REVIEW

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Synthesis and chemistry of fluorine containing bioactive 1,2,4-triazines – an overview

Chemistry of uncondensed 1,2,4-triazines, part III

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Studies on the chemical reactivity of fluorine containing bioactive 1,2,4-triazines are reviewed. The synthesis, unique features and biological significance of these constituents are discussed.

1. Introduction

The great potential of uncondensed 1,2,4-triazines for medical and biological applications [1–19] led to the synthesis of several types of fluorine containing 1,2,4-triazines with enhanced biological activities. During the last few years a great deal of synthetic effort has been spent on 1,2,4-triazines, since the introduction of fluorine led to anti HIV and anticancer agents as well as antimicrobials with potential antifungal properties.

2. Synthesis of fluorine containing 1,2,4-triazines

A convenient and facile synthesis of 5-(trifluoromethyl)-1,2,4-triazines **1**–**3** was carried out upon treatment of 3-hydrazono-1,1,1-trifluoroalkan-2-ones and 3-(methyl-hydrazono)-1,1,1-trifluoroalkan-2-ones with several aldehydes in the presence of aq. NH$_4$OH to afford 5-(trifluoromethyl)-2,3-dihydro-1,2,4-triazines **1** which on oxidation gave 5-(trifluoromethyl)-1,2,4-triazines **2** and 5-(trifluoromethyl)-4,5-dihydro-5-hydroxy-1,2,4-triazines **3** (Scheme 1) [20].

The reaction of nitrile imines **4** (R = COMe, COPh, CO$_2$Me) with α-aminoesters **5** (R^2 = H, Me, CHMe$_2$, Ph, CH$_2$OH, PhCH$_2$) proceeds with no detectable racemization and constitutes a convenient synthetic route to 4,5-dihydro-1,2,4-triazin-6-ones **6** (Scheme 2) [21].
6-(1-Methyl-2-chloro-2,3,3-trifluorocyclobut-2-yl)-1,2,4-triazine-5-ones **8** (R^1 = NH$_2$, MeNH; R^2 = alkylthio, alkylamino, dialkylamino) were prepared as herbicides plant growth regulators desiccants and defoliants [22]. Thus, 2-(1-methyl-2-chloro-2,3,3-trifluorocyclobut-2-yl)-2-oxo-acetamide (**7**) was refluxed with thiocarbohydrazide in HCl to give **8** (R^1 = NH$_2$, R^2 = SH, Scheme 3).

Some new fluorine containing bioactive 1,2,4-triazines **12** derived from fluorinated isatine have been synthesized via condensation of isatines **9** (R: 5- or 6-F, 4-CF$_3$) with 2,3-diaminoquinazolin-4-one (**10**) followed by cyclization in AcOH (Scheme 4) [23].

The synthesis of 4,6-disubstituted-5-thioxo-1,2,4-triazin-3-one (**15**) has been deduced from the reaction of benzoylthioformanilide (**13**) with semicarbazide in AcOH to give semicarbazone **14** which cyclized on refluxing in pyridine (Scheme 5) [24].
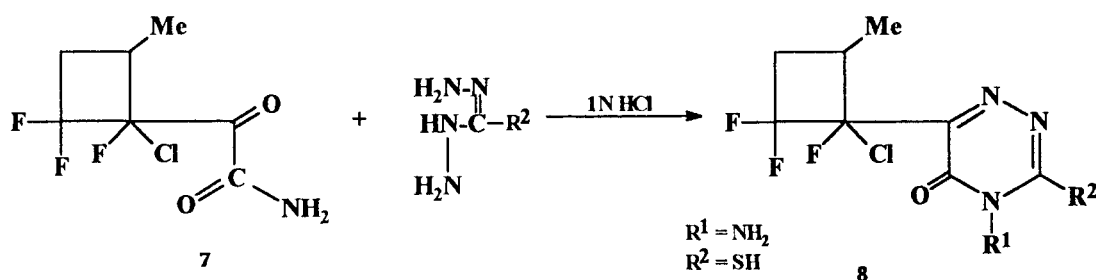
Scheme 1

Scheme 2

6

Scheme 3

$R^1 = NH_2$
$R^2 = SH$
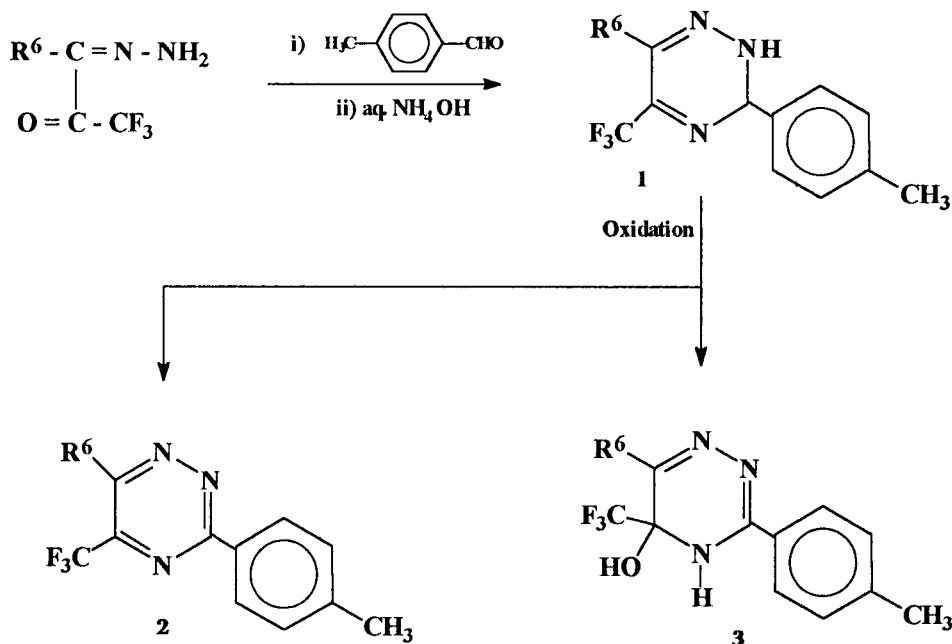
Scheme 4
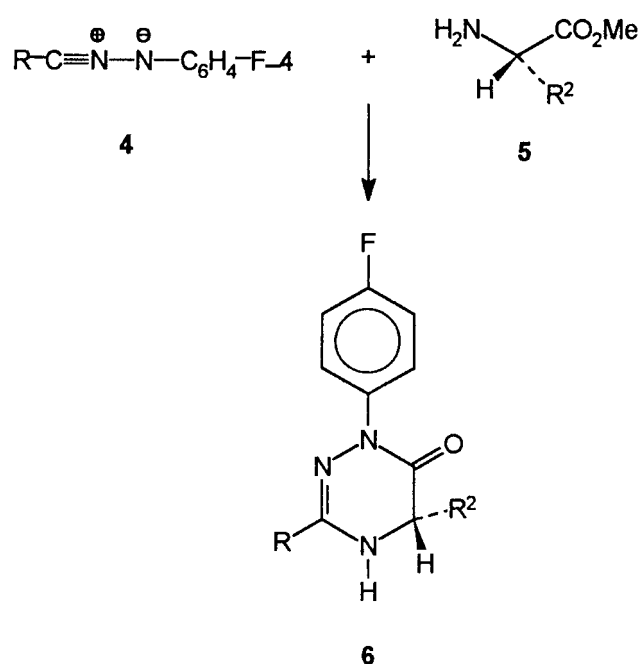
Fluorinated 1,2,4-triazin-3-thiones **17** (R = 4-FC$_6$H$_4$; 3-Cl-4F-C$_6$H$_3$) were prepared by condensation of RNHCSB$_z$ (R = 4-FC$_6$H$_4$; 3-Cl-4F-C$_6$H$_3$) with thiosemicarbazone in H$_2$O-EtOH in the presence of AcOH followed by cyclization of the intermediate **16** in EtOH in the presence of aq. NaOH (Scheme 6) [25].

Fluorine containing 1,2,4-triazines **18** and **19**, which can be used as drugs and agrochemicals were prepared from the corresponding amidazones hydrochlorides and alkyl trifluoropyruvate in Et$_3$N/MeOH under mild conditions (Scheme 7) [26].

