Review

Synthetic Approaches to Biologically Active C-2-Substituted Benzothiazoles

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Abstract: Numerous benzothiazole derivatives are used in organic synthesis, in various industrial and consumer products, and in drugs, with a wide spectrum of biological activity. As the properties of the benzothiazole moiety are strongly affected by the nature and position of substitutions, in this review, covering the literature from 2016, we focus on C-2-substituted benzothiazoles, including the methods of their synthesis, structural modification, reaction mechanisms, and possible pharmacological activity. The synthetic approaches to these heterocycles include both traditional multistep reactions and one-pot atom economy processes using green chemistry principles and easily available reagents. Special attention is paid to the methods of the thiazole ring closure and chemical modification by the introduction of pharmacophore groups.

Keywords: benzothiazole; synthesis; reactivity; biological activity

1. Introduction

Benzothiazole and its numerous derivatives of electron-rich aromatic heterocycles with endocyclic sulfur and nitrogen atoms have attracted the ongoing interest of synthetic chemists due to their unique properties [1–7]. Recently, we have reviewed modern trends in the synthesis of biologically active and industrially important derivatives of 2-mercapto- and 2-aminobenzothiazoles [8,9]. The benzothiazole ring is the key motif of a wide range of biologically active compounds, including antitumor [7,10–27], antimicrobial [28–36], antiviral [37,38], antibacterial [16,24,34,37,39,40], antifungal [13,16,28,34,35,40–42], antiparasitic [32,43,44], antioxidant [19,45], antidiabetic [46], immunomodulating [47], and anti-inflammatory agents [48–50]. Some pharmacologically important C-2-substituted benzothiazole derivatives, such as antidiabetic Fortress, antitumor drugs Zopolrestat and GW 608-lys 38, and antiseptic Haletazol, have found application as commercially available drugs [3,51–53]. C-2-substituted benzothiazoles are also potential sensibilizers [54–57] and optically active materials [58–74]. With this in mind, the present review is devoted to the synthesis and practical application of various 2-substituted benzothiazoles, mainly covering the last five years. Nowadays, much attention is paid to minimizing the formation of toxic organic compounds by applying the methods of green chemistry. The effectiveness of different reactions can be increased by the use of nanocatalysts [75–83], silica- and nanosilica-based catalysts or oxidants [50,84–88], photocatalysts [89–91], solvent-free reactions [50,67,92–97], and the use of ionic liquids or ecologically friendly solvents, such as water or ethanol [98–101]. The effectiveness of reactions can also be increased by microwave [24,39,50,102] or visible light assistance [17,18,41,91,103,104]. However, along with one-pot atom economy reactions, multistep processes are still widely used for the synthesis of C-2-substituted benzothiazoles. Nowadays, in the design of new drugs, the concept of molecular hybridization is actively used. This concept means combining two or more moieties of different biologically active compounds, each of which is known to possess pharmacological activity, in new hybrid molecules, resulting in the enhancement of biological effects and overcoming drug resistance [10–12,17–19,22,23,32–34,46,105,106].
Below, the syntheses of the C-2-substituted benzothiazoles are classified according to the methods of their formation and functionalization.

2. Intramolecular Formation of the C-2-Substituted Benzothiazole Ring

Benzothiazoles 1a–y with alkyl, aryl and hetaryl substituents in position 2 of the ring were prepared in moderate to good yields by a metal-free atom-economic procedure [107]. The cascade process and the R₃ group transfer were initiated by di(t-butyl)peroxide (DTBP) in fluorobenzene. The reaction started with the homolytic fission of DTBP upon heating to give t-butoxy radical, which suffered β-scission to give methyl radical. The proposed mechanism is presented in Scheme 1.

\[
\begin{align*}
\text{DTBP-promoted formation of benzothiazoles 1a–y from ortho-isocyanooaryl thioethers.}
\end{align*}
\]

The copper NHC complex-catalyzed intramolecular S-arylation of various 2-halogenothioanilides was investigated as a route to 2-arylbenzothiazoles 2a–f [108] (Scheme 2). Good yields were obtained both for electron donor and electron acceptor substituents in the aryl rings. The mechanism, including two-electron Cu(I)/Cu(III) catalytic cycles with the intramolecular cyclization of 2-halogenothioanilides to 2-arylbenzothiazoles, was proposed.

\[
\begin{align*}
\text{Scheme 2. Synthesis of 2-arylbenzothiazoles 2a–f via S-arylation of substituted 2-halothioanilides.}
\end{align*}
\]
3. Intermolecular Formation of the C-2-Substituted Benzothiazole Ring

There are many protocols for the design of a benzothiazole ring based on the transition metal catalysis or metal-free syntheses using one-pot processes carried out in the absence of a solvent or in “green” solvents. Thus, the cascade radical cyclization of ortho-isocyanoyl thioethers with organoboric acids promoted by Mn(acac)$_2$, FeCl$_2$, CuCl$_2$ or benzoic peroxyanhydride (BPO) led to various C-2-substituted benzothiazoles 3a–r in 47–89% yield (Scheme 3); the reaction successfully occurred in toluene, fluorobenzene, or ether [109]. The stepwise radical mechanism is similar to that in Scheme 1.

\[
\text{Scheme 3. Metal salt-catalyzed synthesis of benzothiazoles 3a–r from ortho-isocyanoyl thioethers and organoboric acids.}
\]

The alternative visible light-induced, metal-free and oxidant-free cyclization of ortho-isocyanoyl thioethers with ethers provides an efficient route to benzothiazoles functionalized with ether groups 4a–w (Scheme 4). As a photocatalyst, 1,2,3,5-tetrakis-(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN) was used [41]. A similar stepwise radical mechanism was triggered by the excitation of the photocatalyst to 4CzIPN and the single-electron transfer from the ether on 4CzIPN to give α-oxy radical, which reacts with isocyanaryl to form the imidoyl radical. Finally, the intermolecular cyclization of the latter resulted in the formation of the target product and the elimination of the methyl radical (Scheme 4).

\[
\text{Scheme 4. Visible light-induced formation of benzothiazoles 4a–w from isocyanarylthio ethers.}
\]

The synthesis of 2-substituted benzothiazoles 5a–z from o-idoarylisothiocyanates and a series of methylene active compounds mostly in quantitative yield has been reported [110]. The reaction is transition metal-free and proceeds at room temperature in the presence of sodium hydride by the formation of an intramolecular C–S bond. The authors proposed the $S_{RN1}$ mechanism with the formation of radical intermediates (Scheme 5). Sodium hydride reacts with the active methylene compound to give carbanion, which adds to the
isothiocyanate group to form the thioamide intermediate (A). Under alkaline conditions, the latter is transformed to the conjugate base (B), in which a single electron is transferred to the aryl group with the formation of the radical-anion intermediate (C). The latter expels the iodide ion, resulting in biradical intermediates (D) which, in turn, undergo intramolecular recombination to the target products (Scheme 5).

