1,3,4-Oxadiazoles and 1,2,4-Triazolo[3,4-b][1,3,4]thiadiazoles/ thiadiazines as Potential Biodynamic Agents

By

MUKTA

Thesis submitted to the CCS, Haryana Agricultural University, Hisar, in partial fulfilment of the requirements for the degree of

MASTER OF SCIENCE

in

CHEMISTRY

Department of Chemistry and Biochemistry
CCS Haryana Agricultural University
HISAR

1993

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D E D I C A T E D

TO

GOD ALMIGHTY

CERTIFICATE - I

This is to certify that the thesis entitled "1,3,4-Oxadiazoles and 1,2,4-Triazolo[3,4-b][1,3,4]thiadiazoles/thiadiazines as Potential Biodynamic Agents" submitted for the degree of Master of Science in the subject of Chemistry to the CCS, Haryana Agricultural University, is a bonafide research work carried out by Ms. Mukta under my supervision and no part of this thesis has been submitted for any other degree.

The assistance and help received during the course of investigation have been fully acknowledged.

MS Malik
17-2-93

(M.S. Malik)
Major Advisor

CERTIFICATE-II

This is to certify that the thesis entitled "1,3,4-Oxadiazoles and 2,4-Triazolo[3,4-b][1,3,4]thiadiazoles/thiadiazines as Potential Biodynamic Agents" submitted by Ms. Mukta to CCS, Haryana Agricultural University in partial fulfilment of the requirements for the degree of Master of Science in the subject of Chemistry has been approved by the Student's Advisory Committee after an oral examination on the same, in collaboration with an External Examainer.

MAJOR ADVISOR

EXTERNAL EXAMINER 5.3.93

HEAD OF THE DEPARTMENT

DEAN, POST-GRADUATE STUDIES

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I fail to find sufficient words to express my great pleasure to acknowledge the blessings, silent wishes, ethical affection and everlasting inspiration from my parents and benediction from sister Renu, who sacrificed her comforts for my sake at the time of need thus making my path easier to achieve this goal.

Date: Feb. 17, 1993.

Mukta
MUKTA

CONTENTS

PREFACE

Among the various steps involved in the development of physiologically, selective pesticides, the first and foremost step is to design a new molecule which is likely to show desired pesticidal activity. The practical exercise is then started by synthesizing the designed molecule and its congeners followed by their screening. "Structural modification of known leads", which includes (i) recognition of a structural pattern in the lead molecule; (ii) synthesis of analogs with the recognised structural pattern and (iii) bioevaluation of each structural variant, has been the guiding principle for designing and synthesis of new compounds described here.

Based on the interesting antimicrobial activity exhibited by phenoxymethyl hydrazides and their derivatives such as oxadiazoles/ triazolothiadiazoles/thiadiazines; several other new p-tert-butylphenoxymethyl oxadiazoles/triazolothiadiazoles/triazolothiadiazines were designed, synthesized and evaluated for antifungal activity against two phytopathogenic fungi, the results thus obtained are cited in this dissertation. It is hoped that the results discussed here will help in the development of suitable antifungal agents besides providing new leads for future development in the activity of such compounds and, therefore, a definite contribution has been made towards advancement in the existing knowledge of the subject.

This dissertation is organised in a format as approved by the Dean, Post Graduate Studies, Chaudhary Charan Singh Haryana Agricultural University, Hisar. Nomenclature of the new compounds has been made as per norms followed in current volumes of chemical abstracts.

INTRODUCTION

CHAPTER - I

INTRODUCTION

The pesticides are a group of products of immense agricultural and economic importance for crop protection and pest control and have become indispensable in the modern farming. The main aim of applying pesticides is not to manage the pests but to manage their ill effects on crop yield and quality and animal health and well being.

Development of new pesticides which are effective for the optimum control of pests and diseases and are also environmentally acceptable had been the basis of the search for new products all over the world. This will help to minimize the damage already done to the environment.

A pesticide of choice must be toxic against the target pest but should have no or minimal effects on non-target plants and animals. However, commercial pesticides are limited both in terms of their efficiency and selectivity and are also not free from undesirable side effects. Therefore to meet the future demands of safer pesticides, all efforts are needed to be marshalled towards the development of target specific pesticides. This can be achieved by carrying out the manipulations in the promising lead compounds of known activity by chemical synthesis. Therefore synthesis of new compounds with different substituents/functionalities followed by their bioevaluation appears to be the best approach for evolving physiologically selective pesticides.

The fungicide field so far has not seen a breakthrough in the high potency and high selectivity directions though a wide range of heterocyclic ring systems have shown to possess fungicidal activity.

Substituted phenoxyacetic acid esters and their hydrazides are reported to exhibit diverse types of properties like nematicidal (Malik et al., 1989) and antimicrobial (Sangwan et al., 1987). Several other related pyrazoles and pyrazolones (Pathak et al., 1981) have shown significant bacteriostatic, bactericidal and fungicidal actions.

Studies on the derivatives of various heterodiazoles such as oxadiazoles and thiadiazoles synthesized from phenoxy acetic acid hydrazides (Dubey, 1992) have also shown promises for the development of suitable biodynamic agents. Literature reports also clearly indicate that several heterodiazole derivatives (oxadiazoles, triazolothiadiazoles and triazolothiadiazines) display diverse types of other activities including antibacterial, antiinflammatory, analgesic, anticonvulsant, CNS depressent etc. Thus to improve upon the activity, particularly antifungal activity of such compounds, a research project was proposed with the following objectives:

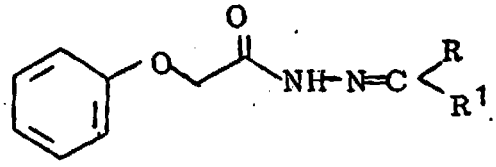
1. To design and synthesize new heterodiazoles with such substituents as would impart the molecule the desired type of biological activity.
2. To characterize the various compounds synthesized and to evaluate their biological activity.

REVIEW OF LITERATURE

CHAPTER - II

REVIEW OF LITERATURE

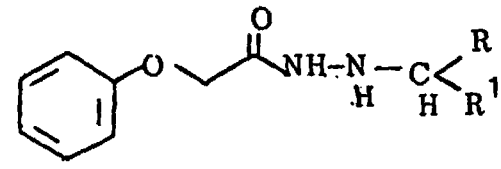
Phenoxyaceticacid hydrazides have been reported to possess wide range of biological activities. The benzylidene derivatives of phenoxyacetic acid hydrazide (I) and its saturated analog II were reported as potential monoamine oxidase inhibitors (Orzalesi et al., 1974).



R= H; Me

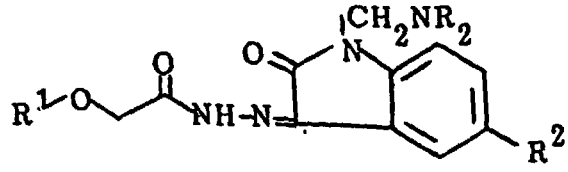
R^1=Me; Ph; $PhCH_2$; COOH

I



II

Phenoxyacetic acid hydrazones of disubstituted indolinone derivatives (III) showed CNS activity and were relatively nontoxic (Agarwal et al., 1982).



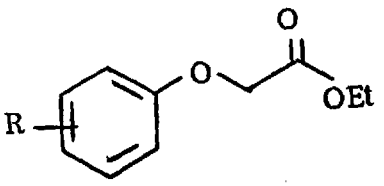
R_2N= 1-pyrolidinyl; morpholino; piperidino; 4-p-tolyl-1-piperazinyl

R^1= 2-naphthyl, p-$NO_2C_6H_4$

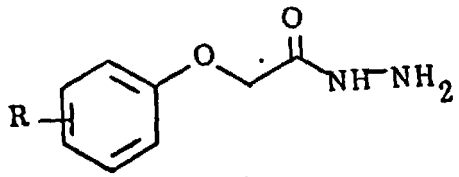
R^2= H; Me

III

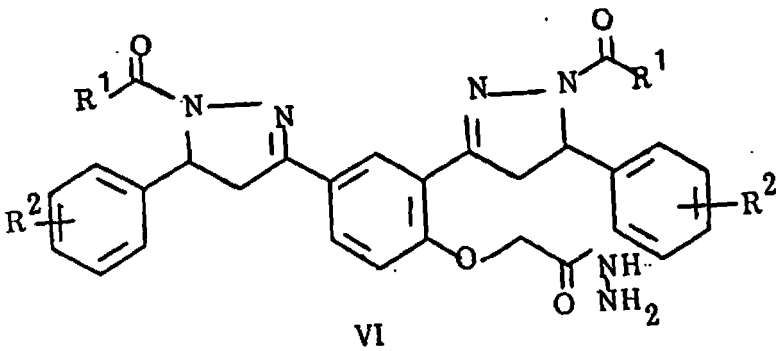
More recently, Malik et al. (1989) reported that various substituted phenoxyacetic acid esters (IV) and their hydrazides (V) exhibited nematicidal activity against plants pathogenic nematodes. The bis(substituted pyrazolyl) phenoxyacetic acid hydrazides (VI) were reported for the antimicrobial activity (Sangwan et al., 1987).



IV

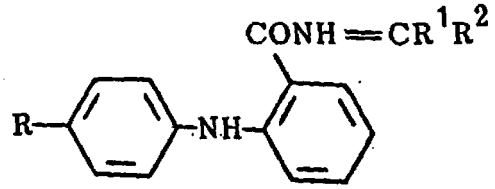


V



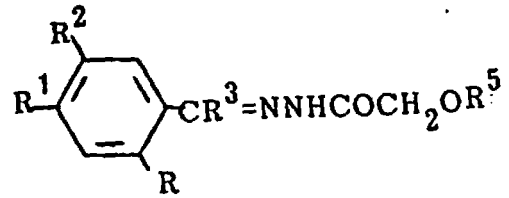
VI

Some aroyl/aryloxyacetyl hydrazones of fluoroaralkyl/diaryl ketones (VII and VIII) were synthesized by Pathak et al. (1981a,b), which exhibited antifungal activity.



R= H; Cl; MeO
R^1=Me; Ph
R^2=4-FeC_6H_4; 2,5-F-MeC_6H_3

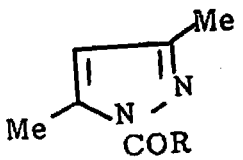
VII



R, R^1= F; H
R^2= H; Me
R^3= Me; Ph
R^4= Ph; 4-ClC_6H_4; 4-$MeOC_6H_4$
R^5= 5,2-Me(Me_2CH)C_6H_3; 4-$Me_3CC_6H_4$

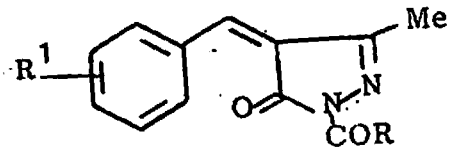
VIII

Several N^1-substituted-3,5-dimethylpyrazoles (IX) and 3-methyl-5-pyrazolones (X) and the related compounds were reported exhibiting antifungal activity (Pathak et al., 1981c and Suman et al., 1981).



R = 4-ClC_6H_4; 2-HOC_6H_4;
2-$PhNHC_6H_4$;
2-$MeC_6H_4OCH_2$;
4-$MeC_6H_4OCH_2$.

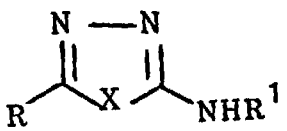
IX



R= same as IX
R^1=H;Cl;HO; Me_2N

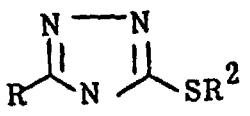
X

Heterocyclic compounds such as oxadiazoles (XI), thiadiazoles (XII) and triazoles (XIII) were prepared and were tested against Aspergillus niger and Helminthium oryzae. These compounds showed moderate to good antifungal activity (Sharma et al., 1982 and Roda et al., 1988a,b).



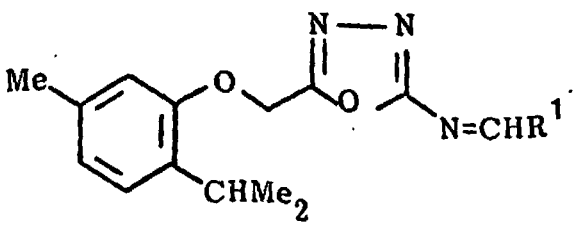
X = 0; S
R = 3,4-$MeCl_6H_3OCH_2$;
2,4-$Me_2C_6H_3OCH_2$;
$PhCH_2$, 2,6-$Me_2C_6H_3OCH_2$
R^1 = 4-$MeOC_6H_5$, $PhCH_2$

XI



R= same as XI
R^2=Me;H

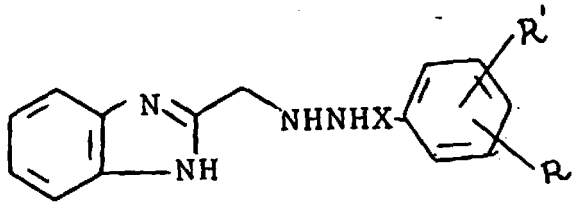
XII



R^1= Ph; HOC_6H_4; Cl-C_6H_4; $Me_2NC_6H_4$; PhCH=CH

XIII

Mishra and Bahel (1985) examined a series of benzimidazoles (XIV) as potential fungicides.



R= H; Me; Bu; Cl

R^1=H; Me

X= CO; $COCH_2O$; CSNH

XIV

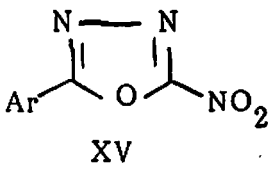
2.1 1,3,4-Oxadiazoles

2.1.1 Monosubstituted 1,3,4-Oxadiazoles

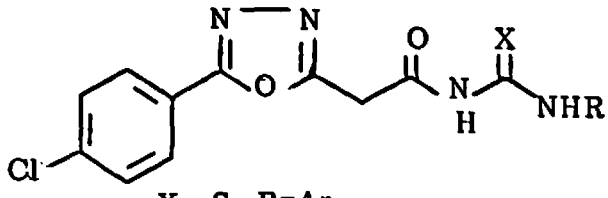
Monosubstituted oxadiazoles such as 2-hydroxyphenyl-1,3,4-oxadiazoles as hypnotic and sedative agents, 2-(1,1-diphenylalkyl)-1,3,4-oxadiazoles as antidiarrheal and 2-(1,2,4-triazol-4-yl)-1,3,4-oxadiazole as fungicides have been reported in literature (Hill, 1984).

2.1.2 Disubstituted 1,3,4-oxadiazoles

Several 2-aryl-5-substituted 1,3,4-oxadiazoles (XV, XVI) have been reported to show bactericidal and fungicidal activity (Hill, 1984; Mehta and Parekh, 1988). Various disubstituted derivatives such as 2,5-diaryl-, 2,5-dialkyl- and 2-alkyl-5-aryl-1,3,4-oxadiazoles have been patented for herbicidal activity particularly against broad-leafed weeds and grasses in crops such as rice and corn (Hill, 1984). Several other 2,5-diaryl-1,3,4-oxadiazoles have been synthesized and tested for their antibacterial and antifungal activities (Dutta et al., 1986; El-Emam et al., 1988; Idoux et al., 1988 and Vansdadia et al., 1988). 2-(2-Carboxyphenyl)-5-aryl-1,3,4-oxadiazoles are reported to act as plant growth regulator (Hill, 1984). 2-(2-Hydroxyphenyl)-5-(4-dimethylaminophenyl)-1,3,4-oxadiazole (XVII) showed antiinflammatory activity against carageenin induced rat paw edema with lower ED_{50} than several non-steroidal antiinflammatory drugs and had less ulcer producing potential in rats (Kumar et al., 1987).



