Support Information

One-pot and catalyst-free synthesis of pyrroloquinolinediones and quinolinedicarboxylates

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Marc Legris, and Wei Zhang*

Content

1. General information

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H-NMR (400 MHz) and ^{13}C-NMR spectra (101 MHz) were recorded on Agilent NMR spectrometers. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in Hertz (Hz). LC-MS were performed on an Agilent 2100 LC with a 6130 quadrupole MS spectrometers. A C18 column (5.0 μm, 6.0 x 50 mm) was used for the separation. The mobile phases were MeOH and H_2O both containing 0.05% CF_3CO_2H. A linear gradient from 25:75 (v/v) MeOH/water to 100% MeOH over 7.0 min at a flow rate of 0.7 mL/min was used as a mobile phase. UV detections were conducted at 210 nm, 254 nm and 365 nm. Low resolution mass spectra were recorded in APCI (atmospheric pressure chemical ionization). Final products were purified on Angela HP-100 pre-LC system with a Venusil PrepG C_{18} column (10 μm, 120 Å, 21.2 mm x 250 mm).

2. General procedure for one-pot synthesis of 1 and 2

A solution of 2-azidebenzaldehyde **3** (1.0 mmol) and *N*-propylmaleimide **4** or dimethyl fumarate **8** (1.1 mmol) in 2.5 mL of CH_3CN was heated under microwaves at 115 ºC for 35 min. The reaction mixture was concentrated and then recrystallized from 3:1 EtOH:H_2O or separated on a semi-prep HPLC with a C_{18} column to afford purified products **1** or **2**.

3. Characterization of products 1 and 2

*2-Methyl-1H-pyrrolo[3,4-b]quinoline-1,3(2H)-dione (**1a**):* white solid (89% yield). MP: 266-268 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (s, 1H), 8.42 (d, J = 8.6 Hz, 1H), 8.06 (dd, J = 8.2, 1.2 Hz, 1H), 7.93 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.82 – 7.65 (m, 1H), 3.33 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 166.1, 150.7, 150.6, 132.8, 132.5, 131.5, 129.9, 129.5, 128.7, 123.0, 24.5. APCIMS m/z: 212.1 (M^+ + 1)

*2-Ethyl-1H-pyrrolo[3,4-b]quinoline-1,3(2H)-dione (**1b**):* white solid (93% yield). MP: 210-212 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.49 – 8.34 (m, 1H), 8.12 – 8.00 (m, 1H), 7.93 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.76 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 3.90 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 165.9, 150.7, 150.6, 132.7, 132.5, 131.5, 129.9, 129.5, 128.7, 123.0, 33.5, 13.8. APCIMS m/z: 226.1 (M^+ + 1)

*2-propyl-1H-pyrrolo[3,4-b]quinoline-1,3(2H)-dione (**1c**):* white solid (90% yield). MP: 183-185 ºC.[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, J = 2.5 Hz, 1H), 8.42 – 8.37 (m, 1H), 8.07 – 8.01 (m, 1H), 7.95 – 7.88 (m, 1H), 7.78 – 7.71 (m, 1H), 3.82 – 3.75 (m, 2H), 1.82 – 1.70 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 166.1, 150.7,150.5, 132.7, 132.6, 131.4, 129.9, 129.5, 128.7, 122.9, 40.1, 21.8, 11.3. APCIMS m/z:

240.1 ($M^+ + 1$)

*2-Cyclohexyl-1H-pyrrolo[3,4-b]quinoline-1,3(2H)-dione (**1d**):* white solid (93% yield). MP: 213-215 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 0.5 Hz, 1H), 8.40 (ddt, J = 8.6, 1.3, 0.7 Hz, 1H), 8.06 – 8.00 (m, 1H), 7.95 – 7.86 (m, 1H), 7.77 – 7.70 (m, 1H), 4.28 (tt, J = 12.3, 3.9 Hz, 1H), 2.28 (qd, J = 12.4, 3.2 Hz, 2H), 1.94 – 1.65 (m, 5H), 1.46 – 1.22 (m, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 166.1, 150.8, 150.4, 132.6, 132.4, 131.4, 129.9, 129.4, 128.8, 122.8, 51.6, 29.7, 25.9, 25.0. APCIMS m/z: 280.1 ($M^+ + 1$)

*2-Benzyl-1H-pyrrolo[3,4-b]quinoline-1,3(2H)-dione (**1e**):* white solid (89% yield). MP: 248-251 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.40 (d, J = 8.4 Hz, 1H), 8.03 (dd, J = 8.2, 1.3 Hz, 1H), 7.92 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.74 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.49 (dt, J = 3.6, 2.1 Hz, 2H), 7.36 – 7.22 (m, 3H), 4.98 (s, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 165.8, 165.7, 150.8, 150.5, 135.8, 132.8, 132.7, 131.5, 129.9, 129.5, 128.8, 128.7, 128.0, 122.9, 42.1. APCIMS m/z: 288.1 ($M^+ + 1$)

*8-Bromo-2-ethyl-1H-pyrrolo[3,4-b]quinoline-1,3(2H)-dione (**1f**):* white solid (83% yield). MP: 172-175 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.08 (d, J = 3.1 Hz, 1H), 8.42 – 8.35 (m, 1H), 8.03 (dd, J = 7.5, 1.0 Hz, 1H), 7.83 – 7.73 (m, 1H), 3.92 (q, J = 7.2 Hz, 2H), 1.40 – 1.32 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 165.4, 151.7, 151.2, 133.3, 132.8, 132.5, 132.3, 128.5, 124.1, 124.0, 33.5, 13.7. APCIMS m/z: 304.0 ($M^+ + 1$)

*7-Bromo-2-ethyl-1H-pyrrolo[3,4-b]quinoline-1,3(2H)-dione (**1g**):* white solid (93% yield). MP: 287-289 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.27 (d, J = 9.0 Hz, 1H), 8.21 (d, J = 2.2 Hz, 1H), 7.99 (dd, J = 9.0, 2.2 Hz, 1H), 3.90 (q, J = 7.2 Hz, 2H), 1.39 – 1.29 (m, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 165.7, 165.3, 150.8, 149.3, 136.2, 132.8, 131.8, 131.3, 129.8, 124.0, 123.8, 33.7, 13.8. APCIMS m/z: 304.0 ($M^+ + 1$)

*2-Benzyl-7-bromo-1H-pyrrolo[3,4-b]quinoline-1,3(2H)-dione (**1h**):* white solid (92% yield). MP: 281-283 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 – 8.52 (m, 1H), 8.27 (d, J = 9.0 Hz, 1H), 8.21 (d, J = 2.2 Hz, 1H), 7.99 (dd, J = 9.0, 2.2 Hz, 1H), 7.52 – 7.46 (m, 2H), 7.36 – 7.27 (m, 3H), 4.99 (s, 2H).^{13}C NMR (101 MHz, $CDCl_3$) δ 165.5, 165.2, 150.6, 149.4, 136.3, 135.6, 132.8, 131.8, 131.5, 130.5, 129.8, 129.6, 128.9, 128.8, 128.1, 124.1, 123.7, 42.2. APCIMS m/z: 366.0 ($M^+ + 1$)

*7-Chloro-2-ethyl-1H-pyrrolo[3,4-b]quinoline-1,3(2H)-dione (**1i**):* white solid (89% yield). MP: 276-278 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 – 8.54 (m, 1H), 8.37 – 8.31 (m, 1H), 8.05 – 8.01 (m, 1H), 7.89 – 7.83 (m, 1H), 3.89 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 165.6, 150.6, 148.9, 135.8, 133.6, 132.8, 131.4, 129.4, 128.4, 123.8, 24.2. APCIMS m/z: 260.1 ($M^+ + 1$)

*7-Propyl-6H-[1,3]dioxolo[4,5-g]pyrrolo[3,4-b]quinoline-6,8(7H)-dione (**1j**):* white solid (81% yield). MP: 201-203 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.65 – 7.62 (m, 1H), 7.26 – 7.22 (m, 1H), 6.22 (d, J = 1.4 Hz, 2H), 3.77 – 3.71 (m, 2H), 1.79 – 1.68 (m, 2H), 0.96 (td, J = 7.4, 1.3 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 166.6, 153.3, 150.3, 149.9, 148.8, 130.4, 126.7, 121.9, 107.6, 104.6, 102.8, 39.9, 21.9, 11.3. APCIMS m/z: 284.1

($M^+ + 1$)

*7-Ethyl-6H-[1,3]dioxolo[4,5-g]pyrrolo[3,4-b]quinoline-6,8(7H)-dione (**1k**):* white solid (85% yield). MP: 273-276 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 – 8.38 (m, 1H), 7.65 (s, 1H), 7.25 (s, 1H), 6.22 (s, 2H), 3.85 (q, J = 7.2 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 166.4, 153.3, 150.3, 149.9, 148.9, 130.4, 126.7, 122.0, 107.7, 104.6, 102.8, 33.3, 13.9. APCIMS m/z: 270.1 ($M^+ + 1$)

*2-Ethyl-5-(trifluoromethyl)-1H-pyrrolo[3,4-b]quinoline-1,3(2H)-dione (**1l**):* white solid (75% yield). MP: 180-182 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.32 – 8.22 (m, 2H), 7.87 – 7.79 (m, 1H), 3.91 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 164.4, 151.3, 147.3, 133.9, 132.6, 132.4, 129.1, 128.4, 124.6, 123.8, 121.9, 33.8, 13.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -59.9. APCIMS m/z: 294.1 ($M^+ + 1$)

*Dimethyl 7-methoxyquinoline-2,3-dicarboxylate (**2a**):* white solid (83% yield). MP: 132-134 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (dd, J = 3.6, 2.9 Hz, 1H), 7.83 – 7.74 (m, 1H), 7.50 (t, J = 8.2 Hz, 1H), 7.28 (tdd, J = 6.5, 4.5, 2.1 Hz, 1H), 4.04 (ddd, J = 3.6, 1.9, 0.8 Hz, 3H), 3.98 – 3.91 (m, 6H).^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 165.6, 163.2, 151.2, 150.3, 139.1, 129.7, 122.2, 119.7, 107.5, 55.8, 53.2, 52.7. APCIMS m/z: 275.1 ($M^+ + 1$)

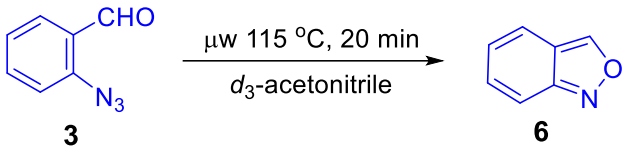
*Dimethyl [1,3]dioxolo[4,5-g]quinoline-6,7-dicarboxylate (**2b**):* white solid (75% yield). MP: 178-179 ºC.[2] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, J = 1.7 Hz, 1H), 7.44 (s, 1H), 7.11 (d, J = 1.5 Hz, 1H), 6.20 – 6.10 (m, 2H), 4.03 – 3.99 (m, 3H), 3.95 – 3.91 (m, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 167.3, 165.8, 153.2, 149.6, 148.5, 147.0, 137.5, 124.7, 120.8, 106.1, 103.2, 102.5, 53.1, 52.8. APCIMS m/z: 289.0 ($M^+ + 1$)

*Dimethyl quinoline-2,3-dicarboxylate (**2c**):* white solid (89% yield). MP: 107-108 ºC.[3] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, J = 0.5 Hz, 1H), 8.23 – 8.17 (m, 1H), 7.96 – 7.90 (m, 1H), 7.89 – 7.82 (m, 1H), 7.70 – 7.63 (m, 1H), 4.05 (s, 3H), 3.97 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 167.11, 165.5, 150.5, 148.0, 139.5, 132.4, 129.8, 128.7, 128.6, 127.0, 122.3, 53.2, 52.9. APCIMS m/z: 245.1 ($M^+ + 1$)

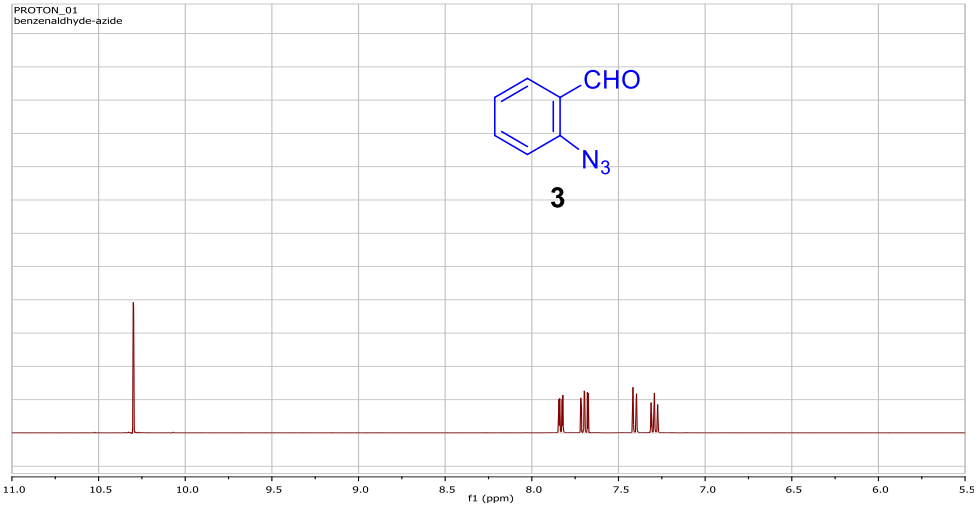
*Dimethyl 6-bromoquinoline-2,3-dicarboxylate (**2d**):* white solid (90% yield). MP: 156-158 ºC.[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.09 (dd, J = 9.9, 5.6 Hz, 2H), 7.93 (dd, J = 9.0, 2.2 Hz, 1H), 4.05 (s, 3H), 3.99 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 165.2, 150.7, 146.6, 138.3, 135.9, 131.4, 130.5, 128.1, 123.3, 123.0, 53.3, 53.0. APCIMS m/z: 323.0 ($M^+ + 1$)

*Dimethyl 6-chloroquinoline-2,3-dicarboxylate (**2e**):* white solid (87% yield). MP: 153-155 ºC.[4] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (t, J = 7.5 Hz, 1H), 8.22 – 8.11 (m, 1H), 7.95 – 7.73 (m, 1H), 7.53 – 7.48 (m, 1H), 4.05 (s, 3H), 3.99 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 165.5, 150.5, 146.3, 140.8, 138.5, 133.4, 131.8, 130.5, 127.9, 125.2, 53.3, 53.1. APCIMS m/z: 279.0 ($M^+ + 1$)

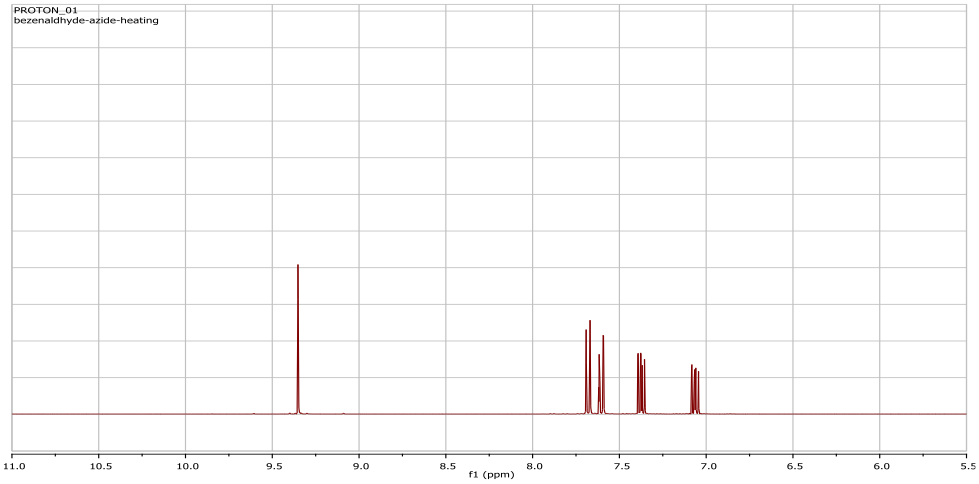
4. ^{1}H-NMR spectra for azidobenzaldehyde **3** and benzisoxazole **6**



