Experimental Procedures and Characterization Data for
Synthesis of Imidazoles via Cascade Reaction of Nitroallylic Acetates with Amidines and
Studies on Their Trypanocidal Activity

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Table S1 Crystal data and structure refinement for 6d (CCDC 1037602)

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Experimental section

General. The melting points recorded are uncorrected. NMR spectra ($^1$H, $^1$H decoupled $^{13}$C and $^{13}$C-APT) were recorded with TMS as the internal standard. The coupling constants (J values) are given in Hz. High resolution mass spectra were recorded under ESI Q-TOF conditions. X-ray data were collected on a diffractometer equipped with graphite monochromated Mo Kα radiation. The structure was solved by direct methods SHELXS-97 and refined by full-matrix least squares against F² using SHELXL-97 software.¹ Amidinium salt 2a was purchased from Sigma-Aldrich and others (2b-h) were prepared following published procedures.²

General procedure for the synthesis of imidazoles 3-4. To a stirred solution of amidine 2 (0.24 mmol) and DABCO (61 mg, 0.5 mmol) in acetonitrile (2 mL) at room temperature, MBH acetate 1 (0.20 mmol) was added. After the completion of reaction (monitored by TLC), the solvent was removed in vacuo and the crude residue was purified by silica gel column chromatography by gradient elution with pet ether/ethyl acetate (20-90%).

Ethyl 2-(4-(4-methoxyphenyl)-2-phenyl-1H-imidazol-5-yl)acetate (3a). Yellow solid; yield 62 mg, 92%; mp 137-138 °C; $ν_{max}$(KBr)/cm⁻¹ 3306, 2982, 2936, 2836, 1730, 1618, 1608, 1508, 1462, 1368, 1336, 1288, 1250, 1177, 1030, 835, 738, 695; δH (CDCl₃) 1.23 (3H, t, J 7.2 Hz), 3.74 (2H, s), 3.79 (3H, s), 4.14 (2H, q, J 7.2 Hz), 6.89 (2H, d, J 8.8 Hz), 7.27-7.38 (3H, m), 7.44 (2H, d, J 8.8 Hz), 7.81 (2H, dd, J 8.2, 1.4 Hz); δC (100 MHz, CDCl₃) 14.3, 32.6, 55.5, 61.5, 114.3, 125.4, 128.7, 128.8, 128.9, 130.0, 145.7, 159.1, 171.5; MS (ES+) m/z (rel intensity) 375 (MK⁺, 27), 359 (MNA⁺, 80), 337 (MH⁺, 100); HRMS (ES+) calcd for C₁₅H₂₁N₂O₃ (MH⁺) 337.1547, found 337.1543.

Ethyl 2-(4-(2,4-dimethoxyphenyl)-2-phenyl-1H-imidazol-5-yl)acetate (3b). Yellow solid; yield 50 mg, 68%; mp 133 °C; $ν_{max}$(KBr)/cm⁻¹ 2962, 2938, 2873, 1734, 1611, 1583, 1501, 1465, 1370, 1304, 1283, 1266, 1210, 1161, 1050, 1033, 917, 836, 774, 736, 704; δH (CDCl₃, 400 MHz) 1.25 (3H, t, J 7.1 Hz), 3.77 (2H, s), 3.84 (3H, s), 3.85 (3H, s), 4.18 (2H, q, J 7.1 Hz), 6.54 (1H, d, J 2.3 Hz), 6.57 (1H, dd, J 8.4, 2.3 Hz), 7.32-7.36 (1H, m), 7.43-7.39 (2H, m), 7.46 (1H, d, J 8.4 Hz), 7.83-7.88 (2H, m); δC (CDCl₃, 100 MHz) 14.4, 34.0, 55.6, 55.8, 61.1, 99.3, 105.1, 112.5, 125.4, 128.7, 128.9, 130.1, 130.7, 144.9, 157.3, 160.8, 171.7; MS (ES+) m/z (rel intensity) 389 (MNA⁺, 40), 367 (MH⁺, 100), 324 (13), 308 (47); HRMS (ES+) calcd for C₂₀H₂₃N₂O₄ (MH⁺) 367.1652, found 367.1653.

