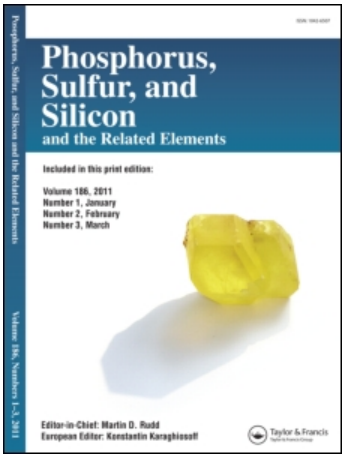


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# Recent Trends in the Chemistry of 4-Amino-1,2,4-triazole-3-thiones

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# Recent Trends in the Chemistry of 4-Amino-1,2,4-triazole-3-thiones

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*The synthesis and reactions of substituted 4-amino-1,2,4-triazole-5-thione derivatives as well as their biological activity are reviewed.*

**Keywords** Aminotriazolthiones; Mannich bases; reactions; Schiff bases; synthesis; triazolothiadiazepines; triazolothiadiazines; triazolothiadiazoles



## INTRODUCTION

In recent decades, a large number of reports concerning 4-amino-1,2,4-triazol-3-thiones have appeared owing to a wide variety of their biological activity. The amino and thioxo groups are ready-made nucleophilic centers for the synthesis of condensed nitrogen and sulfur heterocyclic rings, e.g., triazolothiadiazoles, triazolothiadiazines, and triazolothiadiazepines. Temple[1] reported on the first comprehensive review concerning 4-amino-1,2,4-triazole-5-thione derivatives. Due to the progress that occurs in dealing with the chemistry of substituted 4-amino-1,2,4-triazole-3-thiones as well as their biological activity, we are aiming in this review to shed more attention on the most important reports published within the last 25 years.

## Synthetic Approaches

### *From Thiocarbohydrazide*

Substituted 4-amino-4*H*-1,2,4-triazole-3-thiones **2** were prepared by reacting carboxylic acids together with thiocarbohydrazide (**1**).[2–15] Similarly, 1-(6-methoxy-2-naphthyl)-1-(5′-amino-*s*-triazol-3-yl)ethane-4′-thione (**4**) was prepared by the fusion of **1** with 2-(6-methoxy-2-naphthyl)-propanoic acid (Naproxen 4′-thione, **3**).[16] The carboxylic acid

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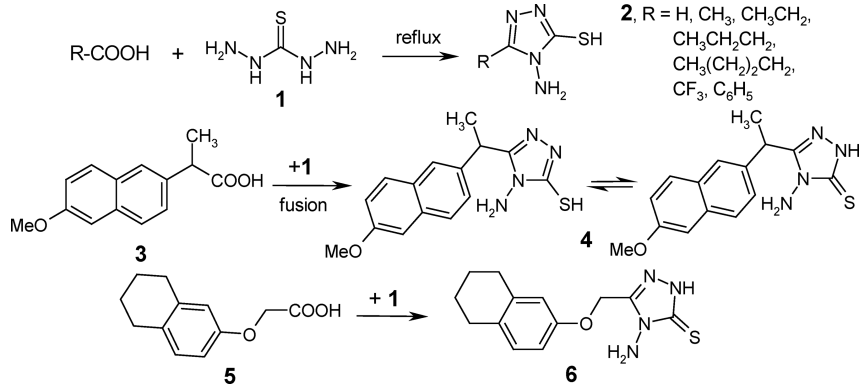
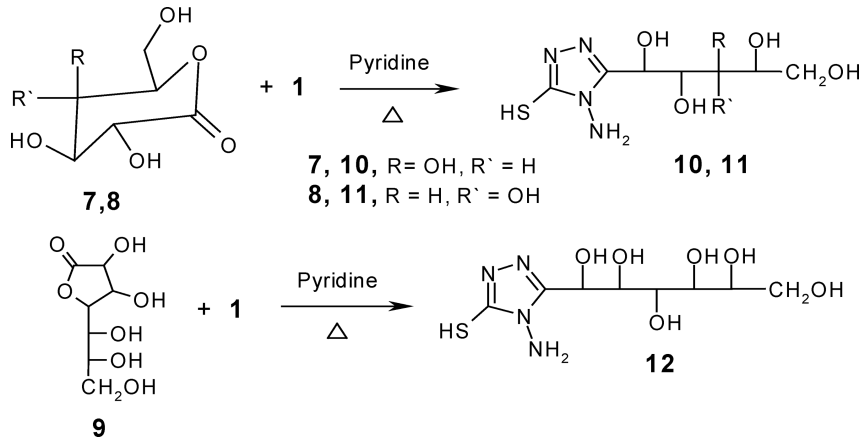
**5** reacted with **1** to produce 3-[(5,6,7,8-tetrahydro-naphthalen-2-yl)-oxymethyl]-4-amino-1,2,4-triazol-5-thione (**6**).[17,18] (Scheme 1)




**SCHEME 1**

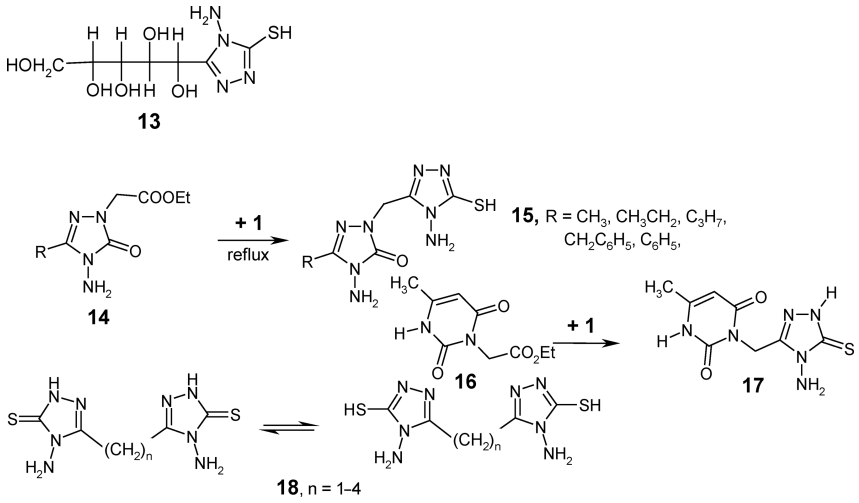
The reaction of 1,4-lactones **7**–**9** with **1** afforded the *Seco* C-nucleosides 4-amino-3-(*D*-gluco- **10** or *D*-galacto- **11** pentitol-1-yl)-1,2,4-triazol-5-thiones and (*D*-glycero-*D*-gulo-hexitol-1-yl)-1,2,4-triazol-5-thiones **12**.[19] (Scheme 2)




**SCHEME 2**

It was reported that 4-amino-3-(*D*-glucopentitol-1-yl)-1,2,4-triazol-5-thione (**13**) and its 3-Me analogue has shown in vivo and in vitro effects on $\alpha$- and $\beta$-glucosidases and $\beta$-glucuronidase, as well as $\alpha$-amylase.[20]

The 5-alkyl-4-amino-2-[4-amino-4*H*-3-oxo-1,2,4-triazol-3-yl]-2,4-dihydro-3*H*-1,2,4-triazol-5-thiones **15** were synthesized by refluxing




**SCHEME 3**

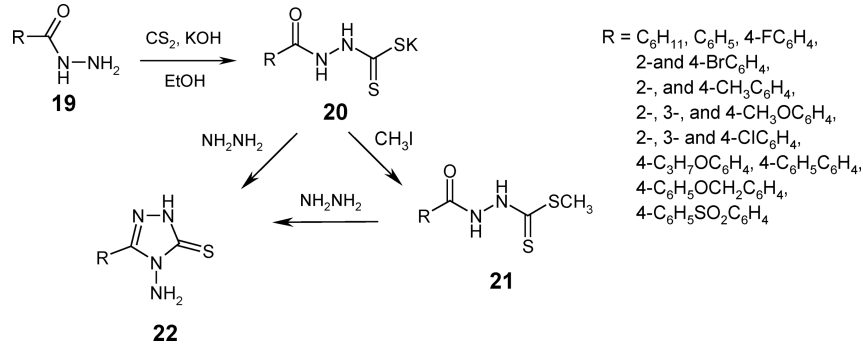


**1** with ethyl (3-alkyl-4-amino-5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-1-yl)acetate **14**.[21] The successful preparation of the aminotriazolthione **17** was achieved, in a 40% yield, during the reaction of the ester **16** with **1** in the presence of sodium methoxide.[14] The one-step reaction between aliphatic dicarboxylic acids and two molar equivalents of **1** gave bis(4-amino-5-thioxo-1,2,4-triazol-3-yl)alkanes **18** in good yields.[22,23] (Scheme 3)

## From Carboxylic Acid Hydrazides

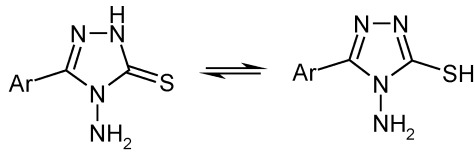
The Hoggarth synthesis[24] of 5-substituted-4-amino-(4*H*)-1,2,4-triazol-3-thiones procedurally starting from the reaction of carboxylic acid hydrazides **19**, which are condensed with carbon disulfide in ethanolic potassium hydroxide to yield the potassium 3-aroyldithiocarbazates **20**. The methylation of **20** with methyl iodide provided with the *S*-alkylated derivatives **21**. These methyl 3-aroyldithiocarbazates **21** are cyclized with hydrazine into 4-amino-4*H*-1,2,4-triazol-3-thiones **22**. Also, the salts **20** can be converted directly to **22** with an excess of hydrazine.[2,3,24–32] (Scheme 4)

In the same manner, 4-amino-5-(*N*-methyl-arylsulfonamido)methyl-1,2,4-triazole-3-thiones were synthesized by the Reid and Heindel approach.[31,33] The 4-amino-5-aryl-1,2,4-triazoles **23** were prepared from the reaction of the corresponding potassium salt of the substituted dithiocarbazinic acids with hydrazine hydrate.[34–36] (Scheme 5)




**19** **20** **21** **22**

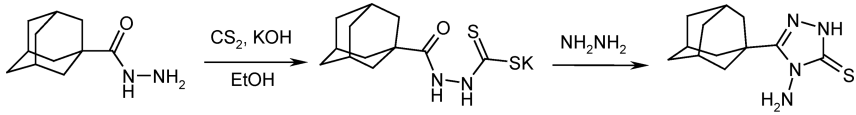
**SCHEME 4**



**23**, Ar = 2- and 4-$OHC_6H_4$, 4-$OHC_6H_4CH_2$, 4-$CH_3CH_2OC_6H_4CH_2$

**SCHEME 5**

Adamantane-1-carbohydrazide (**24**) was condensed with carbon disulfide in ethanolic potassium hydroxide to afford the intermediate potassium acylhydrazine dithioformate (**25**), which underwent a ring closure, with an excess of hydrazine to give 4-amino-3-(*D*-glucopentitol-1-yl)-1,2,4-triazol-5-thione (**26**).[37] (Scheme 6)

