

SYNTHESIS AND STUDY OF SUBSTITUTED
BENZIMIDAZOLES AS POSSIBLE THERAPEUTIC AGENTS

THESIS SUBMITTED
UNIVERSITY OF MUMBAI

FOR THE DEGREE OF
MASTER OF SCIENCE
IN
CHEMISTRY

SUBMITTED BY
YOGESH SADANANDA S. RANE

UNDER THE GUIDANCE OF
DR. ANIL BOBADE

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

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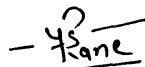
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STATEMENT BY THE CANDIDATE

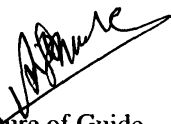
As required by the University Regulation No. R. 2190, I wish to state that the work embodied in this thesis titled “**Synthesis and study of substituted Benzimidazoles as possible therapeutic agent**” forms my own contribution to the research work carried out under the guidance of **Dr. Anil S. Bobade** at the Department of Chemotherapy, **Haffkine Institute for Training, Research and Testing, Mumbai-12**. This work has not been submitted for any other degree of this or any other University. Whenever references have been made to previous works of others, it has been clearly indicated as such and included in the Bibliography.



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INDEX

Sr. No.	Content	Page No.
1]	<u>Part I: -</u>	
	Introduction	1-2
2]	<u>Part II: -</u>	
	Review of Literature	3-24
3]	<u>Part III</u>	
	Plan of work	25-41
3-A]	<u>Part III – A: -</u>	
	1) Chemistry of Benzimidazole	42-44
	2) Chemistry of 2-mercapto Benzimidazole	44-47
3-B]	<u>Part III – B: -</u>	
	1) Chemistry of Intermediates	48-49
	2) Chemistry of Acid Chlorides	50-52
	3) Chemistry of Reduction of Nitro compounds	53-58
	4) Chemistry of Sulfonyl Chloride	59-61
4]	<u>Part IV: -</u>	
	Experimental	62-73
	Synthesis of some 5,6-disubstituted- 2-(N, N-dialkyl thiocarbamido) Benzimidazoles.	
5]	<u>Part V: -</u>	
	Experimental	74-86
	Synthesis of some 5-substituted-2-(1-H- Benzimidazole) Sulfonamides.	

6]	<u>Part VI: -</u>	
	Experimental	87-91
	Synthesis of some 5,6-Disubstituted-2- (Phenyl thiocarbamoyl) Benzimidazoles.	
7]	<u>Part VII: -</u>	
	Experimental	92-96
	Synthesis of some 5,6-Disubstituted-2- Phenoxymethyl Benzimidazoles.	
7-A]	<u>Part VII A: -</u>	
	Spectroscopic Analysis of Synthesized compounds	97-112
8]	<u>Part VIII: -</u>	
	Biological Screening	113-117
9]	<u>Part IX: -</u>	
	Biological Results and Discussion	118-125
9-A]	<u>Part IX A: -</u>	
	Appendix	126
10]	<u>Part X: -</u>	
	Bibliography	127-134
11]	<u>Part XI: -</u>	
	Synopsis	

PART – I
INTRODUCTION

The developing countries have been experiencing an epidemiological transition, with rapid aging of the population together with an increasing incidence of non-communicable diseases linked to changes in life style. The growing prevalence of cancer, cardiovascular diseases, diabetes and other chronic conditions in addition to the long-standing problems of communicable diseases such as cholera, malaria and tuberculosis impose a double burden on health care systems in these countries. In addition there is a pandemic of HIV infection and AIDS, which imposes a particularly heavy burden on developing countries¹.

Each year about 50 million people die throughout the world. Of these, about 6.8 million deaths are registered in the developing market economies, 4.2 million in Eastern Europe, 7 million in the group of least developed countries and 32 million elsewhere in the developing world. Reliable data on causes of death show that, the infections and parasitic diseases continue to pose serious risk to adult health in developing countries. This catalogue of disease account for about 17 million deaths or almost half of all deaths occurring in developing countries. Tuberculosis claims around 3 million lives each year, 90 % of which among the adult population. Pneumonia is the cause of about 2 million adult deaths each year in developing countries.

Other major health risks for adults include malaria, schistosomiasis, hepatitis B and AIDS, each of which account for several thousands of adult deaths each year².

Research in vaccines, pharmaceuticals and medical equipments are becoming even more expensive with the results that, end product are priced out of the reach of developing countries. Yet pressures from manufacturers and donors to adopt

these costly new technologies and even from the general public are intense. The trend seems to be towards more and more expensive treatments for diseases affecting less number of people. In general, it is hoped that Research and Development will develop new and improved preventive therapeutic and enabling technologies, giving attention to simplicity and adaptability to meet the needs of developing countries.

Hence, we must develop new approaches, mechanisms, partnerships and resources that can expedite this process. The problems now being faced may not be susceptible to approaches that have been applied in the past. We cannot continue doing what we have always done. Tomorrow cannot be just more of yesterday. We need flexibility and pragmatism as much as innovation but the stress must invariably be on action.

PART – II
REVIEW OF LITERATURE

FUNGAL INFECTIONS

Fungal diseases have brought misery to millions of people in tropical and subtropical regions mainly due to the unhygienic conditions of their living.

Mycotic infections of humans are conveniently divided into three groups:

- (1) **Dermatophytoses**: - consisting of contagious superficial skin infections that are limited to the epidermal region.
- (2) **Candidiosis**: - affecting the skin and mucous membranes
- (3) The **subcutaneous**, **pulmonary**, **lymphatic** and **systemic mycoses**, which are not contagious.

They are caused by free living saprophytes that invade the skin, lungs, lymphatic tissues and various organs of susceptible hosts who have accidentally been in contact with the fungal environment.

CHEMOTHERAPEUTIC ASPECTS OF FUNGAL INFECTIONS:

There are very few agents available for the treatment of fungal infections mainly because the majority of fungal infections are rarely life threatening to man and are less common and also they are eukaryotic pathogens. It is difficult to develop

drugs, which are specific for fungi without being concomitantly toxic to the man.

The composition of the fungal cell wall, the material surrounding it and the cytoplasmic membrane within cell wall play important role in the permeability of fungi to antifungal agents.

Principle antifungal agents can be divided on the basis of their origin as:

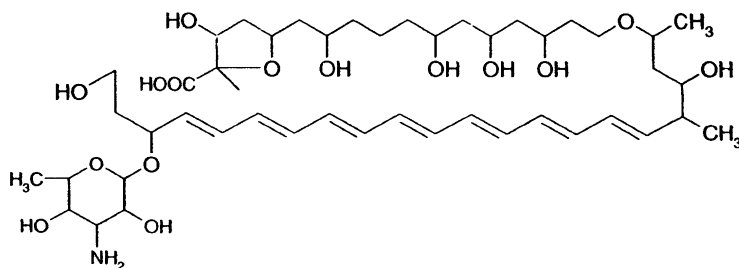
- (1) Antibiotics produced by various microorganisms
- (2) Synthetic chemical compounds.

POLYENE ANTIFUNGAL ANTIBIOTICS:

Polyenes show broad antifungal activity against organisms ranging from yeasts to filamentous fungi and from saprophytic to pathogenic fungi.

NYSATATIN (Tetraene) (I):

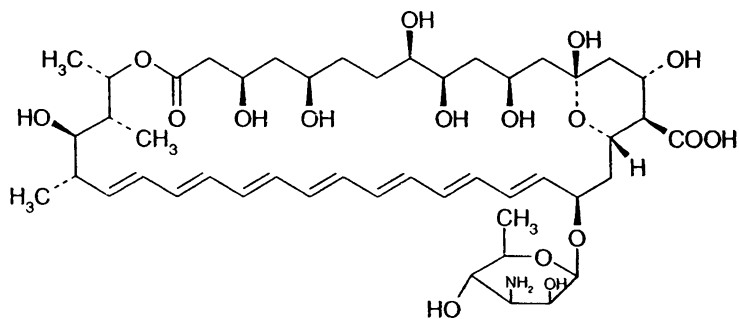
Nystatin (I) is a product of *Streptomyces albulus* or *Streptomyces Noursei* used for the tropical treatment of oral, esophageal, gastro-intestinal and genital Candidiosis, and gastro-intestinal prophylaxis³.



(I)

AMPHOTERICIN B (II):

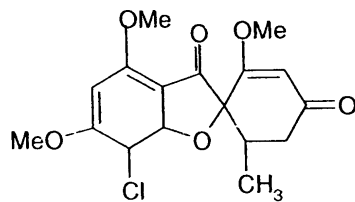
Most Polyenes are restricted to topical use, but Amphotericin B (II) remains the most important weapon in the antifungal armamentarium for the treatment of systemic fungal infections; including disseminated candidiasis, cryptococcosis, aspergillosis, and deep mycoses caused by dimorphic fungi⁴.



(II)

GRISEOFULVIN (III):

Griseofulvin (III) is an orally administered antifungal antibiotic which is commonly used to treat tinea capitis (dermatophytes of the scalp) and infections of the skin and nails with dermatophytes fungi of genera *Epidermophyton*, *Microsporum*, and *Tricophyton*. Yeasts such as *Candida albicans* are not sensitive and drug is of no value in candidiasis and candida paronychia⁵.



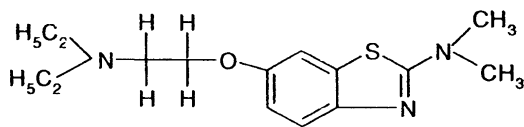
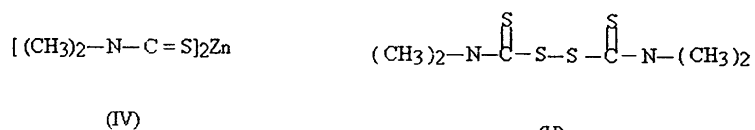
(III)

SYNTHETIC ANTIFUNGALS:

SULPHUR CONTAINING DRUGS:

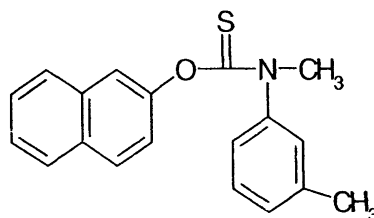
A variety of organic compounds that contain divalent S-atom attached to C-atom have *in vitro* fungistatic action and many of these have been employed in tropical therapy of dermatophytoses.

Dithiocarbamates such as dimethyl derivatives (IV), thioureas such as tetraethyl thiuram disulfide (V) and 6-(β-diethylaminoethoxy)-2-N, N-diethylamino benzothiazole (VI) are some of the examples^{6,7}.



(VI)

Tolnaftate ⁸ (VII) is a thiocarbamate, effective in treatment of most cutaneous mycoses caused by *T. rubrum*, *T. mentagrophytes*, *T. tonsurans*, *E. floccosum*, *M. canis*, *M. audouinii*, *Microsporum gypseum* and *M. furfur*, but it is ineffective against candida. In tinea pedis, the cure rate is around 80% compared with about 95% for Miconazole. Toxic or allergic reactions to Tolnaftate have not been reported.



(VII)

AZOLE DERIVATIVES:

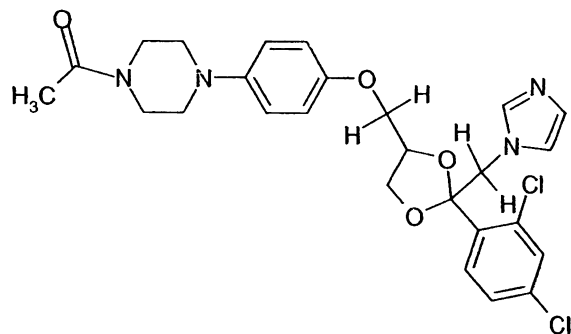
The antifungal azoles are synthetic compounds with one or more 5-membered rings, where each ring contains either two (imidazole) or three (triazole) N- atoms.

IMIDAZOLES:

Imidazoles are one of the two major classes of antifungal azole derivatives, the other being triazoles.

Ketoconazole ⁹ (VIII) the first successful orally absorbable antifungal azole was introduced in 1979. It blocks the fungal

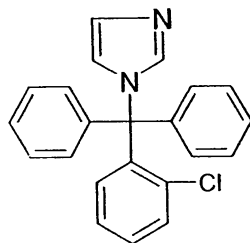
synthesis of ergosterol, which is essential to the integrity of the cell membranes of the nearly all-pathogenic fungi. It has broad spectrum of antifungal activity, which includes *Blastomyces dermatitidis*, *Candida spp*, *Chromomyces*, *Coccidioides immitis*, *dermatophytes*, *Histoplasma capsulatum* and *Paracoccidioides brasiliensis* and *Pseudallescheria boydii*. *Aspergillus*, *Cryptococcus neoformans* and *Sporothrix schenckii* are affected moderately but *mucor* is not.



(VIII)

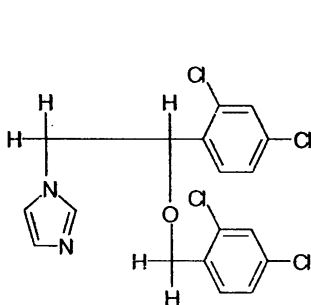
Successful treatment of this endemic mycosis is dependent on the daily dosage, which ranges from 400-800 µg/day and duration of the therapy.

Clotrimazole ^{9-a} (IX) is a broad-spectrum antifungal agent used topically for the treatment of tinea infections and candidiasis. Clotrimazole is supplied as a solution in polyethylene glycol 400, a lotion, and a cream in concentration of 1% for treatment of tinea pedis, tinea cruris, tinea capitis, tinea versicolor, or cutaneous candidiasis. A 1% vaginal cream and tablets of 100 and 500 mg are available for vulvo vaginal candidiasis.

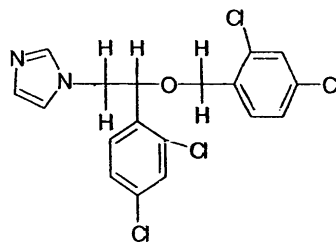


(IX)

Miconazole ^{9-a} (X) is used for the treatment of serious systemic fungal infections such as candidiasis, coccidioidomycosis, cryptococcosis, petriellidiosis and paracoccidioidomycosis, chronic mucocutaneous candidiasis.



(X)

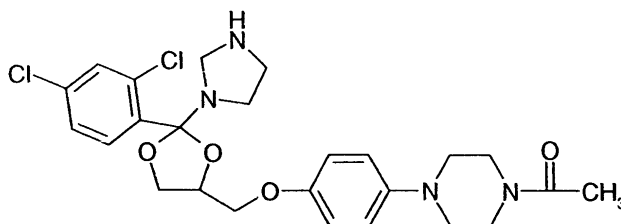


(XI)

Econazole ^{9-a} (XI) is used as a 1% cream for topical treatment of local tinea infections and cutaneous candidiasis.

TRIAZOLES:

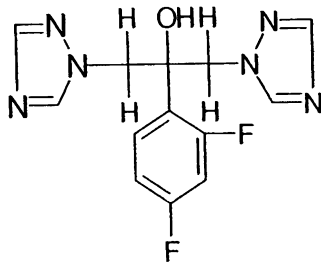
Itraconazole (XII) is a triazole antifungal agent given by mouth for the treatment of oropharyngeal and vulvo vaginal candidiasis, pityriasis versicolor, and of dermatophytes such as tinea pedis, tinea cruris, and tinea corporis¹⁰.



(XII)

At doses ranging from 50-400 µg/day, Itraconazole has been shown to be effective therapy for most of the fungal diseases¹¹.

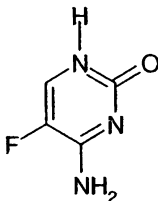
Fluconazole (XIII) is a triazole antifungal administered by mouth or by intravenous infusion in similar doses. It is used for superficial mucosal superficial mucosal (oropharyngeal, oesophageal, or vaginal) candidiasis and for fungal skin infections. It is also given for systemic infections including systemic candidiasis, coccidioidomycosis, and cryptococcosis, and has been tried in blastomycosis, chromoblastomycosis, histoplasmosis, and sporotrichosis¹².



(XIII)

PYRIMIDINE DRUGS:

5-Fluorocytosine (XIV) is effective in systemic Candidiosis and cryptococcosis.



(XIV)

It has very marked selective antifungal activity *in vitro* and *in vivo* against pathogenic yeasts like *Candida albicans* and other species of candida, *Cryptococcus neoformens*, *Torulopsis glabrata* and has moderate activity on fungi such as aspergillus¹³.

Considerable progress in treating systemic fungal infections has been achieved through better application of established anti fungal agents and the development of promising new investigational agents. This ever-expanding battery of

antifungal agents exhibits a wide variety of pharmacokinetic properties, mechanism of action and toxicities. Understanding these parameters is critical for the appropriate use and continued development of these drugs.

The field of antifungal chemotherapy has finally reached the stage where many new agents from different classes of compounds with different mechanisms of actions are being synthesized and extensively studied.

Ideally a new antifungal should possess following characteristics:

- (1) Potent, broad spectrum antifungal activity
- (2) No toxicity
- (3) Flexibility of oral or parental administration
- (4) Favorable pharmacokinetics including complete bioavailability and effective tissue penetration.

Antifungal agents may be classified as to their structure, mode of action and antifungal spectrum of activity. Table 1 lists the common antifungal agents with their adverse effects and drug interactions.

DEVELOPMENTAL STEPS IN ANTIBACTERIAL AGENTS:

The discoveries of antibacterial drugs were started by the introduction of the Dapsone known as Promin in 1940.

In 1944, Worksman newly isolated Streptomycin, as an antibiotic, from the soil organisms *Streptomyces griseus* as a fermentation product.

Although, screening of antibacterial agents will continue to be a possible way to discover useful new drugs, the increasing knowledge of the biochemistry of bacteria makes possible and more rational approach to the biosynthesis of the bacterial cell wall. This indicates the targets for inhibitors of the biosynthetic pathway present specifically in the microorganisms of the bacterium species.

Selective inhibitors could open up new horizons in the therapy of bacterial infections because they will be ineffective in the eukaryotic cells of the host, therefore, potentially will have less toxicity. Furthermore, since they will be ineffective also on other microorganisms, they will not alter the normal microbial flora.

Another specific constituent of pathogenic bacteria is the cord factor and more extensive studies on its biosynthesis might indicate the possibilities of inhibiting its formation.

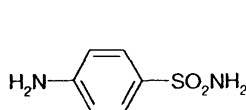
To multiply and cause disease in the host, *Mycobacterium tuberculosis* must acquire iron from the extra cellular environment at sites of replication. To do so, the bacterium releases high affinity iron binding siderophores called exochelins. The molecules share a common core structure with another type of high affinity iron binding molecule located in the cell wall of *M. tuberculosis*: the mycobactins¹⁴. The water-soluble exochelins differ from each other and from water insoluble mycobactins in polarity, which is dependent primarily upon the length and modifications of alkyl side chain. We have investigated the capacity of purified exochelins to remove iron from host high-affinity iron-binding molecules, and to transfer iron to mycobactins. Purified desferri-exochelins rapidly removed iron from human transferrin, whether it was 95% or 40% iron saturated, its approximate percent saturation in human serum, and from human lactoferrin. Desferri-exochelins also removed iron, but at a slower rate, from the iron storage protein ferritin. Purified ferri-exochelins, but not iron transferring, transferred iron to desferri-mycobactins in the cell wall of the live bacteria. To explore the possibility that the transfer iron from exochelins to mycobactins was influenced by their polarity, we investigated the influence of polarity on the iron affinity of exochelins. Exochelins of different polarity exchanged iron equally with each other. This study supports the concept that exochelins acquire iron for *M. tuberculosis* by removing this element from host iron-binding proteins and transferring it to desferri-mycobactins in the cell wall of bacterium. The finding that ferri-exochelins but not iron transferring transfer iron to mycobactins in the cell wall underscores the importance of exochelins in iron acquisitions. This study also shows that the variable alkyl

side chain on the core structure of exochelins and mycobactins, the principal determinant of their polarity, has little or no influence on their iron affinity.

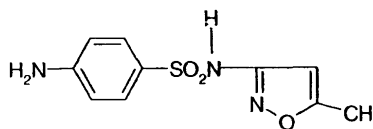
SYNTHETIC ANTIBACTERIAL COMPOUNDS:

SULPHONAMIDES:

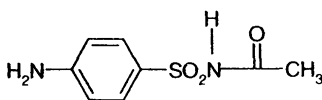
Derivatives of p-aminobenzene sulphonamides were first employed as antibacterial agents. Among these sulphanilamide (XV), sulphamethoxazole (XVI), sulfacetamide (XVII), sulfadiazine (XVIII) and sulfisoxazole (XIX) are the important ones.



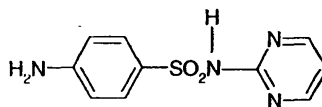
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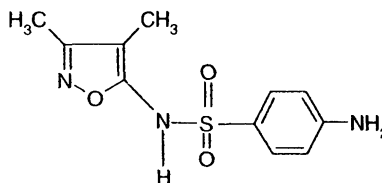
(XVI)



(XVII)



(XVIII)

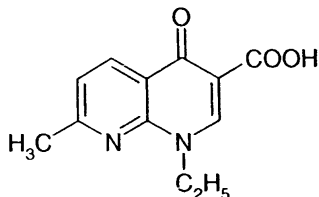


(XIX)

The sulphonamides have a wide range of activity against both Gram-positive and Gram-negative bacteria and are rapidly absorbed by the gastrointestinal tract. However, resistant strains of bacteria to the sulphonamides have become common and hence are used in combination with antibiotics

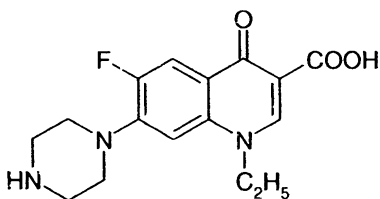
QUINOLONES:

In this class of antibacterial agents Nalidixic acid (XX) is an important compound used mainly for the treatment of Urinary Tract Infections (U.T.I.).

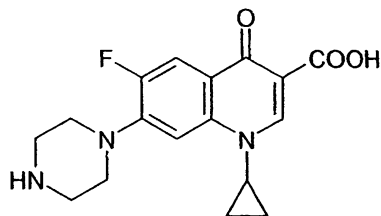


(XX)

Recently, Norfloxacin (XXI) and Ciprofloxacin (XXII) are in use against *E. coli*, various species of *Salmonella*, *Enterobacter* and others^{15, 15-a}.



(XXI)

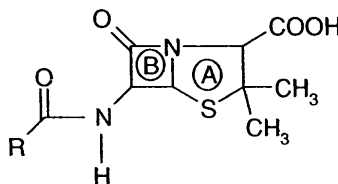


(XXII)

Ciprofloxacin is the most active antibacterial agent having bioavailability of about 60 %. The primary mechanism is inhibition of bacterial DNA- gyrase and is effective in oral and intravenous administrations¹⁶.

PENICILINS (XXIII) :

In 1928, Alexander Fleming discovers penicillin, the most important class 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 large number of infectious diseases.



(XXIII)

The basic structure of penicillin consists of a thiazolidine ring (A) Connected to a β -lactum ring (B) to which is attached a side chain (R) through O=C-NH linkage. The penicillin nucleus is an important requirement for biological activity, alteration of which causes loss of all significant activity. Many of the antibacterial and pharmacological characteristics of penicillins are determined by its side chain (R), which can also alter the susceptibility of the resultant compounds to inactivating enzymes (β -lactamases).

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 prostatic secretions, brain tissue and intraocular fluid.

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

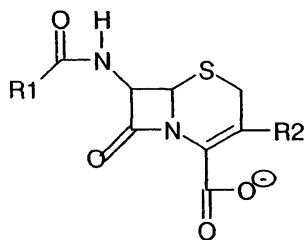
No sooner was the fact established that penicillins are capable of eradicating microorganisms, it was practically administered in every situation where there was a risk of bacterial infection. But after the investigation of prophylaxis under controlled conditions, it is now understood that penicillin 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, have been the hypersensitivity reactions. Such reactions could occur with any dosage form of penicillin, but as the drug is rapidly eliminated the allergic reactions usually subside. In some

cases the symptoms may persist for one or 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.

CEPHALOSPORINS (XXIV) :

The cephalosporins (XXIV) were first introduced in the mid 1960's and were the first β -lactum antibacterials to have broad antibacterial spectrum. Since then, research has produced more microbiologically active cephalosporins, especially against gram-negative organisms, and also some, that are particularly stable in the presence of β -lactamases. Unfortunately until recently, most of these potent Cephalosporins such as Cefotaxime and Ceftazidime could only be administered by intravenous or intramuscular injection, thus necessitating hospitalization.

