Functionalized 1,4-Benzothiazine: Recent Innovations in Synthetic Methodologies and Bio-Evaluation in Medicinal Chemistry

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ABSTRACT

1,4-Benzothiazines are important sulfur- and nitrogen-containing heterocycles with applications in medicinal, pharmaceutical, and materials chemistry. Although classical synthesis generally relies on the conventional condensation of 2-aminothiophenol with 1,3-dicarbonyl compounds, recent research has substantially expanded the synthetic toolbox. During the last decade, important advances have included ultrasound-assisted synthesis, catalyst-free sonochemistry, microwave-assisted reactions, solvent-free cyclization, graphene-oxide catalysis, metal-free catalysis, heterogeneous catalysis, green-solvent synthesis, iodine catalysis, elemental-sulfur C–H sulphuration, copper-mediated coupling, Morita–Baylis–Hillman chemistry, metal-free catalysis, heterogeneous catalysis, Nano catalysis, bioinspired ortho-quinone chemistry, aqueous reactions, continuous-flow synthesis, multicomponent reactions, and other environmentally oriented approaches. 1,4-Benzothiazine derivatives have attracted considerable attention because of their diverse activities, including antimicrobial, antifungal, antitubercular, anti-inflammatory, antioxidant, anticancer, antihypertensive, antiviral, cardiovascular, and central nervous system-related activities.

Keywords: 1,4-Benzothiazine, Multicomponent synthesis, breast cancer, anticancer, antimicrobial activity.

INTRODUCTION

Heterocyclic compounds containing nitrogen and sulfur, benzothiazines are significant due to their potent biological activities and their widespread use as a critical structural component in various bioactive molecules. Benzothiazines can exist as several regioisomeric systems, including 1,2-, 1,3-, 1,4-, 2,1-, 3,1-, 2,3-, and related arrangements. Among them, 1,4-benzothiazine has received considerable attention because its fused benzene–thiazine framework provides a useful platform for structural diversification and biological investigation. (Rundla et al., 2025)

1,4-Benzothiazines are sulfur- and nitrogen-containing fused heterocycles that have attracted continuing interest because of their biological properties and their utility in medicinal and synthetic chemistry(Rai et al., 2017). Recent literature describes their preparation from 2-aminothiophenol using alkenes, enaminones, carboxylic acids and derivatives, furan-2,3-diones, aroylmethylidene malonates and 1,3-dicarbonyl compounds. Catalytic, nanocatalytic and metal-mediated methods have substantially expanded the synthetic scope. The synthesis of 1,4- benzothiazines derivatives has been widely synthesized using classical reactions, typically starting from 2-Aminothiophenol (Rundla et al., 2025).

The major challenge of many classical procedures is the simultaneous requirement for oxidation and cyclization. 2-Aminothiophenol can undergo oxidation of the thiol to disulfide under certain conditions, while competing pathways may generate benzothiazoles.(Hwang et al., 2020) Consequently, recent research has concentrated on improving selectivity and reducing reaction time, solvent consumption and hazardous reagents. (Bhattacharya et al., 2017)

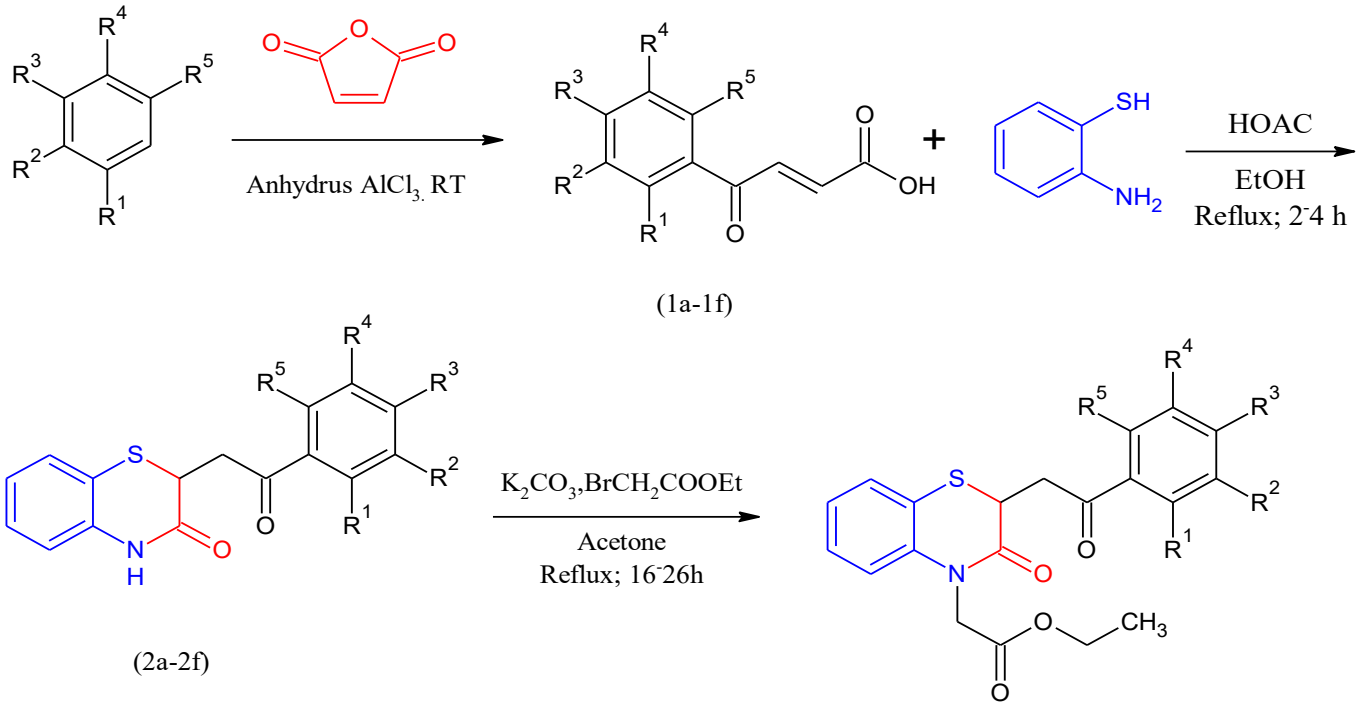
The 1,4- benzothiazines ring system is considered a heterocyclic central structure in S, N-heterocycles, due to its wide-ranging pharmacological and biological effects including antidiabetic, (Taj et al., 2022) anti-hypertensive, (Fringuelli et al., 2005) analgesic,(Warren & Knaus, 1987), antifungal, (Fringuelli et al., 1998) (Schiaffella et al., 2006) anti-HCV,(de Vicente et al., 2009) calcium antagonist, (Nakayama et al., 1992) antibacterial, (Sabatini et al., 2008) antioxidant, (Katselou et al., 2017) anti-inflammatory, (Gowda et al., 2011) antituber-cular, (Coughlin et al., 1995) anticancer, (Mir et al., 2020) (Jacquot et al., 2001) (Gupta et al., 1993) (R. Gupta, n.d.) (Alishba, Ali, et al., 2024; Amin et al., 2024) antipsychotropic, (Inoue et al., 1998) immunomodu- lator, (Corona et al., 1992) antiviral, (Ajani, 2012) antithyroid, (Hornung et al., 2015) cardiovascular activity, (Campiani et al., 1995) antimicrobial (Sharma et al., 2011) antimalarial, (Maheshwari & Goyal, 2016) antipyretic, (Rai et al., 2017) herbicidal, and pesticidal (Rai et al., 2017) activities. They also serve as the central structure in various drugs, including antibiotic and cholesterol-lowering drug (Rundla et al., 2025)

RESEARCH METHODOLOGY

Synthesis, Molecular Docking, and Biological Evaluation of a New Series of Benzothiazinones and Their Benzothiazinyl Acetate Derivatives as Anticancer Agents against MCF-7 Human Breast Cancer Cells and as Anti-Inflammatory Agents

(Ramzan et al., 2023) prepared Aroylacrylic acids (1a–f) by reacting maleic anhydride with anhydrous $AlCl_3$ in an aromatic hydrocarbon solvent at room temperature. After completion, acidification and steam distillation were performed, and the products were isolated by bicarbonate treatment, filtration, and recrystallization.

1,4-Benzothiazinones (2a–f) were synthesized by refluxing β-aroylacrylic acids (3 mmol) (1a–f) with 2-aminothiophenol (3 mmol) in glacial acetic acid (0.7 ml) and absolute ethanol (10-20 ml) for 2–4 h. The resulting precipitates were isolated and recrystallized to afford the pure products.



1a 2a, 3a: R_3 = F, R_1 = R_2 = R_4 = R_5 = H
1b,2b, 3b: R_2 = R_3 = F, R_1 = R_4 = R_5 = H
1c,2c,3c: R_3 = Cl. R_1 = R_2 = R_4 = R_5 = H
1d,2d,3d: R_3 = Br, R_1 = R_2 = R_4 = R_5 =H
1e,2e: R_2 = R_3 = Cl, R_1 = R_4 = R_5 = H
1f, 2f: R2 = Cl, R_3 = CH_3, R_1 = R_4 =R_5 = H

Scheme 1: Synthesis of Benzothiazinones (2a-f) and Benzothiazinyl Acetal Derivatives (3a-d).

The corresponding benzothiazines (0.75 mmol) were treated with ethyl bromoacetate (1.5 mmol) and K_2CO_3 (313 mg, 12.3 mmol) in dry acetone (10−20 mL) under reflux for 16–24 h to obtain 1,4-benzothiazin-4-yl acetates (3a–d). The products were isolated after acidification and purified by column chromatography. (Scheme 1)

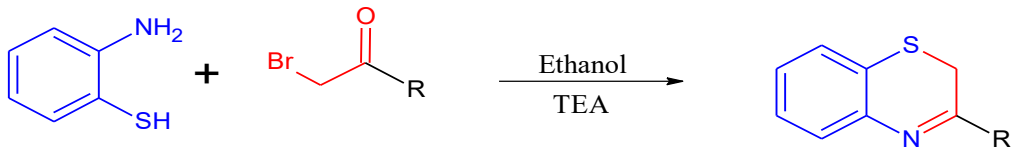
Biological evaluation showed that all synthesized compounds exhibited potent cytotoxic activity against breast cancer, i.e., MCF-7 cells, with 5-fluorouracil (5-FU) as the reference drug. One derivative showed superior cytotoxic activity, with an IC_{50} of 1.29 µM, relative to the remaining compounds in the series. Two derivatives showed superior VEGFR2 kinase inhibitory activity compared with sorafenib, exhibiting IC_{50} values of 0.0528 and 0.0593 µM. Moreover, all derivatives exhibited concentration-dependent inhibition of hemolysis through RBC membrane stabilization, indicating anti-inflammatory potential. The most active derivative showed higher hemolysis inhibition than diclofenac sodium.

Molecular docking and MM/GBSA analyses supported the VEGFR2 binding affinity and antiproliferative potential of the most active derivative, highlighting its potential as a template for developing anticancer and anti-inflammatory agents.

