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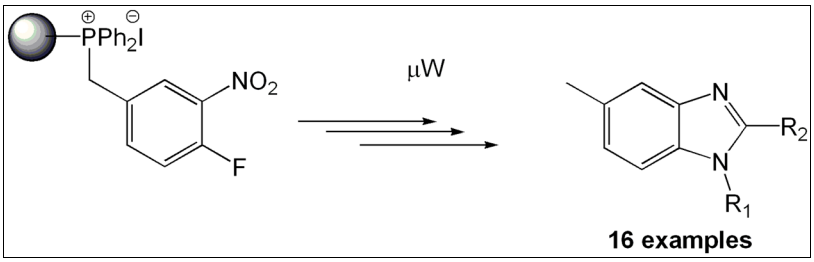


An efficient and rapid microwave-assisted solid-phase method for the synthesis of 5-methyl-1,2-disubstituted benzimidazoles derivatives has been developed. The phosphonium linker, obtained by reaction between polymer-supported triphenylphosphine and 4-fluoro-3-nitrobenzyl iodide, underwent aromatic substitution with primary amines, followed by one-pot reaction with aldehydes in the presence of $SnCl_2 \cdot 2H_2O$, yielded the benzimidazole system under microwave irradiation. The final products were released from the resin with NaOH under microwave irradiation and were obtained in high purity and good overall yield.

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## INTRODUCTION

Solid-phase organic synthesis and microwave-assisted organic synthesis are powerful techniques for rapid generation of structurally diverse molecules for drug discovery [1,2]. The combination of microwave with solid support, microwave-assisted solid-phase synthesis (MASS), offers several advantages over conventional techniques [3]. In fact, in recent years, MASS has emerged as a powerful synthetic tool because not only ensures greater purity of the products but also results in improved yields mainly because of a decrease formation of side products. The use of MASS in modern organic synthesis has received special attention during the synthesis of heterocyclic compounds because of their broad range of pharmacological activities [4–6]. Benzimidazole is an important heterocyclic system with many applications in the field of therapeutics. Benzimidazole and its derivatives present wide ranges of biological activities, such as anticancer, [7] antiviral, [8] antiprotozoan, [9] histamine-H3 antagonist, [10] and, more recently found, as neuroimaging tracers [11,12]. In this context, it has been reported that there is a selective interaction between two well-known benzimidazole derivatives, the antihistamine astemizole and the proton pump inhibitor lansoprazole, and anomalous aggregates of tau protein; therefore, both derivates have been proposed as potential positron emission tomography radiopharmaceutical for *in vivo* early detection of Alzheimer's disease (Figure 1) [13]. As a result, an increasing number of substituted benzimidazoles have been prepared by using both microwave-assisted organic synthesis and solid-phase organic synthesis methodology, because a facile and versatile preparation of substituted benzimidazoles is highly desirable [14]. In the last years, the application of a traceless phosphonium linker during the synthesis of 2-alkylthiobenzimidazoles has been demonstrated [15]. The phosphonium salt formation on a polymer-supported triphenylphosphine (PS-TPP) has recently been exploited for the solid phase synthesis of different molecules with different reaction conditions [16,17]. We have also developed a small library of benzofuroxan and benzofurozan derivatives employing PS-TPP as reagent [18]. In this context, our group is interested on the development of rapid synthesis of azaheterocyclic molecules with neuroprotective and antiprotozoan activity by exploring the possibility to obtain benzimidazole libraries by MASS methodology. Synthetic approaches to 1,2-disubstituted benzimidazoles from *o*-halonitroaromatics have been described; however, this procedure requires a multistep process resulting in compromised yields and purity [19,20]. Here, we describe a MASS route using an *o*-fluronitroaromatic phosphonium linker for the preparation of benzimidazole libraries by exploiting the presence of two sites of chemical diversity in the molecule.

## RESULTS AND DISCUSSION

The synthesis of the benzimidazole derivatives started with the preparation of the 4-fluoro-3-nitrobenzyl iodide

