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Role of uncondensed 1,2,4-triazine derivatives as biocidal plant protection agents – a review*

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The role of uncondensed 1,2,4-triazine derivatives and the related compounds as biocidal plant protection agents such as herbicides, bactericidal, fungicidal, antimicrobial, protozacides, anticoccidal, parasiticides, insecticides, acaricdes and pesticides, is reviewed.

1. Introduction

The chemical protection of plants is based on the use of various organic compounds toxic to harmful organisms, and can be used to control most pests, diseases and weeds in all agricultural crops and various lands and also to treat granaries, storage bins, green houses and grain elevators.

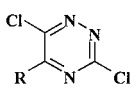
Pesticides for plant protection are produced by the chemical industry and marketed at a comparatively low price, which results in a high justification of their use. The use of pesticides is especially effective in horticulture, where they make it possible to control exceedingly dangerous pests, improve the quality of the products and substantially increase the yield of the fruits. As pests exist in great variety and affect man in many different ways, so the chemical agents used for the control of these pests show endless variation. Many can be grouped in acceptable if rather general, chemical classes, such as 1,2,4-triazines, substituted ureas or pyrimidines, carbamates, organophosphates and other natural products. On the other hand, one of the most importance and applications of uncondensed 1,2,4-triazines is treatment of AIDS and cancer [1–10].

In this review, we report their role as biocidal plant protection agents.

2. Chemistry

2.1. Use as herbicide agents

5-Substituted-3,6-dichloro-1,2,4-triazines **1a–d** were tested for their preemergent herbicidal activity against three weeds, *Echinochloa crus-galli*, *Scirpus-juncoides* and *Eleocharia acicularis*. 5-*tert*-Butylamino- and 5-anilino-3,6-dichloro-1,2,4-triazine derivatives **1a**, **b** exhibited strong herbicidal activity, whereas Me, OMe, PhO substituents at the 5-position decreased their activity. Also, derivatives with substitution at the 3- and/or 6-position failed to show activity. 5-Diisopropylamino- and 5-(2,6-dimethylpiperidino)-1,2,4-triazines **1c**, **d** were selected as promising new herbicides [11].



1

R

a tert - butylamino

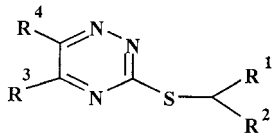
b anilino

R

c diisopropylamino

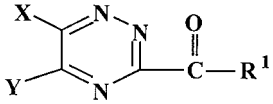
d 2, 6- dimethylpiperidino

Also, the alkylated thio-1,2,4-triazines **2**, (R^1 = alkenyl, cycloalkyl, phenyl, benzyl, naphthyl; R^2 = H, alkyl; R^3 = alkoxy, benzyloxy, carboxy, alkoxy, cyanoalkoxy; R^4 = H, alkyl, alkoxy, phenyl) are prepared and 3-[(m-fluorophenyl)methoxythio]-5-methoxy-1,2,4-triazine **2**, (R^1 = o-methylphenyl, $R^2 = R^4$ = H, R^3 = MeO) at 1.0 kg/h a showed 90–100% control of *Scirpus juncoides* [12].



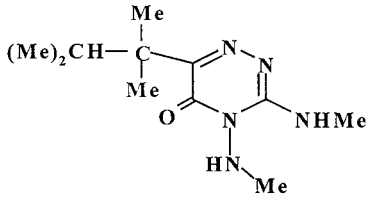
2

Moreover, N-sulfonyltriazine carboxiamides **3** (R^1 = $NHSO_2AnR$; A = O, CH_2, (alkyl) imino; R = (un)substituted (hetero) aryl; X, Y = H, halo, alkyl, alkoxy, (hetero) aryl, n = 0 or 1) have been synthesized and used as herbicides [13].



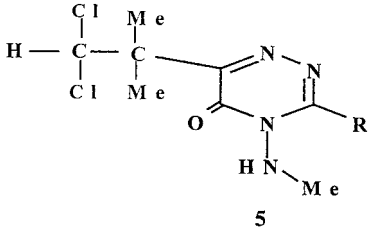
3

Kranz et al. [14], synthesized the 3,4-bis-(methylamino)-6-(2,3-dimethyl-2-butyl)1,2,4-triazin-5 (4*H*)one (4) as a herbizide.



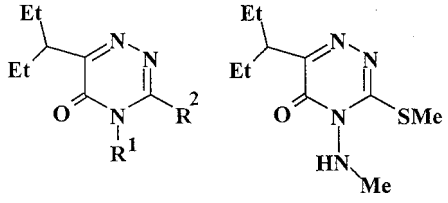
4

Similarly, 6-(1,1-dichloro-2-methyl-2-propyl)-4-methylamino-1,2,4-triazin-5(H)-ones **5,** (R = NHMe, $NHMe_2$) were prepared as herbicides by condensation of **5** (R = SMe) with $MeNH_2$ or Me_2NH [15].



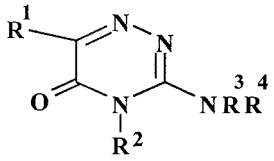
5

One of the most important herbicides, desicants, defoliants and plant growth regulators, are the 6-(3-pentyl)-1,2,4-triazin-5(4H)-ones **6** (R^1 = Me, NH, R^2 = alkylthio). Compounds **6a** and **6b** are superior to a triazine as pre- and postemergent herbicides and are useful as defoliants/desiccants on cotton [16].



6 a 6 b

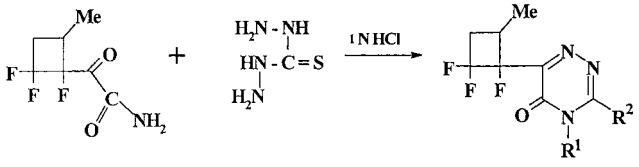
The amino-1,2,4-triazines **7** (R^1R^2 = alkyl, alkoxyalkyl (methyl) cycloalkyl, (un)substituted aralkyl, aryl, aryl; R^3R^4 = H, alkyl, cycloalkyl, R^3R^4N = piperidinyl, morpholinyl) were prepared as herbicides. Thus, compound **7** ($R^1 = Me_2CH$, R^2R^4 = Me, R^3 = H) totally prevented emergence of *Avena fatua* [17].



