

Cu(II) catalyzed oxidation-[3+2] cycloaddition-aromatization cascade: Efficient synthesis of pyrrolo [2, 1-*a*] isoquinolines

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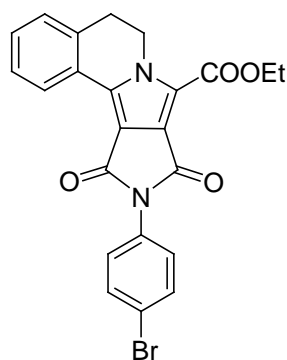
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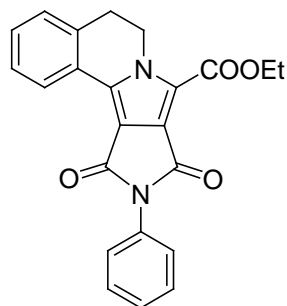
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General information: Commercial reagents were used as received, unless otherwise stated. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with fluorescence F254 were used for thin-layer chromatography (TLC) analysis. ^1H and ^{13}C NMR spectra were recorded on Broker Avance 500, and tetramethylsilane (TMS) was used as a reference. Data for ^1H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). Data for ^{13}C NMR are reported as ppm.

General procedure for the synthesis of lamellarin-type molecules: To a solution of an ethyl 2-(3,4-dihydroisoquinolin-2(1*H*)-yl)acetate (0.1 mmol) and 60 μL of TBHP (3.3 equiv.) in the presence of 10 mol % catalyst CuBr_2 in toluene (1.0 mL) was added a *N*-substituted maleimides (or other dipolarphiles) (0.1 mmol) and the resulting solution was stirred for 48 h at 50 $^\circ\text{C}$. The reaction mixture was directly purified by silica gel chromatography without work-up and fractions were collected and concentrated *in vacuo* to provide the pure desired products.

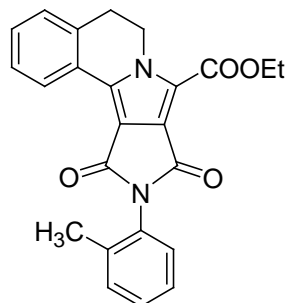


Ethyl 10-(4-bromophenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5H-pyrrolo [3',4':3,4] pyrrolo [2,1-a] isoquinoline-8-carboxylate (5a) (Table 2, entry 7): White solid; Yield: 76%; $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 8.52 (t, 1H, J = 6.5 Hz), 7.58 (d, 2H, J = 8.5 Hz), 7.35-7.40 (m, 2H), 7.27-7.31 (m, 3H), 4.73 (t, 2H, J = 7.0 Hz), 4.40 (q, 2H, J = 7.0 Hz), 3.15 (t, 2H, J = 7.0 Hz), 1.45 (t, 3H, J = 7.5 Hz); ^{13}C NMR (125 MHz, CDCl_3): δ = 162.6, 161.1, 159.4, 133.5, 132.4, 131.9, 131.6, 130.4, 128.5, 127.9, 127.8, 127.6, 125.3, 124.8, 121.3, 118.7, 115.9, 61.6, 43.3, 28.2, 14.1. HR-MS: calcd ($\text{M} + \text{Na}^+$) for $\text{C}_{23}\text{H}_{17}\text{BrN}_2\text{O}_4$, 487.0269; found 487.0273.

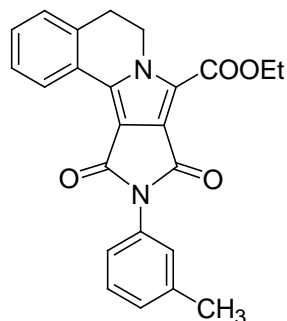


Ethyl 9,11-dioxo-10-phenyl-6,9,10,11-tetrahydro-5H cyclopenta [3,4] pyrrolo [2,1-a] isoquinoline-8-carboxylate (5b) (Table 2, entry 1): White solid; Yield: 57%; $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 8.58 (d, 1H, J = 7.0 Hz), 7.49 (t, 1H, J = 7.5 Hz), 7.36-7.41 (m, 5H), 7.29 (d, 1H, J = 7.0 Hz), 4.78 (t, 2H, J = 7.0 Hz), 4.43 (q, 2H, J = 7.0 Hz), 3.19 (d, 2H, J = 6.5 Hz), 1.47 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, CDCl_3): δ = 163.1, 161.6, 159.7, 133.5, 132.6, 132.4,

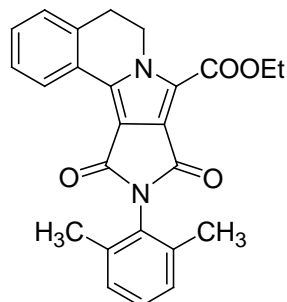
130.3, 128.9, 128.0, 127.9, 127.8, 127.7, 127.1, 125.6, 125.2, 118.7, 116.2, 61.6, 43.4, 28.3, 14.2.
HR-MS: calcd ($M + Na^+$) for $C_{23}H_{18}N_2O_4$, 409.1164; found 409.1169.



Ethyl 9,11-dioxo-10-(o-tolyl)-6,9,10,11-tetrahydro-5H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (5c) (Table 2, entry 2): White solid; Yield: 60%; 1H -NMR (500 MHz, $CDCl_3$): δ = 8.57 (t, 1H, J = 7.5 Hz), 7.29-7.42 (m, 6H), 7.21 (d, 1H, J = 7.5 Hz), 4.84 (m, 1H), 4.74 (m, 1H), 4.42 (q, 2H, J = 7.5 Hz), 3.20 (t, 2H, J = 6.5 Hz), 2.25 (s, 3H), 1.46 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.1, 161.7, 159.7, 136.9, 134.4, 132.4, 131.6, 130.9, 130.3, 129.1, 128.0, 127.6, 126.7, 125.6, 118.6, 116.4, 61.6, 43.4, 28.4, 18.0, 14.1. HR-MS: calcd ($M + Na^+$) for $C_{24}H_{20}N_2O_4$, 423.1321; found 423.1316.

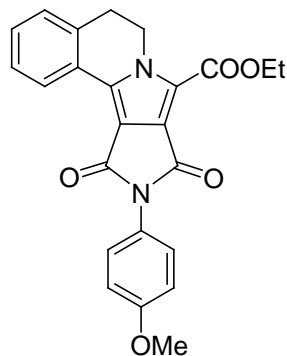


Ethyl 9,11-dioxo-10-(m-tolyl)-6,9,10,11-tetrahydro-5H-pyrrolo [3',4':3,4] pyrrolo [2,1-a] isoquinoline-8-carboxylate (5d) (Table 2, entry 3): White solid; Yield: 77%; 1H -NMR (500 MHz, $CDCl_3$): δ = 8.58 (d, 1H, J = 7.0 Hz), 7.35-7.42 (m, 3H), 7.29 (d, 1H, J = 7.0 Hz), 7.19-7.21 (m, 3H), 4.78 (t, 2H, J = 7.0 Hz), 4.43 (q, 2H, J = 7.0 Hz), 3.18 (t, 2H, J = 7.0 Hz), 2.40 (s, 3H), 1.47 (t, 3H, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.2, 161.7, 159.7, 138.8, 133.4, 132.4, 130.3, 128.7, 128.0, 127.8, 127.6, 125.6, 125.3, 124.3, 118.6, 116.3, 61.6, 43.4, 28.3, 21.4, 14.2. HR-MS: calcd ($M + Na^+$) for $C_{24}H_{20}N_2O_4$, 423.1321; found 423.1322.