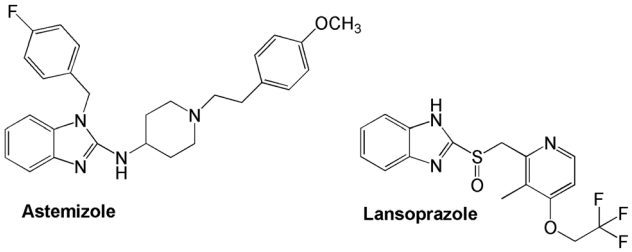


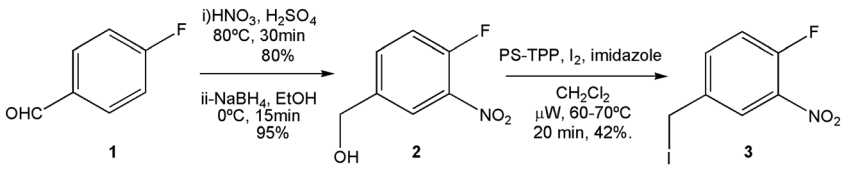

**Figure 1.** Drugs structures based on the benzimidazole scaffold.

**3** from 4-fluorobenzaldehyde **1** (Scheme 1) [21]. After nitration reaction and subsequent $NaBH_4$ reduction of aldehyde group, the resulting benzylic alcohol **2** was converted into iodide **3** using PS-TPP-iodine complex in dry dichloromethane with 45% yield after 48 h at room temperature [22]. The product was isolated after filtration of the polymer-supported phosphine oxide and subsequent aqueous work-up of the filtrate yield a pure compound after chromatographic purification. With the aim to decrease the reaction times, the iodination of alcohol **2** was optimized by using microwave irradiation. The reactions were carried out in a multimode reactor microwave [23,24]. Similar yield was obtained for **3** when alcohol **2** and PS-TPP-iodine complex (1.3 equiv) were irradiated in a closed vessel at 60–70°C (Scheme 1). Under this condition, the reaction time is drastically reduced to 20 min. In order to prepare the *o*-fluronitrobenzene phosphonium salt **4**, benzyl iodide **3** (1.5 equiv) was immobilized on standard PS-TPP resin (3 mmol/g) by irradiating the pre-swollen resin either with DMF or N-methylpyrrolidone (NMP) at 150°C for 5 min (Scheme 2). Under these conditions, complete conversion was achieved as judged by on-bead FTIR monitoring, which result in the appearance of new bands at 1537, 1492, and 1348 $cm^{-1}$ all corresponding to the stretching vibration of the $C_{Ar}$–$NO_2$ bond, and bands 1181 and 1111 $cm^{-1}$ corresponding to $C_{Ar}$–F bond. On the other hand, according to the weight increase and nitrogen analysis, the loading was estimated to be in 1.45–1.55 mmol (90–95%) phosphonium salt per gram support. We also have performed this transformation under conventional conditions (room temperature, 48 h) leading to identical results.

Nucleophilic aromatic displacement ($S_NAr$) of the activated fluoride **4** with commercially available amines provided the immobilized *o*-nitroaniline **5** (Scheme 2). Progress of aromatic substitution was followed by on-bead FTIR spectroscopy monitoring by the disappearance of characteristic nitro group absorbance and presence of characteristic NH vibrations at 3356 and 1665 $cm^{-}1$. A comparison between yields obtained with conventional procedure and microwave heating is shown in Table 1. Both primary amines studied performed better with decreased reaction times when using microwave heating than using conventional condition without heating (room temperature, 24 h). The use of this condition with phenethylamine in DMF resulted in the corresponding immobilized *o*-nitroaniline **5a** in moderate yields after cleavage with NaOH (10%) in MeOH at room temperature for 4 h (entry 1, Table 1). Excellent and quantitative yields were obtained to *o*-nitroaniline **5a** when *o*-fluronitroaromatic **4** and phenethylamine (3.6 equiv) were irradiated in a closed vessel after 10 and 15 min at 120°C, respectively (entries 2 and 3, Table 1). Substitution of the halogen in **4** by *n*-butylamine gave the corresponding *o*-nitroaniline **5b** with greater than 90 and 75% of purity and yield, respectively, as judged by $^1H$ NMR analysis of the cleaved compound (entries 6–8, Table 1). Moreover, similar yields were obtained using both amines when microwave heating (100 or 200 W) was performed during resin cleavage (entries 4, 7, and 8, Table 1). Microwave irradiation also allowed for a faster conversion.

On the other hand, a recent report describe the generation of 2-substituted benzimidazoles directly from 2-nitroanilines by an *in situ* reduction and cyclization using microwave procedure [25]. In this regard, a previous work demonstrate that the benzimidazole system can be efficiently prepared from a support-bound *o*-nitroaniline (SynPhase$^{TM}$ Lanterns) using a "one-pot" reduction–cyclization method, with DMF in the presence of $SnCl_2{\cdot}2H_2O$ at 60°C for 3 h [26]. On the basis of these results, we considered a MASS for the preparation of the benzimidazole skeleton using *o*-nitroaniline phosphonium salt **5** as starting material. During the course of our studies, we initially optimized a microwave-based procedure for the formation of 5-methyl-1-phenethyl benzimidazole **7a** (Table 2). The conversion of *o*-nitroaniline **5a** to supported benzimidazoles **6a** is a two-step process. In the first step, the aniline reacts with DMF presumably via formylation process followed by reduction of the nitro group using $SnCl_2.2H_2O$ and ring closure. The use of $SnCl_2.2H_2O$ in great excess (30 equiv.) in DMF for 24 h produced only a small amount of the desired benzimidazole **7a** (after NaOH