7

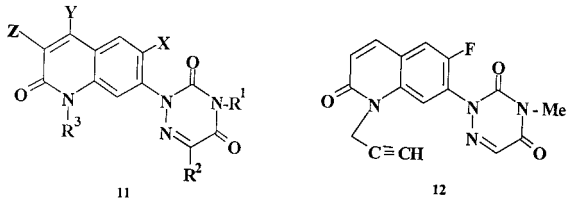
Some new fluorine bearing 1,2,4-triazines have been obtained as herbicides. Thus, 6-(1-methyl-2,3,3-trifluorocyclobut-2-yl)-(1,2,4-triazine-5-ones **10** ($R^1 = NH_2$, MeNH; R_2 = alkylthio, alkylamino, dialkylamino; $R^1 = NH_2$ when R^2 = MeS) were prepared by interaction of **8** with thiocarbohydrazide **9** [18] (Scheme 1).

Scheme 1



8 9 10

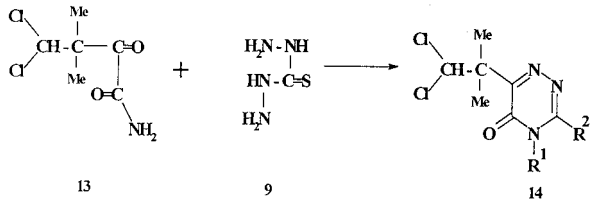
Also, some new fluorine bearing oxoquinolinyl triazine diones **11** and **12** (**11**: R^1 = alkyl, alkenyl, alkynyl, haloalkyl, alkoxyalkyl; R^2 = H, alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, halo; R^3 = H, alkyl, alkenyl, alkynyl, haloalkyl, haloalkenyl, alkoxyalkyl, alkoxycabonyl, CN, NO_2, Z = Y, alkoxy, alkenyl, alkynyl, alkylsulfinyl, alkylsulfonyl) have been obtained as herbicides [19].



11 12

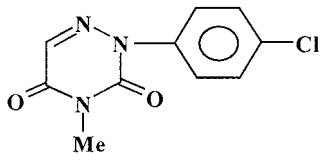
In addition, some new chlorine containing 1,2,4-triazines have been synthesized as herbicides. Thus, 6-(1,1-dichloro-2-methyl-2-propyl)-1,2,4-triazine-5 (4*H*) ones **14** were prepared by cyclocondensation of the 1,2-bicarbonyl compound **13** with thiocarbohydrazide **9** [20] (Scheme 2).

Scheme 2



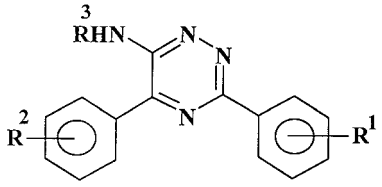
13 9 14

2-(4-Chlorophenyl)-4-methyl-1,2,4-triazine-3,5-dione (**15**) which belongs to a new class of light activated disrupting herbicides is active on both grass and broade of weeds at low rates [21].



15

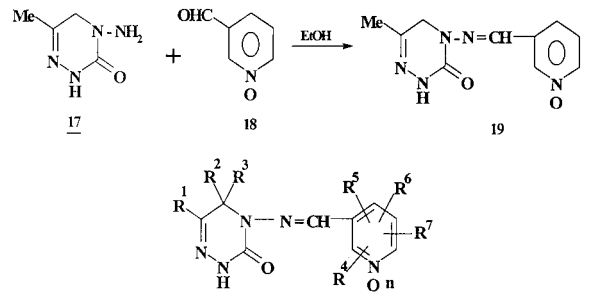
Herbicides containing 6-substituted-3,5-diphenyl-1,2,4-triazines (**16**, R^1 = H, halo, lower haloalkyl; R^2 = halo; lower haloalkyl; R^3 = lower haloalkyl) as active ingredients 1,2,4-triazines have been obtained. Premergence application of 2000 g of **16** (R^1 = p-F, R^2 = m-Cl, R^3 = Et)/La ~ 70% controlled *Echinochloa crus-galli* and *Ipomoea purpurea* [22].



16

Some more 3-oxo-4-(pyridinylmethyleneamino)-1,2,4-triazines **20** (R^1 = alkyl, cycloalkyl, R^2, R^3 = H, alkyl; R^4-R^7 = H, halo, alkyl, NR^2R^3, alkylation; n = 0, 1) were prepared as pesticides. Refluxing 2,3,4,5-tetrahydro-3-oxo-4-amino-6-methyl-1,2,4-triazine (**17**) with pyridine-3-carboxaldehyde N-oxide (**18**) in ethanol yielded compound **19** which at 3 ppm gave > 80% kill of *Bemisia tabaci* on *Phaseolus vulgaris* [23] (Scheme 3).

Scheme 3



17 18 19

20

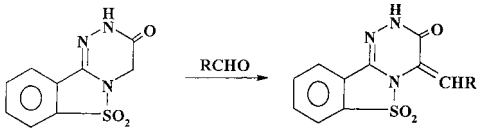
The absorption of metribuzin and its ethylthio analog (ethyl-metribuzin) by protoplasts of downy brome (*Bromus tectorum*) and jointed goatgrass (*Aeyilops cyclindrica*) was assayed by a modified silicone oil centrifugation method. In these experiment, 75–83% of the protoplasts were intact after centrifugation.

Herbicide uptake was mixed within 30 s, the shortest measurement peroid. The absorption of both herbicides was greater than predicted based solely on the volume of protoplasts, indicating that the herbicides had partitioned and/or bound to the membranes. The absorption of ethylmetribuzin and metribuzin by protoplasts was similar and did not vary with temperatures or species.
Herbicide absorption by protoplasts of both species increased linear with increasing concentration (0.01 to 100 μM). In thylalkoides O evolution (photosynthetic electron transport) was more inhibited by metribuzin than by ethyl metribuzin and inhibition correlated with increases in temperature. Thus, the increase in triazinone activity in cells exposed to increasing temperature appears to be due to an increased inhibition of O evolution in thylalkoides and is not related to increased herbicide binding [24].

