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Copper-Catalyzed, One-Pot, Three-Component Synthesis of Benzimidazoles by Condensation and C–N Bond Formation

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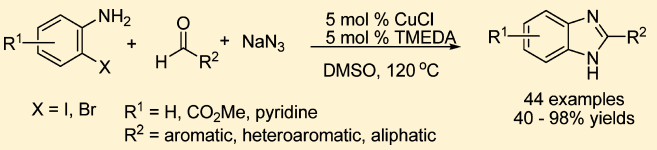
Supporting Information

ABSTRACT: Benzimidazoles were synthesized by the copper-catalyzed, one-pot, three-component reaction of 2-haloanilines, aldehydes, and NaN_3. The reaction was optimized when 2-iodo- or 2-bromoanilines (1.0 equiv), aldehydes (1.2 equiv), NaN_3 (2.0 equiv), 5 mol% of CuCl, and 5 mol % of TMEDA were reacted in DMSO at 120 °C for 12 h. Good yields resulted, and the reaction showed tolerance toward functional groups such as ester, nitro, and chloro. Aliphatic and heteroaromatic aldehydes also afforded the desired products in moderate to good yields.



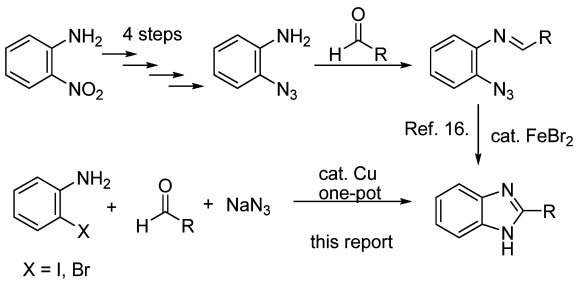
INTRODUCTION

N-Containing heteroaromatic compounds are important structures found in natural and synthetic compounds. Among them, benzimidazole and its derivatives are crucial core structures used to create drugs and materials. They exhibit biological activities such as anticancer,[1] antiulcer,[2] antihypertensive,[3] antibacterial,[4] and enzyme inhibition.[5] They have also been applied in dyes,[6] chemosensing,[7] fluorescence, and corrosion science.[8]

Benzimidazole has various reported syntheses, with two methods used extensively that employ 1,2-diaminoarenes as starting materials. One is the coupling of carboxylic acids,[9] and the other is the condensation of aldehydes.[10] They both have some drawbacks; the former requires strongly acidic conditions and sometimes high reaction temperatures; the latter method requires a stoichiometric oxidant for dehydration. Both syntheses result in side products such as regioisomers and disubstituted products from the 1,2-diaminoarene. Efficient syntheses of benzimidazoles from 2-haloacetanilides,[11] *N*-arylbenzimidamide,[12] 2-haloarylamidine,[13] and arylamino oximes[14] have recently been reported. However, each requires multistep reactions for the preparation of the starting materials. Despite these recent advances including reusable catalytic systems,[15] the development of a simpler method is still required to overcome the limitations of the existing procedures.

In 2008, Driver's group reported the $FeBr_2$-catalyzed synthesis of benzimidazole from 2-azidoaniline and achieved good yields under mild conditions.[16] However, their method has some drawbacks; the starting materials, 2-azidoanilines, require a four-step preparation from 2-nitroaniline and an additional two steps are required for the synthesis of the benzimidazoles. Very recently, the copper-catalyzed, three-component coupling of 2-bromoaldehyde, primary amines, and sodium azide has recently been reported to construct 2*H*-indazoles in high yields by our group.[17] The successful use of sodium azide as a nitrogen source in the one-pot synthesis of 2*H*-indazoles suggests the possibility of the one-pot synthesis of benzimidazoles from sodium azide. Here, we report one-pot, three-component coupling reactions for the syntheses of benzimidazoles (Scheme 1).

Scheme 1. Synthesis of Benzimidazoles from Azides



RESULTS AND DISCUSSION

As a model reaction, 2-iodoaniline, benzaldehyde, and sodium azide were reacted under a variety of reaction conditions (Table 1).

As expected, the desired product was not obtained in the absence of metal catalyst (entry 1); therefore, we employed and tested several transition metals as catalysts. $FeBr_2$, which Driver's group reported as having good activity for the production of 2-azidoarylimine,[15] did not afford the desired products (entry 2). Palladium complexes did not produce the benzimidazole, despite catalyzing the coupling reactions of aryl halides and azide (entries 3 and 4). Nickel catalyst was similarly ineffective (entry 5). Copper complexes afforded 2-phenylbenzimidazole in moderate yields,[18] with CuCl showing the best yield (entry 10), which was improved in the presence of

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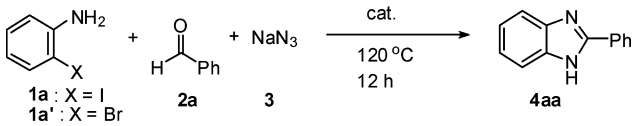
Table 1. Optimized Conditions for the Synthesis of Benzimidazoles[a]



entry	ArX	cat.	ligand[d]	solvent	yield[f] (%)
1	**1a**			DMSO	0
2	**1a**	$FeBr_2$		DMSO	0
3	**1a**	$Pd(OAc)_2$		DMSO	0
4	**1a**	$Pd(CH_3CN)_2Cl_2$		DMSO	0
5	**1a**	$Ni(OAc)_2$		DMSO	0
6	**1a**	$CuCl_2$		DMSO	44
7	**1a**	$Cu(OTf)_2$		DMSO	49
8	**1a**	CuI		DMSO	70
9	**1a**	CuBr		DMSO	71
10	**1a**	CuCl		DMSO	76
11	**1a**	CuCl	DMEDA	DMSO	72
12	**1a**	CuCl	Phenanth[e]	DMSO	65
13	**1a**	CuCl	TMEDA	DMSO	98
14	**1a**	CuCl	TMEDA	toluene	trace
15	**1a**	CuCl	TMEDA	diglyme	trace
16	**1a**	CuCl	TMEDA	DMF	62
17	**1a**	CuCl	TMEDA	NMP	68
18	**1a**	CuCl	TMEDA	DMAc	71
19	**1a**	CuCl[b]	TMEDA[b]	DMSO	98
20	**1a**	CuCl[c]	TMEDA[c]	DMSO	72
21	**1a'**	CuCl	TMEDA	DMSO	94
22	**1a'**	CuCl[b]	TMEDA[b]	DMSO	91

[a]Reaction conditions: **1a** or **1a'** (0.30 mmol), **2a** (0.36 mmol), **3** (0.60 mmol), and catalyst (0.03 mmol) were reacted in solvent (1.0 mL) at 120 °C for 12 h. [b]CuCl (0.015 mmol)/TMEDA (0.015 mmol) was used. [c]CuCl (0.006 mmol)/TMEDA (0.006 mmol) was used. [d]0.03 mmol of ligand was used. [e]1,10-Phenanthroline. [f]Determined by HPLC with internal standard.

