

Supporting Information

Harnessing selective PET and EnT catalysis by Chlorophyll to synthesize N-alkylated quinoline-2(1H)-ones, isoquinoline-1(2H)-ones and 1,2,4-trioxanes

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1.1 General Information

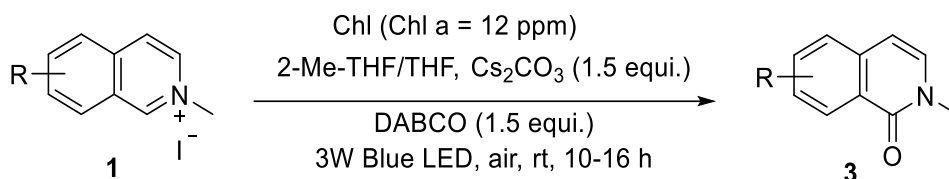
Commercial reagents and solvents were purchased from Merck, Thermo fisher, TCI, Spectrochem, Avra chemicals, and they were directly used without any further purification. Organic solutions were concentrated under reduced pressure using Buchi rotary evaporator and chiller. Flash column chromatography was performed using silica gel (230-400 mesh). Thin layer chromatography (TLC) was performed on Merck (Darmstadt, Germany) TLC Aluminium plates precoated with silica gel 60 F₂₅₄ of size (20 x 20 cm). ¹H and ¹³C NMR were recorded on Bruker 300 MHz (75 MHz) and 400 MHz (100 MHz) instruments, ¹H NMR chemical shifts are reported in parts per million (ppm) relative to residual chloroform (7.26 ppm). ¹³C NMR chemical shifts are reported in ppm relative to chloroform (77.16 ppm) (chemical shifts were internally referenced to TMS). Coupling constants are reported in Hz. Data for ¹H NMR is written following the pattern: chemical shifts (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, dd = doublet of doublet, dt = doublet of triplets, br = broad signal), coupling constants (*J* Hz). Data for ¹³C NMR are reported in terms of chemical shifts only. Melting points were recorded on DBK- Programmable Melting point Apparatus. ESMS were recorded on LC/triple quadrupole mass spectrometer by electrospray ionisation. High resolution mass spectra (HRMS) were acquired on LC/QTOF (quadrupole time of flight) mass spectrometer with electrospray ionisation source.

2.1. Method for estimation of Chlorophyll a

The natural pigment chlorophyll we used was purchased from Tokyo Chemical Industry (TCI, Product No. C0780, EC No. 215-800-7, Lot. CZPVJ-OL). This is a mixture of chlorophyll, lactose and dry gum Arabic (according to the product description). The mass percentage of chlorophyll a content in this reagent was determined, and found to be 0.26% (mass percentage) by measuring the absorbance of chlorophyll at 663 nm and 645 nm in 90% acetone solution following the Wellburn estimation method.

N:B - It was observed that different Lot. of the commercially available chlorophyll contained different concentration of chlorophyll a,¹ so we had estimated the chlorophyll a concentration of a particular bottle before installing reactions with it.

2.2. General procedures for synthesis of compounds 3, 4



N-Alkyl salts of isoquinoline (**1**) and quinoline (**2**) (0.2 mmol) chlorophyll (Chl a = 12 ppm) and Cs₂CO₃ (0.3 mmol), DABCO (0.3 mmol) were added to a glass vial (30 mL) with 2-methyl THF/THF (3 mL), and the reaction mixture was stirred under the irradiation of 3W blue LED (approximately 2 cm away from the light source) under air atmosphere. After completion, the solvent was removed *in vacuo*, then reaction mixture was diluted with brine solution, then extracted with (3 x 50 mL) EtOAc. Thereafter, the combined organic layer was washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography to give desired products **3**, **4** respectively using hexane/ EtOAc as the eluent.

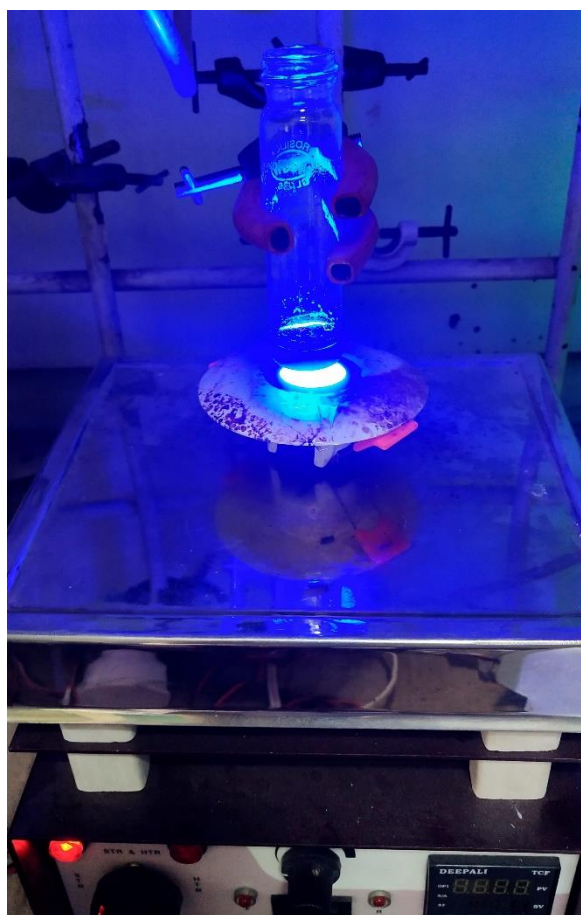


Figure FS1. Experimental set-up employed during photocatalytic reactions. Hyglow 3W blue LED (HY 124 - 3watt gemini E17 Blue) was used for the irradiation purpose.

Following parameters were evaluated during optimization of visible-light mediated photoredox aerobic oxidation of 2-methylisoquinolinium iodide salts (**1**) 0.2 mmol scale. Reactions were analysed via ^1H NMR using dibromomethane (CH_2Br_2) as the internal standard.

Table TS1. Optimization of Conditions for Visible-Light Photoredox Aerobic Oxidation of 2-Methyloquinolinium Iodide (1a).^a

Entry	Solvent	Base	Light Source	Yield (%) ^b
1	H ₂ O-SDS	Cs ₂ CO ₃	3W white LED	12
2 ^c	H ₂ O-SDS	Cs ₂ CO ₃	3W white LED	19
3	H ₂ O-SDS	-	3W white LED	NR
4	H ₂ O-SDS	Cs ₂ CO ₃	3W blue LED	13
5	THF	Cs ₂ CO ₃	3W white LED	24
6	THF	Cs ₂ CO ₃	3W blue LED	87(71) ^d
7	DMSO	Cs ₂ CO ₃	3W blue LED	74
8	MTBE	Cs ₂ CO ₃	3W blue LED	59
9	2-MeTHF	Cs ₂ CO ₃	3W blue LED	79
10	THF	K ₃ PO ₄	3W blue LED	33
11	THF	K ₂ CO ₃	3W blue LED	10
12	THF	NaHCO ₃	3W blue LED	27
13	THF	-	3W blue LED	Trace
14 ^e	THF	Cs ₂ CO ₃	3W blue LED	NR
15	THF	Cs ₂ CO ₃	3W red LED	37
16 ^f	THF	Cs ₂ CO ₃	-	NR
17 ^g	THF	Cs ₂ CO ₃	3W blue LED	Trace

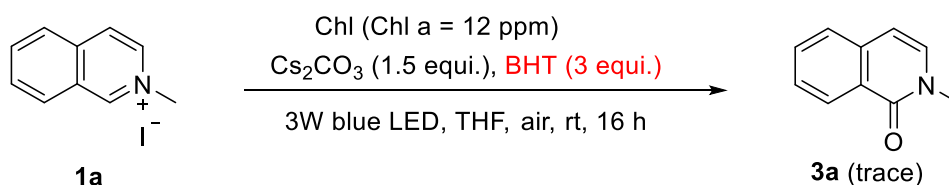
^aReaction conditions: air atmosphere and irradiation with visible light, 2-methyloquinolinium iodide (**1a**) (0.2 mmol), photocatalyst (PC) (12 ppm), base (0.3 mmol), solvent (3 mL), temperature (rt, ~25 °C), time (10 h) in a 30 mL glass vial. ^b Yields were determined by ¹H NMR using dibromomethane as the internal standard. ^c DABCO (0.3 mmol) was added to the reaction medium. ^d Isolated yield. ^e Argon atmosphere instead of air. ^f No light. ^g The reaction was performed in absence of PC for 24 h. NR = no reaction. MTBE=Tert-butyl methyl ether.

3. Mechanistic Investigation

3.1. Control Experiments

Some control experiments were performed to ascertain the mechanism of the photooxidation of N-methylisoquinolinium iodide salt (**1a**). At first 2,6-di-tert-butyl-4-methylphenol (BHT) (radical scavengers) (0.6 mmol, 3 equiv.) was added to the reaction system, the yield of **3a** decreased drastically. Then the singlet oxygen quencher 1,4-diazabicyclo[2.2.2]octane (DABCO) was added, yield of **3a** increased by 8-10%. The observed results excluded the singlet oxygen pathway and suggested the reaction might follow a radical process.

(a)



(b)

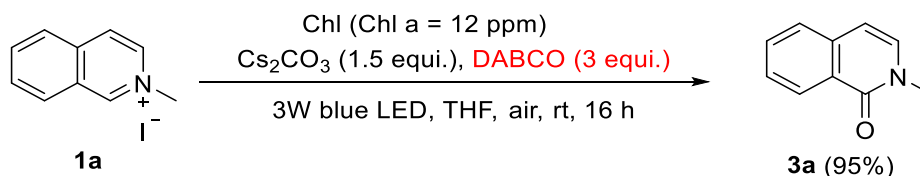


Figure FS2. Control experiments under different conditions. Reaction conditions: air atmosphere and irradiation with 3W blue LED, (**1a**) (0.2 mmol), Chl (PC) (12 ppm), temperature (rt, 25 °C) in a 30 mL glass vial, with: a) 2,6-di-tert-butyl-4-methylphenol (BHT) (0.6 mmol) was added; b) 1,4-diazabicyclo[2.2.2] octane (DABCO) (0.6 mmol) was added in 3 mL THF.

3.2. Stern-Volmer fluorescence quenching experiments

At first, we investigated the excitation and emission spectra of the photocatalyst chlorophyll. A solution of chlorophyll (**PC**) (with chlorophyll a concentration 1.0 μM) in DMSO was chosen as the model. The fluorescence maximum was obtained at 671 nm when excited at 433 nm (excitation maximum of chlorophyll a).

Next, we performed the Stern-Volmer fluorescence quenching experiment on the FlexStation 3 Multi-Mode Microplate Reader. The experiments were conducted by adding 300 μL solution of chlorophyll (Chl a conc. = $1\mu\text{M}$) in DMSO, to individual well of Corning 96 well cell plate, then 1mM solution of quencher in DMSO (**1a**) was added into the well by $5\mu\text{L}$ successively, and the emission spectrum of the sample was recorded (Fig. FS3). The solution was excited at $\lambda = 433\text{ nm}$ (excitation maxima of Chl a) and the emission intensity at $\lambda = 672\text{ nm}$ (670 nm) (emission maxima of Chl a) was observed (Fig. FS4), significant decrease in emission intensity occurred on subsequent addition of quencher. Thereafter we conducted another Stern-Volmer fluorescence quenching experiment to investigate the effect of oxygen. 300 μL solution of chlorophyll ($1\mu\text{M}$) in DMSO was bubbled with oxygen stream for several seconds. The solution was excited at $\lambda = 433\text{ nm}$ and emission intensity at $\lambda = 672\text{ nm}$ was recorded (Fig. FS5) and there was no significant decrease in emission intensity of chlorophyll. As per the observations, probability of an electron transfer between chlorophyll and quencher **1a** could be envisioned.

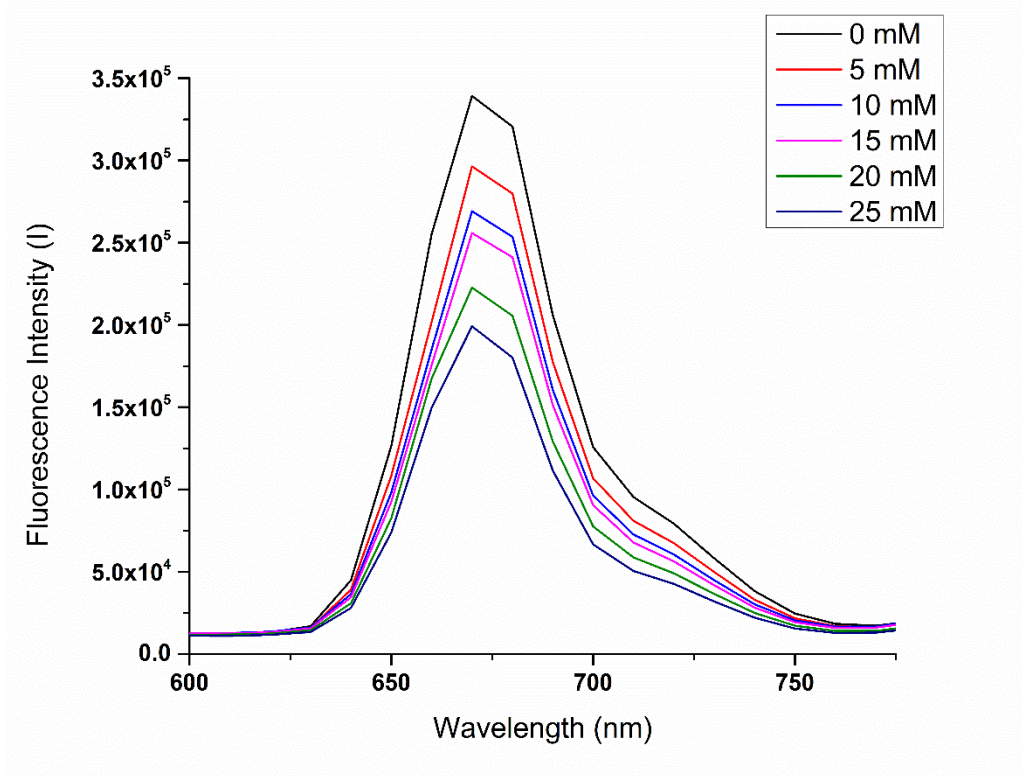


Figure FS3. The fluorescence emission spectra of chlorophyll with different concentration of added quencher (**1a**) excited at 433 nm.