Potential anti-amoebic effects of synthetic 1,4-benzothiazine derivatives against Acanthamoeba castellanii

(Alishba, Ahmed, et al., 2024) Synthesis of 1,4-benzothiazine derivatives by reacting of 2-amino thiophenol (1.0 eq.) in diethyl ether (10 mL) and a few drops of trimethylamine for5 min. The resulting mixture then treated with A suspension of bromo-1-phenylethanones (1.0 equiv.) in the same solvent was then added gradually to the reaction mixture, followed by refluxing at 75–80 °C. After completion, the reaction mixture cooled, poured into ice-cold water, and the precipitate was filtered, washed with water and *n*-hexane, and recrystallized from ethanol. (Scheme 2)

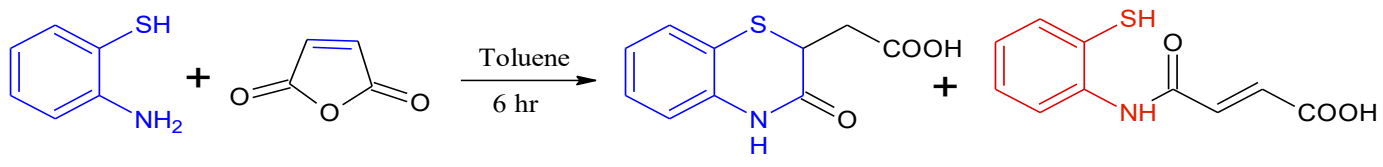
synthesized benzothiazine derivatives exhibited promising in vitro amoebicidal activity against *A. castellanii*, with selected derivatives also inhibiting excystation and encystation. Low cytotoxicity toward HaCaT cells further supported their potential therapeutic and disinfectant applications.



Scheme 2: Synthesis of 1,4-benzothiazines and their substitution patterns.

Design, synthesis, and evaluation of 1,4-benzothiazine-3-one containing bisamide derivatives as dual inhibitors of Staphylococcus aureus with plausible application in a urinary catheter

(Naithani et al., 2024) synthesized 1,4-benzothiazine-3-one bisamide derivatives reaction of Maleic anhydride (2) (4.3 g, 43.93 mM, 1.1 eq) dissolved in toluene (~15 mL) with 2-amino-thiophenol (1) (5 g, 39.94 mM, 1 eq). After stirring for 6 h, an off-white precipitate was obtained. It was filtered, washed with $CHCl_3$, and dried at room temperature without further purification, affording the desired compound as a white solid in 82% yield (7.13 g). (Scheme 3)



(1) (2) (3) 82% (4) Trace

Scheme 3: One pot synthesis of 1,4-benzothiazine-3-carboxylic acid.

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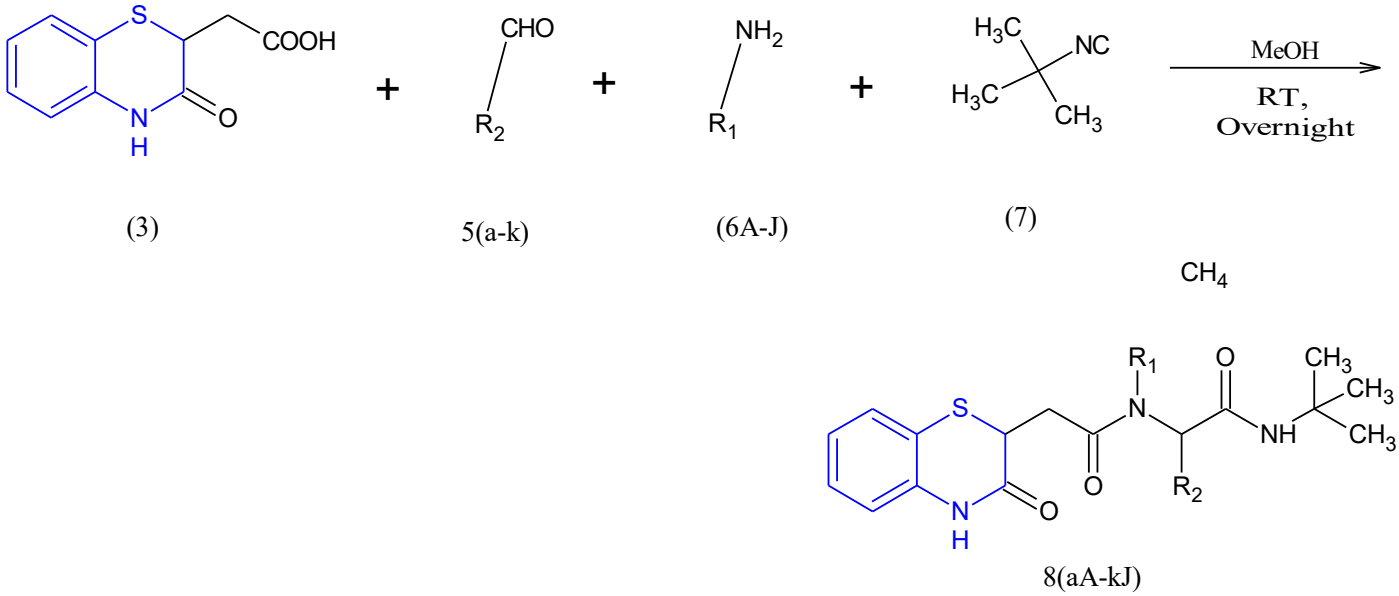
further multicomponent reaction was performed by sequentially combining an amine derivative, carboxylic acid 3, tert-butyl isocyanide 7, and an aldehyde derivative in methanol. The reaction mixture was cooled to 5 °C during reagent addition and subsequently stirred overnight at room temperature (~30 °C), affording the corresponding Product(8). Reactions employing furfural, tryptamine, or phenylethylamine required an elevated temperature of 60 °C to achieve complete conversion. (Scheme 3A)

The synthesized compounds were evaluated for antibacterial activity against both Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus*, *Bacillus cereus*, *Escherichia coli*, and *Vibrio cholerae*. Several compounds showed notable activity against *S. aureus*, Among the tested derivatives, some exhibited superior antibacterial activity compared with the reference drugs gentamicin and actinonine.



Scheme 3A: Synthesis of benzothiazine-3-one containing bisamide derivatives

The compounds were further evaluated for their biofilm inhibitory activity against *S. aureus*. Some compounds showed the highest antibacterial potency, also exhibited excellent biofilm inhibition, indicating their potential dual antibacterial and antibiofilm activity. Furthermore, molecular modeling studies with *S. aureus* peptide deformylase revealed key molecular interactions contributing to the observed biological activity.

A Bioinspired Synthesis of 1,4-Benzothiazines by Selective Addition of Sulfur Nucleophiles to ortho-Quinones

(Halloran et al., 2023) synthesis series of 1,4-benzothiazine derivatives (14–22) was synthesized through a sequential C–S bond formation via deprotection & oxidative cyclization strategy. The ortho-quinone (0.5 mmol, 1eq.) was reacted with *N*-Boc-L-cysteine ester (0.75 mmol, 1.5 eq.) in the presence of magnesium bromide ethyl etherate ($MgBr_2 \cdot Et_2O$ (25 mol%)) and DIPEA (1.5 mmol, 3 eq.) in dry, degassed dioxane (5 mL) at room temperature for 1.5 h, affording the corresponding sulfur–catechol adduct. Subsequent removal of the Boc protecting group using DCM/TFA (1:1) at room temperature for 6 h provided the free amine. Oxidative cyclization with PIDA (1 eq.) in dry, degassed DCM at room temperature for 1.5 h furnished the corresponding 1,4-benzothiazine derivatives after chromatographic purification. (Scheme4)

Leveraging a bio-inspired synthetic paradigm, this robust three-step sequence mirrors the native blueprint of pheomelanogenesis to construct highly functionalized 2H-1,4-benzothiazine derivatives under mild conditions.

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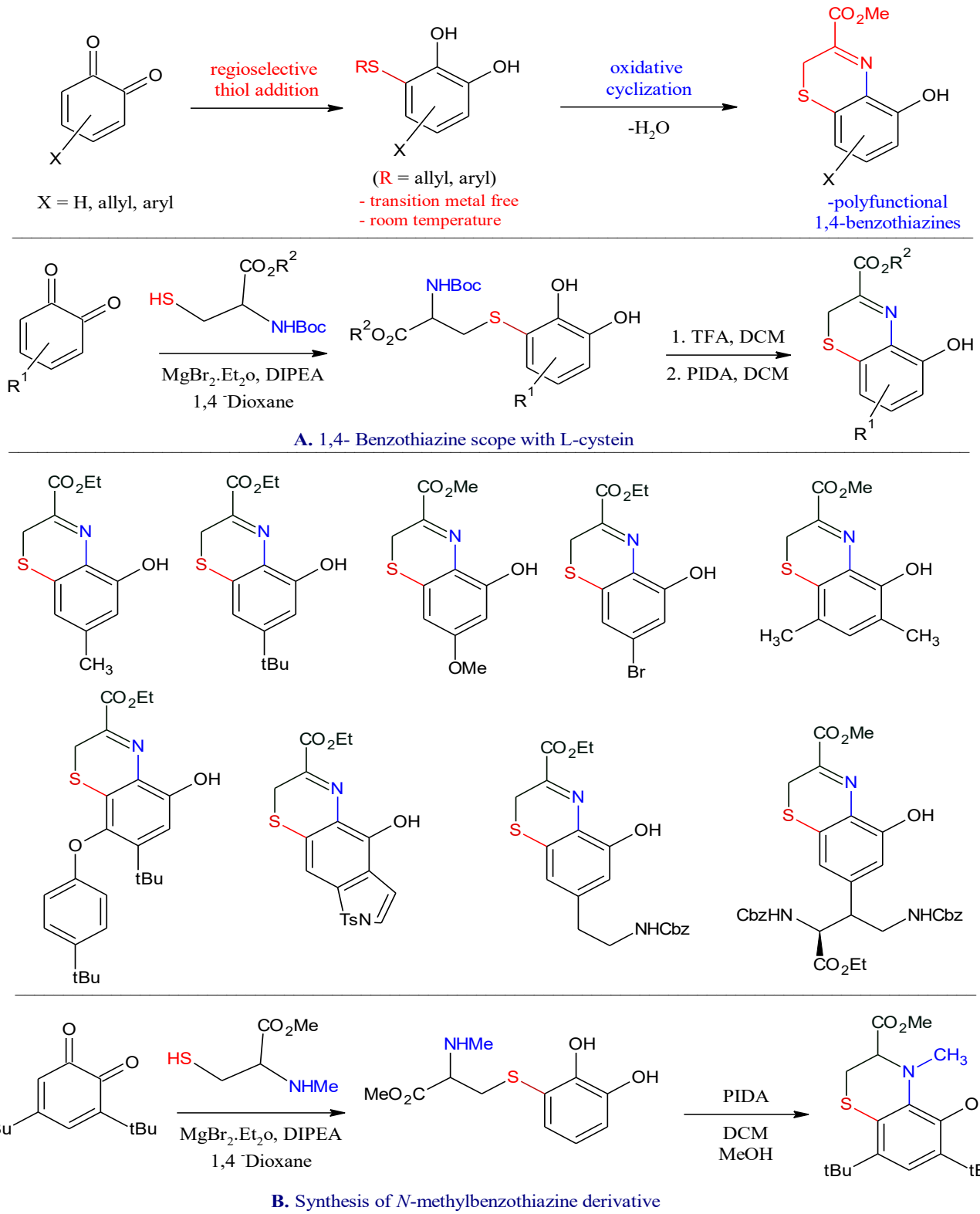

Scheme 4: Synthesis of 1,4-Benzothiazines by Selective Addition of Sulfur-Nucleophiles to ortho-Quinones

Anti-lung Cancer Activity of Synthesized Substituted 1,4-Benzothiazines: An Insight from Molecular Docking & Experimental Studies

