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# Synthesis of Some New 2-Substituted-phenyl-1H-benzimidazole-5-carbonitriles and Their Potent Activity Against *Candida* Species

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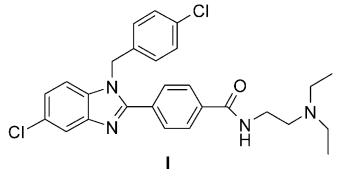
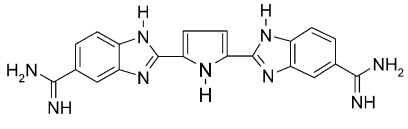
**Abstract**—New 2-substituted-phenyl-1H-benzimidazole-5-carboxylic acids (**35**, **38**), ethyl-5-carboxylate (**36**), -5-carboxamides (**37**, **39**),-5-carboxaldehyde (**42**), -5-chloro (**40**), -5-trifluoromethyl (**41**), and -5-carbonitriles (**44**–**53**, **55**–**67**), -6-carbonitrile (**54**) were prepared and evaluated in vitro against *Candida* species. The cyano substituted compounds **53**, **57**, **58** and **61** exhibited the greatest activity with MIC values of 3.12 μg/mL, values similar to that of fluconazole. 

## Introduction

The synthesis of benzimidazoles has received much attention owing to the varied biological activity exhibited by a number of these compounds. As contributions to this field, in the last decade we reported the preparation, antifungal and anti-histaminic activity[1] of a large series of benzimidazoles. Among them, 4-[5-chloro-1-(4-chlorobenzyl)-1H-benzimidazol-2-yl]-*N*-(2-diethylamino-ethyl)-benzamide **I** and 2,5-bis-[2-(5-amidino)-benzimidazoyl]pyrrole **II**, exhibited potent antifungal activity.[2,3] In connection with these studies, this report describes the preparation and antifungal evaluation of 2-substituted-phenyl-1H-benzimidazole-5-carbonitriles.



I



II

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## Results and Discussion

### Chemistry

The synthetic pathways for preparation of the benzimidazoles listed in Tables 1 and 2 are shown in Schemes 1 and 2. Compounds **32** and **33** were obtained by the $N^1$-alkylation of **2** which was prepared in good yield by condensation of *o*-phenylenediamine with the $Na_2S_2O_5$ adduct of 4-fluorobenzaldehyde in DMF.[4] Compounds **34**, **35** and **38** were also prepared in a similar manner **2**. The carboxyl group of **35** was converted to ethyl ester **36** and the *N*-isopropyl-carboxamide **37**, first by acid chloride formation using $SOCl_2$, then reaction with EtOH and isopropylamine, respectively. **39** was also obtained in the analogous way, starting from **38**. Nucleophilic displacement of the chloro group of 4-($CF_3$ and/or Cl)-nitrobenzenes by reaction with butylamine in DMF gave **5** and **6**, respectively. Their reduction with $H_2$, Pd/C produced **7**, **8**. Condensation of the aromatic *o*-diamines with the $Na_2S_2O_5$ adduct of appropriate benzaldehydes gave **40**, **41** and **43**. The nitrile group of **57** was converted to carboxyaldehyde **42**, by using DIBAL, in a 33% yield. Compounds **44**–**67** were obtained by the same route as **40**, **41**, **43** (Schemes 2 and 4). Related intermediates **9**–**17** and **18**–**27** are given in Table 3. Compound **63** was prepared by etherification of **62**. Since compound **53** exhibited significant antifungal activity, it was planned to relocate the CN group from C-5 to C-6. For this purpose, firstly we have attempted alkylation of compound **44**, with *n*-propyl bromide under strong basic conditions (NaH 95%,

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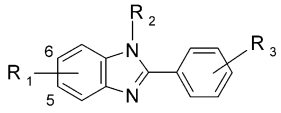
**Table 1.** In vitro antifungal activities and formulas of **32–67**




| Compd | $R_1$ | $R_2$ | $R_3$ | Fungi | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *C. albicans* | | | *C. glabrata* | | | *C. krusei* | | | *C. parapsilosis* | | |
| | | | | GIZ | MIC | MFC | GIZ | MIC | MFC | GIZ | MIC | MFC | GIZ | MIC | MFC |
| **32** | 5,6-H | $(CH_2)_2CH_3$ | 4-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **33** | 5,6-H | $CH_2$–$CH_2$=$CH_2$ | 4-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **34** | 5-$CH_3$ | $(CH_2)_2CH_3$ | 4-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **35** | 5-COOH | $(CH_2)_2CH_3$ | H | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **36** | 5-COOEt | $(CH_2)_2CH_3$ | H | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **37** | 5-$CONHCH(CH_3)_2$ | $(CH_2)_2CH_3$ | H | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **38** | 5-COOH | $(CH_2)_3CH_3$ | 4-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **39** | 5-$CONH_2$ | $(CH_2)_3CH_3$ | 4-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **40** | 5-Cl | $(CH_2)_3CH_3$ | H | 14 | 6.25 | 12.5 | NI | >25 | | 16 | 6.25 | 12.5 | 14 | 12.5 | 25 |
| **41** | 5-$CF_3$ | $(CH_2)_3CH_3$ | 4-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **42** | 5-COH | $(CH_2)_3CH_3$ | H | 11 | 12.5 | 12.5 | NI | >25 | | 13 | 12.5 | 25 | 15 | 12.5 | 25 |
| **43** | 5-$NO_2$ | H | 4-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **44** | 5-CN | H | 4-F | 9 | NT | | NI | NT | | NI | NT | | NI | NT | |
| **45** | 5-CN | H | 4-Cl | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **46** | 5-CN | H | 2-Cl | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **47** | 5-CN | H | 4-$OCH_3$ | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **48** | 5-CN | H | 2,4-*di*-Cl | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **49** | 5-CN | H | 4-OH | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **50** | 5-CN | $CH_2CH_3$ | 4-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **51** | 5-CN | $(CH_2)_2CH_3$ | 3-$NO_2$ | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **52** | 5-CN | $(CH_2)_2CH_3$ | H | 22 | 12.5 | 50 | NI | 25 | 50 | 13 | 50 | 50 | 11 | 25 | 25 |
| **53** | 5-CN | $(CH_2)_2CH_3$ | 4-F | 20 | 6.25 | 25 | NI | 25 | 50 | 10 | 12.5 | 25 | 12 | 12.5 | 25 |
| **54** | 6-CN | $(CH_2)_2CH_3$ | 4-F | NI | 25 | 50 | 18 | 6.25 | 6.25 | 15 | 12.5 | 12.5 | 12 | 6.25 | 12.5 |
| **55** | 5-CN | $(CH_2)_2CH_3$ | 3-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **56** | 5-CN | $(CH_2)_2CH_3$ | 2-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **57** | 5-CN | $(CH_2)_3CH_3$ | H | 23 | NT* | | 13 | NT* | | 20 | NT* | | 18 | NT* | |
| **58** | 5-CN | $(CH_2)_3CH_3$ | 4-F | 24 | 3.12 | 6.25 | 15 | 12.5 | 25 | 24 | 3.12 | 6.25 | 19 | 3.12 | 3.12 |
| **59** | 5-CN | $(CH_2)_2CH_3$ | 2,5-*di*-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **60** | 5-CN | $(CH_2)_2CH_3$ | 3,4-*di*-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **61** | 5-CN | $(CH_2)_2CH_2$ Cl | 4-F | 17 | 3.12 | 25 | NI | 12.5 | 25 | 18 | 6.25 | 12.5 | 13 | 6.25 | 12.5 |
| **62** | 5-CN | $CH_2CH_2OH$ | 4-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **63** | 5-CN | $CH_2CH_2OCH_3$ | 4-F | 21 | 6.25 | 25 | NI | 25 | 50 | NI | 25 | 25 | NI | 12.5 | 25 |
| **64** | 5-CN | $CH(CH_3)_2$ | 4-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **65** | 5-CN | $CH_2CH_2CH(CH_3)_2$ | 4-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **66** | 5-CN | cyclohexyl | 4-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| **67** | 5-CN | $CH_2Ph$ | 4-F | NI | NT | | NI | NT | | NI | NT | | NI | NT | |
| Mic | | | | 35 | 0.19 | 0.56 | 34 | 0.19 | 0.39 | 35 | 0.19 | 0.39 | 46 | 0.39 | 0.78 |
| Flu | | | | 15 | 3.12 | 6.25 | 16 | 12.5 | 25 | 16 | 6.25 | 12.5 | 13 | 6.25 | 12.5 |

