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Evolution in the synthesis of 1,4-benzothiazines over the last decade (2014 to 2024)

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1,4-Benzothiazine (1,4-BT) is a heterocyclic compound consisting of a benzene ring fused with a thiazine ring, incorporating both nitrogen and sulfur atoms. The fusion of the benzene and thiazine frameworks enhances its biological properties, making it a valuable scaffold for designing innovative heterocyclic systems. This versatile and significant member of the heteroarene family bridges synthetic organic chemistry with medicinal, pharmaceutical, and industrial applications. This structural motif demonstrates remarkable potential for accommodating a wide range of substrates and functionalizations, giving rise to diverse biological activities such as antipsychotropic, antiviral, antithyroid, antimicrobial, antifungal, antitubercular, antioxidant, and anti-inflammatory properties. Numerous derivatives have been synthesized as target structures in drug development. This review highlights various synthetic approaches to prepare 1,4-BTs. Well-established methods, such as the reactions of 2-aminothiophenol (2-ATP) with alkenes, enaminones, carboxylic acids, esters, furan-2,3-dione, aroylmethylidene malonate and 1,3-dicarbonyl compounds, are summarized. Additionally, the miscellaneous syntheses of 1,4-BTs were also outlined. These methods have utilized various catalysts, including nanocatalysts and metal-based catalysts, under diverse reaction conditions for efficient synthesis. The deep analysis of the synthesis of 1,4-BTs will grasp the scientific community towards their synthetic aspects and further advances in the field.

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1. Introduction

Heterocyclic compounds are a fundamental category of organic compounds that contain atoms such as nitrogen, sulfur, within their ring structures. These compounds are of immense significance due to their abundance in nature and their vital roles in various biological processes.[1] Many natural products, such as vitamins, hormones, alkaloids, and antibiotics, are heterocyclic in nature. In addition, heterocyclic compounds are crucial in the pharmaceutical, agricultural, and industrial sectors, where they serve as drugs, herbicides, dyes, and agents for corrosion inhibition and material stabilization.[2,3] Out of all the heterocyclic compounds containing nitrogen and sulfur, benzothiazines are significant due to their potent biological

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activities and their widespread use as a critical structural component in various bioactive molecules.[4]

Benzothiazine is a type of heterocyclic compound prepared by the fusion of a benzene ring with a thiazine ring *via* a carbon–carbon bond. Thiazines are six-membered heterocyclic structures that incorporate both nitrogen and sulfur in the same ring. They exist in various regioisomeric forms, such as 1,2-benzothiazines, 2,1-benzothiazines, 1,3-benzothiazines, 3,1-benzothiazines, 1,4-benzothiazine (1,4-BT), 2,3-benzothiazines, and 3,2-benzothiazines, all of which have been developed and evaluated for their pharmacological potential[5] (Fig. 1). Among them, 1,4-BT (Fig. 2) has drawn increasing worldwide attention for their versatile applications.[6,7] Several distinct 1,4-BT have been isolated from different natural sources, including conicaquinones A and B,[8] xanthiside,[9] pheomelanins,[10,11] and xanthizone,[12] all of which serve as examples of 1,4-BT derivatives in nature (Fig. 3).

The 1,4-BT ring system is considered a central structure in S, N-heterocycles, due to its wide-ranging pharmacological and biological effects, including antidiabetic,[13] anti-hypertensive,[14] analgesic,[15,16] antifungal,[17–19] anti-HCV,[20] calcium antagonist,[21] antibacterial,[22] antioxidant,[23] anti-inflammatory,[24] antitubercular,[25] anticancer,[26–32] antipsychotropic,[33] immunomodulator,[34] antiviral,[35] antithyroid,[36] cardiovascular activity,[37] antimalarial,[38] antipyretic,[39] herbicidal, and pesticidal[39] activities. They also serve as the central structure in various drugs, including antibiotic and cholesterol-lowering drug[40] (Fig. 4).[41–44] Moreover, they are widely known to serve in the fields of dyes, photographic developers, and ultraviolet absorption.[45,46] These moieties are advantageous for synthetic applications, due to the wide substrate scope and chemo-selectivity. They are commonly synthesized by condensing 2-aminothiophenol (2-ATP) with alkene, 1,3-dicarbonyls, enaminones, employing oxidative coupling or other methodologies. In recent decades, significant progress can be seen in the literature for the synthesis and exploration of the biological activities of 1,4-BT derivatives.[35,39,46] However, existing reviews have often presented fragmented information, underscoring the need for a comprehensive and cohesive summary of recent advancements. This article provides an overview of various synthetic approaches to 1,4-BT derivatives, focusing on the use of 2-ATP with a range of substrates, including alkenes, carboxylic acids and their derivatives, furan-2,3-dione, enaminones, ketones, epoxides, and 1,3-dicarbonyl compounds. Special emphasis is placed on their synthetic methodologies developed over the past decade, highlighting diverse reaction conditions and strategies employed to construct these biologically significant scaffolds.

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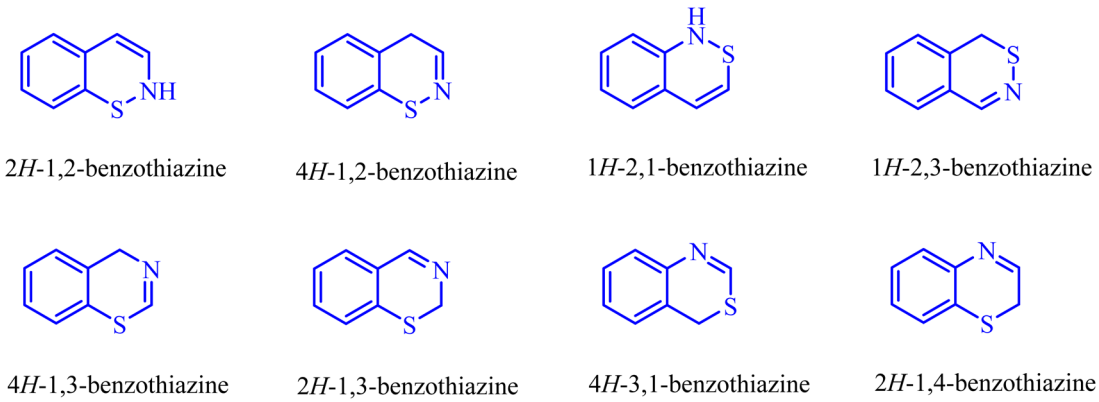


Fig. 1 Structural isomers of benzothiazine molecule.

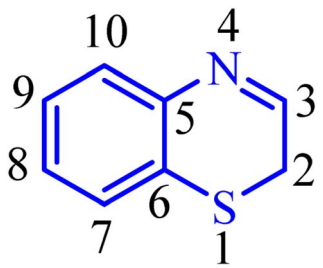


Fig. 2 Skeletal formula of 1,4-BT molecule.

2. Synthesis of 1,4-BT derivatives

The synthesis of 1,4-BT derivatives has been widely studied using classical reactions, typically starting from 2-ATP. In this review, we have explored a variety of synthetic routes involving 2-ATP as a major precursor, which is then interacted with diverse substrates like alkenes, acids and their derivatives, ketones, aroylmethylidene malonates, epoxides, furan-2,3-dione, enaminones, 1,3-dicarbonyl compounds, and many more. Additionally, the miscellaneous synthesis of 1,4-BT was

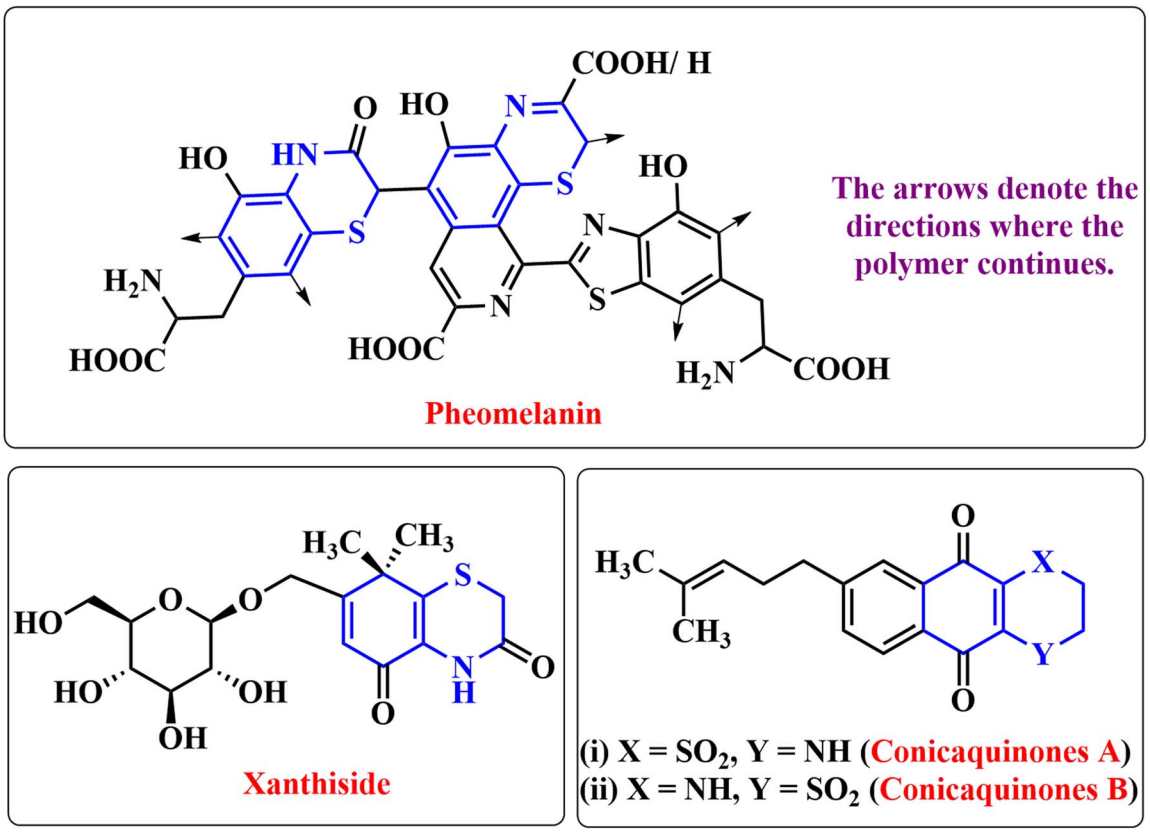


Fig. 3 1,4-BT containing natural products.

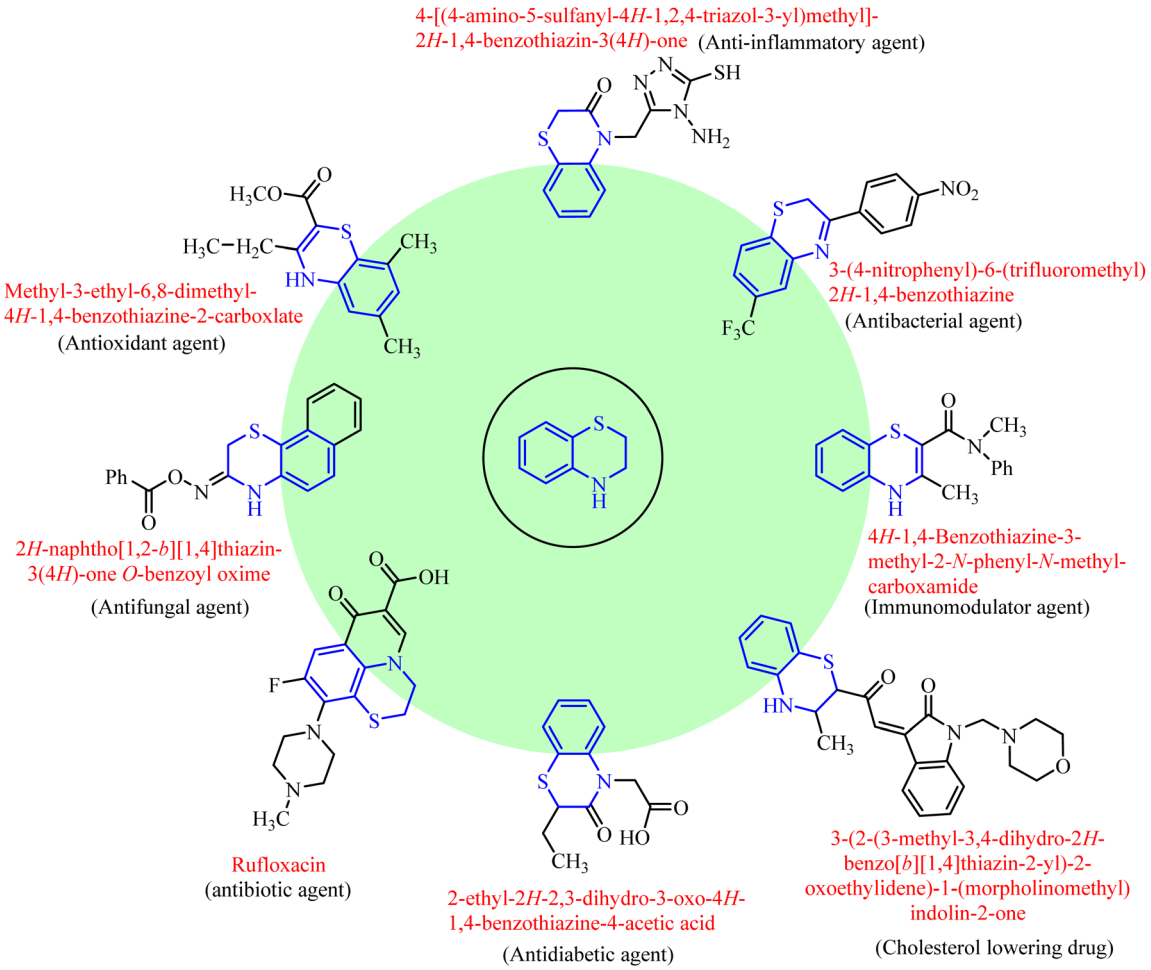


Fig. 4 Reported biologically active molecules containing 1,4-BT moiety.

outlined with various substrates such as benzothiazole, *o*-quinone, 2-bromothiophenol, and others.