(Amin et al., 2023) prepared series of 1,4-benzothiazine derivatives using 2-aminobenzenethiol (1a, 1 mmol, 125 mg) or 2-amino-4-chlorobenzenethiol (1b, 1 mmol, 160 mg) as the starting material. The reaction was carried out in anhydrous acetonitrile (15 mL) in the presence of $NaHCO_3$ (500 mg) and CAN, (1 equiv, 1.096 g). After stirring at room temperature for 10 min, 1,3-dicarbonyl compounds (2a–d, 1 mmol) were introduced, and the reaction mixture was refluxed at 120 °C. The reaction monitoring showed completion after 15 min. The reaction

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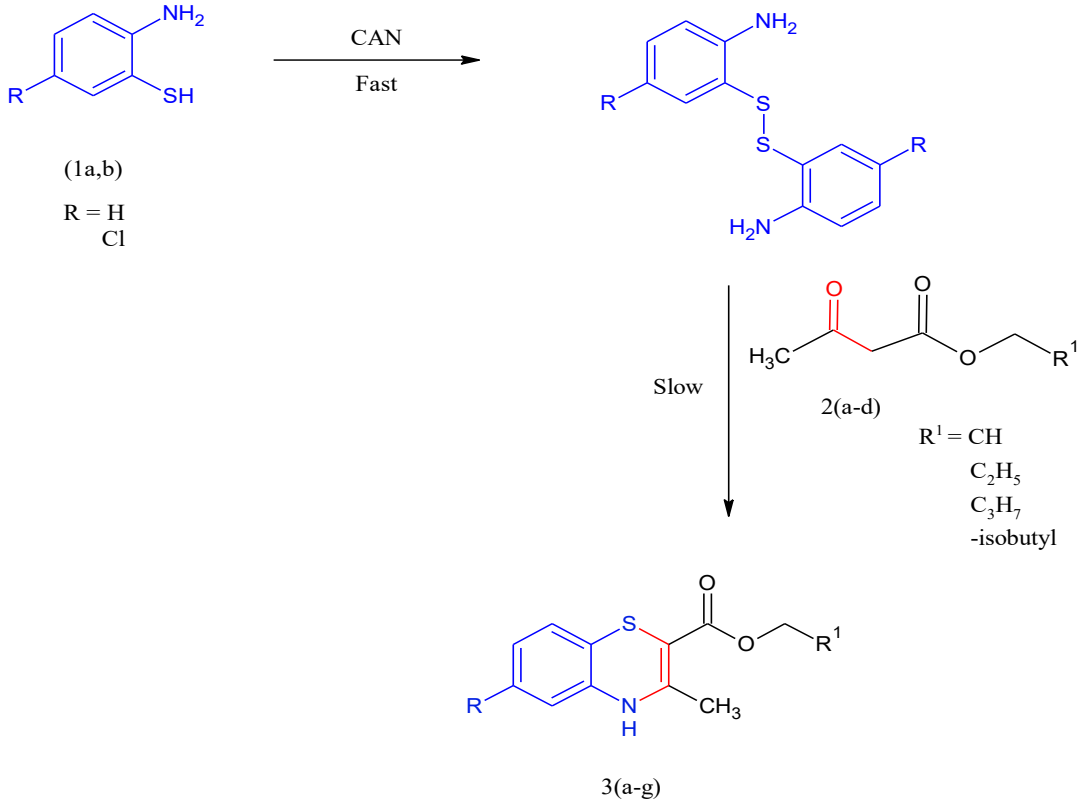
mixture was extracted with ethyl acetate, dried over Na_2SO_4, & purified by column chromatography to afford the corresponding 1,4-benzothiazine derivatives 3a–g. (Scheme 5)

The synthesized benzothiazine derivatives were evaluated for cytotoxic activity against A-549 and C4-2 cancer cell lines using the MTT assay at 10–50 µM concentrations. Some of them exhibited comparatively higher cytotoxicity toward both cell lines. Structure–activity analysis indicated that incorporating an electron-donating methyl group enhanced cytotoxic activity, whereas a chloro substituent reduced it. The most active derivative showed pronounced cytotoxicity against A-549 cells while causing no detectable harmful effect on normal HEK293T cells, suggesting potential selectivity toward cancer cells.



Scheme 5: Synthesis of Benzothiazine derivatives using CAN.

Product Propyl 3-methyl-3,4-dihydro-2H-benzo[b][1,4]thiazine-2-carboxylate was selected for further study and inhibited A-549 cell colony formation in a dose-dependent manner, with 50% inhibition of cell proliferation at 25 µM. The compound significantly reduced A-549 cell migration in a time-dependent manner and downregulated the expression of pro-inflammatory genes, including IL-1α, IL-1β, IL-6, IL-8, vimentin, COX-2, & TNF-α.

Molecular docking studies of selected molecule showed exhibited strong binding with COX-2 and IL-8, with binding affinities of −7.06 and −7.54 kcal/mol, respectively. Furthermore, it showed hydrogen-bond interactions with COX-2 residues Val538 and Tyr373, along with van der Waals interactions involving Gly225, Gly227, Gly533, Gly536, Leu145, His226, Val228, Gln374, and Asn375. It also exhibited strong binding affinity toward the cytokine targets TNF-α, IL-1β, and IL-6.

Flow Synthesis of 1,4-Benzothiazines Using Using Ambivalent Reactivity of (*E*)-β-Chlorovinyl Ketones & 2,2′-Dithiodianilines

(Borra et al., 2022) developed a flow system for the synthesis of 1,4-benzothiazine using ambivalent (*E*)-*β*-chlorovinyl ketones & 2,2′-dithiodianiline with optimized continous flow rates of 0.02 mL/min using TCE as a solvent with a reaction loop volume of 6 mL at 80 °C. They developed a continuous flow synthesis of 1,4-benzothiazines, boasting point of reaction control, defying the inherent limitation of batch reactions to access biologically relevant benzothiazine derivatives. (Scheme 6)

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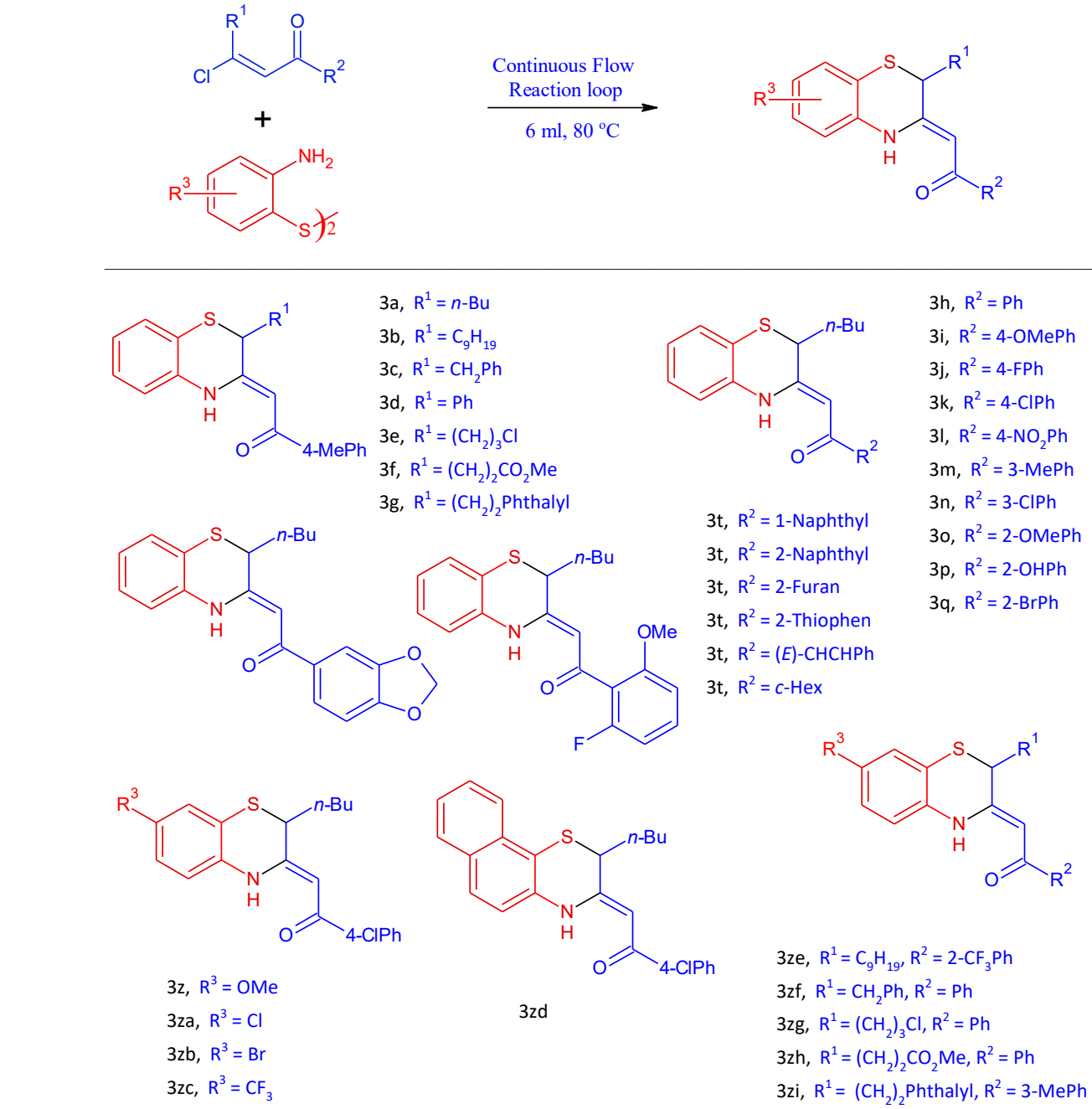

Scheme 6: Continuous flow synthesis of 1,4-benzothiazine using ambivalent (*E*)-*β*-chlorovinyl ketones and 2,2′-dithiodianiline.

Graphene oxide (GO) carbocatalyst for the synthesis of functionalized 1,4-benzothiazines

(Bhattacharya et al., 2017) prepared 1,4-benzothiazines by reaction between 2-aminobenzenethiol (1) and 1,3-diketone (2) in the presence of GO as the catalyst for synthesis of 1,4-benzothiazines with diverse functional groups of pharmaceutical interests. They investigated the reaction using a mixture of 2-aminothiophenol and acetylacetone, as the model reaction. Firstly, they investigated the reaction in different solvents like acetonitrile, DMF, toluene, ethanol and water. Loading of the catalyst GO was started at 50 mg per mmol of 2-aminothiophenol. In that except DMF, other solvents afforded the desired product. Out of the above solvent mentioned poor yield in water. In different solvents except DMF produced the desired product in the range of 56–71% yield, while performing the reaction under complete solvent-free condition and stirring the neat mixture at room temperature, excellent yield of desired product achieved. Thus, Reducing the quantity of GO by 50% i.e. loading of 25 mg also they afforded excellent conversion. However, further decreasing of GO achieved lower yield and without the catalyst GO, the reaction not proceed. (Scheme 7)

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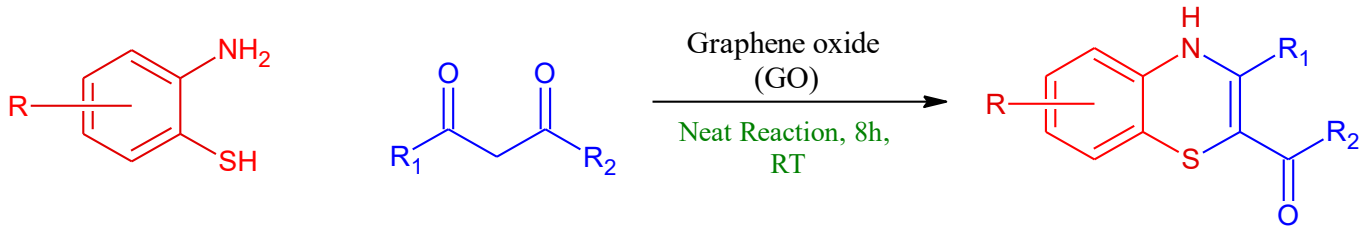


