

Supporting Information

Controllable access to multi-substituted imidazoles via palladium(II)-catalyzed C-C coupling and C-N condensation cascade reaction

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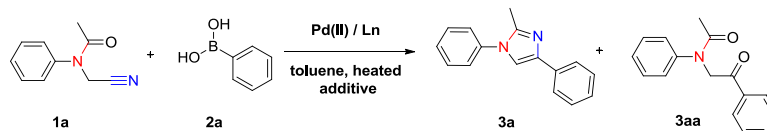
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General experimental:

All reagents were purchased from commercial suppliers and used without further purification. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker 600 NMR spectrometer using DMSO-d₆ (hexadeuterio-dimethyl sulfoxide) as the solvents and TMS (tetramethylsilane) as the internal standard. LCMS (Agilent 1200SL-6110) analysis was conducted for all compounds under the acidic condition: acidic condition refers to water containing 0.05 % TFA/acetonitrile as the mobile phase on Agilent SB-C18 column (1.8 μm, 4.6 x 30 mm), with MS and photodiode array detector (PDA). The following conditions were used: a gradient from 5 to 95% in 5 min (or 7 min) and held at 95% for 1 min; UV detection at 214 and 254 nm; a flow rate of 1.5 ml/min; full scan; mass range from 100 to 1000 amu. Column chromatography was performed on Isco or Biotage using a pre-packed silica gel column, a detector with UV wavelength at 254 nm and 280 nm. High resolution mass (HRMS) was operated in a positive mode of electrospray ionization (ESI) at an orthogonal acceleration time-of-flight (oa-TOF) SYNAPT G2 HDMSTM (Waters, Manchester, UK). Melting point was performed on WRS-1B Digital Melting Point Apparatus.

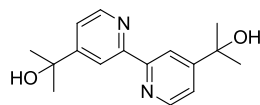
Table 1. Reaction conditions for synthesis of 1, 2, 4-trisubstituted imidazoles



	1a (starting material)	3a (product)	3aa (hydrolyzed product)
No additive	10.1%	62.9%	27.0%
TFA (2.0 equiv)	5.6%	70.6%	23.8%
CF ₃ COONH ₄ (1.0 equiv)	2.4%	93.2%	4.4%

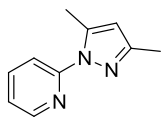
Note: The conversion percent was monitored by LCMS under UV detection at 214 nm; refluxed for 4h.

Synthesis and characterization of 2, 2'-([2, 2'-bipyridine]-4, 4'-diyl) bis (propan-2-ol) (L4)



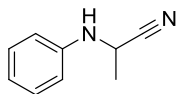
To a solution of dimethyl [2,2'-bipyridine]-4,4'-dicarboxylate (1.2 g, 4.4 mmol) in anhydrous THF (15 mL) was added dropwisely methyl magnesium bromide solution in THF (27 mL, 27 mmol) at -78 °C under N₂ atmosphere. The reaction mixture was warmed to room temperature, and stirred for another 2 hrs. LCMS showed the starting material was converted completely. Quenched the reaction by saturated NH₄Cl at 0 °C, the solvent was removed. The residue was taken up in ethyl acetate and washed with saturated NaHCO₃. The organic solvent was washed with water, brine and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure to get the crude. The residue was purified by reverse phase column chromatography using MeCN/water (ammonia 0.1%) as eluent afford the desired product. White solid (1 g, 83%), m.p. = 149.6-152.8 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 8.61 (dd, J = 5.1, 0.5 Hz, 1H), 8.52 (dd, J = 1.7, 0.5 Hz, 1H), 7.50 (dd, J = 5.1, 1.8 Hz, 1H), 5.36 (s, 1H), 1.48 (s, 6H). ¹³C NMR (151 MHz, DMSO-d₆) δ 160.7, 155.8, 149.3, 120.7, 117.0, 70.9, 31.6. HRMS-ESI (m/z): calcd. for C₁₆H₂₀N₂O₂, [M+H]⁺: 273.1603; found, 273.1608.

Synthesis and characterization of 2-(3,5-dimethyl-1H-pyrazol-1-yl)pyridine (L9)¹.



To a solution of pyridylhydrazine (1.1 g, 10 mmol), and acetylacetone (1.5 mL, 15 mmol) in dry ethanol (40 mL) was added catalytic amount of sulfuric acid. The reaction mixture was refluxed for 3 hrs. LCMS showed the starting material was converted completely. It was cooled to room temperature and the solvent was removed. The residue was taken up in ethyl acetate and washed with aqueous NaOH (30 mL) three times to remove unreacted acetylacetone. Then organic layer was washed with water, brine and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure to get the crude. The residue was purified by flash column chromatography using 5% methanol in dichloromethane afforded the desired product. Yellow oil (1.3 g, 75%), ¹H NMR (600 MHz, DMSO-d₆) δ 8.44 (ddd, J = 4.8, 1.9, 0.8 Hz, 1H), 7.93 (ddd, J = 8.3, 7.4, 1.9 Hz, 1H), 7.80 (dt, J = 8.3, 0.9 Hz, 1H), 7.30 (ddd, J = 7.4, 4.9, 1.0 Hz, 1H), 6.11 (s, 1H), 2.58 (d, J = 0.7 Hz, 3H), 2.20 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 153.5, 149.3, 148.0, 141.2, 139.3, 121.5, 115.7, 109.5, 14.7, 13.85. HRMS-ESI (m/z): calcd. for C₁₀H₁₁N₃, [M+H]⁺: 174.1031; found, 174.1033.

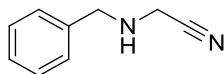
2-(phenylamino) propanenitrile (S1)



To a suspension of aniline (1.5 g, 16 mmol) and cesium carbonate (7.8 g, 24 mmol) in N, N-dimethylformamide (20 mL) was added 2-bromopropanenitrile (2.5 g, 19.2 mmol) at room temperature, the reaction mixture was heated to 80 °C for 10 hrs, and LCMS showed the material was converted to the product completely. Cooled to room temperature and filtered to get clear solution. Poured the mixture into the water, extracted by ethyl acetate (three times), combined the organic solvent, washed with water, brine and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure. Purification of the crude reaction mixture by flash column chromatography using (10%-40%) ethyl acetate in petroleum ether afforded the white solid (2.1 g, 89%). m.p. = 90.4-92.5 °C. ¹H NMR (600 MHz, DMSO-

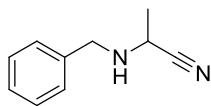
d6) δ 7.20 – 7.16 (m, 2H), 6.74 – 6.68 (m, 3H), 6.19 (d, J = 9.2 Hz, 1H), 4.57 (dq, J = 9.1, 7.0 Hz, 1H), 1.54 (d, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 146.73, 129.54, 121.84, 118.52, 113.91, 19.17. HRMS-ESI (m/z): calcd. for $\text{C}_9\text{H}_{10}\text{N}_2$, $[\text{M}+\text{H}]^+$: 147.0922; found, 147.0925.

2-(benzylamino) acetonitrile (S2)



To a suspension of phenylmethanamine (1.0 g, 9.3 mmol) and N, N-Diisopropyltheylamine (1.44 g, 11.2 mmol) in MeCN (10 mL) was added 2-bromoacetonitrile (0.8 g, 6.0 mmol) at room temperature, the reaction mixture was stirred at room temperature for 10 hrs, and LCMS showed the material was converted to the product completely. Rotavapored in vacuo to remove the organic solvent. The residue was taken up in ethyl acetate, then organic layer washed with water, brine and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure. Purification of the crude reaction mixture by flash column chromatography using (10%-45%) ethyl acetate in petroleum ether afforded the Colorless oil (900 mg, 67%). ^1H NMR (600 MHz, DMSO- d_6) δ 7.35 – 7.30 (m, 4H), 7.28 – 7.23 (m, 1H), 3.75 (d, J = 5.9 Hz, 2H), 3.57 (d, J = 7.2 Hz, 2H), 3.05 – 2.99 (m, 1H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 139.61, 128.73, 128.51, 127.44, 119.36, 52.09, 36.56. HRMS-ESI (m/z): calcd. for $\text{C}_9\text{H}_{10}\text{N}_2$, $[\text{M}+\text{H}]^+$: 147.0922; found, 147.0923.

