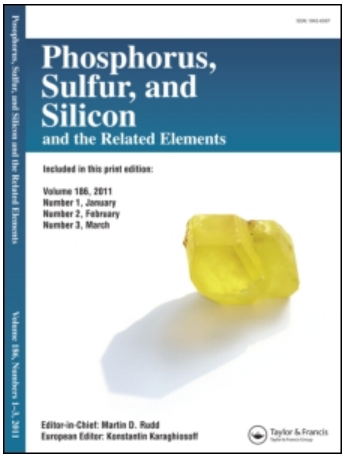

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CHEMISTRY OF UNCONDENSED 1,2,4-TRIAZINES: PART II-SULFUR CONTAINING 5-OXo-1,2,4-TRIAZIN-3-yl MOIETY AN OVERVIEW

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CHEMISTRY OF UNCONDENSED 1,2,4-TRIAZINES: PART II-SULFUR CONTAINING 5-OXo-1,2,4-TRIAZIN-3-yl MOIETY

AN OVERVIEW

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Studies on the chemical constituents of sulfur containing the 5-oxo-1,2,4-triazin-3-yl moiety are reviewed. The synthesis, unique features of the structures and biological significance of these constituents are discussed.

Keywords: Sulfur-1,2,4-triazinone; Chemical constituents; Biocidal

INTRODUCTION

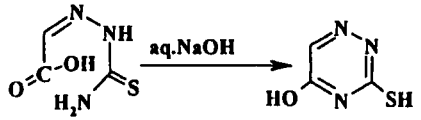
The purpose of this review is to present highlights of the synthesis and chemistry of sulfur-containing 5 -oxo-1,2,4-triazinthione systems with particular reference to biological activities during 1986 to 1996 in view of our investigations of the interested area from the point of view biocidal effect such as biocatalytic[1], anticancer, anti HIV[2–7], antimicrobial[8], center nervous system[9], antivirusce[10], antihelminthic[11], antiinflammatory[12], antifungal infection[13], pesticides[14], antibacterial[15] and as herbicides[16–20].

* Corresponding Author.

SYNTHESIS OF 3-THIOXO-1,2,4-TRIAZINE-5-ONE DERIVATIVES

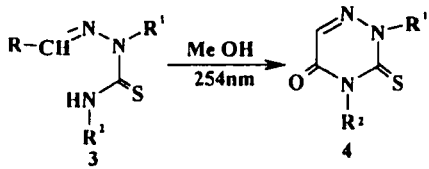
A) From thiosemicarbazides

A facial synthesis of 3-mercapto-5-hydroxy-1,2,4-triazine (**2**) was sited via basic cyclization of thiosemicarbazone[21] **1**.



1 **2**

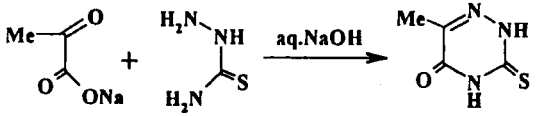
Photochemical cyclization of some aldehyde thiosemicarbazones **3** in MeOH at 254nm furnished[22] 3-thioxo-1,2,4-triazin-5-ones (**4**).



3 **4**

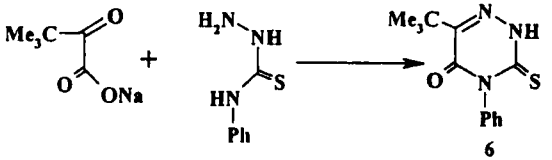
R:CO_2Me, Bz, Me, Ph
R¹,R²:H, Me, Ph

Slouka et., al[23]., reported a simple method for preparation of high purity of 5-substituted-6-azauraciles (**5**) by the heating sodium pyruvate with thiosemicarbazide in diluted NaOH.



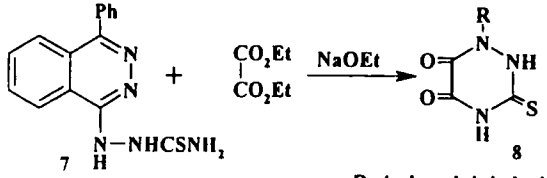
5

Similarly, agrochemical fungicides[24] 4,6-disubstituted-3-thioxo-1,2,4-triazin-5-one (**6**) have been occured from cyclocondensation of N^4-phenylthiosemicarbazide with trimethyl sodium pyruvate.



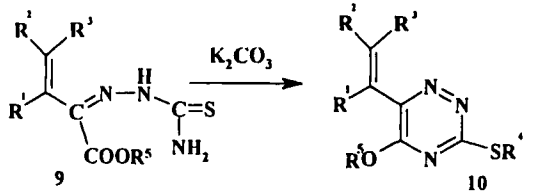
6

Some new fungicidal 1-substituted-3-thioxo-1,2,4-triazin-5,6-dione (**8**) were obtained by the interaction of N^1-substituted thiosemicarbazide (**7**) with diethyl oxalate in an alkaline medium[25].



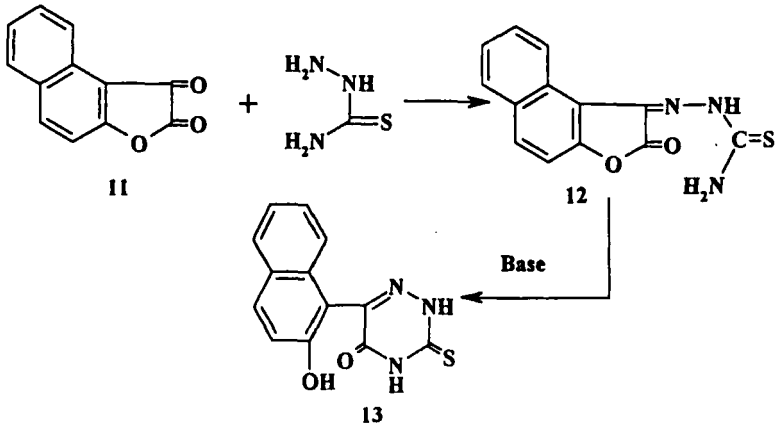
R=4-phenylphthalazin-1-yl

Hirai et., al[26]., prepared 3-substitutedmercapto-5-alkoxy-1,2,4-triazines (**10**) as pesticides via the reactions of oxo-carboxylic acids with thiosemicarbazide followed by cyclization of thiosemicarbazone **9** in the presence of base or acid. These compounds at 500ppm showed a 57.2% killed against Botrytis cinerea in cucumber[26].



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

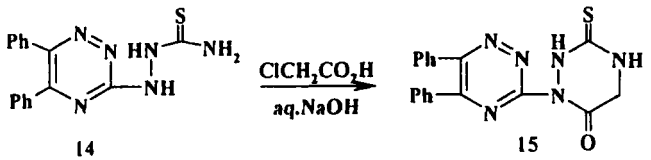
Condensation of 4,5-benzcoumaran-2,3-dione (**11**) with thiosemicarabazide yielded thiosemicarbazone **12**, which was converted into 6-(2-hydroxyl-1-naphthyl)-3-thioxo-1,2,4-triazine-5-one (**13**) in basic medium[27] (Scheme 1).



11 12 13

SCHEME 1

1,2,4-Triazin-3-thiones are biologically active and they proved to be very susceptible to attack by all kinds of nucleophiles leading to addition and subsequently either substitution or cycliaztion and ring transformation. Thus, N^1-substituted thiosemicarbazide (**14**), on reaction with monochloroacetic acid in aq. NaOH, afforded 1-substituted-3-thioxo-5H-1,2,4-triazin-6(2H,4H)-one (**15**)[28].

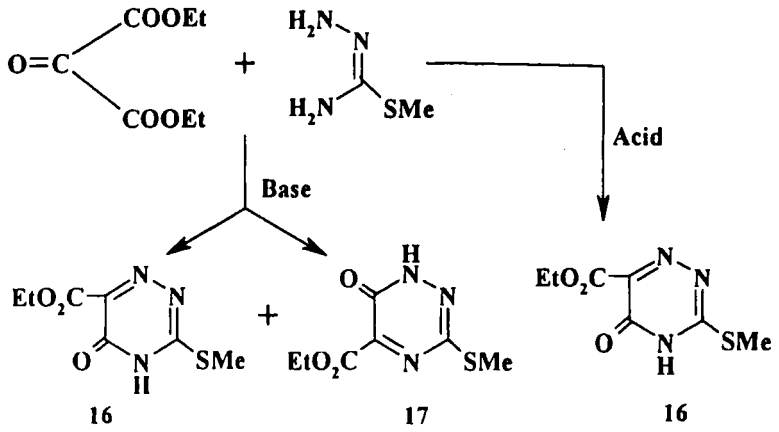


14 15

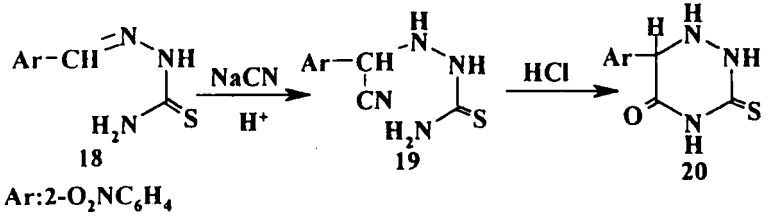
S-Methylthiosemicarbazide on treatment with diethyl carbonate gave the triazine **16** and **17** under basic conditions, and only **16** under acid condition[29] (Scheme 2).

1,6-Dihydro-6-substituted-3-thioxo-1,2,4-triazin-5-one (**20**) was obtained from addition of HCN to thiosemicarbazone **18** followed by acidic hydrolysis of **19** (Scheme 3)[30].

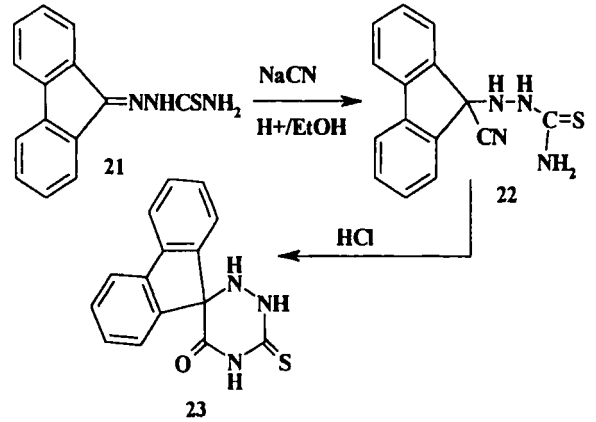
In a similar manner, Abdel-Rahman, et., al[3]., synthesized 1,6-dihydro-3-thioxo-6-spiro-(9-fluorene)-1,2,4-triazin-5(3H,5H)-one **23** as potential anti HIV and anticancer drugs by acidic hydrolysis of **22** (Scheme 4).



SCHEME 2

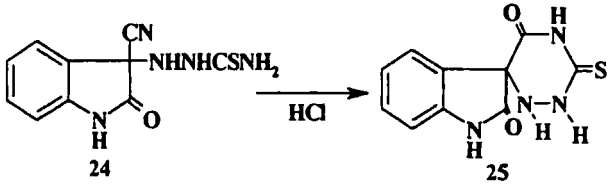


SCHEME 3



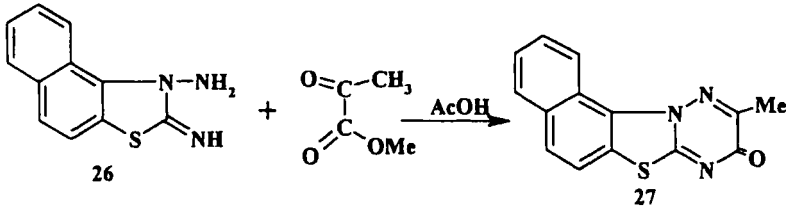
SCHEME 4

Also, 1,6-dihydro-6-spiro-3-thioxo-1,2,4-triazin-5(2H,4H)-one (**25**) was isolated from acidic hydrolysis of 1-cyano-1-(2-hydroxylindol-3-yl)thiosemicarbazide (**24**)[31].



B] Miscellaneous Synthesis

Cyclocondensation of 3-amino-2-iminonaphthic[1,2-d]thiazol (**26**) with α-ketocarboxylic acid led to the synthesis of 2-methyl-3H-naphtho[1,2:4,5]thiazolo[3,2-b][1,2,4]triazin-3-one (**27**)[32].