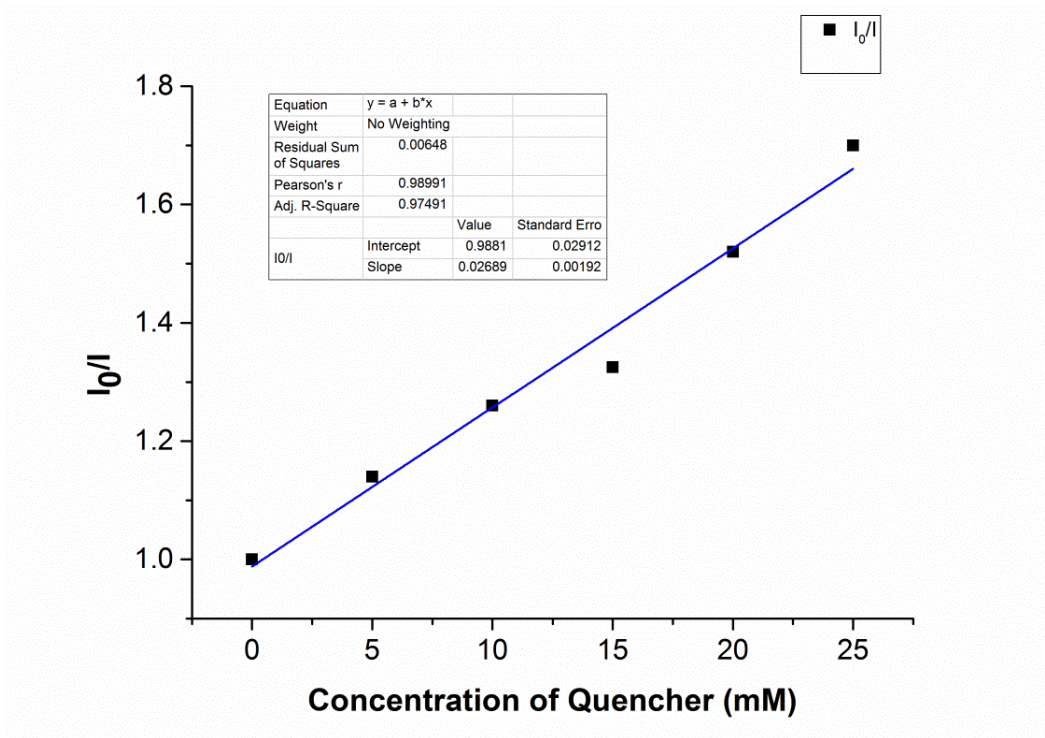


Figure FS4. Chl (PC) emission quenching by **1a**. Linear quenching was observed.

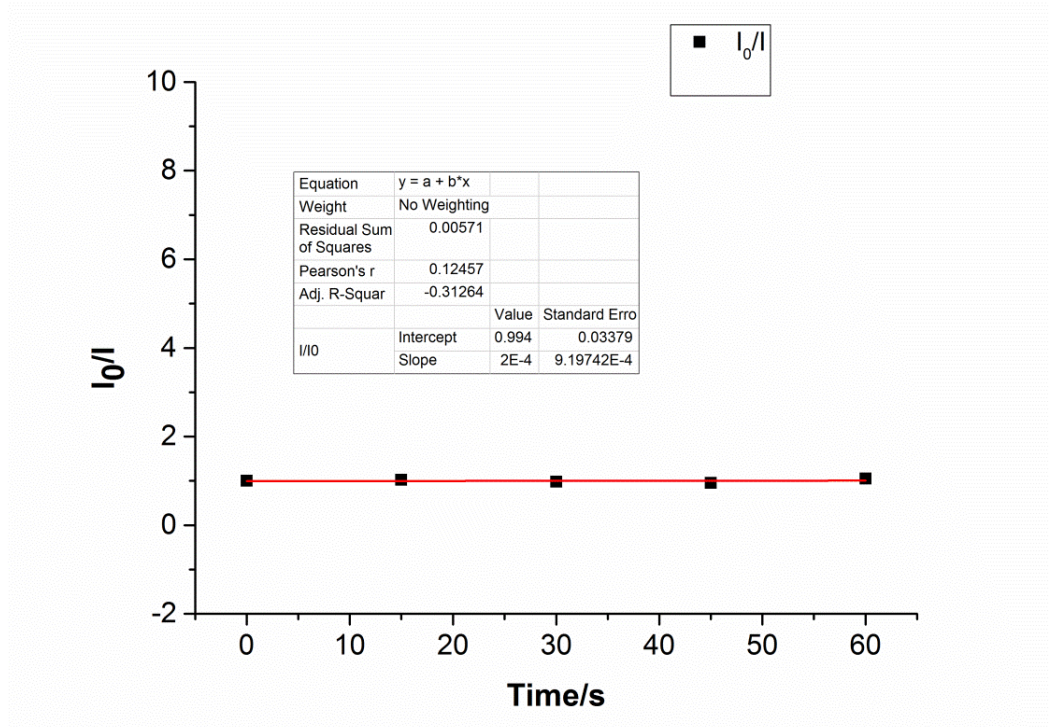


Figure FS5. Chl (PC) emission quenching by oxygen. There was no significant quenching.

3.3. Redox potential estimation of Substrates

3.3A. Estimated Redox potentials of Chl a as per literature reports.²

$$E_{\text{red}}^* (\text{cat}^*/\text{cat}^{\bullet-}) = E_{\text{red}} (\text{cat}/\text{cat}^{\bullet-}) + E_{0,0}$$

$$E_{\text{oxd}}^* (\text{cat}^{\bullet+}/\text{cat}^*) = E_{\text{oxd}} (\text{cat}^{\bullet+}/\text{cat}) - E_{0,0}$$

E^* refers to either S_1 or T_1 excited state, with the corresponding $E_{0,0}$ value ($E_{0,0}^{S_1}$ or $E_{0,0}^{T_1}$)

$E_{\text{red}}^*{}^{S_1} (\text{Chl a}^*/\text{Chl a}^{\bullet-}) = E_{\text{red}} (\text{Chl a}/\text{Chl a}^{\bullet-}) + E_{0,0}^{S_1} = -1.12 + 1.85 \text{ V} = 0.73 \text{ V vs SHE}$. Similarly for $E_{\text{red}}^*{}^{T_1} (\text{Chl a}^*/\text{Chl a}^{\bullet-})$ is found to be 0.22 V vs SHE.

And $E_{\text{oxd}}^*{}^{S_1} (\text{Chl a}^{\bullet+}/\text{Chl a}^*) = E_{\text{oxd}} (\text{Chl a}^{\bullet+}/\text{Chl a}) - E_{0,0}^{S_1} = 0.81 - 1.85 \text{ V} = -1.04 \text{ V vs SHE}$. Similarly for $E_{\text{oxd}}^*{}^{T_1} (\text{Chl a}^{\bullet+}/\text{Chl a}^*)$ is found to be -0.53 V vs SHE (-0.774 V vs SCE).

Thus, Chl a possess $E_{\text{oxd}}^* (\text{Chl}^{\bullet+}/\text{Chl}^*) < 0$; $E_{\text{red}}^* (\text{Chl}^*/\text{Chl}^{\bullet-}) > 0$ (criteria; prerequisite for an efficient photoredox catalyst)^{2a} both in singlet excited state as well as in triplet excited state.

3.3B. CV experiments performed for estimation of redox potentials of Substrates

Cyclic voltammetry (CV) was performed on an EG&G PAR 273 potentiostat/galvanostat with an IBM PS2 computer with EG&G M270 software for data acquisition. The three-electrode cell configuration comprised a platinum sphere, a platinum plate and Ag(s)/AgNO₃ (0.01 M) as the working, auxiliary and reference electrodes respectively. The supporting electrolyte used was tetraethylammonium hexafluorophosphate (C₂H₅)₄N(PF₆). Samples were prepared with a substrate concentration of 0.01 M in a 0.1 M TEAHFP in acetonitrile electrolyte solution. From the result it was found that, $E_{\text{red}} (\mathbf{1a}) = -0.363 \text{ V vs SHE}$ (Figure FS6) is higher than $E_{\text{oxd}}^* (\text{Chl a}) = -0.53 \text{ V vs SHE}$, so the excited state of the photocatalyst chlorophyll a could undergo oxidative quenching readily by donating electron to the substrate (**1a**). As per literature reports the reduction potential of the substrate **2a** is -0.685 V vs SCE ³ and which is also higher than the $E_{\text{oxd}}^* (\text{Chl}) = -0.774 \text{ V vs SCE}$ so the photoredox reaction between Chl and **2a** could occur spontaneously.

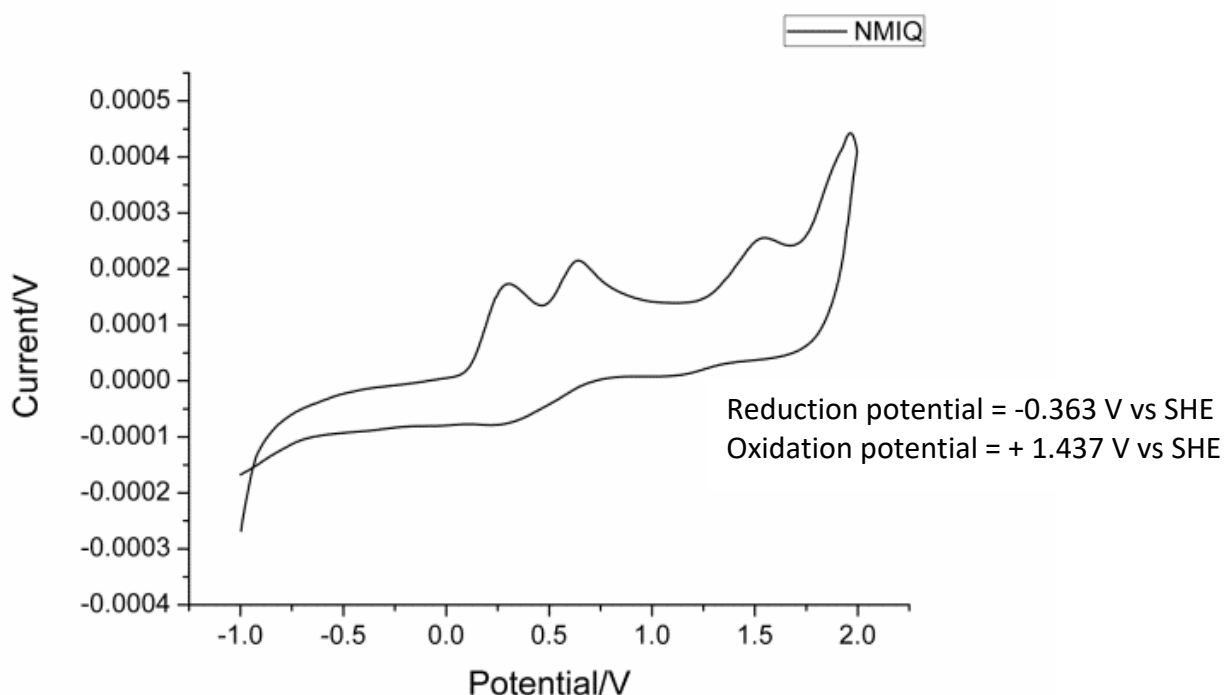


Figure FS6. Cyclic voltammetry experiment of **1a**. Experiment conditions: Init E = 2.0 V, High E = 2.0 V, Low E = -2.0 V, Init P/N = N, Scan Rate = 0.1 V/s, Sample Interval = 0.001 V, Quiet Time = 2s, Sensitivity = $2e^{-4}$ A/V. **1a** (N-methylisoquinolinium iodide salt) (0.01M), tetraethylammonium hexafluorophosphate (0.1 M) in CH_3CN .

3.4. Investigation for EDA complexes

To find out whether chlorophyll could combine with N-alkylquinolinium salts to form electron donor-acceptor (EDA) complexes, UV-visible experiments were performed on LABINDIA UV 3092 Spectrophotometer with a quartz cuvette of 1.0 cm path length. UV-Vis spectra of N-methylquinolinium salt (**2a**) and chlorophyll (**PC**) in DMSO are shown in Fig. FS7 and FS8 respectively. After different concentration of **2a** was added to 10^{-6} M (Chl a = 10^{-6} M in DMSO) solution of **PC** the UV-vis spectra were recorded.

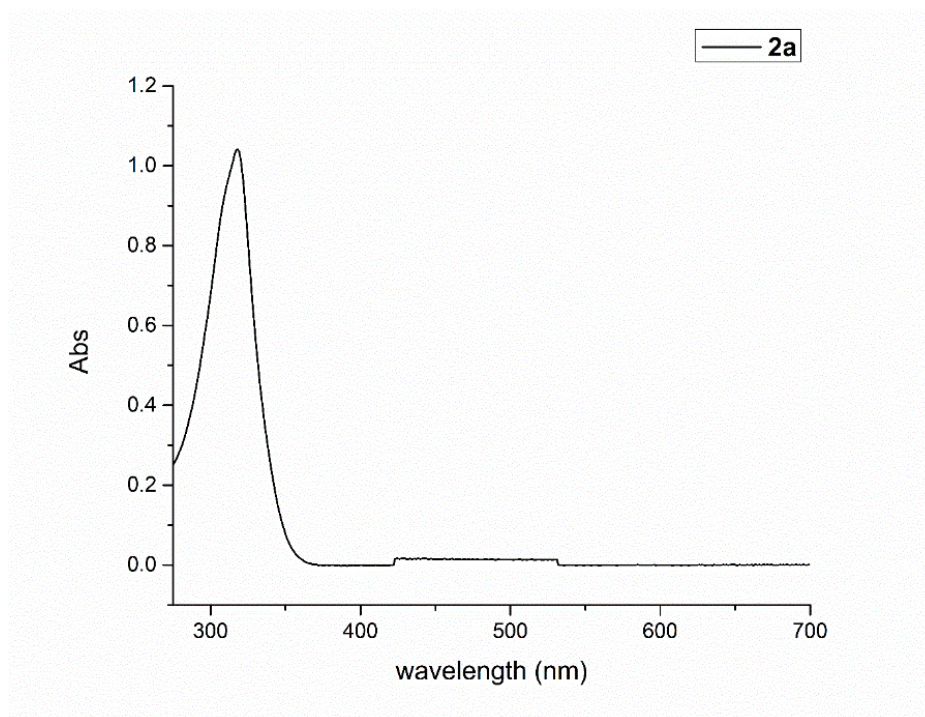


Figure FS7. UV-visible spectrum of **2a** (10^{-4} M in DMSO)

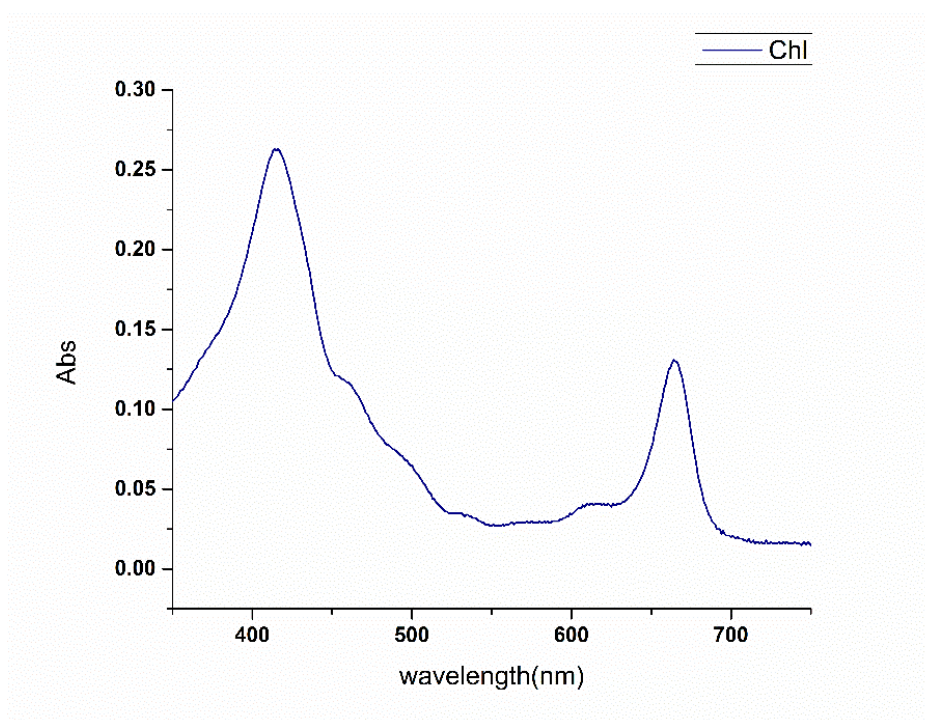


Figure FS8. UV-visible spectrum of Chl (**PC**) (10^{-6} M in DMSO)

As shown in Fig. FS9, there was no bathochromic shift, which ruled out formation of any EDA complex formation in between **PC** and substrate **2a**. However, it was observed that solubility of chlorophyll increased in organic solvent in presence of substrate **2a**.

