Supporting Information

Expedient Synthesis of Eumelanin-Inspired 5,6-Dihydroxyindole-2-Carboxylate Ethyl Ester Derivatives

Andrew H. Aebly, Jeffrey N. Levy, Benjamin J. Steger, Jonathan C. Quirke, and Jason M. Belitsky*

Oberlin College, Chemistry and Biochemistry Department, 119 Woodland Street, Oberlin, OH 44074, USA

E-mail: Jason.Belitsky@oberlin.edu

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General Information

DMICE was purchased from Alfa Aesar, BroadPharm, and Oxchem. All reagents, except for DMICE and N-bromosuccinimide, were used as received from the commercial vendor. DMICE was dissolved in a mixture of dichloromethane/THF and filtered through a short silica plug with EtOAc prior to use. N-bromosuccinimide was recrystallized from benzene. Solvents were purchased from Sigma-Aldrich in anhydrous form and used as received. Column chromatography was performed using silica gel (80-200 mesh, JT Baker). The $^1$H and $^{13}$C NMR spectra were obtained on a Varian 400 MHz instrument using either CDCl$_3$ or d$_6$-acetone (Cambridge Isotopes Laboratories), correcting the chemical shifts (reported in ppm) to the corresponding residual deuterated solvent peak. The following abbreviations were used to identify the multiplicities in the NMR spectra: s (singlet), d (doublet), t (triplet), q (quartet), b (broad), and apt (apparent). High resolution mass spectra (HRMS) were obtained using an Agilent Q-TOF HPLC-MS (University of Michigan) or Kratos MS25 double focusing mass spectrometer (Case Western Reserve University).

Tables

Table S1 Optimization of Suzuki coupling for 7

| Entry | Conditions               | Conversion$^b$ | Yield$^c$ |
|-------|--------------------------|----------------|-----------|
| 1     | dioxane/H$_2$O (11:1), 75 °C | 100%           | 82%       |
| 2     | dioxane/H$_2$O (11:1), 50 °C | 72%           | 71%       |
| 3     | THF/H$_2$O (1:1), 50 °C    | 100%           | 97%       |
| 4$^d$ | THF/H$_2$O (1:1), 50 °C    | 100%           | 89%       |

$^a$Reaction conditions: 7 (0.04 mmol), 4-methoxyphenylboronic acid (0.096 mmol), XPhos Pd G2 (0.0016 mmol), K$_3$PO$_4$ (0.12 mmol), solvent (0.083 M), 3.5h $^b$Determined from crude $^1$H-NMR. $^c$Isolated yield. $^d$4-methoxyphenylboronic acid (0.084 mmol).
Table S2 ¹H-NMR indole N-H chemical shift

| Substituent     | Compound # | Chemical Shift | Compound # | Chemical Shift |
|-----------------|------------|----------------|------------|----------------|
| 4-Phenyl-NMe₂   | 9b         | 8.74           | 10b        | 8.71           |
| 4-Phenyl-OMe    | 9a         | 8.80           | 10a        | 8.64           |
| 4-Phenyl-Me     | 9c         | 8.81           | 10c        | 8.65           |
| 4-Phenyl-F      | 9d         | 8.83           | --         | --             |
| Phenyl          | --         | --             | 10d        | 8.67           |
| 4-Phenyl-CF₃    | 9e         | 9.01           | 10e        | 8.64           |
| 4-Phenyl-CN     | 9f         | 9.05           | 10f        | 8.67           |
| 4-Phenyl-NO₂    | 9g         | 10.94*         | 10g        | 8.73           |
| 3,4-OMe         | 9h         | 8.79           | 10h        | 8.70           |
| 1-naphthyl      | 9i         | 9.09           | --         | --             |
| 3-thiophene     | 9j         | 8.82           | 10i        | 8.81           |
| 3-furan         | 9k         | 8.97           | 10j        | 8.84           |
| 2-benzofuran    | 9l         | 8.98           | 10k        | 10.34          |
| 4-indole        | 9m         | 8.98           | --         | --             |
| 6-indole        | 9n         | 8.84           | 10l        | 8.72           |

Spectra recorded in CDCl₃ except where noted. Chemical shift is in ppm.
*In acetone-d6

Experimental Procedures

Synthesis of 5¹

![Chemical structure of 5](image)

To a 50-mL round bottom flask added ethyl 5,6-dimethoxyindole-2-carboxylate 1 (1 equiv, 0.50 mmol) and partially dissolved in MeCN (2 mL). A solution of NBS (1.05 equiv, 0.525 mmol) in MeCN (7 mL) was added dropwise to the reaction flask over 5 min and allowed to stir at room temperature for an additional 30 min. The reaction was diluted with H₂O and filtered at 0 °C to produce 6: 87% yield (off-white solid). ¹H NMR (400 MHz, CDCl₃) δ 8.83 (s, 1H), 6.98 (s, 1H), 6.82 (s, 1H), 4.43 (q, J = 7.2 Hz, 2H), 3.97 (s, 3H), 3.94 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 161.1, 151.2, 147.1, 130.5, 122.7, 121.4, 101.1, 98.1, 93.9, 61.2, 56.3, 56.2, 14.5.
Synthesis of SI-1

