CHAPTER-I

PREFATORY NOTE

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A large number of heterocyclic compounds are present in all the living beings where these perform important physiological functions they are widely distributed in nature, as nucleic acids, proteins, vitamins, alkaloids and porphyrins. Many antibiotics produced by microorganism contain nitrogenous heterocycles, most important of which are pencillin, thienamycin, oxamycin and cephalosporin.

Since so many natural products are heterocycles, it is expected that unnatural, synthetic five membered heterocycles should exhibit physiological responses. This expectation has been realized because now we have many five membered heterocyclic synthetic drugs and pest control chemicals at hand. It is interesting to note that with respect to the variety of biological activity specially as fungicides five memberd heterocyclic compounds occupy nearly the first place among the other classes of the organic compounds. The wide variations possible in properties of various heterocycles is responsible for their suitability for the specialized reactivities required in the

chemistry of living organisms. A dexterous combination of a physiologically important units has furnished a variety of synthetic drugs and pest control chemicals. In this respect, most versatile are the five membered rings like imidazoles, thiazoles, thiadiazoles, oxadiazoles and triazoles etc.

Specially heterocyclic compounds are associated with broad spectrum of pesticidal activities like fungicides[1-4], bactericides[5-7], insecticides[8-9] and medicinal properties[10-12]. Like wise 1,3,4-thiadiazoles and 1,3,4 oxadiazoles nucleus also possesses pesticidal activities. For example 1,3,4-thiadiazole derivatives were reported to possess fungicidal[13-15] herbicidal[16], bactericidal activity[17,18]. Similarly. 1,3,4-oxadiazoles possess fungicidal[19], insecticidal[20] and bacteridicidal activity[21].

The reason for paying special attention towards fungicidal activity was obvious in light of the grate loss of our essential food supplies both in fields and stores. The extent 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 consequence of which millions of people either died of malnutrition or forced to

imigrate[22]. The downy mildew disease destroyed the vineyards of France, another species *Hemileia vastratrix* caused the disappearance of the coffee plantation and coffee industry in Srilanka. In India about five million tones of grains are lost annually due to fungal diseases of edible corps[23].

In last year, the Second World War (1943) has to face a serious famine one of the reason to which this famine has attributed in the loss in yield to rice due to attach of Helminthosporium leaf spot which had been affecting the crop for the several years.

Severe wheat shortage in Madhya Pradesh (India) during 1946-1947 due to wheat rust and sugarcane red-rot epidemic in Uttar Pradesh (India) in 1938-42 were major nuisance to Indian economy. Even in most advanced countries losses are still very heavy inspite of the adoption of modern methods of crop protections. In 1945 lateblight of potato disease destroyed the potato crops of Ireland. In Ireland, England and certain part of continental Europe potato was the stable diet of the populations. A large number of people died of hunger and may more became diseased due to physical weakness. There was migration of population to other countries including the North

American continent. This single disease forced man to realize the importance of plant disease. As a result, scientific investigations were taken up, the cause of disease control came into existence. Certain fungal species also caused the human and animal disease termed as mycoses. Approximately one million cases of coccidiodo mycoses in California alone were estimated by Ajello[24]. As estimated Palmer[25] and Beadenkoi et al[26]. At least eight million persons in Ohio and Mississippi Valleys have been infected with the species *Histoplasma capusulatum* the causal agent of Histoplasmosis. Fox and Shields have started that the large number of males in united states have some time in their lives been infected by fungi, causing "Athlete" of foot[27].

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

1. Fungistatic action which implies as continuous interference as large the organism is in the contact of toxicant or.
2. Fungicidal action which denotes a persistant action even after the withdrawl of toxicant.

Most of the early used fungicides were inorganic compounds of sulfur, copper, calcium, arsenic, mercury, lead and phosphorous. For example, in 1885 a poisonous mixture of copper sulphate 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. The use of sulphur and copper fungicides dominated the market until 1915 when organomercury seed treatments, derived from discoveries in the pharmaceutical and dyestuffs industries were shown to be highly effective against cereal upto the mild 1960s, the fungicide market comprised broad spectrum, high rate of use, multi-side of action, non-systemic protactants. The announcement of systemic compounds causes a revolution in farmer practice, permitting much greater flexibility of use with increased level of control. New opportunity for fungicides were recognized, particularly in major European crops. Intensive cereal production, characterized by high density monoculture and high level of fertilizer use, was especially responsible and large yield increases were recorded following the adoption of the new systemics for the control of the ancient diseases caused by powdery mildew and rust.

