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An efficient method for the synthesis of *N*-(4-halophenacyl)-2-substituted-benzo[*d*]imidazoles using PEG-400 as green reaction solvent

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ABSTRACT

In this paper, we report a green and efficient method for the synthesis of *N*-substituted benzimidazoles under grinding conditions using PEG-400 as reaction solvent at room temperature. 2-Substituted-1*H*-benzimidazole was prepared from the reaction between various aromatic aldehydes and *o*-phenylenediamine in mortar and pestle under a grinding process using NH_4Cl as catalyst in PEG-400 as green reaction solvent. Additionally, 2-substituted-1*H*- benzimidazole were treated with 4-halophenacylbromide in the K_2CO_3 / PEG system, yielding the corresponding 1-(4-fluoro/bromophenacyl)-2-susbtituted-benzo[d]imidazole (*N*-substituted benzimidazoles). This methodology incorporates inexpensive catalysts, suppressed reaction times, high yields, easy work-up, and the use of green reaction solvents are reported. All of the structures of products were established by spectroscopic and analytical methods. The IR spectra of 2-substituted-1*H*-benzimidazole (2a-e) showed the disappearance of the stretching frequency band at 1680-1695 cm^{-1} due to >C=O of aromatic aldehydes and the presence of stretching bands at 1610-1630 cm^{-1} due to -C=N stretching, which confirms the formation products. Furthermore, ^1H NMR spectra of *N*-substituted benzimidazoles (4a-j) showed the presence of a singlet at δ 6.10-6.25 ppm, indicating the presence of $-CH_2$ in the structure of the phenacyl ring. The mass spectra (EIMS) of the compounds also agree with their molecular formula.

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1. Introduction

The basic structure of 1H-benzimidazole, which serves as the core of numerous biologically active derivatives [1,2]. Benzimidazoles are widely used as key scaffolds in medicinal chemistry because their structure allows for versatile chemical modifications and strong interactions with biological targets [3]. Benzimidazole is well-known as a crucial *N*-heterocyclic core with a unique structure and safety profile. With a purine-like feature and a part of the vitamin B12 derivative, benzimidazole has a privileged substructure so it can easily interact with biopolymers to form a compatibility system for the action of biologically active compounds [4,5]. Benzimidazole-based drugs exhibit a wide range of different biological activities as a result of the change of the groups in the core structure, exhibit bactericidal [6], fungicidal [7], analgesic [8], antiviral [9], and antimicrobial [10,11] properties. Some have cardiovascular applications, while some derivatives have been synthesized and evaluated to inhibit HIV-1 infectivity [12]. Substituted benzimidazole derivatives have found commercial application in veterinarian medicine as anthelmintic agents and in various human therapeutic areas such as the treatment of ulcers and antihistaminic [13]. *N*-substituted benzimidazoles [14,15] effectively inhibited methicillin-resistant *Staphylococcus aureus* growth. Furthermore, *N*-alkylated-2-(substituted phenyl)-1*H*-benzimidazole showed a wide spectrum of antiproliferative [16], antifungal [17], and anti-bacterial agents [18]. Benzimidazole-containing compounds are a broad-spectrum antiparasitic agent recommended by the World Health Organization for clinical use in human and veterinary medicine [19,20]. Various methods [21] have been reported for the synthesis of benzimidazole derivatives with their pharmacological activities in the literature. The initial synthetic methods described in the literature have shown that *o*-phenylenediamine reacts with carboxylic acids or their derivatives [22,23]. Subsequently, synthetic methods replaced carboxylic acids with aldehydes, obtaining 2-substituted and 1,2-substituted benzimidazoles. However, these synthetic procedures showed different complications for long reaction times, under drastic conditions, and with the use of toxic solvents [24,25]. Several catalytic approaches have been developed for the synthesis of disubstituted benzimidazoles, employing catalysts such as TFE (Trifluoroethanol)/HFIP (Hexafluoroisopropanol), CuI/L-proline [26], TMS (Trimethylsilyl) [27], amberlite IR-120 [28] $SiO_2/ZnCl_2$[29], Dowex-50 W [30], SDS (Sodium dodecyl sulfate) micelles, [31],

