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Synthesis and Anti-Microbial Studies of 3-((1H-Benzo[d]imidazol-2-ylthio)methyl)-2H-chromen-2-one Derivatives

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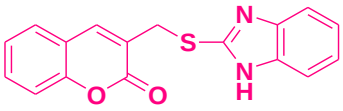
ABSTRACT

A simple and efficient protocol has been utilized to synthesize 3-((1H-benzo[d]imidazol-2-ylthio)methyl)-2H-chromen-2-one derivatives using cesium carbonate. Biological activities of these compounds were found to be effective against various microbial pathogens of human and plants.



1. Introduction

In the past few years the synthesis and screening of small molecules based on natural products as templates have attracted many researchers all around the world [1]. Among the natural products, coumarins and their derivatives are well known for their anti-microbial activities [2, 3]. The 1-benzopyran-2-one moiety, the structural core of coumarins is often found in more complex natural products which is frequently associated with biological activities, such as, anti-cancer, anti-fungal and anti-HIV [4]. Tri-substituted coumarin carbochromen (**1**) [5] is a potent specific coronary vasodilator, similarly seseline (**2**) [6] and is well known for its potent anti-HIV activity (Fig. 1). Among N-heterocyclic compounds benzimidazole is one of the most explored molecules. Kumar et al., have reported that benzimidazole derivatives (**3**) can act as mGluR2 positive allosteric modulators (PAMs) [7]. Recently, novel trisubstituted benzimidazoles (**4**) are known to act as potent anti-tuberculosis agent against Mtb H37Rv [8].

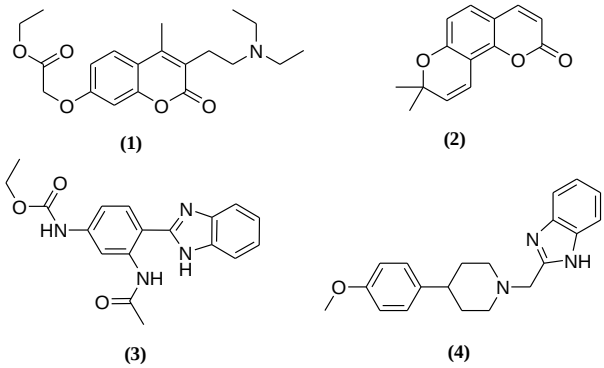
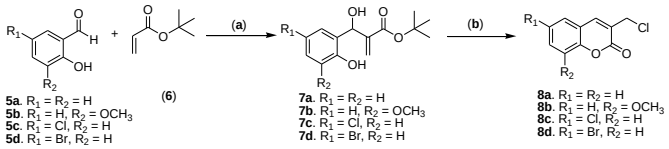


Fig. 1 Representative examples of coumarin and benzimidazole derivatives [5-8]

Our research group is interested in the synthesis of heterocyclic molecules through simple and efficient methodologies. Here, we present a facile methodology for synthesis of 3-((1H-benzo[d]imidazol-2-ylthio)methyl)-2H-chromen-2-one frame work and its anti-micorbial properties against human and plant pathogens [9].

2. Results and Discussion

The synthesis of coumarins is well known in the literature and researchers including Pechmann [10], Claisen [11, 12], Wittig [13] and Knoevenagel [14] have contributed significantly. The synthesis of 3-chloromethyl coumarin derivatives through the halo-methylation of coumarins did not afford the expected products. Thereby, adopting a modified literature protocol [15], we have synthesized 3-chloromethyl coumarin derivatives (**8a-d**), from salicylaldehyde (**5a-d**) and tertiary butyl acrylate (**6**). The reaction of salicylaldehyde (**5a**) and t-butyl acrylate (**6**) in the presence of DABCO affords Baylis-Hillman adduct (**7a**), which undergoes intramolecular cyclization to 3-chloromethyl coumarin (**8a**) in presence of acetic acid and hydrochloric acid (Scheme 1).



Scheme 1 Synthesis of 3-chloromethyl coumarin derivatives (**8a-d**), (a) DABCO/$CHCl_3$ and (b) CH_3COOH/HCl.

The benzimidazole-2-thiones are the most well-known heterocyclic molecules in the field of medicinal chemistry [16]. Unsymmetrical benzimidazole-2-thiones and its derivatives (**9a-c**) were synthesized using *ortho*-phenylene diamine derivatives and carbon disulphide in the presence of sodium hydroxide. Benzimidazoles of electron donating and electron withdrawing substituents were synthesized to generalize the reaction conditions. Interestingly, alkylation of benzimidazole-2-thiones can take place at two possible active sites – S and N, among which S-alkylation is more favorable. However, additional alkylation can take place at the N-site which is of limited interest and has to minimized or eliminated. Therefore mild reaction conditions favoring S-alkylation over the possible N-alkylation have to be designed. Interestingly, S-alkylation

