CHAPTER-I

INTRODUCTION
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Heterocyclic compounds are present in all the living beings, where these perform important physiological functions. Heterocyclic compounds are also very widely distributed in nature as alkaloids, proteins, nucleic acids, porphyrins and vitamins etc. A large number of antibiotics produced by microorganism are nitrogenous heterocyclic compounds most important of which are cephalosporin, penicillin, puromycin, oxamycin and thienamycin. Various types of physiologically important compounds have furnished a variety of synthetic drugs and pest control chemicals. In this respect, more important are the five membered heterocycles like triazoles, thiazoles, thiadiazoles, oxadiazoles and imidazoles etc.

The discovery of the structure of penicillin and vitamin B₁ both possessing the thiazole skeleton has evoked interest among the workers to conduct research on related molecule belonging broadly to the class of "Heterocyclic sulphur compounds". For example, in 1885 a poisonous mixture of CuSO₄ and lime called Bordeaux mixture was found useful to control mildew, and in 1914 Weighton reported that a mixture of sulphur and lime water could be used for this purpose. Most of the early
used fungicides were inorganic compounds of sulphur, calcium, copper, mercury, lead and phosphorus etc. Which are dangerous for human beings and host plants. With the growing consciousness for hazards involved in the use of such inorganic compounds as fungicides, the search for more efficient and less hazardous fungitoxic compounds have always remained desirable.

The use of organic fungicides in 1966 is a major landmark in the history of fungicidal control of the plant disease. However, the successful use of organic synthetics compounds (of non-microbial origin) was first demonstrated by Von Schmeling and Kulka in 1966. The discovery of Oxathienes; Oxacarbene (5,6 dihydro-2-methyl 1,4 oxathiene 3-carboxanilide was soon followed by confirmation of the antifungal activity of pyrimidine derivative and benzaimidazoles derivatives.

Synthetic nitrogenous heterocyclic compounds have attracted much attention in this direction, because they fulfill these requirements as well as are often more specific in action.

The fungicidal nitrogenous heterocyclic compounds are of major importance in a variety of biological applications, especially as medicinal chemicals and agricultural chemicals.
A large number of medicinal chemicals like heterocyclic compounds are either commercially available like penicillin, puramycin, thianamycin etc. or under active clinical investigation mainly as corticoids, progestrogen and antifertility agents. A large number of halogenated heterocyclic compounds which have been covered in a comprehensive review provided by Buu-Hoi under the topics antimetabolites, diuretics, anesthetics, convulsants, antiviral and fungicidal etc.

Nitrogenous heterocyclic compounds have evoked considerable attention in agriculture, mainly as pest control chemicals. Pyrazoles, pyridine and imidazo pyrimidine derivatives are common diuretics and significant anxiolytic for rats. A large variety of antifungal quinoline derivatives have been studied and used as agrochemicals. Several 7-trifluoromethyl sulphinyl acetamido cephalosporins have been used as agricultural fungicides.

Organic compounds of sulphur are highly effective and are the more popular fungicides in use these days. All these compounds are derivatives of dithiocarbamic acid. Thiram, Ziram, Ferbam, Nebam, Zineb and Maneb are well known example of organic sulphur fungicides. The dithiocarbamic acid is unstable in
free state but when it is treated with another molecule of the acid or with some metal, it yields stable and highly fungitoxic compounds.

Another member of the dithio carbamate group is Vapam (Sodium methyl dithiocarbamate), which is available in liquid form. It is soluble in water and used for soil treatment. Vapam has been found to be effective against many fungi, nematodes and certain weeds. Diseases like cotton wilt, damping of papaya, damping of pea, root rot of beet Citrus Nematode root Nematodes of potato have been controlled by soil injection of Vapam.

The principle fungicides included in this group are Glyodin (2-hetradecyl-2-imidazoline acetate), Oxine (8-quinolino 1 or 8 hydroxyquinoline), Dyrene (2,4 dichloro 6-ortho-chloroniline 1,3,5 triazine) and Captan (N-trichloro methyl thio-4-cyclohexene-1,2-dicarboxamide). It was sold under the trade name Captan, Esso, Fungicid 406, Orthocide, Vancide etc. Its most common used was as seed protectant against Pythium. It was also used as soil, drench as well as foliar spray. Folpat (n-trichloromethyl- thalimide) is closely related to Captan and is sold under the trade name of Phalton o-phalton etc. Captafol is chemical cis-N (1,1,2,2
tetrachloro ethyl thio)-4-cyclohexene 1,2-dicarboxamide and is sold under different names such as *Difolatan*, *Difosan*, *Sanspor* etc. Although originally meant for use as foliar spray, it has been found effective as seed dressing fungicides also. It is being used against late and early blight of potato.

