

# The chemistry of mercapto- and thione- substituted 1,2,4-triazoles and their utility in heterocyclic synthesis

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## Abstract

The synthesis and reactions of mercapto- and thione-substituted 1,2,4-triazoles are comprehensively reviewed.

**Keywords:** Mercapto-1,2,4-triazoles, 1,2,4-triazolethiones, thiazolotriazoles, triazolothiadiazoles, triazolothiazines, triazolothiazepines, triazolothiadiazines

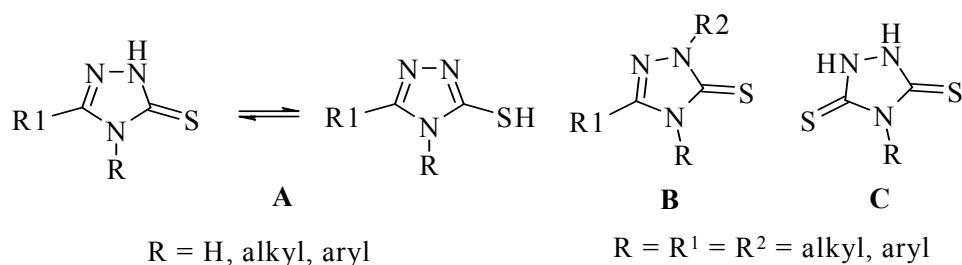
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## 1. Introduction

In the last few decades, the chemistry of 1,2,4-triazoles and their fused heterocyclic derivatives has received considerable attention owing to their synthetic and effective biological importance. For example, a large number of 1,2,4-triazole-containing ring systems have been incorporated into a wide variety of therapeutically interesting drug candidates including anti-inflammatory, CNS stimulants sedatives, antianxiety, antimicrobial agents<sup>1,2</sup> and antimycotic activity such as fluconazole, intraconazole, voriconazole.<sup>3,4</sup> Also, there are known drugs containing the 1,2,4-triazole group e.g. Triazolam<sup>5</sup>, Alprazolam<sup>6</sup>, Etizolam<sup>7</sup>, and Furacylin<sup>8</sup>. Moreover, sulphur-containing heterocycles represent an important group of sulphur compounds that are promising for use in practical applications. Among these heterocycles, the mercapto- and thione-substituted 1,2,4-triazole ring systems **A-C** (Figure 1) have been well studied and so far a variety of biological activities have been reported for a large number of their derivatives, such as antibacterial<sup>9-12</sup>, antifungal<sup>13,14</sup>, antitubercular<sup>15</sup>, antimycobacterial<sup>16</sup>, anticancer<sup>17,18</sup>, diuretic<sup>19,20</sup>, and hypoglycemic<sup>21</sup> properties.



**Figure 1**

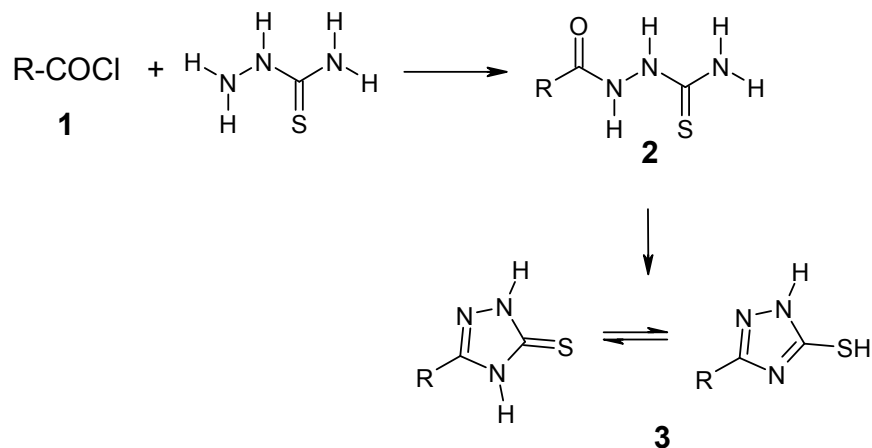
In addition to these important biological applications, mercapto-1,2,4-triazoles are also of great utility in preparative organic chemistry, for example, in the presence of various reagents, undergo different types of reactions to yield other heterocyclic compounds, e.g., thiazolotriazoles, triazolothiadiazoles, triazolothiazines, triazolothiazepines and triazolothiadiazines. Recently<sup>22</sup>, we have reviewed the chemistry of the 4-amino-1,2,4-triazole-3-thiones (**A**, R = NH<sub>2</sub>).

In the present review article the most common and useful procedures for the preparation of the mercapto- and thione-substituted 1,2,4-triazole and their utility for the synthesis of well known heterocyclic ring systems are compiled and discussed, therewith the most attention is paid to reports published within the last 50 years.

## 2. Synthetic approaches

### 2.1. Synthesis of 2,4-dihydro-3*H*-mercapto/thione-1,2,4-triazoles

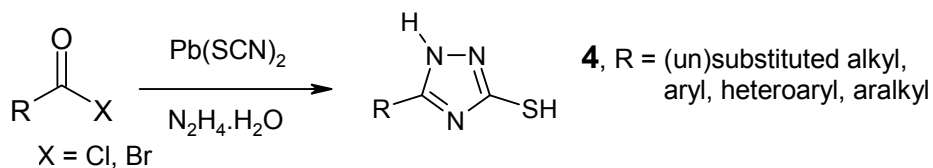
The reaction of carboxylic acid chlorides **1** and thiosemicarbazide gave **2**, which without purification were cyclized in alkaline media to yield the corresponding 2,4-dihydro-3*H*-1,2,4-triazole-3-thiones **3**<sup>23-37</sup> (Scheme 1).



R = H, CH<sub>3</sub>, CF<sub>3</sub>, C<sub>6</sub>F<sub>13</sub>, 1-adamentyl, C<sub>6</sub>H<sub>5</sub>, 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>, 2-, 3-, and 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>, 2-, 3-, and 4-FC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 2,4-(Cl)<sub>2</sub>-5-F-C<sub>6</sub>H<sub>2</sub>, 2,3,5-(F)<sub>3</sub>-4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, 1,3-benzodioxo-5-yl

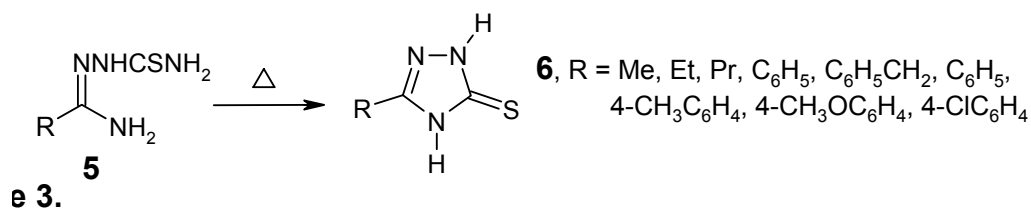
#### Scheme 1

The triazoles **4**<sup>38</sup> were also prepared by reaction of acid halides with a lead (II) thiocyanate and hydrazine hydrate (15%) in a solvent at -70 to + 200°C (Scheme 2).



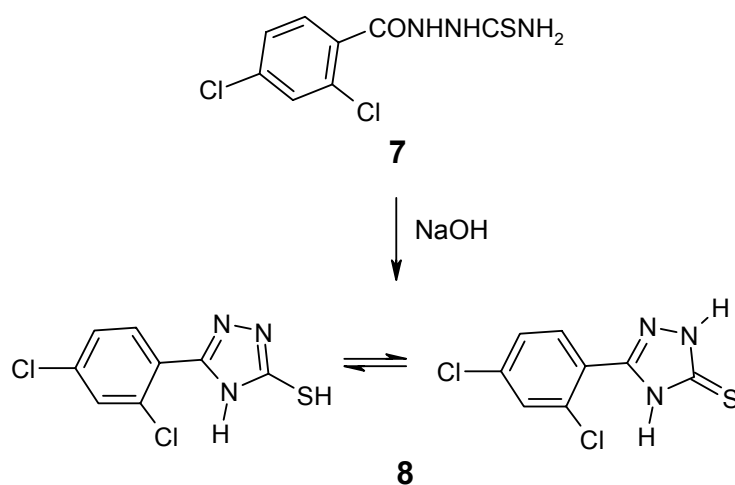
#### Scheme 2

In addition, the triazolethiones **6**<sup>39</sup> can be prepared readily from the thermolysis of thiosemicarbazones **5** (Scheme 3).



## Scheme 3

Goswami *et al.*<sup>40</sup> reported that the oxidative cyclization of 1-(2,4-dichloro-benzoyl)-thiosemicarbazide (**7**) gives the 3-(2,4-dichlorophenyl)-1H-1,2,4-triazole-5-thiol (**8**) (Scheme 4). Compound **8** exhibited antimicrobial activities against *B. Cereus*, *Esch. Coli* and *P. Salanarium*.



## Scheme 4

Moreover, the 1,2,4-triazole-5-thiones **9**<sup>41</sup> and **10**<sup>42</sup> were prepared by cyclization of the corresponding thiosemicarbazide (Figure 2). Compound **9** possessed anti-inflammatory activity<sup>41</sup>.

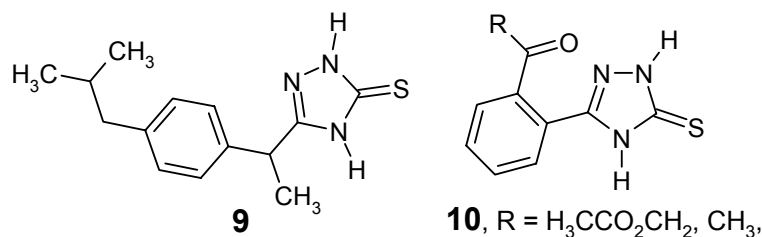
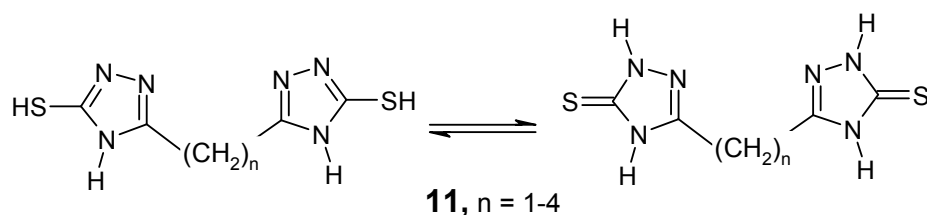


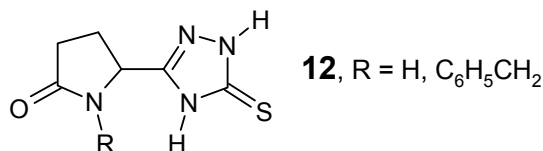
Figure 2

The bis(5-mercapto-4H-1,2,4-triazol-3-yl)alkanes **11**<sup>43</sup> can also be obtained by the directly treating the corresponding aliphatic dicarboxylic acids with thiosemicarbazide (Scheme 5).



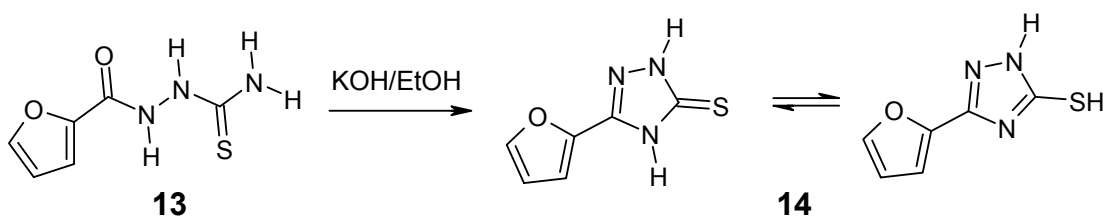
### Scheme 5

Starting from pyrrolutamic esters, 1,2,4-triazole-3-thiones **12**<sup>44</sup>, bonded to a pyrrolidinone ring were synthesized (Figure 3).



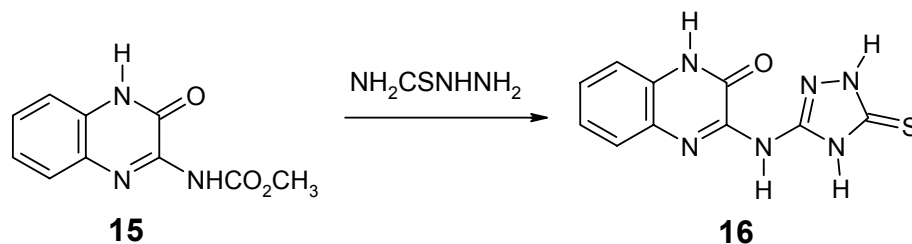
### Figure 3

5-Furan-2-yl-4H-1,2,4-triazole-3-thiol (**14**) was prepared by the reaction of the appropriate 2-furoyl-thiosemicarbazide (**13**) and potassium hydroxide in ethanol for 3 hours under reflux, followed by acidification with acetic acid<sup>45,46</sup> (Scheme 6). It has been reported that the crystal structure of **3** corresponded to the thione form, but they showed thiol-thione tautomerism in solution<sup>47</sup>.



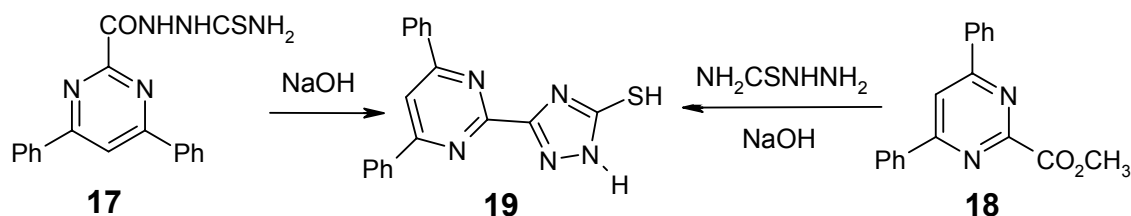
### Scheme 6

Condensation of carbamate **15** with thiosemicarbazide in boiling pyridine via initial nucleophilic attack of the amino group to the ester carbonyl without attack at the carbonyl of the pyrazine ring followed by cyclization to give triazolylquinoxaline **16**<sup>48,49</sup> (Scheme 7).



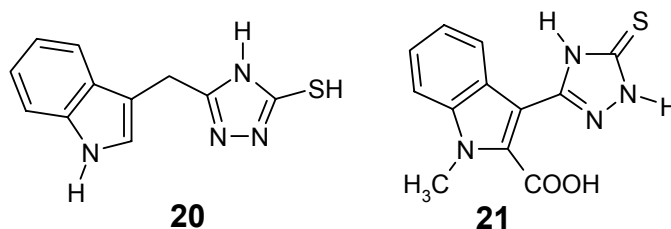
## Scheme 7

5-(4,6-Diphenyl-pyrimidin-2-yl)-1,2,4-triazolin-3-thione (**19**)<sup>50</sup> could be prepared either by base catalyzed cyclization of acylthiosemicarbazide **17** or by the reaction of methyl pyrimidin-2-carboxylate **18** with thiosemicarbazide in the presence of NaOH (Scheme 8).



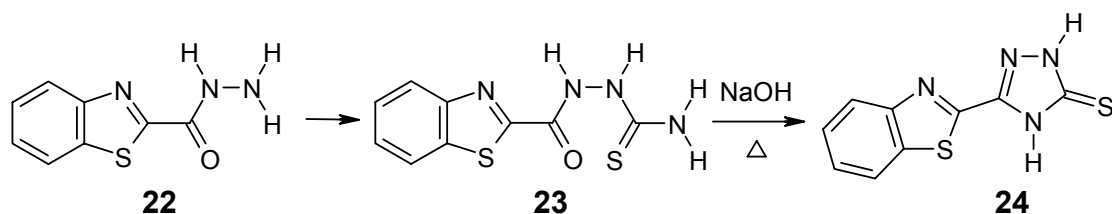
## Scheme 8

Similarly, triazoles **20** and **21** were obtained by the cyclization of the corresponding thiosemicarbazides in alkaline medium<sup>51,52</sup> (Figure 4).



## Figure 4

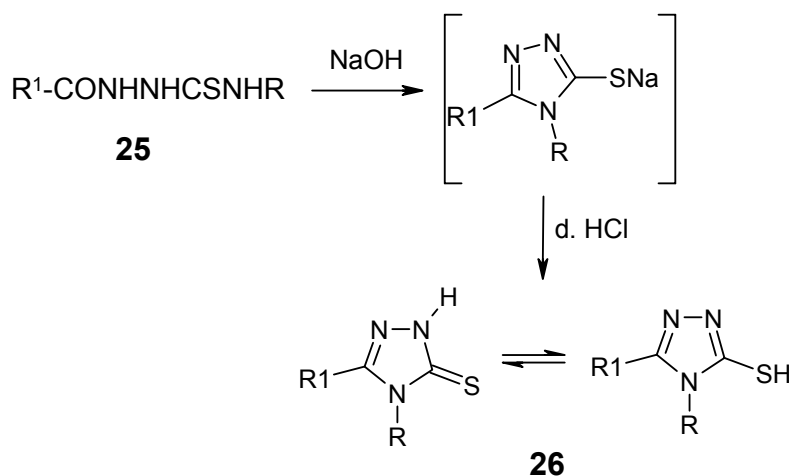
When the reaction of hydrazide **22** with ammonium thiocyanate was carried out in boiling hydrochloric acid, the 1-(2-benzothiazolylcarbonyl)thiosemicarbazide (**23**) was obtained. Upon heating of the later compound with sodium hydroxide, it underwent intramolecular cyclization to give 3-(2-benzothiazolyl)-1,2,4-triazoline-5-thione (**24**)<sup>53</sup> (Scheme 9).