**Scheme 5.** NaH-promoted cyclization of \( o \)-iodoarylthiocyanates with methylene active compounds to C-2-substituted benzothiazoles 5a–z.

Condensation of substituted anilines with benzoyl chlorides with subsequent thionylation with the Lawesson reagent (2,4-bis(4-anisyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide) and Yacobsen cyclization of thioanilides under the action of alkaline solution of \( K_3Fe(CN)_6 \) affords 4-nitrophenyl benzothiazoles 6a–f. The latter were reduced with SnCl\(_2\) to the corresponding 4-aminophenyl benzothiazoles 7a–f in 75–80% yield (Scheme 6) [12]. The condensation of compounds 7a–f with aromatic ethynyl ketones in ethanol affords arylaminobenzothiazolearylpropenones hybrids 8a–r in high yield. The authors demonstrated cytotoxic activity of the obtained products.

Fluorinated or perfluoroalkylated 2-methylbenzothiazoles 9a–h and 10a–h were synthesized from fluoro- or perfluoroalkylanilines in three steps: acylation of the amino group, transformation of the carbonyl group to thiocarbonyl, and catalyzed cyclization (Yacob- sensen reaction). The obtained 2-methylbenzothiazoles 9a–h gave benzothiazolium tosylates 10a–h by heating with methyl tosylate (Scheme 7) [43].
Scheme 6. Successive synthesis of 2-substituted benzothiazoles 6a–f–8a–r from anilines and ketones.

Scheme 7. Synthesis of fluorinated 2-methylbenzothiazoles 9a–h and 10a–h.

Tosylate salts 10a–h have been used as building blocks for the design of fluorinated rhodacyanines 11a–q, which demonstrated high antileishmanial activity (Scheme 8) [43].

Scheme 8. Synthesis of fluorinated benzothiazole rhodacyanines 11a–q with antileishmanial activity.
The reaction of anilines with sulfinylbis[(2,4-dihydroxyphenyl)methanethione] gives benzothiazoles 12a–c a 2,4-dihydroxyphenyl substituent in position 2 of the benzothiazole ring (Scheme 9). The reaction starts with electrophilic substitution and the HF or HCl elimination from the formed thioamide. The perfluorinated product has shown notable activity against human cancer cells [13].

A series of new “head-to-head” aniline-based derivatives of bis-benzothiazole were obtained and their antiproliferative activity was assessed [14]. In the presence of Br₂, benzidine reacts with potassium thiocyanate via cyclization to bis(benzothiazole)diamine. Its hydrolysis with KOH leads to the key intermediate, 3,3'-bis(mercapto)benzidine. The latter reacts with p-substituted benzaldehydes to give bis-substituted benzothiazoles 13a–j (Scheme 10). The products with electron-donor substituents in the benzene ring are less toxic and more effective.

DMSO acts both as the solvent and the oxidant in the metal-free ecologically safe synthesis of C-2-substituted benzothiazoles 14a–g and naphtho [2,1-d]thiazoles 15a–z from N-substituted arylamines and elemental sulfur (Scheme 11) [111]. The advantages of the method are the use of easily accessible anilines, a variety of 1 and 2-naphthylamines and 2-anthranilamide, and tolerance to a wide range of functional groups. 1,3 and 1,4-bisnaphtho [2,1-d]thiazoles linked by the benzene bridge have also been synthesized. The electron-donating groups in the aniline fragment notably increase the yield of the target products. The proposed mechanism is shown in Scheme 11, using the example of naphthylamine. First, amine is oxidized by DMSO to imine (A). The electrophilic attack of elemental sulfur S₈ to the ortho-position of imine (A) gives intermediate (B). The elimination of sulfur S₉,1 and the proton results in the imine thiolate (C), which undergoes nucleophilic intramolecular cyclization to thiazoline (D). Finally, oxidative aromatization of the latter gives rise to the target anelated products 15.
The process is scalable and economic; the yield of the products depends on the principles. An example is the reaction of direct oxidative condensation of aminothiophenols and green chemistry principles. Aldehydes are based on the use of readily accessible 2-aminothiophenols and green chemistry principles. The oxidation of alcohols to aldehydes, the condensation of the latter with aliphatic, heterocyclic or aromatic alcohols to benzothiazoles gives rise to imine/benzothiazolines, and their oxidation to 2-substituted benzothiazoles.

Most reactions of intermolecular formation of the C-2-substituted benzothiazole ring are based on the use of readily accessible 2-aminothiophenols and green chemistry principles. An example is the reaction of direct oxidative condensation of aminothiophenols such as the reaction of 2-aminothiophenol with aliphatic aldehydes may reach 98%. The reaction was carried out without solvent in the presence of charcoal and silica gel (Scheme 13). Microwave assistance in the presence of catalytic amounts of Amberlite IR-120 catalysts gave rise to the target annelated products of sulfur Sn and elemental sulfur. Metal-free synthesis of benzothiazoles is shown in Scheme 11, using the example of naphtho[2,1-d]thiazoles linked by the benzene bridge. The method are the use of easily accessible anilines, a variety of 1 and 2-naphthylamines, and tolerance to a wide range of functional groups. 1,3 and 1,4-bisnaphtho[2,1-d]thiazoles and 2-anthranylamine, and tolerance to a wide range of functional groups. 1,3 and 1,4-bisnaphtho[2,1-d]thiazoles and 2-anthranylamine, and tolerance to a wide range of functional groups.

Another example is the green synthesis of benzothiazoles 17a–t by the condensation of 2-aminothiophenol with various aldehydes in the presence of heterogeneous catalysts. As such, SnP₂O₇ prepared from monoammonium phosphate and SnCl₂ solution, or Sm(NO₃)₃·6H₂O applied on nanosized silica gel, were used. As solvents, ethanol or methanol were employed (Scheme 13, upper reaction). The catalysts can be recycled five times without notable loss of the catalytic activity. Benzaldehydes with electron acceptor or electron donor groups, as well as heterocyclic aldehydes, readily entered the reaction with 2-aminothiophenol (yields: 85–96%); lower yields (68–73%) were obtained for aliphatic aldehydes. However, with microwave assistance, the yield of the reaction of 2-aminothiophenol with aliphatic aldehydes may reach 98%. The reaction was carried out without solvent in the presence of charcoal and silica gel (Scheme 13, bottom reaction) [50]. Microwave assistance in the presence of catalytic amounts of Amberlite IR-120
resin also allowed the authors to obtain a large series of aryl- and hetarylbenzothiazoles 18a–g containing different functional groups from aldehydes and 2-aminothiophenol [24].

Another example is the green synthesis of benzothiazoles 17a–t by the use of heterogeneous catalysts or with microwave assistance.

In other ecologically friendly syntheses of C-2-substituted benzothiazoles from aminothiophenols, cheap water-soluble urea nitrate [35], ionic liquid with the sulfonate anion group playing the role of the heterogeneous catalyst and the solvent (BAIL GEL) [100], or a biocatalyst in the form of a natural carrier of calcined limpet shells coated with ZnCl₂ were used [112].