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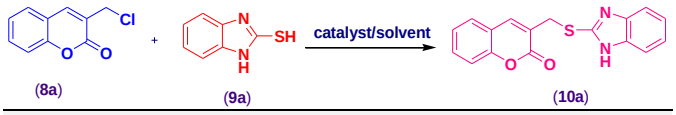
of various biologically active heterocyclic compounds reveals that the reaction can take place only under mild reaction condition. A large number of optimized procedures have been reported where most of the protocols employ various catalytic methods mostly favoring metal based catalysts. To mention, S-alkylation reported by Kang et al. [17] involves elemental sulphur and *n*-BuLi whereas Taniguchi et al. [18] have utilized $NiBr_2$-bpy at a very high temperature. Similarly Guy et al. have reported S-alkylation using copper acetate in presence of pyridine [19]. However the methodology utilized by Hwu et al. to synthesis a series of heterobicycle-coumarin conjugates via S-alkylation requires tedious time consuming purification techniques [20]. In aforementioned strategies harsh reaction conditions, hazardous reagents, time consuming purification techniques and long reaction time hamper the synthetic scope of the reaction. Moreover, side products including sulfonium salts and disulfides may accompany the corresponding S-alkylated products and diminish the yield. Therefore the need for a mild and a straightforward approach for the construction of C-S bond is clearly warranted.

Table 1 Optimization of reaction conditions of S-alkylation

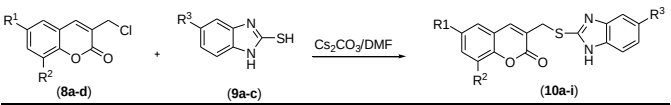


Entry	Base	Solvent	Time (h)	Temperature	Yield[a] (%)
1.	None	DMF	12	150	-
2.	Na_2CO_3	DMF	12	120	32
3.	K_2CO_3	DMF	12	120	37
4.	$Ba(OH)_2$	DMF	12	150	16
5.	$Ca(OH)_2$	DMF	12	150	17
6.	LiOH	DMF	12	150	16
7.	NaOH	DMF	12	150	23
8.	KOH	DMF	12	150	21
9.	Pyridine	DMF	12	150	-
10.	Piperidine	DMF	12	150	-
11.	Et_3N	DMF	12	150	*c*
12.	Aqueous NH_3	CH_3CN	15	*b*	57
13.	Cs_2CO_3	DMF	5	*b*	86

a-Isolated yield. b-Room temperature. c-Traces

In our initial study 3-chloromethyl coumarin (**8a**) and benzimidazole-2-thione (**9a**) compounds were chosen as model reaction to optimize the reaction conditions. The results are summarized in Table 1. In the absence of catalysts and in the presence of a solvent the reaction did not yield the target compound (**10a**) (Table 1, entry 1). In presence of a catalyst, such as sodium carbonate and potassium carbonate (Table 1, entries 2-3) moderate yields were obtained even after a prolonged reaction time. Investigations of strong bases (Table 1, entries 4-8) indicate that they do not favor S-alkylation both at room temperature and at reflux temperature and results in a number of side products. Surprisingly pyridine and piperidine (Table 1, entries 9-10) did not catalyze the reaction whereas triethyl amine (Table 1, entry 11) shows traces of the product (**10a**). In most of the cases extensive purification, more reaction time and the presence of unwanted side products were involved. Interestingly aqueous ammonia shows a better yield at room temperature but its long reaction time and tedious purifications make it unsuitable for the S-alkylation (Table 1, entry 12). Among the studied protocols Cs_2CO_3, favors the expected S-alkylated product (10a) in good yield even at room temperature. Moreover, easy isolation of the product, short reaction time and the absence of unwanted side products makes Cs_2CO_3 the most attractive and superior catalyst among the series tested. The S-alkylation reaction catalyzed by Cs_2CO_3 at a temperature of 150° C shows no significant increase in the yield, however at lower temperature ~ 0-15°C there was considerable decrease in the yield. Among several solvents studied, DMF served as the prime solvent in Cs_2CO_3 catalyzed S-alkylation reactions. However, Cs_2CO_3 being more favorable N-alkylation catalyst has surprisingly yielded S-alkylated product at a promising yield. The possible explanation for this observation is that in 2-mercaptobenzimidazole derivatives the thiols are comparatively stronger acids (pKa = 10) than the acid proton of N_1-H benzimidazole ring (pKa = 16.4). Consequently the larger thiolate ions are better solubilized in aprotic polar solvent, DMF resulting in high reactivity. All the compounds synthesized using Cs_2CO_3 were further analyzed without purification and exhibited nearly 98% pure. Interestingly, the formation of C-S bond catalysed by Cs_2CO_3 was independent of the substrates of the coumarin and benzimidazole-2-thione moieties. The substrates possessing electron rich species (Table 2, entries 4 & 5) showed considerable decrease in yield whereas electron deficient species had better yield (Table 2, entries 3 & 6-9). On the basis of the results summarized, synthesis of 3-chloromethyl coumarin coupled mercapto benzimidazole derivatives are feasible in a short reaction time at room temperature with optimal purity. As a result the identified synthetic strategy not only overcomes harsh and long reaction procedures but also overcomes time consuming purification techniques making them more attractive among the other procedures.