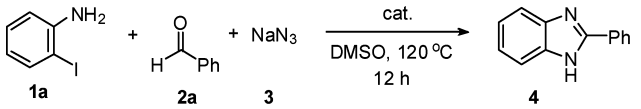
TMEDA ligands (entry 13). The solvent affected the yield of the desired product, with no product obtained in toluene and diglyme (entries 14 and 15). Polar solvents, such as DMF, NMP, and DMAc, showed fair performance, but DMSO was best (entries 16–18). Using the catalyst at 5 mol% and 2 mol % gave yields of 98% and 72%, respectively (entries 19 and 20). The reaction of 2-bromoaniline and aldehydes at 120 °C in the presence of 5 mol% catalyst gave good yields (entry 22). Compared with 2-iodoaniline, 2-bromoaniline showed similar activity in the synthesis of benzimidazole.

To investigate the role of copper and ligand in the synthesis of benzimidazole, we tested a variety of copper sources in the absence or presence of ligand as shown in Table 2. Copper(I) provided the desired product in the range of 24–40% yields (entries 2–4), and copper(II) showed similar yields (entries 6–10) except in the case of $Cu(OAc)_2$ (entry 5). From these results, we found that the oxidation state of copper was not a crucial factor, and the effects of ligands on most of the copper catalysts were weak.

The reaction was optimized when 2-haloanilines (1.0 equiv), aldehydes (1.2 equiv), and NaN_3 (2.0 equiv) reacted in the presence of 5 mol% of CuCl/TMEDA and DMSO at 120 °C for 12 h.

Next, 2-iodo- and 2-bromoanilines were tested in condensation reactions with a variety of substituted aldehydes,

Table 2. Screening of Coppers in the Synthesis of Benzimidazoles[a]



		yield[b] (%)	
entry	catalyst	without ligand	with ligand (TMEDA[c])
1	Cu powder	34	36
2	Cu_2O	24	32
3	Cu_2S	35	31
4	Cu_2Se	36	40
5	$Cu(OAc)_2$	64	69
6	$Cu(acac)_2$	38	42
7	CuO	34	32
8	CuS	26	28
9	$CuCO_3$	40	42
10	$CuSO_4$	47	52

[a]Reaction conditions: **1a** (0.30 mmol), **2a** (0.36 mmol), **3** (0.60 mmol), and catalyst (0.03 mmol) were reacted in DMSO (1.0 mL) at 120 °C for 12 h. [b]Determined by HPLC with internal standard. [c]0.03 mmol of ligand was used.

forming C–N bonds and undergoing cyclization for the synthesis of benzimidazoles (Table 3).

As expected, all of the aldehydes formed corresponding benzimidazoles in good yields. Benzaldehyde showed 90% product yield (entry 1). Aromatic aldehydes with electron-withdrawing groups such as chloro and nitro gave the corresponding benzimidazoles in 75% and 55% yields, respectively (entries 2 and 3). Benzaldehydes with electron-donating groups such as dimethylamino, methyl, and methoxy formed the desired products in good yields (entries 4–6). 2,3- and 3,4-(Methylenedioxyl)benzaldehydes produced the desired benzimidazoles in 62% and 66% yields, respectively (entries 7 and 8). The heteroaryl aldehydes 2-furaldehyde (**2i**) and 2-thiophenecarboxaldehyde (**2j**) reacted smoothly, giving the coupling products in good to excellent yields (entries 9 and 10). 6-Methoxy-2-naphthaldehyde showed product in 98% yield (entry 11). Alkyl aldehydes with bulky groups at the α position afforded the desired products in moderate to good yields (entries 12 and 13). However, butyraldehyde did not give the desired product (entry 14). Formaldehyde afforded benzimidazole in 42% yield (entry 15).

The use of 2-bromoaniline resulted in the desired products with good yields, similar to 2-iodoanilines. Attempts to employ *N,N*-dimethylformamide and *N*-methylformamide failed as their imine products did not form. In general, no strong dependence of product yield on the donating or withdrawing character of the substituted aldehydes was observed.

Anilines bearing ester, chloride, and heteroaromatic groups were next studied (Table 4). Methyl 4-amino-3-iodobenzoate (**1b**), with a base-sensitive group, was condensed with aldehydes and coupled with NaN_3 to produce the desired benzimidazoles in moderate to good yields (entries 1–3). The coupling of benzaldehyde (**2a**) produced a mixture of benzimidazole tautomers (entry 1). The coupling reaction of 5-chloro-2-iodoaniline occurred at the iodide site via copper catalysis. 3-Bromo-2-aminopyridine (**1d**) and 2-bromo-3-aminopyridine (**1e**) afforded products with the same structures (entries 7, 8, and 10 vs entries 12, 13, and 14, respectively). These results are similar to Driver's.[16,19] This reaction

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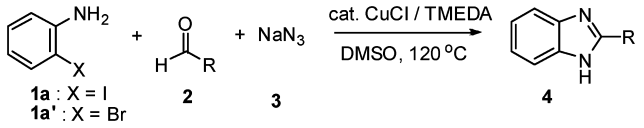
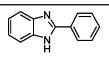
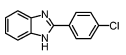
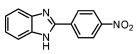
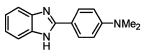
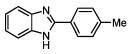
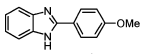
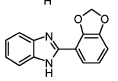
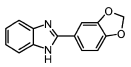
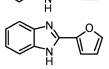
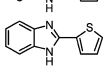
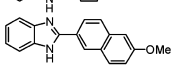
Table 3. Synthesis of Benzimidazoles from 2-Haloanilines and Aldehydes[a]