Fluorine, chlorine, bromine and iodine the members of halogen family have been known to import toxicity to organic molecules. In general halogenations causes a drastic change in physiological behaviour of organic compounds and this has been utilized in the synthesis of a wide range of biologically active compounds. The effect of halogenations on pharmacological properties and mechanism of action has been presented by Chenowith and M.C. Carty⁹.

The growing patent literature of recent years clearly shows that halogenated hetrocyclic compounds possesses useful bactericidal, fungicidal, insecticidal, herbicidal, and antiviral activities (details are given in Chapter-II of this thesis).

The reason for paying special attention to antifungal activity was obvious in light to the great loss to our essential food supplies both in stores and fields. The amount of damage caused by fungi may be realized from the fact that only one fungal species
Phytophthora infestans was responsible for the famine in Ireland in the middle of 19th century, as a result of which millions of people either died of malnutrition or forced to immigrate. 

In the last years of the IIrd world war (1943) Bengal had to face a serious famine. One of the reasons to this famine has been attributed in the loss in yield of rice due to attack of Helminthosporium leaf spot, which had been affecting the crop for the last several years. Wheat shortage in Madhya Pradesh (India) during 1946-47 due to wheat rust and sugarcane red rot epidemic in Uttar Pradesh (India) in 1938-1942 was major nuisance to Indian economy. Even in most advanced countries losses are still very heavy in spite of the adoption of modern methods of crop protections. In 1845 late blight of potato diseased destroyed the potato crop of Ireland. In Ireland, England and Europe potato was the staple diet of the population. A large number of people died of hunger and many more became diseased due to physical weakness. There was migration of the population to other countries. This single disease forced man to result, scientific investigation were taken up, the cause of disease was identified and extensive use of chemicals for plant disease control came into existence.
The human and animal diseases termed as *Mycoses* also caused by certain fungal species. Approximately one million cases of *Coccidioidomycoses* in California alone were estimated by Ajello\textsuperscript{11}.

Palmer\textsuperscript{12} and Beadenko\textsuperscript{f13} et al at least eight million persons in Ohio and Mississippi valley have been infected with the species *Histoplasma Capsulatum* the causal agents of *Histoplasmosis*.

Fox and Shields has started that the large number of males in United States have at some time in their lives being infected by fungi causing athelete foot\textsuperscript{14}.

In addition, the degradative action of fungi covers the deteriotion, weakening and destruction of clothes and other oven fabrics, plastics, wood paints and such other items during storage and use.

Fungitoxicity has been defined as the ability of a chemical to interfere in an adverse way with the vital functions of a fungus by physiochemical means.

Fungitoxic chemical may exhibit-
1. The fungistatic action which implies a continuous interference as long the organism is in the contact of toxicant, or

2. Fungicidal action, which denotes a persistant action even after the removal of toxicant.

The basis of antifungal action of selective toxicity of chemicals to various parts of life: The metabolic processes of plants and fungi. Although different in some respects, are basically similar, so that fungicides are likely to damage both fungus and host plant.

The damage of cells by fungicides may be brought about by one or more of the following mechanism-

1. Injurious effects on cell division and cell walls.
2. Effect on the permeability of cell membrane cell.
3. Effective on enzyme system of the fungal cell.
4. Precipitation and chelation of chemicals.

An ideal fungicide should have the following characteristics-

1. The fungicide may either be toxic to the pathogen concerned or be converted in the host plant to such a fungitoxicant.
2. Alternatively, the substance (or a derivative formed in the plant) may alter the metabolism of the host so that biochemical or physical resistance to pathogen may be induced or enhanced.

3. The systemacity a substance may be absorbed sufficiently and translocated from the point of application to the side of the pathogen and should have a considerable degree of stability within the host plant.

In the light of the above background and with the object of further exploring subject it was considered worthwhile to synthesize new biologically active heterocycles incorporating different toxophoric groups. Thus, evaluation of their biological activity might through some light on the relationship between biological activity and chemical constitution and also might yield some compounds of practical importance. An attempt has been made in this direction.

