Recent Developments and Biological Activities of 2-Aminothiazole Derivatives

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Abstract

Aminothiazole nuclei and their various derivatives have been long used as precursors for the synthesis of biologically active molecules. As a typical heterocyclic amine, 2-aminothiazole is a cornerstone for the synthesis of many compounds, including sulfur drugs, biocides, fungicides, various types of dyes for synthetic fibers and chemical reaction accelerators and as intermediates in the synthesis of antibiotics, where a large number of 2-aminothiazoles have been substituted with different groups for various pharmaceutical purposes, besides their activity as corrosion inhibitors for mild steel protection as well. The synthetic utility of 2-amino-4-substituted-thiazoles, their reactions and biological activities have been surveyed and are presented in this review.

Keywords: 2-aminothiazoles, azo compounds, biological activities, corrosion, synthetic fibers, inhibitors.

1. Introduction

The monoazo heterocyclic compounds containing sulphur and/or nitrogen atoms are of widespread use as building blocks in chemistry, where they are known as biologically active compounds with a broad range of activity, and textile dyes as well.^{1–3} As a typical heterocyclic amine, 2-aminothiazole is the starting point for the synthesis of many compounds, including sulfur drugs, biocides, fungicides, dyes and chemical reaction accelerators and as intermediates in the synthesis of antibiotics, where a large number of 2-aminothiazoles have been substituted with different groups for pharmaceutical purposes,^{4–6} and are also used in the syntheses of various types of dyes for synthetic fibers,^{7–15} beside their activity as corrosion inhibitors for mild steel protection,^{16,17} corrosion inhibitors for copper¹⁸ and as an ionophore in the construction of a lutetium(III)-selective membrane sensor.¹⁹ These derivatives continue to attract the attention of biologists because of their widespread use in the treatment of the biological systems. For instance, many papers have been published on the use of these compounds exhibiting antimicrobial,^{20–22} antifungal and anti-inflammatory activity,²³ anesthetic activity,^{4,24} as antiviral drugs,⁶ anti-leukemic agents,²⁵ antiproliferatives (cytostatic and cytotoxic) with activity against a panel of cell lines (HeLa, L929, HT-29 and T47D),²⁶ as active agents against some enzymes involved in eicosanoid metabolism (5-, 12-, 15-lipoxygenase (LO),

cyclooxygenase-1 and -2 (COX-1 and COX-2)),²⁷ inhibitors anti-TCR antibody induced IL-2 production in mice *in vivo* and reduced lung inflammation in a mouse model of ovalbumin induced allergy/asthma,²⁸ inhibitors for *Mycobacterium tuberculosis* (Mtb, H37Rv and MS, GyrB),^{29,30} as vascular adhesion protein-1 inhibitors (VAP-1),^{31,32} inhibitors of Cdc7 kinase activity in cancer cells,³³ inhibitors of nerve growth factor receptor TrkA,³⁴ inhibitors of p38 α mitogen-activated protein kinase (p38 α MAPK).³⁵ They can also bind to CT-DNA by the intercalative and electrostatic binding mode.³⁶ A clubbed triazolyl thiazole series of cdk5/p25 inhibitors were reported as potentially useful compounds for the possible treatments for Alzheimer's disease.³⁷ Due to its enormous industrial and biological importance, the studies of tautomeric equilibria of 2-aminothiazole and its derivatives have been considered as a hot topic for the scientists.³⁸ The amino-imino tautomeric equilibrium of the isolated, mono-, di- and trihydrate configurations and dimer of 2-aminothiazole and the effects of hydration or self-assistance on the transition state structures corresponding to proton transfer from the amino to imino tautomers, were theoretically and experimentally explored in the gas phase as well as in the solution, which directly affected the orientation of substitution and the product assignments when they reacted with the other compounds.^{39–43} Several spectroscopic investigations, *e.g.* infrared (IR), ultraviolet (UV), density functional theoretical calculations (DFT), Raman spectra (RS),

surface-enhanced Raman spectra (SERS) and nuclear magnetic resonance spectra (NMR), indicated that the 2-aminothiazole derivatives are existing in solution preferentially in the amino tautomer, based on the analysis of their reactivity data.^{44–47} Additionally, the pK_{BH^+} values of 2-aminothiazole and a number of its derivatives showed that these molecules generally exist in the amino aromatic form and are protonated at the aza-nitrogen.⁴⁸

2. Synthesis of 2-Amino-4-substituted-1,3-thiazoles

2. 1. From Ketones and Haloketones

Many 2-amino-4-substituted thiazoles are generally synthesized by Hantzsch thiazole synthesis from α -haloketones and thioureas (or thioamides) in polar solvents.⁴⁹

2. 1. 1. Using Halogen

Ketones of the type **1** react directly with one mol of halogen and two mols of thiourea to give 2-amino halogenated derivatives of the 4-substituted-1,3-thiazole nucleus **2** in excellent yield.^{50,51}

2. 1. 2. Using Oxidizing Agents

An oxidative process can accomplish the formation of 2-amino-4-substituted-1,3-thiazoles **3** by the reaction of the ketone of the type **1** with thiourea, using a variety of oxidizing agents, namely sulfuryl chloride, chlorosulfonic acid, thionyl chloride, sulfur monochloride, sulfur trioxide, sulfuric acid, nitric acid and sulfur.⁵² Oxidation of ketones **1** with thallium(III)-*p*-tosylsulphonate (TTS) in refluxing acetonitrile or dioxane followed by the addition of thiourea, yielded the 2-amino-4-substituted-1,3-thiazoles **3** as free bases in good yields upon basification with aqueous potassium carbonate.⁵³

Reaction of the ketones of the type **1** with thiourea in the presence of *N*-bromosuccinimide (NBS) and benzoyl peroxide as radical initiator furnished 2-amino-4-substituted-1,3-thiazoles of the type **3**.⁵³

