

Metal-free aerobic oxidation of benzazole derivatives.

SUPPORTING INFORMATION

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General procedure for the preparation of benzothiazoles 1a-1g

Procedure A: The aminothiophenol (1.0 equiv) and the carboxylic acid (1.5 equiv) were stirred under microwave irradiation at 210°C. The reaction mixture was cooled and extracted with Et₂O. The combined ethereal extracts were washed with sat. aq. NaHCO₃, brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

Procedure B: To a 1.0 M solution of the carboxylic acid (1.0 equiv) in toluene were added oxalyl chloride (1.0 equiv) and a drop of DMF. The resulting mixture was stirred at room temperature for 2 h and used as such for the next step. The acyl chloride (1.2 equiv) was added to a solution of aminothiophenol (1.0 equiv) and MgSO₄ (4.0 equiv) in toluene (1.25 M) at 0°C. The resulting mixture was heated at reflux for 1 day. NaHCO₃ aq. was added, and the product was extracted with AcOEt (10 mL x 3). The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

Procedure C: To a 0.2 M solution of cysteamine (1.0 equiv) in ethanol were added successively TEA (1.0 equiv) and cyanide (1.0 equiv). The resulting mixture was stirred at 80°C for 1 day. The solvent was evaporated under reduced pressure and the residue was diluted with CH₂Cl₂ and washed with water. The organic layer was dried over MgSO₄, filtered and concentrated. The crude product was purified by flash chromatography on silica gel.

2-(3,4-dimethoxybenzyl)benzo[*d*]thiazole **1a**: The procedure A was followed using 2-aminothiophenol (2.16 mL, 20 mmol) and (3,4-dimethoxyphenyl)acetic acid (5.89 g, 30 mmol). The mixture was heated at 210°C for 1 hour. The crude product was purified by flash chromatography on silica gel (PE:AcOEt). 3.27 g (58%) of the desired adduct (brown solid, M.p.: 66-67°C) were isolated. R_f 0.4 (5:5 PE:AcOEt); $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.99 (d, $J = 8.3$ Hz, 1H), 7.79 (d, $J = 8.1$ Hz, 1H), 7.45 (dd, $J = 8.3, 7.1$ Hz, 1H), 7.34 (dd, $J = 8.1, 7.1$ Hz, 1H), 6.92 (d, $J = 8.1$ Hz, 1H), 6.88 (s, 1H), 6.85 (d, $J = 8.1$ Hz, 1H), 4.38 (s, 2H), 3.88 (s, 3H), 3.86 (s, 3H). $^{13}\text{C NMR}$ (CDCl_3 , 100.6 MHz) δ 171.8, 153.1, 149.0, 148.2, 135.5, 129.5, 125.9, 124.7, 122.6, 121.4, 121.2, 112.1, 111.1, 55.8, 40.2; IR (ν , cm^{-1}): 3002, 2957, 2939, 2911, 2838, 1590, 1517, 1461, 1436, 1419, 1314, 1265, 1241, 1157, 1140, 1028; HRMS calcd for $\text{C}_{16}\text{H}_{15}\text{NO}_2\text{S}$ 285.0823, found 285.0822.

5-chloro-2-(3,4-dimethoxybenzyl)benzo[*d*]thiazole **1b**: The procedure B was followed using (3,4-dimethoxyphenyl)acetic acid (1.29 g, 6.0 mmol) and 2-amino-5-chlorobenzene-1-thiol (800 mg, 5.0 mmol). The crude product was purified by flash chromatography on silica gel (PE:AcOEt). 494 mg (31%) of the desired adduct (brown solid, M.p.: 86-87°C) were isolated. R_f 0.2 (8:2 PE:AcOEt); $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.95 (s, 1H), 7.67 (d, $J = 8.3$ Hz, 1H), 7.29 (d, $J = 8.3$ Hz, 1H), 6.90 (d, $J = 8.1$ Hz, 1H), 6.85 (s, 1H), 6.83 (d, $J = 8.1$ Hz, 1H), 4.35 (s, 2H), 3.86 (s, 3H), 3.85 (s, 3H); $^{13}\text{C NMR}$ (CDCl_3 , 100.6 MHz) δ 174.0, 154.0, 149.1, 148.3, 133.8, 131.9, 129.2, 125.2, 122.5, 122.2, 121.2, 112.1, 111.2, 55.8, 55.8, 40.2; IR (ν , cm^{-1}): 3002, 2960, 2932, 2911, 2835, 1593, 1513, 1468, 1440, 1419, 1262, 1238, 1140, 1067, 1025; HRMS calcd for $\text{C}_{16}\text{H}_{14}\text{ClNO}_2\text{S}$ 319.0434, found 319.0429.

