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Metal-free selective synthesis of 2-substituted benzimidazoles catalyzed by Brönsted acidic ionic liquid: Convenient access to one-pot synthesis of *N*-alkylated 1,2-disubstituted benzimidazoles

Warapong Senapak [a], Rungnapha Saeeng [a], Jaray Jaratjaroonphong [a], Vinich Promarak [b], Uthaiwan Sirion [a, *]

[a] Department of Chemistry and Center of Excellence for Innovation in Chemistry, Faculty of Science, Burapha University, Sangsook, Chonburi 20131, Thailand
[b] School of Molecular Science and Engineering, Vidyasirimedhi Institute of Science and Technology (VISTEC), Wangchan Valley, Wangchan, Rayong 21210, Thailand

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ABSTRACT

A novel efficient method for the selective synthesis of 2-substituted benzimidazoles is described through condensation reaction of *o*-phenylenediamines with a wide rang of aliphatic, aromatic and hetero-aromatic aldehyde substrates using Brönsted acidic ionic liquid as a reusable catalyst under metal-free conditions at ambient temperature. Notably, Dodecylimidazolium hydrogen sulfate ([DodecIm][HSO_4]) is the most efficient catalyst for good to excellent yields of the corresponding products (up to 98%). Subsequently, this protocol was successfully applied for the preparation of *N*-alkylated 1,2-disubstituted benzimidazoles in high to excellent yields *via* sequential one-pot reaction. In addition, catalysts are recycled at least four times without significant loss in activity.

1. Introduction

Benzimidazole is a diverse and important heterocyclic compound in medicine [1,4] and material science [2] (Fig. 1). It is also a useful building block in the preparation of versatile synthetic organic compounds [3,4d,4f,4i]. Numerous benzimidazole derivatives contribute to a pool of inhibitory biological activities [1,3b,4].

Synthetic methods of preparing benzimidazoles have frequently employed two pathways. One includes a coupling reaction of 2-haloanilides and their derivatives *via* transition-metal-catalyzed intramolecular cyclization [5]. A second employs a condensation reaction of *o*-phenylenediamine with a variety of carbonyl-containing molecules and their derivatives such as aldehydes [6], ketones [7] acid chlorides [8], carboxylic acids [4e,9], esters [10], β-ketoesters [11a-b], β-diketones [11c-d], orthoesters [12] and alcohols [13]. The latter method is a more convenient and easy procedure in terms of operation and commercial availability of materials and catalysts. However, this method generally provides products as a mixture of 2-substituted and symmetrical 1,2-disubstituted benzimidazoles through different mechanism pathways [6e,6h,6k] (Scheme 1) because of non-regioselective of amino

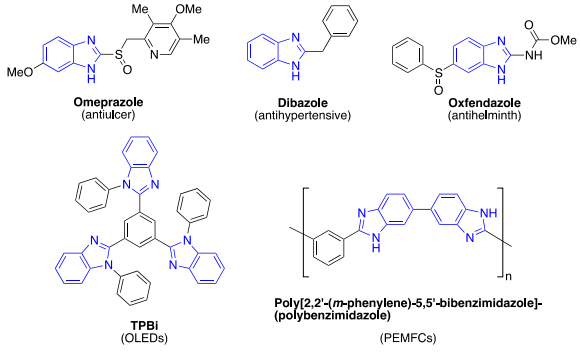

Fig. 1. Example of important benzimidazoles.

* Corresponding author.
E-mail address: uthaiwan@buu.ac.th (U. Sirion).

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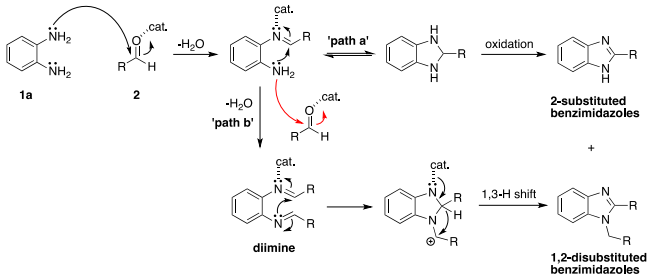


Scheme 1. General mechanism pathways for formation of 2-substituted benzimidazole (pathway a) and 1,2-disubstituted benzimidazole (pathway b).

groups on a benzene ring of *o*-phenylenediamine (**1a**), whereas 2-substituted benzimidazole could be obtained as a sole product in the presence of oxidative agents (Scheme 1, path a) [6h,6j,6r-v]. Among these products, 2-substituted benzimidazoles are more useful in several applications and as intermediates in the preparation of versatile *N*-alkylated 1,2-disubstiuted benzimidazoles [1–4]. Therefore, the search for a novel and efficient strategy for a highly selective synthesis of 2-substituted benzimidazoles *via* simple condensation of *o*-phenylenediamine with a variety of aldehydes without harsh oxidants becomes more of a challenge for chemists.

Catalytic systems toward condensation of *o*-phenylenediamine with various aldehydes for the preparation of 2-substituted benzimidazoles have been reported often with Brönsted and Lewis acids, especially, transition-metal (TM) catalysts such as $Fe(HSO_4)_3$ [6a], $Cu_{3/2}PMo_{12}O_{40}/SiO_2$ [6b], CuO-nanoparticle [6c], Pt@TiO_2 nanoparticle [6d], $SiO_2/ZnCl_2$ [6e], $Zn(OTf)_2$ [6f], $In(OTf)_3$ [6g], $Sc(OTf)_3$ [6h], $TiCl_3OTf$ [6i], CAN [6j], $Bi(NO_3)_3$ [6k], $VOSO_4$ [6l], $LaCl_3$ [6m], SDS [6n], DBSA [6o], $K_2S_2O_8$-$CuSO_4$ [6p] and recently ZnO nanoparticles using a ball-milling technique [6q]. Although most of these catalysts are quite satisfactory, some have serious drawbacks such as unstable, difficult to use, less selective and expensive. In particular, they are not reusable and are considered environmental toxicants. At present, green and metal-free reactions and reusable catalysts are highly desirable for the preparation of pharmaceutical and important biological compounds. Therefore, some attempts have been made to synthesize selective 2-substituted benzimidazoles without metals and/or with reusable catalysts [6e,6n,6t,6w,6x,6y,8a,9a,10a,12a]. However, this still requires harsh conditions such as toxic oxidizing agents, high temperature, microwave radiation, strong acid or base and/or long reaction times.

Brönsted acidic ionic liquids (BAILs) [14–23] have received considerable attention as potential catalysts for acid-promoted organic reactions, as they have been identified as eco-friendly compounds as well as being nontoxic and reusable. To date, many versatile and successful organic reactions have been reported using BAILs as catalysts such as esterification [15], Mannich reaction [16], nitration [17], Beckmann rearrangement [18], Friedlander reaction [19], Michael addition reaction [20] and Friedel-Crafts reaction [21]. In 2010, acidic ionic liquid, [MBsIm][HSO_4], was employed as a catalyst for the synthesis of symmetrical 1,2-disubstituted benzimidazoles (**4**) through condensation of *o*-phenylenediamine with aromatic aldehydes, and 2-substituted benzimidazole was not formed under this condition [22]. Herein, we present an efficient method for the synthesis of selectively 2-substituted benzimidazoles (**3**) *via* condensation of *o*-phenylenediamines (**1**) with a variety of aliphatic, aromatic and heteroaromatic aldehydes (**2**) using Brönsted acidic ionic liquid (BAIL) as a reusable catalyst under metal-free conditions at ambient temperature in a short reaction time. Furthermore, this protocol was utilized for the preparation of *N*-alkylated 1,2-disubstituted benzimidazoles (**5**) in sequential one-pot two-step process (Scheme 2).

2. Results and discussion

A series of BAILs (**I-V**) based-alkylimidazonium cation (Fig. 2) was prepared according to our previous report [21a] (see supporting information) and explored as reusable catalysts for this protocol.