Several inorganic fungitoxic compounds were found dangerous for human beings and host plants. With the growing consciousness for more efficient less hazardous fungitoxic compounds have always remained desirable. Synthetic organic compounds have attracted much attention in this direction because they fulfill these requirements as well as are often more specific in action and offer a wide range of choice. The introduction of fungicides in 1966 as a major land mark in the history of fungicidal control of the plant disease. However the successful of organic synthetic compounds (microbial origin) was first demonstrated by Von Schmeling and Kulka[29] in 1966. The discovery of Oxathin, Oxacarbin, and Carboxin fungicides was soon followed by confirmation of the systemic activity of pyrimidine derivatives[30] and benzimidazole derivatives[31-33].

Newer fungicides are comming up as a result of research pioneered by the discovery of fungicides. The most important and useful of them are nitrogenous and fluorinated heterocyclic compounds e.g. **Glycodin** (2-hepta-decyl-2-imidazo-line acetate), **Oxine** (8-quinolino '1' and '8' hydroxy quinoline and **Captain** (N-trichloro methylthio-4-cyclohexene-1,2-dicarboximide).

In view of the above background and with object of further exploring the subject it was considered worth while to synthesis new fungitoxic five membered heterocyclic compounds designed with toxophoric requirement for fungi. Thus evaluation of their fungicidal activity might through some light on the relationship between chemical constitution and fungicidal activity and also might yield some compounds of practical importance. An attempt has been made in this direction.

This thesis has been divided into four chapters depending upon the nature of the works and the type of the biological activities associated with the synthesized compounds-

1. Prefatory Note
2. A brief review on pesticidal five membered heterocyclic compounds.
3. Synthesis and characterization of five membered heterocyclic compounds.
4. Evaluation of fungicidal activity.

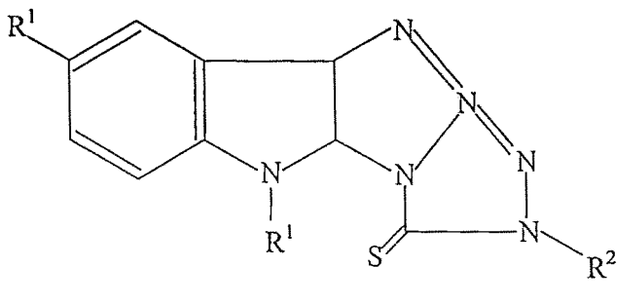
The following four new series of the five membered heterocyclic compounds have been synthesized. All the synthesized compounds have been well characterized by their elemental analysis, IR and ^{1}HNMR spectra.

(1) Bis (4-aryl-5-alkylsulphonyl-1,2,4-triazole-3-yl) methane

1,2,4-triazole derivatives are known to exhibit various types of useful biological activities 3-aryl 1,2,4 triazole (amitrole) is well known commercial herbicides. Similarly, various 1,2,4-triazole derivatives have been reported as bactericidal[34-39] fungicidal[40-44], herbicidal[45-54] and insecticidal[55-58]. Literature review clearly demonstrates that much work has not been done on the synthesis of 2-alkyl [1,2,4]-triazolo-[5,1-b]-benzothiazoles. The earlier methods were not only tedious but time consuming. In this respect short time consuming more convenient route was sought for the preparation of 2-5-dialkyl, 2,7-dialkyl and 2,5,7 trialkyl [1,2,4] triazolo-[5,1-b] benzothiazoles. A number of condensed ring system incorporating thiazole nucleus fused with imidazole, 1,3,4-oxa [thia] diazoles and 1,2,4 triazole ring have been reported as potential fungicides[59-61], bactericides[62,63], herbicides[64,65] and insecticides[66-69].

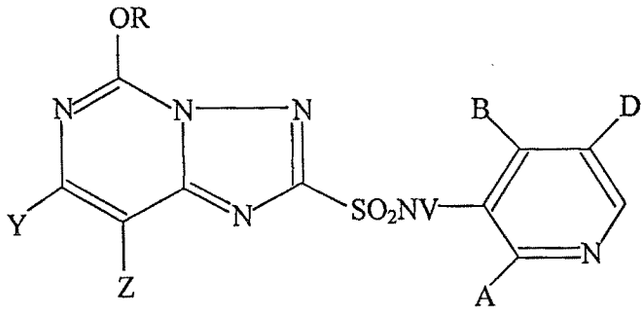
The observations coupled with fact that planarity of a molecule might argument for its fungicidal activity as it often does with the herbicidal[70,71] activity. The toxophoric importance of >N–C(–)–S–moiety also has been well stressed in many pesticides[72-75].