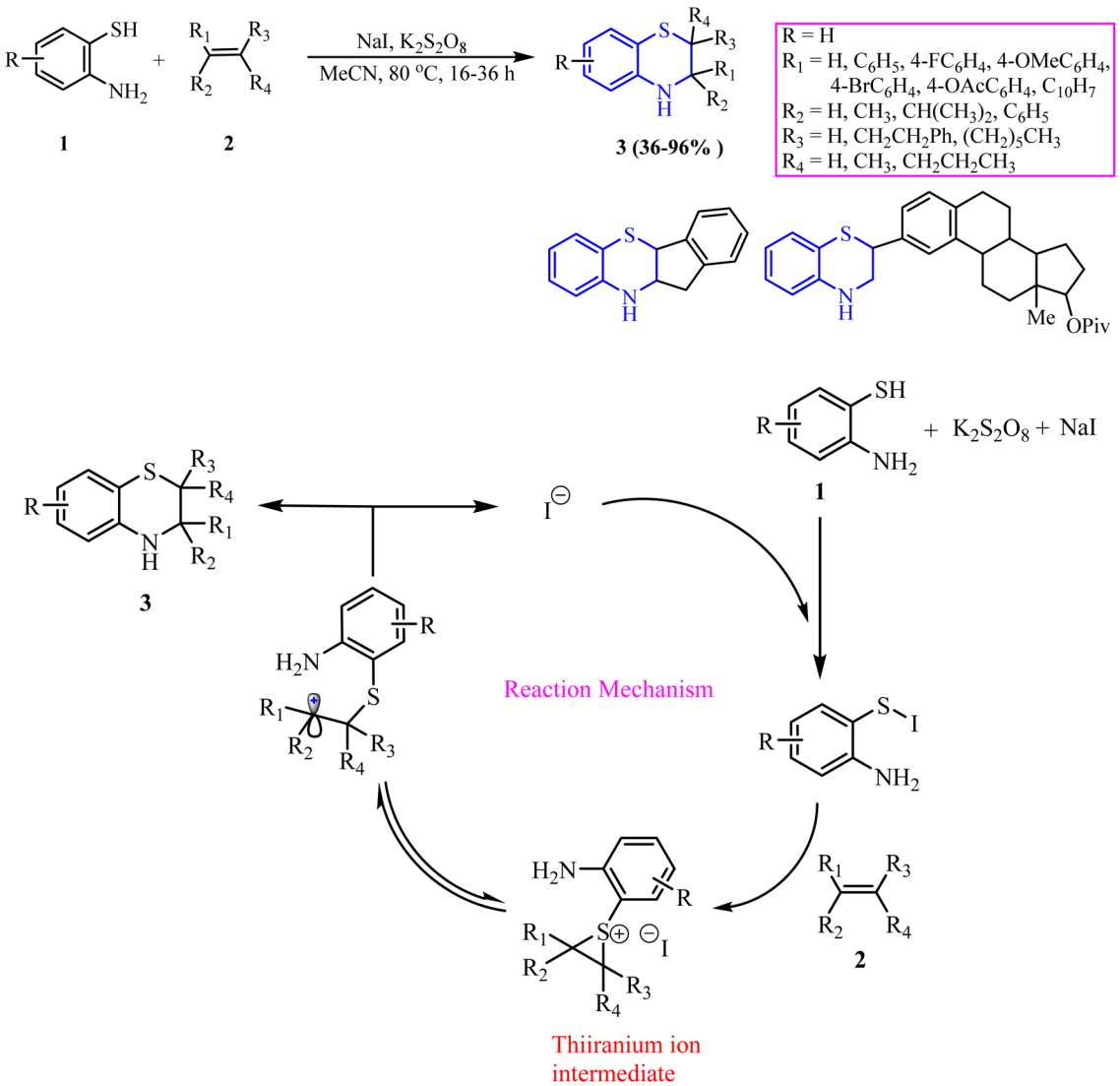
2.1. Reactions of 2-ATP with numerous substrates

This section focuses on the synthesis of 1,4-BT using 2-ATP with diverse substrates, including alkenes, acids and their derivatives, ketones, epoxides, furan-2,3-dione, enaminones, aroylmethylidene malonates, dihydrodimethoxyfuran and 1,3-dicarbonyl compounds. The reactions are carried out under various conditions using a variety of catalysts such as nanocatalysts, metal catalysts, ionic liquid catalysts, and others.

2.1.1. With alkene. Nur-E Alom *et al.*[47] explored a simple, catalytic approach using sodium iodide catalyst to craft both regio- and stereoselectivity of diverse 1,4-BT. Firstly, 2-ATP (**1**), various substituted alkenes (**2**) with 20 mol% catalyst loading were mixed in acetonitrile solvent at 80 °C with potassium persulfate/benzoyl peroxide oxidant to yield 36–96% product (**3**) in 16–36 h. In the mechanism of the reaction, first thiiranium ion was formed as an intermediate then intramolecular thiiranium ion ring opening took place and formed the final product 1,4-BT. The protocol is facile, one-pot, and eco-friendly, however, the drawback includes long reaction time (Scheme 1).

Teli *et al.*[48] developed a method to synthesize 1,4-BT derivatives by reacting 2-ATP (**1**) and styrene (**2**) in a micellar nanoreactor medium. In this method, styrene (1 mmol) (**2**) and *N*BS (1.5 mmol) were initially dissolved in an aqueous cetylpyridinium bromide (CPB) solution (5 mL). The reaction mixture was stirred at 30 °C for 20 h, forming phenacyl bromides (**4**) through a hydrobromination–oxidation cascade. Afterward, these phenacyl bromides were reacted with 2-ATP (1 mmol) (**1**), and the reaction was allowed to proceed for 2–4 h, producing 2-aryl-1,4-BT (**5**) in yields of 65–72%. The mechanism began with micelle-entrapped *N*BS facilitating bromination through cation–π interaction, forming a bromonium intermediate (**I**). A regioselective epoxide ring opening yielded a stable intermediate (**II**), which was then oxidized to phenacyl bromide (**4**). This intermediate underwent micelle-assisted condensation with 1,2-ATP, ultimately leading to the formation of 1,4-BT. The merit of this method is that it is environmentally friendly and does not require organic solvents. A demerit of this synthetic route is the long reaction time and necessity of column chromatography for purification (Scheme 2).

2.1.2. With ketone. Nguyen and Retailleau[49] synthesized novel spirobis(1,4-BT) derivatives from the reaction of 2-ATP (2 mmol) (**1**) with α,α′-enolizable ketone (1 mmol) (**6**) in the

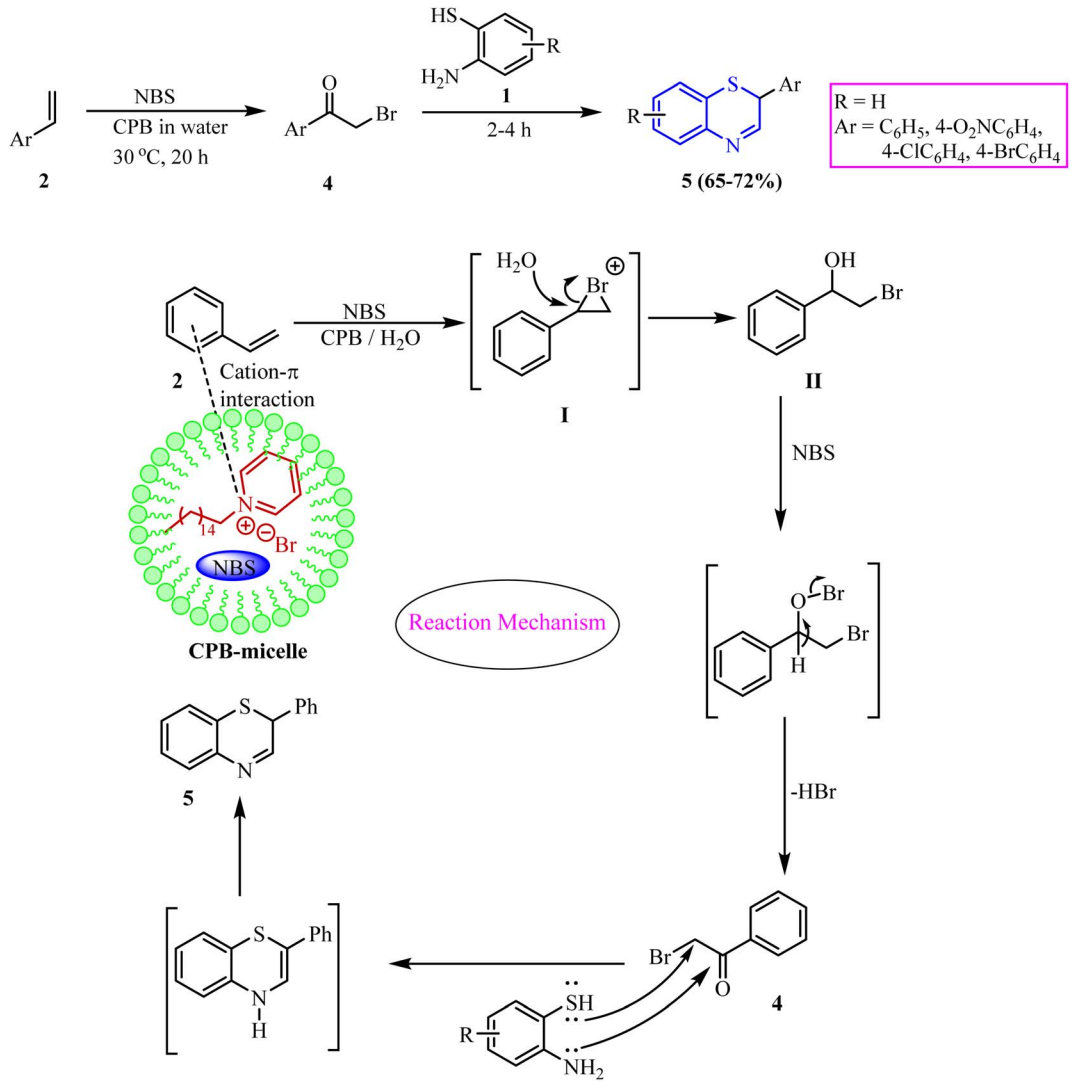


Scheme 1 1,4-BT synthesis using 2-ATP and alkene.

presence of DMSO oxidant and TFA as a catalyst at 80 °C for 16 h *via* Umpolung strategy. Initially, 2-ATP (**1**) was observed to undergo facile oxidative dimerization to form disulfide compounds (**I**), then ketone (**6**) reacted with disulfide compound and formed imine (**II**) as an intermediate followed by enamine reaction through electrophilic cyclization into tetrahydrophenothiazine (**III**), further this underwent to tautomerization and reacted with disulfide compound to form an intermediate which in the presence of acid catalyst converted into final product spirobis(1,4-BT) (**7**) *via* intramolecular cyclization reaction. This reaction is stereoselective and yields were obtained in low to good amounts (9–89%) but the disadvantage included the use of column chromatography (Scheme 3).

The same group[50] developed an effective methodology for the synthesis of different kinds of 2-arylbenzothiazine derivatives *via* a redox condensation reaction between 2-ATP (**1**) and different types of ketones, catalyzed by TFA (10 mol%) in DMSO solvent at 80 °C for 16 h *via* Umpolung strategy. When 2-ATP (**1**) reacted with aryl methyl ketone (1 mmol) (**8**), the dimeric 2-arylbenzothiazines (**9**) were formed in moderate to quite excellent yield (58–85%) while substituted aryl propiophenone (**8**) produced heteropropellanes (**10**) in good yield (67–79%) but when reacted with α-substituted alkyl phenyl ketones (**8**), 3,3-dialkyl-1,4-BT (**11**) were obtained 78–82% (in high yields). The authors tried to synthesize other 1,4-BT using butyrophenone, valerophenone and hexyl phenyl ketone, but the desired products were not form due to their instability in air. However, when R_2 group was replaced with an electron-withdrawing group (CN, CO_2Et) (**12**), the target molecules were synthesized in good yields (70–82%) (**13**). In this protocol, yields of desired product depends upon the size and electronic effect of the alkyl group of the ketones (Scheme 4).

Ya-mei Lin *et al.*[51] synthesized 1,4-BT derivatives using a radical approach. The reaction of 2-ATP (0.375 mmol) (**1**) and α, β-unsaturated ketones (0.250 mmol) (**14**) in MeOH with Cs_2CO_3 (0.125 mmol) as the base at 110 °C for 10 h gave the

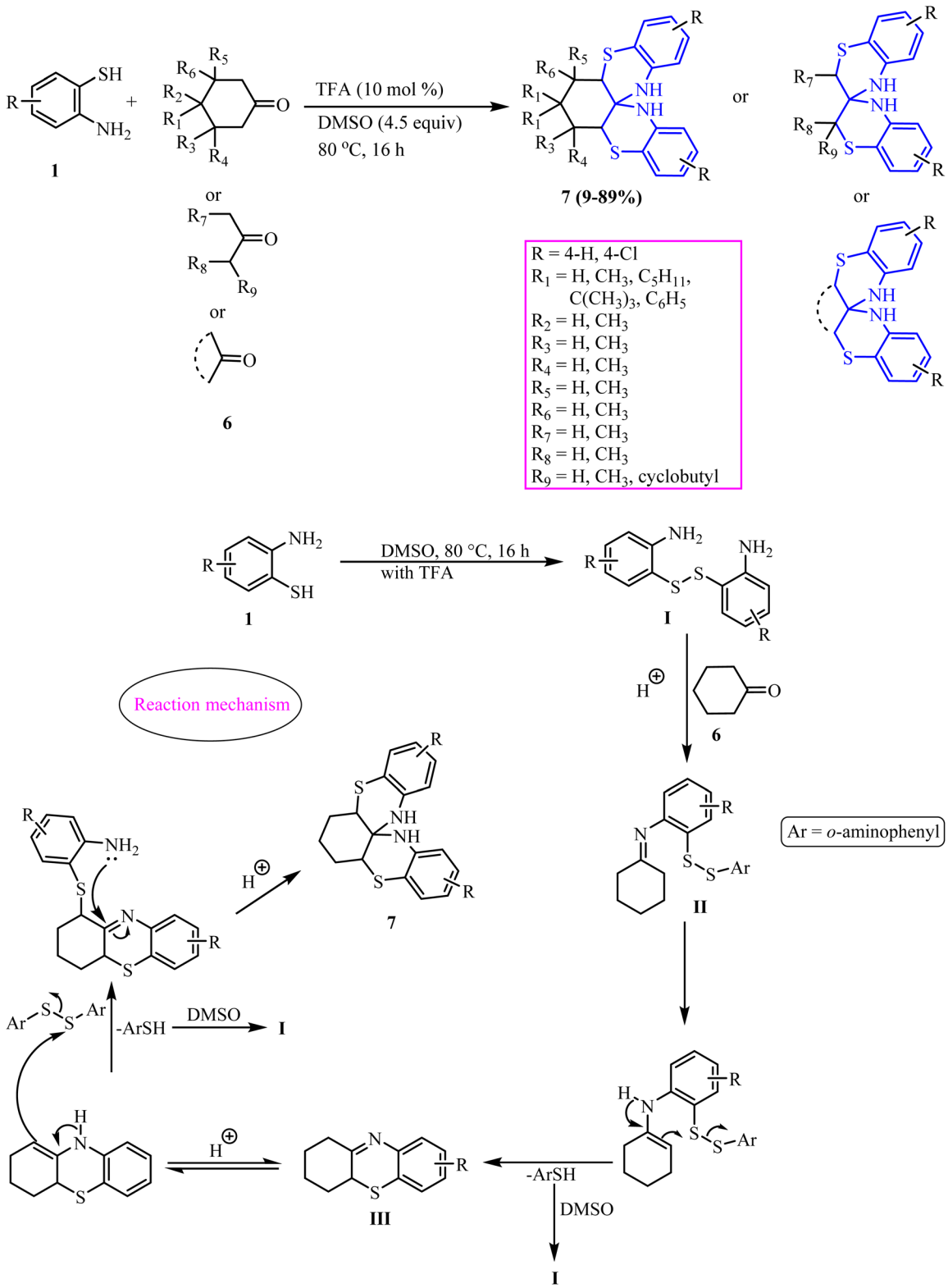


Scheme 2 Synthesis of 1,4-BT using 2-ATP and styrene.

product in moderate to excellent yields (73–90%) (**15**) while linear ketones (0.375 mmol) (**8**) and 2-ATP (1.5 equiv.) (**1**) were used in DMAc solvent, in 64–87% yields (**11**). While for reaction of fluoroalkyl ketones (0.375 mmol) (**12**) with 2-ATP (0.250 mmol) (**1**), the reaction in DMAc with DBU (0.500 mmol) as the base under air at RT for 24 h resulted in 44–91% moderate to high yields (**16**). In the proposed mechanism, the process began with *in situ* generation of thiyl radical (**I**) from 2-ATP (**1**) upon heating in the presence of air. This radical quickly reacted with the enol, formed *via* ketone isomerization, yielding the carbon radical intermediate (**II**). A subsequent single-electron transfer led to the formation of **III**, which underwent intramolecular condensation to afford the final product. The pros of this protocol include high efficiency, sustainability through the use of an eco-benign and transition metal-free approach, and yields from moderate to excellent (Scheme 5).