2-benzylbenzo[*d*]thiazole **1c**: The procedure A was followed using 2-aminothiophenol (1.08 mL, 10 mmol) and phenylacetic acid (2.04 g, 15 mmol). The mixture was heated at 240°C for 40 minutes. The crude product was purified by flash chromatography on silica gel (PE:AcOEt). 1.72 g (77%) of the desired adduct (brown oil) were isolated. R_f 0.5 (8:2 PE:AcOEt); $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 8.01 (d, $J = 8.3$ Hz, 1H), 7.79 (d, $J = 7.8$ Hz, 1H), 7.46 (dd, $J = 7.8, 7.3$ Hz, 1H), 7.38-7.29 (m, 6H), 4.45 (s, 2H); $^{13}\text{C NMR}$ (CDCl_3 , 100.6 MHz) δ 171.1, 153.2, 137.1, 135.6, 129.1, 128.8, 127.3, 125.9, 124.8, 122.7, 121.5, 40.6; IR (ν , cm^{-1}) 3062, 3030, 1646, 1597, 1517, 1496, 1457, 1436, 1311, 1290, 1279, 1245, 1206, 1189, 1112, 1060, 1028, 1014; HRMS calcd for $\text{C}_{14}\text{H}_{11}\text{NS}$ 225.0612, found 225.0612.

2-benzyl-5-chlorobenzo[*d*]thiazole **1d**: The procedure B was followed using phenylacetic acid (819 mg, 6.0 mmol) and 2-amino-5-chlorobenzene-1-thiol (800 mg, 5.0 mmol). The crude product was purified by flash chromatography on silica gel (PE:AcOEt). 482 mg (37%) of the desired adduct (white solid, M.p.: 78-79°C) were isolated. R_f 0.8 (8:2 PE:AcOEt); $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.98 (s, 1H), 7.69 (d, $J = 8.6$ Hz, 1H),

7.37-7.36 (m, 4H), 7.33-7.32 (m, 1H), 7.31-7.30 (m, 1H), 4.43 (s, 2H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 173.3, 154.1, 136.8, 133.9, 131.9, 129.1, 128.9, 127.5, 125.3, 122.6, 122.2, 40.6; IR (v, cm^{-1}) 3065, 3030, 1594, 1548, 1513, 1492, 1461, 1436, 1412, 1300, 1251, 1196, 1147, 1108, 1074, 1029; HRMS calcd for $\text{C}_{14}\text{H}_{10}\text{ClNS}$ 259.0222, found 259.0222.

2-(thiophen-2-ylmethyl)benzo[*d*]thiazole **1e**: The procedure B was followed using 2-thiophene acetic acid (855 mg, 6.0 mmol) and 2-aminothiophenol (541 μL , 5.0 mmol). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2). 1.01 g (87%) of the desired adduct (violet oil) were isolated. R_f 0.5 (100% CH_2Cl_2); ^1H NMR (CDCl_3 , 400 MHz) δ 8.01 (d, $J = 8.1$ Hz, 1H), 7.81 (d, $J = 7.8$ Hz, 1H), 7.47 (dd, $J = 8.1, 7.3$ Hz, 1H), 7.35 (dd, $J = 7.8, 7.3$ Hz, 1H), 7.26 (d, $J = 5.1$ Hz, 1H), 7.05 (d, $J = 3.5$ Hz, 1H), 7.00 (dd, $J = 5.1, 3.5$ Hz, 1H), 4.65 (s, 2H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 170.3, 153.1, 138.7, 135.6, 127.1, 126.9, 126.0, 125.3, 124.9, 122.8, 121.6, 34.6; IR (v, cm^{-1}) 3061, 2901, 1628, 1513, 1457, 1437, 1415, 1363, 1314, 1297, 1255, 1241, 1154, 1133, 1102, 1067, 1035, 1014. HRMS calcd for $\text{C}_{12}\text{H}_9\text{NS}_2$ 231.0176, found 231.0175.