2-(benzylamino) propanenitrile (S3)



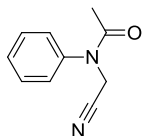
To a suspension of phenylmethanamine (500 mg, 4.6 mmol) and N, N-Diisopropyltheylamine (0.7 g, 5.6 mmol) in MeCN (10 mL) was added 2-bromopropanenitrile (0.8 g, 19.2 mmol) at room temperature, the reaction mixture was stirred at room temperature for 10 hrs, and LCMS showed the material was converted to the product completely. Rotavapored in vacuo to remove the organic solvent. The residue was taken up in ethyl acetate, then organic layer washed with water, brine and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure. Purification of the crude reaction mixture by flash column chromatography using (10%-45%) ethyl acetate in petroleum ether afforded the Colorless oil (500 mg, 67.5%). ^1H NMR (600 MHz, DMSO- d_6) δ 7.35 – 7.30 (m, 4H), 7.25 (ddd, J = 8.5, 5.6, 2.5 Hz, 1H), 3.88 (dd, J = 13.4, 4.7 Hz, 1H), 3.74 – 3.59 (m, 2H), 3.13 – 3.04 (m, 1H), 1.37 (d, J = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 139.85, 128.71, 128.45, 127.37, 121.86, 51.17, 44.79, 19.51. HRMS-ESI (m/z): calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_2$, $[\text{M}+\text{H}]^+$: 161.1079; found, 161.1082.

General procedures for 1a-1s

Method a: To a solution of 2-(phenylamino) acetonitrile (1.0 eq) and pyridine (1.5 eq) in THF (0.1 N) was added dropwisely benzoyl chloride (1.5 eq) at 0 °C, the reaction mixture was stirred for 2 hrs at room temperature. LCMS showed the starting material was converted completely. Filtered to get the clear solution. Removed the organic solvent to get the crude. The residue was taken up in ethyl acetate, and then organic layer was washed with saturated Na_2CO_3 , water, brine and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure. Purification of the crude reaction mixture by flash column chromatography using (5%-25%) ethyl acetate in petroleum ether afforded the desired product.

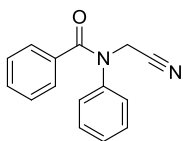
Method b: To a solution of 2-(phenylamino) acetonitrile (1.0 eq) and N, N-diisopropyltheylamine (2.0 eq) in DCM (0.1 N) was added dropwisely 2, 2, 2-trifluoroacetic anhydride (2.0 eq) at 0 °C, the reaction mixture was stirred for 10 hrs at room temperature. LCMS showed the starting material was converted completely. Removed the organic solvent to get the crude. The residue was taken up in ethyl acetate, then organic layer was washed with water, brine and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure. Purification of the crude reaction mixture by flash column chromatography using (5%-25%) ethyl acetate in petroleum ether afforded the desired product.

N-(cyanomethyl)-N-phenylacetamide (1a):



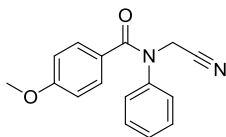
White solid (6.3 g, 95%), m.p. = 63-65 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 7.52 (t, J = 7.6 Hz, 2H), 7.47 (ddd, J = 29.5, 18.7, 7.5 Hz, 6H), 7.45 (t, J = 7.4 Hz, 1H), 7.41 (d, J = 7.6 Hz, 2H), 4.72 (s, 2H), 1.82 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 170.1, 141.87, 130.4, 129.1, 128.1, 117.2, 37.2, 22.3. HRMS-ESI (m/z): calcd. for C₁₀H₁₀N₂O, [M+H]⁺ : 175.0870; found, 175.0871.

N-(cyanomethyl)-N-phenylbenzamide (1b):



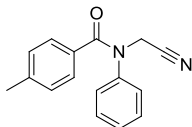
White solid (2.5 g, 96%), m.p. = 103.5-103.8 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 7.35 – 7.30 (m, 5H), 7.27 – 7.21 (m, 5H), 4.94 (s, 2H). ¹³C NMR (151 MHz, DMSO-d₆) δ 170.26, 142.29, 134.73, 130.87, 130.00, 129.05, 128.42, 128.17, 117.02, 38.80. HRMS-ESI (m/z): calcd. for C₁₅H₁₂N₂O, [M+H]⁺ : 237.1028; found, 237.1030.

N-(cyanomethyl)-4-methoxy-N-phenylbenzamide (1c):



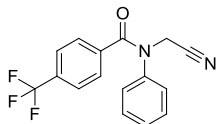
White solid (1.8 g, 60%), m.p. = 70.8-72.1 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 7.35 (dt, J = 10.1, 2.0 Hz, 2H), 7.31 – 7.25 (m, 3H), 7.21 (dd, J = 5.3, 3.3 Hz, 2H), 6.79 – 6.77 (m, 2H), 4.89 (s, 2H), 3.70 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 169.8, 161.3, 142.8, 131.4, 130.0, 127.9 (d, J = 4.0 Hz), 126.4, 117.11, 113.7, 55.7, 39.1. HRMS-ESI (m/z): calcd. for C₁₆H₁₄N₂O₂, [M+H]⁺ : 267.1134; found, 267.1137.

N-(cyanomethyl)-4-methyl-N-phenylbenzamide (1d):



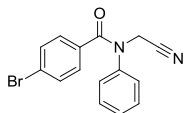
White solid (853 mg, 90%), m.p. = 78.7-80.5 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.34 (t, J = 7.8 Hz, 2H), 7.26 (t, J = 7.4 Hz, 1H), 7.22 (t, J = 7.9 Hz, 4H), 7.04 (d, J = 8.0 Hz, 2H), 4.91 (s, 2H), 2.22 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 170.2, 142.5, 140.9, 131.7, 130.0, 129.2, 128.9, 128.0 (d, J = 3.9 Hz), 117.0, 38.9, 21.3. HRMS-ESI (m/z): calcd. for $\text{C}_{16}\text{H}_{14}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$: 251.1184; found, 251.1184.

N-(cyanomethyl)-N-phenyl-4-(trifluoromethyl)benzamide (1e):



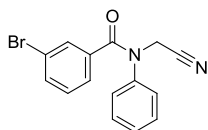
White solid (1.9 g, 85%), m.p. = 66.0-67.8 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.63 (d, J = 8.3 Hz, 2H), 7.54 (d, J = 8.1 Hz, 2H), 7.37 – 7.32 (m, 2H), 7.30 – 7.25 (m, 3H), 4.99 (s, 2H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 168.9, 141.5, 138.9, 130.1, 129.7, 128.6, 128.3, 125.4 (d, J = 3.7 Hz), 116.8, 38.63. HRMS-ESI (m/z): calcd. for $\text{C}_{16}\text{H}_{11}\text{F}_3\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$: 305.0902; found, 305.0906.

4-bromo-N-(cyanomethyl)-N-phenylbenzamide (1f):



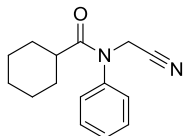
White solid (1.12 g, 94%), m.p. = 106-107.9 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.47 – 7.44 (m, 2H), 7.37 – 7.33 (m, 2H), 7.30 – 7.23 (m, 5H), 4.94 (s, 2H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 169.3, 141.9, 133.9, 131.4, 131.1, 130.1, 128.4, 128.1, 124.4, 116.9, 38.7. HRMS-ESI (m/z): calcd. for $\text{C}_{15}\text{H}_{11}\text{BrN}_2\text{O}$, $[\text{M}+\text{H}]^+$: 315.0137; found, 315.0133.

3-bromo-N-(cyanomethyl)-N-phenylbenzamide (1g):



White solid (1.1 g, 92%), m.p. = 85.7-87.7 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.53 – 7.50 (m, 2H), 7.38 – 7.34 (m, 2H), 7.31 – 7.26 (m, 4H), 7.22 – 7.17 (m, 1H), 4.94 (s, 2H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 168.5, 141.7, 137.0, 133.5, 131.7, 130.5, 130.1, 128.5, 128.2, 127.9, 121.52, 116.8, 38.6. HRMS-ESI (m/z): calcd. for $\text{C}_{15}\text{H}_{11}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$: 315.0133; found, 315.0135.

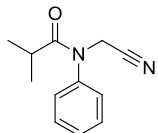
N-(cyanomethyl)-N-phenylcyclohexanecarboxamide (1h):



White solid (740 mg, 81%), m.p. = 91.3-92.5 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.54 (t, J = 7.6 Hz, 2H), 7.48 (t, J = 7.3 Hz, 1H), 7.39 (d, J = 7.5 Hz, 2H), 4.69 (s, 2H), 2.11 (d, J = 10.5 Hz, 1H), 1.60 (dd, J = 15.3, 6.7 Hz, 4H), 1.49 (d, J = 12.7 Hz, 1H), 1.38 – 1.30 (m, 2H),

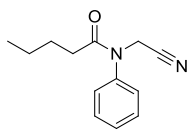
1.14 – 1.05 (m, 1H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 175.5, 141.3, 130.5, 129.3, 128.3, 117.2, 40.8, 29.2, 25.6, 25.38. HRMS-ESI (m/z): calcd. for $\text{C}_{15}\text{H}_{18}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$: 243.1497; found, 243.1501.