Growing literatures, clearly demonstrates pesticidal compounds having s-triazole, 1,3,4-thiadiazole and imidazole rings are potential pesticides. For example- Holla et al. have synthesized some novel -5-mercapto-s-triazolo [3,4-c]-triazino [5,6-b]-indole and the manich base **(1)** (R=H, Cl, Me; R^1=H, Me; R^2=H) as antibacterial agents[76].



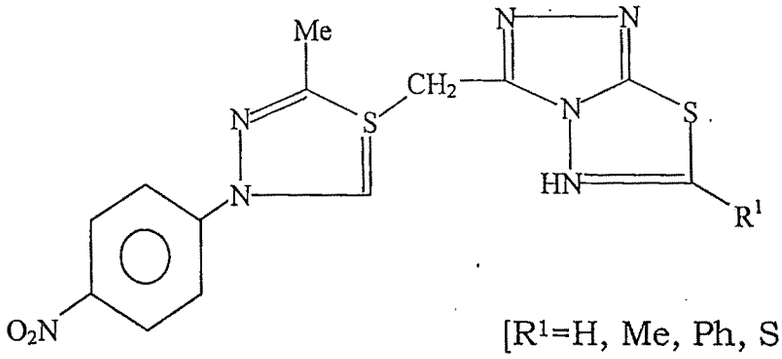
(1)

Dandia et al. have prepared 3-(1,2,4-triazolo-3-imino) indole-2-ones derivatives **(2)** (R=H, 5 or 6, 4-CF_3, 5-Cl) for anti-bacterial activities[77].



(4)

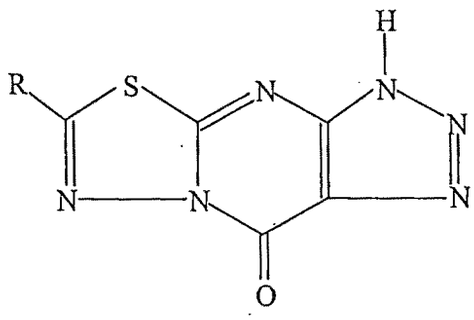
Some substituted 1,2,4-triazolo-[3,4-b]-thiadiazoles of the type **(5)** have been prepared by Patel et al. as potential fungicides[80].



[R^1=H, Me, Ph, SH, OH]

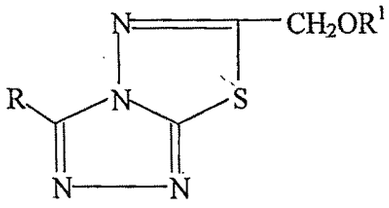
(5)

Sujaki et al. have prepared many compounds of 1,3,4-thiadiazolo-[3,2-a]-1,2,3-triazolo [4,5-b]-pyrimidine-9-(3H) one of the type **(6)** as anti-allergy agents[81]. [R=Ph, CH_2OPh, substituted Ph).



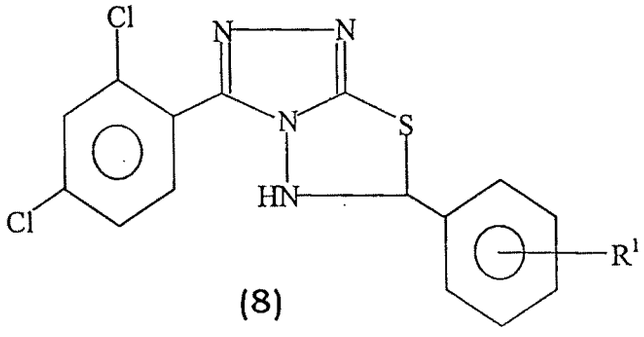
(6)

Zhag Zigi et al. have recorded some of 3-alkyl-6-aryloxy methylene-5-triazolo [3,4-b]-1,3-4-thiadiazoloes of the type **(7)** as fungicidal agents[82].



(7)

Some 6-aryl-3 (2,4-dichloro-phenyl) s-triazolo [3,4-b] [1,3,4]-thiadiazoles of the type **(8)** (R^1=H, 4-Me_2N, 3-Cl, 4-MeO) have been synthesized by Gogai et al. as anti-microbial compounds[83].



