

Supporting Information for
Synthesis of 2,3,4-Trisubstituted Pyrrole Derivatives via [3+2]
Cyclization of Activated Methylene Isocyanides with 4-(Arylidene)-2-
Substituted Oxazol-5(4H) Ones

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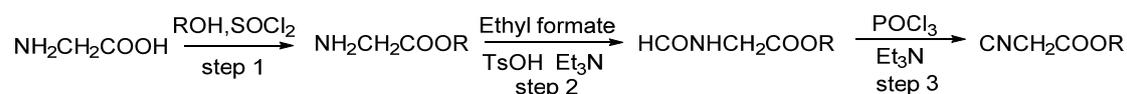
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1. General Methods

NMR data were obtained for ^1H at 400 MHz or 600 MHz, and for ^{13}C at 100 MHz or 151 MHz. Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in CDCl_3 solution. ESI HRMS was recorded on a Waters SYNAPT G2 and Water XEVO G2 Q-ToF. UV detection was monitored at 220 nm. TLC was performed on glass-backed silica plates. Column chromatography was performed on silica gel (200-300 mesh), eluting with ethyl acetate and petroleum ether. Isocyanoacetate **2a**, **2b** and **2g** were commercially available. Isocyanoacetate **2c**, **2d**, **2e** and **2f** were prepared according to the literature procedures¹. 4-(4-methylbenzylidene)-2-phenyloxazol-5(4H)-ones were prepared according to the literature procedures.²

2. General Procedure for the Synthesis of Isocyanoacetate¹

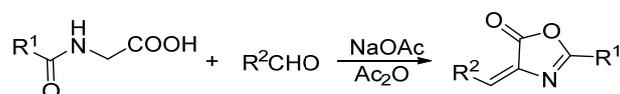


Step 1: A solution of glycine (1.20 g, 10.0 mmol) in isopropyl alcohol (25 mL), thionyl chloride (2.30 mL, 32.0 mmol) was added under the $-10\text{ }^\circ\text{C}$ and stirred 10 minutes, and then the reaction was heated at $40\text{ }^\circ\text{C}$ for 4 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo to furnish a sticky oil.

Step 2: The crude residue was dissolved in ethyl formate (5 mL), TsOH (35 mg) and triethylamine (1.5 mL, 11.0 mmol) were then added. The reaction was heated at reflux for 12 h, before cooling to room temperature and concentrating in vacuo. Column chromatography afforded product as a colourless oil.

Step 3: To a solution of colourless oil in DCM (8 mL) at $0\text{ }^\circ\text{C}$, Triethylamine (4.20 mL, 30.0 mmol) was added, and then POCl_3 (0.93 mL, 10.0 mmol) dropwise. The reaction mixture was stirred for 2 h. Saturated sodium carbonate solution (15 mL) was then added and stirred for 30 min before water was added. The aqueous phase was extracted with DCM and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo to get final product.

3. General Procedure for the Synthesis of Phenyloxazol-5(4H)-ones²



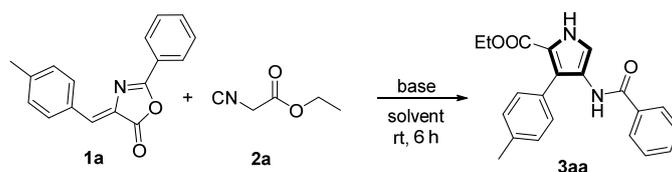
Benzaldehyde or its derivative (5 mmol), N-acetylglycine (5.5 mmol), sodium acetate (2.5 mmol), and acetic anhydride (10 mL) were mixed and heated at $90\text{ }^\circ\text{C}$ under argon with stirring for 4 h. The mixture was left stirring at $25\text{ }^\circ\text{C}$. The precipitate was separated by filtration and washed with ice-cold alcohol, then with water to obtain the oxazolone (49-82% yields).

References:

- [1] J. R. Wolstenhulme, A. Cavell, M. Gredičak, R. W. Driver, M. D. Smith, *Chem. Commun.* 2014, 50, 13585—13588.
[2] Q. An, J. Shen, D. Liu, Y. Liu, W. Zhang, *Org. Lett.* 2017, 19, 2925–2928.

4. Optimization of the Reaction Conditions

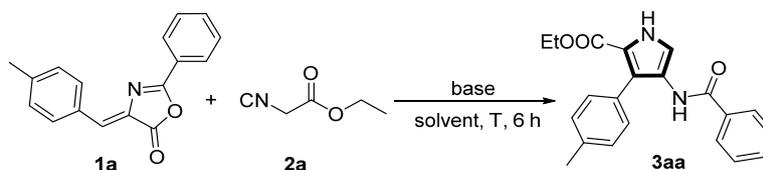
Screening of Conditions^[a]



Entry	DBU/ equiv	Air/Ar	Yield ^[b] /%
1	DBU/1	Air	32
2	DBU/3	Air	44
3	DBU/4	Air	47
4 ^[c]	DBU/2	Ar	34
5 ^[c]	DBU/2	Air, 4Å/20mg	65
6 ^[c]	DBU/2	Air, drying reagent	49
7 ^[c, d]	DBU/2	Air	43
8 ^[c, e]	DBU/2	Air	42

^[a] Reaction conditions unless otherwise specified: 0.05 mmol of **1a**, 1.5 equiv of **2a**, 0.5 mL PhCl, 6 h, Air atmosphere. ^[b] Isolated yield. ^[c] 1.5 mL PhCl. ^[d] 100 °C ^[e] 120 °C.

