Fungi constitute an extremely heterogeneous group of thallophytes, comprising at present approximately 80-100 thousand described species among about 2 billion different kind of living things with many thousands more yet to be investigated and described.

Various systems of classification have been proposed for the fungi. The mycologists are, however, not in much agreement over the subject, as a large number of species or forms are very imperfectly known and their relationship are consequently obscure.

Fungi have been classified (1) into Schizomycetes (bacteria), Myxomycetes (slime molds) and Eumycetes (true fungi). Eumycetes have been further subdivided into four major classes, namely Phycomycetes, Basidiomycetes, Ascomycetes and Fungi Imperfecti.

Species belonging to these groups are mainly plant pathogens (2). However Phycomycetes are pathogenic to fish while many of the species belonging to the group of Fungi Imperfecti (Deuteromycetes), Schizomycetes and Ascomycetes are pathogenic to man and animals.

Though fungi are important plant pathogens several species are pathogenic for man and animals. Comparatively few plant diseases are caused by bacteria. Among the diseases of man and animals, on the other hand, bacterial diseases predominate and the list of important fungal disease is short. Fungi therefore appear to be poorly adapted to parasitic existence in man except in a few instances. Probably all pathogenic fungi exist as saprophyte in soil or on
vegetation or on humus. When these fungi become parasitic in man, the majority change their mode of growth and reproduction. Others which are unable to adopt themselves to a new environment by changing their growth habit fail to become pathogenic and hence relatively few fungi are pathogenic to man and the higher animals and none is an obligate parasite.

Nutritional studies of fungi are few compared to that of bacteria. Gilardi (3) reviewed the essential growth factors and nutritional characteristics of fungi responsible for the systemic and subcutaneous mycoses of man with primary attention on dimorphism, vitamin and amino acid requirements, assimilation patterns and agents demonstrating a beneficial or deleterious effect on the growth etc.

Though not fully investigated, the fungi studied assimilated carbon from all the hexoses excepting the lactose (4-7). Carbohydrate derivatives assimilated include gluconic acid, lactone, glyceraldehyde, pyruvic acid, lactic acid, Kreb cycle intermediates, various amino acids and their derivatives as well as fatty acids. With regard to nitrogen assimilation the amino acids and their derivatives along with the more complex organic compounds, like citrulline, ornithine, asparagine, glutamine, glutathione, glycylglycine, urea (4), acetamide, keratin (8) etc. are worth mentioning.

Various surface active agents including the fatty acids such as oleic acid, generally stimulated the growth of fungi (9-12) and this was attributed to the ability of these agents to allow the nutrient material of the culture medium to come in more intimate contact with the cell thereby increasing the permeability of the cell which in turn facilitated faster utilization of the nutrients with consequent stimulation of growth. Environment detoxifying agents like albumin, starch, agar also enhanced growth. Marvin (11,12) found some non-ionic surface tension reductant to have a stimulatory effect on C. albicans, C. neoformans and Sporotrichum.
Physical modification also had a beneficial effect and includes alteration of the pH of the medium, temperature of incubation, changes in atmosphere of incubation like aeration with CO₂ (13,14), mechanical agitation etc. However the role of O₂ and CO₂ on the growth of fungi was not fully understood.

Results further indicated that agents which had a deleterious effect on the growth of fungi were mainly reducing agents or sulfur containing compounds. Drop in the redox potential where growth was very much retarded or not initiated at all was assumed to be the cause of inhibition. With compounds like methionine, cysteine and thiourea the sulfur radical probably blocked the enzyme systems through the oxidation of -SH- active sites or by functioning as a chelating agent. In support of the above facts it was shown (15) that the fungistatic activity of thiourea was reversed by the addition of compounds which replaced or reconstituted -SH- grouping.

Of all the microbial infections of man the diseases caused by fungi are the most difficult to modify in their course or to prevent. Although fatal fungal diseases in man are less common than bacterial infections they are nevertheless numerically important. The growing health problems in man due to fungal diseases have been pointed out by Reiss (16).

Non-fatal diseases are perhaps as common as any bacterial disease. The commonest skin diseases in man are of such light importance that they are almost disregarded.

With the advent of broad spectrum antibiotics monilial infections appear to have increased. Candida albicans exist in the throat and other parts of the body as saprophytes of normal individuals. When the bacteria are removed, the monilia are permitted to grow unchecked. Certain antibiotics even stimulate their growth. The use of such medicinals and therapeutic agents as broad spectrum antibiotics, antitumour agents, steroids, immunosuppressants, X-ray irradiation and oral
contraceptives have been reported to contribute an increased incidence of superficial cutaneous or deep seated mycoses. The frequency of fungal infections complicating acute leukemia in the period from 1959 to 1964 doubled when compared with the frequency of the preceding five year period (17,18).

The important human pathogens have been described by Conant and his co-workers (19).

Human fungal infections have been classified into two principal groups, the superficial and the systemic.

The main oral fungal infections include Onchomycosis, Angular cheilosis, Gingivostomatitis, Lingua nigra, Lingua geographica etc. The dermatophytic type of superficial infections are caused by Trichophyton species whereas the causative organism of the tinea infections (tinea pedis, tinea cruris, tinea capitis, tinea barbae etc.) are Trichophyton species (rubrum, verrucosum, mentagrophytes tonsurans), Candida albicans, Epidermophyton floccosum and Microsporum species alone or together.

A few of the systemic infections are Histoplasmosis, Blastocytosis, Cryptococcus, Sporotrichosis, Actinomycosis, Nocardiosis, Candidiasis, Chromomycosis and Aspergillosis.

Antifungal is a general term used to describe any agent which is capable of either inhibiting the growth or reproduction of fungi but does not kill (fungistatic) or actually killing fungi or their spores (fungicidal). An antifungal agent has the implied qualification of acting as such against a certain species of fungus or even a variety of fungi. To be active as an antifungal agent whether as a fungicide or a fungistat a compound should possess the following properties: (i) It should be lipoidal (20) for the penetration of fungal cell walls and accumulate at the site of action within or on the surface of fungal cell. (ii) It should be ionic to
interact with the cellular enzymes. (iii) It must have the power to interfere with at least one process vital to the continued existence or growth of the cell.

An ideal antifungal agent should be a compound that is chemically, therapeutically and cosmetically acceptable and active against a wide spectrum of pathogenic fungi without having any toxic side effects to the host, should be capable of administration parenterally or orally and reach the site of the organism in effective concentration. In case of fungi which produce generalized fungal infections it must be administered internally.

No single fungicide is known to meet all the above requirements, although recently a few compounds approaching an ideal single acting fungicide have been prepared.

There have been many attempts to establish structure activity relationships in the chemotherapy of fungal infections. A large number of compounds having diverse chemical structure like various antibiotics, hormones, dequalinium chloride, diamthazole, tolnaftate, chlorphensin, gentian violet, Whitfield's ointment etc., etc. have been shown to possess marked but specific antifungal activity. Consequently it appears that there is no general structure activity relationship in this field.

Classification of antifungal agents, thus presents a problem. In this review these agents have been divided into the following groups based solely on their chemical structure:

(a) Acids.
(b) Acetylenic compounds.
(c) Phenols.
(d) Ethers.
(e) Salicylic acid and its derivatives.
(f) Esters.
(g) Nitro compounds and nitrofurans.
(h) Amines, Amidines, Guanidines and related compounds.

(i) Quaternary ammonium compounds.
(j) Quinolines and Quinones.
(k) Antihistaminic antifungal compounds.
(l) Steroids.
(m) Sulfur compounds.
(n) Heterocyclic compounds.
(o) Antibiotics.
(p) Miscellaneous compounds.
a) **Acids**

Sweat is reputedly fungistatic. Lower fatty acids like propionic, butyric, lactic, ascorbic acids etc. are the constituents of perspiration and these acids or their salts were long known to improve clinical fungus infections. Keeney and Broyles (21) reported the efficacy of sodium propionate in the treatment of certain superficial fungus infections.

*In vitro* studies (22) of the homologues of aliphatic acids with 1-10 carbon atoms have revealed that fungistatic activity increased with the increase in chain length. The activity was found to be dependent on the pH of the test solution. The maximum activity was found at pH 5. Clinically several of the fatty acids or their sodium, calcium and zinc salts have been used in the treatment against tinea cruris, tinea pedis, sycosis barbae etc. Sodium caprylate was found to exhibit good activity against fungal infections of the feet.

Gershon and Permegiani (23) compared activities of 2-fluoro fatty acids with non-fluorinated fatty acids. The maximum activity was observed when the chain length was of 8-14 carbon atoms for the non-fluorinated and of 4-10 carbon atoms for fluorinated fatty acids. The authors believe that the pKa values do not play an important role in exhibiting antifungal activity. 2-Fluoro fatty acids unlike non-fluorinated fatty acids cannot undergo \( \beta \)-oxidation and hence show comparatively little toxicity.

Peck and Rosenfield (24) found that olefinic acids possess antifungal activity greater than the aliphatic homologues. Baker (25) reported that the unsaturated fatty acids having 6-12 carbon atoms or their zinc salts have fungicidal properties. Undecylenic acid itself is a powerful antifungal agent and is used for local applications, ointments or dusting powders for the treatment of tinea pedis, tinea capitis and cruris, moniliasis, mycotic vulvo vaginitis and similar complaints. The zinc salt was often found to be more efficient. Like other fatty acids its antifungal activity was maximum at acid pH.
Iodo-10-undecylenic acid was claimed to be superior to undecylenic acid for the treatment of dermatophytes of the skin of guinea pigs (26). Goodwig (27) and Geigy (28) reported that certain \( \alpha,\beta \)-unsaturated fatty acids and their derivatives possess fungistatic activity. It was reported that sorbic acid, \( \text{CH}_2=\text{CH}-\text{CH}=\text{CH}-\text{COOH} \), was superior to benzoic acid as a fungistatic agent for pharmaceutical preparations (29).

The importance of the terminal vinyl group in determining antifungal activity was demonstrated by Settine et al. (30) who showed that 2,2-dimethyl-3-vinylcyclo-10-undecenoic acid, whereas 1-butane acetic acid was as active as di-n-hexyl pinate and lauryl pinonate or compounds having the dimethylcyclobutane acetic acid group but lacking the vinyl group were not fungistats.

