Synthesis S. Kurhade et al. Paper

Facile Synthesis of *N*-Substituted Benzimidazoles

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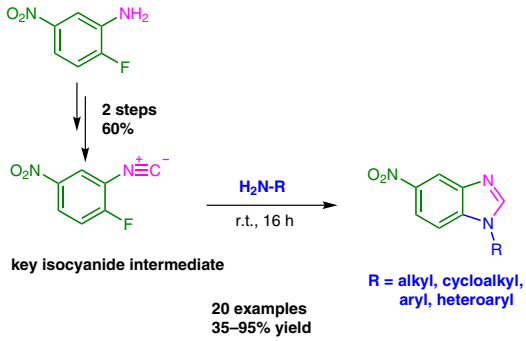

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Abstract A particularly mild and efficient one-pot synthesis of *N*-substituted benzimidazole derivatives was developed. 2-Fluoro-5-nitrophenylisocyanide reacts with a diverse set of primary amines to afford the respective products in moderate to very good yield (35–95%; 20 examples).

Key words isocyanides, nucleophilic aromatic substitution, benzimidazole

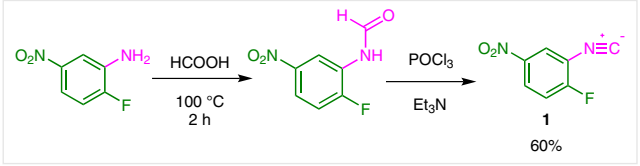
The benzimidazole core is of eminent importance particularly in the field of medicinal chemistry and, based on its wide range of biological activities, has been classified as a 'privileged' structure.[1] Benzimidazole also occurs naturally in *N*-ribosyl-dimethylbenzimidazole, which serves as an axial ligand for cobalt in vitamin B_{12}.[2] Synthetic analogues have been prescribed as anthelmintic, anti-inflammatory, analgesic, anticancer, and vasodilator drugs.[3] The classical benzimidazole synthesis involves the condensation of an *ortho*-phenylene diamine with a carboxylic acid or an acylating agent, normally under rather drastic dehydrating conditions.[4] As a side product, 2-substituted benzimidazoles are often formed under these conditions. *N*-Substituted benzimidazoles are synthesized either by base-mediated direct alkylation of benzimidazoles with alkyl/aryl halides or starting from *N*-substituted nitroanilines, which were reduced and cyclized with orthoformates.[5]

An isocyanide-based copper-catalyzed benzimidazole synthesis has been reported by Lygin and de Meijere. Here the primary amines add onto an isocyano group of *o*-bromoaryl isocyanide, followed by an intramolecular arylation of the amidine intermediate to give *N*-substituted benzimidazoles.[6] Often these kinds of copper-catalyzed reactions are ligand-specific, require high temperature, show limited functional group tolerance, and need to be handled very carefully because they are highly air sensitive. Recently, Boratyński et al. reported the synthesis of new chiral monobenzimidazoles from the reaction between enantiomeric *trans*-1,2-diaminocyclohexane and 2-fluoronitrobenzene in 3–4 steps.[7]

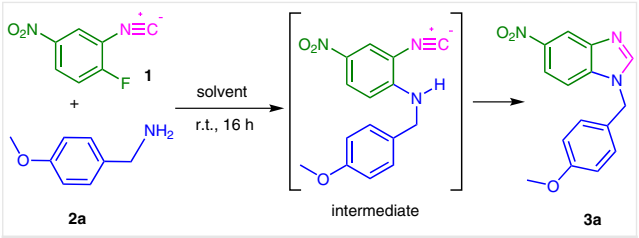
As our group works extensively on isocyanide-based chemistry, we hypothesized that the issues described above could be addressed by using *o*-fluorophenyl isocyanide instead of *o*-bromophenyl isocyanide and by placing an electron-withdrawing functional group such as nitro or cyano in the ring (especially *para* to fluoro) in *o*-fluorophenylisocyanide, capable of undergoing aromatic nucleophilic substitution.