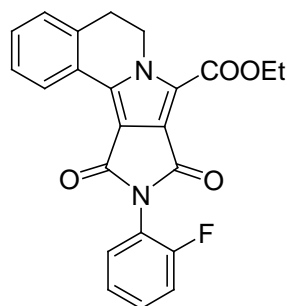


Ethyl 10-(2,6-dimethylphenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5H-pyrrolo [3',4':3,4] pyrrolo [2,1-a] isoquinoline-8-carboxylate (5e) (Table 2, entry 4): White solid; Yield: 50%;

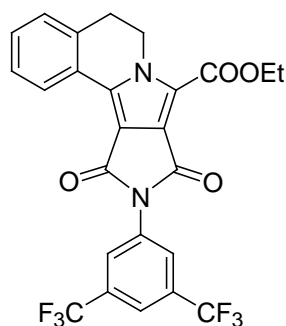
$^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 8.58 (d, 1H, J = 7.5 Hz), 7.36-7.42 (m, 2H), 7.30 (d, 1H, J = 7.0 Hz), 7.24 (t, 1H, J = 7.5 Hz), 7.15-7.17 (m, 2H), 4.80 (t, 2H, J = 7.0 Hz), 4.42 (q, 2H, J = 7.0 Hz), 3.20 (d, 2H, J = 6.5 Hz), 2.21 (s, 3H), 1.46 (t, 3H, J = 7.0 Hz); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ = 163.0, 161.4, 159.7, 137.1, 134.3, 133.3, 132.4, 130.8, 130.3, 129.1, 128.3, 128.0, 127.6, 125.6, 118.6, 116.5, 61.7, 43.4, 28.4, 18.1, 14.1. HR-MS: calcd ($\text{M} + \text{Na}^+$) for $\text{C}_{25}\text{H}_{22}\text{N}_2\text{O}_4$, 437.1477; found 437.1484.



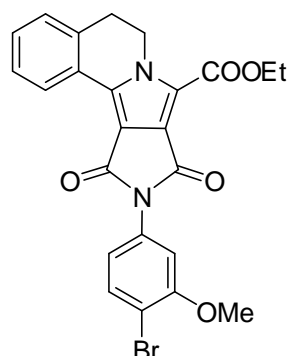
Ethyl 10-(4-methoxyphenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5H-pyrrolo [3',4':3,4] pyrrolo [2,1-a] isoquinoline-8-carboxylate (5f) (Table 2, entry 5): White solid; Yield: 64%; $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 8.57 (d, 1H, J = 7.0 Hz), 7.36-7.42 (m, 2H), 7.28-7.31 (m, 2H), 7.27-7.31 (m, 3H), 7.00 (d, 2H, J = 9.0 Hz), 4.77 (t, 2H, J = 7.0 Hz), 4.42 (q, 2H, J = 7.0 Hz), 3.84 (s, 3H), 3.18 (t, 2H, J = 6.5 Hz), 1.46 (t, 3H, J = 7.5 Hz); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ = 163.4, 162.0, 159.7, 159.0, 133.4, 132.4, 130.3, 128.5, 128.2, 128.0, 127.9, 127.6, 125.6, 125.3, 118.6, 116.3, 114.3, 61.6, 55.5, 43.3, 28.3, 14.2. HR-MS: calcd ($\text{M} + \text{Na}^+$) for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_5$, 439.1270; found 439.1276.



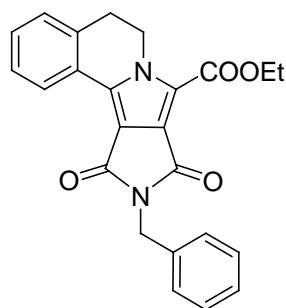
Ethyl 10-(2-fluorophenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5H-pyrrolo [3',4':3,4] pyrrolo [2,1-a] isoquinoline-8-carboxylate (5g) (Table 2, entry 6): White solid; Yield: 61%; $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 8.57 (t, 1H, J = 6.5 Hz), 7.35-7.43 (m, 4H), 7.23-7.30 (m, 4H), 4.79 (t, 2H, J = 7.0 Hz), 4.43 (q, 2H, J = 7.0 Hz), 3.19 (d, 2H, J = 6.5 Hz), 1.46 (t, 3H, J = 7.0 Hz); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ = 162.4, 160.9, 159.6, 159.2, 157.2, 133.6, 132.4, 130.4, 130.3, 128.0, 127.7, 125.5, 125.3, 124.5, 120.4, 120.3, 118.8, 116.6, 116.5, 116.2, 61.7, 43.4, 28.3, 14.15. HR-MS: calcd ($\text{M} + \text{Na}^+$) for $\text{C}_{23}\text{H}_{17}\text{FN}_2\text{O}_4$, 427.1070; found 427.1074.



Ethyl 10-(3,5-bis(trifluoromethyl)phenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (5h) (Table 2, entry 8): White solid; Yield: 80%; $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 8.53 (d, 1H, J = 7.0 Hz), 8.00 (s, 1H), 7.87 (s, 1H), 7.40-7.45 (m, 2H), 7.31 (d, 1H, J = 7.0 Hz), 4.80 (t, 2H, J = 7.0 Hz), 4.46 (q, 2H, J = 7.0 Hz), 3.20 (t, 2H, J = 7.0 Hz), 1.48 (t, 3H, J = 7.0 Hz); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ = 162.1, 160.5, 159.4, 134.2, 134.1, 132.5, 132.4, 130.7, 128.1, 127.9, 127.8, 126.8, 125.2, 124.3, 124.1, 121.9, 120.9, 119.3, 115.4, 61.9, 43.6, 28.3, 14.2. HR-MS: calcd ($\text{M} + \text{Na}^+$) for $\text{C}_{25}\text{H}_{16}\text{F}_6\text{N}_2\text{O}_4$, 545.0912; found 545.0910.

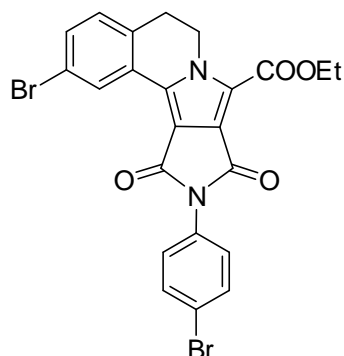


Ethyl 10-(4-bromo-3-methoxyphenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (5i) (Table 2, entry 9): White solid; Yield: 70%; $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 8.54 (d, 1H, J = 7.0 Hz), 8.62 (d, 1H, J = 8.5 Hz), 7.37-7.41 (m, 2H), 7.29 (d, 1H, J = 6.5 Hz), 6.98 (s, 1H), 6.91-6.98 (m, 1H), 4.77 (t, 2H, J = 7.0 Hz), 4.42 (t, 2H, J = 7.0 Hz), 3.91 (s, 3H), 3.19 (d, 2H, J = 6.0 Hz), 1.46 (t, 3H, J = 7.0 Hz); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ = 162.7, 161.3, 159.5, 156.0, 133.6, 133.1, 132.9, 132.4, 130.4, 128.0, 127.9, 127.7, 125.4, 124.9, 120.4, 118.8, 116.0, 111.1, 110.9, 61.7, 56.4, 43.4, 28.3, 14.2.

