Red-shifted two-photon-sensitive phenanthridine photocages: synthesis and characterisation

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General experimental

Chemicals

All reagents were purchased from Merck Group, Fluorochem, Thermo Fischer Scientific, Acros, TCI Europe Research and VWR and used as received unless otherwise stated.

Solvents

Solvents were used as received unless otherwise stated.

Chromatography

Reaction progress was monitored by analytical TLC using Merck aluminium coated plates covered with a 0.2 mm layer of silica gel 60 F_{254}. Product spots were visualised by UV irradiation at 254 nm and subsequent staining with potassium permanganate solution, followed by heating. Column chromatography was carried out with silica gel (33 – 70 µm) supplied by VWR or with an automatic Büchi chromatography system (Pure C-815 Flash) equipped with pre-packed columns from the same supplier. HPLC analyses were performed on a Shimadzu HPLC system with Labsolution® software (Marne-la-Vallée, France) equipped with a Phenomenex® Aeris Widepore™ XB-C_{18} 150 × 4.6 mm, 3.6 µm. Elution was conducted with a flowrate of 1 mL·min^{-1} with the isocratic program: A/B (55/45) for 10 min. Buffer A contained DI water and buffer B HPLC grade MeCN. Solution detection was done with the diode array detector. Products were spectrophotometrically monitored at OD_{280}.

Spectroscopy

^{1}H NMR spectra were recorded at 500 MHz, ^{13}C NMR at 125 MHz and ^{19}F NMR at 76 MHz on Bruker Avance 500 at 300 K as described below unless otherwise stated. The chemical shifts (δ) are quoted relative to residual signals of the solvent on the parts per million (ppm) scale. NMR peaks are reported as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), broad (br), doublet of doublets (dd), doublet of triplets (dt), doublet of doublet of doublets (ddd), doublet of doublet of triplets (ddt), triplet of doublets (dt), doublet of quartets (dq) and preceded by apparent (app.) if required. Coupling constants (*J* values) are reported in Hertz (Hz). Spectra were referenced to the residual deuterated solvent used (for chloroform: 7.26 ppm, ^{1}H; 77.16 ppm, ^{13}C; methanol-d_3: 3.31 ppm, ^{1}H; 49.00 ppm, ^{13}C; acetonitrile-d_2: 1.94 ppm, ^{1}H; 1.31 ppm). Infrared spectra were obtained on FT-IR spectrometer (Perkin Elmer) and deposits were made utilising thin-film deposition technique. High resolution mass spectra were recorded on a ThermoFischer Exactive Orbitrap spectrometer. In the presence of bromine, calculations were carried out with ^{79}Br isotope. UV–vis spectra were recorded on a UV-2700 spectrophotometer (Shimadzu), operating at room temperature (298 K). Sample buffer was used as blank for baseline correction. Fluorescence spectra were obtained on a F-7000 fluorescence spectrometer (Hitachi).

Mono-photonic irradiation

LED strips (405 ± 35 nm, 9.6 W, reference: BDL-F600P-12V-3528-01) were purchased on boulevard-des-leds.fr and powered by a 12 V and 2.9 A transformer. LED emission spectra were checked using the spectrophotometer (Figure S1). Subsequently, irradiation experiments were conducted within a bespoke wooden box, assembled from laser-cut MDF planks (3 mm thick) in a rectangular prism shape with inner dimensions of 5 cm × 10 cm. Within the box's interior, a one-meter-wide LED strip was wound along the inner

surface of the box. The test sample was positioned in a quartz cuvette of 1 cm × 1 cm in the middle of the box, maintaining a 2.5 cm distance between the middle point of the cuvette and the sides (Figure S2).

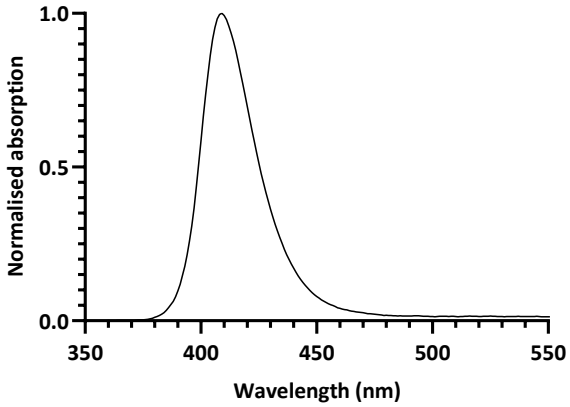


Figure S1: Irradiation box equipped with 405 nm LED strip.

Figure S2: Irradiation box equipped with 400 nm LED strip.

Bi-photonic irradiation

2PA cross sections (σ_2) were derived from the two-photon excited fluorescence (TPEF) cross sections (σ_2 ϕ_f) and the fluorescence emission quantum yield (ϕ_f). TPEF cross sections were measured relative to fluorescein in 0.01 M aqueous NaOH in the 680-1000 nm spectral range[1] using the well-established method described by Xu and Webb[2] and the appropriate solvent-related refractive index corrections.[3] The quadratic dependence of the fluorescence intensity on the excitation power was checked for each sample and all wavelengths. Measurements were conducted using an excitation source delivering fs pulses. A Chameleon Ultra II (COHERENT) with Nd:YVO4-pumped Ti:Sapphire oscillator, generating 140 fs pulses at an 80 MHz repetition rate, was used to scan the 680-1080 nm range. The excitation was focused into the cuvette through a microscope objective (10X, NA 0.25). The fluorescence was detected in epifluorescence mode via a dichroic mirror (Chroma 675dcxru) and a barrier filter (Chroma e650sp-2p) by a compact CCD spectrometer module BWTek BTC112E. Total fluorescence intensities were obtained by integrating the corrected emission. For all compounds, rescaled 1PA and 2PA spectra were superimposed, indicating that the 1P and 2P allowed excited states are the same, which is a hallmark of a non-centrosymmetric probe.

Relative quantum yields

Decaging

Actinometry measurements displayed photon flux value of $I_{405\,nm} = 7.2477 \times 10^{-8}$ einstein·L^{-1}.cm^{-2} determined with ferrioxalate standard.[4]
Starting from quantum yield definition:

$$\Phi_{u,st} = \frac{number\ of\ events}{number\ of\ photon\ absorbed} \quad (1)$$

(1) can be rewritten in the case of ferrioxalate:

$$\Phi_{u,st} = \frac{dn_{Fe^{2+}}}{dt} / \frac{df}{dt}$$

Where $n_{Fe^{2+}}$ represents de amount of iron (II) formed and f is the fraction of light absorbed given by:

$$f = I_0 - I$$

Therefore, the photon flux measure arises from the loss of actinometric ferrioxalate and is given by the equation:

$$-\frac{dn_{Fe^{3+}}}{dt} = \frac{dn_{Fe^{2+}}}{dt} = \Phi_{u,st} f \quad (2)$$

Where I_0 is the incident light intensity in einstein·L^{-1}, $\Phi_{u,st}$ the decaging quantum yield of ferrioxalate, $[Fe^{2+}]$ and $[Fe^{3+}]$ the iron concentrations in mol·L^{-1}.
Iron (II) concentration is derived from the Beer-Lambert law given by:

$$A_{510} = \varepsilon_{510} l [Fe^{2+}]$$

And
$A_{510} = log \frac{I_0}{I}$ Where A_{510} is the absorbance of the phenantroline-Fe^{2+} complex at 510 nm, ε_{510} is the molar absorptivity at 510 nm of this complex in L·mol^{-1}·cm^{-1} and l is the length of the path travelled by light in the sample in cm. Therefore,

$$I_0 = \frac{dn_{Fe^{2+}}}{dt}\left(\frac{1}{\Phi_{u,st}(1 - 10^{-A_{510}})}\right) = \frac{dA_{510}}{dt}\left(\frac{V_{irr} V_{an}}{\varepsilon_{510} l \Phi_{u,st} V_{prel}(1 - 10^{-A_{510}})}\right) \quad (3)$$

Where V_{irr} is the volume of the irradiated solution, V_{an} the volume of the solution analysed in the spectrometer and V_{prel} the volume sampled from the irradiated solution. The experiment is carried out so that the concentration of the actinometric compound and the path length of the exposure cell are sufficiently high to make the kinetics of this reaction approximately zero-order. The value of $\Phi_{u,st}$ taken for these experiments is 1.13.[4]
Finally, the quantum efficiency ($\Phi_{u,x}$) of the photolysis reaction for each phenanthridine cage was calculated from the following equation:

$$\Phi_{u,x} \approx (I_s \sigma t_{90\%})^{-1}$$

Where I_s is the irradiation light intensity divided by the surface of the cuvette irradiated with $I_s = \frac{I_0}{S}$, (S = 9 cm²), σ is the decadic extinction coefficient (1000 × ε, molar extinction coefficient of the molecule at the specified wavelength) and $t_{90\%}$ the time (in second) required to achieve a 90% consumption of the starting material.

Fluorescence

Photo-luminescence quantum yield is defined as the ratio of number of photons emitted to the number of photons absorbed[5] and can be experimentally determined according to the equation:[6]

$$\Phi_{f,x} = \Phi_{f,st} \frac{F_x}{F_{st}} \frac{f_{st}}{f_x} \left(\frac{\eta_x}{\eta_{st}}\right)^2$$

Where x and st denotes the sample and the standard respectively. Φ_f represent the fluorescence quantum yield, F the integral of the fluorescence emission, f the absorption factor, and η the refractive index. f is calculated by the expression:

$$f = 1 - 10^{-A_{\lambda exc}}$$

F is defined as:

$$F = \int_{n}^{m} I_f\left(\lambda_{exc}, \lambda_f\right) d\lambda_f$$

Where I_f is the fluorescence intensity of the compound excited at λ_{exc}, n and m are the lower and upper limit of integration which must cover the entire emission peak of each compound. The values F_x and F_{st} were measured by exciting both fluorescein and sample at the $\lambda_{max,abs}$ of the sample. The reference value for $\Phi_{f,st}$ in NaOH aq. 0.1 M is 0.925.[6] Steady-state fluorescence measurements were performed on dilute solutions (ca. 10^{-6} M, optical density ≤ 0.1) contained in standard 1 cm quartz cuvettes. Fluorescence quantum yields of these dilute chromophore solutions were measured according to literature procedures.[6, 7] The reported fluorescence quantum yield values obtained via this method are within ± 0.005.

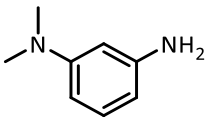
Miscellaneous

Unless stated otherwise, all reaction mixtures were stirred magnetically. All reactions involving moisture sensitive techniques were performed under an atmosphere of dry argon via standard vacuum line techniques and glassware was flame dried and allowed to cool under reduced pressure. Within this text, room temperature is defined as between 19 – 22 °C. Reactions described as being performed at –78 °C were cooled by an acetone bath with submerged solid CO_2 pellets. Reactions performed at 0 °C were cooled with an ice and water bath. Concentration *in vacuo* refers to distillation on a Büchi® rotary evaporator, and where appropriate under high vacuum.

Synthesis & Characterisation

Starting material preparation

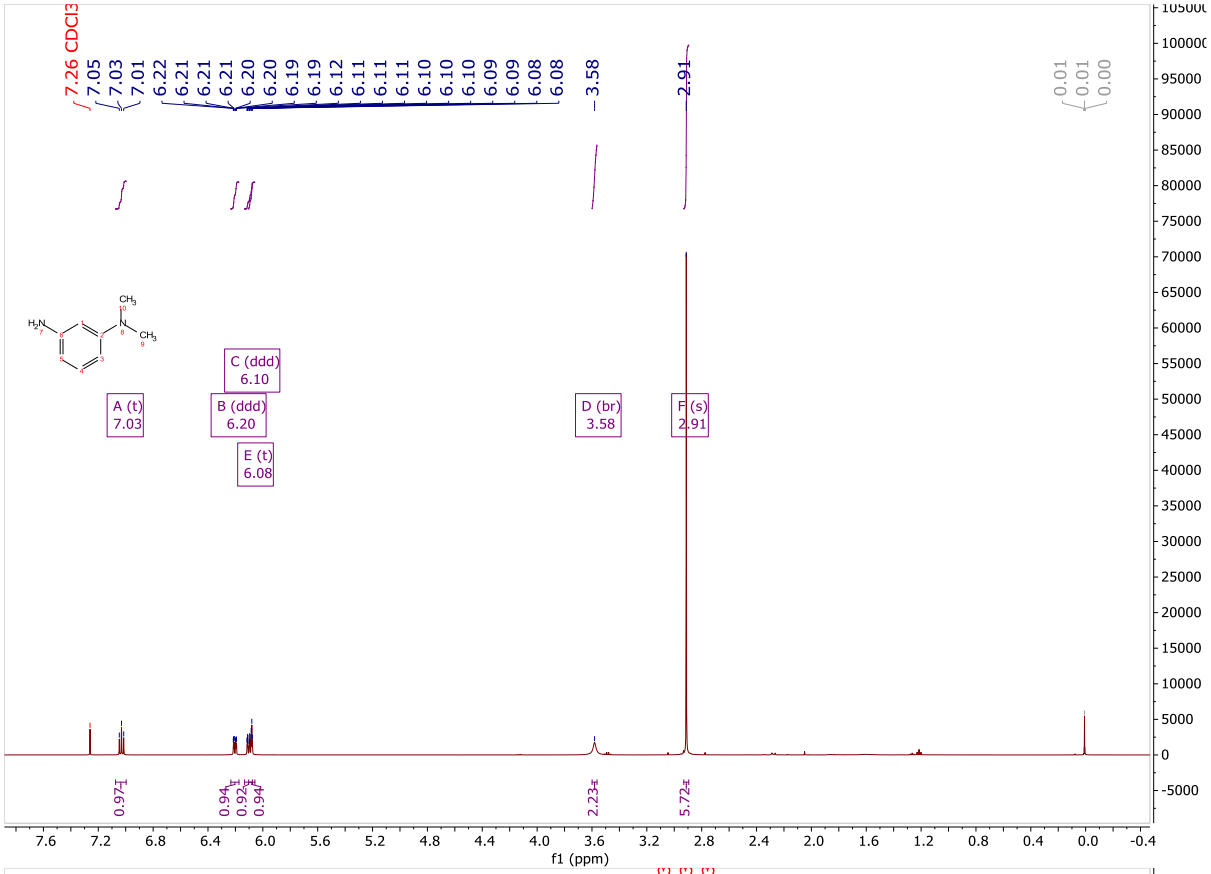
N,N-Dimethylbenzene-1,3-diamine[8]

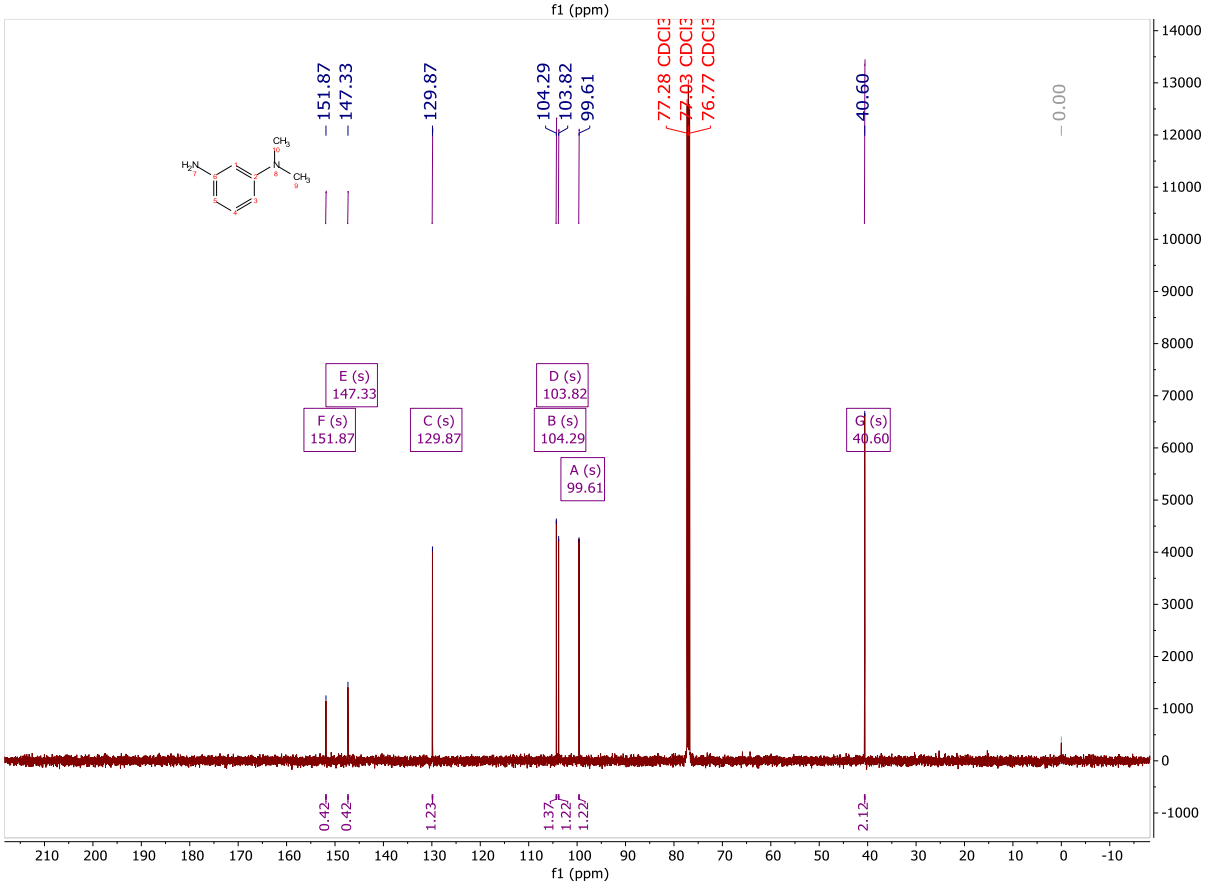


In a three neck round bottom flask, 1.000 g of Pd/C 10% (w/w) was dissolved in EtOAc (200 mL, 0.3 M). The vessel was purged with H_2 (3 × 200 mL) then *N*,*N*-dimethyl-3-nitroaniline (10.00 g, 60.32 mmol, 1 eq.) was added. The reaction was stirred 3 hours at rt under H_2 and it was filtered through a small pad of Celite® and another of silica. The filtrate was concentrated *in vacuo* to afford *N,N*-dimethylbenzene-1,3-diamine as a brown liquid (7.854 g, 57.29 mmol, 96%).

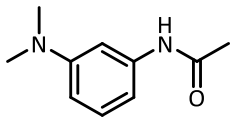
^{1}H NMR (500 MHz, chloroform-*d*) δ 7.03 (t, *J* = 8.0 Hz, 1H), 6.20 (ddd, *J* = 8.2, 2.4, 0.8 Hz, 1H), 6.10 (ddd, *J* = 7.7, 2.1, 0.9 Hz, 1H), 6.08 (t, *J* = 2.3 Hz, 1H), 3.58 (br, 2H), 2.91 (s, 6H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 151.9 (C), 147.3 (C), 129.9 (CH), 104.3 (CH), 103.8 (CH), 99.6 (CH), 40.6 ($2CH_3$); HRMS (ESI) calcd for $C_8H_{13}N_2$ $[M+H]^+$ 137.1073, observed 137.1068.





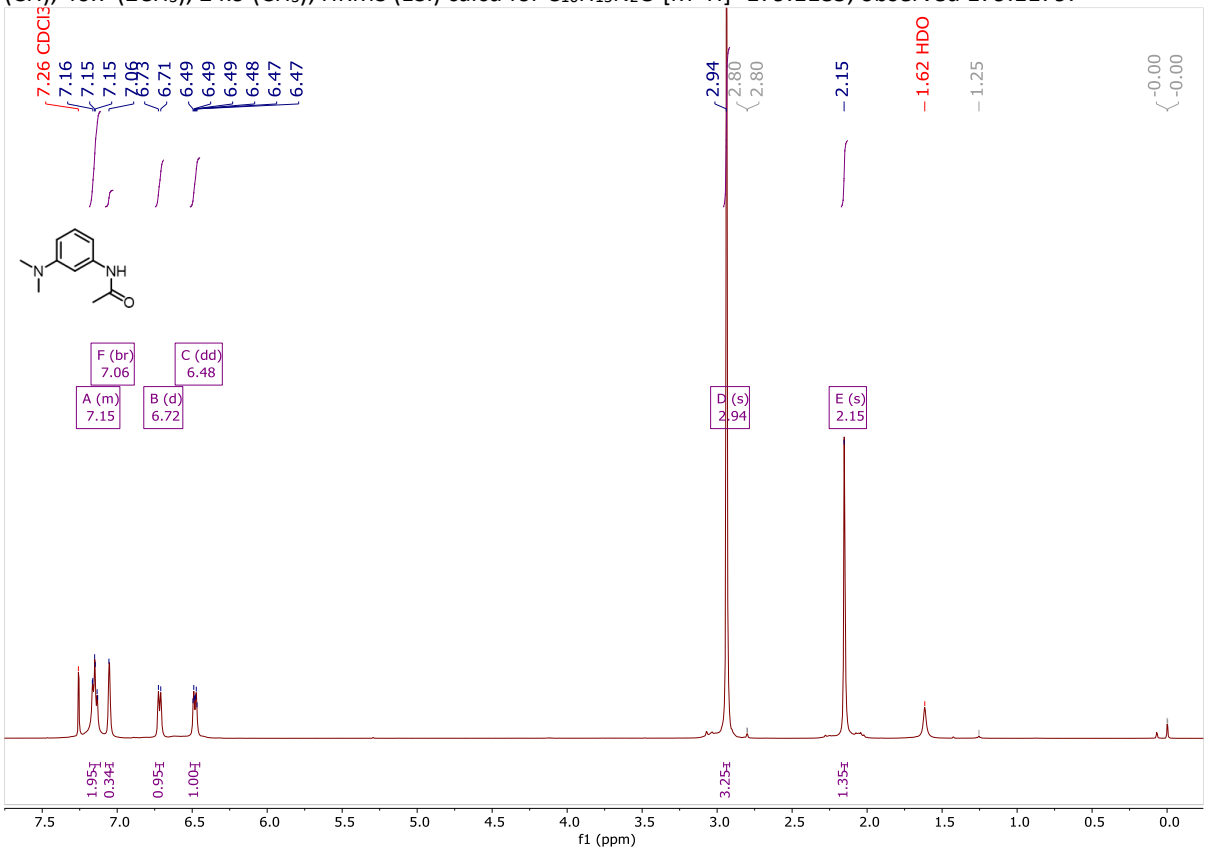
***N*-(3-(Dimethylamino)phenyl)acetamide (1)[9]**

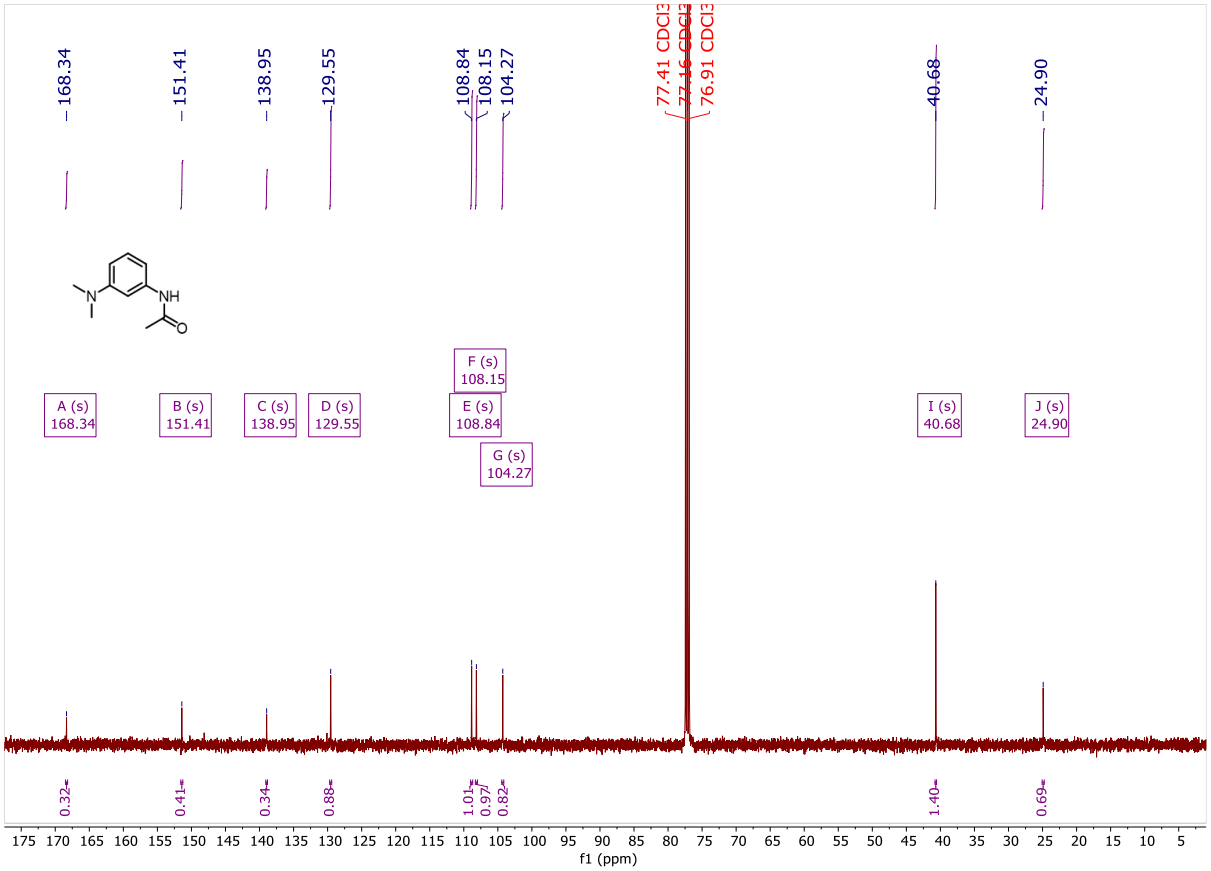


In a round bottom flask, *N,N*-dimethylbenzene-1,3-diamine (1.608 g, 11.73 mmol, 1 eq.) was dissolved in DCM (39 mL, 0.3 M), pyridine (3.35 mL, 35.4 mmol, 3 eq.) and acetic anhydride (5.70 mL, 70.9 mmol, 6 eq.) were added and the reaction was stirred at rt for 3 hours. After reaction completion, the crude mixture was diluted with sat. aq. $NaHCO_3$ (50 mL). The resulting aqueous phase was extracted three times with DCM (3 × 50 mL). The organic layers were combined, washed with brine (5 mL), and then dried over $MgSO_4$. The mixture was concentrated *in vacuo* and purified by flash column chromatography (100% – 50% cyclohexane/EtOAc), yielding **1** (1.956 g, 10.91 mmol, 93%) as a brown liquid.

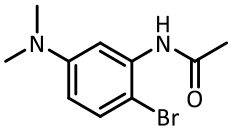
^{1}H NMR (500 MHz, chloroform-*d*) δ 7.18 – 7.11 (m, 2H), 7.06 (br, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.48 (dd, *J* = 8.5, 2.4 Hz, 1H), 2.94 (s, 6H), 2.15 (s, 3H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 168.3 (C), 151.4 (C), 139.0 (C), 129.6 (CH), 108.8 (CH), 108.2 (CH), 104.3 (CH), 40.7 ($2CH_3$), 24.9 (CH_3); HRMS (ESI) calcd for $C_{10}H_{15}N_2O$ $[M+H]^+$ 179.1185, observed 179.1179.





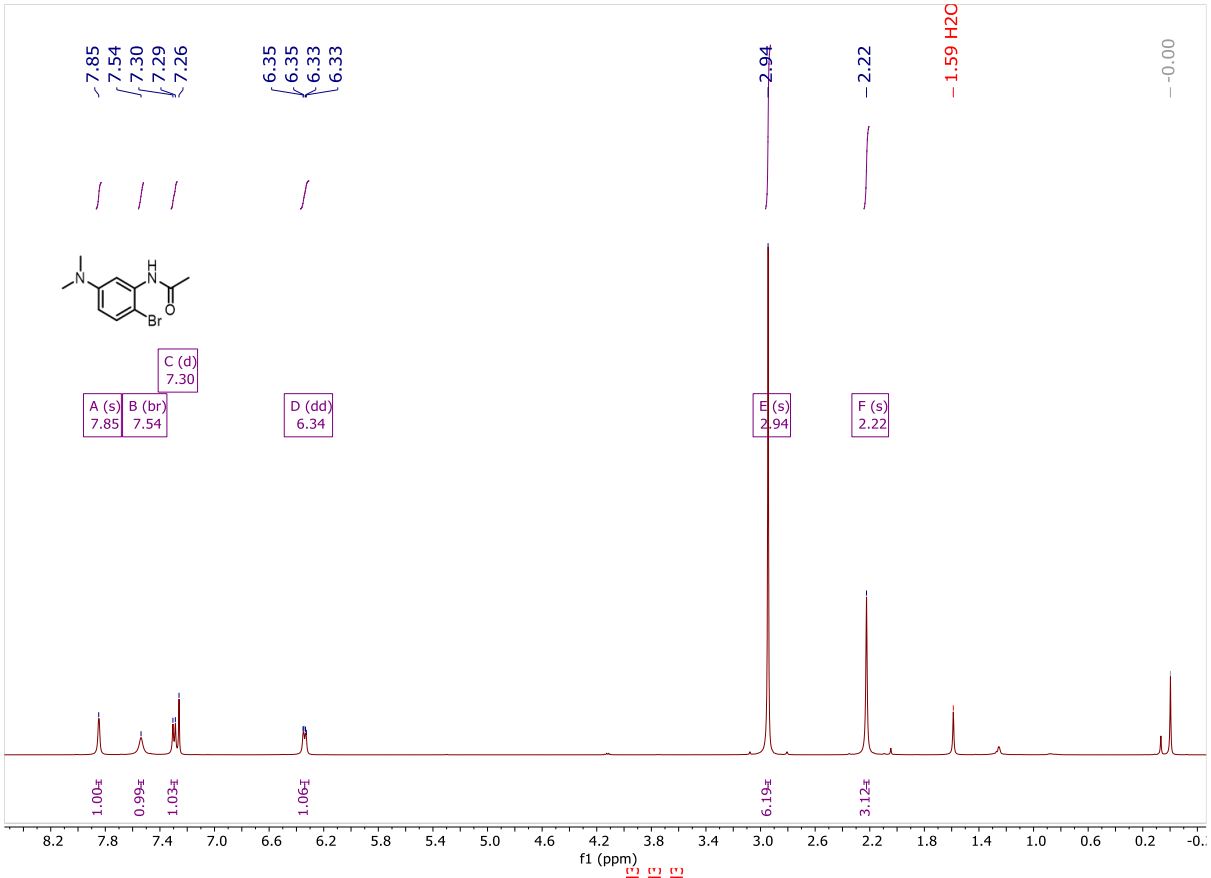
_N_-(2-Bromo-5-(dimethylamino)phenyl)acetamide (2)

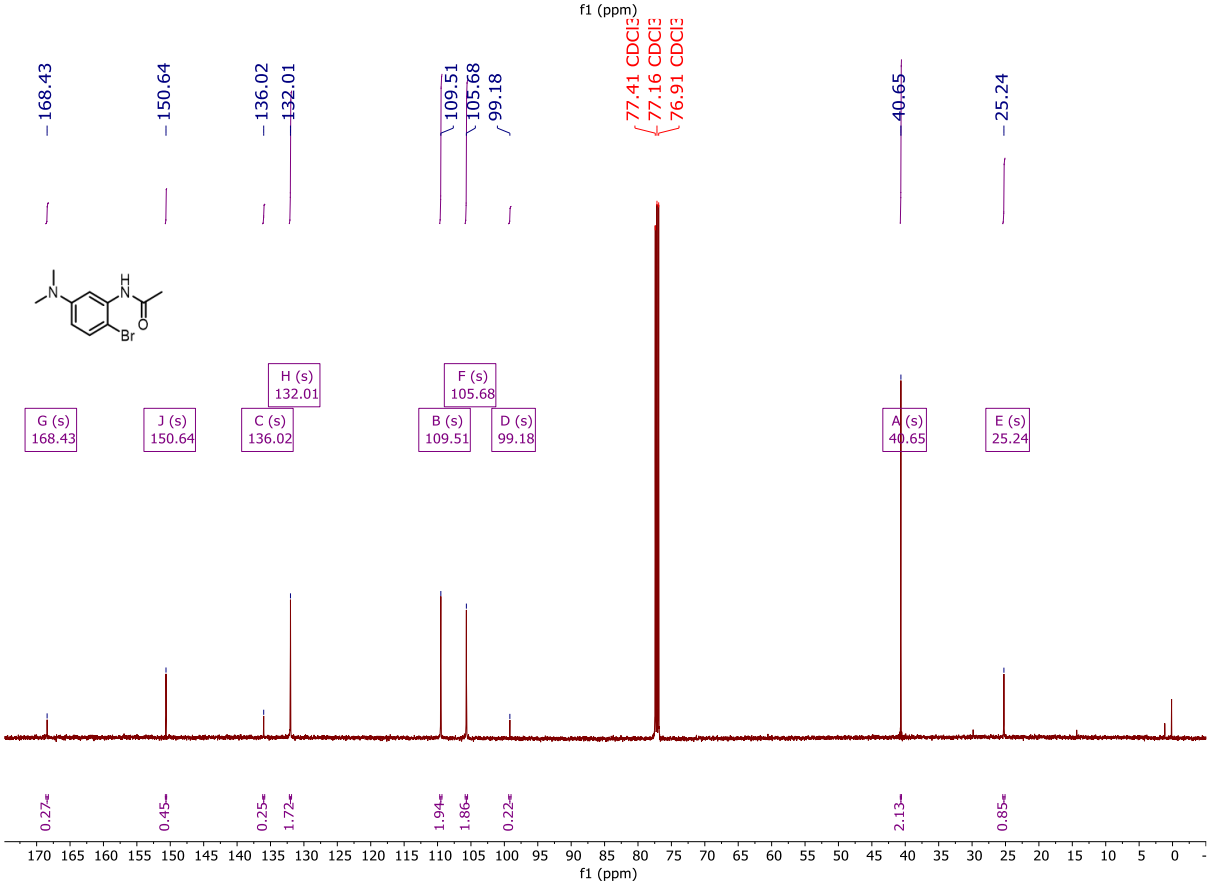


In a round bottom flask, a solution of **1** (1.910 g, 10.72 mmol, 1 eq.) in DCM (30 mL) and a separate solution of NBS (1.908 g, 10.72 mmol, 1 eq.) in DCM (7 mL) were both cooled to -50 °C. The NBS solution was then slowly added to the phenylacetamide solution, and the resulting mixture was stirred at -50 °C for 30 minutes. The reaction mixture was then diluted with H_2O (40 mL) and the resulting aqueous phase was extracted 3 times with DCM (3 × 40 mL). The organic layers were combined, washed with brine (10 mL) and dried over $MgSO_4$. The mixture was then concentrated *in vacuo*. The crude residue was purified by column chromatography (80% cyclohexane/EtOAc) to yield **2** (2.333 g, 9.112 mmol, 85%) as a white solid.

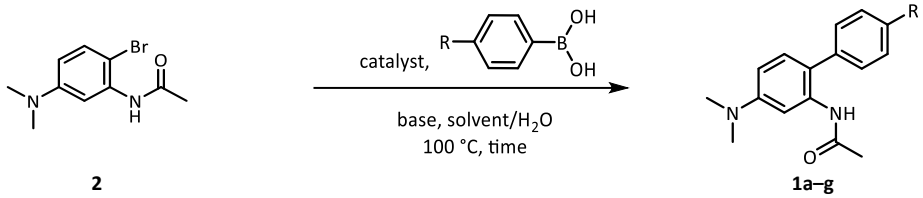
^{1}H NMR (500 MHz, chloroform-*d*) δ 7.85 (s, 1H), 7.54 (br, 1H), 7.30 (d, *J* = 9.0 Hz, 1H), 6.34 (dd, *J* = 9.1, 3.1 Hz, 1H), 2.94 (s, 6H), 2.22 (s, 3H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 168.4 (C), 150.6 (C), 136.0 (C), 132.0 (CH), 109.5 (CH), 105.7 (C), 99.2 (CH), 40.7 ($2CH_3$), 25.2 (CH_3); IR (ν = cm^{-1}) 1279, 1526, 1574, 1599, 1670; HRMS (ESI) calcd for $C_{10}H_{14}BrN_2O$ $[M+H]^+$ 257.0284, observed 257.0279.





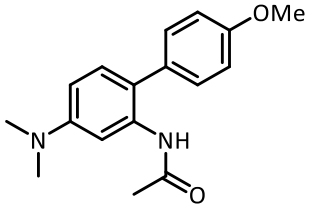
Suzuki-Miyaura couplings



Compound	R	Catalyst	Base	Solvent	Time	Yield
3a (H)	H	$Pd(OAc)_2$	K_3PO_4	MeOH	18 h	77%
	H	$Pd(PPh_3)_4$	Na_2CO_3	THF	18 h	91%
3b (Me)	Me	$Pd(PPh_3)_4$	Na_2CO_3	THF	24 h	49%
3c (OMe)	OMe	$Pd(OAc)_2$	K_3PO_4	MeOH	18 h	59%
3d (NMe_2)	NMe_2	$Pd(OAc)_2$	K_3PO_4	MeOH	24 h	50%
	NMe_2	$Pd(PPh_3)_4$	Na_2CO_3	THF	24 h	59%
3e (F)	F	$Pd(PPh_3)_4$	Na_2CO_3	THF	24 h	91%
3e (NO_2)	NO_2	$Pd(OAc)_2$	K_3PO_4	MeOH	24 h	34%
	NO_2	$Pd(PPh_3)_4$	Na_2CO_3	THF	24 h	54%

Table S1: Optimisation of Suzuki-Miyaura couplings for the synthesis of biaryls.