The synthesis of 2-substituted benzimidazole (**3a**) from *o*-phenylenediamine (**1a**, 1.2 mmol) and benzaldehyde (**2a**, 1.0 mmol) was initially investigated using 20 mol% of acidic ionic liquid-based dodecylimidazolium salts (**I**, **II**, and **III**) in 95% EtOH (20 mL) at room temperature for 3.0 h (Table 1, entries 1–3). The highest yield of the desired product (**3a**) was 98% with catalyst **III**, which consists of HSO_4 anion (entry 3). Lower yields were found in the case of *p*TSA and OTf anions (73 and 86%, respectively) and also generated undesired product (**4a**) in amounts of 10 and 14%, respectively (entries 1 and 2). These results suggest that the counteranion plays the critical role in this protocol [23]. HSO_4 anion exhibited excellent catalytic activity, providing the highest yield of the desired product (**3a**) and better than *p*TSA and OTf anions. Under the same condition, further imidazolium ionic liquids bearing butylsulfonic acid with HSO_4 anion (**IV** and **V**) were investigated as catalysts (entries 4 and 5). Both catalysts **IV** and **V** gave lower yields of the desired product (**3a**) than catalyst **III**. This indicated that acidic ionic liquid with long alkyl-chain on imidazolium cation was a more effective catalyst in facilitating selectively 2-substituted benzimidazole

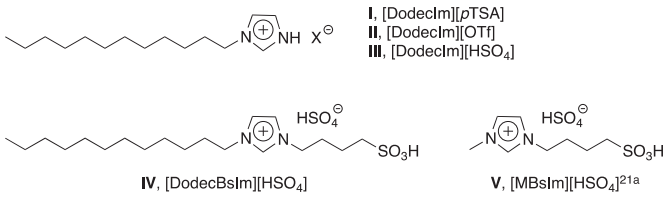
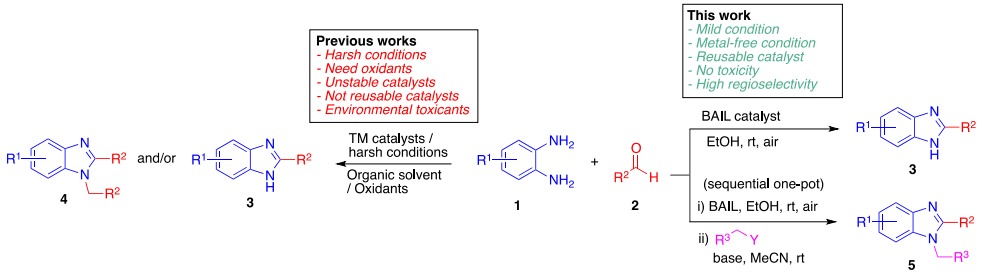
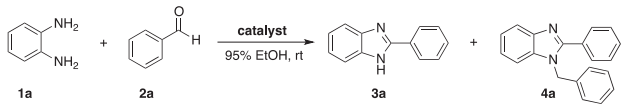


Fig. 2. Brönsted acidic ionic liquids (BAILs).



Scheme 2. Strategies for the synthesis of benzimidazoles.

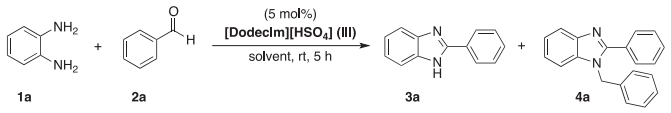
Table 1
Optimization of selective synthesis of 2-substituted benzimidazole.[a]



Entry	Catalyst (mol%)	Solvent (mL)	Time (h)	Yield (%)[b]	
				3a	4a
1	**I** (20)	20	3.0	173	14
2	**II** (20)	20	3.0	86	10
3	**III** (20)	20	3.0	98	0
4	**IV** (20)	20	3.0	78	6
5	**V** (20)	20	3.0	12	0
6	**III** (10)	20	4.0	98	0
7	**III** (5)	20	6.0	98	0
8	**III** (5)	5.0	5.0	98	0
9	**III** (5)	1.0	4.0	83	6
10[c]	**III** (5)	5.0	5.0	85	9
11	H_2SO_4 (5)	5.0	5.0	72	13
12	–	5.0	5.0	68	5

[a] All reactions were conducted with *o*-phenylenediamine (**1a**, 1.2 mmol), benzaldehyde (**2a**, 1.0 mmol), catalyst (5–20 mol%), 95% EtOH (1–20 mL), room temperature for 3–6 h.
[b] Isolated yield.
[c] 1:1 mmol of **1a:2a**.

Table 2
Optimization with various solvent.[a]



Entry	Solvent	Yield (%)[b]	
		3a	4a
1	95% EtOH	98	0
2	99% EtOH	92	0
3	MeOH	73	12
4	H_2O	27 (50)[c]	trace (20)[c]
5	DMF	85	0
6	DMSO	82	trace
7	DCM	30	0
8	DCE	28	0
9	MeCN	25	0
10	[BMIm][Br]	26	11
11	toluene	0	0
12	1,4-Dioxane	0	0
13	THF	0	0

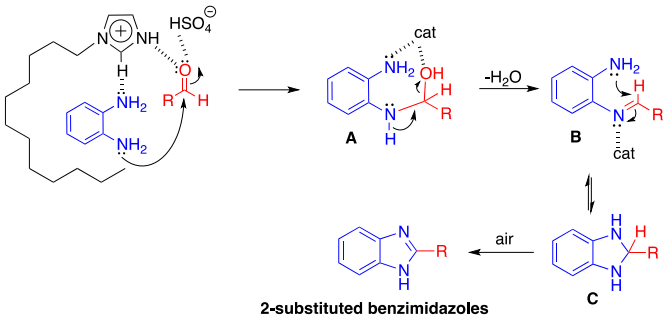
[a] All reactions were conducted with *o*-phenylenediamine (**1a**, 1.2 mmol), benzaldehyde (**2a**, 1.0 mmol), 5 mol% of [DodecIm][HSO_4] (**III**) (5 mol%), solvent (5.0 mL), room temperature for 5 h.
[b] Isolated yield.
[c] 1:2 mmol of **1a:2a**.

formation. Subsequently, the effectiveness of catalyst **III** was examined in decreasing amounts (5 and 10 mol%) resulting the yield of desired product (**3a**) retained being highest (98%) with slightly longer reaction times (entries 6–7). Notably, 5 mol% of catalyst **III** with highly concentrated reaction volume (5 mL of 95% EtOH) produced desired product (**3a**) in the same 98% yield after 5 h (entry 8). While a reduction of 95% EtOH volume to 1.0 mL gave the desired product in lower yield (83%) and generated undesired product (**4a**) in 6% (entry 9). Unfortunately, when *o*-phenylenediamine (**1a**) was reduced to 1.0 mmol, desired product yield (**3a**) declined to 85% and generated undesired product (**4a**) in 9% yield (entry 10). Therefore, the condition for this protocol was chosen with 5 mol% of catalyst **III** in 5.0 mL of 95% EtOH for 5 h (entry 8). In addition, the control reaction was treated with general H_2SO_4 acid under the best condition and found to give lower yields of the desired product (**3a**) in 72% and undesired product (**4a**) in 14% (entry 11). Whereas, the reaction without a catalyst (entry 12) provided a yield below that with catalyst **III**, 68% of the desired product (**3a**) and 5% of undesired product (**4a**).

Under the best condition (Table 1, entry 8), further screening was conducted with various solvents (Table 2). High yields of desired product (**3a**) were obtained with polar and protic solvents such as EtOH, MeOH, DMF and DMSO (entries 1–6), except water that gave low yields due to solubility difficulties with organic molecules (entry 4) due to solubility difficulties with organic molecules (entry 4). In contrast, less polar solvents such as DCM, DCE and MeCN, including ionic liquid ([BMIm][Br]) produced unsatisfactory yields (<30%) of the desired product (**3a**, entries 7–10). No product (**3a**) was obtained in the case of toluene, 1,4-dioxane and THF solvents (entries 11–13) indicating their influence on the protocol in contrast to 95% EtOH, the best solvent in terms of yield of desired product (**3a**).