R = (un)substituted-3-coumarinyl, (un)substituted phenyl

A facile synthesis for the 2-amino-4-substituted-1,3-thiazoles **3** (R = 2-furyl) through a very simple and eco-friendly methodology was reported. Stirring of ketones **1** (R = 2-furyl) with hydroxyl-(tosyloxy)-iodobenzene (HTIB) in dichloromethane at room temperature, provided 2-tosyloxyacetylfuran which underwent smooth transformation with thiourea affording the target compounds **3** in excellent yield.⁵⁴

R = 2-furyl

2. 1. 3. Using Iodine Catalyst

The synthesis of 2-amino-4-substituted-thiazole derivatives **3** has been carried out by treatment of ketones **1** with thiourea and iodine as the catalyst. The synthesized derivatives exhibited promising antiproliferative effect through translational VEGF-A inhibition.^{55–58}

R = C₆H₅, C₆H₄Cl-*p*, C₆H₄OMe-*p*, 4-morpholinophenyl

2. 1. 4. Using Sodium Fluoride Catalyst

Sodium fluoride was found to be a simple, mild and efficient catalyst in the synthesis of 2,4-disubstituted-1,3-thiazoles **3** obtained by condensation reaction of α -haloketones **4** with thiourea.^{24,59–65}

2. 1. 5. From Amidine Derivatives

Reaction of ketones **1** with formamidine disulfide dihydrobromide afforded the corresponding hydrobromide salt of 2-amino-4-substituted-1,3-thiazoles **2**.⁶⁶

Subsequent treatment of the amidino-thioureas and iodothiureas (R₁ = Aryl; R₂ = ArCH₂S), obtained from the condensation reactions of mixtures of amidines, thiuronium salts and isothiocyanates, with α-haloketone 4 led to the formation of 1,3-thiazoles 5 via base-catalysed ring closure process in the presence of 1,8-diazabicyclo [5.4.0]-7-undecene (DBU).^{67,68}

2. 1. 6. From Thiosemicarbazones

Cyclization reaction between the aryl and heteroarylthiosemicarbazones 6 with aliphatic α-haloketones 4 and/or diethyl acetylenedicarboxylate 7, afforded the 2-(2-hydrazinyl)thiazole derivatives 8 with a wide range of substitutions at positions 2-, 4- and 5- and furothiazolones 9 respectively. These compounds exhibited antibacterial activity towards two Gram negative (*Proteus mirabilis* and *Serratia marcescens*) and two Gram positive (*Staphylococcus aureus* and *Bacillus cereus*) bacteria, anti-inflammatory activity, inhibition of the carrageenin-induced oedema, and are considered as antimalarial candidates through inhibition of PfENR protein pathway to kill *Plasmodium falciparum*.^{57,69}

2. 1. 7. From Various Thiourea Derivatives

Cyclization reaction of haloketones 4 and/or dihaloketones 13 with various thiourea derivatives afforded the 2-amino-4-substituted-thiazole derivatives 10–12,

where upon a [5,5]-sigmatropic shift of *N*-phenyl-*N'*-(2-thiazolyl)hydrazines and *N,N'*-bis(2-thiazolyl)hydrazines an acid-catalyzed, benzidine-type rearrangements yielded 2-amino-5-(*p*-aminophenyl)thiazoles 12 and 5,5'-bis(2-aminothiazole)derivatives 14, respectively.⁷⁰

2. 2. From Various Acetophenone Derivatives

Diazoacetophenone 15 was reacted with thiourea to furnish 2-amino-4-phenyl thiazole 3. The reaction has been affected either by heating an intimate mixture of the reactants on the steam bath, or by refluxing an ethanol solution of the reaction components.⁷¹

Bromoacetophenoneoxime 16 and 2-bromo-1-phenylethylidenemalononitrile 17 were reacted with thiourea to give 2-amino-4-phenyl thiazole 3. The ring closure has been accompanied by the elimination of hydroxylamine⁷² or malononitrile,⁷³ respectively.

Cyclocondensation of bromoacetophenone with 2-furoyl thioamide derivatives in diluted acetic acid, gave

a series of 2-amino-5-benzoyl-4-(2-furyl)thiazoles **18**. The synthesized derivatives were screened for *in vitro* anti-tubercular activities against *Mycobacterium tuberculosis* H37Rv using the Microplate Alamar Blue Assay (MABA), for antibacterial activities with agar dilution method against clinical *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pneumoniae* and penicillin-resistant *Streptococcus pneumoniae*,⁷⁴ and exhibited excellent affinity for A_{2A} receptor as well.⁷⁵

Reaction of haloketophenoxybenzene derivative **19** with thiourea gave the 2-amino-5-[4-(4'-nitrophenoxy)phenyl]thiazole (APPT) **20**. Additionally, a series of novel polyimides were prepared by polycondensation of APPT with various aromatic dianhydrides *via* one-step process and multi heterocyclic Schiff bases were also prepared as anticancer agents against human breast, colon and prostate cell lines. Also, the resulting polyimides have high *T_g* values, excellent thermal and thermo-oxidative stability, as well as good solubility in organic solvents. They had good mechanical properties with low dielectric constants, which are preferred in microelectronics applications.^{58,76–79}

R = 2-,4-nitrophenoxyl, imidazolyl

The reaction of bromomethoxyacetophenone derivatives **19** with potassium thiocyanate in dry benzene afforded 2-thiocyanoacetophenones **20**, which underwent cyclization in the presence of alumina-supported ammonium acetate to give 2-aminothiazole analogues **21** as described by Kodomari *et al.* The synthesized compounds exhibited potent and selective human adenosine A3 receptor antagonists.⁸⁰

2. 3. From Aldehydes

A tandem Aza-Friedel–Crafts reaction/Hantzsch cyclization is described to access various polysubstituted 2-amino-1,3-thiazoles **24** from condensation of thiourea with electron-rich (hetero)aromatic rings **22**, aldehydes **23** and α-chloroketones **4**.⁸¹

