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Article

Facile Synthesis of Benzimidazoles via *N*-Arylamidoxime Cyclization

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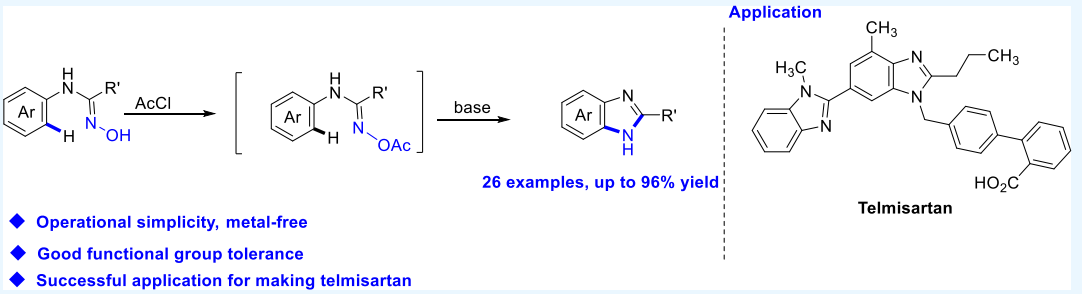

ABSTRACT: A facile synthesis of benzimidazoles was described by a one-pot process containing acylation−cyclization of *N*-arylamidoxime. This method provided an alternative synthesis of benzimidazoles with a certain diversity of substituted groups in acceptable yields (up to 96%). More importantly, the construction of bis-benzimidazole (**8**), the key intermediate for making telmisartan, was achieved by adopting this method that enabled avoiding the undesired nitration with nitric/sulfuric acid and the cyclization in polyphosphoric acid in the existing operations.

INTRODUCTION

Benzimidazole is an important class of N-containing heterocycles that widely exists in a variety of bioactive compounds[1−7] and pharmaceutical active ingredients, such as telmisartan[8,9] and candesartan cilexetil,[10,11] and esomeprazole[12] (Figure 1). Benzimidazole compounds have attracted great interest of researchers, and many synthetic methods were developed due to their various biological activities and wide applications in the past several decades. Generally, benzimidazole compounds were most often constructed by condensation of *o*-phenylenediamines with carboxylic acid derivatives[13−17] as well as aldehydes,[18−20] ketones,[21] primary aliphatic amines,[22] and alcohols[23,24] (Scheme 1A). Additionally, the synthesis of benzamidines from amidines through metal-catalyzed or oxidative cyclization was also explored (Scheme 1B).[25−29] Recently, benzimidazoles were generated from *N*-phenylamidoxime esters with the iridium photocatalyst.[30] *N*-Arylamidoximes have been previously used to prepare various types of heterocycles, such as benzoxazoles,[31] 1,2,4-thiadiazole-5-thiones,[32] 1,2,4-oxadiazole-5-(4*H*)-thiones,[33] and fulleroimidazole derivatives.[34] Nevertheless, the synthesis of benzimidazoles with *N*-arylamidoxime was rarely reported,[35,36] and the functional group scope was rather narrow. Herein, we report a "one-pot" acylation−cyclization method for the synthesis of benzimidazoles with various functional groups from *N*-aryl amidoxime (Scheme 1C). In addition, this method provided an improved approach for making telmisartan, avoiding the undesired nitration with nitric/sulfuric acid and the cyclization with polyphosphoric acid in the existing operations.[37,38]

RESULTS AND DISCUSSION

We started our investigations by screening the cyclization reaction conditions with *N*-arylamidoxime **1** as the model substrate (Table 1). First, *N*-arylamidoxime **1** was acylated by various leaving groups to afford compound **2**, which was then treated with alkaline solution to produce benzimidazole **3**. The types of leaving groups and bases were screened. In the initial screening, *N*-arylamidoxime **1** (1 mmol) was treated with a *p*-TsCl leaving group (1 eq) and *N*,*N*-diisopropylethylamine (DIPEA, 2.5 eq) in acetonitrile (MeCN) to produce benzimidazole **3** in 85% yield (entry 1). Upon replacement with other leaving groups such as *p*-nitrobenzoyloxy, benzoyloxy, and acetoxy, only a trace of benzimidazole **3** was observed (Table 1, entries 2−4, respectively). Furthermore, increasing the reaction temperature showed an ineffective conversion of intermediate **2** (Table 1, entries 5−7).

As an alternative, the reactions were carried out with potassium hydroxide (KOH) to replace DIPEA in acetonitrile, and benzimidazole **3** was obtained in 57−70% yield (Table 1, entries 8−13, respectively). In addition, the reaction in chlorobenzene (PhCl) with DIPEA at 25 °C showed only a

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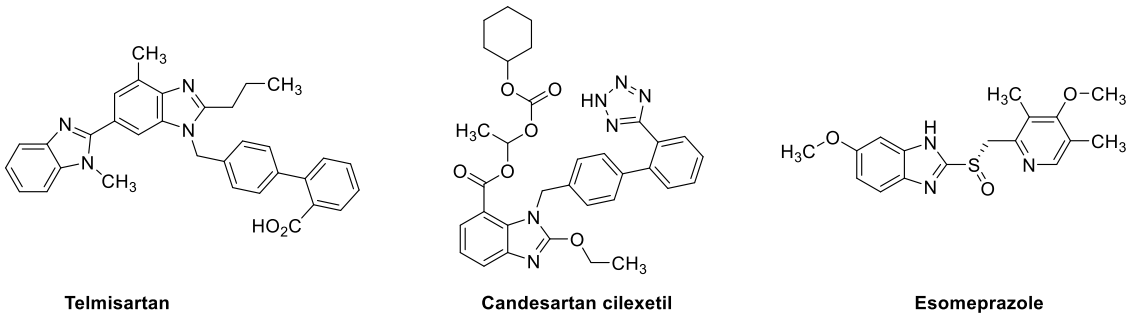
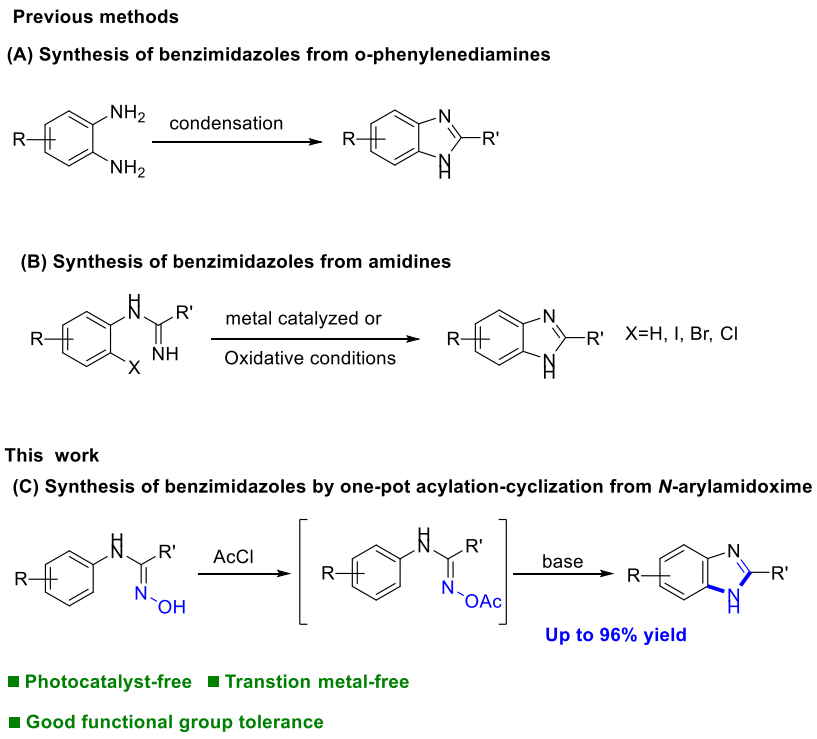


