SUPPORTING INFORMATION

PEG-400 as an efficient and recyclable reaction medium for the synthesis of 2-aryl-2-methyl-4,5-diphenyl-2,3-dihydro-2H-imidazoles

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1.1 General Experimental

All solvents and reagents were used, as received from the suppliers. TLC was performed on Merck Kiesel gel 60, F254 plates with the layer thickness of 0.25 mm. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^1H NMR spectral data were collected at 300, 400 & 500 MHz, while ^{13}C NMR were recorded at 75 MHz. ^1H NMR spectral data are given as chemical shifts in ppm followed by multiplicity (s- singlet; d- doublet; dd- doublet of doublet; t- triplet; q- quartet; m- multiplet), number of protons and coupling constants. ^{13}C NMR chemical shifts are expressed in ppm. HRMS (ESI) spectral data were collected using ORBITRAP High Resolution Mass Spectrometer.

1.2 General Procedure for Synthesis of 2*H*-imidazoles 3a-n

A mixture of benzil **1** (0.210 g, 1 mmol), desired ketone **2a-n** (1 mmol), and ammonium acetate (0.154 g, 2 mmol) were taken in PEG-400 (10 mL) and stirred at room temperature for 4 – 6 h. After completion of the reaction (monitored by TLC), the reaction mass was poured into cold water. The solid imidazole product was filtered, washed with water and dried. The crude product was purified by recrystallization from CH_2Cl_2 /Hexane to afford the corresponding 2*H*-imidazoles **3a-n** as solids with good to excellent yields.

1.3 Analytical Data

2-methyl-2,4,5-triphenyl-2*H*-imidazole (**3a**)¹

Yield 91%; White solid; m.p. 80-81 °C; ^1H NMR (500 MHz, CDCl_3): δ 7.84 (d, J = 7.4 Hz, 2H), 7.57 (d, J = 7.7 Hz, 4H), 7.46 (t, J = 7.2 Hz, 2H), 7.38 (t, J = 7.6 Hz, 6H), 7.31 (t, J = 7.2 Hz, 1H), 1.96 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 154.1, 146.8,

131.4, 130.3, 129.7, 128.4, 125.4, 122.8, 89.4, 22.8; IR (neat): 3020, 2926, 2853, 1676, 1599, 1549, 1446, 1213 cm^{-1} ; ESI-MS m/z : 311 $[\text{M}+\text{H}]^+$; HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{19}\text{N}_2$ $[\text{M}+\text{H}]^+$: 311.15428, found: 311.15400.

2-(4-methoxyphenyl)-2-methyl-4,5-diphenyl-2H-imidazole (3b)²

Yield 88%; White solid; m.p. 126-128 °C; ^1H NMR (500 MHz, CDCl_3): δ 7.82 – 7.69 (m, 2H), 7.62 – 7.52 (m, 4H), 7.48 – 7.40 (m, 2H), 7.37 (t, $J = 7.7$ Hz, 4H), 6.96 – 6.88 (m, 2H), 3.80 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 156.4, 154.2, 140.1, 131.1, 130.4, 128.4, 123.9, 112.4, 89.6, 56.0, 25.8; ESI-MS m/z : 341 $[\text{M}+\text{H}]^+$; HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{21}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 341.16484, found: 341.16477.

2-methyl-4,5-diphenyl-2-*p*-tolyl-2H-imidazole (3c)

Yield 89%; White solid; m.p. 82-84 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.81 – 7.66 (m, 4H), 7.60 – 7.51 (m, 4H), 7.48 – 7.40 (m, 2H), 7.22 – 7.18 (m, 2H), 7.15 – 7.12 (m, 2H), 2.36 (s, 3H), 1.88 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 155.2, 146.0, 132.8, 131.6, 130.8, 129.3, 128.4, 122.7, 89.6, 26.8, 21.1; ESI-MS m/z : 325 $[\text{M}+\text{H}]^+$; HRMS (ESI) m/z calcd for $\text{C}_{23}\text{H}_{21}\text{N}_2$ $[\text{M}+\text{H}]^+$: 325.17047, found: 325.17026.