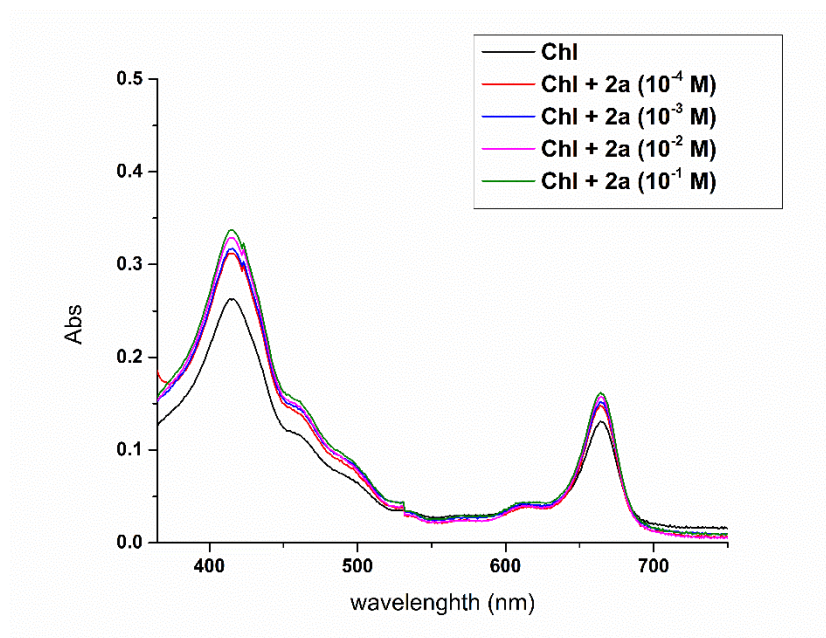


Figure FS9. UV-visible spectra of Chlorophyll (10^{-6} M in DMSO) with different concentration of **2a**. No red-shift band was observed

3.5. Electron Spin-Resonance (ESR) spectroscopy experiments

Electron spin-resonance (ESR) spectra were recorded on a JEOL JES FA200 (X-band). The reactions were performed in glass vial (30 mL) under different conditions, then smaller fractions of the samples were transferred to the capillaries, and ESR spectra were recorded.

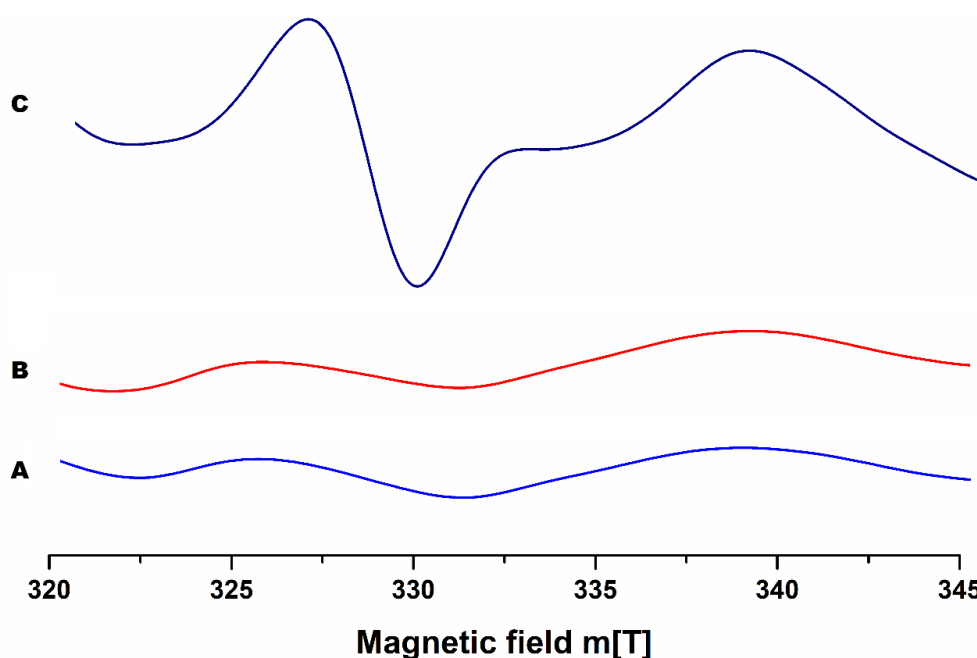


Figure FS10. (A) ESR spectrum of mixture of Chlorophyll (PC), DMPO in DMSO under irradiation of 3W blue LED for 10 min. (B) ESR spectrum of mixture of PC, **1a**, DMPO in DMSO under dark condition for 10 min. (C) ESR spectrum of mixture of PC,**1a**, DMPO in DMSO under irradiation of 3W blue LED for 10 min. **ESR conditions:** Frequency = 9.17 GHz, Power = 0.998 mW, Modulation width = 2.0 mT, Centre field = 390.317 mT, Amplitude = 2.000 x 1 (modulation frequency 100 kHz), Sweep width = 4 x 100 mT, Sweep time = 30 sec, Time constant = 0.03, Temperature = -35 °C

At first, mixture of chlorophyll (containing Chl a; 12ppm), DMPO (0.7 mM) in DMSO was irradiated with 3W blue LED for 10 minutes, then ESR spectrum was recorded (Fig. FS10A). From the spectrum we could ascertain that only chlorophyll could not produce radical under irradiation of visible light. When mixture of **1a** (0.7mM), chlorophyll (Chl a; 12ppm), DMPO (0.7 mM) in DMSO was treated under dark condition for 10 minutes, and ESR spectrum was recorded, no signal was observed then also (Fig. FS10B). Next, mixture of **1a** (0.7mM), chlorophyll (Chl a; 12ppm), DMPO (0.7 mM) in DMSO was irradiated with 3W blue LED for 10 minutes, and ESR spectrum showed a new broad signal (Fig. FS10C) without any detectable hyperfine splitting ($g = 2.0024$, with epr line width = 9 gauss). From the observation it was envisaged that the signal corresponds to pi-radical cation of Chl a, which was formed upon single electron transfer to the substrate N-methylisoquinolinium iodide salt (**1a**). Borg *et al.* and others,⁴ as well as our earlier work⁵ have shown that pi radical cation of chlorophyll a generates an epr signal with $g = 2.0025 \pm 0.0001$ and epr line width = 7-13 gauss, with Gaussian line shape, and absence of hyperfine splitting.

3.6. ^{18}O -Labelling Experiment

The isotope labelling experiment was performed with H_2^{18}O (from Cambridge Isotope Laboratories, Inc., ^{18}O atom 98.1%) and positive ion electrospray mass spectrum (ESI-MS) for the final products was shown in Figure FS11. The result showed that source of oxygen atom in the obtained products (**3-4**) was mainly from the oxygen of air rather than water.

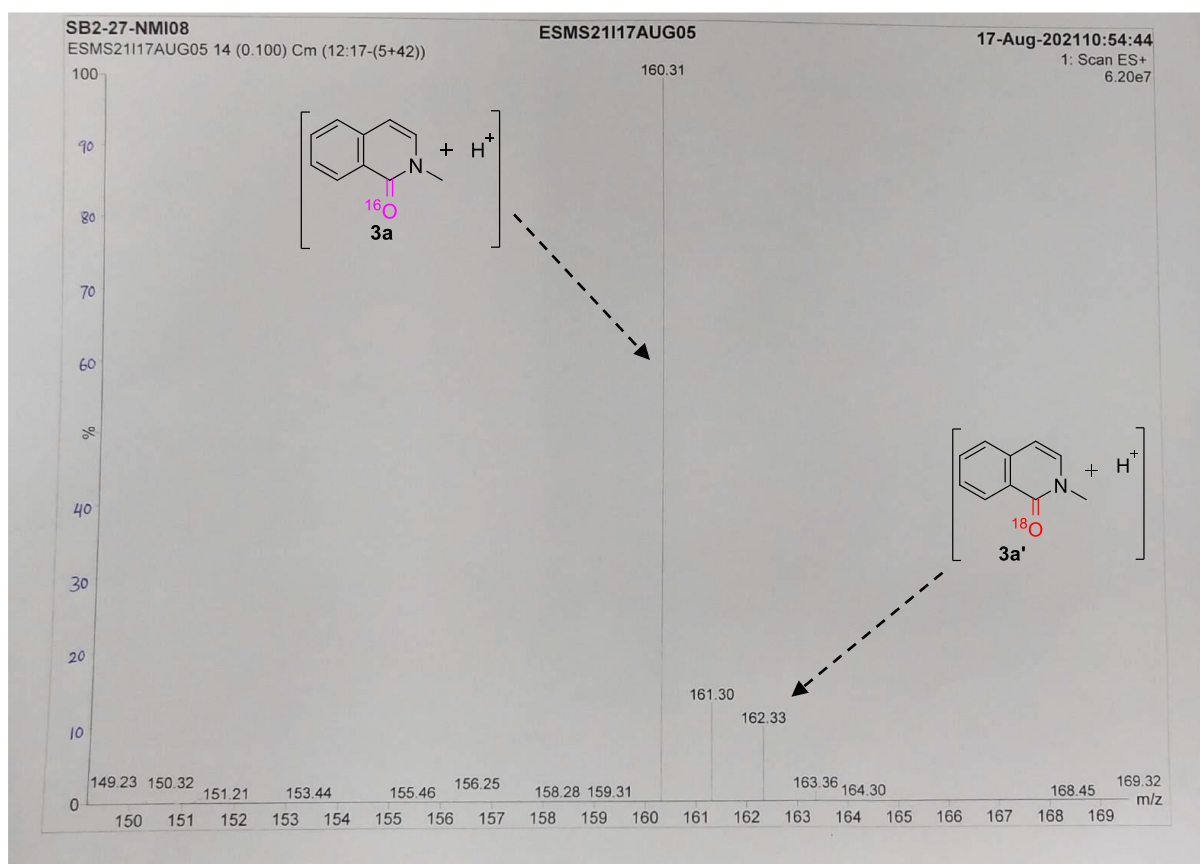
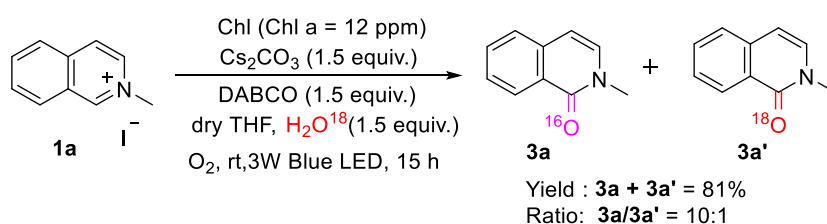
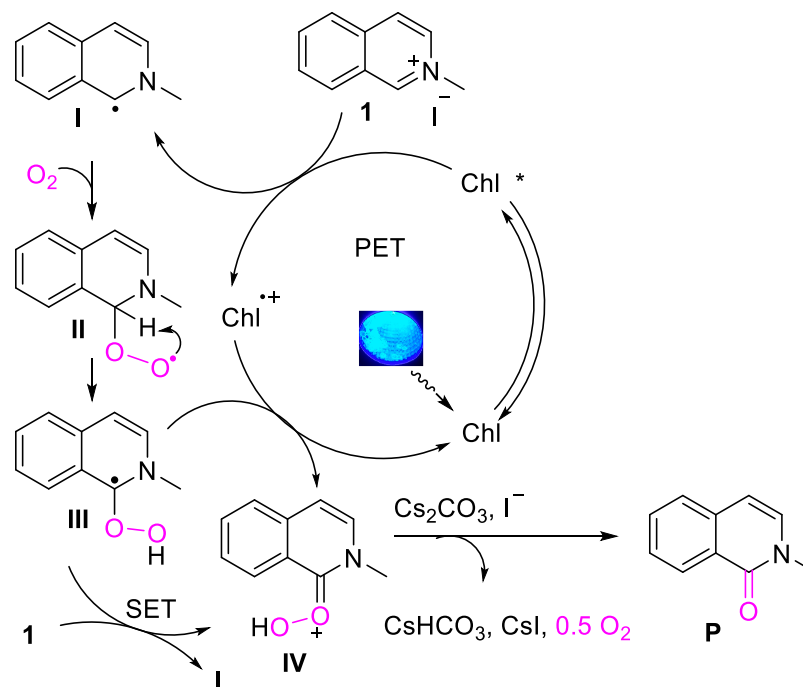


Figure FS11. ^{18}O -Labeling, H_2^{18}O experiment and the ESI-MS positive ion mass spectrum for the final products. Only 10% (approx.) ^{18}O -labelled product **3a'** was observed. Reaction conditions: irradiation with 3 W blue LED under O_2 atmosphere, 2-methylisoquinolin-2-ium iodide (**1a**) (0.2 mmol), Chl (Chl a = 12 ppm), Cs_2CO_3 (0.3 mmol), DABCO (0.3 mmol), H_2^{18}O (0.3 mmol), dry THF (3 mL), temperature (rt, $\sim 25^\circ\text{C}$), time (15 h) in a 25-mL sealed tube.

3.7. Plausible Mechanism



3.8. Evaluation of Green Chemistry metrics⁶ and Eco-Scale⁷ of the current photocatalytic method for the synthesis of 4e.

To demonstrate the synthetic practicability and efficiency of the present visible light mediated aerobic oxidation method, reaction was installed with 1-propylquinolin-1-ium iodide (**2e**) (1.5 g) under the optimised condition and 1-propylquinolin-2(1H)-one (**4e**) was obtained in 65% (0.611 g) yield. To evaluate the greenness of the present method, we have calculated the green chemistry metrics for the synthesis of **4e**. The green chemistry metrics evaluation for the reaction protocol provides an E-factor of 12.55, atom economy of 59.36%, atom efficiency = 38.6%, 100% carbon efficiency and 40.73% reaction mass efficiency (RME) (Table TS2). The Eco-Scale value for the photoredox aerobic oxidation is 59.5 on the scale of 100, which showcases it is an acceptable green method (Table TS3).

