Supporting Information

for

Green synthesis of new chiral 1-(arylamino)imidazo[2,1-a]isoindole-2,5-diones from the corresponding α-amino acid arylhydrazides in aqueous medium

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1. General methods

All reagents and chemicals were purchased from Sigma-Aldrich chemical company and Acros Organic. Solvents used in reactions were dried and distilled before use. Toluene was distilled over sodium metal. Reactions were monitored by thin layer chromatography (TLC) of aliquots using Merck 60 F-254 silica gel plates (0.25 mm layered thickness). Melting points were determined on a Büchi 510 capillary apparatus. NMR spectra were recorded on a Bruker AC-300 spectrometer [300 MHz (1H) and 75 MHz (13C)]. NMR spectra were calibrated on the non-fully deuteried residual solvent signal (ppm): in CDCl3 at 7.26 (proton) and 77.16 (carbon), in C6D6 at 7.16 (proton) and 128.06 (carbon). IR spectra were recorded on a Nicolet 6700 FT-IR, ATR, to support with Diamond accuracy 1 cm−1. Electrospray ionisation (ESI) mass spectrometry data were recorded on an UPLC Waters device (in positive mode); for the voltages of the mass spectrometries, the following abbreviations are used: C Capillary (kV), SC Sampling Cone, EC Extraction Cone. Calibration was performed with sodium formate (range from 100 to 1000 g·mol−1) and the lockspray (lockmass on the leucine encephaline 556.2771 g·mol−1) was used without collision energy; the relative intensity of peaks is given in brackets. Optical rotations were measured by using a Perkin Elmer Polarimeter (Model 341) using a mercury lamp (578 nm).

2. General procedures

2.1. Synthesis of α-amino acid arylhydrazides 3a–m

Freshly distilled arylhydrazine (25 mmol, 2.5 equiv) and (L)-α-amino acid methyl ester hydrochloride (10 mmol, 1 equiv) were mixed in sealed tube well closed in the presence of Et3N (1 equiv). The mixture was heated at 70 °C for 17 h and then diluted
with EtOAc (10 mL), washed with water (3 mL), and dried over MgSO₄. After the evaporation of the solvent in vacuo, Et₂O (10 mL) was added to precipitate the products 3a–m which were obtained, after filtration, as solid compounds.

(L)-Phenylglycine phenylhydrazide (3d): Yield 83%. white solid; mp 138–140 °C. FT-IR (neat, cm⁻¹): 3351, 3227, 3057, 1660, 1590; ¹H NMR (300 MHz, CDCl₃): δ= 1.91 (s, 1H), 4.63 (s, 1H), 6.08 (s, 2H), 6.70–7.19 (m, 5H), 7.34–7.44 (m, 5H), 8.45 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ= 60.11, 113.21, 122.43, 127.23, 128.98, 129.15, 129.78, 133.36, 149.65, 171.09 ppm; ESI(+)-MS CH₃CN [C= 2, SC= 20, EC= 2]: HRMS ES⁺ for C₁₄H₁₅N₃O m/z: [M+H]⁺ Calc. 242.1244, found: 242.1234.

(L)-Cysteine phenylhydrazide (3g): Yield 71%. white solid; mp 98–100 °C; [α]²⁵⁷⁸ = +52.0 ± 2.22 (MeOH, C= 0.59). FT-IR (neat, cm⁻¹): 3214, 3027, 1655, 1601, 1495; ¹H NMR (300 MHz, CDCl₃): δ= 1.72 (s, 1H), 2.75 (dd, 1H, 2J= 13.8 Hz, 3J= 3.9 Hz), 3.14 (dd, 1H, 2J= 13.8 Hz, 3J= 5.4 Hz), 3.67 (dd, 1H, 3J= 3.9 Hz, 3J= 5.4 Hz), 5.18 (s, 1H), 6.10 (s, 2H), 7.18–7.27 (m, 5H), 9.01 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ= 30.11, 59.23, 113.01, 121.45, 129.32, 149.14, 171.02 ppm; ESI(+)-MS CH₃CN [C= 2, SC= 20, EC= 2]: HRMS ES⁺ for C₉H₁₃N₃OS m/z: [M+H]⁺ Calc. 212.0858, found: 212.0859.