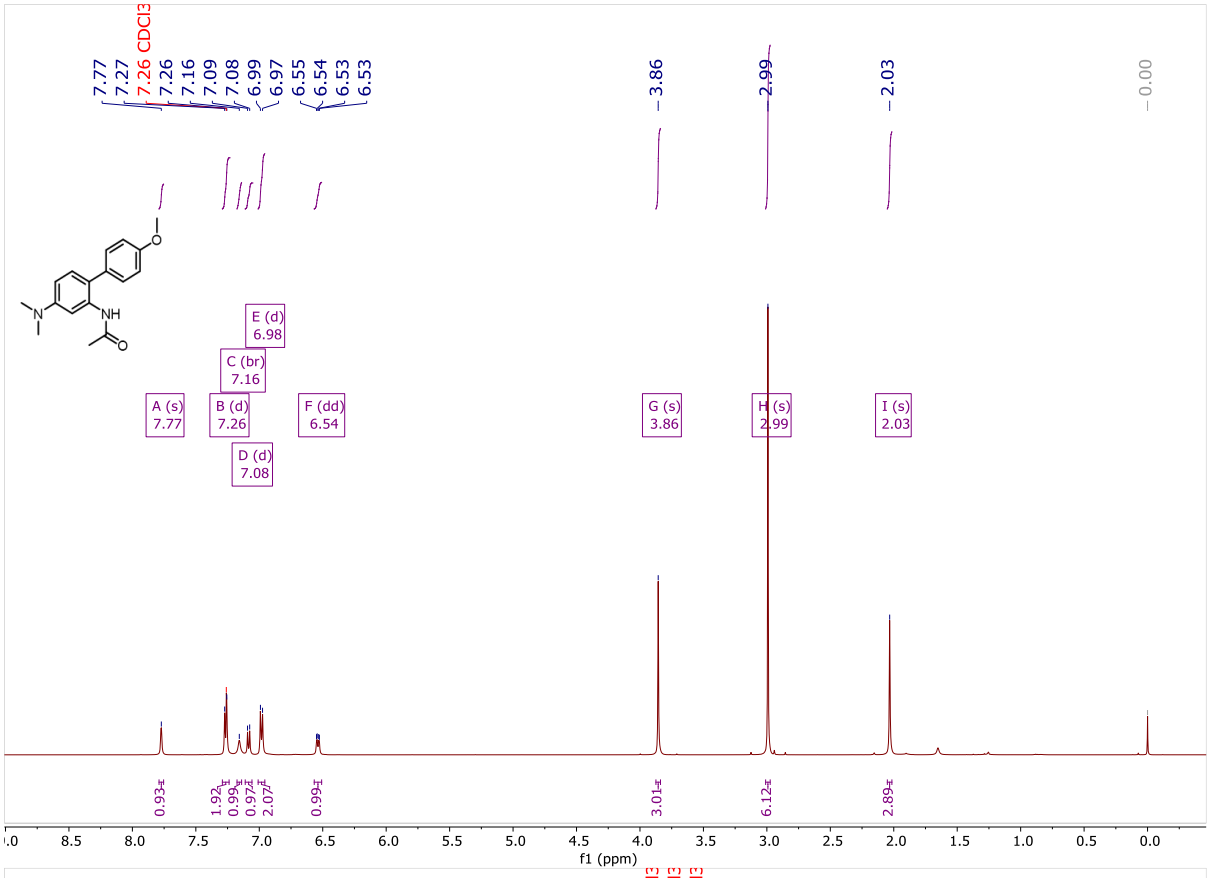
***N*-(4-(Dimethylamino)-4'-methoxy-[1,1'-biphenyl]-2-yl)acetamide (3c)** (adapted from the work of Gao *et al.*)[10]

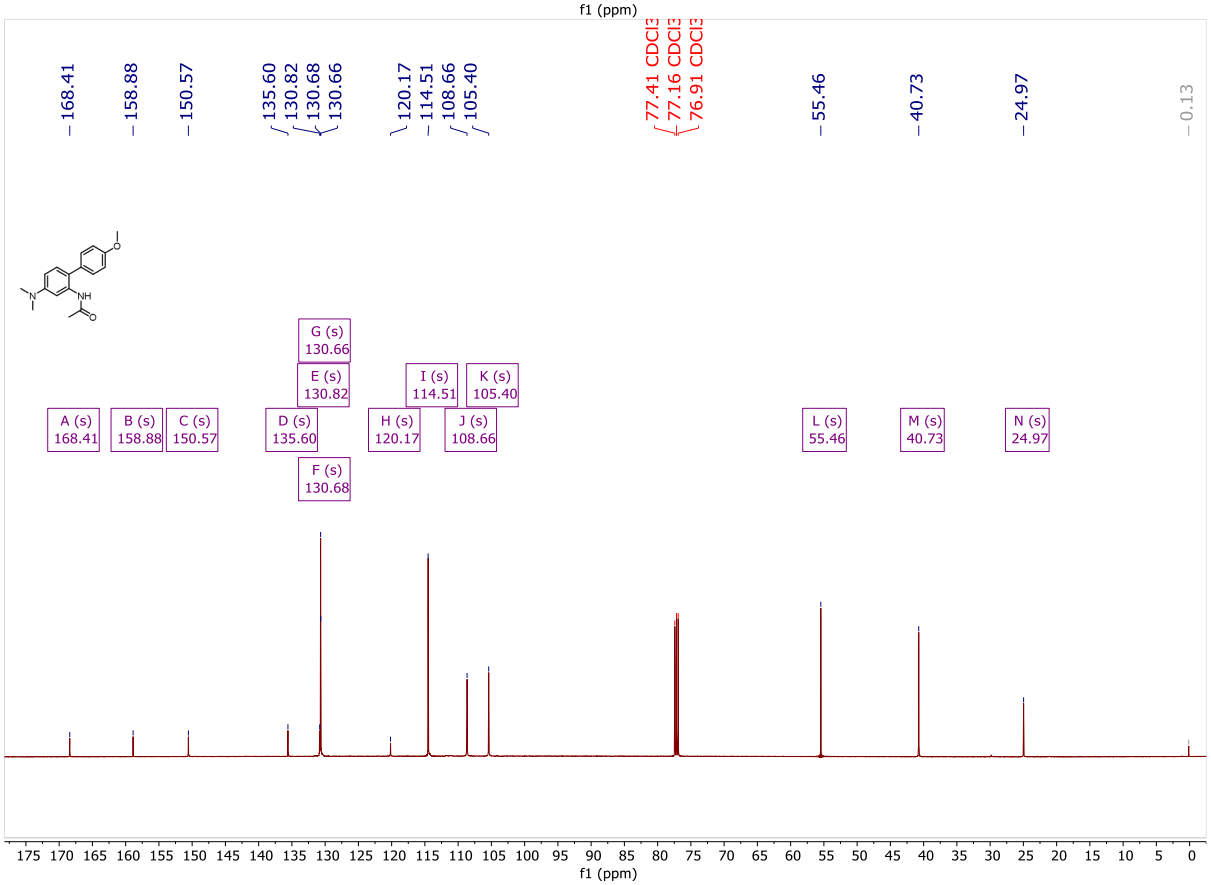


In a Schlenk flask under inert atmosphere, **2** (200.0 mg, 0.7812 mmol, 1 eq.), K_3PO_4 (497.0 mg, 2.343 mmol, 3 eq.), (4-methoxyphenyl)boronic acid (0.8593 mmol, 1.1 eq.), and $Pd(OAc)_2$ (8.8 mg, 62 µmol, 0.05 eq.) were combined. Argon was bubbled through a solvent mixture (MeOH/H_2O (1/1), 0.3 M) for 15 minutes before being added to the reaction mixture. The reaction was stirred at 100 °C for 24 hours. After cooling the reaction mixture to room temperature, it was filtered through a short pad of Celite®, and then diluted with H_2O (20 mL). The resulting aqueous phase was extracted three times with DCM (3 × 20 mL). The organic layers were combined, washed with brine (5 mL), and then dried over $MgSO_4$ before being concentrated *in vacuo*. The crude product was purified by recrystallisation from toluene, followed by EtOH yielding **3c** (131.0 mg, 0.4610 mmol, 59%) as an off-white solid.

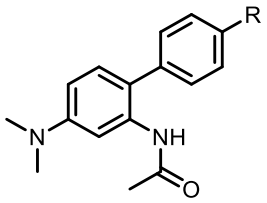
^{1}H NMR (500 MHz, chloroform-*d*) δ 7.77 (s, 1H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.16 (br, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.98 (d, *J* = 8.3 Hz, 2H), 6.54 (dd, *J* = 8.6, 2.6 Hz, 1H), 3.86 (s, 3H), 2.99 (s, 6H), 2.03 (s, 3H)

^{13}C NMR (125 MHz, chloroform-*d*) δ 168.7 (C), 159.1 (C), 150.8 (C), 135.9 (C), 131.1 (C), 130.9 (2CH), 130.9 (CH), 120.4 (C), 114.8 (2CH), 108.9 (CH), 105.7 (CH), 55.7 (CH_3), 41.0 ($2CH_3$), 25.2 (CH_3); IR (ν = cm^{-1}) 1241, 1490, 1559, 1619, 1667, 3318; HRMS (ESI) calcd for $C_{17}H_{21}N_2O_2$ $[M+H]^+$ 285.1492, observed 285.1587.





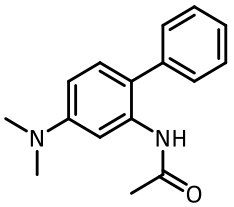
General procedure A for the preparation of bisphenyls



3a, R = H
3b, R = Me
3d, R = NMe_2
3e, R = F
3f, R = NO_2

In a Schlenk flask under inert atmosphere, **2** (200.0 mg, 0.7812 mmol, 1 eq.), Na_2CO_3 (497.2 mg, 1.56 mmol, 2 eq.), the corresponding boronic acid (0.859 mmol, 1.1 eq.) and $Pd(PPh_3)_4$ (9.0 mg, 7.8 µmol, 0.01 eq.) were combined. Argon was bubbled through a solvent mixture (THF/H_2O, 1/3, 0.3 M) for 15 minutes before being added to the reaction mixture. The reaction was stirred at 100 °C for 24 hours. After cooling the reaction mixture to room temperature, it was filtered through a short pad of Celite®, and then diluted with H_2O (20 mL). The resulting aqueous phase was extracted three times with DCM (3 × 20 mL). The organic layers were combined, washed with brine (5 mL), and then dried over $MgSO_4$ before being concentrated *in vacuo*. The crude product was purified by recrystallisation in the corresponding solvent or by column chromatography, yielding the respective biphenyl.

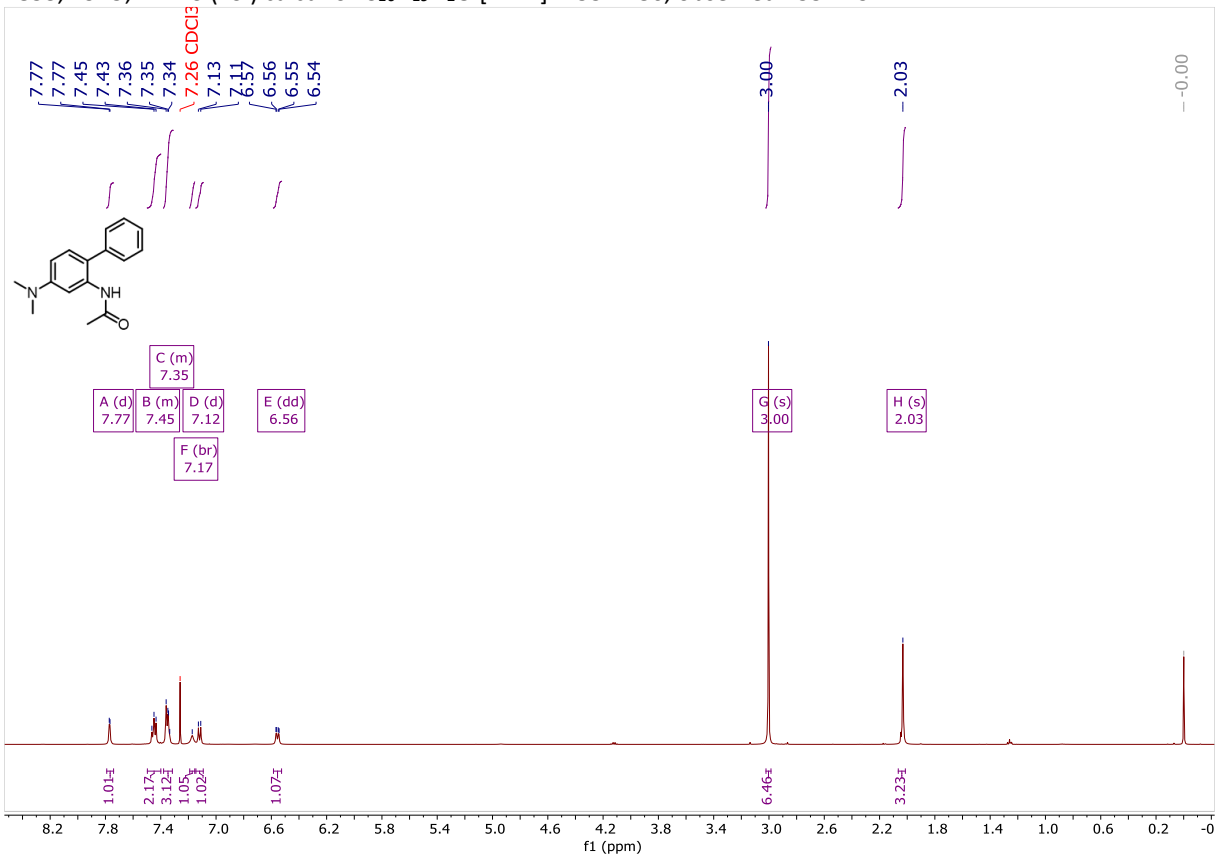
N-(4-(Dimethylamino)-[1,1'-biphenyl]-2-yl)acetamide (3a)[11]

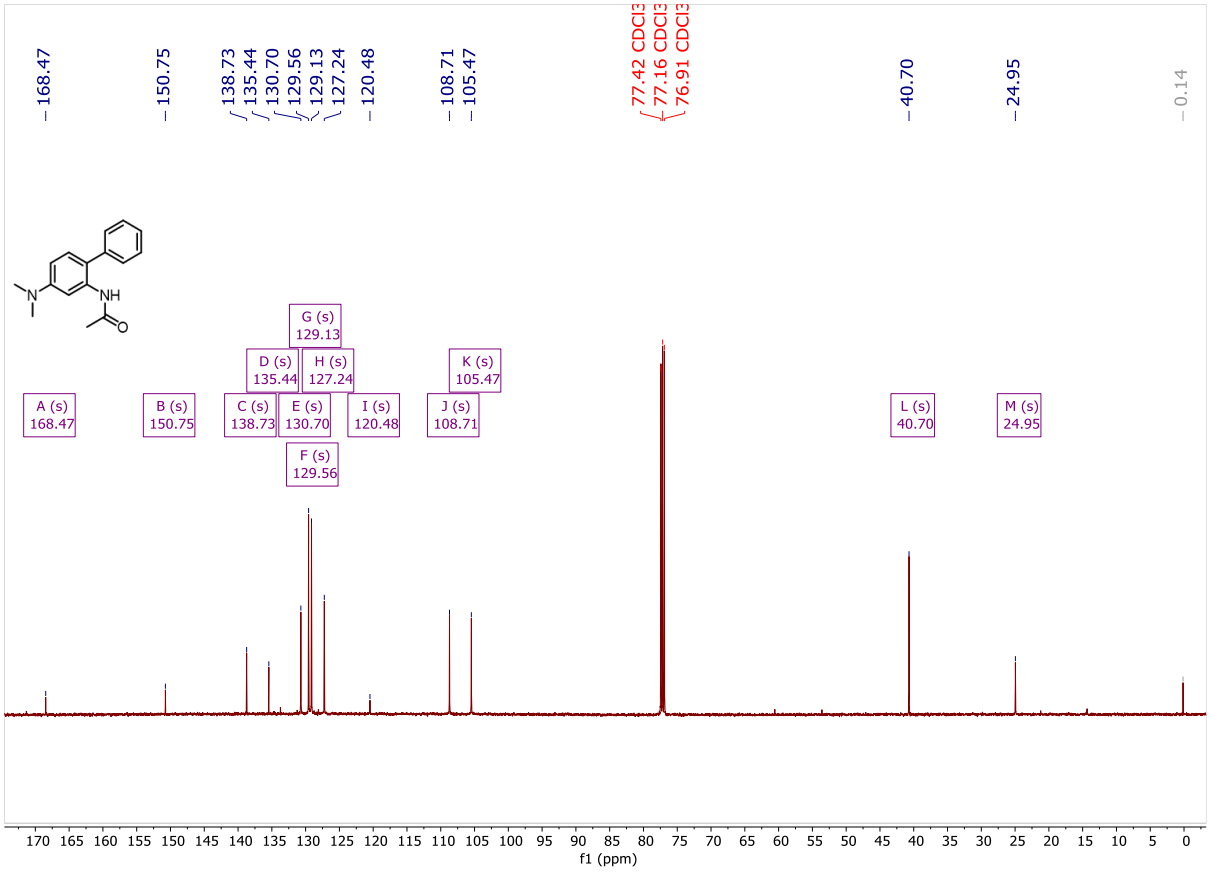


Following general procedure **A**, **3a** (180.7 mg, 0.7110 mmol, 91%) was obtained as an off-white solid by column chromatography (100% – 50% cyclohexane/EtOAc).

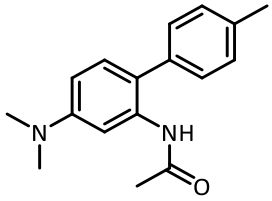
^{1}H NMR (500 MHz, chloroform-*d*) δ 7.77 (d, *J* = 2.6 Hz, 1H), 7.50 – 7.40 (m, 2H), 7.38 – 7.32 (m, 3H), 7.17 (br, 1H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.56 (dd, *J* = 8.5, 2.7 Hz, 1H), 3.00 (s, 6H), 2.03 (s, 3H)

^{13}C NMR (125 MHz, chloroform-*d*) δ 168.5 (C), 150.8 (C), 138.7 (C), 135.4 (CH), 130.7 (CH), 129.6 (2CH), 129.1 (2CH), 127.2 (CH), 120.5 (C), 108.7 (CH), 105.5 (CH), 40.7 ($2CH_3$), 25.0 (CH_3); IR (ν = cm^{-1}) 1488, 1534, 1559, 1663, 2853, 2925; HRMS (ESI) calcd for $C_{16}H_{19}N_2O$ $[M+H]^+$ 255.1486, observed 255.1492.





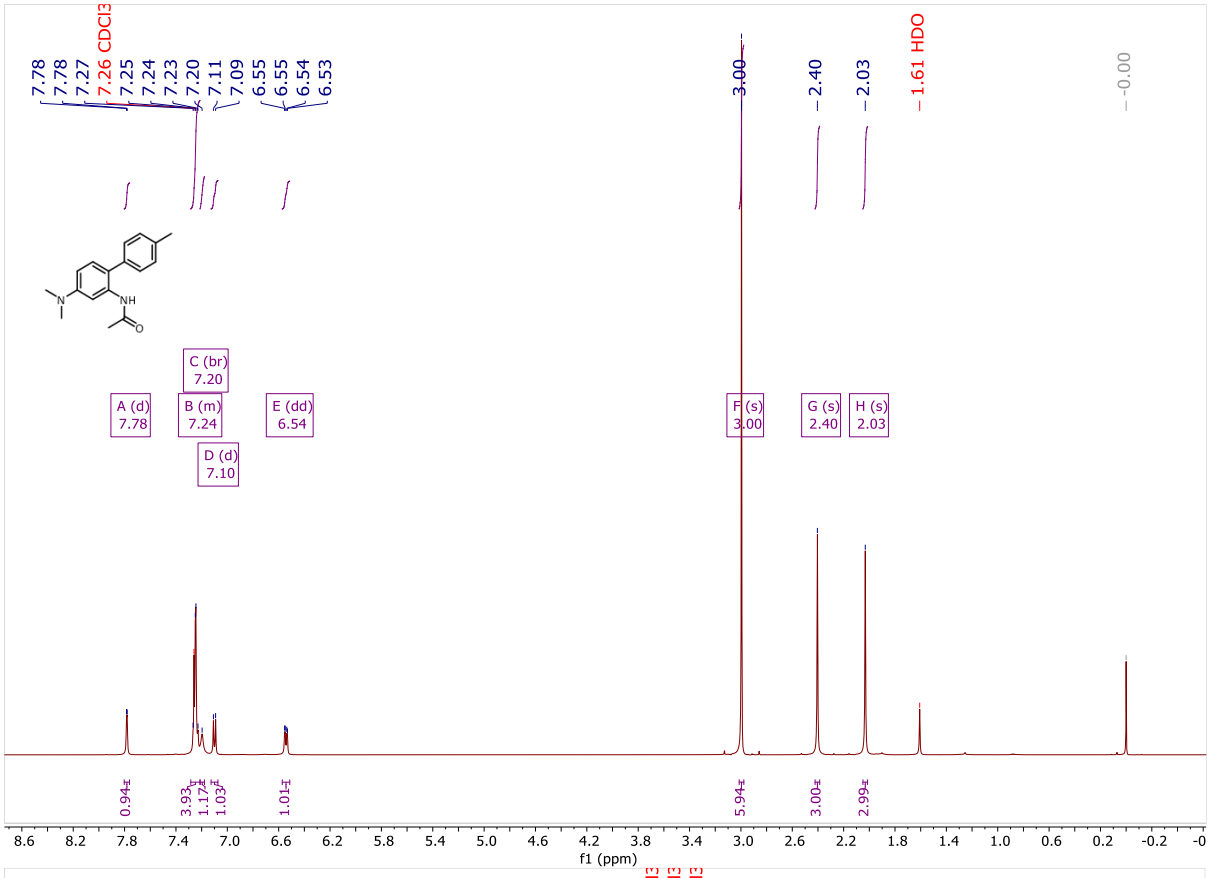
***N*-(4-(Dimethylamino)-4'-methyl-[1,1'-biphenyl]-2-yl)acetamide (3b)**

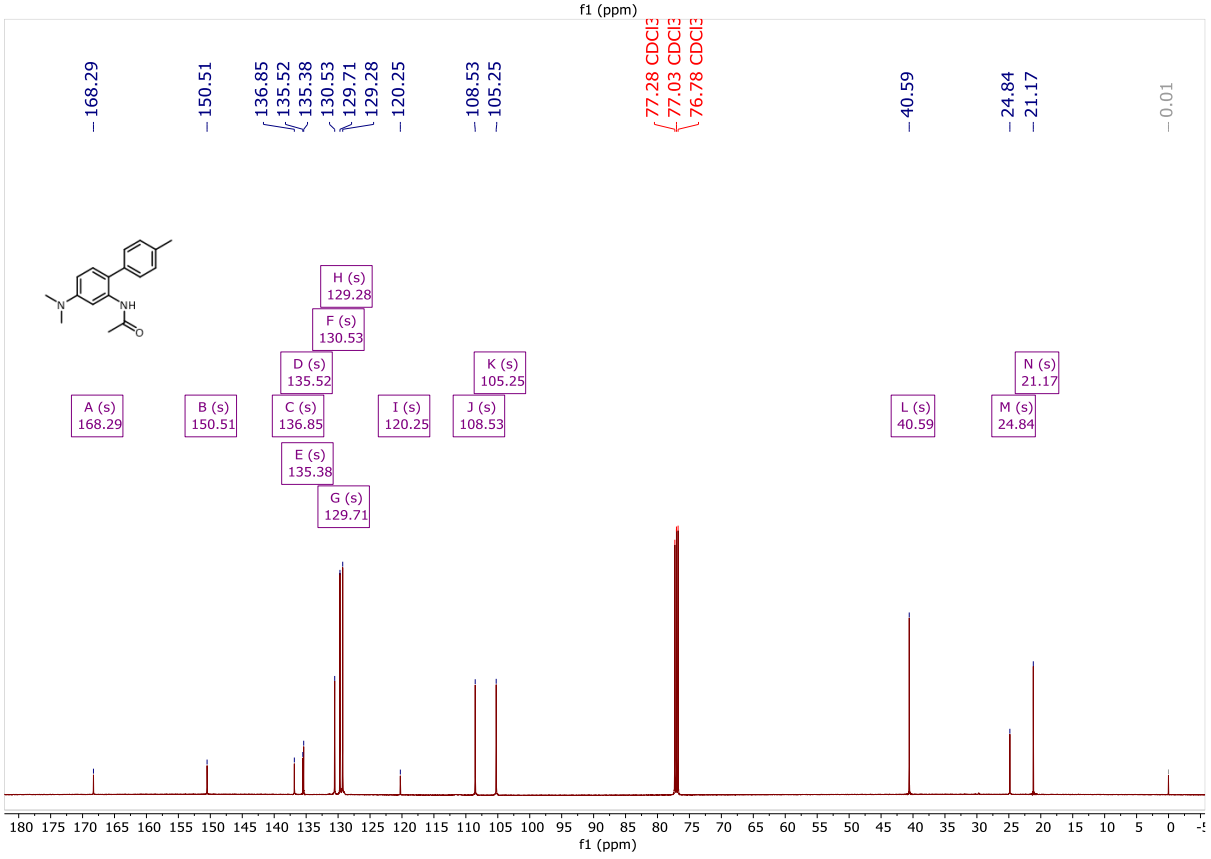


Following general procedure **A**, **3b** (102.6 mg, 0.3827 mmol, 49%) was obtained as an off-white solid by column chromatography (100% – 50% cyclohexane/EtOAc).

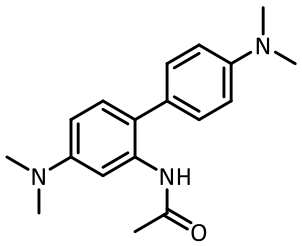
^{1}H NMR (500 MHz, chloroform-*d*) δ 7.78 (d, *J* = 2.6 Hz, 1H), 7.28 – 7.21 (m, 4H), 7.20 (br, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 6.54 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.00 (s, 6H), 2.40 (s, 3H), 2.03 (s, 3H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 168.3 (C), 150.5 (C), 136.9 (C), 135.5 (C), 135.4 (C), 130.5 (CH), 129.7 (2CH), 129.3 (2CH), 120.3 (C), 108.5 (CH), 105.3 (CH), 40.6 ($2CH_3$), 24.8 (CH_3), 21.2 (CH_3); IR (ν = cm^{-1}) 1362, 1619, 1671, 2919, 3276, 3420; HRMS (ESI) calcd for $C_{17}H_{21}N_2O$ $[M+H]^+$ 269.1649, observed 269.1644.





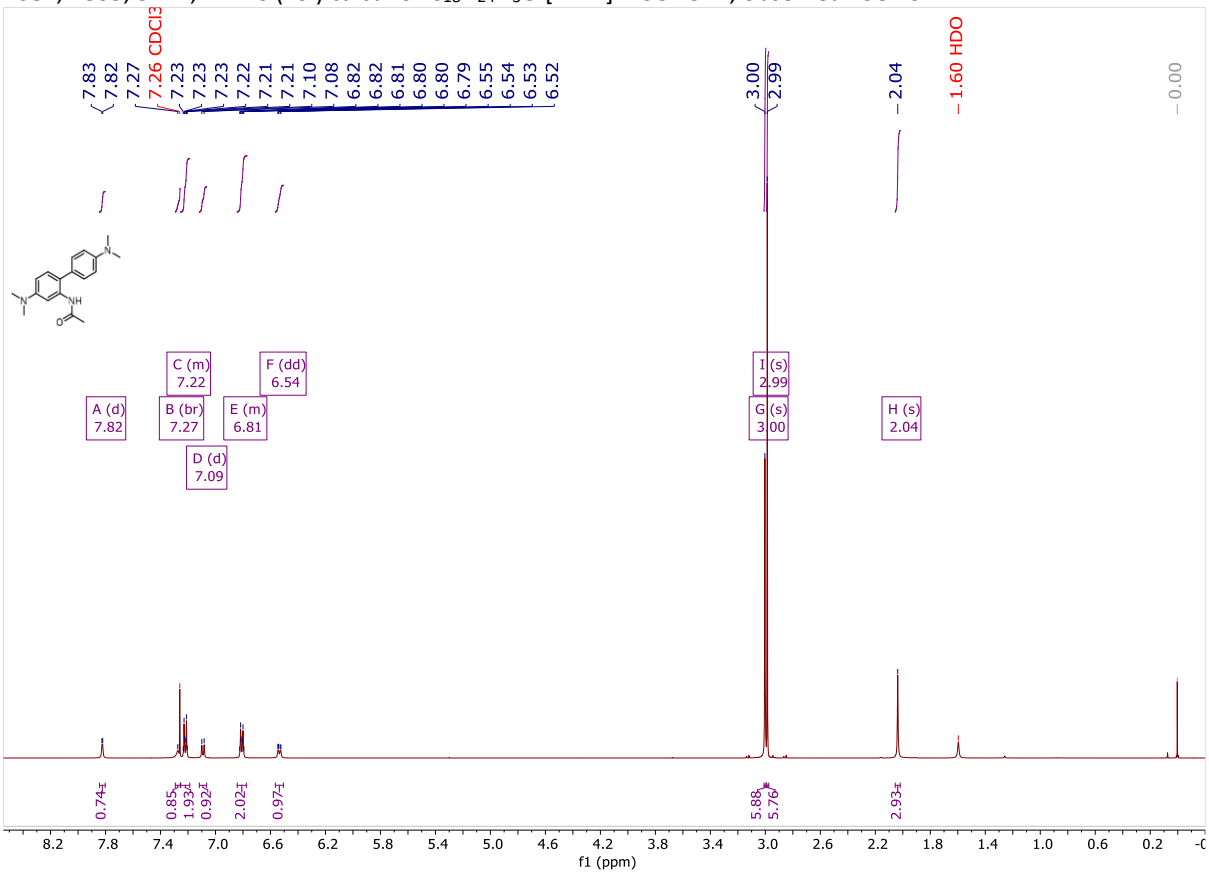
***N*-(4,4'-Bis(dimethylamino)-[1,1'-biphenyl]-2-yl)acetamide (3d)**

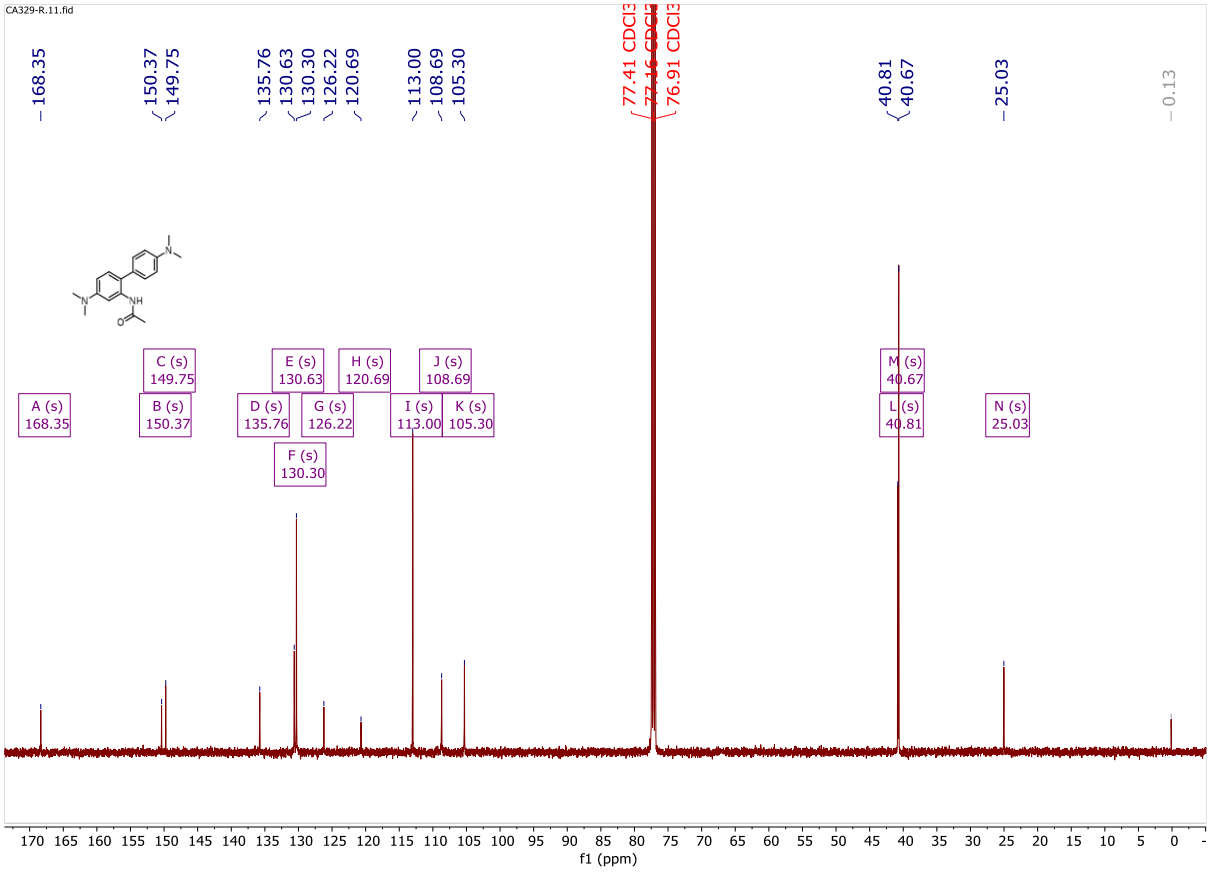


Following general procedure **A**, **3d** (137.1 mg, 0.4614 mmol, 59%) was obtained as an off-white solid by recrystallisation from toluene/*n*-pentane (1/5).

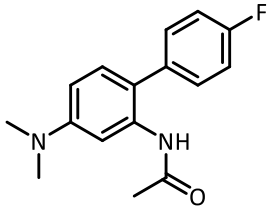
^{1}H NMR (500 MHz, chloroform-*d*) δ 7.82 (d, *J* = 2.8 Hz, 1H), 7.27 (br, 1H), 7.25 – 7.19 (m, 2H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.84 – 6.78 (m, 2H), 6.54 (dd, *J* = 8.4, 2.8 Hz, 1H), 3.00 (s, 6H), 2.99 (s, 6H), 2.04 (s, 3H)

^{13}C NMR (125 MHz, chloroform-*d*) δ 168.4 (C), 150.4 (C), 149.8 (C), 135.8 (C), 130.6 (2CH), 130.3 (CH), 126.2 (C), 120.7 (C), 113.0 (2CH), 108.7 (CH), 105.3 (CH), 40.8 ($2CH_3$), 40.7 ($2CH_3$), 25.0 (CH_3); IR (ν = cm^{-1}) 1488, 1518, 1611, 1684, 2805, 3411; HRMS (ESI) calcd for $C_{18}H_{24}N_3O$ $[M+H]^+$ 298.1911, observed 298.1914.





***N*-(4-(Dimethylamino)-4'-fluoro-[1,1'-biphenyl]-2-yl)acetamide (3e)**

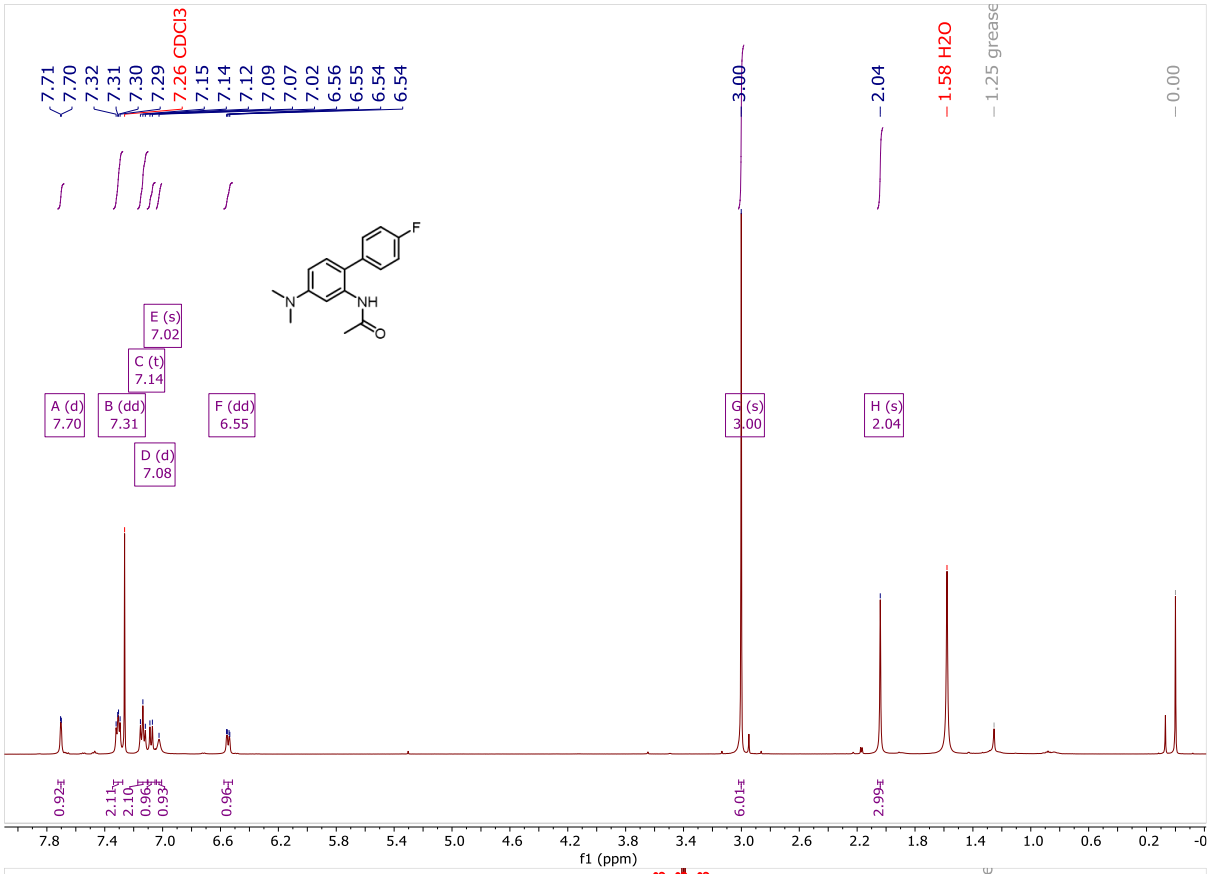


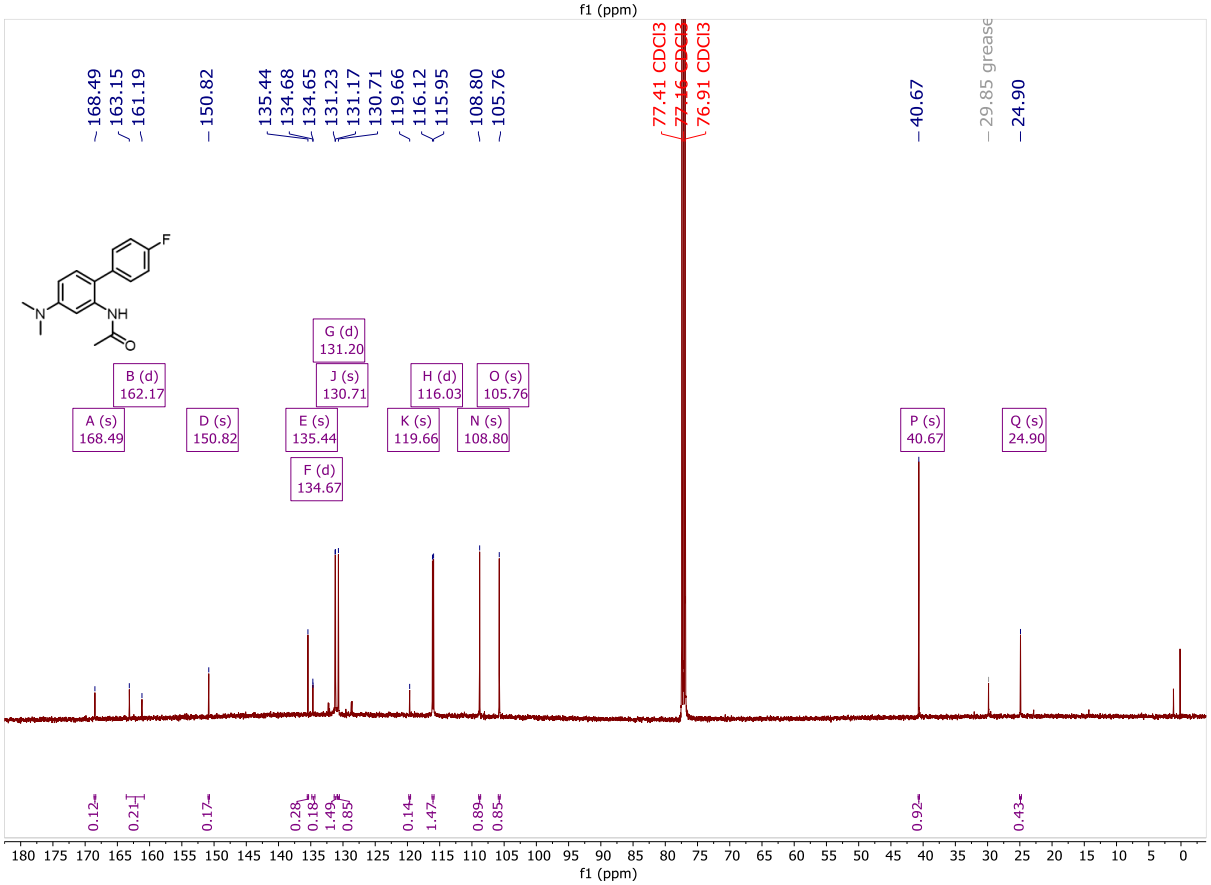
Following general procedure **A**, **3e** (193.5 mg, 0.7084 mmol, 91%) was obtained as an off-white solid by recrystallisation from EtOH/H_2O (1/9).

