superficial mycoses and as a systemic antifungal by oral and intravenous routes in deep mycoses ⁴⁴.

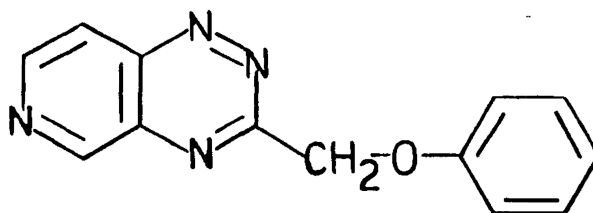
The mode of action studied by Preusser ⁴⁵ on *Candida albicans* and *Trichophyton rubrum* shows that at concentration as low as 1.1×10^{-7} M alterations on the cellular membranes and lysis of the intracytoplasmic organelles, occurred with decomposition of ribosomes .

Miscellaneous

Some pyridotriazines, Triafungin (LXXII) and oxyfungin (LXXIII) have been described as antifungal agents by Wright ^{46,47}.



(LXXII)



(LXXIII)

TRIAZOLES

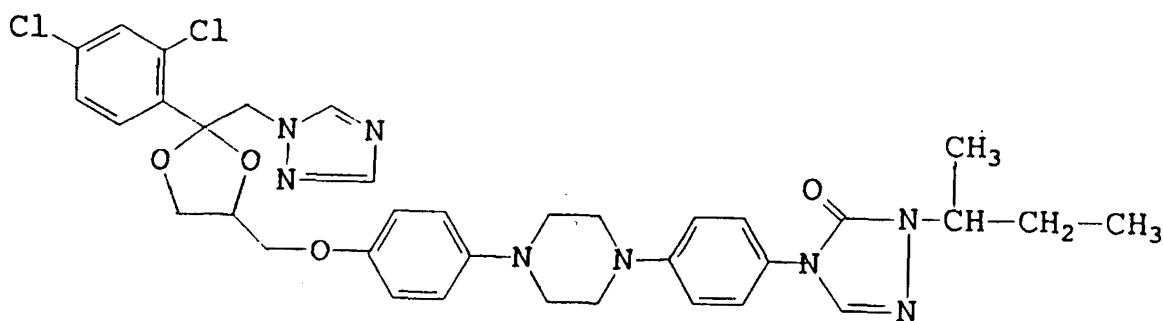
The substitution of the triazole ring for the imidazole ring offers many advantages to these newer azoles ⁴⁸.

- 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 are recently been licensed or are currently being developed and tested.

Itraconazole

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



(LXXIV)

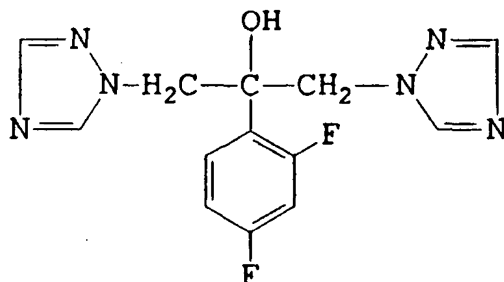
When compared with ketoconazole, its potential advantages include a broader spectrum of activity (including *Aspergillus spp.* and *sporothrix schenckii*), a more desirable pharmacokinetic profile and less toxicity ⁴⁹.

Most of the adverse reactions reported are transient and include gastrointestinal disturbances, dizziness headache, depressed libido (with normal testosterone levels) and leucopenia ⁵⁰.

Fluconazole

Fluconazole (LXXV) 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 comparable activity to that of ketoconazole in inhibition of fungal C-14 demethylase.



(LXXV)

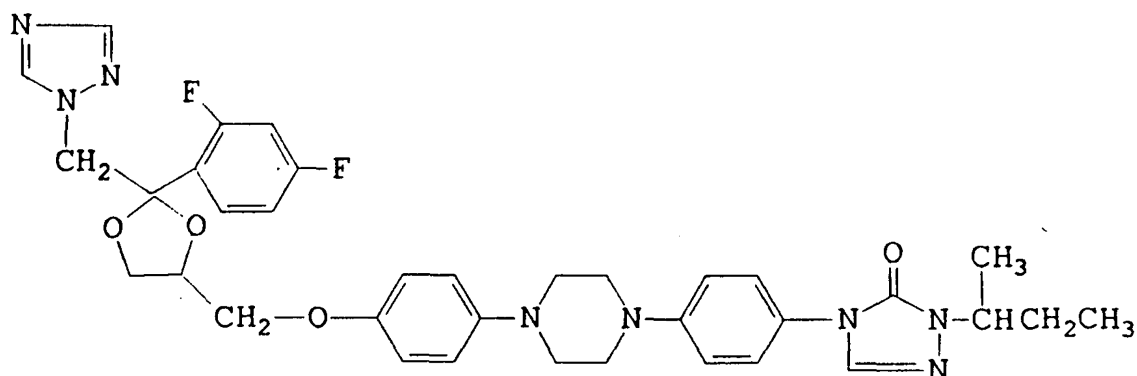
A major point of confusion during the development of this drug, however, has been its relatively low activity *in vitro* compared with its high *in vivo* activity.

It possess 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 G.I. symptoms and elevation in hepatic transaminases have been reported in 5 % of patients receiving the drug ⁵¹. Fluconazole is also a potential candidate for prevention and early treatment of disseminated Candidiasis in granulocytopenic patients ⁵².

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

Saperconazole

Saperconazole (LXXVI) is water soluble, lipophilic fluorinated triazole with similar chemical structures to itraconazole, with two chlorine atoms replaced by fluorine.



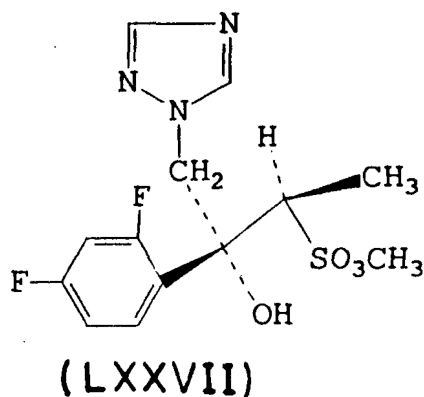
(LXXVI)

It has a broad spectrum of antifungal activity including the dimorphic fungi, *Phacohyphomycetes*, *Cryptococcus* spp. and *Aspergillus* spp.⁵³.

OTHER AZOLES

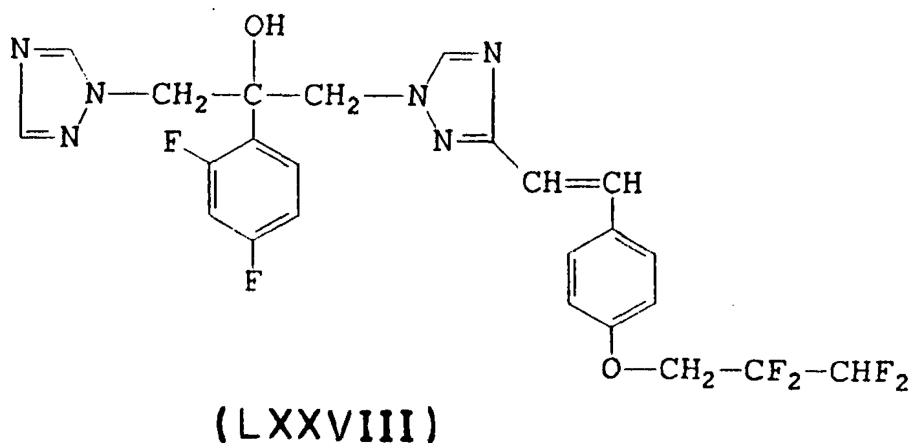
SCH 39304

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



The potent broad spectrum *in vivo* activity of SCH 39304 against *Candida*, *Aspergillus*, *Cryptococcus*, *Blastomyces*, *Coccidioides* and *dematiaceous* moulds held 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

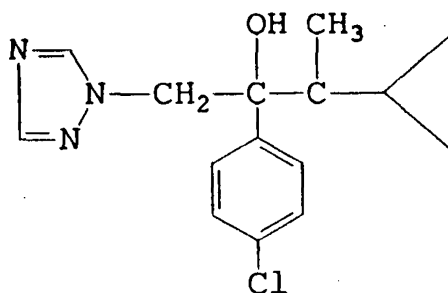


ICI 195739 (LXXVIII) is an orally active bis-triazole with broad spectrum antifungal activity.⁵⁴

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 drug⁵⁵.

SDZ 89-845

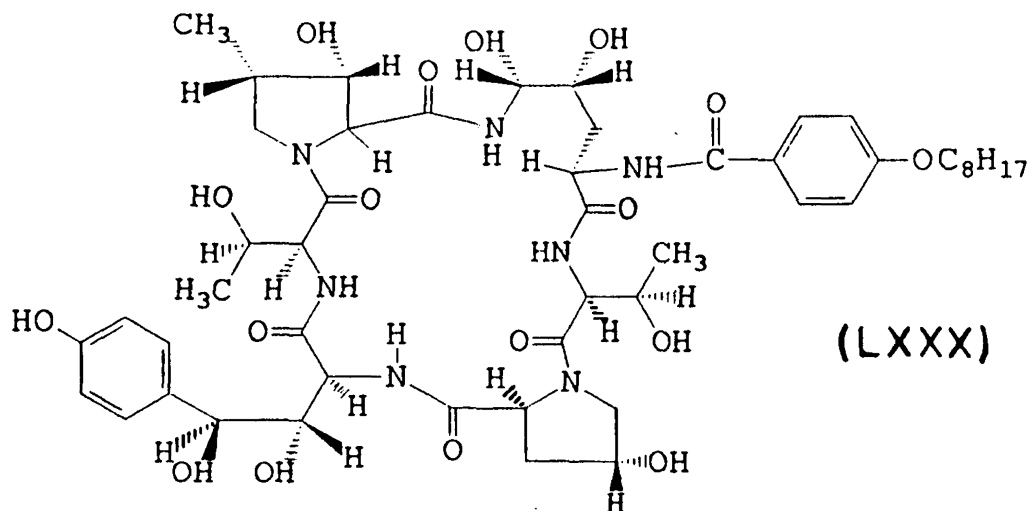
SDZ 890845 (LXXIX) is a triazole antifungal agent that has shown activity in a number of animal models of superficial and systemic fungal infections⁵⁶.



(LXXIX)

LY-121019 (Cilofungin)

Cilofungin (LXXX) is a semisynthetic lipopeptide derived from Echinocandin B by the enzymatic removal of its linoleoyl side chain and chemical replacement with a 4-n-octyloxy-benzoyl group⁵⁷.



(LXXX)

It has a narrow spectrum of antifungal activity limited to *Candida spp.* Specially *C. albicans* and *C. tropicalis* ⁵⁸.

Unfortunately LY-121019 has been withdrawn from clinical trials because of related toxicities. The carrier for the drug is polyethylene glycol which has been shown to cause metabolic acidosis ⁵⁹.

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 and some forms of treatment being consequently less often successful than others. Moreover, microbic 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 and diffusibility into remote areas etc. which, desirable, sometimes lack in useful drugs.

Subsequently, there have been immense advances in 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 empirical, in the field of chemotherapy although sometimes based on reasonable theoretical expectation.

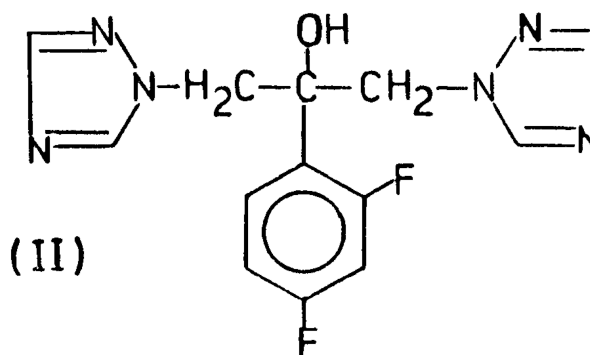
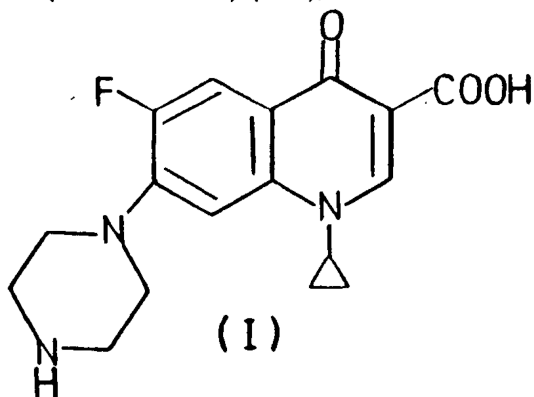
A line of advance other than the discovery of new drugs is the adaptation of old ones. An outstanding example of what can be achieved in this way is presented by the sulfamides. Similar efforts in the field of antibiotics have given fruitful and encouraging results. Most of these changes are produced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

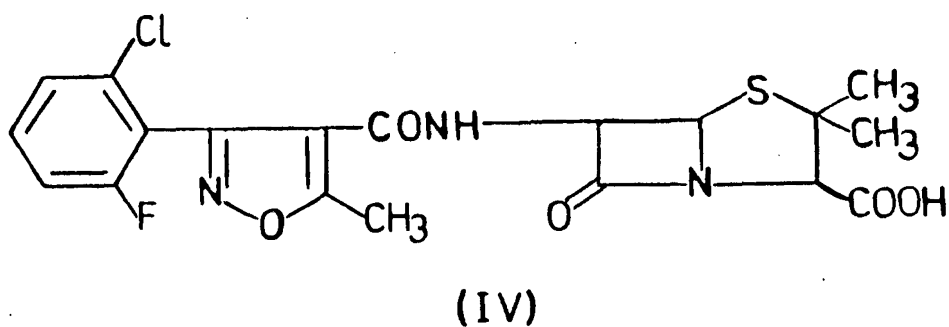
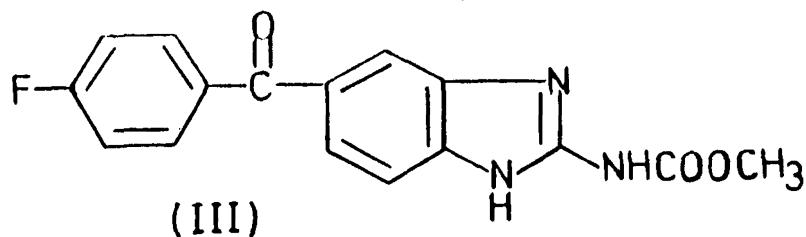
The logic supporting the work presented in this thesis was formulated, bearing in mind the biological activities of known moieties and attempting certain structural modifications or adaptations in light of the recent trends in drug research in incorporating newly emerged pharmacophores on existing moieties.

Extensive biological investigations of organo fluorine compounds during the past few decades have been rapidly translated into useful applications in the field of medicinal chemistry ⁶⁰. The interest in the fluorine containing compounds which hopes to alter the pharmacological properties of drugs for the better is based primarily in the following considerations.

1. Fluorine, the second smallest 'atom' as measured by atomic radius and internuclear distance to carbon would most closely resemble bioactive hydrogen analogues with respect to steric requirements at enzyme receptor sites.
2. Fluorine imparts increased oxidative and thermal stability because the binding energy of the carbon - fluorine bond exceeds that of the carbon-hydrogen bond by over 17 Kcal/mol.
3. Fluorine leads to increased lipid solubility in membranes that would enhance the rate of absorption and *in vivo* transport. In this regard, the trifluoromethyl group is amongst the most lipophilic of all substituents.

Numerous fluorinated compounds are presently in therapeutic use viz. Ciprofloxacin (antibacterial) (I), Fluconazole (antifungal) (II), Flubendazole (anthelmintic) (III), Flucloxacillin (antibacterial) (IV).





Considering the biological importance of fluoro compounds and various bioactive moieties, few series of compounds have been synthesized with fluorine incorporated substituents/moieties as mentioned below.

PART - II

Synthesis of 5,6 - Disubstituted 2 - (alkyl/substituted aryl) amino Benzothiazoles

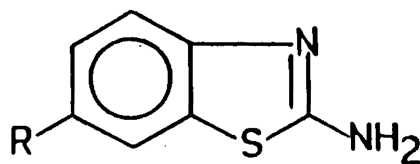
Among the various types of known heterocyclic ring system, benzothiazole nucleus was found to be present in various medically important compounds having antiparasitic^{61, 62}, antibacterial^{63, 64}, antiviral⁶⁵, antitubercular^{66, 67} and antifungal ⁶⁸ activity.

2-Amino-6-substituted benzothiazoles are known to exhibit excellent antibacterial activity. According to Mayer's hypothesis ⁶⁹ " a morphological relationship between mycobacteria and fungi may be parallel by a biochemical relationship" i.e. substances acting as antifungal agents are likely to exhibit antitubercular activity also.

Zarapakar and Nargund ⁷⁰ reported that some benzothiazole derivatives possess excellent antitubercular activity which range upto 0.1 to 0.04 µg/ml *in-vitro*.

During the investigation of the effect of various heterocyclic ring system on mice infected with various influenza virus strains, it was found that the 2-

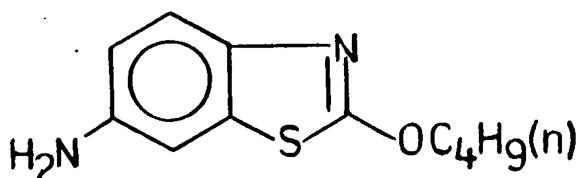
amino-6-substituted benzothiazoles of the type (V) when administered intraperitoneally to the mice gave protection to the mice quite comparable to the aminoadamantane⁶⁵ when substituents in the above benzothiazole moiety are (R = Cl, Br), they exhibit activity at a dose level of 0.5 µg/mice.



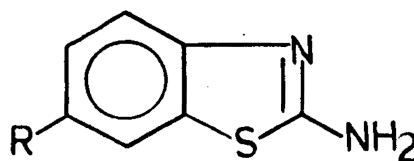
(V)

R = Cl, Me, Br

2-Butoxy-6-amino benzothiazole (VI) showed anti-tuberculosis activity at 0.02 µg/ml *in-vitro*⁷¹ testing. Similarly, 2-amino-6-substituted benzothiazoles of the type (VII) showed minimum inhibitory concentration at 2.5 µg *in-vitro*⁷².



(VI)

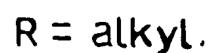
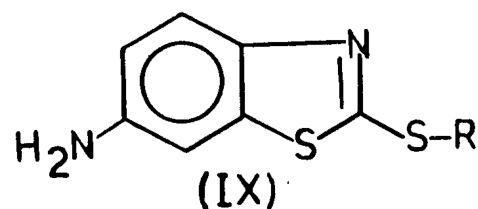
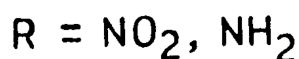
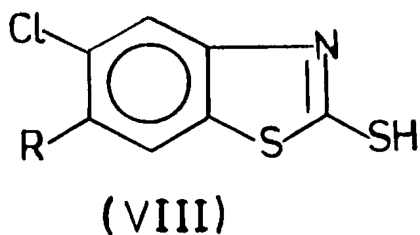


(VII)

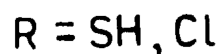
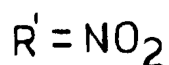
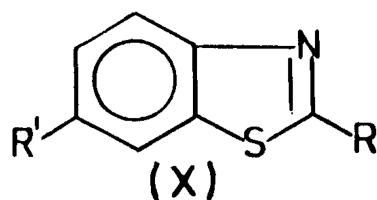
R = NO₂, NH₂

Literature search revealed that 2-mercapto-5,6-disubstituted benzothiazoles (VIII) exhibited *in-vitro* antituberculosis activity at the concentration of 0.2 to 0.4 µg/ml on testing⁷³.

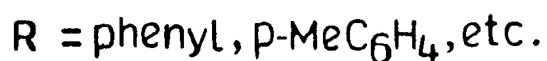
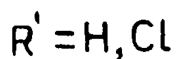
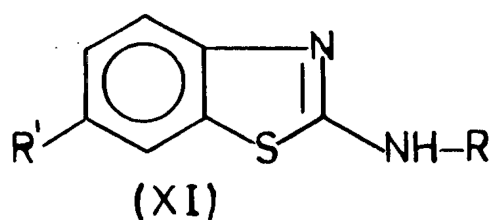
Also 2-alkylthio-6-amino benzothiazole (IX) were also reported to have good antituberculosis activity⁷¹.



Mackie *et al* ⁷⁴ screened large number of 2 and 6-substituted benzothiazoles against liver flukes and they have concluded that 2-chloro and 2-mercapto-6-nitro benzothiazole of type (X) were most effective.

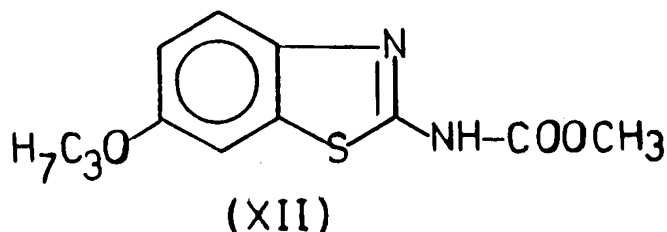


Remarkable advances had been achieved in bactericidal and fungicidal field by introducing an anilino linkage in the benzothiazole derivatives, e.g., 2-substituted anilino benzothiazoles (XI) are useful as bactericides and fungicides ⁷⁵.

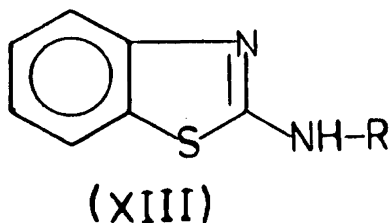


Among the various heterocyclic benzothiazolyl carbamates, Panitz *et al* ⁷⁶ have reported significant anthelmintic activity for Tioxidazole (6-propoxybenzothiazole-2-methyl carbamate) (XII). Particularly, it is active against *Syphacia obevelate*

and *Nematospiroides dubius* in mice at the dose level of 75 mg/kg. It is also active against hookworm and *Trichuris trichiura* in dog at the dose level of 200 mg/kg.

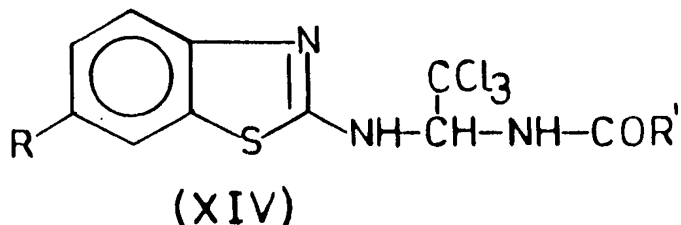


2-Substituted anilino and 2-alkylamine benzothiazoles (XIII) reported from our laboratory, showed promising *in vitro*⁷⁷ activity against *M. tuberculosis* at the dose level of 3.12 µg/ml.



R = alkyl, substituted aryl

Recently Mikulasek S. *et al*⁷⁸ have reported some 2-substituted amino benzothiazoles (XIV) as antimycobacterial agents. The activity of these compounds is comparable to that of isoniazide with lower toxicity.

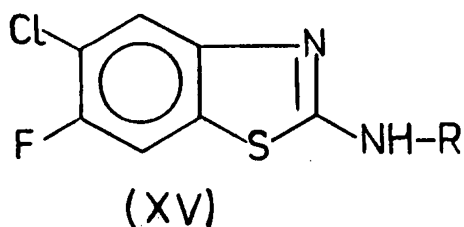


R = Cl, Br

R = H, Me, Ph, etc.

Taking lead from these known facts, it was proposed to synthesize the 5-chloro, 6-fluoro-2-substituted amino benzothiazoles (XV) which were studied for their antifungal, antibacterial and antituberculosis activity. These compounds were synthesized by refluxing the substituted *o*-amino thiophenol with substituted aryl

and alkyl isothiocyanates in non-polar high boiling solvents. They have the following general structure .

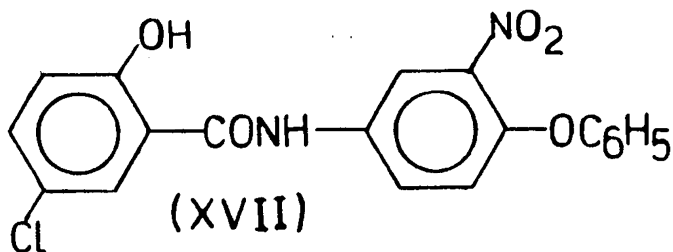
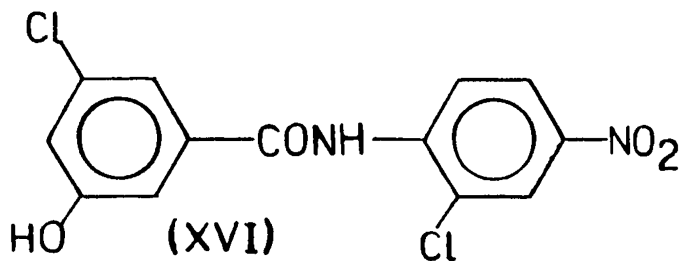


R = alkyl, substituted aryl.

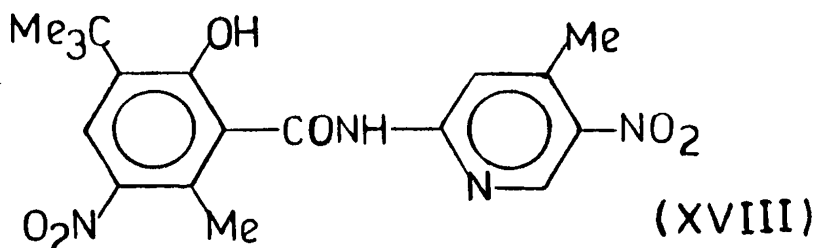
PART - III

Synthesis of 5, 6 - Disubstituted 2 - (substituted phenyl carboxamido) Benzothiazoles.

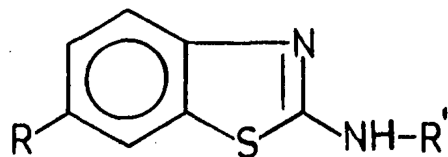
Moderate activity was claimed for 5-chloro-salicylanilide derivative as anthelmintic and antibacterial agent ⁷⁹. The acid amido linkage was found to be responsible for various kinds of activity as seen from the following examples, Niclosamide ⁸⁰ (XVI) a 5-chlorosalicylanilide derivative, is a drug of choice in the treatment of cestodes. Another salicylanilide derivative (XVII) was found to be effective against penicillin resistant *S. aureus* at minimum inhibitory concentration of 0.00609 µg/ml ⁷⁹.



The third compound substituted pyridylamide (XVIII) showed activity against *F. hepatica* ⁸¹.



The 6-substituted-2-substituted benzothiazolyl amido derivative (XIX) showed good activity against *streptococcus* S-86 at 25 µg/ml concentration ⁸².

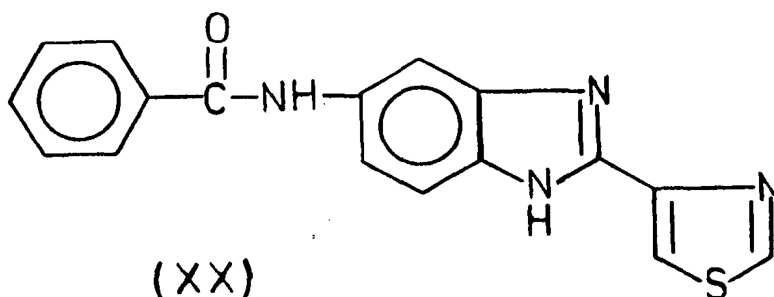


(XIX)

$R = \text{Cl}, \text{NO}_2$

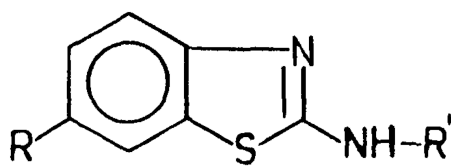
$R' = 4\text{-CH}_3; \text{C}_6\text{H}_4\text{SO}_2; 3,5(\text{NO}_2)_2\text{C}_6\text{H}_3\text{CO}$

D.A. Denham *et. al* ⁸³ reported the excellent antifilarial activity of 5-benzamido-2-(4-thiazolyl) benzimidazole (XX).



(XX)

2-Substituted benzamido benzothiazoles are useful as bacteriocides and fungicides. Benzothiazole is a well known established antifungal as well as bactericidal moiety in fat, paraffin and rubber industries ⁷⁵. The amido linkage is much important for retaining the activity in the lead molecule (XXI).

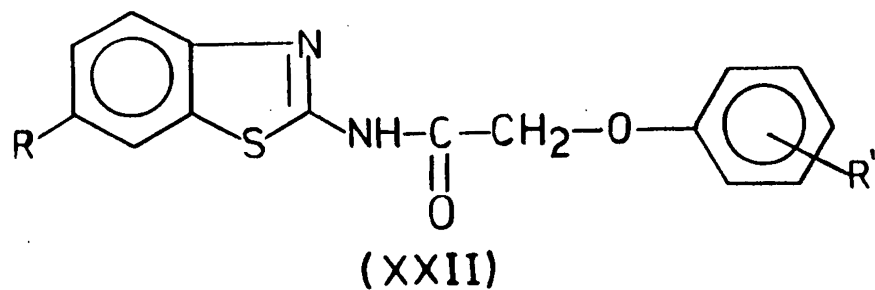


(XXI)

$R = \text{Cl H}$

$R' = 4\text{-Cl C}_6\text{H}_4\text{CO-}$

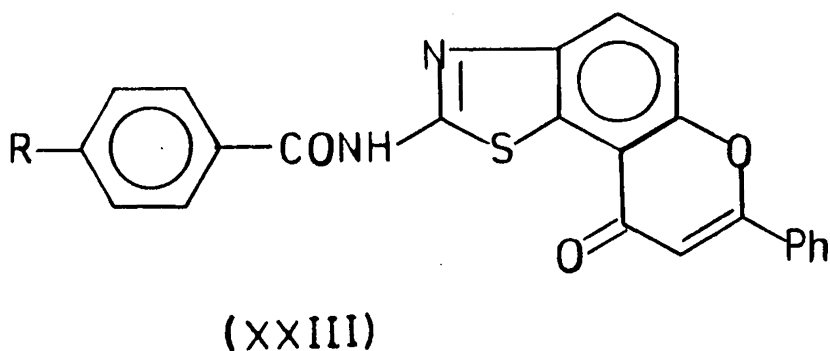
Lacova M *et al* ⁸⁴ have reported compounds of type (XXII) as having good biological activity.



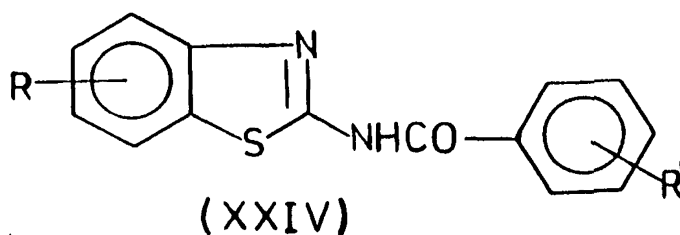
R = Me, Cl

R' = H, Cl

Very recently, Mantripragada Narayenu Sambaiah Thote ⁸⁵ have reported a lead compound (XXIII) containing the benzothiazole moiety and having benzamido substitution in position -2.



All the above examples indicate the importance of the amido linkage in biologically active moieties. Taking into account above facts and the biological importance of fluorine substitution in molecule it was thought worthwhile to synthesize molecule where the active benzothiazole moiety is substituted in position -2 with various fluorine substituted benzamido group. The general structure of the compounds is given below (XXIV). The compounds were studied for antifungal, antibacterial, antitubercular and anthelmintic activity.



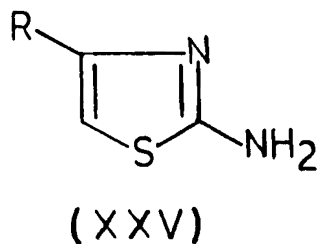
$R = H; 5\text{-Cl}, 6\text{-F}; 5,6\text{-DiCl}$

$R' = 2\text{-F}; 3\text{-F}; 2,6\text{-DiF}; \text{etc}$

PART - IV

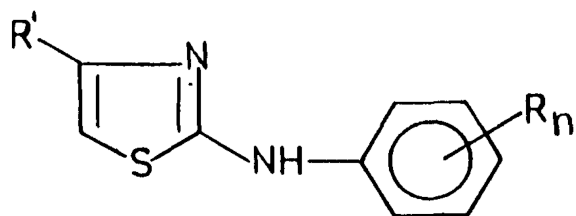
Synthesis of 2-substituted arylidine hydrazino 4-aryl Thiazoles.

In 1965, Romanian research workers Carp *et al*⁸⁶ showed that amino substituent at 2-position of the thiazole molecule (XXV) along with alkyl or substituted aryl group at 4-position imparts bacteriostatic activity to the thiazole molecule.



$R = 4\text{-CH}_3\text{C}_6\text{H}_4, 4\text{-NH}_2\text{C}_6\text{H}_4,$
 $4\text{-ClC}_6\text{H}_4, \text{etc.}$

S.P. Gupta *et al*⁸⁷ have reported that fungitoxicity of 2-aminohalogenonitrophenyl thiazole (XXVI) depends on both thiazole ring as well as on the presence of the phenyl ring. Both halogen and nitro group increases the fungitoxicity when placed in either ortho or para position of the phenyl ring. The phenyl group substituted at 4-position of thiazole ring increases the fungitoxicity in comparison to methyl group. Some of the compounds are found to be active against *Helminthosporium sativum*, *Alternaria tenuis*, *Aspergillus niger* and *Fusarium oxysporium*.

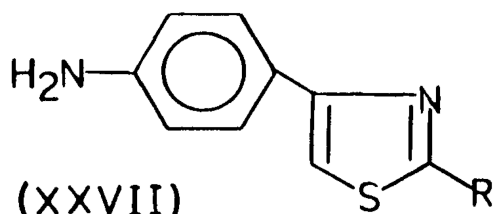


(XXVI)

$R = \text{Halogeno, Me, NO}_2. \quad (n = 2, 3 \text{ or } 4)$

$R' = \text{CH}_3, \text{C}_6\text{H}_5$

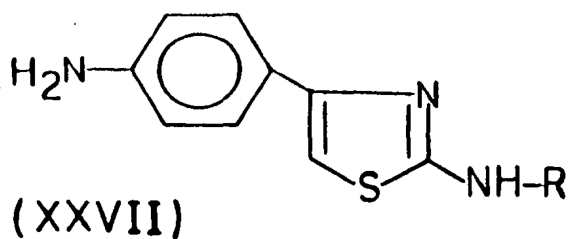
Malvankar *et al*⁸⁸ found that thiazole compound (XXVII) incorporating aryl, substituted aryl group at 4 and 2-position show good antitubercular activity.



(XXVII)

$R = \text{alkyl, aryl, substituted aryl}$

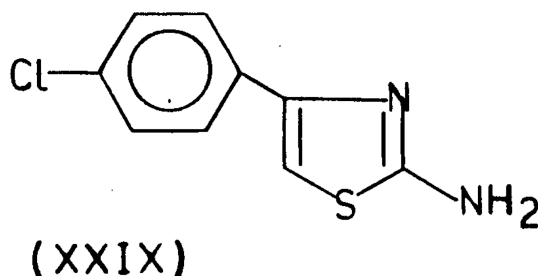
D. B. Ingle *et al*⁸⁹ have synthesized thiazole derivatives of the following types (XXVIII). However, no biological activity results have been reported by the authors.



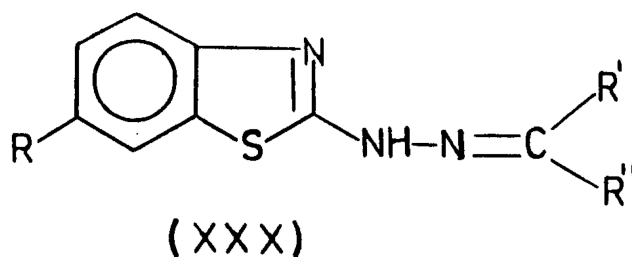
(XXVIII)

$R = \text{Phenyl, 2-Pyridinyl, etc.}$

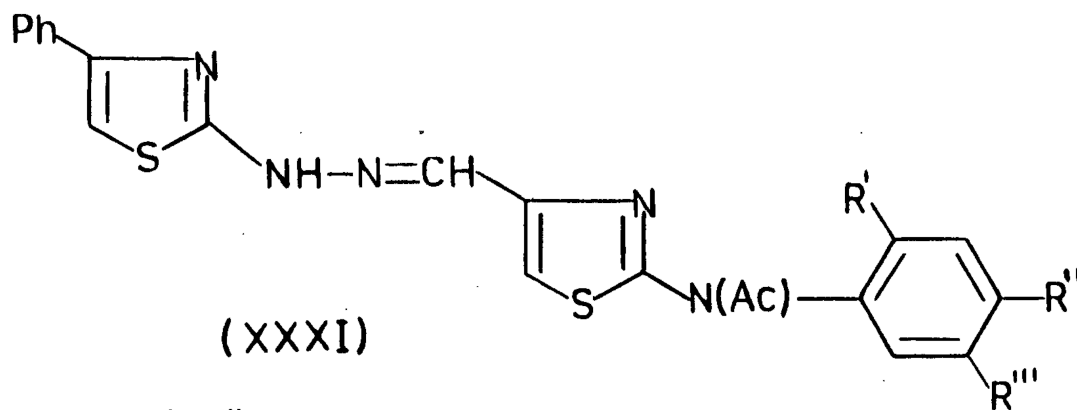
S. K. Singh and associates ⁹⁰ have prepared 2-amino-4-(4-chlorophenyl)thiazole (XXIX) and reported it to inhibit growth of *Trichophyton mentagrophytes* at 25 µg/ml.



In 1993 Zhou *et al* ⁹¹ have reported compounds of type (XXX) which are active against *S. aureus*.

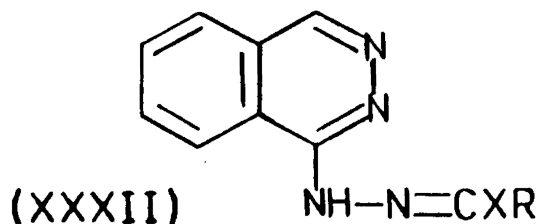


In the same year Likhate *et al* ⁹² have reported 2-substituted thiazolyl hydrazones (XXXI) which are active against *Salmonella typhosa*, Gram positive and Gram negative bacteria.



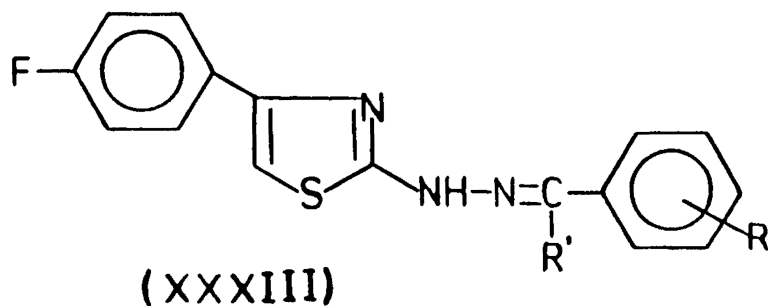
$R', R''' = H, Cl$
 $R'' = H, Cl, Me, \text{etc.}$
 $R', R'', R''' = \text{aryl.}$

Recently, Hydrazones of type (XXXII) have been reported by Shah R.G. *et.al.*⁹³ as possessing antimicrobial activity.



R = (un)substituted phenyl, 1 naphthyl

Careful study of above compounds exemplifies the pharmacophoric importance of the 2,4-disubstituted thiazole moiety and also the presence of the hydrazine linkage in various antimicrobial agents. In view of the above findings a series of 2-substituted arylidine hydrazino 4 - aryl Thiazoles were synthesized having following general structure (XXXIII) and screened for their antifungal, antitubercular and antibacterial activity.



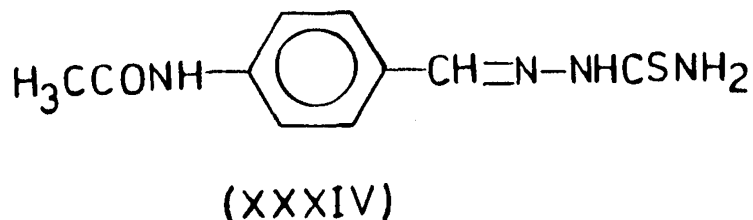
R = 2-F, 3-F, 4-F, etc.

R' = H, CH₃.

PART - V**Synthesis of 3/4 [(Substituted phenyl) 1 - methyl - ene] amino 1,2,4
Triazole**

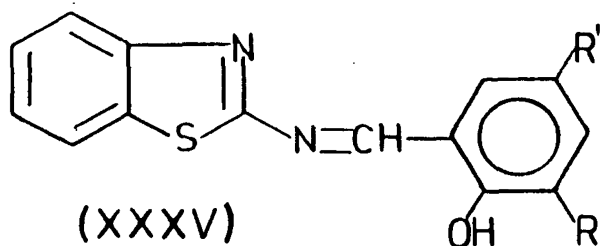
The presence of azomethine linkage in compounds has been known to decrease their toxicity considerably ^{94, 95} Schiff bases from 5-chlorosalicylaldehyde, 5-bromosalicylaldehyde, and 4-N,N-dimethylamino benzaldehyde have shown encouraging antituberculosis activity *in vitro* ^{96, 97}.

The thiosemicarbazone of 4-acetamido benzaldehyde, Thiacetazone (XXXIV) was introduced for the treatment of tuberculosis in 1950.



This was the first synthesized drug that approached the activity of streptomycin in experimental infection in animals ^{98, 99, 100}.

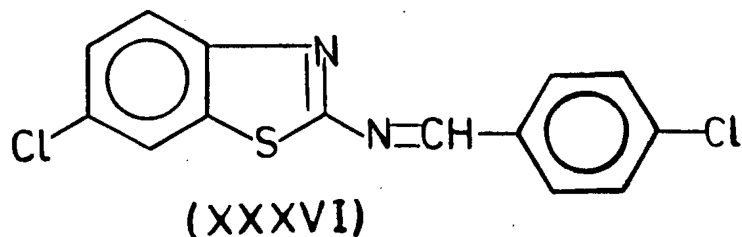
Some schiff bases in the benzothiazole series (XXXV) have been synthesized and their physico-chemical properties were so far studied ¹⁰¹.



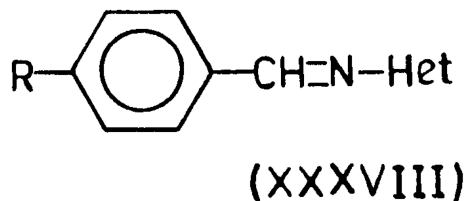
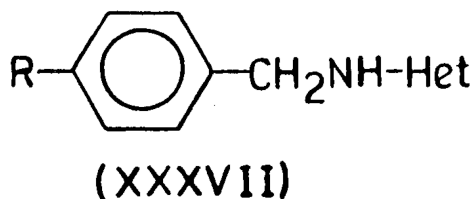
R = OMe, H

R' = H, Br, NO₂

Takahiro Yabuchi *et al*¹⁰² reported the synthesis of N-(*p*-chlorobenzylidene)-2-amino-6-chlorobenzothiazole (XXXVI) and it has got antimicrobial activity.

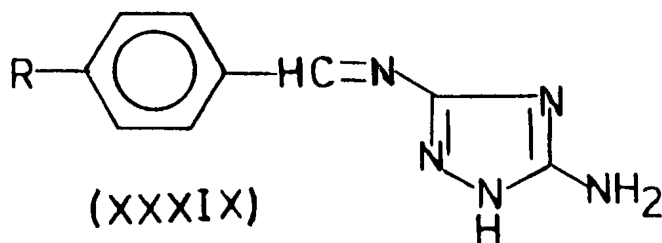


Recently, R. Fioravanti *et al*¹⁰³ have reported antimicrobial properties of some new hetero aryl benzyl amines (XXXVII) and their schiff bases (XXXVIII).



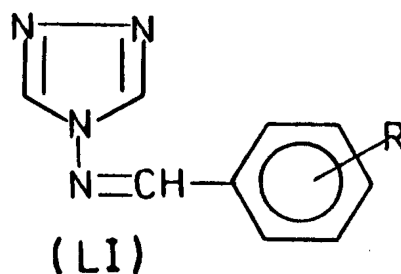
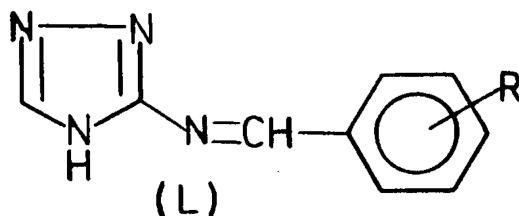
R = H , CH₃, Br, etc

The azomethine linkage is known to impart biological activity to various heterocyclic moieties e.g. Straukas J. *et al*¹⁰⁴ have reported anti-inflammatory activity of triazole schiff bases (XXXIX) .



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

Taking into account the pharmacophoric importance of triazole in various recent line of antifungal drugs, fluconazole, itraconazole, saperconazole and the importance of azomethine linkage that imparts antimicrobial activity, Schiff bases of 3/4 amino triazoles were synthesized which have following structures (L, LI). They were tested for their antifungal, antibacterial antitubercular activity.



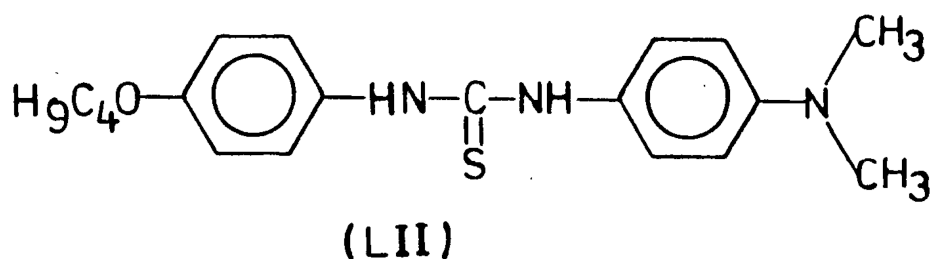
R = 2-F, 3-F, 4-F, etc.

PART - VI

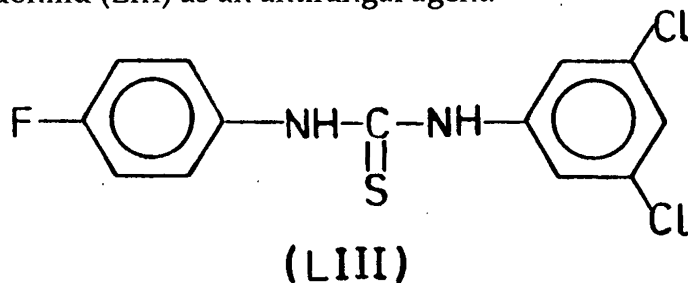
Synthesis of 4(p-chloro phenoxy) 3-chloro phenyl substituted phenyl Thiocarbanilide.

The discovery of definite *in-vitro* antitubercular activity of thiourea, its phenyl and sulphanyl derivatives⁶⁹ and the outstanding tuberculostatic properties of N,N'-di(p-n-butoxy phenyl) thiourea¹⁰⁵⁻¹⁰⁷ revived the interest in thiourea derivatives.

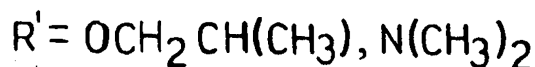
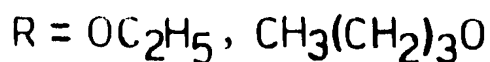
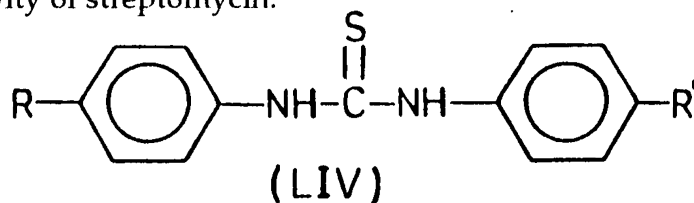
Of several hundreds of thioureas synthesized and tested some bearing alkoxy phenyl group have shown promising activity e.g. Thiambutasine¹⁰⁸ (LII) well known antileprotic agent.



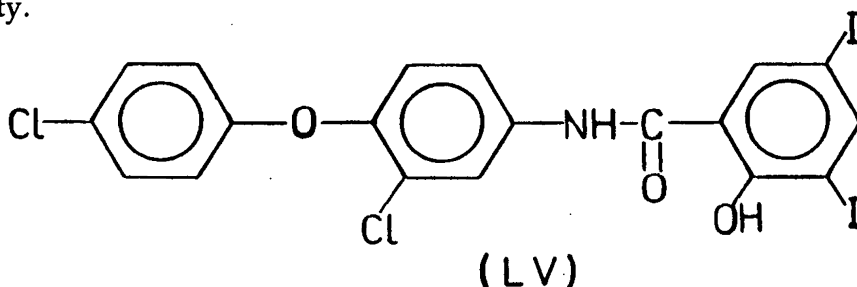
Thioureas not only contribute antitubercular or antileprotic activity but are also reported to possess antifungal as well as antiviral properties. Madan A. G.¹⁰⁹ reported Fluonilid (LIII) as an antifungal agent.



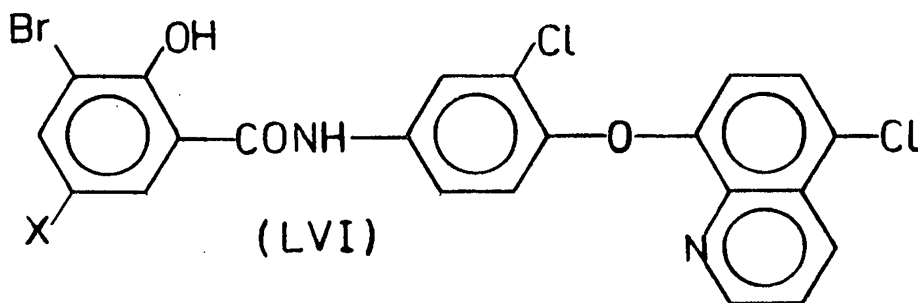
Mayer *et al*¹¹⁰ have reported 4-(*p*-alkoxy phenyl) 4'-substituted thiocarbanilides of general structure (LIV). The antimycobacterial activity of which exceeds the activity of streptomycin.



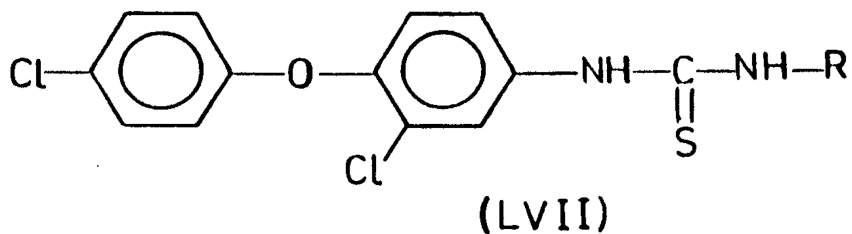
Rafoxanide is a widely used veterinary anthelmintic drug which bears 4-(4-chlorophenoxy)-3-chlorophenyl substituent which is responsible for its enhanced activity.



Recently, Khonkarov *et.al*¹¹¹ reported salicylanilido of following structure having good anthelmintic properties and having low toxicity in nematodes.



Considering the importance of the thioureas and that of 4(*p*-chlorophenoxy) 3-chlorophenyl group, substituted thiourea derivatives (LVII) have been synthesized incorporating 4(*p*-chlorophenoxy) 3-chloro-phenyl substitution which were expected to give better antimicrobial properties. They were screened for antifungal, antitubercular and antibacterial activity.



R = alkyl, substituted aryl

PART 1B

CHEMISTRY

THIS PART DEALS WITH THE CHEMISTRY
OF ALL THE COMPOUNDS / INTERMEDIATES
INVOLVED IN THE WORK.

- ◆ 2 - AMINO BENZOTHAZOLES
- ◆ O - AMINO THIOPHENOLS
- ◆ ISOTHIOCYANATES
- ◆ ACID CHLORIDES
- ◆ 2-SUBSTITUTED BENZAMIDO -5,6
DISUBSTITUTED BENZOTHAZOLES
- ◆ THIOSEMICARBAZONES & SCHIFF BASES
- ◆ HALOGENATION OF KETONES
- ◆ THIAZOLES
- ◆ TRIAZOLES
- ◆ THIOUREAS

CHEMISTRY OF 2-AMINO BENZOTHAZOLES

Various benzothiazoles are known for their manifold medicinal activity particularly as antiparasitic ^{61,62} and antibacterial agents ^{63,64}. 2-substituted amino benzothiazole derivatives are not studied in much detail in literature for their potential biological activities probably due to the difficulties encountered during the preparation of various intermediates. Earlier studies on benzothiazole derivatives reveal the antitubercular activity of 2-substituted alkyl and aryl amino benzothiazoles ⁷⁷. It is now well understood that the various fluorine substituted groups confer good antimicrobial activity to various bioactive molecules. .

With this in view it was thought worthwhile to establish a structure-activity relationship among these derivatives.

General Methods For The Synthesis Of 2-Amino Benzothiazoles.

1. THIOCYANATION REACTION

Thiocyanation is one of the many organic reactions useful to synthetic organic chemist. It is a simple electrophilic reaction showing close similarity with halogenation. Therefore, the reaction is often classified as pseudohalogenation and the reagent as pseudohalogen. As far as chemical reactivity is concerned the thiocyanogen behaves exactly similar as halogen.

The direct substitution of hydrogen atom by a thiocyano group (-SCN) through the use of thiocyanogen (SCN)₂ is commonly referred to as thiocyanation.

Since the reagent is extremely unstable, certain precautions must be observed for its use in the reactions. Thiocyanogen is a liquid which on cooling forms a colorless crystalline solid melting between -30°C to -20°C. At room temperature it polymerizes rapidly to a reddish orange, amorphous mass of indefinite composition known as pseudothiocyanogen. Although, relatively stable in inert dry solvents, thiocyanogen may polymerize in solution, especially, under the catalytic effect, influence of heat, light and moisture.

Due to the extreme sensitivity of thiocyanogen towards hydrolysis and polymerization, it is employed in solution and more commonly is produced *in situ*.

Method for the use of thiocyanogen in substitution reactions

Two general methods, which can be practically applicable have been described for the use of thiocyanogen in substitution reactions-

- i) free thiocyanogen in organic solvents.
- ii) thiocyanogen liberated gradually in organic solvents from a metal thiocyanate by various reagents.

i) Free Thiocyanogen

This method was the first to be employed and is still a useful procedure when the reaction involved is slow, as in addition reactions or when the product is difficult to purify. Usually the only contaminant of the product material is polythiocyanogen, which is entirely insoluble in water and in organic solvents.

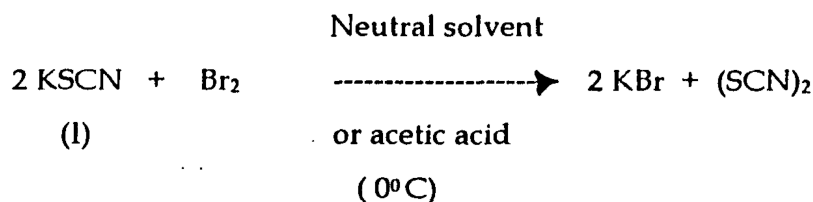
The reagent is prepared by the action of an oxidising agent upon thiocyanic acid or a metal thiocyanate. The oxidation of thiocyanic acid in an organic solvent is accomplished by means of such reagents as lead tetra acetate, lead peroxide or manganese dioxide ¹¹², but the yield is so low that the preparation of metal thiocyanate is much to be preferred. Lead thiocyanate reacts rapidly and quantitatively with bromine to form thiocyanogen and lead bromide, which is removed rapidly by filtration. Halogen carriers such as phenyliodo chloride ¹¹³, sulfuryl chloride ¹¹⁴ or certain N-chloroamides ^{115, 116, 117} can also be used but do not appear to possess any advantage over bromine or chlorine.

Solvents that have been used with thiocyanogen include benzene, bromobenzene, carbon tetrachloride, chloroform, ether, ethylene bromide, carbon disulfide, petroleum ether, methyl acetate, nitromethane, anhydrous formic acid and acetic acid. At low temperatures such solvents as saturated solution of alkali thiocyanates in methanol ^{118,119} or acetone ¹²⁰ can be used. The yield in the thiocyanation of amine is 20-30 % higher when the reaction is carried out in a neutral medium like methanol rather than in acetic acid. The formation of a thiazole is also inhibited in a neutral solvent. Ether is usually not satisfactory because the solvent is attacked and because some of the amine is precipitated as the thiocyanate^{121,122}.

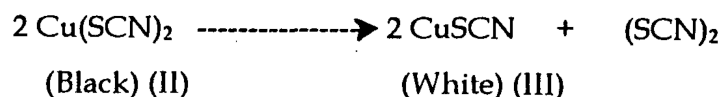
Moisture must be excluded from thiocyanation solution in order to prevent hydrolysis. Another troublesome side reaction, particularly in concentrated solutions is polymerisation, which is induced by light, heat and the presence of hydrolysis products. Polymerisation is reported to be dependent upon the dielectric constant of the solvents^{121,123,124}. Stirring is said to retard polymerisation. For the usual synthetic reaction the preferred procedure is to generate thiocyanogen in a solution of the substance to be thiocyanated at a rate equal to the rate of the removal by reaction. The low concentration of reagent, maintained in this way minimizes polymerisation. The reagent is generated from the thiocyanate salts by a chemical reaction.

ii) Thiocyanogen Generated From Salts By Chemical Reagents.