Scheme 9

## 2.2. Synthesis of 4-alkyl/aryl-mercapto/thione-1,2,4-triazoles

The cyclodehydration of thiosemicarbazides **25** in alkaline medium afforded 4-alkyl/aryl-1,2,4-triazoline-3-thiones **26**<sup>36,38,54-63</sup> (Scheme 10). It has been reported that the compounds **26** exist mainly in a thione form<sup>62</sup>.



R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>11</sub>, CH<sub>2</sub>CH<sub>2</sub>OH, CH<sub>2</sub>CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>, 4-CH<sub>3</sub>O-C<sub>6</sub>H<sub>4</sub>;  
 R<sup>1</sup> = H, Me, Et, Pr, Bu, 3-C<sub>5</sub>H<sub>4</sub>N, C<sub>6</sub>H<sub>5</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>SCH<sub>2</sub>, 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SCH<sub>2</sub>CH<sub>2</sub>,  
 4-ClC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>, 4-BrC<sub>6</sub>H<sub>4</sub>SO<sub>2</sub>CH<sub>2</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>, 2-FC<sub>6</sub>H<sub>4</sub>,

Scheme 10

Lin *et al.*<sup>64</sup> reported that the 4-substituted-4*H*-1,2,4-triazole-3-thiols **27** were prepared by the condensation of 4-substituted-3-thiosemicarbazides with dimethylformamide dimethyl acetal or dimethylacetamide dimethyl acetal (Figure 5).

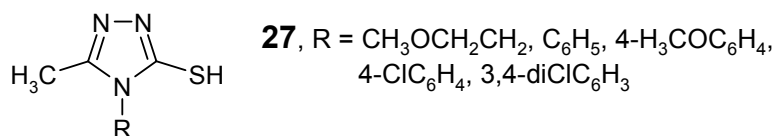


Figure 5

On the other hand, 4-alkyl/aryl-5-nonanoyl/octadecanoyl-2,4-dihydro-3H-1,2,4-triazoline-3-thiones were synthesized as potential antimicrobial agents. The course of synthesis included the reaction of nonanoyl/octadecanoyl hydrazine with selected alkyl/aryl isothiocyanates. The prepared thiosemicarbazides gave by cyclization the required 1,2,4-triazoles **28**<sup>65</sup> (Figure 6).

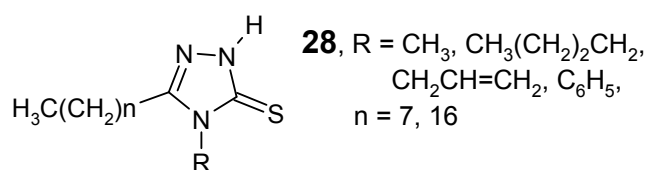


Figure 6

Moreover, a number of 2-hydroxycycloalkyl-substituted 1,2,4-triazoles **29** and **30** were prepared by different methods from *cis*- and *trans*-2-hydroxy-1-cycloalkane-carbohydrazides and their isocyanate or isothiocyanate adducts<sup>66</sup> (Figure 7).

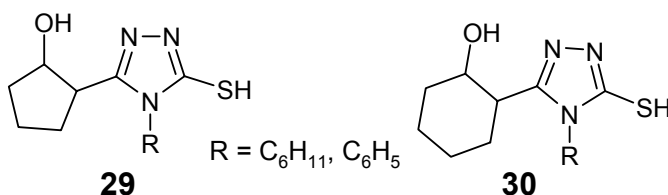
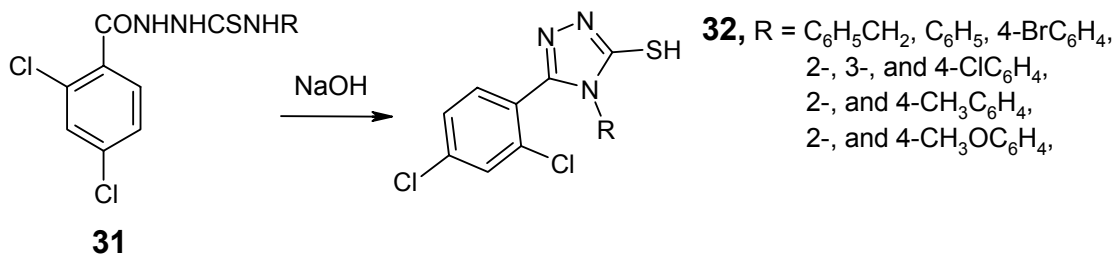


Figure 7

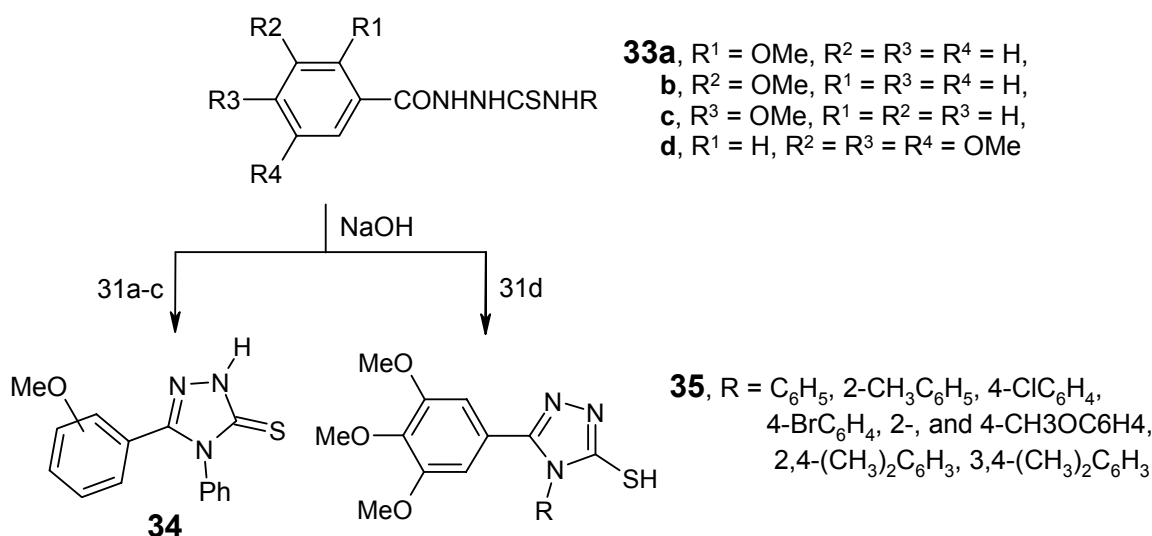
The 1-(2,4-dichlorobenzoyl)-4-arylthiosemicarbazides **31** on oxidative cyclization with 1*N* NaOH solution under reflux resulted in their corresponding 1,2,4-triazole-5-thiols **32**<sup>40</sup> (Scheme 11).



Scheme 11

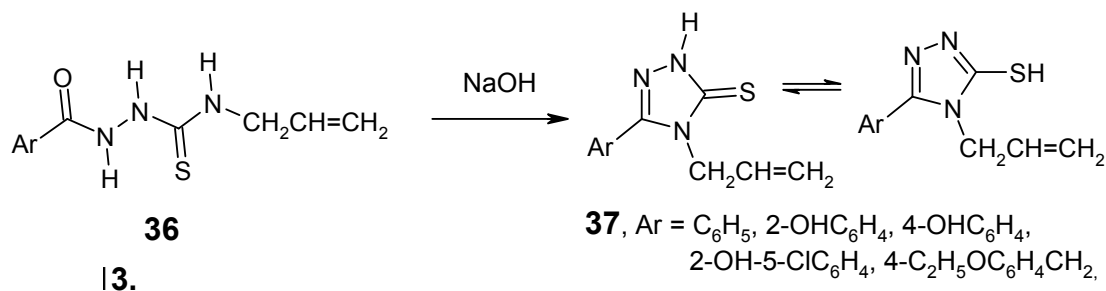


The 1,2,4-triazoles **34**<sup>23,37,67,68</sup> and **35**<sup>57</sup> have also been synthesized by the condensation and cyclization of the corresponding thiosemicarbazides **33a-d** in NaOH solution (Scheme 12).



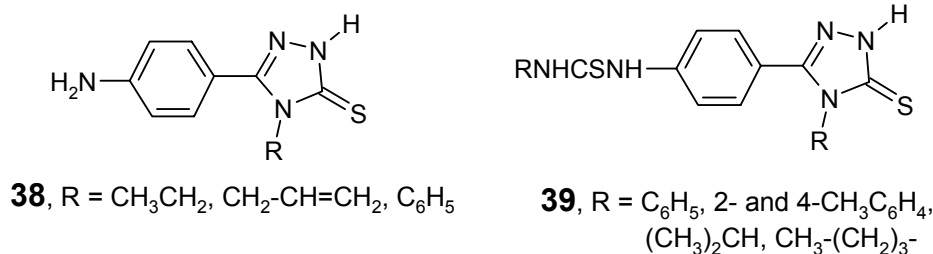
**Scheme 12**

When compounds **36** were refluxed in 2M sodium hydroxide solutions for about 4 hours, they produced 4-allyl-5-aryl-1,2,4-triazoles **37** in good yields<sup>69,70,71</sup> (Scheme 13). While compound **37** may exist in thione-thiol tautomeric forms, the authors reported that in this case the thione structures dominate in the solid state. Compound **37** showed inhibitory effects against *Escherichia coli*, *Bacillus subtilis*, *Salmonella enteritidis*, *Staphylococcus aureus*, *Aspergillus niger* and *Candida albicans*<sup>71</sup>.

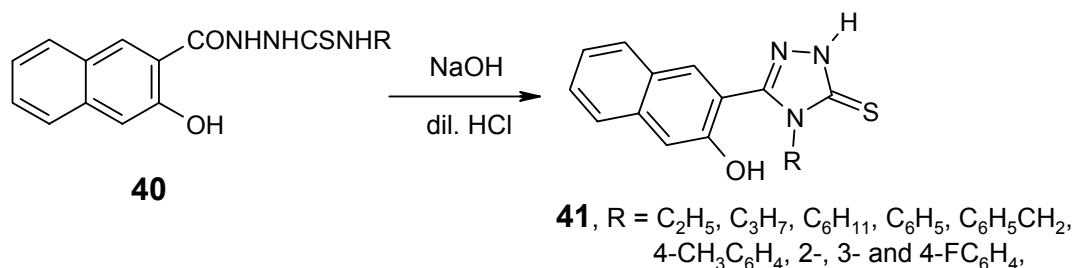


**Scheme 13**

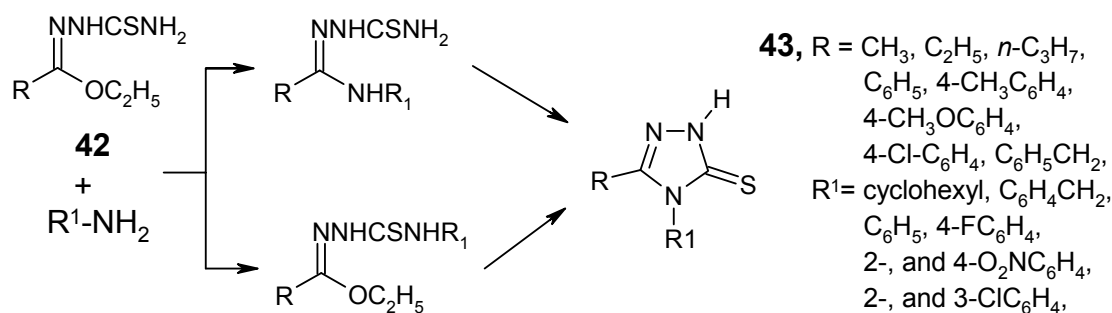
Refluxing the corresponding thiosemicarbazides in alkaline medium performed the 1,2,4-triazolethiones **38**<sup>14,72</sup> and **39**<sup>73</sup> (Figure 8).

**Figure 8**

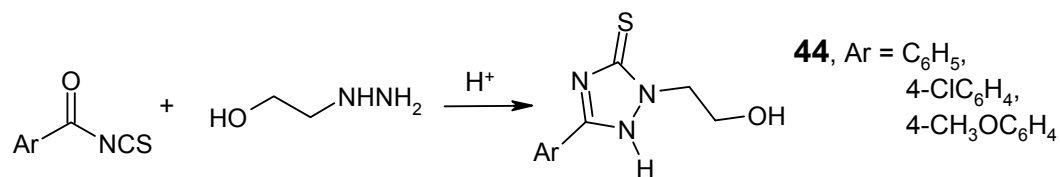
Substituted 1,4-Dihydro-3-(3-hydroxy-2-naphthyl)-5H-1,2,4-triazoline-5-thiones **41**<sup>18,74</sup> were obtained by the cyclization of thiosemicarbazides **40** in sodium hydroxide solution followed by treatment of the reaction mixture with dil. HCl at 0°C (Scheme 14).

**Scheme 14**

4,5-Disubstituted-2,4-dihydro-1,2,4-triazole-3-thiones **43**<sup>38</sup> were obtained by the action of primary amines on thiosemicarbazones of ester **42** (Scheme 15).

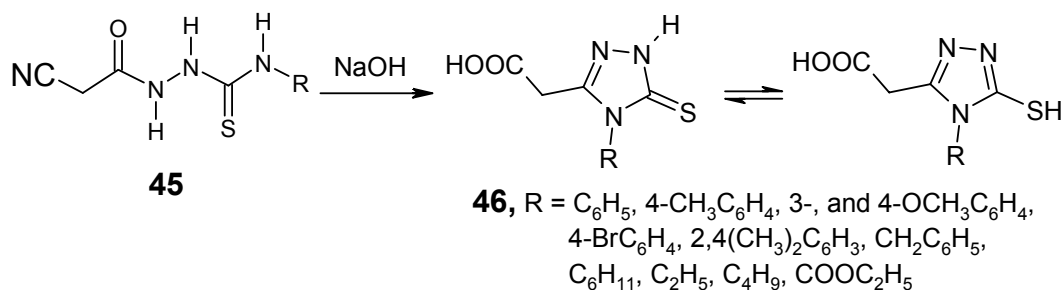
**Scheme 15**

5-Aryl-1,2-dihydro-2-(2-hydroxyethyl)-3H-1,2,4-triazole-3-thiones **44** were prepared from the reaction of 2-hydrazinoethanol with aroyl isothiocyanate in anhydrous benzene and in the presence of *p*-toluenesulfonic acid<sup>75</sup> (Scheme 16).



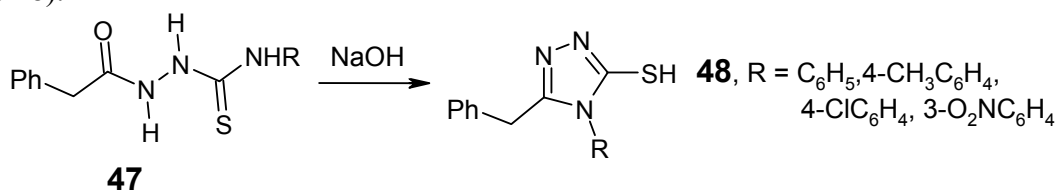
### Scheme 16

The thiosemicarbazide **45** was cyclized with 2% or 10% solutions of sodium hydroxide to the corresponding 4-substituted-5-mercapto-1,2,4-triazole-3-acetic acid **46**<sup>76</sup> (Scheme 17). It has been reported that the compounds **46** exist mainly in a thiol form<sup>76</sup>.



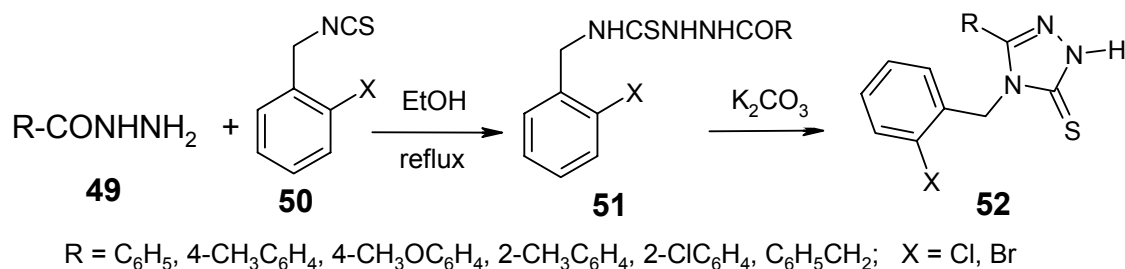
### Scheme 17

The 1-(phenyl acetyl)-4-substituted thiosemicarbazides **47** on refluxing with 2*N* NaOH solution were cyclized into the corresponding 5-benzyl-4-aryl-4H-1,2,4-triazole-3-thiol **48**<sup>77</sup> (Scheme 18).



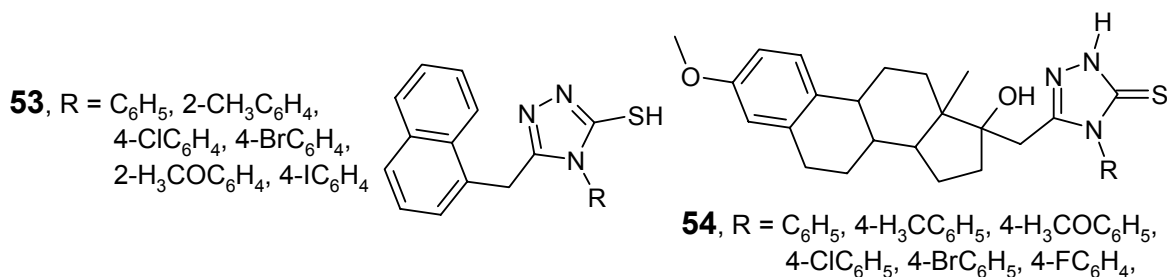
### Scheme 18

4-(2-Halobenzyl)-1,2,4-triazole-3-thiones **52** were synthesized by refluxing the thiosemicarbazide **51** obtained from *o*-halobenzyl isothiocyanate **50** and an acid hydrazide **49**<sup>10,78</sup> (Scheme 19).