Ethyl 2-(4-(3,4-dimethoxyphenyl)-2-phenyl-1H-imidazol-5-yl)acetate (3c). White solid; yield 63 mg, 86%; mp 137 °C; $ν_{max}$(KBr)/cm⁻¹ 2959, 2920, 2850, 1728, 1685, 1512, 1464, 1255, 1224, 1180, 1140, 1025, 765, 736; δH (CDCl₃, 400 MHz)
1.25 (3H, t, J 7.1 Hz), 3.79 (2H, s), 3.86 (3H, s), 3.87 (3H, s), 4.16 (2H, q, J 7.1 Hz), 6.86 (1H, d, J 8.3 Hz), 7.04 (1H, dd, J 8.3, 1.8 Hz), 7.18 (1H, d, J 1.8 Hz), 7.31-7.38 (3H, m), 7.84-7.88 (2H, m); δC (CDCl3, 100 MHz) 14.3, 32.5, 56.0, 61.5, 111.1, 111.4, 119.9, 125.5, 128.8, 129.0, 129.9, 145.7, 148.6, 149.2, 171.4; MS (ES+) m/z (rel intensity) 405 (MK⁺, 3), 389 (MNA⁺, 20), 367 (MH⁺, 100); HRMS (ES+) calcd for C₂₁H₂₃N₂O₄ (MH⁺) 367.1652, found 367.1659.

Ethyl 2-(4-(benzo[d][1,3]dioxol-5-yl)-2-phenyl-1H-imidazol-5-yl)acetate (3d). Yellow solid; yield 64 mg, 91%; mp 136 °C; νmax(KBr/cm⁻¹) 3055s, 2985s, 2926m, 1728vs, 1607s, 1537w, 1504vs, 1484vs, 1370m, 1332m, 1264vs, 1235vs, 1103m, 1040vs, 937s, 894m, 870w, 815s, 773vs, 735vs; δH (CDCl3, 400 MHz) 1.22 (3H, t, J 7.2 Hz), 3.71 (2H, s), 4.13 (2H, q, J 7.1 Hz), 5.92 (2H, s), 6.76 (1H, d, J 8.0 Hz), 6.94 (1H, dd, J 8.0, 1.1 Hz), 6.98 (1H, d, J 1.1 Hz), 7.26-7.32 (3H, m), 7.78 (2H, m); δC (CDCl3, 100 MHz) 14.2, 32.5, 61.5, 101.2, 108.1, 108.6, 121.2, 125.4, 126.3, 128.6, 128.8, 130.0, 145.8, 146.9, 147.9, 171.5; MS (ES+) m/z (rel intensity) 389 (MK⁺, 3), 373 (MNA⁺, 13), 351 (MH⁺, 100); HRMS (ES+) calcd for C₂₀H₁₉N₂O₄ (MH⁺) 351.1339, found 351.1336.

Ethyl 2-(2-phenyl-4-p-tolyl-1H-imidazol-5-yl)acetate (3e). Yellow solid; yield 58 mg, 91%; mp 151-152 °C; νmax(KBr/cm⁻¹) 3306br w, 3044m, 2983m, 2924m, 1734vs, 1594w, 1537w, 1508m, 1463m, 1411m, 1394m, 1369m, 1336w, 1303w, 1180m, 1031s, 823m; δH (400 MHz, CDCl3) 1.22 (3H, t, J 7.1 Hz), 2.34 (3H, s), 3.76 (2H, s), 4.14 (2H, q, J 7.1 Hz), 7.16 (2H, d, J 7.9 Hz), 7.27-7.36 (3H, m), 7.41 (2H, d, J 7.9 Hz), 7.81 (2H, dd, J 8.1, 1.3 Hz); δC (100 MHz, CDCl3) 14.3, 21.4, 32.7, 61.4, 125.4, 127.3, 128.7, 128.9, 130.5, 137.1, 145.8, 171.5; MS (ES+) m/z (rel intensity) 359 (MK⁺, 33), 343 (MNA⁺, 83), 321 (MH⁺, 100); HRMS (ES+) calcd for C₂₀H₂₁N₂O₂ (MH⁺) 321.1598, found 321.1598.

Ethyl 2-(2,4-diphenyl-1H-imidazol-5-yl)acetate (3f). Yellow solid; yield 55 mg, 89%; mp 122-123 °C; νmax(KBr/cm⁻¹) 3318br w, 3060m, 2982m, 1732vs, 1607w, 1591m, 1495s, 1464s, 1413m, 1400w, 1369w, 1251w, 1181m, 1029s, 774m, 698s; δH (400 MHz, CDCl3) 1.19 (3H, t, J 7.1 Hz), 3.74 (2H, s), 4.10 (2H, q, J 7.1 Hz), 7.22-7.35 (6H, m), 7.50 (2H, d, J 7.2 Hz), 7.80 (2H, dd, J 7.9, 1.6 Hz); δC (100 MHz, CDCl3) 14.2, 32.6, 61.4, 125.5, 127.3, 127.4, 128.6, 128.7, 128.8, 130.0, 132.2, 146.2, 171.4; MS (ES+) m/z (rel intensity) 345 (MK⁺, 17), 329 (MNA⁺, 100), 307 (MH⁺, 28); HRMS (ES+) calcd for C₁₉H₁₈N₂O₂ (M⁺Na) 329.1260, found 329.1261.