**Scheme 1**



**Scheme 2** [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

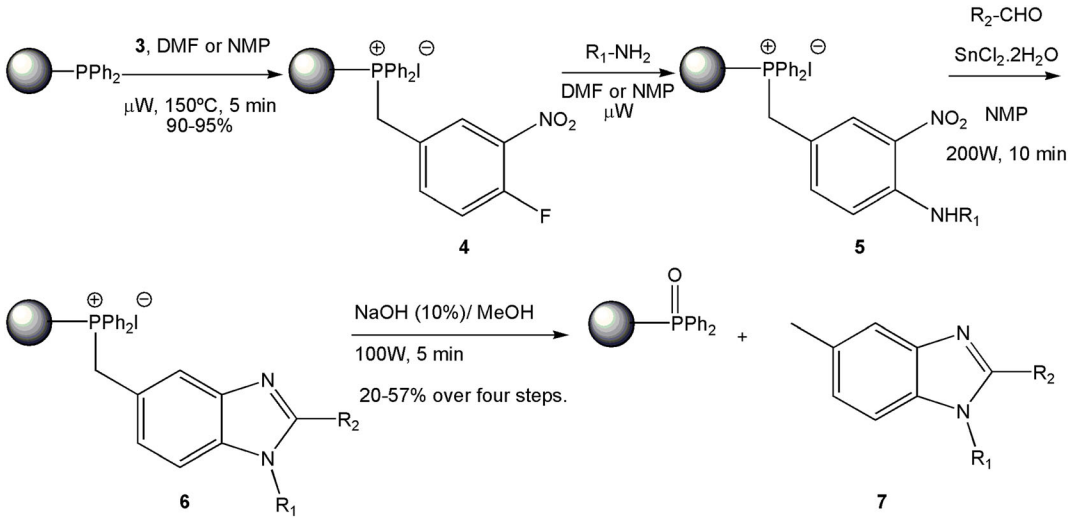



**Table 1**

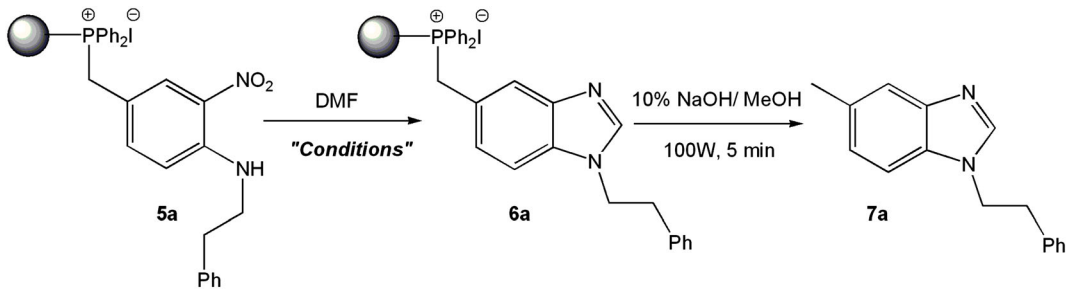
Microwave-assisted synthesis of supported *ortho*-nitroanilines **5**.

| Entry | $R_1$-$NH_2$ | Solvent | Conditions | Cleavage | Product (yield, %)[a] |
|---|---|---|---|---|---|
| 1 | $CH_2CH_2Ph$ | DMF | RT, 24 h | NaOH, RT, 4 h | **5a** (38) |
| 2 | $CH_2CH_2Ph$ | DMF | μW, 120 C, 10 min | NaOH, RT, 4 h | **5a** (90) |
| 3 | $CH_2CH_2Ph$ | DMF | μW, 120 C, 15 min | NaOH, RT, 4 h | **5a** (99) |
| 4 | $CH_2CH_2Ph$ | DMF | μW, 120 C, 10 min | NaOH, 100 W ($T_{max}$ = 85 C), 5 min | **5a** (75) |
| 5 | $CH_2CH_2Ph$ | NMP | μW, 70 C, 20 min | NaOH, 100 W, 5 min | **5a** (50) |
| 6 | $(CH_2)_3CH_3$ | NMP | μW, 70 C, 20 min | NaOH, RT, 4 h | **5b** (80) |
| 7 | $(CH_2)_3CH_3$ | NMP | μW, 70 C, 20 min | NaOH, 100 W, 5 min | **5b** (75) |
| 8 | $(CH_2)_3CH_3$ | NMP | μW, 70 C, 20 min | NaOH, 200 W ($T_{max}$ = 120 C), 5 min | **5b** (80) |

[a]Yields are based on the weight of purified product and relative to the initial loading of the resin (3.0 mmol/g).

**Table 2**

Synthesis of 5-methyl-1-phenethyl benzimidazole **7a** using supported *ortho*-nitroanilines **5a** under microwave conditions.

| Entry | Reagents | Conditions | Yield[a] (%) |
|---|---|---|---|
| |  | | |
| 1 | $SnCl_2.2H_2O$ (30 equiv) | RT, 24 h | 2 |
| 2 | $SnCl_2.2H_2O$ (10 equiv) | 60 C, 3 h | 15 |
| 3 | $SnCl_2.2H_2O$ (10 equiv) | 200 W ($T_{max}$ = 150 C), 10 min | 35 |
| 4 | $SnCl_2.2H_2O$ (10 equiv), $HCO_2H$ (5 equiv) | 200 W ($T_{max}$ = 105 C), 10 min | 18 |
| 5 | $SnCl_2.2H_2O$ (10 equiv), HCOH (2 equiv) | 200 W ($T_{max}$ = 115 C), 10 min | 47 |



[a]Yields are based on the weight of purified product and relative to the initial loading of the resin (3.0 mmol/g).

cleavage) along with other products that were not characterized (entry 1, Table 2). Optimized microwave heating during the synthesis of **7a** resulted in a significantly improved yield compared with thermal conditions (35% vs 15%, entries 2 and 3, Table 2). Finally, because the condensation/cyclization with carboxylic acids and aldehydes during the formation of benzimidazoles is well known, formic acid and *p*-formaldehyde were used in order to improve the yield of **7a** (entries 4 and 5, Table 2). Our best result was a 47% yield when "one-pot" reduction–cyclization was performed with *p*-formaldehyde (2 equiv) under microwave irradiation (200 W, $T_{max}$ = 115°C) for 10 min (entry 5, Table 2).

To illustrate the versatility of this chemistry, a library of 16 benzimidazoles (**7b–p**) was prepared (Table 3). Two amines and eight aldehydes were employed to introduce diversity. In all cases, pure 1,2-disubtituted benzimidazoles were obtained (in an overall manner) in moderate to good yields (between 20 and 57%) after the chromatographic purification.

## CONCLUSIONS

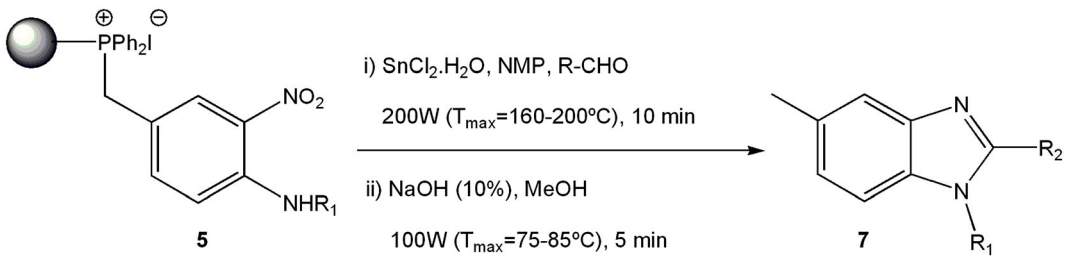
In summary, we have developed an efficient and rapid solid-phase microwave assisted approach for the synthesis of 1,2-disubstituted benzimidazole derivatives. The phosphonium linker, obtained by reaction between PS-TPP and 4-fluoro-3-nitrobenzyl iodide, underwent aromatic substitution with primary amines, followed by one-pot reaction, reduction of the nitro group with tin(II) chloride, and oxidative cyclization of the *ortho*-diaminoaromatic intermediates with aldehydes under microwave irradiation. The final products were released from the resin in a short time using 10% NaOH in MeOH under microwave heating to leave a methyl group at the attachment point and were obtained in moderate overall yield.