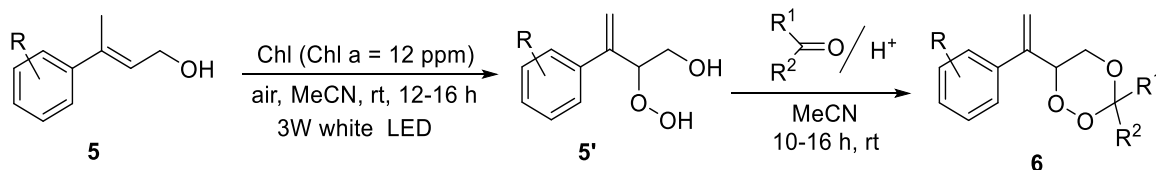
Table TS2. Evaluation of Green Chemistry metrics

<u>Green Chemistry Metrics evaluation</u>			
Atom Economy (%) (AE) = $\frac{\text{Molecular mass of desired product}}{\text{Molecular mass of all reactants}} \times 100$			
Reaction mass efficiency (%) (RME) = $\frac{\text{Mass of desired product}}{\text{Mass of all reactants}} \times 100$			
Environmental factor (E-factor) = $\frac{\text{Total weight of generated waste}}{\text{Weight of end product}} = \frac{\text{Total weight of raw material} - \text{Weight of product}}{\text{Weight of product}}$			
Carbon efficiency = $\frac{\text{Total amount of carbon in product}}{\text{Total amount of carbon in reactant(s)}} \times 100$			
Reactant: 1-propylquinolin-1-ium iodide	1.5g	5.0 mmol	FW 299.15
Base: Cs ₂ CO ₃	2.4g	7.5 mmol	FW 325.82
Solvent: THF (15 mL)	13.32g	---	---
Auxiliary: DABCO	0.84g	7.5 mmol	FW 112.17
Recycled solvent: THF	9.78g		
Product 1-propylquinolin-2(1H)-one	0.611g	3.26 mmol	FW 187.09
Product Yield = 65%			
E-factor = $\frac{1.5+2.4+13.32+0.84-(0.611+9.78)}{0.611} = 12.55$ Kg waste/ 1 Kg product			
AE = $\frac{187.09}{315.15} \times 100 = 59.36\%$			
Atom efficiency = $59.36\% \times 65\% / 100 = 38.6\%$			
Carbon efficiency = $\frac{12}{12} \times 100 = 100\%$			
RME = $\frac{0.611}{1.5} \times 100 = 40.73\%$			

Table TS3. Evaluation of Eco-Scale

<u>Eco-Scale Calculation</u>	
Eco-Scale = 100 - Sum of individual penalties	
Calculation of penalty points:	
Parameters	Penalty points
1. Yield (100 - Percent yield)/2 = 17.5	17.5
2. Price of reaction components (To obtain 10 mmol of final product)	
I. 1-propylquinolin-1-ium iodide (synthesis cost) = 4.5g = US\$1.29	
II. Chlorophyll = 0.235g = US\$0.585	
III. Cs ₂ CO ₃ = 7.47g = US\$2.79	
IV. DABCO = 2.57g = US\$0.7	
V. THF = 40 mL = US\$0.49	
Total Price (USD) = US\$5.85 (< \$10)	
Thus Inexpensive	0
3. Safety	
Toxicity	5
Flammable	5
4. Technical Set up	
Unconventional activation technique (Photochemical method)	2
5. Temperature & time (room temperature, < 24h)	1
6. Work up & purification (Removal of solvent with bp < 100 °C)	0
Classical chromatography	10
Total Penalty Points	= 40.5
Calculation of Eco-Scale:	
Eco-Scale = 100 – Penalty Points = 100 – 40.5 = 59.5 > 50 (Acceptable Synthesis)	
[Score on Eco-Scale: > 75, Excellent; >50, Acceptable; <50, Inadequate]	

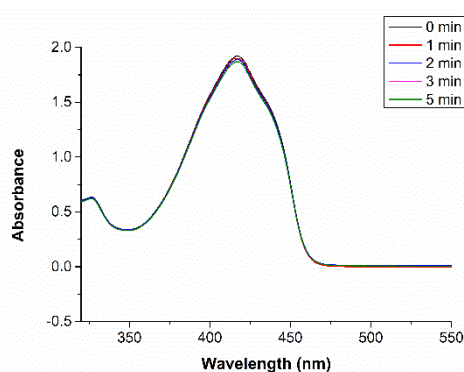
4.1. General experimental procedure for the synthesis of 6



The solution of allylic alcohols (synthesized as per literature methods)⁸ (**5**) (0.2 mmol) and chlorophyll (Chl a = 12 ppm) in CH₃CN (10 mL) were photooxygenated on being irradiated with 3W white LED for 12 hours, under air atmosphere, at ambient temperature, yielding β-hydroxyhydroperoxides **5'**. Progress of reaction was monitored by TLC. After completion of reaction, ketone (0.4 mmol) and p-toluenesulfonic acid (10 mg) were added to the reaction mixture and the reaction mixture was stirred for 10-16 hours at room temperature. After completion, the reaction mixture was concentrated under reduced pressure to remove CH₃CN, diluted with saturated NaHCO₃ solution (5 mL) and water (50 mL), and then extracted with EtOAc (3 x 50 mL). Afterwards the combined organic layer was washed with brine solution, dried over Na₂SO₄, filtered and concentrated using rotary evaporator. The crude product was purified by flash chromatography to give desired product **6** using hexane/ EtOAc as the eluent.

4.2. Investigation of generation of singlet oxygen⁵

(a) DPBF + [Chl] without light



(b) DPBF + [Chl] with light

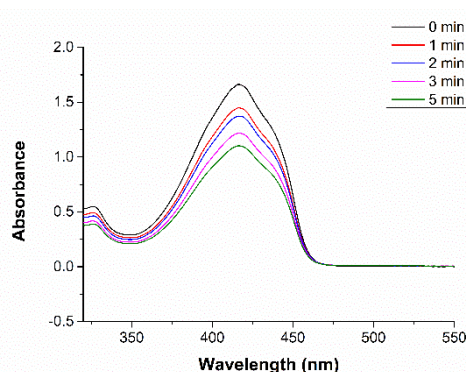
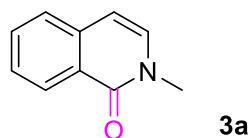
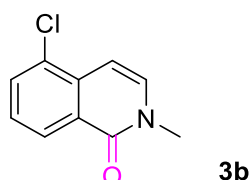


Figure FS12. Time dependent changes in UV spectra of the product formed during oxidation of DPBF (1,3 diphenylbenzo[c]furan) by singlet oxygen. **Fig. FS12a** and **Figure FS12b** indicated that light did significantly enhance the production of singlet oxygen, which can be determined by DPBF. Reactions were performed by using DPBF (1.5 μM), chlorophyll (Chl a=12 ppm) in CH₃CN (2 mL).

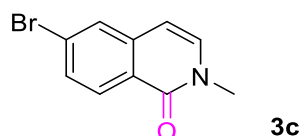
5. Characterisation of the products:



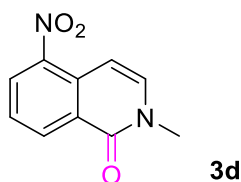
2-Methylisoquinolin-1(2H)-one (3a).³ Eluent: Hexane/EtOAc (1.25:1). Yield 27.6 mg (87%). Pale yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 8.44 (d, *J* = 8.1, 1H), 7.62 (ddd, *J* = 8.1, 7.0, 1.4 Hz, 1H), 7.51 – 7.45 (m, 2H), 7.07 (d, *J* = 7.3 Hz, 1H), 6.48 (d, *J* = 7.3 Hz, 1H), 3.61 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 162.7, 137.2, 132.5, 132.1, 127.8, 126.9, 126.2, 125.9, 106.1, 37.1. HRMS (ESI⁺): Calcd for C₁₀H₁₀NO, [M+H]⁺ *m/z* 160.0757. Found 160.0754.



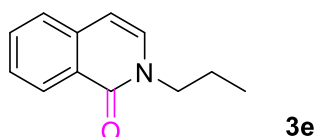
5-Chloro-2-methylisoquinolin-1(2H)-one (3b). Hexane/EtOAc (1.5:1). Yield 32.0 mg (83%). Off white solid, mp 81-83 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.36 (d, *J* = 7.68 Hz, 1H), 7.68 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.16 (d, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.6 Hz, 1H), 3.61 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 162.0, 135.2, 133.6, 132.4, 130.4, 127.7, 127.0, 126.7, 102.2, 37.3. HRMS (ESI⁺): Calcd for C₁₀H₉ClNO, [M+H]⁺ *m/z* 194.0367. Found 194.0368.



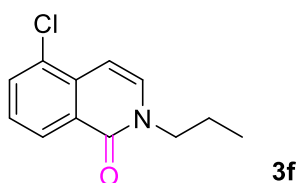
6-Bromo-2-methylisoquinolin-1(2H)-one (3c).³ Hexane/EtOAc (1.5:1). Yield 38.3 mg (81%). White solid, mp 150-152°C. ¹H NMR (300 MHz, CDCl₃) δ 8.27 (d, *J* = 8.6 Hz, 1H), 7.67 (d, *J* = 1.8 Hz, 1H), 7.56 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.09 (d, *J* = 7.3 Hz, 1H), 6.39 (d, *J* = 7.3 Hz, 1H), 3.59 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 162.3, 138.7, 133.9, 130.2, 129.7, 128.4, 127.3, 124.9, 104.9, 37.2. HRMS (ESI⁺): Calcd for C₁₀H₉BrNO, [M+H]⁺ *m/z* 237.9862. Found 237.9864.



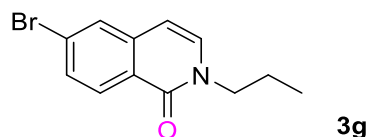
2-Methyl-5-nitroisoquinolin-1(2H)-one (3d).³ Hexane/EtOAc (1.5:1). Yield 36.3 mg (89%). Yellow solid, mp 121-123°C. ¹H NMR (300 MHz, CDCl₃) δ 8.76 (dd, *J* = 8.0, 0.9 Hz, 1H), 8.39 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.55 (t, *J* = 7.87 Hz, 1H), 7.29 (d, *J* = 7.87 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 3.62 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 161.2, 144.7, 136.2, 134.3, 131.1, 129.4, 128.1, 125.8, 100.6, 37.3. HRMS (ESI⁺): Calcd for C₁₀H₉N₂O₃, [M+H]⁺ *m/z* 205.0608. Found 205.0603.



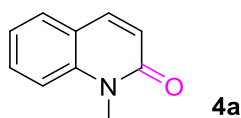
2-Propylisoquinolin-1(2H)-one (3e).³ Hexane/EtOAc (4:1). Yield 29.5 mg (79%). Pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 8.43 (d, *J* = 8.1 Hz, 1H), 7.61 (ddd, *J* = 8.2, 7.1, 1.3 Hz, 1H), 7.49-7.44 (m, 2H), 7.05 (d, *J* = 7.3 Hz, 1H), 6.47 (d, *J* = 7.3 Hz, 1H), 3.96 (dd, *J* = 7.8, 6.9 Hz, 2H), 1.80 (sext, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 162.1, 137.1, 132.0, 131.8, 127.9, 126.7, 126.4, 125.9, 105.9, 51.0, 22.6, 11.3. HRMS (ESI⁺): Calcd for C₁₂H₁₃NO, [M+H]⁺ *m/z* 188.1070. Found 188.1065.



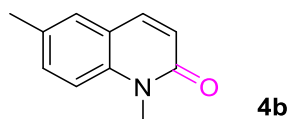
5-Chloro,2-propylisoquinolin-1(2H)-one (3f).⁹ Eluent: Hexane/EtOAc (3:2). Yield 36.7 mg (83%). Pale yellow solid, mp 80-81 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.35 (d, *J* = 8.1, 1H), 7.67 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 6.84 (dd, *J* = 7.6, 0.6 Hz, 1H), 3.96 (dd, *J* = 7.8, 6.8 Hz, 2H), 1.80 (sext, *J* = 7.4, 2H), 0.98 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 161.5, 135.1, 132.9, 132.3, 130.4, 127.9, 126.9, 102.0, 51.2, 22.5, 11.3. HRMS (ESI⁺): Calcd for C₁₂H₁₃ClNO, [M+H]⁺ *m/z* 222.0680. Found 222.0681.



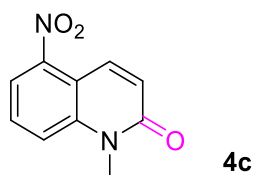
6-bromo-2-propylisoquinolin-1(2H)-one (3g).¹⁰ Hexane/EtOAc (1.5:1). Yield 44.5 mg (84%). Off white solid, mp 137 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.27 (d, *J* = 8.6 Hz, 1H), 7.65 (d, *J* = 1.9 Hz, 1H), 7.55 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 6.38 (d, *J* = 7.4 Hz, 1H), 3.96 – 3.91 (m, 2H), 1.83–1.72 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 161.9, 138.7, 133.3, 130.2, 129.9, 128.4, 127.3, 125.2, 104.8, 51.2, 22.7, 11.4. HRMS (ESI⁺): Calcd for C₁₂H₁₃BrNO, [M+H]⁺ *m/z* 266.0175. Found 266.0171.



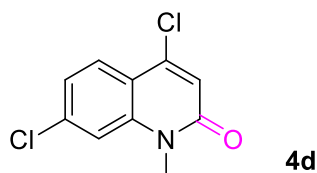
1-Methylquinolin-2(1H)-one (4a).³ Eluent Hexane/EtOAc (2.5:1). /EtOAc (1:1.25). Yield 26.3 mg (83%). Pale yellow solid, mp 70-72°C. ¹H NMR (300 MHz, CDCl₃) δ 7.69 (d, *J* = 9.5 Hz, 1H), 7.59-7.54 (m, 2H), 7.39 (d, *J* = 8.6 Hz, 1H), 7.26-7.20 (m, 1H), 6.74 (d, *J* = 9.5 Hz, 1H), 3.75 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 162.4, 140.1, 139.0, 130.7, 128.8, 122.2, 121.8, 120.8, 114.2, 29.5. HRMS (ESI⁺): Calcd for C₁₀H₁₀NO, [M+H]⁺ *m/z* 160.0757. Found 160.0753.



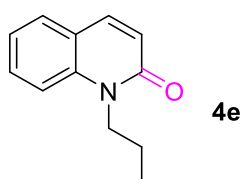
1,6-Dimethylquinolin-2(1H)-one (4b).¹¹ Eluent: Hexane/EtOAc (3:2). Yield 21.1 mg (61%). Pale yellow solid, mp 76-78 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.61 (d, *J* = 9.5 Hz, 1H), 7.40-7.34 (m, 2H), 7.27 (t, *J* = 4.3 Hz, 1H), 6.69 (d, *J* = 9.5 Hz, 1H), 3.70 (s, 3H), 2.42 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 162.4, 138.8, 138.2, 131.9, 131.7, 128.7, 121.8, 120.8, 114.1, 29.5, 20.6. HRMS (ESI⁺): Calcd for C₁₁H₁₂NO, [M+H]⁺ *m/z* 174.0913. Found 174.0909.



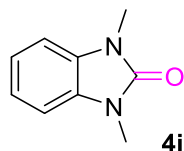
1-Methyl-5-nitroquinolin-2(1H)-one (4c).³ Eluent: Hexane/EtOAc (3:1). Yield 35.9 mg (88%). Orange-red solid, mp 166-168 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.29 (d, *J* = 10.1 Hz, 1H), 7.83 (dd, *J* = 6.6, 2.4 Hz, 1H), 7.77-7.65 (m, 2H), 6.89 (d, *J* = 9.5, 1H), 3.78 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 161.0, 147.8, 141.4, 132.8, 129.9, 125.2, 119.1, 118.5, 113.9, 30.3. HRMS (ESI⁺): Calcd for C₁₀H₉N₂O₃, [M+H]⁺ *m/z* 205.0608. Found 205.0606.



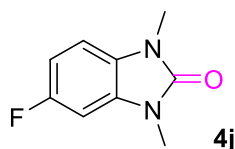
1-Methyl-4,7-dichloroquinolin-2(1H)-one (4d).¹² Eluent: Hexane/EtOAc (4:1). Yield 38.5 mg (85%). Off-white solid, mp 145-147 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.78 (d, *J* = 8.6 Hz, 1H), 7.47 (s, 1H), 7.33 (d, *J* = 1.9 Hz, 1H), 7.23 (m, 1H), 3.67 (s, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 160.3, 139.1, 138.2, 135.1, 133.2, 123.4, 120.7, 114.3, 113.5, 30.0. HRMS (ESI⁺): Calcd for C₁₀H₈Cl₂NO [M+H]⁺ *m/z* 227.9977 Found 227.9979.