Thus, we developed a very simple, room-temperature, one-pot operation to synthesize *N*-substituted benzimidazoles from the reaction between 2-fluoro-5-nitrophenylisocyanide (**1**) and a diverse set of primary amines **2**. The proposed mechanism involves an aromatic nucleophilic displacement of fluorine by the primary amine **2** followed by an intramolecular cyclization.

To test this idea, we had to synthesize **1**, which was expected to be capable of undergoing subsequent nucleophilic aromatic substitution reactions. Thus, starting from 2-fluoro-5-nitroaniline, we synthesized the corresponding isocyanide according to Ugi in the classical sequence formylation and dehydration in 60% overall yield (Scheme 1).

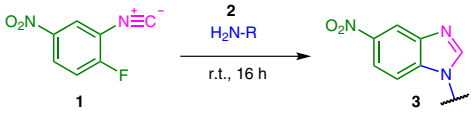


Scheme 1 Synthesis of 2-fluoro-5-nitrophenylisocyanide (**1**)[8]



Scheme 2 Typical synthesis of **3a**

Table 1 Synthesis of Benzimidazole Derivatives **3**



NH_2R **2**	Product **3**	Yield (%)[a]
2a	**3a**	91
2b	**3b**	90
2c	**3c**	95
2d	**3d**	90
2e	**3e**	90
2f	**3f**	80
2g	**3g**	75
2h	**3h**	35
2i	**3i**	65[b]

Table 1 (continued)

NH_2R **2**	Product **3**	Yield (%)[a]
2j	**3j**	75
2k	**3k**	78
2l	**3l**	80
2m	**3m**	80
2n	**3n**	62
2o	**3o**	80
2p	**3p**	60
2q	**3q**	52[c]
2r	**3r**	60[c]

[a] Isolated yield.
[b] Reaction conducted with 4-fluroaniline (3.0 equiv) without solvent.
[c] General Procedure B was followed.

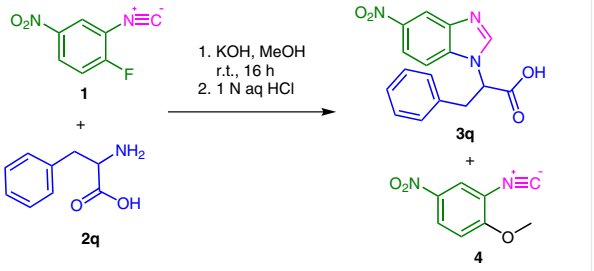
The reaction of **1** and 4-methoxybenzylamine (**2a**) in the presence of triethylamine as base was chosen as a model system for the optimization of the reaction conditions. The reaction worked well at room temperature in 14–18 hours in solvents such as CH_2Cl_2, tetrahydrofuran (THF), and MeOH. However, the highest yield of **3a** (91%) was achieved with CH_2Cl_2 (Scheme 2). With the optimized conditions for **3a** in hand, a range of *N*-substituted benzimidazoles **3b**–**r** was synthesized from isocyanide **1** and a diverse set of primary amines **2b**–**r** (Table 1). In general, all amines

worked well except guanidine and *N*-Cbz-guanidine, which failed to produce the desired product. Clearly, guanidine, with its extensive delocalized charge and strong π-character, is not expected to act like a classical amine.

Electron-rich benzyl amine **2c**, along with *n*-alkyl amines **2b**, **2d**, and **2e**, gave the highest yields of benzimidazole **3**, exceeding those obtained with cycloalkyl amines **2f** and **2g**. The lowest yield was observed with **3h** (35%) using adamantyl amine **2h**, potentially because of the steric hindrance of the bulky adamantane group. Comparatively less nucleophilic 4-fluoroaniline (**2i**) was also found to be suitable for this conversion, furnishing the corresponding benzimidazole **3i** (65%) in slightly lower yield. Heterocyclic amines such as 2-thiophene, 3-pyridine, and indole also worked well to produce the corresponding benzimidazoles in generally very good yields.