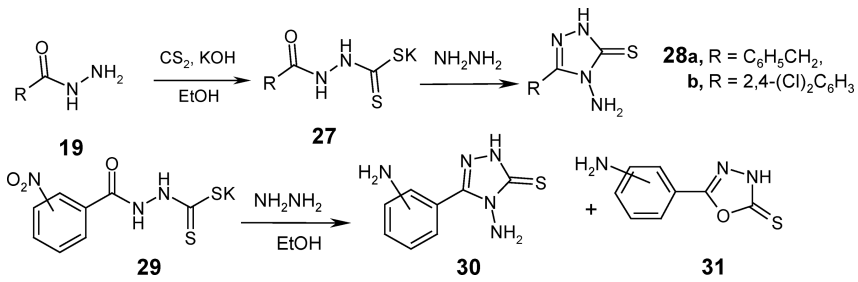



**24** **25** **26**

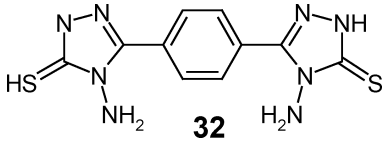
**SCHEME 6**

The reaction of the hydrazines **19** with carbon disulfide in ethanolic potassium hydroxide gave the potassium dithiocarbazate **27**. Hydrazinolysis of **27** leads to the formation of 4-amino-1,2,4-triazol-3-thiones **28a,b**.[38,39] On refluxing the potassium dithiocarbazates **29** with an ethanolic solution of hydrazine, the reaction gave a mixture of 4-amino-1,2,4-triazol-5-thiones **30** and $\Delta^2$-1,3,4-oxadiazoline-5-thiones **31**.[40,41] (Scheme 7)

The 1,4-bis-(5-thioxo-4-amino-*s*-triazol-3-yl)benzene (**32**)[42] was prepared by the reaction of terephthalic acid bishydrazide following the method of Reid and Heindel.[31] (Scheme 8)

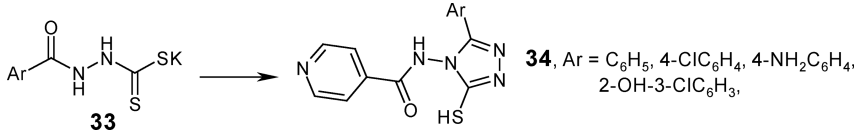



**SCHEME 7**




**SCHEME 8**

4-(*N*-Pyridylcarboxamido)-3-substituted-1,2,4-triazol-5-thiones (**34**) were obtained in a one-pot reaction by heating isonicotinic acid hydrazide with potassium dithiocarbazinates **33**.[43] (Scheme 9)

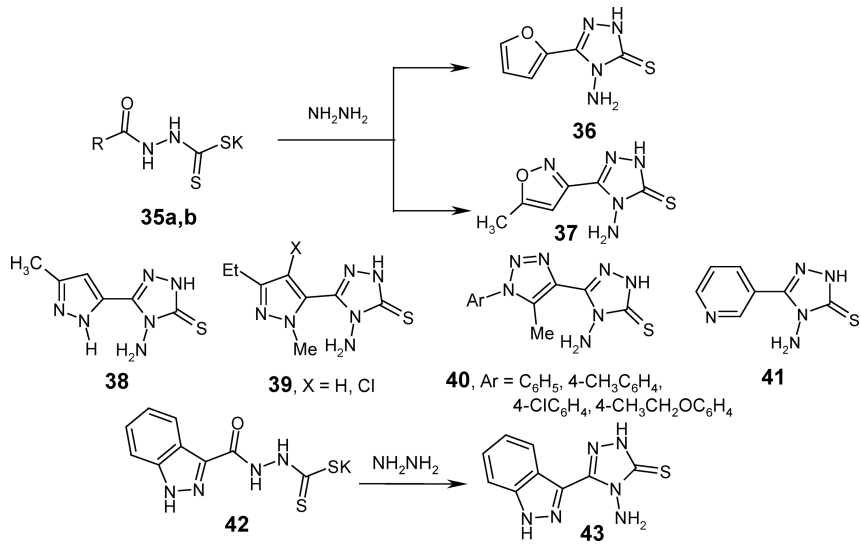



**SCHEME 9**

The ring closure of the potassium 3-(2-furoyl)dithiocarbazate (**35a**) or 3-(5-methyl-isoxazol-3-yl)dithiocarbazate (**35b**) with hydrazine hydrate (85%) afforded the aminotriazolthiones **36**[39,44–46] and **37**,[47,48] respectively. Similarly, triazolethioles **38**,[49] **39**,[50] **40**,[51–54] and **41**[55] were prepared by the cyclization of potassium dithiocarbazates in hydrazine hydrate according to the literature method.[31,56] The reactivity of the potassium indazolyldithiocarbazate **42** toward hydrazine indicated the formation of 4-amino-3-thioxotriazolylindazole **43**.[57] (Scheme 10)

The reaction of 1*H*-benzotriazol-1-acetic acid with carbon disulfide and potassium hydroxide followed by treatment with hydrazine hydrate gave 1-(4-amino-3-thioxo-4*H*-1,2,4-triazol-3-thioxo-5-yl)methyl-1*H*-benzotriazole (**44**).[58]

Carbohydrazides **45a**,**b** reacted with carbon disulfide and potassium hydroxide in ethanol at r.t. to give the potassium salts of dithiocarbazinic acids **46a**,**b**. The formal adducts were then boiled



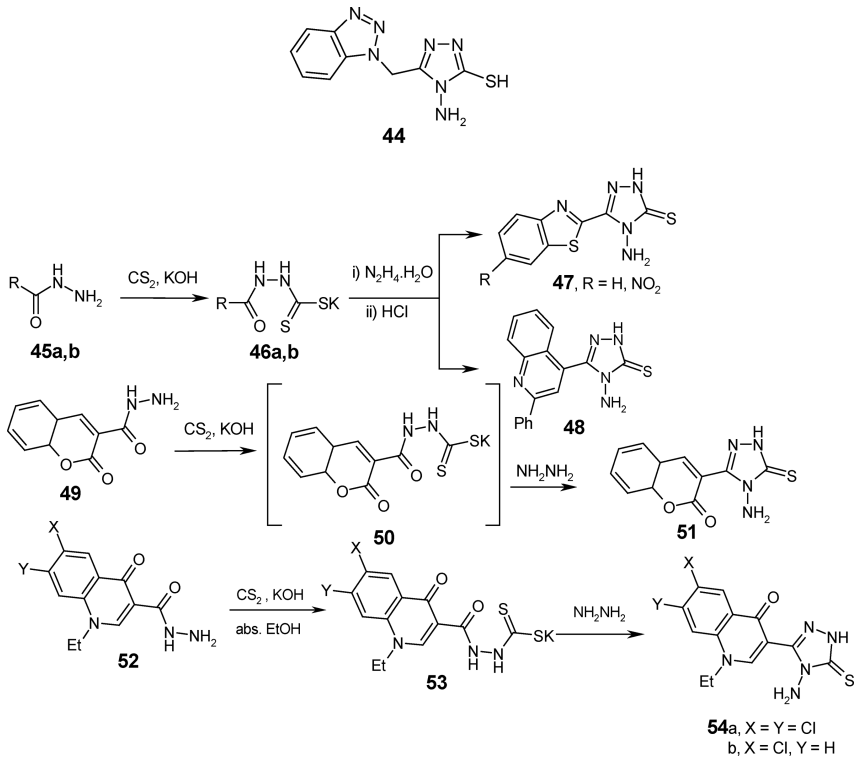

**SCHEME 10**

with hydrazine hydrate in ethanol followed by acidification of the reaction mixture at 0°C to give the 1,2,4-triazoles **47**[59] and **48**.[52,60] 2*H*-2-Oxobenzo-[*b*]pyran-3-hydrazide (**49**) reacted with carbon disulfide in DMF containing potassium hydroxide at r.t. to give the potassium thiocarbamate salt **50**, which was subjected to heterocyclization through its reaction with hydrazine hydrate to afford 4-amino-5-[2*H*-2-oxobenzo[*b*]pyran-3-yl]-1,2,4-triazole-3-thione (**51**).[61] The condensation of the carboxylic acid hydrazides **52** with carbon disulfide and potassium hydroxide in ethanol afforded the potassium 3-quinolonodithiocarbazates **53**. Compound **53** was then cyclized at a refluxing temperature with conc. hydrochloric acid to furnish the triazoles **54a,b** in 60 and 83% yields, respectively.[62] (Scheme 11)

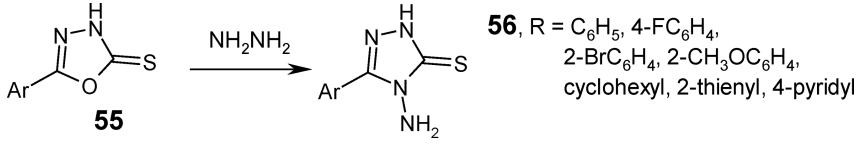
## From 1,3,4-Oxadiazol-5-thiones

In researching an efficient procedure for the conversion of 1,3,4-oxadiazol-5-thiones into 4-amino-1,2,4-triazol-5-thiones, it was reported that was achieved by the reaction of the target oxadiazole with hydrazine hydrate.[14,31,62–69] Thus, Reid and Heindel[31] indicated that the 5-aryl-2-1,3,4-oxadiazol-5-thiones **55** proceeded during the recyclization process to form 4-amino-1,2,4-triazole-3-thiones **56** in a reaction with hydrazine hydrate. (Scheme 12)

By the same way, compounds **58** were synthesized by the hydrazinolysis of oxadiazole **57** with hydrazine hydrate.[21] The reaction of



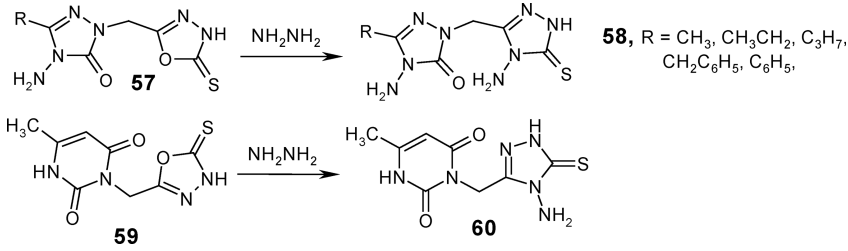
**SCHEME 11**



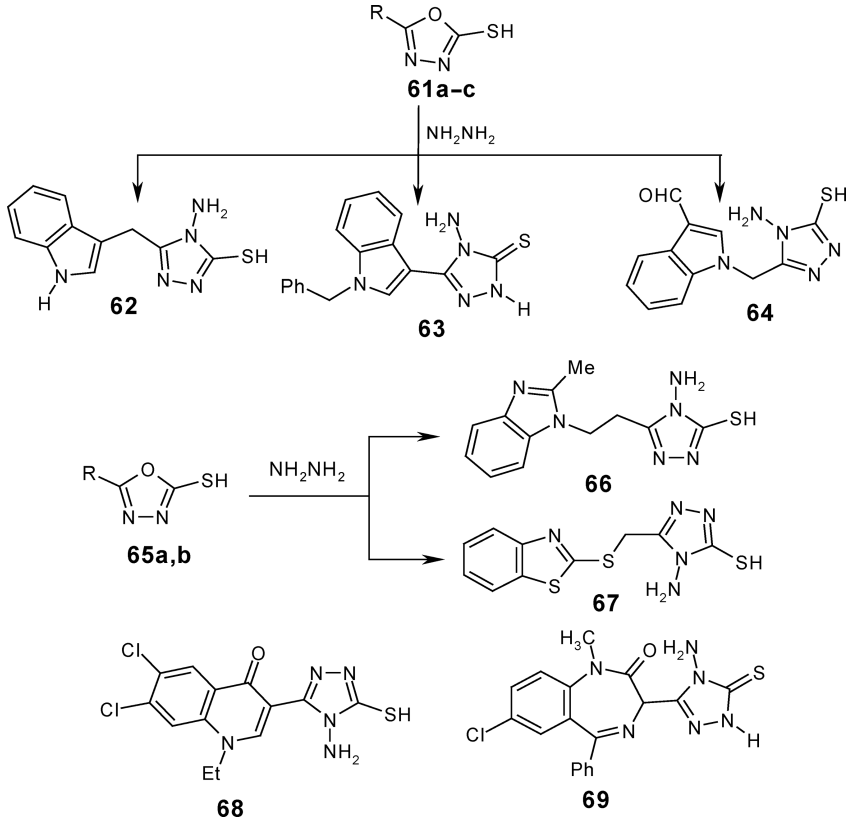
**SCHEME 12**

1,3,4-oxadiazole-3-thione **59** with hydrazine hydrate was studied using different solvents (water, ethanol, and dioxane) and give the aminotriazolethione **60**.[14] (Scheme 13)