The mechanism by which fatty acids act as fungistatics was investigated (31,32) with special emphasis on sorbic acid. In the presence of an excess of \( \alpha,\beta \)-unsaturated fatty acid eg., sorbic acid, the activity of the dehydrogenase system of the fungi was inhibited. This inhibition was believed to be responsible for the antifungal activity and the degree of activity appeared to be a direct function of dosage. Whitaker (33) postulated that the enzyme inhibition by sorbic acid was due to sulfhydryl enzyme inhibition through the formation of a thiohexenoic acid derivative.

Cinnamic acid and its derivatives are known to possess antibacterial, anti-tubercular and antifungal activity. Uppal (34) found that cinnamic acid was more fungicidal than benzoic acid and its activity was of the order of salicylic acid. 2-Methyl-4-chlorophenoxy acetic acid was the most active among a number of phenoxy acetic acids tested (35). The fungistatic activity of phenoxy acetic acids on \( C. \text{ albicans} \), was enhanced (36) by the introduction of groups like \(-\text{COOH}, \text{CH}_3\text{CO}-,\) \(-\text{CHO}\) or \(-\text{SO}_3\text{H}\) in ortho or para positions of the phenyl ring. These compounds were more active against yeast like organisms than against dermatophytes.
Acrylic acid and its derivatives exhibit pronounced antifungal activity (37). A preparation containing \( \alpha,\beta \)-aroylacrylic acid useful against intestinal infections, has been patented (38).

b) Acetylenic Compounds

A great interest arose regarding acetylenic compounds since the discovery of the antifungal activity of capillin(I), 1-phenyl-1-oxohexa-2,4-diyne, isolated from the essential oil of Artemisia Capillaris Thunb. It was reported to possess high antifungal activity (39). A series of compounds related to capillin (40), (II to V), were tested. Compound (II) was more active than (III) suggesting that the carbonyl radical adjacent to the acetylenic linkage was essential. This was not true in compounds (IV) or (V). Substitution of ethyl or methyl did not alter the activity but reduction of acetylenic bonds from 2 to 1 greatly reduced activity. Capillin was the most active against T. asteroids.

\[
\begin{align*}
(I) & \quad \text{Ph-}C\equiv\text{CSC-CH}_3 \\
(II) & \quad R-C-(\text{CSC})_n-R' \\
(III) & \quad R-\text{CH-(CSC)}_n-R' \\
(IV) & \quad \text{Ph-CSC-CH=CH}-R'' \\
(V) & \quad \text{Ph-CSC-CH(OH)-CH=CH-R''} \\
\end{align*}
\]

1-Hydroxy-1-phenyl-2,4-hexadiyne derivatives (41) of the structure (VI) were patented and were found to be useful for the therapy of skin disease by filamentous fungi.
The position of the triple bond in acetylene derivatives plays an important part in determining the activity, as has been studied by Cox and coworkers (42) in a series of isomeric octynoic acids. The Δ-2,3 isomer was active against bacteria while Δ-4,5; Δ-5,6 and Δ-6,7 isomers showed high activity against fungi. The Δ-9,10 acid possessed considerable activity but slightly less than undecylenic acid but that of greater than octynoic acid (43).

Among the -iodo acetylenic fatty acids, 1-C6C-(CH2)n-COOH, (n = 1 to 10) prepared and tested by Ueno and Maeda (44,45) compounds having n as 5 or 6 exhibited significant antifungal activity but were devoid of antibacterial activity.

γ-Iodopropargylaryl ethers having the general formula Ar-O-CH2-C≡C-I (VII) where Ar may represent a phenyl or naphthyl group having at least one substitution as halogen, alkyl, alkoxy, carboxyl or nitro group were found to possess strong antimicrobial activity (46). The most active compound of the series is 2,4,5-trichlorophenyl γ-iodopropargyl ether (Haloprogin, M-1028), (VII-a), which exhibits strong antifungal and antibacterial activity both in vitro and in vivo (47). It is active when applied topically in experimental dermatophytic infections in guinea pigs and appears approximately as active as tolnaftate (48). The other derivatives of haloprogin (VII-a), including mono- and dichlorophenyl compounds also showed fairly high antifungal activity.

Ar-O-CH2-C≡C-I

(VII)

Cl-C≡C-I

(VII-a)

Iodopropargylcarbinol compounds like R1R2-O-(OH)-CH2-C≡C-I where R1 may represent H or R2 may represent an alkyl radical containing 1-6 carbon atoms were reported to
have been used for the control and treatment of water eczema and disease in human and animals caused by A. fumigatus and C. albicans (49).

Several acetylenic derivatives of furan as shown below were tested (50).

(a) \( R^1COC=S\)Ph, (b) \( R^2COC=O\)Ph, (c) \( R^1COC=CR^2 \), (d) \( R^2C\equiv C\)OMe,
(e) \( R^2C\equiv COC(Me)=N-WHCONH_2 \), (f) \( R^2C\equiv COOH \), (g) \( R^2C\equiv C\)OMe, where \( R^1 = 2\)-furyl; \( R^2 = 5\)-bromo-2-furyl and \( R^3 = 5\)-nitro-2-furyl. Fungistatic activity of (a) was comparable to that of nystatin and that of (d) was higher than that of griseofulvin. Fungistatic activity of the compound (b) was insignificant in comparison with that of compound (a) and probably introduction of a nitro group in 5-position of the furan ring caused loss of fungistatic activity.

Among a number of capillin furylvinylacetylenes, capillin furyldiacetylene derivatives and their thio analogues tested (51), the most active antibiotics of this group were VIII, IX-a and IX-b. Introduction of a second triple bond in the side chain increased the antifungal properties.

\[
\begin{align*}
\text{(VIII)} & & \\
\text{(IX)} & & \\
\text{a. } R = C_6H_5Cl; & n = 2 \\
\text{b. } R = C_6H_5; & n = 2
\end{align*}
\]

c) Phenols:

Because of their high efficiency as antibacterial agents, compounds containing phenolic group have been tested against fungi in the treatment of superficial mycoses. Simple phenols like phenol, cresol, resorcinol, \( \beta \)-naphthol, thymol etc., have long been included in antifungal preparations like external mycotic infections.
Klarmann et al. (52-55) reported on the systematic investigation of the germicidal and fungicidal action of monohalogen substituted phenol homologues in relation to chemical constitution. Substitution of halogen atom considerably intensified the microbicidal potency of phenols, substitution in para position being more effective than the ortho substitution. Introduction of alkyl groups into the nucleus of halophenols further increased the activity, the increase being dependent on the number of carbon atoms introduced. Woodward et al. (56,57) investigated the fungicidal activity of miscellaneous alkyl and halogenated phenols and found that halogen atoms increased the fungicidal power 4 to 10 folds. The fungicidal power increased from chlorine to bromine to iodine. The introduction of nitro groups did not increase fungicidal power. Shirk and Corey studied several ortho-chlorophenols and showed that fungistatic activity was not better than parent phenols and the fungistatic activity was low in those ortho chlorophenols which contained alkyl constituent in the remaining ortho position (58).

Podna and Corey (59) observed that fungicidal effectiveness increased 3 to 10 fold by para-chlorination of phenols. Substitution of alkyl, cycloalkyl or aryl groups further significantly enhanced potency of para chlorophenols.

Penta-chlorophenol (60) was found to be highly fungicidal against T. mentagrophytes and T. purpurum, being effective upto 1 in 200,000 dilution and 50 times more effective than salicylic acid. The activity was not affected by addition of serum. It was non-irritant to the human skin and conjunctiva. Since penta-chlorophenol possessed antibacterial activity higher than that of sulfanilamide, sulfathiazole, or nitrofuran, it was recommended against dermal diseases caused by mixed infection.

5-Chloro-2,4,6-trifluoro-5-methylphenol (61) is a strong antifungal and effective anthelmintic agent. 2,4,6-Tribromo-5-methylphenol in a water oil emulsion or rice base is an useful fungicide for the treatment of dermatophytes namely ringworm or athlete's foot.
Resorcinol was long known as a bactericidal and bacteriostatic agent in the treatment of bacterial infections of the skin and mucous membrane and it was clinically used as a fungicide. Brown (62) and later Woodward and coworkers (63) reported fungicidal properties of resorcinol monoethers. The supposition that at least one free hydroxyl group must be present for fungistatic activity (as also for bactericidal activity) was confirmed by Zabrasky and Wright (64). The mono acetate, mono benzoate and monoethyl ether of resorcinol and ring substituted 4-chloro derivatives were as active as undecylenic acid. The monomethyl ether and the 4-chloro derivatives were too irritating whereas resorcinol mono benzoate produced no conjunctival irritation and was found to be one half as toxic as the clinically used resorcinol mono acetate.

Several compounds related to P-naphthol (because of their antibacterial activity) and 2-hydroxynaphtholic acid were prepared by Baichwal et al. (65). In this series alkylation of P-naphthol enhanced bacteriostatic activity only but halogenation increased both bacteriostatic as well as fungistatic activity. The position of substituent and the presence of a free phenolic hydroxy group were however influencing factors. Results indicated that 1-bromonaphthol and 6,6'-dibromo-6'-dinaphthol were the most active against dermatophytes. Five halogenated derivatives of 1,6-dinitro-P-naphthol showed fungistasis at 10 mcg/ml. These authors further showed that 1-bromo, 6-bromo, 1,6-dinitro, 6-γ-hexyl-6'-naphthols and 1,6-dibromo-2-hydroxy-3-naphthanilide possessed good fungistatic properties in the form of an ointment and were non-irritant to intact rabbit skin. The LD50 of 6-γ-hexyl-P-naphthol was 127 mg/kg body weight by interperitoneal administration.

Dithanol (1,8-dihydroxyanthranol) (X), (66), is used in chronic dermatoses especially psoriasis as 0.1-1.5% ointment.
Marsh and coworkers (67) tested several bisphenols and reported that bisphenol bridges consisting of \(-\text{CH}_2\), \(-\text{CH}((\text{CH}_3)_2\), \(-\text{CH}(\text{C}_6\text{H}_5)_2\), \(-\text{CH}=\text{CH}\), and \(-\text{S}-\) were found to be compatible with high activity whereas \(-\text{SO}_2\) and \(-\text{SO}_3\) bridges were less active. The influence of chemical structure on bisphenolic type compounds was reported (68,69). The most active compounds contained two atoms of chlorine para to the hydroxyl group and the bridge substituted at the 2,2' positions. Any deviation from this structure diminished potency. The trichloroethylidene structure linking two moles of para-chlorophenol in the 2,2' positions was the most effective compound studied. Hata et al. (70) observed a \(-\text{S}-\) bridge to be more effective than a \(-\text{CH}_2\) bridge in increasing antifungal effect.

