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INDIUM-MEDIATED REDUCTIVE INTERMOLECULAR COUPLING REACTION OF 2-NITROANILINE WITH AROMATIC ALDEHYDES TO BENZIMIDAZOLES

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Abstract - 2-Nitroaniline and aromatic aldehydes were coupled to give benzimidazoles in high yields in the presence of 2-bromo-2-nitropropane and indium at room temperature.

Since the first reported use of indium in organic synthesis in 1975 by Rieke,[1] its application for organic synthesis has been widely developed due to its low ionic potential and aqueous conditions.[2,3] In particular, indium-mediated reactions in aqueous media have been the focus of synthetic applications because of environmental issues and the ease of the reactions, which do not require flammable anhydrous organic solvents or an inert atmosphere.[4] The first ionization potential of indium (5.8 eV) is much lower than that of zinc (9.4 eV) or tin (7.3 eV), and even magnesium (7.6 eV) and thus indium metal should participate readily in SET (single electron transfer) processes and therefore be a potential reducing reagent. Recently, indium has been extensively used in various reductive reactions: reductive coupling of aldimines,[5] reductive elimination of 1,2-dibromides,[6] pinacol couplings,[7] ketone deoxygenation,[8] reductive dehalogenation of α-halocarbonyl compounds, benzyl halides and halomethylcephalosporins,[9] reduction of azides,[10] and *N*-oxides,[11] reductive coupling of acyl cyanides,[12] reduction of nitrostyrenes,[13] oximes,[14] and other nitro compounds,[2b, 10c, 15, 16d] and selective reduction of heterocyclic rings.[2d]

In our continuing study on the application of 2-bromo-2-nitropropane (BNP) and metals to reductive heterocyclization,[16] we examined indium metal as an electron donor and discovered that 2-bromo-2-nitropropane and indium are effective to reductive cyclization of 2-substituted nitroarenes to give the corresponding 2,1-benzisoxazoles.[16d] For the intermolecular ring formation, we examined intermolecular

coupling/heterocyclization reactions using zinc and BNP recently.[17] Based on these results, we decided to explore the indium-mediated reductive intermolecular coupling reaction of 2-nitroaniline with aromatic aldehydes to give benzimidazoles since indium-mediated organic reactions has been focused on its unique ability of mediating organic reactions in aqueous media. We report here the reductive intermolecular coupling reaction of 2-nitroaniline with aromatic aldehydes to benzimidazoles using indium that shows superior results compared to zinc case.

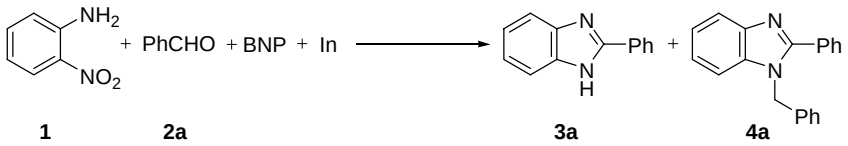
RESULTS AND DISCUSSION

Benzimidazole and its derivatives present interesting biological activities such as bacteriostats, bactericides, insecticides, fungicides, sedatives, anticarcinogens, and phycopharmacological agents.[18] Although there are several ways leading to benzimidazoles, traditional methods of 2-arylbenzimidazole preparation involve the condensation and cyclization of benzoic acid derivatives with *o*-diamino aromatic compounds in the presence of a mineral acid with high temperature.[19] Ochoa *et al*. reported high temperature thermal cyclocondensation of *o*-phenylenediamines with aromatic aldehydes primarily producing three cyclized products (benzimidazoles and quinoxaline) with a variable product ratio depending on the substrate and a combined yield of less than 60%.[19d] Since indium has attracted much attention in synthetic chemistry recently, we decide to examine intermolecular coupling/heterocyclization reactions using indium as an extension of metal-mediated reductive heterocyclization.

As control experiments, various reaction conditions were examined to facilitate the reductive intermolecular coupling reaction of 2-nitroaniline with benzaldehyde and the results are summarized in Table 1. The reaction of 2-nitroaniline (**1**) with benzaldehyde (**2a**) in methanol/water co-solvent in the presence of indium produced the desired 2-phenylbenzimidazole (**3a**) and 1-benzyl-2-phenylbenzimidazole (**4a**) in low yields (Table 1, Entry 1). However, the addition of BNP to the reaction mixture led to a more efficient reductive intermolecular coupling reaction, which is consistent with our previous result [we previously described the usefulness of BNP as a good electron accepting mediator for reductive heterocyclization due to its low-lying antibonding π-orbital].[16] Furthermore, while the reaction in methanol produced **4a** in relatively low yield (Table 1, Entry 2), the reactions with MeOH/H_2O as a solvent dramatically increased the overall yield of cyclized products and gave mainly the 1,2-disubstituted benzimidazole (**4a**) at room temperature. In addition, as shown in Table 1, the reaction carried out in a 2 : 1 mixture (v/v) of MeOH/H_2O solution was the most successful compared to those with other mixtures. The optimum results for the formation of **4a** were seen with 2-nitroaniline/aldehyde (2 equiv)/BNP (4 equiv)/In (5 equiv) in MeOH/H_2O (v/v = 2 : 1) at room temperature (Entry 8, **4a** in 70% yield). Reactions

in a co-solvent such as DMF/H_2O (Entry 13) or THF/H_2O (Entry 14) revealed relatively low yield with low product selectivity as well.