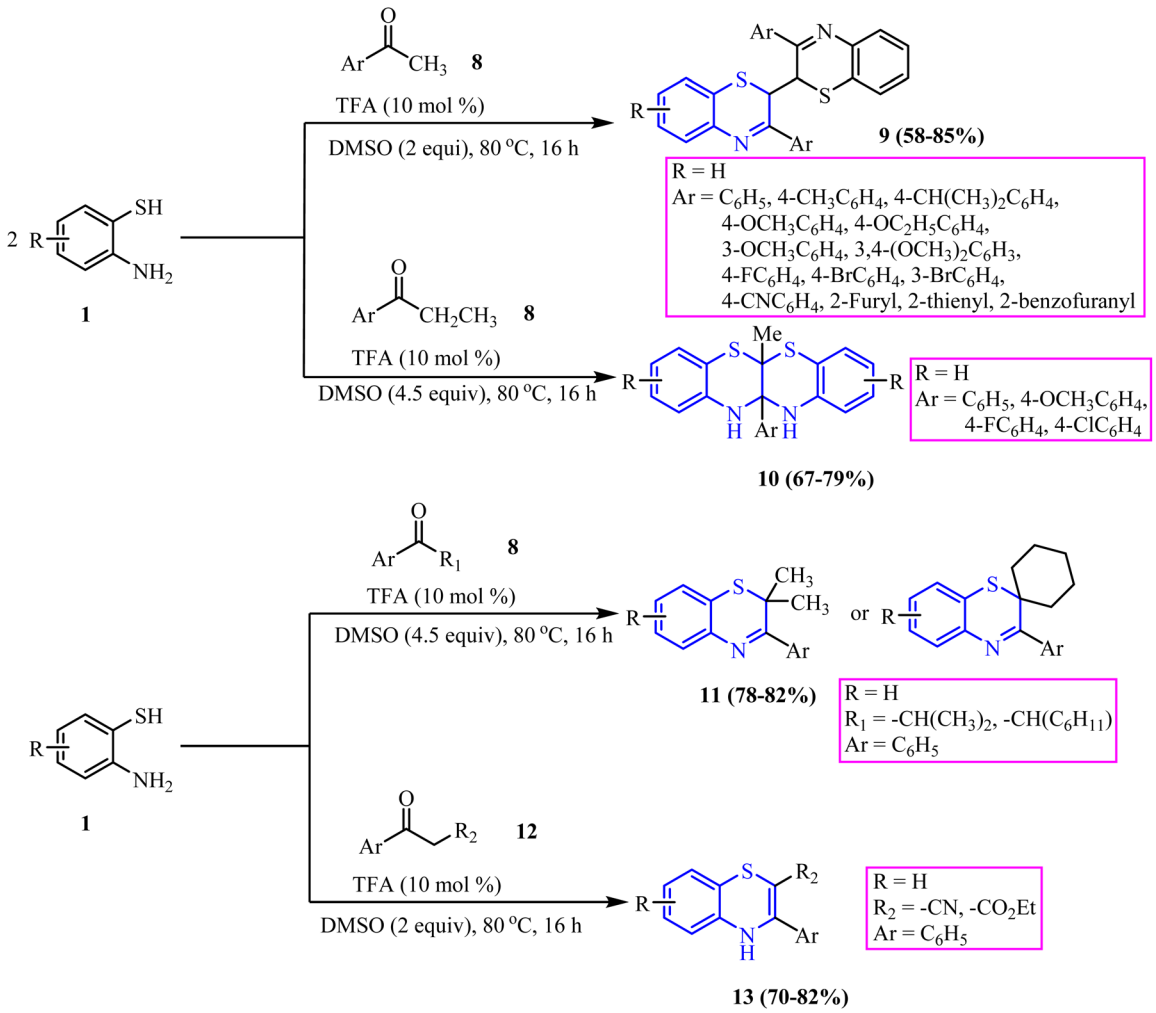
Jinwu Zhao *et al.*[52] reported a three-component, transition-metal-free, aerobic method for synthesizing 1,4-BT *via* the oxidative cyclization/coupling of 2-ATP (0.2 mmol) (**1**), anilines (0.3 mmol) (**17**), and various methyl ketones (0.3 mmol) (**8**) in KI (0.04 mmol), DMSO (0.8 mmol), and chlorobenzene (1.0 mL) as the solvent, under an oxygen atmosphere. The reaction was conducted at 120 °C for 16 h, yielding low to good results (33–78%) (**18**). In the proposed mechanism, methyl ketone (**8**) underwent α-iodination with KI/DMSO to form **I**, which was oxidized *via* Kornblum oxidation (oxygenation) to substituted glyoxal (**II**). Further this reacted with aniline (**17**) *via* aldimine condensation to form imine intermediate (**III**), which subsequently underwent intramolecular nucleophilic addition with 2-ATP (**1**), yielding annulation intermediate **IV**. Finally, oxidative dehydrogenation converted **IV** into the final product (**18**). However, the method has limitations, that includes the use of column chromatography and a relatively tedious workup process (Scheme 6).

2.1.3. With 1,3-dicarbonyl. Bhattacharya *et al.*[53] synthesized diversely functionalized 1,4-BT (**20**) from the reaction of 2-ATP (1 mmol) (**1**) and 1,3-dicarbonyls (1 mmol) (**19**) using graphene oxide as a carbocatalyst at RT to 80 °C for 8–24 h. In this



Scheme 3 Synthesis of 1,4-BT using 2-ATP and ketones.

protocol, the reaction took place without the presence of metals or solvents, resulting in high yields (75–88%) of the products. The catalyst was checked for the recyclability over five consecutive runs. The mechanism of reaction proceeded through the imine intermediate (**III**) formed by reacting 2-ATP (**1**) and 1,3-dicarbonyls (**19**), that converted into its tautomer form (**IV**) and intramolecular oxidative cyclization in the presence of graphene oxide catalyst took place to make 1,4-BT (**20**). In this



Scheme 4 Synthesis of 1,4-BT using 2-ATP and ketones.

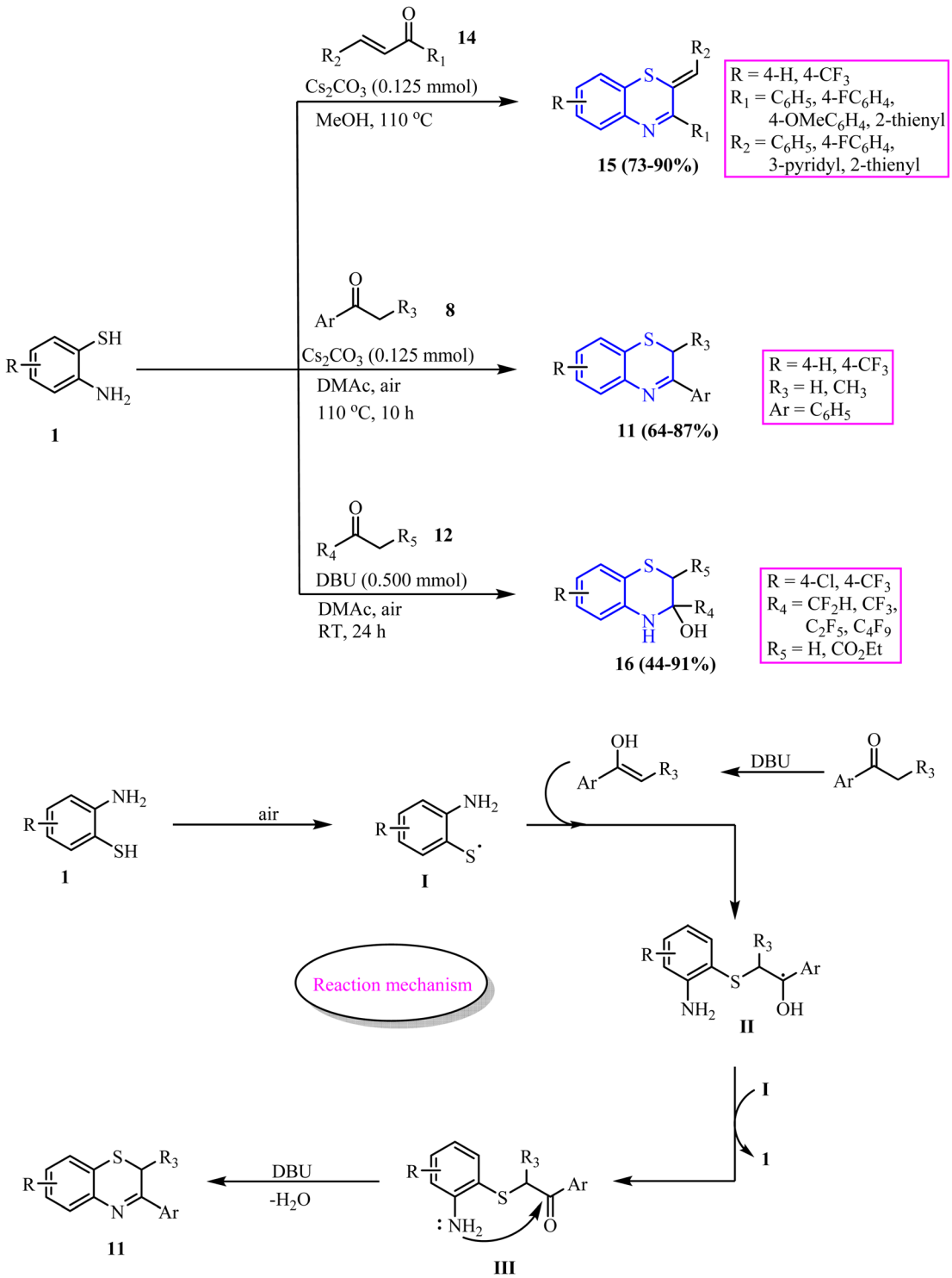
methodology, product was obtained without use of any solvent and metals. The drawback of this method is the use of column chromatography (Scheme 7, Method 1).

Shajeelammal *et al.*[54] synthesized a novel 1-(3-methyl-4*H*-benzo[1,4]thiazin-2-yl) ethenone (**20**) by the reaction of equimolar mixture of 2-ATP (**1**) and acetylacetone(**19**) using methanol as a solvent at RT for 2 days to give excellent yield (98%). In these reaction conditions, 2-ATP readily oxidized to bis(*o*-aminophenyl)disulfide (**V**) and reacted with acetylacetone to form an enamine intermediate (**IX**) which was easily cyclized by the nucleophilic attack and formed novel 1,4-BT derivative. The easily available reactants, high yield and operational simplicity are the characteristics of this method but a long reaction time was considered a major limitation of this method (Scheme 7, Method 2).

1-(3-Methyl-4*H*-1,4-benzothiazin-2-yl)ethenone (**20**) synthesized by Hadda and co-authors[55] through the direct condensation of 2-ATP (40 mmol) (**1**) and penta-2,4-dione (20 mmol) (**19**) in ethanol solvent at RT with stirring for 24 h. Finally, the desired product formed with low yield (36%). However, in this process, by-product 2-[(2-aminophenyl)dithio]aniline (12% yield) and 1-(2-methyl-2,3-dihydro-1,3-benzothiazol-2-yl) acetone (5% yield) were also obtained. Low yield and long reaction time are the drawbacks of this protocol. The product showed antifungal activity against the *albedinis* strain (Scheme 7, Method 3).

M. R. Sangvikar *et al.*[56] developed a convenient one-pot procedure for synthesizing 1,4-BT derivatives (**20**) through the oxidative cyclocondensation of 2-ATP (10 mmol) (**1**) and 1,3-dicarbonyl compounds (10 mmol) (**19**). This reaction was catalyzed by *m*-CPBA/2-IBX (10 mmol) in acetonitrile as the solvent, carried out at 70 °C for 45–75 min, and produced moderate to excellent yields (49–89%). The mechanism involved the oxidation of 2-ATP to disulfide (**V**) by oxidants. The resulting disulfide (**V**) then underwent a reaction with 1,3-dicarbonyl (**19**), leading to intramolecular cyclization and the formation of 1,4-BT. The plus points of this method are its simplicity, short reaction time, efficient, and the use of an eco-friendly oxidizing agent (Scheme 7, Method 4).