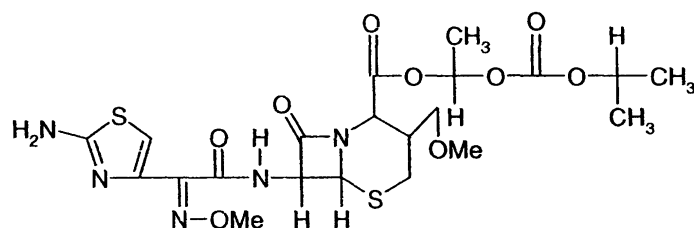


(XXIV)

However, third generation oral cephalosporins have recently been developed. Because of their broad antibacterial spectrum, the cephalosporins have proved valuable for the treatment of respiratory tract infections, particularly Acute

Exacerbations of Chronic Bronchitic (AECB) and bronchopneumonia, which are frequently caused by more than one organism. The newer β -lactum-stable oral cephalosporins, such as *Cefpodoxime proxetil*, are of potential value for these indications.

Cefpodoxime proxetil is the orally administered pro-drug of Cefpodoxime, a broad spectrum third generation cephalosporins antibiotic possessing *in vitro* and *in vivo* bacterial activity comparable or superior to that of currently available oral and parenteral β -lactum antibiotics.

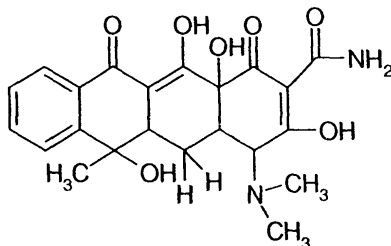


(XXV)

TETRACYCLINS (XXVI) :

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

Microorganisms that have developed resistance to one tetracycline frequently exhibit resistance to the other members of the family.



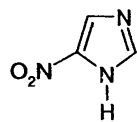
(XXVI)

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.

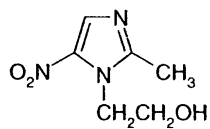
The tetracyclines produce gastrointestinal irritation to varying degrees in some individuals and are more common after oral administration. Diarrhea may also be a side effect, which though frequent, and fluid, do not contain blood or leukocytes. Doxycycline and to a lesser extent other derivatives may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

Biologically active benzimidazoles:

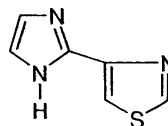
The pharmacological history of several thousands of Imidazoles derivatives has been established over 30 years, after the discovery of the antibacterial and antifungal activity of benzimidazole by Wolley (1944)¹⁷ which later led to the synthesis of benzimidazole derivatives with strong antiprotozoal and anthelmintic properties. The discovery of a the antibacterial (Azomycin, XXVII), a trichomonacide (Metronidazole, XXVIII), anthelmintic agents (Thiabendazole, XXIX and Cambendazole, XXX) and recent drugs such as Omeprazole (XXXI) and Lansoprazole (XXXI) which contain prominently imidazole and benzimidazole nucleus, has added impetus to investigations in these areas with particular emphasis on the synthesis of newer benzimidazole derivatives for pharmacological screening.



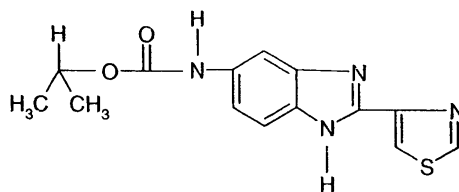
(XXVII)



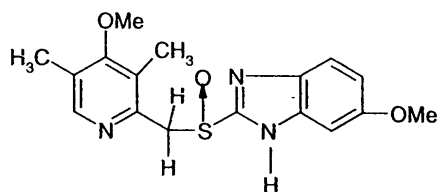
(XXVIII)



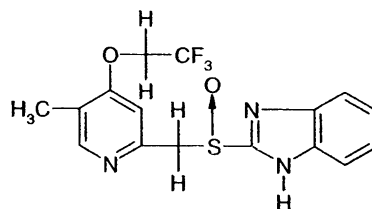
(XXIX)



(XXX)



(XXXI)



(XXXII)

PART – III

PLAN OF WORK

A considerable progress has been made in past fifty years in the chemotherapy of microbial diseases still the development of resistance to the drugs by microbials is an important problem facing the chemotherapist. The rapidity of development of resistance varies widely under different circumstances. Besides, the potent drugs used in the clinical therapy over years are being reported to show newer side effects. Thus, there is always a need for search of newer compounds with potent activity good tolerances, lesser side effects and efficacy against microbial resistant strains.

Abundant evidence from controlled studies have established the clinical efficacy of various drugs employed in the treatment of microbial infections many review clearly emphasize the importance of heterocycles in naturally occurring as well as synthetic agents and are an important class itself possessing the antimicrobial activity.

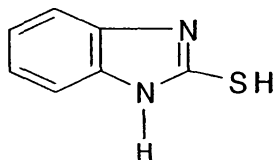
An attempt has been made to synthesize new derivatives of substituted benzimidazoles as potent antibacterial and antifungal agent.

A] 5,6-Disubstituted-2-(N, N-Dialkyl Thiocarbamido)

Benzimidazoles :-

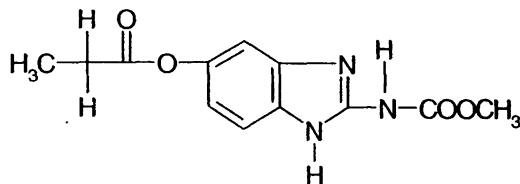
It has been observed from the literature survey that the benzimidazole derivatives shows broad spectrum activities e.g. Mebendazole, Flubendazole, Albendazole etc.

2-mercapto benzimidazole (I) itself is a bacteriostatic and antifungal agent¹⁸.



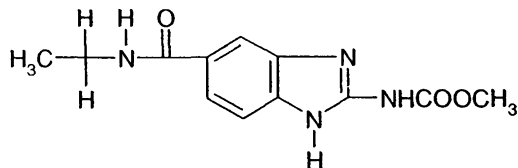
(I)

Recently, Ram *et al* synthesized 5-carboxy-1H-benzimidazol-2-carbamates (II), which were found to be curative against adult *B. pahangi* microfilariae in birds at the dose of 12.5 mg/kg when given for 5 days and also *A. vitae* in birds at 25mg/kg when given for 5 days¹⁹.

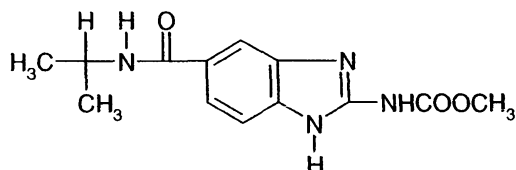


(II)

Also, (III) and (IV) were found to show activity against *B. pahangi* in birds at 25 mg/kg for 5 days and 6.25 mg/kg for 5 days¹⁹, respectively.

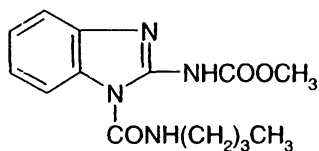


(III)



(IV)

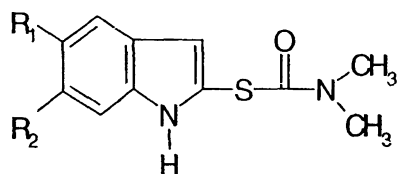
In addition to these, Benomyl (V) was found to show antifungal activity²⁰.



(V)

Thus, considering the importance of dialkyl carbamoyl linkage as an effective group in synthesis of compounds of

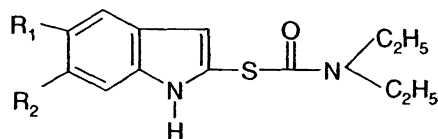
medicinal value, several 5,6-Disubstituted-2-mercapto benzimidazoles have been condensed with N, N-dialkyl carbamoyl chlorides. The resultant compounds depicted as (VI) and (VII) have been then screened for their antibacterial and antifungal properties.



(VI)

R_1 = Phenoxy, Naphthoxy

R_2 = Cl, H



(VII)

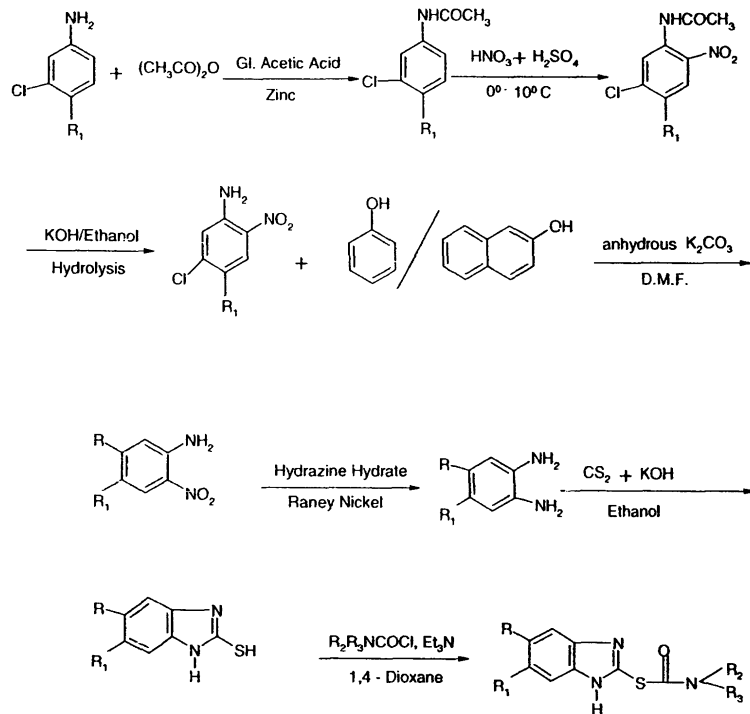
R_1 = Phenoxy, Naphthoxy

R_2 = Cl, H

SCHEME - I

SCHEMATIC REPRESENTATION

Synthesis of 5,6-disubstituted-2-(N,N-dialkyl thiocarbamido) Benzimidazoles



Where,

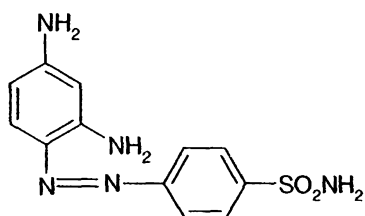
$R_1 = \text{H, Cl}$

$R = \text{Phenoxy, Naphthoxy}$

$R_2 = R_3 = -\text{CH}_3, -\text{C}_2\text{H}_5$

B) 5-Substituted-2-(1-H-benzimidazole) sulfonamides :-

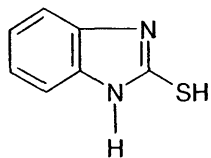
The discovery of antibacterial activity of Prontosil (VII), a sulfonamide, in early 1930's was the beginning of the era of chemotherapy²¹. Thereafter, Sulfonamides have been studied extensively and tested for their antibacterial activities. Presently there are many Sulphonamides in clinical use as antibacterial agents.



(VIII)

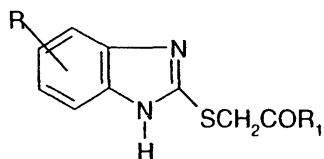
The pharmacological history of several thousands of imidazole derivatives has been established over 30 years, after the discovery of antibacterial and antifungal activities of benzimidazole by Wolley¹⁷ (1944) which later led to the synthesis of benzimidazole derivatives with strong antiprotozoal and anthelmintic properties.

A number of 2-Mercaptobenzimidazole derivatives (IX) have demonstrated a broad spectrum of significant biological activities, i.e. plant growth inhibitors²², bactericidal²³, fungicidal and virucidal²⁴ activities.



(IX)

The following type of Benzimidazoles (X) is known for their diverse biological properties²⁵.

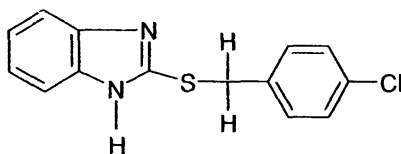


(X)

R = H, CH₃, Cl, NO₂

R₁ = CH₃, Ph

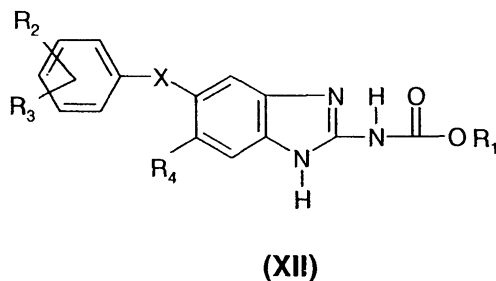
The S-benzyl derivatives of 2-mercapto benzimidazole were found to be broad-spectrum antimicrobials. 4-chlorobenzyl analog (XI) was found to be most active broad-spectrum antimicrobial²⁶.



(XI)

7-nitro-5-benzimidazole Sulfonamides and 4-nitro-6-benzimidazole sulfonamide were found to be excellent antibacterials²⁷.

5-phenoxy-2-substituted benzimidazoles such as 2-carbaloxy amino benzimidazole-5(6)-phenyl ethers (XII) are potent anthelmintics²⁸.



R₁ = alkyl .

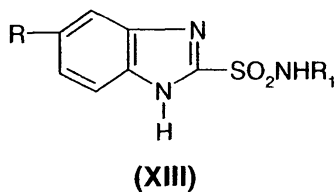
R₂ = Hydrogen, hydroxyl, alkoxy
alkyl, halogen.

R₃ = Hydrogen, hydroxyl, alkoxy
alkyl, halogen.

R₄ = hydrogen, chlorine.

X = oxygen.

The well-known antibacterial activity of Sulfonamides and above facts prompted us to Synthesize some 5-substituted-2-(1-H-benzimidazole) Sulphonamides (XIII) in order to get biologically active compounds.



R = Phenoxy, Naphthoxy

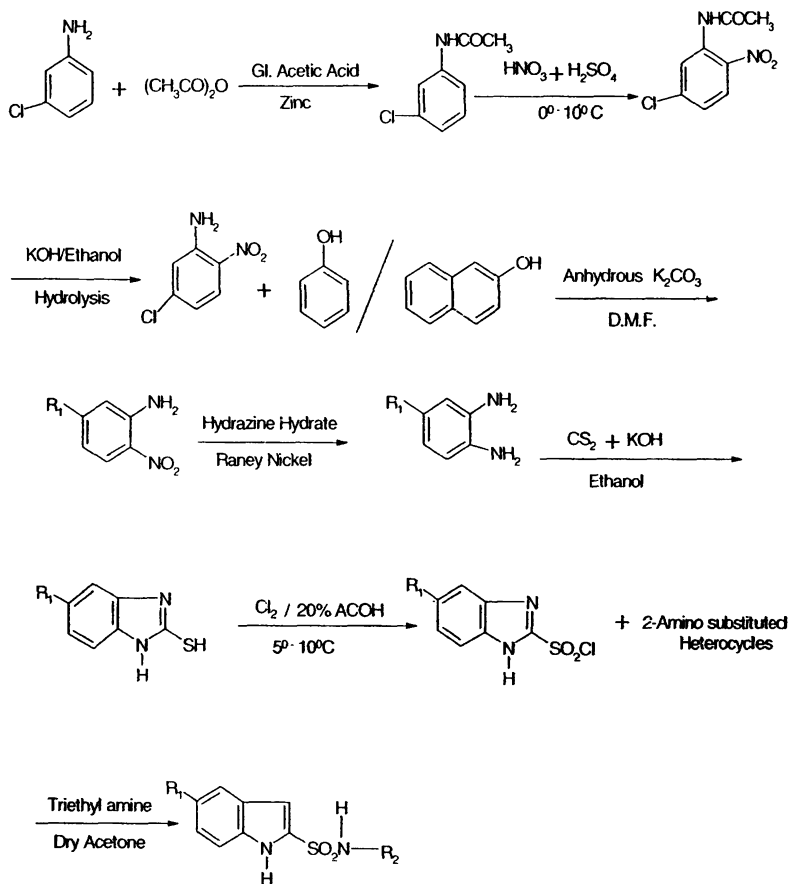
R₁ = H, Simple / Substituted Heterocycles

Thus, title compound is prepared by condensing 2-mercapto benzimidazole molecule having substitution at fifth position with 2-amino substituted heterocycles to get corresponding sulfonamides, which were further screened for their biological activity.

SCHEME - II

SCHEMATIC REPRESENTATION

Synthesis of 5-substituted-2-(1-H-benzimidazole) Sulfonamides



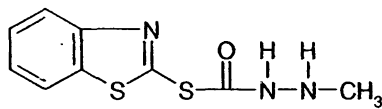
Where, R₁ = Phenoxy, Naphthoxy
 R₂ = Substituted Heterocycles, H

C] 5,6-Disubstituted-2-(Phenyl Thiocarbamoyl)

Benzimidazoles: -

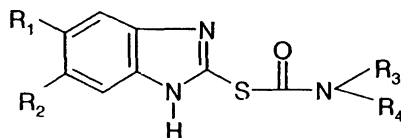
The discovery of new antibacterial (Azomycin), a trichomonicide (metronidazole) and anthelmintic agents (Thiabendazole)²⁹ which contain prominent imidazole nucleus, has added impetus to investigations in these areas with particular emphasis on the synthesis of newer benzimidazole derivatives for biological screening.

Assad and falmly³⁰ synthesized benzimidazoles (XIV) having thiocarbamoyl linkage at 2-position and were found to show inhibition zone of 9-18 mm on various bacteria at a concentration of 0.01 gm / 100ml.



(XIV)

Very recently, Sanjay Palav and B.G. Khadse³¹, (XV) have reported a series of 5,6-disubstituted-2-(N,N-dialkyl Thiocarbamido) benzimidazoles as potential chemotherapeutic agents having antibacterial, antifungal and larvicidal activities.



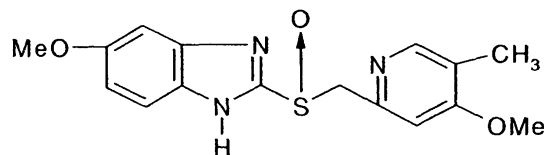
(XV)

R₁ = H, Cl

R₂ = H, Cl, F, OCH₃

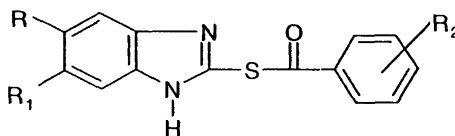
R₃ = R₄ = CH₃, C₂H₅

Also, 5-Methoxy-2-mercaptobenzimidazole has been found as an intermediate for omeprazole³² (XVI), which is a potent antiulcer agent and is used in the treatment of “Zollinger Ellison” syndrome.



(XVI)

Taking into account the above facts and biological importance, a series of compounds (XVII) of 5,6-Disubstituted-2-(Phenyl Thiocarbamoyl) benzimidazoles has been synthesized so as to study their biological activity.



(XVII)

R = Phenoxy, Naphthoxy

R₁ = Cl, H

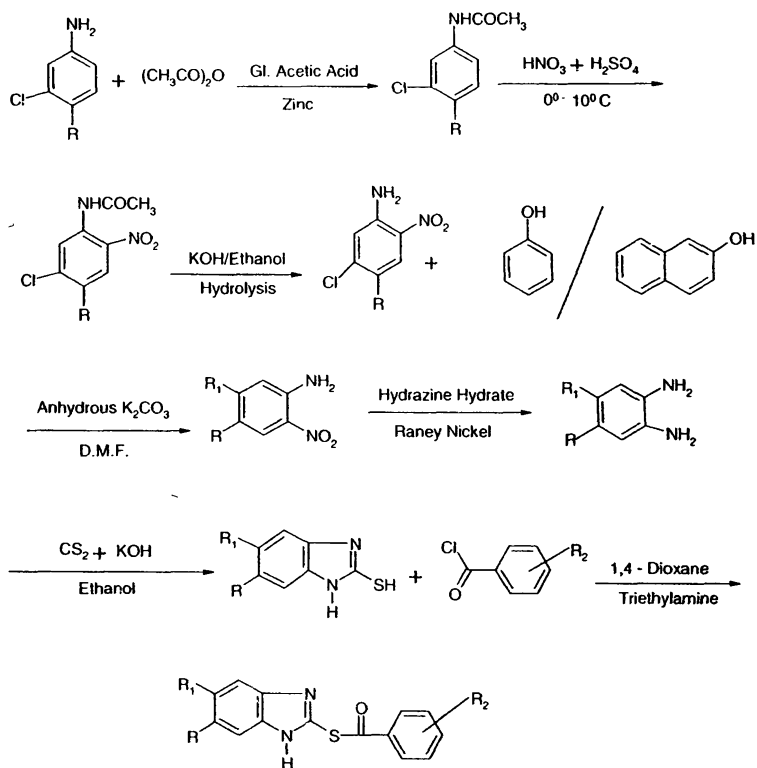
R₂ = H, Cl

Above, compounds were prepared by condensing 5,6-disubstituted-2-mercapto benzimidazoles with biologically active substituted / simple benzoyl chlorides, which have been further screened for their antifungal and antibacterial activities.

SCHEME - III

SCHEMATIC REPRESENTATION

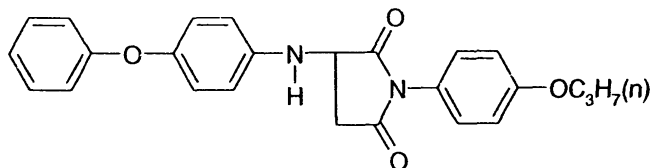
Synthesis of 5,6-Disubstituted-2-(Phenyl thiocarbamoyl) benzimidazoles



Where, $\text{R} = \text{H, Cl}$
 $\text{R}_1 = \text{Phenoxy, Naphthoxy}$
 $\text{R}_2 = \text{H, Cl}$

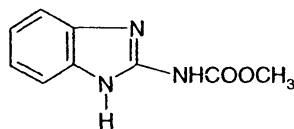
D] **5,6-Disubstituted-2-Phenoxyethyl Benzimidazoles :**

The compounds having ether linkage, namely, 3-(Phenoxy anilino)-N-(n-Propoxy Phenyl) succinimide (XVIII) which inhibited the growth of *M. tubercle* at a concentration of 0.06 $\mu\text{g/ml}^{33}$ *in vitro* testing.

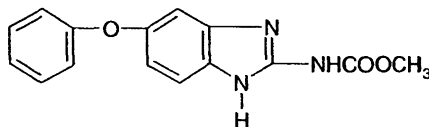


(XVIII)

The efficacy of 2-benzimidazole carbamate (XIX) was found even more than expected³⁴ by substituting phenoxy group at the fifth position of the benzimidazole (XX)



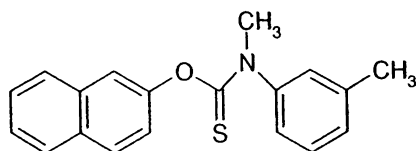
(XIX)



(XX)

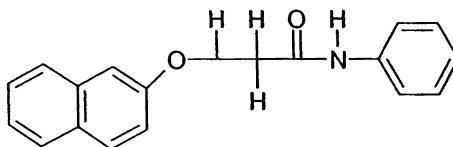
β -Naphthol has been used as an antiseptic, anthelmintic and counter irritant in alopecia³⁵.

β -Naphthol itself does not possess antitubercular activity but its derivatives are well known for their biological effects such as the drug 'Tolnaftate' introduced as an antifungal drug³⁶ having structural formula as shown below (XXI)



(XXI)

(β -Naphthoxy)-Propionanilide (XXII) is a wide spectrum herbicide for the paddies³⁷.



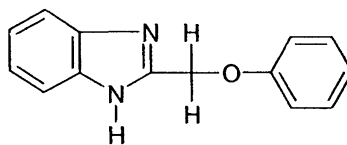
(XXII)

These findings gave us impetus to incorporate the Phenoxy, Naphthoxy molecule in the benzimidazole moiety at fifth position.

A large number of Benzimidazole derivatives have been reported to possess trypanosomicidal and spirocheticidal³⁸ actions and are active against disease caused by protozoa³⁸.

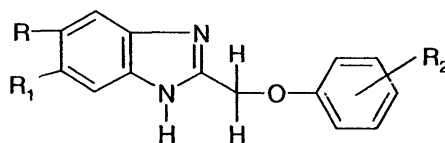
2-Alkoxyethyl Benzimidazoles possess anti-pyretic activity³⁹ some other substituents, when introduced in the position 2, impart antihistaminic⁴⁰, antimalarial⁴¹ and also their utility as local anaesthetics⁴².

It is considered, therefore to be worthwhile to synthesize 2-Phenoxymethyl Benzimidazoles (XXIII) involving variations in phenoxy nucleus for testing purposes⁴³.



(XXIII)

For, further enhancement of biological activity it is very interesting to substitute fifth and sixth position of above benzimidazole molecule (XXIV) to check the effect of substitution on the biological activity.