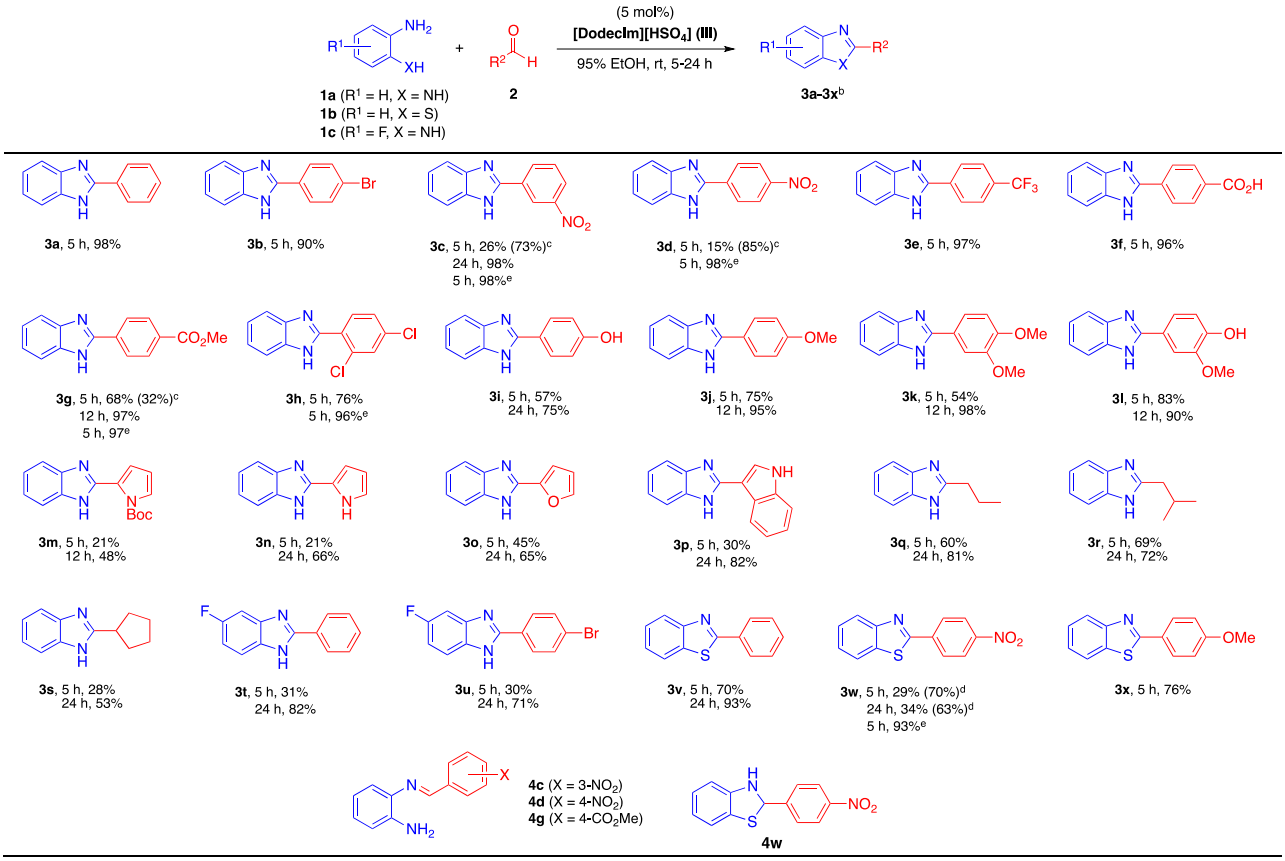
Compared to previous report [22], when a reaction of diamine (**1a**) and aldehyde (**2a**) was conducted with a ratio of 1:2 mmol in water media, yield of undesired product (**4a**) was increased to 20% and the target product (**3a**) was obtained in 50% yield (entry 4, in parentheses) which was in contrary to previous method that compound (**4a**) was afforded as the sole product. These results confirmed that the stoichiometry of diamine and aldehyde played an important role for this reaction; excess aldehyde substrate could lead to the undesired product (**4a**) through the formation of the diimine intermediate (Scheme 1). In addition, trace amount of the diimine was also observed when the reactions were carried out in MeOH, DMSO and [BMIm][Br] (entries 3, 6 and 10). It should be noted that this protocol could prevent the diimine formation probably due to the crucial structure of BAILs as proposed in the mechanism (Scheme 3).

A plausible mechanism for selective synthesis of 2-substituted benzimidazole *via* condensation of *o*-phenylenediamine with aldehydes catalyzed by acidic ionic liquid ([DodecIm][HSO_4]) is proposed in Scheme 3. The effect of catalyst **III** is to force both hydrophobic substrates to become close to the hydrophobic core of the catalyst allowing the reaction to take place more easily. Then hydrophilic imidazolium salt acts as a Brönsted acid to activate aldehyde substrate by coordination at the oxygen atom. On the other hand, amino group of *o*-phenylenediamine is cooperatively coordinated with 2*H*-imidazolium salt *via* hydrogen bonding [13b,13d], this might allow only one side of an amino group to attack an activated aldehyde to form an intermediate **A**, followed by dehydration to form an intermediate **B**. Finally, cyclization to form



Scheme 3. Plausible mechanism for selective synthesis of 2-substituted benzimidazole using [DodecIm][HSO_4] (**III**) as catalyst.

Table 3
Synthesis of 2-substituted benzimidazoles and benzothiazoles with various substances.[a]



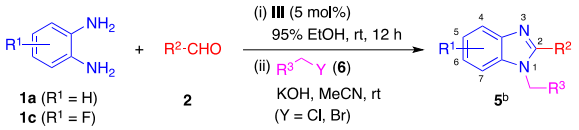
[a]All reactions were conducted with aniline (**1**, 1.2 mmol), aldehyde (**2**, 1.0 mmol), [DodecIm][HSO_4] (**III**) (5 mol%), 95% EtOH (5.0 mL), room temperature for 5-24 h. [b]Relative yields were reported as isolated yields. [c]Imine intermediate (**4c**, **4d** and **4g**). [d]Benzothiazole intermediate (**4w**). [e]60°C.

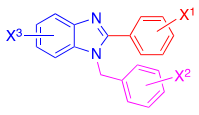
intermediate **C** and oxidation in air provide the corresponding 2-substituted benzimidazoles.

Recycling performance of catalyst **III** was examined with benzaldehyde as substrate. After the first run (Table 1, entry 8), 95% EtOH solvent was removed by evaporation. Catalyst **III** was recovered by simple extraction with water (3 × 2 mL) and the combined water layer was removed leaving catalyst **III**. Recovered catalyst **III** was reused, giving similar yields of the desirable product (**3a**) in 98, 98, 96 and 93% respectively, even after four cycles. NMR analysis confirmed reused catalyst **III** retained its structure.

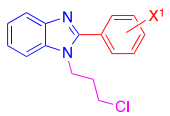
A variety of either aromatic and aliphatic aldehyde substrates were evaluated employing the best condition (Table 1, entry 8). Corresponding products were achieved in good to excellent yields depending on electronic and steric effects of aldehyde substrates (Table 3). Aromatic aldehyde substrates with electron withdrawing substituents, including benzaldehyde produced excellent yields of products **3a** (98%), **3b** (90%), **3e** (97%) and **3f** (96%). While poor solubility groups (-NO_2 and -CO_2Me) on aromatic aldehydes gave lower yield of products **3c** (26%) **3d** (15%) and **3g** (68%) along with imine intermediates (**4c**, **4d** and **4g**) and yield of **3c** improved to excellent yield (98%) when the reaction time was increased to 24 h. A sterically hindered group at *ortho*-position on benzene ring of benzaldehyde reduced the yield of **3h** to 76%. However **3c**, **3d**, **3g** and **3h** improve to excellent yields (96–98%) at an elevated reaction temperature (60 °C). Aromatic aldehyde substrates with electron donating substituents provided moderate yields of products **3i** (57%) and **3k** (54%) and high yields of products **3j** (75%) and **3l** (83%). Highest yields of these products **3i**-**3l** were isolated with prolonged reaction times, 12 h for products **3j**, **3k** and **3l** (90–98%) and 24 h for product **3i** (75%). Heteoaromatic aldehyde substrates were also successfully incorporated using this protocol. Although *N*-Boc-pyrrole-2-carbaldehyde and pyrrole-2-carbaldehyde gave equally low yield (21%) of products **3m** and **3n** with 5 h of reaction time, but yields were increased to 48% of product **3m** after 12 h and 66% of product **3n** after 24 h. While furan-2-carbaldehyde and indole-3-carbaldehyde, which are more reactive heteroaromatic aldehydes, gave higher in acceptable yields of products **3o** (45%) and **3p** (30%) after 5 h, and good yields were performed after 24 h (**3o**, 65% and **3p**, 82%). Interestingly, aliphatic aldehyde substrates also work well using this protocol and gave satisfactory product yields of **3q** (60%) and **3r** (69%), and increased to high yields (81 and 72%, respectively) after 24 h. Indeed, aliphatic aldehyde with a sterically hindered cyclopentanecarbadehyde provided in slightly low yield of product **3s** (28%) and could enhanced to moderate yield (53%) after 24 h. For these aliphatic aldehyde substrates, we found that no any aldol product was observed even long reaction time (24 h). The reactions proceeded slowly; aliphatic aldehyde substrates were remained after reaction (5 h) and observed in trace amount with prolonged reaction time (24 h). Furthermore, 2-amino-4-fluoroaniline (**1c**) was employed as substrate, produced low yields of products **3t** (31%) and **3u** (30%) due to low reactivity of substrate that bear electron-withdrawing fluorine atoms on benzene rings, however yields could be increased (82 and 71%, respectively) after 24 h. In addition, the formation of