GIZ, growth inhibition zone (mm); MIC 100, minimum inhibitory concentrations (μg/mL); MFC, minimum fungicidal concentrations (μg/mL); NI, no inhibition; NT, not tested; NT*, since the compound **57** has no good solubility, it has not been tested by the tube dilution method; Mic, miconazole; Flu, fluconazole.

DMF, at rt) (Scheme 3). As expected, due to the tautomerism of the imidazole moiety alkylation occurred at both the 1 and 3 positions;[5] two regioisomers, **53** and **54**, were formed as a solid mixture which has no sharp mp. Generally, alkylations of benzimidazoles give similar yields of both regioisomers, rarely giving a different ratio,[5] it has been reported that,[6] when 5(6)- or 4(7)-substituted benzimidazoles are alkylated, the product ratios depends on the resonance electronic effects as well as position of the substituent. Here, propylation of **44** (Scheme 3), gave a 2:1 ratio of 1,6- (**54**) and the 1,5-isomers (**53**), according to the NMR data of the mixture. Since the compound **53** was synthesised as described in Scheme 2 by an unambiguous method and therefore readily allows for isomeric identification in the NMR spectra of the mixture. The partial regioselectivity of alkylation of **44** may be attributed to the electron withdrawing effect of the cyano group, since a similar result was noted on alkylation of 4-nitrobenzimidazole.[6] Further studies are necessary to fully understand the influence of electron-withdrawing groups on *N*-alkylation of benzimidazoles.

We were unable to separate the regiosiomers from each other by crystallisation or chromatography. Therefore, it was necessary to develop a selective synthesis for the