## EXPERIMENTAL

Triphenylphosphine resin (100–200 mesh, 1% cross-linked; loading of 3.0 mmol/g) was purchased from Novabiochem (Darmstadt, Germany). All solvents were distilled prior to use. Analytical TLC was performed on silica gel 60F-254 plates and visualized with UV light (254 nm) and/or p-anisaldehyde in acidic ethanolic solution. Column chromatography was performed using silica gel (Scientific Adsorbents Incorporated, 63–200 μm). Melting points were determined with an electrothermal melting point apparatus (Electrothermal 9100, Melting Point Apparatus, Thermo Fisher Scientific, USA) and are uncorrected. Proton NMR spectra were recorded on a Bruker DPX-400 spectrometer (Bruker Corporation, Billerica, MA). The chemical shifts values are expressed in parts per million relative to tetramethylsilane

**Table 3**

5-Methyl-1,2-disubstituted benzimidazolesm.

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| Compound | $R_1$ | $R_2$ | Yield[a] (%) |
|---|---|---|---|
| **7b** | $CH_2CH_2Ph$ | $(CH_2)_4CH_3$ | 50 |
| **7c** | $CH_2CH_2Ph$ | 2-Furyl | 51 |
| **7d** | $CH_2CH_2Ph$ | *p*-F-Ph | 33 |
| **7e** | $CH_2CH_2Ph$ | *p*-Br-Ph | 30 |
| **7f** | $CH_2CH_2Ph$ | *p*-$N(Me)_2$-Ph | 46 |
| **7g** | $CH_2CH_2Ph$ | *p*-NHCOMe-Ph | 30 |
| **7h** | $CH_2CH_2Ph$ | *m-p*-$O,O(CH_2)$-Ph | 57 |
| **7i** | $(CH_2)_3CH_3$ | H[b] | 42 |
| **7j** | $(CH_2)_3CH_3$ | $(CH_2)_4CH_3$ | 19 |
| **7k** | $(CH_2)_3CH_3$ | 2-Furyl | 21 |
| **7l** | $(CH_2)_3CH_3$ | *p*-F-Ph | 30 |
| **7m** | $(CH_2)_3CH_3$ | *p*-Br-Ph | 19 |
| **7n** | $(CH_2)_3CH_3$ | *p*-$N(Me)_2$-Ph | 27 |
| **7o** | $(CH_2)_3CH_3$ | *p*-NHCOMe-Ph | 35 |
| **7p** | $(CH_2)_3CH_3$ | *m-p*-$O,O(CH_2)$-Ph | 20 |

[a]Yields are based on the weight of purified product and relative to the initial loading of the resin (3.0 mmol/g).
[b]DMF was used as solvent.

as internal standard. Mass spectra were determined either on an MSD 5973 Hewlett–Packard or LC/MSD-Series 100 Hewlett–Packard spectrometers (Agilent Technologies, Madrid, Spain) using EI or ESI, respectively. Infrared spectra were recorded on a PerkinElmer 1310 infrared spectrophotometer (PerkinElmer, USA) (the frequencies are expressed in $cm^{-1}$). Structural assignments are based on $^1H$, COSY, HMBC, HMQC, and MS spectroscopies. Microanalyses were performed in Fisons EA 1108 CHNS-O elemental analyzer (Fisons, Waltham, MA) and were within 0.4% of the calculated compositions. Microwave experiments: reactions in sealed vessels were conducted in commercial microwave systems, multimode cavity WX-4000 from, PreeKem Scientific Instruments Co., Ltd. Products (Shanghai, China), with a microwave power delivery system ranging from 100 to 1000 W. Experiments were carried out in closed 60 mL reactors made of Teflon. The temperature was monitored via fiber optic contact thermometer protected in a Teflon-coated gain inserted directly into the reaction mixture. The vessel contents were stirred by means of an adjustable rotating magnetic plate located below the floor of the microwave cavity. Temperature, pressure, and power profiles were monitored using commercially available softwares provided by the manufacturers.

**4-fluro-3-nitrobenzyl iodide (3).** To a suspension of PS-TPP (1.3 mmol) in anhydrous dichloromethane (12 mL) at room temperature was added imidazole (88 mg, 1.3 mmol) and iodine (33 0mg, 1.3 mmol) and stirred for approximately 5 min. The alcohol (170 mg, 1.0 mmol) was then added to the reaction mixture and irradiated in a sealed tube at 60–70°C for 20 min (Power max = 300 W). After cooling at room temperature, the reaction mixture was filtered and washed with dichloromethane. The filtrate was then sequentially washed with aqueous thiosulfate solution (5%) and water, dried over $Na_2SO_4$, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography ($SiO_2$, petroleum ether : EtOAc (7:3)), afforded **3** (0.12 g, 42%) as an orange oil. $^1H$ NMR ($CDCl_3$) $\delta$ (ppm): 4.46 (s, 2H), 7.24 (dd, $J$ = 7.98 Hz, $J$ = 8.62 Hz, 1H), 7.65 (m, 1H), 8.08 (dd, $J$ = 2.37 Hz, $J$ = 6.87 Hz, 1H). ESI–MS, *m/z*: 282 ($M^+ + H$). *Anal*. Calcd for $C_7H_5FINO_2$: C, 29.92; H, 1.79; N, 4.98. Found: C, 30.23; H, 2.09; N, 5.35.