(XXIV)

R = Phenoxy, Naphthoxy

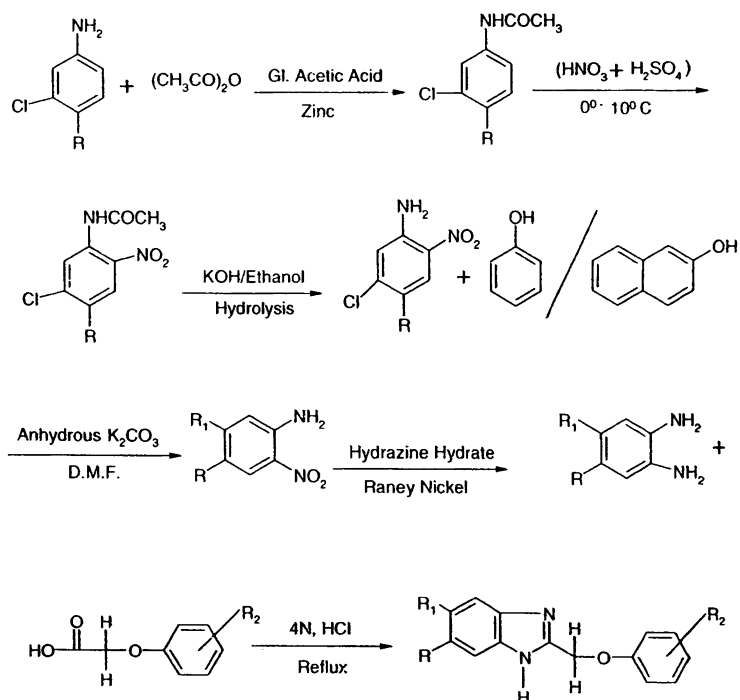
R₁ = Cl, H

R₂ = Cl, H

Above mentioned series of compounds were prepared by condensing 5-6-Disubstituted Ortho Phenylene Diamine with different biologically active substituted / simple phenoxy acetic acids to get respective compounds.

SCHEME - IV
SCHEMATIC REPRESENTATION

Synthesis Of 5,6 - Disubstituted - 2 - Phenoxyethyl Benzimidazoles



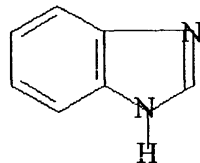
Where, R = H, Cl
 R₁ = Phenoxy, Naphthoxy
 R₂ = H, Cl

PART III– A

- 1) CHEMISTRY OF BENZIMIDAZOLE**
- 2) CHEMISTRY OF 2-MERCAPTO BENZIMIDAZOLE**

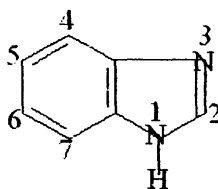
CHEMISTRY OF BENZIMIDAZOLE:

The benzimidazole contains a phenyl ring fused to an imidazole ring as indicated in the structure (I)



(I)

Since compounds of this type are formed by the loss of water, they were called “anhydro-bases” in the very early literature. Only compounds in which the Nitrogen containing groups were ortho to each other formed these compounds. They were expressed as derivatives of O-phenylene diamines. The numbering systems for benzimidazole (II) is as follows:



(II)

Benzimidazole which contains a hydrogen atom attached to nitrogen in the first position readily tautomerise⁴⁴.

Synthesis of benzimidazole:

The last systematic reviews on benzimidazoles were published in 1951⁴⁵ and 1953⁴⁶ although subsequent surveys have appeared in articles^{47,48} covering the chemistry of both imidazoles and benzimidazoles. In the latest reviews⁴⁹ a compilation of the synthesis, reactions and spectroscopic properties of benzimidazoles are presented.

General methods:

Synthesis of benzimidazoles starts practically with O-phenylene diamine. In the literature survey, we have come across the following methods used for the synthesis of benzimidazoles:

- a) By reacting O-phenylene diamines with carboxylic acids^{50,51}.
- b) By reacting O-phenylene diamines with acid chlorides^{52,53} ester⁵⁴ or acid anhydride⁵⁵.
- c) By reacting O-phenylene diamines with amide⁵⁶ or nitrile⁵⁷.
- d) By reacting O-phenylene diamines with aldehyde⁵⁸ or ketone⁵⁹.
- e) By reacting O-phenylene diamines with urea⁶⁰ or thiourea⁶¹.
- f) By reacting O-phenylene diamines with isothiocyanate⁶².

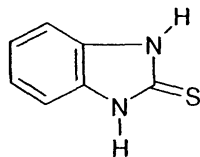
Properties of benzimidazoles:

The benzimidazole nucleus is very stable in character. Benzimidazoles are weakly basic, but somewhat less basic than imidazoles. Accordingly, they are, in general, soluble in dilute

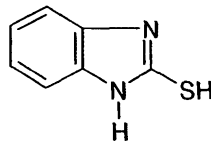
acids. Benzimidazoles are also sufficiently acidic to be soluble in aqueous alkali and form N- metallic compounds.

CHEMISTRY OF 2-MERCAPTOBENZIMIDAZOLE

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



(I)

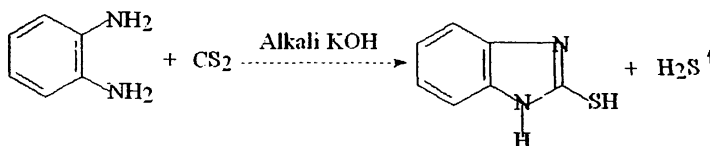


(II)

Different methods for preparation of 2-mercapto benzimidazole

a) Synthesis from O-phenylene diamine and carbon disulphide:

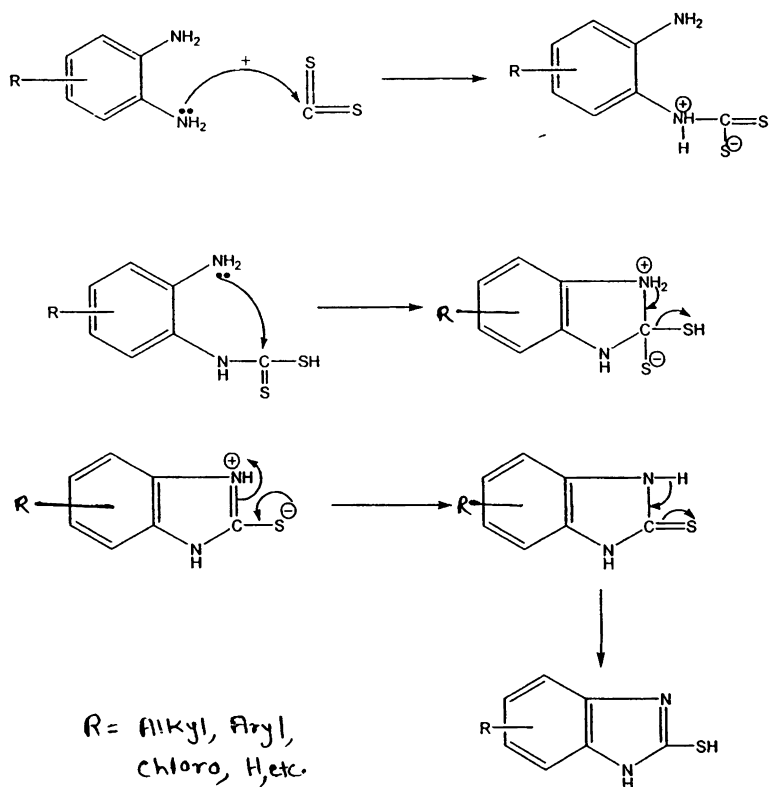
2 – mercapto benzimidazole, in general, may be prepared very conveniently by this method. The reaction is carried out usually by heating the reactants in alcoholic solution with or without the addition of alkali to the reaction mixture. 2-mercapto benzimidazole itself has been prepared by this method^{63, 64}.



(I)

O – phenylene diamines containing substituents on the phenyl ring have been used, which include those containing alkyl⁶⁵, halogen⁶⁶, phenyl⁶⁷, aniline⁶⁸ and sulphonamido⁶⁹ groups.

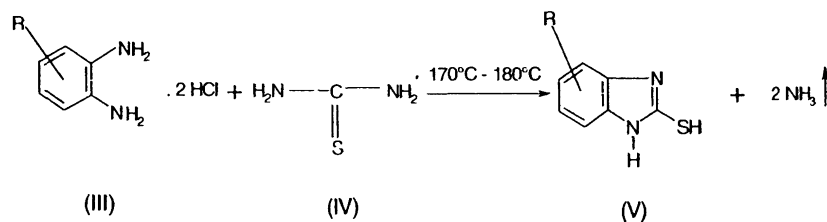
Probable reaction mechanism



b) Synthesis from O-phenylene diamine and thiourea:

This reaction is analogous to the preparation of 2-hydroxyl benzimidazole from O-phenylene diamines and urea. Substituted-2-mercaptobenzimidazoles (V) may be prepared by this method by heating substituted O-phenylene diamine dihydrochloride (III) and thiourea (IV) to 170 – 180°C⁶¹.

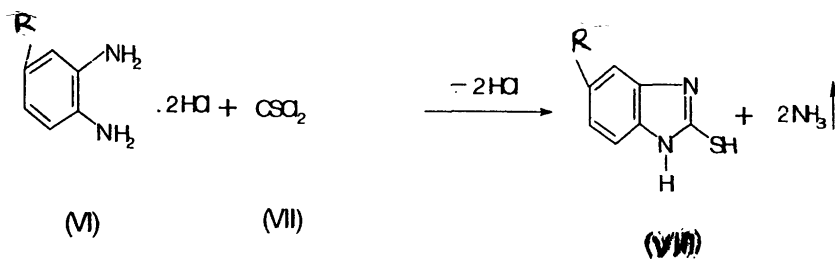
Excellent yields have been obtained by carrying out the reaction in amyl alcohol and heating under reflux until the evolution of ammonia becomes negligible.



R = alkyl, aryl, halogens

c) Synthesis from O – phenylene diamine and thiophosgene

Billeter and Steiner⁷⁰ obtained 2-mercapto benzimidazole (VIII) and 5-methyl-2-mercapto benzimidazole (VIII) by action of thiophosgene on O-phenylene diamine and 3,4-diamino toluene respectively. 3,4- diamino benzene arsonic acid and thiophosgene gave a 78% yield of 2-Mercapto Benzimidazole-5-arsonic acid⁷¹.



d) Miscellaneous methods

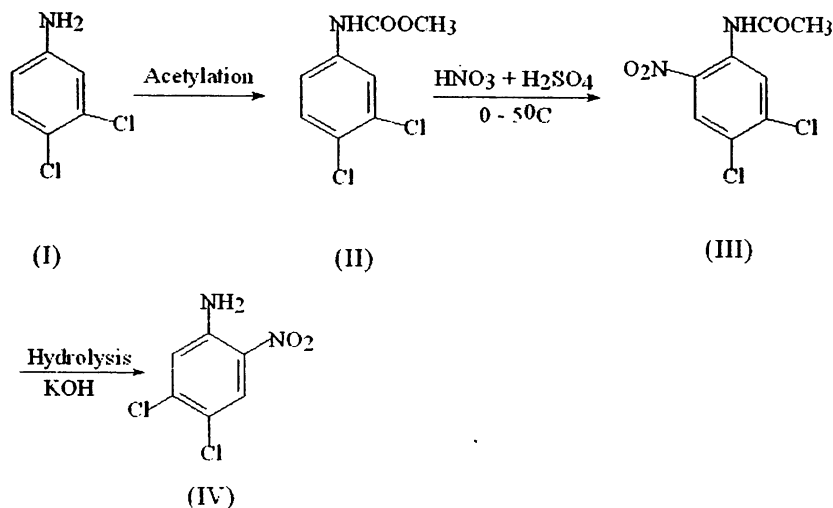
2 – mercapto benzimidazole can be prepared in 84 – 86.5 % yield by the action of potassium ethyl xanthate on O – phenylene diamine⁷². 2–mercapto benzimidazoles have also been prepared from O–phenylene diamine dihydrochloride and ammonium thiocyanate. A solution of the two substances is usually evaporated to dryness on a steam bath and then heated for short time. By this method, 2– mercapto benzimidazole⁶⁶ and 5 – chloro⁷³, 4 – methyl⁷⁴ and 5 – ethyl derivatives of 2 – mercapto benzimidazole have been prepared.

PART III- B: -

- 1. CHEMISTRY OF INTERMEDIATES**
- 2. CHEMISTRY OF ACID CHLORIDES**
- 3. CHEMISTRY OF REDUCTION OF NITRO COMPOUNDS**
- 4. CHEMISTRY OF SULFONYL CHLORIDE**

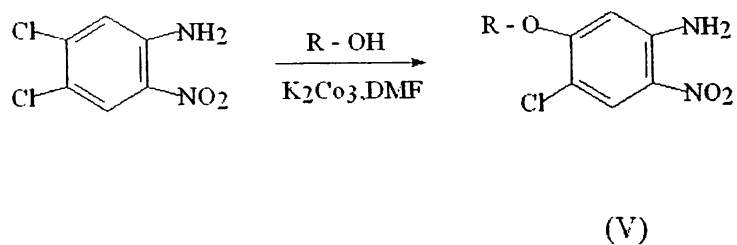
CHEMISTRY OF INTERMEDIATES:

4-chloro-5-substituted-ortho phenylene Diamine is the major intermediate required for the 5-substituted-6-chloro 2 mercapto benzimidazoles. The most convenient route adopted here is that from 3,4-Dichloro aniline (I). It was acetylated and the acetyl derivative (II) was nitrated with concentrated H_2SO_4 and concentrated HNO_3 at $0-5^\circ\text{C}$, exclusively 2-Nitro-4,5-Dichloro acetanilide (III) is obtained, which is further hydrolyzed by applying alkaline hydrolysis method to 2-nitro-4,5-Dichloro aniline (IV) as shown below:



The purified 2-Nitro-4,5-dichloro aniline (IV) was further reacted in the presence of anhydrous potassium carbonate with phenol, β -Naphthol to obtain the corresponding phenoxy and β -

Naphthoxy derivatives (V). The sequence of reaction could be explained as below: -



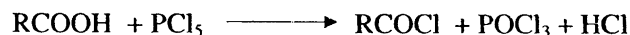
Where R = phenyl, β -Naphthyl.

The above (V) 2-Nitro-4-Chloro-5-substituted derivatives were further converted to corresponding ortho phenylene diamines by reduction with Raney Nickel in presence of Hydrazine Hydrate and ethanol used as solvent.

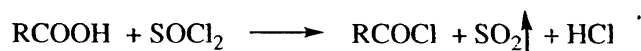
CHEMISTRY OF ACID CHLORIDES

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 the most important.

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

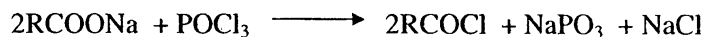


The use of thionyl chloride⁷⁵ for the preparation of acid chlorides presents many advantages in a large number of cases. The reaction result in the formation of Sulphur dioxide and hydrogen chloride in addition to the acid chloride, and the isolation of the chloride is for this reason, a simple matter.

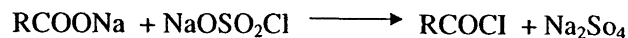
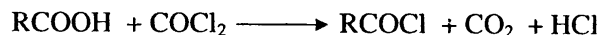


The thionyl chloride must be pure, as the impure product has been known to cause somewhat explosive decomposition in some instances. The procedure consists of mixing the chlorinating agent with acid and heating the mixture, if necessary. The product may be isolated by fractional distillation or if solid,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

Phosphorous oxychloride, 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.



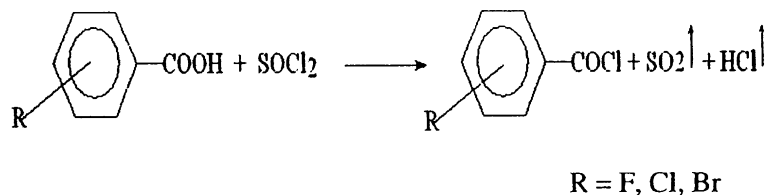
The reaction of phosgene⁷⁶ with carboxyl acids, and *p* – toluene sulphochloride or of sodium chlorosulphonate with salts of carboxylic acids are also used for the preparation of acid chlorides.



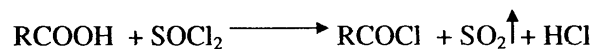
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The acid chlorides are obtained readily through the reaction of sulfonyl chlorides with anhydrous salts of organic acids. The reagents are well mixed and subjected to distillation.

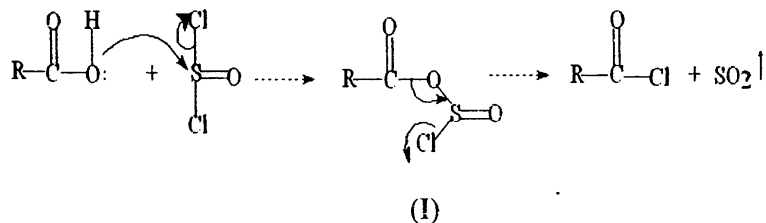
Thus, in the present work all the acid chlorides were prepared by reacting thionyl chloride with corresponding acids.



Reaction mechanism :



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



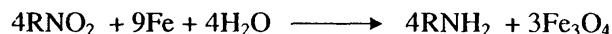
CHEMISTRY OF REDUCTION OF NITRO

COMPOUNDS:

It has long been known that the nature of the product actually formed depends critically upon the reduction conditions. Thus, although Nitro compounds were able to be reduced by using metals such as iron, tin, zinc (in acidic condition), sodium sulphide, ammonium polysulphide (in alkaline medium), ferric chloride, platinum dioxide and Raney nickel etc., the preferred reduction reaction was performed by using activated Raney nickel^{77,78}.

Reduction of nitro compounds involves the progressive replacement of oxygen in the – NO₂ group by hydrogen. Under suitable conditions, aromatic nitro compounds are readily reduced to amino compounds by means of acidic, reducing systems such as metals as iron and tin. In the solution of the metal in acetic acid, the nitro compound is reduced and the amine may be recovered from the reaction mixture by making it alkaline, by steam distillation or filtration.

If catalytic methods are eliminated, iron and zinc are the metals of choice for reductive procedures, in the research laboratory. The advantage of iron is that only a catalytic amount of acid is needed to be added and the iron oxide precipitates out to permit a relatively simple separation.



The disadvantage is that the quality of iron powder from various commercial sources is variable. Some powders give spontaneous, exothermic reduction. Reduction with this reagent may be carried out in benzene or aqueous alcohol. Furthermore, iron powder in acetic acid is capable of reducing aliphatic optically active nitro compounds to the amines with the retention of configuration⁷⁹. Indeed, iron powder and acetic acid is a favorable combination for reduction of aromatic nitro compounds. On the other hand, basic reducing agents such as lithium aluminium hydride lead to racemization.

Zinc is a powerful reducing agent, but utilization of its reducing action is wasteful because of rapid reaction with an acid such as HCl. Successful efforts are to be found out when an abundance of zinc is supplied during the entire reaction period. If the experimenter is fortunate, the hydrochloride of amine will separate but if unfortunate, he must make the entire mixture strongly alkaline and extract with suitable solvent. In this, very often a problem of emulsion formation comes across.

The present authors are impressed with the smooth generation of hydrogen from mossy tin and acid, but prejudiced the difficulty of work-up if the amine hydrochloride does not precipitate from the acid solution.

The entire mixture should be added slowly to a strong alkaline solution. If tin hydroxide precipitates and remains for any length of time, no reasonable amount of sodium hydroxide dissolves the flocculent solid. Certainly, this method does not lend itself well to large-scale reductions. On the other hand, stannous chloride is useful and selective reducing agent for nitro groups when carbonyl groups are present such as in reduction of *m* – nitrobenzaldehyde.

Reduction using Raney nickel

Since all the amino derivatives are highly susceptible to oxidation, the reduction was done by catalytic hydrogenation using Raney nickel as catalyst.

Catalytic methods:

This method^{80, 81, 82} is clean and work-up is so easy that it should be considered the method of choice in the research laboratory. The most common catalysts for the hydrogenation of nitro compounds are platinum and Raney nickel. Supporting catalyst such as platinum on carbon^{83, 84} palladium on carbon^{85, 86, 87} are used.

Solvents and media used for catalytic reductions

Any solvent that is pure and does not react with substrate or products of reduction can be used. Water is the safest solvent but many organic compounds are insoluble in it. The most commonly used ones are alcohol, particularly, methyl and ethyl alcohols. The vapors of methyl alcohol, however, may ignite in presence of palladium catalyst and some times with Raney nickel (depending on its activity). Nevertheless, it is safe if the catalyst is first added to some water provided that neither of these affects the reaction. Once the catalyst is completely covered, the alcohol can be safely added.

Benzene may be used (only if thiophene-free), although it attacks the rubber stoppers in the Parr apparatus and is itself strongly bound to the surface of most catalysts, resulting in decrease in reaction rate.

Solvents that form peroxide should be avoided. For example, dioxane should be used after thorough purification and distillation.

Addition of catalyst:

In general, catalysts active in low-pressure reductions can be safely added to ethyl alcohol. If a large amount of catalyst is to be used, it should be added in portions and mixed until it is wetted with the solvent before another addition is made.

One should not attempt to carry out reduction in pressure reactor, filled beyond about 60-65% capacity, because a free space that is too small results in poor mixing and prolonged reaction time.

Equipment:

For operation, the vessel containing solvent, reactant and catalyst is placed in the reactor, hydrogen is added upto 150 psi and the stirrer is started with heating. The progress of reaction is followed by observation of the drop in pressure. Although, catalytic hydrogenation is potentially hazardous, with proper care it can be as safe as any chemical reaction. After hydrogenation, most catalysts (except for copper chromate) are more pyrophoric

because of hydrogen absorbed on their surface during the reduction. Therefore, care must be taken during filtration. The filter paper must be covered with liquid at all times and not allowed to become dry. Any spent catalyst can be destroyed by digestion in hydrochloric acid. Do not heat the reaction mixture to the desired working temperature before starting agitation. This may be safe under low-pressure conditions but can be hazardous in higher-pressure reductions.

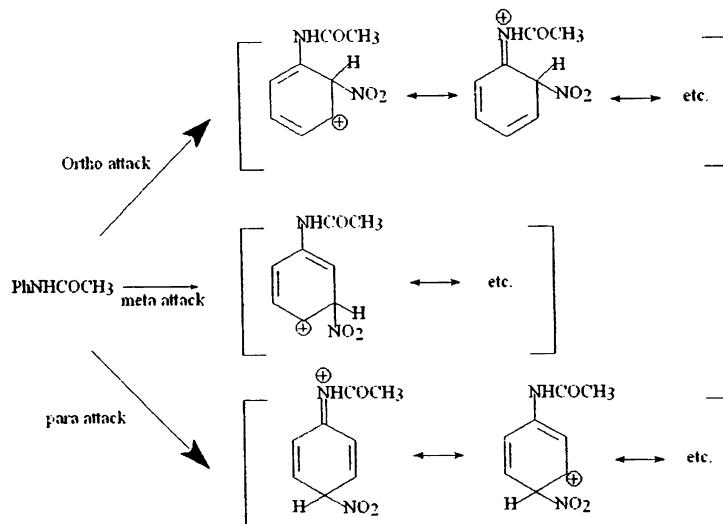
The overall yields of catalytic hydrogenation experiments are 60-80 % and the products obtained in this case are in fairly pure state.

Reduction of 5,6 – Disubstituted Ortho Nitro Anilines⁸⁸:

This reaction is very simple & does not involve external hydrogen gas, so it is non – hazardous. In this reaction first Raney Nickel & 80% Hydrazine hydrate is suspended in alcohol in round bottom flask, reaction is carried on water bath as soon as alcohol starts boiling the slow addition of 5,6 – Disubstituted Ortho phenylene diamine dissolved in alcohol is carried out for 15-20 minutes. After completion of addition, reaction was further refluxed for 6 – 7 hours then Raney Nickel was filtered off and solution was reduced by vacuum distillation and excess of alcohol was removed. Solution was poured on crushed ice & compound obtained, which was further recrystallized by using suitable solvent such as benzene – pet ether (60-80) mixture.

Nitration of acetanilide:

Representative structures for each of the possible cation intermediates are shown as follows⁸⁹ :

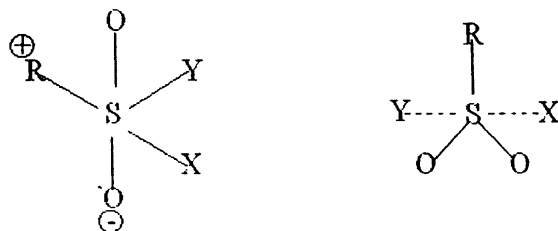


In the intermediate for Meta attack, the positive charge carried in by the NO_2^+ ion must remain on the benzene ring until the proton departs, completing the substitution reaction. On the other hand, with ortho or para attack, π electron density drifts from the electron rich nitrogen atom into ring, dispersing the positive charge, and lowering the energy both of the intermediate and the transition state leading to it. It is thus concluded that in the nitration of acetanilide, ortho and para position are readily attacked than meta positions, although it can't be said that whether it is ortho or para position which is more reactive.

