Functionalized orthoesters as powerful building blocks for the efficient preparation of hetero-aromatic bicycles.

Supporting Information

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General experimental section:

All experiments were performed in flame dried glass apparatus,under an argon atmosphere and with magnetic stirring. All solvents and common reagents were purified by established procedures or used as p.a. grade. Thin layer chromatography was performed on prepared thin layers precoated plates : Silicagel Merck 60 F254. The visualization of spots on TLC plates was effected by exposure to UV, by using basic potassium permanganate solution, by using a vanillin solution or by using an ethanolic phosphomolybdic acid solution. Column chromatography was performed over ROCC Silica gel 60 (40 – 63µ mesh) using the relevant eluent. ^{1}H (300 MHz), ^{13}C (75 MHz), spectra were recorded on Brucker AC-300 Avance II at ambient temperature in $CDCl_3$ or DMSO-*d*6 (Aldrich). Chemical shifts are reported in ppm downfield to tetramethyl silane. Coupling constants are reported and expressed in Hz, splitting patterns are designated as br (broad), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). NMR Fourier transform, integration and peak picking were done with Bruker TopSpin software or with MestRenova software version 6. Infrared spectra were recorded on Shimadzu FTIR-8400S spectrometer and the absorption bands are reported in reciprocal centimeters (cm-1). Mass spectra were recorded on a Finigan TSQ 7000 or Varian Matt 44S. High resolution mass spectra were recorded at U.C.L.-London by Dr Lisa Harris

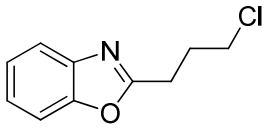
General procedure for the preparation of benzoxazoles and benzothiazoles:

To a 0℃ solution of orthoester (2 mmol, 1 eq.) in DCM (20 mL, 0.1M), $BF_3.OEt_2$ (2 mmol, 1 eq.) was added dropwise followed by the addition of 2-aminophenol or 2-aminothiophenol derivatives (2.2 mmol, 1.1 eq.). The reaction mixture was stirred at r.t until completion of the reaction, as checked by TLC. The reaction was then quenched by the addition of a saturated aqueous solution of $NaHCO_3$. The product was extracted by 3 × 20 mL of DCM, the organic phases were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure and the crude product was purified by chromatography on silica gel or by recrystallization.

General procedure for the preparation of benzimidazoles:

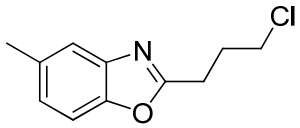
To a 0℃ cooled solution of orthoester (3 mmol, 1.5 eq) in dry DCM (20 mL, 0.1M), $BF_3.OEt_2$ (2 mmol, 1 eq) was added dropwise followed by the addition of the benzene-1,2-diamine derivatives (2 mmol, 1 eq). The reaction mixture was stirred at r.t until completion of the reaction, as checked by TLC. The reaction was then quenched by the addition of a saturated aqueous solution of $NaHCO_3$. The product was extracted by 3 × 20 mL of DCM, the organic phases were dried over $MgSO_4$ and filtered. The solvents were removed under reduced pressure and the crude product was purified by chromatography on silica gel.

2-(3-chloropropyl)benzo[d]oxazole (12a):



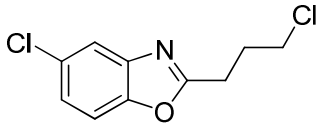
Yield: 82 % - colorless oil. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (9.5/0.5). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.82 – 7.58 (m, 1H), 7.58 – 7.43 (m, 1H), 7.36 – 7.20 (m, 2H), 3.70 (t, *J* = 6.3 Hz, 2H), 3.12 (t, *J* = 7.3 Hz, 2H), 2.37 (dt, *J* = 7.3, 6.3 Hz, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ = 165.6, 150.7, 141.2, 124.6, 124.1, 119.5, 110.3, 43.7, 29.2, 25.7. **IR** (neat) u_{max}/cm^{-1}: 2965, 2913, 1614, 1572, 1454, 1431, 1298, 1277, 1240, 1142, 1003, 930, 829. **MS** (EI +ev) m/z (%): 197 (33), 195 (100), 187 (7), 146 (7), 133 (7). **HRMS** (EI) Calcd for $C_{10}H_{10}ONCl$: 195.0445, found: 195.0437.

2-(3-chloropropyl)-5-methylbenzo[d]oxazole (12b):



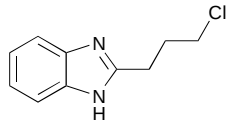
Yield: 80 % - white solid. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (9.5/0.5). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 0.6 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.10 (dd, *J* = 8.3, 0.8 Hz, 1H), 3.69 (t, *J* = 6.3 Hz, 2H), 3.09 (t, *J* = 7.3 Hz, 2H), 2.44 (s, 3H), 2.41 – 2.29 (tt, *J* = 7.3, 6.3, Hz, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ = 165.7, 149.0, 141.4, 134.0, 125.7, 119.5, 109.7, 43.8, 29.3, 25.8, 21.4. **IR** (neat) u_{max}/cm^{-1}: 2907, 1574, 1483, 1452, 1429, 1300, 1259, 1167, 1146, 930, 872. **MS** (EI +ev) m/z (%): 211 (7), 209 (17), 147 (100), 146 (16). **HRMS** (EI) Calcd for $C_{11}H_{12}ONCl$: 209.0602, found: 209.0603. **MP**: 44-45℃.

