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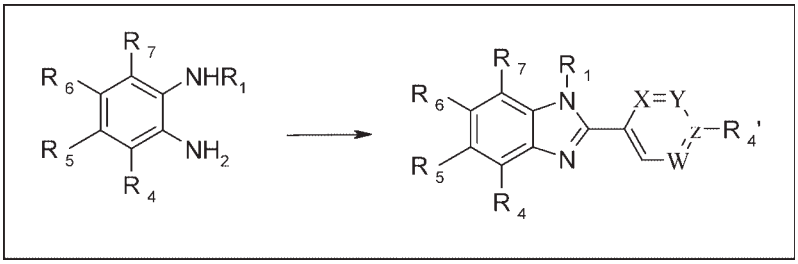

A series of 47 novel N^1-alkylated-2-aryl-5(6)-substituted-1*H*-benzimidazoles and their three novel indole analogues were synthesized and evaluated for *in vitro* antifungal activities against *Candida* species by the tube dilution method. The results showed that compounds **79** and **80**, having pyridine at the position C-2, of benzimidazoles exhibited the greatest activity with MIC values of 6.25–3.12 μg/mL. Indole analogues **108–110** have no inhibitory activity.

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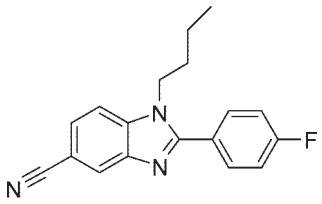
INTRODUCTION

We have already reported the synthesis and potent antifungal evaluation of a series of 2-substituted-phenyl-1*H*-benzimidazole-5-carbonitriles [1]. The study revealed that among the synthesized benzimidazoles compound **I** exhibited greatest antifungal activity with the MIC of 3.12 μg/mL against *Candida albicans*, *Candida krusei*, *Candida glabrata*, and *Candida parapsilosis* (Fig. 1).



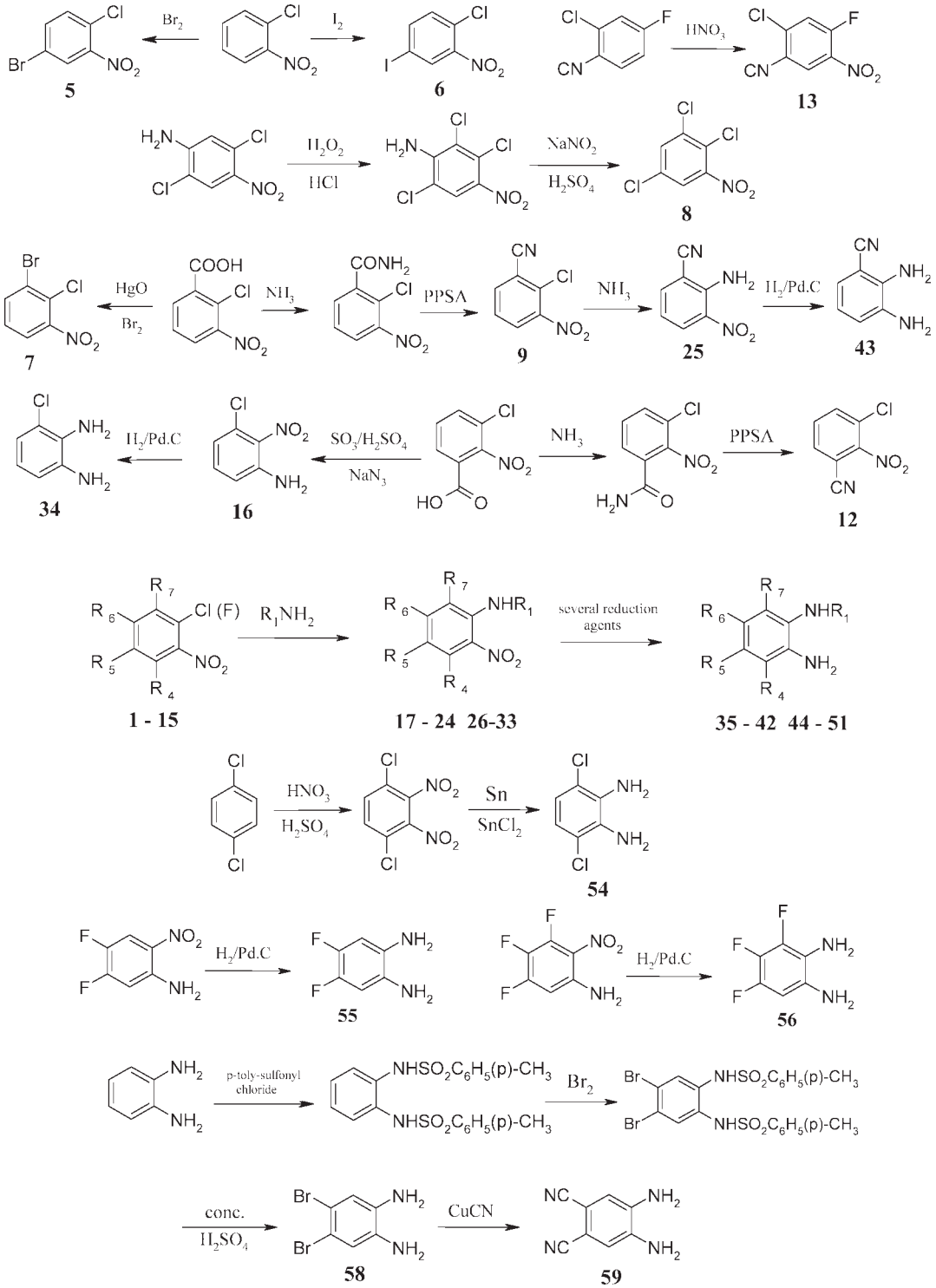
I

We planned to modify the structure of compound **I** in order to find more potent new antifungal agents.

RESULTS AND DISCUSSION

Noncommercial starting material *o*-phenylenediamines were prepared according to the literature methods, which are given in Scheme 1. The synthetic pathways for preparation of the targeted benzimidazoles listed in Table 1 are shown in Schemes 2 and 3. Nucleophilic displacement of the chloro group of **1–15** (Table 2), by the reaction with several amines in *N,N*-dimethylformamide gave **16–33** (Table 3). Their reduction with hydrogen gas by using palladium carbon or tin/hydrochloric acid produced **34–59** (Table 4). Condensation of these derivatives with the sodium metabisulfite adduct of appropriate benzaldehydes gave the targeted benzimidazoles **60–73**, **75**, **78–80**, **83**, **84**, **90–97**, **99–102**, **104** [1]. Heck and Nolley [23] reaction of **73** with (trimethylsilyl)acetylene led to **74a**, whose silyl group was cleaved to yield 5-ethynylbenzimidazole **74**. **77** was prepared by diazotation of **76**, followed by treatment with sodium azide. Acylation of 3-amino-4-(butylamino)benzonitrile with 4-pyridazine and pyrazine carbonyl chlorides gave the corresponding monoamide derivatives **81a** and **82a**, following this cyclization of these compounds with glacial acetic acid and anhydrous sodium acetate afforded **81** and **82**. The nitrile group of **I** was converted to carboxyaldehyde **85**, by using diisobutylaluminum hydride (DIBAL), in a moderato yield, and aldehyde group was transformed to the oxime ether **86**. The 1,2,4-oxadiazol-3-yl-1*H*-benzimidazole **88** was obtained by reaction of **I** first with hydroxylamine to amidoxime **87** and subsequently with acetic anhydride. In addition, another 1*H*-benzimidazole-5-carbonitrile **89a** reacted with sodium azide at high temperature to yield 5-substituted 1*H*-tetrazole **89**. Benzylic cleavage of **97** afforded **98** by reduction with hydrogen gas. Alkylation of tautomeric imidazole NH of **99–102** with butyl bromide in *N,N*-dimethylformamide gave **103**,

Scheme 1. Synthesis of noncommercial *o*-phenylenediamines.

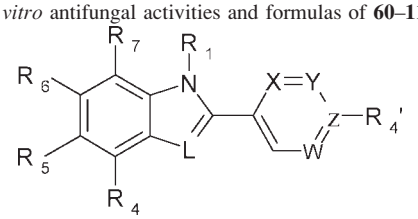


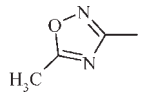
105–107 in good yield. For the preparation of **110** which is the indole analogous of **89a**, first **108** was prepared by the well-known Fischer indole synthesis method (Scheme 3) [24]. Alkylation of this compound gave **109**, then bromine was converted to the nitrile with copper(I) cyanide.

The benzimidazoles **60–110** were tested *in vitro* for antifungal activity against *C. albicans* (ATCC 10231), *C. krusei* (ATCC 6258), *C. parapsilosis* (ATCC 22019), and *C. glabrata* (Clinical isolate) by the tube dilution method [25] and the MIC values are listed in Table 1.

Table 1

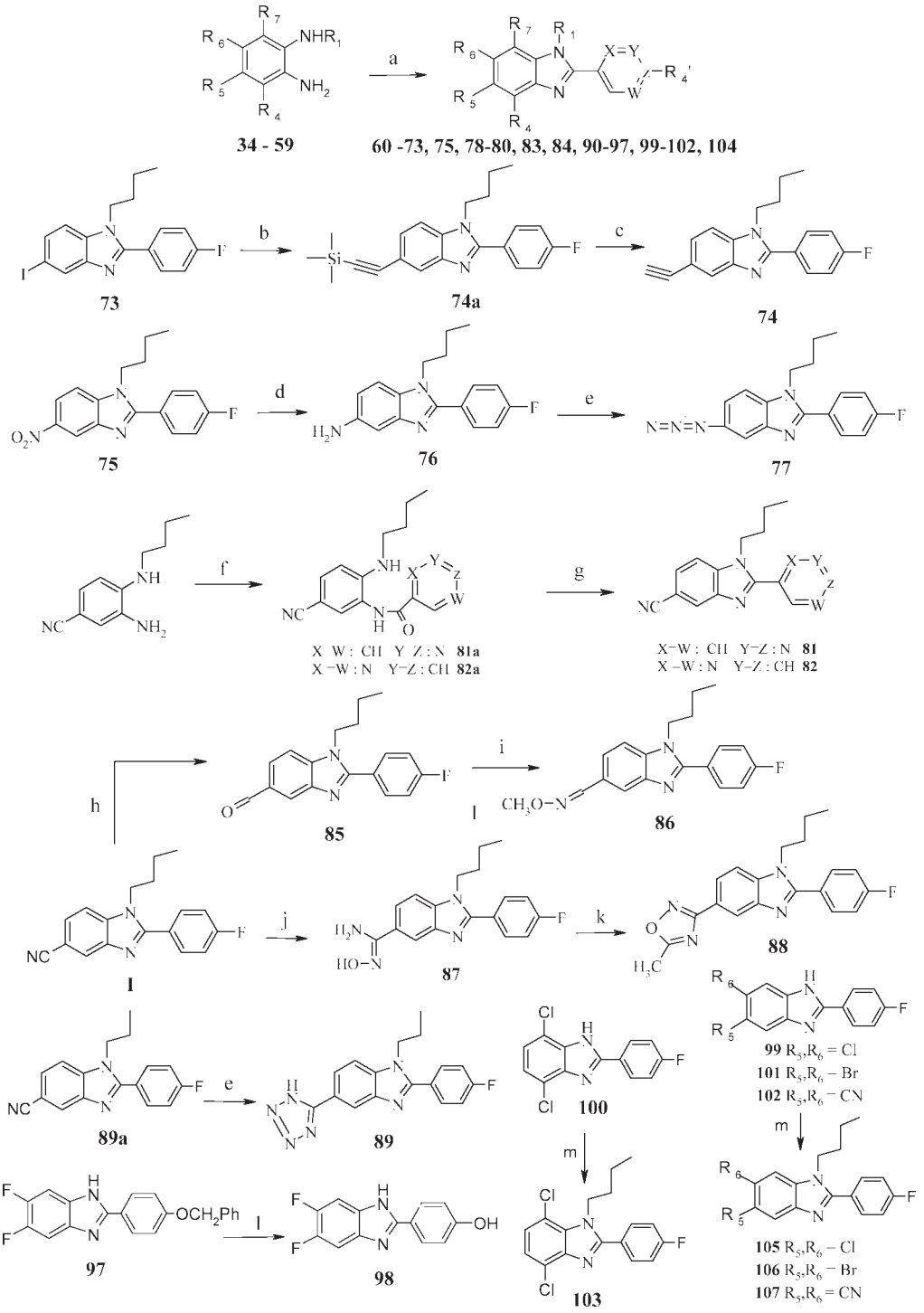
In vitro antifungal activities and formulas of **60–110**.