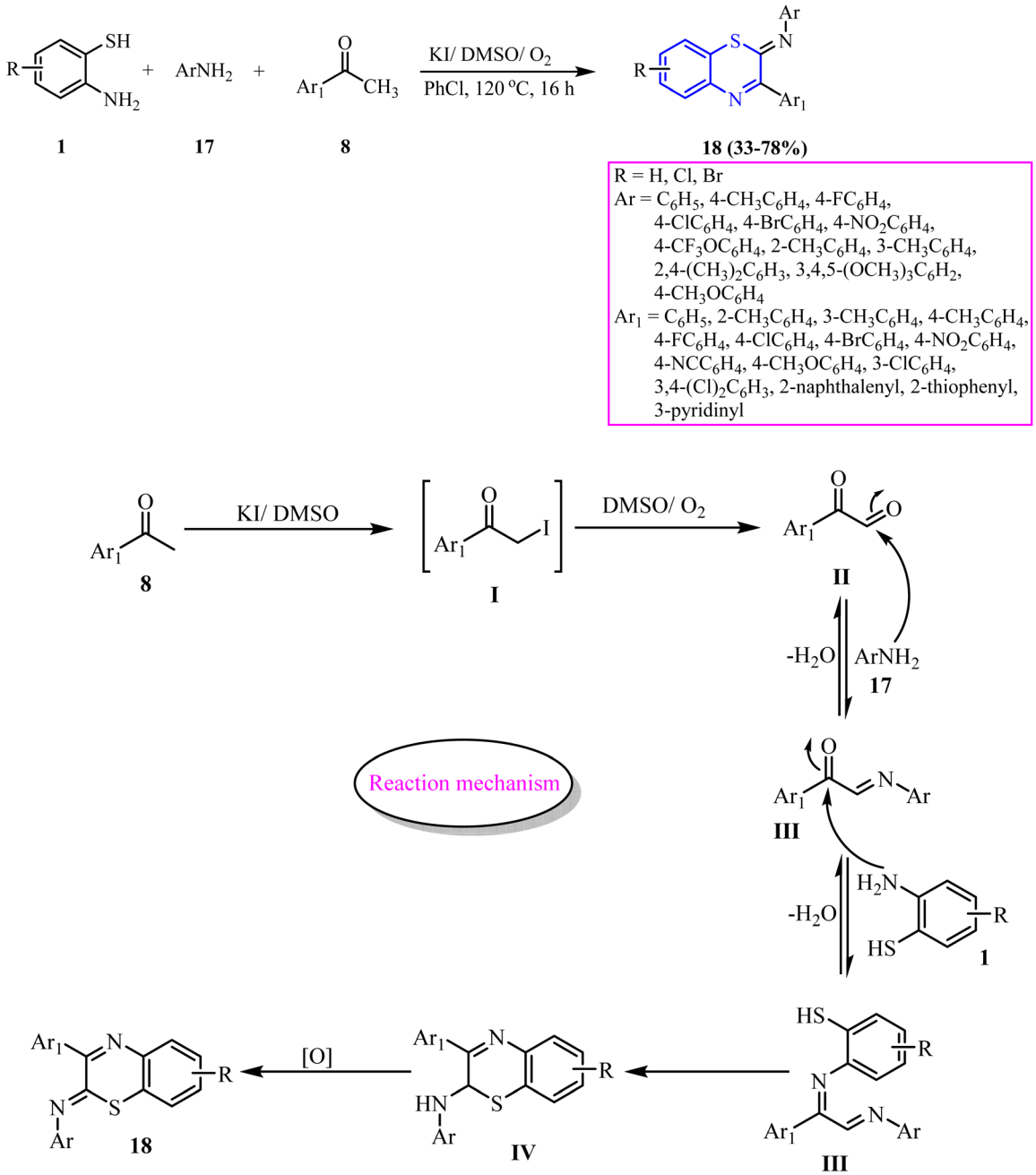
Aminul Islam *et al.*[57] developed a one-pot and efficient method for synthesizing 1,4-BT derivatives (**20**) by reacting 1 mmol 2-ATP (**1**) with 1 mmol 1,3-dicarbonyl compounds (**19**) in the presence of polyethylene glycol (PEG-200) at 80 °C for 4 h. The process is simple, metal-free, eco-friendly, and produced



Scheme 5 Synthesis of 1,4-BT using 2-ATP and ketones.

excellent yields (76–98%) under mild conditions. The reaction mechanism started with PEG-200 protonating the carbonyl carbon, intensifying carbonyl electrophilicity. The 2-ATP attacked, forming an imine, which tautomerized and underwent oxidative cyclization to give the final product. PEG-200, a green and biocompatible solvent, played a crucial role in facilitating metal-free organic reactions. However, the need for column chromatography in the purification step is a limitation of this approach (Scheme 7, Method 5).

Arun Goyal[58] synthesized 1,4-BT derivatives (**20**) through oxidative cyclization by condensing 2-ATP (0.01 mmol) (**1**) with 1,3-dicarbonyl compounds (0.01 mmol) (**19**) in dimethyl sulfoxide (5 mL) under reflux for 50–60 min. The product was obtained in low yields (37–42%). In the reaction mechanism, 2-

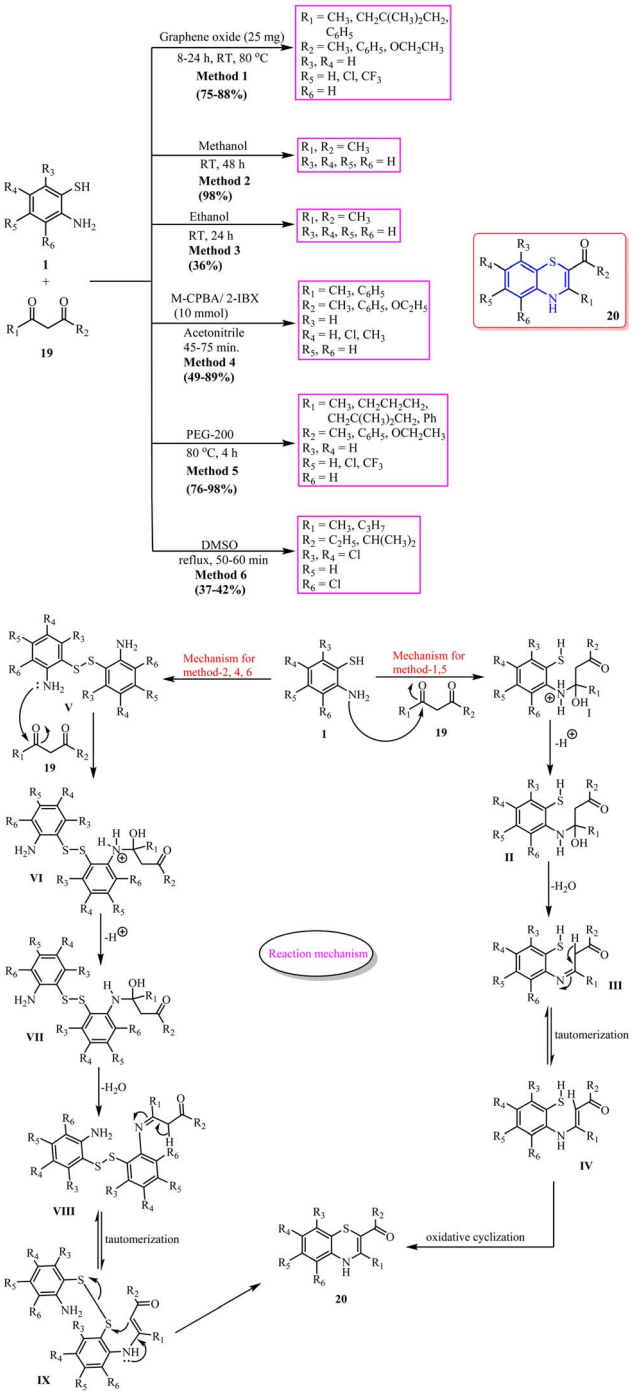


Scheme 6 Synthesis of 1,4-BT using 2-ATP, aniline and ketones.

ATP (**1**) was first oxidized by DMSO to form a disulfide (**V**), which then reacted with 1,3-dicarbonyl (**19**) to produce an enamine intermediate (**X**) that cyclized *via* S–S bond cleavage, yielding the desired product. The antimicrobial activity of the synthesized compounds, including antibacterial and antifungal properties, was evaluated using a method called the agar well diffusion (Scheme 7, Method 6).

The regioselective synthesis of benzo[*b*]indeno[1,2-*e*][1,4]thiazin-11(10*H*)-ones (**22**) was developed by Mor and Khatri[59] using reaction of 3 mmol 2,5-dibromo-2-substituted phenyl-1*H*-indene-1,3(2*H*)-diones (**21**) with 3 mmol 5-substituted-2-ATP (**1**) in the presence of freshly dried ethanol solvent at reflux for 7.5–10 h, then reaction proceeded through the cyclocondensation with 42–60% yields. In the plausible mechanism, first, the NH_2 group of 2-ATP attacked the carbonyl carbon (C-3) of **21**. Then, the SH group of 2-ATP reacted intramolecularly at C-2 of **21**, leading to the elimination of HBr and the formation of intermediate **II**, which later produced desired product (**22**) with removal of water. This protocol is regioselective, efficient, green, reagent-free and catalyst-free. The drawback of this method is the tedious separation of desired products (Scheme 8, Method 1).

Mor and Nagoria[60] reported a method for synthesizing 1,4-BT derivatives (**22**) through the equimolar reaction of 2-aryl-2-bromo-1*H*-indene-1,3(2*H*)-diones (**21**) with 2-ATP (**1**) in 30 mL of



Scheme 7 Synthesis of 1,4-BT using 2-ATP and 1,3-dicarbonyls.

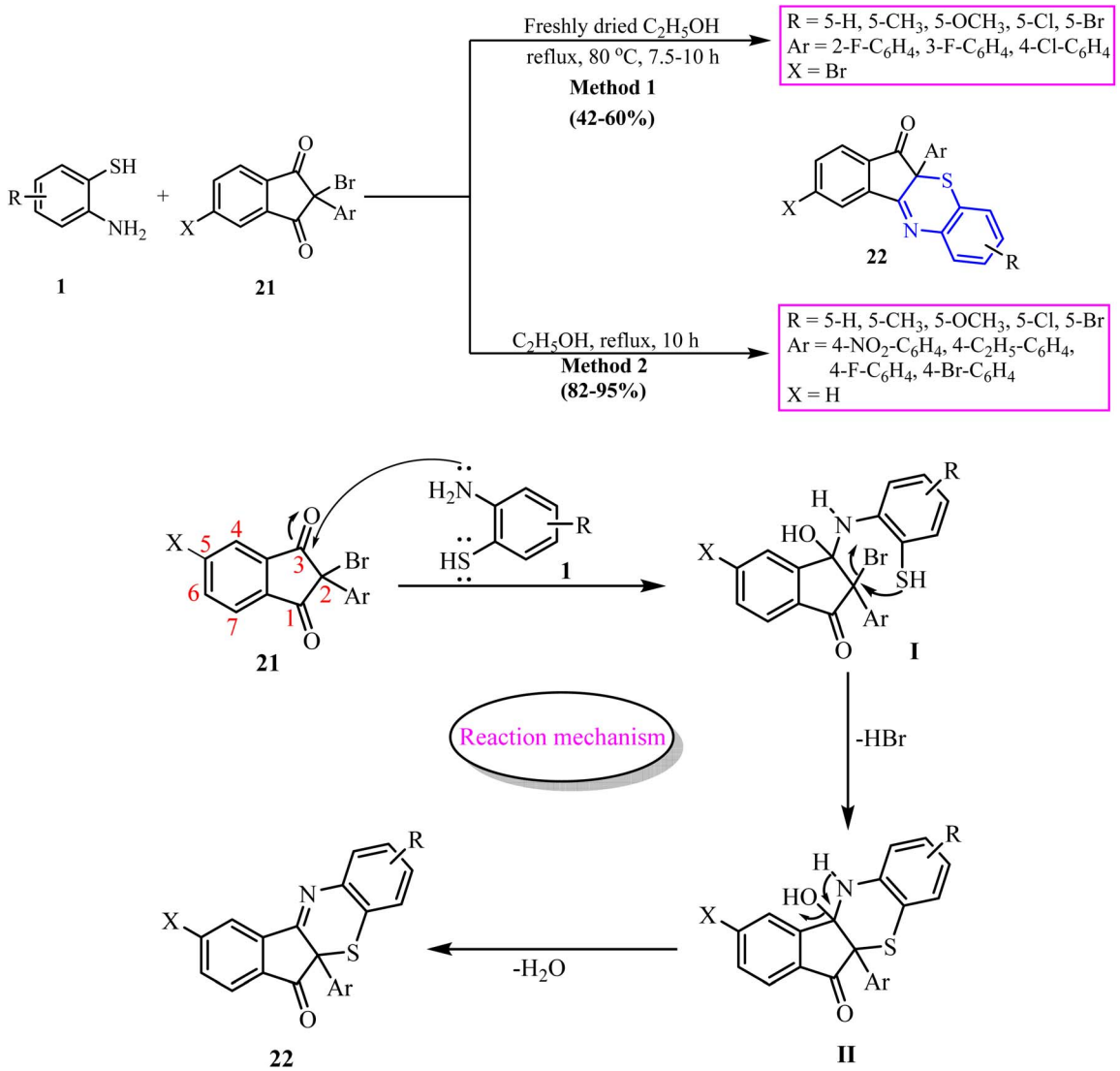
dry ethanol. The reaction was refluxed for 10 h on a water bath, producing yields, 82–95%. This protocol is efficient, green, reagent-free and catalyst-free. A disadvantage of this method is the need for column chromatography (Scheme 8, Method 2).

2.1.4. With coumarin-3-carboxylic acid derivatives. Baharfar and Mohajer[61] synthesized spiro benzothiazine derivatives (**25**) by the three-component reaction of 2-ATP (1 mmol) (**1**), alkyl isocyanide (1 mmol) (**24**) and coumarin-3-carboxylic acid derivative (1 mmol) (**23**) using 25 mg nano biocatalyst (NBC) (Fe_3O_4 NPs@lipase) in dioxane solvent at RT for 1 h. The nano biocatalyst was reusable up to 6 runs. The reaction mechanism began with the Michael addition of isocyanide (**24**) to coumarin-3-carboxylic acid (23), forming intermediate **I**. This intermediate then reacted with bisulfide (**II**), which was generated *in situ via* the oxidation of 2-ATP (**1**). A subsequent intramolecular nucleophilic reaction led to the formation of the final product. Excellent yields (85–95%), optimal reaction conditions, short reaction time and ecofriendly conditions are the additional benefits of this protocol (Scheme 9).

2.1.5. With epoxide. M. Saadouni *et al.*[62] developed a method for synthesizing 1,4-BT derivatives (**27**) through the reaction of epoxide (1 mmol) (**26**) with 2-ATP (1 mmol) (**1**) in acetonitrile solvent under reflux for 25 h. During the reaction, hydrogen cyanide (HCN) generated was efficiently trapped using a 0.1 N KOH solution in a bubbler. The reaction afforded the desired product in a moderate yield of 60%. A major drawback of this method is the prolonged reaction time and the need for flash chromatography during product purification (Scheme 10).

2.1.6. With dihydro dimethoxyfuran. Amani Jaafar *et al.*[63] reported 1,4-BT derivatives synthesis through the reaction of 2-ATP (2 mmol) (**1**) with 2,5-dihydro-2,5-dimethoxyfuran (0.78 mmol) (**28**) in a solvent mixture of 5 mL THF and 10 mL water, catalyzed by a small amount of concentrated H_2SO_4. The reaction was carried out at RT and stirred for 24 h, yielding 1,4-BT derivative in 50% yield (**29**). Furthermore, the compound underwent isomerization to 2-(benzo[*d*]thiazol-2-ylmethyl)-3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine (**30**) with nearly complete conversion (98% yield) with the treatment of HCl in chloroform. The reaction mechanism involved a Michael addition of thiol (**1**) to *in situ*-formed fumaraldehyde, followed by intramolecular condensation to yield the benzothiazine system (**III**). Subsequently, a second 2-ATP molecule participated in the reaction to form the benzothiazole moiety (**V**). Finally, an intramolecular nucleophilic addition by the benzothiazole nitrogen resulted in the formation of compound **29**. The authors further investigated the mechanism of acid-catalyzed isomerization of compound **29** in chloroform, leading to the formation of the final product (**30**). The long reaction time and the requirement for column chromatography represent key limitations of this method (Scheme 11).