5-chloro-2-(3-chloropropyl)benzo[d]oxazole (12c):



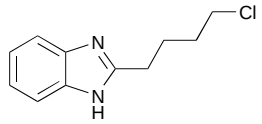
Yield: 85 % - white solid. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (9.5/0.5). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 2.0 Hz, 1H), 7.41 (d, *J* = 8.6 Hz, 1H), 7.28 (dd, *J* = 8.8, 2.0 Hz, 1H), 3.71 (t, *J* = 6.2 Hz, 2H), 3.13 (t, *J* = 7.3 Hz, 2H), 2.49 – 2.26 (tt, *J* = 7.3, 6.2 Hz, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ = 167.2, 149.4, 142.4, 129.7, 125.0, 119.7, 111.1, 43.7, 29.1, 25.8. **IR** (neat) u_{max}/cm^{-1}: 2962, 1609, 1568, 1450, 1427, 1256, 1143, 1055, 918, 802. **MS** (EI +ev) m/z (%): 233 (4), 231 (22), 229(37), 168 (36), 167 (100). **HRMS** (EI) Calcd for $C_{10}H_9ONCl_2$: 229.0056, found: 229.0058. **MP**: 47-48℃.

2-(3-chloropropyl)-1H-benzo[d]imidazole (12d): CAS: 127855-54-3



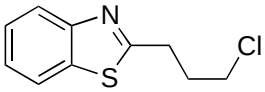
Yield: 83% - colorless solid. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (10:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.56 (s, 1H), 7.28 – 7.21 (m, 4H), 3.66 (t, *J* = 6.1 Hz, 2H), 3.11 (t, *J* = 7.2 Hz, 2H), 2.38 (dq, *J* = 13.4, 6.5 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 153.2, 137.4, 123.1, 44.2, 30.7, 26.0. **IR** (neat) u_{max}/cm^{-1}: 2941, 1622, 1454, 1471, 1220, 1008, 752, 742. **MS** (EI +ev) m/z (%): 202 (29), 162 (23), 149 (100). **MP**: 132-133℃.

2-(4-chlorobutyl)-1H-benzo[d]imidazole (13d):



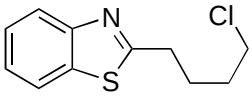
Yield: 73% - white solid. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (10:1).**^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.60-7.57 (m, 2H), 7.29-7.25 (m, 2H), 3.54 (t, *J* = 6.3 Hz, 2H), 3.02 (td, *J* = 7.5, 1.3, 2H), 2.10-2.01 (m, 2H), 1.92-1.83 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 122.8, 114.6, 44.5, 31.8, 28.3, 25.4. **IR** (neat) u_{max}/cm^{-1}: 2956, 1622, 1537, 1456, 1271, 1218, 1022, 736. **MS** (CI +ev) m/z (%) : 211 (8), 209 (26), 173 (100). **HRMS** (CI): Calcd for $C_{11}H_{14}N_2Cl$: 209.0845, found: 209.0849. **MP**: 225-226℃.

2-(3-chloropropyl)benzo[d]thiazole (12e): CAS: 65655-72-3



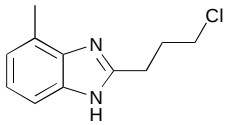
Yield: 84% - yellow oil. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (8:1).**^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8.0 Hz, 1H), 7.87 – 7.84 (m, 1H), 7.50 – 7.45 (m, 1H), 7.45 – 7.35 (m, 1H), 3.69 (dd, *J* = 8.4, 4.4 Hz, 2H), 3.31 (t, *J* = 7.4 Hz, 2H), 2.44 – 2.35 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 170.0, 153.3, 135.1, 126.0, 124.9, 122.7, 121.5, 43.8, 31.8, 31.2. **IR** (neat) υ_{max}/cm^{-1}: 2959, 1737, 1519, 1456, 1434, 1242, 1107, 757. **MS** (EI +ev) m/z (%): 211 (7), 149 (65), 104 (13), 86 (66).