(L)-Tyrosine phenylhydrazide (3j): Yield 77%. white solid; mp 134–136 °C; [α]²⁵⁷⁸ = +15.3 ± 0.3 (MeOH, C= 0.94). FT-IR (neat, cm⁻¹): 3372, 3351, 2903, 1692, 1599, 1253; ¹H NMR (300 MHz, CDCl₃): δ= 3.09 (dd, 1H, 2J= 13.2 Hz, 3J= 6.8 Hz), 3.10 (dd, 1H, 2J= 13.2 Hz, 3J= 6.1 Hz), 4.11 (dd, 1H, 3J= 6.1 Hz, 3J= 6.8 Hz), 5.09 (s, 1H), 6.11 (s, 1H), 6.70 (d, 2H, 3J= 7.4 Hz), 6.88–6.95 (m, 5H), 7.13 (d, 2H, 3J= 7.4 Hz), 8.02 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ= 40.12, 57.01, 113.22, 115.43, 121.76, 128.98, 129.43, 130.76, 150.01, 156.32, 172.34 ppm; ESI(+)-MS CH₃CN [C= 2, SC= 20, EC= 2]: HRMS ES⁺ for C₁₅H₁₇N₃O₂ m/z: [M+H]⁺ Calc. 272.1337, found: 272.1332.

(L)-alanine 4-chlorophenylhydrazide (3k): Yield 69%. white solid; mp 128–130 °C; [α]²⁵⁷⁸ = +23.91 ± 0.69 (MeOH, C= 0.322 ± 0.004). FT-IR (neat, cm⁻¹): 3100, 2900, 1699, 1450; ¹H NMR (300 MHz, CDCl₃): δ= 1.42 (d, 3H, J= 6.7 Hz), 1.63 (s, 2H), 3.65 (q, 1H, J= 6.7 Hz), 6.24 (s, 1H), 6.76 (d, 2H, J= 8.5 Hz), 7.20 (d, 2H, J= 8.5 Hz), 8.97 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ= 21.76, 50.28, 114.78, 125.84, 129.09, 

146.74, 175.39 ppm; ESI(+)−MS CH$_3$CN [C= 2, SC= 20, EC= 2]: HRMS ES+ for C$_9$H$_{12}$ClN$_3$O m/z: [M+H]$^+$ Calc. 214.0673, found: 214.0688.

(L)-phenylglycine 4-chlorophenylhydrazide (3l): Yield 70%. white solid; mp 135–137 °C; [α]$_{25}^{25}$ $^{25}$= +43.51 ± 0.60 (MeOH, C= 0.562 ± 0.004). FT-IR (neat, cm$^{-1}$): 3261, 3190, 2997, 1689; $^1$H NMR (300 MHz, CDCl$_3$): δ= 1.71 (s, 2H), 4.71 (s, 1H), 5.32 (s, 1H), 6.68 (d, 2H, J= 8.4 Hz), 7.16 (d, 2H, J= 8.4 Hz), 7.30–7.47 (m, 5H), 8.62 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ= 61.29, 113.33, 127.56, 128.21, 129.23, 129.36, 130.89, 133.87, 148.48, 172.15 ppm; ESI(+)−MS CH$_3$CN [C= 2, SC= 20, EC= 2]: HRMS ES+ for C$_{14}$H$_{15}$ClN$_3$O m/z: [M+Na]$^+$ Calc. 298.0723, found: 298.0723.

(L)-phenylalanine 4-chlorophenylhydrazide (3m): Yield 74%. white solid; mp 140–142 °C; [α]$_{25}^{25}$ $^{25}$= +24.74 ± 0.30 (MeOH, C= 0.768 ± 0.004). FT-IR (neat, cm$^{-1}$): 3276, 3030, 2926, 1706; $^1$H NMR (300 MHz, CDCl$_3$): δ= 1.60 (s, 2H), 2.92 (dd, 1H, J= 13.0 Hz, J= 7.3 Hz), 3.24–3.28 (m, 1H), 3.76–3.79 (m, 1H), 6.16 (s, 1H), 6.70 (d, 2H, J= 8.4 Hz), 7.20 (d, 2H, J= 8.4 Hz), 7.25 (d, 2H, J= 6.6 Hz), 7.33–7.40 (m, 3H), 8.86 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ= 33.76, 55.65, 114.82, 126.04, 127.13, 128.90, 129.07, 129.56, 137.18, 146.55, 173.83 ppm; ESI(+)−MS CH$_3$CN [C= 2, SC= 20, EC= 2]: HRMS ES+ for C$_{15}$H$_{16}$ClN$_3$O m/z: [M+H]$^+$ Calc. 290.0923, found: 290.0911.

2.2. General procedure for the synthesis of the 1-(arylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-diones 5a–m in water

A mixture of 2-formylbenzoic acid (100 mg, 0.66 mmol, 1 equiv) and α-amino acid aryldrazide (0.66 mmol, 1 equiv) with catalytic amount of SDS (10%) in water (2 mL) in a closed sealed tube was heated at 120 °C (oil bath) for 10 h. The mixture was cooled at room temperature and extracted with EtOAc (3 × 5 mL). The organic phase was dried over MgSO$_4$ and concentrated in vacuo affording the compounds 5a–m with good yields.