### Scheme 19

Several 5-(1-naphthylmethyl)-4-aryl-*s*-triazole-3-thiols **53** were prepared as possible anti-inflammatory agents<sup>79</sup>. Also, estradiol-17 $\alpha$ -triazolines **54** were synthesized and tested *in vitro* for anabolic-catabolic activity and binding affinity to steroid receptors<sup>80</sup> (Figure 9).



### Figure 9

Similarly, the triazoles **55**<sup>81-83</sup>, **56**<sup>84,85</sup>, **57**<sup>84,86</sup>, **58**<sup>87</sup> and **59**<sup>88</sup> were prepared by cyclization of the corresponding 4-substituted-thiosemicarbazides in alkaline medium (Figure 10). Compound **57** ( $\text{R} = \text{C}_2\text{H}_5$ ) showed interesting anti-inflammatory activity<sup>86</sup>. Also compound **58** ( $\text{R} = 4\text{-ClC}_6\text{H}_4$ ) showed significant antifungal and antibacterial activities<sup>87</sup>.

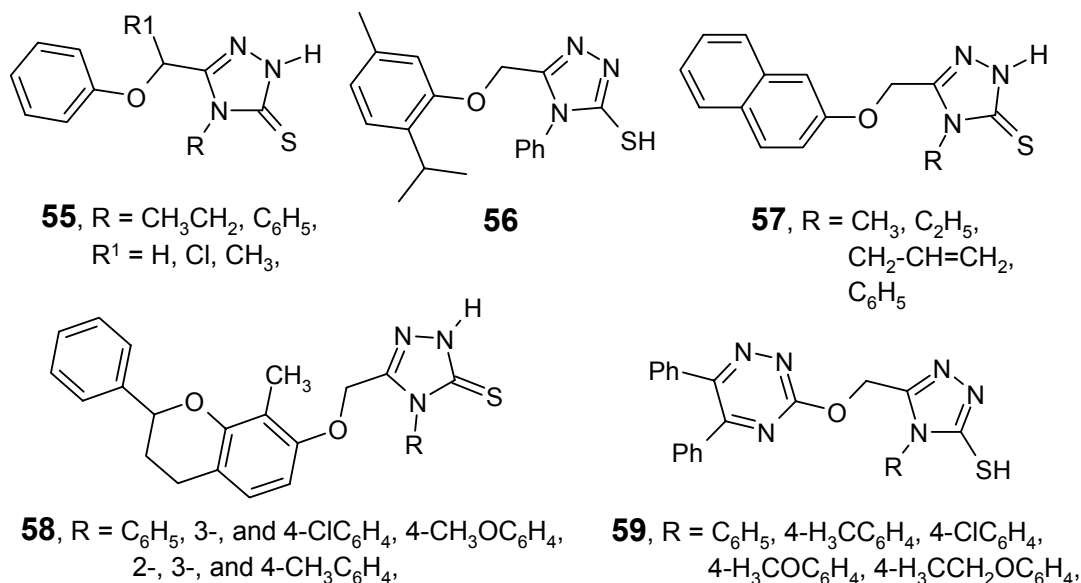
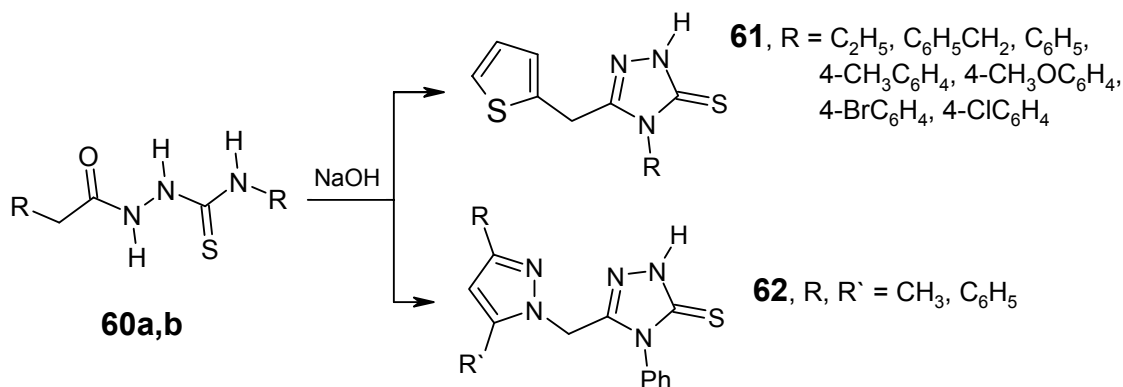


Figure 10

The 1,2,4-triazoline-5-thiones **61**<sup>89</sup> and **62**<sup>90</sup> were synthesized by the cyclization of the corresponding thiosemicarbazide derivatives **60a,b** in NaOH solution (Scheme 20). Compound **61** (R = C<sub>2</sub>H<sub>5</sub>, 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 4-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>) showed antifungal activity against some species belonging to *Trichophyton spp.* known as the causative agents of superficial mycoses<sup>89</sup>.



Scheme 20

Also, the triazolethiones **63**<sup>91</sup>, **64**<sup>92,93</sup> and **65**<sup>94</sup> were synthesized from the corresponding 4-substituted thiosemicarbazides in alkaline medium (Figure 11). Compound **63** (R = CH<sub>3</sub>, CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>) showed antibacterial activity against *Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis*<sup>91</sup>.

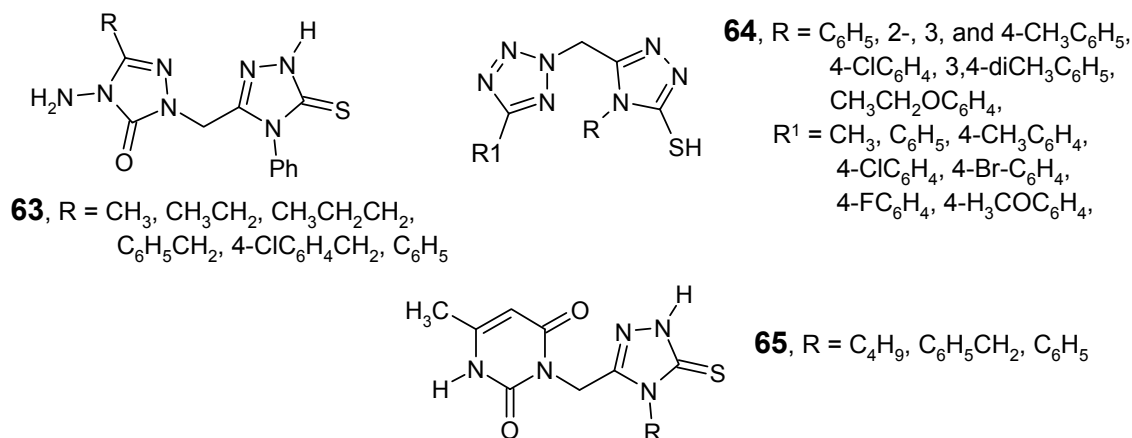
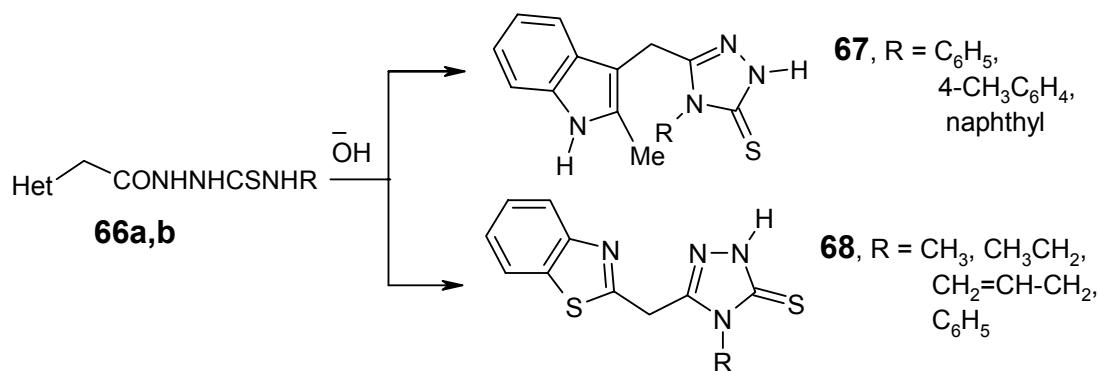


Figure 11

The 3-[(2-methyl-1H-3-indolyl)-methyl]-4-aryl-4,5-dihydro-1H-1,2,4-triazole-5-thiones **67**<sup>95</sup> and 3-(2-benzothiazolylmethyl)-4-substituted-1,2,4-triazoline-5-thione derivatives **68**<sup>96-99</sup> were synthesized by the cyclization of the corresponding thiosemicarbazides **66a,b** in alkaline medium (Scheme 21). Compound **65** showed anti-depressant and anti-convulsant activity<sup>95</sup>.



Scheme 21

A series of 1-(1-carboxymethyl-1H-benzotriazole)-thiosemicarbazides was synthesized and then cyclized with NaOH to afford 1-(4-substituted-4H-1,2,4-triazole-3-thion-5-yl)-methyl-1H-benzotriazoles **69**<sup>100</sup> (Figure 12).

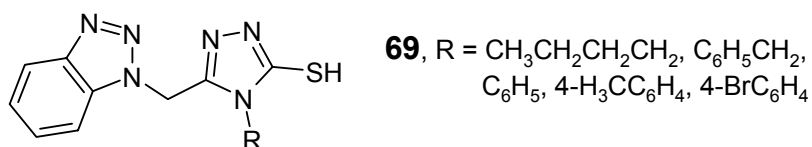
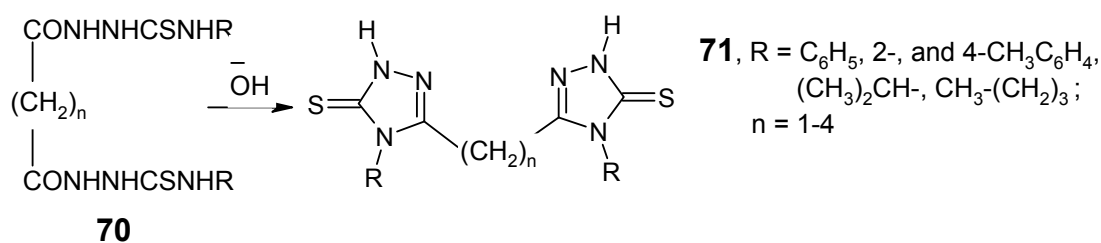


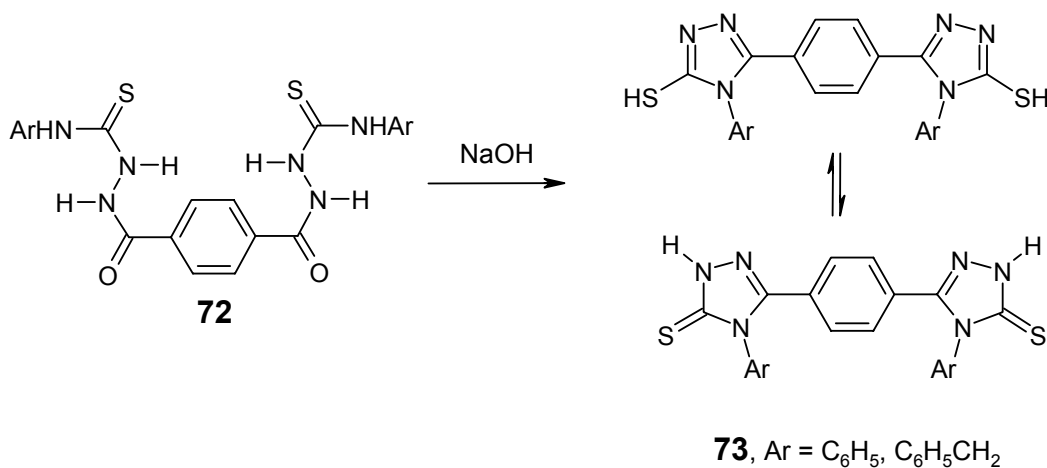
Figure 12

The bis(4-aryl)-3-thio-1,2,4-triazol-5-yl)alkanes **71** were prepared by the base cyclization of the corresponding bis(4-arylthiosemicarbazido)alkanes **70**<sup>73,101-103</sup> (Scheme 22).



### Scheme 22

Shaker *et al.*<sup>104</sup> reported that the treatment of 1,4-phenylene-bis-thiosemicarbazide **72** with sodium hydroxide gives 5,5'-(1,4-phenylene)bis(4-aryl-3-mercapto-1,2,4-triazole) **73** (Scheme 23).



### Scheme 23

A series of hetero-substituted thiosemicarbazides was synthesized and then cyclized in alkaline medium to afford the corresponding triazolethiones **74**<sup>43</sup>, **75**<sup>77,105</sup>, **76**<sup>69,106</sup>, **77**<sup>107,108</sup>, and **78**<sup>109</sup> in excellent yields (Figure 13). Compound **77** exhibited potential and broad-spectrum antitumor activity against most of the tested *subpanel tumour* cell lines (GI50, TGI and LC50 values  $< 100 \mu M$ )<sup>107</sup>. Compound **78** exhibited moderate inhibitory activity against plant pathogenic fungi such as *cucumber grey mold*, *rape scherotium*, *wheat gibberella* and *cotton damping-off* at  $50 \mu g/mL$  concentration<sup>109</sup>.

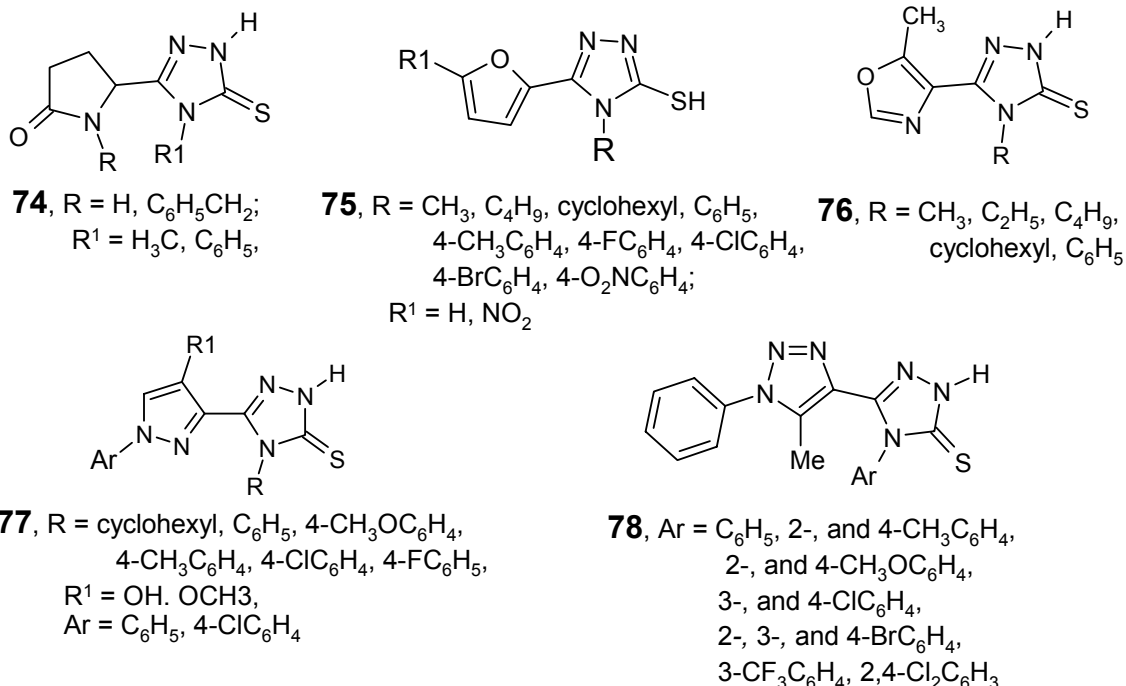
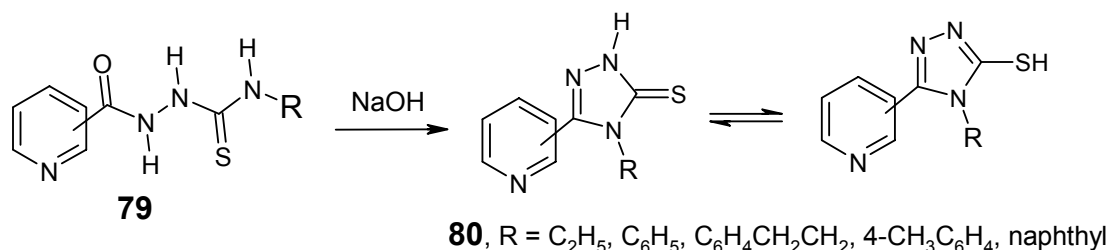


Figure 13

The isomeric substituted thiosemicarbazides **79**, when subjected to react with 4 N NaOH, underwent intramolecular dehydrate cyclization to furnish the corresponding 4-alkyl/aryl-5-(isomeric pyridoyl)-1,2,4-triazole-3-thioles **80**<sup>54,110-113</sup> (Scheme 24). Compound **80** (3-pyridyl) exhibit moderate inhibitory activities at 32 µg/mL against *S. aureus*<sup>113</sup>.