2-(4-chlorobutyl)benzo[d]thiazole (13e):



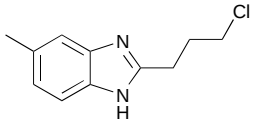
Yield: 90% - yellow oil. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (8:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.95 (d, *J* = 8.2 Hz, 1H), 7.82 – 7.79 (m, 1H), 7.45 – 7.42 (m, 1H), 7.40 – 7.22 (m, 1H), 3.54 (t, *J* = 6.4 Hz, 2H), 3.10 (t, *J* = 7.4 Hz, 2H), 2.04 – 1.91 (m, 2H), 2.00 – 1.79 (m, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ = 171.1, 153.2, 135.1, 125.9, 124.8, 122.6, 121.5, 44.4, 33.4, 31.8, 26.7. **IR** (neat) $\upsilon_{max}/cm^{-1:}$ 2943, 1737, 1519, 1456, 1434, 1311, 1107, 1064, 1012, 757, 725. **MS** (CI +ev) m/z (%): 227 (9), 225 (27), 191 (13), 190 (100), 163 (23), 162 (84), 149 (50). **HRMS**: Calcd for $C_{11}H_{12}NSCl$: 225.0374, found: 225.0374.

2-(3-chloropropyl)-4-methyl-1H-benzo[d]imidazole (12f): CAS: 191794-11-3



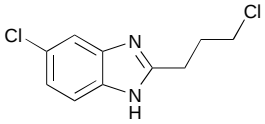
Yield: 92% - beige solid. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (10:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.28 (s, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.04 (d, *J* = 7.3 Hz, 1H), 3.58 (t, *J* = 6.2 Hz, 2H), 3.12 (t, *J* = 7.4 Hz, 2H), 2.56 (s, 3H), 2.40 – 2.25 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 152.8, 137.8, 124.7, 123.1, 122.5, 112.1, 44.2, 30.8, 26.2, 17.1. **IR** (neat) υ_{max}/cm^{-1}: 2862, 1620, 1537, 1444, 1278, 1080, 966, 784, 744. **MS** (CI +ev) m/z (%): 211 (4), 209 (16), 173 (28), 172 (100). **HRMS** (CI): Calcd for $C_{11}H_{14}N_2Cl$: 209.0845, found : 209.0843. **MP**: 101-102℃.

2-(3-chloropropyl)-5-methyl-1H-benzo[d]imidazole (12g): CAS: 1096805-89-8



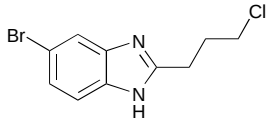
Yield: 73% - slightly brown solid. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (10:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 11.23 (s, 1H), 7.46 (d, *J* = 8.2 Hz, 1H), 7.37 (s, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 3.58 (t, *J* = 6.2 Hz, 2H), 3.14 (t, *J* = 7.4 Hz, 2H), 2.46 (s, 3H), 2.42 – 2.27 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 153.7 138.4, 137.0, 132.2, 123.8, 114.6, 114.2, 44.1, 30.8, 26.4, 21.6. **IR** (neat) υ_{max}/cm^{-1}: 2991, 1620, 1537, 1440, 1278, 1230, 1080, 740. **MS** (CI +ev) m/z (%): 209 (4), 173 (100) 172 (26). **HRMS** (CI): Calcd for $C_{11}H_{14}N_2Cl$: 209.0845, found: 209.0839. **MP**: 102-103℃.

5-chloro-2-(3-chloropropyl)-1H-benzo[d]imidazole (12h):



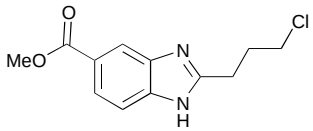
Yield: 85% - beige solid. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (10:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.98 (s, 1H), 7.52 (d, *J* = 1.5 Hz, 1H), 7.44 (d, *J* = 8.6 Hz, 1H), 7.20 (dd, *J* = 8.6, 1.8 Hz, 1H), 3.60 (t, *J* = 6.1 Hz, 2H), 3.11 (t, *J* = 7.3 Hz, 2H), 2.33 (p, *J* = 6.7 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 154.6, 138.8, 136.7, 128.3, 123.2, 115.4, 114.6, 44.0, 30.4, 26.1. **IR** (neat) υ_{max}/cm^{-1}: 2970, 1622, 1504, 1446, 1292, 1058, 800, 702. **MS** (CI +ev) m/z (%) : 229 (4), 195 (32), 194 (34), 193 (100), 192 (64). **HRMS** (CI): Calcd for $C_{10}H_{11}N_2Cl_2$: 229.0299, found: 229.0304. **MP**: 102-103℃.

5-bromo-2-(3-chloropropyl)-1H-benzo[d]imidazole (12i):



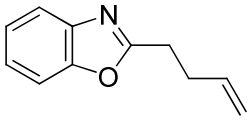
Yield: 84% - slightly brown solid. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (10:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.69 (s, 1H), 7.37 (dd, *J* = 21.3, 8.5 Hz, 2H), 3.62 (td, *J* = 8.7, 3.4 Hz, 2H), 3.10 (t, *J* = 7.3 Hz, 2H), 2.38 – 2.30 (m, 2H). **^{13}C NMR** (75 MHz, DMSO) δ = 155.6, 139.3, 136.3, 125.4, 117.6, 116.3, 114.8, 45.1, 30.3, 25.8. **IR** (neat) υ_{max}/cm^{-1}: 2858, 1620, 1531, 1454, 1407, 1292, 1272, 1049, 912, 804. **MS** (APCI +ev) m/z (%): 277 (11), 275 (36), 273 (28), 240 (11), 239 (95), 237 (100). **HRMS** (CI) Calcd for $C_{10}H_{11}N_2BrCl$: 272.9794, found: 272.9789. **MP**: 94-95℃.