Table 2 Synthesis of 3-Chloromethyl Coumarin coupled benzimidazole -2- thione derivatives (10a-10i)



Entry	Comp. No	R_1	R_2	R_3	Time (h)	Yield (%)
1.	10a	H	H	H	5	86
2.	10b	H	H	CH_3	5.5	61
3.	10c	H	H	NO_2	4	71
4.	10d	H	OCH_3	H	5	61
5.	10e	H	OCH_3	CH_3	5	65
6.	10f	Cl	H	NO_2	4.5	79
7.	10g	Br	H	H	3.5	78
8.	10h	Br	H	CH_3	3	67
9.	10i	Br	H	NO_2	3	95

All synthesized compounds were characterized based on ^1H, ^{13}C NMR, ESI spectral and elemental studies. Coumarin coupled benzimidazole-2-thione derivatives resonates as a singlet in the region δ 7.8-8.1 ppm corresponding to C-4 of the coumarin proton. Similarly the S-CH_2 which acts as a linker between coumarin and benzimidazole-2- thione moieties is observed in the range δ 3.9-4.4 ppm. In coumarin coupled benzimidazoles the NH peak of the benzimidazole moiety resonates in the region around δ 12.05-12.61 ppm which further confirms S-alkylation over the possible N-alkylation. Compounds corresponding to 10b, 10d, 10e & 10h substituted with methyl and methoxy groups (Bimz-CH_3 and Cou-OCH_3) resonates as a singlet around δ 2.38-2.42 ppm and δ 3.87-4.41 ppm respectively. Similarly, the corresponding ^{13}C-NMR spectra of the Bimz-CH_3 and Cou-OCH_3 are observed in the region of δ 21.1-27.5 ppm and δ 54.1-55.6 ppm respectively. The ^{13}C spectra of the corresponding carbonyl group of coumarin coupled benzimidazole -2- thione compounds resonates in the region δ 159-165 ppm, similarly the S-CH_2 linking both heterocyclic moieties is observed around δ 32 ppm. The mass spectral data also were in accordance to the synthesized compounds.

2.1 Antimicrobial Studies

Anti-microbial activity of nine different benzimidazole coumarin derivative were tested against bacterial and fungal pathogens of humans, (*Shigella dysenteriae, Solmonella typhi, Epidermophyton sp., Trichophyton sp.*) and plants (*Xanthomonas oryzae, Pseudomonas fluorescence, Sclerotium sp., Alternaria alta).* These microorganisms are significant in that they produce diseases of importance on their hosts. The human fungal pathogens are dermatophytes for which effective antibiotics are still not available. The present study indicates that the coupled product of coumarin and benzimidazole were effective against almost all bacterial pathogens. Thus, all the nine different 3-chloromethylcoumarin coupled benzimidazole-2-thione compounds (**10a-10i**) were subjected to antimicrobial studies at two different concentrations (25 and 50 μg) (Table 3).

Table 3 Anti-microbial studies of the coumarin coupled benzimidazole-2-thiones (% inhibition)

S. No	Microbe	10a		10b		10f		10g		10h	
		25μg	50μg	25μg	50μg	25μg	50μg	25μg	50μg	25μg	50μg
1.	*Sh. dys.*	65	100	-	80	-	100	-	89	87	-
2.	*So. typ.*	52	100	-	65	-	85	-	80	85	-
3.	*Xa. ory.*	-	-	-	100	-	77	-	-	-	-
4.	*Ps. flu.*	-	90	-	75	-	-	75	100	85	-
5.	*Epi. sp.*	-	-	-	-	-	-	-	-	-	-
6.	*Tri. sp.*	-	-	-	-	-	-	-	-	-	-
7.	*Scl. sp.*	-	-	-	-	-	-	-	-	-	-
8.	*Alt. al.*	-	-	-	-	-	100	-	-	52	-

Notes: ***Sh. dys****-Shigella dysenteriae,* ***So. typ****-Solmonella typhi,* ***Xa. ory****.- Xanthomonas oryzae,* ***Ps. flu****-Pseudomonas flurescence,* ***Epi. sp****. Epidermophyton sp,* ***Tri. sp****.- Trichophyton sp,* ***Scl. sp.*** *Sclerotium sp,* ***Alt. alt****.- Alternaria alta. 100% inhibition (diameter of inhibition zone) (Shigella dysenteriae – 1.4 cm; Solmonella typhi – 1.6 cm; Xanthomonas oryzae – 1.9 cm; Pseudomonas fluorescence – 1.6 cm; Alternaria altata – 1.4 cm).*