Table 4
Sequential one-pot synthesis of *N*-alkylated 1,2-disubstituted benzimidazoles.[a]

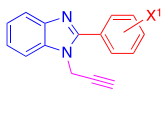




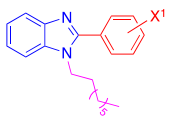
5a (X^1 = H; X^2 = *p*-NO_2; X^3 = H), 0.5 h, 82%
5b (X^1 = H; X^2 = *p*-F; X^3 = H), 0.5 h, 94%
5c (X^1 = H; X^2 = *m*-OMe; X^3 = H), 0.5 h, 98%
5d (X^1 = *p*-Br; X^2 = H; X^3 = H), 1.0 h, 89%
5e (X^1 = *p*-OMe; X^2 = H; X^3 = H), 1.0 h, 77%
5f (X^1 = *p*-CF_3; X^2 = H; X^3 = H), 1.0 h, 89%
5g (X^1 = *p*-Br; X^2 = *m*-OMe; X^3 = H), 1.0 h, 98%
5h (X^1 = *m*,*p*-di-OMe; X^2 = *p*-NO_2; X^3 = H), 2.0 h, 77%
5i (X^1 = *o*,*p*-di-Cl; X^2 = *m*-OMe; X^3 = H), 2.0 h, 98%
5ja (X^1 = *p*-OMe; X^2 = *m*-OMe; X^3 = 5-F), 1.0 h, 41%
5jb (X^1 = *p*-OMe; X^2 = *m*-OMe; X^3 = 6-F), 1.0 h, 39%
5ka (X^1 = *p*-Br; X^2 = H; X^3 = 5-F), 1.0 h, 45%
5kb (X^1 = *p*-Br; X^2 = H; X^3 = 6-F), 1.0 h, 49%



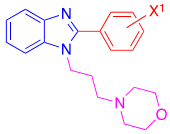
5l (X^1 = H), 48 h, 84%
5m (X^1 = *p*-Br), 24 h, 83%
5n (X^1 = *p*-OMe), 24 h, 95%



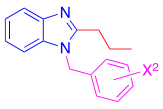
5o (X^1 = H), 3 h, 90%
5p (X^1 = *p*-CF_3), 2 h, 84%



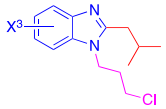
5q (X^1 = H), 48 h, 98%
5r (X^1 = *p*-Br), 24 h, 77%
5s (X^1 = *p*-OMe), 24 h, 80%



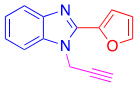
5t[c] (X^1 = H), 15 h, 98%
5u[c] (X^1 = o,*p*-di-Cl), 15 h, 85%



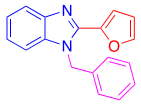
5v (X^2 = H), 1.0 h, 73%
5w (X^2 = *p*-F), 1.0 h, 66%



5xa (X^3 = 5-F), 4.0 h, 35%
5xb (X^3 = 6-F), 4.0 h, 34%



5y, 1.0 h, 74%



5z, 2 h, 65%

[a](i) *o*-phenylenediamine (**1a**, 1.2 mmol) or 2-amino-4-fluoroaniline (**1c**, 1.2 mmol), aldehyde (**2**, 1.0 mmol), [DodecIm][HSO_4] (**III**, 5 mol%), 95% EtOH (5 mL), room temperature for 12 h. (ii) alkyl bromide (**6**, 2.0 mmol), KOH (2.0 mmol), MeCN (5 mL), room temperature for 0.5-24 h. [b]Isolated yield. [c](ii) alkyl chloride (**6**, 2.0 mmol), KOH (2.0 mmol), MeCN (5 mL), TBAI (20 mol%), rt-60°C for 15 h.

benzothiazoles was also explored using this protocol, providing high yields of products **3v** (70%) and **3x** (76%) after 5 h, while excellent yield of **3v** (93%) was obtained after 24 h. Similar result was observed with *para*-nitrobenzaldehyde substrate that provided relatively low yield of product **3w** and generated benzothiazoline intermediate **4w** even prolonged reaction time (24 h) due to poor solubility of substrate and intermediate. However high reaction temperature could improve solubility and provided excellent yields of product **3w** in 93% yield.

Subsequently, synthetic application of this protocol was investigated for the preparation of *N*-alkylated 1,2-disubstituted benzimidazoles (**5**) *via* a sequential one-pot two-step procedure (Table 4). A reactive amino group on 2-substituted benzimidazoles (**3**) could be constructed with several functional groups to generate versatile *N*-alkylated 1,2-disubstituted benzimidazole derivatives (**5**). After condensation reaction of *o*-phenylenediamine (**1a**) or 2-amino-4-fluoroaniline (**1c**) with aldehydes (**2**) in the first step (i), the crude product (**3**) was directly transformed to target products (**5**) *via* conventional *N*-alkylation with various alkyl halide substrates (**6**) in the second step (ii). The corresponding products (**5a-5z**) were obtained in good to excellent yields. Whereas, 2-amino-4-fluoroaniline (**1c**) substrate gave two isomeric products in ratio 1:1 of *N*-alkylated 1,2-disubstituted 5- and 6-fluorobenzimidazoles with good to high total yields of products **5ja** and **5jb** (80%), **5ka** and **5 kb** (94%) and **5xa** and **5xb** (69%).

3. Conclusion

In summary, we have demonstrated an efficient and simple method for the selective synthesis of 2-substituted benzimidazole from *o*-phenylenediamines with aldehydes using Brönsted acidic ionic liquid as reusable catalyst under metal-free conditions at ambient temperature. The acidic ionic liquid based-dodecylimidazolium cation and HSO_4 anion, named [DodecIm][HSO_4] showed the most efficient reusable catalyst to afford the corresponding desirable products in high to excellent yields with a variety of aliphatic, aromatic and heteroaromatic aldehyde substrates. In addition, this method was successfully applied for the preparation of various *N*-alkylated 1,2-disubstituted benzimidazoles in sequential one-pot process.

4. Experimental section

4.1. General remarks

All chemicals were purchased from commercial sources and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded using a BRUKER AVANCE (400 MHz) spectrometer from Burapha University and a BRUKER AVANCE III HD (600 MHz) spectrometer from Vidyasirimedhi Institute of Science and Technology (VISTEC). High-resolution mass spectra (HRMS) data were recorded using a Bruker Daltonics-micrOTOF-Q at Mahidol University and a Bruker Compact QTOF at VISTEC. Infrared spectra were determined on a PERKIN ELMER FT/IR-2000S spectrophotometer. Analytical thin-layer chromatography (TLC) was conducted on precoated TLC plates; silica gel 60 F-254 [E. Merck, Darmstadt, Germany]. Open-column chromatography was carried out using silica gel 60 (0.063–0.200 mm) [E. Merck, Darmstadt, Germany]. Melting points were measured using a Melting point apparatus (Griffin) from Burapha University and a Melting point meter (KRÜSS) from VISTEC.

4.2. General procedure for the synthesis of 2-substituted benzimidazoles

To a solution of [DodecIm][HSO_4]* (5.00 mol%, 16.7 mg) in 95% EtOH (5.00 mL) was added aldehyde (**2**) (1.00 mmol) and *o*-phenylenediamine (**1a**), 2-aminothiophenol (**1b**) or 2-amino-4-fluoroaniline (**1c**) (1.20 mmol) at room temperature respectively. The reaction mixture was stirred at room temperature for 5–24 h and monitored by TLC. After the reaction completed, the ethanol solvent was removed by using rotary evaporator. The crude residue was diluted with water (5.00 mL)# and extracted with ethyl acetate (3 × 5 mL). The combine organic layer was dried over sodium

sulfate anhydrous and concentrated using rotary evaporator. The crude product was purified by column chromatography (SiO_2, 5–50% ethyl acetate/*n*-hexane as eluent depend on each derivatives) to give the desired products **3a-3x**.

Recycling experiment.* After extraction, the water layer[#] was removed to give the catalyst **III. Recovered catalyst **III** was reused directly by adding EtOH and substrates in the next run without purification.