Fluorine containing 1,2,4-triazino[4,3-a]benzimidazol-4-(10H)ones **22** were obtained by the reaction of 2-hydrazinobenzimidazole (**20**) with ethyl pyruvate in neutral medium followed by hydrolysis and cyclization. These compounds display promising antibacterial and antifungal activities (Scheme 8) [27].

Useful as insecticides and acaricides, 3-oxo-4-(thiazol-2-yl-methyleneimino)-2,3,4,5-tetrahydro-6-trifluoromethyl-1,2,4-triazines **26** were prepared [28]. Thus, chloroacetone was added to a mixture of 5-trifluoromethyl-1,3,4-oxadiazol-2(3H)-one (**23**) and NaH in DMF and stirred at room temperature to give the acetone derivative **24** which reacted with N$_2$H$_4$ to give 2,3,4,5-tetrahydro-3-oxo-4-amino-
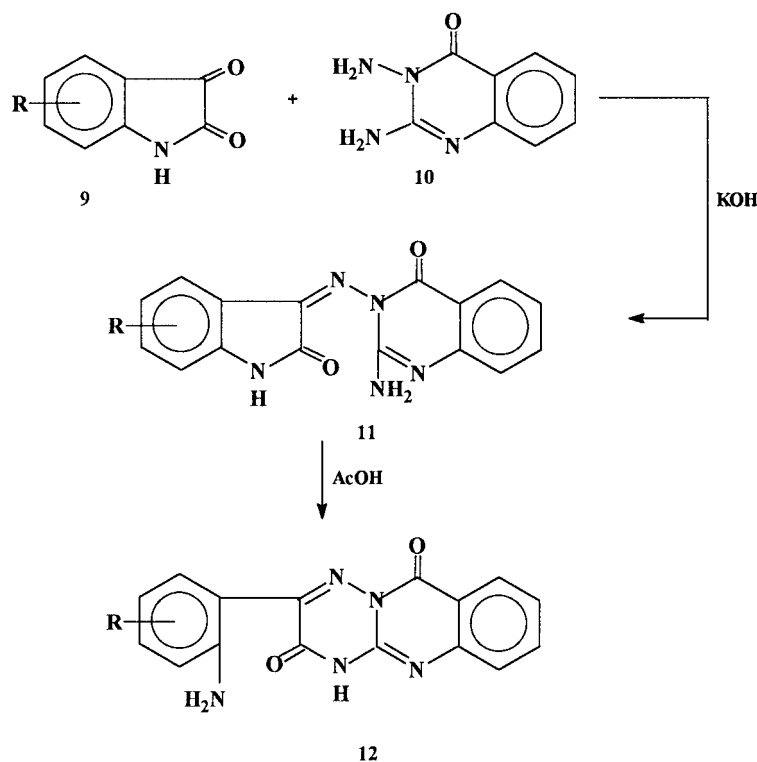
Scheme 5
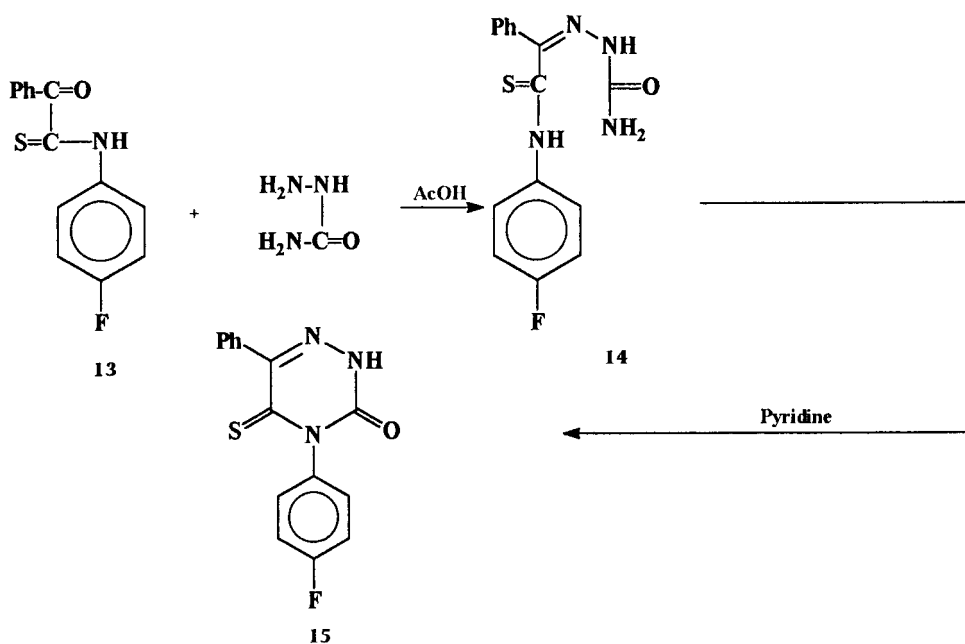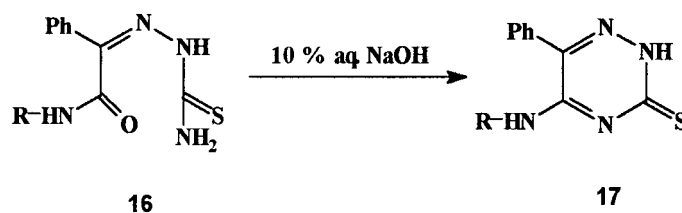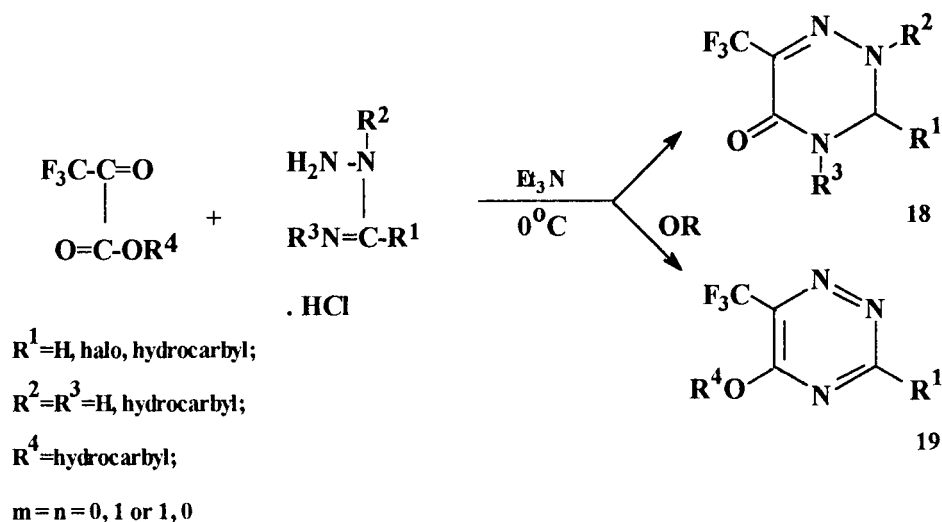

Scheme 6

Scheme 7

R^1=H, halo, hydrocarbyl;

R^2=R^3=H, hydrocarbyl;

R^4=hydrocarbyl;

m = n = 0, 1 or 1, 0

6-(trifluoromethyl)-1,2,4-triazine (**25**) which was condensed with 2-formylthiazole in ethanol to give **26** (Scheme 9) [28].

Antiinflammatory active, fluorinated 4 *H*-(1,2,4)-triazino [3,4-*c*](1,4)-benzoxazines **29** were obtained by alkylation of benzoxazinone **27** with fluorinated phenacyl bromide to give **28** which cyclized with N$_2$H$_4$ to give **29**. Some of these compounds possess significant antiinflammatory activity against carrageenin induced rat paw edema (Scheme 10) [29].

