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Comparative study of the reaction of 2-mercaptobenzimidazole with 2-bromo-1,3-diketones under conventional and green conditions: regioselective access to N/S-difunctionalized benzimidazoles and benzimidazo[2,1-*b*]thiazoles†

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The development of eco-friendly and energy-efficient synthetic methods remains a priority in modern organic chemistry. In this study, we investigated the reaction of 2-mercaptobenzimidazole and 1,3-diketones in the presence of *N*-bromosuccinimide (NBS) under conventional and sustainable conditions. While the DCM-mediated and solvent-free approaches yielded 2-((1-acetyl-1*H*-benzo[4,5]imidazole-2-yl)thio)-1-arylethan-1-one derivatives, the visible-light irradiation strategy promoted a distinct regioselective [3 + 2] cyclo-condensation, affording corresponding cyclized products, *i.e.*, 6-substituted-2-aroyl-3-methylbenzimidazo[2,1-*b*]thiazole derivatives in high yields. These one-step protocols feature an eco-friendly nature, short reaction times, operational simplicity, high efficiency, and excellent selectivity. Structures of the synthesized compounds were confirmed *via* comparative analysis of their R_f values, IR, NMR, and HRMS data, with further structural validation *via* detailed 2D NMR studies, and plausible mechanisms have been proposed for both reaction pathways. Overall, the work highlights condition-driven regioselectivity and the potential of energy-dependent strategies in benzimidazole-based heterocycle synthesis.

Introduction

Benzimidazo[2,1-*b*]thiazole is a fascinating fused heterocyclic scaffold that has gained significant attention across various scientific domains.[1] Its unique structure and diverse reactivity make it appealing for synthetic chemistry, while its broad range of biological activities such as antimicrobial, anticancer, anti-inflammatory, and antiviral properties, positions it as a valuable target in medicinal chemistry.[2] Compounds like Levamisole **1**, with immunomodulatory effects, and Tilomisole (Wy-18,251) (2-(3-(4-chlorophenyl)benzo[4,5]imidazo-[2,1-*b*]thiazol-2-yl)acetic acid) **2**, showing anticancer potential, highlight its therapeutic promise[3,4] (Fig. 1). Recently, Alkhaldi *et al.* reported 3-methylthiazolo[3,2-*a*]benzimidazole–benzenesulfonamide conjugates as potent carbonic anhydrase inhibitors with anticancer activity, further demonstrating the medicinal relevance of benzimidazo[2,1-*b*]thiazole frameworks.[5] This highlights the continuing interest in developing structurally diverse benzimidazothiazole derivatives for therapeutic applications. Additionally, benzimidazo[2,1-*b*]thiazoles have shown potential in material science, especially in organic electronics and sensors, due to their efficient charge transport properties.[6]

Growing interest in benzimidazo[2,1-*b*]thiazole derivatives is evident from numerous synthetic reports detailing their synthesis and functionalization through diverse methodologies. 2-Mercaptobenzimidazole has been widely used as a synthon for synthesizing biologically active benzimidazo[2,1-*b*]

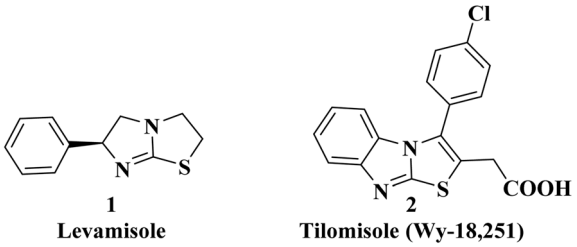

Fig. 1 Structures of Levamisole and Tilomisole (Wy-18,251).

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† Electronic supplementary information (ESI) available: The supporting information consists of additional experimental data (^{1}H, ^{13}C, HMBC, HSQC NMR and HRMS spectra) for final compounds. See DOI: https://doi.org/10.1039/d5ra02681d

thiazoles by reacting with various substrates,[2,5,7–13] such as carbonyl compounds, propargyl bromides/tosylates, active alkynes and 1,1-dibromoalkenes. Additionally, copper-catalyzed coupling reactions,[14,15] *e.g.* 1,2-aminothiolation of 1,1-dibromoalkenes and coupling of *trans*-1,2-diiodoalkenes with 2-mercaptobenzimidazole, 1,2-aminothiolation of terminal alkynes and thioamination of nitrogen compounds has been documented[16,17] (Fig. 2a).

An alternative route is the construction of an imidazole ring by the reaction of 2-aminothiazole with 2-haloarylboronic acid or quinone under Cu(II)-catalyzed and acetic acid-catalyzed reactions,[1,18] respectively (Fig. 2b).

Despite significant advancements in synthesizing benzimidazo[2,1-*b*]thiazole derivatives, several challenges persist, including reliance on metal catalysts, low atom economy, and harsh reaction conditions. These limitations underscore the need for one-step, environmentally sustainable method to enhance efficiency and versatility. Moreover, direct and selective synthesis of acyl-functionalized benzimidazo[2,1-*b*]thiazoles remains underexplored. Addressing these gaps could not only enhance the efficiency and versatility of existing methods but also pave the way for greener practices in drug discovery and material science applications.

Prompted by the aforementioned facts and as a continuation of our ongoing efforts toward the synthesis of biologically significant acylated heterocyclic scaffolds,[19–21] we herein report a study on the reaction of 1,3-diketones, 2-mercaptobenzimidazoles, and *N*-bromosuccinimide (NBS) under various reaction conditions including solvent-mediated, solvent-free and visible-light-assisted protocols. These strategies enable regioselective access to two different products *i.e.* 2-((1-acetyl-1*H*-benzo[4,5]imidazole-2-yl)thio)-1-arylethan-1-one and acyl-functionalized benzimidazo[2,1-*b*]thiazole derivatives.

Result and discussion

Chemistry

As discussed, benzimidazo[2,1-*b*]thiazole derivatives have attracted interest for their biological and material applications, but existing methods often involve multistep procedures, metal catalysts, toxic reagents, and harsh conditions, limiting their sustainability and scalability.[1,5,11–13] To overcome these challenges, we designed a one-pot protocol utilizing 1,3-diketones **3**, 2-mercaptobenzimidazole **5**, and NBS under varying reaction conditions. In principle, the reaction between trielectrophilic (α_1, α_2, α_3) 2-bromo-1,3-diketones **4** and trinucleophilic (β_1, β_2,