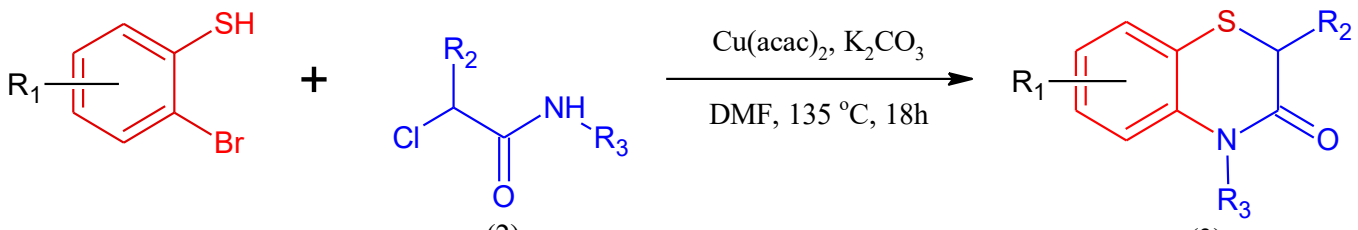
(1) (2) (3)

R = H, Cl, CF3
R_1=CH_3, $CH_2C(CH_3)_2CH_2$, Ph
R_2=CH_3, Ph, OCH_2CH_3

Scheme 7: GO-catalyzed synthesis of functionalized 1,4-benzothiazines at room temperature and solvent-free conditions.

Copper-catalyzed one-pot synthesis of 1,4-benzothiazine-3-ones

(Zhang & Zhang, 2023) reported Copper-mediated C-N coupling reaction between 2-bromothiophenol and 2-haloacetanilide. This protocol affords a simple and efficient approach for the construction of 1,4-benzothiazinone-3-one derivatives, avoiding the limitations of using noble metals and expensive ligands for the first time. (Scheme 8)



(1) (2) (3)

Scheme 8: Copper-catalyzed one-pot synthesis of 1,4-benzothiazine-3-ones

Three-component synthesis of 1,4-benzothiazines via iodide catalyzed aerobic C-H sulfuration with elemental sulfur

(Jiang et al., 2020) Iodide-catalyzed aerobic synthesis of 1,4-benzothiazines via multiple C-H functionalization with elemental sulfur. Transition-metal-free multicomponent strategy for the synthesis of 1,4-benzothiazine derivatives from readily accessible acetophenones, anilines, and elemental sulfur. The reaction was efficiently promoted by a KI in DMSO under O_2 system and involved two equivalents of aniline in the formation of the benzothiazine products. This methodology enabled the facile construction of six-membered 1,4-benzothiazine frameworks from inexpensive and readily available starting materials, providing access to previously unreported derivatives under metal-free conditions.

Potassium Iodide catalyzed synthesis of substituted 1,4-benzothiazines (3) with Substituted Acetophenones (1) (0.4 mmol), Aniline(2a) (0.4 mmol), sulfur (0.8 mmol), KI (50 mol %), DMSO (0.8 mmol), PhCl (2.2 mL), 150 °C, 16 h, under O2. Electron-withdrawing substituents such as NO_2, CN, OCF_3, and CF_3 afforded the corresponding products in moderate to good yields, while F, Cl, and Br substituents in meta and para position were well tolerated. Electron-donating groups, including CH_3, i-Bu, and OCH_3, also provided the desired products in moderate yields. However, ortho-substituted acetophenones gave lower yields, presumably because of steric hindrance. (Scheme 9A)

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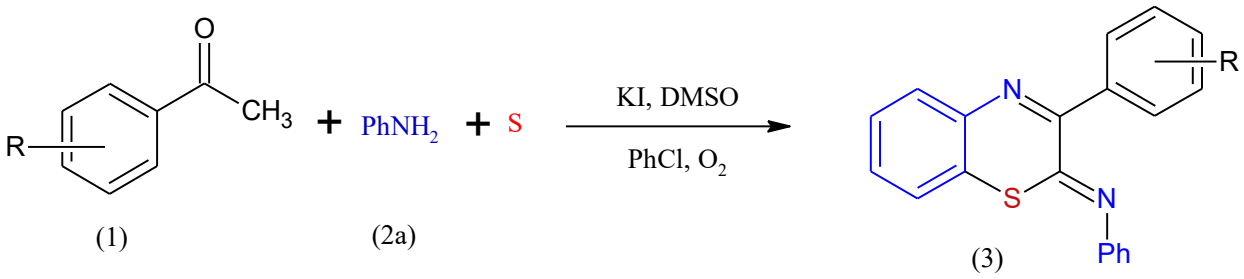
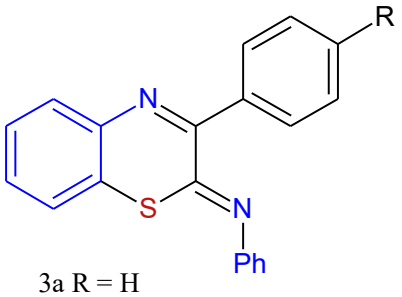
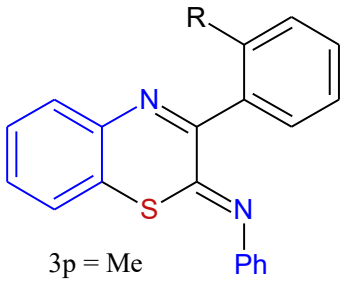


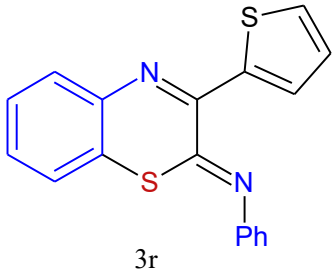
(1) (2a) (3)



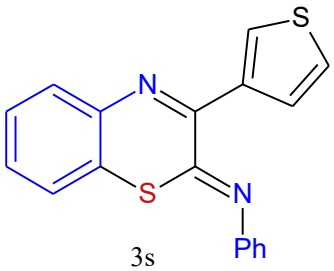
3a R = H
3b R = Me
3c R = i-Bu
3d R = OCH_3
3e R = F
3f R = Cl
3g R = Br
3h R = NO_2
3i R = CN
3j R = OCF_3



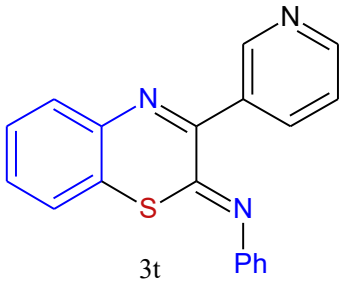
3p = Me
3q = Cl



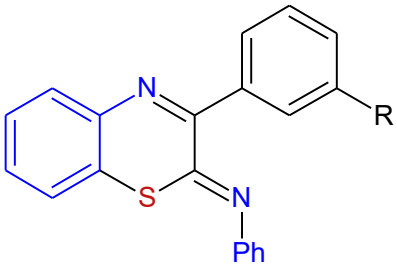
3r



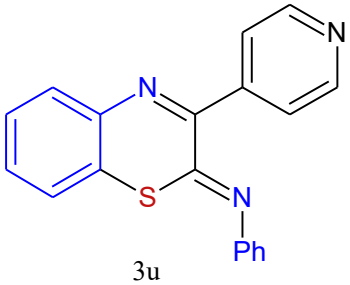
3s



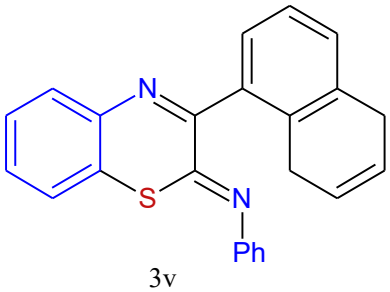
3t



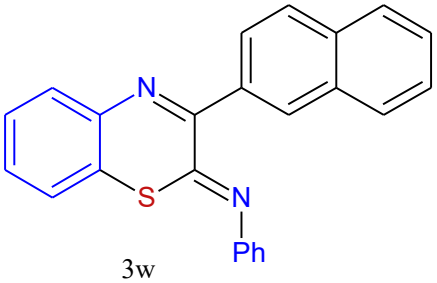
3k R= Me
3l R = OCH_3
3m R = Cl
3o R = CF_3



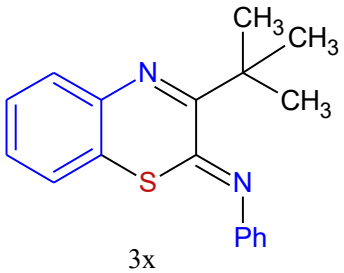
3u



3v



3w



3x

Scheme 9A: Three-component synthesis of 1,4-benzothiazines via iodide catalyzed aerobic C-H sulfuration with elemental sulfur and acetophenone

Potassium Iodide catalyzed synthesis of Substituted 1,4-benzothiazines(4) using Acetophenone(1a) (0.4 mmol), Substituted Aromatic amines(**2)** (0.4 mmol), sulfur (0.8 mmol), KI (50 mol %), DMSO (0.8 mmol), PhCl (2.2 mL), 150 ºC, 16 h, under O2. Para-substituted anilines bearing electron-donating groups afforded the corresponding products in good yields, whereas methoxy- and halogen-substituted substrates showed reduced yields. Dimethyl-substituted anilines also exhibited lower reactivity, highlighting the influence of substituent and position on the reaction outcome. (Scheme 9B)