N-(cyanomethyl)-N-phenylisobutyramide (1i):



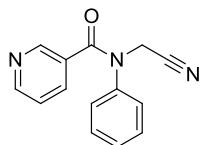
White solid (658 mg, 86%), m.p. = 95.5-96.2 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.54 (dd, J = 10.5, 4.8 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.41 (d, J = 7.3 Hz, 2H), 4.70 (s, 2H), 2.45 – 2.36 (m, 1H), 0.94 (d, J = 6.7 Hz, 6H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 176.7, 141.4, 130.5, 129.3, 128.3, 117.2, 37.5, 30.7, 19.6. HRMS-ESI (m/z): calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$: 203.1184; found, 203.1184.

N-(cyanomethyl)-N-phenylpentanamide (1j):



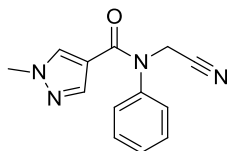
Yellow oil (728 mg, 89%), ^1H NMR (600 MHz, DMSO- d_6) δ 7.53 (t, J = 7.7 Hz, 2H), 7.46 (t, J = 7.4 Hz, 1H), 7.39 (d, J = 7.4 Hz, 2H), 4.71 (s, 2H), 1.47 – 1.39 (m, 2H), 1.18 – 1.11 (m, 2H), 0.75 (t, J = 7.3 Hz, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 172.6, 141.4, 130.4, 129.1, 128.3, 117.2, 37.3, 33.1, 27.1, 22.0, 14.0. HRMS-ESI (m/z): calcd. for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$: 217.1341; found, 217.1339.

N-(cyanomethyl)-N-phenylnicotinamide (1k):



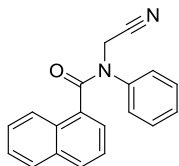
White solid (1.2 g, 86%), m.p. = 86.4-87.5 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 8.49 – 8.46 (m, 2H), 7.74 – 7.70 (m, 1H), 7.38 – 7.34 (m, 2H), 7.29 (ddt, J = 10.3, 8.2, 1.3 Hz, 4H), 4.98 (s, 2H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 168.2, 151.3, 149.4, 141.6, 136.6, 130.8, 130.1, 128.6, 128.4, 123.5, 116.8, 38.5. HRMS-ESI (m/z): calcd. for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}$, $[\text{M}+\text{H}]^+$: 238.1015; found, 238.1018.

N-(cyanomethyl)-1-methyl-N-phenyl-1H-pyrazole-4-carboxamide (1l):



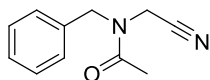
White solid (1.25 g, 87%), m.p. = 79.2-80.6 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.55 – 7.50 (m, 4H), 7.37 – 7.34 (m, 2H), 6.58 (d, J = 0.5 Hz, 1H), 4.82 (s, 2H), 3.70 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 162.8, 141.7, 139.9, 134.8, 130.5, 129.5, 128.9, 117.2, 116.3, 39.0, 38.3. HRMS-ESI (m/z): calcd. for $\text{C}_{13}\text{H}_{12}\text{N}_4\text{O}$, $[\text{M}+\text{H}]^+$: 241.1089; found, 241.1091.

N-(cyanomethyl)-N-phenyl-1-naphthamide (1m):



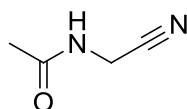
Colorless oil (810 mg, 75%), ^1H NMR (600 MHz, DMSO- d_6) δ 8.01 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.61 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H), 7.54 – 7.50 (m, 1H), 7.41 (d, J = 6.9 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.0 Hz, 2H), 7.15 (t, J = 6.9 Hz, 2H), 7.10 (t, J = 6.9 Hz, 1H), 5.07 (s, 2H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 167.8, 139.3, 131.0, 130.9, 127.8, 127.7, 127.5, 126.6, 126.2, 125.6, 125.4, 124.7, 124.2, 123.0, 122.9, 115.0, HRMS-ESI (m/z): calcd. for $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$: 287.1184; found, 287.1187.

N-benzyl-N-(cyanomethyl) acetamide (1n).



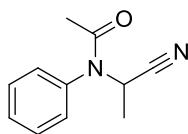
Colorless oil (160 mg, 79%), ^1H NMR (600 MHz, DMSO- d_6) δ 7.40 (t, J = 7.5 Hz, 2H), 7.32 (dd, J = 13.0, 5.8 Hz, 2H), 7.27 (d, J = 7.4 Hz, 3H), 4.68 (s, 2H), 4.56 (s, 1H), 4.31 (s, 2H), 2.18 (s, 1H), 2.10 (s, 3H). ^1H NMR (600 MHz, DMSO, at 70 $^\circ\text{C}$) δ 7.40 (s, 2H), 7.33 (d, J = 6.7 Hz, 1H), 7.29 (d, J = 7.5 Hz, 2H), 4.68 (s, 2H), 4.33 (s, 2H), 2.14 (s, 3H). HRMS-ESI (m/z): calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$: 175.0871; found, 175.0870

N-(cyanomethyl)acetamide (1o)².



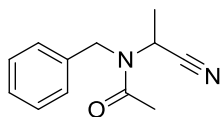
White solid (450 mg, 51%) m.p. = 78.2-80 $^\circ\text{C}$. ^1H NMR (600 MHz, DMSO)- d_6 δ 8.56 (s, 1H), 4.10 (d, J = 5.6 Hz, 2H), 1.87 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 170.37, 118.22, 27.41, 22.50. HRMS-ESI (m/z): calcd. for $\text{C}_4\text{H}_6\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$: 99.0558; found, 99.0557.

N-(1-cyanoethyl)-N-phenylacetamide (1p):



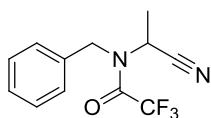
White solid (500 mg, 77.8%), m.p. = 86.1-87.3 $^\circ\text{C}$. ^1H NMR (600 MHz, DMSO- d_6) δ 7.55 (t, J = 7.4 Hz, 2H), 7.50 (t, J = 7.3 Hz, 1H), 7.38 (d, J = 7.4 Hz, 2H), 5.70 (q, J = 7.2 Hz, 1H), 1.73 (s, 3H), 1.31 (d, J = 7.2 Hz, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 169.88 (s), 138.78 (s), 130.62 – 130.57 (m), 130.17 (d, J = 49.7 Hz), 129.67 (s), 119.81 (s), 41.90 (s), 22.94 (s), 17.88 (s). HRMS-ESI (m/z): calcd for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$: 189.1028; found, 189.1029.

N-benzyl-N-(1-cyanoethyl)acetamide (1q).



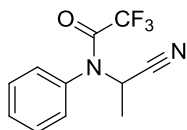
Colorless oil(146mg, 72%), ^1H NMR (600 MHz, DMSO- d_6) δ 7.40 (t, J = 7.1 Hz, 2H), 7.30 (dd, J = 20.4, 7.1 Hz, 3H), 5.13 (d, J = 6.9 Hz, 1H), 4.68 (dd, J = 62.8, 17.5 Hz, 2H), 2.04 (s, 3H), 1.40 (d, J = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 171.04, 137.67, 129.20, 127.88, 126.91, 119.59, 50.64, 42.52, 22.21, 17.44. HRMS-ESI (m/z): calcd. for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$: 203.1184; found, 203.1184.

N-benzyl-N-(1-cyanoethyl)-2, 2, 2-trifluoroacetamide (1r).