No	R_1	R_7	R_6	R_5	R_4	$R_{4'}$	L	X	Y	Z	W	MIC_{100} (μg/mL)			
												C a	*C k*	*C p*	*C g*
60		Cl				F	N	CH	CH	CH	CH	>50	>50	>50	>50
61		CN				F	N	CH	CH	CH	CH	>50	>50	>50	>50
62				CF_3		F	N	CH	CH	CH	CH	12.5	12.5	6.25	12.5
63	butyl	Cl					N	CH	CH	CH	CH	>50	>50	>50	>50
64	butyl	Cl				F	N	CH	CH	CH	CH	>50	>50	>50	>50
65	butyl	Br				F	N	CH	CH	CH	CH	>50	>50	>50	>50
66	butyl	CN				F	N	CH	CH	CH	CH	>50	>50	>50	>50
67	butyl		Cl			F	N	CH	CH	CH	CH	>50	>50	>50	>50
68	butyl		CN			F	N	CH	CH	CH	CH	>50	>50	>50	>50
69	butyl			F		F	N	CH	CH	CH	CH	>50	>50	>50	>50
70	butyl			Cl		F	N	CH	CH	CH	CH	>50	>50	>50	>50
71	butyl			Cl			N	CH	CH	N	CH	>50	>50	>50	>50
72	butyl			Br		F	N	CH	CH	CH	CH	>50	>50	>50	>50
73	butyl			I		F	N	CH	CH	CH	CH	>50	>50	>50	>50
74	butyl			HC≡C—		F	N	CH	CH	CH	CH	>50	>50	>50	>50
75	butyl			NO_2		F	N	CH	CH	CH	CH	>50	>50	>50	>50
76	butyl			NH_2		F	N	CH	CH	CH	CH	>50	>50	>50	>50
77	butyl			N_3		F	N	CH	CH	CH	CH	>50	>50	>50	>50
78	butyl			NC			N	N	CH	CH	CH	>50	>50	>50	>50
79	butyl			NC			N	CH	N	CH	CH	6.25	25	12.5	25
80	butyl			NC			N	CH	CH	N	CH	6.25	12.5	3.12	25
81	butyl			NC			N	CH	N	N	CH	25	25	12.5	25
82	butyl			NC			N	N	CH	CH	N	>50	>50	>50	>50
83	pentyl			NC			N	CH	CH	CH	CH	25	>50	25	>50
84	butyl		Cl	NC		F	N	CH	CH	CH	CH	>50	>50	>50	>50
85	butyl			CHO		F	N	CH	CH	CH	CH	>50	>50	>50	>50
86	butyl			MeO—N=CH—		F	N	CH	CH	CH	CH	>50	>50	>50	>50
87	butyl					F	N	CH	CH	CH	CH	>50	>50	>50	>50
88	butyl					F	N	CH	CH	CH	CH	>50	>50	>50	>50
89	propyl					F	N	CH	CH	CH	CH	>50	>50	>50	>50
90	butyl			CH_3CO		F	N	CH	CH	CH	CH	>50	>50	>50	>50
91	butyl				CN	F	N	CH	CH	CH	CH	>50	>50	>50	>50
92		Br		F_3C			N	CH	CH	CH	CH	>50	>50	>50	>50
93			F	F			N	CH	CH	CH	CH	25	25	3.12	25
94			F	F		F	N	CH	CH	CH	CH	12.5	25	6.25	12.5
95		F	F	F			N	CH	CH	CH	CH	>50	>50	>50	>50
96			F	F			N	CH	CH	N	CH	>50	>50	>50	>50
97			F	F		OBn	N	CH	CH	CH	CH	>50	>50	>50	>50
98			F	F		OH	N	CH	CH	CH	CH	>50	>50	>50	>50
99			Cl	Cl		F	N	CH	CH	CH	CH	>50	>50	>50	>50
100		Cl			Cl	F	N	CH	CH	CH	CH	>50	>50	>50	>50
101			Br	Br		F	N	CH	CH	CH	CH	>50	>50	>50	>50
102			NC	NC		F	N	CH	CH	CH	CH	>50	>50	>50	>50
103	butyl	Cl			Cl	F	N	CH	CH	CH	CH	>50	>50	>50	>50
104	butyl	Cl		Cl		F	N	CH	CH	CH	CH	>50	>50	>50	>50
105	butyl		Cl	Cl		F	N	CH	CH	CH	CH	>50	>50	>50	>50
106	butyl		Br	Br		F	N	CH	CH	CH	CH	25	25	25	25
107	butyl		NC	NC		F	N	CH	CH	CH	CH	>50	>50	>50	>50
108				Br		F	CH	CH	CH	CH	CH	>50	>50	>50	>50
109	propyl			Br		F	CH	CH	CH	CH	CH	>50	>50	>50	>50
110	propyl			NC		F	CH	CH	CH	CH	CH	>50	>50	>50	>50
I	butyl			NC		F	N	CH	CH	CH	CH	1.56	12.5	1.56	25
Flu												1.56	25	3.12	25

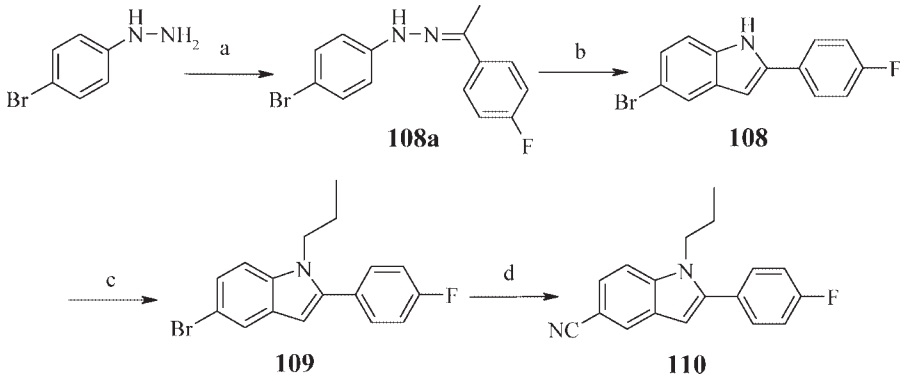
MIC_{100} = Minimum inhibitory concentrations, *C a*, *Candida albicans*; *C k*, *Candida krusei*; *C p*, *Candida parapsilosis*; *C g*, *Candida glabrata*; I, formula in Figure 1; Flu, Fluconazole.

Scheme 2. Synthesis of benzimidazoles **60–107**. Reagents (a) $Na_2S_2O_5$ adduct of the corresponding benzaldehydes; (b) (Trimethylsilyl)-acetylen; (c) KOH/MeOH; (d) $SnCl_2$/HCl; (e) $NaNO_2$-HCl/NaN_3; (f) For **81a**: 4-Pyridazinecarboxylic acid and HBTU; For **82a**: Pyrazinecarbonyl chloride; (g) Glacial acetic acid/anhydrous Na-acetate; (h) DIBAL; (i) Methoxyl-amine HCl; (j) NH_2OH·HCl, *i*-Pr_2NEt; (k) $(CH_3CO)_2O$; (l) Pd.C/H_2; and (m) Butyl bromide/NaH.



The synthesized compounds and reference drugs were dissolved in dimethyl sulfoxide-water (50%) at a concentration of 400 μg/mL. The concentration was adjusted to 100 μg/mL by fourfold dilution with media culture and fungi solution at the first tube. Data was not taken for the initial solution because of the high concentration (12.5%).

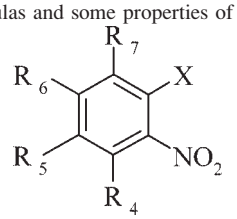
Scheme 3. Synthesis of indole analogues **108–110**. Reagents (a) 4′-fluoroacetophenone, trimethylamine; (b) PPA; (c) Propyl bromide, NaH; and (d) CuCN, *N*-methyl-2-pyrrolidone.



The result demonstrates that some of the benzimidazoles in this series showed the good activity profiles versus some *Candida* species. Among of them, compounds **79** and **80** exhibited the greatest activity with MIC values of 6.25–3.12 μg/mL. These compounds are having pyridine moiety at the position of C-2 instead of phenyl in compound **I** (Fig. 1). Replacement of phenyl moiety to 4-pyridazine (**81**) or pyrazine (**82**) caused to reduce inhibitory activity. Most of the other electron withdrawing group which could be the bioequivalence of cyano at the position of C-5 were tested, however, as no better result were found with them, cyano group was accepted

Table 2

Formulas and some properties of **1–15.**

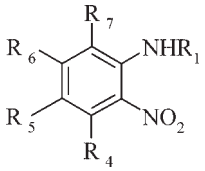


Comp	R_7	R_6	R_5	R_4	X	Formulas	References, physical and spectral data
1	Cl				Cl	$C_6H_3Cl_2NO_2$	Commercial
2		Cl			Cl	$C_6H_3Cl_2NO_2$	Commercial
3			F		Cl	$C_6H_3ClFNO_2$	Commercial
4			Cl		Cl	$C_6H_3Cl_2NO_2$	Commercial
5			Br		Cl	$C_6H_3BrClNO_2$	mp 69°C, ref. 2, 71–72°C
6			I		Cl	$C_6H_3ClINO_2$	mp 74°C, ref. 3, 74.5°C; ^{1}H NMR: δ 7.28 (d, 1H, J = 8.4 Hz), 7.82 (dd, 1H, J = 2, 8.6 Hz), 8.17 (d, 1H, J = 2 Hz)
7	Br				Cl	$C_6H_3BrClNO_2$	ref. 4
8	Cl		Cl		Cl	$C_6H_2Cl_3NO_2$	ref. 5
9	CN				Cl	$C_7H_3ClN_2O_2$	ref. 6
10		CN			Cl	$C_7H_3ClN_2O_2$	ref. 1
11			CN		Cl	$C_7H_3ClN_2O_2$	Commercial
12				CN	Cl	$C_7H_3ClN_2O_2$	mp 65°C,[a] ref. 7 mp 85°C; IR (potassium bromide): 2240 (CN) cm^{-1}; ^{1}H NMR: δ 7.57 (t, 1H, J = 7.6 Hz), 7.69 (dd, 1H, J = 1.2, 7.6 Hz), 7.75 (dd, 1H, J = 1.2, 8.5 Hz)
13		Cl	CN		F	$C_7H_2ClFN_2O_2$	ref. 8, mp 83°C, ref. 9, 84–85°C
14			$COCH_3$		Cl	$C_8H_6ClNO_3$	Commercial
15			NO_2		Cl	$C_6H_3ClN_2O_4$	Commercial

[a]Melting point is not in agreement with the data given in ref. 7. However, our elemental analysis result confirms the structure. *Anal*. Calcd for $C_7H_3ClN_2O_2$: C, 46.05; H, 1.66; N, 15.34. Found C, 45.62; H, 1.695; N, 15.17.

Table 3

Formulas and some properties of **16–33**.