Ar = fused aryl and/or heteraryl rings

R₁ = aliphatic and aromatic substrates

R₂ = aliphatic and aromatic substrates

2. 4. From Chroman Derivatives

Instead of the expected product 2-amino-4-(2,2'-dimethyl-7'-methoxychroman-6'-yl)-5-bromothiazole **27**, the product obtained by the condensation of 6-dibromoacetyl-2,2-dimethyl-7-methoxychroman **25** with thiourea was 2-amino-4-(2,2'-dimethyl-7'-methoxychroman-6'-yl)thiazole **28**. This product could be also obtained by the condensation of 6-bromoacetyl-2,2-dimethyl-7-methoxychroman **26** with thiourea. The products obtained were physically applied to a polyurethane varnish as biocide additives. Their anti-microbial activity, against the targeted microorganisms, increases with an increase in the levels of the biocide additive.^{82,83}

2. 5. From Amines

Action of primary amines on halo-thiocyanato alkenes afforded the 2-amino-1,3-thiazoles, the cyclization taking place with a migration of the sulphur atom on the C=C bond; thus 2-cyclohexylamino-5-propyl-1,3-thiazole **31** was obtained from the condensation of cyclohexylamine **29** and (Z)-bromo-1-thiocyanato-1-pentene **30**.⁸⁴

2. 6. From Imine Derivatives

Halo-methyl ketimines **32** (X = Br, Cl) have been condensed with thiourea in methanol to afford 2-amino-4-substituted thiazoles **3**, whereas the *N*-isopropyl moiety had been lost during the condensation of the halo-ketimines.⁸⁵

R = *t*-Bu, Ph, 4-MeC₆H₄

2. 7. From Nitriles

A series of 2-(2,4-disubstituted-thiazole-5-yl)-3-aryl-3*H*-quinazoline-4-one derivatives **34** were designed and synthesized by reaction of active α -halo derivative **33** of substituted quinazoline with acetonitrile, where the products exhibited selective and dual inhibition against NF-KB, AP-1 mediated transcriptional activation and significant efficiency in the *in vivo* models of inflammation.⁸⁶

R₁ = methyl, phenyl, *p*-chlorophenyl, *p*-CH₃, phenyl
R₂ = CH₃, Ph, NH₂
R₃ = H, Cl, CH₃, OCH₃, COCH₃

Enamines of the type **35** were reacted with elementary sulphur and cyanamide at room temperature without catalyst to give the corresponding 2-amino-4-substituted thiazoles **3**.⁸⁷

R = Ph

The condensation of thiourea and halogeno-nitriles to form salts of 2,4-diaminothiazole is a general reaction, which is, however, limited by the inactivity of the halogens in some substituted nitriles, *e.g.* chloroacetonitrile **36** reacts with thiourea in cold ethanol to give the halogenated salt of 2-halogenated amino-4-substituted thiazole derivative **2**.⁸⁸

R = NH₂; X = Cl

2. 8. From Alkynes

The formation of 2-amino-4-substituted thiazoles **3** (R = C₄H₉, C₆H₅) in a single reaction step from alkynyl(phenyl) iodoniummesylates **37** and thiourea can be rationalized mechanistically by a thiophilic attack of the hypervalent iodine atom on the sulphur atom of the thiocarbonyl group.⁸⁹

2. 9. From Esters

Condensation reaction of bromo ester compound **38** and thiourea in ethanol under reflux afforded the corresponding 2-amino-4-substituted thiazole **3** (R = COOEt), where the prepared compound was a precursor for the synthesis of antiproliferative active compounds in a panel of lung cancer cell lines.⁹⁰

R = COOEt

3. Reactions and Chemistry

3. 1. Reactions Involving the Amino Group

3. 1. 1. Acylation by Carboxylic Acids

2-Amino-4-substituted thiazoles **3** have been condensed with 10-undecenoic acid in the presence of phos-

phorous oxychloride to afford the corresponding acid amide derivatives **39**.⁵³

R = Me, Ph, 4-MeOC₆H₄, 4-Cl-C₆H₄

The coumarin carboxamide derivatives **40** have been prepared from the corresponding coumarincarboxylic acid and 2-amino-4-substituted thiazoles **3**. The compounds have been tested for anti-fungal and antibacterial activity.⁹¹

R = Ph

Condensation reaction of 2-aminothiazole derivatives with various types of carbonyl compounds afforded different thiazols, where 2-amino-4,5-disubstituted thiazoles **3** (R = substituted phenyl; R₁ = H, CH₃) condensed with 4-methoxy-4-oxobutanoic acid, 2-chloroacetyl chloride followed by mercaptoacetic acid and/or 4-chlorobutanoyl chloride to form the thiazole based derivatives **41**, **42** and **43**, respectively. The products were considered as lipid carriers having a significant role in the metabolic syndrome in A-FABP/ap2-deficient mice, including type 2 diabetes, atherosclerosis and anticonvulsant gradients.^{92,93}

R = H, CH₃, substituted phenyl
R₁ = H, CH₃, COOEt

The 2-amino-4-substituted thiazole tetrazole derivatives **44** have been prepared by the treatment of 2-amino-4-substituted thiazoles **3** with a suspension of dipotassium-1*H*-tetrazole-5-carboxylate in acetonitrile containing pyridine. Compounds **44** exhibited inhibition of anti-passive cutaneous anaphylaxis in rats.⁹⁴

R = 4-MeC₆H₄

Imidazo[2,1-*b*]thiazoles **45** and **46** were synthesized through the reaction of 2-aminothiazoles **3** with different acid derivatives. The study of the synthesized compounds indicated a high degree of selectivity for inhibition of RSK2 compared to a spectrum of other related kinases, resulting in selective inhibition of the MCF-7 breast tumor cell line, as well as selective inhibition of the biomarker GSK3.⁹⁵