Table 1. Reactions of 2-nitroaniline with benzaldehyde in the presence of BNP/indium under various reaction conditions



1 **2a** **3a** **4a**

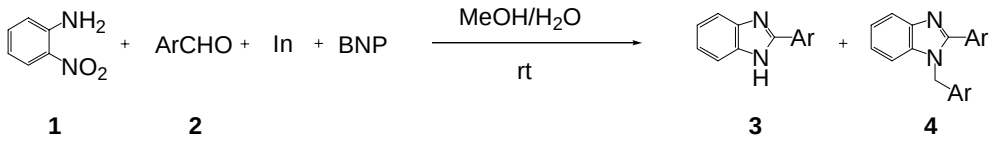
Entry	Molar ratio **1** : **2a** : BNP : In	Solvent	Time (h)	Yield (%)	
				3a	**4a**
1[a]	1 : 2 : 0 : 5	MeOH/ H_2O (v/v = 2 : 1)	48	4	3
2	1 : 2 : 4 : 5	MeOH	24	trace	11
3	1.5 : 1 : 2 : 5	MeOH/ H_2O (v/v = 2 : 1)	3	6	49
4	1 : 2 : 2 : 5	MeOH/ H_2O (v/v = 2 : 1)	6	19	65
5	1 : 2 : 2 : 10	MeOH/ H_2O (v/v = 2 : 1)	2.5	29	62
6	1 : 3 : 2 : 10	MeOH/ H_2O (v/v = 2 : 1)	3	24	58
7	1 : 2 : 3 : 5	MeOH/ H_2O (v/v = 2 : 1)	4	18	63
8	1 : 2 : 4 : 5	MeOH/ H_2O (v/v = 2 : 1)	5	10	70
9	1 : 2 : 4 : 5	MeOH/ H_2O (v/v = 3 : 1)	6	12	60
10	1 : 2 : 1.2 : 5	MeOH/ H_2O (v/v = 2 : 1)	5	33	53
11	1 : 2 : 5 : 5	MeOH/ H_2O (v/v = 2 : 1)	24	15	62
12	1 : 2 : 4 : 5	MeOH/ H_2O (v/v = 1 : 1)	5	31	67
13	1 : 2 : 4 : 5	DMF/ H_2O (v/v = 2 : 1)	12	30	42
14	1 : 2 : 2 : 10	THF/ H_2O (v/v = 2 : 1)	5	22	29
15	1 : 2 : 4 : 5	MeOH/ CH_2Cl_2 (v/v = 2 : 1)	17	trace	7

[a]**1**(81%) and **2** (5%) were recovered.

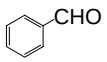
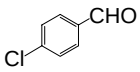
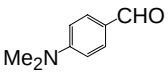
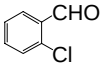
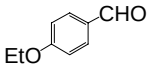
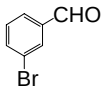
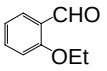
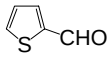
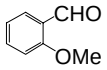
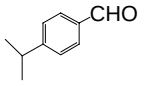
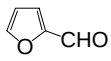
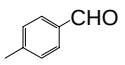
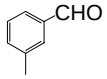
To explore the possibility of using BNP/In conditions for 1,2-disubstituted benzimidazole syntheses, we examined reductive intermolecular coupling reactions of 2-nitroaniline with various aromatic aldehydes bearing diverse groups under the optimized conditions for the formation of **4a**. The results are summarized in Table 2. In most cases, 1,2-disubstituted benzimidazoles (**4**) were easily obtained in good yields accompanying 2-substituted benzimidazoles (**3**) as well. In general, the product selectivity of 1,2-disubstituted benzimidazoles (**4**) over 2-substituted benzimidazoles (**3**) was higher when an alkyl, alkoxy, or amino group -an electron-donating group- was substituted on the benzene ring of aldehyde. It produced 66 – 84% of **4** accompanying 0 – 17% of **3** and it was quite selective result compared to Ochoa's report or our previous zinc/BNP mediated reaction.[17] In particular, the reaction of 4-dimethylaminobenzaldehyde produced **4b** only without any **3b** (Table 2, Entry 2) and similar result was also obtained for the reaction of 2-furaldehyde and 2-nitroaniline (Table 2, Entry 14). However, the product selectivity was lower when a halogen group was substituted on the phenyl ring of aldehyde. For example, when 2-

chlorobenzaldehyde coupled to 2-nitroaniline, the product ratio of 1,2-disubstituted benzimidazole (**4j**) and 2-substituted benzimidazole (**3j**) was nearly 1 : 1 (Table 2, Entry 10) with almost no product selectivity. On the other hand, the reductive coupling reaction of 3-furaldehyde and 2-nitroaniline formed cyclized products in low yield despite a long reaction time (37% overall, 13 h).

Table 2. Reactions of 2-nitroaniline with benzaldehydes (2 equiv.) in the presence of BNP (4 equiv.)/In (5 equiv.) in MeOH/H_2O (2/1, v/v) at room temperature[a]