A simple and efficient synthesis of 2-alkylbenzothiazoles 19a–g was performed by a two-step reaction including the condensation of 2-aminothiophenol with aliphatic aldehydes in the presence of molecular sieves 4Å followed by the oxidation of the formed 2-alkyl-2,3-dihydrobenzo[d]thiazoles with pyridinium chlorochromate (PCC) on silica gel (Scheme 14) [84].

Distinct from aldehydes, ketones react with 2-aminothiophenol via their active methylene group, as proven by the carbonyl group remaining intact in the products. Thus, a series of aromatic 2-acylbenzothiazoles 20a–k was obtained from 2-aminothiophenol, in addition to aromatic or heteroaromatic ketones by reflux in ethanol with CuBr₂ as the oxidant (Scheme 15) [101]. Apparently, the reaction proceeds with N-nucleophilic substitution in α-bromoketone generated from the ketone and CuBr₂. The formed α-aminoketone is further brominated by CuBr₂ and cyclized by the nucleophilic attack of the thiol group on the α-carbon atom with the elimination of HBr and the closing of the ring, as shown in Scheme 15. In the final step, dehydrogenation with a reduction of CuBr₂ to CuBr gives the target 2-acylbenzothiazoles 20a–k.
Scheme 15. The synthesis and possible mechanism of formation of 2-acylbenzothiazoles 20a–k from 2-aminothiophenol and ketones in ethanol.

For the synthesis of new benzothiazole-based hemicyanine sensitizers for solar cells, the ring closure was performed by the reaction of 2-aminothiophenol with isopropyl methyl ketone in the presence of acetic anhydride. Then, 2-methylbenzothiazole formed in a practically quantitative yield reacted with 1,2-oxathiane 2,2-dioxide to give the corresponding sulfonates and, finally, by the reaction with dimethylaminobenzaldehyde or 3,4-dihydroxycyclobut-3-ene-1,2-dione, new sensitizers 21 and 22 were formed (Scheme 16) [56,57].

Scheme 16. Synthesis of benzothiazole-based hemicyanine sensitizers 21 and 22.

Several groups have developed the synthesis of C-2-substituted benzothiazoles 23a–c from 2-aminothiophenols and β-diketones by the use of effective, recycled, cheap and ecologically safe catalysts, such as the montmorillonite clay KSF [113], long-chain ionic liquids [114], sodium dichloroiodate [115], or the Zr-based organometallic catalyst MOF-808 [116]. The mechanism given in Scheme 17 is an example of condensation with the participation of montmorillonite clay [113]. The reaction includes keto-enol tautomerization, the formation of enaminoketone, its cyclization, and the elimination of the enolate. The catalyst is easily separated by simple filtration.
The reaction of the acylation of 2-aminothiophenol with acetic acid by the action of direct concentrated solar radiation on heating in the presence of choline chloride has been studied. The yield of product 24a was 60% (Scheme 18, upper route) [117]. The authors note the chemoselectivity of the process of intramolecular acylation. Choline chloride forms hydrogen bonds with the carbonyl oxygen, thus activating the reagent; moreover, it acts as a phase-transfer catalyst and activates the aniline moiety, facilitating the nucleophilic attack and the formation of the intermediate N-acylated product. The method is a good example of green synthesis, as it is metal-free, oxidant-free, and uses choline chloride, which is an inexpensive, biodegradable and recycled catalyst which can be used in water medium.

Scheme 17. Formation of benzothiazoles 23a–c from 2-aminothiophenols and β-diketones.

A similar approach to 2-methylbenzothiazole 24a from aminothiophenol and malonic acid was described [118]. The method is simple, scalable, and gives only small amounts of by-products (Scheme 18, bottom route).

The yields of compound 24a up to 95% were obtained when using such catalysts as nanoporous TiO2 modified with bis-3-(trimethoxysilylpropyl)ammonium hydrosulfate (TiO2-[bip]-NH2HSO4) [95], a polymer-based solid acidic catalyst [PVP-SO3H][HSO4] [96], or a nanocatalyst on mesoporous silica containing bridge groups of N-sulfonic acid (SA-PMO) [97]. All reactions were carried out under mild conditions and without solvent.

A simple one-pot synthesis of 2-substituted benzothiazoles 25a–k by the reaction of acid chlorides or anhydrides with 2-aminothiophenol in the presence of a basic hetero-
A convenient route to 2-organyl benzothiazoles 26a–k from 2-aminothiophenols and dimethylformamide derivatives was proposed (Scheme 19). The reaction proceeded under mild conditions in high yields, and the catalyst did not lose its activity after 10 times of recycling. No by-products were detected, and the target products were isolated by simple filtration [119].

\[
\text{R}_1 = \text{H}, \text{Cl}, \text{NO}_2; \quad \text{R}_2 = \text{Me}, \text{Ph}, 2\text{ClC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 2\text{-An}, 2\text{-pyridyl}, \text{CH}_2\text{CH}_2\text{COPh}
\]

\[
\text{R}_1 = \text{H}, \text{Cl}, \text{NO}_2; \quad \text{R}_2 = \text{Me}, \text{Ph}, 2\text{ClC}_6\text{H}_4, 4\text{-NO}_2\text{C}_6\text{H}_4, 2\text{-An}, 2\text{-pyridyl}, \text{CH}_2\text{CH}_2\text{COPh}
\]

Scheme 19. Synthesis of 2-substituted benzothiazoles 25a–k from 2-aminothiophenol and acid chlorides or anhydrides in the presence of basic heterogeneous catalyst.

Non-catalyzed cyclocondensation of 2-aminothiophenol with 4-methylbenzaldehyde in DMSO at 190 °C affords 2-(4-tolyl)benzothiazole. The latter undergoes a sequence of transformations leading to dendrimers with terminal benzothiazole groups 27a–c (Scheme 21). Similar reactions were performed with 4-methylcinnamic acid. Photophysical investigation of the obtained dendrimers showed a possibility of their use as additives to sensitized dyes in solar cells [54].
Scheme 21. Synthesis of dendrimers with terminal benzothiazole groups 27a–c.

Now, let us turn to the light-induced syntheses of C-2-substituted benzothiazoles. The method of the synthesis of 2-organylbenzothiazoles 28a–s was developed based on the photooxidative cross-coupling of 2-aminothiophenols with α-oxocarboxylic acids under the action of blue UV irradiation in the presence of H$_2$O$_2$ (Scheme 22). The key step of the radical mechanism of the reaction is the formation of the donor acceptor complex between the reagents. Subsequent decarboxylation and intramolecular cyclization of the intermediate adducts afford the target products. α-Ketoacids and 2-aminothiophenols with various functional groups react readily at room temperature in moderate to good yields without the use of photooxidative or metal-based catalysts [103].

Scheme 22. Photooxidative cross-coupling of 2-aminothiophenols with α-oxocarboxylic acids.