3-Methyl-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5a): Yield 90%. white solid; mp 200–202 °C; $R_f$ 0.23 (EtOAc/c-C$_6$H$_{12}$ 40:60); [α]$_{25}^{25}$ $^{25}$= -17.1 ± 0.4 (MeOH, C= 0.532 ± 0.005). FT-IR (neat, cm$^{-1}$): 3242, 2938, 1702, 1600, 1489, 1403, 1367, 1222; $^1$H NMR (300 MHz, CDCl$_3$): δ= 1.63 (d, 3H, J= 7.2 Hz), 4.72 (q, 1H, J= 7.2 Hz), 5.95 (s, 1H), 6.52 (d, 2H, J= 8.4 Hz), 6.88 (t, 1H, J= 7.2 Hz), 7.08–7.13 (m, 2H), 7.54–7.64 (m, 3H), 7.95 (d, 1H, J= 7.5 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$):
δ = 17.42, 53.68, 73.86, 113.91, 122.03, 124.76, 124.98, 129.19, 130.19, 132.22, 133.16, 142.36, 145.85, 173.31, 174.44 ppm; ESI(+) - MS CH₃CN [C= 2, SC= 20, EC= 2]: HRMS ES⁺ for C₁₇H₁₆N₃O₂ m/z: [M+H]⁺ Calc. 294.1237, found: 294.1230.

3-Isopropyl-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5b):
Yield 70%. white solid; mp 212–214 °C; Rf 0.64 (EtOAc/c-C₆H₁₂ 40:60); [α]₂⁵/₂⁷₈ = + 30.5 ± 0.3 (CHCl₃, C = 0.878 ± 0.004). FT-IR (neat, cm⁻¹): 3228, 2967, 1219, 1709, 1602, 1495, 1398, 1367; ¹H NMR (300 MHz, CDCl₃): δ = 1.11 (d, 3H, J = 6.6 Hz), 1.27 (d, 3H, J = 6.9 Hz), 1.68 (sbr, 1H), 2.40–2.50 (m, 1H), 4.48 (d, 1H, J = 4.2 Hz), 5.92 (s, 1H), 6.36 (s, 1H), 6.54 (d, 2H, J = 7.5 Hz), 6.88 (t, 1H, J = 7.5 Hz), 7.10 (t, 2H, J = 7.5 Hz), 7.52–7.56 (m, 2H), 7.58–7.65 (m, 1H), 7.98 (d, 1H, J = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 18.15, 19.75, 31.32, 63.91, 75.89, 114.24, 122.22, 124.82, 125.07, 129.27, 130.91, 132.39, 133.23, 142.99, 146.29, 173.82, 174.16 ppm; ESI(+)-MS CH₃CN [C= 2, SC= 20, EC= 2]: HRMS ES⁺ for C₁₉H₂₀N₃O₂ m/z: [M+H]⁺ Calc. 322.1555, found: 322.1546.

3-Isobutyl-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5c):
Yield 95%. white solid; mp 230–232 °C; Rf 0.6 (EtOAc/c-C₆H₁₂ 40:60); [α]₂⁵/₂⁷₈ = -2.0 ± 0.2 (CHCl₃, C = 1.016 ± 0.005). FT-IR (neat, cm⁻¹): 3212, 3024, 2956, 1702, 1601, 1494, 1386, 1368, 1213; ¹H NMR (300 MHz, CDCl₃): δ = 1.06 (d, 3H, J = 6.6 Hz), 1.17 (d, 3H, J = 6.6 Hz), 1.64–1.74 (m, 1H), 1.79–1.88 (m, 1H), 1.97–2.06 (m, 1H), 4.66 (dd, 1H, J₁ = 11.4 Hz, J₂ = 3.6 Hz), 5.92 (s, 1H), 6.53 (d, 2H, J = 8.7 Hz), 6.87 (t, 1H, J = 7.5 Hz), 7.07–7.13 (m, 2H), 7.50–7.63 (m, 3H), 7.94 (d, 1H, J = 7.5 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 20.88, 22.75, 24.91, 39.49, 56.56, 73.49, 113.41, 121.50, 124.24, 124.40, 128.67, 130.31, 131.81, 132.56, 141.87, 145.38, 172.96, 173.78 ppm; ESI(+)-MS CH₃CN [C= 2, SC= 20, EC= 2]: HRMS ES⁺ for C₂₀H₂₁N₃O₂ m/z: [M+H]⁺ Calc. 336.1555, found: 332.1546.