2-(4-fluorobenzyl)benzo[*d*]thiazole **1f**: The procedure B was followed using 4-fluorophenylacetic acid (927 mg, 6.0 mmol) and 2-aminothiophenol (541 μL , 5.0 mmol). The crude product was purified by flash chromatography on silica gel (PE:AcOEt). 853 mg (70%) of the desired adduct (yellow oil) were isolated. R_f 0.5 (8:2 PE:AcOEt); ^1H NMR (CDCl_3 , 400 MHz) δ 8.15-8.12 (m, 1H), 7.94-7.91 (m, 1H), 7.62-7.57 (m, 1H), 7.48-7.45 (m, 3H), 7.19-7.14 (m, 2H), 4.54 (s, 2H). ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 170.7, 162.0 (d, $J_{\text{C-F}} = 246.0$ Hz), 153.2, 135.5, 132.8 (d, $J_{\text{C-F}} = 3.0$ Hz), 130.7 (d, $J_{\text{C-F}} = 8.1$ Hz), 126.0, 124.8, 122.7, 121.5, 115.7 (d, $J_{\text{C-F}} = 22.0$ Hz), 39.6; IR (v, cm^{-1}) 3069, 2911, 1600, 1510, 1461, 1433, 1314, 1224, 1161, 1108, 1063, 1018; HRMS calcd for $\text{C}_{14}\text{H}_{10}\text{FNS}$ 243.0518, found 243.0520.

2-(4-methylbenzyl)-4,5-dihydrothiazole **1g**: The procedure C was followed using 2-aminoethane-1-thiol (869 mg, 7.6 mmol) and 4-methylbenzyl cyanide (1.01 mL, 7.6 mmol). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2 :AcOEt). 216 mg (15%) of the desired adduct (yellow oil) were isolated. R_f 0.4 (5:5 CH_2Cl_2 :AcOEt). ^1H NMR (CDCl_3 , 400 MHz) δ 7.18 (d, $J = 8.1$ Hz, 2H), 7.14 (d, $J = 8.1$ Hz, 2H), 4.24 (t, $J = 8.6$ Hz, 2H), 3.79 (s, 2H), 3.26 (t, $J = 8.6$ Hz, 2H), 2.33 (s, 3H). ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 170.7, 136.7, 133.0, 129.3, 128.9, 64.6, 40.3, 34.0, 21.1; IR (v, cm^{-1}) 3020, 2922, 2859, 1666, 1625, 1513, 1433, 1199, 1115, 1004; HRMS calcd for $\text{C}_{11}\text{H}_{13}\text{NS}$ 191.0769, found 191.0759.

General procedure for the preparation of benzimidazoles 3a-3p

Procedure F: The 1,2-phenylenediamine (1.0 equiv) and the carboxylic acid (1.0 equiv) were heated at 190°C for 2 h under stirring. The reaction mixture was cooled at 5°C and neutralized with a 10% aqueous solution of

sodium hydroxide. The mixture was stirred for 24 h. The precipitated product was collected by vacuum filtration, washed with H₂O. Then the solid was solubilized in CH₂Cl₂, dried over MgSO₄, filtered and concentrated *in vacuo*.

Procedure G: To a 1.0 M solution of benzimidazole (1.0 equiv) in DMF were added successively KOH (1.0 equiv), TEBACl (0.1 equiv) and an alkylating agent (1.0 equiv). The mixture was stirred and heated at 50°C for 15 h. The solvent was evaporated under reduced pressure, the residue diluted with AcOEt and washed several times with H₂O. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

Procedure H: To a solution of NaH (1.0 equiv) in DMF (2.24 mL) were added benzimidazole (1.0 equiv) and 4-bromo-1-butene (1.0 equiv). The mixture was stirred at 100°C for 90 min under microwave irradiation. The solvent was evaporated under reduced pressure, the residue diluted with AcOEt and washed several times with H₂O. The organic layer was dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

Procedure I: To a 1.0 M solution of benzothiazole (1.0 equiv) in CH₂Cl₂ were added ethyl chloroformate (1.0 equiv), TEA (1.0 equiv) and DMAP (0.1 equiv). The resulting mixture was stirred at room temperature for 16 h. The resulting mixture was neutralised with an aqueous citric acid solution and the aqueous phase was extracted with CH₂Cl₂. The organic layers were dried over anhydrous MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

Procedure J: To a 1.25 M solution of benzothiazole (1.0 equiv) in pyridine was added 4-methylbenzene-1-sulfonyl chloride (1.0 equiv). The resulting mixture was stirred at room temperature for 30 min. The mixture was neutralised with an aqueous citric acid solution and the aqueous phase was extracted with CH₂Cl₂. The organic layers were dried over anhydrous MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel.