A complete substitution of the halogen atoms in 1,2,4-triazine **30** by fluorine atoms was achieved with potassium fluoride at high temperature [30]. Thus, 3,5,6-trifluoro-1,2,4-triazine (**31**) and 3,5-difluoro-6-chloro-1,2,4-triazine (**32**) were obtained by the treatment of **30** with KF at 450 °C. 3,5,6-Trifluoro-1,2,4-triazine (**31**) is more reactive towards nucleophilic reagents. When treated with methanol at room temperature, it gives a mixture of 5,6-dimethoxy-3-fluoro-1,2,4-triazine (**33**) and 3,5-dimethoxy-6-fluoro-1,2,4-triazine (**34**) in the ratio 2 : 1.
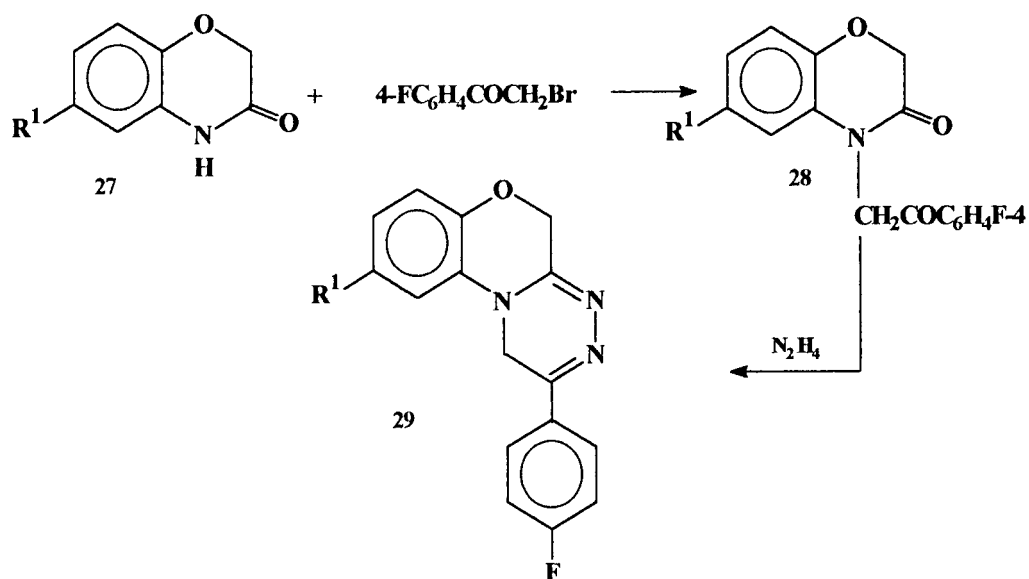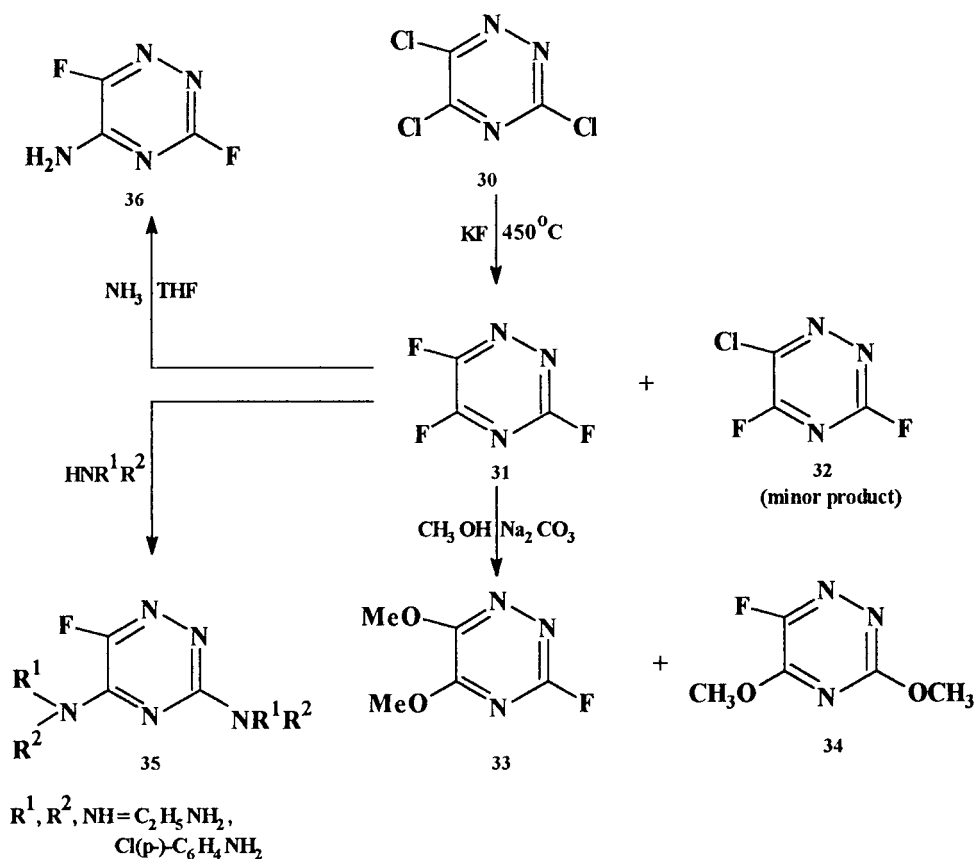
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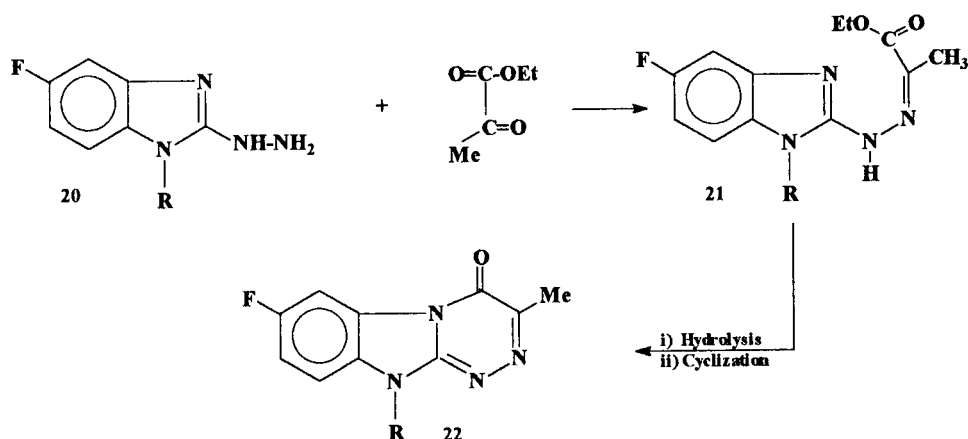
Scheme 9
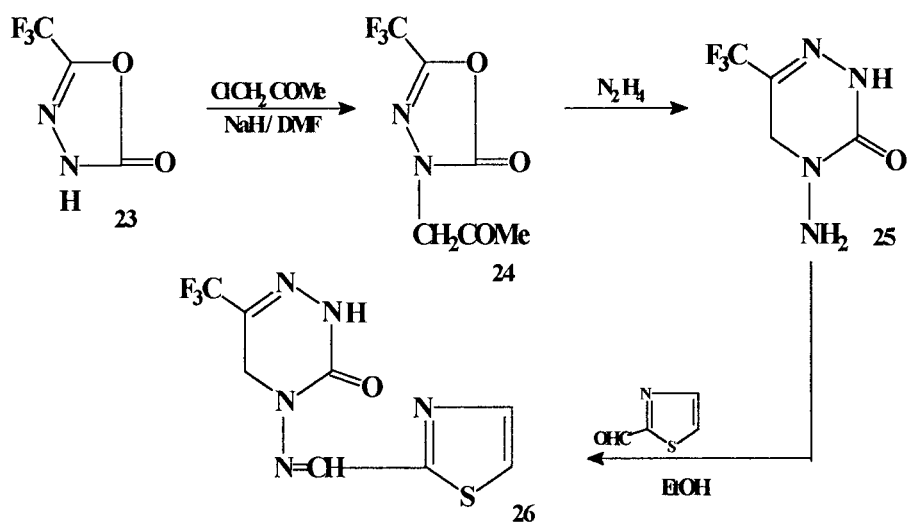
Scheme 10
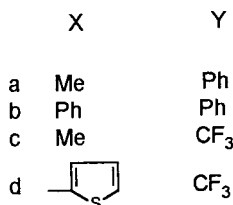

Reaction of **31** with diethylamine and p-chloroaniline results in 3,5-diamino derivatives **35**, while 3,6-difluoro-5-amino-1,2,4-triazine (**36**) was formed on passing ammonia through the solution of triazine **31** in THF (Scheme 11) [30].