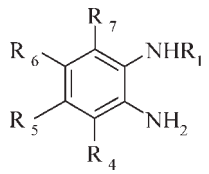


No	R_1	R_7	R_6	R_5	R_4	Formulas	References, physical and spectral data
16	H				Cl	$C_6H_5ClN_2O_2$	mp 108–109, ref. 10 mp 108–108.5; ^{1}H NMR: δ 6.7 (dd, 1H, J = 1.2, 8.4 Hz), 6.82 (dd, 1H, J = 1.2, 8.5 Hz), 7.16 (t, 1H, J = 8.3)
17	*n*-butyl	Cl				$C_{10}H_{13}ClN_2O_2$	Oily; ^{1}H NMR: δ 0.93 (t, 3H), 1.39 (m, 2H), 1.58 (m, 2H), 3.41 (q, 2H), 6.67 (br.s, 1H), 6.72 (t, 1H), 7.48 (dd, 1H, J = 1.6, 8.2 Hz), 7.91 (dd, 1H, J = 1.6, 8.4 Hz); ms: *m/z* 229 (100), 231 (33)
18	*n*-butyl		Cl			$C_{10}H_{13}ClN_2O_2$	Oily, ref. 11
19	*n*-butyl			F		$C_{10}H_{13}FN_2O_2$	ref. 12
20	*n*-butyl			Cl		$C_{10}H_{13}ClN_2O_2$	ref. 1
21	*n*-butyl			Br		$C_{10}H_{13}BrN_2O_2$	Purification: ethyl acetate:hexane (10:90) cc; Oily; ^{1}H NMR: δ 0.98 (t, 3H), 1.48 (m, 2H), 1.71 (m, 2H), 3.28 (q, 2H), 6.75 (d, 1H, J = 8.8), 7.48 (dd, 1H, J = 2.4, 8.8 Hz), 8.03 (br.t, 1H), 8.31 (d, 1H, J = 2.4 Hz); ms: *m/z* 273 (100), 275 (100)
22	*n*-butyl			I		$C_{10}H_{13}IN_2O_2$	Purification: ethyl acetate:hexane (10:90) cc; Oily; ^{1}H NMR: δ 0.985 (t, 3H), 1.48 (m, 2H), 1.70 (m, 2H), 3.28 (q, 2H), 6.64 (d, 1H, J = 9.2 Hz), 7.61 (dd, 1H, J = 2, 9.2 Hz), 8.04 (br.t, 1H), 8.46 (d, 1H, J = 2Hz); ms: *m/z* 321
23	*n*-butyl	Br				$C_{10}H_{13}BrN_2O_2$	Purification: ethyl acetate:hexane (20:80) cc; Oily; ^{1}H NMR: δ 0.92 (t, 3H), 1.38 (m, 2H), 1.58 (m, 2H), 3.25 (q, 2H), 6.05 (br.s, 1H), 6.68 (t, 1H), 7.67 (dd, J = 1.6, 7.6 Hz, 1H), 7.87 (dd, J = 1.6, 8.4 Hz, 1H); ms: *m/z* 273 (100), 275 (100)
24	*n*-butyl	Cl		Cl		$C_{10}H_{12}Cl_2N_2O_2$	Purification: ethyl acetate:hexane (10:90) cc; Oily; ^{1}H NMR: δ 0.93 (t, 3H), 1.37 (m, 2H), 1.58 (m, 2H), 3.4 (q, 2H), 6.72 (br.s, 1H), 7.49 (d, 1H), 7.94 (d, 1H); ms: *m/z* 263 (100), 265 (61), 267(11)
25	H	CN				$C_7H_5N_3O_2$	mp 133–135°C, ref. 13 mp 129–130°C; ^{1}H NMR (Deuteriochloroform + D_2O): δ 6.79 (t, 1H, J = 8 Hz), 7.7 (dd, 1H, J = 1.2, 7.6 Hz), 8.4 (dd, 1H, J = 1.6, 8 Hz)
26	*n*-butyl	CN				$C_{11}H_{13}N_3O_2$	Purification: ethyl acetate:hexane (40:60) cc; mp 37°C; ^{1}H NMR: δ 0.96 (t, 3H), 1.46 (m, 2H), 1.72 (m, 2H), 3.83 (q, 2H), 6.68 (t, 1H), 7.17 (dd, 1H), 8.35 (dd, 1H), 8.46 (br.s, 1H); ms: *m/z* 220 (100)
27	*n*-butyl		CN			$C_{11}H_{13}N_3O_2$	Purification: Cryst. ethanol; mp 83–85°C; ^{1}H NMR: δ 1.02 (t, 3H), 1.48 (m, 2H), 1.72 (m, 2H), 3.30 (q, 2H), 6.85 (dd, 1H), 7.15 (d, 1H, J = 1.5 Hz), 8.03 (br.s, 1H), 8.26 (d, 1H, J = 8.4); ms: *m/z* 220 (100)
28	*n*-butyl			CN		$C_{11}H_{13}N_3O_2$	ref. 1
29	*n*-pentyl			CN		$C_{12}H_{15}N_3O_2$	Purification: Cryst. ethanol; ^{1}H NMR: δ 0.95 (t, 3H), 1.47 (m, 4H), 1.73 (m, 2H), 3.35 (q, 2H), 6.92 (d, J = 9.1, 1H), 7.58 (dd, 1H), 8.41 (br.s, 1H), 8.51 (d, 1H, J = 1.3)
30	*n*-butyl				CN	$C_{11}H_{13}N_3O_2$	Purification: ethyl acetate:hexane (40:60) cc; mp 82–84°C; ^{1}H NMR: δ 0.98 (t, 3H), 1.46 (m, 2H), 1.71 (m, 2H), 3.32 (q, 2H), 7.08 (d, 1H), 7.12 (d, 1H), 7.46 (t, 1H), 8.13 (br.s, 1H); ms: *m/z* 220 (100)
31	*n*-butyl		Cl	CN		$C_{11}H_{12}ClN_3O_2$	Purification: Cryst. ethanol; mp 83°C; ^{1}H NMR: δ 1.02 (t, 3H), 1.49 (m, 2H), 1.75 (m, 2H), 3.34 (q, 2H), 6.94 (s, 1H), 8.38 (s, 1H), 8.5 (s, 1H); ms: *m/z* 254 (100), 256 (33)
32	*n*-butyl			$COCH_3$		$C_{12}H_{16}N_2O_3$	ref. 14
33	*n*-butyl			NO_2		$C_{10}H_{13}N_3O_4$	ref. 15

as a best pharmacophore at this position. Moreover, changing the position of cyano group from C-5, to C-4 (**91**), C-6 (**68**), and C-7 (**66**), did not give better result. In addition, this cyano group was converted to the aldehyde (**85**), oxime (**86**), oxadiazole (**88**), and tetrazole (**89**), unfortunately activity was reduced again. Because we have already reported that, the best group was butyl at position N-1, no more modifications have been done in this study, only compound **83** with *n*-pentyl group was prepared, which also caused to reduce activity. Among the halogenated compounds, the best results were obtained with **93** against *C. parapsilosis* with the MIC

Table 4

Formulas and some properties of **34–59**.



Com	R_1	R_7	R_6	R_5	R_4	Formulas	References, physical and spectral data
34		Cl				$C_6H_7ClN_2$	Oily; ^{1}H NMR: δ 3.45 (br.s, 2H), 3.75 (br.s, 2H), 6.62 (m, 2H), 6.814 (m, 1H); ms: *m/z* 143 (100), 145 (31)
35	*n*-butyl	Cl				$C_{10}H_{15}ClN_2$	Purification: ethyl acetate:hexane (20:80) cc; Oily; ^{1}H NMR: δ 0.94 (t, 3H), 1.43 (m, 2H), 1.56 (m, 2H), 2.92 (t, 2H), 3.95 (br.s, 1H), 6.59 (dd, 1H, *J* = 1.6, 7.2 Hz), 6.76 (m, 2H); ms: *m/z* 199 (100), 201 (36)
36	*n*-butyl		Cl			$C_{10}H_{15}ClN_2$	^{1}H NMR: δ 0.98 (t, 3H), 1.47 (m, 2H), 1.64 (m, 2H), 3.1 (t, 2H), 3.2 (br.s), 6.61 (m, 3H); ms: *m/z* 199 (100), 201 (32)
37	*n*-butyl			F		$C_{10}H_{15}FN_2$	ref. 12
38	*n*-butyl			Cl		$C_{10}H_{15}ClN_2$	ref. 1
39	*n*-butyl			Br		$C_{10}H_{15}BrN_2$	Oily; ^{1}H NMR: δ 0.97 (t, 3H), 1.47 (m, 2H), 1.64 (m, 2H), 3.06 (t, 2H), 3.32 (br.s, 3H), 6.50 (d, 1H, *J* = 8.8), 6.83 (d, 1H, *J* = 2Hz), 6.89 (dd, 1H, *J* = 2.4, 8.4 Hz); ms: *m/z* 243 (100), 245 (100)
40	*n*-butyl			I		$C_{10}H_{15}IN_2$	Oily; ^{1}H NMR: δ 0.96 (t, 3H), 1.46 (m, 2H), 1.63 (m, 2H), 3.06 (t, 2H), 3.32 (br.s, 3H), 6.39 (d, 1H, *J* = 8.8), 6.98 (d, 1H, *J* = 2 Hz), 7.09 (dd, 1H, *J* = 2.1, 8.4 Hz); ms: *m/z* 291 (100)
41	*n*-butyl	Br				$C_{10}H_{15}BrN_2$	Oily; ^{1}H NMR: δ 0.91 (t, 3H), 1.45 (m, 2H), 1.58 (m, 2H), 2.91 (t, 2H), 3.28 (br.s, 1H), 3.98 (br.s, 2H), 6.64 (dd, 1H, *J* = 1.2, 7.6 Hz), 6.74 (t, 1H, *J* = 7.9 Hz), 6.91 (dd, 1H, *J* = 1.6, 8 Hz); ms: *m/z* 243 (100), 245 (100)
42	*n*-butyl	Cl		Cl		$C_{10}H_{14}Cl_2N_2$	Waxy; ^{1}H NMR: δ 0.92 (t, 3H), 1.38 (m, 2H), 1.92 (m, 2H), 3.43 (t, 2H), 6.72 (d, 1H, *J* = 1.2), 6.82 (d, 1H, *J* = 1.2); ms: *m/z* 233 (100), 235 (63), 237 (11)
43		CN				$C_7H_7N_3$	^{1}H NMR: δ 3.43 (br.s, 2H), 4.11 (br.s, 2H), 6.67 (t, *J* = 8 Hz, 1H), 6.84 (d, *J* = 8 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H); ms: *m/z* 134 (100)
44	*n*-butyl	CN				$C_{11}H_{15}N_3$	Oily; ^{1}H NMR (Deuteriochloroform + D_2O): δ 0.94 (t, 3H), 1.43 (m, 2H), 1.58 (m, 2H), 3.19 (t, 2H), 3.28 (br.s, 1H), 3.66 (br.s, 2H), 6.85 (m, 2H), 6.95 (dd, 1H, *J* = 1.6, 7.6 Hz); ms: *m/z* 190 (100)
45	*n*-butyl		CN			$C_{11}H_{15}N_3$	ms: *m/z* 190 (100)
46	*n*-butyl			CN		$C_{11}H_{15}N_3$	ref. 1
47	*n*-pentyl			CN		$C_{12}H_{17}N_3$	Not isolated, because it was immediately getting black colored
48	*n*-butyl				CN	$C_{11}H_{15}N_3$	mp 76–78°C; ^{1}H NMR: δ 0.97 (t, 3H), 1.44 (m, 2H), 1.65 (m, 2H), 3.09 (t, 2H), 4.28 (br.s), 6.78 (m, 2H), 6.91 (m, 1H); ms: *m/z* 190 (100)
49	*n*-butyl		Cl	CN		$C_{11}H_{14}ClN_3$	^{1}H NMR: δ 0.98 (t, 3H), 1.44 (m, 2H), 1.7 (m, 2H), 3.2 (t, 2H), 6.6 (s, 1H), 6.9 (s, 1H); ms: *m/z* 224 (100), 226 (33)
50	*n*-butyl			$COCH_3$		$C_{12}H_{18}N_2O$	ref. 14
51	*n*-butyl			NO_2		$C_{10}H_{15}N_3O_2$	ref. 15
52				CF_3		$C_7H_7F_3N_2$	Commercial
53		Br		CF_3		$C_7H_6BrF_3N_2$	Commercial
54		Cl			Cl	$C_6H_6Cl_2N_2$	refs. 16, and 17
55			F	F		$C_6H_6F_2N_2$	refs. 18, and 19
56		F	F	F		$C_6H_5F_3N_2$	refs. 19, and 20
57			Cl	Cl		$C_6H_6Cl_2N_2$	Commercial
58			Br	Br		$C_6H_6Br_2N_2$	ref. 21
59			CN	CN		$C_8H_6N_4$	ref. 22

values of 3.12 μg/mL. Dramatically reduced antifungal activity was also seen by changing the benzimidazole ring to indoles with similar substitutions (**108–110**). Further studies are needed to confirm these preliminary results and *in vivo* and mode of action studies are required to optimize the effectiveness of this series of compounds.

