REVIEW

Department of Chemistry, Faculty of Education, Ain-Shams University, Roxy, Cairo, Egypt

Chemistry of uncondensed 1,2,4-triazines, part IV
Synthesis and chemistry of bioactive 3-amino-1,2,4-triazines and related compounds – an overview

R. M. ABDEL-RAHMAN

Studies on the chemical reactivity of bioactive 3-amino-1,2,4-triazines are reviewed. The synthesis, unique features and pharmacological significance of theses constituents are discussed.

1. Introduction

As a part of a research program directed towards the preparation of new drugs, we have previously discribed the synthesis, chemistry and chemotherapeutic activities of a series of 3-substituted amino-1,2,4-triazines and related compounds [1–15]. Some 3-amino-1,2,4-triazines form complexes with metal ions and are used for determination of metal traces [14, 15]. In particular, we are interested in uncondensed 1,2,4-triazines as biocidal plant protection as well as anti HIV and anticancer agents [17–21]. 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (lamotrigine) plays a vital role in many biological processes. Synthetic analogs have been prepared which exhibited remarkable pharmacological activity [22–23]. Also, some methods for the determination and isolation of lamotrigine and its metabolite in human plasma, and in guinea pigs have been developed [24–26].

In this review, we report the synthesis, chemical reactivity and pharmacological significance of 3-amino-1,2,4-triazine derivatives and related compounds.

2. Synthesis of 3-amino-1,2,4-triazines

A convenient method for the synthesis of 3-amino-1,2,4-triazines was deduced from treatment of α,β-bioxygen compounds with aminoguanidines [27]. Thus, reaction of RCOCHO ($R = CH_2CHOCH_2OH$) with aminoguanidine bicarbonate in phosphate buffer at pH 7.0 using $CHCl_3$-MeOH-H_2O as the irrigant gave the 3-amino-1,2,4-triazines **1** and **2** (Scheme 1).

Similarly, reactions of aminoguanidine (guanylhydrazine) with 3-deoxy-D-erythro-hexos-2-ulose (**A**), 3-deoxy-D-glycero-pentos-2-ulose (**B**), D-erythro-hexos-2-ulose (**C**), and D-glycero-pentos-2-ulose (**D**) were examined at 37 °C in a solution of pH 7 (phosphate buffer). From compounds **A** and **B**, two major products **3** and **4** were received. The ratio of the products was independent of the amount of aminoguanidine present or the order of mixing the reagents. With compounds **C** and **D** only the 5-substituted triazine derivatives **5** (n = 2,1 respectively), were formed [28].

A non-fluorescent chromophore 2-[(3-amino-1,2,4-triazin-5-yl)-methylene]hydrazinecarboximide amide **6**, was formed during the aerobic reaction between aminoguanidine and glucose in aqueous solution at pH 7.4 [29].

Methylglyoxal was heated with aminoguanidine under physiological conditions [1, 2] to form two isomeric 3-amino-5-methyl-1,2,4-triazines (**7**) and 3-amino-6-methyl-1,2,4-triazines (**8**) (Scheme 2).

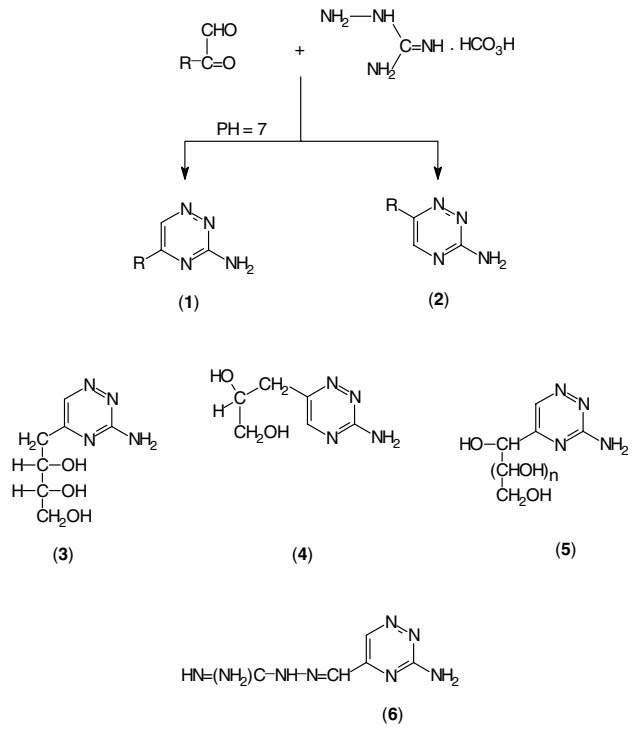
Under the reaction conditions no methylglyoxal-bis-uanyl-hydrazone was detected. Aminoquanidine prevented the irreversible modification of human plasma protein by a physiological concentration of methyl glyoxal (1 mM) [1, 2].

3-Amino-5,6-di(2-pyridyl)-1,2,4-triazine (**9**) was synthesized by condensation of bicarbonyldipyridin-2-yl with aminoguanidine [30].

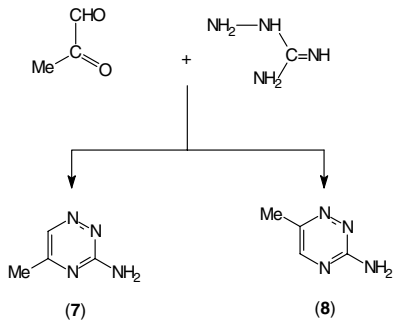
3-Amino-5-methyl-6-phenyl-1,2,4-triazine-4-oxide (**11**) was prepared [31] by PhCO(=NOH)Me with $H_2NN{=}C(SMe) \cdot NH_2.HBr$. Reaction of monoxime with aminoguanidine yielded 3-amino-5-methyl-6-phenyl-1,2,4-triazine (**10**), which was also obtained by deoxygenating of **11** (Scheme 3).

Cyclocondensation of 1-(4-phenylphthalazin-1-yl-amino)-guanidine (**12**) with chloroacetaldehyde diethyl acetal in the presence of NaOEt led [32] to the formation of 3-amino-1-(4-phenylphthalazin-1-yl)-1,6-dihydro-1,2,4-triazine (**13**) as fungicidal agents.

Scheme 1



Scheme 2



(**7**) (**8**)

3-[[2-(2-Propynylthio)phenyl]amino]-1,2,4-triazines (**15**) were prepared starting from as-triazine **14** and 2-aminothiophenol [35]. Thermolysis of **15** in PhBr gave the benzothiopyranilamino-1,2,4-triazines **16** as major products (Scheme 4).

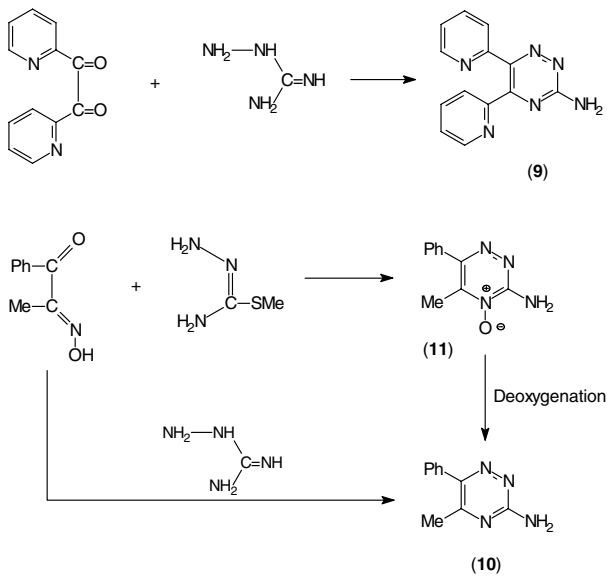
A number of 3-substituted amino-5,6-diphenyl-1,2,4-triazines **18** have been prepared [3] by reaction of 3-chloro-5,6-diphenyl-1,2,4-triazine **17** with the appropriate aliphatic or aromatic amines in DMF (Scheme 5). Compounds **18a**–**18n** showed moderate activity against some bacteria, while compound **18f** had activity against *Candida utilis*. Compound **18f** also showed 46% inhibition at 500 μ_g/ml towards Aspergillus fumigatus [3].

3-Amino-6-methyl-5-styryl-1,2,4-triazines (**20**) were obtained by warming 3-amino-5,6-dimethyl-1,2,4-triazine (**19**) with aldehydes in the presence of NaOEt [17].

The structure of **20** (R = thiophene-2) was deduced from spectral data. The IR spectrum showed ν at 3300 (NH_2), ^{1}H NMR recorded a signal at δ 1.5, 6.5–6.7 due to CH_3 and coupling of CH=CH protons, in addition to two signals at δ 6.8, 7.1–7.5 and 8.82 ppm corresponding to thiophene, CH, NH and NH_2 protons. M/S showed m/z (Int%): M^+ 218 (73.19), and the base peak at 148 (100) due to the methyl butyene thiopheno radical [17].

