Supplemental Material

SYNTHESIS OF NOVEL SPIRO[INDOL-2,2'-PYRROLES] USING ISOCYANIDE BASED MULTICOMPONENT REACTION

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EXPERIMENTAL

All reagents were purchased from TCI and Sigma Aldrich and used without further purification. N-methyl isatin imines were synthesized according to the procedure reported in the literature. All the products were characterized by ^1H NMR, C^{13} NMR, IR, and Fab-Mass analysis. The NMR spectra were recorded on a Bruker AMX-500 MHz instrument at room temperature in CDCl_3 using TMS as an internal reference. Melting points were determined by AS ONE instrument. X-ray data for the compound were collected at room temperature using a Bruker Apex II KY CCD diffractometer with graphite monochromated $\text{MoK}\alpha$ radiation ($\lambda=0.71073\text{\AA}$) with ω -scan method. Crystallographic data of **11** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1037350 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

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General procedure for the synthesis of isatin imines:

A mixture of Isatin (1 mmol) and substituted aniline (1 mmol) were added into 10 ml of absolute ethanol containing a few drops of glacial acetic acid in a 50-ml round bottom flask. The reaction mixture was refluxed for 6h and recrystallized from ethanol to obtain pure products

Synthesis of N-methyl isatin ketal:

A mixture of N-methyl isatin imine (1 mmol) and ethylene glycol (1.2 mmol) were taken in 10 ml benzene. To this catalytic amount of PTSA was added and refluxed for 10h. Benzene was removed and N-methyl isatin ketal was isolated as a white color solid using column chromatography.

Procedure for the hydrolysis of product 13:

Compound 13 (1 mmol) was taken in 10 ml of 2M aq. HCl in THF and stirred at room temperature for 5h. The reaction mixture was basified with 20% NaHCO₃ and extracted with EtOAc, product was isolated as yellow color solid using column chromatography using 20% EtOAc/Hexane.

General procedure for the synthesis of spiro[indole-2,2'-pyrroles] (1-12):

A solution of N-methyl isatin imine (1 mmol), t-Butyl isocyanide (1 mmol) and dimethyl (or) diethyl acetylenedicarboxylate (1 mmol) in 10ml benzene were refluxed for 10-14h. After completion of the reaction monitored by TLC, volatiles were removed under reduced pressure. The crude reaction mixture was subjected to column chromatography using (SiO₂, 15% EtOAc/n-Hexane) yielded 40-71% as yellow color solids in most reactions and some cases as yellow color semi solids were obtained.

Spiro[indole-2,2'-pyrrole]-3-(4-chlorophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one methyl ester 1. Yellow color solid, mp 163-166 °C; **IR:** $\nu_{\max}$ (KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm⁻¹; δ_{H} (500 MHz CDCl₃) 7.48 (2 H, m), 7.30 (1 H, m), 6.77 (2 H, m), 6.64 (1 H, d), 6.61 (1 H, d), 6.47 (1 H, m), 3.90 (3 H, s), 3.63 (3 H, s), 2.82 (3 H, s), 1.49 (9 H, s); δ_{C} (125 MHz, CDCl₃) 167.9, 165.5, 163.9, 161.8, 161.2, 155.2, 149.7, 146.5, 135.3, 135.0, 131.1, 126.4, 119.7, 118.6, 117.8, 116.9, 108.0, 88.1, 56.5, 53.0, 27.98; LCMS: MH⁺, 496.16. Anal. Calcd. For C₂₆H₂₆ClN₃O₅: C, 62.93; H, 5.24; Cl, 7.12; N, 8.45; O, 16.10. Found: C, 62.95; H, 5.23; Cl, 7.14; N, 8.47; O, 16.13.

Spiro[indole-2,2'-pyrrole]-3-(4-bromophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one methyl ester 2. Yellow color solid, mp 200-202 °C; **IR:** $\nu_{\max}$ (KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1} ; δ_{H} (500 MHz CDCl_3) 7.32 (2 H, m), 7.29 (1 H, m), 6.81 (2 H, m), 6.63 (1 H, d), 6.59 (1 H, d), 6.47 (1 H, m), 3.90 (3 H, s), 3.63 (3 H, s), 2.82 (3 H, s), 1.49 (9 H, s); δ_{C} (125 MHz CDCl_3) 165.6, 163.7, 161.6, 161.2, 155.5, 149.2, 146.7, 135.0, 134.7, 129.3, 129.1, 126.7, 119.4, 118.2, 117.8, 108.2, 88.5, 57.5, 52.88, 52.88, 27.7; LCMS: MH^+ , 541.17. Anal. Calcd. For $\text{C}_{26}\text{H}_{26}\text{ClN}_3\text{O}_5$: C, 57.77; H, 4.87; Br, 14.77; N, 7.80; O, 14.80. Found: C, 57.79; H, 4.85; Br, 14.75; N, 7.82; O, 14.80.