Figure 1. Representative benzimidazole-containing drugs.

Scheme 1. (A,B) Previous Methods and (C) This Method for the Synthesis of Benzimidazoles through One-Pot Acylation−Cyclization of *N*-Arylamidoxime



trace of benzimidazole **3** (Table 1, entries 14−16, respectively), whereas the conversion of intermediate **2** to product **3** occurred with over 50% of unreacted **2** remaining at 100 °C (Table 1, entries 17−19). When the reaction temperature was raised to the refluxing temperature of chlorobenzene (132 °C) in the presence of DIPEA, the desired benzimidazole **3** was achieved with moderate isolated yields (Table 1, entries 20 and 21, respectively). In fact, when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used instead of DIPEA, the desired product **3** was obtained with significantly increased isolated yields of over 89% (Table 1, entries 22 and 23, respectively). Thus, we chose our acylation−cyclization process using AcCl as an acylation reagent with DBU as the base in PhCl at refluxing temperature (132 °C) (Table 1, entry 22) as the optimum reaction condition for further studies.

With reliable conditions in hand, we then investigated the scope and generality of the cyclization process (Table 2). It was found that both methyl- and ester-substituted phenyl moieties of *N*-arylamidoxime (**1a−1c**, **1f**, **1k**, **1o**) underwent the reactions smoothly, generating the desired benzimidazoles (**3a−3c**, **3f**, **3k**, **3o**[39]) in comparable yields (65−90%). In addition, electronic effects of the substituents on the phenyl moiety were observed. Methoxy-substituted phenyl substrates (**1d−1e**, **1v**) well participated in the "one-pot" acylation−cyclization reaction, leading to benzimidazoles (**3d−3e**, **3v**) in 85−95% yields, and the chloro- or fluoro-substituted phenyl moiety (**1g−1h**) also resulted in high reaction outcomes (**3g**, 92% yield, **3h**, 85% yield). Furthermore, unsubstituted phenyl moiety substrates (**1**, **1x**) were compatible with this reaction to afford benzimidazole products (**3**, **3x**) with excellent yields (92−96%). In contrast, when an electron-withdrawing substituent such as a nitro group (**1l**, **1m**) and nitrile (**1n**) reacted, the yields of the corresponding products (**3l**, **3m**, **3n**) were decreased (43−75% yield). The yield of benzimidazole **3l** (75% yield) was higher than that of **3m** (55% yield) or **3n** (43% yield), due to the substituent of the amidoxime moiety which was swapped from *n*-propyl to conjugation substituent phenyl. In addition, a series of benzimidazole products could be delivered using substrates bearing substituents on an amidoxime moiety. For example, the ethoxyl or methylthio group at the amidoxime moiety was well tolerated, in which the corresponding products (**3p−3r**, **3s**,[39] **3t**, **3u**,[40] **3w**) were

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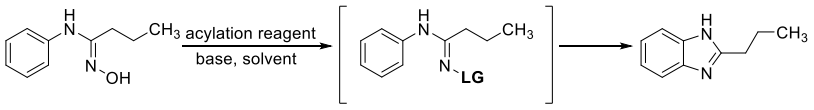
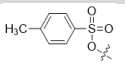
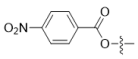
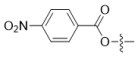
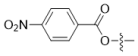
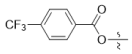
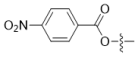
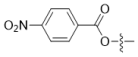
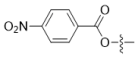
ACS Omega 2022, 7, 45678−45687

Table 1. Optimization of the Cyclization Reaction for Benzimidazole 3



1 2 3

entry	acylation reagent	leaving group	solvent	base	temp (°C)	yield (%)[c]
1	p-TsCl		MeCN	DIPEA	25	85[a]
2	4-NO_2-BzCl		MeCN	DIPEA	25	15[a]
3	BzCl		MeCN	DIPEA	25	trace[a]
4	AcCl		MeCN	DIPEA	25	trace[a]
5	4-NO_2-BzCl		MeCN	DIPEA	reflux (82)	23[a]
6	BzCl		MeCN	DIPEA	reflux (82)	trace[a]
7	AcCl		MeCN	DIPEA	reflux (82)	trace[a]
8	4-NO_2-BzCl		MeCN	KOH	25	70[a]
9	4-CF_3-BzCl		MeCN	KOH	25	60[a]
10	BzCl		MeCN	KOH	25	57[a]
11	AcCl		MeCN	KOH	25	68[a]
12	AcCl		MeCN	KOH	50	68
13	AcCl		MeCN	KOH	reflux (82)	70[a]
14	4-NO_2-BzCl		PhCl	DIPEA	25	trace[a]
15	BzCl		PhCl	DIPEA	25	trace[a]
16	AcCl		PhCl	DIPEA	25	trace[a]
17	4-NO_2-BzCl		PhCl	DIPEA	100	45[a]
18	BzCl		PhCl	DIPEA	100	38[a]
19	AcCl		PhCl	DIPEA	100	35[a]
20	4-NO_2-BzCl		PhCl	DIPEA	reflux (132)	68[a]
21	AcCl		PhCl	DIPEA	reflux (132)	55[a]
22	AcCl		PhCl	DBU	reflux (132)	92[b]
23	Ac_2O		PhCl	DBU	reflux (132)	89[b]

[a]The reactions were performed on the scale of 1 mmol of **1** under the conditions: 1 equiv of acylation reagent, 4 equiv of base. [b]The reactions were performed on the scale of 1 mmol of **1** under the conditions: 1 equiv of acylation reagent, 2.5 equiv of base. [c]The yields were given as isolated yields.