The following four new series of biologically active heterocyclic compounds incorporating toxophoric moiety have been synthesized. All the synthesized compounds have been well characterized by their elemental analysis, IR and $^1$HNMR spectrum.
I. 5-Aryl-4-thioaryl-1-sulpho-2,3,5-triazoles

1,2,4-triazole ring is also associated with various useful pesticidal activities. 3-Amino 1,2,4-triazole, commercially known as amitrole is a well-known commercial herbicide\textsuperscript{15}. 1,2,4-triazole derivatives have been patented as fungicides\textsuperscript{16-18}, herbicides\textsuperscript{19-22}, bactericides\textsuperscript{23-27} and insecticides\textsuperscript{28-30}.

Growing literatures, clearly demonstrates pesticidal compounds having s-triazole, 1,3,4-thiadiazole and imidazole rings and potential pesticides. For example Dandia et al. have synthesized 3-(1,2,4-triazole-3-imino) indole-2-ones derivatives (1) (R=H, 5 or 6, 4-CF\textsubscript{3}, 5-Cl) for their antibacterial activites\textsuperscript{31}.

![Chemical structure of (1)](image)

Fuzaka et al. have prepared compounds (2) (1H-1,2,4-triazole-1-carboxamide) as herbicides\textsuperscript{32}.
Recently, various some N-pyridinyl 1,2,4-triazole [1,5-c]-pyrimidine-2-sulphonamide of the type (3) was reported by Arndt et al. as herbicides. 

\[ \text{(3)} \]
\[ R = \text{C}_1-\text{C}_3 \text{ alkyl}; Y \text{ and } Z = \text{H}, \text{F}, \text{Cl}, \text{Br}, \text{V} = \text{H}, \text{Co}; \]
\[ \text{A and } B = \text{H}, \text{Cl}, \text{Br}; D = \text{H}, \text{F}, \text{Cl} \]

\[ \text{OR} \]

\[ \text{CONET}_2 \]

Recently, various some N-pyridinyl 1,2,4-triazole [1,5-c]-pyrimidine-2-sulphonamide of the type (3) was reported by Arndt et al. as herbicides. 

\[ \text{(3)} \]
\[ R = \text{C}_1-\text{C}_3 \text{ alkyl}; Y \text{ and } Z = \text{H}, \text{F}, \text{Cl}, \text{Br}, \text{V} = \text{H}, \text{Co}; \]
\[ \text{A and } B = \text{H}, \text{Cl}, \text{Br}; D = \text{H}, \text{F}, \text{Cl} \]
Yukimasa et al. have synthesized compound of imidazole derivative (4) as bactericide$^{34}$.

Literature reviews clearly demonstrate that triazole ring is much associated with pesticidal activities therefore it can expect that 2,3,5-triazole ring must be biologically active and we have synthesized the title compound 5-Aryl-4-thioaryl-1-sulpho-2,3,5-triazoles (5) with the hope that the above compound will be pesticides of enhanced potency.
II. 3,7,8-Triaryl-7,8-dihydro-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazolo [3,2-a]-1,3,5-triazine-6-thiones

1,3,4-Thiadiazole nucleus is associated with a broad spectrum of biocidal activity for e.g. fungicides\textsuperscript{35-38}, insecticides\textsuperscript{39,40}, bactericides\textsuperscript{41-43} and herbicides\textsuperscript{44,45}. Possibly by virtue of incorporating >N–C–S–moiety. The toxophoric importance of which has been well stressed in many pesticides\textsuperscript{46,47}. The presence of –C=S– group is also known to enhance the fungicidal activity of heterocyclic compounds\textsuperscript{48}.

1,2,4 triazole ring is also associated with various useful pesticidal activities as described in the 1st series of this chapter.

Many derivatives of 1,3,5 triazines have significance in agriculture as fungicide and herbicides of these Simazine (6) [2-chloro 4,6-bis (ethyl amino) 1,3,5 triazine], Atrazine [2-chloro 4-ethyl amino 6-iso propyl amino 1,3,5 triazine], Prometryne [2-methyl thio 4,6-bis iso propyl amino 1,3,5 triazine], Dyrene [2,4 dichloro 6 (2-chloro anilino 1,3,5 triazine)] and Methoprotryne [2-methyl thio 4-iso propyl amino 6-3-methoxy propyl amino) 1,3,5 triazine] are more outstanding.
Various, thiazolino-triazine derivatives of the type (7) have been synthesized as useful fungicides\textsuperscript{49}.