Coumarin coupled benzimidazole-2-thiones, **10a, 10b** & **10g** exhibit good inhibition against bacterial plant pathogens *Pseudomonas*

fluorescence at 25 µg and 50 µg, but not against fungal plant pathogens. The inhibition activities of the compounds have been calculated from the disappearance of the fluorescence color on treatment with plant pathogen *Pseudomonas fluorescence*. However, compounds **10f** and **10h** were effective against both bacterial plant pathogens and plant fungal pathogen *Alternaria* alta., at 100 & 52% respectively. Interestingly, all the coumarin coupled benzimidazole compounds were effective against human bacterial pathogens *Shigella dysenteriae* and *Solmonella typhi*. Antimicrobial studies on fungal pathogens of human showed that the synthesized compounds exhibits no inhibition against *Epidermophyton sp. and Trichophyton sp.*

3. Experimental Methods

Salicylaldehyde and its derivatives, tertiary butyl acrylate, aromatic aldehydes, aromatic amines, carbondisulphide, DABCO, hydrochloric acid, Cs_2CO_3 were purchased from Sigma Aldrich Pvt. Limited, Bangalore. DMF, CH_3CN, methanol were obtained from local sources and were purified and dried by following the standard experimental procedure. Mass spectral studies were performed in the Esquire 3000 plus instrument.

3.1 Microorganisms

All the microbial human and plant pathogens used in the antimicrobial bio-assay were procured from Department of plant sciences, Guindy campus, University of Madras, India.

3.2 Preparation of Bacterial Inoculum

The bacterial culture of *Shigella dysenteriae* ATCC NO:49345, *Solmonella typhi* ATCC NO:11778, *Xanthomonas oryzae* ATCC NO:35933, *Pseudomonas flurescence* ATCC NO:13525 were used in the antimicrobial study. These bacterial cultures were grown in sterile nutrient broth (Hi Media M002) at 35 ± 2 °C for 18 h. These suspensions were diluted with sterile buffer solution until the solution has an absorbance of 0.28 ± 0.02 at 475 nm, as measured spectrophotometrically. This has a concentration of 1.5-3.0 × 10^8 CFU/mL. On further dilution, a concentration of 1.5-3.0 × 10^5 CFU/mL is obtained, which was used as working bacterial concentration.

3.3 Preparation of Fungal Inoculum

A fresh Fungus culture of Epidermophyton loccosum, ATCC NO:52066, Trichophyton mentagrophytes ATCC NO:9533, Sclerotium rolfsii ATCC NO:26325, Alternaria alternata ATCC NO:56836 were grown in sterile fungal broth (Hi media M 264) inside the test tubes at 25 ± 2°C for 3 days. These cultures were diluted with the sterile buffer solution until the solution has an absorbance of 0.28 ± 0.02 at 475 nm, as measured spectrophotometrically. This has a concentration of 1.5-3.0 × 10^8 CFU/mL. These solutions were further diluted to obtain a final concentration of 2.0-3.0 × 10^6 CFU/mL as the working fungal solution.

3.4 Antimicrobial Bioassay

Muller-Hinton agar (Hi Media M1084) was dispensed into the pre-sterilized petri dishes and inoculated with bacterial and fungal cultures. Bore an 8 mm diameter well in the centre of inoculated agar plate. Two different concentrations (25 µg and 50 µg) of coumarin coupled benzimidazole compounds to be tested were taken in a sterile 250 mL flask containing 50 mL sterile working buffer solution. The test and control specimen were kept in their respective flasks and placed on the wrist-action shaker for 1 h ± 5 min. A solution of 100 µL from each flasks were added to the well and dried. Each plate was incubated at 35 ± 2 °C for 24 h. Fungal cultures were grown on the appropriate Malt extract powder (Hi Media RM 004) media for 3 to 5 days at 25±2 °C. The zone of inhibition is recorded based on the presence and absence of the inhibition surrounding 8 mm diameter well. Leaching is identified through the presence of inhibition around the zone of well.

3.5 General Procedure for Synthesis of Coumarin Coupled Benzimidazole-2-thione Compounds (10a-10i)

A mixture of 3-chloromethylcoumarin **8a** (0.5 g, 2.5 mmol), 2-mercaptobenzimidazole **9a** (0.4 g, 2.5 mmol) and Cs_2CO_3 (0.16 g) in DMF (5 mL) was stirred at room temperature for 5 h. The reaction mixture was then filtered-off and dried, which afforded the expected compound, 3-((1*H*-benzo[*d*]imidazol-2-ylthio)methyl)-2*H*-chromen-2-one, **10a** as a white solid. The compound was used as such for analysis and required no further purifications.