To a scintillation vial covered in tin foil added ethyl 5,6-dimethoxyindole-2-carboxylate 1 (1 equiv, 0.50 mmol) and NBS (4.0 equiv, 2.0 mmol). The starting materials were dissolved in THF (10 mL) and stirred at 65 °C for 2 h, then concentrated in vacuo. The crude product was dissolved in dichloromethane, washed with H₂O, dried with MgSO₄, concentrated and purified via column chromatography (silica, 8:1 hex/EtOAc) to produce SI-1: 69% yield (white solid).

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 8.90 (s, 1H), 7.01 (s, 1H), 4.46 (q, J = 7.0 Hz, 2H), 4.06 – 3.80 (m, 6H), 1.46 (t, J = 7.0 Hz, 3H). \]

\[ \text{C NMR (101 MHz, CDCl}_3\text{)} \delta 160.5, 150.6, 147.8, 129.4, 124.7, 123.9, 101.4, 100.3, 98.4, 61.7, 61.4, 56.6, 14.5. \]

\[ \text{HRMS (ESI) calculated for C}_{13}\text{H}_{14}\text{NO}_{2}\text{Br}_2 ([M+H]^+): 405.9284; found: 405.9282; calculated ([M+2+H]^+): 407.9269; found: 407.9265; calculated ([M+4+H]^+): 409.9249; found: 409.9244.} \]

Synthesis of 7

To a 20mL-scintillation vial covered in tin foil added ethyl 5,6-dimethoxyindole-2-carboxylate 1 (1 equiv, 0.80 mmol), N-bromosuccinimide (4 equiv, 3.20 mmol) and dissolved in acetonitrile (8 mL). The reaction was stirred at 65 °C for 24 h, concentrated in vacuo and filtered through a silica plug (3:1 to 2:1 hexanes:EtOAc) to yield 6. The material was used in the following reaction without further purification.

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 9.04 (s, 1H), 4.47 (q, J = 7.1 Hz, 2H), 3.97 (s, 3H), 3.90 (s, 3H), 1.46 (t, J = 7.1 Hz, 3H). \]

\[ \text{C NMR (101 MHz, CDCl}_3\text{)} \delta 160.3, 150.9, 147.9, 131.9, 126.3, 120.6, 110.4, 99.1, 98.7, 62.0, 61.7, 61.3, 14.5. \]

\[ \text{HRMS (ESI) calculated for C}_{13}\text{H}_{14}\text{NO}_{2}\text{Br}_2 ([M+H]^+): 405.9284; found: 405.9279; calculated ([M+2+H]^+): 407.9269; found: 407.9259; calculated ([M+4+H]^+): 409.9244.} \]

Adapted from Tani et al.¹ In a round-bottom flask 6 was dissolved in AcOH (0.07 M). To the reaction mixture LiBr (2.1 equiv, 0.6288 mmol), m-dimethoxybenzene (2.1 equiv, 0.6288 mmol) H₂SO₄ (2.1 equiv, 0.6288 mmol) was added and stirred at 65 °C for 1h. After cooling to room temperature, the product was precipitated out of solution with the addition of ice and filtered. The crude material was then purified via column chromatography (silica, hexanes:EtOAc: 8:1) to produce 7: 66% yield, two steps (white solid).

\[ \text{H NMR (400 MHz, CDCl}_3\text{)} \delta 8.96 (s, 1H), 7.26 (s, 1H), 4.43 (q, J = 7.1 Hz, 2H), 3.97 (s, 3H), 3.92 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H). \]

\[ \text{C NMR (101 MHz, CDCl}_3\text{)} \delta 161.3, 150.9, 147.9, 131.9, 126.3, 120.6, 110.4, 99.1, 98.7, 62.0, 61.7, 61.3, 14.5. \]

\[ \text{HRMS (ESI) calculated for C}_{13}\text{H}_{14}\text{NO}_{2}\text{Br}_2 ([M+H]^+): 405.9284; found: 405.9279; calculated ([M+2+H]^+): 407.9269; found: 407.9259; calculated ([M+4+H]^+): 409.9244.} \]
Synthesis of 8

Adapted from Buchgraber et al.³ To a 20mL-scintillation vial added ethyl 5,6-dimethoxyindole-2-carboxylate 1 (1 equiv, 0.80 mmol) and dissolved in DMF (0.8 mL). KOH (powdered, 5.03 eq, 4.024 mmol) was added to the reaction vial and stirred at 0°C for 10 min. Over 5-10 minutes, 5 portions of I₂ (1.05 equiv, 0.84 mmol) were added to the reaction vial and continued stirring at 0°C for an additional 30 min, then at r.t. for 45 min. The reaction was quenched by addition of sat NH₄Cl (8 mL) and sat Na₂S₂O₃ (8 mL). The precipitated solid was filtered, then re-dissolved in a mixture of ethyl acetate/dichloromethane, dried with MgSO₄ and concentrated to produce 8: 84% yield (off-white solid).