2.1.7. With dialkyl acetyelenedicarboxylates. Muzey Bahta *et al.*[64] synthesized 1,4-BT derivatives as chemosensors through a two-step reaction process. In the first step, 2-ATP (2 mmol) (**1**) was reacted with diethyl acetylenedicarboxylate (2 mmol) (**31**) at RT for 5 min, leading to the preparation of ethyl(3-oxo-[1,4]benzothiazin-2-ylidene)acetate (**32**). In the second step, the intermediate was further reacted with hydrazine hydrate (2 mmol) in ethanol and reflux at 80 °C for 3 h, yielding 3-oxo-[1,4]-benzothiazin-2-ylidene acetohydrazide (**33**) in a high yield (91%). To study the photochemical properties of synthesised compound, a 10 μM sample in HEPES-buffered solution was treated with several metal perchlorates. The sensor showed good selectivity for Hg^{2+}, with a detection limit of 5.4×10^{-8} M (**34**), evidenced by a new absorption band at 550 nm, a colour shift from yellow to purple, and enhanced fluorescence (Scheme 12).

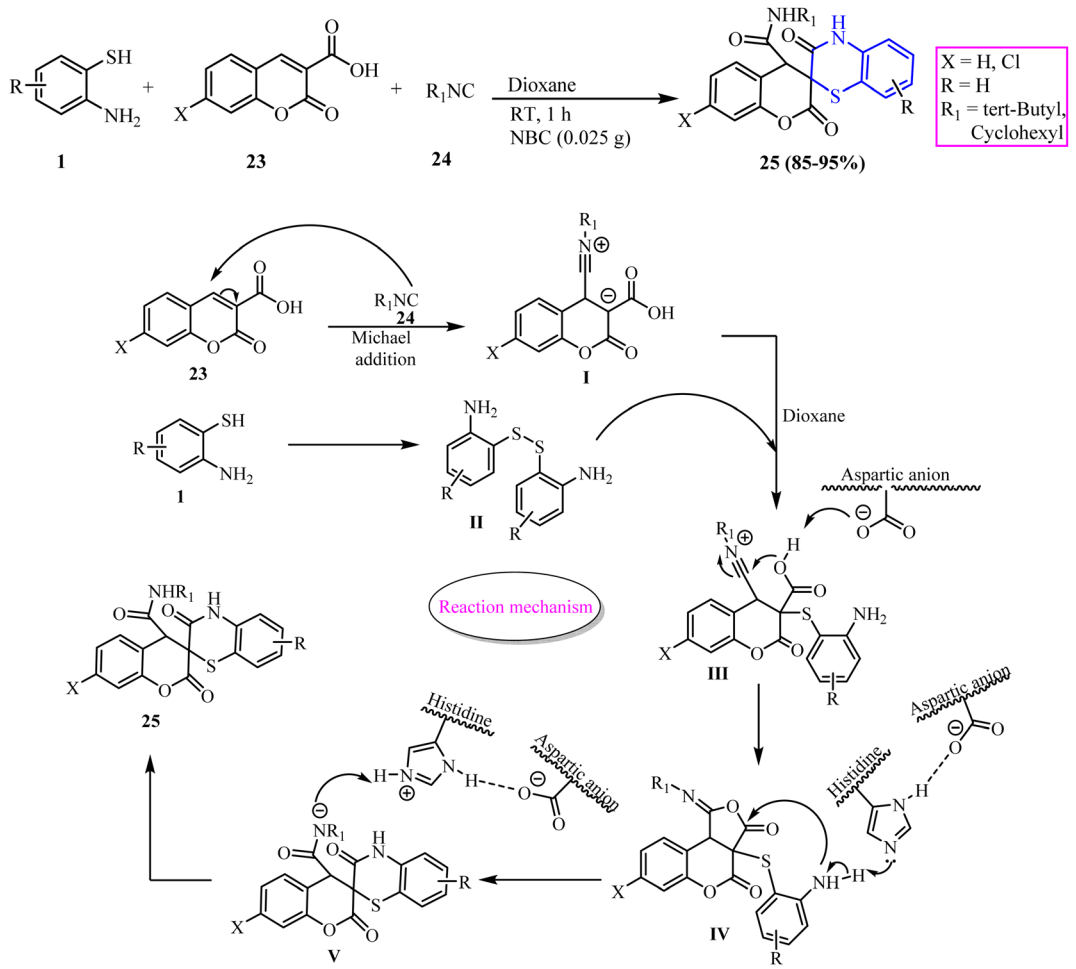


Scheme 8 Synthesis of 1,4-BT using 2-ATP and 1,3-dicarbonyls.

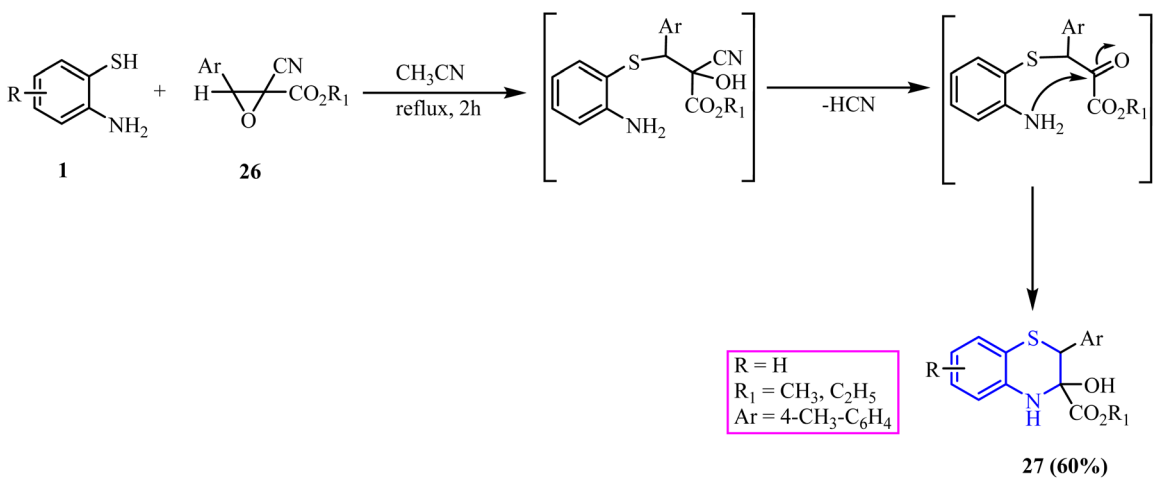
2.1.8. With 2-acetylthiadiazole derivative. The synthesis of 1,4-BT derivatives (**37**) by Sobhi M. Gomha *et al.*[65] involved a two-step reaction. Initially, *N*-(5-(2-bromoacetyl)-3-phenyl-1,3,4-thiadiazol-2(3*H*)-ylidene)benzamide (**36**) was synthesized by reacting *N*-(5-acetyl-3-phenyl-1,3,4-thiadiazol-2(3*H*)-ylidene) benzamide (10 mmol) (**35**) with bromine solution in 1 mL acetic acid (10 mmol) for 2–4 h. In the second step, 1 mmol 2-bromoacetylthiadiazole and 1 mmol 2-ATP (**1**) were heated under reflux in 20 mL ethanol for about 8 h, leading to the formation of the target compound (75%). The protocol is facile, green, and eco-friendly (Scheme 13).

2.1.9. With enaminones. Wan *et al.*[66] achieved the synthesis of 1,4-BT derivatives (**20**) through a cascade C–N bond transamination and C(sp^2)–H sulfenylation reaction. The procedure involved mixing *N*,*N*-dimethyl enaminones (0.3 mmol) (**38**) and 2-ATP (0.3 mmol) (**1**) in ethyl lactate (2 mL) as the green solvent, with I_2 (0.09 mmol) serving as the catalyst. The reaction was conducted under an air atmosphere at 90 °C for 12 hours, giving yields of 66–92%. The reaction mechanism involved transamination between 2-ATP (**1**) and enaminone (**38**), forming NH–enaminone (**I**). It rearranged to methylene imine (**II**), which underwent C–H iodination to yield species (**III**). Further, intramolecular nucleophilic substitution produced intermediate (**IV**), releasing HI. Tautomerization of (**IV**) gave the final product (**20**), while iodine anions were reoxidized to molecular iodine, sustaining the catalytic cycle. The benefits of this method include its environmentally friendly, metal-free, green, and simple nature (Scheme 14).

2.1.10. With 3-aryl-2-bromopropanoic acid esters. Pokhodylo *et al.*[67] reported a two-step synthesis of 1,4-BT derivatives. In the initial stage, arenediazonium bromide (**39**) reacted with methyl or 0.22 mol ethyl acrylate (**40**) in the presence of 3 g of CuBr and 150 mL of acetone at 20–40 °C, yielding 3-aryl-2-bromopropanoates (**41**). In the subsequent step, 3-aryl-2-bromopropanoates (5 mmol) were reacted with 2-ATP (5.5 mmol) (**1**) under solvent-free conditions at 120–160 °C for 30–50 min, resulting in yields of 40–86% for 1,4-BT derivatives (**42**). The plus points of this method are high efficiency, fast reaction



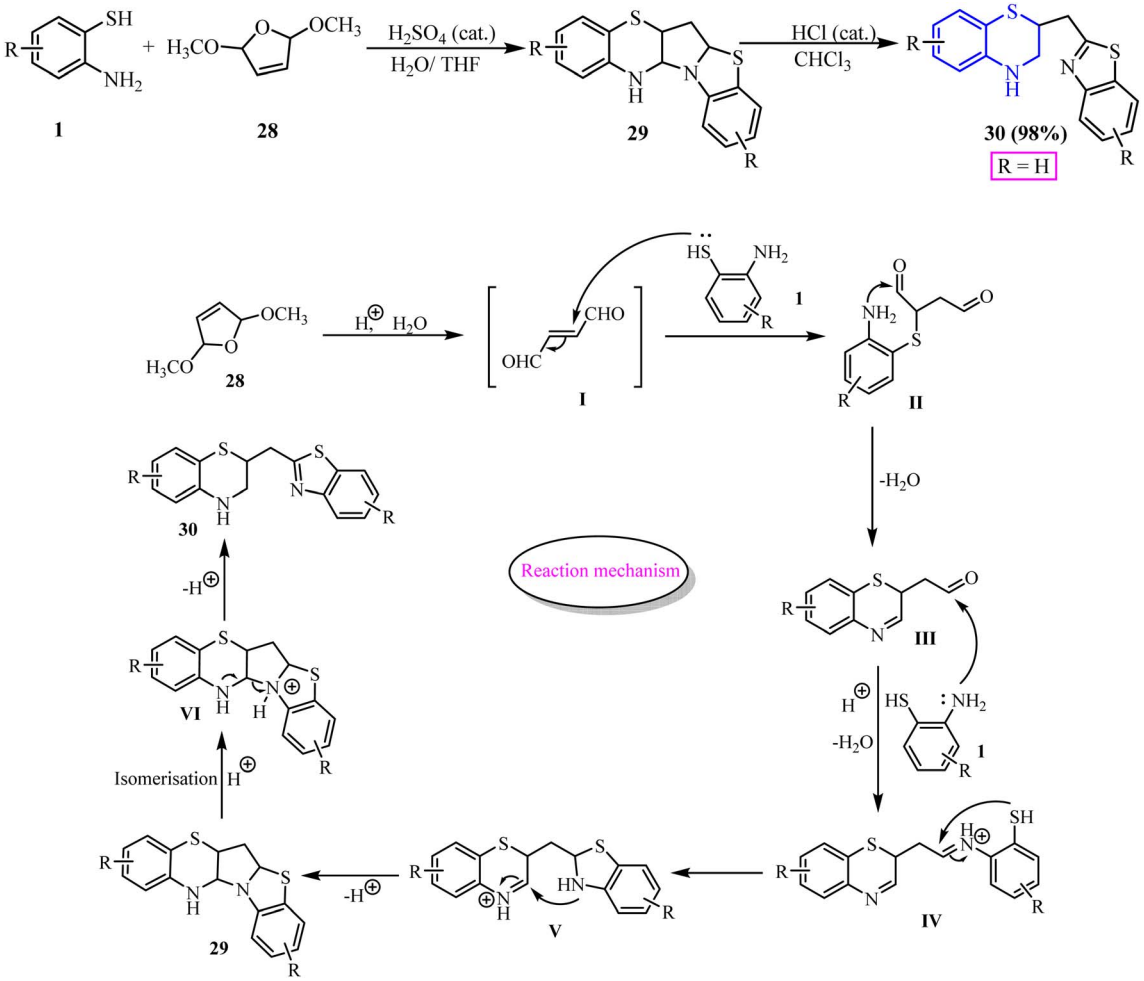
Scheme 9 Synthesis of 1,4-BT using 2-ATP and coumarin-3-carboxylic acid derivatives.



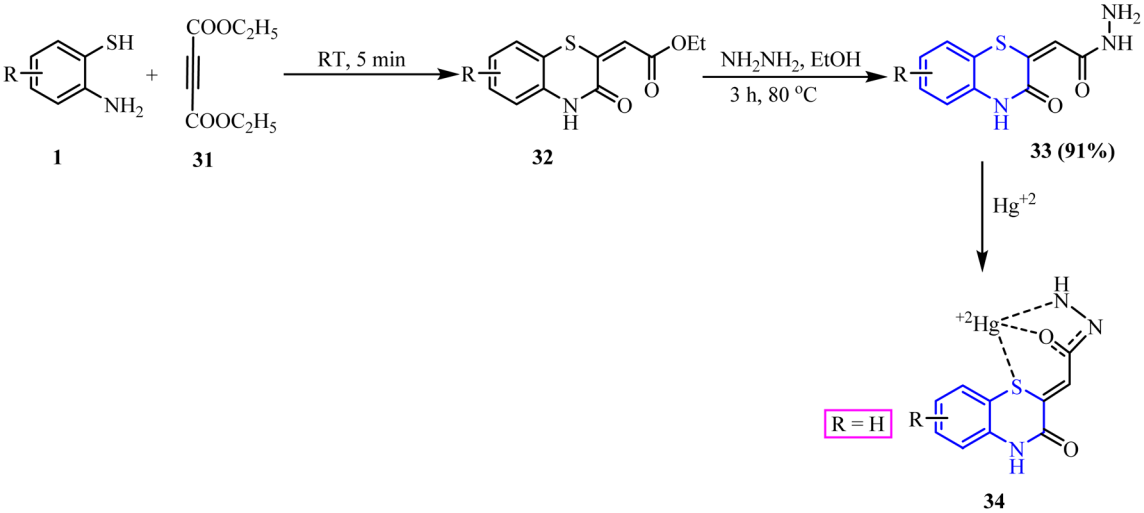
Scheme 10 Synthesis of 1,4-BT using 2-ATP and epoxide.

time, and environmentally friendly solvent-free conditions (Scheme 15).