In a search for new anticancer and anti AIDS agents, the fluorine bearing 3-thioxo-1,2,4-triazin-5-one (**38**) was obtained via acylation of 3-thioxo-6-(2-aminophenyl)-1,2,4-triazin-5(2 H, 4 H)-one (**37**) with ethyl trifluoroacetate (Scheme 12) [7].

Scheme 11

R^1, R^2, NH = C$_2$H$_5$NH$_2$,
Cl(p-)-C$_6$H$_4$NH$_2$

Scheme 12

|	X	Y
a	Me	Ph
b	Ph	Ph
c	Me	CF$_3$
d	thiophene	CF$_3$

64
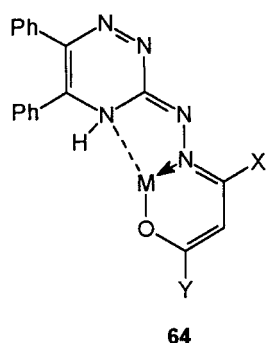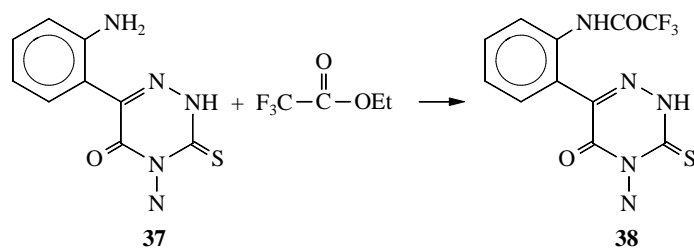
Some new bioactive fluorine bearing 3-thioxo-1,2,4-triazin-5-one derivatives have been synthesized [7]. Thus, alkylation of **38** with chloroacetylated urea in ethanolic NaOH gave 2-(6-aryl-1,2,4-triazin-5-one-3-yl-thio)-N[(alkyl/phenyl)aminocarbonyl]acetamides **39** which on treatment with acetyl bromide in sodium ethoxide afforded hetero-thioether **40**. Also, addition of excess RNCS to **38** yielded the thiocarbamido derivative **41**. Methylation of **38** using MeI in aqueous KOH gave the 2,4-dimethyl-1,2,4-triazin-

85

84

92 A

92 B
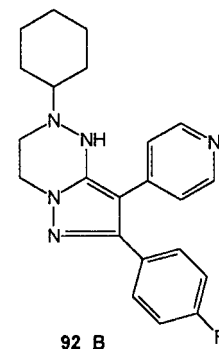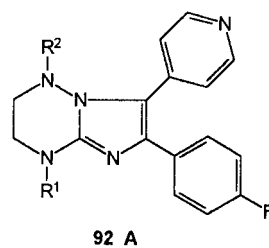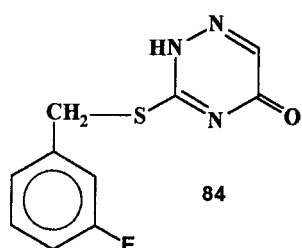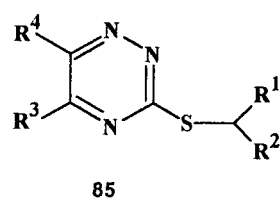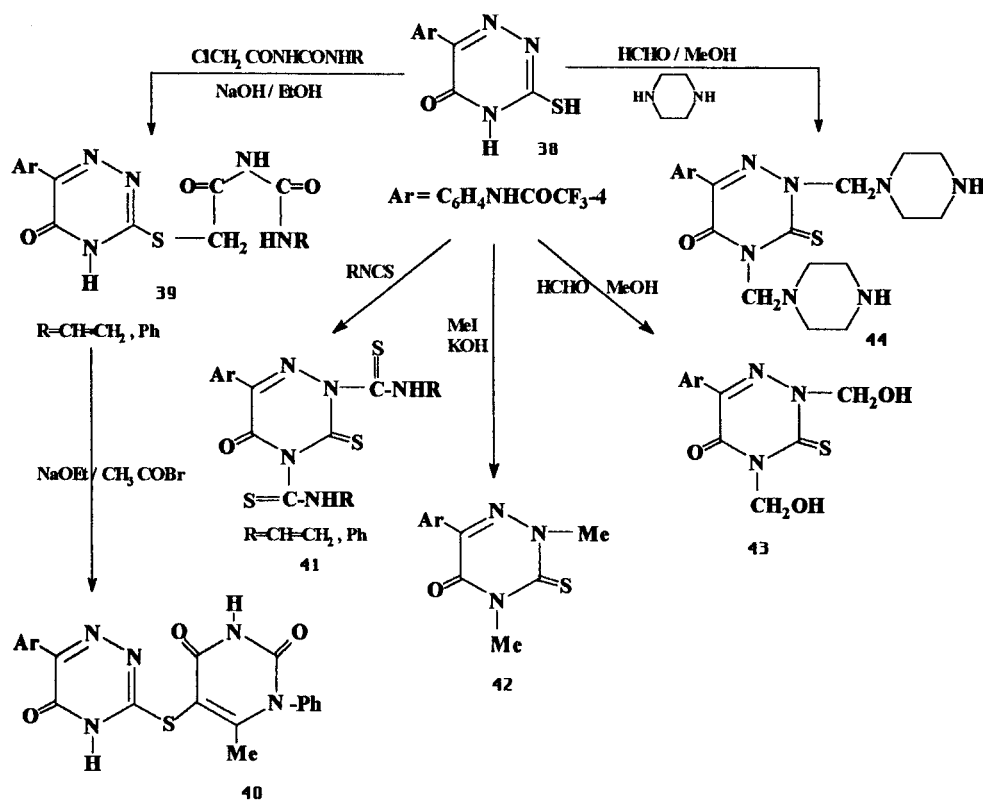
Scheme 13

Scheme 14
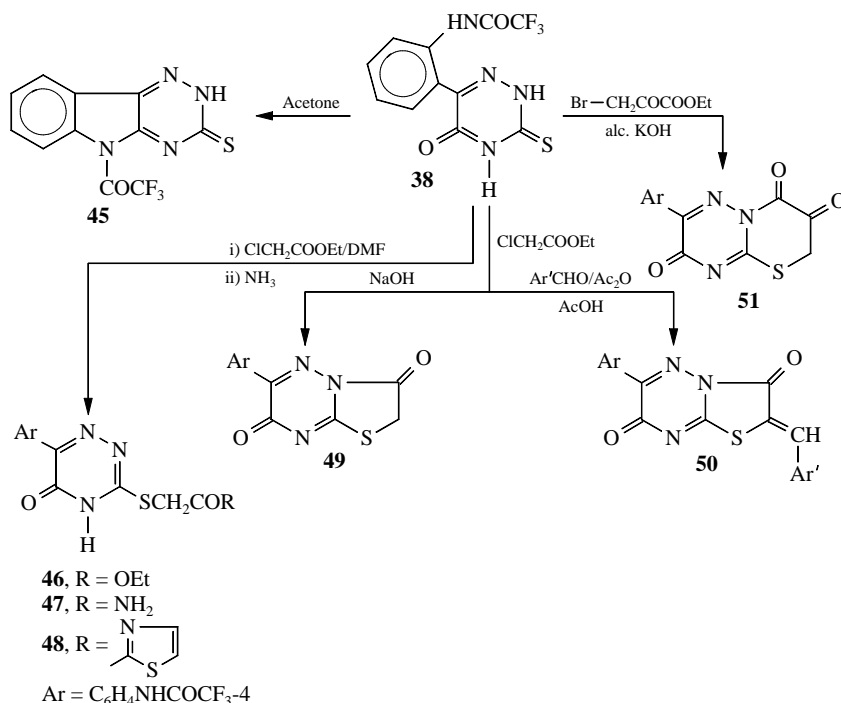
5-one derivative **42**. Also, addition of HCHO in MeOH to **38** furnished 2,4-di(hydroxymethyl)-1,2,4-triazin-5-one (**43**) while treatment of **38** with HCHO−MeOH in the presence of piperazine yielded the Mannich bases **44** (Scheme 13) [7].