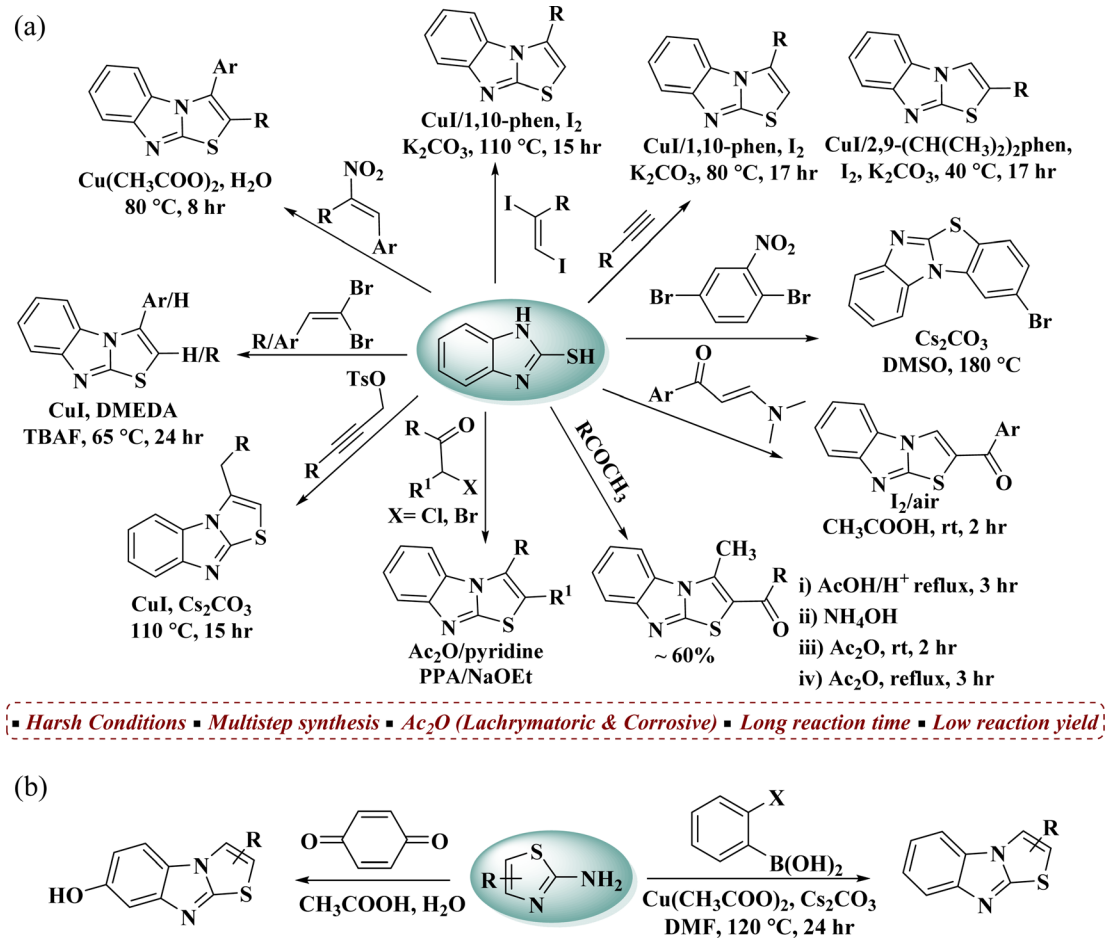


Fig. 2 (a) Synthetic strategies for benzimidazo[2,1-*b*]thiazole using 2-mercaptobenzimidazole as synthon. (b) Alternative synthetic strategies for benzimidazo[2,1-*b*]thiazole using 2-amino thiazoles as synthons.

β_3) 3-mercapto-1,2,4-triazoles **5** introduces regioselectivity in product formation. The more nucleophilic sulphur site (β_2) of 2-mercaptobenzimidazole preferentially attacks the soft site (α_2) of 2-bromo-1,3-diketone, initiating the reaction. However, competition between other sites (α_1 and α_3) and (β_1 and β_3) can lead to four possible regioisomers *viz.* 6-substituted-2-aroyl-3-methylbenzimidazo[2,1-*b*]thiazole **6**, 6-substituted-2-acetyl-3-arylbenzimidazo-[2,1-*b*]thiazole **7**, 7-substituted-2-aroyl-3-methylbenzimidazo-[2,1-*b*]thiazole **8** and 7-substituted-2-acetyl-3-arylbenzimidazo[2,1-*b*]thiazole **9** (Scheme 1).

Keeping in mind the formation of four possible regioisomers, firstly, the reaction of 1-phenylbutane-1,3-dione **3a** with 1,3-dihydro-2*H*-benzimidazole-2-thione **5a** was investigated in the presence of the brominating agent NBS using conventional approaches. The reaction was explored using a range of solvent systems, including DCM, CH_3CN, THF, CH_3OH, C_2H_5OH and H_2O (Runs 1–6, Table 1), as well as under solvent-free conditions (Run 7, Table 1). Optimization experiments showed that the reaction faced challenges with solvents such as THF, CH_3CN, CH_3OH, C_2H_5OH, and H_2O, resulting in low product yields, of up to 35%. However, using DCM solvent at room temperature furnished a single regioisomeric product with high yields of 82% with a retention factor (R_f) value of 0.82, indicated by Thin Layer Chromatography (TLC) (ethyl acetate-petroleum ether (20 : 80, v/v)).

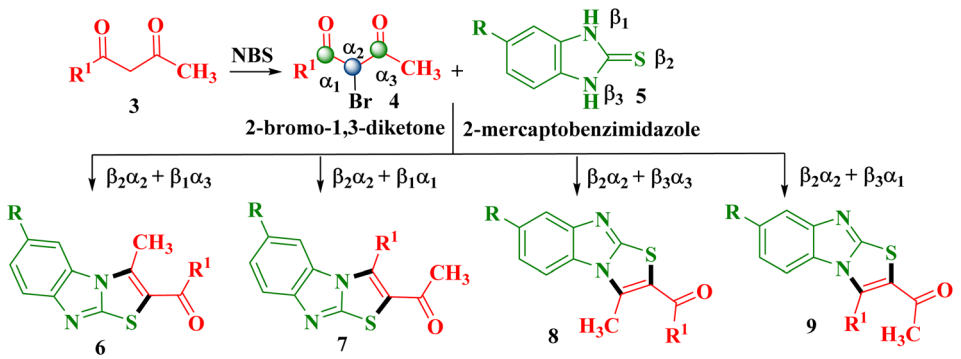
The reaction was further conducted under solvent-free conditions to align the synthetic procedure with environmentally friendly approaches. The solvent-free approach delivered the same regioisomeric product (R_f = 0.82) with an improved yield of 86% in just 20 minutes, highlighting its advantages in terms of operational simplicity, shorter reaction time, and the elimination of hazardous solvents.

In recent years, several studies have highlighted the significance of visible-light-mediated synthesis of benzimidazo[2,1-*b*] thiazoles, emphasizing the advantages of green synthetic methods.[22,23] Moreover, we have carried out the above reaction under visible-light irradiations, specifically, the reaction was performed under the illumination of a 9 W light-emitting diode (LED) lamp, placed 5 cm above the reaction mixture, across a series of experiments (Runs 8–13, Table 1). Interestingly, the product obtained under visible-light conditions displayed a distinct R_f value of 0.56 on TLC, contrasting with the products formed under conventional and solvent-free conditions. Various solvent systems have been tested systematically to identify the most effective conditions to further optimize the LED reaction conditions. Notably, the best results were achieved with ethanol, yielding an impressive 88% in just 30 minutes (Run 12, Table 1). This successful application of visible light and ethanol not only resulted in high yields but also demonstrated the potential for environmentally sustainable chemical transformations.

The attention-grabbing products were comprehensively characterized using various spectral techniques including IR, 1D & 2D NMR ($(^1H–^{13}C)$ HSQC and $(^1H–^{13}C)$ HMBC) and mass spectrometric analysis. Based on these extensive spectral analyses, the compound with an R_f value of 0.82 was identified as a reported N/S-difunctionalized product,[11] namely 2-((1-acetyl-1*H*-benzimidazol-2-yl)thio)-1-phenylethan-1-one **10a**. In contrast, the compound obtained under visible-light conditions, exhibiting an R_f value of 0.56, was characterized and found as the corresponding cyclized product *i.e.* (3-methylbenzo[4,5]imidazo[2,1-*b*]thiazol-2-yl)(phenyl)methanone **6a** (Scheme 2). Notably, when compound **10a** was refluxed with acetic anhydride the corresponding cyclized compound **6a** was obtained.[11] The current synthetic protocol offers several advantages, including a one-step synthesis significantly reduced time, environmentally benign reaction media and reaction conditions, *etc.*

IR spectrum of product **10a** exhibited two strong bands at 1708 cm^{-1} and 1670 cm^{-1}, indicating the presence of two carbonyl groups instead of the expected single band for possible regioisomers **(6–9)**. Conversely, the IR spectrum of product **6a** exhibited a single C=O absorption band at 1680 cm^{-1}, suggesting intramolecular cyclization followed by dehydration in the product.

In the ^1H NMR ($CDCl_3$) analysis of product **10a**, an interesting observation emerged in the aliphatic region, two distinct peaks appeared at δ 2.81 ppm and δ 4.85 ppm, deviating from the expected single peak corresponding to the methyl group for each envisaged regioisomer **(6–9)**. However, in the ^1H NMR (DMSO-d_6) analysis of compound **6a**, a single peak in the aliphatic region at δ 2.73 ppm was observed, contrasting with the spectrum of the N/S-difunctionalized product **10a**, which displayed two peaks at δ 2.81 and 4.85 ppm.



Scheme 1 Possible regioisomeric products by the reaction of 2-bromo-1,3-diketones **4** with 2-mercaptobenzimidazole **5**.