Visible light-induced cascade radical cyclization was performed for the synthesis of benzothiazoles possessing CF$_2$/CF$_3$ substituents in the 2-position, 29a–k and 30a–k, in good yield (Scheme 23). The use of Na$_2$CO$_3$ as a reducing agent facilitated mild fluoroalkylation [90].

Scheme 23. Synthesis of benzothiazoles 29a–k, 30a–k with CF$_2$/CF$_3$ substituents in the 2-position.
The visible light-induced reaction of 2-aminothiophenols with aldehydes was proposed as an economic and safe route to a wide series of benzothiazoles, 31, affording the target products in good yields in the absence of transition metal catalysts or other additives (Scheme 24) [104]. The authors proposed a radical mechanism via diaryldisulfide intermediates.

\[
\text{R} = \text{Me, MeO, F/Cl/Br} \\
\text{R}_1 = \text{Ph, 3/4-An, 3,5-(MeO)}_2\text{C}_6\text{H}_3, 2/3-\text{Tol}, 4-\text{f-BuC}_6\text{H}_4, 2-\text{OH}_2\text{C}_6\text{H}_4, 2-\text{F/Cl/Br/}l-\text{C}_6\text{H}_4, 3-\text{BrC}_6\text{H}_4, 4-\text{F/Cl-C}_6\text{H}_4, 3,4-\text{F}_2\text{C}_6\text{H}_3, 2-\text{Br-4-Me-C}_6\text{H}_3, 3-\text{MeCOOC}_6\text{H}_4, 4-\text{CF}_3\text{C}_6\text{H}_4, 4-\text{AcOC}_6\text{H}_4, 1/2-\text{naphthyl, 3/4-pyridyl, 2-furyl, 2-thienyl, 4'-methyl-2-pyryl, 3-indoly}, n\text{-propyl, cyclopropyl, cyclohexyl, 4-cyclohexenyl, Bz, phenylethyl.}
\]

Scheme 24. Synthesis of benzothiazoles 31 via irradiation of 2-aminothiophenols with aldehydes.

A series of benzothiazolamides, 32a–l, possessing antimicrobial and antifungal activity was prepared in high yields via the cyclocondensation of 2-aminophenol with diethyl oxalate, the hydrolysis of the formed ethyl benzothiazole-2-carboxylate, and amidation with the amides of 4-nitrophenylalanine in the presence of HATU (hexafluorophosphate azabenzotriazole tetramethyl uronium) and DIPEA (diisopropylethylamine) in DMF (Scheme 25) [28].

\[
\text{O}_2\text{N-C}_6\text{H}_4\text{C=O} + \text{NH}_2\text{R} \xrightarrow{\text{HATU, DIPEA, DMF}} \text{32a–l 86–90%}
\]

Scheme 25. Synthesis of benzothiazolamides 32a–l possessing antimicrobial and antifungal activity.

Cyclization of 2-aminophenol with acetyl chloride affords 2-methylaminobenzothiazole, which, when treated with bromoacetic acid, gives 3-carboxymethyl-2-methylbenzothiazolium bromide. The latter enters condensation with aldehydes in acetonitrile in the presence of piperidine as a base to give new chromophores 33a–e containing the benzothiazole moiety and alkyl groups of different chain lengths (Scheme 26). The investigation of photoelectric properties showed that the efficiency of the power transformation for all sensitizers 33a–e increased with the length of the carbon chain [55].
2-Alkyl- and arylsubstituted benzothiazoles 34a–o were synthesized by the solvent-free and metal-catalyst-free reaction of 2-aminothiophenols and N-organylthioamides in the presence of CBr₄ (Scheme 27). The reaction includes the activation of thioamide by the formation of the intermediate with the S–Br bond between the thioamide sulfur atom and CBr₄. The activated thioamide molecule attacks aminothiophenol, and the reaction is completed by intramolecular cyclization and the formation of the target products and N-methylaniline, and the regeneration of the catalyst from H₂S Br–CBr₃. The yields for the aliphatic derivatives were 68–93%; for aromatic, 62–81% [93].

Disulfides can also be used as starting materials for the synthesis of C-2-substituted benzothiazoles. Thus, 2-alkyl and 2-ary(hetaryl)benzothiazoles 35a–k have been prepared by the oxidative coupling of (2-aminoaryl)disulfides and primary alcohols in the presence of initiator DTBP (Scheme 28) [120]. The yields decreased with the steric volume of substituent R₂ in the molecule of the alcohol. The highest yields were obtained for ethanol and benzyl alcohol. No reaction occurred with methanol or isopropanol. The process was initiated by the decomposition of DTBP on heating to l-BuO radicals, which oxidized the alcohol molecule. The stability of the formed radical plays a decisive role in, e.g., methanol forming an unstable primary radical. On the other hand, only primary alcohols can be used because two hydrogens in the α-position are necessary for radical oxidation.

Scheme 26. Sequence of steps for the synthesis of benzothiazole chromophores 33a–e.

Scheme 27. CBr₄-mediated synthesis of 2-alkyl- and arylsubstituted benzothiazoles 34a–o from 2-aminothiophenols and N-organylthioamides.

Scheme 28. Oxidative coupling of (2-aminoaryl)disulfides and primary alcohols.
Ecologically friendly, NaSH-promoted condensation of bis(2-aminophenyl)disulfides and aryl- and hetaryl aldehydes in polyethylene glycol with low-energy microwave assistance allowed to obtain 2-substituted benzothiazoles 36a–q in good yield (Scheme 29) [39]. The method is applicable to benzaldehydes with both electron donor and electron acceptor groups. The presence of NaSH facilitates the fast reduction of disulfides to aminothiophenols. The latter react with benzaldehydes affording the corresponding Schiff bases. Intramolecular oxidative cyclization accomplishes this process.

\[
\text{2,2'-disulfanediyldianilines} + \text{R}_2\text{CHO} \xrightarrow{\text{NaHS, PEG-300, 25W, 20 min}} \text{36a–q 52–95\%}
\]

\(R_1 = \text{H, Cl} \quad R_2 = \text{Ph, 4-Tol, 4-An, Bn, 3-BrC}_6\text{H}_4, 4-\text{NO}_2\text{C}_6\text{H}_4, 3-\text{OMe,}4-\text{OHOC}_6\text{H}_4, 3,4-\text{(MeO)}_2\text{C}_6\text{H}_3, 4-\text{F/Cl-C}_6\text{H}_4, 4-\text{OHOC}_6\text{H}_4, 4-\text{Me}_2\text{NC}_6\text{H}_4, 4-\text{CNC}_6\text{H}_4 \text{ furyl, thieryl.}
\]

Scheme 29. Synthesis of benzothiazoles 36a–q from diaryldisulfides and aryl- and hetarylaldehydes.