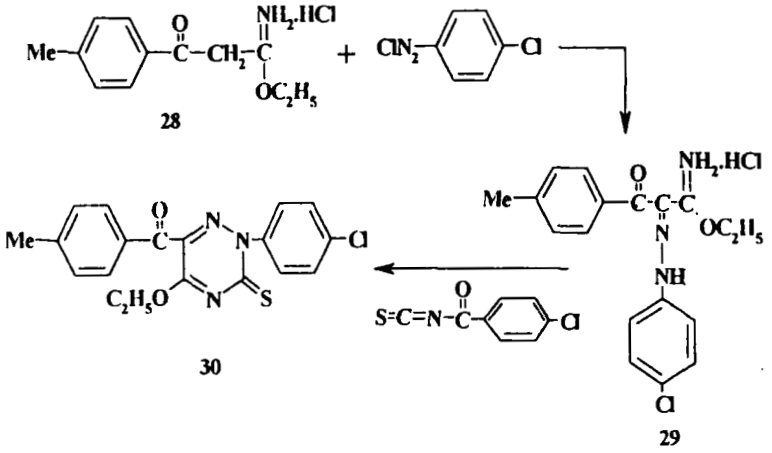


Also, condensation of **28** with 4-chlorobnezenediazonium chloride gave ethyl-α-[2-(4-chlorophenyl)hydrazono]-β-oxo-4-methylbenzenprop-animidate (**29**). Reaction of **29** with 4-chlorobenzoyl isothiocyanate gave 1,2,4-triazin-3-thione (**30**)[33] (Scheme 5).

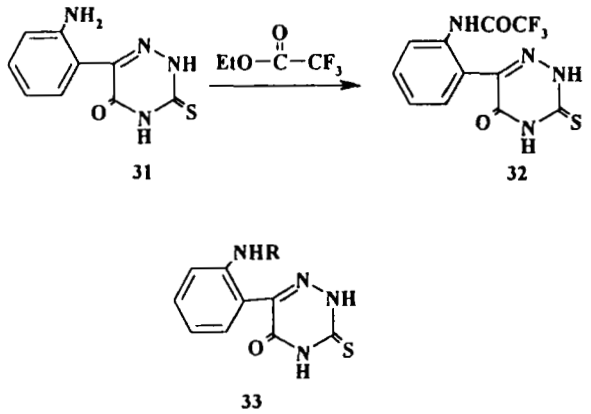
C] preparation of 3-thioxo-6-substituted-1,2,4-triazin-5-ones

Anti-AIDS and anticancer compound **32** was obtained from treatment 6-(2-aminophenyl)-3-thioxo-1,2,4-triazin-5(2H,4H)-one (**31**) with ethyl trifluoroacetate in abs-ethanol with a few drops of piperidine[1].

A series of 6-(2-acyl/alkylaminophenyl)-3-thioxo-1,2,4-triazin-5(2H,4H)-ones (**33**) have been prepared by acylation and/or alkylation of 6-(2-aminophenyl)-3-thioxo-1,2,4-triazin-5(2H,4H)-one (**31**)[12].



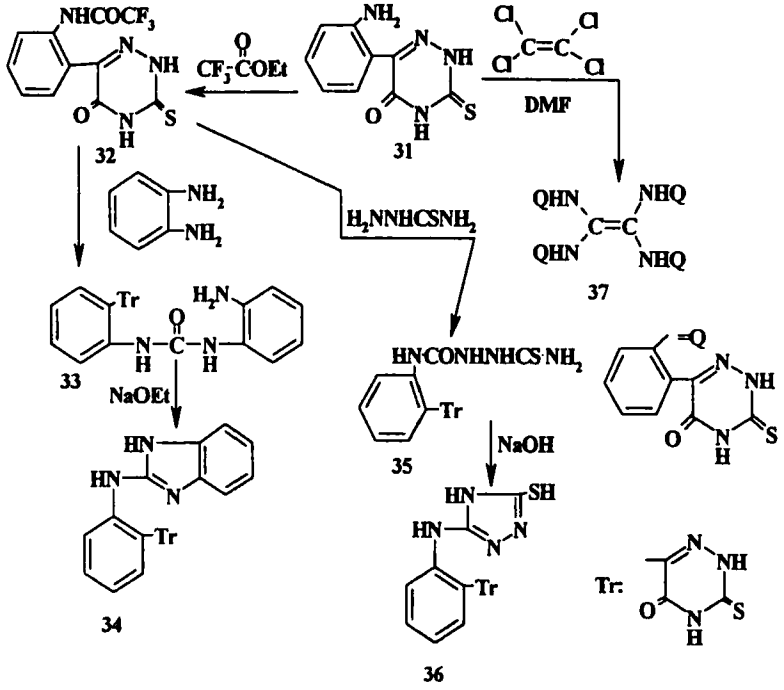
SCHEME 5



R=COR', R':OEt ; CH_2Cl ; 4-$O_2NC_6H_4$; 3,3,4-$(HO)_3C_6H_2$; 3,3,4-$(MeO)_3C_6H_2$
R=CH_2CO_2H, 4-$O_2NC_6H_4CH_2$, 3,3,4-$Me_3C_6H_2COCH_2$, SO_2Ph,
-$SO_2C_6H_4NHCOMe$-4

On the other hand, 6-(2-ethylcarboxyaminophenyl)-3-thioxo-1,2,4-triazin-5(2H,4H)-one (**32**) was used as a starting material for the synthesis of various heterocyclic systems[12]. Thus, **32** reacts with 2-phenylendiamine to form N,N[1]-disubstituted urea **33** which upon cyclization with sodium ethoxide furnished 3-thioxo-6-[2-(benzimidazol-2-yl)aminophenyl]-1,2,4- triazin-5(2H,4H)-one (**34**). Reaction of **32** with thiosemicar-

bazide yields 1,4-disubstitutedsemicarbazide (**35**). Refluxing **35** with aqueous NaOH afforded 3-mercapto-1,2,4-triazole **36**. In addition, alkylation of **31** with tetrachloroethylene furnished tetrasubstituted aminoethylene **37** (Scheme 6)[12].

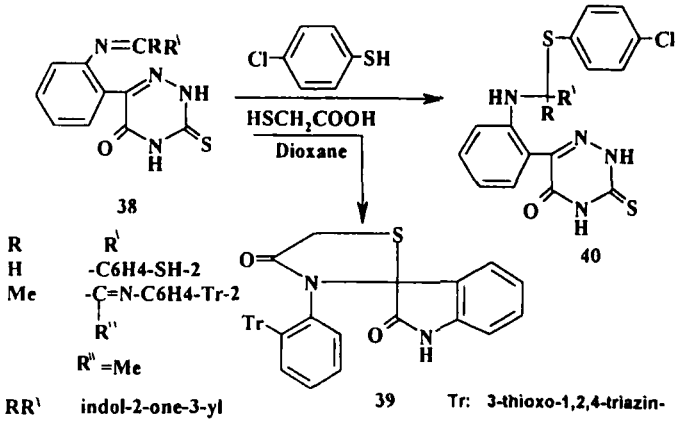


SCHEME 6

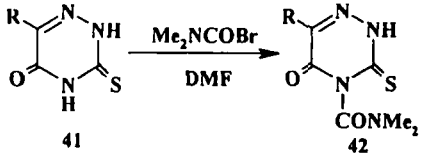
Sulfur containing 1,2,4-triazin-3-thiones **39** and **40** have been obtained by condensation of **31** with aldehydes and ketones followed by addition of mercaptoacetic acid or p-chlorothiophenol (Scheme 7)[9]. The effect of the new compounds **38–40** on the amylolytic activity of some fungi are also recorded, where **39** and **40** showed very high activity[9].

CHEMICAL REACTIVITY OF 3-THIOXO-1,2,4-TRIAZIN-5(2H, 4H)-ONES

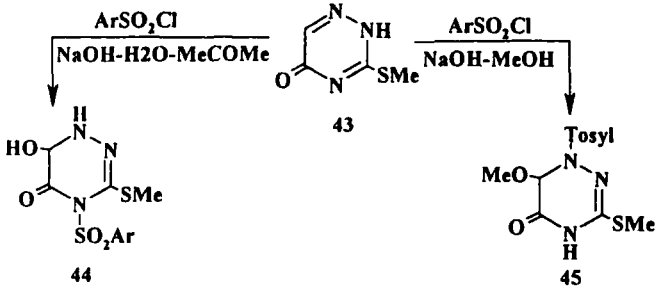
Acylation[34] of dihydro-3-thioxo-1,2,4-triazin-5-one (**41**) with Me_2NCOBr in DMF at ≤ 40°C gave N^4-acyl derivative **42**.



SCHEME 7

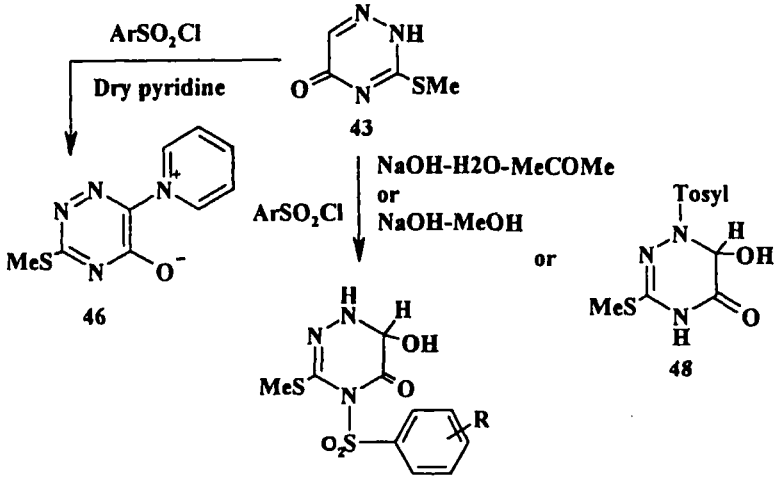


Treatment of 3-methylthio-1,2,4- triazinone **43** with arylsulfonyl chlorides in NaOH-H_2O-CH_3COCH_3 solution gave 3-methylthio-4-arylsulfonyl-5-oxo-6-hydroxy-1,4,5,6-tetrahydro-1,2,4-triazines **44**, while in NaOH-MeOH solution give 1-tosyl-3-methylthio-5-oxo-6-methyloxy-1,4,5,6-tetrahydro-1,2,4-triazine (**45**) (Scheme 8)[35].



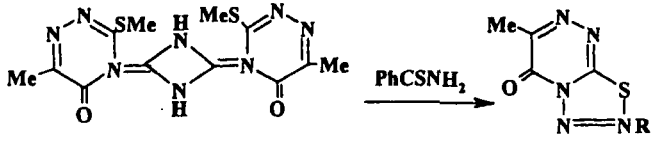
SCHEME 8

On the other hand, 3-methylthio-5-hydroxy-1,2,4-triazine (**43**) reacted with arylsulfonyl chlorides to give triazinylpyridinium betaines **46** in anhydrous pyridine but when NaOH-H_2O-acetone or NaOH-MeOH were used as a reactant and solvent, sulfonyl triazines **47** (R=4-Me, 4-Br, 3-O_2N) or 1-tosyltriazine **48** were obtained, respectively. The above reactions show anomalous properties of nucleophilic attack on the 6-carbon in a 1,2,4-triazine ring[36–37] (Scheme 9).

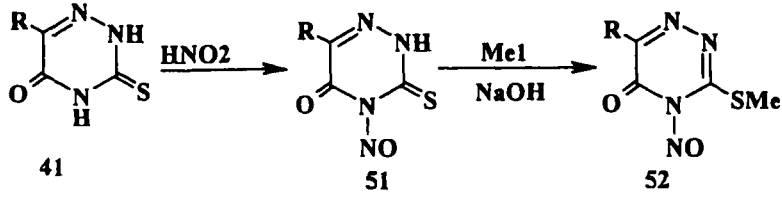


SCHEME 9

Also, reactions of 1,3-diazetidines **49** with $PhCSNH_2$ gave thiadiazolo-triazinones (**50**)[38].



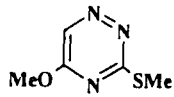
Nitrosation[39] of triazines **41** (R=Me_3C,Ph), by $NaNO_2$ in aqHCl for 1.5–2h at 0°C gave **51**, which were methylated by MeI in alcoholic NaOH to give triazines **52** (Scheme 10).