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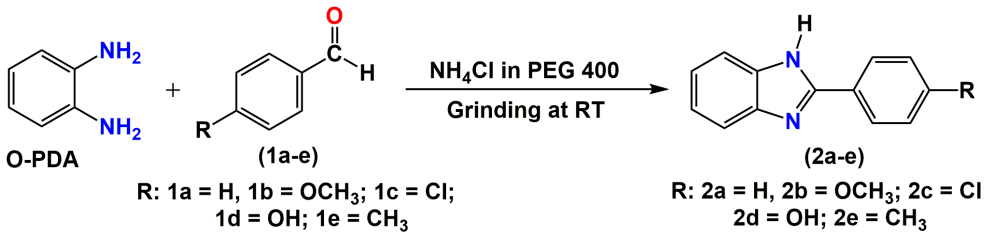
Table 1. Physical and Comparative data of synthesized of 1*H*- benzimidazole (2a-e).

Entry	R	Molecular formula	Reaction condition					
			NH_4Cl in chloroform at room temperature [43]			NH_4Cl in PEG-400 at room temperature grinding		
			Time (h)	Yield (%)	M.p. (°C)	Time (min)	Yield (%)	M.p. (°C)
2a	H	$C_{13}H_{10}N_2$	4	94	294-296	20	96	294-296 [43]
2b	OCH_3	$C_{14}H_{12}N_2O$	6	85	230-232	20	94	230-232 [43]
2c	Cl	$C_{13}H_9N_2Cl$	-	-	-	25	92	264-266
2d	OH	$C_{13}H_{10}N_2O$	6	78	272-274	25	92	272-274 [43]
2e	CH_3	$C_{14}H_{12}N_2$	6	88	278-282	22	90	278-280 [43]



Scheme 1. Synthesis of 2-substituted-1*H*- benzimidazole using NH_4Cl in PEG-400 using the grinding method at room temperature.

silica sulfuric acid [32], $FePO_4$ [33], CAN (Cerric ammonium nitrate) [34], $Cu(NO_3)_2{\cdot}3H_2O$ [35], and $FeCl_3/Al_2O_3$[36] have been reported. In many cases, the reaction shows poor selectivity in terms of *N*-1 substitution, resulting in the formation of a mixture of 1,2-disubstituted and 2-substituted benzimidazoles [37,38]. Furthermore, many of these methods suffer from one or more drawbacks such as the requirement of strong acidic conditions, long reaction times, low yields, tedious work- up procedures, the requirement of excess amounts of reagents and use of toxic reagents, catalysts, or solvents [39,40]. Therefore, there is a strong demand for a highly efficient and environmentally benign method for the synthesis of 2-substituted benzimidazoles. According to published pharmacological reports, the biological properties of the benzimidazole system were strongly influenced by substitution at positions N-1 and C-2 positions; in particular, position N-1 can positively influence the efficacy of chemotherapeutics [41,42]. As part of our research program to develop various synthetic methodologies with active biological scaffolds, we report the synthesis of *N*-substituted benzimidazoles using NH_4Cl as catalyst in PEG-400 as green reaction solvent under the one-pot grinding method under mild reaction conditions.

2. Experimental

2.1. Materials and instrumentation

All chemicals were obtained from commercial sources and used without further purification. The melting points of 1*H*-benzimidazole were determined in an open capillary tube and matched with reported literature [43]. The melting points of *N*-substituted benzimidazoles were also determined in an open capillary method and were uncorrected. Merck precoated silica gel 60 F_{254} (Aluminum sheets) plates were used for analytical thin layer chromatography (TLC). All known organic products were identified by comparing their physical and spectral data with those of authentic samples. IR spectra were recorded on a FTIR-Shimadzu spectrometer. ^{1}H NMR spectra were recorded in DMSO-d_6 on an Avance-300 MHz spectrometer using tetramethyl silane (TMS) as an internal standard. The mass spectra were recorded on an EI-Shimadzu GC-MS spectrometer. The elemental analyzes were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer. The chemicals and solvents used were purified and laboratory grade.