5. General Procedure for Synthesis of 2,3,4-Trisubstituted Pyrroles

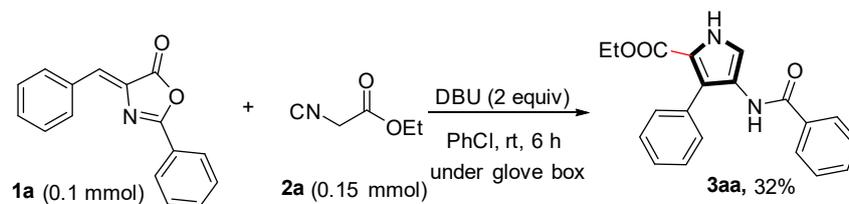


0.1 mmol scale experiments: 4-(4-methylbenzylidene)-2-phenyloxazol-5(4H)-ones **1** (26.4 mg, 0.1 mmol), isocyanoacetate **2** (17.0 mg, 1.5 mmol) and DBU (30.4 mg, 2.0 equiv.) were stirred in PhCl (3.0 mL) at rt for 6 h. After completion, the reaction mixture was purified by flash chromatography eluting with ethyl acetate and petroleum ether (1:5) to give the product **3**.

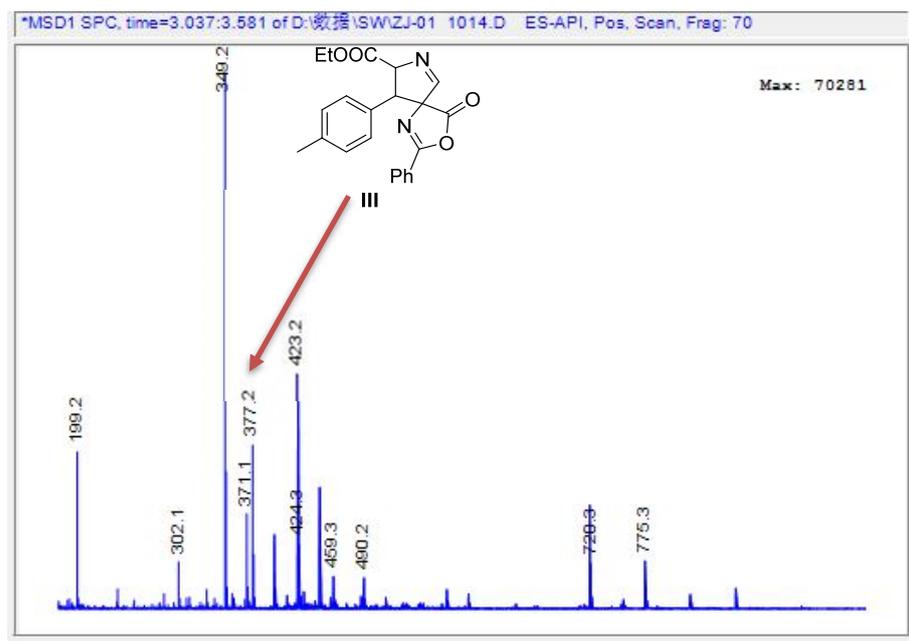
6. Mechanism Study

We have done the reaction to monitor whether hydrogen would be released from the system, however, the reaction system would not generate hydrogen. First, we did a control experiment to put a piece of filter paper which was soaked with phosphomolybdic acid and palladium chloride solution (water is solvent) in a bottle filled with hydrogen. The filter paper changed from yellow to blue black. We put the same filter paper in a test tube that reacts under standard reaction conditions, however, we didn't see a change in the filter paper.

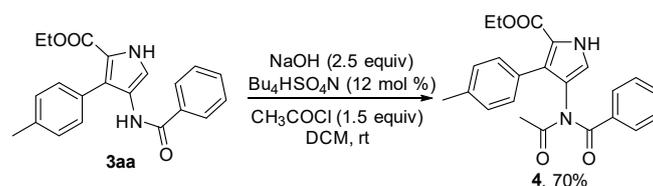
Simultaneously, we did the experiment in the glove box under standard conditions, and **3aa** was obtained in 32% yield. The data imply that the reaction might not undergo an oxidation process during the reaction.



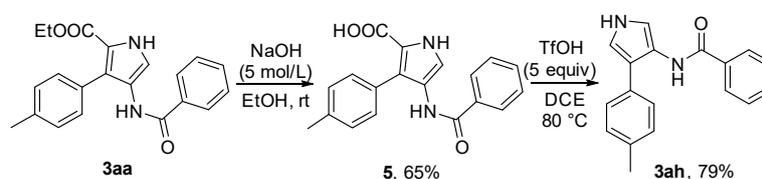
4-(4-methylbenzylidene)-2-phenyloxazol-5(4H)-ones **1** (26.4 mg, 0.1 mmol), isocyanoacetate **2** (17.0 mg, 1.5 mmol) and DBU (30.4 mg, 2.0 equiv.) were stirred in PhCl (3.0 mL) at rt for 0.5 h. Then the reaction mixture was analyzed by LC-MS without purification. The mass spectrum was obtained as below. LC-MS (ESI+): calculated for III m/z [III + H]⁺ (C₂₂H₂₁N₂O₄): 377.2, found: 377.2



7. Synthetic Application of Products



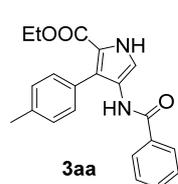
Synthesis of ethyl 4-(N-acetylbenzamido)-3-(p-tolyl)-1H-pyrrole-2-carboxylate **4**: NaOH (5.0 mg, 0.125 mmol) and Bu₄HSO₄N (2.0 mg, 12 mol %) was added to a solution of compound **3aa** (0.1 mmol) in DCM, then the CH₃COCl (1.5 equiv) in DCM was added into the mixture solution and stirred at rt for 10 h. Upon completion, the mixture was then concentrated and the residue was purified by chromatography on silica gel to afford **4** in 70% yields.