Scheme 24

Also, 1,4-disubstituted-thiosemicarbazides **81** were synthesized from the corresponding carbohydrazides and cyclized under mildly basic conditions to 1,2,4-triazoles **82**<sup>114</sup>, **83**<sup>115</sup>, **84**<sup>116</sup> and **85**<sup>117</sup> (Figure 14). Compound **84** (R = 2-Cl, Ar = 3-FC<sub>6</sub>H<sub>4</sub>) exhibited good anti-fungal activity<sup>116</sup>.



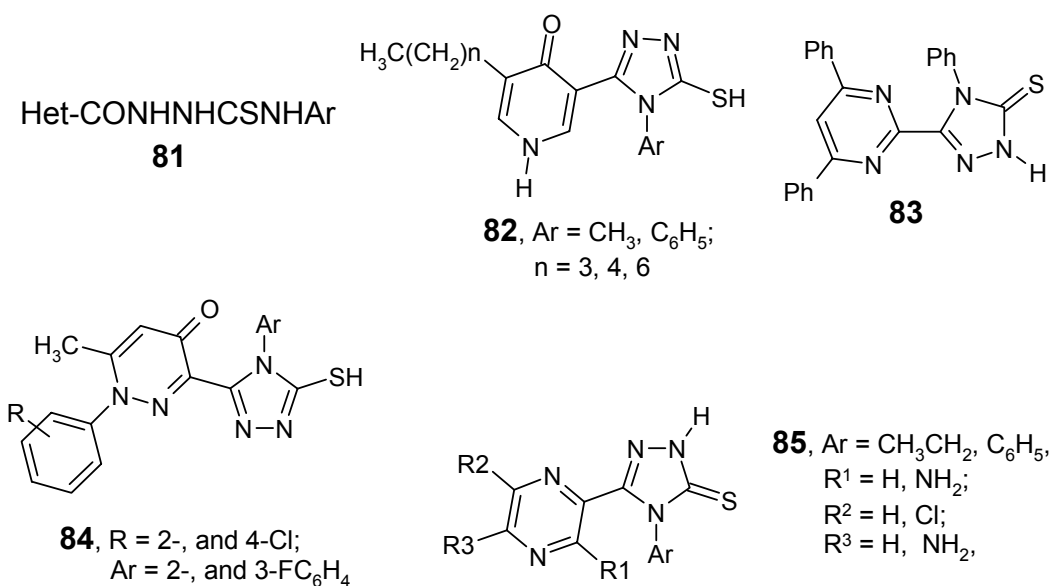


Figure 14

The 5-(2-phenyl-benzimidazol-1-yl-methyl)-4-aryl-4H-1,2,4-triazole-3-thiones were synthesized, and their *in vitro* effects on the rat liver microsomal NADPH-dependent lipid peroxidation (LP) levels were determined<sup>118</sup>. Also, the triazoles **86**<sup>119</sup>, **87**<sup>52</sup>, **88**<sup>120</sup> and **89**<sup>121-124</sup> were synthesized by the cyclization of the corresponding thiosemicarbazides in alkaline medium (Figure 15).

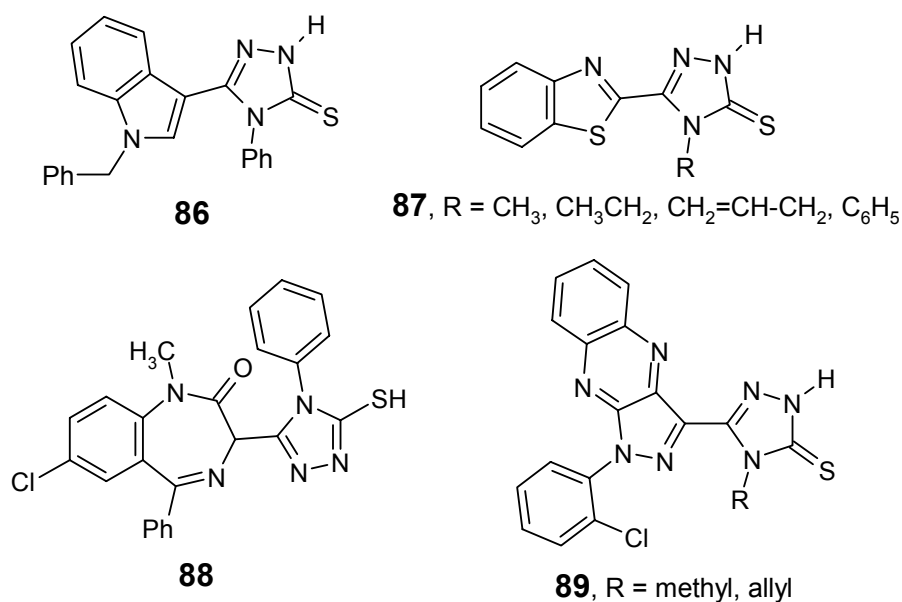
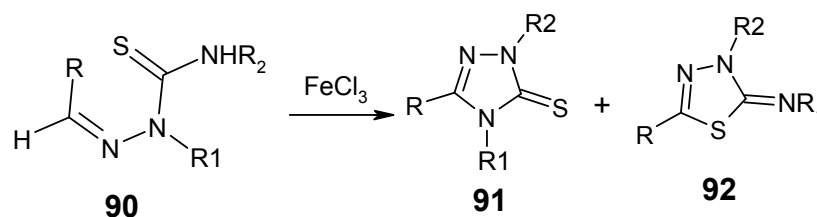


Figure 15

### 2.3. Synthesis of 2,4-dialkyl/aryl-1,2,4-triazolethiones

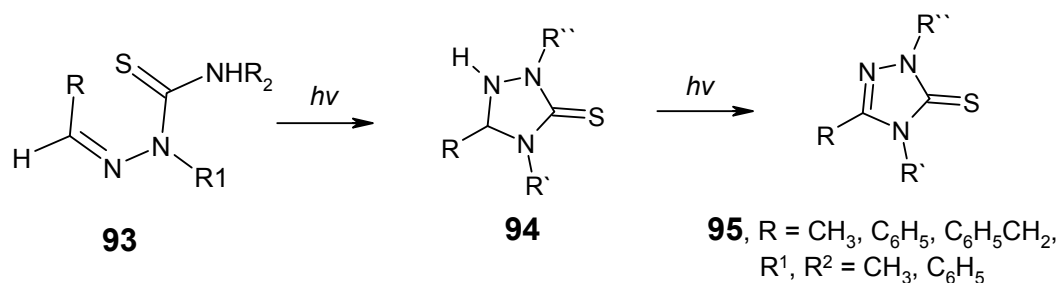
The oxidative cyclization of aldehyde thiosemicarbazones **90** with ferric chloride solutions gave 1,2,4-triazoline **91** and 1,3,4-thiadiazoline **92**<sup>125-127</sup> (Scheme 25).



R = R<sup>1</sup> = CH<sub>3</sub>, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>, C<sub>6</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>5</sub>CO, 3-, and 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 3-, and 4-ClC<sub>6</sub>H<sub>4</sub>, 4-F<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, 3-, and 4-BrC<sub>6</sub>H<sub>4</sub>, 4-H<sub>3</sub>COC<sub>6</sub>H<sub>4</sub>, 4-(H<sub>3</sub>C)<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>;  
R<sup>2</sup> = CH<sub>3</sub>, C<sub>6</sub>H<sub>5</sub>.

#### Scheme 25

The photochemistry behavior of some substituted aldehyde thiosemicarbazones **93** have been investigated in methanol at 254 nm and cyclized to furnish the 5-thioxo-1,2,4-triazolines **95**<sup>128,129</sup> (Scheme 26). The first step of the photoreaction of compound **93** depicted as the cyclization to the 1,2,4-triazolidinethiones **94**, the second step as the photo oxidation of **94** to give **95**<sup>129</sup>.



#### Scheme 26

The reactions between 2,4-disubstituted thiosemicarbazides and orthoesters in refluxing xylene led to the formation of the 1,2,4-triazoline-5-thiones **96**<sup>130</sup> (Figure 16).

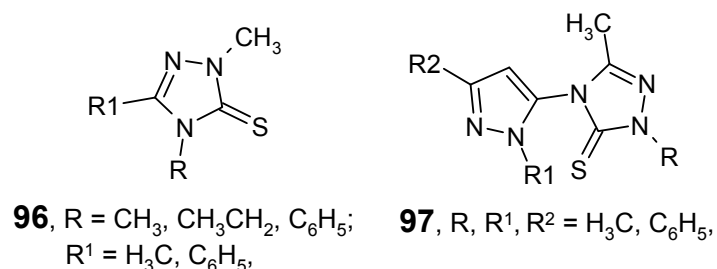
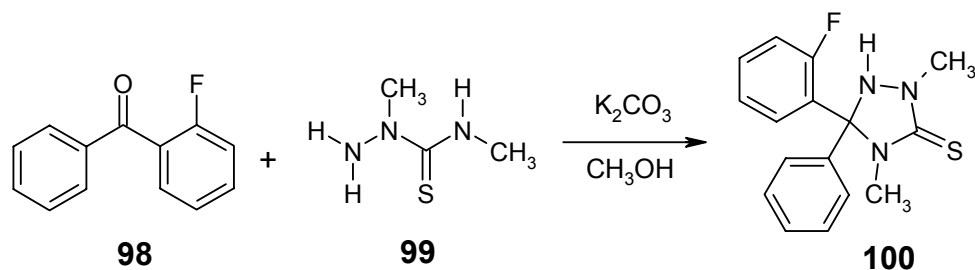


Figure 16

Also, cyclization of pyrazolyl thiosemicarbazides with formic acid-acetic anhydride or with triethyl orthoacetate-acetic anhydride provided 5-methyl-4-(pyrazol-5-yl)-1,2,4-triazole-3-thiones **97**<sup>131</sup> (Figure 16).

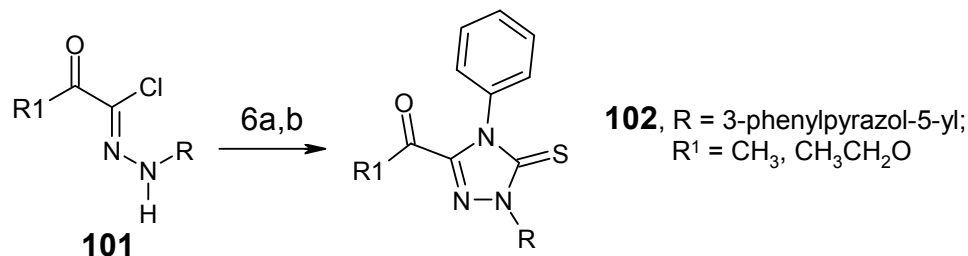
5-Aryl-2,4-dialkyl-2,4-dihydro-3*H*-1,2,4-triazol-3-ones were converted in 55-74% yield to the corresponding 3*H*-1,2,4-triazole-3-thiones by using the combination bis(tricyclohexylstannyl) sulfide/boron-trichloride <sup>132</sup>.

The 2,4-dimethyl-5-(2-fluorophenyl)-5-phenyl-1,2,4-triazolidine-3-thione (**100**)<sup>61</sup> was prepared in low yield by heating a methanolic solution of 2-fluorobenzophenone (**98**) and 2,4-dimethyl-thiosemicarbazide (**99**) in the presence of KOH (Scheme 27).



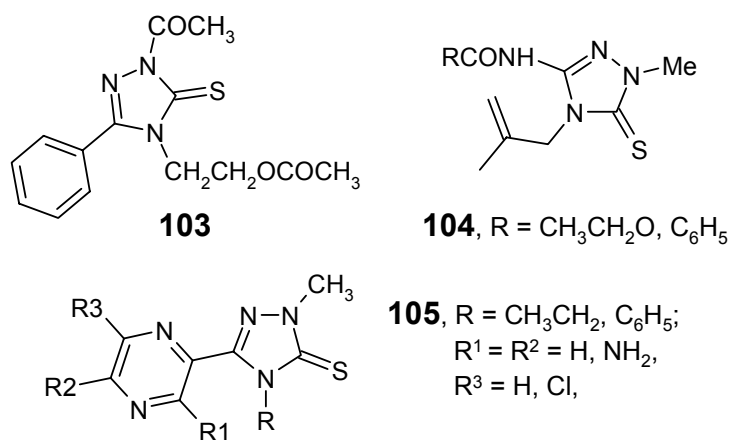
Scheme 27

The carbo(3-phenylpyrazol-5-yl-hydrazonoyl)halides **101** reacted with phenyl isothiocyanate to yield 4-phenyl-1-(3-phenylpyrazol-5-yl)-3-substituted- $\Delta^2$ -1,2,4-triazoline-5-thiones **102**<sup>133</sup> (Scheme 28).



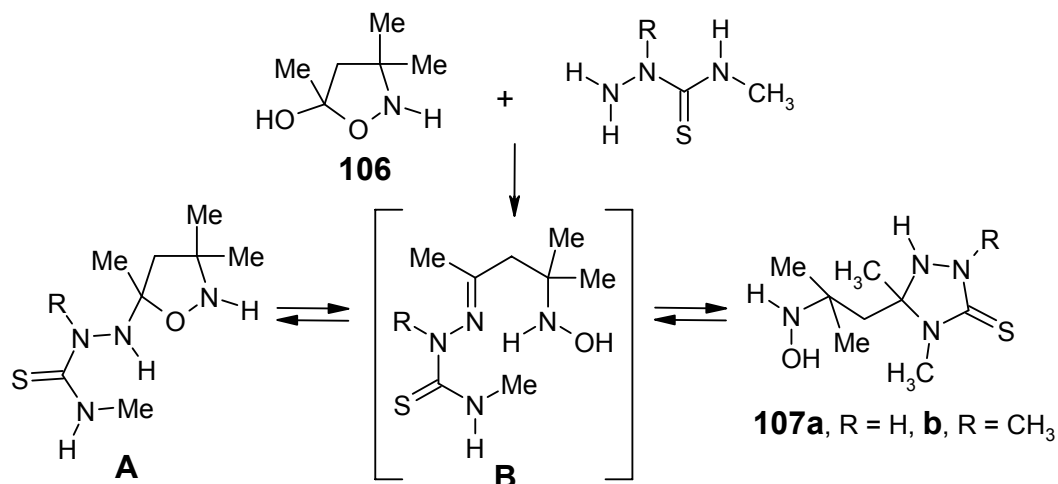
## Scheme 28

1,2,4-Triazole-3-thiones **103**<sup>39</sup>, **104**<sup>134</sup> and **105**<sup>118</sup> were obtained from the corresponding thiosemicarbazones in alkaline medium (Figure 17).



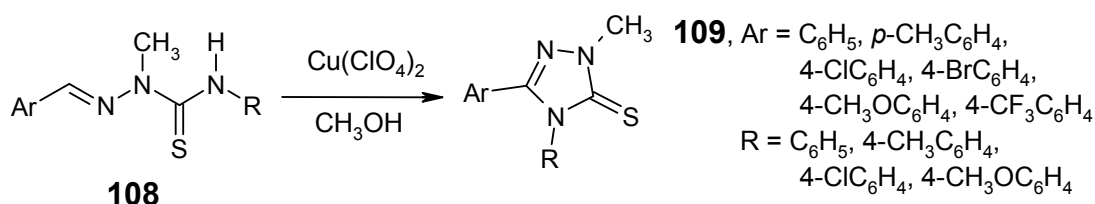
## Figure 17

The products of the condensation of 5-hydroxy-3,3,5-trimethylisoxazolidine (**106**) with 4-phenyl-/2-methyl-4-phenylthiosemicarbazide have predominantly 1,2,4-triazolidine or isoxazolidine structure and do not display ring-ring tautomeric interconversion in solution<sup>135</sup>. Such tautomerism was discovered in studying the structure of **107a** and **107b**, which are the products of **106** with 4-methyl- and 2,4-dimethylthiosemicarbazides. Thiones **107a** and **107b** were formed after brief heating of the starting reagents in methanol at reflux in the presence of catalytic amount of acetic acid<sup>136</sup> (Scheme 29).



Scheme 29

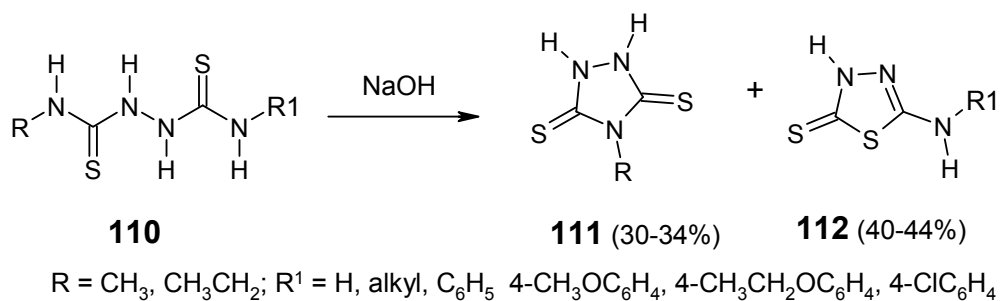
The oxidation of 2-methyl-4-phenyl thiosemicarbazides **108** with cupric perchlorate in methanol gave 1,2,4-triazolines **109**<sup>129</sup> (Scheme 30).