1H NMR (400 MHz, CDCl₃) δ 9.10 (s, 1H), 6.89 (s, 1H), 6.82 (s, 1H), 4.43 (q, J = 7.1 Hz, 2H), 3.98 (s, 3H), 3.94 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H).

13C NMR (101 MHz, CDCl₃) δ 160.9, 151.2, 147.2, 131.0, 125.7, 125.0, 103.3, 93.7, 65.9, 61.3, 56.4, 56.3, 14.5. HRMS (ESI) calculated for C₁₃H₁₅NO₄I ([M+H]+): 376.0040, found: 376.0038.

General Procedure for Suzuki Coupling of 8

To a 1-dram reaction vial with a septum-cap added XPhosPd G2 (4 mol%, 0.0024 mmol), 8 (1 equiv, 0.06 mmol) and corresponding boronic acid (1.25 equiv, 0.075 mmol), evacuated with vacuum and purged with N₂. To the reaction vial added 1,4-dioxane (0.66 mL) and 0.5 M K₃PO₄ (3 equiv, 0.18 mmol). The reaction mixture was heated at 75°C for 20 h and quenched with the addition of H₂O. The crude mixture was extracted with EtOAc (3 x 4 mL), dried with MgSO₄, filtered and concentrated in vacuo. The pure product was isolated via column chromatography (silica, hexanes: EtOAc: 3:2 to 2:1).

ethyl 5,6-dimethoxy-3-(4-methoxyphenyl)-1H-indole-2-carboxylate (9a): 97% yield (white solid). ¹H NMR (400 MHz, CDCl₃) δ 8.80 (s, 1H), 7.49 (d, J = 8.6 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 6.97 (s, 1H), 6.86 (s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 3.86 (s, 3H), 1.26 (d, J = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 162.0, 158.9, 150.5, 146.4, 131.7, 130.9, 126.2, 124.3, 121.3, 121.0, 113.5, 101.7, 93.7, 60.6, 56.3, 56.2, 55.4, 14.4. HRMS (ESI) calculated for C₂₁H₂₁NO₅ ([M+H]+): 355.1420; found: 355.1426.

ethyl 3-(4-(dimethylamino)phenyl)-5,6-dimethoxy-1H-indole-2-carboxylate (9b): 83% yield (off-white solid). ¹H NMR (400 MHz, CDCl₃) δ 8.74 (s, 1H), 7.48 (d, J = 8.7 Hz, 2H), 7.05 (s, 1H), 6.89 – 6.80 (m, 3H), 4.29 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 3.86 (s, 3H), 3.03 (s, 6H), 1.28 (t, J = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 162.1, 150.4, 149.7, 146.2, 131.4, 131.1, 125.0, 121.0, 121.0, 112.1, 102.1, 93.6, 60.5, 56.3, 56.2, 40.8, 14.4. HRMS (ESI) calculated for C₂₁H₂₅N₂O₄ ([M+H]+): 369.1809, found: 369.1819.
ethyl 5,6-dimethoxy-3-(p-tolyl)-1H-indole-2-carboxylate (9c): 96% yield (white solid). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.11 (s, 1H), 7.45 (d, $J = 7.8$ Hz, 2H), 7.27 (d, $J = 7.8$ Hz, 2H), 6.98 (s, 1H), 6.86 (s, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 3.95 (s, 3H), 3.85 (s, 3H), 2.43 (s, 3H), 1.25 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 161.9, 150.5, 146.4, 136.9, 130.9, 130.8, 128.7, 124.6, 121.4, 121.0, 101.8, 93.7, 60.6, 56.3, 56.2, 21.5, 14.3. HRMS (ESI) calculated for C$_{20}$H$_{22}$NO$_4$ ([M+H]+): 340.1543, found: 340.1543.