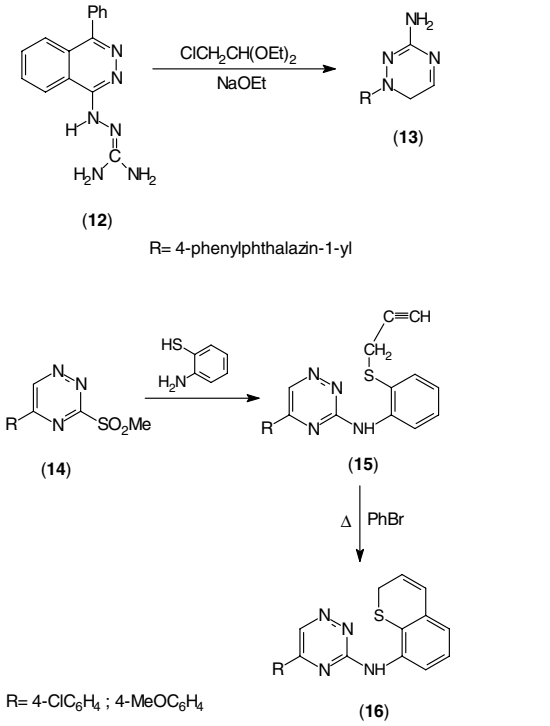
Addition of mercaptoacetic acid to hydrazone **21** resulted in further condensation to 3-substituted amino-5,6-diphenyl-1,2,4-triazine (**22**) [3]. the structure of **22** was established from UV (EtOH) λ_{max} 220 (1,2,4-triazine), 260 (thiazolidin-4-one) and 330 nm (vanilline moiety), the IR spectrum showed ν at 3500–3300 (OH, NH), 3050 (aro-

Scheme 3



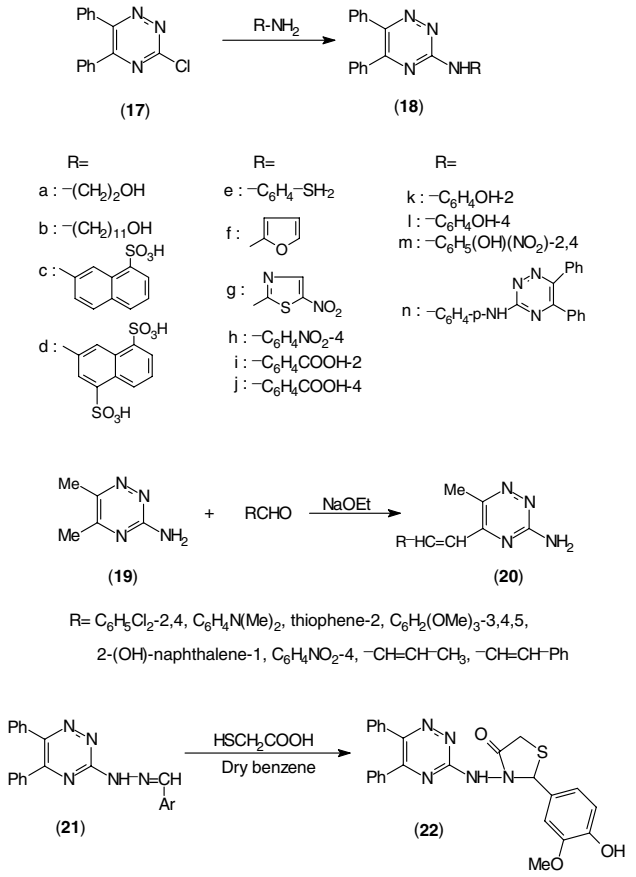
(**9**) (**11**) (**10**)

Scheme 4



(**12**) (**13**) (**14**) (**15**) (**16**)

Scheme 5



(**17**) (**18**) (**19**) (**20**) (**21**) (**22**)

matic CH), 2910 (aliphatic CH), 1650 (C=O), 1470 cm^{-1} (def. CH_2). PMR (DMSO-d_6) recorded signals at δ 1.9 (s, 3 H, CH_3O), 2.5 (s, 2 H, CH_2), 6.8 (s, 1 H, OH), 12.4 (s, 1 H, NH, exchangeable with D_2O). Compound **22** showed antibacterial activity *in vitro* [34].

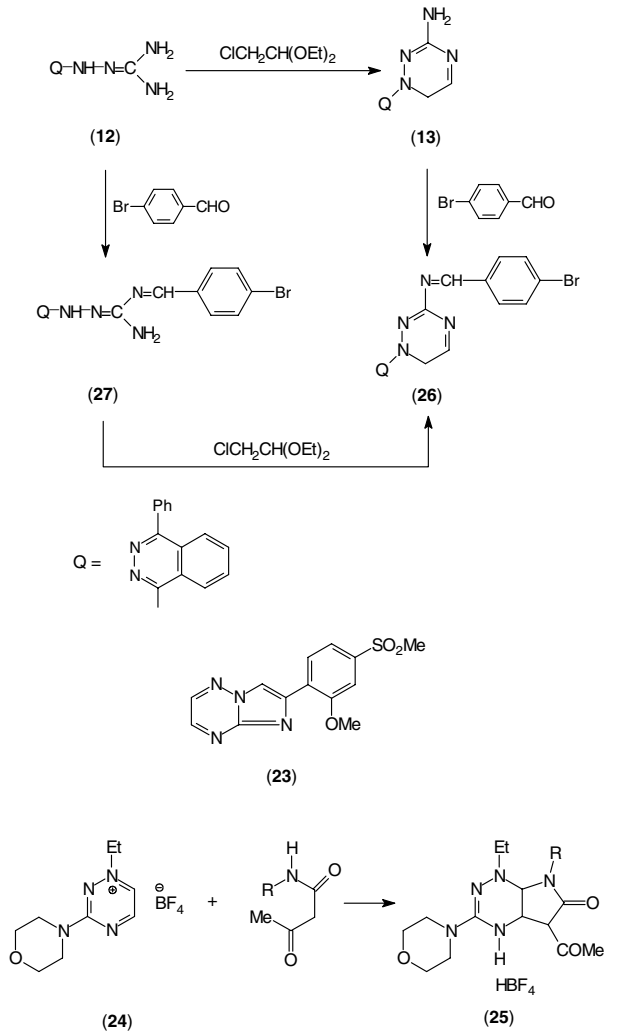
3. Chemical reactivity of 3-amino-1,2,4-triazine derivatives

The reactivity of the 1,2,4-triazine ring depends on the type of activation, the nature of substituents and leaving groups, the character of the nucleophile employed, the stability of δ-adducts, position selectivity and polarity of the solvent [35].

Imidazo[1,2-*b*][1,2,4]triazine (**25**) was protonated at the imidazo nitrogen due to the basicity properties between aryl analogs and the bridge head heterocycle [36].

3-Amino-5,6-(2-pyridyl)-1,2,4-triazine (**9**) was found to be a selective and sensitive reagent for Fe(II) [14]. Similarly, 3-amino-5,6-di(2-pyridyl)-1,2,4-triazine (ADPT) (**9**) was used as a reagent for determination of ruthenium(III), rhodium(III) and palladium(II). All the three metal ions form stable complexes with ADPT, in acidic medium (λ_{max} 465 nm, $\varepsilon = 1.10 \times 10^4$ l/mol cm (Ru), and λ_{max} 405 nm, $\varepsilon = 7.7 \times 10^3$ l/mol cm) (Rb) where as Pd(II) in alkaline medium had λ_{max} 400 nm, $\varepsilon = 6.96 \times 10^3$ l/mol cm) [15].

Scheme 6



Reaction of Ae_3Al with 3-amino-5,6-dimethyl-1,2,4-triazine (**19**) in toluene yielded $[(AlMe_2)]_5[C_{11}H_{15}N_8][AlMe_3][C]$ [37].

Reaction of 1,2,4-triazinium salts **24** with $MeCOCH_2 \cdot CONHR$ (R = Ph, 4-MeC_6H_4, CH_2Ph) yield 1,4,4a,5,7a-hexahydro-6*H*-pyrrolo[3,2-*e*][1,2,4]triazine-6-ones **25**. The first direct annelation to the 1,2,4-triazine ring is based on the diaddition of bifunctional nucleophiles at C-5 and C-6 [38].