3-Phenyl-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5d):
Yield 79%. white solid; mp 217–219 °C; Rf 0.51 (EtOAc/c-C₆H₁₂ 40:60). FT-IR (neat, cm⁻¹): 3286, 3062, 1708, 1602, 1497, 1391, 1361, 1302, 1215; ¹H NMR (300 MHz, CDCl₃): δ = 1.64 (s, 1H), 5.72 (s, 1H), 6.07 (s, 1H), 6.21 (s, 1H), 6.47 (d, 2H, J = 8.1 Hz), 6.86 (t, 1H, J = 14.7 Hz), 7.08 (t, 2H, J = 8.4 Hz), 7.34–7.45 (m, 3H), 7.56–7.68 (m, 5H), 8.02 (d, 1H, J = 7.5 Hz); ¹³C NMR (75 MHz, CDCl₃): δ = 59.52, 73.75, 113.27, 121.47, 124.38, 124.69, 125.87, 127.98, 128.41, 128.70, 130.49, 131.47,
132.91, 134.16, 142.05, 145.16, 170.99, 172.91 ppm; ESI(+)-MS CH$_3$CN [C= 2, SC= 20, EC= 2]: HRMS ES+ for C$_{22}$H$_{17}$N$_3$O$_2$ m/z: [M+H]$^+$ Calc. 356.1394, found: 356.1386.

3-Benzyl-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5e): Yield 78%. white solid; mp 210–212 °C; R$_f$ 0.35 (EtOAc/c-C$_6$H$_{12}$ 40:60); [α]$^2_{578}$ = -8.1 ± 0.3 (CHCl$_3$, C= 0.836 ± 0.004). FT-IR (neat, cm$^{-1}$): 3238, 3030, 1707, 1600, 1492, 1401, 1368, 1221; $^1$H NMR (300 MHz, CDCl$_3$): δ= 1.62 (sbr, 1H), 3.32 (dd, 1H, J= 14.1 Hz, J= 4.8 Hz), 3.39 (dd, 1H, J= 14.1 Hz, J= 4.2 Hz), 4.94 (t, 1H, J= 4.2 Hz), 4.98 (s, 1H), 5.86 (s, 1H), 6.28 (d, 2H, J= 8.1 Hz), 6.83 (t, 1H, J= 7.2 Hz), 7.03 (t, 2H, J= 7.5 Hz), 7.31–7.35 (m, 4H), 7.47 (t, 1H, J= 7.5 Hz), 7.56 (t, 1H, J= 7.5 Hz), 7.93 (d, 1H, J= 7.5 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): δ= 37.40, 59.36, 74.66, 113.76, 121.88, 124.62, 125.00, 127.56, 128.80, 129.15, 130.29, 130.76, 132.08, 133.15, 135.70, 142.63, 145.49, 172.94, 173.76 ppm; ESI(+)-MS CH$_3$CN [C= 2, SC= 20, EC= 2]: HRMS ES+ for C$_{23}$H$_{19}$N$_3$O$_2$ m/z: [M+H]$^+$ Calc. 370.1550, found: 370.1544.

3-(2-(Methylthio)ethyl)-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5f): Yield 71%. white solid; mp 191–193 °C; R$_f$ 0.34 (EtOAc/c-C$_6$H$_{12}$ 40:60); [α]$^2_{578}$ = +33.6 ± 0.4 (CHCl$_3$, C= 0.724 ± 0.004). FT-IR (neat, cm$^{-1}$): 3238, 3017, 1711, 1602, 1494, 1394, 1363, 1214; $^1$H NMR (300 MHz, CDCl$_3$): δ= 2.19 (s, 3H), 2.20–2.28 (m, 1H), 2.39–2.45 (m, 1H), 2.81–2.86 (m, 2H), 4.73 (dd, 1H, J= 7.2 Hz, J= 5.1 Hz), 5.96 (s, 1H), 6.56 (d, 2H, J= 7.8 Hz), 6.89 (t, 1H, J= 7.2 Hz), 7.12 (t, 2H, J= 7.5 Hz), 7.57–7.67 (m, 3H), 7.98 (d, 1H, J= 7.2 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): δ= 15.21, 30.11, 30.43, 57.17, 75.21, 113.92, 121.91, 124.80, 124.95, 129.18, 130.86, 132.01, 132.35, 142.91, 146.13, 173.97, 174.24 ppm; ESI(+)-MS CH$_3$CN [C= 2, SC= 20, EC= 2]: HRMS ES+ for C$_{19}$H$_{20}$N$_3$O$_2$S m/z: [M+H]$^+$ Calc. 370.1550, found: 370.1544.