1a : X = I
1a' : X = Br
2 **3** **4**

entry	1	2 (R)	Product		yield (%)
1	**1a**	Ph		**4aa**	90 (88)[b]
2	**1a**	4-ClC$_6$H$_4$		**4ab**	75 (45)[b]
3	**1a**	4-NO$_2$C$_6$H$_4$		**4ac**	55 (41)[b]
4	**1a**	4-Me$_2$NC$_6$H$_4$		**4ad**	97 (83)[b]
5	**1a**	4-MeC$_6$H$_4$		**4ae**	78 (84)[b]
6	**1a**	4-MeOC$_6$H$_4$		**4af**	82 (65)[b]
7	**1a**	2,3-(OCH$_2$O)C$_6$H$_3$		**4ag**	62 (56)[b]
8	**1a**	3,4-(OCH$_2$O)C$_6$H$_3$		**4ah**	66 (72)[b]
9	**1a**	2-furyl		**4ai**	72 (68)[b]
10	**1a**	2-thionyl		**4aj**	98 (51)[b]
11	**1a**	6-MeO-2-Np		**4ak**	98 (65)[b]
12	**1a**	*i*-Pr		**4al**	52 (61)[b]
13	**1a**	*t*-Bu		**4am**	98 (42)[b]
14	**1a**	*n*-Pr	No product[c]	-	-
15	**1a**	H		**4an**	42 (54)[b]

[a]Reaction conditions: **1a** or **1a'** (2.0 mmol), aldehydes **2** (2.4 mmol), NaN_3 (4.0 mmol), CuCl (0.1 mmol), and TMEDA (0.1 mmol) were reacted in DMSO (6.0 mL) at 120 °C for 12 h. [b]Yield from **1a'**. [c]Only *N*-butylidenebenzene-1,2-diamine was found in 20% yield in the reaction mixture.

mechanism is not regiospecific and produced the more stable tautomer.[20]

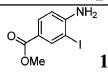
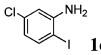
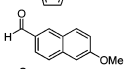
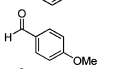
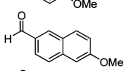
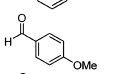
When **1d** and **1e** were employed as anilines, there were three tautomers in their products as shown in Figure 1. These structures were fully optimized at the DFT-B3LYP level and 6-31++G(d,p) basis set in Gaussian 03 suite of programs.[21] These calculations showed that tautomer **A** is the most stable one in most cases; however, tautomer **B** is more stable than tautomer **A** in the case of **4da** and **4ea**.

Finally, tiabendazole,[22] a fungicide and parasiticide with the trade names Mintezol and Tesaderm, was synthesized from this one-pot method in good yields (Scheme 2).

To understand the reaction mechanism, several competitive reactions were conducted (Scheme 3). 2-Azidoaniline was not formed from 2-haloaniline under CuCl catalysis. 2-Azido-*N*-benzylideneaniline was not detected in the reaction mixture; only benzimidazole was formed in 98% yield.

However, 2-azido-*N*-benzylideneaniline produced the desired product in the presence of copper catalysts (Cu_2O: 97%, CuCl: 98% yields). Cu_2O and CuCl showed different product yields in the one-pot reactions (Cu_2O: 32%, CuCl: 98%). The source of

Table 4. Synthesis of Benzimidazole from Substituted 2-Haloanilines[a]

entry	1	2		yield (%)
1	 **1b**		**4ba**	57[b]
2	**1b**		**4bh**	72
3	**1b**		**4bi**	95
4	 **1c**		**4ca**	40
5	**1c**		**4cj**	75
6	**1c**		**4ck**	73
7	 **1d**		**4da**	92
8	**1d**		**4df**	80
9	**1d**		**4dk**	80
10	**1d**		**4do**	45
11	**1d**		**4di**	80
12	 **1e**		**4ea**	81
13	**1e**		**4ef**	98
14	**1e**		**4eo**	40

[a]Reaction conditions: 2-haloanilines **1** (2.0 mmol), aldehydes **2** (2.4 mmol), NaN_3 (4.0 mmol), CuCl (0.1 mmol), and TMEDA (0.1 mmol) were reacted in DMSO (6.0 mL) at 120 °C for 12 h. [b]The ratio of tautomers is 53:47, which was calculated from the 2D NMR.

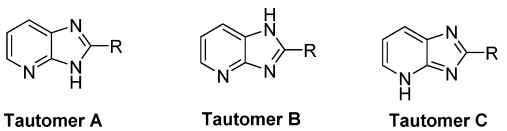


Figure 1. Three tautomers.

Scheme 2. One-Pot Synthesis of Tiabendazole

1a : X = I
1a' : X = Br

Tiabendazole
97% yield from **1a**
88% yield from **1a'**

copper appeared to be much more important in the coupling reactions of aryl halides and azide than in cyclization. These results allow the mechanism in Scheme 4 to be proposed. The condensation of 2-haloaniline and aldehyde afforded 2-halobenzimine **I**. The copper-catalyzed coupling of aryl halides with azide[23] was then followed by cyclization. Two possible paths are suggested; the formation of intermediate **III** (path **A**) and the direct formation of intermediate **IV** without the formation of azidoimine **III** (path **B**). In Scheme 3, the result of (2) supports path **B**, but path **A** was not excluded due to the result of (3). Further mechanistic studies of this reaction system are in progress.[24]

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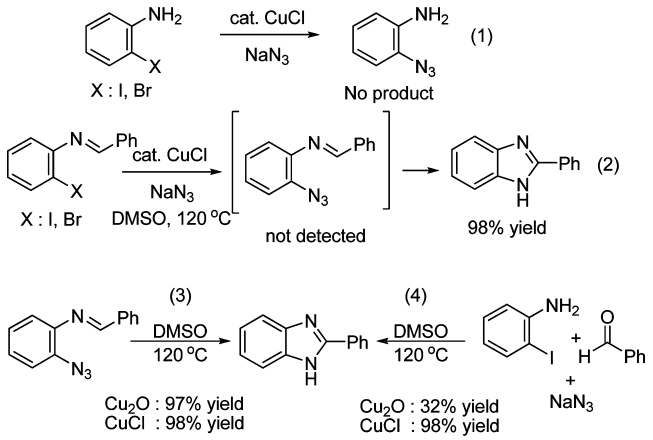
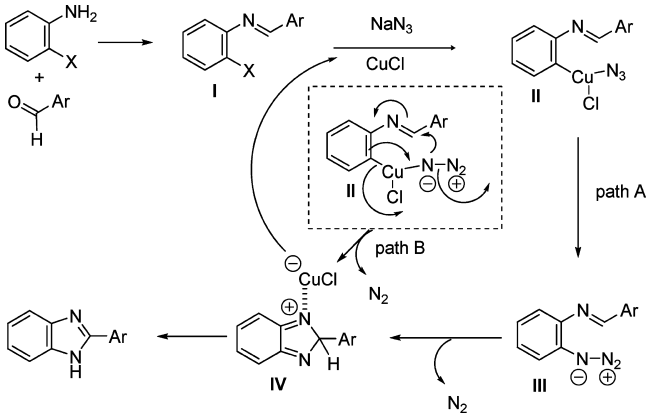
Scheme 3. Cu-Catalyzed Couplings and Cyclization



