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γ-Valerolactone: Promising bio-compatible media for the synthesis of 2-arylbenzothiazole derivatives

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Abstract: A new and efficient protocol was developed for synthesis of benzothiazoles as a potential antimicrobial and antioxidant agent using γ-Valerolactone (GVL) as catalyst and solvent under environmentally friendly conditions. The developed synthetic protocol represents a very simple and a novel route for the synthesis of 2-substituted benzothiazole derivatives. In addition, an ultrasound irradiation technique was successfully implemented for performing the reactions in shorter reaction times. The synthesized benzothiazoles were evaluated for antimicrobial and antioxidant activity and was analysed for ADME properties.

Keywords: Benzothiazoles; γ-valerolactone (GVL); ultrasound irradiation; green protocol; antimicrobial and antioxidant; ADME prediction.

1. Introduction

Solvents have a significant impact on the environment because a large quantity of them is generally used in pharmaceutical productions. They typically account for between 80% and 90% of the mass utilization of a batch operation.[1] Consequently, replacing conventional solvents, which are usually volatile organic compounds, with more environmentally benign media is one of the central issues of the Green Chemistry and a subject of significant academic and commercial interest.[2] In this regard, a variety of unconventional solvents, such as water,[3] ionic liquids,[4] fluorous media,[5] supercritical fluids[6] and polyethylene glycol[7] have been extensively studied and fascinating results have been reported. Although the use of these solvents is still subject to strict limitations, such as low solubility of starting materials and instability of reactive reagents or substrates in water, high prices and lack of data about the toxicity and bio-compatibility for ionic liquids. Therefore, the search of new reaction media is still desirable.

In recent years, the use of bio-based solvents as alternative to conventional organic solvents has received considerable interest among the scientific community.[8,9] Many naturally available products, such as glycerol,[10] ethyl lactate,[11] gluconic acid aqueous solution [12] carbohydrates-based low melting mixtures,[13] have been recognised as safer, sustainable, and biodegradable solvents and catalysts for organic transformation. However, the number of bio based solvents is still limited at this stage, and the scientific community is continuously searching for new sustainable media in order to widen their use in chemical transformation. In this regard, γ-valerolactone, a naturally occurring chemical found in fruits

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and frequently used as a food additive, demonstrates the most important attributes of an ideal sustainable solvent, having high boiling point, high polarity, low melting point, nontoxic and good stability towards acids and bases.[14] Therefore, the use of γ-valerolactone as a green reaction solvent in organic reactions may constitute an important alternative in sustainable chemistry.

In recent years, analogues and derivatives of heterocyclic compounds have attracted wide attention due to their useful biological and pharmacological properties. Benzothiazoles are among the usually widely occurring heterocyclic nuclei in many marine as well as natural plant products, possessing are privileged bicyclic ring system with multiple applications.

In 1950s, a number of benzothiazoles were intensively studied as central muscle relaxants. Since then medicinal chemists have not taken an active interest in this chemical family. Biologists started to pay attention to this series when the pharmacological profile of Riluzole (6-trifluoromethoxy-2-benzothiazolamine) was discovered, which was used to treat amyotrophic lateral sclerosis (Figure 1).[15] Benzothiazoles is an important scaffold with a wide array of interesting biological activities and therapeutic functions including anticancer,[16] antimicrobial,[17] anticonvulsant,[18] antiviral,[19] antitubercular,[20] antimalarial [21]antihelmintic,[22] analgesic,[23] antiinflammtory,[24] antidiabetic,[25] and fungicidal activities.[26] Recently, radiolabeling of some derivatives of benzothiazoles has been developed for PET imaging in the diagnosis of Alzheimer's disease.[27] They were also used as antioxidants, vulcanization accelerators in industry and as a dopant in light-emitting organic electroluminescent devices.[28,30]

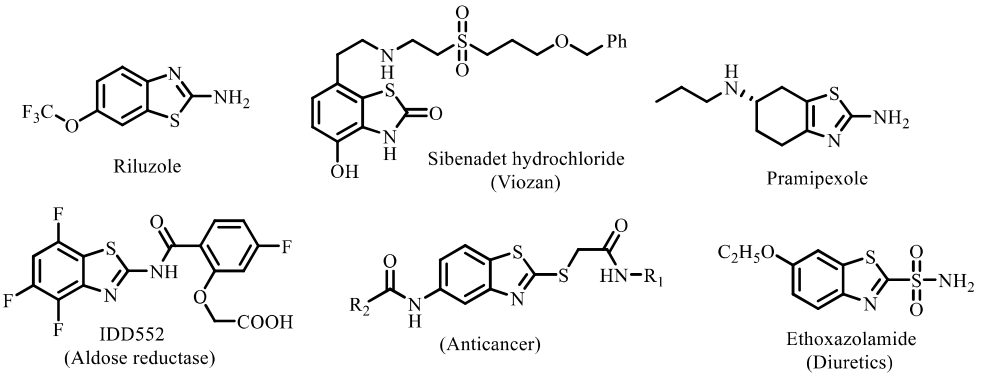


Figure 1. Marketed drugs containing benzothiazole scaffold

The high therapeutic properties of the heterocycles have encouraged the medicinal chemists to synthesize a large number of novel chemotherapeutic agents. Benzothiazole derivatives catalyse the formation of sulphide linkages (reticulation) between unsaturated elastomeric polymers in order to obtain a flexible and elastic cross-linked material. 2-Mercaptobenzothiazole is mainly used as a rubber accelerator in certain specialty products and tire production.

