Supporting Information

Photoredox Catalysis in a Complex Pharmaceutical Setting: Toward the Preparation of JAK2 Inhibitor LY2784544

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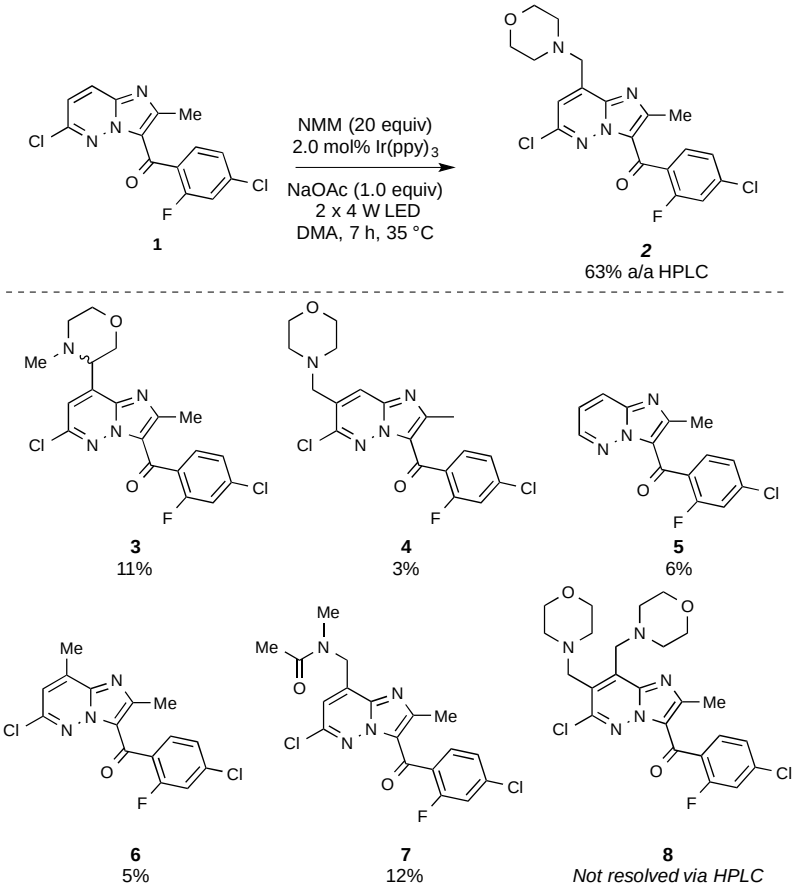
1.0 Initial reaction conditions and HPLC data



Scheme S1. The initial reaction with identified components via HPLC

To a 25 mL round bottom flask (RBF) open to air was added **1** (125 mg, 0.386 mmol, 1.0 equiv), Tris[2-phenylpyridinato-C^2,*N*]iridium(III) ($Ir(ppy)_3$) (5.00 mg, 0.008 mml, 0.02 equiv), sodium acetate (32.0 mg, 390 mmol, 1.0 equiv), DMA (2.5 mL) and *N*-methylmorpholine (0.850 mL, 7.71 mmol, 20 equiv) and the yellow heterogeneous solution was irradiated with 2 × 4 W LED strips placed in a circular loop around the flask. Aluminum foil was placed over the lights around the flask to contain the light (see figure S1). After 1 h the internal temperature of the flask had stabilized at 35 °C. The reaction was monitored via HPLC using an Agilent 1090 fitted with a Eclipse XDB-C8 ZORBAX 993967-90 4.6 x 150 mm column running a gradient of water (0.1% TFA v/v) to 80% Water:MeCN (0.1% TFA v/v) with the detector set to 260 nm.

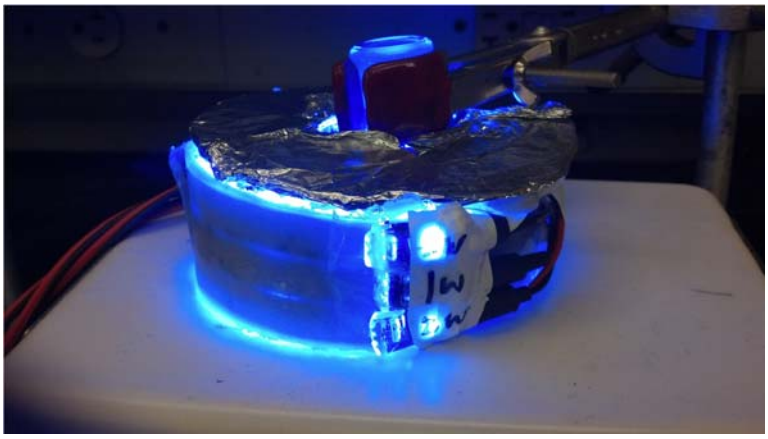


Figure S1. The initial reaction set up with 2 × 4 W LED strips.