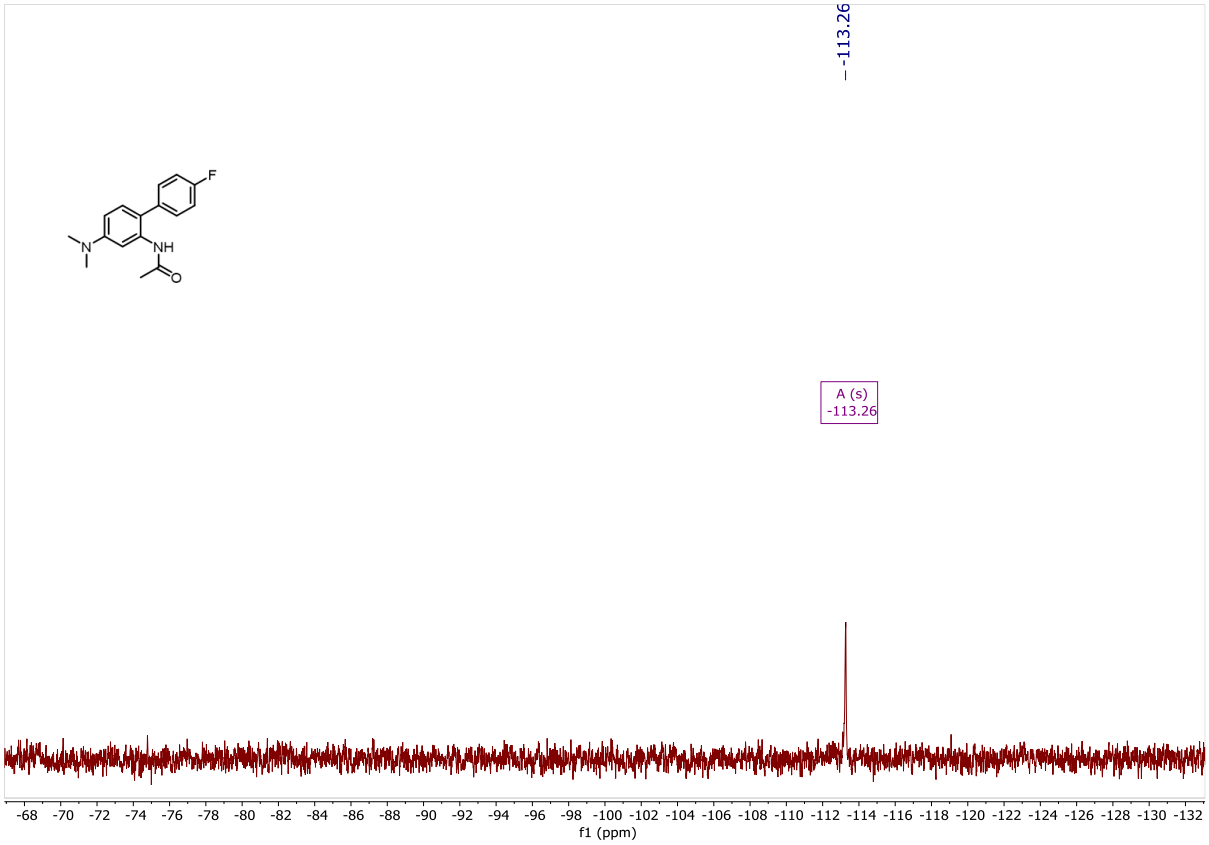
^{1}H NMR (500 MHz, chloroform-*d*) δ 7.70 (d, *J* = 2.7 Hz, 1H), 7.31 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.14 (t, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 8.5 Hz, 1H), 7.02 (br, 1H), 6.55 (dd, *J* = 8.5, 2.6 Hz, 1H), 3.00 (s, 6H), 2.04 (s, 3H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 168.5 (C), 162.2 (d, $^1J_{C\text{-}F}$ = 246.8 Hz, C), 150.8 (C), 135.4 (C), 134.7 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, C), 131.2 (d, $^3J_{C\text{-}F}$ = 7.8 Hz, 2CH), 130.7 (CH), 119.7 (C), 116.0 (d, $^2J_{C\text{-}F}$ = 21.2 Hz, 2CH), 108.8 (CH), 105.8 (CH), 40.7 ($2CH_3$), 24.9 (CH_3).

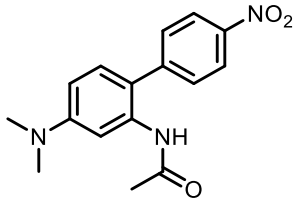
^{19}F NMR (76 MHz, chloroform-*d*) δ –87.48; IR (ν = cm^{-1}) 1218, 1362, 1497, 1653, 2927, 3260; HRMS (ESI) calcd for $C_{16}H_{18}FN_2O$ $[M+H]^+$ 273.1398, observed 273.1396.


7.71
7.70
7.32
7.31
7.30
7.29
7.26 CDCl3
7.15
7.14
7.12
7.09
7.07
7.02
6.56
6.55
6.54
6.54
3.00
2.04
1.58 H2O
1.25 grease
0.00
E (s) 7.02
C (t) 7.14
A (d) 7.70
B (dd) 7.31
F (dd) 6.55
D (d) 7.08
G (s) 3.00
H (s) 2.04
f1 (ppm)


168.49
163.15
161.19
150.82
135.44
134.68
134.65
131.23
131.17
130.71
119.66
116.12
115.95
108.80
105.76
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
40.67
29.85 grease
24.90
G (d) 131.20
B (d) 162.17
J (s) 130.71
H (d) 116.03
O (s) 105.76
A (s) 168.49
D (s) 150.82
E (s) 135.44
K (s) 119.66
N (s) 108.80
F (d) 134.67
P (s) 40.67
Q (s) 24.90
f1 (ppm)



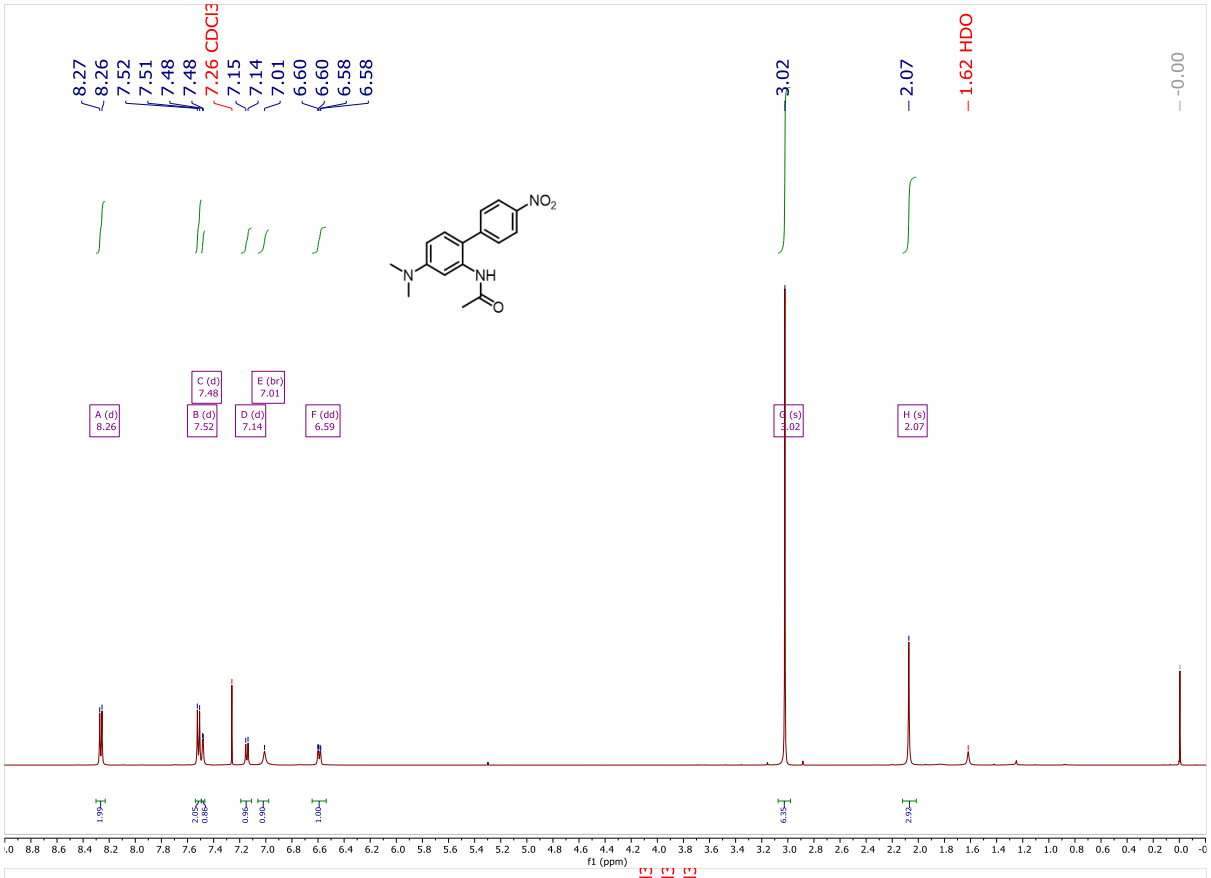
***N*-(4-(Dimethylamino)-4'-nitro-[1,1'-biphenyl]-2-yl)acetamide (3f)**

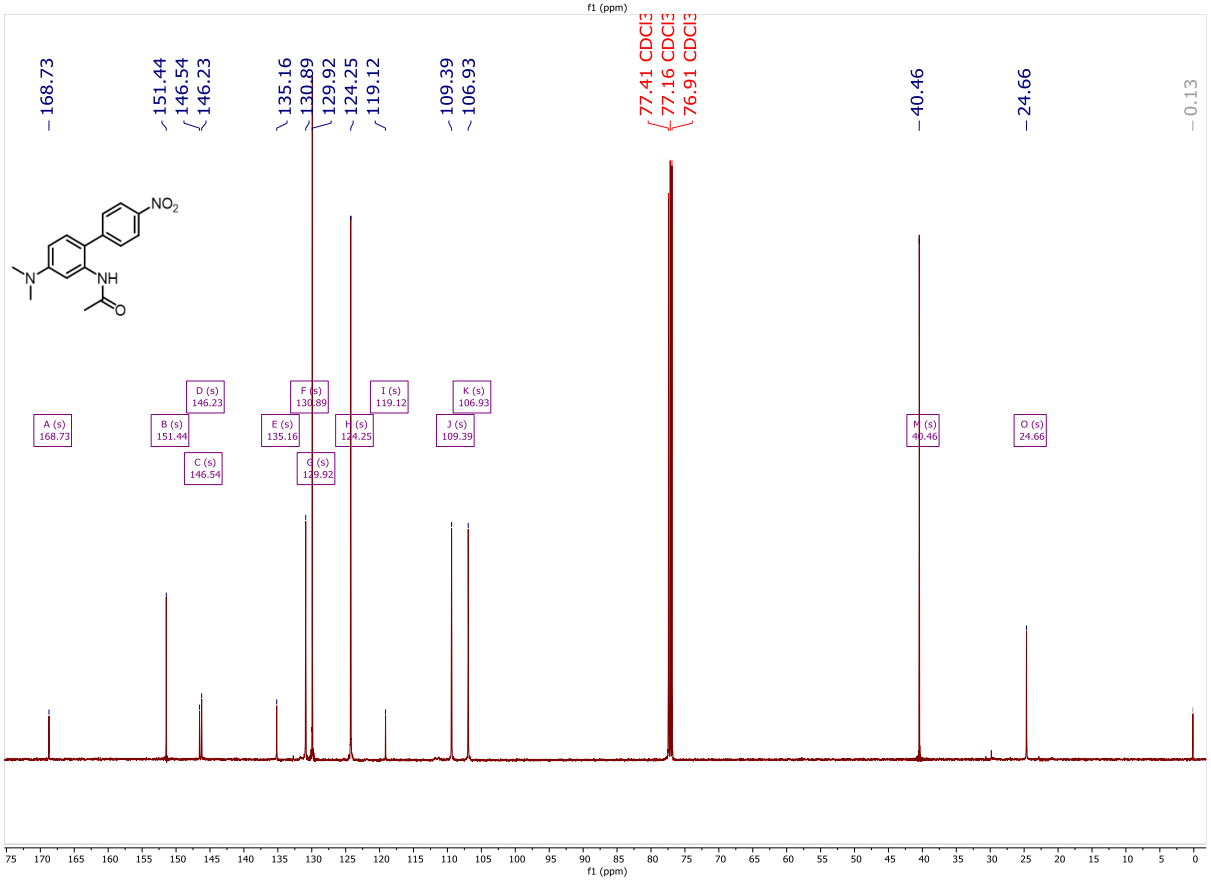


Following general procedure **A**, **3f** (126.2 mg, 0.4219 mmol, 54%) was obtained as a yellow solid by recrystallisation from toluene, followed by recrystallisation from EtOH.

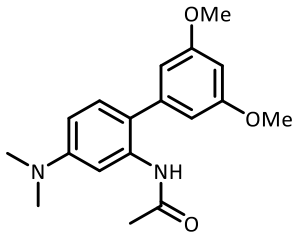
^{1}H NMR (500 MHz, chloroform-*d*) δ 8.29 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 2.6 Hz, 1H), 7.15 (d, *J* = 8.6 Hz, 1H), 6.96 (br, 1H), 6.60 (dd, *J* = 8.7, 2.6 Hz, 1H), 3.03 (s, 6H), 2.08 (s, 3H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 168.7 (C), 151.5 (C), 146.6 (C), 146.2 (C), 135.2 (C), 130.9 (CH), 129.9 (2CH), 124.3 (2CH), 119.1 (C), 109.4 (CH), 106.9 (CH), 40.5 ($2CH_3$), 24.7 (CH_3); IR (ν = cm^{-1}) 1343, 1509, 1648, 2927, 3251; HRMS (ESI) calcd for $C_{16}H_{18}N_3O_3$ $[M+H]^+$ 300.1343, observed 300.1338.





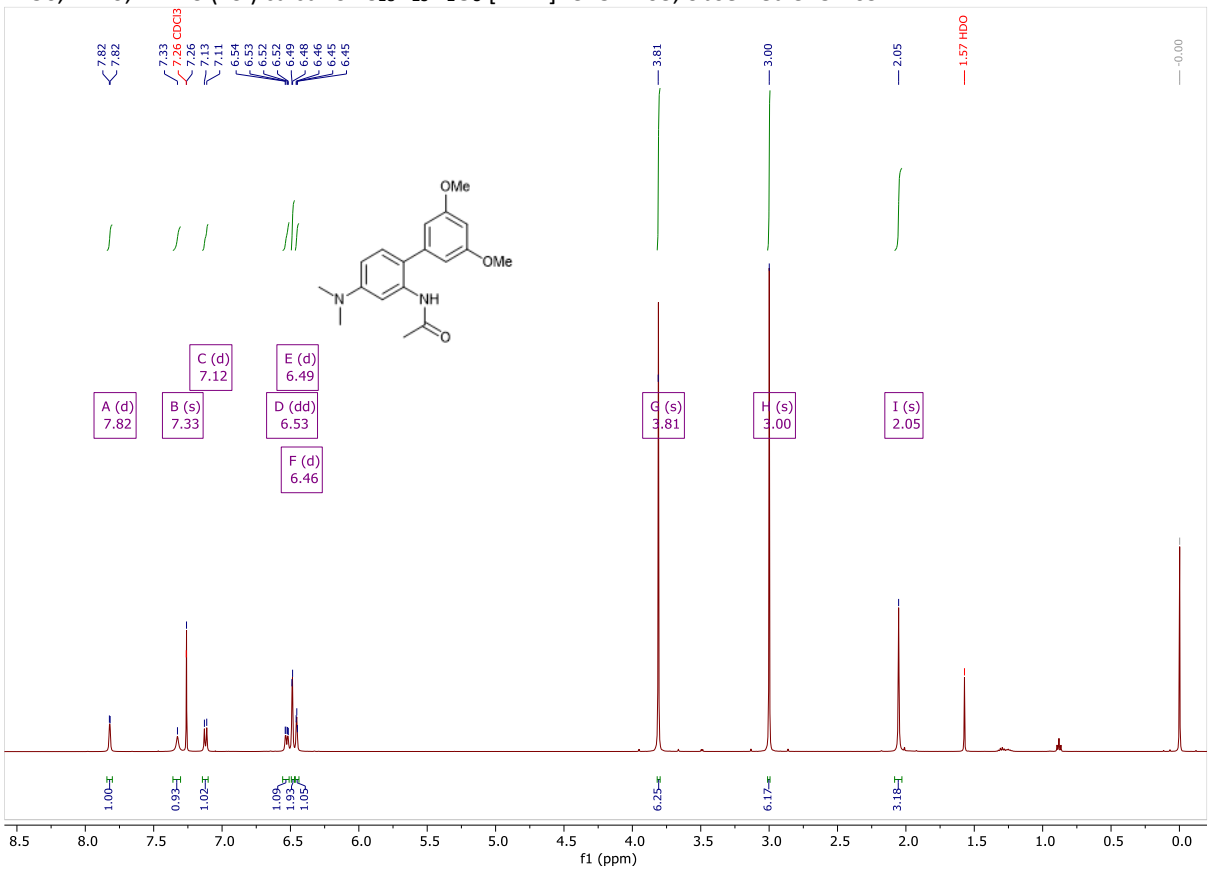
***N*-(4-(Dimethylamino)-3',5'-dimethoxy-[1,1'-biphenyl]-2-yl)acetamide (3g)**

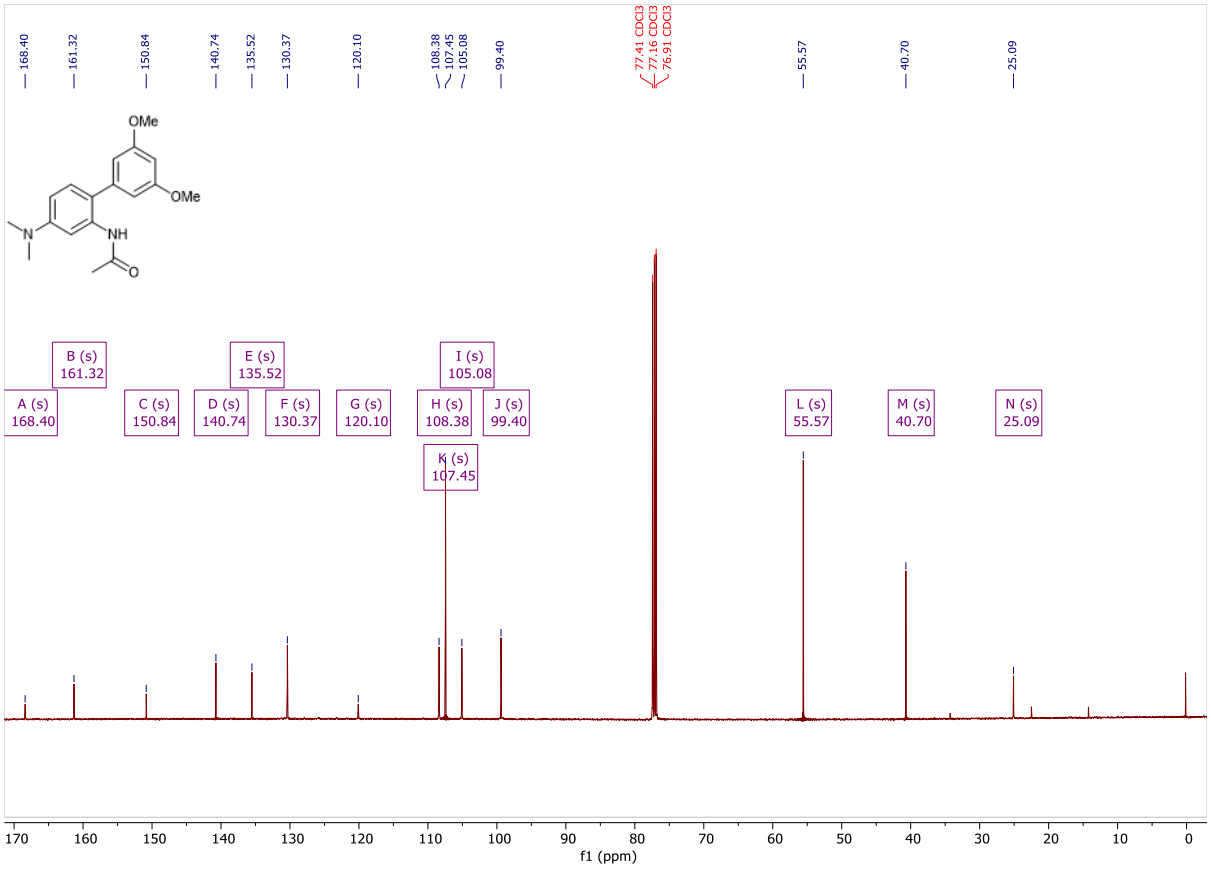


In a Schlenk flask under inert atmosphere, **2** (200.0 mg, 0.7812 mmol, 1 eq.), Na_2CO_3 (497.2 mg, 1.56 mmol, 2 eq.), 3,5-dimethoxyphenylboronic acid (156.32 mg, 0.859 mmol, 1.1 eq.) and $Pd(PPh_3)_4$ (9.0 mg, 7.8 µmol, 0.01 eq.) were combined. Argon was bubbled through a solvent mixture (THF/H_2O, 1/3, 0.3 M) for 15 minutes before being added to the reaction mixture. The reaction was stirred at 100 °C for 24 hours. After cooling the reaction mixture to room temperature, it was filtered through a short pad of Celite®, and then diluted with H_2O (20 mL). The resulting aqueous phase was extracted three times with DCM (3 × 20 mL). The organic layers were combined, washed with brine (5 mL), and then dried over $MgSO_4$ before being concentrated *in vacuo*. The crude product was purified by column chromatography (100% – 50% Cyclohexane/EtOAc), yielding **3g** (125.1 mg, 0.3983 mmol, 51%) as an off-white solid.

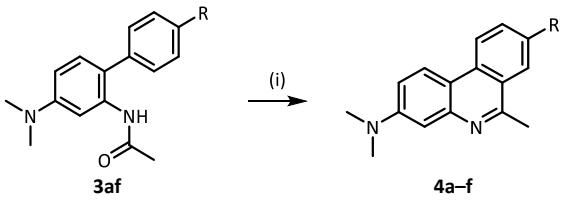
^{1}H NMR (500 MHz, chloroform-*d*) δ 7.82 (d, J = 2.7 Hz, 1H), 7.33 (s, 1H), 7.12 (d, J = 8.5 Hz, 1H), 6.53 (dd, J = 8.5, 2.6 Hz, 1H), 6.49 (d, J = 2.3 Hz, 2H), 6.46 (d, J = 2.3 Hz, 1H), 3.81 (s, 6H), 3.00 (s, 6H), 2.05 (s, 3H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 168.4 (C), 161.3 (C), 150.8 (C), 140.7 (C), 135.5 (C), 130.4 (CH), 120.1 (C), 108.4 (CH), 107.5 (2CH), 105.1 (CH), 99.4 (CH), 55.6 ($2CH_3$), 40.7 ($2CH_3$), 25.1 (CH_3); IR (ν = cm^{-1}) 1683, 1600, 1533, 1456, 1420; HRMS (ESI) calcd for $C_{18}H_{23}N_2O_3$ $[M+H]^+$ 315.1703, observed 315.1694.




168.40
161.32
150.84
140.74
135.52
130.37
120.10
108.38
107.45
105.08
99.40
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
55.57
40.70
25.09
OMe
OMe
N
NH
O
B (s) 161.32
E (s) 135.52
I (s) 105.08
A (s) 168.40
C (s) 150.84
D (s) 140.74
F (s) 130.37
G (s) 120.10
H (s) 108.38
J (s) 99.40
K (s) 107.45
L (s) 55.57
M (s) 40.70
N (s) 25.09
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

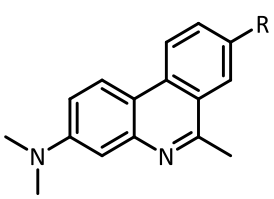
Bischler-Napierlaski reactions



3af **4a–f**

Compound	Cyclising agent	Additive	Temperature	Solvent	Time	Yield
4a (H)	$POCl_3$ neat	None	105 °C	None	18 h	77%
4b (Me)	$POCl_3$ neat	None	105 °C	None	18 h	91%
4c (OMe)	$POCl_3$ neat	None	105 °C	None	24 h	49%
4d (NMe_2)	$POCl_3$ neat	None	105 °C	None	18 h	59%
4e (F)	$POCl_3$ neat	None	105 °C	None	33 h	24%[a]
	Tf_2O/Ph_3PO	None	0 °C to rt	DCM	18 h	traces[b]
	$POCl_3$	PPA	120 °C	None	3 h	83%
4fError! R eference source not found. **(NO_2)**.	$POCl_3$ neat	None	105 °C	None	33 h	5%[a]
	Tf_2O/Ph_3PO	None	0 °C to rt	DCM	18 h	traces[b]
	$POCl_3$	PPA	120 °C	None	19 h	93%

Table S2: Optimisation of Bischler-Napierlaski reaction for the synthesis of phenanthridines. Reagents and conditions: (i) cyclising agent, additive, temperature, time, solvent.



4a, R = H
4b, R = Me
4c, R = OMe
4d, R = NMe_2
4e, R = F
4f, R = NO_2

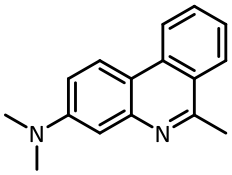
General procedure B for the preparation of phenanthridines 4a–d

In a round bottom flask, **3a–d** (0.3520 mmol, 1 eq.) and $POCl_3$ (1 mL, 10.56 mmol, 30 eq.) were combined. The reaction was stirred under reflux for 24 hours. After cooling the reaction mixture to 0 °C, it was dissolved in MeOH (3 mL) and sonicated until the mixture became homogeneous. The mixture was then basified around pH 11 with 2M aq. NaOH and diluted with H_2O (10 mL). The resulting aqueous phase was extracted three times with DCM (3 × 20 mL). The organic layers were combined, washed with brine (5 mL), and then dried over $MgSO_4$ before being concentrated *in vacuo*. The crude product was purified by recrystallisation in the corresponding solvent or by flash column chromatography, yielding the respective phenanthridine **4a–d**.

General procedure C for the preparation of phenanthridines 4e–f

In a round bottom flask, **3e–f** (0.3520 mmol, 1 eq.), $POCl_3$ (166 µL, 1.76 mmol, 5 eq.) and polyphosphoric acid (480 mg) were combined. The reaction was heated at 120 °C for the appropriate duration. After cooling the reaction mixture to 0 °C, it was then basified around pH 11 with 2M NaOH aq. sonicated until the mixture became homogeneous. The mixture was diluted with H_2O (10 mL) and the resulting aqueous phase was extracted three times with DCM (3 × 20 mL). The organic layers were combined, washed with brine (5 mL), and then dried over $MgSO_4$ before being concentrated *in vacuo*. The crude product was purified by recrystallisation in the corresponding solvent or by flash column chromatography, yielding the respective phenanthridine **4e–f**.

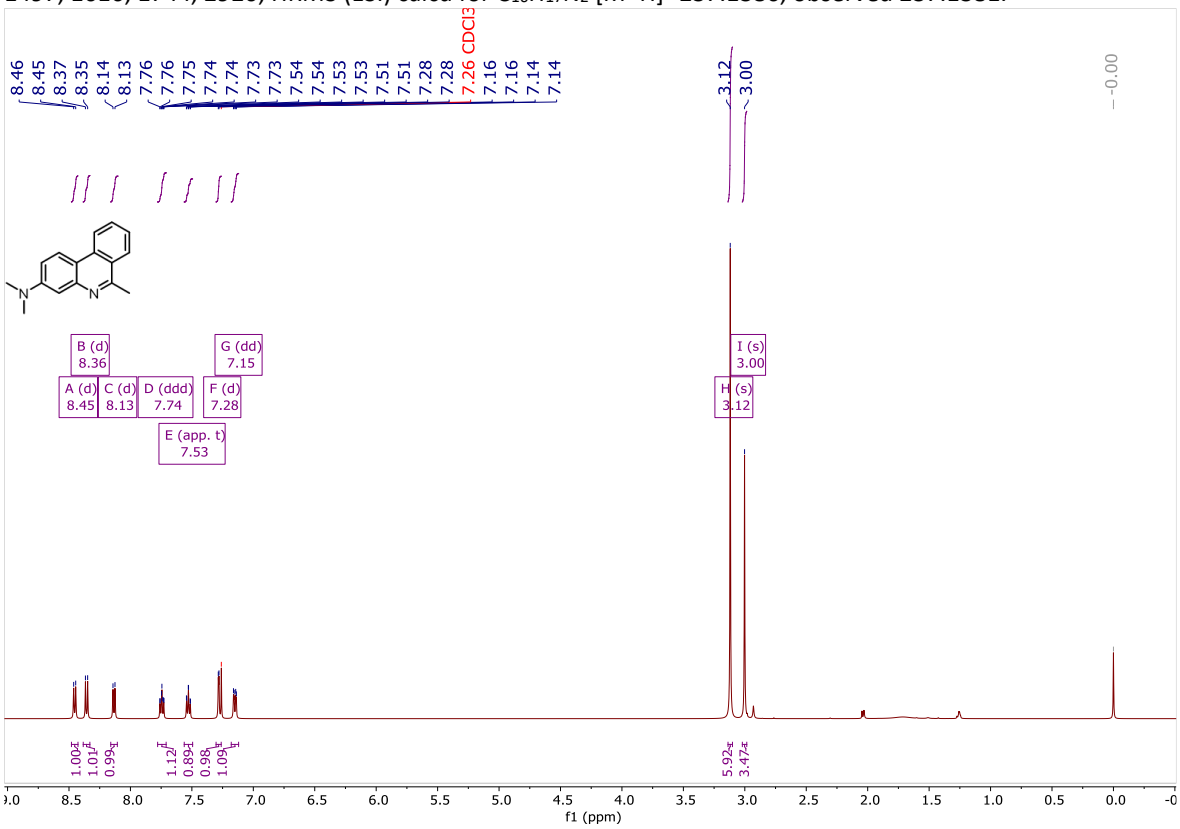
***N,N*,6-Trimethylphenanthridin-3-amine (4a)**

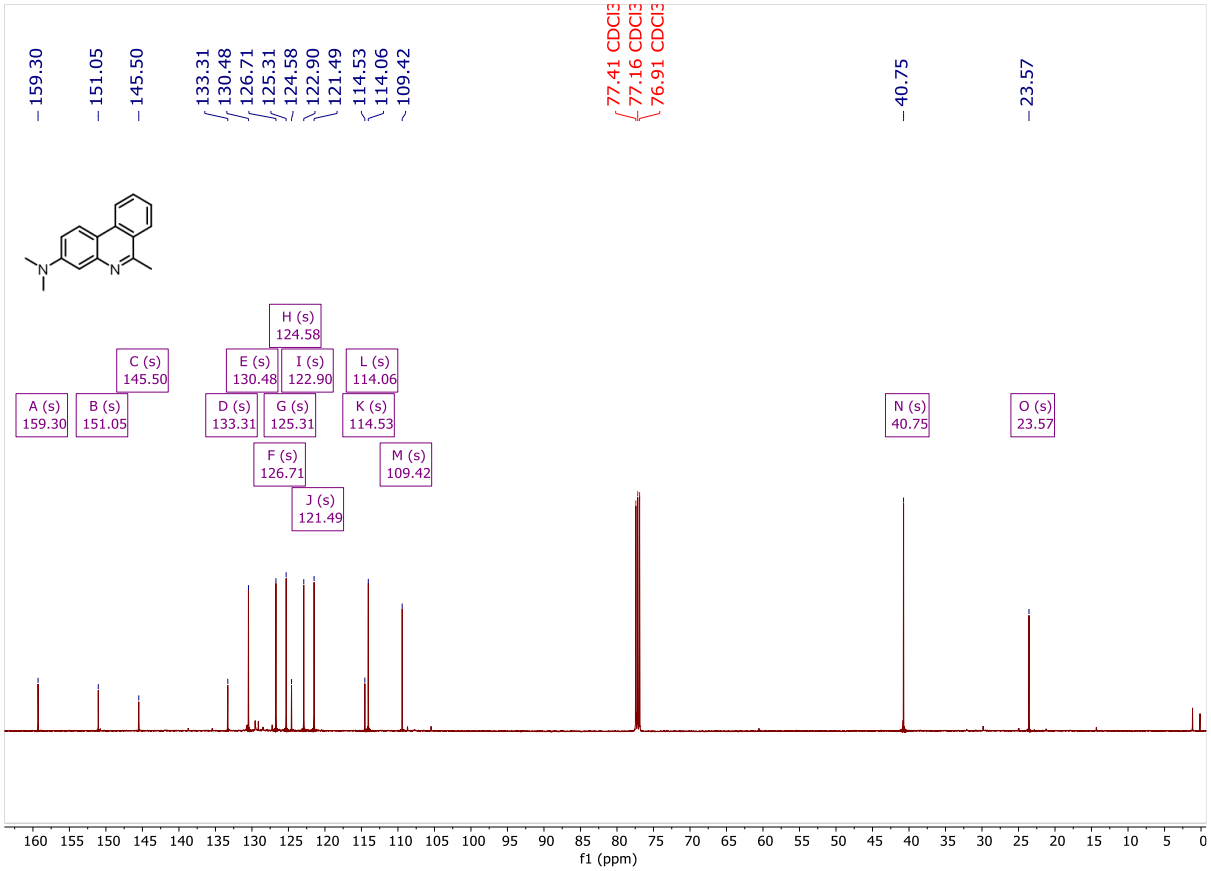


Following general procedure **B**, **4a** (71.5 mg, 0.303 mmol, 86%) was obtained as a red solid by column chromatography (100% – 50% cyclohexane/EtOAc).

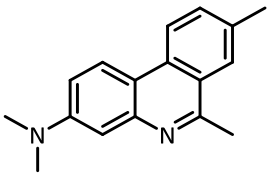
^{1}H NMR (500 MHz, chloroform-*d*) δ 8.45 (d, *J* = 8.3 Hz, 1H), 8.36 (d, *J* = 9.0 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 7.74 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.53 (app. t, *J* = 7.7, 1.1 Hz, 1H), 7.28 (d, *J* = 2.8 Hz, 1H), 7.15 (dd, *J* = 9.0, 2.8 Hz, 1H), 3.12 (s, 6H), 3.00 (s, 3H)

^{13}C NMR (125 MHz, chloroform-*d*) δ 159.3 (C), 151.1 (C), 145.5 (C), 133.3 (C), 130.5 (CH), 126.7 (CH), 125.3 (CH), 124.6 (C), 122.9 (CH), 121.5 (CH), 114.5 (CH), 114.1 (CH), 109.4 (CH), 40.8 ($2CH_3$), 23.6 (CH_3); IR (ν = cm^{-1}) 1371, 1497, 1616, 1744, 2920; HRMS (ESI) calcd for $C_{16}H_{17}N_2$ $[M+H]^+$ 237.1386, observed 237.1381.





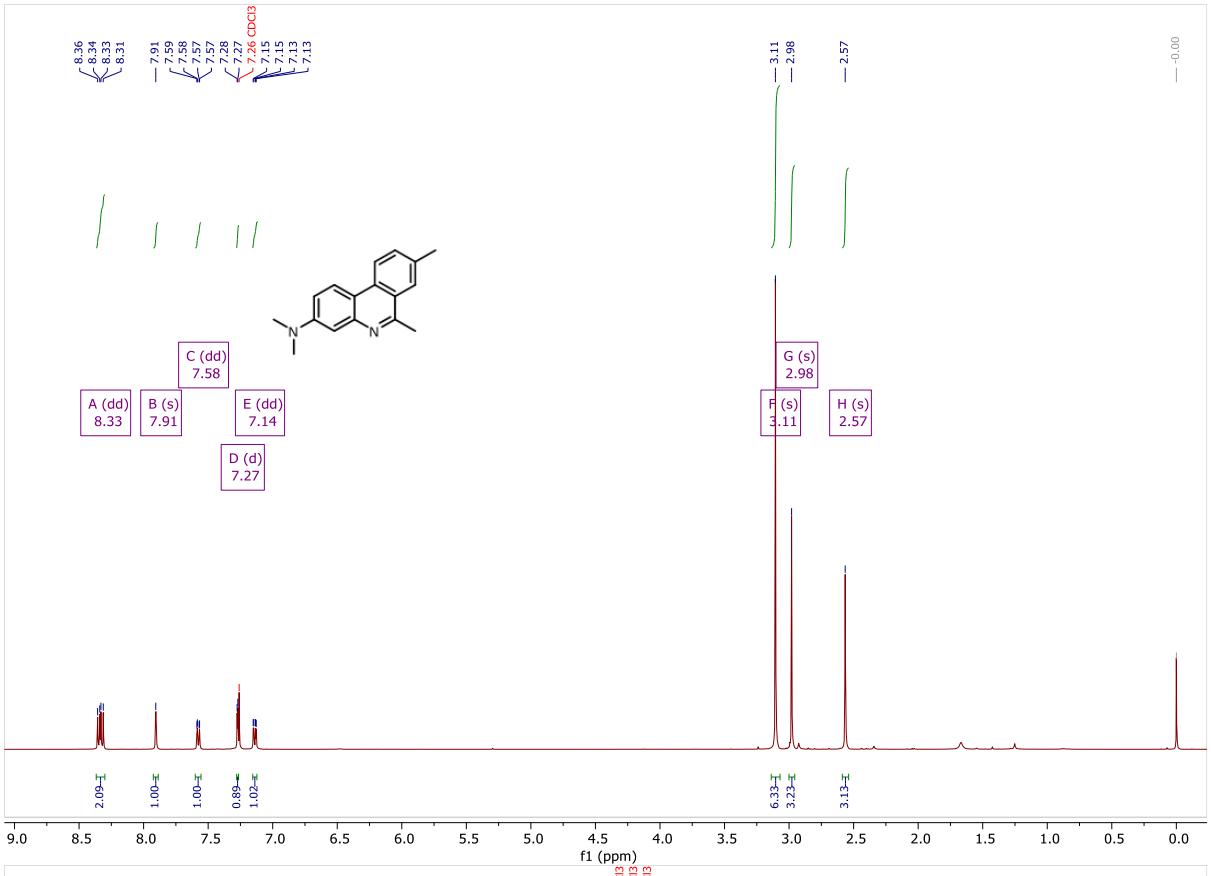
N,*N*,6,8-Tetramethylphenanthridin-3-amine (4b)

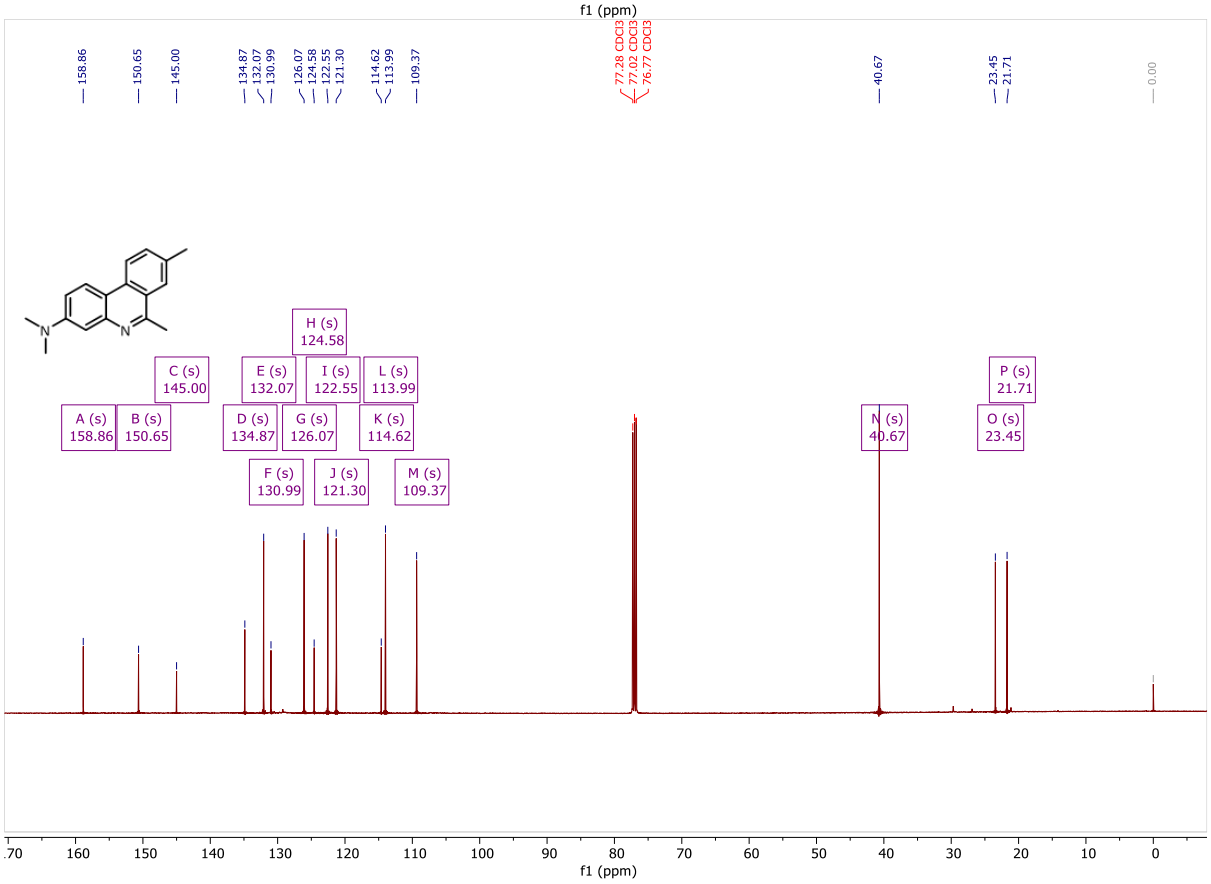


Following general procedure **B**, **4b** (80.1 mg, 0.320 mmol, 91%) was obtained as a yellow solid by column chromatography (100% – 50% cyclohexane/EtOAc).