After very good results from first set of straightforward amines **2a**–**l**, we investigated the functional group tolerance of the reaction. Gratifyingly, the method works well even in presence of alcohol-containing amines **2m**, unprotected diamines for example 1,3-diaminopropane (**2n**) (previously we used mono-Boc-protected diamine **2d**) as well as highly reactive bromoalkylamine **2o**, producing the corresponding benzimidazole **3n** and **3o**, respectively, in good yields. This methodology also worked well with protected amino acids such as methyl tryptophan **2p** to produce potentially useful benzimidazole **3p** in 60% yield.

Interestingly, when we subjected *N*- and *C*-unprotected amino acids DL-phenylalanine **2q** and DL-leucine **2r**, the expected products were formed (Scheme 3). In these cases, we switched to an aqueous solvent and KOH as a base to render the zwitterionic amine of the amino acid more nucleophilic. The products **3q** (52%) and **3r** (60%) were formed in moderate yield along with methoxy substituted nitrophenylisocyanide **4** (20%).



Scheme 3 Synthesis of **3q** from DL-phenylalanine

In conclusion, we have developed a very simple, mild, and unprecedented one-pot benzimidazole synthesis that proceeds in moderate to excellent yields. The methodology offers excellent substrate generality and also demonstrates tolerance towards a range of reactive functional groups. Furthermore, the nitro group in the products **3** offers an additional handle for further derivatization, for example through reduction.

NMR spectra were recorded with a Bruker Avance 500 spectrometer [^{1}H NMR (500 MHz), ^{13}C NMR (126 MHz)]. Chemical shifts for ^{1}H NMR signals are reported as δ values and coupling constants are given in hertz (Hz). The following abbreviations were used for spin multiplicity: s = singlet, d = doublet, t = triplet, dd = double doublet, m = multiplet, br s = broad singlet. Chemical shifts for ^{13}C NMR signals are reported in ppm relative to the solvent peak. Thin-layer chromatography was performed with Fluka precoated silica gel plates (0.20 mm thick, particle size 25 µm). Flash chromatography was performed with a Teledyne ISCO Combiflash Rf, using RediSep Rf Normal-phase Silica Flash Columns (silica gel 60 Å, 230–400 mesh). Reagents were available from commercial suppliers and used without any purification unless otherwise noted. Other reagents were purchased from Sigma Aldrich, ABCR, Acros and AK Scientific and were used without further purification. Electrospray ionization mass spectra (ESI-MS) were recorded with a Waters Investigator Semi-prep 15 SFC-MS instrument.

General Procedure A

To a stirred solution of amine (0.66 mmol) in CH_2Cl_2 (1 mL) were added successively Et_3N (0.66 mmol) and 2-fluoro-5-nitrophenylisocyanide (0.60 mmol). The resulting mixture was stirred at r.t. for 16 h. The solvent was removed under reduced pressure and the residue was purified by using flash chromatography to obtain the product. Note: In the case of amine hydrochloride/hydrobromide salts, Et_3N (1.32 mmol) was used.

General Procedure B

To a suspension of amino acid (0.66 mmol) in MeOH (2 mL), KOH (0.66 mmol) was added and the mixture was stirred at r.t. until complete solubilization of the compound. Then 2-fluoro-5-nitrophenylisocyanide (0.60 mmol) was added and the resulting mixture was stirred at r.t. for 16 h. The solvent was removed under reduced pressure and the residue was suspended in H_2O (3 mL) and acidified to pH ~5 with 1 N aq HCl. The solid precipitate was collected by filtration and dried under vacuo to obtain the product.

1-(4-Methoxybenzyl)-5-nitro-1*H*-benzo[*d*]imidazole (3a)

Obtained by using General Procedure A.