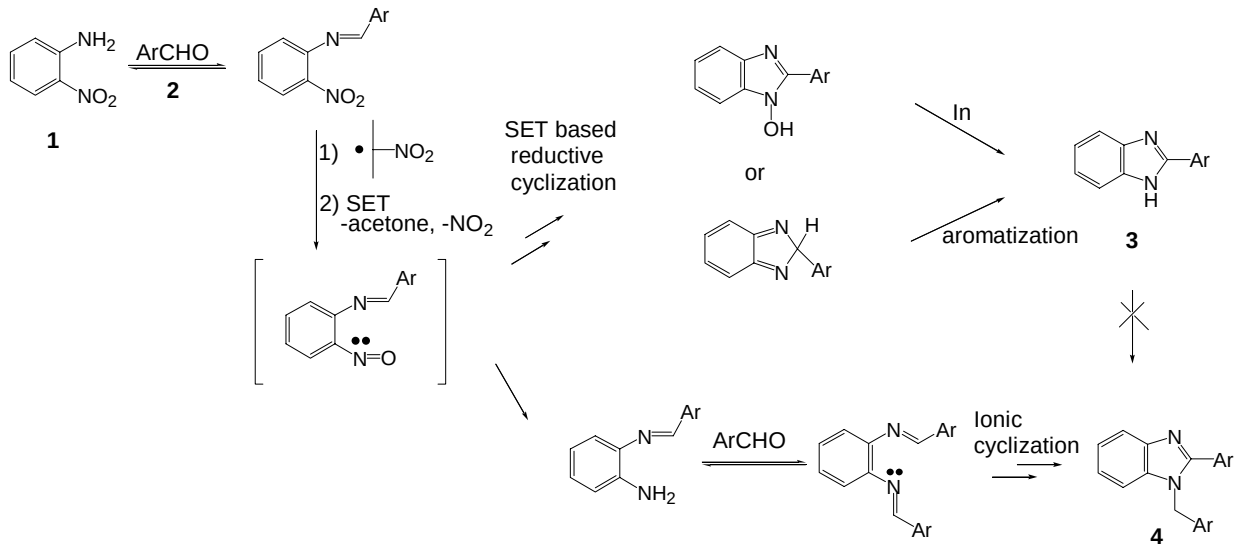
1 **2** **3** **4**

Entry	ArCHO	time (h)	yield (%)		Entry	ArCHO	time (h)	yield (%)	
			3	**4**				**3**	**4**
1		5	10 (**3a**)	70 (**4a**)	9		5	29 (**3i**)	56 (**4i**)
2		6	0 (**3b**)	66 (**4b**)	10		8	37 (**3j**)	41 (**4j**)
3		3	13 (**3c**)	67 (**4c**)	11		7	28 (**3k**)	51 (**4k**)
4		4	14 (**3d**)	75 (**4d**)	12		3	22 (**3l**)	66 (**4l**)
5		5	17 (**3e**)	66 (**4e**)	13		2	20 (**3m**)	70 (**4m**)
6		3	11 (**3f**)	83 (**4f**)	14		3	trace	74 (**4n**)
7		6	12 (**3g**)	68 (**4g**)	15		13	16 (**3o**)	21 (**4o**)
8		3	16 (**3h**)	84 (**4h**)					

[a]All reactions were carried out with 0.3 mmol of 2-nitroaniline.

In our previous communication,[17] we have described our synthetic effort for the reductive coupling reaction of 2-nitroaniline with aromatic aldehydes to benzimidazoles using zinc and BNP. In addition, various control experiments were examined to disclose the reaction path and/or the intermediates of the reaction. Consequently, based on our and other's result,[19d, 20] a plausible reaction path was proposed as shown in Scheme 1. Without doubt, similar tendency was observed when indium was applied instead of zinc.

Scheme 1



Indium is practically unaffected by water, however, finely divided materials can react with water to form hydroxides.[2a] If the indium hydroxide produced *in situ* in our reaction condition, a Cannizzaro-type oxidation-reduction process can be possibly promoted. To examine the possibility of the Cannizzaro-type oxidation-reduction process, additional experiments were carried out. Firstly, reactions of 2-nitroaniline/ benzaldehyde (2 equiv.)/$In(OH)_3$ (0.5 - 1 equiv.) in MeOH/H_2O (2/1, v/v) at room temperature for 24 hr were tried. However, it did not proceed at all and starting substrates were recovered mostly. Addition of BNP to the mixture did not help the reaction to proceed either. Secondly, the mixtures of on-going reaction [2-nitroaniline (**1**)/benzaldehyde (**2a**, 2 equiv.)/BNP (4 equiv.)/In (5 equiv.) in MeOH/H_2O (2/1, v/v) at room temperature] were analyzed by GC-MS with 30 min interval until the reaction completed. If the reaction proceeds with a Cannizzaro-type oxidation-reduction process, the evidence of benzyl alcohol formation should be detected. However, benzyl alcohol was not detected in any stages on GC-MS analysis. The same reaction in the presence of $In(OH)_3$ (0.5 - 1 equiv.) did not show any positive effect also and yield of 1,2-disubstituted benzimidazole (**4a**) was diminished to 30 (1 equiv. $In(OH)_3$) – 60% (0.5 equiv. $In(OH)_3$). Thus the possibility of the Cannizzaro-type oxidation-reduction process could somehow be excluded. More mechanistic study will be done to disclose the detailed reaction path.

Since indium metal can participate readily in SET processes similar to zinc metal, the following subsequent reaction path is quite possible; 1) amino group of 2-nitroaniline and carbonyl group of benzaldehydes can couple each other to form the imine intermediate 2-NO_2-C_6H_4-N=CH-Ar *in situ*, 2) nitro group reduction, 3) nitro group reduction triggered cyclization to 2-arylbenzimidazoles and/or diimine formation followed by cyclization to 1,2-disubstituted benzimidazoles. In addition, the reaction of isolated **3** in our reaction condition did not produce **4** at all. Certainly, 2-arylbenzimidazole (**3**) and 1,2-

disubstituted benzimidazoles (**4**) were formed by the independent path rather than the reductive amination of **3** to **4**.

In conclusion, we have established a new and efficient method for the synthesis of 1,2-disubstituted benzimidazoles from 2-nitroaniline/aldehydes using BNP/In under mild conditions in aqueous media. Unlike BNP/Zn mediated reaction, 1,2-disubstituted benzimidazoles obtained as a major product mostly accompanying 2-substituted benzimidazoles as a minor product.

EXPERIMENTAL

1. General consideration

Most of chemical reagents were purchased from Aldrich and used without further purification in most cases. Solvents were purchased and dried by a standard method. ^{1}H NMR spectra were recorded on 300 MHz Bruker instrument and ^{13}C NMR spectra were recorded on 75 MHz Bruker instrument. Chemical shifts are in ppm from tetramethylsilane (TMS). HRMS spectra were recorded on a JEOL JMS-DX 303 mass spectrometer and GC/MS were recorded on a HP6890 mass spectrometer. IR spectra were recorded on a Nicolet 205 FT-IR. Analytical data were obtained with an EA-1110, CHNS-O CEinstruments. Melting points were determined on an Electrothermal apparatus and are uncorrected.

All the major products were isolated by flash column chromatography on silica gel (230 - 400 mesh ATSM, purchased from Merck) with eluents of mixed solvents (ethyl acetate and hexane).