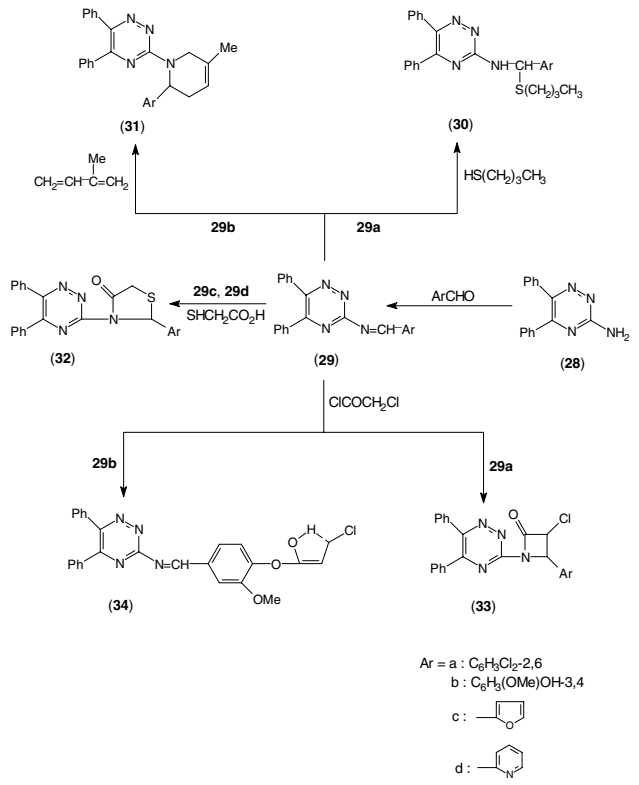
Condensation of **13** with *p*-bromobenzaldehyde formed the azomethine **26** which was also obtained by condensation of **12** with *p*-bromobenzaldehyde to give the aminoguanidone **27** followed by reaction with chloroacetaldehyde diethyl acetal (Scheme 6) [32].

Abdel-Rahman et al. [16] obtained the 3-arylidene-5,6-diphenyl-1,2,4-triazines **29** from condensation of **28** with the appropriate aldehydes. The behavior of **29** towards the addition of some reagents has been studied [39, 40]. Thus, fusion of **29a** with butane-1-thiol produced the thioether **30**, while refluxing **29b** with 2-methyl-1,3-butadiene in dry toluene gave 1-(5′,6′-diphenyl-1′,2′,4′-triazin-3′-yl)-2-aryl-5-methyl-3,6-tetrahydropyridine (**31**) through diene-dienophile-1,3-cycloaddition [41, 42].

Addition of thioglycolic acid [43, 44] to **29c** followed by cyclization via condensation furnished the 2,3-disubstituted-4-thiazolidinones **32a**, **b**. (Scheme 7).

Addition of α,β-bifunctional chloroacetyl chloride to compound **29** indicated that the course of this reaction is governed by the medium and reaction conditions. Thus, cycloaddition of chloroacetyl chloride with 3-arylidene-5,6-diphenyl-1,2,4-triazine (**29a**) was carried out in dry benzene-triethylamine as an acid binding agent to give the corresponding lactam **33** [16]. Refluxing of **29b** with chloroacetyl chloride in the presence of aqueous bicarbonate [45] gave the 3-methoxy-4-chloroacetoxy-benzylidene derivative **34**.

Scheme 7



Addition of sodium ethylate to **29a** yielded the adduct products **35**. Formation of **35** indicated the greater polarity of the nucleophil and gives the possibility of the addition on exo N=C in the position 3 and endo N=C group in 4,5-positions in the 1,2,4-triazine moiety [46].

Zaher et al. [47] reported that fusion of 3-(*N*-arylidenehydrazone)-1,2,4-triazines with thiophenol gives the addition on the 3-hydrazone and 4,5 N=C linkage of the 1,2,4-triazine moiety. Thus, refluxing of **29a** with thiosalicylic acid in dry toluene yielded the desired thioether **36**. 2-Aryl-3-(5′,6′-diphenyl-1′,2′,4′-triazin-3′-yl)-1,3-benzothiazin-4(2*H*)one (**37**) was obtained by refluxing **36** with aqueous NaOH, while fusion of **29a** with thiosalicylic acid and *p*-chlorothiophenol gave the thioethers of the type **38a**, **b**. Moreover, treatment of **38b** with 1,2-dibromoethene in ethanolic KOH led directly to the formation of 1-substituted methyl-4,5-tetrahydroimidazolo[2,3-*c*][1,3,5] triazine (**39**). Reduction of **29a** and or **29b** with Zn-AcOH in ethanol gave hexahydro-5,6-diphenyl-1,2,4-triazin-3-one (**40**) (Scheme 8) [48].

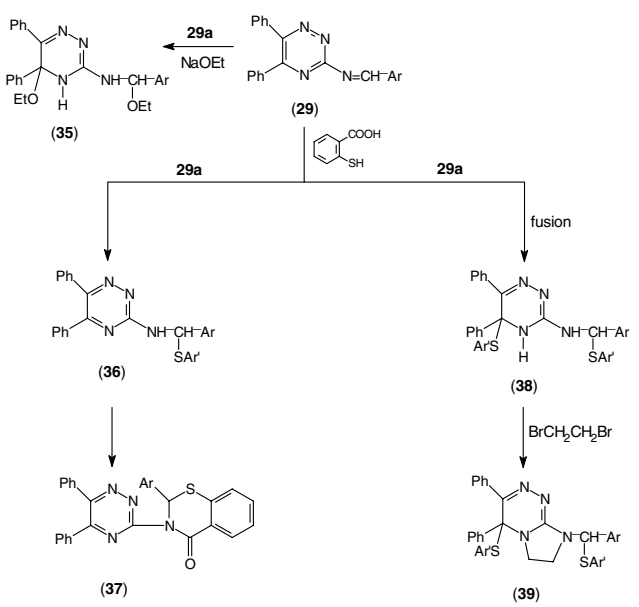
Some heterobicyclic nitrogen systems bearing the 1,2,4-triazine moiety **43**–**49** have been achieved by treatment of 3-amino-6-methyl-5-styryl-1,2,4-triazines **20** with some cyclic and acyclic oxygen compounds followed by heterocyclization [17].

Condensation of **20** with phthalic anhydride, oxazolone (**44**) 3,1-benzoxazin-4-one (**46**) and 4*H*-2,5,6-trisubstituted 1,3,4-oxadiazine (**48**) in dry pyridine yielded the phthalimide **43**, the imidazolone **45**, the quinazolinone **47** and the dihydro-1,2,4-triazine **49** (Scheme 10) [17].

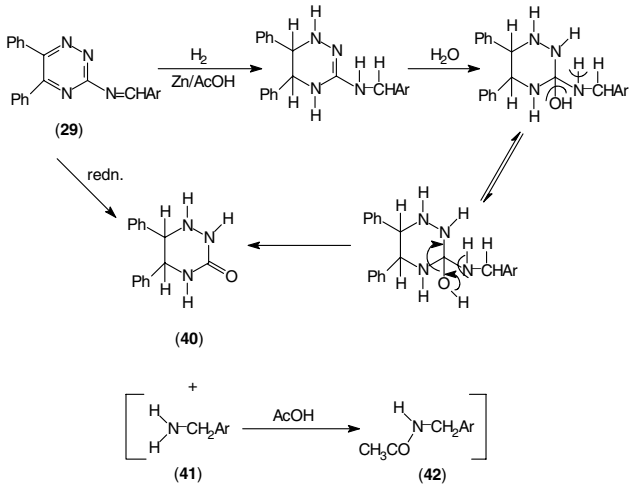
Thiouracil moieties play a vital role in many biological process and are used as intermediates for the synthesis of drugs [49, 50]. Thus, reaction of **20b** with isothiocyanate in DMF afforded the N^1,N^2-disubstituted thioureas **50a**, **b** which upon heterocyclization by warming with malonic acid in a few drops [51] of acetyl chloride, produced the 5H-1-acetyl/phenyl-3-[5-(4′-dimethyl-aminostyryl)-6-methyl-1,2,4-triazin-3-yl]-2-thioxopyrimidin-4,6-diones **51a** and **51b** (Scheme 11) [17].

Similarly, addition of acrylonitrile to compound **20** in pyridine-water yielded 3-cyanoethylamino-1,2,4-triazine (**52**) which on boiling with 5% aqueous HCl [52] led directly to the formation of 2*H*-4-hydroxy-7-methyl-8-(substituted)pyrimido[3,2-*b*][1,2,4]triazine (**53**) (Scheme 12) [17]. The iminopyrimidotriazinone **54** was obtained from refluxing compound **20** with ethyl cyanoacetate in NaOEt [17]. MS of **52** showed the M^+ at m/z (Intr%) 355 (2.47) with the base peak at m/z 302 (100%) due to 3-aminotriazine (Scheme 13) [17].