Ethyl 2-(4-(4-fluorophenyl)-2-phenyl-1H-imidazol-5-yl)acetate (3g). Yellow solid; yield 44 mg, 68%; mp 140-141 °C; νmax(KBr/cm⁻¹) 3314br w, 3065w, 2984m, 2929w, 1732vs, 1607m, 1586w, 1537m, 1506s, 1463m, 1413m, 1369m, 1228s, 1031s, 841m, 694m, 609m; δH (400 MHz, CDCl3) 1.30 (3H, t, J 7.1 Hz), 3.85 (2H, s), 4.25 (2H, q, J 7.1 Hz), 7.14 (2H, t, J 8.7 Hz), 7.35-7.40 (1H, m), 7.45 (2H, d, J 8.7 Hz), 7.62 (2H, br, unresolved), 7.87 (2H, d, J 8.0 Hz); δC (100 MHz, CDCl3) 14.3, 32.1, 61.6, 115.7 (d, J = 21.0 Hz), 125.5, 128.9, 129.2, 129.3, 129.8, 146.1, 162.2 (d, J = 246.0 Hz), 171.3; MS (ES+) m/z (rel intensity) 347 (MNA⁺, 56), 325 (MH⁺, 100); HRMS (ES+) calcd for C₁₉H₁₈FNO₂ (MH⁺) 325.1347, found 325.1340.

Ethyl 2-(4-(4-chlorophenyl)-2-phenyl-1H-imidazol-5-yl)acetate (3h). Yellow solid; yield 46 mg, 67%; mp 130 °C; νmax(KBr/cm⁻¹) 2981s, 2938m, 2872w, 1732vs, 1490s, 1464s, 1409m, 1370m, 1264s, 1210s, 1188s, 1093m, 1031m, 1011m, 835m, 775m, 737m, 705m; δH (CDCl3, 400 MHz) 1.29 (3H, t, J 7.1 Hz), 3.85 (2H, s), 4.23 (2H, q, J 7.1 Hz), 7.34-7.45 (5H, m), 7.55 (2H, d, J 8.4 Hz), 7.84-7.88 (2H, m); δC (CDCl3, 100 MHz) 14.2,
32.2, 61.7, 125.5, 128.6, 128.9, 129.8, 131.1, 133.1, 146.3, 171.3; MS (ES+) m/z (rel intensity) 363 (MNa+, 45), 341 (MH+, 100), 331 (3); HRMS (ES+) calcd for C_{19}H_{18}ClN_{2}O_{2} (MH+) 341.051, found 341.0506.

Ethyl 2-(4-(3-bromophenyl)-2-phenyl-1H-imidazol-5-yl)acetate (3i). Yellow solid; yield 50 mg, 65%; mp 122 °C; v_{\text{max}}(KBr)/cm\(^{-1}\) 3061w, 2981s, 2930m, 2872w, 1735vs, 1586m, 1558m, 1476s, 1464m, 1413w, 1369w, 1182m, 1029s, 887w, 787s, 737s, 707s; δ_{H} (CDCl\(_3\), 400 MHz) 1.27 (3H, t, J 7.1 Hz), 3.79 (2H, s), 4.19 (2H, q, J 7.1 Hz), 7.21 (1H, t, J 7.9 Hz), 7.31-7.39 (4H, m), 7.45 (1H, d, J 7.9 Hz), 7.69 (1H, s), 7.79-7.83 (2H, m); δ_{C} (CDCl\(_3\), 100 MHz) 14.3, 32.0, 61.8, 122.8, 125.6, 125.9, 129.0, 129.1, 129.4, 130.2, 130.3, 134.7, 146.3, 171.1; MS (ES+) m/z (rel intensity) 385 (MH\(^{+}\), 100), 338 (15), 301 (10); HRMS (ES+) calcd for C_{19}H_{18}BrN_{2}O_{2} (MH\(^{+}\)) 385.0546, found 385.0546.

Ethyl 2-(4-(naphthalen-1-yl)-2-phenyl-1H-imidazol-5-yl)acetate (3j). Yellow solid; yield 48 mg, 67%; mp 166 °C; v_{\text{max}}(KBr)/cm\(^{-1}\) 3054w, 2985w, 2929w, 1734m, 1653s, 1462w, 1265m, 1028w, 739s, 705m; δ_{H} (CDCl\(_3\), 400 MHz) 1.19 (3H, t, J 7.1 Hz), 3.64 (2H, s), 4.12 (2H, q, J 7.1 Hz), 7.34-7.39 (1H, m), 7.41-7.54 (6H, m), 7.87-7.90 (4H, m), 7.96 (1H, br, unresolved); δ_{C} (CDCl\(_3\), 100 MHz) 14.2, 32.2, 61.3, 125.4, 126.0, 126.2, 126.6, 128.4, 128.5, 128.8, 128.9, 129.0, 129.9, 132.5, 133.9, 146.1, 171.3; MS (ES+) m/z (rel intensity) 379 (MNa\(^{+}\), 17), 357 (MH\(^{+}\), 100); HRMS (ES+) calcd for C_{23}H_{15}N_{2}O (MH\(^{+}\)) 357.1598, found 357.1592.