The aminotriazolthiones **62**,[63] **63**,[65] and **64**[63] were synthesized by the reaction of 1,3,4-oxadiazole **61a–c** with hydrazine hydrate via a ring-opening reaction. Benzimidazole and benzothiazole were incorporated into a triazole moiety and were synthesized by the reaction of the oxadiazoles **65a**,**b** with hydrazine hydrate (99%) in absolute ethanol, which afforded aminotriazolthiones **66**[66] and **67**.[67] Similarly, the triazoles **68**[62] and **69**[64] were synthesized from the hydrazinolysis of the target oxadiazole with hydrazine hydrate. (Scheme 14)




**SCHEME 13**



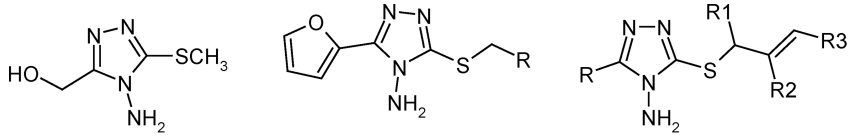

**SCHEME 14**

## CHEMICAL REACTIVITY

### *Alkylation/Arylation and Acylation*

There is limited published data on the reactions of 5-alkyl-4-amino-4*H*-1,2,4-triazol-3-thiones with alkylating agents. Specifically, the reactions with methyl iodide,[9] chloroacetonitrile,[3,7] chloroacetic acid,[11] and substituted phenacyl bromide[11,14,69,70] have been reported. The

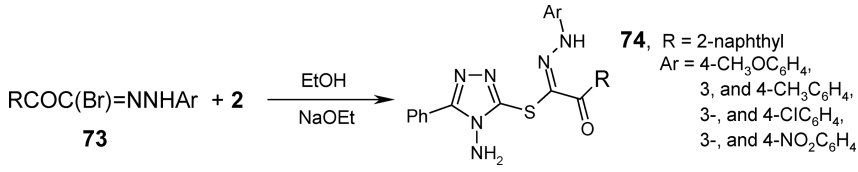
5-methylthio-4*H*-1,2,4-triazol-3-yl-methanol **70** was obtained by the methylation of the corresponding triazoles.[71] Compounds **71** were prepared by the alkylations of compound **36** with alkyl halide in potassium hydroxide ethanol solution.[45] The allylation of **2** in dimethyl formamide containing potassium carbonate gave the *S*-allylated products **72**.[13] (Scheme 15)




**70** **71**, R = $C_6H_5$, 3-$CH_3OC_6H_4$, 4-$CNC_6H_4$, 4-$EtOC_6H_4$ **72**, R = H, Me, Ph; $R^1$, $R^2$, $R^3$ = H, $CH_3$

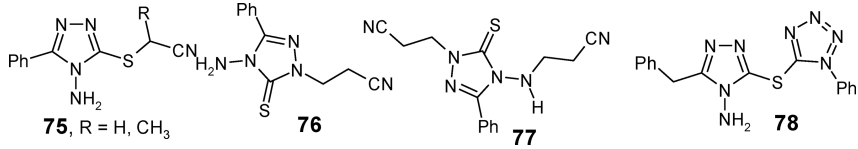
**SCHEME 15**

The reaction of **2** with 2′-aryl-2-oxoethanehydrazonoyl bromide **73** in ethanol in the presence of sodium ethoxide afforded the thiohydrazonate esters **74**.[72] (Scheme 16)




**SCHEME 16**

The substituted triazoles **75–78** were synthesized by the treatment of aminotriazolthiones with halonitriles, acrylonitrile, or chlorotetrazole in ethanol and in the presence of triethyl amine and potassium carbonate.[73,74] (Scheme 17)



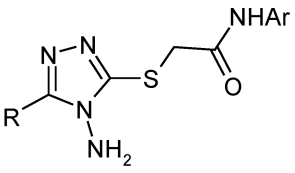

**75**, R = H, $CH_3$ **76** **77** **78**

**SCHEME 17**

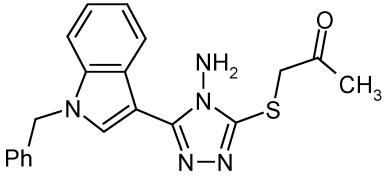
The reaction of **2** with substituted $\alpha$-chloroacetanilides smoothly afforded (5-alkyl-4-amino-4*H*-1,2,4-triazol-3-ylsulfanyl)acetanilide derivatives **79**.[75] (Scheme 18)

The reaction of **63** with chloroacetone gave the corresponding acetonylthio-derivative **80**.[65] Otherwise, the acylation of **66** with acetic anhydride in the presence of glacial acetic acid afforded the acylated derivative **81**.[66] (Scheme 19)

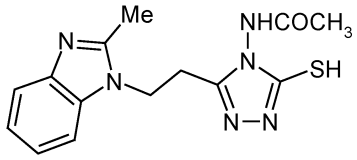
**79**, R = H, $CH_3$, $C_2H_5$, $C_3H_7$, $C_4H_9$, $CF_3$,
Ar = $C_6H_5$, 4-$CH_3C_6H_4$, 2,3-$(CH_3)_2C_6H_3$,
2-, and 4-$CH_3OC_6H_4$, 4-$EtOC_6H_4$,
4-$PhOC_6H_4$, 3,4$(CH_3O)_2C_6H_3$, 4-$FC_6H_4$,
4-$ClC_6H_4$, 4-$BrC_6H_4$, 3,4-$Cl_2C_6H_3$,
4-$NO_2C_6H_4$, 3-$CF_3C_6H_4$



**SCHEME 18**



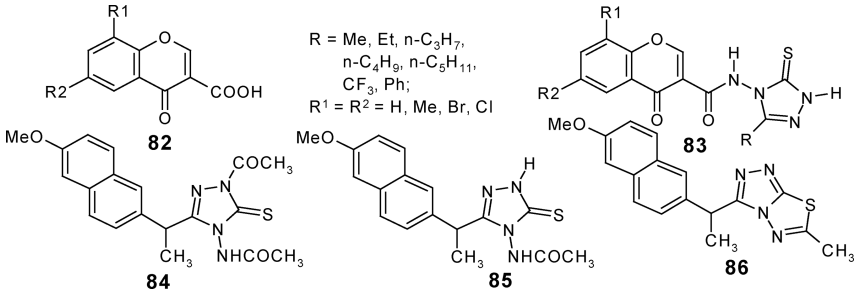
**80**



**81**

**SCHEME 19**

3-carboxychromones **82** reacted with **2** in the presence of phosphorous oxychloride to give (1,2,4-triazol-4-yl)aminocarbonylchromones **83**.[76] When compound **4** was subjected to react with acetic anhydride, the diacetyl derivative **84** was isolated, and the monoacetyl **85** or the fused system **86** was eliminated from consideration on the basis of analytical and spectroscopic data.[16] (Scheme 20)

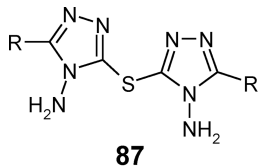



**82** **83** **84** **85** **86**

**SCHEME 20**

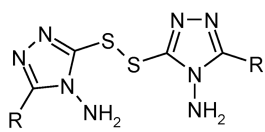
## The Synthesis of Monosulfides and Disulfides

Aminomercaptotriazoles **2**, **22**, or **30** were oxidized by thionyl chloride and a bromine-ethanol mixture to give the corresponding monosulfides **87** and disulfides **88**.[77] (Scheme 21)



**87**

R = H, $CH_3$, $C_2H_5$, $C_3H_7$, $C_6H_5$, 2-$HOC_6H_4$, 2-, 4-$H_2NC_6H_4$,

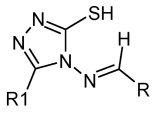


**88**

**SCHEME 21**

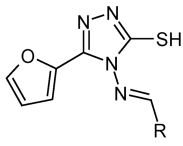
## Synthesis of Schiff Bases and Mannich Derivatives

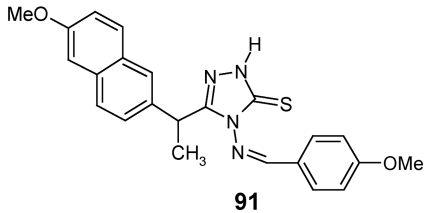
Several azomethine derivatives **89** were prepared by the condensation of **2** or **36** with aldehydes.[39,78–80] The Schiff bases **90** were obtained by the treatment of **36** with different aldehydes under refluxing in an ethanol solution.[44,45] Similarly, the reaction of **4** with 4-anisaldehyde in acetic acid afforded the Schiff base **91**.[16] (Scheme 22)



**89**, R = $C_6H_5$, 4-$H_3CC_6H_4$, 4-$ClC_6H_4$, 3-$NO_2C_6H_4$, 2-naphthyl, $R^1$ = H, Me, 4-$CH_3OC_6H_4$, 4-$ClC_6H_4$, 4-$BrC_6H_4$, Bz, 2-furanyl

**90**, R = $C_6H_5$, 4-$CH_3C_6H_4$, 4-$ClC_6H_4$, 3,4-$(CH_3O)_2C_6H_3$, 2-nitrofuryl



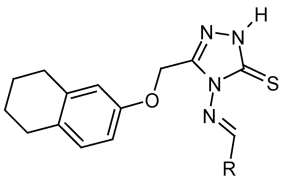


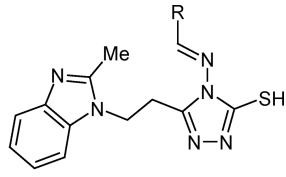
**91**

**SCHEME 22**

The reaction of the triazole **6** or aminotriazolthiones **66** with arylaldehyde in the presence of conc. sulfuric acid using dioxane as a reaction solvent gave the corresponding Schiff bases **92**[18] or **93**.[66] (Scheme 23)

**92**, R = $C_6H_5$, 4-$ClC_6H_4$, 4-$O_2NC_6H_4$, 4-$(H_3C)_2NC_6H_3$, 4-$H_3COC_6H_4$



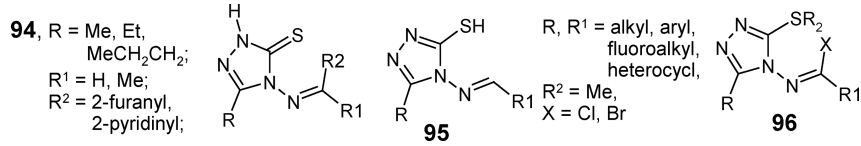


**93**, R = 2-$ClC_6H_4$, 4-$H_3CC_6H_4$

**SCHEME 23**

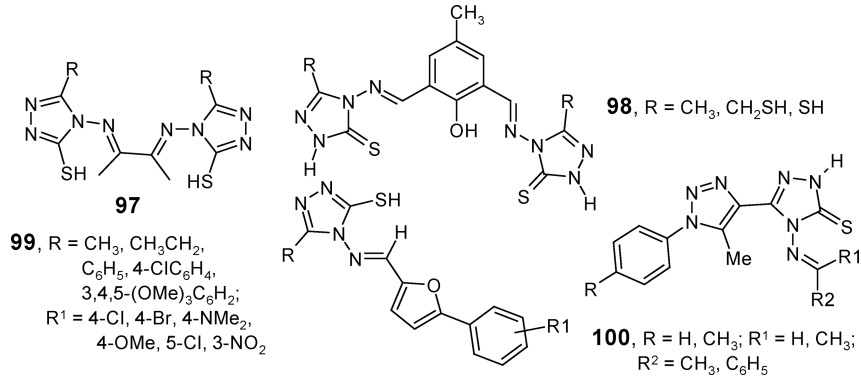
The (methyleneamino)triazolethiones **94**[81] were prepared by the reaction of thiocarbohydrazide with carboxylic acids. Therefore, compounds **94** underwent condensation with the chosen ketones. Aminotriazolthiones **95** and **96** showed inhibitions toward malignant cell

growth.[82] Another interesting class of these types of Schiff bases containing the thiocarbamide group derivatives of 3-aryl-4-amino-1,2,4-triazol-5-thiones was synthesized.[83] (Scheme 24)