In case of acetanilide nitrogen bound to ring has one unshared and available pair of electron, and in each case electron density from this pair drifts into the ring to help dispersion the positive charge carried on by the electrophile attacking either at the ortho or the para position.

Chemistry of Sulfonyl Chloride:

Sulfonamides are highly crystalline particularly the derivatives from Sulfonyl Chloride. The preparation of sulfonamide from sulfonyl chloride is a nucleophilic substitution at RSO_2Cl in a manner similar to the attack of R-COCl , but the mechanism is not the same because a 'tetrahedral' intermediate in this case (I) would have five groups on the central atom⁹⁰.



(I)

Preparation of Sulfonyl Chloride: -

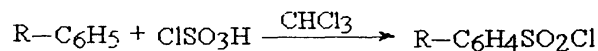
The Sulfonyl Chlorides are prepared by various methods: -

Douglass and Johnson included two thio esters in their general study of the oxidative chlorination of divalent sulfur compounds. They obtained 71% yield of ethane sulfonyl chloride from ethyl thiol acetate and a mixture of benzyl disulfide, benzyl phenyl methane thio sulfonate, and phenyl methane sulfonyl chloride from benzyl thiol acetate⁹¹.

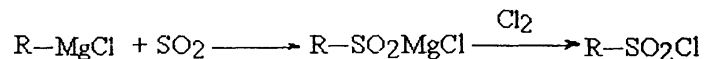
Chlorosulfonic acid is utilized for the conversion of aromatic hydrocarbons to sulfonyl derivatives and can be used in the characterization of unknown hydrocarbons⁹².

In this, Chlorosulfonyl chloride is used to provide the Sulfonyl Chloride ($-\text{SO}_2\text{Cl}$) group to the aromatic hydrocarbon.

Thus, the Sulfonyl Chloride group is introduced to the aromatic nucleus by treatment with an excess of Chlorosulfonic acid in chloroform⁹³.



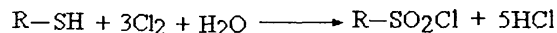
Sulfonyl chlorides have also been prepared by the reaction of Grignard reagent first with SO_2 , and then with chlorine gas⁹⁴.



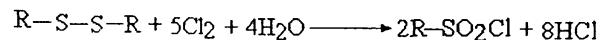
Aliphatic hydrocarbons can also be chlorosulfonated with sulfonyl chloride derivatives⁹⁵, e.g. 2,3-dimethyl butane yields 20% of 2,3-dimethyl butane-1-sulfonyl chloride.

More recently⁹⁶ $(\text{CH}_3)_2\text{CHSCH}_2\text{CO}_2\text{H}$ the sulfide acid (4.71 g.) was subjected to the procedure under "Exhaustive Chlorination". The crude product contained 2-acetoxy propane (1.499 g.), 2-propane sulfonyl chloride (2.284 g.), and Dichloro methane sulfonyl chloride (2.509 g.), determined by a method⁹⁷.

Mercaptans or disulfides on reaction with chlorine in aqueous hydrochloric acid can be converted to sulfonyl chloride⁹⁸. Thus methane mercaptan is converted into methane sulfonyl chloride by simultaneous hydrolysis and chlorination at $40^0\text{-}70^0\text{C}$ in saturated HCl .



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



There are relatively few heterocyclic sulfonamides in which the sulfur atom is joined directly to a carbon of heterocyclic ring. In such a case, sulfonyl chlorides are usually prepared by chlorosulfonation or conversion to sulfonic acid and acid chloride, followed by the amidation to get sulfonamide. The oxidative chlorination at low temperature of such heterocycles has been found to be quite widely applicable for the preparation of these compounds.

Some exceptions have been found in general application of the method to the preparation of sulfonyl chlorides. The instability of many sulfonyl chlorides may account for the exception. On long standing of oxidative chlorination, the decomposition of the product was found to give the corresponding chloro derivative, e.g. 2-mercapto benzimidazole converted to 2-chloro benzimidazole when the reaction is carried out for a long period at room temperature⁹⁹.

PART IV: -

EXPERIMENTAL

- ❖ SYNTHESIS OF SOME 5,6-DISUBSTITUTED-2- (N, N-DIALKYL THIOCARBAMIDO) BENZIMIDAZOLES.

EXPERIMENTAL: -

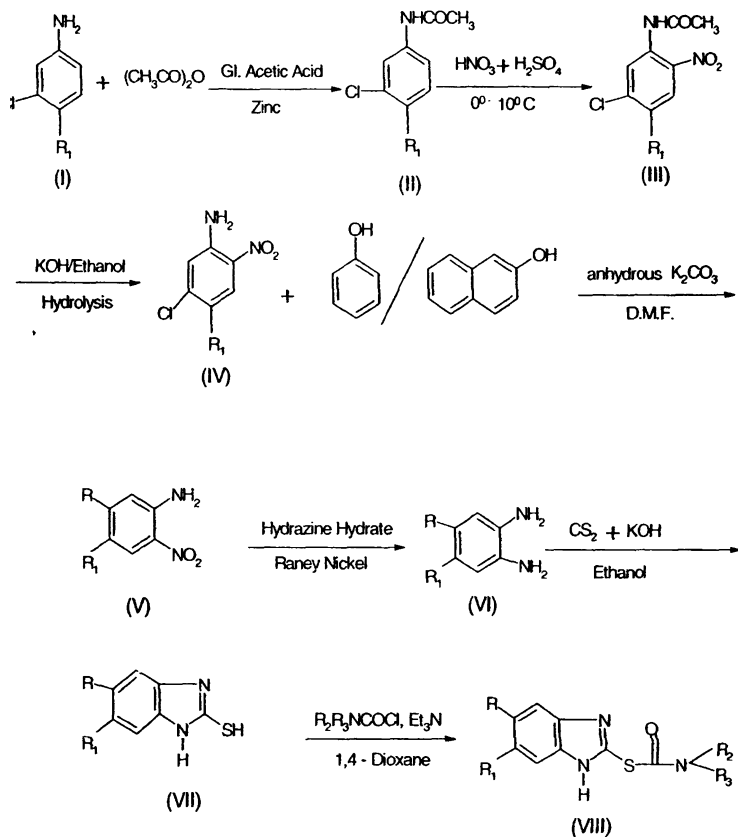
This section deals with the synthesis of 5,6-disubstituted-2-(N,N-dialkyl thiocarbamido) benzimidazoles which involves the following steps.

- 1) Preparation of 3,4-dichloro acetanilide.
- 2) Preparation of 4,5-dichloro-2-nitro acetanilide.
- 3) Preparation of 4,5-dichloro-2-nitro aniline.
- 4) Preparation of 4-chloro-5-Phenoxy/Naphthoxy-2-nitro-aniline.
- 5) Preparation of 4-Chloro-5-Phenoxy/Naphthoxy-ortho phenylene diamine (O.P.D.A).
- 6) Preparation 6-chloro-5-Phenoxy/Naphthoxy-2-mercapto benzimidazole.
- 7) Preparation of 6-Chloro-5-Phenoxy/Naphthoxy-2-(N,N-dialkyl thiocarbamido) benzimidazoles.

SCHEME - I

SCHEMATIC REPRESENTATION

Synthesis of 5,6-disubstituted-2-(N,N-dialkyl thiocarbamido) Benzimidazoles



Where,
 $\text{R}_1 = \text{H}, \text{Cl}$
 $\text{R} = \text{Phenoxy, Naphthoxy}$
 $\text{R}_2 = \text{R}_3 = -\text{CH}_3, -\text{C}_2\text{H}_5$

1) **Preparation of 3,4-dichloro acetanilide (II): -**

In a 500 ml round-bottomed flask equipped with a reflux condenser was placed 3,4-dichloro aniline (I) (33g, 0.2 mol), acetic anhydride (21 ml, 0.2 mol), acetic acid (14 ml, 0.2mol) and 0.1 gm of zinc dust. The reaction mixture was refluxed for 30-45 minutes and then was allowed to cool down at room temperature. It was then poured into 500 ml of ice-water mixture. The solid separated was filtered, washed with cold water and dried. It was then recrystallized from 40 % aqueous ethanol.

Yield: - 36 g. (88%) m.p. 119-120°C
(Lit.¹⁰⁰ m.p. 121°C)

2) **Preparation of 4,5-dichloro-2-nitro acetanilide (III) :-**

A solution of 3,4-dichloro acetanilide (II) 10.2 g. (0.05 mol.) in 15 ml concentrated sulphuric acid was taken into 500 ml three-necked round bottomed flask, equipped with a mechanical stirrer, a thermometer and a dropping funnel. It was stirred at 0⁰-10⁰C. Nitrating mixture (Conc. H₂SO₄ 12 ml, d 1.84 and nitric acid 3.5 ml, d 1.42) was added drop wise at 0⁰ to 10⁰ C. The reaction mixture was stirred for further 2 hours at this temperature. Then reaction mixture i.e., nitrating product was precipitated by pouring the reaction mixture on crushed ice with vigorous stirring, the temperature being maintained at 0⁰C. It was neutralized by liquor ammonia; the crude 4,5-dichloro-2-nitro acetanilide was filtered, washed with ice-cold water,

until neutral pH. The product was recrystallized from ethanol.

Yield: - 9.5 g. (76.5 %) m.p. 123⁰C.
(Lit.¹⁰¹ m.p. 122⁰-124⁰C)

3) **Preparation of 4,5-dichloro-2-nitro aniline (IV): -**

To a solution of 24.9 g. (0.1 mol) of 4,5-dichloro-2-nitro acetanilide (III) in 30 ml of boiling ethyl alcohol was added solution of 5.6 g. (0.1 mol) of KOH in 10 ml of water. It was refluxed for 40 minutes then was diluted with 120 ml of water and distilled until 75 ml of distillate (alcohol and water) was collected. The residue was poured into 150 ml of cold water. The 4,5-dichloro-2-nitro aniline was separated out. It was filtered at the pump and washed with cold water. The crude material was purified from ethanol.

Yield: - 15.69 g. (75.80 %) m.p. 176⁰C
(Lit.¹⁰² m.p. 178⁰-179⁰C)

4) **Preparation of 4-chloro-5-phenoxy/Naphthoxy-2-Nitroaniline (V): -**

A mixture of 2.07 g. (0.01 mol.) of 4,5-dichloro-2-nitro aniline (IV) and 0.94g (0.01 mol.) of phenol or 1.44 g. (0.01 mol.) β – Naphthol with 0.99 g. (0.01 mol.) of potassium carbonate was heated at 115⁰-120⁰C for 6-8 hours in Dimethyl formamide (D.M.F.) with constant stirring. Reaction mixture was kept overnight at room temperature, then it was poured into crushed ice the solid product separated was filtered and recrystallized twice from ethanol.

TABLE - 1

Sr.No.	Product (Name)	Yield (g.)	m.p. (⁰ C)	Elemental Analysis					
				Calculated			Found		
	(Molecular Formula & Molecular Weight)	(%)		% C	%H	% N	%C	%H	%N
1)	4-chloro-2-nitro-5- phenoxy aniline [C ₁₂ H ₉ O ₃ N ₂ Cl] [264.5]	1.88 g. (71.5%)	134 ⁰ C	54.442	3.402	10.586	54.378	3.391	10.498
2)	4-chloro-2-nitro-5- Naphthoxy aniline [C ₁₆ H ₁₁ O ₃ N ₂ Cl] [314.5]	2.07 g. (69.0%)	165 ⁰ C	61.049	3.497	8.903	60.985	3.385	8.813

5) **Preparation of 4-chloro-5-Phenoxy/Naphthoxy ortho phenylene diamine (VI) :-**

In a 500 ml three necked round-bottomed flask equipped with a mechanical stirrer, dropping funnel and a reflux condenser was placed 1g. of Raney Nickel and 80% hydrazine hydrate (10 ml, 0.16 mol.) in 30 ml ethanol. The mixture was heated at 40⁰-50⁰C. To this 4-chloro-5-phenoxy-2-nitro aniline (13.225 g.; 0.05 mol.) (V) or 4-chloro-5-Naphthoxy-2-nitro aniline (15.725 g., 0.05 mol.) (V) In 25 ml alcohol was added drop wise. The reaction mixture was refluxed for 4-6 hours till reduction was completed, monitored by T.L.C. The solution was filtered to remove Raney Nickel which was decomposed in 10% dil. HCl. Excess of ethanol was distilled out under vacuum. The concentrated solution was brought down at room temperature and poured into crushed ice; Solid separated was filtered, dried and recrystallized from benzene pet ether (60-80) mixture.

TABLE - 2

Sr. No.	Product (Name) (Molecular Formula & Molecular Weight)	Yield (g.) (%)	m.p. (^o C)	Elemental Analysis					
				Calculated			Found		
				% C	%H	% N	%C	%H	%N
1)	4-chloro-5-phenoxy ortho phenylene Diamine [C ₁₂ H ₁₁ O ₁ N ₂ Cl] [234.5]	6.435 g. (55%)	84 ^o -85 ^o C	61.407	4.690	11.940	61.337	4.619	11.860
2)	4-chloro-5-Naphthoxy ortho phenylene Diamine [C ₁₆ H ₁₃ O ₁ N ₂ Cl] [284.5]	8.236 g. (58%)	145 ^o C	67.486	4.569	9.841	67.398	4.513	9.798

6) **Preparation of 6-chloro-5-Phenoxy/Naphthoxy-2-mercapto benzimidazole (VII): -**

To potassium hydroxide (0.56 g., 0.01 mol) was added 15 ml ethanol and 3 ml water & potassium hydroxide was dissolved thoroughly. The mixture was kept in ice bath & carbon disulfide (1.35g, 1.1 ml, 0.017 mol.) was added with constant stirring thus potassium ethyl xanthate solution was prepared.

In a 250 ml three necked round-bottomed flask equipped with a dropping funnel and a reflux condenser was placed 4-chloro-5-Phenoxy O.P.D.A. (2.84g, 0.01 mol.) (VI) Or 4-chloro-5-Naphthoxy O.P.D.A (2.34 g, 0.01 mol.) (VI) In 20 ml ethanol. To this, above potassium ethyl xanthate solution was added drop wise. The mixture was further refluxed for 6-8 hours until fumes of hydrogen sulfide gas ceases. The reaction mixture was cooled and then concentrated vacuum to remove most of ethanol. The concentrated solution was poured on crushed ice and neutralized with dil. Hydrochloric acid. The solid separated was filtered, washed with water and dried. It was then recrystallized from ethanol.

TABLE – 3

Sr. No.	Product (Name)	Yield (g.)	m.p. (°C)	Elemental Analysis					
				Calculated			Found		
	(Molecular Formula & Molecular Weight)	%		% C	% H	% N	% C	% H	% N
1)	6-Chloro-5-Phenoxy-2- mercapto benzimidazole [C ₁₃ H ₉ O ₁ N ₂ S ₁ Cl ₁] [276.5]	5.046 g. (73 %)	228 ⁰ C-230 ⁰ C	56.419	3.254	10.126	56.375	3.213	10.075
2)	6-Chloro-5- Naphthoxy-2-mercapto benzimidazole [C ₁₇ H ₁₁ O ₁ N ₂ S ₁ Cl ₁] [326.5]	6.121 g. (75 %)	238 ⁰ C-240 ⁰ C	62.480	3.369	8.575	62.398	3.303	8.498

7) **Preparation of 6-chloro-5-Phenoxy/Naphthoxy-2-(N,N-dialkyl thiocarbamido) benzimidazoles (VIII) :-**

In a 250ml three necked flask equipped with a dropping funnel, mechanical stirrer and a reflux condenser was placed a solution of 6-chloro-5-phenoxy-2-mercapto benzimidazole (0.553g, 0.002 mol.) (VII) Or 6-chloro-5-Naphthoxy-2-mercapto benzimidazole (0.653g, 0.002 mol.) (VII) In 10ml dry 1,4-dioxane and triethylamine (0.10g, 0.003 mol.). It was stirred at 40⁰-50⁰C for about 15 minutes. To this N,N-diethyl/dimethyl carbamoyl/chloride (0.003 mol.) in 10 ml dry 1,4-dioxane was added drop wise with stirring. The reaction mixture was stirred at 50⁰-60⁰C for about 4-6 hours. It was kept overnight at room temperature. The solution was poured into crushed ice. The solid separated was filtered, washed with water and dried. It was then recrystallized from absolute ethanol.

5,6-disubstituted-2-(N,N-dialkyl thiocarbamido) Benzimidazoles :-

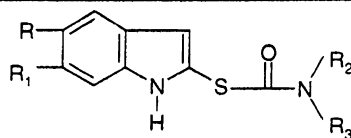


TABLE - 4

								Elemental Analysis					
Sr. No.	R	R ₁	R ₂ = R ₃	Molecular Formula	Mol. Wt	m.p. (°C)	Yield (%)	Required			Found		
								%C	% H	% N	% C	% H	% N
1)	Phenoxy	Cl	CH ₃	C ₁₆ H ₁₄ N ₃ ClSO ₂	347.5	244	70	55.251	4.028	12.086	55.175	3.961	11.986
2)	Phenoxy	H	CH ₃	C ₁₆ H ₁₅ N ₃ SO ₂	313	230	68	61.341	4.792	13.418	61.298	4.725	13.981
3)	Phenoxy	Cl	C ₂ H ₅	C ₁₈ H ₁₉ N ₃ ClSO ₂	376.5	255	72	57.370	5.046	11.155	57.298	4.995	11.098

5,6-disubstituted-2-(N,N-dialkyl thiocarbamido) Benzimidazoles :-

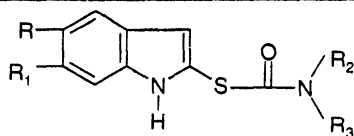


TABLE - 4

4)	Phenoxy	H	C ₂ H ₅	C ₁₈ H ₂₀ N ₃ SO ₂	342.0	249	66	63.157	5.847	12.280	63.103	5.805	12.198
5)	Naphthoxy	Cl	CH ₃	C ₂₀ H ₁₆ N ₃ ClSO ₂	397.5	261	73	60.377	4.025	10.566	60.281	3.991	10.498
6)	Naphthoxy	H	CH ₃	C ₂₀ H ₁₇ N ₃ SO ₂	363.0	252	71	66.115	4.683	11.570	65.971	4.631	11.510
7)	Naphthoxy	Cl	C ₂ H ₅	C ₂₂ H ₂₀ N ₃ ClSO ₂	425.5	278	75	62.044	4.700	9.870	61.901	4.622	9.809
8)	Naphthoxy	H	C ₂ H ₅	C ₂₂ H ₂₁ N ₃ SO ₂	391	263	72	67.519	5.370	10.741	67.429	5.321	10.692

PART V
EXPERIMENTAL

- ❖ SYNTHESIS OF SOME 5-SUBSTITUTED-2- (1-H-BENZIMIDAZOLE) SULFONAMIDES

EXPERIMENTAL:

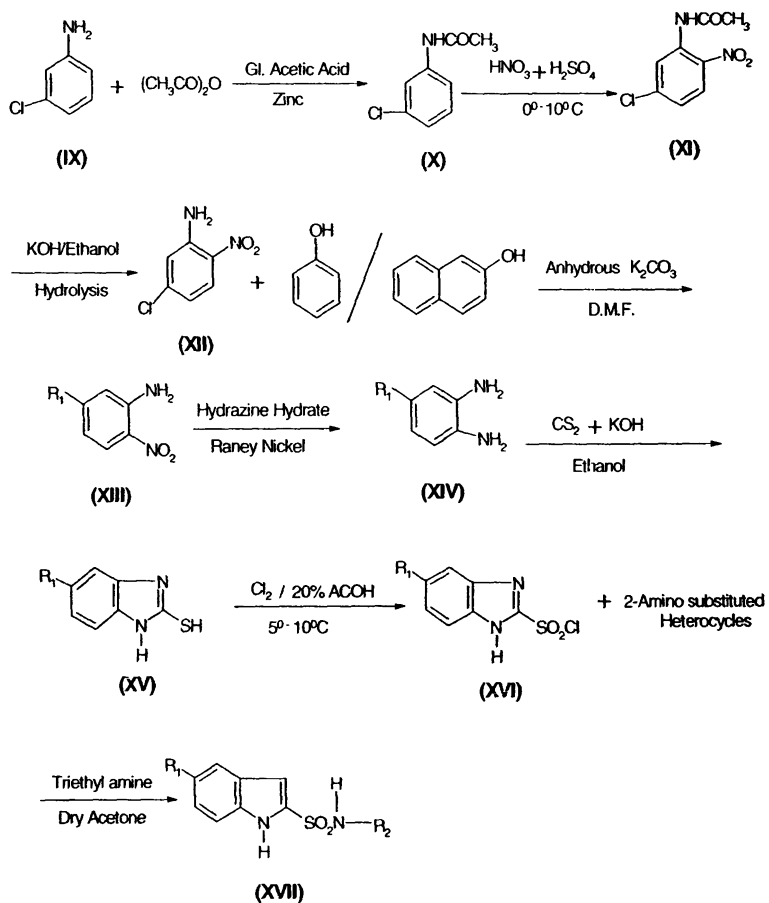
This section deals with the synthesis of some 5-substituted-2-(1-H-benzimidazole) sulfonamides which involves the following steps:

- 1) Preparation of 3-Chloro acetanilide.
- 2) Preparation of 5-Chloro-2-nitro acetanilide.
- 3) Preparation of 5-Chloro-2-nitro aniline.
- 4) Preparation of 5-Phenoxy/Naphthoxy-2-nitro aniline.
- 5) Preparation of 5-Phenoxy/Naphthoxy ortho phenylene Diamine.
- 6) Preparation of 5-Phenoxy/Naphthoxy-2-mercapto benzimidazole.
- 7) Preparation of 5-Phenoxy/Naphthoxy-2-benzimidazole sulfonyl chloride.
- 8) Condensation of 5-Phenoxy/Naphthoxy-2-benzimidazole sulfonyl chloride with various 2-amino heterocycles to synthesize title compound derivatives.

SCHEME - II

SCHEMATIC REPRESENTATION

Synthesis of 5-substituted-2-(1-H-benzimidazole) Sulfonamides



Where, R_1 = Phenoxy, Naphthoxy
 R_2 = Substituted Heterocycles, H

1) **Preparation of 3-Chloro acetanilide (X): -**

In a 500 ml round-bottomed flask, equipped with a reflux condenser, was placed 28.05 g. (0.22 mol.) of m-chloro aniline (IX), 22.45 g. (20.78 ml, 0.22 mol) of acetic anhydride, 13.21 g. (12.7 ml; 0.22 mol) of glacial acetic acid and 0.1g. Of zinc dust. The mixture was boiled gently for 30 minutes and then the hot liquid was poured in a thin stream into a one-liter beaker containing 500 ml of cold water with constant stirring. The reaction mixture was poured into ice and the crude product was filtered at the pump, washed with a little cold water, dried and recrystallized from ethanol.

Yield: - 32.64g. (80%) m.p. 78⁰C
(Lit.¹⁰³ m.p. 77⁰-79⁰C)

2) **Preparation of 5-chloro-2-Nitro acetanilide (XI): -**

A solution of 3-chloro acetanilide 8.475g. (0.05 mol.) (X) In 10 ml concentrated sulphuric acid was taken into 500 ml three necked round bottomed flask, equipped with a mechanical stirrer, a thermometer and a dropping funnel. It was stirred at 0⁰-10⁰C Nitrating mixture (Conc. H₂SO₄, 10 ml, d-1.84 and nitric acid 2.2 ml, d-1.42) was added dropwise at 0⁰-10⁰C. The reaction mixture was further stirred for 2 hours at this temperature.

Then reaction mixture i.e. nitrating product was precipitated by pouring the reaction mixture on crushed ice with vigorous stirring, the temperature being maintained at 0⁰C. It was neutralized by liquor ammonia; the crude 5-

chloro-2-nitro acetanilide was filtered, washed with ice-cold water, until neutral PH. The product was recrystallized from ethanol.

Yield: - 8.045g. (75%) m.p. 116⁰C
(Lit.¹⁰⁴ m.p. 116⁰-118⁰C)

3) **Preparation of 5-Chloro-2-Nitro aniline (XII): -**

To a solution of 21.45g. (0.1 mol.) Of 5-chloro-2-Nitro acetanilide (XI) in 30 ml of boiling ethyl alcohol added a solution of 5.6g. (0.1 mol.) Of KOH in 10 ml of water. It was refluxed for 40 minutes. It was diluted with 120 ml water and distilled until 75 ml of distillate (alcohol and water) was collected. The residue was poured into ice-cold water. The 5-chloro-2-nitro aniline was separated out. It was filtered at the pump and washed with cold water. The crude material was purified from ethanol.