Scheme 30

#### 2.4. Synthesis of 1,2,4-triazole-3,5-dithiones

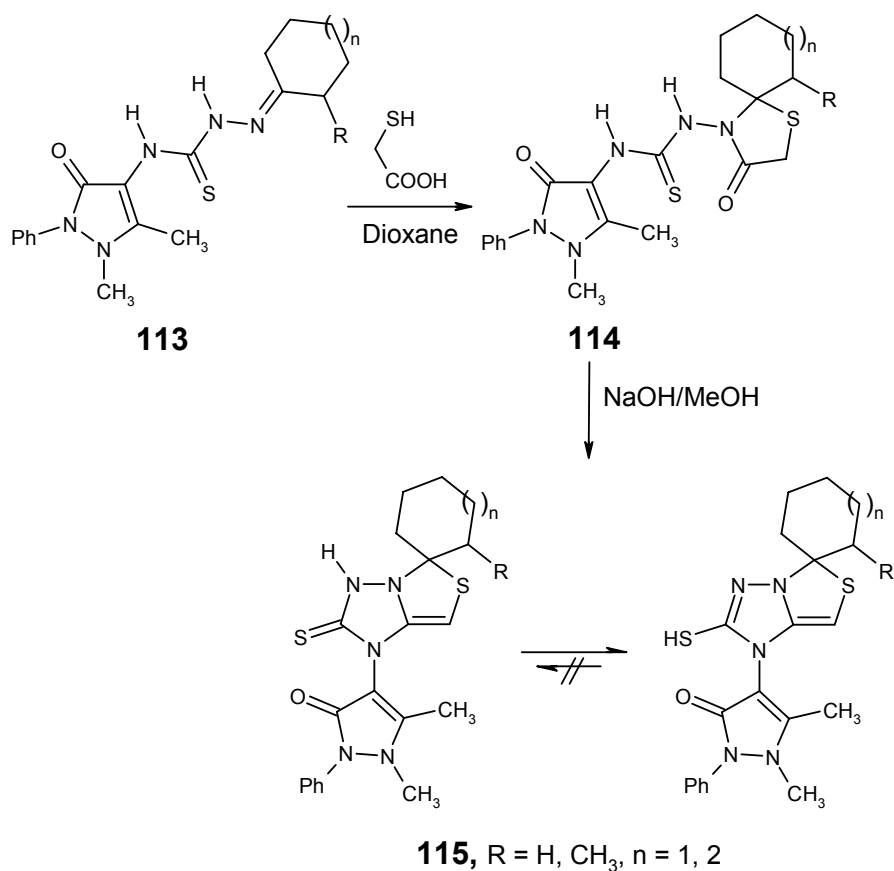
Alkali-catalyzed thermal cyclization of 1-alkyl- and 1,8-dialkyl-2,5-dithiobiureas **110** (R = alkyl, R<sup>1</sup> = H; R, R<sup>1</sup> = alkyl) forms 4-alkyl-1,2,4-triazolidine-3,5-dithiones **108** (R = Me, Et) and 1,3,4-thiadiazoline **112** (R = Pr, Bu). Under the same conditions, 1-alkyl-6-aryl-2,5-dithiobiureas give **112** (R = Ph, substituted Ph) and **111** when the alkyl groups are methyl or ethyl<sup>137</sup> (Scheme 31).



## Scheme 31

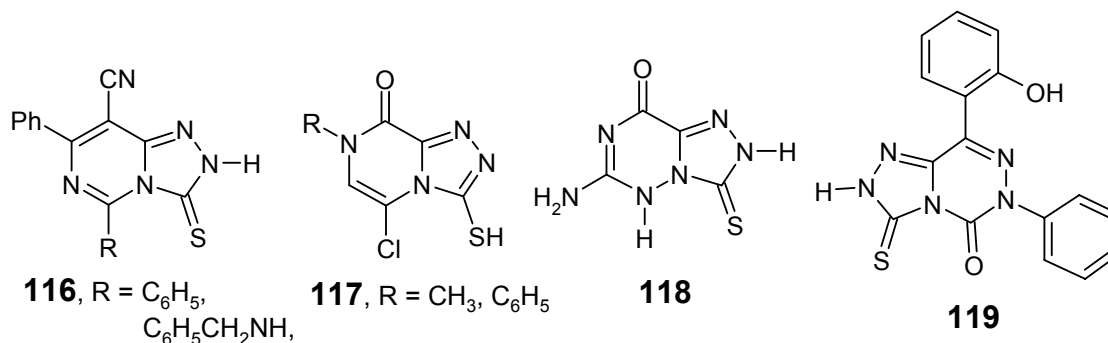
## 2.5. Synthesis of fused mercapto/thione-1,2,4-triazole heterocycles

Shaker<sup>138</sup> reported that the addition-condensation of thiosemicarbazones **113** to mercaptoacetic acid furnished the corresponding cycloalkane spirothiazolidin-4-ones **114**, which on treatment with NaOH underwent cyclization to spiro[1,3]thiazolo[3,4-b]-1,2,4-triazoles **115** (Scheme 32).



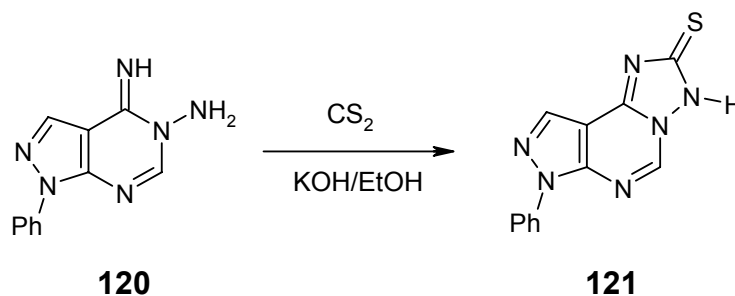
## Scheme 32

The 1,2,4-triazolo[4,3-*c*]pyrimidines **116**<sup>139</sup>, 1,2,4-triazolo[4,5-*b*]pyrazin-2(1*H*)-ones **117**<sup>140</sup> and 1,2,4-triazolo[3,4-*f*][1,2,4]triazinone **118**<sup>141</sup> were synthesized from the reaction of the corresponding hydrazine derivatives with carbon disulfide (Figure 18). Moreover, 1,2,4-triazolo[4,3-*d*][1,2,4]triazine **116** was prepared by nucleophilic cleavage of furan ring of [1]benzofuro[2,3-*e*][1,2,4]triazines<sup>142</sup> (Figure 18).



**Figure 18**

When compound **120** was allowed to react with CS<sub>2</sub>, the pyrazolotriazolo-pyrimidine-2-thione **121** was obtained<sup>143</sup> (Scheme 33).



**Scheme 33**

The triazolophthalazine **122**<sup>144</sup>, thienopyrimidotriazoles **123**<sup>145</sup> and triazolopyrimidopyridazine **124**<sup>146</sup> were prepared from the reaction of CS<sub>2</sub> with the corresponding hydrazine derivatives (Figure 19).

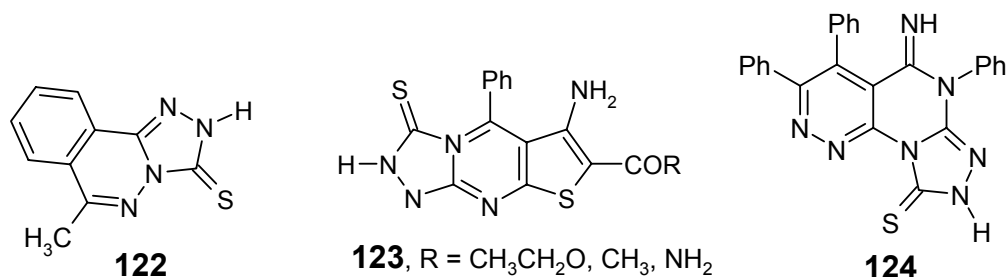


Figure 19

The tricyclic 3(2H)-thioxo-1,2,4-triazolo[4,3-b]pyridazine-6(5H)-ones **125** were synthesized from the reaction of phenyl isothiocyanate with the corresponding hydrazine derivatives<sup>147</sup> (Figure 20).

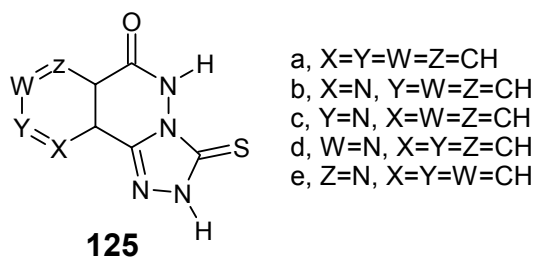
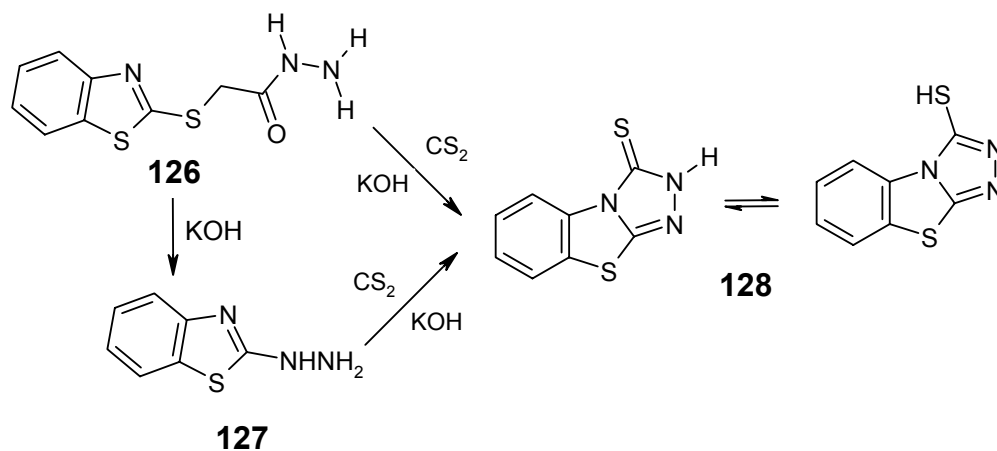


Figure 20

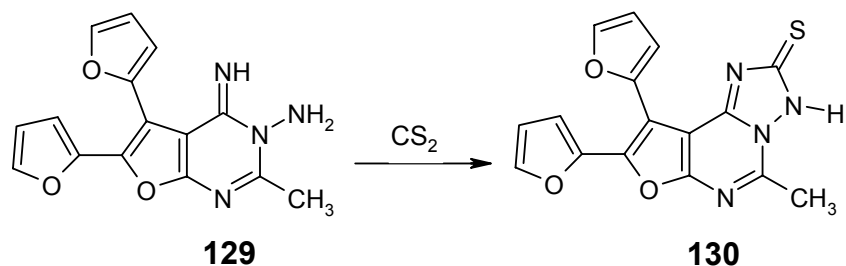
A rearrangement reaction about 2-benzothiazolylthioacetyl hydrazide (**126**) to produce s-triazolo[3,4-b]benzothiazol-3-thiol (**128**) in the presence of  $\text{KOH}$  and  $\text{CS}_2$  was described. Other way to synthesis **128** from 2-benzothiazolylhydrazine (**127**) under the same conditions<sup>148,149</sup> (Scheme 34).



Scheme 34

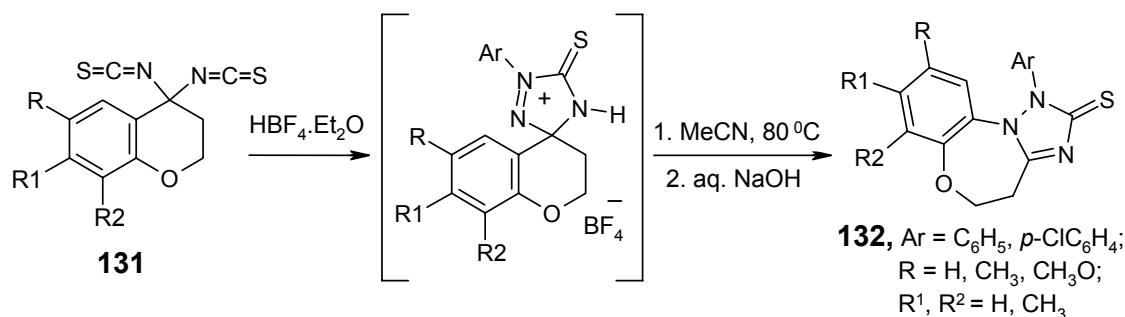


8,9-Di(2-furyl)-2,3-dihydro-5-methylfuro[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine-2-thione (**130**) was prepared from the reaction of compound **129** reacted with carbon disulfide<sup>150</sup> (Scheme 35).



### Scheme 35

A series of 1,2,4-triazolo[2,3-d][1,5]benzoxazepin-2-thiones **132** were achieved via acid-induced ring closure of the geminal arylazo-isothiocyanate compounds **131**<sup>151</sup> (Scheme 36).



### Scheme 36

The cyclization of the 4-amino-3-thioxotriazolylindazole **133** gave the 3-thioxo-triazole **134**<sup>98</sup>, while the triazole **135** was synthesized from pyrrolo[1,2-*a*]thieno[2,3-*e*]pyrazin-5-one<sup>152</sup> (Figure 21).

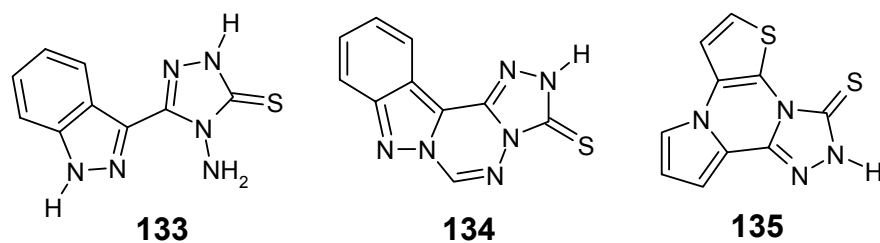
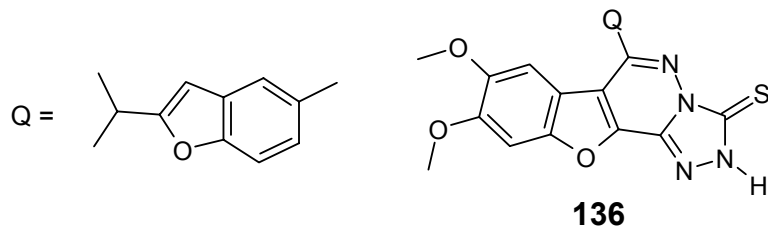


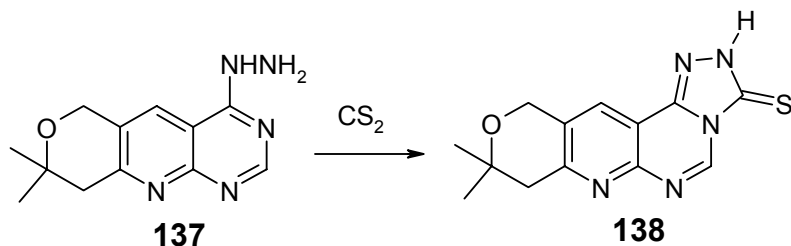
Figure 21

The benzofuro[2,3-*d*]pyridazine fused with 1,2,4-triazole **136** was prepared by the ring closure of 4-hydrazino[1]benzofuro[2,3-*d*]pyridazine, derived from naturally occurring rotenone<sup>153</sup> (Figure 22).



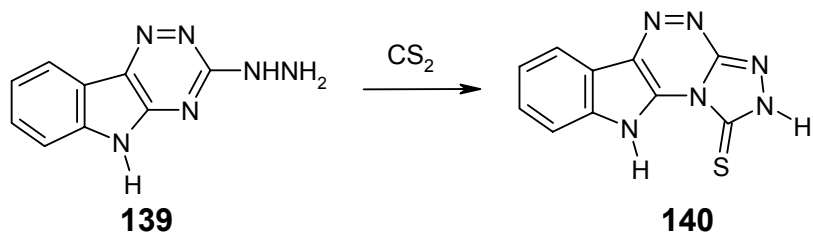
**Figure 22**

The treatment of 4-hydrazino-pyrano[3',4':5,6]pyrido[2,3-*d*]pyrimidine **137** with carbon disulfide led to the formation of pyrano[5',4':5,6]pyrido[3,2-*e*]triazolo[4,3-*c*]-pyrimidine **138**<sup>154</sup> (Scheme 37).



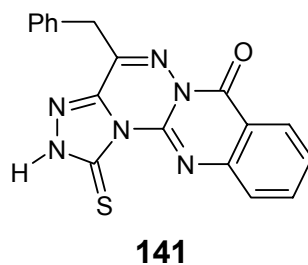
**Scheme 37**

Refluxing 3-hydrazino[1,2,4]triazino[5,6-*b*]indole **139** with carbon disulfide produced 1,2-dihydro-10H-[1,2,4]triazolo[3',4':3,4][1,2,4]triazino[5,6-*b*]indole-1-thione **140**<sup>155</sup> (Scheme 38).