3-(Mercaptoethyl)-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5g): Yield 60%. white solid; mp 202–204 °C; R$_f$ 0.27 (EtOAc/c-C$_6$H$_{12}$ 40:60); [α]$^2_{578}$ = -348 ± 3 (CHCl$_3$, C= 0.664 ± 0.004). FT-IR (neat, cm$^{-1}$): 3318, 3270, 3055, 1703, 1666, 1602, 1479, 1345, 1323; $^1$H NMR (300 MHz, CDCl$_3$): δ= 3.69 (dd, 1H, J= 12.00 Hz, J= 7.5 Hz), 3.80 (s, 1H), 4.02 (dd, 1H, J= 12.3 Hz, J= 7.5 Hz), 4.89 (t, 1H, J= 7.5 Hz), 6.00 (s, 1H), 6.87–6.95 (m, 3H), 7.21–7.30 (m, 2H), 7.50–7.60 (m, 2H), 7.64–7.69 (m, 1H), 7.64–7.69 (d, 1H, J= 7.5 Hz), 8.88 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ= 38.24, 57.65, 66.85, 113.12, 120.96, 123.10, 124.36, 128.78, 129.37,
3-(Hydroxymethyl)-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5h): Yield 77%. white solid; mp 201–203 °C; R$_f$ 0.13 (EtOAc/c-C$_6$H$_{12}$ 40:60); [α]$^2_{578} = -28 \pm 2$ (CHCl$_3$, C= 0.380 ± 0.022). FT-IR (neat, cm$^{-1}$): 3508, 3283, 2923, 1695, 1598, 1498, 1411, 1362; $^1$H NMR(300 MHz, CDCl$_3$): δ = 1.67 (s, 1H), 4.20 (dd, 1H, J= 11.7 Hz, J= 5.4 Hz), 4.36 (dd, 1H, J= 11.7 Hz, J= 4.5 Hz), 4.70–4.72 (m, 1H), 6.11 (s, 1H), 6.44 (d, 2H, J= 8.1 Hz), 6.90 (t, 1H, J= 8.1 Hz), 7.14 (t, 2H, J= 7.8 Hz), 7.58–7.66 (m, 3H), 8.00 (d, 1H, J= 7.2 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): δ= 60.24, 63.46, 75.80, 113.95, 121.92, 124.86, 125.15, 129.34, 130.94, 132.02, 133.49, 143.18, 145.78, 172.83, 174.10 ppm; ESI(+)-MS CH$_3$CN [C= 2, SC= 20, EC= 2]: HRMS ES+ for C$_{17}$H$_{16}$N$_3$O$_2$S m/z: [M+H]$^+$ Calc. 326.0958, found: 326.0950.

3-((1H-indol-3-yl)methyl)-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)dione (5i): Yield 73%. white solid; mp 185–187 °C; R$_f$ 0.18 (EtOAc/c-C$_6$H$_{12}$ 40:60); [α]$^2_{578} = +99 \pm 1$ (MeOH, C= 0.494 ± 0.005). FT-IR (neat, cm$^{-1}$): 3449, 3261, 3057, 1602, 1491, 1460, 1401, 1302, 1221; $^1$H NMR (300 MHz, CDCl$_3$): δ = 1.72 (sbr, 1H), 3.51 (dd, 1H, J= 15.6 Hz, J= 4.5 Hz), 3.59 (dd, 1H, J= 14.7 Hz, J= 3.9 Hz), 4.97 (t, 1H, J= 4.2 Hz), 6.18 (d, 2H, J= 7.8 Hz), 6.79 (t, 1H, J= 7.2 Hz), 6.95–7.00 (m, 2H), 7.08–7.13 (m, 1H), 7.18–7.23 (m, 3H), 7.40–7.46 (m, 2H), 7.55 (t, 1H, J= 7.5 Hz), 7.72 (d, 1H, J= 7.8 Hz), 7.93 (d, 1H, J= 7.5 Hz), 8.24 (s, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$): δ= 27.63, 59.29, 74.66, 110.12, 111.25, 113.68, 119.32, 120.04, 121.73, 122.45, 124.05, 124.53, 124.92, 127.52, 129.04, 130.61, 132.16, 132.96, 136.25, 142.77, 145.47, 173.59, 173.71 ppm; ESI(+)-MS CH$_3$CN [C= 2, SC= 20, EC= 2]: HRMS ES+ for C$_{25}$H$_{21}$N$_4$O$_2$ m/z: [M+H]$^+$ Calc. 409.1659, found: 409.1654.