Synthesis of hydrolysis product **5**: 5 mol/L NaOH (0.45 mL) was added to a solution of compound **3aa** (17.4 mg) in EtOH (0.7ml) and the mixture solution was stirred at rt for 15 h. Upon completion, the mixture was then concentrated and the residue was purified by chromatography on silica gel to afford **5** (10.5 mg) in 65% yield.

Synthesis **3ah**: 5 equiv of TfOH was added to a solution of compound **5** (20 mg) in DCE (1 mL) and the mixture solution was stirred at rt for 1 h. Upon completion, the mixture was then concentrated and the residue was purified by chromatography on silica gel to afford **3ah** (14 mg) in 79% yield.

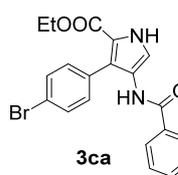
8. Characterization Data and NMR Spectra



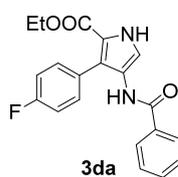
Ethyl 4-benzamido-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxylate (**3aa**). 82% yield. Yellow solid. Mp 164-166 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.25 (s, 1H), 7.88 (d, *J* = 3.1 Hz, 1H), 7.81 (s, 1H), 7.72 – 7.66 (m, 2H), 7.48 (t, *J* = 7.3 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.19 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.2, 160.8, 137.5, 134.2, 131.6, 130.0, 129.2, 128.9, 128.7, 126.8, 122.7, 121.0, 116.9, 113.7, 60.3, 21.3, 14.1 ppm. ESI HRMS: calcd. for C₂₁H₂₀N₂O₃+Na 371.1372, found 371.1366.



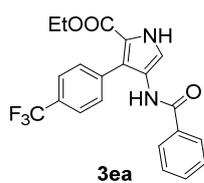
Ethyl 4-benzamido-3-phenyl-1*H*-pyrrole-2-carboxylate (**3ba**). 71% yield. Yellow solid. Mp 155.7-157.7 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.14 (s, 1H), 7.90 (d, *J* = 3.1 Hz, 1H), 7.77 (s, 1H), 7.68 (dt, *J* = 7.0, 1.4 Hz, 2H), 7.52 – 7.38 (m, 8H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.17 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.2, 160.7, 134.1, 132.1, 131.6, 130.2, 128.7, 128.5, 127.8, 126.7, 122.7, 120.9, 117.0, 113.6, 60.3, 14.0 ppm. ESI HRMS: calcd. for C₂₀H₁₈N₂O₃+Na 357.1215, found 357.1215.



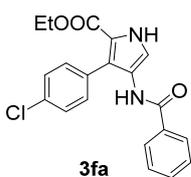
Ethyl 4-benzamido-3-(4-bromophenyl)-1*H*-pyrrole-2-carboxylate (**3ca**). 79% yield. Yellow solid. Mp 154.6-156.6°C. ¹H NMR (400 MHz, CDCl₃) δ 9.23 (s, 1H), 7.87 (d, *J* = 3.1 Hz, 1H), 7.72 – 7.67 (m, 2H), 7.66 (s, 1H), 7.63 – 7.58 (m, 2H), 7.54 – 7.48 (m, 1H), 7.44 (ddt, *J* = 8.5, 6.6, 1.4 Hz, 2H), 7.37 – 7.31 (m, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.4, 160.7, 134.3, 134.0, 131.7, 130.7, 129.7, 128.8, 128.1, 127.9, 126.8, 122.5, 119.4, 117.2, 114.1, 60.5, 14.0 ppm. ESI HRMS: calcd. for C₂₀H₁₇BrN₂O₃+H 413.0501, found 413.0501.



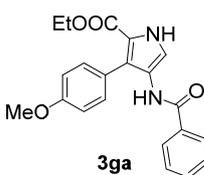
Ethyl 4-benzamido-3-(4-fluorophenyl)-1*H*-pyrrole-2-carboxylate (**3da**). 70% yield. Yellow solid. Mp 165-167 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.34 (s, 1H), 7.86 (d, *J* = 3.2 Hz, 1H), 7.69 (q, *J* = 2.1 Hz, 1H), 7.67 (d, *J* = 1.7 Hz, 2H), 7.54 – 7.47 (m, 1H), 7.47 – 7.39 (m, 4H), 7.21 – 7.14 (m, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.3, 162.4 (d, *J* = 246.0 Hz), 160.7, 134.0, 132.0 (d, *J* = 8.0 Hz), 131.7, 128.8, 128.0 (d, *J* = 4 Hz), 126.7, 122.6, 120.0, 117.1, 115.5 (d, *J* = 21.0 Hz), 114.0, 60.4, 14.1 ppm. ESI HRMS: calcd. for C₂₀H₁₇FN₂O₃+Na 375.1121, found 375.1121.



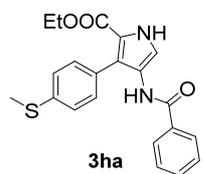
Ethyl 4-benzamido-3-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole-2-carboxylate (**3ea**). 88% yield. Yellow solid. Mp 198.8-200.8 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.25 (s, 1H), 7.89 (d, *J* = 3.1 Hz, 1H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.71 – 7.66 (m, 2H), 7.62 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.54 – 7.49 (m, 1H), 7.47 – 7.41 (m, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.6, 160.4, 136.1 (d, *J* = 1.0 Hz), 133.9, 131.8, 130.7, 129.9 (d, *J* = 32 Hz), 128.8, 126.7, 125.4 (q, *J* = 3.0 Hz), 124.1 (q, *J* = 270.0 Hz), 122.5, 119.6, 117.2, 114.3, 60.5, 14.0 ppm. ESI HRMS: calcd. for C₂₁H₁₇F₃N₂O₃+H 403.1270, found 403.1269.