**General procedure for the preparation of resin-bound o-fluronitrobenzene phosphonium salt (4).** Triphenylphosphine resin (1.5 g, 4.4 mmol/g) was placed in a 60 mL Teflon reactor and swelled with dry DMF or NMP (15 mL) for 10 min. The resin was then treated with benzyl iodide **3** (6.75 mmol, 1.5 equiv) and irradiated in a sealed tube at 160°C for 5 min (Power max = 300 W). After cooling at room temperature, the suspension was filtered and washed three times with DMF (15 mL), dichloromethane (DCM) (15 mL), and diethyl ether (15 mL). The resin **4** was finally dried *in vacuo* at 25°C for 24 h. FTIR (neat): 1537, 1492, 1348, and 1181 $cm^{-1}$.

**General procedure for the preparation and cleavage of resin-bound *o*-nitroaniline (5).** A Teflon tube was charged sequentially with resin-bound phosphonium salt **4** (1.3 g), DMF or NMP (15 mL), and the corresponding amine (3.6 equiv). The test tube was then sealed with Teflon septum and heated 20 min at 70°C for butylamine and 10 min at 150°C for phenethylamine by microwave irradiation. The vial was cooled, and the crude reaction mixture was filtered and washed three times with DMF (15 mL), dichloromethane (15 mL), and diethyl ether (15 mL). The resin **5** was finally dried *in vacuo* at 25°C for 24 h. *Resin-bound o-nitroaniline* (**5a**). FTIR (neat): 3356, 1665, 1492, and 1092 $cm^{-1}$. *Resin-bound o-nitroaniline* (**5b**). FTIR (neat): 3379, 1628, 1523, and 1111 $cm^{-1}$. Cleavage: A suspension of resin **5** (400 mg) in a freshly prepared solution of 10% NaOH in MeOH (4 mL) was irradiated in a sealed tube operated at power 100 W for 5 min ($T_{max}$ = 85°C). The resin was washed with dichloromethane (DCM), the washes were combined, diluted with DCM and water, and neutralized with HCl. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated to give the crude product. After work-up, the residue was purified by column chromatography ($SiO_2$, petroleum ether : EtOAc (7:3)). *N-phenethyl-4-methyl-2-nitroaniline* (**5a**). Orange oil. $^1H$ NMR ($CDCl_3$) $\delta$ (ppm): 2.28 (s, 3H), 3.02 (t, $J$ = 6.8 Hz, 2H), 3.56 (m, 2H), 6.79 (d, $J$ = 8.8 Hz, 1H), 7.26–7.29 (m, 5H), 7.34 (d, $J$ = 8.0 Hz, 1H), 7.99 (s, 1H), 8.00 (bs, 1H). ESI–MS, *m/z*: 257 ($M^+ + H$). *Anal*. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.01; H, 5.89; N, 11.35. *N-buthyl-4-methyl-2-nitroaniline* (**5b**). Yellow oil. $^1H$ NMR ($CDCl_3$) $\delta$ (ppm): 0.97 (t, $J$ = 7.6 Hz, 3H), 1.43 (m, 2H), 1.67 (m, 2H), 2.26 (s, 3H), 3.21 (m, 2H), 6.76 (d, $J$ = 8.8 Hz, 1H), 7.25 (dd, $J$ = 2.0 Hz, $J$ = 8.8 Hz, 1H), 7.97 (d, $J$ = 1.2 Hz, 1H). ESI–MS, *m/z*: 209 ($M^+ + H$). *Anal*. Calcd for $C_{11}H_{16}N_2O_2$: C, 76.44; H, 7.74; N, 13.45. Found: C, 76.05; H, 7.50; N, 13.80.

**General procedure for the preparation and cleavage of resin-bound benzimidazoles (6).** A Teflon tube was charged sequentially with resin-bound *o*-nitroaniline **5** (650 mg), NMP (8 mL), $SnCl_2.2H_2O$ (10 equiv), and the corresponding aldehyde (2 equiv). The reactor tube was sealed with Teflon septum and placed inside the cavity of the microwave reactor, operated at power 200 W for 10 min ($T_{max}$ = 160–200°C). After cooling at room temperature, the suspension was filtered and washed three times with $H_2O$ (15 mL), MeOH (15 mL), DCM (15 mL), and diethyl ether (15 mL). The resin **6** was finally dried *in vacuo* at 25°C for 24 h. Resin-bound benzimidazoles, FTIR (neat, $cm^{-1}$): (**6a**) 1177 and 1114; (**6b**) 1180 and 1112; (**6c**) 1175 and 1111; (**6d**) 1180 and 1114; (**6e**) 1177 and 1111; (**6f**) 1175 and 1115; (**6g**) 3300, 1680, 1530, 1260, 1180, and 1111; (**6h**) 1177, 1110, and 1032; (**6i**) 1179 and 1115; (**6j**) 1179 and 1114; (**6k**) 1181 and 1113; (**6l**) 1180 and 1111; (**6m**) 1177 and 1115; (**6n**) 1177 and 1110; (**6o**) 3400, 1670, 1523, 1259, 1179, and 1113; (**6p**) 1469, 1179, and 1113. Cleavage: A suspension of corresponding resin **6a–p** (200–500 mg) in a freshly prepared solution of 10% NaOH in MeOH (2–5 mL) was irradiated in a sealed tube operated at power 100 W for 5 min ($T_{max}$ = 75–85°C). The resin was washed with DCM, the washes were combined, diluted with DCM and water, and neutralized with HCl. The organic layer was dried over $Na_2SO_4$, filtered, and concentrated to give the crude product. After work-up, the residue was purified by column chromatography ($SiO_2$, mixtures of petroleum ether : EtOAc).