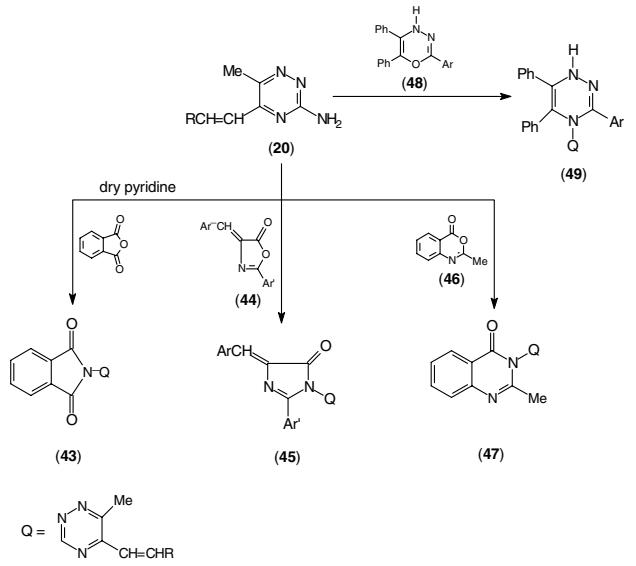
Scheme 8



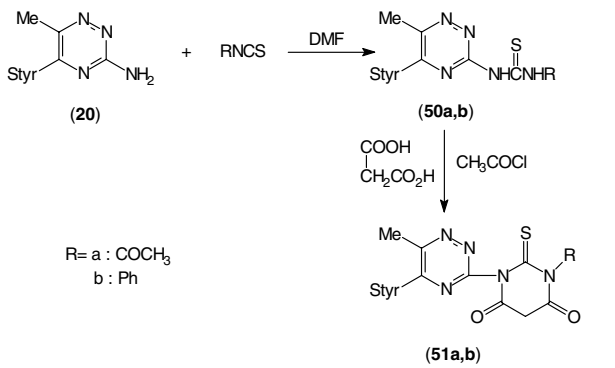
Scheme 9



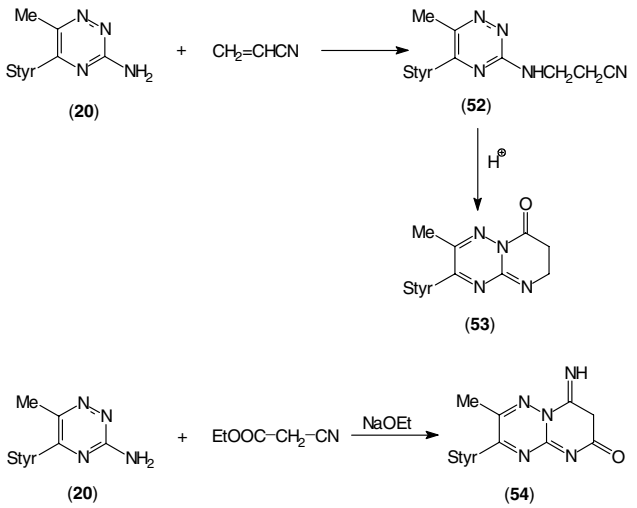
Scheme 10



Scheme 11



Scheme 12

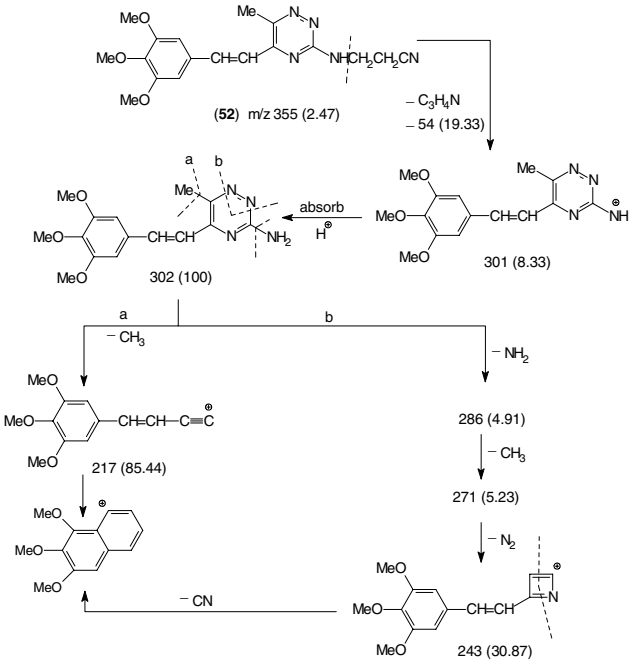


Fusion of **20** with bifunctional oxygen compounds such as 2-ethoxyethanol and diethyl oxalate or ethyl cinnamate led to the formation of imidazolotriazine (**55**), imidazolotriazin-dione (**56**) and 3,4-dihydro-4-phenyl-7-methyl-8-arylpyrimido[3,2-*b*][1,2,4]triazin-2-one (**57**) (Scheme 14) [17]. The presence of a 5-(*p*-dimethylaminostyryl)-1,2,4-triazine moiety in compounds **45** and **54** enhanced the anti HIV and anticancer activities [17].

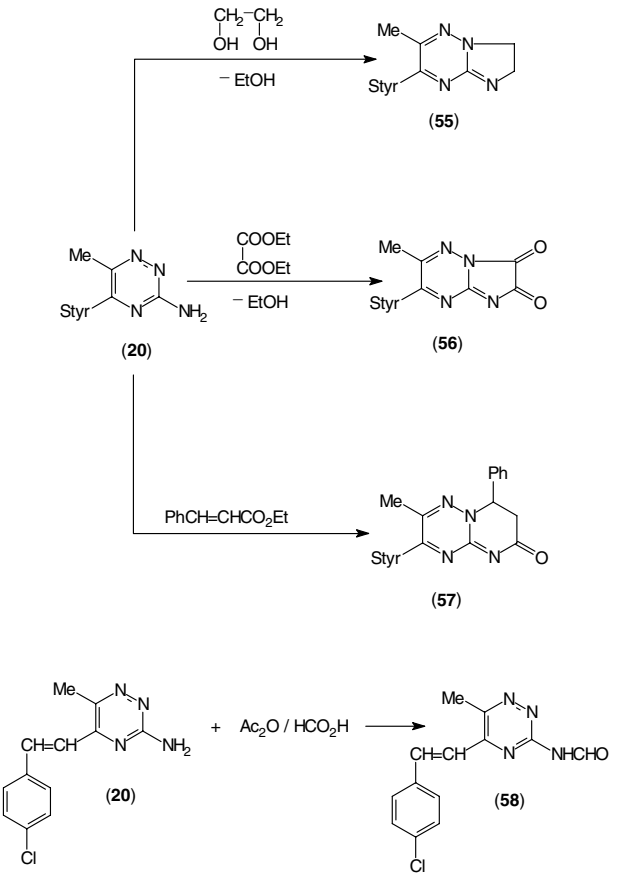
In search for new anti HIV and anticancer agents, Abdel-Rahman et al. [18], received some heterobicyclic nitrogen systems starting from 3-formylamino-as-triazine (**58**) which was obtained from treatment of an ethereal solution of 3-amino-6-methyl-5-p-chlorostyryl-1,2,4-triazine (**20**) with Ac_2O-HCO_2H [53].

Condensation of **58** with ethanolamine in ethanol afforded **59** which upon cyclization with Ac_2O yielded 4,5-dihydro-1-[6-methyl-5-(4′-chlorostyryl)-1,2,4-triazin-3-yl]imidazoline (**60**) (Scheme 15) [18].

Scheme 13



Scheme 14

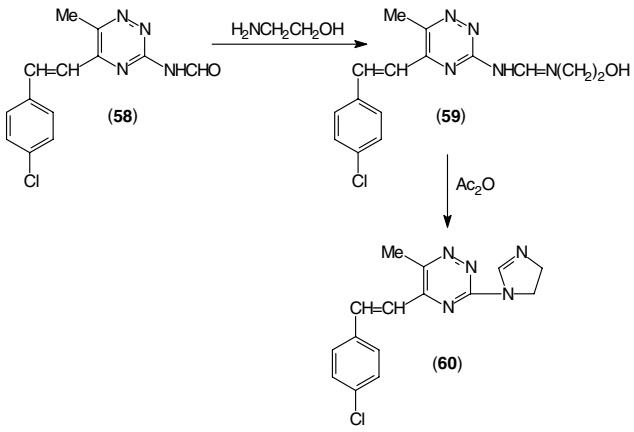


Addition of thiourea to **58** in NaOEt yielded the carbinol **61** which upon cyclization yielded 6-methyl-1-[6-methyl-5-(4′-chlorostyryl)-1,2,4-triazin-3-yl]-1,3,5-triazin-4-thione (**62**) (Scheme 16) [18].

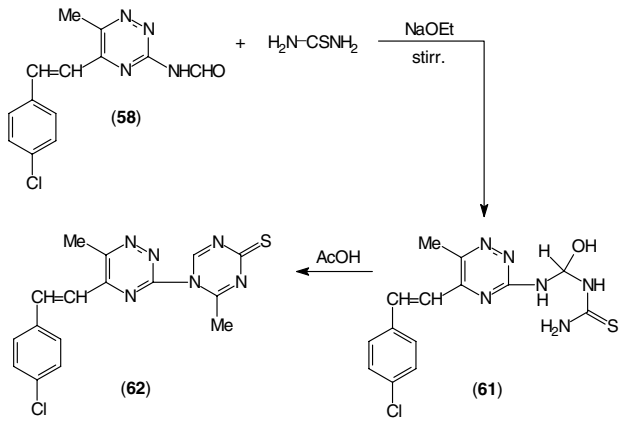
The heterobicyclic nitrogen compounds **63**–**68** have been obtained [18] starting from condensation of amidazone **63** with some oxygen compounds such as acetic acid, diethyl carbonate, α,β-unsaturated-ketoacid, benzoin and isatine in neutral medium (Scheme 17) [18].