EXPERIMENTAL

Mp were measured with a capillary melting point apparatus Electrothermal 9100 and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded with VARIAN Mercury 400 FT-NMR spectrophotometer, δ scale (ppm) in deuteriochloroform, if not stated otherwise. LC/MS analyses were performed with Waters Alliance (equipped with a diode array UV detection monitoring at 254 nm) and Micromass ZQ by using ESI(+) method, if not stated otherwise. Elemental analyses were taken on a Leco 932 CHNS analyser; cc, column chromatography. Compound **89a** was synthesized as described in our previous study [1].

3-Chloro-2-nitrobenzonitrile (12). The mixture of 0.5 g (2.48 mmol) of 3-chloro-2-nitrobenzoic acid toluene (3 mL) and thionyl chloride (2 mL) were heated at 80°C for 4 h. Excess of thionyl chloride and solvent were evaporated, then the residue was stirred in ammonium hydroxide (5 mL) at room temperature for 1 h. The formed precipitate 3-chloro-2-nitrobenzamide was collected. The solid (0.46 g, 2.3 mmol) was added to a solution of PPSA (20 mL), and the mixture was refluxed for 48 h. The reaction mixture was directly carried out to a long silica gel column and eluted with hexanes (200 mL), then dichloromethane. Concentration of the dichloromethane gave the desired nitrile, as a white solid, 0.14 g (33.4%). Then eluting with 5% methanol in dichloromethane recovered 0.16 g of starting material. See Table 2 for spectral data.

2-Amino-3-nitrobenzonitrile (25). The mixture of **9** (0.3 g, 1.65 mmol) and saturated ethanolic ammonia solution (30 mL) were heated in a sealed tube at 120°C for 5 h, ethanol was removed, and washing with water of the residue gave pure compound, 0.2 g (74 %). See Table 3 for spectral data.

General procedure for synthesis of (17–24, 26–33). To a solution of **1–15** (5 mmol) in ethanol (5 mL), butyl or pentyl amine (15 mmol) was added and heated under reflux until the starting material was consumed (determined by TLC, 8–48 h). The mixture was cooled, water was added. The resultant yellow residue was crystallized from ethanol or purified by cc by using the mixture of ethyl acetate-hexane (30–40:70–60) as eluent (Table 3).

General procedure for synthesis of (34, 37, 38, 43–51, 55, 56). Appropriate nitro derivatives (3 mmol) in ethanol (30 mL) were reduced by hydrogenation using 40 psi of H_2 and 10% Pd-C until cessation of H_2 uptake. The catalyst was filtered off on a bed of Celite, washed with ethanol, and the filtrate was concentrated. This procedure was carried out at the atmospheric pressure for compound **33** (Table 4).

General procedure for synthesis of (35, 36, 39–42, 54). Compound **17**, **20–23** (1 mmol), tin(II) chloride dihydrate (0.75 g, 3.33 mmol), a granule tin in the mixture of ethanol (3 mL), hydrochloric acid (3 mL), (for 20 HBr and for 21 sulfuric acid were used without tin(II) chloride), and 1.5 mL water were stirred at room temperature for 6–7 h. For compound 40, the reaction mixture was heated under reflux for 3 h. Then, water and ethyl acetate were added. The pH was rendered basic by addition of an ammonium solution. The slurry was filtered on a Buchner, the resulting solid was washed with ethyl acetate. The combined organic phases were concentrated (Table 4).

General procedure for synthesis of 60–73, 75, 78–80, 83, 84, 90–97, 99–102, 104. The corresponding benzaldehydes (7.5 mmol) were dissolved in 25 mL ethanol and sodium metabisulfite (0.8 g) in 5 mL H_2O was added in portions. The reaction mixture was stirred vigorously and more ethanol was added. The mixture was kept in a refrigerator for a several hours. The precipitate was filtered and dried (yield over 93%). The mixture of these salts (0.5 mmol) and **34–59** (0.5 mmol) in *N*,*N*-dimethylformamide (1 mL) were heated at 120°C for 4 h. The reaction mixture was cooled, poured into water, and the solid was filtered.

7-Chloro-2-(4-fluorophenyl)-1H-benzimidazole (60). Purification, cc, ethyl acetate-hexane (1:3), mp 208°C, yield 56%. ^1H NMR δ (DMSO-d_6): 7.18 (t, 1H), 7.26 (dd, 1H, J = 0.8, 6.4 Hz), 7.4 (t, 2H), 7.52 (d, 1H, J = 6 Hz), 8.25 (br.s, 2H); ms: *m/z* 247 (M +1, 100), 249 (M +3, 34). *Anal*. Calcd for $C_{13}H_8ClFN_2$ HOH: C, 59.00; H, 3.81; N, 10.58. Found C, 58.96; H, 3.80; N, 10.54.

2-(4-Fluorophenyl)-1H-benzimidazole-7-carbonitrile (61). Purification, cc, ethyl acetate-hexane (1:1), mp 224–225°C, yield 47.4%. ^1H NMR δ (DMSO-d_6): 7.35 (t, 1H), 7.43 (t, 2H), 7.67 (d, 1H, J = 7.2 Hz), 7.86 (d, 1H, J = 7.2 Hz), 8.26 (br.s, 2H), 13.5 (br.s, 1H); ms: *m/z* 238 (M +1, 100). *Anal*. Calcd for $C_{14}H_8FN_3$ 0.1 HOH: C, 70.35; H, 3.46; N, 17.57. Found C, 70.44; H, 3.48; N, 17.15.

2-(4-Fluorophenyl)-5-(trifluoromethyl)-1H-benzimidazole (62). Purification, cc, ethyl acetate-hexane (1:1), mp 178–180°C, yield 46.4%. ^1H NMR δ (DMSO-d_6): 7.45 (m, 2H), 7.54 (dd, 1H, J = 1.2, 8.8 Hz), 7.79 (d, 1H, J = 8 Hz), 7.96 (s, 1H), 8.26 (m, 2H), 13.35 (br.s, 1H); ms: *m/z* 281 (M +1, 100). *Anal*. Calcd for $C_{14}H_8F_4N_2$: C, 60.00; H, 2.88; N, 10.00. Found C, 59.63; H, 2.89; N 9.93.

1-Butyl-7-chloro-2-phenyl-1H-benzimidazole (63). Purification, cc, ethyl acetate-hexane (1:4), oily, yield 51.5%. ^1H NMR δ: 0.8 (t, 3H), 1.18 (m, 2H), 1.76 (m, 2H), 4.49 (t, 2H), 7.2 (t, 1H), 7.26 (dd, 1H, J = 1.2, 7.4 Hz), 7.53 (m, 3H), 7.67 (m, 2H), 7.71 (dd, 1H, J = 1.2, 8 Hz); ms: *m/z* 285(M +1, 100), 287 (M +3, 36). *Anal*. Calcd for $C_{17}H_{17}ClN_2$: C, 71.69; H, 6.02; N, 9.84. Found C, 71.24; H, 6.15; N, 9.77.

1-Butyl-7-chloro-2-(4-fluorophenyl)-1H-benzimidazole (64). Purification, cc, ethyl acetate-hexane (1:3), mp 60°C, yield 32%. ^1H NMR δ: 0.8 (t, 3H), 1.18 (m, 2H), 1.75 (m, 2H), 4.46 (t, 2H), 7.25 (m, 4H), 7.66 (m, 3H); ms: *m/z* 303 (M +1, 100), 305 (M +3, 35). *Anal*. Calcd for $C_{17}H_{16}ClFN_2$: C, 67.44; H, 5.33; N, 9.25. Found C, 67.29; H, 5.27; N, 9.23.

7-Bromo-1-butyl-2-(4-fluorophenyl)-1H-benzimidazole (65). Purification, cc, ethyl acetate-hexane (1:1), mp 62°C, yield 53%. ^1H NMR δ: 0.79 (t, 3H), 1,18 (m, 2H), 1.73 (m, 2H), 4.48 (t, 2H), 7.15 (t, 1H), 7.24 (m, 2H), 7.46 (d, 1H, J = 8 Hz), 7.66 (m, 2H), 7.74 (d, 1H, J = 8.4 Hz); ms: *m/z* 347 (M +1, 100), 349 (M +3, 100). *Anal*. Calcd for $C_{17}H_{16}BrFN_2$ 0.2 HOH: C, 58.20 H; 4.71; N, 7.98. Found C, 58.11; H, 4.47; N, 8.08.

1-Butyl-2-(4-fluorophenyl)-1H-benzimidazole-7-carbonitrile (66). Purification, cc, ethyl acetate-hexane (2:8), mp 53–54°C, yield 40.5%. ^1H NMR δ: 0.86 (t, 3H), 1.3 (m, 2H), 1.85 (m, 2H), 4.54 (t, 2H), 7.29 (m, 2H), 7.44 (t, 1H), 7.71 (d, 1H, J = 7.2 Hz), 7.77 (m, 2H), 8.15 (d, 1H, J = 8.4 Hz); ^{13}C NMR δ: 164.2 (d, J = 250 Hz), 155.1, 143.8, 134.6, 131.75 (d, J = 8.3 Hz), 129.4, 125.7 (d, J = 2.5 Hz), 125.5, 123.0, 117.1, 116.4 (d, J = 22.1 Hz), 95.1, 45.4, 33.3, 19.5, 13.67; ms: *m/z* 294 (M +1, 100). *Anal*. Calcd for $C_{18}H_{16}FN_3$: C, 73.70; H, 5.50; N, 14.32. Found C, 73.84; H, 5.61; N, 14.09.

1-Butyl-6-chloro-2-(4-fluorophenyl)-1H-benzimidazole (67). Purification, cc, ethyl acetate-hexane (1:2), mp 100–

101°C, yield 39.7%. ^{1}H NMR δ: 0.88 (t, 3H), 1.27 (m, 2H), 1.75 (m, 2H), 4.16 (t, 2H), 7.19–7.28 (m, 3H), 7.39 (d, 1H, J = 1.6 Hz), 7.65–7.73 (m, 3H); ^{13}C NMR δ: 165.2 (d, J = 249 Hz), 153.8, 141.9, 136.5, 131.5 (d, J = 8.4 Hz), 128.7, 126.6, 123.3, 121, 116.2 (d, J = 22 Hz), 110.4, 44.9, 31.9, 20.1, 13.7; ms: *m/z* 303 (M +1, 100) 305 (M +3, 40). *Anal*. Calcd for $C_{17}H_{16}ClFN_2$: C, 67.44; H, 5.33; N, 9.25. Found C, 67.47; H, 5.31; N, 9.17.