Yield: 0.155 g (91%); off-white solid; mp 137–138 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.73 (d, *J* = 2.0 Hz, 1 H), 8.19 (dd, *J* = 8.9, 2.1 Hz, 1 H), 8.09 (s, 1 H), 7.36 (d, *J* = 8.9 Hz, 1 H), 7.15 (d, *J* = 8.6 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 5.34 (s, 2 H), 3.80 (s, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 160.02, 146.55, 143.86, 143.53, 138.07, 128.88, 126.22, 118.91, 117.26, 114.77, 110.26, 55.45, 49.13.

MS (ESI): *m*/*z* calcd for $C_{15}H_{13}N_3O_3$: 283.10 $[M]^+$; found: 282.28 $[M - H]^+$.

5-Nitro-1-(prop-2-yn-1-yl)-1*H*-benzo[*d*]imidazole (3b)

Obtained by using General Procedure A

Yield: 0.109 g (90%); brown solid; mp 120–121 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.74 (d, *J* = 2.1 Hz, 1 H), 8.29 (dd, *J* = 8.9, 2.1 Hz, 1 H), 8.21 (s, 1 H), 7.58 (d, *J* = 8.9 Hz, 1 H), 5.01 (d, *J* = 2.6 Hz, 2 H), 2.58 (t, *J* = 2.6 Hz, 1 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 145.78, 144.15, 143.46, 137.49, 119.19, 117.38, 110.05, 76.06, 75.06, 35.32.

MS (ESI): *m*/*z* calcd for $C_{10}H_6N_3O_2$: 201.05 $[M]^+$; found: 202.15 $[M + H]^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for [$C_{10}H_7N_3O_2$ + H]$^+$: 202.0611; found: 202.0611.

1-(2,4-Dimethoxybenzyl)-5-nitro-1*H*-benzoimidazole (3c)

Obtained by using General Procedure A.

Yield: 0.179 g (95%); white solid; mp 156–157 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.69 (d, *J* = 1.9 Hz, 1 H), 8.20 (dd, *J* = 8.9, 2.0 Hz, 1 H), 8.11 (s, 1 H), 7.49 (d, *J* = 9.0 Hz, 1 H), 7.13 (d, *J* = 9.0 Hz, 1 H), 6.50–6.42 (m, 2 H), 5.29 (s, 2 H), 3.80 (s, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.76, 158.58, 147.13, 143.56, 143.19, 138.18, 130.58, 118.59, 116.99, 115.08, 110.17, 104.51, 99.00, 55.52, 55.51, 44.79.

MS (ESI): *m*/*z* calcd for $C_{16}H_{15}N_3O_4$: 313.11 [M]$^+$; found: 336.17 [M + Na]$^+$.

***tert*-Butyl [3-(5-Nitro-1*H*-benzo[*d*]imidazol-1-yl)propyl] Carbamate (3d)**

Obtained by using General Procedure A.

Yield: 0.173 g (90%); brown solid; mp 131–132 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.68 (d, *J* = 2.1 Hz, 1 H), 8.24–8.14 (m, 2 H), 7.45 (d, *J* = 8.9 Hz, 1 H), 4.86 (br s, 1 H), 4.30 (t, *J* = 7.0 Hz, 2 H), 3.19 (q, *J* = 6.5 Hz, 2 H), 2.10 (hept, *J* = 6.5 Hz, 2 H), 1.43 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.33, 146.74, 143.78, 143.33, 137.93, 118.84, 117.28, 109.69, 43.05, 37.75, 30.69, 28.45.

MS (ESI): *m*/*z* calcd for $C_{15}H_{20}N_4O_4$: 320.14 [M]$^+$; found: 321.24 [M + H]$^+$, 343.29 [M + Na]$^+$.

***tert*-Butyl (2-{[2-(5-Nitro-1*H*-benzo[*d*]imidazol-1-yl)ethyl]thio}ethyl) Carbamate (3e)**

Obtained by using General Procedure A.