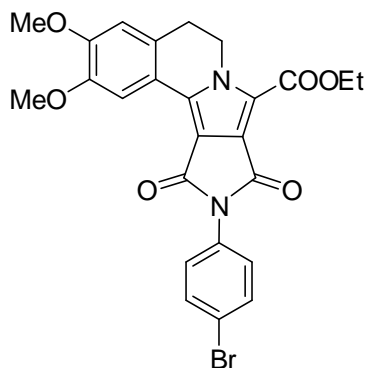


Ethyl 10-benzyl-9,11-dioxo-6,9,10,11-tetrahydro-5H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (5j) (Table 2, entry 10): White solid; Yield: 66%; $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 8.52 (d, 1H, J = 7.5 Hz), 7.44 (d, 2H, J = 7.5 Hz), 7.34-7.41 (m, 3H), 7.31 (t,

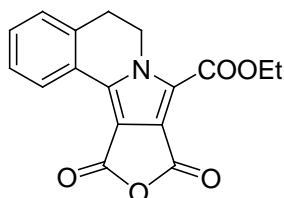
2H, $J = 7.5$ Hz), 7.25 (d, 1H, $J = 8.5$ Hz), 4.80 (s, 2H), 4.72 (t, 2H, $J = 7.0$ Hz), 4.43 (q, 2H, $J = 7.0$ Hz), 3.14 (t, 2H, $J = 6.5$ Hz), 1.48 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 163.8, 162.3, 159.7, 137.1, 133.0, 132.3, 130.2, 128.5, 128.4, 127.9, 127.8, 127.6, 127.5, 125.6, 125.5, 118.3, 116.5, 61.6, 43.3, 41.8, 28.3, 14.2$. HR-MS: calcd ($\text{M} + \text{Na}^+$) for $\text{C}_{24}\text{H}_{20}\text{N}_2\text{O}_4$, 423.1321; found 423.1325.



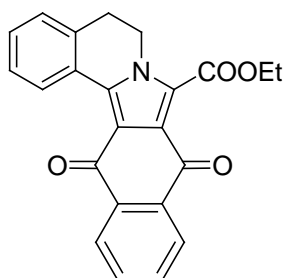
Ethyl 2-bromo-10-(4-bromophenyl)-9,11-dioxo-6,9,10,11-tetrahydro-5H-pyrrolo [3',4':3,4] pyrrolo [2,1-a] isoquinoline-8-carboxylate (5k) (Table 2, entry 11): White solid; Yield: 81%; ^1H -NMR (500 MHz, CDCl_3): $\delta = 8.72$ (d, 1H, $J = 2.0$ Hz), 7.61 (d, 2H, $J = 8.5$ Hz), 7.48-7.62 (m, 1H), 7.31 (d, 2H, $J = 8.5$ Hz), 7.17 (d, 1H, $J = 8.0$ Hz), 4.78 (t, 2H, $J = 7.0$ Hz), 4.43 (q, 2H, $J = 7.0$ Hz), 3.14 (t, 2H, $J = 6.5$ Hz), 1.46 (t, 3H, $J = 7.0$ Hz); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 162.5, 161.0, 159.4, 133.7, 133.2, 131.5, 131.0, 130.4, 129.3, 128.5, 127.2, 121.7, 121.6, 119.3, 61.8, 43.3, 27.9, 14.2$.



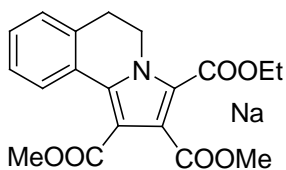
Ethyl 10-(4-bromophenyl)-2,3-dimethoxy-9,11-dioxo-6,9,10,11-tetrahydro-5H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-8-carboxylate (5l) (Table 2, entry 12): Yellow solid; Yield: 72%; ^1H -NMR (500 MHz, CDCl_3): $\delta = 8.23$ (s, 1H), 7.61 (d, 2H, $J = 9.0$ Hz), 7.29 (d, 2H, $J = 9.0$ Hz), 6.78 (s, 1H), 4.75 (t, 2H, $J = 7.0$ Hz), 4.43 (q, 2H, $J = 7.0$ Hz), 3.99 (s, 3H), 3.94 (s, 3H), 1.46 (t, 3H, $J = 7.5$ Hz); ^{13}C NMR (125 MHz, CDCl_3): $\delta = 163.2, 161.3, 159.6, 150.8, 148.6, 132.2, 128.8, 125.7, 124.8, 121.7, 118.6, 110.5, 110.3, 61.6, 56.2, 56.0, 43.6, 27.9, 14.2$.



Ethyl 9,11-dioxo-5,6,9,11-tetrahydrofuro [3',4':3,4] pyrrolo [2,1-a] isoquinoline-8-carboxylate (7a) (Table 3, entry 1): White solid; Yield: 72%; $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 8.35 (d, 1H, J = 5 Hz), 7.42-7.43 (m, 2H), 7.31 (d, 1H, J = 4.5 Hz), 4.81 (t, 2H, J = 7.0 Hz), 4.44 (q, 2H, J = 7.0 Hz), 3.20 (t, 2H, J = 7.0 Hz), 1.47 (t, 3H, J = 7.0 Hz); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ = 159.0, 158.8, 156.9, 134.3, 132.3, 131.1, 128.3, 127.9, 127.7, 124.7, 124.5, 119.4, 119.4, 115.4, 62.0, 43.8, 28.0, 14.1. HR-MS: calcd ($\text{M} + \text{Na}^+$) for $\text{C}_{17}\text{H}_{13}\text{NO}_5$, 334.0691; found 334.0692.



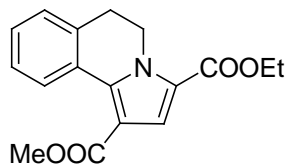
Ethyl 9,14-dioxo-5,6,9,14-tetrahydrobenzo[5,6]isoindolo[1,2-a]isoquinoline-8-carboxylate (7b) (Table 3, entry 2): Yellow solid; Yield: 72%; $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 9.00 (d, 1H, J = 2.5 Hz), 8.30 (dd, 1H, J_1 = 1.5 Hz, J_2 = 7.5 Hz), 8.21-8.23 (m, 1H), 7.67-7.74 (m, 2H), 7.46 (t, 1H, J = 7.0 Hz), 7.39 (t, 1H, J = 7.0 Hz), 7.26-7.28 (m, 1H), 4.55 (q, 2H, J = 7.0 Hz), 4.29 (t, 2H, J = 6.5 Hz), 3.11 (t, 2H, J = 6.5 Hz), 1.50 (t, 3H, J = 7.0 Hz); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ = 179.7, 179.5, 161.4, 135.7, 134.7, 133.6, 133.3, 133.0, 130.1, 128.8, 127.5, 127.4, 126.6, 126.4, 123.2, 117.4, 62.5, 43.2, 29.1, 14.0. HR-MS: calcd ($\text{M} + \text{Na}^+$) for $\text{C}_{23}\text{H}_{17}\text{NO}_4$, 394.1055; found 394.1052.