2.2. Use as bactericidal agents

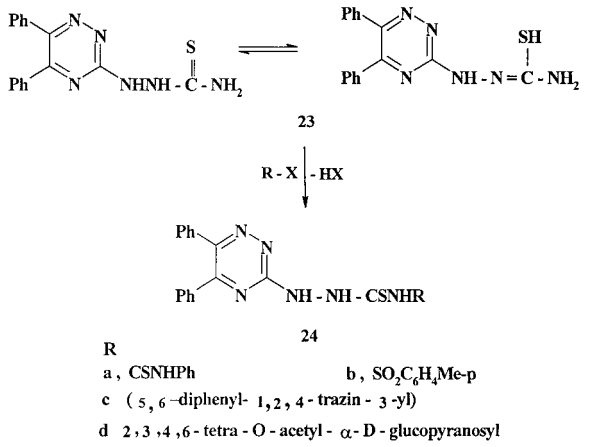
1,2,4-Triazines possess bactericidal properties largely based on the presence of thiol ⇄ thione and or amino ⇄ imino functional groups. 5-Arylidine-1,2,4-triazino[4,3-b]-1,2-benzisothiazol-3-one-6,6-dioxides **22** (R = 4-ClC_6H_4, 2-$O_2NC_6H_4$, 4-BrC_6H_4, 2-BrC_6H_4) were prepared from condensation of compound **21** with aldehydes (Scheme 4). Compounds **22** showed antibacterial activity particularly againsts *Staphylococcus aureus* [25].

Scheme 4

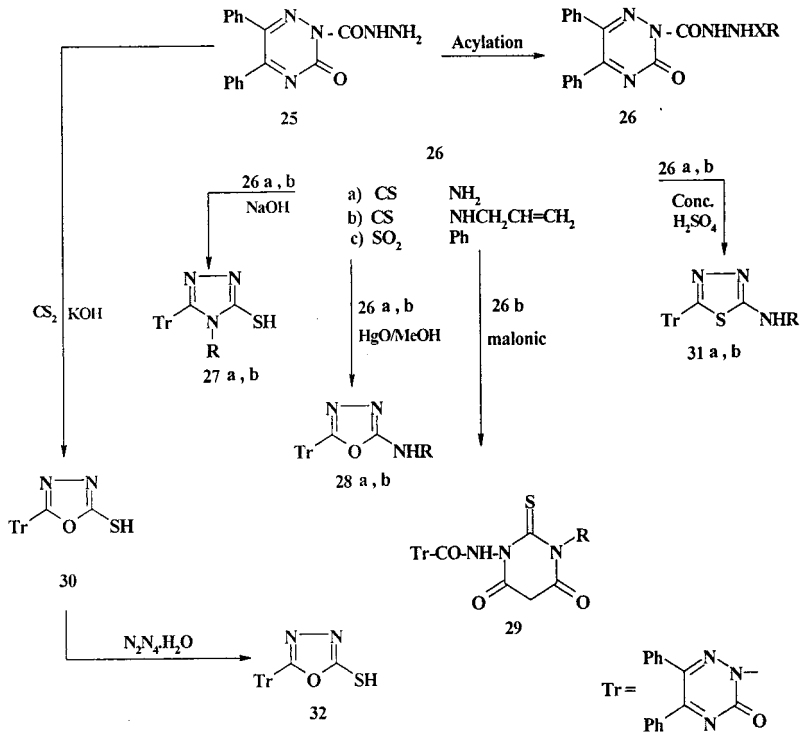


N^4-(5,6-diphenyl-1,2,4-triazin-3-yl) thiosemicarbazide (**23**) when acylated and/or alkylated furnished 1,4-disubstituted the thiosemicarbazides **24a**–**d** (Scheme 5) [26]. Compounds **23** and **24** shows *in vitro* antibacterial activity against the gram positive *Bacillus subtilis* ATCC 6633, and against Escherichia coli as gram negative bacterium. These results confirm the suitability of **24d** as antibacterial agent against *Escherichia coli* and **24b** as antibacterial agent against *Bacillus subtilis*. Compound **23** has a good antibacterial activity against both the bacteria tested [26].
Several new heterocyclic systems bearing a 5,6-diphenyl-1,2,4-triazin-3-one-2-yl moiety have been synthesized by acylation of 2-carboxyhydrazide-5,6-diphenyl-1,2,4-triazin-3-one (**25**) followed by heterocyclization reactions (Scheme 6) [27]. Some the newly synthesized heterocyclic systems were tested in DMF for their antimicrobial activity against *Escherichia coli*, *Proteus vulgaris*, *Serratia marcescens*, *Bacillus cereus*, *Micrococcus iutea* and *C. albicans*. Com-