Yield: 0.198 g (90%); brown solid; mp 120–122 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.74 (d, *J* = 2.2 Hz, 1 H), 8.27 (dd, *J* = 8.9, 2.2 Hz, 1 H), 8.18 (s, 1 H), 7.56 (d, *J* = 9.0 Hz, 1 H), 4.81 (s, 1 H), 4.47 (t, *J* = 6.8 Hz, 2 H), 3.27 (q, *J* = 6.3 Hz, 2 H), 3.02 (t, *J* = 6.8 Hz, 2 H), 2.59 (t, *J* = 6.9 Hz, 2 H), 1.44 (s, 9 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 155.96, 146.69, 143.91, 143.25, 137.77, 119.02, 117.35, 109.76, 45.42, 40.05, 32.36, 31.65, 28.50, 28.47.

MS (ESI): *m*/*z* calcd for $C_{16}H_{22}N_4O_4S$: 366.13 [M]$^+$; found: 311.03 [M – *t*-Bu]$^+$, 367.29 [M + H]$^+$.

(*S*)-1-(8-Methoxy-1,2,3,4-tetrahydronaphthalen-2-yl)-5-nitro-1*H*-benzo[*d*]imidazole (3f)

Obtained by using General Procedure A.

Yield: 0.155 g (80%); brown solid; mp 175–176 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.75 (d, *J* = 2.2 Hz, 1 H), 8.26 (dd, *J* = 9.0, 2.2 Hz, 1 H), 8.12 (s, 1 H), 7.53 (d, *J* = 8.9 Hz, 1 H), 7.21 (t, *J* = 7.9 Hz, 1 H), 6.80 (d, *J* = 7.8 Hz, 1 H), 6.75 (d, *J* = 8.2 Hz, 1 H), 4.86–4.73 (m, 1 H), 3.82 (s, 3 H), 3.46 (dd, *J* = 17.4, 5.7 Hz, 1 H), 3.05 (ddd, *J* = 16.9, 13.8, 8.1 Hz, 2 H), 2.93 (dt, *J* = 17.2, 5.1 Hz, 1 H), 2.38 (td, *J* = 7.8, 5.1 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.23, 144.32, 143.75, 143.32, 137.67, 135.96, 127.47, 121.74, 121.07, 118.66, 117.30, 110.15, 107.60, 55.38, 52.80, 29.99, 28.63, 27.99.

MS (ESI): *m*/*z* calcd for $C_{18}H_{17}N_3O_3$: 323.12 [M]$^+$; found: 324.20 [M + H]$^+$.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for [$C_{18}H_{17}N_3O_3$ + H]$^+$: 324.1342; found: 324.1341.

1-(1-Benzylpiperidin-4-yl)-5-nitro-1*H*-benzo[*d*]imidazole (3g)

Obtained by using General Procedure A.

Yield: 0.151 g (75%); brown solid; mp 162–163 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.73 (d, *J* = 2.1 Hz, 1 H), 8.24 (dd, *J* = 9.0, 2.2 Hz, 1 H), 8.18 (s, 1 H), 7.51 (d, *J* = 9.0 Hz, 1 H), 7.37–7.34 (m, 4 H), 7.32–7.27 (m, 1 H), 4.26 (hept, *J* = 10.4, 5.1 Hz, 1 H), 3.61 (s, 2 H), 3.14–3.10 (m, 2 H), 2.29–2.19 (m, 3 H), 2.19–2.13 (m, 3 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 145.89, 142.68, 142.48, 138.21, 137.75, 128.85, 128.14, 126.93, 117.73, 115.68, 111.38, 61.81, 53.37, 51.93, 31.63.

MS (ESI): *m*/*z* calcd for $C_{19}H_{20}N_4O_2$: 336.16 [M]$^+$; found: 337.24 [M + H]$^+$, 335.03 [M – H]$^+$.

1-(Adamantan-1-yl)-5-nitro-1*H*-1,3-benzodiazole (3h)

Obtained by using General Procedure A.

Yield: 0.062 g (35%); brown solid; mp 198 °C (decomp.).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 2.3 Hz, 1 H), 8.22 (s, 1 H), 8.17 (dd, *J* = 9.1, 2.3 Hz, 1 H), 7.77 (d, *J* = 9.1 Hz, 1 H), 2.40–2.36 (m, *J* = 2.7 Hz, 9 H), 1.91–1.83 (m, 6 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 144.68, 143.67, 143.22, 136.85, 117.70, 117.36, 113.47, 58.36, 42.23, 36.07, 29.61.