Table 1 Optimization of reaction conditions[a]

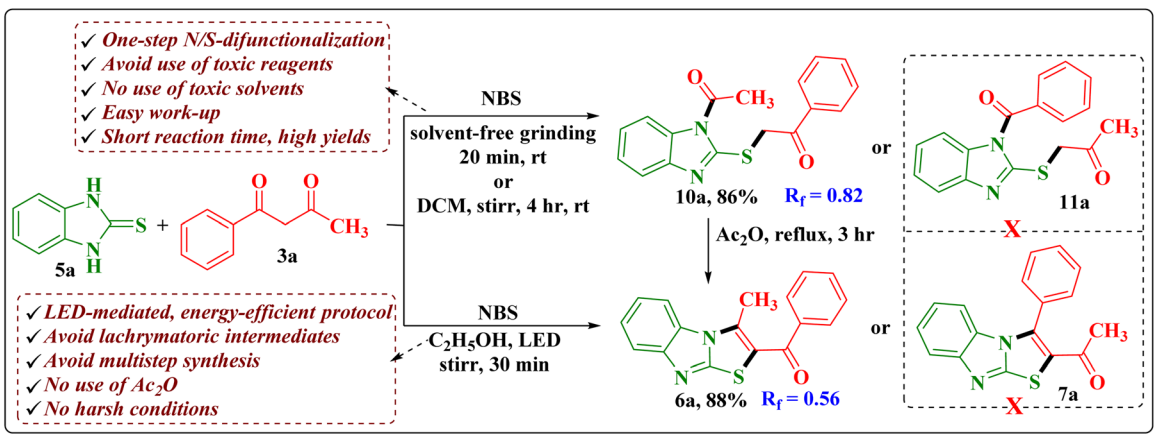
Run	Solvent	Energy source	Time	Yield[b] (%) Product with R_f = 0.82	Product with R_f = 0.56
1	**DCM**	**Rt**	**4 h**	**82**	—
2	CH_3CN	Rt/reflux	5 h	Trace/20	—
3	THF	Rt/reflux	6 h	Trace/10	—
4	CH_3OH	Rt/reflux	3 h	10/30	—
5	C_2H_5OH	Rt/reflux	3 h	10/35	—
6	H_2O	Rt/reflux	2 h	Trace/10	—
7	**Solvent-free**	**Rt**	**20 min**	**86**	—
8	DCM	LED (9 W)	2.5 h	—	58
9	CH_3CN	LED (9 W)	2.5 h	—	56
10	THF	LED (9 W)	9 h	—	Trace
11	CH_3OH	LED (9 W)	2 h	—	63
12	**C_2H_5OH**	**LED (9 W)**	**30 min**	-	**88**
13	H_2O	LED (9 W)	5 h	—	25

[a] Reaction of **3a** (1.0 mmol) and **5a** (1.0 mmol) was reacted as per reaction conditions. [b] Isolated yield.

Additionally, the ^{13}C NMR ($CDCl_3$) spectrum of **10a** provided further validation of the findings from the proton NMR and IR analyses. Notable, the spectrum revealed two distinct peaks in the aliphatic region at δ 26.2 and 40.5 ppm, supporting the formation of interesting product **10a** rather than one of the four probable regioisomers. Consequently, through the comprehensive spectral studies conducted, the product was definitively identified as an N/S-difunctionalized compound, specifically 2-((1-acetyl-1*H*-benzimidazol-2-yl)thio)-1-phenylethan-1-one **10a**. The structural determination of the compound can be rationalized by considering an *in situ* cleavage of the 1,3-diketone moiety. In contrast, the ^{13}C NMR (DMSO-d_6) spectrum of compound **6a** revealed a sole distinctive peak in the aliphatic region at δ 15.7 ppm, indicating the successful formation of the cyclized product, differing from the N,S-difunctionalized product.

Furthermore, the structural characterization of the synthesized compounds was reinforced through meticulous mass spectrometric analysis. For compound **10a**, the mass spectrum revealed a prominent peak at an *m*/*z* value of 311.0786 for $[M + H]^+$, further supported the formation of the N/S-difunctionalized product. Conversely, the mass spectrum of compound **6a** exhibited a distinct peak at *m*/*z* value of 293.0656 for $[M + H]^+$, consisting with the expected cyclized regioisomer *via* dehydration (loss of H_2O, *m*/*z* = 18), confirming the successful formation of the desired compound.

The conclusive evidence for the formation of 2-((1-acetyl-1*H*-benzimidazol-2-yl)thio)-1-phenylethan-1-one **10a** was obtained through a comprehensive analysis involving heteronuclear 2D NMR experiments. The correlations of protons and their corresponding carbon atoms within compound **10a** were meticulously examined (Fig. 3a). The (^1H–^{13}C) HMBC results revealed significant cross-peaks, including the carbonyl carbon (δ 193.9 ppm) exhibiting correlations with the 2′/6′-H proton (δ 8.09–8.11 ppm) of the aryl ring and CH_2 (δ 4.85 ppm), indicating the presence of –CH_2COAr fragment, ruled out the possibility of the formation of regioisomer **11a**. The cross-peak between C-2 (δ 154.3 ppm) of the benzimidazole core and methylene protons (δ 4.85 ppm) indicated the presence of a 2-oxo-2-arylethylthio group at the 2nd position of the benzimidazole ring.



Scheme 2 Synthesis of benzo[4,5]imidazo[2,1-*b*]thiazoles.

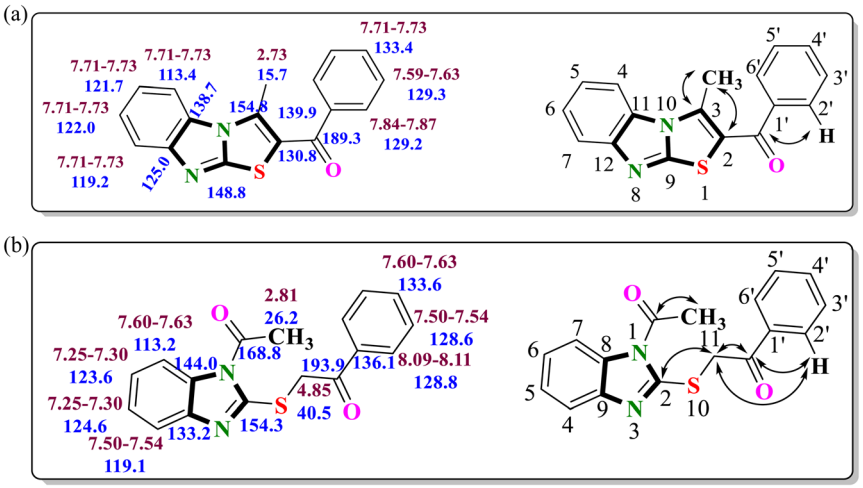


Fig. 3 (a) ^{1}H, ^{13}C and 2D NMR correlations of 2-((1-acetyl-1*H*-benzimidazol-2-yl)thio)-1-phenylethan-1-one **10a**. (b)^{1}H, ^{13}C and 2D NMR correlations data of (3-methylbenzo[4,5]imidazo[2,1-*b*]thiazol-2-yl)(phenyl)methanone **6a**.

Similarly, the cross-peak of carbonyl carbon (δ 168.8 ppm) with methyl protons (δ 26.2 ppm), indicated the presence of the –$COCH_3$ group. All other expected correlations were evident in (^{1}H–^{13}C) HMBC and (^{1}H–^{13}C) HSQC spectra, supported the substituents distribution around the benzimidazole nucleus.