3. 1. 2. Acylation by Acid Anhydrides

Depending on the reaction conditions, 2-amino-4-substituted thiazoles **3** underwent acylation by acid anhydrides, *e.g.* acetic anhydride, propionic anhydride and butyric anhydride, to give the corresponding 3-acyl-2-acylimino-2,3-dihydrothiazoles **47** (R = Ph; R₁ = 4-NO₂; Ar = 4-(Et₂O)₂POCH₂C₆H₄, n = 1, 2, 3) or *N*-(2-thiazolyl) amides **48** (R = Ph, substituted phenyl, β-naphthyl, 2-thienyl; R₁ = H; n = 1, 2, 3). The target derivatives were found to be useful for the treatment of hyperlipidemia, cataracts, diabetes and as antikinoplastid parasite compounds.^{2,96,97}

pared thiazole-amide skeleton exhibited antibacterial activity.⁹⁸

The acylamino derivatives **50** ($R = \text{Me, Ph; } R_1 = \text{H, Cl, Me, NO}_2$), had been prepared by the reaction of phenoxyacetyl chloride derivatives with 2-amino-4-substituted thiazoles **3** and tested in the rat passive cutaneous anaphylaxis (PCA) assay by oral administration.^{53,99}

3. 1. 4. Acylation by Chloroacetyl Chlorides

2-Amino-4-substituted thiazoles **3** had been reacted with chloroacetyl chlorides to give the corresponding 2-(chloroacetyl-amino)-4-substituted-thiazoles **51** showing significant antifungal activity against *Candida albicans*.^{24,100–102} Microwave heating technique was used to prepare optically active thiazole-bearing diamine derivatives **51** ($R = 3,5\text{-(NH}_2)_2\text{C}_6\text{H}_4$).^{103,104}

3. 1. 5. Reaction with Aryl Sulfonyl Chlorides

2-Amino-4-substituted thiazoles **3** were reacted with the appropriate sulfonyl chlorides in pyridine to furnish a series of 2-sulfonamido-thiazoles ($R = \text{Me, Ph, substituted phenyl; Ar} = \text{Ph, substituted phenyl, 4-acetyl-amino-1-naphthyl, 2-arylnaphth[1,2-*d*]oxazol-5-yl}$) **52**. The compounds **52** had been evaluated as inhibitors of rat kidney kynurenine 3-hydroxylase using L-[3-³H] kynurenine as the substrate.^{105,106}

2-Amino-4-substituted thiazoles **3** were reacted with chloromethanesulfonyl chloride to yield the corresponding C-chloro-N-(2-thiazolyl)methane sulfonamides **53**.¹⁰⁷

Sulfanilamidothiazoles **54** ($R = \text{C}_6\text{H}_5, 4\text{-BrC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 2,5\text{-(MeO)}_2\text{C}_6\text{H}_3, 2,4\text{-Cl}_2\text{-C}_6\text{H}_3, 2\text{-naphthyl}$) were synthesized by acylation of 2-amino-4-substituted thiazoles **3** with 4-acetylaminobenzenesulfonyl chloride followed by deacetylation by heating in aqueous NaOH or 80% CH_3COOH .¹⁰⁸

3. 1. 6. Reaction with Alkyl Halides

The 2-(3-aryloxy/arylpropyl)amino-thiazoles **55** ($R = \text{Ph; } R_1 = 2\text{-thienylcarbonyl, PhCO, 4-PhC}_6\text{H}_4$) had been synthesized from the appropriate 3-aryl/arylpropyl chlorides and 2-amino-4-substituted thiazole **3**.¹⁰⁹

3. 1. 7. Reaction with Chloroxamates

Thiazolyloxamates of the structure **56** ($R = \text{Ph, substituted phenyl, biphenyl, cyclohexylphenyl, naphthyl, 2-pyridylmethyl, pentyl; } R_1 = \text{lower alkyl, PhCH}_2$) had been prepared from 2-amino-4-substituted thiazoles **3** by their reaction with alkyl oxalyl chlorides. Compounds **56** were screened for their antiallergic activity in the rat passive cutaneous-anaphylaxis assay.^{53,109–111}

3. 1. 8. Mannich Reaction

Mannich reaction is known by its occurrence at aromatic amines, aldehydes, and 8-hydroxyquinolines giving the biologically active 7-substituted-8-hydroxyquinoline derivatives. Several researchers have extended this reaction to different heterocyclic amines. Thus, 2-amino-4-substituted thiazoles **3** were condensed with benzaldehyde and 8-hydroxyquinoline to give a series of Mannich bases **57**.⁵³

2-Amino-4-phenylthiazole **3** was reacted with 6-hydroxy-4-methylchromen-2-one and formaldehyde in ethanol affording the expected Mannich product 6-hydroxy-4-methyl-5-[(4-phenyl-2-thiazolylamine)-methyl]-chromen-2-one **58**.¹¹²

The reaction of 2-amino-4-substituted thiazoles **3** with 6-hydroxy-4-methylchromen-2-one and/or 7-hydroxy-4-methylchromen-2-one and formaldehyde in acetic acid gave the corresponding chromeno-[1,3]oxazinone **59** and/or **60**, respectively.¹¹²

3. 1. 9. Reaction with Aldehydes

2-Amino-4-substituted thiazoles **3** underwent condensation with different aromatic or heterocyclic aldehydes to give the corresponding Schiff's thiazole bases **61**, which were used to develop **fluorescence chemosensors for detection of Al^{3+} ions** at low concentration range.^{113–118}

3. 1. 10. Reaction with Hydrazonoyl Chlorides

N-(4-(Pyrazol-4-yl)thiazol-2-yl)-*N'*-phenylthiourea derivative **62** was synthesized and then treated with a variety of hydrazonoyl chlorides under basic conditions to afford the corresponding 2-(4-(pyrazol-4-yl)thiazol-2-ylimino)-1,3,4-thiadiazole derivatives **63**. Most of the synthe-

sized compounds were tested for anticancer activity against human hepatocellular carcinoma HepG2, human breast cancer MCF-7 and human lung cancer A549.¹¹⁹

3. 1. 11. Reaction with 3,1-Benzoxazin-4-ones

Condensation of 2-amino-4-substituted thiazoles **3** with substituted 3,1-benzoxazin-4-ones in dry pyridine gave the corresponding thiazolylquinazolones **65** (R = Ph, substituted phenyl, Et, Me₂CHCH₂, thienyl; R₁ = H, Br; R₂ = Me, Ph). The antimicrobial activities of these compounds against a variety of microbes have been determined.¹²⁰