41 51 52

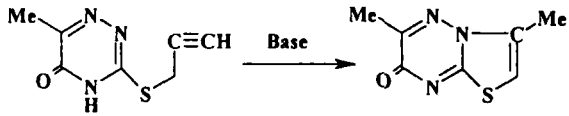
SCHEME 10

The course of the reaction of 3-methylthio-5-methyloxo-1,2,4-triazine (**53**) via mesoionic dimethyl derivatives has been studied[40]. Thus, treatment of **53** with MeI was found to give, depending on the reaction time, a mixture of triazinium iodide. The structural assignments were eventually confirmed by quantum chemistry calculations of net charge distribution, bond length and ispo angles of the C_5-O bonds.



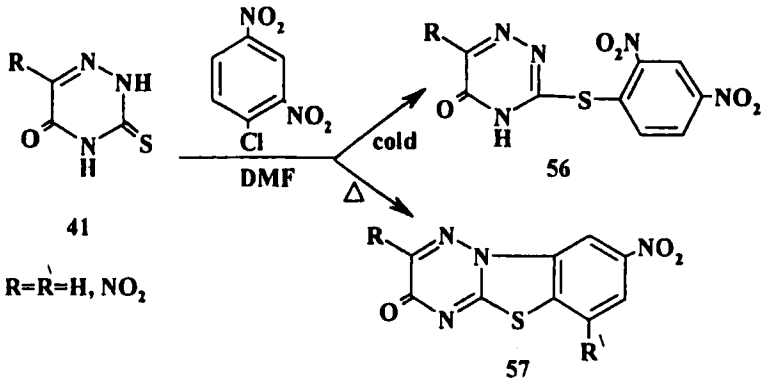
53

Transformation of S-alkynyl-triazinone **54** to 3,6-dimethyl-7H-thiazolo[3,2-b][1,2,4]triazin-7-one (**55**) was performed under basic condition. The formation of **55** may be mainly due to the high reactivity of acetylene towards nucleophiles and isomerization of the intermediate[41].



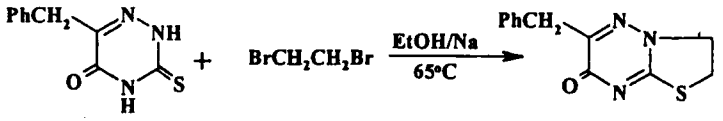
54 55

Reaction of dihydro-3-thioxo-1,2,4-triazinone **41** with 2,4-$(O_2N)_2C_6H_3Cl$ afforded 3-[(2,4-dinitrophenyl)thio]-4,5-dihydro-6-phenyl-1,2,4-triazin-5(4H)-one(**56**) at room temperature in DMF. Compounds **41** gave nitrotriazino[3,2-b]benzothiazolones (**57**, R=R′=H, NO_2) with 2,4-$(O_2N)_2C_6H_3Cl$ or picryl chloride in refluxing DMF (Scheme 11)[10].

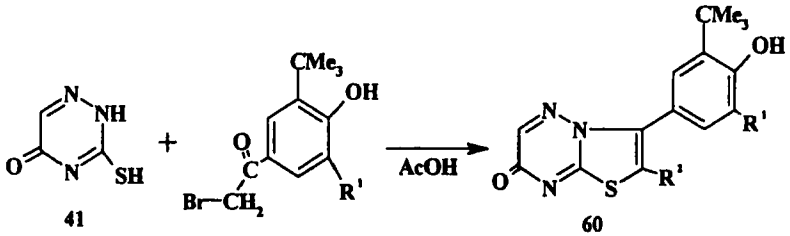


SCHEME 11

Alkylation of 6-benzyl-3-thioxo-1,2,4-triazin-5(4H)-one(**58**) by refluxing with 1,2-dibromoethane in EtOH-Na at 65C° led to the formation of 2,3-dihydro-6-benzyl-7H-thiazolo[3,2-b][1,2,4]triazin-7-one(**59**)[13].

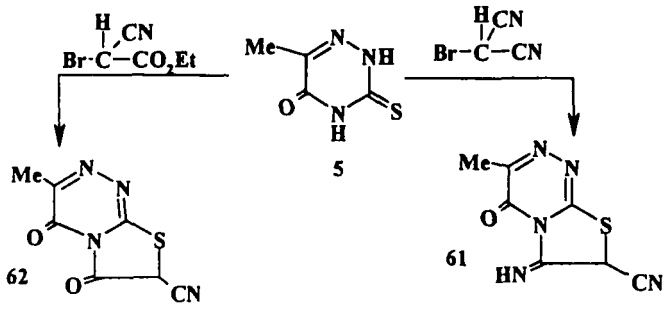


Similarly, antiinflammatory[11] 3-phenyl-7H-thiazolo[3,2-b][1,2,4] triazin-7-ones (**60**) were obtained from stirring compound **41** with 3,5,4-(Me_3C)$OHC_6H_2COC_2Br$ in AcOH at 90C° for 4h.



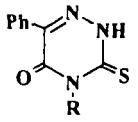
(R^1=C_{1-4} alkyl, CH_2OH, $CH_2NR^4R^5$; R^2=H, C_{1-3} alkyl ; R^3=H,R^1, R^4, R^5=H, C_{1-4} alkyl ; NR^4R^5=hetero ring)

Alkylation of **5** using bromomalononitrile and/or ethyl bromocyanoacetate led to the formation of thiazolo[2,3-c][1,2,4]triazines **61** and **62** (Scheme 12)[42].



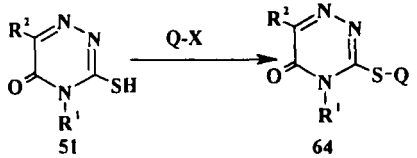
SCHEME 12

Effects of the medium and substituents on the yield of methylation products of 3-thioxo-N^4-substituents-1,2,4-triazin-5-ones **63** have been studied[42]. Thus, methylation of **62** (R=H, Me, H_2N, Me_2NCO, ON, 4-R'C_6H_4N:N; R'=H, O_2N, HO) by MeI was carried out in NaOH-H_2O and in NaOH and by using the MeOH-containing solvent. The yields also depended on the inductive effect of R.



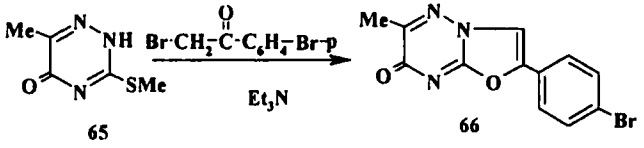
63

In a similar manner[43], treatment of thioxo-triazinone **51** with MeI, allyl chloride and Me_3CBr in presence of NaOH in MeOH-H_2O gave S-alkyl derivatives **64**.



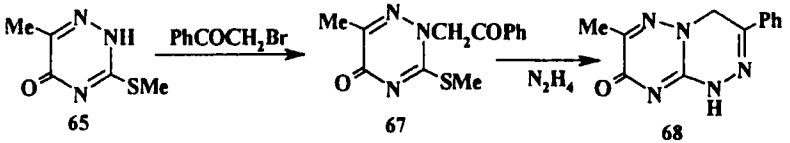
R^2=Me_3C, Ph ; R^1:ON, arylazo ; Q=Me, allyl, Me_3C

3-Methylthio-1,2,4-triazinone (**65**) reacts with p-bromophenacyl bromide in the presence of Et_3N to form oxazolo[3,2-b][1,2,4]triazine (**66**) in high yield[44].



65 66

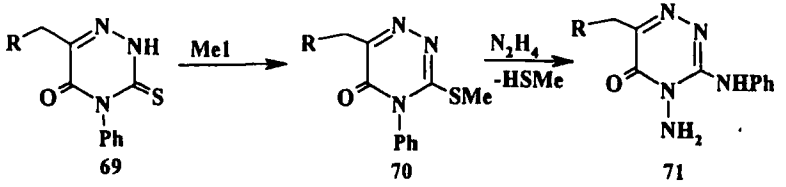
1,2,4-Triazino[4,3-b][1,2,4]triazin-8(1H)-one (**68**) was obtained from treatment of **65** with phenacyl bromide to give N-alkyl **67** followed by hydrazinolysis (Scheme 13)[45].



65 67 68

SCHEME 13

Methylation of 4,6-disubstituted-3-thioxo-1,2,4-triazin-5-ones (**69**) converted it into their corresponding 3-methylthio derivatives **70**. Hydrazinolysis of **70** gave 4-amino-3-anilino-4,5-dihydro-1,2,4-triazin-5-ones (**71**) (Scheme 14)[7]. Formation of **71** occurred via intramolecular nucleophilic attack of N_2H_4 with loss of HSMe group.[7]

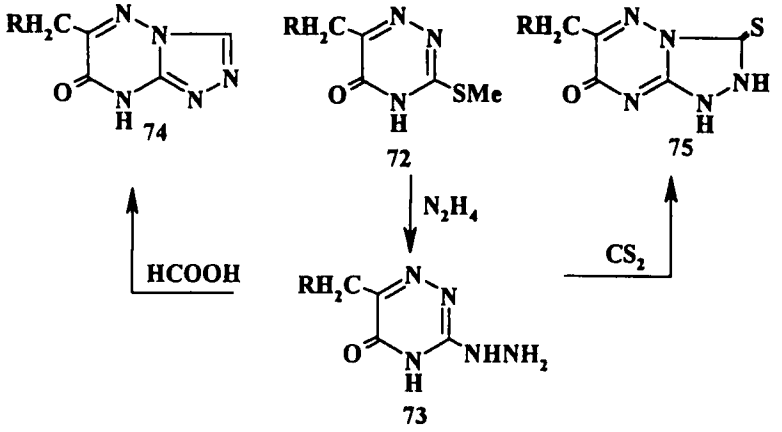


69 70 71

R:4-ClC$_6$H$_4$; 3,4-(MeO)$_2$C$_6$H$_3$; 3,4-(OCH$_2$O)C$_6$H$_3$

SCHEME 14

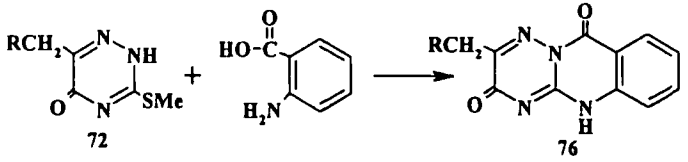
The triazolotriazines **74** and **75** have been obtained from hydrazinolysis of 3-methylthio-6-benzyl-1,2,4-triazin-5(4H)-ones (**72**) followed by cyclization with formic acid or CS_2 (Scheme 15)[46].



R:4-MeOC$_6$H$_4$; 4-Cl-C$_6$H$_4$; 3,4-(MeO)$_2$C$_6$H$_3$

SCHEME 15

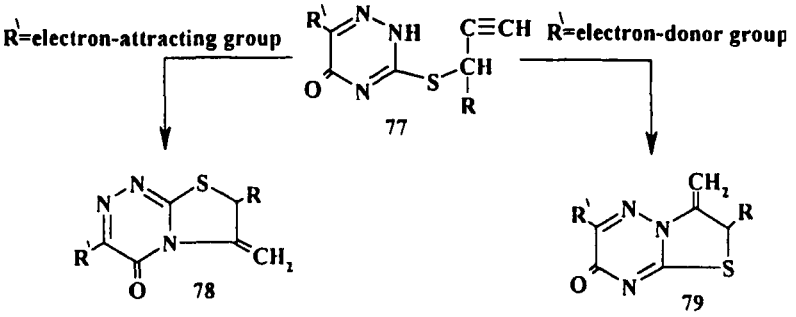
The interaction of compound **72** with anthranilic acid gave the triazino[3,2-b]quinazolinediones **76**, which have a potential biological activity[8].



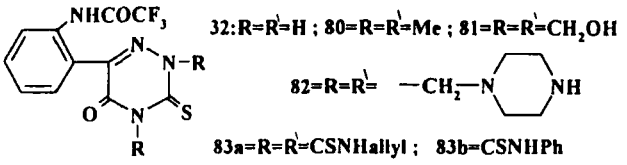
Selective transformation of 3-proparagylthio-1,2,4-triazin-5(2H)-ones (**77**) to thiazolo[2,3-c][1,2,4]triazin-4-ones (**78**) and 3-methylene-2,3-dihydro-7H-thiazolo[3,2-b][1,2,4]triazin-7-ones (**79**) is performed under conditions of Pd(II) salt or NaOH catalysis (Scheme 16)[47].