MS (ESI): *m*/*z* calcd for $C_{17}H_{19}N_3O_2$: 297.15 [M]$^+$; found: 298.11 [M + H]$^+$.

1-(4-Fluorophenyl)-5-nitro-1*H*-benzo[*d*]imidazole (3i)

Obtained from **1** (0.6 mmol), Et_3N (0.66 mmol), and 4-fluroaniline (3.0 mmol) without solvent.

Yield: 0.100 g (65%); white solid; mp 228–229 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.81 (d, *J* = 2.2 Hz, 1 H), 8.28 (dd, *J* = 9.0, 2.1 Hz, 1 H), 8.24 (s, 1 H), 7.56–7.47 (m, 3 H), 7.37–7.30 (m, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 161.67 (d, *J* = 246.4 Hz), 147.57, 143.08 (d, *J* = 45.4 Hz), 137.71, 131.40 (d, *J* = 2.7 Hz), 126.82 (d, *J* = 7.4 Hz), 119.03, 117.01 (d, *J* = 23.0 Hz), 116.91, 116.07, 111.37 (d, *J* = 4.8 Hz).

MS (ESI): *m*/*z* calcd for $C_{13}H_8FN_3O_2$: 257.06 [M]$^+$; found: 258.04 [M + H]$^+$.

5-Nitro-1-(thiophen-2-ylmethyl)-1*H*-benzo[*d*]imidazole (3j)

Obtained by using General Procedure A.

Yield: 0.117 g (75%); white solid; mp 120–121 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.73 (d, *J* = 2.2 Hz, 1 H), 8.24 (dd, *J* = 8.9, 2.1 Hz, 1 H), 8.14 (s, 1 H), 7.47 (d, *J* = 9.0 Hz, 1 H), 7.33 (dd, *J* = 5.1, 1.2 Hz, 1 H), 7.07 (dd, *J* = 3.6, 1.1 Hz, 1 H), 7.01 (dd, *J* = 5.1, 3.5 Hz, 1 H), 5.59 (d, *J* = 0.8 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.12, 143.92, 143.41, 137.70, 136.51, 127.55, 127.52, 126.91, 119.03, 117.29, 110.06, 44.27.

MS (ESI): *m*/*z* calcd for $C_{12}H_9N_3O_2S$: 259.04 [M]$^+$; found: 260.18 [M + H]$^+$.

5-Nitro-1-(pyridin-3-ylmethyl)-1*H*-benzo[*d*]imidazole (3k)

Obtained by using General Procedure A.

Yield: 0.119 g (78%); brown solid; mp 146–147 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.74 (d, *J* = 2.2 Hz, 1 H), 8.64–8.60 (m, 2 H), 8.21 (dd, *J* = 8.9, 2.1 Hz, 1 H), 8.15 (s, 1 H), 7.44 (dt, *J* = 8.0, 2.1 Hz, 1 H), 7.35 (d, *J* = 8.9 Hz, 1 H), 7.31 (dd, *J* = 7.9, 4.8 Hz, 1 H), 5.46 (s, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 150.46, 148.68, 146.37, 144.09, 143.50, 137.74, 134.77, 130.26, 124.18, 119.28, 117.48, 109.99, 47.01.

MS (ESI): *m*/*z* calcd for $C_{13}H_{10}N_4O_2$: 254.08 $[M]^+$; found: 255.20 $[M + H]^+$, 253.00 $[M - H]^+$.

1-[2-(1*H*-Indol-3-yl)ethyl)-5-nitro-1*H*-benzo[*d*]imidazole (3l)

Obtained by using General Procedure A.