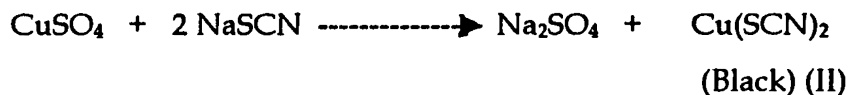
In this method the alkali metal thiocyanate (I) is dissolved in acetic acid or formic acid^{122,125} or better in neutral solvent like methyl acetate, acetone or methanol^{118,126} and then the compound to be thiocyanated is introduced to the above solution. Bromine or chlorine is added to the cooled solution at such a rate that the thiocyanogen reacts as fast as it is liberated. The neutral solvent that is susceptible to attack by halogen is protected by saturating the solution with an appropriate alkali metal halide or by using a large excess of an alkali metal thiocyanate in the reaction mixture. Other reagent for producing thiocyanogen from ammonium thiocyanate have been described -N,N-dichlorourea¹²⁷, N-chloro-acetamide¹¹⁵. The chemical transformation can be written as below :



Cupric thiocyanate¹²⁸, the use of which may be considered still another modification of this general procedure, shows promise of being very effective. It releases thiocyanogen merely by the dissociation of the cupric (II) to cuprous salt (III).



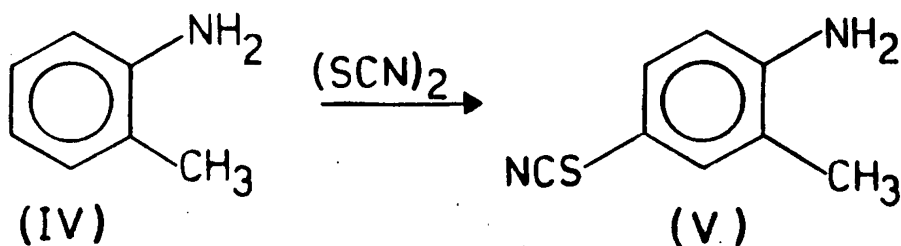
Cupric thiocyanate (II), prepared in advance, or a paste of copper sulfate and sodium thiocyanate in equivalent proportions is added to a solution of the compound in methanol or acetic acid and the mixture is warmed to 35° C - 80° C, until the black cupric thiocyanate has changed completely to the white cuprous thiocyanate.



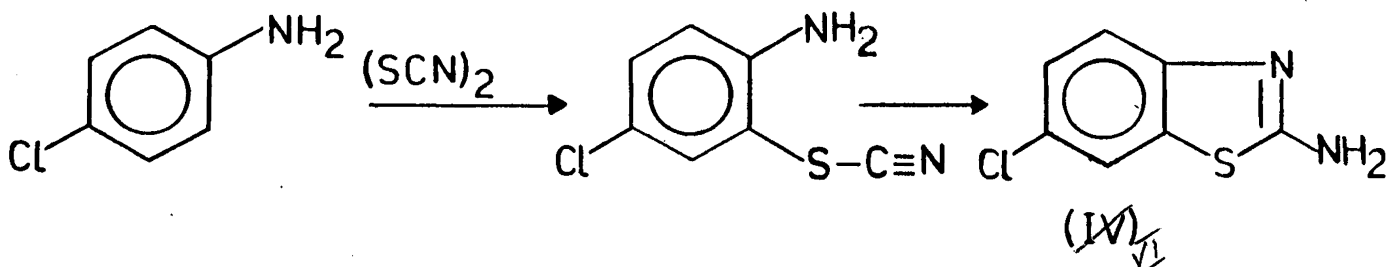
This procedure has the advantage over the others of permitting higher temperatures for thiocyanation.

Thiocyanation of Aromatic Amines

The thiocyano group (-SCN) is introduced into aromatic amines with rapidity. It enters preferentially at a free *para* position if available, otherwise at *ortho* position. For example, *o*-toluidine (IV) is converted to 4-thiocyano-*o*-toluidine (V) (80 % yield) ¹¹⁵.

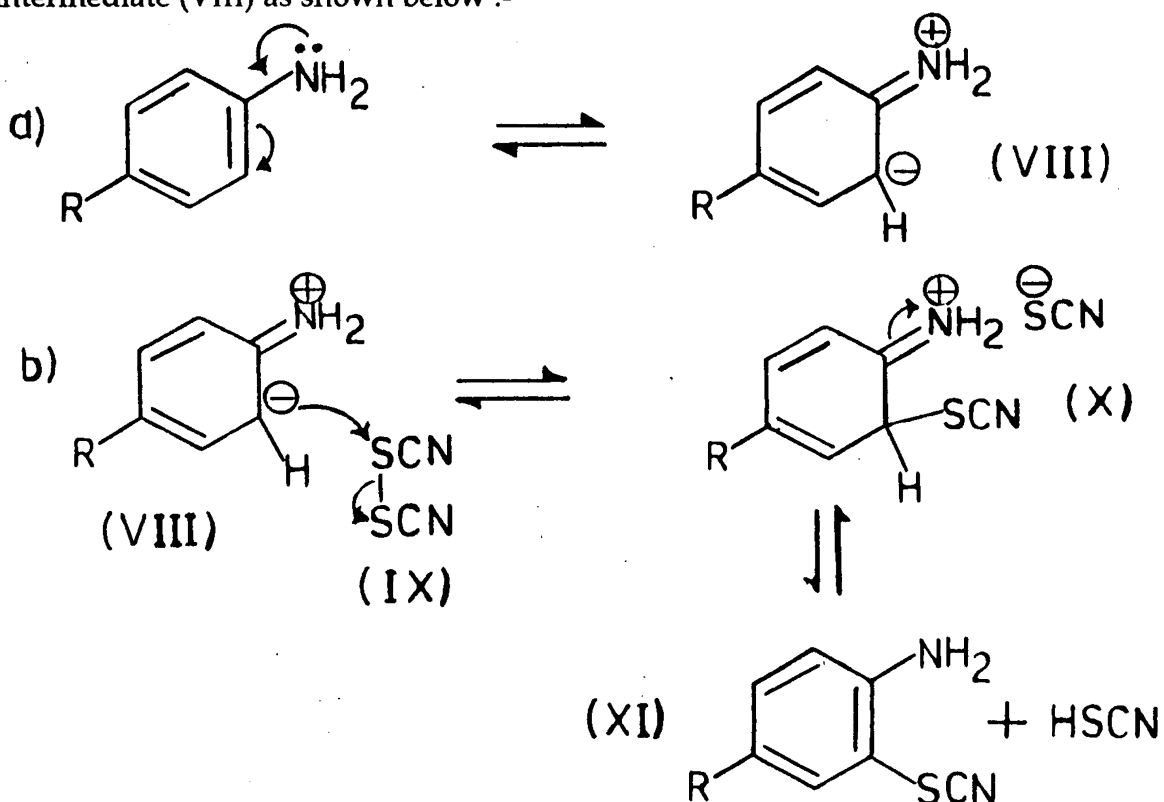


When thiocyanation takes place in the position *ortho* to the primary amino group as in *p*-toluidine, *p*-chloroaniline, *p*-nitroaniline, the final product in such cases is often an amino benzothiazole (VI) formed by a secondary reaction between the amino group and the adjacent thiocyano group. In this secondary reaction, since the amino group is having lone pair of electrons, it will be added to the C=N bond of -SCN group to give resultant 2-amino 6-substituted benzothiazole.



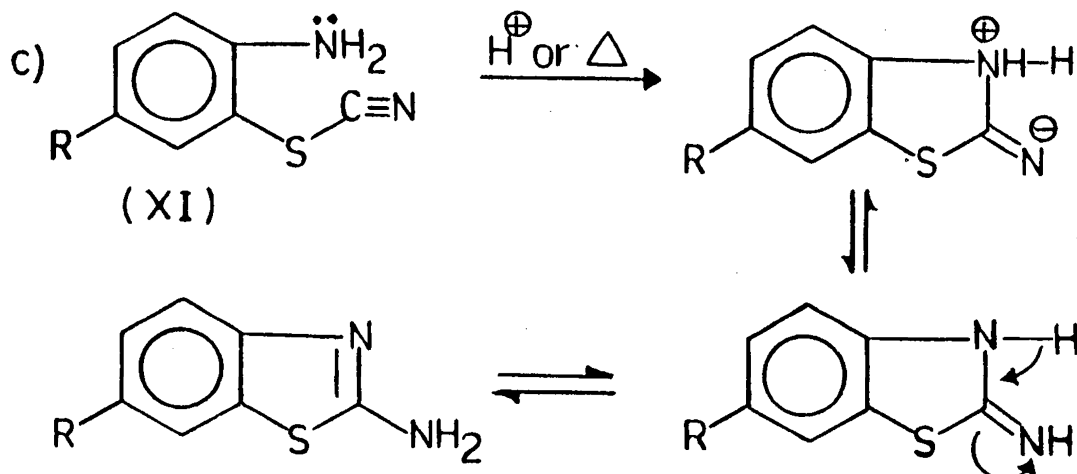
Mechanism:

The mechanism of thiocyanation reaction probably consists of the initial attack of thiocyanogen (IX) to the activated site of 4-substituted aniline (VII) where, due to the mesomeric effect of amino group; the *ortho* position (VIII) contains surplus electrons which renders the site to act as a good electron rich centre, so as to form an intermediate (VIII) as shown below :-

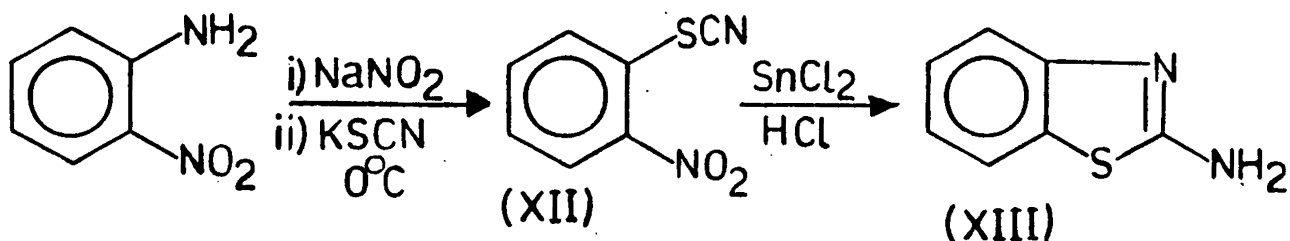


The unstable intermediate species (X) immediately loses a proton to retain the aromatic character of the molecule (XI) which gives higher stability.

(IX), under the influence of acid and heat, adds the NH_2 function to the adjacent thiocyano group as shown below :

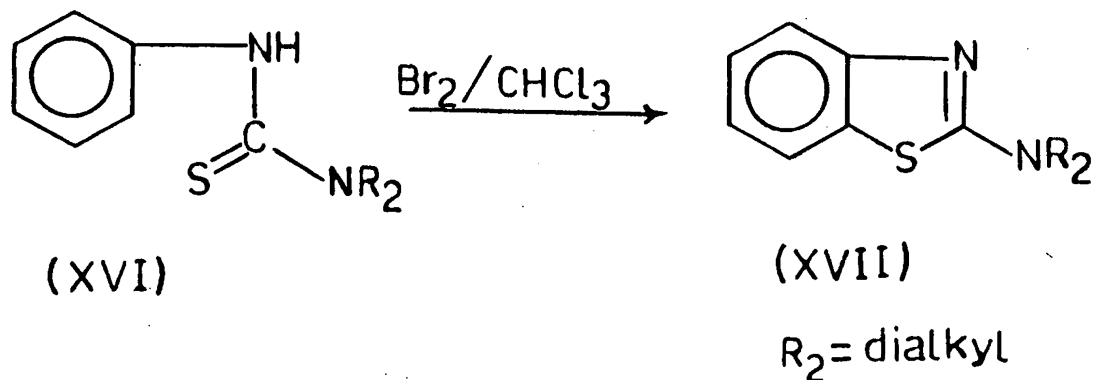
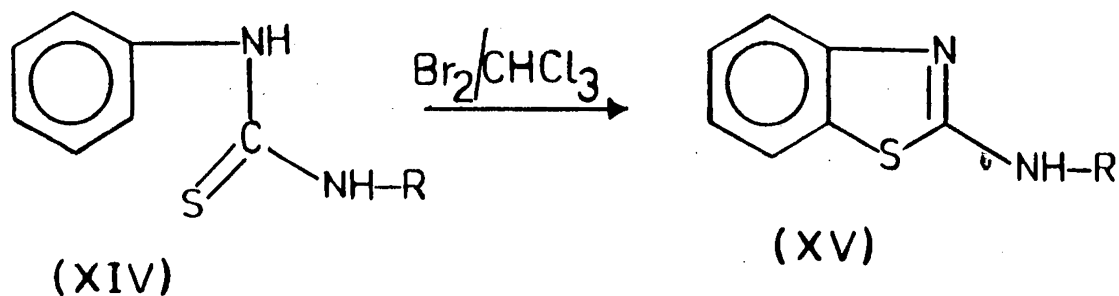


2. 2-Amino benzothiazoles (XIII) have been prepared also from the *o* - thiocyano nitro compounds of the type of (XII) by chemical reduction (stannous chloride in HCl and FeSO₄ in ammonia ^{129,130}. The yields are 60-85%.

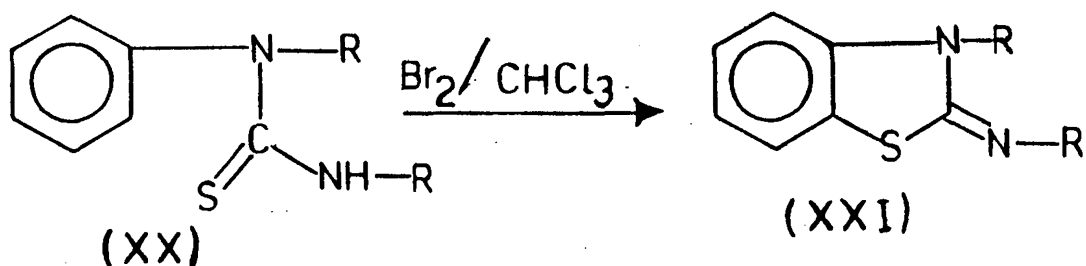
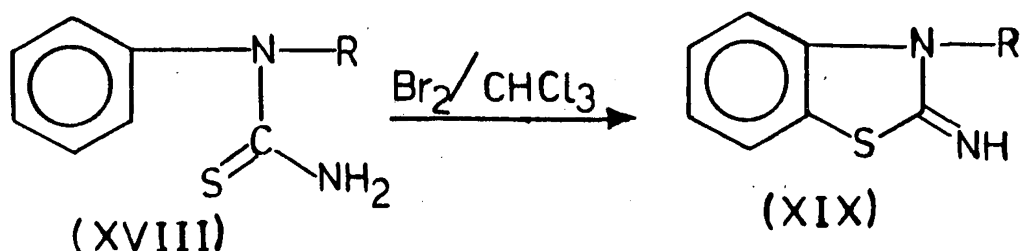


3. Hegerschoff Synthesis

In the Hegerschoff synthesis ^{131,132} bromine in chloroform smoothly converts aryl thioureas into the corresponding 2-amino benzothiazoles in high yields. In this way, N-alkyl (XIV) and N,N-diethyl (XVI) give the corresponding 2-alkylamino (XV) and 2-dialkyl amino (XVII) benzothiazoles ¹³³⁻¹³⁷.

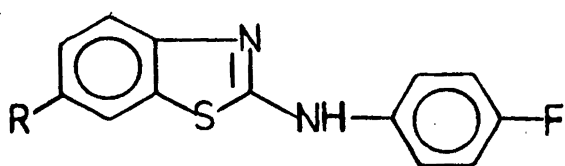
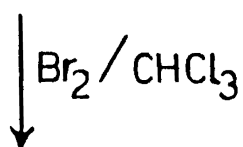
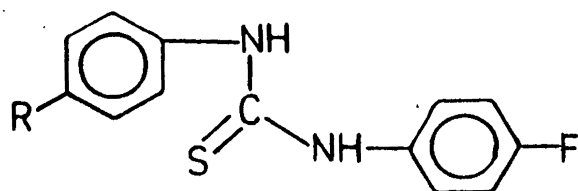
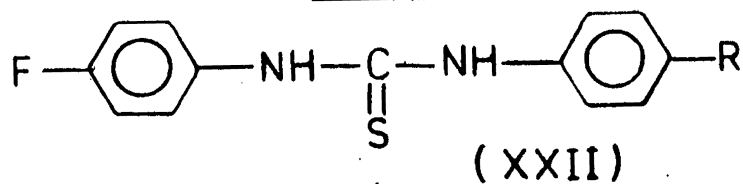


When the alkyl group is attached to the same nitrogen that holds the aryl group as in the arylthioureas of the type (XVIII) and (XX). Cyclisation produces the 2-amino benzothiazolines (XIX) and (XXI) derived from the tautomeric form of the 2-amino benzothiazolones ¹³⁸⁻¹⁴¹.

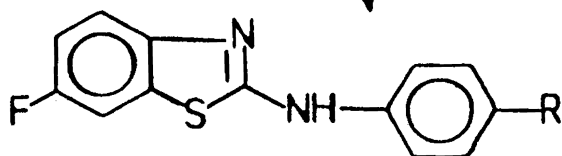
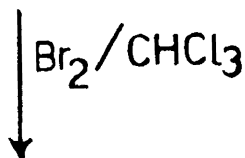
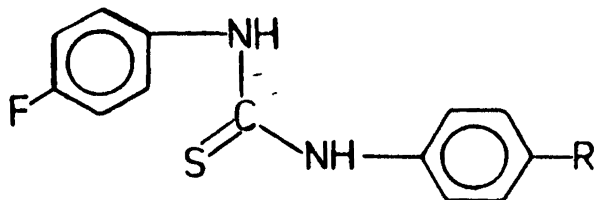


N,N'-Diaryl thioureas readily undergo cyclisation ^{131, 132, 142, 143}. However, when the two aryl groups are dissimilar (XXII and XXIII) there are two possible directions for ring closure as depicted in Scheme I. Generally, the reaction follows only one course and a single product results. The ring closure occurs on the aryl group that is unsubstituted ^{142, 144} or when both aryl groups are substituted in the *para* position, the group that holds the least inactivating substituent is involved in the ring closure. Aryl groups that are substituted particularly with substituents such as bromine, cyano, carbethoxy or nitro groups, participate in ring closure less readily ^{134, 142, 145, 146}. The following reactions are illustrated ¹⁴⁵.

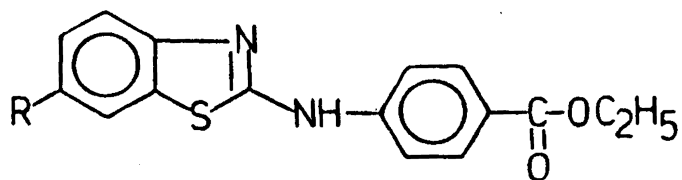
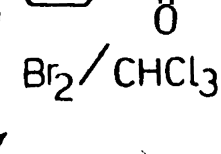
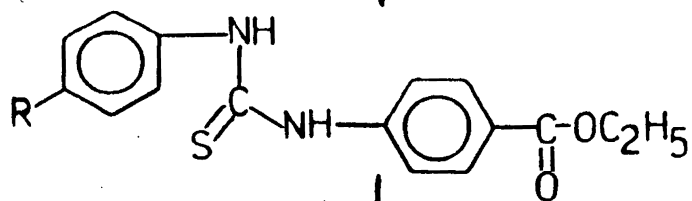
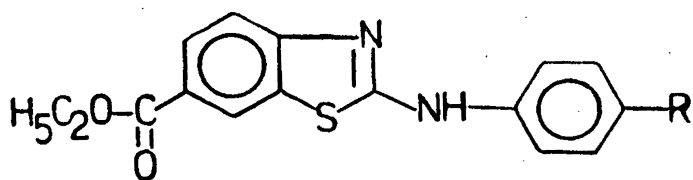
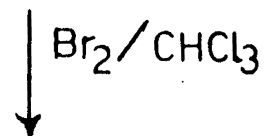
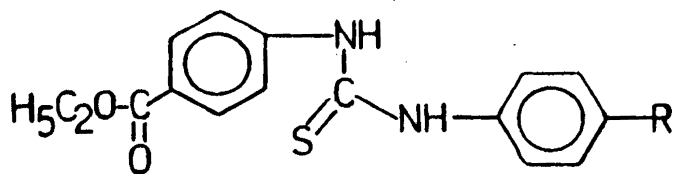
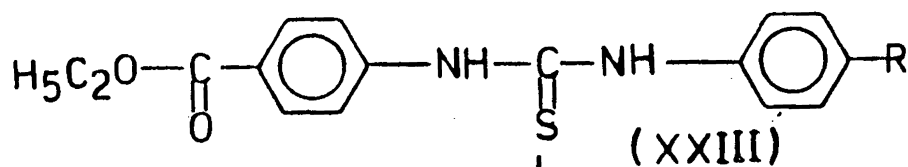
SCHEME - I



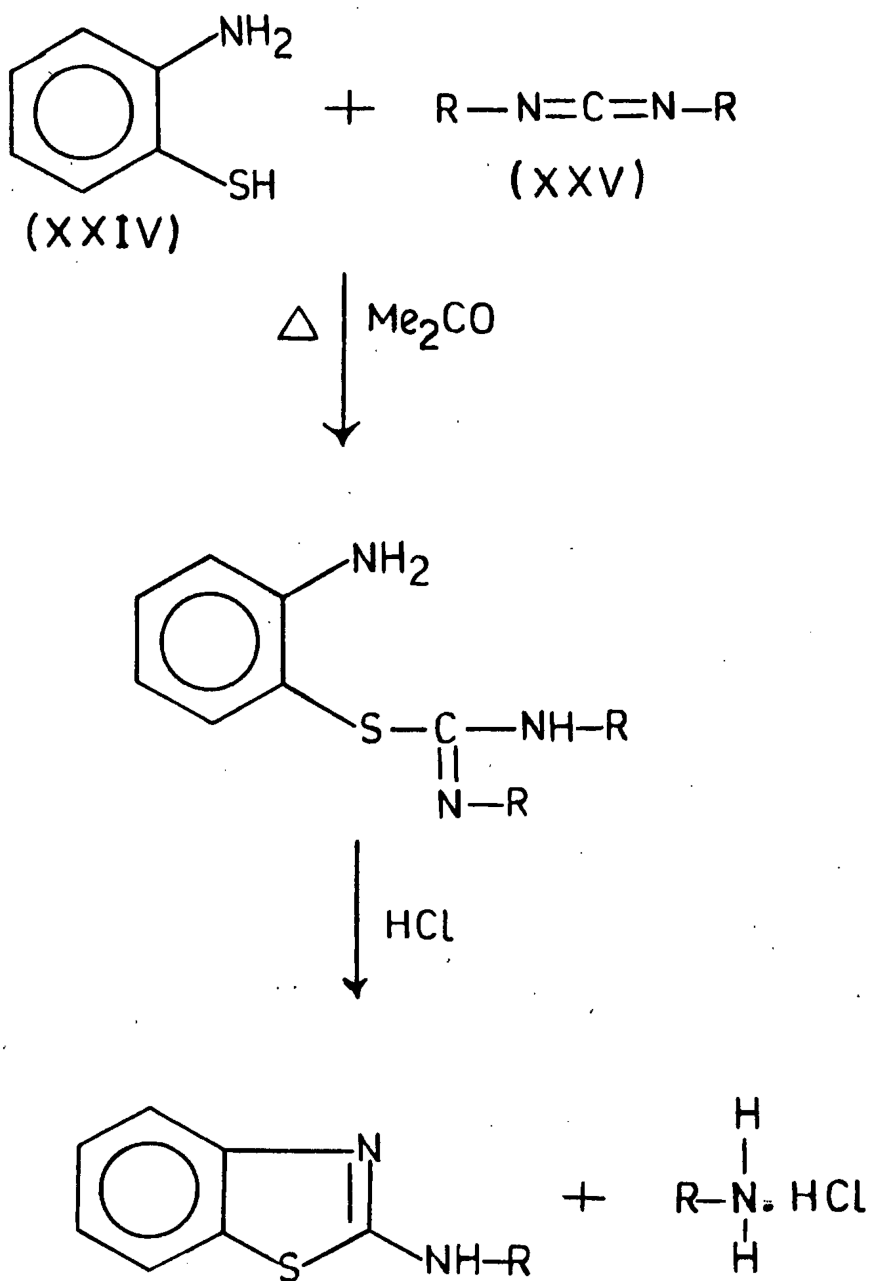
$\text{R} = \text{H}, \text{CH}_3, \text{Br} \text{ etc}$



$\text{R} = \text{NO}_2$

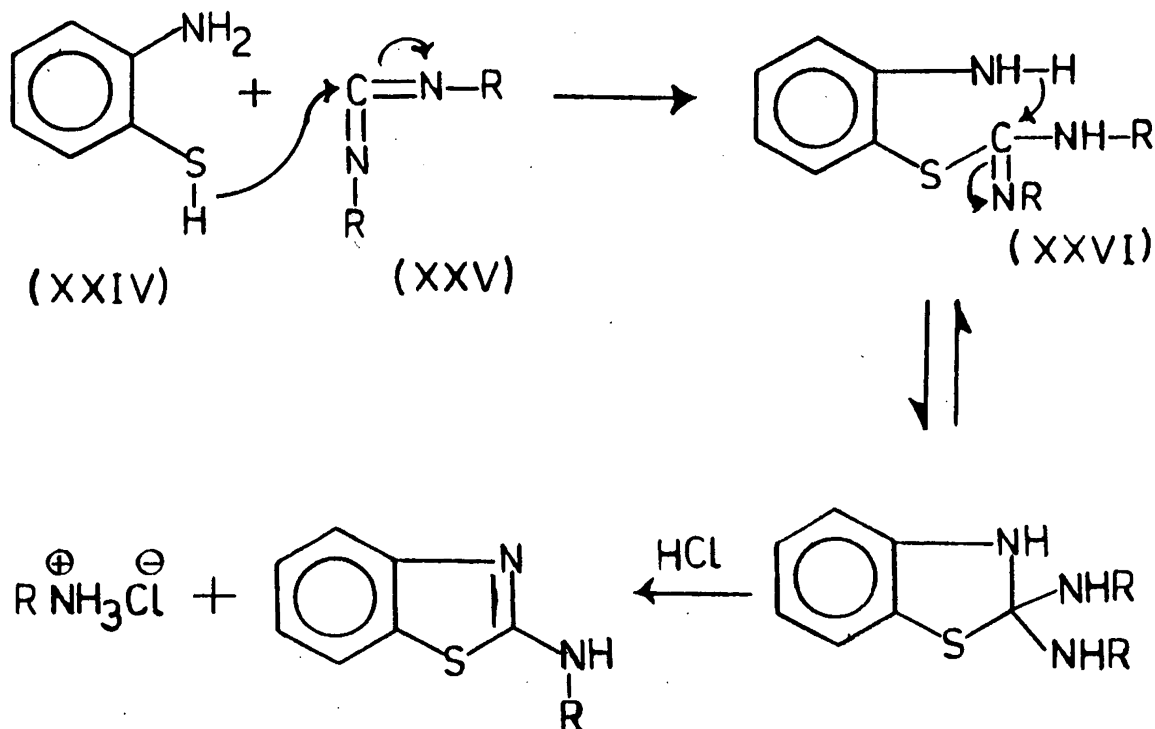


4. In 1962, Frederick Kurzer¹⁴⁷ reported that, 2-substituted amino benzothiazoles are synthesized from cyclisation of isothioureas derived from *o*-amino thiophenol (XXIV) and diaryl carbodiimides (XXV). The reaction can be written as below :

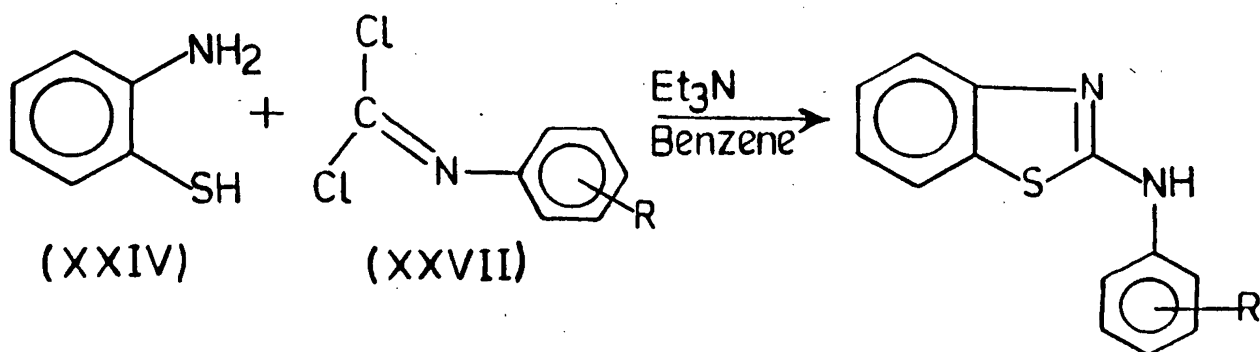


R = aryl

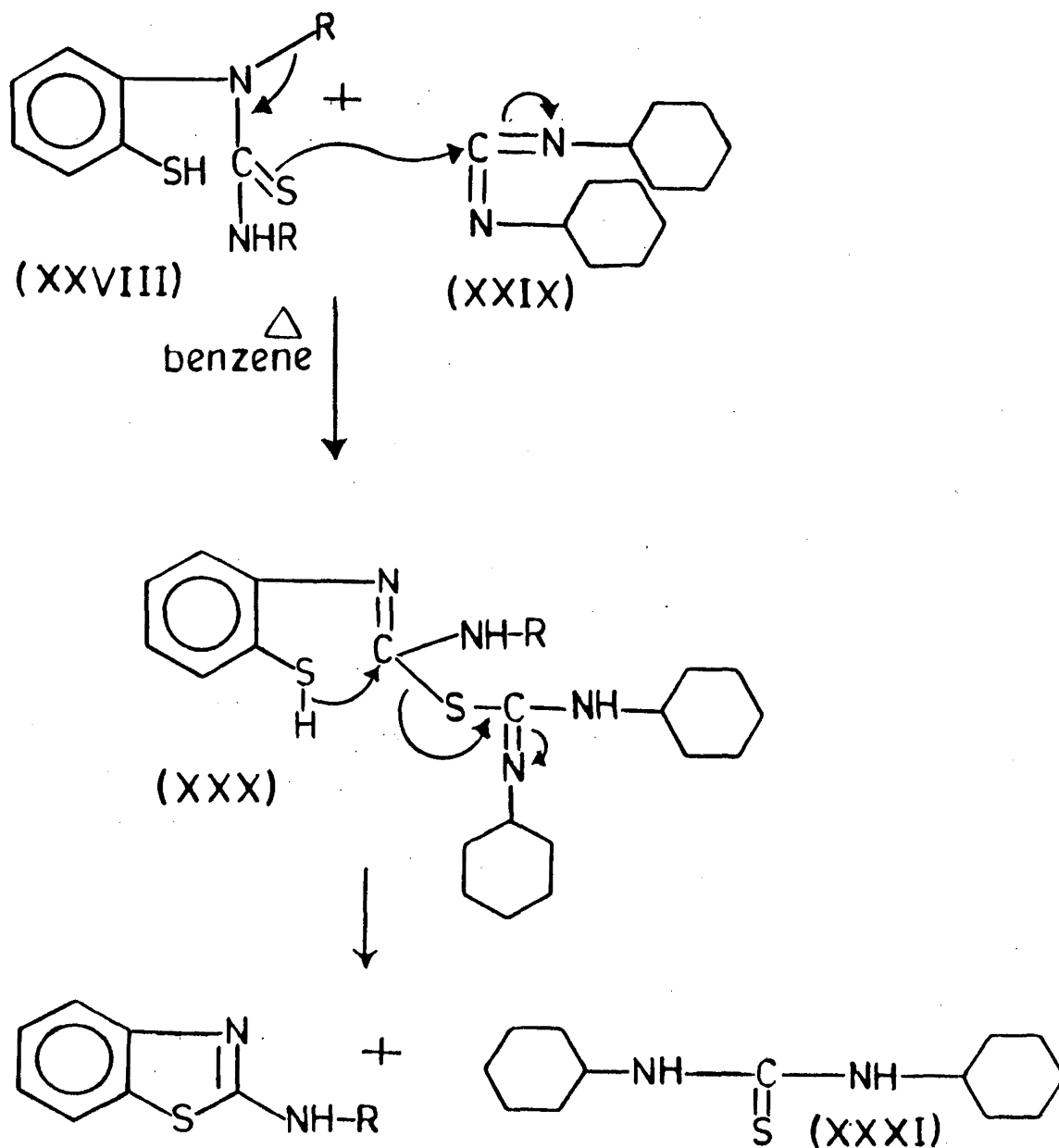
The exact reaction path may be involving the initial addition of thiol group to the $-C=N$ group of diaryl carbodiimide (XXV) to give S-(*o*-aminophenyl)-N,N'-bis aryl isothiureas (XXVI) which instantly loses a mole of arylamine hydrochloride by the action of HCl.



5. In 1964, Bertran Anders ¹⁴⁸ patented the preparation of 2-substituted benzothiazole by the cyclisation of *o*-amino thiophenol (XXIV) and substituted phenyl isocyanide dichloride (XXVII) in the presence of triethylamine at ambient temperature. The reaction can be represented as below :-



6. Recently, 2-substituted amino benzothiazoles are synthesized by treating N-(*o*-mercaptophenyl)-N'-substituted phenyl or alkyl thiourea (XXVIII) with dicyclohexyl carbodiimide (XXIX) in boiling benzene ¹⁴⁹.



The probable explanation that may be given for such type of ring closure is as follows. Initially, the enol form of diaryl thiourea was added to the $-C=N$ groups of dicyclohexyl carbodiimide to give an intermediate species (XXX) which instantly loses a molecule of dicyclohexyl thiourea (XXXI) accomplishing cyclization

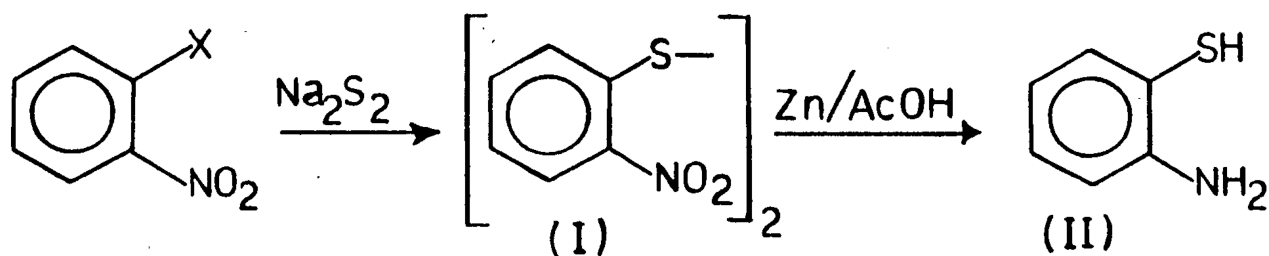
to give required benzothiazole. This new type of reaction will not have any further synthetic applicability since the reactants used are not available easily in a laboratory.

In the present study, the raw material namely, 2-amino-5,6-disubstituted benzothiazoles are synthesized by thiocyanating 3,4-disubstituted anilines with potassium thiocyanate and bromine in acetic acid at cold temperature, according to the literature methods.

CHEMISTRY OF O-AMINO THIOPHENOLS

General methods for the preparation of o-aminophenols :

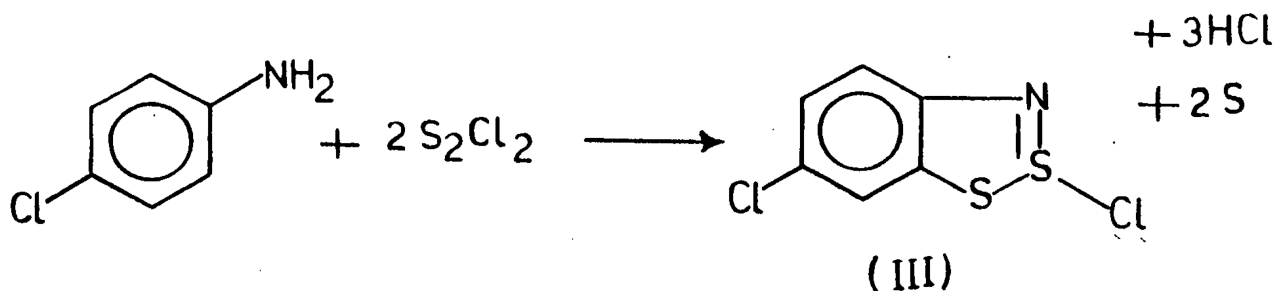
i) Reduction of di-(*o*-nitro phenyl) disulfide (I) by sodium sulfide or by zinc gives the sodium or zinc salt of the *o*-aminothiophenol (II) which is then employed directly in the benzothiazole synthesis¹⁵⁰⁻¹⁵⁹. The reaction of *o*-nitrophenyl halides with an excess of sodium polysulfide yields solution of sodium salts of *o*-aminothiophenols that are satisfactory for the preparation of some benzothiazoles.



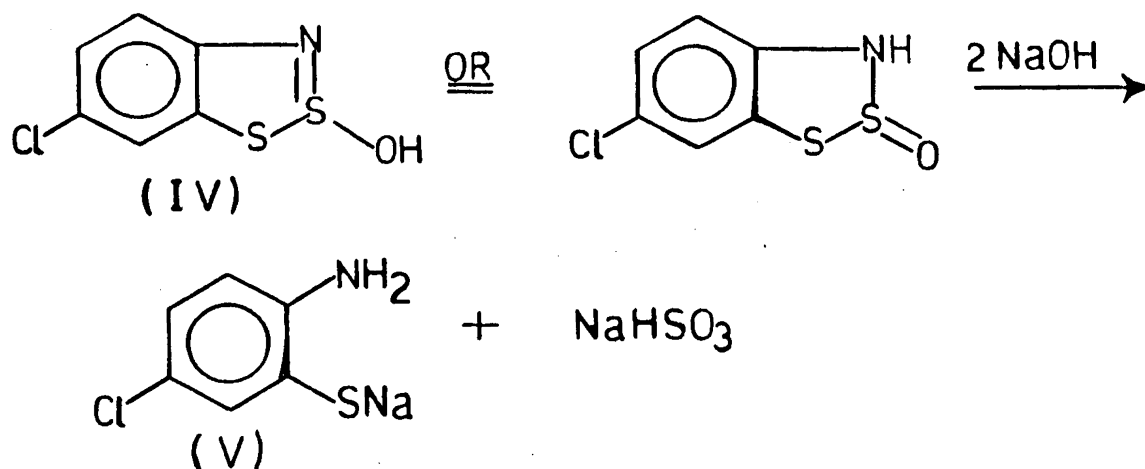
ii) The Herz process :

The Herz process for the preparation of *o*-aminothiophenols from aromatic amines has been applied extensively to the synthesis of benzothiazole intermediates¹⁶⁰⁻¹⁶⁵. The term Herz reaction is used to describe the overall reaction leading to the preparation of *o*-amino benzene thiols by the condensation of aromatic amines (XV) with sulfur chloride and hydrolysis of the condensation product. There are three discernible steps.

In the first step the amine (e.g. *p*-chloroaniline) reacts with sulfur chloride to give a thiazathiolium chloride (III).



Hydrolysis of thiazathiolium chloride (III) (which is called as Herz compound) proceeds through the replacement of chlorine by hydroxyl group to give a thiazathiolium hydroxide (IV). This replacement can usually be carried out in neutral solution, but the hydroxy compound is not always isolated. Aqueous or aqueous alcoholic alkali then opens the five membered ring to give the Na-salt of *o*-amino thiophenols (V) and sodium hydrogen sulphite.



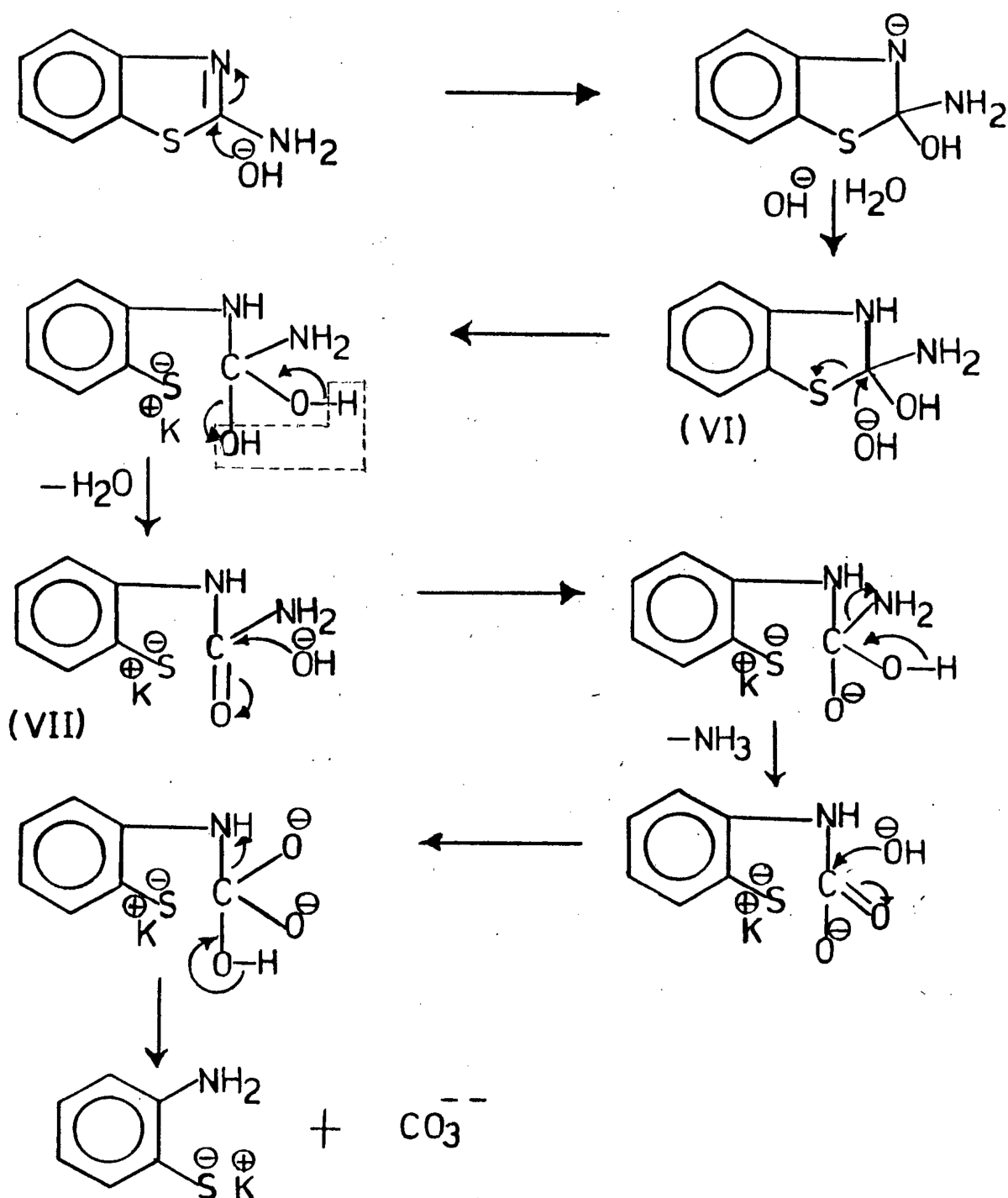
The reaction mixture containing the hydrolysis product can be used directly in many syntheses, but the thiol can be precipitated and collected, if required as the free base or as zinc mercaptide.

The reaction is limited to the preparation of *o*-amino thiophenols containing as substituents in the 5-position Cl or a group which is not replaced by Cl (bromine, diethylamino, ethoxyl, methoxyl or methyl). Because nitro groups are replaced, it is not possible to protect 5-position with a nitro group and subsequently reduce and remove or alter the protecting group in the usual way. This is a severe limitation to the aromatic amines that are unsubstituted in the *para* position to undergo chlorination by sulfur mono chloride^{159,160, 161, 164}.

iii) The alkaline cleavage of benzothiazoles also constitutes a valuable source of *o*-amino thiophenols. In this manner many nuclear substituted amino thiophenols are obtainable from benzothiazoles such as 2-mercapto and 2-amino derivatives that are readily prepared by methods that do not require an *o*-amino thiophenol¹⁶⁴.

Mechanism for the alkaline hydrolysis of 2-amino-5,6-disubstituted benzothiazoles :

The probable mechanism of hydrolysis may involve the initial attack of OH⁻ ion to the imino C-atom of the 2-amino benzothiazoles to give the intermediate which instantaneously gets protonated by the action of water through elimination of OH⁻ ion giving (VI). This intermediate being highly unstable, results into opening of the thiazole nucleus which on further eliminating a molecule of water gives urea derivative (VII). This urea derivative is finally hydrolysed in usual manner as shown below.



CHEMISTRY OF ISOTHIOCYANATES

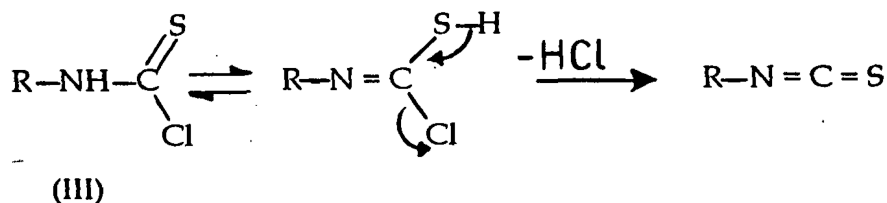
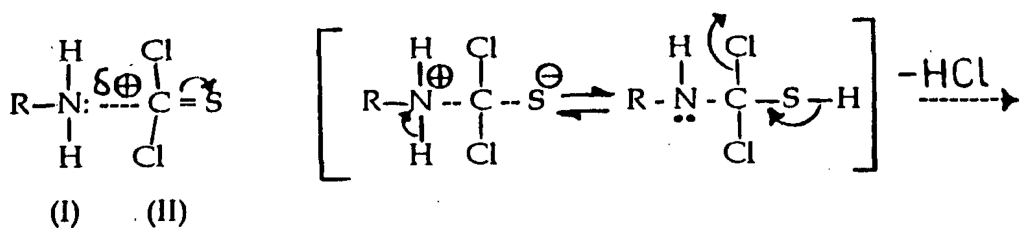
In the past century many sulfur compounds of plant origin attracted attention by their pungent and irritant properties and their abilities to prevent the spoilage of food and fermentation of fruit juices. Two of these substances were revealed to be allyl isothiocyanates and benzyl isothiocyanates. These discoveries marked the beginning of the chemistry of isothiocyanates. Organic isothiocyanates are very interesting and an important class of compounds having general formula $R-NCS$. It goes without saying that our knowledge of isothiocyanates has progressed rapidly both in the chemistry of isothiocyanates and in specialized fields such as the knowledge of interesting biological effects of naturally occurring and synthetic isothiocyanates.

At present many methods are available for the preparation of isothiocyanates but none of them are generally applicable. The choice of method of the preparation of the isothiocyanate will depend upon starting compound which is suitable for the required type isothiocyanate. Organohalides with a reactive halogen and a primary amines serve most frequently as the starting substances. In the case of organohalides a substitution reaction with inorganic thiocyanates is followed by rearrangements, of the resulting thiocyanates into corresponding isothiocyanates. From primary amines, isothiocyanates can be obtained either directly by the action of some sulfur compounds (e.g., thiophosgene, dithiocarbamoyl chloride, trichloromethyl sulfide, etc.) or by converting them into suitable intermediates (dithiocarbamates, dithiocarbazetes, thioureas, etc.) which are then decomposed into isothiocyanates by reaction with various agents.

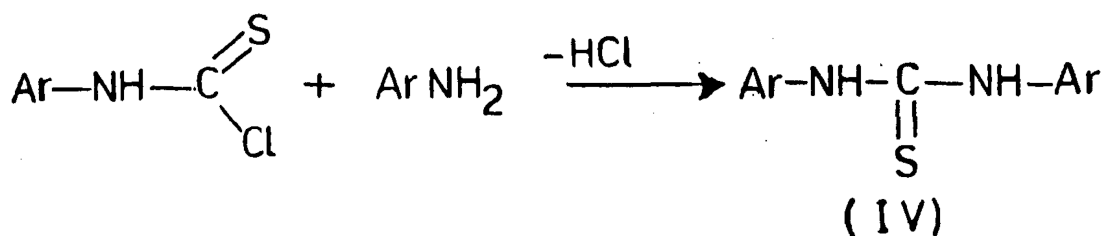
1. Reactions of amines with sulfur compounds :

a) Thiophosgene :

The most generally used method for the preparation of isothiocyanates is based on the direct treatment of the primary amine ¹⁶⁵ (I) with thiophosgene (II). The first product of the reaction is an unstable thiocarbamoyl chloride (III) which splits off hydrogen chloride yielding isothiocyanates ¹⁶⁵. The course of the reaction can be illustrated by the following addition - elimination mechanism.



In the case of aromatic amines, especially with electron accepting substituents, N,N1-disubstituted thioureas (IV) may be formed as by-products ¹⁶⁶.



The formation of thioureas can be prevented by the use of a small excess of thiophosgene. Since isothiocyanates as well as thiophosgene are relatively insensitive to water they can also be prepared in an aqueous medium ¹⁶⁷. Not only free amines but also their salts, particularly hydrochlorides, react with thiophosgene to produce isothiocyanates ¹⁶⁸.

Reaction with free amines is most frequently performed in such a way that chloroform ¹⁶⁹, dichloroethane ¹⁷⁰ or toluene ¹⁷¹ solution of amine is added to the water emulsion of thiophosgene. Hydrogen chloride released in the course of the reaction combines with the strongly basic amine hydrochloride which is very difficult to hydrolyse in water and thus complicates the reaction of thiophosgene with the amine. For this reason, bases are frequently added to the reaction mixture for the binding of hydrochlorides e.g., calcium carbonate ¹⁷⁰, sodium carbonate and sodium bicarbonate ^{172, 173} or triethylamine ¹⁷⁴. It is not advisable to use strong base for this purpose since isothiocyanates are easily hydrolysed in an alkaline medium.

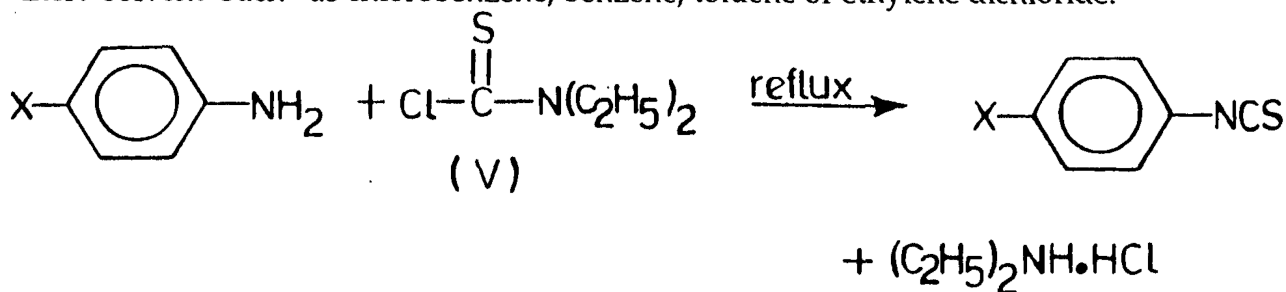
During the preparation of isothiocyanates from the hydrochlorides of primary amines, an aqueous solution of amine hydrochloride is used, maintaining similar reaction conditions as employed with free amines ¹⁷⁰. The addition of CaCO_3 or alkali carbonates keep the reaction mixture neutral and assist in the slight hydrolysis of hydrochloride. This modified thiophosgene method is used primarily for the preparation of aliphatic isothiocyanates and for amines that are sensitive to atmospheric carbon dioxide and oxidation (benzyl amines, some diamines, etc.)

The thiophosgene method, thanks to its versatility and mild reaction conditions, is being used in the synthesis of isothiocyanates of very varied structures.

This is the simplest and most universal method for the preparation of isothiocyanates. It gives high yield and is suitable for the preparation of aliphatic as well as aromatic isothiocyanates. Its importance has increased due to the fact that thiophosgene has become a commercially available reagent, though some authors object to its unpleasant odor and toxicity.

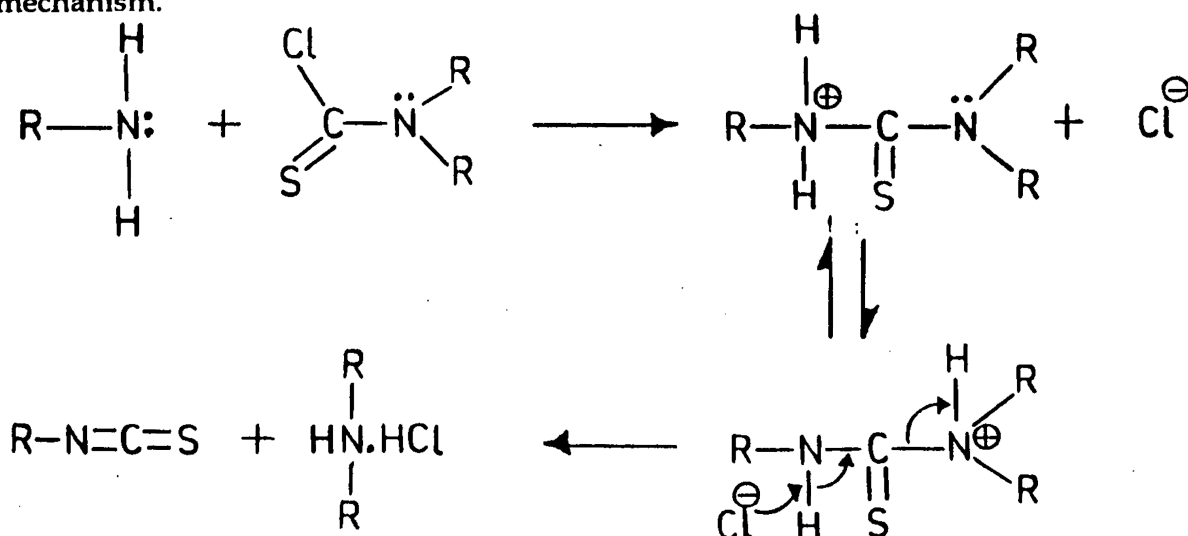
b) Thiocarbamoyl derivatives :

Sayigh and co-workers ¹⁷⁵ have proposed N,N-diethyl thiocarbamoyl chloride (V) as a new reagent which could replace the toxic thiophosgene. It is universally accessible and is suitable for the preparation of aromatic isothiocyanates with electron withdrawing substituents. It is a one-step method and consists in the heating of the aromatic amine with N,N-diethyl thiocarbamoyl chloride (V) in an inert solvent such as chlorobenzene, benzene, toluene or ethylene dichloride.



The yields decreases with the increasing basicity of amines. The limiting pKa value of the reaction medium is 4.6. Under these conditions phenyl isothiocyanate is

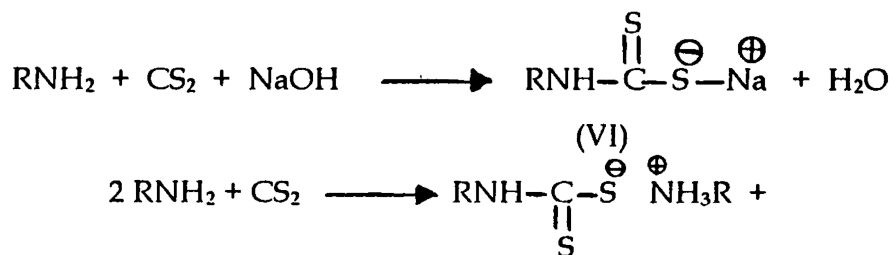
formed from aniline in a very poor yield. Reaction probably takes place via SN^2 mechanism.



2. Decomposition of dithiocarbamic acid and its salts or esters:

a) Decomposition by heavy metal salts :

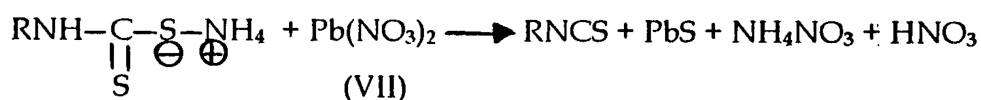
Synthesis takes place in two steps. In the first step the corresponding salts of dithiocarbamic acid (VI) are prepared by the action of carbon disulfide and alkali^{176,177} or ammonia¹⁷⁸ on the aqueous or organic (alcohol, methylene chloride, toluene, etc.) solution of the primary amine. Aliphatic amines reacts with carbon disulfide in the absence of other bases yielding alkyl ammonium dithiocarbamates¹⁷⁹.



Where R = alkyl

Obviously, amines whose basicity is so low that they do not form dithiocarbamates, cannot be used (e.g., nitroanilines).

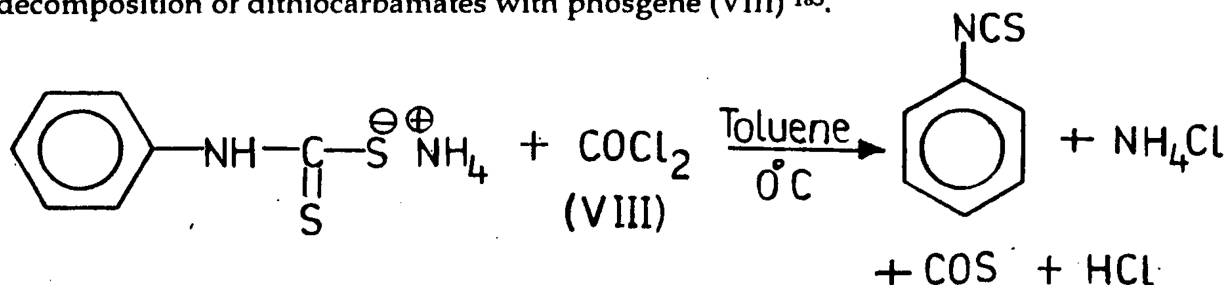
In the second step, heating of alkaline dithiocarbamates with heavy metal salts (VII) in an aqueous medium produces unstable heavy metal dithiocarbamates which decomposes easily into isothiocyanates and metal sulfides.