Some substituted 1,3,4-thiadiazolo [3,2-a]-s-triazine-5-phenyl-7-thiones and imidazo [2,1,b]-1,3,4-thiadiazole-5-ones of the type (8) has been synthesized by Andotra et al. as fungicides\textsuperscript{50}.
Okada and George have synthesized 1,3,5-triazinium perchlorate (9) as medicinal compounds \(^{51}\).

Patel H.M. and Desai K.R. have synthesized some new 2-(P-F-anilino-4-aryl ureido-6-[2'-mercapto-4'-oxaquinaxoline-3'-phenyl]-4''-yl-amino-s-triazine (10) (R = unsubstituted Ph) as antibacterial agents \(^{52}\).

Some 2-mercapto 1,4-bis (aryl)-1,3,5-triazine 6-(1H)-thione (11) (R\(^1\)=CO\(_2\)H, H; R\(^2\)=H, C\(_6\)H\(_5\); R\(^3\)=H; R\(^4\)=CO\(_2\)H, CHO; Ar=4-ClC\(_6\)H\(_4\), 4-NO\(_2\)C\(_6\)H\(_4\); Ar\(^\prime\)=4-ClC\(_6\)H\(_4\)) has been recorded as potential anti-thyroid agent \(^{53}\) by Lakhan R et al.
Some 6-methyl-4-trihalomethyl-1,3,5-triazines (12) (R¹= CCl₃, CFCl₂, R²=H, COR₅, CSR₅, CO₂R₅, CONHR₆, SO₂R₆; R₅, R₆=H, alkyl, cycloalkyl (un) substituted Ph, Phenylalkyl; R³, R⁴=H, alkyl; A=bond (un) branched (o-interrupted) alkenyl; X=bond, O; Ar=Ph (un) substituted hetero aryl) has been reported as herbicides⁵⁴.

Some new 1,3,4-oxadiazolo-[3,2-a] [1,3,5]-triazine-5 (6H, 7H)-thiones (13) (R=H, 2Cl, 2-OMe, 4-OMe; R¹=H, 2-Me, 4-Me) have been patented as potential fungicides⁵⁵.
Keeping the above observation in view 3,7,8-triazyl-7,8-dihydro-1,2,4-triazolo [3,4-b]-1,3,4-thiadiazolo [3,2-a]-1,3,5-triazine-6-thiones (14) have been synthesized with the hope that fusion of the bio-labile 1,2,4 triazole, 1,3,4-thiadiazole and 1,3,5-triazine nuclei might result in the pesticides of enhanced potency.
III. 5-Aryl-4,5,6,7-tetrahydrobenzothiazolo [3,2-a] [1,3,5]-triazine-3-thione.

Thiazolyl derivatives have been used clinically for the treatment of bacterial\textsuperscript{55-58} and in view of their increasing importance in pharmaceutical and biological field\textsuperscript{59,60}.

Substituted 4-amino acetyl-2-nitro-4'-methyl diphenyl-amines and 4-(2-amino-4-thiazolyl)-2-nitro-4'-methyl diphenyl amines of the type (15) have been reported as promising antifungal compounds\textsuperscript{61}.

![Chemical structure of (15)](image)

(15)

Some thiazolylethanes of the type (16) have been reported as insecticides or their intermediates by Yagihara et al\textsuperscript{62}.

![Chemical structure of (16)](image)

(16)
Substituted 4,5,6,7-tetrahydrobenzothiazole-4-carboxylic acids, their esters and amides possesses anti-inflammatory and analgesic properties\textsuperscript{63} and in dental pain and severe headache\textsuperscript{64}.

Recently 3 aryl-1-[(E)-cyanomethylidene]-1H-pyrido [2,1-b]-benzothiazolo-4-carbonitriles (17) have been reported as pesticide by Srivastava et al\textsuperscript{65}.

\begin{center}
\begin{tikzpicture}
\node (1) at (0,0) {\includegraphics[scale=0.5]{example}};
\node (2) at (1,2) {\textbf{(17)}};
\end{tikzpicture}
\end{center}

Similarly, 1,3,5-triazine nucleus is also associated with broad spectrum of pesticidal activities as described in the II\textsuperscript{nd} series of this Chapter.