**Table 2.** Physical and spectral data for compounds **32–67**

| Comp. | Mp (°C) | Yield (%) | Formulas<br>Calculated<br>Found | $^1$H NMR | Mass (62 or 70 eV, EI) | Isolation |
|---|---|---|---|---|---|---|
| **32** | 82–83 | 81 | $C_{16}H_{15}FN_2$<br>C: 75.59H: 5.94 N: 11.02<br>C: 75.59H: 6.05 N: 11.00 | (DMSO-$d_6$) 0.5–0.8 (t, 3H), 1.4–1.9 (m, 2H), 4.1–4.4 (t, 2H), 7.1–7.9 (8H) | 254 ($M^+$, 100), 239 (23), 224 (66), 211 (22.6), 129 (16.2), 77 (44.5) | EtOAc/*n*-hexane (1:3) cc |
| **33** | 98–99 | 79 | $C_{16}H_{13}FN_2$<br>C: 76.19H: 5.19 N: 11.10<br>C: 76.38H: 5.18 N: 11.06 | (DMSO-$d_6$) 4.8 (3H), 5.2 (d, 1H), 6.0 (m, 1H), 7.2 (2H), 7.4 (m, 2H), 7.5 (m, 1H), 7.7 (d, 1H, $J_0$ = 8.3), 7.8 (2H) | 251 (M−1, 76.5), 236 (7.34), 225 (4.5), 211 (42.2), 121 (17.8), 90 (23.9), 41 (100) | EtOAc/*n*-hexane (1:3) cc |
| **34** | 95 | 41 | $C_{17}H_{17}FN_2$<br>C: 76.11H: 6.34 N: 10.44<br>C: 75.84H: 6.37 N: 10.57 | (DMSO-$d_6$) 0.7 (t, 3H, $J$ = 7.3), 1.65 (m, 2H), 2.4 (s, 3H), 4.2 (t, 2H, $J$ = 7.2), 7.1 (dd, 1H, $J_o$ = 8.6, $J_m$ = 1.28), 7.4 (3H), 7.5 (d, 1H, $J_o$ = 8.1), 7.8 (2H) | 269 (M + 1, 62.9), 253 (9.7), 239 (57.7), 225 (9.8), 121 (31.9), 77 (8.84), 41 (100) | Crys. EtOH (60%) |
| **35** | 217 | 57 | $C_{17}H_{16}N_2O_2$<br>C: 72.84H: 5.75 N: 9.99<br>C: 72.39H: 5.72 N: 9.90 | (DMSO-$d_6$) 0.715 (t, 3H), 1.67 (m, 2H), 4.29 (t, 2H), 7.57–7.79 (6H), 7.91 (dd, 1H, $J_0$ = 8.5, $J_m$ = 1.5), 8.25 (s, 1H) | ESI: 281 (M + 1, 100) | Crys. isopropanol |
| **36** | 91–92 | 77 | $C_{19}H_{20}N_2O_2$<br>C: 74.00H: 6.54 N: 9.08<br>C: 73.81H: 6.57 N: 9.08 | (DMSO-$d_6$) 0.715 (t, 3H), 1.35 (t, 3H), 1.67 (q, 2H), 4.313 (m, 4H), 7.58–7.9(7H), 8.27 (s, 1H) | ESI: 309 (M + 1, 100) | EtOAc/*n*-hexane (1:3) cc |
| **37** | 210–211 | 81 | $C_{20}H_{23}N_3O$<br>C: 74.74H: 7.21 N: 13.07<br>C: 74.47H: 7.05 N: 13.02 | (DMSO-$d_6$) 0.7 (t, 3H), 1.2 (d, 6H), 1.7 (m, 2H), 4.1 (m, 1H), 4.35 (t, 2H), 7.66 (3H), 7.77 (d, 1H, $J_0$ = 7.9), 7.85 (2H), 7.91 (dd, 1H, $J_0$ = 8.5, $J_m$ = 1.5), 8.25 (2H) | 320.5 ($M^+$, 5.49), 263 (24.3), 220 (8.92), 102 (4.43), 77 (4), 41 (100) | EtOAc cc |
| **38** | 250 | 75.4 | $C_{18}H_{17}FN_2O_2$<br>C: 69.22H: 5.49 N: 8.97<br>C: 69.39H: 5.49 N: 9.09 | (DMSO-$d_6$) 0.74 (t, 3H), 1.12 (m, 2H), 1.63 (m, 2H), 4.31 (t, 2H), 7.39–7.9 (6H), 8.24 (s, 1H) | ESI: 313 (M + 1, 100) | Crys. isopropanol |
| **39** | 185–186 | 91 | $C_{18}H_{18}FN_3O.0.2HOH$<br>C: 68.60H: 5.88 N: 13.34<br>C: 68.63H: 5.83 N: 13.27 | (DMSO-$d_6$) 0.7 (t, 3H), 1.1 (m, 2H), 1.6 (m, 2H), 4.3 (t, 2H), 7.2–8.05 (6H), 8.25 (s, 1H) | ESI: 312 (M + 1, 100) | Crys EtOH (50%) |
| **40** | 65–67 | 49 | $C_{17}H_{17}ClN_2$<br>C: 71.80H: 6.02 N: 9.85<br>C: 71.62H: 6.16 N: 9.70 | (DMSO-$d_6$) 0.7 (t, 3H), 1.05 (m, 2H), 1.6 (m, 2H), 4.3 (t, 2H), 7.25 (d, 1H, $J_0$ = 8.6), 7.5 (3H), 7.7 (dd, 1H, $J_0$ = 8.6, $J_m$ = 1.6), 7.8 (3H) | 284 ($M^+$, 100), 286 (M + 2, 27), 255 (77), 241 (99), 163 (60.7) | EtOAc/*n*-hexane (1:4) cc |
| **41** | 55–56 | 53.5 | $C_{18}H_{16}F_4N_2$<br>C: 64.28H: 4.80 N: 8.33<br>C: 64.34H: 4.90 N: 8.24 | ($CDCl_3$) 0.7(t, 3H), 1.07(m, 2H), 1.6 (m, 2H), 4.05(t, 2H), 7.0(2H), 7.2 (d, 1H,$J_0$ = 8.5), 7.4(d, 1H, $J_0$ = 8.5), 7.55(2H), 7.9(s, 1H) | 336 ($M^+$, 40.2), 307 (8.6), 293 (35.9), 280 (23), 121 (22.1), 95 (15.9), 83 (100) | EtOAc/*n*-hexane (1:3) cc |
| **42** | 94–95 | 33 | $C_{18}H_{18}N_2O{\cdot}0.15HOH$<br>C: 76.90H: 6.56 N: 9.97<br>C: 76.98H: 6.71 N: 9.39 | ($CDCl_3$) 0.8 (t, 3H), 1.2 (m, 2H), 1.7 (m, 2H), 4.3 (t, 2H), 7.4 (d, 1H, $J_0$ = 8.5), 7.5 (3H), 7.7 (2H), 7.9 (dd, 1H $J_0$ = 8.4, $J_m$ = 1.3), 8.3 (s, 1H), 10 (s, 1H) | 278 ($M^+$, 100), 249 (15.7), 235 (42.6), 221 (12.4), 157 (1.8), 77 (6.5) | EtOAc/*n*-hexane (2:3) cc |
| **43** | 264–265 | 67.6 | $C_{13}H_8FN_3O_2{\cdot}0.7HOH$<br>C: 57.86H: 3.51 N: 15.57<br>C: 57.87H: 3.54 N: 15.52 | (DMSO-$d_6$) 7.4 (2H), 7.7 (d, 1H), 8.1 (d, 1H), -8.2 (2H), 8.4 (s, 1H) | ESI: 258 (M + 1, 100) | Crys. EtOH (70%) |
| **44** | 238–240 | 78 | $C_{14}H_8FN_3{\cdot}1.5HOH$<br>C: 63.60H: 4.10 N: 15.90<br>C: 63.29H: 3.92 N: 15.91 | (DMSO-$d_6$) 7.4–8.35 (7H), 13.4 (br.s., 1H). | 237 ($M^+$, 100), 218 (2), 121 (18.2), 96 (7.6), 75 (15.7) | EtOAc/*n*-hexane (1:1) cc |
| **45** | 237–239 | 64.2 | $C_{14}H_8ClN_3{\cdot}1.85HOH$<br>C: 58.58H: 4.11 N: 14.6<br>C: 58.52H: 4.12 N: 14.4 | (DMSO-$d_6$) 7.55–8.32 (7H), 13.5 (br.s., 1H). | 253 ($M^+$, 100), 255 (27.8), 217 (18.8), 149 (2.8), 137 (14.1), 115 (10.5), 109 (16.6), 89 (15.9), 75 (19.4) | Crys. EtOAc/*n*-hexane (50%) |
| **46** | 125–126 | 56.9 | $C_{14}H_8ClN_3{\cdot}0.4HOH$<br>C: 64.45H: 3.40 N: 16.10<br>C: 64.73H: 3.45 N: 16.13 | (DMSO-$d_6$) 7.5–8.3 (7H), 13.3 (s, 1H). | 253 ($M^+$, 100), 255 (30.2), 218 (26.5), 137 (12.4), 116 (5.9), 89 (10.7), 75 (16.95) | EtOAc/*n*-hexane (1:3) cc |
| **47** | 218–219lit.[12] 221 | 76.3 | $C_{15}H_{11}N_3O$ | (DMSO-$d_6$) 3.85 (s, 3H), 7.1–8.2 (7H), 13.3 (br.s., 1H). | 249 ($M^+$,100), 234 (33.9), 206 (44.8), 133 (5.3), 90 (8.9) | Crys. isopropanol. (70%) |
| **48** | 248–250 | 64.8 | $C_{14}H_7Cl_2N_3$<br>C: 58.33H: 2.43 N: 14.58<br>C: 58.39H: 2.70 N: 14.42 | (DMSO-$d_6$) 7.55–8.3 (6H), 13.3 (br.s., 1H). | 287 ($M^+$, 80), 289 (51.3), 291 (8.2), 252 (10.9), 217 (17.8), 171 (9.3), 144 (3.7), 126 (4.5), 115 (10.5), 100 (10.6) | Crys. EtOH |
| **49**[a] | Lit.[13] 317 | 80.2 | $C_{14}H_9N_3O$ | (DMSO-$d_6$) 6.9 (2H), 7.5 (1H), 7.65 (1H), 8.02 (3H). | 235 ($M^+$, 9.5), 207 (7.5), 179 (4.2), 119 (36.7), 103 (9.5), 91 (33.5), 76 (34.2), 41 (100) | Crys. EtOH (70%) |
| **50** | 140 | 64.2 | $C_{16}H_{12}FN_3{\cdot}0.5HOH$<br>C: 70.06H: 4.78 N: 15.30<br>C: 70.05H: 4.72 N: 15.29 | (DMSO-$d_6$) 1.3 (t, 3H), 4.3 (q, 2H), 7.4 (2H), 7.7 (dd, 1H, $J_0$ = 8.5, $J_m$ = 1.57), 7.8–7.9 (3H), 8.2 (d, 1H, $J_m$ = 1.3) | 265($M^+$, 100), 250 (53), 237 (55.7), 170 (16.7), 143 (12.9), 121 (84), 95 (22.5), 75 (30.3) | Crys. EtOH |