1-Butyl-2-(4-fluorophenyl)-1H-benzimidazole-6-carbonitrile (68). Purification, cc, ethyl acetate-hexane (1:3), mp 128°C, yield 72% [26]. ^{1}H NMR δ: 0.88 (t, 3H), 1.28 (m, 2H), 1.79 (m, 2H), 4.23 (t, 2H), 7.25 (m, 2H), 7.55 (d, 1H, J = 8.4 Hz), 7.71 (m, 2H), 7.74 (s, 1H), 7.84 (d, 1H, J = 8 Hz); ^{13}C NMR δ: 164.2 (d, J = 250 Hz), 156.2, 146.2, 135.5, 131.5 (d, J = 8.4 Hz), 126.2, 125.9, 121.1, 120.1, 116.4 (d, J = 18 Hz), 115.3, 105.8, 45.2, 32.1, 20.2, 13.7; ms: *m/z* 294(M +1,100). *Anal*. Calcd for $C_{18}H_{16}FN_3$: C, 73.70; H, 5.50; N, 14.32. Found C, 73.48; H, 5.56; N, 14.15.

1-Butyl-5-fluoro-2-(4-fluorophenyl)-1H-benzimidazole (69). Purification, cc, ethyl acetate-hexane (1:3), mp 82–83°C, yield 29%. ^{1}H NMR δ: 0.86 (t, 3H), 1.26 (m, 2H), 1.77 (m, 2H), 4.19 (t, 2H), 7.06 (m, 1H), 7.25 (m, 2H), 7.32 (m, 1H), 7.46 (dd, 1H, J = 2, 9.4 Hz), 7.67 (m, 2H); ms: *m/z* 287(M +1, 100). *Anal.* Calcd for $C_{17}H_{16}F_2N_2$: C, 71.31; H, 5.63; N, 9.78. Found C, 71.26; H, 5.49; N, 9.84.

1-Butyl-5-chloro-2-(4-fluorophenyl)-1H-benzimidazole (70). Purification, cryst., ethyl acetate-hexane, mp 81–82°C, yield 31.5%. ^{1}H NMR δ: 0.87 (t, 3H), 1.25 (m, 2H), 1.76 (m, 2H), 4.18 (t, 2H), 7.18–7.37 (m, 4H), 7.68 (m, 2H), 7.77 (d, 1H, J = 2 Hz); ^{13}C NMR δ: 163.9 (d, J = 250 Hz), 154.1, 144.1, 134.4, 131 (d, J = 8.3 Hz), 128.2, 126.6, 123.4, 119.9, 116.2 (d, J = 21 Hz), 111.1, 44.9, 32, 20.1, 13.7; ms: *m/z* 303 (M +1, 100) 305 (M +3, 40). *Anal*. Calcd for $C_{17}H_{16}ClFN_2$: C, 67.44; H, 5.33; N, 9.25. Found C, 67.33; H, 5.25; N, 9.24.

1-Butyl-5-chloro-2-(pyridin-4-yl)-1H-benzimidazole (71). Purification, cryst., ethyl acetate-hexane, mp 96–98°C, yield 34%. ^{1}H NMR δ: 0.82 (t, 3H), 1.22 (m, 2H), 1.74 (m, 2H), 4.18 (t, 2H), 7.25 (dd, 1H, J = 2, 8.6 Hz), 7.29 (dd, 1H, J = 0.8, 8.8 Hz), 7.6 (dd, 2H, J = 1.6, 4.6 Hz), 7.75 (t, 1H), 8.75 (dd, 2H, J = 1.6, 4.4 Hz); ms: *m/z* 286 (M +1, 100), 288 (M +3, 35). *Anal*. Calcd for $C_{16}H_{16}ClN_3$ 0.25 HOH: C, 66.2; H, 5.73; N, 14.48. Found C, 66.4; H, 5.56; N, 14.29.

1-Butyl-5-bromo-2-(4-fluorophenyl)-1H-benzimidazole (72). Purification, ethyl acetate-hexane (2:8), mp 77–79°C, yield 84% [27]. ^{1}H NMR δ: 0.86 (t, 3H), 1.25 (m, 2H), 1.75 (m, 2H), 4.18 (t, 2H), 7.19–7.31 (m, 3H), 7.4 (dd, 1H, J = 1.6, 8.8 Hz), 7.68 (m, 2H), 7.92 (d, 1H, J = 1.2 Hz); ^{13}C NMR δ: 164.2 (d, J = 249 Hz), 153.9, 144.6, 134.8, 131.5 (d, J = 8.4 Hz), 126.6, 126, 123, 116.4 (d, J = 22 Hz), 115.6, 111.55, 44.9, 32, 20.1, 13.7; ms: *m/z* 347 (M +1, 100) 349 (M +3, 100). *Anal*. Calcd for $C_{17}H_{16}BrFN_2$: C, 58.80; H, 4.64; N, 8.07. Found C, 58.51; H, 4.68; N, 8.13.

1-Butyl-5-iodo-2-(4-fluorophenyl)-1H-benzimidazole (73). Purification, ethyl acetate-hexane (2:8), mp 125–126°C, yield 88%. ^{1}H NMR δ: 0.86 (t, 3H), 1.25 (m, 2H), 1.75 (m, 2H), 4.18 (t, 2H), 7.15–7.29 (m, 3H), 7.58 (d, 1H, J = 8.8 Hz), 7.69 (m, 2H), 8.14 (s, 1H); ms: *m/z* 395 (M +1, 100). *Anal*. Calcd for $C_{17}H_{16}FIN_2$: C, 51.79; H, 4.09; N, 7.11. Found C, 51.72; H, 4.24; N,7.20.

1-Butyl-5-nitro-2-(4-fluorophenyl)-1H-benzimidazole (75). Purification, cc, ethyl acetate-hexane (3:7), mp 160–162°C, yield 62%. ^{1}H NMR δ: 0.86 (t, 3H), 1.27 (m, 2H), 1.77 (m, 2H), 4.26 (t, 2H), 7.25 (m, 2H), 7.45 (d, 1H, J = 9.2 Hz), 7.71 (m, 2H), 8.21 (dd, 1H, J = 2.4, 9 Hz), 8.64 (d, 1H, J = 2.4 Hz); ms: *m/z* 314 (M +1, 100). *Anal*. Calcd for $C_{17}H_{16}FN_3O_2$: C, 65.17; H, 5.15; N, 13.41. Found C, 65.37; H, 5.20; N, 13.35.

1-Butyl-2-(pyridin-2-yl)-1H-benzimidazole-5-carbonitrile (78). Purification, cc, ethyl acetate-hexane (1:1), mp 117–119°C, yield 38%. ^{1}H NMR δ: 0.93 (t, 3H), 1.37 (m, 2H), 1.85 (m, 2H), 4.85 (t, 2H), 7.41 (m, 1H), 7.51 (d, 1H, J = 8.8 Hz), 7.57 (dd, 1H, J = 1.6, 8.2 Hz), 7.88 (td, 1H, J = 1.6, 8 Hz), 8.14 (d, 1H, J = 0.8 Hz), 8.39 (d, 1H, J = 7.6 Hz), 8.72 (dd, 1H, J = 1, 4 Hz); ^{13}C NMR δ: 152.5, 150.0, 149.0, 142.3, 139.5, 137.2,126.5, 125.3, 125.2, 124.6, 120.1, 111.4, 105.8, 45.9, 32.3, 20.2, 13.8; ms: *m/z* 277 (M +1, 100). *Anal.* Calcd for $C_{17}H_{16}N_4$ 0.15 $C_4H_8O_2$: C, 73.01; H, 5.98; N, 19.35. Found C, 73.42; H, 5.88; N, 19.12.

1-Butyl-2-(pyridin-3-yl)-1H-benzimidazole-5-carbonitrile (79). Purification, cc, ethyl acetate-hexane (2:1), mp 130–131°C, yield 52%. ^{1}H NMR δ: 0.85 (t, 3H), 1.26 (m, 2H), 1.77 (m, 2H), 4.25 (t, 2H), 7.44–7.59 (m, 3H), 8.06 (d, 1H, J = 7.6 Hz), 8.10 (s, 1H), 8.77 (d, 1H, J = 4.8 Hz), 8.94 (d, 1H, J = 1.2 Hz); ^{13}C NMR δ: 153.4, 151.5, 149.8, 142.9, 138.6, 137.1, 126.6, 126.3, 125.4, 123.9, 119.9, 111.6, 106.2, 45.2, 32.2, 20.1, 13.7; ms: *m/z* 277(M +1, 100). *Anal.* Calcd for $C_{17}H_{16}N_4$: C, 73.87; H, 5.84; N, 20.27. Found C, 73.76; H, 5.82; N, 20.01.

1-Butyl-2-(pyridin-4-yl)-1H-benzimidazole-5-carbonitrile (80). Purification, cc, chloroform-isopropanol (10:2), mp 135–137°C, yield 47%. ^{1}H NMR δ (DMSO-d_6): 0.74 (t, 3H), 1.12 (m, 2H), 1.62 (m, 2H), 4.41 (t, 2H), 7.74 (dd, 1H, J = 1,6, 8.4 Hz), 7.83 (dd, 2H, J = 1.6, 4.4 Hz), 7.95 (d, 1H, J = 8.8 Hz), 8.3 (d, 1H, J = 1.4 Hz), 8.82 (dd, 2H, J = 1.6, 4.4 Hz); ^{13}C NMR δ (DMSO-d_6): 153.5, 151.1, 142.6, 139.4, 137.8, 127, 125.4, 124.1, 120.4, 113.6, 105.4, 44.9, 31.9, 19.8, 13.9; ms: *m/z* 277(M +1, 100). *Anal.* Calcd for $C_{17}H_{16}N_4$. 0.5 HOH: C, 71.55; H, 6.00; N, 19.63. Found C, 71.28; H, 5.73; N, 19.33.

1-Pentyl-2-phenyl-1H-benzimidazole-5-carbonitrile (83). Purification, cc, ethyl acetate-hexane (1:3), mp 124–125°C, yield 17.5%. ^{1}H NMR δ: 0.83 (t, 3H), 1.24 (m, 4H), 1.8 (m, 2H), 4.25 (t, 2H), 7.47 (d, 1H, J = 7.6 Hz), 7.56 (m, 4H), 7.7 (m, 2H), 8.13 (d, 1H, J = 0.8 Hz); ^{13}C NMR δ: 156.4, 142.9, 138.5, 130.6, 129.8, 129.4, 129.1, 126.2, 125.2, 120.1, 111.3, 105.7, 45.2, 29.6, 28.9, 22.2, 14.0; ms: *m/z* 290 (M +1, 100). *Anal.* Calcd for $C_{19}H_{19}N_3$: C, 78.86; H, 6.62; N, 14.52. Found C, 78.66; H, 6.72; N, 14.39.

1-Butyl-6-chloro-2-(4-fluorophenyl)-1H-benzimidazole-5-carbonitrile (84). Purification, cc, ethyl acetate-hexane (1:4), mp 138°C, yield 34%. ^{1}H NMR δ: 0.89 (t, 3H), 1.28 (m, 2H), 1.77 (m, 2H), 4.21 (t, 2H), 7.27 (t, 2H), 7.53 (s, 1H), 7.7 (m, 2H), 8.1 (s, 1H); ^{13}C NMR δ: 164.1 (d, J = 251 Hz), 156.0, 141.3, 138.9, 131.3 (d, J = 8.4 Hz), 130.2, 126.1, 125.4 (d, J = 3.1 Hz), 116.9, 116.3 (d, J = 22 Hz), 111.7, 107.0, 45.0, 31.7, 19.8, 13.4; ms: *m/z* 328 (M +1, 100) 330 (M +3, 35). *Anal.* Calcd for $C_{18}H_{15}ClFN_3$: C, 65.96; H, 4.61; N, 12.82. Found C, 65.75; H, 4.59; N, 12.87.