Procedure K: To a 1.0 M solution of aldehyde (1.5 equiv) in MeOH were added successively the amine (1.0 equiv), the isocyanide (1.0 equiv) and the acid (1.0 equiv). The resulting mixture was stirred at 80°C for 15 min under microwave irradiation. After removal the excess of MeOH, the crude Ugi adduct was used as such for the

next step. It was dissolved in a solution of 10% TFA in 1,2-dichloroethane (0.085 M) and the resulting mixture was stirred at 130°C for 20 min under microwave irradiation. The solvent was evaporated *in vacuo* and crude material partitioned between NaHCO₃ and AcOEt. The organic layer was washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

2-(3,4-dimethoxybenzyl)-1*H*-benzo[*d*]imidazole **3a**: The procedure F was followed using 1,2-phenylenediamine (2.16 g, 20 mmol) and (3,4-dimethoxyphenyl)acetic acid (3.92 g, 20 mmol). 3.76 g (70%) of the desired adduct (white solid, M.p.: 160-161°C) were isolated. R_f 0.2 (8:2 CH₂Cl₂:AcOEt); ¹H NMR (DMSO, 400 MHz) δ 12.23 (br s, 1H), 7.52 (br s, 1H), 7.41 (br s, 1H), 7.11-7.10 (m, 2H), 6.97 (s, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.6 Hz, 1H), 4.09 (s, 2H), 3.72 (s, 3H), 3.70 (s, 3H). ¹³C NMR (DMSO, 100.6 MHz) δ 153.9, 148.6, 147.5, 143.4, 134.4, 129.9, 121.5, 120.8, 120.7, 118.2, 112.6, 111.8, 110.9, 55.5, 55.4, 34.6; IR (ν, cm⁻¹) 2999, 2939, 2911, 2835, 1593, 1517, 1457, 1440, 1419, 1262, 1238, 1154, 1140, 1028; HRMS calcd for C₁₆H₁₆N₂O₂ 268.1212, found 268.1216.

2-(4-methylbenzyl)-1*H*-benzo[*d*]imidazole **3b**: The procedure F was followed using 1,2-phenylenediamine (2.16 g, 20 mmol) and *p*-tolylacetic acid (3.00 g, 20 mmol). 3.50 g (79%) of the desired adduct (white solid, M.p.: 198-199°C) were isolated. R_f 0.3 (8:2 CH₂Cl₂:AcOEt); ¹H NMR (DMSO, 400 MHz) δ 12.28 (br s, 1H), 7.52 (br s, 1H), 7.41 (br s, 1H), 7.21 (d, *J* = 8.1 Hz, 2H), 7.12-7.10 (m, 4H), 4.12 (s, 2H), 2.25 (s, 3H). ¹³C NMR (DMSO, 100.6 MHz) δ 153.7, 143.3, 135.5, 134.5, 129.0, 128.6, 121.5, 120.9, 118.2, 110.9, 34.5, 20.6; IR (ν, cm⁻¹) 3020, 2911, 2859, 2741, 1625, 1590, 1537, 1513, 1485, 1458, 1440, 1419, 1391, 1321, 1273, 1224, 1115, 1035, 1001; HRMS calcd for C₁₅H₁₄N₂ 222.1157, found 222.1155.

5-chloro-2-(4-methylbenzyl)-1*H*-benzo[*d*]imidazole **3c**: The procedure F was followed using 4-chloro-1,2-diaminobenzene (2.85 g, 20 mmol) and *p*-tolylacetic acid (3.00 g, 20 mmol). 3.94 mg (77%) of the desired adduct (brown solid, M.p.: 151-152°C) were isolated. R_f 0.4 (8:2 CH₂Cl₂:AcOEt); ¹H NMR (CDCl₃, 400 MHz) δ 10.52 (br s, 1H), 7.38 (s, 1H), 7.33 (d, *J* = 8.8 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 1H), 7.05-7.01 (m, 4H), 4.11 (s, 2H), 2.24 (s, 3H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 155.2, 139.1, 136.9, 132.8, 129.5, 128.7, 127.8, 122.7, 115.4, 114.6, 35.1, 20.9; IR (ν, cm⁻¹) 3022, 2923, 2868, 2754, 2703, 1520, 1453, 1418, 1280, 1064, 1028; HRMS calculated for C₁₅H₁₃ClN₂ 256.0767, found 256.0767.

(2-benzyl-1*H*-benzo[*d*]imidazol-6-yl)(phenyl)methanone **3d**: The procedure F was followed using 3,4-diaminobenzophenone (4.24 g, 20 mmol) and phenylacetic acid (2.72 g, 20 mmol). 3.87 g (62%) of the desired adduct (yellow solid, M.p.: 55-56°C) were isolated. R_f 0.4 (8:2 CH₂Cl₂:AcOEt); ¹H NMR (CDCl₃, 400 MHz) δ 9.43 (br s, 1H), 8.01 (s, 1H), 7.82 (d, *J* = 7.8 Hz, 2H), 7.77 (d, *J* = 8.3 Hz, 1H), 7.62 (dd, *J* = 7.6, 7.3 Hz, 1H), 7.56-7.49 (m, 3H), 7.27-7.25 (m, 5H), 4.27 (s, 2H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 197.2, 156.4, 138.1, 135.7, 132.1, 131.7, 130.0, 129.3, 128.9, 128.9, 128.5, 128.2, 127.2, 124.9, 118.0, 114.5, 35.6. IR (ν, cm⁻¹) : 3058, 3030, 1649, 1618, 1601, 1578, 1530, 1499, 1450, 1415, 1322, 1304, 1290, 1245, 1224, 1182, 1115, 1077, 1025, 1004; HRMS calcd for C₂₁H₁₆N₂O 312.1263, found 312.1251.