Over the past few decades, several methods have been developed for the synthesis of benzothiazole scaffolds. For instance, condensation reaction of 2-aminothiophenol with carboxylic acids,[31] acid chloride,[32] aldehydes,[33] nitriles[34] and β-diketones,[35] as well as the metal-free oxidative cyclization/dehydrogenation of cyclohexanones and thioureas under aerobic condition,[36] have been developed. Additionally, iodine[37] or p-TsOH[38] catalysed benzothiazole synthesis and silica supported solvent free synthesis of 2-arylbenzothiazole under microwave irradiation,[39] H_2O_2/HCl in ethanol[40] and $LiBr_2$[41] catalyzed have already been discovered. Nowadays, several novel approaches like metal free intramolecular cyclization of 2-halo-*N*-phenylthioacetamide,[42] and visible-light driven photo redox catalytic formation of 2-substituted benzothiazoles through radical cyclization of thioanilides,[43] have also been developed.

Unfortunately, many of these processes endure limitations, such as extreme reaction conditions, low yields, dreary workup procedures and co-occurrence of several side reactions. Thus, the introduction of green methods to overcome these limitations is still an important experimental challenge.

Since, above heterocycles having tremendous significance in various areas, organic chemists have challenge to overwhelm them by searching a surrogate for the conventional bases, which can work in water, and to develop efficient methods for this nucleus using milder, non-hazardous and inexpensive reagents. With the inspiration of our earlier work, [44] we explored the use of γ-valerolactone[44a] in the development of environmentally benign and sustainable process, for the straightforward synthesis of 2-

arylbenzthiazoles by condensation of 2-aminobenzenethiol and benzaldehyde at 100 ºC in γ-valerolactone as a solvent and catalyst. To the best of our knowledge, there is no report available in the literature for the synthesis of 2-arylbenzthiazoles derivatives using γ-valerolactone as a green and reusable bio-based solvent.

2. Experimental

2*.1. Chemical and Instruments*

All chemicals were purchased from Sigma-Aldrich and S. D. Finechem companies and used without further purifications. ^{1}H NMR spectra were recorded on a Bruker 400 MHz DPX spectrometer with tetramethylsilane as internal standard and the chemical shifts are reported in δ units. Analytical grade organic solvents such as hexane, methanol, ethyl acetate, diethyl ether etc. were used for the chemical synthesis. Thin layer chromatography was performed on pre-coated silica gel 60 F_{254} aluminium sheets (E. Merck, Germany) using various solvent system and spots were identified by UV light.

*2.2. General procedure for the synthesis 2-substituted benzothiazoles **3(a-t)**:*

*Conventional method**:** o*-Aminothiophenol **1** (1 mmol), aromatic aldehydes **2a-t** (1 mmol) in GVL (5 mL) were added into a round bottom flask and heated at 100 °C for the period of time as indicated in Table 3. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured into an ice-cold water. The solid was filtered and washed with water, dried and purified by crystallization from ethanol.

Ultrasound method: o-Aminothiophenol **1** (1.0 mmol), aromatic aldehydes **2a-t** (1.0 mmol), in GVL (5 mL) were added into a round bottom flask. The reaction flask was placed into an ultrasonic cleaner bath, where the surface of the reactants was slightly lower than the water level and irradiated at 25-30 °C for the period of time as indicated in Table 3. The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was poured onto crushed ice; the precipitate was filtered and washed with water, dried and purified by crystallization from ethanol.

*2.3. Spectral data of compounds **3(a-t)***

*2-Phenylbenzothiazole (**3a**):* The product was obtained as yellow needles (Yield = 95%); m.p. 112-114ºC (lit. m.p. 115-116 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.03-8.16 (m, 3H), 7.91 (d, *J* = 8 Hz, 1H), 7.46-7.60 (m, 4H), 7.34-7.44 (m, 1H); ESI-MS (MeOH): *m/z*: 212 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $[C_{13}H_9NS+H]^+$: 212.0534 $[M+H]^+$; found: 212.0542.

*2-o-Tolyl-benzothiazole (**3c**):* The product was obtained as yellow needles (Yield = 93%); mp 58-60ºC (lit. m.p. 52-54 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.06 (d, *J* = 8.03 Hz, 1H), 7.96-8.02 (m, *J* = 8.03 Hz, 2H), 7.90 (d, *J* = 8.03 Hz, 1H), 7.49 (t, *J* = 7.28 Hz, 1H), 7.37 (t, *J* = 7.28 Hz, 1H), 7.28-7.33 (m, *J* = 7.91 Hz, 2H), 2.43 (s, 3H); ESI-MS (MeOH): *m/z*: 226 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $[C_{14}H_{11}NS+H]^+$: 226.0690 $[M+H]^+$; found: 226.0695.