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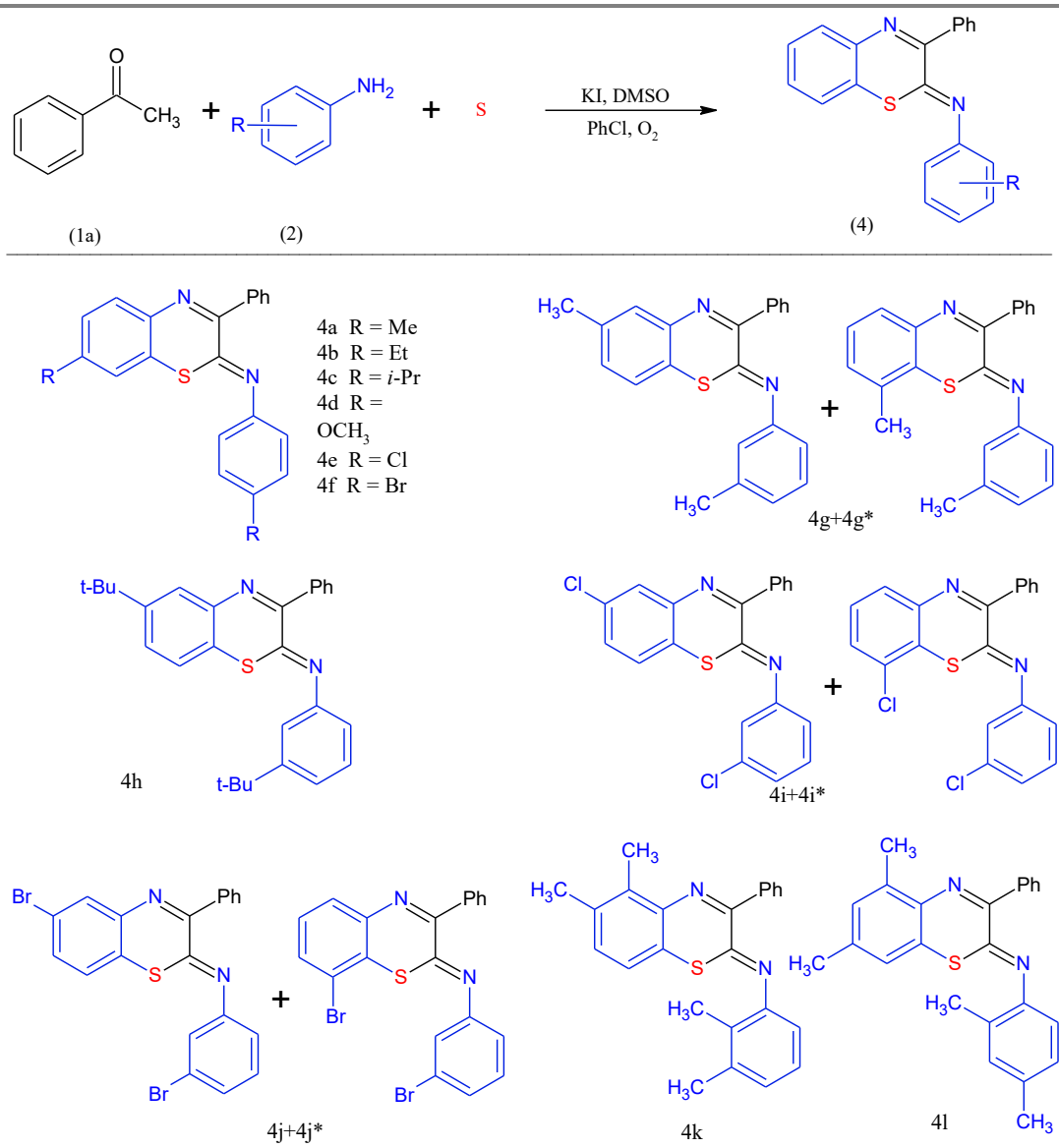

Scheme 9B: Three-component synthesis of 1,4-benzothiazines via iodide catalyzed aerobic C-H sulfuration with elemental sulfur and aniline

Regioselective synthesis of 1,4-benzothiazines via intramolecular S_NAr^F and S_NAr^H cyclization

(Hill & Wipf, 2026) Developed a regioselective synthetic strategy for accessing 1,4-benzothiazine derivatives via intramolecular SNArF and SNArH cyclization, combining experimental observations with computational investigations.

Fluoro-nitroaniline was employed as the starting material, undergoing nucleophilic aromatic substitution reactions to construct thiol-containing intermediates. Subsequent microwave-assisted cyclization was explored for 1,4-benzothiazine formation; however, the reaction preferentially occurred via fluoride displacement at C-2 rather than at the targeted C-6 position.

The reaction predominantly afforded the C-2 fluoro regioisomer, across the different leaving groups examined. The observed regioselectivity was attributed mainly to electronic factors, which enabled intramolecular SNArH cyclization at C-2 to compete with SNArF substitution at C-6.

Computational analysis revealed a higher LUMO electron density at C-2, supporting the experimentally observed regioselectivity. Fukui function calculations further indicated that C-2 was the more reactive site. Additionally, studies using a dinitro-substituted model suggested that suitable substitution patterns could alter the electronic distribution and reverse this regioselective preference.

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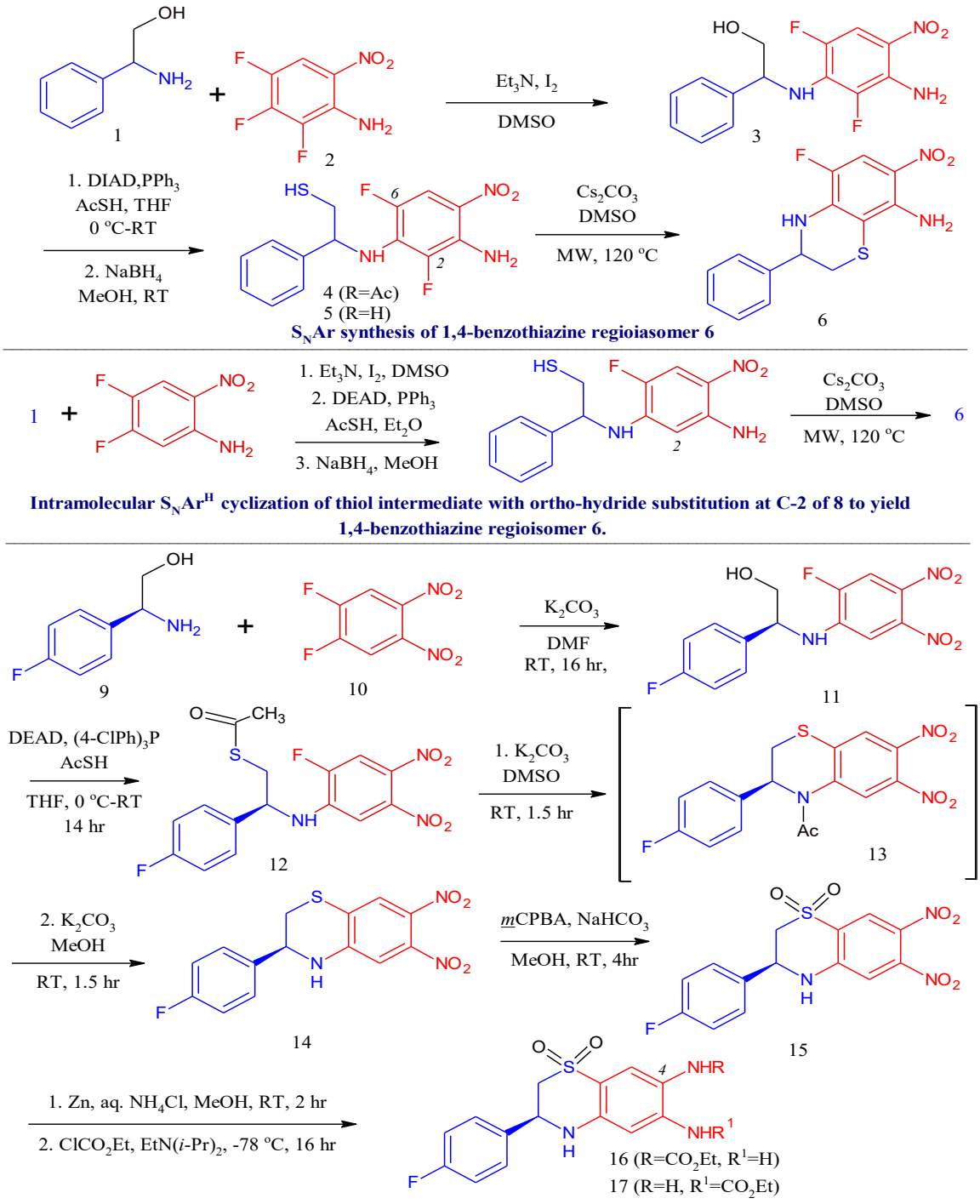
A symmetrically dinitro-activated substrate was developed to minimize the electronic bias and promote the formation of the desired regioisomer through successive SNAr reactions. The optimized pathway involved several transformations, namely condensation, Mitsunobu reaction, saponification, oxidation, reduction, and N-acylation, to furnish the target 1,4-benzothiazine. Overall, the strategy demonstrates how the integration of theoretical calculations and experimental methods can support the development of regioselective routes to 1,4-benzothiazine derivatives. (Scheme 10)



Scheme 10: Regioselective synthesis of functionalized 1,4-benzothiazines via intramolecular S_NAr^F and S_NAr^H cyclizations.

Synthesis of Some Acyclonucleosides Analogs of 1,4-Benzothiazine and Their Sulfonates Derivatives: Crystal Structure, Spectroscopic Characterization, DFT Calculations, Hirshfeld Surface Analysis, and Molecular Docking With Mycobacterium tuberculosis

(Irrou et al., 2025) achieved N-Alkylation of 1,4-benzothiazine using the acyclic alkylating agents 4-bromobutyl acetate (2a), and (bromo methoxy) ethyl acetate (2b) (0.6 mmol, 100 mg) with 1,4-benzothiazine (1). The

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reaction employed potassium tert-butoxide (0.9 mmol, 100 mg) as the base, tetrahydrofuran (20 mL) as the solvent, and 18-crown-6 (0.05 g, 0.2 mmol) as a catalyst. After 2 h at room temperature, the mixture was filtered, concentrated, and chromatographed on silica gel to afford the N-alkylated products 3a and 3b.

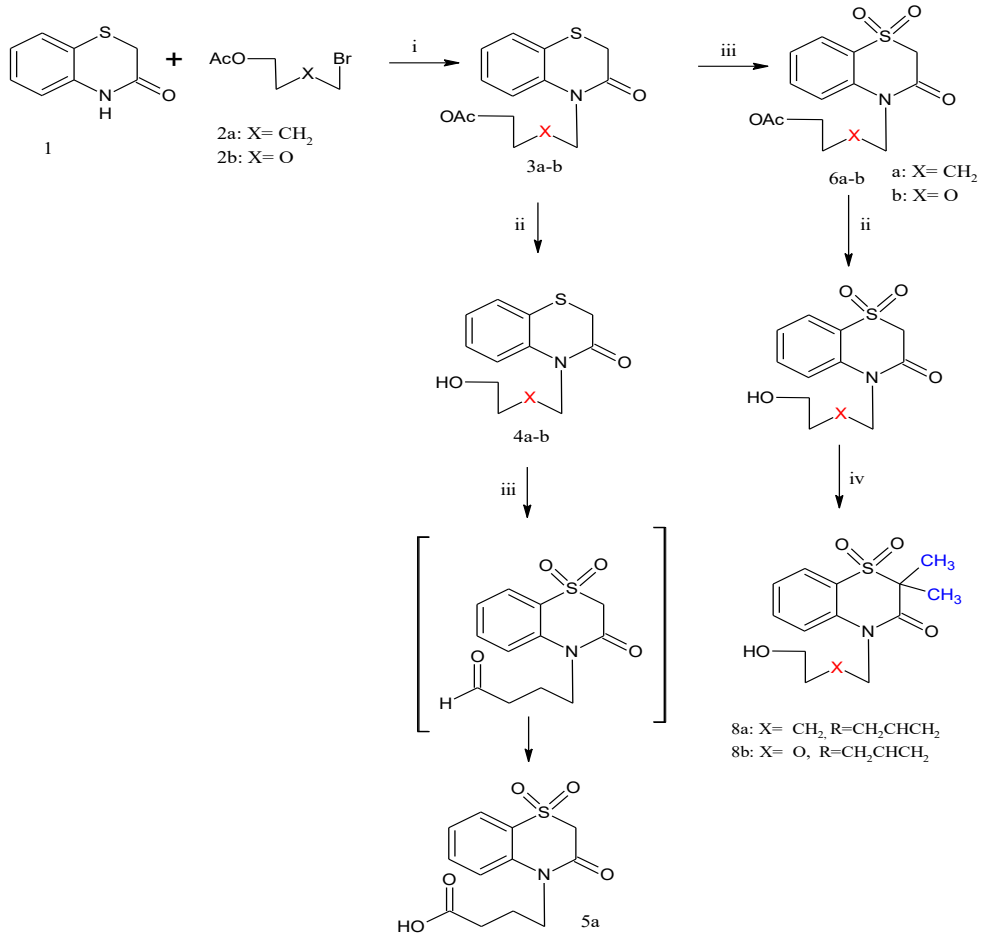
Deprotection of the protected acyclic nucleosides 3a and 3b (1 mmol) was performed in 30 mL of dry methanol saturated with ammonia. After confirmation of complete deprotection by chromatography, the solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography using ethyl acetate/hexane (40:60, v/v) to give the desired acyclic nucleosides 4a and 4b.