Methyl 2-(3-chloropropyl)-1H-benzo[d]imidazole-5-carboxylate (12j):



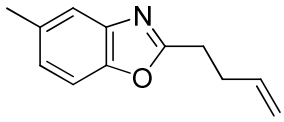
Yield: 85% - beige solid. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (10:1).**^{1}H NMR** (300 MHz, $CDCl_3$) δ = 9.72 (s, 1H), 8.29 (s, 1H), 7.95 (dd, *J* = 8.5, 1.4 Hz, 1H), 7.56 (d, *J* = 8.5 Hz, 1H), 3.92 (s, 3H), 3.60 (t, *J* = 6.1 Hz, 2H), 3.16 (t, *J* = 7.4 Hz, 2H), 2.38 – 2.33 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 167.9, 156.4, 142.2, 138.1, 124.3, 124.0, 116.9, 114.4, 77.5, 77.1, 76.6, 52.2, 44.0, 30.5, 26.4. **IR** (neat) υ_{max}/cm^{-1}: 2621, 1714, 1625, 1573, 1433, 1313, 1209, 1081, 763, 740. **MS** (ESI +ev) m/z (%): 255 (33), 253 (100), 217 (24). **HRMS** (ESI): Calcd for $C_{12}H_{14}N_2Cl$: 253.0744, found: 253.0744. **MP**: 74-76℃.

2-(but-3-enyl)benzo[d]oxazole (16a):



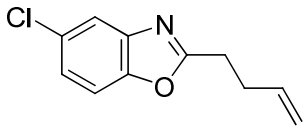
Yield: 85 % - colorless oil. **Purification**: **c**hromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (9.5/0.5). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.83 – 7.58 (m, 1H), 7.55 – 7.38 (m, 1H), 7.36 – 7.18 (m, 2H), 5.91 (ddt, *J* = 16.8, 10.2, 6.5 Hz, 1H), 5.16 – 5.02 (m, 2H), 3.03 (t, *J* = 7.6 Hz, 2H), 2.65 (dt, *J* = 13.9, 6.9 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 166.40, 150.76, 141.30, 136.20, 124.44, 124.04, 119.55, 116.05, 110.23, 30.55, 28.09. **IR** (neat) υ_{max}/cm^{-1}: 2930, 2918, 2853, 1614, 1572, 1454, 1435, 1269,1242, 1151, 1002, 916, 744. **MS** (EI +ev) m/z (%): 173 (100), 172 (54), 132 (39), 104 (19). **HRMS** (EI) Calcd for $C_{11}H_{10}NO$: 172.0757, found: 172.0755.

2-(but-3-enyl)-5-methylbenzo[d]oxazole (16b):



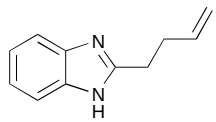
Yield: 80 % - colorless oil. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (9.5/0.5). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.46 (s, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 5.91 (ddt, *J* = 16.8, 10.3, 6.5 Hz, 1H), 5.13 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.04 (dd, *J* = 10.2, 1.3 Hz, 1H), 3.02 (t, *J* = 7.6 Hz, 2H), 2.64 (m, 2H), 2.46 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 166.4, 149.0, 141.5, 136.2, 133.78, 125.4, 119.5, 116.0, 109.5, 30.6, 28.1, 21.3. **IR** (neat) υ_{max}/cm^{-1} : 2951, 2905, 2853, 1678, 1573, 14581, 1426, 1259,1157, 997, 914, 797. **MS** (EI +ev) m/z (%): 187 (53), 186 (100), 146(32), 118 (17). **HRMS** (EI) Calcd for $C_{12}H_{12}ON$: 186.0913, found: 186.0907.

2-(but-3-enyl)-5-chlorobenzo[d]oxazole (16c):



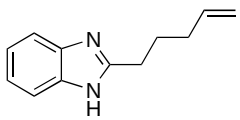
Yield: 88 % - colorless oil. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (9/1). **^{1}H NMR** (300 MHz, CDCl3) δ = 7.65 (s, 1H), 7.39 (d, *J* = 8.6 Hz, 1H), 7.32 – 7.13 (m, 1H), 5.90 (ddt, *J* = 16.8, 10.3, 6.5 Hz, 1H), 5.08 (m, 2H), 3.03 (t, *J* = 7.6 Hz, 2H), 2.64 (q, *J* = 6.9 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 167.9, 149.3, 142.46, 136.0, 129.6, 124.8, 119.6, 116.2, 111.0, 30.5, 28.1. **IR** (neat) υ_{max}/cm^{-1}: 2905, 2891, 2849, 1659, 1634, 1454, 1377, 1242, 1144, 1022, 914, 744. **MS** (CI +ev) m/z (%): 210 (30), 209 (26), 208 (100), 207 (46), 206 (31). **HRMS** (CI) Calcd for $C_{11}H_{11}ONCl$: 208.0529, found: 208.0527.