2.2. General procedure for the synthesis of 2-substituted-1H- benzimidazole (2a-e)

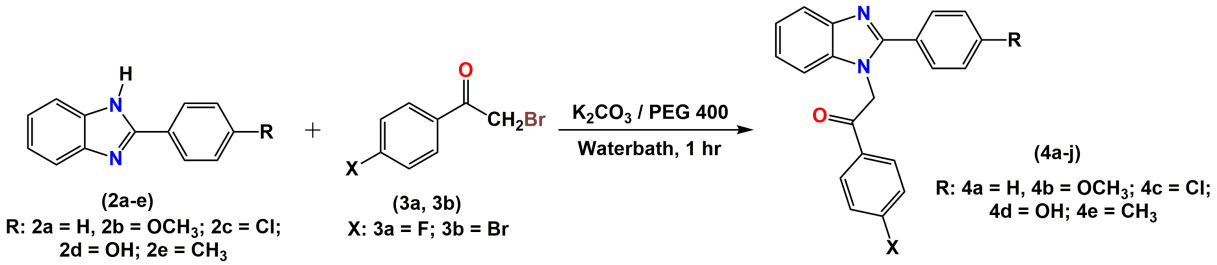
An equimolar mixture of substituted aromatic benzaldehyde (**1a**-**e**) (0.01 moles) and 1,2-phenylenediamine (0.01 moles) was taken in mortar. To this, add NH_4Cl (0.04 moles) as a catalyst and PEG-400 (5 mL) as reaction solvent. Grind the reaction mixture for 20-25 minutes as shown in Table 1 at room temperature. The completion of the reaction was monitored by TLC. After completion of the reaction, we work up with cold water. The solid product obtained was filtered and washed with water. The crude product was recrystallized from suitable solvent. The melting point and yield of the product were recorded. (Table 1, Scheme 1).

2-Phenyl-1H-benzimidazole (**2a**): Color: Pale White. Yield: 96%. M.p.: 294-296 °C. FT-IR (KBr, ν, cm^{-1}): 3426 (-NH), 3042 (Ar-CH), 1631 (-C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.06 (bs, 1H, NH), 6.82 (d, 2H, aromatic), 6.98(d, 2H, aromatic), 7.06 (t, 1H, aromatic), 7.28 (m, 2H, aromatic), 7.52 (m, 2H, aromatic). MS (EI, *m/z* (%)):194 (M^+, 100). Anal. calcd. for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42%. Found: C, 80.41; H, 5.22; N, 14.38%.

2-(4-Methoxyphenyl)-1H-benzimidazole (**2b**): Color: Yellow White. Yield: 94%. M.p.: 230-232 °C. FT-IR (KBr, ν, cm^{-1}): 3294 (-NH), 3103 (Ar-CH), 1601 (-C=N), 1186 (-OCH_3). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 3.70 (d, 3H, OCH_3), 6.12 (bs, 1H, NH), 6.94 (d, 2H, aromatic), 6.98 (d, 2H, aromatic), 7.20 (d, 2H, aromatic), 7.58 (d, 2H, aromatic). MS (EI, *m/z* (%)): 224 (M^+, 100). Anal. calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49%. Found: C, 74.95; H, 5.41; N, 12.53%.