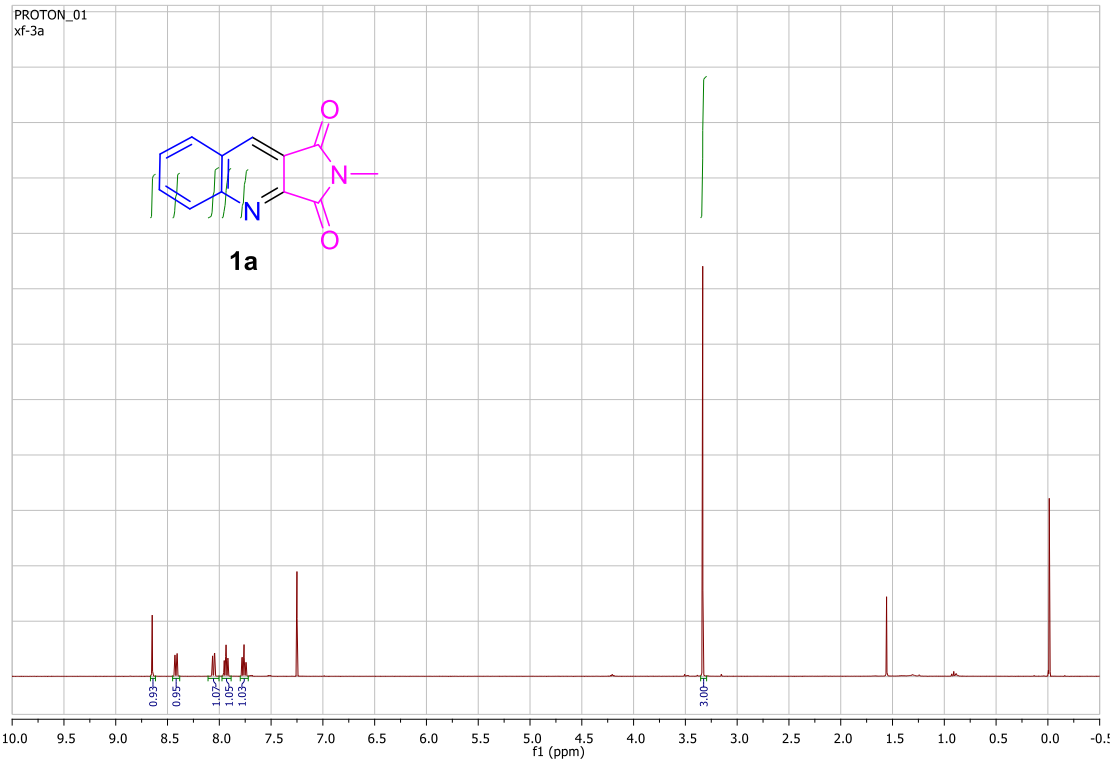
3 **6**

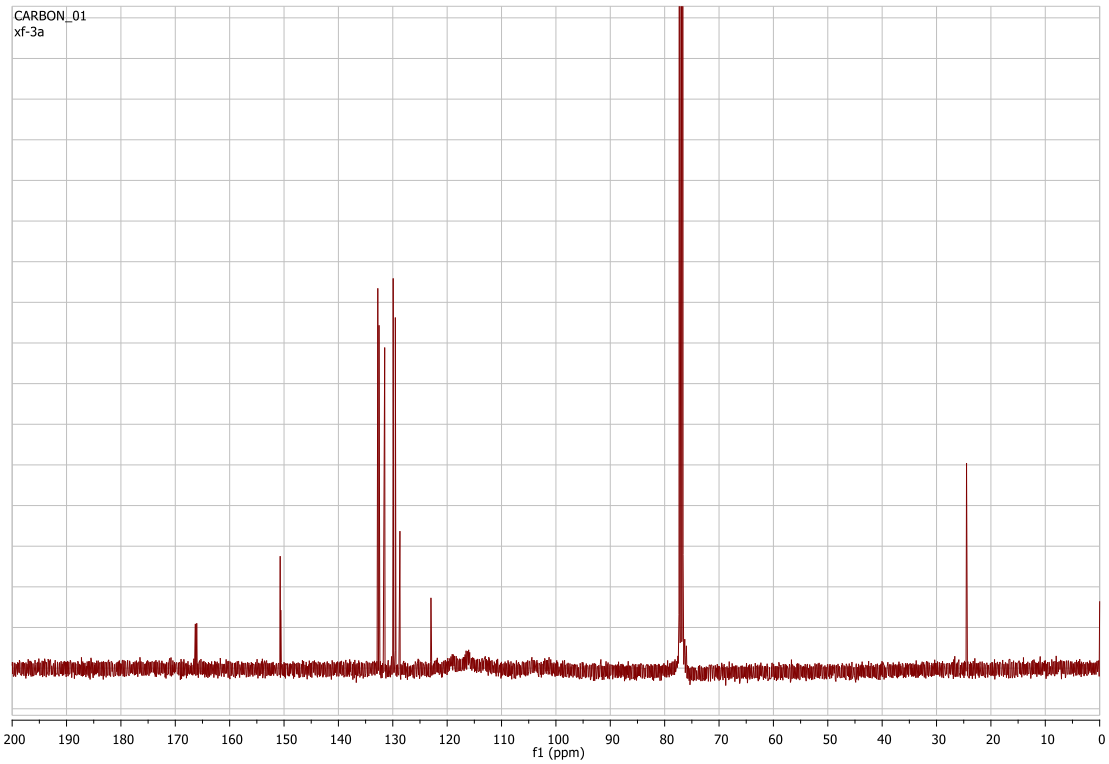


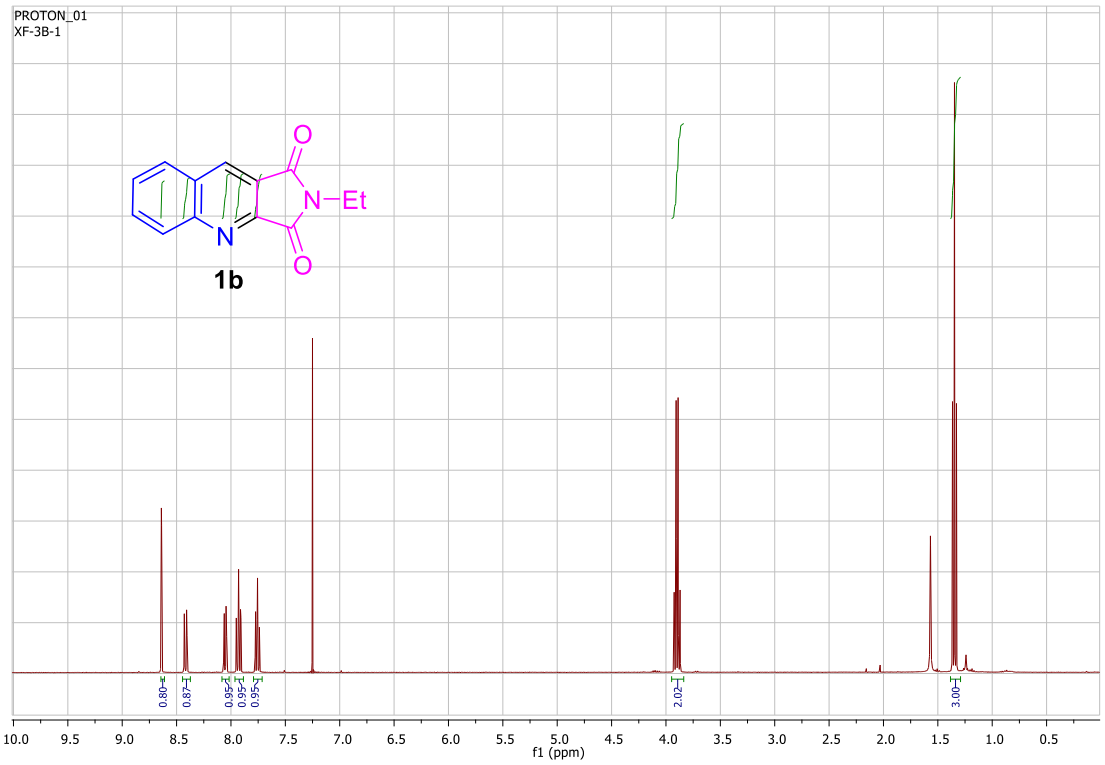
3



5. NMR Spectra of Products



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N
O
1b
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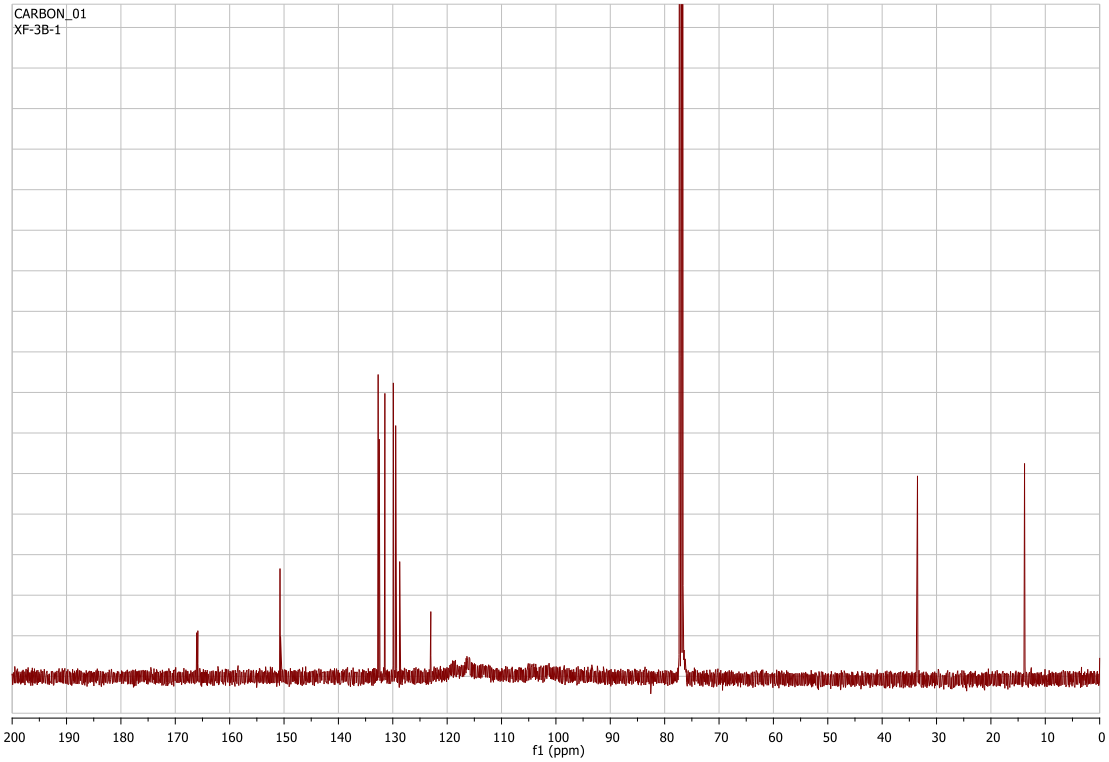
0.87
0.95
0.95
0.95
2.02
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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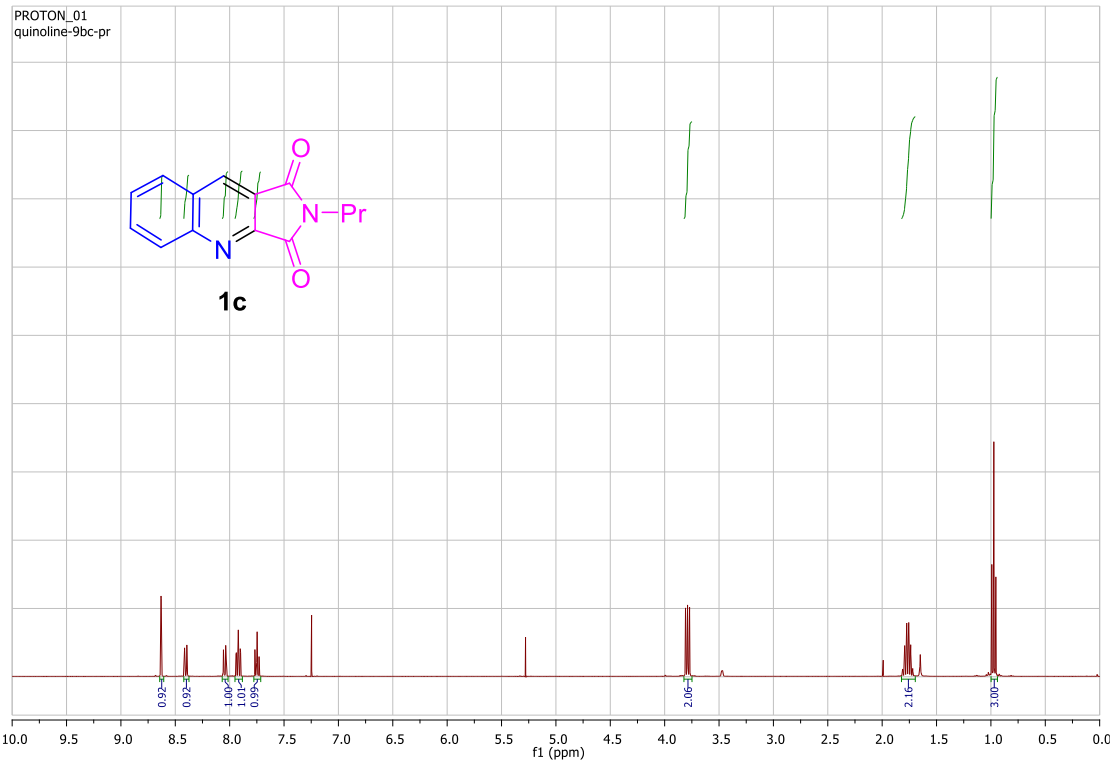
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O
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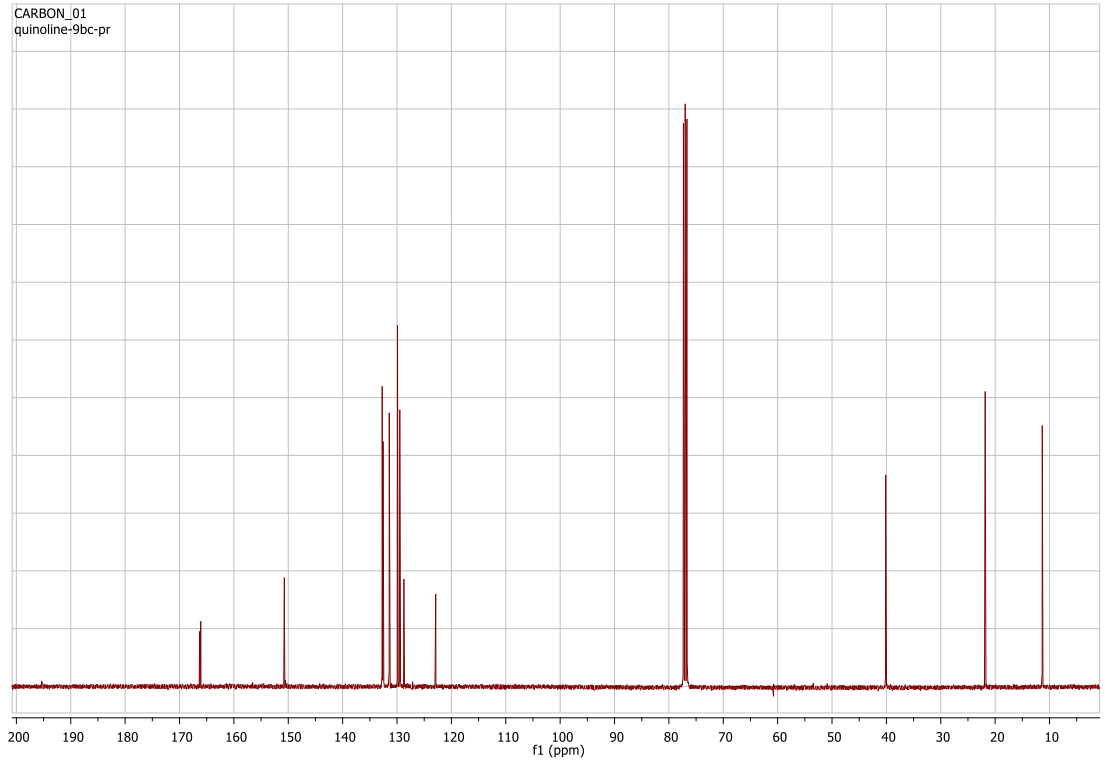
1.01
0.99
2.06
2.16
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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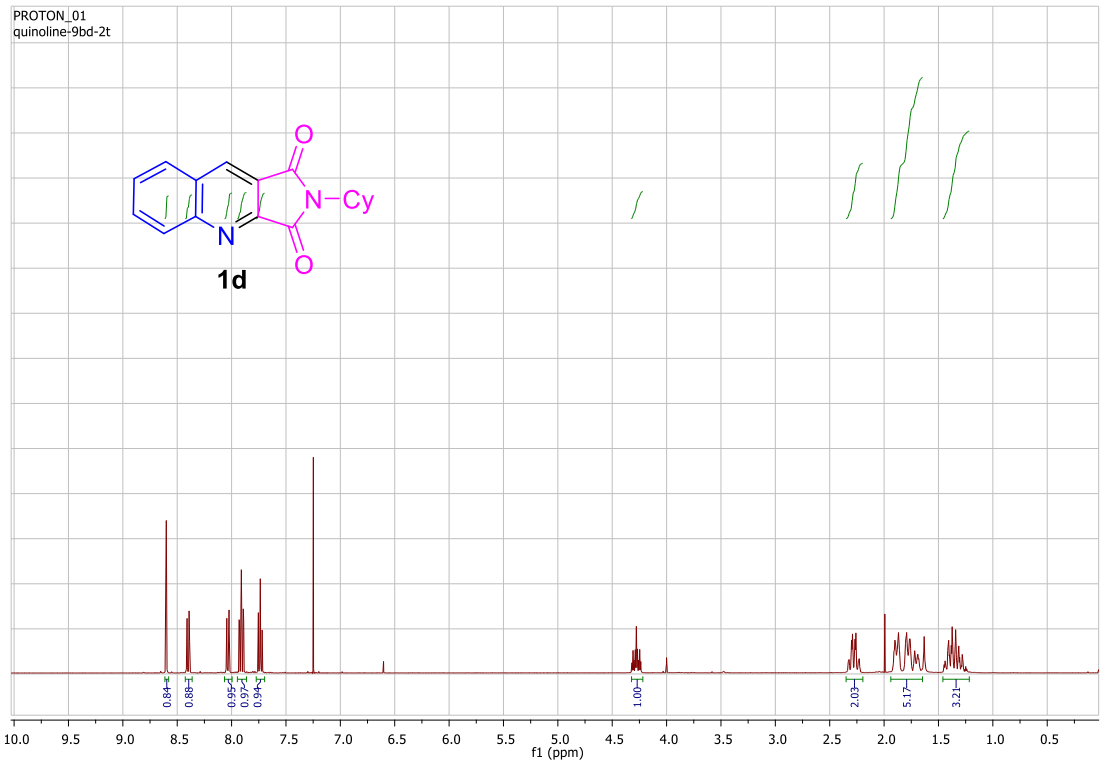
f1 (ppm)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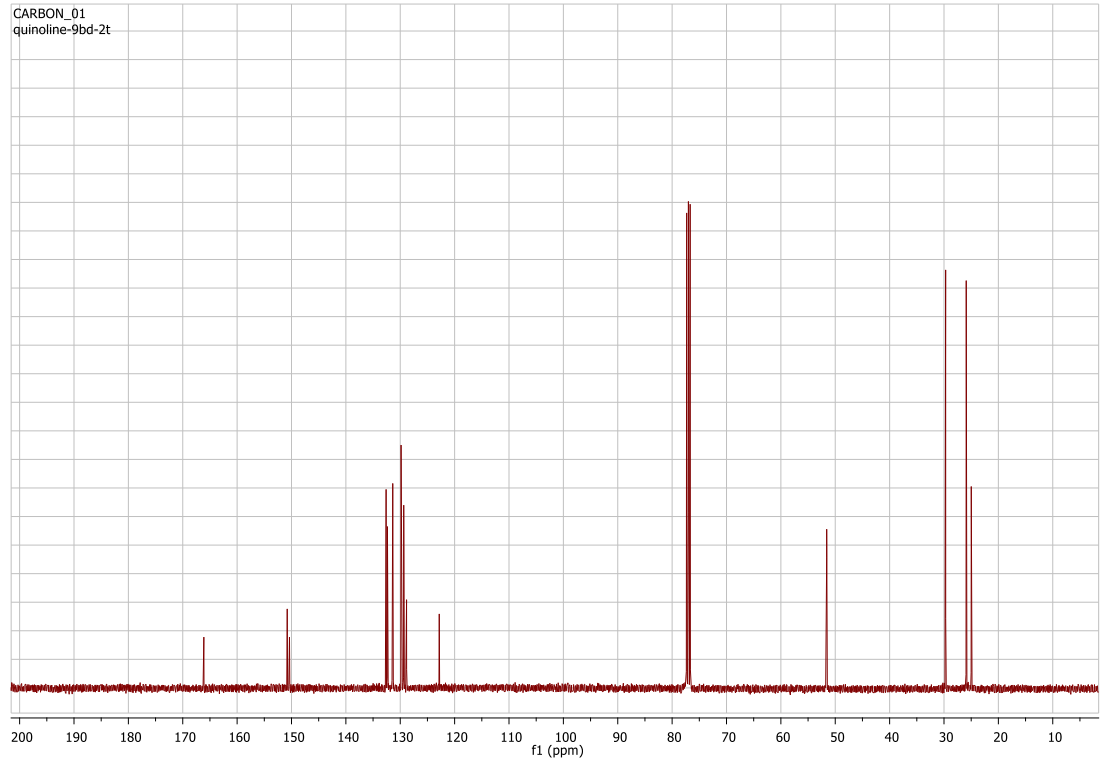
0.95
0.97
0.94
1.00
2.03
5.17
3.21
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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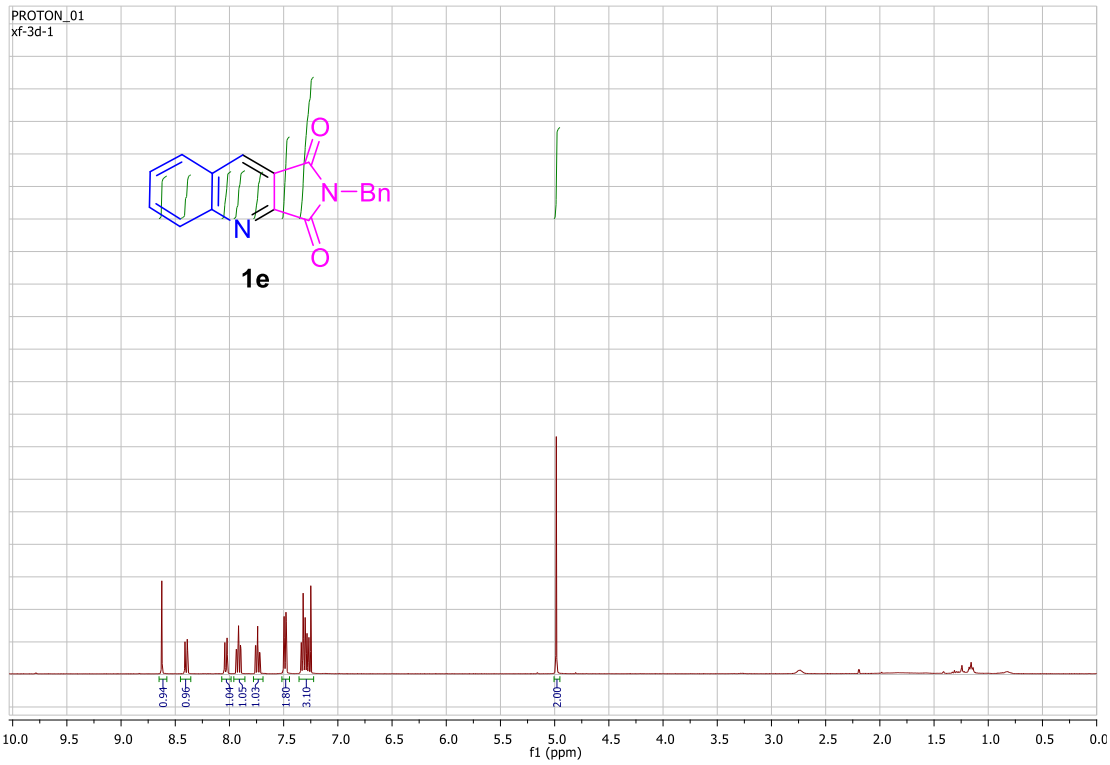