2-(but-3-en-1-yl)-1H-benzo[d]imidazole (16d): CAS: 5838-57-3



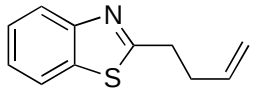
Yield: 75% - white solid. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (10:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.59 – 7.56 (m, 2H), 7.28 – 7.23 (m, 2H), 5.97 – 5.88 (m, 1H), 5.17 – 5.05 (m, 2H), 3.07 (t, *J* = 7.5 Hz, 2H), 2.65 (q, *J* = 7.4 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 154.2, 138.2, 136.8, 122.4, 116.4, 114.7, 32.0, 28.6. **IR** (neat) υ_{max}/cm^{-1}: 2894, 2717, 1622, 1539, 1448, 1423, 1272, 1033, 916, 740. **MS** (APCI +ev) m/z (%): 173 (100), 159 (6). **MP**: 166-167℃.

2-(pent-4-en-1-yl)-1H-benzo[d]imidazole (17d):



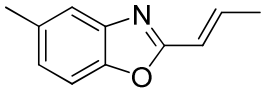
Yield: 75% - orange solid. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (10:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 10.43 (s, 1H), 7.57 (dt, *J* = 6.6, 3.3 Hz, 2H), 7.27 – 7.22 (m, 2H), 5.78 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.05 – 4.97 (m, 2H), 2.99 – 2.94 (m, 2H), 2.16 (dd, *J* = 13.8, 6.8 Hz, 2H), 2.04 – 1.94 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 154.9, 137.6, 122.21, 115.5, 114.7, 33.2, 28.7, 27.3. **IR** (neat) υ_{max}/cm^{-1}: 2929, 2833, 1639, 1589, 1537, 1446, 1423, 1315, 1271, 1222, 1027, 908, 781. **MS** (APCI, +eV) m/z (%): 187 (100), 145 (47), 132 (78). **HRMS** (APCI): Calcd for $C_{12}H_{15}N_2$: 187.1229, found: 187.1231. **MP**: 185-186 ℃.

2-(but-3-en-1-yl)benzo[d]thiazole (16e):



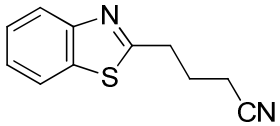
Yield: 95% - yellow oil. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (10:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.97 (d, J = 8.1 Hz, 1H), 7.83 (d, J = 7.9 Hz, 1H), 7.47 – 7.37 (m, 1H), 7.34 – 7.32 (m, 1H), 5.90 (ddt, J = 16.8, 10.2, 6.5 Hz, 1H), 5.16 – 5.03 (m, 2H), 3.24 – 3.19 (m, 2H), 2.68 – 2.61 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 171.2, 153.2, 136.4, 135.2, 125.9, 124.7, 122.6, 121.5, 116.2, 33.7, 33.4. **IR** (neat) υ_{max}/cm^{-1}: 3074, 2916, 1641, 1519, 1434, 1311, 1242, 1062, 914, 757. **MS** (EI +ev) m/z (%): 189 (100), 174 (36), 148 (33). **HRMS:** Calcd for $C_{11}H_{12}NS$: 190.0691, found: 190.0696.

(E)-5-methyl-2-(prop-1-enyl)benzo[d]oxazole (21):



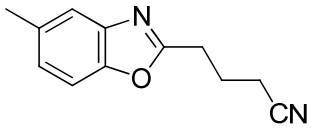
Yield: 80 % - colorless oil. **Purification**: **c**hromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (9.5/0.5). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.44 (d, *J* = 0.5 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 7.09 (d, *J* = 8.3 Hz, 1H), 6.99 (dq, *J* = 15.8, 6.9 Hz, 1H), 6.52 – 6.34 (dq, *J* = 15.8, 1.7 Hz, 1H), 2.44 (s, 3H), 1.99 (dd, *J* = 6.9, 1.7 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 162.5, 148.4, 142.1, 138.6, 134,0, 125.8, 119.61, 118.3, 109.5, 21.4, 18.6. **IR** (neat) υ_{max}/cm^{-1}: 2952, 2920, 2845, 1668, 1539, 1446, 1261, 1192,1182, 1165, 962, 797. **MS** (EI +ev) m/z (%): 173 (100), 172 (35), 172 (35), 147 (26). **HRMS** (EI) Calcd for $C_{11}H_{11}NO$: 173.0835, found: 173.0834.