3. 1. 12. Reaction with Nitriles

The 2-amino-4-substituted thiazoles **3** upon reaction with aryl or alkyl isocyanates gave *N*-aryl/alkyl-*N'*-(2-thiazolyl)ureas **66** (R = Ph, 2-pyridyl; R = butyl, cyclohexyl, Ph, 4-ClC₆H₄, 4-MeOC₆H₄, 3,5-(MeO)₂C₆H₃, PhCH=CH; X = O).^{121–123} Also a number of *N*-substituted-*N'*-(4-aryl-2-thiazolyl) thiocarbamides **66** (R = Ph, substituted phenyl; R₁ = Et, PhCH₂, Ph, substituted phenyl, tetra-*O*-acetyl-β-D-glucopyranosyl; X = S) had been similarly synthesized as antitubercular compounds.^{124–127}

A series of aroylurea and/or thiourea derivatives **67** had been prepared by the reaction of 2-amino-4-substitut-

ed thiazoles **3** with aroylisocyanate and/or isothiocyanate, respectively. These products have also been tested for insecticidal, fungicidal and herbicidal activities, where the 2-amino-4-substituted thiazolyl derivatives **67** (R = CF₃, Me, Ph; Ar = 2-BrC₆H₄, Ph) showed the highest insecticidal activity.^{128,129}

N-(4-Aryl-2-thiazolyl)thioureas **68** (R = C₆H₅, 4-MeOC₆H₄, 4-ClC₆H₄) have been synthesized by the reaction of 2-amino-4-substituted thiazoles **3** with ammonium thiocyanate and benzoyl chloride in dry acetone, followed by alkaline hydrolysis with 10% NaOH. Further condensation of **68** with phenacyl bromides proceeded in ethanol to give the dithiazol-2-ylamines **69** (R = C₆H₅, 4-MeOC₆H₄, 4-ClC₆H₄; Ar = Ph, substituted phenyl). The synthesized compounds exhibited antiinflammatory activity.¹³⁰

2-Amino-4-phenylthiazole **3** has been condensed with 4-(dicyanomethylene)-3-methyl-1-phenyl-2-pyrazolin-5-one to afford the pyrazolinone derivatives **70**.¹³¹

N-(4-Phenyl-2-thiazolyl)acetamide **71** has been obtained from the reaction of 2-amino-4-substituted thiazole **3** with acetonitrile in the presence of anhydrous aluminum chloride.¹³²

2-Amino-4-substituted thiazoles **3** had been reacted with acrylonitrile derivatives (R = alkyl, alkenyl, alkynyl, alkoxy, alkenoxy, alkylsulfonyl, cycloalkyl; R₁ = CN, 1*H*-tetrazol-5-yl)inethoxide-ethanol to give 2-thiazolyl-amino-propenenitriles **72**.⁵³

2-Amino-4-phenylthiazole **3** was reacted with diethyl 3-amino-2-cyano-2-pentendioate to yield the corresponding amide derivatives **73**.¹³³

3. 1. 13. Reaction with Carbon Disulphide and Methyl Iodide

The reaction of 2-amino-4-substituted thiazoles **3** with carbon disulphide and methyl iodide in the presence of concentrated aqueous NaOH gave the corresponding dimethyl-*N*-(4-aryl-2-thiazolyl)dithiocarbonimidates **74**.¹³⁴

3. 1. 14. Reaction with α,β -Unsaturated Compounds

Thiazoline-pyrimidinyl compound **75** was prepared by the condensation of 2-amino-4-phenylthiazole **3** with 2-benzylideneindan-1,3-dione.¹³⁵

3. 1. 15. Miscellaneous Reactions

2-Amino-4-substituted-thiazoles **3** had been readily deaminated using nitric oxide (NO) in the presence of catalytic amount of oxygen to afford the corresponding thiazoles **76**.¹³⁶

N- α -(4-Phenyl-2-thiazolyl)triphenylphosphinimine **77** was simply prepared by the reaction of 2-amino-4-phenyl thiazole **3** with triphenylphosphine (TPP) in the presence of triethylamine (TEA) and carbon tetrachloride (CTC).¹³⁷

N,N'-Bis-(4-phenyl-2-thiazolyl)formamidine **78** was formed as a result of the reaction between 2-amino-4-phenylthiazole **3** with 1,3,5-triazine. The intermediate **78** postulated for this reaction type could be identified in an interception reaction by means of secondary amines. As the prototype, the reaction of piperidine with the intermediate product to form 4-phenyl-*N*-((piperidin-1-yl)methylene)thiazol-2-amine **79** (having antibacterial activity) has been reported.¹³⁸

In the presence of an appropriate acid-binding agent (e.g. piperidine acetate or sodium acetate), 2-amino-4-substituted thiazoles **3** had been reacted with 2,4,6-triarylpyrylium salts *via* pyrylium ring transformation yielding 2,4,6-triaryl-1-(4-phenyl-2-thiazolyl)-pyridinium perchlorates **80**.¹³⁹

Imidazolines **81** have been prepared by the reaction of 2-methylthio-2-imidazoline with 2-amino-4-phenylthiazole **3** and exhibited bactericidal activity.¹⁴⁰

9-(4'-Phenyl-2'-thiazolylamino)acridine derivatives **82** ($R = \text{Ph}$; $R_1 = \text{H}, 3\text{-Cl}, 1\text{-Me}, 3\text{-Me}$) were prepared as fungicides by treatment of 2-amino-4-substituted thiazoles **3** with the corresponding 9-chloroacridines.¹⁴¹

2-Amino-4-substituted thiazoles **3** as nucleophiles have been reacted with 2-phenylimidazo[2,1-*b*]oxadiazole-5,6-dione to give the urea derivatives **83** ($R_1 = 5\text{-phenyl-1,3,4-oxadiazol-2-yl}$).¹⁴²

2-Amino-4-substituted thiazoles **3** have been reacted with 2-phenyl-2-oxazolin-5-one to give the corresponding hippurylaminothiazoles **84**. Ethoxymethylene-2-oxazolin-5-one on the other hand have been reacted with 2-amino-4-substituted thiazoles **3** to give the corresponding 4-(2'-thiazolylaminomethylene)-2-oxazolin-5-ones **85**.¹⁴³