3-(4-Hydroxybenzyl)-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5j): Yield 66%. white solid; mp 222–224 °C; R$_f$ 0.32 (EtOAc/c-C$_6$H$_{12}$ 40:60); [α]$^2_{578} = -58.7 \pm 0.6$ (MeCN, C= 0.552 ± 0.004). FT-IR (neat, cm$^{-1}$): 3274, 3203, 2985, 1706, 1673, 1598, 1517, 1493, 1412, 1220; $^1$H NMR (300 MHz, CDCl$_3$): δ = 3.25–3.37 (m, 2H), 4.94 (t, 1H, J= 4.2 Hz), 5.11 (s, 1H), 5.82 (sbr, 1H), 5.93 (s, 1H), 6.31 (d, 2H, J= 7.8 Hz), 6.82–6.88 (m, 3H), 7.08 (t, 2H, J= 8.1 Hz), 7.22 (d, 2H, J= 8.1 Hz), 7.37 (d, 1H, J= 7.5 Hz), 7.48–7.53 (m, 1H), 7.60 (t, 1H, J= 7.5 Hz), 7.97 (d, 1H, J= 7.5 Hz);
$^{13}$C NMR (75 MHz, CDCl$_3$ + some drops of CD$_3$CN): $\delta$ = 36.35, 59.42, 74.20, 113.39, 115.52, 116.48, 121.32, 124.56, 126.60, 128.91, 130.50, 131.09, 131.88, 132.94, 142.53, 145.44, 155.92, 172.65, 173.67 ppm; ESI(+) - MS CH$_3$CN [C= 2, SC= 20, EC= 2]: HRMS ES$^+$ for C$_{23}$H$_{19}$N$_3$O$_3$ m/z: [M$+$H]$^+$ Calc. 386.1499, found: 386.1492.

1-(4-chlorophenylamino)-3-methyl-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5k): Yield 69%. white solid; mp 214–216 °C; $R_f$ 0.34 (EtOAc/c-C$_6$H$_{12}$ 40:60); $[\alpha]_{578}^{25}$ = -54.67 ± 0.28 (CH$_3$CN, C= 0.765 ± 0.004). FT-IR (neat, cm$^{-1}$): 3324, 3221, 2932, 1716, 1611, 1400, 1392, 1233; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 1.52 (d, 3H, $J$ = 7.2 Hz), 4.65 (q, 1H, $J$ = 7.2 Hz), 5.84 (s, 1H), 6.30 (d, 2H, $J$ = 8.7 Hz), 6.93 (d, 2H, $J$ = 8.7 Hz), 7.44–7.57 (m, 3H), 7.88 (d, 1H, $J$ = 7.4 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 17.41, 53.67, 74.08, 115.07, 124.70, 125.08, 126.83, 129.09, 131.03, 132.12, 133.34, 142.19, 144.67, 173.29, 174.85 ppm; ESI(+) - MS CH$_3$CN [C= 2, SC= 20, EC= 2]: HRMS ES$^+$ for C$_{17}$H$_{13}$ClN$_3$O$_2$ m/z: [M$+$H]$^+$ Calc. 328.0853, found: 328.0850.

1-(4-chlorophenylamino)-3-phenyl-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5l): Yield 70%. white solid; mp 221–223 °C; $R_f$ 0.52 (EtOAc/c-C$_6$H$_{12}$ 40:60); $[\alpha]_{578}^{25}$ = +14.19 ± 2.27 (MeOH, C= 0.155 ± 0.020). FT-IR (neat, cm$^{-1}$): 3274, 2985, 1706, 1598, 1220; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 5.78 (s, 1H), 6.08 (s, 1H), 6.42 (d, 2H, $J$ = 8.7 Hz), 7.05 (d, 2H, $J$ = 8.7 Hz), 7.41–7.49 (m, 3H), 7.63–7.74 (m, 5H), 8.07 (d, 1H, $J$ = 7.3 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 65.89, 74.35, 115.06, 124.56, 125.33, 126.35, 127.28, 128.98, 129.23, 129.98, 131.16, 133.55, 134.99, 142.37, 144.41, 171.63, 173.12 ppm; ESI(+) - MS CH$_3$CN [C= 2, SC= 20, EC= 2]: HRMS ES$^+$ for C$_{22}$H$_{17}$ClN$_3$O$_2$ m/z: [M$+$H]$^+$ Calc. 390.1139, found: 390.1132.