3.5.1 3-((1H-Benzo[d]imidazol-2-ylthio)methyl)-2H-chromen-2-one, (10a)

Yield: 0.62 g, (86%); m.p. 85-87 °C; ^{1}H NMR(300 MHz, $CDCl_3$), δ_H 7.87 ppm (s, 1H, Cou-*H*), 7.48-7.32 ppm (m, 4H, Bimz-*H*), 7.24-7.12 ppm (m, 4H, Cou-*H*), 4.33 ppm (s, 2H, Cou-C*H*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 153.5 ppm (1C, Cou-*C*=O), 141.7 ppm (1C, Bimz-*C*=*N*), 131.7 ppm (2C, Bimz-*C*), 128.0 ppm (2C, Bimz-*C*), 125.2 ppm (2C, Bimz-*C*), 124.7 ppm (1C, Cou-*C*), 124.5 ppm (1C, Cou-*C*), 124.3 ppm (1C, Cou-*C*), 122.5 ppm (1C, Cou-*C*), 122.4 ppm (1C, Cou-*C*), 119.1 ppm (1C, Cou-*C*), 116.6 ppm (1C, Cou-*C*), 116.5 ppm (1C, Cou-*C*), 32.3 ppm (1C, Bimz-*C*H$_2$). ESIMS Calcd for $C_{17}H_{12}N_2O_2S$: 308.4, Found: 308.9. Anal. Calcd for $C_{17}H_{12}N_2O_2S$: C, 66.22; H, 3.92; N, 9.08; O, 10.38; S, 10.40. Found: C, 66.13; H, 3.74; N, 9.18; O, 10.26; S, 10.29.

3.5.2 3-((5-Methyl-1H-benzo[d]imidazol-2-ylthio)methyl)-2H-chromen-2-one, (10b)

A mixture of 3-chloromethylcoumarin **8a** (0.5 g, 2.5 mmol), 5-methyl-1H-benzo[d]imidazole-2-thiol **9b** (0.42 g, 2.5 mmol) and Cs_2CO_3 (0.16 g) in DMF (5 mL) afforded compound **10b** as a white solid. Yield 0.50 g, (61%). m.p. 94-98 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 8.11 ppm (s, 1H, Cou-*H*), 7.66-7.55 ppm (m, 2H, Bimz-*H*), 7.41-7.29 ppm (m, 4H, Cou-*H*), 6.93 ppm (d, *J = 8.4 Hz*, 1H, Bimz-*H*), 4.38 ppm (s, 2H, Cou-C*H*$_2$), 2.38 ppm (s, 3H, Bimz-C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 160.1 ppm (1C, Cou-*C*=O), 152.8 ppm (1C, Bimz-*C*=*N*), 148.4 ppm (1C, Bimz-*C*), 140.8 ppm (1C, Bimz-*C*), 131.7 ppm (1C, Bimz-*C*), 130.7 ppm (1C, Bimz-*C*), 130.6 ppm (1C, Bimz-*C*), 128.3 ppm (1C, Bimz-*C*), 124.7 ppm (1C, Cou-*C*), 124.6 ppm (1C, Cou-*C*), 123.1 ppm (1C, Cou-*C*), 122.8 ppm (1C, Cou-*C*), 119.0 ppm (1C, Cou-*C*), 118.8 ppm (1C, Cou-*C*), 117.5 ppm (1C, Cou-*C*), 116.0 ppm (1C, Cou-*C*), 32.3 ppm (1C, Bimz-*C*H$_2$), 21.1 ppm (1C, Bimz-*C*H$_3$). ESIMS Calcd for $C_{18}H_{14}N_2O_2S$ 322.4, Found: 322.9. Anal. Calcd for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69; O, 9.93; S, 9.95. Found: C, 67.13; H, 4.26; N, 8.57; O, 9.85; S, 9.76.

3.5.3 3-((5-Nitro-1H-benzo[d]imidazol-2-ylthio)methyl)-2H-chromen-2-one, (10c)

A mixture of 3-chloromethylcoumarin **8a** (0.5 g, 2.5 mmol), 5-nitro-1H-benzo[d]imidazole-2-thiol **9c** (0.5 g, 2.5 mmol) and Cs_2CO_3 (0.16 g) in DMF (5 mL) afforded compound **10c** as a yellow solid. Yield: 0.64 g, (71%). m.p. 110-115 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 8.33 ppm (1H, Bimz-N*H*), 8.03 ppm (s, 1H, Cou-*H*), 7.99 ppm (d, *J = 3 Hz*, 1H, Bimz-*H*), 7.56-7.40 ppm (m, 4H, Cou-*H*), 7.24-7.16 ppm (m, 2H, Bimz-*H*), 4.36 ppm (s, 2H, Cou-C*H*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 165.7 ppm (1C, Cou-*C*=O), 160.2 ppm (1C, Bimz-*C*=*N*), 158.1 ppm (1C, Bimz-*C*), 147.6 ppm (1C, Bimz-*C*), 146.4 ppm (1C, Bimz-*C*), 145.8 ppm (1C, Bimz-*C*), 137.8 ppm (1C, Bimz-*C*), 136.4 ppm (1C, Bimz-*C*), 132.9 ppm (1C, Cou-*C*), 129.4 ppm (1C, Cou-*C*), 129.2 ppm (1C, Cou-*C*), 123.8 ppm (1C, Cou-*C*), 122.5 ppm (1C, Cou-*C*), 121.1 ppm (1C, Cou-*C*), 118.0 ppm (1C, Cou-*C*), 115.6 ppm (1C, Cou-*C*), 35.8 ppm (1C, Bimz-*C*H$_2$). ESIMS Calcd for $C_{17}H_{11}N_3O_4S$: 353.4, Found: 353.9. Anal. Calcd for $C_{17}H_{11}N_3O_4S$: C, 57.78; H, 3.14; N, 11.89; O, 18.11; S, 9.07. Found: C, 57.54; H, 3.07; N, 11.73; O, 18.03; S, 9.13.