Ethyl 2-(4-(furan-2-yl)-2-phenyl-1H-imidazol-5-yl)acetate (3k). Yellow solid; mp 131-132 °C; yield 44 mg, 74%; v_{\text{max}}(KBr)/cm\(^{-1}\) 3448br s, 2983w, 2927w, 1735vs, 1665w, 1463m, 1370w, 1338w, 1266w, 1184w, 1026m, 738m; δ_{H} (400 MHz, CDCl\(_3\)) 1.25 (3H, t, J 7.1 Hz), 3.95 (2H, s), 4.17 (2H, q, J 7.1 Hz), 6.41 (1H, dd, J 3.3, 1.8 Hz), 6.57 (1H, d, J 3.3 Hz), 7.27-7.38 (4H, m), 7.82 (2H, dd, J 8.1, 1.4 Hz); δ_{C} (CDCl\(_3\) 100 MHz) 14.3, 32.2, 61.5, 105.7, 111.5, 125.5, 128.9, 129.7, 141.4, 146.2, 171.3; MS (ES+) m/z (rel intensity) 335 (MK\(^{+}\), 28), 320 (MHNa\(^{+}\), 50), 319 (MNa\(^{+}\), 100), 297 (MH\(^{+}\), 8); HRMS (ES+) calcd for C_{17}H_{16}N_{2}NaO_{3} (MNa\(^{+}\)) 319.1053, found 319.1054.

Ethyl 2-(2-phenyl-4-(thiophen-2-yl)-1H-imidazol-5-yl)acetate (3l). Yellow liquid; yield 39 mg, 62%; v_{\text{max}}(neat)/cm\(^{-1}\) 2983w, 2927w, 1733vs, 1623w, 1463w, 1328w, 1200w, 1027m, 849w, 735s, 696s; δ_{H} (CDCl\(_3\), 400 MHz) 1.29 (3H, t, J 7.2 Hz), 3.90 (2H, s), 4.22 (2H q, J 7.1 Hz), 7.07 (1H, dd, J 5.1, 3.6 Hz), 7.23 (1H, dd, J 3.6, 1.0 Hz), 7.27 (1H, dd, J 5.1, 1.0 Hz), 7.32-7.42 (3H, m), 7.85 (2H, m); δ_{C} (CDCl\(_3\), 100 MHz) 14.3, 31.9, 61.7, 124.1, 124.6, 125.5, 127.7, 128.9, 129.7, 146.0, 171.1; MS (ES+) m/z (rel intensity) 335 (MNa\(^{+}\), 10), 313 (MH\(^{+}\), 100); HRMS (ES+) calcd for C_{17}H_{17}N_{2}O_{2}S (MH\(^{+}\)) 313.1005, found 313.1010.

(E)-Ethyl 2-(2-phenyl-4-styryl-1H-imidazol-5-yl)acetate (3m). Yellow solid, yield 39 mg, 58%; mp 134° C; v_{\text{max}}(neat)/cm\(^{-1}\) 3061w, 2982w, 2963w, 2927w, 1735s, 1599w, 1528w, 1478m, 1463m, 1400w, 1370w, 1263s, 1180m, 1096w, 1028s, 959m, 774s, 738vs, 695vs; δ_{H} (CDCl\(_3\), 400 MHz) 1.28 (3H, t, J 7.1 Hz), 3.75 (2H, s), 4.20 (2H, q, J 7.1 Hz), 6.82, 6.95 (2H, ABq, J 16.2 Hz), 7.18-7.24 (2H, m), 7.25-7.38 (6H, m), 7.75-7.80 (2H, m); δ_{C} (CDCl\(_3\), 100 MHz) 14.3, 32.2, 61.7, 116.1, 125.5, 126.3, 126.9, 127.4, 128.8, 129.7, 137.5, 146.7, 171.6; MS (ES+) m/z (rel intensity) 371 (MK\(^{+}\), 13), 355 (MNa\(^{+}\), 100), 333 (MH\(^{+}\), 100); HRMS (ES+) calcd for C_{21}H_{17}N_{2}O_{2}S (MH\(^{+}\)) 333.1598, found 333.1598.