4-(4'-Phenyl-2'-thiazolyl)-1-thia-4-azaspiro[4,5]decan-3-one **86** has been prepared by refluxing equivalent quantities of a mixture of cyclohexanone, mercaptoacetic acid and 2-amino-4-phenylthiazole **3** in benzene or toluene.⁵³

Synthesis of *N*-(4'-aryl-2'-thiazolyl)-2,2-diarylmethines **87** was carried out by acylation of 2-amino-4-substituted thiazoles **3** followed by chlorination of the produced amides with phosphorus pentachloride to form the imidochlorides **88**, which have been condensed with resorcinol in the presence of anhydrous aluminum chloride.⁵³

3. 2. Cyclization Reactions

3. 2. 1. Formation of Thiazolopyrimidin-5-ones

3. 2. 1. 1. Reaction with β -Ketoester

The 3,7-disubstituted-thiazolo[3,2-*a*]pyrimidin-5-ones **89** ($\text{R} = \text{Me}, \text{Ph}, p\text{-MeC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4$; $\text{R}_1 = \text{Me}, \text{Ph}$ and $\text{R} = \text{Me}, \text{Ph}$; $\text{R}_1 = \text{CH}=\text{CHR}_2$; $\text{R}_2 =$ substituted and unsubstituted pyridyl) were obtained from the reaction of 2-amino-4-substituted thiazoles **3** with the corresponding β -ketoester.^{144–146}

3. 2. 1. 2. Reaction with Diethyl

Ethoxymethylenemalonate

2-Amino-4-substituted thiazoles **3** were reacted with diethyl ethoxymethylenemalonate (DEMM) to furnish the corresponding 3-substituted-6-carbethoxy-thiazolo [3,2-*a*]pyrimidin-5-ones **90**.¹⁴⁴

3. 2. 1. 3. Reaction with 2-Acetylbutyrolactone

The reaction of 2-amino-4-substituted thiazoles **3** with 2-acetylbutyrolactone and phosphorus oxychloride gave 6-chloroethyl-7-methylthiazolo[3,2-*a*]pyrimidin-5-ones **91**. The synthesized compounds exhibited increased potency towards CNS SNB-75 and renal UO-31 cancer cell lines.¹⁴⁷

$\text{R} = \text{Ph}$ optionally substituted by 1-2 of halo, C_{1-4} alkyl, C_{1-4} -alkoxy and CF_3

3. 2. 1. 4. Reaction with Chloronicotinic Acids

2-Amino-4-substituted thiazoles **3** were reacted with 2-chloronicotinic acid to furnish 3-aryl-5*H*-pyrido[2,3-*d*]thiazolo[3,2-*a*]pyrimidin-5-ones **92** ($\text{R} = \text{C}_6\text{H}_5, 4\text{-MeC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4, 4\text{-BrC}_6\text{H}_4$). The reaction of 2-amino-4-substituted thiazoles **3** with 2-chloropyridine-3-carbonyl chloride afforded 9-aryl-5-oxo-5*H*-pyrido[3',2':5,6]pyrimido[2,1-*b*]thiazoles **93** ($\text{R} = \text{C}_6\text{H}_5, 4\text{-MeOC}_6\text{H}_4, 4\text{-ClC}_6\text{H}_4$).¹⁴⁸

3. 2. 2. Formation of Thiazolo[3,2-*a*]pyrimidin-7-ones

3. 2. 2. 1. Reaction with Ethyl Propiolates

2-Amino-4-substituted thiazoles **3** were reacted with 3-substituted propiolic acid esters to give the corresponding 3,5-disubstitutedthiazolo[3,2-*a*]pyrimidin-7-ones **94**.^{149–151}

R = Me, Ph, 4-Cl- C_6H_4 , 4-Br- C_6H_4 , 4-MeO- C_6H_4 , 4-O $_2$ N- C_6H_4 ;
 R₁ = H, Me, Ph, CH₂Cl, COOEt

3. 2. 2. Reaction with Methyl Acrylate

2-Amino-4-substituted thiazoles **3** were reacted with methyl acrylate in the presence of hydroquinone or with bromopropionic acid to give 5,6-dihydrothiazolo[3,2-*a*]pyrimidin-7-ones **95**.¹⁵²

3. 2. 3. Formation of Pyrimidin-5,7-diones

2-Alkylamino-4-phenylthiazoles **96** (R = Me, Ph; R₁ = Me, cyclopropyl) were prepared by acylation reaction of 2-amino-4-substituted thiazole **3**, followed by catalytic reduction. The products were precursor intermediates for the synthesis of the mesoionic thiazolo[3,2-*a*]pyrimidin-5,7-diones **97** obtained by thermal condensation with bis(2,4,6-trichlorophenyl)ethyl malonate and were showed to inhibit cyclic-AMP phosphodiesterase and displayed weak hypotensive effects *in vivo*.¹⁵³

3. 2. 4. Formation of Imidazothiazoles

2-Amino-4-substituted thiazoles **3** were reacted with α-halocarbonyl compounds **4**, e.g. (un)substituted phenacyl bromides, *N,N*-disubstituted chloroacetamides, 2-bromoacetylchromones, 3-bromo-2-oxopropionic acid ethyl

ester, to give the corresponding 3,6-disubstituted-imidazo[2,1-*b*]thiazoles **98** with antiinflammatory and analgesic activities.^{90,154–156}

R = phenyl, substituted phenyl, -naphthyl, Me, COOEt;
 R₁ = phenyl, substituted phenyl, Et₂NCl, EtHNCl, MeHNCl, C₆H₁₀NCl,
 substituted-6-chromonyl, COOEt;
 X = Br, Cl