3.5.4 3-((1H-Benzo[d]imidazol-2-ylthio)methyl)-8-methoxy-2H-chromen-2-one, (10d)

A mixture of 8-methoxy-3-chloromethylcoumarin **8b** (0.5 g, 2.2 mmol), 2-mercaptobenzimidazole **9a** (0.33 g, 2.2 mmol) and Cs_2CO_3 (0.14 g) in DMF (5 mL) afforded compound **10d** as a white solid. Yield 0.40 g, (61%). m.p. 128-130 ºC. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 7.92 ppm (s, 1H, Cou-*H*), 7.28-7.11 ppm (m, 4H, Bimz-*H*), 7.02-6.93 ppm (m, 3H, Cou-*H*), 4.41 ppm (s, 3H, Cou-OC*H*$_3$), 3.92 ppm (s, 2H, Cou-C*H*$_2$). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 159.9 ppm (1C, Cou-*C*=O), 146.3 ppm (1C, Bimz-*C*=*N*), 142.4 ppm (2C, Bimz-*C*), 141.5 ppm (2C, Bimz-*C*), 140.8 ppm (2C, Bimz-*C*), 136.5 ppm (1C, Cou-*C*), 123.9 ppm (1C, Cou-*C*), 123.7 ppm (1C, Cou-*C*), 122.6 ppm (1C, Cou-*C*), 119.1 ppm (1C, Cou-*C*), 118.9 ppm (1C, Cou-*C*), 113.3 ppm (1C, Cou-*C*), 113.0 ppm (1C, Cou-*C*), 55.6 ppm (1C, Cou-O*CH*$_3$), 31.3 ppm (1C, Cou-*CH*$_2$). ESIMS Calcd for $C_{18}H_{14}N_2O_3S$: 338.4, Found: 338.9. Anal. Calcd for $C_{18}H_{14}N_2O_3S$: C, 63.89; H, 4.17; N, 8.28; O, 14.18; S, 9.48. Found: C, 63.71; H, 4.09; N, 8.11; O, 14.06; S, 9.32.

3.5.5 8-Methoxy-3-((5-methyl-1H-benzo[d]imidazol-2-ylthio)methyl)-2H-chromen-2-one, (10e)

A mixture of 8-methoxy-3-chloromethylcoumarin **8b** (0.5 g, 2.2 mmol), 5-methyl-1H-benzo[d]imidazole-2-thiol 9**b** (0.36 g, 2.2 mmol) and Cs_2CO_3 (0.14 g) in DMF (5 mL) afforded compound **10e** as a white solid. Yield 0.35 g, (65%). m.p. 110-113 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 7.82 ppm (s, 1H, Cou-*H*), 7.36-7.13 ppm (m, 3H, Bimz-*H*), 7.10-6.91 ppm (m, 3H, Cou-*H*), 4.30 ppm (s, 2H, Cou-C*H*$_2$), 3.87 ppm (s, 3H, Cou-OC*H*$_3$), 2.37 ppm (s, 3H, Bimz-C*H*$_3$). ^{13}C NMR (75 MHz, $CDCl_3$,), δ_C 158.9 ppm (1C, Cou-*C*=O), 145.1 ppm (1C, Bimz-*C*=*N*), 139.6 ppm (1C, Bimz-*C*), 135.9 ppm (1C, Bimz-*C*), 132.7 ppm (1C, Bimz-*C*), 131.8 ppm (1C, Bimz-*C*), 125.8 ppm (1C, Bimz-*C*), 122.6 ppm (1C, Bimz-*C*), 117.6 ppm (1C, Cou-*C*), 115.9 ppm (1C, Cou-*C*),

113.9 ppm (1C, Cou-*C*), 113.7 ppm (1C, Cou-*C*), 112.3 ppm (1C, Cou-*C*), 111.9 ppm (1C, Cou-*C*), 111.7 ppm (1C, Cou-*C*), 110.1 ppm (1C, Cou-*C*), 54.1 ppm (1C, Cou-O*CH₃*), 30.8 ppm (1C, Cou-*CH₂*), 27.5 ppm (1C, Bimz-*CH₃*). ESIMS Calcd for $C_{19}H_{16}N_2O_3S$: 352.4, Found: 352.9. Anal. Calcd for $C_{19}H_{16}N_2O_3S$: C, 64.76; H, 4.58; N, 7.95; O, 13.62; S, 9.10. Found: C, 64.59; H, 4.37; N, 7.71; O, 13.45; S, 8.98.