Spiro[indole-2,2'-pyrrole]-3-(2-chlorophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one methyl ester 3. Yellow color solid, mp 148-152 °C; **IR:** $\nu_{\max}$ (KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1} ; δ_{H} (500 MHz CDCl_3) 7.31 (1 H, dd), 7.25 (1 H, m), 7.17 (1 H, m), 7.03 (1H, m), 6.79 (1 H, d), 6.58 (1 H, d), 6.39 (2 H, m), 3.84 (3 H, s), 3.52 (3 H, s), 2.77 (3 H, s), 1.47 (9 H, s); δ_{C} (125 MHz CDCl_3) 164.5, 163.7, 160.9, 159.8, 154.7, 146.7, 134.1, 129.17, 126.7, 125.4, 123.9, 122.5, 118.1, 117.6, 116.9, 107.1, 87.4, 51.4, 50.3, 26.81; LCMS: MH^+ , 496.16. Anal. Calcd. For $\text{C}_{26}\text{H}_{26}\text{ClN}_3\text{O}_5$: C, 62.93; H, 5.24; Cl, 7.12; N, 8.45; O, 16.10. Found: C, 62.95; H, 5.23; Cl, 7.14; N, 8.47; O, 16.13.

Spiro[indole-2,2'-pyrrole]-3-(3-chlorophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one methyl ester (4). Yellow color solid, mp 195-197 °C; **IR:** $\nu_{\max}$ (KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1} ; δ_{H} (500 MHz CDCl_3) 7.31 (2 H, t), 7.14 (1 H, m), 6.86 (1 H, t), 6.76 (1 H, d), 6.62 (1 H, m), 6.58 (1 H, t), 6.47 (1 H, t), 3.90 (3 H, s), 3.64 (3 H, s), 2.83 (3 H, s), 1.50 (9 H, s); δ_{C} (125 MHz CDCl_3) 165.5, 163.9, 161.5, 161.2, 155.5, 151.9, 146.7, 135.1, 135.1, 130.6, 126.8, 124.0, 118.1, 118.0, 117.8, 116.3, 108.2, 88.5, 57.5, 52.88, 52.8, 28.0; LCMS: MH^+ , 496.16. Anal. Calcd. For $\text{C}_{26}\text{H}_{26}\text{ClN}_3\text{O}_5$: C, 62.93; H, 5.24; Cl, 7.12; N, 8.45; O, 16.10. Found: C, 62.95; H, 5.23; Cl, 7.14; N, 8.47; O, 16.13.

Spiro[indole-2,2'-pyrrole]-3-(2,4-dichlorophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one methyl ester 5. Yellow color solid, mp 146-148 °C; **IR:** $\nu_{\max}$ (KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1} ; δ_{H} (500 MHz CDCl_3) 7.46 (1 H, m), 7.30 (1 H, m), 7.23 (1 H, m), 6.80 (1H, d), 6.65 (1 H, d), 6.52 (2 H, m), 3.94 (3 H, s), 3.59 (3 H, s), 2.82 (3 H, s), 1.52 (9 H, s); δ_{C} (125 MHz CDCl_3) 165.5, 163.9, 161.5, 161.2, 155.5, 151.9, 146.7, 135.1, 135.1, 130.6, 126.8, 124.0, 118.12, 118.09, 117.8, 116.3, 116.1, 108.2, 88.5, 57.5, 53.0, 27.7; LCMS:

MH⁺, 529.12. Anal. Calcd. For C₂₆H₂₅Cl₂N₃O₅: C, 58.84; H, 4.77; Cl, 13.38; N, 7.95; O, 15.06. Found: C, 58.86; H, 4.75; Cl, 13.39; N, 7.90; O, 15.08.