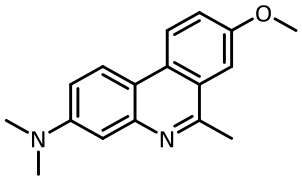
^{1}H NMR (500 MHz, chloroform-*d*) δ 8.34 (dd, *J* = 13.3, 8.7 Hz, 2H), 7.93 – 7.89 (m, 1H), 7.58 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.28 (d, *J* = 2.7 Hz, 1H), 7.14 (dd, *J* = 9.0, 2.7 Hz, 1H), 3.11 (s, 6H), 2.98 (s, 3H), 2.57 (s, 3H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 158.9 (C), 150.7 (C), 145.0 (C), 134.9 (C), 132.1 (CH), 131.0 (C), 126.1 (CH), 124.6 (C), 122.6 (CH), 121.3 (CH), 114.6 (C), 114.0 (CH), 109.3 (CH), 40.7 ($2CH_3$), 23.4 (CH_3), 21.7 (CH_3); IR (ν = cm^{-1}) 1364, 1497, 1617, 2799, 2917; HRMS (ESI) calcd for $C_{17}H_{19}N_2$ $[M+H]^+$ 251.1543, observed 251.1537.





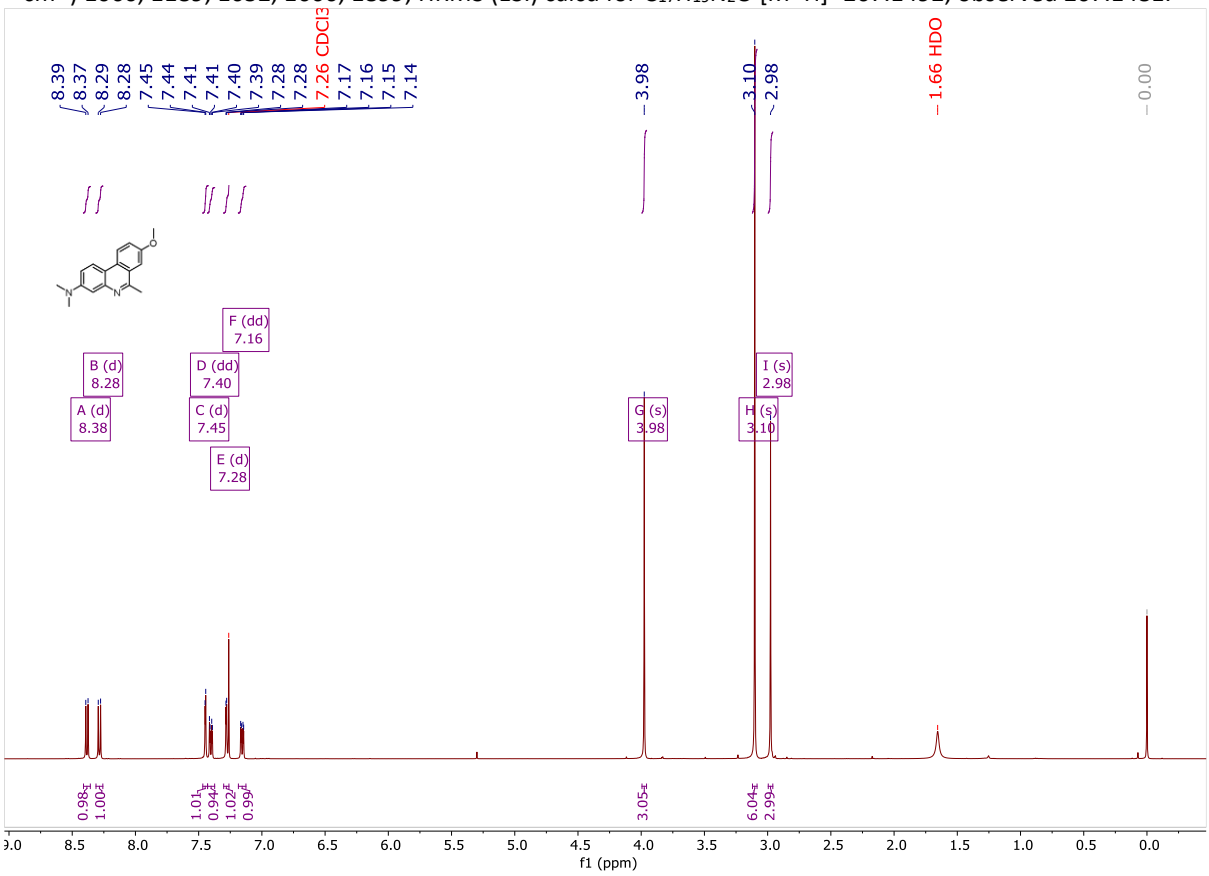
***N*,*N*,6,8-Tetramethylphenanthridin-3-amine (4c)**

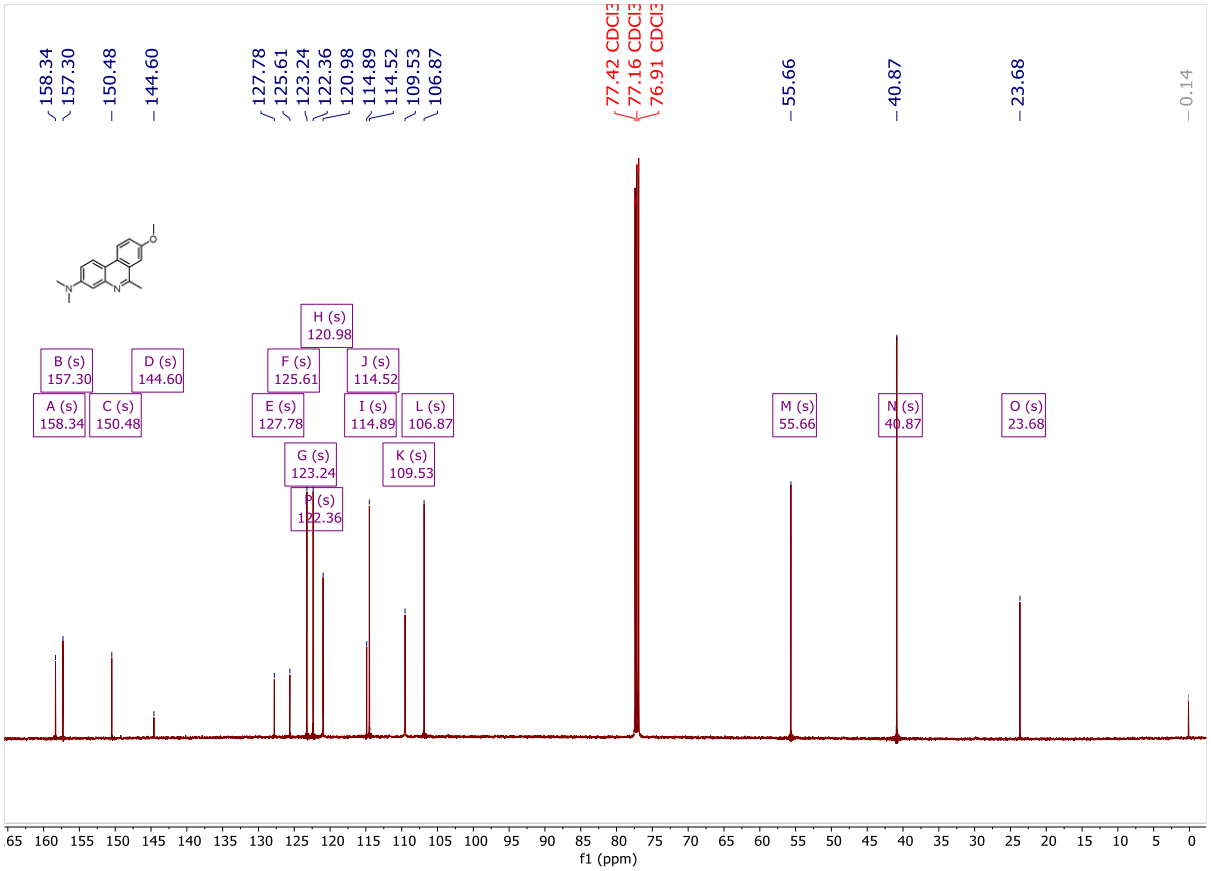


Following general procedure **B**, **4c** (64.6 mg, 0.243 mmol, 69%) was obtained as a yellow solid by column chromatography (100% – 50% cyclohexane/EtOAc).

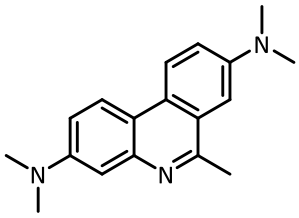
^{1}H NMR (500 MHz, chloroform-*d*) δ 8.38 (d, *J* = 9.0 Hz, 1H), 8.28 (d, *J* = 9.1 Hz, 1H), 7.45 (d, *J* = 2.6 Hz, 1H), 7.40 (dd, *J* = 9.0, 2.6 Hz, 1H), 7.28 (d, *J* = 2.7 Hz, 1H), 7.16 (dd, *J* = 9.1, 2.7 Hz, 1H), 3.98 (s, 3H), 3.10 (s, 6H), 2.98 (s, 3H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 158.3 (C), 157.3 (C), 150.5 (C), 144.6 (C), 127.8 (C), 125.6 (C), 123.2 (CH), 122.4 (CH), 121.0 (CH), 114.9 (C), 114.5 (CH), 109.5 (CH), 106.9 (CH), 55.7 (CH_3), 40.9 ($2CH_3$), 23.7 (CH_3); IR (ν = cm^{-1}) 1060, 1189, 1652, 1666, 1899; HRMS (ESI) calcd for $C_{17}H_{19}N_2O$ $[M+H]^+$ 267.1492, observed 267.1481.





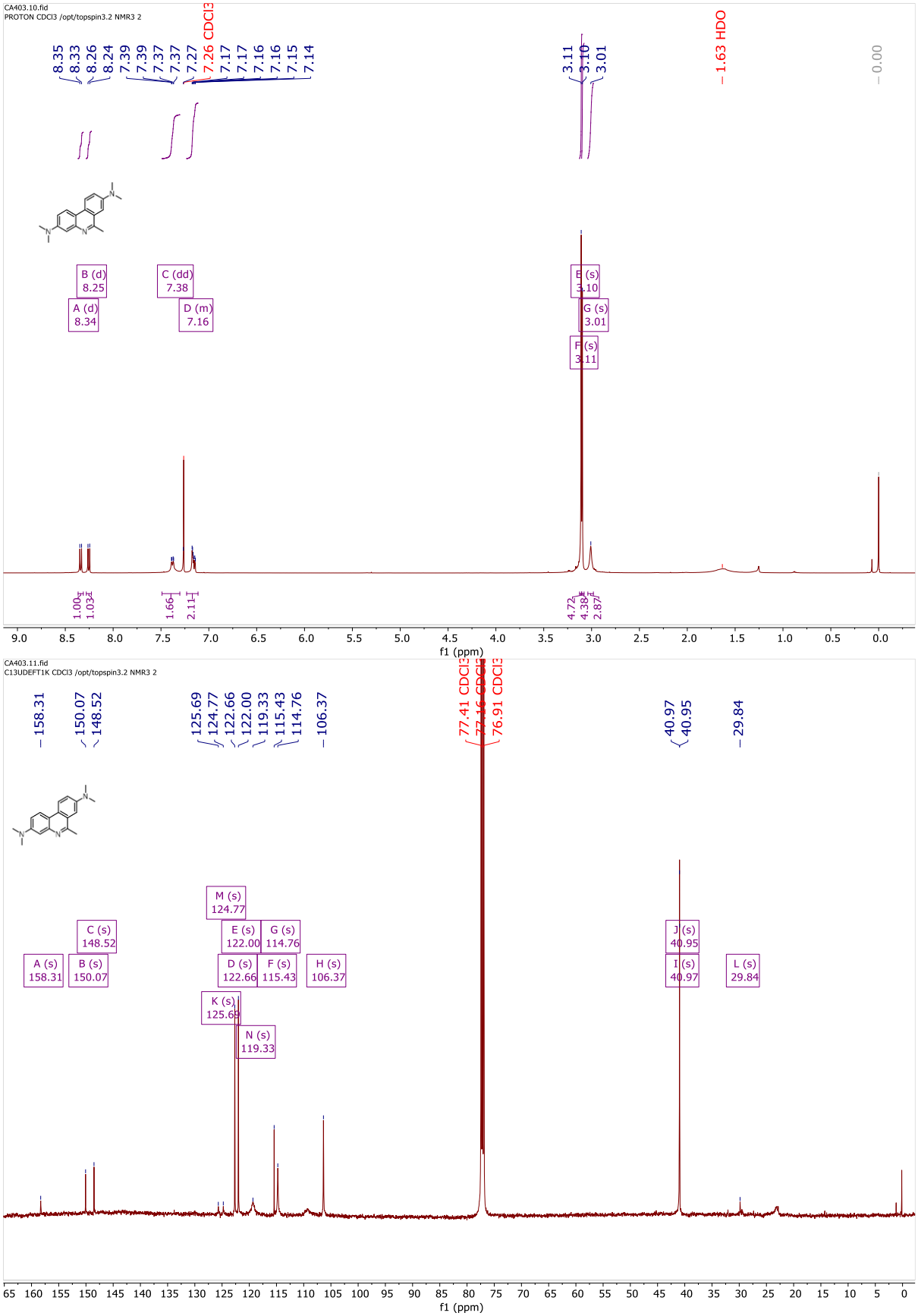
N^3,N^3,N^8,N^8,6-Pentamethylphenanthridine-3,8-diamine (4d)



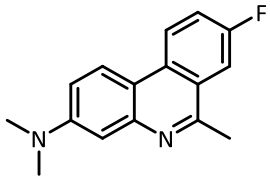
Following general procedure **B**, **4d** (54.0 mg, 0.194 mmol, 55%) was obtained as a brown solid by column chromatography (100% – 95% DCM/MeOH).

^{1}H NMR (500 MHz, chloroform-*d*) δ 8.34 (d, *J* = 9.1 Hz, 1H), 8.25 (d, *J* = 9.1 Hz, 1H), 7.38 (dd, *J* = 9.0, 2.5 Hz, 2H), 7.23 – 7.11 (m, 2H), 3.11 (s, 6H), 3.10 (s, 6H), 3.01 (s, 3H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 158.3 (C), 150.1 (C), 148.5 (C), 125.7 (C), 124.8 (C), 122.7 (2CH), 122.0 (2CH), 199.3 (C) 115.4 (CH), 114.8 (C), 106.4 (CH), 41.0 ($2CH_3$), 41.0 ($2CH_3$), 29.9 (CH_3); IR (ν = cm^{-1}) 1206, 1389, 1507, 1619, 2925; HRMS (ESI) calcd for $C_{18}H_{22}N_3$ $[M+H]^+$ 280.1808, observed 280.1805.



8-Fluoro-*N*,*N*,6-trimethylphenanthridin-3-amine (4e)

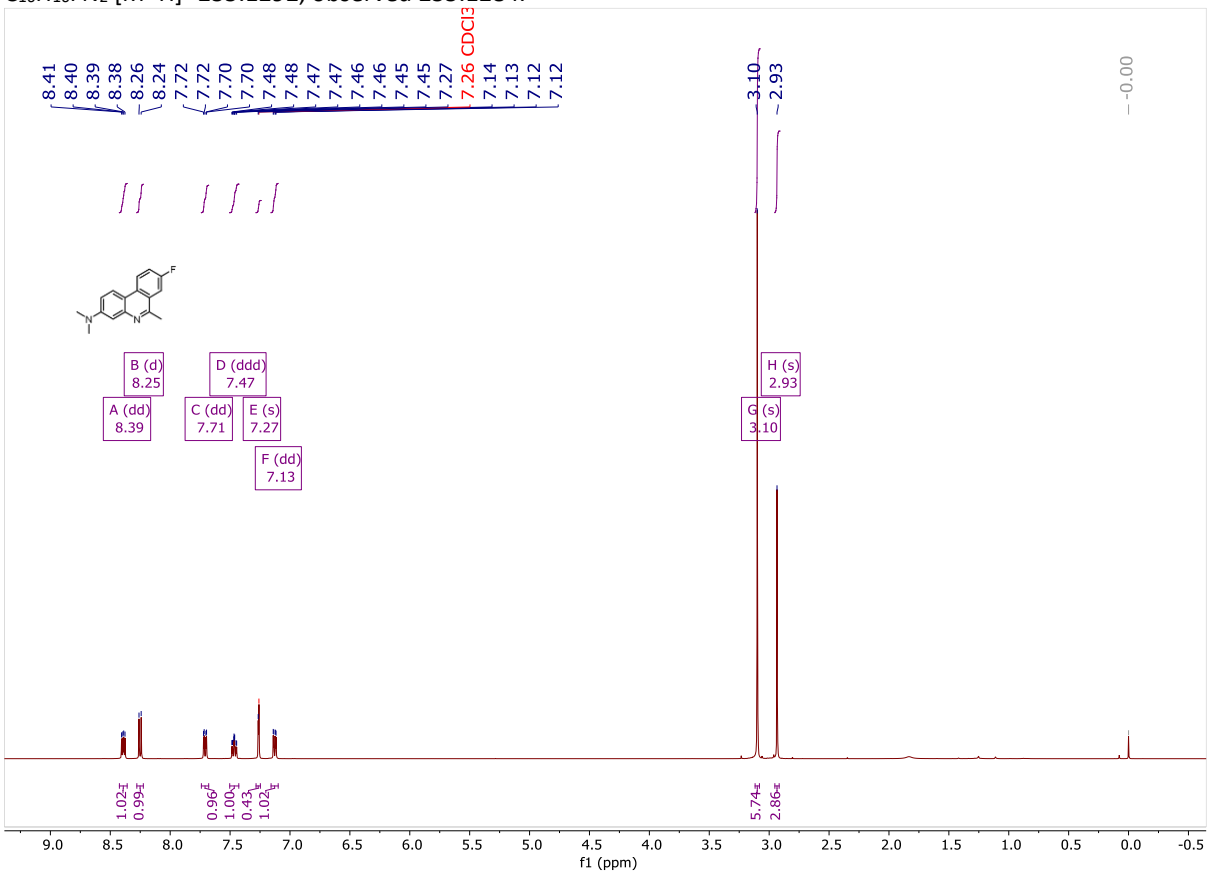


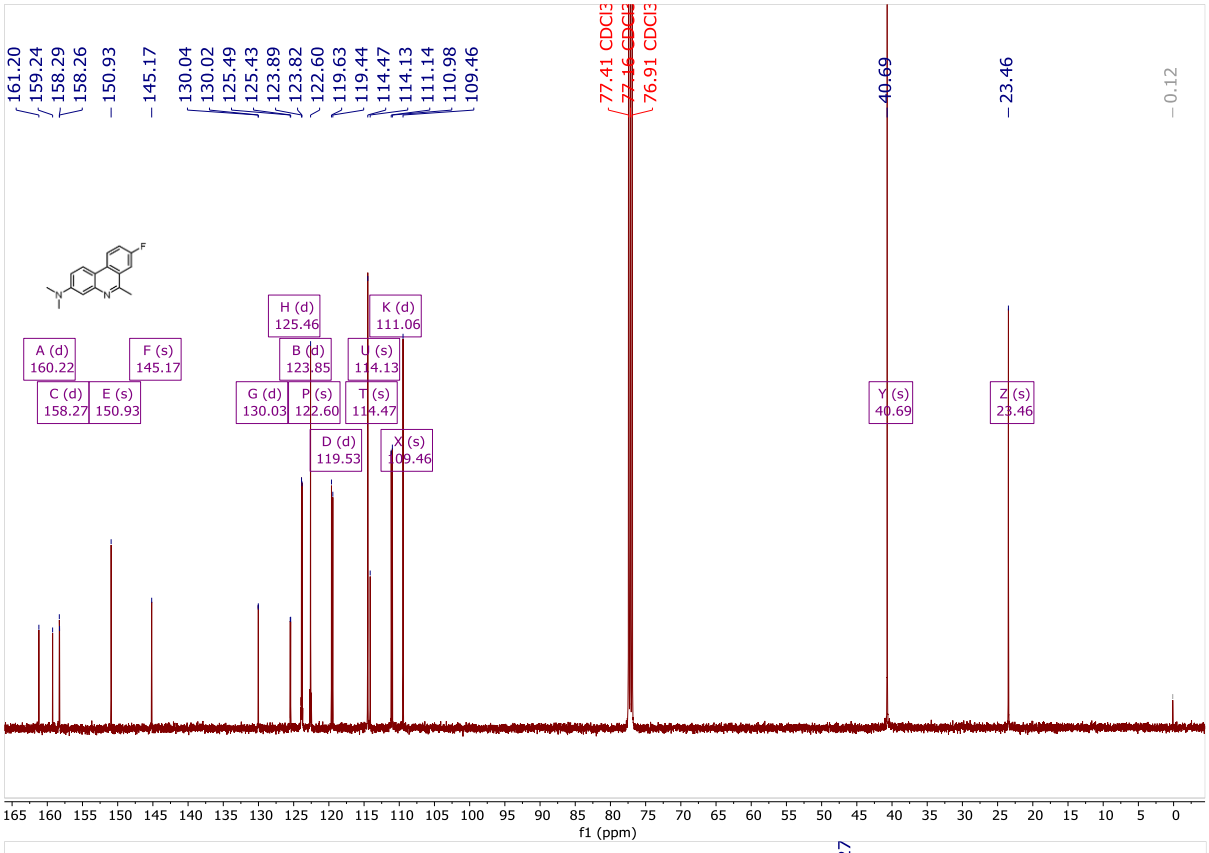
Following general procedure **C**, **4e** (65.3 mg, 0.257 mmol, 73%) was obtained as a yellowish solid by recrystallisation from toluene.

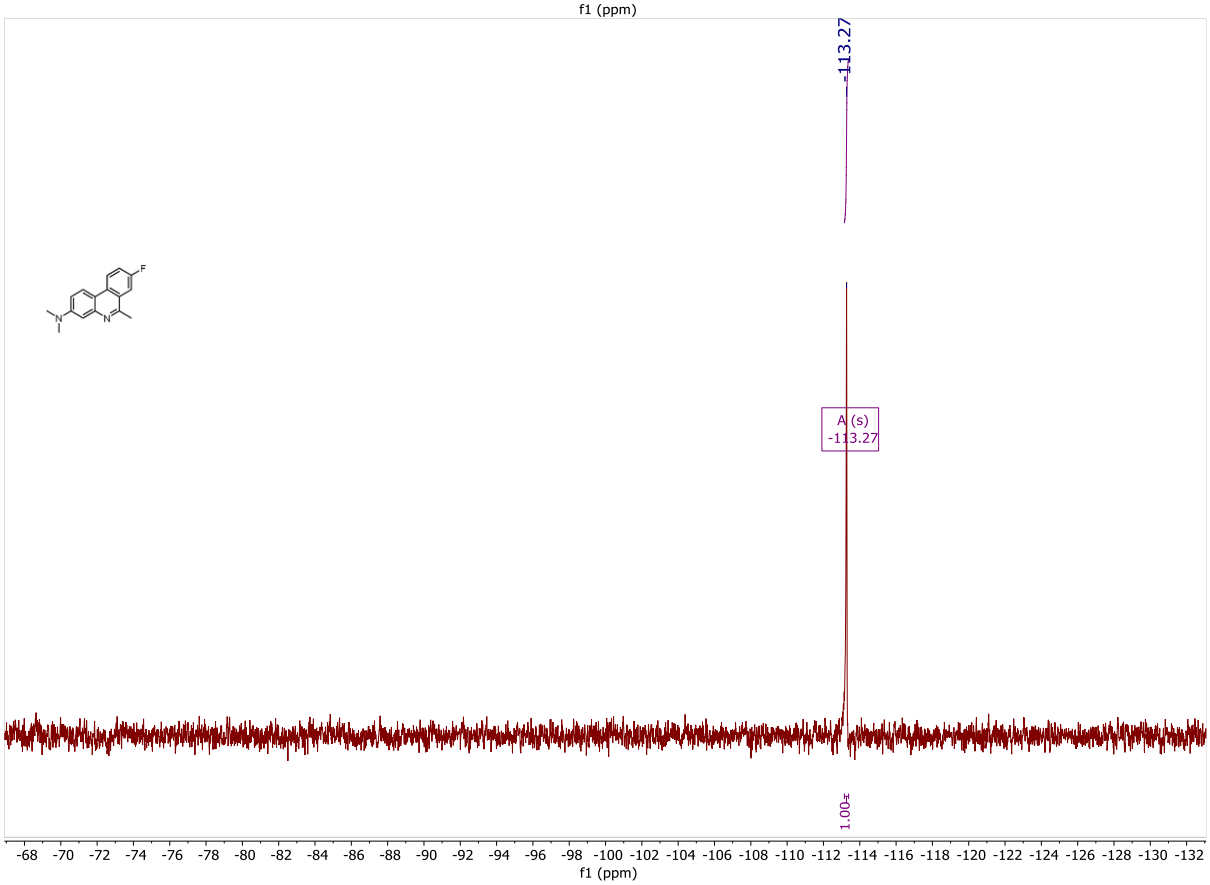
^{1}H NMR (500 MHz, chloroform-*d*) δ 8.39 (dd, *J* = 9.1, 5.3 Hz, 1H), 8.25 (d, *J* = 9.1 Hz, 1H), 7.71 (dd, *J* = 9.9, 2.7 Hz, 1H), 7.47 (ddd, *J* = 9.1, 8.1, 2.6 Hz, 1H), 7.27 (s, 1H), 7.13 (dd, *J* = 9.0, 2.7 Hz, 1H), 3.10 (s, 6H), 2.93 (s, 3H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 160.2 (d, $^{1}J_{C\text{-}F}$ = 245.6 Hz, C), 158.3 (d, $^{4}J_{C\text{-}F}$ = 4.0 Hz, C), 150.9 (C), 145.2 (C), 130.0 (d, $^{4}J_{C\text{-}F}$ = 1.8 Hz, C), 125.5 (d, $^{3}J_{C\text{-}F}$ = 7.3 Hz, C), 123.9 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz, CH), 122.6 (CH), 119.5 (d, $^{2}J_{C\text{-}F}$ = 23.8 Hz, CH), 114.5 (CH), 114.1 (C), 111.1 (d, $^{2}J_{C\text{-}F}$ = 21.0 Hz, C), 109.5 (CH), 40.7 ($2CH_3$), 23.5 (CH_3).

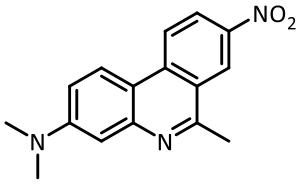
^{19}F NMR (76 MHz, chloroform-*d*) δ -89.02; IR (ν = cm^{-1}) 1187, 1247, 1366, 1499, 1617, 2928; HRMS (ESI) calcd for $C_{16}H_{16}FN_2$ $[M+H]^+$ 255.1292, observed 255.1284.







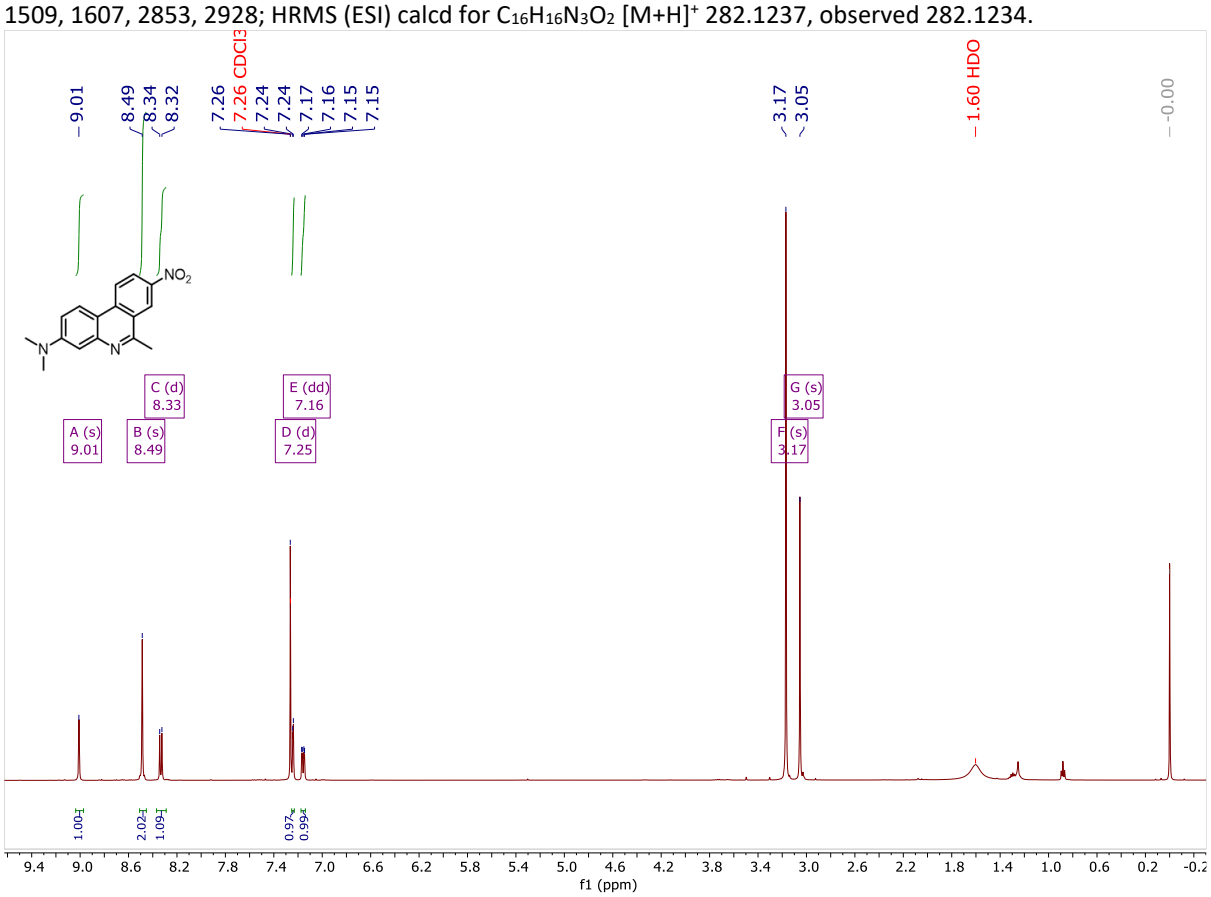
***N*,*N*,6-Trimethyl-8-nitrophenanthridin-3-amine (4f)**

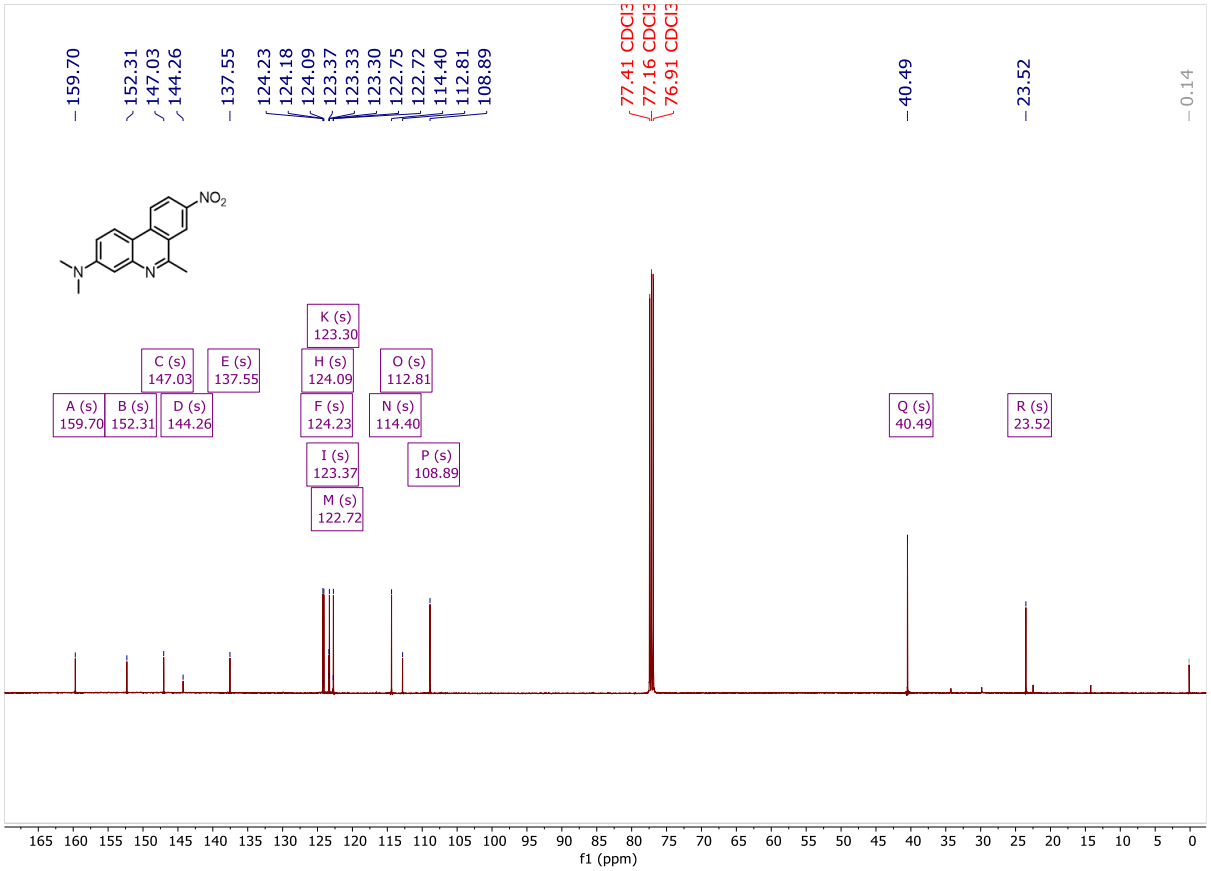


Following general procedure **C**, **4f** (93.0 mg, 0.331 mmol, 94%) was obtained as an orange solid by column chromatography (100% – 50% cyclohexane/EtOAc).

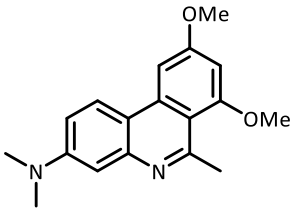
^{1}H NMR (500 MHz, chloroform-*d*) δ 9.00 (dd, *J* = 1.9, 0.9 Hz, 1H), 8.52 – 8.44 (m, 2H), 8.32 (d, *J* = 9.1 Hz, 1H), 7.24 (d, *J* = 2.7 Hz, 1H), 7.15 (dd, *J* = 9.1, 2.7 Hz, 1H), 3.17 (s, 6H), 3.05 (s, 3H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 159.7 (C), 152.3 (C), 147.0 (C), 144.3 (C), 137.5 (C), 124.2 (CH), 124.1 (CH), 123.4 (C), 123.3 (CH), 122.7 (CH), 114.4 (CH), 112.8 (C), 108.9 (CH), 40.5 ($2CH_3$), 23.5 (CH_3); IR (ν = cm^{-1}) 1343, 1509, 1607, 2853, 2928; HRMS (ESI) calcd for $C_{16}H_{16}N_3O_2$ $[M+H]^+$ 282.1237, observed 282.1234.