3.5.6 6-Chloro-3-((5-nitro-1H-benzo[d]imidazol-2-ylthio)methyl)-2H-chromen-2-one, (10f)

A mixture of 6-chloro-3-chloromethylcoumarin **8d** (0.5g, 2.2 mmol), 5-nitro-1H-benzo[d]imidazole-2-thiol **9c** (0.43 g, 2.2 mmol) and Cs_2CO_3 (0.14 g) in DMF (5 mL) afforded compound **10f** as a yellow solid. Yield 0.67 g, (79%). m.p. 220-223 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 8.35 ppm (s, 1H, Bimz-*NH*), 8.02 ppm (d, *J = 1.8 Hz*, 1H, Bimz-*H*), 7.998 ppm (s, 1H, Cou-*H*), 7.42-7.38 ppm (m, 2H, Bimz-*H*), 7.36-7.17 ppm (m, 3H, Cou-*H*), 4.42 ppm (s, 2H, Cou-C*H₂*). ^{13}C NMR (75 MHz, $CDCl_3$,), δ_C 160.7 ppm (1C, Cou-*C*=O), 159.2 ppm (1C, Bimz-*C*=*N*), 157.2 ppm (1C, Bimz-*C*), 145.0 ppm (1C, Bimz-*C*), 142.7 ppm (1C, Bimz-*C*), 140.2 ppm (1C, Bimz-*C*), 139.6 ppm (1C, Bimz-*C*), 139.4 ppm (1C, Bimz-*C*), 130.1 ppm (1C, Cou-*C*), 129.5 ppm (1C, Cou-*C*), 128.9 ppm (1C, Cou-*C*), 128.5 ppm (1C, Cou-*C*), 127.3 ppm (1C, Cou-*C*), 125.6 ppm (1C, Cou-*C*), 125.1 ppm (1C, Cou-*C*), 118.6 ppm (1C, Cou-*C*), 34.8 ppm (1C, Bimz-*C*H2). ESIMS Calcd for $C_{17}H_{10}ClN_3O_4S$: 387.8, Found: 387.9. Anal. Calcd for $C_{17}H_{10}ClN_3O_4S$: C, 52.65; H, 2.60; Cl, 9.14; N, 10.84; O, 16.50; S, 8.27. Found: C, 52.46; H, 2.51; Cl, 9.03; N, 10.72; O, 16.39; S, 8.12.

3.5.7 3-((1H-Benzo[d]imidazol-2-ylthio)methyl)-6-bromo-2H-chromen-2-one, (10g)

A mixture of 6-bromo-3-chloromethylcoumarin **8c** (0.5 g, 1.8 mmol), 2-mercaptobenzimidazole **9a** (0.27 g, 1.8 mmol) and Cs_2CO_3 (0.12 g) in DMF (5 mL) afforded compound 10**g** as a white solid. Yield 0.55 g, (78%). m.p. 280-285 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 12.24 ppm (s, 1H, Bimz-N*H*), 7.99 ppm (s, 1H, Cou-*H*), 7.74-7.56 ppm (m, 4H, Bimz-*H*), 7.23-7.12 ppm (m, 3H, Cou-*H*), 4.42 ppm (s, 2H, Cou-C*H₂*). ^{13}C NMR(75 MHz, $CDCl_3$), δ_C 163.5 ppm (1C, Cou-*C*=O), 151.7 ppm (1C, Bimz-*C*=*N*), 142.7 ppm (2C, Bimz-*C*), 137.9 ppm (2C, Bimz-*C*), 123.2 ppm (2C, Bimz-*C*), 124.5 ppm (1C, Cou-*C*), 121.7 ppm (1C, Cou-*C*), 119.8 ppm (1C, Cou-*C*), 117.6 ppm (1C, Cou-*C*), 115.3 ppm (1C, Cou-*C*), 114.8 ppm (1C, Cou-*C*), 112.9 ppm (1C, Cou-*C*), 113.5 ppm (1C, Cou-*C*), 35.3 ppm (1C, Bimz-*C*H2). ESIMS Calcd for $C_{17}H_{11}BrN_2O_2S$: 387.3, Found: 387.9. Anal. Calcd for $C_{17}H_{11}BrN_2O_2S$: C, 52.73; H, 2.86; Br, 20.63; N, 7.23; O, 8.26; S, 8.28. Found: C, 52.27; H, 2.67; Br, 20.47; N, 7.09; O, 8.17; S, 8.19.