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N
O
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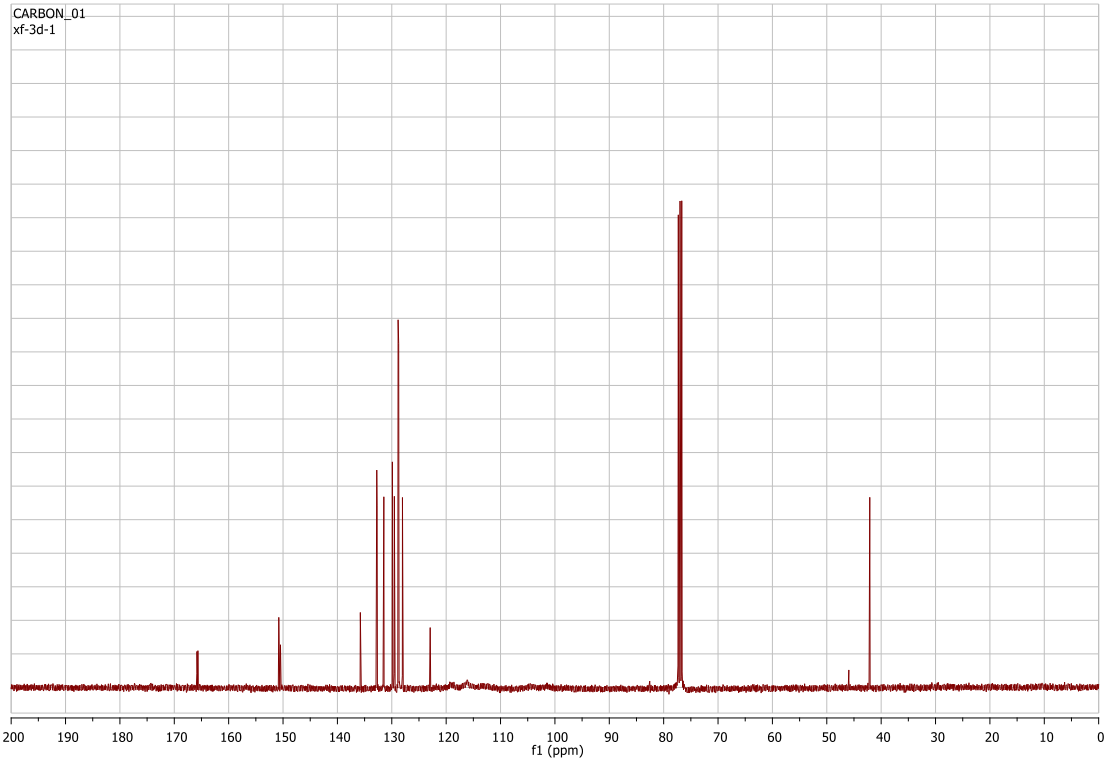
0.96
1.04
1.05
1.03
1.80
3.10
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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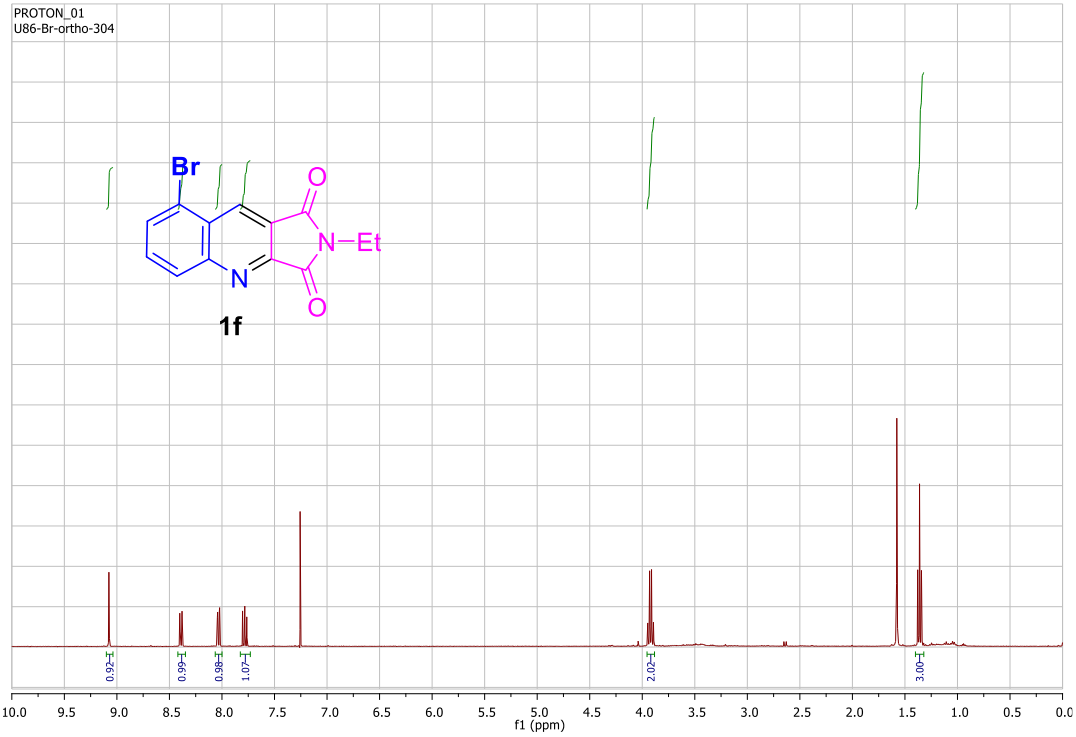
f1 (ppm)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U86-Br-ortho-304
Br
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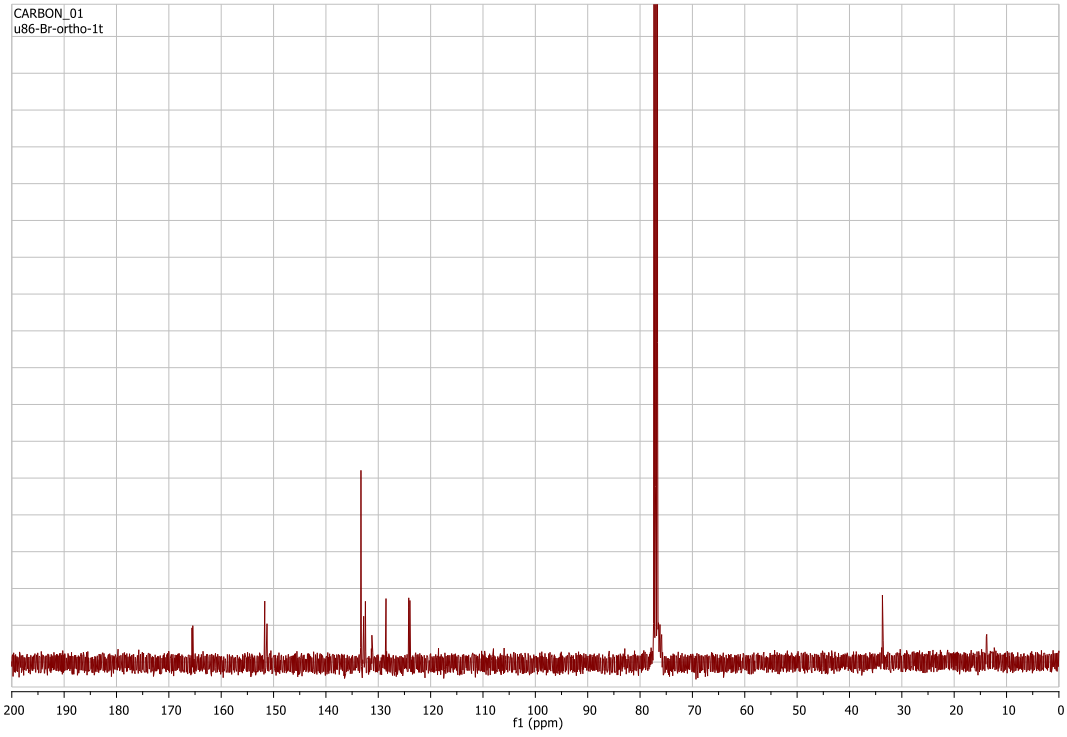
N–Et
N
O
1f
0.92
0.99
0.98
1.07
2.02
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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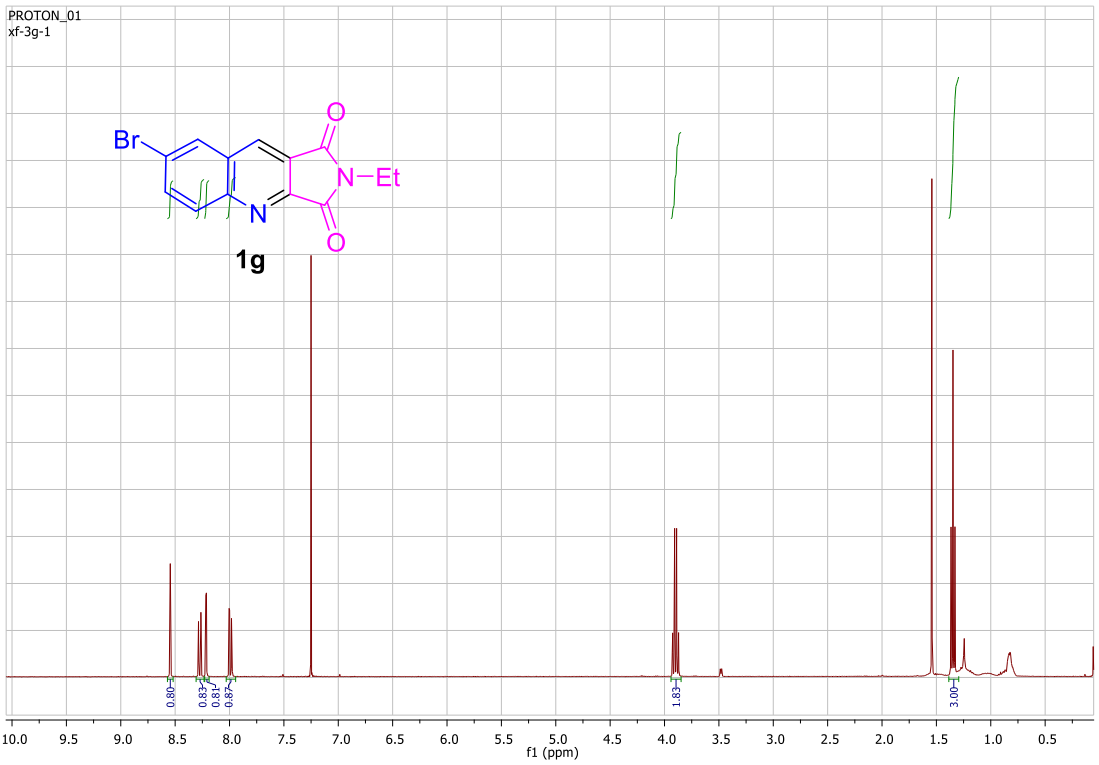
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Br
O
N–Et
N
O
1g
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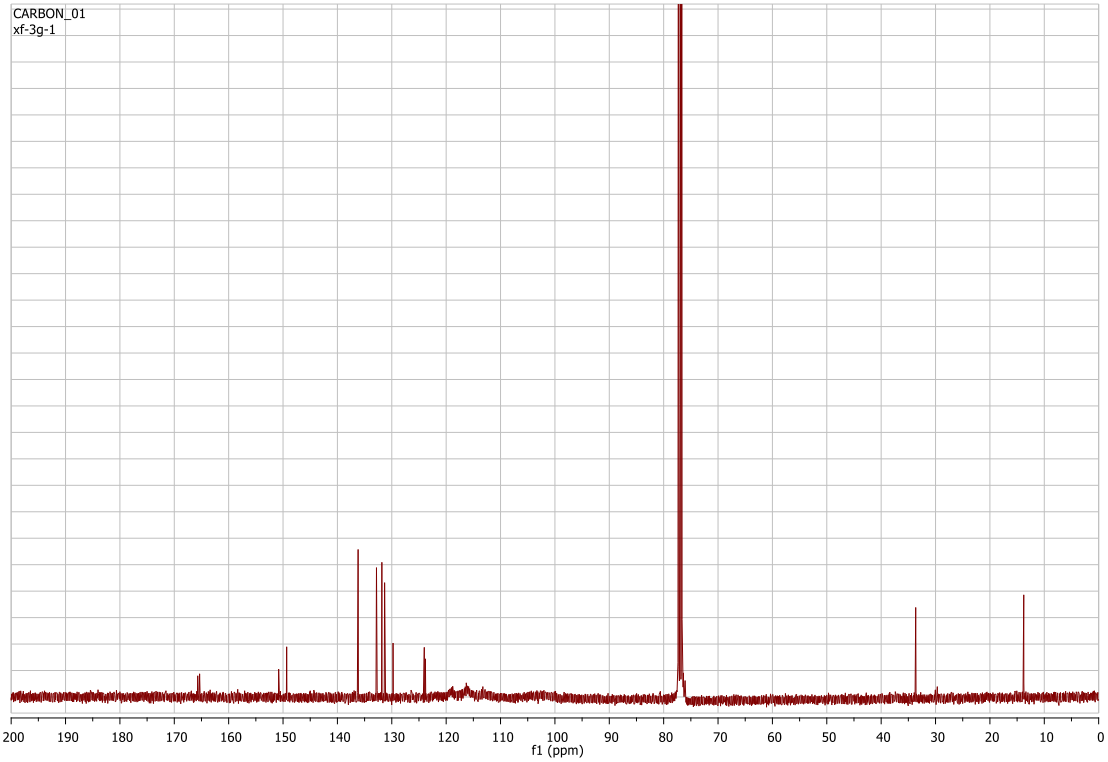
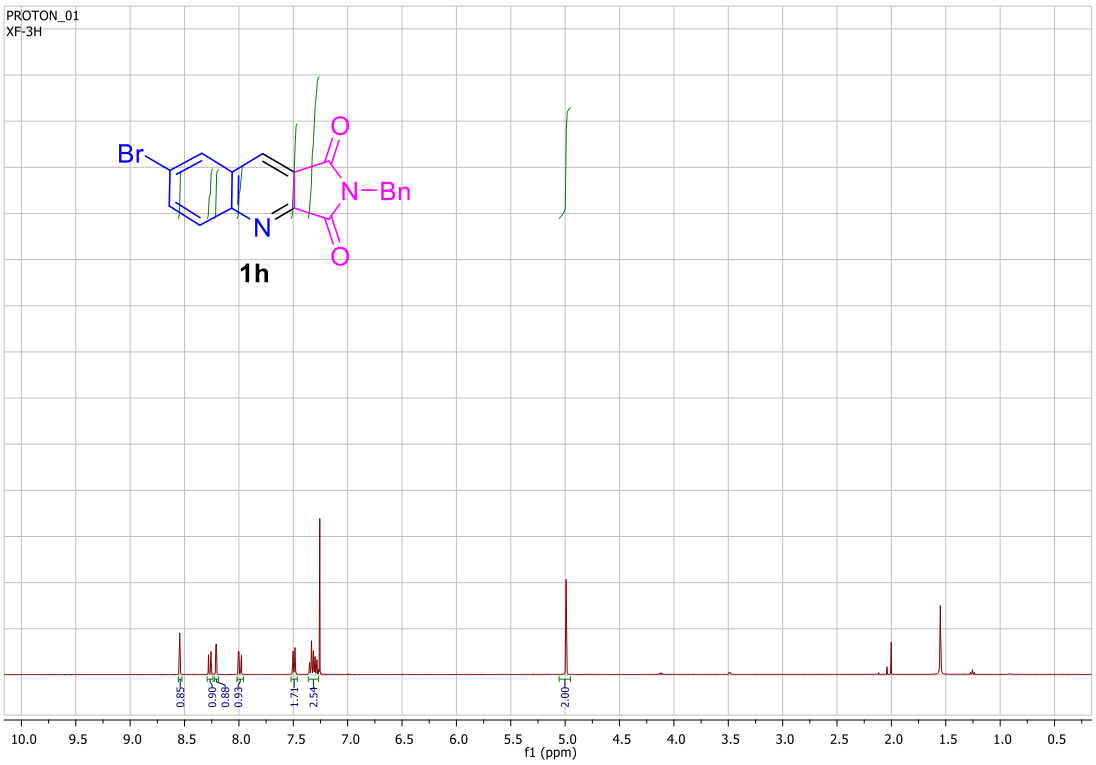
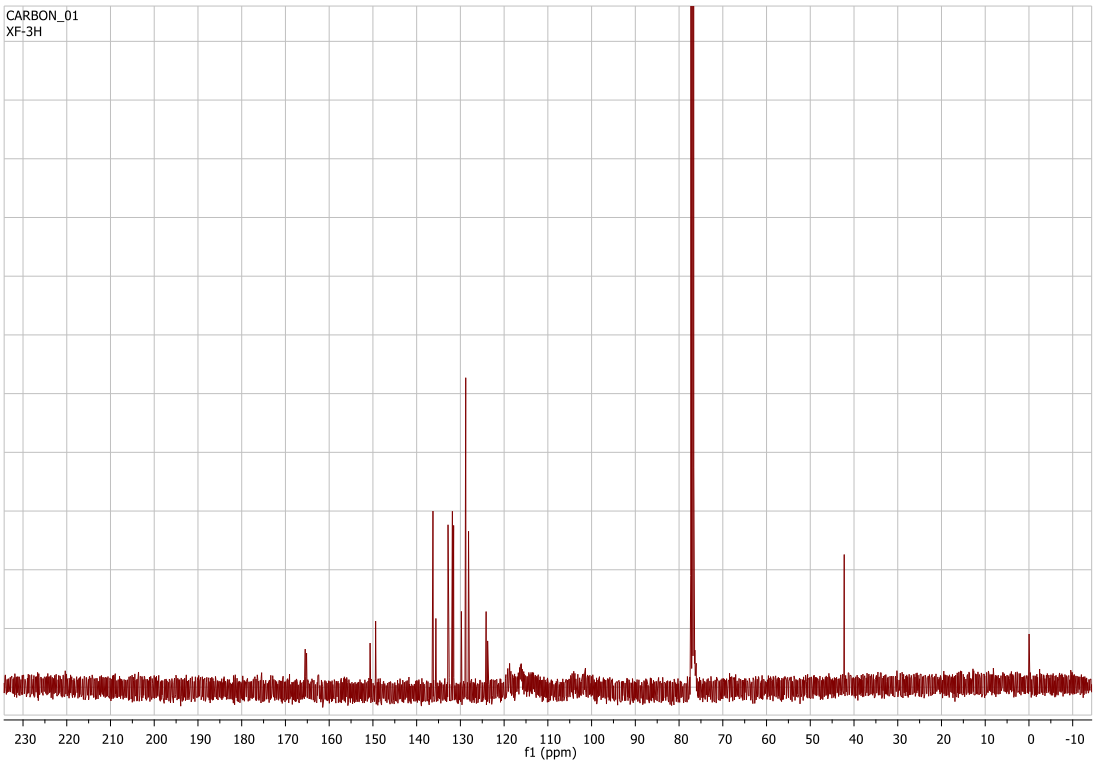
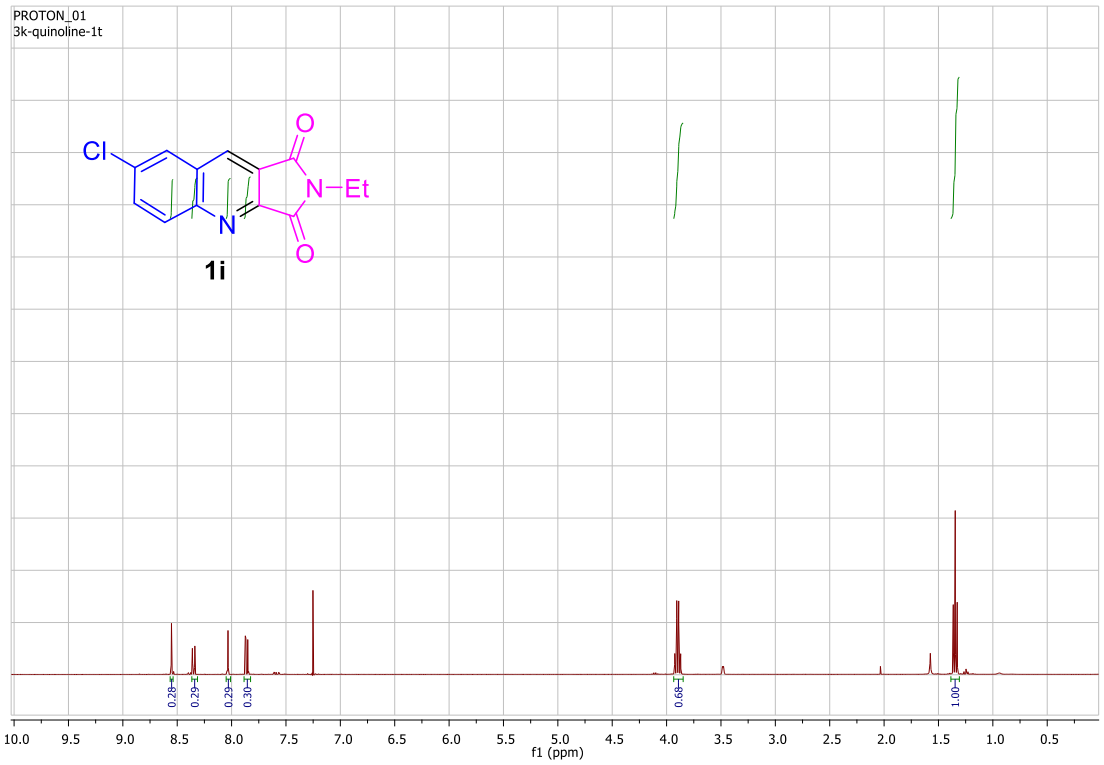
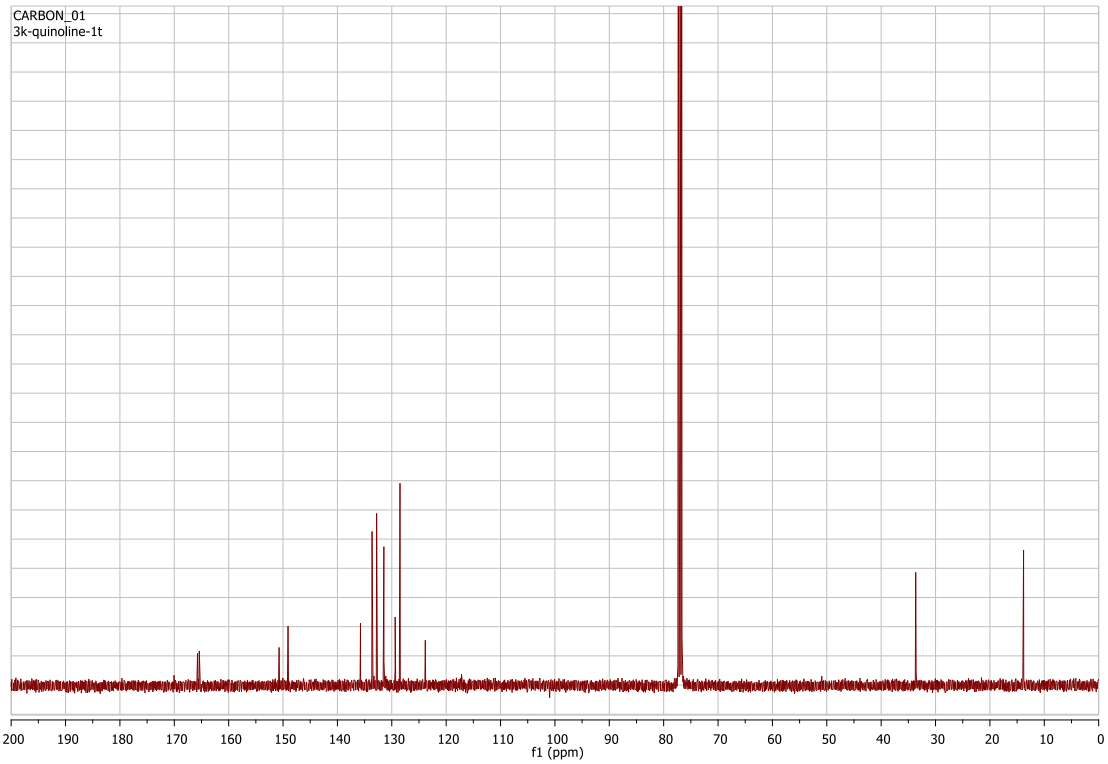
0.83
0.81
0.87
1.83
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