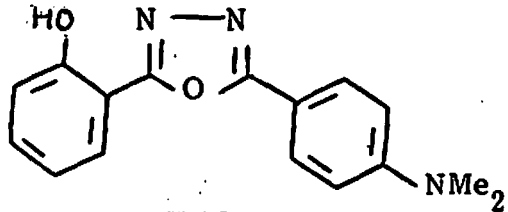
XV



X= S; R=Ar

X= O; R=Ar

XVI

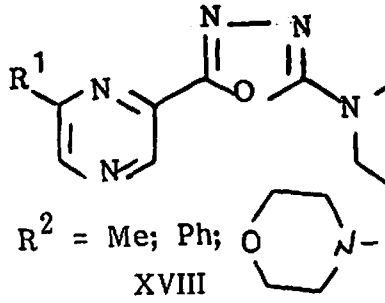


XVII

Ten symmetrical 2,5-diaryl/heteroaryl-1,3,4-oxadiazoles were found to show CNS depressant activity. Some of these compounds reversed reserpine-induced depressive syndrome and showed anticonvulsant activity (Sharma and Tandon, 1984). 2,5-Di(4-methylphenyl)-1,3,4-oxadiazole was reported to induce dose-dependent fetal resorption in hamsters through subcutaneous or oral route (Mehrotra et al., 1986).

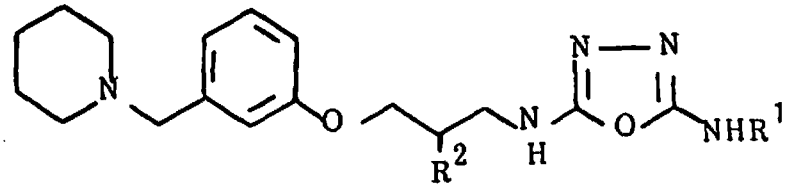
Various 2-amino-5-substituted-1,3,4-oxadiazoles were found to act as muscle relaxants (Hill, 1984) and antiinflammatory agents (Rani et al., 1990) and also showed antimicrobial activities (Daultabad and Mirajkar, 1988; Hill, 1984; Mano et al., 1976 and Rani et al., 1990). Several 2-substituted amino-5-substituted-1,3,4-oxdiazoles were described to exhibit antimicrobial (Labouta et al., 1989), bactericidal (Andotra et al., 1992), anthelmintic (Loiseau et al., 1990), H_2-antihistaminic (Kraemer and Schunack, 1986b) and amebicidal

(Andotra et al., 1989) activities. A pyrazinyl substituted-1,3,4-oxadiazole (XVIII) exhibited low tuberculostatic activity (Pancechowska-Ksepko et al., 1988). Derivatives of 1,3,4-oxadiazole-2,5-diamine substituted at both amino groups such as XIX and XX were found to exhibit H_2-antihistamine activity (Kraemer and Schunack, 1986b; Kraemer et al., 1987).



R^2 = Me; Ph;

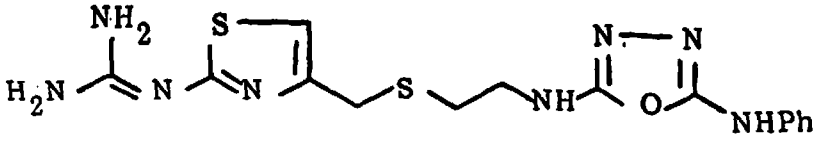
XVIII



R^1 = Me; Ph

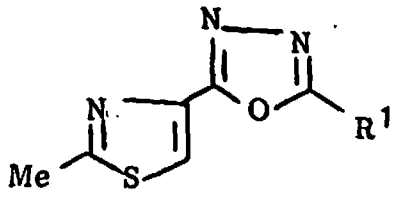
R^2 = H; Me

XIX



XX

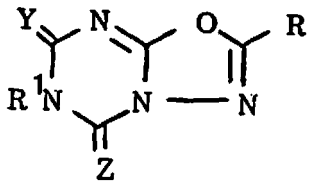
Sawhney et al. (1992) synthesized certain thiazolyloxadiazoles (XXI) when tested none of them exhibited antiinflammatory or anthelmintic activity.



R^1 = Ph; p-$MeOC_6H_4$; p-ClC_6H_4

XXI

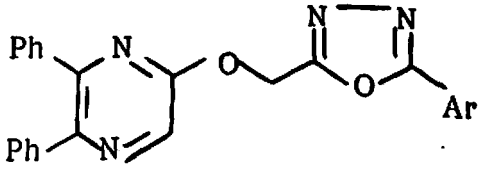
1,3,4-Oxadiazoles (3,2-a)-s-triazine-5,7-dithiones XXII and their analogs were synthesized and screened for their antifungal activity (Singh et al., 1992).



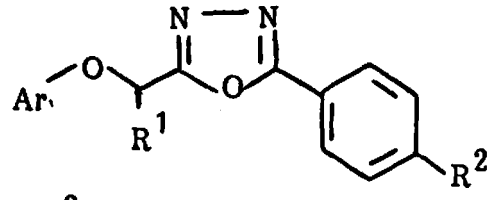
R = Ph, R^1= Ph; O-tolyl
Y = Z = S
Y = S; Z=O
Y = O; Z=S

XXII

Derivatives of 5-aryl-2-hydroxymethyl-1,3,4-oxadiazole have been reported to show analgesic, antiinflammatory, anticonvulsive, diuretic and antiemetic properties (Hill, 1984). Recently some such derivatives of type XXIII with antiinflammatory activity (Abd El-Samii, 1991b, 1992) and XXIV with antimicrobial activity (Roda et al., 1988; Srivastava et al., 1991) have been described.



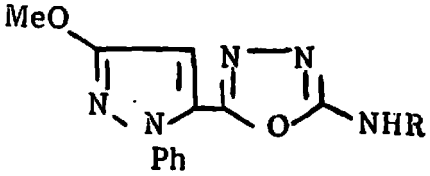
XXIII



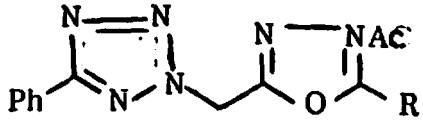
R^2= H; Me

XXIV

Antibacterial activity of some substituted 1,3,4-oxadiazole derivatives (XXV, XXVI) have been evaluated (El-Feky et al., 1992 and Mahajan et al., 1992).

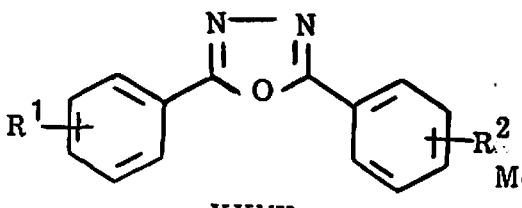


XXV

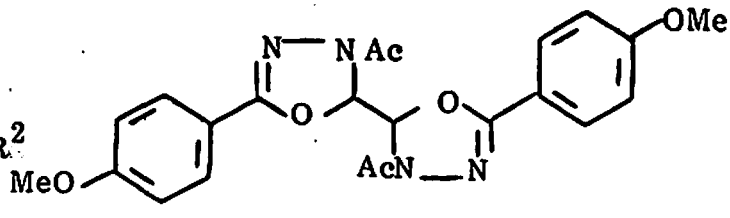


XXVI

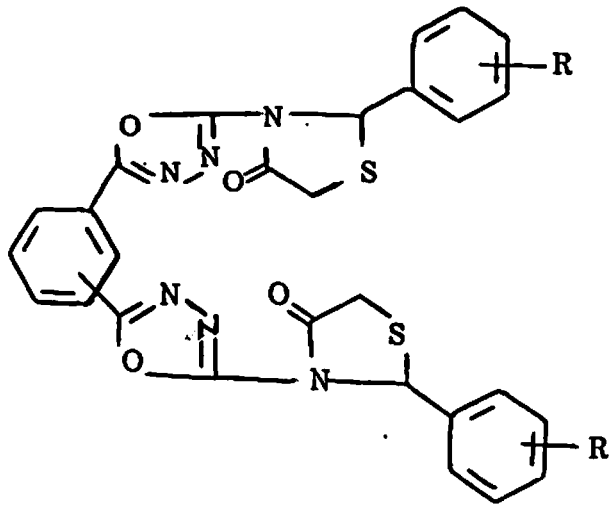
Shaban et al. (1992) synthesized disubstituted oxadiazoles (XXVII) and bis(oxadiazoles) (XXVIII) and were tested for nematocidal, insecticidal and herbicidal activity. Various 5,5'-(disubstituted phenylene)bis[2-(4-oxo-2-phenyl-3-thiazolidinyl)-1,3,4-oxadiazoles] (XXIX), showed growth inhibitory activity against R. solani, C. capsicum and F. oxysporum (Dubey, 1992).



XXVII



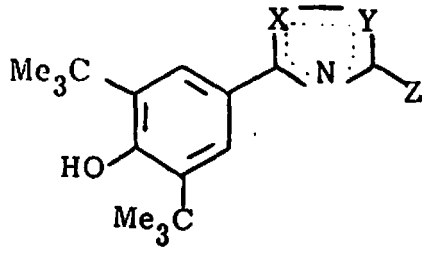
XXVIII



R=H; OMe

XXIX

Novel 1,2,4-oxadiazoles/thiadiazoles XXX) were prepared and evaluated as dual inhibitors of 5-lipoxygenase and cycloxygenase in rat basophilic leukemia (RBL-1) cells. Several of these compounds showed oral efficacy in the rat carageenan footpad edema (CFE) and mycobacterium foot-pad edema (MFE) antiinflammatory models, without concomitant gastric ulceration (Unagst et al., 1992).

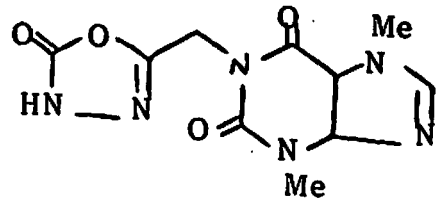


X= N;O , Y = O; N; S

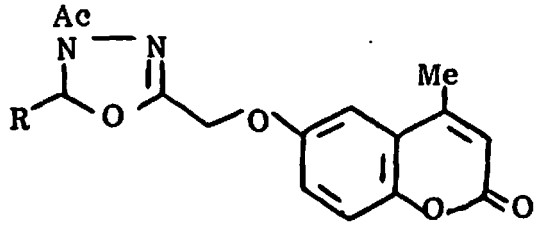
Z= Me; CH_2NMe_2; NH_2; CHCHO; $SO_2C_6H_4Me$-4

XXX

Bactericial activity of some oxdiazolthione (XXXI) (Romeih et al., 1992) and coumarinyloxymethyloxadiazoles (XXXII) (El-Ansary et al., 1992 and Singh et al., 1992) were observed.



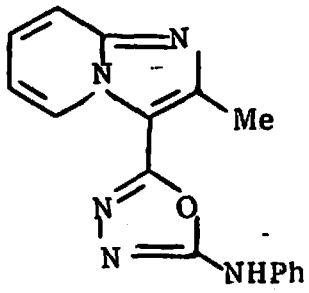
XXXI



R= Ph; substituted Ph; PhCH=CH

XXXII

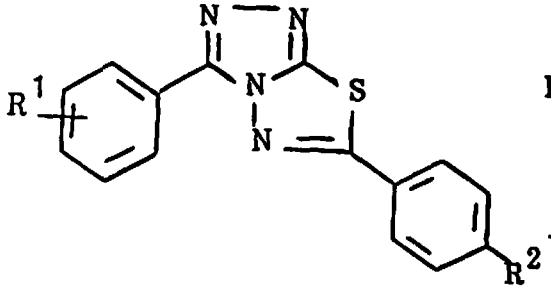
Anticonvulsant activity of certain methylimidazolyloxadiazolylhydrazide (XXXIII) was suggested by Cesur et al. (1993).



XXXIII

2.2 1,2,4-Triazolo[3,4-b][1,3,4]thiadiazoles

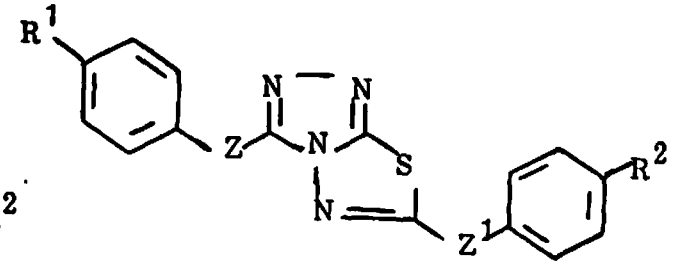
Several 3,6-disubstituted-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles are reported in literature for various types of biological activities. Among such derivatives XXXIV with antimicrobial (Eweiss and Bahajaj, 1987), antibacterial activity (El-Barbary et al., 1991) XXXV with CNS depressant and anti-inflammatory (Deshmukh et al., 1984) XXXVI with CNS, hypochlosterolemic and hypotensive (Mody et al., 1982), XXXVII with analgesic and antiinflammatory (Prasad et al., 1986) and XXXVIII with herbicidal (Narasaiah et al., 1989) activities are worth mentioning.



R^1= H; 4-Me; 2-Cl; 4-Cl;
2-Br; 3-Br; 4-Br; 2-Me

R^2= H; Cl; Me

XXXIV



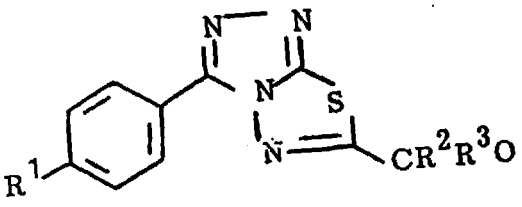
R^1 = H; Cl; OMe

R^2= H; Cl

Z = bond; CH_2; CH_2CH_2; CHPh

Z^1 = bond; CH_2

XXXV

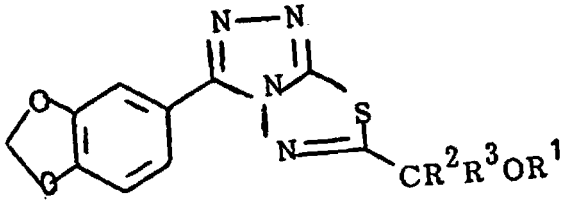


R^1, R^6= H; Cl

R^2, R^3, R^5 = H; Me

R^4= H; Me; Cl

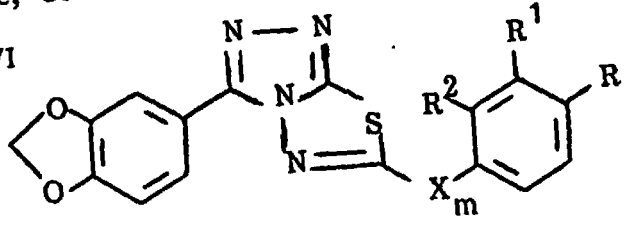
XXXVI



R^1= Ph; substituted Ph

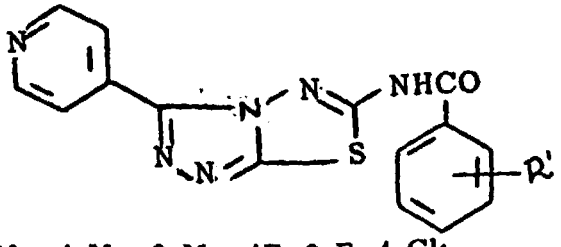
R^2,R^3= H; Me

XXXVII



XXXVIII

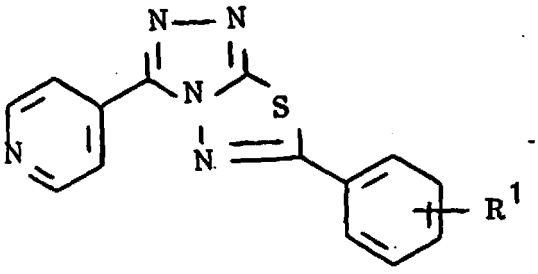
Zhang et al. (1992a,b) synthesized several 3-(4'-pyridyl)-6-aroylamino-1,2,4-triazole[3,4-b][1,3,4]thiadiazoles XXXIX tested their antibacterial activity.



