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SYNTHESIS OF 5-SUBSTITUTED BENZOTHIAZOLIN-2′-THIOMETHYLENE-1,3,4-OXADIAZOLINE-2-THIONES: A REVIEW OF SYNTHETIC METHODOLOGIES

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Abstract: This review presents a comprehensive analysis of the synthetic routes leading to 5-substituted benzothiazolin-2′-thiomethylene-1,3,4-oxadiazoline-2-thiones, a class of heterocyclic compounds that combine benzothiazoline and 1,3,4-oxadiazoline-2-thione moieties connected via a thiomethylene bridge. The review systematically examines the two principal synthetic strategies: (1) the convergent approach based on the nucleophilic substitution reaction between 5-substituted-1,3,4-oxadiazoline-2-thiones and N-(benzothiazol-2-yl)-2-chloroacetamides; and (2) the linear approach involving condensation of (2-benzothiazolylthio)acetic acid derivatives with carboxylic acid hydrazides followed by cyclodehydration. The synthesis of key precursors—namely 5-substituted-1,3,4-oxadiazoline-2-thiones via ring-closure reactions of acid hydrazides with carbon disulfide, and benzothiazolin-2-thione derivatives via thiation or direct functionalization—is critically discussed. Representative reaction conditions, yields, and spectroscopic characterization data are summarized to provide a practical reference for researchers interested in this hybrid heterocyclic scaffold, which has attracted attention for its potential antimicrobial and cytotoxic biological activities.

Introduction

Heterocyclic compounds containing sulfur and nitrogen atoms constitute one of the most extensively studied classes of organic molecules due to their remarkable biological activities and pharmaceutical applications [0]. Among these, the 1,3,4-oxadiazoline scaffold has attracted considerable attention as a privileged pharmacophore exhibiting antimicrobial, anti-inflammatory, and cytotoxic properties [2][7]. Similarly, the benzothiazoline ring system has demonstrated broad-spectrum biological activity, and compounds derived from benzothiazoline-2-thione (2-mercaptobenzothiazoline) have found widespread applications in medicinal chemistry and materials science [0][6].

The molecular hybridization of benzothiazoline and 1,3,4-oxadiazoline-2-thione moieties through a thiomethylene linker (–SCH_2–) has emerged as a rational strategy for generating new chemical entities with enhanced pharmacological profiles. This structural motif is exemplified by 5-substituted benzothiazolin-2′-thiomethylene-1,3,4-oxadiazoline-2-thiones, which feature a benzothiazoline ring linked via a thiomethylene bridge to a 1,3,4-oxadiazoline-2-thione core bearing a substituent at the 5-position. The conjugation of these two bioactive heterocyclic units through a flexible sulfur-containing linker is anticipated to modulate conformational freedom, influence electronic distribution, and consequently affect the biological target interactions of these hybrid molecules [15][21].

The synthesis of 1,3,4-oxadiazoline-2-thiones has been well documented, with the most common method being the ring-closure reaction of carboxylic acid hydrazides with carbon disulfide under basic conditions [15]. For example, 5-substituted-1,3,4-oxadiazolin-2-thiones can be prepared in moderate to good yields by treating appropriately substituted acid hydrazides with carbon disulfide in the presence of potassium hydroxide in ethanolic medium [15][13]. Similarly, benzothiazoline-2-thione derivatives have been synthesized through various approaches, including the direct functionalization of 2-mercaptobenzothiazoline and the cyclization of ortho-aminothiophenols [19][0].

Although the individual heterocyclic components have been extensively studied, the literature concerning their hybrid derivatives linked by a thiomethylene bridge remains relatively scarce. The objective of this review is to provide a comprehensive survey of the synthetic

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methodologies available for the construction of 5-substituted benzothiazolin-2′-thiomethylene-1,3,4-oxadiazoline-2-thiones, encompassing the preparation of key precursors, the strategies for thiomethylene bridge formation, and the characterization of the resulting hybrid molecules.

Materials and Methods

Synthesis of 5-Substituted-1,3,4-oxadiazoline-2-thiones (Key Precursors)

The 5-substituted-1,3,4-oxadiazoline-2-thiones represent the most critical precursors for the construction of the target hybrid molecules. The standard synthetic protocol involves the ring-closure reaction of appropriately substituted carboxylic acid hydrazides with carbon disulfide. In a representative procedure described by Kaplancikli and coworkers, 5-substituted-1,3,4-oxadiazolin-2-thiones (1a–b) were synthesized by treating the corresponding acid hydrazides with carbon disulfide in the presence of potassium hydroxide in ethanol, yielding the desired oxadiazoline-2-thiones in satisfactory yields (62–78 %) after acidification [15].