Some new fluorine containing 2,4-disubstituted-3-thioxo-1,2,4-triazin-5-ones (**80–83**) have been obtained from reaction of **32** with excess MeI, HCHO-MeOH, HCHO-MeOH-peprazine and substituted isothiocyanate[1].

Alkylation of compound **32** using halo-compounds such as, monochloroacetic acid, ethyl chloroacetate, bromopyruvic acid and chloroacetylate-



SCHEME 16

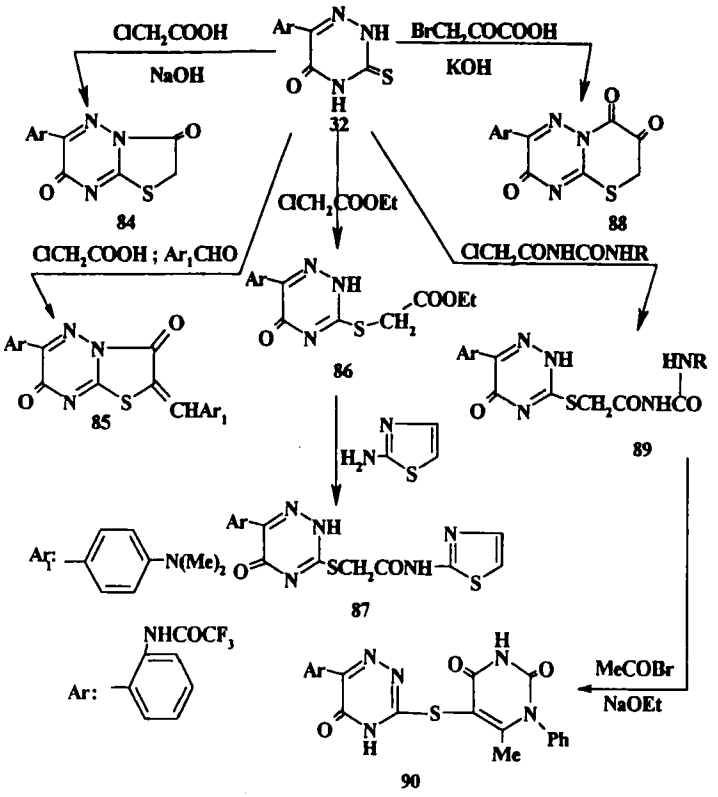


dureas in basic medium produced the desired heterocyclic systems **84–90** (Scheme 17)[1]. The latter compounds showed a moderate effect in vitro anti HIV activity[1].

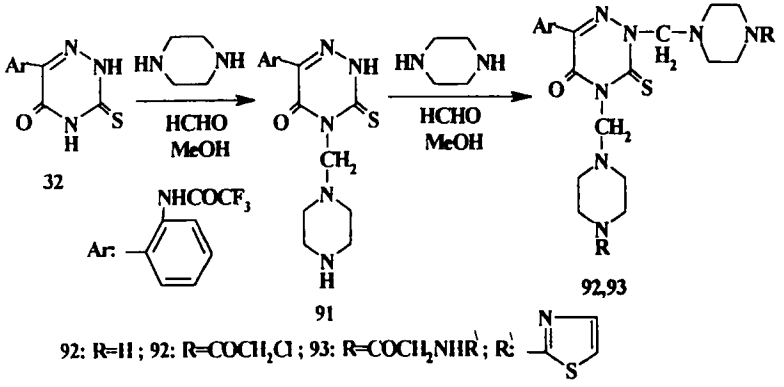
In a search for new anticancer agents, flourine bearing substituted-3-thioxo-1,2,4-triazin-5-ones (**91–93**) have been obtained by alkylation of compound **32**, where Mannish bases of the type N^4-substituted and N^2, N^1-disubstituted-3-thioxo-1,2,4-triazin-5-ones (**91–93**) have been produced (Scheme 18)[2].

Reaction of **32** with chloroacetamide in DMF gave rise to the S-alkylated **94**, which on treatment with PhNHCOOEt in dry benzene gave the compound **89**. Hydroxymethylation of **89** yielded N-hydroxymethyl derivative **95**. Also. Hydrazinolysis of **32** gave the hydrazine derivative **96**, which upon addition of PhNCS in MeOH afforded N^2,N^2-disubstituted thiosemicarbazide **97**. Mannish base **98** was obtained from reaction **97** with peprazine in HCHO-MeOH. Compound **98**, also was obtained from hydrazinolysis of **91** followed by addition of PhNCS in MeOH (Scheme 19)[2].

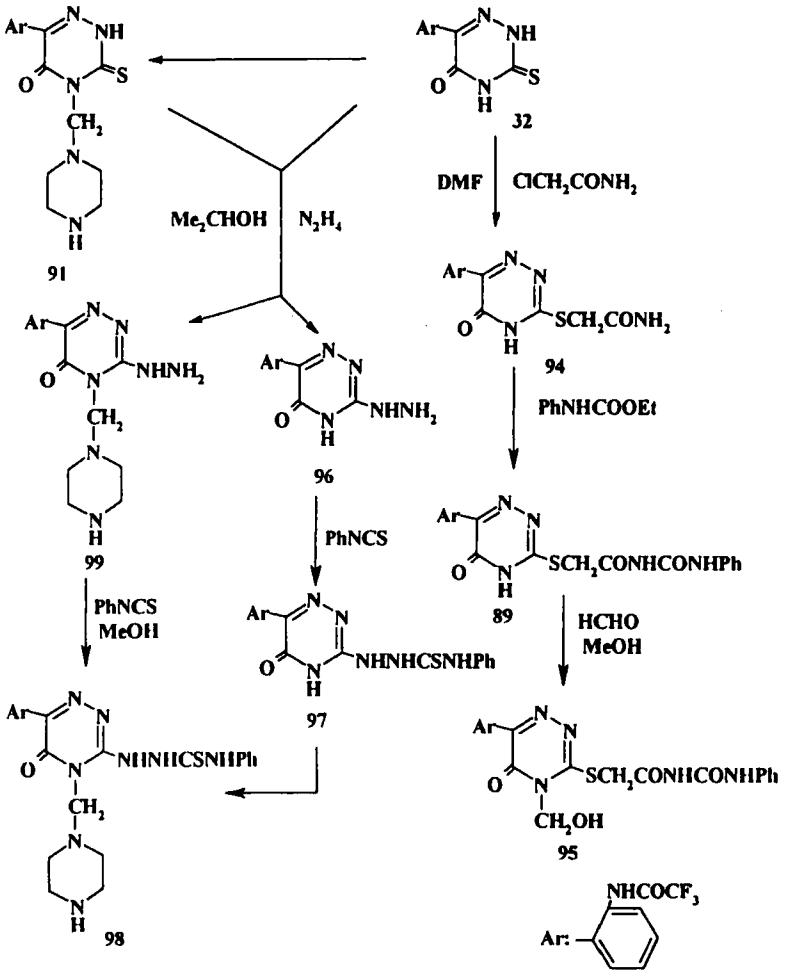
All the prepared compounds **82–87** and **91–99** were screened for in vitro anticancer activity were compound **82** showed an effective activity against



SCHEME 17



SCHEME 18

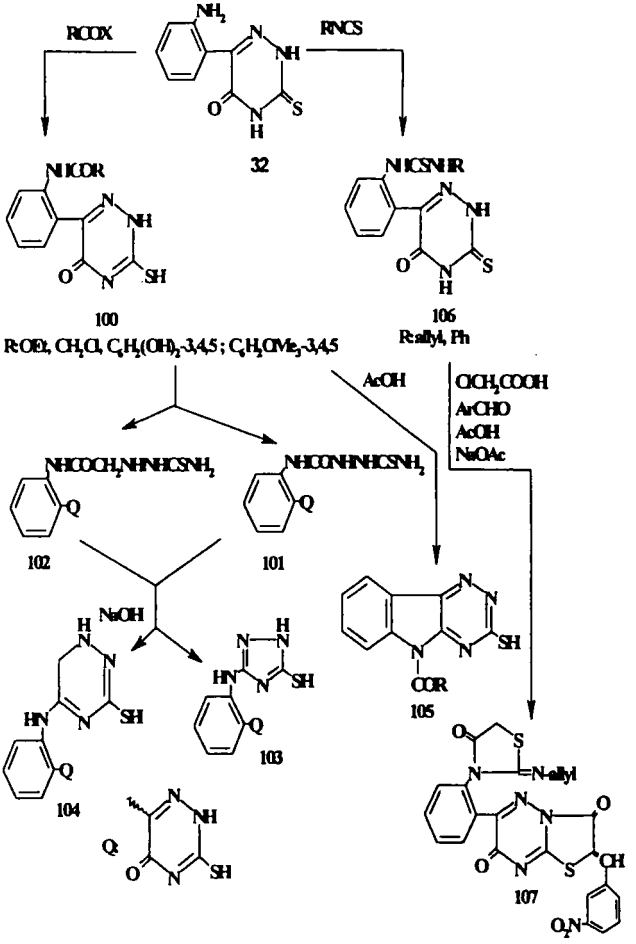


SCHEME 19

some cancer cells such as leukemia/Lymphoma, small/Non Small Cell Lung, while compound **89** showed a lethal activity against Small Cell Lung, Colon and Melanoma cell[2].

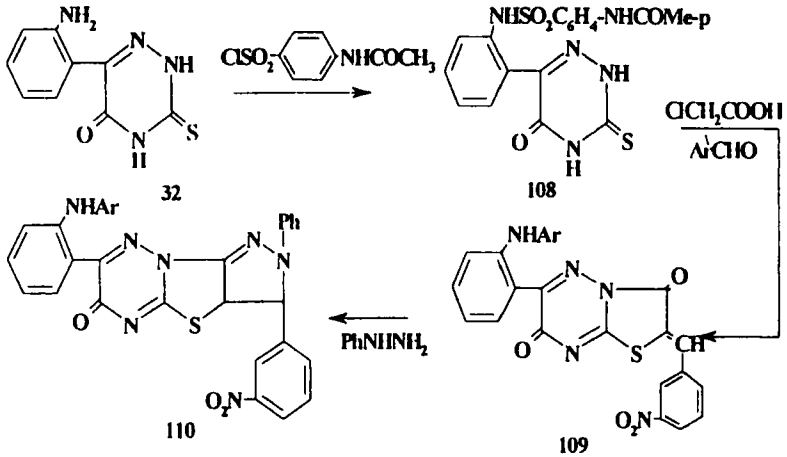
Some new heterocyclic systems containing 3-thioxo-1,2,4-triazin-5-one derivatives have been obtained from N-acylaminophenyl and/or N-alkylaminophenyl derivatives. Thus, acylation and alkylation of **32** fol-

lowed by reaction with thiosemicarbazide yielded N^1-acyl-thiosemicarbazides **101** and **102**. Basic cyclization of the latter compounds afforded 3-mercapto-1,2,4-triazole **130** and 3-mercapto-1,2,4-triazine **104**. 3-Mercapto-5-aroyl-1,2,4-triazino[5,6-b]indoles(**105**) were obtained from refluxing **100** with glacial AcOH. Addition of isothiocyanate derivatives to **32** afforded N,N′-disubstituted thiourea **106**, which upon refluxing with monochloroacetic acid and aromatic aldehydes in the presence of AcOH-NaOAc led to the direct formation of 2-arylidin-6-[2-(4-oxo-thiazolidin-3-yl)phenyl]-thiazolo[3,2-b]triazin-3,7-dione (**107**) (Scheme 20)[12].



SCHEME 20

Similarly, treatment of **108** with aromatic aldehyde and monochloroacetic acid in the presence of AcOH-NaOAc produced 3-arylidin-6-arylthiazolo[3,2-b][1,2,4]triazin-3,7-diones (**109**), which on boiling with $PhNHNH_2$ in ethanol-piperidine yielded the triheterocyclic system **110** (Scheme 21)[12].