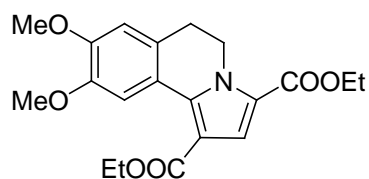
$\text{C}_{19}\text{H}_{19}\text{NNaO}_6$
Exact Mass: 380.1110
Mol. Wt.: 380.3470
m/e: 380.1110 (100.0%),
381.1144 (21.1%), 382.1177
(2.1%), 382.1153 (1.2%)
C, 60.00; H, 5.04; N, 3.68; Na,
6.04; O, 25.24

3-Ethyl 1,2-dimethyl 5,6-dihydropyrrolo [2,1-a] isoquinoline-1,2,3-tricarboxylate (7c) (Table 3, entry 3): White solid; Yield: 68%; $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ = 8.15 (t, 1H, J = 4.5 Hz), 7.31-7.33 (m, 2H), 7.26 (d, 1H, J = 3.5 Hz), 4.55 (t, 2H, J = 6.5 Hz), 4.30 (q, 2H, J = 7.0 Hz), 3.92 (s, 3H), 3.83 (s, 3H), 3.30 (t, 2H, J = 6.5 Hz), 1.35 (t, 3H, J = 7.0 Hz); $^{13}\text{C NMR}$ (125 MHz, CDCl_3): δ = 166.6, 163.8, 159.8, 136.8, 134.3, 129.3, 128.3, 127.4, 127.0, 126.7,

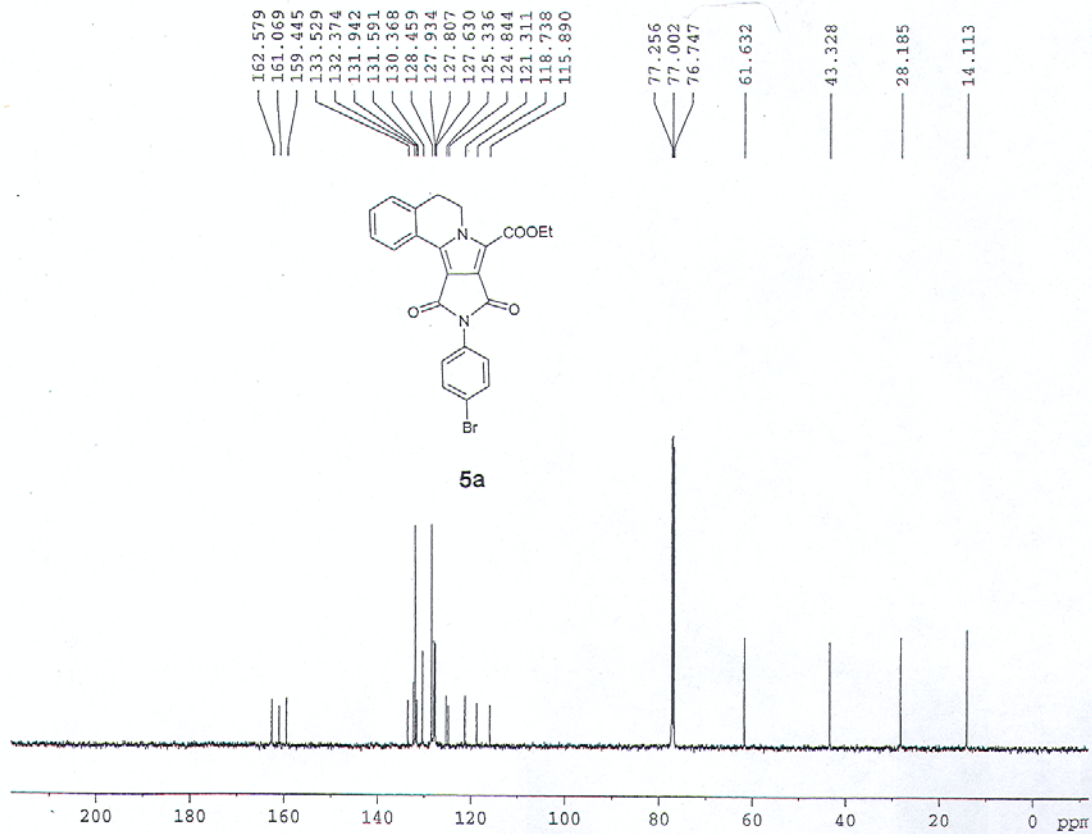
126.3, 119.0, 110.4, 61.1, 52.5, 51.8, 42.5, 29.3, 14.0. HR-MS: calcd ($M + Na^+$) for $C_{19}H_{19}NO_6$, 380.1110; found 380.1111.