*2-(2-Chlorophenyl)-benzothiazole (**3f**):* The product was obtained as an orange solid (Yield = 90%); mp 80-82ºC (lit. m.p. 76-78 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.18-8.29 (m, 1H), 8.14 (d, *J* = 8.16 Hz, 1H), 7.96 (d, *J* = 7.91 Hz, 1H), 7.49-7.59 (m, 2H), 7.37-7.48 (m, 3H); ESI-MS (MeOH): *m/z*: 246 $[M+H]^+$, 248 $[M+2+H]^+$; HRMS (ESI): *m/z* calcd for $[C_{13}H_8NSCl+H]^+$: 246.0144 $[M+H]^+$; found: 246.0148.

*2-(4-Fluorophenyl)-benzothiazole (**3g**):* The product was obtained as orange needles (Yield = 92%); mp 101-103ºC (lit. m.p. 98-100°C); ESI-MS (MeOH): *m/z*: 230 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $[C_{13}H_8FNS+H]^+$: 230.0440 $[M+H]^+$; found: 230.0444.

*2-(3-Bromophenyl)-benzothiazole (**3h**):* The product was obtained as red needles (Yield = 92%); mp 88-90ºC (lit. m.p. 84-86 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.28 (s, 1H), 8.08 (d, *J* = 8.16 Hz, 1H), 7.99 (d, *J* = 7.78 Hz, 1H), 7.92 (d, *J* = 8.03 Hz, 1H), 7.62 (d, *J* = 8.03 Hz, 1H), 7.51 (t, *J* = 7.72 Hz, 1H), 7.33-7.44 (m, 2H); ESI-MS (MeOH): *m/z*: 290 $[M+H]^+$, 292 $[M+2+H]^+$; HRMS (ESI): *m/z* calcd for $[C_{13}H_8NSBr+H]^+$: 289.9639$[M+H]^+$; found: 289.9645.

*2-Benzothiazol-2-yl-phenol (**3l**):* The product was obtained as yellow needles (Yield = 91%); mp 130-132ºC (lit. m.p. 127-128 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 12.51 (s, 1H), 7.99 (d, *J* = 7.91 Hz, 1H), 7.88-7.92 (m, 1H), 7.69 (dd, *J* = 1.44, 7.84 Hz, 1H), 7.46-7.54 (m, 1H), 7.35 - 7.44 (m, 2H), 7.11 (dd, *J* = 0.82, 8.34 Hz, 1H), 6.92-6.99 (m, 1H); ESI-MS (MeOH): *m/z*: 228 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $[C_{13}H_9NOS+H]^+$: 228.0483 $[M+H]^+$; found: 228.0487.

*2-Benzothiazol-2-yl-6-methoxy-phenol (**3m**):* The product was obtained as a white solid (Yield = 92%); mp 179-181ºC; ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 12.73 (br. s., 1H), 8.01 (d, *J* = 8.16 Hz, 1H), 7.90 (d, *J* = 8.03 Hz, 1H), 7.51 (t, *J* = 7.65 Hz, 1H), 7.41 (t, *J* = 7.59 Hz, 1H), 7.32 (d, *J* = 7.91 Hz, 1H), 6.99 (d, *J* = 7.91 Hz, 1H), 6.90 (t, *J* = 7.91 Hz, 1H), 3.96 (s, 3H); ESI-MS (MeOH): *m/z*: 258 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $[C_{14}H_{11}NO_2S+H]^+$: 258.0589 $[M+H]^+$; found: 258.0585.

*2-Naphthalen-2-yl-benzothiazole (**3p**):* The product was obtained as a yellow solid (Yield = 94%); mp 128-130ºC (lit. m.p. 130-132 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 10.41 (s, 1H), 9.26 (d, *J* = 8.53 Hz, 1H), 8.11 (d, *J* = 8.28 Hz, 2H), 7.97 - 8.04 (m, 2H), 7.89-7.95 (m, 1H), 7.52 - 7.75 (m, 4H). ESI-MS (MeOH): *m/z*: 262 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $[C_{17}H_{11}NS+H]^+$: 262.0690 $[M+H]^+$; found: 262.0687.

*2-Pyridin-2-yl-benzothiazole (**3q**):* The product was obtained as a red needles (Yield = 94%); mp 133-135ºC (lit. m.p. 136-137 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.69 (td, *J* = 0.69, 4.02 Hz, 1H), 8.38 (d, *J* = 7.91 Hz, 1H), 8.09 (d, *J* = 7.91 Hz, 1H), 7.93 - 8.00 (m, 1H), 7.85 (dt, *J* = 1.63, 7.72 Hz, 1H), 7.51 (dt, *J* = 1.25, 7.65 Hz, 1H), 7.36-7.45 (m, 2H); ESI-MS (MeOH): *m/z*: 213 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $[C_{12}H_8N_2S+H]^+$: 213.0486 $[M+H]^+$; found: 213.0489.