1-[1-Butyl-2-(4-fluorophenyl)-1H-benzimidazol-5-yl]ethanone (90). Purification, cc, ethyl acetate-hexane (1:3), mp 75–77°C, yield 21.5%. ^{1}H NMR δ: 0.88 (t, 3H), 1.27 (m, 2H), 1.83 (m, 2H), 2.68 (s, 3H), 4.35 (t, 2H), 7.28 (m, 2H), 7.56 (d, 1H, J = 8.4 Hz), 7.85 (m, 2H), 8.11 (d, 1H, J = 8.8 Hz), 8.46

(s, 1H); ^{13}C NMR δ: 198.1, 163.9 (d, J = 250 Hz), 154.8, 142.8, 139.1, 132.5, 131.4 (d, J = 8.5 Hz), 126.4 8 (d, J = 3.4 Hz), 123.2, 121.8, 116.3 (d, J = 22 Hz), 110.3, 44.9, 32.1, 26.9, 20.1, 13.7; ms: *m/z* 311 (M +1,100). *Anal.* Calcd for $C_{19}H_{19}FN_2O$: C, 73.53; H, 6.17; N, 9.03. Found C, 73.82; H, 6.53; N, 8.58.

1-Butyl-2-(4-fluorophenyl)-1H-benzimidazole-4-carbonitrile (91). Purification, cc, ethyl acetate-hexane (2:8), mp 83–84°C, yield 44.5%. ^{1}H NMR δ: 0.87 (t, 3H), 1.26 (m, 2H), 1.76 (m, 2H), 4.24 (t, 2H), 7.25 (m, 2H), 7.35 (t, 1H), 7.63 (dd, 2H, J = 1.6, 7.6 Hz), 7.74 (m, 2H); ^{13}C NMR δ: 164.1 (d, J = 250 Hz), 155.2, 144.1, 136.1, 131.8 (d, J = 8.4 Hz), 127.5, 126 (d, J = 3.1 Hz), 122.6, 117.0, 116.4 (d, J = 21.3 Hz), 115.0, 103.3, 45.1, 32.0, 20.0, 13.6; ms: *m/z* 294 (M +1,100). *Anal.* Calcd for $C_{18}H_{16}FN_3$: C, 73.70; H, 5.50; N, 14.33. Found C, 74.19; H, 5.74; N, 13.94.

7-Bromo-5-(trifluoromethyl)-2-phenyl-1H-benzimidazole (92). Purification, cc, ethyl acetate-hexane (1:1), mp 179–181°C, yield 59%. ^{1}H NMR δ (DMSO-d_6): 7.57 (m, 3H), 7.72 (s, 1H), 7.88 (s, 1H), 8.2 (d, 2H, J = 5.2 Hz), 13.98 (br.s, 1H); ms: *m/z* 341 (M +1,100) 343 (M +3,100). *Anal.* Calcd for $C_{14}H_8BrF_3N_2$: C, 49.29; H, 2.36; N, 8.21. Found C, 49.1; H, 2.41; N, 8.17.

5,6-Difluoro-2-phenyl-1H-benzimidazole (93). Purification, cc, ethyl acetate-hexane (1:1), mp 213–215°C, yield 77%. ^{1}H NMR δ (DMSO-d_6): 7.43 (m, 5H), 7.99 (d, 2H, J = 6.8 Hz), 13.03 (br.s, 1H); ms: *m/z* 231 (M +1,100). *Anal.* Calcd for $C_{13}H_8F_2N_2$: C, 67.82; H, 3.50; N, 12.17. Found C, 68.00; H, 3.57; N, 11.98.

5,6-Difluoro-2-(4-fluorophenyl)-1H-benzimidazole (94). Purification, cc, ethyl acetate-hexane (1:2), mp 207–209°C, yield 81%. ^{1}H NMR δ (DMSO-d_6): 7.4 (m, 2H), 7.64 (t, 2H), 8.17 (m, 2H); ms: *m/z* 249 (M +1,100). *Anal.* Calcd for $C_{13}H_7F_3N_2$: C, 62.91; H, 2.84; N, 11.29. Found C, 63.04; H, 2.84; N, 11.28.

5,6,7-Trifluoro-2-phenyl-1H-benzimidazole (95). Purification, cryst., ethyl acetate-hexane, mp 215–216°C, yield 77%. ^{1}H NMR δ (DMSO-d_6): 7.4–7.66 (m, 4H), 8.17 (dd, 2H, J = 1.2, 8 Hz); ms: *m/z* 249 (M +1,100). *Anal.* Calcd for $C_{13}H_7F_3N_2$. 0.5 HOH: C, 60.70; H, 3.13; N, 10.89. Found C, 60.75; H, 3.06; N, 10.96.

5,6-Difluoro-2-(pyridin-4-yl)-1H-benzimidazole (96). Purification, cc, ethyl acetate-ethanol (95:5) mp > 300°C, yield 61.5%. ^{1}H NMR δ (DMSO-d_6): 7.71 (br.s, 2H), 8.04 (m, 2H), 8.74 (m, 2H), 13.5 (br.s, 1H); ms: *m/z* 232 (M +1,100). *Anal.* Calcd for $C_{12}H_7F_2N_3$: C, 62.34; H, 3.05; N, 18.17. Found C, 62.77; H, 3.29; N, 17.65.

2-[4-(Benzyloxy)phenyl]-5,6-difluoro-1H-benzimidazole (97). Purification, cc, ethyl acetate-hexane (1:2), mp 215–217°C, yield 33.7%. ^{1}H NMR δ (DMSO-d_6): 5.17 (s, 2H), 7.16 (d, 2H, J = 9.2 Hz), 7.32–7.52 (m, 6H), 7.64 (m, 1H), 8.05 (d, 2H, J = 8.8 Hz), 12.98 (s, 1H); ms: *m/z* 337 (M +1,100). *Anal.* Calcd for $C_{20}H_{14}F_2N_2O$. 0.1 $C_4H_8O_2$. 0.25 HOH: C, 70.07; H, 4.41; N, 8.01. Found C, 70.04; H, 4.13; N, 8.14.

5,6-Dichloro-2-(4-fluorophenyl)-1H-benzimidazole (99). Purification, cryst., ethyl acetate-hexane, mp 278–280°C, yield 69.5%. ^{1}H NMR δ: 7.19 (m, 2H), 7.58 (s, 1H), 7.82 (s, 1H), 8.17 (m, 2H); ms: *m/z* 281 (M +1,100) 283 (M +3, 63) 285 (M +5, 13). *Anal.* Calcd for $C_{13}H_7Cl_2FN_2$: C, 55.54; H, 2.51; N, 9.97. Found C, 55.52; H, 2.46; N, 9.92.

4,7-Dichloro-2-(4-fluorophenyl)-1H-benzimidazole (100). Purification, cc, ethyl acetate-hexane (2:8), mp 242°C, yield 71.4%. ^{1}H NMR δ (DMSO-d_6): 7.31 (s, 2H), 7.43 (t, 2H), 8.38 (m, 2H), 13.48 (br.s, 1H); ms: *m/z* 281 (M +1, 100) 283 (M +3, 72) 285 (M +5, 15). *Anal.* Calcd for $C_{13}H_7Cl_2FN_2$. 0.25 $C_4H_8O_2$. 0.4 HOH: C, 54.18; H, 3.18; N, 9.03. Found C, 54.03; H, 3.07; N, 9.07.

5,6-Dibromo-2-(4-fluorophenyl)-1H-benzimidazole (101). Purification, cryst., ethanol, mp 273–275°C, yield 68.4%. ^{1}H NMR δ (DMSO-d_6): 7.4 (m, 2H), 7.96 (s, 2H), 8.2 (m, 2H); ms: *m/z* 369 (M +1, 50), 371 (M +3, 100), 373 (M +5, 48). *Anal.* Calcd for $C_{13}H_7Br_2FN_2$ 0.25 HOH: C, 41.69; H, 2.02; N, 7.48. Found C, 41.50; H, 1.99; N, 7.61.

2-(4-Fluorophenyl)-1H-benzimidazole-5,6-dicarbonitrile (102). Purification, cc, (1) ethyl acetate-hexane (1:1), (2) ethyl acetate, (3) ethyl acetate-ethanol (95:5), mp > 300°C, yield 59.8%. ^{1}H NMR δ (DMSO-d_6): 7.48 (t, 2H), 8.31 (m, 2H), 8.44 (s, 2H); ms: *m/z* 263 (M +1,100). *Anal.* Calcd for $C_{15}H_7FN_4$. 0.75 HOH: C, 65.33; H, 3.11; N, 20.32. Found C, 64.94; H, 3.76; N, 20.53.

1-Butyl-5,7-dichloro-2-(4-fluorophenyl)-1H-benzimidazole (104). Purification, cc, (1) dichloro-methane-hexane (2:8) (2) ethyl acetate-ethanol (1:9), mp 58°C, yield 27.3%. ^{1}H NMR δ: 0.81 (t, 3H), 1.17 (m, 2H), 1.74 (m, 2H), 4.44 (t, 2H), 7.25 (m, 3H), 7.65 (m, 3H); ^{13}C NMR δ: 163.8 (d, J = 250 Hz), 155.8, 145.6, 131.6 (d, J = 8.4 Hz), 130.1, 128.0, 126.0 (d, J = 3.8 Hz), 124.5, 118.6, 116,8, 116.1 (d, J = 22 Hz), 45.7, 34.0, 19.4, 13.4; ms: *m/z* 337 (M +1, 100) 339 (M +3, 60) 341 (M +5, 11). *Anal.* Calcd for $C_{17}H_{15}Cl_2FN_2$: C, 60.55; H, 4.48; N, 8.31. Found C, 60.14; H, 4.44; N, 8.32.

1-Butyl-5-trimethylsilanylethylnyl-2-(4-fluorophenyl)-1H-benzimidazole (74a). To the mixture of **73** (0.69 mmol, 0.272 g) and (trimethylsilyl)acetylene (0.081g) in *N,N*-dimethyl formamide (1 mL) and triethylamine (1 mL) 10 mg of bis(triphenyl-phosphine)palladium (II) chloride and 2 mg of copper(I) iodide were added, and the mixture was stirred for 4.5 h at 45°C. The solvent was then removed *in vacuo* and the resulting residue was dissolved in acetonitrile and ether and washed with water. The solvent was removed *in vacuo*. The crude product was used without purification, yield 0.100 g. ms: *m/z* 365 (M +1, 100).

1-Butyl-5-ethynyl-2-(4-fluorophenyl)-1H-benzimidazole (74). 0.1 g (0.27 mmol) of **74a** and 1*N* potassium hydroxide (0.5 mL) was added 2.5 mL methanol. The mixture was stirred for 1.5 h at 25°C. The solvent was then removed *in vacuo*. The residue was purified by cc chloroform-ethyl acetate (20:0.5), mp 114–115°C, yield 31%. ^{1}H NMR δ: 0.86 (t, 3H), 1.26 (m, 2H), 1.76 (m, 2H), 3.06 (s, 1H), 4.19 (t, 2H), 7.24 (m, 2H), 7.34 (d, 1H, J = 8.8 Hz), 7.45 (dd, 1H, J = 1.6, 8.2 Hz), 7.69 (m, 2H), 7.96 (s, 1H); ^{13}C NMR δ: 163.7 (d, J = 249 Hz), 153.9, 142.8, 135.9, 131.24 (d, J = 8.4Hz), 126.9, 126.5 (d, J = 2.8 Hz), 124.1, 116.0, 116.02 (d, J = 22.1 Hz), 110.2, 84.4, 75.7, 44.6, 31.9, 19.9, 13.5; ms: *m/z* 293 (M +1, 100). *Anal.* Calcd for $C_{19}H_{17}FN_2$: C, 78.05; H, 5.86; N, 9.58. Found C, 77.69; H, 5.88; N, 9.46.