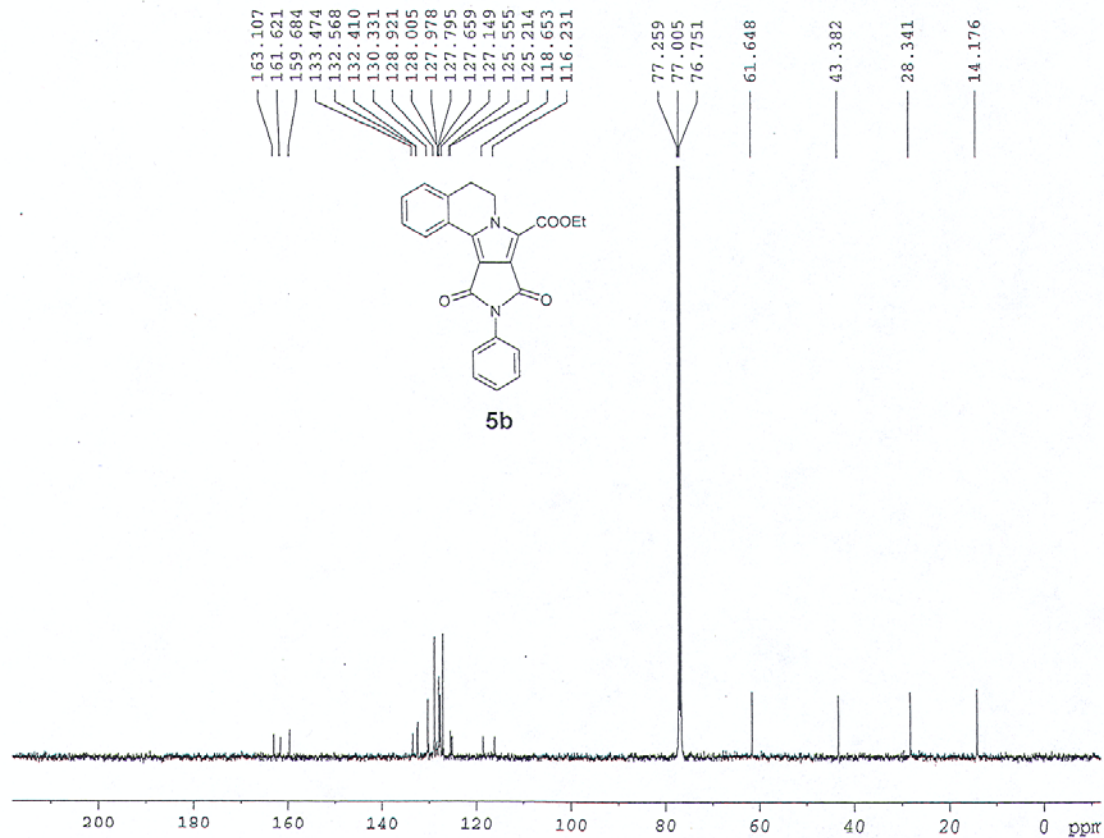
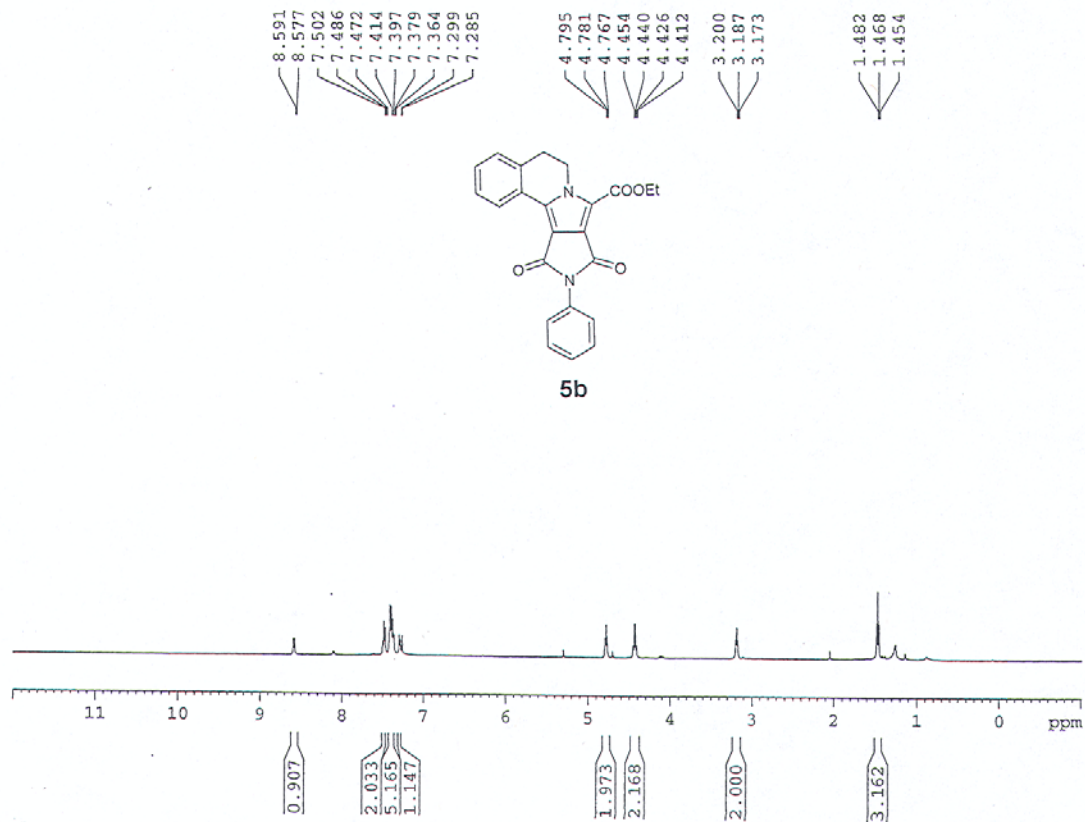


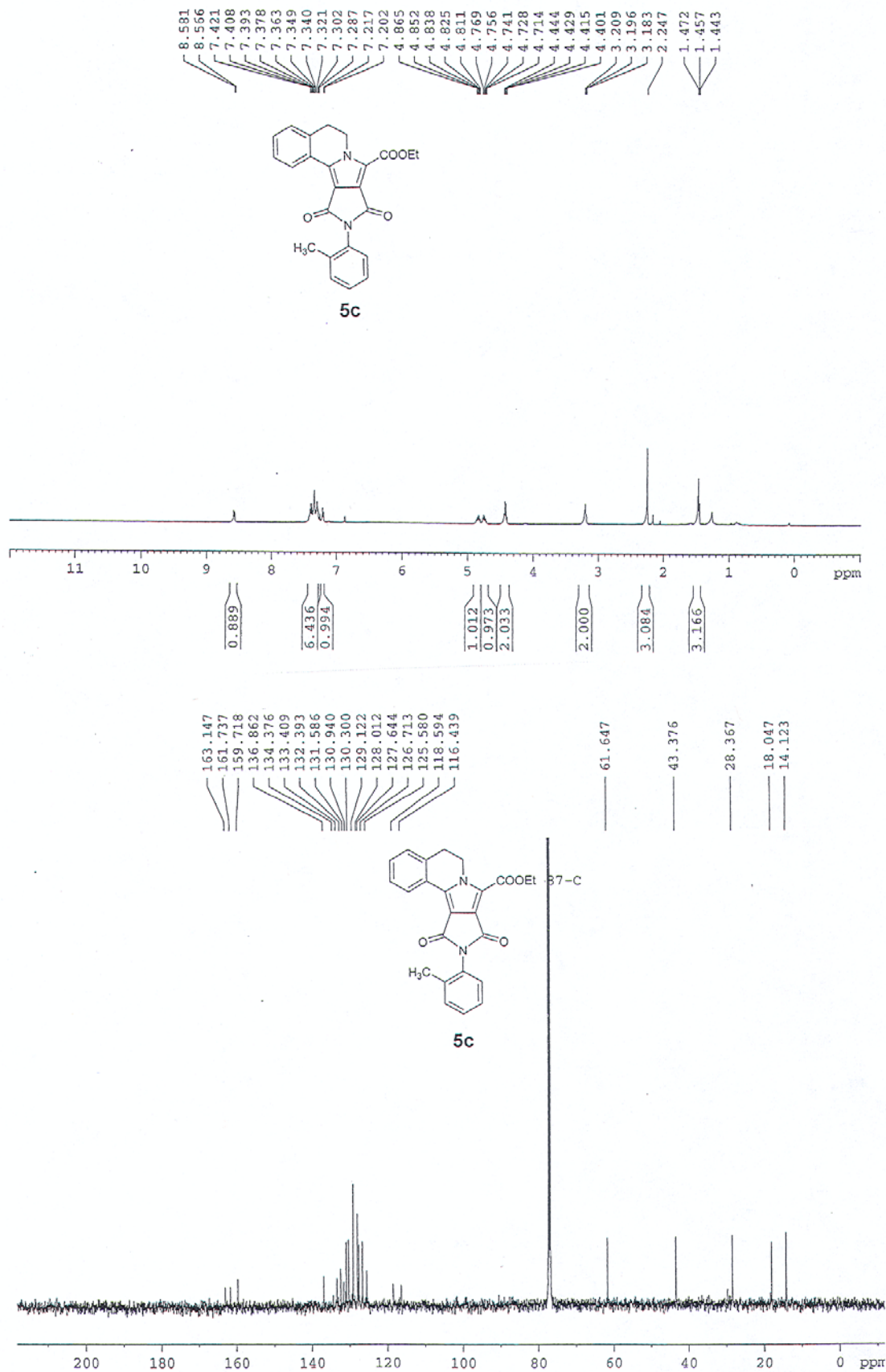
3-Ethyl 1-methyl 5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (7d) (Table 3, entry 4): White solid; Yield: 70%; 1H -NMR (500 MHz, $CDCl_3$): δ = 8.43 (d, 1H, J = 7.5 Hz), 7.49 (s, 1H), 7.28-7.36 (m, 2H), 7.24 (d, 1H, J = 7.5 Hz), 4.60 (t, 2H, J = 6.5 Hz), 4.32 (q, 2H, J = 7.0 Hz), 3.86 (s, 3H), 3.02 (t, 2H, J = 6.5 Hz), 1.38 (t, 3H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.0, 160.9, 137.8, 134.1, 128.9, 128.4, 127.3, 127.1, 127.0, 121.3, 121.1, 111.9, 60.3, 51.4, 42.3, 29.5, 14.4. HR-MS: calcd ($M + Na^+$) for $C_{17}H_{17}NO_4$, 322.1055; found 322.1058.