2-(3,4-dimethoxyphenyl)-2-methyl-4,5-diphenyl-2H-imidazole (3d)

Yield 78%; Pale yellow solid; m.p. 80-81 °C; ^1H NMR (300 MHz, CDCl_3): δ 7.79 (d, $J = 7.0$ Hz, 4H), 7.67 – 7.60 (m, 6H), 6.96 – 6.74 (m, 3H), 3.76 (s, 3H), 3.70 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 154.2, 150.8, 147.9, 140.4, 131.5, 130.5, 128.6, 114.6, 109.7, 89.1, 56.9, 25.8; ESI-MS m/z : 371 $[\text{M}+\text{H}]^+$; HRMS (ESI) m/z calcd for $\text{C}_{24}\text{H}_{23}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 371.17595, found: 371.17612.

2-methyl-4,5-diphenyl-2-(3,4,5-trimethoxyphenyl)-2H-imidazole (3e)

Yield 86%; White solid; m.p. 92-94 °C; ^1H NMR (300 MHz, CDCl_3): δ 7.94 (d, J = 7.6 Hz, 4H), 7.51 – 7.40 (m, 6H), 6.61 (s, 2H), 3.90 (s, 6H), 3.84 (s, 3H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3): δ 154.2, 146.7, 139.8, 138.8, 131.4, 130.9, 128.5, 108.1, 90.3, 60.5, 56.9, 22.5; IR (neat): 3025, 1600, 1550, 1497, 1440, 1396, 1356, 1253, 1224, 1168, 1128, 1108, 1023 cm^{-1} ; ESI-MS m/z : 401 $[\text{M}+\text{H}]^+$; HRMS (ESI) m/z calcd for $\text{C}_{25}\text{H}_{25}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 401.18597, found: 401.18639.

2-(4-fluorophenyl)-2-methyl-4,5-diphenyl-2H-imidazole (3f)³

Yield 82%; Pale yellow solid; m.p. 105-107 °C; ^1H NMR (500 MHz, CDCl_3): δ 7.98 (d, J = 7.9 Hz, 4H), 7.60 – 7.52 (m, 6H), 7.34 (d, J = 7.7 Hz, 2H), 7.27 (t, J = 7.1 Hz, 2H), 1.91 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 160.8, 154.2, 143.0, 132.1, 130.9, 128.0, 124.7, 115.7, 89.6, 26.8; ESI-MS m/z : 329 $[\text{M}+\text{H}]^+$; HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{18}\text{FN}_2$ $[\text{M}+\text{H}]^+$: 329.14540, found: 329.14558.

2-(4-bromophenyl)-2-methyl-4,5-diphenyl-2H-imidazole (3g)

Yield 88%; Pale yellow solid; m.p. 100-101 °C; ^1H NMR (300 MHz, CDCl_3): δ 7.96 (d, J = 7.1 Hz, 4H), 7.91 (d, J = 8.1 Hz, 2H), 7.56– 7.48 (m, 6H), 7.21 (t, J = 7.0 Hz, 2H), 1.94 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 160.1, 141.1, 132.4, 131.2, 130.9, 128.0, 124.8, 120.7, 90.1, 25.9; ESI-MS m/z : 389 $[\text{M}+\text{H}]^+$; HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{18}\text{BrN}_2$ $[\text{M}+\text{H}]^+$: 389.06534, found: 389.06543.

2-(4-nitrophenyl)-2-methyl-4,5-diphenyl-2H-imidazole (3h)

Yield 86%; Yellow solid; m.p. 97-99 °C; ^1H NMR (300 MHz, CDCl_3): δ 7.82 – 7.69 (m, 2H), 7.62 – 7.52 (m, 4H), 7.47 – 7.41 (m, 2H), 7.37 (t, J = 7.7 Hz, 4H), 6.96 – 6.88 (m, 2H), 1.93

(s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 155.1, 149.6, 145.1, 131.7, 130.5, 128.7, 124.2, 122.1, 89.4, 22.8; ESI-MS m/z : 356 $[\text{M}+\text{H}]^+$; HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{18}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$:

356.13990, found: 356.14012.