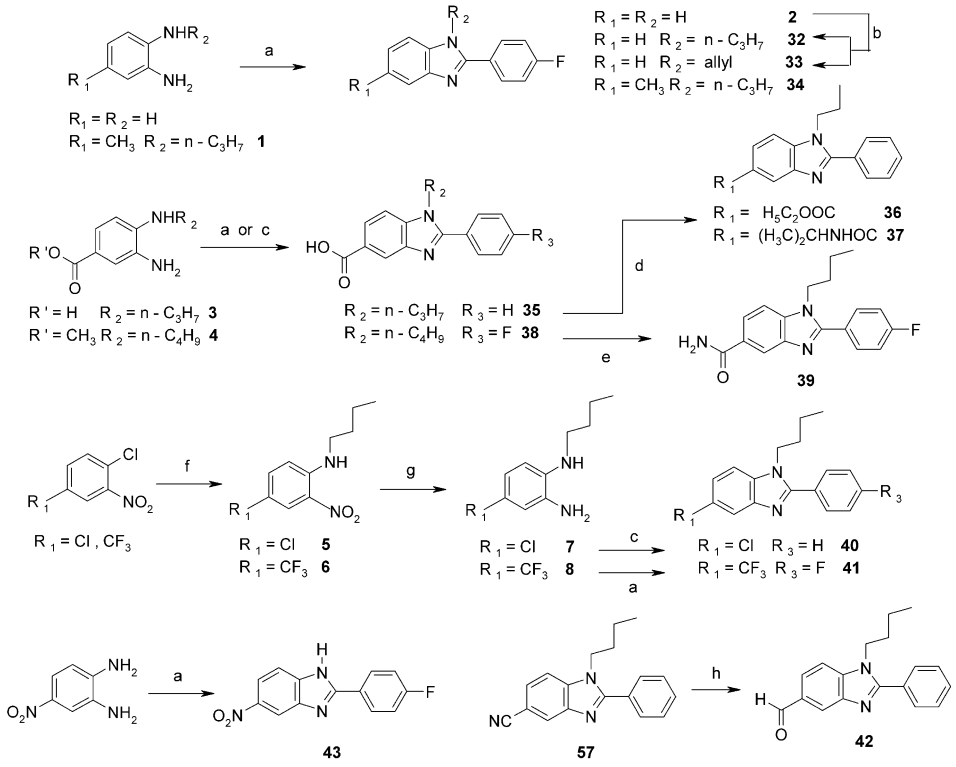
(*continued*)

Table 2 (*continued*)