2-(4-Chlorophenyl)-1H-benzimidazole (**2c**): Color: Yellow White. Yield: 92%. M.p.: 264-266 °C. FT-IR (KBr, ν, cm^{-1}): 3290 (-NH), 3115 (Ar-CH), 1612 (-C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.41 (bs, 1H, NH), 7.05 (d, 2H, aromatic), 6.99 (d, 2H, aromatic), 7.24 (d, 2H, aromatic), 7.65 (d, 2H, aromatic). MS (EI, *m/z* (%)): 228 (M^+, 100), 230 (M+2). Anal. calcd. for $C_{13}H_9N_2Cl$: C, 68.28; H, 3.97; N, 12.25%. Found: C, 68.31; H, 3.95; N, 12.28%.

2-(4-Hydroxyphenyl)-1H-benzimidazole (**2d**): Color: Creamy White. Yield: 92%. M.p.: 272-274 °C. FT-IR (KBr, ν, cm^{-1}): 3379 (-NH), 3211 (-OH), 3078 (Ar-CH), 1626 (-C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 6.10 (bs, 1H, NH), 6.82 (d, 2H, aromatic), 6.98 (d, 2H, aromatic), 7.21 (d, 2H, aromatic), 7.52 (d, 2H, aromatic), 10.45 (s, 1H, OH). MS (EI, *m/z* (%)): 210 (M^+, 100). Anal. calcd. for $C_{13}H_{10}N_2O$: C, 74.27; H, 4.79; N, 13.33%. Found: C, 74.31; H, 4.76; N, 13.35%.



Scheme 2. Synthesis of *N*-(4-fluoro/bromophenacyl)-2-susbtituted-benzo[d]imidazole using K_2CO_3 in PEG-400 as reaction solvent.

2-(4-Methylphenyl)-1H-benzimidazole (**2e**): Color: Pale White. Yield: 90%. M.p.: 278-280 °C. FT-IR (KBr, ν, cm^{-1}): 3346 (-NH), 3024 (Ar-CH), 2923 (-CH_3), 1598 (-C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 2.54 (d, 3H, CH_3), 6.09 (bs, 1H, NH), 6.84 (d, 2H, aromatic), 6.96 (d, 2H, aromatic), 7.18 (d, 2H, aromatic), 7.58 (d, 2H, aromatic). MS (EI, *m/z* (%)): 208 (M$^+$, 100). Anal. calcd. for $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45%. Found: C, 80.76; H, 5.83; N, 13.41%.

2.3. General procedure for the synthesis of N-(4-bromo phenacyl)-2-susbtituted-benzo[d]imidazole (4a-j)

An equimolar mixture of 2-substituted-1*H*- benzimidazole (**2a**-**e**) (0.01 mole) and 4-substituted phenacylbromide (**3a**, **3b**) (0.01 mole) was mixed in 10 mL PEG-400 as a solvent taken in 25 mL of round bottom flask. The catalytic amount of K_2CO_3 (1 g) was added into the flask. The reaction mixture was heated in a water bath for 1 hour. The completion of the reaction was monitored by TLC. After completion of the reaction, the mixture was cooled to room temperature and poured into cold water. The solid was separated and then filtered. The crude product obtained was recrystallized from suitable solvent. The yield and melting point of the product were determined (Scheme 2).

N-(4-Fluorophenacyl)-2-phenyl-1H-benzimidazole (**4a**): Color: Yellow White. Yield: 78%. M.p.: 302-304 °C. FT-IR (KBr, ν, cm^{-1}): 3051 (Ar-CH), 1670 (-CO), 1615 (-C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.28 (d, 2H, Ar-H), 7.45 (d, 2H, Ar-H), 7.15-8.15. (m, 9H, Ar-H), 6.15 (s, 2H, -CH_2). MS (EI, *m/z* (%)): 330 (M$^+$, 100). Anal. calcd. for $C_{21}H_{15}N_2OF$: C, 76.35; H, 4.58; N, 8.48%. Found: C, 76.38; H, 4.55; N, 8.51%.