4-(benzo[d]thiazol-2-yl)butanenitrile (22): CAS: 21344-52-5



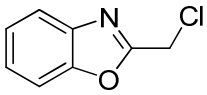
Yield: 95% - colorless oil. **Purification**: chromatography on silica gel: Eluent: Dichloromethane. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.98 (d, *J*=7.9, 1H), 7.91 – 7.81 (m, 1H), 7.54 – 7.43 (m, 1H), 7.43 – 7.34 (m, 1H), 3.28 (t, *J*=7.2, 2H), 2.56 (t, *J*=7.2, 2H), 2.37 – 2.24 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 168.7, 153.2, 135.0, 126.1, 125.07, 122.7, 121.6, 119.0, 32.4, 24.7, 16.5. **IR** (neat) υ_{max}/cm^{-1}: 2974, 2947, 2921, 2868, 2245, 1520, 1454, 1435, 1311, 1242, 1113, 879, 862, 760, 729. **MS** (EI +ev) m/z (%): 202 (29), 162 (23), 149 (100). **HRMS** (EI) Calcd for $C_{11}H_{10}N_2S$: 202.0559, found: 202.0559.

4-(5-methylbenzo[d]oxazol-2-yl)butanenitrile (23):



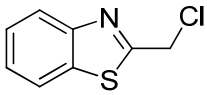
Yield: 75% - colorless oil. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (9/1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.46 (s, 1H), 7.36 (d, *J*=8.3, 1H), 7.15 (s, 1H), 3.10 (t, *J*=7.1, 2H), 2.59 (t, *J*=7.1, 2H), 2.46 (s, 3H), 2.35 – 2.21 (quintuplet, *J*=7.1, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 164.7, 145.0, 141.2, 134.2, 125.95, 119.6, 118.9, 109.8, 27.1, 22.4, 21.4, 16.6. **IR** (neat) υ_{max}/cm^{-1}: 2947, 2921, 2842, 2263, 1731, 1574, 1429, 1261, 1242, 1157, 945, 802. **MS** (EI +ev) m/z (%): 200 (52), 160 (52), 147 (100), 146 (23). **HRMS** (EI) Calcd for $C_{12}H_{12}ON_2$: 200.0944, found: 200.0947.

2-(chloromethyl)benzo[d]oxazole (24):



Yield: 85 % - colorless oil. **Purification**: recrystallization with ethanol: Eluent: Petroleum ether/Ethyl acetate (9/1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.76 – 7.74 (m, 1H), 7.58 – 7.55 (m, 1H), 7.43 – 7.34 (m, 2H), 4.76 (s, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ = 160.8, 151.1, 140.8, 125.9, 124.8, 120.5, 110.9, 36.35. **IR** (neat) u_{max}/cm^{-1}: 3046, 3037, 1614, 1572, 1452, 1348, 1294, 1240, 1175, 1142, 1003, 959, 837. **MS** (APCI +ev) m/z (%): 188 (37), 186 (100), 150 (76), 114 (30). **HRMS** (APCI) Calcd for $C_{10}H_{10}ONCl$: 186.0318, found: 186.0316.

2-(chloromethyl)benzo[d]thiazole (25):

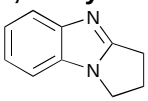


Yield: 94 % - colorless oil. **Purification**: chromatography on silica gel: Eluent Petroleum ether/Ethyl acetate (9/1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 8.03 (d, *J* = 8.1 Hz, 1H), 7.91 (dd, *J* = 7.9, 0.5 Hz, 1H), 7.52 (td, *J* = 7.8, 1.3 Hz, 1H), 7.47 – 7.40 (m, 1H), 4.96 (s, 2H).**^{13}C NMR** (75 MHz, $CDCl_3$) δ = 166.8, 152.8, 135.8, 126.5, 125.7, 123.4, 121.8, 42.0.**IR** (neat) u_{max}/cm^{-1}: 3045, 3052, 1512, 1456, 1433, 1313, 1281, 1261, 1112, 1013, 858, 758. **MS** (ESI +ev) m/z (%): 186 (37), 184 (100), 163 (27). **HRMS** (ESI**)** Calcd for $C_{10}H_{10}ONCl$: 183.9985, found: 183.9982.

General procedure for cyclisation:

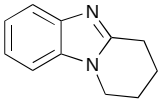
To a solution of the benzimidazole derivative (1 mmol, 1 eq) in dry THF (10 mL, 0.1M) was added NaH (1.1 mmol, 60% in oil, 1.1 eq). The reaction mixture was stirred at reflux until complete conversion. Then, a saturated aqueous solution of $NaHCO_3$ was added. The layers were separated and the aqueous phase was extracted with 3 x 10 mL of DCM. The organic phases were pooled, dried over Na_2SO_4, filtered and the solvents were removed under reduced pressure. The crude product was then purified by flash chromatography if needed.