R^1= 4-OMe; 4-Me; 3-Me; 4F; 3-F; 4-Cl;
3-Cl; 4-Br; 3-Br; 4-I; 4-NO_2

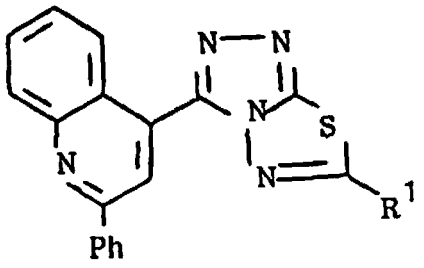
XXXIX

The 3,6-diaryl/heteroaryl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles such as XL, XLI and related bis compound XLII were reported to exhibit significant antimicrobial activity (Zhang and Chen, 1991a,b; 1992 and El-Khawass and Sayeda, 1990). The related homologs such as 3-(aryl/heteroaryl)methyl-6-substituted-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles (XLIII) with fungicidal (Pant et al., 1983) XLIV with bactericidal and fungicidal (Patel et al., 1990), XLV with antimicrobial (El-Khawass and Habib, 1989) and XLVI with antibacterial and mutagenic (Ovsepyan et al., 1990) activities have appeared in current literature.

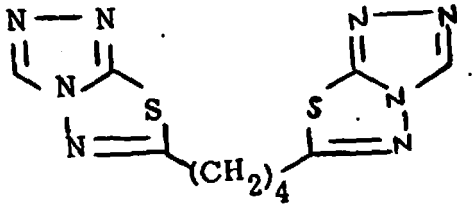


R^1=Me; OMe; NO_2; Br; Cl; I

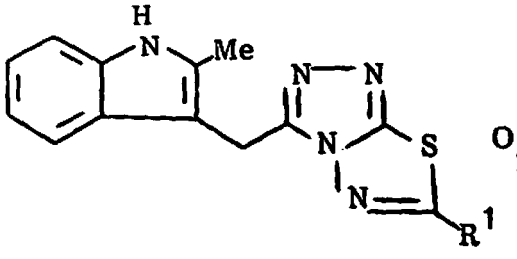
XL



XLI

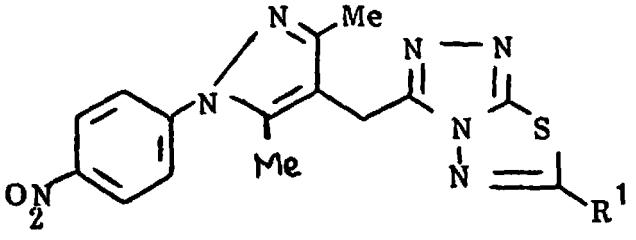


XLII



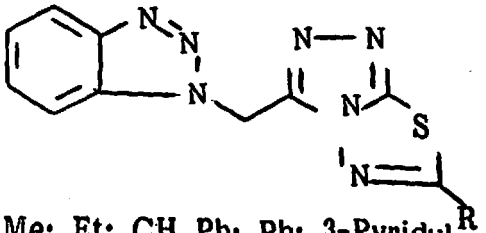
R^1= Me; Bu; Ph

XLIII



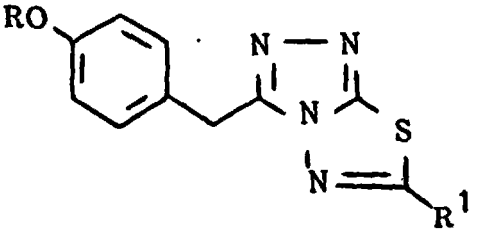
R^1= Me; Bu; Ph

XLIV



R= Me; Et; CH_2Ph; Ph; 3-Pyridyl

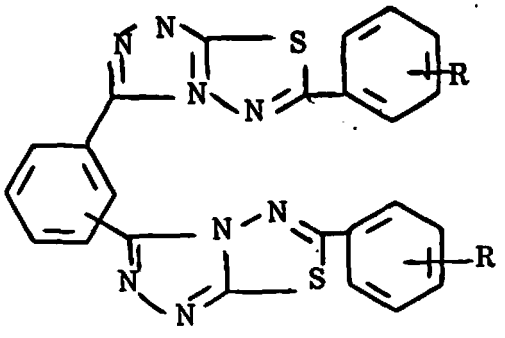
XLV



R=Me; R^1= H; Me

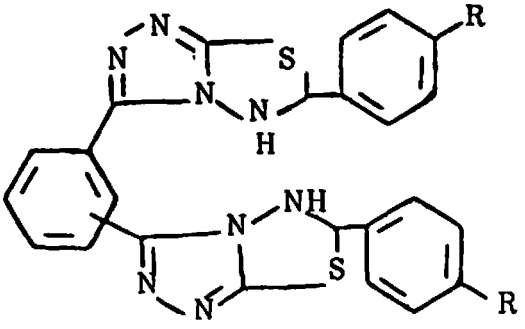
XLVI

Certain 3,3'-(1,4-phenylene)-bis(6-substitutedphenyl-1,2,4-triazolo [3,4-b][1,3,4]thiadiazoles (XLVII) and their dihydro analogs (XLVIII) have been shown to exhibit moderate to good antifungal activity against three strains of fungi (Dubey, 1992).



R= 4-NO_2; 2-Cl

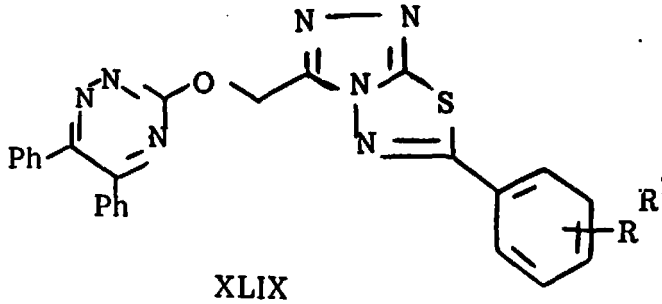
XLVII



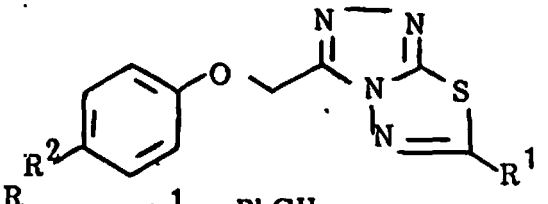
R= Cl; OMe; H

XLVIII

Derivatives of 3-(hydroxy/mercapto)methyl-1,2,4-triazolo[3,4-b] [1,3,4]thiadiazoles such as XLIX with antiinflammatory (Abd El-Samii et al., 1991), L and LI with anthelmintic (El-Khawass et al., 1989), and LII with antifungal (Bano et al., 1992a, Dwivedi et al., 1992) and anthelmintic (Husain and Kumar, 1992) activities have been described.

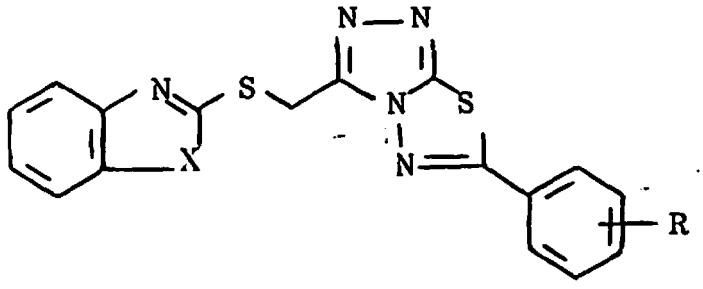


XLIX



L: R^1 = $PhCH_2$

LI: R^1 = H; SH; NHAr

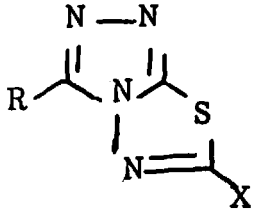


X= O; S; NH

R= H; 4-NO_2; 3-NO_2; 4-Cl; 2-Cl;
4-NH_2; 2-NH_2; 4-OH

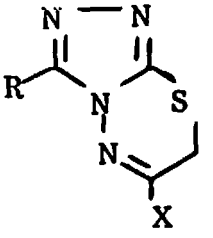
LII

Certain triazolothiadiazoles/thiadiazines (LIII and LIV) when tested against Pseudomonas aeruginosa or Bacillus subtilis were found inactive, though some showed activity against E. coli, Staphylococcus aureus and Bacillus manganicus (Bayoumy et al., 1992).

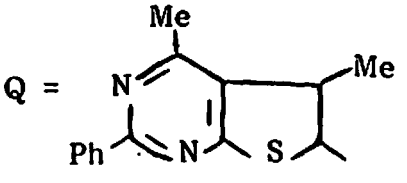


R= Q; X= Ph;
p-ClC_6H_4

LIII



R= Q; X= Ph; Substituted Ph



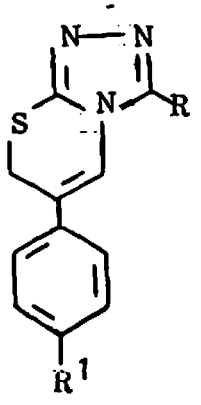
LIV

2.3 1,2,4-Triazolo[3,4-b][1,3,4]thiadiazines

2.3.1 Disubstituted 1,3,4-thiadiazines

Several 3,6-disubstituted phenyl derivatives have various types of biological activities as reported in literature. However, a large number of monosubstituted and trisubstituted derivatives have also been reported.

A series of 3,6-disubstituted-7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine derivatives LV have been reported as antiparasitic drugs (El Dawy et al., 1983). Some other such derivatives were selectively active against E. coli, Staphylococcus aureus and Bacillus manganicus (Bayoumy et al., 1992).



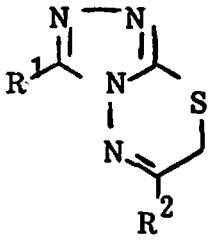
R= Ph; 4-ClC_6H_4; 4-BrC_6H_4; 4-MeC_6H_4; 4-$OMeC_6H_4$; 4-$H_2NC_6H_4$

R^1= H; NO_2; Cl; Br; Me; MeO

LV

Ghannoum et al. (1983) synthesized several derivatives of 3-aryl-6-phenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines and tested against bacteria (both gram positive as well as gram negative), yeast and fungi. The above

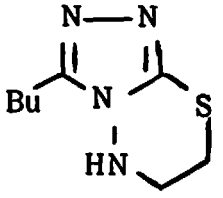
compounds were found more active against yeast. Various 3-alkyl-4-amino-4H-1,2,4-triazolothiadiazines LVI and LVII were reported to have bactericidal activity (Jagmohan et al., 1987).



R^1 = Bu; Me_2CHCH_3

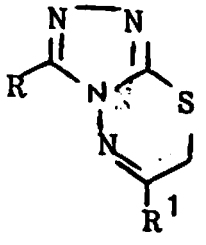
R^2 = 4-BrC_6H_4

LVI



LVII

3-Alkyl-5-substituted 1,2,4-triazolo[3,4-b][1,3,4]thiadiazines LVIII didn't show significant fungicidal or bactericidal activity (Jagmohan et al., 1983 and Dwivedi et al., 1992).

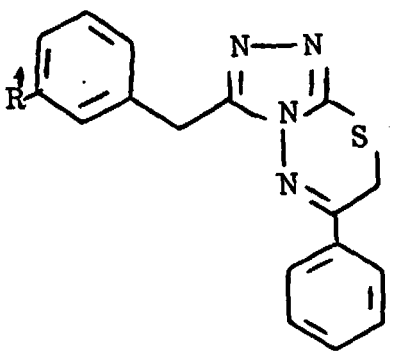


R= Pentyl; CF_3 ; R^1=Ph;4-ClC_6H_4

LVIII

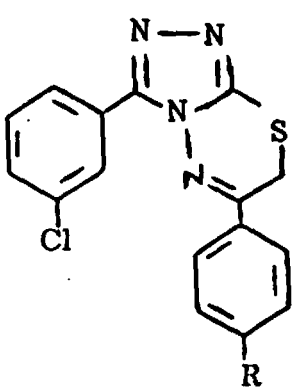
3,6-Diarylderivatives of 7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines have moderate antifungal activity (Mazzone et al., 1987).

Several 7H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines (LIX) were screened for antimicrobial activity (Eweiss et al., 1988).



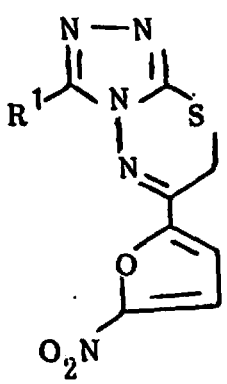
LIX

The other related 3-alkyl-7H-6-(5-nitrofuryl)-1,2,4-triazolo[3,4-b][1,3,4]-thiadiazines (LX) exhibited bactericidal activity (Holla et al., 1988). m-(Chlorophenyl)triazolothiadiazines (LXI) when tested for diuretic, bactericidal and fungicidal activity were found inactive as diuretics in rats (Jagmohan et al., 1988).



R=H; Cl;Br; NO_2; Ph

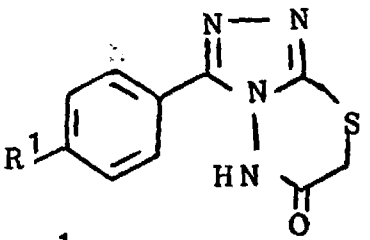
LXI



R^1=H,alkyl, Ph,HOC_6H_4,ClC_6H_4, tolyl; anisyl; $O_2NC_6H_4$,$PhCH_2$

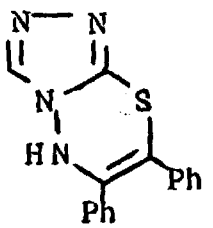
LX

Compounds such as 5H-3-(substituted phenyl)-1,2,4-triazolo[3,4-b][1,3,4]-thiadiazol-6(7H)-thiones (LXII) and other related heterocyclic thiadiazines (LXIII) showed bactericidal and fungicidal activity (Jagmohan et al., 1989).



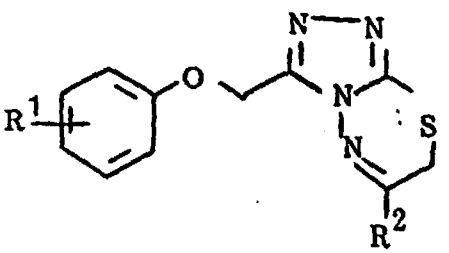
R^1=Cl; OCH_3,CH_3,Br

LXII

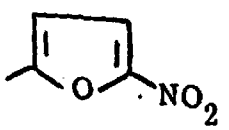


LXIII

A very high degree of in vitro antibacterial activity was reported and shown by 7H-3-aryloxymethyl-6-(5-nitro-2-furyl)-1,2,4-triazolo[3,4-b][1,3,4]-thiadiazines (LXIV) (Holla et al., 1989).