N-(4-Fluorophenacyl)-2-(4-methoxyphenyl)-1H-benzimidazole (**4b**): Color: Pale Yellow. Yield: 80%. M.p.: 266-268 °C. FT-IR (KBr, ν, cm^{-1}): 3068 (Ar-CH), 1675 (-CO), 1622 (-C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.26 (d, 2H, Ar-H), 8.09 (d, 2H, Ar-H), 7.41 (d, 2H, Ar-H), 7. 26 (d, 2H, Ar-H), 7.15-7.35. (m, 4H, Ar-H), 6.16 (s, 2H, -CH_2), 3.65 (s, 3H, -OCH_3). MS (EI, *m/z* (%)): 360 (M$^+$, 100). Anal. calcd. for $C_{22}H_{17}N_2O_2F$: C, 73.32; H, 4.75; N, 7.77%. Found: C, 73.29; H, 4.78; N, 7.79%.

N-(4-Fluorophenacyl)-2-(4-chlorophenyl)-1H-benzimidazole (**4c**): Color: Yellow. Yield: 82%. M.p.: 278-280 °C. FT-IR (KBr, ν, cm^{-1}): 3065 (Ar-CH), 1672 (-CO), 1614 (-C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.22 (d, 2H, Ar-H), 8.10 (d, 2H, Ar-H), 7.51 (d, 2H-Ar-H), 7.42 (d, 2H, Ar-H), 7.22-7.38. (m, 4H, Ar-H), 6.21 (s, 2H, -CH_2). MS (EI, *m/z* (%)): 364 (M$^+$, 100), 366(M+2). Anal. calcd. for $C_{21}H_{14}ClN_2OF$: C, 69.14; H, 3.87; N, 7.68%. Found: C, 69.11; H, 3.89; N, 7.65%.

N-(4-Fluorophenacyl)-2-(4-hydroxyphenyl)-1H-benzimidazole (**4d**): Color: Light Yellow. Yield: 80%. M.p.: 256-258 °C. FT-IR (KBr, ν, cm^{-1}): 3205 (-OH), 3105 (Ar-CH), 1668 (-CO), 1620 (-C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 10.72 (s, 1H, OH), 8.16 (d, 2H, Ar-H), 7.85 (d, 2H, Ar-H), 7.46 (d, 2H, Ar-H), 7. 11 (d, 2H, Ar-H), 7.15-7.38. (m, 4H, Ar-H), 6.16 (s, 2H, -CH_2). MS (EI, *m/z* (%)): 346 (M$^+$, 100). Anal. calcd. for $C_{21}H_{15}N_2O_2F$: C, 72.82; H, 4.37; N, 8.09%. Found: C, 72.84; H, 4.35; N, 8.11%.

N-(4-Fluorophenacyl)-2-(4-methylphenyl)-1H-benzimidazole (**4e**): Color: Yellow. Yield: 76%. M.p.: 304-306 °C. FT-IR (KBr, ν, cm^{-1}): 3132, 3090 (Ar-CH), 1672 (-CO), 1622 (-C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.18 (d, 2H, Ar-H), 7.91 (d, 2H, Ar-H), 7.42 (d, 2H, Ar-H), 7. 09 (d, 2H, Ar-H), 7.16-7.35 (m, 4H, Ar-H), 6.16 (s, 2H, -CH_2), 2.38 (s, 3H, CH_3). MS (EI, *m/z* (%)): 344 (M$^+$, 100). Anal. calcd. for $C_{22}H_{17}N_2OF$: C, 76.73; H, 4.98; N, 8.13%. Found: C, 76.75; H, 4.95; N, 8.15%.