The acyclic nucleosides 4a, 5a, and 5b (1 mmol) in acetic acid (5 mL) were added dropwise to an aqueous solution of $KMnO_4$ (1.8 mmol) with stirring at room temperature. After 2 h, 20% sodium thiosulfate pentahydrate was added to quench the excess permanganate. The precipitate was filtered and recrystallized from ethanol to obtain 5a, while 6a and 6b were extracted with ethyl acetate, dried over Na_2SO_4, concentrated under vacuum, and recrystallized from ethanol to give the products as solids. The same deprotection process was followed for deprotection of Compounds 7a, 7b.

Benzothiazine 7a or 7b (1.1 mmol) was treated with allyl bromide (2.2 mmol) and K_2CO_3 in anhydrous DMF at room temperature for 6 h. After filtration and vacuum evaporation, the residue was purified by silica gel chromatography (ethyl acetate/hexane, 40:60) and crystallized.

Single-crystal X-ray diffraction, frontier molecular orbital analysis, and Hirshfeld surface analysis were performed to examine the structures, electronic properties, and molecular packing of derivatives 5a, 6b, 7a, and 8b.

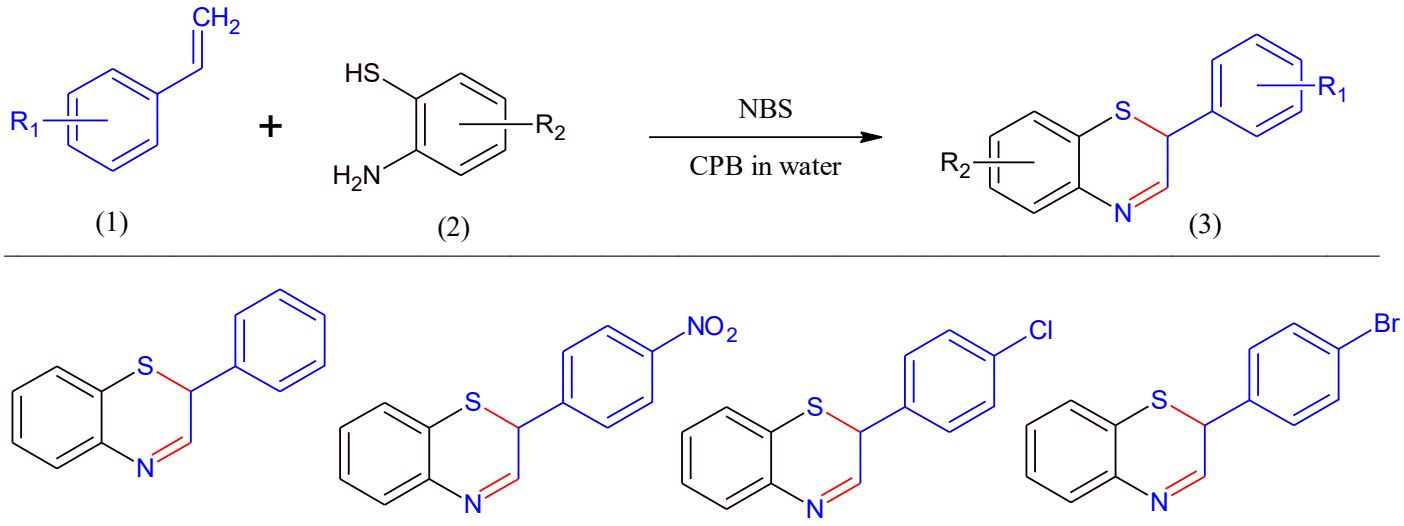
Molecular docking of ligands 5a, 6b, 7a, and 8b against the DprE1 enzyme from *M. tuberculosis* (PDB: 4P8K, chain A) was performed using AutoDock Vina. All compounds showed favorable binding interactions with the target, with 5a displaying particularly favorable binding energy and interactions. (Scheme 11)



Scheme 11: Synthesis of 1,4-benzothiazine and their derivatives (3a,b - 8a,b)

Micelle-mediated synthesis of 1,4-benzothiazine scaffolds from styrenes

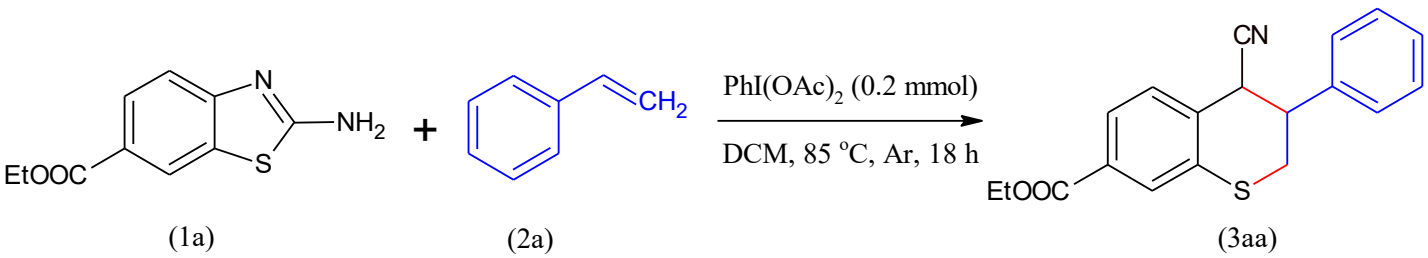
(Teli et al., 2024) reported a micelle-mediated synthesis of 2-aryl-1,4-benzothiazines from styrene and 2-aminothiophenol using NBS in an aqueous cetylpyridinium bromide (CPB) medium. Styrene was first converted in situ to phenacyl bromide using NBS, followed by condensation with 2-aminothiophenol to furnish the corresponding 1,4-benzothiazines. A CPB micellar medium was prepared by dissolving cetylpyridinium bromide (76.8 mg, 1.0 mmol) in double-distilled water (200 mL) and stirring for 1 h above the Kraft temperature to form micellar assemblies. (Scheme 12)



Scheme 12: Micelle-mediated synthesis of 1,4-benzothiazine scaffolds from styrenes

Facile preparation of dihydro-1,4-benzothiazine derivatives via oxidative ring-expansion of 2-aminobenzothiazoles with olefins

(Sun & Bao, 2022) optimized the reaction conditions using ethyl 2-aminobenzo[d]thiazole-6-carboxylate(1a) and styrene (2a) as model substrates, affording the product ethyl 4-cyano-3-phenyl-3,4-dihydro-2Hbenzo[b][1,4]thiazine-7-carboxylate (3aa) with iodobenzene diacetate ($PhI(OAc)_2$) (2 equiv.) as an oxidant in DCM under an argon atmosphere at 85 °C for 18 h. (Scheme 13)



Scheme 13: 1,4-benzothiazine derivatives via oxidative ring-expansion of 2-aminobenzothiazoles with olefins.

Under the optimized conditions, various electron-withdrawing groups, including –Br, –Cl, –F, and $–CF_3$, were tolerated, yielding the corresponding dihydro-1,4-benzothiazine derivatives. Additionally, 2-aminobenzothiazoles substituted with 5-Cl, 5-Br, 4-F, and 4,6-diF groups produced the desired derivatives in moderate yields.

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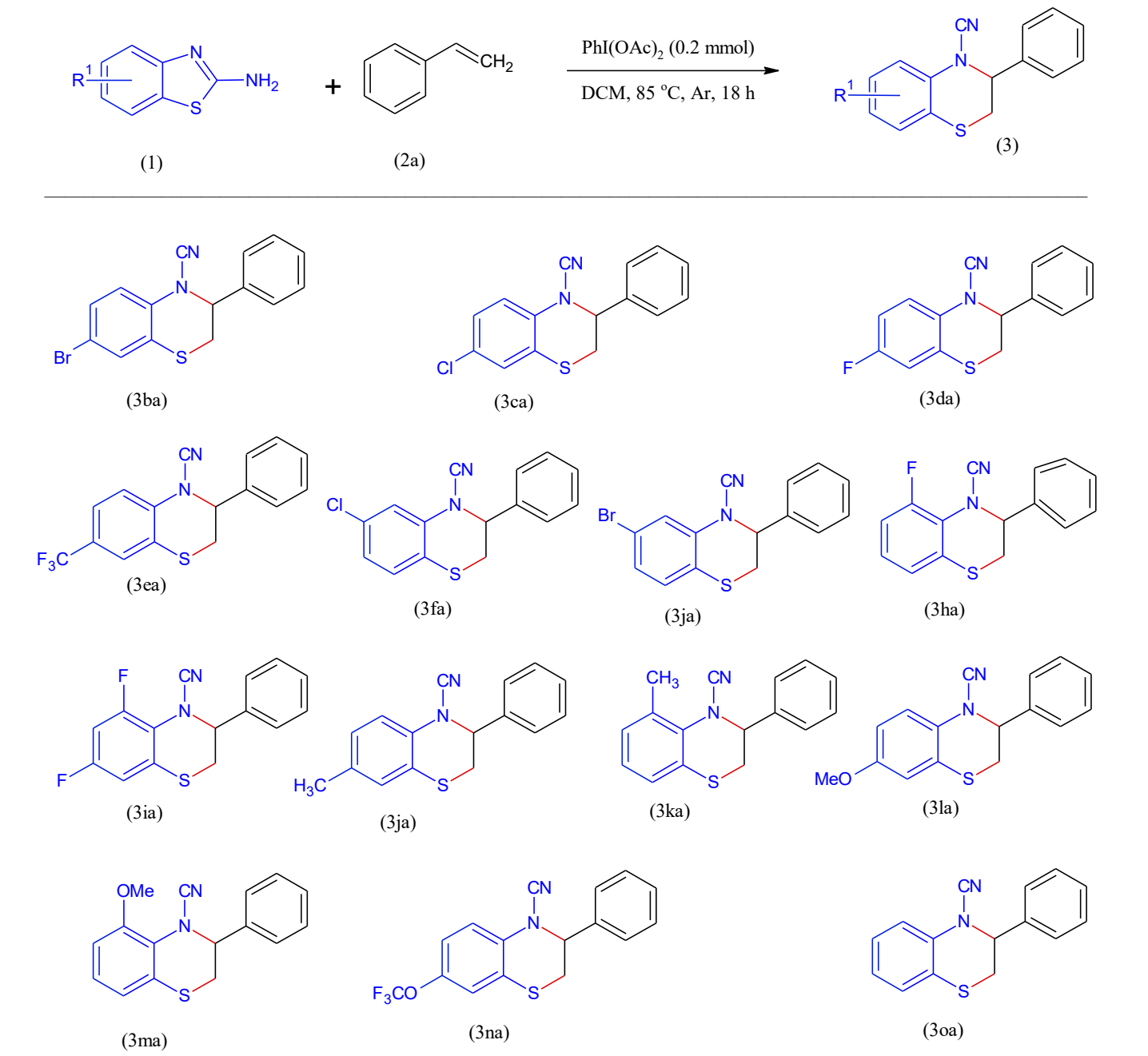

Scheme 13A: Synthesis 1,4-benzothiazine with 2-aminobenzothiazoles

The substrate scope demonstrated the effectiveness of the method across various alkenes. Styrenes bearing electron-donating groups, such as –Me, –tBu, –OMe, –OAc, attached to the para position of the phenyl group, produced the desired products in excellent yields, whereas halogen- and phenyl-substituted derivatives attached to para position of phenyl group (–Br, –Cl) afforded moderate to good yields. In contrast, strong electron-withdrawing substituents, , such as –CF3, –CO2Me, and –NO2, is present at the para position of the phenyl group of styrene were unreactive. Ortho-bromo- and ortho-chlorostyrenes afforded the corresponding products in moderate yields, whereas meta-fluorostyrene gave a low yield. Naphthyl- and thiophenyl-substituted alkenes produced the desired products in good yields, while 2-phenylpropylene gave an excellent yield. Ethoxyethene and phenyl(vinyl)sulfane afforded moderate yields, whereas tert-butyloxyethene gave a low yield. Ethyl acrylate was unsuitable for the reaction. The substrate scope was further extended to internal alkenes, with 1-phenylpropene affording the desired product in an excellent yield, while stilbene gave a moderate yield. The E/Z configuration of internal alkenes had little influence on the reaction outcome. Cyclic alkenes, including 2,3-dihydrofuran and indene, were also compatible, producing the corresponding products in moderate and good yields, respectively.