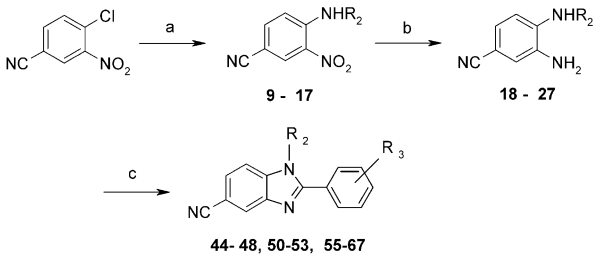
| Comp. | Mp (°C) | Yield (%) | Formulas Calculated Found | $^1$H NMR | Mass (62 or 70 eV, EI) | Isolation |
|---|---|---|---|---|---|---|
| **51** | 130–1 | 51 | $C_{17}H_{14}N_4O_2 \cdot 0.25HOH$<br>C: 65.60H: 4.70 N: 18.02<br>C: 65.61H: 4.71 N: 18.11 | (DMSO-$d_6$) 0.7 (t, 3H), 1.7 (m, 2H), 4.3 (t, 2H), 7.7 (d, 1H), 7.9 (2H), 8.2 (2H), 8.3 (d, 1H), 8.6 (s, 1H) | 307 (M + 1, 1.95), 231 (2.78), 218 (1.5), 149 (3.2), 115 (2.7), 102 (8.4), 76 (19.4), 41 (100) | Crys. EtOH (70%) |
| **52** | 178 | 68.7 | $C_{17}H_{15}N_3$<br>C: 78.16H: 5.74 N: 16.09<br>C: 77.87H: 5.72 N: 16.16 | (DMSO-$d_6$) 0.7 (t, 3H), 1.6 (m, 2H), 4.3 (t, 2H), 7.6 (3H), 7.7 (d, 1H, $J_0$ = 8.3), 7.8 (2H), 7.9 (d, 1H, $J_0$ = 8.4), 8.2 (s, 1H) | 261($M^+$, 4.9), 232 (5.9), 154 (3.9), 103 (7.7), 77 (18.6), 41 (100) | Crys. EtOH (60%) |
| **53** | 142–144 | 77. 8 | $C_{17}H_{14}FN_3$<br>C: 73.11H: 5.05 N: 15.04<br>C: 73.08H: 5.11 N: 14.88 | (DMSO-$d_6$) 0.72 (t, 3H), 1.66 (m, 2H), 4.32 (t, 2H), 7.44 (2H), 7.7 (d, 1H, $J_0$ = 9), 7.84–7.88 (m, 2H), 7.90 (dd, 1H, $J_0$ = 8.5 $J_m$ = 1.2, H-6), 8.23 (s, 1H, H-4) | 279 ($M^+$, 56.9), 264 (13.7), 250 (73.5), 237 (24.8), 154 (19.7), 121 (37.7), 102 (33), 75 (40.6), 41 (100) | Crys. EtOH (60%) |
| **54** | 160–162 | 81 | $C_{17}H_{14}FN_3$<br>C: 73.11H: 5.05 N: 15.04<br>C: 73.13H: 5.01 N: 14.98 | (DMSO-$d_6$) 0.73 (t, 3H), 1.68 (m, 2H), 4.31 (t, 2H), 7.43 (2H), 7.61 (d, 1H, $J_0$ = 8.3), 7.82–7.88 (m, 3H), 8.36 (s, 1H, H-7) | 279($M^+$, 17.1), 264 (5), 250 (34.4), 237 (7.2), 154 (7), 121 (8.6), 102 (5.4), 75 (12.7), 41 (100) | Crys. EtOH (60%) |
| **55** | 152–153 | 60.9 | $C_{17}H_{14}FN_3$<br>C: 73.11H: 5.05 N: 15.04<br>C: 73.25H: 5.11 N: 15.04 | (DMSO-$d_6$) 0.7 (t, 3H), 1.6 (m, 2H), 4.3 (t, 2H), 7.4 (2H), 7.6 (2H), 7.7 (d, 1H, $J_0$ = 8.4), 7.9 (dd, 1H, $J_0$ = 8.4, $J_m$ = 1.6), 8.2 (s, 1H) | 279 ($M^+$, 5.2), 264 (1.4), 250 (7.5), 237 (1.5), 154 (2), 121 (8.3), 101 (3.2), 95 (7.5), 75 (14), 41 (100) | Crys. EtOH (60%) |
| **56** | 133–134 | 53.2 | $C_{17}H_{14}FN_3$<br>C: 73.11H: 5.05 N: 15.04<br>C: 73.20H: 5.13 N: 15.02 | (DMSO-$d_6$) 0.7 (t, 3H), 1.6 (m, 2H), 4.3 (t, 2H), 7.5 (2H), 7.8 (3H), 8.0 (d, 1H, $J_0$ = 8.4), 8.3 (s, 1H) | ESI: 280 (M + 1, 100) | EtOAc/*n*-hexane (1:3) cc |
| **57** | 158–160 | 57.5 | $C_{18}H_{17}N_3$<br>C: 78.52H: 6.22 N: 15.27<br>C: 77.95H: 6.21 N: 15.17 | (DMSO-$d_6$) 0.7 (t, 3H), 1.1 (m, 2H), 1.6 (m, 2H), 4.3 (t, 2H), 7.5 (3H), 7.6 (d, 1H, $J_0$ = 8.4), 7.7 (2H), 7.9 (d, 1H, $J_0$ = 8.4), 8.2 (s, 1H) | ESI: 276 (M + 1, 100) | EtOAc/*n*-hexane (1:3) cc |
| **58** | 103–104 | 64.5 | $C_{18}H_{16}FN_3 \cdot 0.35HOH$<br>C: 72.15H: 5.61 N: 14.02<br>C: 72.03H: 5.47 N: 13.96 | (DMSO-$d_6$) 0.7 (t, 3H), 1.1 (m, 2H), 1.6 (m, 2H), 4.3 (t, 2H), 7.4 (2H), 7.7 (d, 1H, $J_0$ = 8.4), 7.8–7.9 (3H), 8.2 (s, 1H) | 294 (M + 1, 6), 264(2), 250 (13), 237 (3.6), 154 (1.6), 121 (9), 95 (3.2), 41 (100) | Crys. EtOH (60%) |
| **59** | 115–116 | 58 | $C_{17}H_{13}F_2N_3$<br>C: 68.68H: 4.40 N: 14.14<br>C: 68.48H: 4.34 N: 14.05 | (DMSO-$d_6$) 0.7 (t, 3H), 1.6 (m, 2H), 4.2 (t, 2H), 7.55 (2H), 7.65 (1H), 7.72 (dd, 1H, $J_0$ = 8.4, $J_m$ = 1.6), 7.95 (d, 1H, $J_0$ = 8.4), 8.2 (s, 1H) | ESI: 298 (M + 1, 100) | EtOAc/*n*-hexane (1:3) cc |
| **60** | 110 | 59 | $C_{17}H_{13}F_2N_3$<br>C: 68.68H: 4.40 N: 14.14<br>C: 68.95H: 4.66 N: 14.07 | (DMSO-$d_6$) 0.7 (t, 3H), 1.6 (m, 2H), 4.3 (t, 2H), 7.6–7.7 (3H), 7.9 (2H), 8.2 (s, 1H) | ESI: 298 (M + 1, 100) | EtOAc/*n*-hexane (1:3) cc |
| **61** | 111–112 | 53.7 | $C_{17}H_{13}ClFN_3 \cdot 0.1HOH$<br>C: 64.70H: 4.21 N: 13.30<br>C: 64.57H: 4.20 N: 13.22 | (DMSO-$d_6$) 2.1 (m, 2H), 3.5 (t, 2H), 4.4 (t, 2H), 7.4 (2H), 7.7 (d, 1H, $J_0$ = 8.4), 7.8–7.9 (3H), 8.2 (s, 1H) | 313 ($M^+$, 26.6), 315 (11.5), 279 (9.9), 264 (26.2), 250 (83.9), 154 (18.9), 121 (36.7), 95 (10.3), 75 (12.1), 41 (100) | Crys. EtOH (50%) |
| **62** | 155–157 | 67 | $C_{16}H_{12}FN_3O \cdot 0.75HOH$<br>C: 65.18H: 4.61 N: 14.25<br>C: 65.46H: 4.57 N: 14.14 | (DMSO-$d_6$) 3.75 (t, 2H), 4.3 (t, 2H), 7.4 (2H), 7.65 (dd, 1H, $J_0$ = 8.4, $J_m$ = 1.48), 7.8 (d, 1H, $J_0$ = 9), 7.95 (2H), 8.2 (d, 1H, $J_m$ = 1.23) | 281 ($M^+$, 12.4), 250 (100), 236 (6.2), 154 (14.7), 121 (6.6), 94 (2.5), 75 (2.9) | Crys. EtOH (60%) |
| **63** | 127–128 | 77 | $C_{17}H_{14}FN_3O \cdot 0.1HOH$<br>C: 68.70H: 4.82 N: 14.14<br>C: 68.69H: 4.91 N: 14.03 | ($CDCl_3$) 3.3 (s, 3H), 3.8 (t, 2H, $J$ = 5.25), 4.4 (t, 2H, $J$ = 5.27), 7.25 (2H), 7.59 (2H), 7.8 (2H), 8.15 (s, 1H) | 295 ($M^+$, 74), 263 (15), 249 (100), 236 (13), 222 (21), 154 (21), 121 (6), 94 (4) | Crys. EtOH (85%) |
| **64** | 190–191 | 79.4 | $C_{17}H_{14}FN_3 \cdot 0.5HOH$<br>C: 70.80H: 5.24 N: 14.57<br>C: 70.76H: 5.01 N: 14.65 | (DMSO-$d_6$) 1.6 (d, 6H), 4.65 (m, 1H), 7.4 (2H), 7.6 (dd, 1H, $J_0$ = 8.4, $J_m$ = 1.46), 7.8 (2H), 8.0 (d, 1H, $J_0$ = 8.4), 8.2(s, 1H) | 280 (M + 1, 9.7), 264 (3.14), 237 (21.5), 121 (13.36), 95 (4.4), 75 (4.68), 43 (100) | Crys. EtOH |
| **65** | 132 | 72.5 | $C_{19}H_{18}FN_3$<br>C: 74.25H: 5.90 N: 13.67<br>C: 74.34H: 6.01 N: 13.67 | (DMSO-$d_6$) 0.75 (d, 6H), 1.4 (m, 1H), 1.5 (m, 2H), 4.3 (t, 2H), 7.4 (2H), 7.7 (dd, 1H, $J_0$ = 8.5, $J_m$ = 1.5), 7.85 (3H), 8.2 (s, 1H) | 307 ($M^+$, 100), 264 (15.7), 250 (85.6), 237 (18.6), 154 (12.7), 121 (12.2), 102 (17.8), 95 (8.2) | Crys. EtOH |
| **66** | 211–212 | 72 | $C_{20}H_{18}FN_3 \cdot 0.4HOH$<br>C: 73.56H: 5.80 N: 12.86<br>C: 73.72H: 5.69 N: 12.89 | (DMSO-$d_6$) 1.2–1.4 (m, 3H), 1.6 (1H), 1.8–1.9 (4H), 2.2 (m, 2H), 4.2 (m, 1H), 7.4 (2H), 7.6 (dd, 1H, $J_0$ = 8.6, $J_m$ = 1.65), 7.73 (2H), 8.1 (d, 1H, $J_0$ = 8.6), 8.2 (d, 1H, $J_m$ = 1.47) | 319 ($M^+$, 14), 237 (37.8), 121 (16.1), 115 (14.6), 83 (35.5), 55 (100) | Crys. EtOH |
| **67** | 153 | 80.6 | $C_{21}H_{14}FN_3$<br>C: 77.05H: 4.31 N: 12.84<br>C: 76.88H: 4.51 N: 12.79 | (DMSO-$d_6$) 5.6 (s, 2H), 6.9–7.7 (11H), 8.27 (s, 1H) | 327 ($M^+$, 17.6), 237 (2.9), 121 (6.5), 91 (100), 75 (7.2) | Crys. EtOH (50%) |