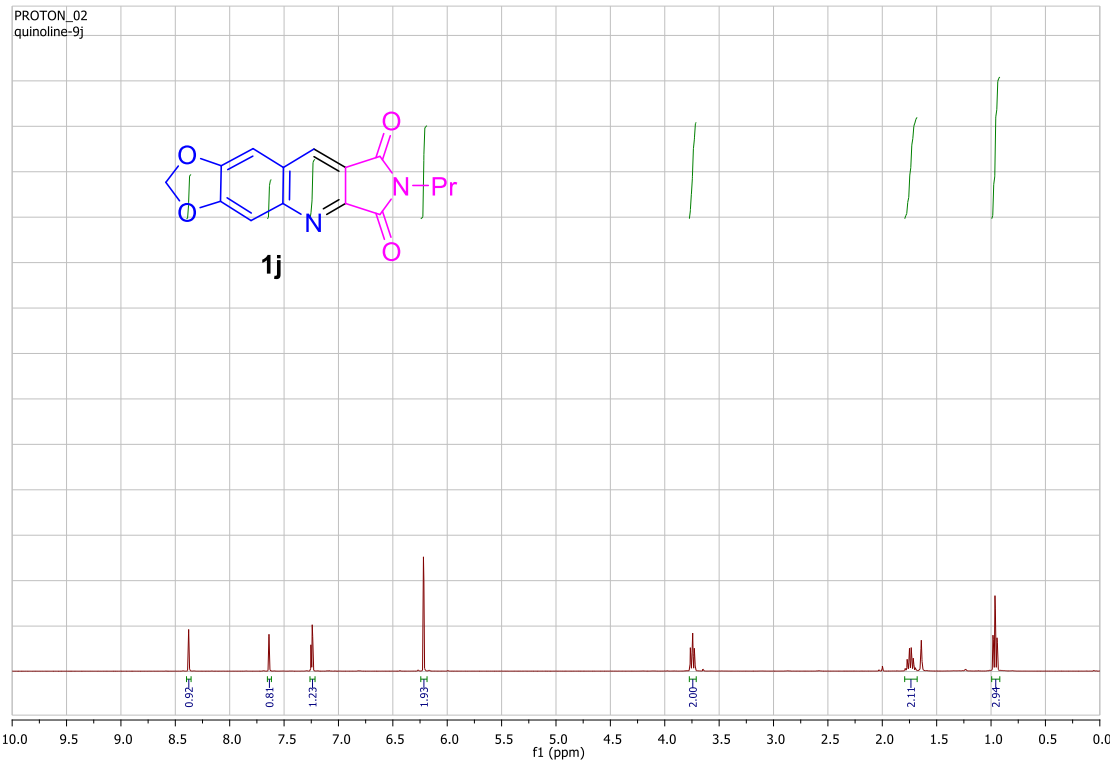

CARBON_01
xf-3g-1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

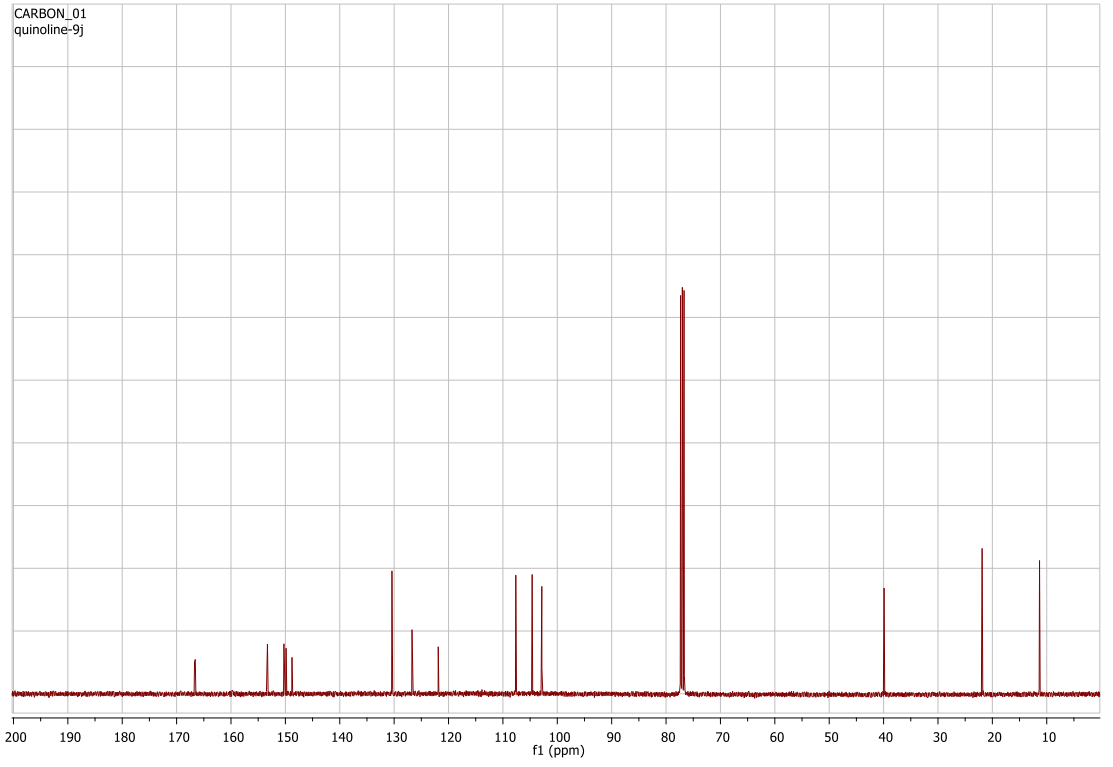

PROTON_01
XF-3H
Br
O
N–Bn
N
O
1h
0.85
0.90
0.89
0.93
1.71
2.54
2.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

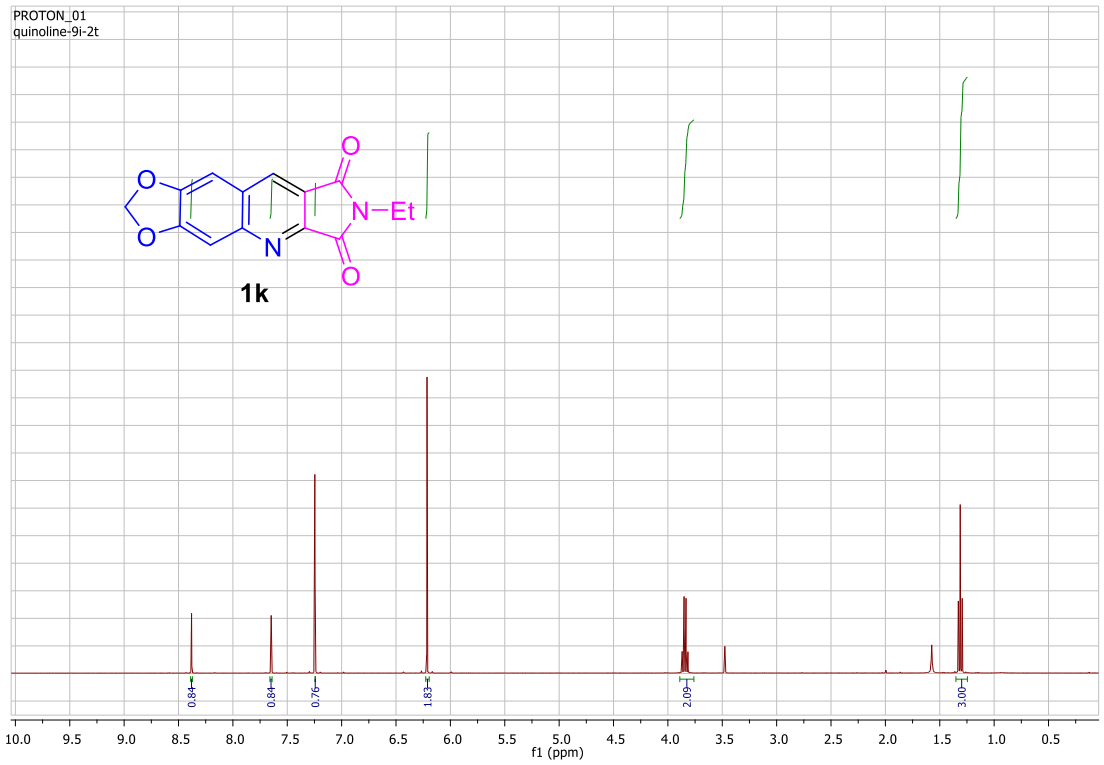

CARBON_01
XF-3H
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

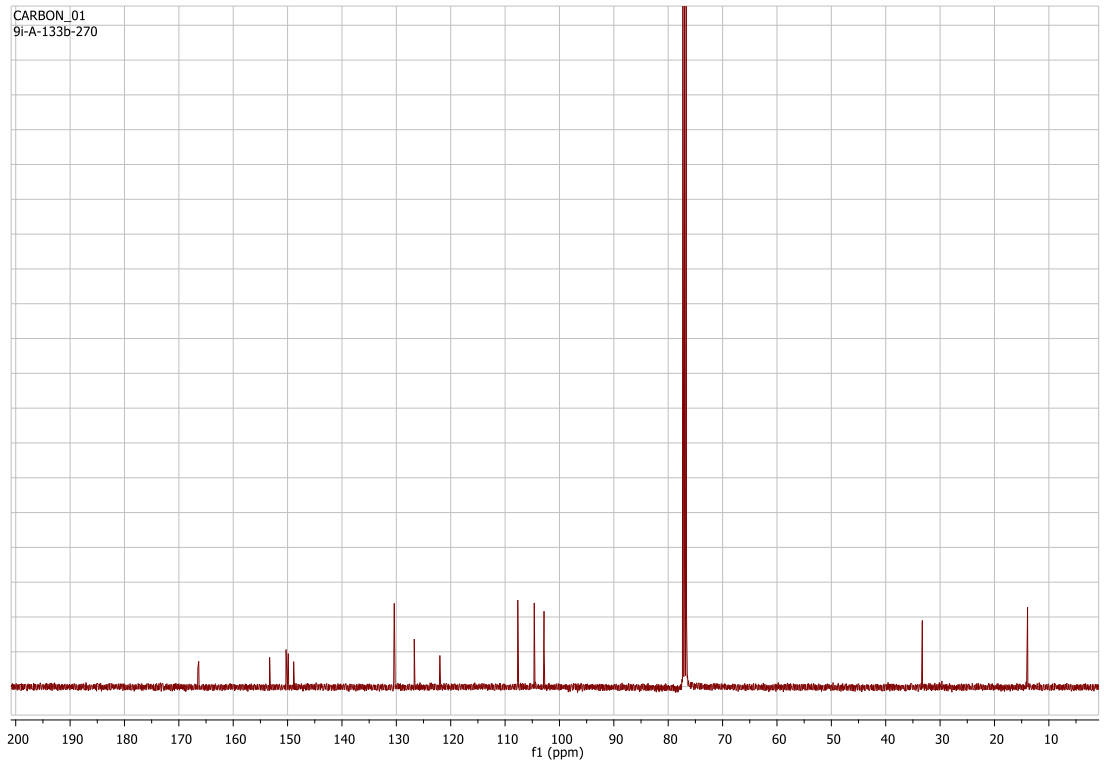

PROTON_01
3k-quinoline-1t
Cl
O
N–Et
N
O
1i
0.28
0.29
0.29
0.30
0.69
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