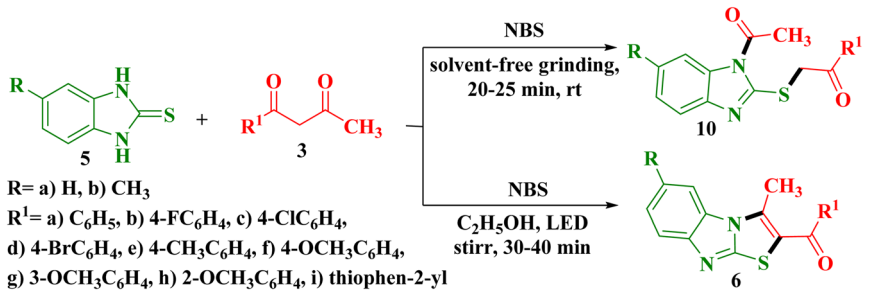
Additionally, a thorough characterization of regioisomer **6a** was also achieved through extensive 2D NMR spectral studies, conclusively identified the product as the regioisomer (3-methylbenzo[4,5]imidazo[2,1-*b*]thiazol-2-yl)(phenyl)methanone **6a**. The (^{1}H–^{13}C) HMBC spectrum of the compound showed correlation peaks of methyl protons (δ 2.73 ppm) with C-2 (δ 130.8 ppm) and C-3 (δ 154.8 ppm), confirming the presence of the methyl group at the 3rd position of benzo[4,5]imidazo[2,1-*b*] thiazole core (Fig. 3b). Similarly, a cross peak between carbonyl carbon at δ 189.3 ppm and 2′/6′-H protons (δ 7.84–7.87 ppm) of the aryl ring indicated the presence of carbonyl carbon adjacent to the aryl ring, thereby, eliminating the possibility of regioisomers with acetyl group **7** and **9**. The formation of 7-substituted-2-aroyl-3-methylbenzimidazo[2,1-*b*]thiazoles **8** was also ruled out, as the HMBC spectrum of the 7-methyl-substituted product did not indicate any correlation between the methyl group protons and the C-12 carbon (δ 125.0 ppm). Therefore, the regioisomeric structure of the final compounds was assigned as 6-substituted-2-aroyl-3-methylbenzimidazo[2,1-*b*]thiazoles **6**.

After optimizing reaction conditions and identifying specific regioisomeric structures, an extensive investigation of substrate tolerance was undertaken. This investigation utilized optimized protocols: a solvent-free protocol for synthesizing N/S-difunctionalized product, 2-((1-acetyl-1*H*-benzimidazol-2-yl) thio)-1-arylethan-1-one **10(a–e)** and a visible-light-mediated synthesis for (3-methylbenzo[4,5]imidazo[2,1-*b*]thiazol-2-yl)(aryl)methanone **6(a–n)**. The substrate scope of the reaction protocols was explored by taking a diverse array of unsymmetrical 1,3-diketones, featuring aryl moieties with electron-donating or electron-withdrawing substituents, which were subjected to the reaction (Scheme 3). Remarkably, the results highlighted the versatility of the reaction procedure, demonstrating its smooth progression with various substituents. Considering the electron-donating and electron-withdrawing groups associated with the diketones, it was observed that the reaction exhibited enhanced yields when the aryl moiety featured an electron-donating group (Table 2). The present one-step synthetic protocol for N/S-difunctionalized product **10** represents significant advantages over previously reported methods,[24] including eco-friendliness, short reaction period, high yields, easy workup, and high regioselectivity.

Proposed mechanism

(a) The proposed potential mechanism for the unexpected synthesis of 2-((1-acetyl-1*H*-benzo[4,5]imidazole-2-yl)thio)-1-arylethan-1-one **10(a–e)** is illustrated in Scheme 4a. Initially, 2-mercaptobenzimidazole undergoes S-alkylation by replacing the bromine in 2-bromo-1,3-diketones with sulphur, leading to the formation of intermediate **A**. Subsequently, the nucleophilic attack of nitrogen atom on less sterically hindered and more electrophilic carbonyl carbon adjacent to the CH_3 group provides favourable sites for the intramolecular cyclization of **A**. However, instead of intramolecular cyclization, the reaction leads to the *N*-acylation of intermediate **A** *via* C–C bond cleavage,[24,25] thus generating an unexpected N/S-difunctionalized product; 2-((1-acetyl-1*H*-benzo[4,5]imidazole-2-yl)thio)-1-arylethan-1-one **10**. Upon refluxing with acetic anhydrid, the carbonyl group adjacent to the thioether moiety in compound **10** undergoes acetylation to form intermediate **B**. Intermediate **B** undergoes intramolecular cyclization yielding **C**, which subsequently undergoes dehydration and deacylation to furnish the desired cyclized product **6**.

(b) The possible mechanistic pathway for the regioselective synthesis of (3-methylbenzo[4,5]imidazo[2,1-*b*]thiazol-2-yl)(aryl) methanone **6(a–n)** is depicted in Scheme 4b. Initially, under the influence of visible light, homonuclear fission occurs in both the S–H bond of 2-mercaptobenzimidazole **5** and the C–Br bond

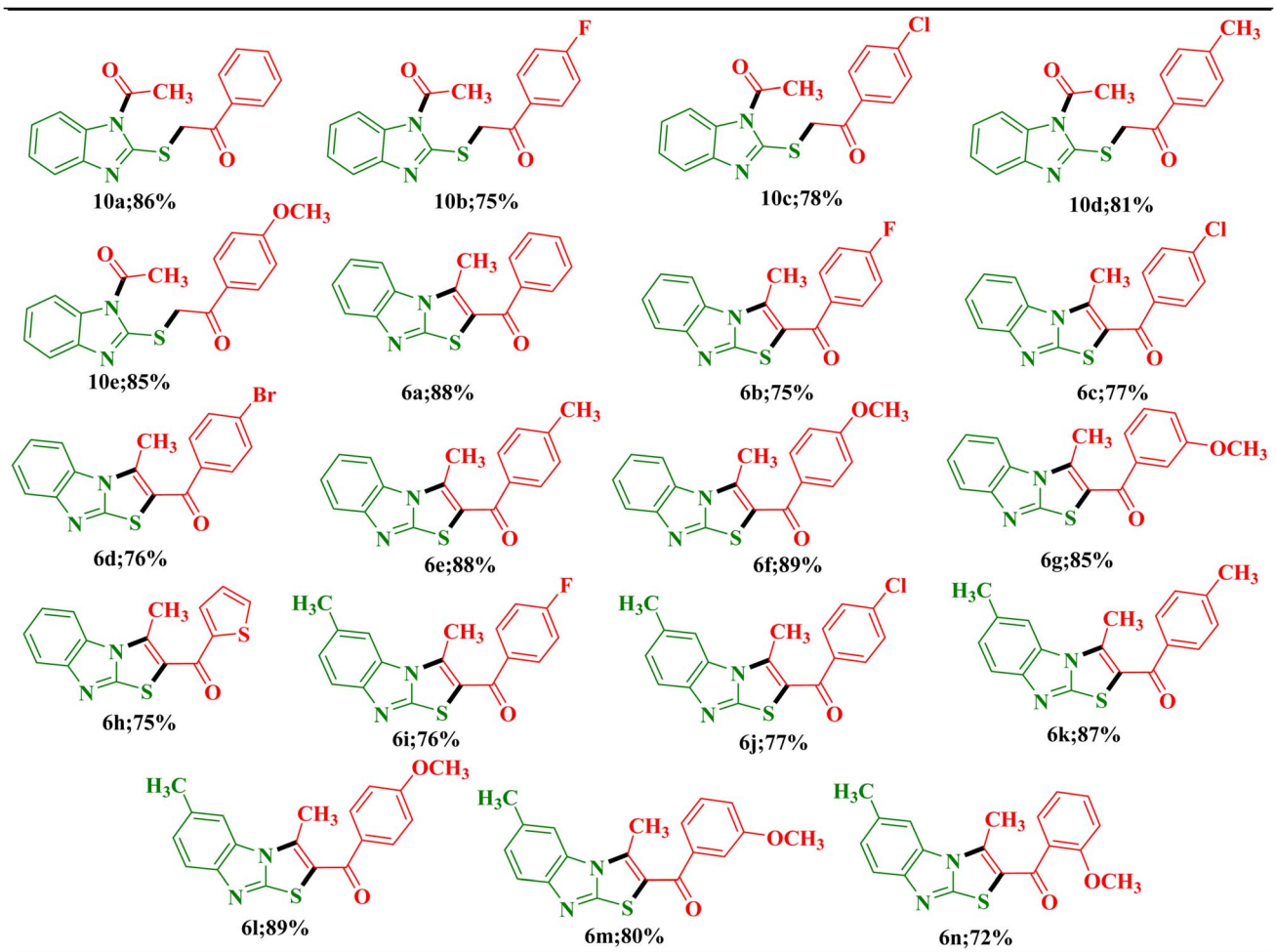


Scheme 3 Synthesis of benzimidazole analogous.