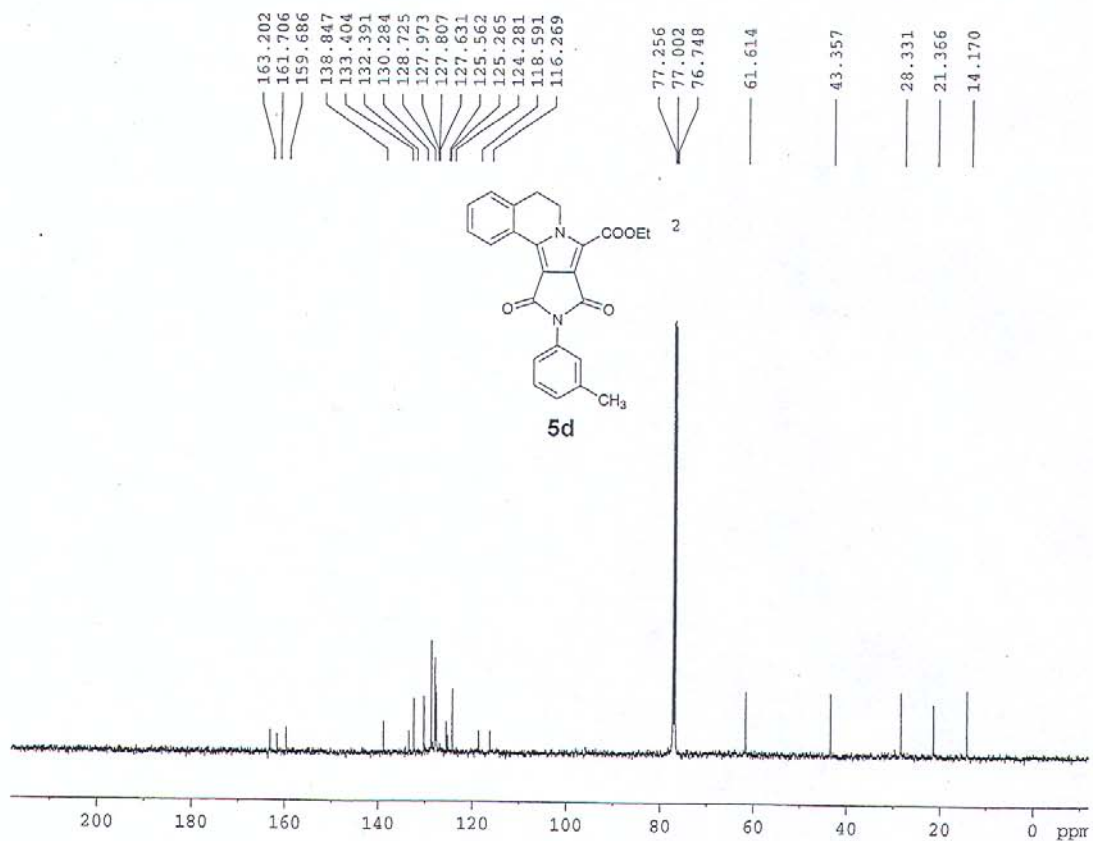
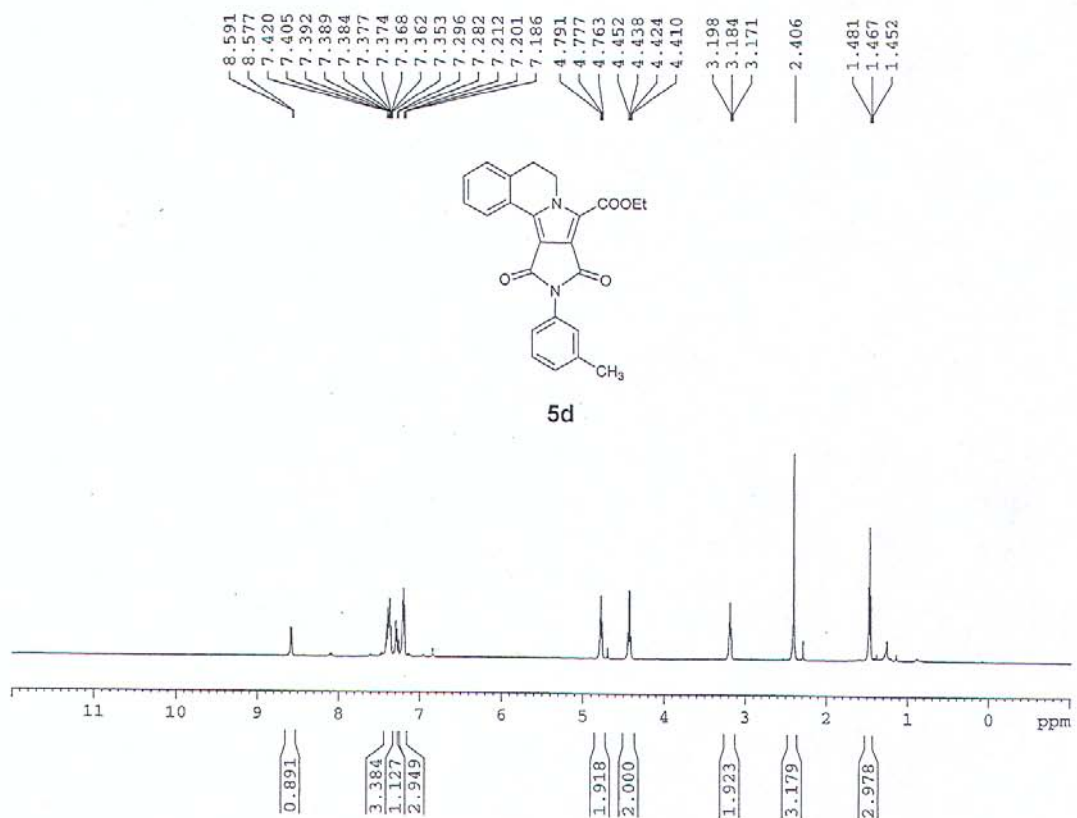