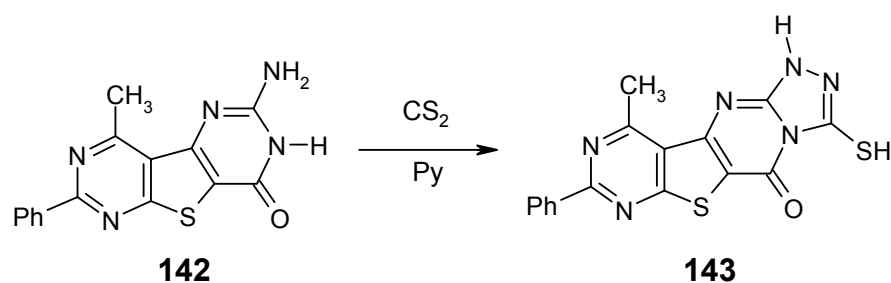


**Scheme 38**

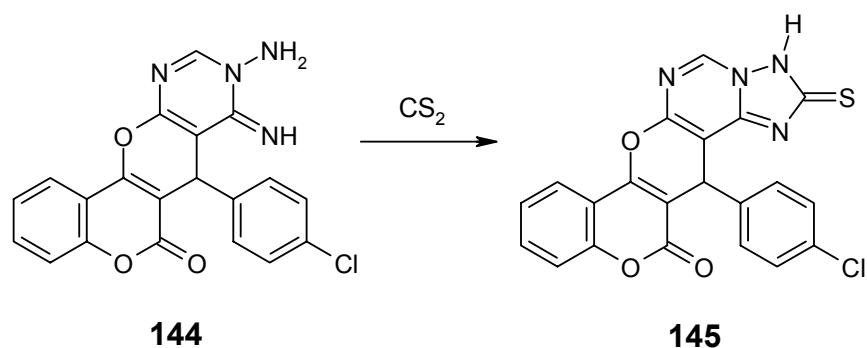
Similarly, 1,2,4-triazolo[4',3':4,5][1,2,4]triazino[3,2-*b*]quinazolin-7-one **141** was prepared from the corresponding hydrazine<sup>156</sup> (Figure 23).

**Figure 23**

When the compound **142** was allowed to react with carbon disulfide, the 3-mercapto-10-methyl-8-phenyl-1(1H)-triazolo[3'',4'':2,3]pyrimido[5',6':4,5]thieno[2,3-d]pyrimidin-5-one (**143**) was obtained<sup>157</sup> (Scheme 39).

**Scheme 39**

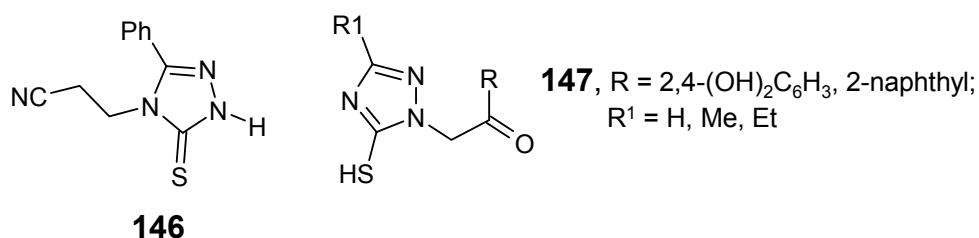
Also, the treatment of **144** with carbon disulfide in alcoholic potassium hydroxide solution gave benzopyrano[3',4':5,6]pyrano[3,2-e][1,2,4]triazolo[1,5-c]pyrimidine-2-thione **145**<sup>158</sup> (Scheme 40).

**Scheme 40**

### 3. Chemical reactivity

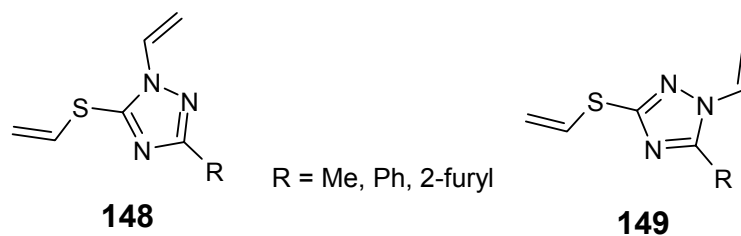
#### 3.1. Alkylation and arylation

The reaction of 1,2,4-triazoline-5-thione **6** with acrylonitrile afforded the *N*-substituted adduct **146**<sup>159</sup>. Triazoles **147** were prepared as potential fungicides by treating **3** with  $\text{RCOCH}_2\text{R}^2$  ( $\text{R}^2 = \text{Cl}, \text{Br}$ )<sup>160</sup> (Figure 24).



**Figure 24**

Catalytic vinylation of triazolethione **6** by acetylene over  $\text{Cd}(\text{OAc})_2$  or  $\text{CuCl}$  at 15 atm. gave mixtures containing triazoles **148** and **149**<sup>161</sup> (Figure 25).



**Figure 25**

The triazole **150** was prepared in 55-88.2% yield by treatment of **3** with  $\text{R}^1\text{C.tplbond.CCOPh}$ . The same reaction in the presence of 2%  $\text{NaOH}$  gave a mixture of **151** and **152**<sup>162</sup>. Also, reaction of **3** with  $\text{PhC.tplbond.CCN}$  in a molar ratio (1:2) gave **153**<sup>163</sup> (Figure 26).

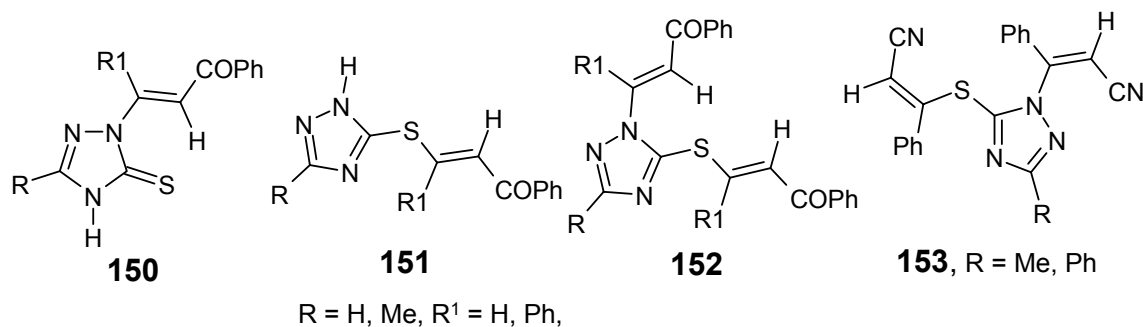


Figure 26

The alkylation of **3** with alkyl halide in refluxing ethanol gave 32-99% yields of 5-alkylthio-1,2,4-triazoles **154**<sup>164,165</sup> which had moderate bacteriostatic activity and diuretic activity that increased with the size of R (Figure 27).

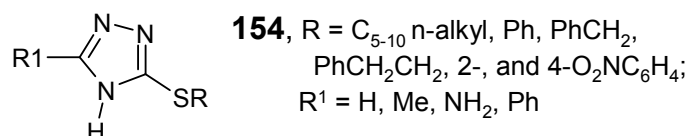


Figure 27

The *S*-alkylated derivatives **155** were prepared by the alkylation of the corresponding triazolethiones<sup>23,64,166</sup> (Figure 28).

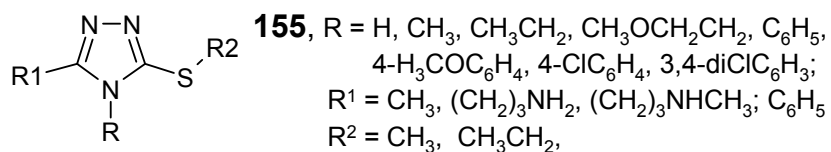


Figure 28

3-Vinylthio-1,2,4-triazoles **156** were prepared in 35-80% yields by addition of HC.tplbond.CH to the corresponding triazolethione in the presence of KOH in an autoclave 2h at 14 atm. and 160 °C.<sup>167</sup> The reaction of triazole **3** with ethyl bromoacetate or propynyl bromide leads to the ethyl-(3-substituted-1,2,4-triazol-5-yl-thio)acetate **157**<sup>168</sup> and prop-3-ynylthio-*s*-triazoles **158**<sup>169,170</sup> (Figure 29).

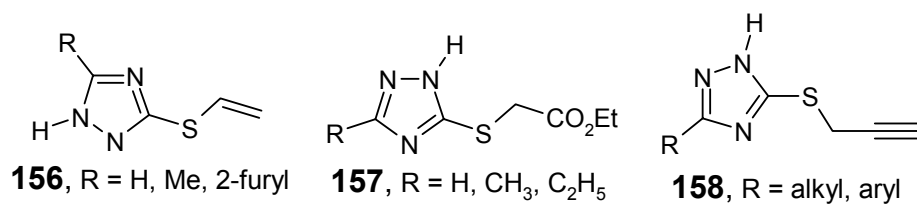


Figure 29

Addition reaction of epichlorohydrin with the corresponding triazolethiones gave *S*-alkylated product **159**<sup>171,172</sup> (Figure 30).

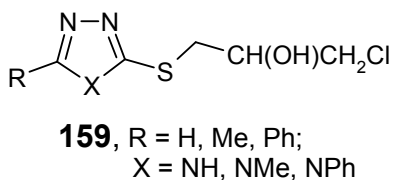
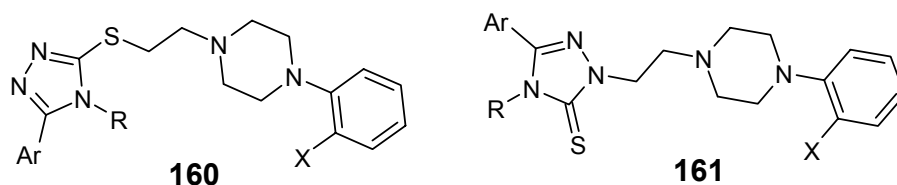


Figure 30

When 1-(2-chloroethyl)-4-(2-methoxyphenyl)piperazine reacted with triazoles **6** in alkaline medium gave both the *S*-alkylated **160** and the *N*-alkylated isomers **161** were obtained<sup>69,173</sup> (Figure 31).



R = H, NH<sub>2</sub>; Ar = C<sub>6</sub>H<sub>5</sub>, 2-, and 4-ClC<sub>6</sub>H<sub>4</sub>, 4-H<sub>3</sub>CC<sub>6</sub>H<sub>4</sub>, H<sub>7</sub>C<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>SC<sub>6</sub>H<sub>4</sub>; X = OCH<sub>3</sub>, NO<sub>2</sub>

Figure 31

The reaction of 1-iodobutane or 2-bromo-1-(2,3-dihydro-1,4-benzodioxin-6-yl)-1-ethanone with triazoles **3** or **34** gave the corresponding alkyl sulfanyl derivatives **162** and **163**, respectively<sup>37</sup> (Figure 32).

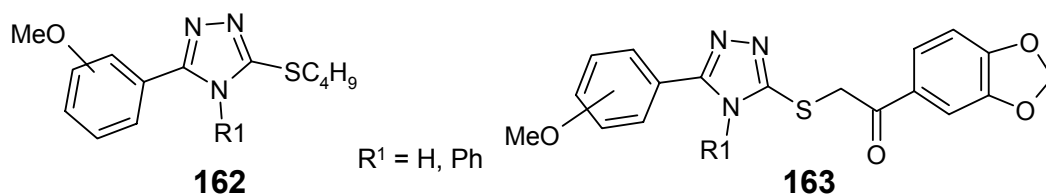
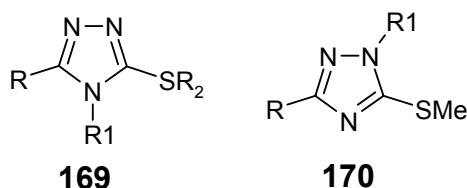


Figure 32

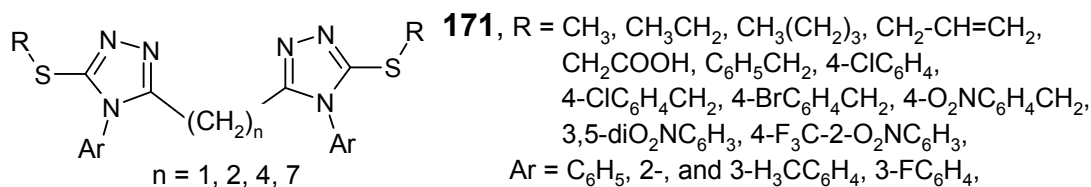


Glycosidation of 1,2,4-triazoline-5-thiones ( $R = H, Me, R^1 = H; R = Ph, 4\text{-pyridyl}, R^1 = Ph$ ) with  $R^2Br$  ( $R^2 = \text{tetra-}o\text{-acetyl-D-glucopyranosyl, -galactopyranosyl, tri-}o\text{-acetyl-D-xylopyranosyl}$  and  $L\text{-arabinopyranosyl}$ ) in aq. acetone containing KOH gave 14-88% yields of glycosides **169** which showed significant anti-inflammatory, analgesic, neurotropic, and antihypoxic activity. Deprotection of **169** ( $R = Me, R^1 = H, R^2 = \text{tri-}o\text{-acetyl-}\beta\text{-D-xylopyranosyl}$ ) with NaOMe in absolute methanol gave 68% **169** (same  $R, R^1; R^2 = -\beta\text{-D-xylopyranosyl}$ )<sup>179</sup>. Also, 3,5-disubstituted-1,2,4-triazole **170** ( $R = H, Me, \text{or Et}, R^1 = H$ ) derivatives and their  $N$ -glycosides ( $R^1 = \text{tetraacetylglucos-amine}$  or  $N\text{-acetylglucosamine}$ ) were prepared and tested for antiviral action against RNA-3 poliomyelitis in tissue culture<sup>180</sup> (Figure 36).



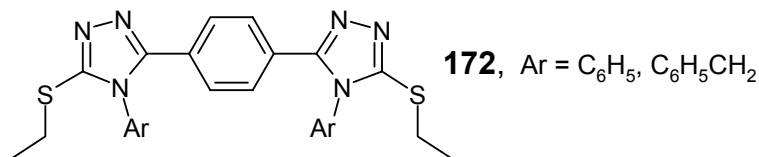
**Figure 36**

The bis[4-aryl-3-alkylthio-1,2,4-triazol-5-yl]alkanes **171** were prepared by the action of alkyl halides on bis[4-aryl-1,2,4-triazoline-5-thione-5-yl]alkanes **71** in aqueous sodium hydroxide (5%)<sup>11,73,181</sup> (Figure 37).



**Figure 37**

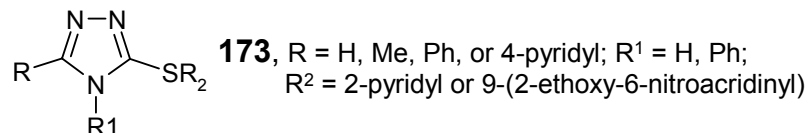
The reaction of **73** with ethyl iodide in DMF at room temperature and in the presence of anhydrous potassium carbonate gave 5,5'-(1,4-phenylene)bis(3-ethylthio-4-phenyl-/benzyl-1,2,4-triazole) **172**<sup>104</sup> (Figure 38).



**Figure 38**

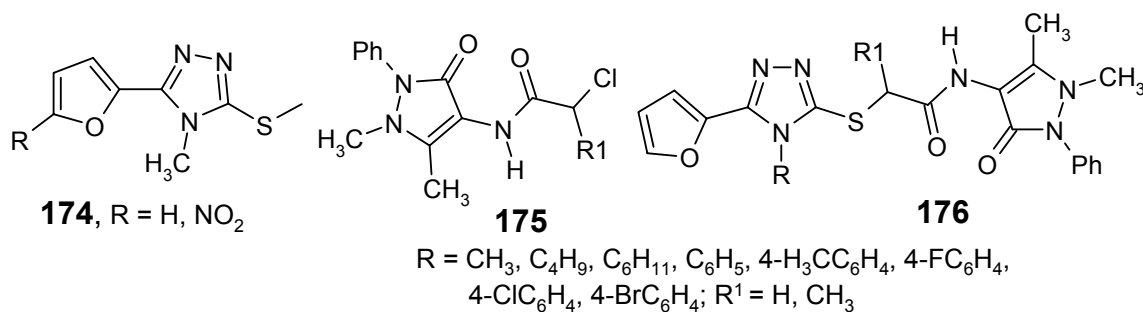


5-Heteroarylthio-1,2,4-triazoles **173** were prepared by reaction of 1,2,4-triazole-5-thiones **3** or **26** with 2-bromopyridine or 2-ethoxy-6-nitro-9-chloroacridine. Compound **173** exhibited anti-inflammatory, analgesic, neurotropic, and antihypoxic activity in rats and mice<sup>182,183</sup> (figure 39).



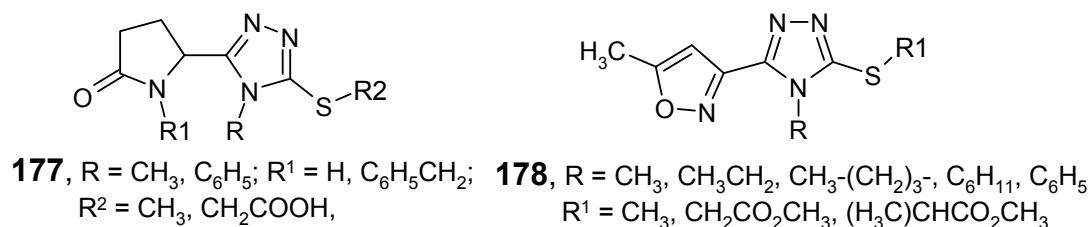
**Figure 39**

The alkylation of **75** with methyl iodide or 4-(chloroacetyl/ $\alpha$ -chloropropionyl)-2,3-dihydropyrazoles **175** in alkaline medium resulted in the production of the *S*-alkylated derivatives **174**<sup>105</sup> and **176**<sup>184</sup> (Figure 40). Compound **176** were evaluated for in vitro antibacterial and antifungal activity<sup>184</sup>.



**Figure 40**

The alkylation of **12** or **76** with alkyl halide produced the *S*-allylated products **177**<sup>44</sup> and **178**<sup>54,106</sup>, respectively (Figure 41).



**Figure 41**

Compounds **80** when treated with chloroacetic acid and benzyl chloride, yielded carboxymethylthio- **179** and benzylthio-5-(isomeric pyridyl)-1,2,4-triazoles **180**<sup>112,113,185</sup> (Figure 42).