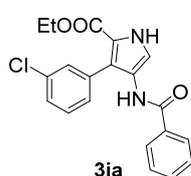
Ethyl 4-benzamido-3-(4-chlorophenyl)-1*H*-pyrrole-2-carboxylate (**3fa**). 70% yield. Yellow solid. Mp 174.8-176.8 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.18 (s, 1H), 7.87 (d, *J* = 3.2 Hz, 1H), 7.72 – 7.66 (m, 2H), 7.65 (s, 1H), 7.54 – 7.48 (m, 1H), 7.48 – 7.37 (m, 6H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.20 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.4, 160.5, 134.0, 133.8, 131.8, 131.6, 130.6, 128.8, 128.7, 126.7, 122.6, 119.7, 117.1, 114.0, 60.4, 14.1 ppm. ESI HRMS: calcd. for C₂₀H₁₇ClN₂O₂+H 369.1006, found 369.1006.



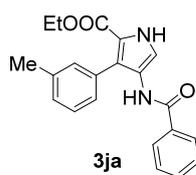
Ethyl 4-benzamido-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (**3ga**). 56% yield. Yellow solid. Mp 154.1-156.1 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.09 (s, 1H), 7.87 (d, *J* = 3.1 Hz, 1H), 7.77 (s, 1H), 7.69 (dd, *J* = 8.2, 1.3 Hz, 2H), 7.53 – 7.46 (m, 1H), 7.46 – 7.35 (m, 4H), 7.07 – 6.99 (m, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.88 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.2, 160.7, 159.2, 134.1, 131.6, 131.4, 128.7, 126.7, 124.0, 122.8, 120.7, 116.9, 114.0, 113.5, 60.2, 55.3, 14.2 ppm. ESI HRMS: calcd. for C₂₁H₂₀N₂O₄+Na 387.1321, found 387.1320.



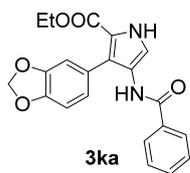
Ethyl 4-benzamido-3-(4-(methylthio)phenyl)-1*H*-pyrrole-2-carboxylate (**3ha**). 42% yield. Yellow solid. Mp 182.1-184.1 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.09 (s, 1H), 7.88 (d, *J* = 3.1 Hz, 1H), 7.74 (s, 1H), 7.72 – 7.67 (m, 2H), 7.53 – 7.47 (m, 1H), 7.43 (dd, *J* = 8.2, 6.6 Hz, 2H), 7.41 – 7.34 (m, 4H), 4.22 (q, *J* = 7.1 Hz, 2H), 2.55 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.3, 160.6, 138.3, 134.1, 131.7, 130.6, 128.8, 128.5, 126.7, 126.3, 122.7, 120.4, 117.0, 113.7, 60.3, 15.6, 14.2 ppm. ESI HRMS: calcd. for C₂₁H₂₀N₂O₃S+H 381.1273, found 381.1275.



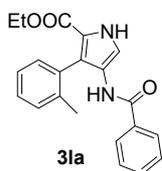
Ethyl 4-benzamido-3-(3-chlorophenyl)-1*H*-pyrrole-2-carboxylate (**3ia**). 86% yield. Yellow solid. Mp 152.7-154.7 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.32 (s, 1H), 7.88 (s, 1H), 7.70 (dt, *J* = 7.1, 1.4 Hz, 3H), 7.54 – 7.47 (m, 2H), 7.46 – 7.36 (m, 4H), 7.34 (dt, *J* = 7.0, 1.8 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.4, 160.7, 134.3, 134.0, 131.7, 130.7, 129.7, 128.8, 128.1, 127.9, 126.8, 122.5, 119.4, 117.2, 114.1, 60.5, 14.0 ppm. ESI HRMS: calcd. for C₂₀H₁₇ClN₂O₃+Na 391.0825, found 391.0823.



Ethyl 4-benzamido-3-(*m*-tolyl)-1*H*-pyrrole-2-carboxylate (**3ja**). 81% yield. Yellow solid. Mp 155.4-157.4°C. ¹H NMR (400 MHz, CDCl₃) δ 9.20 (s, 1H), 7.89 (d, *J* = 3.1 Hz, 1H), 7.81 (s, 1H), 7.68 (dt, *J* = 7.1, 1.4 Hz, 2H), 7.52 – 7.45 (m, 1H), 7.45 – 7.35 (m, 3H), 7.31 – 7.19 (m, 3H), 4.21 (q, *J* = 7.1 Hz, 2H), 2.42 (s, 3H), 1.18 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.1, 160.8, 138.1, 134.2, 131.9, 131.6, 131.0, 128.7, 128.5, 128.4, 127.0, 126.7, 122.7, 120.9, 116.9, 113.6, 60.2, 21.4, 14.0 ppm. ESI HRMS: calcd. for C₂₁H₂₀N₂O₃+Na 371.1372, found 371.1368.