Scheme 4. Proposed Mechanism



CONCLUSION

In summary, an efficient synthesis of benzimidazoles was developed involving one-pot, three-component reactions of 2-haloanilines, aldehydes, and NaN_3 in the presence of copper catalysts. This system shows several advantages: it requires no preparation of the starting materials as they are commercially available; it does not require the isolation of intermediates; it provides easy purification procedure by simple column chromatography; and it shows applicability with a broad range of substrates. For example, 2-iodo- and 2-bromoanilines, aliphatic, and heteroaromatic aldehydes afforded the desired products. In addition, substrates bearing base-sensitive functional groups also showed good yields.

EXPERIMENTAL SECTION

General Method for the Preparation of 1*H*-Benzimidazole. CuCl (10 mg, 0.1 mmol), 2-iodoaniline (483 mg, 2.0 mmol) (**1a**) or 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**) or methyl 4-amino-3-iodobenzoate (554 mg, 2.0 mmol) (**1b**) or 5-chloro-2-iodoaniline (507 mg, 2.0 mmol) (**1c**) or 2-amino-3-bromopyridine (346 mg, 2.0 mmol) (**1d**) or 3-amino-2-bromopyridine (346 mg, 2.0 mmol) (**1e**), NaN_3 (260 mg, 4.0 mmol), *N,N,N′,N′*-tetramethylethylenediamine (TMEDA) (12 mg, 0.1 mmol), and aldehydes (2.4 mmol) were reacted in 6.0 mL of DMSO. The reaction mixture was heated to 120 °C for 12 h. After cooling, the mixture was poured into the EtOAc (50.0 mL), washed with brine (25.0 mL) and water (2 × 25.0 mL), dried over $MgSO_4$, and passed through a Celite. Evaporation of the solvent under reduced pressure provided the crude product, which was purified by column chromatography (hexane/EtOAc = 1:1) to afford the final product.

2-Phenyl-1*H*-benzimidazole[25] (4aa) (Entry 1 in Table 3). 2-Iodoaniline (438 mg, 2.0 mmol) (**1a**) was coupled with benzaldehyde (255 mg, 2.4 mmol) (**2a**) to give 350 mg (1.8 mmol, 90%) of **4aa** as a pale yellow solid after chromatography [342 mg (1.8 mmol, 88%) of **4a′a** was obtained from 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**)]: mp 292–294 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.92 (br s, 1H), 8.22–8.17 (m, 2H), 7.68 (d, J = 6.6 Hz, 1H), 7.58–7.46 (m, 4H), 7.21 (dd, J = 8.7, 3.6 Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ 151.2, 143.8, 135.0, 130.2, 129.8, 128.9, 126.4, 122.5, 121.7, 118.9, 111.3; IR (KBr) 3044, 1622, 1587, 1537, 1458, 1439, 1407, 1312, 1274 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{11}N_2$ [M + H]$^+$ 195.0922, found 195.0922.

2-(4-Chlorophenyl)-1*H*-benzimidazole[26] (4ab) (Entry 2 in Table 3). 2-Iodoaniline (438 mg, 2.0 mmol) (**1a**) was coupled with 4-chlorobenzaldehyde (337 mg, 2.4 mmol) (**2b**) to give 343 mg (1.5 mmol, 75%) of **4ab** as a pale yellow solid after chromatography [206 mg (0.9 mmol, 45%) of **4a′b** was obtained from 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**)]: mp 289–291 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.02 (br s, 1H), 8.21 (d, J = 8.7 Hz, 2H), 7.67–7.63 (m, 4H), 7.25–7.22 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ 150.2, 143.7, 135.0, 134.5, 129.1, 129.1, 128.2, 122.8, 121.9, 119.0, 111.5; IR (KBr) 3051, 1689, 1581, 1555, 1428, 1273, 745, 729 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{10}ClN_2$ [M + H]$^+$ 229.0533, found 229.0532.

2-(4-Nitrophenyl)-1*H*-benzimidazole[27] (4ac) (Entry 3 in Table 3). 2-Iodoaniline (438 mg, 2.0 mmol) (**1a**) was coupled with 4-nitrobenzaldehyde (363 mg, 2.4 mmol) (**2c**) to give 263 mg (1.1 mmol, 55%) of **4ac** as a brown solid after chromatography [196 mg (0.8 mmol, 41%) of **4a′c** was obtained from 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**)]: mp 259–260 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.05 (br s, 1H), 8.00 (ddd, J = 15.3, 7.8, 1.2 Hz, 2H), 7.87 (td, J = 7.5, 1.2 Hz, 1H), 7.76 (td J = 7.8, 1.5 Hz, 1H), 7.61 (br s, 2H), 7.25 (d, J = 4.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO) δ 149.0, 147.3, 143.6, 134.6, 132.6, 130.9, 124.3, 123.1, 121.9, 119.2, 111.7; IR (KBr) 3063, 1526, 1445, 1415, 1378, 1347, 1319 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{10}N_3O_2$ [M + H]$^+$ 240.0773, found 240.0774.

2-(4-Dimethylaminophenyl)-1*H*-benzimidazole[28] (4ad) (Entry 4 in Table 3). 2-Iodoaniline (438 mg, 2.0 mmol) (**1a**) was coupled with ethyl 4-(dimethylamino)benzaldehyde (358 mg, 2.4 mmol) (**2d**) to give 460 mg (1.94 mmol, 97%) of **4ad** as a pale yellow solid after chromatography [394 mg (1.7 mmol, 83%) of **4a′d** was obtained from 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**)]: mp 273–275 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.53 (br s, 1H), 7.98 (d, J = 9.0 Hz, 2H), 7.55 (br s, 1H), 7.43 (br s, 1H), 7.14–7.08 (m, 2H), 6.82 (d, J = 9.0 Hz, 2H), 2.99 (s, 6H); ^{13}C NMR (75 MHz, DMSO) δ 152.3, 151.3, 144.1, 135.0, 127.6, 121.6, 121.2, 118.0, 117.4, 111.9, 110.7, 39.9 ; IR (KBr) 3051, 2917, 2808, 1609, 1503, 1438, 1400, 1200 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{16}N_3$ [M + H]$^+$ 238.1344, found 238.1354.