*2-Thiophen-2-yl-benzothiazole (**3r**):*The product was obtained as a red solid (Yield = 93%); mp 100-102ºC (lit. m.p. 98-102 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.03 (d, *J* = 8.28 Hz, 1H), 7.85 (d, *J* = 7.91 Hz, 1H), 7.62-7.70 (m, 1H), 7.43-7.53 (m, 2H), 7.34-7.40 (m, 1H), 7.14 (dd, *J* = 3.76, 4.89 Hz, 1H). ESI-MS (MeOH): *m/z*: 218 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $[C_{11}H_7NS_2+H]^+$: 218.0098 $[M+H]^+$; found: 218.0094.

*2-(1H-Indole-2-yl)-benzothiazole (**3s**):* The product was obtained as a yellow solid (Yield = 94%); mp 146-148ºC (lit. m.p. 144-146 °C)^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.58 (s, 1H), 8.46 (d, *J* = 6.53 Hz, 1H), 8.05 (d, *J* = 7.91 Hz, 1H), 7.99 (d, *J* = 2.76 Hz, 1H), 7.89 (d, *J* = 7.78 Hz, 1H), 7.43 - 7.52 (m, 2H), 7.29-7.38 (m, 3H); ESI-MS (MeOH): *m/z*: 251 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $[C_{15}H_{10}N_2S+H]^+$: 251.0643 $[M+H]^+$; found: 251.0647.

*2-Furan-2-yl-benzothiazole (**3t**):* The product was obtained as a yellowish orange needles (Yield = 93%); mp 102-104ºC (lit. m.p. 103-104 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.05 (d, *J* = 8.16 Hz, 1H), 7.89 (d, *J* = 7.91 Hz, 1H), 7.61 (s, 1H), 7.48 (d, *J* = 7.40 Hz, 1H), 7.39 (d, *J* = 7.65 Hz, 1H), 7.20 (d, *J* = 3.39 Hz, 1H), 6.54-6.64 (m, 1H); ESI-MS (MeOH): *m/z*: 202 $[M+H]^+$; HRMS (ESI): *m/z* calcd for $[C_{11}H_7NOS+H]^+$: 202.0327$[M+H]^+$; found: 202.0329.

2.4. Antibacterial Activity

Minimum inhibitory concentration (MIC) values for bacteria were determined according to the two-fold broth micro-dilution method using Muller-Hinton broth in 96-well micro-test plates recommended by National Committee for Clinical Laboratory Standards (NCCLS) guidelines (NCCLS.[45] The antimicrobial susceptibility testing of newly synthesized compounds was performed *In Vitro* against bacterial strains *viz*., Gram-positive *Staphylococcus Aureus* (ATCC No. 29737), *Micrococcus Luteus* (ATCC No. 398) and Gram negative *Escherichia Coli* (NCIM No. 2256) and *Pseudomonas Fluorescens* (NCIM No. 2173), respectively, to find out minimum inhibitory concentration (MIC). The MIC was defined as the lowest concentrations of a compound that completely inhibits the growth of each strain. Serial twofold dilutions of all the samples were prepared in triplicate in micro titer plates and inoculated with suitably prepared cell suspension to achieve the required initial concentration. Serial dilutions were prepared for screening. Dimethylsulfoxide (DMSO) was used as solvent control. Ampicilin and kanamycin were used as standard antibacterial drugs. The concentration range of the tested compounds and standard was between 128-0.5 µg/mL. The plates were incubated at 37 °C for all micro-organisms; absorbance at 595 nm was recorded to assess the inhibition of cell growth after 24 h. The compounds demonstrated promising antibacterial activity were selected for MIC studies. The MIC was determined by assaying at 128, 64, 32, 16, 8, 4, 2, 1 and 0.5 µg/mL concentrations along with the standards at the same concentrations.

2.5. Antifungal Activity

The antifungal activity was evaluated against three human pathogenic fungal strains, such as *Candida albicans* (NCIM 3471), *Fusarium oxysporum* (NCIM 1332) and *Aspergillus flavus* (NCIM 539), which are often encountered clinically and were compared with standard drug fluconazole and miconazole. Minimum inhibitory concentration (MIC) values were determined using standard agar method as per CLSI (formerly, NCCLS) guidelines (Approved Standard M7-A6, vol. 23. 2003).[46] The standards used in the study were dissolved in a suitable solvent. The primary solutions were further diluted to the final strength using test medium. The medium yeast nitrogen base (Himedia, India) was dissolved in Phosphate buffer pH 7 and it was autoclaved at 110 °C for 10 minutes. The suitable concentration of the standards was incorporated in the medium. The fungal strains were freshly subcultered on to Sabouraud dextrose agar (SDA) and incubated at 25 °C for 72 h. The fungal cells were suspended in sterile distilled water and diluted to obtain 105 cells/mL. 10 µL of standardized suspension was inoculated onto the control plates and the media incorporated with the antifungal agents. The inoculated plates were incubated at 25 °C for 48 h. The readings were recorded at the end of 48 and 72 h.