ethyl 3-(4-fluorophenyl)-5,6-dimethoxy-1H-indole-2-carboxylate (9d): 90% yield (white solid). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.01 (s, 1H), 7.72 (d, $J = 8.2$ Hz, 2H), 7.67 (d, $J = 8.2$ Hz, 2H), 6.90 (s, 1H), 6.89 (s, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 3.96 (s, 3H), 3.86 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 161.7, 150.8, 146.9, 138.0, 130.9, 130.9 (2C), 129.2 ($^2$J$_{CF}$ = 32 Hz), 124.9 ($^1$J$_{CF}$ = 4 Hz), 124.5 ($^1$J$_{CF}$ = 272 Hz), 122.8, 121.7, 120.7, 101.1, 93.8, 60.9, 56.3, 56.0, 14.24. HRMS (ESI) calculated for C$_{19}$H$_{19}$NO$_4$F ([M+H]+): 394.1261, found: 394.1265.

ethyl 5,6-dimethoxy-3-(4-(trifluoromethyl)phenyl)-1H-indole-2-carboxylate (9e): 90% yield (white solid). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.01 (s, 1H), 7.72 (d, $J = 8.2$ Hz, 2H), 7.67 (d, $J = 8.2$ Hz, 2H), 6.90 (s, 1H), 6.89 (s, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 3.96 (s, 3H), 3.86 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 161.7, 150.8, 147.1, 139.3, 131.8, 131.4, 130.9, 122.2, 121.7, 120.4, 119.3, 110.8, 100.8, 93.8, 61.0, 56.4, 56.0, 14.3. HRMS (ESI) calculated for C$_{19}$H$_{19}$NO$_4$ ([M+H]+): 394.1339, found: 395.1342.

eethyl 3-(4-cyanophenyl)-5,6-dimethoxy-1H-indole-2-carboxylate (9f): 96% yield (white solid). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.01 (s, 1H), 7.72 (d, $J = 8.2$ Hz, 2H), 7.67 (d, $J = 8.2$ Hz, 2H), 6.90 (s, 1H), 6.89 (s, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 3.96 (s, 3H), 3.86 (s, 3H), 1.22 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 161.8, 152.0, 148.4, 147.6, 142.9, 132.7, 132.6, 123.8, 123.0, 121.8, 121.0, 101.9, 95.5, 61.2, 56.5, 56.2, 14.6. HRMS (ESI) calculated for C$_{19}$H$_{19}$N$_2$O$_4$ ([M+H]+): 371.1238; found: 371.1237.
ethyl 3-(3,4-dimethoxyphenyl)-5,6-dimethoxy-1H-indole-2-carboxylate (9h): 95% yield (white solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.79 (s, 1H), 7.16 – 7.09 (m, 2H), 7.01 – 6.96 (m, 2H), 6.87 (s, 1H), 4.28 (q, \(J = 7.1\) Hz, 2H), 3.96 (s, 6H), 3.91 (s, 3H), 3.86 (s, 3H), 1.26 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 161.9, 150.6, 148.4, 148.4, 146.5, 130.9, 126.5, 124.4, 123.0, 121.4, 121.1, 114.1, 110.9, 101.8, 93.7, 60.7, 60.5, 56.3, 56.1, 14.5. HRMS (ESI) calculated for C\(_{22}\)H\(_{24}\)NO\(_5\) ([M-H])\(^{+}\): 386.1598, found: 386.1601.

ethyl 5,6-dimethoxy-3-(naphthalen-1-yl)-1H-indole-2-carboxylate (9i): 87% yield (white solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.09 (s, 1H), 7.92 (d, \(J = 8.2\) Hz, 2H), 7.68 (d, \(J = 8.5\) Hz, 1H), 7.60 – 7.51 (m, 2H), 7.47 (ddd, \(J = 8.1, 6.7, 1.2\) Hz, 1H), 7.39 (ddd, \(J = 8.3, 6.7, 1.3\) Hz, 1H), 6.94 (s, 1H), 6.65 (s, 1H), 4.04 – 3.95 (m, 5H), 3.71 (s, 3H), 0.73 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 162.2, 150.6, 146.5, 133.7, 133.1, 132.3, 131.0, 128.4, 128.2, 127.8, 126.6, 125.8, 125.7, 125.3, 123.3, 122.1, 122.1, 101.9, 93.8, 60.4, 56.3, 56.3, 13.6. HRMS (ESI) calculated for C\(_{23}\)H\(_{22}\)NO\(_4\) ([M-H])\(^{+}\): 376.1543; found: 376.1545.

ethyl 5,6-dimethoxy-3-(thiophen-3-yl)-1H-indole-2-carboxylate (9j): 94% yield (white solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.82 (s, 1H), 7.54 – 7.48 (m, 1H), 7.44 – 7.35 (m, 2H), 7.07 (s, 1H), 6.86 (s, 1H), 4.31 (q, \(J = 7.1\) Hz, 2H), 3.95 (s, 3H), 3.89 (s, 3H), 1.30 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 162.2, 150.9, 146.9, 134.1, 131.3, 130.5, 124.6, 124.4, 121.9, 121.3, 119.4, 102.2, 94.0, 61.1, 56.7, 56.5, 14.7. HRMS (ESI) calculated for C\(_{17}\)H\(_{18}\)NO\(_3\)S ([M-H])\(^{+}\): 332.0951, found: 332.0948.