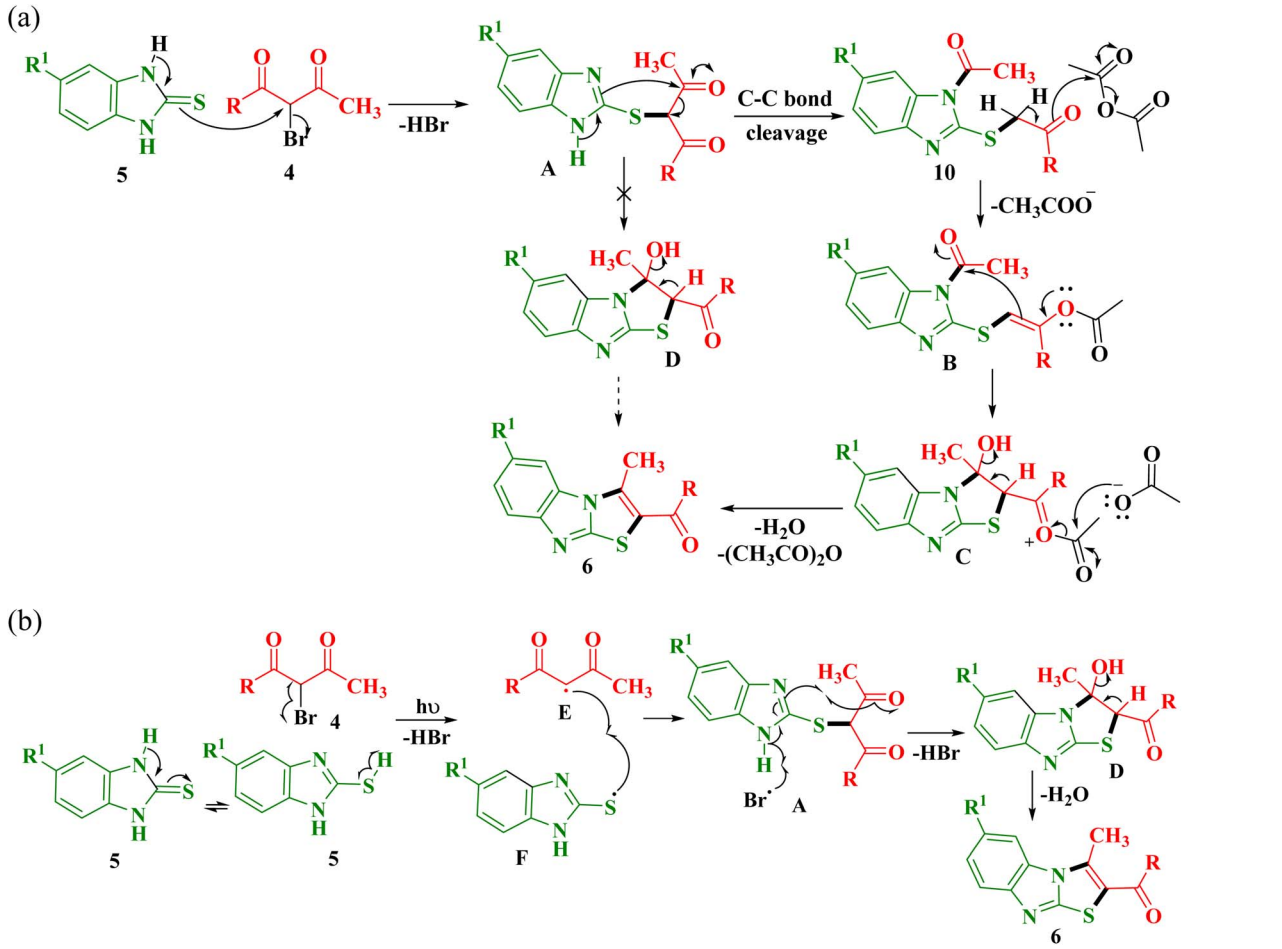
of 2-bromo-1,3-diketones **4**, leading to the formation of free radicals **E** and **F**, respectively, which mutually share their electrons to form the S-alkylated intermediate **A**. Subsequently, the bromine free radical initiates the homolytic cleavage of the N–H bond, leading to the formation of a new *N*-benzimidazole radical. This radical, in conjunction with the less sterically hindered carbonyl carbon and an oxygen atom, forms a stable complex, 3-hydroxy-3-methyl-2,3-dihydrobenzo[4,5]imidazo-[2,1-*b*]thiazol-2-yl)(aryl)methanone **D**, which finally undergoes dehydration to yield exclusive final cyclized product **6**.

To support the proposed reaction mechanism, controlled experiments with radical initiation and trapping were systematically conducted. Under standard conditions, the addition of free radical initiator benzoyl peroxide[26,27] significantly

Table 2 Substrate scope[a]



[a] Reaction conditions: a mixture of **5(a–b)** (1.0 mmol) and **3(a–i)** (1.0 mmol) in the presence of NBS in 10.0 mL ethanol was reacted.



Scheme 4 (a) Proposed mechanism for the N/S-difunctionalized product: 2-((1-acetyl-1*H*-benzo[4,5]imidazole-2-yl)thio)-1-arylethan-1-one **10(a–e)**. (b) Proposed mechanism for the cyclized product: (3-methylbenzo[4,5]-imidazo[2,1-*b*]thiazol-2-yl)(aryl)methanone **6(a–n)**.

enhanced the reaction yield (**6a**; 92%) and a better reaction rate. In contrast, the introduction of radical scavenger TEMPO[28,29] to the reaction mixture resulted in notable inhibition, yielding only 18% of product **6a**. These results strongly suggest a free radical pathway involvement, with benzoyl peroxide improving and TEMPO inhibiting the reaction. However, solvent-free controlled experiments showed no significant impact on reaction yield and rate, supporting the proposed ionic mechanism for product formation.

Conclusion

In conclusion, a comparative study has been carried out for the regioselective synthesis of benzimidazole-based heterocycles *via* the reaction of 2-mercaptobenzimidazoles **5(a–b)** with 1,3-diketones **3(a–i)** in the presence of NBS under both conventional and sustainable conditions. Under DCM-mediated and solvent-free conditions, 2-((1-acetyl-1*H*-benzo[4,5]-imidazole-2-yl)thio)-1-arylethan-1-ones **10(a–e)** were obtained, whereas visible-light-mediated conditions furnished 6-substituted-2-aroyl-3-methylbenzimidazo[2,1-*b*]thiazoles **6(a–n)**. The formation of these structurally distinct scaffolds was confirmed through comparative analysis of their R_f values, IR, NMR, and HRMS data, with further structural validation *via* detailed 2D NMR studies. Proposed reaction mechanisms suggest that the formation of N/S-difunctionalized products proceeds *via* a C–C bond cleavage through an ionic pathway, while the visible-light-induced products are formed through a free-radical mechanism, supported by radical initiation and trapping experiments. Both developed protocols are metal-free, environmentally benign, and operationally simple, offering excellent yields within short reaction times. These green methodologies pave the way for the efficient synthesis of structurally diverse and potentially bioactive thiazole-fused benzimidazole derivatives. Further investigations, including exploration of a broader substrate scope and biological evaluation coupled with structure–activity relationship (SAR) studies of these compounds, are currently underway in our laboratory.

Experimental

Melting points were taken with an electric digital Melting Point Apparatus (MEPA) in open capillaries and may be uncorrected. Thin-layer chromatography (TLC) utilized Merck Kieselgel 60

F254 silica gel plates, visualized under UV light (254 nm). LED of 9 W power positioned 5 cm from the reaction mixture in an Erlenmeyer borosilicate flask. Spectroscopic analyses included IR spectra recorded on a Buck Scientific IR M-500 spectrophotometer with KBr pellets (υ_{max} in cm^{-1}). Proton (^1H) and carbon-13 (^{13}C) NMR spectra were acquired on a Bruker instrument at frequencies of 400 MHz and 101 MHz, respectively, using $CDCl_3$ and DMSO-d^6 as solvents. Chemical shifts were expressed in parts per million (ppm) and coupling constants (J) in Hz, with TMS as the internal standard. High-resolution mass spectra (HRMS) were obtained in ESI^+ mode at SAIF, Panjab University, Chandigarh. The reaction was carried out under visible-light irradiation using a 9 W white LED lamp (Havells India Ltd), positioned 5 cm above the reaction mixture. The reaction setup ensured uniform exposure to light throughout the process.