2.6. Antioxidant Activity

Antioxidant activities of the synthesized compounds **3a-t** were measured using 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay.[47] The hydrogen atom or electron donation ability of some compounds were measured from the bleaching of the purple coloured methanol solution of DPPH. The spectrophotometric assay uses the stable radical DPPH as a reagent. 1 mL of various concentrations of the test compounds (5, 10, 25, 50 and 100 µg/mL) in methanol was added to 4 mL of 0.004% (w/v) methanol solution of DPPH. The reaction mixture was incubated at 37 °C. The scavenging activity on DPPH was determined by measuring the absorbance at 517 nm after 30 min. All tests were performed in triplicate and the mean values were entered. The percent of inhibition (I %) of free radical production from DPPH was calculated by the following equation % of scavenging = [(*A*control – *A*sample)/(*A*sample × 100)], where, *A*control is the absorbance of the control (DPPH radical without test sample), *A*sample is the absorbance of the test sample (DPPH radical with test sample). The control contains all reagents except the test samples. A lower IC_{50} value indicates the greater antioxidant activity. The IC_{50} (concentration required to scavenge 50% of the radicals) were calculated to evaluate the potential antioxidant activities. Butylated hydroxytoluene (BHT) was used as a standard drug for the comparison of antioxidant activity and the observed results are summarized in Table 4.

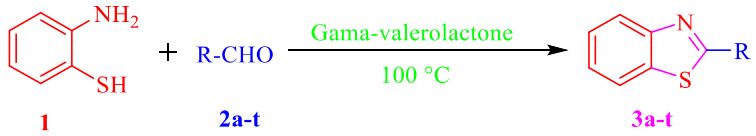
2.7. Computational Study and ADME Properties

The success of a drug is determined not only by good efficacy but also by an acceptable ADME (absorption, distribution, metabolism and excretion) profile. In the present study, we have calculated molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (miLog *P*), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB) and Lipinski's rule of five,[48] using Molinspiration online property calculation toolkit.[49] Absorption (% ABS) was calculated by: % ABS = 109-(0.345×TPSA).[50] Drug-likeness model score (a collective property of physic-chemical properties, pharmacokinetics and pharmacodynamics of a compound is represented by a numerical value) was computed by MolSoft[51] software.

3. Result and Discussion

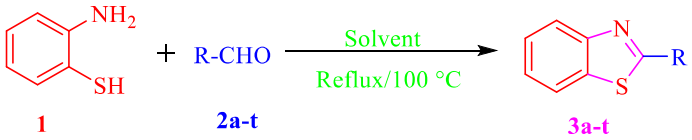
3.1. Synthesis

An efficient and greener protocol for the synthesis of 2-arylbenzthiazoles (**3a-t**) using γ-valerolactone as a solvent and catalyst is established. Comparative study for the synthesis of 2-arylbenzothiazoles using conventional as well as ultrasonication method is discussed (Scheme 1). Remarkable advantages of the present synthetic strategy over the others are shorter reaction times, higher isolated yields, no extra catalytic system and simple work-up procedure.



Scheme 1. γ-Valerolactone catalyzed synthesis of 2-arylbenzthiazoles

In order to find the best experimental conditions, on preliminary basis, the condensation reaction of 2-aminobenzenethiol (**1**) and benzaldehyde (**2a**) at 100 ºC was considered as a standard model reaction for optimizing the reaction conditions (Scheme 2).



Scheme 2. Standard model reaction

Keeping the significance of above discussed aspects and in the context of green chemistry, it has been decided to prefer γ-Valerolactone (GVL) as a solvent in our initial study for optimization of temperature effect.

For evaluation of temperature effect, this reaction was performed at room temperature, 40, 60 ºC, 80 ºC and 100 ºC conditions (Table 1, entries 1-5). The reactions at room temperature, 40 and 60 ºC afforded the products in good yields but took longer reaction period for completion. On the other hand, at higher temperatures, 80 and 100 ºC, the product was obtained in excellent yield. At 100 ºC, the reaction proceeded smoothly towards completion in excellent yield (95%).

Table 1. Screening of reaction at different temperatures[a]

Entry	Solvent	Temp (°C)	Time	Yield[b] (%)
1	GVL	RT	9 h	80
2	GVL	40	8 h	83
3	GVL	60	4 h	85
4	GVL	80	2 h	88
5	GVL	100	1 h	95

[a]Reaction conditions: **1a** (1 mmol), **2** (2 mmol), **3a** (1 mmol) in solvent (5 mL); [b]Isolated yields.

After finalizing the temperature condition for this reaction, the next step was to choose suitable solvent. Various solvents like ethanol, methanol, water, THF, DMF, acetonitrile, toluene, isopropyl alcohol (IPA) and GVL (Table 2, entries 2-10) were tested and compared their results with the GVL mediated reaction. Prior to using the solvents, the reaction was examined under neat conditions, but it failed to afford more than 55% yield in 3 hr (Table 2, entries 1). Subsequent reaction was performed in DMF, THF, toluene and acetonitrile, but gave lower yields. Ethanol and methanol were found to be compatible with the reaction conditions with moderate yields. The reaction in GVL proceeded smoothly. Then we decided to use it for this reaction.