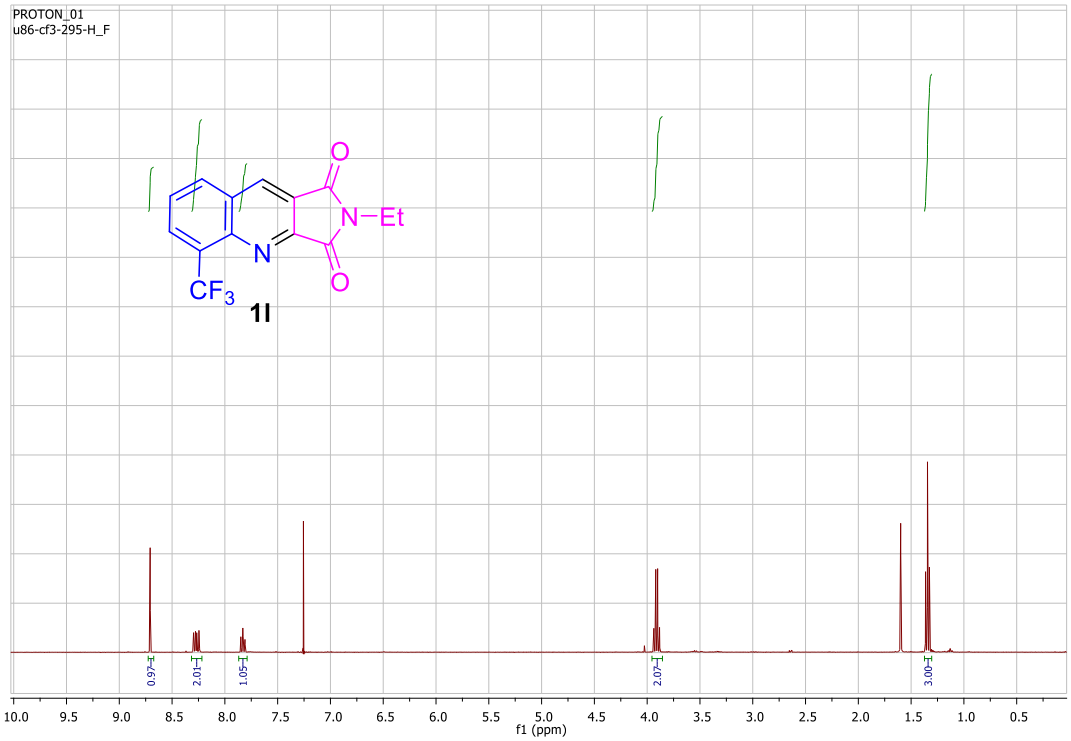

CARBON_01
3k-quinoline-1t
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

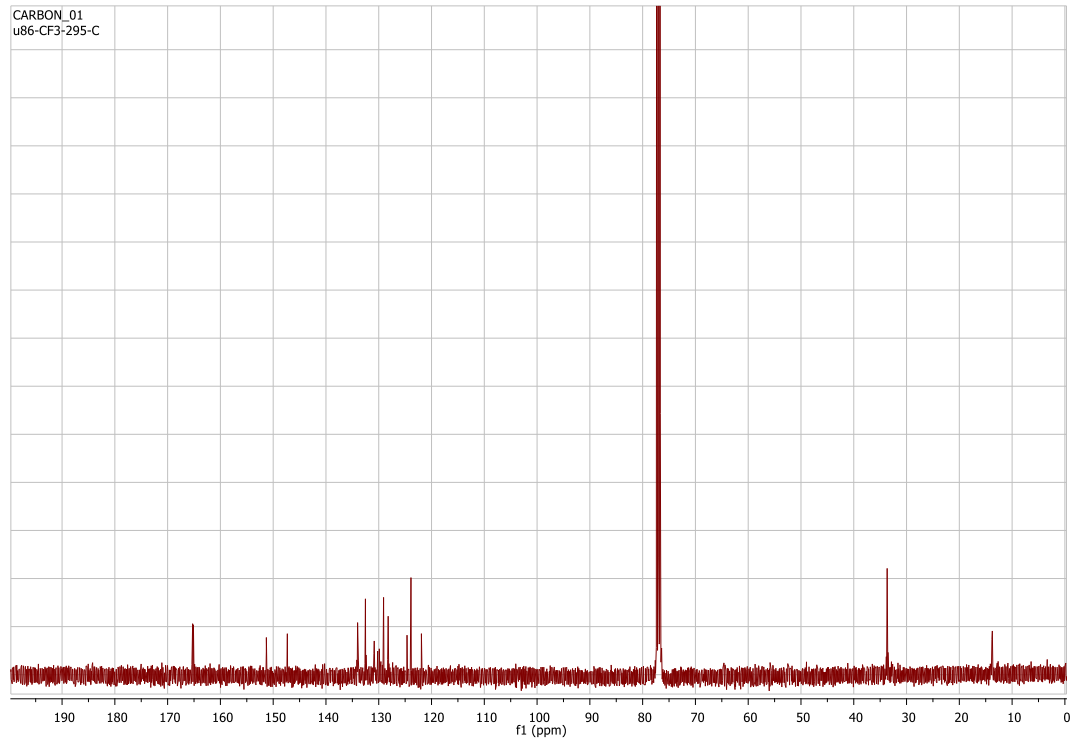

PROTON_02
quinoline-9j
O
O
N
N—Pr
O
O
1j
0.92
0.81
1.23
1.93
2.00
2.11
2.94
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

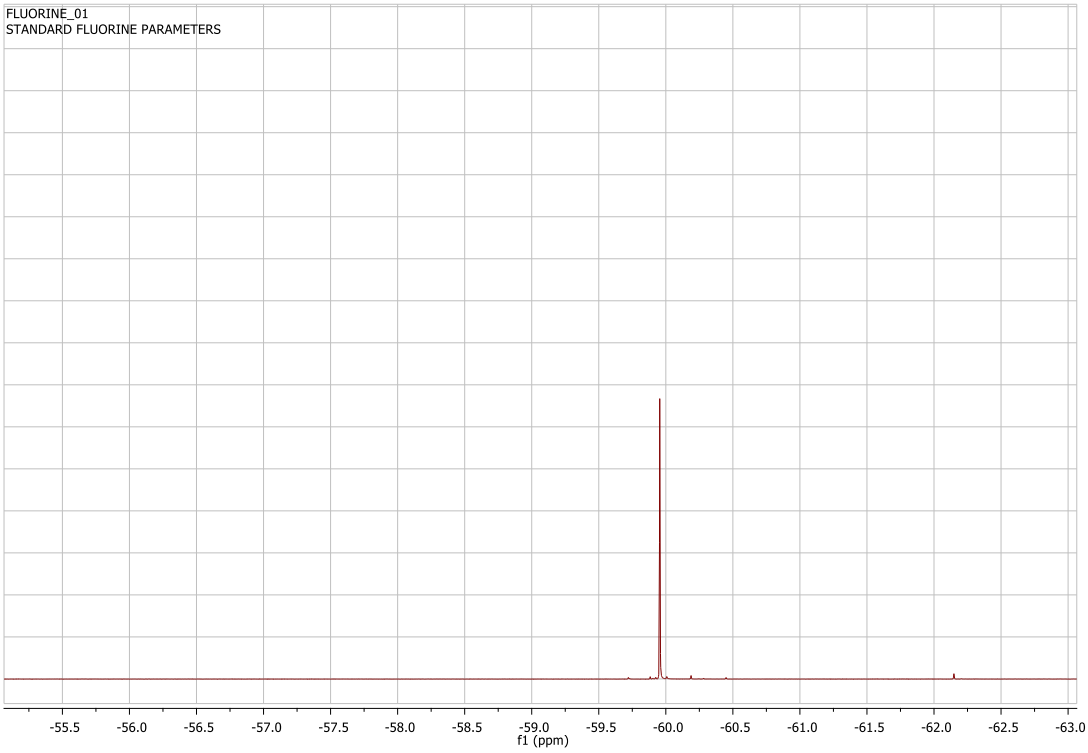

CARBON_01
quinoline-9j
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

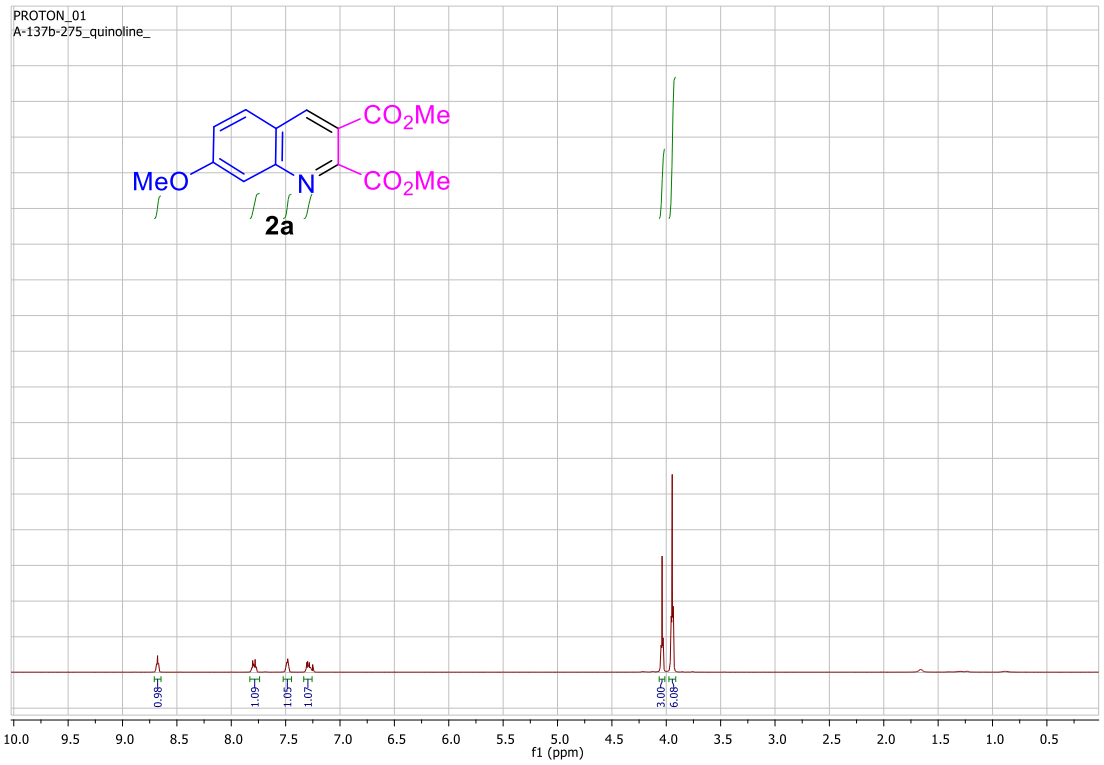

PROTON_01
quinoline-9i-2t
O
O
N
N–Et
O
1k
0.84
0.84
0.76
1.83
2.09
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

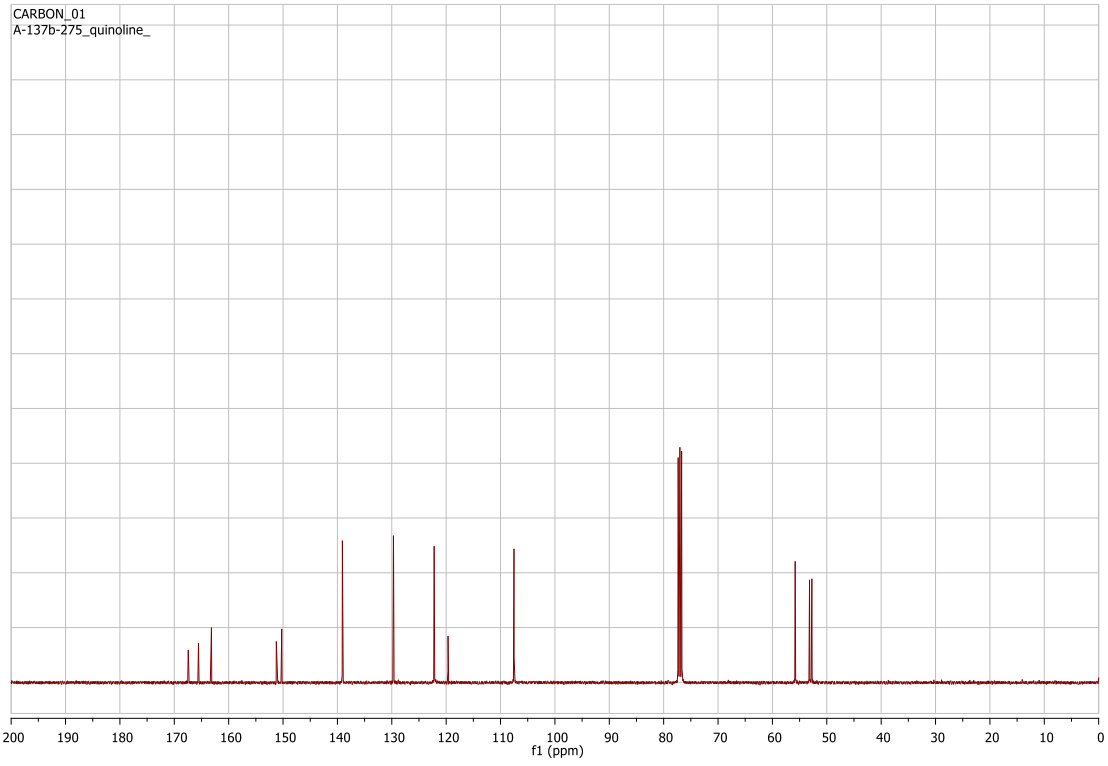

CARBON_01
9i-A-133b-270
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

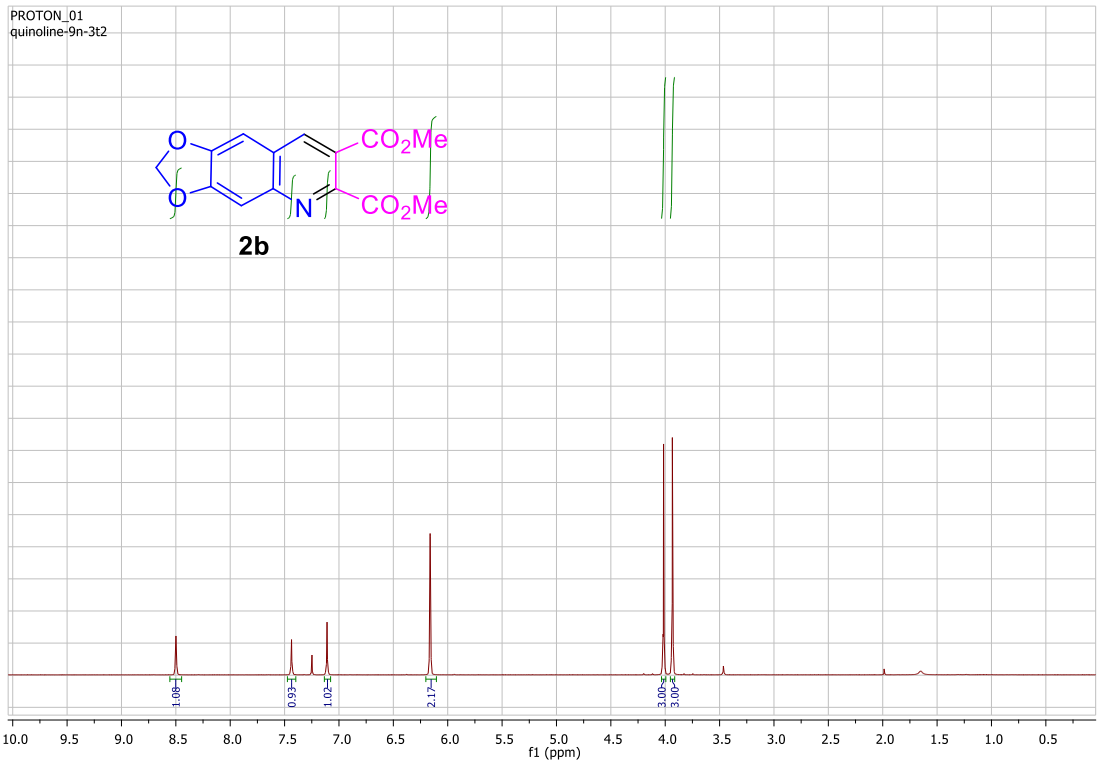

PROTON_01
u86-cf3-295-H_F
O
N–Et
N
O
CF3
1l
0.97
2.01
1.05
2.07
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

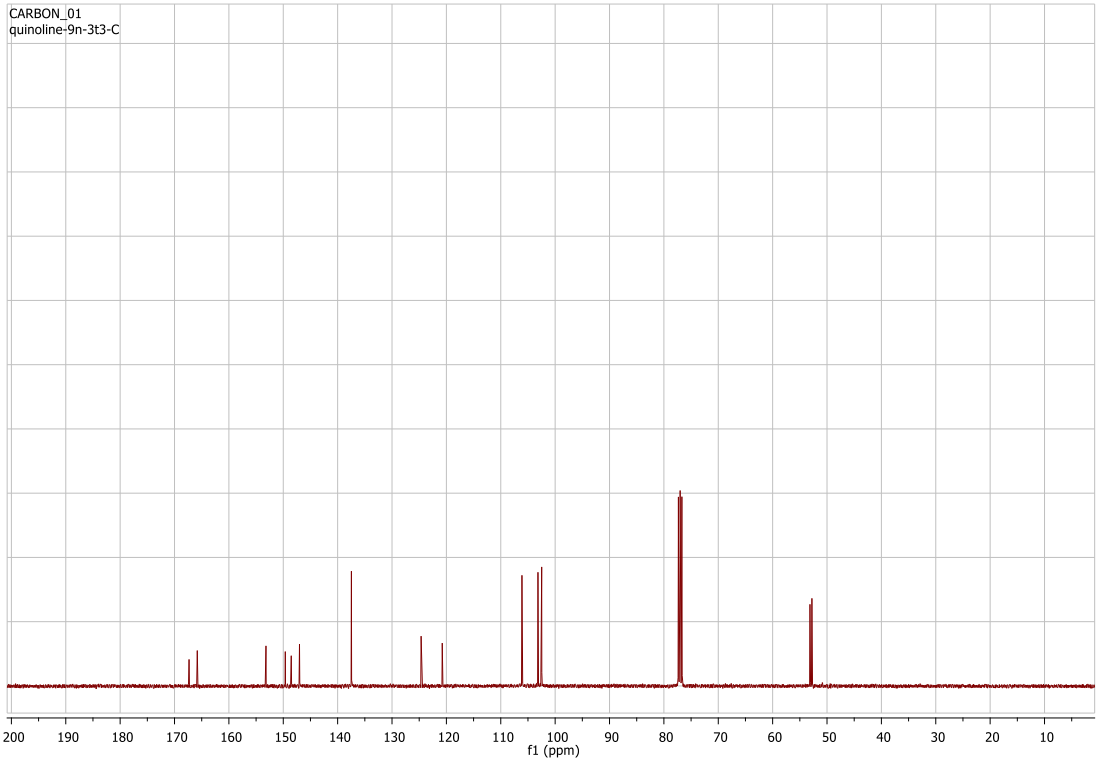

CARBON_01
u86-CF3-295-C
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

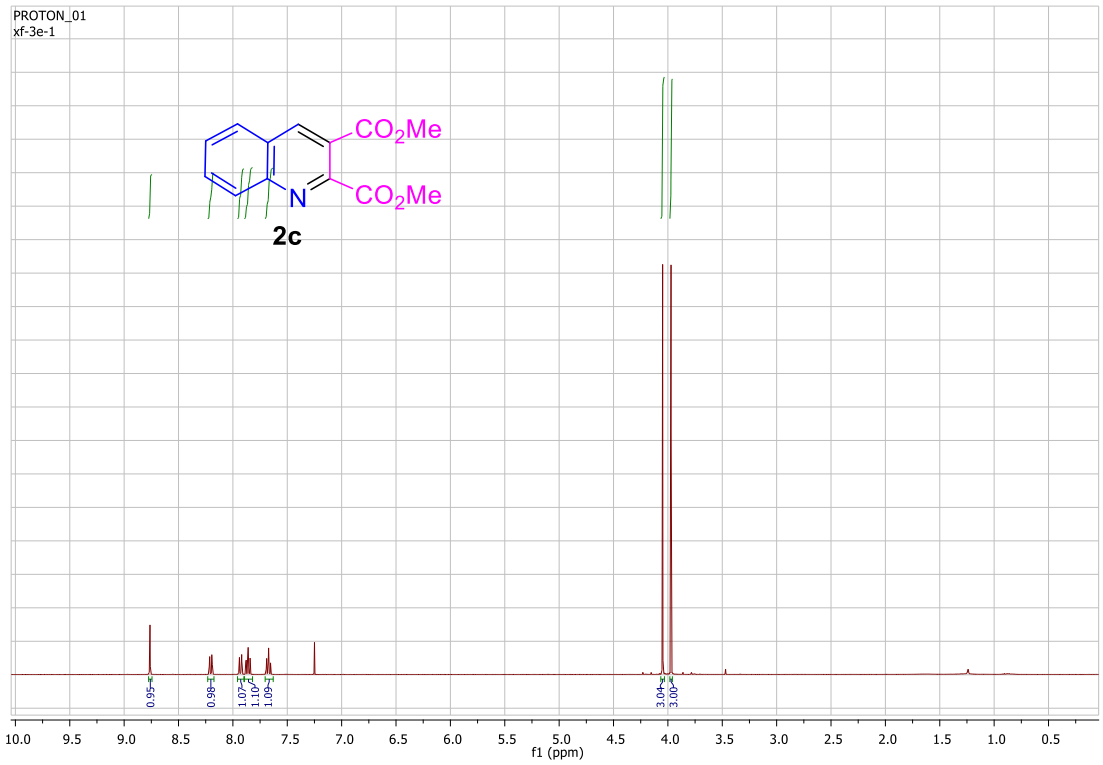

FLUORINE_01
STANDARD FLUORINE PARAMETERS
-55.5
-56.0
-56.5
-57.0
-57.5
-58.0
-58.5
-59.0
-59.5
-60.0
-60.5
-61.0
-61.5
-62.0
-62.5
-63.0
f1 (ppm)