1,3-Diketones were synthesized using methods described in the literature.[20] Commercially available 2-mercaptobenzimidazole (Avra Chemicals, India) and NBS (Avra Chemicals, India) were used without any purification.

General method for preparation of 6-substituted-2-aroyl-3-methylbenzimidazo[2,1-*b*]thiazoles 6(a–n)

1,3-Diketones **3** (1.0 mmol) were ground with *N*-bromosuccinimide (1.0 mmol) in a dry mortar for 15–30 min, forming a thick paste. The mixture was then transferred to a conical flask and stirred with 15 mL of absolute ethanol under visible-light irradiation. Next, 2-mercaptobenzimidazoles **5** (1.0 mmol) were added and stirred for 30–40 min until completion, monitored by TLC using ethyl acetate–petroleum ether (20 : 80, v/v). Excess ethanol was removed under reduced pressure and the reaction mixture was neutralized with aqueous sodium bicarbonate. The obtained solid products **6(a–n)** were recrystallized using ethanol and dried, yielding high-purity products.

2-Benzoyl-3-methylbenzo[4,5]imidazo[2,1-*b*]thiazole 6a. Creamish solid; mp. 125 °C; yield: 88%; IR (KBr, cm^{-1}): 1680 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.04–8.02 (d, 1H, ^3J = 8.0 Hz, 4H), 7.86–7.84 (m, 2H, 2′,6′-H), 7.75–7.70 (m, 2H, 4′,7H), 7.62–7.58 (m, 2H, 3′,5′-H), 7.45–7.41 (m, 1H, 6H), 7.34–7.31 (m, 1H, 5H), 2.73 (s, 3H, 3-CH_3); ^{13}C NMR (101 MHz) δ (ppm) 189.3, 154.8, 148.8, 139.9, 138.7, 133.4, 130.8, 129.3, 129.2, 125.0, 122.0, 121.7, 119.2, 113.4, 15.7; anal. calcd. for $C_{17}H_{12}N_2OS$: C, 69.84; H, 4.14; N, 9.58% found: C, 69.80; H, 4.11; N, 9.53%.

2-(4-Fluorobenzoyl)-3-methylbenzo[4,5]imidazo[2,1-*b*]thiazole 6b. White solid; mp. 203 °C; yield: 75%; IR (KBr, cm^{-1}): 1678 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.04–8.02 (d, 1H, ^3J = 8.0 Hz, 4H), 7.98–7.94 (m, 2H, 2′,6′-H), 7.75–7.73 (d, 1H, ^3J = 8.0 Hz, 7H), 7.46–7.40 (m, 3H, 3′,5′,6H), 7.35–7.30 (m, 1H, 5H), 2.74 (s, 3H, 3-CH_3); ^{13}C NMR (101 MHz) δ (ppm) 187.8, 166.5, 164.0, 154.8, 148.8, 139.8, 135.2 (d, $^3J_{CF}$ = 12 Hz), 132.4 (d, $^2J_{CF}$ = 36 Hz), 132.3, 130.8, 125.0, 122.0, 121.4, 119.2, 116.5, 116.3, 113.3, 15.8; ^{19}F NMR (376 MHz) δ (ppm) −105.5.

2-(4-Chlorobenzoyl)-3-methylbenzo[4,5]imidazo[2,1-*b*]thiazole 6c. Creamish solid; mp. 204.5 °C; yield: 77%; IR (KBr, cm^{-1}): 1686 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.04–8.02 (d, 1H, ^3J = 8.0 Hz, 4H), 7.88–7.86 (m, 2H, 2′,6′-H), 7.78–7.76 (d, 1H, ^3J = 8.0 Hz, 7H), 7.48–7.46 (m, 2H, 3′,5′-H), 7.44–7.42 (m, 1H, 6H), 7.35–7.32 (m, 1H, 5H), 2.80 (s, 3H, 3-CH_3); ^{13}C NMR (101 MHz) δ (ppm) 187.5, 153.8, 147.6, 141.2, 138.6, 131.5, 131.2, 130.4, 128.2, 124.9, 121.9, 120.9, 119.1, 112.9, 15.4; anal. calcd. for $C_{17}H_{11}ClN_2OS$: C, 62.48; H, 3.39; N, 8.57% found: C, 62.40; H, 3.33; N, 8.48%.

2-(4-Bromobenzoyl)-3-methylbenzo[4,5]imidazo[2,1-*b*]thiazole 6d. Brown solid; mp. 244.5 °C; yield: 76%; IR (KBr, cm^{-1}): 1694 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.04–8.02 (d, 1H, ^3J = 8.0 Hz, 4H), 7.84–7.78 (m, 4H, 2′,3′,5′,6′-H), 7.75–7.73 (d, 1H, ^3J = 8.0 Hz, 7H), 7.46–7.42 (m, 1H, 6H), 7.35–7.31 (m, 1H, 5H), 2.74 (s, 3H, 3-CH_3); ^{13}C NMR (101 MHz) δ (ppm) 188.2, 154.8, 148.8, 140.1, 137.7, 132.4, 131.3, 130.8, 127.4, 125.0, 122.0, 121.3, 119.3, 113.4, 15.8; HRMS (ESI) m/z for $C_{17}H_{11}BrN_2OS$: 370.9831 $[M + H]^+$, 372.9811 $[M + H + 2]^+$ (1 : 1); anal. calcd. for $C_{17}H_{11}BrN_2OS$: C, 55.00; H, 2.99; N, 7.55% found: C, 54.93; H, 2.91; N, 7.50%.

2-(4-Methylbenzoyl)-3-methylbenzo[4,5]imidazo[2,1-*b*]thiazole 6e. Dark brown solid; mp. 100.5 °C; yield: 88%; IR (KBr, cm^{-1}): 1682 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.01–7.99 (d, 1H, ^3J = 8.1 Hz, 4H), 7.77–7.74 (m, 2H, 2′,6′-H), 7.74–7.72 (d, 1H, ^3J = 8.0 Hz, 7H), 7.44–7.39 (m, 3H, 3′,5′,6H), 7.33–7.29 (m, 1H, 5H), 2.73 (s, 3H, 4′-CH_3), 2.43 (s, 3H, 3-CH_3); ^{13}C NMR (101 MHz) δ (ppm) 188.7, 154.8, 148.8, 144.0, 139.3, 135.9, 130.8, 129.8, 129.5, 124.9, 121.9, 121.6, 119.2, 113.3, 21.7, 15.7; anal. calcd. for $C_{18}H_{14}N_2OS$: C, 70.56; H, 4.61; N, 9.14% found: C, 70.51; H, 4.55; N, 9.10%.

2-(4-Methoxylbenzoyl)-3-methylbenzo[4,5]imidazo[2,1-*b*]thiazole 6f. Brown solid; mp. 169 °C; yield: 89%; IR (KBr, cm^{-1}): 1680 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.05–8.03 (d, 1H, ^3J = 8.0 Hz, 4H), 7.90–7.87 (d, 2H, ^3J = 8.7 Hz, 2′,6′-H), 7.75–7.73 (d, 1H, ^3J = 8.0 Hz, 7H), 7.45–7.41 (t, 1H, ^3J = 8.0 Hz, 6H), 7.34–7.30 (t, 1H, ^3J = 8.0 Hz, 5H), 7.13–7.11 (d, 2H, ^3J = 8.7 Hz, 3′,5′-H), 3.89 (s, 3H, 4′-OCH_3), 2.77 (s, 3H, 3-CH_3); ^{13}C NMR (101 MHz) δ (ppm) 187.6, 163.8, 154.8, 148.8, 138.6, 132.1, 130.8, 124.8, 121.9, 121.5, 119.2, 114.6, 113.3, 56.2, 15.8; anal. calcd. for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69% found: C, 67.01; H, 4.33; N, 8.61%.