The general reaction may be represented as follows:

$R–CONHNH_2 + CS_2 \rightarrow R–(C_2N_2OSH)–thione$ (1)

where R represents the 5-substituent, which may be aryl, alkyl, or heteroaryl groups depending on the starting hydrazide employed.

Characterization data for representative 5-substituted-1,3,4-oxadiazoline-2-thiones include characteristic IR absorption bands for C=S stretching (1250–1300 cm^{-1}) and N–H stretching (3100–3200 cm^{-1}), while ^1H NMR spectra display the NH proton of the oxadiazoline ring as a broad singlet at δ 10.5–12.0 ppm [15][16]. The ^{13}C NMR spectra exhibit the thiocarbonyl carbon (C=S) signal at approximately δ 177–180 ppm [15].

Alternative methods for the preparation of 1,3,4-oxadiazoline-2-thiones have been reported by Mashaly and coworkers, who synthesized 5-[(1-benzoylamino)styren-1-yl]-1,3,4-oxadiazoline-2-thiones through a similar cyclocondensation strategy starting from the corresponding hydrazide precursors [16]. Additionally, Kelarev and colleagues have reported the synthesis of 1,3,4-oxadiazoles containing benzothiazolylthiomethyl groupings via condensation of (2-benzothiazolylthio)acetic acid derivatives with carboxylic acid hydrazides [14].

Synthesis of Benzothiazoline-2-thione Derivatives

Benzothiazoline-2-thione, also known as 2-mercaptobenzothiazoline, is readily available either commercially or through established synthetic procedures. The compound can be obtained via the reaction of 2-aminothiophenol with carbon disulfide under basic conditions, or through the thiation of benzothiazolin-2-one using phosphorus pentasulfide or Lawesson's reagent [6][17]. The chemistry of benzothiazoline-2-thione has been extensively explored by various research groups, particularly with regard to its alkylation and functionalization reactions [17].

The alkylation of benzothiazoline-2-thione proceeds regioselectively at the exocyclic sulfur atom. As demonstrated in a study of cyanoethylation reactions, benzothiazoline-2-thione undergoes mono-cyanoethylation upon treatment with acrylonitrile, affording 3-(2-cyanoethyl)benzothiazoline-2-thione derivatives [17]. This regioselective S-alkylation behavior is of paramount importance for the subsequent construction of the thiomethylene bridge connecting the benzothiazoline and oxadiazoline moieties.

Construction of the Thiomethylene Bridge: Convergent Strategy

The most direct and widely employed strategy for the synthesis of 5-substituted benzothiazolin-2′-thiomethylene-1,3,4-oxadiazoline-2-thiones involves a convergent approach wherein the thiomethylene linkage is established through a nucleophilic substitution (S_n2) reaction between preformed 5-substituted-1,3,4-oxadiazoline-2-thiones and appropriate N-(benzothiazol-2-yl)-2-chloroacetamide electrophiles [15].

In the representative protocol reported by Kaplancikli and coworkers, N-(benzothiazol-2-yl)-2-[[5-substituted-1,3,4-oxadiazol-2-yl]sulfanyl]acetamide derivatives (3a–j) were synthesized by the reaction of 5-substituted-1,3,4-oxadiazolin-2-thiones (1a–b) with N-(benzothiazol-2-yl)-2-chloroacetamides in the presence of potassium carbonate as a base in acetone at reflux temperature [15]. The general reaction scheme is as follows:

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5-R-oxadiazoline-2-thione + ClCH₂CONH-(benzothiazol-2-yl) → 5-R-oxadiazole-2-S-CH₂CONH-(benzothiazol-2-yl) (2)

This nucleophilic substitution proceeds through the thiolate anion generated in situ from the oxadiazoline-2-thione upon deprotonation by potassium carbonate. The thiolate subsequently attacks the electrophilic methylene carbon of the chloroacetamide, displacing the chloride leaving group and establishing the thiomethylene bridge [15].

The reaction conditions—refluxing acetone, potassium carbonate as base, and reaction times of 6–12 hours—were found to be optimal for obtaining the desired products in yields ranging from 52 to 76 % after purification by recrystallization from ethanol [15]. The chemical structures of the products were confirmed by IR, ^{1}H NMR, ^{13}C NMR, FAB^{+}-MS, and elemental analysis [15].

An analogous approach has been described by Rajeeva and coworkers for the synthesis of benzothiazolyl oxadiazole derivatives. In their work, 5′-(1,3-benzothiazole-2-yl)-1′,3′,4′-oxadiazole-2′-(3H)-thione (3) was prepared in a single step from 1,3-benzothiazole-2-carboxyhydrazide (2) through reaction with carbon disulfide in the presence of potassium hydroxide in ethanolic medium [13]. This compound was subsequently employed as a substrate for Mannich reactions with formaldehyde and substituted amines, yielding 2-(5′-mercapto-4′-substituted methylamino-1′,3′,4′-oxadiazole-2′-yl)benzothiazoles (4a$_1$–a$_{10}$) [13].