Yield: - 13.041g. (75.6%) m.p. 121⁰C
(Lit.¹⁰⁵ m.p. 122⁰-124⁰C)

4) **Preparation of 5-Phenoxy/Naphthoxy-2-Nitro aniline (XIII): -**

A mixture of 1.725g. (0.01 mol.) of 4,5-dichloro-2-nitro aniline (XII) and 0.94 g. (0.01 mol.) of Phenol or 1.44g. (0.01 mol.) Of β -Naphthol with 0.99 g. (0.01 mol.) of potassium carbonate was heated at 115⁰-120⁰C for 6-8 hours in Dimethyl Formamide (D.M.F.) with constant stirring. Reaction mixture was kept overnight at room temperature, then it was poured into crushed ice the solid product separated was filtered and recrystallized twice from ethanol.

TABLE - 5

Sr. No.	Product (Name)	Yield (g.)	m.p. (°C)	Elemental Analysis					
				Calculated			Found		
	(Molecular Formula & Molecular Weight)	(%)		% C	%H	% N	%C	%H	%N
1)	5-phenoxy-2-Nitro aniline, [C ₁₂ H ₁₀ O ₃ N ₂] [230]	1.656 g. (72%)	103 ⁰ - 105 ⁰ C	62.608	4.347	12.173	62.578	4.306	12.075
2)	5-Naphthoxy-2-Nitro aniline [C ₁₆ H ₁₂ O ₃ N ₂] [280]	1.960 g. (70%)	115 ⁰ - 117 ⁰ C	68.571	4.285	10.000	68.483	4.188	9.915

5) **Preparation of 5-Phenoxy / Naphthoxy Ortho
Phenylene Diamine (XIV): -**

In a 500 ml three necked round-bottomed flask equipped with a mechanical stirrer, dropping funnel and reflux condenser was placed 1g. Of Raney Nickel and 80% hydrazine hydrate at (10 ml, 0.16 mol.) in 30 ml ethanol. The mixture was heated at 40⁰ - 50⁰ C. To this 5-phenoxy-2-Nitro aniline (11.5 g, 0.05 mol.) (XIII) Or 5-Naphthoxy-2-Nitro aniline (14.0g, 0.05mol.) (XIII) In 25 ml alcohol was added dropwise. The reaction mixture was refluxed for 4-6 hours till reduction was completed, monitored by T.L.C. The solution was filtered to remove Raney Nickel which was decomposed in 10% dil. HCl. excess of ethanol was distilled under vacuum. The concentrated solution was brought down at room temperature and was poured into crushed ice. Solid separated was filtered, dried and recrystallized from benzene-pet ether (60-80) mixture.

TABLE - 6

Sr. No.	Product (Name)	Yield (g.)	m.p. (°C)	Elemental Analysis					
				Calculated			Found		
	(Molecular Formula & Molecular Weight)	(%)		% C	%H	% N	%C	%H	%N
1)	5-phenoxy ortho Phenylene Diamine [C ₁₂ H ₁₂ O ₁ N ₂] [200]	5g. (50%)	60 ⁰ -62 ⁰ C	72.000	6.000	14.000	71.935	5.986	13.905
2)	5-Naphthoxy ortho Phenylene Diamine [C ₁₆ H ₁₄ O ₁ N ₂] [250]	6.5 g. (52%)	75 ⁰ -77 ⁰ C	76.800	5.600	11.200	76.713	5.581	11.105

6) **Preparation of 5-Phenoxy/Naphthoxy-2-mercapto benzimidazole (XV): -**

To potassium Hydroxide (0.56 g., 0.01 mol.) was added 15 ml ethanol and 3 ml water & potassium hydroxide was dissolved thoroughly. The mixture was kept in ice-bath and carbon disulfide (1.35 g., 1.1 ml, 0.017 mol.) was added with constant stirring thus potassium ethyl xanthate solution was prepared.

In a 250 ml three necked round-bottomed flask equipped with a dropping funnel and a reflux condenser was placed 5-Phenoxy O.P.D.A. (2.00 g., 0.01 mol.) (XIV)
Or 5-Naphthoxy O.P.D.A. (2.50

TABLE - 7

Sr. No.	Product (Name)	Yield (g.)	m.p. (⁰ C)	Elemental Analysis					
				Calculated			Found		
	(Molecular Formula & Molecular Weight)	%		% C	% H	% N	% C	% H	% N
1)	5-Phenoxy-2- mercapto benzimidazole [C ₁₃ H ₁₀ O ₁ N ₂ S ₁] [242]	4.29 g. (71 %)	245 ⁰ C-247 ⁰ C	64.462	4.132	11.570	64.399	4.103	11.485
2)	5-Naphthoxy-2- mercapto benzimidazole [C ₁₇ H ₁₂ O ₁ N ₂ S ₁] [292]	5.04 g. (69 %)	260 ⁰ C-262 ⁰ C	69.863	4.109	9.589	69.785	3.088	9.473

7) **Preparation of 5-Phenoxy/Naphthoxy-2-benzimidazole**
Sulfonyl Chloride (XVI): -

5-phenoxy-2-mercapto benzimidazole 2.42 g. (0.01 mol.) (XV)/ 5-naphthoxy-2-mercapto benzimidazole 2.92 g. (0.01 mol.) (XV) Was charged to a jacketed vessel, followed by 17.3 ml (0.302 mol.) of acetic acid and 2.2 ml of water (0.12 mol.) stirring was commenced (300 rpm) and the mixture was heated to 30⁰ C to completely dissolve the solids. A nitrogen purge was then applied and the vessel content cooled to approximately 4⁰ C. The nitrogen flow was stopped, the vessel was sealed, and chlorine gas was bubbled into the mixture over 35 minutes (Tmax 13.8⁰ C). A green coloration developed and the chlorine supply was shut off. The green coloration discharged after several seconds indicating that the reaction was not completed and addition of chlorine was resumed for 5 minutes resulting in an exotherm from 11.6⁰ C- 13.3⁰ C. The green color persisted after shutting off the chlorine supply indicating that end of reaction had been reached. Total amount of chlorine used was 2.56 g. (90.036 mol.). The vessel was vented to the atmosphere, purged with nitrogen and heated to 15⁰ C. The mixture was discharged, allowed to warm to room temperature and then evaporated to low volume. Toluene 10.7 ml (0.01 mol.) was charged to the mixture, which was then re-evaporated. The toluene addition/re-evaporation procedure was repeated. The mixture was filtered on suction and dried in vacuum oven at 40⁰ C for overnight. Solid product obtained was immediately used

for next procedure because derivatives of sulfonyl chlorides are highly unstable.

1) 5-Naphthoxy-2-(1-H-Benzimidazole)sulfonyl

Chloride¹⁰⁶:

Yield: 2.74 gm. (80%).

2) 5-Phenoxy-2-(1-H-Benzimidazole) sulfonyl chloride¹⁰⁶:

Yield: 2.313 gm. (75%).

8) **Preparation of title compounds derivatives by condensation of 5-Phenoxy/Naphthoxy-2-benzimidazole Sulfonyl Chloride with 2-amino heterocycles (XVII):-**

In a dry three necked flask equipped with a water condenser, guard tube, dropping funnel, stopper and magnetic needle, 1.203 g. (0.0039 mol.) of 5-Phenoxy –2– benzimidazole Sulfonyl chloride (XVI)/1.398 g. (0.0039 mol.) of 5-Naphthoxy-2-benzimidazole sulfonyl chloride (XVI) was dissolved in 10 ml of dry acetone. To this was added 0.39 g. (0.55 ml, 0.004 mol.) of triethyl amine. The mixture was stirred so as to reach the temperature of 60⁰C. At this temperature (0.0039 mol.) of 2-amino heterocycles dissolved in 5ml of dry acetone, was added dropwise through the dropping funnel over a period of 15 minutes. The reaction mixture was then stirred at 60⁰C for 4-6 hours. Reaction mixture was concentrated to get the desired product. It was recrystallized from methanol.

5-substituted-2-(1-H-Benzimidazoles) Sulfonamides :-

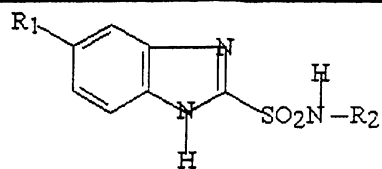


Table – 8

							Elemental Analysis					
Sr NO	R ₁	R ₂	Molecular Formula	Mol. Wt	m.p. °C	Yield %	Required			Found		
							%C	% H	% N	% C	% H	% N
1)	Phenoxy	H	C ₁₃ H ₁₁ N ₃ SO ₃	289	190-192	60	53.979	3.806	14.532	53.868	3.785	14.498
2)	Naphthoxy	H	C ₁₇ H ₁₃ N ₃ SO ₃	339	210-212	63	60.176	3.834	12.389	60.058	3.798	12.306
3)	Phenoxy	Pyridine	C ₁₈ H ₁₄ N ₄ SO ₃	366	140-142	53	59.016	3.825	15.300	58.972	3.779	15.225
4)	Naphthoxy	Pyridine	C ₂₂ H ₁₆ N ₄ SO ₃	416	180-182	56	63.461	3.846	13.461	63.372	3.789	13.378

5-substituted-2-(1-H-Benzimidazoles) Sulfonamides :-

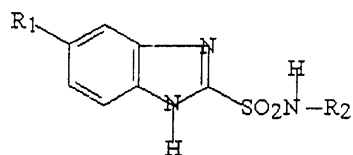


Table – 8

5)	Phenoxy	thiazole	C ₁₆ H ₁₂ N ₄ S ₂ O ₃	372	143	51	51.612	3.225	15.053	51.465	3.178	14.988
6)	Naphthoxy	thiazole	C ₂₀ H ₁₄ N ₄ S ₂ O ₃	422	169	59	56.872	3.317	13.270	56.671	3.306	12.945
7)	Phenoxy	Benzo thiazole	C ₂₀ H ₁₄ N ₄ S ₂ O ₃	422	163	54	56.872	3.317	13.270	56.61	3.306	12.945
8)	Naphthoxy	Benzo thiazole	C ₂₄ H ₁₆ N ₄ S ₂ O ₃	472	189- 191	62	61.016	3.389	11.864	60.938	3.288	11.663

PART VI
EXPERIMENTAL

- ❖ SYNTHESIS OF SOME 5,6-DISUBSTITUTED-2-
(PHENYL THIOCARBAMOYL) BENZIMIDAZOLES

EXPERIMENTAL: -

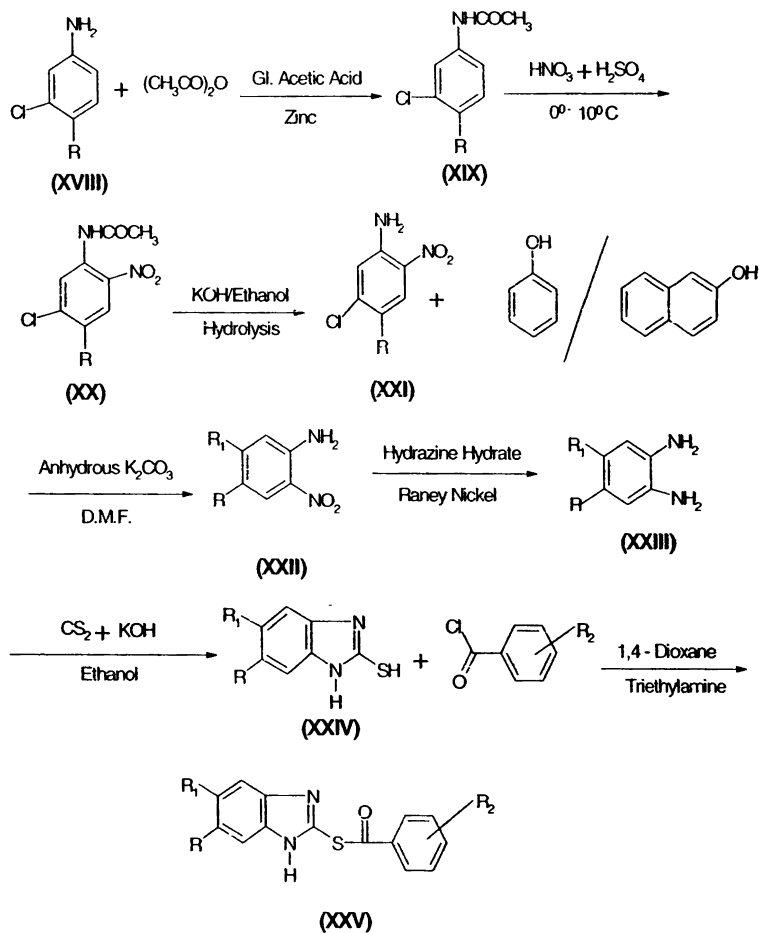
This section deals with the synthesis of 5,6-Disubstituted-2-(Phenyl Thiocarbamoyl) Benzimidazole which involves the steps which are already explained in section IV and V, experimental elaborated up to preparation of 6-Chloro-5-Phenoxy/Naphthoxy-2-mercapto benzimidazole and 5-Phenoxy/naphthoxy-2-mercapto benzimidazole will remain same.

6-chloro-5-phenoxy/Naphthoxy-2-mercapto benzimidazole and 5-phenoxy/naphthoxy-2-mercapto benzimidazole condensed with simple or substituted biologically active acid chlorides to synthesize title compound derivatives.

SCHEME - III

SCHEMATIC REPRESENTATION

Synthesis of 5,6-Disubstituted-2-(Phenyl thiocarbamoyl) benzimidazoles



Where, $R = \text{H, Cl}$
 $R_1 = \text{Phenoxy, Naphthoxy}$
 $R_2 = \text{H, Cl}$

Synthesis of title compound derivatives by condensation of 6-chloro-5-phenoxy/naphthoxy-2-mercapto benzimidazole or 5-phenoxy/naphthoxy-2-mercapto benzimidazole with simple/substituted acid chlorides (XXV): -

In a 250ml three necked round bottomed flask equipped with a dropping funnel, reflux condenser with a guard tube, was placed a mixture of triethyl amine (0.003 mol., 0.10g.) and a solution of 6-chloro-5-phenoxy/naphthoxy-2-mercapto benzimidazole or 5-phenoxy/naphthoxy-2-mercapto benzimidazole (0.002 mol.) in 10 ml dry 1,4-dioxane. The reaction mixture was stirred on a mechanical stirrer at 50⁰-60⁰C for about 30 minutes.

To this was added dropwise a solution of simple/substituted benzoyl chloride (0.001 mol) in 10 ml dry 1,4-dioxane at the same temperature. After the addition, the reaction mass was stirred for 4-6 hours. It was kept overnight at room temperature. .

The solution was poured into crushed ice. The solid separated out was filtered and washed with water and dried. It was then recrystallized from ethanol.

5,6-disubstituted-2-(Phenyl thiocarbamoyl) Benzimidazoles :-

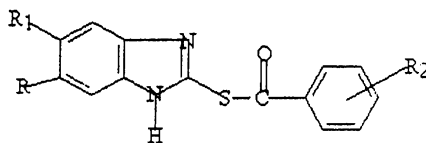


Table – 9

								Elemental Analysis					
Sr. No	R	R ₁	R ₂	Mol. Formula	Mol. Wt	m.p. °C	Yield %	Required			Found		
								%C	% H	% N	% C	% H	% N
1)	H	Phenoxy	H	C ₂₀ H ₁₄ O ₂ N ₂ S	346	168	51	69.364	4.046	8.092	69.297	3.909	7.983
2)	H	Naphthoxy	H	C ₂₄ H ₁₆ O ₂ N ₂ S	396	182	58	72.727	4.040	7.070	72.618	3.898	6.971
3)	Cl	Phenoxy	H	C ₂₀ H ₁₃ O ₂ N ₂ SCl	380.5	175	60	63.074	3.416	7.358	62.978	3.333	7.298
4)	Cl	Naphthoxy	H	C ₂₄ H ₁₅ O ₂ N ₂ SCl	430.5	208-210	62	66.898	3.484	6.504	66.770	3.392	6.477
5)	H	Phenoxy	3,4-dichloro	C ₂₀ H ₁₂ O ₂ N ₂ SCl ₂	415	170-172	52	57.831	2.891	6.746	57.725	2.795	6.698

5,6-disubstituted-2-(Phenyl thiocarbamoyl) Benzimidazoles :-

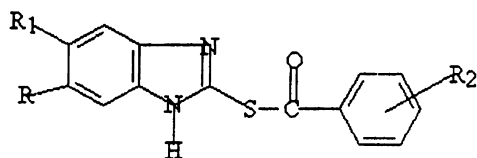


Table – 9

6)	Cl	Phenoxy	3,4-dichloro	C ₂₀ H ₁₁ O ₂ N ₂ SCl ₃	449.5	215-217	55	53.392	2.447	6.229	53.301	2.398	6.198
7)	Cl	Naphthoxy	3-chloro	C ₂₄ H ₁₅ O ₂ N ₂ SCl	430.5	188	59	66.898	3.484	6.504	66.792	3.402	6.479
8)	Cl	Naphthoxy	2,4-dichloro	C ₂₄ H ₁₃ O ₂ N ₂ SCl ₃	499.5	177	61	57.657	2.602	5.605	57.597	2.557	5.571
9)	Cl	Phenoxy	4-chloro	C ₂₀ H ₁₂ O ₂ N ₂ SCl ₂	415	169	62	57.831	2.891	6.746	57.798	2.798	6.688
10)	Cl	Naphthoxy	4-chloro	C ₂₄ H ₁₄ O ₂ N ₂ SCl ₂	465	196-198	65	61.935	3.010	6.021	61.875	2.985	5.985

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PART VII EXPERIMENTAL

- ❖ SYNTHESIS OF SOME 5,6-DISUBSTITUTED-2-PHENOXYMETHYL BENZIMIDAZOLES

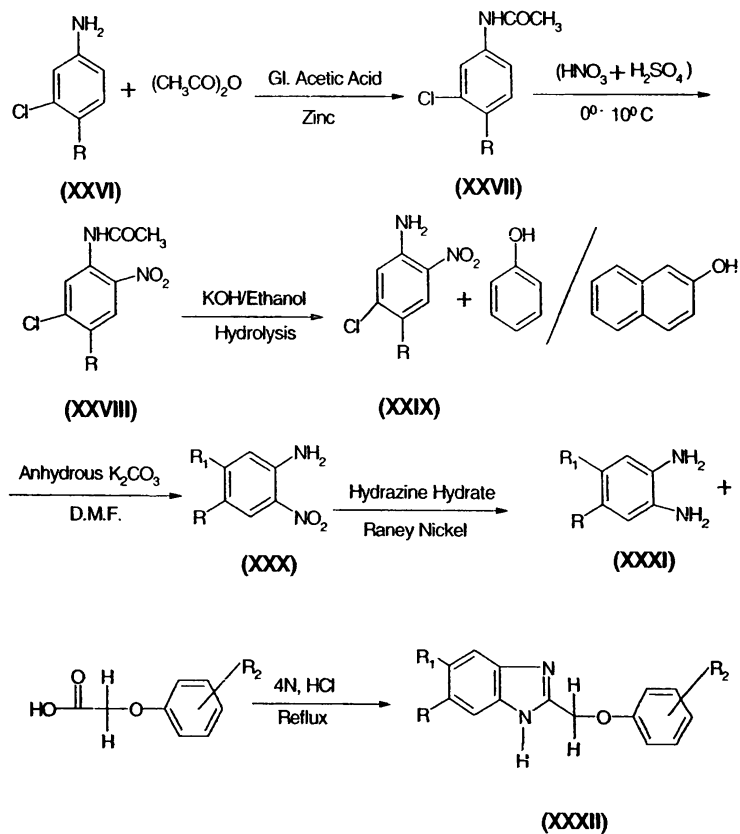
EXPERIMENTAL: -

This section deals with the synthesis of 5,6-disubstituted-2-phenoxyethyl benzimidazoles which involves the steps already explained in section IV and V, experimental elaborated upto preparation of 6-chloro-5-phenoxy/naphthoxy ortho phenylene diamine will remain same.

6-chloro-5-phenoxy/naphthoxy O.P.D.A. or 5-phenoxy / naphthoxy O.P.D.A. was condensed with simple or substituted phenoxy acetic acids to synthesize title compound derivatives.

SCHEME - IV
SCHEMATIC REPRESENTATION

Synthesis Of 5,6 - Disubstituted - 2 - Phenoxyethyl Benzimidazoles



Where, R = H, Cl
 R_1 = Phenoxy, Naphthoxy
 R_2 = H, Cl

**Preparation of 5,6-Disubstituted-2-phenoxyethyl
benzimidazoles¹⁰⁷ (32): -**

A mixture of 6-chloro-5-phenoxy/naphthoxy O.P.D.A. or 5-phenoxy/naphthoxy O.P.D.A. (0.02 mol.), appropriate phenoxyacetic acid (0.03 mol.), and 4N-HCl (20ml) was refluxed for about 1 – 2 hours. The product was then cooled and kept overnight. The title compound derivatives were precipitated by adding ammonia solution and recrystallized from a mixture of ethanol and ethyl acetate.

5,6-Disubstituted-2-(Phenoxy methyl) Benzimidazoles :-

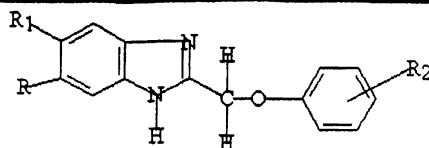


Table – 10

								Elemental Analysis					
Sr. No	R	R ₁	R ₂	Molecular Formula	Mol. Wt	m.p. °C	Yield %	Required			Found		
								%C	% H	% N	% C	% H	% N
1)	H	Naphthoxy	H	C ₂₄ H ₁₈ N ₂ O ₂	366	135	55	78.688	4.918	7.650	78.663	4.905	7.620
2)	Cl	Naphthoxy	H	C ₂₄ H ₁₇ N ₂ O ₂ Cl	400.5	152	66	71.910	4.244	6.991	71.895	4.210	6.950
3)	H	Phenoxy	H	C ₂₀ H ₁₆ N ₂ O ₂	316	116	51	75.949	5.063	8.860	75.913	4.955	8.830
4)	Cl	Phenoxy	H	C ₂₀ H ₁₅ N ₂ O ₂ Cl	350.5	129	59	68.473	4.279	7.988	68.413	4.243	7.958
5)	Cl	Phenoxy	2,4-dichloro	C ₂₀ H ₁₃ N ₂ O ₂ Cl ₃	419.5	147	62	57.210	3.098	6.678	57.193	3.989	6.638

5,6-Disubstituted-2-(Phenoxy methyl) Benzimidazoles :-

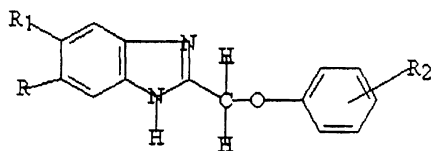


Table – 10

6)	Cl	Naphthoxy	2,4-dichloro	$C_{24}H_{15}N_2O_2Cl_3$	469.5	183	68	61.341	3.194	5.963	61.327	3.153	5.923
7)	H	Phenoxy	4-chloro	$C_{20}H_{15}N_2O_2Cl$	350.5	131	59	68.473	4.279	7.988	68.423	4.237	7.958
8)	Cl	Phenoxy	4-chloro	$C_{20}H_{14}N_2O_2Cl_2$	385	145	65	62.337	3.636	7.272	62.297	3.606	7.239
9)	H	Naphthoxy	4-chloro	$C_{24}H_{17}N_2O_2Cl$	400.5	138	53	71.910	4.244	6.991	71.890	4.210	6.932
10)	Cl	Naphthoxy	4-chloro	$C_{24}H_{16}N_2O_2Cl_2$	434.5	160	62	66.283	3.682	6.444	66.253	3.632	6.401

PART VII A

**SPECTROSCOPIC ANALYSIS OF
SYNTHESIZED COMPOUNDS**

Infra-red Spectroscopy (IR):-

Infrared spectroscopy is one of the most powerful analytical techniques used by the modern chemist. Its most important use has been for the identification of organic compounds, because their spectra are generally complex and provided numerous maxima and minima that can be employed for comparison purposes. The infrared technique has several advantages over the other usual methods of spectral analysis (X-ray diffraction, electron spin resonance, etc.). It provides useful information about the structure of a molecule quickly, without involving lengthy evaluation methods.

Perhaps, the most powerful function of infrared spectroscopy is of establishing conclusively the identity of two samples that have identical spectra when determined in the same medium. The region between $1430\text{--}910\text{ cm}^{-1}$ in an infrared spectrum is called the finger print region. No two different molecules have the same set of absorption bands in this region. Although similar molecules may show very similar spectra in the region between $4000\text{--}1430\text{ cm}^{-1}$ there will almost always be discernible differences in the finger print region.

The compounds prepared in this present investigation have been characterized by their infrared spectrum.

The fundamental groups present in this class of compounds are listed below:

- i) 5-Substituted benzimidazole ring.
- ii) Aromatic ether.
- iii) C-S (sulphide) linkage.
- iv) Imidazole ring.
- v) Halogen Linkage, C-X (X = halogen atom).