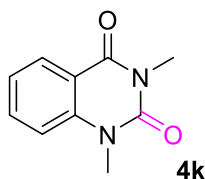
1-propylquinolin-2(1H)-one (4e).¹³ Eluent: Hexane/EtOAc (4:1). Yield 25.0 mg (67%). Pale yellow oil. ¹H NMR (300 MHz, CDCl₃) δ 7.66 (d, *J* = 9.5 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.35 (d, *J* = 8.9 Hz, 1H), 7.21 (td, *J* = 7.4, 1.0 Hz, 1H), 6.70 (d, *J* = 9.5 Hz, 1H), 4.31 – 4.20 (m, 2H), 1.77 (dt, *J* = 15.0, 7.5 Hz, 2H), 1.05 (t, *J* = 7.4 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 162.2, 139.3, 139.0, 130.6, 129.0, 121.96, 121.93, 121.0, 114.3, 43.9, 20.9, 11.4. HRMS (ESI⁺): Calcd for C₁₂H₁₄NO, [M+H]⁺ *m/z* 188.1070. Found 188.1062.



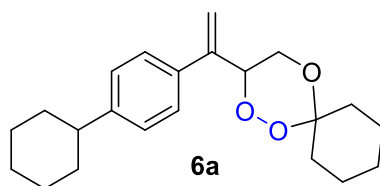
1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one(4i).³ Eluent: Hexane/EtOAc (4:1). Yield 20.4 mg (63%). Off-white solid, mp 105-107 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.12-7.09 (m, 2H), 6.98-6.95 (m, 2H), 3.42 (s, 6H). ¹³C NMR (75 MHz, CDCl₃) δ 154.8, 130.1, 121.3, 107.4, 27.2. ESMS (ESI⁺): Calcd for C₉H₁₁N₂O, [M+H]⁺ m/z 163.2. Found 163.3.



5-fluoro-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one (4j).¹⁴ Eluent: Hexane/EtOAc (4:1). Yield 19.5 mg (54%). Off-white solid, mp 132-134 °C. ¹H NMR (300 MHz, CDCl₃) δ 7.08 (dd, *J* = 8.7, 4.4 Hz, 1H), 7.01 – 6.89 (m, 2H), 3.78 (s, 3H), 3.77 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 171.22, 160.1 (d, *J*_{C-F} = 242.8 Hz), 133.04, 128.98, 110.2 (d, *J*_{C-F} = 24.2 Hz), 109.3 (d, *J*_{C-F} = 9.5 Hz), 96.8 (d, *J*_{C-F} = 28.2 Hz), 31.51. ¹⁹F NMR (283 MHz, CDCl₃) δ -118.72. ESMS (ESI⁻): Calcd for C₉H₈FN₂O, [M-H]⁻ m/z 180.2. Found 179.3.

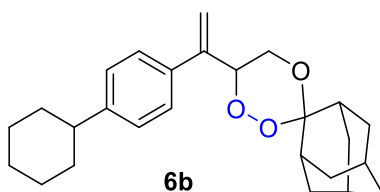


4-methoxy-1-methylquinazolin-2(1H)-one (4k).¹⁵ Eluent: Hexane/EtOAc (3:1). Yield 14.8 mg (39%). Off-white solid, mp 162-164 °C. ¹H NMR (300 MHz, CDCl₃) δ 8.23 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.68 (ddd, *J* = 8.4, 7.2, 1.6 Hz, 1H), 7.31 – 7.17 (m, 2H), 3.61 (s, 3H), 3.49 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 162.1, 151.4, 140.5, 135.1, 129.0, 123.1, 115.6, 113.6, 30.9, 28.6. ESMS (ESI⁺): Calcd for C₁₀H₁₁N₂O₂, [M+H]⁺ m/z 191.2. Found 191.4.

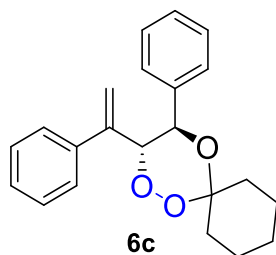


3-(1-(4-cyclohexylphenyl)vinyl)-1,2,5-trioxaspiro[5.5]undecane (6a).¹⁶

Eluent: Hexane/EtOAc (49:1). Yield 39.6 mg (58%). Off-white semi-solid compound. ¹H NMR (300 MHz, CDCl₃) δ 7.32 (d, *J* = 8.2, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 5.48 (s, 1H), 5.26 (d, *J* = 3.7 Hz, 1H), 5.25-5.22 (m, 1H), 3.96 (dd, *J* = 11.9, 10.3 Hz, 1H), 3.76 (dd, *J* = 11.9, 2.9 Hz, 1H), 2.50 (b s, 1H), 2.27-2.18 (m, 1H), 2.05-2.01 (m, 1H), 1.85 – 1.73 (m, 6H), 1.63 – 1.55 (m, 5H), 1.47-1.36 (m, 7H). ¹³C NMR (100 MHz, CDCl₃) δ 148.3, 143.4, 136.2, 127.1, 126.3, 115.5, 102.7, 80.4, 63.0, 44.3, 34.8, 34.5, 29.1, 27.0, 26.2, 25.7, 22.4, 22.4. HRMS (ESI⁺): Calcd for C₂₂H₃₁O₃, [M+H]⁺ *m/z* 343.2268. Found 343.2260.



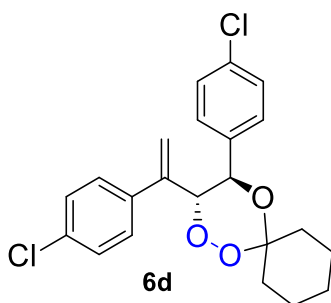
(1r,3r,5r,7r)-6'-(1-(4-cyclohexylphenyl)vinyl)spiro[adamantane-2,3'-[1,2,4]trioxane] CDRI 99/411 (6b).¹⁶ Eluent: Hexane/EtOAc (49:1). Yield 40.2 mg (51%). Off-white semi-solid compound. ¹H NMR (300 MHz, CDCl₃) δ 7.34 (d, *J* = 8.2 Hz, 2H), 7.18 (d, *J* = 8.2 Hz, 2H), 5.48 (s, 1H), 5.28 – 5.24 (m, 2H), 3.95 (dd, *J* = 11.8, 10.6 Hz, 1H), 3.78 (dd, *J* = 11.9, 3.0 Hz, 1H), 2.97 (s, 1H), 2.52 – 2.47 (m, 1H), 2.09 – 1.95 (m, 3H), 1.86 (b s, 8H), 1.77-1.66 (m, 5H), 1.64-1.57 (m, 2H), 1.48 – 1.22 (m, 5H). ¹³C NMR (75 MHz, CDCl₃) δ 148.4, 143.6, 136.3, 127.2, 126.4, 115.5, 104.8, 80.3, 62.6, 44.4, 37.4, 36.5, 34.6, 33.8, 33.7, 33.5, 33.2, 29.6, 27.4, 27.1, 26.3. HRMS (ESI⁺): Calcd for C₂₆H₃₅O₃, [M+H]⁺ *m/z* 395.2581. Found 395.2574.



(3R,4R)-4-phenyl-3-(1-phenylvinyl)-1,2,5-trioxaspiro[5.5]undecane (6c)¹⁷

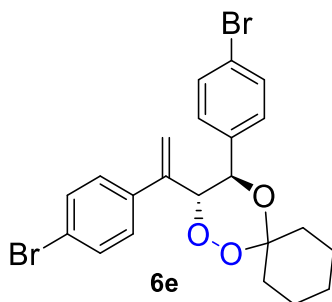
Eluent:Hexane/EtOAc (98:2). Yield 14.9 mg (22%). White solid, mp 77-79 °C.

¹H NMR (300 MHz, CDCl₃) δ 7.29 – 7.25 (m, 2H), 7.24 – 7.20 (m, 3H), 7.19-7.17 (m, 3H), 7.06 – 7.03 (m, 2H), 5.47 (s, 1H), 5.42 (s, 1H), 5.01(d, J=9.6,1H), 4.98 (d, J=9.6,1H), 2.47 – 2.38 (m, 1H), 2.16-2.07 (m, 1H), 1.75 (m, 2H), 1.69 – 1.47 (m, 5H), 1.45 – 1.35 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 143.9, 139.8, 137.1, 128.5, 128.3, 128.2, 128.0, 127.7, 126.9, 120.5, 103.4, 87.3, 74.5, 35.3, 30.0, 25.7, 22.6, 22.4.

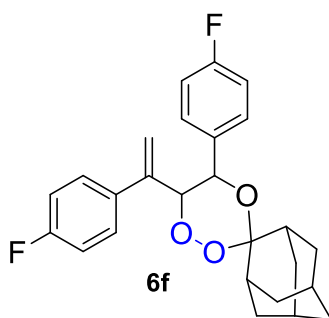


(3R,4R)-4-(4-chlorophenyl)-3-(1-(4-chlorophenyl)vinyl)-1,2,5-trioxaspiro[5.5]undecane(6d)¹⁷

Eluent:Hexane/EtOAc (98:2). Yield 17.0 mg (21%). Oil. ¹H NMR (400 MHz, CDCl₃) δ 7.26 – 7.21 (m, 6H), 7.12 – 7.10 (m, 2H), 5.39 (b s, 1H), 5.37 (b s, 1H), 4.58 (d, J = 8.5 Hz, 1H), 4.52 (d, J = 8.5 Hz, 1H), 1.87 – 1.83 (m, 2H), 1.77 – 1.65 (m, 6H), 1.47 (m 2H). ¹³C NMR (100 MHz, CDCl₃) δ 143.8, 137.5, 136.3, 133.9, 133.9, 129.1, 128.6, 128.4, 128.0, 118.5, 110.4, 85.9, 81.6, 36.8, 36.8, 25.2, 24.0, 23.9.



(3R,4R)-4-(4-bromophenyl)-3-(1-(4-bromophenyl)vinyl)-1,2,5-trioxaspiro[5.5]undecane (6e)¹⁷. Eluent:Hexane/EtOAc (98:2). Yield 16.7 mg (17%). Oil. ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.34 (m, 4H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.02 – 6.91 (m, 2H), 5.47 (s, 1H), 5.41 (s, 1H), 4.92 (d, *J* = 9.6 Hz, 1H), 4.87 (d, *J* = 9.6 Hz, 1H), 2.38 – 2.31 (m, 1H), 2.13 – 2.05 (m, 1H), 1.74 – 1.43 (m, 8H). ¹³C NMR (75 MHz, CDCl₃) δ 142.5, 138.4, 136.0, 131.6, 129.5, 128.6, 122.6, 122.2, 121.4, 103.6, 87.1, 73.6, 35.2, 30.0, 25.6, 22.5, 22.3.

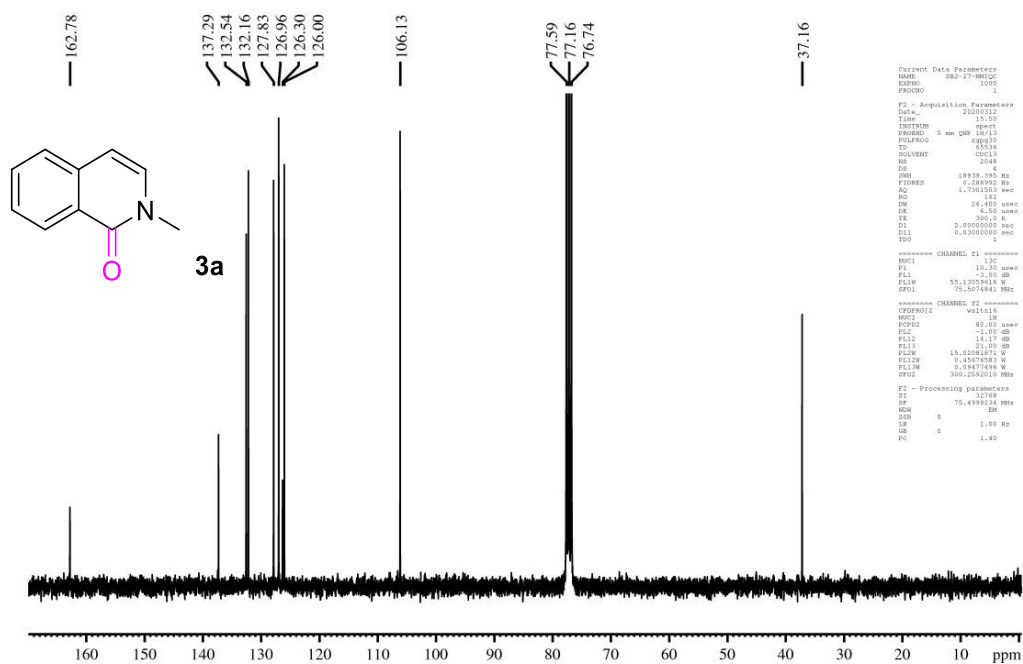
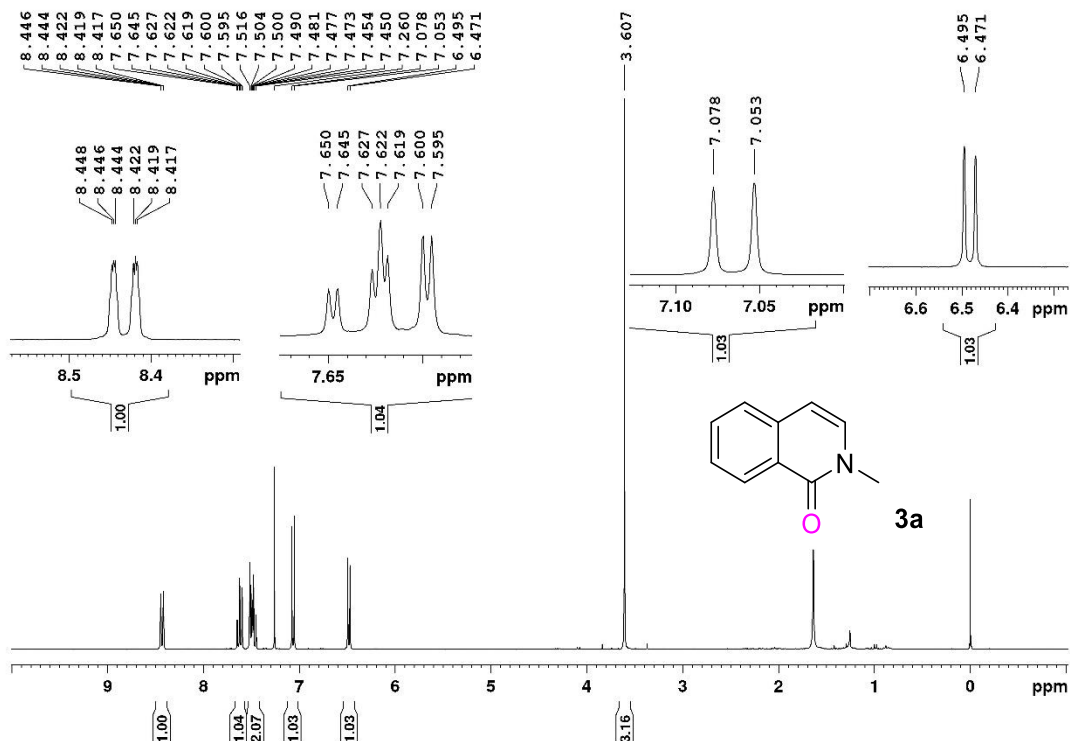


(1r,3r,5r,7r)-5'-(4-fluorophenyl)-6'-(1-(4-fluorophenyl)vinyl)spiro[adamantane-2,3'-[1,2,4]trioxane]](6f)¹⁷
 Eluent:Hexane/EtOAc (49:1). Yield 26.3 mg (31%). White solid. mp 103-105 °C
¹H NMR (300 MHz, CDCl₃) δ 7.27 – 7.22 (m, 2H), 7.05– 7.01 (m, 2H), 6.95 – 6.85 (m, 4H), 5.45 (s, 1H), 5.40 (s, 1H), 4.94 (d, *J* = 9.6 Hz, 1H), 4.89 (d, *J* = 9.6 Hz, 1H), 3.07 (s, 1H), 2.14 – 1.58 (m, 13H). ¹³C NMR (75 MHz, CDCl₃) δ 162.8 (d, *J*_{C-F}=246.9 Hz) 162.6(d, *J*_{C-F}=247.4 Hz), 143.0,135.9, 133.3, 129.6 (d, *J*_{C-F}=8.1 Hz) 128.6 (d, *J*_{C-F}=8.1 Hz), 120.4, 115.5 (d, *J*_{C-F}= 21.7 Hz), 115.2 (d, *J*_{C-F}= 21.7 Hz) 105.7, 87.2, 73.3, 37.4, 36.8, 33.7, 33.5, 33.3, 30.5, 27.4, 27.3.