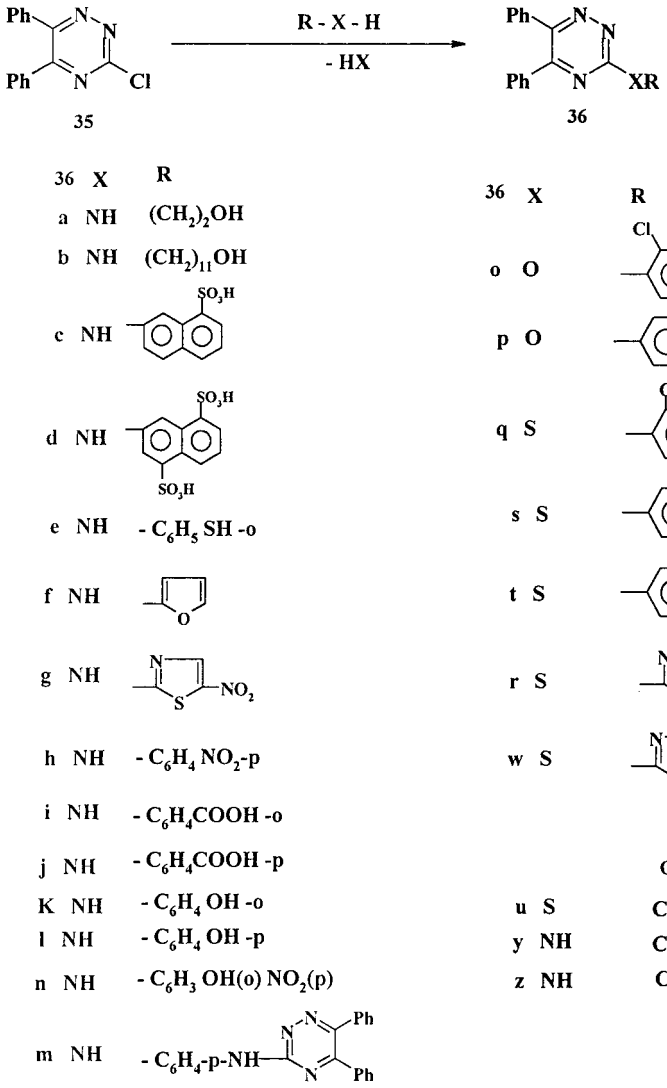
Scheme 5



Scheme 6



Scheme 7

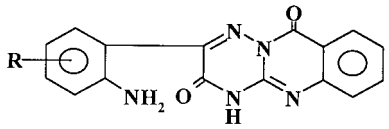


pounds **27b**, **28b**, **29b**, and **30** showed very promising activity against all the strains tested which may be attributed to the presence of an allyl thiocarbamate moiety. Furthermore, compounds **31a**, and **32** showed a moderate effect, maybe due to the parent heterocyclic systems [27].

Some new quinoxalino [2′,3′ : 4,5]thiazolo[3,2-*b*]indolo[2,3-*e*][1,2,4]triazines **33**, and isomeric quinoxlino[2′,3′ : 4,5]-thiazolo[2,3-*c*]indolo[2,3-*e*][1,2,4]triazines **34** have been obtained and used as bacteridial agents [28].

A number of 3-substituted-5,6-diphenyl-1,2,4-triazines **36** have been synthesized by the reaction of appropriate aliphatic or aromatic amines, phenols, thiophenols and guanidine derivatives with 3-chloro-5,6-diphenyl-1,2,4-triazine (**35**) (Scheme 7). 1-(5,6-diphenyl-1,2,4-triazin-3-yl) aminoguanidine (**37a**) undergoes alkylation, acylation and condensation with aldehydes to yield the 1,4-disubstituted aminoguanidines **37b**–**d**, **38a**–**c**. The 3-heteroaryl-5,6-diphenyl-1,2,4-triazines **39**, **40** and **41** have been obtained by cyclocondensation of **37a** with *p*-hydroxy-phenylpyruvic acid, triethyl orthoformate and hexafuoroacetylacetone (Scheme 7) [29]. The *in vitro* antibacterial activity of **36**–**42** (in 1% methanol) was tested by the diffusion method using the solid glycerine-peptone medium against *Bacillus subtilis* ATCC 6633, *Staphylococcus aureus* ATCC 6538 p, *Streptococcus lactis diacetylactic* and *Escherichia coli*. Chloramphenicol was used as standard for the antibacterial activity. The results showed that **38a** was the most active compound against *S. lactis*, *E. coli* and *B. subtilis*, while **36u** was the only compound active against *S. aureus*. In addition, compounds **37c** and **36b** were moderately active against *S. lactis* [29].

Some new fluorine containing aryl-triazinoquinazoliones **42** (R = 5 or 6-F, 4-CF_3) have been synthesized and those with R = 5-F showed a significant antibacterial activity [30].