N-(4-Bromophenacyl)-2-phenyl-1H-benzimidazole (**4f**): Color: Bright Yellow. Yield: 78%. M.p.: 310-312 °C. FT-IR (KBr, ν, cm^{-1}): 3021 (Ar-CH), 1668 (-CO), 1618 (-C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.22 (d, 2H, Ar-H), 7.86 (d, 2H, Ar-H), 7.25-8.18. (m, 9H, Ar-H), 6.15 (s, 2H, -CH_2). MS (EI, *m/z* (%)): 390 (M$^+$, 100), 392 (M+2). Anal. calcd. for $C_{21}H_{15}N_2OBr$: C, 64.47; H, 3.86; N, 7.16%. Found: C, 64.45; H, 3.88; N, 7.19%.

N-(4-Bromophenacyl)-2-(4-methoxyphenyl)-1H-benzimidazole (**4g**): Color: Light Yellow. Yield: 76%. M.p.: 246-248 °C. FT-IR (KBr, ν, cm^{-1}): 3077 (Ar-CH), 1671 (-CO), 1628 (-C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.12 (d, 2H, Ar-H), 7.81 (d, 2H, Ar-H), 7.38 (d, 2H, Ar-H), 7. 16 (d, 2H, Ar-H), 7.11-7.31 (m, 4H, Ar-H), 6.11 (s, 2H, -CH_2), 3.65 (s, 3H, -OCH_3). MS (EI, *m/z* (%)): 420 (M$^+$, 100). 422 (M+2). Anal. calcd. for $C_{21}H_{17}N_2O_2Br$: C, 62.72; H, 4.07; N, 6.65%. Found: C, 62.75; H, 4.09; N, 6.62%.

N-(4-Bromophenacyl)-2-(4-chlorophenyl)-1H-benzimidazole (**4h**): Color: Yellowish. Yield: 82%. M.p.: 284-286 °C. FT-IR (KBr, ν, cm^{-1}): 3056 (Ar-CH), 1675 (-CO), 1605 (-C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.15 (d, 2H, Ar-H), 7.88 (d, 2H, Ar-H), 7.41 (d, 2H, Ar-H), 7. 11 (d, 2H, Ar-H), 7.08-7.28 (m, 4H, Ar-H), 6.15 (s, 2H, -CH_2). MS (EI, *m/z* (%)): 424 (M$^+$, 100), 426 (M+2). Anal. calcd. for $C_{21}H_{14}N_2OClBr$: C, 59.25; H, 3.31; N, 6.58%. Found: C, 59.22; H, 3.34; N, 6.55%.

N-(4-Bromophenacyl)-2-(4-hydroxyphenyl)-1H-benzimidazole (**4i**): Color: Pale Yellow. Yield: 80%. M.p.: 268-270 °C. FT-IR (KBr, ν, cm^{-1}): 3195 (-OH), 2998 (Ar-CH), 1656 (-CO), 1610 (-C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 10.35 (s, 1H, OH), 8.21 (d, 2H, Ar-H), 7.92 (d, 2H, Ar-H), 7.35 (d, 2H, Ar-H), 7. 15 (d, 2H, Ar-H), 7.11-7.35 (m, 4H, Ar-H), 6.08 (s, 2H, -CH_2). MS (EI, *m/z* (%)): 406 (M$^+$ ion), 408(M+2). Anal. calcd. for $C_{21}H_{15}N_2O_2Br$: C, 61.93; H, 3.71; N, 6.88%. Found: C, 61.95; H, 3.73; N, 6.85%.

N-(4-Bromophenacyl)-2-(4-methylphenyl)-1H-benzimidazole (**4j**): Color: Light Yellow. Yield: 75%. M.p.: 298-300 °C. FT-IR (KBr, ν, cm^{-1}): 3126, 3085 (Ar-CH), 1670 (-CO), 1616 (-C=N). ^{1}H NMR (300 MHz, DMSO-d_6, δ, ppm): 8.18 (d, 2H, Ar-H), 7.88 (d, 2H, Ar-H), 7.42 (d, 2H, Ar-H), 7. 18 (d, 2H, Ar-H), 7.12-7.38 (m, 4H, Ar-H), 6.15 (s, 2H, -CH_2), 2.41 (s, 3H, CH_3). MS (EI, *m/z* (%)): 404 (M$^+$ ion), 406(M+2). Anal. calcd. for $C_{22}H_{17}N_2OBr$: C, 65.20; H, 4.23; N, 6.91%. Found: C, 65.23; H, 4.21; N, 6.93%.