ethyl 3-(furan-3-yl)-5,6-dimethoxy-1H-indole-2-carboxylate (9k): 83% yield (white solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.97 (s, 1H), 7.71 (s, 1H), 7.65 (d, \(J = 7.6\) Hz, 1H), 7.57 (d, \(J = 8.0\) Hz, 1H), 7.55 (s, 1H), 7.34 – 7.24 (m, 2H), 6.87 (s, 1H), 4.43 (q, \(J = 7.1\) Hz, 2H), 3.99 (s, 3H), 3.97 (s, 3H), 1.41 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 161.7, 150.6, 146.5, 142.3, 141.6, 131.0, 121.6, 120.7, 117.7, 114.9, 112.7, 101.8, 93.7, 60.8, 56.4, 56.2, 14.5. HRMS (ESI) calculated for C\(_{17}\)H\(_{18}\)NO\(_5\) ([M-H])\(^{+}\): 316.1178; found: 316.1179.

ethyl 3-(benzofuran-2-yl)-5,6-dimethoxy-1H-indole-2-carboxylate (9l): 96% yield (off-white solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.98 (s, 1H), 7.71 (s, 1H), 7.65 (d, \(J = 7.3\) Hz, 1H), 7.61 – 7.50 (m, 2H), 7.34 – 7.26 (m, 2H), 6.86 (s, 1H), 4.43 (q, \(J = 7.1\) Hz, 2H), 3.99 (s, 3H), 3.96 (s, 3H), 1.41 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 161.1, 154.6, 151.3, 150.8, 146.8, 130.9, 129.3, 124.1, 122.9, 121.9, 121.2, 120.0, 113.2, 111.0, 106.9, 103.7, 93.4, 61.2, 56.4, 56.2, 14.6. HRMS (ESI) calculated for C\(_{21}\)H\(_{20}\)NO\(_5\) ([M-H])\(^{+}\): 366.1336, found: 366.1336.
ethyl 5,6-dimethoxy-1H,1'H-[3,4'-biindole]-2-carboxylate (9m): 91% yield (white solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.98 (s, 1H), 8.24 (s, 1H), 7.43 (d, \(J = 7.4\) Hz, 1H), 7.33 – 7.26 (m, 2H), 7.17 (app t, \(J = 2.8\) Hz, 1H), 6.90 (s, 1H), 6.88 (s, 1H), 6.36 – 6.26 (m, 1H), 4.21 – 4.09 (m, 2H), 3.96 (s, 3H), 3.75 (s, 3H), 1.01 (t, \(J = 7.1\) Hz, 3H).

13\(^C\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) 161.9, 150.5, 148.4, 148.3, 146.5, 130.9, 126.5, 124.3, 122.9, 121.3, 121.1, 114.1, 110.9, 101.7, 93.7, 60.7, 56.3, 56.2, 56.1, 14.5. HRMS (ESI) calculated for C\(_{22}\)H\(_{21}\)N\(_2\)O\(_4\) ([M+H]\(^+\)): 365.1496, found: 365.1492.

ethyl 5,6-dimethoxy-1H,1'H-[3,6'-biindole]-2-carboxylate (9n): 87% yield (off-white solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.84 (s, 1H), 8.24 (s, 1H), 7.72 (d, \(J = 8.2\) Hz, 1H), 7.59 (s, 1H), 7.32 (dd, \(J = 8.2, 1.4\) Hz, 1H), 7.26 – 7.24 (m, 1H), 7.02 (s, 1H), 6.87 (s, 1H), 6.63 – 6.60 (m, 1H), 4.25 (q, \(J = 7.1\) Hz, 2H), 3.96 (s, 3H), 3.82 (s, 3H), 1.21 (t, \(J = 7.1\) Hz, 3H).

13\(^C\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) 162.0, 150.5, 146.4, 135.9, 130.9, 127.6, 127.2, 125.7, 124.7, 123.1, 121.4, 120.0, 113.0, 102.7, 102.1, 93.6, 60.6, 56.4, 56.2, 14.4. HRMS (ESI) calculated for C\(_{21}\)H\(_{21}\)N\(_2\)O\(_4\) ([M+H]\(^+\)): 365.1496, found: 365.1492.