Spiro[indole-2,2'-pyrrole]-3-(3-chlorophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one ethyl ester 6. Yellow color solid, mp 138-140 °C; **IR:** $\nu_{\max}$ (KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm⁻¹; δ_{H} (500 MHz CDCl₃) 7.28-7.32 (2 H, m), 7.14 (1 H, m), 6.87 (1 H, t), 6.76 (1 H, m), 6.63 (1H, d), 6.55 (1H, d), 6.47 (1H, m), 4.37 (2 H, q), 4.08 (2 H, q), 2.83 (3 H, s), 1.51 (9 H, s), 1.37 (3 H, t), 0.99 (3 H, t); δ_{C} (125 MHz CDCl₃) 165.7, 164.1, 161.2, 160.7, 155.6, 152.0, 146.2, 135.3, 135.1, 130.7, 126.9, 124.0, 118.3, 118.1, 117.8, 116.1, 108.2, 88.4, 62.1, 57.4, 27.8, 14.2, 13.5; LCMS: MH⁺, 524.01. Anal. Calcd. For C₂₈H₃₀ClN₃O₅: C, 64.18; H, 5.77; Cl, 6.77; N, 8.02; O, 15.27. Found: C, 64.16; H, 5.75; Cl, 6.75; N, 8.04; O, 15.27.

Spiro[indole-2,2'-pyrrole]-3-(4-chlorophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one ethyl ester 7. Yellow color semi solid; **IR:** $\nu_{\max}$ (KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm⁻¹; δ_{H} (500 MHz CDCl₃) 7.34 (2 H, m), 7.29 (1 H, t), 6.82 (2 H, d), 6.62 (2 H, d), 6.46 (1 H, t), 4.37 (2 H, q), 4.08 (2 H, q), 2.83 (3 H, s), 1.50 (9 H, s), 1.36 (3 H, t), 0.97 (3 H, t); δ_{C} (125 MHz CDCl₃) 165.7, 163.9, 161.2, 160.7, 155.6, 149.3, 146.2, 135.3, 134.9, 129.6, 129.2, 126.7, 119.3, 118.4, 117.6, 108.1, 88.5, 62.1, 57.4, 27.79, 14.2, 13.5; LCMS: MH⁺, 524.01. Anal. Calcd. For C₂₈H₃₀ClN₃O₅: C, 64.16; H, 5.79; Cl, 6.75; N, 8.04; O, 15.27. Found: C, 64.18; H, 5.77; Cl, 6.77; N, 8.024 O, 15.25.

Spiro[indole-2,2'-pyrrole]-3-(4-bromophenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one ethyl ester 8. Yellow color semi solid; **IR:** $\nu_{\max}$ (KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm⁻¹; δ_{H} (500 MHz CDCl₃) 7.49 (2 H, t), 7.30 (1 H, t), 6.77 (2 H, m), 6.62 (1 H, d), 6.58 (1 H, d), 6.47 (1 H, t), 4.38 (2 H, q), 4.08 (2 H, q), 2.82 (3 H, s), 1.50 (9 H, s), 1.37 (3 H, t), 0.98 (3 H, t); δ_{C} (125 MHz CDCl₃) 165.6, 163.8, 161.1, 160.7, 155.5, 149.7, 146.2, 135.2, 134.9, 132.5, 126.7, 119.7, 118.3, 117.6, 116.8, 108.1, 88.4, 62.1, 28.0, 14.0, 13.5; LCMS: MH⁺, 568.46. Anal. Calcd. For C₂₈H₃₀BrN₃O₅: C, 59.16; H, 5.32; Br, 14.06; N, 7.39; O, 14.07. Found: C, 59.14; H, 5.32; Br, 14.08; N, 7.37; O, 14.09.

Spiro[indole-2,2'-pyrrole]-3-(4-methylphenyl)imine-3',4'-dicarboxylicacid-1'-t-butyl-5'-one ethyl ester 9. Yellow color semi solid; **IR:** $\nu_{\max}$ (KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm⁻¹; δ_{H} (500 MHz CDCl₃) 7.24 (1 H, m), 7.18 (2 H, d), 6.77 (2 H, d), 6.59 (2 H, t), 6.42 (1 H, t), 4.37 (2 H, q), 4.07 (2 H, q), 2.82 (3 H, s), 2.37 (3 H, s), 1.51 (9 H, s), 1.36 (3 H, t), 0.96 (3 H, t); δ_{C} (125 MHz CDCl₃) 165.7, 163.0, 161.30, 160.8, 155.3,

148.2, 135.2, 134.4, 133.4, 130.0, 129.7, 126.8, 118.8, 117.6, 117.4, 115.2, 107.8, 88.5, 62.04, 57.3, 28.0, 14.2, 13.5;
LCMS: MH^+ , 503.59. Anal. Calcd. For $C_{29}H_{33}N_3O_5$: C, 69.17; H, 6.60; N, 8.34; O, 15.89. Found: C, 69.17; H, 6.60; N, 8.34; O, 15.89.