**SCHEME 24**

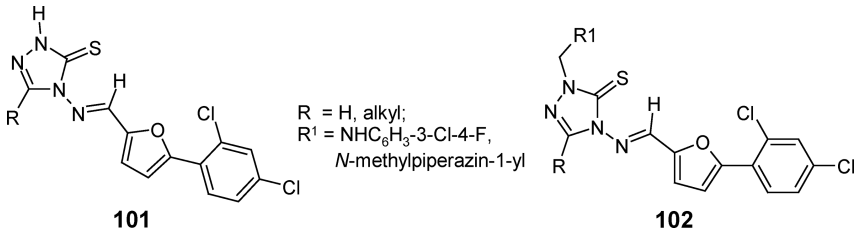
The *N*, *N*′-1,2-ethanediylidene-bis[3-thioxo-1,2,4-triazol-4-amines **97** were prepared in a 60% yield by the condensation of **2** with diacetyl.[84] The condensation of 2,6-diformyl-*p*-cresol and two equivalents of 4-amino-1,2,4-triazol-5-thiones gave the Schiff bases **98**.[85] The Schiff bases 4-amino-5-alkyl/aryl-2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **99** were prepared via a facile method in glacial acetic acid as a solvent and catalyst.[86,87] The condensation of **40** with benzaldehyde or acetone gave the Schiff bases **100**.[53] (Scheme 25)




**SCHEME 25**

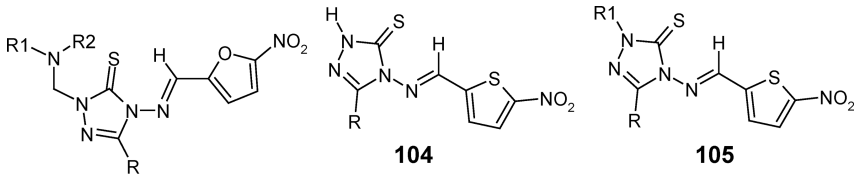
On reacting aminotriazolthione **2** with 2,4-dichlorophenylfurfural in the presence of a few drops of conc. sulfuric acid as a catalyst produced Schiff bases **101** in good yields. These Schiff bases were then treated with a primary/secondary amine in the presence of formaldehyde to produce Mannich bases **102**.[88] (Scheme 26)

Similarly, the preparation of some Mannich bases **103** was described.[89] Meanwhile, the reaction of 5-nitro-2-(diacetoxymethyl)-thiophene with **21** to yield the Schiff bases **104**. Treating the aforementioned Schiff bases with formaldhyde and amines dialkyl amines gave the expected Mannich bases **105**.[90,91] (Scheme 27)




**101** **102**

**SCHEME 26**



**103**, R = Me, Et, 4-$ClC_6H_4OCH_2$, 4-$MeC_6H_4OCH_2$; $NR^1R^2$ = piperidino, morpholino

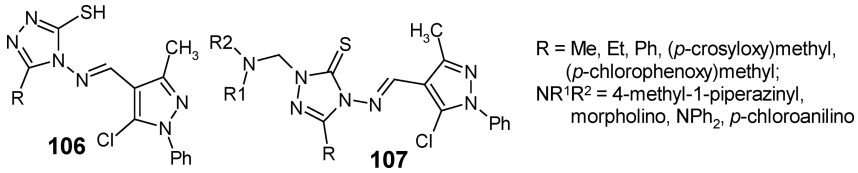
**104** **105**

R = H, alkyl, (un)substituted Ph, $PhOCH_2$, $PhCH_2$; $R^1 = R^2R^3NCH_2$ ($R^2 = R^3 = Ph$; $R^2$ = 4-$ClC_6H_4$, $R^3$ = H; $R^2R^3NH$ = morpholine, piperidine)

**SCHEME 27**



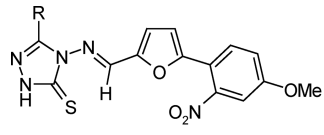
The Mannich reaction of 3-substituted-4-(3-aryl-4-sydnonylidene)-amino-1,2,4-triazol-5-thiones with formaldehyde and the appropriate amines resulted in the formation of 1-amino-methyl-3-substituted-4-(3-aryl-4-sydnonylidene)amino-1,2,4-triazole-5-thiones.[92] The Mannich reaction of [(pyrazolylmethylene)amino]triazolethiols **106** with formaldehyde and amines resulted in the regioselective formation triazolethiones **107**.[93] (Scheme 28)




**106** **107**

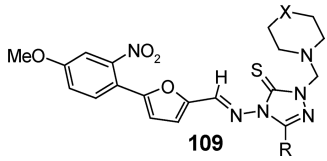
**SCHEME 28**

It was reported on the synthesis of 3-substituted-4-[5-(4-methoxy-2-nitrophenyl)-2-furfurylidene]amino-1,2,4-triazol-5-thiones **108**.[94,95] On the treatment of **108** with formaldehyde and various secondary amines, the reaction furnished the formation of the Mannich bases **109**.[95] (Scheme 29)




**108**

R = H, Me, Et, Pr,
2-ClC$_6$H$_4$OCH$_2$,
4-ClC$_6$H$_4$OCH$_2$,
2,4-Cl$_2$C$_6$H$_3$OCH$_2$,
4-Cl-3-MeC$_6$H$_4$OCH$_2$,
X = O, NMe

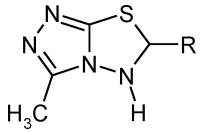



**109**

**SCHEME 29**

## Synthesis of Triazolothiadiazoles

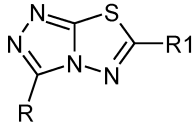
The triazolo[3,4-*b*]-1,3,4-thiadiazolines **110** were prepared in a 55–75% yield by treating **2** with dry gaseous hydrogen chloride in cold ether, followed by decantation of the ether, the replacement with absolute ethanol, and refluxing the reaction mixture with aromatic aldhydes in the presence of sodium acetate.[96] (Scheme 30)




**110**, R = Me, Ph, 3-O$_2$NC$_6$H$_4$,
3,4-(CH$_2$O$_2$)C$_6$H$_3$,
2-H$_2$N-4,5-(CH$_2$O$_2$)C$_6$H$_2$

**SCHEME 30**

3-alkyl/aryl-4-amino-1,2,4-triazol-5-thiones **2** or **21** were reacted with carboxylic acids or carboxylic acids chlorides to yield 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles **111**.[97–105] (Scheme 31)

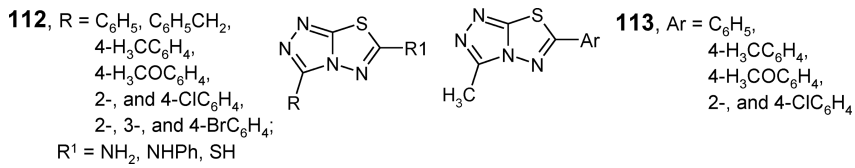



**111**, R = H, Me, Et, Pr, (H$_3$C)$_2$CHCH$_2$, C$_6$H$_5$, C$_6$H$_5$CH$_2$,
C$_6$H$_5$(CH$_2$)$_2$, C$_6$H$_5$(CH$_2$)$_3$, 4-CH$_3$C$_6$H$_4$;
R$^1$ = Me, Et, (H$_3$C)$_2$CHCH$_2$, C$_6$H$_5$, 4-MeOC$_6$H$_4$,
3-, and 4-O$_2$NC$_6$H$_4$, 2-, and 4-ClC$_6$H$_4$,
3,5-(O$_2$N)$_2$C$_6$H$_3$, 4-FC$_6$H$_4$,
C$_6$H$_5$CH=CH, 4-ClC$_6$H$_4$OCH$_2$

**SCHEME 31**

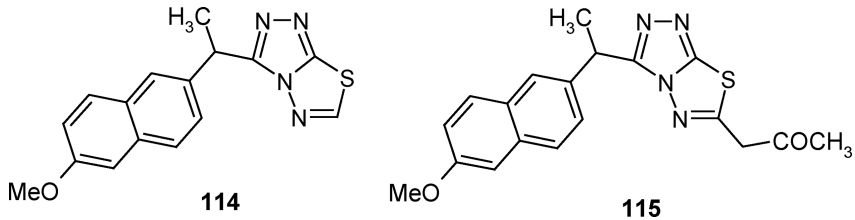
Yanchenko et al.[106] indicated a method for obtaining derivatives of 7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles based upon the alkylations of **2** with $\alpha$-chloroacetanilides, followed by cyclization of the intermediate by phosphorus oxychloride.[106] Thus, the reaction of aminotriazolthiones **21** with bromocyanide, phenylisothiocyanate, carbon disulfide, and aromatic nitriles afforded the corresponding cyclized products *s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles **112**[7,107] and **113**,[108] respectively. (Scheme 32)

Some 5,6-dihydro-s-triazolo[3,4-*b*]-1,3,4-thiadiazoles were synthesized by the reaction of aromatic aldehydes with aminotriazolthiones **2**



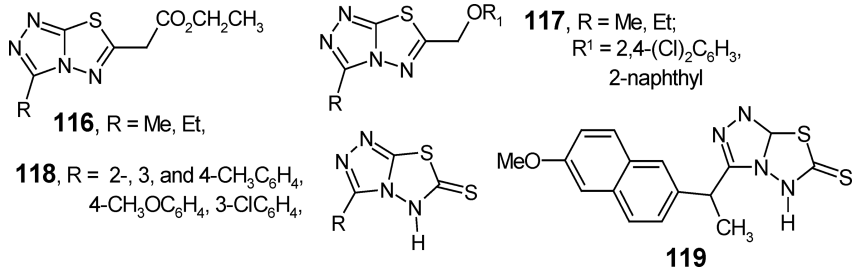

**SCHEME 32**

or **21** in the presence of a catalytic amount of *p*-toluenesulfonic acid in unsealed vessels by microwave irradiation using dimethyl formamide as an energy transfer medium.[109,110] The reaction with formic acid and/or ethyl acetoacetate yielded the corresponding triazolothiadiazole derivative **114** or **115**, respectively.[16] (Scheme 33)



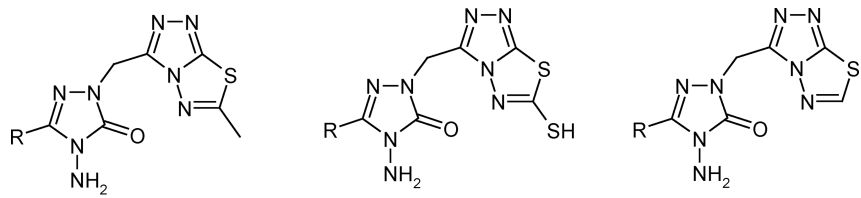

**SCHEME 33**

The reaction of cyanoacetic ester, 2,4-dichlorophenoxyacetic acid, or 2,4-dichloro-naphthoxyacetic acid with **2** gave 50–62% triazolothiadiazoles **116**[111] or **117**.[112] Whereas, interestingly, an addition of carbon disulfide to **21** or **4** in the presence of pyridine yielded compounds **118**[29] and **119**.[16] (Scheme 34)



