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Recent trends in the chemistry of 2-aminobenzothiazoles

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Recent trends in the chemistry of 2-aminobenzothiazoles

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The chemistry of 2-aminobenzothiazoles has gained increased interest in both synthetic organic chemistry and biological fields, since a large number of developments in the use of such compounds, covering the literature up to 2007, seem to be of considerable value. The present review presents their synthetic methods and chemical reactions. The reactions are subdivided in groups that cover reactions at the amino substituent without touching the benzene ring and reactions which involve both nitrogen in the formal amidine system to give fused heterocyclic systems. Most imaginable reaction types have been successfully applied and used, as many of the synthesized compounds exhibit interesting biological activity in various fields.

Keywords: 2-aminobenzothiazoles; condensation; cyclization; substitution; heterocycles

1. Introduction

2-Aminobenzothiazoles are highly reactive compounds. They are extensively utilized as reactants or reaction intermediates since the NH_2 and endocyclic *N* functions are suitably situated to enable reactions with common *bis* electrophilic reagents to form a variety of fused heterocyclic compounds. In addition, the diverse biological activities reported for many derivatives of benzothiazoles have also drawn the attention of biochemists in the last decade. Although the chemistry of 2-aminobenzimidazole has been reviewed in the literature (*1*), the chemistry of 2-aminobenzothiazole has not been reviewed until now. The main objective of the present survey is to provide a comprehensive account of the synthetic utility of 2-aminobenzothiazoles in building various isolated and fused heterocycles and to highlight their potential in evolving better chemotherapeutic agents.

2. Synthesis of 2-aminobenzothiazoles

The synthesis of 2-aminobenzothiazoles may be carried out in several ways. The most versatile and economical method involves the treatment of various substituted arylthioureas (which are

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synthesized via treatment of an arylamine with isothiocyanate) with oxidizing agent or cyclizing agent using different reaction conditions to yield 2-aminobenzothiazoles.

The following are some of the methods which have been used to prepare 2-aminobenzothiazoles.

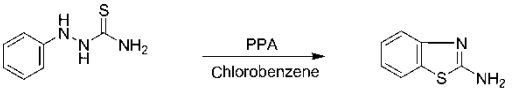
2.1. *Using polyphosphoric acid (PPA)*

Lebedenko (*2*) reported that heterocyclization of 1-phenyl thiosemicarbazide **1** with polyphosphoric acid in chlorobenzene afforded 2-aminobenzothiazole **2a** in 85% yield (Scheme 1).

2.2. *Using oxidative cyclization with bromine ($Br_2/CHCl_3$)*

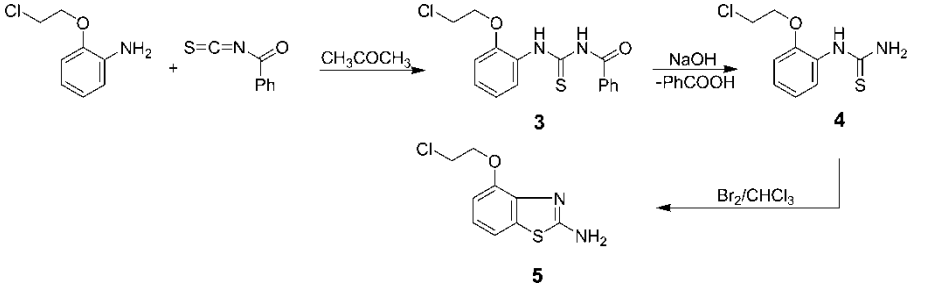
2-Aminobenzothiazole **5** was prepared in three consequential steps by treatment of benzoylisothiocyanate, prepared *in situ* by treatment of benzoyl chloride and ammonium thiocyanate in boiling acetone, with 2-(2-chloroethoxy)aniline to give the benzoyl thiourea derivative **3**, followed by hydrolysis of **3** by heating in sodium hydroxide to afford aryl thiourea **4**, which underwent oxidative cyclization when treated with Br_2 in chloroform to give 2-aminobenzothiazole **5** in 91% yield (Scheme 2) (*3*).

6-Chloro-4-(trifluoromethyl)-2-aminobenzothiazole **8** was prepared by oxidative cyclization of 4-chloro-2-(trifluoromethyl)phenylthiourea **6** with bromine in chloroform to give compound **7**, followed by basification with NH_3 (Scheme 3) (*4*, *5*).



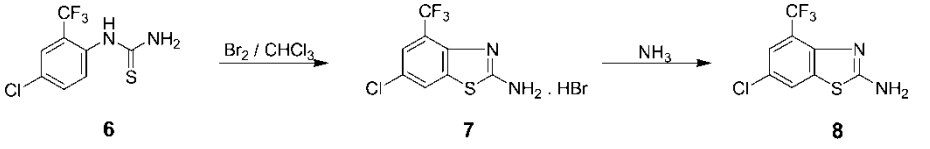
1 **2a**

Scheme 1.



3 **4** **5**

Scheme 2.



6 **7** **8**

Scheme 3.

2.3. *Using sodium nitrite ($NaNO_2$)*

1-Benzoyl-3-phenylthiourea **9** was heterocyclized by using a mixture of sodium nitrite and sulphuric acid to give *N*-(4-nitrobenzothiazol-2-yl)benzamide **10**, which upon treatment with 20% H_2SO_4 and NH_2SO_3H led to the formation of 2-amino-4-nitrobenzothiazole **2b** (Scheme 4) (*6*).

2.4. *Using benzyltrimethylammonium tribromide ($PhCH_2NMe_3Br_3$)*

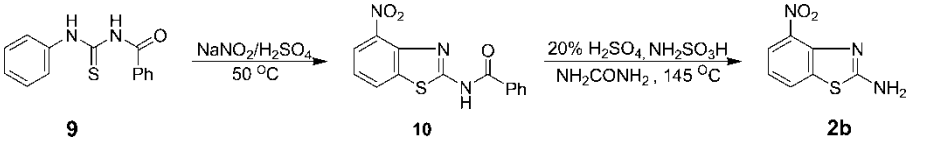
Benzyltrimethylammonium tribromide is used as a stable electrophilic bromine source for the conversion of arylthiourea **11** to 2-aminobenzothiazole, following the Hugerschoff reaction in acetonitrile to furnish 2-aminobenzothiazole **12** (Scheme 5) (*7*, *8*).

2.5. *Using sulfuryl chloride (SO_2Cl_2)*

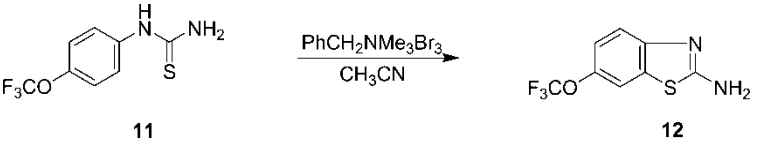
Allen and coworkers have reported that the reaction of *p*-toluidine with sodium thiocyanate in chlorobenzene and in the presence of sulfuric acid gave thiourea **13**. Warming thiourea **13** with sulfuryl chloride at 50° C furnished 2-amino-6-methylbenzothiazole **2c** (Scheme 6) (*9*).

2.6. *Using transition metals*

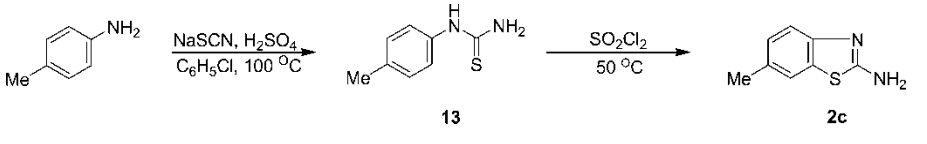
Batey and coworkers (*10*) have reported a convenient synthesis of 2-aminobenzothiazole derivative **15** using a copper- and/or palladium-catalyzed intramolecular C–S bond formation by cross-coupling between an arylhalide and thiourea functionality of compound **14** (Scheme 7).



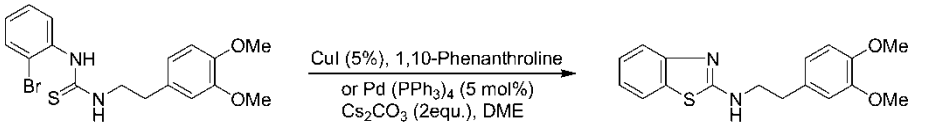
Scheme 4.



Scheme 5.



Scheme 6.

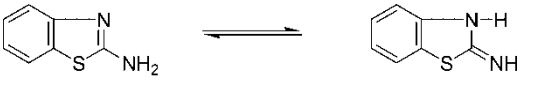


14 **15**

Scheme 7.

3. Chemical properties

The 2-aminobenzothiazole structure can be represented by tautomerizm of the imino-enamine type (A⇌ B) as follows:



A **B**

This tautomerizm explains the greater reactivity and lower stability with respect to electrophilic reagents. In general, the chemical properties of 2-aminobenzothiazoles are determined by the character of the thiazole ring, the benzene ring condensed with it and the amino group. The presence of an amino group leads to the development of new properties that are associated with the manifestation of basicity and, in addition to this, changes the properties of the thiazole ring. In contrast to 2-aminobenzoxazole, the carbon atom in the 2-position of 2-aminobenzothiazole has a relatively low partial positive charge, and this leads to an increase in the basicity of the amino group bonded to this atom, as a result of which it undergoes cyclization (*11*). Electrophilic substitution reactions of the benzene ring in 2-aminobenzothiazole take place in the 6-position. The authors will discuss the reactions involving the thiazole ring and the amino group.

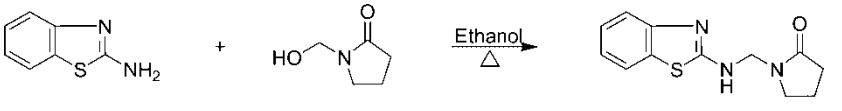
4. Reactions of 2-aminobenzothiazoles

4.1. *Alkylation reactions*

Reaction of 2-aminobenzothiazole **2a** with 1-(hydroxymethyl)-2-pyrrolidinone in boiling ethanol afforded 1-((benzothiazol-2-ylamino)methyl)pyrrolidin-2-one **16** (Scheme 8) (*12*).

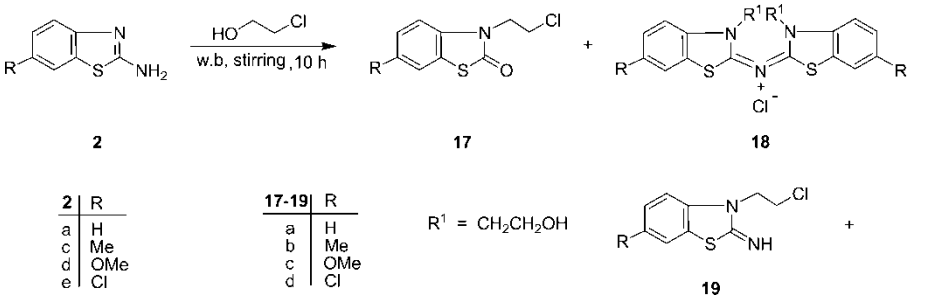
Warming 2-aminobenzothiazoles **2** with ethylene chlorohydrin gave a mixture of 3-(β-chloroethyl)benzothiazolin-2-one **17**, *bis*[3-(β-hydroxyethyl)-6*R*-benzothiazol-2-ylidene-ammonium chlorides **18** and small amounts of 2-imino-3-(β-hydroxyethyl)-6*R*-benzothiazoline **19** (Scheme 9) (*13*).

Treatment of 2-aminobenzothiazole **2a** with an excess of 3-furfuryloxy-1,2-epoxypropane in the presence of a catalytic amount of water gave a mixture of 2-(γ-furfuryloxy-β-hydroxypropyl)imino-3-(γ-furfuryloxy-β-hydroxypropyl)-2,3-dihydrobenzo-thiazole **20** and 2-imino-3-(γ-furfuryloxy-3-hydroxypropyl)-2,3-dihydrobenzothiazole **21** (Scheme 10) (*14*).

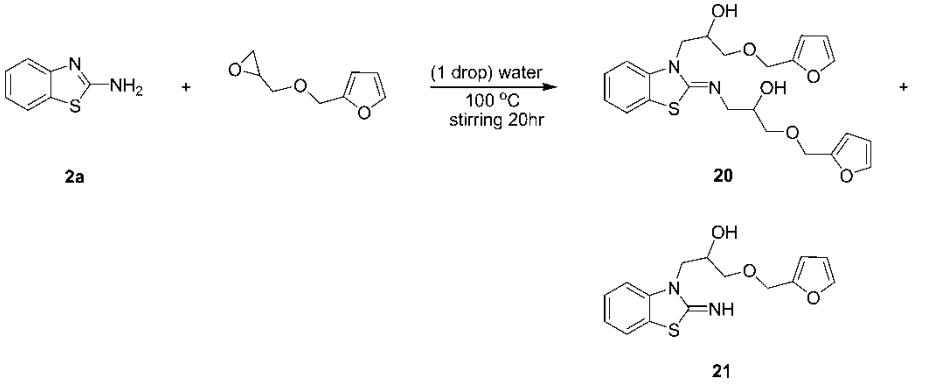


2a **16**

Scheme 8.



Scheme 9.

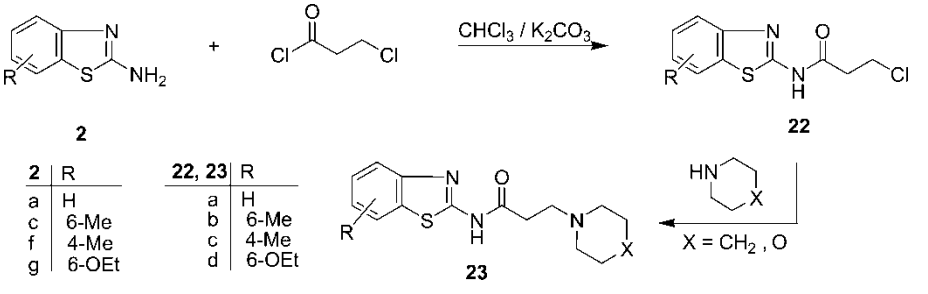


Scheme 10.