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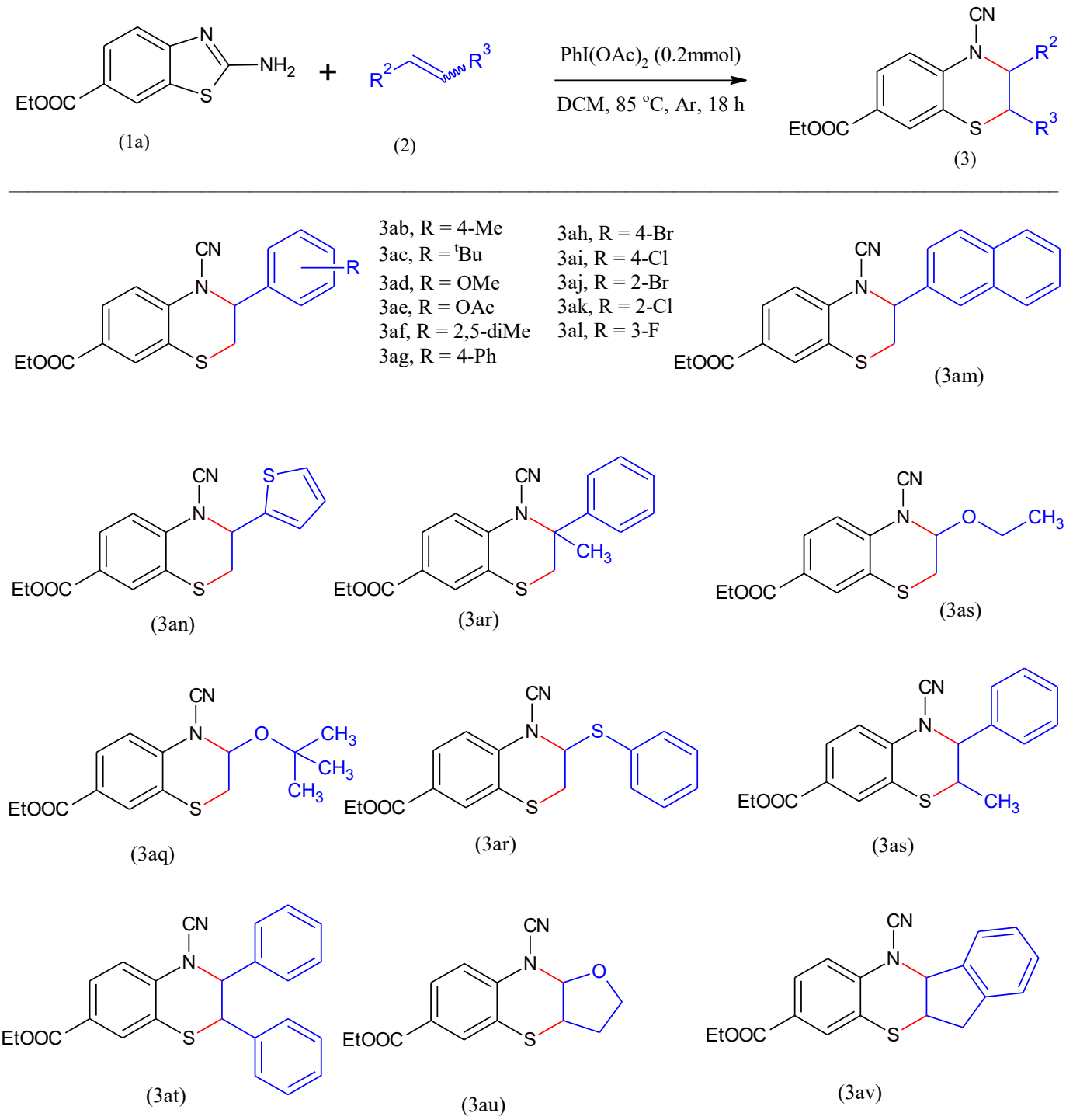

Scheme 13B: Synthesis 1,4-benzothiazine with olefins.

Derivatives of benzo-1,4-thiazine-3-carboxylic acid and the corresponding amino acid

(Kisszékelyi et al., 2022) Condensation of 2-aminothiophenols (1) with bromopyruvic acid and its esters (2) afforded 4H-benzo-1,4-thiazines (3) bearing carboxylic acid or ester groups at the C-3 position. The reaction showed significant temperature-dependent instability, with complete decomposition occurring within 10 min under reflux conditions, while the corresponding acid (3aa) was not obtained. In general, the synthesized benzothiazine derivatives 3 exhibited limited stability, being relatively stable in the solid state but prone to decomposition in solution. The formation of dimers 4a and 4b was also observed during the synthesis of (3ac). The corresponding dimeric benzothiazine derivative was subsequently synthesized to further explore this reaction pathway. (Scheme 14)

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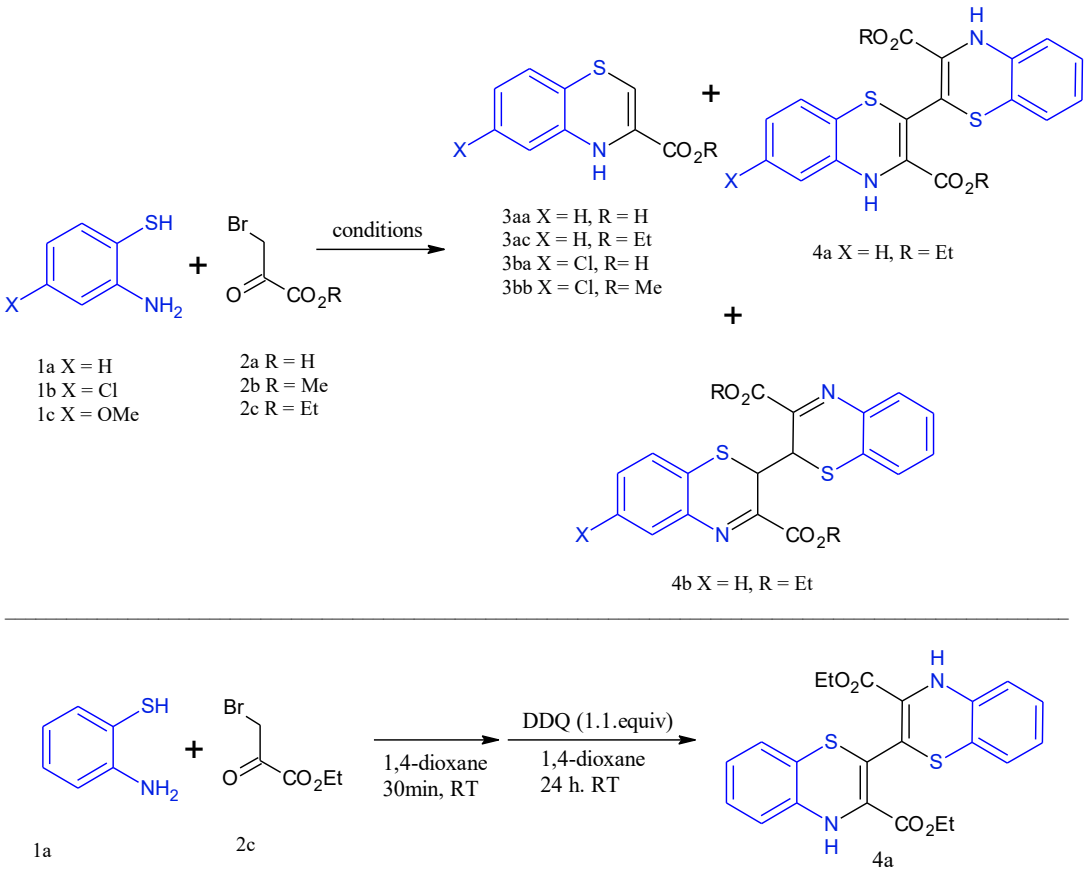
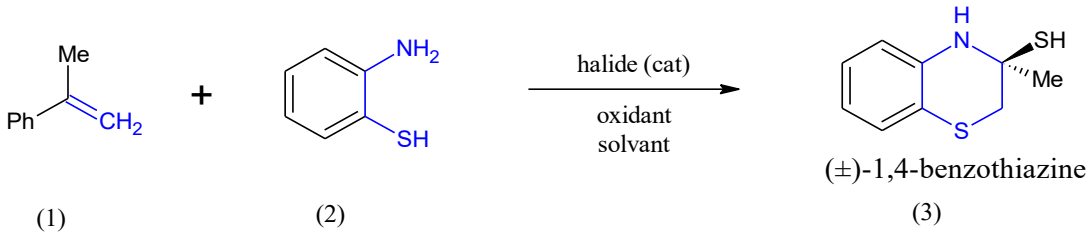


Scheme 14: Synthesis of dimer under oxidative reaction conditions.

Catalytic Regio- and Stereoselective Alkene Sulfenoamination for 1,4-Benzothiazine Synthesis

(Alom et al., 2019) selected α-methylstyrene and 2-aminothiophenol as model substrates for optimizing the reaction conditions. The initial combination of NaI, 10% as the catalyst, potassium persulfate ($K_2S_2O_8$) as the terminal oxidant, and DCE as the solvent at 80 °C afforded the desired 1,4-benzothiazine product in poor yield. Solvent and oxidant screening identified MeCN and $K_2S_2O_8$ as the best-performing combination among the conditions investigated. Different iodide catalysts exhibited only a marginal influence on the reaction outcome, whereas lowering the temperature to 50 °C resulted in a poorer yield. Control experiments demonstrated that the absence of the oxidant completely inhibited product formation, while omission of the iodide catalyst resulted in a low yield. Based on these optimization studies, Sodium iodide (NaI, 10 mol%) as the catalyst, potassium persulfate ($K_2S_2O_8$) as the oxidant, and acetonitrile (MeCN) as the solvent were selected as the optimal reaction conditions for subsequent substrate-scope investigations. (Scheme 15)



Scheme 15: Regio- and Stereoselective Alkene Sulfenoamination for 1,4-Benzothiazine Synthesis

The optimized reaction conditions were applicable to various styrene derivatives, including sterically hindered substrates, with excellent yields and tolerance of bromo, fluoro, and methoxy functionalities. Cis- and trans-disubstituted styrenes and trisubstituted alkenes exhibited excellent diastereoselectivity. In contrast, monosubstituted aliphatic olefins showed modest regioselectivity, whereas a steroid-derived alkene afforded the desired product in moderate yield with excellent regioselectivity.