2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole (26a): CAS: 7724-48-3



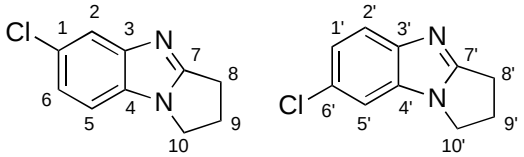
Yield: 93% - white solid. **Purification:** no purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.75 – 7.69 (m, 1H), 7.31 – 7.20 (m, 3H), 4.10 (t, *J* = 7.0 Hz, 2H), 3.07 (t, *J* = 7.6 Hz, 2H), 2.77 – 2.66 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 161.2, 148.8, 132.4, 121.7, 121.6, 119.5, 109.5, 42.7, 26.0, 23.5. **IR** (neat) u_{max}/cm^{-1}: 3407, 2918, 1623, 1525, 1415, 1280, 1217, 1004, 908. **MS** (APCI +ev) m/z (%): 159 (100), 131 (62), 92 (24). **MP:** 105-106℃.

1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-a]pyridine (26b): CAS: 5622-83-3



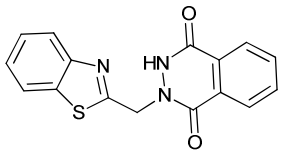
Yield: 95% - white solid. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (6:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.70 – 7.67 (m, 1H), 7.30 – 7.21 (m, 3H), 4.09 (t, *J* = 6.0 Hz, 2H), 3.10 (t, *J* = 6.4 Hz, 2H), 2.18 – 1.99 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 151.7, 122.1, 121.7, 118.9, 108.7, 42. 5, 25.5, 22.7, 20.8. **IR** (neat) u_{max}/cm^{-1}: 2916, 2850, 1668, 1614, 1510, 1313, 1284, 1004, 904. **MS** (CI +ev) m/z (%): 173 (100), 132 (64). **MP**: 98-99℃.

6-(and 7-)chloro-2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazole (26c and 26c'): CAS: 10252-95-6



Yield: 95% - white solid. **Purification**: chromatography on silica gel: Eluent: Petroleum ether/Ethyl acetate (6:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.67 – 7.57 (m, 1H), 7.28 – 7.16 (m, 2H), 4.07 (dt, *J* = 12.5, 6.9 Hz, 2H), 3.05 (t, *J* = 7.6 Hz, 2H), 2.76 – 2.67 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 162.5 and 162.1 (C_7 and $C_{7'}$), 149.6 and 147.4 (C_3 and $C_{3'}$), 132.9 and 130.9 (C_1 and $C_{6'}$), 127.3 and 127.1 (C_4 and $C_{4'}$), 122.1 and 122.0 (C_6 or $C_{1'}$), 120.2 and 119.2 (C_5 and $C_{5'}$), 110.1 and 109.7 (C_2 and $C_{2'}$), 42.9 and 42.7 (C_{10} and $C_{10'}$), 25.9 (C_8 and $C_{8'}$), 23.5 and 23.4 (C_9 and $C_{9'}$). **IR** (neat) υ_{max}/cm^{-1}): 2908, 2854, 1614, 1525, 1454, 1406, 1325, 1290, 1263, 1054, 973, 912, 810. **MS** (CI +ev) m/z (%): 195 (34%), 193 (100). **HRMS** (CI) Calcd for $C_{10}H_{10}N_2Cl$: 193.0532, found: 193.0535.

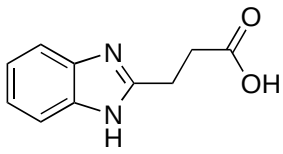
2-(benzo[d]thiazol-2-ylmethyl)-2,3-dihydrophthalazine-1,4-dione (28):



A mixture of phthalhydrazide **27** (86 mg, 0.53 mmol, 1 eq.), benzothiazole **25** (100 mg, 0.54 mmol, 1.02 eq.), K_2CO_3 (80 mg, 0.58 mmol, 1.1 eq.), and NaBr (60 mg, 0.58 mmol, 1.1 eq) in DMF (3 mL) was stirred at 80 ℃ for 4 h. To the mixture, H_2O (1 mL) was added. The precipitate was filtered and washed with cold H_2O (1 mL). The crude solid was recrystallized from EtOH (5 mL) to give the ester **28**.

Yield: 85 % - white solid. **Purification**: recrystallization with ethanol. **^{1}H NMR** (300 MHz, DMSO-d_6) δ = 12.10 (brs, 1H), 8.30 (d, J = 7.5 Hz, 1H), 8.19 – 7.97 (m, 5H), 7.62 – 7.50 (m, 2H), 5.86 (s, 2H).**^{13}C NMR** (75 MHz, DMSO-d_6) δ = 168.6, 159.9, 153.5, 149.7, 135.5, 134.9, 133.7, 129.9, 127.5, 126.5, 125.1, 124.3, 123.8, 123.5, 80.2, 66.6. **IR** (neat) υ_{max}/cm^{-1}: 3340, 2937, 1667, 1519, 1393, 1190, 1103, 11045, 775. **HRMS** (APCI) Calcd for $C_{10}H_{10}ONCl$: 310.0647, found: 310.0645. **MP**: 130- 131℃.