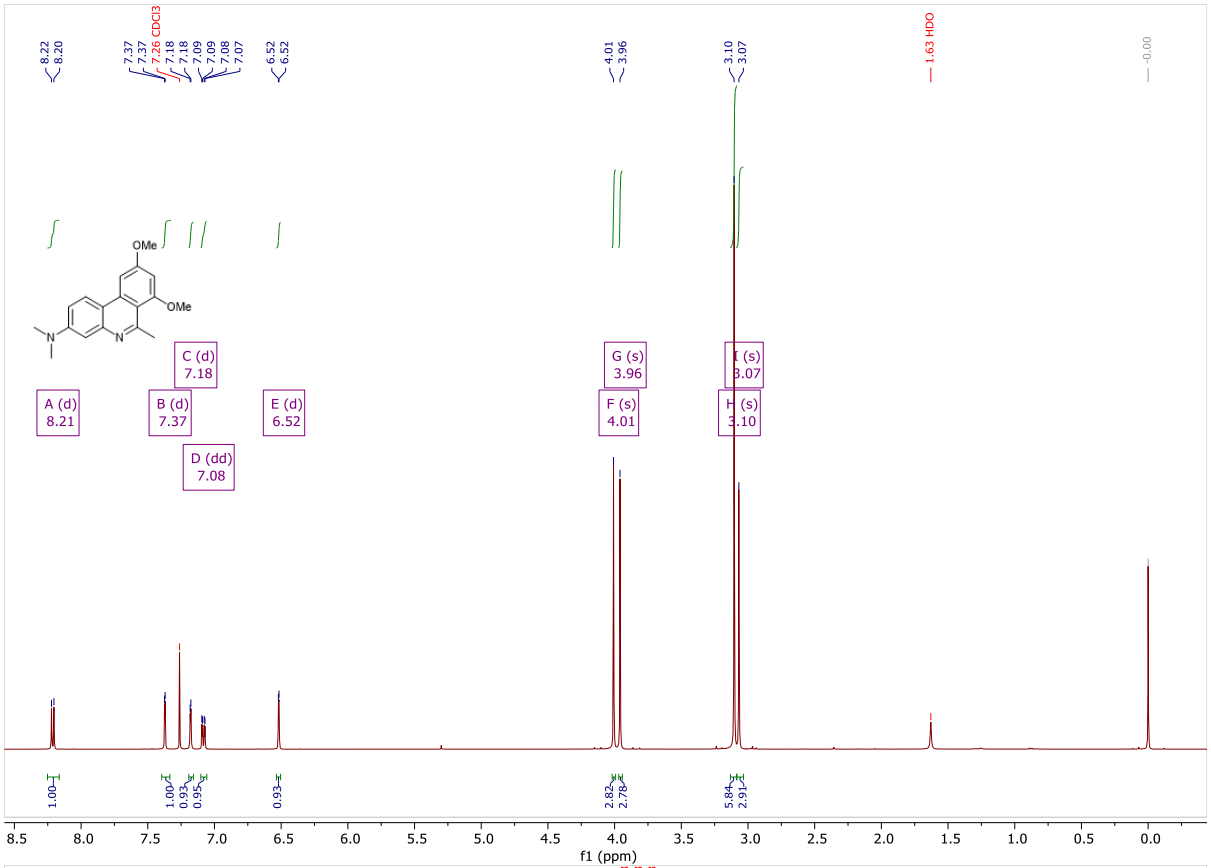


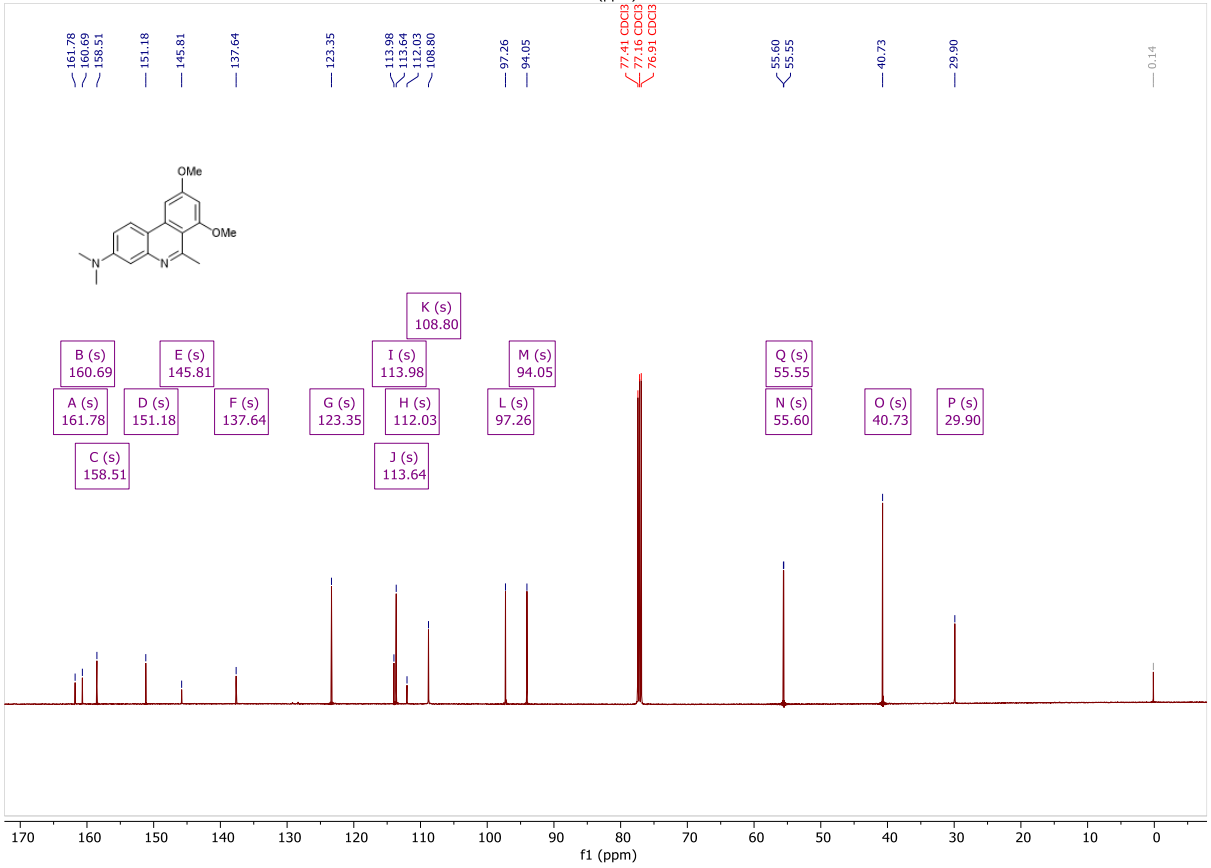


7,8,9-trimethoxy-*N*,*N*,6-trimethylphenanthridin-3-amine (4g)



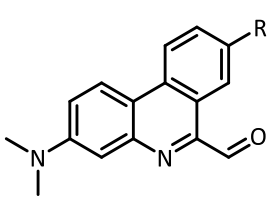
In a round bottom flask, **3g** (110.1 mg; 0.3520 mmol, 1 eq.), $POCl_3$ (165.6 µL, 1.760 mmol, 5 eq.) and polyphosphoric acid (480.0 mg) were combined. The reaction was heated at 120 °C for the appropriate duration. After cooling the reaction mixture to 0 °C, it was then basified around pH 11 with 2M NaOH aq. sonicated until the mixture became homogeneous. The mixture was diluted with H_2O (10 mL) and the resulting aqueous phase was extracted three times with DCM (3 × 20 mL). The organic layers were combined, washed with brine (5 mL), and then dried over $MgSO_4$ before being concentrated *in vacuo*. The crude product was purified by flash column chromatography (100% – 50% Cyclohexane/EtOAc), yielding **4g** (50.9 mg, 0.172 mmol, 49%) as a yellow solid.
^{1}H NMR (500 MHz, chloroform-*d*) δ 8.21 (d, J = 9.1 Hz, 1H), 7.37 (d, J = 2.3 Hz, 1H), 7.18 (d, J = 2.7 Hz, 1H), 7.08 (dd, J = 9.1, 2.7 Hz, 1H), 6.52 (d, J = 2.3 Hz, 1H), 4.01 (s, 3H), 3.96 (s, 3H), 3.10 (s, 6H), 3.07 (s, 3H).
^{13}C NMR (125 MHz, chloroform-*d*) δ 161.8 (C), 160.7 (C), 158.5 (C), 151.2 (C), 145.8 (C), 137.6 (C), 123.4 (CH), 114.0 (C), 113.6 (CH), 112.0 (C), 108.8 (CH), 97.3 (CH), 94.1 (CH), 55.6 (CH_3), 55.6 (CH_3), 40.7 ($2CH_3$), 29.9 (CH_3).; IR (ν = cm^{-1}) 1614, 1584, 1529, 1373, 1354; HRMS (ESI) calcd for $C_{18}H_{21}N_2O_2$ $[M+H]^+$ 297.1598, observed 297.1589.





Oxidations

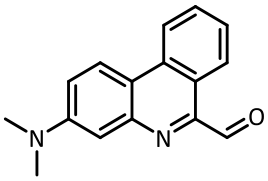
***General procedure D for the preparation of phenanthridine-6-carbaldehydes* 5a–f**



5a, R = H
5b, R = Me
5c, R = OMe
5d, R = NMe_2
5e, R = F
5f, R = NO_2

In a round bottom flask, SeO_2 (18.4 mg, 0.166 mmol, 1.2 eq.) and dioxane (0.56 mL, 0.25 M) were stirred under reflux for 1 hour. The corresponding phenanthridine **4a–f** (0.139 mmol, 1 eq.) was then added. The reaction was stirred under reflux for 3 hours. After cooling the reaction mixture to room temperature, it was filtered through a small pad of Celite®. The mixture was concentrated *in vacuo*, purified by recrystallisation in the corresponding solvent or by flash column chromatography, yielding the respective carbaldehydes **5a–f**.

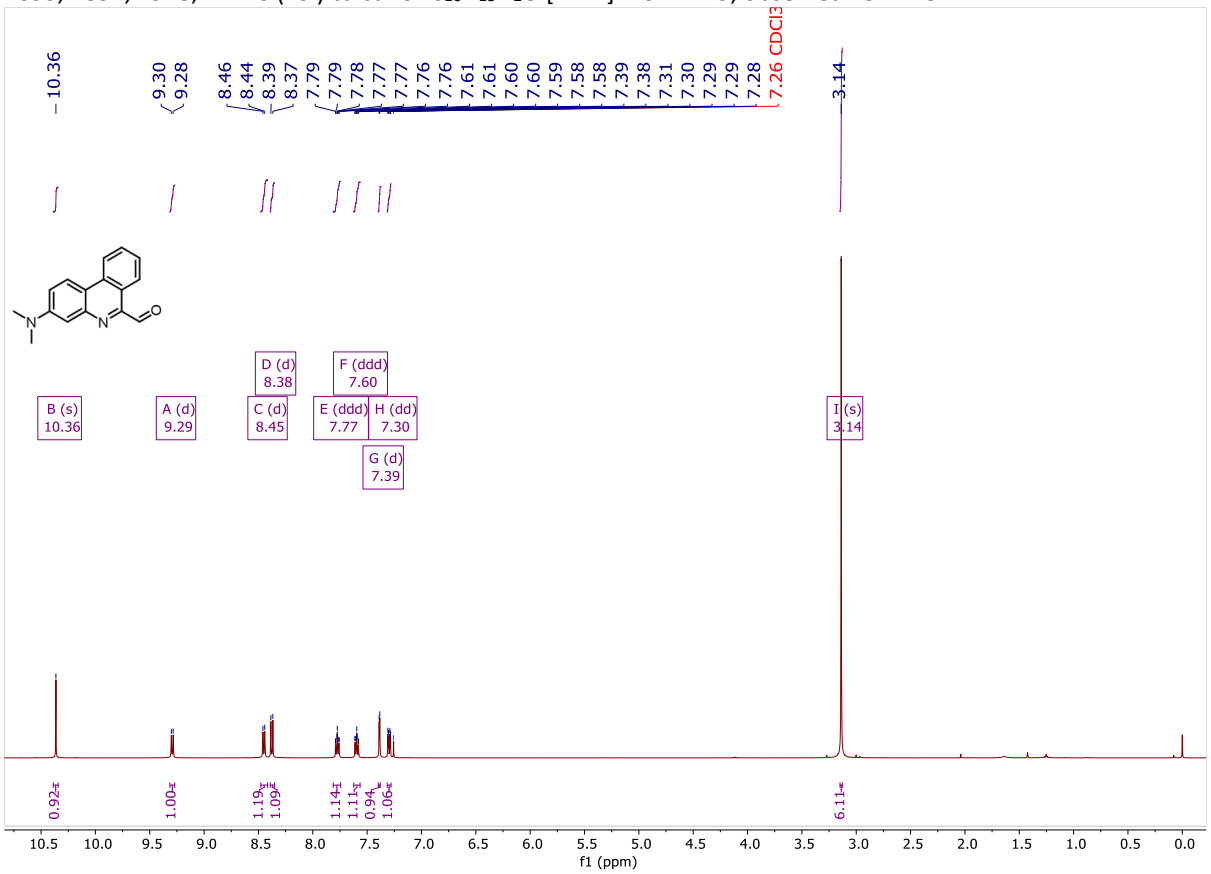
3-(Dimethylamino)phenanthridine-6-carbaldehyde (5a)

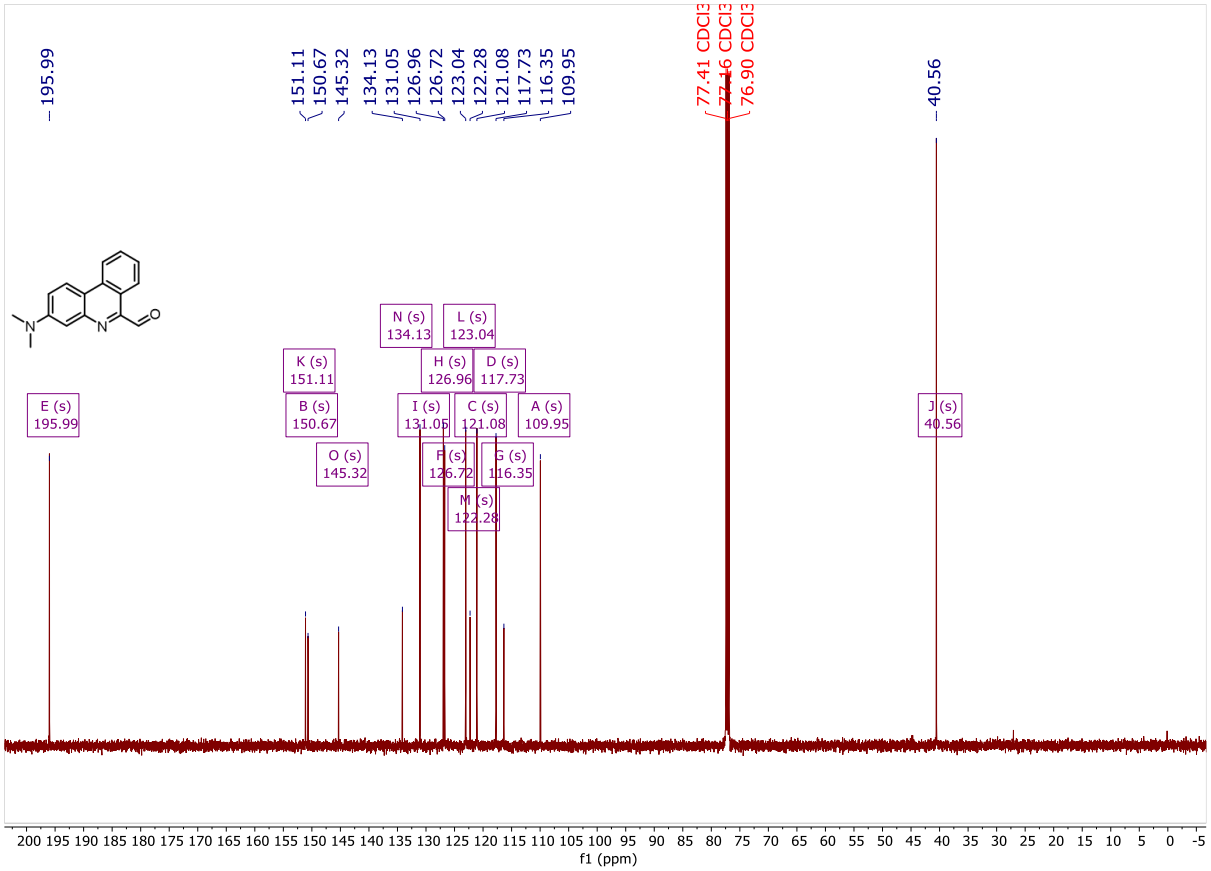


Following general procedure **D**, **5a** (76.8 mg, 0.307 mmol, 83%) was obtained as a brown solid by recrystallisation from EtOH.

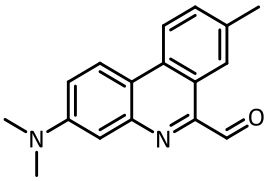
^{1}H NMR (500 MHz, chloroform-*d*) δ 10.36 (s, 1H), 9.29 (d, *J* = 8.4 Hz, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 8.38 (d, *J* = 9.2 Hz, 1H), 7.77 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.60 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.39 (d, *J* = 2.8 Hz, 1H), 7.30 (dd, *J* = 9.1, 2.8 Hz, 1H), 3.14 (s, 6H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 196.0 (CH), 151.1 (C), 150.7 (C), 145.3 (C), 134.1 (C), 131.1 (CH), 127.0 (CH), 126.7 (CH), 123.0 (CH), 122.3 (C), 121.1 (CH), 117.7 (CH), 116.4 (C), 110.0 (CH), 40.6 ($2CH_3$); IR (ν = cm^{-1}) 1616, 1695, 2857, 2928; HRMS (ESI) calcd for $C_{16}H_{15}N_2O$ $[M+H]^+$ 251.1179, observed 251.1181.





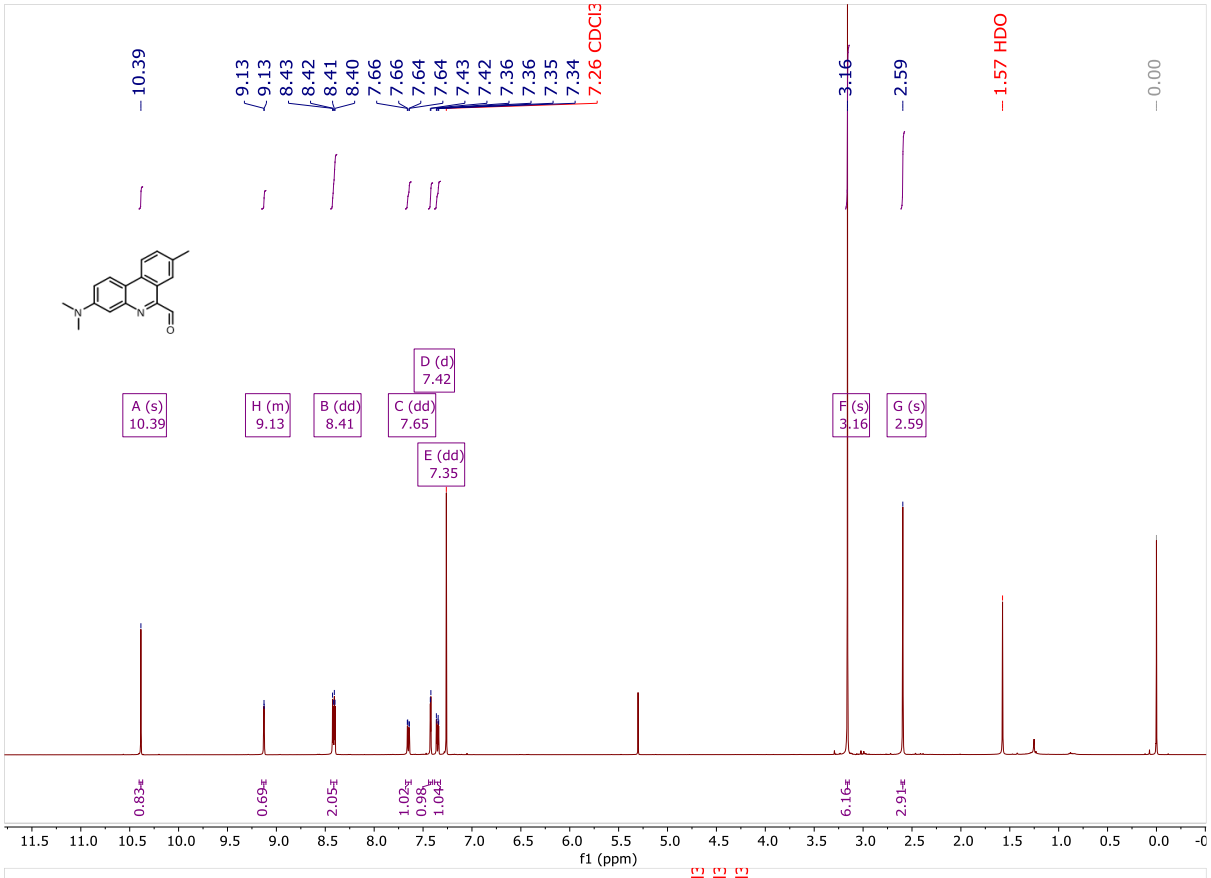
3-(Dimethylamino)-8-methylphenanthridine-6-carbaldehyde (5b)

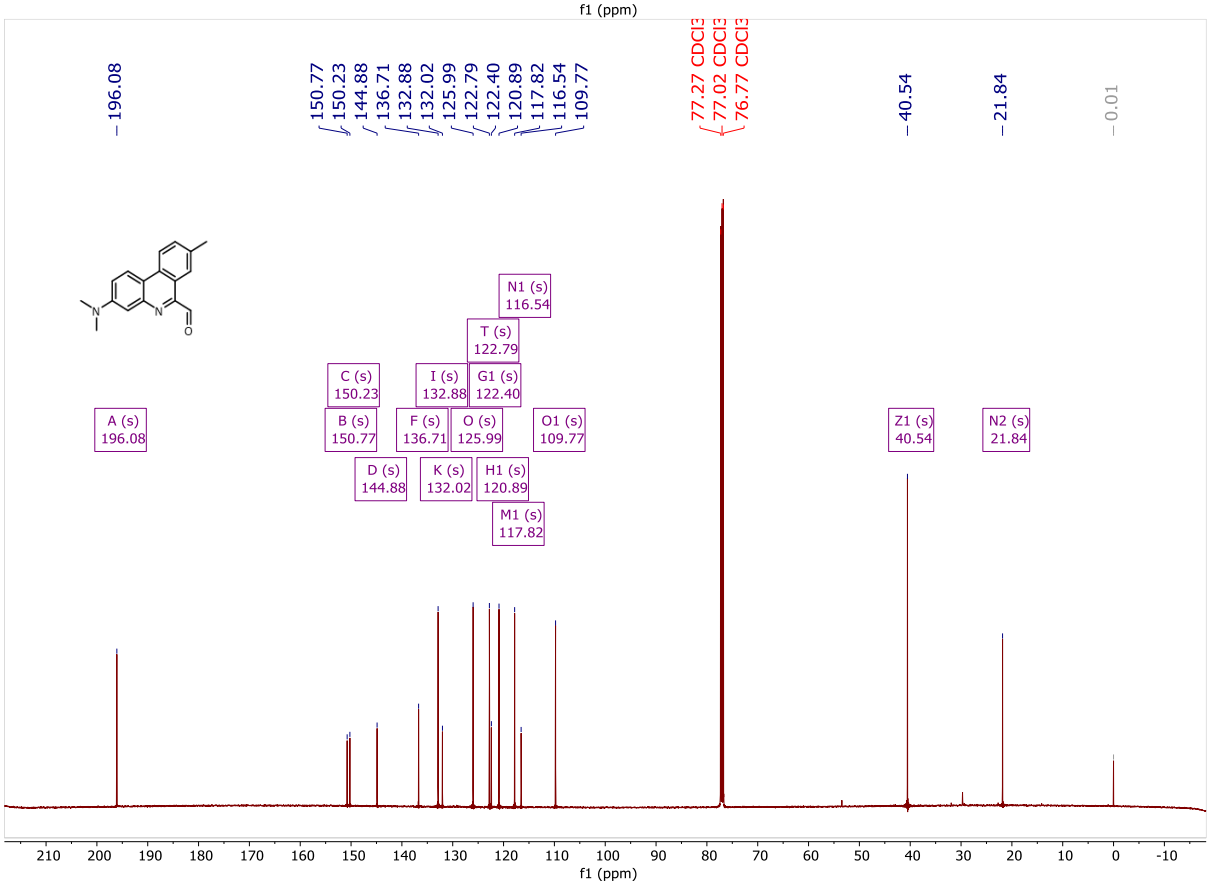


Following general procedure **D**, **5b** (57.6 mg, 0.218 mmol, 59%) was obtained as a brown solid by column chromatography (100% – 50% cyclohexane/EtOAc).

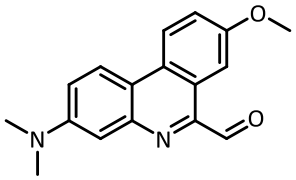
^{1}H NMR (500 MHz, chloroform-*d*) δ 10.39 (s, 1H), 9.15 – 9.11 (m, 1H), 8.41 (dd, *J* = 8.8, 3.9 Hz, 2H), 7.65 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.42 (d, *J* = 2.7 Hz, 1H), 7.35 (dd, *J* = 9.1, 2.8 Hz, 1H), 3.16 (s, 6H), 2.59 (s, 3H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 196.1 (CH), 150.8 (C), 150.2 (C), 144.9 (C), 136.7 (C), 132.9 (CH), 132.0 (C), 126.0 (CH), 122.8 (CH), 122.4 (C), 120.9 (CH), 117.8 (CH), 116.5 (C), 109.8 (CH), 40.5 ($2CH_3$), 21.8 (CH_3); IR (v = cm^{-1}) 1057, 1370, 1497, 1615, 1694, 2853; HRMS (ESI) calcd for $C_{17}H_{17}N_2O$ $[M+H]^+$ 265.1336, observed 265.1333.





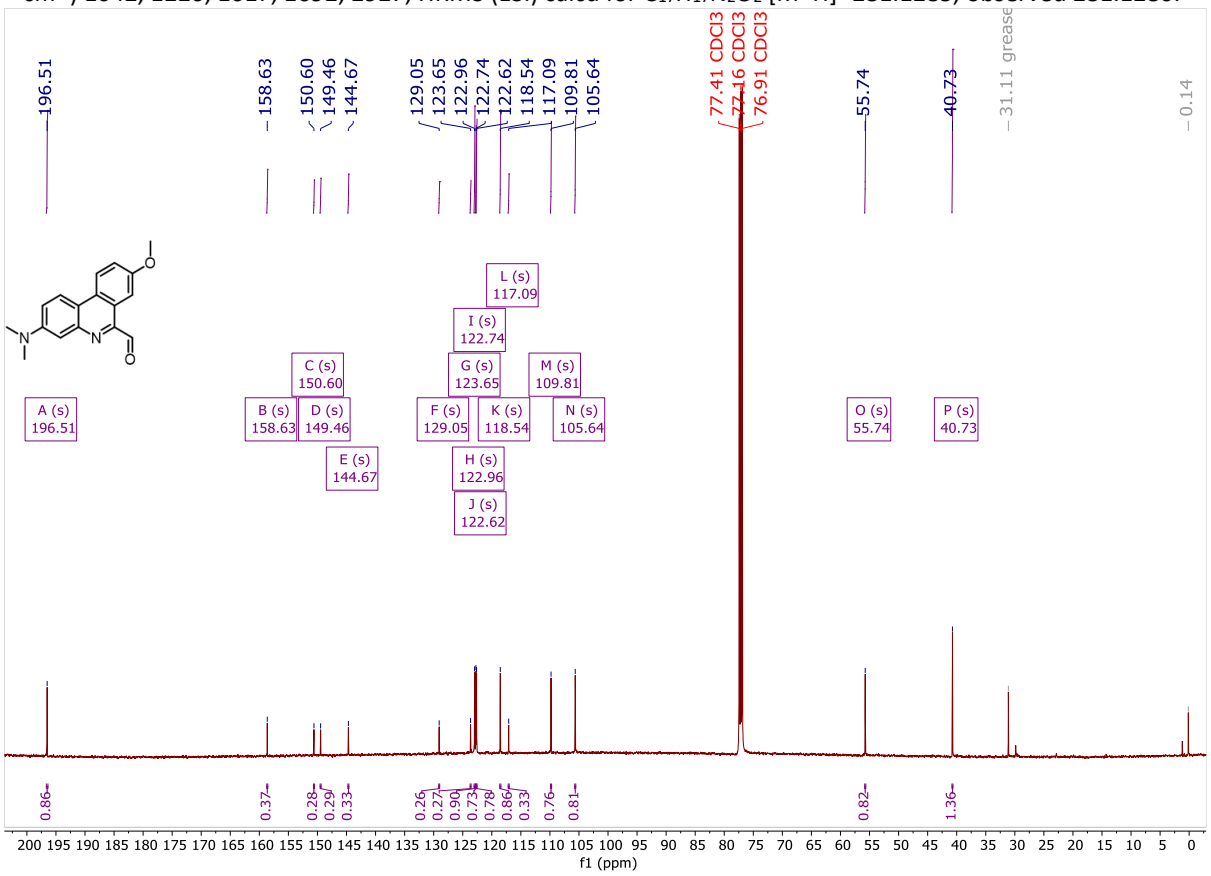
3-(Dimethylamino)-8-methoxyphenanthridine-6-carbaldehyde (5c)

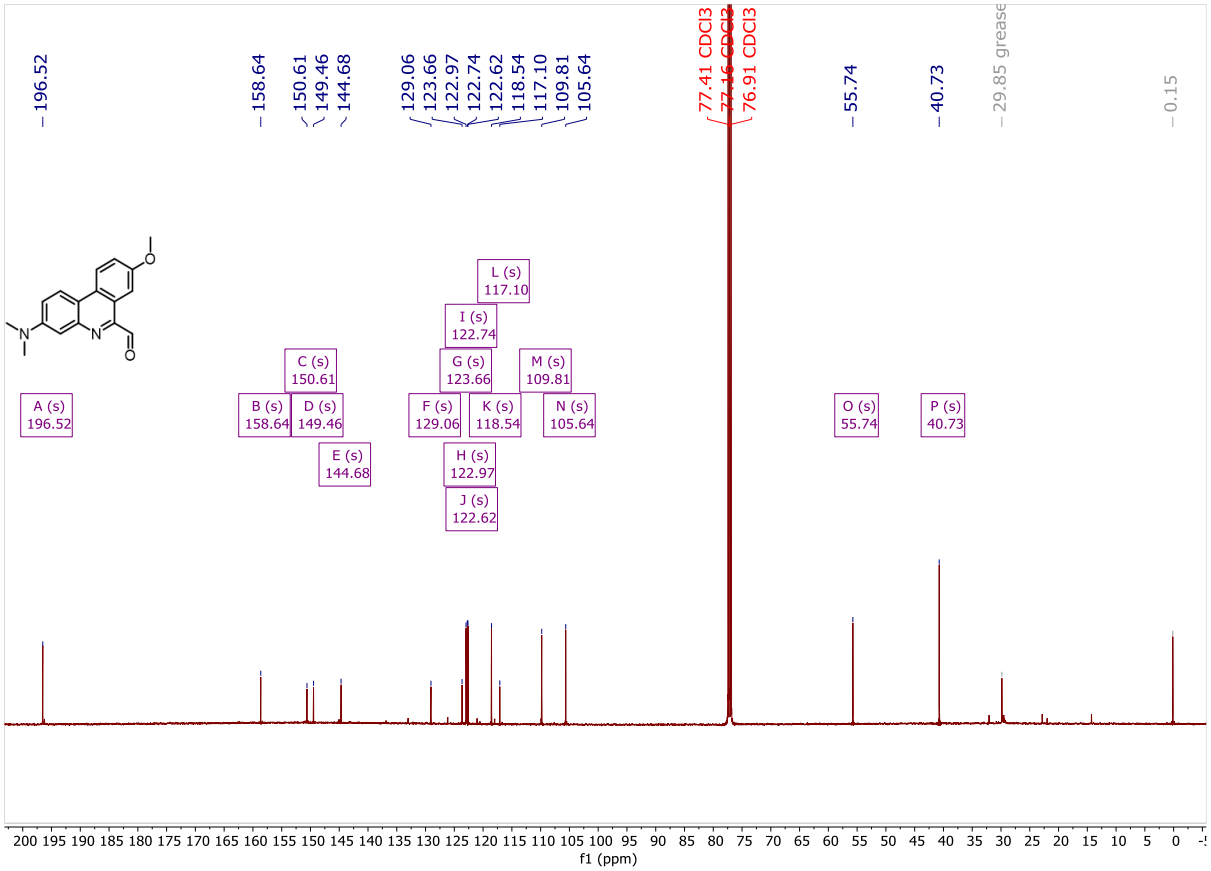


Following general procedure **D**, **5c** (36.4 mg, 0.130 mmol, 35%) was obtained as a red solid by column chromatography (100% – 0% cyclohexane/EtOAc).

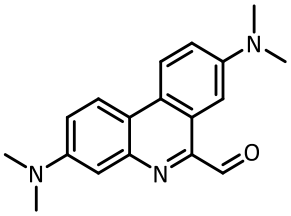
^{1}H NMR (500 MHz, chloroform-*d*) δ 10.40 (s, 1H), 8.82 (d, *J* = 2.7 Hz, 1H), 8.43 (d, *J* = 9.1 Hz, 1H), 8.38 (d, *J* = 9.1 Hz, 1H), 7.47 (dd, *J* = 9.1, 2.7 Hz, 1H), 7.42 (d, *J* = 2.7 Hz, 1H), 7.37 (dd, *J* = 9.1, 2.7 Hz, 1H), 4.01 (s, 3H), 3.15 (s, 6H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 196.5 (CH), 158.6 (C), 150.6 (C), 149.5 (C), 144.7 (C), 129.1 (C), 123.7 (C), 123.0 (CH), 122.7 (CH), 122.6 (CH), 118.5 (CH), 117.1 (C), 109.8 (CH), 105.6 (CH), 55.7 (CH_3), 40.7 ($2CH_3$); IR (ν = cm^{-1}) 1042, 1220, 1617, 1692, 2927; HRMS (ESI) calcd for $C_{17}H_{17}N_2O_2$ $[M+H]^+$ 281.1285, observed 281.1280.





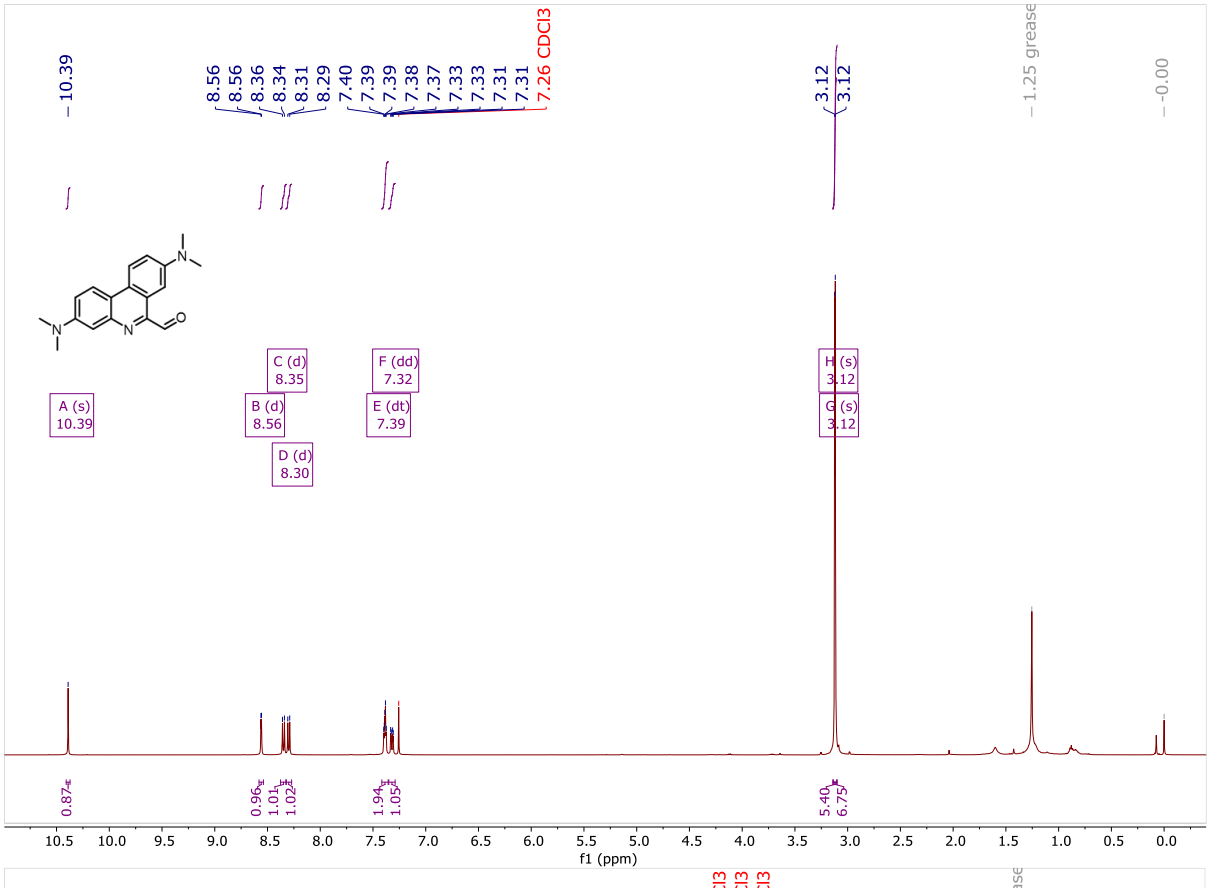
3,8-Bis(dimethylamino)phenanthridine-6-carbaldehyde (5d)

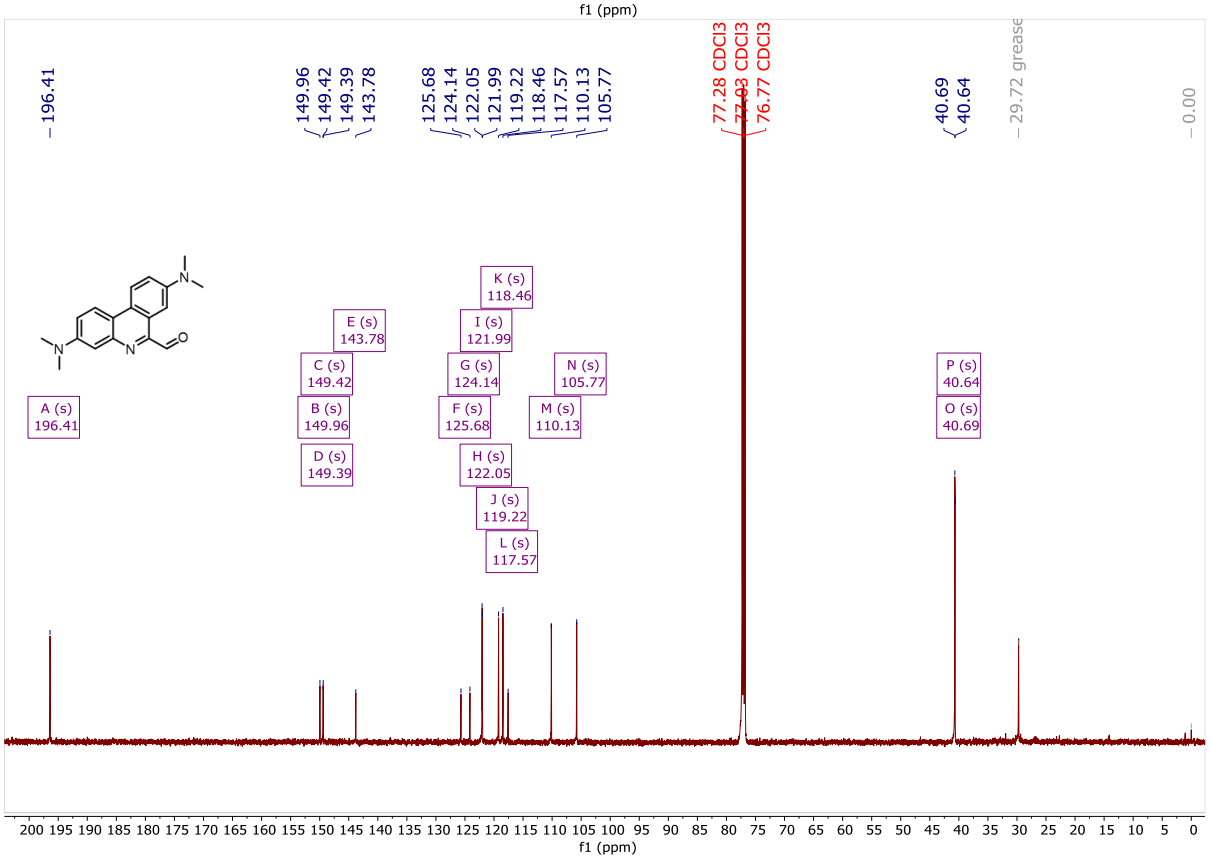


Following general procedure **D**, **5d** (52.2 mg, 0.178 mmol, 48%) was obtained as a purple solid by recrystallisation from EtOH.