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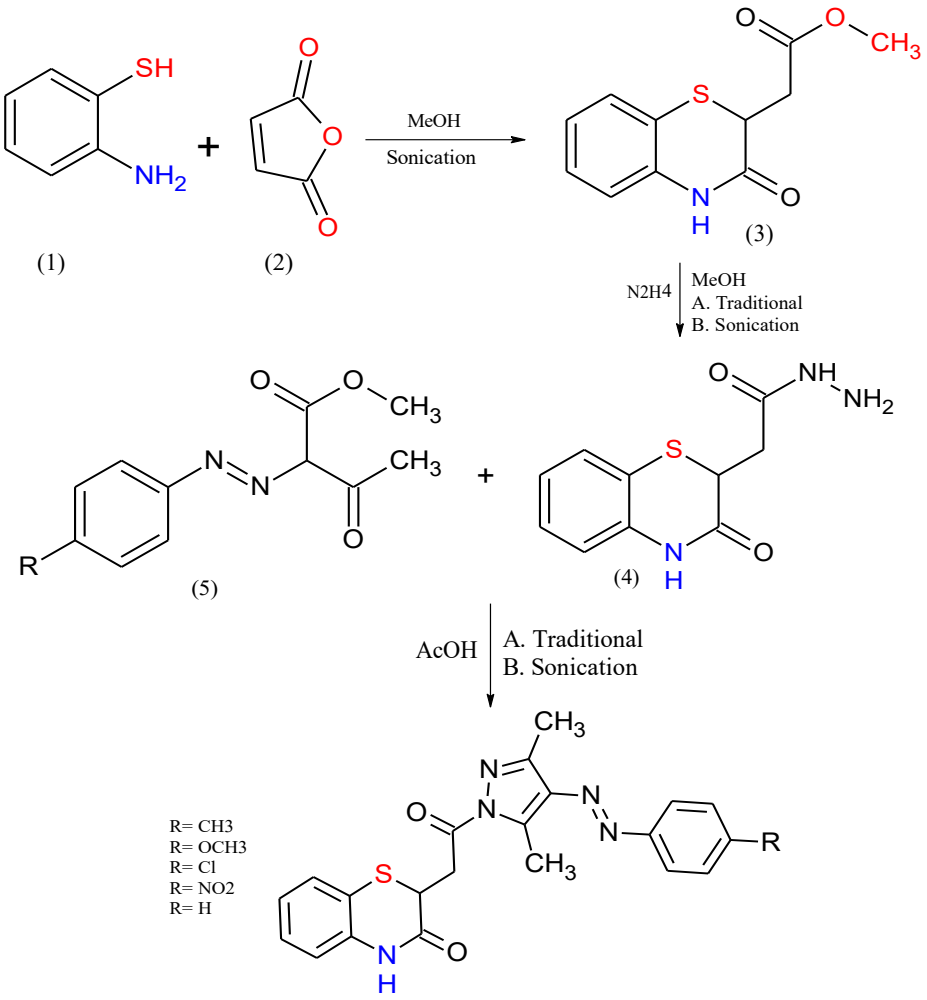
Ultrasound-assisted synthesis using maleic anhydride

(Dabholkar & Gavande, 2016) prepared substituted 1,4 benzothiazine using 2-Aminothiophenol (1) (1.25 g, 0.01 mol), maleic anhydride (2) (0.98 g, 0.01 mol), methanol (25 mL) and Conc. H2SO4 (98%, 2 mL) was taken and sonicated for 10 min. After completion of the reaction cooled solid thus obtained was washed with 5% sodium bicarbonate solution and extracted with dichloromethane to afford (3) provided Yield 87%. They also provided a comparison of the sonication menthod with the conventional method & in conventical method and reaction time is about 6-7hr. and yield is 72%.

Furthermore Compound (3) (2.37g, 0.01 mole) is converted to 2-hydrazinocarbonylmethyl-3,4-dihydro-3-oxo-2H-1,4-benzothiazine (4) using hydrazine hydrate (0.02 mole) in methanol via sonication (8 min.) with yield 80% and for conventical method reported time is 6 hrs. with 70% yield.

Compound (4) (1.18g, 0.005mole) and 3-(4-Methylphenylazo)-2,5-pentadione (5)1.32g, 0.005 mole) reacted with glacial acetic acid (20 ml) under sonication for 24 min. and in conventical method maintained 9 h. after completion of reaction of reaction cooled, poured in crushed ice; the solid mass that separated out was filtered, washed with water and crystallized with ethanol to get desired compound 2H,4H-2-[3,5-dimethyl-4-(methyl)-phenyl azo pyrazol-1-yl] carbonyl methyl-3-oxo-1,4-benzothiazine (6). They reported yield 82-87% in sonication method and in 60-72% yield in conventional method. (Scheme 16)



Scheme 16: Synthesis of 3,4-Dihydro-2-methoxycarbonylmethyl-3-oxo-2H-1,4-benzothiazine(3) through sonication.

The synthesized compounds reported antimicrobial activity against the following microorganisms: (a) Gram-negative: Escherichia coli, Pseudomonas putide; (b) Gram-positive: Bacillus subtilis, Streptococcus lactis; (c) Fungi: Aspergillus niger, Penicillium sp.; (d) Yeast: Candida albicans. The compounds showed good activity towards Gram-positive bacteria, but were less active against Gram-negative bacteria.

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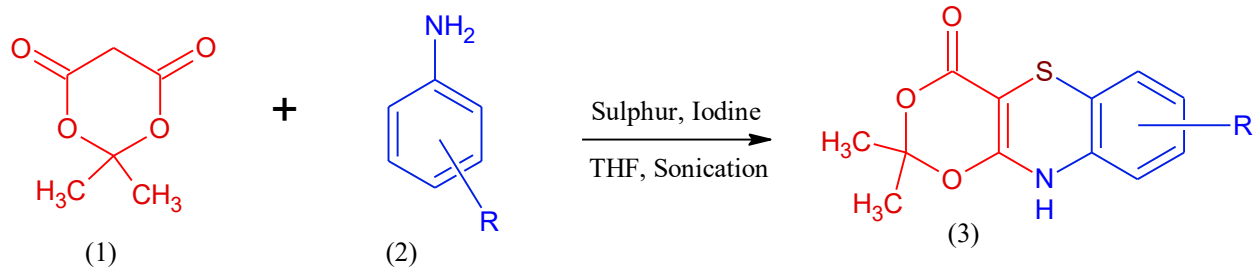
Synthesis of fused Benzothiazine derivative by Sonication technique

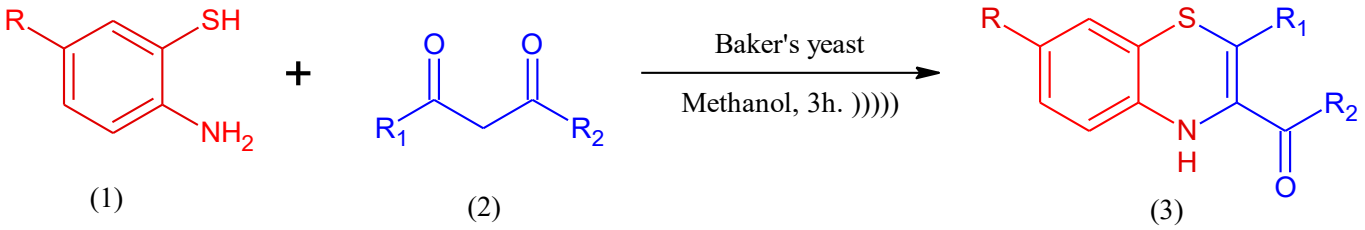
(Dabholkar et al., 2015) *Synthesized of fused Benzothiazine derivatives by* using of Meldrums acid(1) (0.05 mol), Aromatic primary amine(2) (0.05 mol) and Sulphur (1g), iodine (0.15g) and THF (5cm3) as a solvent and Sonicated for 15-20 minutes on a sonicaton bath. After completion of the reaction, the concentrated reaction mixture cooled and poured onto ice-cold water, solid separated was filtered, washed with dilute HCl and CS2, dried, and recrystallized from absolute alcohol to obtain pure *fused Benzothiazine derivative(3)s*. The yield reported from 61 to 82 %. Synthesized benzothiazines compounds were further reported their antimicrobial activity which showed good activities against Gram positive as well as Gram negative bacteria. (Scheme 17)



Scheme 17: Synthesis of *Benzothiazine by* using of Meldrums acid and Aromatic primary amine with Sulphur

Baker's yeast catalyzed synthesis of 1,4-benzothiazines under ultrasonication

(Pratap et al., 2011) performed synthesis of 1,4-benzothiazines using 2-aminobenzenethiol (10mmol) in methanol(25mL), via active dry baker's yeast(2g) and dicarbonyl (10mmol). Then the mixture sonicated at 20kHz for 3hat25–30◦C. This involves the oxidative cyclo condensation with 2-aminobenzenethiols with 1,3-dicarbonyl compounds, expedited by baker's yeast as a whole cell biocatalyst at ambient temperature. The oxidative co-enzymes, NAD+/FAD, produced by baker's yeast are crucial for the conversion of 2-aminobenzenethiols into corresponding disulfides. (Scheme 18)



Scheme 18: Baker's yeast catalyzed synthesis of 1,4-benzothiazines under ultrasonication

CONCLUSION

The 1,4-benzothiazine scaffold has attracted considerable research interest in medicinal chemistry because of its structural versatility and the diverse biological activities associated of its several derivatives. Recent advances in synthetic methodology have enabled the preparation of functionalized benzothiazine molecular frameworks through oxidative cyclization, annulation, metal-mediated reactions, and alternative catalytic strategies, allowing the introduction of different functional groups into the core structure. The utilization of different substrates and reaction parameters has further expanded the scope of structural modification to the molecular framework and facilitated the development of novel derivatives. Biological evaluations have exihibited promising antimicrobial, antitubercular, anti-inflammatory, antioxidant, and anticancer activities, highlighting their potential in medicinal chemistry. Molecular docking & structure–activity relationship studies have revealed useful insights into the interactions between selected derivatives and biological targets. Despite significant preliminary biological findings, translating these results into clinically useful therapeutic applications remains limited. Future research should focus on developing sustainable and efficient synthetic methods, establishing clear structure–activity relationships, and conducting comprehensive pharmacological, toxicity, and mechanistic studies. These efforts may support the further development of 1,4-benzothiazine derivatives as potential molecules for future drug discovery.

LIST OF ABBREVIATIONS

CAN: Ceric ammonium nitrate

CPB: Cetylpyridinium bromide

DCE: 1,2-dichloroethane

DCM: Dichloromethane

DIPEA: N,N-Diisopropylethylamine

DMF: N,N-Dimethylformamide

DMSO: Dimethyl Sulfoxide

GO: Graphene oxide

NBS: N-bromosuccinimide

NaI: Sodium iodide

MeCN: Acetonitrile

MM/GBSA: Molecular Mechanics/Generalized Born Surface Area

PIDA: Phenyliodine(III) diacetate

TCE: 1,1,2-trichloroethane

TFA: Trifluoroacetic Acid

THF: Tetrahydrofuran

DATA AVAILABILITY STATEMENT

No new data were generated or analysed during the preparation of this review article. All information discussed in this review was obtained from previously published literature only.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

ACKNOWLEDGEMENTS

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