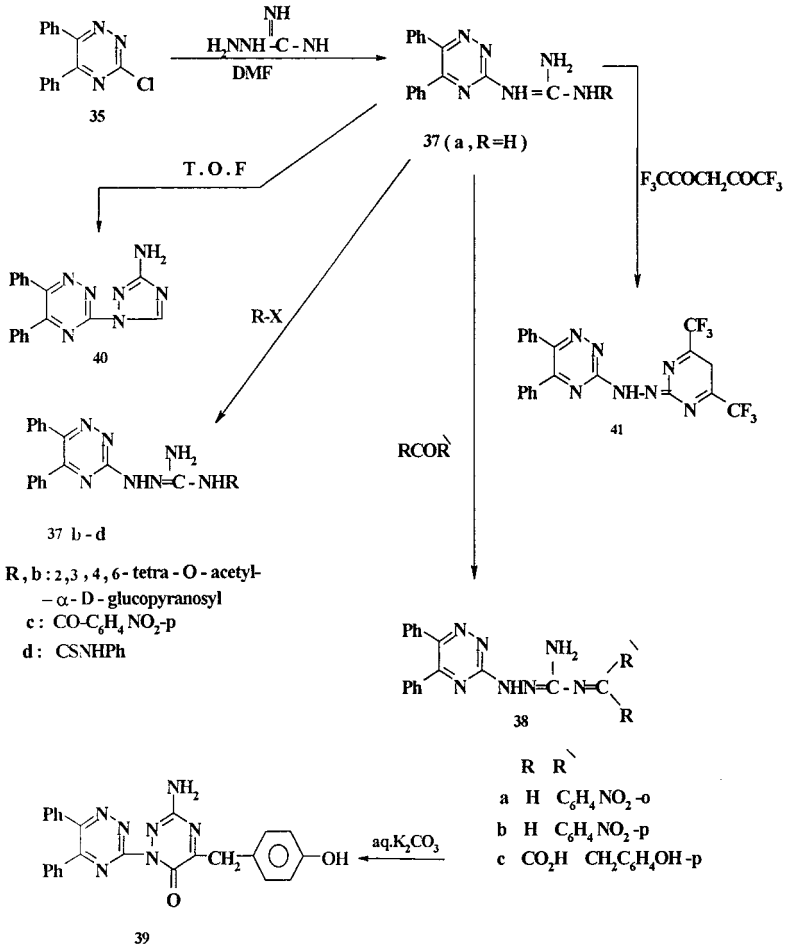


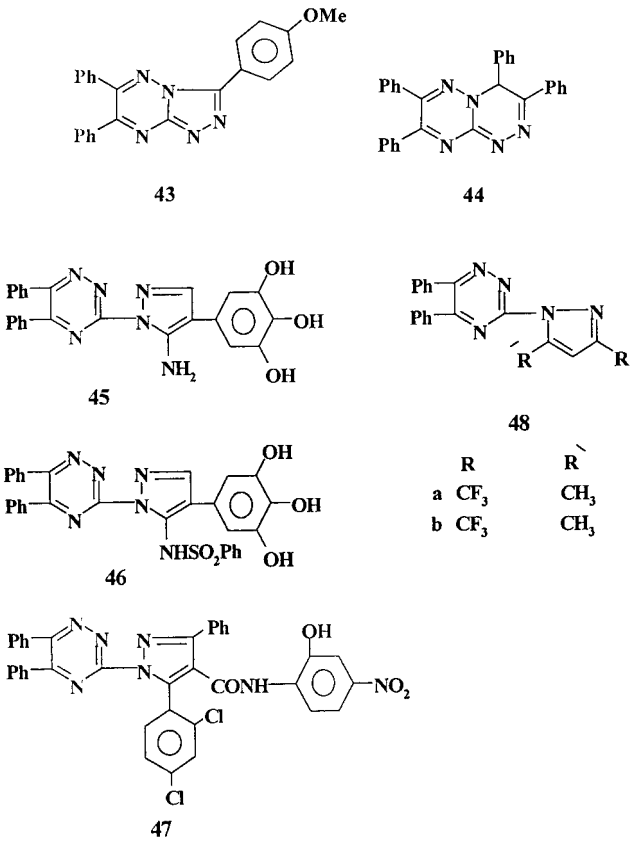
42

Many heterobicyclic systems such as s-triazolotriazine **43** and 1,2,4-triazinotriazine **44** have been obtained and exhibited a bactericidal effect [31].

Some new 3-(3′,5′-disubstituted pyrazol-1′-yl)-5,6-diphenyl-1,2,4-trazines and their related compounds have been synthesized and evaluated [32]. Compounds **45**–**48** were active against *Staphylococcus aureus*, *B. subtilis* and *E. coli* [32].

Scheme 8





2.3. Use as fungicidal agents

Fungal diseases which attack the tropical crops include black pod of cocoa, sigataka of bananas, blister blight of tea, vascular wilt of plams, and blast diseases of rice all of great economic importance.

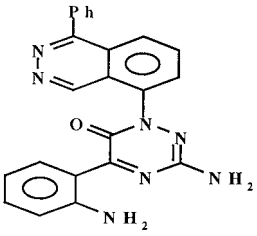
A fungus growing in groundnuts when stored in damp condition produces remarkably toxic aflatoxin which was responsible for the death of many thousand turkeys in Britain in the 1950s and believed to be responsible for the high incidence of certain stomach diseases in man. In temperate regions, various fungal diseases of cereals are attracting increasing attention.

The fungicidal activity of 3-substituted-5,6-diphenyl-1,2,4-triazines (368537) was studied against *Candida utilis* and *Aspergillus fumigatus*. Only four compounds, **36f** > **36u** > **36z** > **37a** were active against *C. utilis*, while the compounds **36h** and **36w** were moderately active against *A. fumigatus*. In addition, compound **36h** showed 46% inhibition at a concentration of 500 μg/ml [29].

On the other hand, fluorine bearing 1-(5,6-diphenyl-1,2,4-triazin-3-yl)-3-trifluoromethyl-5-methyl) trifluoromethyl-pyrazoles **48a, b** were active against *Aspergillus niger* and *Penicillum notatum* [32].

3-Amino-1-(4-phenylphthalazin-1-yl)-5-substituted-1,2,4-triazin-6-one (**49**) exhibited antifungal activity against *Aspergillus niger* and *Penicillum oxalicum* [33].

The agrochemical fungicide 4,6-disubstituted-3-thioxo-1,2,4-triazin-5-one (**51**) was obtained from cyclocondensation of the N^4-phenylthiosemicarbazide **50** with trimethyl sodium pyruvate [34] (Scheme 9).



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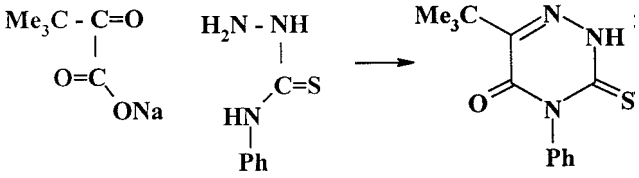
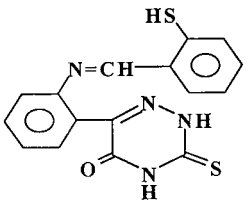
Scheme 9



50 51

Abdel-Rahman et al. [35] prepared some new 3,6-diheteroaryl-1,2,4-triazin-5-ones and reported their effect on the amylolytic activity of some fungi, where the compounds **42**–**55** showed very high activity towards *A. flavus, A. fumigatus, A. nidulaus, A. niger, A. terreus, A. terricola, P. chermesimum, P. chrysogenum, P. funiculosum, P. meleagrinum* and *M. spinosus* [35].