2.1.11. With substituted bromo acetophenones. The synthesis of 1,4-BT derivatives (**11**) was carried out by Alishba *et al.*[68] through a one-pot procedure. In this reaction, 2-ATP (1 eq.) (**1**) and various substituted bromoacetophenones (1 eq.) (**4**) were combined in the presence of trimethylamine as a base, with diethyl ether (10 mL) as a solvent. The mixture was refluxed at 75–80 °C, resulting in a good yield of 65–86%. The reaction mechanism initiated as the sulfur atom of 2-ATP (**1**) acting as a nucleophile attacked the α-carbon of bromoacetophenone (**4**), facilitating Br departure. Then, the NH_2 group interacted with

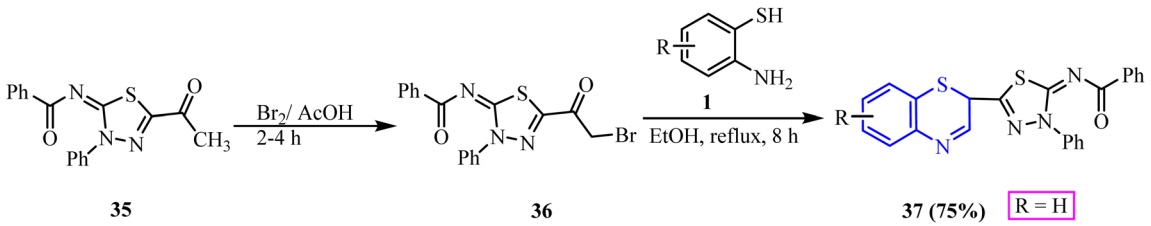


Scheme 11 Synthesis of 1,4-BT using 2-ATP and 2,5-dihydro-2,5-dimethoxyfuran.

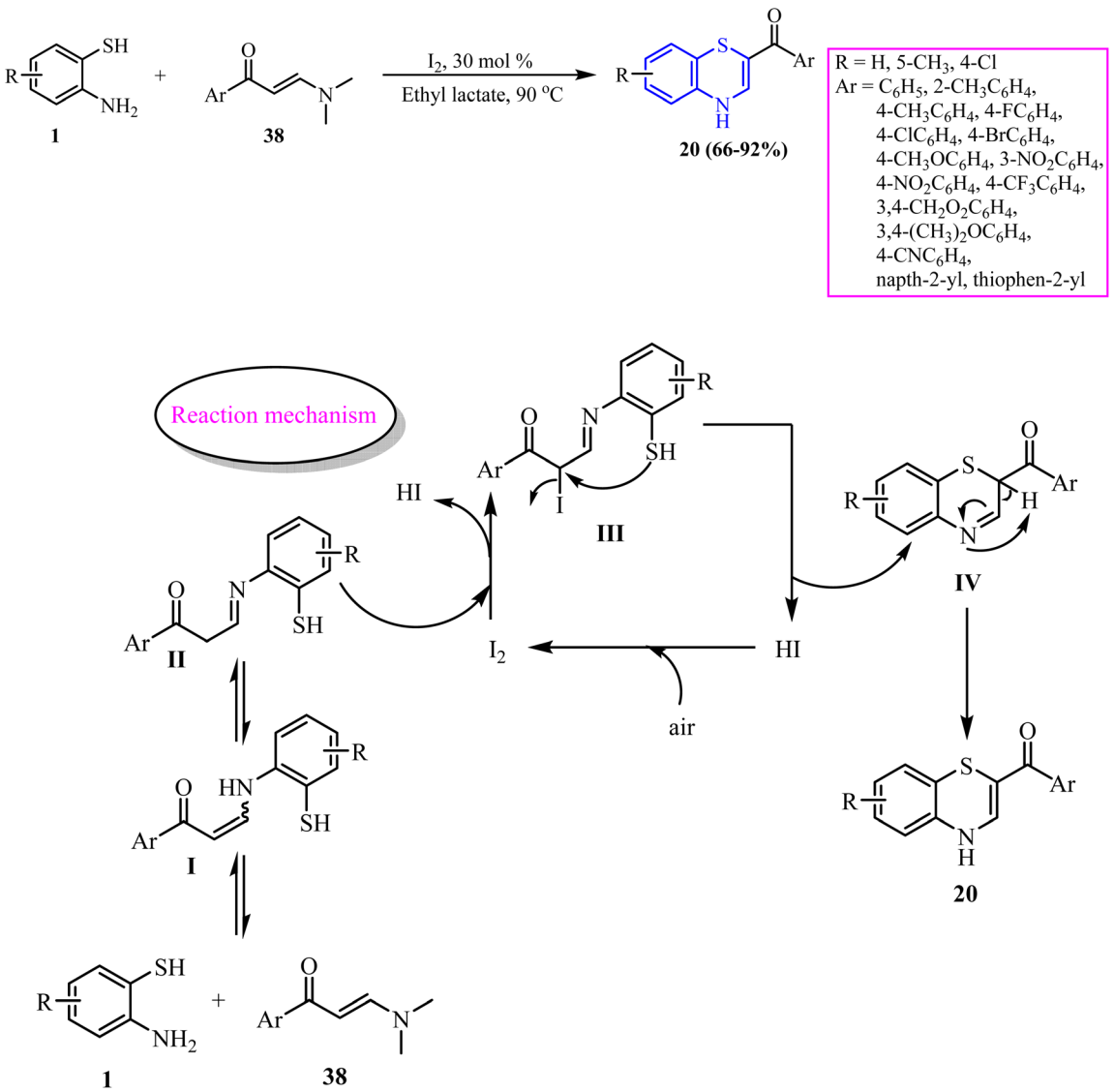


Scheme 12 Synthesis of 1,4-BT using 2-ATP and dialkyl acetyelenedicarboxylates.

the carbonyl carbon, leading to cyclization (**II**). Finally, the ring formed with the help of a base, eliminating water to produce the 1,4-BT ring (**11**). The compounds were tested for amoebicidal potential against *Acanthamoeba castellanii in vitro*. Among the synthesized derivatives, the most potent were 3-(2,4-dichlorophenyl)-2*H*-benzo[*b*][1,4]thiazine, 3-([1,1′-biphenyl]-4-yl)-2*H*-



Scheme 13 Synthesis of 1,4-BT using 2-ATP and 2-acetylthiadiazole.

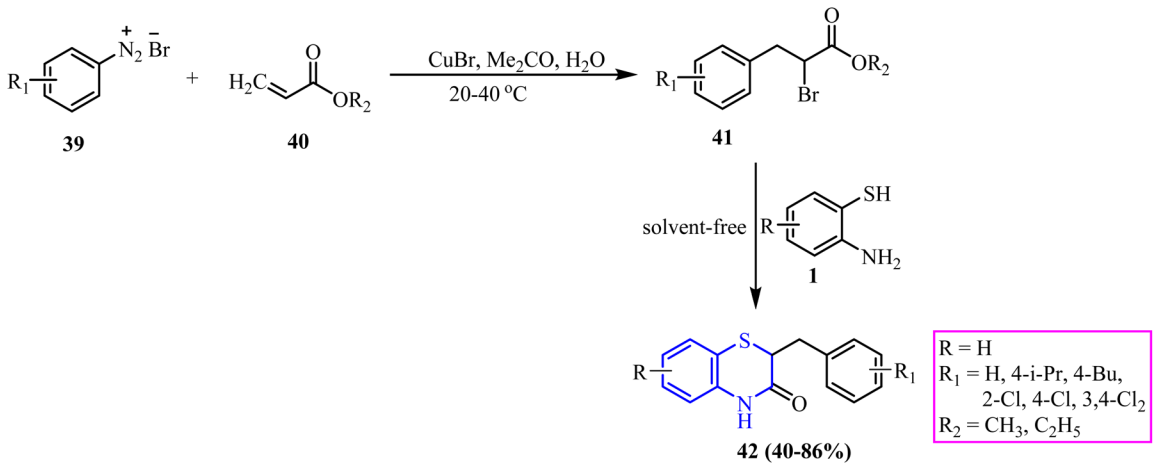


Scheme 14 Synthesis of 1,4-BT using 2-ATP and enaminones.

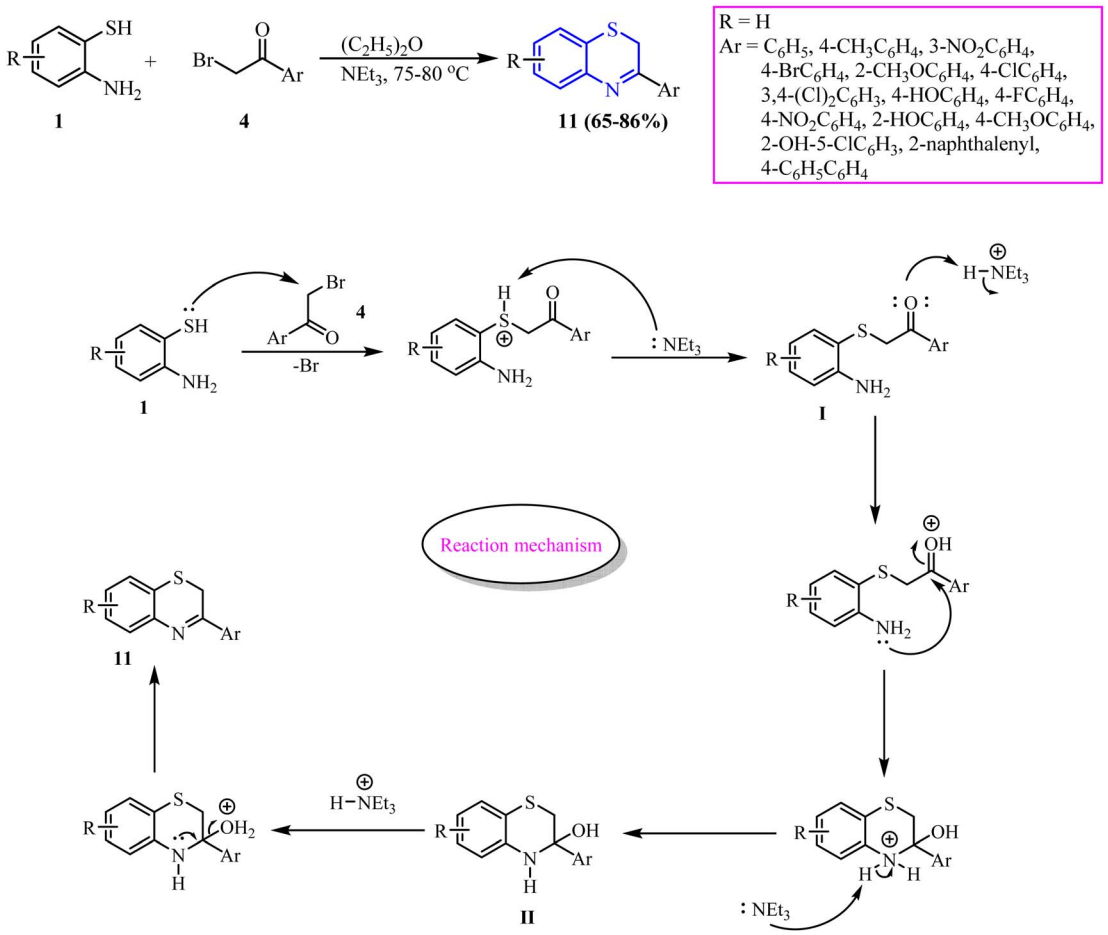
benzo[*b*][1,4]thiazine, and 2-(2*H*-benzo[*b*][1,4]thiazin-3-yl)-4-chlorophenol (Scheme 16).

2.1.12. With pyrrolo[2,1-*c*][1,4]oxazinetriones. Tret'yakov *et al.*[69] developed a method to synthesize 1,4-BT derivatives (**44**) by reacting 2-ATP (1.5 mmol) (**1**) with 8-aroylpyrrolo[2,1-*c*][1,4]oxazine-1,6,7-triones (1.5 mmol) (**43**) in 1,4-dioxane at RT for 1–2 min. The reaction mechanism involved Michael addition of the SH group of 2-ATP to pyrrolediones (**43**), followed by intramolecular oxazine ring opening, leading to the final product. This approach is eco-friendly, simple, one-pot, and provides high yields (78–86%) (Scheme 17).

2.1.13. With furan-2,3-dione. Tretyakov *et al.*[70] synthesized a 1,4-BT derivative (**46**) by dissolving 2-ATP (3 mmol) (**1**) in anhydrous $CHCl_3$ (5 mL) and then mixing it with 5-aryl-4-(3-arylquinoxalin-2-yl)furan-2,3-diones (3 mmol) (**45**) in anhydrous $CHCl_3$ (15 mL) at 20 °C for 5–10 min. A precipitate formed



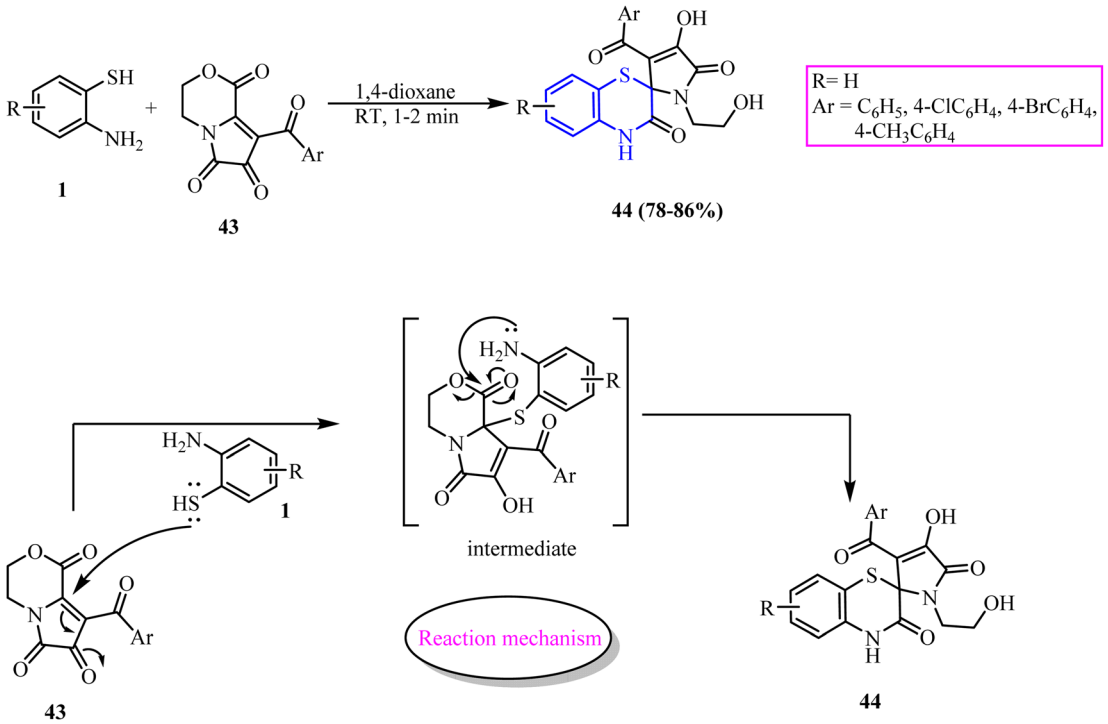
Scheme 15 Synthesis of 1,4-BT using 2-ATP and 3-aryl-2-bromopropanoic acid esters.