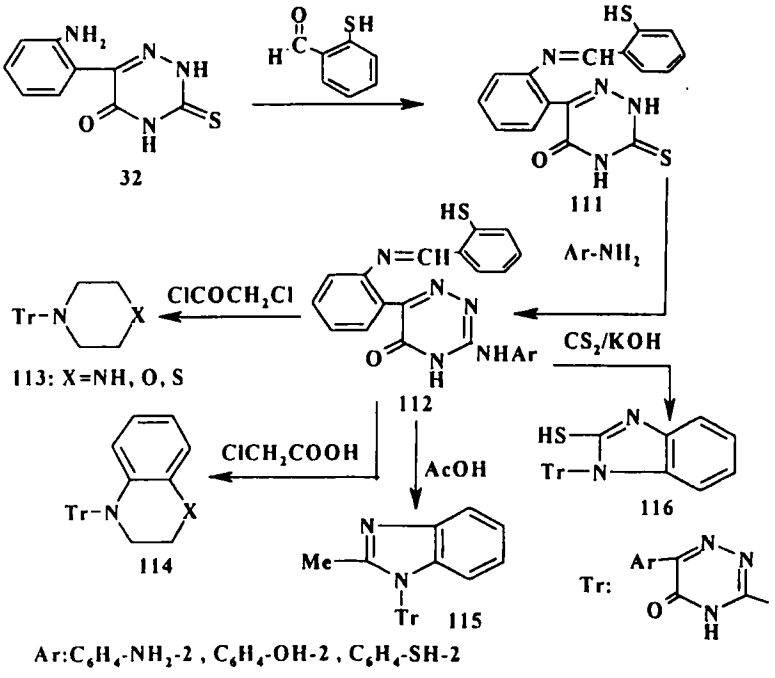


SCHEME 21

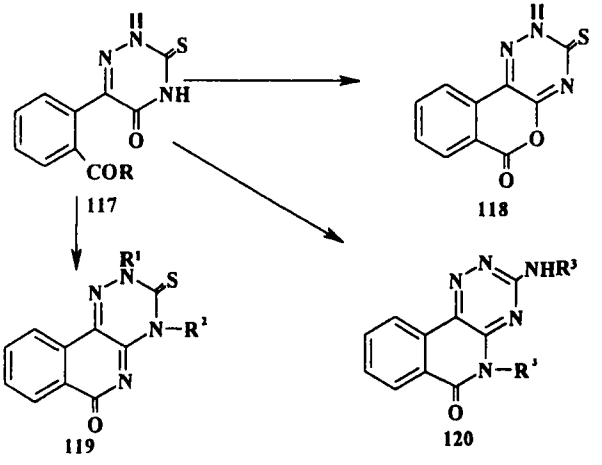
3-Heteroaryl-6-(2-arylidinephenyl)-1,2,4-triazin-5-ones (**113–116**) were obtained from aminolysis of **32** followed by ring closure reactions with chloroacetyl chloride, monochloroacetic acid, acetic acid and CS_2in KOH (Scheme 22)[9]. The effect of these compounds on the amylolytic activity of some fungi were studied, were compound **112c** showed a large effect towards Penicillium meleagrium.[9]

Recently, Hejsek et, al[49]., treated 2-(6-azauracil-5-yl)benzoic acid **117** (R=OH) with N, N^1-dicyclohexylcarbodiimide via cyclization reactions to give 1,2-dihydro-1,2,4-triazino[5,6-c]isocoumarin-3-ones (**118**). A series of substituted 1,2,4-triazino[5,6-c]isoquinolines (**119**, R^1=R^2=H, Me) and **120** (R^3=Ph, NH_2, N=CHPh) have been obtained from these compounds (Scheme 23)[49].

1,6-Dihydro-3-(2H)-thioxo-6-spiro-(9-fluorene)-1,2,4-triazin-5-(H)-one (**23**) has been used to synthesize several analogous compounds via nucleophilic substitution reactions and some of the new products possessed



SCHEME 22



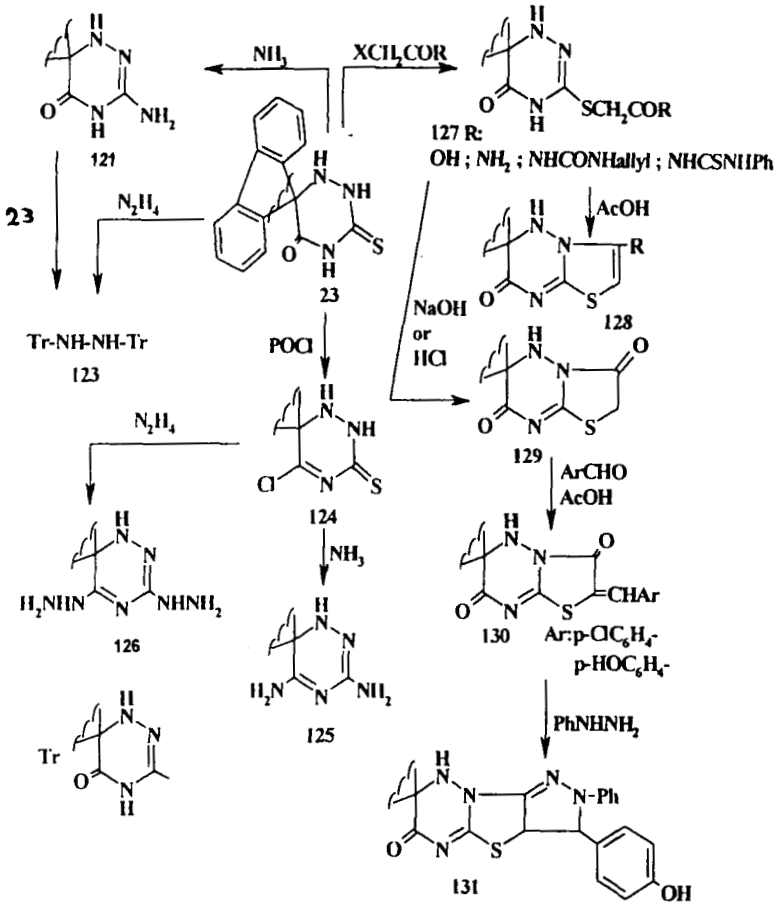
SCHEME 23

good anti HIV and anticancer activities[3]. Thus, reaction of **23** with ammonia and or N_2H_4 in ethanol afforded 3-amino/hydrazino derivatives **121** and **122**, respectively. Refluxing of **122** with **23** in isopropanol furnished bis-compound **123**, while chlorination of **23** using $POCl_3$ gave 5-chlorotriazine **124**. The interaction between **124** and ammonia or N_2H_4 in isopripyl alcohol afforded 3,5-diamino/ 3,5-dihydrazino-triazines **125** and **126**. Alkylation of **23** using monochloroacetic acid, chloroacetamide, 1-chloroacetyl-3-allylurea or 1-chloroacetyl-3-phenylthiourea in basic media afforded S-alkyl derivatives **127**, which underwent acidic, basic and/or neutral cyclization leading the heterocyclic **128** and **129**. Condensation of **129** with aromatic aldehydes AcOH yielded the arylidenes **130**, which on refluxing with $PhNHNH_2$led to the direct formation of 3,7,8-trihydro-3-aryl-2-phenyl-7-spiro-(9-fluorene)-pyrazolino[3,4:3,2]thiazolo [4,5-b][1,2,4]triazin-6-one (**131**) (Scheme 24)[3].

Some new heterobicyclic systems **132–136** were obtained from treatment of **23** with phenacyl bromide, malonic acid and/or ethyl bromoacetate in basic medium[3]. Elimination of the SH group from **23** by active methylene groups such as acetylanilides in sodium ethoxide afforded the malonamides **135**, which upon fusion with $PhNHNH_2$gave 3-methyl-1-phenyl-5-substitutedamino-4-[1,6-dihydro-6-spiro-(9-fluorene)-5(4H)oxo-1,2,4-triazin-3-yl]pyrazole (**136**). Reaction of **23** with ethylenetetrachloride in DMF furnished tetrasubstituted ethylenic derivative **137** (Scheme 25)[3].

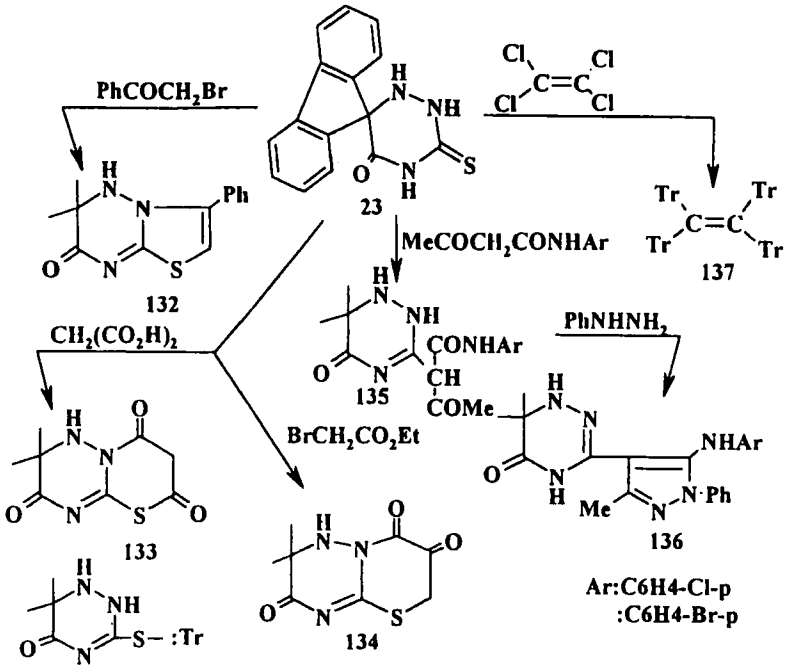
The results for the synthesized compounds **121–137** indicated that compound **124, 128, 129** and **137** showed significant activity against HIV in vitro and it is interesting to note that introduction of ethylenic, and thiourea function to mercapto-1,2,4-triazinone **23** moiety increases anti HIV activity, while the other tested compounds showed little or moderate activity[3]. On the other hand, most of the new compounds have been evaluated for in vitro antitumor activity under different concentrations, a sulforhodamine B(SRB) protein assay was used to estimate cell viability or growth by determining GI_{50}, TGI and IC_{50} values. The results of antitumor activity for the synthesized compounds indicated that **137** is moderately active[3].

A number of heterocyclic compounds such as, 1,3,5-thiazine, thiazolidinone, pyridine, pyrimidinedione, imidazole, quinazolnone and 1,2,4-triazinone derivatives have been deduced[4]from compound **23**. Thus, compound **23** was allowed to react with ammonium thiocyanate in EtOH/HCl to give



SCHEME 24

thiocarboxamido derivative **138** which on refluxing with pivolyl chloride in DMF-EtOH gave 6,7-dihydro-4-(t-butyl)-2-thioxo-7-spiro-(9-fluorene)-1,3,5-thiadiazino[3,2-b][1,2,4]triazin-8-one (**139**). Thioether **140** was obtained from refluxing a mixture of **138** and monochloroacetic acid in the presence NaOAc-EtOH, while refluxing of **138** with CS_2 in KOH gave 4-mercapto-2-thioxo-1,3,5-thiadiazino[3,2-b] [1,2,4]triazin-8-one (**141**) which was subjected to the reaction with monochloroacetic acid in

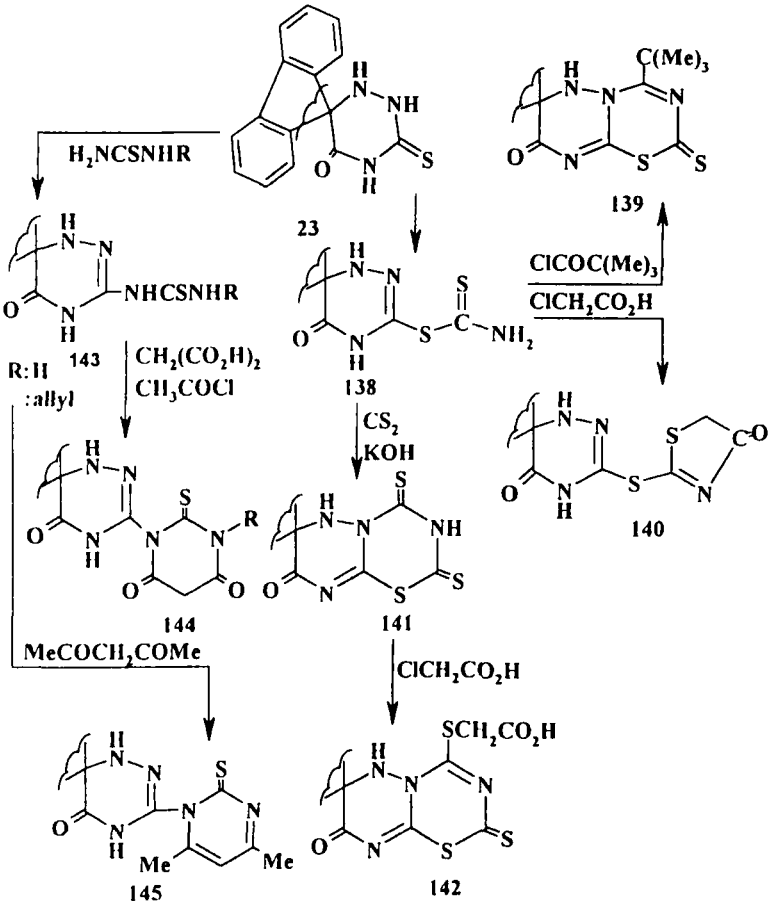


SCHEME 25

NaOAc-EtOH to afford 6,7-dihydro-4-carboxymethylmercapto-2-thioxo-7-spiro-(9-fluorene)-1,3,5-thiadiazino [3,2-b][1,2,4]triazin-8-one (**142**) (Scheme 26)[4].