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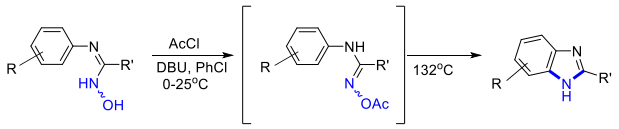
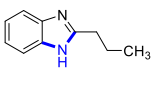
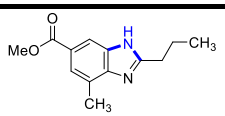
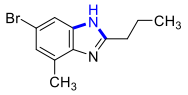
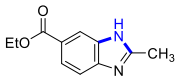
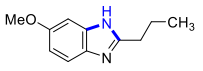
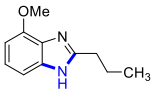
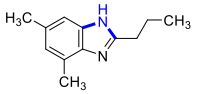
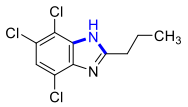
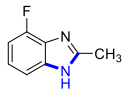
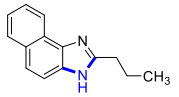
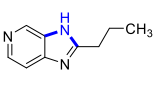
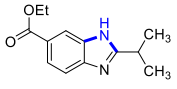
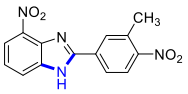
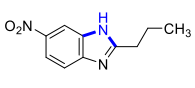
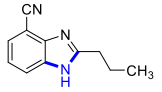
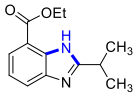
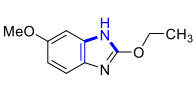
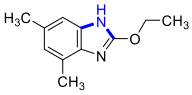
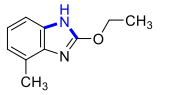
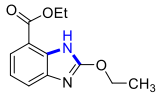
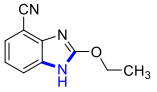
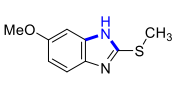
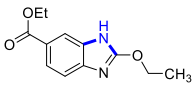
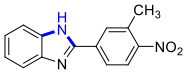
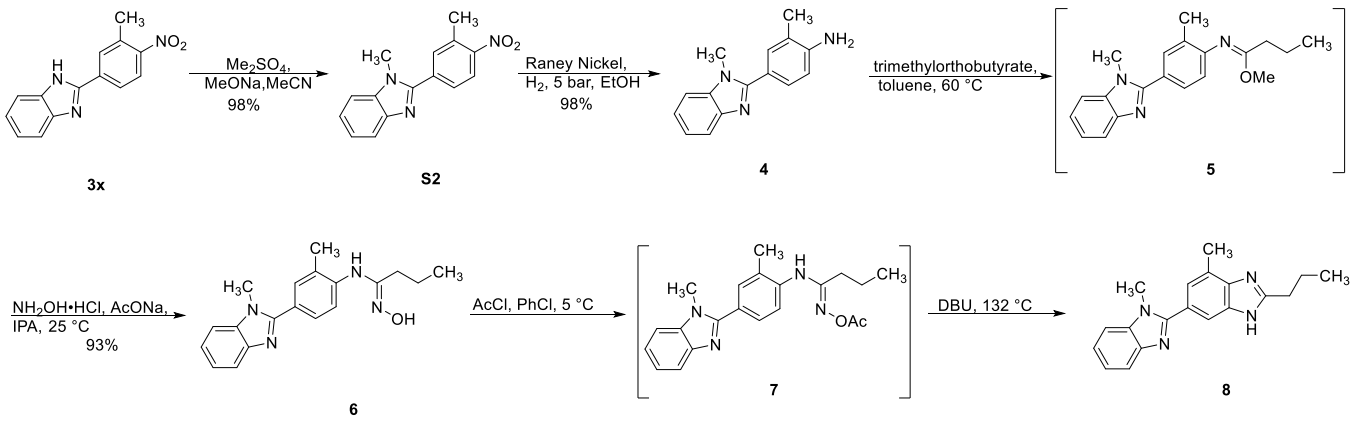
Table 2. Substrate Scope of the Cyclization Reaction for Benzimidazoles[a]



				
3	**3a**	**3b**[c]	**3c**	**3d**
92%	90%	93%	85%	95%
				
3e	**3f**	**3g**	**3h**[c]	**3i**
92%	90%	92%	85%	90%
				
3j	**3k**	**3l**	**3m**[41]	**3n**[41]
70%	88%	75%	55%	43%
				
3o	**3p**	**3q**	**3r**	**3s**
65% (3:1)[b]	75%	65%	55%	35% (3:1)[b]
				
3t[41]	**3u**	**3v**	**3w**[c]	**3x**
38%	35%	85%	45%	96%

[a]The reactions were performed on the scale of 1 mmol of **1**, **1a−1x**, under the conditions: 1.2 equiv of acylation reagent, 2.5 equiv DBU, PhCl as a solvent, 132 °C. The yields were given as isolated yields. [b]Ratio of regioisomeric products. See the Supporting Information for the structure of the minor isomers. [c]Tautomers were obtained. See the Supporting Information for the structure of the tautomer.