**General Procedure for the Di-Suzuki Coupling of 7**

To a 1-dram reaction vial with a septum-cap added XPhosPd G2 (4 mol%, 0.0024 mmol), 7 (1 equiv, 0.04 mmol) and corresponding boronic acid (2.4 equiv, 0.096 mmol), evacuated with vacuum and purged with N\(_2\). To the reaction vial added THF (0.17 M) and 0.5 M K\(_3\)PO\(_4\) (0.17 M). The reaction mixture was heated at 50 °C for 3.5 h and quenched with the addition of H\(_2\)O. The crude mixture was extracted with EtOAc (3 x 4 mL), dried with MgSO\(_4\), filtered and concentrated in vacuo. The pure product was isolated via column chromatography (silica, hexanes: EtOAc: 2:1 to 9:1).

ethyl 5,6-dimethoxy-4,7-bis(4-methoxyphenyl)-1H-indole-2-carboxylate (10a): 95% yield (white solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.64 (s, 1H), 7.56 (d, \(J = 8.1\) Hz, 2H), 7.51 (d, \(J = 8.2\) Hz, 2H), 7.11 (d, \(J = 2.2\) Hz, 1H), 7.08 (d, \(J = 8.2\) Hz, 2H), 7.05 (d, \(J = 8.3\) Hz, 2H), 4.33 (q, \(J = 7.1\) Hz, 2H), 3.91 (s, 3H), 3.90 (s, 3H), 3.82 (s, 3H), 3.66 (s, 3H), 1.34 (t, \(J = 7.1\) Hz, 3H).

13\(^C\) NMR (101 MHz, CDCl\(_3\)) \(\delta\) 161.9, 159.4, 159.0, 150.0, 146.2, 133.0, 131.3, 130.9, 128.4, 127.8, 127.4, 127.4, 126.1, 123.6, 118.4, 114.7, 113.9, 109.1, 61.6, 61.4, 61.1, 55.53, 55.45, 14.5. HRMS (ESI) calculated for C\(_{27}\)H\(_{27}\)NO\(_6\) ([M\(^+\)]\(^+\)): 461.1838; found: 461.1826.
ethyl 4,7-bis(4-(dimethylamino)phenyl)-5,6-dimethoxy-1H-indole-2-carboxylate (10b): 95% yield (yellow solid). ^1H NMR (400 MHz, CDCl_3) δ 8.71 (s, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 2.2 Hz, 1H), 6.88 (dd, J = 8.5, 6.3 Hz, 4H), 4.32 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 3.68 (s, 3H), 3.05 (s, 6H), 3.04 (s, 6H), 1.34 (t, J = 7.1 Hz, 3H). ^13C NMR (101 MHz, CDCl_3) δ 162.0, 150.1, 150.0, 149.8, 146.1, 133.3, 130.9, 130.4, 127.4, 127.4, 124.1, 123.5, 121.7, 118.3, 112.9, 112.3, 109.5, 61.5, 61.3, 60.9, 40.7, 40.7, 14.5. HRMS (ESI) calculated for C_{29}H_{34}N_{5}O_{4} ([M+H]^+): 488.2544, found: 488.2539.

ethyl 5,6-dimethoxy-4,7-di-p-tolyl-1H-indole-2-carboxylate (10c): 84% yield (white solid). ^1H NMR (400 MHz, CDCl_3) δ ^1H NMR (400 MHz, CDCl_3) δ 8.65 (s, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 7.9 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 7.10 (d, J = 2.2 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 3.67 (s, 3H), 2.47 (s, 3H), 2.46 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). ^13C NMR (101 MHz, CDCl_3) δ 161.9, 149.9, 146.2, 137.8, 137.2, 133.1, 132.9, 131.0, 130.0, 129.9, 129.6, 129.1, 127.9, 127.8, 123.5, 118.8, 109.1, 61.6, 61.4, 61.0, 21.5, 14.5. HRMS (ESI) calculated for C_{27}H_{28}NO_{4} ([M+H]^+): 430.2013, found: 430.2010.

ethyl 5,6-dimethoxy-4,7-diphenyl-1H-indole-2-carboxylate (10d). 95% yield (white solid). ^1H NMR (400 MHz, CDCl_3) δ 8.67 (s, 1H), 7.66 − 7.40 (m, 10H), 7.09 (d, J = 2.2 Hz, 1H), 4.33 (q, J = 7.1 Hz, 2H), 3.75 (s, 3H), 3.67 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H). ^13C NMR (101 MHz, CDCl_3) δ 161.9, 149.9, 146.2, 136.1, 134.0, 132.8, 130.2, 129.8, 129.2, 128.4, 128.2, 128.1, 128.0, 127.5, 123.6, 119.1, 109.0, 61.7, 61.5, 61.1, 14.5. HRMS (ESI) calculated for C_{25}H_{26}NO_{4} ([M+H]^+): 402.1700, found: 402.1699.