2-*p*-Tolyl-1*H*-benzimidazole[29] (4ae) (Entry 5 in Table 3). 2-Iodoaniline (438 mg, 2.0 mmol) (**1a**) was coupled with 4-methylbenzaldehyde (288 mg, 2.4 mmol) (**2e**) to give 325 mg (1.56 mmol, 78%) of **4ae** as a white solid after chromatography [350 mg (1.7 mmol, 84%) of **4a′e** was obtained from 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**)]: mp 275–277 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.81 (br s, 1H), 8.07 (d, J = 8.1 Hz, 2H), 7.57 (br s, 2H), 7.36 (d, J = 7.8 Hz, 2H), 7.21–7.16 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 151.4, 139.5, 129.5, 127.4, 126.4, 122.0, 21.0; IR (KBr) 3052, 2962, 2914, 1616, 1587, 1501, 1446, 1430, 1273 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{13}N_2$ [M + H]$^+$ 209.1079, found 209.1077.

2-(4-Methoxyphenyl)-1*H*-benzimidazole[30] (4af) (Entry 6 in Table 3). 2-Iodoaniline (438 mg, 2.0 mmol) (**1a**) was coupled with 4-methoxybenzaldehyde (327 mg, 2.4 mmol) (**2f**) to give 368 mg (1.64 mmol, 82%) of **4af** as a white solid after chromatography [292 mg (1.3 mmol, 65%) of **4a′f** was obtained from 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**)]: mp 222–225 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.74 (br s, 1H), 8.14–8.09 (m, 2H), 7.57–7.54 (m, 2H), 7.20–7.14 (m, 2H), 7.13–7.09 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 160.6, 151.3, 128.0, 122.7, 121.8, 114.4, 55.3; IR (KBr) 3053, 2963, 2914, 1616, 1501, 1430, 1321, 1273 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{13}N_2O$ [M + H]$^+$ 225.1028, found 225.1024.

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2-(Benzo[1,3]dioxol-4-yl)-1*H*-benzimidazole (4ag) (Entry 7 in Table 3). 2-Iodoaniline (438 mg, 2.0 mmol) (**1a**) was coupled with 2,3-(methylenedioxy)benzaldehyde (360 mg, 2.4 mmol) (**2g**) to give 295 mg (1.24 mmol, 62%) of **4ag** as a white solid after chromatography [267 mg (1.1 mmol, 56%) of **4a′g** was obtained from 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**)]: mp 194−196 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.25 (s, 1H), 7.66−7.60 (m, 3H), 7.23−7.18 (m, 2H), 7.07−6.98 (m, 2H), 6.26 (s, 2H); ^{13}C NMR (75 MHz, DMSO) δ 148.0, 147.0, 144.8, 122.1, 120.1, 112.4, 109.4, 101.7; IR (KBr) 3046, 2902, 1465, 1396, 1244, 1190, 1056, 933 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{11}N_2O_2$ [M + H]$^+$ 239.0820, found 239.0804.

2-(Benzo[1,3]dioxol-5-yl)-1*H*-benzimidazole[31] (4ah) (Entry 8 in Table 3). 2-Iodoaniline (438 mg, 2.0 mmol) (**1a**) was coupled with piperonal (360 mg, 2.4 mmol) (**2h**) to give 314 mg (1.32 mmol, 66%) of **4ah** as a pale brown solid after chromatography [343 mg (1.4 mmol, 72%) of **4a′h** was obtained from 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**)]: mp 239−240 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.75 (br s, 1H), 7.75−7.69 (m, 2H), 7.62 (br s, 1H), 7.50 (br s, 1H), 7.18−7.08 (m, 3H), 6.12 (s, 2H); ^{13}C NMR (75 MHz, DMSO) δ 151.2, 148.8, 147.9, 143.8, 135.1, 124.3, 122.0, 120.9, 118.5, 111.3, 108.8, 106.5, 101.6; IR (KBr) 3052, 2907, 1619, 1476, 1453, 1247, 1228, 1039 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{11}N_2O_2$ [M + H]$^+$ 239.0820, found 239.0826.

2-(Furan-2-yl)-1*H*-benzimidazole[32] (4ai) (Entry 9 in Table 3). 2-Iodoaniline (438 mg, 2.0 mmol) (**1a**) was coupled with furan-2-carbaldehyde (231 mg, 2.4 mmol) (**2i**) to give 265 mg (1.44 mmol, 72%) of **4ai** as a pale brown solid after chromatography [250 mg (1.4 mmol, 68%) of **4a′i** was obtained from 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**)]: mp 285−287 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.91 (br s, 1H), 7.94 (dd, J = 1.8, 0.9 Hz, 1H), 7.55 (br s, 2H), 7.22−7.18 (m, 3H), 6.73 (dd, J = 3.3, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO) δ 145.6, 144.6, 143.6, 134.2, 122.4, 121.8, 118.7, 112.3, 111.4, 110.5; IR (KBr) 3053, 1630, 1525, 1416, 1363, 1278, 1233 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_9N_2O$ [M + H]$^+$ 185.0715, found 185.0715.

2-(Thien-2-yl)-1*H*-benzimidazole[31] (4aj) (Entry 10 in Table 3). 2-Iodoaniline (438 mg, 2.0 mmol) (**1a**) was coupled with 2-thiophenecarboxaldehyde (269 mg, 2.4 mmol) (**2j**) to give 393 mg (1.96 mmol, 98%) of **4aj** as a pale yellow solid after chromatography [188 mg (1.0 mmol, 51%) of **4a′j** was obtained from 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**)]: mp 342−343 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.94 (br s, 1H), 7.83 (dd, J = 3.6, 1.2 Hz, 1H), 7.72 (dd, J = 5.0, 1.1 Hz, 1H), 7.62−7.59 (m, 1H), 7.50 (dd, J = 6.9, 2.1 Hz, 1H), 7.24−7.14 (m, 3H); ^{13}C NMR (75 MHz, DMSO) δ 147.0, 143.6, 134.7, 133.7, 128.8, 128.3, 126.7, 122.6, 121.7, 118.5, 111.1; IR (KBr) 3047, 3008, 1569, 1450, 1423, 1312, 1275, 1233 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_9N_2S$ [M + H]$^+$ 201.0486, found 201.0484.