2-(3-Methoxylbenzoyl)-3-methylbenzo[4,5]imidazo[2,1-*b*]thiazole 6g. Brownish solid; mp. 178.5 °C; yield: 85%; IR (KBr, cm^{-1}): 1690 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.04–8.02 (d, 1H, ^3J = 8.0 Hz, 4H), 7.75–7.73 (d, 1H, ^3J = 8.0 Hz, 7H), 7.53–7.49 (m, 1H, 5′-H), 7.45–7.40 (m, 2H, 6,6′-H), 7.36–7.30 (m, 2H, 5,2′-H), 7.28–7.26 (dd, 1H, J = 8.0 Hz, J = 2.0 Hz, 4′-H), 3.84 (s, 3H, 3′-OCH_3), 2.73 (s, 3H, 3-CH_3); ^{13}C NMR (101 MHz) δ (ppm) 189.0, 159.8, 154.9, 148.8, 140.1, 130.8, 130.6, 125.0, 121.9, 121.7, 121.4, 119.6, 119.2, 113.7, 113.4, 56.0, 15.8; anal. calcd. for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69% found: C, 66.98; H, 4.30; N, 8.58%.

3-Methyl-(2-(2-thiophen)oyl)-benzo[4,5]imidazo[2,1-*b*]thiazole 6h. Brownish crystal; mp. 166 °C; yield: 75%; IR (KBr, cm^{-1}): 1677 (C=O); ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 8.19–8.17 (dd, 1H, J = 5.2 Hz, J = 1.1 Hz, 3′-H), 8.09–8.07 (m, 2H, 4,5′-H), 7.76–7.74 (d, 1H, ^3J = 8.0 Hz, 7H), 7.47–7.43 (m, 1H, 6H), 7.37–7.33 (m, 2H, 5,4′-H), 2.98 (s, 3H, 6-CH_3); ^{13}C NMR (101 MHz) δ (ppm) 179.6, 154.5, 148.7, 143.2, 139.3, 136.7, 135.7, 130.7, 129.4, 125.0, 122.0, 119.2, 118.8, 113.4, 15.5; anal. calcd.

for $C_{15}H_{10}N_2OS_2$: C, 60.38; H, 3.38; N, 9.39% found: C, 60.30; H, 3.33; N, 9.35%.

2-(4-Fluorobenzoyl)-3-methyl-6-methylbenzo[4,5]imidazo [2,1-*b*]thiazole 6i. Yellowish solid; mp. 188 °C; yield: 76%; IR (KBr, cm^{-1}): 1682 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.96–7.92 (m, 2H, 2′,6′-H), 7.87–7.84 (m, 1H, 4H), 7.60–7.58 (d, 1H, ^3J = 8.0 Hz, 7H), 7.44–7.40 (m, 2H, 3′,5′-H), 7.12–7.10 (d, 1H, ^3J = 8.0 Hz, 6H), 2.71 (s, 3H, 3-CH_3), 2.47 (s, 3H, 5-CH_3); ^{13}C NMR (101 MHz) δ (ppm) 187.8, 164.0, 154.1, 149.1, 146.9, 139.8, 135.3–135.2 (d, $^3J_{CF}$ = 12 Hz), 132.4–132.3 (d, $^2J_{CF}$ = 36 Hz), 131.5, 130.9, 126.3, 121.0, 118.8, 116.5, 116.3, 113.2, 21.7, 15.1; ^{19}F NMR (376 MHz) δ (ppm) −103.9.

2-(4-Chlorobenzoyl)-3-methyl-6-methylbenzo[4,5]imidazo [2,1-*b*]thiazole 6j. Creamish solid; mp. 196 °C; yield: 77%; IR (KBr, cm^{-1}): 1686 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.88–7.84 (m, 3H, 4,2′,6′-H), 7.66–7.64 (d, 2H, ^3J = 8.0 Hz, 3′,5′-H), 7.52–7.51 (m, 1H, 7H), 7.13–7.11 (d, 1H, ^3J = 8.0 Hz, 6H), 2.69 (s, 3H, 3-CH_3), 2.45 (s, 3H, 5-CH_3); ^{13}C NMR (101 MHz) δ (ppm) 188.0, 154.7, 149.3, 140.0, 138.3, 137.4, 134.6, 131.2, 129.5, 128.8, 123.3, 121.1, 119.1, 112.8, 21.7, 15.7; HRMS (ESI) *m*/*z* for $C_{18}H_{13}ClN_2OS$: 341.0503 $[M + H]^+$, 343.0514 $[M + H + 2]^+$ (3 : 1); anal. calcd. for $C_{18}H_{13}ClN_2OS$: C, 63.43; H, 3.84; N, 8.22% found: C, 63.39; H, 3.75; N, 8.16%.

2-(4-Methylbenzoyl)-3-methyl-6-methylbenzo[4,5]imidazo [2,1-*b*]thiazole 6k. Creamish solid; mp. 198 °C; yield: 87%; IR (KBr, cm^{-1}): 1676 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.87–7.85 (m, 1H, 4H), 7.76–7.73 (m, 2H, 2′,6′-H), 7.60–7.58 (d, 1H, ^3J = 8.0 Hz, 7H), 7.40–7.38 (d, 2H, ^3J = 8.0 Hz, 3′,5′-H), 7.13–7.11 (d, 1H, ^3J = 8.0 Hz, 6H), 2.70 (s, 3H, 3-CH_3), 2.45 (s, 3H, 5-CH_3), 2.43 (s, 3H, 4′-CH_3); ^{13}C NMR (101 MHz) δ (ppm) 189.3, 154.8, 148.8, 139.9, 138.7, 133.8, 130.8, 129.2, 125.6, 122.5, 120.7, 118.5, 112.5, 21.1, 15.1, 15.0; anal. calcd. for $C_{19}H_{16}N_2OS$: C, 71.22; H, 5.03; N, 8.74% found: C, 71.16; H, 4.99; N, 8.69%.

2-(4-Methoxybenzoyl)-3-methyl-6-methylbenzo[4,5]imidazo [2,1-*b*]thiazole 6l. Yellowish crystal; mp. 206 °C; yield: 89%; IR (KBr, cm^{-1}): 1670 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.88–7.86 (d, 2H, ^3J = 8.0 Hz, 2′,6′-H), 7.84–7.83 (m, 1H, 4H), 7.61–7.59 (d, 1H, ^3J = 8.0 Hz, 7H), 7.25–7.23 (d, 1H, ^3J = 8.0 Hz, 6H), 7.12–7.10 (d, 2H, ^3J = 8.0 Hz, 3′,5′-H), 3.88 (s, 3H, 4′-OCH_3), 2.75 (s, 3H, 3-CH_3), 2.48 (s, 3H, 5-CH_3); ^{13}C NMR (101 MHz) δ (ppm) 187.0, 163.2, 153.6, 146.3, 138.0, 131.5, 130.8, 130.4, 130.3, 125.6, 120.5, 118.2, 114.0, 112.5, 55.6, 21.2, 15.2; anal. calcd. for $C_{19}H_{16}N_2O_2S$: C, 67.84; H, 4.79; N, 8.33% found: C, 67.76; H, 4.77; N, 8.28%.

2-(3-Methoxybenzoyl)-3-methyl-6-methylbenzo[4,5]imidazo [2,1-*b*]thiazole 6m. Creamish crystal; mp. 187 °C; yield: 80%; IR (KBr, cm^{-1}): 1672 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.90–7.88 (m, 1H, 5′-H), 7.53–7.48 (m, 2H, 6′,6H), 7.40–7.39 (m, 1H, 4H), 7.35–7.34 (m, 1H, 2′-H), 7.27–7.25 (m, 1H, 4′-H), 7.15–7.13 (m, 1H, 7H), 3.84 (s, 3H, 3′-OCH_3), 2.71 (s, 3H, 3-CH_3), 2.46 (s, 3H, 5-CH_3); ^{13}C NMR (101 MHz) δ (ppm) 188.4, 159.2, 154.2, 148.6, 139.6, 139.5, 134.0, 130.0, 128.3, 122.6, 120.8, 118.9, 118.5, 113.1, 112.3, 55.4, 21.2, 15.1; anal. calcd. for $C_{19}H_{16}N_2O_2S$: C, 67.84; H, 4.79; N, 8.33% found: C, 67.77; H, 4.79; N, 8.30%.