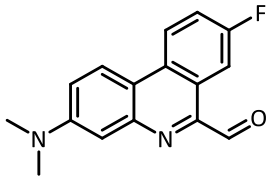
^{1}H NMR (500 MHz, chloroform-*d*) δ 10.39 (s, 1H), 8.56 (d, *J* = 2.7 Hz, 1H), 8.35 (d, *J* = 9.2 Hz, 1H), 8.30 (d, *J* = 9.1 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.32 (dd, *J* = 9.1, 2.8 Hz, 1H), 3.12 (s, 6H), 3.12 (s, 6H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 196.4 (CH), 150.0 (C), 149.4 (C), 149.4 (C), 143.8 (C), 125.7 (C), 124.1 (CH), 122.1 (CH), 122.0 (CH), 119.2 (CH), 118.5 (CH), 117.6 (C), 110.1 (CH), 105.8 (CH), 40.7 ($2CH_3$), 40.6 ($2CH_3$); IR (ν = cm^{-1}) 1423, 1441, 1656, 1721, 2820, 1721; HRMS (ESI) calcd for $C_{18}H_{20}N_3O$ $[M+H]^+$ 294.1601, observed 294.1595.





3-(Dimethylamino)-8-fluorophenanthridine-6-carbaldehyde (5e)

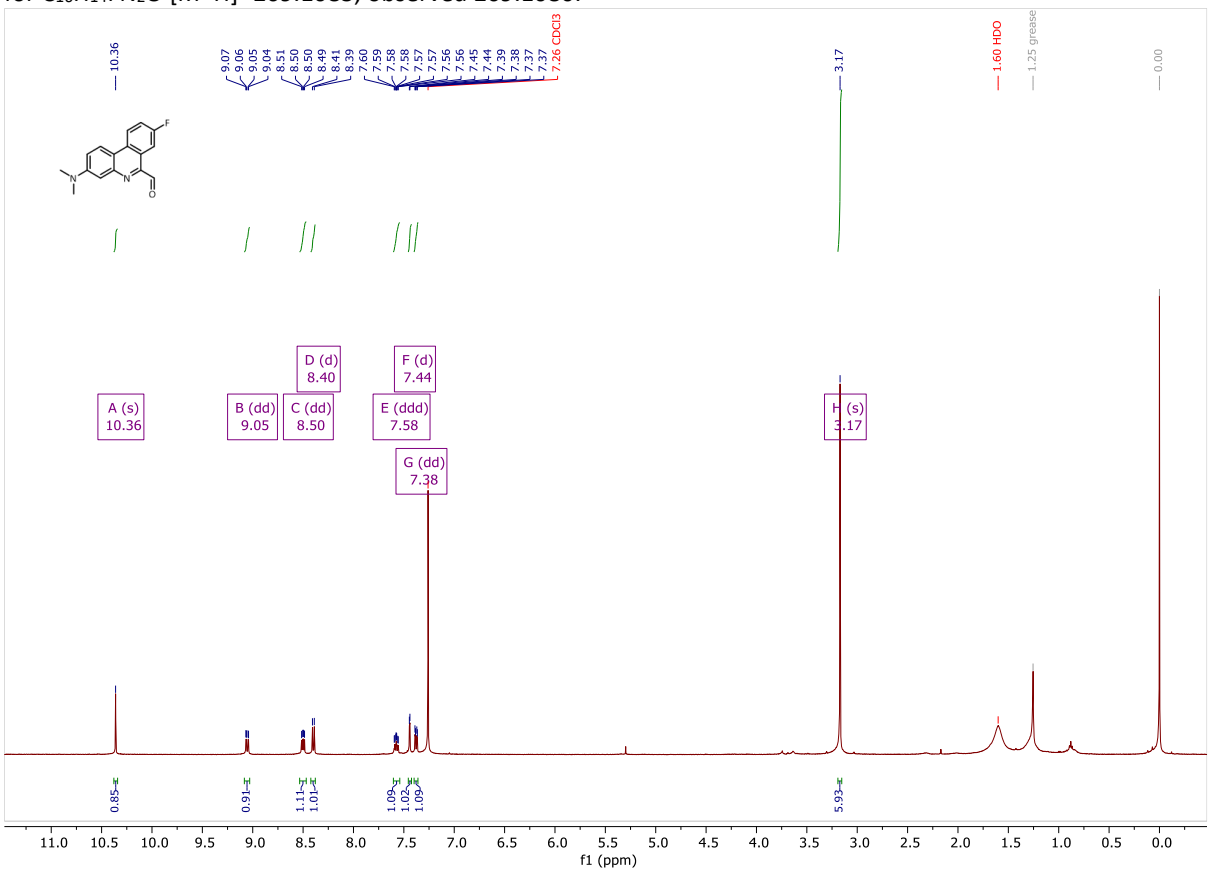


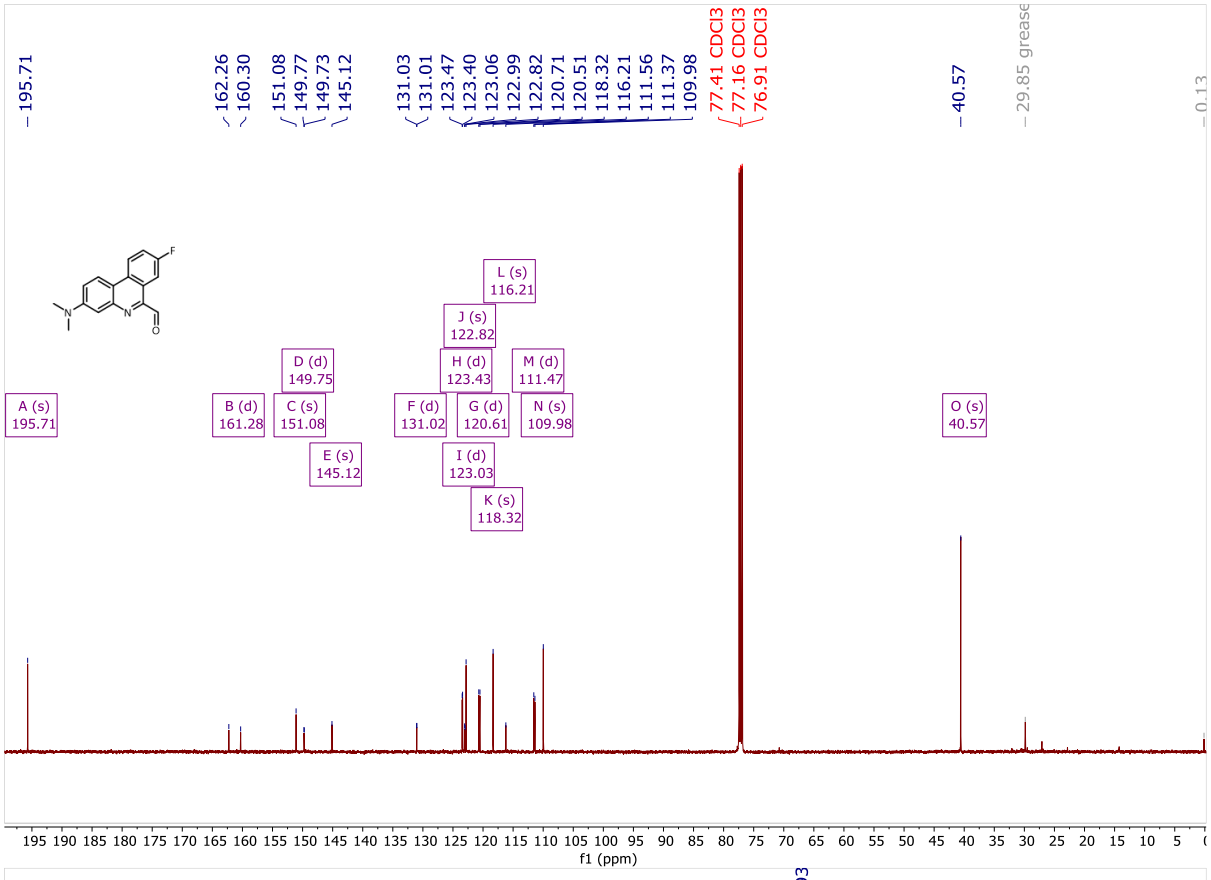
Following general procedure **D**, **5e** (48.5 mg, 0.181 mmol, 49%) was obtained as a red solid by column chromatography (100% – 70% cyclohexane/EtOAc).

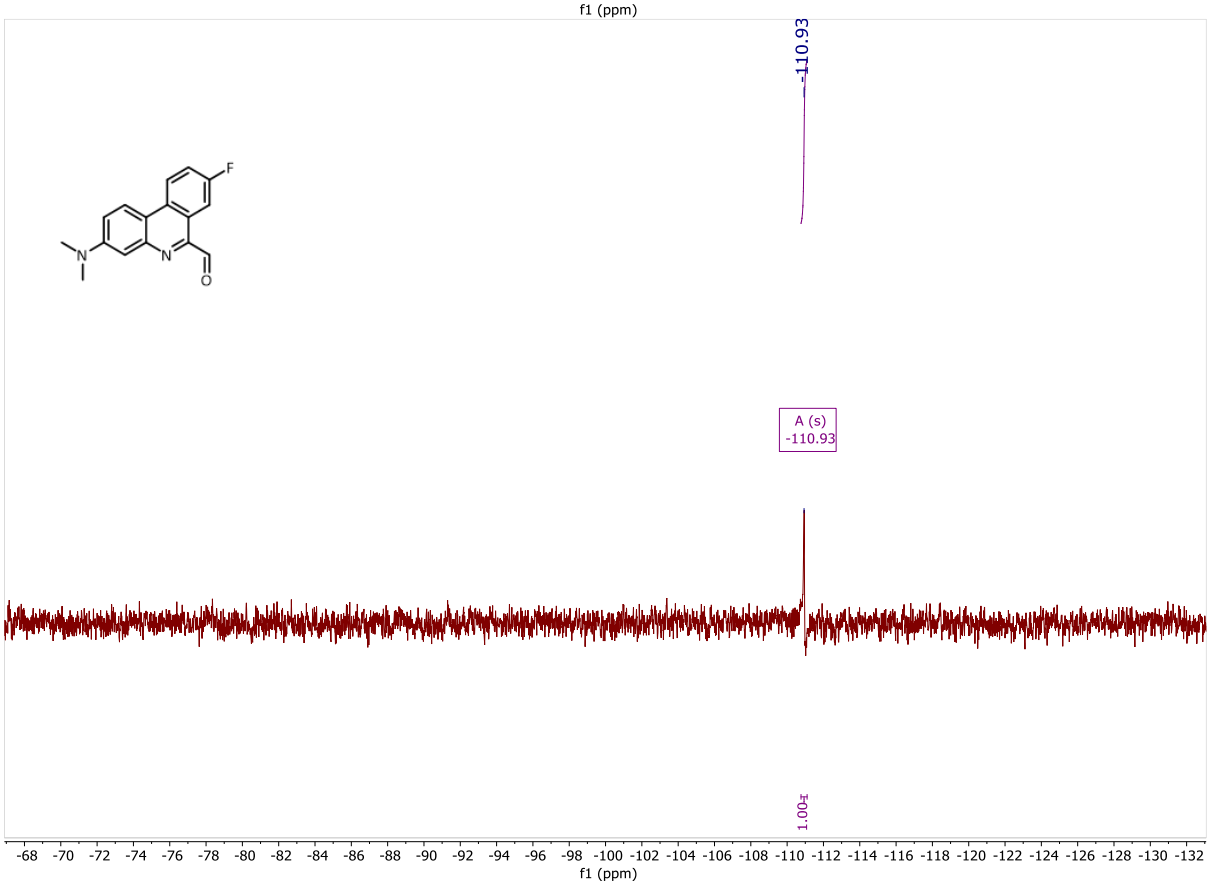
^{1}H NMR (500 MHz, chloroform-*d*) δ 10.33 (s, 1H), 9.02 (dd, *J* = 10.5, 2.7 Hz, 1H), 8.45 (dd, *J* = 9.2, 5.3 Hz, 1H), 8.34 (d, *J* = 9.1 Hz, 1H), 7.55 (ddd, *J* = 9.1, 7.9, 2.7 Hz, 1H), 7.40 (d, *J* = 2.7 Hz, 1H), 7.34 (dd, *J* = 9.1, 2.8 Hz, 1H), 3.15 (s, 6H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 195.6 (CH), 161.2 (d, $^{1}J_{C\text{-}F}$ = 246.9 Hz, C), 151.0 (C), 149.6 (d, $^{4}J_{C\text{-}F}$ = 4.8 Hz, C), 145.0 (C), 130.9 (d, $^{4}J_{C\text{-}F}$ = 1.8 Hz, C), 123.3 (d, $^{3}J_{C\text{-}F}$ = 8.5 Hz, CH), 122.9 (d, $^{3}J_{C\text{-}F}$ = 9.5 Hz, C), 122.7 (CH), 120.5 (d, $^{2}J_{C\text{-}F}$ = 24.5 Hz, CH), 118.2 (CH), 116.07 (C), 111.3 (d, $^{2}J_{C\text{-}F}$ = 23.4 Hz, CH), 109.9 (CH), 40.4 ($2CH_3$).

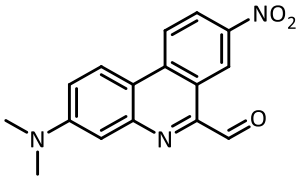
^{19}F NMR (76 MHz, chloroform-*d*) δ -110.93; IR (ν = cm^{-1}) 1420, 1491, 1617, 1692, 2853, 2927; HRMS (ESI) calcd for $C_{16}H_{14}FN_2O$ $[M+H]^+$ 269.1085, observed 269.1080.







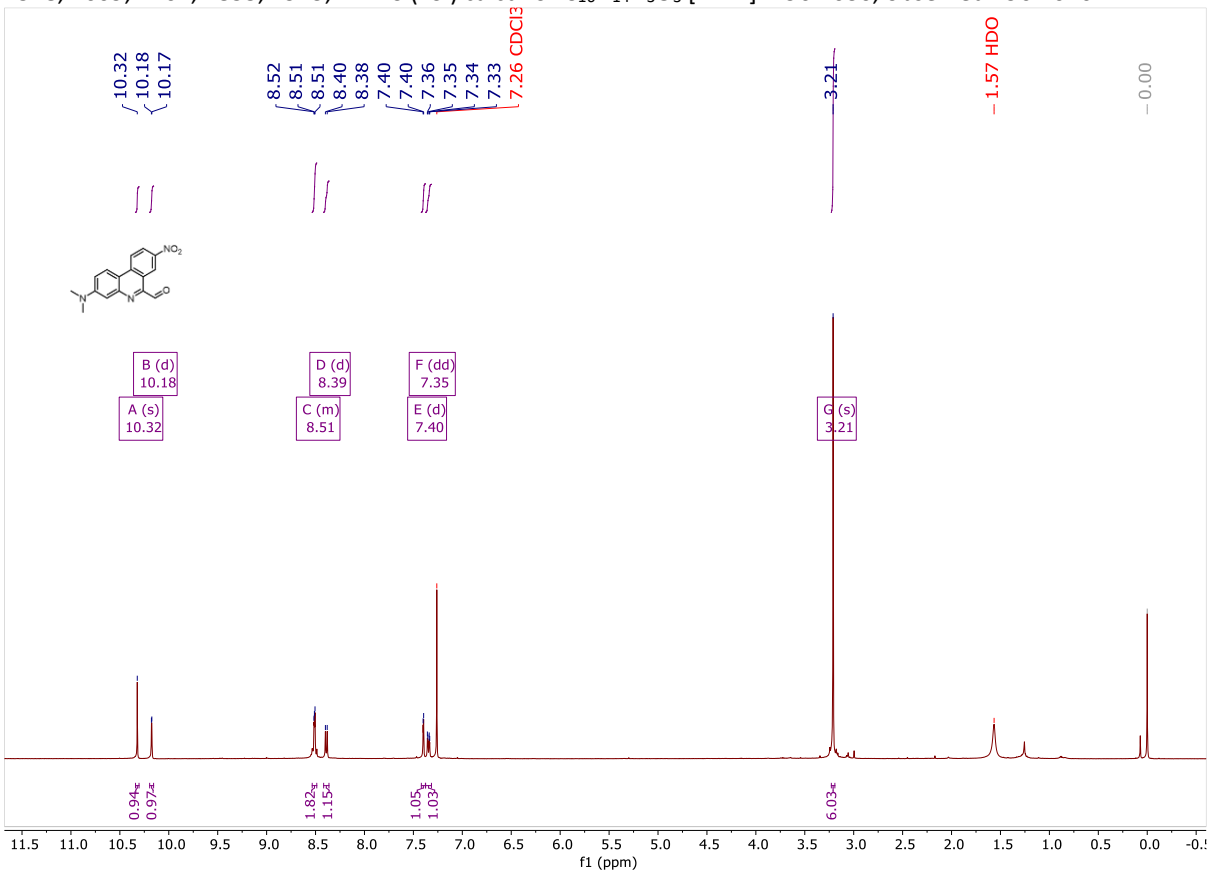
3-(Dimethylamino)-8-nitrophenanthridine-6-carbaldehyde (5f)

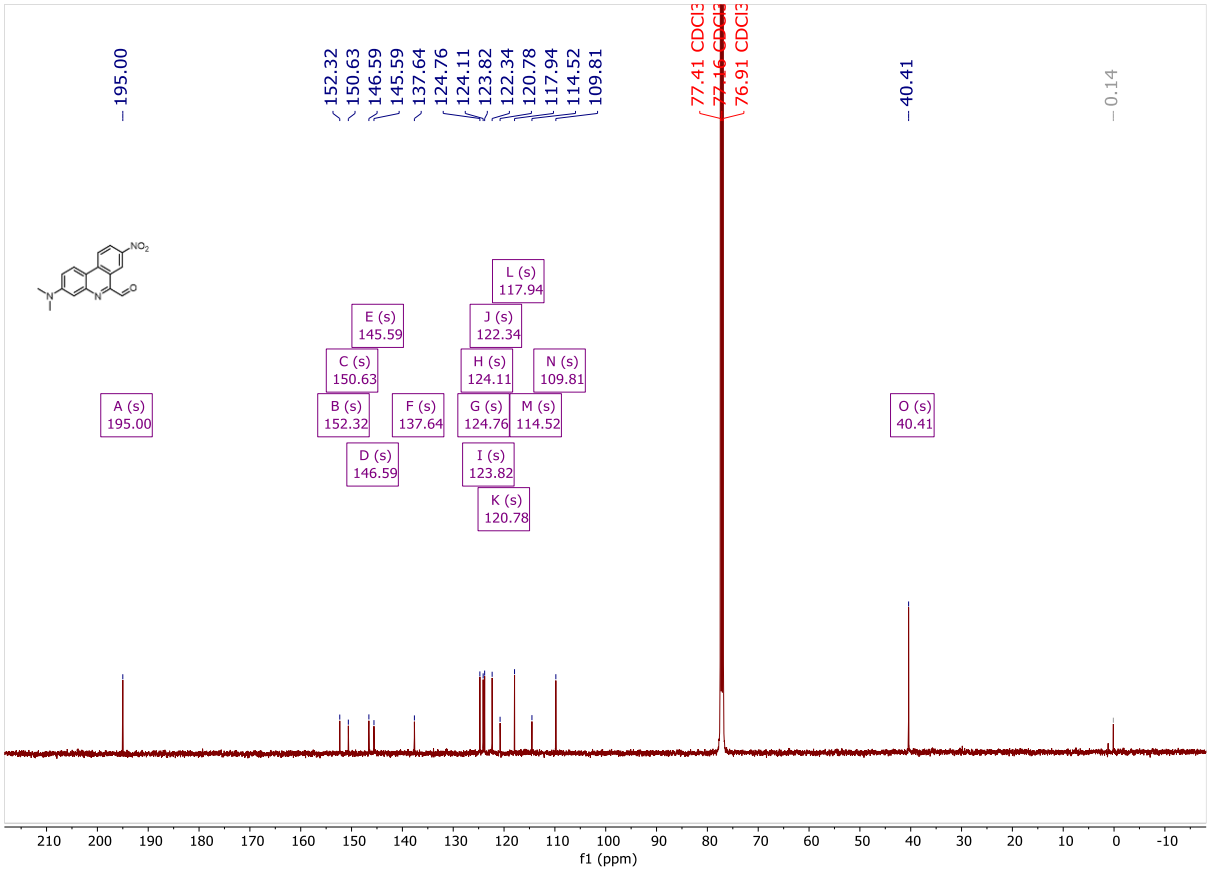


Following general procedure **D**, **5f** (29.5 mg, 0.100 mmol, 27%) was obtained as a dark orange by recrystallisation from toluene, followed by recrystallisation from EtOH.

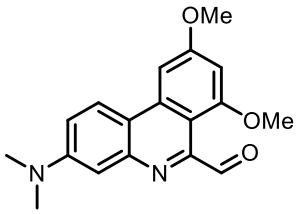
^{1}H NMR (500 MHz, chloroform-*d*) δ 10.32 (s, 1H), 10.18 (d, *J* = 2.1 Hz, 1H), 8.53 – 8.49 (m, 2H), 8.39 (d, *J* = 9.1 Hz, 1H), 7.40 (d, *J* = 2.7 Hz, 1H), 7.35 (dd, *J* = 9.1, 2.8 Hz, 1H), 3.21 (s, 6H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 195.0 (CH), 152.3 (C), 150.6 (C), 146.6 (C), 145.6 (C), 137.6 (C), 124.8 (CH), 124.1 (CH), 123.8 (CH), 122.3 (CH), 120.8 (C), 117.9 (CH), 114.5 (C), 109.8 (CH), 40.4 ($2CH_3$); IR (ν = cm^{-1}) 1370, 1518, 1609, 1704, 2855, 2923; HRMS (ESI) calcd for $C_{16}H_{14}N_3O_3$ $[M+H]^+$ 296.1030, observed 296.1026.





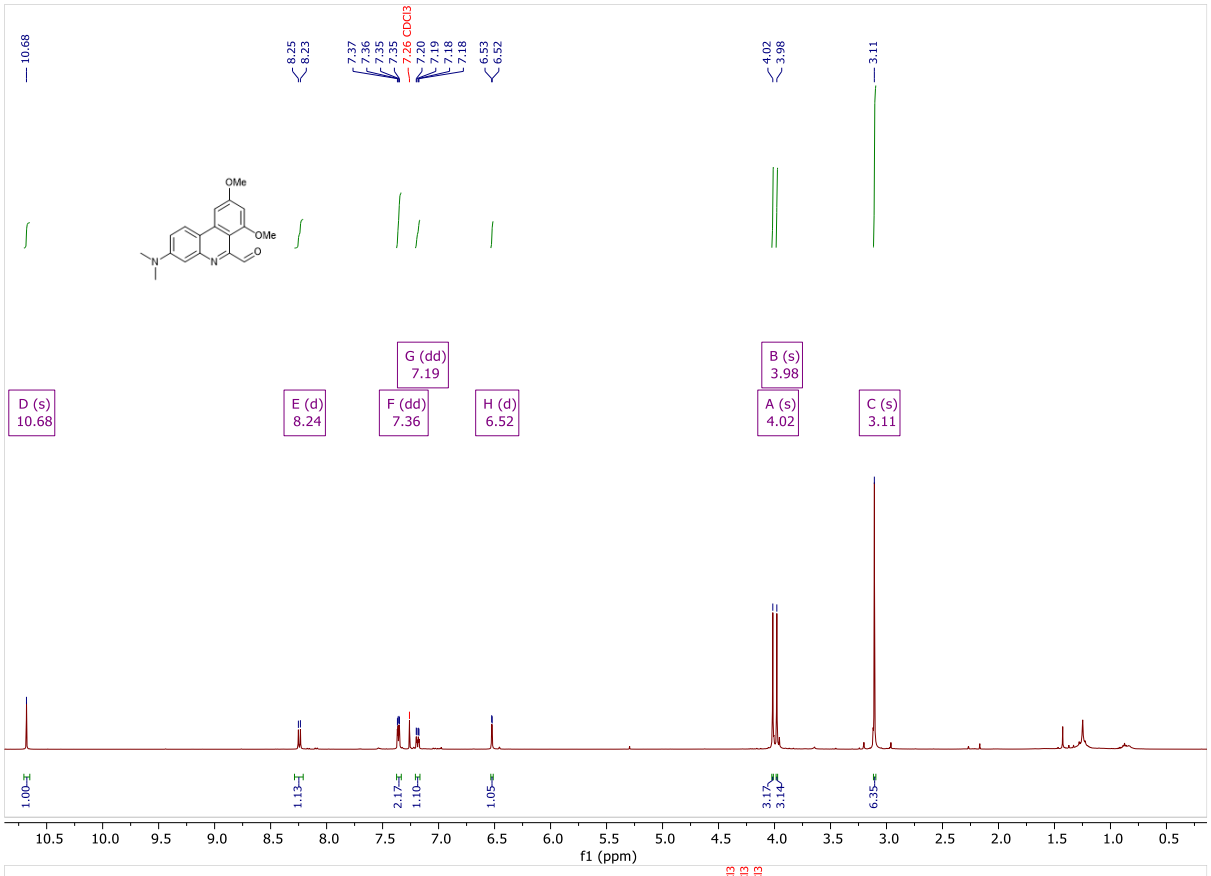
3-(dimethylamino)-7,9-dimethoxyphenanthridine-6-carbaldehyde (5g)



In a round bottom flask, SeO_2 (18.4 mg, 0.166 mmol, 1.2 eq.) and dioxane (0.56 mL, 0.25 M) were stirred under reflux for 1 hour. **4g** (41.2 mg, 0.139 mmol, 1 eq.) was then added. The reaction was stirred under reflux for 3 hours. After cooling the reaction mixture to room temperature, it was filtered through a small pad of Celite®. The mixture was concentrated *in vacuo*, purified by by flash column chromatography (100% – 50% cyclohexane/EtOAc, yielding **5g** (22.9 mg, 0.074 mmol, 20%) as a dark orange solid.

^{1}H NMR (500 MHz, chloroform-*d*) δ 10.68 (s, 1H), 8.24 (d, J = 9.1 Hz, 1H), 7.36 (dd, J = 6.5, 2.4 Hz, 2H), 7.19 (dd, J = 9.1, 2.8 Hz, 1H), 6.52 (d, J = 2.1 Hz, 1H), 4.02 (s, 3H), 3.98 (s, 4H), 3.11 (s, 7H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 194.1 (CH), 162.9 (C), 158.7 (C), 154.9 (C), 151.3 (C), 145.8 (C), 137.4 (C), 123.4 (CH), 115.7 (CH), 114.7 (C), 110.2 (CH), 109.9 (C), 97.5 (CH), 94.2 (CH), 56.1 (CH_3), 55.8 (CH_3), 40.6 ($2CH_3$); IR (ν = cm^{-1}) 1614, 1576, 1531, 1363, 1267, 1215; HRMS (ESI) calcd for $C_{18}H_{19}N_2O_3$ $[M+H]^+$ 311.1390, observed 311.1383.


10.68
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8.23
7.37
7.36
7.35
7.35
7.26 CDCl3
7.20
7.19
7.18
7.18
6.53
6.52
4.02
3.98
3.11
OMe
OMe
N
O
G (dd)
7.19
B (s)
3.98
D (s)
10.68
E (d)
8.24
F (dd)
7.36
H (d)
6.52
A (s)
4.02
C (s)
3.11
1.00
1.13
2.17
1.10
1.05
3.17
3.14
6.35
10.5
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
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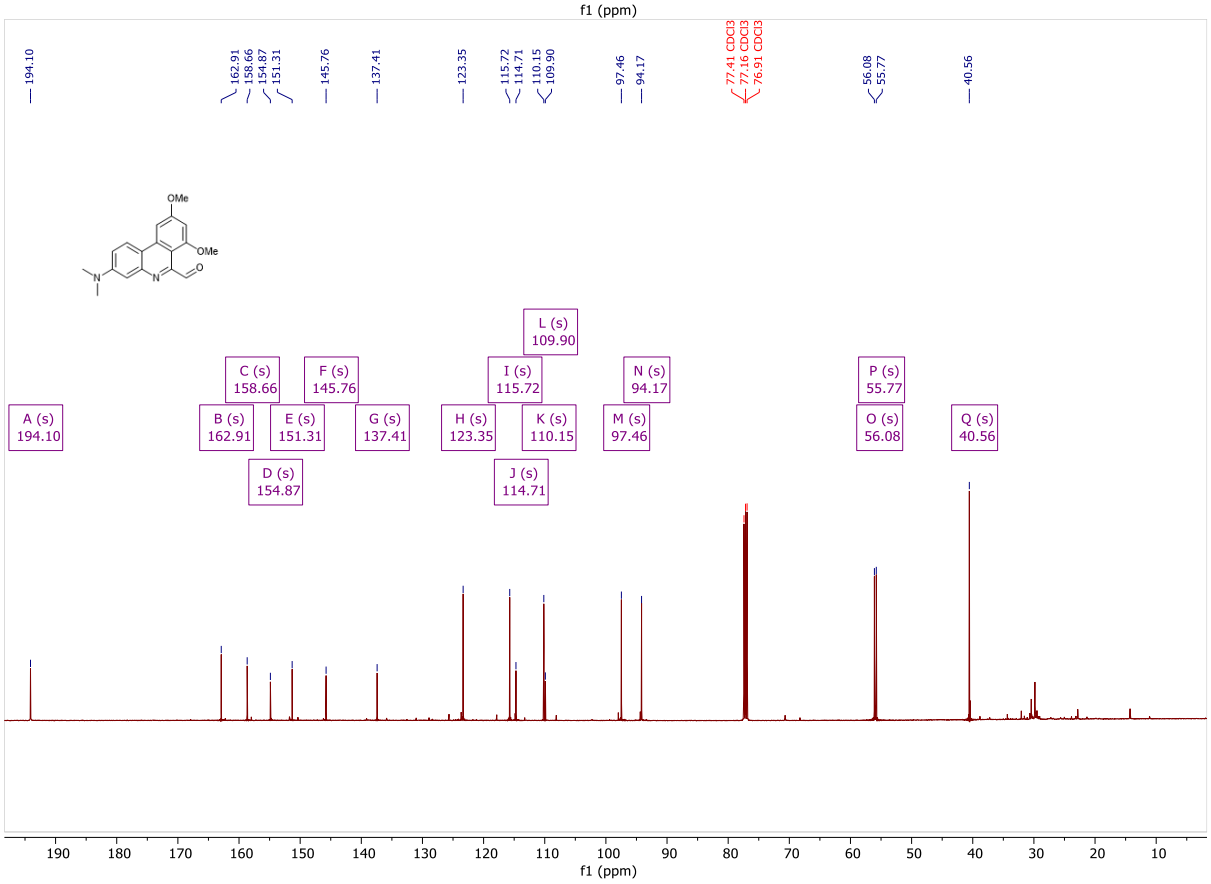
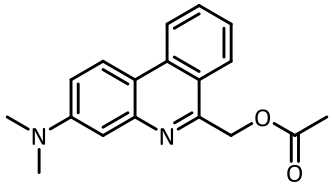
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


194.10
162.91
158.66
154.87
151.31
145.76
137.41
123.35
115.72
114.71
110.15
109.90
97.46
94.17
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
56.08
55.77
40.56
OMe
OMe
N
O
L (s)
109.90
C (s)
158.66
F (s)
145.76
I (s)
115.72
N (s)
94.17
P (s)
55.77
A (s)
194.10
B (s)
162.91
E (s)
151.31
G (s)
137.41
H (s)
123.35
K (s)
110.15
M (s)
97.46
O (s)
56.08
Q (s)
40.56
D (s)
154.87
J (s)
114.71
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

Reduction/acetylation sequences

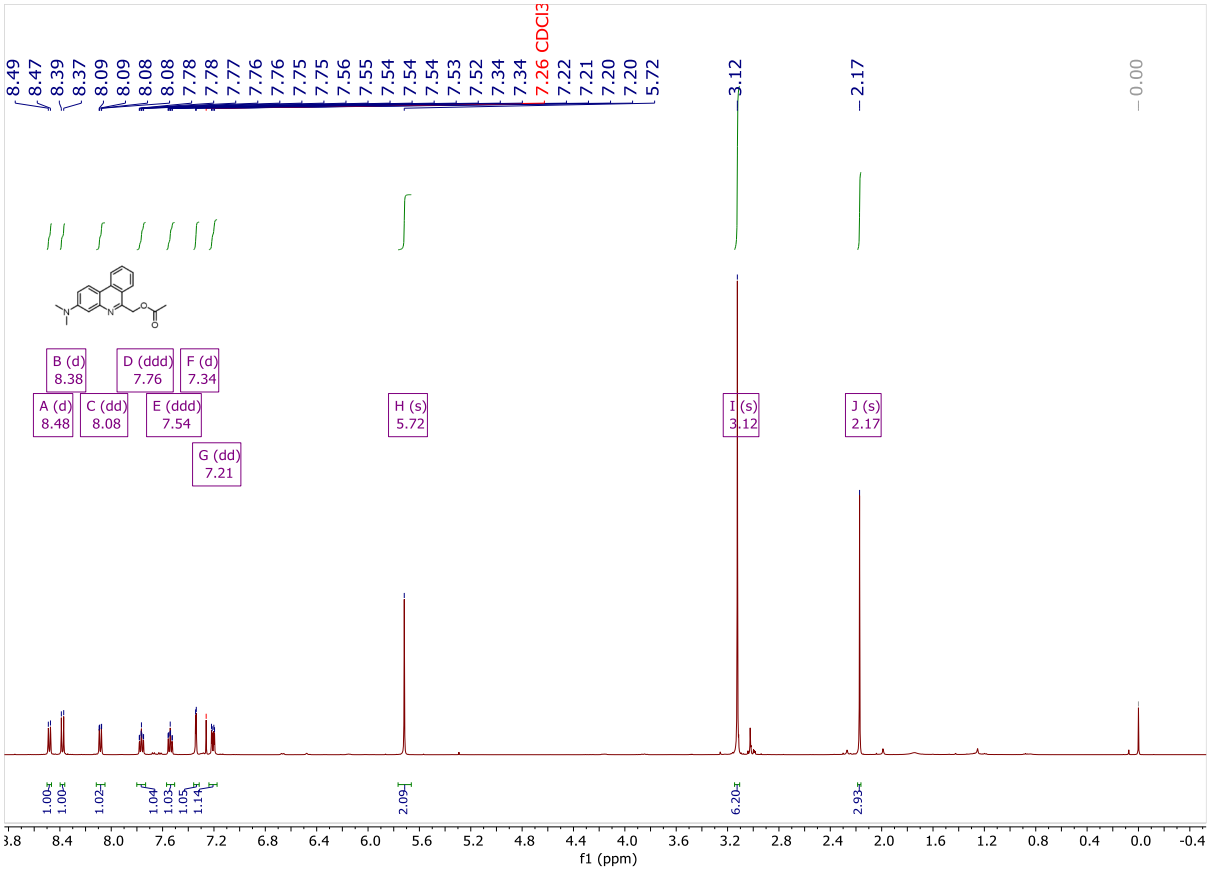
(3-(Dimethylamino)phenanthridin-6-yl)methyl acetate (6a)

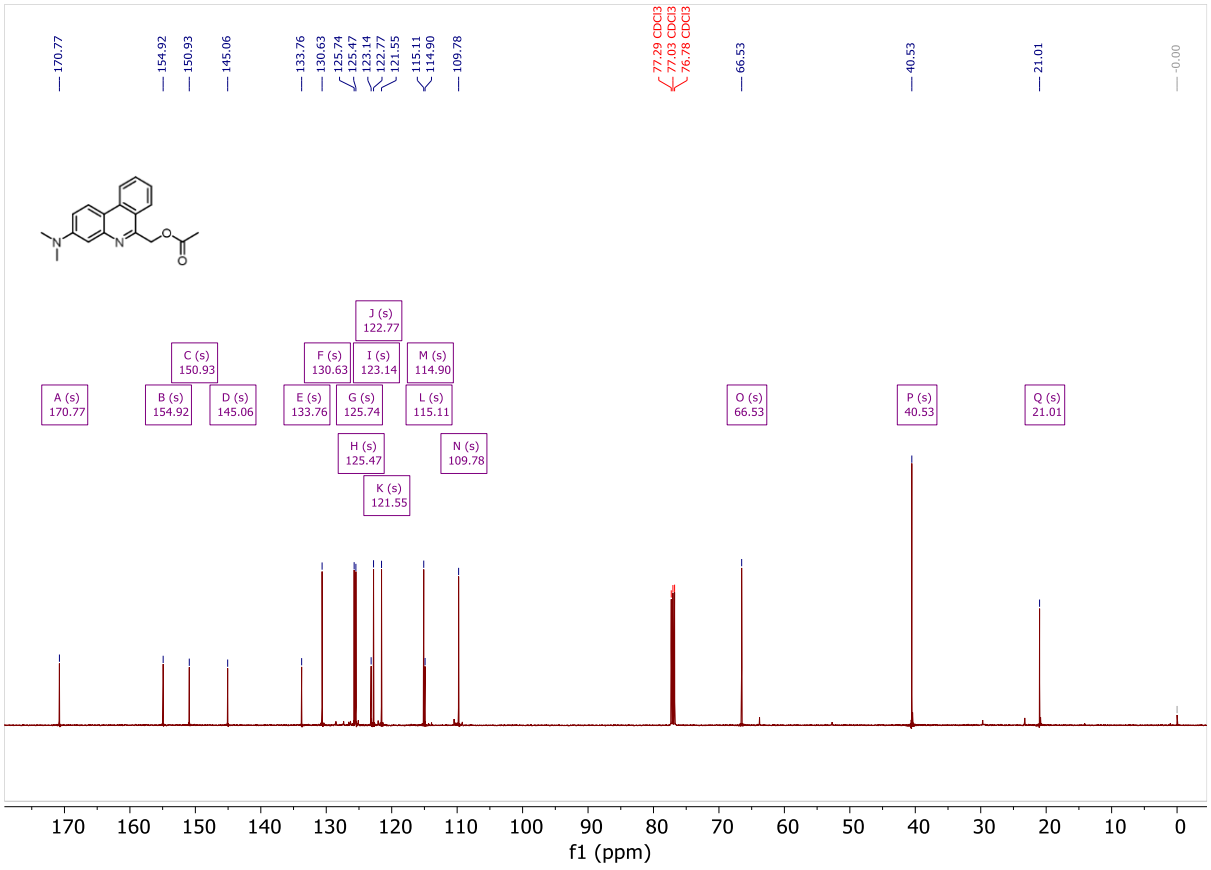


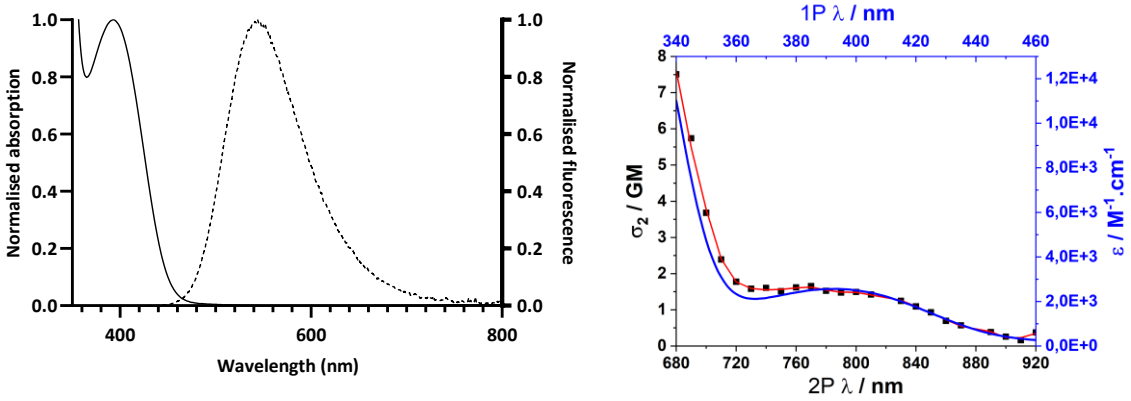
In a round bottom flask under inert atmosphere, **5a** (0.037 mmol, 1 eq.) was dissolved in EtOH (1 mL, 37 mM). After cooling the reaction mixture to 0 °C, $NaBH_4$ (0.037 mmol, 1 eq.) was added and the reaction mixture was stirred at rt for 15 min. After reaction completion, the crude mixture was diluted with H_2O (10 mL). The resulting aqueous phase was extracted three times with DCM (3 × 10 mL). The organic layers were combined, washed with brine (5 mL), and then dried over $MgSO_4$ before being concentrated *in vacuo*. The residue was dissolved in DCM (1 mL, 37 mM), triethylamine (0.11 mmol, 3 eq.) and acetic anhydride (0.22 mmol, 6 eq.) were added and the reaction was stirred at rt for 3 hours. After reaction completion, the crude mixture was diluted with sat. aq. $NaHCO_3$ (10 mL). The resulting aqueous phase was extracted three times with DCM (3 × 10 mL). The organic layers were combined, washed with brine (5 mL), and then dried over $MgSO_4$. The mixture was concentrated *in vacuo* and purified by flash column chromatography (100% – 50% cyclohexane/EtOAc), yielding **6a** (6.2 mg, 0.021 mmol, 57%) as a yellowish oil.