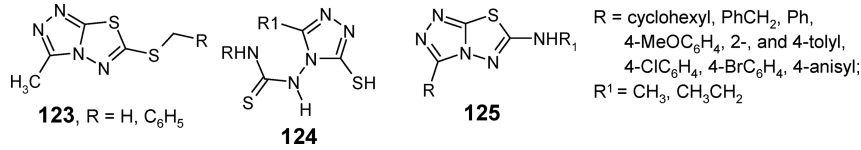

**SCHEME 34**

Compound **15** was led to react with acetic acid to produce 5-alkyl-4-amino-2-[(6-methyl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazol-3-yl)methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-ones **120**, while its condensation with carbon disulphide or formic acid afforded the triazolothidaizoles, respectively, compounds **121** and **122**.[21] (Scheme 35)



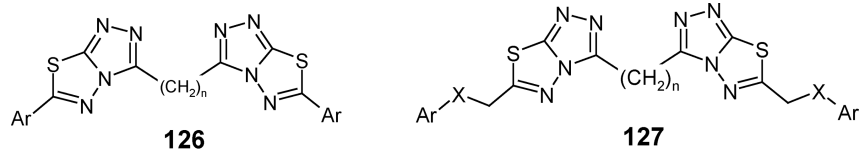

**SCHEME 35**

It was also reported that compound **2** reacted quantitatively with $RCH_2SCN$ or $R^1SCN$ in polyphosphoric acid or dry dimethyl formamide to give 1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazoles **123**[113] and thioureas **124**,[114,115] respectively in a high yield. The cyclodehydrosulfuration of **124** afforded 6-(arylamino)-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazoles **125**.[114,115] (Scheme 36)




**SCHEME 36**

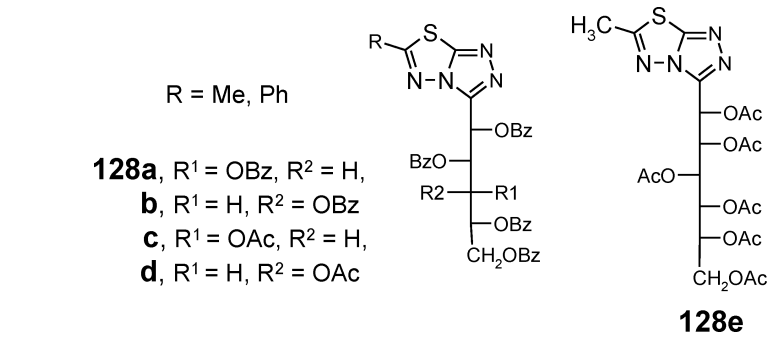
The cyclization of **18** with substituted aromatic carboxylic acids, substituted aryloxyacetic acids, and substituted anilinoacetic acids yielded the condensed triazolothiadiazolyl alkanes **126** and **127**.[23] (Scheme 37)



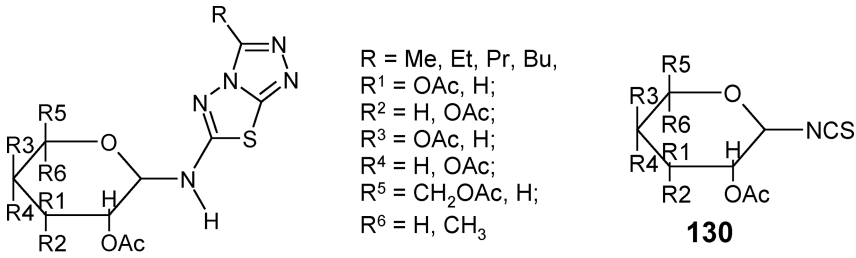

**SCHEME 37**

Treatment, under reflux, of compounds **11**–**13** with benzoyl chloride in pyridine or acetic anhydride directly afforded the cyclized products 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles **128a–e**.[19] (Scheme 38)

3-alkyl/aryl-6-(1′-*N*-$\beta$-*D* or $\alpha$-*L*-acetylated-glycopyranosyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles **129** were obtained by the condensation of 1,2,4-triazoles **2** and $\beta$-isothiocyanate **130**.[116] (Scheme 39)

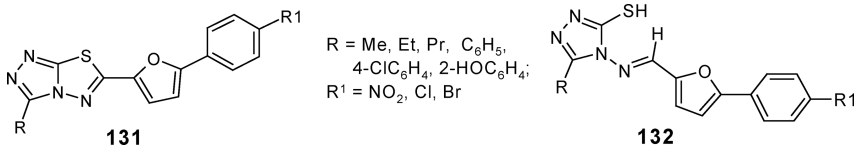



**SCHEME 38**




**SCHEME 39**

6-(5-Aryl-2-furyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles **131** were prepared by the intramolecular cyclization of (furfurylideneamino)triazoles **132** with thionyl chloride or a bromine-acetic acid mixture. Compounds **131** were prepared in a better yield by the cyclization of aminotriazoles **21** or **22** with arylfuroic acid.[117,118] (Scheme 40)

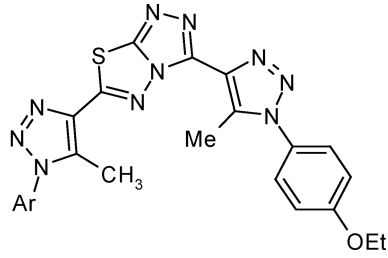



**SCHEME 40**

Refluxing aminotriazolthiones **21** with 2-phenyl-1,2,3-triazole-4-carboxylic acid and phosphorous oxychloride gave 68% of 3-trifluoromethyl-6-(2′-phenyl-1′,2′,3′-triazol-4′-yl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazole.[119] The 3-[1-(4-ethoxyphenyl)-5-methyl-1,2,3-triazol-4-yl]-6-substituted-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles **133** were synthesized by the condensation of aminotriazolthione **40** with various

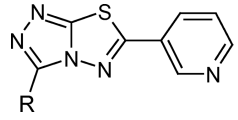
5-methyl-1-substituted–1,2,3-triazol-4-carboxylic acid in the presence of phosphorous oxychloride.[54] (Scheme 41)

**133**, Ar = 4-$CH_3C_6H_4$, 3-, and 4-$ClC_6H_4$, 3, and 4-$BrC_6H_4$, 2,5-$Cl_2C_6H_3$, 4-$CH_3OC_6H_4$, 4-$C_2H_5C_6H_4$




**SCHEME 41**

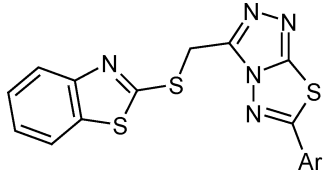
The reaction of **2** or **21** with nicotinic acid in the presence of phosphorous oxychloride proceeded to give the 3-alkyl/aryl-6-(3′-pyridyl)-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles **134**.[55] (Scheme 42)




**134**, R = $CH_3$, $CH_3CH_2$, $C_6H_5$, 2-and 4-$BrC_6H_4$, 4-$CH_3C_6H_4$, 2-, 3-, and 4-$CH_3OC_6H_4$, 2- and 4-$ClC_6H_4$

**SCHEME 42**

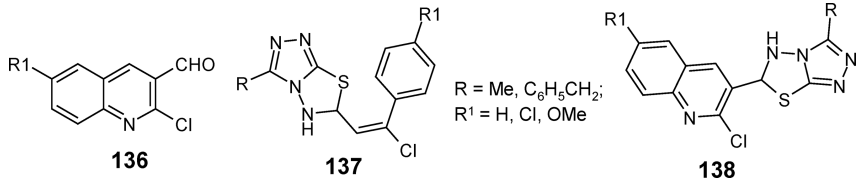
2-Aryl-3-(3-alkyl/aryl-5,6-dihydro-*s*-triazolo[2,4-*b*]-1,3,4-thiadiazolyl)indoles were prepared by the condensation of 1*H*-indole-3-carboxaldehyde with **2** or **21** under microwave irradiation (M.W.) in the presence of piperidine and p-toluenesulfonic acid using ethanol-DMF as a solvent of energy transfer media.[120,121] When compound **84** was heated with aromatic acids in phosphorous oxychloride, the reaction products were identified as 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles **135**.[67] (Scheme 43)




**135**, Ar = $C_6H_5$, 4-$HOC_6H_4$, 3-, and 4-$O_2NC_6H_4$, 2-, and 4-$ClC_6H_4$, 2-, and 4-$H_2NC_6H_4$

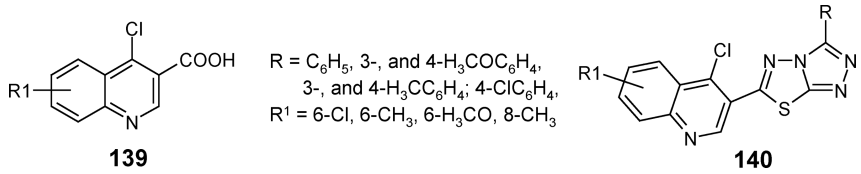
**SCHEME 43**

The fusion of aminotriazolthiones **2** or **21**, with chlorocinnamaldehydes or chloroquinoline-carboxaldehyde **136**, supported by either silica or alumina under microwave irradiation (M.W.) gave the triazolothiadiazoles **137**[122] and **138**.[122–125] (Scheme 44)



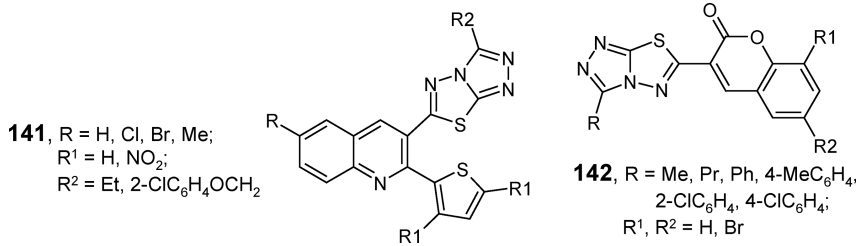

**SCHEME 44**

Similarly, the reaction of quinoline-3-carboxylic acids **139** with **21** in the presence of phosphorous oxychloride on refluxing or under M.W. irradiation gave (4-chloroquinoline-3-yl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles **140**.[126] (Scheme 45)




**SCHEME 45**

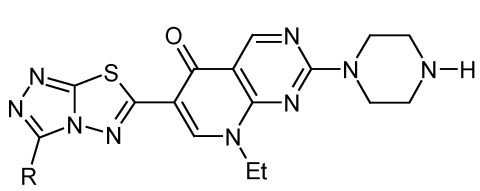
Several triazolo[3,4-*b*]-1,3,4-thiadiazoles **141**[127] and **142**[128] were prepared by cyclo-condensation of **2** or **21** with some selected carboxylic acids. (Scheme 46)



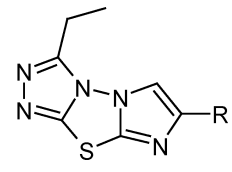

**SCHEME 46**

3-(alkyl or 3′-chlorophenyl)-6-pipemidic-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles **143** were synthesized by the condensation of 4-aminotriazol-3-thiones with pipemidic acid in the presence of phosphorous oxychloride.[129] A facile synthesis of imidazo[1,2-*d*]-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazoles **144** was achieved by the condensation of **21** with cyanogen bromide to give 6-amino-3-ethyl-s-triazolo[3,4-*b*]-1,3,4-thiadiazole followed by treatment with $\alpha$-halo-ketones.[130] (Scheme 47)

The synthesis of triazolo[3,4-*b*]-1,3,4-thiadiazolidine-*spiro*[6′,4]-isoxazol-5-one **146** was reported. The key of their successful preparation