Scheme 2. Postapplication for the Synthesis of Bis-Benzimidazole (8)



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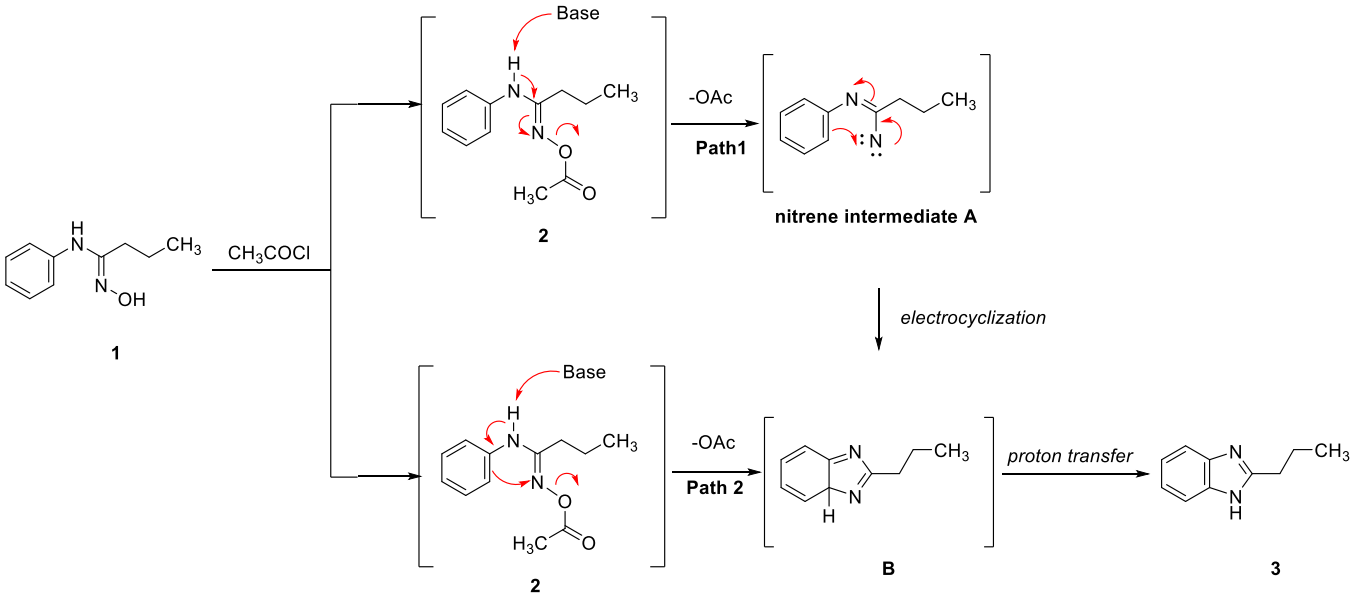
Scheme 3. Plausible Mechanism for the Cyclization Step



furnished in 35−75% yields. Notably, substrates carrying the 1-naphthyl moiety (**1i**) and pyridyl moiety (**1j**) were applicable in this protocol, giving rise to **3i** (90% yield) and **3j** (70% yield), demonstrating broad applicability of the present reaction to the synthesis of invaluable imidazole derivatives.

Next, we demonstrated the utility of our cyclization approach by applying it to construct the key intermediate bis-benzimidazole **8** for telmisartan (Scheme 2). First, aniline **4** could be easily synthesized in two steps in 96% yield from **3x** through *N*-methylation of the imidazole moiety and catalytic hydrogenation of the nitro group. Subsequently, *N*-arylamidoxime **6** was prepared via the displacement of hydroxylamine with *N*-arylbutyrimidate **5**, which was obtained by the condensation of aniline **4** with trimethylorthobutyrate in total 93% yield. *N*-Arylamidoxime **6** further converted to bis-benzimidazole **8** using our optimized conditions with an isolated yield of 96%.

Based on the references[34] and above-mentioned experimental facts, the plausible mechanism for the cyclization of *N*-arylamidoxime is depicted in Scheme 3. First, *N*-arylamidoxime **1** reacts with acetyl chloride to afford **2** which is to form an acetoxy leaving group. Afterward, the deacetoxylation of **2** promoted by a base would follow path 1 to produce the nitrene intermediate **A**, which in turn undergoes electrocyclization or C−H insertion to form the intermediate **B** and involves two sequential proton transfer steps to provide benzimidazole **3**. In addition, an alternative pathway via the direct cyclization to generate the intermediate **B** was also plausible (Path 2).

CONCLUSIONS

In summary, the synthesis of benzimidazoles by one-pot acylation−cyclization of *N*-arylamidoxime was developed in acceptable yields and exhibited good substituent tolerance. The precious metal, expensive ligands, and harsh reaction conditions were excluded in this approach, and the nitration and subsequent reduction steps required for the preparation of *o*-phenylenediamine were eliminated. In addition, the utility of the method was demonstrated in the synthesis of the key intermediate bis-benzimidazole (**8**) for telmisartan without using nitric acid, sulfuric acid, and polyphosphoric acid. Further extension of this *N*-arylamidoxime cyclization approach is ongoing in our laboratory.

EXPERIMENTAL SECTION

General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400, 500, or 600 Hz instrument. Data for ^{1}H NMR were presented as the chemical shift in ppm, and multiplicities were denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Data for ^{13}C NMR were reported as the chemical shift. The ESI mass spectra were determined on a Thermo Fisher FINNIGAN LTQ instrument. All high-resolution mass spectra (HRMS) results were obtained on an Agilent 1290-6545 UHPLC-QTOF LC/MS spectrometer. Thin-layer chromatography was performed on silica gel plates (GF-254). DCM refers to dichloromethane. Flash column chromatography was carried out using commercially available 200−300 mesh under pressure unless otherwise indicated. All commercially available chemicals and solvents were directly used without further purification unless otherwise noted.

General Procedure. *Synthesis of Benzimidazoles* ***3, 3a−3w.*** To a mixture of **1**, **1a−1w** (1 mmol) and DBU (2.5 mmol) in chlorobenzene (3 mL) was added acetyl chloride (1.2 mmol), and the mixture was stirred for 60 min at 5 °C. Afterward, the reaction mixture was stirred for 1−5 h at 132 °C. Then the reaction mixture was cooled to 25 °C and quenched with water. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by silica-gel column chromatography to give **3**, **3a−3w**.