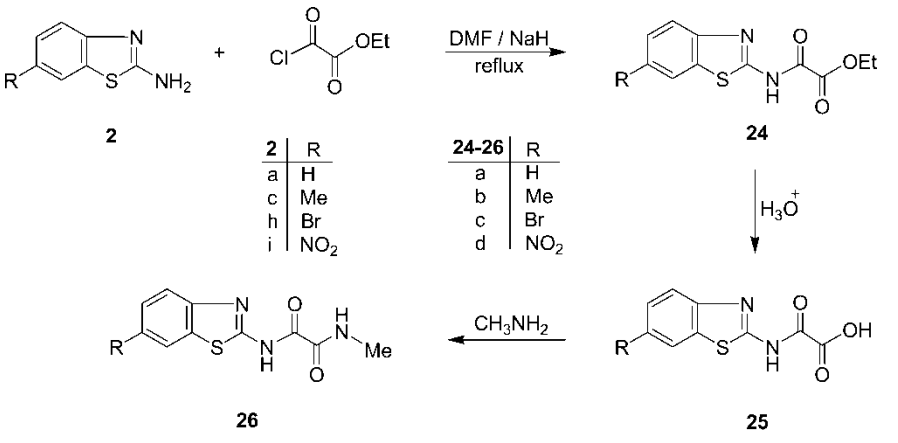
4.2. *Acylation reactions*

Mehra *et al.* (*15*) have reported that the reaction of β-chloropropionyl chloride with 2-aminobenzothiazoles **2** gave β-chloropropionamide derivatives **22**, which was treated with secondary amines to afford aminopropionyl-2-aminobenzothiazoles **23**. Compounds **22** and **23** have showed local anesthetic activity (Scheme 11) (*15*).

On the other hand, when 2-aminobenzothiazoles **2** reacted with ethyl-2-chloroglyoxylate, benzothiazolyl-2-oxamic esters **24** were obtained, which hydrolyzed to give *N*-(benzothiazol-2-yl) oxalamides **25**. Treatment of **25** with methylamine furnished **26** in high yield. Compounds **26** were reported in LD_{50}, hypoglycomic, diuretic, antiflammatory and antihypoxic activities (Scheme 12) (*16–18*).



Scheme 11.



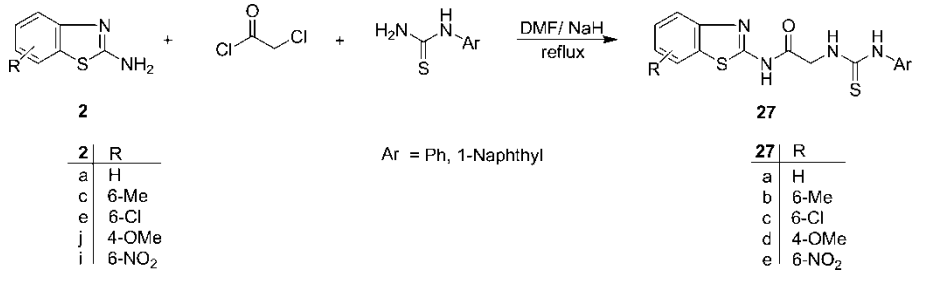
Scheme 12.

N^1-(Benzothiazol-2-ylacetylamino)-N^2-aryl thioureas **27** have been synthesized by the reaction of 2-aminobenzothiazoles **2** with chloroacetyl chloride, followed by treatment with thiourea derivatives. Compounds **27** showed inhibition of *Helminthosporium sativum* growth (Scheme 13) (*19*).

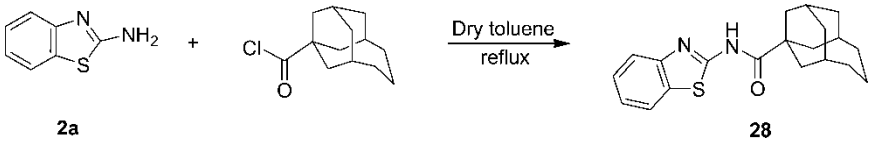
2-Aminobenzothiazole **2a** has been treated with 1-adamantane carbonyl chloride in boiling dry toluene to give the corresponding *N*-(2-benzothiazolyl)-1-adamantane carboxamide **28** (Scheme 14) (*20*, *21*).

Refluxing of 2-aminobenzothiazoles **2** with benzoyl chlorides in DMF containing a catalytic amount of sodium hydride furnished *N*-benzoylbenzothiazole derivatives **29** in 60–70% yields. Compounds **29** have shown anticancer activity (Scheme 15) (*22–24*).

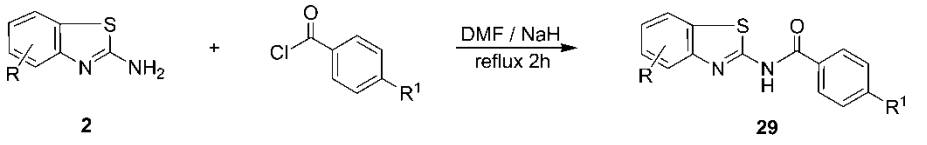
Reaction of 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carbonyl chloride with 2-aminobenzothiazole **2a** in refluxing pyridine yielded 5-chloro-3-methyl-1-phenyl-1*H*-pyrazole-4-carboxamide **30** in a good yield (Scheme 16) (*25*).



Scheme 13.



Scheme 14.



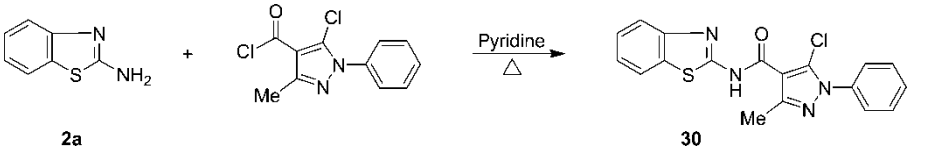
2

2	R
d	6-OMe
j	4-OMe
k	5-OMe

29

29	R	R^1
a	6-OMe	OMe
b	4-OMe	CN
c	5-OMe	NO_2

Scheme 15.

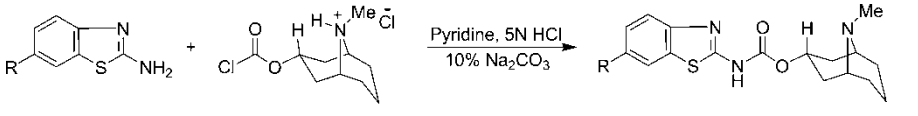


2a **30**

Scheme 16.

Treatment of chloroformate derivative **31** with 2-aminobenzothiazoles **2** in dry pyridine and in the presence of 5N HCl followed by neutralization with 10% aqueous Na_2CO_3 furnished carbamate derivatives **32** (Scheme 17) (*26*).

Acylation of 6-(trifluoromethyl)-2-aminobenzothiazole **2i** with *p*-nitrophenyl chloroformate in DMF containing a catalytic amount of piperidine yielded *p*-nitrophenyl[6-(trifluoromethyl)-2-benzothiazolyl]carbamate **33**. Treatment of **33** with 1-(3-chloropyridin-2-yl)piperazine gave 4-(3-chloropyridin-2-yl)-*N*-(6-(trifluoromethyl)benzothiazol-2-yl) piperazine-1-carboxamide **34** (Scheme 18) (*27*).

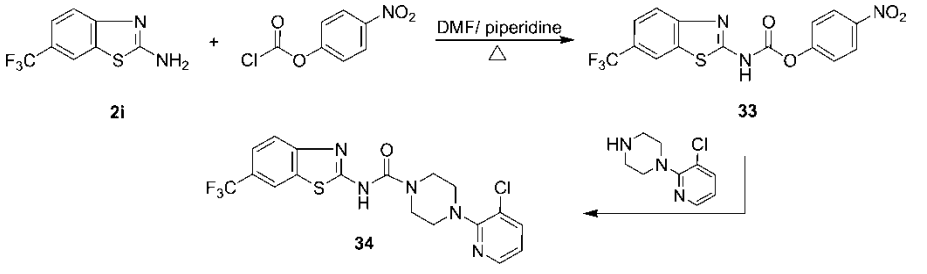


2 **31** **32**

2	R
a	H
d	OMe

32	R
a	H
b	OMe

Scheme 17.



2i **33** **34**

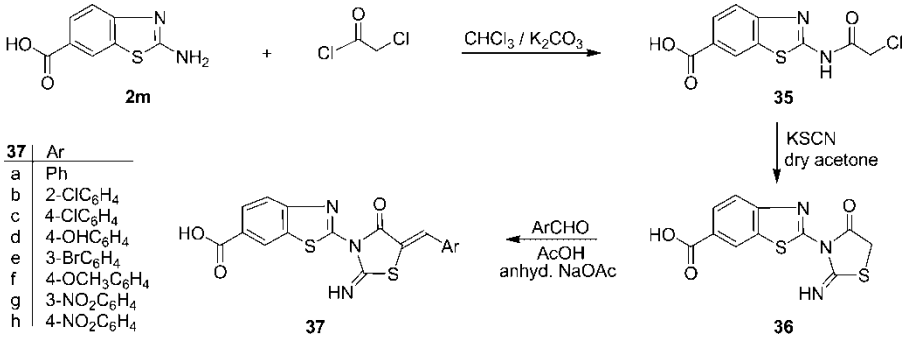
Scheme 18.

Condensation of 2-aminobenzothiazole-6-carboxylic acid **2m** with chloroacetyl chloride in refluxing chloroform and in the presence of anhydrous K_2CO_3 gave 2-(2-chloroacetylamino)benzothiazole-6-carboxylic acid **35** in 81% yield. When compound **35** was treated with KSCN in refluxing acetone, it yielded 2-(2-imino-4-oxo-thiazolidin-3-yl)benzothiazole-6-carboxylic acid **36** in 70% yield.

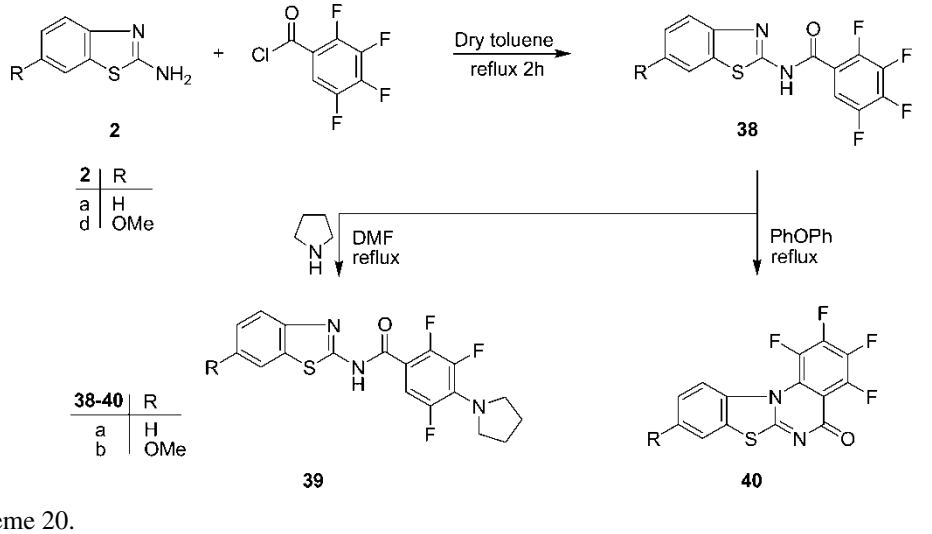
Condensation of compound **36** with various aromatic aldehydes in a basic medium afforded a series of 2-[5-(arylidene)-2-imino-4-oxo-thiazolidin-3-yl]benzothiazole-6-carboxylic acid **37**. The thiazolidinyl benzothiazoles **37** have shown antibacterial and antifungal activity (Scheme 19) (*28*).

Acylation of 2-aminobenzothiazoles **2** with tetrafluorobenzoyl chloride in boiling toluene gave tetrafluoro-*N*-(benzothiazol-2-yl)benzamides **38** in 77–84% yields. Heating amide **38** in DMF and in the presence pyrrolidine resulted only in the replacement of the F^4 atom to yield compound **39**. On the other hand, heating compounds **38** in the diphenyl ether proved to be an efficient procedure for the preparation of tetracyclic quinazolinones **40** (Scheme 20) (*29*).

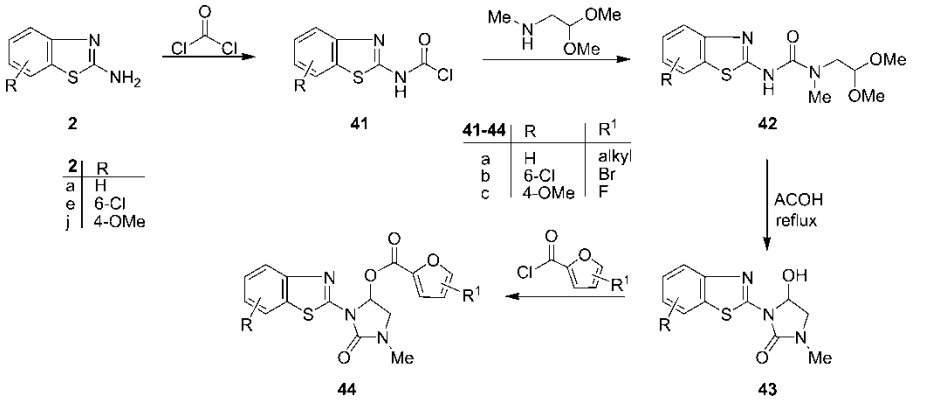
2-Aminobenzothiazoles **2** were treated with phosgene to give benzothiazol-2-ylcarbamic chlorides **41**, which react with 2-methylaminoacetaldehyde dimethyl acetal to give **42**, which cyclized in an acidic medium to form hydroxyimidazolidinone derivatives **43**. Acylation of **43** with 2-furoyl



Scheme 19.