\(\alpha\)-Ketoacids react with 2,2'-disulfanediyldianilines in the presence of Na\(S_2O_5\) via condensation with the amino groups and subsequent cyclization by the nucleophilic addition of sulfur to the C=N bond (Scheme 30) [121]. The intermediate disulfides (A) suffer the S-S bond splitting and decarboxylation finally affords C-2-substituted benzothiazoles 37a–p in moderate to excellent yields. The highest yields in the experiment were obtained for electron-withdrawing substituents in the aromatic ring of \(\alpha\)-ketoacid. The reaction is metal-free and proceeds with the evolution of ecologically safe CO\(_2\). The presence of Na\(S_2O_5\) is required for complete conversion and for obtaining maximal yields of the target products.

\[
\text{2-aminophenyl disulfides} + 2\text{HO-CO-R}_2 \xrightarrow{\text{Na}_{2}S_{2}O_{5}, \text{DMSO, 100°C, 1–4h}} \text{37a–p 41–90\%}
\]

\(R_1 = \text{H, Cl} \quad R_2 = \text{Me, Ph, 4-MeC}_6\text{H}_4, 2/4-\text{OMeC}_6\text{H}_4, 4-\text{F/BrC}_6\text{H}_4, 2,4-\text{Cl}_2\text{C}_6\text{H}_3, 2-\text{BrC}_6\text{H}_4\)

Scheme 30. The synthesis and probable mechanism of formation of benzothiazoles 37a–p by the reaction of 2,2'-disulfanediyldianilines with \(\alpha\)-ketoacids.

Very recently, the reaction of ortho-haloanilides with alkali metal sulfides was reported [122]. The reaction proceeds upon heating in DMF in the presence of heterogeneous catalyst MCM-41-NHC-CuI via the CuI-catalyzed substitution of halogen by sulfur, and cyclization with dehydration and regeneration of the catalyst (Scheme 31). A series of C-2-substituted benzothiazoles 38 were obtained in good yields.
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Scheme 31. The mechanism of formation of benzothiazoles 38 from haloanilides and M2S.

C-2-substituted benzothiazoles can also be prepared by different one-pot multicomponent reactions. Thus, the effective three-component reaction of redox cyclization allowed the authors to obtain a series of 2-arylbenzothiazoles 39 [123,124]. The reaction was easy to handle, catalyzed by cheap copper acetate, tolerated a wide range of functional groups, was scalable, and used readily available reagents: haloanilines, stable non-toxic arylacetic acids or benzyl chlorides, and elemental sulfur (Scheme 32). The yields varied from good to excellent. The key step both in the reaction with arylacetic acids and with benzyl chlorides is the copper-catalyzed formation of diarylsulfides.

Scheme 32. Synthesis of 2-arylbenzothiazoles 39 from halogenoanilines, arylacetic acids or benzyl chlorides, and sulfur.

An effective and ecologically friendly methodology has been described for the synthesis of C-2-substituted benzothiazoles 40a–l and 41a–c (Scheme 33) [87]. The one-pot three-component reaction of 2-idoaniline, aryl- or hetaryl aldehydes and thiourea was catalyzed by ferromagnetic catalyst Cu(0)–Fe3O4@SiO2/NH2cel and was carried out with water as the solvent. The catalyst was easily retrieved with a magnet. A large number of products were obtained in good yields, and the electronic effects in the substituents did not affect the course of the reaction.

The alternative metal-free reaction of anilines, elemental sulfur and ethers in the presence of TBHP and KI gives rise to 2-organylbenzothiazoles 42a–r (Scheme 34) [125]. The nature and position of the substituents in the aniline moiety have no substantial effect on the yield of the target products. The reaction with cyclic ethers proceeds with ring opening leading to heterocyclic alcohols 43a–c in good yields.
Scheme 33. Synthesis of benzothiazoles 40a–l and 41a–c from 2-iodoaniline, thiourea and aryl- or hetaryl aldehydes.

Scheme 34. Synthesis of benzothiazoles 42a–r and 43a–c from anilines, ethers and sulfur.

The cyclization of anilines is assumed to be initiated by the selective splitting of the C(sp^3)-H bond in ethers in the presence of TBHP and KI. As a rule, the first step of reactions of this type is the formation of a radical, (here, t-BuO·). The latter is formed by the reaction of TBHP with KI.

Similar one-pot reactions leading to 2-hetarylbenzothiazoles from anilines, elemental sulfur and 2-methylquinolines or benzaldehydes have been described [126,127].

A three-component reaction of 2-aminothiophenols, oxalyl chloride and thiols in the presence of tetrabutylammonium iodide (TBAI) allowed the authors to obtain a wide series of 2-aryl- and arylbenzothiazol-2-carbothioates [40a–r] which, after oxidative cyclization, affords the final product.

Scheme 35. Synthesis of benzothiazoles 44 from aminothiophenols, oxalyl chloride and thiols.

The metal-free assembly of C-2-substituted benzothiazoles 45a–g, 46a–f or 47a–l based on the reaction of arylamines, elemental sulfur and styrenes or arylacetylenes in N-methylpyrrolidin-2-one (NMP) has been reported (Scheme 36) [128]. The C-S bond was formed by direct thiylation of the C-H bond in aromatic amine with elemental sulfur, acting both as the source of sulfur and the oxidant. The addition of NH₄I increased the
yield, which was also affected by the nature and position of substituents in the phenyl ring. A possible mechanism for the formation of the C-2-substituted benzothiazoles is given in Scheme 36, using the example of aniline with sulfur and styrene. Aniline reacts with sulfur to give adduct (A), which further reacts with styrene to give polysulfide (B). The latter adds another aniline molecule leading to thioamide (C). The S-S bond in the latter is split to form thioamide (D) which, after oxidative cyclization, affords the final product.

Scheme 36. Synthesis and mechanism of formation of benzothiazoles 45a–g, 46a–f or 47a–l by the reaction of arylamines, sulfur and styrenes or arylacetylenes.

Later, the strategy of a highly atom economical Cu(II)-catalyzed assembly of benzothiazoles from 2-iodoanilines, alkenes and elemental sulfur—avoiding the use of ecologically undesirable thiophenols—was developed by another group [129].

4. Synthesis of C-2-Substituted Benzothiazoles via the Introduction of Substituents at the 2-Position

A particular class of reactions is the functionalization of the already existing benzothiazole motif at the 2-position. This approach has already led to the synthesis of a large number of compounds including those possessing different pharmacological activity. For example, benzothiazoles are alkylated with acetonitrile at the 2-position in the presence of lithium t-butoxide and dioxane as a cosolvent to give 2-methylbenzothiazoles 48a–e (Scheme 37) [130].

A simple approach to 2-arylbenzothiazoles 49a–i based on the coupling reaction between benzothiazole and arylsulfamates was proposed [131]. The reaction proceeds in the presence of a catalyst and cocatalyst with nickel bromide and 1,10-phenanthroline monohydrate (Scheme 38).
A sequence of reactions including the acylation of benzothiazole and the amidoalkylation of indole at the 3-position with N-acylbenzothiazolium intermediate and oxidation of the formed products 50a–e with o-chloranil leading to benzocamalexin 51 (Scheme 39) [132,133]. The latter is the benzo-analogue of the natural plant-produced antimicrobial substance phytoalexin inhibiting the growth of parasites. The method is advantageous over other methods of heteroaromatic ring coupling, as it does not require expensive catalysts of air- and moisture-sensitive organometallic reagents, results in high yields, and is scalable.