2. General procedure for the reductive intermolecular coupling reaction

To a stirred solution of 2-nitroaniline (41.4 mg, 0.3 mmol), aldehyde (0.6 mmol) and indium dust (173 mg, 1.5 mmol) in MeOH (1.0 mL)/H_2O (0.5 mL) was added 2-bromo-2-nitropropane (0.127 mL, 1.2 mmol) at rt. The reaction mixture was stirred for a fixed time and poured into a solution of 10% aqueous NH_4Cl. The mixture was extracted with CH_2Cl_2 (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The residue was eluted with ethyl acetate/hexane (v/v = 5/95 - 10/90) through a silica gel column to give **3** and **4**. Solid product was recrystallized from acetone/hexane co-solvent.

2-Phenylbenzimidazole (**3a**)[19c, 21] white solid; mp 295.0-296.0 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.19 (d, J = 3.7 Hz, 2H), 7.44-7.64 (m, 5H), 8.14-8.19 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 151.2, 143.8, 135.0, 130.2, 129.9, 129.0, 126.4, 122.5, 121.7, 118.9, 111.3; IR (KBr) 3443, 3047, 1477, 1463, 1444, cm^{-1}; GC-MS m/z (rel. intensity) 194 (100, M^{+}), 166 (6), 97 (6), 77 (5); HRMS (EI) calcd for $C_{13}H_{10}N_2$

194.0844, found 194.0844.

1-Benzyl-2-phenylbenzimidazole (4a)[22] white solid; mp 135.0-136.0 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.57 (s, 2H), 6.98 (d, *J* = 6.2 Hz, 2H), 7.21-7.28 (m, 5H), 7.50-7.53 (m, 4H), 7.69-7.74 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.1, 143.1, 136.4, 136.0, 129.9, 129.5, 129.3, 129.1, 128.8, 127.8, 125.9, 123.1, 122.7, 120.0, 110.5, 48.4; IR (KBr) 3031, 2947, 1463 cm^{-1}; GC-MS m/z (rel. intensity) 284 (100, M^+), 207 (6), 193 (7), 180 (3), 166 (3), 152 (5), 103 (1), 91 (85), 77 (6); HRMS (EI) calcd for $C_{20}H_{16}N_2$ 284.1312, found 284.1312; Anal. Calcd for $C_{20}H_{16}N_2$: C, 84.48; H, 5.67; N, 9.85. Found: C, 84.34; H, 5.69; N, 9.78.

1-(4-Dimethylaminophenylmethyl)-2-(4-dimethylaminophenyl)benzimidazole (4b) white solid; mp 168.0-169.0 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.93 (s, 6H), 3.00 (s, 6H), 5.37 (s, 2H), 6.66-6.75 (m, 4H), 7.02 (d, J = 8.8 Hz, 2H), 7.14-7.29 (m, 3H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.82 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 151.2, 149.9, 143.3, 136.4, 130.3, 126.9, 124.3, 122.1, 119.2, 117.3, 112.8, 111.8, 110.4, 48.0, 40.5, 40.2; IR (KBr) 3049, 2979, 2929, 2784, 1592, 1441 cm^{-1}; GC-MS m/z (rel. intensity) the compound **4b** seemed to decompose when it was analyzed by GC-MS; HRMS (EI) calcd for $C_{20}H_{26}N_4$ 370.2157, found 370.2199; Anal. Calcd for $C_{24}H_{26}N_4$: C, 77.80; H, 7.07; N, 15.12. Found: C, 77.51; H, 7.12; N, 15.05.

2-(4-Ethoxyphenyl)benzimidazole (3c)[21c, 21d] white solid; mp 228.8-229.5 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (t, *J* = 7.0 Hz, 3H), 4.11 (q, *J* = 7.0 Hz, 2H), 6.98-7.02 (m, 2H), 7.16 (dd, *J* = 3.1, 6.1 Hz, 2H), 7.55 (dd, *J* = 3.1, 6.1 Hz, 2H), 8.11 (dd, *J* = 2.0, 6.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9, 151.4, 143.9, 135.0, 128.0, 122.5, 122.1, 121.4, 118.5, 114.8, 111.0, 63.3, 14.6; IR (KBr) 3052, 2971, 2924, 2878, 1612, 1472, 1437, 1250 cm^{-1}; GC-MS m/z (rel. intensity) 238 (100, M^+), 210 (89), 192 (3), 181 (25), 154 (4), 119 (4), 105 (30), 90 (5), 77 (4).

1-(4-Ethoxyphenylmethyl)-2-(4-ethoxyphenyl)benzimidazole (4c) white solid; mp 144.7-145.6 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (t, *J* = 7.0 Hz, 3H), 1.37 (t, *J* = 7.0 Hz, 3H), 3.89-4.04 (m, 4H), 5.31 (s, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 7.15 (d, *J* = 3.9 Hz, 2H), 7.18-7.26 (m, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.77 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 158.4, 154.2, 143.2, 136.1, 130.7, 128.3, 127.2, 122.6, 122.4, 122.3, 119.6, 114.9, 114.6, 110.4, 63.5, 63.4, 47.9, 14.8, 14.7; IR (KBr) 3056, 2975, 2874, 2929, 1612, 1511, 1441, 1246 cm^{-1}; GC-MS m/z (rel. intensity) 372 (47, M^+), 237 (2), 209 (6), 180 (2), 135 (100), 119 (3), 107(61), 90 (4), 77 (6); HRMS (EI) calcd for $C_{20}H_{14}N_2O_2$ 372.1838, found 372.1848; Anal. Calcd for $C_{20}H_{14}N_2O_2$: C, 77.39; H, 6.49;N, 7.52. Found: C, 77.67; H, 6.57; N, 7.71.