In the light of the above observation 4,5,6,7-tetrahydrobenzothiazoles nucleus has been fused with 1,3,5-triazine nucleus, resulting the title compounds 5-aryl-4,5,6,7-tetrahydrobenzothiazolo [3,2-a] [1,3,5]-triazine-3-thione (18) which might result in the fungicides of enhanced potency.
IV. 4-Methyl-6-phenyl-2-phenylimino-1,3-dithiolo and oxathiolo [4,5-d] pyrazole.

Pyrazoles derivatives and pyrazoline derivatives are associated with broad spectrum of pesticidal activities like antifungal, antibacterial, anti-inflammatory, antitubercular, analgesic, insecticidal, antiparasitic and antiviral activity. Some of these compounds have also shown anticonvulsant and anticancer properties. Recent literature describe the investigations of a few derivatives of pyrazoles as possible anti-inflammatory agents. Likewise some pyrazoles are also used as agrochemical dyestuffs.

Some Pyrazoline and isoxazoline derivatives have displayed wide range of biological and pharmacological activities.

Pyrazole and its several substituted derivatives are inhibitor and deactivator of liver alcohol dehydrogenase.
Okada et al. have been synthesized various 5-alkoxy pyrazolo-3-carboxamides (19) as agricultural fungicides\textsuperscript{66}.

\[
\begin{array}{c}
\text{R}^1 = C_{1-4} \text{ alkyl, aryl,} \\
= C_{1-4} \text{ alkyl, NO}_2, \text{ cyano,} \\
= \text{CF}_3, \\
\text{Y = CH, N}
\end{array}
\]

Mohan, Jag; Kumar et al. have been recorded pyrazolo [3',4':4,5] thiaozolo [3,2-b]-2-triazoles a condensed bridged nitrogenous heterocyclic compounds of type (20) as antifungal agents\textsuperscript{84}.
Recently various intermediate of pyrazole derivatives (21) and (22) R\textsuperscript{1a}=optionally substituted C\textsubscript{1-22} alkyl or optionally substituted C\textsubscript{7-11} alkyl R\textsuperscript{2a}=H, optionally substituted C\textsubscript{1-12} alkyl optionally substituted C\textsubscript{3-6} cycloalkyl optionally substituted, C\textsubscript{3-6} alkynyl optionally substituted acyl or optionally substituted sulphonyl R\textsubscript{3}=HC\textsubscript{1-6} alkyl or halogeno and R is optionally substituted carbomoyl or optionally substituted acylaminal have been prepared as herbicides\textsuperscript{85}.

![Pyrazole Derivatives](image1)

(21)

(22)

Recently various some new pyrazolo thiadiazoles (23) [R\textsuperscript{1}=H, R\textsuperscript{2}=2-Cl, C\textsubscript{6}H\textsubscript{4}, 4-ClC\textsubscript{6}H\textsubscript{4}, 2-O\textsubscript{2}NC\textsubscript{6}H\textsubscript{4}] has been reported as antimicrobials\textsuperscript{86} agents by Srivastva S.D. et al.

![Pyrazolo Thiadiazoles](image2)

(23)
On the observation of above review the pyrazole ring is associated with 1,3-dithiolo and 1,3-oxathiolo ring to prepare the title compound 4-methyl-6-phenyl-2-phenylimino-1,3-dithiolo [4,5-d] pyrazole (24) and 4-methyl-6-phenyl-2-phenylimino-1,3-oxathiolo [4,5-d] pyrazole (25) with the hope that association of the biolabile triazole ring, 1,3-dithiolo ring and 1,3-oxathiolo nuclei might be result to the pesticides of enhanced potency.

![Diagram of compound 24](image)

![Diagram of compound 25](image)
Evaluation of fungicidal activity-

The fungicidal activity of seventy compounds was evaluated invitro against *Puccinia recondita* and *Ustilagonuda maydis* by the usual agar plate technique$^{87}$. At, 1000, 100 and 10ppm concentrations using Czapek's agar medium as described in Chapter-IV of this thesis. A commercial fungicide, **Dithane M-45** (Manganous ethylene bis-dia thio carbamate with zinc ions) was also tested under. Similar conditions for comparing the results. The screening results have been reported and discussed in Chapter-IV of this thesis.
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