Scheme 20.



2	R
a	H
e	6-Cl
j	4-OMe

41-44	R	R^1
a	H	alkyl
b	6-Cl	Br
c	4-OMe	F

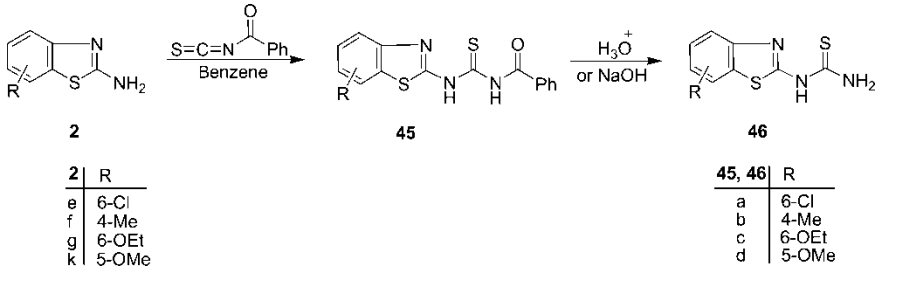
Scheme 21.

chloride gave 1-(2-benzothiazolyl)-3-methyl-5-(2-furoyloxyl)-2-imidazolidione derivatives **44** (Scheme 21) (*30–32*).

4.3. *Reaction with isothiocyanates and isocyanates*

2-Aminobenzothiazoles **2** reacted with benzoyl isothiocyanate in boiling benzene to give benzoyl thioureas **45**. Acid or alkaline hydrolysis of thioureas **45** furnished *N*-(2-benzothiazolyl) thioureas **46** (Scheme 22) (*33*).

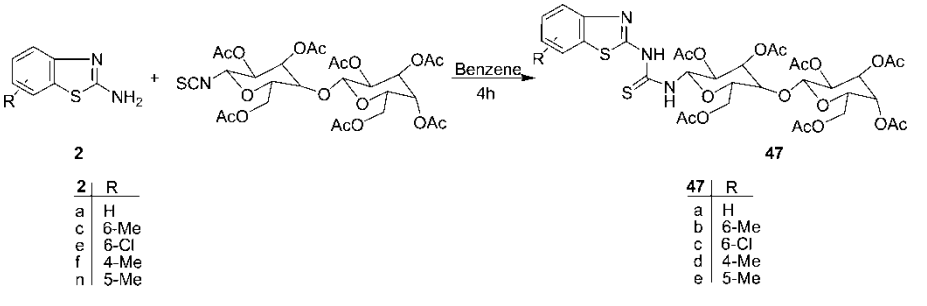
Refluxing of hepta-*O*-acetyl-β − *D*-lactosyl isothiocyanate and 2-aminobenzothiazoles **2** in benzene at 90° C afforded 1-hepta-*O*-acetyl-β − *D*-lactosyl-3-[2-*N*-substituted benzothiazolyl]thioureas **47** in good yields (Scheme 23) (*34*).



2	R
e	6-Cl
f	4-Me
g	6-OEt
k	5-OMe

45, 46	R
a	6-Cl
b	4-Me
c	6-OEt
d	5-OMe

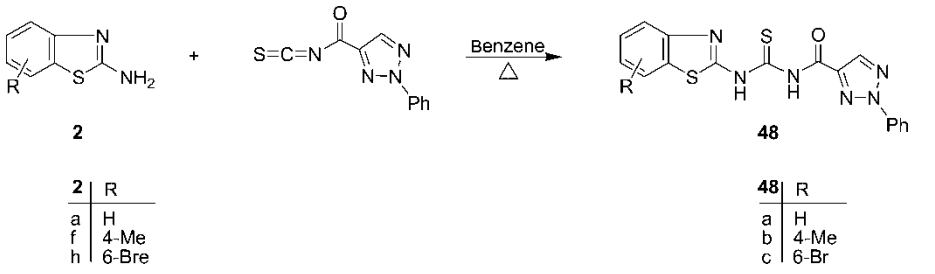
Scheme 22.



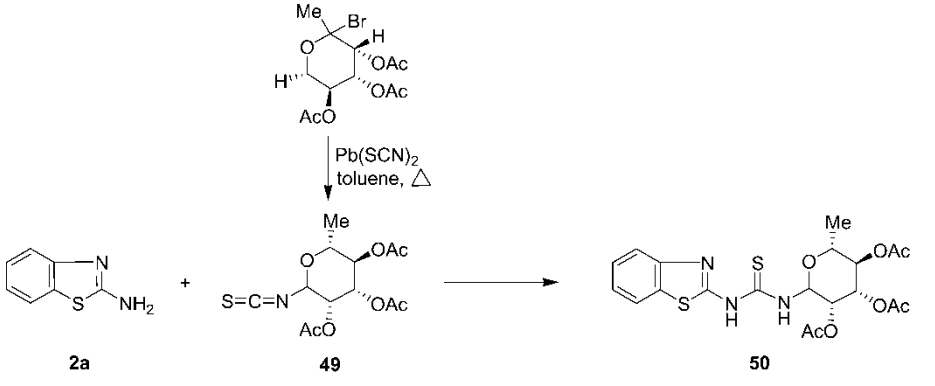
2	R
a	H
c	6-Me
e	6-Cl
f	4-Me
n	5-Me

47	R
a	H
b	6-Me
c	6-Cl
d	4-Me
e	5-Me

Scheme 23.



Scheme 24.

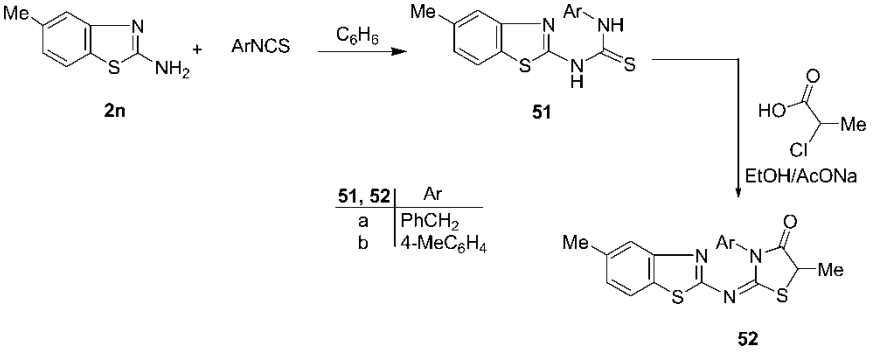


Scheme 25.

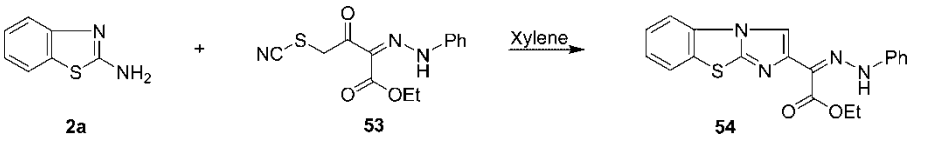
Thiourea derivatives **48** were synthesized by addition of 2-aminobenzothiazoles **2** to 2-phenyl-1,2,3-triazole-4-formylisothiocyanate in boiling benzene (Scheme 24) (*35*).

Tian *et al.* (*36*) have reported that treatment of triacetyl-α-*L*-rhamnosyl bromide with $Pb(SCN)_2$ in boiling toluene gave 2,3,4-tri-*O*-acetyl-α-*L*-rhamnopyranosyl isothiocyanate **49**, which reacted with 2-aminobenzothiazole **2a** to afford 2-(3-benzothiazol-2-ylthioureido)-6-methyltetrahydro-2*H*-pyran-3,4,5-triyl triacetate **50** (Scheme 25).

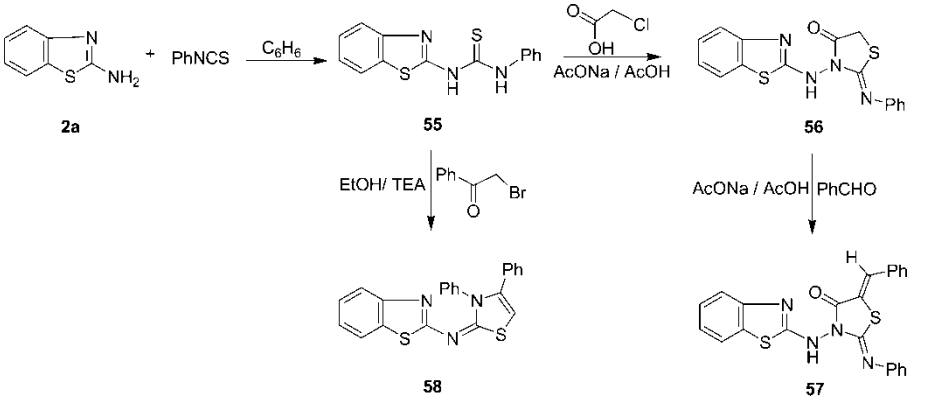
The reaction of 2-amino-5-methylbenzothiazole **2n** with aryl isothiocyanates in benzene afforded 2-benzothiazolyl thiocarbamates **51**, which cyclized with 2-chloropropionic acid in ethanolic sodium acetate to give thiazolidin-4-one derivatives **52** (Scheme 26) (*37*).



Scheme 26.



Scheme 27.



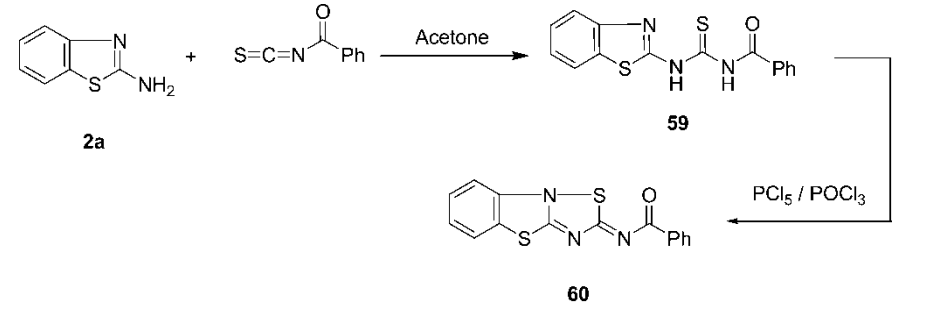
Scheme 28.

Treatment of **53** with 2-aminobenzothiazole **2a** in refluxing xylene furnished compound **54** (Scheme 27) (*38*).

The interaction of 2-aminobenzothiazole **2a** with phenyl isothiocyanate gave thiourea **55**, which underwent cyclocondensation with chloroacetic acid to afford thiazolidin-4-one **56**. Reaction of compound **56** with benzaldehyde yielded the benzylidene derivative **57**. Refluxing **55** with phenacyl bromide in ethanolic triethylamine furnished thiazoline derivative **58** (Scheme 28) (*39*).

N-(Benzothiazol-2-ylcarbamothioyl)benzamide **59** was obtained by the reaction of 2-aminobenzothiazole **2a** with benzoyl isothiocyanate. Cyclization of **59** with Lewis acid such as PCl_5 or $POCl_3$ furnished [1,2,4]thiadiazolo[3,2-*b*]benzothiazole derivative **60** (Scheme 29) (*40*, *41*).

2-Aminobenzothiazoles **2** and phenyl isocyanates were reacted in DMF in the presence of 2,6-dimethylaminopyridine and triethylamine as a basic catalyst to furnish urea derivatives **61** in 40–60% yield (Scheme 30) (*22*).



Scheme 29.

2

2	R
c	6-Me
e	6-Cl
n	5-Me

61

61	R	R^1
a	5-Me	H
b	6-Me	OMe
c	6-Cl	F

Scheme 30.

4.4. *Reactions with carbonyl compounds*

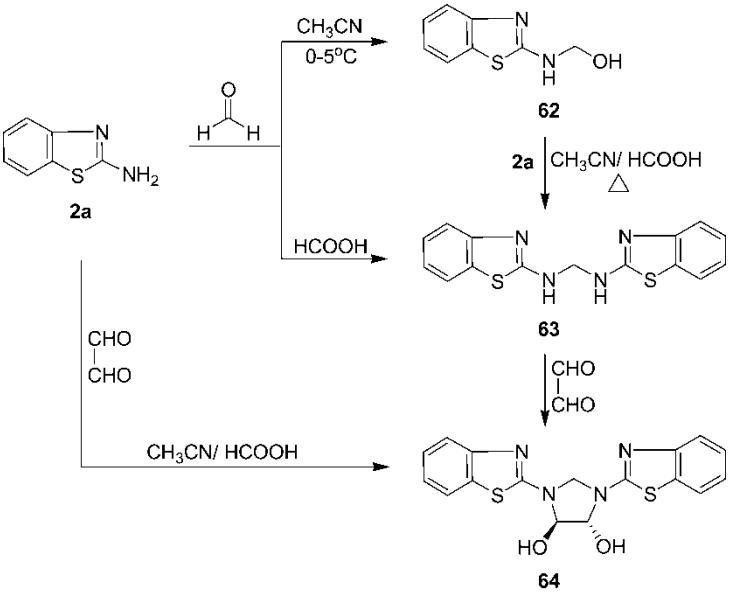
4.4.1. *Reaction with aldehydes*

Treatment of **2a** with formaline in acetonitrile at 0–5° C furnished *N*-hydroxymethyl benzothiazole **62**. When the reaction was carried out in formic acid under reflux, it afforded *N*,*N*'-*bis*(2-benzothiazolyl)methanediamine **63**, which cyclized to imidazole derivative **64** upon treatment with glyoxal. Compound **63** could also be obtained via treatment of **62** with **2a** in acetonitrile containing a catalytic amount of formic acid. The imidazole derivative **64** could also be obtained in a one-pot reaction of **2a**, formaline and glyoxal under acidic conditions (Scheme 31) (*42*, *43*).