2-benzyl-5-nitro-1*H*-benzo[*d*]imidazole **3e**: The procedure F was followed using 4-nitrobenzene-1,2-diamine (3.06 g, 20 mmol) and phenylacetic acid (2.72 g, 20 mmol). 2.93 g (58%) of the desired adduct (brown solid, M.p.: 84-85°C) were isolated. R_f 0.6 (8:2 CH₂Cl₂:AcOEt); ¹H NMR (CDCl₃, 400 MHz) δ 12.03 (br s, 1H), 8.32 (s, 1H), 8.10 (d, *J* = 8.3 Hz, 1H), 7.45 (d, *J* = 8.3 Hz, 1H), 7.20-7.17 (m, 5H), 4.21 (s, 2H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 158.4, 158.3, 143.3, 135.2, 129.0, 128.9, 127.5, 118.4, 113.8, 112.3, 35.8; IR (ν, cm⁻¹) : 3098, 3040, 2925, 2838, 1628, 1600, 1517, 1475, 1454, 1415, 1339, 1314, 1283, 1067, 1021; HRMS : calculated for C₁₄H₁₁N₃O₂ 253.0851, found 253.0852.

2-phenethyl-1*H*-benzo[*d*]imidazole **3f**: The procedure F was followed using 1,2-phenylenediamine (541 mg, 5 mmol) and 3-phenylpropanoic acid (702 μL, 5 mmol). 841 mg (76%) of the desired adduct (yellow solid, M.p.: 158-159°C) were isolated. R_f 0.2 (9:1 CH₂Cl₂:AcOEt); ¹H NMR (CDCl₃, 400 MHz) δ 10.24 (br s, 1H), 7.53-7.51 (m, 2H), 7.25-7.18 (m, 5H), 7.10-7.09 (m, 2H), 3.20-3.18 (m, 2H), 3.15-3.14 (m, 2H); ¹³C NMR (CDCl₃, 100.6 MHz) δ 154.1, 140.2, 137.9, 128.6, 128.2, 126.4, 122.4, 114.6, 34.2, 30.9; IR (ν, cm⁻¹) 3058, 3026, 2922, 2856, 2741, 2625, 1625, 1600, 1569, 1537, 1496, 1454, 1436, 1276, 1224, 1150, 1081, 1028, 1004. HRMS calcd for C₁₅H₁₄N₂ 222.1157, found 222.1161.

5-methyl-2-(thiophen-2-ylmethyl)-1*H*-benzo[*d*]imidazole **3g**: The procedure F was followed using 3,4-diaminotoluene (2.44 g, 20 mmol) and 2-thiopheneacetic acid (2.84 g, 20 mmol). 3.84 g (84%) of the desired adduct (brown solid, M.p.: 128-129°C) were isolated. R_f 0.3 (100% CH₂Cl₂); ¹H NMR (CDCl₃, 400 MHz) δ

10.18 (br s, 1H), 7.41 (d, $J = 7.8$ Hz, 1H), 7.29 (s, 1H), 7.14-7.13 (m, 1H), 7.05 (d, $J = 7.8$ Hz, 1H), 6.86-6.85 (m, 2H), 4.39 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 152.5, 138.4, 136.9, 132.1, 130.0, 127.0, 126.5, 124.9, 123.7, 114.7, 114.4, 29.8, 21.6; IR (ν , cm^{-1}): 3020, 2918, 2866, 2758, 1625, 1593, 1523, 1447, 1415, 1279, 1224, 1185, 1143, 1077, 1021; HRMS : calculated for $\text{C}_{13}\text{H}_{12}\text{N}_2\text{S}$ 228.0721, found 228.0730.