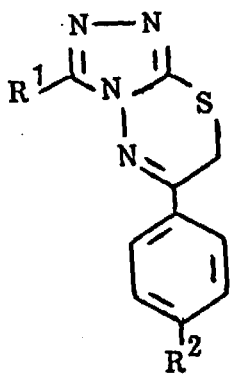


R^1=H; 4-Me; 2-Me; 4-Cl
3-Cl; 4-Br; 4,3-Cl(Me)

R^2 = 

LXIV

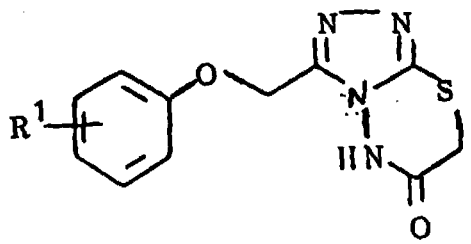
Several new derivatives of 2,6-diaryl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines (LXV) and triazolothiadiazinones (LXVI) displayed significant antimicrobial and antiinflammatory activity (Abd El Fattah, B., 1989).



R_1 = [R^1OCH_2; (R^1=o, m,p -ClC_6H_4; p-MeC_6H_4], 3-pyridyl

R^2=Br;Cl;Me;MeO

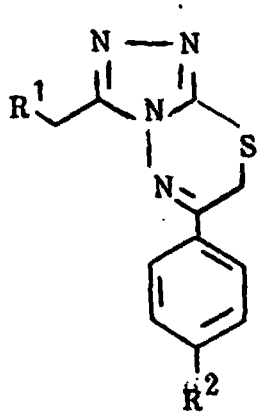
LXV



R^1=3-Cl;4-Cl;4-Me

LXVI

El-Khawass et al. (1989) tested various derivatives of 3,6-disubstituted phenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines (LXVII) for antimicrobial activity.

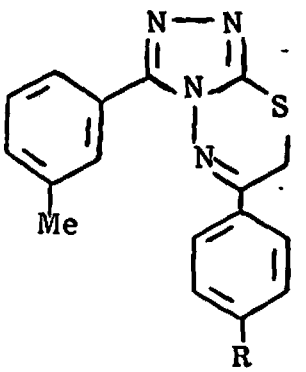


R^1 = benzotriazol-1-yl

R^2 = H;Br;Cl;Me;OMe

LXVII

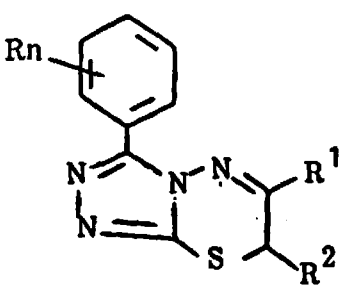
7H-3-m-tolyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazones (LXVIII) were synthesized by Jagmohan et al. in 1989 and compounds were found active against Staphylococcus aureus.



R= Br; Cl; NO_2; Ph

LXVIII

Carboxymethyl- and carboxy derivatives of 7H- and 5H- 1,2,4-triazolo[3,4-b][1,3,4]thiadiazines, LXIX were screened for antiinflammatory, analgesic and antimicrobial activities. Few showed analgesic (R_n=3,4-OCH_2) activity while others [R_n=3,4,5-$(MeO)_3$] exhibited antiinflammatory activity but none of the compounds had both the activities (Mazzone et al., 1990).

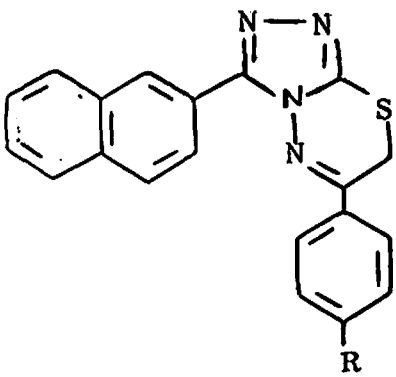


Rn=OCH_2O or R=MeO, EtO with n=2 or 3

R^1= Ph or substituted phenyl, R^2= H

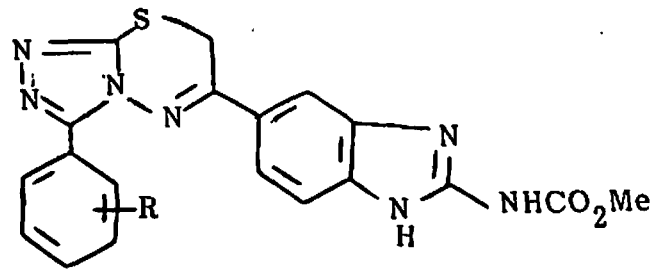
LXIX

7H-(3-Naphthyl)-6-substituted phenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine (LXX) were tested for antibacterial and antifungal activities (Jagmohan et al., 1990). 6-(3-aryl-(7H)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazin-6-yl)-benzimidazole-2-carbamate (LXXI) derivatives when evaluated for their anthelmintic activity were found inactive (Rao et al., 1990).



R= NO_2; Cl; Br

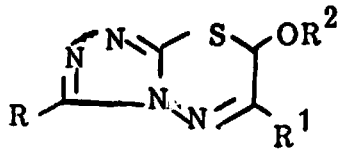
LXX



R= H; 4-Cl; 4-F; 3-F, 2,4-Cl_2; 4-MeO

LXXI

Bactericidal and antimicrobial activity of 3,6-disubstituted triazolothiadiazine derivatives (LXXII) were studied and only chloro and nitro substituted phenyl derivatives were found active (Chande et al., 1990). Some new 3-substituted cycloalka (e)-1,2,4-triazolo[3,4-b][1,3,4] thiadiazines (LXXIII) have been reported as potential antibacterial, antifungal and anthelmintic agents. (Chande et al., 1992)

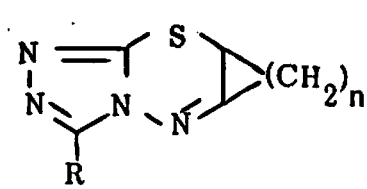


R= Me; Et; Ph; 4-MeC_6H_4; 4-pyridyl

R^1= 4-ClC_6H_4

R^2= 4-$O_2NC_6H_4$

LXXII

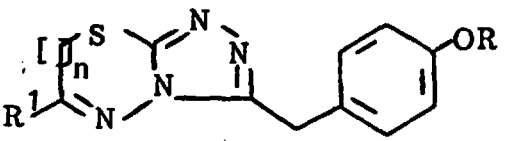


n=3,4

R=Me; Et; Ph; 4-MeC_6H_4; 4-ClC_6H_4; 4-pyridyl; $PhOCH_2$; 4-$MeC_6H_4OCH_2$

LXXIII

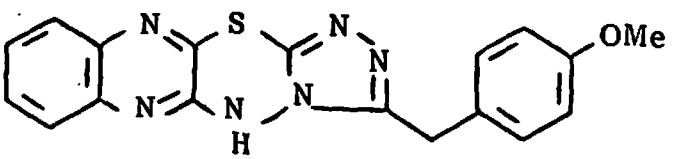
Condensed triazolothiadiazines (LXXIV) and triazolothiadiazinoquinoxalines (LXXV) were reported for their toxicity, antibacterial activity and mutagenicity by Ovsepyan et al., 1991.



R= CH_3; Et; Pr; $CHMe_2$; CHMeEt

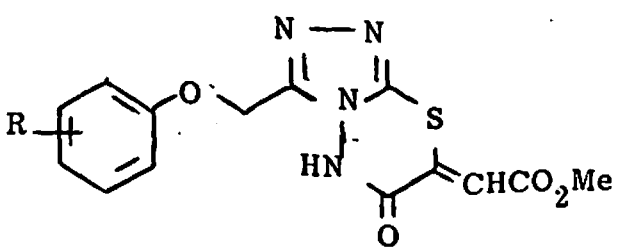
R^1= OMe; p-$C_6H_4NO_2$

LXXIV



LXXV

Various 1,2,4-triazolo[3,4-b][1,3,4]thiadiazinone (LXXVI) have been reported as potential antiinflammatory agents (El-Feky et al., 1991).

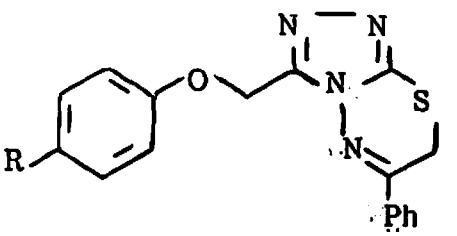


R= H; 2-, 3-, 4-Cl; 2-, 3-, 4-Me

LXXVI

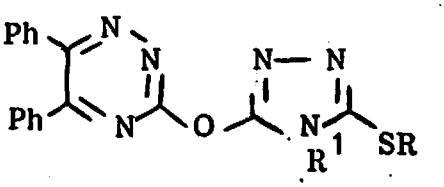
Awad Ibrahim et al. (1991) synthesized various derivatives of 3-aryloxymethyl-6-phenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines (LXXVII) and

when screened for antimicrobial activity and antiinflammatory activity (LXXVIII) were found inactive (Abd El-Samii et al., 1991). Certain other homologs(LXXIX) were tested for analgesic, antiinflammatory, anthelmintic and analgesic activities (Prasad et al., 1990; Ramalingam et al., 1991 and Prakash Mhanvar et al., 1991).



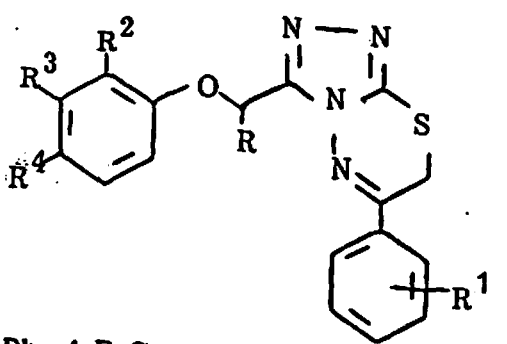
R= H; Cl; Me

LXXVII



RR^1= CH_2CR^2N

LXXVIII



R= Ph; 4-BrC_6H_4

R^1=H; Me; Br

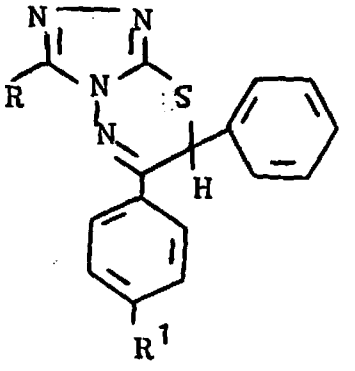
R^2=H; Cl; Me

R^3 = H, R^4= H; Cl,

R^3R^4=OCH_2O

LXXIX

Antimicrobial activity of various 3-substituted phenyl-6,7-diaryl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines (LXXX) were tested and found that only substituents at 6-position and 4-Cl derivatives were active (Chande et al., 1991).



R= Me; Et; p-MeC_6H_4; 4'-pyridiyl, $PhOCH_2$; p-$MeC_6H_4OCH_2$; p-$ClC_6H_4OCH_2$

R^1= H; Me; Cl

LXXX

III

MATERIALS AND METHODS

CHAPTER - III

MATERIAL AND METHODS

3.1 General Techniques

Melting points were determined in open capillaries using Ganson's electrical melting point apparatus or in sulphuric acid bath and are uncorrected. Homogeniety of compounds was routinely checked on silica gel-G TLC plates using 1:1, 1:5 and 3:7 ethyl acetate-hexane mixture as irrigant. The IR spectra were run on "Hitachi 270-50" or "Schimadzu-234" spectrophotometers as nujol mull and frequencies are expressed in cm^{-1}. The ^1H NMR spectra were recorded on "Varian EM-360" (60 MHz) or "Varian EM-390" (90 MHz) instruments in $CDCl_3$ using TMS as internal reference and chemical shifts are expressed in δ ppm units. The compounds were analysed for nitrogen and sulphur and the values were found within ±0.4% of the theoretical values.

3.2 Experimental protocols

3.2.1 Chemistry

Ethyl (p-tert-butylphenoxy)acetate (II)

A mixture of p-tert-butylphenol (I, 15g, 100 mmole), ethyl chloroacetate (12.5g, 100 mmole), potassium carbonate (17.9g, 130 mmole) and dimethyl-formamide (100 ml) was stirred at room temperature for 48 hr. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water several times,

dried over sodium sulphate and concentrated to give II, yield 18.6 g (78.8%).

p-tert-Butylphenoxyacetic acid hydrazide (III)

A solution of II (23.6 g, 100 mmole) and hydrazine hydrate (25 ml; excess) in absolute ethanol (50 ml) was refluxed for 4 hr. The reaction mixture was cooled and poured onto ice-water with continuous stirring. The solid thus separated was filtered, washed successively with water and 50% aqueous ethanol to give III, yield 19.7 g (88.7%), m.p. 112°.

IR: 3060 (NH), 1650 (C=O)

^{1}H NMR (60 MHz): 1.33 [9H, s, $C(CH_3)_3$], 4.53 (2H, s, OCH_2), 6.73-7.40(4H, m, Aromatic H).

Analysis: $C_{12}H_{18}N_2O_2$ (N)

p-tert-Butylphenoxyacetic acid (IV)

A solution of II (2.36 g, 0.01 mole) and methanolic sodium hydroxide (4%, 20 ml) was stirred at room temperature for 24 hr. The reaction mixture was diluted with water and filtered. The clear filtrate was acidified with dilute hydrochloric acid. The solid thus separated, washed thoroughly with water and dried to give IV, yield 1.76 g (84.6%), m.p. 74°.

Analysis : $C_{12}H_{16}O_3$

2,5-Bis(p-tert-butylphenoxymethyl)-1,3,4-oxadiazole (V)

A solution of hydrazide III (1.11 g, 5 mmole), p-tert-butylphenoxyacetic acid (1.04 g, 5 mmole), and phosphorus oxychloride (5 ml) was refluxed for 1.5 hr. The reaction mixture was cooled and poured onto ice-water The precipitated solid was filtered, washed successively with aqueous sodium bicarbonate and water. The product was recrystallized with aqueous methanol to give V, yield 1.4 g (71%), m.p. 160°.

IR: 1650 (C=N).

^{1}H NMR (60 MHz): 1.33 [18H, s, 2 x $C(CH_3)_3$], 4.55 (4H, s, 2 x OCH_2), 6.73-7.36 (8H, m, Aromatic H).

Analysis: $C_{24}H_{30}N_2O_3$ (N)

5-(p-tert-Butylphenoxymethyl)-2-chloromethyl-1,3,4-oxadiazole (VI)

A solution of III (1.11 g, 5 mmole), chloroacetic acid (0.47 g, 5 mmole) and phosphorus oxychloride (10 ml) was refluxed for 1.5 hr. The reaction mixture was cooled and poured onto ice-water. The precipitated solid was filtered, washed successively with aqueous sodium bicarbonate and water. The residual product was purified by column chromatography over silica gel using mixture of ethyl acetate-hexane as eluant to get VI, yield 1.23 g (58%), m.p. 150°.

Analysis: $C_{14}H_{17}N_2O_2Cl$ (N)

refluxed for 2 hr. The reaction mixture was cooled and poured onto ice-water. The solid thus separated was filtered and washed several times with water to get VIIa, yield (64%), m.p. 148°.