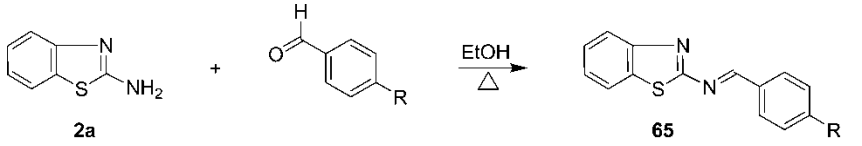
In addition, condensation of **2a** with aromatic aldehydes in boiling ethanol furnished Schiff base **65** in good yields (Scheme 32) (*44–49*).

N′-(2-Benzothiazolyl)formamidine derivatives **66** were prepared by condensation of heterocyclic formamide derivatives with 2-aminobenzothiazoles **2** in the presence of $SOCl_2$.

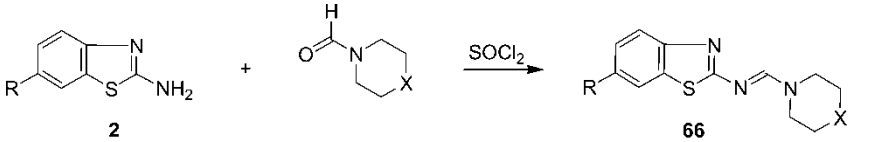
Compounds **66** have shown fungicidal activity against Alternaria, *Botrytis cinerea*, *Fusarium nivale* and *Tilletia foetida* (Scheme 33) (*50*).



Scheme 31.



Scheme 32.

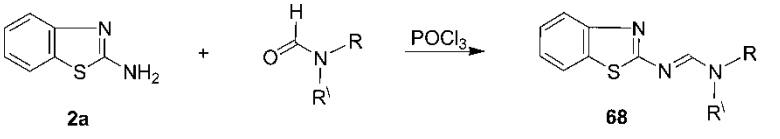


Scheme 33.

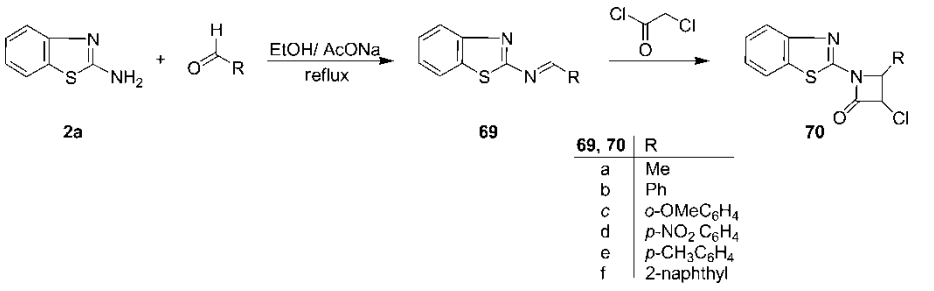
Scheme 34.

2-Aminobenzothiazoles **2** were treated with Vilsmeier-Haack reagents, prepared *in situ* from formamides and benzene sulphonyl chloride, to give *N*-(2-benzothiazolyl) formamidines **67** (Scheme 34) (*51*).

The reaction of 2-aminobenzothiazole **2a** with formamides in the presence of $POCl_3$ (1:5:2) gave formamidine derivatives **68** (Scheme 35) (*52*).



Scheme 35.



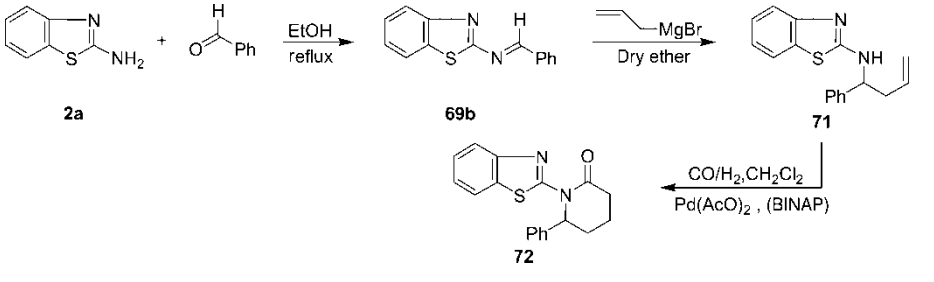
Scheme 36.

Refluxing 2-aminobenzothiazole **2a** with aromatic aldehydes in ethanolic sodium acetate solution gave Schiff bases **69**, which cyclized with chloroacetyl chloride in ethanolic triethylamine to afford 1-benzothiazol-2-yl-3-chloro-4-substituted-azetidin-2-ones **70** (Scheme 36) (*53*, *54*).

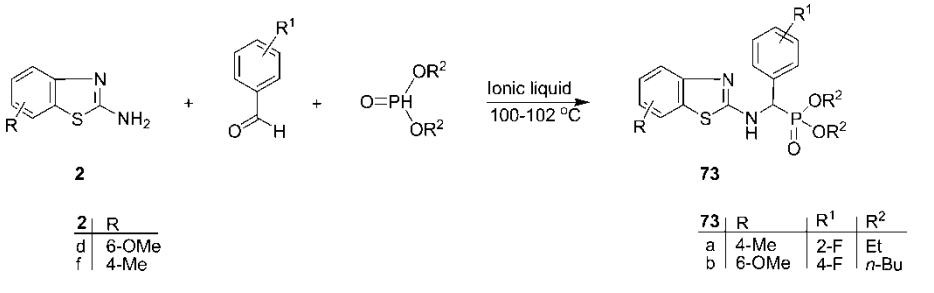
Condensation of **2a** with benzaldehyde in boiling ethanol furnished Schiff base **69b**, which reacted with allyl magnesium bromide in dry ether to give *N*-alkyl adduct **71**. Treatment of **71** with a mixture of carbon monoxide and hydrogen in dichloromethane in the presence of palladium acetate and BINAP led to the formation of 1-(benzothiazol-2-yl)-6-phenylpiperidin-2-one **72** in 90% yield (Scheme 37) (*55*).

The multi-component reactions of 2-aminobenzothiazoles **2**, *o*,*o*-dialkylphosphite and aromatic aldehyde in ionic liquids at 100–102° C led to the formation of α-aminophosphonates **73** containing benzothiazole and fluorine moiety. Compounds **73** were evaluated for their anticancer activities (Scheme 38) (*56*).

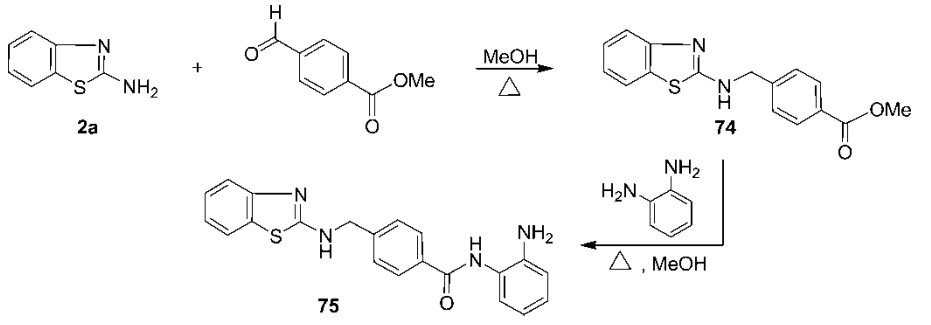
Bressi *et al.* (*57*) have reported that the reaction of methyl 4-formylbenzoate with **2a** in boiling methanol furnished compound **74**, which condensed with *o*-phenylene diamine to form *N*-(2-aminophenyl)-4-((benzothiazol-2-ylamino)methyl)benzamide **75** (Scheme 39) (*57*).



Scheme 37.



Scheme 38.



Scheme 39.

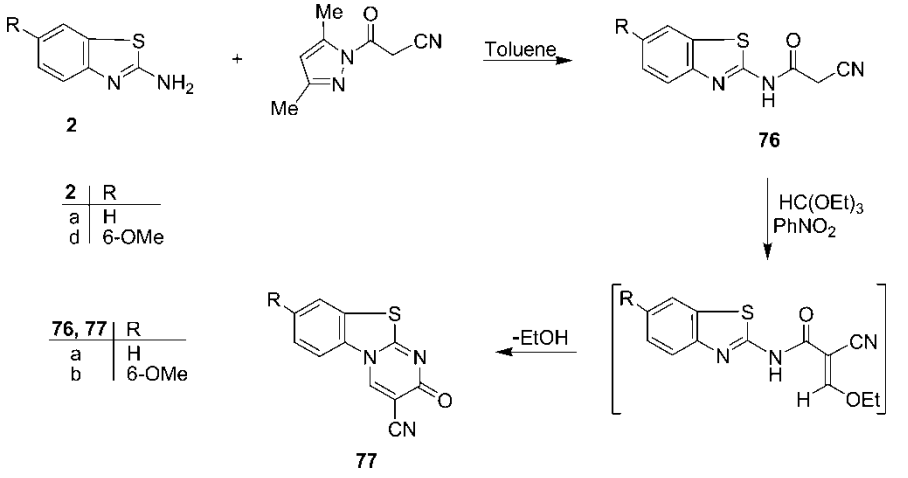
4.4.2. *Reaction with ketones*

Treatment of 2-aminobenzothiazoles **2** with 1-cyanoacetyl-3,5-dimethylpyrazole in boiling toluene resulted in the formation of the corresponding cyanoacetamides **76** in 91% yields. Heating **76** with triethyl orthoformate in nitrobenzene furnished 2-oxo-2*H*-pyrimido[2,1-*b*]benzothiazole-3-carbonitrile **77** (Scheme 40) (*58–60*).

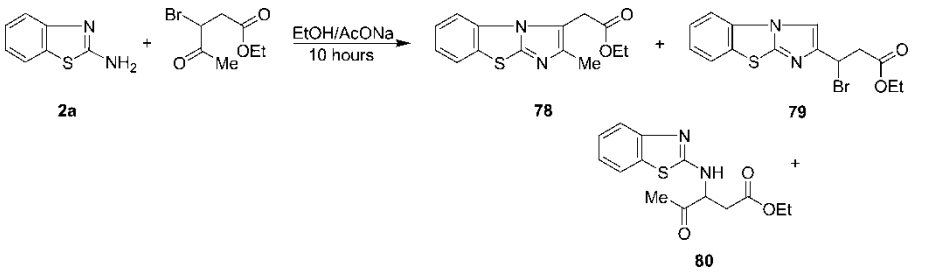
Cyclocondensation of 2-aminobenzothiazole **2a** with ethyl 3-bromo-4-oxopentanoate in ethanolic sodium acetate solution afforded a mixture of ethyl 2-methylimidazo[2,1-*b*] benzothiazole-3-acetate **78**, ethyl-2-imidazo[2,1-*b*]benzothiazole-3-propionate **79** and ethyl-3-(benzothiazol-2-yl)amino-4-oxopentanoate **80** (Scheme 41) (*61*).

4.4.3. *Reaction with acids*

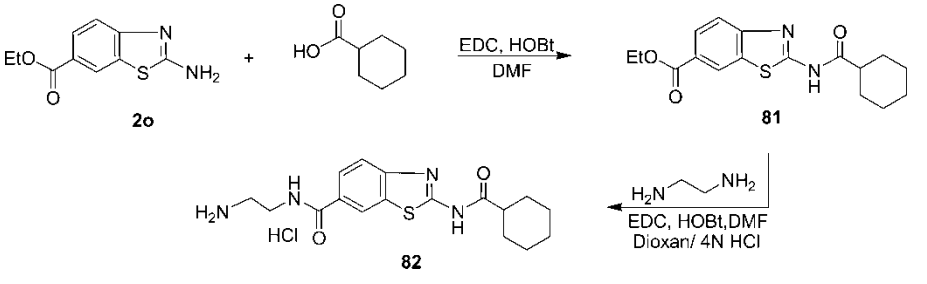
2-[(Cyclohexanecarbonyl)amino]benzothiazole-6-carboxylic acid **81** was prepared via the reaction of ethyl-2-amino-benzothiazole-6-carboxylate **2o** with cyclohexanecarboxylic acid in DMF and in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) and 1-hydroxybenzotriazole (HOBt) at room temperature. Reaction of **81** with ethylene diamine in DMF and in the presence of EDC, HOBt and 4 N HCl-dioxane at room temperature afforded



Scheme 40.



Scheme 41.



Scheme 42.

2-[(cyclohexanecarbonyl)amino]-*N*-(2-aminoethyl)benzothiazole-6-carboxamide hydrochloride **82** in 86% yield (Scheme 42) (*62*).

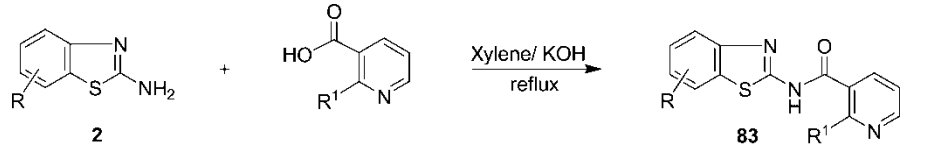
Condensation of nicotinic acid derivatives with 2-aminobenzothiazoles **2** afforded *N*-(benzothiazol-2-yl)nicotinamide derivatives **83** (Scheme 43) (*63*, *64*).

N′-[2-(5,6-dimethylbenzothiazoly)]-*N*-furfuryloxamide **84** has been synthesized by the reaction of 2-amino-5,6-dimethylbenzothiazole **2p** with *N*-furfuryl oxamic acid (Scheme 44) (*65*).

Reaction of 2-aminobenzothiazole **2a** with anthranilic acid in dry pyridine afforded a mixture of compounds **85** and **86**. Compounds **85** showed anticonvulsant activity (Scheme 45) (*66*, *67*).