5-Ttrifluoroacetyl-3-thioxo-1,2,4-triazino[5,6-*b*]indole (**45**) was obtained by refluxing **38** in dry acetone. Reaction of **38** with ethyl chloroacetate in DMF followed by aminoly-

sis yielded the acetamide **47**, while refluxing of **38** with monochloroacetic acid in NaOH afforded thiazolo[3,2-*b*]-[1,2,4]triazin-3,7-dione (**49**). The latter reaction when carried out in the presence of ArCHO/Ac₂O yielded 2-arylidene-6-arylthiazolo[3,2-*b*][1,2,4]triazin-3,7-dione (**50**). Finally, alkylation of **38** using ethyl bromopyruvate in basic medium gave 7-aryl-2*H*-thiazino[3,2-*b*][1,2,4]triazino-3,4,8-trione (**51**) (Scheme 14) [7].

Scheme 15

Scheme 16

Scheme 17

61   62(R = Me, CF₃)

Scheme 18

63

(Ca–d)

X : Me, Ph, Me, C₄H₃S-2
Y : Ph, Ph, CF₃, CF₃

Scheme 19

65   66
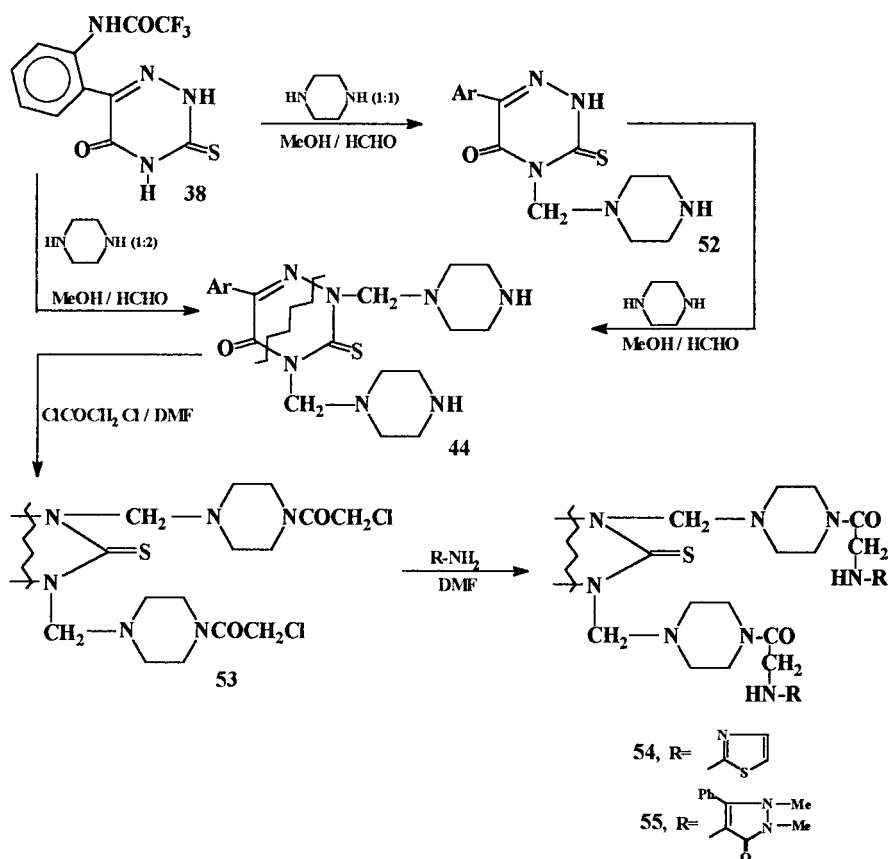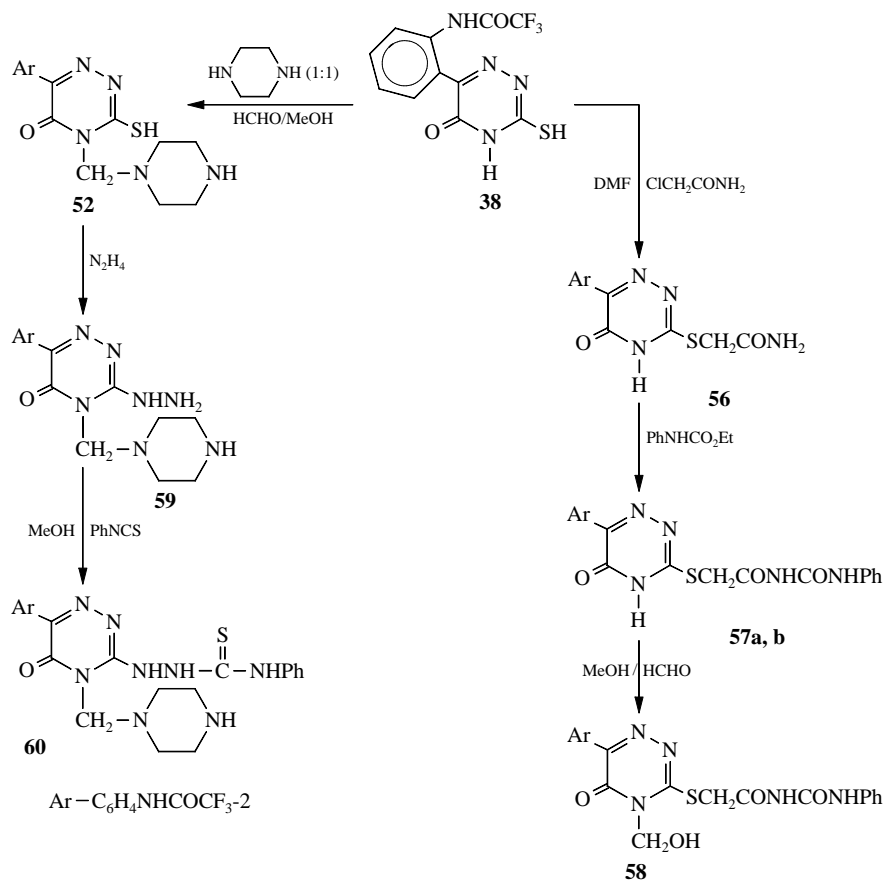
In continuation of a previous work in the area of biologically active 3-thioxo-1,2,4-triazin-5-one derivatives [7], the synthesis of fluorine bearing trisubstituted 3-thioxo-1,2,4-triazin-5-ones and evaluation of their anticancer activity has been reported [8]. Thus, the Mannich base derivatives **52–55*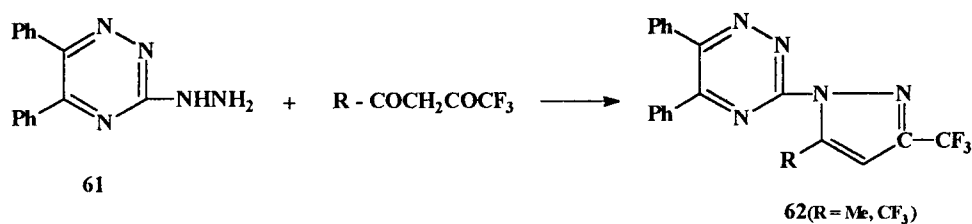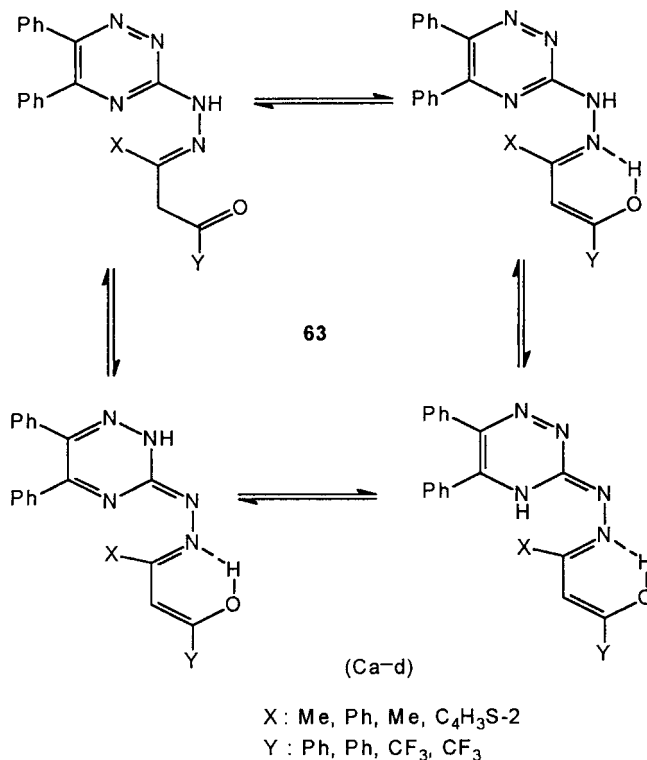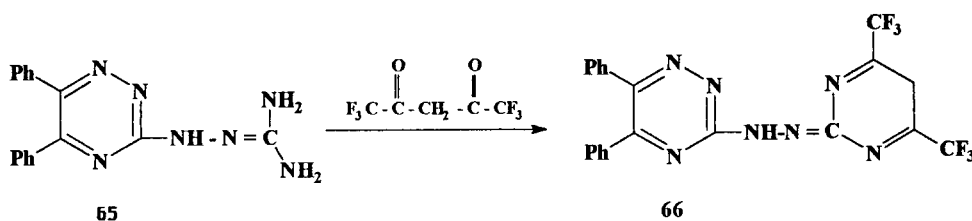* were obtained by the treatment of compound **38** with HCHO/MeOH in piperazine followed by acylation using chloroacetyl chloride and amination of the product (Scheme 15) [8].