Analysis: $C_{19}H_{20}N_2O_2$ (N)

N^2-Benzoyl-p-tert-butylphenoxyacetic acid hydrazide (VIII)

A solution of III (1.11 g, 5 mmole), benzoyl chloride (0.70 g, 5 mmole) and pyridine (10 ml) was stirred to get a clear solution and then kept overnight. The reaction mixture was then poured onto crushed ice. The solid thus obtained was filtered and washed several times with water to remove the traces of pyridine and then dried to give VIII, yield 0.90 g (68%), m.p. 162°.

Analysis: $C_{19}H_{22}N_2O_3$ (N)

p-tert-Butylphenoxyacetic acid-[2-(dithiocarboxy)hydrazide]monopotassium salt (IX)

A mixture of III (4.44 g, 20 mmole), potassium hydroxide (1.34 g, 24 mmole), carbon disulphide (1.14 g, 15 mmole) and absolute alcohol (40 ml) was stirred for 24 hr. The reaction mixture was diluted with hexane, the separated solid was filtered and dried to give IX, yield 5.44 g (81%), m.p. 146°.

Analysis: $C_{13}H_{17}N_2S_2O_2K$

The crude salt was used as such in further conversions.

4-Amino-5-(p-tert-butylphenoxymethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (X)

A mixture of IX (3.36 g, 10 mmole), distilled water (10 ml) and hydrazine hydrate (10 ml, 20 mmole) was refluxed with stirring for 3 hr. The reaction mixture was cooled and filtered and diluted with water. The same was acidified with acetic acid. The solid thus separated was filtered, washed with water, dried and crystallized from methanol to give X, yield 1.55 g (56%), m.p. 175°.

IR: 2550 (SH), 1600 (C=N)

^{1}H NMR (90 MHz): 1.26 [9H s, $C(CH_3)_3$], 4.6 and 4.76 (2H, 2-singlets of different tautomers, OCH_2), 6.73-7.30 (4H, m, Aromatic H).

Analysis: $C_{13}H_{18}N_4OS$ (N,S).

3-(p-tert-Butylphenoxymethyl)-6-phenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (XIa, R^1=H)

A mixture of X (1.39 g, 5 mmole), benzoic acid (0.61 g, 5 mmole) and phosphorus oxychloride (10 ml) was refluxed for 6 hr. The reaction mixture was cooled and poured onto ice-water with stirring. The solid thus precipitated was filtered, washed successively with aqueous sodium bicarbonate and water. The product was crystallized from methanol to give XIa, yield 69%, m.p. 129°.

IR: 1600 (C=N)

^{1}H NMR (60 MHz): 1.33 [9H, s, $C(CH_3)_3$], 5.53 (2H, s, OCH_2), 6.97-8.01 (9H, m, Aromatic H)

Analysis: $C_{20}H_{20}N_4OS$ (N,S).

In a similar way the compounds XIb-c were also prepared starting from appropriate intermediates.

3-(p-tert-Butylphenoxymethyl)-6-(4-nitrophenyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (XIb, R = 4-NO_2)

Yield 67%, m.p. 112°

Analysis: $C_{20}H_{19}N_5O_3S$ (N,S).

3-(p-tert-Butylphenoxymethyl)-6-(2-chlorophenyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (XIc, R = 2-Cl)

Yield 69%, gummy solid.

Analysis: $C_{20}H_{19}N_4OSCl$ (N,S).

3,6-Bis(p-tert-butylphenoxymethyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (XII)

Yield 88%, waxy solid.

Analysis: $C_{25}H_{30}N_4OS$ (N,S)

3-(p-tert-Butylphenoxymethyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole-6(5H)-thione (XIII)

Carbon disulphide (0.5 ml) was added dropwise to a solution of X (1.39 g, 5 mmole) in pyridine (10 ml) with stirring at room temperature. The resulting mixture was refluxed with stirring at 100° for 24 hr. Pyridine was removed from the reaction mixture under reduced pressure and

poured onto ice-water with stirring. The solid thus precipitated was filtered, washed with water, dried and crystallized from ethanol to give XIII, yield 1.72 g (54%), m.p. 145°.

Analysis: $C_{14}H_{16}N_4SO_2$ (N,S).

3-(p-tert-Butylphenoxymethyl)-5,6-dihydro-6-phenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (XIVa, R^1 = H)

A mixture of X (1;39 g, 5 mmole), benzaldehyde (0.053 g, 5 mmole), p-toluenesulphonic acid (10 mg) and benzene (25 ml) was refluxed for 48 hr with continuous removal of water. Benzene was stripped off from the mixture under reduced pressure. The reaction mixture was cooled and partitioned between ethyl acetate and water. The organic layer was separated, washed with water several times, dried over sodium sulphate and concentrated to give XIVa, yield 1.05 g (58%), as a viscous gum.

Analysis: $C_{20}H_{21}N_4OS$ (N,S).

In a similar way, the compounds XIVb-g were prepared starting from appropriate intermediates.

3-(p-tert-Butylphenoxymethyl)-5,6-dihydro-6-(4-methoxyphenyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (XIVb, R^1= 4-OMe)

Yield 65%, gummy solid.

Analysis: $C_{21}H_{23}N_4O_2S$ (N,S).

3-(p-tert-Butylphenoxymethyl)-5,6-dihydro-6-(2-chlorophenyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (XIVc, R^1 = 2-Cl)

Yield 58%, gummy solid.

Analysis: $C_{20}H_{20}N_4O_3SCl$ (N,S).

3-(p-tert-Butylphenoxymethyl)-5,6-dihydro-6-(3-nitrophenyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (XIVd, R^1= 3-NO_2)

Yield 63%, gummy solid.

Analysis: $C_{20}H_{20}N_5O_3S$ (N,S).

3-(p-tert-Butylphenoxymethyl)-5,6-dihydro-6-(2-methoxyphenyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (XIVe, R^1 = 2-OMe)

Yield 62%.

Analysis: $C_{21}H_{23}N_4O_2S$ (N,S).

3-(p-tert-Butylphenoxymethyl)-5,6-dihydro-6-(2,4-dimethoxyphenyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole [XIVf, R^1= 2,4-$(OMe)_2$]

Yield 67% , gummy solid.

Analysis: $C_{22}H_{25}N_4O_3S$ (N,S)

3-(p-tert-Butylphenoxymethyl)-5,6-dihydro-6-(3,4-dimethoxyphenyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole [XIVg, R^1 = 3,4-$(OMe)_2$]

Yield 64%, gummy solid.

Analysis: $C_{22}H_{25}N_4O_3S$ (N,S).

3-(p-tert-Butylphenoxymethyl)-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine-6 (7H)- one (XV)

A mixture of X (1.39 g, 5 mmole), chloroacetic acid (0.07 g, 7.5 mmole) and freshly fused sodium acetate (0.82 g, 10 mmole) in absolute ethanol (20 ml) was refluxed for 24 hr and then cooled. The resulting solid was washed with water and crystallized from ethanol. Yield 1.15 g (77%), m.p. 168°.

Analysis: $C_{15}H_{17}N_4OS$ (N,S).

3-(p-tert-Butylphenoxymethyl)-7-(4-methoxyphenyl)methylene-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine-6-one (XVIa, R' = 4-OMe)

A mixture of XV (0.301 g, 1 mmole), 4-methoxybenzaldehyde (0.136 g, 1 mmole), freshly fused sodium acetate (0.1 g, 12 mmole) in glacial acetic acid (4 ml) was refluxed for 8 hr. The reaction mixture was concentrated and residual mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed several times with water, dried over sodium sulphate and concentrated to give XVIa as a viscous oil, yield 52%.

Analysis: $C_{23}H_{23}N_4O_3S$ (N,S).

XVIb-d were also prepared by this method using suitable intermediates.

3-(p-tert-Butylphenoxymethyl)-7-(2-chlorophenyl)methylene-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazin-6-one (XVIb, R' = 2-Cl)

Yield 48% .

Analysis: $C_{22}H_{20}N_4O_2ClS$ (N,S).

3-(p-tert-Butylphenoxymethyl)-7-(4-methylphenyl)methylene-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazin-6-one (XVIc, R' = 4-Me)

Yield 52%

Analysis: $C_{23}H_{23}N_4O_2S$ (N,S).

3-(p-tert-Butylphenoxymethyl)-7-(2,4-dimethoxyphenyl)methylene-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazin-6-one (XVId, R' = 2,4(OMe)$_2$)

Yield 54%, m.p. 138°.

Analysis: $C_{24}H_{25}N_4O_2S$ (N,S).

3-(p-tert-Butylphenoxymethyl)-5H-6,7-diphenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine(XVII)

A mixture of X (1.39 g, 5 mmole) and benzoin (1.06 g, 5 mmole) in absolute ethanol (20 ml) was warmed to get a clear solution and was then added to a hot solution (2N) of KOH (2.0 ml) and refluxed for 4 hr. The resulting solid was filtered, washed with water and then crystallized from ethanol to give XVII. Yield 0.72 g (32%), m.p. 112°.

Analysis: $C_{27}H_{25}N_4OS$ (N,S).

p-tert-Butylphenoxyacetic acid (2-phenylmethylene)hydrazide (XIXa, R^1=H, R^2=II)

A solution of III (1.11 g, 5 mmole) and benzaldehyde (0.53 g, 5 mmole), in absolute alcohol (10 ml) was refluxed for 3 hr. The reaction mixture was cooled and diluted with water. The solid thus separated was filtered, washed successively with water and 50% ethanol. The product was crystallized from aqueous ethanol to give XIXa. Yield 1.08g (70%), m.p. 165°.

IR: 3040 (NH), 1680 (C=O), 1600 (C=N).

Analysis: $C_{19}H_{22}N_2O_2$ (N)

In a similar way the compounds XIXb-i were prepared starting from appropriate intermediates as indicated.

p-tert-Butylphenoxyacetic acid [2-(4-methoxyphenyl)methylene]hydrazide (XIXb, R^1= 4-OMe, R^2=H)

Yield 66%, m.p. 170°.

^{1}H NMR (60 MHz): 1.28 [9H, s, $C(CH_3)_3$], 3.84 (3H, s, OCH_3), 4.65 (2H, s, OCH_2), 6.83-8.16 (8H, m, Aromatic H).

Analysis: $C_{20}H_{24}N_2O_3$ (N)

p-tert-Butylphenoxyacetic acid [2-(2-chlorophenyl)methylene]hydrazides (XIXc, R^1= 2-Cl, R^2 = H)

Yield 68%, m.p. 125°.

IR: 3040 (NH), 1660 (C=O), 1600 (C=N)

Analysis: $C_{19}H_{21}N_2O_2Cl$ (N)

p-tert-Butylphenoxyacetic acid [2-(2,4-dimethoxyphenyl)methylene]hydrazide [XIXd, R^1= 2,4-$(OMe)_2$, R^2=H]

Yield 70%, m.p. 134°

IR: 3040 (NH), 1660 (C=O), 1600 (C=N)

Analysis: $C_{21}H_{26}N_2O_4$ (N)

p-tert-Butylphenoxyacetic acid [2-(4-dimethylaminophenyl)methylene]hydrazide (XIXe, R^1= 4-NMe_2, R^2=H)

Yield 72%, m.p. 130°.

Analysis: $C_{21}H_{21}N_3O_2$ (N)

p-tert-Butylphenoxyacetic acid [2-(3-nitrophenyl)methylene]hydrazide (XIXf, R^1= 3-NO_2, R^2=H)

Yield 65%, m.p. 138°.

Analysis: $C_{19}H_{21}N_3O_4$ (N)

p-tert-Butylphenoxyacetic acid [2-(4-methylphenyl)methylene]hydrazide (XIXg, R^1=H-Me, R^2=H)

Yield 62%, m.p. 160°.

Analysis: $C_{20}H_{24}N_2O_2$ (N)

p-tert-Butylphenoxyacetic acid [2-(2-methoxyphenyl)methylene]hydrazide (XIXh, R^1= 2-OMe, R^2=H)

Yield 63%, m.p. 130°

Analysis: $C_{20}H_{24}N_2O_3$ (N)

p-tert-Butylphenoxyacetic acid [2-(3,4-dimethoxyphenyl)methylene]hydrazide (XIXi, R^1= 3,4-$(OMe)_2$, R^2=H]

Yield 69%, m.p. 165°.

Analysis: $C_{21}H_{26}N_2O_4$ (N)

p-tert-Butylphenoxyacetic acid-(2-phenyl)ethylene hydrazide (XVIIIa, R^1=H, R^2= CH_3)

Yield 63%, m.p. 124°.

IR: 3040 (NH), 1680 (C=O), 1600 (C=N)

^{1}H NMR (60 MHz): 1.33 [9H, s, $C(CH_3)_3$], 2.23 (3H, s, CH_3), 4.70, 5.16 (2H, 2 singlets of different tautomers, OCH_2), 6.83-7.76 (9H, m, Aromatic H).

Analysis: $C_{20}H_{24}N_2O_2$ (N)

p-tert-Butylphenoxyacetic acid-[2-(4-bromophenyl)ethylene]hydrazide (XVIIIb, R^1= 4-Br, R^2= CH_3)

Yield 65%, m.p. 137°

Analysis: $C_{20}H_{23}N_2O_2Br$ (N)

p-tert-Butylphenoxyacetic acid-[2-(4-chlorophenyl)ethylene]hydrazide (XVIIIc, R^1= 4-Cl, R^2= CH_3)

Yield 68%, m.p. 93°

Analysis: $C_{20}H_{23}N_2O_2Cl$ (N)

3-(p-tert-Butylphenoxyacetamido)-2,3,4,5-tetrahydro-2-phenyl-4-oxo-thiazole (XXa, R^1= H)

A solution of XIXa (0.31 g, 1 mmole), mercaptoacetic acid (0.1 g, 1 mmole) and benzene (20 ml) was refluxed for 48 hr with continuous removal of water. The reaction mixture was cooled and benzene was distilled off under reduced pressure. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed several times with water to remove the traces

of mercaptoacetic acid, dried over sodium sulphate and concentrated, to give XXa as viscous oil, yield 0.21 g (54%).

Analysis: $C_{21}H_{24}N_2O_3S$ (N,S).

In a similar way the compounds XXb-h were prepared starting from appropriate intermediates.

3-(p-tert-Butylphenoxyacetamido)-2,3,4,5 -tetrahydro-2-(4-methoxyphenyl)-4- oxothiazole (XXb, R^1 = 4-OMe)

Yield 57%, Viscous gum.

^1H NMR (90 MHz): 1.33 [9H, s, $C(CH_3)_2$], 3.9 (3H, s, OCH_3),
4.63 (2H, s, OCH_2), 5.12 (1H, s, CH),
6.91-7.90 (8H, m, Aromatic H).

Analysis: $C_{22}H_{26}N_2O_4S$ (N,S).

3-(p-tert-Butylphenoxyacetamido)-2,3,4,5-tetrahydro-2-(2-chlorophenyl)-4-oxothiazole (XXc, R^1= 2-Cl)

Yield 58%, viscous gum.

Analysis: $C_{21}H_{23}N_2O_3SCl$ (N,S).

3-(p-tert-Butylphenoxyacetamido)-2,3,4,5-tetrahydro-2-(4-methylphenyl)-4-oxothiazole (XXd, R^1= 4-Me)

Yield 57%, viscous gum.

Analysis: $C_{22}H_{26}N_2O_3S$ (N,S).

3-(p-tert-Butylphenoxyacetamido)-2,3,4,5-tetrahydro-2-(2-methoxyphenyl)-4-oxothiazole (XXe, R^1= 2-OMe)

Yield 53%, viscous gum.