For the decomposition of dithiocarbamates, mercury salts ^{179, 180}, lead nitrate ^{181, 182, 183}, cupric sulfate ¹⁸⁰, ferric chloride ¹⁸⁴, etc. were used.

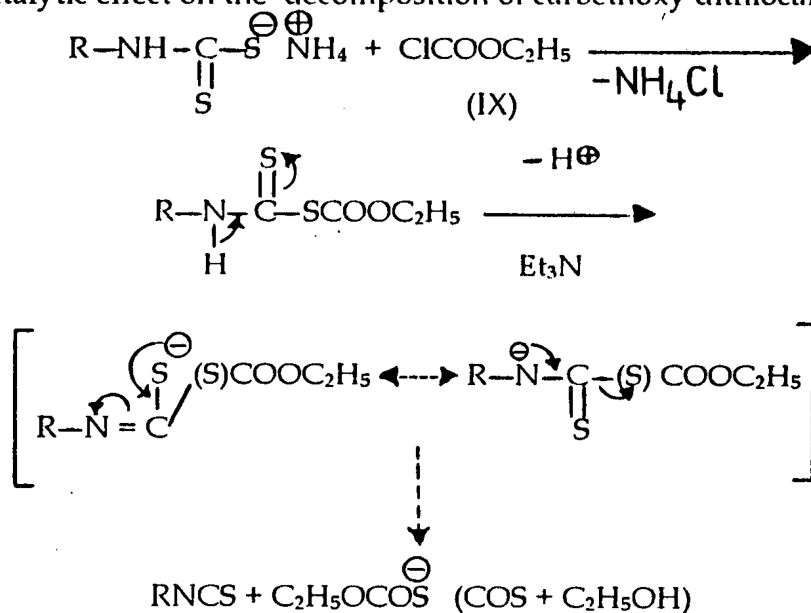
b) Decomposition of chlorine containing compounds :

Some aromatic isothiocyanates are advantageously prepared by the decomposition of dithiocarbamates with phosgene (VIII) ¹⁸⁵.

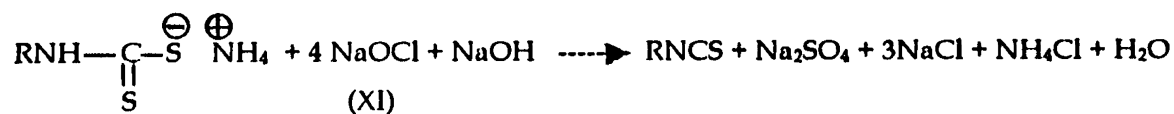


The phosgene method failed to succeed in the preparation of some isothiocyanates with electron withdrawing substituents (4-bromophenyl isothiocyanate, nitrophenyl isothiocyanates etc.). It furnished very good yields in case of 4-hydroxyphenyl isothiocyanate which could not be managed by the thiophosgene method.

The decomposition of dithiocarbamates with ethyl ¹⁸⁶⁻¹⁹⁰ or methyl ¹⁹¹ chloroformates (IX) produces aliphatic isothiocyanates in very good yields. Reaction takes place via the unstable carbethoxy dithiocarbamate (X) which decomposes into isothiocyanate, carbonyl sulfide and ethanol. Bases, like alkali and triethylamine, have a catalytic effect on the decomposition of carbethoxy dithiocarbamate ^{192, 193, 194}.

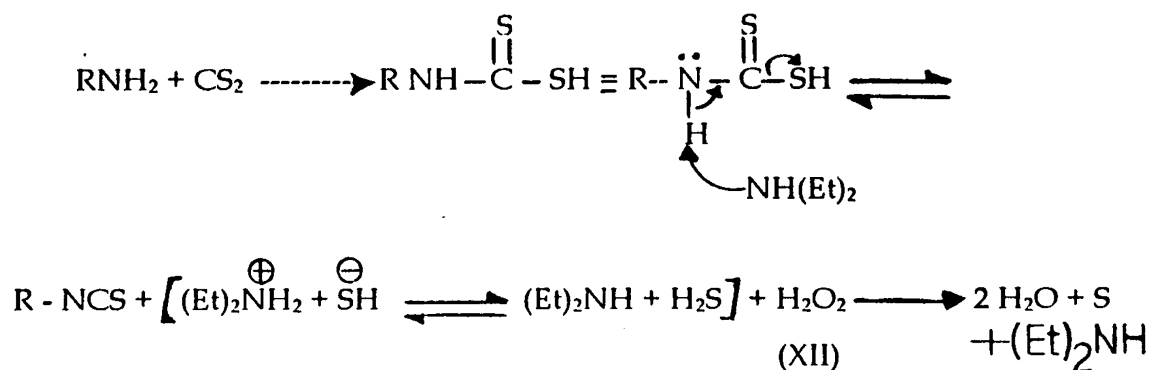


Aliphatic and aromatic isothiocyanates can be also prepared by the oxidative decomposition of dithiocarbamates by sodium hypochloride (XI) in an alkaline medium ^{195,196}.



c) Decomposition by hydrogen peroxide :

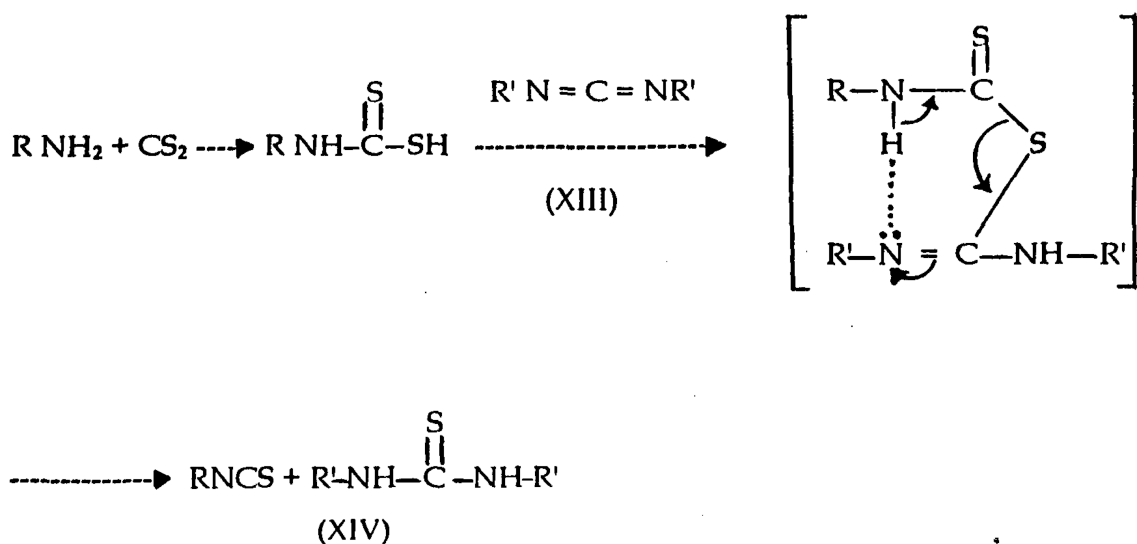
Treatment of a mixture of primary amine and carbon disulfide with hydrogen peroxide (XII) in the presence of secondary aliphatic amine produces a rapid exothermic reaction which gives isothiocyanates ¹⁹⁷.



This one-step reaction is suitable for the preparation of aliphatic isothiocyanates. Thioureas are produced as by-products.

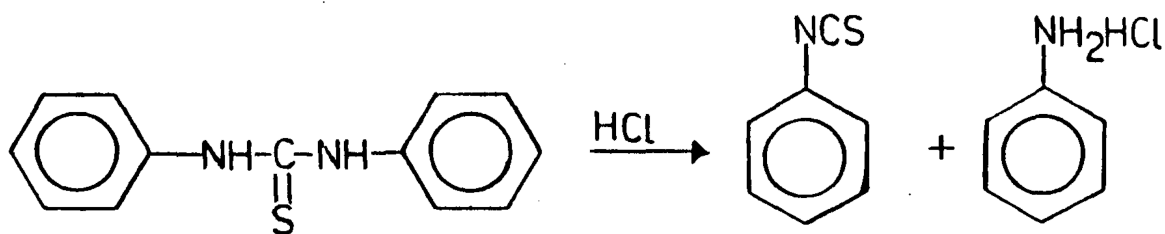
d) Decomposition's involving carbodiimides :

Primary amines react with carbon disulfide and dicyclohexyl carbodiimides (XIII) in a suitable organic solvent at temperatures below 0°C, forming isothiocyanate and 1,3-dicyclohexyl thioureas (XIV). For the preparation of aliphatic isothiocyanates, ether or tetrahydrofuran ¹⁹⁸ proved to be a good solvent. Aromatic amines react under identical conditions only with a one-half molar equivalent of carbodiimide yielding quantitatively, symmetrical diaryl dithioureas. If, however, the reaction is carried out in pyridine, and in some cases in the presence of the molar equivalent of triethylamine, then isothiocyanates are also formed from aromatic primary amines in very good yields ¹⁹⁹.



3. Decomposition of thioureas :

Aromatic amines can be prepared by the decomposition of sym-diarylthioureas (XV) with acids such as hydrochloric acid ²⁰⁰⁻²⁰², sulfuric acid ^{203,204} and phosphoric acid. The salt of the corresponding arylamine is formed as by-product ²⁰⁵.



Isothiocyanates are also obtained by the decomposition of N-monoarylthioureas during prolonged heating in chlorobenzene ^{206,207}.

In the present work for the preparation of isothiocyanates thiophosgene was used for final reaction, so as to minimize the side reactions, and to effect a clean work-up of reactions, which gives a desired product of high purity.

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 gas are 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 chloride ²¹⁰ for the preparation of acid chlorides presents many advantages in a large number of cases. The reaction results in the formation of sulfur dioxide and hydrogen chloride in addition to the acid chloride, and the isolation of the chloride, is for this reason, a simple matter.

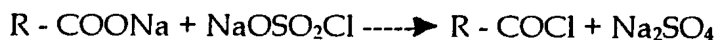
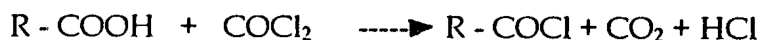


The thionyl chloride must be pure, as the impure product has been known to cause somewhat explosive decomposition in some instances. The procedure consists in mixing the chlorinating agent with acid and heating the mixture, if necessary. The product may be isolated by fractional distillation or if solid,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

Phosphorous oxychloride, reacting with the sodium salt of carboxylic acid gives acid chlorides. This method is of importance with acids which undergo decomposition with other chlorides of phosphorous.

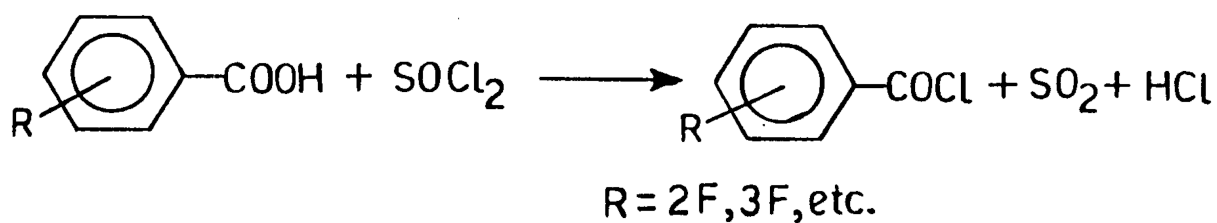


The reaction of phosgene ²¹¹ with carboxyl acids, and *p*-toluene sulfochloride or of sodium chlorosulfonate with salts of carboxylic acids are also used for the preparation of acid chlorides.



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.

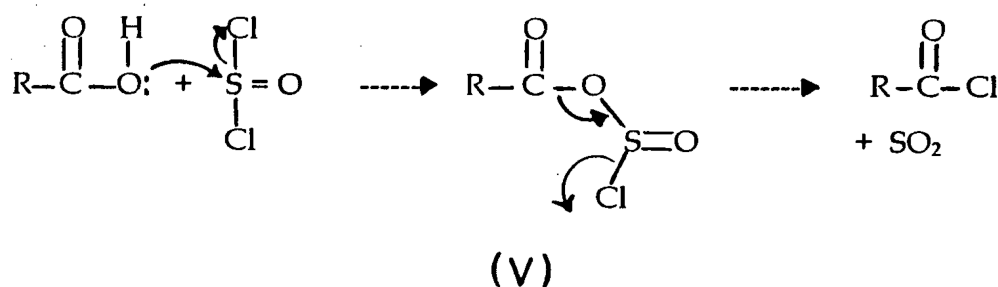
Thus, in the present work all the benzoyl chlorides were prepared by reacting thionyl chloride, with corresponding benzoic acids.



Reaction mechanism :

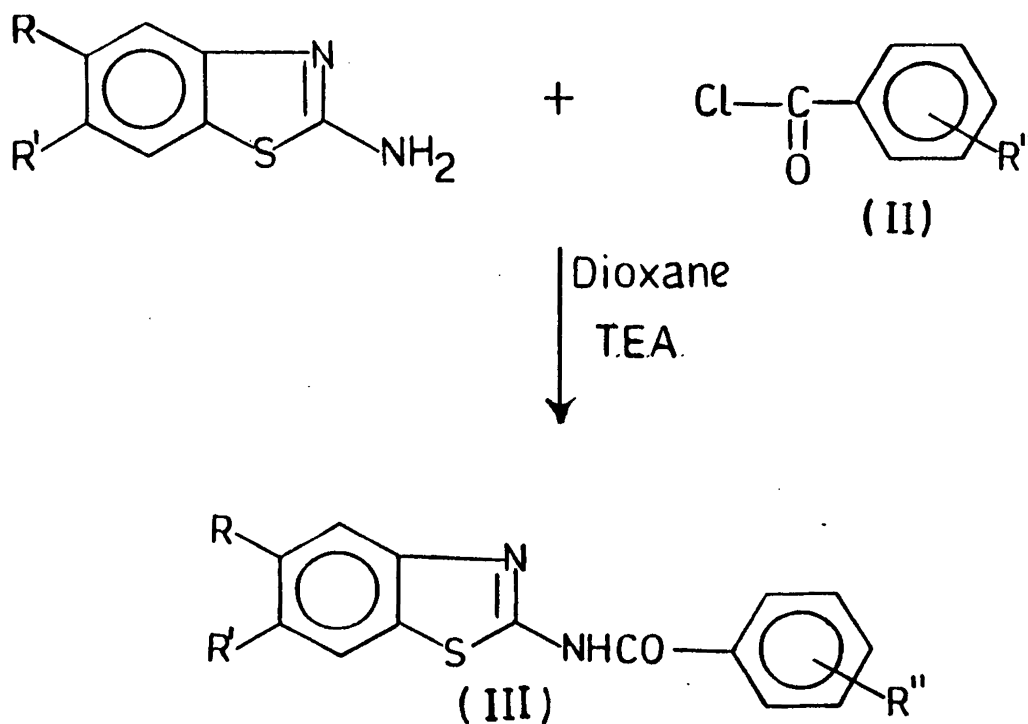


Acids and their salts are the only common starting materials for the synthesis of acid chlorides and several reagents are utilized as sources of nucleophilic chloride. All the reagents form reactive intermediate (V), so that the leaving group in the substitution is not hydroxy group.



CHEMISTRY OF 2-SUBSTITUTED BENZAMIDO-5,6-DISUBSTITUTED
BENZOTHAZOLES:

Simple substituted benzanilides are reported for various types of biological activities e.g., as antifungal ²⁰⁸, anthelmintic ⁷⁹ and antimicrobial agents ⁷⁹. Also, the amino derivatives of substituted benzothiazoles are reported to possess marginal bactericidal activity ²⁰⁹. In view of this, few 2-substituted benzamido-5,6-disubstituted benzothiazoles (III) were synthesized by condensing substituted benzoyl chlorides (II) with 2-amino-5,6-disubstituted benzothiazole (I) in non-polar solvent at elevated temperature. The synthetic route can be represented as below :-

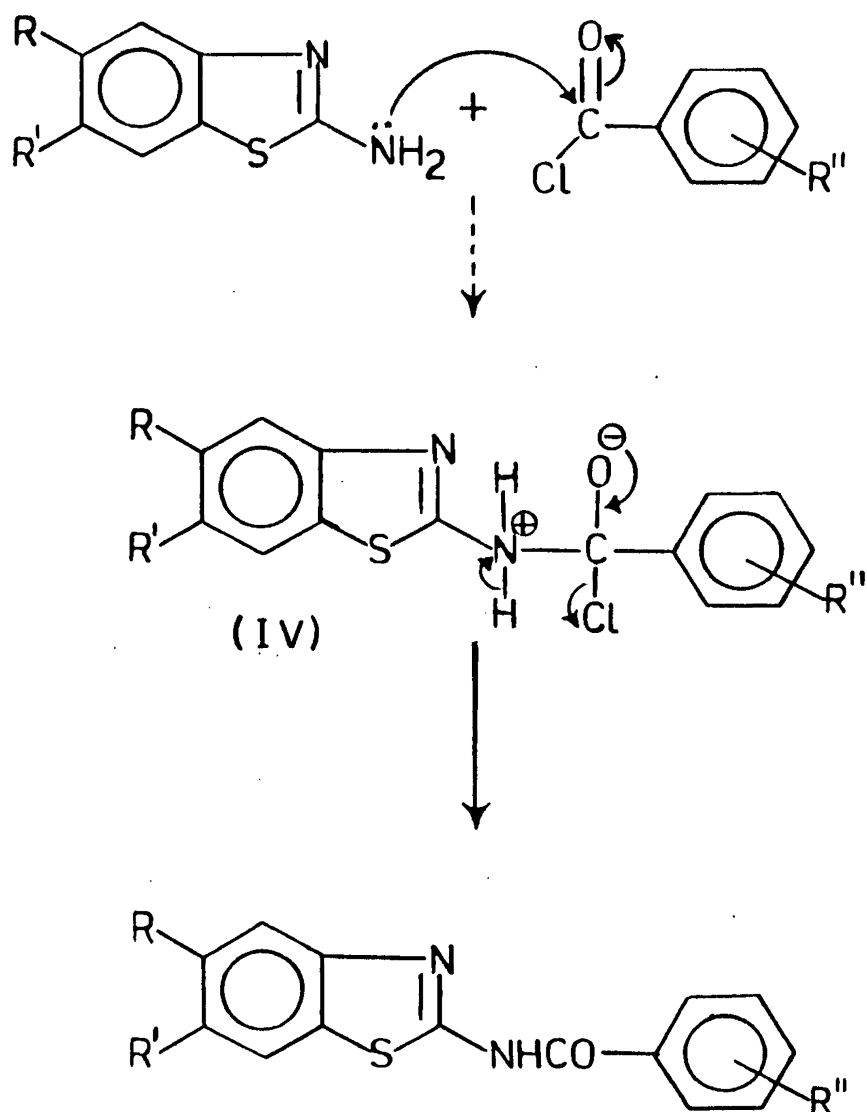


Since the amino group at 2-position of benzothiazole nucleus is in the imino form due to mesomeric effect of cyclic -C=N- linkage, it is obviously less reactive than usual aromatic amino group. 2-Amino-5,6-disubstituted benzothiazole reacts with acid chlorides in benzene at reflux temperature ¹⁰². Since the 2-amino-5,6-disubstituted benzothiazoles are absolutely insoluble in benzene, a above procedure could not be adopted, and therefore, other inert solvents were tried.

Dioxane was a better solvent to dissolve the reactants. When 2-amino-5,6-disubstituted benzothiazole was reacted with acid chloride in dioxane at reflux temperature in the presence of triethylamine as catalyst, on work up directly gave the pure product.

Mechanism of reaction :

The acid chlorides are readily attacked by nucleophile at the carbonyl carbon. The resulting adduct (IV) eliminates chloride ion. So, although, each step of the reaction is theoretically reversible, the reaction by-product is hydrogen chloride gas, which was usually abstracted by the base from the reaction mixture; shifting the equilibrium to the side of the product.



CHEMISTRY OF THIOSEMICARBAZONES AND SCHIFF BASES

Schiff bases and thiosemicarbazones share very similar chemistry the reason being that, both these classes of compounds are formed by the condensation of amino and carbonyl function of aldehyde or ketone.

The presence of azomethine linkage in compounds has been shown to decrease their toxicity considerably ^{94,95}. Schiff bases of various aldehydes have shown encouraging antituberculosis activity *in vitro* in our laboratory ^{236,237}.

Schiff ²³⁸, for the first time, reported the condensation of primary amines with carbonyl compounds. Hence, the condensation products are referred to as 'Schiff bases'.

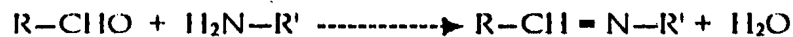


Aromatic amines and aldehydes can be condensed as above to give Schiff bases. The literature describes many procedures to prepare Schiff bases. The important methods are listed below :

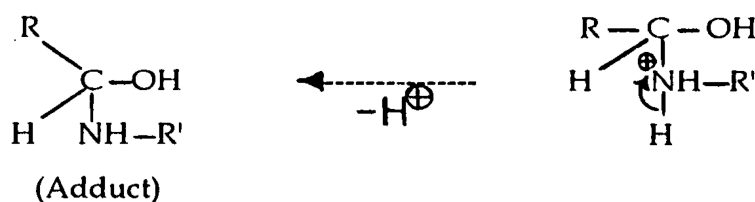
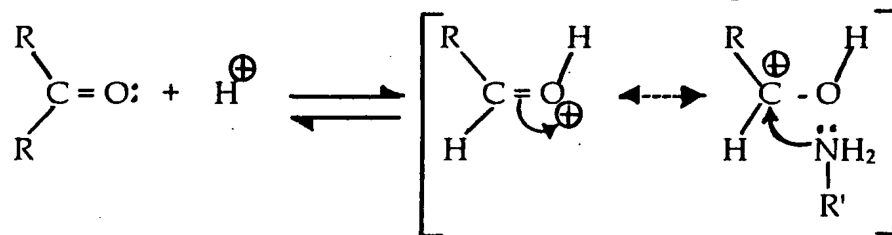
- 1) The simplest method appears to be the one in which condensation of equimolecular quantities of an amine and an aldehyde is effected in boiling methanol.
- 2) In 1946, Tipson and Clapp ²³⁹, obtained Schiff bases by refluxing the amine and aldehyde in toluene with a few drops of piperidine. The water formed during the course of the reaction was removed by employing a Dean-Stark trap.
- 3) In 1950, Hayes *et al.* ²⁴⁰ prepared Schiff bases by heating a mixture of an aldehyde and amine in benzene and removing water formed during the reaction using Dean-Stark apparatus.
- 4) In 1953, Giovambettista and Rabassa ²⁴¹ suggested acetic acid as a catalyst for the synthesis of Schiff bases in good yields.

As the first method was found to give Schiff bases in good yields, it was followed initially during the course of this investigation. Later on, it was found that the use of a few drops of acetic acid improved the yield.

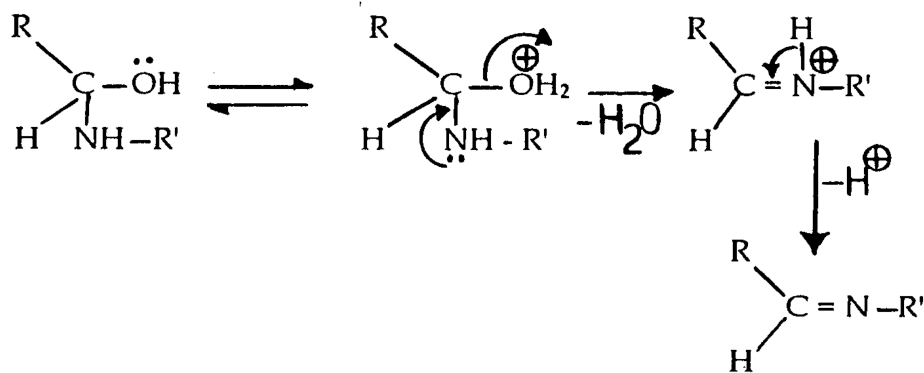
Reaction mechanism :



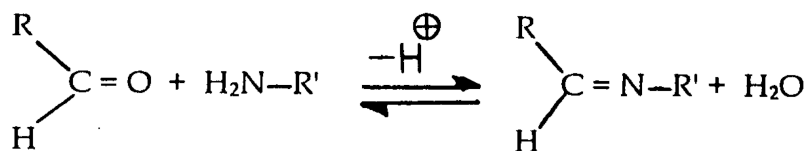
Addition of amines to aldehydes under mild acid catalysis. The acid catalyst protonates the carbonyl oxygen and promotes the attack of nucleophilic amines.



The adduct that is formed in this reaction undergoes a further reaction to eliminate water and form a carbon nitrogen double bond.



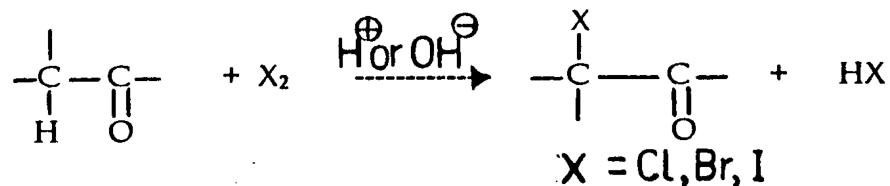
The overall reaction :



Hence, the combination of modified first and the fourth method was used during the synthesis of the schiff bases and thiosemicarbazones.

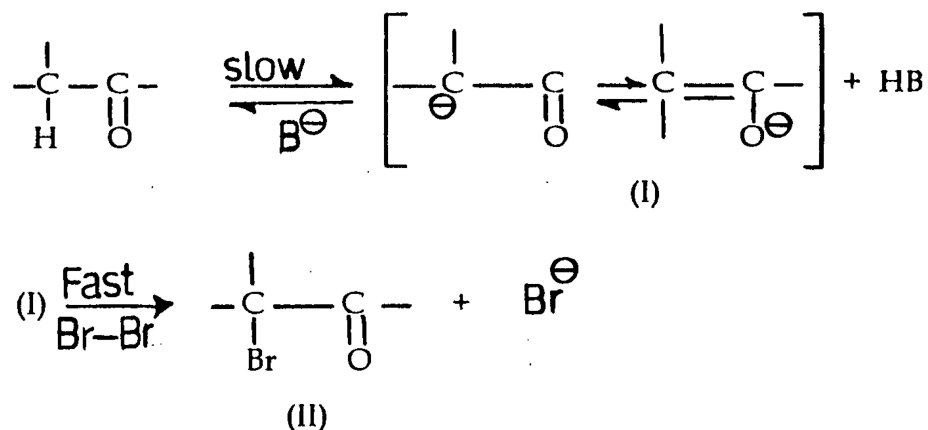
CHEMISTRY OF HALOGENATION OF KETONES

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



Base-promoted halogenation of ketones

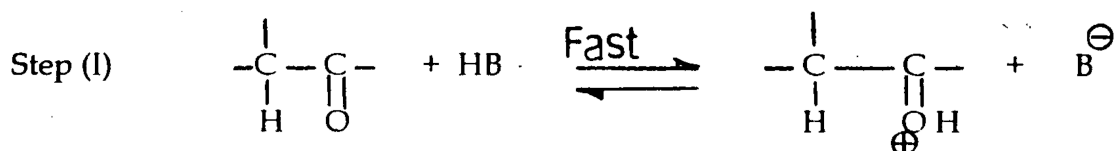
When basic catalysts are used, the base slowly abstracts a proton from the ketone to form carbanion (I) which then rapidly reacts with bromine to yield the bromoketone (II)

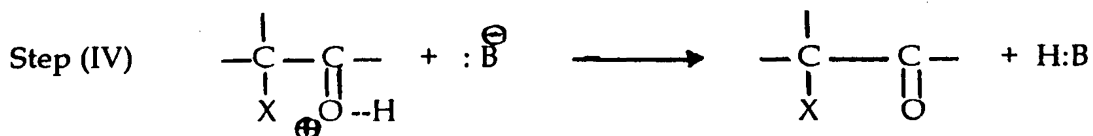
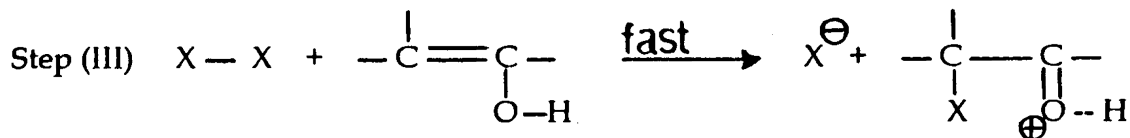
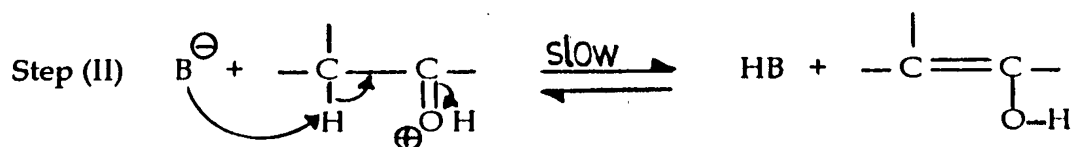


Since the rate of generation of carbanion determines the overall rate of the reaction it is the rate determining step. As fast as the carbanions are generated they are snapped by the bromine molecule.

Acid-catalysed halogenation of ketones

Acids like bases speedup 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 2 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 halogen to give the haloketone.

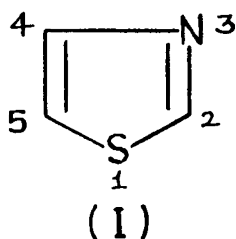
Solvents like chloroform, carbon tetra chloride, diethyl ether can be used conveniently with better results. When diethyl ether is used as a solvent, aluminum chloride is often added to prompt enolization.

It is observed during bromination that presence of sunlight or slight heating at initial stages, facilitates the initiation of the reaction. Heat or light may help bromine molecule to get polarised as $\text{Br}^{\bullet}$ radical, which would favour the attack of polarised Br_2 molecule or Br^+ on the enol form of the ketone.

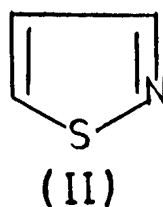
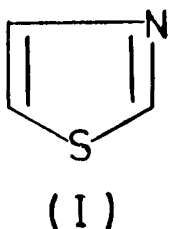
Cupric halide have occasionally being used to halogenate aromatic ketones particularly if the used of free halogen caused nuclear halogenation e.g. with phenolic ketones. The copper II halide presumably catalyses enol formation then transfers halogen to enol giving α -haloketone.

CHEMISTRY OF THIAZOLES

The thiazole heterocycle (I) was first delineated by Hantzsch and Weber ²¹². Further they have rightly described it as "the pyridine of the thiophene series". Since it closely resembles both the heterocycles viz. pyridine and thiophene. Despite this the reactivity of thiazole by and large is similar to that of pyridine.



The thiazole moiety exists in two different configurations (I) and (II) as thiazole and isothiazole respectively.



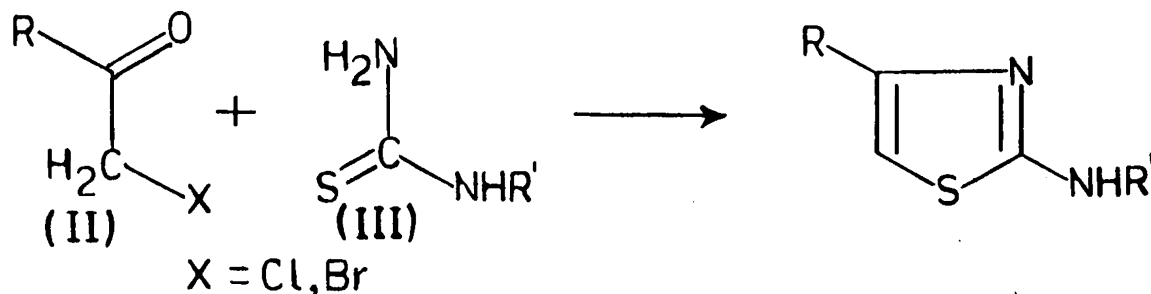
The thiazole derivatives have been more extensively studied as compared to the isothiazole derivatives, since they appear as important structural requirement in innumerable naturally occurring compounds possessing diverse properties.

The thiazole derivatives appear in the composition of Vitamin B1 (thiamine) and in the penicillins. Many fungicides, pesticides and bacteriocides are derivatives of 2-amino thiazoles. Other thiazole derivatives possess mito-depressive and mito-static properties ²¹³. Certain Schiff bases derived from 2-amino/2-phenyl thiazoles and their derivatives show diuretic properties ²¹⁴. Mercapto thiazole derivatives are used to accelerate the vulcanization of rubber while alkyl and acyl thiazoles are known to be flavouring agents. Several thiazole derivatives have been isolated from natural products.

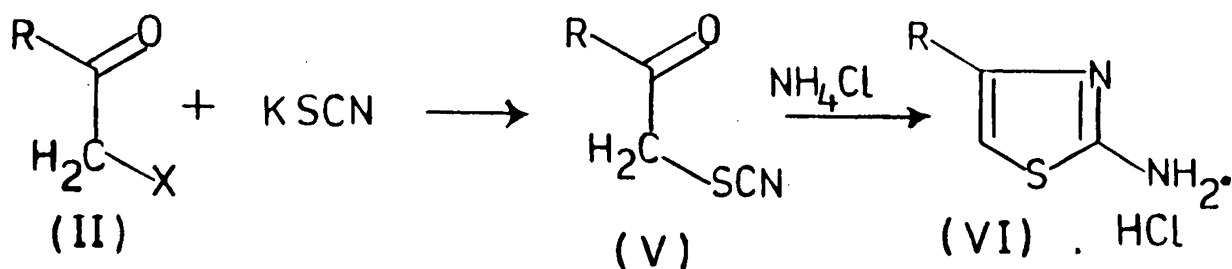
General Methods For The Synthesis Of Thiazole Derivatives.

A) Methods of preparation of amino thiazoles and its derivatives.

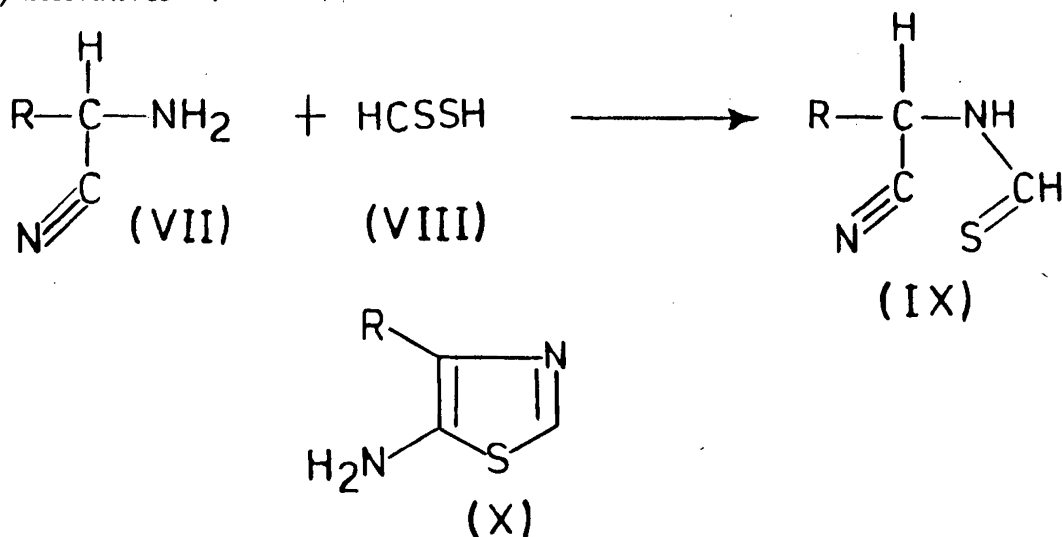
i) The most common method employed for the synthesis of substituted thiazole has been the one described by Hantzsch ²¹⁵. The reaction between α - halo carbonyl compound (II) and thiourea / substituted thiourea (III) yields the respective 2-amino thiazole or its derivatives (IV).



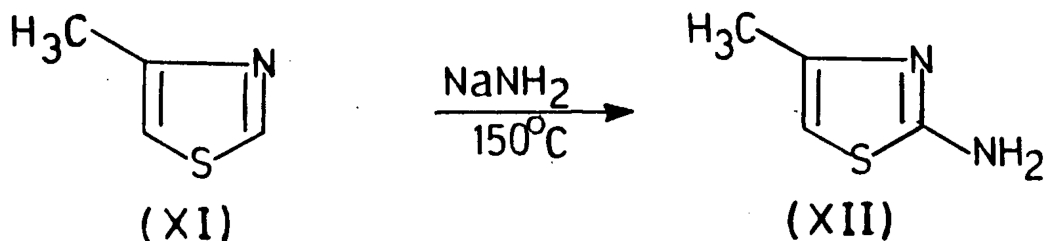
ii) Potassium thiocyanate reacts with α - halo carbonyl compound (II) to yield α - thiocyanato ketone (V) which on treatment with ammonium chloride obtains the hydrochloride of 2-amino thiazole (VI) ²¹⁶.



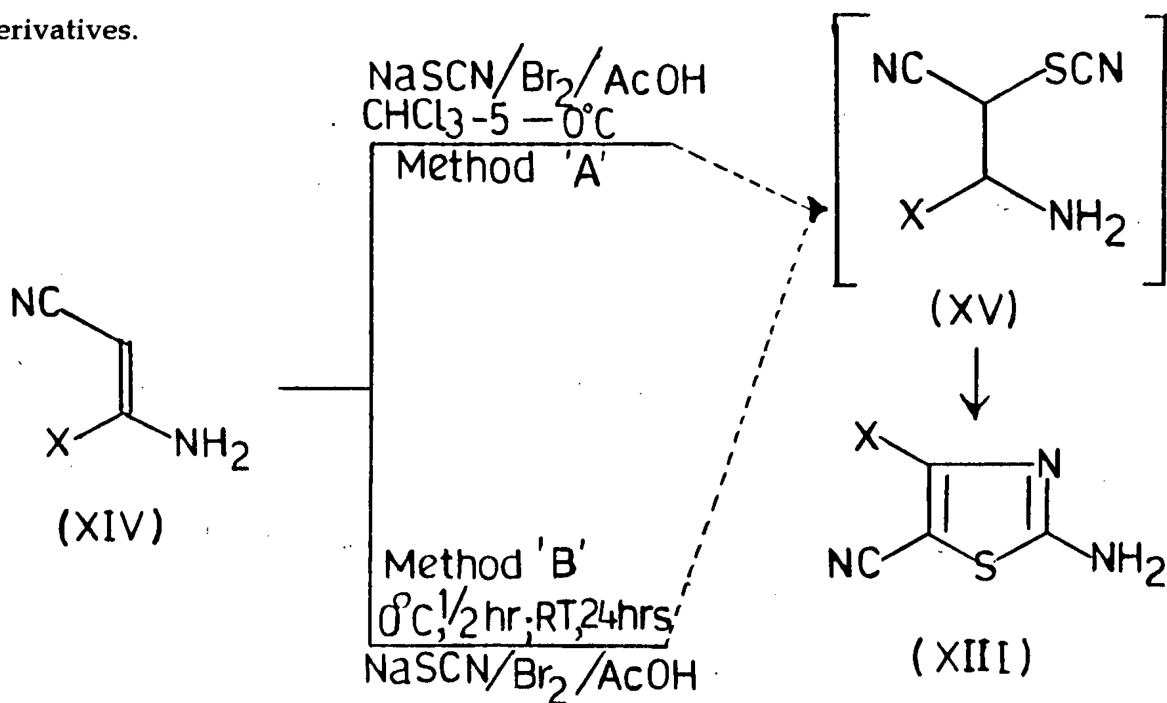
iii) α - Aminonitrile (VII) reacts with dithioformic acid (VIII) at room temperature to obtain an intermediate (IX) which cyclises to yield the 5-amino thiazole (X) derivatives ²¹⁷.



iv) 2-Amino 4-methyl thiazole (XII) is formed by heating 4-methyl thiazole (XI) with sodamide for 15 hours at 150°C ²¹⁸. This reaction is extensively studied for the preparation of 2-amino pyridine but has received less attention in the case of thiazole nucleus.

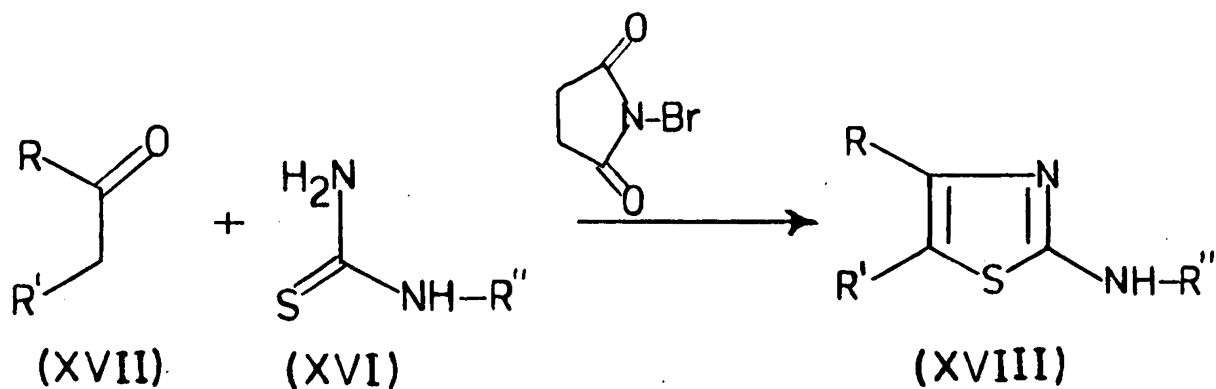


v) Recently, Maria, T. C. *et al.* have reported ²¹⁹ an improved procedure for the preparation of 2,4-diamino thiazoles (XIII) by reacting 3-amino 3-(dialkylamino)-propene nitriles (XIV) with sodium thiocyanate in presence of bromine and acetic acid. The intermediate (XV) formed cyclises rapidly to form the thiazole (XIII) derivatives.

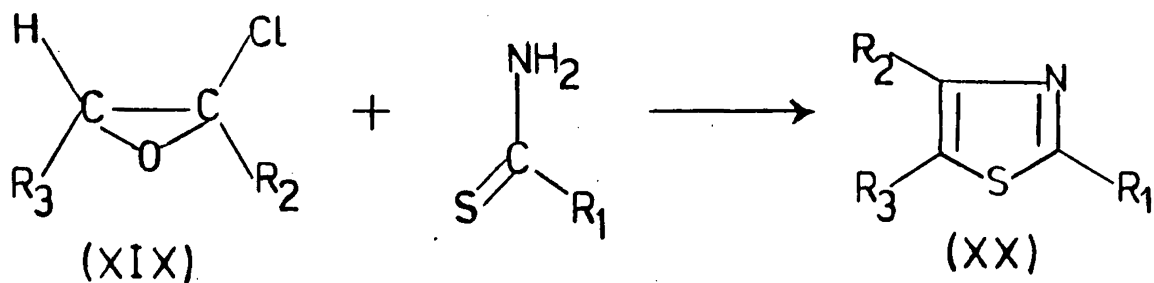


x = Pyrrolidino, piperidino, morpholino, 4-methyl piperazino, benzylamino etc.

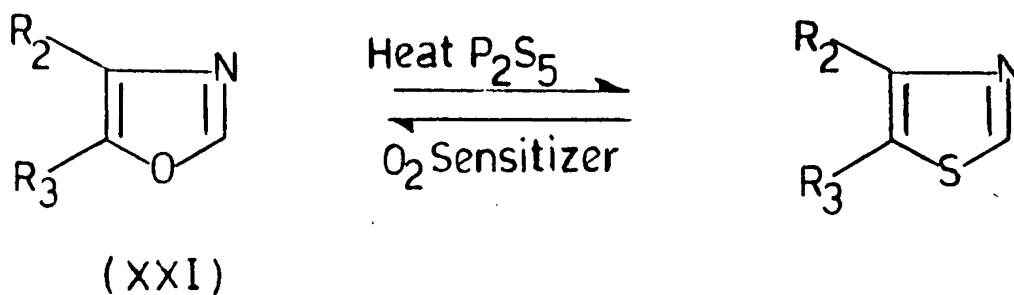
vi) The reaction of substituted thiourea (XVI) with ketones (XVII) in presence of N-bromosuccinimide furnishes the 2-amino thiazole derivatives (XVIII) ²²⁰.



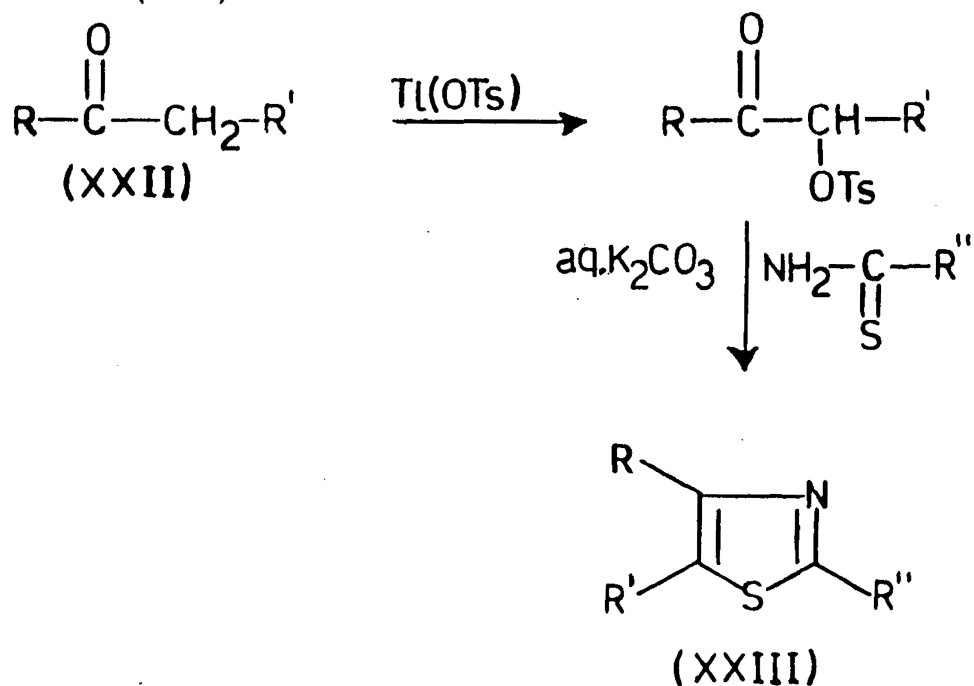
vii) 1-Chloro-1,2 epoxides (XIX) condensed with thioamides leads to 2,4,5 trisubstituted thiazoles (XX) ²²¹.



viii) Thiazoles from oxazoles were also reported ²²². Oxazoles (XXI) heated with P_2S_5 can be converted to thiazoles.

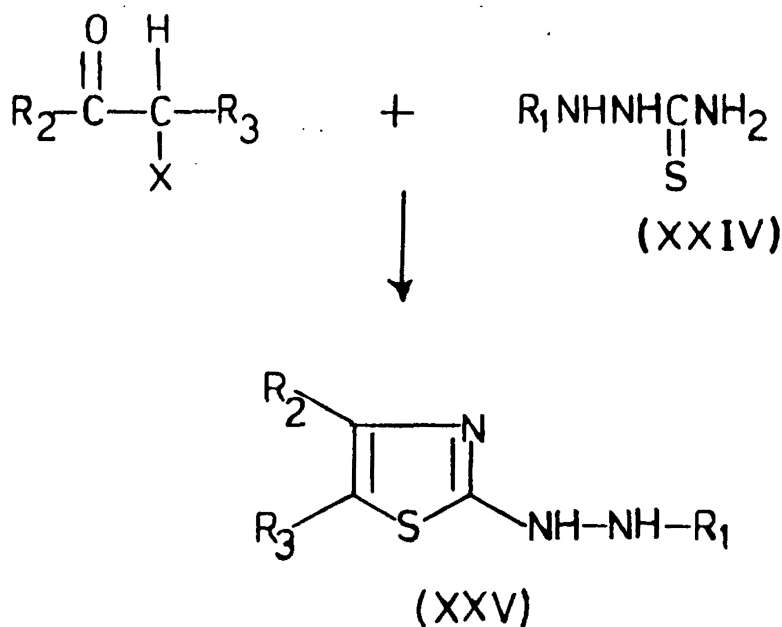


ix) Enolisable ketones (XXII) react with thioamides / substituted thioamides in acetonitrile in presence of thallium (III) *p*-tolyl sulphonate (TTS) to yield 2-substituted thiazoles (XXIII) ²²³.

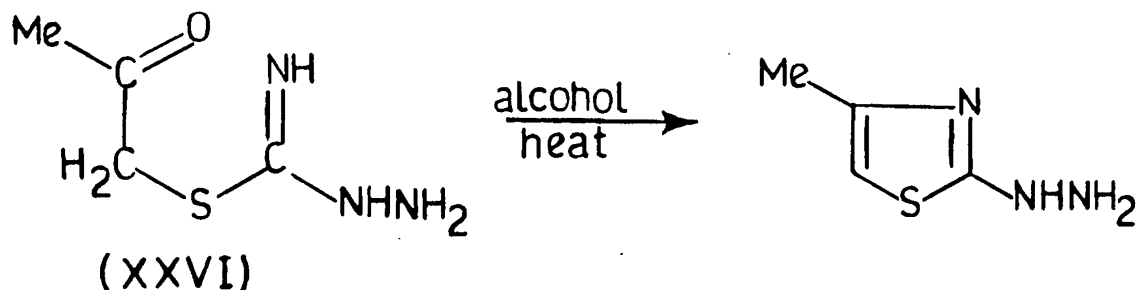


B) Methods for the synthesis of 2-hydrazino thiazoles and its derivatives.

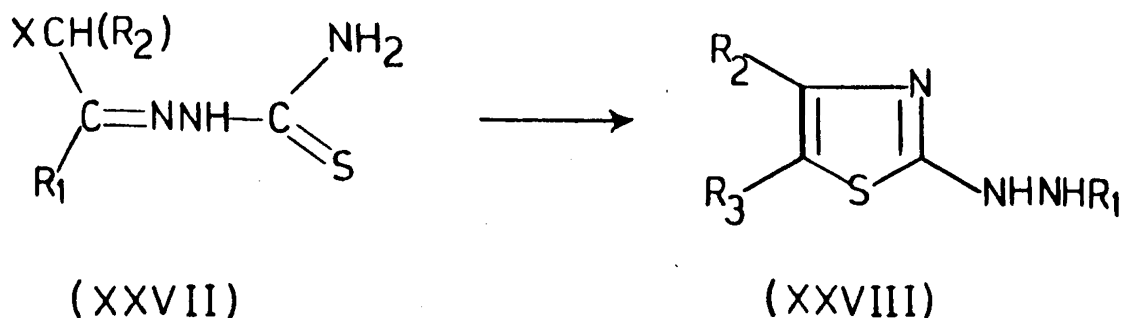
i) Thiosemicarbazides (XXIV) $\text{R}_1 = \text{H}$, yield the 2-hydrazino thiazoles (XXV) on reaction with α - halocarbonyl compounds and several derivatives of this type have been reported with ^{224,225} $\text{R}_1 = \text{R}_3 = \text{H}$ and $\text{R}_2 = \text{CH}_3, \text{Ph}$.



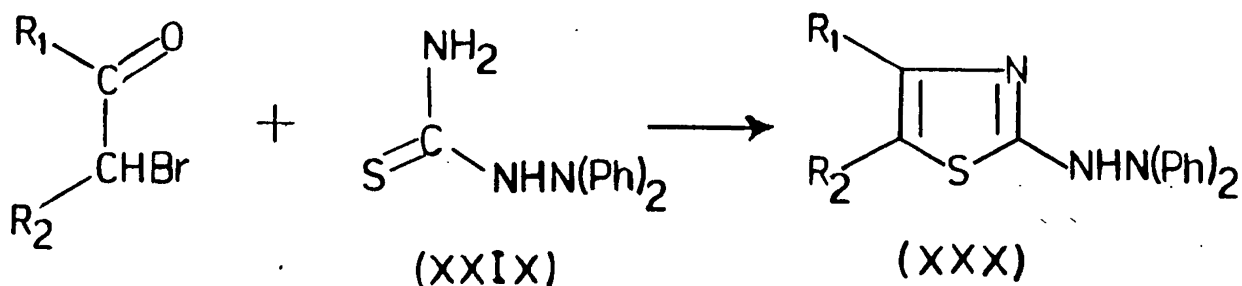
ii) With chloroacetone in neutral medium acyclic intermediate (XXVI) gives thiazoles analogous to those obtained ^{226,227} with thiourea and thioamides.



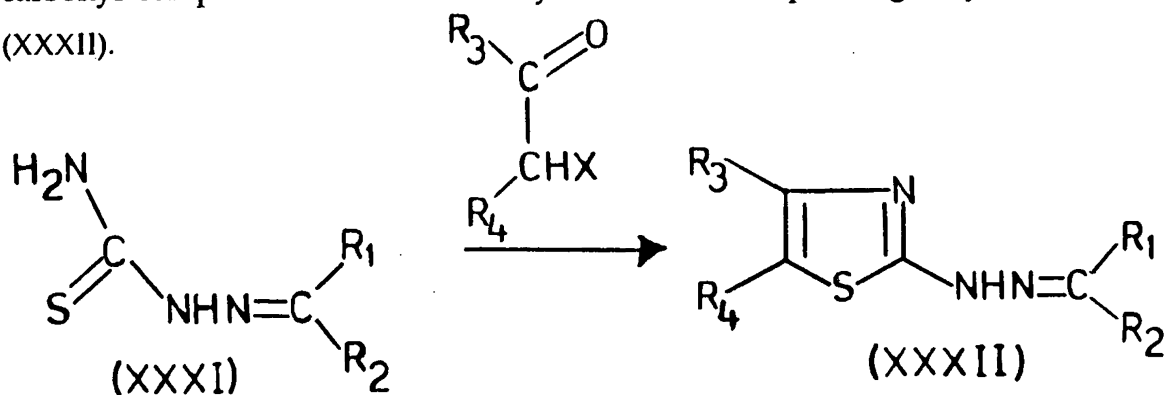
iii) Under acidic conditions, thiosemicarbazone intermediate (XXVII) has been isolated, this can be cyclised in alcohol into the corresponding 2-hydrazino thiazole (XXVIII) in the presence of benzaldehyde ^{228, 229, 230}.



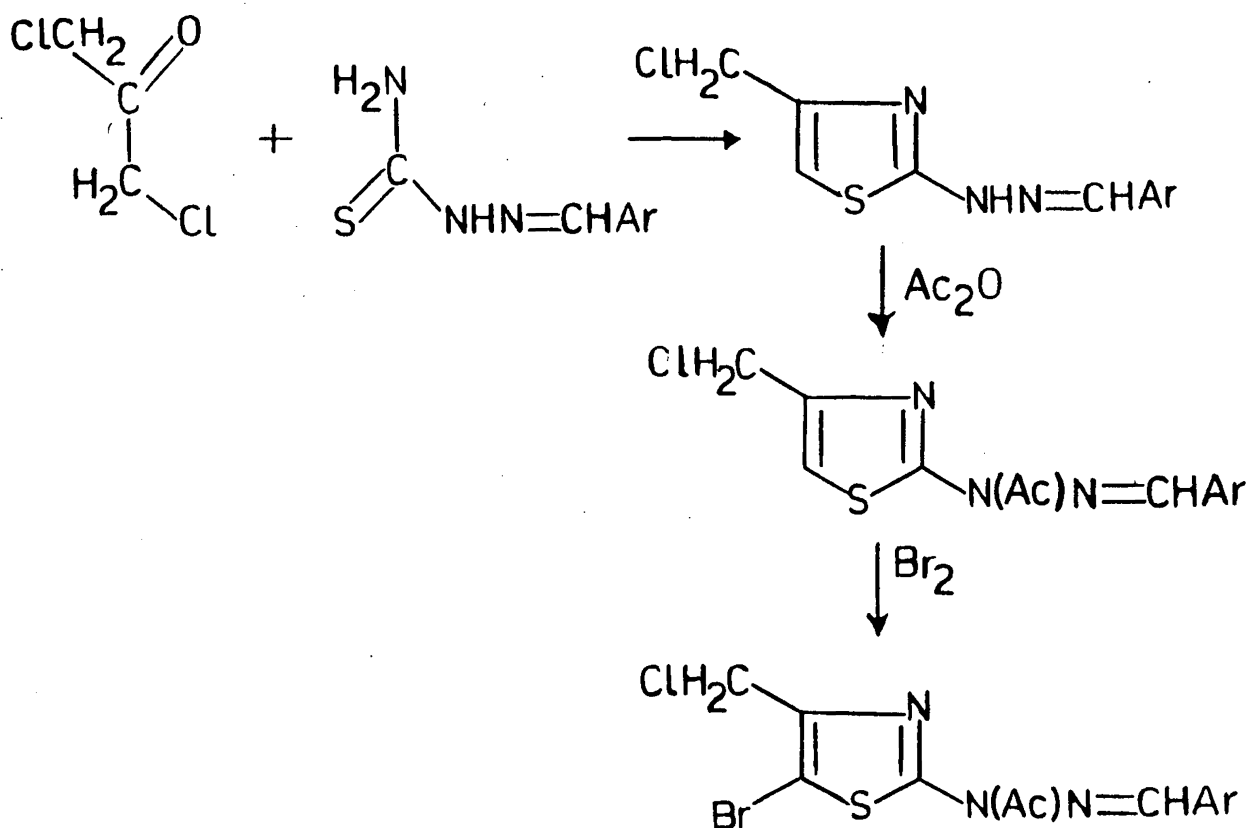
iv) Disubstituted thiosemicarbazide such as (XXIX) gave α - hydrazino derivatives (XXX), R₁ = CH₃ and C₆H₅ and R₂ = H, CH₃, C₆H₅ the yield ranges between 60-90% ²³¹.



v) Thiosemicarbazones of general formula (XXXI) react either with α - halo carbonyl compounds ^{232, 233, 234} to yield the corresponding 2-hydrazino thiazoles (XXXII).



vi) The interaction of sym-dichloroacetone with thiosemicarbazones similarly yields 2- arylidene hydrazino-4-chloro methyl thiazoles ²³⁵ which can be further acylated and brominated .