3-benzyl-1-(4-chlorophenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5m): Yield 68%. white solid; mp 225–227 °C; $R_f$ 0.32 (EtOAc/c-C$_6$H$_{12}$ 40:60); $[\alpha]_{578}^{25}$ = -45.18 ± 1.59 (CH$_3$CN, C= 0.830 ± 0.028). FT-IR (neat, cm$^{-1}$): 3203, 2985, 1706, 1598, 1220; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 3.25–3.37 (m, 2H), 4.94 (t, 1H, $J$ = 4.2 Hz), 5.11 (s, 1H), 5.82 (s, 1H), 5.93 (s, 1H), 6.31 (d, 2H, $J$ = 7.8 Hz), 6.82–6.88 (m, 3H), 7.08 (t, 2H, $J$ = 8.1 Hz), 7.22 (d, 2H, $J$ = 8.1 Hz), 7.37 (d, 1H, $J$ = 7.5 Hz), 7.48–7.53 (m, 1H), 7.60 (t, 1H, $J$ = 7.5 Hz), 7.97 (d, 1H, $J$ = 7.5 Hz); $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ = 36.35, 59.42, 74.20, 113.39, 115.52, 116.48, 121.32, 124.56, 126.60, 128.91, 130.50, 131.09, 131.88, 132.94, 142.53, 145.44, 155.92, 172.65, 173.67 ppm;
ESI(+)-MS CH₃CN [C= 2, SC= 20, EC= 2]: HRMS ES⁺ for C₂₃H₁₉ClN₃O₂ m/z: [M+H]⁺ Calc. 404.2354, found: 404.2335.

3. ¹H NMR, ¹³C -NMR, DEPT 135, COSY NMR, HSQC NMR, HMBC NMR, NOESY NMR and FT-IR spectra of the products 5

Methyl-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5a)

³¹H NMR spectrum of the compound 5a in CDCl₃ at 300 MHz
$^1$H NMR spectrum of the compound 5a in CDCl$_3$ at 300 MHz

$^{13}$C NMR spectrum of the compound 5a in CDCl$_3$ at 75 MHz
DEPT 135 NMR spectrum of the compound 5a in CDCl₃ at 75 MHz

COSY NMR spectrum of the compound 5a in CDCl₃
HSQC NMR spectrum of the compound 5a in CDCl₃

HMBC NMR spectrum of the compound 5a in CDCl₃
NOESY NMR spectrum of the compound 5a in CDCl₃

FT-IR spectrum of the compound 5a
3-Isopropyl-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5b)

**Chemical Structure**

![Chemical Structure Image]

**NMR Spectrum**

**1H NMR spectrum of the compound 5b in CDCl3 at 300 MHz**
$^1$H NMR spectrum of the compound 5b in CDCl$_3$ at 300 MHz

$^{13}$C NMR spectrum of the compound 5b in CDCl$_3$ at 75 MHz
DEPT 135 NMR spectrum of the compound 5b in CDCl₃ at 75 MHz

HSQC NMR spectrum of the compound 5b in CDCl₃
HMBC NMR spectrum of the compound 5b in CDCl₃

COSY NMR spectrum of the compound 5b in CDCl₃
NOESY NMR spectrum of the compound 5b in CDCl₃

FT-IR spectrum of the compound 5b
3-Isobutyl-1-(phenylamino)-1H-imidazo[2,1-\textit{a}]isoindole-2,5(3H,9bH)-dione (5c)

\[ \text{\textsuperscript{1}H NMR spectrum of the compound 5c in CDCl} \text{\textsubscript{3} at 300 MHz} \]
$^1$H NMR spectrum of the compound $5c$ in CDCl$_3$ at 300 MHz

$^{13}$C NMR spectrum of the compound $5c$ in CDCl$_3$ at 75 MHz
DEPT 135 NMR spectrum of the compound 5c in CDCl$_3$ at 75 MHz

FT-IR spectrum of the compound 5c
3-Phenyl-1-(phenylamino)-1H-imidazo[2,1-α]isoindole-2,5(3H,9bH)-dione (5d)

$^1$H NMR spectrum of the compound 5d in CDCl$_3$ at 300 MHz
$^1$H NMR spectrum of the compound $5d$ in CDCl$_3$ at 300 MHz

$^{13}$C NMR spectrum of the compound $5d$ in CDCl$_3$ at 75 MHz
FT-IR spectrum of the compound 5d
3-Benzyl-1-(phenylamino)-1H-imidazo[2,1-α]isoindole-2,5(3H,9H)-dione (5e)

$^1$H NMR spectrum of the compound 5e in CDCl$_3$ at 300 MHz
$^1$H NMR spectrum of the compound 5e in CDCl$_3$ at 300 MHz