The chemoselective alkylation/arylation of benzothiazoles with aldehydes and benzyl alcohols in the presence of a heterogeneous nanocomposite catalyst and oxidant with graphene oxide–Fe₃O₄ in polyethylene glycol (Scheme 40) affords 2-alkyl(aryl)-substituted benzothiazoles 49a–i.

A practical green synthesis of 6-substituted 2-(2-hydroxy(methoxy)phenyl)benzothiazoles 55a–i, including mesylate salts 55a–f, was elaborated (Scheme 41) [15]. The reaction was catalyst-free and used the ecologically safe and cheap solvents of glycerol and acetic acid. The optimization of the reaction conditions, solvents, and the reagents allowed the authors to carry out the reaction with compounds with hydrolytically unstable substituents. The relationship between the structure and biological activity for new compounds was studied, such as 2-hydroxyphenyl- and 2-methoxyphenylbenzothiazole with different substituents in the C-6 position of the benzothiazole fragment. The presence of the nitro or cyano group
in the C-6 position of the benzothiazole ring was found to increase the antiproliferative activity. The replacement of the cationic amidine fragment in the C-6 position by the ammonium group led to the increase in antitumor activity against other types of tumor cells. The presence of a hydroxy group in the 2-aryl fragment of 2-arylbenzothiazole molecule considerably improved the antitumor selectivity without affecting the surrounding tissues.

\[
\begin{align*}
\text{Scheme 40. Alkylation/arylation of benzothiazoles with aldehydes or benzyl alcohols.}
\end{align*}
\]

Various acyl groups were introduced in benzothiazoles in the presence of a Fe(II) triflate catalyst by the reaction of benzothiazole and its derivatives with cyclobutanone oximes (Scheme 42) [135]. A wide spectrum of alkylbenzothiazoloaryketones 56a–k was synthesized with a good selectivity and tolerance to the functional groups. The proposed method was an alternative to the conventional Friedel–Crafts acylation, allowing the authors to prepare new compounds inaccessible by other methods. The mechanism included several steps: Fe(II)→Fe(III)-induced SET-reduction of cyclobutanone oximes leading to iminyl radical (A) of Fe(III); ring opening in (A) to form the highly reactive cyanoalkyl radical (B); the capture of CO to give radical (C); and the addition to benzothiazole resulting in the radical (D). The oxidation of the latter by Fe(III) with subsequent deprotonation with a base gives alkylhetaryketones 56a–k.
The modification of substituents in the C-2 position is a widely used reaction; some examples are considered below. The condensation of N-benzyl-2-methylbenzothiazolium bromide prepared by the alkylation of 2-methylbenzothiazole with benzyl bromide and N-ethylcarbazole dialdehyde gives rise to the formation of the carbazole–benzothiazole hybrid fluorescent probe 57 (Scheme 43) [106]. This fluorophore showed a quick response, in addition to high selectivity and sensitivity in the detection of SO2. Moreover, good biocompatibility and a precise localization in the mitochondria were found.

A large series of potentially biologically active drugs, in particular, antitumor agents, based on benzothiazol-2-ylacetonitrile (BTA) has been described [10,11,16]. Below, some examples of the use of this synthon and the products thereof are given. In the synthesized hybrids, the benzothiazole fragment has different substituted heterocyclic rings in the C-2 position, such as thiazole, thiazinane, thiophene, pyrrole, thienopyrimidine, indole, furan, pyridine, chromene, quinoline, triazoloquinoline, triazepinoquinoline, etc. The pyridine or furan hybrids 58 or 59 are formed by the reaction of benzothiazol-2-ylacetonitrile containing an active methylene group with 2-(2,4-dimethoxybenzylidene)malononitrile or ethyl-2-chloro-3-oxobutanoate (Scheme 44) [10].

The reaction of BTA with carbon disulfide gives ketene acetal, which reacts with α-chloroethyl acetate resulting in thiophenebenzothiazole 60. Hydrazinolysis of the latter and condensation of the hydrazide with phthalic or acetic anhydride in the presence of acetic acid results in the corresponding amides 61 and 62 in good yields. The reaction of BTA with phenylisothiocyanate and phenacyl bromide affords the corresponding thiophene derivative 63 (Scheme 45) [10]. Compounds 61 and 62 have shown high antitumor activity to different cell lines.
A similar two-step approach led to the thiazole-pyrazole 64 or -thiophene 65 hybrids (Scheme 46) [10].

Compound 65 was further functionalized by the reaction of cyclocondensation with formic acid, chloroacetyl chloride, ethyl cyanoacetate, or ethylenediamine to give benzothiazole thienopyrimidine 66a–c or the imidazoline derivative 67 (Scheme 47) [11]. The latter compound, similar to compounds 61 and 62 above, has shown high antitumor activity to different cell lines.
Scheme 47. Synthesis of benzothiazole-thienopyrimidine 66a–c or thiophenoimidazoline 67 hybrids.

The cyclization of compound 65 with Meldrum acid resulted in the formation of the tricyclic system 68 (Scheme 48) [11].

Scheme 48. Synthesis of hybrid molecule 68.

The polyheterocyclic compound 69 containing a tetrazole ring was obtained by the treatment of product 60 (Scheme 45) with triethyl formate and heating in acetic acid in the presence of sodium azide (Scheme 49) [11].

Scheme 49. Synthesis of polycyclic hybrid molecule 69.

The nucleophilic addition of the amino group of compound 60 to the cyano group of 2-(4-(4-chlorophenyl)thiazol-2-yl)acetonitrile with subsequent intramolecular cyclization and the elimination of ethanol leads to the formation of compound 70 with the thienopyrimidinone ring (Scheme 50) [11].

Scheme 50. Cyclization with the pyrimidinone ring formation in 70.

The iminoquinoline derivative 71 was synthesized by the Knoevenagel reaction using bromosalicyl aldehyde as the carbonyl component and benzothiazol-2-yl acetonitrile,
followed by intramolecular cyclization and reflux with hydrazine hydrate in ethanol (Scheme 51) [10].

The cascade multicomponent reaction of product 71 with p-chlorobenzaldehyde and benzothiazol-2-ylacetanilide in dioxane led to the formation of the triazepine derivative 72 (Scheme 52) [11].

A series of biologically active compounds was obtained from 2-[3(4)-aminophenyl]benzothiazoles 73 or 74 [17,18,20,29]. Thus, the reaction of (3-aminophenyl)benzothiazole 73 with ethyl acetylacetonate with the subsequent formation of the pyrazole ring by the reaction with hydrazines afforded 2-benzothiazolyl pyrazole derivatives containing hydrazone spacers 75a,b (Scheme 53) [17].