Table 2. Screening of solvents[a]

Entry	Solvent	Temp (°C)	Time	Yield[b] (%)
1	-	80	3 h	55
2	Ethanol	Reflux	5 h	88
3	Methanol	Reflux	6 h	85
4	Water	Reflux	6 h	45
5	THF	Reflux	4 h	68
6	DMF	80	5 h	70
7	MeCN	80	5 h	65
8	Toluene	80	4 h	68
9	IPA	80	6 h	78
10	GVL	100	1 h	95

[a]Reaction conditions: **1a** (1 mmol), **2** (2 mmol), **3a** (1 mmol) in solvent (5 mL); [b]Isolated yields.

We were pleased to find that among the conditions screened, the corresponding 2-arylbenzthiazole was obtained in excellent yield in GVL at 100 ºC. In a simplified way, to understand the role of GVL it should be noted that it binds with the organic substrates (electrophiles) to increase their electrophilicity. Plausible mechanism involved in the synthesis of 2-arylbenzthiazole is depicted in Figure 2.

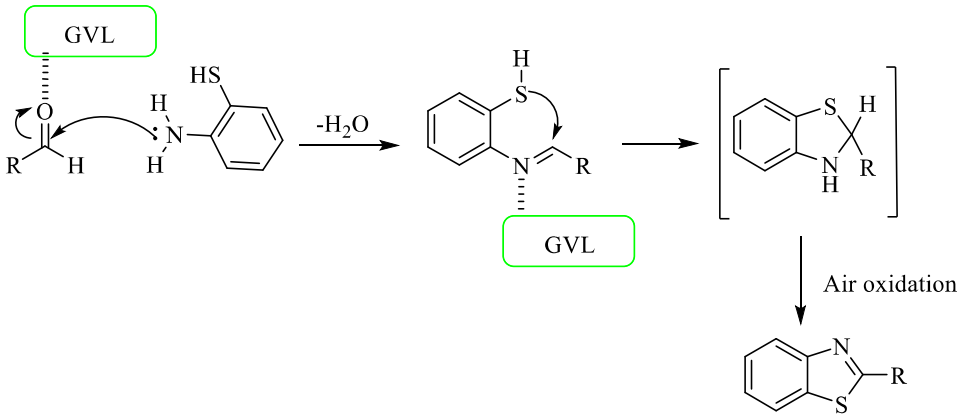


Figure 2. Plausible mechanism for the preparation of 2-arylbenzothiazole derivatives

Considering the applications of ultrasound to promote various organic transformations, we next attempted to carry out the model reaction using optimized reaction conditions under ultrasound irradiation at 25-30 °C with a view to explore whether, the reaction could be expedited and the product yield could be enhanced. It was observed that, ultrasonic irradiation led to relatively higher yields and the reaction time reduced significantly as compared to conventional methods. It was presumed that the efficiency using ultrasound irradiation is due to the cavitation phenomena, i.e. the energy is more efficiently transmitted to the substrate compared to the conventional methods. Thus, ultrasonic irradiation was found to have a beneficial effect on the synthesis of 2-arylbenzothiazole derivatives, which was superior to the conventional method with respect to yield, reaction time, simplicity and safety.

Table 3. Synthesis of 2-aryl benzothiazole derivatives **3(a-t)**

Comp	Ar	Ultrasound method[a]		conventional method[a]		M. P. (°C)
		Time (min)	Yield[b] (%)	Time (min)	Yield[b] (%)	
3a	-C_6H_5	10	95	60	95	112-114
3b	4-$CH_3C_6H_4$	15	92	70	92	82-84
3c	2-$CH_3C_6H_4$	12	93	65	93	58-60
3d	4-$OCH_3C_6H_4$	12	91	60	91	121-123
3e	4-ClC_6H_4	10	92	75	92	115-117
3f	2-ClC_6H_4	12	90	70	90	80-82
3g	4-FC_6H_4	15	92	70	92	101-103
3h	3-BrC_6H_4	15	92	65	92	88-90
3i	4-$NO_2C_6H_4$	15	93	70	93	228-230
3j	3-$NO_2C_6H_4$	15	92	75	92	200-202
3k	4-HOC_6H_4	12	90	40	90	230-232
3l	2-HOC_6H_4	10	91	65	91	130-132
3m	2-HO-3-$MeOC_6H_3$	10	92	60	92	179-181
3n	2-HO-6-$MeOC_6H_3$	12	90	60	90	108-110
3o	4-$N(CH_3)_2C_6H_4$	12	90	60	90	181-183
3p	2-naphthalyl	10	94	60	94	128-130
3q	2-pyridinyl	12	94	70	94	133-135
3r	2-thiophenyl	12	93	70	93	100-102
3s	2-indolyl	10	94	55	94	146-148
3t	2-furyl	15	93	55	93	102-104

[a]Reaction conditions: *o*-Aminothiophenol **1** (1 mmol) and benzaldehyde **2a** (1 mmol) in GVL (5 mL) at 100 °C.
[b]Isolated yield.