cc, column chromatography; ESI, Elektrospray ionization.

[a]Compound **49**[13] was prepared according to the literature method.




**Scheme 1.** Reagents: (a) $Na_2S_2O_5$ adduct of 4-fluorobenzaldehyde; (b) *n*-propyl or allyl bromide/NaH/DMF; (c) $Na_2S_2O_5$ adduct of benzaldehyde; (d) for **36**; $SOCl_2$/EtOH for **37**; $SOCl_2$/isopropylamine; (e) $SOCl_2/NH_3$; (f) butylamine/DMF; (g) $H_2$, Pd/C; (h) DIBAL.



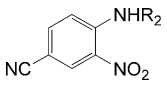
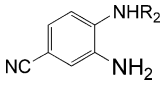

**Scheme 2.** Reagents: (a) corresponding amines; (b) $H_2$, Pd/C; (c) corresponding $Na_2S_2O_5$ adduct of the benzaldehydes/DMF.

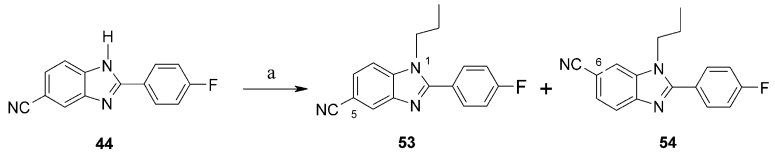
other isomer **54** and the approach is outlined in Scheme 4. Compound **28**[7] was prepared by chlorination of 4-aminobenzonitrile with *N*-chlorosuccinimide. The amino group of compound **28** was converted to nitro **29**,[8] by diazotation followed by nitritation. Compound **54** was prepared in similar manner with **53** starting from **29** (Scheme 4).

## Biological Results

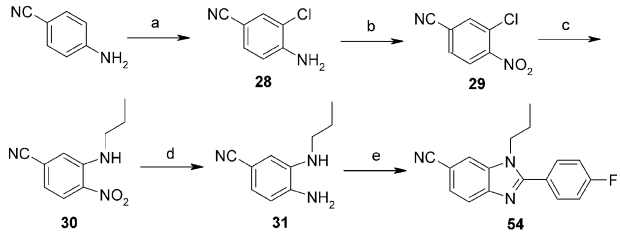
All described benzimidazoles, **32**–**67**, were tested in vitro for antibacterial activity against Gram positive *Bacillus subtilis* (ATCC 6633) and *Staphylococcus aureus* (ATCC 25923), Gram negative *Escherichia coli* (ATCC 25922) bacteria and antifungal activity against *Candida albicans* (ATTC 10231), *Candida glabrata* (Clinical isolate), *Candida krusei* (ATCC 6258), *Candida parapsilosis* (ATCC 22019) by agar diffusion method, which was already reported by us.[2] All the synthesised compounds were solved in 1,2-propylene glycol (1500 μg/mL), 0.02 mL (one drop) of these solutions was dropped to paper disk (6 mm in diameter) and placed on an agar plate containing bacteria or fungi cells. Propylene glycol as a control has no inhibition zone. The diameter of the growth inhibition zone around the paper disc was measured after incubation. The results obtained indicate that most of these compounds were only poorly active or completely in active against bacteria. However, compounds **40**, **42**, **52**, **53**, **57**, **58**, **61** and **63** showed good activity against *Candida* species with $>20$ mm growth inhibition zone, which was better than fluconazole, in the control experiments (Table 1). In addition, the tube dilution method[9] was also employed for the active compounds in agar diffusion method. Related compounds were dissolved in propylene glycol (15.6%) at 100 μg/mL concentration as starting dose. The most active compound **58** exhibits an MIC value of 3.12 μg/mL against *C. albicans*, *C krusei* and *C. parapsilosis*. The data (Table 1) show that, introduction of electron-withdrawing groups such as, aldehyde, chlorine and cyano at C-5 gives a good profile of antifungal activity. In contrast, no significant activity was found for trifluoromethyl, carboxyl, ester and amide. Consequently, there is not a clear correlation between electron attracting effects of substituents and antifungal activity. Since