Various bisphenols (71) and thiobisphenols are fungistats (68) for topical use. Hexachlorophene \([\text{bis}(3,5,6\text{-trichloro}\text{-2-hydroxyphenyl})\text{methane}]\) (XI), although mainly used as a non-irritant, potent antibacterial agent good results were obtained in the treatment of certain dermatoses, particularly against monilial intertrigo. Barr and coworkers (72) reported a product containing phenylmercuric acetate and a bisphenol such as dichlorophene or hexachlorophene as an useful agent in the treatment of superficial fungus infections like ringworm or athlete's foot.
In the thiobisphenol series tested by Gump and Walter (73) as well as Tashika and his coworkers (74), 2,2'-thiobis-4,6-dichlorophenol and 2,2'-thiobis-4-chloro-phenol showed stronger antifungal action than benzalkonium chloride, butyl-p-hydroxybenzoate, 8-quinolinol, salicylanilide and undecylenic acid but not phenylmercuric acetate.

d) Ethers:

Several substituted ethers showed promising antifungal activity (75) and a few of them have been included here.

1-Phenoxy or p-chlorophenoxypropan-2-ol (XII) exhibited marked fungistatic and fungicidal activity against superficial mycotic infections and are now used in the treatment of athlete's foot. Chlorphensin(mycil) or 3-p-chlorophenoxypropane-1,2-diol (XIII, 76) is a potent antifungal, antibacterial and trichomonocidal compound with little toxicity and is mainly used in the treatment of athlete's foot, dhobi itch, pruritus ani and pruritus vulvae. The phenyl ethers of propylene glycol or glycerol showed promise as non-toxic fungicide.

\[
\begin{align*}
\text{X} & \quad \text{O-CH}_2\text{-CHOH-CH}_2 \\
& \quad \text{X} = \text{H or Cl} \\
\end{align*}
\]

\[
\begin{align*}
\text{Cl-} & \quad \text{O-CH}_2\text{-CH(OH)-CH}_2\text{OH} \\
& \quad \text{(XIII)} \\
\end{align*}
\]

A number of antifungal isothiocyanates were found to contain ether group (77). Local anesthetics containing aryl ether group were fungistatic. Many of the anti-histaminics also contained ether group (78). Aryl alkamine ether (79) and the
morpholinoalkyl ethers of halogenated phenols (78,80) exhibited high antifungal activity. These findings suggest that aryl or aralkyl ether group may confer antifungal activity on various chemical structures.

e) Salicylic Acid Derivatives:

Because of its keratolytic action salicylic acid has been included in many remedies for dermatophytes. Several of its derivatives have found their way into the therapy of fungal diseases, of particular interest being 3,5-dibromo salicylaldehyde (81), used topically as a fungicide.

Salicylamides and anilides showed marked analgesic property, many of these were later found to exhibit good antifungal activity. Faust et al. (82,83) prepared a large number of its derivatives and reported that 2-alkyloxybensamide was the most potent analgetic. However several compounds notably 3,5-diisopropylsalicylamide exhibited marked antifungal activity. Of a number of phenylsalicylamides tested (84) some compounds showed high activity against dermatophytes in addition to the analgesic activity. The most potent compound being N-n-butyl-3-phenylsalicylamide. 2-n-Pentyloxybensamide (XIV), is a slow acting fungicide and is of greater fungistatic potency than undecylenic acid, salicylanilide, nystatine and phenylmercuric acetate. It has a specific action against dermatophytes. Salicylanilide in the form of an ointment was used in the treatment of ringworm of the scalp. A mixture of salicylanilide with undecylenic acid or its salts was patented (85).
Like other cases, halogenation tends to increase the antifungal activity of salicylanilides also. The 3-chloro and 4-chlorosalicylanilides tested by Wayne-Schultz (86) showed greater antifungal activity than salicylanilide. The 5-chlorosalicylanilide have also been used in fungal therapy (87). The position of hydroxy and chloro group in o-, m- and p-hydroxybenzanilides are of special importance in view of high degree of activity (88). Among a series of salicylanilides (89) the dichloroanilides of salicylic acid showed the most powerful antifungal activity. 3,5-Dichlorosalicylanilide (XV) in a concentration of 0.3-1.5 mcg/ml was fungicidal against dermatophytes and only slightly toxic when administered subcutaneously (90).

3,5,4'-Tribromosalicylanilide (XVI) and 5,4'-dibromosalicylanilide (XVII) (known as bromosalanes) have a high degree of antibacterial and antifungal activity with low toxicity and show promise for use in medical formulations (91). High in vitro activity (92) is observed against various species of Trichophyton, Microsporum and Epidermophyton by a series of N-dichloriodosalicylanilide, N-dichloriodo-4'-chlorosalicylanilide, N-dichloriodo-4'-bromosalicylanilide and N-dichloriodo-4'-iodosalicylanilide. The first two members have an anticandida effect. The whole series of compounds are characterized by their low toxicity.

5,5'-Dibromosalicylic (XVIII) has also been used in the therapy of fungal diseases (93).
Salicylhydroxamic acid, an antitubercular agent, is used as a topical antifungal agent (81). 4'-Thiocyanatosalicylanilide showed a high order of antifungal activity, equal to that of the best antibiotic, but it had no activity against candida or saprophytic fungi in vitro (94). Of the 73 azomethines tested by Rotmistrov et al. (95), salicylideneaniline, salicylidene-o-aminophenol (XIX), salicylidene-o-chloroaniline, salicylidene-p-bromoaniline, and salicylidene-p-aminoacetanilide were highly active against T. gypseum and C. albicans in vitro.

\[
\text{CH}_2\text{N-} \\
\text{OH} \quad \text{HO}
\]

(XIX)

Aliphatic and aromatic acid hydrazones and thiosemicarbazones (96) of 5-chlorosalicylaldehyde showed varying degrees of activity against pathogenic fungi.

As pointed out by Balchawal and his colleagues (97), the fungistatic activities of compounds structurally related to salicylanilide suggested the possible involvement of hydrogen bonding of the anilide hydrogen atom and chelation by phenolic and acidic oxygen atoms. The participation of sulfhydryl groups was also suggested by these authors.
f) Esters:

A number of esters like m-cresyl acetate, pyrogallol triacetate, 1,2-propanediol diacetate, triacetin (glyceryl triacetate) etc. have been found to possess valuable antifungal property. 1,2-Propanediol diacetate (98) is as active as sulfonamides and nitrofurans against dermatophytes which invade the mucous membrane. It is free from toxic side effects. Triacetin (glyceryl triacetate) is used topically. Its fungicidal activity is due to the slow release of acetic acid formed by the hydrolysis of the esterase of skin and the rate of release is self limited because as the pH drops to 4, the esterase are inactive preventing further hydrolysis (99).

Alkylesters of p-hydroxybenzoic acid (paraben) have long been known to possess antibacterial and antifungal activity. Huppert studied p-hydroxybenzoic esters with upto 16 carbon atoms in the alkyl chain. Maximum activity against C. albicans and C. neoformans was found with the hexyl or heptyl esters. These esters were considerably more active than caprylic acid, sorbic acid or tetramethylthiuram disulfide (100).

Therapeutically active ointments for combating dermatophytic type infections were reported to contain (101, 102) ethyl, isobutyl or secondarybutyl vanillate in polyethylene glycol. Oral administration of ethyl vanillate was reported to have clinical success (103–105) against coccidioidomycosis and histoplasmosis. Various esters like methyl, ethyl, propyl and benzyl esters of p-aminobenzoic acid were used for healing skin diseases as fungicidal ointments (106).

Undecenoic esters of 8-hydroxyquinoline (XX) and the salts of these esters are effective as medicaments against skin diseases caused by fungi particularly on the feet (107). Ethers of p-hydroxybenzoic esters (XXI) showed high in vitro antifungal activity but the activity was greatly reduced in the presence of serum. Diethylaminoethyl fencholate (XXII) has been used clinically in histoplasmosis (108) and it
showed equal or superior antifungal action when compared with diphenyl pyraline, gliotoxin, diamthazole, nitrofuranylmethyl ether and Cu 3-phenyl salicylate in vitro (108, 109).

\[
\text{R} = \text{alkyl} \\
\text{n} = \text{small integer}
\]

(XX) \hspace{1cm} (XXI) \hspace{1cm} (XXII)

3-Methyl-5-isopropylphenyl esters (110, 111) particularly the pyrrolidinyl or morpholinyl esters showed pronounced activity towards dermatophytes and were useful in the treatment of trichophytic dysidrosis, ungual mycosis and epidermatophytes. Its action is only local apparently keratinoplastic and not keratinolytic.

Esulan, ethyl ester of thiosulfanilic acid (XXIII) showed fungistatic and fungicidal activity at a concentration of 1:16,000 - 1:60,000. It is used as a drug for the treatment of epidermophytosis of the feet (112).

\[
\text{H}_2\text{N}-(\text{XXIII}) \\
\text{SO}_2\text{SC}_2\text{H}_5
\]

g) Nitrocompounds and Nitrofurans:

York and Reese (113) reported that compounds in general containing a \(-\text{C}==\text{C}-\text{NO}_2\) group had antifungal activity. McGowan (114) found that compounds in which the
Electrophilic nitro group was attached to an alkene side chain appeared to be several times more effective as compared to, when it was attached to an unsaturated ring. Edwards and Pianka (115) tested ethylenic compounds and found that ethoxy carbonyl and methyl carbonyl groups attached to ethylenic bonds were less active than nitro groups.

Nitrostyrenes and some arylaliphatic nitro compounds exhibited antifungal activity. 4-Nitrocinnamic acid and β-(5-nitro-2-thienyl) acrylic acid derivatives having ethylenic bridge as well as a nitro group showed high in vitro bactericidal and fungicidal properties (116). β-Nitrostyrenes and its γ-methoxy, acetoxy, methyl and γ-methoxy β-methyl derivatives (118) possess high degree of activity against pathogenic fungi. Huitrick et al. (119) reported that in the series of para substituted β-nitrostyrenes (substituents being chloro, bromo, nitro, acetoxy, hydroxy and diethylamino groups) the fungistatic activity was related to the ability of withdrawing electrons from the double bond.