2-(3,4-dichlorophenyl)-2-methyl-4,5-diphenyl-2H-imidazole (3i)

Yield 79%; Pale yellow solid; m.p. 102-104 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.79 (d, $J = 7.0$ Hz, 4H), 7.65 – 7.51 (m, 7H), 7.34 (s, 1H), 7.13 (d, $J = 7.8$ Hz, 1H), 1.92 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 154.1, 146.7, 133.2, 131.4, 130.8, 128.7, 127.4, 122.0, 89.5, 29.1; ESI-MS m/z :

379 $[\text{M}+\text{H}]^+$; HRMS (ESI) m/z calcd for $\text{C}_{22}\text{H}_{17}\text{Cl}_2\text{N}_2$ $[\text{M}+\text{H}]^+$: 379.07633, found: 379.07651.

2-(furan-2-yl)-2-methyl-4,5-diphenyl-2H-imidazole (3j)³

Yield 86%; Pale yellow solid; m.p. 82-83 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.89 (d, $J = 7.9$ Hz, 4H), 7.61 (d, $J = 6.9$ Hz, 1H), 7.55-7.50 (m, 6H), 6.41 (t, $J = 7.9$ Hz, 1H), 6.14 (d, $J = 7.1$ Hz, 1H), 1.92

(s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 158.1, 152.1, 141.9, 139.6, 133.1, 131.7, 130.9, 128.7, 112.0, 106.1, 59.5, 22.6; ESI-MS m/z : 301 $[\text{M}+\text{H}]^+$; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 301.13409, found: 301.13426.

2-methyl-4,5-diphenyl-2-(thiophen-2-yl)-2H-imidazole (3k)³

Yield 89%; Pale yellow solid; m.p. 88-90 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.91 (d, $J = 7.2$ Hz, 4H), 7.58-7.51 (m, 6H), 7.44 (d, $J = 7.1$ Hz, 1H), 6.91 (t, $J = 8.1$ Hz, 1H), 6.84 (d, $J = 7.9$ Hz, 1H), 1.88

(s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 160.1, 140.3, 131.5, 129.7, 128.2, 127.0, 126.4, 125.1, 89.5, 27.6; ESI-MS m/z : 317 $[\text{M}+\text{H}]^+$; HRMS (ESI) m/z calcd for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{S}$ $[\text{M}+\text{H}]^+$: 317.11124, found: 317.11102.

2-(2-methyl-4,5-diphenyl-2H-imidazol-2-yl)pyridine (3l)

Yield 81%; Pale yellow solid; m.p. 91-93 °C; ^1H NMR (500 MHz, CDCl_3): δ 7.84 (d, J = 7.4 Hz, 2H), 7.57 (d, J = 7.7 Hz, 4H), 7.46 (t, J = 7.2 Hz, 2H), 7.38 (t, J = 7.6 Hz, 6H), 7.31 (t, J = 7.2 Hz, 1H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 154.1, 146.8, 131.4, 130.3, 129.7, 128.4, 125.4, 122.8, 89.4, 22.8; ESI-MS m/z : 312 $[\text{M}+\text{H}]^+$; HRMS (ESI) m/z calcd for $\text{C}_{21}\text{H}_{18}\text{N}_3$ $[\text{M}+\text{H}]^+$: 312.15007, found: 312.15026.

2-methyl-2-(naphthalen-1-yl)-4,5-diphenyl-2H-imidazole (3m)

Yield 88%; White solid; m.p. 120-121 °C; ^1H NMR (500 MHz, CDCl_3): δ 8.30 (s, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.89 (d, J = 8.6 Hz, 2H), 7.87 – 7.82 (m, 1H), 7.62 (d, J = 7.4 Hz, 4H), 7.48 (t, J = 6.5 Hz, 4H), 7.41 (t, J = 7.6 Hz, 4H), 2.05 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 152.1, 140.6, 133.6, 131.6, 130.4, 129.9, 128.9, 127.0, 126.4, 124.6, 123.3, 88.2, 23.1; ESI-MS m/z : 361 $[\text{M}+\text{H}]^+$; HRMS (ESI) m/z calcd for $\text{C}_{26}\text{H}_{21}\text{N}_2$ $[\text{M}+\text{H}]^+$: 361.16993, found: 361.17014.