2-(2-Ethoxyphenyl)benzimidazole (3d)[23] white solid; mp 151.0 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.43 (t, *J* = 6.8 Hz, 3H), 4.32 (q, *J* = 6.8 Hz, 2H), 7.05-7.24 (m, 4H), 7.41-7.47 (m, 1H), 7.62 (br s, 2H), 8.23 (d, *J* = 7.7 Hz, 1H), 11.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.8, 149.2, 142.8, 134.6, 131.2, 130.2, 122.1, 121.8, 120.8, 118.7, 118.5, 113.0, 111.9, 64.0, 14.3; IR (KBr) 3072, 2987, 2969, 2921, 1604, 1460, 1400, 1249 cm^{-1}; GC-MS m/z (rel. intensity) 238 (47, M^+), 223 (100), 209 (7), 194 (88), 181 (27), 166 (2), 154 (3), 119 (12), 102 (3), 91 (6), 77 (8).

1-(2-Ethoxyphenylmethyl)-2-(2-ethoxyphenyl)benzimidazole (4d) white solid; mp 112.6-113.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.11 (t, *J* = 7.0 Hz, 3H), 1.25 (t, *J* = 7.0 Hz, 3H), 3.84-3.94 (m, 4H), 5.21 (s, 2H), 6.52 (d, *J* = 7.5 Hz, 1H), 6.58-6.64 (m, 1H), 6.70 (d, *J* = 8.3 Hz, 1H), 6.84-6.95 (m, including *J* = 7.5, 8.3 Hz, 2H), 7.02-7.20 (m, 4H), 7.29-7.35 (m, 1H), 7.43 (dd, *J* = 1.7, 7.5 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.7, 155.7, 152.6, 143.2, 135.3, 132.5, 131.2, 128.3, 127.7, 124.4, 122.2, 121.8, 120.6, 120.1, 119.9, 119.6, 111.7, 110.8, 110.7, 63.7, 63.4, 43.3, 14.7, 14.4; IR (KBr) 3072, 2980, 1591, 1446, 1400, 1242 cm^{-1}; GC-MS m/z (rel. intensity) 372 (51, M^+), 357 (88), 343 (5), 327 (16), 313 (10), 299 (13), 283 (39), 269 (5), 251 (3), 237 (60), 221 (10), 195 (15), 181 (12), 135 (100), 107 (37), 91 (35), 77 (28); HRMS (EI) calcd for $C_{24}H_{24}N_2O_2$ 372.1838, found 372.1835; Anal. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39 H, 6.49; N, 7.52. . Found: C, 77.38; H, 6.64; N, 7.53.

2-(2-Methoxyphenyl)benzimidazole (3e)[21c, 21d] white solid; mp 185.0-186.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08 (s, 3H), 7.07 (d, *J* = 8.4 Hz, 1H), 7.12-7.18 (m, 1H), 7.23-7.30 (m, 2H), 7.40-7.46 (m, 1H), 7.66 (br s, 2H), 8.60 (dd, *J* = 1.8, 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 148.9, 142.7, 134.7, 131.2, 129.7, 122.0, 121.5, 120.9, 118.4, 118.1, 112.1, 111.9, 55.8; IR (KBr) 3173, 2964, 2932, 1584, 1476, 1243 cm^{-1}; GC-MS m/z (rel. intensity) 224 (100, M^+), 205 (4), 194 (67), 181 (9), 119 (37), 102 (3), 90 (10), 77 (6).

1-(2-Methoxyphenylmethyl)-2-(2-methoxyphenyl)benzimidazole (4e) white solid; mp 153.0-156.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (s, 3H), 3.81 (s, 3H), 5.26 (s, 2H), 6.69-6.74 (m, 1H), 6.76-6.87 (m, 2H), 6.98 (d, *J* = 8.4 Hz, 1H), 7.05-7.11 (m, 1H), 7.18-7.33 (m, 4H), 7.44-7.51 (m, 1H), 7.56 (dd, *J* = 1.8, 7.5 Hz, 1H), 7.87 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 156.4, 152.4, 143.3, 135.5, 132.3, 131.3, 128.3, 127.6, 124.4, 122.4, 121.9, 120.7, 120.3, 119.73, 119.71, 110.71, 110.70, 109.8, 55.1, 55.0, 43.5; IR (KBr) 3064, 3043, 2959, 2943, 1604, 1452, 1243 cm^{-1}; GC-MS m/z (rel. intensity) 344 (64, M^+), 329 (6), 313 (30), 299 (3), 283 (14), 223 (100), 195 (12), 121 (47), 91 (67), 77 (9); HRMS (EI) calcd for $C_{22}H_{20}N_2O_2$ 344.1525, found 344.1530; Anal. Calcd for $C_{22}H_{20}N_2O_2$: C, 76.72; H, 5.85; N, 8.13. Found: C, 76.51; H, 5.87; N, 8.17.

2-[4-(1-Methylethyl)phenyl]benzimidazole (3f)[24] white solid; mp 250.0-253.0 ^{o}C; ^{1}H NMR (300 MHz, DMSO) δ 1.24 (d, *J* = 1.3 Hz, 3H), 1.24 (d, *J* = 1.3 Hz, 3H), 2.92-3.00 (m, 1H), 7.13-7.23 (m, 2H), 7.41 (d, *J* = 7.9 Hz, 2H), 7.50 (d, *J* = 7.1 Hz, 1H), 7.64 (d, *J* = 7.3 Hz, 1H), 8.09 (d, *J* = 7.9 Hz, 2H), 12.82 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 150.3, 143.9, 135.1, 127.9, 126.9, 126.5, 122.3, 121.5, 118.7, 111.2, 33.4, 23.7; IR (KBr) 3434, 3059, 2960, 2912, 2888, 1440, 1275 cm^{-1}; GC-MS m/z (rel. intensity) 236 (64, M^+), 221 (100), 207 (80), 193 (4), 115 (2), 103 (9), 92 (8), 77 (3).