5-Amino-1-butyl-2-(4-fluorophenyl)-1H-benzimidazole HCl (76). Compound **75** (0.24 g, 0.767 mmol), tin(II) chloride dihydrate (0.375 g, 1.66 mmol), a granule tin in the mixture of ethanol (2 mL), hydrochloric acid (2 mL), and 1 mL water were stirred at 50°C for 2 h. Then water was added, pH was rendered basic by addition of dilute sodium hydroxide solution, extracted with ethyl acetate. The slurry was filtered on a Buchner, the resulting solid was washed with ethyl acetate.

The combined organic phases was concentrated, crystallization of crude product from ethanolic hydrogen chloride gave **76**, mp 265–267°C, yield 57.1%. ^{1}H NMR δ (DMSO-d_6): 0.75 (t, 3H), 1.16 (m, 2H), 1.68 (m, 2H), 4.36 (t, 2H), 7.29 (d, 1H, J = 8.4 Hz), 7.55 (m, 3H), 7.95 (m, 3H); ms: m/z 284 (M +1, 100). *Anal*. Calcd for $C_{17}H_{18}FN_3$. HCl: C, 63.85; H, 5.99; N, 13.14. Found C, 63.59; H, 5.96; N, 12.98.

5-Azido-1-butyl-2-(4-fluorophenyl)-1H-benzimidazole (77). A cooled solution of **76** (0.16 g, 0.5 mmol) was dissolved in 2 mL of aqueous 9*M* HCl and slowly a sodium nitrite aqueous solution (0.76 mL, 1.2 mmol) was added. The reaction temperature was not allowed to rise above 5°C. The mixture was stirred in an ice bath for 1 h. A solution of 0.6 mL of sodium azide (1.7 mmol) and sodium acetate (0.25g) was added at 0°C and stirred for 1 h. Then, the mixture was allowed to warm to room temperature and stirred for 1 h. Potassium carbonate is added to neutralize the mixture and extracted with ethyl acetate. The solvent was then removed *in vacuo*, the residue was chromatographed by using ethyl acetate-hexane (2:8), mp 85–87°C, yield 25.2%. ^{1}H NMR δ: 0.87 (t, 3H), 1.27 (m, 2H), 1.77 (m, 2H), 4.19 (t, 2H), 6.99 (dd, 1H, J = 2, 8.6 Hz), 7.23 (m, 2H), 7.36 (d, 1H, J = 8.8 Hz), 7.46 (d, 1H, J = 2 Hz), 7.69 (m, 2H); ^{13}C NMR δ: 163.9 (d, J = 249 Hz), 154.2, 144.2, 135.2, 133.6, 131 (d, J = 8.2 Hz), 126.8, 116.3 (d, J = 21.4 Hz), 115, 111.3, 109.9, 44.9, 32.1, 20.1, 13.7; ms: m/z 310 (M +1, 100). *Anal*. Calcd for $C_{17}H_{16}FN_5$: C, 66.00; H, 5.21; N, 22.64. Found C, 66.09; H, 5.28; N, 22.32.

N-[2-(butylamino)-5-cyanophenyl]pyridazine-4-carboxamide (81a). A mixture of 4-pyridazinecarboxylic acid (0.11 g, 0.89 mmol), triethylamine (0.41 mL), 3-amino-4-butylaminobenzonitrile (0.18 g, 0.95 mmol), and *O*-(Benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyl-uronium hexafluorophosphate (HBTU) (0.366 g, 0.96 mmol) in *N*,*N*-dimethylformamide (1 mL) was stirred at room temperature for 20 h, water was added to the reaction mixture, then extracted with ethyl acetate and evaporated. The residue was purified by cc (4:1 toluene/methanol), to give **81a** as a white solid (6.75 g, 71%); mp 214–215°C; ^{1}H NMR (DMSO-d_6) δ: 0.89 (t, 3H), 1.35 (m, 2H), 1.51 (m, 2H), 3.15 (q, 2H), 6.38 (t, 1H, J = 6 Hz, deuterium oxide-exchangeable), 6.76 (d, 1H), 7.52 (m, 2H), 8.14 (m, 1H), 9.51 (d, 1H, J = 5.2 Hz), 9.68 (s, 1H), 10.1 (s, 1H, deuterium oxide-exchangeable), ms: m/z 296 (M +1, 100).

1-Butyl-2-(pyridazin-4-yl)-1H-benzimidazole-5-carbonitrile (81). 0.1 g (0.33 mmol) of **81a** and 0.1 g of sodium acetate was dissolved in 1 mL glacial acetic acid. The mixture was stirred for 4.5 h at 100°C. Then poured into ice-water and filtered. The precipitate was purified by silicagel cc (ethyl acetate-ethanol, 10:0.1), mp 148°C, yield 38%. ^{1}H NMR δ: 0.94 (t, 3H), 1.36 (m, 2H), 1.87 (m, 2H), 4.35 (t, 2H), 7.57 (d, 1H, J = 8 Hz), 7.66 (dd, 1H, J = 1.6, 8.6 Hz), 7.91 (dd, 1H, J = 2.4, 5.6 Hz), 8.20 (s, 1H), 9.47 (dd, 1H, J = 0.8, 5.8 Hz), 9.63 (m, 1H); ms: m/z 278 (M +1, 100). *Anal*. Calcd for $C_{16}H_{15}N_5$: C, 69.30; H, 5.45; N, 25.25. Found C, 69.81; H, 5.80; N, not available.

N-[2-(butylamino)-5-cyanophenyl]pyrazine-2-carboxamide (82a). 0.124 g (1 mmol) of pyrazinecarboxylic acid, thionyl chloride (2 mL), and toluene (5 mL) were heated at reflux for 4 h. After removal of the solvent, a mixture of 3-amino-4-butylaminobenzonitrile 0.189 g (1 mmol), dichloromethane (5 mL), and pyridine (0.5 mL) were added, the residue and the whole was stirred and reflux overnight. The reaction mixture was evaporated, washed with sodium carbonate solution (5%), extracted with ethyl acetate, and washed with water. The organic layer was dried over sodium sulfate, and evaporated. The residue was purified by silicagel cc (ethyl acetate-hexane, 50%), mp 130–133°C, yield 0.11 g, 37.28%. ^{1}H NMR (DMSO-d_6): δ 0.87 (t, 3H), 1.33 (m, 2H), 1.49 (m, 2H), 3.12 (q, 2H), 6.16 (t, 1H, J = 5.6 Hz, deuterium oxide-exchangeable), 6.74 (m, 1H), 7.48 (m, 2H), 8.84 (m, 1H), 8.91 (d, 1H, J = 2.8 Hz), 9.23 (d, 1H, J = 1.6 Hz), 10.16 (s, 1H, deuterium oxide-exchangeable); ^{13}C NMR (DMSO-d_6): δ 163.4, 148.5, 148.2, 145.7, 144.6, 143.9, 132.7, 131.6, 122.86, 120.7, 111.25, 95.8, 42.69, 31.1, 20.3, 14.4; ms: m/z 296 (M +1, 100).

1-Butyl-2-(pyrazin-2-yl)-1H-benzimidazole-5-carbonitrile (82). 0.1 g (0.33 mmol) of **82a** and 0.1 g of sodium acetate was dissolved in 1 mL glacial acetic acid. The mixture was stirred for 4.5 h at 100°C. Then poured into ice-water and filtered. The precipitate was purified by silicagel cc (ethyl acetate-hexane 1:1), mp 174–175°C, yield 33%. ^{1}H NMR δ (DMSO-d_6): 0.87 (t, 3H), 1.3 (m, 2H), 1.77 (m, 2H), 4.82 (t, 2H), 7.77 (d, 1H, J = 8 Hz), 7.98 (d, 1H, J = 8.4 Hz), 8.37 (s, 1H), 8.84 (dd, 2H, J = 2.4, 10.2 Hz), 9.51 (s, 1H); ^{13}C NMR δ (DMSO-d_6): 150.3, 146.1, 145.9, 145.5, 144.3, 142.1, 139.9, 127.3, 125.6, 120.3, 113.5, 105.6, 45.7, 32.4, 20.0, 14.1; ms: m/z 278 (M +1, 100). *Anal*. Calcd for $C_{16}H_{15}N_5$: C, 69.30; H, 5.45; N, 25.25. Found C, 69.00; H, 5.44; N, 24.84.

1-Butyl-2-(4-fluorophenyl)-1H-benzimidazol-5-carboxaldehyde (85). To a solution of **I** (0.293 g, 1 mmol) in dry dichloromethane (20 mL), 3 mL of DIBAL (1.0*M* solution in dichloromethane) was added and the mixture was heated at reflux for 3h under nitrogen atmosphere. Cool dilute sulfuric acid (15 mL) was added and stirred overnight, dichloromethane was removed and the residue was neutralized with dilute sodium carbonate solution, then extracted with ethyl acetate and evaporated. The residue was purified by silicagel cc (ethyl acetate-hexane 2:3), mp 85–86°C, yield 31.5%. ^{1}H NMR δ: 0.885 (t, 3H), 1.29 (m, 2H), 1.79 (m, 2H), 4.26 (t, 2H), 7.26 (m, 2H), 7.52 (d, 1H, J = 8.4 Hz), 7.72 (m, 2H), 7.9 (dd, 1H, J = 1.2, 8.8 Hz), 8.27 (s, 1H), 10.1 (s, 1H); ^{13}C NMR δ: 192.3, 164.05 (d, J = 250 Hz), 155.2, 143.1, 140.1, 132.2, 131.5 (d, J = 9.1 Hz), 126.3 (d, J = 1.1Hz), 124.3, 123.45, 116.3 (d, J = 22 Hz), 110.9, 45.1, 32.1, 20.1, 13.7; ms: m/z 297 (M +1, 100). *Anal*. Calcd for $C_{18}H_{17}FN_2O$: C, 72.96; H, 5.78; N, 9.45. Found C, 73.05; H, 6.01; N, 9.10.

1-Butyl-2-(4-fluorophenyl)-1H-benzimidazole-5-carbaldehyde O-methyloxime (86). A solution of **85** (0.1 g, 0.33 mmol) and of methoxylamine hydrochloride (0.028 g, 0.33 mmol) in 1 mL of pyridine and 3 mL of absolute ethanol was refluxed for 3 h. Solvent was removed *in vacuo*, water was added and extracted with ethyl acetate and evaporated. The residue was crystallized from ethanol, mp 104–105°C, yield 38.3%. ^{1}H NMR δ (DMSO-d_6): 0.78 (t, 3H), 1.17 (m, 2H), 1.67 (m, 2H), 3.93 (s, 3H), 4.32 (t, 2H), 7.45 (t, 2H), 7.65 (dd, 1H, J = 1.4, 8.5 Hz), 7.71 (d, 1H, J = 8.5 Hz), 7.86 (m, 2H), 7.91 (s, 1H), 8.36 (s, 1H); ms: m/z 326 (M +1, 100). *Anal*. Calcd for $C_{19}H_{20}FN_3O$: C, 70.12; H, 6.20; N, 12.92. Found C, 70.34; H, 6.30; N, 12.61.

1-Butyl-2-(4-fluorophenyl)-N′-hydroxy-1H-benzimidazole-5-carboximidamide (87). To a stirring solution of compound **I** (1 mmol, 0.293 g) in ethanol (50 mL) was added hydroxyl-

amine hydrochloride (1.43 mmol, 0.1 g) followed by *N,N*,-diisopropylethylamine (1.43 mmol, 0.184 g). The solution was heated to reflux and after 6 h, it was concentrated. Residue was washed with water and crystallized from ethanol, mp 230–233°C, yield 66%. ^{1}H NMR δ (DMSO-d_6): 0.72 (t, 3H), 1.1 (m, 2H), 1.6 (m, 2H), 4.26 (t, 2H), 5.84 (s, 2H), 7.40 (t, 2H), 7.62 (m, 2H), 7.81 (m, 2H), 7.95 (s, 1H), 9.54 (s, 1H); ms: *m/z* 327 (M +1, 100). *Anal.* Calcd for $C_{18}H_{19}FN_4O\cdot 0.4$ HOH·0.25 C_2H_6O: C, 64.38; H, 6.22; N, 16.23. Found C, 64.46; H, 5.79; N, 15.93.