Anticandidal properties of β-nitrostyrene derivatives were investigated by Bilich and coworkers (120, 121). Among the compounds examined 4-bromo β-methyl β-nitrostyrene showed the highest fungistatic (1-5′1 mcg/ml) and bacteriostatic effect on various species. The therapeutic effect against visceral candidiosis was similar to that of nystatin. It was effective in the therapy of rabbit skin candidiosis and was moderately toxic.

Among a series of arylaliphatic compounds of the general formula Ar.CH(OR)CBrNO_2.R' tested, 2-bromo-2-nitro-1-phenyl-1-propyl methyl ether was the most active (122,123). This compound was successful in the treatment of glabrous skin caused by T. rubrum. Preliminary clinical trials of this compound as 1% vanishing cream showed little toxicity, low irritancy, apparently low sensitizing index and a high degree of efficiency against mycotic lesions of glabrous skin (124).
1-Methyl-3-nitro-1-nitrosoguanidine (XXIV) (125) an antileukemic compound is comparable to the polyene antibiotics in fungistatic action *in vitro*.

\[
\text{NO} \\
\text{H}_3\text{C}-\text{N}-\text{C}=\text{NH} \\
\text{NH-NO}_2
\]

(XXIV)

Nitrofuran derivatives like furaspor (5-nitrofurfuraloxime) (XXV), furacin, aldehyde 5-nitro 2-furfural/semicarbazone were found to possess outstanding fungistatic property (126). A related compound 5-nitro 2-furfuryl-5-chloropropionate was highly active against Coccidioides immitis (127). Structure activity relationship was studied by Novikov et al. (XXVI) (128) among simple nitrofurans and furaldoximes. It was concluded that the antifungal activity did not correlate antibacterial activity. Introduction of a nitro group at 5-position facilitated fungicidal activity but the introduction of a second nitro group decreased the effect (128a).

Various unsaturated aldehydes ketones, acetals, acylals and oximes of 5-nitrofurans were studied (129) *in vitro* by Hillers and coworkers. Some of them had fungistatic activity comparable to that of nystatin and griseofulvin against Epidermophyton and Trichophyton. 3-(5-Nitrofururylidene)-2-butanone and 5-(5-nitrofururylidene)-2-pentenone were the most active compounds among some nitrofuran derivatives tested by Jeney and Zsolnai against thread forming dermatophytes, T. gypseum and Epidermophyton species (130). The antimicrobial activity of these
compounds was attributed not only to the 5-nitro-2-furyl group but also to the physicochemical properties such as solubility, protein binding and cell permeability.

Albrecht and coworkers (151) recently reported the antimicrobial activity of several nitrofurfurylidene, nitrothaylidene and nitropyrrylmethylen derivative of indanones and 1,2,3,4-tetrahydro-1-naphthalenes. Of the 74 compounds tested in vitro and in vivo 5-amino-2-(5-nitrofurfurylidene)-1-indanone (XXVII) was generally the most active having the minimum inhibitory concentration (MIC) against S. aureus - 0.024 mcg/ml, T. mentagrophytes - 0.78 mcg/ml and E. coli - 0.012 mcg/ml.

![Image of compound XXVII](image)

b) Amides, Amines, Amidines, Guanidine and Related Compounds:

Some N-substituted undecylamides, N- and isopropanol amides (132) were claimed to be effective fungicide for cosmetics. A preparation obtained from an equivalent amount of undecylenic acid and methanesine possess unique effect on areas topically infected with bacteria and fungi (133).

Among a number of diphenylamine derivatives tested by Sakai et al. 4-(2-diethylaminoethyl)diphenylamine and N-acetyl-4-pentloxydiphenylamine showed the strongest activity against C. albicans (134). Diamidinodiphenylamine dihydrochloride(135) showed high activity against H. capsulatum and C. neoformans.

Berkley (136) tested 159 alkyl diamines and showed that highest antimicrobial and antifungal activity was shown by the N,N-diaryl N,N'-dimethyl (or N,N'-diethyl)-ethylenediamines. The activity was found to diminish (with some exceptions) on
chain cyclization, however quaternization of inactive diamines with alkyl groups often imparted activity. In the \( H - \alpha - naphthyl - N, N', N' - trialkylethylenediamines \) (XXVIII) tested by Scudé and Grail (137) a high \textit{in vitro} antifungal activity (1:400,000) was shown by compounds where \( R \) was a long chain alkyl radical containing 6-14 carbon atoms and \( R_1 \) and \( R_2 \) were short chain alkyl radicals. These compounds were found to be useful in the fungus infection of skin such as ringworm of the scalp, barber's itch and athlete's foot. Paromikyan (138) studied several derivatives of \( N - alkyl - N - benzofurfuryl \) \( N', N' - dialkyl polymethyleneamines \) (XXIX) and showed that the longer the polymethylene chain the better was the effect and change of methyl or ethyl radical of the first nitrogen causes lowering or disappearance of the activity.

![XXVIII](image1)

![XXIX](image2)

Triphenylmethane dyes like malachite green, gentian violet and basic fuchsin have been used in the topical therapy of dermatophytosis as well as candidiosis of the skin and mucous membrane. Boehm (139) observed leucomethyl green to exhibit a relatively good inhibitory effect when applied to the skin. In most cases the leuco bases were found to possess stronger antifungal effect than the dyes and transformation of the leuco bases to the dyes by the fungi was also observed.

In view of the interesting trypanocidal activity shown by certain diamidino-alkanes, notably diamidinoundecane dihydrochloride, a large number of aromatic diamidines were prepared by Ashley and coworkers (140,141). Many of these compounds were found to possess potent antibacterial and antifungal activity in addition to their anticipated trypanocidal activity.
Stilbamidine (4,4'-diaminostilbene) (XXX; X=H) and 2-hydroxystilbamidine (XXX; X = OH) were shown to be active against Blastomyces dermatitidis infection in mice (142).

\[
\text{NH}_2\text{C} - \text{CH} - \text{C} - \text{NH}_2
\]

(XXX) \( X = \text{H, OH} \)

Though systemic blastomycoses and actinomycoses were cured with intravenous stilbamidine solution (143), the danger of trigeminal nerve damage by stilbamidine led its replacement by 2-hydroxystilbamidine (144). When administered daily by intravenous infusion, a 90% cure rate with low toxicity was achieved against blastomycosis. Several reviews discussed (145,146) the relative efficacies of 2-hydroxystilbamidine isethionate and amphotericin B.

Propamidine (XXXI; \( n = 3 \)) and pentamidine (XXXI; \( n = 5 \)) have marked activity against a wide range of pathogenic bacteria and fungi (147-149). Although propamidine was mainly used as an antibacterial agent in the treatment of septic wounds and burns, it was also used in the treatment of local mycotic infections particularly ringworm of the scalp by \( M. \) canis.

\[
\text{NH}_2\text{C} - \text{O} - (\text{CH}_2)_n - \text{O} - \text{C} - \text{NH}_2
\]

(XXXI)

4,4'-Diaminodiphenylamine dihydrochloride (XXXII) was shown to be more active in vitro than hydroxystilbamidine isethionate against \( M. \) mycetomi, the organism responsible for Madura foot. It showed more activity than sulfonamide, sulfone or other aromatic diamidines against South American Blastomycosis (150).
A number of antimicrobial $N^1, N^5$-substituted bisguanides possess considerable in vitro antifungal activity. One of the most active compounds was $N^1, N^5$-di(3,4-dichlorobenzylbiguanide) (XXXIII) (151). Substitution of iodine for chlorine or replacement of the halogen substituted benzyl group by a $\alpha, \beta$-diphenylethyl group gave compounds possessing good fungistatic potency. 1,1'-Hexamethylene bis-$[5(p$-chlorophenyl$)$biguanide] (XXXIV) a similar compound is a topical antiseptic agent (151).

\[ \text{(XXXII)} \]

\[ \text{Cl} \quad - \quad \text{CH}_2 \quad - \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{NH} \quad - \quad \text{CH}_2 \quad - \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{NH} \quad - \quad \text{Cl} \]

\[ \text{(XXXIII)} \]

\[ \text{Cl} \quad - \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{NH} \quad - \quad (\text{CH}_2)\_6 \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{NH} \quad - \quad \text{C} \quad - \quad \text{NH} \quad - \quad \text{Cl} \]

\[ \text{(XXXIV)} \]

i) **Quaternary Ammonium Salts:**

Alkyl benzyltrimethylammonium chloride (Roccal) (XXXV) although a skin sterilizing agent had been recommended against superficial fungus infections (75). Laurylpyridinium chloride was particularly active against T. mentagrophytes and was recommended for clinical investigation in the therapy of tinea pedis (152). 4-Bromobenzyl-3-(4-chloro-5-methyl-2-isopropylphenoxy)propyldimethylammonium chloride (Halopenium) (XXXVI), an antifungal agent was active against candida species. $N^1$-Dodecanoyl-$N^1$-methylaminoethyl(phenylcarbamylmethyl)dimethylammonium chloride(XXXVII)
was characterized by having high activity against monilial infections caused by C. albicans (153).

\[
\begin{align*}
\text{Cl}^- & \quad \text{Me} \\
\text{Ph-CH}_2\text{N-Me}_2 \text{R} & \quad \text{Br-CH}_2\text{NMe}_2\text{CH}_3 \text{O-CH}_2\text{I} \\
R = \text{alkyl from C}_5\text{H}_{17} \text{ to C}_{13}\text{H}_{37} & \\
(XXXV) & \\
\text{Cl}^- & \quad \text{Me} \\
\text{Ph-NH.CO.CH}_2\text{NMe}_2\text{CH}_3 \text{CO(CH}_2\text{)}_0 \text{Me} & \\
(XXVII) & \\
\text{Cl}^- & \quad \text{Me} \\
\text{Ph-NH.CO.CH}_2\text{NMe}_2\text{CH}_3 \text{CO(CH}_2\text{)}_0 \text{Me} & \\
(XXXVI) & \\
\text{Cl}^- & \quad \text{Me} \\
\text{Ph-NH.CO.CH}_2\text{NMe}_2\text{CH}_3 \text{CO(CH}_2\text{)}_0 \text{Me} & \\
(XXXIX) & \\
\end{align*}
\]

Cycloparaffinate (XXXVIII) (99) in the form of topical ointment is used in the treatment of pruritus ani and mycotic infections of the hand and feet. The most characteristic quaternary ammonium salt, a complex of iodine and a quaternary salt of acylcholaminoformylmethylpyridinium chloride (XXXIX) was found to be effective as a vaginal douche in monilia infection and also for the local treatment of fungal infections of scalp and feet (154). The antimicrobial activity was supposed to be derived from the slow release of elemental iodine and unlike tincture of iodine, it did not cause skin irritation.

\[
\begin{align*}
\text{Me(CH}_2\text{)}_n \text{CO.O.CH}_2\text{NMe}_2\text{CH}_3 \text{CO(CH}_2\text{)}_0 \text{Me} & \\
\text{I}_2 \\
n = 6 \text{ to } 12 & \\
(XXXIX) & \\
\end{align*}
\]
The antimicrobial activity of a series of alkyltrimethylammonium bromide was studied by Korai and Takeichi (155) and they observed a relationship between the activity and the alkyl chain length of the quaternary ammonium bromide.