In vitro anticancer testing of compounds **40–44** was reported where compound **44** showed [7] activity against some cancer cells such as Lukemia/Lymphoma, Small/Non Small Cell Lung. The biological screening results of the present studies indicate that the introduction of a piperazine moiety into fluorinated 3-thioxo-1,2,4-triazin-5-one causes an improvement in activity [7, 8].

The action of some nitrogen compounds on compound **38** was also reported. Thus, treatment of **38** with chloroacetamide in DMF resulted in the S-alkyl derivative **56** which in reaction with *N*-ethoxycarbonylaniline in dry benzene gave the *N*-[(6,2'-trifluoroacetamido)phenyl-1,2,4-triazin-5-one-3-yl)thiomethylcarbonyl-*N'*-phenylurea **57**. The *N*-hydroxymethyl derivative **58** was also obtained by treatment of **57** with HCHO in MeOH. The analog **60** was obtained from hydrazinolysis of **52** followed by addition of PhNCS in MeOH (Scheme 16) [8].

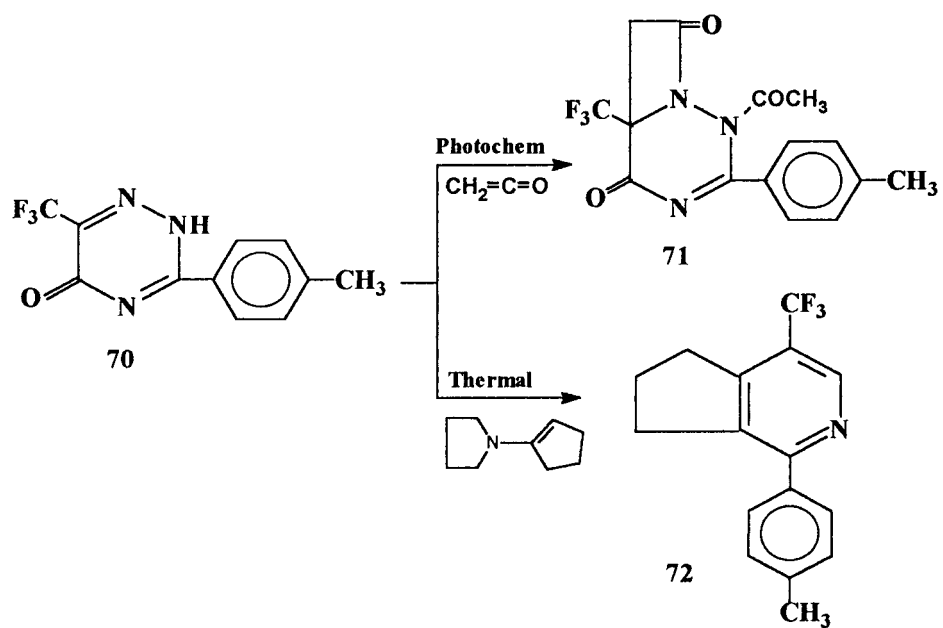Abdel-Rahman synthesized the antimicrobial fluorinated pyrazoles **62** via cyclocondensation of **61** with fluorinated acetylacetone in absolute ethanol (Scheme 17) [2].

Also, fluorinated hydrazonotriazines **63** and **64** were obtained and used for the analytical determination of Ni(II), Co(II), Zn(II), Mn(II), Cd(II), Fe(III), UO₂(II) and Ln(III)
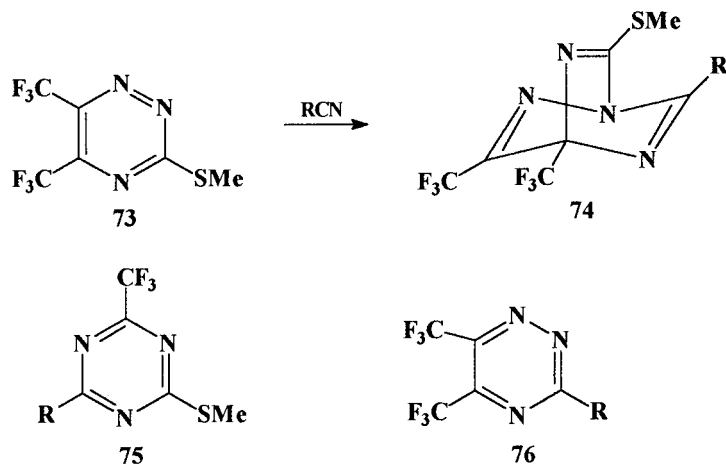
Scheme 20
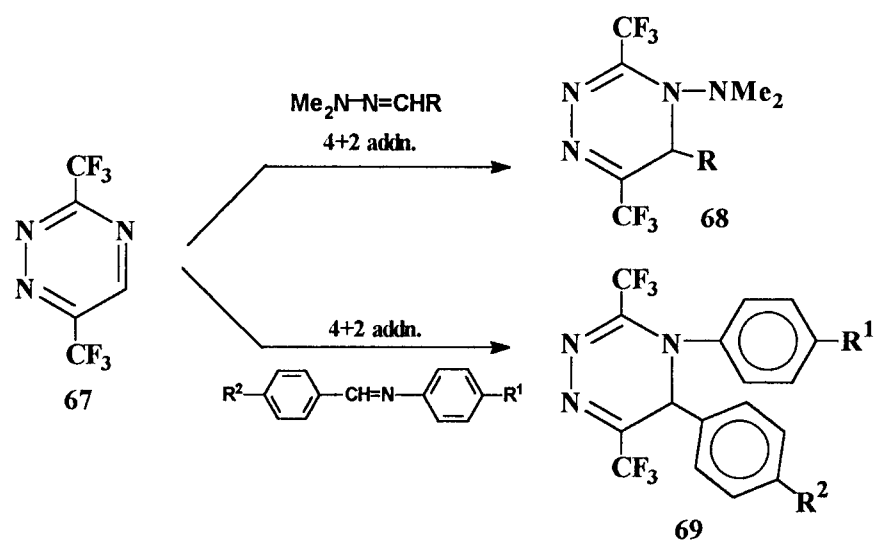
Scheme 21

Scheme 22

[15, 17]. The presence of a strong withdrawing group, as in **63** and **64** ($-CF_3$), makes the ligands behave as diprotic bidentate (ON) donors towards different metal ions [15, 17].

The coordination sites in **64a**–**d** ligands are enolic oxygen and nitrogen atoms of azomethine and triazine groups. The most probable chelation of these ligands are shown as:

Finally, the hexafluoropyrimidine derivative **66** was produced by treatment of the aminoguanidine derivative **65** with hexafluoroacetylacetone (Scheme 19) [1].

3. Chemistry of fluorine containing 1,2,4-triazines

Electron-rich carbon-nitrogen double bonds act as hetero-dienophiles towards 3,6-bis(trifluoromethyl)-1,2,4-triazine (**68**). Thus, the electron-rich C=N bonds of $Me_2NN:CHR$ (R = H, Ph, 4-MeOC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$, CH=NNMe$_2$) and of 4-R^{1}C$_6$H$_4$N=CHC$_6$H$_4$R^2-4 (R = H, NMe$_2$, R^2 = NMe$_2$; R^1 = R^2 = OMe) are effective dienophiles towards the electron-deficient-cis-azine system in the title compounds (Scheme 20) [31].