Spiro[indole-2,2'-pyrrole]-3-(o-chlorophenyl)imine-3',4'-dicarboxylic acid-1'-t-butyl-5'-one ethyl ester 10. Yellow color solid, mp 160-162 °C; **IR:** ν_{max} (KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1} ; δ_H (500 MHz $CDCl_3$) 7.30 (2 H, m), 7.18 (1 H, m), 6.83 (1 H, t), 6.66 (1 H, d), 6.53 (1 H, d), 6.55 (1 H, d), 6.47 (1 H, m), 4.36 (2 H, q), 4.08 (2 H, q), 2.82 (3 H, s), 1.50 (9 H, s), 1.37 (3 H, t), 0.99 (3 H, t); δ_C (125 MHz $CDCl_3$) 165.7, 164.1, 161.1, 160.7, 155.6, 152.1, 146.2, 135.2, 135.1, 135.1, 130.6, 126.9, 126.8, 124.0, 118.3, 118.1, 117.8, 116.1, 108.2, 88.4, 62.13, 62.0, 57.4, 27.8, 14.2, 14.1; LCMS: MH^+ , 524.01. Anal. Calcd. For $C_{28}H_{30}ClN_3O_5$: C, 64.16; H, 5.75; Cl, 6.77; N, 8.04; O, 15.25. Found: C, 64.16; H, 5.79; Cl, 6.77; N, 8.04; O, 15.25.

Spiro[indole-2,2'-pyrrole]-3-(phenyl)imine-3',4'-dicarboxylic acid-1'-t-butyl-5'-one ethyl ester 11. Yellow color solid, mp 184-186 °C; **IR:** ν_{max} (KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1} ; δ_H (500 MHz $CDCl_3$) 7.38 (2 H, t), 7.28 (1 H, m), 7.16 (1 H, t), 6.87 (2 H, m), 6.61 (1 H, d), 6.49 (1 H, d), 6.41 (1 H, t), 4.37 (2 H, q), 4.07 (2 H, q), 2.83 (3 H, s), 1.52 (9 H, s), 1.36 (3 H, t), 0.97 (3 H, t); δ_C (125 MHz $CDCl_3$) 165.7, 163.2, 161.3, 160.8, 155.4, 150.9, 146.2, 135.3, 134.6, 129.53, 126.8, 124.0, 118.7, 117.7, 117.5, 107.9, 88.5, 62.0, 57.4, 27.8, 14.2, 13.5; LCMS: MH^+ , 489.56. Anal. Calcd. For $C_{28}H_{31}N_3O_5$: C, 68.69; H, 6.36; N, 8.58; O, 16.36. Found: C, 68.69; H, 6.738; N, 8.58; O, 16.36

Spiro[indole-2,2'-pyrrole]-3-(2,4-dichlorophenyl)imine-3',4'-dicarboxylic acid-1'-t-butyl-5'-one ethyl ester 12. Yellow color semi solid ; **IR:** ν_{max} (KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1} ; δ_H (500 MHz $CDCl_3$) 7.46 (1 H, m), 7.34 (1 H, m), 7.23 (1 H, dd), 6.65 (2 H, d), 6.49-6.56 (2 H, m), 4.39 (2 H, q), 4.04 (2 H, q), 2.84 (3 H, s), 1.52 (9 H, s), 1.37 (3 H, t), 0.93 (3 H, t); δ_C (125 MHz $CDCl_3$) 165.6, 164.5, 161.45, 160.35, 156.0, 146.4, 135.4, 133.6, 129.9, 129.4, 128.0, 126.4, 124.5, 120.1, 118.6, 118.0, 108.3, 88.4, 62.2, 57.5, 27.5, 14.1, 14.1; LCMS: MH^+ , 558.45. Anal. Calcd. For $C_{28}H_{29}Cl_2N_3O_5$: C, 60.22; H, 5.23; Cl, 12.72; N, 7.50; O, 14.32. Found: C, 60.20; H, 5.23; Cl, 12.72; N, 7.48; O, 14.36.