Construction of the Thiomethylene Bridge: Linear Strategy

An alternative linear approach for synthesizing compounds containing the benzothiazolylthiomethyl–oxadiazole connectivity has been reported by Kelarev and collaborators. This strategy involves the initial preparation of (2-benzothiazolylthio)acetic acid derivatives, which are subsequently condensed with carboxylic acid imino ester hydrochlorides or carboxylic acid hydrazides, followed by cyclodehydration to construct the oxadiazole ring [14].

In this methodology, the thiomethylene bridge is formed prior to the construction of the oxadiazole heterocycle. The key step involves the condensation of (2-benzothiazolylthio)acetic acid hydrazides with carboxylic acid derivatives, followed by cyclodehydration under the action of phosphorus oxychloride ($POCl_3$) to afford the corresponding 1,3,4-oxadiazole derivatives [14]. The reaction may be schematically represented as follows:

(Benzothiazolyl-S-CH₂)-CONHNH₂ + R-COX → (Benzothiazolyl-S-CH₂)-oxadiazole-R (3)

where X represents a suitable leaving group.

An additional synthetic route described by the same authors involves the reaction of 2-mercaptobenzothiazole with 2-chloromethyl-1,3,4-oxadiazoles in the presence of sodium methoxide, which directly furnishes the benzothiazolylthiomethyl–oxadiazole conjugates through nucleophilic substitution [14]. This approach is complementary to the convergent strategy described previously, as it employs a preformed oxadiazole bearing a chloromethyl group as the electrophilic component.

Alternative Approaches to Heterocycle-Heterocycle Linkage

Several other synthetic routes for connecting benzothiazole and oxadiazole pharmacophores have been explored in the literature. A series of 3-[(5-aryl-1,3,4-oxadiazol-2-yl)methyl]benzo[d]thiazol-2(3H)-ones was synthesized by the reaction of (5-substituted-2-oxobenzothiazolin-3-yl)-acetohydrazide with various aromatic acids in $POCl_3$ under reflux conditions [6]. This protocol highlights the versatility of the acetohydrazide intermediate as a linchpin for heterocycle assembly.

Similarly, compounds bearing 1,3,4-oxadiazole and benzothiazole units connected through sulfur-containing linkages have been prepared for antimicrobial evaluation. The synthetic approach involved the preparation of oxadiazole-2-thione intermediates, which were subsequently alkylated with appropriate benzothiazole-containing electrophiles [9].

Spectroscopic Characterization of Target Compounds

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The structural elucidation of the synthesized 5-substituted benzothiazolin-2′-thiomethylene-1,3,4-oxadiazoline-2-thiones relies on a combination of spectroscopic techniques. In the IR spectra, characteristic absorption bands are observed for the N–H stretching of the amide group (3200–3300 cm^{-1}), the C=O stretching of the amide carbonyl (1650–1680 cm^{-1}), the C=N stretching of the oxadiazole and benzothiazole rings (1590–1620 cm^{-1}), and the C–S–C stretching vibrations (680–720 cm^{-1}) [15].

In the ^{1}H NMR spectra, the methylene protons of the thiomethylene bridge (–SCH_2–) appear as a characteristic singlet at δ 4.00–4.30 ppm, while the amide NH proton resonates as a broad singlet at δ 10.50–11.50 ppm [15]. The aromatic protons of the benzothiazole ring system are observed in the range δ 7.20–8.10 ppm with coupling patterns consistent with ortho-disubstituted benzene derivatives. The ^{13}C NMR spectra display signals for the thiocarbonyl carbon (C=S) at δ 177–180 ppm, the amide carbonyl (C=O) at δ 165–168 ppm, and the methylene carbon of the thiomethylene bridge at δ 35–38 ppm [15].

Mass spectrometric analysis (FAB^{+}-MS) provides molecular ion peaks [M^{+}] and fragment ions consistent with the proposed structures. Elemental analysis (C, H, N, S) data are generally within ±0.4 % of the calculated values, confirming the purity and composition of the synthesized compounds [15].

Results and Discussion

The comprehensive review of the literature reveals two principal synthetic paradigms for the construction of 5-substituted benzothiazolin-2′-thiomethylene-1,3,4-oxadiazoline-2-thiones: a convergent strategy based on nucleophilic substitution, and a linear strategy based on sequential condensation and cyclodehydration.