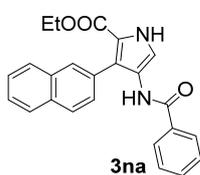
Ethyl 4-benzamido-3-(benzo[*d*][1,3]dioxol-5-yl)-1*H*-pyrrole-2-carboxylate (**3ka**). 55% yield. Yellow solid. Mp 175.9-177.9°C. ¹H NMR (400 MHz, CDCl₃) δ 9.23 – 9.05 (m, 1H), 7.86 (d, *J* = 3.1 Hz, 1H), 7.79 (s, 1H), 7.75 – 7.67 (m, 2H), 7.56 – 7.40 (m, 3H), 6.99 – 6.85 (m, 3H), 6.03 (s, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100MHz, CDCl₃) δ 164.2, 160.6, 147.8, 147.3, 134.1, 131.6, 128.8, 126.8, 125.5, 123.1, 122.8, 120.6, 117.0, 113.5, 111.2, 108.3, 101.2, 60.3, 14.1 ppm. ESI HRMS: calcd. for C₂₁H₁₈N₂O₅+Na 401.1113, found 401.1114.



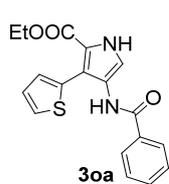
Ethyl 4-benzamido-3-(*o*-tolyl)-1*H*-pyrrole-2-carboxylate (**3la**). 74% yield. Yellow solid. Mp 178.2-180.2°C. ¹H NMR (400 MHz, CDCl₃) δ 9.17 (s, 1H), 7.84 (d, *J* = 3.1 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.42 – 7.37 (m, 1H), 7.36 (s, 1H), 7.34 – 7.28 (m, 2H), 7.28 – 7.22 (m, 2H), 7.22 – 7.15 (m, 2H), 4.07 (p, *J* = 7.1 Hz, 2H), 2.11 (s, 3H), 1.01 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100MHz, CDCl₃) δ 163.1, 159.8, 136.8, 133.1, 130.5, 130.4, 129.3, 129.2, 127.7, 127.2, 125.7, 124.8, 121.9, 119.0, 116.3, 112.4, 59.1, 18.8, 12.9 ppm. ESI HRMS: calcd. for C₂₁H₂₀N₂O₃+H 349.1552, found 349.1551.



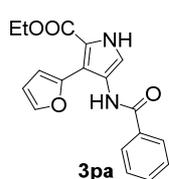
Ethyl 4-benzamido-3-(2-bromophenyl)-1*H*-pyrrole-2-carboxylate (**3ma**). 55% yield. Yellow solid. Mp 187.2-189.2°C. ¹H NMR (400 MHz, CDCl₃) δ 9.14 (s, 1H), 7.87 (d, *J* = 3.1 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 1H), 7.71 – 7.65 (m, 2H), 7.52 – 7.35 (m, 6H), 7.32 – 7.26 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 1.09 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100MHz, CDCl₃) δ 164.5, 160.5, 134.2, 133.4, 132.8, 132.8, 131.6, 129.7, 128.7, 127.3, 126.8, 124.6, 122.8, 119.8, 117.7, 113.8, 60.3, 13.9 ppm. ESI HRMS: calcd. for C₂₀H₁₇BrN₂O₃+Na 435.0320, found 435.0320.



Ethyl 4-benzamido-3-(naphthalen-2-yl)-1*H*-pyrrole-2-carboxylate (**3na**). 40% yield. Yellow solid. Mp 211.7-213.7 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.35 (s, 1H), 8.01 (d, *J* = 3.1 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 2H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.58 (dd, *J* = 8.1, 7.0 Hz, 1H), 7.51 (ddd, *J* = 8.2, 6.8, 1.4 Hz, 2H), 7.47 – 7.36 (m, 5H), 7.32 – 7.24 (m, 2H), 3.99 (q, *J* = 7.1 Hz, 2H), 0.78 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.3, 160.9, 134.0, 133.8, 132.3, 131.5, 129.7, 128.6, 128.5, 128.4, 126.6, 126.4, 126.0, 125.9, 125.4, 123.6, 118.4, 118.3, 113.7, 60.1, 13.5 ppm. ESI HRMS: calcd. for C₂₄H₂₀N₂O₃+Na 407.1372, found 407.1369.



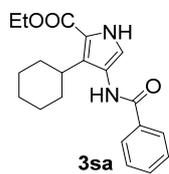
Ethyl 4-benzamido-3-(thiophen-2-yl)-1*H*-pyrrole-2-carboxylate (**30a**). 54% yield. Yellow solid. Mp 171.0-173.0 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.25 (s, 1H), 8.04 (s, 1H), 7.89 (d, *J* = 3.2 Hz, 1H), 7.78 – 7.72 (m, 2H), 7.54 – 7.48 (m, 1H), 7.48 – 7.41 (m, 3H), 7.23 – 7.15 (m, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.2, 160.4, 134.1, 132.2, 131.7, 128.8, 128.4, 127.4, 126.8, 126.6, 123.5, 117.8, 113.5, 112.9, 60.5, 14.1 ppm. ESI HRMS: calcd. for C₁₈H₁₆N₂O₃S+Na 363.0779, found 363.0782.



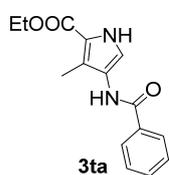
Ethyl 4-benzamido-3-(furan-2-yl)-1*H*-pyrrole-2-carboxylate (**3pa**). 44% yield. Yellow solid. Mp 166.4-168.4 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.48 (s, 1H), 9.11 (s, 1H), 8.01 (d, *J* = 3.2 Hz, 1H), 7.90 (dt, *J* = 6.7, 1.6 Hz, 2H), 7.58 (d, *J* = 1.9 Hz, 1H), 7.57 – 7.45 (m, 3H), 7.31 (d, *J* = 3.5 Hz, 1H), 6.58 (dd, *J* = 3.5, 1.9 Hz, 1H), 4.37 (q, *J* = 7.2 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.2, 159.9, 148.3, 140.9, 134.4, 131.6, 128.8, 126.8, 123.1, 115.4, 114.0, 111.9, 110.8, 110.0, 60.6, 14.4 ppm. ESI HRMS: calcd. for C₁₈H₁₆N₂O₄+Na 347.1008, found 347.1008.