Further to establish the scope of optimized reaction conditions and in order to generalize the synthetic procedure, variety of electronically divergent aromatic aldehydes were treated with *o*-aminothiophenol under conventional and ultrasound irradiation method. The presence of electron-withdrawing and electron donating groups on the aromatic rings did not affect the yield. More importantly, various hetero aryl aldehydes were observed to be well tolerated under optimized conditions, furnishing the product in good yields. All the results are compiled in Table 3. The structures of synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, Mass spectra and elemental analysis (Supporting information).

3.2. Antibacterial Activity

The synthesized compounds **3a-t** were screened for antibacterial activity against the two Gram positive and two Gram negative bacterial strains and the results are given in Table 4.

For bacterial strain *S. aureus*, it can be seen that, the compounds **3d**, **3e**, **3** and **3j** showed excellent inhibitory activity with MIC value 4 µg/mL, which is equivalent to ampicilin (MIC 4 µg/mL). For bacterial strain *M. luteus*, compounds **3c**, **3f**, **3h**, **3i**, **3k**, **3l** and **3t** exhibited four-fold antibacterial activity

with MIC value 4 µg/mL and compounds **3d**, **3j**, **3m**, **3p**, **3r** and **3s** with MIC value 8 µg/mL exhibited two-fold more activity and compounds **3b**, **3g**, **3n**, **3o** and **3q** displayed equivalent activity as compared to the clinical drug ampicilin (MIC 16 µg/mL). For bacterial strain *E. coli* and *P. fluorescens*, all the synthesized compounds exhibited moderate antibacterial activity compared to the standard drug.

3.3. Antifungal activity

All the synthesized compounds **3a-t** showed good to moderate activity against all the tested fungal strains (Table 4). Compounds **3b**, **3c**, **3h** and **3k** with MIC value 4 µg/mL exhibited four-fold more activity compared with the standard drug miconazole and compounds **3d**, **3f**, **3l**, **3m**, **3o**, **3p** and **3t** with MIC value 8 µg/mL exhibited two-fold more activity compared to the miconazole against the fungicidal strain *C. albicans*. Compounds **3a**, **3e**, **3g**, **3i**, **3j**, **3n**, **3q**, **3r** and **3s** with MIC value 16 µg/mL exhibited equivalent activity compared with the standard drug miconazole.

Compounds **3c** and **3f** with MIC value 4 µg/mL exhibited four-fold more activity compared with the standard drug miconazole and compounds **3b**, **3h**, **3j**, **3k**, **3l**, **3p**, **3s** and **3t** with MIC value 8 µg/mL exhibited two-fold more activity and compounds **3a**, **3d**, **3e**, **3g**, **3m**, **3n**, **3o**, **3q** and **3r** with MIC value 16 µg/mL exhibited equivalent activity compared with the standard drug miconazole for the fungicidal strain *F. oxysporum*.

Table 4. *In vitro* antimicrobial and antioxidant activities of compounds **3a-t** (µg/mL)

Compounds	Gram positive bacteria IC_{50}		Gram negative bacteria IC_{50}		Antifungal activity IC_{50}			DPPH IC_{50}
	SA	***ML***	***EC***	***PF***	***CA***	***FO***	***AF***	
3a	32	32	32	16	16	16	16	22.1
3b	16	16	16	16	4	8	8	27.3
3c	16	4	8	8	4	4	8	23.1
3d	4	8	8	8	8	16	8	20.1
3e	4	32	8	8	16	16	16	18.3
3f	4	4	8	8	8	4	8	25.1
3g	16	16	8	8	16	16	32	15.1
3h	16	4	16	16	4	8	8	25.3
3i	8	4	16	16	16	32	16	20.3
3j	4	8	16	16	16	8	8	21.3
3k	16	4	8	4	4	8	4	12.2
3l	8	4	8	16	8	8	8	14.3
3m	8	8	8	16	8	16	8	14.1
3n	16	16	16	8	16	16	16	13.2
3o	32	16	8	8	8	16	16	24.6
3p	16	8	8	16	8	8	16	28.8
3q	16	16	16	8	16	16	16	29.3
3r	8	8	16	8	16	16	16	26.5
3s	8	8	16	16	16	8	16	23.8
3t	8	4	8	8	8	8	16	25.4
Ampicilin	4	16	4	2	NA	NA	NA	NA
Kanamycin	2	2	2	2	-	NA	NA	NA
Miconazole	NA	NA	NA	NA	16	16	16	NA
Fluconazole	NA	NA	NA	NA	2	2	4	NA
BHT	NA	NA	NA	NA	NA	NA	NA	16.5

SA: *S. aureus*; ML: *M. luteus*; EC: E. Coli; PF: *P. fluorescens*; CA: *C. albicans*; FO: *F. oxysporum*; AF: *A. flavus;* BHT: *Butylated hydroxy toluene*; NA*: Not applicable*

Compounds **3k** with MIC value 4 µg/mL exhibited four-fold more activity and compounds **3b**, **3c**, **3d**, **3f**, **3h**, **3j**, **3l** and **3m** with MIC value 8 µg/mL exhibited two-fold more activity and compounds

3**a**, **3e**, **3i**, **3n, 3o**, **3p**, **3q**, **3r**, **3s** and **3t** with MIC value 16 µg/mL exhibited equivalent activity compared with the standard drug miconazole against the fungicidal strain *A. flavus*.