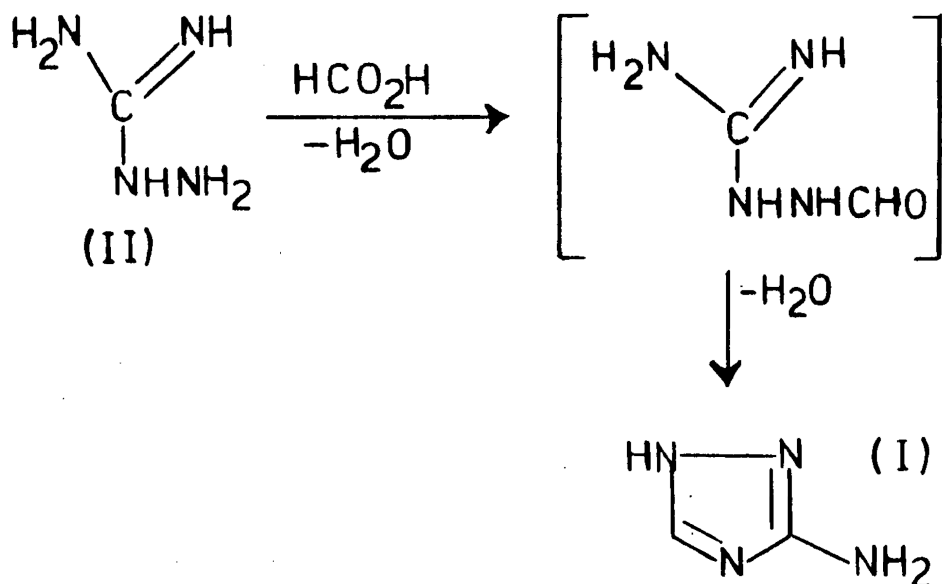
In our course of synthetic work , we used the fifth method for the preparation of the 2-arylidene hydrazino 4-aryl thiazoles. In this method the α - haloketone was condensed with various substituted thiosemicarbazones to yield title thiazoles.

CHEMISTRY OF TRIAZOLES

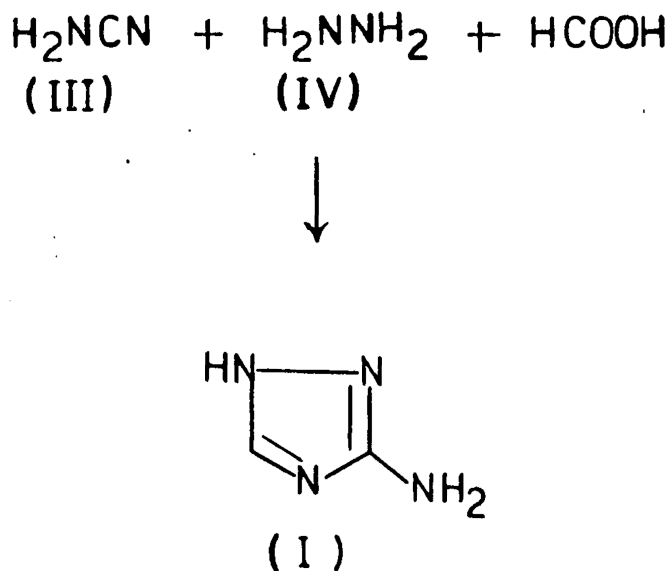
General Methods of the syntheses of Amino Triazole derivatives

A) Methods of preparation of 3-amino triazoles and its derivatives.

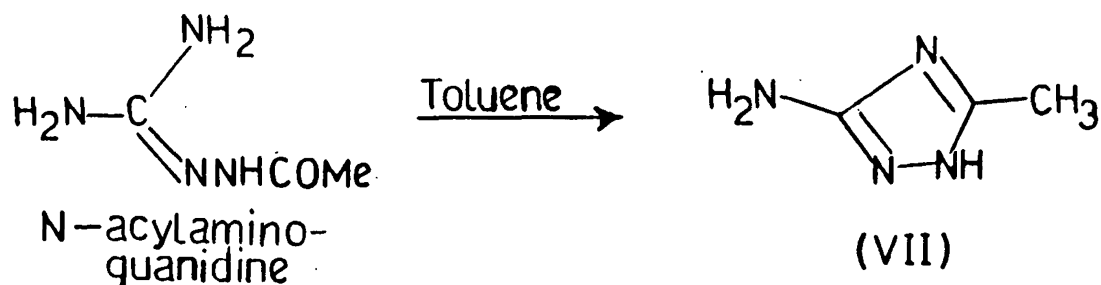
i) The preparation of 3-amino triazole (I) was readily accomplished by heating a mixture of an amino guanidine (II) salt of (H_2CO_3 , HCl , HNO_3 , H_2SO_4) and formic acid in toluene and separating the water formed in reaction ^{242, 243}.



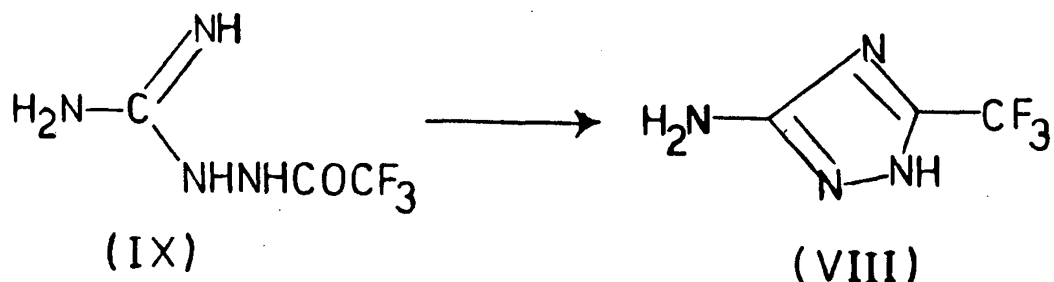
ii) Pure 3-amino triazole has also been claimed to result from the interaction of an equimolar mixture of cyanamide (III) and hydrazine (IV) with formic acid ²⁴⁴.



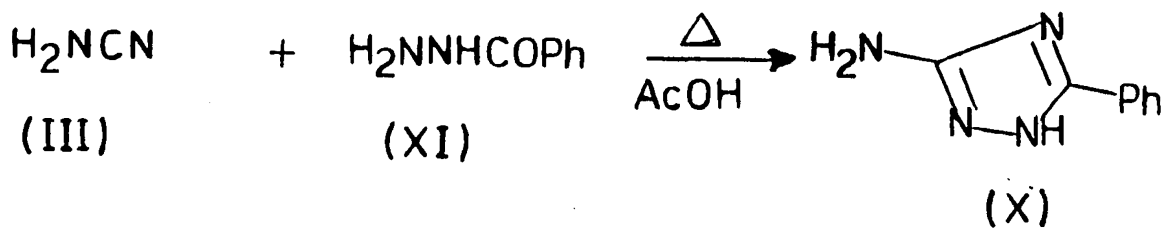
iii) The conversion of N-acylamino guanidines (VI) to 3-amino -5-alkyl triazoles (VII) has been effected by azeotropic removal of water in hot toluene ²⁴⁵ and by treatment with dilute base either at room temperature ^{246, 247} or at reflux ^{248, 249}.



iv) Excellent yields of perfluoroalkyl 3-amino triazole (VIII) were obtained by the thermal dehydration of the hydrazides of perfluoro carboxylic acids (IX). The cyclisation of this type of hydride in basic medium was unsuccessful.

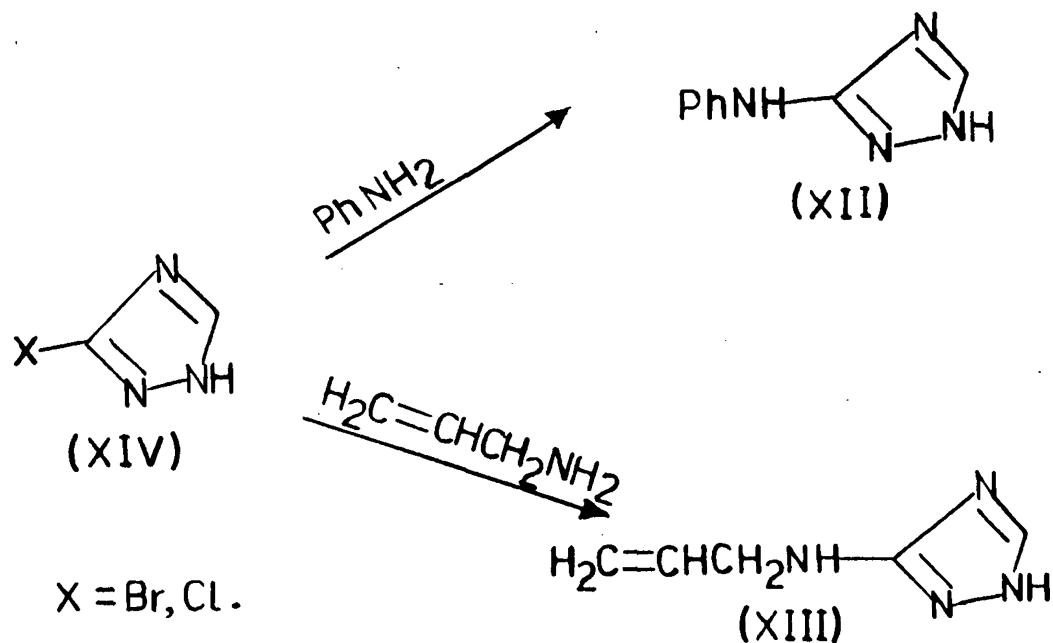


v) The 3-amino-5-aryl triazoles (X) are prepared by treatment of aroyl hydrazines (XI) with cyanamide (III) in acetic acid under reflux ²⁴⁸.

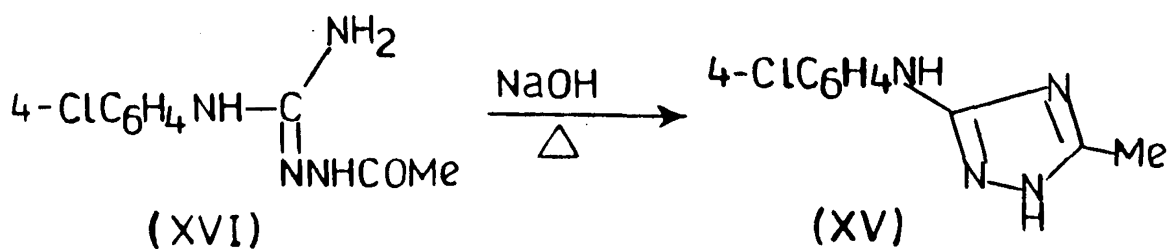


Various 3-amino-5-aryl triazoles are reported to be prepared by various methods including the cyclisation of N-arylamino guanidines either in hot base or fusion of solid at temperatures greater than 100°C ^{248, 250-252}.

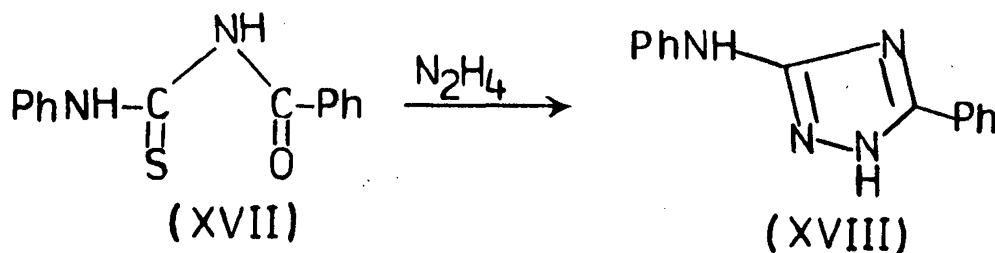
vi) The simple 3-substituted amino triazoles (XII) and (XIII) are easily prepared in high yields by amination of 3-bromo or 3-chloro triazoles (XIV) with alkyl and aryl amines at temperatures greater than 130°C ²⁵³⁻²⁵⁵.



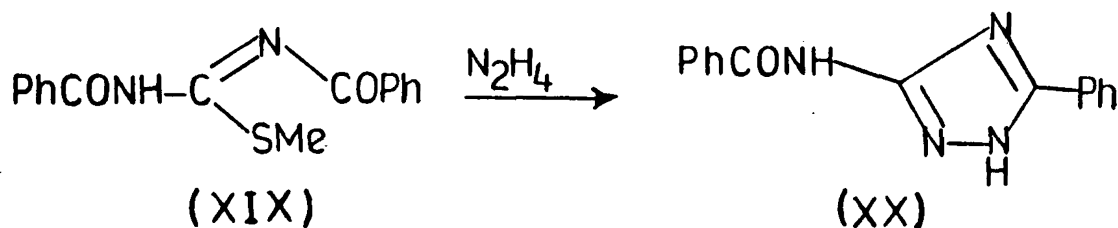
vii) Excellent yields of 3-arylamino 5-alkyl triazoles (XV) were produced by the cyclisation of preformed N-aryl-N'-acylamino guanidines with aqueous sodium hydroxide ^{252, 256}. This method is illustrated by the conversion of (XVI) to (XV) in which cyclisation occurred between the carbonyl function and the unsubstituted amino group.



viii) 3-Aryl-1-benzoylthioureas (XVII) react with hydrazine in hot toluene to give 3-aryl-amino-5-phenyl triazoles (XVIII) ²⁵⁷.

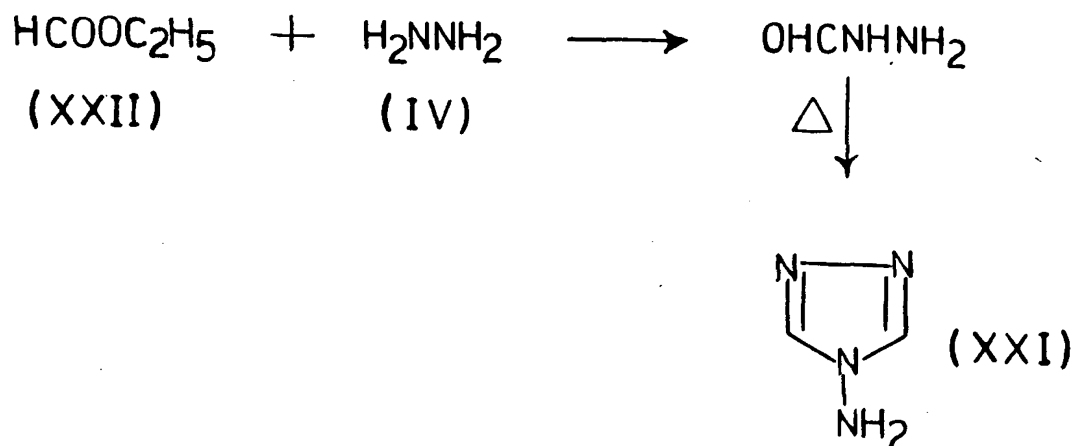


Under similar conditions the conversion of 3-alkyl-1-benzoyl thioureas to triazoles was unsuccessful. In contrast the 1,3- dibenzoyl 5-methyl isothiuronium compound (XIX) and hydrazine hydrate in refluxing ethanol gave 85% yield of 3-benzamide 5-phenyl triazole (XX) ²⁵⁸.

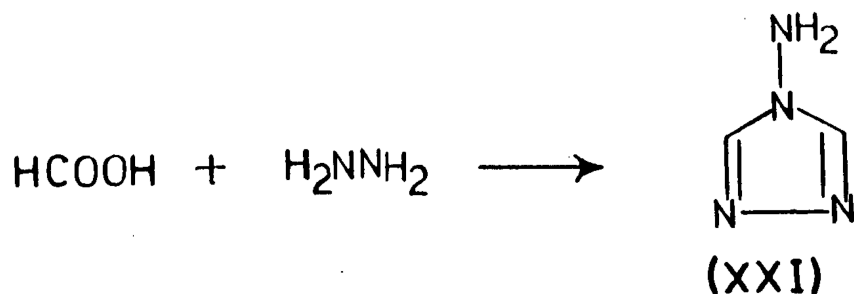


B) Methods of preparation of 4-amino triazoles and its derivatives.

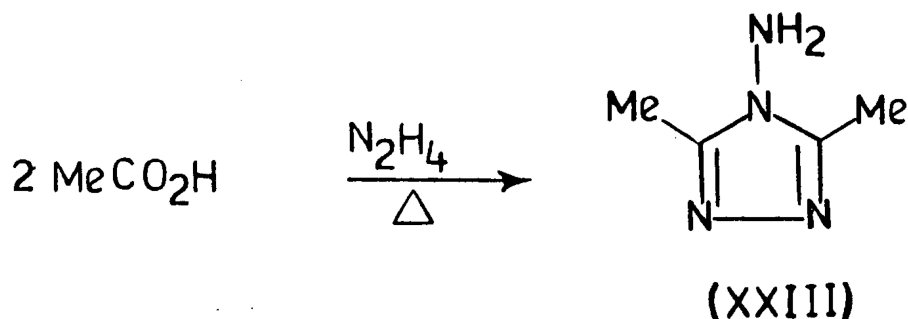
i). 4-Amino triazole (XXI) has been prepared ^{259, 260} by reaction of ethyl formate (XXII) with hydrazine (IV) to give formhydrazide, which was heated at 150 to 200°C to effect self condensation to give (XXI).



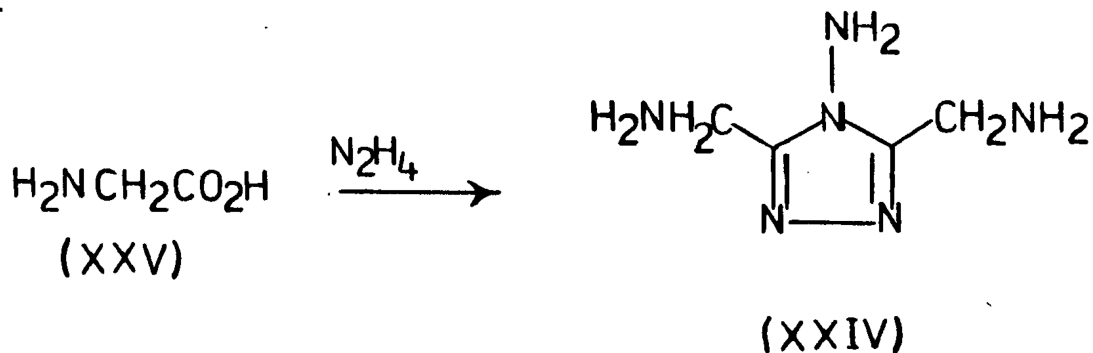
Similar interaction of formic acid and hydrazine gave good yield of 4-amino triazole (XXI) ²⁶¹⁻²⁶³.



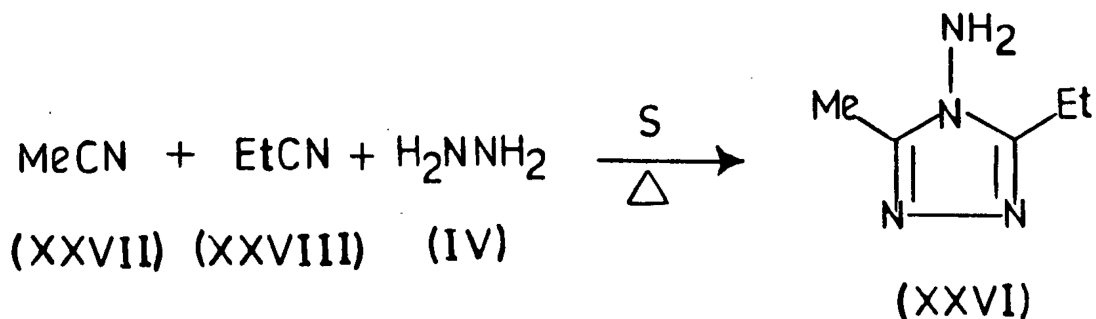
ii) Other carboxylic acids and their functional derivatives have also been used to prepare alkyl and substituted alkyl-4-amino triazoles e.g. acetic acid and hydrazine hydrate at a high temperature gave 3,5-dimethyl-4-amino triazole (XXIII) ^{261, 262, 264}.



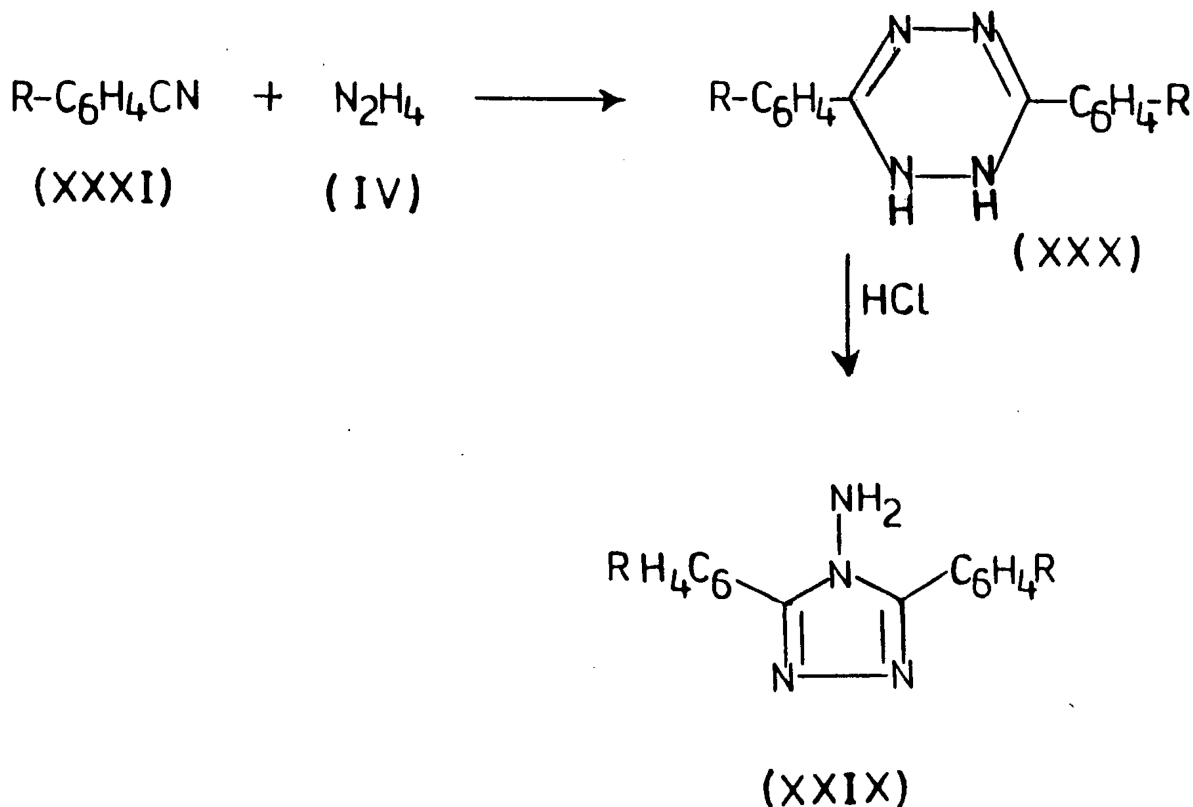
iii) Similar reactions have been reported for the preparation of 4-amino-3,5-bis(aminoalkyl) triazoles ²⁶⁵⁻²⁶⁸ which is prepared by reaction of glycine (XXV) with hydrazine to give (XXIV).



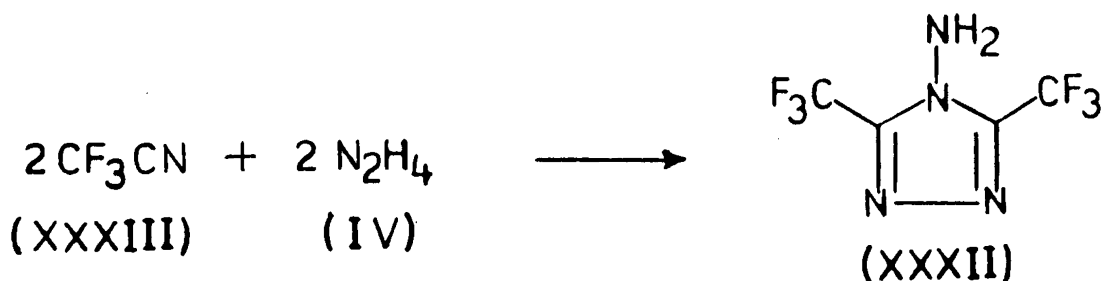
iv) Sulfur or sulfur containing compounds catalyze the formation of 4-amino triazoles e.g. 4-amino triazole (XXVI) substituted at 3,5 position with different substituents was prepared by the reaction of equimolar amounts of acetonitrile (XXVII) and propionitrile (XXVIII) with a mixture of hydrazine (IV) and sulfur ²⁶⁹.



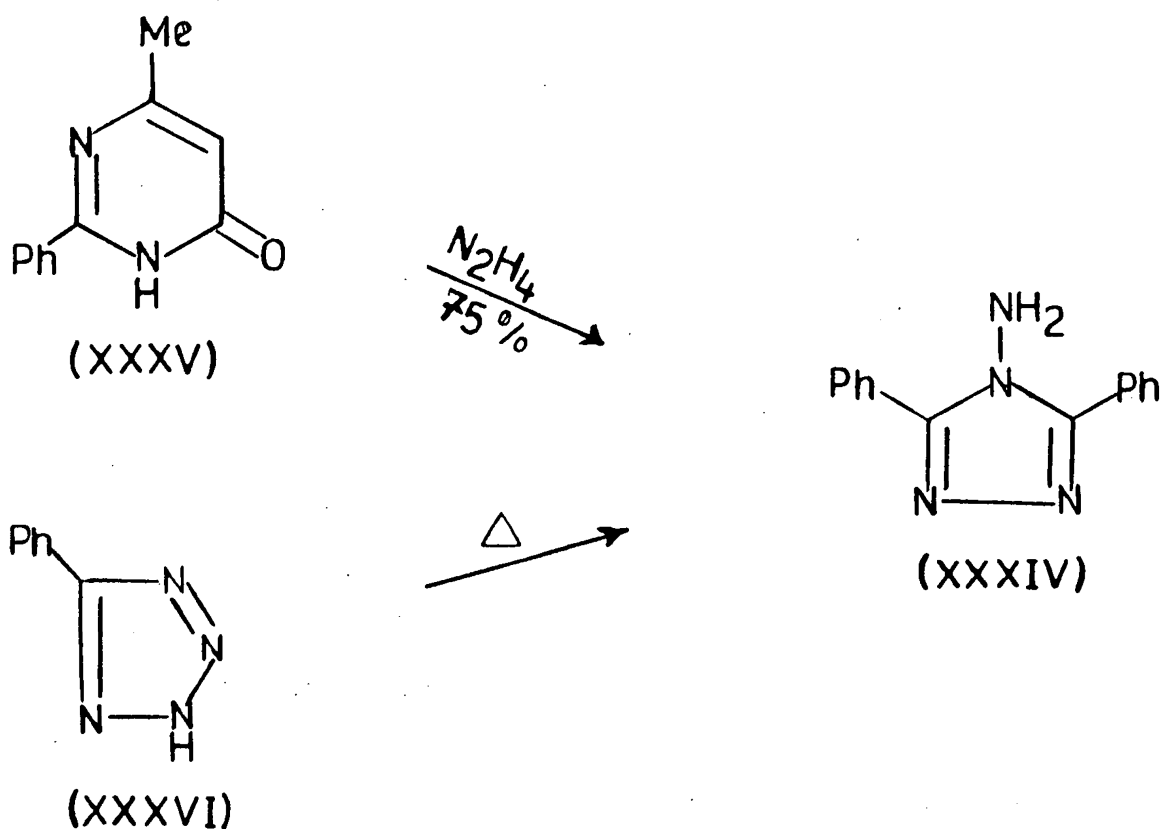
v) The preparation of 4-amino 3,5 diaryltriazoles (XXIX) are usually effected by the acidic rearrangement of 1,2 dihydrotetrazines (XXX) which are obtained by the reactions of equimolar amounts of aryl nitriles (XXXI) and hydrazine (IV) in refluxing benzene or toluene ²⁷⁰.



vi) Perfluoroalkyl triazoles (XXXII) are prepared by various methods e.g. per fluoro acetonitrile (XXXIII) with hydrazine (IV) in a sealed tube at room temperature gave (XXXII) ²⁷¹.



vii) 4-Amino 3,5-diphenyl triazoles (XXXIV) are also formed from the decomposition of other hetero aromatic ring system e.g. reaction of oxo pyrimidine (XXXV) with hydrazine ²⁷² and also the thermolysis of 5-phenyl tetrazole (XXXVI) in various solvents ²⁷³ give (XXXIV).

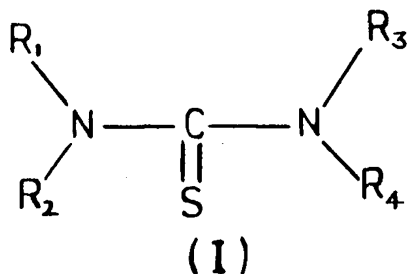


CHEMISTRY OF THIOUREAS

Since the first syntheses of thiourea and its derivatives were made in about 1870, a vast literature on these compounds has accumulated. In fact an extensive knowledge of the properties and principles of syntheses 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).



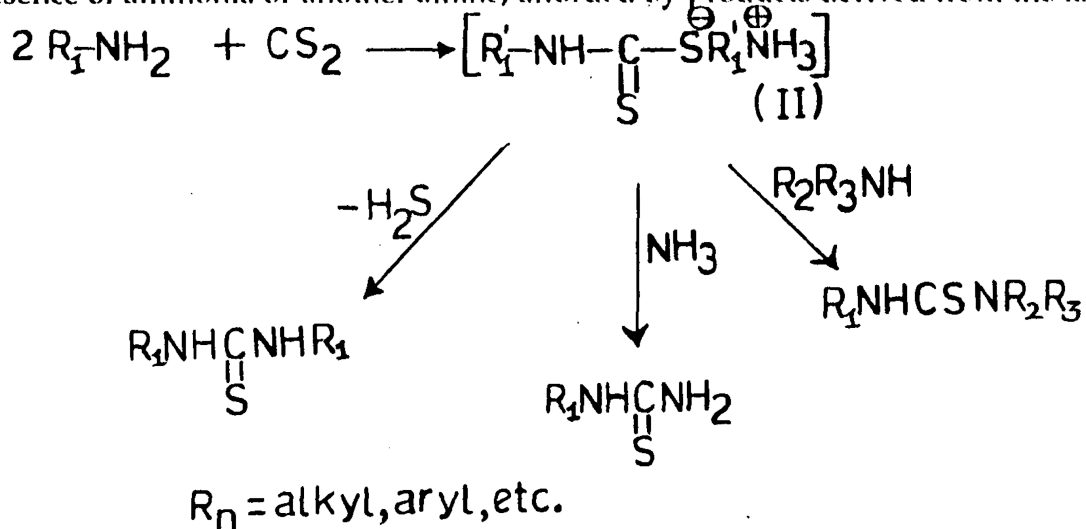
$\text{R}_n = \text{H, Alkyl, Aryl, etc.}$

Summary of general synthetic methods

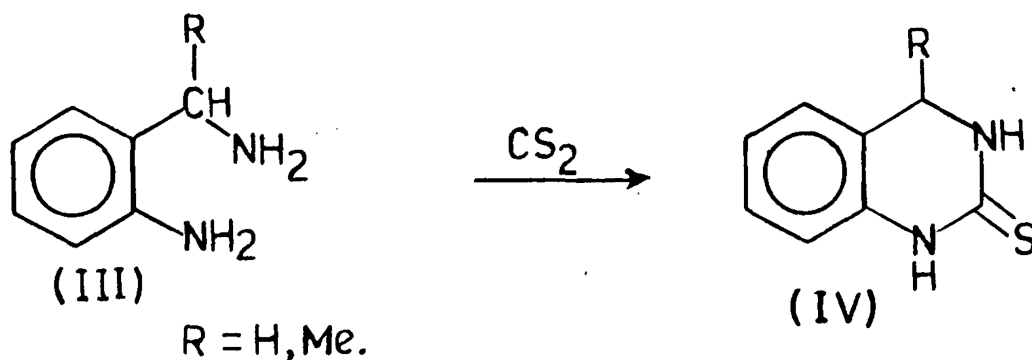
As a synthetic route to thioureas the direct thionation of the carbonyl group of ureas by means of phosphorous pentasulfide is of minor significance. Apparently, it applies to the synthesis of tetra substituted thioureas and certain heterocycles having an incorporated thiourea moiety ^{274, 275}.

However several other well established methods are available for the syntheses of thioureas. One of the cheapest methods of preparing symmetrical thioureas is based on the reaction of primary amines (I) with carbon disulfide ^{274, 275, 276}.

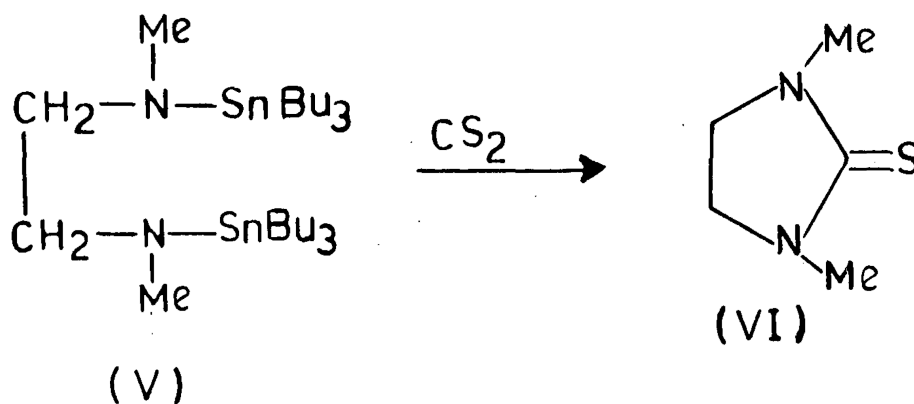
The mechanism of this is not quite clear, but apparently an intermediate ammonium dithiocarbamate (II) is involved as the reaction, when carried out in the presence of ammonia or another amine, afforded by products derived from the latter.



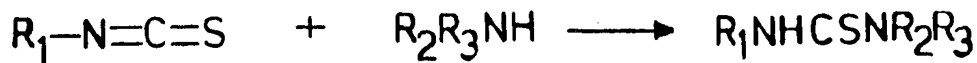
The reaction is influenced by catalysts such as elemental sulfur, hydrogen peroxide, hydroxide ions, iodine and pyridine and is applicable also to the syntheses of cyclic thioureas as exemplified by the preparation of (III) from (IV) ²⁷⁷.



An interesting variation involves the reaction of the tributyltin- substituted ethylene diamine (V) with carbon disulfide affording the cyclic thiourea (VI) ²⁷⁸.



Perhaps the most important standard method of synthesizing thiourea is based on the reaction of alkyl and aryl isothiocyanates with ammonia or amines²⁷⁹. By this reaction monosubstituted 1,3-disubstituted, and 1,1,3-tri substituted thioureas can be obtained.



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 of amine derivatives such as ketimines by hydroxylamines, imino esters and amidines ^{274,275,276}. The same reaction is used to synthesize the various thioureas and have been tabulated in Table no. 10.

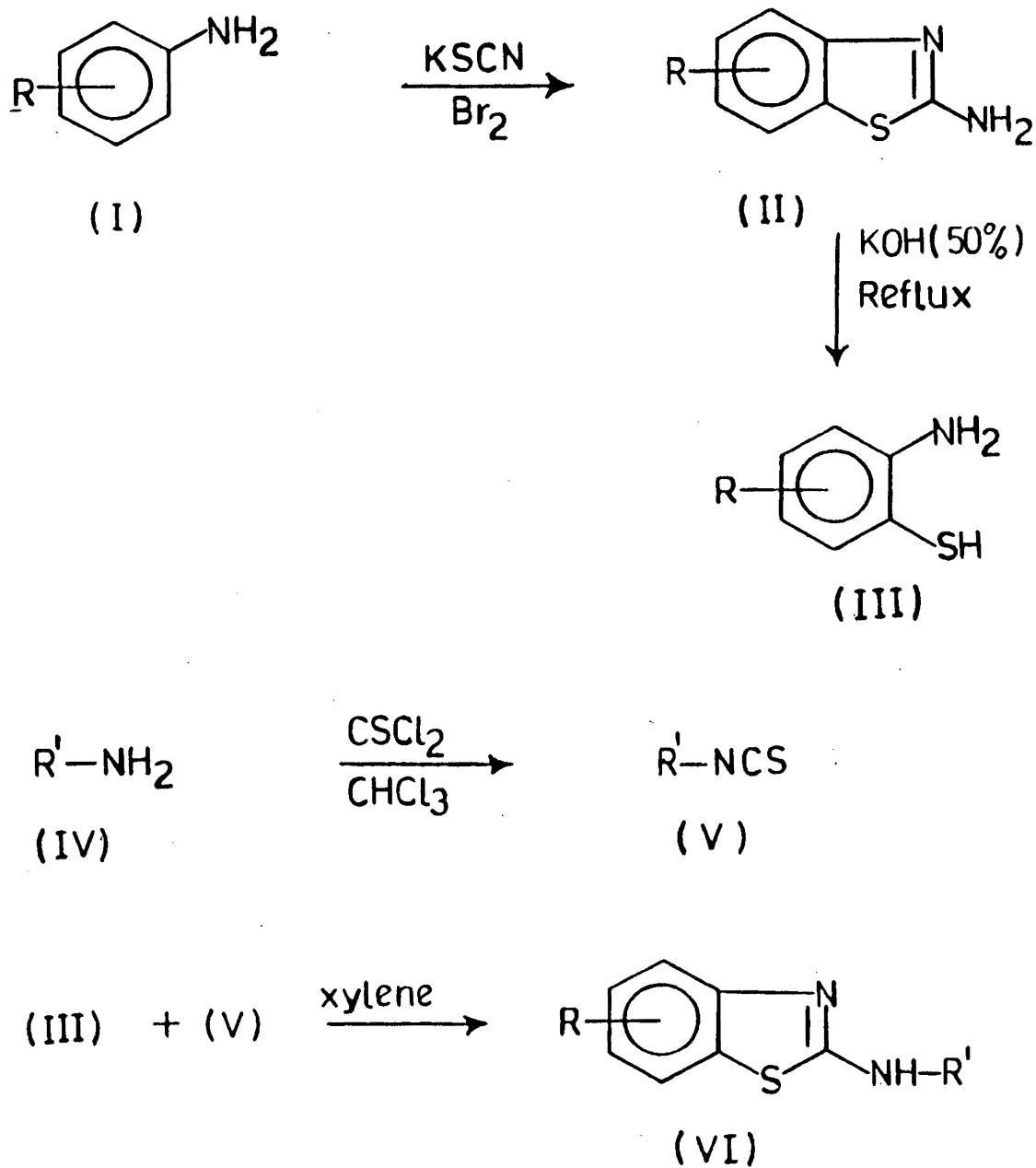
PART I C

SCHEMATIC REPRESENTATION
OF THE SERIES OF
COMPOUNDS SYNTHESISED

SCHEME II

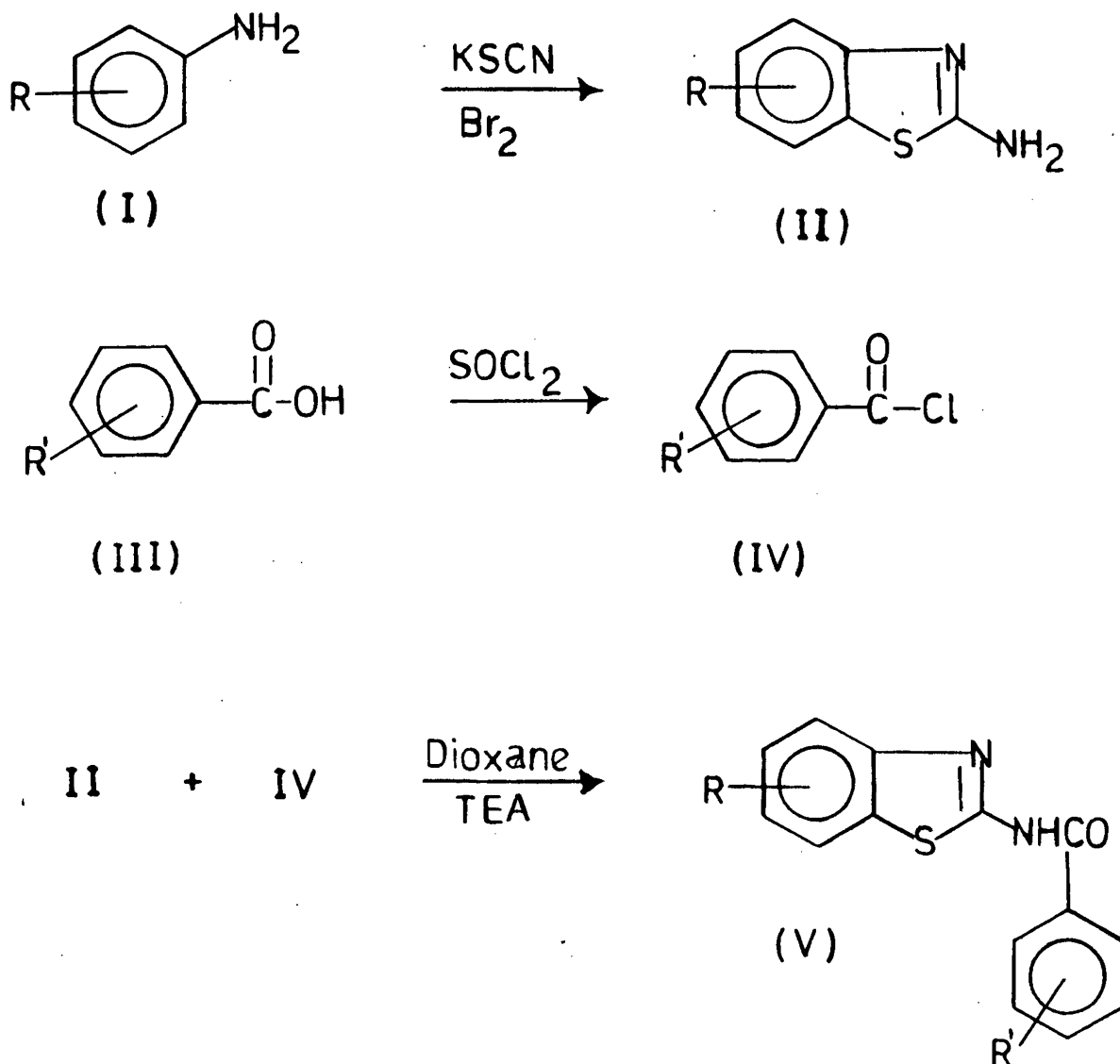
109

Synthesis of 5,6 - Disubstituted 2 - (alkyl/substituted aryl) amino
Benzothiazoles



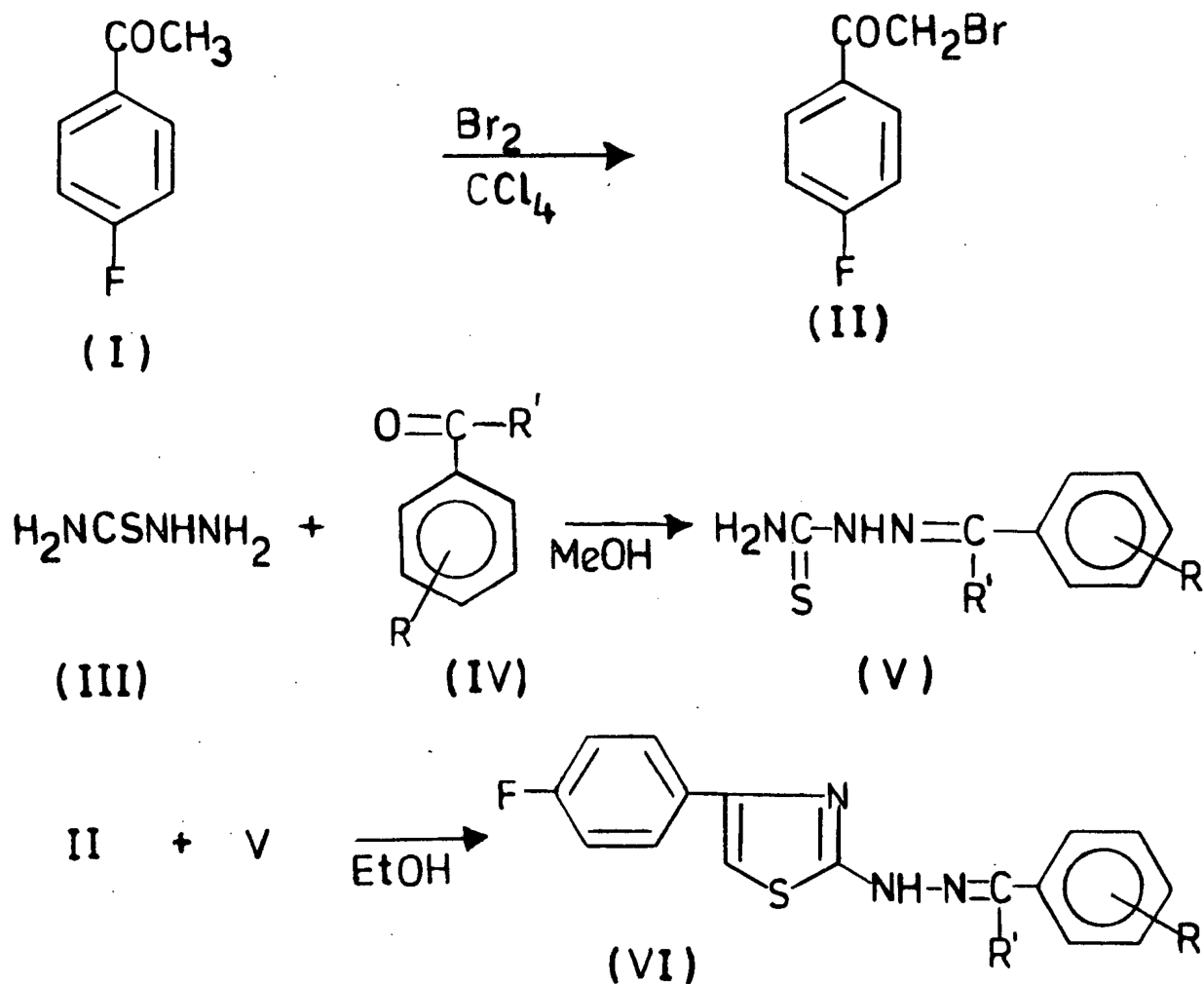
SCHEME III

Synthesis of 5, 6 - Disubstituted 2 - (substituted phenyl carboxamido)
Benzothiazoles.



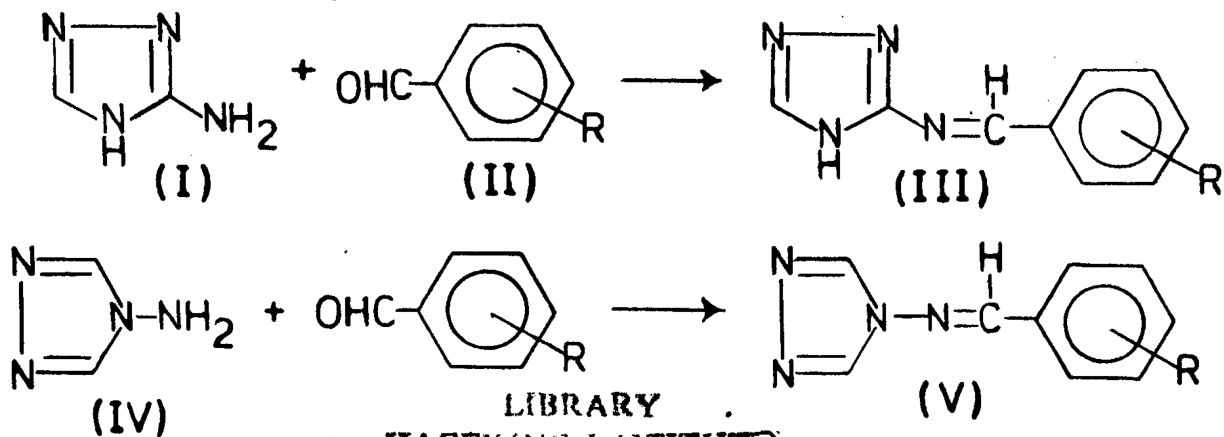
SCHEME IV

Synthesis of 2-substituted arylidene hydrazino 4-aryl Thiazoles.

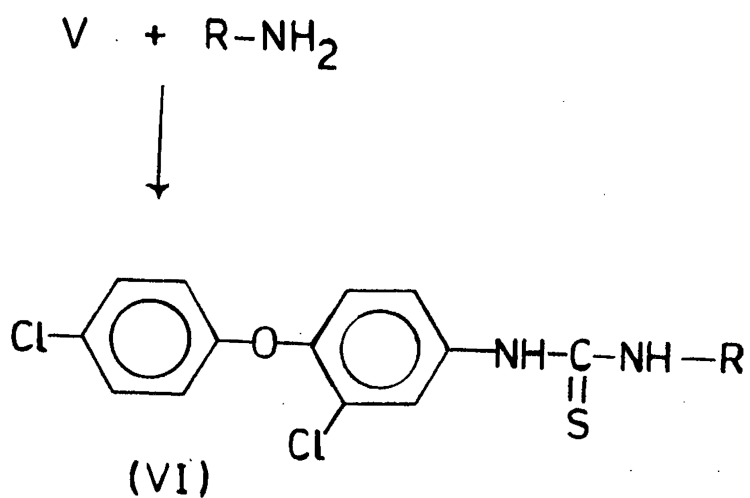
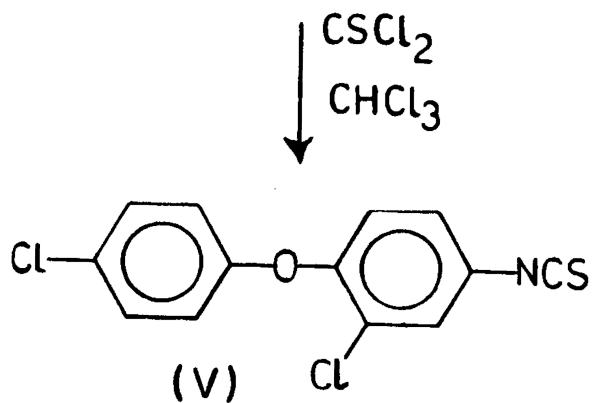
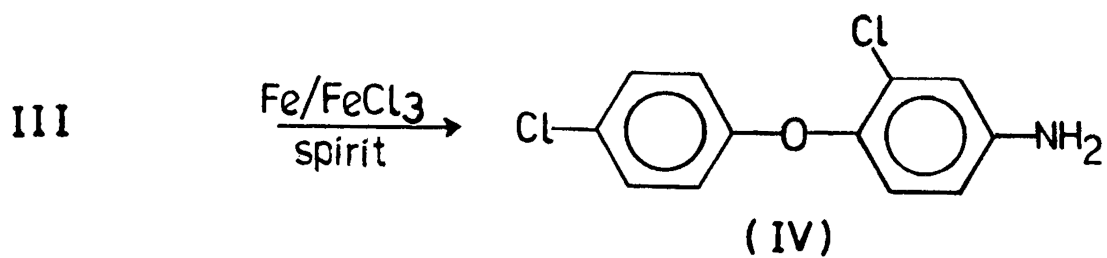
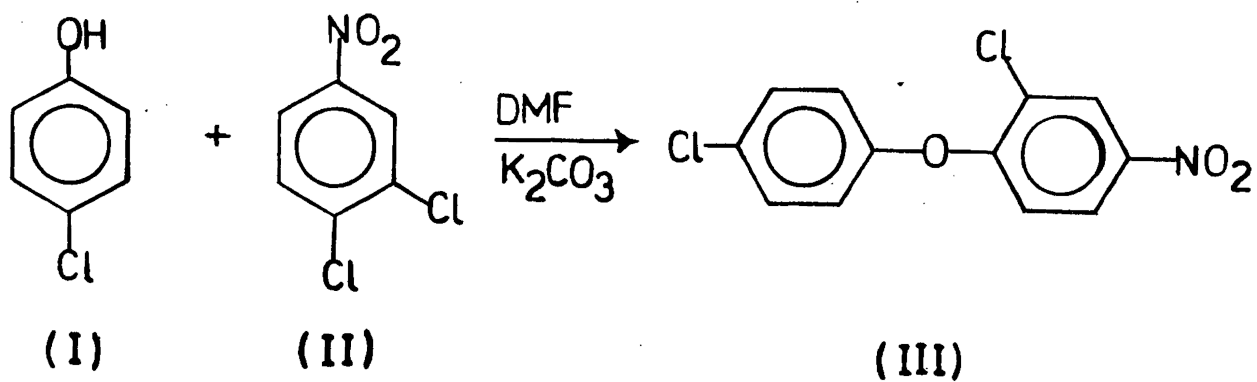


SCHEME V

Synthesis of 3/4 [(Substituted phenyl) 1 - methyl - ene] amino 1,2,4 Triazole



Synthesis of 4(*p* - chloro phenoxy) 3 - chloro phenyl substituted phenyl
Thiocarbanilide.



PART II

SYNTHESIS OF 5, 6 - DISUBSTITUTED 2 - (SUBSTITUTED ARYL / ALKYL) AMINO BENZOTHAZOLES

This part deals with the syntheses of 5,6-disubstituted 2-(substituted aryl/alkyl) amino benzothiazoles which involves the following steps.

- 1) Synthesis of 5,6-disubstituted 2-amino benzothiazoles.
- 2) Synthesis of 2-amino -4-chloro-5fluoro thiophenol.
- 3) Synthesis of substituted aryl/alkyl isothiocynates.
- 4) Synthesis of title compounds by condensation of 2-amino -4-chloro-5-fluoro thiophenol with various substituted aryl/alkyl isothiocynates.

1) **Synthesis of 2-amino 5-chloro-6-fluoro benzothiazole:**

In a 2 lt. three necked round bottomed flask equipped with water condenser, mechanical stirrer and dropping funnel was placed 3-chloro-4-fluoro aniline (30 gm, 0.2 m), potassium thiocyanate (40 gm, 0.412 m) and 500 ml acetic acid. To this Bromine (48 g, 0.3 m) in 500 ml acetic acid was added dropwise maintaining the temperature between 30-35 °C. After the addition was over, the reaction mixture was stirred for 1 hour. The reaction mass was filtered and basified with liq. ammonia and the precipitated solid was filtered and washed with water. To yield 20 gm (47.9 %) of product .The two isomers viz. 5-chloro-6-fluoro 2-amino benzothiazole and 6-fluoro 7-chloro 2-amino benzothiazole were separated by column chromatography using benzene-ethyl acetate (1:1) mixture.

5-chloro-6-fluoro 2-amino benzothiazole : M.P. 216-218 °C

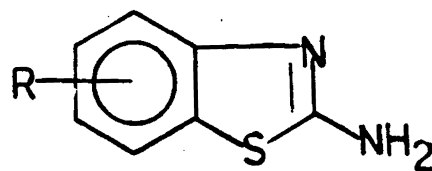
Lit ²⁸⁰ M.P. = 217- 220 °C

6-fluoro 7- chloro 2-amino benzothiazole : M.P. 187-189 °C.

Lit ²⁸⁰ M.P. = 189-192 °C.

Similarly other substituted benzothiazoles have been prepared and their physical constants have been given in TABLE NO. 2 .

TABLE 2
5,6-DISUBSTITUTED 2-AMINO BENZOTHAZOLES



SR NO.	R	YIELD %	M.P./B.P.		REFERENCES
			Observed	Reported	
1.	5-Cl,6-F	47.9	216-18°C	217-220°C	280
2.	5,6-DiCl ₂	52.0	188°C	185-90°C	289

2) Synthesis of 2-amino -4-chloro-5-fluoro thiophenol.

In a 100ml round bottomed flask equipped with water condenser was placed 2-amino 5-chloro 6-fluoro benzothiazole (10.125 gm, 0.05 m) and freshly prepared 50 % KOH solution (40 ml). The flask was heated on an oil bath with occasional shaking till evolution of ammonia ceases. The reaction mixture was allowed to cool down to room temperature. It was then diluted with water and made acidic with 4N acetic acid at 0-5 °C. The solid separated was filtered and washed with water. It was then recrystallised from chloroform.

Yield : 3.73 gms (42%)

M.P. = 140 °C

Lit ²⁸⁰ M.P. = 140 -142 °C

3) General method of synthesis of substituted aryl / alkyl isothiocyanates .

Synthesis of *p*-chloro phenyl isothiocyanate :

In a 250 ml three necked round bottomed flask equipped with water condenser, mechanical stirrer and dropping funnel was placed *p*-chloro aniline (5.00 gm, 0.039m) in solution of aqueous acetic acid and dilute hydrochloric acid (20 ml).The mixture was stirred at 15 °C for 20-30 min. A solution of thiophosgene (6.12 gm, 0.0532) in chloroform 20 ml was added dropwise maintaining the temperature at 0°C. The reaction mixture was further stirred for 4 hrs. The chloroform layer was seperated, washed with water till neutral pH, dried on anhydrous sodium sulfate. The chloroform was evaporated to dryness to give the resultant product.

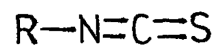
Yield : 3.12 gm (48 %)

M.P. = 45-46 °C

Lit ¹⁹⁴ M.P. = 46.5 °C

Similarly other substituted aryl/alkyl isothiocanates have been prepared and their physical constants have been given in TABLE NO. 3.