Spectral data of compounds **3a** [5e-h,6a-c,6f-j,6l-s,6u,6z,6aa-ae,7,8a,9a,12a], **4a** [6e,6h,6n-o,6u,6y,6aa,22], **3b** [5d,6c,6i,6o,6ab,6ad,7], **3c** [6a-b,6f,6j-k,6n,6aa,7], **3d** [5d-e,5g,6a-c,6i,6k,6m,6o,6r,6aa-ae,7,8a], **3e** [5h,6l,6ad], **3f** [6l,7], **3g** [7], **3h** [6r,6aa,7], **3i** [6b-c,6i-j,6m-n,6q-r,6aa,7], **3j** [5d-e,5g,6a-c,6f,6h-j,6l,6n-o,6r-s,6ab,6ad-ae,7,11b], **3k** [6r,6ab], **3l** [6l], **3n** [6o], **3o** [5e,6b,6h-i,6m-o,6s,6ab,6ad], **3p** [6k,6p,6u], **3q** [3a,6n,6ab,11b,6ae], **3r** [3a,26], **3s** [6z], **3t** [5d,5g,6p,6u], **3v** [5f,6a,6c,6j,6l,6n,6p-q,6u,6ab,6ac,8a,11b,12a], **3w** [6a,6c,6j,6n,6ac,8a], and **3x** [5f,6a,6c,6j,6l,6n,6ab,11b], were previously described in the literature.

4.2.1. 2-Phenylbenzimidazole (*3a*)

CAS Number 716-79-0; as a white solid (197.3 mg, 98%, Table 3, rt, 5 h); m.p. 276–278 °C; $R_f = 0.31$ (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3036, 2958, 1463, 1445, 1411, 1276, 968, 739, 703, 498 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.15–7.25 (m, 2H), 7.47–7.59 (m, 4H), 7.67 (d, $J = 7.6$ Hz, 1H), 8.18 (d, $J = 7.2$ Hz, 2H), 12.91 (brs, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ: 122.06, 126.42, 126.42, 128.90, 128.90, 129.79, 130.17, 151.22; HRMS (ESI) *m/z* $C_{13}H_{10}N_2$ $[M+H]^+$ calcd 195.0922, found 195.0923.

4.2.2. 2-(2-Pyrrolyl-N-Boc)benzimidazole (*3m*)

As a white solid (135.9 mg, 48%, Table 3, rt, 12 h); m.p. 266–268 °C; $R_f = 0.26$ (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3060, 2980, 2684, 1743, 1317, 1158, 1097, 735 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.28 (s, 9H), 6.38 (t, $J = 3.2$ Hz, 1H), 6.67 (dd, $J = 3.2$, 1.6 Hz, 1H), 7.14–7.24 (m, 2H), 7.45–7.50 (m, 2H), 7.62 (d, $J = 7.6$ Hz, 1H), 12.54 (brs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 27.05, 27.05, 27.05, 84.03, 110.93, 111.02, 117.26, 118.60, 121.22, 122.25, 123.71, 124.51, 134.13, 143.05, 145.26, 148.29; HRMS (ESI) *m/z* $C_{16}H_{17}N_3O_2$ $[M+H]^+$ calcd 284.1399, found 284.1414.

4.2.3. 2-(4-Bromophenyl)-6-fluorobenzimidazole (*3u*)

As a yellow solid (206.7 mg, 71%, Table 3, rt, 24 h); m.p. 252–254 °C; $R_f = 0.29$ (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3449, 1633, 1259, 1138, 1007, 799 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 7.08 (t, $J = 8.4$ Hz, 1H), 7.39 (brs, 1H), 7.59 (brs, 1H), 7.77 (d, $J = 8.8$ Hz, 2H), 8.09 (d, $J = 8.8$ Hz, 2H), 13.13 (brs, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ: 110.45, 123.41, 128.32, 128.32, 129.08, 131.96, 131.96, 151.64, 158.74 (d, $J_{CF} = 228.0$ Hz); HRMS (ESI) *m/z* $C_{13}H_8BrFN_2$ $[M+H]^+$ calcd 290.9933, found 290.9939.

4.2.4. Imine intermediate (*4c*)

As a orange solid (176.0 mg, 73%, Table 3, rt, 5 h); m.p. 101–102 °C; $R_f = 0.63$ (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3479, 3377, 3076, 1606, 1528, 1351, 750, 674 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 5.32 (s, 2H), 6.58 (t, $J = 7.2$ Hz, 1H), 6.75 (d, $J = 7.2$ Hz, 1H), 7.01 (t, $J = 7.2$ Hz, 1H), 7.19 (d, $J = 7.8$ Hz, 1H), 7.80 (t, $J = 7.8$ Hz, 1H), 8.32 (d, $J = 7.8$ Hz, 1H), 8.46 (d, $J = 7.2$ Hz, 1H), 7.78 (s, 1H), 8.834 (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ: 114.90, 116.00, 117.13, 122.75, 124.96, 128.31, 130.22, 134.35, 138.28, 144.36, 148.27, 154.01, 160.18; HRMS (ESI) *m/z* $C_{13}H_{11}N_3O_2$ $[M+H]^+$ calcd 242.0930, found 242.0999.

4.2.5. Imine intermediate (*4d*)

As a brown solid (204.3 mg, 85%, Table 3, rt, 5 h); m.p. 128–130 °C; $R_f = 0.45$ (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3462, 3371, 1596, 1516, 1342, 851, 755, 688 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 5.42 (brs, 2H), 6.57 (t, $J = 8.0$ Hz, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 7.02 (t, $J = 8.0$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 8.26 (d, $J = 8.8$ Hz, 2H), 8.34 (d, $J = 8.8$ Hz, 2H), 8.84 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 115.07, 116.01, 117.01, 123.81, 123.81, 128.81, 129.36, 129.36, 133.94, 142.34, 144.88, 148.30, 153.41; HRMS (ESI) *m/z* $C_{13}H_{10}N_3O_2$ $[M+H]^+$ calcd 242.0930, found 242.0939.

4.2.6. Imine intermediate (*4g*)

As a orange solid (81.3 mg, 32%, Table 3, rt, 5 h); m.p. 198–200 °C; $R_f = 0.70$ (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 2925, 2844, 1718, 1435, 1279, 1120, 743 cm^{-1}; ^1H NMR (600 MHz, DMSO-d_6) δ: 3.89 (s, 3H), 5.28 (brs, 2H), 6.57 (t, $J = 7.2$ Hz, 1H), 6.74 (d, $J = 7.8$ Hz, 1H), 7.00 (t, $J = 7.8$ Hz, 1H), 7.19 (d, $J = 7.8$ Hz, 1H), 8.06 (d, $J = 7.8$ Hz, 2H), 8.13 (d, $J = 7.8$ Hz, 2H), 8.76 (s, 1H); ^{13}C NMR (151 MHz, DMSO-d_6) δ: 52.27, 114.89, 116.10, 116.99, 128.27, 128.61, 128.61, 129.44, 129.44, 131.09, 134.51, 140.69, 144.39, 154.84, 165.92; HRMS (APCI) *m/z* $C_{15}H_{14}N_2O_2$ $[M+H]^+$ calcd 255.1134, found 255.1171.

4.2.7. 2-(4-Nitrophenyl)benzothiazoline (*4w*)

As a yellow solid (163.1 mg, 63%, Table 3, rt, 24 h); m.p. 210–212 °C; $R_f = 0.22$ (10% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3345, 1519, 1472, 1346, 1256, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.43 (s, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 6.81 (t, $J = 7.6$ Hz, 1H), 6.70 (t, $J = 7.6$ Hz, 1H), 7.06 (d, $J = 7.6$ Hz, 1H), 7.69 (d, $J = 8.4$ Hz, 2H), 8.20 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 68.19, 110.35, 121.28, 121.68, 123.94, 123.94, 125.75, 125.83, 125.83, 127.11, 145.74, 147.70, 149.25; HRMS (APCI) *m/z* $C_{13}H_{11}N_2O_2S$ $[M+H]^+$ calcd 259.0541, found 259.0552.

4.3. General procedure for the synthesis of N-alkylated 1,2-disubstituted benzimidazoles

To a solution of [DodecIm][HSO_4]* (5.00 mol%, 16.7 mg) in 95% EtOH (5.00 mL) was added aldehyde (**2**) (1.00 mmol) and *o*-phenylenediamine (**1a**) (1.20 mmol, 129.8 mg) or 2-amino-4-fluoroaniline (**1c**) (1.20 mmol, 151.2 mg) at room temperature respectively. The reaction mixture was stirred at room temperature for 12 h and then ethanol solvent was removed by rotary evaporator. The crude residue was diluted with water (5.00 mL)[#] and extracted with ethyl acetate (3 × 5 mL). The combine organic layer was concentrated using rotary evaporator. Then crude residue was dissolved in acetonitrile (5.00 mL), followed by adding KOH (2.00 mmol, 112 mg) and alkyl halide (2.00 mmol) at room temperature respectively. The reaction mixture was stirred at room temperature for 0.5–24 h. After the reaction completed, the reaction mixture was neutralized with sat. NH_4Cl and extracted with ethyl acetate (3 × 15 mL). The combine organic layer was dried over sodium sulfate anhydrous and concentrated using rotary evaporator. The crude product was purified by column chromatography (SiO_2, 10–50% ethyl acetate/*n*-hexane as eluent depend on each derivatives) to give the desired products **5a-5z**.