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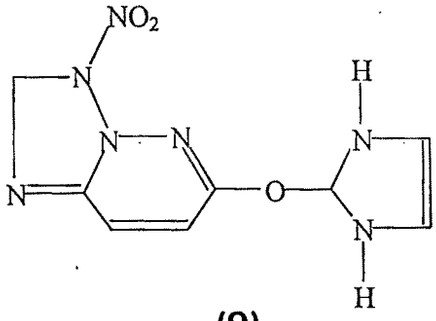
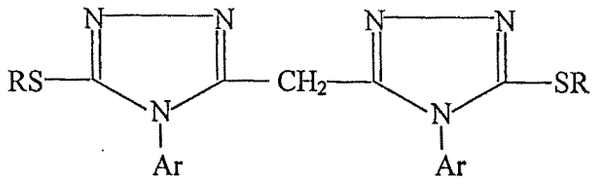
Yukimasa et al. have prepared compounds of imidazole derivatives of the type **(9)** as antibacterials[84].



(9)

The tuberculotherapeutic activity of 1,2,4-triazoles is well known, which is due to their basic nature and the presence of active hydrogen, in the ring. But however, very little is known about bis (1,2,4-triazoles). Keeping the above observations in view the title compounds bis (4-aryl-5-alkyl sulphide-1,2,4-triazole-3-yl) methane **(10)** and bis (4-aryl-5-alkyl sulphonyl-1,2,4-triazole-3-yl) methane **(11)** have been synthesized with the hope that it might result in the fungicides of enhanced potency.



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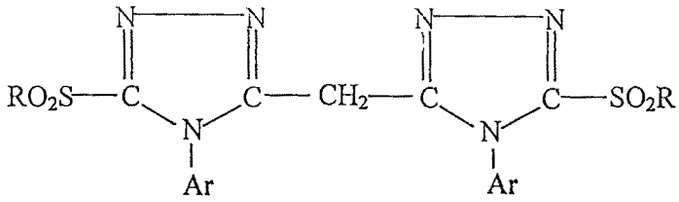
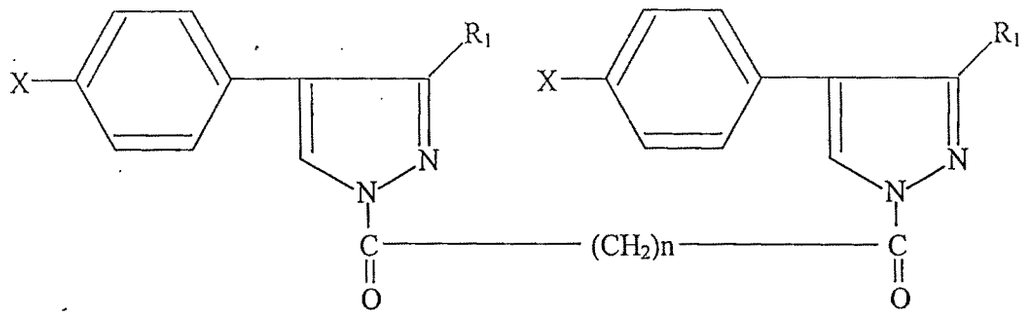


(11)

(2) Bis [3-alkyl/aryl-5-(4-haloaryl)]-N-alkanedione

Recently, the chemistry of pyrazole derivatives has aroused great interest with report of the series of COX-1 and COX-2 inhibitors especially, celecoxib (SC-58393) one of the best COX-2 inhibitors which is now available in the market[85]. Pyrazole and pyrazole derivatives are well known for their various biological activities[86]. Many pyrazole derivatives have shown anti-inflammatory[87], antipyretic[88], antihypertensive[89], antibacterial and antifungal activities[90].

Keeping in view the biological importance and medicinal utility, the Bis [3-alkyl/aryl-5-(4-haloaryl)]-N-alkane dione **(12)**] have been synthesized with the hope they will be fungicide of choice.



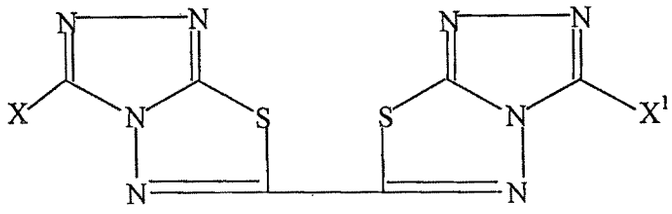
(12)

(3) 6-6'-Bis-3-substituted 1,2,4-triazolo (3,4-b) (1,3,4)-thiadiazoles.