TABLE 3
SUBSTITUTED ARYL/ALKYL ISOTHIOCYANATES



SR NO.	R	YIELD	M.P./B.P. °C		REFERENCES
			OBSERVED	REPORTED	
1.	p-Cl-C ₆ H ₄	48	45-46	46.9	194
2.	p-OC ₂ H ₅ -C ₆ H ₄	73	58-61	53-54	290
3.	Allyl	70	B.P.149-151	151	291
4.	Butyl	69	B.P.166-168	167	292
5.	3,5-DiCl ₂ , 4-OH-C ₆ H ₂	53	96-98	98	293
6.	3,4-DiOCH ₃ , 6-CN-C ₆ H ₂	58	115-20	120	303
7.	3-Cl, 4F-C ₆ H ₃	61	Oil	-	*
8.	3,4-DiCl-C ₆ H ₃	64	39-40	40	294

* = Obtained from Laboratory.

4) General method for synthesis of 5,6-disubstituted 2-(substituted aryl/alkyl) amino benzothiazoles .

Synthesis of 2-(4-chloro phenyl amino) -5-chloro-6 fluoro benzothiazole

In a 100ml round bottomed flask equipped with water condenser was placed a mixture of 2-amino-4-chloro-5fluoro thiophenol (0.4438 gm, 0.0025 m) and *p*-chlorophenyl isothiocyanate (0.424 gm, 0.0025 m) in 15 ml *o*-xylene. It was refluxed on an oil bath for 4 hrs till evolution of H₂S ceases. The reaction mixture was allowed to cool to room temperature and filtered. It was then recrystallised from alcohol.

Yield : 0.563 gms (72%)

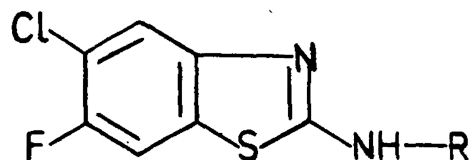
M.P. : 239 °C.

Elemental analysis of C ₁₃ H ₆ Cl ₂ FN ₂ S :	C%	H%	N%
Calculated	49.84	2.24	8.95
Found	50.23	2.64	8.32

All the anilino derivatives were synthesized by the similar procedure and are reported along with their physical data in TABLE NO. 4.

TABLE 4

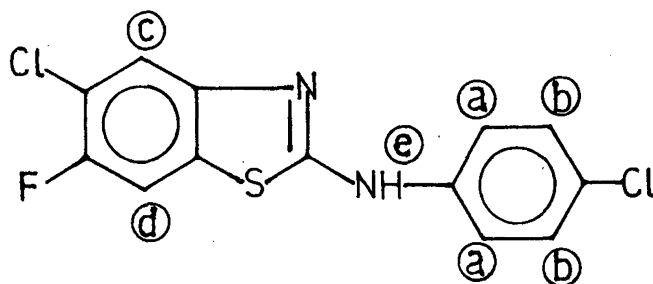
5,6-DISUBSTITUTED 2-(SUBSTITUTED ARYL/ALKYL) AMINO BENZOTHAZOLES



SR NO.	R	MOLECULAR FORMULA	MOL. WT.	M.P. °C	YIELD %	ELEMENTAL ANALYSIS					
						CALCULATED			FOUND		
						C	H	N	C	H	N
1.	4-Cl-C ₆ H ₄	C ₁₃ H ₇ Cl ₂ FN ₂ S	313	239	72	49.84	2.24	8.95	50.23	2.64	8.32
2.	OC ₂ H ₅ -C ₆ H ₄	C ₁₅ H ₁₂ ClFN ₂ OS	322.6	206	59	55.79	3.71	8.68	55.21	3.95	8.14
3.	Allyl	C ₁₀ H ₈ ClFN ₂ S	242.5	118	52	49.48	3.30	11.55	49.62	2.94	11.04
4.	C ₄ H ₉	C ₁₁ H ₁₂ ClFN ₂ S	258.6	130	63	51.04	4.64	10.82	49.84	4.96	10.35
5.	3,5-DiCl,4-OH-C ₆ H ₂	C ₁₃ H ₆ Cl ₃ FN ₂ OS	363.5	260	65	42.92	1.65	7.70	42.68	1.13	7.22
6.	2-CN,4,5-DiOCH ₃ -C ₆ H ₂	C ₁₆ H ₁₁ ClFN ₃ O ₂ S	363.5	135	38	52.82	3.03	11.55	52.38	2.89	11.35
7.	3,Cl,4-F-C ₆ H ₃	C ₁₃ H ₆ Cl ₂ F ₂ N ₂ S	331	231	71	47.13	1.82	8.46	46.86	1.47	8.23
8.	3,4-DiCl-C ₆ H ₃	C ₁₃ H ₆ Cl ₃ FN ₂ S	347.5	228	58	44.89	1.73	8.06	44.35	1.48	7.85

Spectral Studies of 5,6-disubstituted 2-(substituted aryl/alkyl) amino benzothiazoles [TABLE No. 4]

2-(4-chloro phenyl amino) -5-chloro-6 fluoro benzothiazole (compd.no 1)



IR (KBr) cm : 3230 (-NH-); 1620, 1449 (Aromatic); 1569, 1494, 1070 (Thiazole);
1324 (Aromatic -NH-); 867 (benzene with 2 adjacent H atoms);
820, 742 (C-Halo)

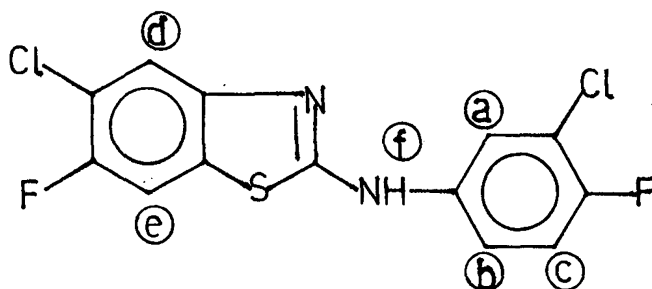
PMR (DMSO) δ : 7.39-7.45 (d, 2H, b); 7.75-7.81 [m, 3H (2H, a; 1H, d)];
7.96-7.99 (d, 1H, c); 10.75 (s, 1H, e).

Ms : m/z 313 (M^+)

2-(4-ethoxy phenyl amino) -5-chloro-6 fluoro benzothiazole (compd.no.2)

IR (KBr) cm : 3236 (-NH-); 2924 (Alkyl); 1628, 1448 (Aromatic);
1567, 1513, 1047 (Thiazole); 1327 (Aromatic -NH-);
1250 (Ar-O-R); 871 (benzene with 2 adjacent H atoms);
818, 714 (C-Halo).

2-(3-chloro,4-fluoro phenyl amino) -5-chloro-6 fluoro benzothiazole (compd.no.7)



IR (KBr) cm : 3193 (-NH-); 1621, 1455 (Aromatic); 1561, 1504, 1072 (Thiazole);
1325 (Aromatic -NH-); 858 (benzene with 2 adjacent H atoms);
823, 750 (C-Halo).

PMR ($CDCl_3$) δ : 7.39-7.45 (t, 1H, a); 7.54-7.60 (m, 1H, b);
7.818-7.848 (d, 1H, e); 7.969-7.999 (d, 1H, d); 8.12-8.15 (q, 1H, c);
10.818 (s, 1H, f).

Ms : m/z 331 (M^+)

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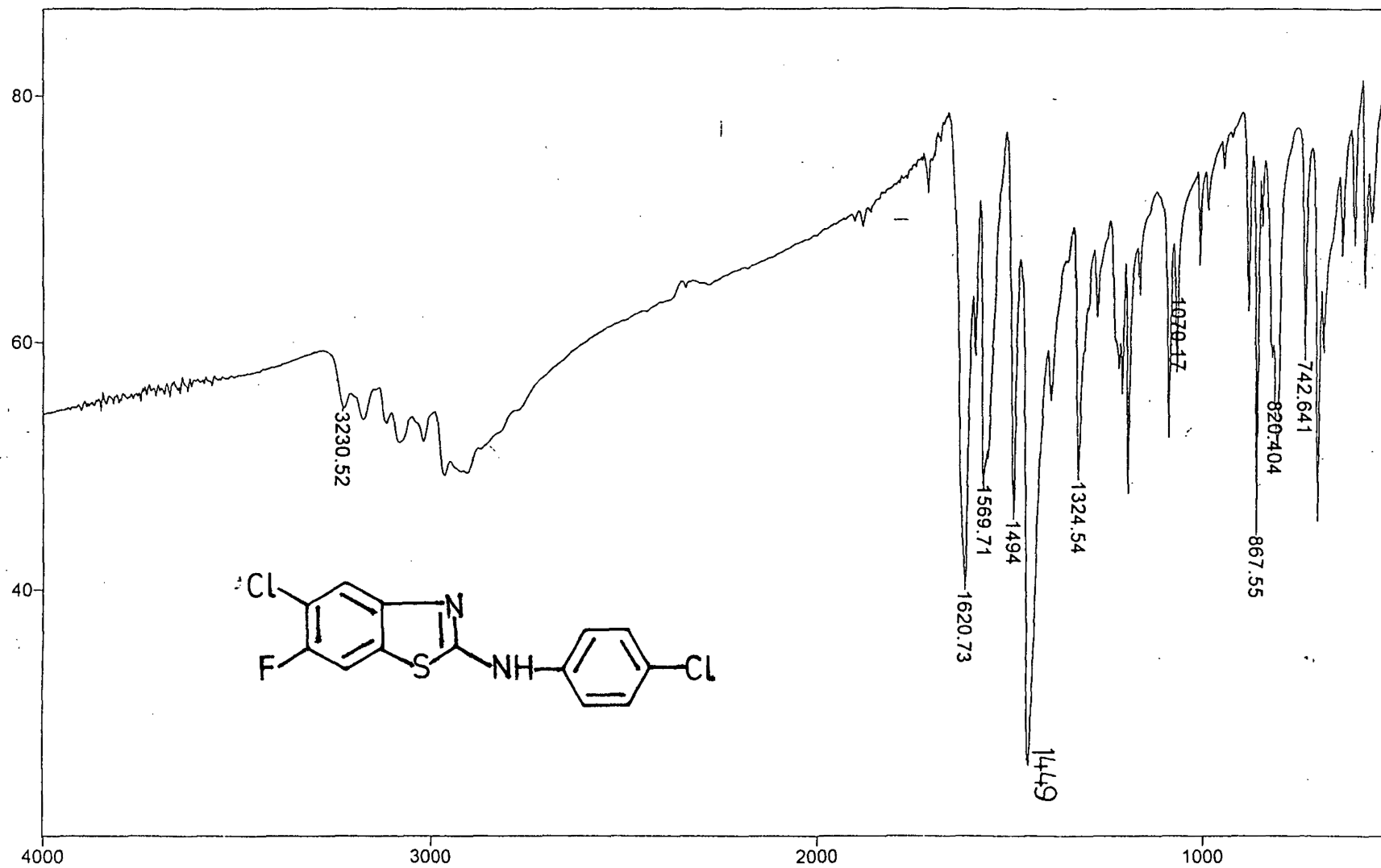
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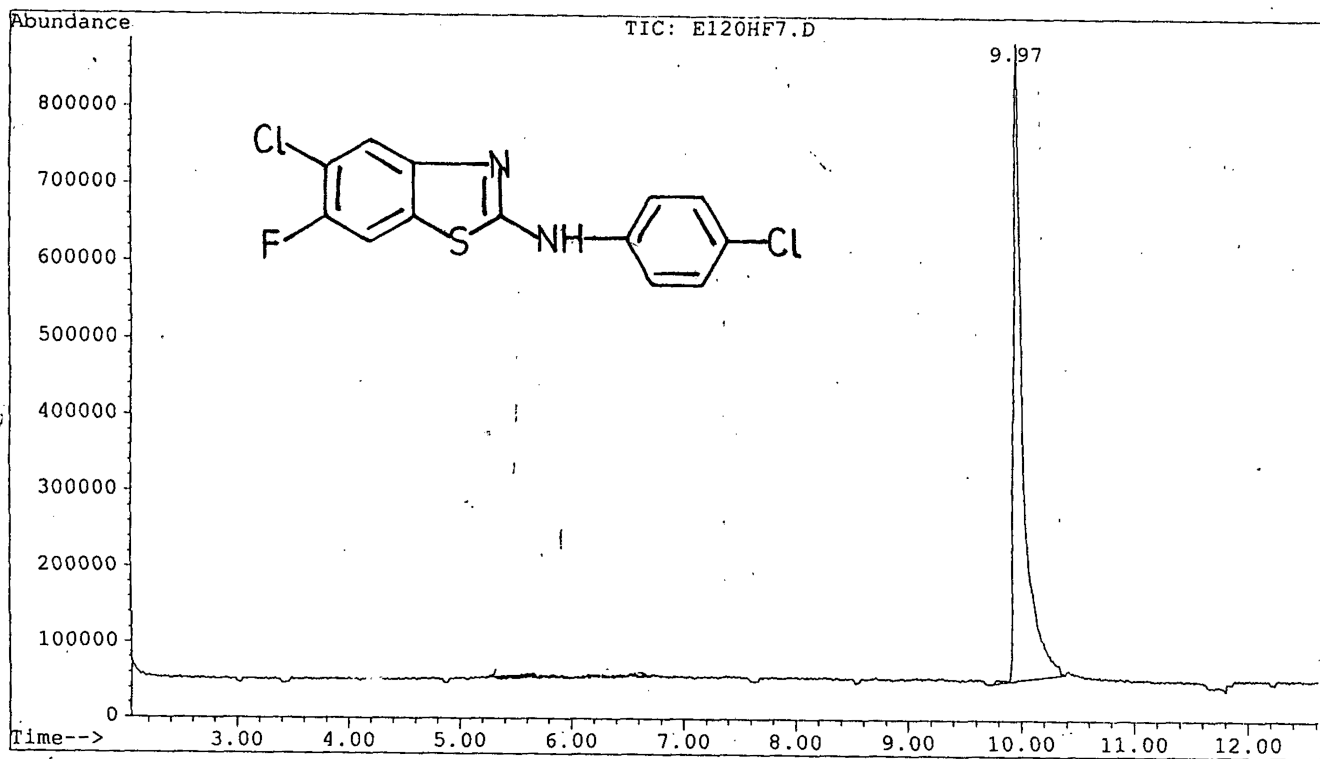
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Graphics Report

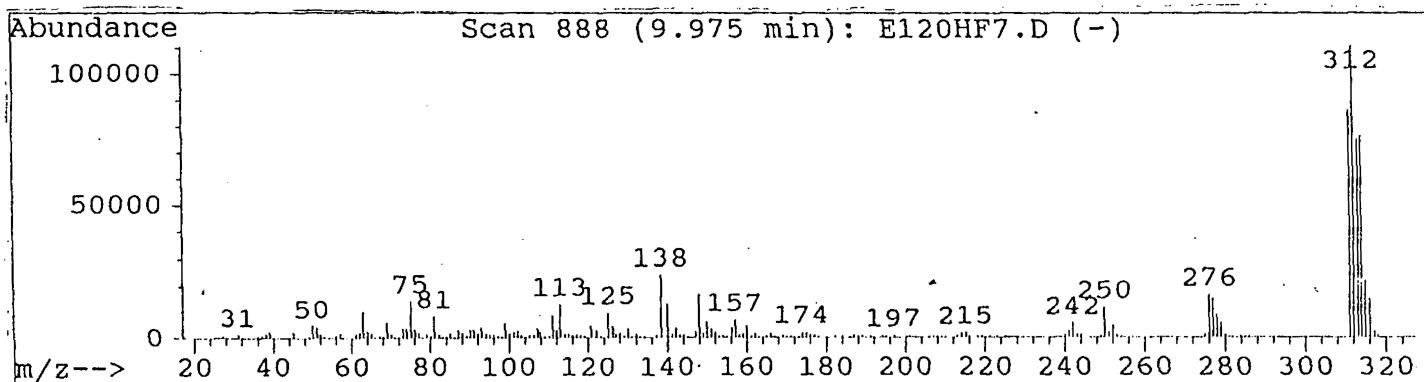
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Wed Jan 01 14:13:12 1997

Page 1 of 2



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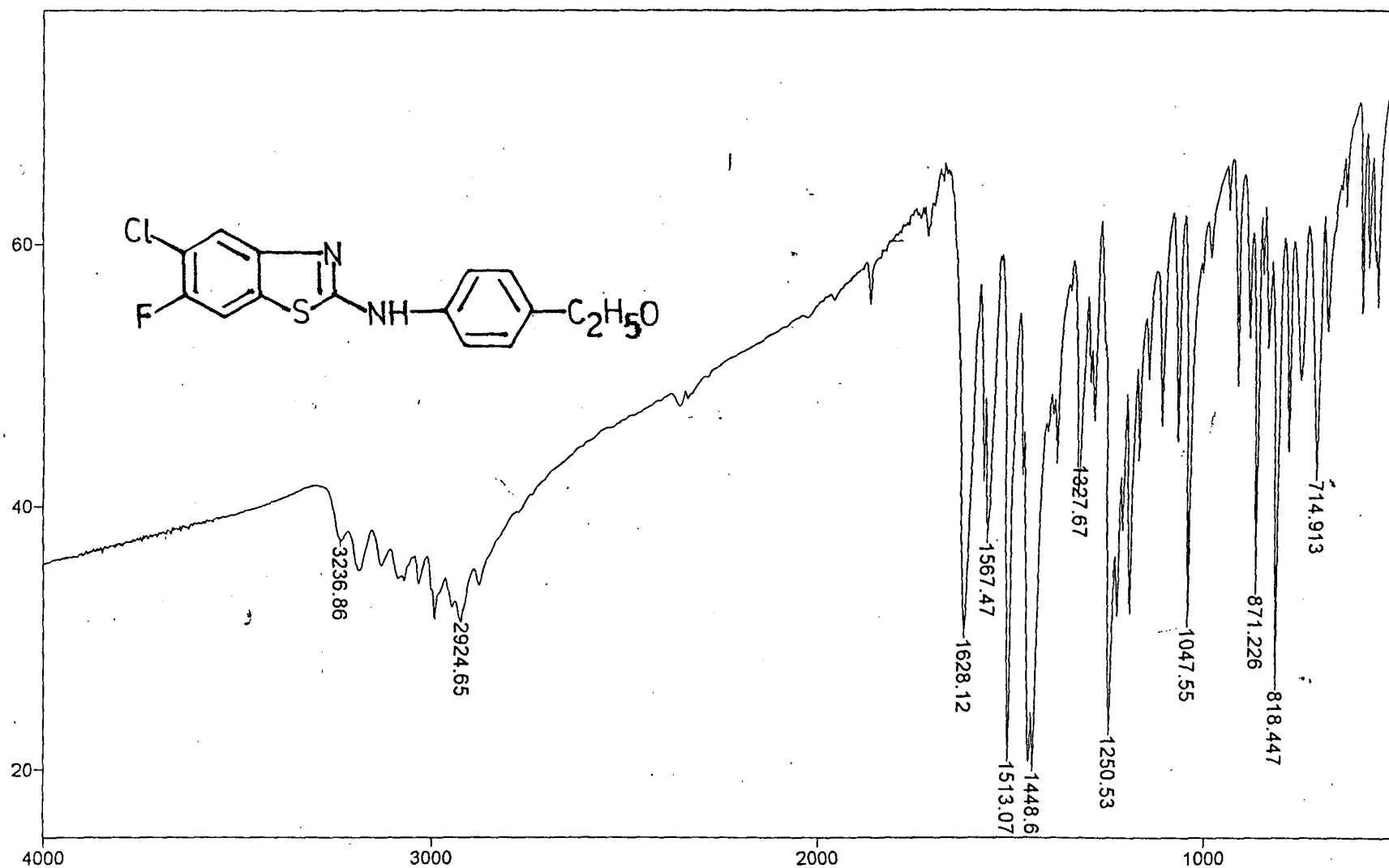
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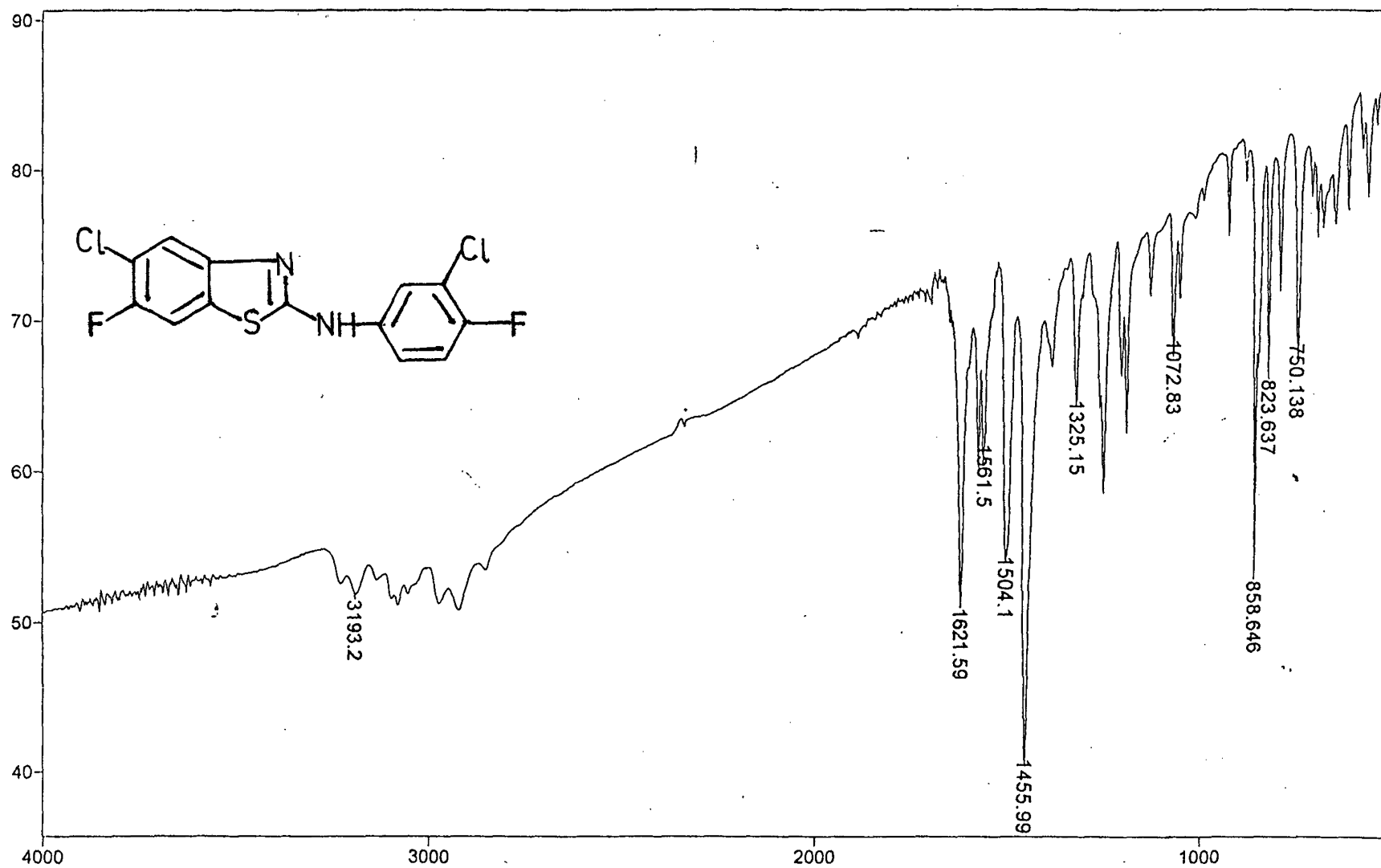
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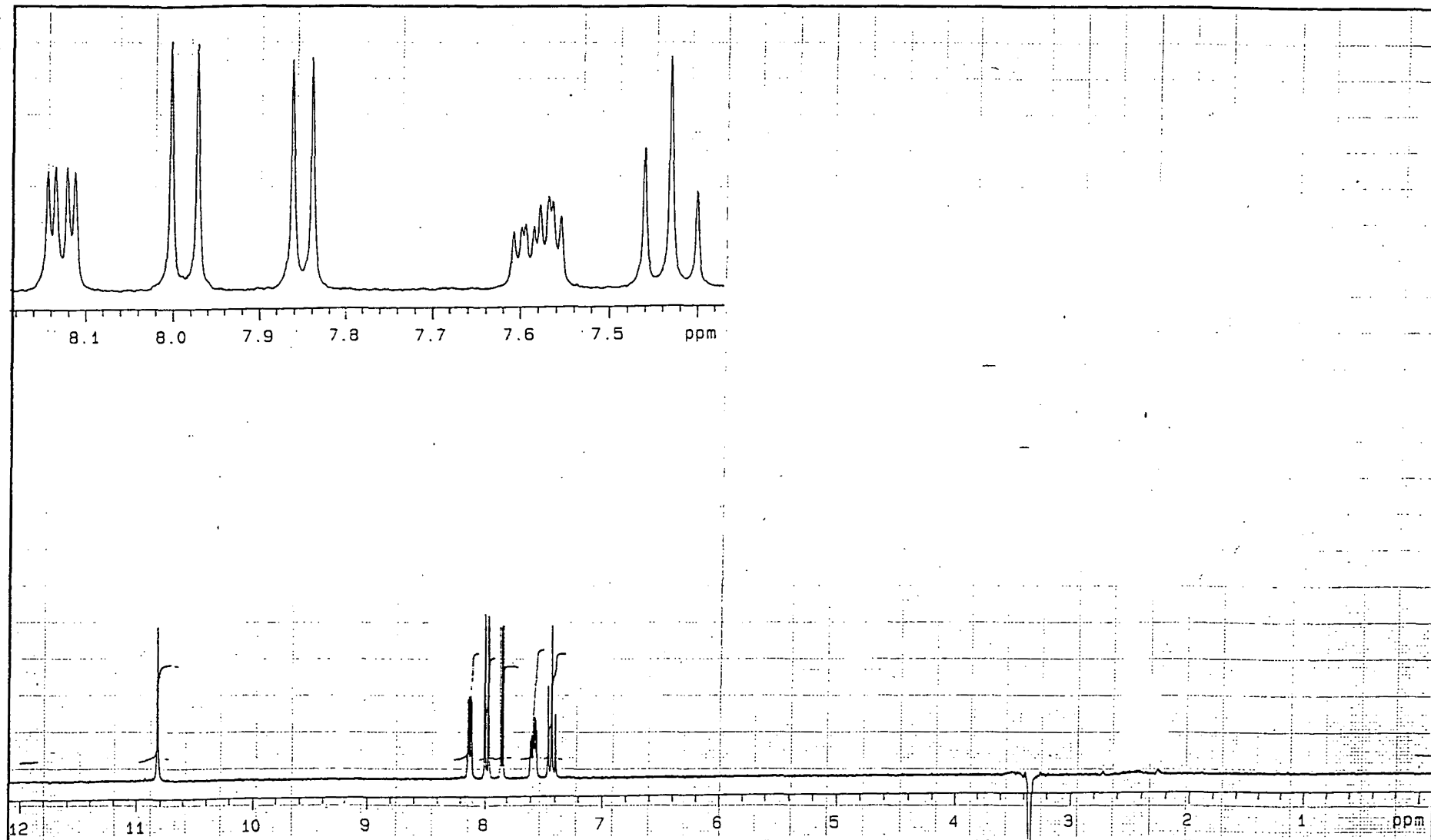
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PART NO 997259

CHART XL SERIES



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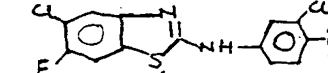
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LB 0.500 Hz AF not used sec CCD
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Reference

EXPERIMENT
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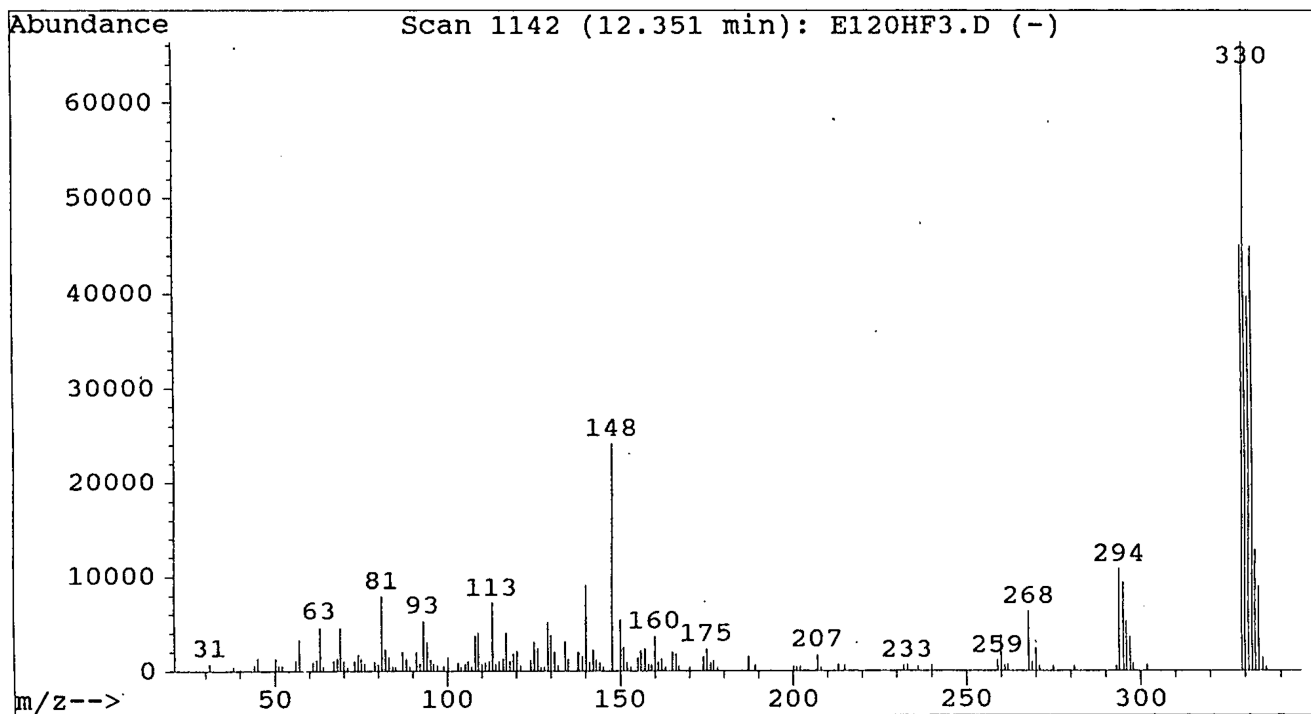
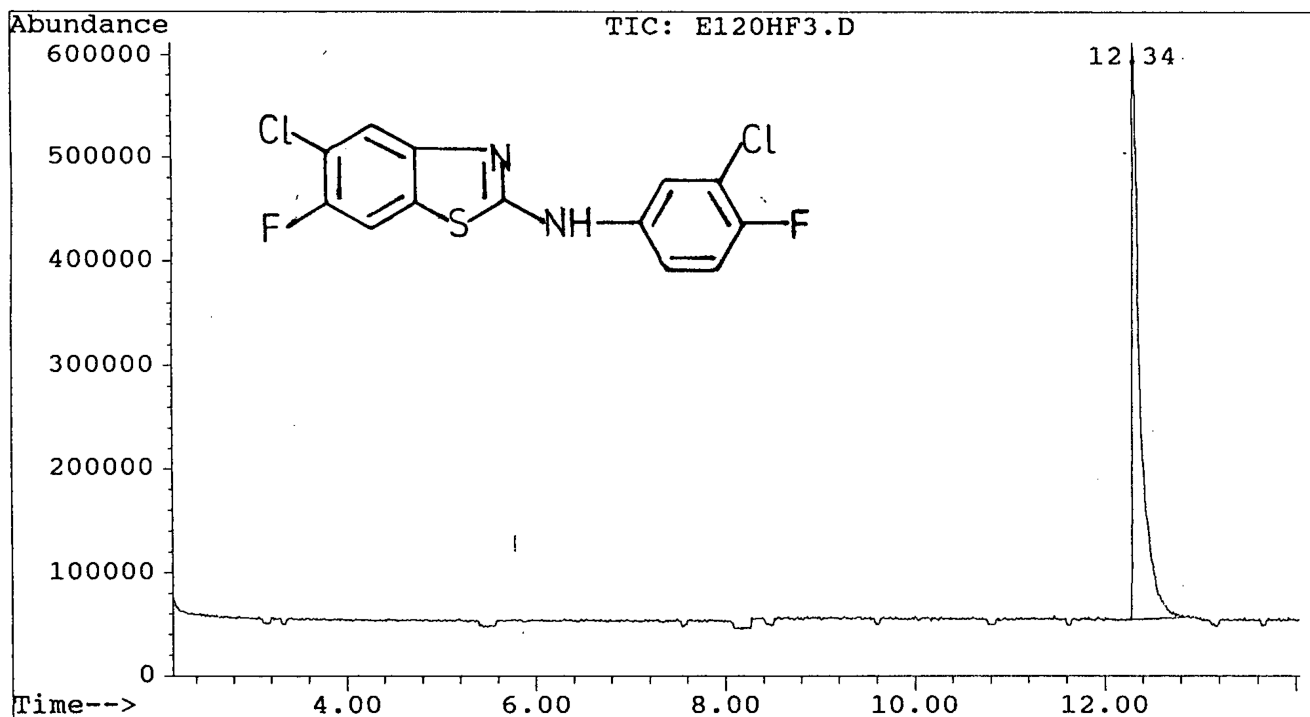
SAMPLE

ANL7

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varian

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PART III

SYNTHESIS OF
5, 6 - DISUBSTITUTED 2 - (SUBSTITUTED
PHENYL CARBOXAMIDO)
BENZOTHAZOLES

This part deals with the syntheses of 5,6-disubstituted 2-(substituted phenyl carboxamido) benzothiazoles which involves the following steps.

- 1) Synthesis of 5,6-disubstituted 2-amino benzothiazoles.
- 2) Synthesis of substituted benzoyl chlorides.
- 3) Synthesis of title compounds by condensation of 5,6-disubstituted 2-amino benzothiazoles with various substituted benzoyl chlorides.

1) Synthesis of 5,6-disubstituted 2-amino benzothiazoles.

The synthesis of benzothiazoles used in the synthesis of the title compounds has been described in **Part II** and the benzothiazoles are represented with their physical data in TABLE NO. 2 .

2) Synthesis of substituted Benzoyl Chlorides.

Synthesis of 2,6-difluoro benzoyl chloride.

A mixture of 2,6 difluoro benzoic acid (3.16 gm, 0.02 m) and freshly distilled thionyl chloride (3.57 gm, 0.03 m) in 25 ml dry benzene was taken in 100 ml round bottomed flask equipped with reflux condenser and a guard tube. The reaction mixture was refluxed on steam bath with occasional shaking till evolution of HCl gas ceases. Excess of thionyl chloride was distilled out along with benzene. The residual oil was distilled under vacuum at 15 mm.

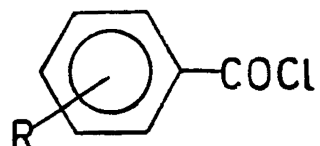
Yield : 2.75 gm (78%)

B.P._{15mm} = 77 °C

Lit ²⁸¹ B.P._{15mm} = 76 - 79 °C

Similarly other substituted benzoyl chlorides have been prepared and their physical constants have been given in TABLE NO. 5 .

TABLE 5
SUBSTITUTED BENZOYL CHLORIDES



SR NO.	R	YIELD	BOILING POINT		REFERENCES
			OBSERVED	REPORTED	
1.	H	72	194-98	194-98	295
2.	2-F	68	73(20mm)	66-67(15mm)	296
3.	3-F	71	75(25mm)	68-69(15mm)	296
4.	4-F	74	72(20mm)	69-70(15mm)	296
5.	2,6-DiF ₂	78	77(15mm)	76-79(15mm)	281
6.	2-CF ₃	70.5	105(25mm)	90(16mm)	297
7.	3-CF ₃	62	89(25mm)	89(23mm)	298

3) General method for synthesis of 5,6 Disubstituted 2-(substituted phenyl carboxamido) Benzothiazoles.

Synthesis of 5,6 Disubstituted 2-(2,6 difluoro phenyl carboxamido) Benzothiazole.

In a 100 ml three necked flat bottomed flask equipped with a dropping funnel, reflux condenser with guard tube was placed a mixture of triethylamine (0.101gm , 0.001 m) and 2-amino, 5-chloro 6-fluoro benzothiazole (0.203 gm, 0.001 m) and 10 ml dry 1,4 dioxane. The reaction mixture was stirred on a magnetic stirrer at 50-60 °C for 30 min. To this is added dropwise a solution of 2,6 difluoro benzoyl chloride (0.177gm, 0.001 m) in 10 ml dry 1,4-dioxane at the same temperature. After the addition, the reaction mass was stirred for 2 hrs. It was then poured onto crushed ice. The solid separated out was filtered and washed with 1 % potassium bicarbonate and water. It was then recrystallised from ethanol.

Yield : 0.216 gm (63%)

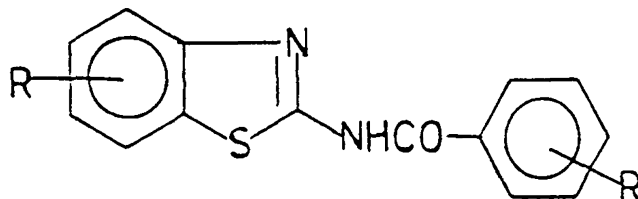
M.P. : 266 °C.

Elemental analysis of $C_{14}H_6ClF_3N_2OS$:	C%	H%	N%
Calculated	49.05	1.75	8.17
Found	48.52	1.34	8.64

In a similar manner all the other 5,6 disubstituted 2-(substituted phenyl carboxamido) Benzothiazoles have been synthesized and whose physical data has been represented in TABLE NO. 6 .

TABLE 6

5,6-DISUBSTITUTED 2-(SUBSTITUTED PHENYL CARBOXAMIDO) BENZOTHAZOLES



SR NO.	R	R'	MOLECULAR FORMULA	MOL. WT.	M.P. °C	YIELD %	ELEMENTAL ANALYSIS					
							CALCULATED			FOUND		
							C	H	N	C	H	N
1.	5-Cl, 6-F	H	C ₁₄ H ₈ ClFN ₂ OS	306.5	263	54	54.81	2.61	9.13	54.53	2.57	9.42
2.	5-Cl, 6-F	2-F	C ₁₄ H ₇ ClF ₂ N ₂ OS	324.5	262	61	51.77	2.15	8.63	51.53	2.26	8.37
3.	5,6-DiCl	2-F	C ₁₄ H ₇ Cl ₂ FN ₂ OS	341.56	240	63	49.19	2.05	8.20	49.39	2.27	8.25
4.	5-Cl, 6-F	3-F	C ₁₄ H ₇ ClF ₂ N ₂ OS	324.5	259	58	51.77	2.15	8.63	51.47	2.06	8.77
5.	5,6-DiCl	3-F	C ₁₄ H ₇ Cl ₂ FN ₂ OS	341.56	245	62	49.19	2.05	8.20	49.09	1.97	7.89
6.	5-Cl, 5-F	4-F	C ₁₄ H ₇ ClF ₂ N ₂ OS	324.5	258	60	51.77	2.15	8.63	51.95	2.37	8.95
7.	5,6-DiCl	4-F	C ₁₄ H ₇ Cl ₂ FN ₂ OS	341.56	>270	55	49.19	2.05	8.20	49.58	2.34	8.43
8.	5-Cl, 6-F	2,6-DiF	C ₁₄ H ₆ ClF ₃ N ₂ OS	342.5	266	63	49.05	1.75	8.17	48.52	1.34	8.64
9.	5,6-DiCl	2,6-DiF	C ₁₄ H ₆ Cl ₂ F ₂ N ₂ OS	359	251	60	46.79	1.67	7.80	46.47	1.88	7.65
10.	5-Cl, 6-F	2-CF ₃	C ₁₅ H ₇ ClF ₄ N ₂ OS	374.5	215	67	48.06	1.87	7.47	48.37	1.69	7.23
11.	5,6-DiCl	2-CF ₃	C ₁₅ H ₇ Cl ₂ F ₃ N ₂ OS	391.5	225	48	45.98	1.79	7.15	46.35	1.91	7.35
12.	5-Cl, 6-F	3-CF ₃	C ₁₅ H ₇ ClF ₄ N ₂ OS	374.5	248	58	48.06	1.87	7.47	47.77	2.01	7.68
13.	5,6-DiCl	3-CF ₃	C ₁₅ H ₇ Cl ₂ F ₃ N ₂ OS	391.5	258	47	45.98	1.79	7.15	45.75	1.61	6.84

Spectral studies of 5,6-disubstituted 2-(substituted phenyl carboxamido) benzothiazoles [TABLE No. 6].

5-chloro,6-fluoro 2-(phenyl carboxamido) Benzothiazole. (compd.no.1)

IR (KBr) cm : 3230 (-NH-); 1671 (-CONH); 1602 , 1453 (Aromatic);
1559 (Aromatic-NH-); 714 (C-halo) .

PMR (CDCl₃) δ : 7.50 - 8.20 [(m, 7H, Ar-H ; 1H, -NH-)]

5-chloro,6-fluoro 2-(2-fluoro phenyl carboxamido) Benzothiazole. (compd.no.2)

IR (KBr) cm : 3398 (-NH-); 1681 (-CONH); 1619 , 1450 (Aromatic);
1538 (Aromatic-NH-); 716 (C-halo) .

5-chloro,6-fluoro 2-(2,6 difluoro phenyl carboxamido) benzothiazole.
(compd.no.8)

IR (KBr) cm : 3200 (-NH-); 1686 (-CONH); 1624 , 1466 (Aromatic);
1559 (Aromatic-NH-); 715 (C-halo) .

PMR (CDCl₃) δ : 7.00 - 7.70 (m, 5H, Ar-H) ; 12.8 (s, 1H, -NH-).

Ms : m/z 342 (M⁺)

File # 1 = BAM1

Mode= 2 (Mid-IR)

3/21/97 5:06 PM

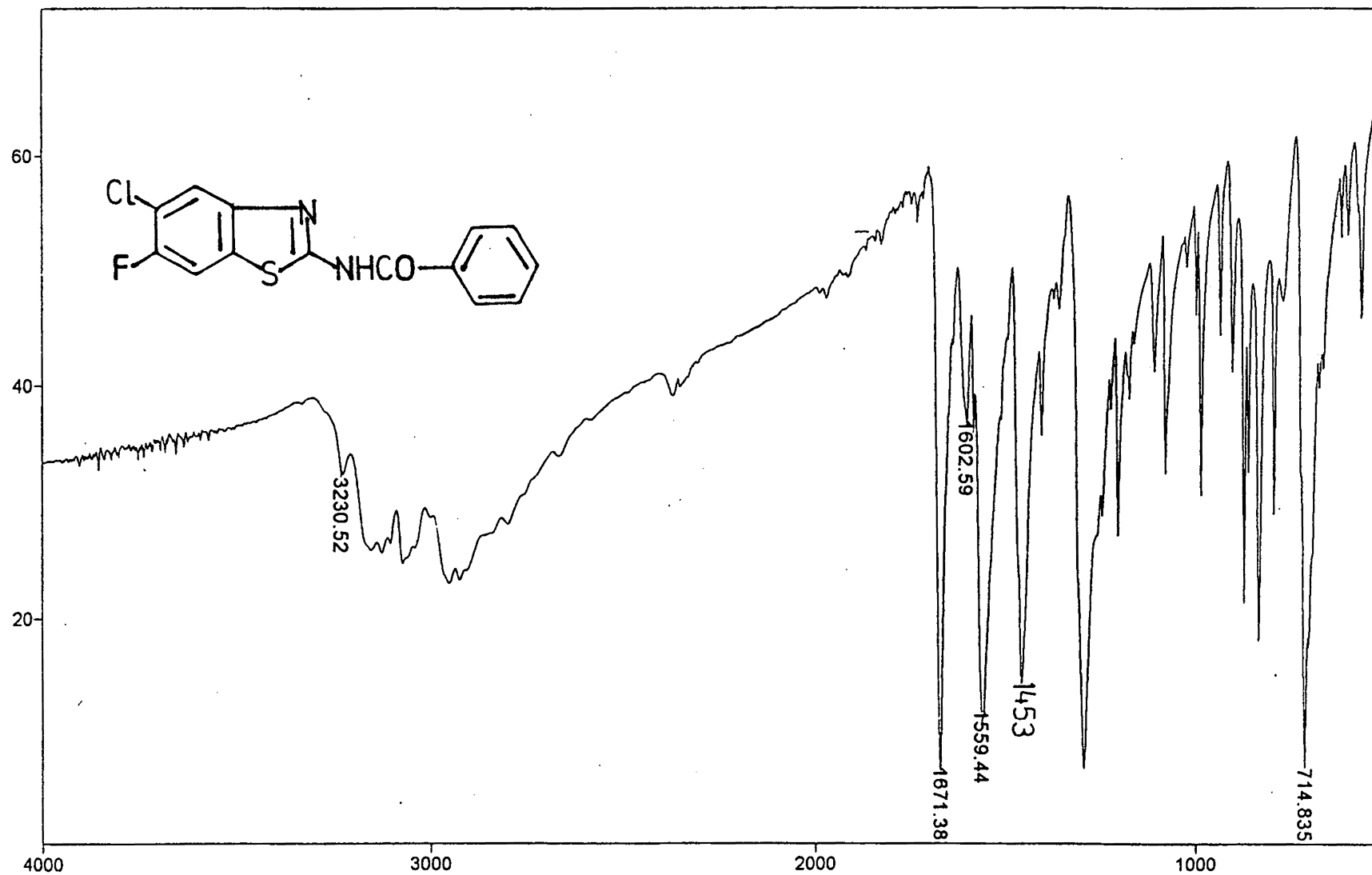
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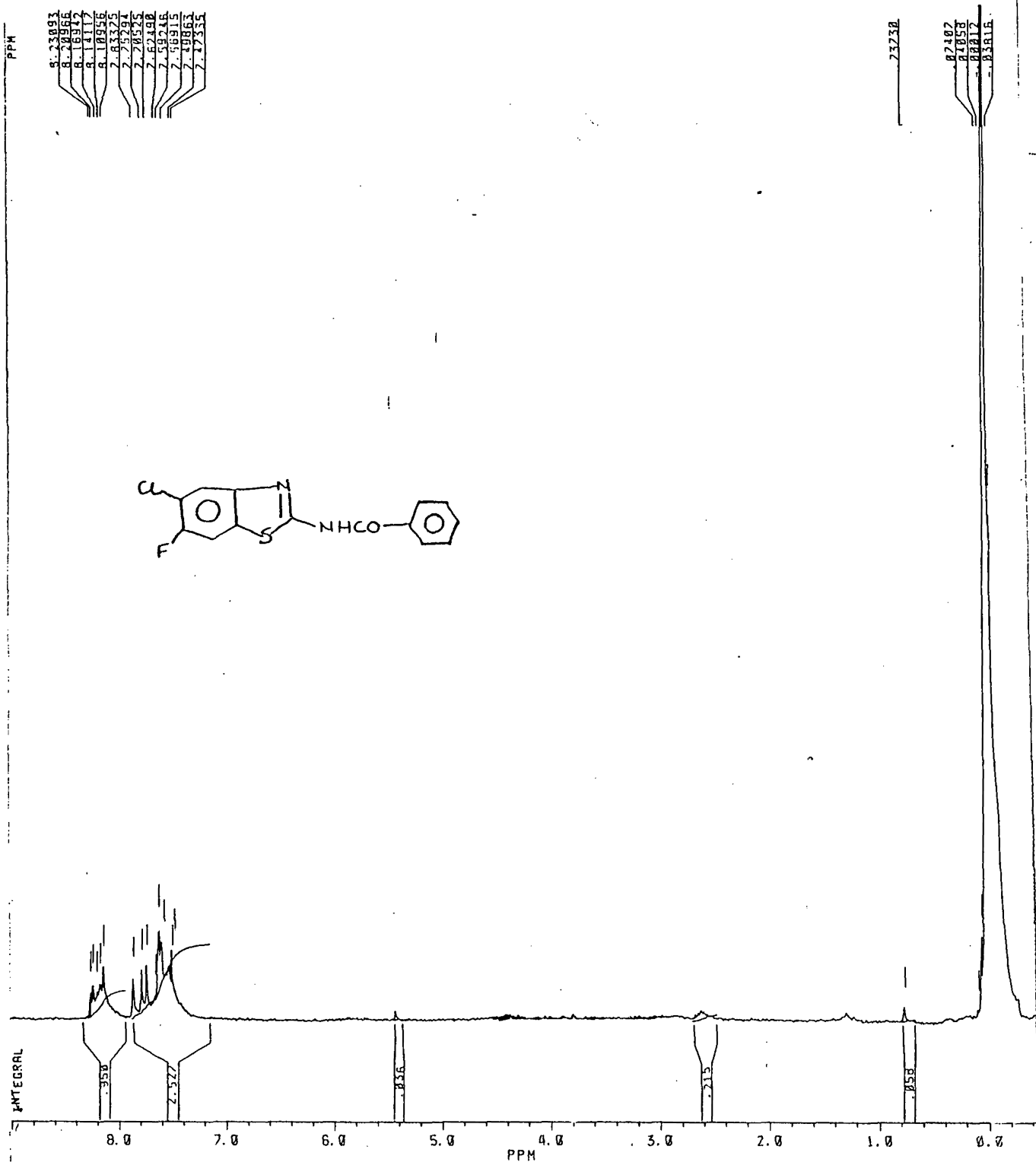
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Apod= Cosine

Zero Filling= 1 x



Transmittance / Wavenumber (cm⁻¹)



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Mode= 2 (Mid-IR)

3/21/97 4:58 PM

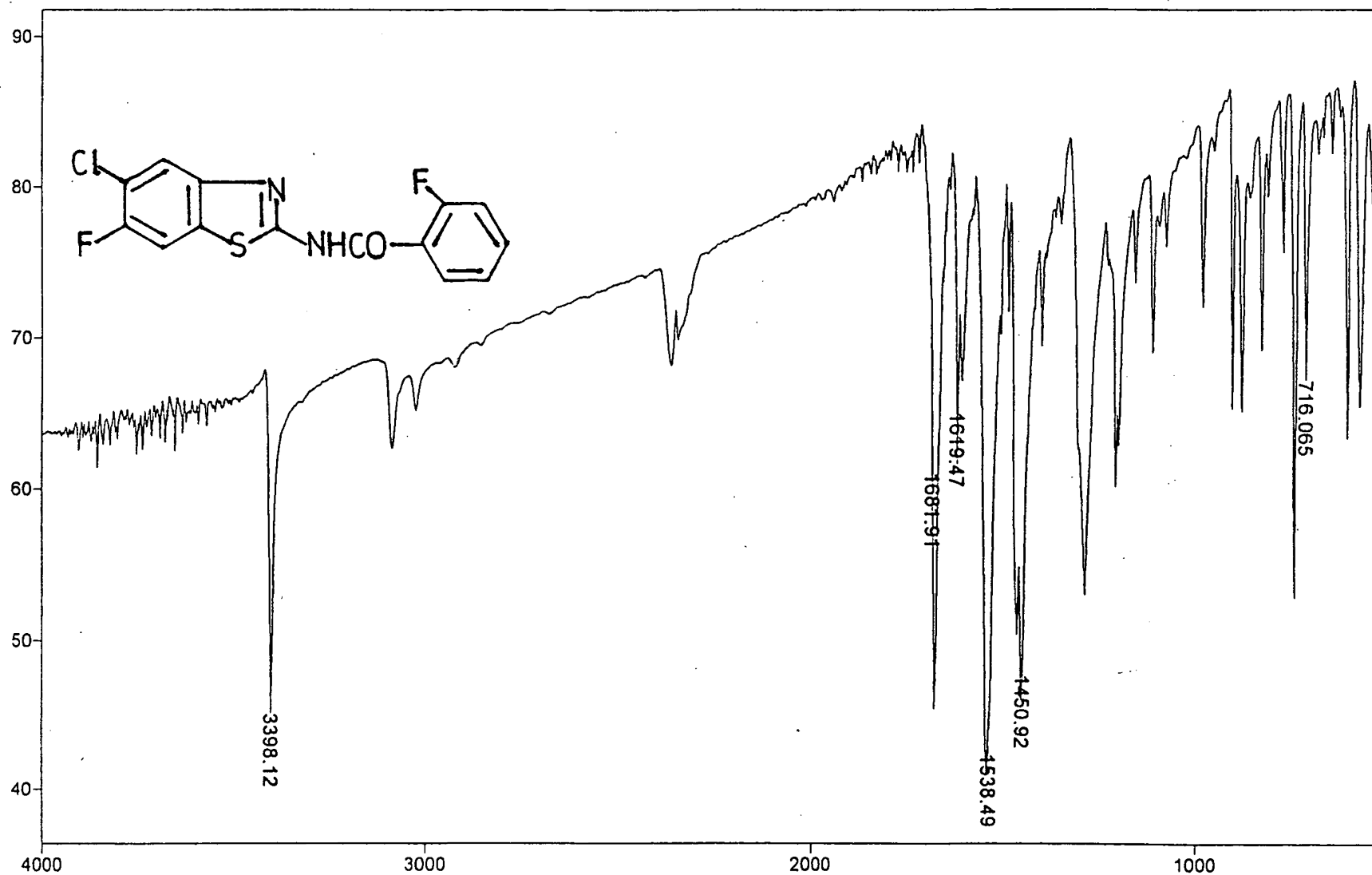
Sample Description: 2F

Scans= 10 Slow

Res=4 cm⁻¹

Apod= Cosine

Zero Filling= 1 x



Transmittance / Wavenumber (cm⁻¹)

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Mode= 2 (Mid-IR)