The target compounds **144** and **145** have been synthesized via treatment of **23** with thiourea to give 1,3-disubstituted thiourea **143** followed by ring closure reactions with bioxo-compounds. (Scheme 26)[4].

Methylation of **23** by treatment with MeI in aq. NaOH afforded the 3-methylthio derivative **146**, which on boiling with ethanolamine and/or anthranilic acid in sodium ethoxide gave pentahydro-6-spiro-(9-fluorene)imidazolo[1,2-b][1,2,4]triazin-7-one (**147**) and trihydro-3-spiro-(9-fluorene)-1,2,4-triazino [2,3,-a]quinazolin-2,6-dione (**148**) respectively (Scheme 27)[4]. Also, N-alkyl derivatives **149** were produced from reaction of **23** with excess MeI, HCHO-MeOH, EI and HCHO-MeOH/piperidine. Thiazolidinone **151** was obtained from conden-

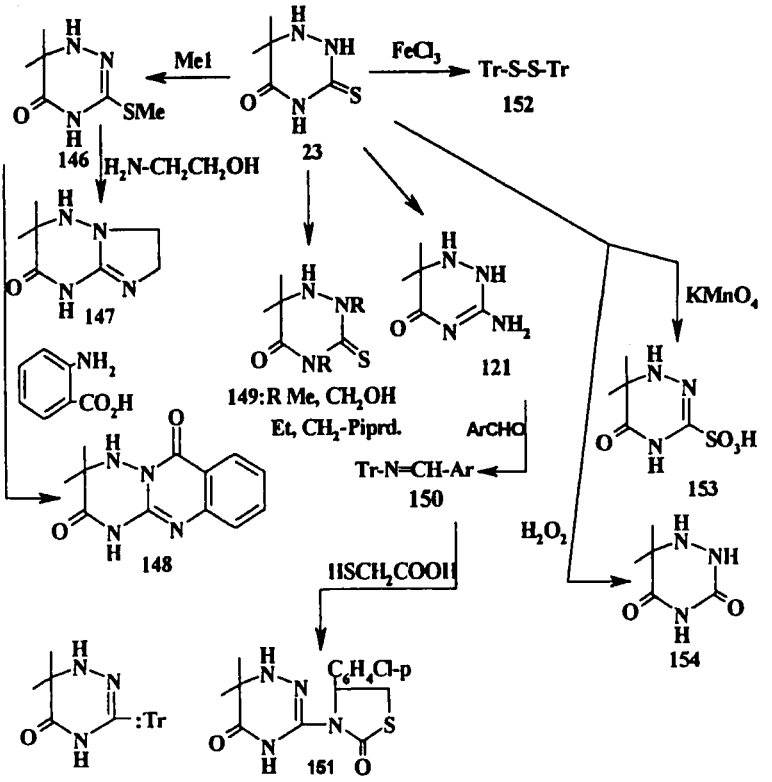


SCHEME 26

sation of **121** with aromatic aldehydes, followed by cycloaddition with mercaptoacetic acid (Scheme 27)[4].

Oxidation of **23** by treatment with $FeCl_3$, $KMnO_4$and H_2O_2 in EtOH resulted the disulphide **152**, sulphonic acid **153** and 1,6-dihydro-6-spiro-(9-fluorene)-1,2,4-triazin-3,5(2H,4H)dione(**154**) respectively (Scheme 27)[4].

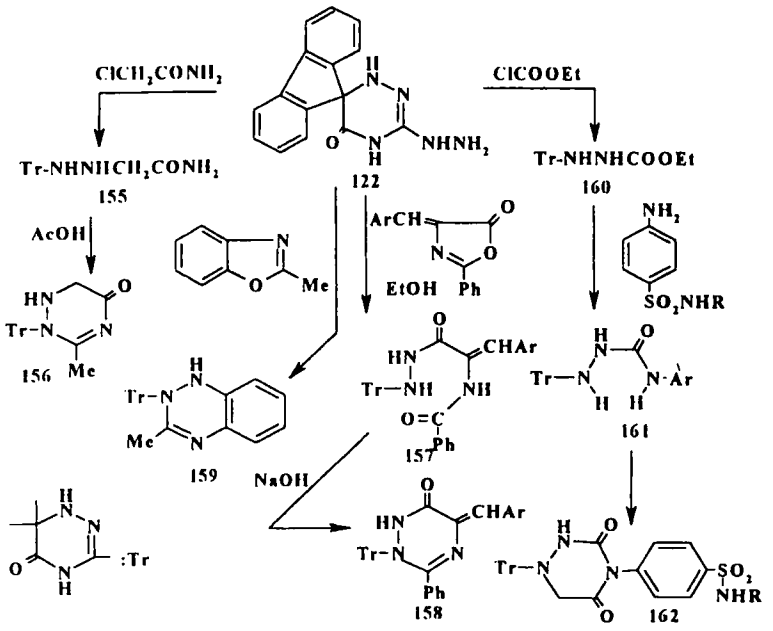
Only **139** showed a high percent control of both infected and unfected values followed by **138, 154, 152, 141** and **146** in the comparison of the



SCHEME 27

standard agent azidothymidine (**AZT**). These compounds, were active as inhibitors, the other tested compounds did not possess any activity against HIV. The results of antitumor activity, showed that only **138** possessed moderate activity, while the compounds **139–142** possessed lower antitumor acivity[4].

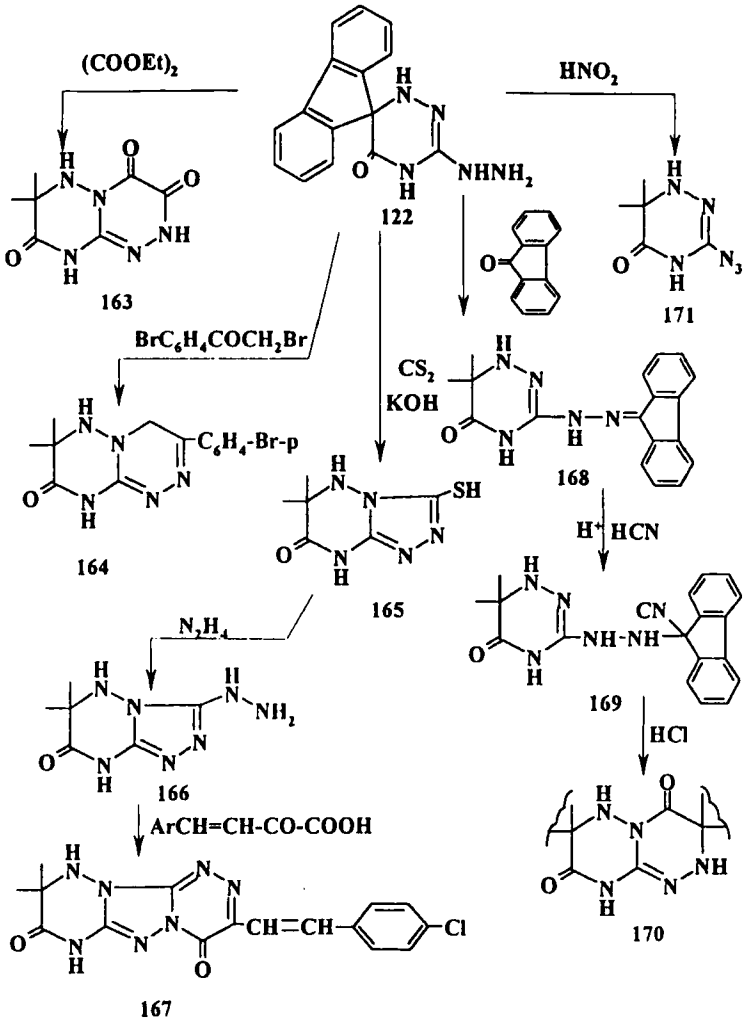
The synthesis of 1,2,4-triazines bearing a 1,2,4-triazine moiety and of 1,2,4-triazolo[4,3-b][1,2,4]triazinones have been achieved by reaction of 1,6-dihydro-3-hydrazino-6-spiro-(9-fluorenyl)-1,2,4-triazin-5(4H)-one (**122**) with various oxo- and halo-compounds. Thus, interaction of **122** with chloroacetamide, oxazolone, 2-methylbenzoxazole and sulfadiazine followed by ring closure reactions led to the formation of isolated heterobicyclic systems **156, 158, 159**, and **162** respectively (Scheme 28)[6].



SCHEME 28

Further, some new fused 1,2,4-triazinone **163–170**, were obtained from refluxing of **122** with diethyl oxalate, p-bromophenacyl bromide, CS_2/KOH and fluorene-9-one in the presence of suitable medium (Scheme 29)[6]. Diazodization of **122** using nitrous acid led to the formation of azido derivative **171**. The structure of **171** was based on MS. The new compounds **155–171** were tested in view of possible pharmacoloical activity. The introduction of azido group in the 1,2,4-triazinone nucleus **171** results in the enhancement of the HIV activity, while the hydrazo derivative **169** has a higher sensitivity in the anticancer activity[6].

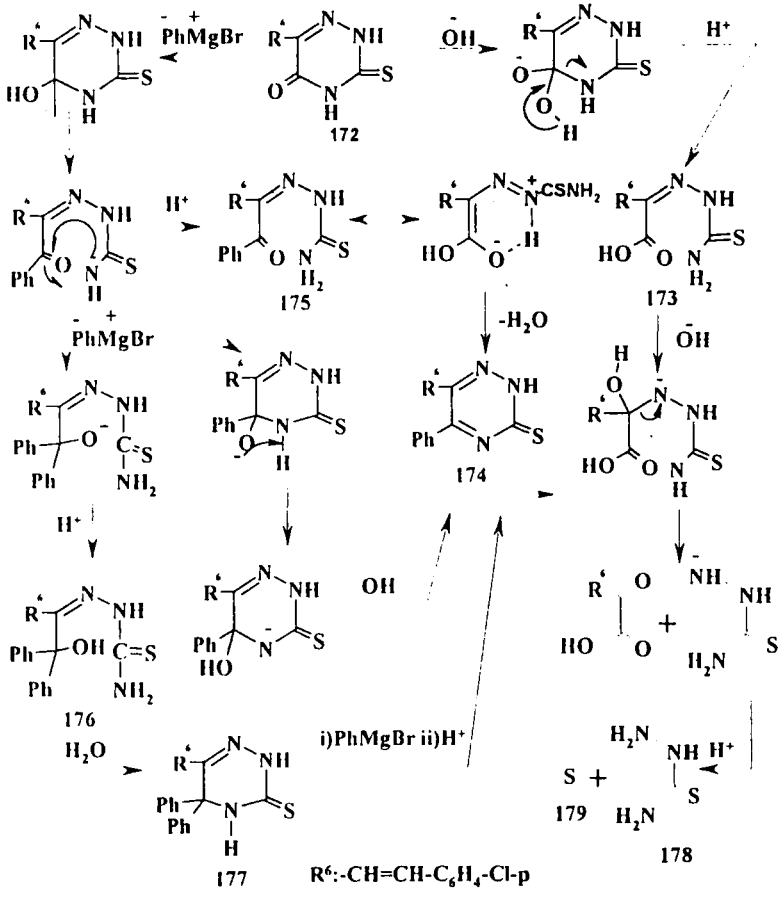
The action of phenylmagnesium bromide on 6-p-chlorstyryl-3-thioxo-1,2,4-triazin-5-one (**172**) was studied. A mixture of seven products, **173–179**, was obtained (Scheme 30)[50]. It is logical that the first step of the reaction may be the addition of a nucleophile (Ph, OH) at the more reactive 5-position, thus leading to the formation of the thiosemicarbazones **173, 175** and 5,6-disubstituted-1,2,4-triazin-3-thione **174**. The isolation of **178** may be explained through the nucleophilic attack (OH) at the imino double bonds of **173–176** (Scheme 30)[50].