Benzimidazoles ***3.*** Following the general procedure, **3** was obtained from **1** (180 mg, 1.0 mmol). The residue was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 30/1) to give **3**[41] (147 mg, 92%) as a light yellow solid; m.p. 155−157 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (brs, 1H), 7.56 (dd, J = 6.0, 3.2 Hz, 2H), 7.35−7.16 (m, 2H), 2.93 (t, J = 7.6 Hz, 2H), 1.95−1.86 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 155.59, 138.54, 122.09,

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114.58, 31.21, 21.77, 13.85; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{10}H_{13}N_2$ 161.1073, found 161.1071.

Benzimidazoles ***3a***. Following the general procedure, **3a** was obtained from **1a** (251 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3a**[37] (210 mg, 90%) as a white solid; m.p. 143−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (brs, 1H), 8.11 (s, 1H), 7.77 (s, 1H), 3.91 (s, 3H), 2.93 (t, J = 7.6 Hz, 2H), 2.57 (s, 3H), 1.94−1.83 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.08, 157.34, 141.81, 137.53, 124.64, 124.21, 124.06, 114.28, 52.06, 31.30, 21.76, 17.10, 13.82; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{13}H_{17}N_2O_2$ 233.1285, found: 233.1281.

Benzimidazoles ***3b***. Following the general procedure, compound **3b**[42] was obtained from **1b** (271 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3b** (235 mg, 93%) as a white solid; m.p. 125−128 °C; two sets of ^{1}H NMR data representing two isomers (10:9) were observed as indicative of the presence of tautomerism; ^{1}H NMR (400 MHz, DMSO-d_6, major isomer) δ 12.30 (s, 1H), 7.51 (s, 1H), 7.08 (s, 1H), 2.77 (t, J = 7.1 Hz, 2H), 2.45 (s, 3H), 1.78 (dt, J = 14.3, 7.2 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, major isomer) δ 156.78, 144.90, 130.26, 124.78, 118.41, 113.43, 111.35, 30.90, 21.44, 17.09, 14.16; ^{1}H NMR (400 MHz, DMSO-d_6, minor isomer) δ 12.24 (s, 1 H), 7.40 (s, 1H), 7.08 (s, 1H), 2.77 (t, J = 7.1 Hz, 2H), 2.48 (s, 3H), 1.78 (dt, J = 14.3, 7.2 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, minor isomer) δ 155.65, 142.30, 135.39, 133.59, 124.22, 123.20, 113.85, 30.98, 21.44, 16.75, 14.16; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{14}BrN_2$ 253.0335, found: 253.0332.

Benzimidazoles ***3c***. Following the general procedure, compound **3c** was obtained from **1c** (223 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3c**[43] (175 mg, 85%) as a white solid; m.p. 172−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.98 (dd, J = 8.5, 1.4 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 4.42 (q, J = 7.1 Hz, 2H), 2.70 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$) δ 167.38, 153.70, 142.37, 138.15, 124.60, 123.89, 114.26, 60.98, 15.13, 14.38.

HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{13}N_2O_2$ 205.0972, found: 205.0969.

Benzimidazoles ***3d***. Following the general procedure, compound **3d**[44] was obtained from **1d** (208 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3d** (181 mg, 95%) as a white solid; m.p. 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, J = 8.7 Hz, 1H), 6.97 (d, J = 1.3 Hz, 1H), 6.83−6.74 (m, 1H), 3.73 (s, 3H), 2.82 (t, J = 7.5 Hz, 2H), 1.86−1.72 (m, 2H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.44, 154.53, 137.99, 132.47, 115.19, 111.86, 97.54, 55.87, 30.91, 21.61, 13.79; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{15}N_2O$ 191.1179, found: 191.1177.

Benzimidazoles ***3e***. Following the general procedure, compound **3e**[45] was obtained from **1e** (208 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3e** (175 mg, 92%) as a white solid; m.p. 130−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.07 (m, 2H), 6.67 (dd, J = 7.5, 1.2 Hz, 1H), 3.94 (s, 3H), 2.90 (t, J = 7.4 Hz, 2H), 2.03−1.76 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.02, 148.38, 139.72, 128.69, 122.60, 107.48, 102.62, 55.50, 31.11, 21.70, 13.85; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{11}H_{15}N_2O$ 191.1179, found: 191.1176.

Benzimidazoles ***3f***. Following the general procedure, compound **3f** was obtained from **1f** (206 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3f** (170 mg, 90%) as a white solid; m.p. 170−171 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 7.34 (s, 1H), 7.20 (s, 1H), 3.16−3.12 (m, 2 H), 2.59 (s, 3H), 2.49 (s, 3H), 2.07−1.86 (m, 2H), 1.07 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 153.34, 136.78, 131.05, 128.62, 127.96, 123.66, 110.13, 27.87, 20.61, 20.14, 15.14, 12.36; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{17}N_2$189.1386, found: 189.1383.

Benzimidazoles ***3g***. Following the general procedure, compound **3g** was obtained from **1g** (280 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3g** (241 mg, 92%) as a foamy solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.12 (s, 1H), 7.52 (s, 1H), 2.84 (t, J = 7.5 Hz, 2H), 1.87−1.75 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 159.62, 132.68, 131.23, 130.70, 128.14, 119.37, 117.78, 29.65, 22.65, 13.94; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{10}H_{10}Cl_3N_2$262.9904, found: 262.9898.

Benzimidazoles ***3h***. Following the general procedure, compound **3h**[46] was obtained from **1h** (170 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3h** (128 mg, 85%) as a white solid m.p. 194−196 °C; two sets of ^{1}HNMR data representing two isomers (3:1) were observed as indicative of the presence of tautomerism; ^{1}H NMR (400 MHz, DMSO-d_6, major isomer) δ 12.47 (s, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.13−7.03 (m, 1H), 6.99−6.84 (m, 1H), 2.49 (s, 3H). ^{1}HNMR (400 MHz, DMSO-d_6, minor isomer) δ 12.71 (s, 1H), 7.34 (d, J = 7.6 Hz, 1H), 7.13−7.03 (m, 1H), 7.01−6.89 (m, 1H), 2.49 (s, 3H). ^{13}C{1H} NMR (100 MHz, DMSO-d_6) δ 152.98 (d, J = 247.7 Hz), 152.37, 138.08 (d, J = 9.4 Hz), 132.11 (d, J = 16.2 Hz), 122.28 (d, J = 7.2 Hz), 107.59, 106.71 (d, J = 17.6 Hz), 15.01; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_8H_8FN_2$151.0666, found: 151.0662.