2-(6-Methoxynaphthalene-2-yl)-1*H*-benzimidazole (4ak) (Entry 11 in Table 3). 2-Iodoaniline (438 mg, 2.0 mmol) (**1a**) was coupled with 6-methoxy-2-naphthaldehyde (447 mg, 2.4 mmol) (**2k**) to give 538 mg (1.96 mmol, 98%) of **4ak** as pale brown solid after chromatography [357 mg (1.3 mmol, 65%) of **4a′k** was obtained from 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**)]: mp 220−222 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.97 (br s, 1H), 8.65 (s, 1H), 8.25 (d, J = 7.2 Hz, 1H), 7.96 (dd, J = 8.4, 3.6 Hz, 2H), 7.68(d, J = 6.9 Hz, 1H), 7.54 (d J = 6.3 Hz, 1H), 7.40 (s, 1H), 7.27−7.18 (m, 3H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 158.2, 151.5, 144.0, 135.1, 135.0, 130.1, 128.2, 127.4, 125.8, 125.4, 124.4, 122.5, 121.7, 119.5, 118.7, 111.3, 106.1, 55.4; IR (KBr) 3050, 2990, 2943, 1629, 1606, 1429, 1397, 1359, 1318, 1255 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{15}N_2O$ [M + H]$^+$ 275.1184, found 275.1187.

2-Isopropyl-1*H*-benzimidazole[33] (4al) (Entry 12 in Table 3). 2-Iodoaniline (438 mg, 2.0 mmol) (**1a**) was coupled with isobutyraldehyde (173 mg, 2.4 mmol) (**2l**) to give 167 mg (1.04 mmol, 52%) of **4al** as a white solid after chromatography [195 mg (1.2 mmol, 61%) of **4a′l** was obtained from 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**)]: mp 232−234 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.12 (br s, 1H), 7.45 (br m, 2H), 7.13−7.07 (m, 2H), 3.13 (hept, J = 6.9 Hz, 1H), 1.34 (d, J = 7.2 Hz, 6H); ^{13}C NMR (75 MHz, DMSO) δ 159.8, 143.0, 134.3, 121.3, 120.7, 118.2, 110.7, 28.4, 21.4; IR (KBr) 3051, 2971, 2883, 1534, 1455, 1415, 1273 cm^{-1}; HRMS (FAB) calcd for $C_{10}H_{13}N_2$ [M + H]$^+$ 161.1079, found 161.1040.

2-*tert*-Butyl-1*H*-benzimidazole[33] (4am) (Entry 13 in Table 3). 2-Iodoaniline (438 mg, 2.0 mmol) (**1a**) was coupled with pivalaldehyde (207 mg, 2.4 mmol) (**2m**) to give 342 mg (1.96 mmol, 98%) of **4am** as pale yellow solid after chromatography [146 mg (0.8 mmol, 42%) of **4a′m** was obtained from 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**)]: mp 303−306 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.07 (br s, 1H), 7.54−7.51 (m, 1H), 7.42−7.39 (m, 1H), 7.14−7.06 (m, 2H), 1.39 (s, 9H); ^{13}C NMR (75 MHz, DMSO) δ 162.2, 142.8, 134.6, 121.4, 120.7, 118.3, 110.8, 33.2, 29.3; IR (KBr) 3050, 2964, 2872, 1532, 1451, 1410, 1274, 1220 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_{15}N_2$ [M + H]$^+$ 175.1235, found 175.1234.

Benzimidazole[34] (4an) (Entry 15 in Table 3). 2-Iodoaniline (438 mg, 2.0 mmol) (**1a**) was coupled with formaldehyde (72 mg, 2.4 mmol) (**2n**) and $MgSO_4$ (722 mg, 6.0 mmol) to give 99 mg (0.84 mmol, 42%) of **4an** as a white solid after chromatography [128 mg (1.1 mmol, 54%) of **4a′n** was obtained from 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**)]: mp 169−171 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.52 (br s, 1H), 8.25 (s, 1H), 7.64−7.58 (m, 2H), 7.22−7.16 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ 142.0, 138.1, 121.8, 115.4; IR (KBr) 3113, 3062, 1770, 1581, 1458, 1409, 1245, 747 cm^{-1}; HRMS (FAB) calcd for $C_7H_7N_2$ [M + H]$^+$ 119.0609, found 119.0608.

Compound 4ba[35] (Entry 1 in Table 4). Methyl 4-amino-3-iodobenzoate (554 mg, 2.0 mmol) (**1b**) was coupled with benzaldehyde (255 mg, 2.4 mmol) (**2a**) to give 288 mg (1.14 mmol, 57%) of **4ba** as a pale brown solid after chromatography: mp 189−191 °C (T: indentified peaks from one tautomer, nd: nonindentified peaks); ^{1}H NMR (300 MHz, DMSO) δ 13.26 (br s, 0.5 H, nd), 13.25 (br s, 0.5 H, nd), 8.27 (br s, 0.5 H, nd), 8.20 (d, J = 4.5 Hz, 2H, nd), 8.12 (br s, 0.5 H, nd), 7.87 (d, J = 4.8 Hz, 0.5H, T), 7.85 (d, J = 5.1 Hz, 0.5H, T), 7.75 (d, J = 5.1 Hz, T), 7.63 (d, J = 4.8 Hz, 0.5 Hz, T), 7.59−7.53 (m, 3H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 166.8 (nd), 166.6 (T), 154.2 (nd), 153.4 (nd), 147.3 (T), 143.4 (nd), 138.5 (T), 134.7 (T), 130.5 (nd), 130.4 (nd), 129.5 (nd), 129.4 (nd), 129.0 (nd), 126.8 (nd), 126.7 (nd), 123.7 (T), 123.5 (nd), 123.3 (nd), 122.8 (T), 120.4 (T), 118.7 (nd), 112.9 (T), 111.4 (nd), 52.0 (nd), 51.9 (nd); IR (KBr) 3315, 2949, 1694, 1542, 1435, 1299, 1229 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{13}N_2O_2$ [M + H]$^+$ 253.0977, found 253.0977.