6. References:

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7. NMR Spectra of the Products:



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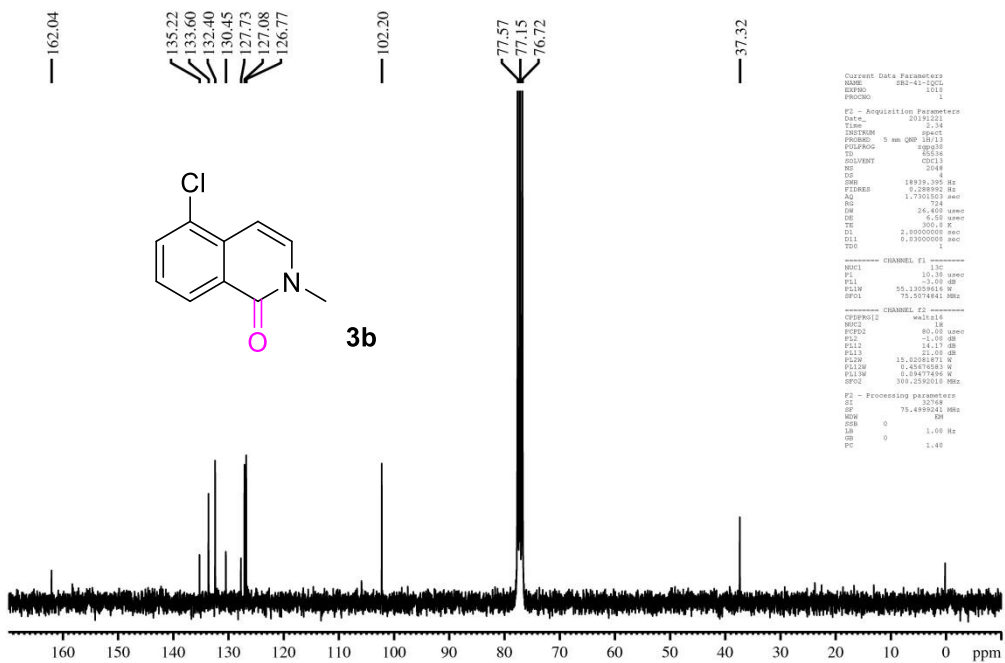
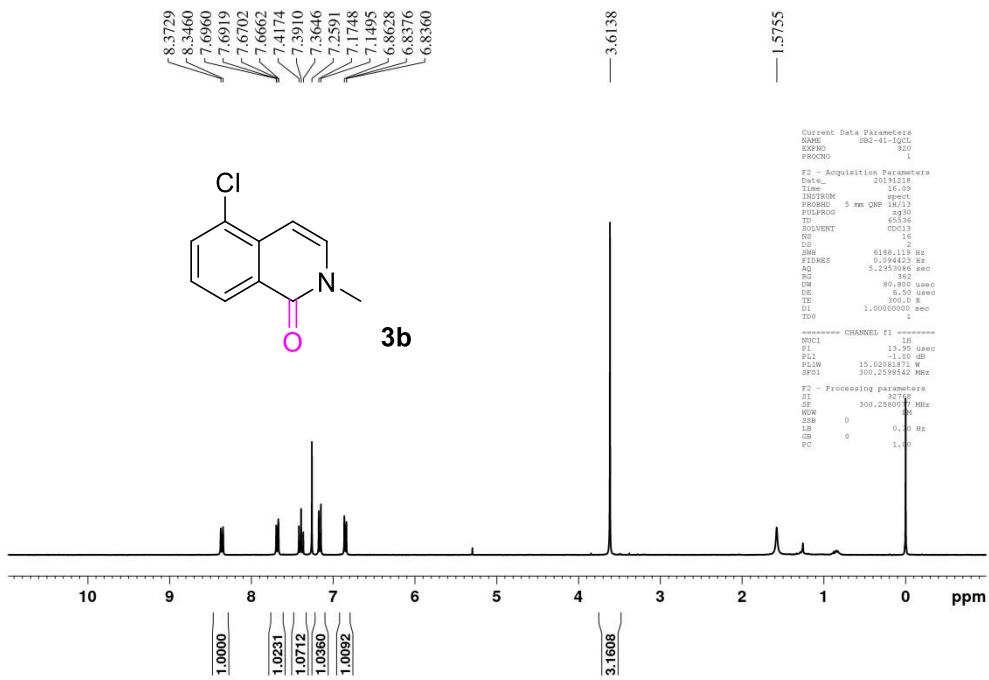
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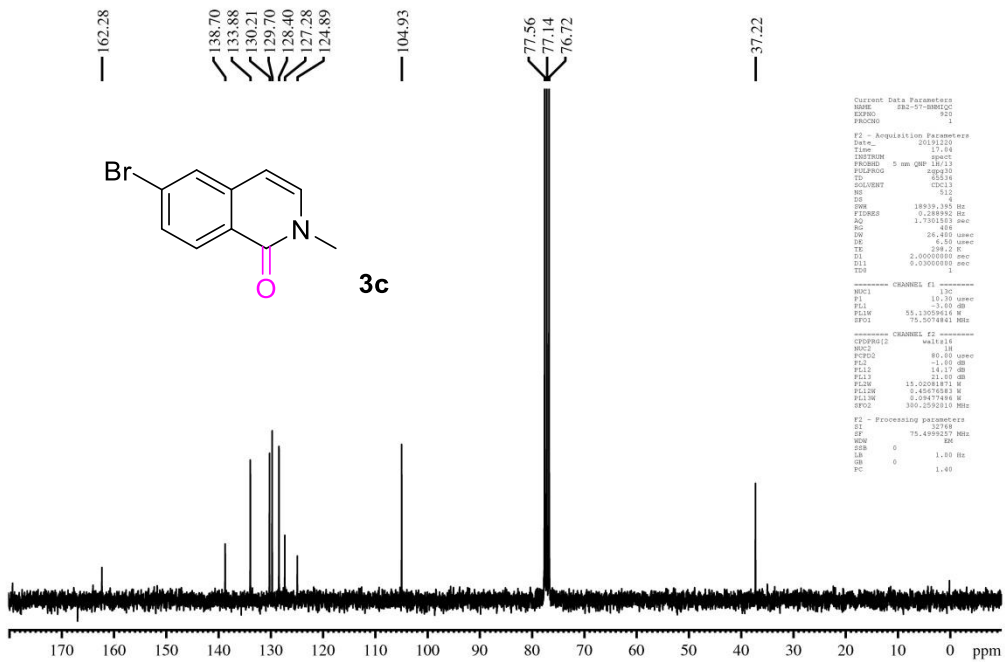
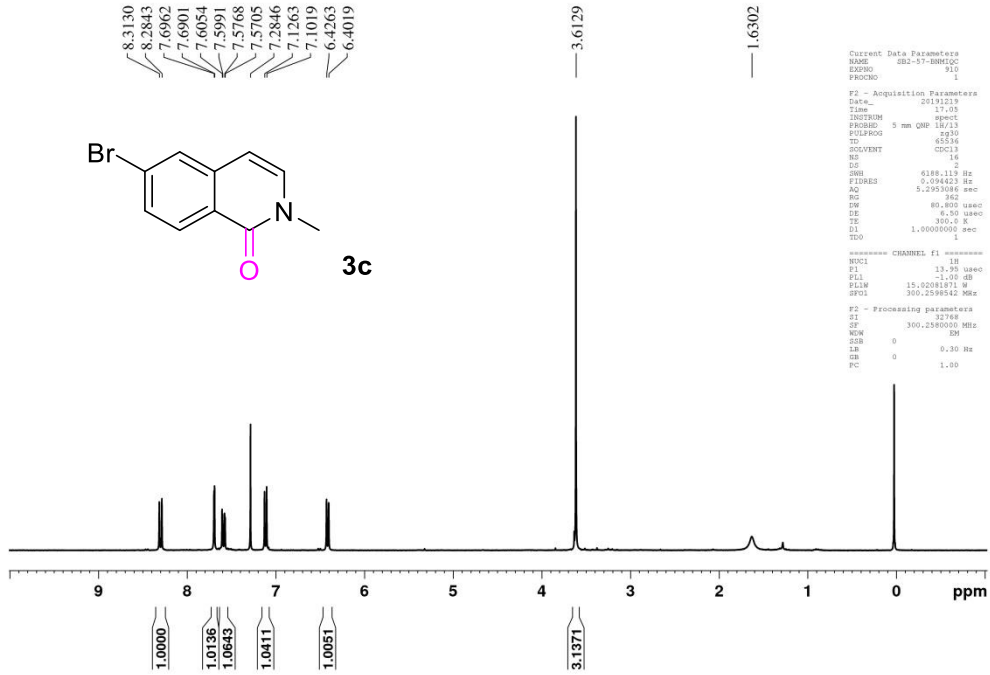
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D11 0.3000000 sec
TD 1