Ethyl 2-(4-cyclohexyl-2-phenyl-1H-imidazol-5-yl)acetate (3n). White solid; yield 42 mg, 67%; mp 167 °C; v_{\text{max}}(KBr)/cm\(^{-1}\) 2926vs, 2852s, 1733vs, 1459m, 1397w, 1248m, 1028m, 734s, 713s.
692s; δ_H (CDCl₃, 400 MHz) 1.18-1.28 (1H, m, merged with t), 1.25 (3H, t, J 7.2 Hz), 1.35 (2H, qt, J 12.4, 2.3 Hz), 1.49 (2H, qd, J 12.4, 2.3 Hz), 1.72 (1H, br d, J 12.4 Hz), 1.83 (4H, t, J 14.3 Hz), 2.62 (1H, tt, J 12.4, 3.4 Hz), 3.65 (2H, s), 4.14 (2H, q, J 7.2 Hz), 7.37-7.27 (3H, m), 7.76-7.80 (2H, m); δ_C (CDCl₃, 100 MHz) 14.3, 26.0, 26.8, 32.5, 33.2, 35.5, 61.2, 125.3, 128.5, 128.9, 130.3, 144.6, 171.5; MS (ES+) m/z (rel intensity) 314 ([(M+2]+, 33), 313 (MH⁺, 100); HRMS (ES+) calcd for C₁₉H₂₅N₂O₂ (MH⁺) 313.1911, found 313.1908.

**Ethyl 2-(4-phenyl-2-p-tolyl-1H-imidazol-5-yl)acetate (4a).** Yellow solid; yield 44 mg, 69%; mp 171 °C; ν_max(KBr)/cm⁻¹ 3054m, 2981s, 2926s, 2871m, 1735vs, 1609w, 1593w, 1495s, 1449m, 1389w, 1369w, 1300m, 1265s, 1250s, 1185vs, 1029m, 825m, 768m, 734vs, 700vs; δ_H (CDCl₃, 400 MHz) 1.25 (3H, t, J 7.1 Hz), 2.35 (3H, s), 3.82 (2H, s), 4.18 (2H, q, J 7.1 Hz), 7.18 (2H, d, J 8.1 Hz), 7.29 (1H, t, J 7.5 Hz), 7.39 (2H, t, J 7.5 Hz), 7.55 (2H, d, J 7.5 Hz), 7.74 (2H, d, J 8.1 Hz); δ_C (CDCl₃, 100 MHz) 14.3, 21.5, 32.4, 61.5, 125.4, 127.1, 127.4, 127.8, 128.8, 139.7, 138.9, 146.1, 171.4; MS (ES+) m/z (rel intensity) 343 (MNa⁺, 33), 321 (MH⁺, 100), 159 (8); HRMS (ES+) calcd for C₂₀H₂₁N₂O₂ (MH⁺) 321.1598, found 321.1590.

**Ethyl 2-(4-chlorophenyl)-4-phenyl-1H-imidazol-5-yl)acetate (4c).** Yellow solid; yield 37 mg, 54%; mp 167 °C; ν_max(KBr)/cm⁻¹ 3083m, 2925w, 2852w, 1735s, 1647m, 1493m, 1481m, 1449m, 1370w, 1266m, 1216w, 1185w, 1092w, 1028w, 1014w, 835w, 766m, 738vs, 700s; δ_H (CDCl₃, 400 MHz) 1.25 (3H, t, J 7.1 Hz), 3.79 (2H, s), 4.17 (2H, q, J 7.1 Hz), 7.26-7.29 (1H, m), 7.29 (2H, d, J 8.4 Hz), 7.36 (2H, t, J 7.5 Hz), 7.49 (2H, d, J 7.7 Hz), 7.71 (2H, d, J 8.4 Hz); δ_C (CDCl₃, 100 MHz) 14.3, 32.5, 61.6, 126.7, 127.4, 127.5, 128.4, 128.9, 129.1, 132.1, 134.6, 145.0, 171.5; MS (ES+) m/z (rel intensity) 363 (MNa⁺, 13), 341 (MH⁺, 100), 248 (21), 102 (38); HRMS (ES+) calcd for C₁₉H₁₈ClN₂O₂ (MH⁺) 341.1051, found 341.1051.