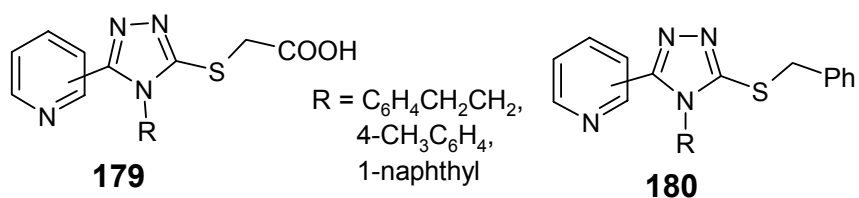


Figure 42

The methylation of compounds **82** or **84** with methyl iodide gave the corresponding **181**<sup>114</sup> and **182**<sup>116</sup> (Figure 43).

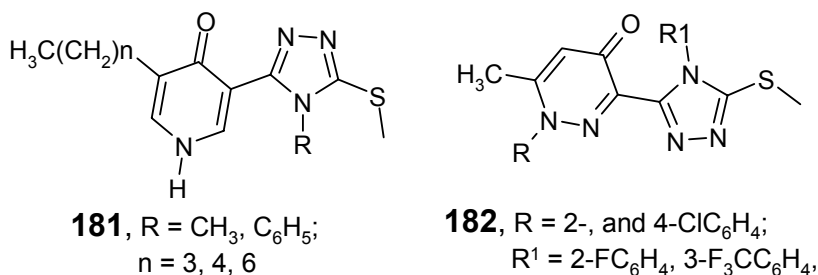


Figure 43

Compound **86** was treated with diethylaminoethyl chloride hydrochloride and with 4-(2-chloro-ethyl)morpholine hydrochloride in refluxing ethanol in the presence of anhydrous sodium acetate to give the corresponding *S*-alkylated products **183** and **184**, respectively<sup>119</sup> (Figure 44).

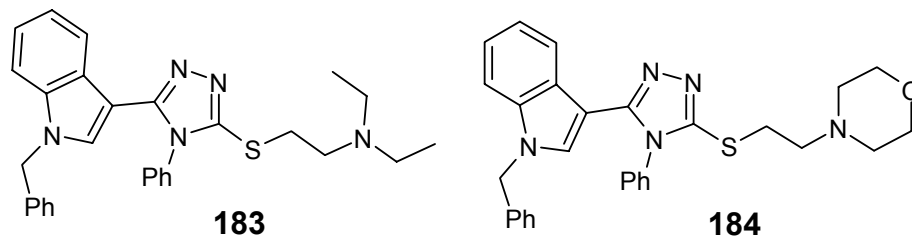


Figure 44

The alkylation of **69** or **87** with ethyl iodide<sup>100</sup> or methyl iodide<sup>53</sup> or the hydrochlorides of *N,N*-disubstituted- $\beta$ -chloroethylamines<sup>186</sup> in an alkaline medium resulted in the production of **185** or **186** or **187** respectively (Figure 45).

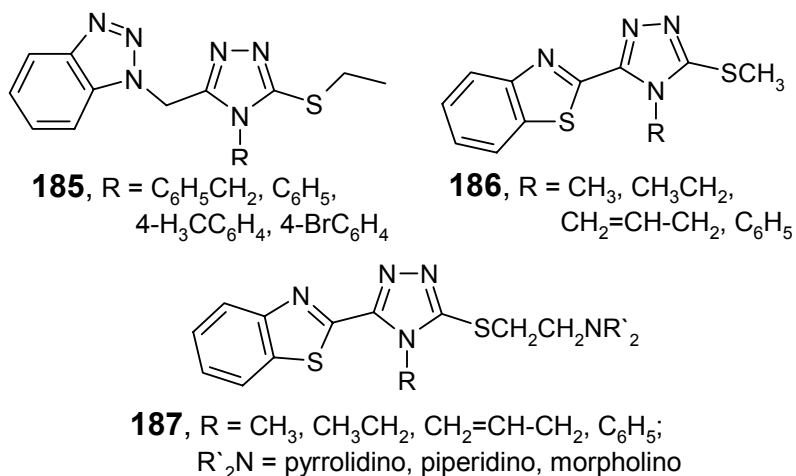


Figure 45

The *S*-alkylated derivatives **188**<sup>145</sup> or **189**<sup>158</sup> were synthesized from the reaction of the triazolothione **123** or **141** with  $\alpha$ -halo compounds, respectively (Figure 46).

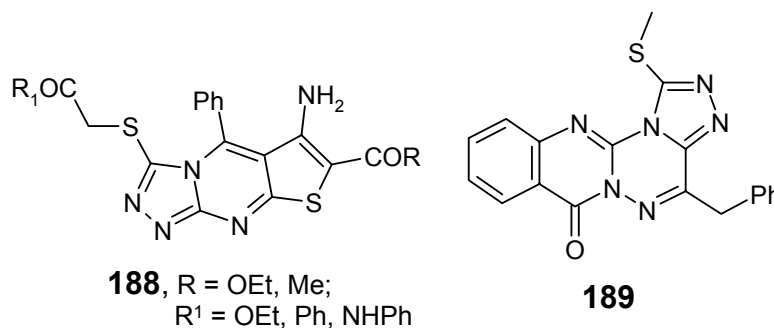


Figure 46

### 3.2. Synthesis of monosulfides and disulfides

When 3-methyl-1,2,4-triazole-5-thione (**6**), was allowed to react with diethyl azodicarboxylate, disulfide **190** was obtained<sup>187</sup>. Similarly, the disulfides **191** were prepared from **117**<sup>140</sup> (Figure 47).

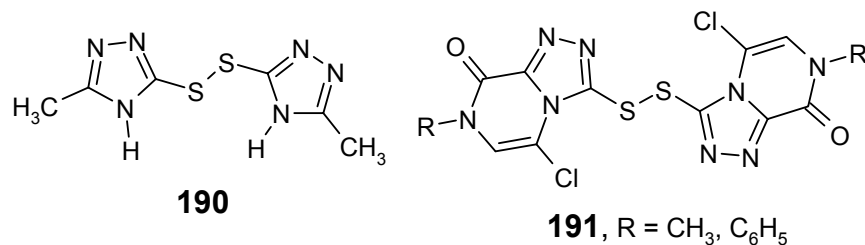


Figure 47

### 3.3. Synthesis of mannich base derivatives

It has been found that the Mannich and double Mannich reaction starting from *s*-triazolo[3,4-*b*]benzothiazol-3-thiol **128** to prepare some biologically active Mannich bases **192-194**<sup>149</sup> (Figure 48).

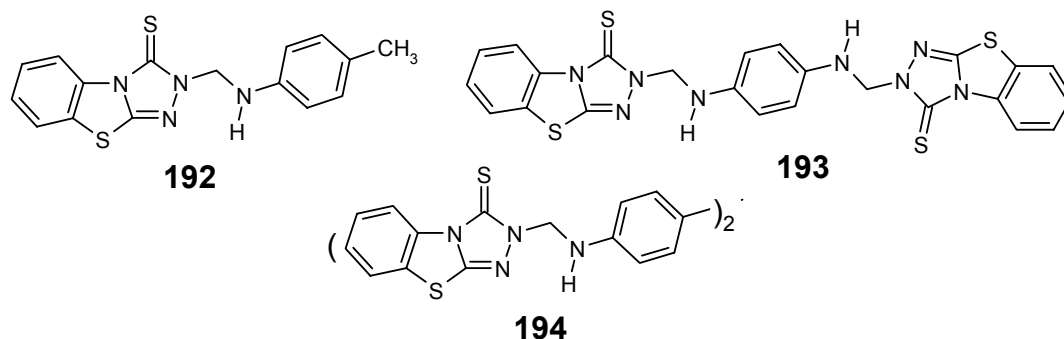


Figure 48

### 3.4. Synthesis of thiazolotriazoles

The reaction of 1,2,4-1*H*-triazole **8** with  $\alpha$ -haloketones and with 1,2-dibromoethane leading to the formation of thiazolotriazole **195**.<sup>188</sup> 1,2,4-Triazolone-3-thiones **104** upon treatment with sulfuric acid or bromine cyclize to derivatives of thiazolo[2,3-*c*][1,2,4]-triazole **196** and **197** respectively<sup>189</sup> (Figure 49).

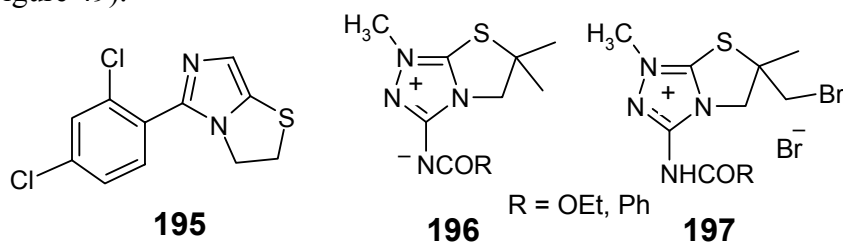
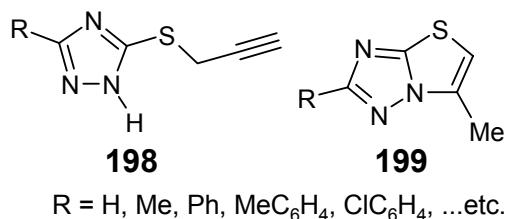
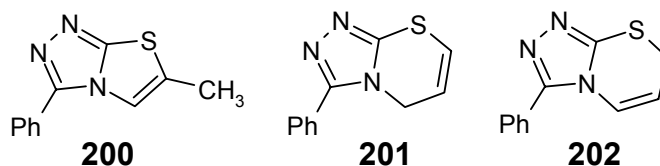


Figure 49

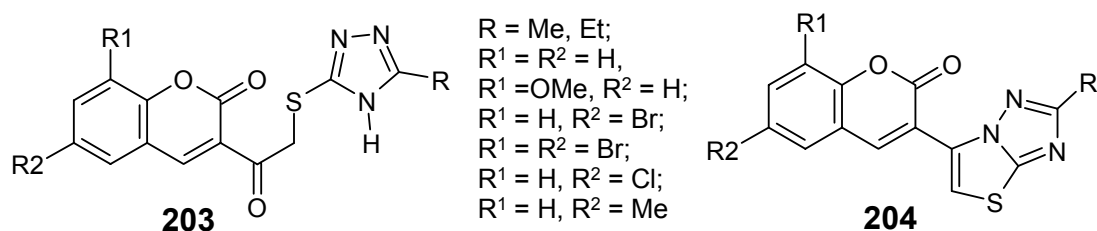
The facile and regioselective synthesis of 2-substituted-5-methylthiazolo[3,2-*b*]-1,2,4-triazoles **199** proceeded via  $\text{H}_2\text{SO}_4$  catalyzed cyclization of the corresponding (propynylthio)triazoles **198**<sup>190-194</sup> (Figure 50).

**Figure 50**

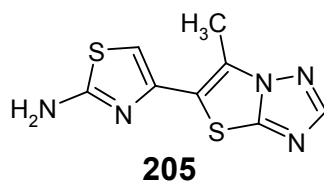
The interaction of 4-allyl-1,2,4-triazole-3-thione **37** with iodine proceeds with the formation of a mixture of the iodo derivatives of thiazolotriazole and triazolothiazine which on elimination of HI gave the corresponding thiazolo[2,3-c]-1,2,4-triazole **200** and a mixture of 1,2,4-triazolo[3,4-b][1,3]thiazines **201** and **202** respectively<sup>195</sup> (Figure 51).

**Figure 51**

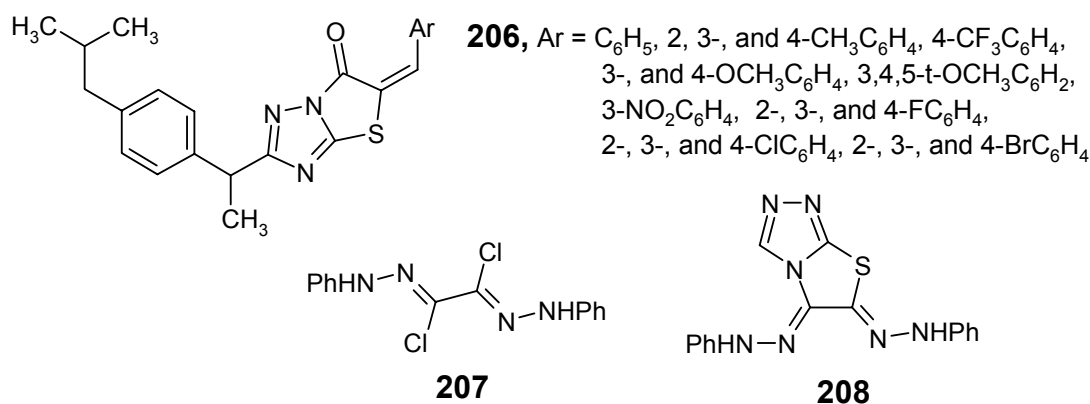
The triazoles **7** were condensed with either 3-(2-bromoacetyl)coumarins or with 3-acetylcoumarins using bromine in the presence of trichloro-(*N,N*-ethylene-bis-aminobenzamide)lanthanum or samarium as a catalyst, followed by cyclization of the intermediate 3-alkyl-5-coumarinacyl-thio-*s*-triazoles **203** using PPA resulting in the formation of 3-alkyl-5-coumarinylthiazolo[3,2-*b*]triazoles **204**<sup>196</sup> (Figure 52).

**Figure 52**

Cyclization of 1H-1,2,4-triazole-3-thiol **3** (R = H) with 3-chloro-2,4-pentadione in ethanol followed by bromination of the resulting 2-acetyl-3-methyl-1,2,4-triazolo[3,2-*b*]thiazole with Br<sub>2</sub> in 47% aq. HBr, and refluxing 2-bromoacetyl-3-methyl-1,2,4-triazolo[3,2-*b*]thiazole with thiourea in ethanol afforded **205**<sup>197</sup> (Figure 53).

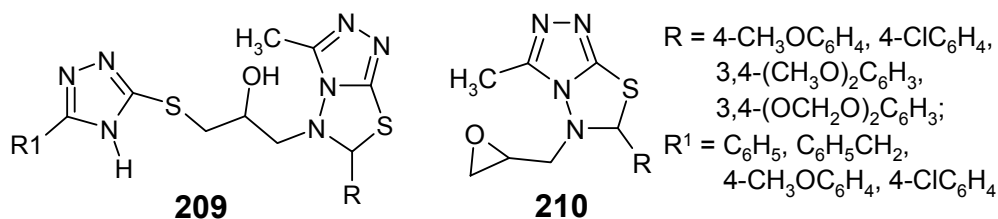
**Figure 53**

The 6-benzylideneethiazolo[3,2-b][1,2,4]triazole-5(6H)-ones **206** were synthesized by treatment of **9** with chloroacetic acid and substituted or non-substituted benzaldehydes in the presence of sodium acetate, acetic acid and acetic anhydride<sup>41,198,199</sup> (Figure 54). Also, triazolothiazoles **208** was synthesized via cycloaddition of bis-hydrazonoyl chloride **207** with **3**<sup>200</sup> (Figure 54).

**Figure 54**

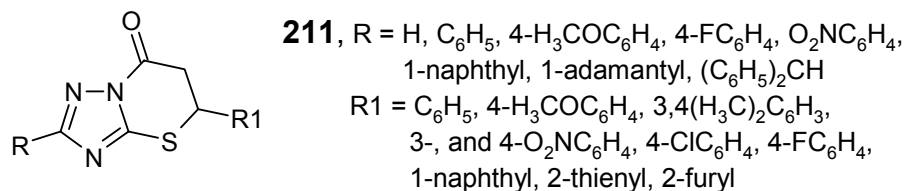
### 3.5. Synthesis of triazolothiadiazoles

The triazolothiadiazoles **209** have been synthesized by ring opening of various triazolo[3,4-b][1,3,4]thiadiazoles **210**<sup>201</sup> with **6** (Figure 55).

**Figure 55**

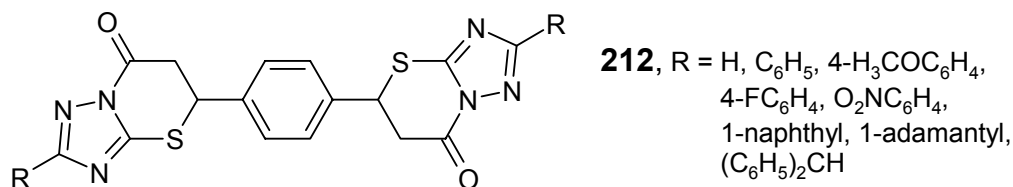
### 3.6. Synthesis of triazolothiazines

The condensation of triazolinethiones **3** or **7** with 3-aryl-2-propenoyl chlorides or 3-aryl-acryloyl chloride gave 5-aryl-5,6-dihydro-7H-[1,2,4]triazolo[5,1-b][1,3]thiazin-7-ones **211**<sup>202,203</sup> (Figure 56).



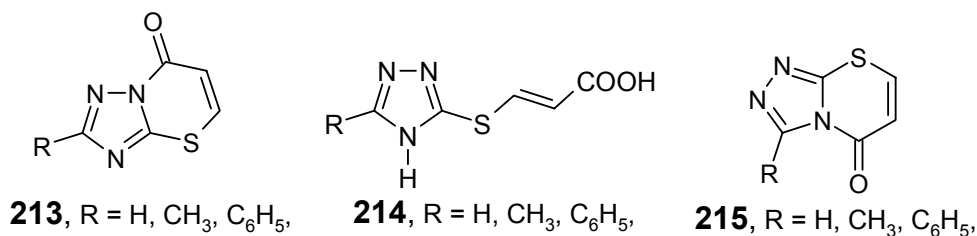
**Figure 56**

The condensation of **3** with 3-(4-[2-(chlorocarbonyl)ethenyl]phenyl)-acryloyl chloride in pyridine gave benzene-1,4-diaryl-bis-2-R-5-aryl-[1,2,4]triazolo[5,1-b]-[1,3]thiazin-7-ones **212**<sup>202</sup> (Figure 57).