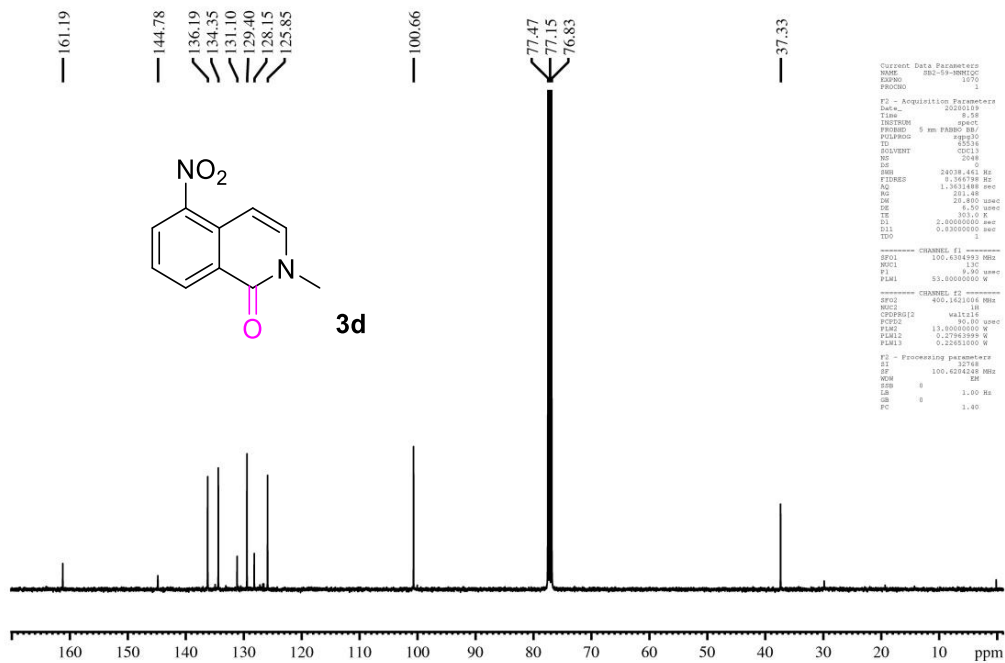
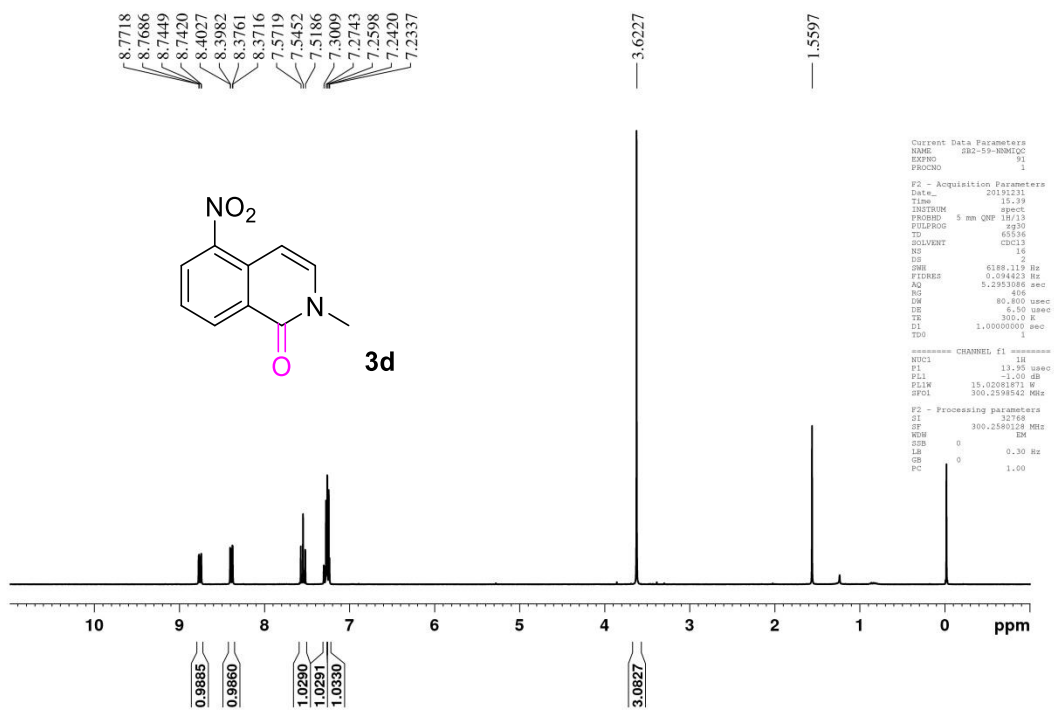
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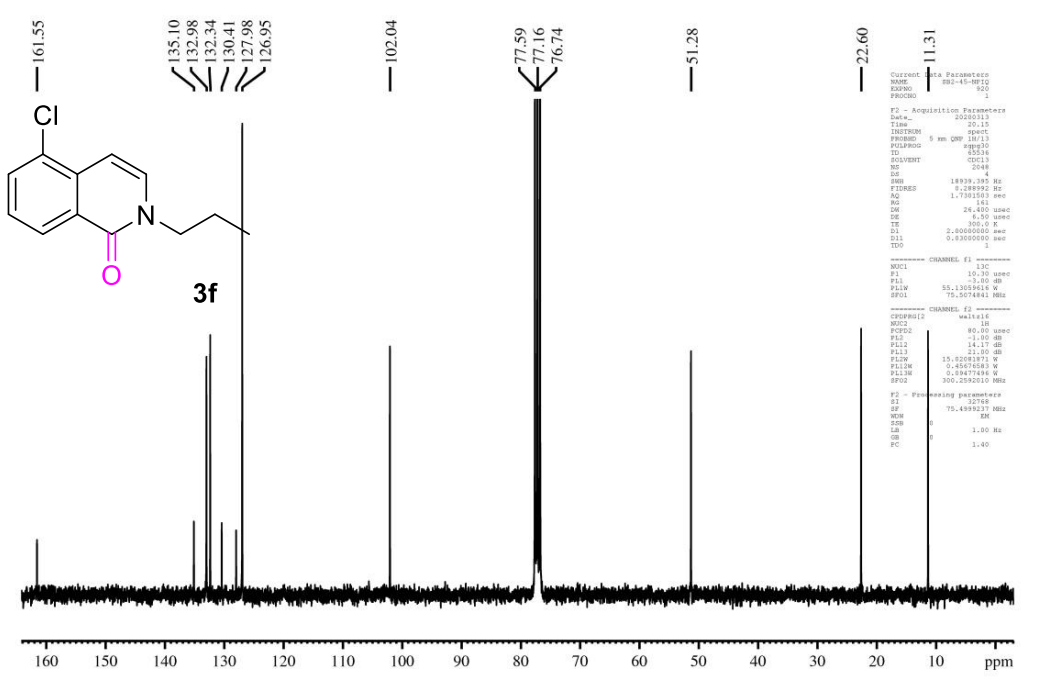
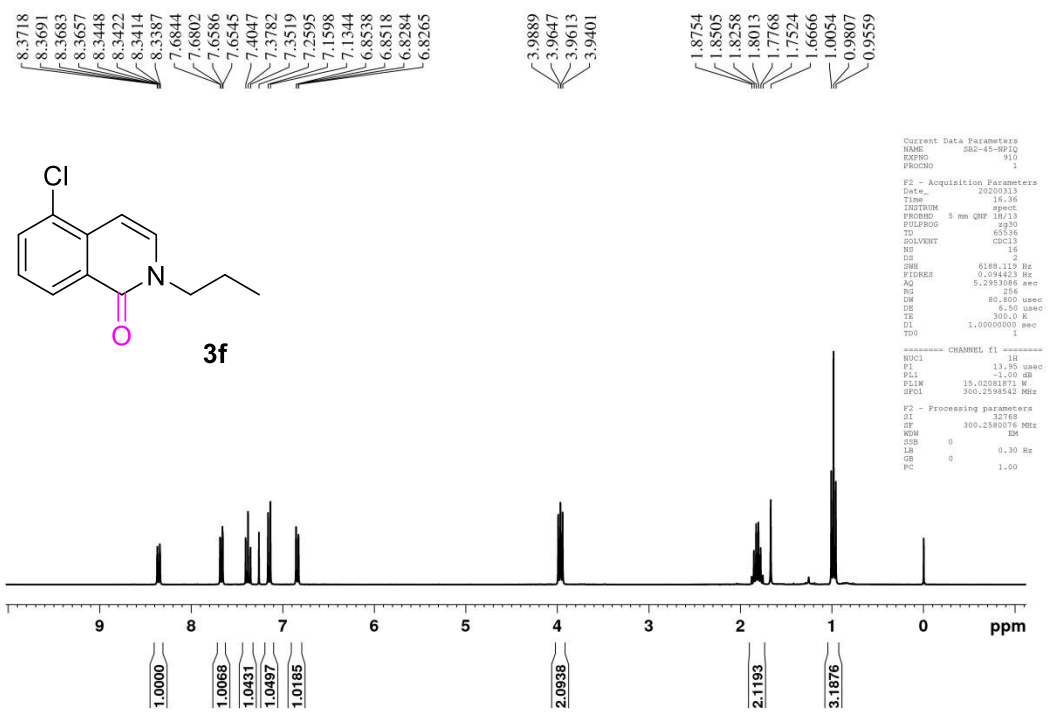
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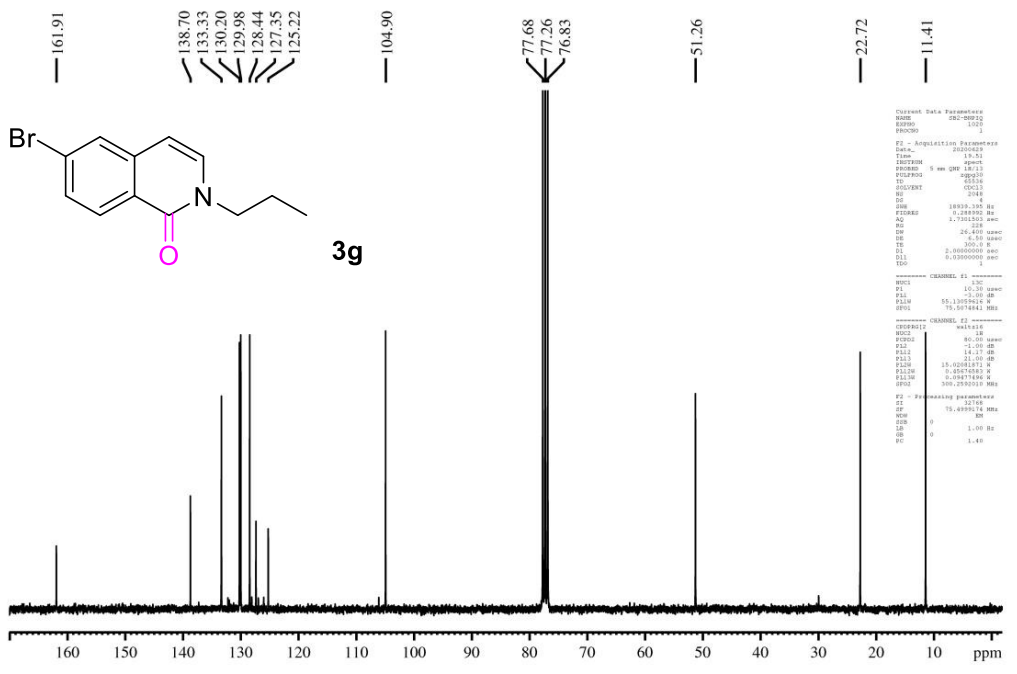
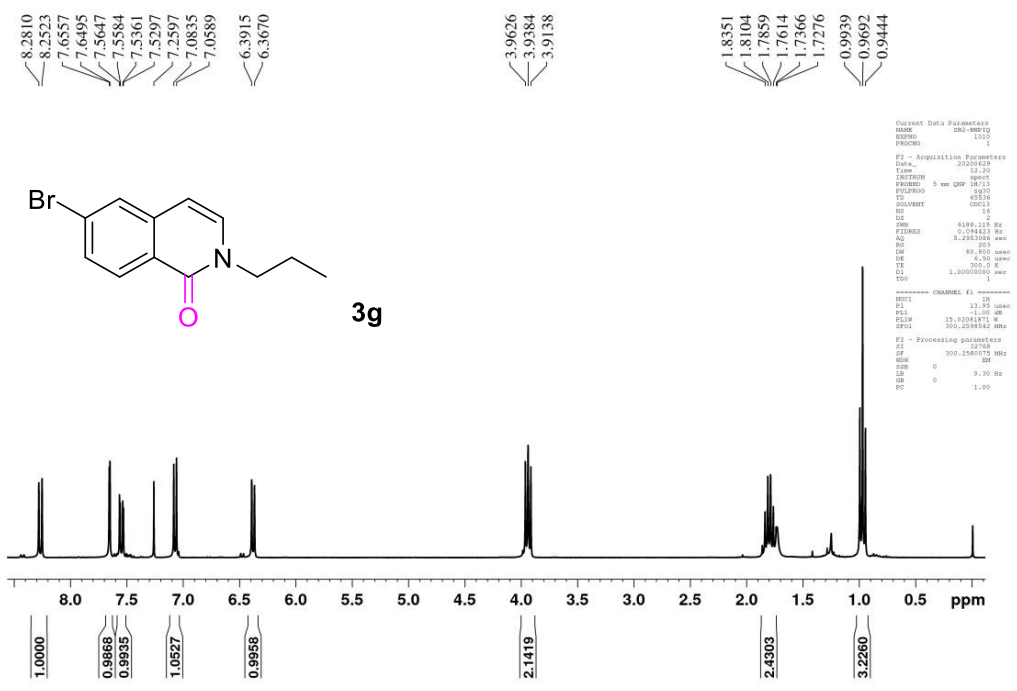
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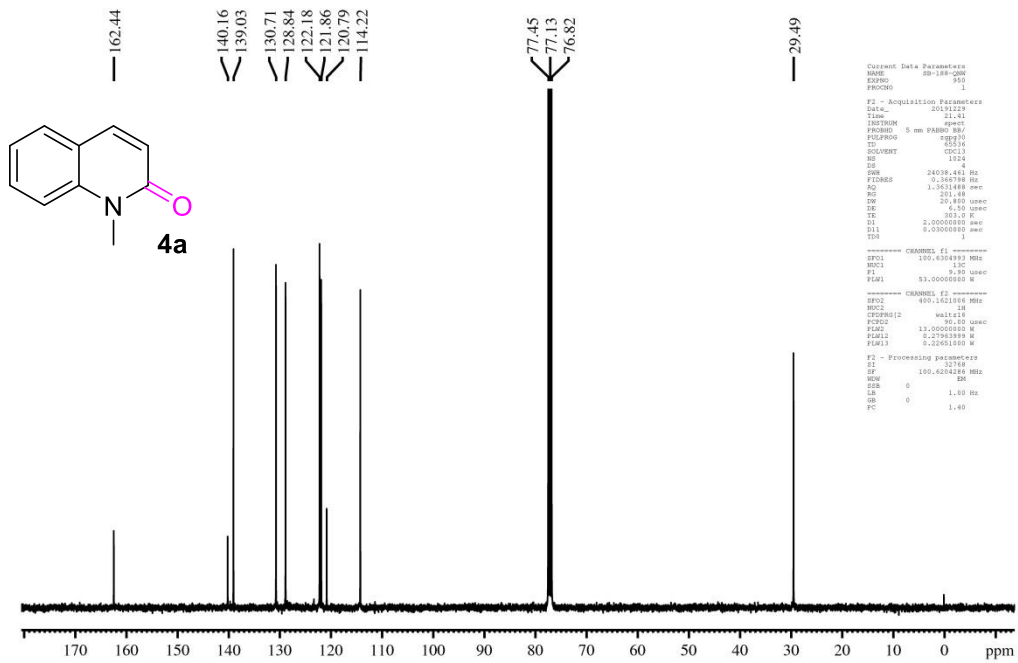
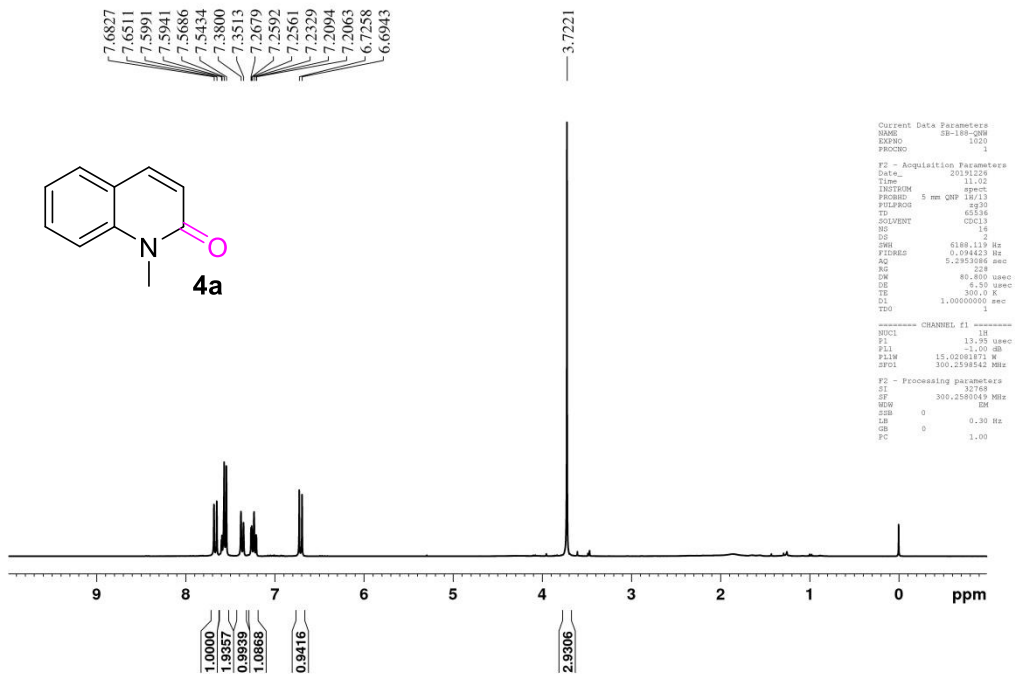


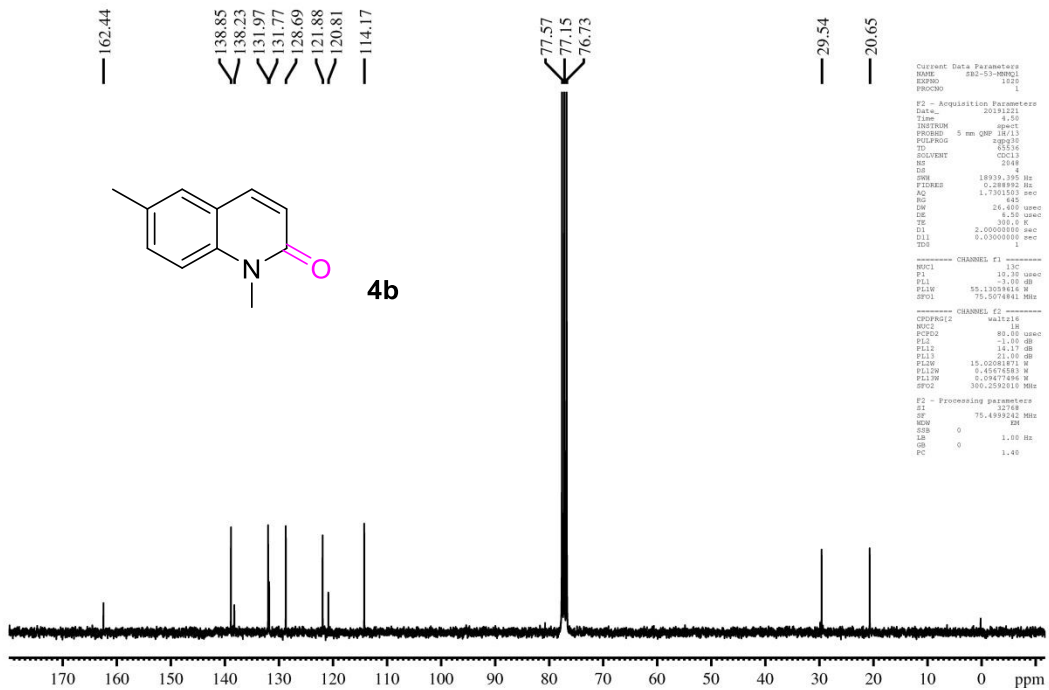
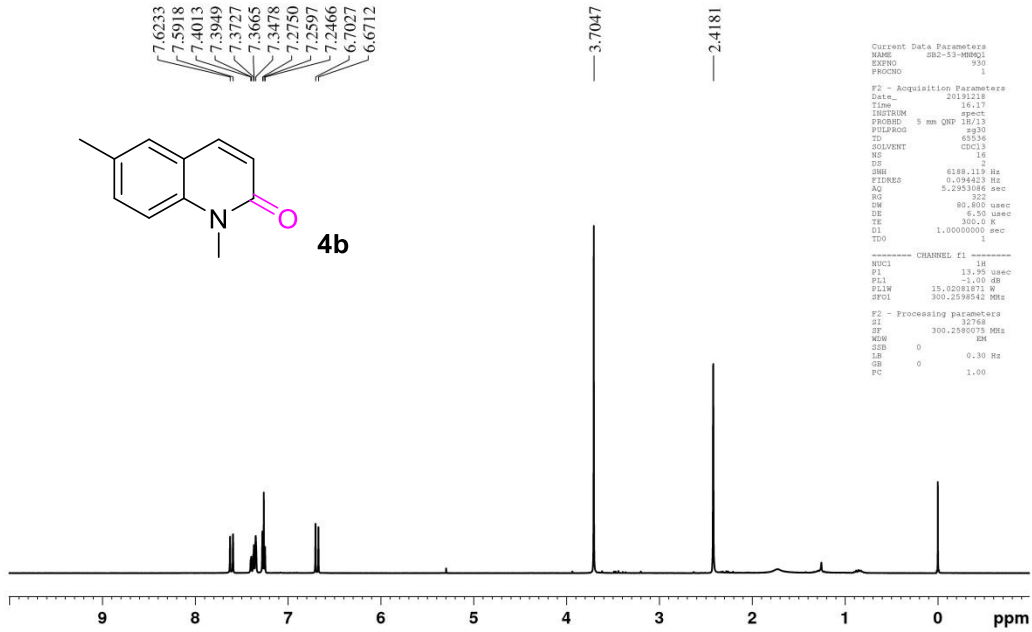