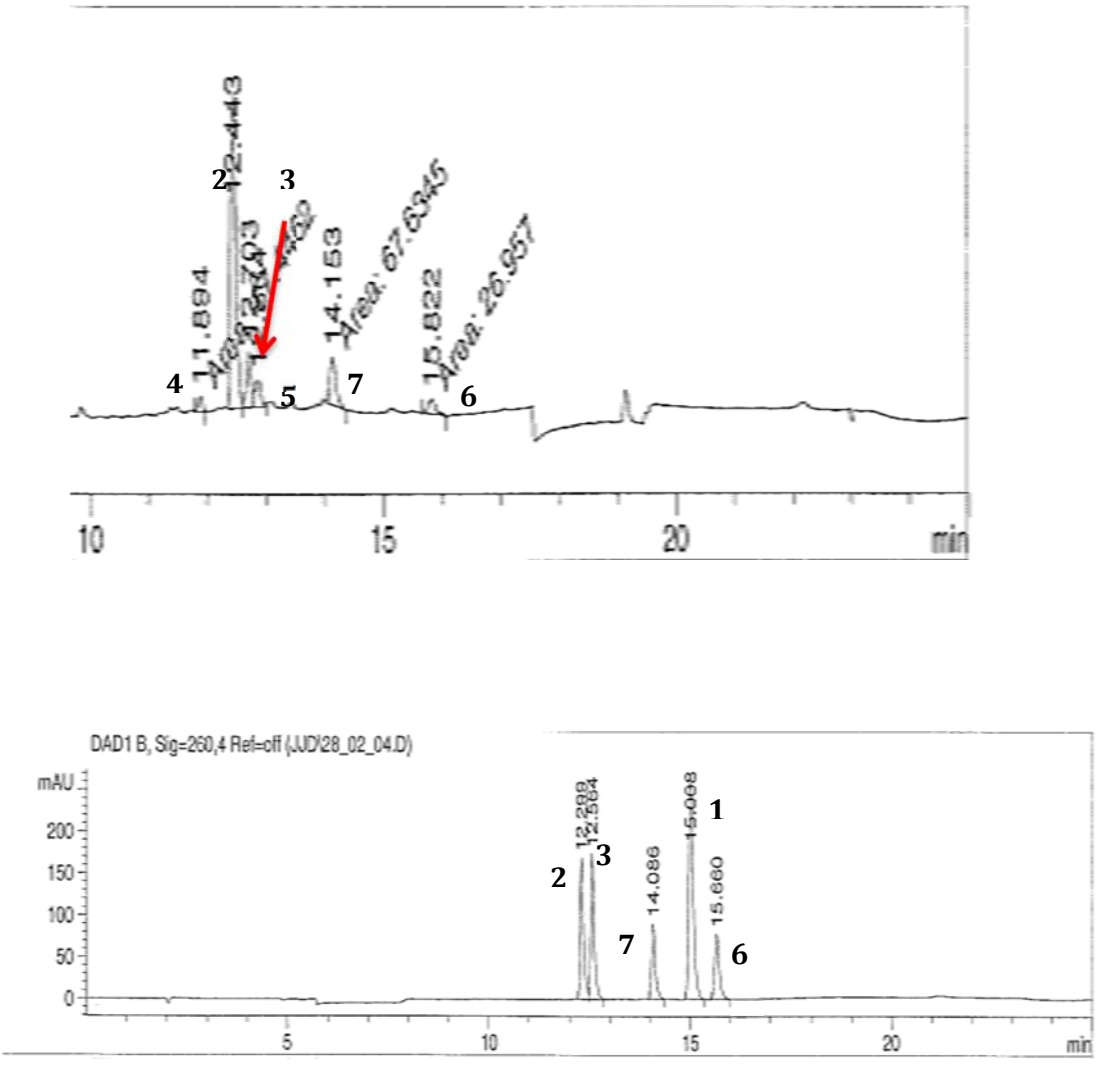


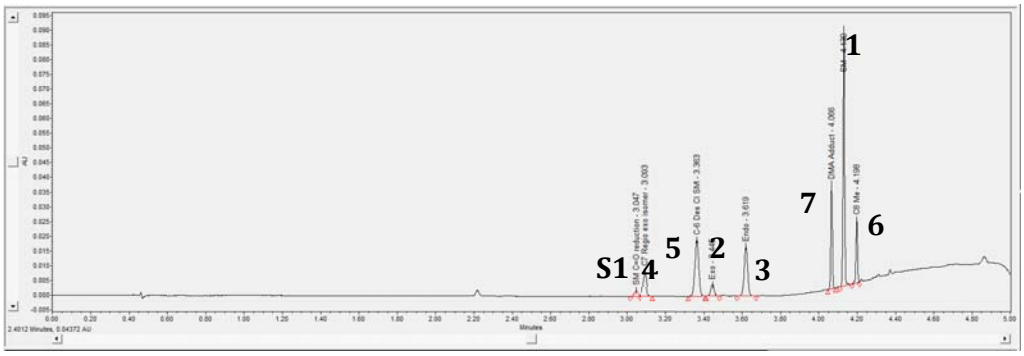
Figure S2. HPLC trace and standards

2.0 Additional optimisation information

General procedure for reaction optimisation

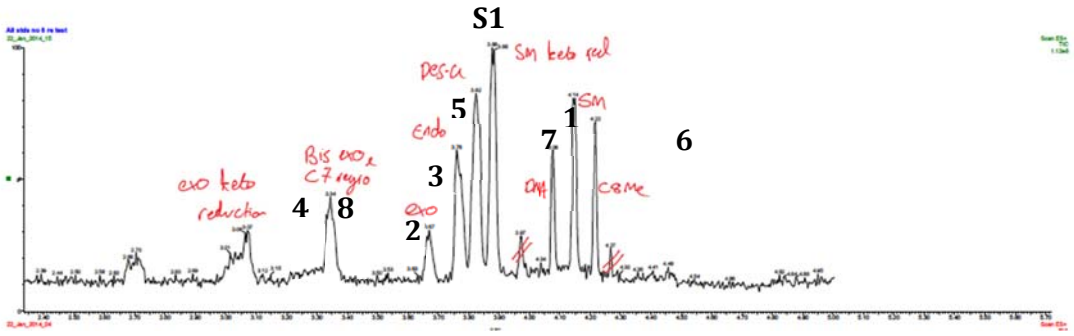
To a 10 mL RBF was added **1** (75.0 mg, 0.231 mmol, 1.0 equiv), sodium acetate (19.0 mg, 0.231 mmol, 1.0 equiv), $Ir(ppy)_3$ (1.50 mg, 2.31 µmol, 0.01 equiv), DMA (1.50 mL) and *N*-methylmorpholine (510 µL, 4.63 mmol, 20 equiv) to give a heterogeneous yellow solution. The flask was placed in a 25 mL jacketed beaker with *i*PrOH as the internal coolant connected to a recirculating heater chiller set to the required temperature. The flask was stirred for 2 min open to air before switching on the stated number of LED strips. (see figure S5) The reaction was monitored via UPLC and after a given time worked up with the addition of EtOAC (50 mL) followed by washing with water (50 mL) and 5% LiCl (2 × 25 mL). The organic phase was then dried (Na_2SO_4) and concentrated *in vacuo* to give a crude product that was purified via automated column chromatography under the stated conditions.