3.4. Antioxidant activity

All the synthesized compounds **3a-t** showed good to moderate antioxidant activity as compared to the standard drug BHT (Table 4). The compounds **3k** (12.2 µg/mL), **3l** (14.3 µg/mL), **3m** (14.1 µg/mL) and **3n** (13.2 µg/mL) with *hydroxy*- substituent on phenyl ring have shown excellent activity as compared to standard drug. Again, the compound **3g** (15.1 µg/mL) with *fluoro*- group showed excellent antioxidant activity as compared to the BHT. The remaining compounds exhibited good to moderate antioxidant activity as compared to standard drug BHT.

3.5. Computational Study and ADME Properties

A computational study of all the synthesized 2-aryl benzothiazole derivatives **3a-t** was performed for prediction of ADME properties and the value obtained is presented in Table 5. It was observed that, the compounds exhibited a good % ABS (% absorption) ranging from 88.74 to 104.55%. Furthermore, none of the synthesized compounds violated Lipinski's rule of five (miLog $P \leq 5$). A molecule likely to be developed as an orally active drug candidate should show no more than one violation of the following four criteria: miLog *P* (octanol-water partition coefficient) ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10 and number of hydrogen bond donors ≤ 5.[52] The larger the value of the drug likeness model score, the higher is also probable that the particular molecule will be active. All the tested compounds followed the criteria for orally active drug and therefore, these compounds may have a good potential for eventual development as oral agents.

Table 5. Pharmacokinetic parameters important for good oral bioavailability

Cpd	% ABS	TPSA (A^2)	n-ROTB	MV	MW	miLog *P*	n-ON	n-OHNH	Lipinski violation	Drug-likeness model score
Rule	-	-	-	-	< 500	≤ 5	< 10	< 5	≤ 1	-
3a	104.55	12.89	1	186.00	211.29	4.29	1	0	0	-1.13
3b	104.55	12.89	1	202.56	225.32	4.74	1	0	0	-0.81
3c	104.55	12.89	1	202.56	225.32	4.69	1	0	0	-0.93
3d	101.36	22.13	2	211.54	241.31	4.35	2	0	0	-0.45
3e	104.55	12.89	1	199.53	245.73	4.97	1	0	0	-0.29
3f	104.55	12.89	1	199.53	245.73	4.92	1	0	0	-0.69
3g	104.55	12.89	1	190.93	229.28	4.45	1	0	0	-0.41
3h	104.55	12.89	1	203.88	290.19	5.08	1	0	1	-1.20
3i	88.74	58.72	2	209.33	256.29	4.25	4	0	0	-0.71
3j	88.74	58.72	2	209.33	256.29	4.22	4	0	0	-0.96
3k	97.57	33.12	1	194.02	227.29	3.81	2	1	0	-0.62
3l	97.57	33.12	1	194.02	227.29	4.02	2	1	0	-0.71
3m	94.39	42.35	2	219.56	257.31	3.83	3	1	0	-0.41
3n	94.39	42.35	2	219.56	257.31	4.03	3	1	0	-0.37
3o	103.43	16.13	2	231.91	254.36	4.39	2	0	0	-0.89
3p	104.55	12.89	1	229.99	261.35	5.47	1	0	1	-1.15
3q	100.10	25.78	1	181.84	212.28	3.14	2	0	0	-1.09
3r	104.55	12.89	1	176.71	217.32	4.07	1	0	0	-1.46
3s	99.10	28.68	1	214.98	250.33	4.39	2	1	0	-1.52
3t	100.02	26.03	1	167.57	201.25	3.43	2	0	0	-1.48

4. Conclusion

A facile, economic, and green protocol for the synthesis of benzothiazoles as a potential antimicrobial and antioxidant agent by cyclocondensation of *o*-aminothiophenol and aldehydes using γ-valerolactone as a catalyst as well as solvent has been described. The reaction conditions are mild accepting several functional groups present in the molecules and the reactions proceed under essentially neutral conditions, thus reducing the possibility of many unwanted side reactions. In addition, comparative study of the developed protocol with the known methods reveals the following advantages: (i) This strategy is higher yielding under mild reaction conditions. (ii) All the reported methods have been performed in either organic solvents or ethanol, in contrast, we have used greener medium, i.e. GVL. (iii) In comparison to others, separate catalyst used but in this study solvent acts as a catalyst that there is ~~so~~ no need of additional catalyst to catalyse the reaction. The synthesized benzothiazoles were evaluated for antimicrobial and antioxidant activity and also analysed for ADME properties.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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