2-benzyl-1*H*-benzo[*d*]imidazole **3h**: The procedure F was followed using 1,2-phenylenediamine (1.08 g, 10 mmol) and phenylacetic acid (1.36 g, 10 mmol). 2.00 g (96%) of the desired adduct (white solid, M.p.: 76-77°C) were isolated. R_f : 0.2 (9:1 CH_2Cl_2 :AcOEt); ^1H NMR (CDCl_3 , 400 MHz) δ 14.52 (br s, 1H), 7.71-7.69 (m, 2H), 7.57-7.56 (m, 2H), 7.38-7.36 (m, 2H), 7.06-7.04 (m, 3H), 4.57 (s, 2H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 151.8, 133.2, 130.8, 129.1, 129.0, 127.8, 125.8, 114.0, 32.2; IR (ν , cm^{-1}) 3037, 2904, 2800, 2730, 2618, 2507, 1628, 1569, 1517, 1492, 1461, 1436, 1391, 1297, 1289, 1224, 1185, 1157, 1122, 1081, 1021; HRMS calcd for $\text{C}_{14}\text{H}_{12}\text{N}_2$ 208.1000, found 208.0995.

2-(3,4-dimethoxybenzyl)-1-ethyl-1*H*-benzo[*d*]imidazole **3i**: The procedure G was followed using the benzimidazole **3a** (1.50 g, 5.6 mmol) and EtI (447 μL , 5.6 mmol). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2 :AcOEt). 1.18 g (71%) of the desired adduct (white solid, M.p.: 90-91°C) were isolated. R_f : 0.5 (2:8 CH_2Cl_2 :AcOEt); ^1H NMR (CDCl_3 , 400 MHz) δ 7.78-7.76 (m, 1H), 7.29-7.26 (m, 3H), 6.80-6.78 (m, 3H), 4.26 (s, 2H), 4.09 (q, $J = 7.3$ Hz, 2H), 3.84 (s, 3H), 3.80 (s, 3H), 1.15 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 152.8, 149.2, 147.9, 142.7, 135.0, 128.8, 122.2, 121.8, 120.5, 119.5, 111.5, 111.1, 109.2, 55.9, 55.8, 38.7, 34.2, 14.6; IR (ν , cm^{-1}): 3054, 2939, 2911, 2838, 1590, 1517, 1468, 1426, 1332, 1262, 1234, 1185, 1143, 1025; HRMS calcd for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2$ 296.1525, found 296.1520.

1-(4-(*tert*-butyl)benzyl)-2-(4-methylbenzyl)-1*H*-benzo[*d*]imidazole **3j**: the procedure G was followed using the benzimidazole **3b** (1.5 g, 6.75 mmol) and *p-tert*-butylbenzyl bromide (1.24 mL, 6.75 mmol). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2 :AcOEt). 1.76 g (71%) of the desired adduct (white solid, M.p.: 172-173°C) were isolated. R_f 0.6 (8:2 CH_2Cl_2 :AcOEt); ^1H NMR (CDCl_3 , 400 MHz) δ 7.81 (d, $J = 7.6$ Hz, 1H), 7.28-7.26 (m, 3H), 7.23-7.21 (m, 2H), 7.09-7.07 (m, 4H), 6.88 (d, $J = 7.6$ Hz, 2H), 5.15 (s, 2H), 4.22 (s, 2H), 2.30 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 153.6, 150.8, 142.6, 136.5, 135.8, 133.0, 132.9, 129.4, 128.3, 125.9, 125.7, 122.4, 122.0, 119.5, 109.6, 46.7, 34.5, 34.1, 31.2, 21.0; IR (ν , cm^{-1})

3044, 2960, 2873, 1513, 1461, 1408, 1360, 1286, 1265, 1251, 1161, 1115, 1021, 1004; HRMS calcd for $C_{26}H_{28}N_2$ 368.2252, found 368.2255.

1-(but-3-en-1-yl)-2-(3,4-dimethoxybenzyl)-1*H*-benzo[*d*]imidazole **3k**: The procedure H was followed using the benzimidazole **3a** (300 mg, 1.12 mmol) and 4-bromo-1-butene (114 μ L, 1.12 mmol). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2 :AcOEt). 96 mg (27%) of the desired adduct (yellow oil) were isolated. R_f 0.3 (8:2 CH_2Cl_2 :AcOEt); 1H NMR ($CDCl_3$, 400 MHz) δ 7.76-7.75 (m, 1H), 7.30-7.23 (m, 3H), 6.78 (s, 3H), 5.71-5.61 (m, 1H), 5.03 (d, $J = 10.4$ Hz, 1H), 4.96 (d, $J = 16.9$ Hz, 1H), 4.25 (s, 2H), 4.06 (t, $J = 7.3$ Hz, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 2.23 (q, $J = 7.3$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 153.1, 149.1, 147.9, 142.5, 135.1, 133.6, 128.7, 122.2, 121.8, 120.5, 119.5, 117.9, 111.5, 111.1, 109.4, 55.8, 43.4, 34.3, 33.5; IR (ν , cm^{-1}) 3058, 2939, 2838, 1590, 1517, 1461, 1422, 1335, 1265, 1234, 1140, 1032; HRMS calcd for $C_{20}H_{22}N_2O_2$ 322.1681, found 322.1679.