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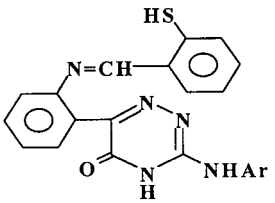
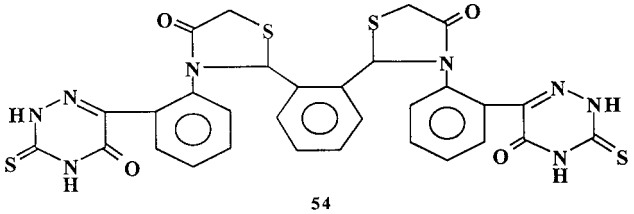


53 , Ar $C_6H_4NH_2$-o C_6H_4OH-o C_6H_4SH-o



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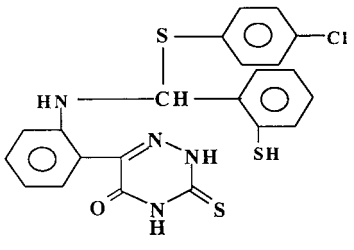

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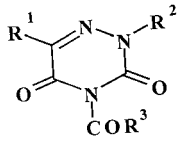
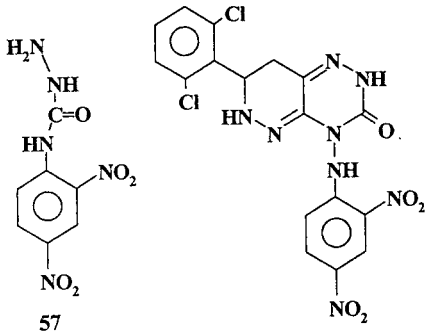


56

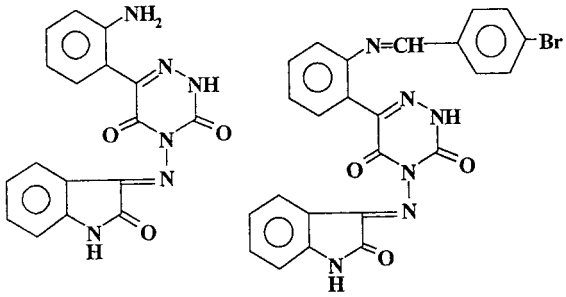
N-Substituted-1,2,4-triazin-3,5-dianes **56** have been synthesized as agrochemical fungicides as well and **56** (R′ = tert-Bu, $R^2 = NH_2$, R^3 = p-chlorobenzoyl) controlled 90 and 100% *Phytophthora infestans* in miniature dwarf tomato seedings (*P. capsici*, and *P. infestants*) at 100 and 500 ppm [36].

Abdel-Rahman et al. [37] prepared 4,6-disubstituted-1,2,4-triazin-3,5(2*H*) diones and related heterobicyclic systems and evaluated then against the growth of some phytopathogenic fungi associated with wheat grains, i.e., *Alternaia alterara, Helimen thosporium sativum* and *Fusarium moniliforme*. Compounds **57**–**60** were the most active. The best control of *F. moniliforme* was achieved by 1000 μg/ml of compound **57** (85% germination) and compound **59** (73–75% germination) [37].

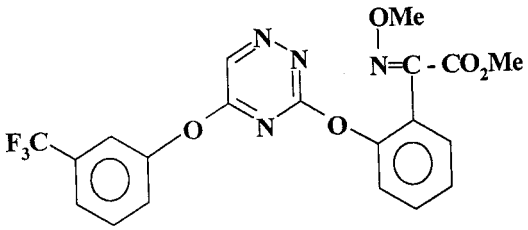
Methods for the preparation of fluorinated oxime ethers [(heteroaryloxy) oximino benzene acetates] and their use as agrochemical fungicides were reported [38]. Thus, a fungicidal formulation contains Me(E)−O-methyl-α-{2-[(5-[3-(trifluoromethyl)phenoxyl]-1,2,4-triazin-3-yl]oxyl} phenyl-α-oximinoacetate (**61**), (10%) benzyl alcohol (30%), Ca dedecylbenzenesulfonate (5%), nomylphenyl ethoxide (10%), and alkyl benzenes (45%) [38].



57 58



59 60



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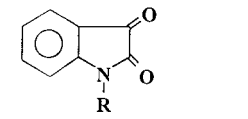
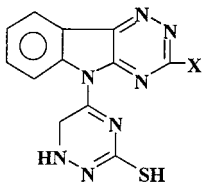
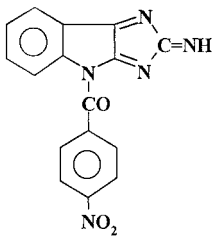


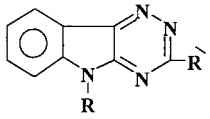
62 , R : a H
b $COCH_2Cl$
c $COC_6H_4NO_2$-p
d COC_6H_4Cl-p
e COC_6H_4OMe-p



63 , X = SH , NH_2

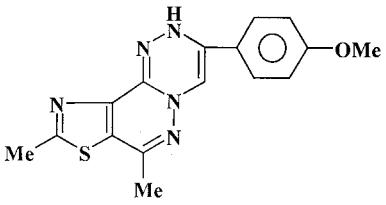


64



65

	R	R`
a	COC_6H_4Cl-p	CH_2CN
b	$COC_6H_4NO_2$-p	SH
c	COC_6H_4OMe-p	OH
d	COC_6H_4Cl-p	NH_2



66

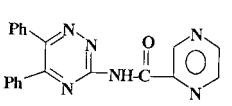
In search for new fungicidal agents 3-substituted 1,2,4-triazinoindoles and related compounds have been prepared and their antifungal activity has been determined both *in vitro* and *in vivo* against the fungus *Aspergillus niger* using benomyl as standard [39]. Firstly, ED50 values were determined *in vitro* by regression analysis of the log-probit transformed date [40], where compounds **62c** and **62d** are more fungitoxic to *Aspergillus niger* than others.

The results showed that compound **63b** is more fungitoxic than compound **63a** indicating that the amino group enhances the fungitoxicity compared to the mercapto group. The fungal growth is greatly inhibited by compound **64** indicating that $COC_6H_4-NO_2$-p and NH groups are the important fungitoxiphores. Also the presence of a NH_2 group in **65** increases its fungitoxicity. Compound **65b** is more fungitoxic than other members of **65**. Dekker [41] suggested that substitution at position 1 or 2 in the indole nucleus of an active compound (e.g. 3-phenylindole) cancels activity almost completely. This leads to the conclusion that the NH_2 group plays an important role in the creation of antifungal derivatives. Secondly, *in vivo* used benomyl at 1 g/kg gives a better control of seed rot of sorghum [42]. At 5 g/kg, compound **64** has fungitoxicity similar to that of benomyl according to its ED_{50} value and controlling seed rot [39].