Recycling experiment.* After extraction, the water layer[#] was removed to give the catalyst **III. Recovered catalyst **III** was reused directly by adding EtOH and substrates in the next run without purification.

Spectral data of compounds **5b** [24], **5c** [24], **5l** [3c], **5o** [26], and **5q** [25], were previously described in the literature.

4.3.1. 1-(4-Nitrobenzyl)-2-phenylbenzimidazole (*5a*)

As a yellow solid (268.8 mg, 82%); m.p. 136–138 °C; $R_f = 0.13$ (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3060, 1602, 1522, 1344, 745, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.55 (s, 2H), 7.16 (d,

J = 8.0 Hz, 1H), 7.24–7.31 (m, 3H), 7.36 (t, J = 7.2 Hz, 1H), 7.44–7.54 (m, 3H), 7.60–7.65 (m, 2H), 7.90 (d, J = 8.0 Hz, 1H), 8.21 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 47.77, 109.94, 120.23, 123.06, 123.40, 124.27, 124.27, 126.82, 126.82, 128.87, 128.87, 129.03, 129.03, 129.56, 130.15, 135.53, 143.10, 143.53, 147.53, 153.94; HRMS (APCI) *m/z* $C_{20}H_{15}N_3O_2$ $[M+H]^+$ calcd 330.1243, found 330.1244.

*4.3.2. 1-Benzyl-2-(4-bromophenyl)benzimidazole (**5d**)*

As a white solid (321.6 mg, 89%); m.p. 141–143 °C; R_f = 0.23 (10% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3059, 2941, 1612, 1495, 1446, 1409, 1361, 1012, 840, 737, 725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.45 (s, 2H), 7.09 (d, J = 6.4 Hz, 2H), 7.22–7.38 (m, 6H), 7.57 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.32, 110.46, 120.00, 122.87, 123.31, 124.51, 125.80, 127.88, 128.90, 129.12, 130.68, 131.97, 136.10, 142.98, 152.92; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{20}H_{15}BrN_2$ 363.0497, found 363.0495.

*4.3.3. 1-Benzyl-2-(4-methoxyphenyl)benzimidazole (**5e**)*

As a white solid (240.2 mg, 77%); m.p. 137–139 °C. R_f = 0.46 (40% EtOAc/*n*-hexane); IR (KBr): ν_{max} 2971, 1610, 1483, 1452, 1363, 1180, 1035, 843, 744, 735, 727 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.85 (s, 3H), 5.45 (s, 2H), 6.97 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 7.2 Hz, 2H), 7.18–7.25 (m, 2H), 7.28–7.37 (m, 4H), 7.64 (d, J = 8.4 Hz, 2H), 7.86 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.35, 55.31, 110.31, 114.19, 119.73, 122.41, 122.52, 122.73, 125.93, 127.69, 129.01, 130.66, 136.11, 136.52, 143.17, 154.12, 160.94; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{21}H_{18}N_2O$ 315.1497, found 315.1497.

*4.3.4. 1-Benzyl-2-(4-trifluoromethanephenyl)benzimidazole (**5f**)*

As a white solid (313.1 mg, 89%); m.p. 133–135 °C; R_f = 0.31 (15% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3033, 2950, 1619, 1495, 1450, 1417, 1127, 854, 742, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.47 (s, 2H), 7.10 (d, J = 6.8 Hz, 2H), 7.24–7.30 (m, 2H), 7.31–7.39 (m, 4H), 7.72 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 7.90 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.35, 110.55, 120.20, 123.02, 123.61, 123.78 (q, J_{CF} = 271.0 Hz), 125.67 (q, J_{CF} = 3.0 Hz), 125.76, 127.96, 129.16, 129.56, 131.69 (q, J_{CF} = 33.0 Hz), 133.53, 135.97, 136.17, 143.02, 152.39; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{21}H_{15}F_3N_2$ 353.1266, found 353.1267.

*4.3.5. 1-(3-Methoxybenzyl-2-(4-bromophenyl)benzimidazole (**5g**)*

As a white solid (386.4 mg, 98%); m.p. 127–129 °C; R_f = 0.28 (10% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3028, 2970,2937, 1609, 1583, 1441, 1456, 1048, 831, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.74 (s, 3H), 5.41 (s, 2H), 6.63 (s, 1H), 6.67 (d, J = 7.6 Hz, 1H), 6.84 (dd, J = 8.4, 2.0 Hz, 1H), 7.23–7.30 (m, 3H), 7.33 (td, J = 8.0, 1.6 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 7.87 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.22, 55.15, 110.42, 111.78, 112.87, 117.97, 119.99, 122.83, 123.29, 124.47, 128.92, 130.23, 130.67, 131.95, 136.16, 137.78, 143.02, 152.89, 160.18; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{21}H_{17}BrN_2O$ 393.0603, found 393.0602.

*4.3.6. 1-(4-Nitrobenzyl)-2-(3,4-dimethoxyphenyl)benzimidazole (**5h**)*

As a yellow solid (299.1 mg, 77%); m.p. 153–155 °C. R_f = 0.48 (50% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3075, 2987, 2934, 1607, 1588, 1521, 1504, 1453, 1434, 1341, 1143, 1020, 852, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.80 (s, 3H), 3.91 (s, 3H), 5.56 (s, 2H), 6.88 (d, J = 8.4 Hz, 1H), 7.05 (dd, J = 8.4, 2.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.24–7.28 (m, 2H), 7.30 (d, J = 8.8 Hz, 2H), 7.35 (t, J = 7.6 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 8.22 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 47.23, 55.39, 55.59, 110.72, 111.69, 112.36, 119.19, 121.56, 122.01, 122.41, 122.73, 124.02, 127.30, 135.92, 142.66, 144.95, 146.85, 148.69, 150.19, 153.31; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{22}H_{19}N_3O_4$ 390.1454, found 390.1458.

*4.3.7. 1-(3-Methoxybenzyl)-2-(2,4-dichlorophenyl)benzimidazole (**5i**)*

As a colorless oil (378.7 mg, 98%); R_f = 0.43 (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3055, 2934, 1599, 1586, 1490, 1451, 1262, 1041, 979, 781, 745, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.66 (s, 3H), 5.19 (s, 2H), 6.45 (s, 1H), 6.50 (d, J = 7.6 Hz, 1H), 6.73 (dd, J = 8.4, 1.6 Hz, 1H), 7.12 (t, J = 8.0 Hz, 1H), 7.23–7.32 (m, 4H), 7.37 (d, J = 8.4 Hz, 1H), 7.53 (d, J = 1.6 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.05, 55.07, 110.61, 112.42, 112.99, 118.72, 120.21, 122.64, 123.38, 127.34, 128.45, 129.70, 129.84, 133.06, 134.84, 135.10, 136.82, 137.14, 142.90, 150.07, 159.83; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{21}H_{16}Cl_2N_2O$ 383.0718, found 383.0718.

*4.3.8. 1-(3-Methoxybenzyl)-2-(4-methoxyphenyl)-5-fluorobenzimidazole (**5ja**)*

As a white solid (148.4 mg, 41%); m.p. 105–107 °C; R_f = 0.28 (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3055, 2942, 1602, 1576, 1478, 1465, 1437, 1386, 1253, 1138, 1028, 838, 789 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.74 (s, 3H), 3.85 (s, 3H), 5.41 (s, 2H), 6.64 (s, 1H), 6.68 (d, J = 7.6 Hz, 1H), 6.85 (dd, J = 8.0, 1.6 Hz, 1H), 6.95–7.01 (m, 3H), 7.11 (dd, J = 8.8, 4.4 Hz, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.53 (dd, J = 8.8, 1.6 Hz, 1H), 7.65 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.47, 55.20, 55.36, 105.43 (d, J_{CF} = 24.0 Hz), 110.67 (d, J_{CF} = 10.0 Hz), 111.02 (d, J_{CF} = 26.0 Hz), 111.82, 112.91, 114.28, 118.05, 121.90, 130.25, 130.63, 132.57, 137.79, 143.39 (d, J_{CF} = 12.0 Hz), 155.50, 159.63 (d, J_{CF} = 236.0 Hz), 160.22, 161.09; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{22}H_{19}FN_2O_2$ 363.1509, found 363.1510.