Yield: 0.147 g (80%); brown solid; mp 241–242 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.84 (s, 1 H), 8.52 (d, *J* = 2.2 Hz, 1 H), 8.41 (s, 1 H), 8.14 (dd, *J* = 9.0, 2.2 Hz, 1 H), 7.79 (d, *J* = 9.0 Hz, 1 H), 7.52 (d, *J* = 8.0 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.07 (ddd, *J* = 8.0, 6.9, 1.2 Hz, 1 H), 7.03 (d, *J* = 2.4 Hz, 1 H), 6.97 (td, *J* = 7.4, 6.9, 1.0 Hz, 1 H), 4.63 (t, *J* = 7.2 Hz, 2 H), 3.27 (t, *J* = 7.1 Hz, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 148.18 (d), 142.57, 142.44, 138.30, 136.13, 126.87, 123.35, 121.07, 118.42, 118.12, 117.74, 115.62 (d), 111.42, 111.08, 110.06, 45.41, 25.48.

MS (ESI): *m*/*z* calcd for $C_{17}H_{14}N_4O_2$: 306.11 $[M]^+$; found: 307.12 $[M + H]^+$, 305.04 $[M - H]^+$.

3-(5-Nitro-1*H*-benzo[*d*]imidazol-1-yl)-3-phenylpropan-1-ol (3m)

Obtained by using General Procedure A.

Yield: 0.143 g (80%); brown solid; mp 133–135 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.96 (s, 1 H), 8.54 (d, *J* = 2.2 Hz, 1 H), 8.12 (dd, *J* = 9.0, 2.2 Hz, 1 H), 7.82 (d, *J* = 9.0 Hz, 1 H), 7.50–7.44 (m, 2 H), 7.39–7.32 (m, 2 H), 7.32–7.25 (m, 1 H), 5.93 (dd, *J* = 9.0, 6.6 Hz, 1 H), 4.77 (t, *J* = 4.8 Hz, 1 H), 3.46–3.37 (m, 1 H), 3.35–3.26 (m, 2 H), 2.69 (ddt, *J* = 14.3, 9.0, 5.5 Hz, 1 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 146.52, 142.86, 142.62, 139.73, 137.95, 128.85, 128.09, 126.77, 118.02, 115.75, 111.56, 57.07, 56.28, 36.50.

MS (ESI): *m*/*z* calcd for $C_{16}H_{15}N_3O_3$: 297.11 $[M]^+$; found: 298.17 $[M + H]^+$, 295.84 $[M - H]^+$.

3-(5-Nitro-1*H*-benzo[*d*]imidazol-1-yl)propan-1-amine (3n)

Obtained by using General Procedure A.

Yield: 0.116 g (62%); yellow solid; mp 90 °C (decomp.).

^{1}H NMR (500 MHz, MeOD): δ = 8.54 (d, *J* = 2.1 Hz, 1 H), 8.47 (s, 1 H), 8.24 (dd, *J* = 9.0, 2.2 Hz, 1 H), 7.80 (d, *J* = 9.0 Hz, 1 H), 4.46 (t, *J* = 7.3 Hz, 2 H), 2.81 (t, *J* = 7.4 Hz, 2 H), 2.15 (quint, *J* = 7.3 Hz, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6 + MeOD): δ = 148.60, 143.16, 142.94, 138.65, 118.29, 116.05, 111.44, 42.66, 37.94, 31.85.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{10}H_{12}N_4O_2 + H]^+$: 221.1033; found: 221.1033.

1-(3-Bromopropyl)-5-nitro-1*H*-benzo[*d*]imidazole (3o)

Obtained by using General Procedure A.

Yield: 0.136 g (80%); pale-yellow solid; mp 106–107 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.74 (d, *J* = 2.2 Hz, 1 H), 8.27 (dd, *J* = 8.9, 2.2 Hz, 1 H), 8.14 (s, 1 H), 7.53 (d, *J* = 8.9 Hz, 1 H), 4.49 (t, *J* = 6.6 Hz, 2 H), 3.35 (t, *J* = 5.8 Hz, 2 H), 2.43 (dt, *J* = 6.6, 5.6 Hz, 2 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 146.54, 143.94, 143.31, 137.83, 119.06, 117.39, 109.72, 43.28, 32.14, 29.32.