4.4.4. *Reaction with acid anhydride*

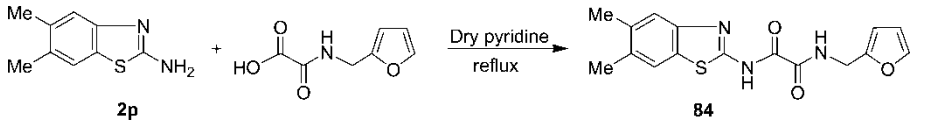
Acylation of 2-aminobenzothiazole **2a** with acetic anhydride furnished 2-acetamidobenzothiazole **87**, which was nitrated with nitric acid to give compound **88**. Compound **88** could also be obtained



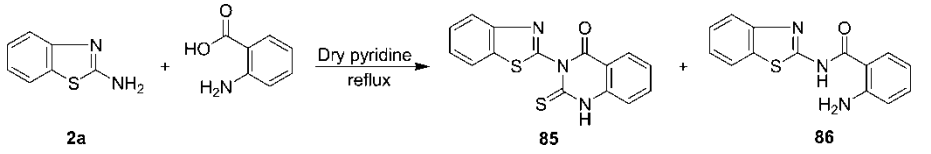
2	R
a	H
d	6-OMe
c	6-Me
p	5, 6-Me_2
i	6-NO_2

83	R	R^1
a	H	Cl
b	6-OMe	3-(trifluoromethyl)aniline
c	6-Me	H
d	5, 6-Me_2	H
e	6-NO_2	H

Scheme 43.



Scheme 44.



Scheme 45.

in a one-pot reaction of **2a** with a mixture of sulphuric acid, acetic anhydride and nitric acid. Acid-catalyzed hydrolysis of **88** furnished 2-amino-6-nitrobenzothiazole **2j** (Scheme 46) (*68*).

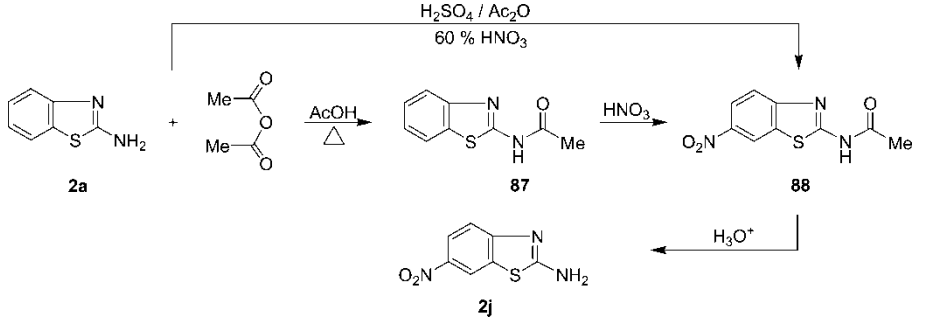
Fusion of 2-aminobenzothiazole **2a** with phthalic anhydride afforded *N*-benzothiazolylphthalimide **89** (Scheme 47) (*69*).

Condensation of 2-aminobenzothiazoles **2** with cantharidin in refluxing toluene containing a catalytic amount of triethylamine gave the corresponding cantharimide derivatives **90** (Scheme 48) (*70*).

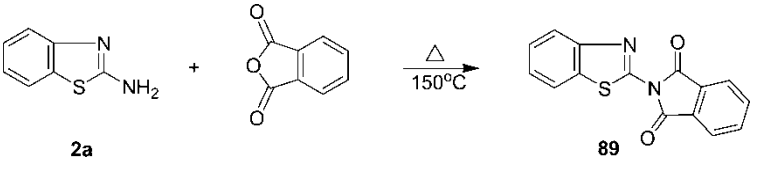
Heating 2-aminobenzothiazole **2a** with diphenic anhydride gave the amide derivative **91** (Scheme 49) (*71*).

4.4.5. *Reaction with esters*

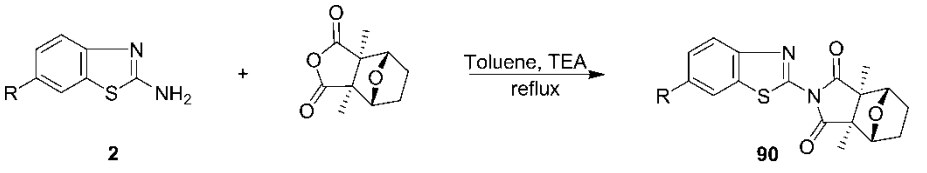
Reaction of 2-aminobenzothiazole **2a** with diethyloxalate in ethanolic piperidine solution delivered ethyl benzothiazolyloxamate **92**, which at 10 mg/kg inhibits anaphylaxis in rats (Scheme 50) (*72*).



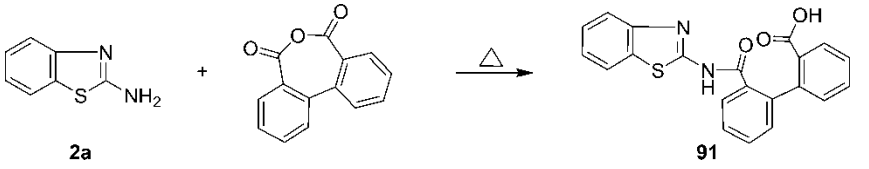
Scheme 46.



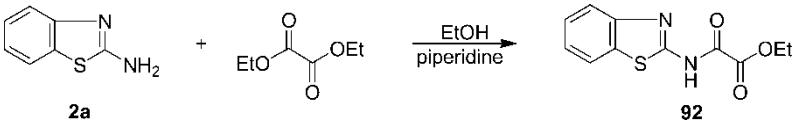
Scheme 47.



Scheme 48.



Scheme 49.



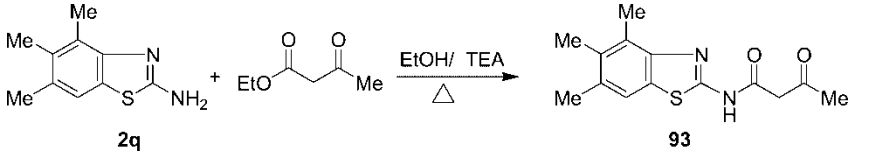
Scheme 50.

Condensation of 2-aminobenzothiazole **2q** with ethyl acetoacetate in boiling ethanolic triethylamine furnished *N*-benzothiazol-2-yl-3-oxobutanamide **93** (Scheme 51) (*73*).

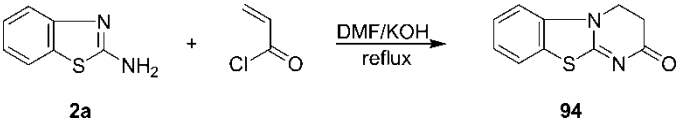
4.5. *Substitutions involving heterocyclization*

2-Aminobenzothiazole **2a** has been reacted with acryloyl chloride to give pyrimido[2,1-*a*]benzothiazole **94** (Scheme 52) (*74*).

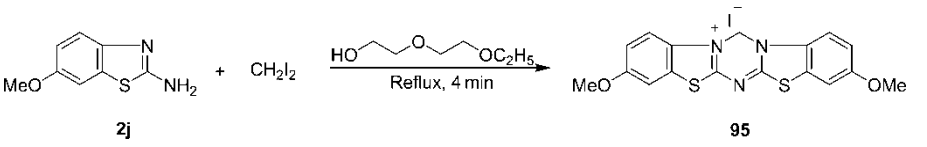
Cyclocondensation of 2-amino-6-methoxybenzothiazole **2j** with methylene iodide in refluxing ether gave the corresponding 7*H*-3,11-dimethoxy-dibenzothiazolo[1,2-*a*:2',1'-*d*][1,3,5]-triazin-6-ium **95** in 62% yield (Scheme 53) (*75*).



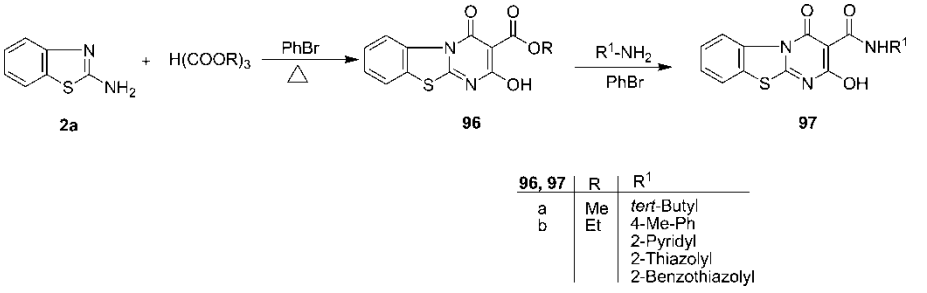
Scheme 51.



Scheme 52.



Scheme 53.



Scheme 54.

Cyclocondensation of **2a** with an excess of trialkyl orthoformate in bromobenzene afforded the fused 4*H*-pyrimido[2,1-*b*]benzothiazol-4-one **96**, which condensed with different primary aliphatic as well as aromatic amines to form the carboxamide derivatives **97** (Scheme 54) (*76*).

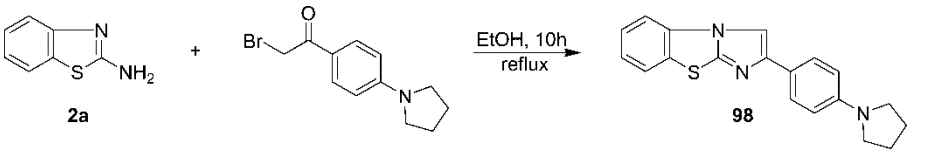
Condensation of (4-pyrrolidin-1-yl)phenacyl bromide with 2-aminobenzothiazole **2a** in refluxing ethanol yielded imidazo[2,1-*b*]benzothiazole **98** in 16% yield (Scheme 55) (*77*).

Addition of epichlorohydrin to a solution of 2-aminobenzothiazole **2a** in glacial acetic acid gave the hydrochloride salt **99**. Neutralization of **99** with NH_4OH solution produced 3-hydroxy-2,3,4,5-tetrahydropyrido [2,1-*b*]benzothiazole **100** in 90% yield (Scheme 56) (*78*).

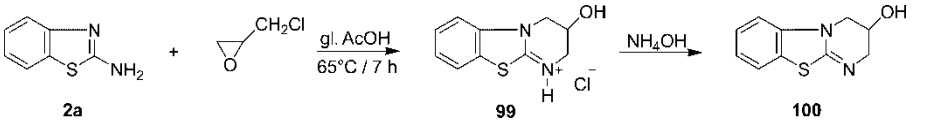
One-pot condensation reaction of 1,3-cyclohexanedione with benzaldehyde and 2-aminobenzothiazole **2a** in boiling *n*-butanol furnished fused benzothiazolo[3,2-*a*] quinazolinone **101** in 40% yield (Scheme 57) (*46*).

Cyclocondensation of *p*-nitrophenacyl bromide with 2-aminobenzothiazole **2a** in refluxing ethanol afforded imidazo[2,1-*b*]benzothiazole derivative **102**, which upon reduction with Fe in 2-propanol delivered the amino derivative **103**. The addition of compound **103** to isoxazolyl isocyanate in methylene chloride gave the urea derivative **104** (Scheme 58) (*79*).

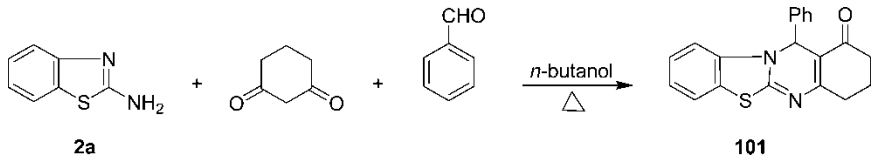
Reaction of 2-aminobenzothiazoles **2** with diethyl trichlorophenyl malonate in boiling ethanol led to the formation of pyrimido[2,1-*b*]benzothiazole derivatives **105** (Scheme 59) (*80*).



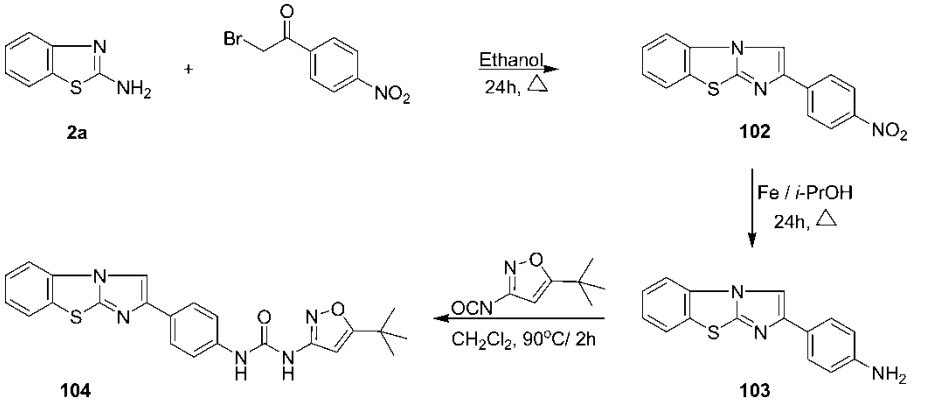
Scheme 55.



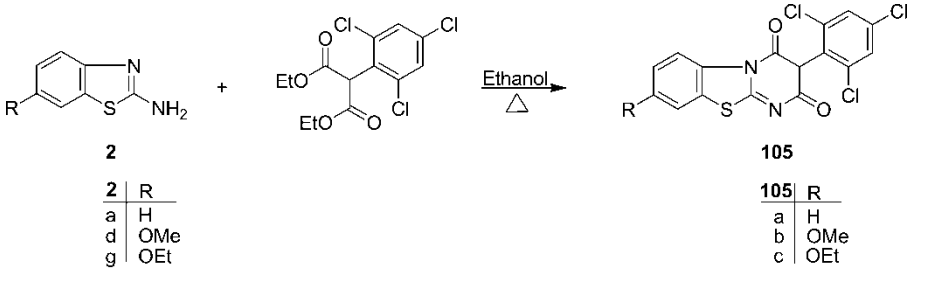
Scheme 56.



Scheme 57.