Thioether are known to possess biocidal activities [4–10], while the 3-amino-1,2,4-triazine derivatives also have potential biological activities [17–21]. Based on these obser-

Scheme 15



Scheme 16



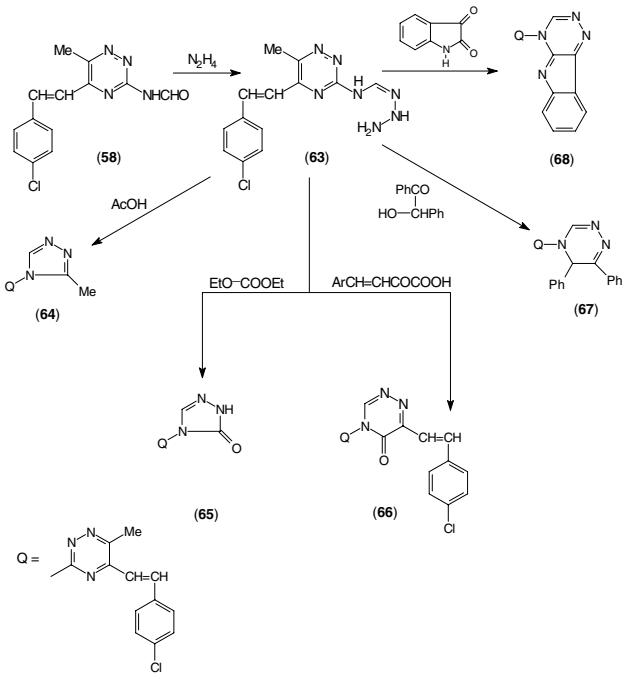
vations, compounds **20a**–**f** were treated with 4-chlorothiophenol to yield the thioethers **69a**–**d** and **70a**, **b** (Schemes 18, 19) [18].

The UV absorption spectrum of **69** recorded λ_{max} (log ε) 290 (2.5) nm due to the inhibition of conjugation of side chain 1,2,4-triazine, while that of **70** showed λ_{max} (log ε) 331.5 (2.67) and 290 (2.91) nm. The IR spectrum of **70** recorded absorption bands at ν 3100 (NH_2), 1650 (C=C), 1070 cm^{-1} (C–S–C). The MS of **69** revealed the presence of M^+ at m/z 425 (0.48), 123 (10.14) in addition to the base peak at m/z 159 due to 4-methylbytyene chlorophenyl radical [18].

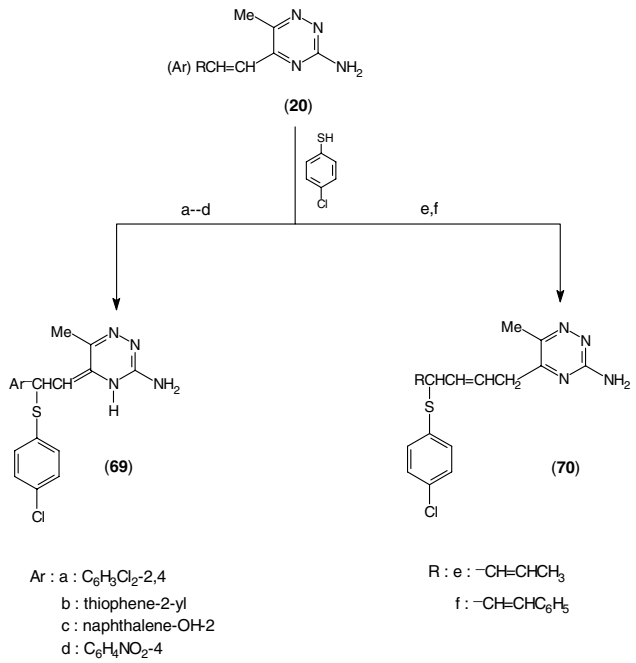
Compound **70b** was strongly effective towards HIV and tumours, while **70a** and **69** had a moderate activity towards HIV with lower activity towards tumour cases [18].

Abdel-Rahman et al. [54] prepared some new substituted pyrazoles containing the 1,2,4-triazine moiety as antimicrobial agents. Treatment of benzoylacetonitriles **71** in the presence of DMF gave 3-substituted amino-5,6-diphenyl-

Scheme 17

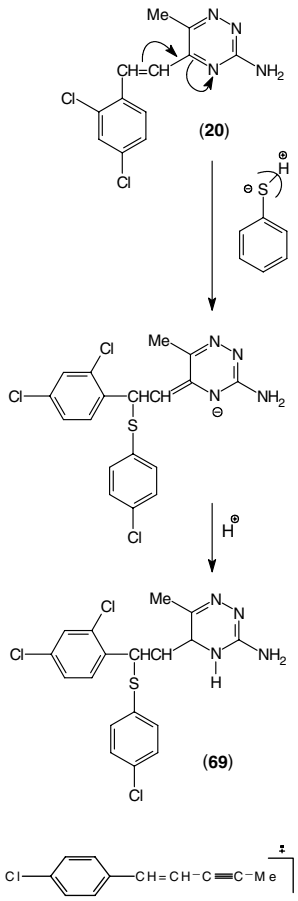


Scheme 18

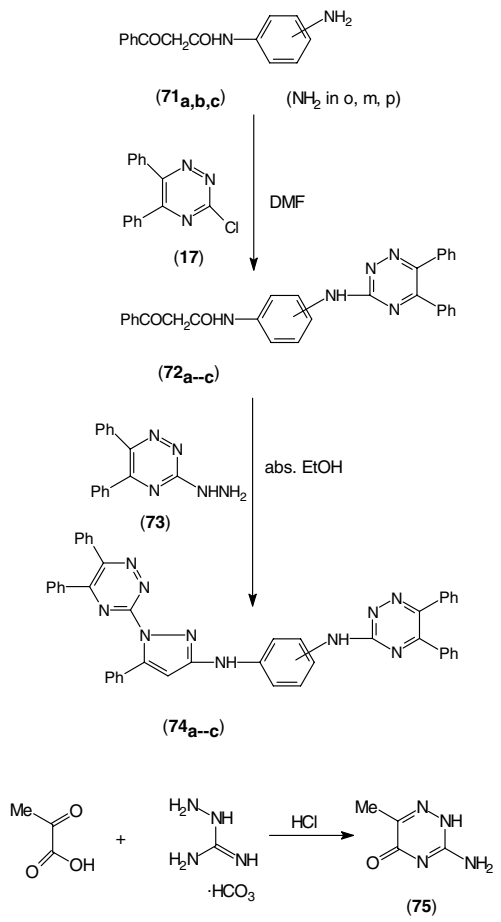


1,2,4-triazine (**72**), refluxing compound **72** with 3-hydrazino-5,6-diphenyl-1,2,4-triazine (**73**) in abs. ethanol yielded the 1-(5′,6′-diphenyl-1,2,4-triazin-3′-yl)-3-arylamino-5-phenylpyrazolines **74** (Scheme 20).

Scheme 19



Scheme 20



The UV spectrum of **74** (EtOH λ_{max} nm) revealed absorption bands at 285 ($n - \pi^*$), 255 ($n - \sigma^*$) and 200 ($\pi - \pi^*$) and the IR spectra recorded the presence of NH, C=N and aryl groups in the absence of a C=O group, the ^{1}H NMR spectrum (60 MHz, DMSO-d_6) showed signals at δ 5 corresponding to a methine proton at position 4 of the pyrazoline moiety, 6.9–8.5 due to aromatic protons, in addition the resonances at 11.1 and 11.5 ppm assigned to bonded NH protons of aminopyrazolines/1,2,4-triazine. Compound **74** exhibited a strong antibacterial activity *in vitro* against *Candida albicans*, *Bacillus cereus* and *Staphylococcus aureus*, but was inactive against *Klebsiella aerogenes* [54].

4. Synthesis and chemistry of 3-amino-5-oxo-1,2,4-triazine derivatives

3-Amino-6-methyl-1,2,4-triazin-5(2*H*)one (**75**) was obtained from boiling a solution of aminoguanidine bicarbonate with pyruvic acid in hydrochloric acid [11].

Imidazo[1,2-*b*][1,2,4]triazines (R^1 = Ph, R^2 = H, Me, Et) (**76**) were produced from refluxing compound **75** with α-haloketone in a mixture of ethanol-triethylamine [12].

3-Amino-6-substituted-1,2,4-triazin-5(4*H*)ones (R = alkyl, alkenyl, alkynyl) (**78**) were prepared as herbicides from a mixture of 4-amino-6-*tert*-butyl-3-methylthio-1,2,4-triazin-5-one (**77**), alkyl alcohol, Et_3N and 2,3-epoxy-1-propanol at room temperature in 60 h [55].