5-Substituted benzimidazole ring :

This ring structure¹⁰⁸ shows three absorption bands in the region between 900-800 cm^{-1} . The bands are normally differentiated into 3 regions of absorption: 900-870 cm^{-1} , 830-812 cm^{-1} and 820-800 cm^{-1} .

Aromatic ether :

The aromatic ethers¹⁰⁹ are characterized by a strong absorption band in the region between 1300-1175 cm^{-1} . A secondary absorption band of medium intensity appears in the region between 1070-1000 cm^{-1} .

C-S (sulphide linkage) :

All the compounds prepared, have been identified by the absorption band, which represents the sulphide linkage. These are characterized¹¹⁰ by an absorption band in the region between 1440-1415 cm^{-1} .

A stretching vibration¹¹⁰ is assigned to the C-S linkages, which occur in the region 700-610 cm^{-1} . But this band is usually weak and sometimes may be absent.

Imidazole ring :

The ring stretching¹¹¹ vibration of the imidazole ring is obtained at 1550 cm^{-1} . This is assigned to the C = N stretching vibration.

Halogen compounds (C – X):

Where X = Chlorine atom.

The C-Cl stretching vibrations^{112,113} are characterized by absorption peaks in the region between 760-600 cm^{-1} .

Nuclear Magnetic Resonance Spectroscopy (NMR): -

Nuclear Magnetic Resonance Spectrophotometer makes use of a magnet, a radio frequency device, a detector and an amplifier. The detection system is used to note that energy being transferred from the radio frequency beam to the nucleus.

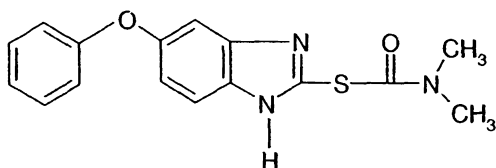
The sample under investigation is taken in glass tube, which is placed between the pole faces of a magnet. A radio frequency source is made to fall on the sample. It can be done by feeding energy (Radio Frequency Source) into a coil wound round the sample tube. A signal is detected if the nuclei in the sample resonate with the source, i.e. ΔE , energy required to flip the proton is same as that of the source. Energy is transferred from the source via nuclei to the detector coil. The output from the detector can be fed to a cathode ray oscillograph or to a strip chart recorder after amplification (at a steady external field, different sets of proton will absorb or come to resonance at different values of the radio frequencies.) etc.

Protons being in different electronic environments in a molecule cannot resonate exactly at same radio frequency. For practical purposes, radio frequency source is held steady at the steady frequency and field strength is varied by placing small electro magnet to the pole faces of the main magnet. By increasing the current flowing through these electromagnets, the total field strength is increased.

As the field strength increases until resonance with the radio frequency source take place. As a proton (or a set of equivalent protons) comes to resonance, the signal from the detector produces a peak on the chart paper. The NMR spectrum consists of series of peaks that correspond to different applied field strengths. Each peak means a set of proton.

5-Phenoxy-2-N, N-(Dimethyl Thiocarbamido) benzimidazole:

(Refer Table No: - 4)

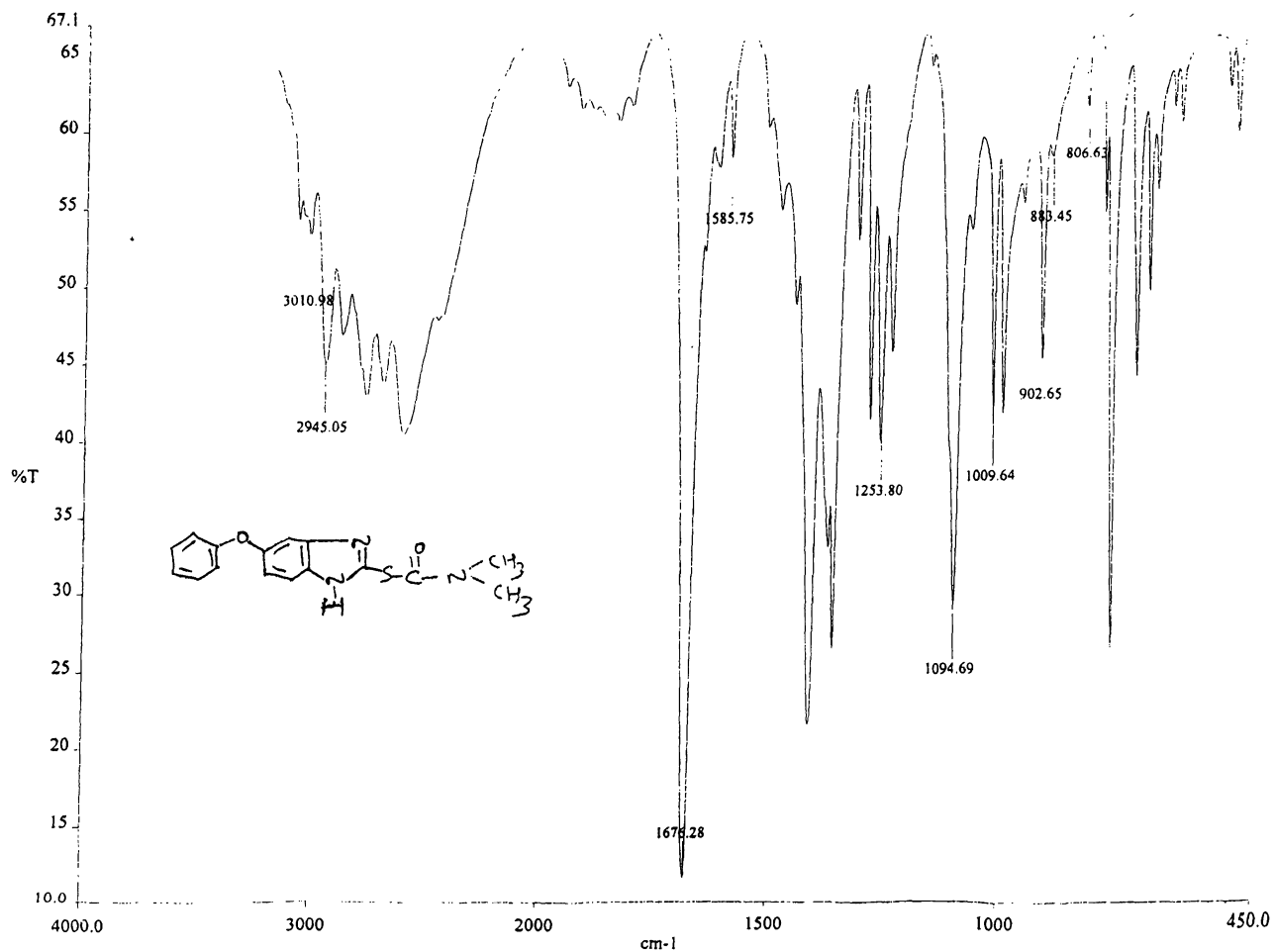


Spectral Analysis: - IR (KBR) Cm^{-1}

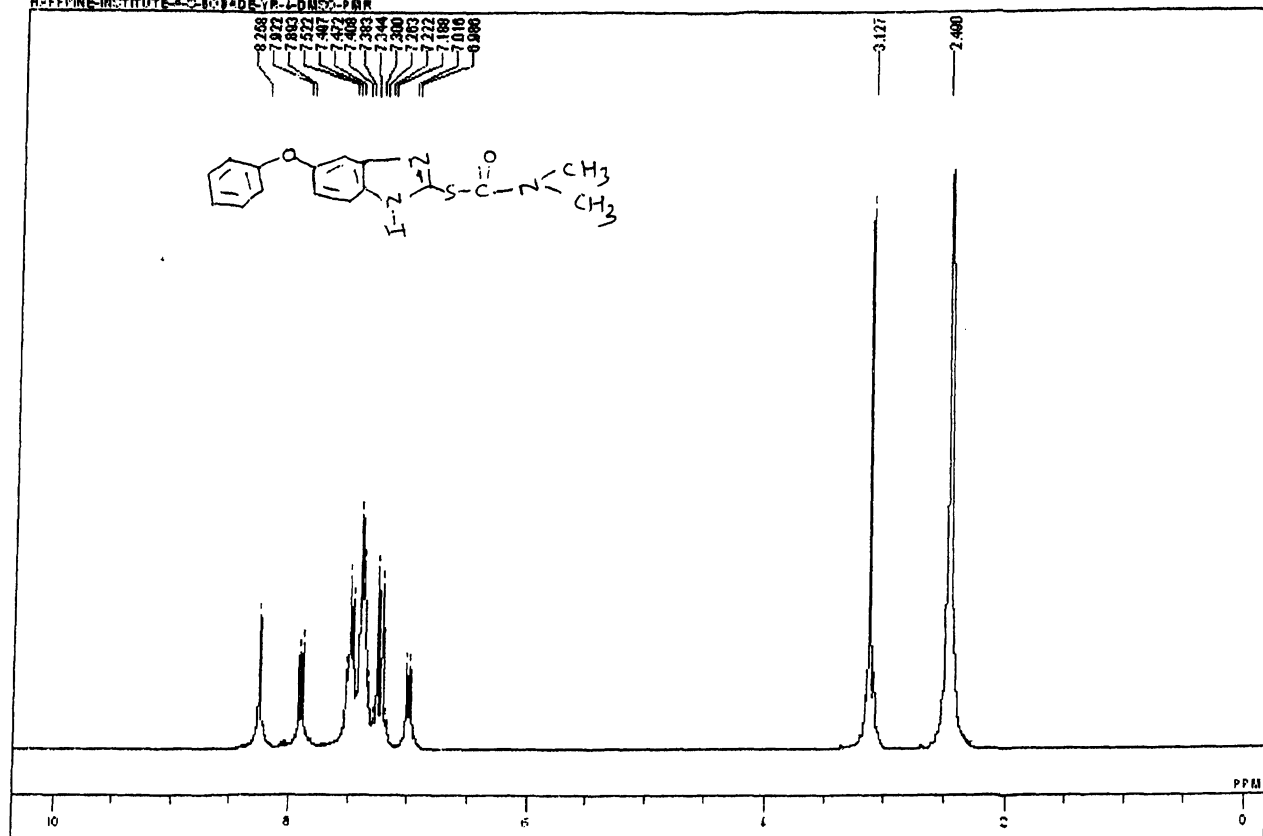
Wave Number	Assignment
3010.98	(-NH)
2945.05	(-CH ₃)
1676.28	(C=O)
1253.80	(-N-C=O)
1094.69	(-N-C-S-)
1009.64	(Ar-O-Ar)
902.65, 883.45, 806.63	(5-substituted benzimidazole)

PMR (DMSO-d₆) δ : -

6.986-8.258	[m, 9H (8H, Ar-H), 1H (-NH)]
3.127	[s, 6H (-CH ₃) ₂]



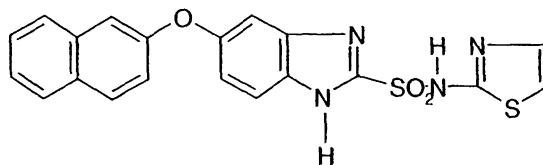
0.15.12.05 HAPPIE-INSTITUTE-A-C-FOBADE-YOGECH-RANE-Y-P-L-DNCO-PRP AN
 HAPPIE-INSTITUTE-A-C-FOBADE-Y-P-L-DNCO-PRP



5-Naphthoxy-2-[(2^l-thiazolyl)sulfonamido]-(1-H)-

benzimidazole:-

(Refer Table No: - 8)



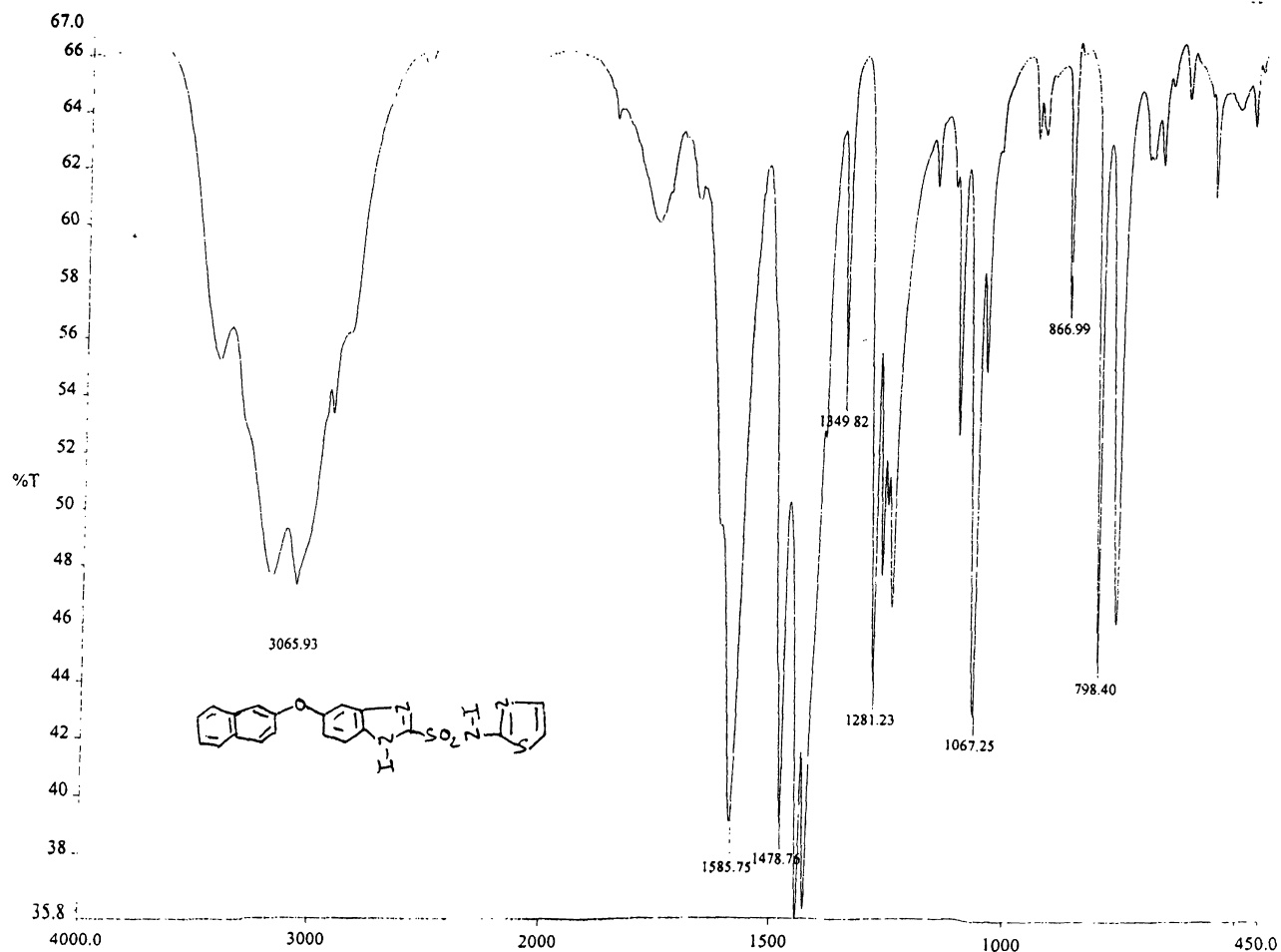
Spectral Analysis: - IR (KBR) Cm⁻¹

Wave Number	Assignment
3065.93	(-NH)
1349.82	(-SO ₂ NH-)
1478.86	(C-C of C ₆ H ₆)
1281.23, 1067.25	(Ar-O-Ar)
1585.75	(C=N-)
866.99, 798.40	(5-substituted benzimidazole)

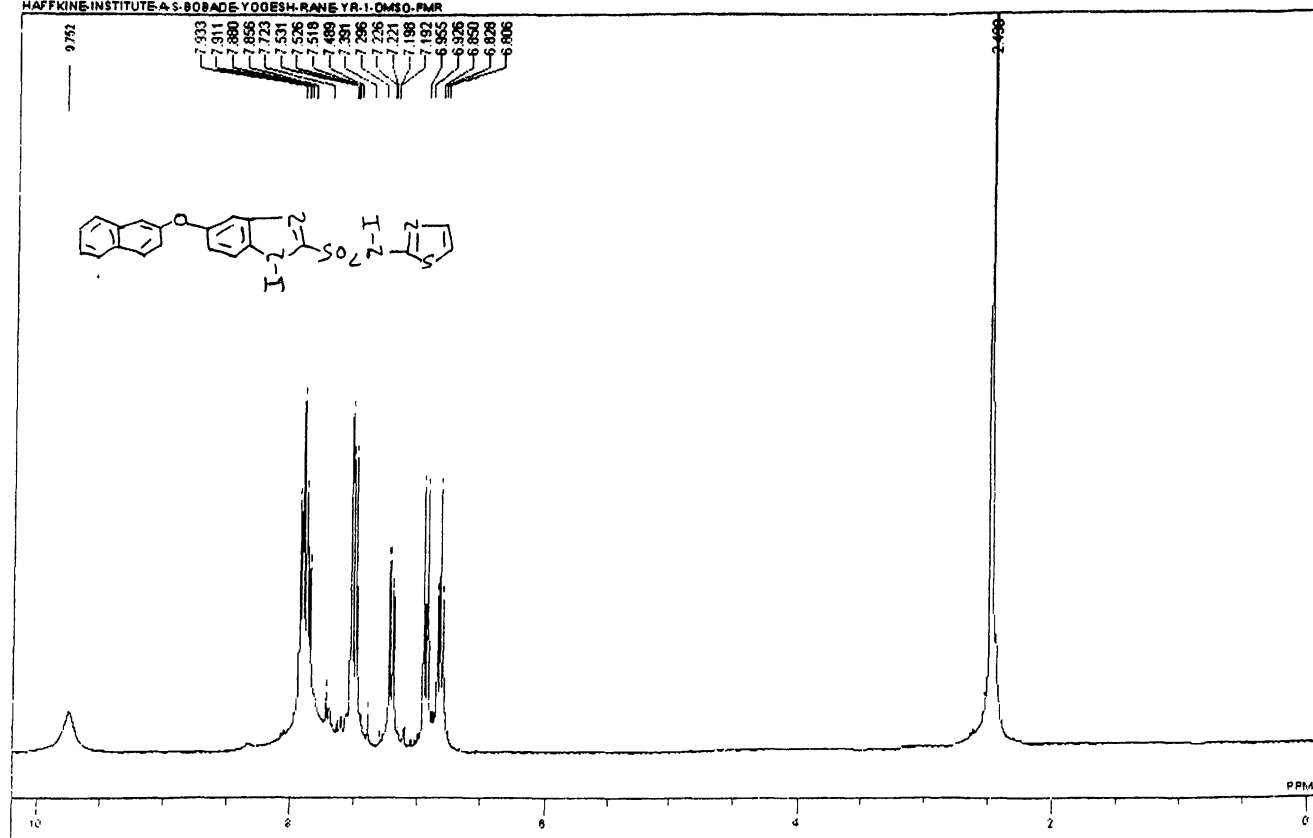
PMR (DMSO-d₆) δ: -

6.806-7.933	[m, 13H (10H, Ar-H), 1H (- NH), 2H (Thiazole)]
9.752	[bs, 1H (-NH)]

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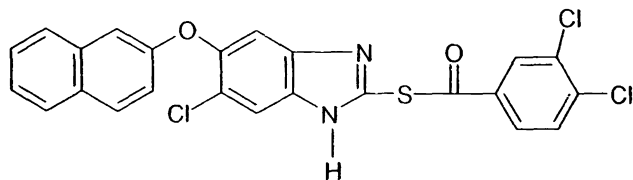
D:\38 11.08\HAFFKINE INSTITUTE-A.S.80\BADE.YOOESH-RANE.YR-1-DMSO-FMR.a1s
 HAFFKINE INSTITUTE-A.S.80\BADE.YOOESH-RANE.YR-1-DMSO-FMR



5-Naphthoxy-6-Chloro-2-(3',4'-dichloro)-phenyl

thiocarbamoyl benzimidazole:-

(Refer Table No: - 9)



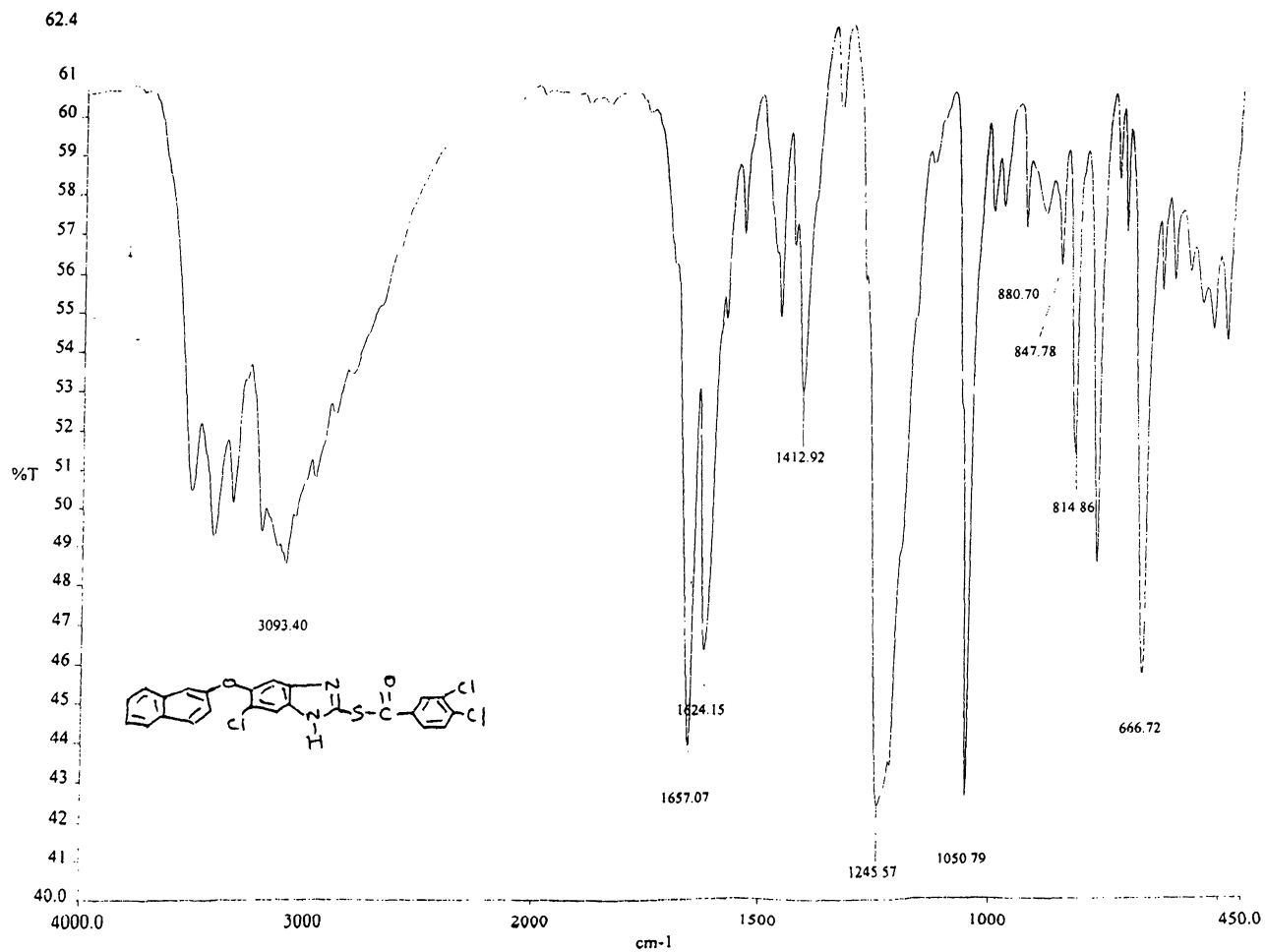
Spectral Analysis: - IR (KBR) Cm^{-1}

Wave Number	Assignment
3093.40	(-NH)
1657.07	(C=O)
1412.92	(C-S-)
1245.57, 1050.79	(Ar-O-)
880.70, 847.78, 814.86	(5-substituted benzimidazole)
1624.15	(C=N-)
666.72	(C-Cl)