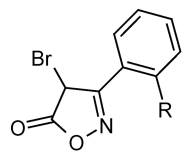
**143**, R = Me, Et, 3-$ClC_6H_4$



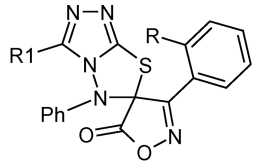
**144**, R = 4-$ClC_6H_4$, 4-$BrC_6H_4$

**SCHEME 47**

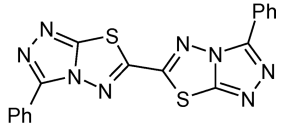
depended on reacting **145** with 4-anilino-3-substituted-1,2,4-triazol-5-thione,[131] whereas refluxing compound **2** with oxalic acid yielded the bis triazolothiadiazole **147**.[98] (Scheme 48)



**145**



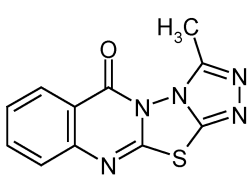
**146**, R = H, Cl;
$R^1$ = Me, Et, (un)substituted phenyl



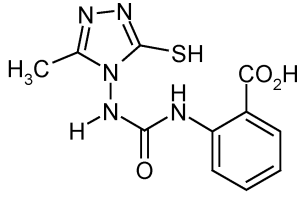
**147**

**SCHEME 48**

Triazolothiadiazole **148** was synthesized by reacting isatoic anhydride with 4-amino-3-methyl-1,2,4-triazol-5-thione and the subsequent cyclization of the intermediate **149** with phosphorous oxychloride and phosphorous trichloride.[132] (Scheme 49)



**148**



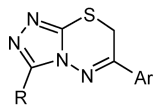
**149**

**SCHEME 49**

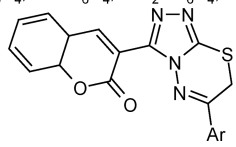
## The Synthesis of Triazolothiadiazines

It was reported on the preparation of triazolo[3,4-*b*]-1,3,4-thidiazine **150** during the reaction of aminotriazolthione **2** or **21** with substituted phenacyl bromide.[7,76,102] The treatment of 1,2,4-triazole-3-thione **51** with 4-substituted phenacyl bromide in absolute ethanol containing potassium carbonate resulted in cyclocondensation

to give 6-aryl-3-[2*H*-2-oxobenzo[*b*]pyran-3-yl]-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines **151a**, **b**.[61] (Scheme 50)



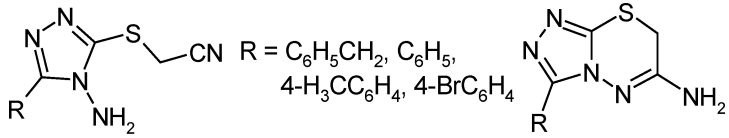
**150**, R = H, Me, Et, Pr, Bu, $CF_3$, Ph, $PhCH_2$, 4-$MeC_6H_4$, 4-$MeOC_6H_4$, 2-, and 4-$ClC_6H_4$, 2-, 3-, and 4-$BrC_6H_4$, Ar = Ph, 4-$MeC_6H_4$, 2,3-$Me_2C_6H_3$, 2-, and 4-$MeOC_6H_4$, 2-$EtOC_6H_4$, 3-$CF_3C_6H_4$, 4-$ClC_6H_4$, 4-$BrC_6H_4$, 4-$O_2NC_6H_4$, 3,4-$Cl_2C_6H_3$,



**151**a, Ar = $C_6H_5$, b, Ar = 4-$CH_3C_6H_4$

**SCHEME 50**

The cyclization of 4-amino-5-aryl-3-cyanomethylthio-1,2,4-triazoles **75** or **152** in the presence of conc. sulfuric acid gave 60–81% of 7*H*-6-amino-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazines **153**.[7] (Scheme 51)



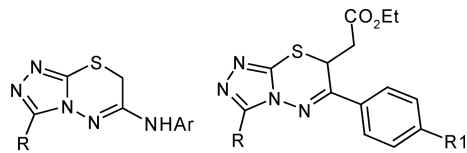
R = $C_6H_5CH_2$, $C_6H_5$, 4-$H_3CC_6H_4$, 4-$BrC_6H_4$

**152** **153**

**SCHEME 51**

Heating **79** in boiling phosphorus oxychloride resulted in an intramolecular ring closure with the formation of 7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines **154**.[76,106,133] Similarly, several 7-carbethoxy-methyl-*s*-triazolo[3,4-*b*]thiadiazines **155** have been synthesized by the reaction of appropriate ethyl $\beta$-aroyl-$\beta$-bromopropionates with **2**.[134] (Scheme 52)

**154,** R = H, Me, Et, Pr, Bu, $CF_3$, Ar = $C_6H_5$, 4-$MeC_6H_4$, 2,3-$Me_2C_6H_3$, 2-, and 4-$MeOC_6H_4$, 2-$EtOC_6H_4$, 3-$CF_3C_6H_4$, 2-, and 4-$ClC_6H_4$, 4-$BrC_6H_4$, 4-$O_2NC_6H_4$, 3,4-$Cl_2C_6H_3$,

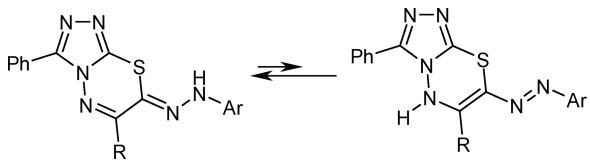


**155**, R = H, Me; $R^1$ = H, Cl, OMe

**SCHEME 52**

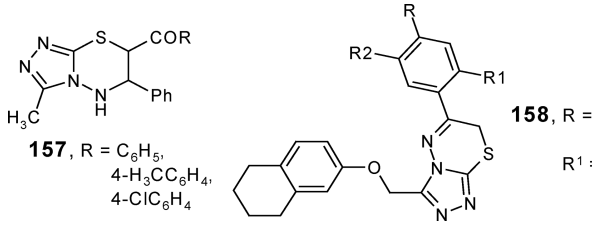
The conversion of thiohydrazonate esters **74** into the triazolothiadiazines **156** was affected by their treatment with acetic acid.[72] (Scheme 53)

Triazolothiadiazines **157** were prepared in a 60–80% yield by the reaction of hydrazones **89** with $\alpha$-bromomethylene derivatives in the



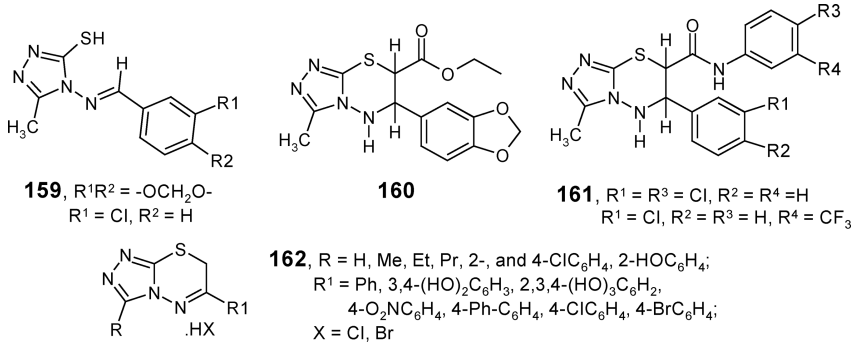

**SCHEME 53**

presence of triethyl amine and chloroform.[135] 7*H*-1,2,4-triazolo-[3,4-*b*]-1,3,4-thiadiazines **158** were obtained by condensing triazole **6** with phenacyl bromides in ethanol.[18] (Scheme 54)




**SCHEME 54**

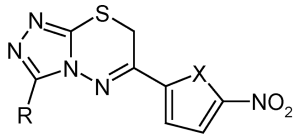
6,7-dihydro-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines **160** and **161** were prepared by the alkylation of the Schiff bases **159** using ethyl chloroacetate or substituted $\alpha$-chloro-acetanilides.[136] It was also reported on the synthesis the triazolthiadiazines **162** via the cyclocondensation of triazole **2** with $\alpha$-bromomethylene compounds.[98,137,138] (Scheme 55)




**SCHEME 55**

The reaction of 4-amino-3-(*D*-glycero-*D*-gulo-hexitol-1-yl)-1,2,4-triazol-5-thione with phenacyl bromide afforded 3-(*D*-gluco-, *D*-galacto-pentitol-1-yl)- and 3-(*D*-glycero-, *D*-gulohexitol-1-yl)-6-phenyl-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine.[139] The triazoles **2**,

**21**, or **22** underwent a cyclocondensation reaction with 2-bromoacetyl-5-nitrofuran or 2-bromoacetyl-5-nitrothiophene to give the corresponding *s*-triazolo[3,4-*b*]-1,3,4-thiadiazines **163a** and **163b**, respectively.[140–142] (Scheme 56)

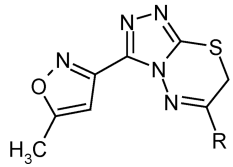


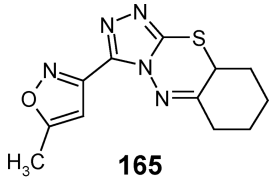
**163a**, X = O, R = H, alkyl, Ph, 4-$HOC_6H_4$, 4-$ClC_6H_4$, tolyl, anisyl, $O_2NC_6H_4$, $PhCH_2$
**b**, X = S, R = H, Me, Ph, 2-tolyl, 2-naphthyloxymethylene

**SCHEME 56**

In the same manner, the reaction of **37** with chloroacetaldehyde or 2-bromo-4′-substituted-acetophenone or 2-bromocyclohexanone afforded 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines **164** and 6,7,8,9-tetrahydro-1,2,4-triazolo[4,3-*b*]-4,1,2-benzothiadiazine **165**.[48] (Scheme 57)

**164**, R = H, $C_6H_5$, 4-$BrC_6H_4$, 4-$H_3CC_6H_4$, 4-$ClC_6H_4$



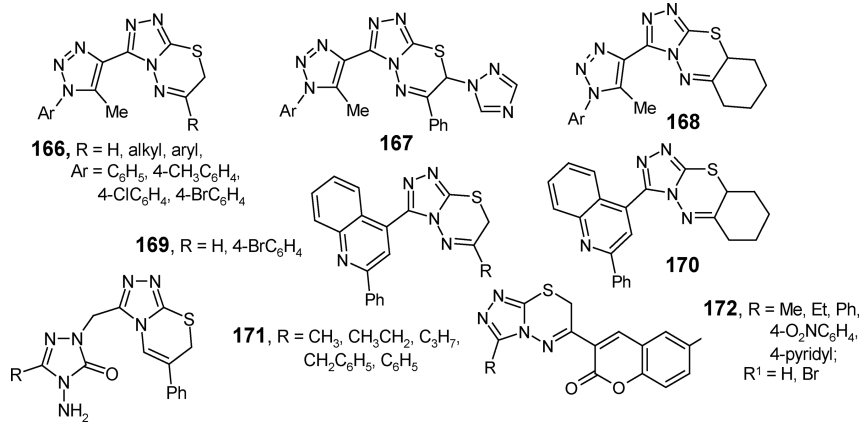


**165**

**SCHEME 57**

7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines **166–170**[52,53,143,144] were obtained during the reactions of **40** and **48** with chloroacetaldehyde or $\omega$-bromoacetophenones, or 2-bromo-cyclohexanone. The synthesis of 5-alkyl-4-amino-2-[(6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*]-1,3,4-thiadiazin-3-yl) methyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-ones **171** were performed by the treatment of compound **15** with $\alpha$-bromoacetophenone.[21] A series of 3-coumarinyl-s-triazolo-1,3,4-thiadiazines **172** was synthesized by the cyclocondensation of bromoacetylcoumarins with aminotriazolthiones.[145,146] The reactions of 4-bromoacetyl-3-methoxy-3-methyl-6,6-diphenyl-1,2-dioxane with **6** yielded 4-[3-(5-alkyl-1,2,4-triazolo[3,4-*b*]-2,3-dihydro-6*H*-1,3,4-thiadiazinyl)]-1,2-dioxanes in moderate yields (43–46%).[147] (Scheme 58)