Decamethylenebis(4-aminoquinaldinium chloride), Dequalinium chloride (XL), although introduced primarily as an antibacterial agent is now used as a topical antifungal agent in the treatment of certain fungal diseases, notably lingua nigra (156,157) and the multiform vaginal conditions (158). In combination with prednisolone it is marketed as Déqualone-P in the form of a cream. 4-Aminoquinidine, particularly 4-aminoquinaldiniumlauryl acetate (laurodin) possess antifungal activity in vitro of the same order as that of dequalinium chloride against C. albicans.

Hexadecamethylenebis(isoquinolinium chloride) (XLII), a fungistatic agent, is used topically for the treatment of tinea infections of the skin, in particular tinea pedis (159,160).

\[
\text{N}_1^1, N_2^1 - \text{Decamethylene-N}_1^4, N_2^4 - \text{-decamethylenebis(4-aminoquinaldinium) acetate},
\]

DDAD (XLII) (161,162) exhibited a broad spectrum activity, in vitro against a wide range of bacteria and fungi. \( N_1^4, N_2^4 - \text{-Decamethylenebis(4-aminoquinaldinium) acetate} \)
(XLII) (163) showed high antimicrobial activity with low topical toxicity. It is used for the treatment of fungal infections due to C. albicans, T. mentagrophytes and T. vaginalis on skin and mucosa.

\[
\text{NH-}(\text{CH}_2\text{)}_{10}\text{NH} \quad , \quad 2\text{CH}_3\text{COO}^-
\]

(XLII)

\[
\text{NH-}(\text{CH}_2\text{)}_{10}\text{NH} \quad , \quad 2\text{CH}_3\text{COOH}
\]

(XLIII)

Toshio et al. (164,165) believed that the activity of the dequalinium salts were probably due to their cationic structure. On coming in contact with the organism dequalinium salts seemed to change the permeability of the cell membrane and release certain intracellular components.

3) Quinoline and Quinones:

Oxine has long been known to possess outstanding antifungal action against T. mentagrophytes (166) and although rarely used internally, it has been marketed successfully as skin lotion in superficial mycotic infections.

5,7-Dichloro-8-hydroxy-2-methylquinoline, chlorquinaldol, (XLIV) is used locally as a cream or ointment in concentration of 5-5% in the treatment of superficial mycotic infections (167). It also showed antibacterial and amoebicidal
activity. Both iodochlorohydroxyquinoline (Vioform) and 5,7-diiodo-8-hydroxy-
quino line (Diiodoquin) have been used in the topical treatment of certain pyogenic 
fungal infections of the skin, the last compound has also been used in a variety of 
vaginal infections. Vioform, has been successfully used in otomycosis, an infection 
of the ear caused by A. niger (168). The bromo analogs like broxyquinoline (XLV; 
\(R = H\)) and brobenzoxalidine (XLV; \(R = \text{COC}_6\text{H}_5\)), an intestinal antiseptic and 
fungicide, showed promise in the treatment of superficial mycoses of the skin in the 
form of an ointment (169).

\[
\begin{align*}
\text{(XLIV)} & \quad \text{Br} \\
\text{(XLV)} & \quad \text{Cl}
\end{align*}
\]

Ethers and esters of 8-hydroxy-2-quinolylacrylic acid, exhibited excellent 
antifungal activity against dermatophytes and are used in the treatment of athlete's 
foot (170). These compounds were more active compared to the free acid (171) and 
the potency increased with the increase in halogen content. Several other quinoline 
compounds exhibited pronounced activity (172-174).

The fungicidal action of 5,7-dichloro-8-hydroxyquinoline was reversed by the 
addition of a minute quantity of \(\text{Fe}\), which supports the concept of chelation (175) 
as the mechanism of its action. As a general rule the antifungal activity of the 
quino linols was attributed to the ability of the formation of chelate.

Gershon and Parmegiani (176) found that although of weaker magnitude, the 
antifungal activity of the substituted 8-methoxyquinolines paralleled the activity 
of the corresponding 8-quinolinols indicating that chelation was not the sole mode
of action of the 8-quinolinols and strategically placed substituents could alter the antifungal activity. These authors have developed a hypothesis regarding the secondary mechanism of the activity of the substituted 8-quinolinols (177) in addition to chelation. This theory implicated the fungal spore wall as a barrier against the potential antifungal agent.

In the study of a series of copper complexes of 5-substituted 8-quinolinols, the substituents being H, F, Cl, Br, I and NO₂, the inhibitory activity was observed either at low levels of complex or the compounds were inactive contrary to the generally accepted notion that the prechelated 8-quinolinol was more fungitoxic than the free ligand. It was true only when the 5-substituents were H or F or in some cases chlorine only. A hypothesis based on steric factors in conjunction with electrostatic consideration was thus needed.

Regarding the geometrical shape of the hole, these authors point (178), that if the holes in the wall were circular, compounds like bis-5-substituted 8-nitroquinolinol (5-substitution by H or F or Cl) Cu II complexes would be expected to exhibit some fungal inhibition. The inactivity of these compounds thus suggests an elliptical or hexagonal geometry of the holes. Thus it appeared to the authors that the effective barrier was the spore wall and the activity was dependent on the perforation of the spore wall and the inactivity was due to exclusion.

Benzoquinone and naphthoquinone derivatives were found to be inhibitory to many fungi including some of the human pathogens (179; 180). Tetrachloro-para-benzoquinone (chloranil) was studied clinically in different forms of ringworm of the scalp and was found to be devoid of any toxic or irritating action of the skin. Its activity was attributed to the loosely combined chlorine (181).
Among a series of heterocyclic ortho-benzoquinones studied by Tappi and Formi et al. (182,183) as well as Collins (184) ortho-benzoquinone furoxane showed marked fungistatic potency which was reduced by the introduction of halogen, nitro, alkoxy and alkyl groups in the quinone nucleus.

Acylamidonaphthoquinones, particularly 2-acylamido-1,4-naphthoquinone (185) inhibited the growth of fungi and are specially useful for the control of ringworm.

\[ \text{C}_6\text{H}_5\text{CH}_2\text{NCH}_2\text{CH}_2\text{N(CH}_3)_2 \]
\[ \text{C}_6\text{H}_5\text{CH}_2\text{NCH}_2\text{CH}_2\text{N(CH}_3)_2 \]
\[ \text{C}_6\text{H}_5\text{CH}_2\text{NCH}_2\text{CH}_2\text{N(CH}_3)_2 \]

k) **Antihistaminic Antifungal Compounds**

Since histidine and histamine enhances the growth of pathogenic fungi (186) it was logical to suppose that antihistaminic drugs might have deleterious effect on pathogenic fungi. Landis and Krop (187) showed that in 1:64,000 or more dilutions theophorin (XLVI), diastrin (XLVII), benadryl (XLVIII), pyribenzamine (XLIX), thymylene (L) and neoantergan (LI) in decreasing order of effectiveness, were fungistatic for T. mentagrophytes. Agar plate testing of antergan (LII), phenergan (LIII), antistine (LIV), benadryl, tagathen (LV), neoantergan, pyribenzamine and theophorine showed that the first two compounds to be the most effective (188).
A water insoluble dry salicylate prepared from a water soluble salt (as HCl, maleate, citrate) of an antihistaminic base (eg. benadryl) and Na, K, NH₄ salt of salicylic acid was found to be particularly useful in the treatment of athletes' foot (189).

From the testing of a large number of antihistaminics, Mitchell and his coworkers (190) indicated that the fungistatic potency of the drugs was independent of their antihistaminic action. The most striking observation was the effectiveness of phenothiazine derivatives. Chlorination apparently increased the activity of the parent compound and the benzene ring seemed superior to pyridine.

However, Okazaki and Kawaguchi (191) pointed out that the antihistaminic drugs that were effective contained benzhydrol, phenothiazine, benzylaniline groups in their molecules. These groups themselves showed much stronger fungistatic and sporostatic effect than antihistaminic activity. The fungicidal action seemed to be due to their nuclear group and not due to their antihistaminic activity.
1) Steroids:

The pathogenic action of microorganisms depends not only upon the characteristics of the invading organism but also on the condition of the host. Hormones have been used in a variety of human pathological conditions and this has stimulated the search of hormonal influence in this field. Like the antibiotics, widely used hormones like cortisone (192,193), oestradiol (194) etc. have adverse effect on fungal diseases.

Testosterone, unlike cortisone showed, a slight beneficial effect in experimental aspergillosis in mice. Methyltestosterone, diethylstilbestrol, combined androgen and oestrogen was successfully employed in experimental coccidioidomycosis in animals and in man (195).

Stilbestrol (XVI) has achieved reasonable success clinically as an antifungal agent namely in the ringworm of the scalp in human and along with oestrone in tinea capitis (196). Stilbestrol was the most active compound among 24 oestrogens and related compounds tested (197). Replacement of the phenolic-OH group of stilbestrol with methoxy group or reduction to hexestrol decreased activity. According to Fox and coworkers (197) there is no relationship between oestrogenic and fungistatic activity.

\[
\text{(LVI)}
\]

3-\beta-Methoxy-5-androsten-16-\beta-ol exhibited a fungistatic activity in vitro against H. capsulatum equal to that of stilbamidine disethionate (198).