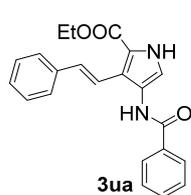
Ethyl 4-benzamido-3-(*tert*-butyl)-1*H*-pyrrole-2-carboxylate (**3ra**). 55% yield. Yellow solid. Mp 135.3-137.3 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.26 (s, 1H), 7.98 (s, 1H), 7.88 – 7.81 (m, 2H), 7.60 – 7.43 (m, 4H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.57 (s, 9H), 1.36 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 165.3, 160.0, 134.7, 131.7, 131.6, 128.8, 126.8, 121.1, 117.3, 117.1, 60.3, 33.4, 31.2, 14.4 ppm. ESI HRMS: calcd. for C₂₀H₂₆N₂O₃+Na 365.1841, found 365.1843.



Ethyl 4-benzamido-3-cyclohexyl-1*H*-pyrrole-2-carboxylate (**3sa**). 60% yield. Yellow solid. Mp 173.1-175.1 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.98 (s, 1H), 7.92 – 7.82 (m, 2H), 7.77 (s, 1H), 7.63 – 7.43 (m, 4H), 4.32 (q, *J* = 7.1 Hz, 2H), 3.40 (tt, *J* = 12.6, 3.3 Hz, 1H), 1.87 (tt, *J* = 10.8, 3.1 Hz, 4H), 1.76 (ddd, *J* = 24.9, 13.3, 3.4 Hz, 3H), 1.44 (ddd, *J* = 16.8, 8.5, 3.7 Hz, 2H), 1.37 (t, *J* = 7.1 Hz, 3H), 1.28 (tt, *J* = 13.0, 3.1 Hz, 1H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.7, 160.9, 134.6, 131.6, 128.9, 127.5, 126.8, 122.1, 116.5, 115.8, 60.1, 35.3, 32.4, 27.1, 26.4, 14.4 ppm. ESI HRMS: calcd. for C₂₀H₂₄N₂O₃+Na 363.1685, found 363.1690.

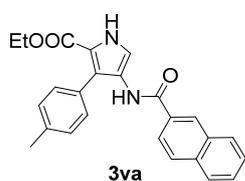


Ethyl 4-benzamido-3-methyl-1*H*-pyrrole-2-carboxylate (**3ta**). 52% yield. Yellow solid. Mp 180.0-182.0 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.86 (s, 1H), 7.91 – 7.82 (m, 2H), 7.60 – 7.52 (m, 3H), 7.52 – 7.46 (m, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.36 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.9, 161.3, 134.4, 131.7, 128.8, 126.9, 122.9, 117.6, 117.5, 114.7, 60.2, 14.5, 9.1 ppm. ESI HRMS: calcd. for C₁₅H₁₆N₂O₃+H 273.1239, found 273.1245.

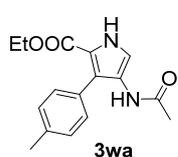


Ethyl (*E*)-4-benzamido-3-styryl-1*H*-pyrrole-2-carboxylate (**3ua**). 42% yield. Yellow solid. Mp 160.5-162.5 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.16 (s, 1H), 8.12 (s, 1H), 7.91 – 7.83 (m, 2H), 7.78 (d, *J* = 3.1 Hz, 1H), 7.66 (d, *J* = 17.0 Hz, 1H), 7.58 – 7.44 (m, 5H), 7.37 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.33 – 7.24 (m, 1H), 6.92 (d, *J* = 17.0 Hz, 1H), 4.36 (q, *J* = 7.1 Hz, 2H), 1.39 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz,

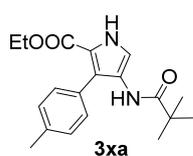
CDCl₃) δ 164.6, 160.8, 137.3, 134.2, 131.8, 131.0, 128.9, 128.8, 127.8, 126.8, 126.2, 121.8, 121.3, 118.2, 117.8, 115.2, 60.6, 14.4 ppm. ESI HRMS: calcd. for C₂₄H₂₄N₂O₃+Na 411.1685, found 411.1688.



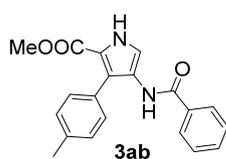
Ethyl 4-(2-naphthamido)-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxylate (**3va**). 66% yield. Yellow solid. Mp 206.5-208.5 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.13 (s, 1H), 8.23 (d, *J* = 1.8 Hz, 1H), 8.01 – 7.80 (m, 5H), 7.72 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.54 (tt, *J* = 7.0, 5.2 Hz, 2H), 7.39 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 7.8 Hz, 2H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.44 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.3, 160.7, 137.6, 134.7, 132.6, 131.4, 130.1, 129.3, 129.0, 128.9, 128.6, 127.8, 127.7, 127.5, 126.8, 123.1, 122.8, 121.0, 116.9, 113.7, 60.3, 21.3, 14.1 ppm. ESI HRMS: calcd. for C₂₅H₂₂N₂O₃+Na 421.1528, found 421.1530.