Equivalent amounts of 2-amino-4-substituted thiazoles **3** and the halogenated arylhydrazono ketones were refluxed in ethanol in the presence of triethylamine, affording 6-arylazo-3,5-disubstituted-imidazo[2,1-*b*]thiazoles **99** (R = Ph; R₁ = Me, OEt, Ph, substituted phenyl, heteroaryl; Ar = Ph, substituted phenyl; X = Cl, Br) in good yields.^{157,158}

Reaction of 2-amino-4-substituted thiazoles **3** with 4-iodo-2-(methylthio)pyrimidine and oxone afforded a series of imidazo[2,1-*b*]thiazole derivatives **100** and **101**, respectively. The products showed potent activities against melanoma cell lines.¹⁵⁹

6-Hydroxy-3-substituted thiazolo[3,2-*a*]benzimidazoles **102** were synthesized by condensation of 2-amino-

no-4-substituted thiazoles **3** with *p*-benzoquinone in acetic acid.¹⁶⁰

3. 2. 5. Formation of Thiazoloquinones and Quinazoline Derivatives

Thiazoloquinones **103** were obtained in 40–50% yield by refluxing 2-amino-4-substituted thiazoles **3** with 2,3-dichloronaphthoquinone in ethanol.¹⁶¹ Also, 2-amino-4-phenylthiazole was reacted with 2,3-dichloroquinazoline to give the quinazoline derivative **104**.⁵³

2-Amino-4-substituted thiazoles **3** were reacted with chloranil in glacial acetic acid at room temperature to give the corresponding 2,5-dichloro-3,6-bis(2'-thiazolylamino)-1,4-benzoquinone **105** (R = Me, Ph, 4-MeC₆H₄, 4-MeOC₆H₄, 4-ClC₆H₄).¹⁶² A mixture of **106** (Z-form) and **107** (E-form) was obtained by heating 2-aminothiazoles with chloranil in ethanolic medium.⁵³

3. 2. 6. Reaction with Aromatic Amines

2-Amino-4-substituted thiazoles **3** were reacted at room temperature with perchloromethylmercaptan to give the corresponding 2-thiazolyl trichloromethanesulphenamides **108** which on treatment with aromatic amines afforded the 3,5-disubstituted-3*H*-thiazolo[2,3-*c*][1,2,4]thiadiazoles **109** with antibacterial activity.¹⁶³

3. 3. Nucleophilic Reactions

3. 3. 1. Reaction with Aliphatic and Aromatic Amines

A novel series of 2-acetamido and 2-propanamido derivatives of 4-substituted thiazoles **110** was designed and synthesized by the reaction of 2-amino-4-substituted thiazoles **3** with chloroacetyl chloride derivatives, followed by the reaction with secondary aromatic and/or aliphatic amines. The synthesized compounds were subjected to NCI *in vitro* assessment for their antitumor activity and remarkable GI values of 75.5, 69.3, 96.2 and 92.7% to the Leukemia CCRF-CEM cell line were determined.¹⁶⁴

3.3.2. Sulphonation

Hurd and Karasch found out that fuming sulfuric acid converted the 2-amino-4-substituted thiazoles **3** to the corresponding 2-thiazolyl-sulfamic acids **111** (R = Me, Ph) at low temperatures, whereas at higher temperatures, the sulfamic acid was converted into an isomeric amino sulfonic acid **112** (R = Me).¹⁶⁵

3.3.3. Chlorosulphonation

Acetylation of 2-amino-4-substituted thiazoles **3** followed by chlorosulphonation under controlled conditions gave 2-acetyl-amino-4-substituted-thiazole-5-sulfonyl chloride **113**.⁵³

3.3.4. Halogenation

2-Amino-4-substituted thiazoles **3** gave the 2-amino-5-halothiazoles **114** (R = Me, Ph; X = Br, Cl) when subjected to the conditions of halogenation using benzenesulphenyl halide.^{166,167}

3.3.5. Formylation

Vilsmeier–Haack formylation of 2-amino-4-substituted thiazoles **3** by POCl₃–DMF yielded the corresponding 5-formylthiazole **115** through electrophilic attack at C-5.¹⁶⁸

3.3.6. Azo Coupling Reactions

2-Amino-4-substituted thiazoles **3** underwent coupling reactions when treated with aromatic diazonium salts or diazotized sulphanilamides to give the corresponding 2-amino-5-arylazothiazoles **116** (R = Me, Ph, 4-ClC₆H₄; R₁ = H, Me, OMe, 4-Cl, 4-phenoxy, 4-(4-chloro-

phenoxy) and/or **117** (R = Ph, substituted phenyl; R₂ = H, guanidino, 2-thiazolyl, 2-pyrimidyl and other heterocycles), respectively.^{169–171}

New antipyryl azo dyes of the type **119** were prepared by diazo coupling of 4-antipyryl diazonium chloride with 2-hydrazono-4-substituted thiazole derivatives **118**. These dyes showed high ability as disperse dyes for dyeing polyester fabrics with acceptable fastness properties.¹⁷²

Diazotized aryl amines were coupled with 2-amino-4-substituted-thiazoles **3** to give 5-arylaazo-2-amino-thiazoles **120**, which on reaction with different reagents, such as benzoyl chloride and acetic anhydride yielded the corresponding 2-(N-benzoylamino)-5-arylazothiazole derivatives **121** and 2-(N-acetylamino)-5-arylazothiazole **122**. These mono azo dyes were applied to polyester as disperse dyes and their fastness properties were evaluated.⁷

R, R₁ = Ph, H; 4-antipyryl, H; Ph, Me; 4-antipyryl, Me
Ar = C₆H₅, 4-MeC₆H₄, 4-MeOC₆H₄, 4-O₂NC₆H₄, 4-BrC₆H₄

Coupling of the diazotized 2-amino-2,4-disubstituted-thiazoles **123** ($R = \text{CH}_3$; $R_1 = \text{COCH}_3$) with various *N*-alkyl derivatives of aniline afforded the corresponding 2-azoaryl-2,4-disubstituted-thiazoles **124**. The products were applied as disperse dyes and their dyeing performance has been assessed on cellulose triacetate fabric. The dyed fabrics show good light fastness, very good rubbing, perspiration, washing fastness and excellent sublimation fastness. These dyes have been found to give bright yellow to maroon color shade with very good depth and levelness on fabric,¹⁷³ while **124** ($R_1 = R_2 = \text{Cl}$; $R_3 = \text{C}_2\text{H}_4\text{OH}$; $R_4 = \text{H}$) dyed polyester fiber with superior depth and levelness and fair to very good light fastness, very good to excellent washing and rubbing fastness properties.¹⁷⁴