Compound 4bh (Entry 2 in Table 4). Methyl 4-amino-3-iodobenzoate (554 mg, 2.0 mmol) (**1b**) was coupled with piperonal (360 mg, 2.4 mmol) (**2h**) to give 427 mg (1.44 mmol, 72%) of **4bh** as a pale yellow solid after chromatography: mp 269−271 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.10 (br s, 1H), 8.14 (s, 1H), 7.82 (dd, J = 8.4, 1.5 Hz, 1H), 7.74 (dd, J = 8.1, 1.8 Hz, 1H), 7.68 (d, J = 1.8 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 8.1 Hz, 1H), 6.13 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 166.7, 153.7, 149.2, 147.9, 123.5, 123.2, 121.4, 108.8, 106.7, 101.7, 52.0; IR (KBr) 3291, 2952, 2895, 1692, 1616, 1486, 1287, 1245, 1043 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{13}N_2O_4$ [M + H]$^+$ 297.0875, found 297.0875.

Compound 4bi (Entry 3 in Table 4). Methyl 4-amino-3-iodobenzoate (554 mg, 2.0 mmol) (**1b**) was coupled with furan-2-carbaldehyde (231 mg, 2.4 mmol) (**2i**) to give 460 mg (1.9 mmol, 95%) of **4bi** as a brown oil after chromatography: ^{1}H NMR (300 MHz, DMSO) δ 13.30 (br s, 1H), 8.15 (br s, 1H), 8.00 (dd, J = 1.5, 0.6 Hz, 1H), 7.84 (dd, J = 8.4, 1.2 Hz, 1H), 7.65 (br s, 1H), 7.29 (dd, J = 3.5, 0.8 Hz, 1H), 6.76 (dd, J = 3.6, 1.8 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 166.7, 145.3, 144.9, 123.5, 112.6, 111.8, 52.1; IR (KBr) 3123, 2951, 1714, 1622, 1435, 1307, 1219 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{11}N_2O_3$ [M + H]$^+$ 243.0770, found 243.0771.

Compound 4ca[32] (Entry 4 in Table). 5-Chloro-2-iodoaniline (507 mg, 2.0 mmol) (**1c**) was coupled with benzaldehyde (255 mg, 2.4 mmol) (**2a**) to give 183 mg (0.8 mmol, 40%) of **4ca** as pale yellow solid after chromatography: mp 212−213 °C; H NMR (300 MHz, DMSO) δ 13.09 (br s, 1H), 8.18−8.14 (m, 2H), 7.64−7.47 (m, 5H), 7.23 (dd, J = 8.4, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, DMSO) δ 152.7, 130.2, 129.7, 129.0, 126.6, 122.4; IR (KBr) 3095, 1621, 1584, 1439,

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1385, 1308, 1275 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{10}ClN_2$ [M + H]$^+$ 229.0533, found 229.0534.

Compound 4cj[36] (Entry 5 in Table 4). 5-Chloro-2-iodoaniline (507 mg, 2.0 mmol) (**1c**) was coupled with 2-thiophenecarboxaldehyde (269 mg, 2.4 mmol) (**2j**) to give 352 mg (1.5 mmol, 75%) of **4cj** as a pale brown solid after chromatography: mp 223−225 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.22 (br s, 1H), 7.85 (dd, J = 3.6, 1.2 Hz, 1H), 7.77−7.75 (m, 1H), 7.61 (d, J = 1.8 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.26−7.19 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ 148.4, 133.1, 129.3, 128.4, 127.3, 126.4, 122.4; IR (KBr) 3064, 1620, 1568, 1438, 1416, 1060 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_8ClN_2S$ [M + H]$^+$ 235.0097, found 235.0098.

Compound 4ck (Entry 6 in Table 4). 5-Chloro-2-iodoaniline (507 mg, 2.0 mmol) (**1c**) was coupled with 6-methoxy-2-naphthaldehyde (447 mg, 2.4 mmol) (**2k**) to give 451 mg (1.46 mmol, 73%) of **4ck** as a pale brown solid after chromatography: mp 205−207 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.16 (br s, 1H), 8.65 (d, J = 1.2 Hz, 1H), 8.23 (dd, J = 8.7, 1.8 Hz, 1H), 7.97 (dd, J = 8.7, 3.2 Hz, 2H), 7.65−7.60 (m, 2H), 7.41 (d, J = 2.4 Hz, 1H), 7.28−7.21 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 158.3, 135.2, 130.1, 128.1, 127.4, 126.1, 124.8, 124.3, 119.5, 106.1, 55.4; IR (KBr) 3066, 1629, 1483, 1394, 1267, 1210 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{14}ClN_2O$ [M + H]$^+$ 309.0795, found 309.0794.

Compound 4da[37] (Entry 7 in Table 4). 2-Amino-3-bromopyridine (346 mg, 2.0 mmol) (**1d**) was coupled with benzaldehyde (255 mg, 2.4 mmol) (**2a**) to give 359 mg (1.84 mmol, 92%) of **4da** as a pale yellow solid after chromatography: mp 284−286 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.48 (br s, 1H), 8.34 (dd, J = 4.8, 1.5 Hz, 1H), 8.25−8.21 (m, 2H), 8.02 (d, J = 7.5 Hz, 1H), 7.61−7.51 (m, 3H), 7.25 (dd, J = 8.1, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO) δ 152.7, 143.8, 130.5, 129.7, 129.0, 126.7, 118.1; IR (KBr) 3047, 1536, 1462, 1412, 1276, 941, 771, 700 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{10}N_3$ [M + H]$^+$ 196.0875, found 196.0875.

Compound 4df[37] (Entry 8 in Table 4). 2-Amino-3-bromopyridine (346 mg, 2.0 mmol) (**1d**) was coupled with 4-methoxybenzaldehyde (327 mg, 2.4 mmol) (**2f**) to give 360 mg (1.6 mmol, 80%) of **4df** as a pale brown solid after chromatography: mp 238−240 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.34 (br s, 1H), 8.29 (dd, J = 4.8, 1.5 Hz, 1H), 8.20−8.15 (m, 2H), 7.95 (dd, J = 8.1, 1.5 Hz, 1H), 7.20 (dd, J = 7.8, 4.8 Hz, 1H), 7.15−7.10 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 161.1, 152.8, 143.3, 128.4, 122.1, 117.8, 114.4, 55.4; IR (KBr) 3120, 3058, 1621, 1489, 1439, 1407, 1370, 1253 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{12}N_3O$ [M + H]$^+$ 226.0980, found 226.0979.