**Ethyl 2-(2,3-chlorophenyl)-4-phenyl-1H-imidazol-5-yl)acetate (4d).** Yellow solid; yield 46 mg, 67%; mp 147 °C; ν_max(KBr)/cm⁻¹ 2981w, 2924w, 2852w, 1734vs, 1588w, 1492w, 1451m, 1249m, 1183m, 1028m, 763m, 698m; δ_H (CDCl₃, 400 MHz) 1.29 (3H, t, J 7.1 Hz), 3.87 (2H, s), 4.23 (2H, q, J 7.1 Hz), 7.29-7.34 (3H, m), 7.41 (2H, t, J 7.6 Hz), 7.57 (2H, d, J 7.6 Hz), 7.74 (1H, dt, J 6.9, 1.9 Hz), 7.87 (1H, t, J 1.9 Hz); δ_C (CDCl₃, 100 MHz) 14.3, 32.3, 61.7, 123.5, 125.6, 127.4, 127.9, 130.3, 131.3, 132.1, 135.0, 144.4, 171.4; MS (ES+) m/z (rel intensity) 379 (MK⁺, 25), 363 (MNa⁺, 90), 341 (MH⁺, 100), 322 (19); HRMS (ES+) calcd for C₁₉H₁₈ClN₂O₂ (MH⁺) 341.1051, found 341.1050.

**Ethyl 2-(2-methylphenyl-1H-imidazol-5-yl)acetate (4e).** Yellow liquid; yield 30 mg, 62%; ν_max(neat)/cm⁻¹ 2978w, 2925m, 2854w, 1735vs, 1598w, 1448w, 1371w, 1267w, 1181w, 1028m, 766m, 737m, 701m; δ_H (CDCl₃, 400 MHz) 1.24 (3H, t, J 7.1 Hz), 2.35 (3H, s), 3.73 (2H, s), 4.16 (2H, q, J 7.1 Hz), 7.7 (1H, t, J 7.4 Hz), 7.36 (2H, t, J 7.4 Hz), 7.47 (2H, d, J 7.4 Hz); δ_C (CDCl₃, 100 MHz) 13.8, 14.3, 32.3, 61.4, 123.5, 127.2, 128.9, 132.1, 133.0, 144.2, 171.3; MS (ES+) m/z (rel intensity) 246 ([(M+2]+, 17), 245 (MH⁺, 100); HRMS (ES+) calcd for C₁₄H₁₇N₂O₂ (MH⁺) 245.1285, found 245.1282.

**Ethyl 2-(2-methylthio)-4-phenyl-1H-imidazol-5-yl)acetate (4f).** Yellow liquid; yield 18 mg, 32%; ν_max(neat)/cm⁻¹ 2985w, 2929w, 1732s, 1608w, 1495w, 1398w, 1370w, 1250m, 1217m, 1178m, 1028m, 758s, 699m; δ_H (CDCl₃, 400 MHz) 1.23 (3H, t, J 7.1 Hz), 2.55 (3H, s), 3.75 (2H, s), 4.16 (2H, q, J 7.2 Hz), 7.26 (1H, t, J 7.5 Hz), 7.36 (2H, t, J 7.5 Hz), 7.49 (2H, unresolved dd, J 7.5 Hz); δ_C (CDCl₃, 100 MHz) 14.3, 17.1, 32.4, 61.5, 125.6, 127.2, 127.4, 128.8, 132.0, 135.5, 141.3, 171.2; MS (ES+) m/z (rel intensity) 315 (MK⁺,
17), 299 (MNa\(^+\), 37), 277 (MH\(^+\), 100), 203 (3); HRMS (ES\(+\)) calcd for C\(_{14}\)H\(_{17}\)N\(_2\)O\(_2\)S (MH\(^+\)) 277.1005, found 277.1005.

**General procedure for the hydrolysis of imidazole ester 3.** To a stirred solution of imidazole 3a or 3d (0.2 mmol) in EtOH/H\(_2\)O (1.8:0.2 ml) was added KOH (15 mg, 0.26 mmol) at room temperature. The stirring was continued till the starting material completely disappeared (2-3 h). Then amberlyte 15 acid resin (50 mg) was added and the reaction mixture was stirred for 30 min in order to neutralise the excess KOH. The resin was filtered through a pad of celite and the solvent was evaporated in *vacuo*. The solid was washed with diethyl ether and was sufficiently pure for further reaction.

2-(4-(4-Methoxyphenyl)-2-phenyl-1H-imidazol-5-yl)acetic acid (5a). White solid; yield 52 mg, 84%; mp 225-227 °C; \(\nu_{\text{max}}\) (KBr)/cm\(^{-1}\) 3445br m, 3065w, 2932m, 2834w, 1655m, 1591s, 1555s, 1506s, 1370vs, 1256s, 1186m, 1037m, 902w, 836m, 767w; \(\delta_H\) (DMSO-d\(_6\), 500 MHz) 3.67 (2H, s), 3.79 (3H, s), 7.02 (2H, d, \(J 8.2\) Hz), 7.34 (1H, t, \(J 7.5\) Hz), 7.45 (2H, t, \(J 7.5\) Hz), 7.57 (2H, d, \(J 7.5\) Hz), 7.98 (2H, d, \(J 8.2\) Hz); \(\delta_C\) (DMSO-d\(_6\), 125 MHz) 33.0, 55.1, 114.0, 124.8, 128.0, 128.7, 130.4, 144.2, 158.2, 172.1; MS (ES+) m/z (rel intensity) 310 ([M+2]\(^+\), 38), 309 (MH\(^+\), 100); HRMS (ES+) calcd for C\(_{18}\)H\(_{17}\)N\(_2\)O\(_3\) (MH\(^+\)) 309.1234, found 309.1232.