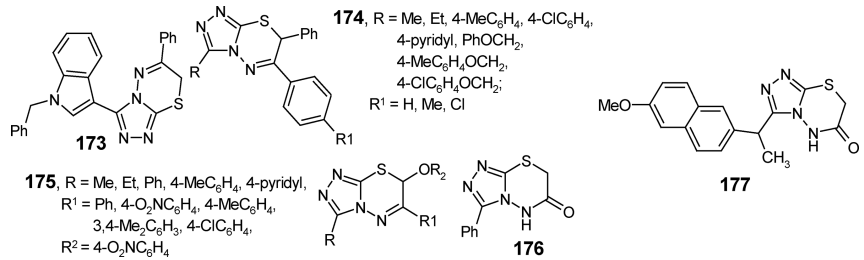
Refluxing triazole **63** with phenacyl bromide in ethanol produced 7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazine **173**.[65] Moreover, triazolothiadiazines **174** were prepared via the cyclocondensation of *p*-$R^1C_6H_4COCHBrPh$ with the corresponding triazoles.[148] The reaction of




**SCHEME 58**



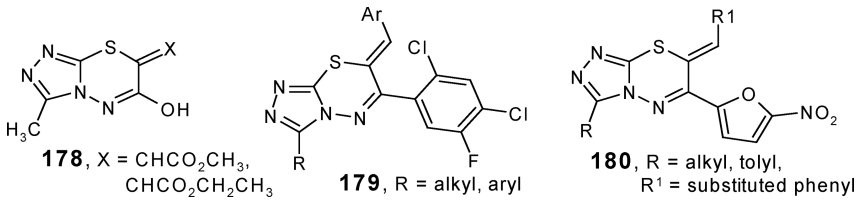
triazoles **2** or **21** with $R^1COCHBrOR^2$ or chloroacetic acid gave, respectively the corresponding 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines **175**[149] and **176**.[29,98] Similarly, the reaction of compound **4** with ethyl chloroacetate yielded the triazolothiadiazine derivative **177**.[16] (Scheme 59)




**SCHEME 59**

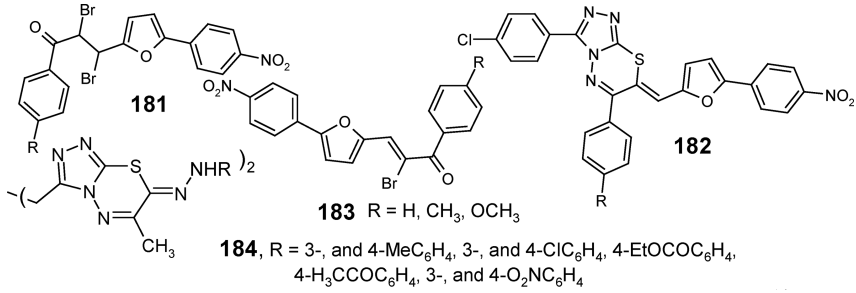
Di(alkyl/aryl)-6,6-bi[7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazinyl] prepared by reacting triazoles **2** or **21** with 1,4-dibromo-2,3-butanedione.[150] While the reaction of **2** with dimethyl acetylenedicarboxylate and diethyl acetylenedicarboxylate afforded the expected triazolo[3,4-*b*]-1,3,4-thiadiazine **178**.[102] Besides, 7-arylidene-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines **179**[151,152]and **180**[153] were prepared during the reaction of **2** or **21** with 2-bromo-3-aryl-2-propen-1-ones. (Scheme 60)

2,3-dibromo-1-aryl-3-[5-(*p*-nitrophenyl)furyl]-propan-1-ones **181** were dehydro-brominated in the presence of triethyl amine and were then condensed with **21** to give 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines **182**. The alternative synthesis of **182** through $\alpha$-bromo-1-aryl-3-(5-aryl-2-furyl)-2-propenone **183** was condensed with **45** in the




**SCHEME 60**

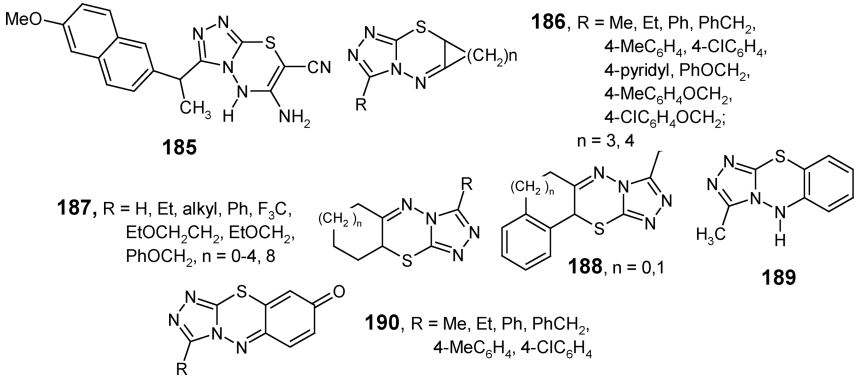
presence of ethanolic potassium hydroxide to give **182**.[154] Compounds 4-[3-methyl/aryl-7*H*-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazin-6-yl]-3-arylsydnones have been synthesized by treating 4-bromoacetyl-3-arylsydnones with 3-substituted-4-amino-1,2,4-triazol-5-thione.[155] 1,2-bis (7-arylhydrazono-7*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazin-3-yl)ethane derivatives **184** were synthesized by the reaction of **18** (n = 2) with two equivalents of *N*-aryl-2-oxopropane-hydrazonoyl chloride in ethanol in the presence of sodium ethoxide.[156] (Scheme 61)



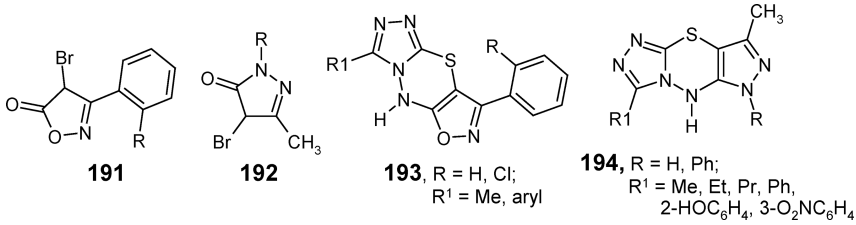

**SCHEME 61**

Compound **185** was also prepared by the reaction of **4** with bromomalononitrile.[16] Triazolo[3,4-*b*]-1,3,4-thiadiazines **186** were prepared by the cyclocondensation of 2-bromo-cyclopentanone and 2-bromocyclohexanone with triazoles **2** or **21**.[157] The reaction of cyclic $\alpha$-haloketones or 2,4-dinitrochlorobenzene with **2** gave triazolo-thiadiazines **187**,[5,158] or **188**[5,158] or 5*H*-1,2,4-triazolo[3,4-*b*]-1,3,4-benzothidiazine **189**[102] respectively. Whereas, 3-substituted-1,2,4-triazolo[4,3-*b*]-4,1,2-benzothiadiazin-8-ones **190** were synthesized by the cyclocondensation of **2** or **21** with *p*-benzoquinone.[8,159] (Scheme 62)

4-bromo-3-arylisoxazol-5(4*H*)-ones **191** or bromomethylpyrazolones **192** underwent cyclocondensation with **2** or **21** to give 5*H*-*s*-triazolo[3,4-*b*]isoxazolo[5,4-*e*]-1,3,4-thia-diazines **193**[131] and pyrazolotriazolothiadiazines **194**,[160] respectively. (Scheme 63)

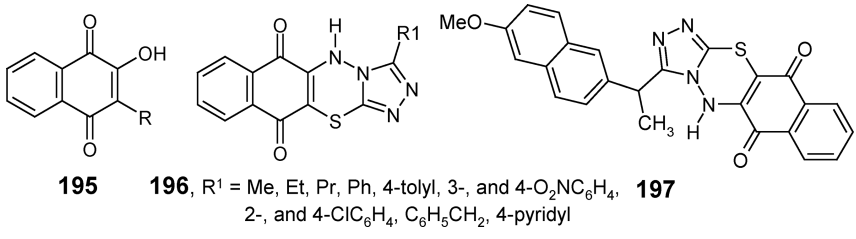



**SCHEME 62**



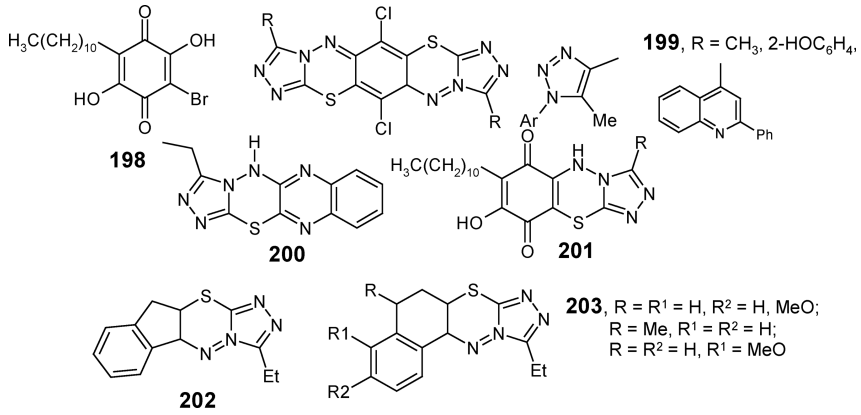

**SCHEME 63**

Lawsone **195** (R=H) was brominated photochemically in carbon tetrachloride with *N*-bromosuccinimide using BzOOBz as a radical initiator to give bromolawsone **195** (R=Br). The cyclization of **195** with compounds **2** or **21** gave 69–93% of naphtha[2,3-*e*]-s-triazolo[3,4-*b*]-1,3,4-thiadiazine-6,11-diones **196**.[161] Similarly, the reaction of **4** with 2,3-dichloro-naphthoquinone affected cyclization to furnish the corresponding triazolothiadiazine derivative **197** through the elimination of two molecules of hydrochloric acid.[16] (Scheme 64)



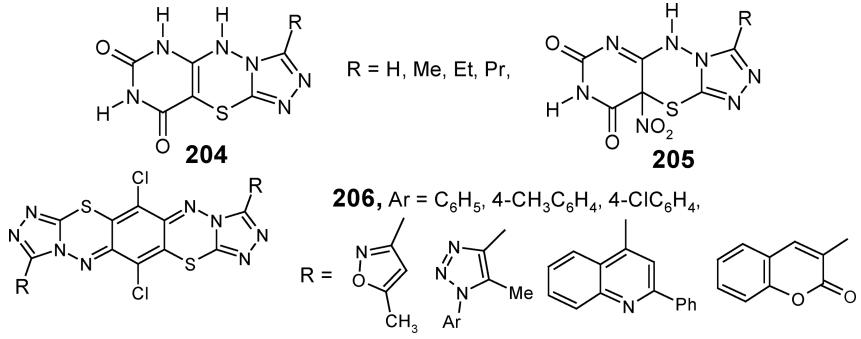

**SCHEME 64**

The interaction of chloranil or 2,3-dichloroquinoxaline or bromoembelin (**198**) with the aminotriazolthiones gave the triazolothiadiazinocyclohexadiene **199**[52,98,138] or triazolothiadiazinoquinoxaline **200**,[137,138] and 1,2,4-triazolo[3,4-*b*]-4,1,2-benzothiadiazines **201**.[162] Indenotriazolothiadiazine **202** was obtained by the acid-catalyzed cyclization of 2-bromo-1-indanone with **2**. Analogously, naphthotriazolothiadiazines **203** were obtained from **2** and bromotetralones.[163] (Scheme 65)