3-(1H-benzo[d]imidazol-2-yl)propanoic acid (Procodazole) (29): CAS: 23249-97-0

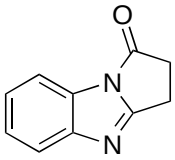


Ozone was passed through a -78℃ solution of 2-(pent-4-en-1-yl)-1H-benzo[d]imidazole (**16d**) (172 mg, 1 mmol, 1 eq.) in dry DCM (20 mL, 0.05M) until the solution turned blue. Then, Me_2S (0.148 mL, 2 mmol, 2 eq.) was added at room temperature and the mixture was stirred overnight. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ and the product was extracted 3 x 20 mL of DCM. The organic phases were collected, dried over Na_2SO_4, filtered and the solvents were removed under reduced pressure.

The crude aldehyde was dissolved in DMF (10 mL, 0.1M) and oxone (675 mg, 1.1 eq.) was then added all at once. After stirring at room temperature for 24h, a saturated aqueous solution of $NaHCO_3$ was added and the product was extracted with 3 x 10 mL of DCM. The organic phases were collected, dried over Na_2SO_4, filtered and the solvents were removed under reduced pressure.

Yield: 52% - pale beige solid. **Purification**: recrystalisation in EtOH/ water. **^{1}H NMR** (300 MHz, DMSO-d_6) δ = 7.45 (dd, *J* = 5.9, 3.1 Hz, 2H), 7.10 (dd, *J* = 5.9, 3.1 Hz, 2H), 3.03 (t, *J* = 7.2 Hz, 2H), 2.78 (t, *J* = 7.2 Hz, 2H). **^{13}C NMR** (75 MHz, DMSO-d_6) δ = 173.9, 154.3 121.6, 114.9, 49.0, 31.7, 24.2. **IR** (neat) υ_{max}/cm^{-1}: 3542, 3330, 2904, 1733, 1631, 1585, 1402, 1290, 1016, 777. **MS** (APCI +ev) m/z (%): 191 (9), 173 (100). **MP:** 226-228℃.

2,3-dihydro-1H-benzo[d]pyrrolo[1,2-a]imidazol-1-one (30): CAS: 19950-82-4



Procodazole (200 mg, 1.052 mmol, 1 eq.) was dissolved in Ac_2O (4.96 mL, 52.6 mmol, 50 eq.) and the mixture was stirred for 2h at 100℃. The acetic anh ydride was removed under vacuum, the resulting brown solid was washed with cold acetone and then dried under reduced pressure to give the pure product **30**.

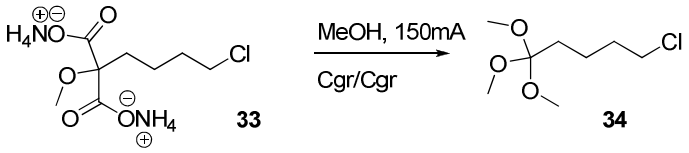
Yield: 79% - slightly yellow solid. **Purification**: no purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.87 (d, J = 7.5 Hz, 1H), 7.67 (dd, J = 7.2, 1.2 Hz, 1H), 7.38 – 7.28 (m, 2H), 3.29 – 3.16 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 169.9, 162.1, 149.3, 128.48, 125.4, 124.3, 120.0, 113.0, 34.5, 21.2. **IR** (neat) υ_{max}/cm^{-1}: 2968, 2916, 1758, 1704, 1616, 1552, 1433, 1379, 1323, 1186, 1155, 1014, 808, 750. **MS** (EI +ev) m/z (%): 172 (7), 144 (37), 158 (43). **MP**: 175-176℃.

General procedure for the electrolysis of ammonium salt:

Mathot, C.; Lam, K.; Lucaccioni F.; Markó, I.E. *Unpublished work*.

An undivided cell of 50 mL capacity bearing a cooling jacket was dried at 200℃ and equipped with two graphite carbon electrodes of 4.5 cm² and a magnetic stir bar. Ammonium salt of malonic acid (3 mmol) was dissolved in 50 mL of p.a. methanol under stirring and cooling. Then, the intensity of the current was fixed at 150 mA (33 mA.cm-²) by using a DC power supply, and the mixture was electrolyzed until completion of the reaction, shown by homogenization of the solution. Solvent was removed under reduce pressure, 20 mL of diethyl ether was added and the solution was filtered. The solvent was then removed under reduce pressure affording the crude orthoester that can be used directly or distillates under reduce pressure.

Example of **5-chloro-1,1,1-trimethoxypentane (34):**



33 **34**

Yield: 81% - slightly yellow oil. **Purification**: no purification. **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 3.54 (t, J = 6.7 Hz, 2H), 3.24 (s, 9H), 1.72 –1.85 (m, 4H), 1.44 – 1.56 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ = 115.7, 49.6, 44.9, 32.4, 29.7, 20.4. **IR** (neat) υ_{max}/cm^{-1}: 2945, 1460, 1439, 1304, 1290, 1240, 1159, 1101, 1036, 983, 876, 818, 731. **MS** (CI +ev) m/z (%):165 (100), 161 (47), 129 (24). **HRMS** (CI) Calcd for $C_7H_{14}O_2Cl$: 165.0682, found: 165.0683.