ethyl 2-(3,4-dimethoxybenzyl)-1*H*-benzo[*d*]imidazole-1-carboxylate **3l**: The procedure I was followed using the benzimidazole **3a** (1.00 g, 3.73 mmol). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2 :AcOEt). 996 mg (79%) of the desired adduct (white solid, M.p.: 99-100°C) were isolated. R_f 0.3 (9:1 CH_2Cl_2 :AcOEt); 1H NMR ($CDCl_3$, 400 MHz) δ 7.91-7.89 (m, 1H), 7.75-7.73 (m, 1H), 7.35-7.33 (m, 2H), 6.88 (s, 1H), 6.84 (d, $J = 8.1$ Hz, 1H), 6.78 (d, $J = 8.1$ Hz, 1H), 4.56 (s, 2H), 4.49 (q, $J = 7.1$ Hz, 2H), 3.84 (s, 3H), 3.83 (s, 3H), 1.46 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 154.7, 150.2, 148.7, 147.7, 142.2, 132.9, 128.9, 124.6, 124.3, 120.9, 119.8, 115.0, 112.0, 110.9, 64.0, 55.8, 36.3, 14.1; IR (ν , cm^{-1}) 2996, 2939, 2915, 2835, 1750, 1513, 1454, 1374, 1335, 1293, 1262, 1234, 1206, 1150, 1120, 1095, 1025; HRMS calcd for $C_{19}H_{20}N_2O_4$ 340.1423, found 340.1426.

2-(4-methylbenzyl)-1-tosyl-1*H*-benzo[*d*]imidazole **3m**: The procedure J was followed using the benzimidazole **3b** (1.00 g, 4.50 mmol). The crude product was purified by flash chromatography on silica gel (CH_2Cl_2 :AcOEt). 1.32 g (78%) of the desired adduct (white solid, M.p.: 255-256°C) were isolated. R_f 0.8 (8:2 CH_2Cl_2 :AcOEt); 1H NMR ($CDCl_3$, 400 MHz) δ 7.98-7.96 (m, 1H), 7.72-7.70 (m, 1H), 7.39 (d, $J = 8.1$ Hz, 2H), 7.35-7.33 (m, 2H), 7.17 (d, $J = 7.8$ Hz, 2H), 7.08-7.05 (m, 4H), 4.59 (s, 2H), 2.34 (s, 3H), 2.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 153.2, 145.5, 141.8, 136.5, 135.0, 133.0, 132.8, 129.8, 129.2, 129.0, 126.9, 124.8, 124.5, 120.1, 113.6,

35.3, 21.6, 21.1; IR (ν , cm^{-1}) 3058, 3023, 2929, 1598, 1541, 1517, 1454, 1377, 1286, 1255, 1227, 1185, 1168, 1150, 1122, 1091, 1049, 1018; HRMS calcd for $\text{C}_{22}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$ 376.1245, found 376.1241.

N-cyclohexyl-2-(2-(3,4-dimethoxybenzyl)-1*H*-benzo[*d*]imidazol-1-yl)butanamide **3n**: The procedure K was followed using propanal (109 μL , 1.5 mmol), *tert*-butyl *N*-(2-aminophenyl)carbamate (208 mg, 1.0 mmol), cyclohexyl isocyanide (124 μL , 1.0 mmol) and (3,4-dimethoxyphenyl)acetic acid (196 mg, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (PE:AcOEt). 386 mg (89%) of the desired adduct (white solid, M.p.: 156-157°C) were isolated. R_f 0.1 (5:5 PE:AcOEt); ^1H NMR (CDCl_3 , 400 MHz) δ 7.79-7.77 (m, 1H), 7.38-7.36 (m, 1H), 7.27-7.25 (m, 1H), 7.22-7.18 (m, 1H), 6.84-6.79 (m, 3H), 4.72-4.69 (m, 1H), 4.48 (d, $J = 15.6$ Hz, 1H), 4.41 (br s, 1H), 4.09 (d, $J = 15.6$ Hz, 1H), 3.83 (s, 3H), 3.77 (s, 3H), 3.50-3.47 (m, 1H), 2.36-2.29 (m, 1H), 2.20-2.13 (m, 1H), 1.47-1.40 (m, 5H), 1.22-1.11 (m, 2H), 0.94-0.88 (m, 1H), 0.68-0.64 (m, 3H), 0.50-0.44 (m, 2H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 166.8, 153.9, 149.6, 148.3, 142.8, 133.2, 128.5, 122.8, 122.5, 120.4, 119.8, 111.8, 111.4, 111.2, 60.6, 55.9, 55.7, 48.1, 34.7, 32.5, 32.3, 25.2, 24.7, 24.5, 22.4, 10.6; IR (ν , cm^{-1}): 2936, 2859, 1674, 1517, 1457, 1265, 1238, 1158, 1140, 1025; HRMS calcd for $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}_3$ 435.2522, found 435.2522.