*4.3.9. 1-(3-Methoxybenzyl)-2-(4-methoxyphenyl)-6-fluorobenzimidazole (**5jb**)*

As a white solid (141.2 mg, 39%); m.p. 141–143 °C; R_f = 0.23 (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3076, 2970, 1599, 1476, 1458, 1435, 1420, 1387, 1245, 1179, 1028, 993, 849, 807, 785 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.75 (s, 3H), 3.85 (s, 3H), 5.36 (s, 2H), 6.63 (s, 1H), 6.68 (d, J = 7.6 Hz, 1H), 6.82–6.90 (m, 2H), 6.97 (d, J = 8.8 Hz, 2H), 7.00–7.08 (m, 1H), 7.24–7.30 (m, 1H), 7.62 (d, J = 8.4 Hz, 2H), 7.73–7.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.46, 55.21, 55.36, 97.14 (d, J_{CF} = 27.0 Hz), 110.91 (d, J_{CF} = 24.0 Hz), 111.87, 112.94, 114.27, 118.08, 120.35 (d, J_{CF} = 10.0 Hz), 121.93, 130.29, 130.59, 136.22 (d, J_{CF} = 13.0 Hz), 137.55, 139.32, 154.82, 159.64 (d, J_{CF} = 239.0 Hz), 160.24, 161.01; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{22}H_{19}FN_2O_2$ 363.1509, found 363.1510.

*4.3.10. 1-Benzyl-2-(4-bromophenyl)-5-fluorobenzimidazole (**5ka**)*

As a white solid (170.9 mg, 45%); m.p. 167–169 °C; R_f = 0.43 (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3032, 1622, 1590, 1464, 1440, 1412, 1362, 1143, 831, 797 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.43 (s, 2H), 7.01 (t, J = 9.2 Hz, 1H), 7.08 (d, J = 7.2 Hz, 2H), 7.12 (dd, J = 8.8, 4.4 Hz, 1H), 7.30–7.39 (m, 3H), 7.51–7.57 (m, 3H), 7.60 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.49, 105.70 (d, J_{CF} = 24.0 Hz), 110.87 (d, J_{CF} = 10.0 Hz), 111.63 (d, J_{CF} = 26.0 Hz), 124.75, 125.74, 128.02, 128.61, 129.19, 130.59, 132.05, 132.59, 135.77, 143.42 (d, J_{CF} = 13.0 Hz), 154.34, 159.66 (d, J_{CF} = 237.0 Hz); HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{20}H_{14}BrFN_2$ 381.0403, found 381.0403.

*4.3.11. 1-Benzyl-2-(4-bromophenyl)-6-fluorobenzimidazole (**5 kb**)*

As a white solid (186.1 mg, 49%); m.p. 149–151 °C; R_f = 0.37 (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3032, 1618, 1513, 1467, 1451, 1409, 1363, 1011, 797, 824 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.39 (s, 2H), 6.89 (dd, J = 8.4, 2.0 Hz, 1H), 7.05–7.10 (m, 3H), 7.30–7.39 (m, 3H), 7.53 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.4 Hz, 2H), 7.78 (dd, J = 8.8, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.49, 97.21 (d, J_{CF} = 28.0 Hz), 111.30 (d, J_{CF} = 25.0 Hz), 120.79 (d, J_{CF} = 10.0 Hz),

124.62, 125.76, 127.44, 128.06, 128.62, 129.22, 130.56, 132.04, 135.55, 136.26 (d, J_{CF} = 13.0 Hz), 153.64 (d, J_{CF} = 3.0 Hz), 159.84 (d, J_{CF} = 240.0 Hz); HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{20}H_{14}BrFN_2$ 381.0403, found 381.0400.

*4.3.12. 1-Chloropropyl-2-(4-bromophenyl)benzimidazole (**5m**)*

As a white solid (289.1 mg, 83%); m.p. 119–121 °C; R_f = 0.31 (10% EtOAc/*n*-hexane); IR (KBr): ν_{max} 2921, 1612, 1599, 1451, 1435, 1365, 1250, 827, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.24 (pentet, *J* = 6.8 Hz, 2H), 3.46 (t, *J* = 6.0 Hz, 2H), 4.45 (t, *J* = 7.2 Hz, 2H), 7.30–7.37 (m, 2H), 7.44–7.49 (m, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 8.4 Hz, 2H), 7.81–7.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 32.26, 41.46, 41.89, 109.92, 120.12, 122.82, 123.24, 124.49, 129.12, 130.75, 132.09, 135.46, 142.90, 152.38; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{16}H_{14}BrClN_2$ 349.0107, found 349.0100.

*4.3.13. 1-Chloropropyl-2-(4-methoxyphenyl)benzimidazole (**5n**)*

As a yellow solid (285.8 mg, 95%); m.p. 73–75 °C; R_f = 0.57 (40% EtOAc/*n*-hexane); IR (KBr): ν_{max} 2939, 1608, 1455, 1426, 1365, 1251, 1179, 1023, 837, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.24 (pentet, *J* = 7.6 Hz, 2H), 3.46 (t, *J* = 6.0 Hz, 2H), 3.88 (s, 3H), 4.44 (t, *J* = 7.6 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.28–7.34 (m, 2H), 7.42–7.47 (m, 1H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.79–7.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 32.28, 41.61, 41.86, 55.35, 109.75, 114.25, 119.75, 122.35, 122.51, 122.74, 130.63, 135.41, 142.81, 153.51, 160.83; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{17}H_{17}ClN_2O$ 301.1108, found 301.1108.

*4.3.14. 2-(4-Trifluoromethanephenyl)-1-propargylbenzimidazole (**5p**)*

As a white solid (252.3 mg, 84%); m.p. 121–123 °C; R_f = 0.34 (10% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3175, 2971, 2115, 1615, 1458, 1417, 1314, 1324, 1165, 1109, 848, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 2.52 (brs, 1H), 4.94 (d, *J* = 2.0 Hz, 2H), 7.36–7.45 (m, 2H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.75, 74.35, 77.00, 110.06, 120.26, 123.25, 123.77, 123.78 (q, J_{CF} = 271.0 Hz), 125.85 (q, J_{CF} = 4.0 Hz), 129.68, 131.90 (q, J_{CF} = 33.0 Hz), 133.05, 135.43, 142.77, 151.40; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{17}H_{11}F_3N_2$ 301.0953, found 301.0957.

*4.3.15. 1-Octyl-2-(4-bromophenyl)benzimidazole (**5r**)*

As a yellow oil (294.3 mg, 77%); R_f = 0.34 (10% EtOAc/*n*-hexane); IR (KBr): ν_{max} 2925, 1613, 1599, 1451, 1404, 1365, 1329, 1076, 1010, 832, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.86 (t, *J* = 7.2 Hz, 3H), 1.15–1.30 (m, 10H), 1.72–1.85 (m, 2H), 4.20 (t, *J* = 7.6 Hz, 2H), 7.28–7.35 (m, 2H), 7.39–7.43 (m, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.8 Hz, 2H), 7.79–7.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.01, 22.52, 26.59, 28.88, 28.99, 29.69, 31.62, 44.70, 110.10, 119.94, 122.46, 122.86, 124.19, 129.57, 130.76, 131.92, 135.54, 142.95, 152.41; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{21}H_{25}BrN_2$ 385.1279, found 385.1279.

*4.3.16. 1-Octyl-2-(4-methoxyphenyl)benzimidazole (**5s**)*

As a yellow oil (268.5 mg, 80%); R_f = 0.43 (40% EtOAc/*n*-hexane); IR (KBr): ν_{max} 2926, 1611, 1534, 1482, 1454, 1386, 1365, 1249, 1175, 1028, 836, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 0.86 (t, *J* = 7.2 Hz, 3H), 1.15–1.30 (m, 10H), 1.82 (pentet, *J* = 7.2 Hz, 2H), 3.89 (s, 3H), 4.20 (t, *J* = 7.6 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.27–7.32 (m, 2H), 7.37–7.42 (m, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.78–7.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.01, 22.53, 26.63, 28.91, 29.01, 29.66, 31.65, 44.65, 55.31, 109.94, 114.09, 119.61, 122.18, 122.37, 122.82, 130.66, 135.50, 142.89, 153.58, 160.66; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{22}H_{28}N_2O$ 337.2280, found 337.2285.