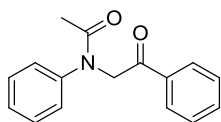
White solid (150 mg, 62%) m.p. = 67.8-68.4 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.43 (t, J = 7.3 Hz, 2H), 7.37 (t, J = 7.2 Hz, 1H), 7.33 (d, J = 7.4 Hz, 2H), 4.89 – 4.72 (m, 3H), 1.46 (d, J = 6.9 Hz, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 135.04, 129.31, 128.65, 127.66, 117.86, 117.14, 51.23, 45.14, 16.41. HRMS-ESI (m/z): calcd. for $\text{C}_{12}\text{H}_{11}\text{F}_3\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$: 257.0902; found, not detected

N-(1-cyanoethyl)-2, 2, 2-trifluoro-N-phenylacetamide (1s): method b,



White solid (400 mg, 48%) m.p. = 44.8-46.7 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.57 (m, 3H), 7.49 (m, 2H), 5.71 (q, J = 7.1 Hz, 1H), 1.42 (d, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 156.09, 155.85, 134.80, 130.90, 130.80, 130.05, 129.92, 118.35, 117.13, 115.22, 45.30, 17.12. HRMS-ESI (m/z): calcd. for $\text{C}_{11}\text{H}_9\text{F}_3\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$: 243.0745; found, 243.0747.

N-(2-oxo-2-phenylethyl)-N-phenylacetamide (3aa):



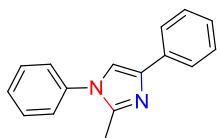
White solid, m.p. = 102.2-104.2 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.99 (d, J = 7.4 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.54 (t, J = 7.7 Hz, 2H), 7.46 (t, J = 7.7 Hz, 2H), 7.42 (d, J = 7.2 Hz, 2H), 7.35 (t, J = 7.2 Hz, 1H), 5.15 (s, 2H), 1.87 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 194.7, 169.7, 143.9, 135.3, 134.1, 129.9, 129.3, 128.3, 128.2, 128.11, 56.4, 39.5, 22.4. HRMS-ESI (m/z): calcd. for $\text{C}_{16}\text{H}_{15}\text{NO}_2$, $[\text{M}+\text{H}]^+$: 254.1181; found, 254.1177 .

General procedures for 3a-3o

The starting material of N-(cyanomethyl)-N-phenylacetamide (87mg, 0.5mmol), substrates bronc acid (2a-2o, 0.75 mmol), $\text{Pd}(\text{CF}_3\text{COO})_2$ (16.6 mg, 0.05 mmol), 4,4'-di-tert-butyl-2,2'-bipyridine (13.4 mg, 0.05 mmol) and $\text{CF}_3\text{COONH}_4$ (75 mg, 0.5 mmol) were

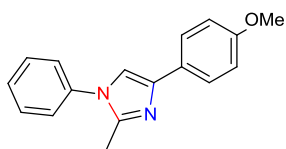
added to a bottle vial, and then anhydrous Toluene (2.0 mL) was added and sealed by cap. The reaction mixture was refluxed for 4-6 hrs (Monitored by LCMS until the starting material was disappeared). Cooled to room temperature and removed the organic solvent to get the crude. The residue was taken up in ethyl acetate, and then organic layer was washed with saturated NaHCO_3 , water, brine and dried over anhydrous Na_2SO_4 . The solvent was removed under reduced pressure. The residue was purified by reverse phase column chromatography using MeCN/water as eluent afford the desired product

2-methyl-1, 4-diphenyl-1H-imidazole (3a):



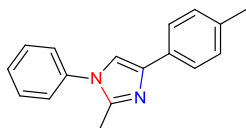
Yellow solid (85 mg, 73%), m.p. = -71-73 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.82 – 7.79 (m, 3H), 7.57 (t, J = 7.7 Hz, 2H), 7.52 (d, J = 7.4 Hz, 2H), 7.48 (t, J = 7.3 Hz, 1H), 7.36 (t, J = 7.7 Hz, 2H), 7.20 (t, J = 7.4 Hz, 1H), 2.34 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 144.6, 139.6, 138.0, 134.7, 130.0, 128.9, 128.5, 126.7, 125.6, 124.7, 117.5, 14.1. HRMS-ESI (m/z): calcd. for $\text{C}_{16}\text{H}_{14}\text{N}_2$, $[\text{M}+\text{H}]^+$: 235.1235; found, 235.1235.

4-(4-methoxyphenyl)-2-methyl-1-phenyl-1H-imidazole (3b):



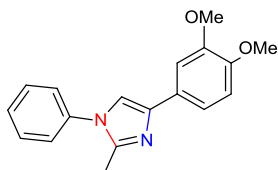
White solid (100 mg, 76%), m.p. = 118.2-120.1 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.74 – 7.70 (m, 2H), 7.68 (s, 1H), 7.56 (dd, J = 10.6, 4.9 Hz, 2H), 7.52 – 7.49 (m, 2H), 7.47 (t, J = 7.3 Hz, 1H), 6.93 (dd, J = 6.8, 4.8 Hz, 2H), 3.77 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 158.4, 144.3, 139.6, 138.0, 130.0, 128.3, 127.4, 125.9, 125.6, 116.2, 114.3, 55.5, 14.1. HRMS-ESI (m/z): calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}$, $[\text{M}+\text{H}]^+$: 265.1341; found, 265.1341.

2-methyl-1-phenyl-4-(p-tolyl)-1H-imidazole (3c):



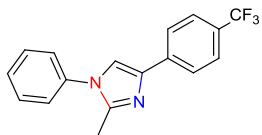
white solid (102 mg, 82%), m.p. = 142.8-144.5 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.74 (s, 1H), 7.69 (d, J = 8.1 Hz, 2H), 7.58 – 7.54 (m, 2H), 7.52 – 7.50 (m, 2H), 7.47 (dt, J = 8.5, 1.2 Hz, 1H), 2.33 (s, 3H), 2.30 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 144.4, 139.7, 138.0, 135.7, 132.0, 130.0, 129.5, 128.4, 125.6, 124.7, 116.9, 21.2, 14.1. HRMS-ESI (m/z): calcd. for $\text{C}_{17}\text{H}_{16}\text{N}_2$, $[\text{M}+\text{H}]^+$: 249.1392; found, 249.1394.

4-(3, 4-dimethoxyphenyl)-2-methyl-1-phenyl-1H-imidazole (3d):



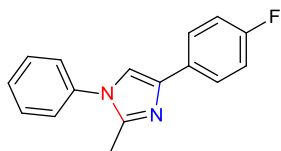
Yellow solid (130 mg, 90%), m.p. = 87.5-88.2 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 7.76 (s, 1H), 7.57 (t, J = 7.7 Hz, 2H), 7.52 (d, J = 7.3 Hz, 2H), 7.48 (t, J = 7.3 Hz, 1H), 7.38 (d, J = 1.9 Hz, 1H), 7.33 (dd, J = 8.3, 1.9 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 2.34 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 149.2, 148.0, 144.8, 139.5, 137.9, 130.0, 128.4, 127.5, 125.6, 116.9, 116.7, 112.4, 108.6, 55.97, 55.90, 14.0. HRMS-ESI (m/z): calcd. for C₁₈H₁₈N₂O₂, [M+H]⁺: 295.1447; found, 295.1445.

2-methyl-1-phenyl-4-(4-(trifluoromethyl)phenyl)-1H-imidazole (3e):



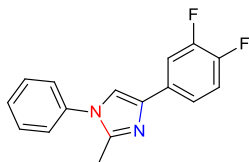
Yellow solid (121 mg, 80%), m.p. = 69.9-72.6 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 8.03 (s, 1H), 8.01 (d, J = 8.1 Hz, 2H), 7.71 (d, J = 8.3 Hz, 2H), 7.60 – 7.56 (m, 2H), 7.54 (d, J = 7.1 Hz, 2H), 7.50 (t, J = 7.2 Hz, 1H), 2.35 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 145.3, 138.7, 138.1, 137.7, 130.10, 128.7, 125.9, 125.9, 125.9, 125.7, 125.0, 119.5, 14.1. HRMS-ESI (m/z): calcd. for C₁₇H₁₃F₃N₂, [M+H]⁺: 303.1109; found, 303.1106.

4-(4-fluorophenyl)-2-methyl-1-phenyl-1H-imidazole (3f):



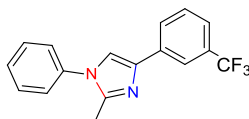
Yellow oil (80 mg, 64%). ¹H NMR (600 MHz, DMSO-d₆) δ 7.84 – 7.80 (m, 3H), 7.57 (tt, J = 3.8, 1.9 Hz, 2H), 7.53 – 7.50 (m, 2H), 7.49 (ddd, J = 7.3, 4.0, 1.2 Hz, 1H), 7.21 – 7.16 (m, 2H), 2.34 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 162.2, 160.6, 144.7, 138.6, 137.9, 131.2, 130.0, 128.5, 126.51 (d, J = 7.9 Hz), 125.6, 117.4, 115.8, 115.7, 14.1. HRMS-ESI (m/z): calcd. for C₁₆H₁₃FN₂, [M+H]⁺: 253.1141; found, 253.1145.