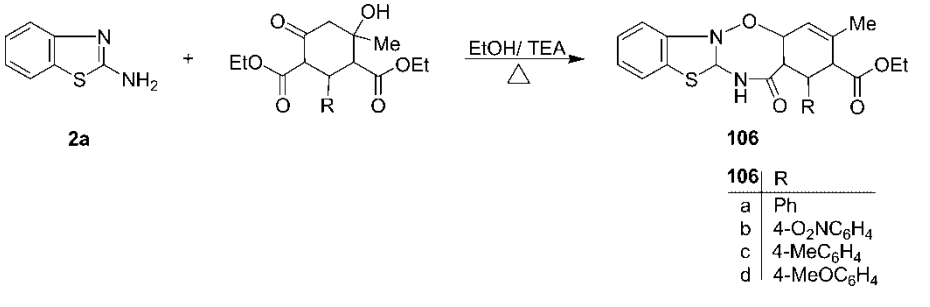


Scheme 58.



Scheme 59.

Cyclocondensation of cyclohexanonedicarboxylates with 2-aminobenzothiazole **2a** in refluxing ethanol containing a catalytic amount of triethylamine gave compounds **106**. Compounds **106** have shown bactericidal and fungicidal activities (Scheme 60) (*81*).



Scheme 60.

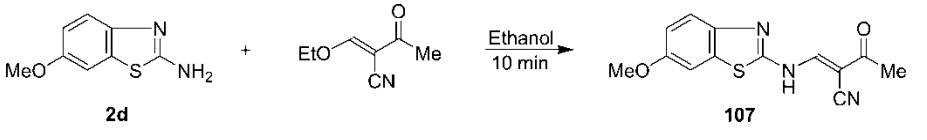
4.6. *Reaction with alkenes and alkynes*

Cernuchova *et al.* (*82*) published the reaction of 2-ethoxymethylene-3-oxobutanenitrile with 2-amino-6-methoxybenzothiazole **2d** in ethanol, which furnished 2-acetyl-3-(6-methoxybenzothiazol-2-ylamino)acrylonitrile **107** (Scheme 61) (*82*).

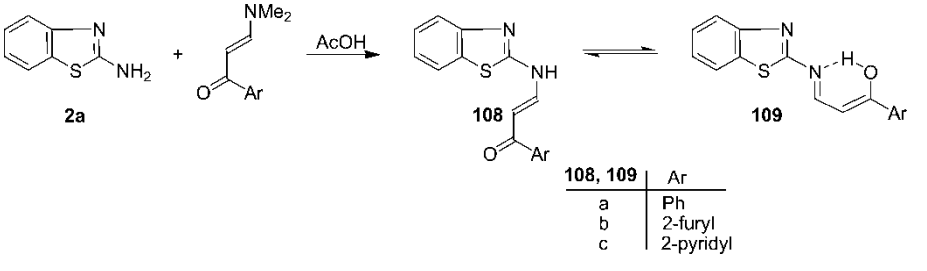
2-Aminobenzothiazole **2a** reacted with enaminones in acetic acid to yield only the heteroaromatic aminoenones **108**. These products are believed to exist in equilibrium with enoles **109**, which are stabilized through hydrogen bonding (Scheme 62) (*83*).

2-Aminobenzothiazole **2a** was condensed with diethyl ethoxymethylene malonate (DEEM) in petroleum ether to form diethyl 2-((benzothiazol-2-ylamino)methylene)malonate **110**, which was thermally cyclized to the next higher 4*H*-pyrimido[2,1-*b*]benzothiazole-3-carbethoxy-4-one **111** in 28% yield. The cyclic product **111** was prepared in a better yield (49%) by the direct reaction of 2-aminobenzothiazole **2a** with DEEM in boiling ethanol (Scheme 63) (*84*).

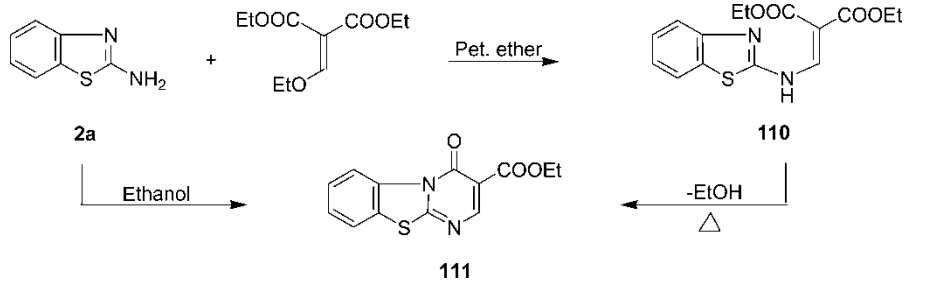
The Michael addition reaction of 2-aminobenzothiazole **2a** with dimethyl 2-amino-fumarate in methanol furnished pyrimido[2,1-*b*]benzothiazole derivative **112**, which underwent alkaline hydrolysis to give compound **113**. Similarly, the addition of 2-aminobenzothiazole **2a** to both dimethyl acetylenedicarboxylate and DEEM in methanol gave the corresponding fused pyrimido[2,1-*b*]benzothiazoles **114** and **116**, which underwent alkaline hydrolysis to the corresponding pyrimidobenzothiazoles **115** and **113**, respectively (Scheme 64) (*85*, *86*).



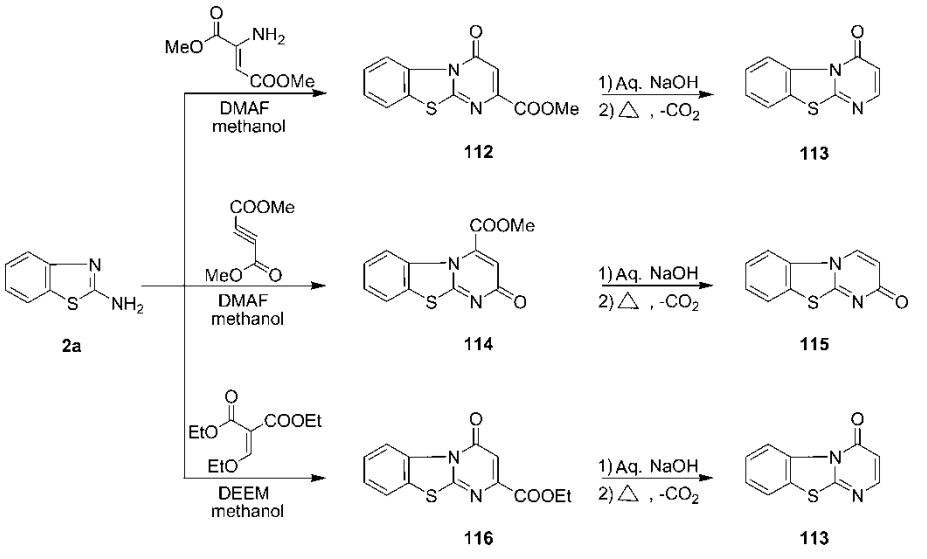
Scheme 61.



Scheme 62.



Scheme 63.

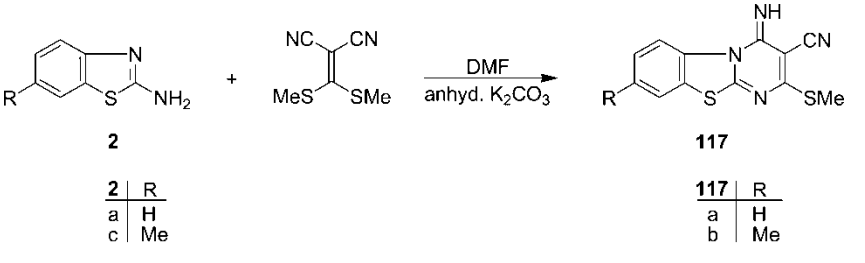


Scheme 64.

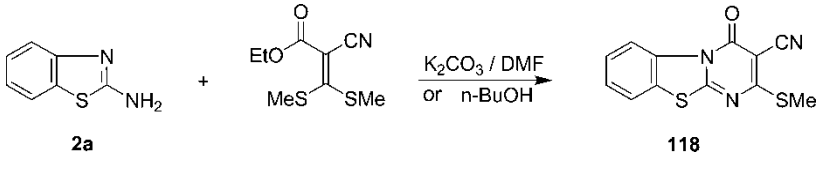
2-Aminobenzothiazoles **2** reacted with *bis*(methylthio)methylene malononitrile in DMF containing anhydrous potassium carbonate to afford 3-cyano-4-imino-2-methylthio-4*H*-pyrimido[2,1-*b*] benzothiazoles **117** (Scheme 65) (*87*).

4*H*-Pyrimido[2,1-*b*]benzothiazole-2-thiomethyl-3-cyano-4-one **118** has been prepared by the reaction of 2-aminobenzothiazoles **2a** with ethyl 2-cyano-3,3-*bis*(methylthio)acrylate in DMF and in the presence of anhydrous potassium carbonate. Compound **118** could also be obtained via condensation of **2a** with 3-*bis*(methylthio)acrylate in boiling butanol (Scheme 66) (*88*, *89*).

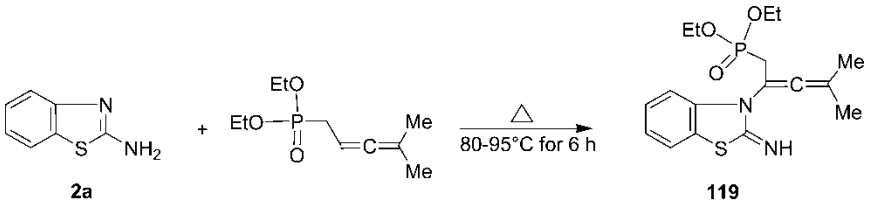
Refluxing diethyl-3-methylbut-1,2-dienylphosphonate with 2-aminobenzothiazole **2a** gave diethoxyphosphoryl-2-(2-imino-2,3-dihydrobenzothiazol-3-yl)-3-methylbut-2-ene **119** in 51% yield (Scheme 67) (*90*).



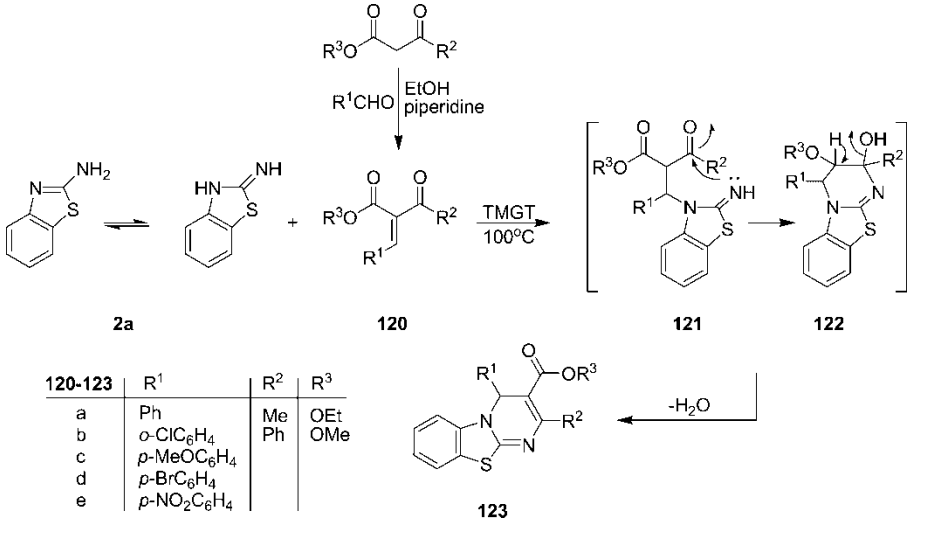
Scheme 65.



Scheme 66.



Scheme 67.



120-123	R^1	R^2	R^3
a	Ph	Me	OEt
b	*o*-ClC_6H_4	Ph	OMe
c	*p*-$MeOC_6H_4$		
d	*p*-BrC_6H_4		
e	*p*-$NO_2C_6H_4$		

Scheme 68.

The Knoevengel condensation of aldehydes and β-ketoester in a basic medium produced 3-arylidene-2,4-pentanedione **120**. The Michael addition of **2a** to **120** in 1,1,3,3-*N*,*N*,*N*,*N*′-tetramethylguanidinium trifluoroacetate as an ionic liquid at 100° C afforded 4*H*-pyrimido[2,1-*b*]benzothiazoles **123** via the non-isolable intermediates **121** and **122** (Scheme 68) (*91*).

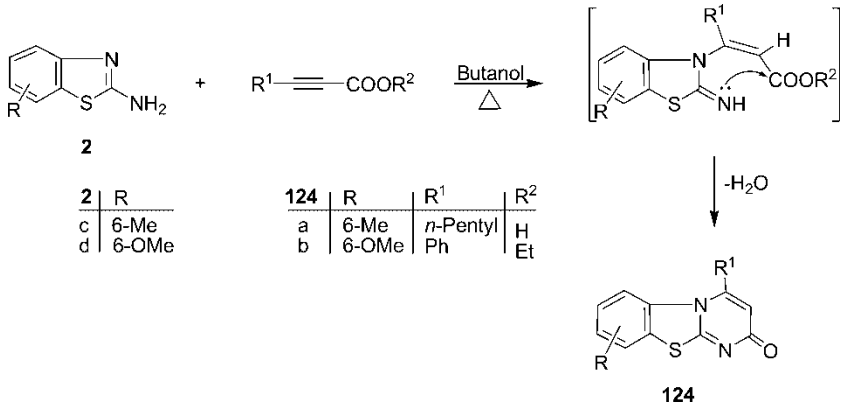
The Michael addition of 2-aminobenzothiazoles **2** to acetylenic acids or esters in *n*-butanol led to the formation of 2*H*-pyrimido[2,1-*b*] benzothiazol-2-ones **124** in 68–86% yield (Scheme 69) (*92*, *93*).

4.7. *Reaction with hydrazines*

Treatment of 2-aminobenzothiazoles **2** with hydrazine hydrate in boiling ethylene glycol containing acid as a catalyst led to the formation of 2-hydrazinobenzothiazoles **125** (*94*, *95*).

When **125** reacted with acetyl acetone in ethanol, it afforded 2-(3,5-dimethyl-*H* pyrazol-1-yl) benzothiazole derivatives **126** (*96*).