Abdel-Rahman, prepared 3-(2′-mercaptoanilino)-6[2′-1,3-disubstituted urea)phenyl]-1,2,4-triazin-5(4*H*)one (**80**) from fusion of **79** with 2-aminothiophenol [56]. Heating **79** with primary aromatic amines in the presence of dry benzene gave the 1,3-disubstituted ureas (**81**) (Scheme 21).

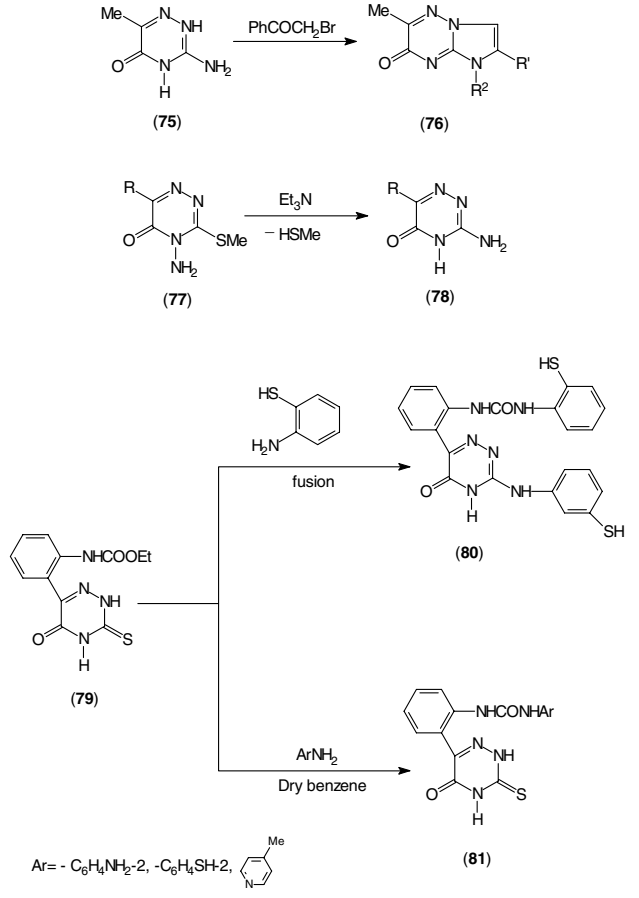
Similarly, Abdel-Rahman et al. obtained 3-arylamino-6-(2-arylidinephenyl)-1,2,4-triazin-5-ones **83** by interaction of **82** with primary aromatic amines in the presence of isopropyl alcohol [57]. Acylation and alkylation of **83** with chloroacetyl chloride and monochloroacetic acid in the presence of aqueous sodium hydroxide [43] yielded the isomeric systems **84** and **85** (Scheme 22). In the UV spectrum of **84** and **85** the shift in wave length λ_{max} at pH 13 is diagnostic for a phenol (**84a**) and the intense k-band at 265 nm is indicative for a chromophore conjugated with the ring. Compounds **82** and **83** showed a strong effect towards the tested fungi, which could be attributed to the thiophenol and thioether moieties in the bicyclic systems [43].

Refluxing **77** with AcOH-fused AcONa and CS_2 in KOH led to the 2-methylbenzimidazole **86** or the 2-mercaptobenzimidazole **87** (Scheme 23) [57].

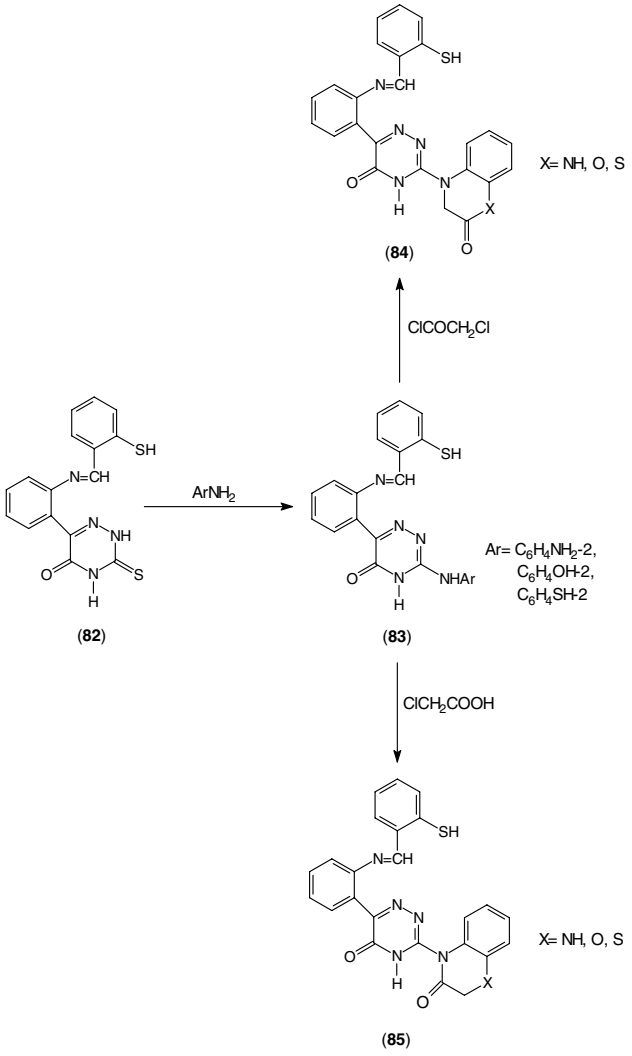
Reaction of mercapto-1,2,4-triazin-5(4*H*)one (**88**) with ammonia in ethyl alcohol yielded the 3-amino-triazine **89**. Structure **89** was proved by chlorination of **88** using $POCl_3$ to give **90**. Aminolysis of **90** yielded the 3,5-diamino-1,2,4-triazine **91** (Scheme 24) [39]. Compound **90** showed significant activity against HIV while compounds **90** and **91** showed anticancer activity [19].

Boiling compound **92** with ethanolamine and/or anthranilic acid in NaOEt yielded the interesting heterobicyclic systems. 2,3,5,6,8-perhydro-6-spiro-(9′-fluorine)-imidazolo[1,2-*b*][1,2,4]triazin-7-one (**93**) and 1,3,4-trihydro-3-

Scheme 21

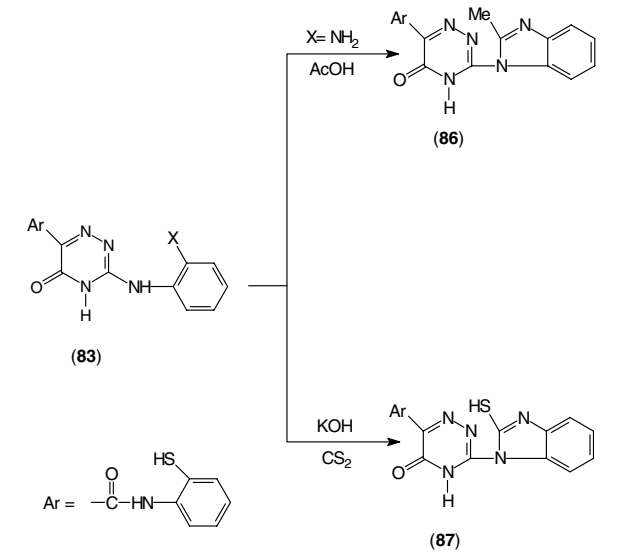


Scheme 22

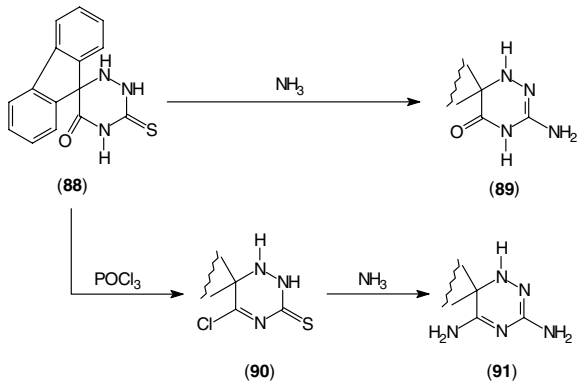


spiro-(9′-fluorine)-1,2,4-triazino[2,3-*a*]quinazolin-2,6-dione (**94**), respectively (Scheme 25). Compounds **92**–**94** showed anti HIV and anticancer activities [20].

Scheme 23



Scheme 24



Condensation of **89** with *p*-chlorobenzaldehyde in ethanol gave the corresponding arylidene **95** which upon cycloaddition with equimolar amounts of mercaptoacetic acid in dry benzene yielded 1,6-dihydro-3-[2′-(*p*′-chlorophenyl)-4′-oxo-thiazolin-3′-yl]-6-spiro-(9′-fluorine)-1,2,4-triazin-5(4*H*)-one (**96**) (Scheme 26) [20].