4-(4-(3, 4-dimethoxyphenyl)-1-phenyl-1H-imidazol-2-yl)-1-methyl-1H-pyrazole (3g):



Yellow oil (88 mg, 65%). ¹H NMR (600 MHz, DMSO-d₆) δ 7.90 (s, 1H), 7.78 (ddd, J = 12.3, 7.9, 2.0 Hz, 1H), 7.66 – 7.62 (m, 1H), 7.57 (tt, J = 3.9, 1.9 Hz, 2H), 7.53 – 7.48 (m, 3H), 7.42 (dt, J = 10.7, 8.6 Hz, 1H), 2.33 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 145.0, 137.8, 137.7, 130.1, 128.6, 125.6, 121.2, 118.4, 118.1, 118.0, 113.3, 113.2, 14.0. HRMS-ESI (m/z): calcd. for C₁₆H₁₂F₂N₂, [M+H]⁺: 271.1047; found, 271.1048.

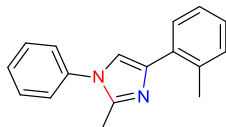
2-methyl-1-phenyl-4-(3-(trifluoromethyl)phenyl)-1H-imidazole (3h):



White solid (100 mg, 46%), m.p. = 93.6-94.6 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 8.14 (s, 1H), 8.09 (d, J = 7.8 Hz, 1H), 8.05 (s, 1H), 7.62 – 7.57 (m, 3H), 7.54 (dt, J = 6.0, 2.4 Hz, 3H), 7.50 (ddd, J = 7.2, 4.0, 1.3 Hz, 1H), 2.36 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ

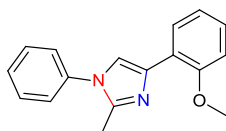
145.2, 138.0, 137.8, 135.8, 130.1, 129.8, 128.6, 128.3, 125.6, 123.1, 120.8, 118.9, 14.1. HRMS-ESI (m/z): calcd. for $C_{17}H_{13}F_3N_2$, $[M+H]^+$: 303.1109; found, 303.1182.

2-methyl-1-phenyl-4-(o-tolyl)-1H-imidazole (3i):



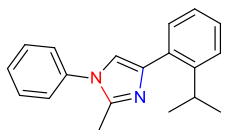
Yellow solid (74 mg, 60%), m.p. = 72.3–74 °C. 1H NMR (600 MHz, DMSO- d_6) δ 7.86 (d, J = 7.7 Hz, 1H), 7.59 – 7.53 (m, 4H), 7.51 (s, 1H), 7.48 (ddd, J = 8.5, 3.5, 1.6 Hz, 1H), 7.22 (t, J = 7.4 Hz, 2H), 7.16 – 7.12 (m, 1H), 2.48 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 143.7, 138.9, 137.9, 134.6, 133.7, 131.1, 130.0, 128.4, 128.1, 126.6, 126.1, 125.7, 119.6, 22.2, 14.1. HRMS-ESI (m/z): calcd. for $C_{17}H_{16}N_2$, $[M+H]^+$: 249.1392; found, 249.1394.

4-(2-methoxyphenyl)-2-methyl-1-phenyl-1H-imidazole (3j):



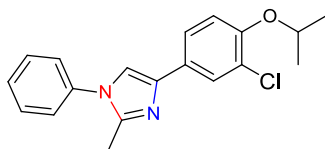
White solid (40 mg, 31%), m.p. = 117.2–118.5 °C. 1H NMR (600 MHz, DMSO- d_6) δ 8.11 (dd, J = 7.7, 1.8 Hz, 1H), 7.65 (s, 1H), 7.56 (dt, J = 9.2, 1.8 Hz, 2H), 7.53 – 7.46 (m, 3H), 7.20 (ddd, J = 8.2, 7.4, 1.8 Hz, 1H), 7.05 (d, J = 7.8 Hz, 1H), 6.99 (td, J = 7.5, 1.0 Hz, 1H), 3.88 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 156.0, 143.5, 138.0, 135.3, 130.0, 128.4, 127.5, 126.9, 125.7, 122.8, 120.8, 120.7, 111.5, 55.6, 14.0. HRMS-ESI (m/z): calcd. for $C_{17}H_{16}N_2O$, $[M+H]^+$: 265.1341; found, 265.1342.

2-(3-bromophenyl)-4-(3, 4-dimethoxyphenyl)-1-phenyl-1H-imidazole (3k):



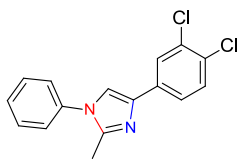
Colorless oil (65 mg, 47%). 1H NMR (600 MHz, DMSO- d_6) δ 7.59 – 7.53 (m, 4H), 7.52 (dd, J = 7.7, 1.4 Hz, 1H), 7.49 – 7.46 (m, 1H), 7.39 – 7.36 (m, 2H), 7.26 (td, J = 7.6, 1.4 Hz, 1H), 7.18 (td, J = 7.5, 1.3 Hz, 1H), 3.74 – 3.66 (m, 1H), 2.36 (s, 3H), 1.19 (d, J = 6.9 Hz, 6H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 146.4, 143.7, 139.6, 137.9, 133.1, 130.0, 129.7, 128.3, 127.5, 125.8, 125.7, 125.6, 119.0, 28.90, 24.51, 14.21. HRMS-ESI (m/z): calcd. for $C_{19}H_{20}N_2$, $[M+H]^+$: 277.1705; found, 277.1707.

4-(3-chloro-4-isopropoxyphenyl)-2-methyl-1-phenyl-1H-imidazole (3l):



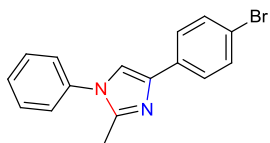
Yellow oil (105 mg, 65%). 1H NMR (600 MHz, DMSO- d_6) δ 7.82 (d, J = 2.1 Hz, 1H), 7.80 (s, 1H), 7.69 (dd, J = 8.5, 2.1 Hz, 1H), 7.56 (dd, J = 10.5, 5.0 Hz, 2H), 7.52 – 7.50 (m, 2H), 7.48 (dd, J = 11.6, 4.2 Hz, 1H), 7.16 (d, J = 8.7 Hz, 1H), 4.66 (dt, J = 12.1, 6.0 Hz, 1H), 2.33 (s, 3H), 1.30 (d, J = 6.0 Hz, 6H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 151.87, 144.64, 138.28, 137.95, 130.07, 128.65, 128.49, 126.16, 125.60, 124.40, 123.22, 117.21, 116.54, 71.70, 22.36, 14.14. HRMS-ESI (m/z): calcd. for $C_{19}H_{19}ClN_2O$, $[M+H]^+$: 327.1264; found, 327.1271.

4-(3, 4-dichlorophenyl)-2-methyl-1-phenyl-1H-imidazole (3m):



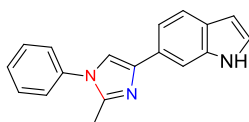
White solid (102 mg, 68%), m.p. = 92-93 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 8.02 (t, J = 2.7 Hz, 1H), 8.01 (s, 1H), 7.78 (dd, J = 8.4, 2.0 Hz, 1H), 7.63 – 7.60 (m, 1H), 7.60 – 7.56 (m, 2H), 7.54 – 7.51 (m, 2H), 7.51 – 7.48 (m, 1H), 2.34 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 145.2, 137.7, 137.24, 135.5, 131.8, 131.2, 130.1, 128.7, 128.6, 126.1, 125.6, 124.7, 119.1, 14.1. HRMS-ESI (m/z): calcd. for C₁₆H₁₂Cl₂N₂, [M+H]⁺: 303.0456; found, 303.0458.

4-(4-bromophenyl)-2-methyl-1-phenyl-1H-imidazole (3n):



White solid (70mg, 45 %), m.p. = 105.7-106.8 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 7.89 (s, 1H), 7.77 – 7.74 (m, 2H), 7.59 – 7.47 (m, 7H), 2.33 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 144.9, 138.5, 137.8, 134.0, 131.8, 130.0, 128.6, 126.7, 125.7, 119.4, 118.2, 14.1. HRMS-ESI (m/z): calcd. for C₁₆H₁₃BrN₂, [M+H]⁺: 313.0340; found, 313.0343.