Compound 4dk (Entry 9 in Table 4). 2-Amino-3-bromopyridine (346 mg, 2.0 mmol) (**1d**) was coupled with 6-methoxy-2-naphthaldehyde (447 mg, 2.4 mmol) (**2k**) to give 441 mg (1.6 mmol, 80%) of **4dk** as a pale brown solid after chromatography: mp 282−283 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.53 (br s, 1H), 8.74 (s, 1H), 8.35−8.27 (m, 2H), 8.03−7.86 (m, 3H), 7.42 (d, J = 2.7 Hz, 1H), 7.28−7.23 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 158.5, 153.0, 143.7, 135.4, 130.2, 128.1, 127.4, 126.4, 124.8, 124.3, 119.6, 118.0, 106.2, 55.3; IR (KBr) 3075, 1629, 1595, 1519, 1503, 1259, 1211 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{14}N_3O$ [M + H]$^+$ 276.1137, found 276.1135.

Compound 4do[37] (Entry 10 in Table 4). 2-Amino-3-bromopyridine (346 mg, 2.0 mmol) (**1d**) was coupled with 2-pyridinecarboxaldehyde (257 mg, 2.4 mmol) (**2o**) to give 177 mg (0.9 mmol, 45%) of **4do** as a pale yellow solid after chromatography: mp 227−229 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.52 (br s, 1H), 8.78−8.76 (m, 1H), 8.41−8.36 (m, 2H), 8.07−7.99 (m, 2H), 7.59−7.55 (m, 1H), 7.30−7.25 (m, 1H); ^{13}C NMR (75 MHz, DMSO) δ 152.2, 149.5, 148.0, 144.5, 137.7, 125.3, 121.9, 118.5; IR (KBr) 3053, 1592, 1444, 1412, 1268 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_9N_4$ [M + H]$^+$ 197.0827, found 197.0829 .

Compound 4di[38] (Entry 11 in Table 4). 2-Amino-3-bromopyridine (346 mg, 2.0 mmol) (**1d**) was coupled with furan-2-carbaldehyde (231 mg, 2.4 mmol) (**2i**) to give 296 mg (1.6 mmol, 80%) of **4di** as a pale brown solid after chromatography: mp 226−227 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.49 (br s, 1H), 8.33 (d, J = 3.6 Hz, 1H), 7.99−7.95 (m, 2H), 7.31 (dd, J = 3.6, 0.9 Hz, 1H), 7.23 (dd, J = 7.8, 4.8 Hz, 1H), 6.76 (dd, J = 3.6, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO) δ 148.7, 145.4, 145.0, 143.9, 135.4, 126.2, 119.1, 118.1, 112.5, 112.0; IR (KBr) 3085, 1631, 1590, 1517, 1415, 1264 cm^{-1}; HRMS (FAB) calcd for $C_{10}H_8N_3O$ [M + H]$^+$ 186.0667, found 186.0667.

Compound 4ea[37] (Entry 12 in Table 4). 3-Amino-2-bromopyridine (346 mg, 2.0 mmol) (**1e**) was coupled with benzaldehyde (255 mg, 2.4 mmol) (**2a**) to give 316 mg (1.62 mmol, 81%) of **4ea** as a pale yellow solid after chromatography: mp 284−286 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.48 (br s, 1H), 8.34 (dd, J = 4.8, 1.5 Hz, 1H), 8.25−8.21 (m, 2H), 8.02 (d, J = 7.5 Hz, 1H), 7.61−7.51 (m, 3H), 7.25 (dd, J = 8.1, 4.8 Hz, 1H); ^{13}C NMR (75 MHz, DMSO) δ 152.7, 143.8, 130.5, 129.7, 129.0, 126.7, 118.1; IR (KBr) 3047, 1536, 1462, 1412, 1276, 941, 771, 700 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{10}N_3$ [M + H]$^+$ 196.0875, found 196.0875.

Compound 4ef[37] (Entry 13 in Table 4). 3-Amino-2-bromopyridine (346 mg, 2.0 mmol) (**1e**) was coupled with 4-methoxybenzaldehyde (327 mg, 2.4 mmol) (**2f**) to give 441 mg (1.96 mmol, 98%) of **4ef** as a pale yellow solid after chromatography: mp 238−240 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.34 (br s, 1H), 8.29 (dd, J = 4.8, 1.5 Hz, 1H), 8.20−8.15 (m, 2H), 7.95 (dd, J = 8.1, 1.5 Hz, 1H), 7.20 (dd, J = 7.8, 4.8 Hz, 1H), 7.15−7.10 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, DMSO) δ 161.1, 152.8, 143.3, 128.4, 122.1, 117.8, 114.4, 55.4; IR (KBr) 3120, 3058, 1621, 1489, 1439, 1407, 1370, 1253 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{12}N_3O$ [M + H]$^+$ 226.0980, found 226.0978.

Compound 4eo[37] (Entry 14 in Table 4). 3-Amino-2-bromopyridine (346 mg, 2.0 mmol) (**1e**) was coupled with 2-Pyridinecarboxaldehyde (257 mg, 2.4 mmol) (**2o**) to give 157 mg (0.8 mmol, 40%) of **4eo** as a pale yellow solid after chromatography: mp 227−229 °C; ^{1}H NMR (300 MHz, DMSO) δ 13.52 (br s, 1H), 8.78−8.76 (m, 1H), 8.41−8.36 (m, 2H), 8.07−7.99 (m, 2H), 7.59−7.55 (m, 1H), 7.30−7.25 (m, 1H); ^{13}C NMR (75 MHz, DMSO) δ 152.2, 149.5, 148.0, 144.5, 137.7, 125.3, 121.9, 118.5; IR (KBr) 3053, 1592, 1444, 1412, 1268 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_9N_4$ [M + H]$^+$ 197.0827, found 197.0824.

Synthesis of Tiabendazole.[39] 2-Iodoaniline (438 mg, 2.0 mmol) (**1a**) was coupled with thiazole-4-carboxaldehyde (272 mg, 2.4 mmol) to give 390 mg (1.94 mmol, 97%) of tiabendazole as a pale yellow solid after chromatography [354 mg (1.8 mmol, 88%) of Tiabendazole was obtained from 2-bromoaniline (344 mg, 2.0 mmol) (**1a′**)]: mp 294−297 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.96 (br s, 1H), 9.33 (d, J = 2.1 Hz, 1H), 8.44 (d, J = 2.1 Hz, 1H), 7.58 (br s, 2H), 7.23−7.17 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ 154.8, 147.4, 146.9, 123.0, 118.8; IR (KBr) 3093, 3045, 1578, 1405, 1306 cm^{-1}; HRMS (FAB) calcd for $C_{10}H_8N_3S$ [M + H]$^+$ 202.0439, found 202.0440.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Stability of tautomers and copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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