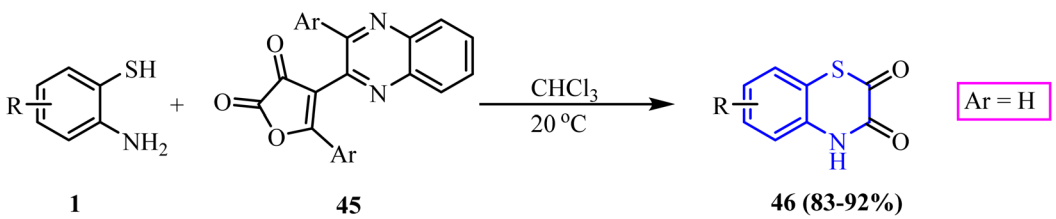
Scheme 16 Synthesis of 1,4-BT using 2-ATP and substituted bromo acetophenones.

after a few hours, and the products were obtained in good yields (83–92%) (Scheme 18).

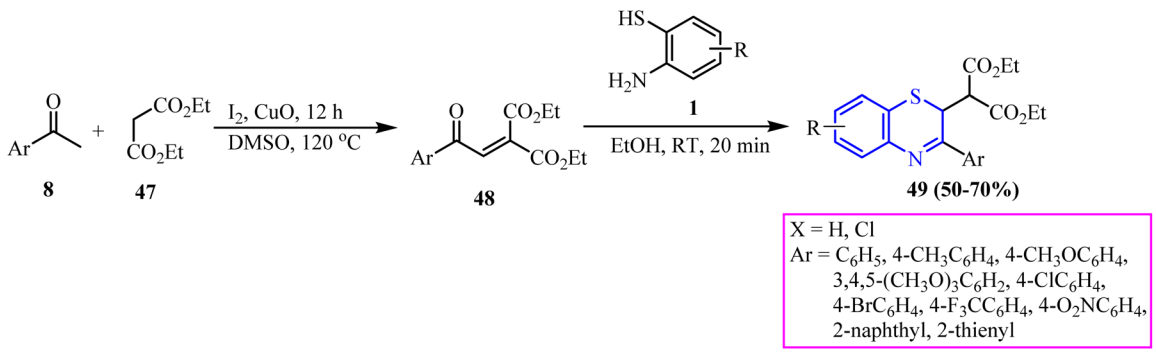
2.1.14. With aroylmethylidene malonates. Meenakshi *et al.*[71] reported the synthesis of novel 1,4-BT derivatives (50–70%) (**49**) through a cyclocondensation reaction involving aroylmethylidene malonates (1 mmol) (**48**) and 2-ATP (1 mmol) (**1**) in ethanol (5 mL), with the reaction mixture stirred at RT for 20 min. Aroylmethylidene malonates (25–54%) were synthesized using an oxidative condensation reaction of aryl methyl ketones (1 mmol) (**8**) with diethyl malonate (1 mmol) (**47**) in the



Scheme 17 Synthesis of 1,4-BT using 2-ATP and pyrrolo[2,1-*c*][1,4]oxazinetriones.



Scheme 18 Synthesis of 1,4-BT using 2-ATP and furan-2,3-dione.

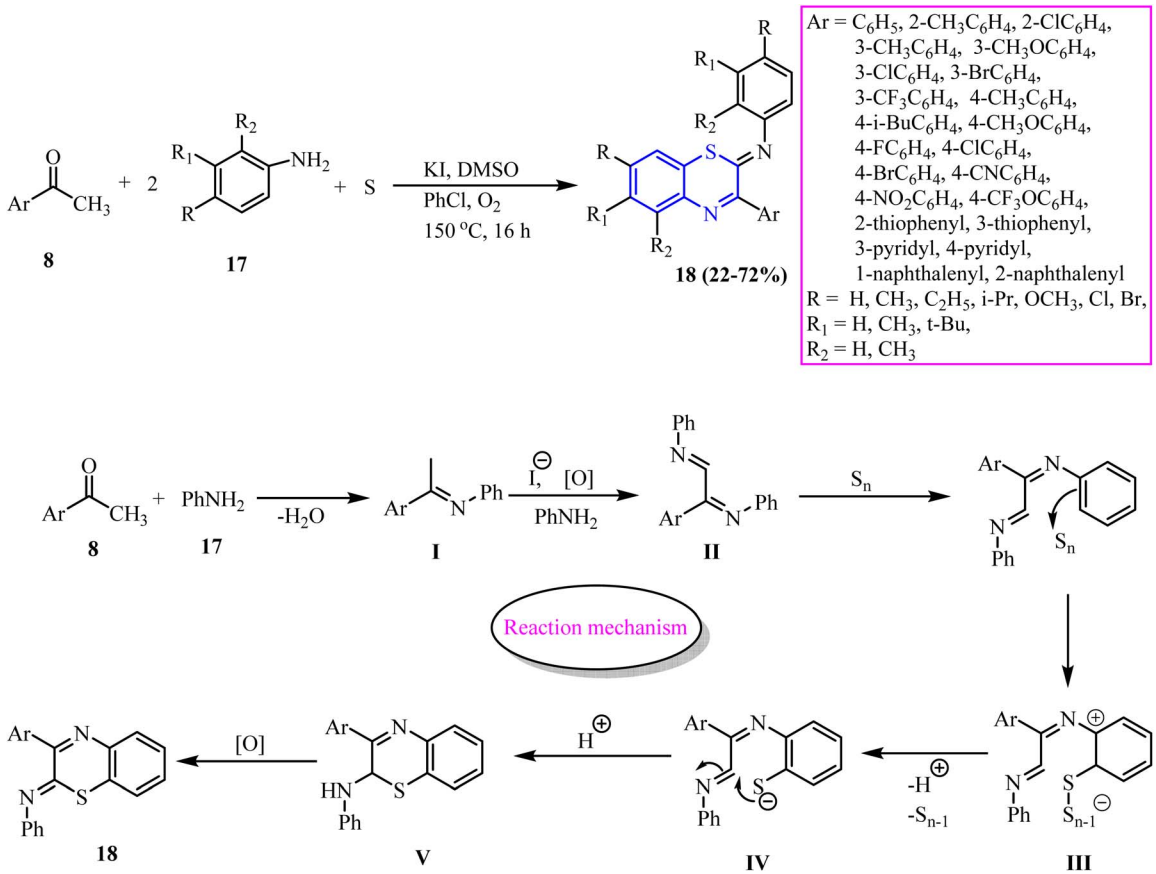


Scheme 19 Synthesis of 1,4-BT using 2-ATP and aroylmethylidene malonates.

presence of iodine (1.1 mmol), CuO (1.1 mmol), and DMSO (5 mL), stirring at 120 °C for 12 h. A demerit of this protocol is the necessity for column chromatography. *In vitro* studies revealed that the compound diethyl 2-[3-(2-naphthyl)-2*H*-benzo[1,4]thiazin-2-yl]malonate significantly inhibited COX-2, demonstrating its potential as a COX-2 inhibitor (Scheme 19).

2.2. Miscellaneous synthesis of 1,4-BTs

The miscellaneous synthesis of 1,4-BT in this part involves employing diverse starting materials such as 2-bromothiophenol, benzothiazole, *o*-quinone, substituted 2-(2-(2-aminophenyl)disulfanyl)benzenamines, 2-aminobenzothiazoles, and anilines.

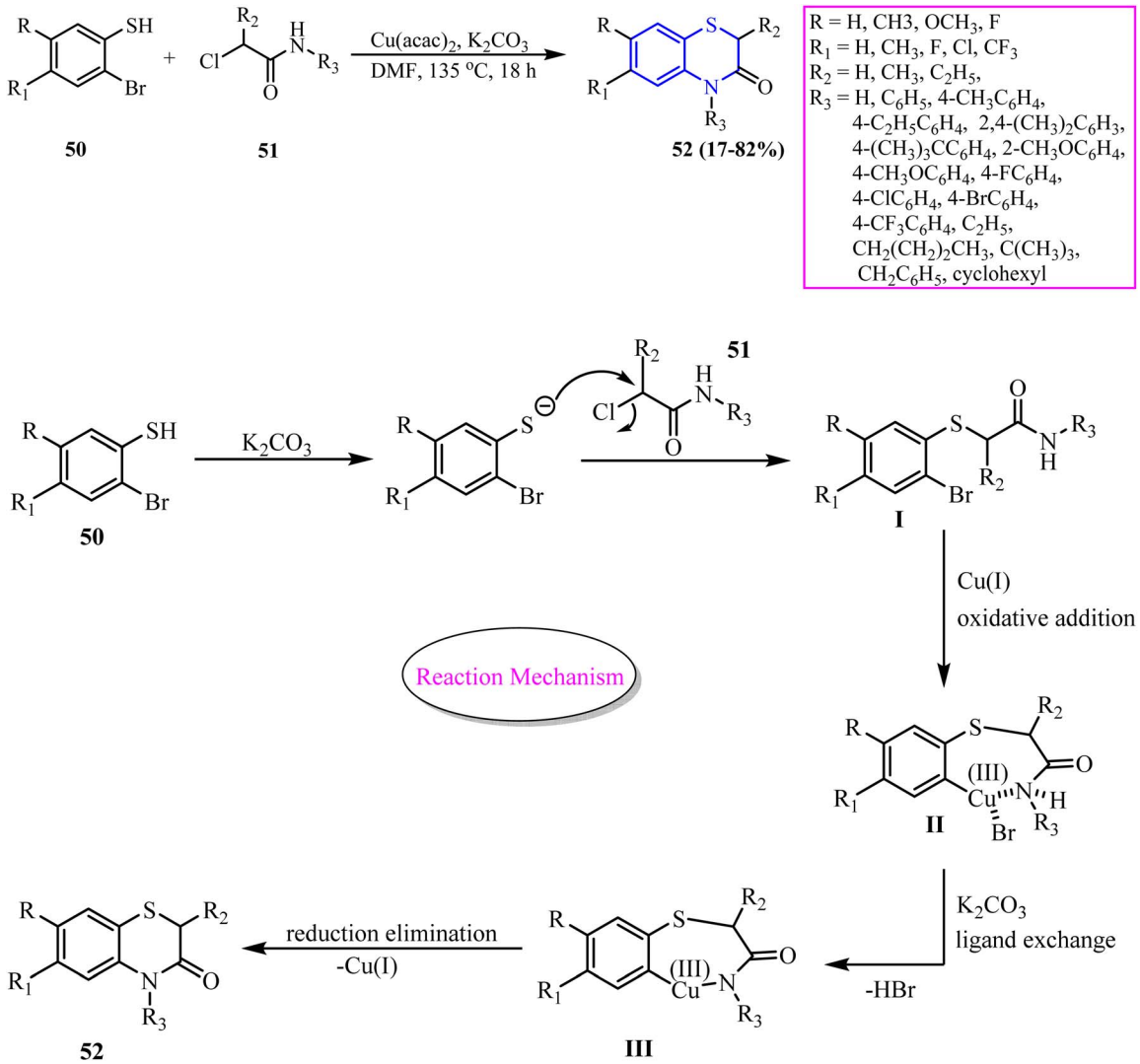


Scheme 20 Synthesis of 1,4-BT using ketones, aniline and sulfur.

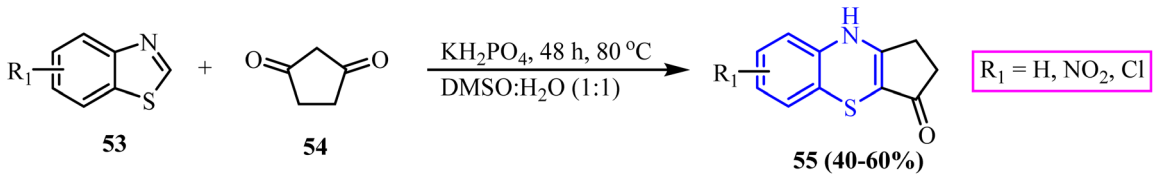
Jiang *et al.*[72] developed an iodide-catalyzed, aerobic method for synthesizing 1,4-BT derivatives (**18**) through multiple C–H functionalization with elemental sulfur. The reaction involved reacting various acetophenone (0.4 mmol) (**8**), substituted aniline (0.4 mmol) (**17**), and elemental sulfur (0.8 mmol) with DMSO (0.8 mmol) and chlorobenzene as the solvent, along with KI (0.1 mmol) as the catalyst at 150 °C for 16 h. The oxidative cyclization resulted in lower to good product yields (22–72%). The reaction mechanism initiated with the condensation of acetophenone (**8**) and aniline (**17**), forming imine intermediate (**I**). Under oxidative conditions (KI/DMSO/O_2), the methyl group in **I** was oxidized and reacted with another aniline molecule, forming intermediate **II**, which was detected by GC-MS. Subsequently, elemental sulfur participated in an electrophilic attack at the *ortho* position of aniline, leading to intermediate **III**. This further transformed into sulfurated imine **IV** through elimination of S_{n-1} and deprotonation. Finally, intermediate **IV** underwent cyclization and aromatization of intermediate **V** under oxidative conditions, yielded the final product. This method works under transition metal-free conditions, employing dioxygen as a green oxidant (Scheme 20).

An efficient copper-mediated C–S and C–N Ullmann coupling reaction for the synthesis of 1,4-BT derivatives (**52**) was reported by Lingyu Zhang *et al.*[73] The reaction of 2-bromothiophenol (0.5 mmol) (**50**) with *N*-alkyl-substituted chloroacetamide (1.2 equiv.) (**51**) occurred in the presence of $Cu(acac)_2$ (10% mol) as a catalyst, K_2CO_3 (2.6 equiv.) as a base, and DMF as a solvent at 135 °C under N_2 for 18 h. This reaction led to the formation of the desired products in yields from 17–82%. In the mechanism, initially, a nucleophilic substitution reaction took place between 2-bromothiophenol and *N*-alkyl-substituted chloroacetamide in the presence of K_2CO_3, resulting in intermediate **I**. This intermediate was subsequently subjected to oxidative addition with Cu(I), forming intermediate **II**. Ligand exchange and hydrogen bromide elimination under basic conditions led to the transformation of intermediate **II** into intermediate **III**, which finally converted into the desired product through reductive elimination. The demerits of this procedure are the need for column chromatography and long reaction time (Scheme 21).