3. Results and discussion

Replacement of toxic solvents with environmentally benign solvents is the broad focus area of green chemistry. The utility of alternative reaction solvents, including water [44], ionic liquid [45], supercritical media [46], and polyethylene glycol (PEG) [47,48], is growing rapidly. Numerous green and sustainable methodologies for the synthesis of benzimidazole derivatives are reported in the literature [49-52].

Table 2. Physical and analytical data of the synthesized *N*-(4-fluoro / bromophenacyl)-2-susbtituted-benzo [d]imidazole (**4a-j**).

Entry	R	X	Molecular formula	Yield (%)	M.p. (°C)
4a	H	F	$C_{21}H_{15}N_2OF$	78	302-304
4b	OCH_3	F	$C_{22}H_{17}N_2O_2F$	80	266-268
4c	Cl	F	$C_{21}H_{14}ClN_2OF$	82	278-280
4d	OH	F	$C_{21}H_{15}N_2O_2F$	80	256-258
4e	CH_3	F	$C_{22}H_{17}N_2OF$	76	304-306
4f	H	Br	$C_{21}H_{15}N_2OBr$	78	310-312
4g	OCH_3	Br	$C_{22}H_{17}N_2O_2Br$	76	246-248
4h	Cl	Br	$C_{21}H_{14}N_2OClBr$	82	284-286
4i	OH	Br	$C_{21}H_{15}N_2O_2Br$	80	268-270
4j	CH_3	Br	$C_{22}H_{17}N_2OBr$	75	298-300

Recently, liquid polymers have emerged as an alternative green reaction media in organic synthesis. Polyethylene glycol (PEG-400) has attracted attention toward organic chemists because of its solvating ability and aptitude to act as a phase transfer catalyst, negligible vapor pressure, easy recyclability, ease of workup, and eco-friendly nature. Continuing our studies on the development of new, selective and environmentally friendly methodologies using PEG-400 as a reaction solvent [53-57] for the preparation of biologically active compounds, herein, we report the applications of polyethylene glycol-400 (PEG-400) as an efficient and green reaction medium for the synthesis of *N*-substituted benzimidazoles using NH_4Cl under the one-pot grinding method at mild reaction conditions. Initially, we started the synthesis of 2-substituted-1*H*-benzimidazole in chloroform using reported method [43]. The time required for the completion of the reaction was 4-5 h. To minimize the reaction time and for better yields, we proceed the reaction of o-phenylene diamine (o-PDA) with benzaldehyde as model reaction using NH_4Cl as catalyst in polyethylene glycol-400 (PEG-400) as reaction solvent under the grinding method at room temperature, as shown below. The progress of the reaction mixture was monitored by thin layer chromatography (TLC). The product was formed and isolated in 20 minutes with an excellent yield (96%). After optimizing the reaction condition, all other substituted derivatives were also synthesized by the same procedure as represented in Scheme 1. Substitution and physicochemical data of synthesized compounds are shown in Table 1.

The 2-substituted-1*H*- benzimidazole formed treated with p-fluoro or bromo phenacylbromide in the presence of K_2CO_3 / PEG under mild heating conditions yielded 1- (4-bromo / fluoro phenacyl) -2-susbtituted-benzo [d]imidazole. 4-Substituted phenacyl bromide (3) was prepared by the method previously reported [58] with good yield. Now, various 2-substituted-1*H*-benzimidazoles (2a-e) were reacted with 4-bromophenacyl bromide (3) using K2CO3 in presence of PEG-400 as the reaction green reaction solvent under heating conditions to give the corresponding 1-(4-Fluoro/bromophenacyl)-2-substituted-benzo[*d*]imidazoles (4a-j) as represented in Scheme 2. The various substitution and physicochemical data of synthesized *N*-(4-bromophenacyl)-2-susbtituted-benzo[*d*]imidazole compounds are shown in Table 2.