1-[4-(1-Methylethyl)phenylmethyl]-2-[4-(1-methylethyl)phenyl]benzimidazole (4f)[25] white solid; mp 176.0-178.0 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (d, *J* = 7.0 Hz, 6H), 1.34 (d, *J* = 7.0 Hz, 6H), 2.91-3.07 (m, 2H), 5.51 (s, 2H), 7.11 (d, *J* = 8.1 Hz, 2H), 7.23-7.40 (m, 7H), 7.71 (d, *J* = 8.3 Hz, 2H), 7.93 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 150.8, 148.3, 143.1, 136.0, 133.7, 129.2, 127.4, 127.0, 126.8, 125.8, 122.7, 122.4, 119.7, 110.5, 48.1, 34.0, 33.7, 23.9, 23.8; IR (KBr) 3054, 2958, 2923, 2866, 1462, 1450, 1418, 1332 cm^{-1}; GC-MS m/z (rel. intensity) 368 (100, M^+), 353 (30),337 (10), 325 (2), 309 (2), 283 (1), 235 (5), 219 (7), 207 (3), 194 (2), 133 (95), 117 (16), 105 (18), 91 (10), 77 (3); HRMS (EI) calcd for $C_{26}H_{28}N_2$ 368.2249, found 368.2249; Anal. Calcd for $C_{26}H_{28}N_2$: C, 84.74 H, 7.66; N, 7.60. Found: C, 83.99; H, 7.90; N, 7.54.

2-(4-Methylphenyl)benzimidazole (3g)[21] white solid; mp 275.0-278.0 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.39 (s, 3H), 7.20 (d, *J* = 5.1 Hz, 2H), 7.37 (d, *J* = 7.9 Hz, 2H), 7.53 (br s, 1H), 7.64 (br s, 1H), 8.08 (d, *J* = 7.9 Hz, 2H), 12.84 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.4, 143.8, 139.6, 136.0, 129.5, 127.4, 126.4, 122.3, 121.5, 118.7, 111.2, 21.0; IR (KBr) 3421, 2960, 2920, 2861, 2756, 1427, 1275 cm^{-1}; GC-MS m/z (rel. intensity) 208 (100, M^+), 192 (4), 116 (3), 103 (13), 90 (5), 77 (2).

1-(4-Methylphenylmethyl)-2-(4-methylphenyl)benzimidazole (4g)[26] white solid; mp 131.0-133.0 ^{o}C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H), 2.38 (s, 3H), 5.38 (s, 2H), 6.97 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 7.14-7.31 (m, 5H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.83 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.2, 143.1, 139.9, 137.3, 136.0, 133.4, 129.6, 129.4, 129.0, 127.1, 125.8, 122.7, 122.4, 119.7, 110.4, 48.1, 21.4, 21.0; IR (KBr) 3024, 2917, 2861, 1411, 1249 cm^{-1}; GC-MS m/z (rel. intensity) 312 (92, M^+), 297 (1), 208 (21), 192 (6), 116 (3), 105 (100), 90 (7), 77 (10); HRMS (EI) calcd for $C_{22}H_{20}N_2$ 312.1628, found 312.1628; Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.62; H, 6.83; N, 8.97.

2-(3-Methylphenyl)benzimidazole (3h)[21d, 24] white solid; mp 215.1-215.7 ^{o}C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.30 (s, 3H), 7.21-7.33 (m, 4H), 7.64 (dd, *J* = 3.1, 6.0 Hz, 2H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.96 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ151.3, 143.8, 138.2, 135.0, 130.5, 130.1, 128.8, 127.0, 123.6, 122.5,

121.6, 118.8, 111.3, 21.1; IR (KBr) 3049, 2974, 2917, 2877, 2788, 1592, 1441, 1270 cm^{-1}; GC-MS m/z (rel. intensity) 208 (100, M^+), 192 (3), 180 (3), 116 (3), 103 (10), 91 (6), 77 (2).

1-(3-Methylphenylmethyl)-2-(3-methylphenyl)benzimidazole (4h) white solid; mp 96.5-98.4 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.30 (s, 3H), 5.35 (s, 2H), 6.80-6.88 (m, 2H), 7.02-7.05 (m, 1H), 7.12-7.28 (m, 6H), 7.32-7.37 (m, 1H), 7.52 (s, 1H), 7.78-7.83 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 143.1, 138.8, 138.6, 136.5, 136.2, 130.7, 130.2, 129.9, 128.9, 128.50, 128.49, 126.6, 126.0, 123.1, 122.9, 122.6, 119.9, 110.5, 48.4, 21.5, 21.4; IR (KBr) 3064, 2957, 2909, 1608, 1449, 1386, 1250 cm^{-1}; GC-MS m/z (rel. intensity) 312 (100, M^+), 297 (5), 221 (5), 207 (5), 192 (4), 180 (2), 116 (2), 105 (80), 90 (6), 77 (11); HRMS (EI) calcd for $C_{22}H_{20}N_2$ 312.1626, found 312.1622; Anal. Calcd for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.45; H, 6.50; N, 9.04.

2-(4-Chlorophenyl)benzimidazole (3i)[21, 27] white solid; mp 277.0-281.0 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 7.19-7.27 (m, 2H), 7.47-7.52 (m, 2H), 7.57-7.61 (m, 2H), 8.16-8.21 (m, 2H); ^{13}C NMR (75 MHz, DMSO) δ 150.1, 143.7, 135.0, 134.5, 129.1, 129.0, 128.1, 122.8, 121.9, 119.0, 111.4; IR (KBr) 3441, 3052, 3000, 2954, 2848, 2750, 1427, 1275 cm^{-1}; GC-MS m/z (rel. intensity) 228 (100, M^+), 193 (12), 166 (4), 114 (5), 102 (2), 90 (5), 75 (2).