Analysis: $C_{22}H_{26}N_2O_4S$ (N,S).

3-(p-tert-Butylphenoxyacetamido)-2,3,4,5-tetrahydro-2-(3-nitrophenyl)-4-oxothiazole (XXf, R^1= 3-NO_2)

Yield 55%, viscous gum .

Analysis: $C_{21}H_{23}N_3O_5S$ (N,S).

3-(p-tert-Butylphenoxyacetamido)-2,3,4,5-tetrahydro-2-(2,4-dimethoxyphenyl)-4-oxothiazole [XXg , R^1= 2,4-$(OMe)_2$]

Yield 58%, viscous gum.

Analysis: $C_{23}H_{29}N_2O_5S$ (N,S).

3-(p-tert-Butylphenoxyacetamido)-2,3,4,5-tetrahydro-2-(3,4-dimethoxyphenyl)-4-oxothiazole [XXh, R^1= 3,4-$(OMe)_2$]

Yield 58%, gummy solid .

IR: 3160 (N-H), 1660 (C=O).

Analysis: $C_{23}H_{29}N_2O_5S$ (N,S).

p-tert-Butylphenoxyacetic acid(2-aminothioxomethyl)hydrazide (XXI)

A solution of III (11.1 g, 50 mmole), potassium thiocynate (15.2 g, 150 mmole), concentrated hydrochloric acid (12 ml) and water (100 ml) was refluxed with stirring for 36 hr. The reaction mixture was cooled, the separated solid was filtered, washed with water and crystallized from ethanol to give XXI, yield 5.6 g (40%), m.p. 150°.

IR: 3200 (NH), 1660 (C=O), 1220 (C=S).

Analysis: $C_{13}H_{19}N_3O_2S$ (N,S).

p-tert-Butylphenoxyacetic acid 2-[{(4-methoxyphenyl)methyleneamino}thioxomethyl]hydrazide (XXIIa, R^1= 4-OMe).

A solution of XXI (1.4 g, 5 mmole), 4-methoxybenzaldehyde (0.68 g, 5 mmole), freshly fused sodium acetate (0.82 g, 10 mmole) and glacial acetic acid (15 ml) was refluxed for 6 hr. The reaction mixture was cooled and diluted with water. The solid thus separated was filtered, washed successively with water and ethanol. The product thus formed was crystallized from glacial acetic acid to give XXIIa, yield 1.4 g (70%), m.p. 158°.

Analysis: $C_{21}H_{25}N_3O_3S$ (N,S).

In a similar way compounds XXIIb-g were prepared.

p-tert-Butylphenoxyacetic acid-2-[{(2-methoxyphenyl)methyleneamino}thioxomethyl]hydrazide (XXIIb, R^1= 2-OMe)

Yield 68%, m.p. 128°.

Analysis: $C_{21}H_{25}N_3O_3S$ (N,S).

p-tert-Butylphenoxyacetic acid 2-[{(4-methylphenyl)methyleneamino}thioxomethyl]hydrazide (XXIIc, R^1= 4-Me).

Yield 62%, m.p. 199°.

Analysis: $C_{21}H_{25}N_3O_2S$ (N,S).

p-tert-Butylphenoxyacetic acid 2-[{(2-chlorophenyl)methyleneamino}thioxomethyl]hydrazide (XXIId, R^1= 2-Cl)

Yield 69%, m.p. 280°d.

Analysis: $C_{20}H_{22}N_3O_2SCl$ (N,S).

p-tert-Butylphenoxyacetic acid 2-[{(3-nitrophenyl)methyleneamino} thioxo-methyl]hydrazide (XXIIe, R^1= 3-NO_2)

Yield 65%, m.p. 158°.

Analysis: $C_{20}H_{22}N_4O_4S$ (N,S).

p-tert-Butylphenoxyacetic acid 2-[{(2,4-dimethoxyphenyl)methyleneamino} thioxo-methyl]hydrazide [XXIIf, R^1= 2,4-$(OMe)_2$]

Yield 72%, m.p. 122°.

Analysis: $C_{22}H_{27}N_3O_4S$ (N,S).

p-tert-Butylphenoxyacetic acid 2-[{(3,4-dimethoxyphenyl)methyleneamino}thioxo - methyl]hydrazide [XXIIg, R^1= 3,4-$(OMe)_2$]

Yield 67%, m.p. 98°.

Analysis: $C_{22}H_{27}N_3O_4S$ (N,S).

3.2.2 Bio-assay

The compounds belonging to different structural patterns as explained in schemes 1-6 were screened for their growth inhibitory activity against two phytopathogenic fungi mainly Rhizoctonia solani and Fusarium oxysporum. The culture for them were maintained on Czapek's Dox agar slants (Tuite, 1969) at 5°.

Bavistin (2-methoxycarbamoylbenzimidazole) was used as a standard fungicide for assessing the fungitoxicity of compounds under study.

A loopful of the fungal culture was inoculated from the slants into the broth and the broth was incubated at 30±1° for 24 hr. This was

used as such for testing the compounds against mycelial growth by applying two fold serial dilution technique (Sangwan et al., 1983a).

A stock solution of the compound was prepared by dissolving it in dimethylsulphoxide, to get a concentration of 1.0 mg ml^{-1}. To the stock solution (0.2 ml) was added the seeded broth (1.8 ml) to form the first dilution. One ml from this dilution was diluted further by adding it to one ml of the seeded broth to give the second dilution. The procedure was repeated to get a set of six concentrations corresponding to 100, 50, 25, 12.5, 6.25 and 3.13 μg ml^{-1}. A set of tubes containing only the seeded broth was kept as control. The tubes were incubated for 72 hr in dark at 30±1° and the last tube (with minimum concentration) without any growth of fungus was taken as minimum inhibitory concentration (MIC) expressed as μg ml^{-1}. A compound with a MIC value of 50 μg ml^{-1} was considered active.

IV

RESULTS AND DISCUSSION

CHAPTER - IV

RESULTS AND DISCUSSION

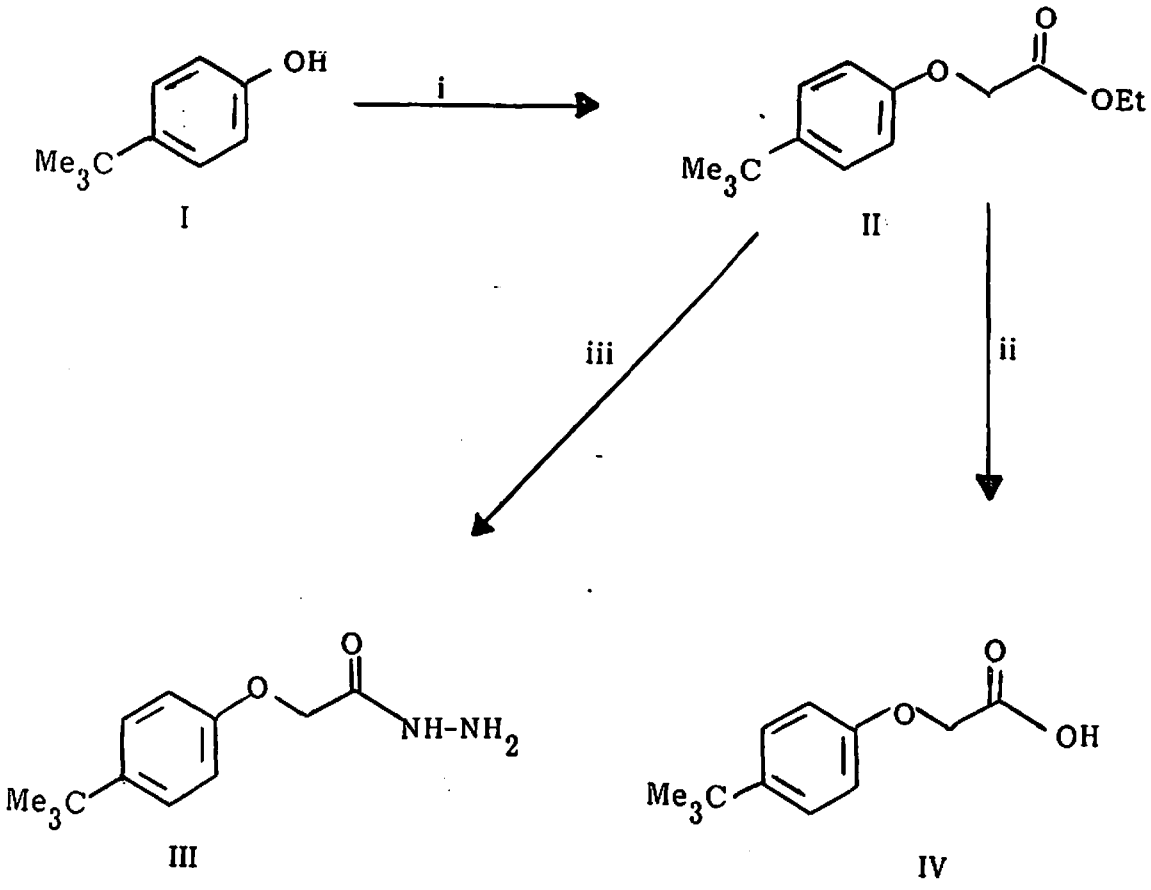
4.1 Chemistry

4.1.1 5-(p-tert-Butylphenoxymethyl)-2-substituted-1,3,4-oxadiazoles

The synthetic strategy adopted for the preparation of title compounds is outlined in Scheme 1 and 2.

Alkylation of p-tert-butylphenol (I) with ethyl chloroacetate gave ethyl p-tert-butylphenoxyacetate (II). Hydrazinolysis of II with hydrazine hydrate in refluxing ethanol gave p-tert-butylphenoxyacetic acid hydrazide (III). The compound III displayed characteristic bands at 1650 cm^{-1} (for C=O) and 3060 cm^{-1} for NH stretching in its IR spectrum. Hydrolysis of II with methanolic sodium hydroxide at room temperature gave p-tert-butylphenoxyacetic acid (IV) (Scheme 1).

Cyclisation of p-tert-butylphenoxyacetic acid hydrazide (III) with substituted aromatic acids (Scheme 2) in refluxing phosphorus oxychloride gave invariably two products. The major product was separated by crystallization and identified as 5-(p-tert-butylphenoxymethyl)-2-substituted phenyl-1,3,4-oxadiazoles (VIIIa-d, Scheme 2). The minor product though could not be purified but in the reaction of III with benzoic acid it gave identical R_f values with the corresponding N^2-benzoyl-p-tert-butylphenoxyacetic acid hydrazide (VIII), prepared by the reaction of III with benzoylchloride in pyridine. Cyclisation of VIII in refluxing phosphorus oxychloride furnished VIIa, suggesting that cyclisation of III to VIIa-c took place via intermediates of the type VIII.



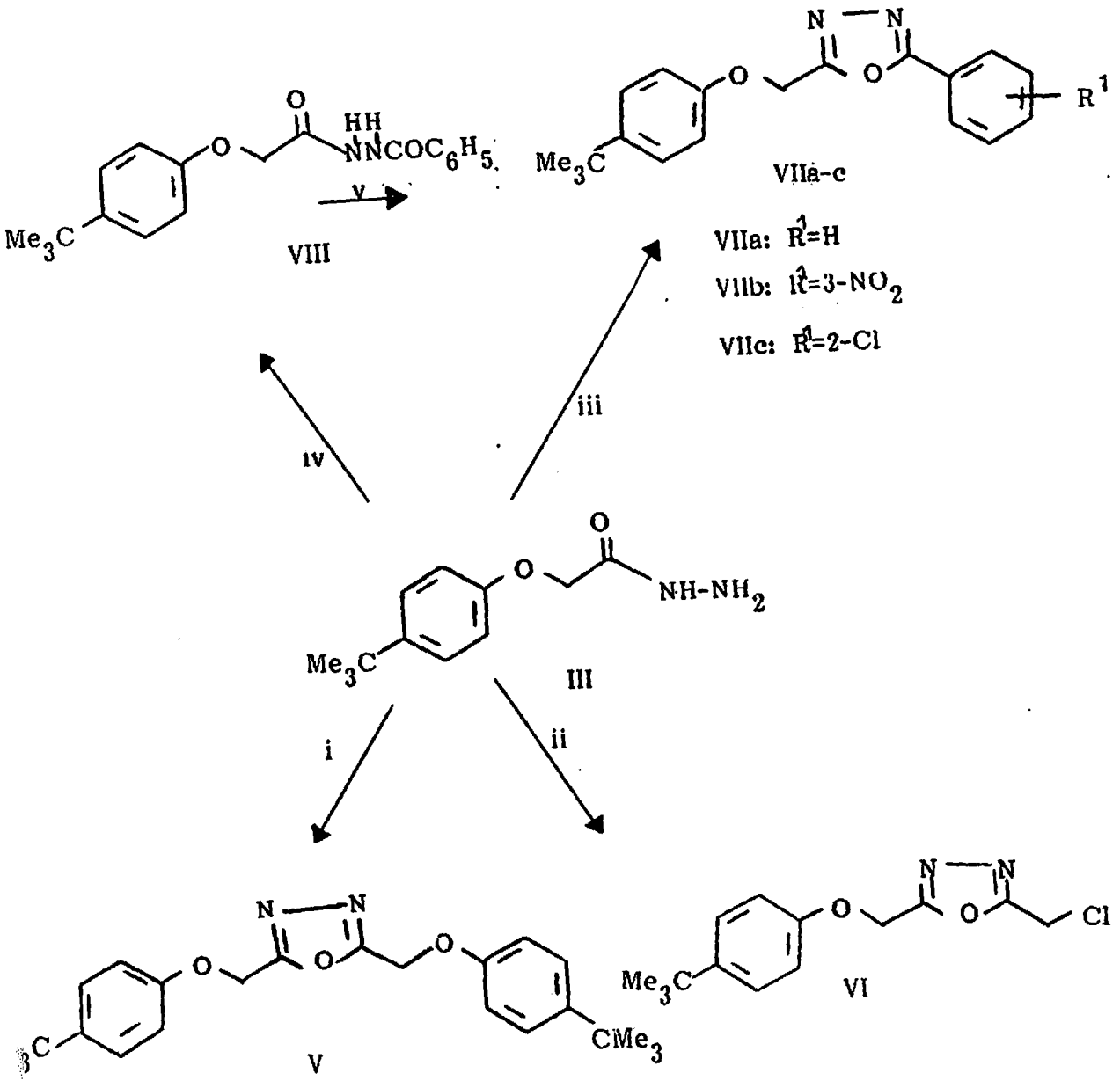
SCHEME-1

Reagents and Reaction Conditions

i) $ClCH_2CO_2Et$; K_2CO_3, DMF, RT.

ii) NaOH, MeOH, RT.

iii) NH_2-NH_2, H_2O, EtOH, Reflux.



SCHEME-2

Reagents and Reaction Conditions

i) 4-$C(CH_3)_3C_6H_4COCH_2CO_2H$, $POCl_3$, Reflux.

ii) $ClCH_2CO_2H$, $POCl_3$, Reflux.

iii) $RC_6H_4CO_2H$, $POCl_3$, Reflux.

iv) C_6H_5COCl, Pyridine, RT.

v) $POCl_3$, Reflux.