1-Butyl-2-(4-fluorophenyl)-5-(5-methyl-1,2,4-oxadiazol-3-yl)-1H-benzimidazole (88). To a stirring solution of **87** (0.070 g, 0.214 mmol) in 1,2-dichloroethane was added acetic anhydride (1 g, 0.97 mL, 10.2 mmol) and then the mixture was heated to 75°C. After 10 h, the reaction was cooled to room temperature and concentrated under reduced pressure. Water was added and the mixture was made alkaline with dilute sodium carbonate solution, then extracted with ethyl acetate. The organic layer was washed with water and evaporated, the residue was purified by cc eluting with first ethyl acetate-hexane 50%, later ethyl acetate-ethanol (99:1) to give **88** (0.025 g, 33.3%), mp 120–122°C, ^{1}H NMR δ: 0.86 (t, 3H), 1.27 (m, 2H), 1.78 (m, 2H), 2.66 (s, 3H), 4.22 (t, 2H), 7.23 (t, 2H), 7.47 (d, 1H, J = 8 Hz), 7.71 (m, 2H), 8.03 (d, 1H, J = 8.8 Hz), 8.51 (s, 1H); ms: *m/z* 351 (M +1, 100). *Anal.* Calcd for $C_{20}H_{19}FN_4O\cdot 0.1$ $C_4H_8O_2$: C, 68.21; H, 5.56; N, 15.59. Found C, 68.35; H, 5.54; N, 15.36.

2-(4-Fluorophenyl)-1-propyl-5-(1H-tetrazol-5-yl)-1H-benzimidazole (89). A mixture of **89a** (0.1 g, 0.358 mmol), sodium azide (0.11 g, 1.7 mmol), and ammonium chloride (0.11 g, 2.056 mmol) in *N,N*-dimethylformamide (1 mL) was stirred at 145°C for 24 h. After cooling, the mixture was diluted with water, acidified to pH 3 with dilute HCl and extracted with ethyl acetate. The organic layer was washed with water and evaporated. The residue was purified by c.c. eluting with first ethyl acetate, later ethyl acetate-ethanol (9:1) to give **89**, mp 126–128°C, yield 19.1%. ^{1}H NMR δ: 0.68 (t, 3H), 1.64 (m, 2H), 4.26 (t, 2H), 7.39 (t, 2H), 7.83 (m, 3H), 7.97 (d, 1H, J = 7.6 Hz), 8.32 (s, 1H); ^{13}C NMR δ (DMSO-d_6): 163.7 (d, J = 250 Hz), 163.15, 156.7, 154.5, 143.1, 138.0, 132.3 (d, J = 9.2 Hz), 127.1, 122.2, 119.2, 118.5, 116.7 (d, J = 22 Hz), 112.7, 46.4, 23.1, 11.4; ms: *m/z* 323 (M +1,100). *Anal.* Calcd for $C_{17}H_{15}FN_6$. HOH: C, 59.99; H, 5.03; N, 24.69. Found C, 60.03; H, 5.07; N, 24.41.

5,6-Difluoro-2-(4-hydroxyphenyl)-1H-benzimidazole (98). Compound **97** (0.12 g, 0.357 mmol) in ethanol (10 mL) were reduced by hydrogenation using 40 psi of H_2 and 10% Pd-C until cessation of hydrogen uptake. The catalyst was filtered off on a bed of Celite, washed with ethanol, and the filtrate was concentrated. The residue was crystallized from ethanol, mp 286–287°C, yield 43.2%. ^{1}H NMR δ (DMSO-d_6): 6.88 (d, 2H, J = 8.4 Hz), 7.47 and 7.6 (br.s, 2H), 7.94 (d, 2H, J = 8.8 Hz), 10.0 (s, 1H), 12.87 (s, 1H); ms: *m/z* 247 (M +1,100). *Anal.* Calcd for $C_{13}H_8F_2N_2O\cdot 0.5C_4H_8O_2$: C, 62.07; H, 4.17; N, 9.65. Found C, 62.55; H, 4.29; N, 9.37.

General procedure for synthesis of 103, 105–107. A mixture of **99–102** (1 mmol), *n*-butylbromide (1 mmol), and sodium hydride (95%, 1.25 mmol) in *N,N*-dimethylformamide (1mL) was stirred at 60°C for 5 h. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and concentrated *in vacuo*.

1-Butyl-4,7-dichloro-2-(4-fluorophenyl)-1H-benzimidazole (103). Purification, cc, ethyl acetate-hexane (2:8), mp 93–94°C, yield 52.5%. ^{1}H NMR δ: 0.81 (t, 3H), 1.18 (m, 2H), 1.74 (m, 2H), 4.46 (t, 2H), 7.22 (m, 4H), 7.67 (m, 2H); ms: *m/z* 337 (M +1, 100) 339 (M +3, 63), 341 (M +5, 13). *Anal.* Calcd for $C_{17}H_{15}Cl_2FN_2$: C, 60.54; H, 4.48; N, 8.31. Found C, 60.73; H, 4.58; N, 8.29.

1-Butyl-5,6-dichloro-2-(4-fluorophenyl)-1H-benzimidazole (105). Purification, cc, ethyl acetate-hexane (1:3), mp 85–86°C, yield 70.5%. ^{1}H NMR δ: 0.88 (t, 3H), 1.26 (m, 2H), 1.76 (m, 2H), 4.17 (t, 2H), 7.24 (m, 2H), 7.51 (s, 1H), 7.68 (m, 2H), 7.87 (s, 1H); ms: *m/z* 337 (M +1, 100) 339 (M +3, 57). 341 (M +5, 13). *Anal.* Calcd for $C_{17}H_{15}Cl_2FN_2$: C, 60.55; H, 4.48; N, 8.31. Found C, 60.5; H, 4.39; N, 8.31.

1-Butyl-5,6-dibromo-2-(4-fluorophenyl)-1H-benzimidazole (106). Purification, cryst., ethanol, mp 100–101°C, yield 72.8%. ^{1}H NMR δ: 0.87 (t, 3H), 1.26 (m, 2H), 1.75 (m, 2H), 4.15 (t, 2H), 7.23 (m, 2H), 7.68 (m, 3H), 8.05 (s, 1H); ^{13}C NMR δ: 165.0, 162.6, 154.5, 143.4, 135.8, 131.3, 131.2, 126.0, 125.9, 124.3, 117.9, 117.6, 116.2, 116.0, 114.6, 44.8, 31.7, 19.8, 13.4. ms: *m/z* 425 (M +1, 51), 427 (M +3, 100), 429 (M +5, 50). *Anal.* Calcd for $C_{17}H_{15}Br_2FN_2$: C, 47.92; H, 3.55; N, 6.57. Found C, 47.52; H, 3.45; N, 6.73.

1-Butyl-2-(4-fluorophenyl)-1H-benzimidazole-5,6-dicarbonitrile (107). Purification, cc, ethyl acetate-hexane (3:7), mp 158–160°C, yield 36.6%. ^{1}H NMR δ (DMSO-d_6): 0.76 (t, 3H), 1.14 (m, 2H), 1.64 (m, 2H), 4.4 (t, 2H), 7.49 (t, 2H), 7.91 (m, 2H), 8.57 (s, 1H), 8.75 (s, 1H); ms: *m/z* 319 (M +1, 100). *Anal.* Calcd for $C_{19}H_{15}FN_4$. 0.15 $C_4H_8O_2$: C, 71.0; H, 4.92; N, 16.89. Found C, 71.16; H, 4.95; N, 16.78.

1-(4-Fluorophenyl)ethanone (4-bromophenyl) hydrazone (108a). A mixture of 4-bromo-phenylhidrazine HCl (1.12 g, 5 mmol), 4′-fluoroacetophenone (0.69 g, 5 mmol), and triethylamine (1 mL) in ethanol (10 mL) was heated to 80°C for 3 h. The mixture was allowed to cool and water was added. The resultant precipitate was filtered and dried under vacuum, yield 1.34 g, 87.3%.

5-Bromo-2-(4-fluorophenyl)-1H-indole (108). Compound **108a** (0.92 g, 3 mmol) in polyphosphoric acid (25 g) was heated to 120°C for 4 h. After cooling to room temperature, the resultant reaction solution was poured into a mixture of ice and water, and the solution was basified with 10% sodium hydroxide solution. The resultant precipitate was filtered, washed with water, crystallized from ethanol, mp 178–179°C, ref. 28; 180°C, yield 85%. ^{1}H NMR δ (DMSO-d_6): 6.87 (s, 1H), 7.21 (dd, 1H, J = 2, 8.8 Hz), 7.33 (m, 3H), 7.71 (s, 1H), 7.91 (m, 2H), 11.77 (s, 1H); ^{13}C NMR δ (DMSO-d_6): 162.9, 160.4, 138.1, 135.6, 130.4, 128.2, 127.2, 127.1, 123.8, 121.9, 115.9, 115.7, 113.1, 111.7, 98.1; ms [ESI(−)]: *m/z* 288 (M −1, 100) 290 (M +2, −1, 100). *Anal.* Calcd for $C_{14}H_9BrFN$: C, 57.95; H, 3.13; N, 4.83. Found C, 57.73; H, 3.04s; N, 4.98.

5-Bromo-2-(4-fluorophenyl)-1-propyl-1H-indole (109). A solution of **108** (0.58 g, 2 mmol) and sodium hydride (0.072 g, 3 mmol) was stirred in dry *N,N*-dimethylformamide (3 mL) at 0°C for 30 min, and then propyl bromide (0.30 g, 2.5 mmol) was added dropwise and the resulting mixture was stirred at room temperature for 16 h and then poured into ice-water and extracted with ethyl acetate (3 × 10). The organic phase was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The residue was crystallized from ethyl acetate-hexane, yield 63.3%, mp 55–56°C; ^{1}H NMR δ (DMSO-

d_6): 0.63 (t, 3H), 1.53 (m, 2H), 4.14 (t, 2H), 6.51 (s, 1H), 7.28 (dd, 1H, $J = 2$, 8.4 Hz), 7.36 (m, 2H), 7.55 (d, 1H, $J = 8.8$ Hz), 7.59 (m, 2H), 7.75 (d, 1H, $J = 2$ Hz); ms: *m/z* 332 (M +1, 100) 334 (M +3, 100). *Anal*. Calcd for $C_{17}H_{15}BrFN$: C, 61.46; H, 4.55; N, 4.22. Found C, 61.43; H, 4.56; N, 4.38.

5-Cyano-2-(4-fluorophenyl)-1-propyl-1H-indole (110). A mixture of **109** (0.332 g, 1 mmol) and cuprous cyanide (0.270 g, 3 mmol) in 5 mL of 1-methyl-2-pyrrolidinone was heated at 120°C for 6 h in a Parr Digestion Bomb. The mixture was cooled to room temperature and washed with 10 mL water, by stirring with water for 15 min and decanting the water layer. The washed reaction mixture was mixture with 8 mL of ethylenediamine and 5 mL of water. The resultant precipitate was filtered, washed with 15 mL of 10% sodium cyanide solution then water and dried. Crude product was purified by using cc (ethyl acetate-hexane 1:3), mp 141-143°C, yield 23.7%. ^{1}H NMR δ (DMSO-d_6): 0.63 (t, 3H), 1.52 (m, 2H), 4.20 (t, 2H), 6.67 (s, 1H), 7.37 (t, 2H), 7.52 (dd, 1H, $J = 1.4$, 8.6 Hz), 7.61 (m, 2H), 7.77 (d, 1H, $J = 8.6$ Hz), 8.09 (d, 1H, $J = 1$ Hz); ms: *m/z* 279 (M +1,100). *Anal*. Calcd for $C_{18}H_{15}FN_2$. 0.15 HOH: C, 76.93; H, 5.49; N, 9.96. Found C, 77.04; H, 5.76; N, 9.47.

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