$^{13}$C NMR spectrum of the compound 5e in CDCl$_3$ at 75 MHz
FT-IR spectrum of the compound 5e
3-(2-(Methylthio)ethyl)-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5f)

\[ \text{HNMR spectrum of the compound 5f in CDCl}_3 \text{ at 300 MHz} \]

\[ \text{1H NMR spectrum of the compound 5f in CDCl}_3 \text{ at 300 MHz} \]
\(^{13}\text{C NMR}\) spectrum of the compound 5f in CDCl\(_3\) at 75 MHz

DEPT 135 NMR spectrum of the compound 5f in CDCl\(_3\) at 75 MHz
COSY NMR spectrum of the compound 5f in CDCl₃ at 300 MHz

HSQC NMR spectrum of the compound 5f in CDCl₃ at 300 MHz
HMBC NMR spectrum of the compound 5f in CDCl$_3$ at 300 MHz

NOESY NMR spectrum of the compound 5f in CDCl$_3$ at 300 MHz
FT-IR spectrum of the compound 5f
3-(Mercaptomethyl)-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5g)

\[ \text{H NMR spectrum of the compound 5g in CDCl}_3 \text{ at 300 MHz} \]
$^1$H NMR spectrum of the compound 5g in CDCl$_3$ at 300 MHz

$^1$H NMR spectrum of the compound 5g in CDCl$_3$ at 300 MHz
$^{13}$C NMR spectrum of the compound 5g in CDCl$_3$ at 75 MHz

FT-IR spectrum of the compound 5g
3-(Hydroxymethyl)-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5h)

$^1$H NMR spectrum of the compound 5h in CDCl$_3$ at 300 MHz
$^{13}$C NMR spectrum of the compound 5h in CDCl$_3$ at 75 MHz

DEPT 135 NMR spectrum of the compound 5h in CDCl$_3$ at 75 MHz
HSQC NMR spectrum of the compound 5h in CDCl$_3$

HMBC NMR spectrum of the compound 5h in CDCl$_3$
COSY NMR spectrum of the compound 5h in CDCl₃

NOESY NMR spectrum of the compound 5h in CDCl₃
FT-IR spectrum of the compound 5h
3-((1H-Indol-3-yl)methyl)-1-(phenylamino)-1H-imidazo[2,1-α]isoindole-2,5(3H,9bH)dione (5i)

$\text{\^{1}H NMR spectrum of the compound 5i in CDCl$_3$ at 300 MHz}$
$^1$H NMR spectrum of the compound 5i in CDCl$_3$ at 300 MHz

$^{13}$C NMR spectrum of the compound 5i in CDCl$_3$ at 75 MHz
FT-IR spectrum of the compound 5i
3-(4-Hydroxybenzyl)-1-(phenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5j)

^1H NMR spectrum of the compound 5j in CDCl₃ at 300 MHz
$^1$H NMR spectrum of the compound 5j in CDCl$_3$ at 300 MHz

$^1$H NMR spectrum of the compound 5j in CDCl$_3$ at 300 MHz
$^{13}$C NMR spectrum of the compound 5j in CDCl$_3$ + CD$_3$CN at 75 MHz

DEPT 135 NMR spectrum of the compound 5j in CDCl$_3$ + CD$_3$CN at 75 MHz
HSQC NMR spectrum of the compound 5j in CDCl₃

HMBC NMR spectrum of the compound 5j in CDCl₃
COSY NMR spectrum of the compound 5j in CDCl₃

NOESY NMR spectrum of the compound 5j in CDCl₃
FT-IR spectrum of the compound 5j
1-(4-Chlorophenylamino)-3-methyl-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5k)

$^1$H NMR spectrum of the compound 5k in CDCl$_3$ at 300 MHz
$^{13}$C NMR spectrum of the compound 5k in CDCl$_3$ at 75 MHz

FT-IR spectrum of the compound 5k
1-(4-Chlorophenylamino)-3-phenyl-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5l)

$\text{\textsuperscript{1}H NMR spectrum of the compound 5l in CDCl}_3 \text{ at 300 MHz}$
$^{13}$C NMR spectrum of the compound 5l in CDCl$_3$ at 75 MHz

FT-IR spectrum of the compound 5l
3-Benzyl-1-(4-chlorophenylamino)-1H-imidazo[2,1-a]isoindole-2,5(3H,9bH)-dione (5m)

$^1$H NMR spectrum of the compound 5m in CDCl$_3$ at 300 MHz
$^{13}$C NMR spectrum of the compound 5m in CDCl$_3$ at 75 MHz

FT-IR spectrum of the compound 5m