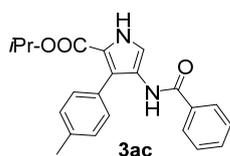
Ethyl 4-acetamido-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxylate (**3wa**). 26% yield. Yellow solid. Mp 202.8-204.8 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.08 (s, 1H), 7.68 (d, *J* = 3.1 Hz, 1H), 7.26 (s, 3H), 6.97 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.41 (s, 3H), 2.04 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 167.2, 160.6, 137.4, 130.0, 129.1, 128.9, 122.7, 120.6, 116.8, 113.5, 60.2, 23.7, 21.3, 14.1 ppm. ESI HRMS: calcd. for C₁₆H₁₈N₂O₃+Na 287.1396, found 287.1390.



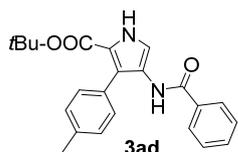
Ethyl 4-pivalamido-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxylate (**3xa**). 28% yield. Yellow solid. Mp 146.8-148.8 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.92 (s, 1H), 7.64 (d, *J* = 3.1 Hz, 1H), 7.27 (s, 1H), 7.24 – 7.16 (m, 4H), 4.13 (q, *J* = 7.1 Hz, 2H), 2.34 (s, 3H), 1.12 (d, *J* = 4.5 Hz, 12H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 175.5, 160.7, 137.4, 129.9, 129.1, 128.9, 122.8, 120.7, 116.6, 113.1, 60.2, 39.1, 27.5, 21.3 14.1 ppm. ESI HRMS: calcd. for C₁₉H₂₄N₂O₃+Na 351.1685, found 351.1682.



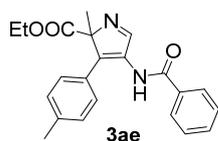
Methyl 4-benzamido-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxylate (**3ab**). 71% yield. Yellow solid. Mp 169.3-171.3 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.14 (s, 1H), 7.89 (d, *J* = 3.1 Hz, 1H), 7.80 (s, 1H), 7.72 – 7.66 (m, 2H), 7.52 – 7.46 (m, 1H), 7.45 – 7.39 (m, 2H), 7.37 – 7.28 (m, 4H), 3.73 (s, 3H), 2.43 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.2, 161.1, 137.6, 134.1, 131.6, 129.9, 129.4, 128.8, 128.7, 126.8, 122.8, 121.1, 116.6, 113.7, 51.3, 21.3 ppm. ESI HRMS: calcd. for C₂₀H₁₈N₂O₃+Na 357.1215, found 357.1214.



Isopropyl 4-benzamido-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxylate (**3ac**). 61% yield. Yellow solid. Mp 154.4-156.4 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.14 (s, 1H), 7.87 (d, *J* = 3.1 Hz, 1H), 7.80 (s, 1H), 7.69 (dd, *J* = 7.2, 1.8 Hz, 2H), 7.52 – 7.46 (m, 1H), 7.42 (dd, *J* = 8.2, 6.6 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 7.31 – 7.24 (m, 2H), 5.10 (p, *J* = 6.2 Hz, 1H), 2.43 (s, 3H), 1.18 (d, *J* = 6.2 Hz, 6H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.2, 160.2, 137.5, 134.2, 131.6, 130.1, 129.2, 129.0, 128.7, 126.8, 122.7, 120.9, 117.3, 113.3, 67.9, 21.8, 21.34 ppm. ESI HRMS: calcd. for C₂₂H₂₂N₂O₃+Na 385.1528, found 385.1527.



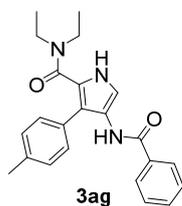
Tert-butyl 4-benzamido-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxylate (**3ad**). 50% yield. Yellow solid. Mp 147.3-149.3 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.99 (s, 1H), 7.84 (d, *J* = 3.1 Hz, 1H), 7.75 (s, 1H), 7.68 (dt, *J* = 7.1, 1.4 Hz, 2H), 7.51 – 7.46 (m, 1H), 7.42 (dd, *J* = 8.2, 6.6 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 2.42 (s, 3H), 1.40 (s, 9H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.1, 160.2, 137.3, 134.2, 131.5, 130.1, 129.3, 129.2, 128.7, 126.7, 122.6, 120.3, 118.3, 112.8, 81.1, 28.2, 21.3 ppm. ESI HRMS: calcd. for C₂₃H₂₄N₂O₃+Na 399.1685, found 399.1678.



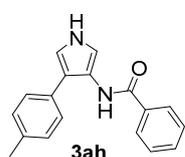
Ethyl 4-benzamido-2-methyl-3-(*p*-tolyl)-2*H*-pyrrole-2-carboxylate (**3ae**). 52% yield. Yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ 9.17 (s, 1H), 7.88 (s, 1H), 7.79 (dd, *J* = 7.2, 1.7 Hz, 2H), 7.61 – 7.54 (m, 1H), 7.48 (dd, *J* = 8.3, 6.9 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 4.18 (qd, *J* = 7.1, 4.9 Hz, 2H), 2.40 (s, 3H), 1.60 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 169.6, 165.1, 163.2, 144.7, 138.9, 133.3, 133.2, 132.4, 130.2, 128.9, 128.8, 127.4, 127.2, 83.9, 61.9, 21.3, 19.5, 14.0 ppm. ESI HRMS: calcd. for C₂₂H₂₂N₂O₃+Na 385.1528, found 385.1522.