ethyl 5,6-dimethoxy-4,7-bis(4-(trifluoromethyl)phenyl)-1H-indole-2-carboxylate (10e). 92% yield (white solid). ^1H NMR (400 MHz, CDCl_3) δ 8.64 (s, 1H), 7.83 (d, J = 8.1 Hz, 2H), 7.75 (d, J = 16.8, 7.6 Hz, 7H), 7.05 (d, J = 2.2 Hz, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.76 (s, 3H), 3.68 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H). ^13C NMR (101 MHz, CDCl_3) δ 161.6, 149.9, 146.3, 139.6, 137.6, 132.3, 130.5 (2C), 130.4 (J_{C,F} = 32 Hz), 130.2 (2C), 129.7 (J_{C,F} = 32 Hz), 128.6, 127.4, 126.2 (J_{C,F} = 4 Hz), 125.4 (J_{C,F} = 4 Hz), 124.4 (J_{C,F} = 272 Hz), 124.2 (J_{C,F} = 272 Hz), 123.5, 118.4, 108.5, 61.8, 61.6, 61.4, 14.5. HRMS (ESI) calculated for C_{27}H_{22}NO_{4}F_{6} ([M+H]^+): 538.1448, found: 538.1444.
ethyl 4,7-bis(4-cyanophenyl)-5,6-dimethoxy-1H-indole-2-carboxylate (10f): 76% yield (white solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.67 (s, 1H), 7.86 (d, \(J = 8.1\) Hz, 2H), 7.82 (d, \(J = 8.1\) Hz, 2H), 7.78 – 7.69 (m, 4H), 7.03 (d, \(J = 2.1\) Hz, 1H), 4.35 (q, \(J = 7.1\) Hz, 2H), 3.75 (s, 3H), 3.66 (s, 3H), 1.36 (t, \(J = 7.1\) Hz, 3H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 161.5, 149.8, 146.3, 140.7, 138.7, 133.0, 132.9, 132.3, 132.0, 131.0, 130.6, 128.9, 128.1, 127.3, 123.3, 119.0, 118.7, 118.3, 112.2, 111.5, 108.2, 61.8, 61.6, 61.5, 14.5. HRMS (ESI) calculated for C\(_{27}\)H\(_{22}\)N\(_3\)O\(_4\) ([M+H]\(^+\))$: 452.1605, found: 452.1598.

ethyl 5,6-dimethoxy-4,7-bis(4-nitrophenyl)-1H-indole-2-carboxylate (10g): 90% yield (yellow solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.73 (s, 1H), 8.43 (d, \(J = 8.7\) Hz, 2H), 8.39 (d, \(J = 8.7\) Hz, 2H), 7.82 (d, \(J = 8.7\) Hz, 2H), 7.80 (d, \(J = 8.7\) Hz, 2H), 7.05 (d, \(J = 2.1\) Hz, 1H), 4.35 (q, \(J = 7.1\) Hz, 2H), 3.77 (s, 3H), 3.68 (s, 3H), 1.36 (t, \(J = 7.1\) Hz, 3H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 161.5, 149.9, 147.7, 147.4, 146.4, 142.7, 140.6, 132.0, 131.1, 130.8, 129.1, 127.1, 124.6, 123.7, 123.3, 118.2, 108.2, 61.8, 61.6, 61.5, 14.5. HRMS (ESI) calculated for C\(_{25}\)H\(_{22}\)N\(_3\)O\(_6\) ([M+H]\(^+\))$: 492.1401, found: 492.1394.

ethyl 4,7-bis(3,4-dimethoxyphenyl)-5,6-dimethoxy-1H-indole-2-carboxylate (10h): 95% yield (white solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.70 (s, 1H), 7.21 – 7.10 (m, 5H), 7.08 – 7.01 (m, 2H), 4.33 (q, \(J = 7.1\) Hz, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 3.93 (s, 3H), 3.92 (s, 3H), 3.75 (s, 3H), 3.68 (s, 3H), 1.35 (t, \(J = 7.1\) Hz, 3H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 161.8, 149.9, 149.5, 148.9, 148.8, 148.5, 146.1, 132.9, 128.7, 127.8, 127.6, 126.4, 123.6, 122.5, 121.8, 118.5, 113.5, 113.1, 111.8, 111.1, 109.0, 61.6, 61.4, 61.1, 56.3, 56.1, 56.0, 14.51. HRMS (ESI) calculated for C\(_{29}\)H\(_{22}\)NO\(_8\) ([M+H]\(^+\))$: 522.2122, found: 522.2122.