In situ yields were calculated by obtaining a concentration of the requisite analyte (20 µL reaction sample) via a UPLC calibration curve (5 individual points of 3 separate samples) and calculating yield *via* the known volume of the reaction. At ≤20 °C no significant loss of volume due to either NMM or DMA evaporation was observed. UPLC methods were created for both a Waters® Acuity H-Class UPLC fitted with a PDA or QDA mass detector accordingly.



	Name	Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type
1	SM C=O reduction	3.047	0.550	1.145	SM C=O reduction	0.636		James1	2624	1.79	2115	VV		mg/ml	Found
2	C7 Regio exo isomer	3.093	0.822	0.593	C7 regio exo isomer	0.181		James1	10340	7.06	8583	VB		mg/ml	Found
3	C-6 Des Cl SM	3.363	0.420	0.387	C-6 Des Cl SM	0.407		James1	26872	18.35	19251	BB		mg/ml	Found
4	Exo	3.445	0.487	1.058	Exo	0.266		James1	5040	3.44	3995	BV	0.003	mg/ml	Found
5	Endo	3.619	0.192	0.434	Endo	0.102		James1	21498	14.68	17007	VV		mg/ml	Found
6	DMA Adduct	4.066	1.423	0.319	DMA Adduct	0.679		James1	19716	13.46	35813	BB		mg/ml	Found
7	SM	4.130	0.228	0.259	SM	0.253		James1	48355	33.02	88504	VV	0.019	mg/ml	Found
8	C8 Me	4.198	0.801	0.405	C8 Me	0.791		James1	11992	8.19	21874	VV		mg/ml	Found