3/21/97 4:47 PM

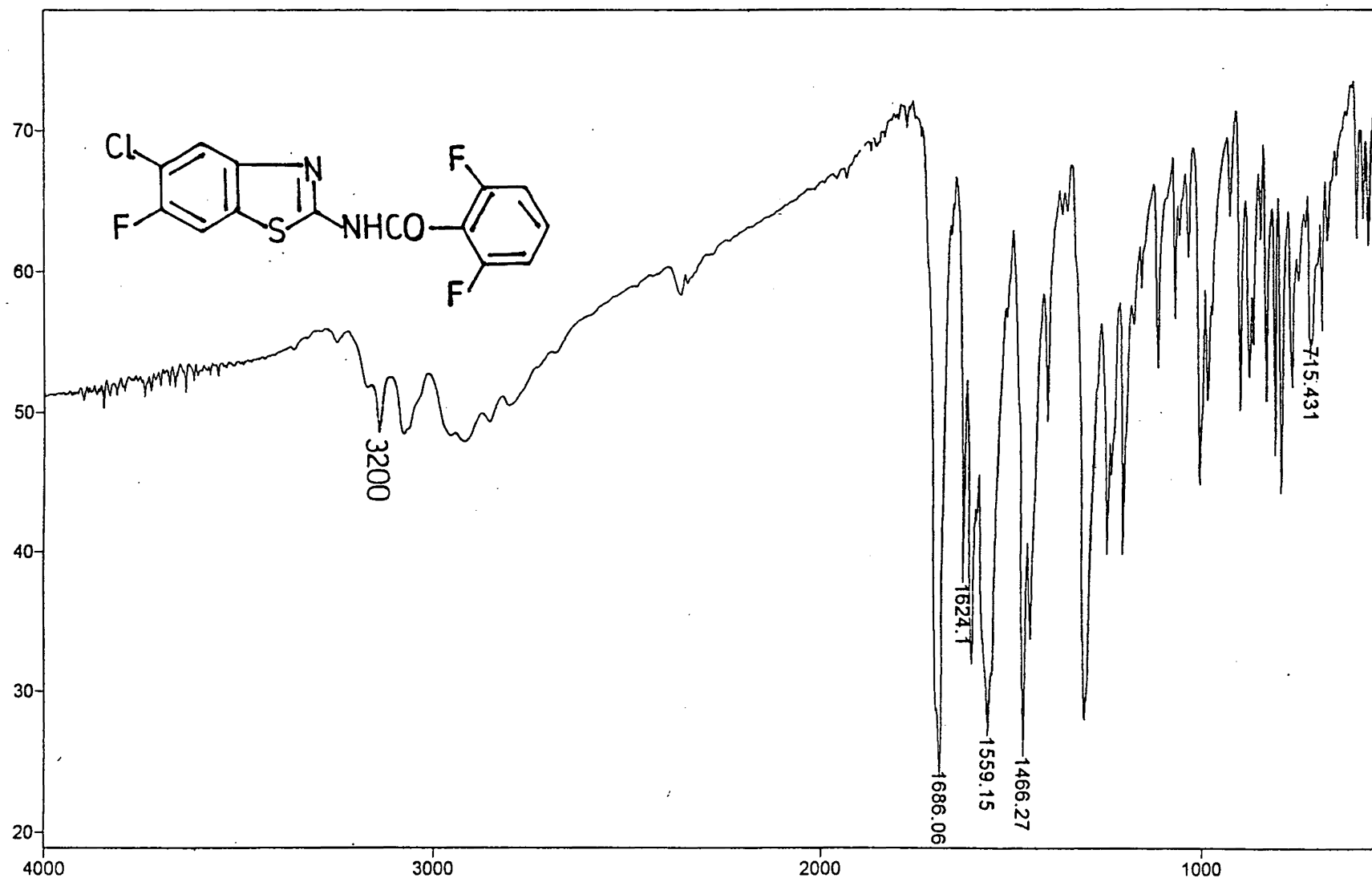
Sample Description: 26DiF

Scans= 10 Slow

Res=4 cm-1

Apod= Cosine

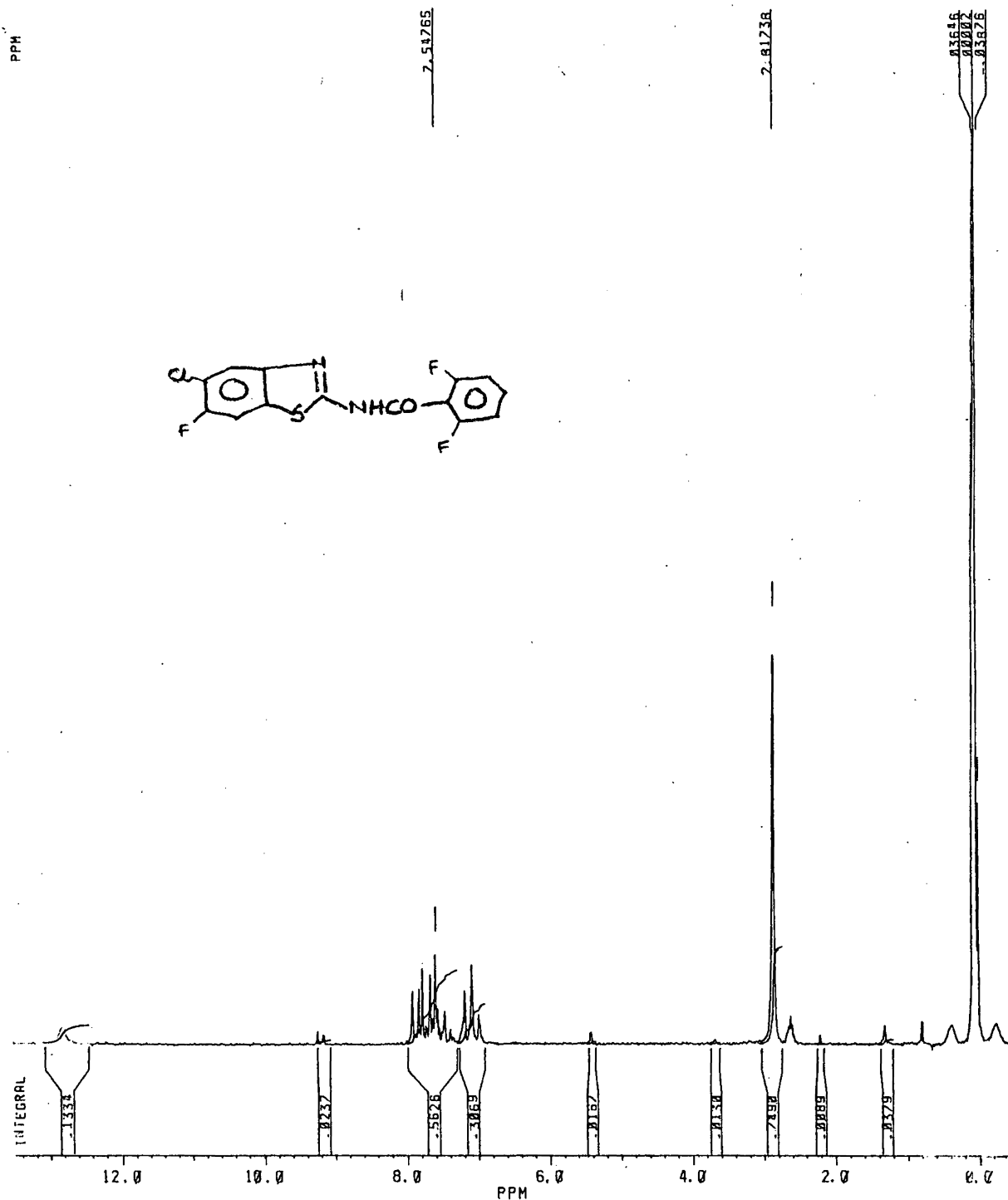
Zero Filling= 1 x



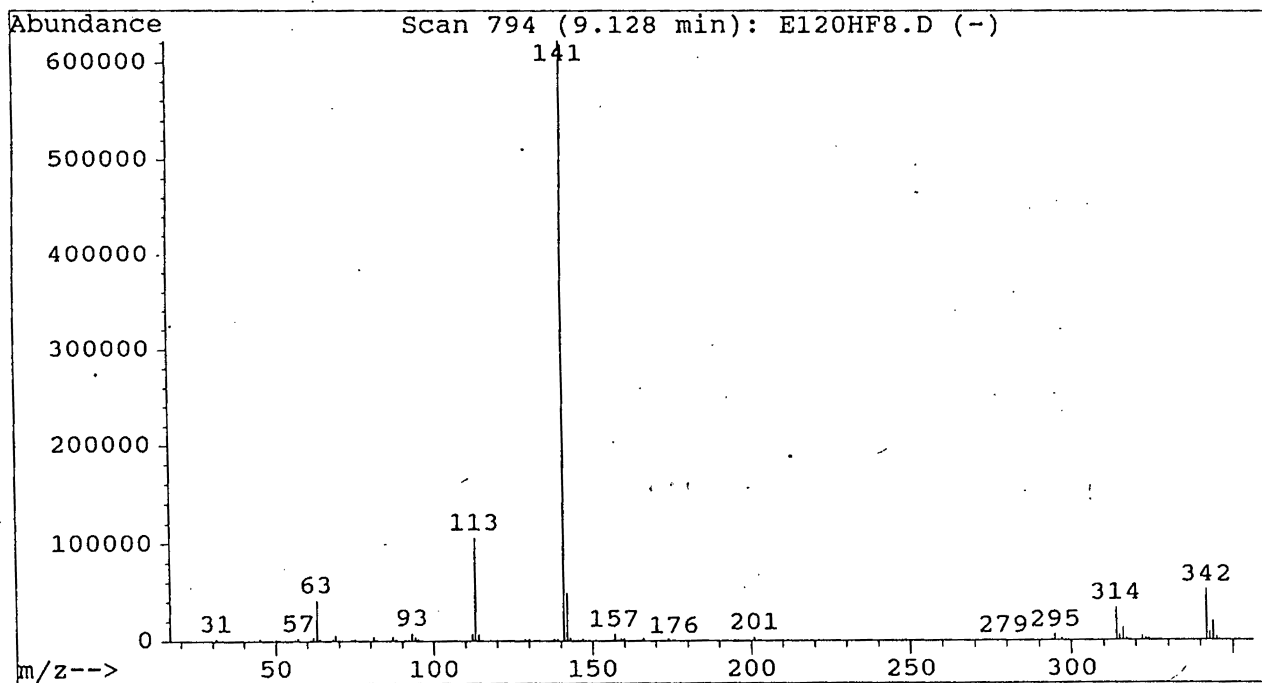
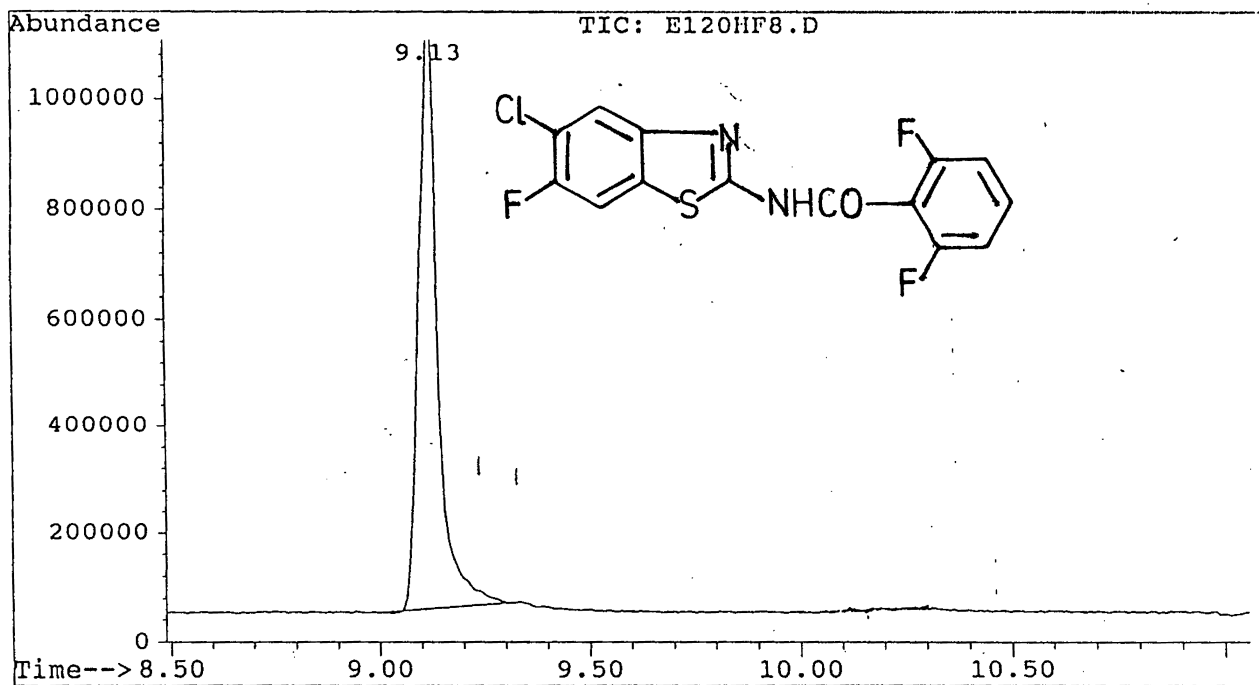
Transmittance / Wavenumber (cm-1)

m-8

SWM-1/COCL3/DMSO/19/12/95



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Operator : SVL
Acquired : 1 Jan 97 2:10 pm using AcqMethod KS
Instrument : GCD
Sample Name: BAM 8
Misc Info : 200-10-250-25-275-15MIN. - IN MeOH-HP-5
Vial Number: 1



PART IV

SYNTHESIS OF
2 - ARYLIDENE HYDRAZINO 4 - ARYL
THIAZOLES

This part deals with the synthesis of 2-arylidine hydrazino 4-(*p*-fluorophenyl) thiazoles which involves the following steps :

- 1) Preparation of *p*-fluoro phenacyl bromide.
- 2) Preparation of substituted benzaldehyde/acetophenone thiosemicarbazones.
- 3) Synthesis of title compounds by condensation of *p*-fluoro phenacyl bromide with various substituted benzaldehyde/acetophenone thiosemicarbazones .

1) Preparation of *p*-fluoro phenacyl bromide.

In a dry 100 ml three necked round bottom flask equipped with a dropping funnel and calcium chloride guard tube and one of the necks were connected to the trap for absorbing hydrogen bromide gas evolved during the reaction was placed in a ice-salt bath over a magnetic stirrer unit. *p*-Fluoroacetophenone 6.91gm (0.05m) in 20 ml carbontetrachloride was placed in the flask and cooled to 0 °C. When 9.9 gms (0.05m) of bromine is added dropwise through dropping funnel with constant stirring. After a short induction period the bromine drops reacted immediately to give pale yellow solution. After complete addition of bromine the mixture was stirred for half an hour. The reaction mixture is then washed with water and 5% sodiumthiosulfate followed by water washings. It is dried over anhydrous sodium sulfate. After removal of carbontetrachloride under vacuum an oil is obtained. Which quickly crystalized. The product was further recrystalized in hexane.

Yield 9.7 gms (89%)

M.P. = 49 °C

Lit ²⁸² M.P. = 48-50 °C

2) Preparation of substituted benzaldehyde/acetophenone thiosemicarbazones.

Preparation of 4-trifluoromethyl benzaldehyde thiosemicarbazone

In a 50 ml round bottomed flask equipped with reflux condenser was taken thiosemicarbazide (0.456 gm, 0.005m) in 10 ml methanol it is slightly warmed to obtain a clear solution . To this is added one drop of acetic acid and *p* - trifluoromethyl benzaldehyde (0.871 gm, 0.005m) in 5ml methanol . The mixture was refluxed on a water bath 3 - 4 hrs. The solid obtained was filtered and recrystallized from ethanol.

Yield : 0.952 gms (77%)

M.P. = 167 °C

Lit ²⁸³ M.P. = 167-168 °C

3) General method for the preparation of 2- substituted arylidene hydrazino - 4-(*p*-fluoro phenyl) thiazoles .

Preparation of 2- [(*p* - trifluoromethyl phenyl) - 1 - methyl-ene] hydrazino- 4 -(*p*- fluoro phenyl)thiazole.

In a 50 ml round bottomed flask equipped with a condenser and a guard tube was placed *p*-fluorophenacyl bromide (217 mg, 0,001 mole) and *p* - trifluoromethyl benzaldehyde thiosemicarbazone (0.247 gm, 0.001 mole) in 20 ml of dry ethanol. The reaction mixture was refluxed for four hours. The solvent was concentrated and the hydrobromide salt was treated with liq. ammonia to obtain the free base which was filtered and washed with water till free from ammonia. The crude product was recrystallised from methanol.

Yield : 0.234gm (64%)

M.P. 220 °C

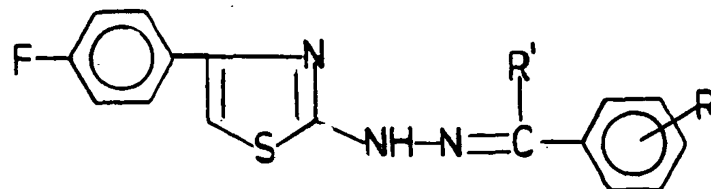
Elemental analysis of $C_{17}H_{11}F_4N_3S$:	C%	H%	N%
Calculated	55.83	3.01	11.49
Found	55.34	2.86	11.72

In a similar manner all the other 2-arylidene hydrazino 4-(*p*-fluorophenyl) thiazoles have been synthesized and whose physical data has been represented in TABLE NO. 7.

All the fluorinated aldehydes /ketones used in the synthetic work were obtained from FLUKA Chemie AG.

TABLE 7

2-ARYLIDINE HYDRAZINO 4-ARYL THIAZOLES



SR NO.	R	R'	MOLECULAR FORMULA	MOL. WT.	M.P. °C	YIELD %	ELEMENTAL ANALYSIS					
							CALCULATED			FOUND		
							C	H	N	C	H	N
1.	2-F	H	C ₁₆ H ₁₁ F ₂ N ₃ S	315.39	205	58	60.88	3.49	13.32	61.47	3.67	13.12
2.	3-F	H	C ₁₆ H ₁₁ F ₂ N ₃ S	315.39	214	60	60.88	3.49	13.32	60.87	3.14	13.68
3.	4-F	H	C ₁₆ H ₁₁ F ₂ N ₃ S	315.39	209	60	60.88	3.50	13.32	61.25	3.28	13.53
4.	4-CF ₃	H	C ₁₇ H ₁₁ F ₄ N ₃ S	365.4	220	64	55.83	3.01	11.49	55.34	2.86	11.72
5.	2-CF ₃	H	C ₁₇ H ₁₁ F ₄ N ₃ S	365.4	215	54	55.83	3.01	11.49	56.34	3.23	11.67
6.	3-CF ₃	H	C ₁₇ H ₁₁ F ₄ N ₃ S	365.4	195	50	55.83	3.01	11.49	56.28	2.87	11.39
7.	2-F	CH ₃	C ₁₇ H ₁₃ F ₂ N ₃ S	329.42	163	55	62.00	3.95	12.76	62.37	3.59	12.48
8.	3-F	CH ₃	C ₁₇ H ₁₃ F ₂ N ₃ S	329.42	165	54	62.00	3.95	12.76	61.73	4.12	12.94
9.	4-F	CH ₃	C ₁₇ H ₁₃ F ₂ N ₃ S	329.42	251	46	62.00	3.95	12.76	62.28	3.68	12.57
10.	3-CF ₃	CH ₃	C ₁₈ H ₁₃ F ₂ N ₃ S	379.43	245	51	56.93	3.43	11.07	57.23	3.78	11.23
11.	H	CF ₃	C ₁₇ H ₁₁ F ₄ N ₃ S	365.4	248	55	55.83	3.01	11.49	55.78	3.37	11.86

Spectral Studies of 2-arylidine hydrazino 4-(*p*-fluorophenyl) thiazoles
[TABLE No. 7].

2- [(*p* - trifluoromethyl phenyl) - 1 - methyl-ene] hydrazino-
4 -(*p*- fluoro phenyl)thiazole. (compd.no.4)

IR (KBr) cm : 1638 (C=N) ; 1597,1512,1066 (Thiazole) ; 1014 (monofluorination);
834 (1,4,substituted aromatic).

PMR (CDCl₃) δ : 6.74 (s, 1H, -NH-) ; 8.36 (s, 1H, -N=CH-) ;
7.08-7.83 [m, 9H, (8H, Ar-H; 1H, thiazole-C₅-H)]

2- [(*p* -fluoro phenyl) - 1 - methyl(methyl)-ene] hydrazino-
4 -(*p*- fluoro phenyl)thiazole. (compd.no.9)

IR (KBr) cm : 2924 (alkyl) ; 1620 (C=N) ; 1599,1507,1050 (Thiazole) ;
1105 (monofluorination); 840 (1,4 substituted aromatic).

PMR (CDCl₃) δ : 2.44 (s,3H, -CH₃-) ; 6.75 (s, 1H, -NH-) ;
7.00 -7.87 [m, 9H, (8H, Ar-H; 1H, thiazole-C₅-H)]

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Mode= 2 (Mid-IR)

2/25/97 6:00 PM

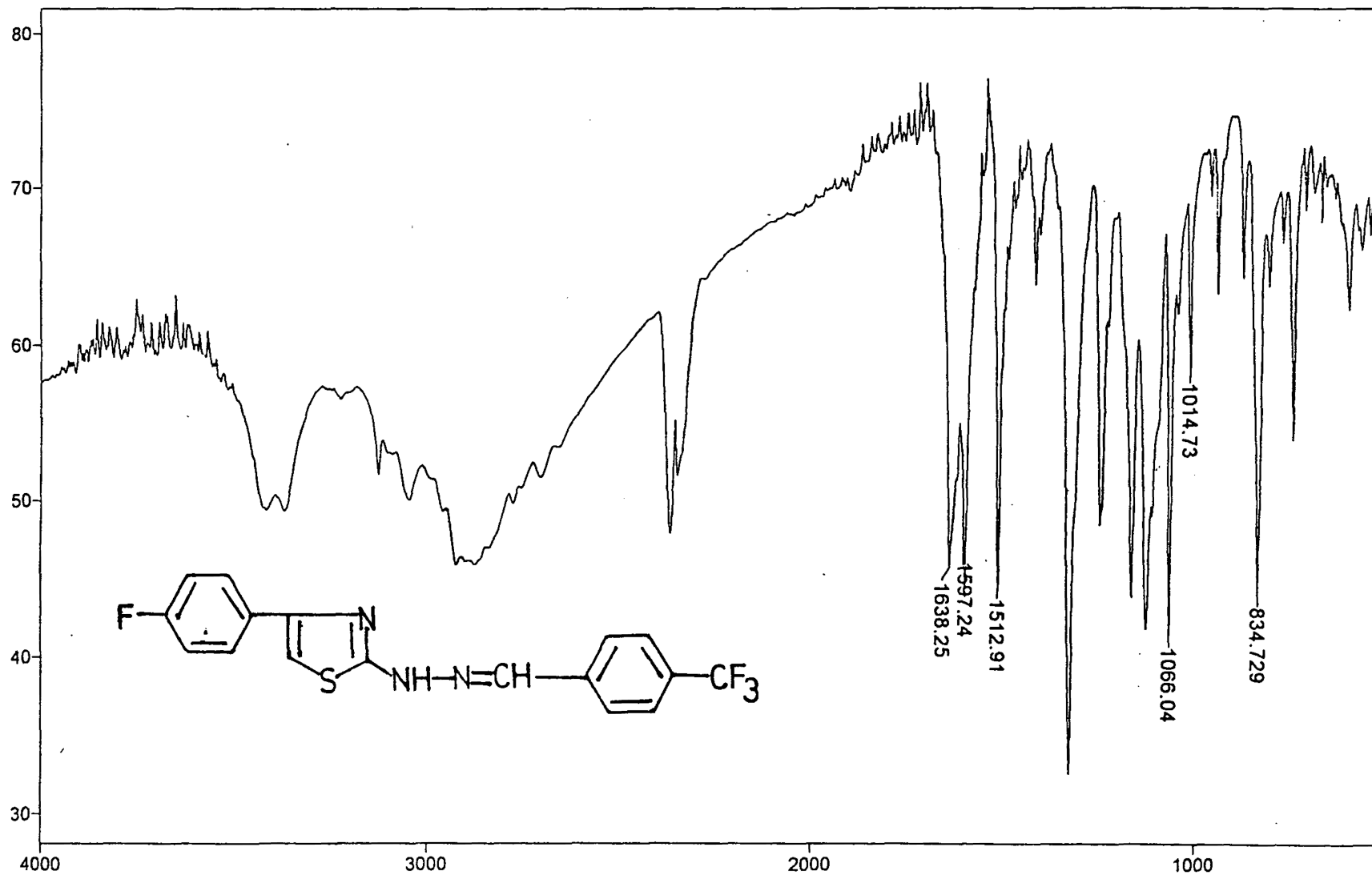
Sample Description: hydrazinoth

Scans= 10 Slow

Res=4 cm-1

Apod= Cosine

Zero Filling= 1 x

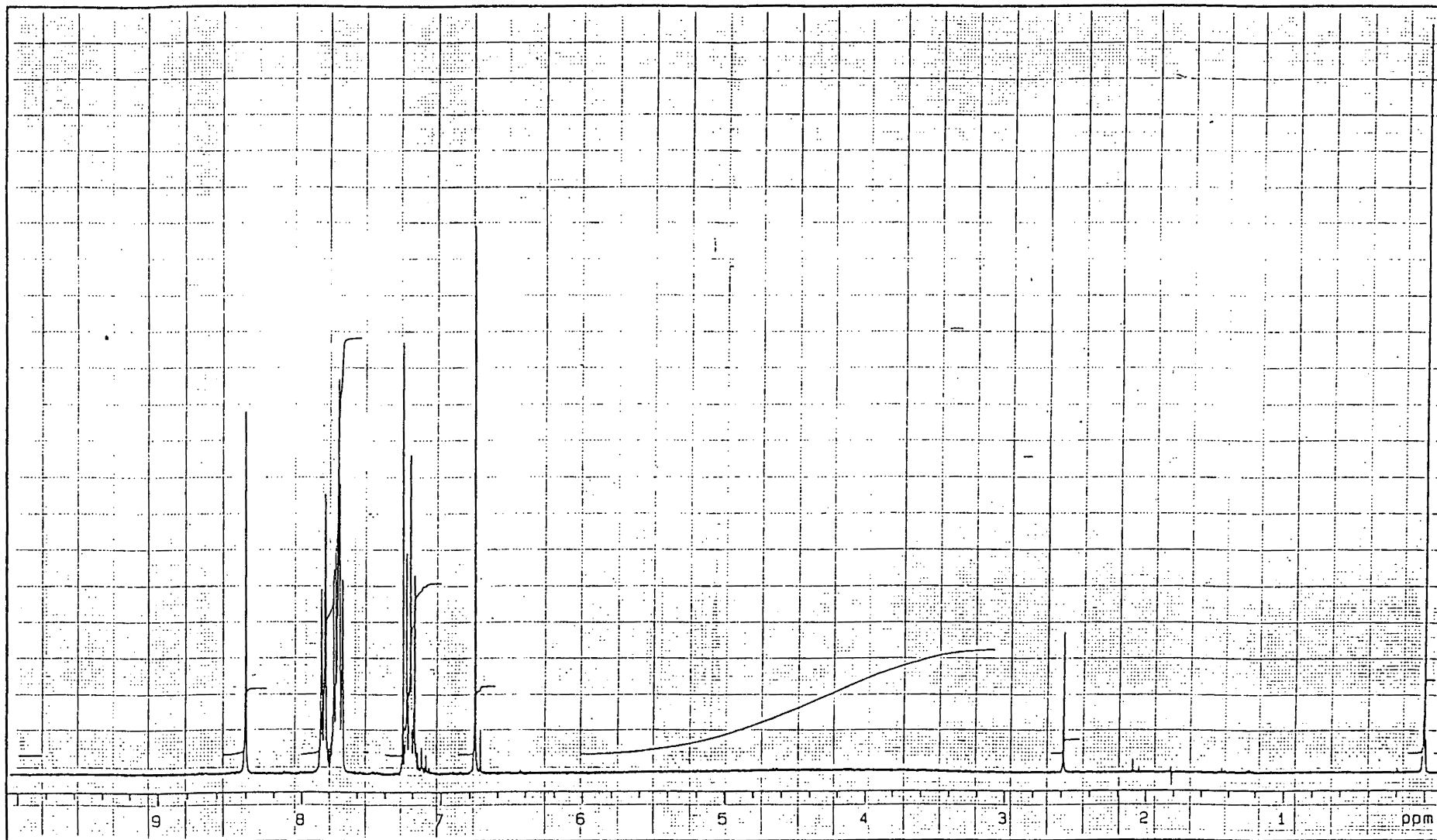


Transmittance / Wavenumber (cm-1)

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PART NO 987259

CHART XL SERIES

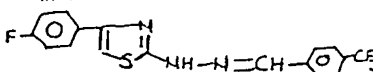


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Acq. Time 4.001 sec Delay 0 sec
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DECOUPLE
Nucleus H1 Offset 317.2 Hz
Mode 11 Power 20 dB
Modulation Mode C Freq. 200 Hz
Pulse Width μsec Power Mode not used

PLOT/PROCESSING
P1 not used RE sec CD sec
LB 0.100 Hz not used sec CD
Width 3993.3 Hz/ppm Start 33.3 Hz/ppm
Reference

EXPERIMENT
Pulse Sequence s2pu1 SAMPLE
Tube O.D. mm HT-4
Temp not used °C
Solvent cdcl3
Number
File
Date 3-27-75
varian



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Mode= 2 (Mid-IR)

2/25/97 6:29 PM

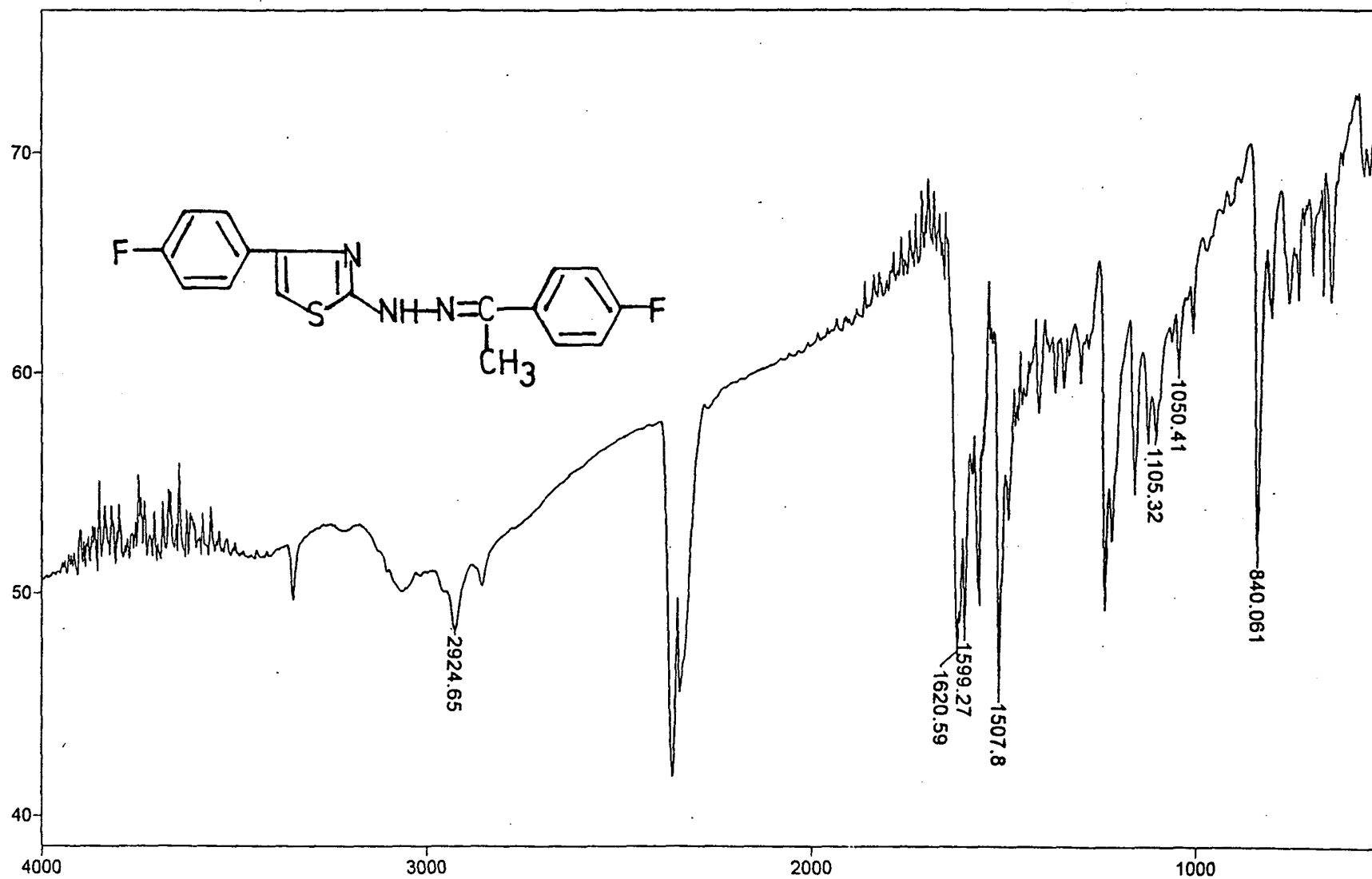
Sample Description: hydrazino

Scans= 10 Slow

Res=4 cm-1

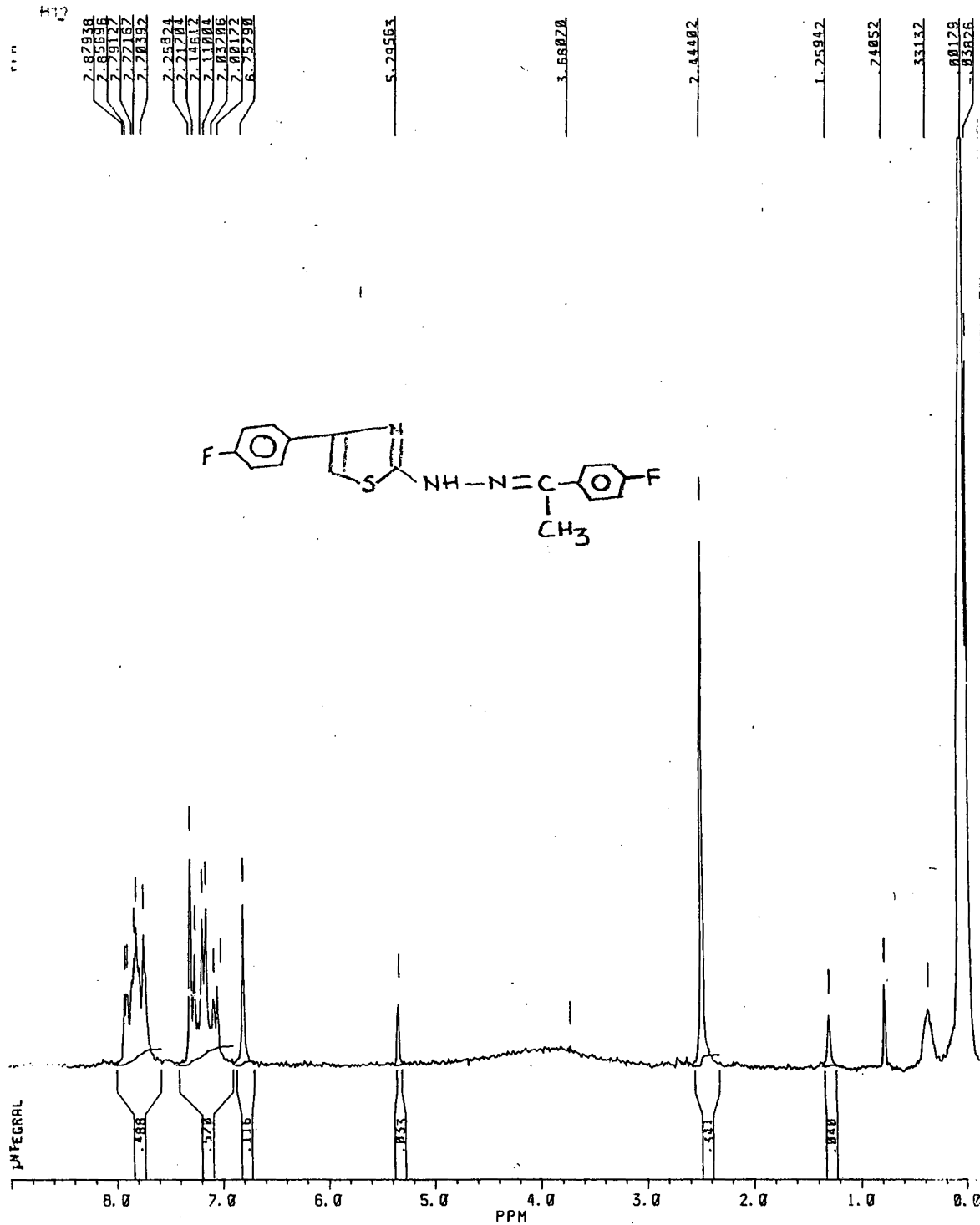
Apod= Cosine

Zero Filling= 1 x



Transmittance / Wavenumber (cm-1)

SWM-1/CDCL3/18/12/95



PART V

SYNTHESIS OF
3/4 [(SUBSTITUTED PHENYL) 1 -
METHYL - ENE] AMINO 1, 2, 4
TRIAZOLES

This part deals with the synthesis of which 3 / 4 - [(substituted phenyl) - 1 - methyl-ene] amino 1,2,4 triazoles involves the following steps :

- 1) Preparation of 3 / 4 - amino 1,2,4 triazoles.
- 2) Synthesis of title compounds by condensation of 3 / 4 - amino 1,2,4 triazoles with various substituted benzaldehydes .

1) a. Synthesis of 3 amino 1H, 1,2,4 triazole

In a 100 ml round bottomed flask equipped with a reflux condenser was placed (10 gm, 0.074m) of finely powdered aminoguanidine bicarbonate. To this was added (3.55 gm, 2.96 ml ; 0.077m) 98-100% formic acid gradually in 0.5 ml portion in 15-20 minutes with gentle swirling the flask. When the gas evolution ceases and the mass is dissolved the aminoguanidine formate is held at a temperature of 120 °C for 5 hrs. The solution was then cooled and 37.5 ml (95%) ethanol was added the product is dissolved by heating and the solution is filtered hot. The product is obtained by evaporation of ethanol at 100 °C. The product was recrystallised from ethanol

Yield : 5.72 gms (92%)

M.P. = 152-154 °C

Lit.²⁸⁴ M.P. = 152-156 °C.

1) b. Synthesis of 4 amino 1H, 1,2,4 triazole

In a 250 ml round bottomed flask fitted with a reflux condenser was placed (10 gm, 0.135m) ethyl formate in 10 ml ethanol . To this was added (6.8gm, 0.136m) 99% hydrazine hydrate in 15-20 mins with gentle stirring. When reaction has subsided the reaction mixture was heated on a steam bath for 18-20 hrs. The reaction mass was concentrated to about 5-7 ml under vacuum and further heated to 200 °C for 3 to 4 hrs. It was then cooled to room temperature and treated with charcoal in 10 ml ethanol. After filtration it was diluted with 5 ml pet. ether and cooled to 10 °C. It is filtered and washed with 5 ml (1: 2 ethanol:pet. ether). It was further crystallised from 20 ml (1:1,ethanol: pet. ether)

Yield : 7.35 gms (65%)

M.P. = 80-81 °C

Lit. ²⁸⁵ M.P. = 82 °C.

2) General method for the preparation of 3/4 - [(substituted phenyl) - 1 - methyl-ene] amino 1,2,4 triazoles.

Synthesis of 3- [(2- fluoro, 4- trifluoromethyl phenyl) - 1 - methyl-ene] amino1,2,4 triazole.

In a 50 ml round bottomed flask equipped with a reflux condenser was placed 3-amino 1,2,4 -triazole (0.420 gms, 0.005 m) in 5 ml dry methanol it is slightly warmed if in order to obtain a clear solution. To this was added 2- fluoro, 4- trifluoromethyl benzaldehyde (0.960 gms, 0.005 m) dissolved in 5 ml methanol and refluxed on a water bath for 3-4 hrs. It was then cooled to room temperature. The solid separated was filtered and recrystallized from ethanol.

Yield : 1.01 gm (78%)

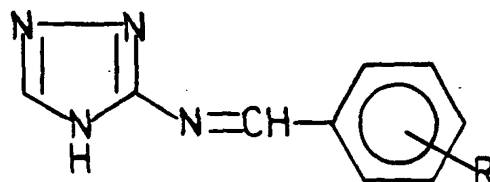
M.P. = 116 °C

Elemental analysis of $C_{10}H_6F_4N_4$	:	C%	H%	N%
Calculated		46.51	2.33	21.71
Found		45.94	1.86	21.03

In a similar manner all the other 3 / 4 - [(substituted phenyl) - 1 - methyl-ene] amino 1,2,4 triazoles have been synthesized and whose physical data has been represented in TABLE NOS. 8 and 9 respectively .

TABLE 8

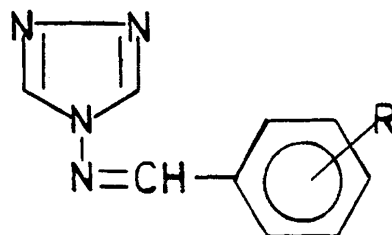
3-[(SUBSTITUTED) PHENYL] 1-METHYL-ENE] AMINO 1,2,4-TRIAZOLES



SR NO.	R	MOLECULAR FORMULA	MOL. WT.	M.P. °C	YIELD %	ELEMENTAL ANALYSIS					
						CALCULATED			FOUND		
						C	H	N	C	H	N
1.	4-F	C ₉ H ₇ FN ₄	190.11	185	54	56.81	3.68	29.46	57.03	3.87	29.12
2.	2-F	C ₉ H ₇ FN ₄	190.11	135	60	56.81	3.68	29.46	56.67	3.43	29.52
3.	3-F	C ₉ H ₇ FN ₄	190.11	138	72	56.81	3.68	29.46	57.19	3.95	28.08
4.	2-CF ₃	C ₁₀ H ₇ F ₃ N ₄	240.12	131	58	49.98	2.91	23.32	49.75	2.68	23.18
5.	3-CF ₃	C ₁₀ H ₇ F ₃ N ₄	240.12	202	64	49.98	2.91	23.32	50.34	3.28	23.68
6.	4-CF ₃	C ₁₀ H ₇ F ₃ N ₄	240.12	146	71	49.98	2.91	23.32	49.87	2.85	23.25
7.	2-Cl, 6-F	C ₉ H ₆ ClFN ₄	224.5	168	65	48.10	2.67	24.94	47.86	2.89	24.79
8.	2-F, 4-CF ₃	C ₁₀ H ₆ F ₄ N ₄	258	116	78	46.51	2.32	21.70	45.94	1.86	21.03

TABLE 9

4-[(SUBSTITUTED) PHENYL] 1-METHYL-ENE] AMINO 1,2,4-TRIAZOLES



SR NO.	R	MOLECULAR FORMULA	MOL. WT.	M.P. °C	YIELD %	ELEMENTAL ANALYSIS					
						CALCULATED			FOUND		
						C	H	N	C	H	N
1.	4-F	C ₉ H ₇ FN ₄	190.11	184	52	56.81	3.68	29.46	56.53	3.57	29.52
2.	2-F	C ₉ H ₇ FN ₄	190.11	134	63	56.81	3.68	29.46	57.06	3.85	29.12
3.	3-F	C ₉ H ₇ FN ₄	190.11	137	68	56.81	3.68	29.46	56.48	3.35	29.68
4.	2-CF ₃	C ₁₀ H ₇ F ₃ N ₄	240.12	130	54	49.98	2.91	23.32	50.43	3.07	23.52
5.	3-CF ₃	C ₁₀ H ₇ F ₃ N ₄	240.12	184	68	49.98	2.91	23.32	49.73	2.77	23.12
6.	4-CF ₃	C ₁₀ H ₇ F ₃ N ₄	240.12	148	67	49.98	2.91	23.32	50.23	3.15	23.68
7.	2-Cl, 6-F	C ₉ H ₆ ClFN ₄	224.5	166	61	48.10	2.67	24.94	48.43	2.48	25.02
8.	2-F, 4-CF ₃	C ₁₀ H ₆ F ₄ N ₄	258	113	65	46.51	2.32	21.70	46.84	2.07	21.52

Spectral studies of 3 / 4 [(substituted phenyl) - 1 - methyl-ene] amino 1,2,4 triazoles [TABLE No. 8 & 9].

3- [(2-chloro-6 -fluoro phenyl) - 1 - methyl-ene] amino 1,2,4 triazole.

[Table No. 8 , compd.no.7]

IR (KBr) cm : 1613 (schiff base, C=N);1569 (N-heterocycles conjugated C=C & C=N)
920 (C-N); 776 (C-Cl).

PMR (CDCl₃) δ : 7.27 - 7.31 [m, 5H (3H, Ar-H ; 1H, triazole - C₅-H ;
1H, triazole - NH-)] ; 8.92 (s, 1H, -N=CH-).

3- [(2- fluoro, 4- trifluoromethyl phenyl) - 1 - methyl-ene] amino 1,2,4 triazole.

[Table No. 8 ,compd.no.8]

IR (KBr) cm : 1625 (schiff base, C=N);1578 (N-heterocycles conjugated C=C & C=N)
; 1051 (polyfluorination) ; 916 (C-N); 743 (C-Cl).

PMR (CDCl₃) δ : 7.25 - 8.36 [m, 5H (3H, Ar-H ; 1H, triazole - C₅-H ;
1H, triazole - NH-)] ; 9.20 (s, 1H, -N=CH-).

Ms : m/z 258 (M⁺)

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2/25/97 6:56 PM

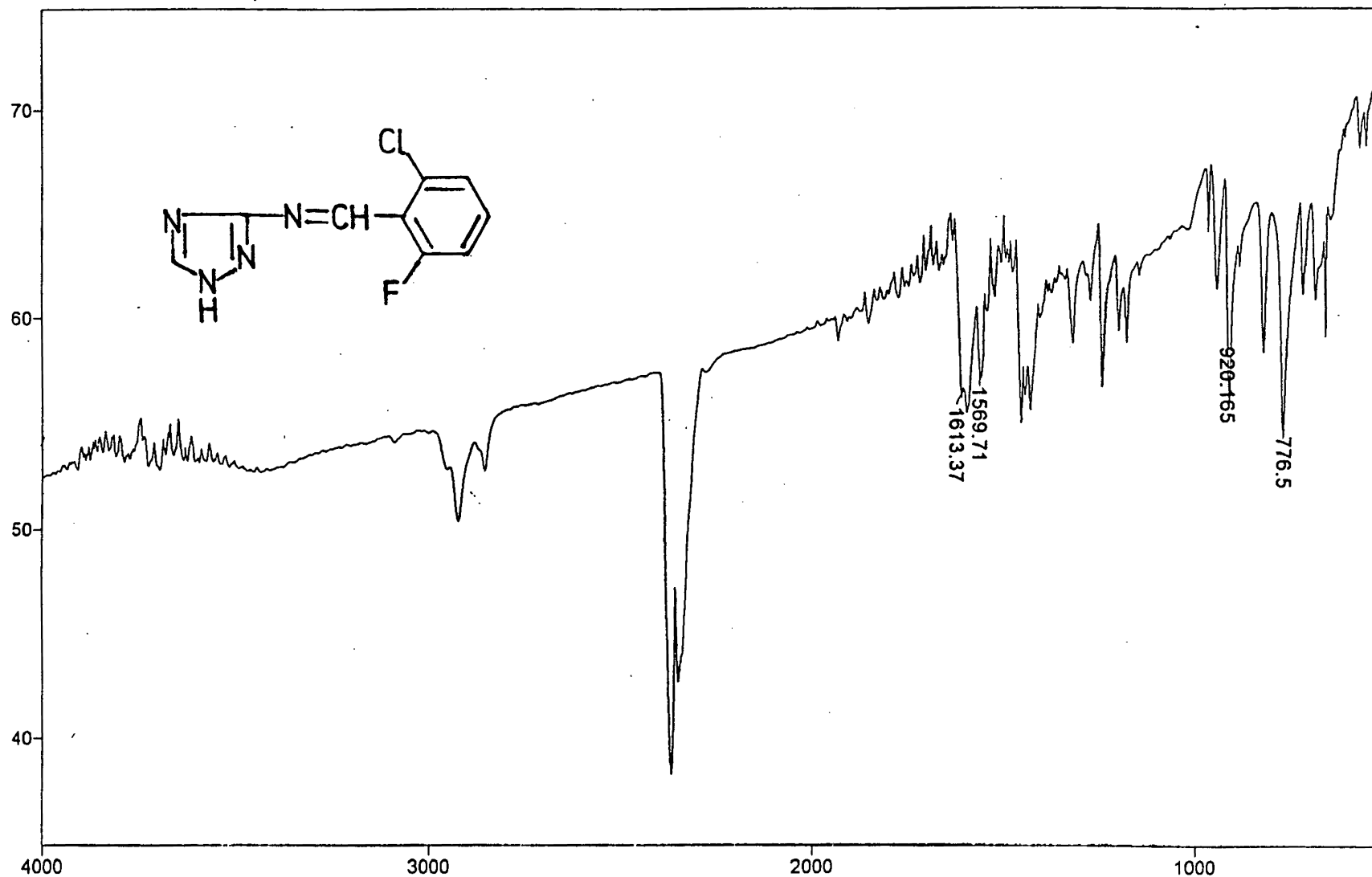
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Res=4 cm-1

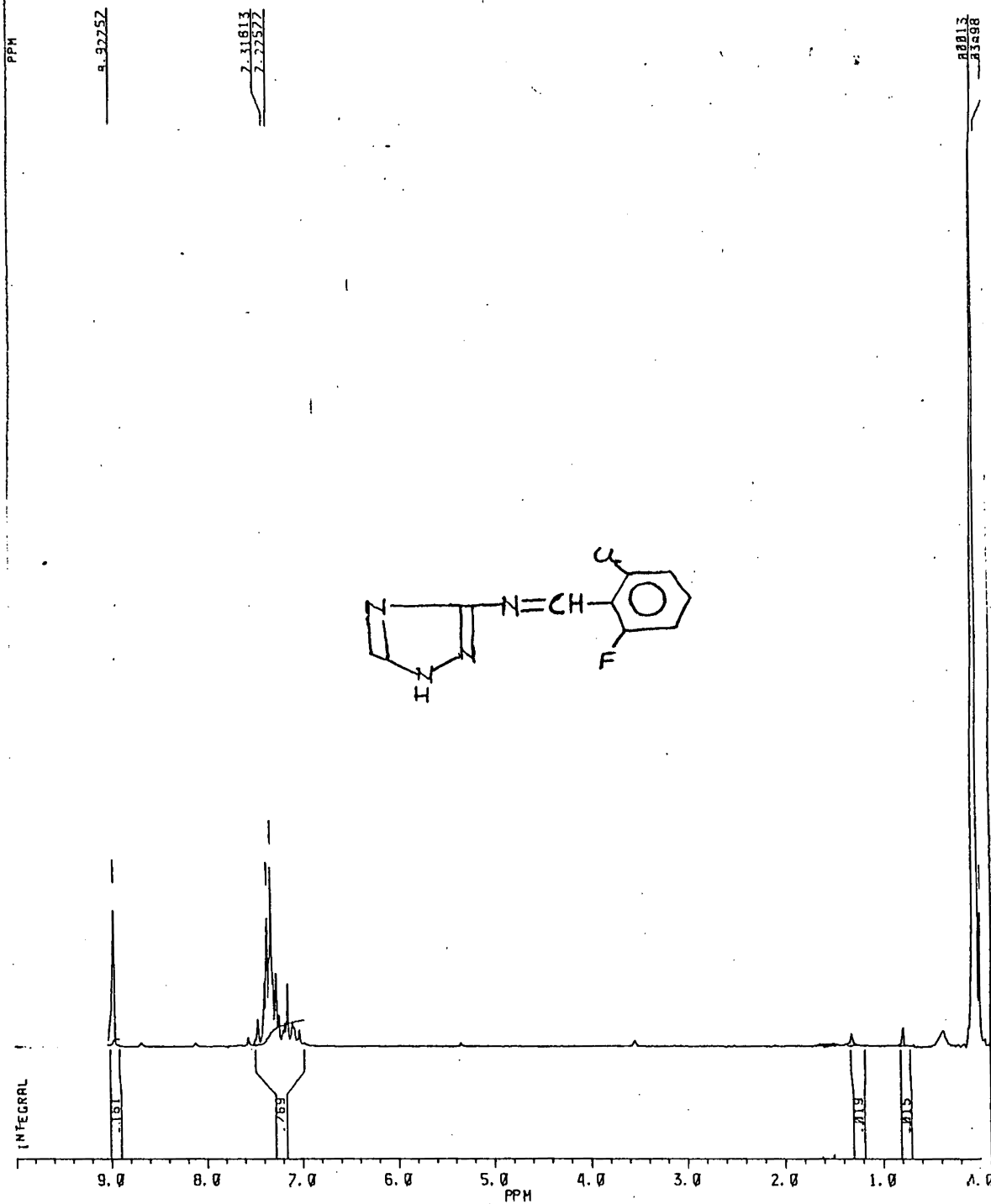
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Zero Filling= 1 x



Transmittance / Wavenumber (cm-1)

2
SWM/COCL3/19/12/95



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Mode= 2 (Mid-IR)

2/25/97 6:13 PM

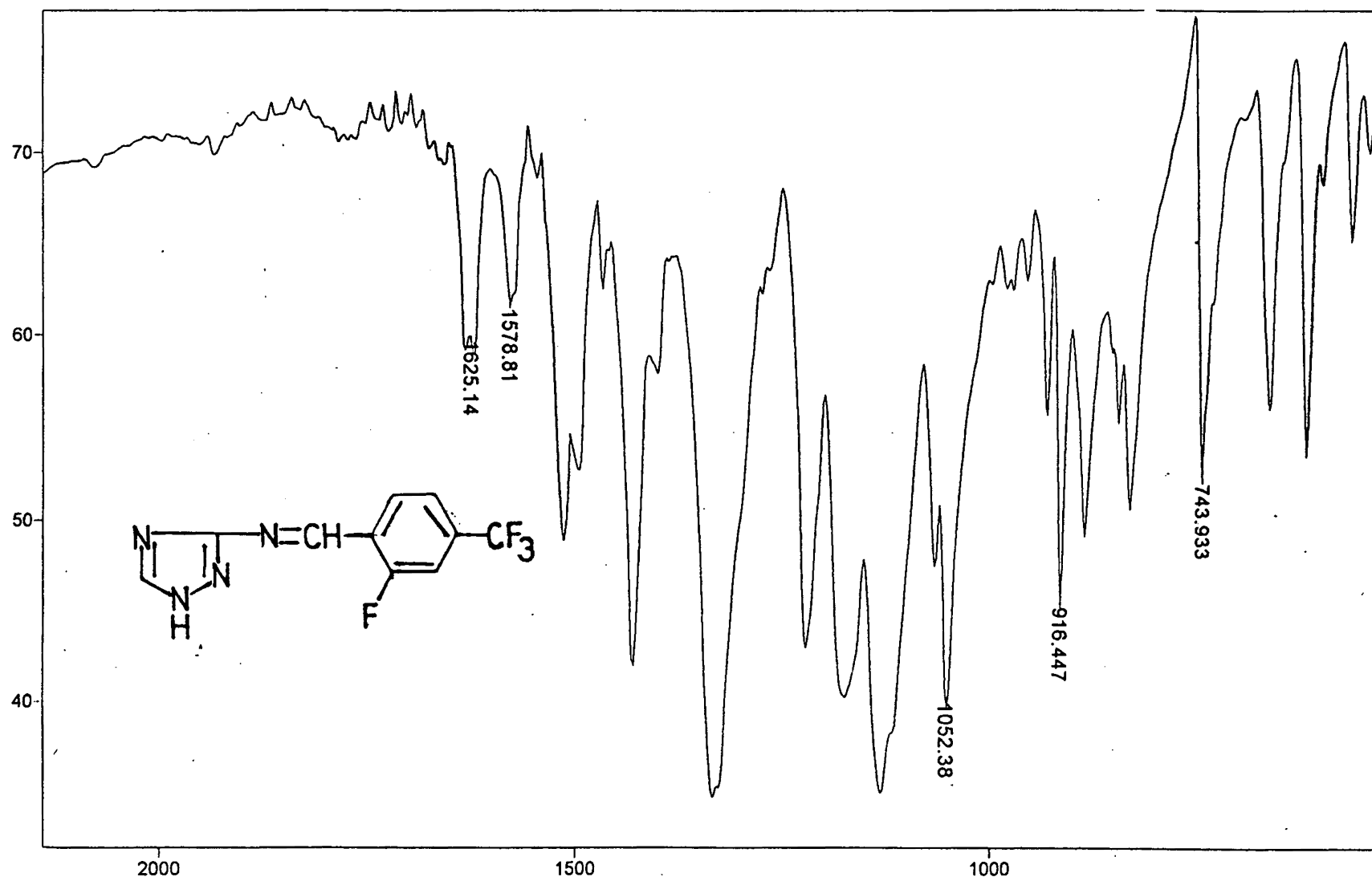
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Scans= 10 Slow

Res=4 cm-1

Apod= Cosine

Zero Filling= 1 x



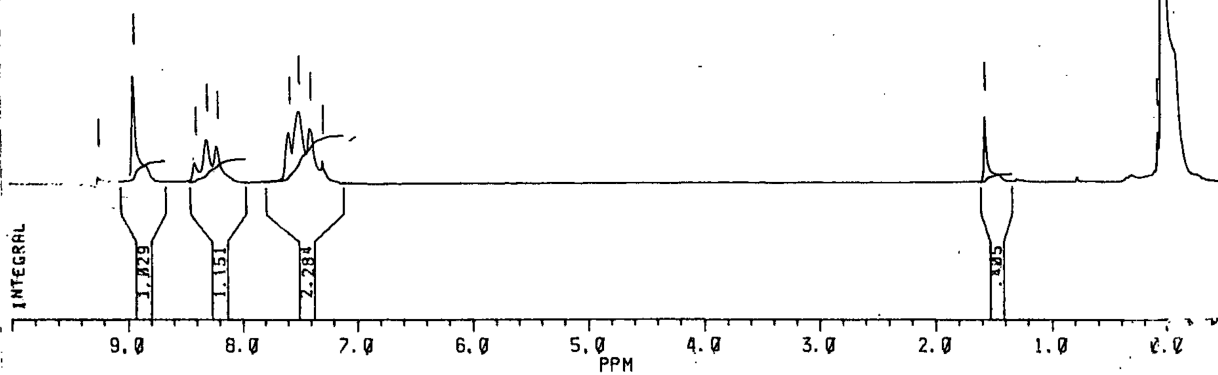
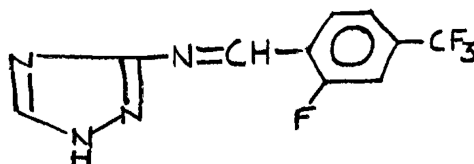
Transmittance / Wavenumber (cm-1)

SWM-2/CDCL3/20/12/95

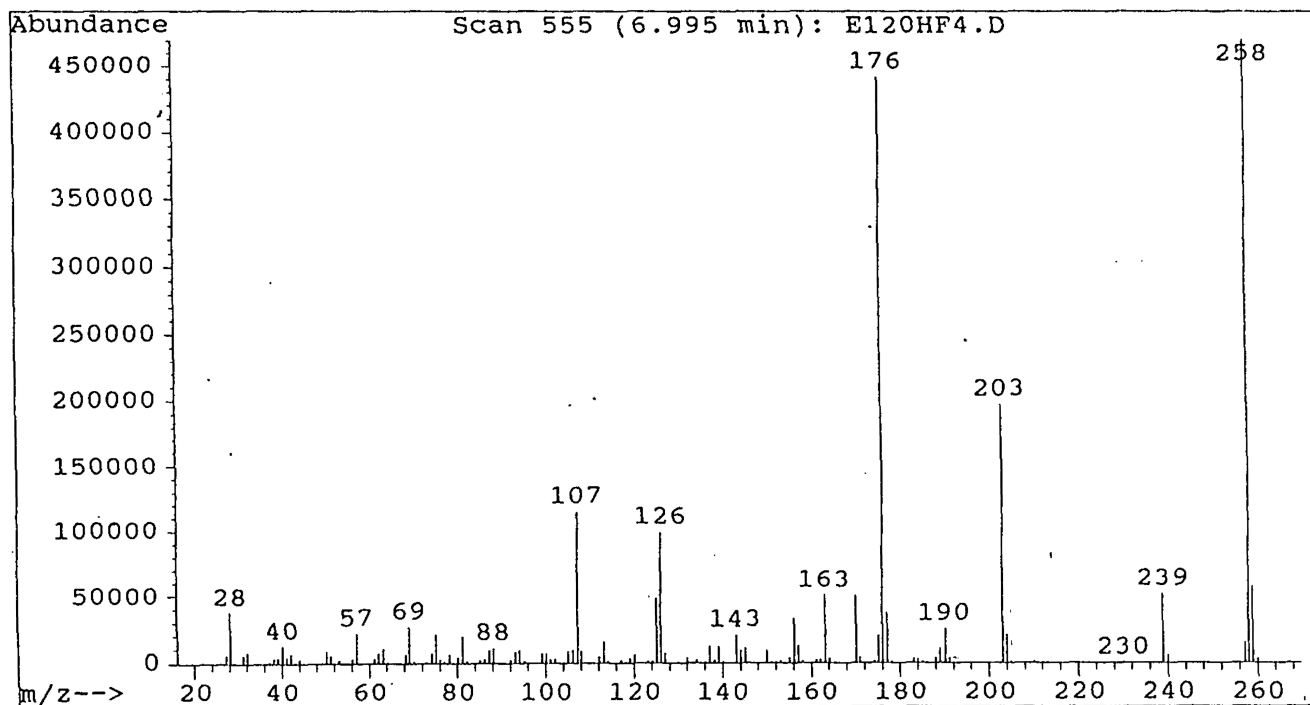
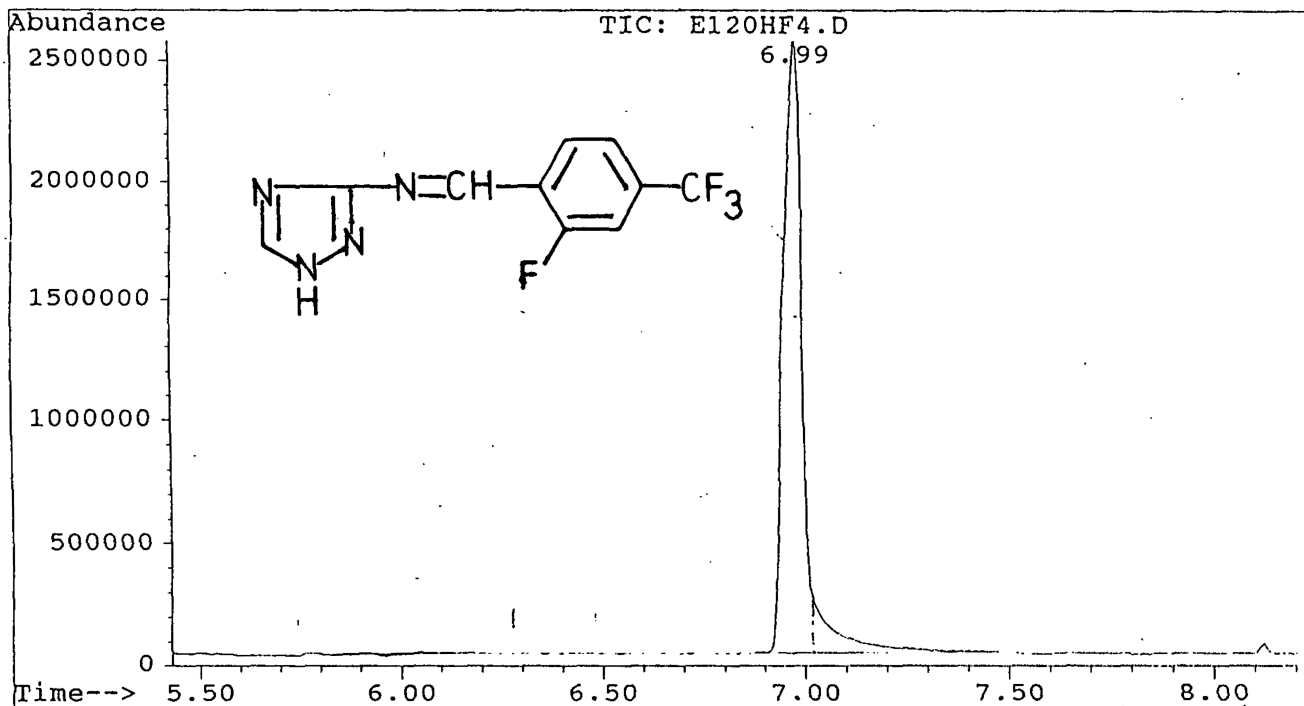
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1.52206

0.3219
0.00076



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PART VI

SYNTHESIS OF
4 (p-CHLOROPHENOXY) 3 -
CHLOROPHENYL, SUBSTITUTED PHENYL
THIOCARBANILIDES

This part deals with the syntheses of 4-(*p*-chloro phenoxy) -3-chloro phenyl, substituted phenyl thiocarbanilides which involves the following steps.