Benzimidazoles ***3i***. Following the general procedure, compound **3i**[47] was obtained from **1i** (230 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3i** (190 mg, 90%) as a white solid; m.p. 90−93 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.36−8.28 (m, 1H), 8.09−8.01 (m, 1H), 7.97−7.89 (m, 1H), 7.78−7.67 (m, 2H), 7.67−7.60 (m, 1H), 3.22 (t, J = 7.7 Hz, 2H), 2.08−1.95 (m, 2H), 1.11 (t, J = 7.3 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 153.08, 132.64, 132.61, 130.30, 129.33, 129.26, 128.69, 127.91, 122.09, 121.98, 113.12, 29.28, 22.13, 13.82; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{14}H_{15}N_2$ 211.1230, found: 211.1226.

Benzimidazoles ***3j***. Following the general procedure, compound **3j** was obtained from **1j** (180 mg, 1.0 mmol). The crude product was purified by silica-gel column

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chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3j** (113 mg, 70%) as a foamy solid; ^{1}H NMR (400 MHz, CD_3OD) δ 9.37 (s, 1H), 8.69 (d, J = 6.5 Hz, 1H), 8.24 (d, J = 6.5 Hz, 1H), 3.18 (t, J = 7.6 Hz, 1H), 2.05−1.94 (m, 2H), 1.10 (t, J = 7.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 164.72, 145.00, 135.15, 134.63, 131.58, 111.27, 29.86, 20.43, 12.52; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_9H_{12}N_3$ 162.1026, found: 162.1023.

Benzimidazoles ***3k***. Following the general procedure, compound **3k**[48] was obtained from **1k** (250 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3k** (205 mg, 88%) as a foamy solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 0.7 Hz, 1H), 8.26 (dd, J = 8.6, 1.4 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H), 4.46 (q, J = 7.1 Hz, 2H), 3.59 (dt, J = 14.0, 7.0 Hz, 1H), 1.60 (d, J = 7.0 Hz, 6H), 1.45 (t, J = 7.1 Hz, 4H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 166.80, 162.56, 135.29, 132.19, 129.90, 128.26, 116.50, 114.89, 62.83, 29.08, 20.38, 14.61; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{17}N_2O_2$ 233.1285, found: 233.1282.

Benzimidazoles ***3l***. Following the general procedure, compound **3l** was obtained from **1l** (316 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3l** (224 mg, 75%) as a light yellow solid; m.p. 154−156 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 8.09−7.90 (m, 2H), 7.69 (d, J = 1.1 Hz, 1H), 7.60−7.44 (m, 1H), 7.37−7.18 (m, 1H), 7.00 (dd, J = 8.1, 1.0 Hz, 1H), 2.08 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 167.95, 152.83, 150.48, 142.18, 135.22, 134.51, 134.47, 133.49, 133.47, 128.11, 127.06, 125.82, 125.27, 125.07, 19.72; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{14}H_{14}N_4O_4$ 299.0775, found: 299.0772.

Benzimidazoles ***3m***. Following the general procedure, compound **3m**[49] was obtained from **1m** (223 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3m** (113 mg, 55%) as a light yellow solid; m.p. 160−162 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 8.66 (d, J = 1.9 Hz, 1H), 8.46 (dd, J = 9.0, 2.1 Hz, 1H), 7.97 (d, J = 9.0 Hz, 1H), 3.28−3.20 (m, 2H), 2.07−1.95 (m, 2H), 1.12 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 158.86, 145.89, 134.82, 130.75, 121.08, 114.31, 110.08, 28.32, 20.12, 12.39; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{10}H_{12}N_3O_2$ 206.0924, found: 206.0921.

Benzimidazoles ***3n***. Following the general procedure, compound **3n** was obtained from **1n** (223 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3n** (113 mg, 55%) as a light yellow solid; m.p. 168−169 °C. ^{1}H NMR (400 MHz, CD_3OD) δ 8.12 (d, J = 8.3 Hz, 1H), 8.02 (d, J = 7.7 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 3.24 (t, J = 7.7 Hz, 2H), 2.12−1.93 (m, 2H), 1.13 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 157.02, 131.81, 131.62, 130.56, 126.08, 118.79, 113.97, 97.97, 28.09, 20.48, 12.40; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{11}H_{12}N_3$ 186.1026, found: 186.1024.

Benzimidazoles ***3k*** *and* ***3o***. Following the general procedure, compounds **3k** and **3o** were obtained from **1o** (250 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 50/1) to afford compound **3o** (151 mg, 65%) as a foamy solid and silica-gel column chromatography (DCM/MeOH = 50/1 to 20/1) to afford **3k** (50 mg, 22%); for compound **3o** ^{1}H NMR (400 MHz, CD_3OD) δ 8.22 (d, J = 7.7 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.76−7.68 (m, 1H), 4.57 (q, J = 7.1 Hz, 1H), 3.72 (dd, J = 14.0, 7.0 Hz, 1H), 1.59 (d, J = 7.0 Hz, 1H), 1.48 (t, J = 7.1 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 165.82, 162.51, 134.81, 131.80, 128.38, 126.46, 120.40, 117.97, 62.93, 28.87, 21.01, 14.72; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{13}H_{17}N_2O_2$ 233.1285, found: 233.1283.

Benzimidazoles ***3p***. Following the general procedure, compound **3p** was obtained from **1p** (210 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3p** (144 mg, 75%) as a foamy solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 8.7 Hz, 1H), 6.94 (d, J = 2.4 Hz, 1H), 6.75 (dd, J = 8.7, 2.4 Hz, 1H), 4.58 (d, J = 7.1 Hz, 2H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.11, 155.72, 137.01, 130.44, 113.82, 109.54, 98.52, 66.28, 56.02, 14.73; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{10}H_{13}N_2O_2$ 193.0982, found: 193.0979.

Benzimidazoles ***3q***. Following the general procedure, compound **3q** was obtained from **1q** (210 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3q** (124 mg, 65%) as a foamy solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.77 (s, 1H), 4.57 (q, J = 7.1 Hz, 2H), 2.42 (s, 3H), 2.38 (s, 3H), 1.42 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.87, 136.76, 133.17, 131.02, 123.54, 122.45, 111.60, 65.88, 21.49, 16.83, 14.62; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{11}H_{15}N_2O$ 191.1179, found: 191.1176.