1-(4-Chlorophenylmethyl)-2-(4-chlorophenyl)benzimidazole (4i) white solid; mp 139.0-141.5 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 5.40 (s, 2H), 7.02 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 7.7 Hz, 1H), 7.24-7.28 (m, 1H), 7.29-7.38 (m, 3H), 7.42-7.46 (m, 2H), 7.57-7.61 (m, 2H), 7.87 (d, J = 7.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.8, 143.0, 136.3, 135.8, 134.6, 133.8, 130.4, 129.3, 129.1, 128.3, 127.2, 123.4, 123.0, 120.1, 110.3, 47.7; IR (KBr) 3038, 2923, 2853, 1473, 1439, 1091 cm^{-1}; GC-MS m/z (rel. intensity) 352 (52, M^+), 317 (1), 227 (4), 192 (4), 125 (100), 102 (3), 90 (13), 77 (3); HRMS (EI) calcd for $C_{20}H_{14}N_2Cl_2$ 352.0534, found 352.0538; Anal. Calcd for $C_{20}H_{14}N_2Cl_2$: C, 68.00; H, 3.99; N, 7.93. Found: C, 67.95; H, 3.98; N, 7.93.

2-(2-Chlorophenyl)benzimidazole (3j)[21c, 21d, 27a] white solid; mp 229.7-230.5 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20-7.28 (m, 2H), 7.29-7.35 (m, 2H), 7.36-7.43 (m, 1H), 7.61 (dd, J = 3.1, 6.0 Hz, 2H), 8.25-8.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 143.2, 134.6, 132.1, 131.6, 131.2, 130.3, 130.0, 127.4, 122.7, 121.7, 119.1, 111.7; IR (KBr) 3448, 3061, 2921, 2854, 1443, 1404, 1053 cm^{-1}; GC-MS m/z (rel. intensity) 228 (100, M^+), 193 (15), 166 (4), 138 (2), 114 (4), 96 (6), 75 (2).

1-(2-Chlorophenylmethyl)-2-(2-chlorophenyl)benzimidazole (4j) white solid; mp 166.3-167.2 ^oC; ^1H NMR (300 MHz, $CDCl_3$) δ 5.36 (s, 2H), 6.63 (d, J = 6.4 Hz, 1H), 7.03-7.09 (m, 1H), 7.14-7.36 (m, 6H), 7.40-7.54 (m, 3H), 7.89 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.5, 143.0, 134.8, 134.3,

133.2, 132.3, 132.1, 131.4, 129.9, 129.6, 129.5, 128.9, 127.7, 127.1, 126.9, 123.3, 122.7, 120.3, 110.5, 45.7; IR (KBr) 3029, 2959, 2920, 1612, 1437, 1394, 1355, 1278, 1161, 1045 cm^{-1}; GC-MS m/z (rel. intensity) 352 (90, M^+), 317 (87), 281 (7), 227 (4), 180 (5), 152 (4), 125 (100), 90 (15), 77 (6); HRMS (EI) calcd for $C_{20}H_{14}N_2Cl_2$ 352.0534, found 352.0536; Anal. Calcd for $C_{20}H_{14}N_2Cl_2$: C, 68.00; H, 3.99; N, 7.93. Found: C, 67.52; H, 4.07; N, 7.95.

2-(3-Bromophenyl)benzimidazole (3k)[28] white solid; mp 224.0-225.0 °C; ^{1}H NMR (300 MHz, DMSO) δ 7.16-7.20 (m, 2H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.52-7.60 (m, 3H), 8.03 (d, *J* = 7.9 Hz, 1H), 8.22-8.25 (m, 1H); ^{13}C NMR (75 MHz, DMSO) δ 149.6, 143.7, 135.0, 132.5, 132.4, 131.2, 128.9, 125.4, 123.0, 122.3, 122.0, 119.1, 111.6; IR (KBr) 3410, 3045, 2959, 2917, 1561, 1437, 1398, 1072 cm^{-1}; GC-MS m/z (rel. intensity) 272 (100, M^+), 207 (8), 193 (69), 166 (8), 137 (5), 96 (16), 76 (5).

1-(3-Bromophenylmethyl)-2-(3-bromophenyl)benzimidazole (4k) white solid; mp 106.0-107.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.30 (s, 2H), 6.86-6.89 (m, 1H), 7.06-7.28 (m, 6H), 7.33-7.36 (m, 1H), 7.41-7.45 (m, 1H), 7.50-7.54 (m, 1H), 7.77-7.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.3, 142.9, 138.4, 135.8, 133.0, 132.3, 131.7, 131.2, 130.7, 130.2, 129.0, 127.4, 124.5, 123.6, 123.2, 123.1, 122.9, 120.2, 110.3, 47.7; IR (KBr) 3045, 2928, 1569, 1468 cm^{-1}; GC-MS m/z (rel. intensity) 442 (100, M^+), 361 (70), 335 (6), 281 (12), 257 (3), 206 (6), 192 (6), 169 (74), 152 (4), 140 (5), 102 (8), 90 (45), 77 (8); HRMS (EI) calcd for $C_{20}H_{14}N_2Br_2$ 439.9524, found 439.9496; Anal. Calcd for $C_{20}H_{14}N_2Br_2$: C, 54.33; H, 3.19; N, 6.34. Found: C, 54.44; H, 3.20; 6.38.

2-(2-Thienyl)benzimidazole (3l)[19c, 21a, 21b, 29] white solid; mp >330 °C; ^{1}H NMR (300 MHz, DMSO) δ 7.12-7.25 (m, 3H), 7.50 (d, *J* = 6.6 Hz, 1H), 7.60 (d, *J* = 6.9 Hz, 1H), 7.72 (d, *J* = 4.8 Hz, 1H), 7.83 (d, *J* = 3.6 Hz, 1H), 12.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 143.6, 134.7, 133.7, 128.8, 128.3, 126.7, 122.6, 121.8, 118.5, 111.1; IR (KBr) 3060, 3015, 2940, 2858, 1568, 1417, 1274, 1235 cm^{-1}; GC-MS m/z (rel. intensity) 200 (100, M^+), 174 (4), 156 (5), 110 (2), 90 (3), 78 (1).