Tricyclic heterocycles thiazolo[4,5-d]pyridazino[2,3-c] 2H-1,2,4-triazines 66 were prepared and had activity against *C. albicans* [43].

Some heterobicyclic systems bearing an 1,2,4-triazine moiety **27**–**32** exhibited very promising antifungal activity [27]. Abdel-Rahman et al. [44] synthesized the 3-(1,2,4-triazin-3-yl)-1,2,4-triazine derivatives **67**–**72**. The effect of the newly synthesized compounds on the activity of cellobiase, an enzyme produced by thermophilic fungi, namely *Thermomyces lanuginosus*, and *Chaetomium thermophilum* was studied. The procedure for determining cellobiase activity was adopted Reesem and Mandel [45]. The released reducing sugar was estimated colorimetrically at 540 nm as an indication for the enzyme activity [46, 47].

Only compound **67** showed higher activity against *Thermomyces lanuginosus* while compounds **67**–**72** acting towards *Chaetomium thermophilum* increased the amounts of reducing sugar. Other compounds tested showed a lethal activity against the fungi. In order to understand the relationship between structure and activity, it was found that the introduction of a pyrazin-3-yl-carboxmide moiety to 1,2,4-triazine (**67**) resulted in a much higher activity. Furthermore, phenolic groups at 5-, 6-position of the 1,2,4-triazine (**68**) gave better activity. A comparison of activity of compounds **69**, **70**, **71** and **72** revealed that they were more effective than the control. This enhanced activity is attributed to the presence of 4-chlorophenyl-5,6-diphenyl-1,2,4-triazine [48] and pyrazine [49] moieties.



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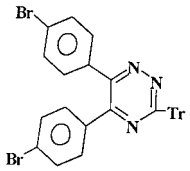

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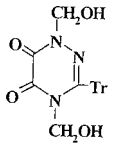

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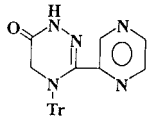
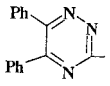


70

71

72 Ar: C_6H_4OH-4
Ar: C_6H_4Cl-4

Tr:



2.4. Use as antimicrobial agents

The antimicrobial agent **74** was obtained from fusion of the bis-compound **73** with p-chlorothiophenole (Scheme 10) [31].

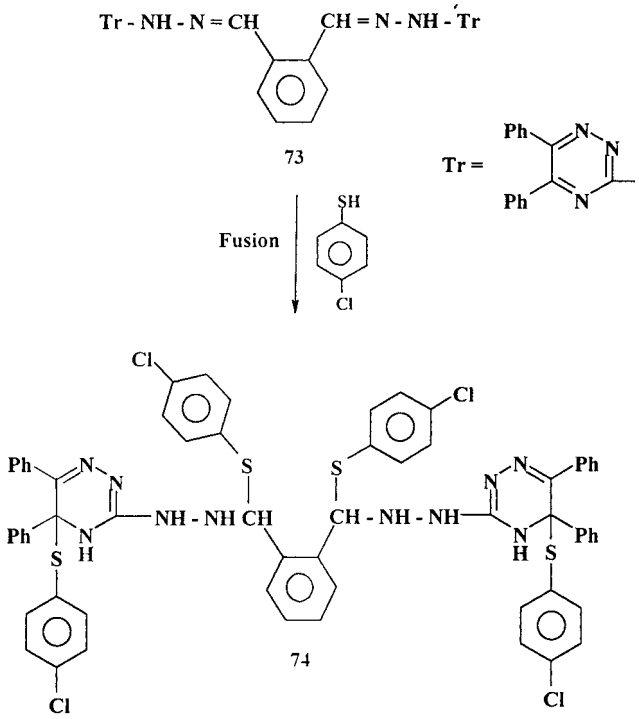
The antimicrobial and antihelminthic compounds **75** and **76**, also useful as dye intermediates, were prepared by reacting isatin and thiosemicarbazone with sodium hydroxide and subsequent alkylation (Scheme 11) [50].

Similarly, 1,2,4-triazines **78** (R^1, R^2, R^3 = H, C_{1-12} alkyl; R^4 = H′C_{1-24} alkyl, alkenyl, alkynyl; R^5 = H, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl) were prepared as pesticides (Scheme 12) [51]. Compound **80** killed 57.2% *Botrytis cinereain* in cucumber at 500 ppm [51].

In addition, 1,2,4-triazino[4,3-*a*]benzimidazol-4(10*H*) ones **81**, (R = H, Me, Ph, CH; X = H, Me, F) were obtained and used as antimicrobial agents [52] as well as substituted 10-methyl-1,2-dihydro-1-oxo-1,2,4-triazino[4,5-a]-indoles **82** (R = H, Cl, MeO, EtO; R′ = H, Me) [53].