**Table 3.** Formulas, mp and yields of **9**–**17** and **18**–**27**

| Compd | $R_2$ | Formula | Mp (°C) | Lit. mp | Yield (%) |
|---|---|---|---|---|---|
| | |  | | | |
| **9** | $-CH_2CH_3$ | $C_9H_9N_3O_2$ | 134–135 | Lit.[17] (131–132) | 88.6 |
| **10** | $-CH_2CH_2CH_3$ | $C_{10}H_{11}N_3O_2$ | 116–117 | Lit.[17] (116) | 96.4 |
| **11** | $-CH_2CH_2CH_2CH_3$ | $C_{11}H_{13}N_3O_2$ | 71–72 | Lit.[17] (69) | 92.7 |
| **12** | $-CH_2CH_2CH_2Cl$ | $C_{10}H_{10}ClN_3O_2$ | 152–153 | | 58 |
| **13** | $-CH_2CH_2OH$ | $C_9H_9N_3O_3$ | 135 | Lit.[17] (135) | 91 |
| **14** | $-CH(CH_3)_2$ | $C_{10}H_{11}N_3O_2$ | 110–113 | Lit.[2] (110–113) | 93.8 |
| **15** | $-CH_2CH_2CH(CH_3)_2$ | $C_{12}H_{15}N_3O_2$ | 100–101 | | 94.3 |
| **16** | Cyclohexyl | $C_{13}H_{15}N_3O_2$ | 110–111 | Lit.[18] (110–111) | 93.2 |
| **17** | Benzyl | $C_{14}H_{11}N_3O_2$ | 130 | Lit.[19] (128) | 52.6 |
| | |  | | | |
| **18** | –H | $C_7H_7N_3$ | 115 | Lit.[20] (114–116) | 94 |
| **19** | $-CH_2CH_3$ | $C_9H_{11}N_3$ | 129 | | 85.5 |
| **20** | $-CH_2CH_2CH_3$ | $C_{10}H_{13}N_3$ | 115–116 | Lit.[2] (115–116) | 95.6 |
| **21** | $-CH_2CH_2CH_2CH_3$ | $C_{11}H_{15}N_3$ | 102–103 | | 90.9 |
| **22** | $-CH_2CH_2CH_2Cl$ | $C_{10}H_{12}ClN_3$ | 115 | | 91 |
| **23** | $-CH_2CH_2OH$ | $C_9H_{11}N_3O$ | 132–133 | | 89.5 |
| **24** | $-CH(CH_3)_2$ | $C_{10}H_{13}N_3$ | 97–98 | Lit.[2] (97–98) | 95 |
| **25** | $-CH_2CH_2CH(CH_3)_2$ | $C_{12}H_{17}N_3$ | 99–100 | | 91.7 |
| **26** | Cyclohexyl | $C_{13}H_{17}N_3$ | 143–144 | | 89.3 |
| **27** | Benzyl | $C_{14}H_{13}N_3$ | 128 | | 85.7 |




**Scheme 3.** Reagents: (a) *n*-propyl bromide/NaH/DMF.




**Scheme 4.** Reagents: (a) *N*-chlorosuccinimide; (b) $NaNO_2$/HCl–$Cu_2O$/$NaNO_2$; (c) propylamine; (d) $H_2$, Pd/C; (e) $Na_2S_2O_5$ adduct of the *p*-fluorobenzaldehydes/DMF.

the cyano substituted compounds exhibited the greatest antifungal activity, a number of analogues, **44**–**67** were made with this substituent at C-5 or C-6. Compounds with *n*-butyl, *n*-propyl and 3-chloropropyl at the $N^1$ position exhibited the best results. Little or no activity was found for the non $N^1$-substituted derivatives **44**–**49**. Substitution on the 2-phenyl group of this system plays a role in the antifungal activity. Many of the substitutions on the phenyl ring result in lowering of the antifungal activity. However, fluoro substituents are tolerated (cf., **53** to **52**), although, they do not significantly enhance the activity. Multiple fluoro substitutions result in lowering of the activity (cf., **59** and **60** to **53**). There are striking differences in antifungal activity with the location of the cyano group at position C-5 or C-6. The 1,5-isomer, compound **53**, has potent antifungal activity against *C. albicans*, whereas the 1,6-isomeric analogue **54** shows little antifungal activity. In contrast, compound **54** has better activity against *C. glabrata* than **53**.

## Conclusion

This work demonstrates that compounds **52**–**54**, **57**, **58** and **61** having butyl or propyl at N-1, phenyl or *p*-fluorophenyl rings at C-2 and cyano at C-5 or C-6 show similiar activity with fluconazole against *Candida* species in vitro. In vivo studies of compound **58** and its mechanism of action are in progress.

## Experimental

Melting points were measured with a capillary melting point apparatus (Buchi SMP and Buchi 9100) and are uncorrected. $^1$H NMR were recorded on a Varian GX400 spectrometer (Atlanta) in DMSO-$d_6$, chemical shifts (δ) are in ppm relative to TMS, and coupling constants (*J*) are reported in Hertz. Mass spectra were taken on Micromass UK. Platform II LC-Ms spectrometers by using EI (62 or 70 eV) were performed by TUBITAK (Instrumental Analyse Lab., Ankara, Turkey) and Georgia Institute of Technology (Atlanta, GA, USA) by using ESI. Microanalyses were performed by Atlantic Microlab Inc, (Norcross, Atlanta, GA, USA). Column chromatography was accomplished on silica gel 60 (40–63 μm particle size) (Merck). Compound **5**,[10] **6**,[2] **7**,[10] **8**[2] were prepared according to the literature methods.

***N*-Propyl-2-amino-4-methylaniline (1).** Mixture of 4-chloro-3-nitrotoluene (5 mL) and propylamine (30 mL) were heated in sealed tube at 100 °C, for 10 h. Excess of propylamine was removed and 4-methyl-2-nitro-*N*-propylaniline was obtained as red-coloured oily residue. The spectral data were consistent with literature.[11] The oily residue was dissolved in EtOH (40 mL), and the solution hydrogenated using 10% Pd/C as a catalyst at room temperature at 35 psi. The reaction was stopped after cessation of $H_2$ uptake. The catalyst was filtered through a bed of Celite, washed with EtOH, and concentrated to provide **1** as a dark brown-coloured oil, which was used in subsequent steps without purification.

### Synthesis of (2, 34, 35, 40, 41, 43–48, 50–62, 64–67)

Appropriate benzaldehydes (15 mmol) were dissolved in 50 mL EtOH and sodium metabisulfite (1.6 g) in 10 mL water was added in portions. The reaction mixture was stirred vigorously and more EtOH was added. The mixture was kept in a refrigerator for a several hours. The precipitate was filtered and dried (yield over 90%). The mixture of these salts (2 mmol) and appropriate 1,2-phenylenediamines in DMF (5 mL) were heated at 130 °C for 4 h. The reaction mixture was cooled, poured into the water, and the solid was filtered. Purification procedure and some spectral findings of the synthesized compounds are given in Table 1. Mp of **2** 255–256 °C. Lit.[14] 258 °C.