Katagiri et al. studied the role of the CF$_3$-group in photo and thermal cycloaddition of 1,2,4-triazines with olefins. Thus, photochemical [2 + 2] cycloaddition of **70** with ketene gave the azetidine derivative **71**, while thermal [4 + 2] cycloaddition of **70** with 1-pyrrolidinocyclopentane led to the formation of **72** (Scheme 21) [32].

Also, the reactivity of cyanamides toward electron-acceptor substituted 1,2,4-triazines was studied [33]. Thus, cycloaddition of RCN (R = Me$_2$N,1-pyrrolidinyl, piperidino, morpholino) exclusively across C$_5$/N$_2$ of the 1,2,4-triazine nucleus **73** yielded the bicyclic compound **74** as an intermediate. Elimination of trifluoroacetonitrile leads to the formation of 1,3,5-triazines **75** as the main reaction products, the minor products, 1,2,4-triazines **76** were formed by loss of Me thiocyanate (Scheme 22).

Similarly, the use of cyanamide as side chain dienophile in the intramolecular [4 + 2]-cycloaddition with fluorinated 1,2,4-triazines has been reported [34]. The (2-cyano-amino)ethoxytriazine **77** did not undergo intramolecular cycloaddition on heating but rearranged to the triazinone **78**. Its isomers 1,2,4-triazine **79** underwent intramolecular cycloaddition followed by elimination of N$_2$ to give the pyrazinooxazine **80** (Scheme 23).

Methods for the preparation of fluorinated oxime ethers [(heteroaryloxy)oximino-benzene acetates] and their use as agrochemical fungicides are reported [35].

Methyl(E)-O-methyl-α-(2-phenoxyphenyl)-α-oximinoacetate (**81**) was treated with 3-(methanesulfonyl)-5-[(trifluoromethyl)phenyl]-1,2,4-triazine (**82**) to give Me(E)-O-methyl-α-[2-[(5-[3-(trifluoromethyl)phenoxyl]-1,2,4-triazin-3-yl]oxy]phenyl-α-oximinoacetate (**83**) (Scheme 18) [35].

A fungicidal formulation contains **83** (10%) benzyl alcohol (30%), Ca dodecylbenzenesulfonate (5%), nonylphenyl ethoxide (10%), and alkylbenzenes (45%) [35].

Scheme 23
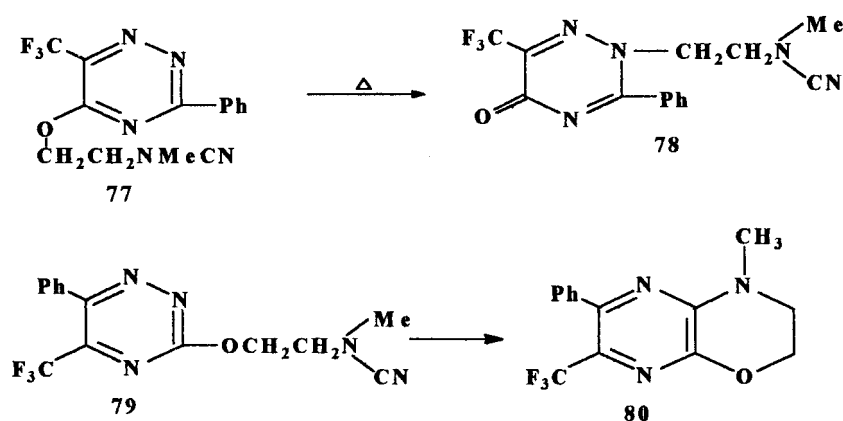
Scheme 24

Scheme 25

86

MeI/ NaH
MgSO$_4$

87
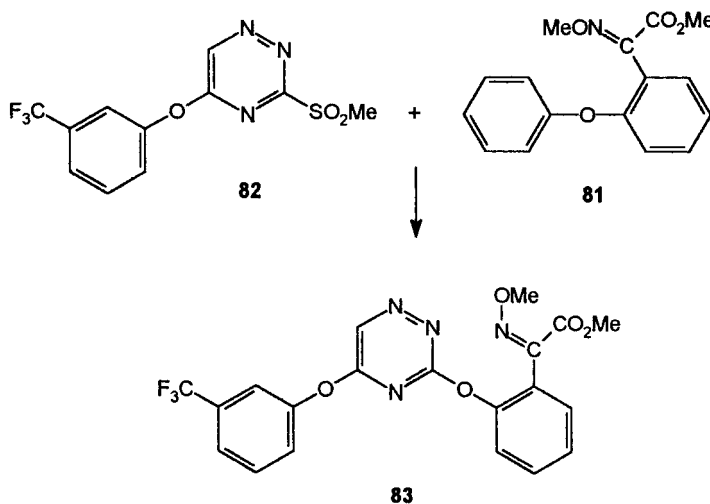
[X= O, S ; Y= O, S, CO, CH(OH), R^3= CN ;
R^1= haloalkyl, R^2= H, halo, haloalkyl ; R^3= H, alkyl ;
R^4= R^2, alkyl ; R^5= H, (halo) alkyl, aralkyl, alkynyl]

The mercaptotriazines **85** known as herbicides (R^1 = alkenyl, cycloalkyl, Ph, benzyl, naphthyl, R^2 = H, alkyl; R^3 = alkoxy, benzyloxy, cyanoalkoxy; R^4 = H, alkyl alkoxy, Ph) are prepared from the corresponding 1,2,4-triazine. Thus,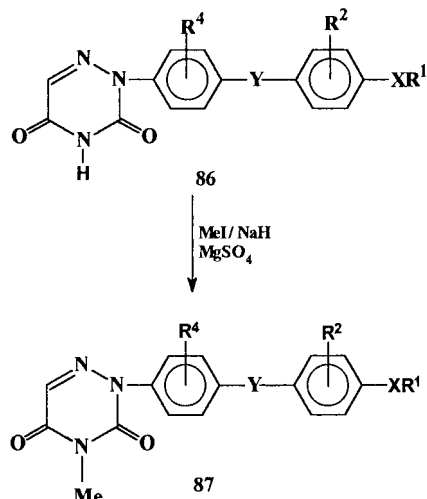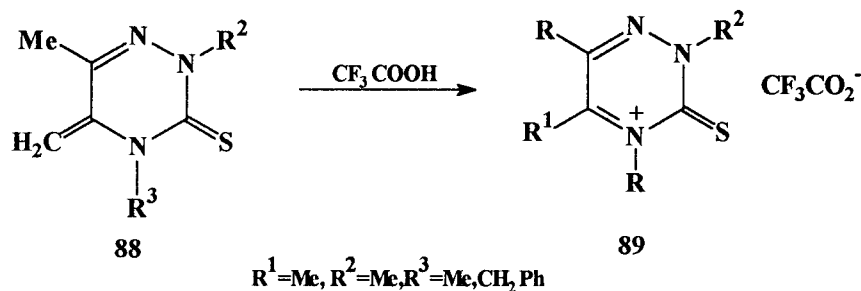 3-[(*m*-fluorophenyl)methylthio]-1,2,4-triazin-5(2 H)-one (**84**) in THF with CH$_2$N$_2$ in Et$_2$O at room temperature for 1 h to gives 3-[(*m*-fluorophenyl)methylthio]-5-methoxy-1,2,4-triazine (**85**). Compound **85** [R^1 = *o*-methylphenyl, R^2 = R^4 = H, R^3 = MeO] at 1.0 kg/ha showed 90–100% control of *Scirpus juncoides* [36].

Fluorine containing 1,2,4-triazin-3,5-diones **87**, useful as protozoacids, were obtained by alkylation of **86** using MeI/NaH in MgSO$_4$ (Scheme 25). Administration of **86** at a dose of 50 ppm orally in chickens gave complete control of coccidosis [37].

Treatment of 1,2,4-triazin-3-thione derivatives **88** with CF$_3$CO$_2$H afforded the thiotriazinium cations **89** (Scheme 26) [38].