Suliman *et al.*[74] reported a method for the synthesis of 1,4-BT derivatives (**55**) through the cleavage reaction of benzothiazole (0.5 mmol) (**53**) with cyclopentane-1,3-dione (1 mmol) (**54**) in the presence of potassium dihydrogen phosphate (KH_2PO_4) as a base (1 mmol) in a DMSO/H_2O (1 : 1) solvent mixture. The reaction was stirred for 48 h under air at 80 °C, yielding moderate results (40–60%). This approach is environmentally friendly, proceeds under mild conditions, and does not require any transition metals. However, the long reaction time and the



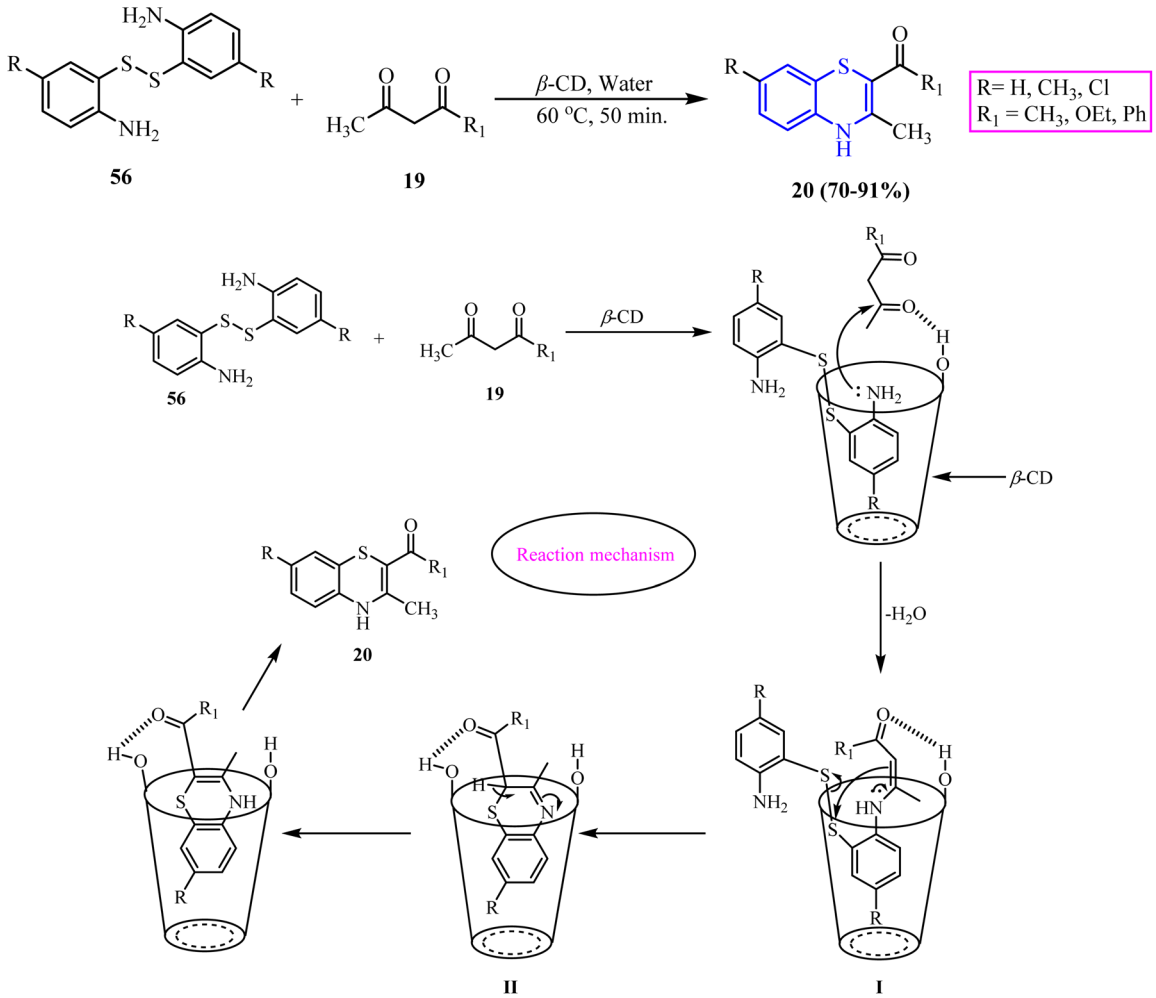
Scheme 21 Synthesis of 1,4-BT using 2-bromothiophenol and chloroacetamide.



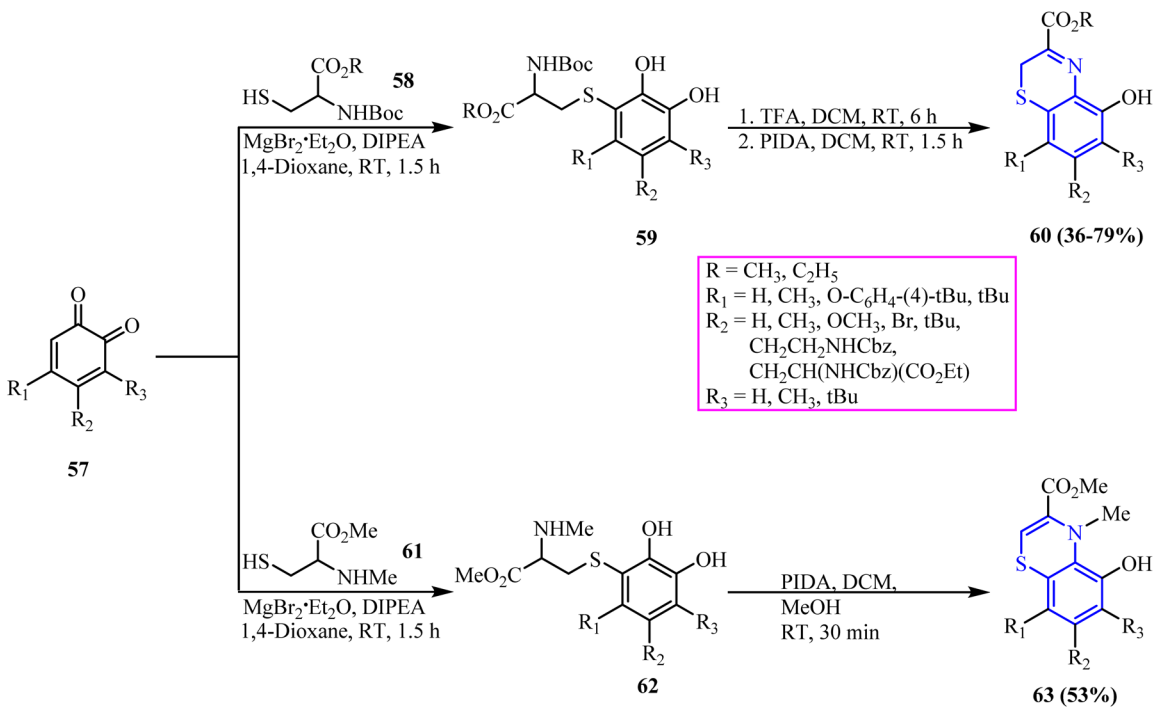
Scheme 22 Synthesis of 1,4-BT using benzothiazole and cyclopentane-1,3-dione.

need for column chromatography are the demerits of this method (Scheme 22).

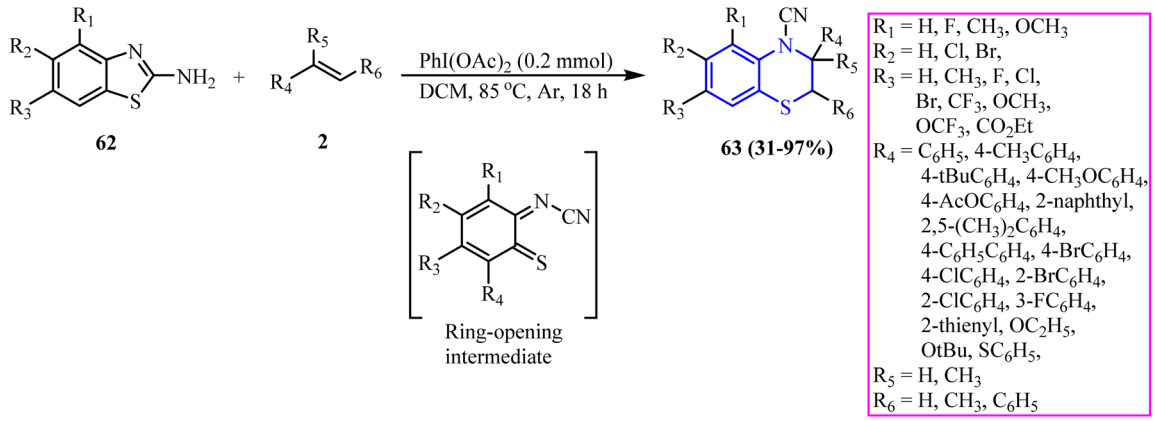
Londhe *et al.*[75] developed a novel method for synthesizing 1,4-BT derivatives (**20**) using a biomimetic strategy. This approach involved the cyclocondensation of substituted 2-(2-(2-aminophenyl)disulfanyl)benzenamines (1 mmol) (**56**) with 1,3-dicarbonyl compounds (2 mmol) (**19**) in the presence of a supramolecular catalyst, *β*-cyclodextrin (*β*-CD) (1 mmol), in water (20 mL), at neutral pH. The reaction was carried out under stirring at 60 °C for 50 min, yielding the desired products in excellent yields (70–91%). In the proposed reaction mechanism, aqueous *β*-CD served as a host, offering a hydrophobic cavity and a hydrophilic exterior, facilitating the formation of non-covalent, reversible supramolecular complexes with 1,3-dicarbonyl compounds (**19**). This enhanced solubilization effect increased the availability of the 1,3-dicarbonyl compound for interaction with 2-(2-(2-aminophenyl)disulfanyl)benzenamine (**56**), which was encapsulated within the hydrophobic cavity of *β*-CD. The reaction proceeded *via* the formation of an enamine intermediate (**I**), followed by intramolecular cyclization, ultimately led to the



Scheme 23 Synthesis of 1,4-BT using substituted 2-(2-(2-aminophenyl)disulfanyl)benzenamines and 1,3-dicarbonyl compounds.



Scheme 24 Synthesis of 1,4-BT using *o*-quinones and *N*-Boc-L-cysteine ester.



Scheme 25 Synthesis of 1,4-BT using 2-aminobenzothiazoles and alkenes.

desired product (**20**). The advantages of this approach include its one-pot, rapid execution, environmental friendliness, and cost-effectiveness, though the necessity for column chromatography for purification is a demerit (Scheme 23).

The bioinspired synthetic route to 1,4-BT derivatives, reported by Halloran *et al.*,[76] involved the selective addition of sulfur nucleophiles to *o*-quinones. The process began with a regioselective reaction between *o*-quinone (0.5 mmol) (**57**) and *N*-Boc-L-cysteine ester (0.75 mmol) (**58**) in the presence of magnesium bromide ethyl etherate ($MgBr_2 \cdot Et_2O$) (0.125 mmol), DIPEA (1.5 mmol), and dry, degassed dioxane (5 mL) at RT for 1.5 h, producing a sulfur-catechol adduct as the crude product (**59**). This crude material was dissolved in DCM/TFA (1 : 1) (10 mL) and stirred for 6 h at RT, which removed the Boc group. Further, the catechol was oxidized using phenyl iodoacetic acid (PIDA) (1 equiv.) in dry, degassed DCM (20 mL) for 1.5 h at RT, generating an *o*-quinone *in situ*. The quinone underwent condensation and tautomerization, yielding 1,4-BT derivatives (**60**) with moderate to good yields (36–79%). On the other hand, when reacting 3,5-di-*tert*-butyl-*ortho*-quinone (1 mmol) with *N*-methyl cysteine methyl ester (1.5 mmol) (**61**), the final step was conducted in DCM/MeOH (4 : 1) solvent to yield *N*-methyl benzothiazine 53% (**63**). The need for column chromatography is a demerit of this approach (Scheme 24).

Sun and Bao[77] developed an efficient metal-free method for synthesizing 1,4-BT derivatives *via* oxidative ring expansion of 2-aminobenzothiazoles with alkenes. Initially, substituted 2-aminobenzothiazoles (0.1 mmol) (**62**) were treated with iodobenzene diacetate [$PhI(OAc)_2$] (0.2 mmol) in DCM (1 mL) under an argon atmosphere at 85 °C for 18 h. This led to the oxidative ring-opening of the 2-aminobenzothiazoles, followed by a [4 + 2] cycloaddition with various alkenes (0.3 mmol) (**2**), resulting in the formation of cyanamide-containing dihydro-1,4-BT derivatives (**63**) with moderate to good yields (31–97%). A demerit of this procedure is the need for flash column chromatography (Scheme 25).

3. Conclusion

1,4-BT derivatives have emerged as a crucial motif in organic synthesis, with significant applications in medicinal, pharmaceutical, and industrial fields. This review presents a comprehensive exploration of the recent methods employed for the preparation of 1,4-BT derivatives over the past decade. Most of the mentioned protocols are based on simple, cost-effective, and environmentally friendly approaches, providing high yields, extensive functionalization, and easy workups with minimal use of hazardous reagents and recyclable catalysts under ambient reaction conditions. However, some methods involve the use of harmful solvents and harsh reaction conditions that can negatively impact the environment. These reactions raise environmental concerns and highlight the need for more sustainable and eco-friendly methods in the field. This review aims to offer researchers insights into overcoming new challenges in creating straightforward, economical, and green methods for synthesizing 1,4-BT derivatives to serve mankind.

Abbreviations

$[PhI(OAc)_2]$	Iodobenzene diacetate
1,4-BT	1,4-Benzothiazine
2-ATP	2-Aminothiophenol
2-IBX	2-Iodoxybenzoic acid
Anti-HCV	Anti-Hepatitis C virus
Boc	*tert*-Butyloxycarbonyl
$CHCl_3$	Chloroform
COX-2	Cyclooxygenase-2
CPB	Cetylpyridinium bromide
Cs_2CO_3	Caesium carbonate
$Cu(acac)_2$	Copper(II) acetylacetonate
CuO	Copper oxide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIPEA	*N*,*N*-Diisopropylethylamine
DMAc	*N*,*N*-Dimethylacetamide
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
HCN	Hydrogen cyanide
HEPES	4-(2-Hydroxyethyl)piperazine-1-ethanesulfonic acid
K_2CO_3	Potassium carbonate

KH_2PO_4	Potassium dihydrogen phosphate
KI	Potassium iodide
KOH	Potassium hydroxide
m-CPBA	*meta*-Chloroperbenzoic acid
MeOH	Methanol
NBC	Nanobiocatalyst
*N*BS	*N*-Bromosuccinimide
PEG	Polyethylene glycol
PIDA	Phenyl iodoacetic acid
RT	Room temperature
TFA	Trifluoroacetic acid
β-CD	β-Cyclodextrin

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

The authors confirmed that this article has no conflict of interest.

Acknowledgements

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