**3-Amino-4-propylaminobenzoic acid (3).** 3-Nitro-4-propylaminobenzoic acid[15] (8.91 mmol) was dissolved in EtOH (40 mL), and the solution hydrogenated at room temperature at 35 psi catalytic amount of 10% Pd/C. The reaction was stopped after cessation of $H_2$ uptake. The reaction mixture was filtered through a bed of Celite, washed with EtOH, and the product concentrated to provide dark violet-coloured powder, which was used in subsequent steps without purification, mp 140 °C.

**Methyl 3-amino-4-butylaminobenzoic acid (4).** Mixture of methyl 4-chloro-3-nitrobenzoic acid[16] (2 g, 9 mmol) and butylamine (3 g, 41 mmol) in DMF (5 mL) were heated on the water bath for 3 h. The mixture was allowed to cool, the resultant yellow precipitate was filtered and washed with water. Crystallisation of the crude product from EtOH–$H_2O$ gave methyl 4-butylamino-3-nitrobenzoic acid,[21] mp 50–51 °C, yield 55%, $C_{12}H_{16}N_2O_4$. Reduction of this ester (1.5 g, 6 mmol) in similar manner with **3** gave **4** as violet colour, mp 95–97 °C, yield 95%, $C_{12}H_{18}N_2O_2$.

**Synthesis of (9–17).** To a solution of 4-chloro-3-nitrobenzonitrile (2 g, 10.98 mmol) in DMF (3 mL), an appropriate amine (41 mmol) was added on ice bath. After being warmed to rt, the reaction mixture was heated on a water bath until the starting material was consumed (determined by TLC, 1–3 h). The mixture was cooled to ice bath (0–4 °C) and water was added. The resultant yellow precipitate was filtered, washed with water, crystallised from EtOH. For the synthesis of **12**, 3-chloropropylamine HCl (1.42 g, 10.98 mmol) and anhydrous $K_2CO_3$ (1.5 g, 10.98 mmol) was used, crude product was crystallised from $CHCl_3$–EtOH (20:80).

The melting points and yields for these compounds are listed in Table 3.

**Synthesis of (18–27).** Appropriate nitro derivatives (8 mmol) in EtOH (75 mL) were reduced by hydrogenation using 40 psi of $H_2$ and 10% Pd/C (200 mg) until cessation of $H_2$ uptake. The catalyst was filtered off on a bed of Celite, washed with EtOH, and the filtrate was concentrated. The crude diamines were used directly without purification. The melting points and yields for these compounds are listed in Table 3.

**4-Nitro-3-propylaminobenzonitrile (30).** To a solution of compound **29**[8] (0.3 g, 1.65 mmol) in DMF (1 mL), propylamine (7 mmol) was added on ice bath. After being warmed to rt, the reaction mixture was heated on a water bath for 2 h until the starting material was consumed. The mixture was cooled to ice bath (0–4 °C) and water was added. The resultant yellow precipitate was filtered, washed with water, crystallised from EtOH, mp 105 °C, yield 85%, IR ν (CN) 2235 $cm^{-1}$.

**4-Amino-3-propylaminobenzonitrile (31).** Compound **30** (0.3 g, 8 mmol) in EtOH (75 mL) was reduced by hydrogenation using 40 psi of $H_2$ and 10% Pd/C (40 mg) until cessation of $H_2$ uptake. The catalyst was filtered off on a bed of Celite, washed with EtOH, and the filtrate was concentrated in vacuo. The crude amine was crystallised from EtOH–$H_2O$ as white-coloured compound, mp, 113 °C, yield 90%, IR ν 2216 (CN) $cm^{-1}$.

**Synthesis of 32 and 33.** A mixture of **2** (0.5 g, 2.36 mmol), *n*-propylbromide or allyl bromide (2.45 mmol) and NaH (90%) (0.13 g) in DMF (5 mL) was stirred at 60 °C for 5 h. The reaction mixture was poured into water and extracted with EtOAc. The extract was washed with water, dried over $Na_2SO_4$ and concentrated in vacuo.

**Ethyl 1-propyl-2-phenyl-1H-benzimidazol-5-carboxylate (36).** Compound **35** (0.2 g, 0.71 mmol) in $SOCl_2$ (15 mL) was heated at reflux for 2 h at 80 °C. The excess of $SOCl_2$ was evaporated completely, and the residue was dissolved in EtOH (10 mL), heated for 1 h, and EtOH was evaporated.

***N*-Isopropyl 1-propyl-2-phenyl-1H-benzimidazol-5-carboxamide (37).** Compound **35** (0.2 g, 0.71 mmol) in $SOCl_2$ (15 mL) was heated under reflux for 2 h at 80 °C. Excess of $SOCl_2$ was evaporated, and the residue was dissolved in $CH_2Cl_2$ (10 mL). Isopropylamine (0.8 mL) was added, and the mixture was heated at reflux for 1 h, then EtOH was evaporated.

**1-Butyl-2-(4-fluorophenyl)-1H-benzimidazol-5-carboxylic acid (38).** Compound **4** and the $Na_2S_2O_5$ salt of *p*-fluorobenzaldehyde were allowed to react in a similar manner as **2.** After 4 h, the reaction mixture was made alkaline with 5% NaOH (10 mL) solution and heated on a water bath for 1 h, then the reaction mixture was acidified with acetic acid, and the product precipitated.

**1-Butyl-2-(4-fluorophenyl)-1H-benzimidazol-5-carboxamide (39). 39** was prepared in similar manner as **37,** from **38** (0.2 g, 0.64 mmol) and 5 mL of $NH_4OH$ (25%) as a colourless powder.

**1-Butyl-2-(phenyl)-1H-benzimidazol-5-carboxaldehyde (42).** To solution of **57** (0.3 g, 1.02 mmol) in dry $CH_2Cl_2$ (20 mL), 3 mL of DIBAL (1.0 M solution in $CH_2Cl_2$) was added, and the mixture was heated at reflux for 3 h under nitrogen atmosphere. Cool dilute $H_2SO_4$ acid (15 mL) was added and stirred overnight. $CH_2Cl_2$ was removed, and the residue was neutralised with dilute $Na_2CO_3$ solution and extracted with EtOAc.

**5-Cyano-2-(4-fluorophenyl)-1-(2-methoxyethyl)-1H-benzimidazole (63).** A mixture of **62** (0.28 g, 1 mmol), iodomethane (0.213 g, 1.5 mmol) and NaH (90%) (0.1 g) in DMF (4 mL) was stirred at rt, for 2 h. The reaction mixture was poured into water, the precipitate was filtered and washed with water.

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