Figure S3. UPLC standards and example of peak matching/purity information



Example of peak resolution via mass selection of 422

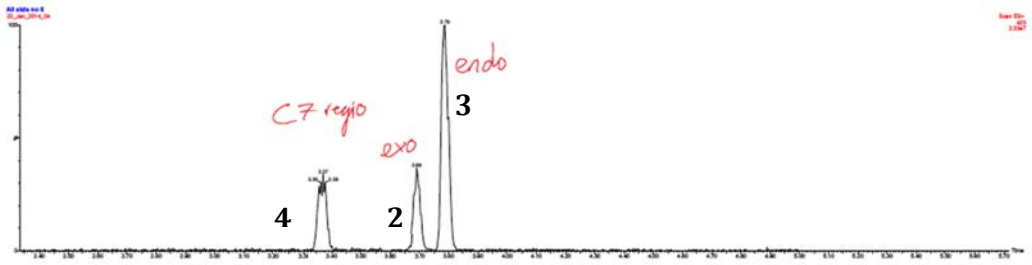
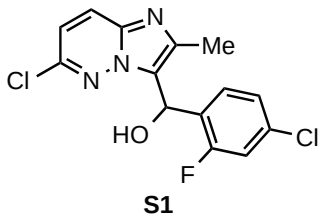


Figure S4. UPLC mass detection (QDa) showing standards and mass selection.

(4-chloro-2-fluorophenyl)(6-chloro-2-methylimidazo[1,2-*b*]pyridazin-3-yl)methanol. S1



S1

The formation of this impurity was hypothesized but not observed.

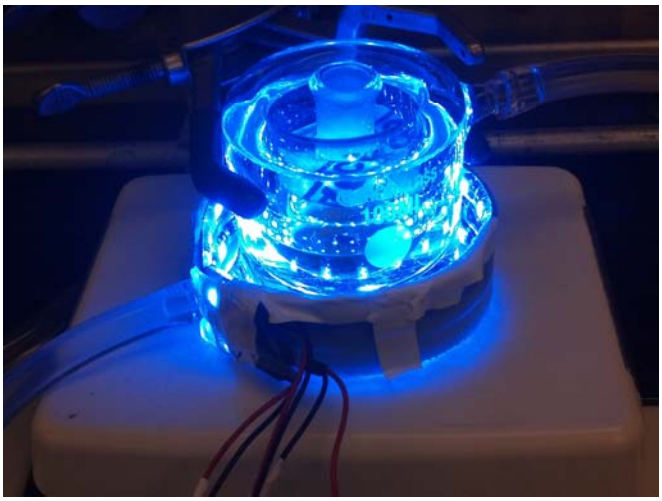


Figure S5. Reaction set up with jacketed beaker and chiller.

At 0 °C condensation was formed on the outside of the beaker on humid days. This had no apparent effect on reactivity. Further lowering the temperature to –5 °C caused significant ice formation overnight and prevented efficient reactions at this temperature.