1-Ethyl-3-(alkylthio)-5-phenyl-1,2,4-triazinium tetrafluoroborate (**90**) (R = Me, PhCH$_2$) underwent an unusual dimerization on treatment with Et$_3$N in MeOH or EtOH to give 4a,4b,9,10-tetrahydro-1,3,6,8,8a,10a-hexaazaphenanthrenes **91** (Scheme 27) [39].

Scheme 26

88

CF$_3$COOH

89   CF$_3$CO$_2^-$

R^1=Me, R^2=Me, R^3=Me, CH$_2$ Ph

Scheme 27

90

Et$_3$N
Alcohol

91

Scheme 28

93

X= 5-F, 6-F, 7-F, 8-F

aq. K$_2$CO$_3$

94

ClCH$_2$CH$_2$NR$_2$·HCl
NaOH

95
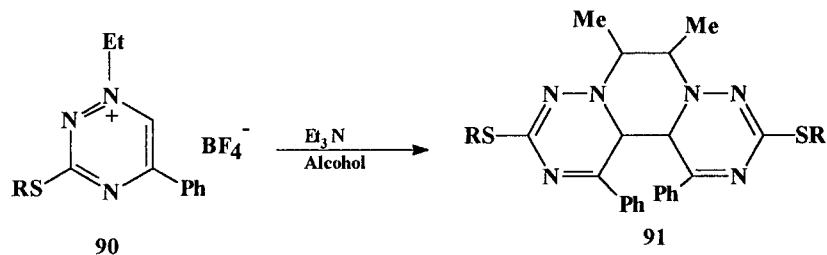
6-(4-Fluorophenyl)-7-(4-pyridyl)-1,2,3,4-tetrahydroimid-azolo[1,2-*b*][1,2,4]-triazines **92A** (R^1 = R^2 = H; R^1 = R^2 = acyl) have been prepared and tested as inhibitors of interleukin-1 and tumor necrosis factor, **92** (R^1 = R^2 = H) had an IC$_{50}$ for inhibition of interleukin 1 of $1.3-1.5 \times 10^{-7}$ M [40].

In addition, pyrazolo[5,1-*c*][1,2,4]triazines with interleukin-1 and tumornecrosis factor inhibitor activity were studied [41].

Thus, 2-cyclohexyl-7-(4-fluorophenyl)-8-(4-pyridinyl)-1,2,3,4-tetrahydropyrazolo[5,1-*c*][1,2,4]triazine (**92B**) was prepared [41]. It demonstrated an IC$_{50}$ of 8.8×10^{-8} M against the production of interleukin-1.
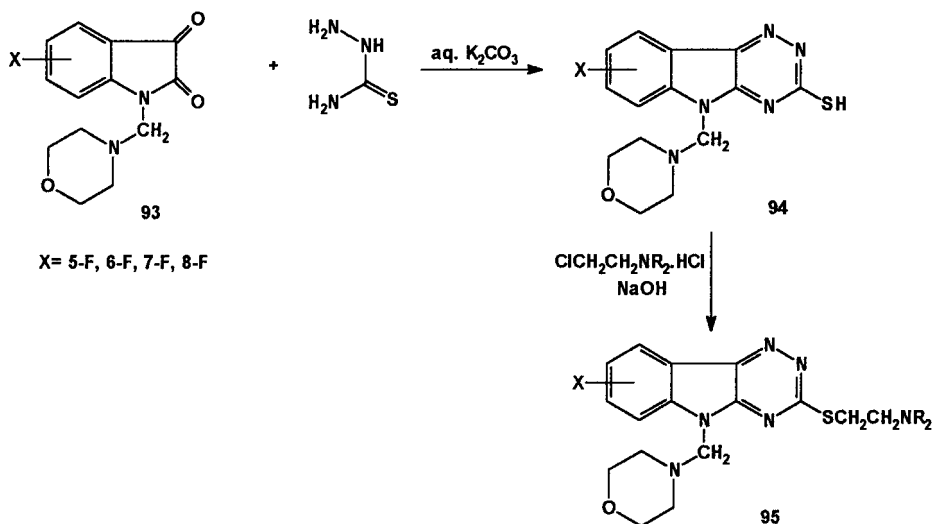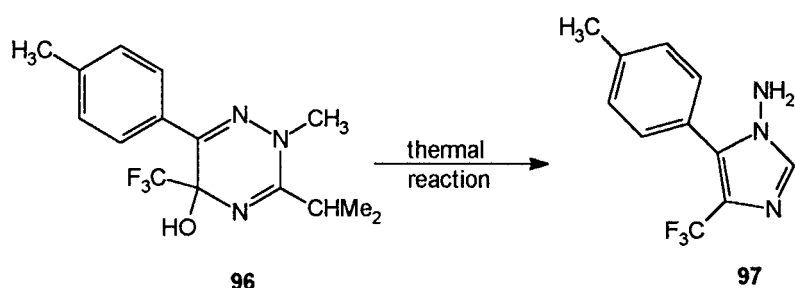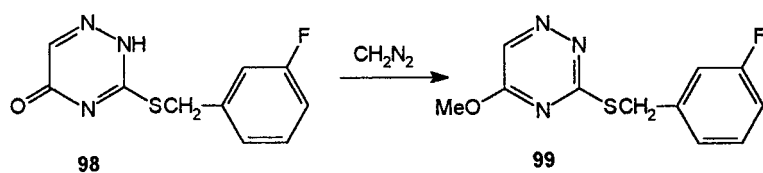
A series of new antibacterial, fungicidal and antiviral fluorine containing 3-dialkyl-aminoethylthio-5-morpholino-methyl[1,2,4]triazino[5,6-*b*]indoles **95** were obtained by the treatment of different 1-dialkylamino-2-chloroethane hydrochlorides with fluorinated 5-morpholonomethyl[1,2,4]-triazino[5,6-*b*] indole-3-thiones **94** in the presence of sodium hydroxide (Scheme 28) [42].

Thermal reaction of 5-(trifluoromethyl)-2,3-dihydro-1,2,4-triazines **96** afforded 1-amino-4-(trifluoromethyl)imidazoles **97** (Scheme 29) [20].

The introduction of a fluorine atome in 1,2,4-triazine moieties led to enhanced bioactive properties particularly as herbicides [43–45]. Thus, 3-[(3-fluorophenyl)methylthio-

Scheme 29

Scheme 30

Scheme 31

Scheme 32

1,2,4-triazin-5($2H$)one (**98**) in THF with CH_2N_2 in Et_2O at room temperature for 1 h gave 3-[(3-fluorophenyl)methylthio]-5-methoxy-1,2,4-triazine (**99**) (Scheme 30) [43]. Compound **99** at a dose of 1.0 kg/ha showed a 90–100% control of *Scirpus juncoides* [43].

Also, the propynylquinolinyltriazine dione **101** was obtained from the interaction between $3,4\text{-}F_2C_6H_3NO_2$ with the nitrophenylpropionate **100** (Scheme 31). Compounds **100** and **101** are used as herbicides [44].

Herbicides containing 6-substituted-3,5-diphenyl-1,2,4-triazines (**105**, R^1 = H, halo, lower haloalkyl; R^2 = halo, lower haloalkyl; R^3 = lower haloalkyl) have been prepared [45]. 1,2,4-Triazines **104** and 1,2,4-triazine-N-oxides **103** (R^1, R^2, R^3 = same as above) are synthetic intermediates for **105**. Thus, 5-(3-chlorophenyl)-3-(4-fluorophenyl)-1,2,4-triazine (**102**) was heated with AcOH and aq. H_2O_2 at 90–95 °C for 5 h to give 5-(3-chlorophenyl)-3-(4-fluorophenyl)-1,2,4-triazine-1-oxide (**103**), which was refluxed with $POCl_3$ with stirring for 5 h to give 6-chloro-5-(3-chlorophenyl)-3-(4-fluorophenyl)-1,2,4-triazine (**104**). Compound **104** was treated with 1,4-dioxane and aq. $EtNH_2$ at 150 °C for 2 h to give **105** (R^1 = 4-F, R^2 = 3-Cl, R^3 = Et) (Scheme 32). Preemergence application of 2000 gV/ha ∼70% controlled *Echinochloa crus-galli* and *Lpomoea purpurea,* vs. ∼30% and 0%, respectively for amitrole [45].

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