4-(3, 4-dimethoxyphenyl)-2-(naphthalen-1-yl)-1-phenyl-1H-imidazole (3o):

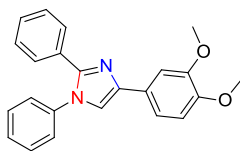


Yellow solid (75 mg, 55%), m.p. = 194.9-196.2 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 11.04 (s, 1H), 7.86 (s, 1H), 7.71 (s, 1H), 7.59 – 7.55 (m, 2H), 7.55 – 7.52 (m, 2H), 7.50 – 7.43 (m, 3H), 7.31 – 7.28 (m, 1H), 6.38 (ddd, J = 2.8, 1.8, 0.8 Hz, 1H), 2.36 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 144.2, 141.0, 138.2, 136.8, 130.0, 128.3, 128.03, 126.9, 125.7, 125.6, 120.3, 117.0, 116.2, 107.4, 101.5, 14.26. HRMS-ESI (m/z): calcd. for C₁₈H₁₅N₃, [M+H]⁺: 274.1344; found, 274.1344.

General procedures for 3jb-3jw

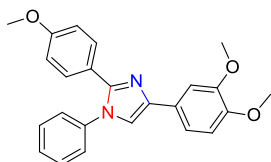
The starting material of substrates (**1b-1s**, 0.5 mmol), (3,4-dimethoxyphenyl)boronic acid (137 mg, 0.75 mmol), Pd(CF₃COO)₂ (16.6 mg, 0.05 mmol), 4,4'-di-tert-butyl-2,2'-bipyridine (13.4 mg, 0.05 mmol) and CF₃COONH₄ (75 mg, 0.5 mmol) were added to a bottle glass, and then anhydrous Toluene (2.0 ml) was added and sealed by cap. The reaction mixture was refluxed for 4-6 hrs (Monitored by LCMS until the starting material was disappeared). Cooled to room temperature and removed the organic solvent to get the crude. The residue was taken up in ethyl acetate, and then organic layer was washed with saturated NaHCO₃, water, brine and dried over anhydrous Na₂SO₄. The solvent was removed under reduced pressure. The residue was purified by reverse phase column chromatography using MeCN/water as eluent afford the desired product

4-(3, 4-dimethoxyphenyl)-1,2-diphenyl-1H-imidazole (3jb):



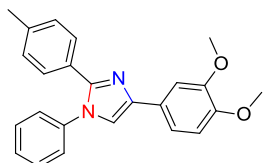
White solid (125 mg, 70%), m.p. = 166.7-167.2 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.96 (s, 1H), 7.51 – 7.45 (m, 4H), 7.44 (dd, J = 8.2, 1.9 Hz, 1H), 7.37 (ddd, J = 6.9, 5.7, 1.9 Hz, 4H), 7.34 – 7.31 (m, 3H), 6.99 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 149.3, 148.3, 146.0, 141.0, 138.6, 130.7, 130.0, 128.79, 128.77, 128.70, 127.4, 126.4, 119.6, 117.2, 112.4, 108.9, 56.0, 55.9. HRMS-ESI (m/z): calcd. for $\text{C}_{23}\text{H}_{20}\text{N}_2\text{O}_2$, $[\text{M}+\text{H}]^+$: 357.1603; found, 357.1659.

4-(3,4-dimethoxyphenyl)-2-(4-methoxyphenyl)-1-phenyl-1H-imidazole (3jc):



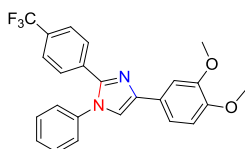
White solid (110 mg, 57%), m.p. = 153.8-155.4 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.90 (s, 1H), 7.50 (dd, J = 11.3, 4.3 Hz, 2H), 7.47 – 7.41 (m, 3H), 7.37 – 7.34 (m, 2H), 7.30 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.3 Hz, 1H), 6.88 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H), 3.78 (s, 3H), 3.74 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 159.7, 149.3, 148.2, 146.0, 140.76, 138.7, 130.1, 130.0, 128.6, 127.5, 126.4, 123.2, 119.1, 117.2, 114.1, 112.4, 108.9, 55.98, 55.96, 55.6. HRMS-ESI (m/z): calcd. for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_3$, $[\text{M}+\text{H}]^+$: 387.1709; found, 387.1707.

4-(3,4-dimethoxyphenyl)-1-phenyl-2-(p-tolyl)-1H-imidazole (3jd):



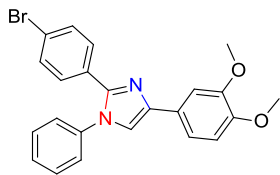
Yellow solid (114 mg, 62%), m.p. = 60-62 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.93 (s, 1H), 7.51 – 7.44 (m, 4H), 7.43 (dd, J = 8.3, 1.9 Hz, 1H), 7.36 – 7.33 (m, 2H), 7.28 – 7.24 (m, 2H), 7.12 (d, J = 7.9 Hz, 2H), 6.98 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.28 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 149.3, 148.3, 146.2, 140.9, 138.7, 138.2, 130.0, 129.2, 128.6, 127.9, 127.4, 126.3, 119.4, 117.2, 112.4, 108.9, 55.9, 21.2. HRMS-ESI (m/z): calcd. for $\text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_2$, $[\text{M}+\text{H}]^+$: 371.1760; found, 371.1769.

4-(3, 4-dimethoxyphenyl)-1-phenyl-2-(4-(trifluoromethyl)phenyl)-1H-imidazole (3je):



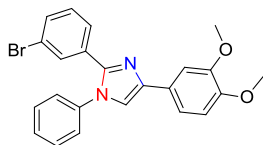
White solid (170 mg, 80%), m.p. = 68.8-70.5 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 8.06 (s, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.59 (d, J = 8.2 Hz, 2H), 7.55 – 7.48 (m, 4H), 7.46 (dd, J = 8.2, 1.9 Hz, 1H), 7.44 – 7.40 (m, 2H), 7.00 (d, J = 8.4 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 149.3, 148.5, 144.5, 141.5, 138.2, 134.5, 130.2, 129.2, 128.87, 128.66, 127.0, 126.4, 125.7, 125.6, 125.4, 123.6, 120.6, 117.3, 112.4, 108.9, 55.9. HRMS-ESI (m/z): calcd. for $\text{C}_{24}\text{H}_{19}\text{F}_3\text{N}_2\text{O}_2$, $[\text{M}+\text{H}]^+$: 425.1477; found, 425.1479.

2-(4-bromophenyl)-4-(3, 4-dimethoxyphenyl)-1-phenyl-1H-imidazole (3jf):



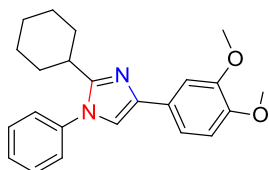
White solid (107 mg, 49%), m.p. = 76.5-78.4 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.99 (s, 1H), 7.55 – 7.50 (m, 4H), 7.49 (dt, J = 5.5, 2.3 Hz, 1H), 7.47 (d, J = 1.8 Hz, 1H), 7.44 (dd, J = 8.2, 1.9 Hz, 1H), 7.40 – 7.37 (m, 2H), 7.32 – 7.30 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 149.3, 148.4, 144.9, 141.2, 138.4, 131.7, 130.6, 130.1, 129.9, 129.0, 127.2, 126.4, 122.2, 120.0, 117.3, 112.4, 108.9, 56.0, 55.9. HRMS-ESI (m/z): calcd. for $\text{C}_{23}\text{H}_{19}\text{BrN}_2\text{O}_2$, $[\text{M}+\text{H}]^+$: 435.0708; found, 435.0706.

2-(3-bromophenyl)-4-(3,4-dimethoxyphenyl)-1-phenyl-1H-imidazole (3ig):



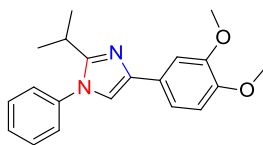
White solid (172 mg, 79%), m.p. = 60.1-62.6 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.99 (s, 1H), 7.58 (t, J = 1.7 Hz, 1H), 7.55 – 7.48 (m, 4H), 7.47 (d, J = 1.9 Hz, 1H), 7.44 (dd, J = 8.2, 2.0 Hz, 1H), 7.42 – 7.39 (m, 2H), 7.31 – 7.24 (m, 2H), 6.99 (d, J = 8.4 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 149.4, 148.4, 144.4, 141.3, 138.3, 132.9, 131.4, 131.1, 130.8, 130.1, 129.1, 127.4, 127.1, 126.5, 121.9, 120.2, 117.3, 112.5, 109.0, 56.0. HRMS-ESI (m/z): calcd. for $\text{C}_{23}\text{H}_{19}\text{BrN}_2\text{O}_2$, $[\text{M}+\text{H}]^+$: 435.0708; found, 435.0710.