Benzimidazoles ***3r***. Following the general procedure, compound **3r** was obtained from **1r** (184 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3r** (97 mg, 55%) as a foamy solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 7.5 Hz, 1H), 7.05 (t, J = 7.7 Hz, 1H), 6.94 (d, J = 7.5 Hz, 1H), 4.60 (q, J = 7.1 Hz, 2H), 2.51−2.42 (m, 3H), 1.43 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.96, 136.87, 135.00, 131.13, 122.34, 121.45, 111.70, 66.02, 16.86, 14.62; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{10}H_{13}N_2O$ 177.1022, found: 177.1020.

Benzimidazoles ***3s*** *and* ***3w***. Following the general procedure, compound **3s**[50] and **3w** were obtained from **1s** (252 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 80/1 to 50/1) to afford compound **3s** (82 mg, 35%) as a foamy solid and silica-gel column chromatography (DCM/MeOH = 50/1 to 20/1) to afford **3w** (28 mg, 12%) as a foamy solid; for compound **3s** ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (brs, 1H), 7.78−7.64 (m, 2H), 7.30−7.04 (m, 1H), 4.62 (q, J = 7.1 Hz, 2H), 4.49−4.36 (m, 2H), 1.54−1.40 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.34, 153.28, 136.56, 127.97, 117.21, 117.05, 115.73, 107.10, 61.08, 55.77, 9.35, 9.17; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{12}H_{15}N_2O_3$ 235.1077, found: 235.1073; for compound **3w** ^{1}HNMR data representing two isomers (1:1) were observed as indicative of the presence of tautomerism for **3w**. ^{1}H NMR (400 MHz, DMSO-d_6, two isomer mixture) δ 12.22 (s, 0.5H), 12.16 (s, 0.5H), 7.96 (s, 0.5H), 7.81 (s, 0.5H), 7.72 (dd, J = 8.3, 1.6 Hz, 1H), 7.44 (d, J = 8.3 Hz, 0.5H), 7.31 (d, J = 8.3 Hz, 0.5H), 4.60−4.45 (m, 2H), 4.30 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, two isomer mixture) δ 166.87, 166.70, 160.81, 159.98, 145.74,

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141.28, 137.16, 132.97, 122.97, 122.80, 122.70, 122.40, 118.40, 116.83, 111.39, 110.01, 66.24, 66.11, 60.74, 14.92, 14.73; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_3$ 235.1077, found: 235.1074.

Benzimidazoles ***3t***. Following the general procedure, compound **3t** was obtained from **1t** (205 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3t** (71 mg, 38%) as a foamy solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.9 Hz, 1H), 7.45 (dd, J = 7.7, 0.5 Hz, 1H), 7.20 (t, J = 7.9 Hz, 1H), 4.68 (q, J = 7.1 Hz, 2H), 1.50 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 160.51, 143.36, 133.70, 125.30, 121.24, 118.04, 115.25, 98.87, 66.65, 14.89; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{10}H_{10}N_3O$ 188.0818, found: 188.0815.

Benzimidazoles ***3u***. Following the general procedure, compound **3u** was obtained from **1u** (212 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 20/1) to afford the title compound **3u** (68 mg, 35%) as a foamy solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 1H), 7.33 (d, J = 8.7 Hz, 1H), 6.97 (s, 1H), 6.74 (dd, J = 8.7, 2.4 Hz, 1H), 3.77 (s, 3H), 2.67 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 155.16, 150.19, 139.83, 134.63, 114.44, 110.06, 96.98, 55.37, 13.90; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_9H_{11}N_2OS$ 195.0587, found: 195.0585.

Benzimidazoles ***3v***. Following the general procedure, compound **3v**[51] was obtained from **1v** (164 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 30/1) to give **3v** (110 mg, 75%) as a light yellow solid; m.p. 168−169 °C; ^{1}H NMR (500 MHz, Acetone-d_6) δ 8.28 (s, 1H), 7.33 (d, J = 4.2 Hz, 1H), 7.17 (t, J = 7.9 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 3.99 (s, 1H); ^{13}C{^{1}H}NMR (125 MHz, acetone-d_6) δ 150.94, 142.66, 131.52, 127.09, 124.84, 110.13, 105.04, 57.02; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_8H_9N_2O$ 149.0709, found 149.0708.

Benzimidazoles ***3w***. Following the general procedure, compound **3w** was obtained from **1w** (252 mg, 1.0 mmol). The crude product was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 30/1) to give **3w** (106 mg, 45%) as a foamy solid; ^{1}H NMR data representing two isomers (1:1) were observed as indicative of the presence of tautomerism for **3w**. ^{1}H NMR (400 MHz, DMSO-d_6, two isomer mixture) δ 12.22 (s, 0.5 H), 12.16 (s, 0.5 H), 7.96 (s, 0.5H), 7.81 (s, 0.5H), 7.72 (dd, J = 8.3, 1.6 Hz, 1H), 7.44 (d, J = 8.3 Hz, 0.5H), 7.31 (d, J = 8.3 Hz, 0.5H), 4.60−4.45 (m, 2H), 4.30 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6, two isomer mixture) δ 166.87, 166.70, 160.81, 159.98, 145.74, 141.28, 137.16, 132.97, 122.97, 122.80, 122.70, 122.40, 118.40, 116.83, 111.39, 110.01, 66.24, 66.11, 60.74, 14.92, 14.73; HRMS (ESI): m/z $[M + H]^+$ calcd for $C_{12}H_{15}N_2O_3$ 235.1077, found: 235.1074.

Synthesis of Compound ***3x***. Acetyl chloride (2.06 g, 26.25 mmol) was added to a flask containing **1x** (6.8 g, 25 mmol), DBU (9.45 g, 62.5 mmol), and chlorobenzene (75 mL) at 5 °C. Then, the resulting mixture was stirred for 30 min at 5 °C. After being refluxed for 1 h, the reaction mixture was cooled to 25 °C and then quenched by water. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 30/1) to give **3x** (6.0 g, 96%) as a light yellow solid; m.p. 221−223 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.33 (s, 1H), 8.31 (s, 1H), 8.25−8.16 (m, 2H), 7.66 (dd, J = 5.9, 3.2 Hz, 2H), 7.32−7.23 (m, 2H), 2.64 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 149.46, 149.35, 139.93, 134.75, 134.18, 130.85, 130.75, 125.83, 125.31, 123.24, 115.90, 20.34; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{14}H_{12}N_3O_2$ 254.0924, found 254.0919.