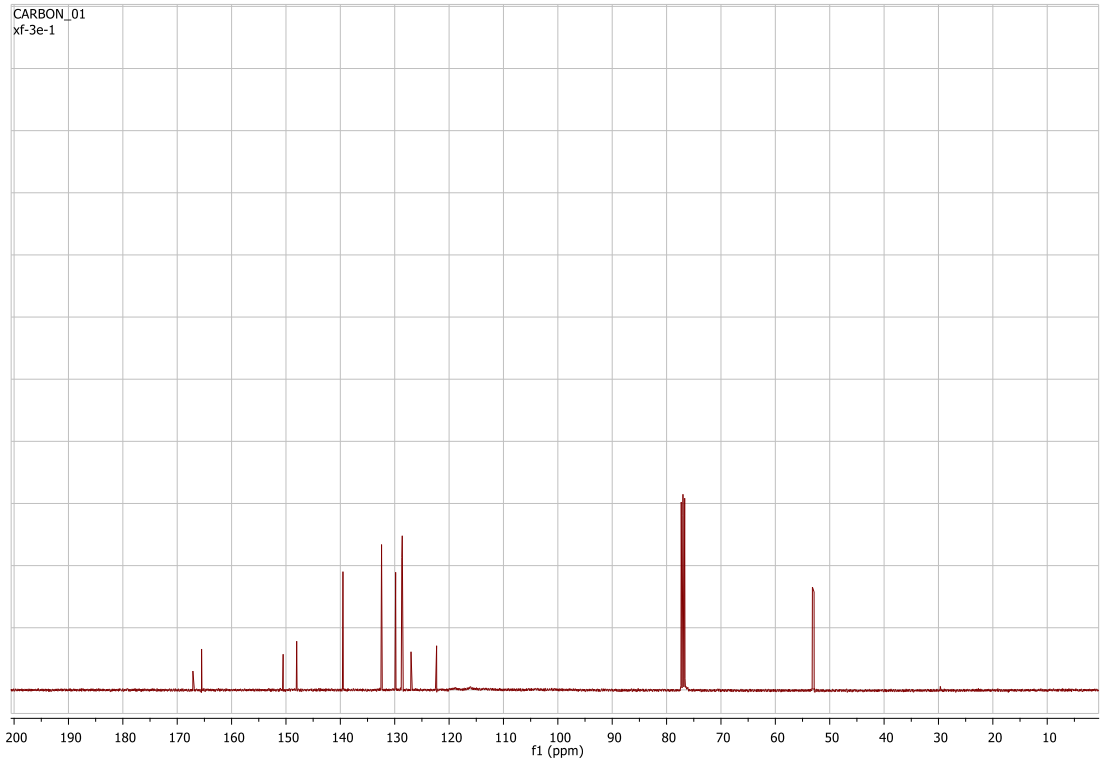

PROTON_01
A-137b-275_quinoline_
CO2Me
CO2Me
MeO
N
2a
0.98
1.09
1.05
1.07
3.00
6.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

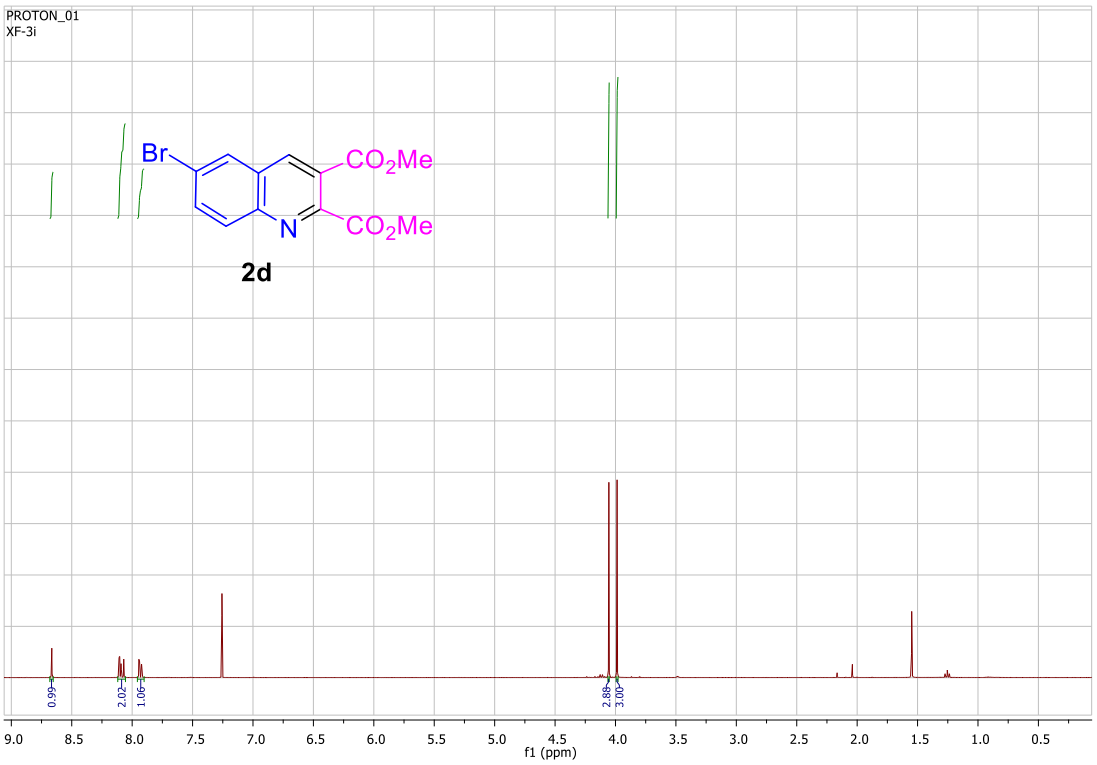

CARBON_01
A-137b-275_quinoline_
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

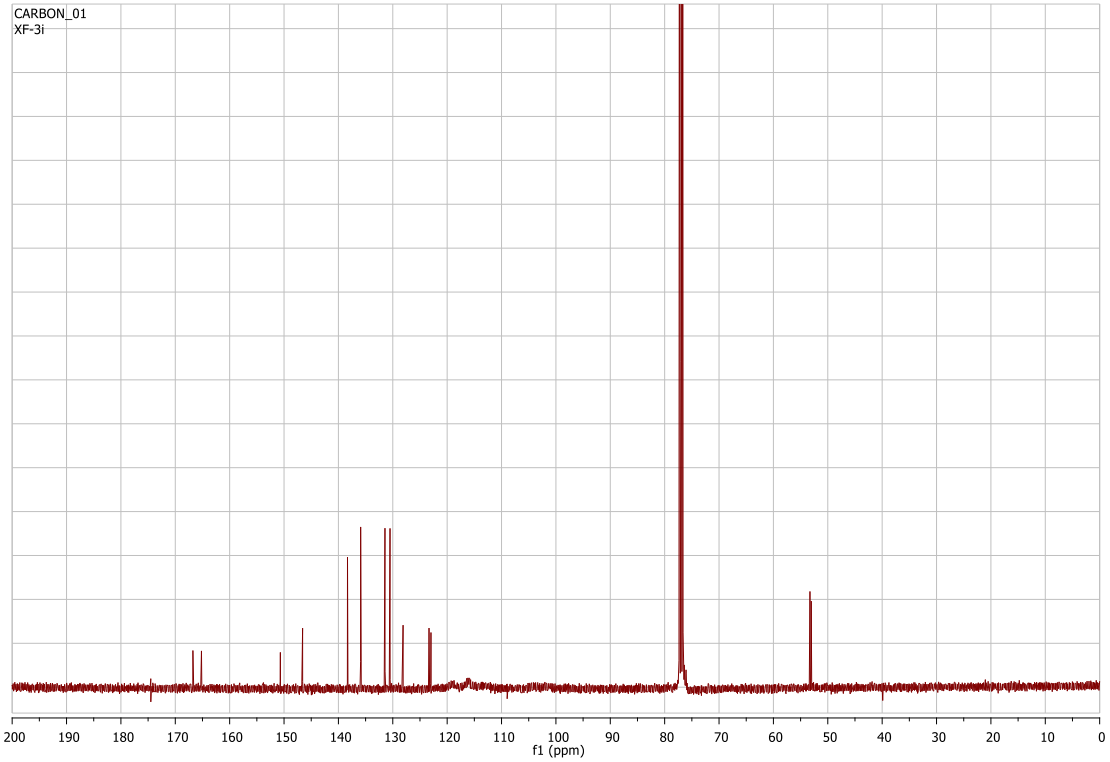

PROTON_01
quinoline-9n-3t2
O
O
N
CO2Me
CO2Me
2b
1.08
0.93
1.02
2.17
3.00
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

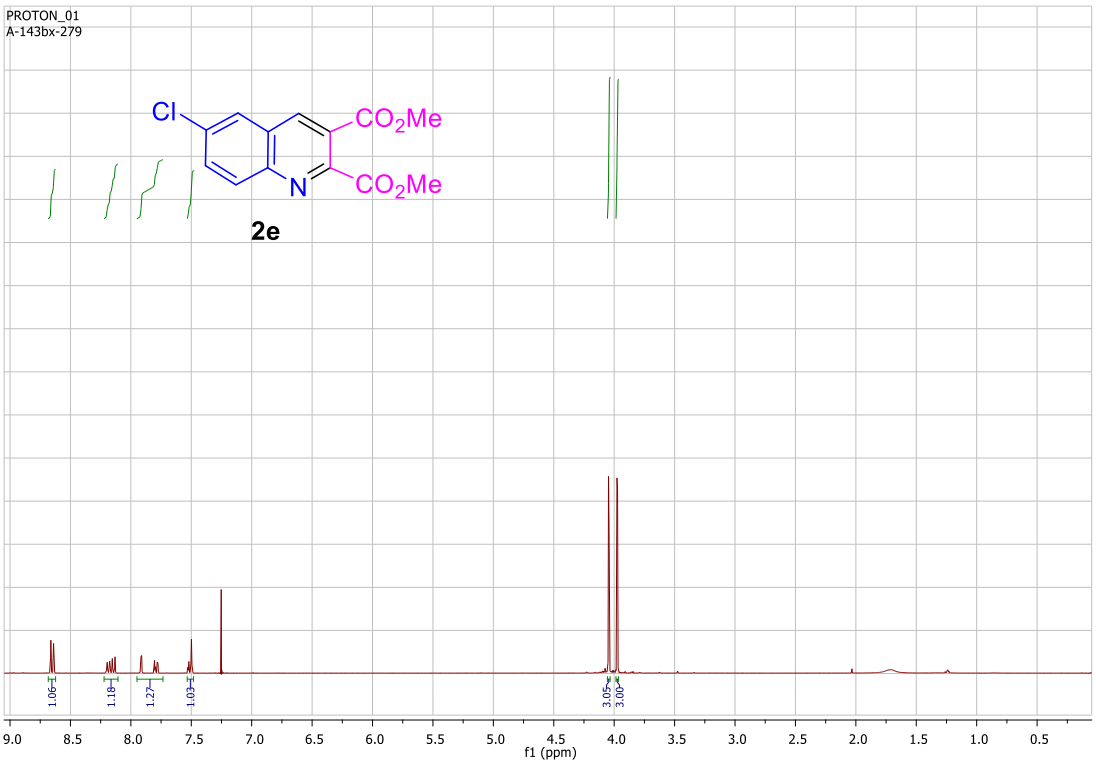

CARBON_01
quinoline-9n-3t3-C
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

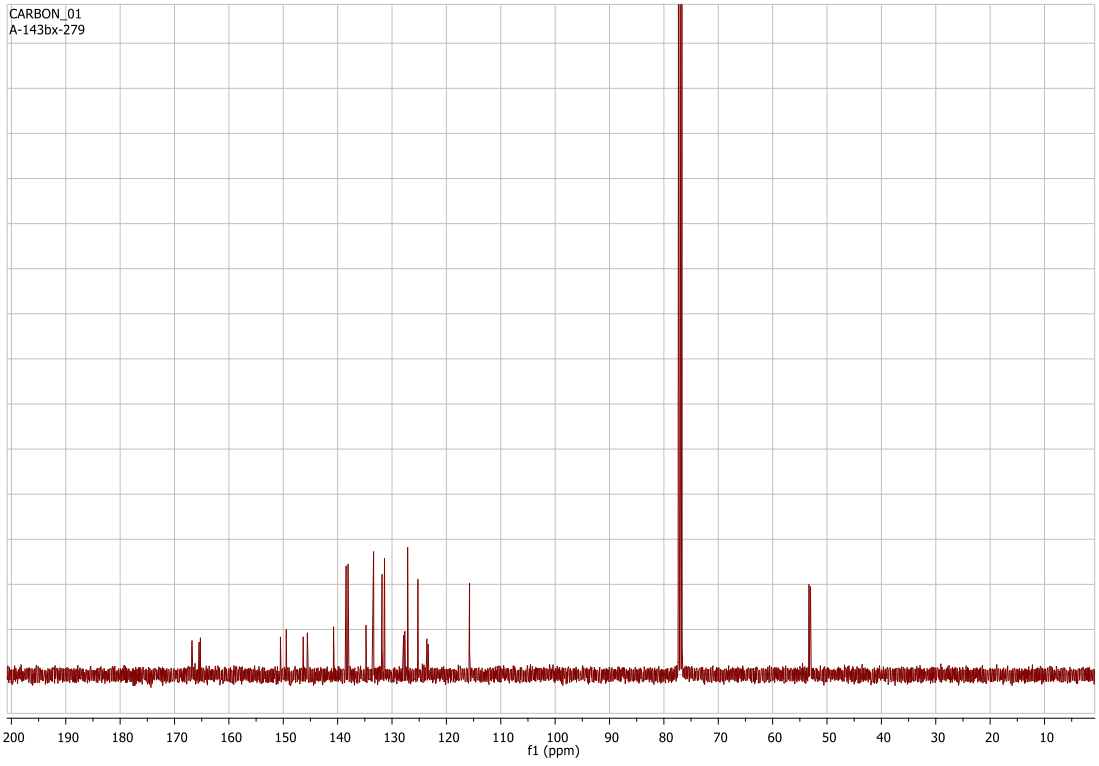

PROTON_01
xf-3e-1
CO2Me
CO2Me
N
2c
0.95
0.98
1.07
1.10
1.09
3.04
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


CARBON_01
xf-3e-1
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


PROTON_01
XF-3i
Br
CO2Me
CO2Me
N
2d
0.99
2.02
1.06
2.89
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


CARBON_01
XF-3i
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


PROTON_01
A-143bx-279
Cl
CO2Me
CO2Me
N
2e
1.06
1.18
1.27
1.03
3.05
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


CARBON_01
A-143bx-279
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

6. Green chemistry metrics analysis

The following formulae were used for calculating Atom Economy (AE), Atom Efficiency (AEf), Carbon Efficiency (CE), Reaction Mass Efficiency (RME), Optimum Efficiency (OE), Mass Productivity (MP), Mass Intensity (MI) and Process Mass Intensity (PMI), E factor, Solvent and Water Intensity (SI and WI).[5-13]

$$\mathbf{AE} = \frac{\textbf{Molecular weight of product}}{\textbf{Total molecular weight of reactants}} \mathbf{X\ 100}$$

$$\mathbf{AEf} = \mathbf{AE\ X\ yield}\%$$

$$\mathbf{CE} = \frac{\textbf{Amount of carbon in the product}}{\textbf{Total carbon present in reactants}} \mathbf{X\ 100}$$

$$\mathbf{RME} = \frac{\textbf{Mass of isolated product}}{\textbf{Total mass of reactants}} \mathbf{X\ 100}$$

$$\mathbf{OE} = \frac{\mathbf{RME}}{\mathbf{AE}} \mathbf{X\ 100}$$

$$\mathbf{MI} = \frac{\textbf{Total mass of input material in a process or process step}}{\textbf{Mass of product}}$$

$$\mathbf{PMI} = \frac{\textbf{Total mass of input material in the whole process}}{\textbf{Mass of product}}$$

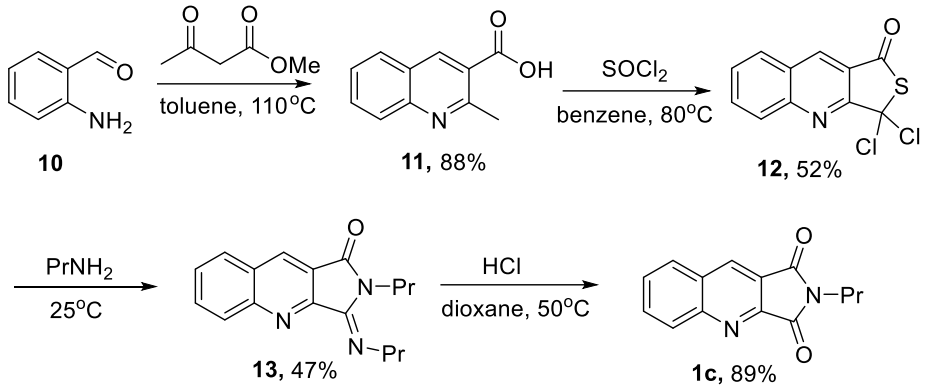
$$\mathbf{MP} = \frac{\mathbf{1}}{\mathbf{PMI}} \mathbf{X\ 100}$$

$$\mathbf{E\ Factor} = \mathbf{PMI} - \mathbf{1}$$

$$\mathbf{SI} = \frac{\textbf{Total mass of solvents excl. water in the whole process}}{\textbf{Mass of product}}$$

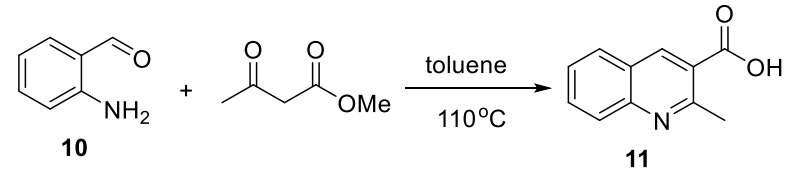
$$\mathbf{WI} = \frac{\textbf{Total mass of water used in the whole process}}{\textbf{Mass of product}}$$

6.1. Published synthetic method - Process A (T. Van Esa, B. Staskun, S. *Afr. J. Chem.* 2003, *56*, 40-46)



This is a four-step synthesis. Reported procedures for the synthesis of compound **1c** do not always contain all the required information; therefore, some realistic assumptions were used where appropriate and are italicized in the calculations given below. Drying agents, when used, were not included in the calculations.

Step 1: Synthesis of 2-methylquinoline-3-carboxylic acid (11)



MW: 121.05 MW: 116.05 MW: 187.06

Experimental procedure: To a stirred solution of 206 mg (1.70 mmol) of 2-aminobenzaldehyde **10** in 15 mL of toluene, was added 217 mg (1.87 mmol) of methyl acetoacetate and the solution was refluxed for 24 h. The reaction mixture was cooled to room temperature, evaporated to one-half its volume, and then cooled to 0 °C in an ice bath. The solid was filtered and washed with 1:1 ether: hexane (*assuming use of each 2 mL)* to give 280 mg (88%) of compound **11**.