3.5.8 6-Bromo-3-((5-methyl-1H-benzo[d]imidazol-2-ylthio)methyl)-2H-chromen-2-one, (10h)

A mixture of 6-bromo-3-chloromethylcoumarin **8c** (0.5 g, 1.8 mmol), 5-methyl-1H-benzo[d]imidazole-2-thiol **9b** (0.3 g, 1.8 mmol) and Cs_2CO_3 (0.12 g) in DMF (5 mL) afforded compound, **10h** as a white solid. Yield 0.50 g, (67%). m.p. 275-279 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 12.05 ppm (s, 1H, Bimz-N*H*), 7.93 ppm (s, 1H, Cou-*H*), 7.66-7.56 ppm (m, 3H, Bimz-*H*), 7.50-6.99 ppm (m, 3H, Cou-*H*), 4.39 ppm (s, 2H, Cou-C*H₂*), 2.42 ppm (s, 3H, Bimz-CH_3). ^{13}C NMR (75 MHz, $CDCl_3$,), δ_C 159.7 ppm (1C, Cou-*C*=O), 151.7 ppm (1C, Bimz-*C*=*N*), 147.9 ppm (1C, Bimz-*C*), 139.1 ppm (1C, Bimz-*C*), 138.7 ppm (1C, Bimz-*C*), 133.5 ppm (1C, Bimz-*C*), 133.1 ppm (1C, Bimz-*C*), 132.7 ppm (1C, Bimz-*C*), 129.7 ppm (1C, Cou-*C*), 128.2 ppm (1C, Cou-*C*), 125.9 ppm (1C, Cou-*C*), 122.7 ppm (1C, Cou-*C*), 120.3 ppm (1C, Cou-*C*), 117.6 ppm (1C, Cou-*C*), 117.2 ppm (1C, Cou-*C*), 116.3 ppm (1C, Cou-*C*), 30.8 ppm (1C, Bimz-*C*H2), 21.1 ppm (1C, Bimz-*C*H3). ESIMS Calcd for $C_{18}H_{13}BrN_2O_2S$: 401.3, Found: 402.8. Anal. Calcd for $C_{18}H_{13}BrN_2O_2S$: C, 53.88; H, 3.27; Br, 19.91; N, 6.98; O, 7.97; S, 7.99. Found: C, 53.71; H, 3.15; Br, 19.78; N, 6.76; O, 7.81; S, 7.76.

3.5.9 6-Bromo-3-((5-nitro-1H-benzo[d]imidazol-2-ylthio)methyl)-2H-chromen-2-one, (10i)

A mixture of 6-bromo-3-chloromethylcoumarin **8c** (0.5 g, 1.8 mmol), 5-nitro-1H-benzo[d]imidazole-2-thiol **9c** (0.35 g, 1.8 mmol) and Cs_2CO_3 (0.12 g) in DMF (5 mL) afforded compound **10i** as a yellow solid. Yield 0.75 g, (95%). m.p. 224-227 °C. ^{1}H NMR (300 MHz, $CDCl_3$), δ_H 12.61 ppm (s, 1H, Bimz-N*H*), 8.17 ppm (s, 1H, Cou-*H*), 8.03-7.56 ppm (m, 3H, Bimz-*H*), 7.52-7.12 ppm (m, 3H, Cou-*H*), 4.42 ppm (s, 2H, Cou-C*H₂*). ^{13}C NMR (75 MHz, $CDCl_3$), δ_C 156.9 ppm (1C, Cou-*C*=O), 147.6 ppm (1C, Bimz-*C*=*N*), 144.8 ppm (1C, Bimz-*C*), 143.9 ppm (1C, Bimz-C), 138.9 ppm (1C, Bimz-*C*), 138.6 ppm (1C, Bimz-*C*), 136.5 ppm (1C, Bimz-*C*), 135.1 ppm (1C, Bimz-*C*), 130.6 ppm (1C, Cou-*C*), 129.2 ppm (1C, Cou-*C*), 125.4 ppm (1C, Cou-*C*), 123.8 ppm (1C, Cou-*C*), 122.9 ppm (1C, Cou-*C*), 122.7 ppm (1C, Cou-*C*), 122.3 ppm (1C, Cou-*C*), 121.8 ppm (1C, Cou-*C*), 35.6 ppm (1C, Bimz-*C*H2). ESIMS Calcd for $C_{17}H_{10}BrN_3O_4S$: 432.3, Found: 432.8. Anal. Calcd for $C_{17}H_{10}BrN_3O_4S$: C, 47.24; H, 2.33; Br, 18.49; N, 9.72; O, 14.81; S, 7.42. Found: C, 47.09; H, 2.17; Br, 18.28; N, 9.55; O, 14.69; S, 7.29.

4. Conclusion

In conclusion, we have developed an efficient and convenient method for synthesis of 3-((1H-Benzo[d]imidazol-2-ylthio)methyl)-2H-chromen-2-one derivatives. The protocol is applicable for a wide variety of substrates using commercially available starting materials. The procedure used is also well suited for library synthesis and drug discovery efforts. The short reaction time and simple purification techniques render this method particularly attractive for efficient synthesis of biologically and medicinally interesting molecules. The antimicrobial studies of coumarin coupled benzimidazole hybrids show that they exhibit selective anti-microbial activity against both plant and human pathogens even at both 25 and 50 µg.

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