Synthesis of Compound ***S2***. Dimethyl sulfate (2.62 g, 20 mmol) was added to a flask containing **3x** (5.06 g, 20 mmol), sodium methanolate (2.16 g, 40 mmol), and dry acetonitrile (50 mL) at 5 °C. After being stirred for 3 h at 25 °C and then quenched by water, the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 30/1) to give **S2**[28] (5.24 g, 98%) as a yellow solid; m.p. 186−188 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.17 (d, J = 8.5 Hz, 1H), 8.03 (d, J = 0.9 Hz, 1H), 7.96 (dd, J = 8.4, 1.7 Hz, 1H), 7.70 (dd, J = 19.3, 7.9 Hz, 2H), 7.41−7.25 (m, 2H), 3.94 (s, 3H), 2.64 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 150.88, 149.16, 142.37, 136.73, 134.56, 133.39, 133.28, 127.92, 124.76, 123.02, 122.33, 119.30, 110.84, 31.81, 19.49. HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{15}H_{14}N_3O_2$ 268.1081, found 268.1079.

Synthesis of Compound ***4***. **S2** (5.34 g, 20 mmol) was reduced with Raney nickel (0.1 g) and hydrogen (5 bar) in ethanol (100 mL) 30 °C for 12 h. The insoluble substances were filtered away, and the filtrate was removed by a rotary evaporator to give **4**[28,29] (4.65 g, 98%) as a white solid; m.p. 148−150 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.60 (dd, J = 4.5, 3.7 Hz, 1H), 7.50 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.2 Hz, 1H), 7.27−7.14 (m, 2H), 6.77 (d, J = 8.2 Hz, 1H), 5.37 (s, 2H), 3.83 (s, 3H), 2.17 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 154.74, 148.76, 143.15, 137.13, 131.60, 128.30, 121.94, 121.91, 121.28, 118.77, 117.61, 113.86, 110.46, 32.20, 17.92. HRMS (ESI) m/z calcd for $C_{15}H_{16}N_3$ $[M + H]^+$: 238.1339, found 238.1336.

Synthesis of Compound ***5***. To a suspension of **4** (4.22 g, 17.8 mmol) in toluene (20 mL) were added trimethyl orthobutyrate (2.9 g, 19.6 mmol) and acetic acid (1.06 g, 17.8 mol). The resulting mixture was heated for 3 h at 60 °C and concentrated in vacuo to give **5** (5.8 g, 100%) which was used for the next step without further purification; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80−7.77 (m, 1H), 7.61 (s, 1H), 7.47 (dd, J = 8.0, 1.8 Hz, 1H), 7.36−7.33 (m, 1H), 7.27 (dd, J = 5.9, 3.0 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 2.16 (s, 3H), 2.12−2.06 (m, 2H), 1.53 (m, 2H), 0.83 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 163.18, 153.71, 148.58, 142.35, 136.06, 131.07, 128.98, 127.02, 123.92, 121.99, 121.82, 120.30, 119.06, 109.01, 52.80, 31.39, 31.26, 18.96, 17.45, 13.38; HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{20}H_{23}N_3O$ 322.1914, found 322.1911.

Synthesis of Compound ***6***. Sodium acetate (2.9 g, 35.6 mmol) was added to a flask containing hydroxylamine hydrochloride (2.46 g, 35.8 mmol) and isopropyl alcohol (40 mL) under an ice bath, and the mixture was stirred for 30 min at 0−5 °C. To the reaction mixture was added a solution of **5** (5.8 g, 17.8 mmol) in isopropyl alcohol (5 mL) at 0−5 °C. After being stirred for 16 h at 25 °C, the reaction mixture offered a viscous solid. The viscous solid was filtered, and the wet cake was washed with isopropyl alcohol (5 mL). The wet cake was suspended in water (20 mL) and stirred at 20−25 °C

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for 2 h. The precipitated solid was filtered and dried in a vacuum at 50 °C, affording **6** (5.34 g, 93%) as a white solid; m.p. 153−155 °C; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.89−7.81 (m, 1H), 7.72 (d, J = 1.3 Hz, 1H), 7.58 (dd, J = 8.1, 1.8 Hz, 1H), 7.43−7.38 (m, 1H), 7.37−7.29 (m, 2H), 7.24 (d, J = 8.2 Hz, 1H), 7.00 (br, 1H), 3.91 (s, 3H), 2.39 (s, 3H), 2.35−2.28 (m, 2H), 1.50−1.38 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.25, 153.21, 142.68, 138.92, 136.53, 133.34, 132.06, 127.58, 126.90, 125.24, 122.90, 122.62, 119.75, 109.62, 31.81, 30.94, 19.51, 17.98, 13.64; HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{23}N_4O$ 323.1866, found 323.1863.

Synthesis of Compound ***8***. Acetyl chloride (412 mg, 5.25 mmol) was added to a flask containing **6** (1.6 g, 5 mmol), DBU (1.89 g, 12.5 mmol), and chlorobenzene (15 mL) at 5 °C. Then the resulting mixture was stirred for 30 min at 5 °C. After being refluxed for 1 h, the reaction mixture was cooled to 25 °C and then quenched by water. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica-gel column chromatography (DCM/MeOH = 100/1 to 30/1) to give **8**[37] (1.43 g, 96%) as a white solid; m.p. 130−132 °C; ^{1}HNMR (400 MHz, DMSO-d_6) δ 7.75 (s, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.44 (s, 1H), 7.33−7.18 (m, 2H), 3.90 (s, 3H), 2.85 (t, J = 7.5 Hz, 2H), 2.59 (s, 3H), 1.89−1.78 (m, 2H), 0.98 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6): δ 156.20, 154.33, 142.49, 138.87, 136.60, 124.14, 123.13, 122.88, 121.90, 121.70, 118.61, 113.38, 110.29, 31.71, 30.58, 21.04, 16.79, 13.71; HRMS (ESI): m/z [M + H]$^+$ calcd for $C_{19}H_{21}N_4$ 305.1761, found: 305.1756.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c06554.

Experimental details and compound characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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