Condensation of the isomeric 4-aminophenylbenzothiazole 74 with aromatic aldehydes or ketones in glacial acetic acid or in the presence of conc. H2SO4 leads to benzothiazoles with the azomethine bonds 76a–p and 76q–s (Scheme 54) [18]. These Schiff bases show anticancer activity and compounds possessing dihydroxy groups with very high inhibitive activity.

With chloroacetyl chloride, compound 74 forms 2-substituted benzothiazole with chloroacetamide group 77 which, upon the reaction with substituted piperazines, gives 2-aryl benzothiazole derivatives 78a–o possessing anticancer activity. The reaction of 74 with propargyl bromide followed by cyclization of alyazines to the triple bond gives products with the 1,2,3-triazole motif 79a–k in 67–91% yields (Scheme 55) [20].
Scheme 54. Synthesis of benzothiazoles 76a–p and 76q–s from 4-aminophenylbenzothiazole 74 and aldehydes or ketones.

With primary and secondary amines, compound 77 reacts with the formation of a large library of heterocyclic benzothiazole derivatives 80a–m and 81a–о, for which anticancer activity has been evaluated (Scheme 56) [21].

The synthesis of azo-linked-substituted benzothiazoles 82 and 83 in good yield by the diazotation of 2-(5’-amino-2’-hydroxyphenyl)benzothiazole was reported [32]. Diazotization was performed under the usual conditions with subsequent treatment with N,N-dibutyl-4-phenylthiazole-2-amine in acidic medium upon cyclization of arylazides to the triple bond gives aryl benzothiazole derivatives 80a–m and 81a–о, for which anticancer activity has been evaluated (Scheme 56) [21].

Using the reaction of the diastereoselective ketene-imine cycloaddition, sixteen new benzothiazole β-lactam conjugates have been synthesized [33]. The reaction was performed by the treatment of (benzothiazol-2-yl)phenols with bromoacetic acid in DMF in the presence of solid K$_2$CO$_3$. The subsequent reaction of the obtained oxacyclic acids with the Schiff bases in the presence of tosyl chloride gave the target cis-β-lactams 84a–p in yields from 60 to 90% (Scheme 58). The obtained hybrids showed good antimicrobial and antimalarial activity. The presence of the nitrophenyl group at the C-4 atom of the β-lactam ring, or anisyl, tolyl, or naphthyl groups on the N-1 atom of the β-lactam ring enhances the antimicrobial activity.
been described [64]. For this, 3-(benzo[d]thiazol-2-yl)phenols with bromoacetic acid in DMF in the presence of solid K$_2$CO$_3$. The subsequent reaction of the obtained oxyacetic acids with formed by the treatment of (benzothiazol-2-yl)phenols with bromoacetic acid in DMF in the presence of tosyl chloride gave the target Schiff bases in the presence of catalytic amounts of acetic acid in dry ethanol (Scheme 60).

Scheme 56. Benzothiazole hybrid molecules 80a–m and 81a–o with potential anticancer activity.

$$\text{R}_3 = \text{H, 4-F/Cl/Br, 2/3-Cl, 2,6-Cl}_2, 3\text{-Cl-4-F, 4-NO}_2, 2/4\text{-Me/OMe/OH, 4-SO}_2\text{NH}_2$$

Scheme 57. Synthesis of the azo-linked benzothiazole hybrid molecules 82 and 83.

Scheme 58. Synthesis of benzothiazole β-lactam conjugates 84a–p.
The introduction of 2-(4-hydroxyphenyl)benzothiazole in the reaction with propargyl bromide in the presence of a base affords 2-(4-propargyloxyphenyl)benzothiazole, which enters cycloaddition reactions with various azides in the presence of copper fluorapatite, leading to benzothiazole–triazole hybrid molecules 85a–t (Scheme 59) [22].

Scheme 59. Synthesis of polyfunctional derivatives of benzothiazole 85a–t.

As mentioned above, a number of hydroxyl-derivatives of benzothiazole demonstrate fluorescent properties. For example, the synthesis of the benzothiazole-based water-soluble biochemosensor 86 used for the detection of intracellular zinc and aluminum ions has been described [64]. For this, 3-(benzo[d]thiazol-2-yl)-2-hydroxy-5-methylbenzaldehyde is prepared by successive treatment of hydroxymethylphenylbenzothiazole with trifluoroacetic acid and diaminomalononitrile in the presence of catalytic amounts of acetic acid in dry ethanol (Scheme 60).

Scheme 60. Synthesis of benzothiazole chemosensor 86 for the detection of Zn2+ and Al3+ ions.

Another green and efficient approach to luminophores is mechanochemical, solvent-free synthesis [65]. A mixture of 2-(2-hydroxyphenyl)benzothiazole, hexamethylenetetramine, trifluoroacetic acid and silica gel was thoroughly grinded for 3 h. The obtained product was purified by chromatography and grinded with benzophenone hydrazone for 0.5 h. The synthesized dye 87 (Scheme 61) can be used for the detection of Cu2+ both in solution and in the solid phase.

The syntheses based on the hydroxyphenyl derivatives of benzothiazole were reported as fluorescent probes 88a–c for the detection of esterase in curing various diseases [60,66], and trace amounts of Hg2+ [67], Cu2+ and S2– ions [68] were found (Scheme 62).
The products showed strong emission in both solid and aggregated states and a low emission in solvents of different polarities.

Scheme 61. Synthesis of the benzothiazole luminophore 87 for the detection of Cu$^{2+}$ ions.

Scheme 62. Synthesis of benzothiazole fluorescent probes 88a-c.

Nitrophenyl 2-(2-hydroxyphenyl)benzothiazole derivatives with –Ar–, –Ar–C=C– and –Ar–C≡C– linkers have been synthesized by the Suzuki, Heck, and Sonogashira reactions, respectively (Scheme 63) [136]. The presence of the strong electron acceptor group 4-NO$_2$C$_6$H$_4$ facilitates a charge transfer and affects the photophysical properties of the molecules. It also facilitates various intermolecular interactions. In the Heck reaction, the substrate was first acetylated with acetic anhydride, and the formed acetate was introduced to the reaction with (E)-4-nitrostyrene to obtain the acetate-protected product. Further deprotection under alkaline conditions gave the target product d-HBT-NO$_2$. To investigate the fluorescent properties of the products, they were converted to the corresponding methoxy derivatives by the action of methyl iodide. Nitrophenyl 2-(2-anisyl)benzothiazole 89b was found to be most promising for further investigation.

Scheme 63. Synthesis of bridged benzothiazole fluorescent probes 89a-c.

The Pd(PPh$_3$)$_4$-catalyzed Suzuki coupling of 2-(benzothiazol-2-yl)-5-bromophenol and commercially available carboxylic acids gave three positional isomers 90a-c (Scheme 64) [69]. The products showed strong emission in both solid and aggregated states and a low emission in solvents of different polarities.
Benzothiazole-2-carbaldehyde was used for the synthesis of new anti-HIV drug biotin-BMMP 91 [37]. First, the aldehyde was quantitatively reduced with NaBH₄ to the corresponding alcohol, which was brominated with PBr₃. The bromine atom in the formed 2-(bromomethyl)benzothiazole was replaced by pyrimidine thiol, as shown in Scheme 65. Subsequent hydrazinolysis and the EDC-mediated conjugation of primary amine with biotine gave the target biotine-BMMP in 96% yield.