***5-Methyl-1-phenethyl-1H-benzimidazole (7a).*** Reddish oil; $^1H$ NMR ($CDCl_3$) $\delta$ (ppm): 2.51 (s, 3H), 3.13 (t, $J$ = 7.2 Hz, 2H), 4.38 (t, $J$ = 7.2 Hz, 2H), 7.03–7.05 (m, 2H), 7.14 (dd, $J$ = 1.2 Hz, $J$ = 8.4 Hz, 1H), 7.25–7.28 (m, 3H), 7.29 (d, $J$ = 8.4 Hz, 1H), 7.57 (s, 1H), 7.61 (s, 1H). $^{13}C$ NMR ($CDCl_3$): $\delta$ 22.0, 36.4, 47.5, 109.5, 120.2, 124.5, 127.2, 128.5, 131.2, 138.1, 143.5. EI–MS, *m/z* (abundance, %): 236 ($M^+$, 80), 145 (100), 118 (13), 91 (23). *Anal*. Calcd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.82; N, 11.85. Found: C, 80.95; H, 6.50; N, 11.60.

***5-Methyl-2-pentyl-1-phenethyl-1H-benzimidazole (7b).*** Yellow oil; $^1H$ NMR ($CDCl_3$) $\delta$ (ppm): 0.92 (t, $J$ = 6.8 Hz, 3H), 1.31 (m, 4H), 1.69 (m, 2H), 2.42 (t, $J$ = 7.6 Hz, 2H), 2.50 (s, 3H), 3.09 (t, $J$ = 6.8 Hz, 2H), 4.28 (t, $J$ = 7.2 Hz, 2H), 7.01–7.03 (m, 2H), 7.08 (dd, $J$ = 1.2 Hz, $J$ = 8.0 Hz, 1H), 7.25–7.31 (m, 3H), 7.21 (d, $J$ = 8.0 Hz, 1H), 7.55

(d, $J$ = 0.8 Hz, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 14.1, 21.0, 22.2, 27.5, 32.1, 36.42, 45.5, 109.3, 120.3, 123.2, 128.0, 129.1, 132.2, 138.3, 156.4. ESI–MS, *m/z*: 306.1 ($M^+$ + H). *Anal*. Calcd for $C_{21}H_{26}N_2$: C, 82.31; H, 8.55; N, 9.14. Found: C, 81.98; H, 8.10; N, 9.40.

***2-(Furan-2-yl)-5-methyl-1-phenethyl-1H-benzimidazole (7c).*** Brown oil; $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 2.51 (s, 3H), 3.13 (t, $J$ = 7.6 Hz, 2H), 4.65 (t, $J$ = 7.6 Hz, 2H), 6.60 (dd, $J$ = 2.0 Hz, $J$ = 3.6 Hz, 1H), 7.10–7.13 (m, 2H), 7.16–7.20 (m, 3H), 7.22–7.32 (m, 3H), 7.59 (s, 1H), 7.63 (dd, $J$ = 0.8 Hz, $J$ = 1.6 Hz, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 22.4, 37.4, 47.2, 100.3, 111.7, 112.5, 120.1, 128.5, 129.6, 133.5, 139.0, 144.3, 145.3. ESI–MS, *m/z*: 303.2 ($M^+$ + H). *Anal*. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N,11.01. Found: C, 75.915; H, 7.40; N, 11.35.

***2-(4-Fluorophenyl)-5-methyl-1-phenethyl-1H-benzimidazole (7d).*** Yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 2.54 (s, 3H), 3.07 (t, $J$ = 7.2 Hz, 2H), 4.50 (t, $J$ = 7.2 Hz, 2H), 6.77 (d, $J$ = 6.4 Hz, 2H), 7.11–7.14 (m, 3H), 7.16–7.20 (m, 2H), 7.30–7.33 (m, 2H), 7.25 (d, $J$ = 8.0 Hz, 1H), 7.41 (d, $J$ = 8.4 Hz, 1H), 7.71 (s, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 22.1, 36.1, 46.2, 110.1, 117.1, 118.2, 125.2, 128.1, 129.4, 131.1, 132.3, 133.1, 151.2, 163.5. ESI–MS, *m/z*: 331.0 ($M^+$ + H). *Anal*. Calcd for $C_{22}H_{19}FN_2$: C, 79.97; H, 5.80; N, 5.75. Found: C, 79.64; H, 5.43; N, 5.37.

***2-(4-Bromophenyl)-5-methyl-1-phenethyl-1H-benzimidazole (7e).*** Yellow solid; mp 88–89 C, $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 2.55 (s, 3H), 3.06 (t, $J$ = 7.2 Hz, 2H), 4.41 (t, $J$ = 7.2 Hz, 2H), 6.86–6.88 (m, 2H), 7.18–7.25 (m, 3H), 7.23 (d, $J$ = 8.4 Hz, 2H), 7.36 (d, $J$ = 8.0 Hz, 1H), 7.53 (d, $J$ = 8.4 Hz, 2H), 7.63 (s, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 21.6, 36.3, 47.1, 110.3, 120.2, 124.2, 129.1, 131.2, 132.4, 134.0, 137.2, 144.1, 153.7. ESI–MS, *m/z*: 391.2 ($M^+$ + H). *Anal*. Calcd for $C_{22}H_{19}BrN_2$: C, 67.53; H, 4.89; N, 7.16. Found: C, 67.82; H, 5.19; N, 7.43.

***2-(4-N,N-Dimethylaminophenyl)-5-methyl-1-phenethyl-1H-benzimidazole (7f).*** Yellow oil; $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 2.52 (s, 3H), 3.06 (s, 6H), 3.12 (t, $J$ = 8.0 Hz, 2H), 4.44 (t, $J$ = 8.0 Hz, 2H), 6.75 (d, $J$ = 9.2 Hz, 2H), 7.05 (m, 2H), 7.25 (m, 3H), 7.13 (dd, $J$ = 0.8 Hz, $J$ = 8.0 Hz, 1H), 7.29 (d, $J$ = 8.4 Hz, 1H), 7.47 (d, $J$ = 8.8 Hz, 2H), 7.65 (s, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 22.1, 36.1, 40.3, 46.7, 109.3, 112.3, 118.5, 123.2, 120.2, 124.2, 128.2, 129.5, 130.4, 134.0, 137.1, 154.3. EI–MS, *m/z* (abundance, %): 355 ($M^+$, 100), 264 (93), 220 (17), 145 (13). *Anal*. Calcd for $C_{24}H_{25}N_3$: C, 81.09; H, 7.09; N, 11.82. Found: C, 81.36; H, 7.42; N, 11.67.