Spiro[indole-2,2'-pyrrole]-3-(4--chlorophenyl)imine-3',4'-dicarboxylicacid-1'-pentyl-5'-one ethyl ester 13. Yellow color solid, mp 116-119 °C ; **IR:** $\nu_{\max}$ (KBr) 1728, 1667, 1658, 1618, 1418, 1240, 1041 cm^{-1} ; δ_{H} (500 MHz CDCl_3) 7.31-7.34 (3 H, m), 6.75-6.77 (2 H, m), 6.67 (1 H, d), 6.57 (1 H, m), 6.48 (1 H, t), 4.39 (2 H, q), 4.12 (2 H, q), 3.22 (2 H, t), 2.75 (3 H, s), 1.60 (4 H, m), 1.39 (3 H, t), 1.26 (2 H, m), 1.04 (3 H, t), 0.83 (3 H, t); δ_{C} (125 MHz CDCl_3) 165.0, 163.6, 161.4, 160.2, 156.9, 149.1, 143.9, 137.8, 135.1, 129.6, 129.3, 126.7, 119.5, 117.7, 107.9, 87.3, 62.3, 62.0, 40.6, 29.2, 27.9, 22.2, 14.1, 13.9, 13.6; LCMS: MH^+ , 558.45. Anal. Calcd. For $\text{C}_{28}\text{H}_{29}\text{Cl}_2\text{N}_3\text{O}_5$: C, 60.22; H, 5.23; Cl, 12.72; N, 7.50; O, 14.32. Found: C, 60.20; H, 5.23; Cl, 12.72; N, 7.48; O, 14.36. LCMS: MH^+ , 537. Anal. Calcd. For $\text{C}_{29}\text{H}_{32}\text{ClN}_3\text{O}_5$: C, 64.72; H, 5.99; Cl, 6.61; N, 7.81; O, 14.87. Found: C, 64.74; H, 5.99; Cl, 6.59; N, 7.79; O, 14.89

Analytical data for Hydrolyzed compound:

Spiro[indole-2,2'-pyrrole]-3-one-3',4'-dicarboxylicacid-1'-pentyl-5'-one ethyl ester. Yellow color solid, mp 236-240 °C ; **IR:** $\nu_{\max}$ (KBr) 1740, 1736, 1660, 1618, 1240, 1041 cm^{-1} ; δ_{H} (500 MHz CDCl_3) 7.59 (1 H, t), 7.64 (1 H, dd), 6.82-6.87 (2 H, m), 4.42 (2 H, q), 4.04 (2 H, q), 3.22 (2 H, t), 2.75 (3 H, s), 1.44 (2 H, m), 1.38 (3 H, t), 1.22 (4 H, m), 0.97 (3 H, t); δ_{C} (125 MHz CDCl_3) 192.38, 165.06, 161.20, 159.61, 145.78, 140.40, 138.88, 125.59, 119.9, 118.79, 108.79, 85.61, 62.42, 62.14, 40.72, 28.97, 28.27, 27.75, 22.07, 14.05, 13.81, 13.34; LCMS: MH^+ , 428. Anal. Calcd. For $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_6$: C, 64.45; H, 6.59; N, 6.56; O, 22.40. Found: C, 64.47; H, 6.61; N, 6.54; O, 22.38

Crystallographic data for 11

X-ray data for the compound were collected at room temperature using a Bruker Apex II KY CCD diffractometer with graphite monochromated Mo- $\text{K}\alpha$ radiation ($\lambda=0.71073\text{\AA}$) with ω -scan method.¹ Unit cell dimensions were determined using 4483 reflections. Integration and scaling of intensity data were accomplished using SAINT program.¹ The structures were solved by Direct Methods using SHELXS97² and refinement was carried out by full-matrix least-squares technique using SHELXL97.³

The structure of the product was established by X-ray analysis of 11 as shown in figure 1. The molecule was crystallized in triclinic system with space group *PI* with two molecules in the unit cell.

Crystal data

Table 3

Crystal data and structure refinement for Spiro [indole-2, 2'-pyrrole]-3-(phenyl) imine-3', 4'-dicarboxylic acid-1'-t-butyl-5'-one ethyl ester

Empirical formula	C ₂₈ H ₃₁ N ₃ O ₅
Formula weight	489.56
Temperature	293K
Wavelength	0.71073 Å
Crystal system	triclinic
Space group	P -1
Unit cell dimensions	
<i>A</i>	8.8628(18) Å
<i>B</i>	11.142(2) Å
<i>C</i>	14.304(3) Å
Volume	1270.8(4) Å ³
<i>Z</i>	4
Calculated density	1.279 g/cm ³
Absorption coefficient	0.089 mm ⁻¹
<i>F</i> (0 0 0)	520
Crystal size	0.45 □ 0.35 □ 0.25 mm ³

Fig 2. Crystal packing of 11