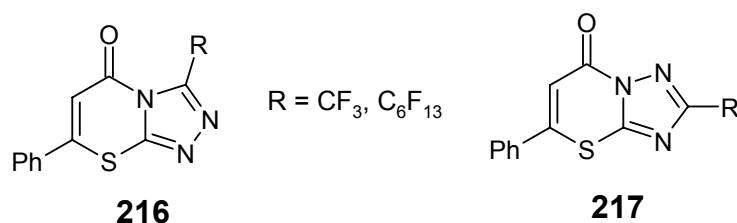
**Figure 57**

The 1,2,4-triazolo[5,1-b][1,3]thiazin-7-ones **213** have been first prepared by Peter *et al.*<sup>204</sup> by cyclization of **3** with diethyl ethoxymethylenemalonate in fair to good yields. Also, Heindel *et al.*<sup>205</sup> have synthesized this heterocyclic system by condensation of **3** with methyl propionate, hydrolysis of the resulting *S*-acrylic esters to the corresponding *S*-acrylic acids **214**, and subsequent cyclization to **213** or **215**. The cyclization of **214** to **213** or **215** using thionyl chloride has also been reported as an independent synthesis (Figure 58).



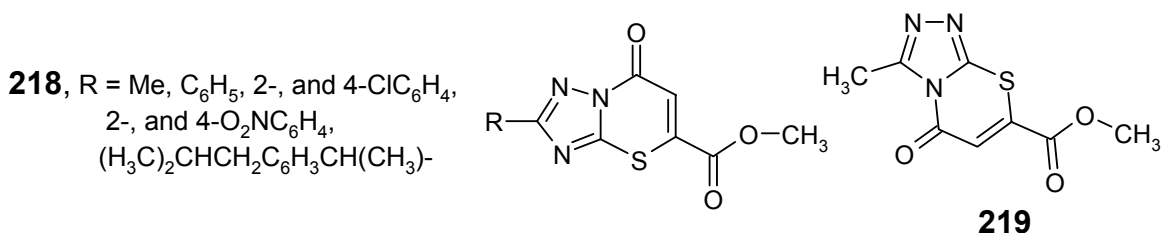
**Figure 58**

The 5-(perfluoroalkyl)triazole-3-thiols **3** reacts with methyl phenylpropynoate in boiling acetic acid or in boiling ethanol to form a mixture of the isomers 5H-1,2,4-triazolo[3,4-b][1,3]thiazin-5-one **216** and 7H-1,2,4-triazolo[5,1-b][1,3]thiazin-7-one **217** in a total yield of 70-80% and a 10:1 ratio<sup>206</sup> (Figure 59).



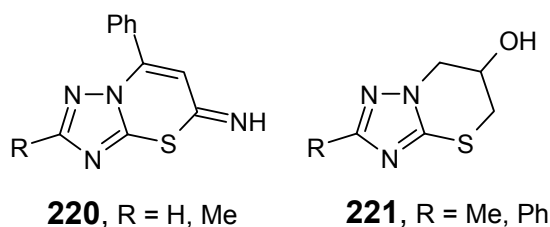
**Figure 59**

The addition of dimethylacetylene dicarboxylate or diethyl azodicarboxylate was obtained to **3** afforded in cycloadducts, which were identified as **218**<sup>187,207,208</sup> or **219**<sup>187</sup> (Figure 60). Compound **218** showed most remarkable anti-inflammatory activity in the carrageenan and serotonin induced diarrhea test<sup>208</sup>.



**Figure 60**

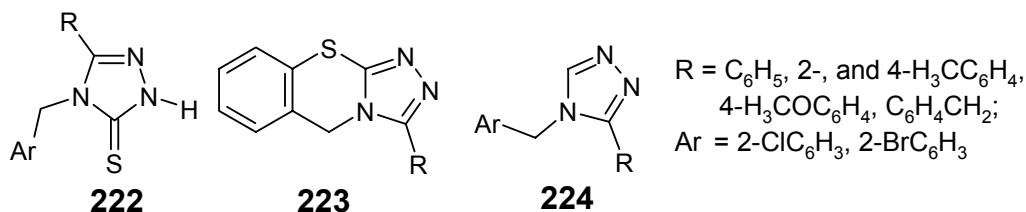
Reaction of triazolethione **3** with 1 mol PhC.tplbond.CCN or epibromohydrin gave **220**<sup>163</sup> or 3-hydroxy-1,2,4-triazolo[5,1-b]-1,3-thiazines **221**<sup>171,209,210</sup> (Figure 61).



**Figure 61**

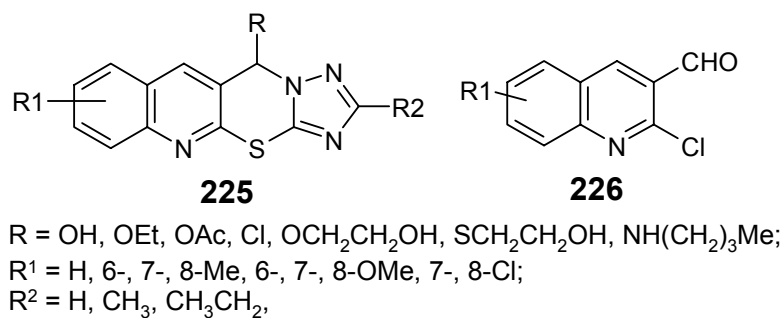


The photo cyclization of substituted 1,2,4-triazole-3-thiones **222**, under base-mediated conditions, afforded 1,2,4-triazolo[3,4-b]-1,3-(4H)-benzothiazines **223** with the desulfurization product **224**<sup>211,212</sup> (Figure 62).



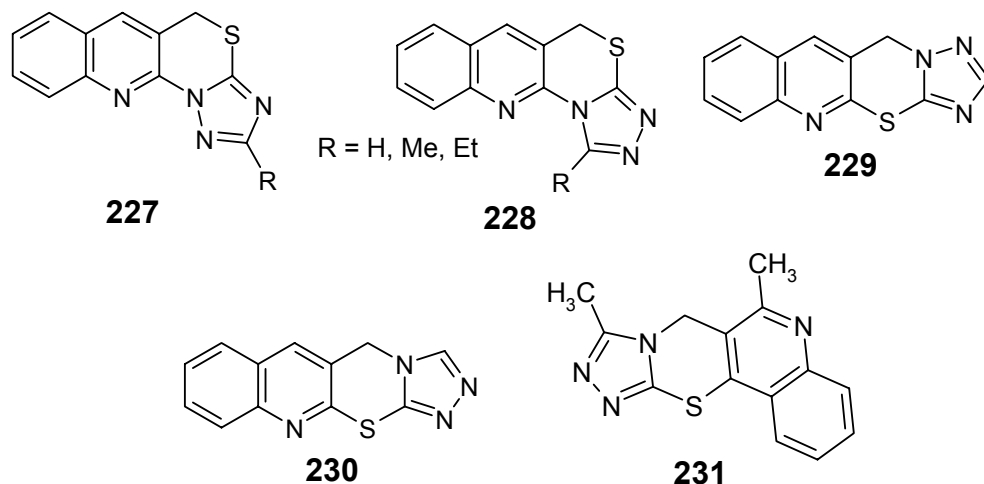
**Figure 62**

1,2,4-Triazolo[5',1':2,3][1,3]thiazino[6,5-b]quinolines **225** have been synthesized by the reaction of 2-chloroquinoline-3-carboxaldehydes **226** with **3** and subsequent transformations of the hydroxyl group of **225** ( $R = \text{OH}, R^1 = R^2 = \text{H}$ )<sup>213</sup> (Figure 63).

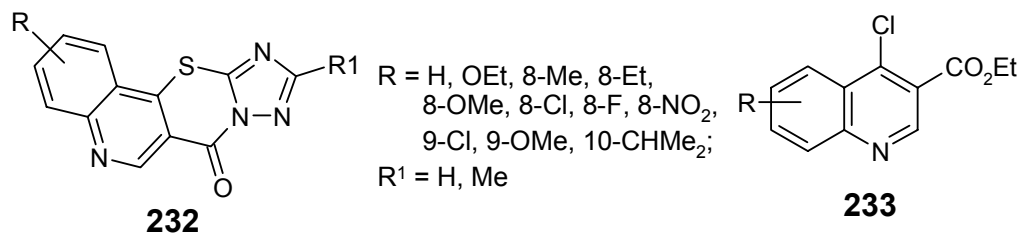


**Figure 63**

Similarly, synthesis of 1,2,4-triazolothiazinoquinoline **227-231**<sup>214-216</sup> was described starting from 2-chloro-, or 4-chloro-3-(chloromethyl)quinoline and **3** (Figure 64).

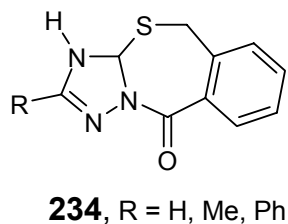
**Figure 64**

5H-1,2,4-Triazolo[5,1:2,3][1,3]thiazino[5,6-c]quinolin-5-ones **232**<sup>217</sup> were prepared in 42-89% yield by the cyclocondensation of chloroquinoline carboxylates **233** with **3** in presence of  $K_2CO_3$  in DMF (Figure 65).

**Figure 65**

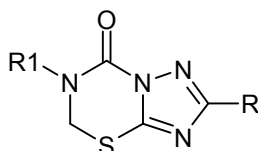
### 3.7. Synthesis of triazolothiazepines

Triazolobenzothiazepinones **234**<sup>218</sup> were synthesized in a regioselective manner via reaction of **3** with 2-chloromethyl-benzoyl chloride in good yields (Figure 66).

**Figure 66**

### 3.8. Synthesis of triazolothiadiazines

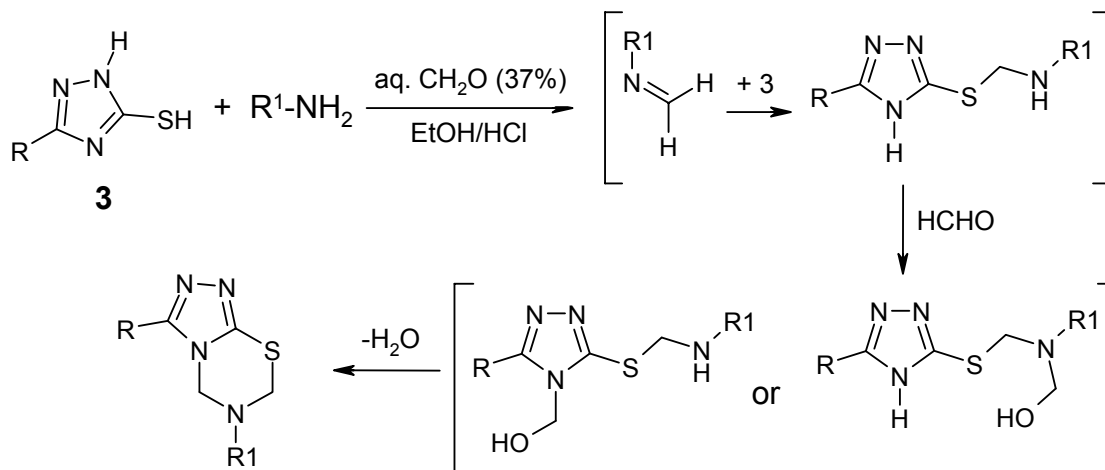
1,2,4-Triazolo[5,1-b][1,3,5]thiadiazin-7-ones **235**<sup>35</sup> were obtained in good yield by the reactions of **3** with *N*-substituted-*N*-chloromethylcarbonyl chloride in the presence of potassium carbonate in DMF at room temperature (Figure 67).



**235**, R = 2-, 3-, and 4-FC<sub>6</sub>H<sub>4</sub>, 2,4-diCl-5FC<sub>6</sub>H<sub>2</sub>;  
R<sup>1</sup> = C<sub>2</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>5</sub>

**Figure 67**

The di-Mannich reaction of **3** with aromatic amines and a formaldehyde solution in the presence of ethanol-HCl solution was used to produce the Mannich base namely 3,6-disubstituted-1,2,4-triazolo[3,4-b][1,3,5]thiadiazines **236**<sup>219</sup> (Scheme 41). The resulting compounds **236** showed antibacterial activity against *B. bob*; *S. aureus* and *E. coli* at 800, 100 and 50 ppm concentrations<sup>219</sup>.

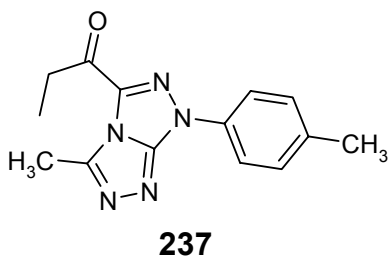


**236**, R = C<sub>6</sub>H<sub>5</sub>, 2-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>,  
R<sup>1</sup> = C<sub>6</sub>H<sub>5</sub>, 4-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>, 2-, and 3-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>

**Scheme 41**

### 3.9. Miscellaneous reactions

The 1,2,4-triazolo[3,4-c][1,2,4]triazole **237**<sup>220</sup> were prepared by reaction of 5-allylmercapto-3-methyl-1,2,4-triazole with ethyl chloroglyoxalate p-tolylhydrazone was described (Figure 68).



**Figure 68**

It has been found that two regioselective synthetic approaches for the 1H-[1,2,4]-triazolo[3,4-c][1,2,4]triazoles **243** via reaction of hydrazonoyl halide **238** with 3-methylthio-5-phenyl-1,2,4-triazole (**155**) and base catalyzed cyclization of *N*-phenyl-*N*-(5-phenyl-*s*-triazol-3-yl)thiohydrazides **239** were reported<sup>221</sup>. The structure of **243** was rationalized in terms of the initial formation of the amidrazones **240** as intermediates rather than **241** which cyclize in situ through elimination of methanethiol as soon as they are formed to give **243** as end products. Compound **243** exhibited antimicrobial activity against *Escherichia coli*, *Bacillus subtilis* and *Pseudomonas aeruginosa* (Figure 69).

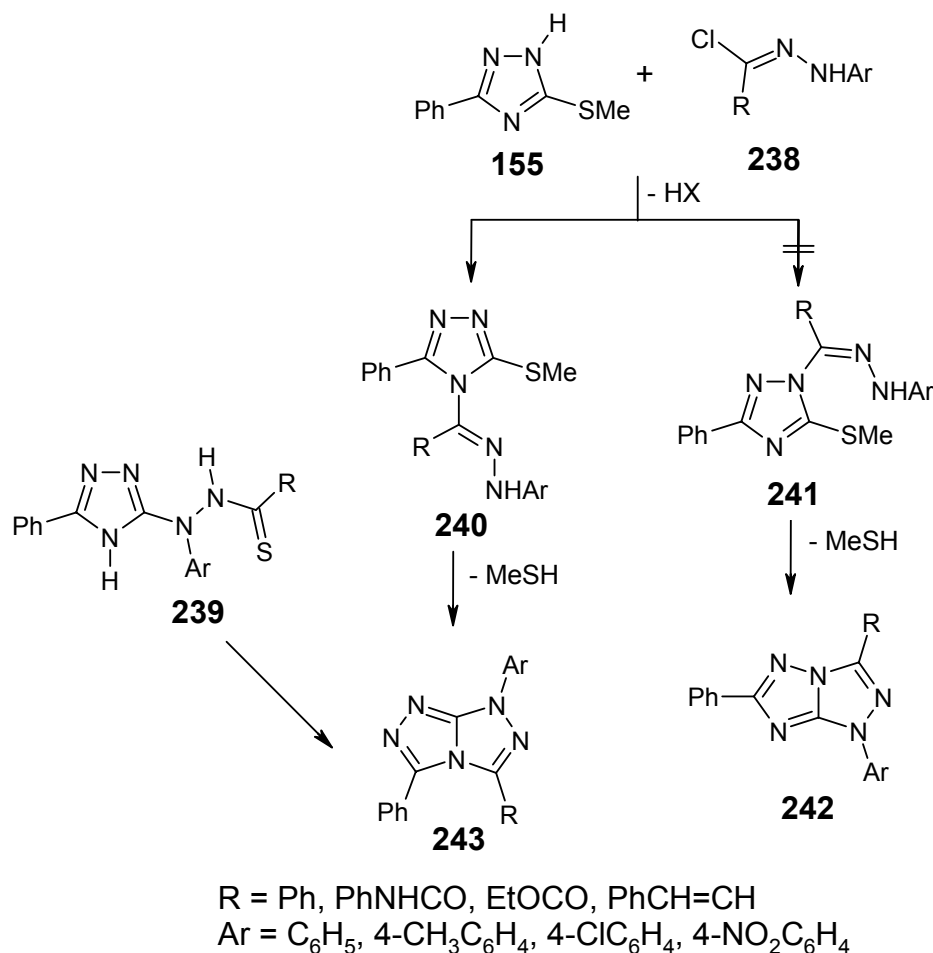


Figure 69

## 4. Conclusions

In this review the most important procedures used for the synthesis of mercapto-1,2,4-triazoles have been compiled and discussed. The mercapto/thioxo-1,2,4-triazole has proved to be a rich source of various heterocyclic compounds. Literature data published in the last 50 years have been included to help the reader to find information appropriate for the the chemistry of mercapto/thioxo-1,2,4-triazoles and their utility in heterocyclic synthesis.

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## Biographical Sketch



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