ethyl 5,6-dimethoxy-4,7-di(thiophen-3-yl)-1H-indole-2-carboxylate (10i): 99% yield (off-white solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.81 (s, 1H), 7.65 – 7.57 (m, 2H), 7.56 – 7.52 (m, 1H), 7.49 (d, \(J = 4.8\) Hz, 1H), 7.46 (dd, \(J = 5.0, 3.0\) Hz, 1H), 7.42 (d, \(J = 4.8\) Hz, 1H), 4.36 (q, \(J = 7.1\) Hz, 2H), 3.78 (s, 3H), 3.71 (s, 3H), 1.38 (t, \(J = 7.1\) Hz, 3H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 161.8, 150.2, 146.4, 135.9, 133.8, 132.8, 129.5, 128.8, 127.9, 126.4, 124.9, 124.5, 124.1, 123.3, 122.9, 114.0, 109.2, 61.5, 61.3, 61.2, 14.5. HRMS (ESI) calculated for C\(_{21}\)H\(_{29}\)NO\(_8\)S\(_2\) ([M+H]\(^+\))$: 414.0828, found: 414.0827.
ethyl 4,7-di(furan-3-yl)-5,6-dimethoxy-1H-indole-2-carboxylate (10j): 81% yield (off-white solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.84 (s, 1H), 7.96 - 7.89 (m, 1H), 7.64 (d, \(J = 1.6\) Hz, 1H), 7.58 (d, \(J = 1.6\) Hz, 1H), 7.34 (d, \(J = 2.1\) Hz, 1H), 6.95 - 6.90 (m, 1H), 6.85 - 6.77 (m, 1H), 4.39 (q, \(J = 7.1\) Hz, 2H), 3.84 (s, 3H), 3.78 (s, 3H), 1.40 (t, \(J = 7.1\) Hz, 3H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 161.8, 150.3, 146.5, 143.8, 142.9, 141.9, 141.1, 132.7, 127.9, 122.8, 119.9, 119.0, 117.9, 111.8, 111.2, 109.9, 109.2, 61.3, 61.2, 61.0, 14.6. HRMS (ESI) calculated for C\(_{21}\)H\(_{20}\)NO\(_6\) ([M+H]+): 382.1285, found: 382.1282.

ethyl 4,7-di(benzofuran-2-yl)-5,6-dimethoxy-1H-indole-2-carboxylate (10k): 91% yield (light green solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.34 (s, 1H), 8.03 (d, \(J = 2.4\) Hz, 1H), 7.73 - 7.63 (m, 4H), 7.61 (d, \(J = 1.0\) Hz, 1H), 7.57 (d, \(J = 1.0\) Hz, 1H), 7.41 - 7.27 (m, 4H), 4.50 (q, \(J = 7.2\) Hz, 2H), 4.08 (s, 3H), 3.99 (s, 3H), 1.50 (t, \(J = 7.1\) Hz, 3H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 161.0, 154.6, 153.7, 151.5, 151.0, 150.0, 147.3, 129.3, 129.0, 127.6, 124.9, 124.2, 123.6, 123.6, 123.5, 122.9, 121.6, 121.2, 112.4, 110.99, 110.97, 108.7, 107.5, 107.1, 105.3, 61.4, 60.3, 56.4, 14.5. HRMS (ESI) calculated for C\(_{29}\)H\(_{24}\)NO\(_6\) ([M+H]+): 482.1598, found: 482.1595.

ethyl 5',6'-(dimethoxy-1H,1'H,1''H-[6,4':7,6'']-terindole)-2'-carboxylate (10l): 78% yield (white solid). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.72 (s, 1H), 8.38 (s, 3H), 8.35 (s, 2H), 7.82 (d, \(J = 8.1\) Hz, 1H), 7.78 (d, \(J = 8.1\) Hz, 1H), 7.68 (s, 1H), 7.63 (s, 1H), 7.43 (dd, \(J = 8.1, 1.4\) Hz, 1H), 7.36 (dd, \(J = 8.1, 1.4\) Hz, 1H), 7.34 - 7.27 (m, 2H), 7.16 (d, \(J = 2.2\) Hz, 1H), 6.70 - 6.60 (m, 2H), 4.29 (q, \(J = 7.1\) Hz, 2H), 3.73 (s, 3H), 3.66 (s, 3H), 1.30 (t, \(J = 7.1\) Hz, 3H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 162.0, 150.0, 146.2, 133.3, 130.0, 128.6, 127.7, 127.6, 127.3, 125.3, 124.9, 123.9, 122.6, 121.7, 121.4, 120.4, 119.6, 112.7, 112.4, 109.5, 102.8, 102.7, 61.7, 61.5, 61.0, 14.5. HRMS (ESI) calculated for C\(_{29}\)H\(_{26}\)N\(_3\)O\(_4\) ([M+H]+): 480.1918, found: 480.1916.

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NMR Spectra
S-36
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HESI Scan (0.141-0.199 min, 8 Scans) Frag=175.6V AHA-33_ESI_19-24-2017.d Subtract (2)

HESI Scan (0.143-0.218 min, 10 Scans) Frag=175.6V AHA-30_ESI_19-24-2017.d Subtract (2)