**SCHEME 65**

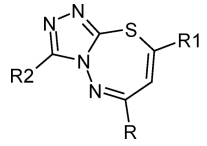
Thiadiazinediones **204** were synthesized by reaction of triazoles **2** with 5-bromo-barbituric acid.[6] Similarly, thiadiazine diones **205** were obtained by the reaction of **2** with 5-bromo-5-nitrobarbituric acid and a ring closure with polyphosphoric acid.[6] When ethanolic solutions of **13** or **18** or **26** or **51** were treated with chloranil in the presence of anhydrous sodium acetate, bis-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazino[5′,6′-b:5′,6′-*e*]cyclo-hexyl-1,4-dienes **206** were obtained.[48,52,61] (Scheme 66)




**SCHEME 66**

## The Synthesis of Triazolothiadiazepines

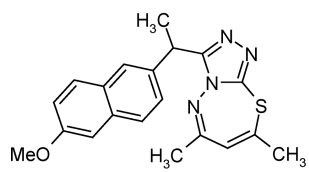
$\alpha$-bromochalcones were utilized, which were prepared by the dehydrobromination of RCOCHBrCHBrR,[1] in a reaction with **2** in alcoholic potassium hydroxide and produced triazolothiadiazepines **207**.[164] (Scheme 67)



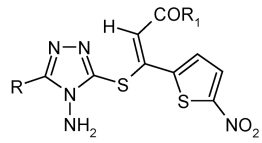
**207**, R = Ph; $R^1$ = 4-$MeOC_6H_4NH$, $R^2$ = H, Me, Et, Pr, 4-$MeC_6H_4OCH_2$, 4-$ClC_6H_4OCH_2$, 2-$MeC_6H_4OCH_2$, 2-$ClC_6H_4OCH_2$;
R = $R^1$ = 4-$MeOC_6H_4NH$, $R^2$ = Et, 2-$MeC_6H_4OCH_2$;
R = Ph, $R^1$ = 4-$MeC_6H_4$, $R^2$ = Et, Ph;
R = 4-$ClC_6H_4$, $R^1$ = 4-$MeOC_6H_4NH$, $R^2$ = Et

**SCHEME 67**

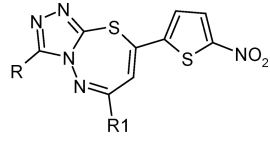
The reaction of compound **4** with acetylacetone gave the triazolothiadiazepine derivative **208**.[16] The acetylenic ketones substituted with 5-nitro-2-thienyl were condensed with 1,2,4-triazoles **2** or **21** in ethanol to give the Michael adducts **209**, which on treatment with conc. sulfuric acid yielded 6-aryl-8-(5-nitro-2-thienyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thia-diazepines **210**. Thiadiazepines **210** were also synthesized from the reaction of heterocyclic $\alpha$-bromochalcone derivatives, i.e., 5-nitro-2-thienyl, with aminotriazoles using sodium acetate as a catalyst.[165] (Scheme 68)



**208**



**209**



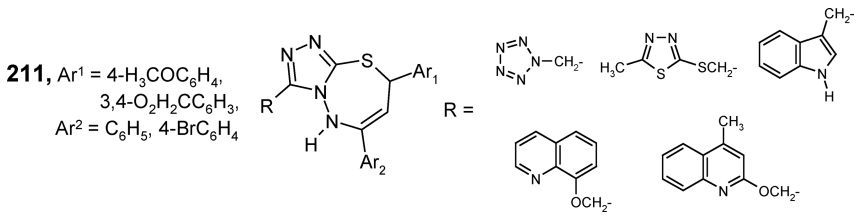
**210**

R = Me, Et, (un)substituted Ph; $R^1$ = (un)substituted Ph

**SCHEME 68**

The reaction of 2-bromopropenones with 3-substituted-4-amino-1,2,4-triazol-5-thione resulted in the formation of novel 3-substituted-6-(3-arylsydnonyl)-8-aryl-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines.[166] The reaction of aminotriazolthiones and substituted chalcones supported by basic alumina or in a solution phase under microwave irradiation afforded 5-substituted-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines **211**.[167] (Scheme 69)

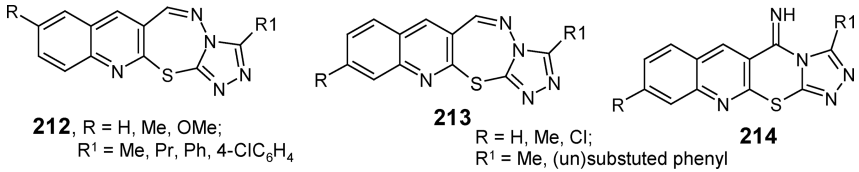
4,6-dichloro-2-methylthio-pyrimidine-5-carbaldehyde reacted with **2** or **21** that led to the formation of 7-substituted-9-methylthiopyrimido-[4,5-*f*]-1,2,4-triazolo-[3,4-*b*]-1,3,4-thia-diazepines.[168] A series of 6a,7-dihydro-6*H*-7(4-aryl)-6-phenyl[1]-benzo-pyrano-1,2,4-triazolo[3,4-*b*]




**SCHEME 69**

benzothiadiazepines was prepared by the reaction of triazoles **2** or **21** with (*E*)-6-chloro-3-(4-chlorobenzylidine)flavanone and (*E*)-6-chloro-3-(4-methoxy-benzylidine)-flavanone in refluxing toluene, containing piperidine as catalyst.[169]

The reaction of 6-substituted-2-chloro-3-formyl-quinoline and aminotriazolthiones **2** or **21** afforded 1,2,4-triazolo[3,4-*b*]-1,3,4-quinolinothiadiazepines **212** rather than the expected Schiff bases. Compounds **212** could also be prepared by the reaction of **2** or **21** with 6-substituted quinolines.[170] The synthesis of *s*-triazolothiadiazepinoquinolines **213** and the facile intramolecular rearrangement of **213** to *s*-triazolothiazinoquinolines **214** involving *N*, *N*-bond scission is reported.[171] (Scheme 70)




**SCHEME 70**

## Biological Activity

Substituted 4-amino-1,2,4-triazol-3-thione derivatives have proved to be an interesting class of heterocycles. Some of the 1,2,4-triazoles displayed a broad spectrum of biological activities, including antifungal, insectidical, fungicide, antibacterial, and herbicidal properties.[172–176] It was reported[58,177] that the thioxo group was a necessary part for their biological activities of 1,2,4-triazole derivatives. For example, the aminotriazolthione **4** exhibited a remarkable antifungal activity.[16] The 4-amino-3-(*D*-glucopentitol-1-yl)-1,2,4-triazol-5-thione (**13**) and its 3-methyl analogue showed a reversible inhibition of some hepatic glycosidases.[20] The triazoles **22** (Ar = 4-$OHC_6H_4$, 2-OH-5-$ClC_6H_3$, 4-$C_2H_5O$-$C_6H_4CH_2$) were reported to possess good antibacterial and antifungal activities especially against *Escherichia*, *Bacillus subtilis*,

*Salmonella enteritidis*, *Staphylococcus aureus*, *Aspergillus niger*, and *Candida albicans*.[36] Also, compound **66** was found to be moderately active against *Bacillus cereus*.[66]

The Schiff base **97** had fungicidal activity against *C. albicans* and *A. niger*, and it had bactericidal activity against *Escherichia coli* and *Bacillus cirroflagellosus*.[84] The Schiff base derivatives **89**,[80] **98**,[85] and **103**[89]are reported to exhibit antimicrobially activities. Triazoles **102** have been showed to exhibit fungicidal and herbicidal properties.[88] Schiff bases **104** and their Mannich bases **105** showed antibacterial and antifungal activity.[91] Also, compounds **108** (R = H, $CH_3$, 2-$ClC_6H_4OCH_2$, 4-$ClC_6H_4OCH_2$, 2,4-$Cl_2C_6H_3OCH_2$) and their Mannich bases **109** display antimicrobial, analgesic, anthelmintic, and anticancer activities.[94,95] Some Mannich bases carrying morpholino and *N*-methylpiperazino were found to be promising antibacterial agents.[86] Whereas Sydnone-*N*-Mannich bases possess antimicrobial, antiinflammatory, analgesic, and CNS depressant activities.[178]



Although there are not many triazoles fused to thiadiazoles or thiadiazines, a number of them are incorporated into a wide variety of therapeutically important compounds possessing a broad spectrum of biological activities.[18,23,37,152,154] For example, the triazolothiadiazole 3,6-substituted by aryl, alkyl, or heterocyclic groups are associated with diverse pharmacological activities such as antimicrobial, bactericidal, antiinflammatory, antiviral, antihypertensive anthelmintic and analgesic effects.[99,100,118,179–181] The thiadiazoles **111**[104] and **115**[16] exhibited remarkable larvicidal[104] and antifungal[16] activities. Some 3-alkyl-6-aryl-5,6-dihydro-s-triazolo[3,4-*b*]-1,3,4-thiadiazoles showed significant antiinflammatory activity.[109] The 3-alkyl-6-aryloxymethylene-s-triazolo-[3,4-*b*]-1,3,4-thiadiazoles **117** have herbicidal and fungicidal activities.[112] The antimicrobial activities of compounds **121** and **122** were investigated to 10 standard organisms including bacterial and fungal strains.[21] The thioureas **124** and 1,2,4-triazolo[3,4-b]-1,3,4-thiadiazoles **125** are reported to possess fungicidal activities against *A. niger* and *Helminthosporium oryzae* (as potential pesticides).[115]6-(5-aryl-2-furyl)-1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazoles **131** are useful as bactericides.[117] Triazolothiadiazole **134** showed fungicidal and herbicidal activities.[55] Some 2-substituted phenyl-3-(3-alkyl/aryl-5,6-dihydro-s-triazolo[3,4-*b*]-1,3,4-thiadiazol-6-yl)indoles[121]and **138**[124,125] are reported to exhibit antiinflammatory, antibacterial, and antifungal activities.

1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines have been shown to possess a wide spectrum of interesting biological and pharmacological activities.[58,148,152,182–187] Thiadiazines **163a,b** were screened for their antibacterial activity against both Gram-positive and Gram-negative

bacteria. The screening results indicate that compounds containing chlorine substituents are significantly active against *E. coli*.[140,141] Also, thiadiazine derivatives **166–170**,[52] **172**,[146] **173**,[65] **174**,[148] **175**,[149] **182**[155] and **198**[52] are reported to exhibit antibacterial activities. The 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazines **179** were tested for their antibacterial and anticancer properties. Among the tested compounds, **179** (R = Et, Ar = 3,4-dimethoxyphenyl) showed the highest degree of antibacterial activity against *S. anreus*, and an evaluation of the LD50 value of this compound was carried out. In preliminary anticancer screening studies, **179** (R = Me, Ar = 3,4-dimethylenedioxyphenyl; R = Me, Ar = 4-chlorophenyl; R = Me, Ar = 3,4-dimethoxy-phenyl).[152] The 4-[3-methyl/aryl-7*H*-s-triazolo[3,4-*b*]-1,3,4-thiadiazin-6-yl]-3-aryl-sydnones have shown significant antibacterial activity.[155] Compound **185** exhibited a remarkable antifungal activity.[16] The 3-substituted-cycloalkane-*s*-triazolo[3,4-*b*]-1,3,4-thiadiazines **186** were reported to possess good antibacterial, antifungal, and anthelmintic activities.[157] A series of thiadiazepines are reported to exhibit antifungal activity.[16,169]



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