17-\beta-Amino-3,4-androstadiene, 17-\beta-amino-5-androstene and their salts showed high activity against C. albicans (MIC; 1 mcg/ml) and a wide spectrum of antimicrobial activity (199).
21-Hydroxy progesterone (200) inhibited the growth of dermatophytes more potently than progesterone and eight additional monohydroxyprogesterones.

20α-(2-Cyanoethylamino)-5-pregnene was the most active and 20α-(2-cyanoethylamino)-3,5-pregnadiene was the most potent among a number of pregnene and pregnadienes tested (201).

m) Sulfur Compounds:

Sulfur and its compounds are reputedly plant fungicides and free sulfur as ointments or colloidal preparations have long been used in the therapy of superficial fungal infections. SeS₂ effective against dandruff also inhibits dermatophytes.

In view of their broad antimicrobial spectrum Miller and Elson (202) studied various dithiocarbamic acids and other thio derivatives and revealed that among the derivatives of dithiocarbamates (LVII), thiuram monosulphides (LVIII) and thiuram disulphides (LIX) tested, the lower members, especially the N-methyl and N-ethyl compounds were more active than the higher alkyl derivatives. Kligman and Rosenweig (203) showed that the dithiocarbamates possess lower LD₅₀ and much greater activity than naphthoquinone in presence of blood. Dimethyl dithiocarbamate, tetramethylthiuram disulfide have been topically used for dermatophytes. Ringworm infections of the nails was successfully treated with tetramethylthiuram disulfide and dimethyl aurylbenzylammonium chloride (204). Collins and Wiese (205) have shown that the dialkyl esters of bisdithiocarbamic acid possess superior activity to that of undecylenic acid. Aeration of disodium ethylenebisdithiocarbamate (LX) produced a highly active compound hexahydro-1,3,6-thiadiazepine-2,7-dithione (206).

\[ \text{LVII} \quad \text{LVIII} \quad \text{LIX} \quad \text{LX} \]

\[ R = \text{alkyl}, \ M = \text{metal} \]
Shah and Jones (207) suggested that dithiocarbamates prepared from ortho-phenylenediamine and 4-chloro-α-phenylenediamine possess higher antifungal activity than the derivatives prepared from ethylenediamine.

Several variations produced a large number of compounds of varying activity (208-210).

Thomae (211) and Wildfeuer (212) have reported 2-benzoxazolyl-N-methyl-N-(1-naphthyl)dithiocarbamate (LXI) to have selective effect against trichophyton infections of guinea pigs when locally applied. The toxicity of the compound was extremely low and was well tolerated on the skin with no evidence of sensitivity reactions making its prognosis for clinical application promising.

Vander Kerk reported (213) that in contrast to the lower dialkyl dithiocarbamates and the thiuram disulfides the bis-dithiocarbamates and disothiocyanates exert fungistatic effect even in the presence of L-histidine. The fungitoxicity of these two compounds were due to the reaction between the fungicide and the essential -SH components of the cell (214) and not superficially restricted to coenzyme A only. Vander Kerk and Klöping (215) confirmed the hypothesis previously developed that the antifungal activity of bis-dithiocarbamates was attributed to their transformation into the corresponding disothiocyanates. Recently (216) it has been reported that a compound S-(N-benzylthiocarbamoyl) cysteine, Ph-CH$_2$-NH-$\text{C(=S)}$-S-CH$_2$-CH(NH$_2$)-COOH,
useful against polynephritis, cystitis, urethritis and yeast infections, was found to be cleaved in the alkaline medium of the duodenum into cysteine and antimycotic PhCH₂NCS.

Weuffen and coworkers (217) showed that in general the fungistatic index of isothiocyanates was greater than the dithiocarbamates which in turn was greater than the thiourea derivatives. p-Bromophenylisothiocyanate (218) was the most effective compound in vitro and in vivo among a number of halogen derivatives of isothiocyanates tested. Of the various benzyl, benzoyl and phenyl isothiocyanates tested the benzyl isothiocyanate exhibited the highest fungistatic and bacteriostatic effect (219).

Aryloxyalkyl (LXII) and aralkoxyalkylthiocyanates (LXIII) (220) were found to be useful against pathogenic diseases. In general thiocyano compounds showed stronger fungistatic activity than thiocyano free compounds (221). 2,6-Dichloro-4-thiocyanatoaniline (LXIV) exhibited the highest activity among the p-thiocyanatooanilines tested (222) against experimental dermatophyte infections. Clinically it showed good effectiveness. 2-Formamido-5-thiocyanothiazoles and 2-acetamido-5-thiocyanothiazole possess strong antifungal activity (223).
p-Chlorophenylthiol methacrylate and p-chlorophenylthiol furoate were shown to be the most active antifungal and antibacterial thiol esters tested (224).

Dithiol derivatives (LXV) are found to be useful in the treatment of moniliasis caused by C. albicans and are applicable to skin, mucosa or vagina (225).

\[
\begin{align*}
\text{S} & \quad \text{O} \\
\text{S} & \quad \text{C} \quad \text{H} \\
& \quad \text{R} \\
\end{align*}
\]

(LXV)

Compounds of the general formula \(\text{Ar-SCH}_2\text{(CH}_2\text{)}_n\text{-X}\) where \(\text{Ar}\) is a phenyl, \(Z\) is hydrogen or an alkyl radical containing 1-5 carbon atoms, \(n\) is 0 to 4, and \(X\) is a hydroxy or a carboalkoxy radical the alkyl group containing 1-3 carbon atoms are used for the treatment of fungal skin infections (226).

A series of unsymmetrical disulfides, \(\text{R-C(O)SS-R'}\) were tested (227, 228) against \(\text{H.capsulatum}\). The most active compounds \((\text{in vitro})\) were those where both \(\text{R}\) and \(\text{R'}\) were unbranched alkyl or unsubstituted phenyl moities.

Various diphenyl sulfide, diphenyl sulfone, diphenylsulfoxide and their substituted derivatives have been used for controlling fungus diseases (229). Of the two compounds 5,5'-dihydroxy 2,2'-dihydroxidiphenylsulfide and 5,5'-dichloro-2,2'-dihydroxidiphenylsulfide tested, the latter compound, Fenticlor (LXVI) was more active both \(\text{in vitro}\) and \(\text{in vivo}\) (230, 231). Good results were obtained in erythrasma, pityriasis versicolor and epidermophytosis. 2,2'-Diaminodiphenyl disulphide (LXVII) (232) with a smaller antibacterial effect had a very important anticanada effect. The preparation is only slightly toxic when administered subcutaneously and does not induce irritation of the skin and mucous membrane in laboratory animals and human being.
Disulfides with various substituents of the type (LXVIII) were tested by Gialdi and coworkers (233). Some of them showed high activity. In the series of carbamoyl and sulfamoyl disulfides (234,235) active compounds were obtained with bis(2-carbamoylphenyl) disulfides (LXIX), bis(2-sulfamoylphenyl) disulfides, or by the product of oxidative closure of (LXIX), i.e. the N-substituted benzisothiazolones (LXX). Compounds (LXIX) (R = butyl) and (LXX) (R = cyclohexyl) were tested clinically and showed equal or greater antifungal activity than drugs in current use.

A number of urea and thiourea derivatives (236) active against Gram-positive and Gram-negative organisms have shown antifungal activity comparable to sulfonamide drugs with low acute toxicity. Of particular interest are 1-(2-cyclohexylidene cyclohexylidene) thiourea and 1-alkyl-3-(2-cyclohexylidene cyclohexylidene) urea.
N,N'-diaryl thioureas, 3-fluoro-3'-methoxythiocarbanilide and N-(3-fluorophenyl)-
N'-2-thiazolylthiourea were reported. 3,5-Dichloro-4-fluorothiocarbanilide
possessing anti-inflammatory and antifungal activity was patented. The compound
was successful against fungal infections in the hands and feet of human. N-Hydroxy-
N'-methylthiourea (Noxythiolin) was proved to be clinically effective in treating
vaginal candida infections.

Ercoli (241) recently patented 2-undecenyl-2-thiopseudourea hydrobromide and
hydroiodide, for use in cosmetics, lotions and ointments in the treatment of bacterial and fungal infections of skin and scalp.

Ercoli et al. (242) also reported undecen-1-ylthiopseudourea iodide to be a potent anti-
fungal antibacterial agent for topical use.

Some base substituted cyclic ureas (243) of the type (LXXI) have been patented
having useful \textit{in vitro} and \textit{in vivo} activity against Trichophyton and Candida.

\[ R_1 R_2 N(CH_2)_n N \quad R = \text{C}_{14}H_{29}, \text{C}_{16}H_{35} \]
\[ R_1 = R_2 = \text{C}_9H_5, \quad n = 2 \text{ or} \]
\[ R_1 R_2 = \text{pyrrolidino}, \quad n = 2 \]

(LXXI)

The chemotherapeutic relationship between fungi and tuberculosis (244) as well
as the high tuberculostatic properties of the thiosemicarbazones prompted Benns
and coworkers (245) to investigate the antifungal activity of thiosemicarbazones.
Their conclusion was that the most effective compounds were derived from aliphatic
aldehydes. Manowitz and Walter (246) also reported that thiosemicarbazones derived
from unsaturated aldehydes with chain lengths of 10-12 carbon atoms, were the most
active. Taniyama and Yukio (247) noted that salicylaldehyde and 2-hydroxyacetophenonesthiosemicarbazones were potent and introduction of a nitro or a bromo group enhanced activity. 5-Chlorosalicylaldehydethiosemicarbazone and pyridoxalthiosemicarbazone hydrochloride were potent chemotherapeutic agents with low toxicity in mice (248).

The selenosemicarbazones particularly 2-phenyl selenosemicarbazones were 10 to 100 times more effective than the corresponding sulfur and oxygen analogs (249). The cause may be due to their relative ability of complex formation. However it was pointed out by Benns (246) that the mode of action of the thiosemicarbazones were different from that shown by the dithiones and 8-hydroxyquinolines.