*4.3.17. 1-Morpholinopropyl-2-phenylbenzimidazole (**5t**)*

CAS Number 32926-95-7; as a colorless oil (314.9 mg, 98%); R_f = 0.13 (50% EtOAc/*n*-hexane); IR (KBr): ν_{max} 2954, 2850, 2805, 2340, 1737, 1601, 1444, 1392, 1272, 1117, 745, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.91 (pentet, *J* = 6.8 Hz, 2H), 2.20–2.28 (m, 6H), 3.60 (t, *J* = 4.0 Hz, 4H), 4.37 (t, *J* = 7.2 Hz, 2H), 7.29–7.33 (m, 2H), 7.43–7.47 (m, 1H), 7.50–7.54 (m, 3H), 7.71–7.75 (m, 2H), 7.80–7.84 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.22, 42.27, 53.25, 54.97, 66.63, 109.92, 119.77, 122.17, 122.48, 128.51, 129.12, 129.51, 130.52, 135.48, 142.91, 153.45; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{20}H_{23}N_3O$ 322.1919, found 322.1958.

*4.3.18. 1-Morpholinopropyl-2-(2,4-dichlorophenyl)benzimidazole (**5u**)*

As a colorless oil (330.2 mg, 85%); R_f = 0.17 (50% EtOAc/*n*-hexane); IR (KBr): ν_{max} 2953, 2854, 1598, 1552, 1446, 1400, 1371, 1115, 827, 782, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.83 (pentet, *J* = 7.2 Hz, 2H), 2.20 (t, *J* = 6.8 Hz, 2H), 2.26 (brt, *J* = 4.0 Hz, 4H), 3.61 (t, *J* = 4.4 Hz, 4H), 4.15 (t, *J* = 7.6 Hz, 2H), 2.29–2.37 (m, 2H), 7.41 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.45–7.50 (m, 2H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.81–7.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.23, 42.16, 53.33, 55.04, 66.71, 110.10, 120.27, 122.47, 123.10, 127.39, 128.89, 129.77, 132.95, 134.79, 135.10, 136.80, 142.96, 149.69; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{20}H_{21}Cl_2N_3O$ 390.1140, found 390.1144.

*4.3.19. 2-Propyl-1-phenylbenzimidazole (**5v**)*

As a colorless oil (182.7 mg, 73%); R_f = 0.48 (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3032, 2963, 2931, 1615, 1509, 1496, 1454, 1409, 1356, 741, 727 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.02 (t, *J* = 7.2 Hz, 3H), 1.88 (sextet, *J* = 7.2 Hz, 2H), 2.88 (t, *J* = 7.6 Hz, 2H), 5.37 (s, 2H), 7.02–7.07 (m, 2H), 7.22–7.34 (m, 6H), 7.82 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.92, 20.96, 29.39, 46.78, 109.42, 119.13, 121.91, 122.19, 126.02, 127.77, 128.88, 135.25, 135.95, 142.51, 155.24; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{17}H_{18}N_2$ 251.1548, found 251.1550.

*4.3.20. 2-Propyl-1-(4-fluorophenyl)benzimidazole (**5w**)*

As a colorless oil (177.2 mg, 66%); R_f = 0.46 (40% EtOAc/*n*-hexane); IR (KBr): ν_{max} 2969, 2932, 1606, 1508, 1460, 1408, 1220, 1157, 820, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.01 (t, *J* = 7.2 Hz, 3H), 1.86 (sextet, *J* = 7.6 Hz, 2H), 2.81 (t, *J* = 7.6 Hz, 2H), 5.31 (s, 2H), 6.96–7.04 (m, 4H), 7.16–7.28 (m, 3H), 7.77 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.95, 21.00, 29.42, 46.19, 109.32, 115.90 (d, J_{CF} = 21.0 Hz), 119.26, 122.08, 122.33, 127.76 (d, J_{CF} = 8.0 Hz), 131.71 (d, J_{CF} = 3.0 Hz), 135.10, 142.52, 155.11, 162.22 (d, J_{CF} = 245.0 Hz); HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{17}H_{17}FN_2$ 269.1454, found 269.1454.

*4.3.21. 1-Chloropropyl-2-isobutyl-5-fluorobenzimidazole (**5xa**)*

As a yellow oil (94.1 mg, 35%); R_f = 0.20 (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 2959, 1625, 1597, 1484, 1445, 1409, 1367, 1134, 959, 853, 796 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.04 (d, *J* = 6.8 Hz, 6H), 2.26 (pentet, *J* = 6.8 Hz, 2H), 2.28–2.38 (m, 1H), 2.77 (d, *J* = 7.2 Hz, 2H), 3.55 (t, *J* = 6.0 Hz, 2H), 4.32 (t, *J* = 6.8 Hz, 2H), 6.99 (td, *J* = 9.2, 2.4 Hz, 1H), 7.24–7.29 (m, 1H), 7.40 (dd, *J* = 9.2, 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.54, 28.03, 32.23, 36.19, 40.52, 41.39, 105.05 (d, J_{CF} = 24.0 Hz), 109.27 (d, J_{CF} = 10.0 Hz), 110.13 (d, J_{CF} = 26.0 Hz), 131.18, 143.05 (d, J_{CF} = 12.0 Hz), 155.90, 159.20 (d, J_{CF} = 235.0 Hz); HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{14}H_{18}ClFN_2$ 269.1221, found 269.1229.

*4.3.22. 1-Chloropropyl-2-isobutyl-6-fluorobenzimidazole (**5xb**)*

As a yellow oil (91.4 mg, 34%); R_f = 0.17 (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 2959, 2928, 1624, 1599, 1481, 1467, 1446, 1407, 1367, 1176, 1135, 959, 830, 809 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 1.04 (d, *J* = 6.8 Hz, 6H), 2.25 (pentet, *J* = 6.4 Hz, 2H), 2.28–2.38 (m, 1H),

2.76 (d, $J = 7.6$ Hz, 2H), 3.55 (t, $J = 6.4$ Hz, 2H), 4.28 (t, $J = 7.2$ Hz, 2H), 6.98 (td, $J = 9.6$, 2.4 Hz, 1H), 7.04 (dd, $J = 8.8$, 2.4 Hz, 1H), 7.64 (dd, $J = 8.8$, 4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.58, 28.02, 32.10, 36.17, 40.59, 41.40, 95.98 (d, $J_{CF} = 27.0$ Hz), 110.08 (d, $J_{CF} = 25.0$ Hz), 110.08 (d, $J_{CF} = 25.0$ Hz), 134.80 (d, $J_{CF} = 13.0$ Hz), 138.96, 155.06 (d, $J_{CF} = 3.0$ Hz), 159.33 (d, $J_{CF} = 238.0$ Hz); HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{14}H_{18}ClFN_2$ 269.1221, found 269.1221.

4.3.23. 2-(2-Furyl)-1-propargylbenzimidazole (**5y**)

As a yellow solid (164.2 mg, 74%); m.p. 79–81 °C; $R_f = 0.28$ (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3210, 3009, 2919, 2118, 1608, 1511, 1457, 1389, 1335, 1022, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.37 (t, $J = 1.6$ Hz, 1H), 5.27 (d, $J = 2.0$ Hz, 2H), 6.64 (brt, $J = 1.2$ Hz, 1H), 7.30–7.40 (m, 3H), 7.51 (d, $J = 8.0$ Hz, 1H), 7.68 (brs, 1H), 7.82 (d, $J = 6.8$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 34.54, 73.66, 77.20, 109.78, 112.21, 113.82, 119.64, 123.47, 123.66, 134.65, 141.99, 143.17, 144.42, 144.56; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{14}H_{10}N_2O$ 223.0871, found 223.0871.

4.3.24. 2-(2-Furyl)-1-phenylbenzimidazole (**5z**)

As a white solid (179.3 mg, 65%); m.p. 131–133 °C; $R_f = 0.34$ (20% EtOAc/*n*-hexane); IR (KBr): ν_{max} 3031, 1619, 1514, 1450, 1424, 1227, 1026, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.56 (dd, $J = 3.2$, 1.6 Hz, 1H), 7.14 (d, $J = 6.8$ Hz, 2H), 7.23–7.34 (m, 7H), 7.58 (brs, 1H), 7.84 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 48.21, 109.92, 111.99, 112.66, 119.81, 122.84, 123.19, 126.16, 127.66, 128.83, 135.68, 136.29, 143.02, 143.98, 144.37, 145.15; HRMS (APCI) *m/z* $[M+H]^+$ calcd $C_{18}H_{14}N_2O$ 275.1184, found 275.1189.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2019.05.014.

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