All of the structures of products were established by spectroscopic and analytical methods. The IR spectra of all 2-substituted-1*H*- benzimidazole (2a-e) showed disappearance of stretching frequency band at 1680-1695 cm^{-1} due to >C=O of aromatic aldehydes and presence of stretching bands at 1610-1630 cm^{-1} due to -C=N stretching, which confirms the formation products. The ^1H NMR spectra of the compounds (2a-e) showed the broad signal at δ6.05-6.41 ppm indicating the presence of -NH in 1*H*-benzimidazole. The spectroscopic characterization (IR, NMR & Mass) data of 1*H*-benzimidazoles were compared with the reported literature [43] and found to be consistent with the reported data. Furthermore, the newly formed *N*-(4-fluoro/bromophenacyl)-2-susbtituted-benzo[d]imidazoles were also confirmed by spectroscopic methods. The IR spectra of all *N*-substituted benzimidazoles (4a-j) showed characteristic stretching bands at 1665-1675 cm^{-1} revealing the confirmation of presence of >C=O in the structure of the *N*-substituted 4-fluoro / bromophenacyl ring. The ^1H NMR spectra of the compounds (4a-j) showed presence of singlet at δ6.10-6.25 ppm indicating the presence of -CH_2 in the phenacyl ring structure. The absence of broad signals of -NH also confirms the formation of N-substituted compounds. The phenolic proton appeared as a singlet near δ10.5-11.5, while other aromatic and aliphatic protons were observed in the regions excepted. The mass spectra (EIMS) of compounds were also in agreement with their molecular formula.

4. Conclusions

In summary, here we report a simple and green method for the synthesis of *N*-(4-fluoro/bromophenacyl)-2-susbtituted-benzo[d]imidazoles derivatives under mild reaction conditions. Initially, 2-substituted-1*H*- benzoimidazole was prepared from the reaction between various aromatic aldehydes and *o*-phenylenediamine using NH_4Cl as catalyst in PEG-400 as reaction solvent under the grinding method at room temperature is described. Further, 2-substituted-1*H*- benzimidazole was treated with 4-fluoro/bromo phenacylbromide in the K_2CO_3/PEG-400 reaction system, yielding the corresponding 1-(4-fluoro/bromophenacyl)-2-substituted-benzo[d] imidazoles (*N*-substituted benzimidazoles). This present methodology incorporates inexpensive catalyst, suppressed reaction time, high yields, with easy work-up, and the application of PEG as a green reaction solvent is reported.

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CRediT authorship contribution statement

Conceptualization: Shankaraiah Guruvaiah Konda; Methodology: Sadashiv Sahebrao Nagre, Saket Dattatray Jore, Rupali Dattatray Jeughale; Software: Sanket Dattatray Jore, Rupali Dattatray Jeughale; Validation: Shankaraiah Guruvaiah Konda; Formal Analysis: Sanket Dattatray Jore, Rupali Dattatray Jeughale; Investigation: Sadashiv Sahebrao Nagre; Resources: Rupali Dattatray Jeughale, Sanket Jore; Data Curation: Sanket Dattatray Jore, Rupali Dattatray Jeughale; Writing - Original Draft: Sadashiv Sahebrao Nagre, Shankaraiah Guruvaiah Konda; Writing - Review and Editing: Shankaraiah Guruvaiah Konda, Sadashiv Sahebrao Nagre; Visualization: Sadashiv Sahebrao Nagre; Supervision: Shankaraiah Guruvaiah Konda; Project Administration: Sadashiv Sahebrao Sahebrao Nagre, Shankaraiah Guruvaiah Konda.

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