A series of antifungal compounds called naphthiomates were described by Noguchi and his coworkers (250). These compounds exhibited narrow but extremely potent antifungal spectrum. Among them 2-naphthyl-N-methyl-N-3-tolythionocarbamate (LXXII; R = m-tolyl) and 2-naphthyl-N-methyl-N-1-naphthylthionocarbamate (LXII; R = naphthyl) have received considerable attention (251). Tolnaftate (LXII) exhibited a fungistatic concentration of 0.008 mcg/ml and a fungicidal concentration 0.08 mcg/ml for all the common pathogenic dermatophytes but was not effective against yeasts, bacteria or the deep fungi. It was effective in tinea corporis, tinea cruris, tinea pedis, erythrasma and was claimed to be non-irritating, non-sensitizing and free from side reactions (252-254).

\[
\text{R} = \text{m-tolyl or } \beta\text{-naphthyl}
\]

(LXXII)

In view of its high activity several chemical modifications of tolnaftate were reported (255-256). A number of thionocarbamates were patented (257, 258) and all
of them were claimed to be useful fungicide for skin disease.

Although widely applied in the antibacterial field sulfonamide therapy is of considerable importance in systemic fungal infections. Mayer and coworkers successfully applied (259, 260) several sulfonamides namely sulfanilamide, sulfathiazole, sulfamethazine, sulfisooxazole, sulfathiourea, sulfadiazine and sulfapyrazine etc. in the therapy of mice infected with H. capsulatum. Sulfadiazine was superior to sulfathiourea (under identical conditions). For sulfanilamide the oral route was more effective than the interperitonial (i.p) route and nitrosulfathiazole was superior to aminosulfathiazole.

The value of sulfonamide therapy, in combination with penicillin and other antibiotics in actinomycosis, is long known. Treatment of nocardiosis (Madura foot) with sulfonamide therapy along with surgical measure is the most satisfactory yet known. The pulmonary form of infection by C. neoformans as C. meningitis have shown good response to sulfonamide therapy.

Successful use of 6-sulfanilamido-2,4-dimethylpyrimidine (Elkosin) in localized form of South American Blastomycoses has been reported. Local lesions were treated by topical application of a sulfonamide in addition to systemic treatment (261).

1) Heterocyclic Compounds:

Horsfall and Rich (262) assayed 166 heterocycles containing pyrrole, indole, pyrazole, imidazole, thiazole, pyridine, pyrimidine, phenazine and phenothiazine nuclei and concluded that the unsubstituted nucleus was seldom fungitoxic. The addition of lipophilic substitution often induces toxicity whereas polar groups increased the toxicity.

Nonylpyrazole exhibited outstanding antimicrobial activity in vitro. The 4-nitro and the 4-halo derivative also retained the activity (263). 1-Isopropyl-3,5-dimethyl-4-nitrosopyrazole and fungicidal compositions thereof were reported to be used against ringworm in cattle (264).
Isonicotinic acid hydrazide (INH) (265) showed moderate activity against several fungi. The locally applicable dermatological products contain substituted 2-hydroxy-pyridine-1-oxide, its Zn-salts or higher alkylamine salts (266). \(1-(2-\text{Alkenyloxy})-2(1H)\)-pyridones (LXXIII) where \(R\) and \(R'\) may be methallyl, \(H\); 1:3 dimethyl-2-buteryl, 5-methyl, 2-hexenyl, 6-methyl etc. were found to be useful for topical fungal infections in human (267). Recently McCoy and coworkers took patent for 4,6-diaminopyridine hydrochloride for its usefulness in the treatment of infections caused by \(C.\) neoformans. It could be administered orally @ 90-210 mg/kg (268).

![Chemical Structure of LXXIII](image)

5-Amino-1,3-bis(2-ethylhexyl)-5-methylhexahydropyrimidine (hexitidine or sterisil) (LXXIV), introduced as a vaginal gel, had favourable response in a variety of dermatoses (269). Examination of various substituted hexahydropyrimidines showed that substituents like 1-methylheptyl and 2-ethylhexyl at 1 and 3 positions exhibited high activity (270). High *in vitro* activity was also observed in some 2,4-bis-(arylamino)-5-methylpyrimidines (LXXV) (271).

![Chemical Structures of LXXIV and LXXV](image)

One of the most important compound in this series is 5-fluorocytosine (LXXVI), an antimetabolite of cytosine (272). This relatively nontoxic compound was effective...
against experimental infections of C. neoformans and C. albicans when administered orally or parenterally (273). The clinical efficacy by oral therapy was also reported. Several N^4-Acylated-5-fluorocytosine was nontoxic and had activity against C. albicans infection in mice. In contrast to 5-fluorocytosine the 6-fluoro, 5-chloro or the 5-bromo derivatives exhibited low activity (274).

\[
\text{H}_2\text{N} \quad \text{OH} \\
\text{(LXXVI)}
\]

Strong in vitro antymycotic activity was found in some 2-phenylpyridazine derivatives (LXXVII) (275). Among a number of 2-(nitrophenyl)pyridazine derivatives tested by Takahashi (276) some of them revealed stronger antitubercular and antifungal activity in vitro than 2-phenylpyridazine.

\[
\text{N-Ar} \\
\text{(LXXVII)}
\]

1-p-Chlorobenzyl-2-methylbenzimidazole (chlormidazole) (LXXVIII) was recommended either alone or in combination with thyroticin or xanthocillin for the local treatment of dermatomycosis (277). 1-[2,4-Dichloro-8-(2,4-dichlorobenzyloxy)phenethyl] imidazole was reported to be effective both orally and topically in experimental mycoses of guinea pigs. It was found to be effective in the treatment of tinea pedis (278) and Candida vaginitis (279) in human.

\[
\text{Me} \\
\text{(LXXVIII)}
\]
Methyl-5-(or 4)-(3,5-dimethyl-1-triazeno)imidazole-4(or 5) carboxylate (LXXIX) (280) exhibited pronounced (in vitro) broad spectrum activity against both fungi and bacteria, comparable to that of amphotericin B or nystatin. It was however less toxic than certain 1,2,3-selenadiazoles possessing antifungal activity (281).

![Methyl-5-(or 4)-(3,5-dimethyl-1-triazeno)imidazole-4(or 5) carboxylate (LXXIX)](image)

One of the most promising synthetic antifungal agent is diphenyl(2-chlorophenyl)-1-imidazolylmethane (LXXX), clotrimazole, Bay b-5097, an orally applicable substance. It exhibited a broad spectrum of activity against a wide range of organisms (282). Excellent results were obtained in human with aspergillosis, candidal septicemia, endocarditis, pneumonia and polynephritis. Oral therapy with clotrimazole was similar to that shown with griseofulvin but the topical therapy was less successful than with tolnaflate. The in vitro activity against Histoplasma, Cryptococcus and Coccidioides species was comparable to amphotericin B while against dermatophytes, the activity was greater than that of griseofulvin, comparable to that of pyrrolnitrin but less than that of tolnaftate (283).

![Diphenyl(2-chlorophenyl)-1-imidazolylmethane (LXXX)](image)

The consistent result obtained in particular with severe systemic mycoses and the advantage that this drug appears to possess over the classical antifungal agents encouraged Casidio and his coworkers (284) to examining of its congeners. It was
observed that the activity was retained if one of the two phenyl groups of chlortrimazole was replaced by a 2-pyridyl radical (LXXXI) or if the two phenyl groups were connected ortho to form a fluorene system (LXXXII). Compound (LXXXII) exhibited even better activity than chlortrimazole \textit{in vitro}.

Several compounds with structure (LXXXIII) showed promise in evaluation (285). Therapeutic activity against dermatomycoses was also observed in some diimidazolyl methanes of the type (LXXXIV) (286). Some \(\alpha,\alpha\)-disubstituted 1-benzylmidazoles (LXXXV) useful as antimycotic agents in human and veterinary therapy were prepared by Draber \textit{et al.} (287).

\begin{align*}
\text{R}^t-(\text{CH}_2)_n-\text{O}-&\text{C}=&\text{N}-(\text{LXXXIII}) \\
\text{R}=\text{H}; n=1 \text{ and } \text{Ar}, \text{Ar}^t=\text{halogenated} & \text{phenyl} \\
\text{R}^t, \text{R}^\alpha, \text{R}^\beta=\text{H, H, H; } p-\text{Cl, H, H; } p-\text{Cl, H, CH}_3 & \text{ etc.} \\
\text{R} &= \text{Cyclohexyl, phenyl;} & \text{R}^t &= \text{Pyridyl, tertiarybutyl} \\
\text{LXXXV}
\end{align*}
High in vitro activity was observed in compounds of the type (LXXXVI) and also of the type (LXXXVII) (288).

\[
\begin{align*}
R &= \text{CH}_3 \text{ or } p-\text{substd. phenyl}; \\
R_1 &= \text{OCH}_3 \text{ or } 2R_1 = 0; \\
R_2 &= \text{H}, \text{CH}_3 \text{ or } C_6H_5
\end{align*}
\]

(LXXXVI)

\[
\begin{align*}
R_1 &= \text{H,CH}_3\text{, C}_6\text{H}_5; \\
R_2 &= \text{CMe}_3\text{, C}_6\text{H}_5 \text{ or } p-\text{ClC}_6\text{H}_4 \\
R_n &= 2,3,4-\text{Cl}_3 \text{ or } p-\text{Cl} \\
\end{align*}
\]

(LXXXVII)

α-Phenanthroline exhibited a stronger growth inhibiting effect against T. interdigitale than either the p or m-phenanthroline. The most potent compound was 2,3-dimethyl-1,10-phenanthroline (LXXXVII) useful for the treatment of mycotic conditions of human skin (289).

\[
\begin{align*}
\text{CH}_3 \\
\text{CH}_3 \\
\text{NH} \\
\text{N} \\
\text{C}_{10}H_{12}
\end{align*}
\]

(LXXXVIII)

Silverman and Heimann reported (290) some benzocoumarin compounds like 3-carboalkoxy-4-hydroxybenzocoumarin to be useful in controlling fungus infection in human such as ringworm of the scalp or skin.

2-Amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-oxadiazole (LXXXIX) was used successfully in curing fungus infections in mice (291). Deoxyfrenolicin (XC) and acetyl deoxyfrenolicin showed inhibitory activity against experimental ringworm in guinea pigs (292).
Among several benzo thiazole derivatives tested (293), marked activity was shown by several compounds of the type (XCI). The activity remained unaffected when tested in presence of 10% horse serum. The compound, 2-dimethylamino-6-(2-diethylaminoethoxy)-benzothiazole (Asterol or Diamthazole) (XCII) was introduced in the market as a potent antifungal agent effective against a wide range of superficial fungal infections of skin, hair and nails.