^{1}H NMR (500 MHz, chloroform-*d*) δ 8.50 (d, *J* = 8.3 Hz, 1H), 8.40 (d, *J* = 9.0 Hz, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 7.78 (ddd, *J* = 8.4, 6.9, 1.3 Hz, 1H), 7.55 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.35 (d, *J* = 2.7 Hz, 1H), 7.22 (dd, *J* = 9.1, 2.7 Hz, 1H), 5.72 (s, 2H), 3.13 (s, 6H), 2.18 (s, 3H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 170.9 (C), 155.1 (C), 151.1 (C), 145.2 (C), 133.9 (C), 130.8 (CH), 125.9 (CH), 125.6 (CH), 123.3 (C), 122.9 (CH), 121.7 (CH), 115.3 (CH), 115.1 (C), 110.0 (CH), 66.7 (CH_2), 40.7 ($2CH_3$), 21.2 (CH_3); IR (ν = cm^{-1}) 1443, 1497, 1615, 1742, 2928, 1372; HRMS (ESI) calcd for $C_{18}H_{19}N_2O_2$ $[M+H]^+$ 295.1441, observed 295.1437.

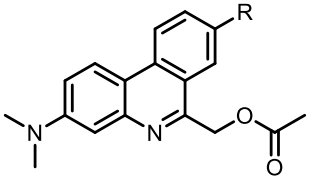






UV–vis spectrum of **6a**.
Conditions: Measured in DMSO at 0.025 mM; λ_{abs} = 395 nm; ε_{395} = 2600 $M^{-1}{\cdot}cm^{-1}$.
Fluorescence spectrum of **6a**.
Conditions: Measured in DMSO; λ_{exc} = 395 nm; λ_{em}^{max} = 544 nm; Φ_F = 0.25

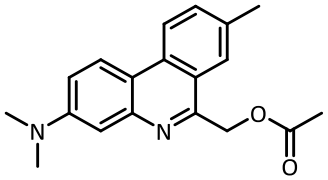
General procedure E for the preparation of phenanthridine-6-methyl acetate 6b–f



6b: R = Me
6c: R = OMe
6d: R = NMe_2
6e: R = F
6f: R = NO_2

In a round bottom flask under inert atmosphere, **5b–f** (0.037 mmol, 1 eq.) was dissolved in acetic anhydride (1 mL, 16 mM). After cooling the reaction mixture to 0 °C, $NaBH_4$ (0.074 mmol, 2 eq.) was added and it was stirred for 16 h. After reaction completion, the mixture was concentrated *in vacuo* and purified by flash column chromatography, yielding the respective acetates **6b–f**.

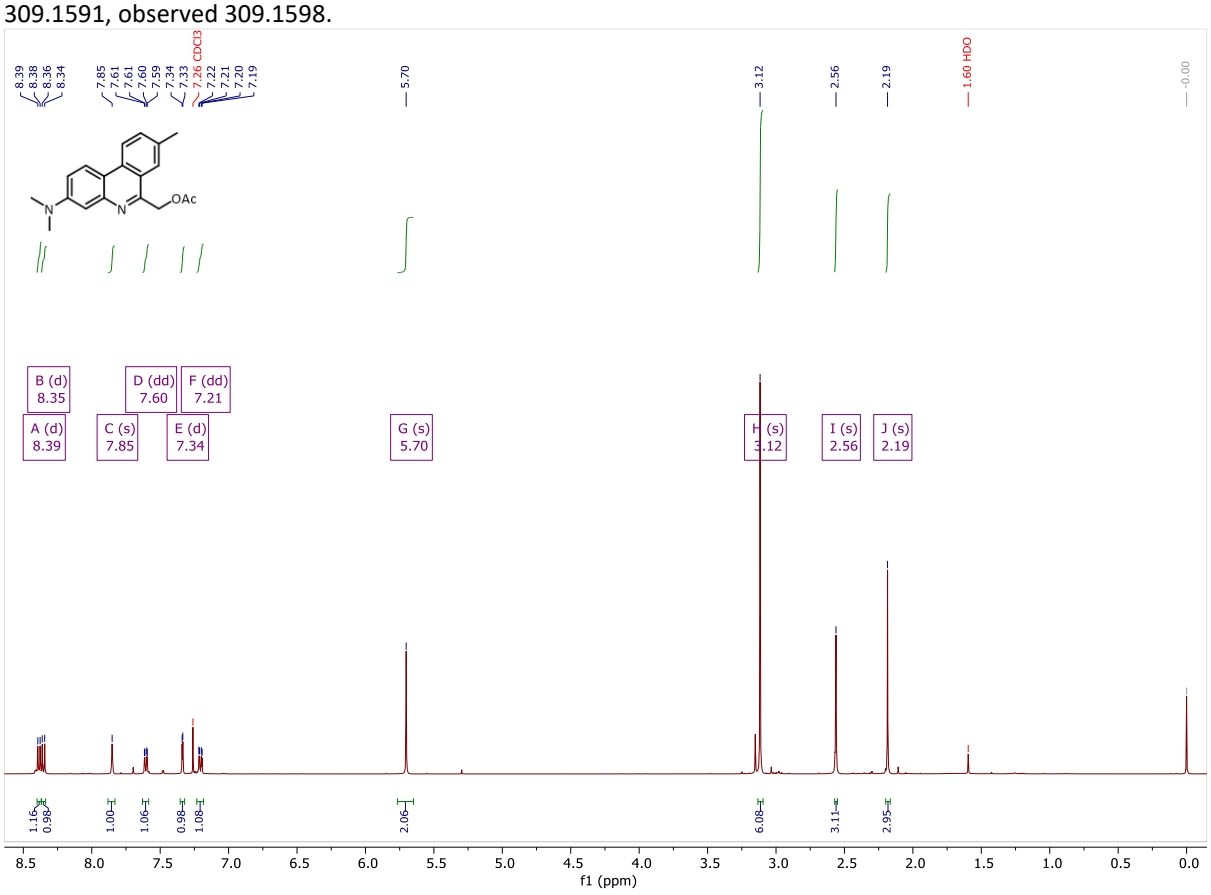
(3-(Dimethylamino)-8-methylphenanthridin-6-yl)methyl acetate (6b)

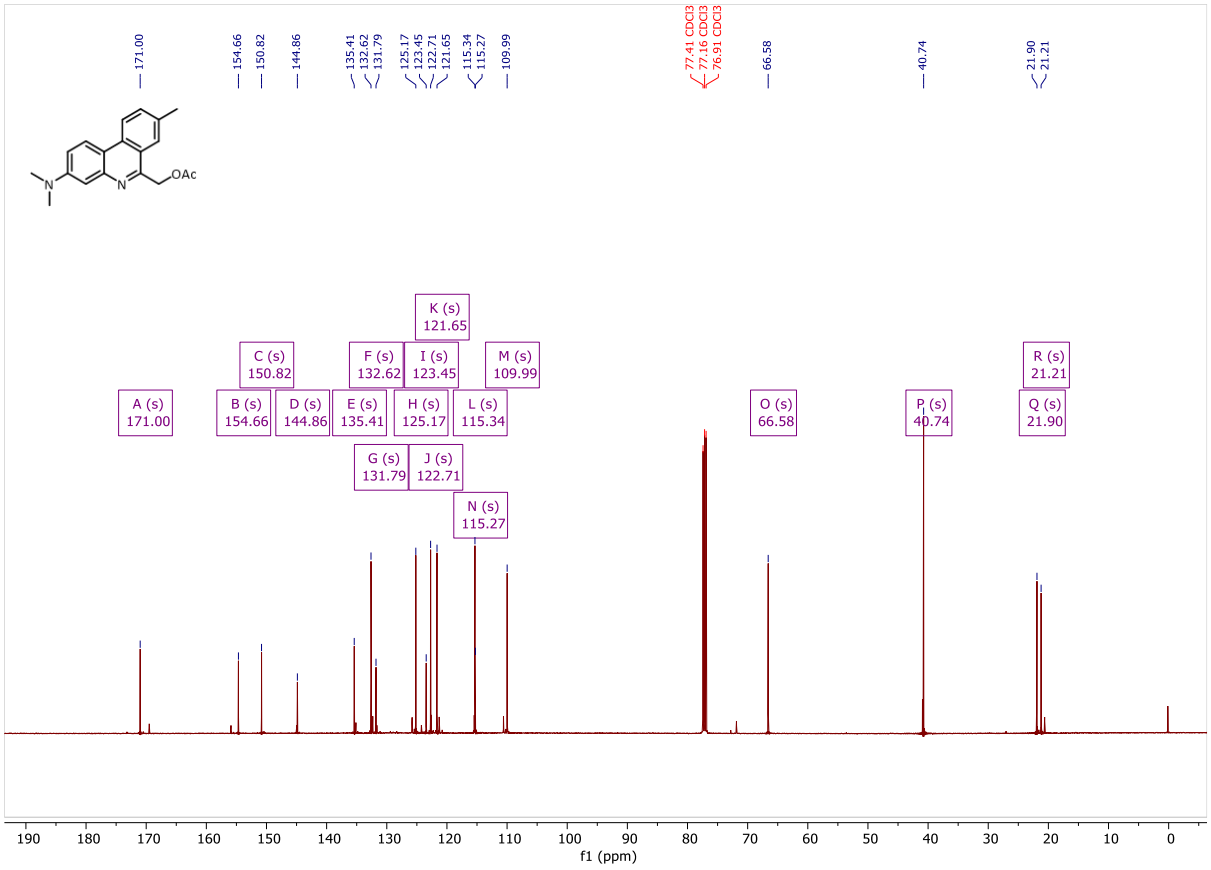


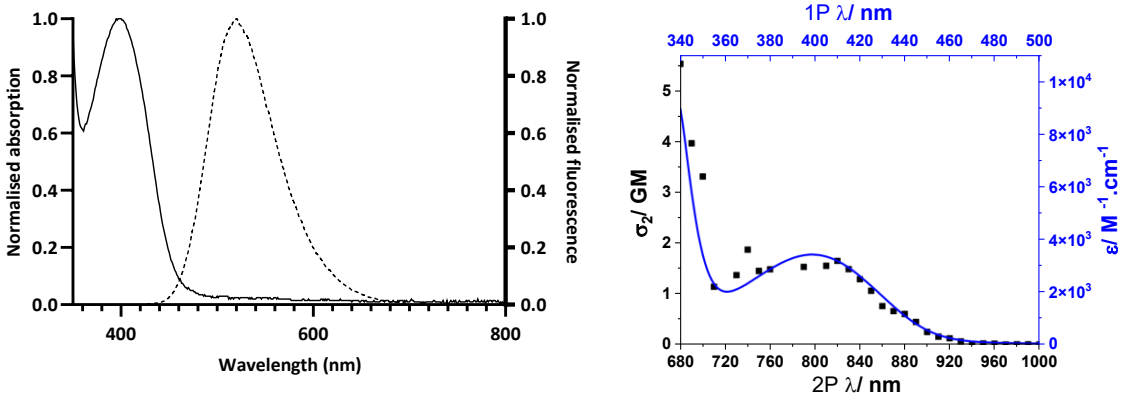
Following general procedure **E**, **6b** (6.5 mg, 0.021 mmol, 58%) was obtained as an orange solid by column chromatography (100% – 50% cyclohexane/EtOAc).

^{1}H NMR (500 MHz, chloroform-*d*) δ 8.39 (d, J = 8.4 Hz, 1H), 8.35 (d, J = 9.0 Hz, 1H), 7.85 (s, 1H), 7.60 (dd, J = 8.5, 1.8 Hz, 1H), 7.34 (d, J = 2.7 Hz, 1H), 7.21 (dd, J = 9.1, 2.7 Hz, 1H), 5.70 (s, 2H), 3.12 (s, 6H), 2.56 (s, 3H), 2.19 (s, 3H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 171.0 (C), 154.7 (C), 150.8 (C), 144.9 (C), 135.4 (C), 132.6 (CH), 131.8 (C), 125.2 (CH), 123.5 (C), 122.7 (CH), 121.7 (CH), 115.3 (CH), 115.3 (C), 110.0 (CH), 66.6 (CH_2), 40.7 ($2CH_3$), 21.9 (CH_3), 21.2 (CH_3).; IR (ν = cm^{-1}) 1739, 1616, 1497, 1364, 1236; HRMS (ESI) calcd for $C_{19}H_{21}N_2O_2$ $[M+H]^+$ 309.1591, observed 309.1598.

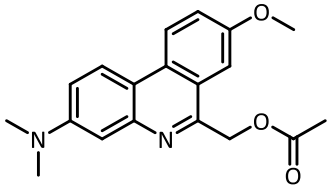






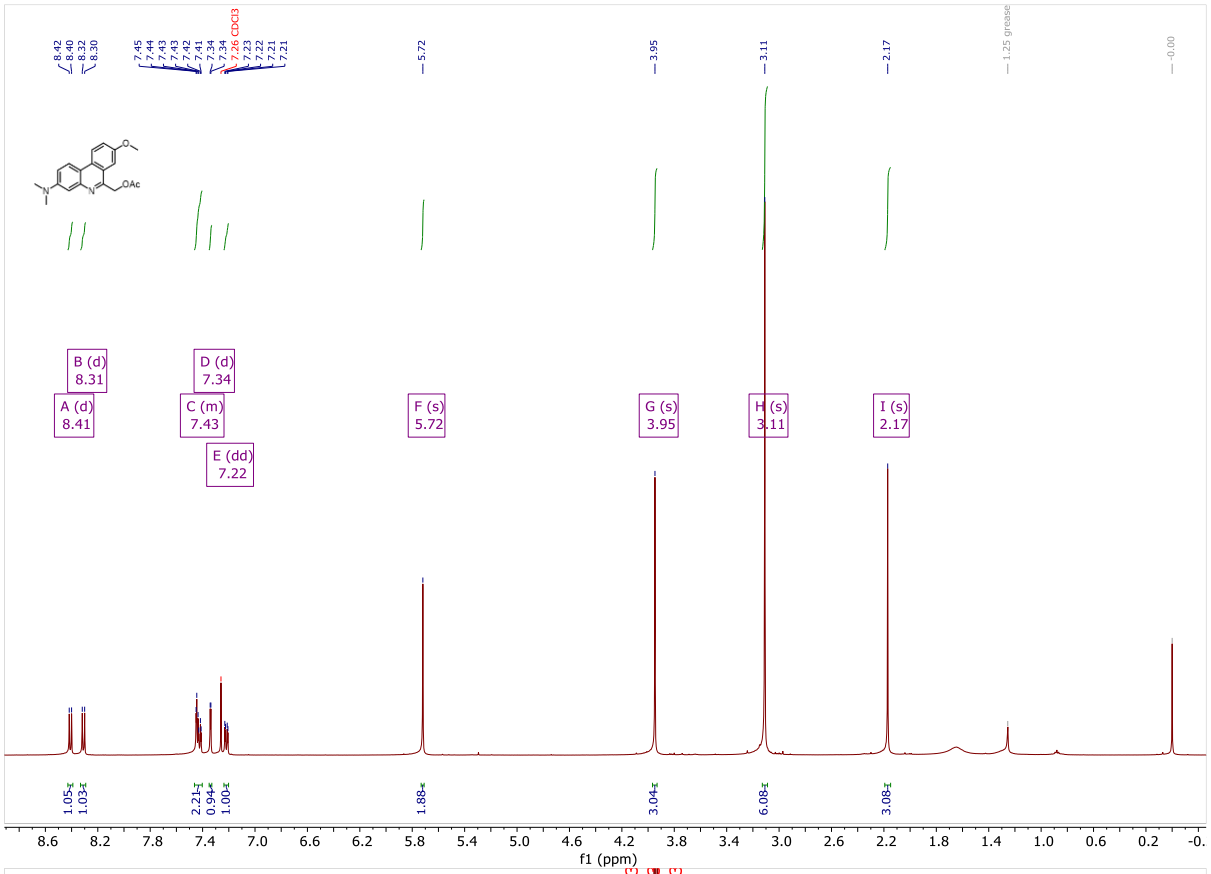
UV–vis spectrum of **6b**.
Conditions: Measured in DMSO at 0.1 mM; λ_{abs} = 395 nm; ε_{395} = 2000 $M^{-1}{\cdot}cm^{-1}$.
Fluorescence spectrum of **6b**.
Conditions: Measured in DMSO; λ_{exc} = 395 nm; λ_{em}^{max} = 520 nm; Φ_F = 0.67.

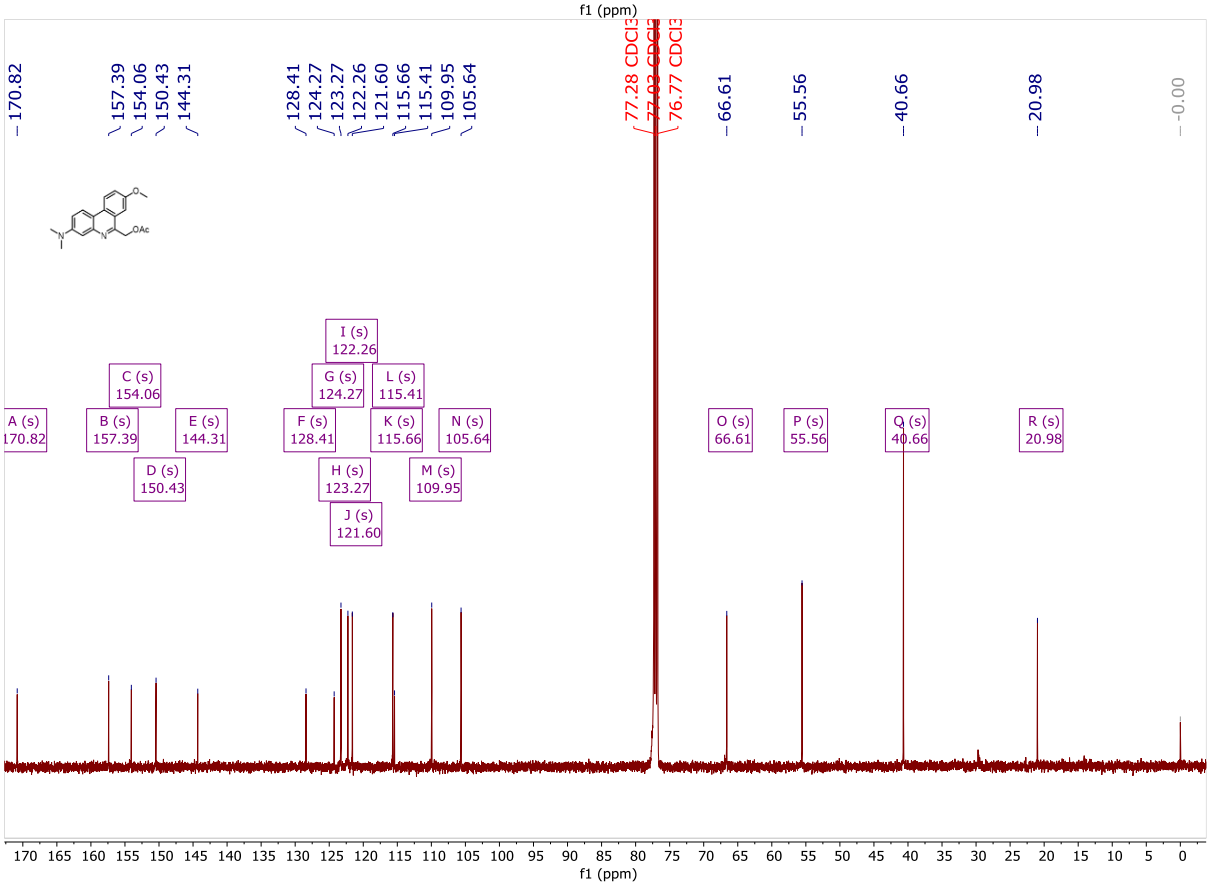
(3-(Dimethylamino)-8-methoxyphenanthridin-6-yl)methyl acetate (6c)

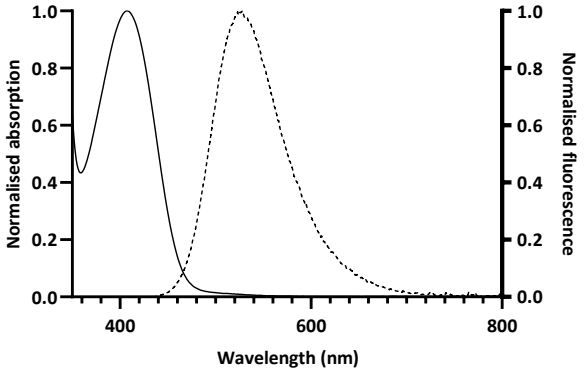


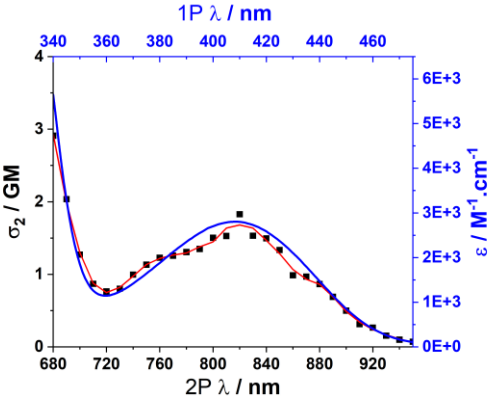
Following general procedure **E**, **6c** (4.5 mg, 0.014 mmol, 38%) was obtained as a dark yellow oil by column chromatography (100% – 50% cyclohexane/EtOAc).
^{1}H NMR (500 MHz, chloroform-*d*) δ 8.39 (d, *J* = 8.9 Hz, 1H), 8.29 (d, *J* = 9.1 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.33 (d, *J* = 2.7 Hz, 1H), 7.21 (dd, *J* = 9.0, 2.8 Hz, 1H), 5.71 (s, 2H), 3.94 (s, 3H), 3.10 (s, 6H), 2.17 (s, 3H).

^{13}C NMR (125 MHz, chloroform-*d*) δ 171.0 (C), 157.4 (C), 154.1 (C), 150.5 (C), 144.4 (C), 128.5 (C), 124.3 (C), 123.4 (CH), 122.4 (CH), 121.7 (CH), 115.7 (CH), 115.5 (C), 110.0 (CH), 105.7 (CH), 66.7 (CH_2), 55.7 (CH_3), 40.8 ($2CH_3$), 21.1 (CH_3); IR (ν = cm^{-1}) 1497, 1619, 1736, 2855, 2927; HRMS (ESI) calcd for $C_{19}H_{21}N_2O_3$ $[M+H]^+$ 325.1547, observed 325.1537.



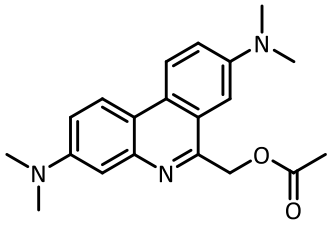




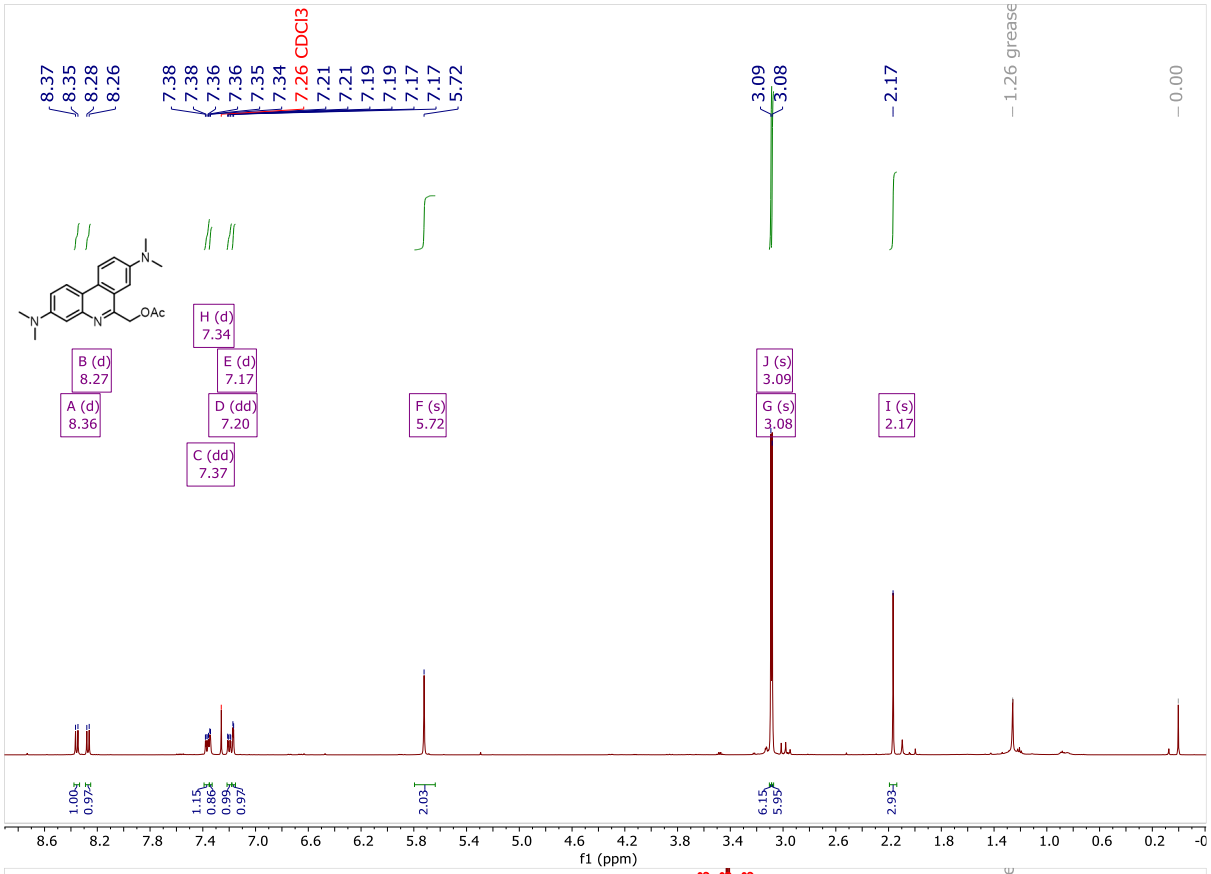


UV–vis spectrum of **6c**.
Conditions: Measured in DMSO at 0.06mM; λ_{abs} = 408 nm; ε_{408} = 2700 $M^{-1}{\cdot}cm^{-1}$.
Fluorescence spectrum of **6c**.
Conditions: Measured in DMSO; λ_{exc} = 408 nm; λ_{em}^{max} = 528 nm; Φ_F = 0.30.

(3,8-bis(Dimethylamino)phenanthridin-6-yl)methyl acetate (6d)



Following general procedure **E**, **6d** (6.7 mg, 0.020 mmol, 54%) was obtained as a red gum by column chromatography (100% – 50% cyclohexane/EtOAc).
^{1}H NMR (500 MHz, chloroform-*d*) δ 8.36 (d, *J* = 9.2 Hz, 1H), 8.27 (d, *J* = 9.1 Hz, 1H), 7.37 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.34 (d, *J* = 2.7 Hz, 1H), 7.20 (dd, *J* = 9.0, 2.7 Hz, 1H), 7.17 (d, *J* = 2.7 Hz, 1H), 5.72 (s, 2H), 3.09 (s, 6H), 3.08 (s, 6H), 2.17 (s, 3H).
^{13}C NMR (125 MHz, chloroform-*d*) δ 171.0 (C), 154.2 (C), 150.1 (CH), 148.6 (CH), 143.6 (C), 125.3 (C), 124.8 (C), 122.8 (CH), 122.0 (CH), 119.3 (C), 116.2 (CH), 115.8 (C), 110.4 (C), 105.4 (CH), 66.8 (CH_2), 40.9 ($2CH_3$), 40.9 ($2CH_3$), 21.1 (CH_3); IR (ν = cm^{-1}) 1499, 1617, 1740, 2853, 2925; HRMS (ESI) calcd for $C_{20}H_{24}N_3O_2$ $[M+H]^+$ 338.1863, observed 338.1853.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3.09
3.08
2.17
1.26 grease
0.00
OAc
H (d) 7.34
B (d) 8.27
E (d) 7.17
A (d) 8.36
D (dd) 7.20
C (dd) 7.37
F (s) 5.72
J (s) 3.09
G (s) 3.08
I (s) 2.17
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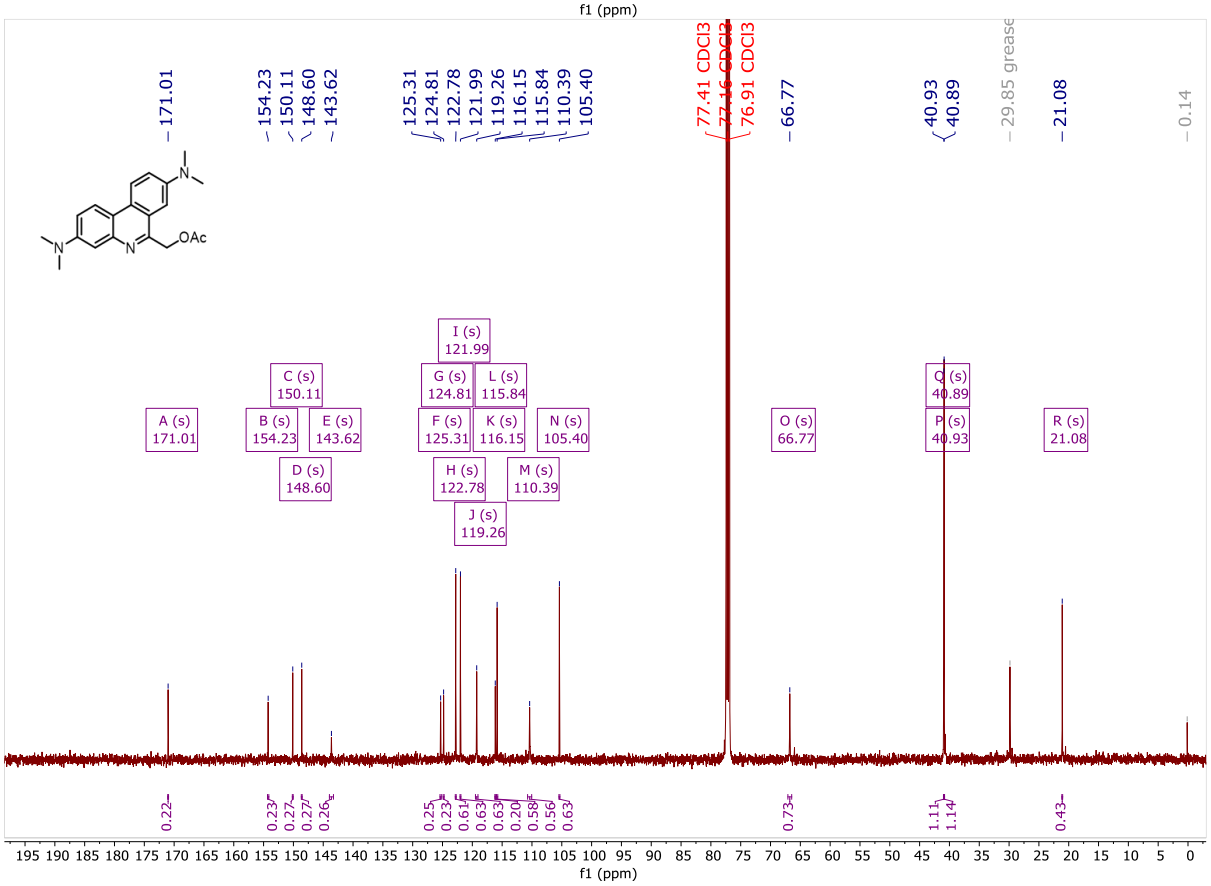
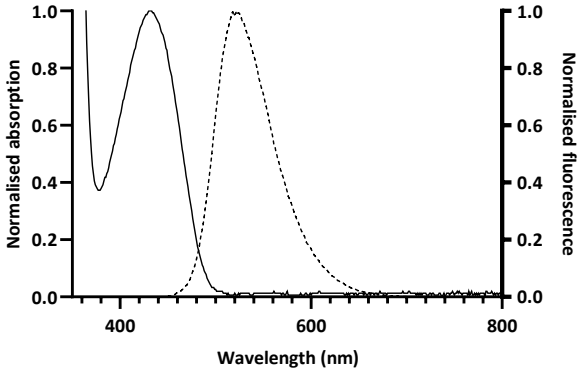
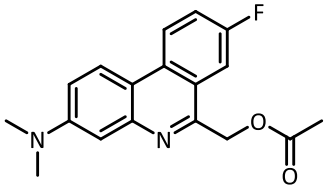
0.97
1.15
0.86
0.99
0.97
2.03
6.15
5.99
2.93
f1 (ppm)


171.01
154.23
150.11
148.60
143.62
125.31
124.81
122.78
121.99
119.26
116.15
115.84
110.39
105.40
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
66.77
40.93
40.89
29.85 grease
21.08
0.14
OAc
I (s) 121.99
C (s) 150.11
G (s) 124.81
L (s) 115.84
Q (s) 40.89
A (s) 171.01
B (s) 154.23
E (s) 143.62
F (s) 125.31
K (s) 116.15
N (s) 105.40
O (s) 66.77
P (s) 40.93
R (s) 21.08
D (s) 148.60
H (s) 122.78
M (s) 110.39
J (s) 119.26
0.22
0.23
0.27
0.27
0.26
0.25
0.23
0.61
0.63
0.63
0.20
0.58
0.56
0.63
0.73
1.11
1.14
0.43
f1 (ppm)

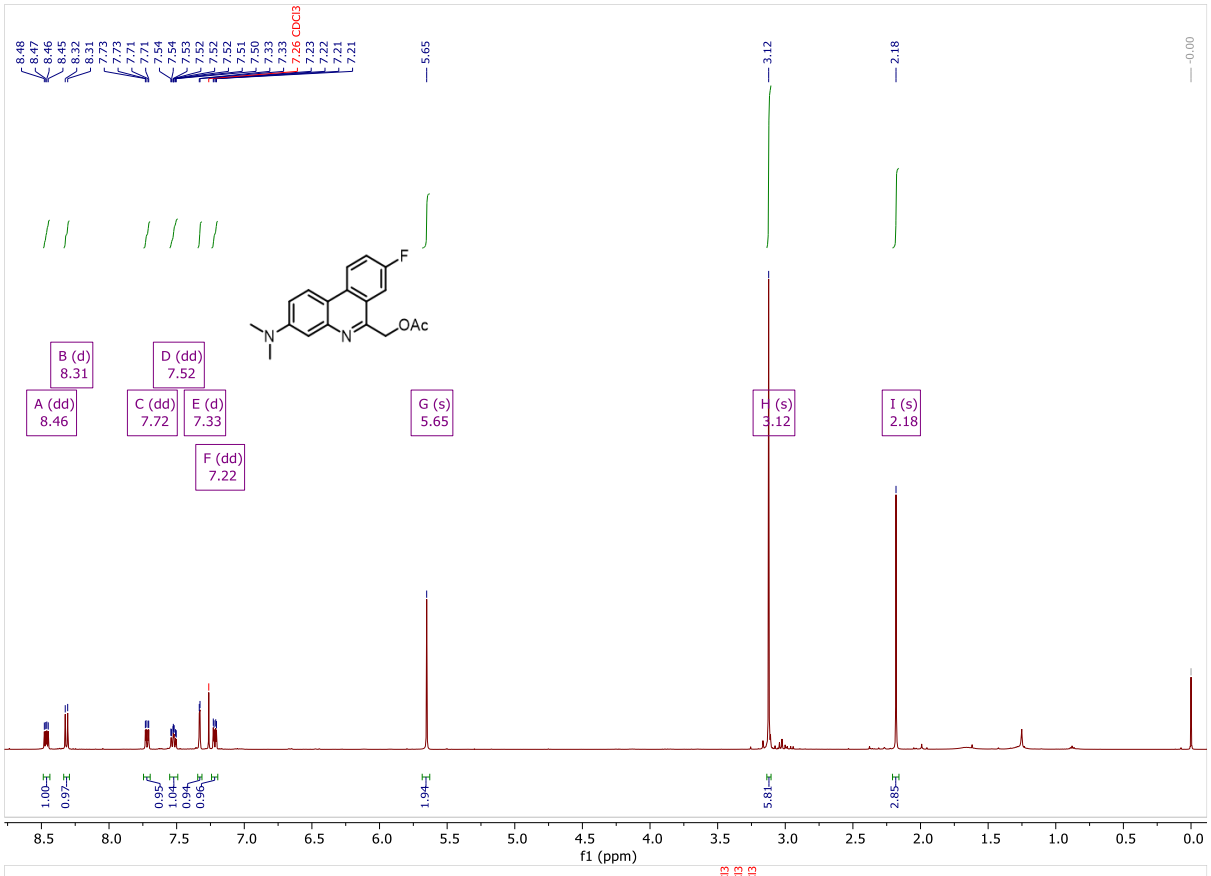


UV–vis spectrum of **6d**.
Conditions: Measured in DMSO at 0.1 mM; λ_{abs} = 430 nm; ε_{407} = 1500 $M^{-1}\cdot cm^{-1}$.
Fluorescence spectrum of **6d**.
Conditions: Measured in DMSO; λ_{exc} = 430 nm; λ_{em}^{max} = 518 nm; Φ_F = 0.44

(3-(Dimethylamino)-8-fluorophenanthridin-6-yl)methyl acetate (6e)



Following general procedure **E**, **6e** (9.4 mg, 0.030 mmol, 80%) was obtained as an orange solid by column chromatography (100% – 50% cyclohexane/EtOAc).
^{1}H NMR (500 MHz, chloroform-*d*) δ 8.47 (dd, *J* = 9.1, 5.3 Hz, 1H), 8.32 (d, *J* = 9.1 Hz, 1H), 7.73 (dd, *J* = 9.8, 2.6 Hz, 1H), 7.52 (ddd, *J* = 9.1, 8.1, 2.6 Hz, 1H), 7.34 (d, *J* = 2.7 Hz, 1H), 7.22 (dd, *J* = 9.0, 2.7 Hz, 1H), 5.66 (s, 2H), 3.12 (s, 6H), 2.17 (s, 3H).
^{13}C NMR (125 MHz, chloroform-*d*) δ 170.7 (C), 160.4 (d, $^{1}J_{C\text{-}F}$ = 246.4 Hz, C), 154.3 (d, $^{4}J_{C\text{-}F}$ = 4.2 Hz, C), 151.1 (CH), 145.0 (C), 130.8 (C), 124.3 (d, $^{3}J_{C\text{-}F}$ = 7.3 Hz, CH), 124.2 (d, $^{3}J_{C\text{-}F}$ = 8.2 Hz, CH), 122.7 (CH), 120.1 (d, $^{2}J_{C\text{-}F}$ = 24.2 Hz, CH), 115.8 (CH), 114.8 (C), 110.4 (d, $^{2}J_{C\text{-}F}$ = 21.7 Hz, CH), 110.1 (C), 66.7 (CH_2), 40.7 ($2CH_3$), 21.1 (CH_3).
^{19}F NMR (76 MHz, chloroform-*d*) δ -112.50; IR (ν = cm^{-1}) 1372, 1499, 1619, 1748, 2851, 2925; HRMS (ESI) calcd for $C_{18}H_{18}FN_2O_2$ $[M+H]^+$ 313.1347, observed 313.1341.