1-(2-Thienylmethyl)-2-(2-thienyl)benzimidazole (4l)[30] white solid; mp 152.0-153.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (s, 2H), 6.86-6.70 (m, 2H), 7.12-7.16 (m, 1H), 7.23-7.40 (m, 4H), 7.46-7.53 (m, 2H), 7.82-7.85 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 142.9, 137.5, 135.8, 130.9, 128.2, 127.4, 126.5, 126.3, 125.6, 123.1, 122.7, 121.6, 119.8, 109.9, 44.6; IR (KBr) 3095, 3072, 2929, 1449, 1421, 1219 cm^{-1}; GC-MS m/z (rel. intensity) 296 (78, M^+), 199 (6), 172 (4), 109 (2), 97 (100), 77 (2); HRMS (EI) calcd for $C_{16}H_{12}N_2S_2$ 296.0442, found 296.0448; Anal. Calcd for $C_{16}H_{12}N_2S_2$: C, 64.83; H, 4.08; N, 9.45. Found: C, 64.82; H, 4.07; N, 9.46.

2-(3-Thienyl)benzimidazole (3m)[19c] white solid; mp 320 °C (decomp); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (dd, *J* = 3.3, 6.0 Hz, 2H), 7.37 (dd, *J* = 3.0, 5.1 Hz, 1H), 7.52 (dd, *J* = 3.3, 6.0 Hz, 2H), 7.77 (dd, *J* = 1.2, 5.1 Hz, 1H), 8.09 (dd, *J* = 1.2, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 143.8, 134.5, 132.6, 127.6, 126.4, 125.0, 122.3, 121.7, 118.7, 111.2; IR (KBr) 3076, 2924, 2850, 1573, 1425, 1340, 1274 cm^{-1}; GC-MS m/z (rel. intensity) 200 (100, M^+), 174 (10), 156 (8), 110 (3), 90 (4), 78 (1).

1-(3-Thienylmethyl)-2-(3-thienyl)benzimidazole (4m)[19d] white solid; mp 149.0-152.4 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.50 (s, 2H), 6.90-6.96 (m, 2H), 7.25-7.39 (m, 4H), 7.44 (dd, *J* = 2.9, 5.1 Hz, 1H), 7.52-7.56 (m, 1H), 7.64-7.68 (m, 1H), 7.82-7.86 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.5, 143.0, 138.8, 135.8, 131.8, 128.9, 128.0, 127.9, 127.2, 125.42, 125.37, 123.3, 122.9, 119.9, 109.9, 44.0; IR (KBr) 3103, 2917, 2843, 1452, 1324, 1254 cm^{-1}; GC-MS m/z (rel. intensity) 296 (76, M^+), 281 (4), 263 (5), 199 (3), 172 (2), 97 (100), 77 (2); HRMS (EI) calcd for $C_{16}H_{12}N_2S_2$ 296.0442, found 296.0441; Anal. Calcd for $C_{16}H_{12}N_2S_2$: C, 64.83; H, 4.08; N, 9.45. Found: C, 64.89; H, 4.08; N, 9.47.

1-(2-Furanylmethyl)-2-(2-furanyl)benzimidazole (4n) white solid; mp 98.4-99.3 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ5.56 (s, 2H), 6.15-6.22 (m, 2H), 6.52-6.55 (m, 1H), 7.14 (d, *J* = 3.3 Hz, 1H), 7.20-7.26 (m, 3H), 7.39-7.45 (m, 1H), 7.57 (d, *J* = 1.2 Hz, 1H), 7.68-7.73 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 145.3, 143.91, 143.86, 142.9, 142.6, 135.4, 123.2, 122.8, 119.7, 112.8, 112.0, 110.5, 109.9, 108.3, 41.6; IR (KBr) 3146, 3049, 2924, 2850, 1604, 1507, 1383, 1254 cm^{-1}; GC-MS m/z (rel. intensity) 264 (100, M^+), 235 (2), 206 (2), 183 (9), 156 (3), 115 (1), 102 (3), 81 (90); HRMS (EI) calcd for $C_{16}H_{12}N_2O_2$ 264.0899, found 264.0895; Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 71.64; H, 4.60; N, 10.50.

2-(3-Furanyl)benzimidazole (3o)[19c] white solid; mp 302.6-303.2 °C; ^{1}H NMR (300 MHz, DMSO) δ 7.08 (s, 1H), 7.14-7.20 (m, 2H), 7.50-7.60 (m, 2H), 7.84-7.87 (m, 1H), 8.38 (s, 1H), 12.70 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 144.6, 143.7, 142.3, 13 4.2, 122.2, 121.6, 118.5, 118.0, 110.9, 108.9; IR (KBr) 3126, 3056, 1631, 1425 cm^{-1}; GC-MS m/z (rel. intensity) 184 (100, M^+), 156 (26), 143 (4), 129 (10), 103 (7), 92 (6), 78 (3).

1-(3-Furanylmethyl)-2-(3-furanyl)benzimidazole (4o) white solid; mp 111.8-112.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26 (s, 2H), 6.20 (s, 1H), 6.85 (d, *J* = 1.2 Hz, 1H), 7.13 (s, 1H), 7.18-7.30 (m, 3H), 7.33 (d, *J* = 1.8 Hz, 1H), 7.46-7.50 (m, 1H), 7.72-7.77 (m, 1H), 7.81(s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 144.2, 143.8, 143.1, 142.2, 139.5, 135.6, 123.0, 122.6, 121.3, 119.7, 116.4, 110.5, 109.6, 108.9, 40.3; IR (KBr) 3153, 3103, 3049, 2954, 1596, 1456, 1324, 1281, 1161, 1021 cm^{-1}; GC-MS m/z (rel. intensity) 264 (100, M^+), 235 (24), 221 (3), 207 (17), 184 (3), 171(2), 155 (3), 142 (3), 129 (3), 115 (3),

102 (3), 90 (8), 81 (95); HRMS (EI) calcd for $C_{16}H_{12}N_2O_2$ 264.0899, found 264.0895; Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.70; H, 4.65; N, 10.63.

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