***2-(4-Acetamidophenyl)-5-methyl-1-phenethyl-1H-benzimidazole (7g).*** Brown oil; $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 2.17 (s, 3H), 2.53 (s, 3H), 3.06 (t, $J$ = 7.2 Hz, 2H), 4.40 (t, $J$ = 7.6 Hz, 2H), 6.90 (m, 2H), 7.16–7.21 (m, 3H), 7.29 (d, $J$ = 8.4 Hz, 2H), 7.34 (d, $J$ = 8.0 Hz, 1H), 7.53 (d, $J$ = 8.4 Hz, 2H), 7.60 (s, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 22.5, 24.4, 36.5, 46.4, 110.3, 120.3, 126.5, 128.5, 129.3, 136.4, 138.1, 142.2, 153.2, 169.6. EI–MS, *m/z* (abundance, %): 369 ($M^+$, 92), 278 (100), 236 (57). *Anal*. Calcd for $C_{24}H_{23}N_3O$: C, 78.02; H, 6.27; N, 11.37. Found: C, 78.43; H, 6.49; N, 11.70.

***2-(3,4-Methylendioxophenyl)-5-methyl-1-phenethyl-1H-benzimidazole (7h).*** Cream solid; mp 129–130 C, $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 2.54 (s, 3H), 3.07 (t, $J$ = 7.2 Hz, 2H), 4.42 (t, $J$ = 7.2 Hz, 2H), 6.06 (s, 2H), 6.86 (d, $J$ = 6.0 Hz, 1H), 6.88 (s, 1H), 6.92–6.95 (m, 3H), 7.15 (dd, $J$ = 1.2 Hz, $J$ = 8.4 Hz, 1H), 7.16–7.24 (m, 3H), 7.33 (d, $J$ = 8.0 Hz, 1H), 7.62 (s, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 22.2, 36.5, 47.4, 102.5, 108.1, 109.2, 110.6, 120.1, 122.2, 123.3, 124.5, 128.5, 129.6, 132.1, 133.5, 139.2, 148.5, 149.1, 153.5. ESI–MS, *m/z*: 357.1 ($M^+$ + H). *Anal*. Calcd for $C_{23}H_{20}N_2O_2$: C, 77.51; H, 5.66; N, 7.86. Found: C, 77.30; H, 5.98; N, 8.21.

***1-Buthyl-5-methyl-1-H-benzimidazole (7i).*** Reddish oil; $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.94 (t, $J$ = 7.6 Hz, 3H), 1.33 (m, 2H), 1.84 (m, 2H), 2.50 (s, 3H), 4.13 (t, $J$ = 7.2 Hz, 2H), 7.12 (d, $J$ = 8.0 Hz, 1H), 7.31 (d, $J$ = 8.0 Hz, 1H), 7.61 (s, 1H), 7.84 (s, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 17.1, 20.0, 22.0, 33.4, 45.5, 109.2, 120.1, 123.1, 124.5, 132.1, 133.4, 143.2. ESI–MS, *m/z*: 189.2 ($M^+$ + H). *Anal*. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.15; H, 8.86; N, 14.40.

***1-Buthyl-5-methyl-2-pentyl-1H-benzimidazole (7j).*** Reddish oil; $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.97 (t, $J$ = 7.4 Hz, 3H), 0.99 (t, $J$ = 7.2 Hz, 3H), 1.36–1.47 (m, 6H), 1.87 (m, 2H), 2.48 (s, 3H), 2.86 (t, $J$ = 8.0 Hz, 2H), 4.08 (t, $J$ = 7.2 Hz, 2H), 7.08 (dd, $J$ = 1.2 Hz, $J$ = 8.4 Hz, 1H), 7.20 (d, $J$ = 8.4 Hz, 1H), 7.56 (s, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 14.3, 21.2, 23.1, 28.3, 32.4, 32.6, 43.5, 109.2, 119.5, 124.2, 125.2, 132.5, 133.7, 155.1. EI–MS, *m/z*(abundance, %): 258 ($M^+$, 46), 215 (66), 187 (88), 160 (100%); 146 (76%). *Anal*. Calcd for $C_{17}H_{26}N_2$: C, 79.02; H, 10.14; N, 10.84. Found: C, 79.38; H, 10.45; N, 11.25.

***1-Buthyl-2-(furan-2-yl)-5-methyl-1H-benzimidazole (7k).*** Reddish oil; $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.94 (t, $J$ = 7.2 Hz, 3H), 1.37 (m, 2H), 1.83 (m, 2H), 2.50 (s, 3H), 4.45 (t, $J$ = 7.2 Hz, 2H), 6.62 (dd, $J$ = 2.0 Hz, $J$ = 3.6 Hz, 1H), 7.13 (dd, $J$ = 1.2 Hz, $J$ = 8.4 Hz, 1H), 7.27 (d, $J$ = 8.4 Hz, 1H), 7.29 (m, 1H), 7.60 (s, 1H), 7.64 (dd, $J$ = 0.8 Hz, $J$ = 1.6 Hz, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 14.1, 20.3, 22.5, 32.2, 45.4, 109.2, 112.5, 113.2, 119.6, 124.3, 133.2, 134.6, 142.3, 143.8, 146.1. EI–MS, *m/z* (abundance, %): 254 ($M^+$, 100), 211 (73), 197 (13). *Anal*. Calcd for $C_{20}H_{18}N_2O$: C, 79.44; H, 6.00; N,9.26. Found: C, 79.85; H, 6.31; N, 9.56.