2-(4-(Benzo[d][1,3]dioxol-5-yl)-2-phenyl-1H-imidazol-5-yl)acetic acid (5d). White solid; yield 51 mg, 79%; mp 211-213°C; \(\nu_{\text{max}}\) (KBr)/cm\(^{-1}\) 3343br m, 3064m, 2925m, 2778w, 1652m, 1553s, 1490s, 1360s, 1238s, 1104m, 1038s, 1004m, 937s, 905m, 816w, 676w; \(\delta_H\) (DMSO-d\(_6\), 400 MHz) 3.69 (2H, s), 6.06 (2H, s), 7.01 (1H, d, \(J 7.9\) Hz), 7.13 (1H, d, \(J 7.9\) Hz), 7.22 (1H, s), 7.35 (1H, t, \(J 7.3\) Hz), 7.46 (2H, t, \(J 7.4\) Hz), 7.99 (2H, d, \(J 7.9\) Hz); \(\delta_C\) (DMSO-d\(_6\), 100 MHz) 32.6, 101.0, 107.2, 108.5, 120.2, 124.9, 128.0, 128.7, 130.4, 144.2, 146.1, 147.5, 172.0; MS (ES+) m/z (rel intensity) 345 (MNa\(^+\), 27), 324 ([M+2]\(^+\), 17), 323 (MH\(^+\), 100); HRMS (ES+) calcd for C\(_{18}\)H\(_{17}\)N\(_2\)O\(_3\) (M\(^+\)) 323.1026, found 323.1026.

**General procedure for the synthesis of amides 7.** To a stirred solution of imidazole carboxylic acid 5 (0.3 mmol) in DCM (4 ml) PCl\(_3\) (123 mg, 0.6 mmol) was added and the reaction mixture was refluxed for 1.5 h. Then the reaction mixture was cooled to 0 °C and ammonia gas was bubbled through the reaction mixture for 30 min. After the completion of the reaction (~1 h, monitored by TLC), the reaction mixture was diluted with DCM. The organic phase was washed with water (3 × 5 ml) and dried over anhyd Na\(_2\)SO\(_4\). The combined organic layers were concentrated *in vacuo* and the residue was purified by silica gel column chromatography (90% EtOAc/petroleum ether).

2-(4-(4-Methoxyphenyl)-2-phenyl-1H-imidazol-5-yl)acetamide (7a). White solid; yield 69 mg, 75%; mp 130-132 °C; \(\nu_{\text{max}}\) (KBr)/cm\(^{-1}\) 3472br m, 2823w, 1606br s, 1383vs, 1352vs, 1246m, 1179w, 1040w, 775s, 707w; \(\delta_H\) (CDCl\(_3\) + DMSO-d\(_6\) 4:1, 500 MHz) 3.65 (2H, s), 3.83 (3H, s), 6.11 (1H, br s), 6.96 (2H, d, \(J 8.3\) Hz), 7.32 (1H, t, \(J 7.5\) Hz), 7.39-7.44 (2H, m), 7.53 (2H, d, \(J 7.5\) Hz), 8.01 (2H, d, \(J 8.3\) Hz); \(\delta_C\) (CDCl\(_3\) + DMSO-d\(_6\) 4:1, 125 MHz) 34.5, 55.1, 113.8, 125.1, 128.0, 128.4, 128.7, 130.2, 145.6, 158.6, 173.0; MS (ES+) m/z (rel intensity) 330 (MNa\(^+\), 22), 309 ([M+2]\(^+\), 38), 308 (MH\(^+\), 100), 263 (93); HRMS (ES+) calcd for C\(_{18}\)H\(_{17}\)N\(_2\)O\(_2\) (MH\(^+\)) 308.1394, found 308.1392.