- 1) Synthesis of 2-chloro -4-nitro phenyl 4'-chloro phenyl ether.
- 2) Synthesis of 3-chloro -4-(*p*-chloro phenoxy) aniline .
- 3) Synthesis of 3-chloro-4-(*p*-chloro phenoxy) phenyl isothiocyanate.
- 4) Synthesis of title compounds by condensation of 3-chloro-4-(*p*-chloro phenoxy) phenyl isothiocyanate with various substituted amines.

1) Synthesis of 2-chloro -4-nitro phenyl 4'-chloro phenyl ether.

In a 250 ml three necked round bottomed flask equipped with water condenser, mechanical stirrer and dropping funnel was dissolved (6.7 gm, 0.0521 m) of *p*-chlorophenol in 10 ml dry dimethyl formamide. To this was added (8.64 gm, 0.0625 m) of anhydrous potassium carbonate. The mixture was heated to 100-110 °C in oil bath. To this was added 3,4-dichloro nitrobenzene (10 gm, 0.0521 m) in 10 ml dimethyl formamide . After the addition reaction mixture was refluxed for 6-8 hrs. Excess of dimethyl formamide was removed under reduced pressure. The residue was poured onto 100 gms of crushed ice. Resultant solid was filtered, washed with water. It was then recrystallised from methanol.

Yield : 12.4 gms (83.7 %)

M.P. = 110 °C.

Lit ²⁸⁶ M.P. = 108-110 °C

2) Synthesis of 3-chloro -4- (*p*-chloro phenoxy) aniline .

In a 250 ml 3 necked round bottomed flask equipped with water condenser, mechanical stirrer and dropping funnel was dissolved (10gm, 0.0352m) of 2-chloro -4-nitro phenyl 4'-chloro phenyl ether in 10 ml of sprit. To this is added 8 gm of iron powder . The mixture is refluxed for ½ hr. A solution of FeCl₃ 0.6 gm in 10 ml of 50 % spirit is added to this under reflux slowly in ½ hr. The reaction mixture is refluxed for 8-10 hrs . It is then filtered on hyflo bed filterate is concentrated to give amine which is crystalized from alcohol.

Yield : 7.24 (81%)

M.P. = 80 °C

Lit ²⁸⁷ M.P. = 80-81 °C



3) Synthesis of 3-chloro-4-(*p*-chloro phenoxy) phenyl isothiocyanate.

In a 100 ml three necked round bottomed flask equipped with water condenser, mechanical stirrer and dropping funnel was placed 3-chloro-4- (*p*-chloro phenoxy) aniline (4.5 gm, 0.018m) in a solution of acetic acid and hydrochloric acid (10 ml) . The mixture was stirred at 15 °C for 20-30 min. A solution of thiophosgene (3.06 gm , 2.03 ml , 0.027m) in 20 ml chloroform was added dropwise maintaining the temperature at 0 °C. The reaction mixture was further stirred for 4 hrs. The chloroform later was seperated washed with water till pH is neutral , dried on anhyd, sodium sulfate. The chloroform was evaporated to dryness to give the product.

Yield : 3.43 gm (64.4%)

M.P. = 134 °C

Lit ²⁸⁸ M.P. = 136 °C

4) General method of synthesis of 4-(*p*-chloro phenoxy) -3-chloro phenyl, substituted phenyl thiocarbanilide.

Synthesis of 4-(*p*-chloro phenoxy) -3- chloro phenyl, 4'-(*p*-chloro phenoxy) -3'-chloro phenyl thiocarbanilide.

In a 50 ml round bottomed flask equipped with a reflux condenser are placed 3- chloro - 4- (*p*- chloro phenoxy) phenyl isothiocyanate (0.250 gm, 0.000845m) and 3- chloro - 4- (*p*- chloro phenoxy) aniline (0.215 gm, 0.000845m) , Both previously dissolved in 8 ml of toluene. The reaction mixture is refluxed for 6-8 hrs. After cooling to room temperature added 8 ml hexane , white solid separates which is filtered and recrystallized from alcohol.

Yield : 0.325 gm (70%)

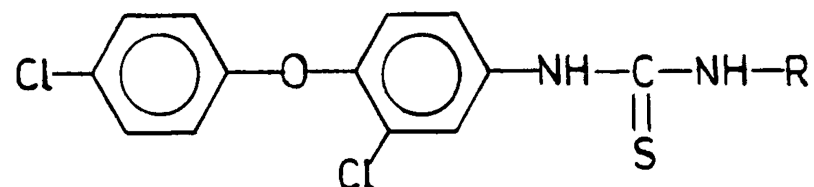
M.P. = 157 °C

Elemental analysis of $C_{25}H_{16}Cl_4N_2O_2S$:	C%	H%	N%
Calculated	54.55	2.91	5.09
Found	54.06	2.34	5.42

In a similar manner all the other 4-(*p*-chloro phenoxy) -3- chloro phenyl, substituted phenyl thiocarbanilides have been synthesized and whose physical data has been represented in TABLE NO. 10.

TABLE 10

4(p-CHLOROPHENOXY)3-CHLOROPHENYL, SUBSTITUTED PHENYL THIOCARBANILIDES



SR NO.	R	MOLECULAR FORMULA	MOL. WT.	M.P. °C	YIELD %	ELEMENTAL ANALYSIS CALCULATED			ANALYSIS FOUND		
						C	H	N	C	H	N
1.	3-Cl, 4-F-C ₆ H ₄	C ₁₉ H ₁₂ Cl ₃ FN ₂ OS	441.5	134	62	51.64	2.72	6.34	51.23	2.57	6.52
2.	3-Cl-C ₆ H ₃ -O-C ₆ H ₄ -3-Cl	C ₂₅ H ₁₆ Cl ₄ N ₂ O ₂ S	550	157	70	54.55	2.91	5.09	54.06	2.34	5.42
3.	3,4-Cl ₂	C ₁₉ H ₁₂ Cl ₄ N ₂ OS	458	122	58	49.78	2.62	6.11	49.39	2.47	6.25
4.	C ₄ H ₉	C ₁₇ H ₁₈ Cl ₂ N ₂ OS	369	130	64	55.28	4.88	7.59	55.51	4.67	7.67
5.	OC ₂ H ₅ -C ₆ H ₄	C ₂₁ H ₁₈ Cl ₂ N ₂ O ₂ S	433	118	73	58.20	4.16	6.46	58.37	4.28	6.23
6.	p-Cl-C ₆ H ₄	C ₁₉ H ₁₃ Cl ₃ N ₂ OS	423.5	126	61	53.83	3.07	6.61	53.56	3.25	6.46
7.	2,4-F-C ₆ H ₃	C ₁₉ H ₁₂ Cl ₂ F ₂ N ₂ OS	425	138	53	53.64	2.82	6.59	53.37	2.58	6.23
8.	2-F-C ₆ H ₃ -O-C ₆ H ₃ -2-Cl, 4-CF ₃	C ₂₆ H ₁₅ Cl ₃ F ₄ N ₂ O ₂ S	601.5	142	48	51.87	2.49	4.66	52.40	2.32	4.89
9.	3-CF ₃ , 4-Cl-C ₆ H ₃	C ₂₀ H ₁₂ Cl ₃ F ₃ N ₂ OS	491.5	148	58	48.83	2.44	5.69	49.19	2.75	5.48

Spectral studies of 4-(*p*-chloro phenoxy) -3-chloro phenyl, substituted phenyl thiocarbanilides [TABLE No. 10].

4-(*p*-chloro phenoxy) -3- chloro phenyl, 4'-(*p*-chloro phenoxy) -3'- chloro phenyl thiocarbanilide. [TABLE No. 10 ,compd.no.2]

IR (KBr) cm : 3180 (aromatic sym. ether) ; 1588 (aromatic) ;
1482 (polysubstituted benzene); 1332 (-C=S) ;
1250 (ether); 845 (benzene ring with 2-adjacent -H atoms) ;
752 (C-Halo) .

PMR (CDCl₃) δ : 6.65 - 7.52 (m, 14H, Ar-H) ; 7.71 (s, 2H, -NH-) .

4-(*p*-chloro phenoxy) -3- chloro phenyl, 3',4'-dichloro phenyl thiocarbanilide.

[TABLE No. 10 compd. no. 3]

IR (KBr) cm : 3186 (aromatic sym. ether) ; 1583 (aromatic) ;
1482 (polysubstituted benzene) ; 1333 (-C=S) ;
1244 (ether); 845 (benzene ring with 2 adjacent -H atoms) ;
757 (C-Halo) .

PMR (CDCl₃) δ : 6.65 - 7.50 (m, 10H, Ar-H) ; 7.87 (s, 2H, -NH-) .

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2/25/97 6:45 PM

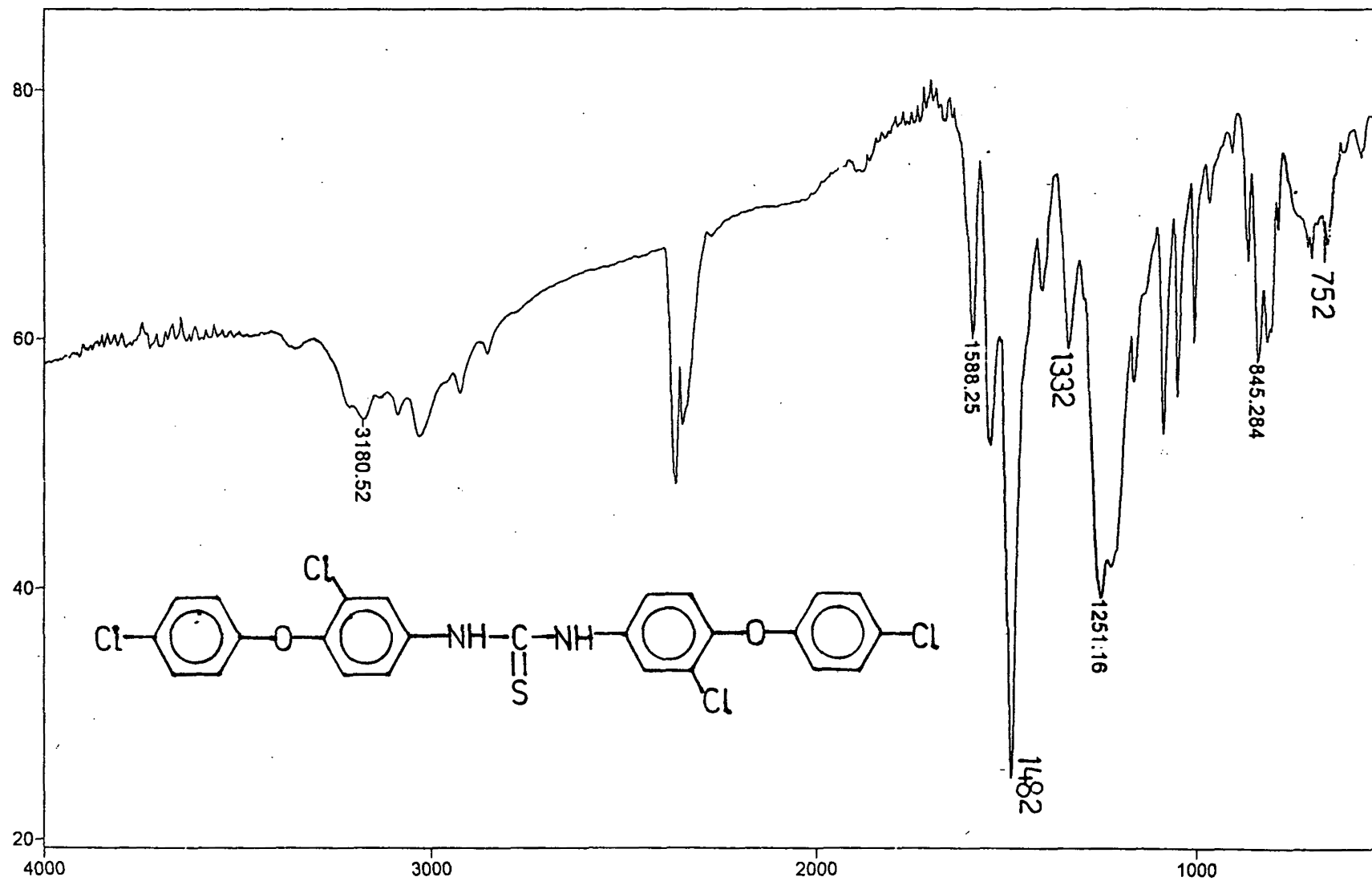
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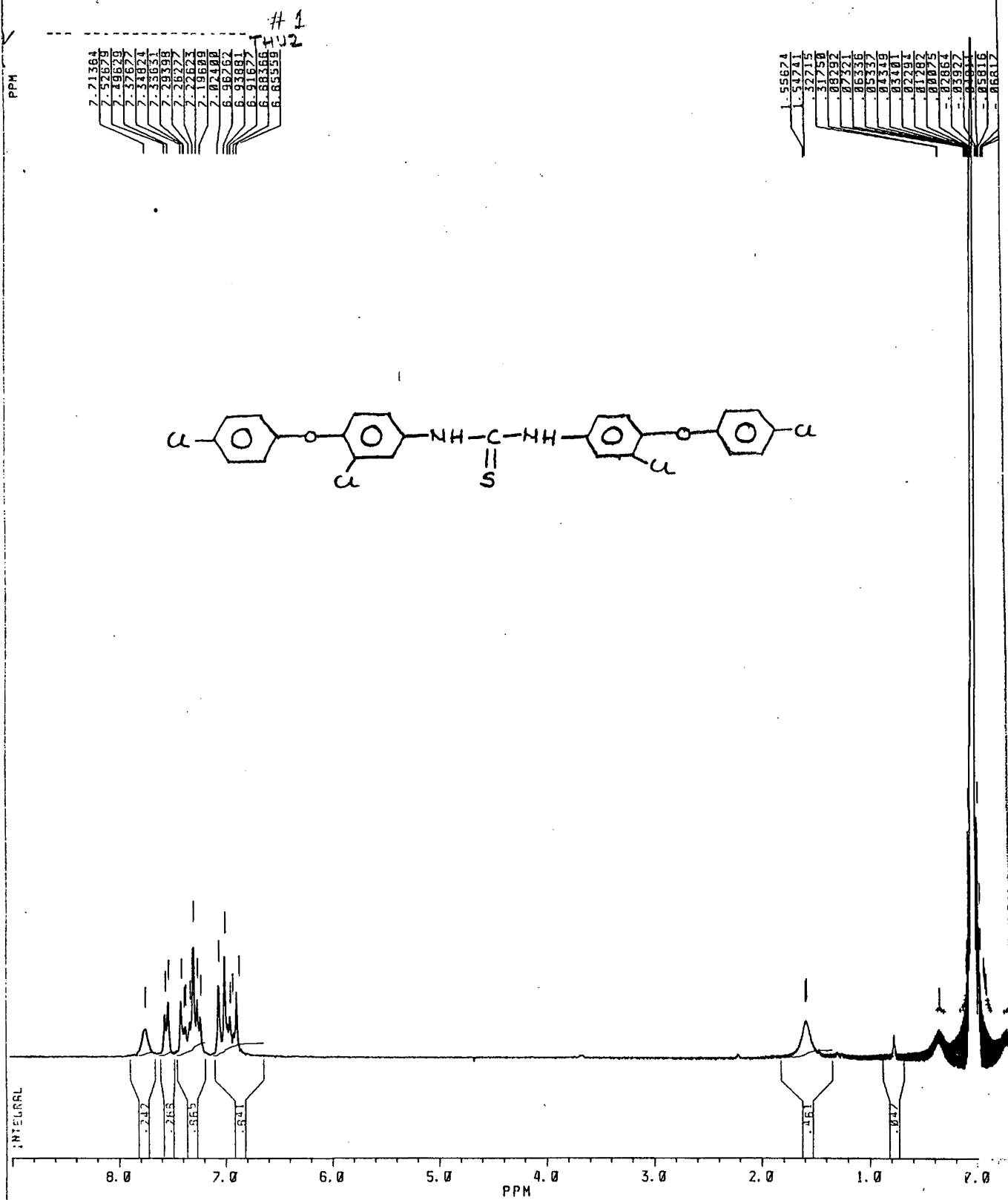
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Zero Filling= 1 x



Transmittance / Wavenumber (cm-1)



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2/25/97 5:41 PM

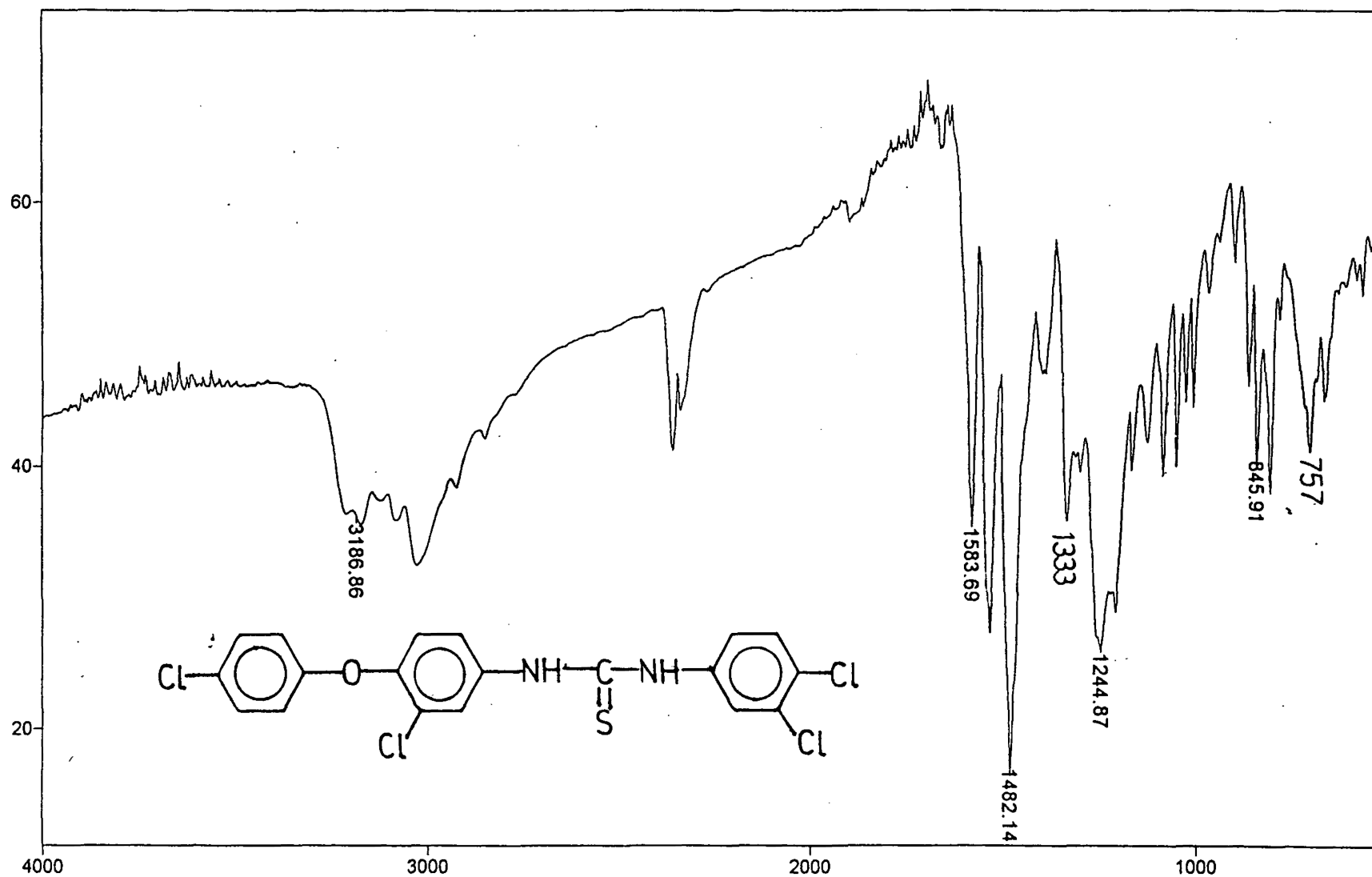
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Scans= 10 Slow

Res=4 cm-1

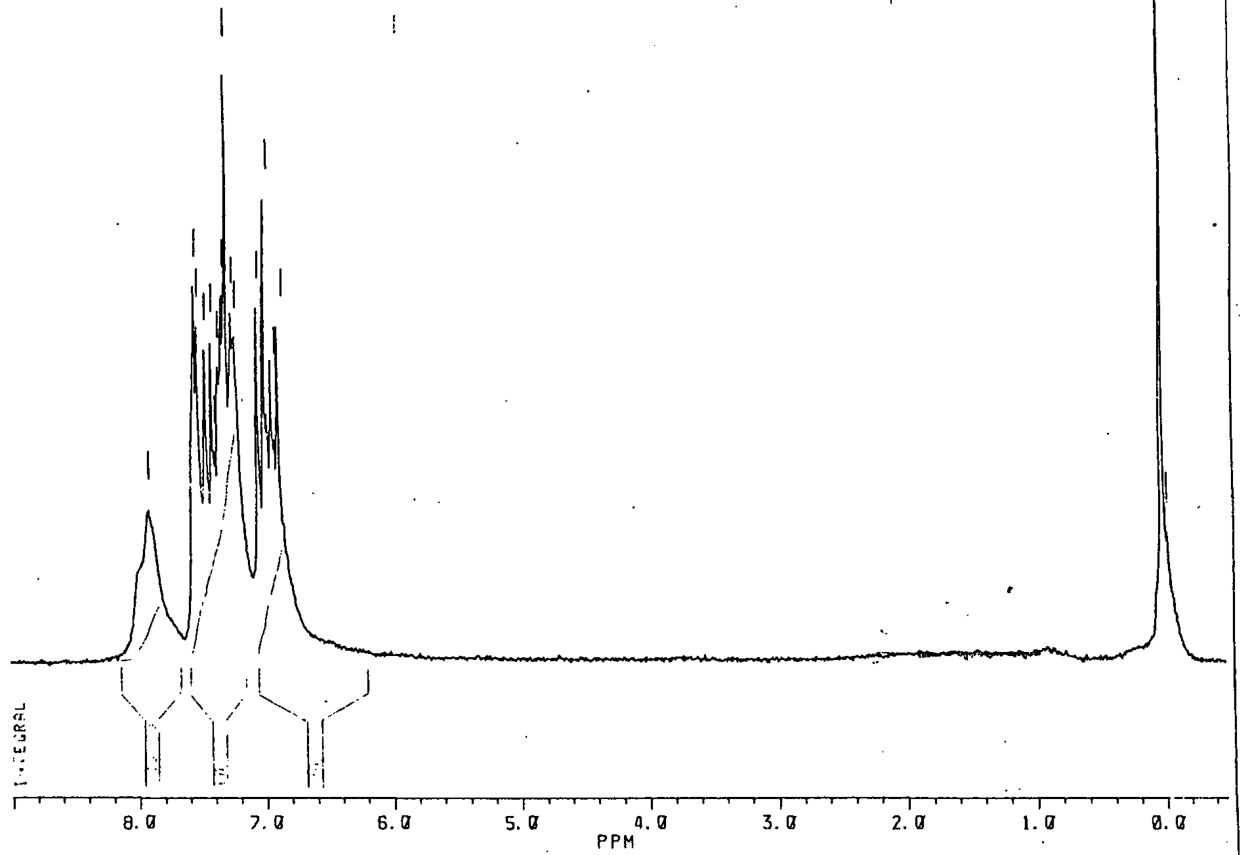
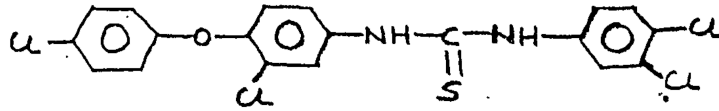
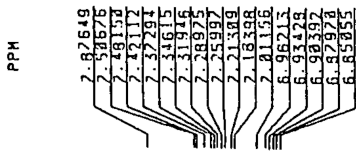
Apod= Cosine

Zero Filling= 1 x



Transmittance / Wavenumber (cm-1)

#1/CDCL3/25/11/95/THU3



PART VII

**BIOLOGICAL RESULTS AND
DISCUSSIONS**

BIOLOGICAL RESULTS AND DISCUSSION

The compounds synthesized in the present investigation have been subjected to various biological screening programmes based on their structural features so as to ascertain their suitability as potential chemotherapeutic agents.

The various screening programmes carried out have been in the *in vitro* study against *H₃₇Rv* strain of *Mycobacterium tuberculosis* for estimating antitubercular activity and the *in vitro* study against species of Gram-positive and Gram-negative bacteria. viz. *Staphylococcus aureus* ATCC 3750 (*S. aureus*) and *Salmonella typhi* NCTC 786 (*S. typhi*) for estimating antimicrobial activity.

Similarly various screening programmes conducted have been in the *in vitro* study against various strains of fungi, viz. *Candida albicans*, *Trichophyton rubrum* and *Trichophyton mentagrophytes*.

In the anthelmintic screening the test compounds have been subjected to *in vivo* screening against *Hymenolepis nana* in the mice.

The methodology adopted for the various biological screening programmes undertaken in this study has been described in the following section.

Antitubercular Screening

The test compounds have been subjected to *in vitro* screening by the tube dilution technique employing the human virulent *H₃₇Rv* strain of *M. tuberculosis*. In this method, using a Kirchner's medium containing Tween-80 as described by Rake *et al* ²⁹⁹, dispersed growth of *M. tuberculosis* was obtained.

Screening Procedure

Sterile Kirchner's media (4.35 ml) was dispensed in each borosilicate test tube (150 x 20 mm). The test compounds (20 µg) were dissolved in a suitable solvent (10 ml) such as dimethyl formamide (DMF) dilute HCl, ethanol as the case may be.

The serial drug dilutions were made in such a way as to give various final drug concentrations of 200, 100, 50, 25, 12.5, 6.25 mg/ml. Sterile normal bovine serum (0.5 ml) was added to each test tube. The inoculum of standard suspension (0.1 ml) of *M. tuberculosis* (*H₃₇Rv* strain) 10⁶ bacilli/ml was added at the end. The tubes were incubated at 37^o C for ten days 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 i.e. minimum inhibitory concentration (MIC) .

Control tubes with ethambutol as standard drug and tubes without any drug were kept for comparison. Also the solvents used for dissolving the substances under study were similarly tested to see that they did not affect the growth of the culture at the concentrations used under these experimental conditions. Ethambutol inhibited the growth of *M. Tuberculosis* at a concentration of 0.04 µg/ml.

Screening against other bacterial infections

The test compounds have been subjected to *in vitro* screening by the tube dilution technique ³⁰⁰ against various species of Gram positive and Gram negative bacteria viz. *S. aureus*, and *S. typhi* using Mueller-Hinton broth as the culture medium.

Screening Procedure

Sterile Mueller-Hinton broth (4.35 ml) was dispersed in each borosilicate test tube (150 X 20 mm). The test compounds (20 µg) were dissolved in a suitable solvent (10 ml) such as dimethyl Formamide (DMF), dilute HCl, ethanol as the case may be.

The serial drug dilution were made in such a way as to give various final drug concentrations of 200, 100, 50, 25, 12.5, 6.25. The inoculum of standard suspension (0.1 ml) of the desired bacterial strain (*S. aureus* or *S. typhi*) containing 10⁶ bacilli/ml was added at the end. The tubes were incubated at 37°C for 24 hrs. 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) .

Control tubes with ampicillin as standard drug and tubes without any drug were kept for comparison. Also the solvents used for dissolving the substances under study were similarly tested to see that they did not affect the growth of the culture at the concentrations used under these experimental conditions Ampicillin inhibited the growth of *S. aureus* and *S. typhi* at concentrations of 0.5 and 0.4 µg/ml respectively.

Antifungal Screening

The organisms employed in the test were 1) *Candida albicans* 2) *Trichophyton rubrum* 3) *Trichophyton mentagrophytes*. These organisms were maintained on

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

Test Medium

The liquid medium described by E. Joan Stokes *et.al* ³⁰¹ was used for screening the compounds for their antifungal activity. The final pH of the medium was adjusted to 5.2. This test medium was dispensed in requisite amounts varying from 4.4 to 4.85 ml in sterile tubes. To these were added the requisite test solution in graded concentrations varying from 200 to 6.25 mg/ml.

Preparation of innoculum

Candida albicans

A 48 hours old growth on Sabouraud's agar slant was suspended in 4-5 ml of the test medium with the help of platinum loop. The cell count of suspension (yeast phase) was carried out using Neubaur chamber and then diluted with requisite volume of the medium to give a final concentration of 5×10^6 cells per ml.

T. rubrum and *T. mentagrophytes*

To a 12 to 14 days old growth on Sabouraud's agar slant, 5 ml of sterile test medium and 3-4 sterile glass beads (3 mm diameter) were added and gently shaken for 10 minutes. The supernatant was decanted into another sterile tube and the count of spores in the suspension was carried out using Neubauer chamber. Final strength of the innoculum was adjusted to 5×10^6 spores per ml, using test medium.

Screening Procedure

To each test tube was then added 0.1 ml of standardized innoculum of the test organism. The tubes were then incubated at room temperature (28-30°C) in a dark place. The presence or absence of growth was noted visually after 7 days in case of *Candida albicans* and after 14 days in case of *T. rubrum* and *T. mentagrophytes*.

Miconazole was used as standard drug for control and also tubes without any drug were kept for comparison.

Anthelmintic Screening

The compounds mentioned in Table no. (13) were screened for their *in vivo* anthelmintic activity against *Hymenolepis nana* in mice. The method used is the one described by Agarwal, Alka. et al ³⁰².

Screening Procedure

Each male mouse (18-20 gms, 4 weeks old) of the total 95 mice given an oral inoculum of 100 mature eggs collected from mature worm of *H. nana*. The infected mice were divided into 19 groups of 5 mice each. 2 groups of mice were used for each of the 9 test compounds. The two groups were treated on the 17th or 18th daily with either single dose of 100 mg or repeated dose of 50 mg of each compound. One group of mice was kept as control. The mice were sacrificed on the 5th post treatment day.

At autopsy the entire small intestine was removed and laid on a background of black glass and contents were removed by expression. The number heads of *H. nana* worm was counted.

The drug action is expressed in terms of percentage efficacy (% efficacy) on the basis of reduction of worms following treatment. The drug response was calculated on the mice cleared of the infection as compared to the untreated control group.

RESULTS AND DISCUSSION

Part II : 5,6-disubstituted 2-(alkyl/substituted aryl) amino benzothiazoles

In this series 8 compounds have been synthesized. The screening results exhibit the minimum inhibitory concentration (MIC) against Gram positive bacteria in the range of 25-100 µg/ml. Table no 11 Compound no. 3, 4, 5 and 6.

Table no. 11 Compound no. 3 where the substitution is allylamino at the 2-position of benzothiazole moiety has shown activity against *S typhi* at the concentration of 25 ug/ml and 50 ug/ml for *S aureus*.

For antifungal screening it is observed that Table no. 11 compound no. 3, 4, 5, 6 and 8 are active in the range of 50-200 ug/ml.

Here also Table no. 11 compound no. 3 has shown activity at 50 $\mu\text{g/ml}$ against *T. mentagrophytes* and *T. rubrum*.

Table no. 11 Compound no. 6 is active against all the species of fungi at 200 $\mu\text{g/ml}$.

The most active compound in this series for antifungal activity is Table no. 11 compound no. 8 where electron withdrawing chlorine group is present at 3 and 4 position on the phenyl ring in the anilino substituent.

All the compounds of this series have been evaluated for their *in vitro* antitubercular activity against *H₃₇Rv* strain of *mycobacterium Tuberculosis* but unfortunately none of the compounds have shown activity upto 200 $\mu\text{g/ml}$.

Part III: 5,6- disubstituted 2- (substituted phenyl carboxamido) benzothiazoles

In this series totally 13 compounds were screened against the bacterial species of *S. typhi* and *S. aureus*. The results once again were very discouraging. None of the compounds have shown significant activity. Only Table no. 12 compound no. 11 and 13 has shown activity at 100 $\mu\text{g/ml}$ for both species.

All these compounds were subjected for antifungal activity and the results were some what encouraging as compared to the antibacterial screening. Eight compounds have shown activity against three species at 100 $\mu\text{g/ml}$.

In Table no. 12 compound no. 11 which is the most active compound the trifluoromethyl substituent is present at *o*-position of phenyl ring of phenyl carboxamido linkage.

Out of thirteen compounds, three compounds viz. (5, 10 and 13 of Table no. 12) have exhibited MIC at 50 $\mu\text{g/ml}$ against *H₃₇Rv* strain of *mycobacterium tuberculosis* which are having electron withdrawing trifluoromethyl substituent in various position of phenyl ring. Rest of compounds have not shown activity upto 200 $\mu\text{g/ml}$.

Above results show that electron withdrawing group enhances the activity of the parent moiety remarkably against *M tuberculosis*.

In this series total nine compounds have been screened for *in vivo* anthelmintic activity against *Hymenolepis nana* in mice.

The percentage efficacy of the compounds has been shown in the Table 13. compound no. 1 and 2 are having percentage efficacy greater than 75 % for double dose treatment indicating that the compounds are active. Both these compounds have the chlorine and fluorine substituents in position 5 and 6 of benzothiazole moiety and fluorine substituted in *o*- and *m*- position in the benzamido linkage . This indicates that the presence of fluorine substitution in benzothiazole moiety enhances the anthelmintic activity as compared to their chlorine substituted analogues. Since rest of the compounds have shown moderate activity.

Part IV : **2- arylidine hydrazino 4- substituted aryl thiazoles.**

In this series total eleven compounds have been synthesized and screened for their *in vitro* antitubercular, antifungal and antibacterial activity and the screening results exhibit the minimum inhibitory concentration (MIC) against Gram positive bacteria in the range of 100-200 µg/ml viz. (compound nos. 1, 6, 9 and 11 of Table no. 14). The antibacterial activity is not much encouraging.

Similar results were observed in the antifungal screening. Seven compounds have shown antifungal activity ranging from 100-200 µg/ml. Compound no. 2, 3, 7 and 11 of Table no. 14 have shown activity at 100 µg/ml against both the species *T. mentagrophytes* and *T. rubrum* Compound no. 11 is the most active compound which has shown activity against *S typhi*, *S aureus*, *T mentagrophytes*, *T rubrum* *C albicans* and *H₃₇Rv* strain of *mycobacterium tuberculosis* where the trifluoromethyl group is present in the aliphatic linkage.

Antitubercular activity in this series is appeared to be governed by the trifluoromethyl group which is present in the phenyl ring and plays a vital role in the antitubercular activity.

In general the activity exhibited by these compounds against bacterial, fungal and tubercular micro-organisms is not much significant.

Part V : 3/4 [(Substituted phenyl)1-methyl-ene] amino 1,2,4-triazoles.

3-[(Substituted phenyl)1-methyl-ene] amino 1,2,4-triazoles

The compounds synthesized in this series too have proven inactive against Gram positive bacteria taken for testing.

The antitubercular testing results once again reveal a distinct preference for presence of fluoro substituent at the *o*-position of the phenyl ring (Table no. 15 compound no. 2) rest of the compounds have not shown any antitubercular activity.

Similar results were observed when they were tested for antifungal activity for all the species. Only compound no 5 [Table no. 15] has shown activity against *T. rubrum* at 100 µg/ml.

In general it can be inferred from the biological results that the compounds do not possess any significant biological activity.

4-[(Substituted phenyl) 1- methyl-ene] amino 1,2,4- triazole.

After studying the effect of azomethine linkage at 3-position of triazole it was thought that activity may enhance if azomethine linkage is substituted at 4- position of triazole.

In this series total of eight compounds were synthesized and screened against *S. aureus*, *S. typhi*. Only compound no. 4 of Table no. 16 has shown activity against *S. typhi* at 100 µg/ml and *S. aureus* at 200 µg/ml. Rest of the compounds have not shown any antibacterial activity.

In all eight compounds of this series have been screened against *C. albicans*, *T. rubrum* and *T. mentagrophytes* for *in vitro* antifungal activity. Only compound no. 3, 5 and 6 of Table no. 16 have shown MIC at 100 µg/ml for *T. mentagrophytes* and *T. rubrum* rest of the compounds have not demonstrated any activity.

These compounds were found to be inactive when screened for antitubercular activity.

Part VI : 4(p-Chlorophenoxy)3- chloro phenyl substituted phenyl thiocarbanilide

The compounds in this series exhibit a very low level of antifungal activity when screened against various species of fungi viz., *T. mentagrophytes*, *T. rubrum* and *C. albicans*. Total of nine compounds were synthesized and screened for antifungal activity. compound nos. 3, 4, 5, 6 and 7 of Table no. 17 have shown antifungal activity ranging from 50-200 µg/ml.

Compound no. 4 [Table no. 17] is the most active compound against *T.mentagrophytes* and *T. rubrum* which shows the activity at 50 µg/ml and 200 µg/ml against *C albicans* where the aliphatic linkage is present at the one nitrogen of the thiourea.

The compounds when screened for antitubercular activity have shown moderate activity. Table no. 17 Compound nos. 3, 4, 5, 6 and 7 have shown activity ranging from 100-200 µg/ml against *H₃₇Rv* strain of *mycobacterium tuberculosis*.

The compounds have once again exhibited very marginal activity.

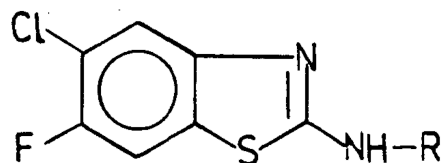
While investigating the *in vitro* antibacterial activity of the compounds it was observed that the compounds have shown meagre antibacterial activity against *S. aureus* and *S. typhi* . Table no. 17 compound nos. 3, 4, 5, 6 and 7 have shown activity ranging from 50-200 µg/ml against both the organisms

It can be inferred that the antibacterial activity of these compounds is favoured by presence of the chlorine substituents i.e. Table no. 17 compound nos. 3 and 6 have shown activity ranging from 50-100 µg/ml as compared to the activity of compound nos. 4, 5, and 7 (Table no. 17) which have shown activity ranging from 100-200 µg/ml and contain substituents viz. Allyl, *p*-ethoxy phenyl and 2,4 difluoro phenyl

Thus it can be said that though the activity is marginal it is favoured by presence of chlorine substituents on the phenyl ring.

TABLE 11

5,6-DISUBSTITUTED 2-(SUBSTITUTED ARYL/ALKYL) AMINO BENZOTHAZOLES

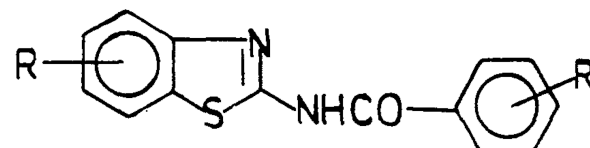


SR. NO.	R	ANTIBACTERIAL		ANTIFUNGAL		ANTITUBERCULAR	
		<i>S. typhi</i>	<i>S. aureus</i>	<i>T. mentagrophytes</i>	<i>T. rubrum</i>	<i>C. albicans</i>	H37Rv
1.	p-Cl-C ₆ H ₄	-	-	-	-	-	-
2.	p-OC ₂ H ₅ -C ₆ H ₄	-	-	-	-	-	-
3.	Allyl	25	50	50	50	-	-
4.	n-Butyl	100	100	-	200	20	-
5.	3,5-DiCl ₂ ,4-OH-C ₆ H ₂	100	100	50	100	-	-
6.	2-CN, 4,5-DiOCH ₃ -C ₆ H ₂	50	25	200	200	200	-
7.	3-Cl,4-F-C ₆ H ₃	-	-	-	-	-	-
8.	3,4-DiCl ₂ -C ₆ H ₃	-	-	50	50	200	-

- = Inactive at 200 ug/ml

TABLE 12

5,6-DISUBSTITUTED 2-(SUBSTITUTED PHENYL CARBOXAMIDO) BENZOTHAZOLES

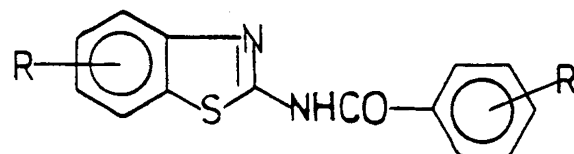


SR. NO.	R	R'	ANTIBACTERIAL		ANTIFUNGAL		ANTITUBERCULAR	
			<i>S. typhi</i>	<i>S. aureus</i>	<i>T. mentagrophytes</i>	<i>T. rubrum</i>	<i>C. albicans</i>	H ₃₇ Rv
1.	5-Cl, 6-F	H	-	-	-	-	-	-
2.	5-Cl, 6-F	2-F	-	-	-	-	-	-
3.	5,6-Cl ₂	2-F	-	-	-	-	-	-
4.	5-Cl, 6-F	3-F	-	-	-	-	-	-
5.	5,6-Cl ₂	3-F	-	-	100	100	100	50
6.	5-Cl, 5-F	4-F	-	-	100	100	200	-
7.	5,6-Cl ₂	4-F	-	-	-	-	-	-
8.	5-Cl, 6-F	2,6-F ₂	-	-	100	-	200	-
9.	5,6-Cl ₂	2,6-F ₂	-	-	100	-	-	-
10.	5-Cl, 6-F	2-CF ₃	-	-	100	-	-	50
11.	5,6-Cl ₂	2-CF ₃	100	100	100	100	100	-
12.	5-Cl, 6-F	3-CF ₃	-	-	100	-	-	-
13.	5,6-Cl ₂	3-CF ₃	100	100	100	100	-	50

- = Inactive at 200 ug/ml

TABLE 13

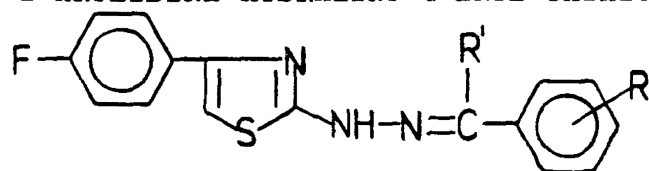
5,6-DISUBSTITUTED 2-(SUBSTITUTED PHENYL CARBOXAMIDO) BENZOTHAZOLES



SR. No.	R	R'	SINGLE DOSE 100 mg		DOUBLE DOSE 50 mg	
			Percentage Efficacy	Drug Response	Percentage Efficacy	Drug Response
1.	5-Cl, 6-F	2-F	69.70	40	77.27	60
2.	5-Cl, 6-F	3-F	73.74	20	75.76	60
3.	5,6-DiCl	3-F	51.52	-	67.17	20
4.	5-Cl, 6-F	4-F	48.48	-	56.56	20
5.	5,6-DiCl	4-F	36.36	20	65.15	40
6.	5-Cl, 6-F	2,6-DiF	28.28	-	52.02	20
7.	5,6-DiCl	2,6-DiF	47.98	-	55.05	20
8.	5-Cl, 6-F	3-CF ₃	17.67	-	45.45	-
9.	5,6-DiCl	3-CF ₃	Toxic	Toxic	Toxic	Toxic

TABLE 14

2-ARYLIDINE HYDRAZINO 4-ARYL THIAZOLES

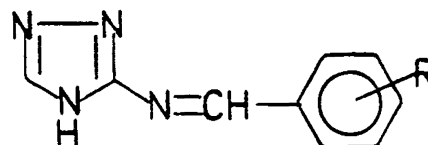


SR. NO.	R	R'	ANTIBACTERIAL		ANTIFUNGAL		ANTITUBERCULAR	
			S. typhi	S. aureus	T. mentagrophytes	T. rubrum	C. albicans	H37Rv
1.	2-F	H	100	200	200	200	-	-
2.	3-F	H	-	-	100	100	-	-
3.	4-F	H	-	-	100	100	-	-
4.	4-CF ₃	H	-	-	-	-	-	-
5.	2-CF ₃	H	-	-	200	200	-	50
6.	3-CF ₃	H	100	200	-	-	-	50
7.	2-F	CH ₃	-	-	100	100	-	200
8.	3-F	CH ₃	-	-	-	-	-	-
9.	4-F	CH ₃	200	100	200	200	-	50
10.	3-F	CH ₃	-	-	-	-	-	-
11.	H	CF ₃	200	200	100	100	100	100

- = Inactive at 200 ug/ml

TABLE 15

3-[(SUBSTITUTED) PHENYL] 1-METHYL-ENE] AMINO 1,2,4-TRIAZOLES

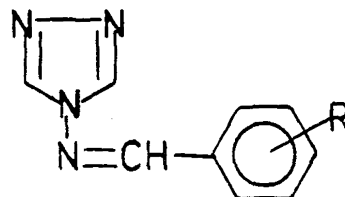


SR. NO.	R	ANTIBACTERIAL			ANTIFUNGAL		ANTITUBERCULAR
		<i>S. typhi</i>	<i>S. aureus</i>	<i>T. mentagrophytes</i>	<i>T. rubrum</i>	<i>C. albicans</i>	H ₃₇ Rv
1.	4-F	-	-	-	-	-	-
2.	2-F	-	-	-	-	-	-
3.	3-F	-	-	100	100	-	-
4.	2-CF ₃	100	200	-	-	-	-
5.	3-CF ₃	-	-	100	100	-	-
6.	4-CF ₃	-	-	100	100	-	-
7.	2-Cl, 6-F	-	-	-	-	-	-
8.	2-F, 4-CF ₃	-	-	-	-	-	-

- = Inactive at 200 ug/ml

TABLE 16

4-[(SUBSTITUTED) PHENYL] 1-METHYL-ENE] AMINO 1,2,4-TRIAZOLES

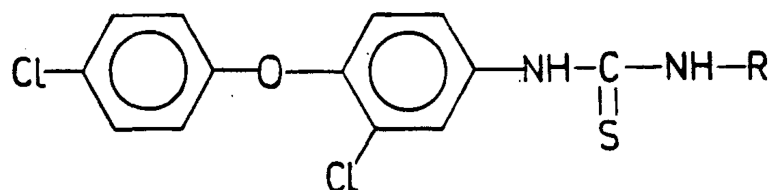


SR. NO.	R	ANTIBACTERIAL			ANTIFUNGAL		ANTITUBERCULAR H ₃₇ Rv
		<i>S. typhi</i>	<i>S. aureus</i>	<i>T. mentagrophytes</i>	<i>T. rubrum</i>	<i>C. albicans</i>	
1.	4-F	-	-	-	-	-	-
2.	2-F	-	-	-	-	-	200
3.	3-F	-	200	-	-	-	-
4.	2-CF ₃	-	-	-	-	-	-
5.	3-CF ₃	-	200	-	100	-	-
6.	4-CF ₃	-	-	-	-	-	-
7.	2-Cl, 6-F	-	-	-	-	-	-
8.	2-F, 4-CF ₃	-	-	-	-	-	-

- = Inactive at 200 ug/ml

TABLE 17

4(p-CHLOROPHENOXY)3-CHLOROPHENYL, SUBSTITUTED PHENYL THIOCARBANILIDES



SR. NO.	R	ANTIBACTERIAL		ANTIFUNGAL		ANTITUBERCULAR	
		S. typhi	S. aureus	T. mentagrophytes	T. rubrum	C. albicans	H ₃₇ Rv
1.	3-Cl, 4-F-C ₆ H ₄	-	-	-	-	-	-
2.	3-Cl-C ₆ H ₃ -O-C ₆ H ₄ -3-Cl	-	-	-	-	-	-
3.	3,4-Cl ₂	100	200	100	100	200	200
4.	C ₄ H ₉	200	200	50	50	200	100
5.	OC ₂ H ₅ -C ₆ H ₄	200	-	200	200	-	100
6.	p-Cl-C ₆ H ₄	50	200	200	200	-	200
7.	2,4-F-C ₆ H ₃	200	-	200	200	-	200
8.	2-F-C ₆ H ₃ -O-C ₆ H ₃ -2-Cl,4-CF ₃	-	-	-	-	-	-
9.	3-CF ₃ ,4-Cl-C ₆ H ₃	-	-	-	-	-	-

- = Inactive at 200 ug/ml

CONCLUSION

CONCLUSION

The present investigation was focused on the synthesis of novel organic compounds of possible therapeutic value. To evaluate their efficacy, they were screened for their *in vitro* antitubercular, antifungal and antibacterial activity and also *in vivo* anthelmintic activity.

In **Part II** the synthesis of 5,6- disubstituted -2-(alkyl/substituted aryl) amino benzothiazoles has been described. The anti-microbial activity of the series (Table no.11) reveals following points.

- 1) The presence of fluorine substituent in aryl amino side chain and in the benzothiazole moiety has shown unexpected meagerness in imparting anti microbial property to benzothiazole nucleus.
- 2) It is also observed that multisubstituted arylamino linkage having chlorine, hydroxy, methoxy, and nitrile, substituent impart antifungal and antibacterial properties to the compound.
- 3) All the compounds are inactive in antitubercular screening.

In **Part III** the syntheses of 5,6 disubstituted 2-(substituted phenyl carboxamido) benzothiazoles has been described. From the antimicrobial screening results (Table no 12) following observations are made,

- 1) All compounds are almost in active against *S. typhi* and *S. aureus*.
- 2) The antifungal activity is imparted to some compounds as an effect of disubstitution of Fluorine in phenyl carboxamido linkage and also the presence of trifluoromethyl substituent in phenyl carboxamido linkage is responsible for the antitubercular activity.

- 3) The anthelmintic screening gives encouraging results (Table no. 13). The presence of fluorine in the phenyl carboxamido side chain and also in the benzothiazole moiety imparts good anthelmintic activity to compounds with percentage efficacy greater than 75 % and drug response of 60%.

Part IV describes the synthesis of 2-arylidine hydrazino 4-substituted aryl thiazoles. The antimicrobial activity results indicate that the presence of the trifluoro methyl group in the arylidine ring and also in the hydrazino side chain is contributing more to the activity imparted to the compounds as compared to the fluorine substituted analogues.

Part V describes the synthesis of 3/4[(substituted phenyl)-1-methyl-ene] amino triazole. The compound have not shown any encouraging activity in antimicrobial screening despite the presence of triazole nucleus and fluorine substituted aryl side chain.

In **Part VI** the synthesis of 4(*p*-chloro phenoxy)3-chlorophenyl substituted phenyl thiocarbanilides is described. The compounds in this series exhibit very low level of antimicrobial activity. It is observed that the presence of the aliphatic substitution in one of the nitrogen of thiourea illicit better antimicrobial activity.

Though it may be concluded that the present investigation is not successful in rendering any new organic compound more active than the existing drugs, in the class of infections for which these compounds were screened. It may be worth while to pursue further investigations with related compounds bearing in mind certain trends observed in the present investigation as a part of the efforts to discover novel and potent drugs.

REFERENCES

1. Burger A (1990) Preface in Hansch C, Sammes P G and Tayler J B(EDS)
Comprehensive Medicinal Chemistry Vol I p 1 Pergamon Press Oxford.
- 2a. Stoll N, *J Parasitol.*, **33** (1947) 1.
- 2b. Schmidt G.D. , Roberts L.S. **Foundations Of Parasitology** (1989) 4th Edn. Times
mirror/mosby College publishing.
3. Wright W H, Schaffer J M, *J Parasitol.*, **16** (1929) 107.
4. Wright W H, Schaffer J M , *J Parasitol.*, **18** (1931) 44.
5. Lomidze N L, *Tropicheskoi Meditsiny Tbilisi.*, **1** (12) (1970) 35; Cited from **Prog in
Drug Res.**, **26** (1982) 13.
6. Brown H D, Matzuk A R, Ilves I R, Paterson L H, Harris S A, Sarett L H, Egerton J R,
Yakstis J J, Campbell W C, Cuckler A C, *J Am. Chem Soc.*, **83** (1961) 1764.
7. Tocco D J, Buhs R P, Brown H D, Matzuk A R, Mertel H E, Harman R E, Trenner N
R, *J Med Chem.*, **7** (1964) 399.
8. Brugmans J P, Thienpont B C, Wijngarden I V, Vanparijs O F, Schuermans V L,
Lauwers H L, *J Am Med Assoc.*, **217** (1971) 313.
9. Seo B S, Cho S Y, Kang S Y, Chai J Y, *Korean J Parasitol.*, **15** (1977) 11; cited from
Prog in Drug Res., **26** (1982) 21.
10. Panitz E, *J Helminthol.*, **51** (1977) 23.
11. Khadse B G, Chaudhari D T, Patil A M, Kamat V R, **Bull Haffkine Inst.** **5** (1977) 56.
12. Khadse B G, Shah M H, Deliwala C V, **Bull Haffkine Inst.**, **3** (1975) 27.
13. Khadse B G, Shah M H, Deliwala C V, Bhide M B, Mahajan S S, Bhat M V, **Bull
Haffkine Inst.** , **5** (1977) 9.
14. Raeymaekers A H M, Allewijn F T N, Vandenberg J, Bemoen P J A, Van Offenwert
T T T, Janssen P A J, *J Med. Chem.*, **9** (1966) 545.
- 15a. **World Health Statistics quarterly (WHO)** **49** (2) (1996) 115.
- 15b. WHO Model Prescribing Information : **Drugs used in Mycobacterial Diseases.**,
(1991) 3.
16. Ranadive S N, Banerjee K., **ICMR Bulletin** **19** (1989) 11.
17. Mackaness G B, Smith N. **Amer. Rev. Tubercul.**, **67** (1953) 322.
18. Davidson P T, Goble M, Lester W. **Chest** **61:** (1972) 574-578. Cited from **Drugs** **43** (5)
1992 Drug treatment of Tuberculosis - 1992.