MS (ESI): *m*/*z* calcd for $C_{10}H_{10}BrN_3O_2$: 283.0 $[M(^{79}Br) + H]^+$, 285.0 $[M(^{81}Br) + H]^+$; found: 284.06 $[M(^{79}Br) + H]^+$, 286.01 $[M(^{81}Br) + H]^+$.

Methyl 3-(1*H*-Indol-3-yl)-2-(5-nitro-1*H*-benzo[*d*]imidazol-1-yl)propanoate (3p)

Obtained by using General Procedure A.

Yield: 0.130 g (60%); brown solid; mp 179–180 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.75 (br s, 1 H), 8.60 (s, 1 H), 8.46 (d, *J* = 2.2 Hz, 1 H), 8.09 (dd, *J* = 9.0, 2.2 Hz, 1 H), 7.78 (d, *J* = 9.0 Hz, 1 H), 7.51 (d, *J* = 7.9 Hz, 1 H), 7.23 (d, *J* = 8.1 Hz, 1 H), 7.03–6.99 (m, 1 H), 6.95–6.91 (m, 1 H), 6.89 (d, *J* = 2.4 Hz, 1 H), 5.99 (dd, *J* = 10.4, 5.4 Hz, 1 H), 3.82–3.71 (m, 5 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 169.74, 147.59, 142.79, 142.14, 138.30, 135.89, 126.65, 123.82, 121.13, 118.59, 118.07, 117.93, 115.67, 115.64, 111.45, 108.17, 58.43, 52.97, 26.78.

MS (ESI): *m*/*z* calcd for $C_{19}H_{16}N_4O_4$: 364.12 $[M]^+$; found: 365.15 $[M + H]^+$, 363.26 $[M - H]^+$.

2-(5-Nitro-1*H*-benzo[*d*]imidazol-1-yl)-3-phenylpropanoic Acid (3q)

Obtained by using General Procedure B.

Yield: 0.097 g (52%); brown solid; mp 213–214 °C.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.60 (s, 1 H), 8.46 (d, *J* = 2.3 Hz, 1 H), 8.11 (dd, *J* = 9.0, 2.2 Hz, 1 H), 7.80 (d, *J* = 9.1 Hz, 1 H), 7.17–7.04 (m, 5 H), 5.88 (dd, *J* = 11.1, 5.1 Hz, 1 H), 3.68–3.55 (m, 2 H).

^{13}C NMR (126 MHz, DMSO-d_6): δ = 170.92, 148.14, 143.17, 142.53, 138.82, 136.80, 129.07, 128.76, 127.19, 118.48, 116.04, 111.87, 59.38, 36.68.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $[C_{16}H_{13}N_3O_4 + H]^+$: 312.0978; found: 312.0978.

4-Methyl-2-(5-nitrobenzoimidazol-1-yl)pentanoic Acid (3r)

Obtained by using General Procedure B.

Yield: 0.100 g (60%); brown solid; mp 182–184 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 2.0 Hz, 1 H), 8.53 (s, 1 H), 8.29 (dd, *J* = 9.0, 2.0 Hz, 1 H), 7.59 (d, *J* = 9.1 Hz, 1 H), 5.17 (dd, *J* = 10.2, 5.5 Hz, 1 H), 2.33–2.24 (m, 1 H), 2.22–2.12 (m, 1 H), 1.53–1.38 (m, 1 H), 0.98 (d, *J* = 6.6 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 171.92, 145.86, 144.48, 140.00, 137.35, 119.75, 116.08, 110.95, 57.87, 40.85, 25.04, 22.75, 21.55.

MS (ESI): *m*/*z* calcd for $C_{13}H_{15}N_3O_4$: 277.11 $[M]^+$; found: 278.07 $[M + H]^+$, 276.12 $[M - H]^+$.

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Supporting Information

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