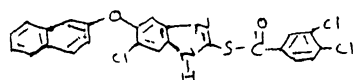
PMR (DMSO- d_6) δ : -

6.825-7.947	[m, 13H(12H, Ar-H), 1H(-NH)]
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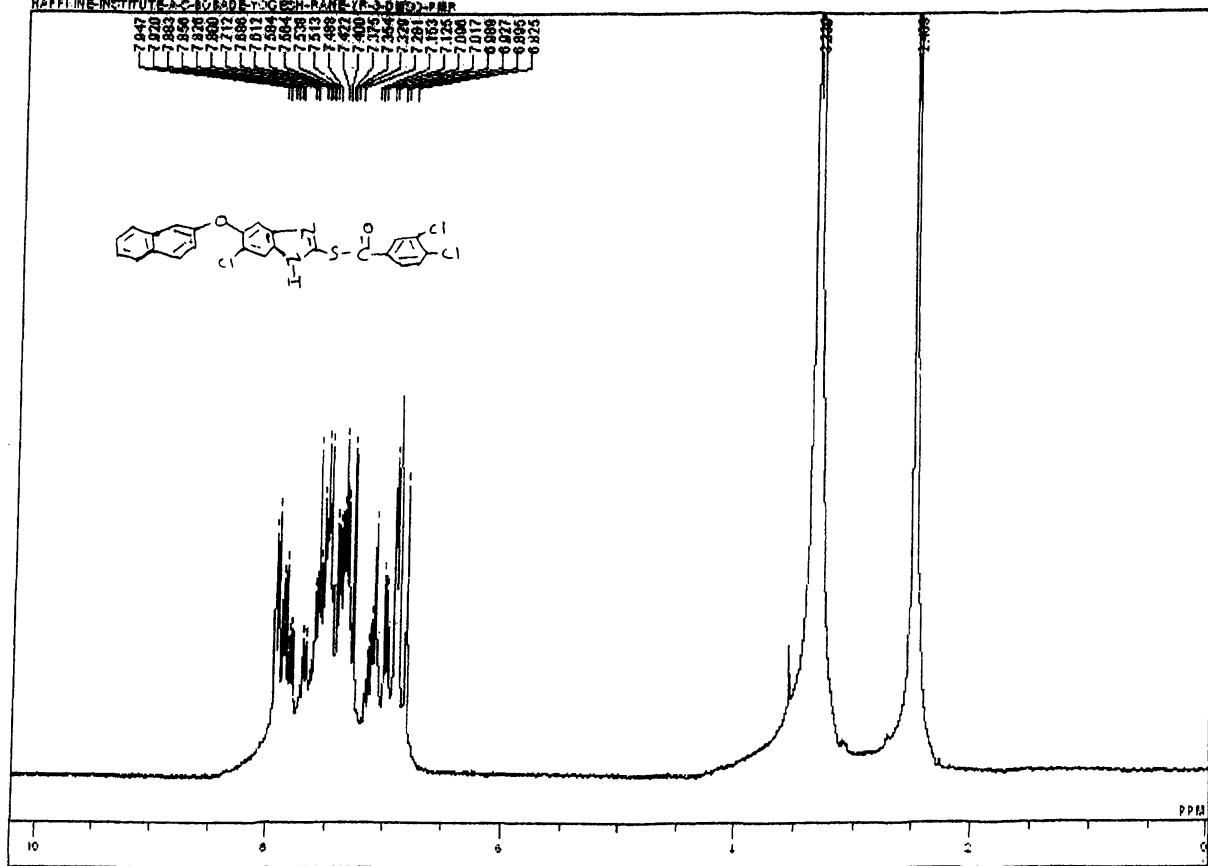
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DOS 1108 HAPPHINE-INSTITUTE-A-C-60640E-YUGEN-PANE-VF-Q-DNCH-P-PR-AB
 HAPPHINE-INSTITUTE-A-C-60640E-YUGEN-PANE-VF-Q-DNCH-P-PR-AB



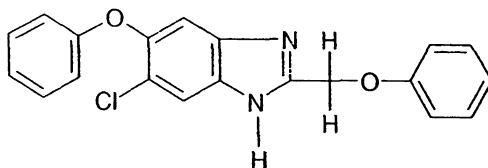
7.947
 7.920
 7.883
 7.856
 7.828
 7.800
 7.772
 7.744
 7.716
 7.688
 7.660
 7.632
 7.604
 7.576
 7.548
 7.520
 7.492
 7.464
 7.436
 7.408
 7.380
 7.352
 7.324
 7.296
 7.268
 7.240
 7.212
 7.184
 7.156
 7.128
 7.100
 6.988
 6.977
 6.965
 6.925



PPR

5-Phenoxy-6-Chloro-2-phenoxymethyl benzimidazole:-

(Refer Table No: - 10)



Spectral Analysis: - IR (KBR) Cm^{-1}

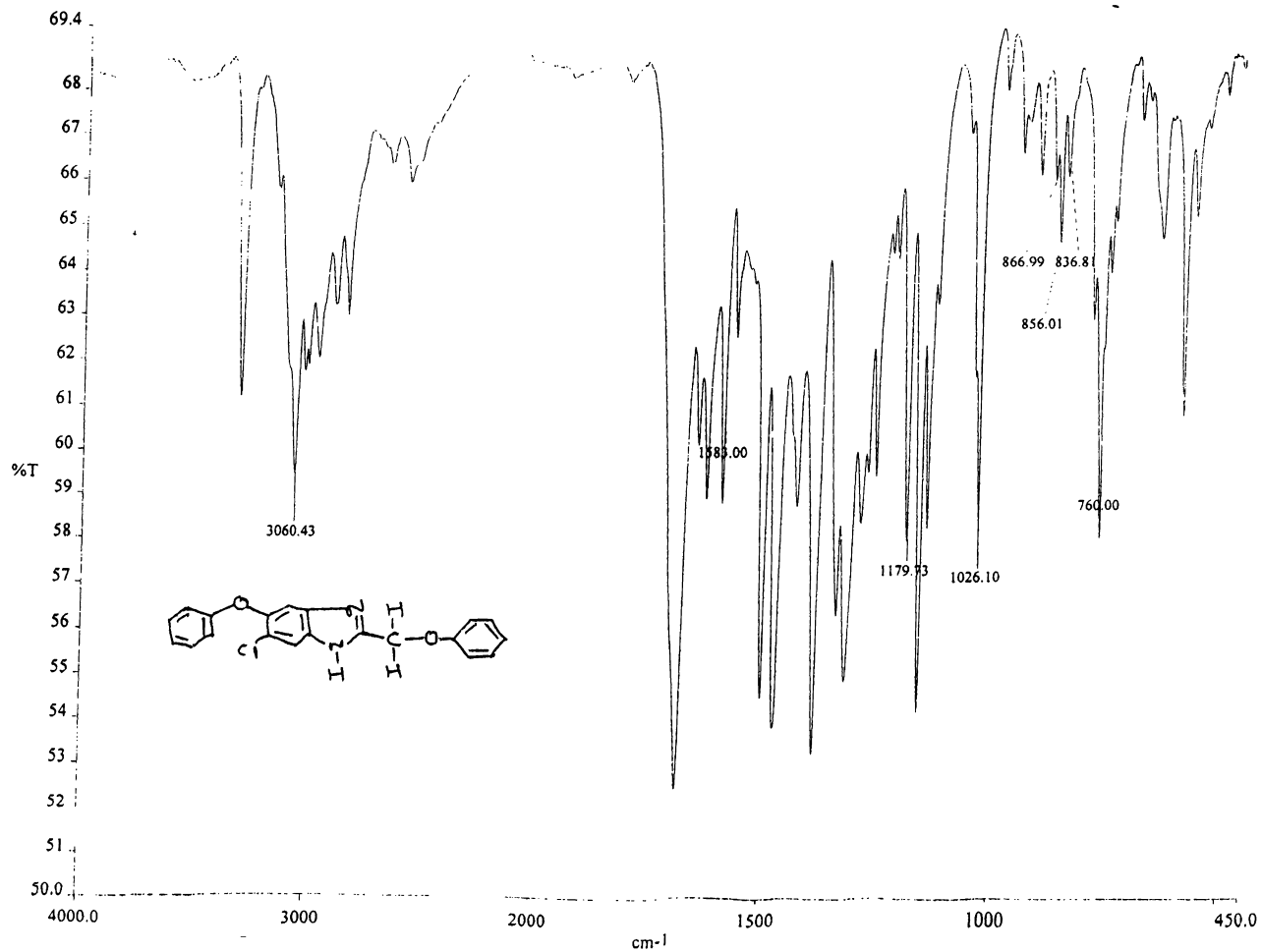
Wave Number	Assignment
3060.43	(-NH)
1179.73	(Ar-O-Ar)
1026.10	(Ar-O-CH ₂)
866.99, 856.01, 836.81	(5-substituted benzimidazole)
1583.00	(C=N)
760.00	(C-Cl)

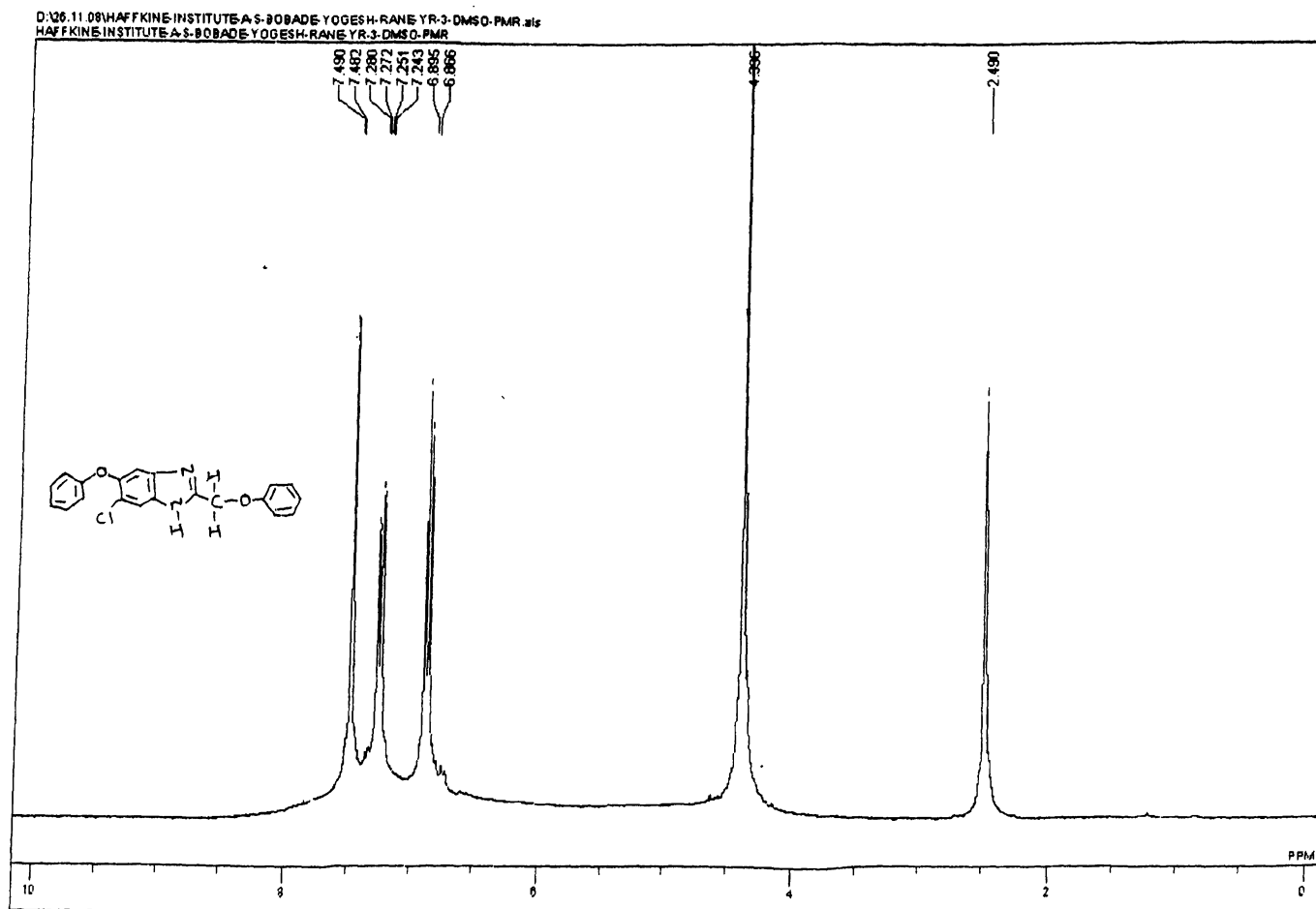
PMR (DMSO-d₆) δ : -

6.866-7.490	[m, 13H(12 H, Ar-H), 1H(-NH)]
4.396	[s, 2H(-CH ₂)]

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PART VIII

BIOLOGICAL SCREENING

Biological Screening: -

The compounds synthesized in the present study have been subjected to antibacterial and antifungal screening based on their structural features.

The *in vitro* testing of these compounds was carried out against gram positive and gram-negative bacteria viz. *Staphylococcus aureus* (ATCC 3750) *Salmonella typhi* (NCTC 786) and against fungal culture of *Candida albicans*.

SCREENING AGAINST BACTERIAL INFECTIONS: -

The test compounds have been subjected to *in vitro* screening by the tube dilution technique¹¹⁴ against gram positive and gram-negative bacteria viz. *S.aureus* and *S. typhi*, using **Mueller-Hinton (M.H.)** broth as the culture medium.

SCREENING PROCEDURE :-

PREPARATION OF Drug Solution :-

0.01gm (10 mg) of drug sample dissolved in 10ml Dimethyl sulfoxide (D.M.S.O.) to give stock solution of 1000 µg /ml.

Serial dilutions of drug samples can be prepared as follows

2ml drug stock solution+8ml M.H. broth	- 200 µg
1ml drug stock solution+9ml M.H. broth	- 100 µg
0.5ml drug stock solution+9.5ml M.H. broth	- 50 µg
0.4ml drug stock solution+9.6ml M.H. broth	- 40 µg
0.2ml drug stock solution+9.8ml M.H. broth	- 20 µg
0.1ml drug stock solution+9.9ml M.H. broth	- 10 µg

Controls:

Media Control

Sterilized medium was kept as a control so as to assure sterility of the medium. If this control shows the growth, it means that medium is not properly sterilized and in that case results are not valid.

Culture Control

It contains sterilized medium and culture of the organism under test. It should show growth in the medium which assures optimum pH, and sufficient nutrients to promote growth. If no growth is observed, then the medium is considered to be faulty and results are not reliable.

Solvent Control

It contains sterilized medium, solvent used to dissolve the drug and the suspended culture in it. Organism should show growth in the quantity of solvent used to prepare the drug stock solution. If growth is not observed, it can be concluded that the solvent inhibits the growth of the organism under test and the results are not valid.

Turbidity Control

It contains the medium and the drug stock solution. The turbidity is observed against the growth in different drug dilutions. It assures reliability against misinterpretations between growth and turbidity due to the drug.

Standard Control

Order of standard drug corresponding to that of the drug under test. The inhibition of growth was observed against the standard.

Sterile Mueller-Hinton broth was dispensed in each borosilicate test tube (150 X 20 mm) as per requirement, and was further autoclaved at 15-pound pressure at 120°C for half an hour. This sterile media was used for further procedure. The drug compounds 0.01 gm (10 mg) was dissolved in D.M.S.O (10 ml).

The serial dilutions were made in such a way as to give various final drug concentrations of 200, 100, 50, 40, 20, 10 µg /ml etc. The inoculums of standard suspension (0.1 ml) of the desired bacterial strain (*S.aureus*, *S. typhi*) containing 10⁶ bacilli / ml was added at the end. The tubes were incubated at 37°C for 24 hours and then examined for the presence or absence of the growth of the test organisms. The lowest concentration, which showed no visible growth, was taken as end point called as Minimum Inhibitory concentration (M.I.C.)

Control tubes with Ampicillin and Trimethoprim were used as standard drugs and tubes without drugs were kept for comparison. Also the solvent D.M.S.O. used for dissolution of test samples was similarly tested to see that they did not affect the growth of the culture at the concentration used under these experimental conditions.

[Ampicillin (M.I.C=0.01 µg/ml) against Gram positive bacteria *S. aureus* and Trimethoprim (M.I.C=1 µg/ml) against gram negative bacteria *S. typhi* and Miconazole (M.I.C=0.625 µg /ml) against *C. albicans*.]

SCREENING AGAINST FUNGAL INFECTIONS: -

The organism employed in the test was *Candida albicans*; which was maintained on sabouraud's agar slants by regular sub culturing, *C. albicans* was subcultured every week.

SCREENING PROCEDURE: -

The test compounds have been subjected to *in vitro* screening by the tube dilution method serial dilutions of drug samples were prepared as explained earlier only the difference is that instead of Mueller Hinton broth, culture media employed was Sabouraud's broth. Serial dilutions of drug samples were prepared in graded concentrations varying from 200 µg/ml to 10 µg/ml.

Preparation of Innoculum: -

Candida albicans: -

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

Sabouraud's broth was dispensed in each borosilicate test tube (150X20mm) as per requirement and autoclaved. The drug compounds 0.01gm (10 mg) were dissolved in D.M.SO. (10 ml.). The serial dilutions were made in such way that to give various final drug concentrations of 200, 100, 50, 40, 20, 10 µg /ml etc. The Innoculum of standard suspension (0.1ml) of *Candida albicans* strain containing 5×10^6 cells per ml was added at the end. The tubes were

incubated at 37⁰C for 48 hours and then examined for the presence or absence of the growth of the test organisms. The lowest concentration, which showed no visible growth, was taken as end point called as Minimum Inhibitory Concentration (M.I.C)

Control tubes with Miconazole as standard drug & tubes without any drug were kept for comparison. Also the solvent D.M.S.O. used for dissolution of test samples was similarly tested to see that they did not affect the growth of the culture at the concentration used under these experimental conditions.

Miconazole was used as a standard compounds for the antifungal screening program. It is active against *Candida albicans* at a concentration of 0.625 µg/ml.

PART IX

BIOLOGICAL RESULTS AND DISCUSSION

Biological Results and Discussion: -

The present investigation reveals that there is close relationship between structure of compounds and its biological activity.

All above-mentioned compounds have shown moderate antifungal and antibacterial activity (Refer Table No: 11). It was found that Compound No. 7, 8 is highly active than rest of the compounds because these compounds contain diethyl linkage and Naphthoxy ring. Due to the presence of hyperconjugation as well as diethyl groups, these compounds are more potent.

It was also noticed that chloro substituted compounds are more active than compounds without chloro substitutions chlorine is electronegative group which enhances the activity of the compound. Comparison of the activity between the compounds with and without chloro substitutions. Are given below (Refer Table No. 11).

[Compound No: - 1>Compound No: - 2, Compound No: - 3>Compound No: - 4, Compound No: - 5>Compound No: - 6, Compound No: - 7>Compound No: - 8]

Conclusion: -

So it is observed that compounds containing diethyl groups, Naphthoxy and chloro substitution were more active than other compounds in series.

5,6-Disubstituted-2-(N,N-Dialkyl thiocarbamido) benzimidazoles:-

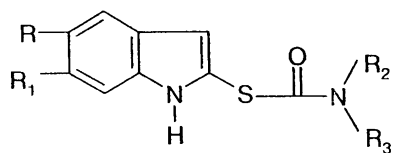


Table No. 11

Sr. No.	R	R ₁	R ₂ = R ₃	<i>S. aureus</i>	<i>S. typhi</i>	<i>C. albicans</i>
1)	Phenoxy	Cl	CH ₃	100	100	200
2)	Phenoxy	H	CH ₃	200	200	N.A.
3)	Phenoxy	Cl	C ₂ H ₅	100	100	200
4)	Phenoxy	H	C ₂ H ₅	200	200	N.A.
5)	Naphthoxy	Cl	CH ₃	100	100	200
6)	Naphthoxy	H	CH ₃	200	200	200
7)	Naphthoxy	Cl	C ₂ H ₅	50	50	100
8)	Naphthoxy	H	C ₂ H ₅	100	100	200

N.A.: - Not Active upto 200 µg/ml

It was observed that Compound No. 2,4,6,8 (Refer Table No: 12) containing Naphthoxy group due to hyperconjugation effect has shown more activity than compounds containing Phenoxy group Compound No. 1,3,5,7.

Compound No. 1 was found inactive for antifungal screening and moderately active for antibacterial screening. It is because this molecule is structurally very simple and not highly substituted.

Compound No. 4,7,8 was found highly active in the series because these molecules are highly substituted and due to biologically active substitutions, are highly active.

Conclusion:

It was observed that compounds having higher substitutions, hyper conjugation and biologically active substitutions are highly active.

5-substituted-2-(1-Hbenzimidazole) sulfonamides :-

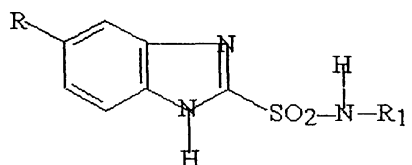


Table No. 12

Sr. No.	R	R ₁	<i>S. aureus</i>	<i>S. typhi</i>	<i>C. albicans</i>
1)	Phenoxy	H	200	200	N.A.
2)	Naphthoxy	H	100	200	200
3)	Phenoxy	Pyridine	200	100	200
4)	Naphthoxy	Pyridine	100	50	100
5)	Phenoxy	Thiazole	200	200	200
6)	Naphthoxy	Thiazole	100	100	100
7)	Phenoxy	Benzothiazole	100	50	200
8)	Naphthoxy	Benzothiazole	50	50	100

The testing results in (Table-13) once again revealed that Compound No: - 1 and 2 are structurally very simple molecules and were not highly substituted Compound No: - 1&2 were found inactive in antifungal screening and compound No. 1 was found inactive against Gram Negative bacteria *S.typhi* Compound No. 6 & 8 are highly active in the series because these molecules are highly substituted and having more no. of electro negative groups i.e. chloro groups, than Compound No. 1,2,3,4,7,9,10 which are moderately active.

Conclusion: -

It was concluded that biological activity enhanced when there were more electron withdrawing groups were present in the molecule.

5,6-Disubstituted-2-(Phenyl thiocarbamoyl) Benzimidazoles :-

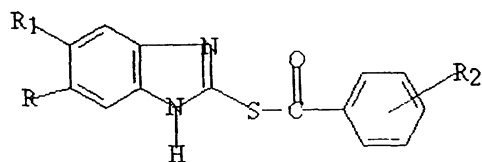


Table No. 13

Sr. No.	R	R ₁	R ₂	<i>S. aureus</i>	<i>S. typhi</i>	<i>C. albicans</i>
1)	H	Phenoxy	H	200	N.A.	N.A.
2)	H	Naphthoxy	H	200	200	N.A.
3)	Cl	Phenoxy	H	200	200	200
4)	Cl	Naphthoxy	H	100	200	200
5)	H	Phenoxy	3,4-dichloro	100	100	200
6)	Cl	Phenoxy	3,4-dichloro	50	100	100
7)	Cl	Naphthoxy	3-chloro	100	100	200
8)	Cl	Naphthoxy	2,4-dichloro	50	50	100
9)	Cl	Phenoxy	4-chloro	50	100	200
10)	Cl	Naphthoxy	4-chloro	100	100	200

Antibacterial and antifungal screening results in (Table No: 14) have shown the same pattern explained earlier. Compound No.- 1,3 were found both Negative in antifungal screening where as Compound No.- 3 was found inactive against Gram Negative bacteria *S.typhi* because these molecules are very simple, sixth position of benzimidazole molecule in these compounds was not substituted and phenoxy acetic acid used in synthesis of these compounds was simple.

Compound No.- 5 & 6 are highly active because these are highly substituted molecules and contain more no. of electronegative groups; where as Compound No.- 2,4,7,8,9,10 have shown moderate activity.

When we have compared Compound No. 5 & 6 it was found that due to presence of Naphthoxy ring in Compound No. 6 i.e. hyper conjugation effect is more than Compound No.- 5, so compound No. 6 is more active.

Conclusion: -

By all above discussions it was concluded that biological activity enhanced by or dependent on

- 1) No. Of electronegative groups.
- 2) Hyper conjugation.
- 3) Biologically active substitutions.
- 4) Highly substituted moieties.

5,6-Disubstituted-2-Phenoxy methyl Benzimidazoles :-

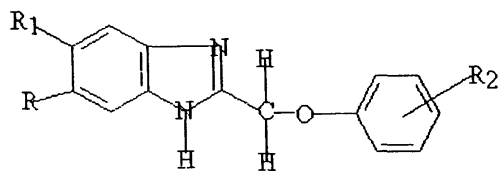


Table No. 14

Sr. No.	R	R ₁	R ₂	<i>S. aureus</i>	<i>S. typhi</i>	<i>C. albicans</i>
1)	H	Naphthoxy	H	200	200	N.A.
2)	Cl	Naphthoxy	H	200	200	200
3)	H	Phenoxy	H	200	N.A.	N.A.
4)	Cl	Phenoxy	H	200	200	200
5)	Cl	Phenoxy	2,4-dichloro	100	100	200
6)	Cl	Naphthoxy	2,4-dichloro	50	50	100
7)	H	Phenoxy	4-chloro	100	200	200
8)	Cl	Phenoxy	4-chloro	100	200	200
9)	H	Naphthoxy	4-chloro	100	200	200
10)	Cl	Naphthoxy	4-chloro	100	100	200

PART IX A: -

APPENDIX

- 1) Melting points were determined in open glass capillaries using Thermanik Precision melting point cum Boiling Point Apparatus [Model C-PMB-2] and were uncorrected.
- 2) Purity of the compounds was verified by precoated T.L.C. plates [E. Merck Kieselgel].
- 3) Elemental analysis was carried out on Thermo Finnegan Flash and EA 1112.
- 4) The IR Spectra were recorded using KBr Pellets on Perkin Elmer spectro photometer.
- 5) The ^1H NMR Spectra were recorded on [Joel-AMX-400 (300MHz)] spectro photometer using T.M.S. as an internal standard.
- 6) Solvents used in the synthesis were redistilled, and dried by using suitable drying agents, wherever required.