N-(4-chlorobenzyl)-4-methyl-2-(2-(4-methylbenzyl)-1*H*-benzo[*d*]imidazol-1-yl)pentanamide **3o**: The procedure K was followed using isovaleraldehyde (162 μL , 1.5 mmol), *tert*-butyl *N*-(2-aminophenyl)carbamate (208 mg, 1.0 mmol), *p*-chlorobenzyl isocyanide (152 μL , 1.0 mmol) and *p*-tolylacetic acid (150 mg, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (PE:AcOEt). 386 mg (84%) of the desired adduct (yellow solid, M.p.: 136-137°C) were isolated. R_f 0.3 (5:5 PE:AcOEt); ^1H NMR (CDCl_3 , 400 MHz) δ 7.77 (d, $J = 8.1$ Hz, 1H), 7.41 (d, $J = 8.1$ Hz, 1H), 7.28 (dd, $J = 8.1, 7.3$ Hz, 1H), 7.20 (dd, $J = 8.1, 7.3$ Hz, 1H), 7.12-7.10 (m, 4H), 6.98 (d, $J = 7.1$ Hz, 2H), 6.68 (d, $J = 7.3$ Hz, 2H), 4.82 (t, $J = 6.6$ Hz, 1H), 4.71 (br s, 1H), 4.52 (d, $J = 16.2$ Hz, 1H), 4.04 (d, $J = 16.2$ Hz, 1H), 3.92 (d, $J = 5.8$ Hz, 2H), 2.31-2.24 (m, 1H), 2.17 (s, 3H), 2.00-1.93 (m, 1H), 1.39-1.30 (m, 1H), 0.98 (d, $J = 6.6$ Hz, 3H), 0.80 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 168.0, 153.2, 142.8, 137.4, 135.8, 133.5, 133.2, 133.0, 130.0, 128.5, 128.5, 128.3, 123.0, 122.5, 119.8, 111.9, 57.1, 42.7, 38.1, 34.6, 24.7, 22.7, 22.3, 20.9; IR (ν , cm^{-1}) 3048, 2957, 2929, 2870, 1680, 1510, 1492, 1461, 1395, 1269, 1091, 1018; HRMS calcd for $\text{C}_{28}\text{H}_{30}\text{ClN}_3\text{O}$ 459.2077, found 459.2076.

2-(2-benzyl-5-chloro-1*H*-benzo[*d*]imidazol-1-yl)-*N*-(4-methoxybenzyl)acetamide **3p**: The procedure K was

followed using formaldehyde (112 μL , 1.5 mmol), *tert*-butyl *N*-(2-amino-5-chlorophenyl)carbamate (243 mg, 1.0 mmol), *p*-methoxybenzyl isocyanide (147 μL , 1.0 mmol) and phenylacetic acid (136 mg, 1.0 mmol). The crude product was purified by flash chromatography on silica gel (PE:AcOEt). 289 mg (69%) of the desired adduct (white solid, M.p.: 190-191°C) were isolated. R_f 0.5 (5:5 PE:AcOEt); ^1H NMR (CDCl_3 , 400 MHz) δ 7.60 (d, $J = 8.6$ Hz, 1H), 7.26-7.18 (m, 7H), 6.95 (d, $J = 7.8$ Hz, 2H), 6.77 (d, $J = 7.8$ Hz, 2H), 5.49 (br s, 1H), 4.62 (s, 2H), 4.21 (s, 2H), 4.12 (d, $J = 5.3$ Hz, 2H), 3.76 (s, 3H); ^{13}C NMR (CDCl_3 , 100.6 MHz) δ 165.5, 159.1, 154.1, 141.1, 135.8, 135.1, 129.2, 129.1, 128.9, 128.4, 128.3, 127.5, 123.6, 120.6, 114.0, 109.4, 55.2, 47.4, 43.0, 34.4; IR (v, cm^{-1}) 3278, 3065, 3030, 2929, 2838, 1659, 1558, 1517, 1461, 1248, 1175, 1032; HRMS calcd for $\text{C}_{24}\text{H}_{22}\text{ClN}_3\text{O}_2$ 419.1401, found 419.1403.













































