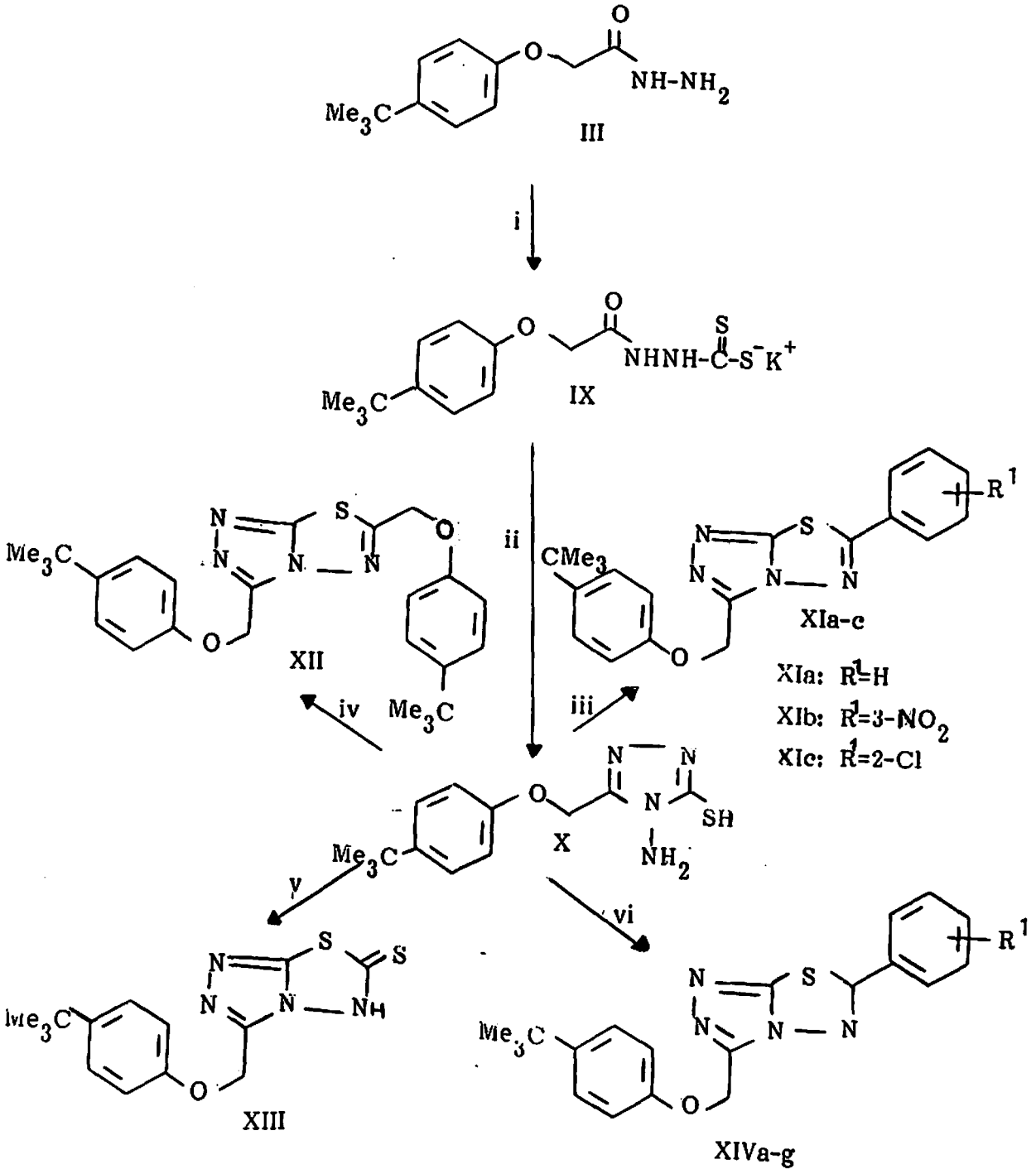
The conversions were monitored by disappearance of carbonyl stretching frequency at 1650 cm^{-1} and appearance of C=N stretching at 1600-1620 cm^{-1}.

The hydrazide (III) on cyclisation with p-tert-butylphenoxyacetic acid (IV) in refluxing phosphorus oxychloride gave the corresponding symmetrical compound 2,5-bis(p-tert-butylphenoxymethyl)-1,3,4-oxadiazole (V). The product was confirmed by IR spectrum in which the disappearance of C=O peak took place at 1660 cm^{-1} and a new signal at 1620 cm^{-1} corresponding to C=N appeared. Cyclisation of III with chloroacetic acid in refluxing phosphorus oxychloride gave 5-(p-tert-butylphenoxymethyl)-2-chloromethyl-1,3,4-oxadiazole (VI). The compound showed a positive Beilstein test for chlorine and exhibited characteristic IR and ^1H NMR spectrum.

4.2 3-(p-tert-Butylphenoxymethyl)-6-substituted-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles

The synthetic route adopted for the preparation of the title compounds is outlined in Scheme 3.

p-tert-Butylphenoxyacetic acid 2-(dithiocarboxy)hydrazide monopotassium salt (IX), required as starting material was synthesized by treatment of p-tert-butylphenoxyacetic acid hydrazide (III) with carbon disulphide and potassium hydroxide in ethanol in good yield. The potassium salt (IX) was cyclised with hydrazine hydrate to furnish 4-amino-5-(p-tert-butylphenoxymethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (X) in good yield. The IR spectrum of X showed bands



SCHEME-3

Reagents and Reaction Conditions

i) CS_2, KOH, EtOH, RT.

ii) NH_2-NH_2.H_2O, Reflux.

contd.....

iii) RC_6H_4COOH, $POCl_3$, Reflux.

iv) 4-$C(CH_3)_3$-C_6H_4COOH, $POCl_3$, Reflux.

v) CS_2, Pyridine, Reflux.

vi) RC_6H_4CHO, p-TSA, C_6H_6, Reflux.

Substituents

Compound Number	R^1
XIVa	H
XIVb	4-OMe
XIVc	2-Cl
XIVd	3-NO_2
XIVe	2-OMe
XIVf	2,4-$(OMe)_2$
XIVg	3,4-$(OMe)_2$

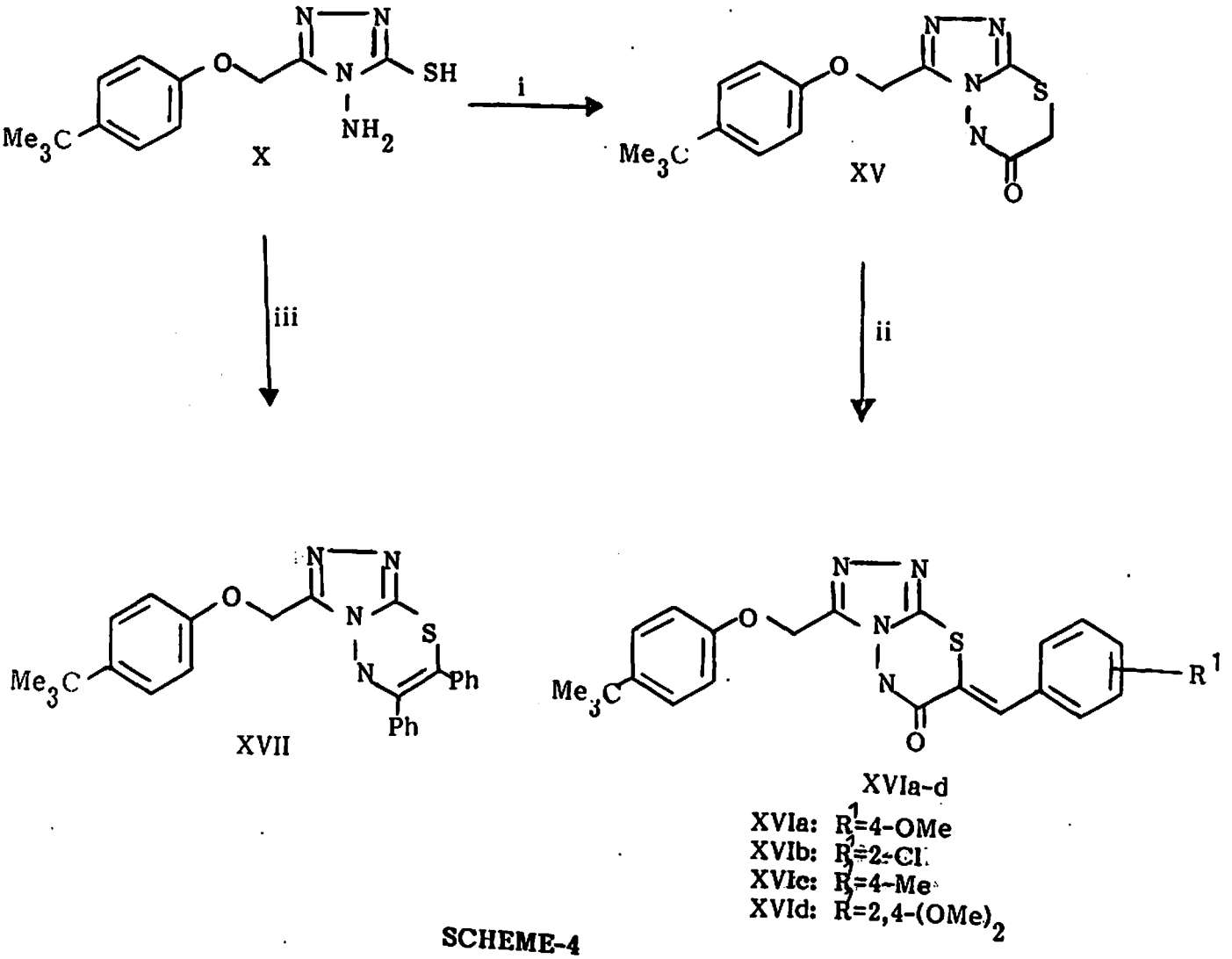
at 2550 cm^{-1} (for SH) and at 1600 cm^{-1} (for C=N). Condensation of X with substituted aromatic acids in refluxing phosphorus oxychloride furnished the title compounds 3-(p-tert-butylphenoxymethyl)-6-substituted phenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles (XIa-c). The conversion of X into XIa-c resulted in disappearance of SH and NH stretchings and appearance of bands around 1600 cm^{-1} for C=N stretching in XIa-c thereby confirming their structures.

The triazolethione X on condensation with p-tert-butylphenoxyacetic acid (IV) in refluxing phosphorus oxychloride gave the corresponding symmetrical compound, 3,6-bis(p-tert-butylphenoxymethyl)-1,2,4-triazolo[3.4-b][1,3,4]thiadiazole (XII). Its structure was confirmed by disappearance of SH and NH stretchings in the resulting product.

Condensation of triazolethione X with carbon disulphide in refluxing pyridine afforded 3-(p-tert-butylphenoxymethyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole-6(5H)-thione (XIII).

The related 5,6-dihydro analogs, 3-(p-tert-butylphenoxymethyl)-5,6-dihydro-6-substituted phenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles (XIVa-g) were prepared by condensation of X with substituted benzaldehydes in the presence of p-toluenesulphonic acid in refluxing benzene in good yields. The IR spectra of these compounds showed absorption at 1600 cm^{-1} for C=N.

The assigned structure XIVa-g were further confirmed by ^1H NMR spectra and analytical data.



XVIa: R^1=4-OMe
XVIb: R^1=2-Cl
XVIc: R^1=4-Me
XVId: R^1=2,4-$(OMe)_2$

SCHEME-4

Reagents and Reaction Conditions

i) $ClCH_2COOH$, AcONa, EtOH, Reflux.

ii) RC_6H_4CHO, AcONa, AcOH, Reflux.

iii) Ph-CHOHCOPh, EtOH, Reflux.

4.3 Synthesis of 3-(p-tert-butylphenoxymethyl)-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazines

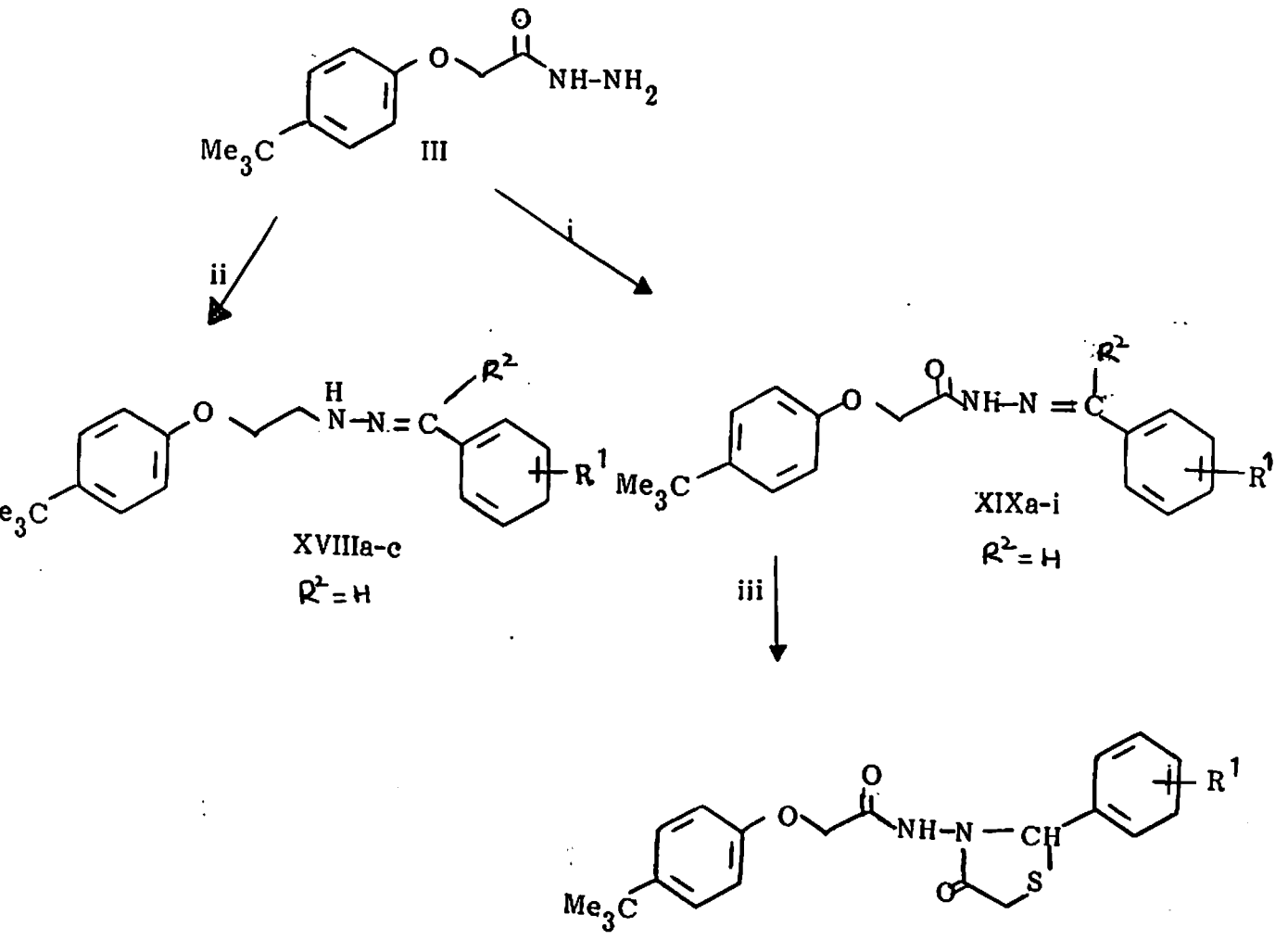
The adopted synthetic strategy outlined in Scheme 4, involved the refluxing of 4-amino-5-(p-tert-butylphenoxymethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (X) with chloroacetic acid in ethanol and gave 3-(p-tert-butylphenoxymethyl)-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazin-6(7H)-one (XV). This transformation was confirmed by appearance of band for C=O stretching at 1680 cm^{-1} in addition to a band of C=N at 1600 cm^{-1} in the IR spectrum.