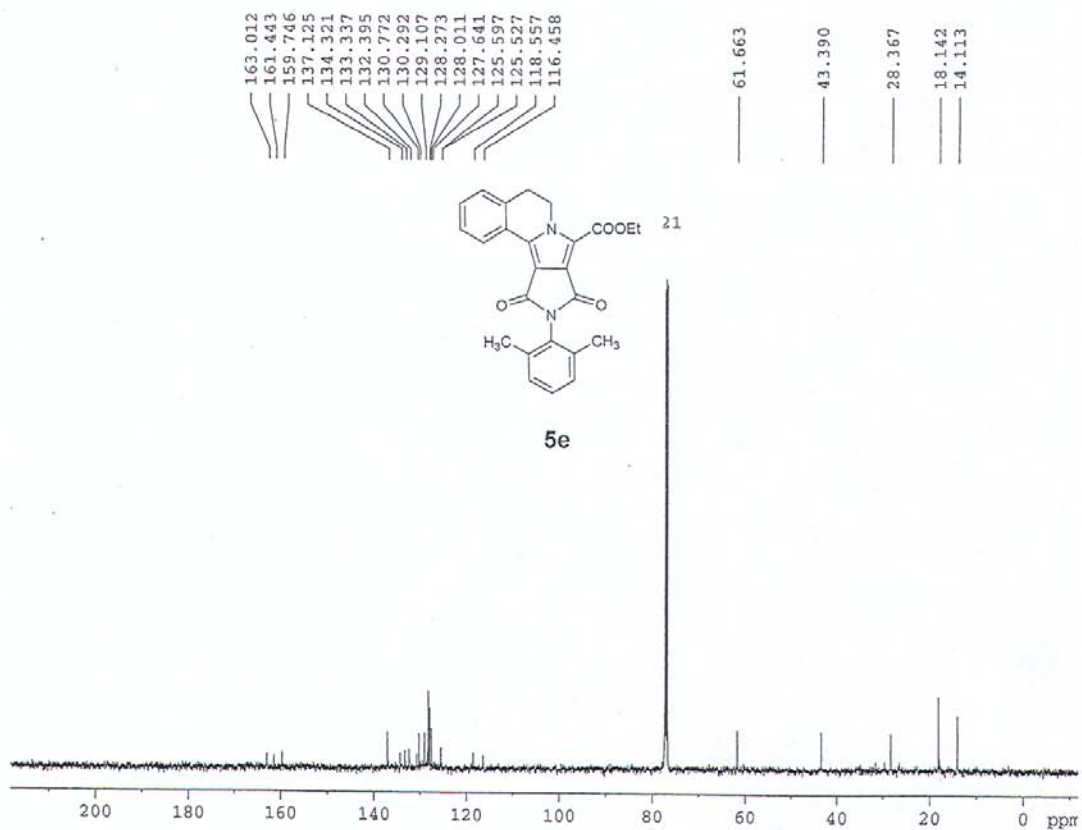
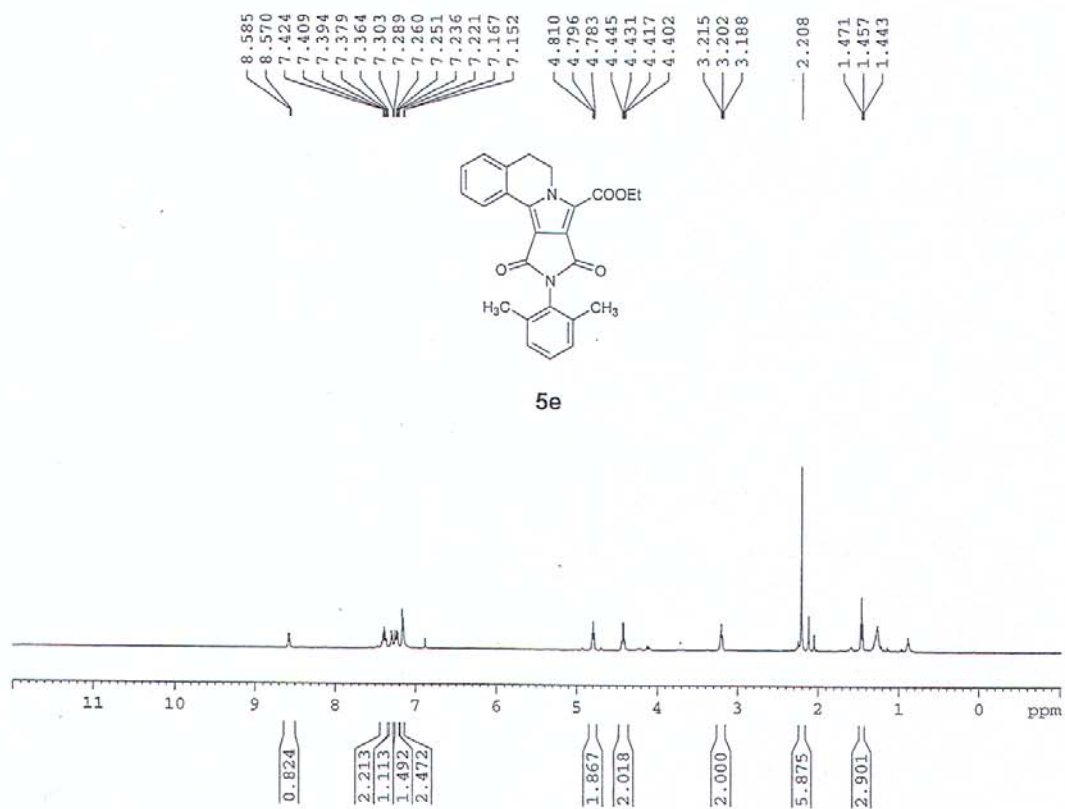
Diethyl 8,9-dimethoxy-5,6-dihydropyrrolo[2,1-a]isoquinoline-1,3-dicarboxylate (7e) (Table 3, entry 5): White solid; Yield: 37%; 1H -NMR (500 MHz, $CDCl_3$): δ = 8.35 (s, 1H), 7.47 (s, 1H), 6.72 (s, 1H), 4.58 (t, 2H, J = 6.5 Hz), 4.30 (q, 4H, J = 7.0 Hz), 3.95 (s, 3H), 3.90 (s, 3H), 2.94 (t, 2H, J = 6.5 Hz), 1.37 (t, 6H, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 164.6, 160.9, 149.4, 147.5, 138.2, 127.2, 121.5, 120.6, 119.9, 112.3, 111.4, 110.2, 60.2, 60.1, 56.1, 55.9, 42.4, 28.9, 14.4, 14.4.