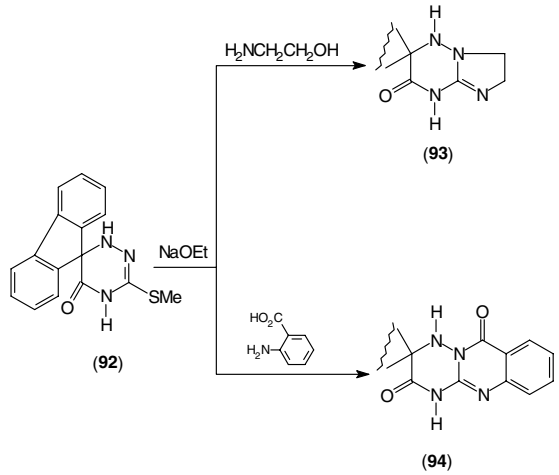
The 3-heteroaryl-1,2,4-triazin-5(1*H*)ones **99**–**102** and the related compound **100** have been obtained via addition of allyl isothiocyanate to 3-hydrazino-triazinone **97** followed by heterocyclization with malonic acid in drops of acetyl chloride and basic cyclization. Condensation of 3-hydrazino-triazinone **97** with benz-3,1-oxazin-4-one (**98**) was done in dry pyridine (Scheme 27). Compound **101** had remarkable antitumor effects and a moderate activity against HIV [21].

1,6-Dihydro-3-dimethylamino-4-methyl-1,2,4-triazin-ones **103** were obtained as herbicides from refluxing 1-amino-2,2,3-trimethyl-guanidinium hydroxy-2-cyclohexylacetonitrile in the presence of MeOH-Et_3N [58]. Compounds **103** were said to have superior herbicidal activity and selectivity pre and postemergent [58].

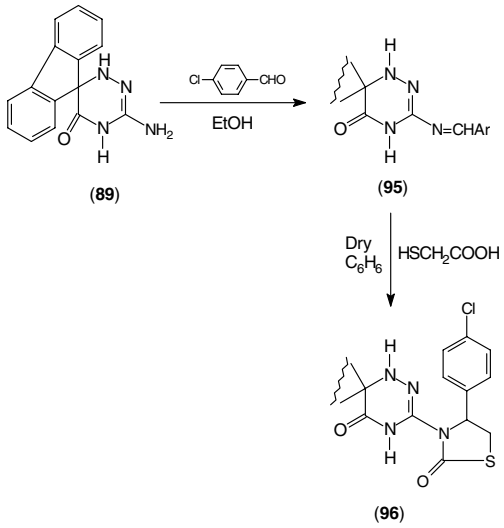
Mansour et al. reported the conversion of 3-methylthio-1,2,4-triazin-5-one (**104**) to the corresponding 4-amino-3-anilino-4,5-dihydro-1,2,4-triazin-5-one (**105**) by refluxing with N_2H_4 [59]. Compounds **104**, **105** exhibited antiviral, antibacterial, antimycobacterial, antifungal and antiyeast activity [59].

1,2,3,4-Tetrahydropyrimido[2,1-*c*][1,2,4]triazine-3,6-diones **107** were obtained from intramolecular cyclization of [2-(al-

Scheme 25



Scheme 26

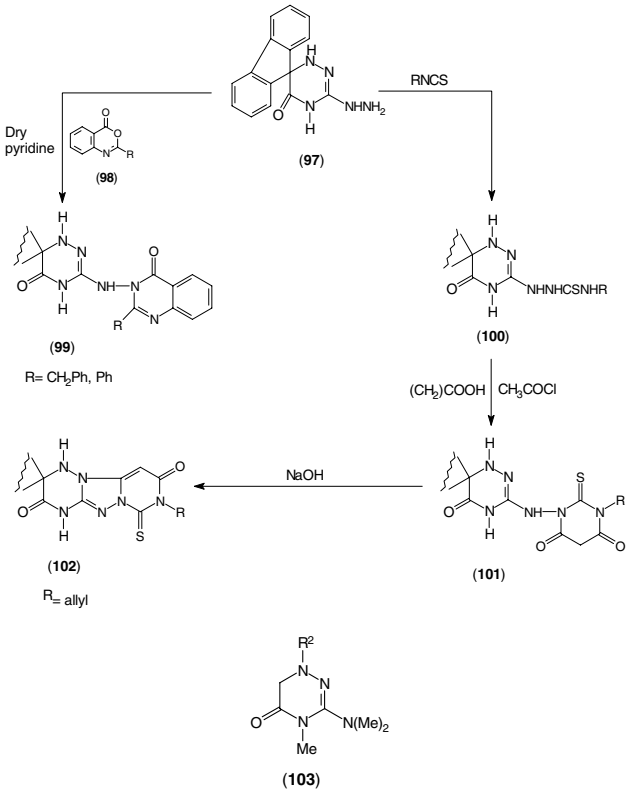


kylthio)-3,4-dihydro-6-methyl-4-oxo-3-pyrimidin-yl]acetic acid hydrazides **106** in boiling DMF containing benzyl amine [60].

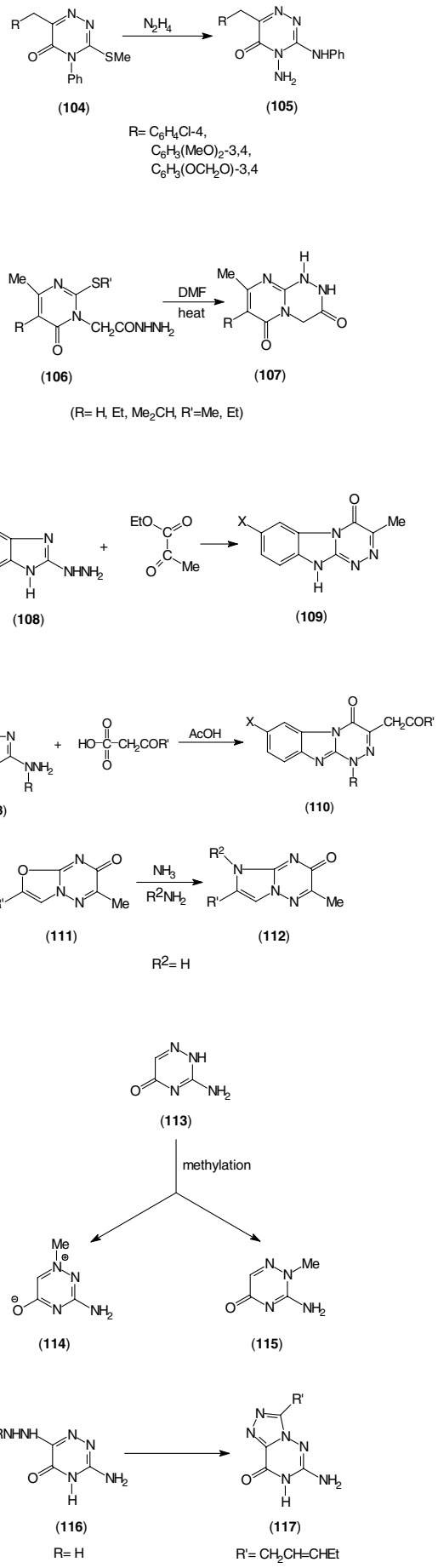
Similarly, antimicrobial [61] 1,2,4-triazino[4,3-*a*]benzmidazol-4-(10*H*)-ones **109**, (X=H, Me, $PhCH_2$; X=Me, F, R = H) were obtained from reaction of 2-hydrazinobenzimidazole (**108**) with ethyl pyruvate in neutral medium followed by hydrolysis and cyclization. The compounds **109** exhibited antibacterial and antifungal activities.

On the other hand, treatment of hydrazinobenzimidazoles **108**, (R = H, Et, $HOCH_2CH_2$) with aroyloxopropanoic acids $R'COCH_2COCO_2H$ (R′=Ph, p-anisyl, p-Cl or p-BrC_6H_4) in AcOH afforded triazinobenzimidazoles **110** [62].