8.48
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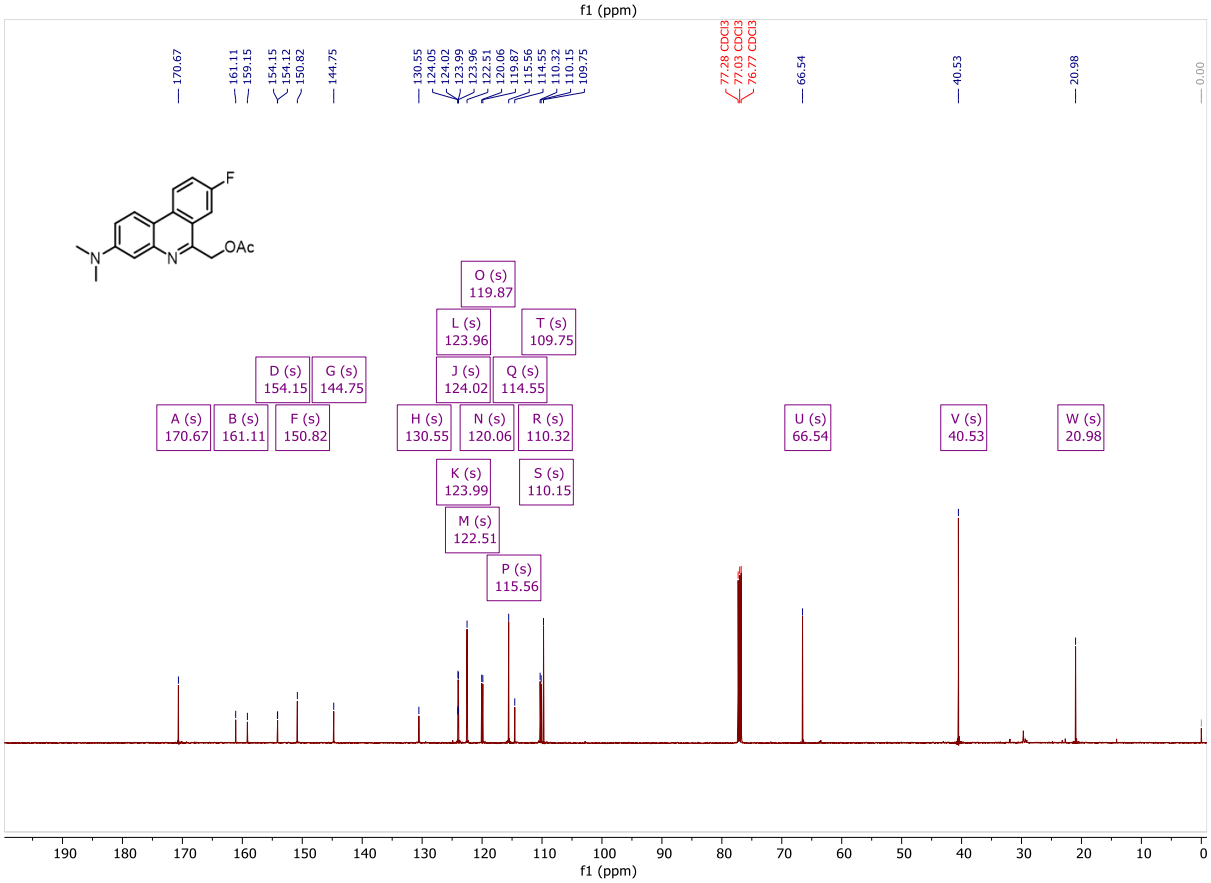
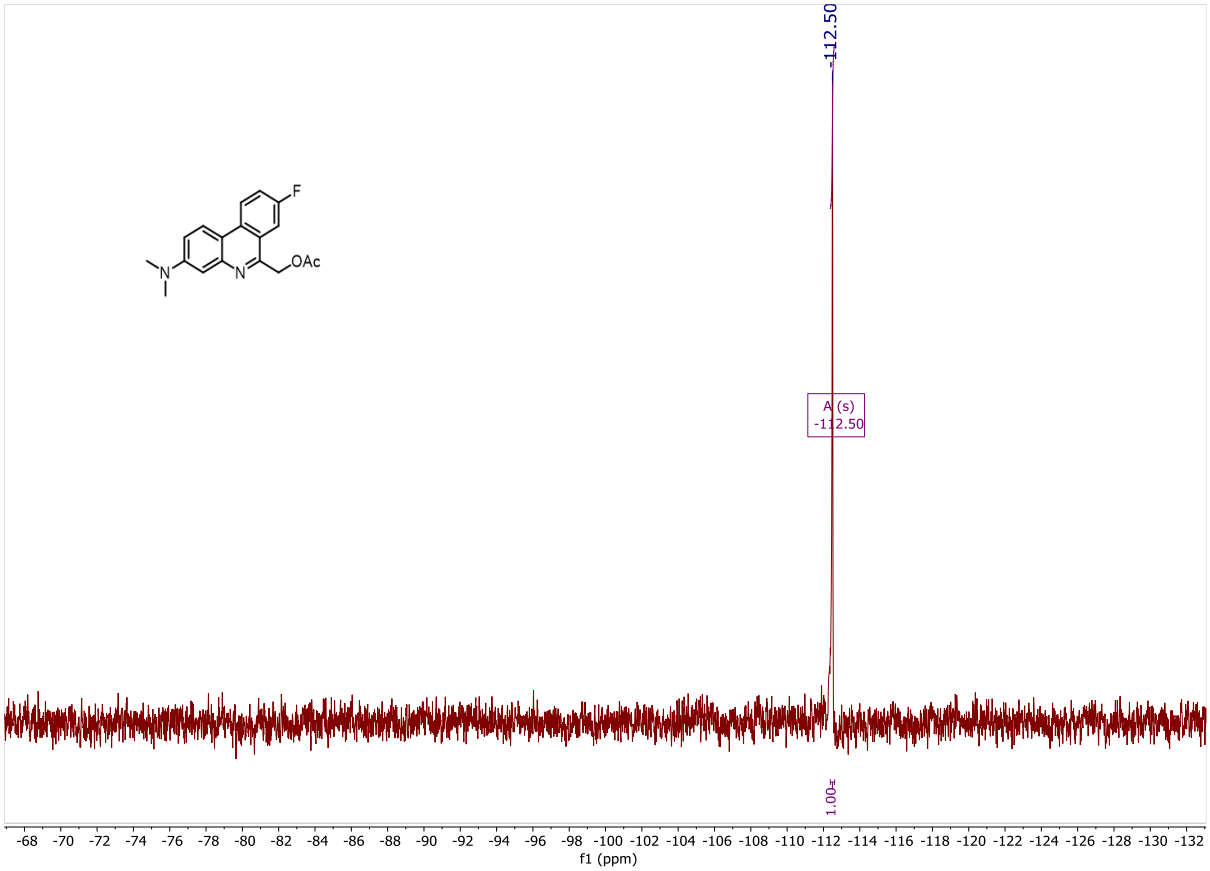
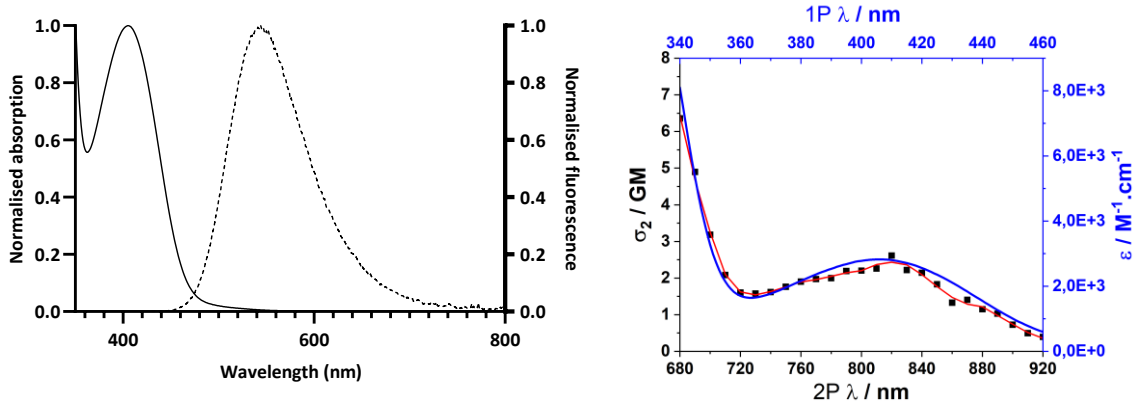
8.46
8.45
8.32
8.31
7.73
7.73
7.71
7.71
7.71
7.54
7.54
7.53
7.52
7.52
7.52
7.51
7.50
7.33
7.33
7.26 CDCl3
7.23
7.22
7.21
7.21
5.65
3.12
2.18
0.00
F
N
OAc
B (d)
8.31
D (dd)
7.52
A (dd)
8.46
C (dd)
7.72
E (d)
7.33
F (dd)
7.22
G (s)
5.65
H (s)
3.12
I (s)
2.18
1.00
0.97
0.95
1.04
0.94
0.96
1.94
5.81
2.85
f1 (ppm)

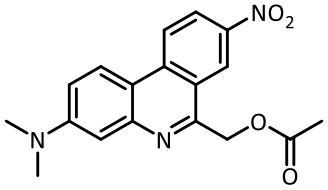

170.67
161.11
159.15
154.15
154.12
150.82
144.75
130.55
124.05
124.02
123.99
123.96
122.51
120.06
119.87
115.56
114.55
110.32
110.15
109.75
77.28 CDCl3
77.03 CDCl3
76.77 CDCl3
66.54
40.53
20.98
0.00
F
N
OAc
O (s)
119.87
L (s)
123.96
T (s)
109.75
D (s)
154.15
G (s)
144.75
J (s)
124.02
Q (s)
114.55
A (s)
170.67
B (s)
161.11
F (s)
150.82
H (s)
130.55
N (s)
120.06
R (s)
110.32
U (s)
66.54
V (s)
40.53
W (s)
20.98
K (s)
123.99
S (s)
110.15
M (s)
122.51
P (s)
115.56
f1 (ppm)





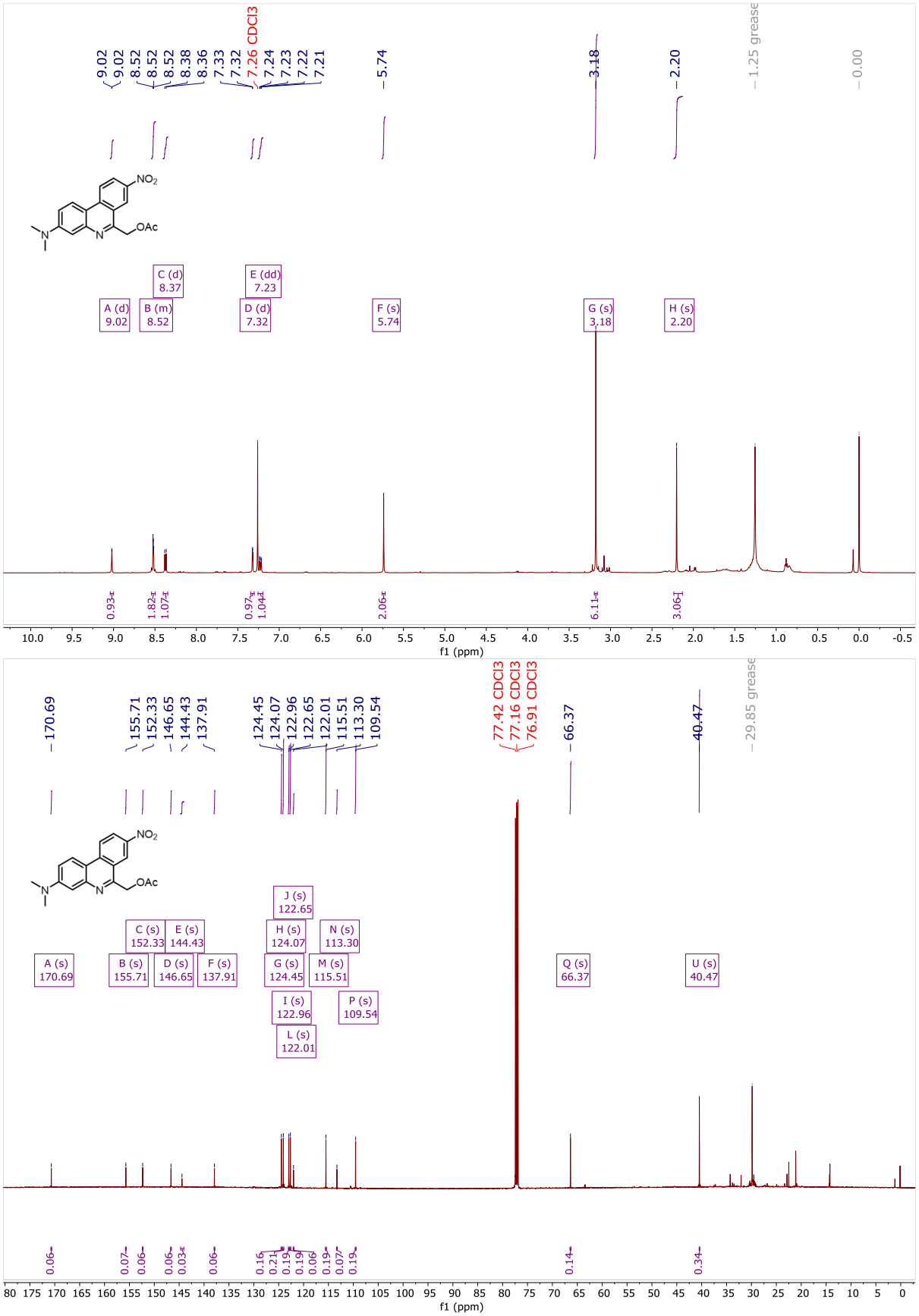
UV–vis spectrum of **6e**.
Conditions: Measured in DMSO at 0.06mM; λ_{abs} = 406 nm; ε_{406} = 2500 $M^{-1}{\cdot}cm^{-1}$.
Fluorescence spectrum of **6e**.
Conditions: Measured in DMSO; λ_{exc} = 406 nm; λ_{em}^{max} = 544 nm; Φ_F = 0.24.

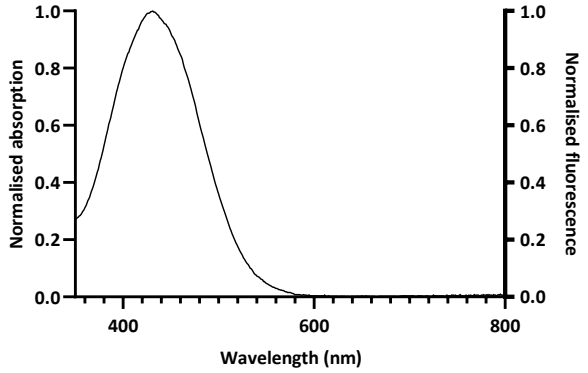
(3-(Dimethylamino)-8-nitrophenanthridin-6-yl)methyl acetate (6f)



Following general procedure **E**, **6f** (5.1 mg, 0.015 mmol, 40%) was obtained as an orange solid by column chromatography (100% – 50% cyclohexane/EtOAc).
^{1}H NMR (500 MHz, chloroform-*d*) δ 9.02 (d, *J* = 2.0 Hz, 1H), 8.54 – 8.50 (m, 2H), 8.37 (d, *J* = 9.1 Hz, 1H), 7.32 (d, *J* = 2.7 Hz, 1H), 7.23 (dd, *J* = 9.1, 2.8 Hz, 1H), 5.74 (s, 2H), 3.18 (s, 6H), 2.20 (s, 3H).

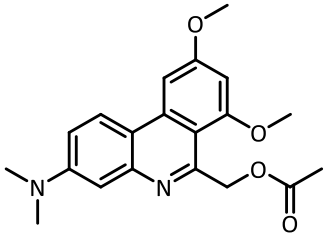
^{13}C NMR (125 MHz, chloroform-*d*) δ 170.7 (C), 155.7 (C), 152.3 (C), 146.7 (C), 144.4 (C), 137.9 (C), 124.5 (CH), 124.1 (CH), 123.0 (CH), 122.7 (CH), 122.0 (C), 115.5 (CH), 113.3 (C), 109.5 (CH), 66.4 (CH_2), 40.5 ($2CH_3$), 29.9 (CH_3); IR (ν = cm^{-1}) 1653, 1684, 1748, 2855, 2925; HRMS (ESI) calcd for $C_{18}H_{18}N_3O_4$ $[M+H]^+$ 340.1292, observed 340.1289.



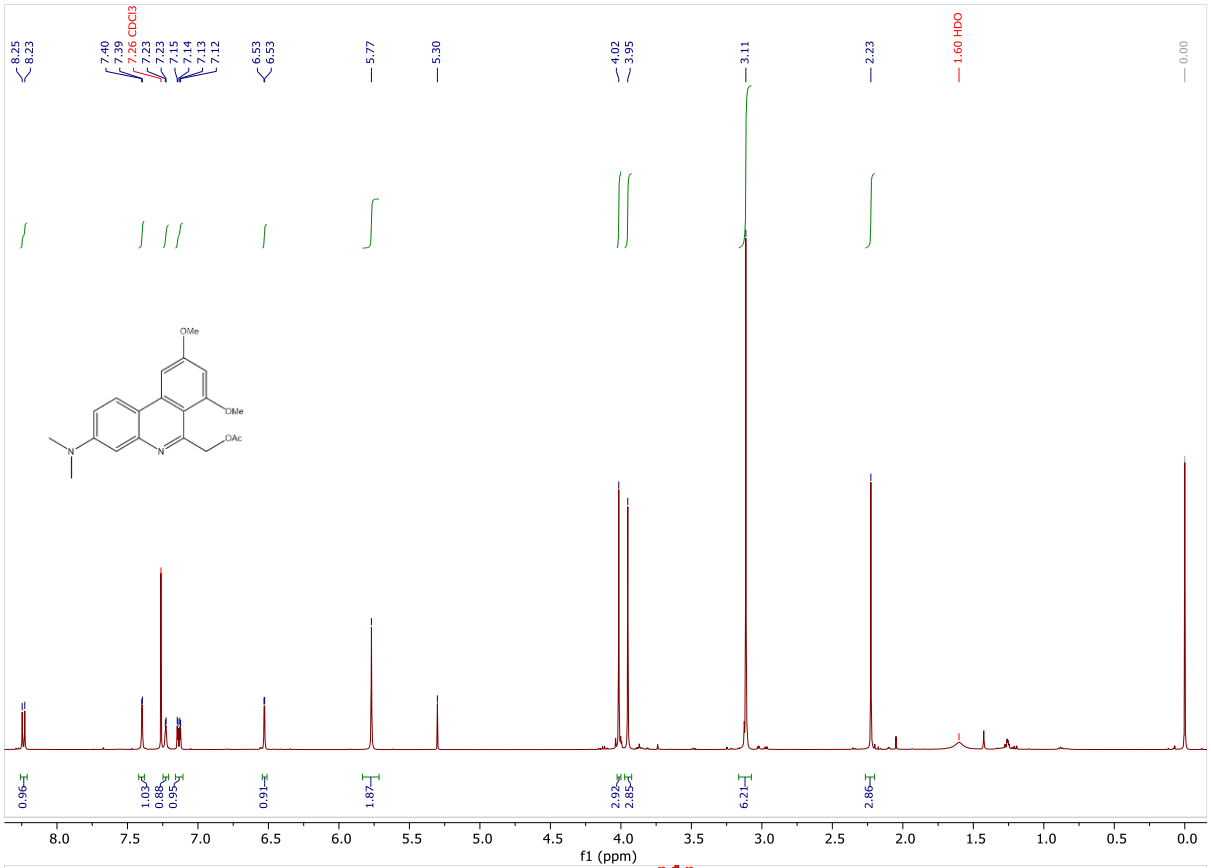


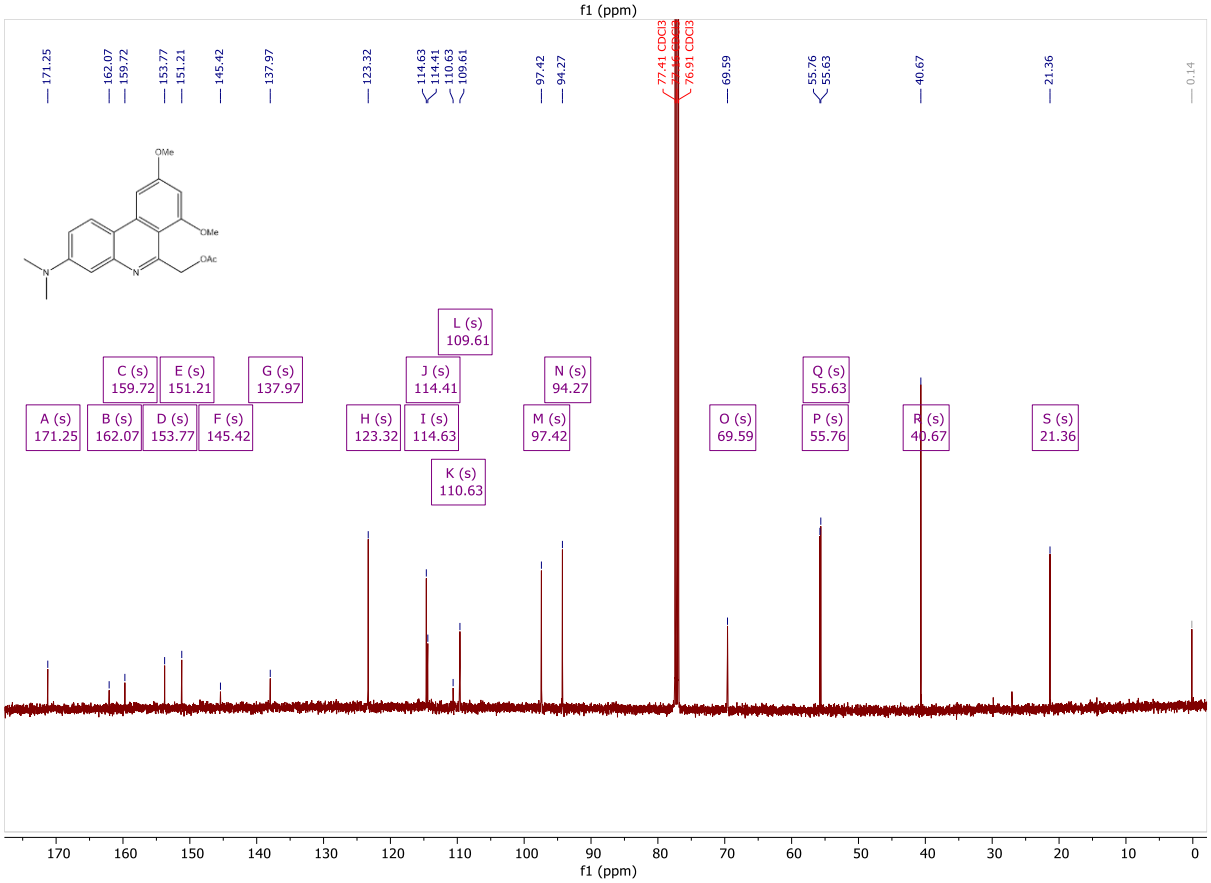
UV–vis spectrum of **6f**.
Conditions: Measured in DMSO at 0.1 mM; λ_{abs} = 431 nm; ε_{425} = 4300 $M^{-1}{\cdot}cm^{-1}$.

(3-(Dimethylamino)-7,9-dimethoxyphenanthridin-6-yl)methyl acetate (6g)



In a round bottom flask under inert atmosphere, **5g** (11.5 mg, 0.037 mmol, 1 eq.) was dissolved in acetic anhydride (1 mL, 16 mM). After cooling the reaction mixture to 0 °C, $NaBH_4$ (2.8 mg, 0.074 mmol, 2 eq.) was added and it was stirred for 16 h. The mixture was concentrated *in vacuo* and purified by flash column chromatography (100% – 0% cyclohexane/EtOAc), yielding **6g** (3.9 mg, 0.011 mmol, 29%) as an orange solid.
^{1}H NMR (500 MHz, chloroform-*d*) δ 8.24 (d, J = 9.2 Hz, 1H), 7.40 (d, J = 2.3 Hz, 1H), 7.23 (d, J = 2.7 Hz, 1H), 7.14 (dd, J = 9.1, 2.7 Hz, 1H), 6.53 (d, J = 2.2 Hz, 1H), 5.77 (s, 2H), 4.02 (s, 3H), 3.95 (s, 3H), 3.11 (s, 6H), 2.23 (s, 3H).
^{13}C NMR (125 MHz, chloroform-*d*) δ 171.3 (C), 162.1 (C), 159.7 (C), 153.8 (C), 151.2 (C), 145.4 (C), 138.0 (C), 123.3 (CH), 114.6 (CH), 114.4 (C), 110.6 (C), 109.6 (CH), 97.4 (CH), 94.3 (CH), 69.6 (CH_2), 55.8 (CH_3), 55.6 (CH_3), 40.7 ($2CH_3$), 21.4 (CH_3); IR (ν = cm^{-1}) 1734, 1614, 1584, 1456, 1373, 1267; HRMS (ESI) calcd for $C_{20}H_{23}N_2O_4$ $[M+H]^+$ 355.1653, observed 355.1641.


8.25
8.23
7.40
7.39
7.26 CDCl3
7.23
7.23
7.15
7.14
7.13
7.12
6.53
6.53
5.77
5.30
4.02
3.95
3.11
2.23
1.60 HDO
0.00
OMe
OMe
OAc
N
N
0.96
1.03
0.88
0.95
0.91
1.87
2.92
2.85
6.21
2.86
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)


171.25
162.07
159.72
153.77
151.21
145.42
137.97
123.32
114.63
114.41
110.63
109.61
97.42
94.27
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
69.59
55.76
55.63
40.67
21.36
0.14
OMe
OMe
OAc
N
N
L (s)
109.61
C (s)
159.72
E (s)
151.21
G (s)
137.97
J (s)
114.41
N (s)
94.27
Q (s)
55.63
A (s)
171.25
B (s)
162.07
D (s)
153.77
F (s)
145.42
H (s)
123.32
I (s)
114.63
M (s)
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O (s)
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R (s)
40.67
S (s)
21.36
K (s)
110.63
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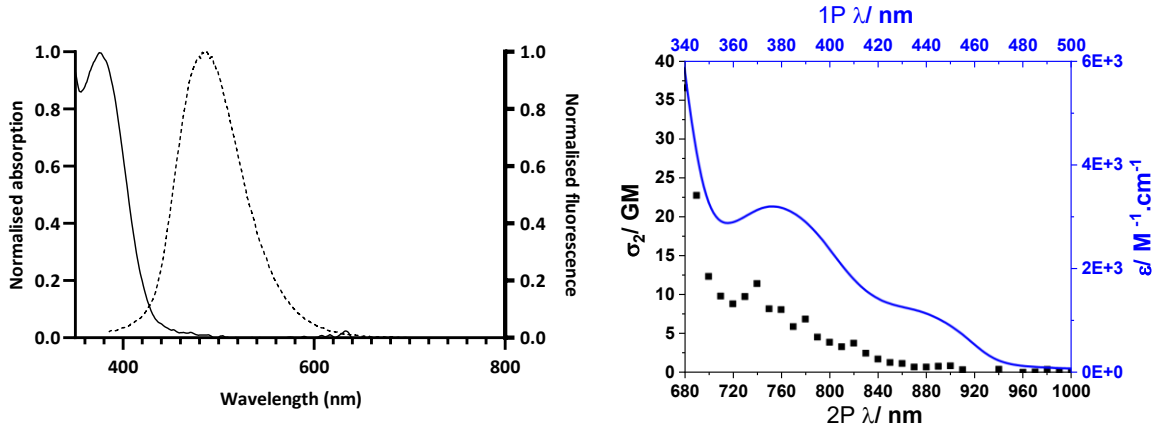
f1 (ppm)



UV–vis spectrum of **6g**.
Conditions: Measured in DMSO at 0.1 mM; λ_{abs} = 376 nm; ε_{376} = 1140 $M^{-1}{\cdot}cm^{-1}$.
Fluorescence spectrum of **6g**.
Conditions: Measured in DMSO; λ_{exc} = 376 nm; λ_{em}^{max} = 487 nm; Φ_F = 0.51.

Table S3: Photochemical data of phenanthridines in DMSO.

Compound	λ_{abs} (nm)	ε_{405} (M^{-1} cm^{-1})	Φ_u[a]	$\varepsilon_u{=}\varepsilon_{405}$ Φ_u	δ_u (GM)[b]
6a (H)	395	1800	2.7%	48.6	4.9×10^{-2}
6b (Me)	400	1900	6.0%	114	9×10^{-2}
6c (OMe)	407	2700	2.6%	70.2	4.7×10^{-2}
6e (F)	410	2500	0.9%	22.5	2.3×10^{-2}
6f (NO_2)	431	2800	-	-	-

[a]$t_{90\%}$ was determined in MeCN/Tris (1/1) 20 mM, pH 7.4. [b]Derived from the uncaging quantum yield values and 2PA cross-sections at λ_{A2P}^{max} determined by 2PEF experiments (1 GM = 10^{-50} cm^4 s^{-1}).

Dark stability

The stability of our compounds towards dark hydrolysis was assessed by monitoring the decline in the area under the curve (AUC) of each compound by HPLC in the solvent of photolysis (MeCN/Tris, 1/1, v/v) over one week at room temperature (21 °C). Figure S3 shows, for each compound, the decrease of the recorded AUC normalised by its AUC at the beginning of the experiment. A significant amount of starting material degraded for cages bearing an EWG (F (**6e**) and NO_2 (**6f**)) however the others remained relatively stable after one week, evidencing that the rate of solvolysis was not competitive with the rate of the uncaging reactions upon photolysis duration.

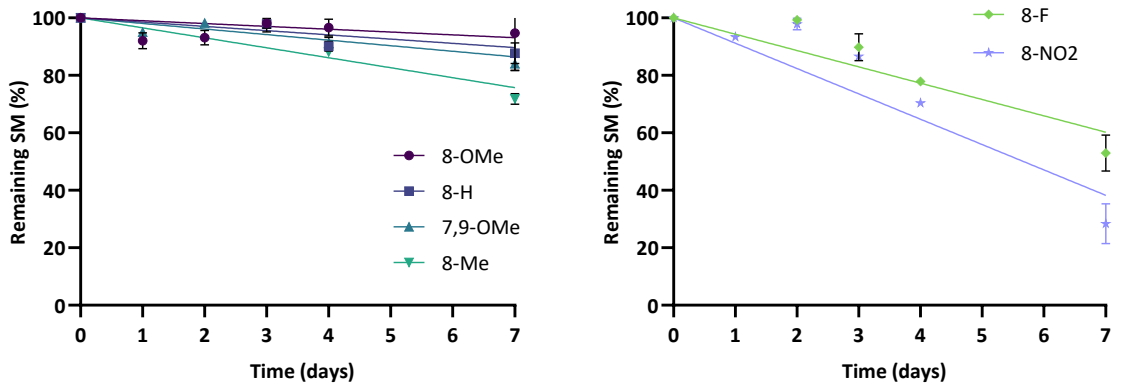


Figure S3: Evolution of the AUC monitored by HPLC of compounds **6a–c**, **6e–g** over time starting from the normalised absorption spectrum at t = 0.

Release kinetics

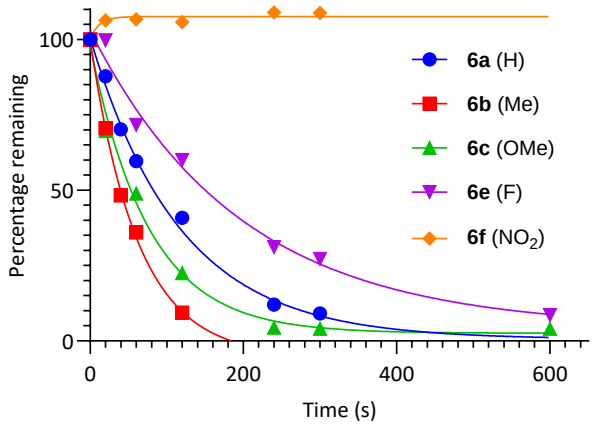


Figure S4: Kinetic follow-up of the photorelease of **6a–f** mediated by 1PE (LED, 405 nm). The remaining percentage was determined by HPLC analysis and is the average of three runs. Lines are least-squares fits of the data to a simple exponential decay.

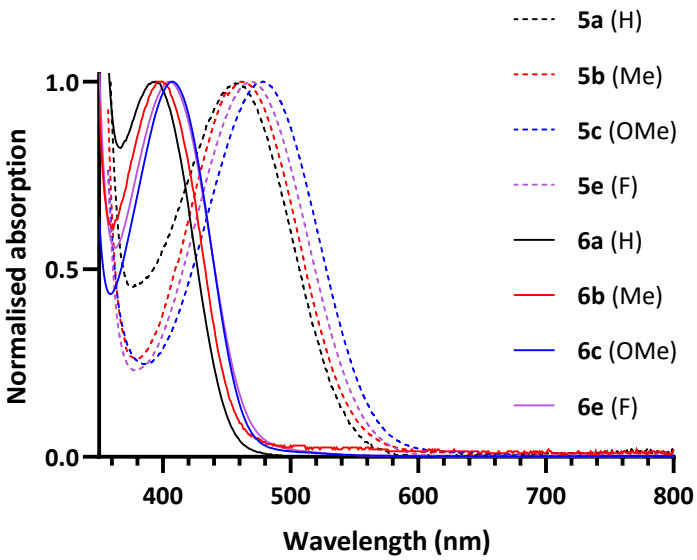
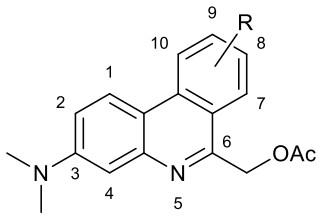


Figure S5: Comparison of phenanthridines **6** (-OAc) UV-Vis spectra and their corresponding aldehydes **5**.

Computational method

The geometry of the ground (S_0) and first singlet excited (S_1) states were optimised in the gas phase in the framework of the Density Functional Theory (DFT) using the M06-2X exchange–correlation functional[12] and the 6-311G++(d,p) basis set. All structures were characterized as real minima of the potential energy surface on the basis on their positive vibrational force constants. Ground state optimized geometries were used to compute the vertical transition energies and excited state properties by employing the Time-Dependent Density Functional Theory (TD-DFT) at the M06-2X/6-311G++(d,p) level. Solvent effects were taken into account in these calculations by using the Integral Equation Formalism of the Polarizable Continuum Model (IEF-PCM).[13] The photo-induced charge transfer was analyzed on the basis of vertical electronic transitions, by considering the difference $\Delta\mu^{vert}_{01}$ in the electric dipoles of the S_0 and S_1 states. Using the approach reported in these references,[14, 15] $\Delta\mu^{vert}_{01}$ was further decomposed as $\Delta\mu^{vert}_{01} = q^{CT} \times D_{CT}$, where q^{CT} is the photo-induced charge transfer, *i.e.* the global amount of charge transferred upon light excitation, and D_{CT} is the distance over which this charge is transferred. All calculations were performed using the Gaussian 16 package.[16]

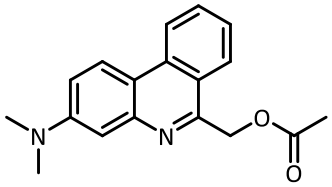
Table S4: CT excitation descriptors obtained for various -OMe phenanthridine derivatives.



Compound	$\lambda_{01}{}^{a}$	$\Delta\mu^{vert}{}_{01}$	q^{CT}	D_{CT}
7-OMe	396	6.50	0.62	2.20
8-OMe (**6c**)	407	6.53	0.61	2.23
9-OMe	388	6.53	0.61	2.38
10-OMe	402	7.06	0.62	2.65
7,9-OMe (**6g**)	381	8.12	0.64	2.05
7,8,9-OMe	389	6.01	0.61	2.06

[a]*Fudge factor* corrected value.

Coordinates of geometry-optimised compounds



C -3.52916900 0.96768500 0.25560600
C -3.53977500 -0.43351200 -0.00384100
C -2.30967800 -1.04847200 -0.24668800
C -1.11548400 -0.31059600 -0.26117800
C -1.11504700 1.07953400 -0.02034300
C -2.35964300 1.68739900 0.24199100
N 0.04999500 -1.01905200 -0.51054500
C 1.18043400 -0.38829100 -0.53365400
C 1.31654400 1.03714100 -0.31640000
C 0.14654600 1.78395900 -0.05302100
C 2.56918000 1.68582400 -0.37056000
C 2.66119700 3.04352100 -0.16640100
C 1.49908600 3.78921500 0.10057000
C 0.26787500 3.17532500 0.15587200
H -4.45249900 1.48735800 0.46979100
H -2.22898700 -2.11057500 -0.42996200
H -2.41365600 2.74958400 0.44521300
H 3.46611800 1.11230000 -0.56726800
H 3.62404600 3.53728100 -0.21001900
H 1.57262900 4.85816500 0.26260200
H -0.61078700 3.77365800 0.35858300
N -4.72099400 -1.13781000 -0.01919700
C -4.66150000 -2.58833100 -0.07307600
C -5.92270100 -0.52417800 0.52511000
H -4.13150400 -3.01233800 0.78960600
H -5.67453700 -2.98345500 -0.08983600
H -4.15761300 -2.91945400 -0.98365400
H -5.80203700 -0.23842100 1.57731100
H -6.20229900 0.36295800 -0.04639600
H -6.74194600 -1.23552300 0.45121100
O 3.21923400 -1.22023900 0.36036200
C 4.37085500 -1.90625400 0.28175300
O 4.71041500 -2.49364600 -0.71464100
C 5.14038100 -1.83288700 1.56654700
H 5.35238800 -0.78938900 1.80303200
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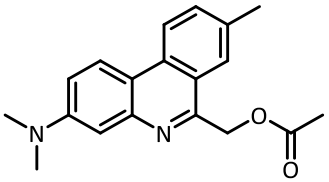

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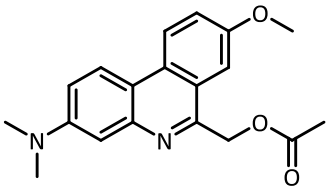

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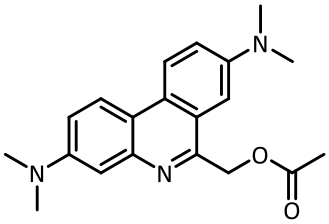

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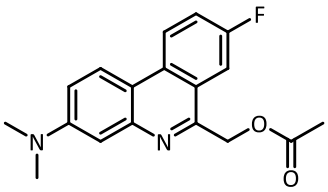

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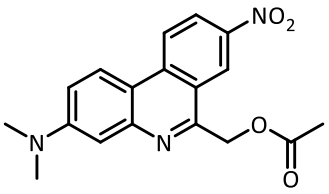

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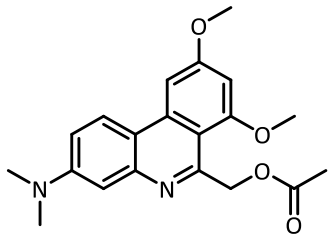

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Author Contributions

Célest Attiach: Investigation; Methodology; Writing – review and editing. Amit Kumar: Investigation (supporting). Jonathan Daniel: Investigation; Validation. Mireille Blanchard-Desce: Supervision; Writing – review and editing. Peter Dalko: Conceptualization; Funding Acquisition. Antoine Maruani: Conceptualization; Supervision; Funding Acquisition; Writing – original draft. All authors have read and agreed to the published version of the manuscript

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