2-cyclohexyl-4-(3,4-dimethoxyphenyl)-1-phenyl-1H-imidazole (3jh):



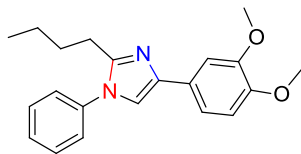
Yellow solid (126 mg, 70%), m.p. = 176.8-178.0 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.64 (s, 1H), 7.58 (t, J = 7.7 Hz, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.46 (d, J = 7.4 Hz, 2H), 7.36 (d, J = 1.9 Hz, 1H), 7.34 (dd, J = 8.2, 1.9 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 2.61 (tt, J = 11.6, 3.4 Hz, 1H), 1.80 – 1.69 (m, 4H), 1.64 – 1.55 (m, 3H), 1.27 – 1.10 (m, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 152.17, 149.28, 148.04, 137.97, 130.10, 128.84, 126.45, 117.14, 116.80, 112.40, 108.89, 55.98, 35.47, 32.26, 26.13, 25.88. ^{13}C NMR (151 MHz, DMSO- d_6) δ 152.9, 149.2, 148.0, 139.6, 138.0, 130.1, 128.8, 127.9, 126.5, 117.1, 116.9, 112.3, 108.8, 55.9, 25.9, 22.3. HRMS-ESI (m/z): calcd. for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_2$, $[\text{M}+\text{H}]^+$: 363.2073; found, 363.2075.

4-(3,4-dimethoxyphenyl)-2-isopropyl-1-phenyl-1H-imidazole (3ji):



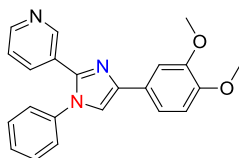
White solid (111 mg, 69%), m.p. = 102.4-105 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.66 (s, 1H), 7.58 (dd, J = 10.4, 4.8 Hz, 2H), 7.53 – 7.47 (m, 3H), 7.37 – 7.34 (m, 2H), 6.94 (d, J = 8.3 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.00 – 2.93 (m, 1H), 1.19 (s, 3H), 1.18 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 152.9, 149.2, 148.0, 139.6, 138.0, 130.1, 128.8, 127.9, 126.5, 117.1, 116.9, 112.3, 108.8, 55.95, 25.9, 22.3. HRMS-ESI (m/z): calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_2$, $[\text{M}+\text{H}]^+$: 323.1760; found, 323.1762.

2-butyl-4-(3, 4-dimethoxyphenyl)-1-phenyl-1H-imidazole (3jj):



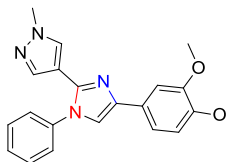
Yellow oil (96 mg, 57%). ^1H NMR (600 MHz, DMSO- d_6) δ 7.69 (s, 1H), 7.59 – 7.54 (m, 2H), 7.51 – 7.46 (m, 3H), 7.37 (d, J = 1.9 Hz, 1H), 7.34 (dd, J = 8.3, 2.0 Hz, 1H), 6.94 (d, J = 8.4 Hz, 1H), 3.80 (s, 3H), 3.76 (s, 3H), 2.67 – 2.59 (m, 2H), 1.55 (dt, J = 15.2, 7.5 Hz, 2H), 1.25 (dd, J = 14.8, 7.4 Hz, 2H), 0.79 (t, J = 7.4 Hz, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 149.3, 148.1, 148.0, 139.7, 138.0, 130.0, 128.6, 127.9, 126.0, 117.0, 116.8, 112.4, 108.8, 56.0, 55.9, 30.2, 26.7, 22.2, 14.0. HRMS-ESI (m/z): calcd. for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_2$, $[\text{M}+\text{H}]^+$: 337.1916; found, 337.1915.

4-(4-(3, 4-dimethoxyphenyl)-1-phenyl-1H-imidazol-2-yl)pyridine (3jk):



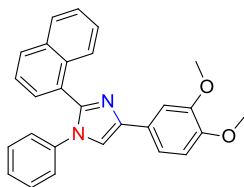
Yellow solid (87 mg, 49%), m.p. = 79.2-81.5 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 8.55 (d, J = 1.6 Hz, 1H), 8.51 (dd, J = 4.8, 1.6 Hz, 1H), 8.04 (s, 1H), 7.74 – 7.71 (m, 1H), 7.54 – 7.48 (m, 4H), 7.46 (dd, J = 8.2, 2.0 Hz, 1H), 7.43 – 7.41 (m, 2H), 7.37 (ddd, J = 8.0, 4.8, 0.7 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 149.5, 149.4, 149.2, 148.5, 143.6, 141.6, 138.2, 135.9, 130.2, 129.1, 127.1, 126.8, 126.5, 123.7, 120.2, 117.3, 112.4, 109.0, 56.0. HRMS-ESI (m/z): calcd. for $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_2$, $[\text{M}+\text{H}]^+$: 358.1556; found, 358.1559.

4-(4-(3, 4-dimethoxyphenyl)-1-phenyl-1H-imidazol-2-yl)-1-methyl-1H-pyrazole(3jl):



Yellow solid (127 mg, 71%), m.p. = 60-62 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 7.80 (s, 1H), 7.65 (s, 1H), 7.59 – 7.53 (m, 3H), 7.46 – 7.44 (m, 2H), 7.43 (d, J = 1.9 Hz, 1H), 7.39 (dd, J = 8.2, 2.0 Hz, 1H), 7.07 (d, J = 0.6 Hz, 1H), 6.97 (d, J = 8.4 Hz, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 149.3, 148.2, 140.9, 140.7, 138.2, 137.4, 130.1, 129.3, 127.5, 127.0, 121.1, 118.1, 117.1, 112.8, 112.4, 108.9, 56.0, 55.9, 39.0. HRMS-ESI (m/z): calcd. for $\text{C}_{21}\text{H}_{20}\text{N}_4\text{O}_2$, $[\text{M}+\text{H}]^+$: 361.1665; found, 361.1668.

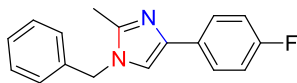
4-(3, 4-dimethoxyphenyl)-2-(naphthalen-1-yl)-1-phenyl-1H-imidazole (3jm):



Yellow solid (81 mg, 40%), m.p. = 78.6-80.9 °C. ^1H NMR (600 MHz, DMSO- d_6) δ 8.14 (s, 1H), 7.99 – 7.94 (m, 2H), 7.87 (d, J = 8.4 Hz, 1H), 7.53 – 7.45 (m, 6H), 7.30 – 7.26 (m, 2H), 7.25 – 7.20 (m, 3H), 7.00 (d, J = 8.4 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (151

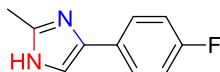
MHz, DMSO-d₆) δ 149.4, 148.3, 145.1, 141.1, 138.1, 133.5, 132.2, 129.7, 129.6, 129.6, 128.7, 128.6, 128.1, 127.5, 127.2, 126.6, 126.0, 125.5, 125.2, 118.1, 117.3, 112.5, 109.0, 56.0, 55.9. HRMS-ESI (m/z): calcd. for C₂₇H₂₂N₂O₂, [M+H]⁺: 407.1760; found, 407.1762.

benzyl-4-(4-fluorophenyl)-2-methyl-1H-imidazole (3jn):



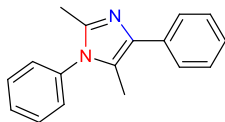
Yellow oil (120 mg, 90%). ¹H NMR (600 MHz, DMSO-d₆) δ 7.76 – 7.71 (m, 2H), 7.60 (s, 1H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.30 (t, *J* = 7.3 Hz, 1H), 7.21 (d, *J* = 7.3 Hz, 2H), 7.17 – 7.12 (m, 2H), 5.17 (s, 2H), 2.29 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 162.01, 160.41, 145.17, 138.12, 137.78, 131.71, 129.24, 128.06, 127.50, 126.23, 126.17, 116.86, 115.73, 115.59, 49.36, 13.25. HRMS-ESI (m/z): calcd. for C₁₇H₁₅FN₂, [M+H]⁺: 267.1298; found, 267.1300.