Analysis of the Convergent Strategy

The convergent approach, as exemplified by the work of Kaplancikli and coworkers, offers several practical advantages for the synthesis of the target hybrid molecules [15]. First, the preformation of both heterocyclic components—the 5-substituted-1,3,4-oxadiazoline-2-thione and the N-(benzothiazol-2-yl)-2-chloroacetamide—allows for independent optimization of the synthesis of each building block. Second, the nucleophilic substitution reaction that establishes the thiomethylene bridge proceeds under relatively mild conditions (potassium carbonate, refluxing acetone) and tolerates a variety of substituents at the 5-position of the oxadiazoline ring [15]. Third, the convergent nature of the approach is amenable to the rapid generation of compound libraries for biological screening, as variations in the 5-substituent can be introduced through the choice of the starting acid hydrazide.

The yields obtained in this transformation (52–76 %) are acceptable for multi-step synthetic sequences, and the products are readily purified by recrystallization [15]. A limitation of this approach is the requirement for the preparation of N-(benzothiazol-2-yl)-2-chloroacetamides as electrophilic partners, which adds an additional synthetic step to the overall sequence.

Analysis of the Linear Strategy

The linear approach reported by Kelarev and colleagues provides an alternative route that constructs the oxadiazole ring after the thiomethylene linkage has been established [14]. This strategy is particularly advantageous when the (2-benzothiazolylthio)acetic acid derivatives are readily accessible and when the cyclodehydration conditions ($POCl_3$) are compatible with the desired substitution pattern on the oxadiazole ring. The method has been successfully applied to the synthesis of a series of 2,5-disubstituted 1,3,4-oxadiazoles containing the 2-benzothiazolylthiomethyl grouping in good yields [14].

However, the use of $POCl_3$ as a dehydrating agent requires careful control of reaction conditions to avoid side reactions, and the strongly acidic conditions may be incompatible with acid-sensitive functional groups. An attractive variant of this approach involves the direct coupling of 2-mercaptobenzothiazole with 2-chloromethyl-1,3,4-oxadiazoles under basic conditions (sodium methoxide), which circumvents the need for aggressive dehydrating reagents [14].

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A comparative evaluation of the two principal synthetic strategies is summarized in Table 1

Criterion	Convergent Strategy (Kaplancikli et al.)	Linear Strategy (Kelarev et al.)
Key bond-forming step	S_n2 substitution at thiomethylene bridge	Cyclodehydration to form oxadiazole
Number of steps (from commercial materials)	3–4 steps	3–5 steps
Typical overall yield	40–55 %	35–50 %
Functional group compatibility	Broad; mild basic conditions	Limited; acidic conditions ($POCl_3$)
Suitability for library synthesis	Excellent	Moderate

Spectroscopic Characterization and Structure Confirmation

The spectroscopic data reported for the synthesized compounds are fully consistent with the proposed structures. The appearance of the thiomethylene bridge as a distinct singlet in the ^1H NMR spectrum at δ 4.00–4.30 ppm provides unambiguous evidence for the formation of the C–S–C linkage. Similarly, the presence of the thiocarbonyl carbon signal in the ^{13}C NMR spectrum at δ 177–180 ppm confirms the retention of the oxadiazoline-2-thione moiety in the final products [15].

Biological Activity Profile

Although the primary focus of this review is on synthetic methodology, it is noteworthy that several of the synthesized 5-substituted benzothiazolin-2′-thiomethylene-1,3,4-oxadiazoline-2-thione derivatives have demonstrated promising antimicrobial and cytotoxic activities in preliminary biological evaluations [15][13]. The compounds bearing 4-methoxyphenoxymethyl substituents on the oxadiazole ring exhibited particularly potent anti-candidal activity, while several derivatives showed significant antibacterial activity against *Pseudomonas aeruginosa* [15]. These biological results validate the molecular hybridization strategy and underscore the pharmaceutical potential of this class of compounds.

Conclusion

The synthesis of 5-substituted benzothiazolin-2′-thiomethylene-1,3,4-oxadiazoline-2-thiones can be accomplished through two complementary synthetic approaches. The convergent strategy, involving nucleophilic substitution of 5-substituted-1,3,4-oxadiazoline-2-thiones with N-(benzothiazol-2-yl)-2-chloroacetamides, offers operational simplicity, mild reaction conditions, and excellent suitability for the generation of structurally diverse compound libraries. The linear approach, based on the condensation of (2-benzothiazolylthio)acetic acid derivatives with hydrazides followed by cyclodehydration, provides an alternative route that may be advantageous when specific substitution patterns are required.

Both strategies yield the target hybrid molecules with acceptable overall yields and permit structural diversification through variation of the substituents on either heterocyclic component. The spectroscopic characterization data for these compounds are well established and provide reliable benchmarks for the identification of new derivatives. Given the demonstrated antimicrobial and cytotoxic activities of these hybrid heterocycles, continued exploration of their synthetic chemistry and biological properties represents a promising direction for medicinal chemistry research.

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