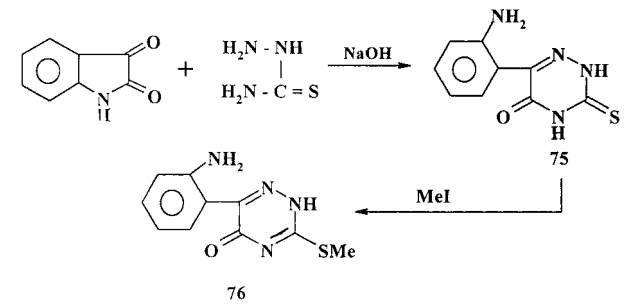
Antimicrobial fluorine containing 1,2,4-triazino[4,3-*a*]benzimidazol-4(10*H*)ones **85** were obtained from the reaction

Scheme 10

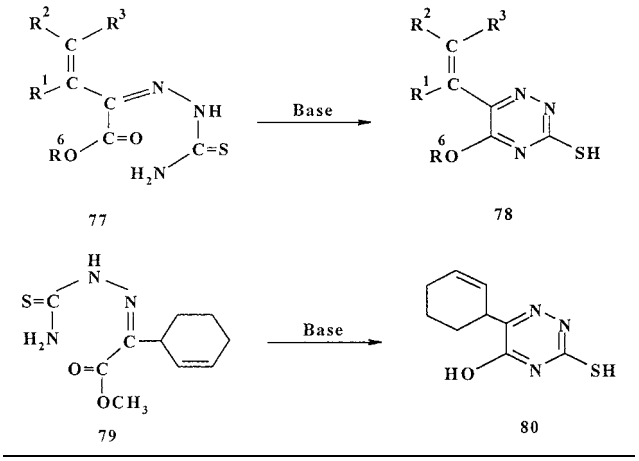


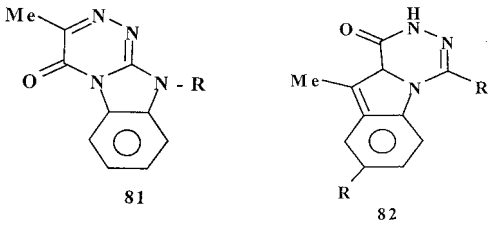
of 2-hydrazinobenzimidazole (**83**) with ethyl pyruvate in neutral medium followed by hydrolysis and cyclization (Scheme 13) [54].

Scheme 11

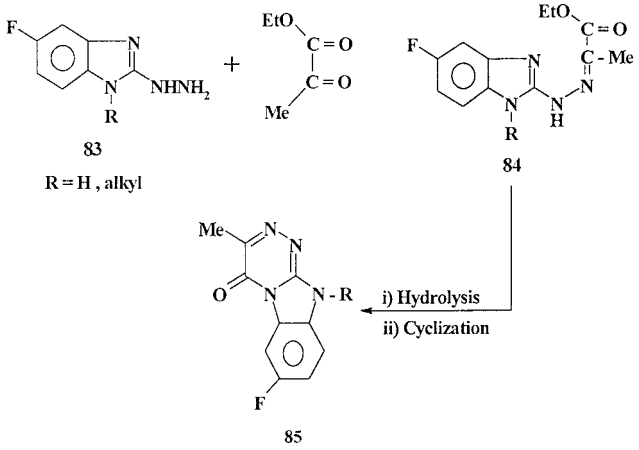


Scheme 12





Scheme 13

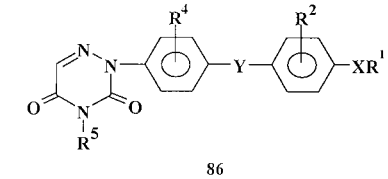


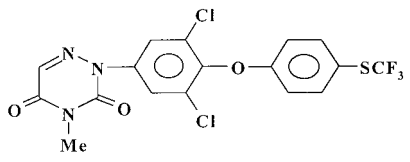
2.5. Use as agents against cocidosis (Protozoacides)

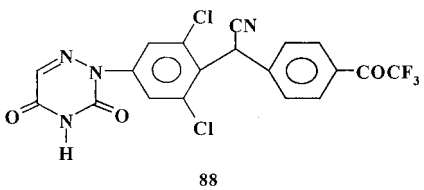
Fluorine containing 1,2,4-triazin-3,5-diones **86** and **87** have been obtained as protozoacides. Compounds **86** gave complete control of coccidosis in chicken at 50 ppm orally [55] as well as compound **88** [56].

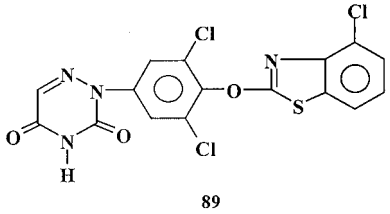
Some more 2-substituted-1,2,4-trazin-3,5-diones **89** were obtained as parasiticides; they gave 100% control of *Gyrodactylus arcuatus* in sticklebacks at 10 ppm [57].

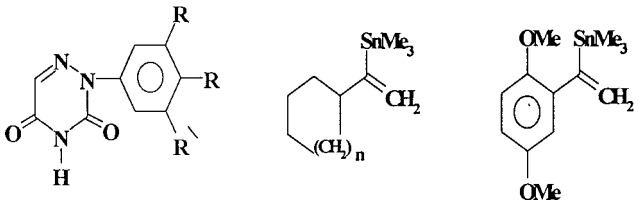
Palladium mediated coupling of 2-(4-iodoaryl)-1,2,4-trazin(2H, 4H)-3,5-diones **90** (R = R′ = Cl, R = CF_3, R′ = H)





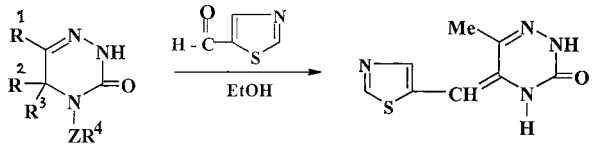




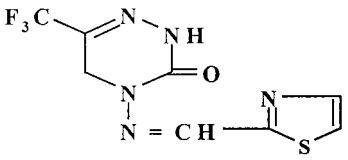


90 91 92

Scheme 14



90 94



95

with substituted vinylstannanes **91** and **92** has been tested. The triazines obtained had excellent *in vitro* anticoccidial activity [58].

N^4-Substituted-1,2,4-triazin-3-ones **93** ($R' = H$, substituted cycloalkyl, R^2, $R^3 = H$, alkyl, $R^4 =$ (substituted) 5 or 6-membered heterocycl, $Z = N:CH$, $NHCH_2$) have been obtained as insecticides and acaricides [59] (Scheme 14). Compound **94** gave complete control of *Aphis cracciuora* at 400 ppm [59].

Finally, 3-oxo-4-heterocycly-methylamino-1,2,4-triazines **95** were prepared by Josef et al. as insecticides and acaricides [60].

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