2,2,4,5-tetraphenyl-2H-imidazole (3n)

Yield 91%; Off-white solid; m.p. 196-198 °C; ^1H NMR (500 MHz, CDCl_3): δ 7.84 (d, J = 7.4 Hz, 4H), 7.57 (d, J = 7.7 Hz, 4H), 7.46 (t, J = 7.2 Hz, 4H), 7.38 (t, J = 7.6 Hz, 6H), 7.31 (t, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3): δ 165.1, 141.5, 132.6, 130.3, 129.7, 128.2, 127.4, 124.8, 109.4; ESI-MS m/z : 373 $[\text{M}+\text{H}]^+$; HRMS (ESI) m/z calcd for $\text{C}_{27}\text{H}_{21}\text{N}_2$ $[\text{M}+\text{H}]^+$: 373.17047, found: 373.17025.

1.4 References

1. [Armesto, D.](#); [Bosch, P.](#); [Horspool, W. M.](#); [Ortiz, M. J.](#) *Tetrahedron Lett.* **1987**, 28, 4605 - 4608.
2. [White, D. M.](#); [Sonnenberg, J. J.](#) *J. Org. Chem.* **1964**, 29, 1926 - 1930.
3. Boominathan, S. S. K.; Chen, C.-Y.; Huang, P.-J.; Hou, R.-J.; Wang, J.-J. *New J. Chem.*, **2015**, 39, 6914 - 6918.

1.5 Cytotoxicity evaluation

The synthesized imidazole derivatives 3a-n, were further assessed for *in vitro* cytotoxicity on the basis of the measurement of *in vitro* growth in 96 well plates by cell-mediated reduction of tetrazolium salt to form water insoluble formazan crystals using the standard MTT assay using doxorubicin as positive control. The cytotoxicity was evaluated against four different cancer cell lines, namely, cervical cancer (HeLa), human alveolar adenocarcinoma (A549) and breast adenocarcinoma (MDA-MB-231, MCF-7). Dose-response curves were plotted for the test compounds and controls after correction by subtracting the background absorbance from that of the blanks. The antitumor potency of the compounds indicated by IC₅₀ values (50% inhibitory concentration) was calculated from the plotted absorbance data for the dose-response curves. IC₅₀ values (in μM) were expressed as the average of two independent experiments.

Table 1 *In vitro* cytotoxicity (IC₅₀ in μM) of novel 2*H*-imidazoles against different human cancer cell lines

Compounds	IC ₅₀ (μM)			
	HeLa (Cervical)	MDA-MB231 (Breast)	MCF-7 (Breast)	A549 (Lung cancer)
3a	28.0	23.6	16.0	17.9
3b	96.5	77.6	>100	>100
3c	32.7	25.8	21.4	10.2
3d	78.2	45.6	52.7	65.5
3e	>100	>100	>100	>100
3f	88.6	67.8	61.9	>100

3g	>100	11.4	16.9	19.6
3h	11.2	12.7	15.2	17.2
3i	>100	>100	>100	>100
3j	>100	>100	>100	>100
3k	>100	>100	>100	>100
3l	>100	>100	>100	>100
3m	>100	>100	>100	>100
3n	>100	>100	>100	>100
Doxorubicin (standard)	0.451	0.501	1.05	1.21

1.6 Copies of spectra

¹H NMR Spectrum of compound 3a

¹³C NMR Spectrum of compound 3a

HRMS Spectrum of compound 3a

IR Spectrum of compound 3a

¹H NMR Spectrum of compound 3b

¹³C NMR Spectrum of compound 3b

HRMS Spectrum of compound 3b

^1H NMR Spectrum of compound 3c

^{13}C NMR Spectrum of compound 3c

^1H NMR Spectrum of compound 3d

^{13}C NMR Spectrum of compound 3d

¹H NMR Spectrum of compound 3e

¹³C NMR Spectrum of compound 3e

HRMS Spectrum of compound 3e

IR Spectrum of compound 3e

¹H NMR Spectrum of compound 3f

¹³C NMR Spectrum of compound 3f

¹H NMR Spectrum of compound 3g

¹H NMR Spectrum of compound 3h

^{13}C NMR Spectrum of compound 3h

HRMS Spectrum of compound 3h

^1H NMR Spectrum of compound 3i

^{13}C NMR Spectrum of compound 3i

HRMS Spectrum of compound 3i

¹H NMR Spectrum of compound 3j

^{13}C NMR Spectrum of compound 3l

^1H NMR Spectrum of compound 3m

^{13}C NMR Spectrum of compound 3m

^1H NMR Spectrum of compound 3n

^{13}C NMR Spectrum of compound 3n