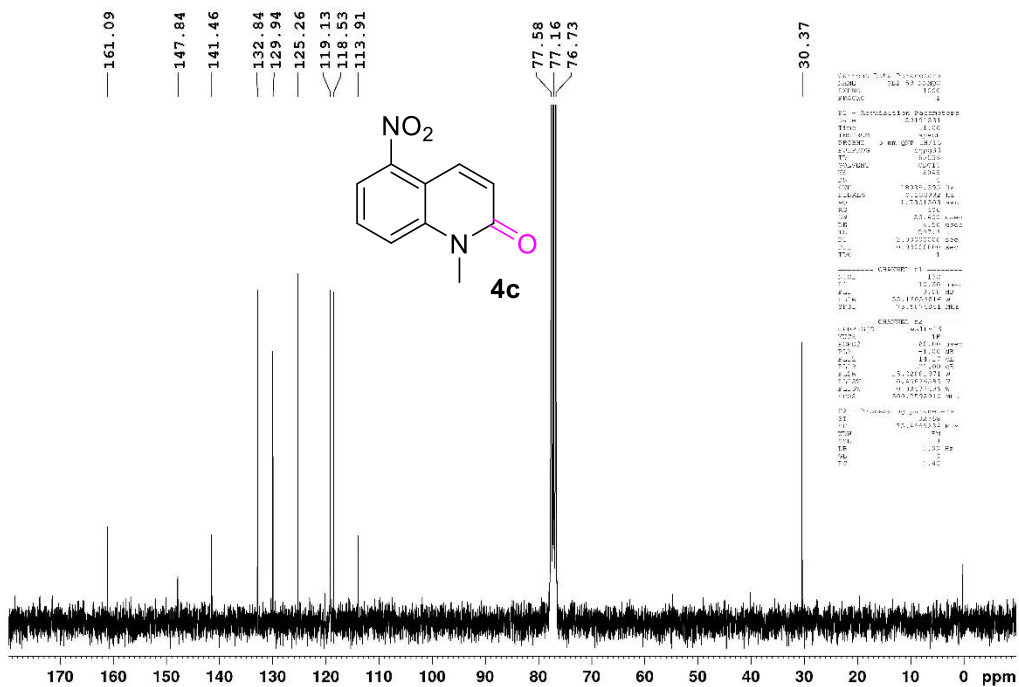
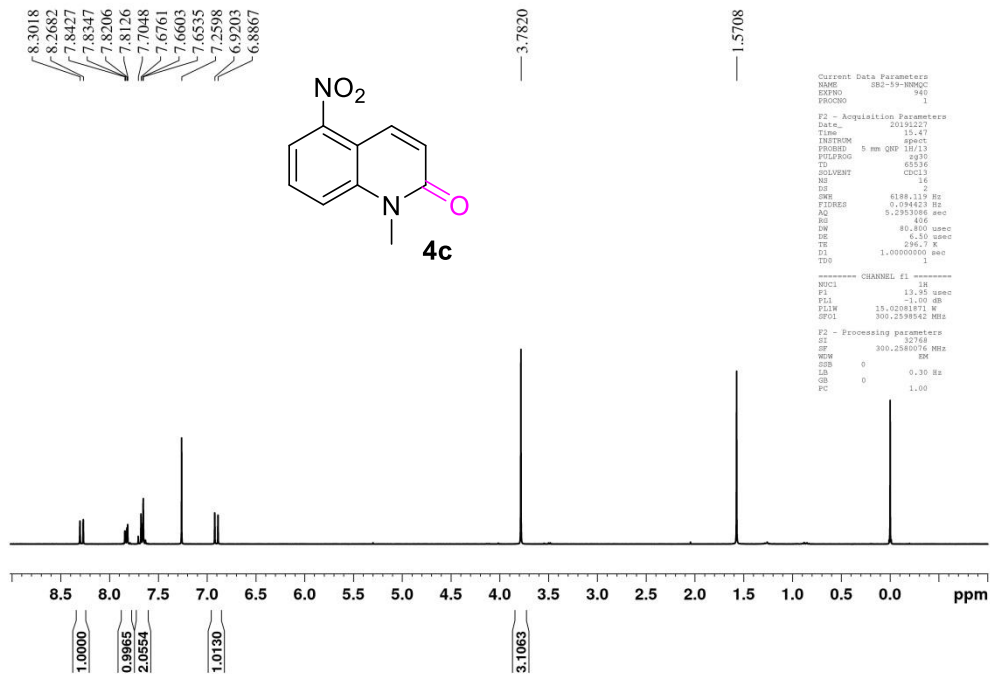


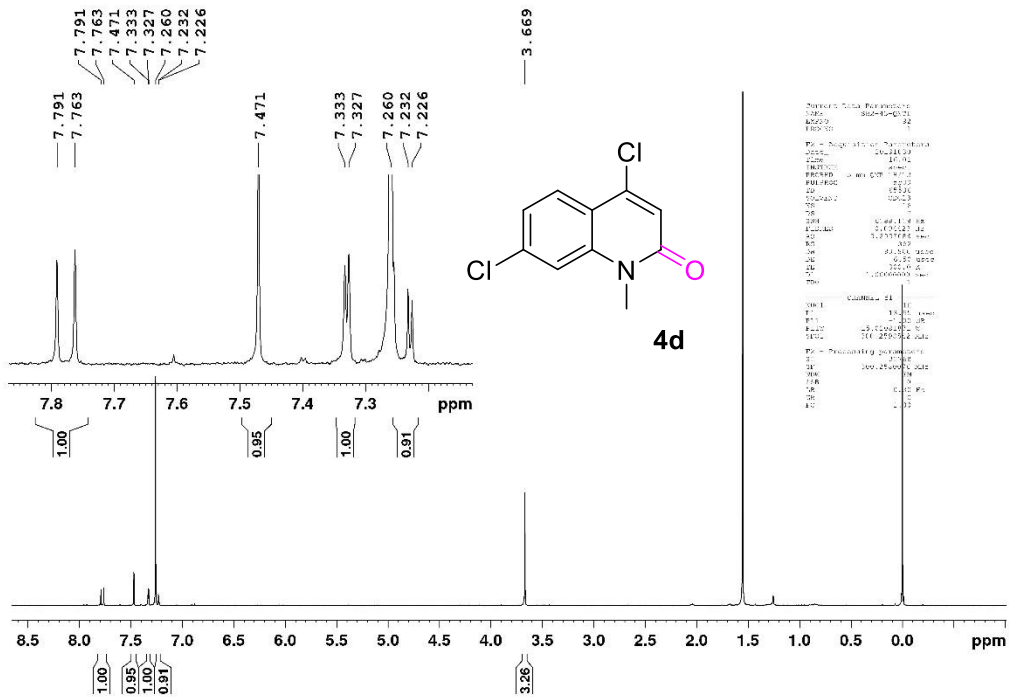






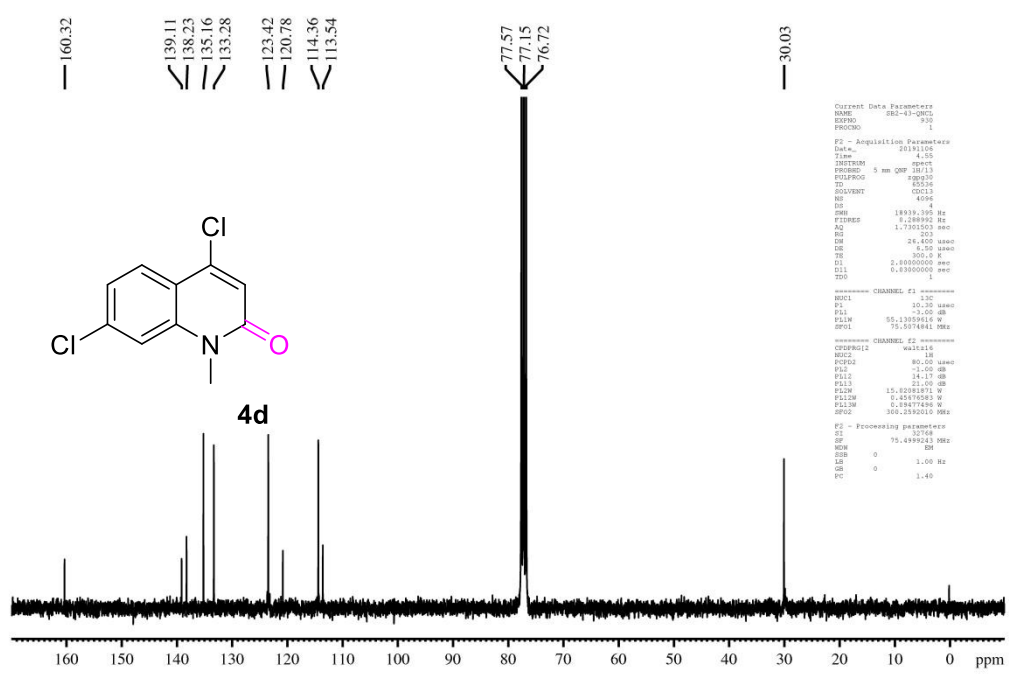






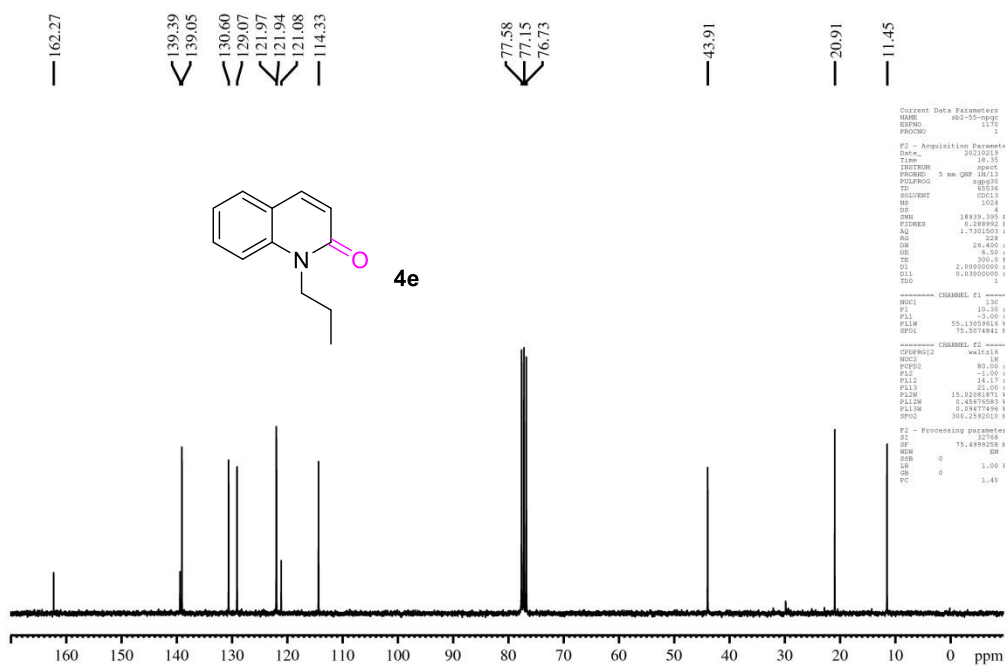
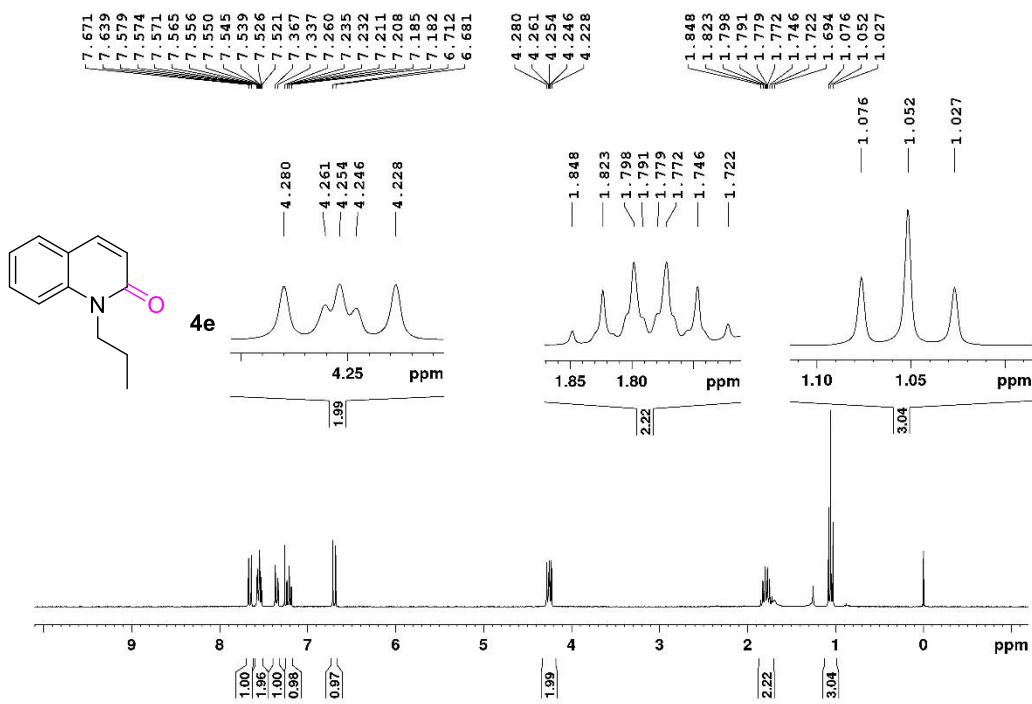
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DCL          2.0000000 sec
DIL          0.0300000 sec
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PL2          -1.00 dB
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PL13         14.17 dB
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PL15         0.45870583 W
PL16         0.2887460 W
SFO2         400.1436010 MHz

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