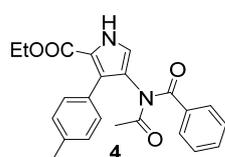
Ethyl 4-benzamido-2-benzyl-3-(*p*-tolyl)-2*H*-pyrrole-2-carboxylate (**3af**). 52% yield. Yellow solid. Mp 140.8-142.8 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.04 (s, 1H), 7.83 (s, 1H), 7.67 – 7.59 (m, 2H), 7.51 – 7.40 (m, 1H), 7.36 (dd, *J* = 8.2, 6.9 Hz, 2H), 7.24 (d, *J* = 7.9 Hz, 2H), 7.12 – 6.96 (m, 5H), 6.78 (dd, *J* = 7.3, 2.3 Hz, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.80 (d, *J* = 13.6 Hz, 1H), 3.14 (d, *J* = 13.6 Hz, 1H), 2.37 (s, 3H), 1.15 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 168.3, 163.4, 162.8, 140.4, 137.8, 133.8, 133.4, 132.1, 131.3, 129.3, 129.2, 128.2, 127.8, 126.4, 126.3, 126.1, 125.6, 85.6, 61.0, 38.0, 20.3, 13.0 ppm. ESI HRMS: calcd. for C₂₈H₂₆N₂O₃+Na 461.1841, found 461.1842.



4-benzamido-*N,N*-diethyl-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxamide (**3ag**). 49% yield. Yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ 9.27 (s, 1H), 7.84 (s, 1H), 7.74 (dt, *J* = 10.3, 2.1 Hz, 3H), 7.54-7.38 (m, 3H), 7.27 (d, *J* = 1.9 Hz, 4H), 3.20 (s, 4H), 2.41 (s, 3H), 0.86 (s, 6H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.3, 164.1, 137.3, 134.4, 131.4, 130.1, 129.1, 128.7, 126.8, 121.2, 120.2, 115.6, 111.7, 21.2, 12.7 ppm. ESI HRMS: calcd. for C₂₃H₂₅N₃O₂+Na 398.1844, found 398.1844.

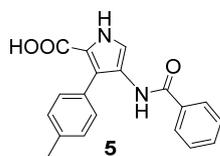


N-(4-(*p*-tolyl)-1*H*-pyrrol-3-yl)benzamide (**3ah**). 74% yield. Yellow liquid. ¹H NMR (400 MHz, CDCl₃) δ 8.27 (s, 1H), 8.00 (s, 1H), 7.83-7.74 (m, 2H), 7.66 (t, *J* = 2.6 Hz, 1H), 7.55-7.39 (m, 3H), 7.39-7.30 (m, 2H), 7.30-7.20 (m, 2H), 6.77 (t, *J* = 2.7 Hz, 1H), 2.40 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.2, 136.3, 134.6, 131.4, 131.2, 130.0, 128.7, 127.8, 126.8, 120.0, 116.7, 114.3, 110.2, 21.1 ppm. ESI HRMS: calcd. for C₁₈H₁₆N₂O+Na 299.1160, found 299.1160.

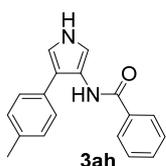


Ethyl 4-(*N*-acetylbenzamido)-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxylate (**4**). 70% yield. White solid. Mp 149.8-151.8 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.47 (s, 1H), 7.43 - 7.34 (m, 1H), 7.35 - 7.20 (m, 4H), 7.20 - 7.05 (m, 4H), 6.94 (d, *J* = 3.3 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.37 (s, 3H), 2.24 (s, 3H), 1.12 (t, *J* = 7.1 Hz, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 174.3, 173.0, 160.7, 137.4, 135.0, 131.5,

130.1, 128.6, 128.6, 128.5, 127.8, 123.6, 120.4, 118.7, 60.4, 25.2, 21.3, 14.0 ppm. ESI HRMS: calcd. for C₂₃H₂₂N₂O₄+Na 413.1477, found 413.1470.



4-benzamido-3-(*p*-tolyl)-1*H*-pyrrole-2-carboxylic acid (**5**). 65% yield. Brown solid. Mp 206.6-208.6 °C. ¹H NMR (400 MHz, DMSO) δ 11.69 (s, 1H), 9.24 (s, 1H), 7.85 – 7.75 (m, 2H), 7.48 (dt, *J* = 29.5, 7.3 Hz, 4H), 7.29 (d, *J* = 7.8 Hz, 2H), 7.16 – 7.07 (m, 3H), 2.29 (s, 3H) ppm. ¹³C NMR (100 MHz, DMSO) δ 166.4, 162.3, 135.9, 134.9, 131.7, 130.6, 130.5, 128.7, 128.4, 127.8, 126.2, 121.5, 119.2, 117.6, 21.2 ppm. ESI HRMS: calcd. for C₁₉H₁₆N₂O₃+Na 343.1059, found 343.1056.



N-(4-(*p*-tolyl) pyridin-3-yl) benzamide (**3ah**). 78% yield. Yellow liquid. ¹H NMR (600 MHz, CDCl₃) δ 8.19 (s, 1H), 8.02 (s, 1H), 7.81 (d, *J* = 7.6 Hz, 2H), 7.70 (d, *J* = 2.5 Hz, 1H), 7.49 (dt, *J* = 33.7, 7.5 Hz, 3H), 7.36 (d, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 7.8 Hz, 2H), 6.79 (t, *J* = 2.6 Hz, 1H), 2.42 (s, 3H) ppm. ¹³C NMR (100 MHz, CDCl₃) δ 164.2, 136.3, 134.6, 131.4, 131.2, 130.0, 128.7, 127.8, 127.8, 126.8, 120.0, 116.7, 114.3, 110.2, 21.1 ppm. ESI HRMS: calcd. for C₁₈H₁₆N₂O+K 315.0900, found 315.0898.