***1-Buthyl-2-(4-fluorophenyl)-5-methyl-1H-benzimidazole (7l).*** Yellow solid; mp 59–61 C, $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.89 (t, $J$ = 7.2 Hz, 3H), 1.25 (m, 2H), 1.77 (m, 2H), 2.52 (s, 3H), 4.18 (t, $J$ = 7.6 Hz, 2H), 7.14 (dd, $J$ = 1.2 Hz, $J$ = 8.4 Hz, 1H), 7.21 (t, $J$ = 8.8 Hz, 2H), 7.30 (d, $J$ = 8.4 Hz, 1H), 7.61 (s, 1H), 7.69 (m, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ 13.7, 20.1, 22.2, 32.5, 44.7, 110.4, 116.5, 120.2, 123.2, 124.5, 128.3, 132.2, 133.6, 134.6, 153.4, 162.1. ESI–MS, *m/z*: 283.3 ($M^+$ + H). *Anal*. Calcd for $C_{18}H_{19}FN_2$: C, 76.57; H, 6.78; N, 9.92. Found: C, 76.28; H, 6.47; N, 9.62.

***2-(4-Bromophenyl)-1-buthyl-5-methyl-1H-benzimidazole (7m).*** Yellowish solid; mp 89–91 C, $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.87 (t, $J$ = 7.6 Hz, 3H), 1.24 (m, 2H), 1.76 (m, 2H), 2.52 (s, 3H), 4.21 (t, $J$ = 7.6 Hz, 2H), 7.18 (dd, $J$ = 1.2 Hz, $J$ = 8.4 Hz, 1H), 7.32 (d, $J$ = 8.4 Hz, 1H), 7.61 (d, $J$ = 8.8 Hz, 2H), 7.65 (s, 1H), 7.68 (d, $J$ = 8.8 Hz, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ 14.2, 20.6, 22.5, 32.1, 44.2, 110.1, 120.5, 125.7, 126.5, 129.3, 130.0, 132.3, 133.2, 142.7, 153.0. EI–MS, *m/z* (abundance, %): 342 ($M^+$, 87%), 313 (12), 301 (16), 220 (100%). *Anal*. Calcd for $C_{18}H_{19}BrN_2$: C, 62.98; H, 5.58; N, 8.16. Found: C, 62.64; H, 5.22; N, 8.51.

***1-Buthyl-2-(4-N,N-dimethylaminophenyl)-5-methyl-1H-benzimidazole (7n).*** Brown solid; mp 95–96 C, $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.92 (t, $J$ = 7.2 Hz, 3H), 1.31 (m, 2H), 1.82 (m, 2H), 2.51 (s, 3H), 3.06 (s, 6H), 4.20 (t, $J$ = 7.6 Hz, 2H), 6.87 (d, $J$ = 9.2 Hz, 2H), 7.09 (dd, $J$ = 0.8 Hz, $J$ = 8.0 Hz, 1H), 7.28 (d, $J$ = 8.0 Hz, 1H), 7.59 (s, 1H), 7.61 (d, $J$ = 9.2 Hz, 2H). $^{13}$C NMR ($CDCl_3$): $\delta$ 14.0, 20.1, 22.2, 32.6, 40.4, 45.4, 110.4, 112.6, 118.3, 119.6, 124.5, 130.1, 132.3, 134.2, 135.4, 151.2, 154.1. ESI–MS, *m/z*: 308.2 ($M^+$ + H). *Anal*. Calcd for $C_{20}H_{25}N_3$: C, 78.14; H, 8.20; N, 13.67. Found: C, 78.44; H, 8.53; N, 13.99.

***2-(4-Acetamidophenyl)-1-buthyl-5-methyl-1H-benzimidazole (7o).*** Yellow solid; mp 93–95 C, $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.90 (t, $J$ = 7.2 Hz, 3H), 1.35 (m, 2H), 1.79 (m, 2H), 2.27 (s, 3H), 2.53 (s, 3H), 4.22 (t, $J$ = 7.4 Hz, 2H), 7.23 (dd, $J$ = 1.2 Hz, $J$ = 8.4 Hz, 1H), 7.37 (d, $J$ = 8.0 Hz, 1H), 7.44 (d, $J$ = 8.0 Hz, 2H), 7.62 (s, 1H),

7.77 (d, $J = 8.4$ Hz, 2H), 9.47 (s, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 14.4, 20.6, 22.8, 24.2, 33.1, 44.9, 110.6, 118.4, 120.7, 122.6, 124.3, 130.1, 132.7, 133.6, 134.2, 140.1, 153.4, 170.2. EI–MS, *m/z* (abundance, %): 321 ($M^+$, 100%), 292 (18), 278 (35), 236 (27%). *Anal*. Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.31; H, 7.67; N, 13.32.

***1-Buthy-2-(3,4-methylendioxophenyl)-5-methyl-1H-benzimidazole (7p).*** Cream solid; mp 77–79 C, $^1$H NMR ($CDCl_3$) $\delta$ (ppm): 0.88 (t, $J = 7.6$ Hz, 3H), 1.25 (m, 2H), 1.76 (m, 2H), 2.51 (s, 3H), 4.21 (t, $J = 7.6$ Hz, 2H), 6.08 (s, 2H), 6.95 (d, $J = 8.0$ Hz, 1H), 7.14 (dd, $J = 0.8$ Hz, $J = 8.0$ Hz, 1H), 7.21 (s, 1H), 7.23 (dd, $J = 1.6$ Hz, $J = 8.0$ Hz, 1H), 7.30 (d, $J = 8.4$ Hz, 1H), 7.63 (s, 1H). $^{13}$C NMR ($CDCl_3$): $\delta$ 13.5, 19.8, 22.1, 30.6, 46.3, 102.6, 109.4, 110.2, 111.7, 116.3, 126.1, 126.4, 128.1, 128.5, 130.0, 137.5, 149.1, 149.7, 150.9. EI–MS, *m/z* (abundance, %): 308 ($M^+$, 100%), 279 (72), 252 (30), 235 (43%). *Anal*. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.39; H, 6.86; N, 9.22.

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