Many 1,3,4-thiadiazole nucleus is associated with a broad spectrum of biocidal activity, for example fungicides[91-94], insecticides[95,96], bactericides[97-100] and herbicides[101-103] possibly by virtue of incorporating >N–C–S– moiety. The toxophoric importance of which has been well stressed in many pesticides[104,105].

Similarly, 1,2,4-triazole is also associated with broad spectrum of pesticidal activities[34-84] as described in the first series (chapter-I) of this thesis. Compound having 1,2,4-triazole moiety and N-bridged heterocyclics derived from them are endowed with variety of biological activities and have a wide range of therapeutic properties[106-110]. Thiadiazole nucleus present in triazolothiadiazoles incorporating >N-C-S linkage exhibits wide range of biological activities.

Keeping the above observations in view we have to fuse the biolabile 1,2,4-triazole nuclei with 1,3,4-oxadiazole nuclei to synthesized the title compound 6-6'-bis-3-substituted 1,2,4-triazolo (3,4-b) (1,3,4)-thiadiazoles **(13-15)** with the hope of that this combination would give the fungicide of enhanced potency.



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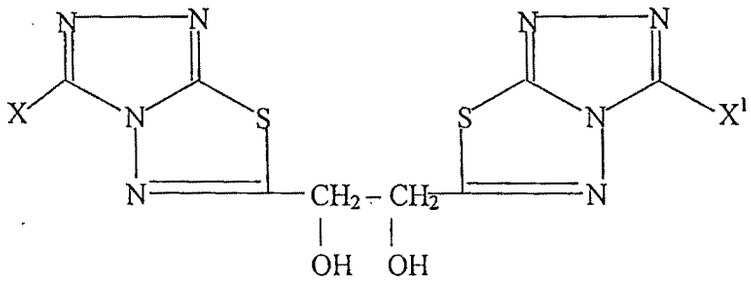

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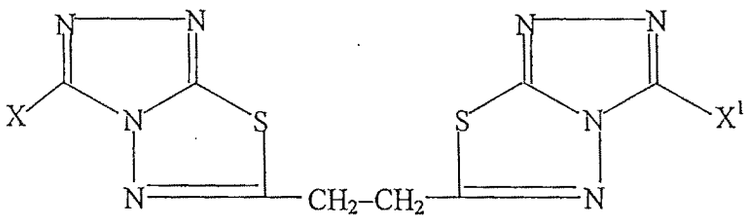
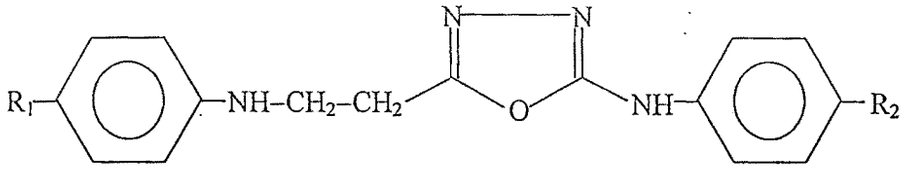


(15)

(4) 5-{2-[(4-Substituted phenyl) amino] ethyl}-N-(4-substituted phenyl)-1,3,4-oxadiazol-2-amine

1,3,4-Oxadiazole derivatives are known to exhibit various useful biological activities including herbicidal[111-115], fungicidal[116-118], bactericidal[119-122], insecticidal[123-126], viricidal[127] and to show a broad spectrum of medicinal properties[128-132].

Persual of the above literature and the observation that biological activities are shown by 1,3,4-oxadiazoles specially when properly substituted at 2 and 5 positions. Hence, some new title compounds 5-{2-[(4-substituted phenyl) amino] ethyl}-N-(4-substituted phenyl)-1,3,4-oxadiazol-2-amine **(16)** have been synthesized with the hope that these compounds will be fungicides of enhanced potency.



(16)

EVALUATION OF FUNGICIDAL ACTIVITY :

The fungicidal activity of seventy eight compounds were evaluated against *Phytophthora infestans* and *Helminthosporium oryzae* by the usual agar plate technique[133] at 1000, 100 and 10ppm concentration using Czapek's agar medium as described in Chapter-IV of this thesis. A commercial fungicide, **Dithane M-45** (Manganous Ethylene Bisdithiocarbamate 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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