Scheme 64. Synthesis of isomeric benzothiazole fluorescent probes 90a–c.

2-Acetylbenzothiazole is often used for the synthesis of hybrid molecules. Benzothiazoles containing thieno[2,3-β]pyridine moieties 92a and 92b were obtained in two steps: the bromination of 2-acetylbenzothiazole; and cyclization with mercaptonicotine nitrile (Scheme 66) [137].

Scheme 65. Synthesis of Biotin-BMMP 91 from benzothiazole-2-carbaldehyde.

Scheme 66. Synthesis of benzothiazole–thieno[2,3-β]pyridine hybrid molecules 92a,b.
2-Acetylbenzothiazole has also been used for the synthesis of thiazole-, benzothiazole-, and benzofuran-containing molecules, as well as bis-benzothiazole derivatives. The main advantage of these reactions is their easy handling and cheap starting materials [105]. The transformations leading finally to benzothiazoles 93a–c with ethyldenehydrazinyl linkers are shown in Scheme 67. The components of condensation were prepared by the reaction of 2-acetylbenzothiazole with thiosemicarbazide or with bromine. The subsequent reactions of compounds A and B gave the target hybrid molecules.

![Scheme 67. Synthesis of benzothiazole hybrids 93a–c.](image)

2-Bromacetyl benzothiazole reacts with mono- and bis-N-amino-2-mercaptotriazoles to give hybrid molecules 94a,b and 95a–d with one or two triazolothiadiazine moieties (Scheme 68) [105].

![Scheme 68. Synthesis of benzothiazoles with triazolothiadiazine fragments 94a,b and 95a–d.](image)

In a similar way, 2-bromacetyl benzothiazole with bis(thiosemicarbazones) affords hybrid molecules 96a–c linked by the aliphatic spacer via phenoxy groups (Scheme 69) [105].

Condensation of benzothiazole-2-carbohydrazide with 1H-indole-3-carbaldehydes gives rise to the formation of N-acylhydrazone derivatives 97a–e possessing antitumor activity (Scheme 70) [19]. The products are shown to exist as the E-diastereomers. The method is characterized by mild conditions, high yields, and easy handling.
Condensation of benzothiazole-2-carboxyhydrazide with 1,3,4-oxadiazole fragments 99a–j with pronounced biological activity were synthesized via a multistep reaction sequence [23]. In the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and hydroxybenzotriazole (HOBt), benzothiazole-2-carboxylic acid reacts with 4-hydroxy-3,5-dimethoxybenzohydrazide to form hydrazide, which cyclizes via thionation with Lawesson’s reagent. Esterification of the product of cyclization and subsequent aminomethylation with formaldehyde and primary or secondary amines allowed the authors to prepare a large series of benzothiazole-based oxadiazole Mannich bases, demonstrating its enhanced antidiabetic activity 98a–v (Scheme 71).

A series of benzothiazole-based condensed derivatives with 1,3,4-oxadiazole fragments 99a–j with pronounced biological activity were synthesized via a multistep reaction sequence [23]. In the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and hydroxybenzotriazole (HOBt), benzothiazole-2-carboxylic acid reacts with 4-hydroxy-3,5-dimethoxybenzohydrazide to form hydrazide, which cyclizes via thionation with Lawesson’s reagent. Esterification of the product of cyclization and subsequent hydrazinolysis and cyclization with substituted benzoic acids afford new polyfunctional heterocycles 99a–j (Scheme 72).
by the reaction of diethyl chlorophosphate with benzothiazole containing iminocouma-
100a,b
eresidue in the C-2 position has been reported [138]. The target products were syn-
thesized by the use of triethylamine, conc. hydrochloric acid, and organic Good’s buffers
(Scheme 73). Synthesis of polyfunctional 2-substituted benzothiazoles 99a–j.

The synthesis of highly sensitive probes for the detection of chemical warfare agents
100a,b by the reaction of diethyl chlorophosphate with benzothiazole containing iminocouma-
rine residue in the C-2 position has been reported [138]. The target products were syn-
thesized by the use of triethylamine, conc. hydrochloric acid, and organic Good’s buffers
(Scheme 73).

Scheme 72. Synthesis of polyfunctional 2-substituted benzothiazoles 99a–j.

The functionalization of the phenylene fragment of benzothiazole is another pos-
sibility of modification. However, we were able to find only one example of such a trans-
formation. A microwave-assisted regioselective three-component reaction of 2-methyl-
5-aminobenzothiazole, aromatic aldehydes and 2-hydroxy-1,4-naphthoquinone in acetic
acid afforded polycyclic condensed acridine derivatives 102a–h [102]. The sequence of
reactions included the Knoevenagel reaction, the intermolecular Michael addition with
subsequent intramolecular nucleophilic cyclization, and the reactions of dehydration and
oxidation. The MW-assisted [2+2+1] cyclization of acridinediones 101a–n with aldehydes
in the presence of ammonium acetate results in the oxazolole–thiazolole-condensed acri-
dine ensembles 102a–h (Scheme 74). The proposed procedure is simple to perform, uses
readily available reagents, provides selective modification of the acridine framework, and
is characterized by a high efficiency of bond formation.

Scheme 73. Benzothiazole-based probes 100a,b for the detection of chemical warfare agents.

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dine ensembles 102a–h (Scheme 74). The proposed procedure is simple to perform, uses
readily available reagents, provides selective modification of the acridine framework, and
is characterized by a high efficiency of bond formation.
6. Conclusions

In summary, the versatile range of synthetic approaches to the C-2 derivatives of benzothiazole developed in the last five years is indicative of the relentless interest in this heterocycle, which is very promising from both a synthetic and biological point of view. In the present review, the methods of synthesis of the title compounds were divided into: (i) intra- and (ii) intermolecular assembling of the benzothiazole ring, (iii) the introduction of substituents at the 2-position, and (iv) the functionalization of the phenylene fragment. Among them, those including the thiazole ring closure and the modification of substituents at the C-2 position were dominant. Along with traditional multistep synthetic methods, new ecologically friendly atom economy one-pot procedures have been developed, which are the basis of modern organic synthesis. For the most interesting processes, only tentative mechanisms are given. Recent studies in this field have allowed the discovery of new C-2-substituted derivatives of benzothiazole and proven them to be good candidates for numerous drugs with various types of biological activity. Their pharmacological and biological activity strongly depend on the nature and position of the substituents, both in the benzene ring of the benzothiazole cycle and in the heterocycles formed by the functionalization of benzothiazole. The authors hope that this review will help the development of the targeted synthesis of benzothiazoles and their analogues.

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