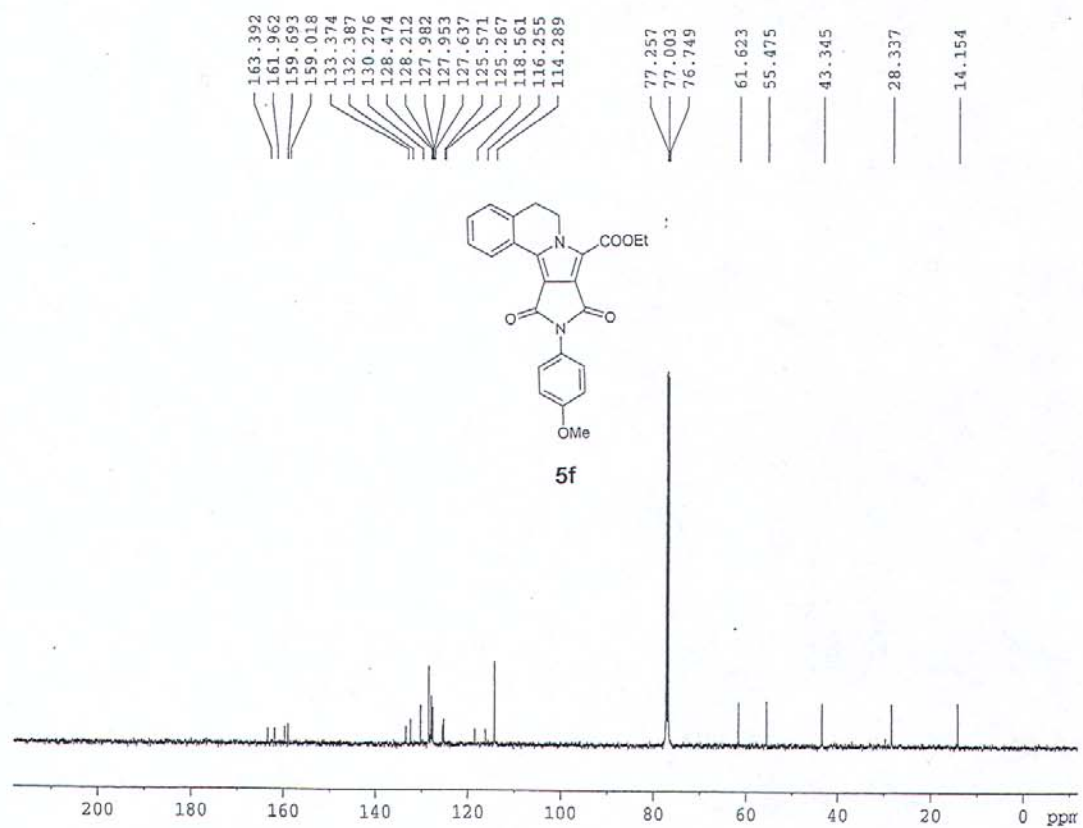
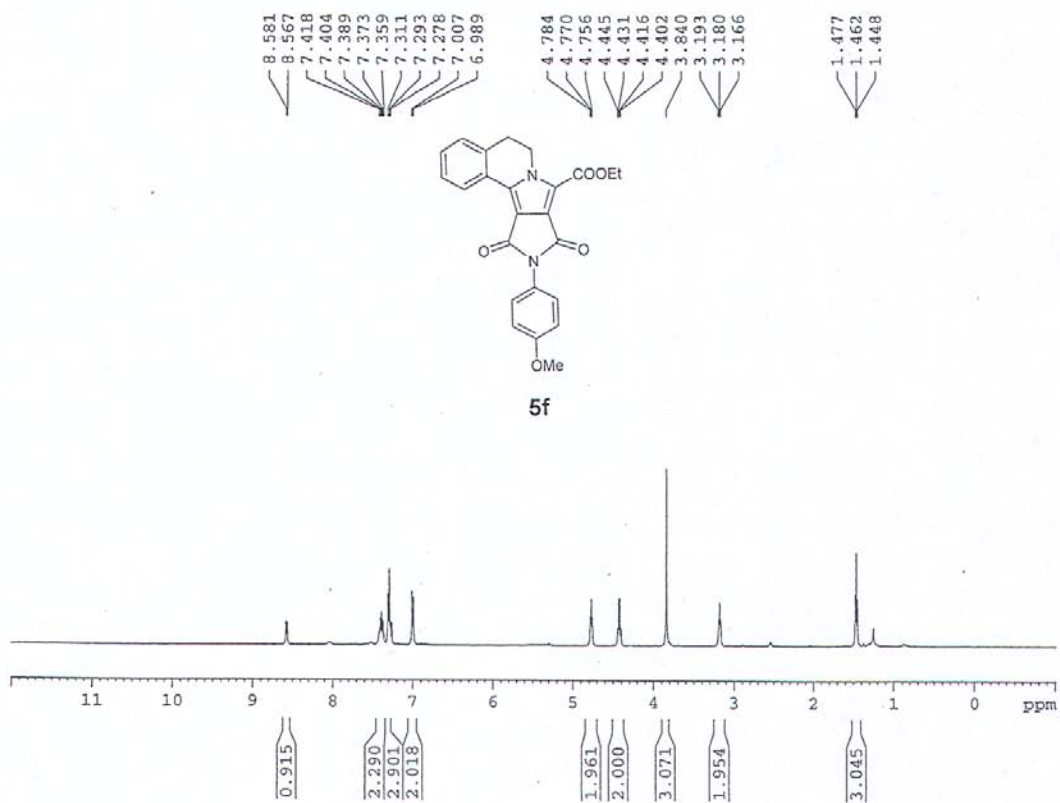




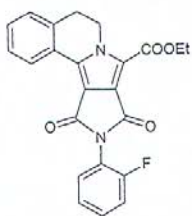




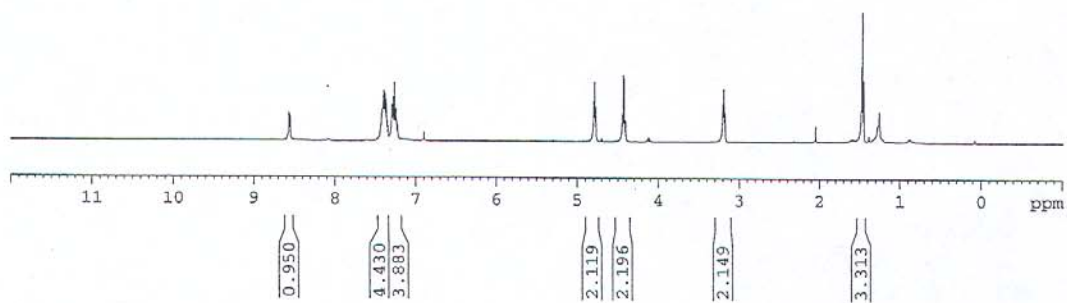




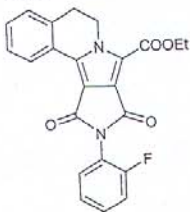
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5g



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14.146



5g