Materials used for metrics calculations: 2-aminobenzaldehyde **10** (206 mg, 1.70 mmol), methyl acetoacetate (217 mg, 1.87 mmol), toluene (15 mL, 12.9 g), ether (2 mL, 1.41 g), hexane (2 mL, 1.32 g), compound 14 (280 mg, 1.50 mmol).

$$\mathbf{AE}\ (\mathbf{11}) = \frac{\mathbf{187.06}}{\mathbf{121.05 + 116.05}}\mathbf{X}\ \mathbf{100} = \mathbf{78.89}$$

$$\mathbf{AEf}\ (\mathbf{11}) = \frac{\mathbf{78.89}}{\mathbf{100}}\mathbf{X}\ \mathbf{88} = \mathbf{69.43}$$

$$\mathbf{CE}\ (\mathbf{11}) = \frac{\mathbf{11}\ \boldsymbol{X}\ \mathbf{0.00149}}{\mathbf{7}\ \boldsymbol{X}\ \mathbf{0.0017 + 5}\ \boldsymbol{X}\ \mathbf{0.00187}}\mathbf{X}\ \mathbf{100} = \mathbf{77.44}$$

$$\mathbf{RME}\ (\mathbf{11}) = \frac{\mathbf{280}}{\mathbf{206 + 217}}\mathbf{X}\ \mathbf{100} = \mathbf{66.19}$$

$$\mathbf{OE}\ (\mathbf{11}) = \frac{\mathbf{66.19}}{\mathbf{78.89}}\mathbf{X}\ \mathbf{100} = \mathbf{83.90}$$

$$\mathbf{MI}\ (\mathbf{11}) = \frac{\mathbf{0.206 + 0.217 + 12.9 + 1.41 + 1.32}}{\mathbf{0.28}} = \mathbf{57.33}$$

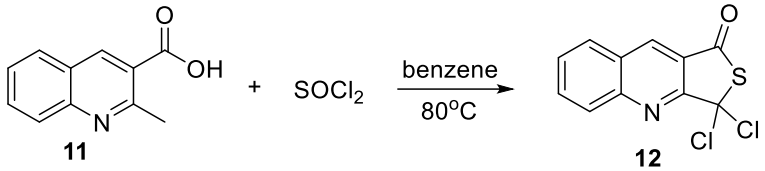
$$\mathbf{MP}\ (\mathbf{11}) = \frac{\mathbf{100}}{\mathbf{57.33}} = \mathbf{1.74}$$

$$\mathbf{E\ Factor}\ (\mathbf{11}) = \mathbf{57.33 - 1} = \mathbf{56.33}$$

$$\mathbf{SI}\ (\mathbf{11}) = \frac{\mathbf{15.63}}{\mathbf{0.28}} = \mathbf{55.82}$$

$$\mathbf{WI}\ (\mathbf{11}) = \frac{\mathbf{0}}{\mathbf{0.28}} = \mathbf{0}$$

Step 2: Synthesis of 3, 3-Dichlorothieno[*3,4-b*]quinolin-1(3*H*)-one (12)



11 MW: 187.06 MW: 117.90 **12** MW: 268.95

Experimental procedure: Compound **11** (3.00 g, 16.0 mmol) was heated with a large excess of $SOCl_2$ (10 mL) under reflux for 3 h. Evaporation of the reaction gave a residue of compound 15 which was freed from occluded $SOCl_2$ by azeotropic distillation with benzene (*assuming use of 10 mL*), to afford 2.23 g (52%) of compound **12** as colorless crystals.

Materials used for metrics calculations: Compound 14 (3.0 g, 16.0 mmol), $SOCl_2$ (10 mL, 16.31 g), benzene (10 mL, 8.74 g), compound 15 (2.23 g, 8.29 mmol).

$$\mathbf{AE}\ (\mathbf{12}) = \frac{\mathbf{268.95}}{\mathbf{187.06 + 117.90}}\mathbf{X}\ \mathbf{100} = \mathbf{88.2}$$

$$\mathbf{AEf}\ (\mathbf{12}) = \frac{\mathbf{88.2}}{\mathbf{100}}\mathbf{X}\ \mathbf{52} = \mathbf{45.86}$$

$$\mathbf{CE}\ (\mathbf{12}) = \frac{\mathbf{11}\ \boldsymbol{X}\ \mathbf{0.00829}}{\mathbf{11}\ \boldsymbol{X}\ \mathbf{0.016}}\mathbf{X}\ \mathbf{100} = \mathbf{51.70}$$

$$\textbf{RME}\ (12) = \frac{2.23}{3.0 + 16.31}\textbf{X}\ 100 = 11.55$$

$$\textbf{OE}\ (12) = \frac{11.55}{88.2}\textbf{X}\ 100 = 13.09$$

$$\textbf{MI}\ (12) = \frac{3.0 + 16.31 + 8.74}{2.23} = 12.58$$

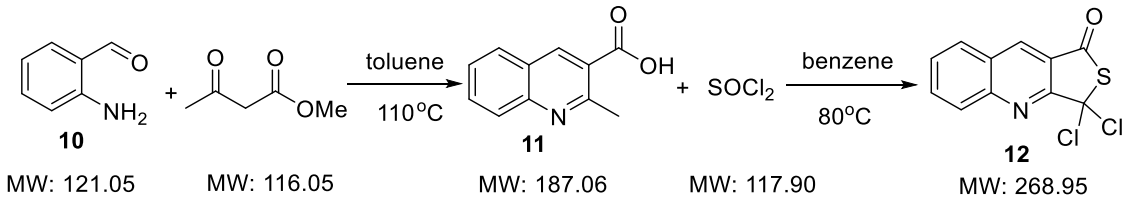
$$\textbf{MP}\ (12) = \frac{100}{12.58} = 7.95$$

$$\textbf{E Factor}\ (12) = 12.58 - 1 = 11.58$$

$$\textbf{SI}\ (12) = \frac{8.74}{2.23} = 3.92$$

$$\textbf{WI}\ (12) = \frac{0}{2.23} = 0$$

Cumulative metrics for compound 12:



$$\textbf{AE}\ (\textbf{12 cumulative}) = \frac{268.95}{121.05 + 116.05 + 117.90}\textbf{X}\ 100 = 75.76$$

$$\textbf{AEf}\ (\textbf{12 cumulative}) = \frac{75.76}{100}\textbf{X}\ 45.76 = 34.67$$

$$\textbf{CE}\ (\textbf{12 cumulative}) = \frac{11\ X\ 0.00077}{7\ X\ 0.0017 + 5\ X\ 0.00187}\textbf{X}\ 100 = 40.04$$

$$\textbf{RME}\ (\textbf{12 cumulative}) = \frac{2.23}{\frac{3.0}{0.6619} + 16.31}\textbf{X}\ 100 = 10.7$$

$$\textbf{OE}\ (\textbf{12 cumulative}) = \frac{10.7}{75.76}\textbf{X}\ 100 = 14.12$$

$$\textbf{MI}\ (\textbf{12 cumulative}) = \frac{3.0\ \textbf{X}\ 57.33 + 16.31 + 8.74}{2.23} = 88.36$$

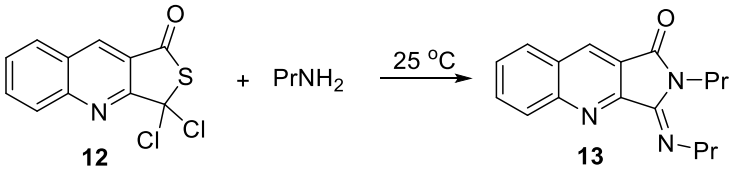
$$\textbf{MP}\ (\textbf{12 cumulative}) = \frac{100}{88.36} = 1.13$$

$$\textbf{E Factor}\ (\textbf{12 cumulative}) = 88.36 - 1 = 87.36$$

$$\textbf{SI}\ (\textbf{12 cumulative}) = \frac{24.37}{2.23} = 10.93$$

$$\textbf{WI}\ (\textbf{12 cumulative}) = \frac{0}{2.23} = 0$$

Step 3: Synthesis of 2-Propyl-3-propylimino-2,3-dihydro-pyrrolo[*3,4-b*]quinolin-1-one (13)



12 MW: 268.95 MW: 59.07 **13** MW: 281.15

Experimental procedures: Compound **12** (422 mg, 1.56 mmol) was added batchwise (over 5–10 min) with stirring to ice-cold propylamine (5 mL), after which the reaction was kept at room temperature for 24 h. Excess amine was evaporated at reduced temperature and pressure, and the residue treated with H_2O (2 mL) and $CHCl_3$ (5 mL). Evaporation of the $CHCl_3$ extract gave a mixture of compound 16 and propylthiocarbamoyl amide. The mixture was extracted with hot hexane (5 mL) after which the sparingly soluble amide was removed by filtration. Evaporation of the hexane filtrate and washings gave crude compound **13** (207 mg, 47%).

Materials used for metrics calculations: Compound **12** (422 mg, 1.56 mmol), propylamine (5 mL, 3.60 g, 60.9 mmol), H_2O (2 mL, 2.0 g), $CHCl_3$ (5 mL, 7.46 g), hexane (5 mL, 3.30 g), compound 16 (207 mg, 0.73 mmol).

$$\mathbf{AE}\ \ (\mathbf{13}) = \frac{\mathbf{281.15}}{\mathbf{268.95 + 59.07}}\mathbf{X}\ \ \mathbf{100} = \mathbf{85.71}$$

$$\mathbf{AEf}\ \ (\mathbf{13}) = \frac{\mathbf{85.71}}{\mathbf{100}}\mathbf{X}\ \ \mathbf{47} = \mathbf{40.28}$$

$$\mathbf{CE}\ \ (\mathbf{13}) = \frac{\mathbf{17}\ \boldsymbol{X}\ \mathbf{0.00073}}{\mathbf{11}\ \mathbf{X}\ \mathbf{0.00156} + \mathbf{3}\ \boldsymbol{X}\ \mathbf{0.0609}}\mathbf{X}\ \ \mathbf{100} = \mathbf{6.26}$$

$$\mathbf{RME}\ \ (\mathbf{13}) = \frac{\mathbf{0.207}}{\mathbf{0.422 + 3.60}}\mathbf{X}\ \ \mathbf{100} = \mathbf{5.15}$$

$$\mathbf{OE}\ \ (\mathbf{13}) = \frac{\mathbf{5.15}}{\mathbf{85.71}}\mathbf{X}\ \ \mathbf{100} = \mathbf{6.0}$$

$$\mathbf{MI}\ \ (\mathbf{13}) = \frac{\mathbf{0.422 + 3.60 + 2.0 + 7.46 + 3.30}}{\mathbf{0.207}} = \mathbf{81.07}$$

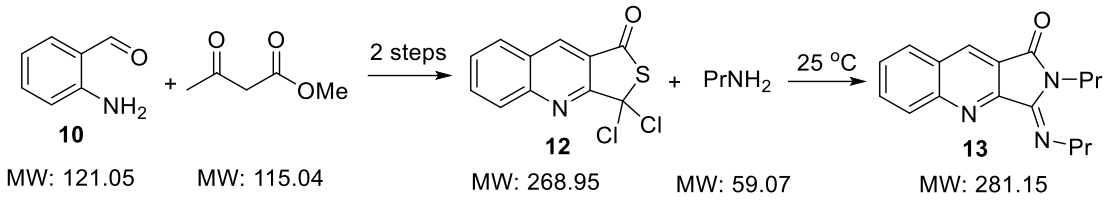
$$\mathbf{MP}\ \ (\mathbf{13}) = \frac{\mathbf{100}}{\mathbf{81.07}} = \mathbf{1.23}$$

$$\mathbf{E\ Factor}\ \ (\mathbf{13}) = \mathbf{81.07 - 1} = \mathbf{80.07}$$

$$\mathbf{SI}\ \ (\mathbf{13}) = \frac{\mathbf{10.76}}{\mathbf{0.207}} = \mathbf{51.98}$$

$$\mathbf{WI}\ \ (\mathbf{13}) = \frac{\mathbf{2}}{\mathbf{0.207}} = \mathbf{9.66}$$

Cumulative metrics for compound 13:



$$\textbf{AE (13 cumulative)} = \frac{281.95}{\frac{268.95}{0.7576} + 59.07} \textbf{X } 100 = 67.9$$

$$\textbf{AEf (13 cumulative)} = \frac{67.9}{100} \textbf{X } 21.5 = 14.6$$

$$\textbf{CE (13 cumulative)} = \frac{17 \ X \ 0.00036}{7 \ X \ 0.0017 + 5 \ X \ 0.00187 + 3 \ X \ 0.0609} \textbf{X } 100$$

$$= 3.02$$

$$\textbf{RME (13 cumulative)} = \frac{0.207}{\frac{0.422}{0.107} + 3.60} \textbf{X } 100 = 2.74$$

$$\textbf{OE (13 cumulative)} = \frac{2.74}{67.9} \textbf{X } 100 = 4.04$$

$$\textbf{MI (13 cumulative)} = \frac{0.422 \ \textbf{X } 88.36 + 3.60 + 2.0 + 7.46 + 3.30}{0.207} = 259.17$$

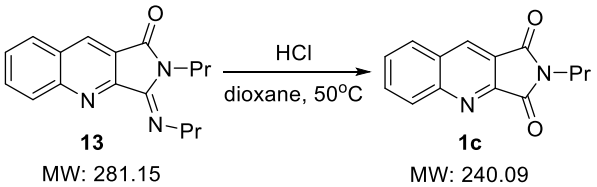
$$\textbf{MP (13 cumulative)} = \frac{100}{259.17} = 0.39$$

$$\textbf{E Factor (13 cumulative)} = 259.17 - 1 = 258.17$$

$$\textbf{SI (13 cumulative)} = \frac{35.13}{0.207} = 169.71$$

$$\textbf{WI (13 cumulative)} = \frac{2}{0.207} = 9.66$$

Step 4: Synthesis of 2-propyl-2, 3-dihydro-pyrrolo[3,4-b]quinoline-1,3-dione (1c)



Experimental procedures: A mixture of compound **1**3 (220 mg, 0.78 mmol) and aqueous 2 mol/L HCl (1 mL) in 1,4-dioxane (3 mL) was kept at 50°C overnight. Cooling and filtering provided crude compound 1c (167 mg, 0.70 mmol; 89%). Recrystallization from EtOH: H_2O (*assuming use of EtOH:H_2O = 3:1, total 1 mL*), afford 159 mg (*assuming 95% of*

recrystallization yield) of compound **1c**.

Materials used for metrics calculations: Compound 16 (220 mg, 0.78 mmol), 2 mol/L HCl (1 mL, 1.0 g), 1,4-dioxane (3 mL, 3.10 g), EtOH (0.75 mL, 0.59 g), H_2O (0.25 mL, 0.25 g), compound 1c (159 mg, 0.67 mmol).

$$\mathbf{AE\ (1c)} = \frac{\mathbf{240.09}}{\mathbf{281.15}}\mathbf{X\ 100} = \mathbf{85.39}$$

$$\mathbf{AEf\ (1c)} = \frac{\mathbf{85.4}}{\mathbf{100}}\mathbf{X\ 89} = \mathbf{76.0}$$

$$\mathbf{CE\ (1c)} = \frac{\mathbf{14\ X\ 0.00066}}{\mathbf{17\ X\ 0.00078}}\mathbf{X\ 100} = \mathbf{69.7}$$

$$\mathbf{RME\ (1c)} = \frac{\mathbf{0.159}}{\mathbf{0.22}}\mathbf{X\ 100} = \mathbf{72.27}$$

$$\mathbf{OE\ (1c)} = \frac{\mathbf{72.27}}{\mathbf{85.39}}\mathbf{X\ 100} = \mathbf{84.63}$$

$$\mathbf{MI\ (1c)} = \frac{\mathbf{0.22 + 1.0 + 3.10 + 0.59 + 0.25}}{\mathbf{0.159}} = \mathbf{12.96}$$

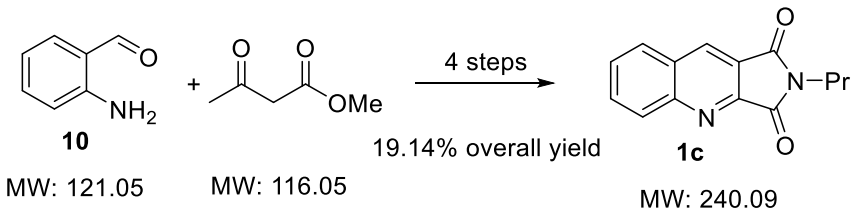
$$\mathbf{MP\ (1c)} = \frac{\mathbf{100}}{\mathbf{12.96}} = \mathbf{7.72}$$

$$\mathbf{E\ Factor\ (1c)} = \mathbf{12.96 - 1} = \mathbf{11.96}$$

$$\mathbf{SI\ (1c)} = \frac{\mathbf{4.69}}{\mathbf{0.159}} = \mathbf{29.5}$$

$$\mathbf{WI\ (1c)} = \frac{\mathbf{0.25}}{\mathbf{0.159}} = \mathbf{1.57}$$

Cumulative metrics for compound 1c:



$$\mathbf{AE\ (1c\ cumulative)} = \frac{\mathbf{240.09}}{\mathbf{281.15/0.679}}\mathbf{X\ 100} = \mathbf{57.98}$$

$$\mathbf{AEf\ (1c\ cumulative)} = \frac{\mathbf{57.98}}{\mathbf{100}}\mathbf{X\ 19.14} = \mathbf{11.09}$$

$$\mathbf{CE\ (1c\ cumulative)} = \frac{\mathbf{14\ X\ 0.00066}}{\mathbf{7\ X\ 0.0017 + 5\ X\ 0.00187 + \ 3\ X\ 0.0609}}\mathbf{X\ 100}$$

$$= \mathbf{4.54}$$

$$\mathbf{RME\ (1c\ cumulative)} = \frac{\mathbf{0.159}}{\mathbf{0.22/0.0274}}\mathbf{X\ 100} = \mathbf{1.98}$$

$$\mathbf{OE\ (1c\ cumulative)} = \frac{\mathbf{1.98}}{\mathbf{57.98}}\mathbf{X\ 100} = \mathbf{3.42}$$

$$\mathbf{PMI\ (1c\ cumulative)} = \frac{\mathbf{0.22\ X\ 259.17 + 3.10 + 1.0 + 0.59 + 0.25}}{\mathbf{0.159}} = \mathbf{389.67}$$

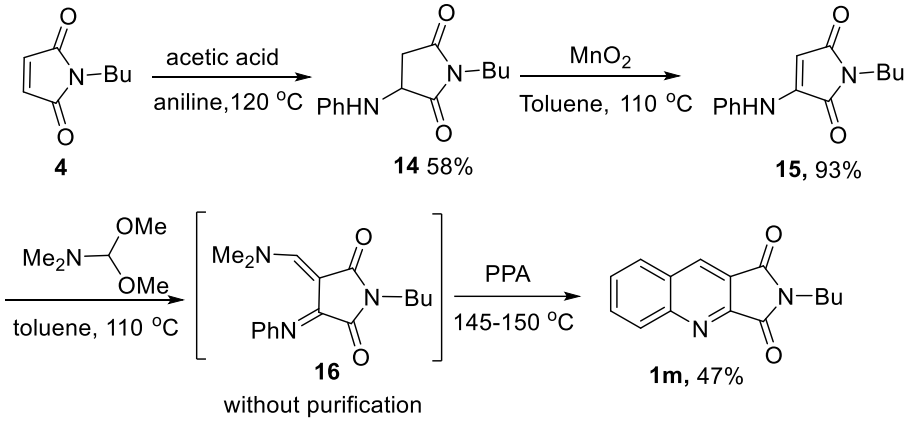
$$\mathbf{MP\ (1c\ cumulative)} = \frac{\mathbf{100}}{\mathbf{389.67}} = \mathbf{0.256}$$

$$\mathbf{E\ Factor\ (1c\ cumulative)} = \mathbf{389.67 - 1} = \mathbf{388.67}$$

$$\mathbf{SI\ (1c\ cumulative)} = \frac{\mathbf{39.82}}{\mathbf{0.159}} = \mathbf{250.44}$$

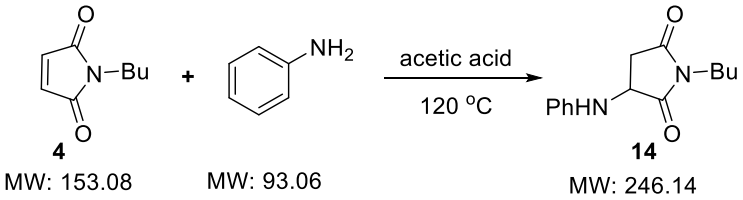
$$\mathbf{WI\ (1c\ cumulative)} = \frac{\mathbf{2.25}}{\mathbf{0.159}} = \mathbf{14.15}$$

6.2. Published synthetic method - Process B (D. R. Maulding, *J. Heterocyclic Chem.* **1988**, *25*, 1777-1779)



This is a four-step synthesis, but only three separation steps. Reported procedures for the synthesis of compound **1m** do not always contain all the required information; therefore, some realistic assumptions were used where appropriate and are italicized in the calculations given below. Drying agents, when used, were not included in the calculations.