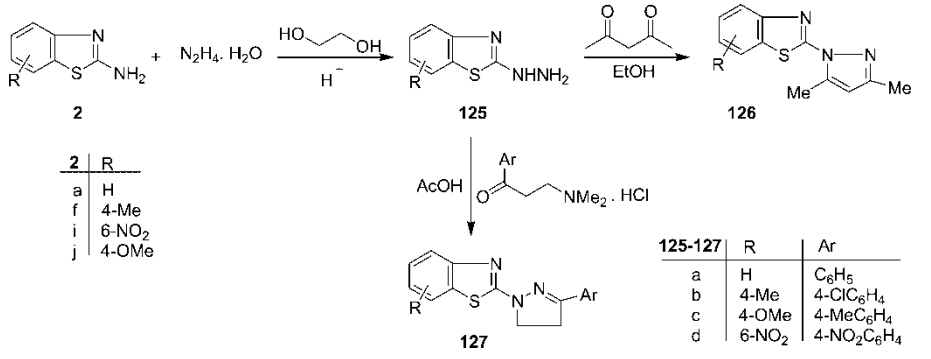
On the other hand, cyclocondensation of **125** with 3-(dimethylamino)propiophenone hydrochlorides in acetic acid gave 1-(benzothiazole-2-yl)-3-phenylpyrazoles **127** (Scheme 70) (*97*).



2	R
c	6-Me
d	6-OMe

124	R	R^1	R^2
a	6-Me	*n*-Pentyl	H
b	6-OMe	Ph	Et

Scheme 69.



2	R
a	H
f	4-Me
i	6-NO_2
j	4-OMe

125-127	R	Ar
a	H	C_6H_5
b	4-Me	4-ClC_6H_4
c	4-OMe	4-MeC_6H_4
d	6-NO_2	4-$NO_2C_6H_4$

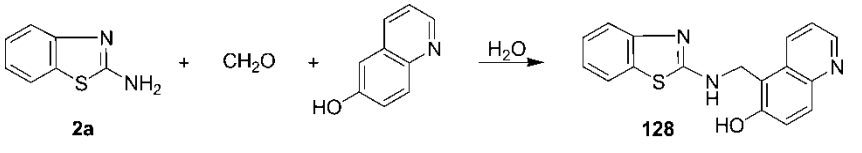
Scheme 70.

4.8. *Mannich reaction*

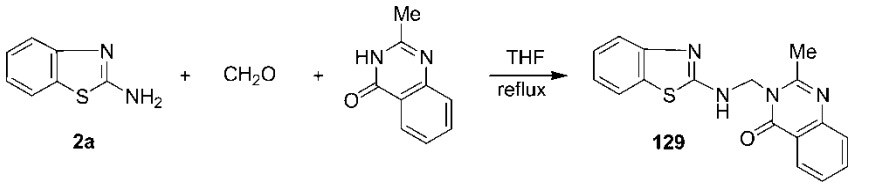
The three components condensation reactions of **2a**, formaldehyde and 6-hydroxyquinoline in water afforded the Mannich adduct 5-(2'-aminobenzothiazolomethyl)-6-hydroxyquinoline **128** (Scheme 71) (*98*).

Condensation of **2a** with formaldehyde and 2-methyl-3*H*-quinazolin-4-one in refluxing THF yielded Mannich base of 2-methyl-3-(2-benzothiazolyl-aminomethyl)quinazolin-4-one **129**. Compound **129** showed antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain (Scheme 72) (*99*).

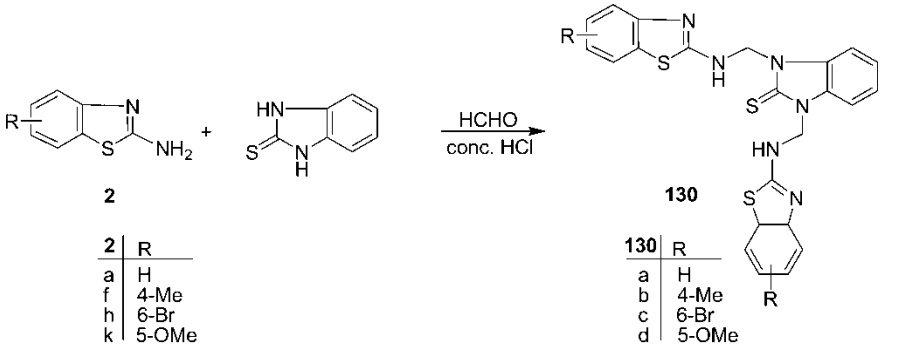
The double Mannich reaction of 2-aminobenzothiazoles **2** with benzimidazoline-2-thione and formaldehyde in the presence of a catalytic amount of concentrated HCl afforded 1,3-*bis*[(substituted aminobenzothiazolyl)methyl] benzimidazoline-2-thione **130** (Scheme 73).



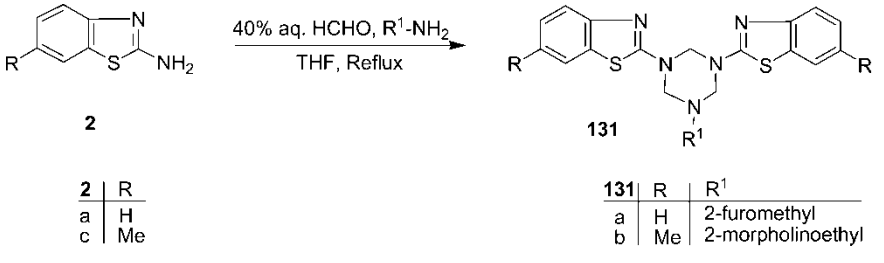
Scheme 71.



Scheme 72.



Scheme 73.



Scheme 74.

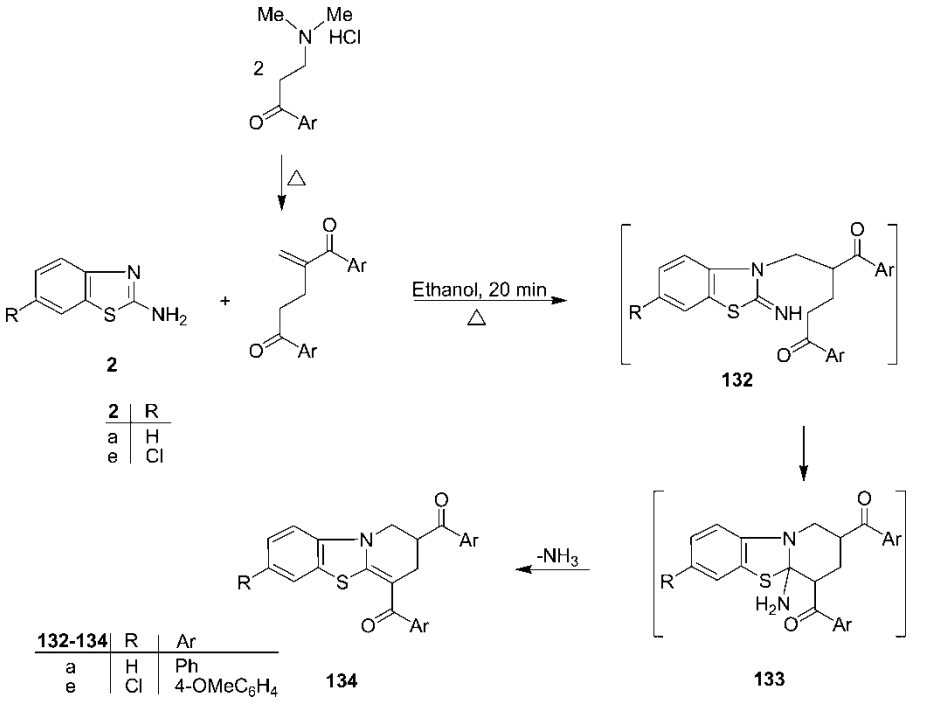
Compound **130** showed antiviral activity against tobacco mosaic virus and cucumber green mottle mosaic virus both in *vivo* and *in vitro* and also showed antibacterial activity (*100*, *101*).

Cyclocondensation of 2-aminobenzothiazoles **2** with 40% formaline and aliphatic primary amines in THF resulted in the formation of 1,3-di(benzothiazol-2-yl)-1,3,5-triazinanes **131** in good yields (Scheme 74) (*102*).

2-Aminobenzothiazoles **2** were treated with two equivalents of β-(dimethylamino)propiophenone hydrochlorides in refluxing ethanol to produce 2,4-diaroyl-2,3-dihydro-1*H*-pyrido[2,1-*b*][1,3]benzothiazoles **134** in 50% yield via the non-isolable intermediates **132** and **133** (Scheme 75) (*103*).

4.9. *Reaction with carbon disulphide (CS_2)*

Treatment of 2-aminobenzothiazole **2a** with carbon disulfide in DMF with one equivalent of base furnished the mono salt **135**, whereas the dibasic salt **136** was obtained with two equivalents of the base. Alkylation of thiocarbamate derivatives **135** and **136** with methyl iodide afforded methyl thiocarbamates **137** and **138**, respectively.



Scheme 75.

Heating compound **137** with **2a** gave *N*,*N*-*bis*(benzothiazol-2-yl)thiourea **139**. Oxidation of **139** with *N*-bromosuccinimide (NBS) in CH_2Cl_2 afforded tetraazathiapentalene **140** (Scheme 76) (*104*).

Dithiomethylcarboimidate benzothiazole **138** was obtained via the reaction of 2-aminobenzothiazole **2a** with carbon disulfide in a basic medium followed by addition of two equivalents of methyl iodide. Reaction of **138** with *o*-phenylene diamine in refluxing DMF furnished the benzimidazole derivative **141** (Scheme 77) (*105*, *106*).

4.10. *Coupling reactions*

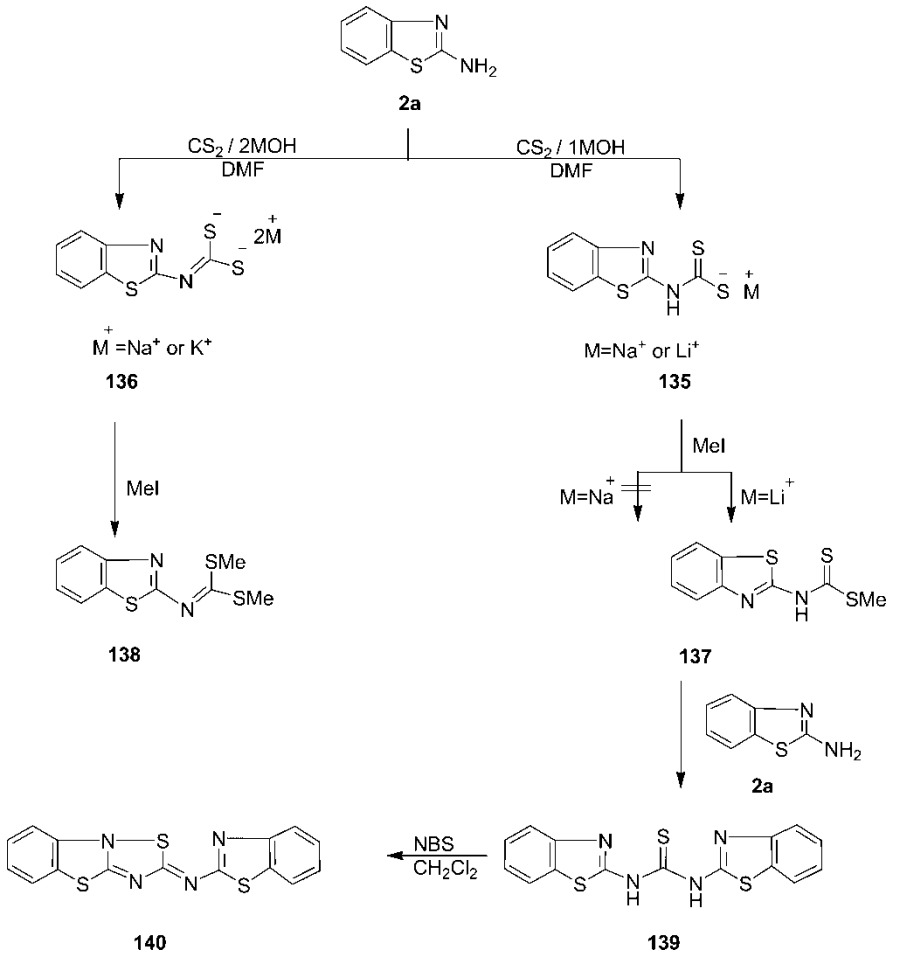
Diazotization of 2-aminobenzothiazole **2a** followed by hydrolysis with hypophosphoric acid afforded benzothiazole **142**, which underwent reductive cleavage to give *o*-aminothiophenol **143** when treated with hydrazine hydrate (Scheme 78) (*107*).

Diazotization of 2-aminobenzothiazoles **2** with nitrosyl sulfuric acid gave benzothiazole diazonium sulfate **144**, which coupled with *N*,*N*-disubstituted aniline in acetic acid to give *p*-*N*,*N*-disubstituted phenyl azobenzothiazoles **145** (Scheme 79) (*108*, *109*).

2-(2'-Benzothiazolylazo)-5-aminobenzoic acid **146** was obtained via coupling of benzothiazole diazonium salt with 2,5-diaminobenzoic acid in acetic acid (Scheme 80) (*110*).

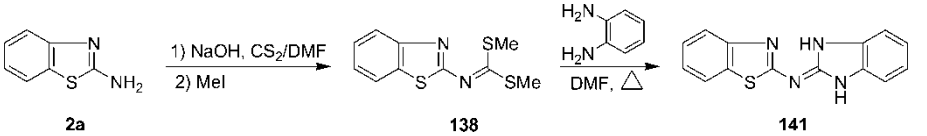
Weixing *et al.* have reported that the coupling reaction of benzothiazole diazonium salt with 3-hydroxy-2-naphthoic acid furnished 1-(2-benzothiazolylazo)-2-hydroxy-3-naphthoic acid **147** (Scheme 81) (*111*).