SCHEME 29

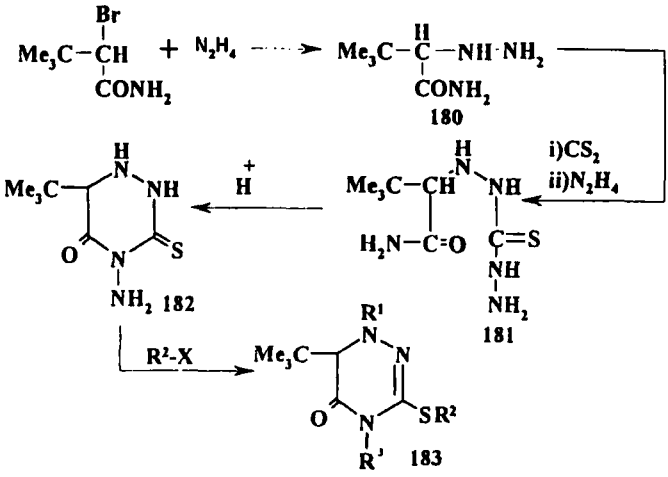
SYNTHESIS OF 4-AMINO-6-SUBSTITUTED-3-THIOXO-1,2,4-TRIAZIN-5(2H,4H)ONES

the triazinones **183** (R=C_{0-3} cycloalkyl, branched dialkyl, R^1=H. alkyl, allyl, propargyl, tosyl, CH_2CO_2Et, (un) substituted CH_2Ph; R^2=Me, Et,



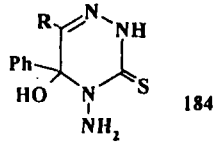
SCHEME 30

allyl; R^3=Me, aminoalcohol) were prepared[51]. Thus, α-bromoacetamide was treated with N_2H_4 to give α-hydrazinoacetamide **180**, which on refluxing with CS_2 followed by N_2H_4 gave 1,4-disubstituted thisemicarbazide **181**, which cyclized on treatment with acid to the thione **182**. Alkylation of **182** resulted S-alkyl **183** (R^1=H, R^2=Me, R^3=NH_2), which at 1.25/100m^2 preemergence gave total control of e.g. abutilon theophrasti (Scheme 31)[51].



SCHEME 31

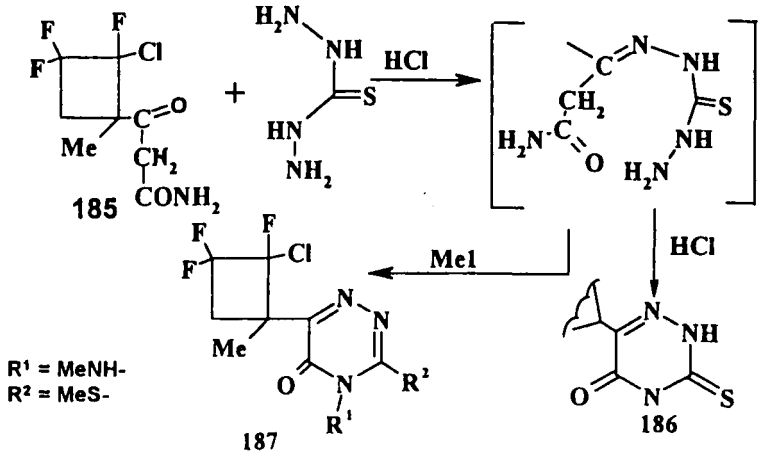
Cyclocondensation of $H_2NNHCSNHNHR$ (R=H, Me_2CH, Ph) with carbonyl compounds such as phenylglyoxal gave aminotriazinethiones **184** (R=H, Et)[52].



184

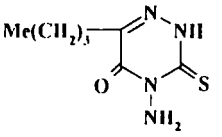
6-(1-Methyl-2-chloro-2,3,3-trifluorocyclobutyl)-1,2,4-triazine-5(4H)-ones, **187** (R^1=NH_2, MeNH; R^2=alkylthio, alkylamino; R^1=NH_2 when R^2=MeS), were prepared as herbicides plant growth regulators, desiccants and defoliants[16]. Thus, 2-oxo-acetamide **185** was refluxed with thiocarbohydrazide in one normal HCl to give **186**. Methylation of **186** produced **187** (R^1=MeNH, R^2=MeS) (Scheme 32)[16].

On the other hand, 6-alkyl(aryl)-4-amino-3-thioxo-1,2,4-triazin-5(2H,4H)-ones (**188**, R=alkyl, allyl) were prepared by Grignard reaction of di-Et oxalate followed by treatment with thiocarbohydrazide in refluxing EtOH-H_2O containing HCl[53].



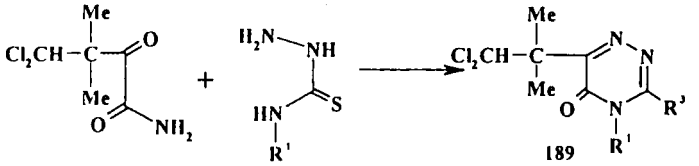
185 187 186

SCHEME 32



188

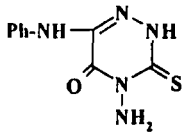
Similarly, 6-(1,1-dichloro-2-methyl-2-propyl)-1,2,4-triazin-5(4H) ones (**189**), R^1=NH_2, Me; R^2=alkylthio, alkylamino, dialkylamino; when R^1=NH_2, R^2=SMe) as herbicides were prepared via cyclocondensation of thiocarbohydrazide[54].



189

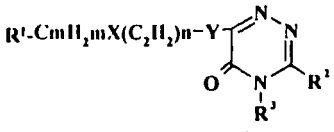
Ethyl thioxanilate condensed with thiocarbohydrazide to give the corresponding 4-amino-6-phenylamino-3-thioxo-1,2,4-triazine (**190**)[55].

Also, 4-amino-6-substituted-3-mercapto-1,2,4-triazin-5-one (**191**, R^1=Ph, heterocyclic group; R^2=alkyl, allyl, alkenyl. R^3=NH_2, or alkanoylamino; m=0–2; n=1–3; x=O, S. Y=S or amino) or their salts, as



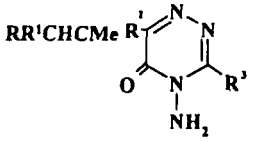
190

antiulcer agents, were prepared from treatment of thiocarbohydrazide with phenylpyruvic acid[56].



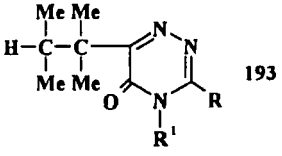
191

Kranz et., al[57]., obtained 3,6-disubstituted-4-amino-1,2,4-triazin-5-ones [**192**, R=H, R^2=Me, R^1=alkoxy, (un) substituted Ph, PhO; R=H, R^2=Et, R^1=alkoxy; RR^1=halo, R^2=Me; R^3=alkyamino, dialkylamino] by conversion of $PhCH_2CMe_2CO_2H$ into acid chlorides, then treating with Me_3SCN to give acylcyanide, followed by cyclocondensation with thiocarbohydrazide.



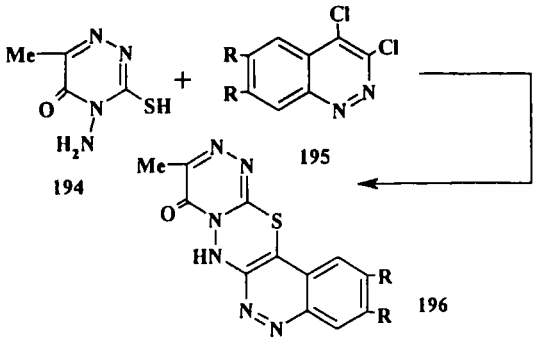
192

Similarly, 6-(2,3-dimethylbut-2-yl)-1,2,4-triazin-5-ones (**193**, R = alkylthio, alkylamino, dialkylamino; R^1=Me, R^2,R^3=C=N; R=H, alkyl, cyanoalkyl, cycloalkenyl, (un) substituted Ph) were prepared via treatment of Me_2CHCMe_2COCN with thiocarbohydrazide[58].



193

1,2,4-Triazino[3,4:2,3][1,2,4]thiadiazino[5,6-c]cinnolin-9-one (**196**, R=H) was prepared by cyclocondensation of the appropriate amino-(thioxo-)triazine **194** with chlorocinnoline (**195**, R=H) (Scheme 33)[59].

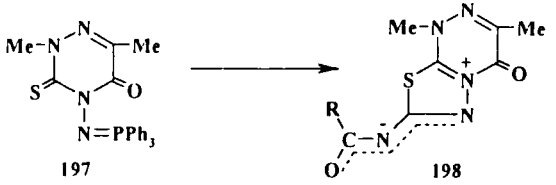


SCHEME 33

CHEMISTRY OF 4-AMINO-6-SUBSTITUTED-3-THIOXO-1,2,4-TRIAZIN-5(2H,4H)-ONES

A) Aza Witting Reaction

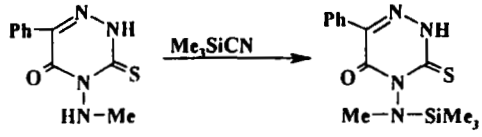
Aza Witting-type reaction of iminophosphorane (**197**) with several type of iso (thio) cyanate leads to 1,3,4-thiadiazolo[2,3-c][1,2,4]triazines (**198**), such as **198** (R=OEt, Ph), which display mesoionic or Zwitter ionic character[60].



B) Silylation

Mono and bis(trimethylisily)aminotriazinones (**200**) have been successively obtained[61]. Thus, 3-thioxo-4-methylamino-6-phenyl-1,2,4-tri-

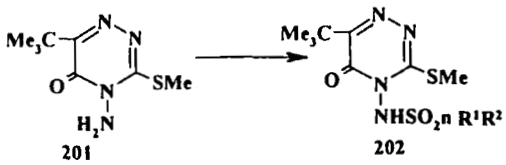
azin-5(4H)-one (**199**) was refluxed with Me_3SiCN until the pot temperature reached 175°C to give **200** (R=Me_3Si; R^1=Ph, R^2=Me). Compound **200** is a more effective preemergence herbicides than currently used herbicides[61].



199 200

C) Sulfonation

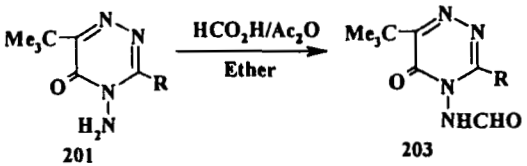
6-Terbutyl-3-methylthio-4-sulfimido-1,2,4-triazin-5-ones (**202**, R = alkyl, arylalkyl, substituted aryl; R^2=alkyl, alkoxyalkyl, alkylthioalkyl. Substituted aryl, arylalkyl; n=0 or 1) were obtained as herbicides[62] from treatment of N^4-aminotriazine **201** with a mixture of DMSO-CH_2Cl and $(CF_3SO_2)_2O$ at-8°C.



201 202

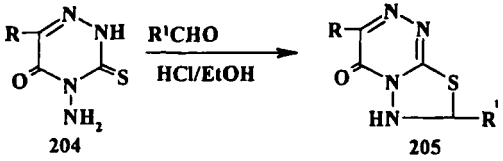
D) Formylation

4-Formylamino-6-tertbutyl-1,2,4-triazin-5-one (**203**, R=alkoxy, alkylthio, alkylamino, dialkylamino) are obtained as herbicides via treatment of the corresponding N^4-aminotriazine (**201**) with a mixture of HCO_2H-Ac_2O in dry ether[18].