Step 1: Synthesis of 1-butyl-3-(phenylamino)pyrrolidine-2,5-dione (14)



Experimental procedures: A solution of 9.9 g (0.065 mole) of *N*-butylmaleimide **4** and 35 mL of acetic acid was treated with 6.51g (0.07 mole) of aniline and the resulting solution

was heated at 120°C for 30 min. The solution was cooled and poured into 280 mL of water. The amorphous material was collected and recrystallized from isopropyl alcohol (*assuming use of 30 mL*), gave 9.3 g (58%) of off-white crystal of compound **14**.

Materials used for metrics calculations: *N*-Butylmaleimide **4** (9.9 g, 0.065 mole), acetic acid (35 mL, 36.7 g), aniline (6.5 g, 0.07 mole), water (280 mL, 280 g), isopropyl alcohol (30 mL, 23.6 g), compound **14** (9.3 g, 0.038 mole).

$$\mathbf{AE}\ \ (\mathbf{14}) = \frac{\mathbf{246.14}}{\mathbf{153.08 + 93.06}}\mathbf{X}\ \ \mathbf{100} = \mathbf{100}$$

$$\mathbf{AEf}\ \ (\mathbf{14}) = \frac{\mathbf{58}}{\mathbf{100}}\mathbf{X}\ \ \mathbf{100} = \mathbf{58}$$

$$\mathbf{CE}\ \ (\mathbf{14}) = \frac{\mathbf{14}\ \ \boldsymbol{X}\ \ \mathbf{0.037}}{\mathbf{8}\ \ \boldsymbol{X}\ \ \mathbf{0.065 + 6}\ \ \boldsymbol{X}\ \ \mathbf{0.07}}\mathbf{X}\ \ \mathbf{100} = \mathbf{56.5}$$

$$\mathbf{RME}\ \ (\mathbf{14}) = \frac{\mathbf{9.3}}{\mathbf{9.9 + 6.51}}\mathbf{X}\ \ \mathbf{100} = \mathbf{56.67}$$

$$\mathbf{OE}\ \ (\mathbf{14}) = \frac{\mathbf{56.67}}{\mathbf{100}}\mathbf{X}\ \ \mathbf{100} = \mathbf{56.67}$$

$$\mathbf{MI}\ \ (\mathbf{14}) = \frac{\mathbf{9.9 + 36.7 + 6.51 + 280 + 23.6}}{\mathbf{9.3}} = \mathbf{38.36}$$

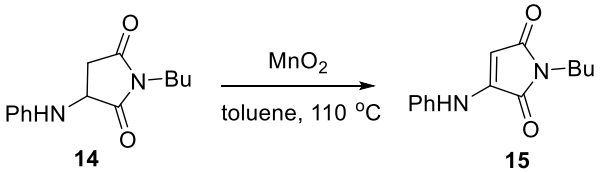
$$\mathbf{MP}\ \ (\mathbf{14}) = \frac{\mathbf{100}}{\mathbf{38.36}} = \mathbf{2.61}$$

$$\mathbf{E\ Factor}\ \ (\mathbf{14}) = \mathbf{38.36 - 1} = \mathbf{37.36}$$

$$\mathbf{SI}\ \ (\mathbf{14}) = \frac{\mathbf{60.3}}{\mathbf{9.3}} = \mathbf{6.48}$$

$$\mathbf{WI}\ \ (\mathbf{14}) = \frac{\mathbf{280}}{\mathbf{9.3}} = \mathbf{30.11}$$

Step 2: Synthesis of 1-bButyl-3-(phenylamino)-1*H*-pyrrole-2,5-dione (15)



14 MW: 246.14 **15** MW: 244.13

Experimental procedures*:* A mixture of 2.46 g (0.01 mole) of compound **14**, 2.61 g (0.03 mole) of activated manganese dioxide and 15 mL of toluene was refluxed for 5 h. The hot mixture was filtered and the solid was washed with 5 mL of hot toluene. Cooling the filtrate gave 2.3 g (93%) of red-orange solid. Recrystallization from isopropyl alcohol (*assuming use of 7 mL*), afford 2.19 g (*assuming 95% of recrystallization yield*) of compound **15**.

Materials used for metrics calculations: Compound 10 (2.46 g, 0.01 mole), manganese dioxide (2.61 g, 0.03 mole), toluene (20 mL, 17.3 g), isopropyl alcohol (7 mL, 5.5 g), compound **15** (2.19 g, 0.009 mole).

$$\mathbf{AE}\ (\mathbf{15}) = \frac{\mathbf{244.12}}{\mathbf{246.14}}\mathbf{X}\ \mathbf{100} = \mathbf{99.18}$$

$$\mathbf{AEf}\ (\mathbf{15}) = \frac{\mathbf{99.18}}{\mathbf{100}}\mathbf{X}\ \mathbf{95} = \mathbf{94.22}$$

$$\mathbf{CE}\ (\mathbf{15}) = \frac{\mathbf{14}\ \boldsymbol{X}\ \mathbf{0.009}}{\mathbf{14}\ \boldsymbol{X}\ \mathbf{0.01}}\mathbf{X}\ \mathbf{100} = \mathbf{89.76}$$

$$\mathbf{RME}\ (\mathbf{15}) = \frac{\mathbf{2.19}}{\mathbf{2.46}}\mathbf{X}\ \mathbf{100} = \mathbf{89.02}$$

$$\mathbf{OE}\ (\mathbf{15}) = \frac{\mathbf{89.02}}{\mathbf{99.18}}\mathbf{X}\ \mathbf{100} = \mathbf{89.76}$$

$$\mathbf{MI}\ (\mathbf{15}) = \frac{\mathbf{2.46} + \mathbf{2.61} + \mathbf{17.3} + \mathbf{5.5}}{\mathbf{2.19}} = \mathbf{12.73}$$

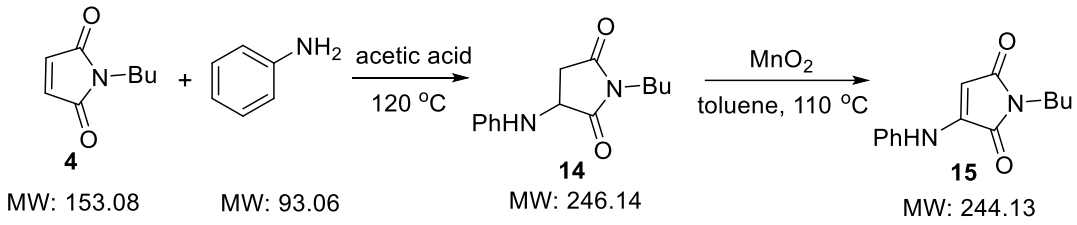
$$\mathbf{MP}\ (\mathbf{15}) = \frac{\mathbf{100}}{\mathbf{12.73}} = \mathbf{7.86}$$

$$\mathbf{E\ Factor}\ (\mathbf{15}) = \mathbf{12.73} - \mathbf{1} = \mathbf{11.73}$$

$$\mathbf{SI}\ (\mathbf{15}) = \frac{\mathbf{22.8}}{\mathbf{2.19}} = \mathbf{10.41}$$

$$\mathbf{WI}\ (\mathbf{15}) = \frac{\mathbf{0}}{\mathbf{2.19}} = \mathbf{0}$$

Cumulative metrics for compound 15:



MW: 153.08 MW: 93.06 MW: 246.14 MW: 244.13

$$\mathbf{AE}\ (\mathbf{15\ cumulative}) = \frac{\mathbf{244.12}}{\mathbf{153.08} + \mathbf{93.06}}\mathbf{X}\ \mathbf{100} = \mathbf{99.18}$$

$$\mathbf{AEf}\ (\mathbf{15\ cumulative}) = \frac{\mathbf{99.18}}{\mathbf{100}}\mathbf{X}\ \mathbf{54.10} = \mathbf{54.65}$$

$$\mathbf{CE}\ (\mathbf{15\ cumulative}) = \frac{\mathbf{14}\ \boldsymbol{X}\ \mathbf{0.009}}{\mathbf{8}\ \boldsymbol{X}\ \mathbf{0.065} + \mathbf{6}\ \boldsymbol{X}\ \mathbf{0.07}}\mathbf{X}\ \mathbf{100} = \mathbf{13.40}$$

$$\mathbf{RME}\ (\mathbf{15\ cumulative}) = \frac{\mathbf{2.19}}{\mathbf{2.46/0.566}}\mathbf{X}\ \mathbf{100} = \mathbf{50.45}$$

$$\mathbf{OE}\ (\mathbf{15\ cumulative}) = \frac{\mathbf{50.45}}{\mathbf{99.18}}\mathbf{X}\ \mathbf{100} = \mathbf{50.87}$$

$$\mathbf{MI\ \ (15\ \ cumulative)} = \frac{\mathbf{2.46\ \ X\ \ 38.36 + 2.61 + 17.3 + 5.5}}{\mathbf{2.19}} = \mathbf{54.69}$$

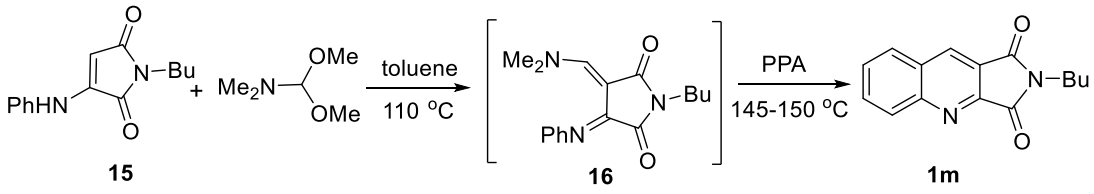
$$\mathbf{MP\ \ (15\ \ cumulative)} = \frac{\mathbf{100}}{\mathbf{54.69}} = \mathbf{1.83}$$

$$\mathbf{E\ Factor\ \ (15\ \ cumulative)} = \mathbf{54.69 - 1 = 53.69}$$

$$\mathbf{SI\ \ (15\ \ cumulative)} = \frac{\mathbf{83.1}}{\mathbf{2.19}} = \mathbf{37.95}$$

$$\mathbf{WI\ \ (15\ \ cumulative)} = \frac{\mathbf{280}}{\mathbf{2.19}} = \mathbf{127.85}$$

Steps 3&4: Synthesis of 2-butyl-1*H*-pyrrolo[3,4-b]quinoline-1,3(2*H*)-dione (1m)



Experimental procedures: A solution of 244 mg (1.0 mmole) of compound **15**, 238 mg (2.0 mmole) of dimethylformamide dimethyl acetal and 5 mL of toluene was refluxed for 3 h. Evaporation of toluene gave a dark red-brown gum of compound **16**, which was heated in 6 g of polyphosphoric acid at 145-150 °C for 15 min. The solution was poured into 60 mL of cold water, and the resulting dark solid was collected and heated with 8 mL of methanol. Filtration of the hot mixture and evaporation of filtrate gave 120 mg (47%) of crude product. Recrystallization from methanol (*assuming use of 0.4 mL*) gave 114 mg of white solid (*assuming 95% of recrystallization yield*) of compound **1m**.

Materials used for metrics calculations: compound **15** (0.244 g, 0.001mole), dimethylformamide dimethyl acetal (0.238 g, 0.002 mole), toluene (5 mL, 4.33 g), polyphosphoric acid (6 g, 0.062 mole), water (60 mL, 60 g), methanol (8.4 mL, 6.64 g), compound **1m** (0.114 g, 0.45 mmole).

$$\mathbf{AE\ \ (1m)} = \frac{\mathbf{254.11}}{\mathbf{244.12 + 119.09}}\mathbf{X\ \ 100} = \mathbf{69.96}$$

$$\mathbf{AEf\ \ (1m)} = \frac{\mathbf{69.96}}{\mathbf{100}}\mathbf{X\ \ 95} = \mathbf{66.46}$$

$$\mathbf{CE\ \ (1m)} = \frac{\mathbf{15\ \ X\ \ 0.00045}}{\mathbf{14\ \ X\ \ 0.001 + 5\ \ X\ \ 0.002}}\mathbf{X\ \ 100} = \mathbf{28.06}$$

$$\mathbf{RME\ \ (1m)} = \frac{\mathbf{0.114}}{\mathbf{0.244 + 0.238}}\mathbf{X\ \ 100} = \mathbf{23.65}$$

$$\mathbf{OE\ (1m)} = \frac{\mathbf{23.65}}{\mathbf{69.96}}\mathbf{X\ 100} = \mathbf{33.81}$$

$$\mathbf{MI\ (1m)} = \frac{\mathbf{0.244 + 0.238 + 4.33 + 6 + 60 + 6.64}}{\mathbf{0.114}} = \mathbf{679.4}$$

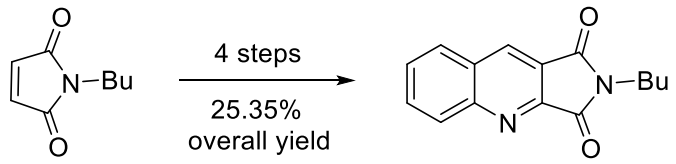
$$\mathbf{MP\ (1m)} = \frac{\mathbf{100}}{\mathbf{679.4}} = \mathbf{0.15}$$

$$\mathbf{E\ Factor\ (1m)} = \mathbf{679.4 - 1} = \mathbf{678.4}$$

$$\mathbf{SI\ (1m)} = \frac{\mathbf{16.97}}{\mathbf{0.114}} = \mathbf{148.86}$$

$$\mathbf{WI\ (1m)} = \frac{\mathbf{60}}{\mathbf{0.114}} = \mathbf{526.32}$$

Cumulative metrics for compound 1m:



4 **1m**

$$\mathbf{AE\ (1m\ cumulative)} = \frac{\mathbf{254.11}}{\frac{\mathbf{244.12}}{\mathbf{0.9918}} + \mathbf{119.09}}\mathbf{X\ 100} = \mathbf{69.58}$$

$$\mathbf{AEf\ (1m\ cumulative)} = \frac{\mathbf{69.58}}{\mathbf{100}}\mathbf{X\ 25.35} = \mathbf{17.64}$$

$$\mathbf{CE\ (1m\ cumulative)} = \frac{\mathbf{15\ X\ 0.00045}}{\mathbf{8\ X\ 0.065 + 6\ X\ 0.07 + 2\ X\ 5}}\mathbf{X\ 100} = \mathbf{61.53}$$

$$\mathbf{RME\ (1m\ cumulative)} = \frac{\mathbf{0.114}}{\frac{\mathbf{0.244}}{\mathbf{0.5045}} + \mathbf{0.238}}\mathbf{X\ 100} = \mathbf{15.8}$$

$$\mathbf{OE\ (1m\ cumulative)} = \frac{\mathbf{15.8}}{\mathbf{69.58}}\mathbf{X\ 100} = \mathbf{22.71}$$

$$\mathbf{PMI\ (1m\ cumulative)} = \frac{\mathbf{0.244X54.69 + 0.238 + 4.33 + 6 + 60 + 6.64}}{\mathbf{0.114}}$$

$$= \mathbf{794.31}$$

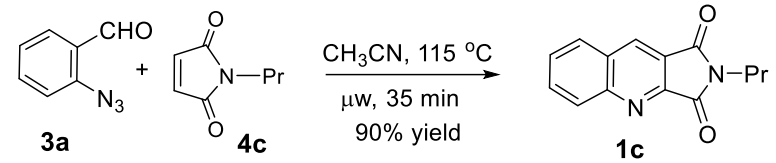
$$\mathbf{MP\ (1m\ cumulative)} = \frac{\mathbf{100}}{\mathbf{794.31}} = \mathbf{0.13}$$

$$\mathbf{E\ Factor\ (1m\ cumulative)} = \mathbf{794.31 - 1} = \mathbf{793.31}$$

$$\mathbf{SI\ (1m\ cumulative)} = \frac{\mathbf{60.3 + 22.8 + 16.97}}{\mathbf{0.114}} = \mathbf{877.81}$$

$$\mathbf{WI\ (1m\ cumulative)} = \frac{\mathbf{340}}{\mathbf{0.114}} = \mathbf{2982.46}$$

6.3. Current Method, Process C (1c as an example)



This is a one-pot synthesis with only one step of separation for the final product.

General procedure for the synthesis of **1c.** To a solution of 2-azidobenzaldehyde **3a** (147 mg, 1.0 mmol), and N-propylmaleimide **4c** (153 mg, 1.1 mmol) in 2.5 mL of CH_3CN was heated under microwaves at 115 ºC for 35 min. The reaction mixture upon the completion of the reaction as monitored by LC-MS. The reaction mixture was concentrated and then recrystallized from 3:1 EtOH:H_2O (2.0 mL), afford 216 mg (90 %) of compound **1c**.

Materials used for metrics calculations: 2-azidobenzaldehyde (0.147 g, 1.0 mmol), N-propylmaleimide (0.153 g, 1.1 mmol), CH_3CN (2.5 mL, 1.965 g), EtOH (1.13 mL, 1.18 g), water (0.5 mL, 0.5 g) and compound **1c** (0.216 g, 0.9 mmole).

$$\mathbf{AE}\ (\mathbf{1c}) = \frac{\mathbf{240.09}}{\mathbf{147.04 + 139.06}}\mathbf{X}\ \mathbf{100} = \mathbf{83.92}$$

$$\mathbf{AEf}\ (\mathbf{1c}) = \frac{\mathbf{83.92}}{\mathbf{100}}\mathbf{X}\ \mathbf{90} = \mathbf{75.53}$$

$$\mathbf{CE}\ (\mathbf{1c}) = \frac{\mathbf{14}\ \boldsymbol{X}\ \mathbf{0.0009}}{\mathbf{7}\ \boldsymbol{X}\ \mathbf{0.0001 + 7}\ \boldsymbol{X}\ \mathbf{0.0011}}\mathbf{X}\ \mathbf{100} = \mathbf{85.68}$$

$$\mathbf{RME}\ (\mathbf{1c}) = \frac{\mathbf{0.216}}{\mathbf{0.147 + 0.153}}\mathbf{X}\ \mathbf{100} = \mathbf{72.0}$$

$$\mathbf{OE}\ (\mathbf{1c}) = \frac{\mathbf{72}}{\mathbf{83.92}}\mathbf{X}\ \mathbf{100} = \mathbf{85.79}$$

$$\mathbf{PMI}\ (\mathbf{1c}) = \frac{\mathbf{0.147 + 0.153 + 1.965 + 1.18 + 0.5}}{\mathbf{0.216}} = \mathbf{18.26}$$

$$\mathbf{MP}\ (\mathbf{1c}) = \frac{\mathbf{100}}{\mathbf{18.26}} = \mathbf{5.476}$$

$$\mathbf{E\ Factor}\ (\mathbf{1c}) = \mathbf{18.26 - 1} = \mathbf{17.26}$$

$$\mathbf{SI}\ (\mathbf{1c}) = \frac{\mathbf{3.145}}{\mathbf{0.216}} = \mathbf{14.56}$$

$$\mathbf{WI}\ (\mathbf{1c}) = \frac{\mathbf{0.5}}{\mathbf{0.216}} = \mathbf{2.31}$$

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