Scheme 27



Scheme 28

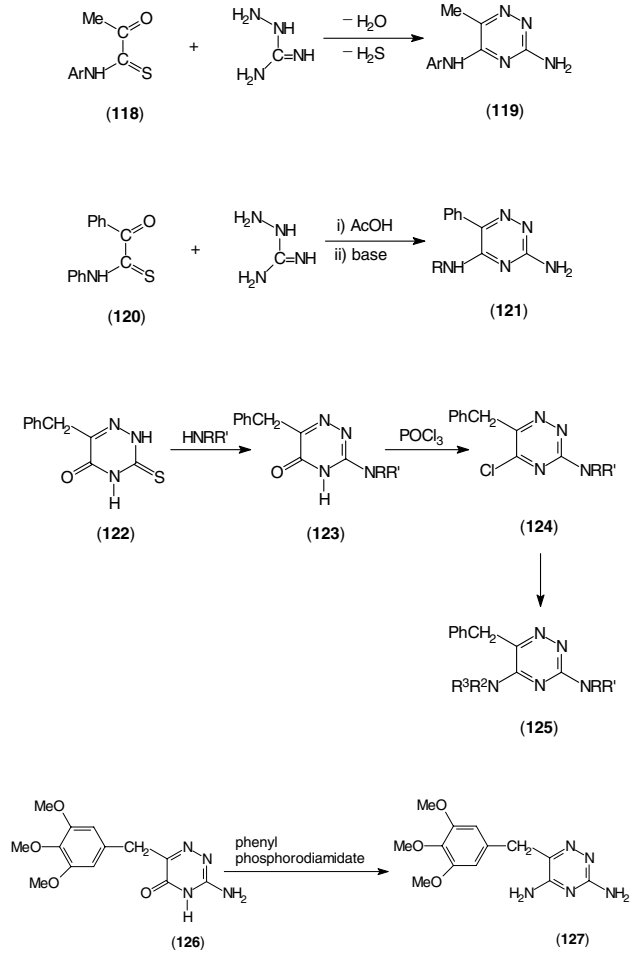


Heravi et al. reported that ring transformation of oxazolo[5,2-*b*][1,2,4]triazinone (**111**) occured on treatment with ammonia and primary amines to afford the corresponding imidazo[1,2-*b*][1,2,4]triazines **112**, (R^2 = H, Me, Et) [13].
Methylation [63] of 3-amino-1,2,4-triazin-5(2*H*)one (**113**) gave a mixture of 3-amino-1-methyl-1,2,4-triazinium-5-olate (**114**) and 3-amino-2-methyl-1,2,4-triazin-5(2*H*)-one (**115**) (Scheme 28) [68].
Dehydrative coupling of **116** (R = H) with 2-hexenoic acid in dry DMF in the presence of 1-ethyl-3-(3-dimethylamino-propyl)carbiimide hydrochloride gave the intermediate **116** (R = $COCH_2CH$=CHEt) which on heating in ethylene glycol at 200 °C afforded the ring cyclized product 6-amino-3-(2-penten-1-yl)-1,2,4-triazolo[3,4-*f*][1,2,4]triazin-8(7*H*)one (**117**, R = CH_2CH=CHEt) [64].

5. Synthesis, chemistry and analysis of 3,5-diamino-1,2,4-triazine derivatives (lamotrigine)

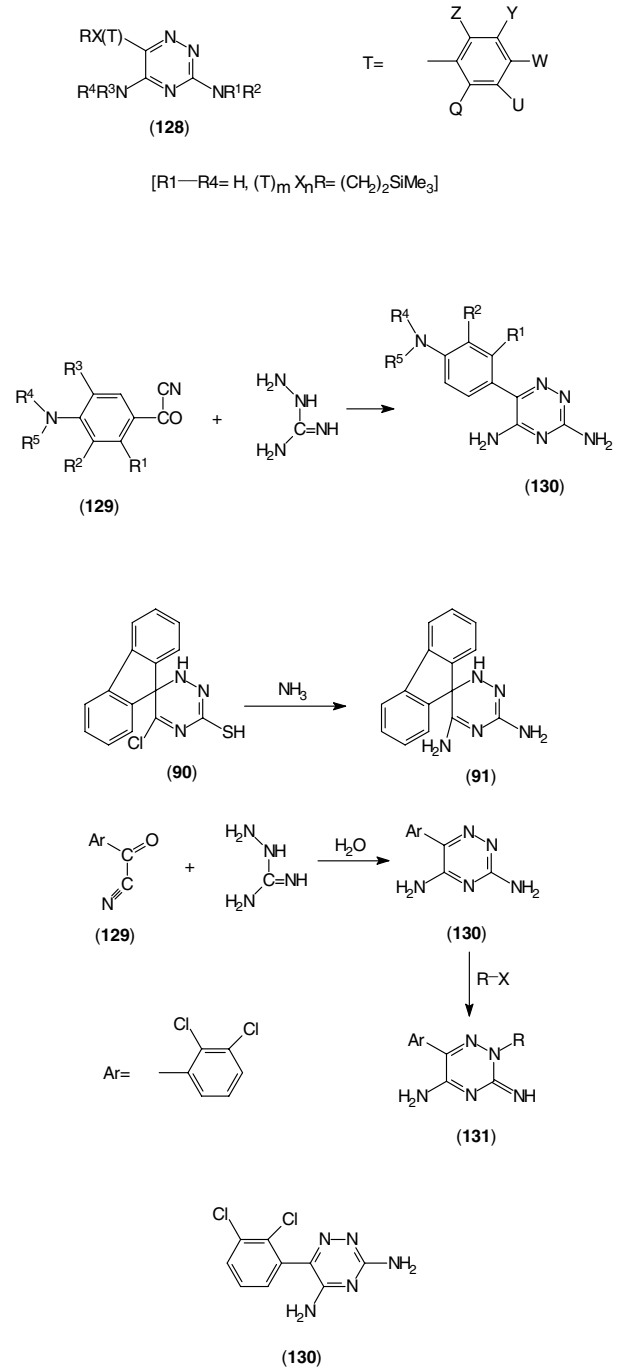
In recent years much attention has been focused on the synthesis of some interesting 3,5-diamino-1,2,4-triazine derivatives, in particular, 3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (lamotrigine) which plays a vital role in many biological processes. Very little work has been done on the chemistry of 3,5-diamino-1,2,4-triazine derivatives but their biocidal effects were extensively studied. Synthesis of 3-amino-5-substituted phenyl amino-6-methyl-1,2,4-triazine (**119**) was achieved by cyclocondensation of α-acetyl-thioformanilide (**118**) with aminoguanidine [65].

Scheme 29



Similary, benzoylthioformanilides (**120**) were condensed with aminoguanidine dihydrochloride in acetic acid medium, then refluxed in alkaline medium (pH 8–9) to give the 3-amino-5-substituted amino-6-phenyl-1,2,4-triazines **121** [66].
3,5-Substituted (diamino)-6-benzyl-1,2,4-triazines **125** were obtained by chlorination of 6-benzyl-3-thioxo-1,2,4-triazin-5-one (**122**) followed by aminolysis (Scheme 29) [67].
The 3,5-diamino-1,2,4-triazine derivative **127** was obtained from reaction of 3-amino-6-[3,4,5-trimethoxybenzyl]-1,2,4-triazin-5(4*H*)one (**126**) with phenyl phosphorodiamidate [68].
6-Substituted-3,5-diamino-1,2,4-triazines **128** as insecticizes were synthesized via cyclization of 4,4,-dimethyl-4-silapentanoyl cyanide with aminoguanidine [69].

Scheme 30



Conversion of 2,5,3-$Cl_2(NH_2)C_6H_2CO_2H$ to 2,3,5-$Cl_3C_6H_2 \cdot COCN$ (**129**), followed by cyclocondensation with aminoguanidine, nitratien and reduction yielded the 6-aminophenyl-3,5-diamino-1,2,4-triazines **130**. Compound **130** (R^1-$R^3 = Cl$, $R^4 = R^6 = H$) had an IC_{50} of < 10 μM against glutamate release from rat brain slices [70].

Abdel-Rahman et al. [19], obtained 1,6-dihydro-3,5-diamino-6-substituted-1,2,4-triazine (**91**) via aminolysis of 1,6-dihydro-5-chloro-3-mercapto-6-substituted-1,2,4-triazine (**90**).

3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine (lamotrigine system) is useful for the prevention or treatment of pain or edema [4] and against kainate [6].

Thus, novel antiarrhythmic agents **131** ($R = Me_2CH$, Et) have been prepared from cyclocondensation of compound **129** with aminoguanidine followed by alkylation of **130** (Scheme 30) [5].

An immunofluorometric assay is suitable for analysis of lamotrigine in plasma samples [8].

Also, Doig et al. [9], used liquid chromatography mass spectrometry for the identification of urinary metabolities of lamotrigine (**130**).

Some more specific methods have been described [10] as validation of a radioimmuno assay for the determination of human plasma concentrations of lamotigine. Analysis of lamotrigine and lamotrigin-2-N-glucuronide in guinea pig blood and urine can be done by reserved-phase ion-pairing liquid chromatography [24].

Remmel et al. [25], reported that a quaternary ammonium glucuronide is the major metabolite of lamotrigine in guinea pigs. Similary, the same author, reported [26] the isolation and characterization of a novel quaternary ammonium-linked glucuronide of lamotrigine.

Wootton et al. [22] compared the pharmacokinetics of lamotrigine in patients with chronic renal failure and healthy volunteers and the results indicate that impaired renal function will have little effect on the plasma concentration of lamotrigine achieved for a given dosing regimen [22]. Finally, lamotrigine is reported to be a progress in antiepileptic drug therapy [23].

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Prof. Dr. R. M. Abdel-Rahman
Chemistry Department
Faculty of Education
Ain Shams University
Roxy, Cairo
Egypt