201 203

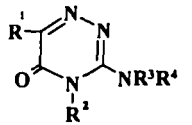
On the other hand, cyclocondensation of aminotriazinethiones (**204**, R=Me, Ph) with R^1CHO[R^1=Ph; O_2NPh; (un) substituted 3,4-(methylenedioxy)phenyl, $HO(MeO)C_6H_3$] yielded thiadizolo[2,3-e] [1,2,4]triazines (**205**)[63].



204 **205**

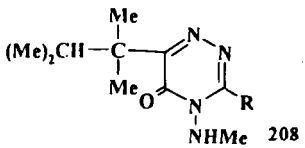
E) Chloronation and Amination

The aminotriazinones (**207**, R^1R^2=alkyl, alkoxyalkyl (methyl) cycloalkyl, (Un) substituted aralkyl, aryl; R^3R^4=H, alkyl, (methyl) cycloalkyl, R^3R^4 N=piperidinyl, morpholinyl) were obtained as herbicides, via chloronation of 6-alkyl-mercapto-4-alkyl-1,2,4-triazin-5(4H)-ones (**206**) with Cl_2CO in 91% yield and aminated with Me_2NH in PhMe. Compound **207** (R=Me_2CH, R^2R^4=Me) prevented emergence of Avena fatua[64].



207

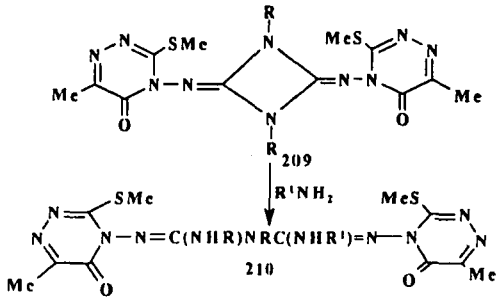
3,4-Bis-(methylamino)-6-(2,3-dimethyl-2-butyl)-1,2,4-triazin-5 (4H)-ones (**208**, R=NHMe) were obtained as a herbicide by amination of thioalkyl precursors (**208**, R=SR; R=alkyl) with $MeNH_2$ in Me_2CHOH containing AcOH[65].



208

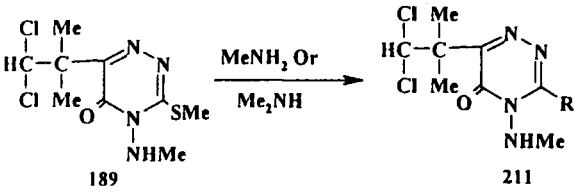
On the other hand, pentasubstituted biguanides (**210**, R=Ph, C_6H_4Cl-4, $C_6H_4OMe_4$; R^1=Me, alkyl, $CH_2CH_2NH_2$, CH_2CH_2OH, CH_2CO_2Me,

CH_2Ph, C_6H_4Cl-4. $(CH_2)_5$, NMe_2) were obtained by reacting bis (triazinylimino)diazetidines (**209**) with RNH_2 (Scheme 34)[66].



SCHEME 34

Also, 6-(1,1-dichloro-2-methyl-2-propyl)-4-methylamino-1,2,4-triazin-5(4H)-ones (**211**, R=NHMe, NMe_2) were obtained as herbicides by condensation of **189** (R=SMe) with $MeNH_2$or Me_2NH[19].



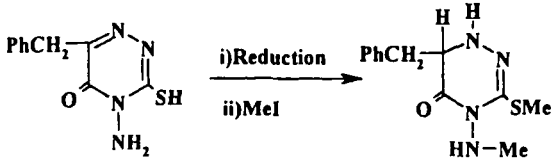
F) Photoinduced deamination reactions

photokinetics show that the deamination reactions of 4-amino-3-methylthio-1,2,4-triazinones (**201**, $R^1=NH_2$) is dependent on oxygen, water and that the 3-methylthio-1,2,4-triazine-5-ones (**212**, R^1=H) were formed in an intermolecular reaction. The participation of an H-transfer from the amino group to carbonyl oxygen (intramolecular) is negligible under environmental conditions[67].

201, R^1:NH_2, R=CMe_3
212, R^1:H, R=CMe_3

G) Reduction

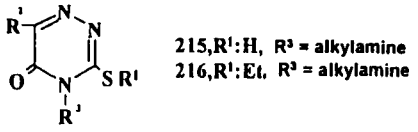
3-Alkylthio-4-methylamino-1,6-dihydro-1,2,4-triazin-5(4H)-ones (**214**) were obtained by the reduction of 3-thioxo-4-amino-1,2,4-triazin-5-one (**213**) and successive S-alkylation[68].



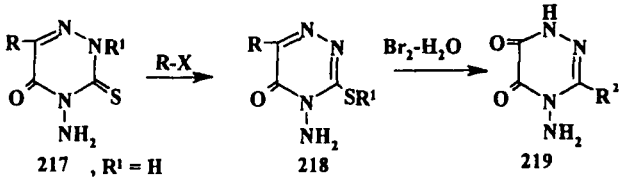
213

H) Alkylation

Alkylation of 4-substitutedamino-3-methylamino-1,2,4-triazin-5-ones (**215**, R=H, alkyl, alkenyl, aryl, aralkyl; R^2=alkyl, alkenyl, aralkenyl, aryl, aralkyl; R^3=alkylamino) by refluxing with EtSH containing KOH gave **216** (R^1=Et) as herbicides[17].



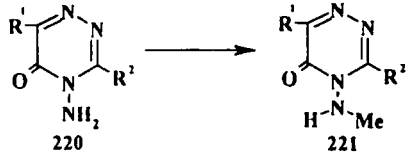
While, alkylation of aminotriazinone **217** (R=H, Me, Me_3C; R^1=H) with various alkylation agents gave mixture of **217** (R^1=Me, Et, CH_2Ph. CH_2CH: CH_2) and **218**. Oxidation of **218** (R=H; R^1=Me) with Br_2 in H_2O and MeOH yielded **219** (R^2=SMe, S(O)Me) and **218** (R=MeO; R=Me) respectively. Compound **219** underwent further alkylation at the N-1 position (Scheme 35)[69].



217 , R^1 = H **218** **219**

SCHEME 35

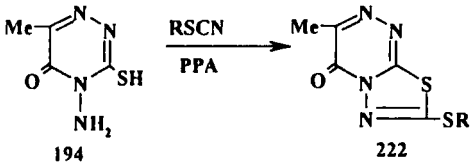
Herbicidal and insecticidal N^4-alkylamino-3-alkylthio-6-substituted 1,2,4-triazin-5(4H)-ones (**221**, R^1=alkyl, haloalkyl, 2-furyl, 2-thienyl, (Un) substituted cycloalkyl; Ph, $PhCH_2$: R^2=MeS, EtS, R^3R^4N; R^3=H, Me; R^4=alkyl, alkynyl, cyclopropyl. Cyclopropyl methyl) were obtained via methylation of the corresponding aminotriazine **220** using Bu_4N^+Br as phase-transfer catalyst[70].



220 **221**

I) Cycloaddition Reactions

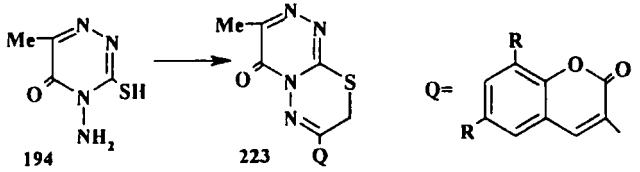
2-Alkylthio-6-(Me/CH_2Ph)-5-oxo-5H-1,3,4-thiadiazolo[2,3-c] [1,2,4]triazines (**222**) were obtained by cycloaddition of triazinone **194** with RSCN catalyzed by polyphosphoric acid[71].



194 **222**

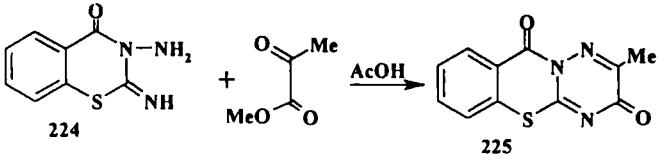
J) Cyclocondensation Reactions

Condensation of 4-amino-5-oxo-3-thioxo-6-methyl-1,2,4-triazine (**194**) with 3-(ω-bromoacetyl) coumarins in anhydrous EtOH and DMF, led to the direct formation of 7-(2-oxo-2H-1-benzopyran-3-yl)-methyl-4H,8H-[1,2,4]triazino[3,4-b][1,2,4]thiadiazin-4-ones (**223**, R=H, Br, Cl; R_1=H, MeO, Br, Cl)[72].



194 **223**

Finally, 2-substituted 3H, 10H-[1,2,4]triazino[6,1-b][1,3]benzothiazine-3,10-diones (225) was isolated from cyclocondensation of aminoiminodihydrobenzothiazinone (224) with some α-oxo-carboxylic esters in AcOH.[73]



CONCLUSION

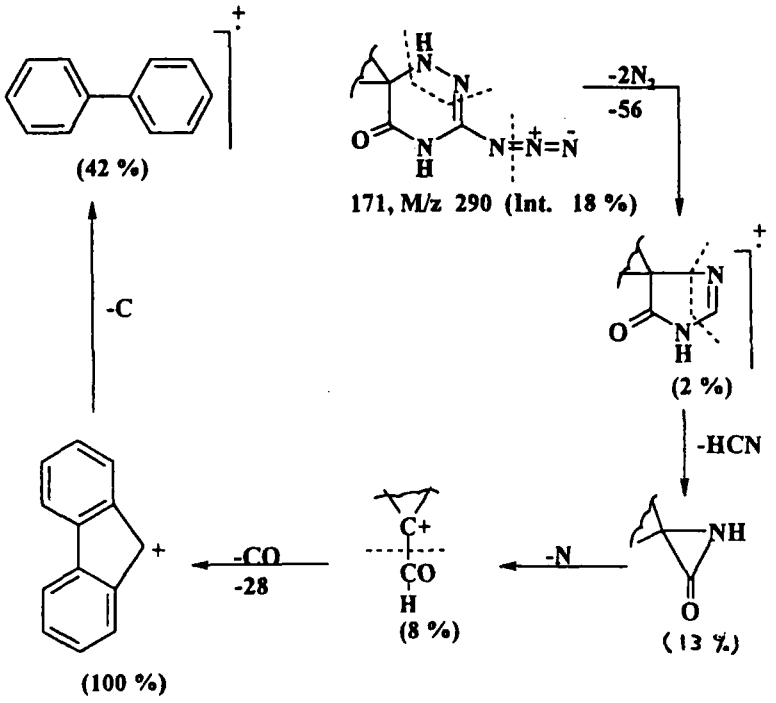
In this review we have focused on synthesis of 3-thioxo-6-substituted-1,2,4-triazin-5-ones and 4-amino-6-substituted-3-thioxo-1,2,4-triazin-5-ones. The number of possible combinations of uncondensed 1,2,4-triazine rings with other heterocyclic rings is large. Both physical and chemical data for the titled compounds synthesized are also scant. From the results described in this review several features emerge concerning the chemical reactivity of these interesting prepared compounds[74,75].

The use of 1,2,4-triazinthione moieties as precursors awaits further systematic development. Many opportunities for discovering noval synthesis and reactions still exist in this field. More significant to us is their medicinal and pharmaceutical applications as agents for anticancer, anti AIDS, antimicrobial, CNS and as herbicides.

In addition, the spectral studies of 3-thioxo-1,2,4-triazin-5-ones have been recorded.[1–6,9,72] For example, the fine structure of compound **171** was based on MS (Scheme 36)[6].

ABOUT THE AUTHOR

Reda Mohammady Abdel-Rahman was born in Banha, Kaluobia, Egypt in 22 April 1951. He attended Banha Secondary School from 1966 to 1969. He obtained his B. Sc. and M. Sc degrees from Faculty of Science, Ain-shams University, Cairo, in 1975 and 1978, respectively. He received



SCHEME 36

his ph. D. in 1982 from the same university with a thesis entitled; Reactions with Uncondensed 1,2,4-triazines containing Active Groups, under the supervision of prof. H.A. Zaher. After a period of teaching, he was pointed as Assistant professor and then Professor of organic chemistry with 75 publications in the iterested journals of organic-biochemistry. From Development Program and National Effort, to discover drugs effective in the treatment of AIDS and drug synthesis for anticancer screen in co-operation with Prof. Dr. V. L. Narayanan, Prof. Dr. John P. Bader, and Prof. Dr. Michael R. Grever, National Cancer Institute (Institute of Health), Bethesda, Maryland, U.S.A.

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