Coupling of *m*-phenylene bisdiazonium salt with two equivalent amounts of **2a** furnished 1,3-*bis*(benzothiazolylaminoazo)benzene **148**. Compound **148** can be used as a fluorescent reagent to detect Cu(II) in basic media containing β-CD or as a chromogenic agent of metal ions (Scheme 82) (*112*).

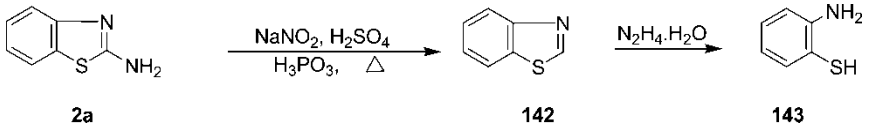


Scheme 76.

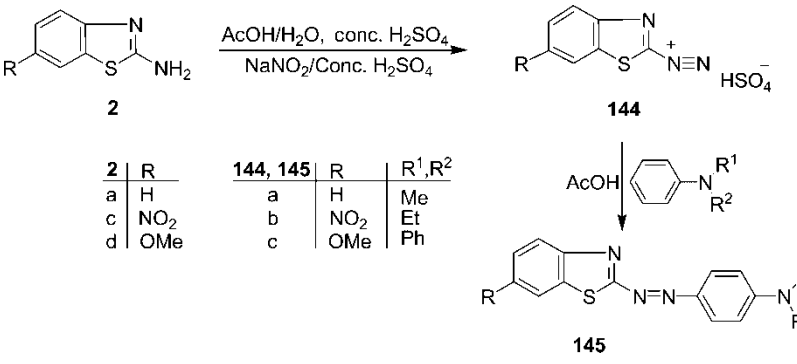
Diazotization of 2-aminobenzothiazole **2a** with nitrosyl sulfuric acid furnished the corresponding diazonium salt, which coupled with 3,3′,5,5′-tetramethylbenzidine in aqueous HCl (27%) to produce 4,4′-*bis*(2-benzothiazolyldiazeneamino)-3,3′,5,5′-tetramethylbiphenyl **149** (Scheme 83) (*113*).



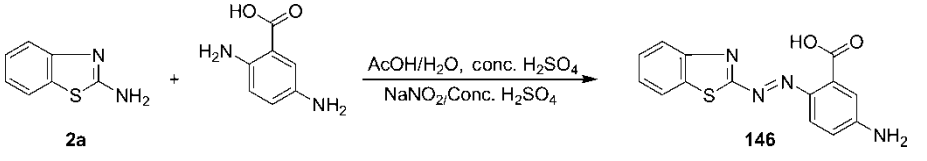
Scheme 77.



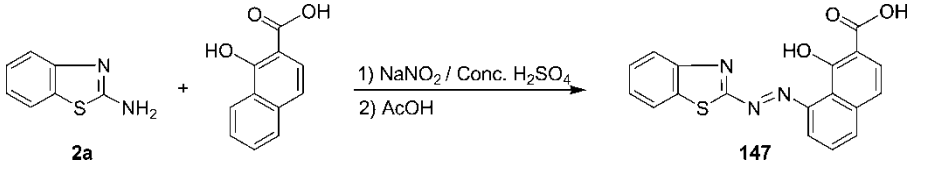
Scheme 78.



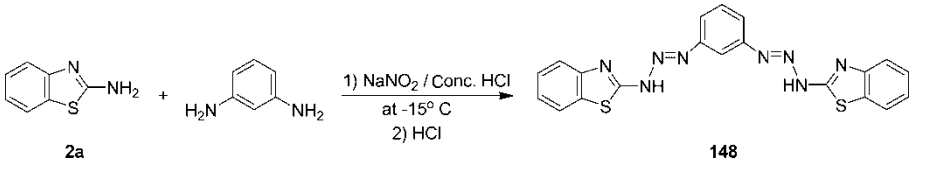
Scheme 79.



Scheme 80.



Scheme 81.



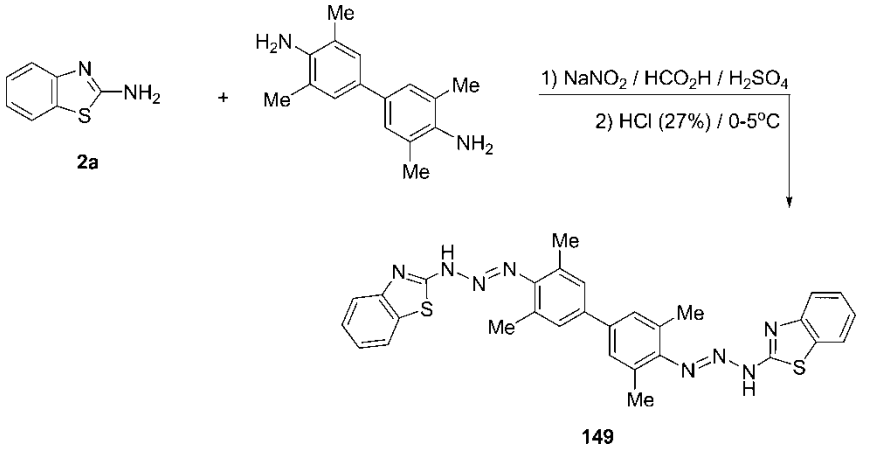
Scheme 82.

4.11. *Miscellaneous reactions*

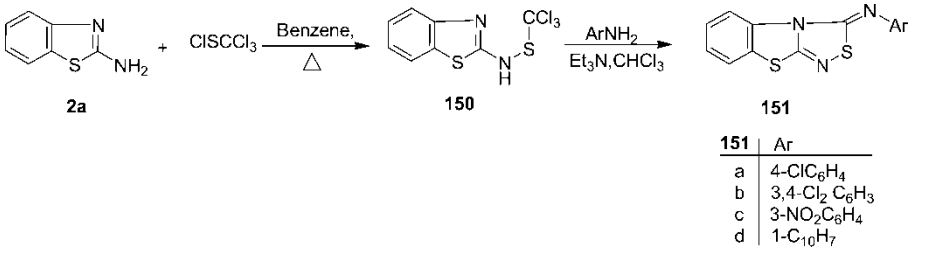
Compound **2a** reacted with 1,1,1-trichloromethanesulfenyl chloride yielding 1,1,1-trichloro-*N*-(2-benzothiazolyl)methane sulfenamide **150**. Cyclization of **150** with aromatic amines in chloroform containing a catalytic amount of triethylamine furnished 1,2,4-thiazolo[3,4-*b*]benzothiazole derivatives **151** (Scheme 84) (*114*).

N,*N*-Dimethyl-*N*′-chlorosulfonylchloroformamidine was treated with 2-amino-benzothiazole **2a** in refluxing xylene to give a mixture of [1,2,4,6]thiatriazino[3,2-*b*]benzothiazole dioxide **152** and [1,2,4,6]thiatriazino[3,4-*b*]benzothiazole dioxide **153** (Scheme 85) (*115*).

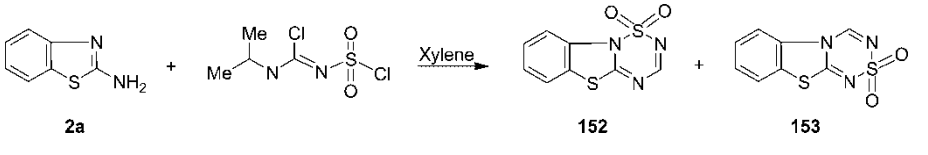
Compound **154** was synthesized by the reaction of 2-thiomethyl-3-cyano-8-methylpyrimido [2,1-*b*]benzothiazol-4-one with 2-aminobenzothiazole **2a** in refluxing benzene (Scheme 86) (*116*).



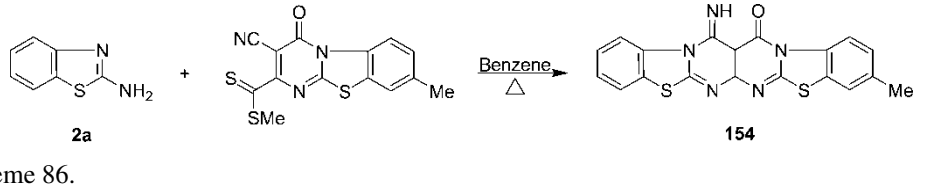
Scheme 83.



Scheme 84.

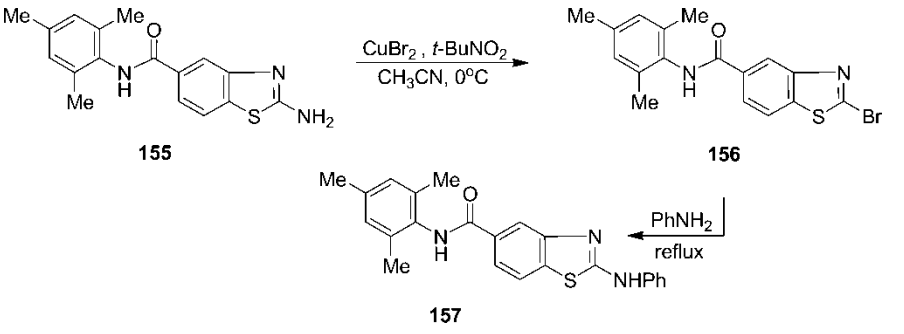


Scheme 85.



Scheme 86.

Treatment of 2-aminobenzothiazole-6-carboxamides **155** with two equivalents of both copper (Π) bromide and *tert*-butyl nitrite in acetonitrile at 0° C led to the formation of carboxamides **156**. Reaction of **156** with aniline under reflux afforded the secondary amine **157** (Scheme 87) (*117*).



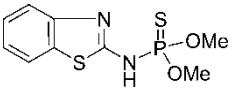
155 **156** **157**

Scheme 87.

5. 2-Aminobenzothiazoles in pharmaceutical and industrial chemistry

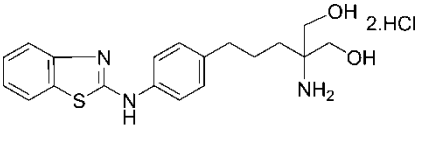
The synthesis and reaction of 2-aminobenzothiazoles have been a topic of interest for research for over a century because they possess a variety of important biological activities and have been developed for the treatment of diabetes, muscle relaxants, analgesia, tuberculosis, epilepsy, inflammation and viral infection (*118*).

Dimethyl-benzothiazol-2-ylphosphoramidothioate **158** has some inhibitory effect against human laryngocarcinoma (squamous) (*119*).



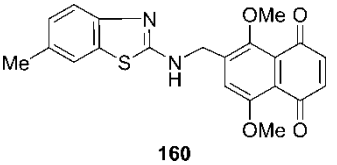
158

2-Amino-2-[3-[4-(benzothiazol-2-ylamino)phenyl]propyl]-1,3-propanediol dihydrochloride **159** at 100 mg/kg showed 81% inhibition against DNFB-induced delayed hypersensitivity in mice (*120*).



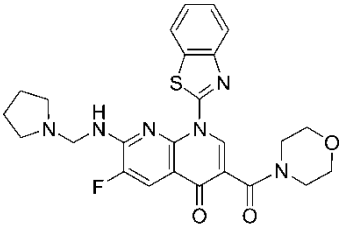
159

2-[(6-Methyl-1,3-benzothiazol-2-yl)aminomethyl] -5,8-dimethoxy-1,4-naphtho-quinone **160** showed high activity against the solid cancer cell line SNU-1. It also showed better antitumor activity in mice bearing S-180 cells in the peritoneal cavity (*121*).



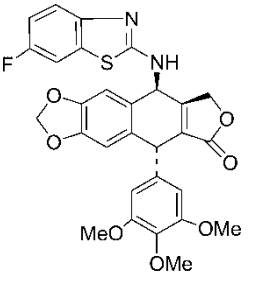
160

1-(Benzothiazol-2-yl)-6-fluoro-3-(morpholine-4-carbonyl)-7-(pyrrolidin-1-ylmethyl- amino)-1,8-naphthyridin-4(1*H*)-one **161** was used as an antiproliferative agent (*122*).



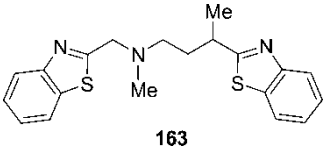
161

The podophyllotoxin derivative of 2-aminobenzothiazole **162** has been evaluated for its cytotoxicity against six human cancer cell lines, with some representatives showing promising anticancer activity (*123*).



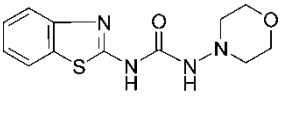
162

Benzothiazole dimer derivative **163** was synthesized and evaluated by *in vitro* competition assay using [125I] TZDM for their specific binding affinities to Aβ fibrils. In particular, compound **163** showed the most excellent binding affinity ($K_i = 0.53$ nM), compared with PIB ($K_i = 0.77$ nM) for benzothiazole binding sites of Aβ1-42 fibrils. This result suggests a possibility of a potential AD diagnostic probe for detection of Aβ fibrils (*124*).



163

*N*1-(Benzothiazol-2-yl)-*N*3-morpholinourea **164** have the highest cytotoxic activity and showed high antimicrobial activity against *Mycobacterium tuberculosis* H37Rv, *E. coli*, *S. aureus* and *C. albicans.* Again, compound **164** showed the best activity against *M. tuberculosis* H37Rv (*125*).



164

6. Conclusion

2-Aminobenzothiazoles are easily available and offer countless modifications by numerous reaction modes in various positions due to their high reactivity. This has been comprehensively documented. Apart from the synthetic interest, the known and expected biological or medicinal activities of the numerous derivatives deserve particular mention. The field is far from being exhausted in all of its subdivisions, and many new developments and uses await exploration. In fact, more recent work used some of the title compounds for reactions both at the amino function and at C-2 of the 1,3-thiazole moiety, and new azo dyes with favorable dyeing properties have already been synthesized (*11*).

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