2-(4-(Benzo[d][1,3]dioxol-5-yl)-2-phenyl-1H-imidazol-5-yl)acetamide (7d). Light pink solid; yield 69 mg, 72%; mp 213-215 °C; \(\nu_{\text{max}}\) (KBr)/cm\(^{-1}\) 3180br s, 2923m, 1666s, 1486s, 1404w, 1233s, 1104w, 1039s, 935w, 813w, 695m; \(\delta_H\) (CD\(_3\)OD + CDCl\(_3\) 4:1, 400 MHz) 3.58 (2H, s), 5.94 (2H, s), 6.82 (1H, d, \(J 8.0\) Hz), 7.01 (1H, dd, \(J 8.0, 1.7\) Hz), 7.05 (1H, d, \(J 1.5\) Hz), 7.29-7.40 (3H, m), 7.84 (2H, dd, \(J 8.6, 1.3\) Hz); \(\delta_C\) (CD\(_3\)OD + CDCl\(_3\) 4:1, 100 MHz) 34.5, 102.2, 109.0, 109.3, 122.3, 126.4, 129.6, 129.7, 130.9,
147.2, 148.3, 149.0, 175.5; MS (ES+) m/z (rel intensity) 360 (MK⁺, 13), 344 (MNa⁺, 43), 322 (MH⁺, 100); HRMS (ES+) calcd for C₁₈H₁₅N₂O₃Na (MNa⁺) 344.1006, found 344.1005.

2-(4-(Benzo[d][1,3]dioxol-5-yl)-2-phenyl-1H-imidazol-5-yl)ethanol (6d). To a stirred solution of LAH (0.4 mmol, 16 mg) in THF (3 ml) at 0 ºC was slowly added ester 3d (0.2 mmol, 70 mg) in THF (1 ml). The reaction mixture was allowed to warm to ambient temperature and stirred for additional 12 h. After the completion of reaction (~ 12 h, monitored by TLC), saturated aqueous NH₄Cl (5 ml) was added, the mixture was filtered through a celite pad and the filtrate was extracted with ethyl acetate (3x5 ml). The combined organic layer was washed with brine (3x5 ml) and water (3x5 ml), dried over anhyd Na₂SO₄ and concentrated in vacuo. The residue was purified by silica gel column chromatography by eluting with 70% EtOAc/petroleum ether. White solid; Yield 44 mg, 74%; νmax(KBr)/cm⁻¹ 3399 br s, 2888w, 2515m, 2233w, 2077w, 1655w, 1488s, 1341w, 1231br s, 1039br s, 1117m, 886w, 813m, 774w, 694m; δH (CDCl₃, 500 MHz) 2.95 (2H, t, J 7.1 Hz), 3.84 (2H, t, J 7.1 Hz), 5.95 (2H, s), 6.86 (1H, d, J 8.0 Hz), 7.08 (1H, dd, J 8.0, 1.7 Hz), 7.12 (1H, d, J 1.6 Hz), 7.34 (1H, tt, J 6.7, 1.2 Hz), 7.42 (2H, t, J 7.8 Hz), 7.88 (2H, dd, J 7.2, 1.4 Hz); δC (CD₂OD+CDCl₃, 125 MHz) 30.1, 62.4, 101.9, 109.0, 109.1, 122.1, 126.2, 127.7, 129.3, 129.6, 130.9, 146.5, 147.8, 148.8; MS (ES+) m/z (rel intensity) 331 (MNa⁺, 6), 310 ([M+2]⁺, 28), 309 (MH⁺, 100); HRMS (ES+) calcd for C₁₈H₁₇O₃N₂ (M⁺) 309.1234, found 309.1236.

Trypanocidal Assay. Stock solutions of the compounds were prepared in dimethyl sulfoxide (DMSO), with the final concentration of the latter in the experiments never exceeding 0.1%. Preliminary experiments showed that DMSO has no deleterious effect on the parasites when its concentration is up to 0.5%. Bloodstream trypomastigotes of the Y strain were obtained at the peak of parasitaemia from infected albino mice, isolated by differential centrifugation and resuspended in Dulbecco’s modified Eagle medium (DME) to a parasite concentration of 10⁵ cells/mL in the presence of 10% of mouse blood. This suspension (100 µL) was added in the same volume of each compound previously prepared at twice the desired final concentrations. Cell counts were performed in Neubauer chamber and the trypanocidal activity was expressed as IC₅₀, corresponding to the concentration that leads to lysis of 50% of the parasites.

The activity of benznidazole (reference compound) reported by Moraes et al³ is almost two orders of magnitude higher than the figure reported by us (Table 4, main text). This is despite the fact that both studies employed the same parasite form (trypomastigotes) and strain (Y strain). However, the experimental conditions employed by Moraes et al³ for the evaluation of the trypanocidal activity of benznidazole were completely different from that we used in our studies. We simulated the conditions of blood bank (4°C in the presence of blood), and such conditions drastically impact the IC₅₀ values. The time of treatment (24 h in our work vs 96 h by Moraes et al) and the origin of trypomastigotes (bloodstream forms isolated from mice in our work and culture-derived forms in case of Moraes et al) also lead to the remarkable oscillation in the drug’s activity, including benznidazole. In order to compare with the effect of our compounds, we referenced benzidazole IC₅₀ value previously published by our group in 2008 under the same conditions.⁴

References