2-(2-Methoxybenzoyl)-3-methyl-6-methylbenzo[4,5]imidazo [2,1-*b*]thiazole 6n. Whitish solid; mp. 195 °C; yield: 72%; IR (KBr, cm^{-1}): 1684 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 7.86–7.84 (m, 1H, 6′-H), 7.63–7.58 (m, 2H, 4′,6H), 7.44–7.41 (m, 1H, 4H), 7.25–7.23 (m, 2H, 3′,5′-H), 7.15–7.11 (m, 1H, 7H), 3.80 (s, 3H, 2′-OCH_3), 2.63 (s, 3H, 3-CH_3), 2.46 (s, 3H, 5-CH_3); ^{13}C NMR (101 MHz) δ (ppm) 188.4, 156.8, 140.1, 134.6, 133.3, 133.2, 131.5, 128.8, 126.4, 123.7, 121.4, 118.8, 113.3, 112.5, 56.3, 21.7, 14.1; anal. calcd. for $C_{19}H_{16}N_2O_2S$: C, 67.84; H, 4.79; N, 8.33% found: C, 67.74; H, 4.75; N, 8.25%.

General method for preparation of 2-((1-acetyl-1*H*-benzimidazol-2-yl)thio)-1-arylethan-1-one 10(a–e)

1,3-Diketones **3** (1.0 mmol) were grounded with NBS (1.0 mmol) in a dry mortar for 15–30 min to form a thick paste. Subsequently, 2-mercaptobenzimidazole **5** (1.0 mmol) was added and the reaction mixture was further grounded thoroughly at room temperature for 15–20 min. Reaction progress was monitored by TLC using ethyl acetate–petroleum ether (20 : 80, v/v). After completion, 30 mL of saturated sodium bicarbonate solution was added and the mixture was filtered to obtain the crude solid. N/S-difunctionalized benzimidazole derivatives **10(a–e)**, were recrystallized from ethanol and dried, yielding high-purity products.

1-Acetyl-2-((2-oxo-2-phenylethyl)thio)benzo[4,5]imidazole 10a. Whitish crystals; mp. 171.5 °C; yield: 86%; IR (KBr, cm^{-1}): 1708 cm^{-1} (C=O), 1670 cm^{-1} (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.11–8.09 (m, 2H, 2′,6′-H), 7.63–7.60 (m, 2H, 4,7H), 7.54–7.50 (m, 3H, 3′,4′,5′-H), 7.30–7.25 (m, 2H, 5,6H), 4.85 (s, 2H, CH_2), 2.81 (s, 3H, CH_3); ^{13}C NMR (126 MHz) δ (ppm) 193.9, 168.8, 154.3, 144.0, 136.1, 133.6, 133.2, 128.8, 128.6, 124.6, 123.6, 119.1, 113.2, 40.5, 26.2; anal. calcd. for $C_{17}H_{14}N_2O_2S$: C, 65.79; H, 4.55; N, 9.03% found: C, 65.73; H, 4.50; N, 9.00%.

1-Acetyl-2-((2-oxo-2-(4-fluorophenyl)ethyl)thio)benzo[4,5] imidazole 10b. Creamy white solid; mp. 189 °C; yield: 75%; IR (KBr, cm^{-1}): 1724 cm^{-1} (C=O), 1690 cm^{-1} (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm) 8.06–8.04 (d, 1H, ^3J = 8.0 Hz, 7H), 7.98–7.93 (m, 2H, 2′,6′-H), 7.77–7.75 (d, 1H, ^3J = 8.0 Hz, 4H), 7.47–7.41 (m, 3H, 3′,5′,6H), 7.36–7.32 (m, 1H, 5H), 5.65 (s, 2H, CH_2), 2.74 (s, 3H, CH_3); ^{13}C NMR (126 MHz) δ (ppm) 187.3, 166.0, 154.2, 147.7, 139.2, 134.6 (d, $^3J_{CF}$ = 12 Hz), 131.9–131.8 (d, $^2J_{CF}$ = 40 Hz), 130.2, 124.6, 121.6, 118.5, 116.0, 115.8, 112.9, 38.8, 15.3; ^{19}F NMR (376 MHz) δ (ppm) −110.1.

1-Acetyl-2-((2-oxo-2-(4-chlorophenyl)ethyl)thio)benzo[4,5] imidazole 10c. Yellowish solid; mp. 143 °C; yield: 78%; IR (KBr, cm^{-1}): 1714 cm^{-1} (C=O), 1692 cm^{-1} (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.07–8.05 (d, 1H, ^3J = 7.8 Hz, 7H), 7.98–7.95 (m, 2H, 2′,6′-H), 7.77–7.75 (d, 1H, ^3J = 7.8 Hz, 4H), 7.44–7.38 (m, 3H, 3′,5′,6H), 7.34–7.32 (m, 1H, 5H), 5.51 (s, 2H, CH_2), 2.75 (s, 3H, CH_3); ^{13}C NMR (126 MHz) δ (ppm) 187.8, 154.7, 148.2, 139.8, 132.4, 132.2, 130.7, 125.1, 122.1, 119.1, 116.6, 116.3, 113.4, 39.4, 15.8; anal. calcd. for $C_{17}H_{13}ClN_2O_2S$: C, 59.22; H, 3.80; N, 8.12% found: C, 59.18; H, 3.08; N, 8.05%.

1-Acetyl-2-((2-oxo-2-(4-tolyl)ethyl)thio)benzo[4,5]imidazole 10d. Greyish solid; mp. 181.5 °C; yield: 81%; IR (KBr, cm^{-1}): 1718 cm^{-1} (C=O), 1680 cm^{-1} (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.04–8.02 (d, 1H, ^3J = 8.0 Hz, 7H), 7.78–7.76 (m,

2H, 2′,6′-H), 7.75–7.74 (m, 1H, 4H), 7.43–7.40 (m, 2H, 3′,5′-H), 7.34–7.32 (m, 1H, 6H), 6.91–6.90 (m, 1H, 5H), 5.65 (s, 2H, CH_2), 2.75 (s, 3H, CH_3), 2.44 (s, 3H, 4′-CH_3); ^{13}C NMR (126 MHz) δ (ppm) 188.8, 154.8, 148.8, 144.0, 139.3, 135.9, 130.8, 129.8, 129.5, 124.9, 121.9, 119.2, 113.3, 39.4, 21.7, 15.7; HRMS (ESI) *m*/*z* for $C_{18}H_{13}FN_2OS$: 325.0997 $[M + H]^+$; anal. calcd. for $C_{18}H_{16}N_2O_2S$: C, 66.65; H, 4.97; N, 8.64% found: C, 66.62; H, 4.91; N, 8.60%.

1-Acetyl-2-((2-oxo-2-(4-methoxyphenyl)ethyl)thio)benzo[4,5] imidazole 10e. Buff coloured solid; mp. 229.5 °C; yield: 85%; IR (KBr, cm^{-1}): 1718 cm^{-1} (C═O), 1680 cm^{-1} (C═O); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 8.10–8.08 (d, 2H, ^3J = 8.0 Hz, 2′,6′-H), 7.64–7.63 (m, 1H, 7H), 7.56–7.54 (m, 1H, 4 H), 7.31–7.24 (m, 2H, 5,6H), 6.98–6.96 (d, 2H, ^3J = 8.0 Hz, 3′,5′-H), 4.83 (s, 2H, CH_2), 3.89 (s, 3H, 4′-OCH_3), 2.82 (s, 3H, CH_3); ^{13}C NMR (126 MHz) δ (ppm) 192.2, 168.7, 163.9, 154.3, 143.9, 133.2, 130.9, 128.9, 124.5, 123.5, 119.0, 113.8, 113.2, 55.5, 40.3, 26.2; anal. calcd. for $C_{18}H_{16}N_2O_3S$: C, 63.51; H, 4.74; N, 8.23% found: C, 63.48; H, 4.71; N, 8.20%.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

The authors declare no competing interest.

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