4-(4-fluorophenyl)-2-methyl-1H-imidazole (3jo):



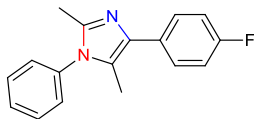
Yellow solid (45 mg, 51%) m.p. = 143-145.1 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 11.84 (s, 1H), 7.76 – 7.68 (m, 2H), 7.39 (s, 1H), 7.15 (t, *J* = 8.8 Hz, 2H), 2.30 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 161.87, 160.27, 144.62, 126.20, 126.15, 115.72, 100.13, 14.34. HRMS-ESI (m/z): calcd. for C₁₀H₉FN₂, [M+H]⁺: 177.0828; found, 177.0830.

2, 5-dimethyl-1, and 4-diphenyl-1H-imidazole (3jp):



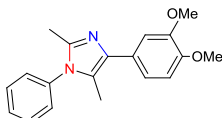
White solid (75 mg, 63%) m.p. = 93-94.1 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 7.66 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.44 – 7.37 (m, 4H), 7.22 (t, *J* = 7.3 Hz, 1H), 2.16 (s, 3H), 2.15 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 143.56, 136.60, 135.93, 135.25, 130.19, 129.29, 128.77, 128.17, 126.72, 126.17, 124.35, 14.13, 11.44. . HRMS-ESI (m/z): calcd. for C₁₇H₁₆N₂, [M+H]⁺: 249.1329; found, 249.1331.

4-(4-fluorophenyl)-2, 5-dimethyl-1-phenyl-1H-imidazole (3jq):



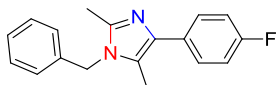
Colorless oil (100 mg, 75%). ¹H NMR (600 MHz, DMSO-d₆) δ 7.72 – 7.65 (m, 2H), 7.60 (t, *J* = 7.6 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.41 (d, *J* = 7.7 Hz, 2H), 7.22 (t, *J* = 8.9 Hz, 2H), 2.15 (s, 3H), 2.13 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 161.84, 160.24, 143.62, 136.54, 134.41, 132.40, 130.20, 129.32, 128.50, 128.44, 128.14, 124.17, 115.64, 115.50, 40.42, 40.28, 40.14, 40.00, 39.86, 39.73, 39.59, 14.07, 11.31. HRMS-ESI (m/z): calcd. for C₁₇H₁₅FN₂, [M+H]⁺: 267.1298; found, 267.1309.

4-(3, 4-dimethoxyphenyl)-2, 5-dimethyl-1-phenyl-1H-imidazole (3jr):



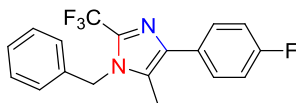
White solid (70 mg, 45%) m.p. = 135.4-136.5 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 7.60 (dd, *J* = 10.3, 4.8 Hz, 2H), 7.56 – 7.51 (m, 1H), 7.43 – 7.38 (m, 2H), 7.26 (d, *J* = 1.9 Hz, 1H), 7.12 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 2.15 (s, 3H), 2.12 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 149.15, 147.66, 143.22, 136.65, 135.22, 130.18, 129.24, 128.86, 128.15, 123.39, 118.91, 112.35, 110.90, 56.02, 55.87, 14.04, 11.34. HRMS-ESI (*m/z*): calcd. for C₁₉H₂₀N₂O₂, [M+H]⁺ : 309.1603; found, 309.1602.

Benzyl-4-(4-fluorophenyl)-2, 5-dimethyl-1H-imidazole (3js):



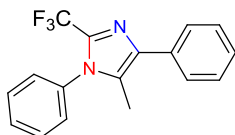
Yellow oil (60 mg, 36%). ¹H NMR (600 MHz, DMSO-d₆) δ 7.65 – 7.61 (m, 2H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 1H), 7.21 – 7.16 (m, 2H), 7.04 (d, *J* = 7.3 Hz, 2H), 5.18 (s, 2H), 2.29 (s, 3H), 2.25 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 161.71, 160.10, 143.90, 137.71, 134.29, 132.71, 129.29, 128.47, 128.42, 127.79, 126.51, 123.55, 115.53, 115.39, 46.67, 13.63, 10.63. HRMS-ESI (*m/z*): calcd. for C₁₈H₁₇FN₂, [M+H]⁺: 281.1454; found, 281.1457.

1-(1-benzyl-4-(4-fluorophenyl)-5-methyl-1H-imidazol-2-yl)-2, 2, 2-trifluoroethanone (3jt):



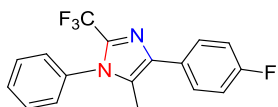
Yellow oil (80 mg, 57%). ¹H NMR (600 MHz, DMSO-d₆) δ 7.73 – 7.68 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.30 – 7.24 (m, 2H), 7.06 (d, *J* = 7.5 Hz, 2H), 5.44 (s, 2H), 2.30 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 162.56, 160.94, 136.64, 136.32, 134.01, 133.76, 130.67, 130.65, 129.39, 129.35, 129.29, 128.11, 126.08, 120.48, 118.70, 115.90, 115.76, 48.00, 10.24. HRMS-ESI (*m/z*): calcd. for C₁₈H₁₄F₄N₂, [M+H]⁺: 335.1171; found, 335.1180.

5-methyl-1, 4-diphenyl-2-(trifluoromethyl)-1H-imidazole (3ju):



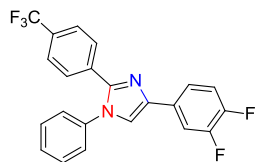
Yellow solid (95 mg, 63%) m.p. = 95-97.1 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 7.72 (d, *J* = 7.4 Hz, 2H), 7.65 – 7.62 (m, 3H), 7.55 – 7.51 (m, 2H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.34 (dd, *J* = 10.6, 4.2 Hz, 1H), 2.17 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 136.71, 134.71, 134.04, 130.64, 130.14, 129.09, 128.28, 127.54, 127.26, 10.80. HRMS-ESI (*m/z*): calcd. for C₁₇H₁₆N₂, [M+H]⁺ : 303.1109; found, 303.1114.

4-(4-fluorophenyl)-5-methyl-1-phenyl-2-(trifluoromethyl)-1H-imidazole (3jv):



White solid (91 mg, 57%) m.p. = 90.8-92.7 °C. ¹H NMR (600 MHz, DMSO-d₆) δ 7.77 – 7.72 (m, 2H), 7.63 (dd, *J* = 6.7, 3.6 Hz, 3H), 7.53 (dd, *J* = 6.3, 3.1 Hz, 2H), 7.32 – 7.27 (m, 2H), 2.15 (s, 3H). ¹³C NMR (151 MHz, DMSO-d₆) δ 162.60, 160.98, 135.86, 134.67, 130.67, 130.55, 130.15, 130.03, 129.27, 129.21, 128.27, 116.05, 115.91, 10.71. ¹H NMR (600 MHz, DMSO-d₆) δ 11.84 (s, 1H), 7.76 – 7.68 (m, 2H), 7.39 (s, 1H), 7.15 (t, *J* = 8.8 Hz, 2H), 2.30 (s, 3H). HRMS-ESI (*m/z*): calcd. for C₁₇H₁₂F₄N₂, [M+H]⁺: 321.1015; found, 321.1012.

4-(3, 4-difluorophenyl)-1-phenyl-2-(4-(trifluoromethyl)phenyl)-1H-imidazole (3jw):



White solid (1.2 g, 60%), m.p. = 168-169.2 °C, ^1H NMR (600 MHz, DMSO- d_6) δ 8.20 (s, 1H), 7.91 (ddd, J = 12.0, 7.9, 1.9 Hz, 1H), 7.77 (dd, J = 8.5, 2.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.2 Hz, 2H), 7.56 – 7.46 (m, 4H), 7.44 – 7.41 (m, 2H). ^{13}C NMR (151 MHz, DMSO- d_6) δ 145.1, 139.4, 138.0, 134.2, 131.9, 130.3, 129.4, 129.3, 126.5, 125.7, 125.7, 125.4, 123.62, 122.1, 121.6, 118.3, 118.2, 113.7, 113.6. HRMS-ESI (m/z): calcd. for $\text{C}_{22}\text{H}_{13}\text{F}_5\text{N}_2$, $[\text{M}+\text{H}]^+$: 401.1077; found, 401.1081.

References:

- (1) Das, T.; Chakraborty, A.; Sarkar, A. *Tetrahedron Lett.* **2014**, 55 (52), 7198.
- (2) Palumbo Piccionello, A.; Musumeci, R.; Cocuzza, C.; Fortuna, C. G.; Guarcello, A.; Pierro, P.; Pace, A. *Eur. J. Med. Chem.* **2012**, 50, 441.