Condensation of XV with substituted benzaldehydes in the presence of freshly fused sodium acetate in refluxing glacial acetic acid gave the corresponding substituted phenylmethylene derivatives, 3-(p-tert-butylphenoxymethyl)-7-substituted phenylmethylene)-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazin-6-one (XVIa-d). Cyclocondensation of 4-amino-5-(p-tert-butylphenoxymethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (X) with benzoin when refluxed in absolute alcohol in an alkaline medium furnished 3-(p-tert-butylphenoxymethyl)-5H-6,7-diphenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine (XVII).

The structure of the compounds were corroborated by their nitrogen and sulphur analytical data.

4.4. Synthesis of 3-(p-tert-butylphenoxyacetamido)-2,3,4,5-tetrahydro-2-substituted phenyl-4-oxothiazoles

The synthesis of the title compounds is outlined in Scheme 5.



SCHEME-5

Reagents and Reaction Conditions

i) $R^1C_6H_4CHO$, EtOH, Reflux.

ii) $R^1C_6H_4COCH_3$, EtOH, Reflux.

iii) $SHCH_2COOH$, C_6H_6, Reflux.

Substituents	
Compound Number	R^1
XVIIIa	H
XIXa, XXa	H
XIXb, XXb	4-OMe

contd..

Compound No.	R^1
XIXc, XXc	2-Cl
XVIIIb	4-Br
XVIIIc	4-Cl
XIXd, XXg	2,4-$(OMe)_2$
XIXe	4-NMe_2
XIXf, XXf	3-NO_2
XIXg, XXd	4-Me
XIXh, XXe	2-OMe
XIXi	3,4-$(OMe)_2$

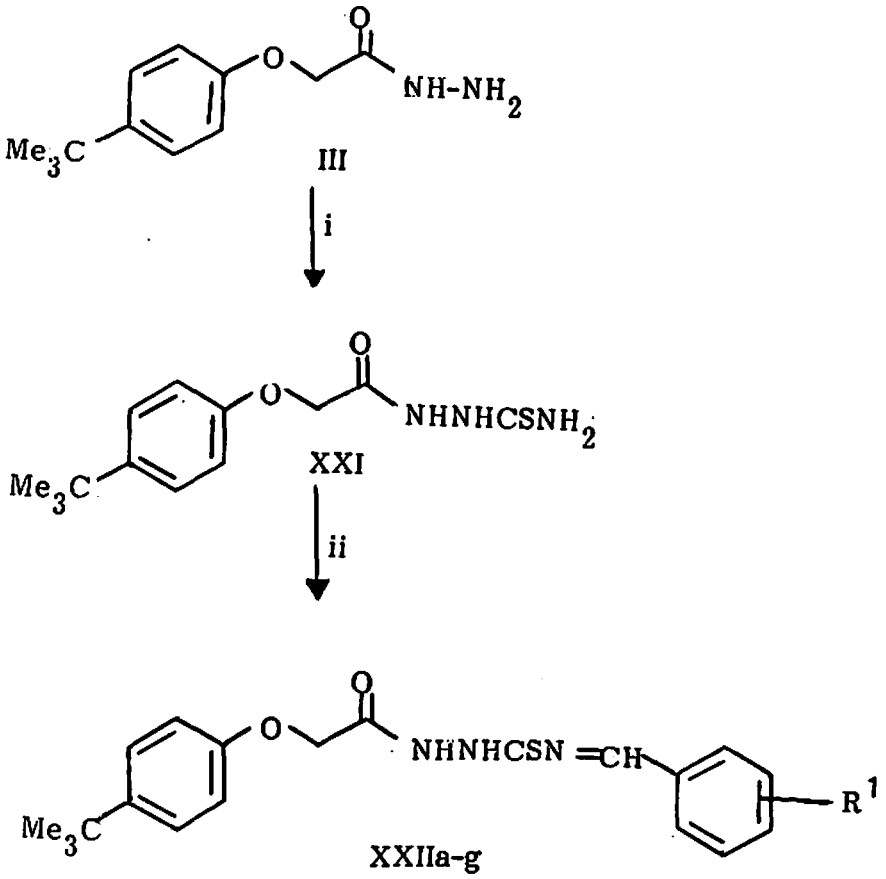
Condensation of p-tert-butylphenoxyacetic acid hydrazide (III) with the substituted benzaldehydes and acetophenones in absolute ethanol furnished the compounds p-tert-butylphenoxyacetic acid-2-[(substituted phenyl)methylene/ethylene]hydrazides (XIXa-i)(XVIIIa-c). The band at 1600 cm^{-1} for C=N was appeared in the IR spectra. ^1H NMR spectrum of the compound described in experimental section fully corroborated the assigned structure. Cyclisation of p-tert-butylphenoxyacetic acid [2-(substituted phenyl)methylene]hydrazides (XIXa-i) with mercaptoacetic acid in refluxing benzene resulted in the formation of title compounds 3-(p-tert-butylphenoxyacetamido)-2,3,4,5-tetrahydro-2-phenyl-4-oxothiazole (XXa-g) in excellent yields. The appearance of strong bands at 1660 cm^{-1} (for C=O) and at 3160 cm^{-1} (for NH) in IR spectra confirmed their structures.

The assigned structures were further corroborated by their nitrogen and sulphur analytical data.

4.5 Synthesis of p-tert-butylphenoxyacetic acid-2-[{(4-substituted phenyl)methyleneamino}thioxomethyl]hydrazides

The synthetic approach to the title compounds is outlined in Scheme 6.

p-tert-Butylphenoxyacetic acid hydrazide (III) was converted into the corresponding p-tert-butylphenoxyacetic acid (2-aminothioxomethyl) hydrazide (XXI) by its treatment with potassium thiocyanate in aqueous hydrochloric acid under refluxing, in good yield.



SCHEME-6

Reagents and Reaction Conditions

i) KCNS, HCl, Reflux.

ii) RC_6H_4CHO, AcONa, AcOH, Reflux.

Substituents

Compound Number	R^1
XXIIa	4-OMe
XXIIb	2-OMe
XXIIc	4-Me
XXIId	2-Cl
XXIIe	3-NO_2
XXIIf	2,4-$(OMe)_2$
XXIIg	3,4-$(OMe)_2$

The IR spectra displayed the appearance of characteristics band for N-H at 3200 cm^{-1} in addition to bands for C-O at 1660 cm^{-1} and C=S at 1220 cm^{-1}.

Condensation of p-tert-butylphenoxyacetic acid(2-aminothioxomethyl) hydrazide (XXI) with substituted benzaldehydes in the presence of freshly fused sodium acetate was refluxed in glacial acetic acid to furnish the title substituted phenylmethylene derivatives, p-tert-butylphenoxyacetic acid-2-[{(substituted phenyl)methyleneamino}thioxomethyl]hydrazide (XXIIa-g).

The IR spectra displayed the appearance of three characteristic bands for C=N, C=O and NH stretchings at 1600, 1660 and 3200 cm^{-1}, respectively in addition to a band for C=S at 1220 cm^{-1}. The structures were further confirmed by their nitrogen and sulphur analytical data.

4.6 Biological activity

The antifungal activity results of disubstituted 1,3,4-oxadiazole, 1,3,4-triazolo[3,4-b][1,3,4]thiadiazole/thiadiazine, their intermediates and related compounds are described in table 4.1.

The persual of data presented in Table 4.1 indicates that all the compounds showed activity against R. solani and F. oxysporum except II, III, VIIc, IX, X, XIa, XIVe, XVIIIa, XVIIIb, XIXa, XIXc, XIXg, XIXh, XIXi XXb, XXIIg and the rest were found active against R. solani or F. oxysporum at or below a concentration of 50 $\mu g\ ml^{-1}$. The compounds VIIa, VIIb, VIII were active against F. oxysporum only at a concentration

Table 4.1. In vitro growth inhibitory activity of disubstituted 1,3,4-oxadiazoles, 1,3,4-triazolothiadiazoles, 1,3,4-triazolothiadiazines, their intermediates and related compounds against phytopathogenic fungi.

Compound No.	Minimum inhibitory concentration ($\mu g\ ml^{-1}$)	
	F. oxysporum	R. solani
II	> 100	> 100
III	> 100	> 100
IV	50	100
V	50	100
VI	100	100
VIIa	100	100
VIIb	100	100
VIIc	> 100	> 100
VIII	100	> 100
IX	> 100	> 100
X	> 100	> 100
XIa	> 100	> 100
XIb	12.5	50
XIc	25	50
XII	25	> 100
XIII	25	6.25
XIVa	100	100
XIVb	> 100	> 100
XIVc	25	> 100
XIVd	50	100

contd...

Table 4.1 contd...

Compound No.	Minimum inhibitory concentration (μg ml^{-1})	
	F. oxysporum	R. solani
XIVe	>100	>100
XIVf	50	50
XIVg	50	50
XV	50	50
XVIa	50	50
XVIb	25	100
XVIc	25	50
XVId	50	50
XVII	25	50
XVIIIa	> 100	>100
XVIIIb	>100	>100
XVIIIc	>100	>100
XIXa	>100	>100
XIXb	50	>100
XIXc	> 100	>100
XIXd	50	>100
XIXe	> 100	25
XIXf	>100	25
XIXg	> 100	>100
XIXh	>100	> 100
XIXi	> 100	>100
XXa	>100	100

contd...

Table 4.1 contd...

Compound No.	Minimum inhibitory concentration (ug ml^{-1})	
	F. oxysporum	R. solani
XXb	> 100	>100
XXc	50	100
XXd	25	50
XXe	> 100	50
XXf	25	50
XXg	25	>100
XXI	50	50
XXIIa	50	>100
XXIIb	50	>100
XXIIc	50	50
XXIId	50	>100
XXIIe	50	50
XXIIf	100	50
XXIIg	> 100	>100
Bavistin	3·17	0·79

of 100 $\mu g\ ml^{-1}$ while V, XIVd, XXa, XXc were active at 100 $\mu g\ ml^{-1}$ of concentration against R. solani. It was concluded that compounds inhibited the growth of F. oxysporum fungus to a greater extent as compared to R. solani. For example, IV, V, XIb, XIc, XII, XIII, XIVc, XIVd, XIVf, XIVg, XVIb-c, XVII, XIXb, XIXd, XXc, XXd, XXf, XXIIa, XXIIb and XXIId were active at a concentration varying from 25-50 $\mu g\ ml^{-1}$. The compounds XIVf, XIVg, XV, XVIa, XVId, XXI, XXIIc, XXIIe restricted the growth of both the fungi at a concentration of 50 $\mu g\ ml^{-1}$. The compound XIb inhibited the growth of F. oxysporum at a concentration of 12.5 $\mu g\ ml^{-1}$ and XII was active at 6.25 $\mu g\ ml^{-1}$ against R. solani.

Fifteen compounds XIb, XIc, XIII, XIVf, XIVg, XV, XVIa, XVIc, XVId, XVII, XXd, XXf, XXI, XXIIc and XXIIe showed activity against both the tested fungi. However, from the mixed pattern of activity obtained, no specific structure activity correlation could be drawn. However, in general triazolothiadiazoles were more active than triazolothiadiazines, whereas oxadiazoles were least active.

V

SUMMARY

CHAPTER - V

SUMMARY

Arylheterodiazoles such as oxadiazoles, thiadiazoles and triazoles are well known for their antifungal activity. This prompted us to synthesize and evaluate p-tert-butylphenoxymethyloxadiazoles, triazolothiadiazoles and triazolothiadiazines.

Hydrazinolysis of ethyl p-tert-butylphenoxy acetate (II) with hydrazine hydrate provided p-tert-butylphenoxyacetic acid hydrazide (III). The ester (II) on reaction with methanolic sodium hydroxide gave p-tert-butylphenoxyacetic acid (V). Cyclisation of hydrazide (III) with substituted aromatic acid furnished 5-(p-tert-butylphenoxymethyl)-2-substituted phenyl-1,3,4-oxadiazoles (VII a-c). The conversion was found to take place via the formation of N^2-benzoyl-p-tert-butylphenoxyacetic acid hydrazide (VIII). Cyclisation of p-tert-butylphenoxyacetic acid hydrazide (III) with p-tert-butylphenoxyacetic acid (IV) and chloroacetic acid gave symmetrical 2,5-bis(p-tert-butylphenoxymethyl)-1,3,4-oxadiazole (V) and 5-(p-tert-butylphenoxymethyl)-2-chloromethyl-1,3,4-oxadiazole (VI) respectively.

The hydrazide III on treatment with carbon disulphide and potassium hydroxide resulted in the formation of p-tert-butylphenoxyacetic acid 2-(dithiocarboxy)hydrazide monopotassium salt (IX) which on cyclisation with hydrazine hydrate gave 4-amino-5-(p-tert-butylphenoxymethyl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (X).

Condensation of X with substituted aromatic acid; p-tert-butylphenoxyacetic acid, carbon disulphide and substituted aromatic benzaldehydes gave 3-(p-tert-butylphenoxymethyl)-6-substituted phenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (XIa-c); 3,6-bis(p-tert-butylphenoxymethyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (XII); 3-(p-tert-butylphenoxymethyl)-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole-6(5H)-thione (XIII) and 3-(p-tert-butylphenoxymethyl)-5,6-dihydro-6-substituted phenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole (XIVa-g) respectively.

Cyclisation of X with chloroacetic acid and benzoin furnished 3-(p-tert-butylphenoxymethyl)-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine-6(7H)-one (XV) and 3-(p-tert-butylphenoxymethyl)-5H-6,7-diphenyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine (XVII). XV on condensation with substituted aromatic benzaldehydes gave 3-(p-tert-butylphenoxymethyl)-7-(4-methoxyphenyl)methylene-5H-1,2,4-triazolo[3,4-b][1,3,4]thiadiazine-6-one (XVIa-d).

Condensation of III with substituted benzaldehydes/acetophenones gave Schiff's base XVIIIa-c; XIXa-i, which were further cyclised with mercaptoacetic acid to give 3-(p-tert-butylphenoxyacetamido)-2,3,4,5-tetrahydro-2-(substituted phenyl)-4-oxothiazole (XXa-h).

Treatment of III with potassium thiocynate in acidic medium furnished p-tert-butylphenoxyacetic acid(2-aminothioxomethyl)hydrazide (XXI), which on condensation with substituted aromatic benzaldehydes gave p-tert-butylphenoxyacetic acid-2-[{(substituted phenyl)methyleneamino}thioxomethyl] hydrazide (XXIIa-g).

The conversions were monitored by concomitant expected change in the IR and ^1H NMR spectra of the products and further corroborated by N and S analytical data.

The compounds were tested for in vitro growth inhibitory activity against Fusarium oxysporum and Rhizoctonia solani by two fold serial dilution technique. The activity results were compared with a standard fungicide, bavistin. Some compounds were found active at concentration varying from 25-50 $\mu g\ ml^{-1}$. XIb was active at 12.5 $\mu g\ ml^{-1}$ of concentration against F. oxysporum and XIII at 6.25 $\mu g\ ml^{-1}$ against R. solani

In general, triazolothiadiazoles and their dihydro analogs showed better pattern of activity as compared to triazolothiadiazines and oxadiazoles.

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