$R_1, R_2 = \text{CH}_3, \text{COCH}_3; \text{Cl}, \text{Cl}$

$R_3, R_4 = \text{H}, \text{H}; \text{CH}_3, \text{H}; \text{C}_2\text{H}_5, \text{H}; \text{H}, \text{CH}_3; \text{H}, \text{Cl}; \text{C}_2\text{H}_4\text{OH}, \text{H}$

Azo coupling of 5-formylaminothiazole derivative **3** ($R_1 = \text{OCH}_3$; $R_2 = \text{CHO}$) as the diazo component and *N,N*-diethylaniline afforded the formyl aminothiazole dye **125**. The synthesized asymmetrical 2D charge transfer chromophores showed good nonlinear optical response and good thermal stability as well.¹⁷⁵

$R_1 = -\text{OCH}_3; R_2 = -\text{CHO}$

3.3.7. Complexation

Treatment of Na_2PdCl_4 with two equivalents of amino- or acetylamino-thiazoles as ligand (*L*) afforded *trans*- $[\text{PdCl}_2\text{L}_2]$ complexes **126–130** in which the introduced ligands were coordinated to palladium through the endocyclic nitrogen as shown by X-ray crystal structures.¹⁷⁶

Copper(II) Schiff base coordination compounds of dienes with heterocyclic aldehydes and 2-amino-5-methyl-thiazole **132** were synthesized by stepwise reactions from the starting materials $[\text{Cu}(\text{dienX}_2\text{Y}_2)]$ **131** with 2-amino-4,5-disubstituted-thiazole **3** ($R_1 = \text{H}$, $R_2 = \text{CH}_3$). The isolated compounds are monomers, paramagnetic and electrolytic compounds of the type 1:1.¹⁷⁷

$R_1 = \text{H}; R_2 = \text{CH}_3 \quad \text{X} = \text{O}, \text{S}; \text{Y} = \text{Cl}, \text{Br}, \text{NO}_3$

Synthesis of three coordination compounds $\text{Co}(\text{L})_2$, $\text{Ni}(\text{L})_2$, and $\text{Cu}(\text{L})_2$ **133** (*L* = bis[(4*R*,5*R*)-4-methyl-5-phenyl-4,5-dihydrothiazol-2-yl]-amine) prepared by template reactions from the optically active ligand (4*R*,5*R*)-4-methyl-5-phenyl-4,5-dihydrothiazol-2-yl-amine **3** and $\text{CoCl}_2 \cdot 6\text{H}_2\text{O}$, $\text{NiBr}_2 \cdot 3\text{H}_2\text{O}$ or $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$. The template reactions involved the condensation of two molecules of thiazol-2-ylamine and elimination of one NH_3 .¹⁷⁸

3. 4. Miscellaneous Reactions

3. 4. 1. Nitrosation Reaction

2-Amino-4-phenylthiazole **3** underwent nitrosation at position 5 when treated with isoamylnitrite to give the corresponding 5-nitroso derivative which can be reduced by zinc in acetic acid followed by condensation with benzaldehyde to produce 2-amino-4-phenyl-5-benzalaminothiazole **134**.¹⁷⁹

3. 4. 2. Reaction with Rhodamine

2-Amino-4-phenylthiazole **3** reacted with rhodamine (S-cyanothiohydroxylamine) at position 5 to produce the corresponding 2-amino-4-phenyl-5-rhodanothiazole **135**.¹⁸⁰

The 2-amino-*N*-substituted maleimidothiazoles **136** (R = halo, C₁₋₄ alkyl, phenyl, substituted phenyl, 2-furyl, 2-thienyl; R₁ = H, aliphatic or aromatic group; X = CN, C₁₋₆ alkylsulfonyl, SO₂-Ph) were prepared by the reaction of 2-amino-4-substituted thiazoles **3** with 2-chloromaleimides.¹⁸¹

3. 4. 4. Reaction with Triazines

2-Amino-4-substituted thiazoles **3** were reacted in acetic anhydride with 3-aryl-1,2,4-triazin-5(2*H*)-one compounds, yielding 1-acetyl-3-aryl-6-(2-acetyl-amino-5-thiazolyl)-1,6-dihydro-1,2,4-triazin-5-(2*H*)-ones **137**.¹⁸²

R = Ph; Ar = Ph, 4-ClC₆H₄, 4-MeC₆H₄

3. 4. 5. Reaction with Thiourea and Iodine

Synthesis of bis(2-amino-5-thiazolyl)sulphides **138** has been achieved by reacting appropriate 2-amino-4-substituted thiazole **3** with thiourea and elemental iodide at room temperature in the presence of sodium hydroxide.¹⁸³

R = CH₃, CH₃CHCOOEt, C₂H₅, C₂H₅CHCOOEt

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Povzetek

Aminotiazolski obroč in njegovi najrazličnejši derivati se že dolgo uporabljajo kot izhodne spojine za sinteze biološko aktivnih molekul. 2-aminotiazol, kot tipični predstavnik heterocikličnih aminov, je osnova za sintezo mnogih spojin, ki vključujejo sulfa zdravila, biocide, fungicide, različne tipe barvil za sintetična vlakna in pospeševalce kemijskih reakcij. Poleg tega nastopajo 2-aminotiazolski derivati kot intermediati pri sintezah antibiotikov, kjer so pogosto substituirani z različnimi skupinami, v odvisnosti od njihove končne farmacevtske namembnosti. Znana je tudi njihova aktivnost v vlogi inhibitorjev korozije pri zaščiti jekla. V tem preglednem članku predstavljam sintezno uporabnost 2-amino-4-substituiranih tiazolov, njihove reakcije in biološke učinke.