19. Kushner S, Dalalian H, Sanjurjo J L, Bach F L, Safir S R, **J.Am.Chem. Soc. 74, (1952) 3617.**
20. Kucks M A, Pects E A, Forbes M, **Am. Rev. Resp. Dis. 87 : (1963)805-806.**
21. Dogmagk G, G, **Deut. Med. Wochensehr., 61 : (1931) 250.**
22. Mietzsch F and Klarer J., **Ger Pat. 607537 (1935) Cited from Chem. Abstr. 29: 4135 (1935).**
23. Jaffe A, Chabbert Y A, Semonin O, **Antimicrobial Agents and chemotherapy 22, (1982) 942.**
24. Malouin F, Bryan L E, **Antimicrobial Agents and chemotherapy 30 (1986) 1.**
25. Chen Y L ; **J. Antibiot., 44 : (1991) 970.**
26. Mark J. Suto John M. Domagata and Paul F. Miller **Annual Reports in Medicinal Chemistry, 27: (1992) 119, Academic Press, WC, California.**
27. Barrear M, Antoine M, Beni chon J L, Deseonclosis J F, Girand P, Robin M, Wentzler S, Picault G, Desnotter J F, Rotin O, and Bouanchaud D H, **31st Interscience conference on Antimicrobial agents and chemotherapy, (1991) 369.**
28. Barlkovitz D, Corraz A, Dietoner K, Georjopapadakoa N, Keith D Mook, R. PnuessD and Wei CC, **31st Interscience conference on Antimicrobial agents and Chemotherapy, (1991) 824.**
29. Hirai K, Hissaka M, Niwat Y, Yasui T, Fukuda H, Ishizaki T, Suzur S, and Nishino K, **30th International conference on Antimicrobial agents and Chemotherapy, (1990) 385.**
30. Biskid G, Dikucht H A, Fallat V, Keith D D, Lipschitz ER, McGarry C M, McGarry D H, Rossman P and Siebelist J, **30th International Conference on antimicrobial agents and chemotherapy, (1990) 403,.**
31. Lyman C A, Walsh T J, **Drugs 44 (1992) 9.**
32. Kovacs J A, Koracs AA, Blis M, Wright W C, Gill VJ, Tuazon CV, **Ann. Intern. Med., 103 (1985) 533.**
33. Kerridge D., **Advances in Microbiological physiology 27 (1986) 1.**
34. Grunberg E., Titsworth E., Bennet M.; **Antimicrobial agents and chemotherapy 3 (1964) 566.**
35. Hazen E L, Brown R, **Science (1950) 423.**

36. Grove J F, Ismay D., Macmillan J., Mulhottan TPC, Rogers MAt, **Chem Ind.**, **11** (1951) 219.
37. Weinberg ED, **Annals of New York Academy of Sciences**, **148** (1968) 587.
38. Leavell UW Jr. **The Diagnosis and treatment of Fungal infections**, Robinson HM Ed, Thomas Springfield, **111**, (1974) 89.
39. Campbell Ah, **Experimental Chemotherapy Vol. 3** Schnitzer RJ, Hawking F. Eds, Academic Press New york (1964).
40. Brown R, **Experimental Chemotherapy Vol. 3** Schnitzer RJ, Hawking F, Eds. Academic Press New York (1964).
41. Rippon J W, **Medical Mycology Suanders, Philadelphia** (1974) 531.
42. Plempel M, Bartmann K, Buchel K H, Rogel E, **Post Grad Med. J.** **50** (1974) 11.
43. Thienpont D, Van Cj, Nveten JM, Niemegur CJE, Marsboom R, **Arzneimittel Forschung** **25**, (1975) 224.
44. Godefroi EF, Heeres J, Van Cj, **J. Med. Chem**, **12** (1969) 784.
45. Preusser Hj, Von Dw, **Trichophyton rubrum Mykosen**, **58** (1975) 453.
46. Wright GC, Bayless AV, Gray JE, **German Offen** **2,427,382** cited from **Chem. Abstr.** **82**, (1975) 171087.
47. Wright GC, Bayless AV, Gray JE, **German Offen** **2,427,377** cited from **Chem Abstr** **82** (1975) 171088 .
48. Richardson K, Cooper K, Marriott MS, Tarbit MH, Troke PF, **Review of infections Diseases** **12**, (1990) S 267.
49. Warnick DW, **J Antimicrobial and chemotherapy** , **24** (1989) 275.
50. Grabill JR, **Infections Disease Clinics of North America**, **2** (1988) 805.
51. Saag MS, Dismukes WE, **Emphasis in New Triazoles Antimicrobial agents and chemotherapy.** **32** (1988) 1.
52. Welch TJ, McCully C, Rinaldi MG, Wallace JC, Babs FM, **Antimicrobial agents and chemotherapy** **34** (1990) 1281.
53. Van CJ, Van GF, Janssen PAJ, **Revista Iberica de Micologia** **5** (1988).
54. Ryley JF, MCgregor S, Wilson RG, **Annals of New York Academy of Sciences** **544** (1988) 310.
55. Fromtling R A, **Clinical Micorbiology Reviews**, **1**(1988) 187.

56. Schaudé M, Petramyi J. Nungassner JG, Acherbauer H, Mieth H, **Revisa Iberica de Micologia** 5 (1988).
57. Gordee RS, Zechner DJ, Eillis LF, Thakker AL, Howard LL. **J Antibiotics** 37, (1984) 1054.
58. Hobbs M, Perfect JK, Durack D. **Eur J. Clin. Microbiol and Infectious Diseases** 7 (1988) 77.
59. Melchingev W, Mueller J, **Mykosen** 30, (1987) 605.
60. Chenoweth, M.B. and McCarthy ,L.P. **Pharmacol. Rev.** 15 : (1963) 673-707.
61. Singh Girish Chandara, **Indian J. Appl. Chem.**, (1968) . 31-34.
62. Mackie A. and Misra A.L., **J. Chem. Soc.**, (1954) 2577.
63. Palmer P.J., Trigg R.B. and Warrington J.V., **J. Med. Chem.**, 14 (1971) 1228.
64. Palmer P.J., Ward R.J. and Warrington J.V., **J. Med. Chem.**, 14 (1971) 1226.
65. Stig Akerfeldt **J. Med. Chem.** 13 (1970) 1012-13.
66. Palmer P.J., Trigg R.B. and Warrington J.V., **J. Med. Chem.**, 14 (1971) 248.
67. Frank C., Pennington W.D., Celmer W.M., McLamere V.V., Bergert and Sememans, I.A. **J. Am. Chem. Soc.**, 75, (1953)109.
68. Pepeff Ivance, Buchhelz Bernard Miller, Herald J., **U.S. Pat.**, 3,519,630 (July 1970)
Cited from **Chem. Abstr.** 73. 76154f (1970).
69. Mayer R.L., **Rev. Medicale France**, 3 (1941), 19 Cited from **Chem. Abstr.** 36, 51991 (1942).
70. Zarapkar S.S., (1971) **Ph.D Thesis Univ. of Bombay**.
71. Lewis Arthur and Shepard G.,. "Medicinal Chemistry", Vol. 1, 3rd Eds. Burger, Alfred, (1970) 449.
72. Freedlander B.L. and French F.A. **Proceedings of the Society for Exptl. Biol. Med.** 66, (1947) 362-65. Cited from **Chem. Abstr.** 42, 3073g (1948).
73. Logemann W., Galimbert S., Tosolini G., Decarneri I., and Coppi G.,. (Carlo Erba S.P.A. Milan), **Farmaco (Pavia)**, Ed, **Sci.**, 16, (1961) 795-816; Cited from **Chem. Abstr.** 57, 7242f (1962).
74. Mackie Ernst Juker, Buu-Hoi N.P., Graig J.C. and Tate M.R., **Progr. Drug. Res.**, (1961) III, 97.
75. Donche Alain, Fister Alain, Arretz Emmanuel, , **Ger. Offen. Pat.** 2,133,649; (June 1972) Cited from **Chem. Abstr.** 76, 99647v (1972).

76. Panitz E, Danniels P.J.L., Losbenberg D., Mafissi V.M.M., and Waitz J.A., , **Experimentia**, 34(6), (1978) 733.
77. Khadse BG, Madhuben R. Patel, Lokhande SR., **Bull. Haff. Instt.**, 7(1), (1979) 11.
78. Mikulasek S, OdelerovaZ, Sutoris V, Perjessy A, Salcaniova E, **Chem. Zvesti** 32(5) (1978) 691-700. Cited from **Chem. Abstr.** 90: 186849v.
79. Singh Harbindra, Singh A.K., Sharma Satyavan, Iyer R.N. and Srivastava O.P., **J. Med. Chem.**, 20 (6) (1977) 826.
80. Lioted E.L., **Practitioner**, 181, (1961) 679.
81. Lee Richard, Martin Sach, George S., , **Brit. Pat.** 1,400, 540; (16th July 1975) Cited from **Chem. Abstr.** 83, 164014x (1975).
82. Chough Yunsung, Kim Kee Won, , **Yakak Heeji Pat**, 1971, 15(3-4) (1971) 83-6 (Korean); Cited from **Chem. Abstr.** 80 59890v (1974).
83. Denham D.A., Surville R.S., Rosemary Roger and Nelson, , **Trop Die. Bull.**, 76(9), (Sept. 1979) **Abstr. No.** 2295.
84. Locova M, Guozdjakova A, Chovancova J, Volna F, **Chem Zvesti** 38(5) (1984) 693-8. Cited from **Chem. Abstr.** 102: 113358r.
85. Mantripragada Narayenu, Sambaiah Thote, **Bull Chem Soc. Japan** (1994) 67(8) 2326-8 (Eng) Cited from **Chem . Abstr.** 122 : 31391v.
86. Carp E., Toma A., "Al I Cuza" Iasi Sect., 11 (1965) 67; Cited from **Chem. Abstr.**, 63 : 14843 (1965).
87. Gupta S.P., Rani S., **J. Ind. Chem. Soc.** 55 (1978) 730.
88. Malvankar T.S., Sabnis S.S., Patel M.R., Deliwala C.V., **Bull. Haff. Inst.** 2 (1974) 28.
89. Mane R.A., Ingle D.B., **Ind. J. Chem.**, 22B (1983) 81.
90. Singh S.K., Naim S.S., Sharma S., **Ind. J. Chem.**, 28B (1989) 786.
91. Zhou, Xunjun J. **Chin Pharm. Sci.** 1993 2(2) 151-5 (Eng) Cited from **Chem. Abstr.** 121 : 9212v.
92. Likhate M.A., Fernandes P.S., **J. Indian Counc. Chem.** 1993 9 (1) 29-32 (Eng) Cited from **Chem. Abstr.** 121 : 83148v.
93. Shah, R.G. , Bhavsar, S.B. , Parikh, A.R. **J. Sci. Islamic Rep. Iran** 2(3-4) (1991) 107-10 (Eng) Cited from **Chem. Abstr.** 121: 108671a.
94. Popp F.D., **J. Med. Chem.**, 7, (1964), 210.

95. Popp F.D., *J. Org. Chem.*, **26**, (1961), 1566.
96. Patil A.M., Chaudhari D.T., Patel M.R. and Sabnis S.S., *Bull. Haff. Instt.* **5**(3), (1977) 107.
97. Patil A.M., Chaudhari D.T., Patel M.R. and Sabnis S.S., *Bull. Haff. Instt.* **6**(1), (1978) 36.
98. Lehmann J., *Lancet*, **1**, (1946), 14-15.
99. Lewis A. and Shepherd 'Medicinal Chemistry' **1**, (1970) 423.
100. Rich A.R. and Follis R.H. *Bull. Johns. Hopkins. Hosp.* **62**, (1938) 177.
101. Michel Conte, Robert Gulielmett and Jacques Metrger. *Bull. Soc. Chim. Fr.*, (8) (1967) 2834-41 (Fr.) Cited from *Chem. Abstr.* **68** : 78190k (1968).
102. Takahiro Yabuuch, Masakatu Hisaki and Ryuichi Kimura *Chem. Pharmaceuti. Bull.*, **23**(3), (1975). 659-663.
103. Fioravanti R, Biava V, Porretta GC, Landolfi C; *Eur J. Med. Chem*, **30** (1995) 123-132.
104. Straukas J, Astrauskas V, *Biologia* **1994** (1) 21-5 (Russ). Cited from *Chem. Abstr.* **122** : 31426k.
105. Mayer R.L., Eisman P.C., and Knopka E. A. *Proc. Soc. Exp. Biol. N.Y.* **82** (1953) 769.
106. Huebner C.F., Marsh J.L. Mizzoni. R.M., *J. Am. Chem. Soc.*, **75** (1953) 2274.
107. Bui-Hoi N.P., Xuong N.D., and Suo V.T., *J. Chem. Soc.*, (1958) 2815.
108. Davy T F. *Leprosy Rev.* **29** (1958) 25.
109. Madan A G. *Belg. Pat.* **613,154** (1962) cited from *Chem. Abstr.* **58**. 474f.
110. Mayer R.L. Konopkaa E A. Eisman P C. Parker F and Robbins S L. *Am. Rev. Tuberc.* **70** (1954) 130.
111. Khonkarov, Kh.Zh ; Sevbo, D. P. ; Mikhailitsyn, F.S. ; Veretennikova, N.L.; Lykova, T.I; Lebedeva, M.N; Lychko, N.D; *Med. Parazit. Parazit. Bolezni* **1994** (1) 52-4 (Russ) Cited from *Chem. Abstr.* **121**: 83009a.
112. Kaufmann and Kogler *Ber.* **58**, (1925). 1553.
113. Fichter and Schonmann *Helv. Chim. Acta.*, **19** (1936) 1411.
114. Spangler and Muller N.. *U.S. Pat.*, **1,687,596**. (1929) Cited through *Chem. Abstr.* **23** **154** (1929).
115. Likhosherstov and Petrov, J. *Gen. Chem. USSR.* **3** (1933) 759. Cited through *Chem. Abstr.* **28**, (1934) 2690.

116. Likhosherstov and Petrov, J. Gen. Chem. USSR. 3 (1933) 183. Cited through Chem. Abstr. 28, 1677 (1934).
117. Likhosherstov and Aldoshin J. Gen. Chem. USSR. 5 (1935), 981.
Cited through Chem. Abstr. 30, 1033 (1936).
118. Kaufmann Ber. 62, (1929). 390.
119. The Grasselli Chemical Co.. Brit. Pat., 431,064 (1st July 1935) Cited through Chem. Abstr. 29, 8220 (1935).
120. Fialkov and Kleiner J. Gen.Chem. USSR 11, (1941) 671. Cited through Chem. Abstr. 35. 7307 (1941).
121. Soderback, Ann. 419, (1919) 217.
122. Kaufmann and Oehring Ber. 59, (1926). 187.
123. Kaufmann and Hansen Schmidt Arch. Pharm. 263, (1923). 692.
124. Bhatnagar, Kapur and Khosla J. Indian Chem. Soc. 17, (1940). 529.
125. Zaboev, S.A. and Kudryavitzev, N.A. J. Gen. Chem. USSR, 5, (1935) 1607; Cited through Chem. Abstr. 30: 21824 (1936).
126. Kaufmann and Weber. Arch. Pharm. 267, (1929) 192.
127. Kaufmann. Angew. Chem. 54, (1941) 168.
128. Kaufmann and Kuchler. Ber. 67, (1934) 944.
129. Ochiai and Katada J. Pharm. Soc. Japan, (1940) 60, 211, 543.
130. Boggust and Cocker. J. Chem. Soc. (1949) 355.
131. Huger Schoff. Ber. 34, (1901) 3130.
132. Huger Schoff. Ber. 36, (1903) 3121.
133. Hunter. J Chem. Soc. (1926) 2951.
134. Hunter and Soyka J Chem Soc. (1926) 2958.
135. Hunter and Parken J Indian Chem Soc. 9, (1932) 357.
136. Farooq, Hunter and Jaffery J Indian Chem Soc. 10, (1933) 189.
137. Dyson J Indian Chem. Soc. 8 (1931) 147.
138. Hunter and Jones J Chem Soc. (1930) 2190.
139. Passing. J Prakt. Chem. 153 (2), (1939) 1.
140. Cressman Org. Syntheses, 27, (1947) 53.
141. Konig, Kleist, and Gotze. Ber, 64, (1931) 1664.

142. Edward, M, Van Duzec U S Pat 2,179,987, (Nov. 14, 1940), Cited through Chem. Abstr. 34, 16901.
143. Hunter. J. Chem. Soc. (1925) 127, 2023.
144. Hoffmann. Ber. 12, (1879) 1126.
145. Hoffmann Ber. 13, (1880). 9.
146. Dyson, Hunter and Morris J. Chem. Soc. (1927) 1186.
147. Kurzer Frederick and Sanderson, P M J. Chem. Soc. (1962) 230.
148. Anders, Bertran and Engelbert, Kuchie Belgin Pat. 632, 576. (1963) Cited through Chem. Abstr. 61. 8321f (1964).
149. Mohsen, O A, Habib, M E, Aboulwata, N S and Omaina, M, Syntheses, 12, (1977) 864.
150. Bogert, M T and Dee-Snell, Foster J Am. Chem. Soc. 46, (1924) 1308.
151. Bogert, M T and Stull, Arthur J Am. Chem. Soc. 48, (1926) 248.
152. Bogert Marston Taylor and Smidt, Loenard J Am. Chem. Soc. 49, (1927) 1315, 3135.
153. Bogert, M T and Husted, H, J Am. Chem. Soc. 54, (1932) 3394.
154. Hauser Helv. Chim. Acta., 11 (1928). 198.
155. Lankelma, H P and Knauf, A E., J Am. Chem. Soc. 53, (1931) 309, 2654.
156. Lankelma, H P and Vopicka E., J Am. Chem. Soc. 58, (1936) 609.
157. Kiprianov, Suitnik and Grigopveva J. Gen. Chem. USSR 6 (1936) 232-5, Cited through Chem. Abstr. 30, 48596 (1936).
158. Patitcolas, P, Sureau, J, Frenkiel, and Goupil R Bull. Soc. Chim. France, (1949). 103-12.
159. Bogert and Naiman J. Am. Chem. Soc. 57, (1935) 1529.
160. Blomquist, A T and Diuguid, L T J Org Chem 12 (1947) 718.
161. Elderfield, R C and Short, F W J Org Chem 17, (1952) 758.
162. Zubarovskii J Gen Chem USSR 17, (1947) 613.
163. Bogert Rec. Trav. Chim, 54, (1935) 917.
164. Bogert, M T and Fox, Herbert, H J Am Chem. Soc. 61, (1939) 2013.
165. Dyson, G M and George H J , J. Chem. Soc. 125, (1924) 1702.
166. Dyson, G M, George H J and Hunter R F, J. Chem. Soc. (1927) 436.
167. Mekee, H L and Bost, R W J. Am. Chem. Soc. 68, (1946) 2506.
168. Siefken, W Ann. Chem., 562, (1947) 75.

169. Dyson, G M, and Hunter R F, *J. Soc. Chem. Ind.* **45** (1926) 81.
- 170 "Methoden der Organischen Chemie" (Houben-Weyl) (1955) IX, Thieme Verlag, Stuttgart, pp 875-877.
171. Beaver, D J, Roman, D O and Stoffel, L J *J. Am. Chem. Soc.*, **79** (1957) 1236.
172. Schutz, O E and Gauri, K K *Arch. Pharm.* **295** (1962) 146.
173. Brintziner, H, Pfannstiel, K and Koddenbusch, H *Chem. Ber.* **82** (1949) 393.
174. Friis, D *Acta Chem Scand*, **19** (1965). 766.
175. Sayigh, A A R, Ulrich, H and Potta, J S *J Org. Chem.* **30** (1965) 2405.
176. Jale, A L *J Am. Chem. Soc.* **75** (1953) 675.
177. Saccardi, P *Gazz Chim Ital.*, **75** (1945) 87.
178. Losanitsch S M *Chem Ber* **24** (1891) 3021.
179. Hoffmann, A. W. *Chem Ber* **8** (1875) 107.
180. Loose G and Weddige H *Liebigs Ann Chem* **636** (1960) 144.
181. Hoffmann, A. W: *Ann Chem* **373** (1909)201.
182. Anschutz, R *Ann Chem* **359** (1908) 202.
183. Dains, F B, Brenster, R C and Olander, C P *.Org Syntheses Coll., I* (1932) 447, John Wiley, New York.
184. Goldschmidt, S and Martin, K *Patent Ger.* **700, 436.** (1936) Houben-Weyl, Vol. IX, George Thieme Verlag, Stuttgart, (1955) p 869.
185. Hartke K. *Arch. Pharm.* **299** (1966) 174.
186. Andreasch, R. *Monatsh* **27** (1906) 1221.
187. Andreasch, R. *Monatsh* **31** (1906) 788.
188. Kaluza, L *Monatsh*, **30** (1909)717.
189. Nagele, M *Montash*, **33** (1912) 948.
190. Neil, G J O and Pattison, F L M *J. Am. Chem. Soc.* **79**, (1957) 1956.
191. Schering, A G *Brit Pat.* 892,790. (1962), Mar. 28 Cited through *Chem. Abstr.* **57** : 4552d (1962).
192. Hodgkins, J E and Ettlinger, M G *J Org Chem* **21** (1956) 404.
193. Hodgkins J E, Reeves W P and Lui Y T *J Am Chem Soc.* **83** (1961) 2532.
194. Hodgkins, J E and Reeves, W P *J Org Chem* **29** (1964)3098.
195. Schimdt, E, Zaller, F, Moosmuler, F and Kammerl, E *Ann. Chem.* **585**, 230,233. (1954)

196. Schmidt E, Ross D, Kittle J, Von Dusel, H H and Wamster K **Ann Chem** 636, (1960) 144.
197. Johar, G S, Agarwal, U and Rao P B **Ind. J Chem** 8 (1970) 759.
198. Jochims, J C and Seeliger, A **Angew. Chem.** 79, (1967) 151.
199. Jochims, J C **Chem. Ber.** 101, (1968)1746.
200. Mentz, W and Weith W. **Z. Chem.** (1869) 589.
201. Leconte, J N and Chence, L H **J Am. Chem. Soc.** 71, (1949) 2240.
202. Volinkin N I, Obshch, Zh. Khim. 37. (1957), 483.
203. Lieberman, C I and Natanson, S. **Chem. Ber.** 13, (1880) 1576.
204. Bly, R S, perkins, G A and Lewis, W I **J. Am. Chem. Soc.** 44, (1922) 2897.
205. Hoffmann, A W **Chem. Ber.**, 15, (1888).985.
206. Baxter, J N, Cymerman-Craig, J, Moyle, M and White, R A
Chem and Ind. (1954).785.
207. Baxter, J N, Cymerman-Craig, J, Moyle, M and White, R A.
J. Chem Soc. (1954) 659.
208. Rotmistrov, M M, Kulik, G V and Vasilevska, I O. **Farmatsevt. Zh. (kiev)**, 17
No.3, (1962) 45-7. Cited through **Chem. Abstr.** 58, 10642d (1963).
209. Chough, Yun, Sung, Kim, Keewon **Yakhak Hoeji**, 15 (3-4) (1971) 83-6 (Korean);
Cited through **Chem. Abstr.** 80, 59890v (1974).
210. Auwers and Risse. **Ber.** 64, (1931) 2220.
211. Hentschel **Ber.** 17, (1884) 1285.
212. Hantzsch A R and Weber H J, **Ber.** 20 : (1887) 3118.
213. Gagui, F; Suci, T; Henegar, O and Gyorifi, Z; **Arch. Pharm. Weinheim**, 303;
(1970) 102, Cited from **Chem. Abstr.** 72; 129446 (1970).
214. Bissin, P; Tetu, O and Selim, M; **Chim Ther.**, 4; (1969), 220; Cited from
Chem. Abstr 71; 101762.
215. Hantzsch A R and Weber H J, **Ber.** 21 : (1888) 930.
216. Mathes R A, Gregory J T, **J. Am. Chem. Soc.** 74: (1952), 3867.
217. Cook A H, Downer J D and Heilbron I, **J. Am. Chem. Soc.** (1948), 1262.
218. Ochiai, E and Nagsawa, F; **J Pharm. Soc. Japan**, 59; (1939), 43 .
219. Maria, T C, Onnis, V., **Synthesis** (1993) 199.
220. Dahiya R and Pujari, H K; **Ind. J. Chem.**, 25B : (1986), 966.

221. Durgayan, A A; Titanyam, S A and Kazaryan, R; **Izvest Akad Nauk Armyam SSR Khim Nauki** 14; 165 (1961) Cited from **Chem. Abstr.** 56; 4741.
222. **U S Pat.** 2,652,396.
223. Khanna M S; Chandra, P; Garg and Ram P Kapoor; **Ind J Chem**, 32B: (1993), 364.
224. V S Bhagwat and K S Nargund, **J Indian Chem Soc.**, 45, (1968), 270 .
Cited from **Chem. Abstr.** 69, 106602.
225. S. Bilinski and L Bielak, **Ann Univ M Curie Skladowska Swit.** 21 (1966), 263.
226. J L B Smith and R H Sapiro **Trans Roy Soc. S Africa** 18, (1929), 229.
Cited from **Chem. Abstr.** 24 : 2130.
227. G Fodor and G. Wilhelm, **Acta Chim Asad Sci Hung**, 2; (1952), 189.
Cited from **Chem. Abstr.** 48: 3346.
228. H. Beyer, H Hohem and W Laessig **Chem. Ber.** 85, (1952), 1122 . Cited from **Chem. Abstr.** 47; 11183.
229. H Beyer, W Laessig and G Rulhig, **Chem. Ber.** 86, (1953), 764.
Cited from **Chem. Abstr.** 48; 10736.
230. H Beyer, W Laessig, E Bulka, and D Behrens, **Chem. Ber.** 87, (1954) , 1392.
Cited from **Chem. Abstr.** 49 15868.
231. H Beyer, C Kroger and M Zander **Chem. Ber.** 88, (1955), 1283.
Cited from **Chem. Abstr.** 50, 6433.
232. I Smiti and M Coman, **Ann. Chim, France**, 7, (1972), 33.
Cited from **Chem. Abstr.** 77, 75156.
233. M S Solanki and J P Trivedi **J Indian Chem Soc.** 49, (1972) 37.
234. A Gursoy, **Istanbul Univ. Beezaulik Fak Meemuasi** 10, 87 (1974);
Cited from **Chem . Abstr.** 82 : 12512.
235. I Smiti and M Coman, **Bull. Soc. Chim, France**, 9, (1969), 3276. Cited from **Chem. Abstr.** 72, 21635.
236. Patil, A M, Chaudhari, D T, Patel M R and Sabnis, S S. **Bull. Haff. Instt.** 5 (3), (1977) 107.
237. Patil, A M, Chaudhari, D T, Patel M R and Sabnis, S S **Bull. Haff. Instt.** 6 (1), (1978).36.
238. Schiff, H **Arm. Chem.** 131, (1864), 118.
239. Tipson, Stuart, R and Clapp, M A **J Org. Chem.** 11,(1946), 292..

240. Hayes, K, Gever, G and Orchutt, J *J Am. Chem. Soc.* **72**, (1950), 1205.
241. Giovambattista, N and Rabassa, R *Hev. Assoc. Bioquim, Argentina*, **18**, (1953)
220-2. Cited through *Chem. Abstr.* **49**, (1955) 205f.
242. R Zweidler and E Keller, *US Pat.* **2,784,184** (1957). Cited through
Chem Abstr. **51**: 13934h
243. M. Niese and D. Delfis *US Pat.* **2, 875, 209** (1959), Cited through
Chem. Abstr. **53**: 17151e.
244. T Oshima, S Hata, H Takamatsu, M Okuda and M Yokota, *Jap. Patent*, **72, 08,**
820 (1972) Cited through *Chem. Abstr.* **76** : 153796h.
245. K. Thomas, *British Patent* **1,053,085** (1966) Cited through
Chem. Abstr. **66** : 46427k.
246. L I Bagal, M S Pevzner, V A Lopyrev and E A Yurchak *USSR patent* **176,913** (1965)
Cited through *Chem. Abstr.* **64** : 12685d.
247. S G Boots and C C Onen, *J. Heterocyclic Chem.* **4**, (1967), 272 . Cited through
Chem. Abstr. 32651n.
248. V Grinstein and G I Chipin *Zh. Obshch Khim* **31** 886 (1961) Cited through
Chem. Abstr. **55** : 23507a.
249. L I Bagal, M S Pevzner and V A Lopurev *Khim Geterotsiki Soedin Sb 1:*
Azotsoderzhashchie Geterotskly **184** (1967). Cited through
Chem. Abstr. **70** : 77877u
250. V C Chambus, *J Am. Chem. Soc.* **82**, (1960) , 605. Cited through
Chem. Abstr. **54**: 9937a.
251. K L Shepardd, J W Mason, O W Woltersdorf, J H Jones, H. James and E J
Cragoel, *J Med. Chem.* **12**, 280 (1969). Cited through *Chem. Abstr.* **70** : 96755u
252. F Russo, M Santagati and G Poppalardo, *Ann. Chim. (Rome)* **62**, (1972), 351.
Cited through *Chem. Abstr.* **77**: 126518h.
253. H G O Becker and V Eisenschmidt, *Z. Chem* **8**, 105 (1968). Cited through
Chem. Abstr. **68** : 95761q.
254. H. Becker and K Wehner, *Brit. Pat.* **1,157,256** (1969) Cited through
Chem. Abstr. **71**: 81375s.
255. J L Barascut, P Viablafont and J Dauni, *Bull. Soc. Chim. France* (1975) 1649.
Cited through *Chem. Abstr.* **84** : 17241m.

256. H Genhlen, J Dost and J Cemak, *Justus Liebigs Ann. Chem.* **643**, (1961), 116.
Cited through Chem. Abstr. 55: 24728c.
257. R Sgarbi, *Chim. Ind (Milan)* **48**, (1966), 18. Cited through Chem. Abstr. 64: 9727d.
258. J S Dowidson, *Chem. Ind. (London)*, **11**, (1972), 464. Cited through
Chem. Abstr. 77 : 48344g.
259. C F H Allen and A Bell *Org. Synthesis* **24** (1944), 12. Cited through
Chem. Abstr. 38 : 58283.
260. Y Kato and I Hirao, *Kyushu Kogyo Daigaku Kenkyu Hokoku*, No 14 (1964), 35.
Cited through Chem Abstr. 61 : 14662g.
261. R M Herbst and J A Garrison, *J Org. Chem.* **18**, (1953), 872 . Cited through
Chem Abstr. 48: 7006c.
262. S S Navikov, V A Rudenko and V M Brusnikina, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk* 1961, 1148. Cited through Chem. Abstr. 55:27282f.
263. K Mizushima, M Saheki, H Shillna and A Hamada, *Japanese Pat.* **71 35, 056** (1971)
Cited through Chem. Abstr. 76 : P3867t.
264. K Byalkovskii-Krupin and V A Lopyrev *Matody Paluch. Khim. Reaktiv Prep* **22**,
(1970) 92 Cited through Chem. Abstr. 77: 5410h.
265. A J Boulton and A R Latritzky, *J Chem. Soc.* (1962) 2083. Cited through
Chem. Abstr. 57: 5911g.
266. F Wiloth, *Ger. Pat.* **1,135,920** (1962) Cited through Chem. Abstr. 58: 8071d.
267. M Taniyama, T Nagaoka, T Okauchi and T Takada, *Japanese Pat.* **9221** (1962) Cited
through Chem. Abstr. 59: 10065h.
268. E P Krysin, S N Levchenko, L G Andronova and M M Nakenina *USSR Pat.* **491,636**
(1975) Cited through Chem. Abstr. 84: 90156s.
269. R A Bowie, M D Gardner, D G Neilson, K M Watson, S Mahmood and V Ridd
J. Chem. Soc., Perin Trans 1, (1972), 2395. Cited through Chem Abstr. 77: 152130v.
270. P Grammaticakis, *C R Acad. Sci. Paris* **258**, (1964), 1262. Cited through
Chem. Abstr. 60:14508e.
271. H C Brown and D Pilipovich, *J Amer. Chem. Soc.* **82**, (1960), 4700 Cited through
Chem. Abstr. 55: 6474c.
272. F. Baumabach, H G Henning and G Hilgetag, *Z Chem*, **4**, (1964), 67. Cited through
Chem. Abstr. 60: 12006c.

273. R Huisgen, J Sauer and M Seidel, **Justus Liebigs Ann. Chem.** **654**, (1962), 146 Cited through Chem. Abstr. 57: 5909c.
274. F. Dous, 'Organic Compounds of Sulphur, Selenium and Tellurium' ed. D.H. Reid, The Chemical Society, London, 1973, Vol. 2 Chapter 4.
275. F. Dous, 'Organic Compounds of Sulphur, Selenium and Tellurium' ed. D.H. Reid, The Chemical Society, London, 1975, Vol. 3 Chapter 5.
276. S. Mc Kenzie in F. Dous, 'Organic Compounds of Sulphur, Selenium and Tellurium' ed. D.H. Reid, The Chemical Society, London, 1970, Vol. 1 Chapter 5.
277. G. Kempter, H L Ziegner and G Moser **Z. Chem**, **11**, (1971), 12.
278. S Sakai, Y Asai, Y Kiyohara, K Itoh and Y Ishii ,**Organometallic Chem. Synth.** **1**, (1970-1971), 45.
279. D. C. Schroeder, **Chem. Rev.**, **55**, (1955) 181.
280. Cecchetti, V. , Fravelini, A. , Fringuelli, R. , Mascellani, G. , Pagella, P. , Segre, G. , Terni, P. , **J. Med. Chem.** **30** (1987) 465-73.
281. **Dictionary Of Organic Compounds , Chapman & Hall. 6th Edn Vol. 4**
D- 0 - 05135.
282. Kihara, M. , Kashimoto, M, Kobayashi, Y. , **Tetrahedron** **48** (1) (1992) 67-78 .
283. Bernstein, J. , Yale, H. L. , Losee, K. , Holsing, J. M. , Lott, W.A. **J. Am. Chem. Soc.** **73** (1951) 906-12.
284. Sjostedt, G. , Gringas, L. **Organic Synthesis Coll. Vol. III** 95-96.
285. Allen, C.F.H. , Alan, B. **Organic Synthesis Coll. Vol. III** 96-98.
286. Mason, G.W. , Brooker, E.G. **Proc. N.Z. Weed Pest Contr. Conf. No. 21** (1968) 163-72 (Eng) Cited through C.A. 70 : 77494s.
287. Sjogren, E.B. , Rider, M.A. , Nelson, P.H. , Bingham, S. Jr. , Poulton, A.L. , Emmanuel, M.A. and Komuniecki, R. **J. Med. Chem.** **34** (1991) 3295-3301.
288. Wolfgang, R. , Schoenowsky, H. , Hoerlein, G. , Winkelmann, E. (Farbwerke Hoechst A. G.) **Ger. Offen.** **2,334,355** (Cl. C07c A 61k) !6 JAN 1973
APPL P23 34 355. 7-42, 06 JUL 1973 20 pp. Cited through C.A. 82 : 139800x .
289. Mosanto Chemicals Ltd. (by Donald, W. , David, A.L.) **Brit.** **873602**
Appl 19 DEC 1957 Cited through C.A. 56 : P2454b.
290. Galstukhova, N.B. and Shchukina, M.N. **Zhur. Obschei. Khim.** **31** (1961) 1090-2.
Cited through C.A. 55 : 24778d.

291. Heilbron, I and Bunbury, N.M. " **Dictionary Of Organic Compounds " Vol. I**
(1953) p57.
292. Heilbron, I and Bunbury, N.M. " **Dictionary Of Organic Compounds " Vol. I**
(1953) p395.
293. Reifschneider, Walter (Dow Chemical Co.) **U.S. 3,655,773 (Cl. 260 - 609; C07c)**
11 Apr 1972 15,864 02 Mar 1970. 3pp. Cited through C.A. 77 : P5171f.
294. Eugene Lieber and J. Ramchandran **Can. J. Chem. 37 (1959), 101-9 .**
295. Vogel, A.I. " **A Textbook Of Practical Organic Chemistry " (1956) p792.**
296. Kennichi, F. , Hisao, K. , Taichiro, O. , Yoshiaki, I. Hiroshi, S. **Nippon Kagaku**
Zasshi. 79 (1958) 1120-4 Cited through C.A. 54 : 5519a .
297. **Dictionary Of Organic Compounds , Chapman & Hall. 6th Edn Vol. 4**
T- 0 - 04881.
298. **Dictionary Of Organic Compounds , Chapman & Hall. 6th Edn Vol. 4**
D- 0 - 04882.
299. Rake, G. , Jambor, W.P. , Mckee, C.M. , Pansy, F. , Wiselogle, F.Y. , Donovic, R. ,
Am. Rev. Tubercul. 60 (1949) 121.
300. Koneman, E.V. , Janda, W.M. , Allen, S.D. , Sommers, H.M. , Dowell, V.R. , Winn,
W.C. , " **Color Atlas And Textbook Of Diagnostic Microbiology . " J.B.**
Lippincott Company, 3rd Edn. , (1988), 487.
301. E. Joan Stokes, **Clinical Bacteriology, 4th Edn. , (1975), 226.**
302. Agarwal, A. , Agarwal, S.K. , Bhakuni, D.S. , Gupta, S. , and Khatiyar, J.C. . **Ind.J.**
Chem. 28B(11) , (1989), 943
303. Amschler, Herman ; Krastinat, Walter. **Ger Offen 2,258,561 (Cl. C07d),**
20 JUN 1973 , Lux Appl. 64,387, 02 DEC 1971 99pp. Cited through
C.A. 79 : P78841a

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 has been run on Eastman Kodak pre-coated silica gel plates of type K 301 R and E.Merck pre-coated silica gel plates of type 60 F 254.
3. The Infrared spectra were recorded on a BOMEM MB-104 Fourier Transform Infrared Spectrometer
4. The PMR spectra were recorded on Brucker AC 80 MHz. Spectrometer and Varian 300 MHz. Spectrometer using TMS as internal reference .
5. The mass spectra have been recorded on a HEWLETT PACKARD HP G1800 A GCD spectrometer.

SYNOPSIS

SYNOPSIS

Mankind has always been afflicted by diseases and ailments and it is evident from ancient reports that he has attempted to control these afflictions from time immemorial by testing himself with herbs, berries and other substances gathered from his environment. The earliest of such reports appears on a Sumerian clay tablet from 2100 B.C. which lists a number of recipes but unfortunately without indicating their proper usage. Since then the use of natural medicine elaborated and proliferated for several thousand years in various civilizations and has been well documented in their respective records.

Sometime in the 18th century the situation in Europe was one where physicians were realizing the limitations of these natural products. With the founding of organic chemistry as a science and the realization of the restrictions of natural products, the scene was set for a systemic investigation into the active ingredients present in therapeutic herbs. This coupled with the potential of organic chemistry to synthesize hitherto unknown compounds gave birth to the field of *Medicinal Chemistry*.

Medicinal Chemistry is the study of those chemicals which have anticipated beneficial effects on disordered living systems. At its heart is chemistry, *organic chemistry*, but no medicinal chemist is merely interested in the chemical properties of the molecule under investigation. The entire logic and all the efforts towards the synthesis of any new compound are for an anticipated biological activity. But it happens most frequently that they result in its lack of activity.

Amidst the frequent, but much needed failures and seldom occurring breakthroughs the strife of medicinal chemistry continues for various reasons, more saliently for

1. Higher efficacy and lower toxicity.
2. Drug resistance of various micro-organisms.

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 with incorporation of *fluorinated* substituents on various active moieties such as *thiazoles* , *benzothiazoles* , *triazoles* , *thioureas* , *etc* and will be documented in the thesis .

The thesis will consist of the following parts...

PART 1 :- Introduction , Review of literature & Plan of Work.

PART 2 :- Synthesis of 5,6 - disubstituted 2 - (substituted alkyl / aryl) amino benzothiazoles.

PART 3 :- Synthesis of 5,6 - disubstituted 2 - (substituted phenyl carboxamido) benzothiazoles.

PART 4 :- Synthesis of 2- arylidene hydrazino 4-aryl thiazoles.

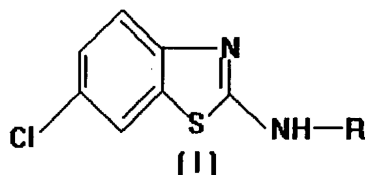
PART 5 :- Synthesis of 3/4 [(substituted phenyl) 1- methyl - ene] amino 1,2,4 triazole.

PART 6 :- Synthesis of 4(p-chlorophenoxy)3- chlorophenyl , substituted phenyl thiocarbanilide.

PART 7 :- Biological screening .

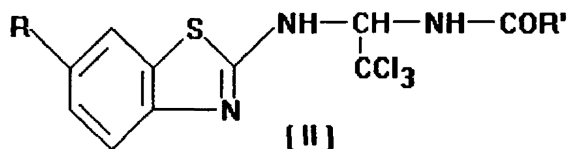
**PART 2 :- SYNTHESIS OF 5,6 - DISUBSTITUTED 2-(SUBSTITUTED -
ALKYL/ARYL) AMINO BENZOTHAZOLES.**

The 2 - substituted amino benzothiazole derivatives have been studied extensively in literature for various types of biological activities . In our laboratory it has been reported earlier ¹ that 6-chloro, 2 - substituted alkyl/aryl amino benzothiazoles (I) have promising antitubercular activity .



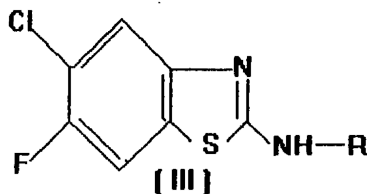
Where R = Alkyl or substituted aryl.

Some 2 - substituted amino benzothiazoles (II) have also been reported by Mikulaseck S . et al. ² as antimycobacterial agents. The biological activity of these compounds is similar to that of *Isoniazide* with lower toxicity .



Where R = Cl , Br , etc. R' = H, Me, Ph, CH₂Cl , etc.

Based on the above facts a series of compounds of 2 - substituted alkyl / aryl amino benzothiazoles (III) were synthesized with the incorporation of chlorine and fluorine on the position 5 and 6 of benzothiazole respectively with an aim to obtain compounds with enhanced activities .

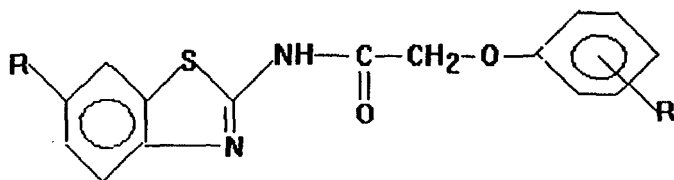


Where R = Alkyl, substituted Aryl.

PART 3 :- SYNTHESIS OF 5,6 - DISUBSTITUTED 2- (SUBSTITUTED PHENYL CARBOXAMIDO) BENZOTHAZOLES .

The importance of 2 - substituted amino benzothiazole moiety in imparting biological activity to various compounds has already been mentioned above .

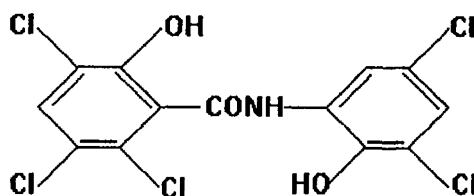
Lacova M. *et al.*³ have reported compounds of type (IV) as having good biological activity.



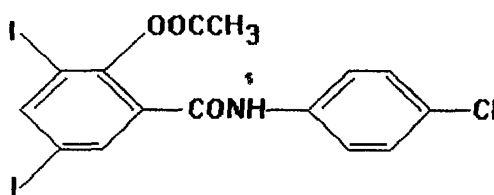
(IV)

Where R = Me, Cl etc R' = H, Cl .

Also literature study shows that *Oxyclozanide* (V) and *Clioanide* (VI) have very good anthelmintic properties.^{4,5}

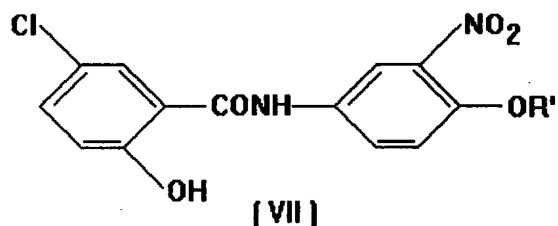


(V)



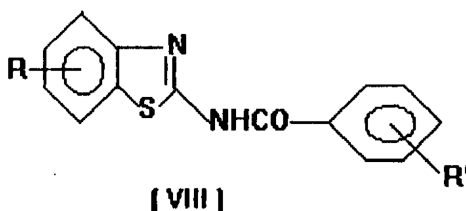
(VI)

Compounds of type (VII) have been reported to possess antifungal and antitubercular activities.⁶



Where R = aryl, ethyl.

From the above literature findings and taking into consideration the importance of 2-substituted amino benzothiazole moiety, compounds of type (VIII) were synthesised and tested for their antifungal, antibacterial, and antitubercular activities. Some compounds of this series have also been screened for their *in-vivo* anthelmintic activity against *H. nana*.

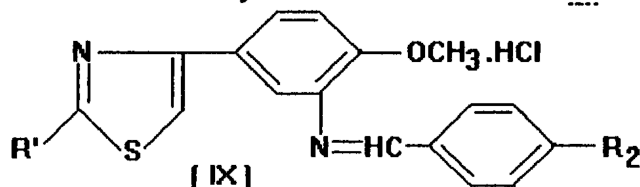


Where R = H ; 5- Cl ,6- F ; 5,6- Di Cl ;etc

R' = 2- F ; 3- F ; 4- F ; 2,6- Di F ; etc.

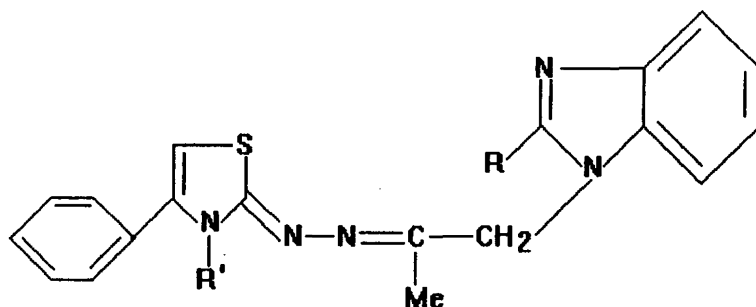
PART 4 :- SYNTHESIS OF 2-SUBSTITUTED ARYLIDENE HYDRAZINO 4-ARYL THIAZOLES.

The thiazole moiety is one of the most exploited moieties as antimicrobial agents. Sabnis *et. al.*⁷ have reported thiazoles of type (IX) as having good antitubercular activity.



Where R' = phenyl, benzyl ; R = NHCOOCH₃, N(CH₃)₂

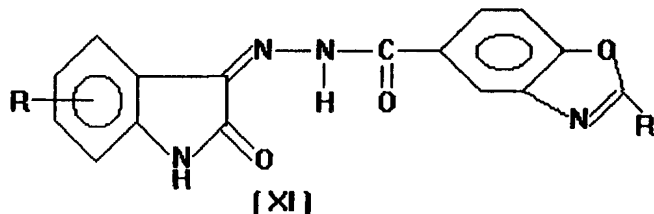
Recently some new thiazoles (X) with the hydrazino linkage have been reported to possess antimicrobial properties ⁸.



(X)

Where R = Me, Et etc. ; R' = substituted Phenyl, Phenyl.

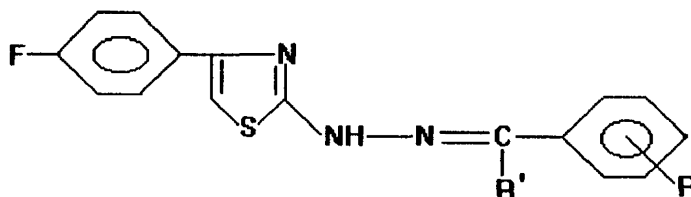
Saranga *et al.*⁹ have reported a series of compounds (XI) which have the hydrazino linkage which is responsible for the antimicrobial activity.



(XI)

Where R = H, 5-Br, 7-Cl, etc. ; R' = H, Me, Et, etc.

In view of the above findings and the importance of 2,4 - disubstituted thiazole moiety, a new series of 2,4 - disubstituted thiazoles (XII) was synthesised with a hydrazino linkage in 2 - position to yield compounds with good antimicrobial activity.

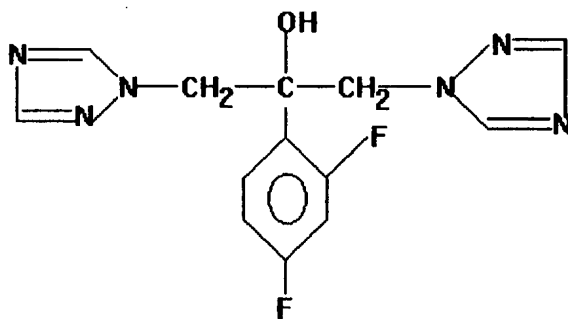


(XII)

Where R = 2-F, 3-F, 4-F etc. R' = H, CH₃.

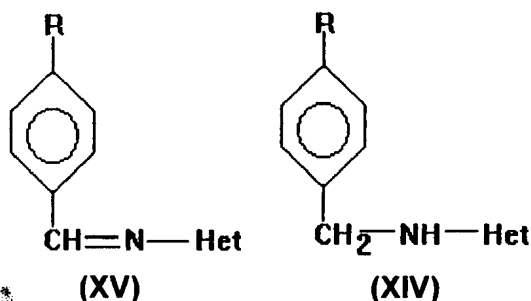
**PART 5 :- 3/4 [(SUBSTITUTED PHENYL) 1 - METHYL - ENE]
AMINO 1,2,4 TRIAZOLE .**

The importance of 1,2,4 Triazole moiety as a major pharmacophoric requirement to possess enhanced antifungal activity is well manifested by its inevitable presence in the most recent class of antifungal drugs viz. *Fluconazole* (XVII) ¹⁰ .



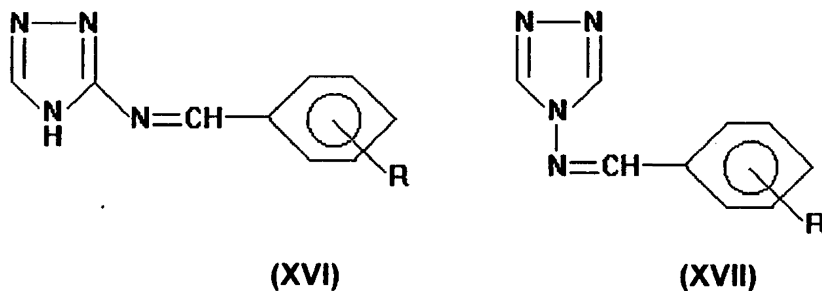
(XIII)

Recently *R. Fioravanti et al.*¹¹ have reported antimicrobial activity of some new heteroaryl benzylamines (XIV) and their schiff bases (XV).



Where R = H, CH₃, Br, F, etc.

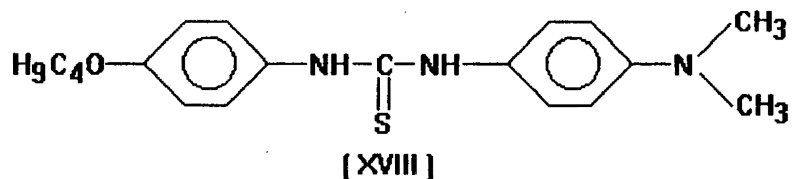
Thus taking into consideration the importance of the triazole nucleus and the pharmacophoric importance of schiff bases as mentioned above, schiff bases of 3/4 amino - 1,2,4 triazoles (XVI) & (XVII) were synthesized and screened for their antifungal, antibacterial and antitubercular activity.



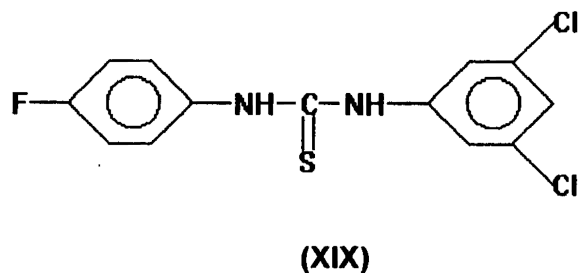
Where R = 2-F, 3-F, 4-F etc.

**PART 6 : - SYNTHESIS OF 4(p-CHLORO PHENOXY)3- CHLORO
PHENYL SUBSTITUTED PHENYL THIOCARBANILIDE.**

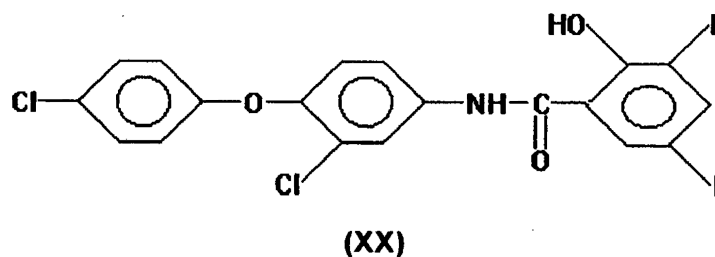
1,3 - Disubstituted thioureas are well documented in literature for their biological activity eg. *Thiambutasine* ¹² (XVIII).



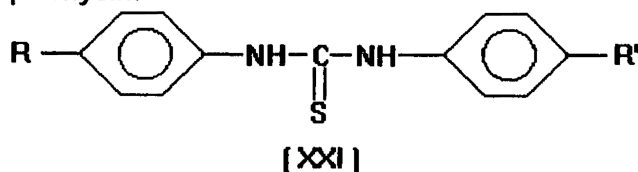
Fluonilide (XIX)¹³ is a well known antifungal agent which is a simple substituted thiourea .



Rafoxanide (XX) is a widely used veterinary anthelmintic .



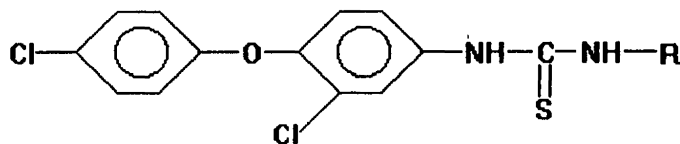
Mayer et.al.¹⁴ have reported few diphenyl thioureas derivatives (thiocarbanalides) of general structure (XXI) the activity of which exceeds the activity of streptomycin.



Where



Taking all the above facts into account the synthesis of following series of compounds (XXII) was effected and their biological screening was carried out .



(XXII)

Where R = C₄H₉ , p-OC₂H₅ C₆H₄, p-Cl C₆H₅ etc.

PART 7 :- BIOLOGICAL SCREENING

The compounds reported herein have been subjected to elemental and spectroscopic analysis and the results were found to be satisfactory.

The compounds reported in parts 2 , 3 , 4 , 5 & 6 have been screened for their *in vitro*. antitubercular, antibacterial, antifungal and anthelmintic activity.

ANTITUBERCULAR SCREENING.

The *in vitro* . antitubercular screening of the compounds was carried out by the tube dilution technique employing the human virulent H₃₇Rv strain of *M. Tuberculosis* . By this method using *Kirchners medium* containing Tween-80 as described by *Rake et al.*¹⁵ dispersed growth of *M . Tuberculosis* was obtained.

ANTIBACTERIAL SCREENING .

The compounds described in parts 2 to 6 were also subjected to *in vitro* tests against other bacteria viz. *S.aureus*, *S.typhi*. The culture medium employed in the screening was *Mueller-Hinton broth*¹⁶ .

ANTIFUNGAL SCREENING .

The compounds have also been screened for their antifungal activity *in vitro*. by the *Tube Dilution technique*¹⁷ against fungal strains viz. *C. albicans* *T. rubrum* and *T. mentagrophytes* .

ANTHELMINTIC SCREENING.

Some of the compounds described in part 3 have also been screened for their *in vivo* anthelmintic activity¹⁸ against *H. nana*. The results are awaited

The standard drugs used were *ETHAMBUTOL* for antitubercular screening, *AMPICILLIN* for antibacterial screening , *MICONAZOLE* for antifungal screening and *MEBENDAZOLE* for anthelmintic screening.

REFERENCES :

1. Khadse, B G., Patel, M R., & Lokhande, S R., **Bull.Haff. Instt. , 9(3) , (1981)**
12 - 14 .
2. Mikulasek, S., Odelerova, Z., Sutoris, V., Perjessy, A., Solcaniova, E., **Chem. Zvesti, 32(5), (1978) , 691-700. Cited from Chemical Abstracts 90: 186849v**
3. Lacova, M., Gvozdzakova, A., Chovancova, J., Volna, F., **Chem. Zvesti, 38(5), (1984) , 693-8. Cited from Chemical Abstracts 102: 113358r**
4. Broom, A W., Cairns, J P., Crossley, N S., Jones, W G M., & Stevans, A M.,
Ind. Chim. Belg., 32 (1962) 204.
5. Paul J. A. Presidente, Stuart E. Knapp, Michael W. Schlegel,
Jack N. Armstrong., **Am. J. Vet. Res. 33, (1972) 1593.**
6. Singh, H., Singh, A K., Sharma, S., Iyer, R N., **J. Med. Chem. , 20(6) (1977)**
826-829.
7. Sabnis, S S., Chaudhari, D T., Patel, M R., Patil, A M., **Bull.Haff. Instt. , 5(3) ,**
(1977) 12 - 14 .
8. Ashour, F A., Habib, N S., Soliman, R., EL- Taibbi, M., **Bull. Fac. Pharm.**
31(3) (1993), 381-6.
9. Saranga, P M., Reddy, V M., **Ind.J. Pharm. Sci. 56(5), (1994) 174-7.**
10. Richardson, K., Brammer, K W., Marriot, M S., & Troke, P F., **Antimicrob. Agents Chemother. 27 (1985) 832.**
11. Fioravanti, R., Biava, V., Porretta, G C., Landolfi, C., **Eur.J.Med. Chem. 30**
(1995) 123-132.

12. Davy, T F., **Leprosy Rev** **29** (1958) 25.
13. Madan, A G., **Belg. pat.** **613,154** (1962) Cited from **Chemical Abstracts**
58: 474f.
14. Mayer, R L., Konopka, E A., Eisman, P C., Parker, F., & Robbins, S L.,
Am.Rev.Tuberc. **70** (1954) 130.
15. Rake, G., Jambor, W P., Mckee, C M., Pansy, F., Wiselogle, F Y.,
Donovic,R., **Am. Rev.Tuberc.** **60** (1949) 121.
16. Koneman, E V., Janda, W M., Allen, S D., Sommers, H M., Dowell, V R.,
Winn, W C., '**Color Atlas and Textbook of Diagnostic Microbiology**'. J.B.
Lippincott Company, **3rd edn.** , (1988) 487.
17. E.Joan Stokes, **Clinical Bacteriology** , **4th edn** (1975), 226.
18. Agarwal, A., Agarwal, S K., Bhakuni, D S., Gupta, S., & Katiyar, J C.,
Ind. J.Chem. **28B(11)** , (1989) , 943.



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