PART X

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PART – XI: -

SYNOPSIS

SYNOPSIS
OF THE THESIS TO BE SUBMITTED
TO THE UNIVERSITY OF MUMBAI
FOR THE DEGREE OF
MASTER OF SCIENCE IN ORGANIC CHEMISTRY

TITLE OF THE PROPOSAL : SYNTHESIS AND STUDY OF SUBSTITUTED
BENZIMIDAZOLES AS POSSIBLE
THERAPEUTIC AGENT

NAME OF THE: : YOGESH SADANANDA RANE
CANDIDATE

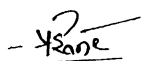
BASIC QUALIFICATION : B.Sc. [March 2003] & PG D.M.L.T.
OF CANDIDATE

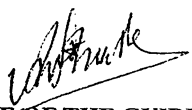
NAME AND : DR.ANIL SHRIDHAR BOBADE
DESIGNATION : (SCIENTIFIC OFFICER)
OF GUIDE

PLACE OF RESEARCH : DEPARTMENT OF CHEMOTHERAPY,
WORK HAFKINE INSTITUTE FOR TRAINING
RESEARCH AND TESTING.

NUMBER AND DATE : 21, 7/12/06.
OF REGISTRATION

DATE OF SUBMISSION: 5/12/08
OF SYNOPSIS


SIGNATURE OF THE CANDIDATE
(YOGESH S. RANE)


SIGNATURE OF THE GUIDE
(DR. ANIL S.BOBADE)

INTRODUCTION

Medicinal chemistry is a science whose roots lie in all branches of chemistry and biology. It concerns essentially the understanding and explanation of the mechanisms of the action of drugs. On this basis it attempts to establish relationship between chemical structure and biological activity and to link biodynamic behavior to the chemical reactivity and physical properties of therapeutic agents.

Medicinal chemistry also involves the isolation, characterization, and synthesis of compounds that can be used in medicine for the prevention treatment and cure of disease. Medicinal chemistry thus provides the chemical basis for the interdisciplinary field of therapeutics.

By contributing therapeutic agents, chemists have made possible some of the proudest achievements of human and veterinary medicine and animal husbandry. Chemists have created new drugs and hormones, as well as vitamins and other essential biochemicals, and have developed methods of production that have made these substances available at reasonable cost.

For many centuries the search for therapeutic substances centered on investigation of herbs grown in gardens of religious establishment where the sick found the shelter. In the Nineteenth Century, the advent of analytical and synthetic chemistry signaled an important change in direction of the alkaloids, that were purified, and simple molecules such as acetylsalicylic acid were synthesized.

However, the true era of medicinal chemistry really began in 1930's with the preparation and use of the antibacterial sulfonamide drugs. The history of medicine was, from that time on, to be dominated by medicinal therapeutics. Today, a large number of diseases are cured or at least controlled by drug therapy. Thus, the fight against bacterial and fungal infections has been largely won, and significant progress has been made in treating mental, pulmonary, inflammatory and cardiovascular conditions. In addition, some cancers and certain forms of leukemia are cured by chemotherapy.

Heterocyclic Chemistry has time and again proved them to be invaluable in the field of medicinal chemistry. Several heterocyclic derivatives

find important applications in the compounds of therapeutic value. **Benzimidazole** is one of the biologically active molecules and is useful for several purposes ranging from anthelmintic agents, antibacterial to immune-suppressive agents.

2-Mercapto benzimidazole itself is an antibacterial and antifungal agent and substitution at second, fifth and sixth position of this molecule enhances biological activity of it.

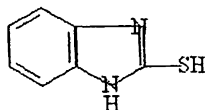
Thus the thesis of the planned work will be divided into following sections:

- 1] Introduction
- 2] Review of Literature
- 3] Plan of Work
- 4] Series I: Synthesis of some 5,6-Disubstituted-2- (N, N-Dialkyl Thiocarbamido) Benzimidazoles.
- 5] Series II: Synthesis of some 5-Substituted-2- (1-H-benzimidazole) Sulphonamides
- 6] Series III: Synthesis of some 5,6-Disubstituted-2-(Phenyl Thiocarbamoyl) Benzimidazoles.
- 7] Series IV: Synthesis of some 5,6-Disubstituted-2-Phenoxyethyl Benzimidazoles
- 8] Biological Screening
- 9] Results and Discussions
- 10] References

1. Synthesis of some 5,6-Disubstituted-2- (N, N-Dialkyl Thiocarbamido)

Benzimidazoles.

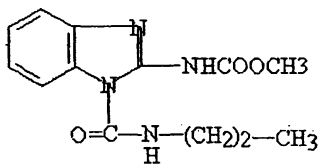
2-mercapto Benzimidazole (I) itself is a Bacteriostatic & Antifungal agent¹.



[I]

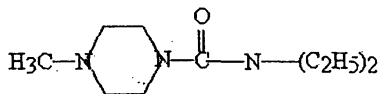
A number of Benzimidazole derivatives have demonstrated a broad spectrum of significant biological activity such as Mebendazole² & Flubendazole³.

Benomyl [II] is another Antifungal compound having Benzimidazole moiety with a carbamido linkage⁴.



[II]

N, N-Diethyl Carbamazepine (Hetzaran) (III) having N, N- Diethyl Carbamoyl linkage is a well-marked Antifilarial agent⁵.

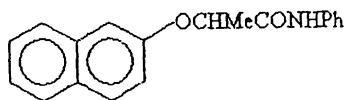


[III]

Thus presence of Diethyl carbamoyl linkage enhances the antifungal and antibacterial activity of molecule.

Further Enhancement of Biological activity of Benzimidazole nucleus can be done by substitution of Phenoxy & Naphthoxy linkage at fifth position.

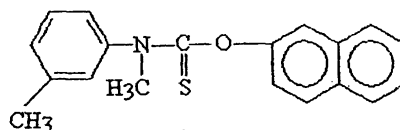
β -Naphthol has been used as an antiseptic & anthelmintic agent⁶. The derivatives of β -Naphthol are well known for their biological effects. β -Naphthoxy Propionanilide (IV) is a wide spectrum herbicide for rice paddies⁷.



[IV]

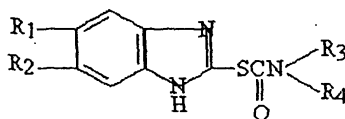
Phenol used as a general disinfectant⁸, it has been used internally & externally as an antiseptic⁸.

Drug Tolnaftate (V) is known to possess moderate antifungal activity⁹.



[V]

So, considering the importance of Dialkyl Carbamoyl linkage as an effective intermediate in preparation of compound of medicinal value, we have condensed 5,6-disubstituted benzimidazoles with N, N-Dialkyl Carbamoyl Chloride to synthesize 5,6-Disubstituted-2- (N, N-Dialkyl Thiocarbamido) Benzimidazoles [VI].



[VI]

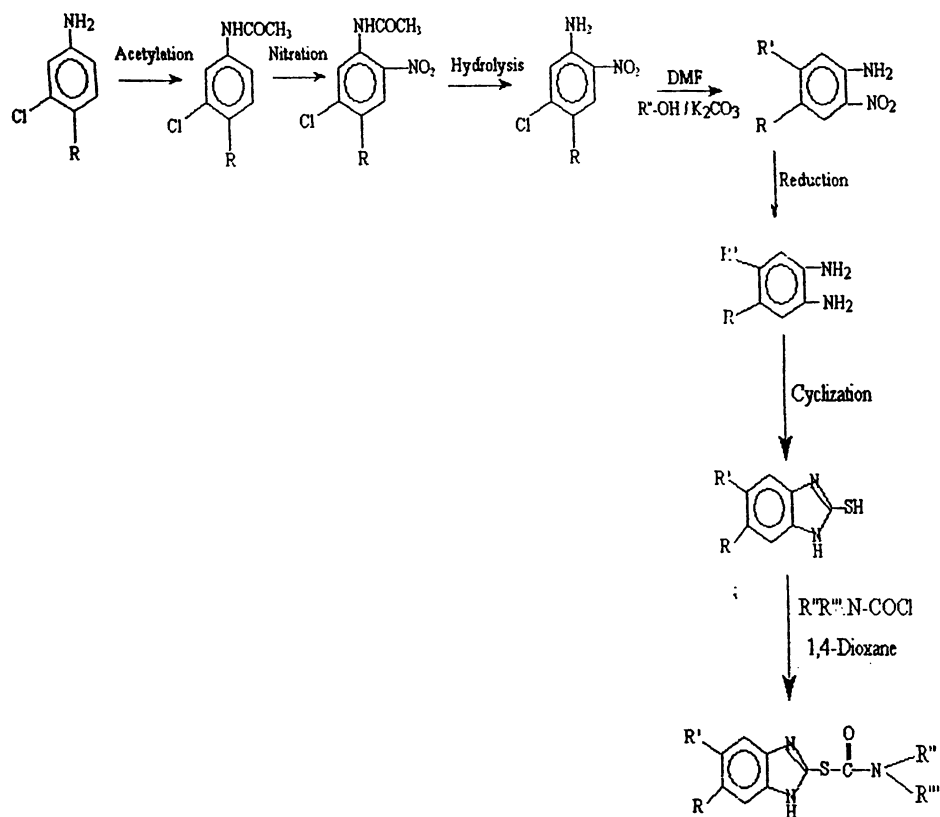
Where R₁ = Phenoxy, Naphthoxy

R₂ = Cl, H

R₃ = R₄ = -CH₃; -C₂H₅

We've synthesized total 6-10 compounds in this series, which have been further screened for their antifungal and antibacterial activities.

SCHEMATIC REPRESENTATION:



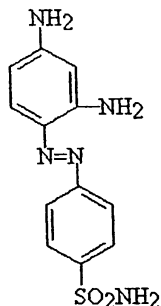
R = H, Cl

R' = Phenoxy, Naphthoxy

R'' = R''' = C₂H₅, CH₃

2. Synthesis of some 5-Substituted-2-(1-H-benzimidazole) Sulphonamides:-

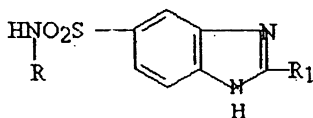
The discovery of the antibacterial activity of Prontosil (VII), a sulfonamide, in early 1930's was the beginning of the era of the Chemotherapy¹⁰. Thereafter sulphonamides have been studied extensively & large number of sulphonamides were prepared & studied for their Anti-Bacterial activity.



[VII]

Presently, there are many sulphonamides in clinical use as anti-bacterials. 7-nitro-5-benzimidazole sulphonamides & 4-nitro-6-benzimidazole sulphonamides have been found to be excellent anti-bacterials¹¹.

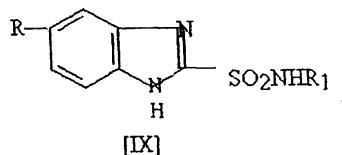
Similarly, 5 (or 6) substituted benzimidazoles sulphonamides (VIII) & its 2-methyl derivatives are found to inhibit the growth of polio & influenza B virus¹². Thus presence of sulphonamido group at fifth and seventh position found to be useful to enhance antibacterial activity.



[VIII]

Where R = H, substituted phenyl Heterocycles
R₁ = H, -CH₃

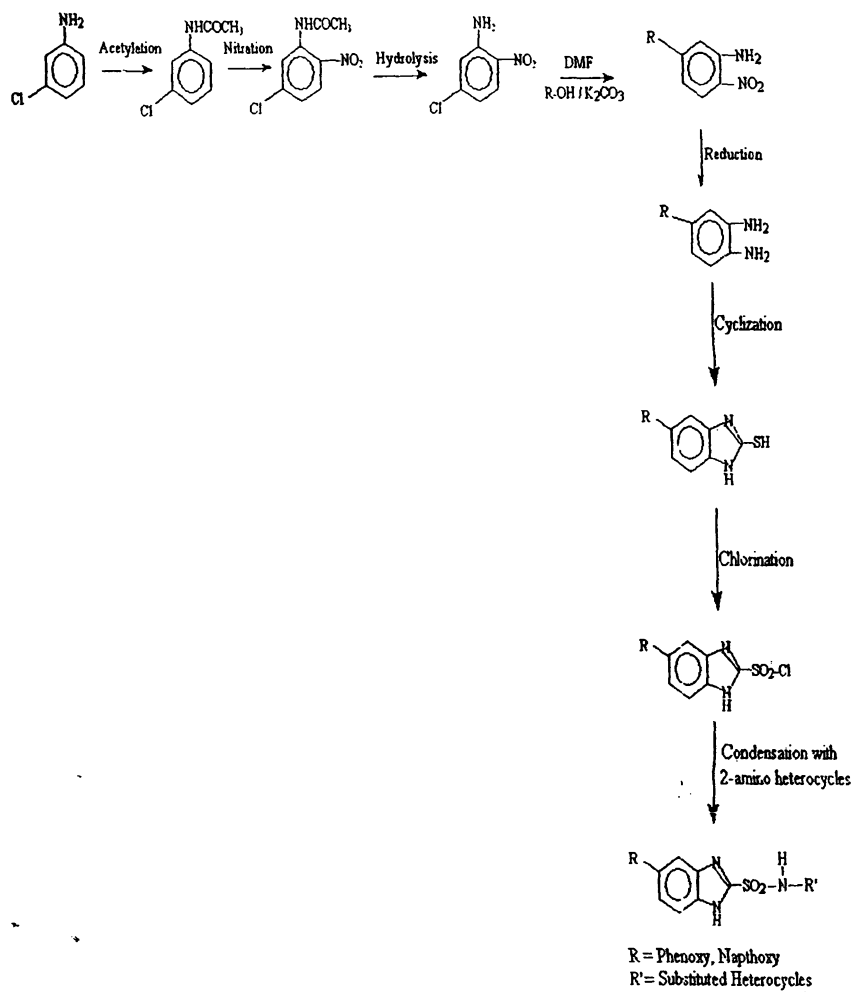
The well-known anti-bacterial activity of Sulphonamides & above facts prompted us to synthesize some 5-substituted 2-(1-H-benzimidazole) sulphonamides (IX) in order to get biologically active compounds.



Where R = Phenoxy, Naphthoxy, Cl
R₁ = H, simple/substituted heterocycles

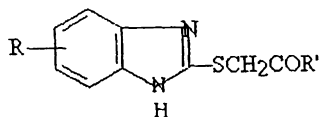
Thus, title compound is prepared by condensing 2-Mercapto Benzimidazole molecule having substitution at fifth position with 2-Amino substituted heterocycles to get corresponding sulphonamides. Thus we have synthesized 6-10 compounds in this series, which have been further screened for their antifungal and antibacterial activities.

SCHEMATIC REPRESENTATION:



3. Synthesis of some 5,6-Disubstituted- 2-(Phenyl Thiocarbamoyl) Benzimidazoles.

Following type of Benzimidazoles (X) are well known for their diverse biological properties¹³.

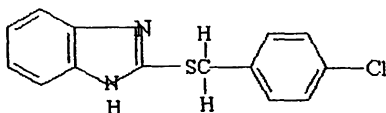


[X]

Where R = H, CH₃, Cl, NO₂

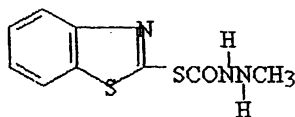
R' = Me, Ph.

A development occurred in the field of benzimidazole with emergence of broad-spectrum anti-microbial compounds¹⁴ (XI).



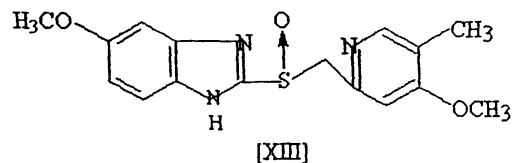
[XI]

Also, Assad & Falmy¹⁵ synthesized benzothiazoles (XII) having thiocarbamoyl linkage at 2nd position & were found to show inhibition zone of 9-18 mm on various bacteria at a concentration of 0.019/ 100ml.



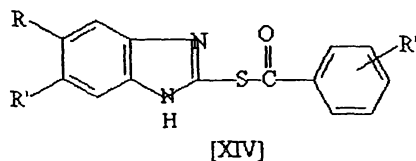
[XII]

5-methoxy-2-mercapto benzimidazole has been found as an intermediate for Omeprazole¹⁶ (XIII), which is a potent anti-ulcer agent & is used in treatment of "Zollinger Ellison" Syndrome.



All, the above examples indicate the importance of benzimidazole nucleus & thiocarbonyl linkage at second position of benzimidazole nucleus.

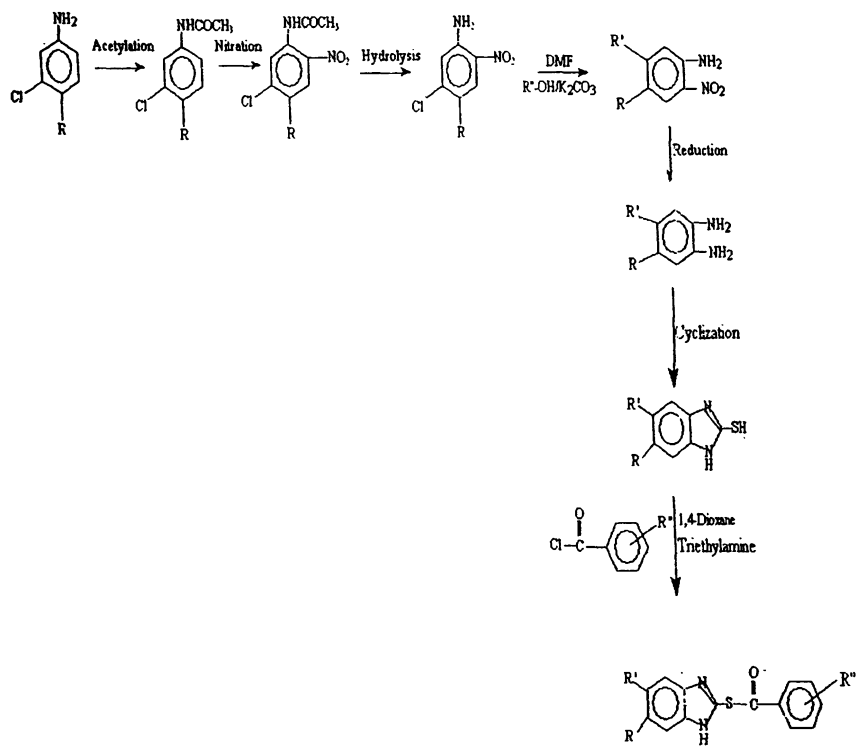
Taking into account the above facts & biological importance, a series of compounds (XIV) of 5,6-disubstituted (Phenyl Thiocarbonyl) benzimidazoles has been effected so as to study their anti-bacterial activities.



Where R = Phenoxy, Naphthoxy
 R' = Cl, H
 R'' = H, Cl

Above, compounds were prepared by condensing 5,6-disubstituted-2-Mercapto Benzimidazoles with substituted biologically active benzoyl chloride. We've prepared 6-10 compounds of such type, which have been further screened for their antifungal and antibacterial activities.

SCHEMATIC REPRESENTATION:



$R = H, Cl$
 $R' = \text{Phenoxy, Naphthoxy}$
 $R'' = H, Cl$

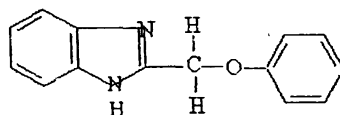
4. Synthesis of some 5,6-Disubstituted-2-Phenoxymethyl Benzimidazoles :-

A large number of Benzimidazole derivatives have been reported to possess trypanosomicidal & spirocheticidal¹⁷ action and are active against the disease caused by protozoa.

2-Alooxymethyl Benzimidazoles possess anti-pyretic activity¹⁸. Some other substituents, when introduced in the position 2, impart anti-histaminic¹⁹ anti-malarial²⁰⁻²¹ & also their utility as local anaesthetics²².

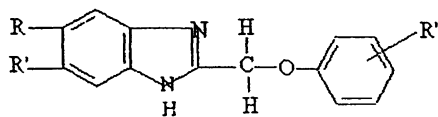
In general the compound having substituents at position 2 have been found to be very much pharmacologically active²³.

It is considered, therefore to be worthwhile to synthesize 2-Phenoxymethyl Benzimidazoles (XV) involving variations in phenoxy nucleus for testing purposes.



[XV]

For, further enhancement of biological activity it is very interesting to substitute Fifth & Sixth position of above molecule (XVI) to check the effect of substitution on the biological activity.



[XVI]

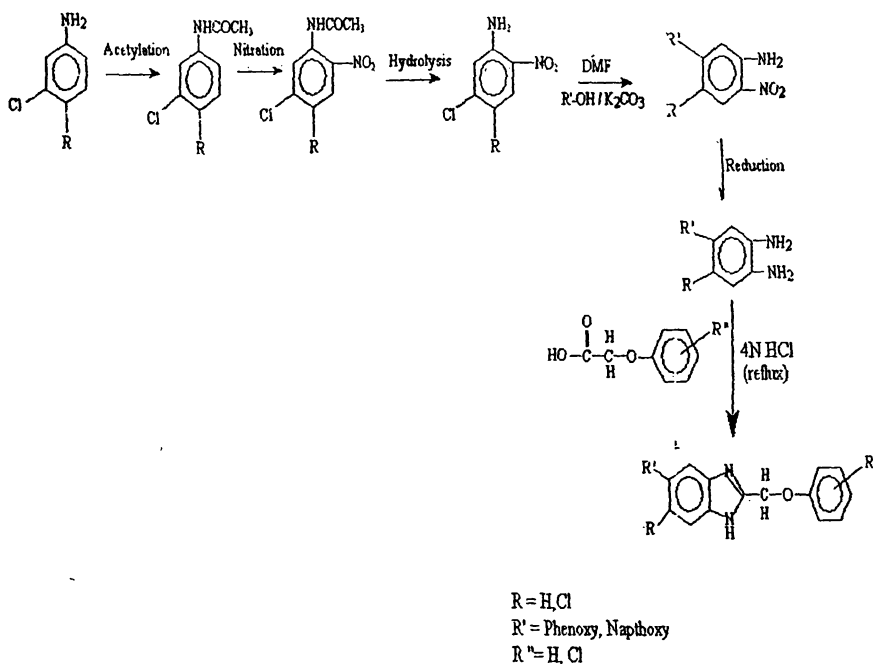
Where R = Phenoxy, Naphthoxy

R' = Cl, H

R'' = Cl, H

Above mentioned series of compounds are prepared by condensing 5,6-Disubstituted ortho phenylene diamine with different substituted biologically active phenoxy acetic acid to get respective compounds. Thus we've synthesized 6-10 compounds, which have been further screened for their antifungal and antibacterial activities.

SCHEMATIC REPRESENTATION:



Thus we've synthesized total 30-35 compounds and elucidation of these compounds confirmed by Thin Layer Chromatography (T.L.C.), Carbon, Hydrogen, Nitrogen, Sulphur (C, H, N, S) Analysis, Proton Magnetic Resonance (PMR) Spectroscopy, Infra-Red Spectroscopy (IR) and same compounds have been screened for their antibacterial and antifungal activities.

Biological Screening

The compounds reported in the above-mentioned series have been subjected to *Invitro* antibacterial screening their results will be discussed in the thesis.

The test compounds (10 mg) were dissolved in suitable solvent (10mL) such as Dimethyl sulfoxide (DMSO), so as to prepare compound stock solution of concentration 100 Mgm/mL.

The test compounds were subjected to invitro screening by the tube dilution technique against Gram-positive and Gram-negative bacteria Viz. *Staphylococcus aureus. ATCC 3750* and *Salmonella typhi 786* using Mueller-Hinton broth as the culture medium²⁴. The tubes were incubated at 37°C for overnight and then examined for the presence or absence of growth of the test organisms. The lowest concentration that showed no visible growth was taken as an end point i.e. **Minimum Inhibitory Concentration (MIC)**.

Compounds reported in series in I, II, III and IV were also screened for their antifungal activity by the tube dilution technique²⁵ against fungal strains viz. *Candida albicans*.

In different screening methods, the standard drugs employed were *trimethoprim* as general anti-bacterial agent and *miconazole* as an anti-fungal agent.

The results of the above antibacterial and antifungal screening will be discussed in the thesis.

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