5,7-Dichloro-2-amino-4-hydroxybenzothiazole (XCIII), a compound related to asterol was found to be active against actinomycetes but other variations of this series were inactive (294). Halethazole, 5-chloro-2- diethylaminoethoxyphenylbenzothiazole (XCIV), is still used as an antiseptic and antifungal agent (295).
2-(4'-Thiazoly)-benzimidazole, thiabendazole (XCV), a broad spectrum systemic anthelmintic exhibited a high \textit{in vitro} activity (1-2 mcg/ml) against \textit{T. mentagrophytes}. Several clinical studies have shown it to be potentially useful in superficial fungus infections of the skin, particularly dermatophytic infections of groin and feet (296, 297). Given orally at 25 mg/kg/day it was successful in the treatment of patients with chromomycosis. Several closely related 2-substituted imidazo[1,2-a] pyridines (XCVI) demonstrated broad antifungal activity (298).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure}
\caption{Structures of compounds XCV and XCVI.}
\end{figure}

N-Trichloromethylthiotetrahydrophthalimide (Captan) was found to possess significant activity against phytopathogens. Studies of the various trichloromethylthio derivatives of hydantoin, phthalimide, 5-pyrazoline, uracil, succinimide etc. proved that 5-(1-ethylamyl)-3-trichloromethylthiohydantoin, chlordantoin (XCVII), was the most active compound and the least toxic to rats. In the form of a 1% cream it has shown considerable activity against \textit{Candida vaginitis} (299). 1-(5-Nitro-2-furfurylideneamino)-5 alkylhydantoin showed strong antifungal activity \textit{in vitro} (300). Some 1,2,4-dithiazoles (XCVIII) and rhodanine derivatives (XCIX) also possess considerable fungicidal activity (301).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure}
\caption{Structures of compounds XCVII, XCVIII, and XCIX.}
\end{figure}
Studies (302) of several thiadiazine dibenzthiones and monobenzthiones suggested that compounds (C) were useful in the treatment of all types of dermatomycoses including mixed infection with yeasts or Keratinophilic molds. High *in vitro* activity against *T. mentagrophytes* (3'12 mcg/ml) was exhibited by 3-aminothiazoline-2-thione and 4H-1,3,4-thiadiazine derivatives (303). Thiazoles of the type (CI) where *R* represents a tolyl group and *X* a hydrogen atom were found to be useful for treating *tinea capitis*, *tinea unguium*, *tinea corporis*, Erythrasma etc. (304).

\[
\text{R} = R_1 = \text{PhCH}_2 \\
\text{R} = \text{PhCH}_2 \text{ and } R_1 = \text{CH}_2\text{COOH}
\]

\[
\text{R} = p-\text{tolyl}
\]

\[
\text{S} \begin{array}{c}
\text{N} \\
\text{R} \\
\text{R}_1
\end{array} \begin{array}{c}
\text{S} \\
\text{C}_6\text{H}_4\text{X}
\end{array}
\]

**Antibiotics:**

Penicillin is still used in the treatment of actinomycosis (306) preferably in conjunction with a sulfonamide or potassium iodide. Streptomycin was found to be effective in the treatment of actinomycosis of the spine. Most of the broad spectrum antibiotics like tetracyclines, chloramphenicol, erythromycin were also found to be helpful in the treatment of actinomycosis. Erythromycin possesses therapeutic activity against acute and chronic brucellosis.

Griseofulvin (7-chloro-4,6,2'-trimethoxy-6-methylgris-2'-en-3,4-dione) (CII), a metabolite of Penicillium griseofulvum is a near perfect drug (306) regularly effective and essentially non-toxic. The drug is specifically active against all the superficial dermatophytes including all the pathogenic species of trichophyton, epi democratophyton and microsporon. Several modifications of griseofulvin have appeared (307-311).
Pyrrolnitrin, \[3-(2\text{-nitro}-3\text{-chlorophenyl})-4\text{-chloropyrrole}\] (CIII), produced by several species of the genus pseudomonas exhibited high activity as a topical preparation in the treatment of superficial dermatophytoses in animals and in man (312,313).

Chloroflavonin (CIV), isolated from the cultures of A. candidus exhibited a high \textit{in vitro} MIC (0.08 mcg/ml) against various fungi (314,315).

Saramycetin (X-5079), a polypeptide antibiotic exhibited useful clinical effectiveness against histoplasmosis, North and South American blastomycosis, aspergillosis, sporotrichosis and phycomycosis (316) with low toxicity.
Mycophenolic acid (CV) successfully cured experimental trichophytosis in guinea pigs without producing any skin irritation (317).

Because of its toxicity to animal tissue, cycloheximid (actidione CVI), has rarely been used in medical mycology and mainly employed to eradicate fungal plant pathogens (318).

Over 50 polyene antibiotics have now been discovered, a few of them have come into clinical use, although so far exclusively as local application and principally for the treatment of candidiosis.

Variotin (CVII) has been used in the form of an ointment in the treatment of ringworm infections (319).

Nystatin (CVIII), formerly called fungicidin, was isolated from a strain of streptomyces noursei. Nystatin has proved of value in the treatment of superficial
monilial infections, in vaginal moniliasis (320), in oral candidiosis and in onychomycosis (321).

Despite its several side effects amphotericin B (CIX) is the only major weapon available today to combat systemic mycoses like cryptococcosis (323), blastomycosis, histoplasmosis, coccidioidomycosis (324) and chromoblastomycosis (325).
Candididin, isolated from Streptomyces griseus gave excellent results in the treatment of vaginal moniliasis (326), C. vaginitis and fair results in cutaneous moniliasis (327). Levorin, another heptaeone of the candididin group, was reported to be superior to nystatin (328) in the treatment of various infections caused by C. albicans.

Hamycin, isolated from the species of streptomyces pimprina thirum, appears to differ from other antifungal heptaeones on the basis of physical, chemical and biological properties. Hamycin appears to be more effective than nystatin against C. albicans. Hamycin is now considered to be an outstanding drug in vaginal candididiosis (329), blastomycosis and bronchopulmonary aspergillosis due to A. fumigatus and it appears to be less toxic than alternative methods of therapy.

p) Miscellaneous Compounds:

2'-Hydroxy-4',6'-dimethyl-5-chloroacetophenone is effective in the treatment of athletes' foot or other fungal diseases (330). 4-Hydroxyalkanophenones were found to be useful for topical administration against ringworm, palmarplanter mycoses, athlete's foot and pytiriasis versicolor. The 3-chloro-4-hydroxyvalerophenone
showed good local tolerance on rabbit skin (331). Among a number of 3-1-amino-
propiophenones, the 3-morpholino- and 3-piperidinopropiophenones exhibited promising
antifungal activity, particularly against the dermatophytes (332).

Benzhydroxamic acid, salicylhydroxamic acid, 10-undecenoic hydroxamic acid,
exhibited interesting antifungal activity (333). Among a number of sesquiterpenoid
hydroxamic acids tested, homofarnesylhydroxamic acid showed the strongest activity
being equal to that of nystatin (334).

Schmeigelberger and Bellinger reported (335) that esters of 2,2,4-trimethyl-1,5-
pentanediol, especially the diacetate was effective fungicide, harmless to the skin.

Kolsa recently patented (336) 2-(α-hydroxybenzyl)acrylanilides (CXI), which
were found to be more effective than griseofulvin in treating guinea pigs infected
with T. mentagrophytes.

\[
\begin{align*}
\text{R} & = \text{Cl}; \quad \text{R'} = \text{H} \\
\text{CH(OH)C}_{6}\text{H}_{5} & \quad \text{R} \\
\text{N-COCH=CH}_{2} & \quad \text{R'}
\end{align*}
\]

(CXI)

A preparation containing 1% iodobenzoic acid and 11% triethanolamine gave good
to excellent cure rates in vaginal infections (337). N-α-Naphthylidoacetamide in
an 1-2% ointment gave 50% cure rate in experimental dermatophytosis and candidiosis
in guinea pigs (338).

Oral administration of KI was found to be of value in localized lymphocutaneous
infections. Subcutaneous phycomycosis was successfully treated with KI whereas
attempt with griseofulvin or nystatin was unsuccessful (339).

Chlorindanol, 7-chloro-4-indanol (CXII) was found to be highly active against
pathogenic fungi and was well tolerated by skin, eyes, genitals and mucosa (340).
Godefroi and his coworkers (341) tested a number of 1-(1-indanyl) and 1-(1-tetralyl)-imidazole-5-carboxylates. Of these ethonamidate, ethyl-1-(1-tetralyl)-imidazole-5-carboxylate (CXIII), showed outstanding in vitro antifungal activity.

(Tetrahydronaphthalene derivatives like 2-(4-chlorophenyl)-1-\[4,2(N,N-diethylamino)-ethoxyphenyl\]-1,2,3,4-tetrahydronaphthalene (CXIV) exhibited valuable pharmaceutical properties. These compounds were found to be useful in the treatment of topical fungal infection of dermatophytes (athlete's foot) and against chronic infections of skin by actinomycetes (342).
PRESENT WORK

A critical survey of the literature of antifungal agents reveals that the antifungal activity is exhibited by a wide variety of compounds. They include from the tiny fatty acid molecule to large macrocyclic structures as in amphotericin B, nystatin etc., from a purely inorganic compound to some complex metal containing compounds, from compounds devoid of nitrogen to compounds having a high percentage of nitrogen, from compounds having unsaturation to purely saturated ones. Whereas in some cases halogenation or nitration increase the antifungal activity of the parent compound, their introduction have some adverse effects on the others. As we proceed through the literature we find that various functional groups can confer antifungal activity on a wide variety of structures. Presence of antifungal activity in antihistaminic, antileukemic compounds also point to the diversity in activity. The role of various sulfur compounds starting from simple thiols thiocarbamates to thioheterocyclic moiety are also worth mentioning.

Thus it seems that a particular compound becomes active as an antifungal agent when certain physiological as well as physicochemical properties best fit that particular compound. Accordingly, in the present dissertation mainly five different types of compounds have been prepared and screened. These types of compounds have been mentioned in the preface of this dissertation and they have been described in details in the following chapters.