Table 1 Entry 2
Using 0.231 mmol of 1 with a 1 W LED light strip at 5 °C for 8 h

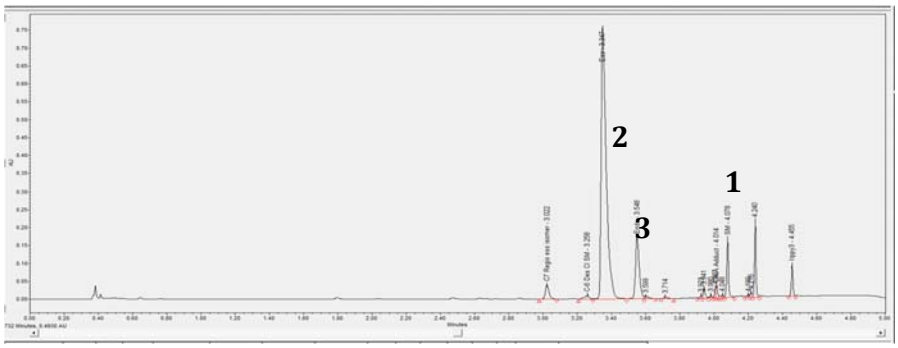


Figure S6. UPLC trace for Table 1 Entry 2

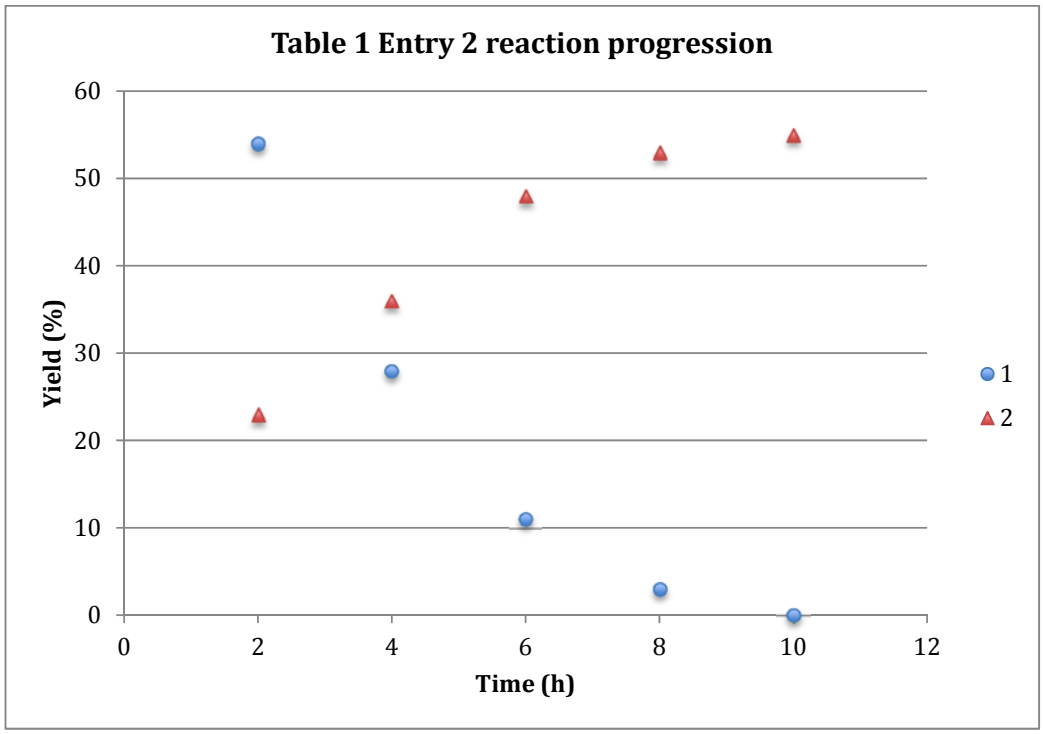


Figure S7. Reaction progression (yield of **1** and **2**) of Table 1 Entry 2.

Table 1 Entry 3

Using 0.50 mmol of **1** with a 1 W LED light strip at 22 °C for 16 h

Figure S8. Showing the similar surface area of the standard reaction (0.231 mmol) and a reaction at twice the scale (0.5 mmol).

2.1 Reactions on different scale with the same surface area (cm^2/mmol)

Reaction performed on a 0.13 mmol scale in a 21 mm diameter vial (27 cm^2/mmol) for 16 h.

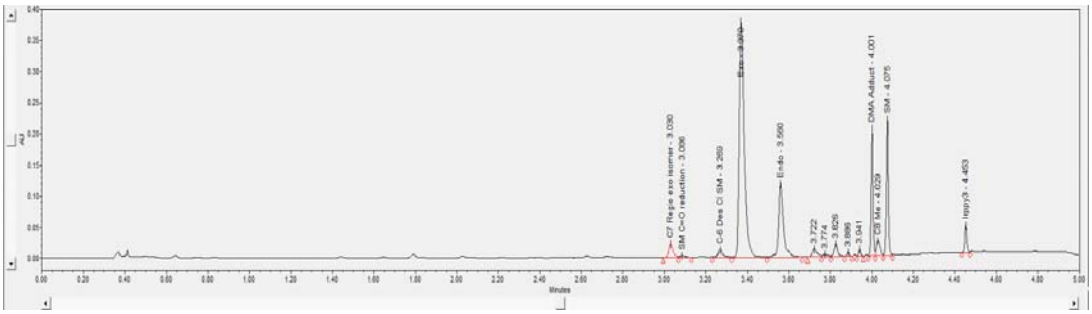


Figure S9. 0.13 mmol scale in a 21 mm diameter vial (27 cm^2/mmol)

Reaction performed on a 0.22 mmol scale in a 27 mm diameter vial (26 cm^2/mmol) for 16 h.

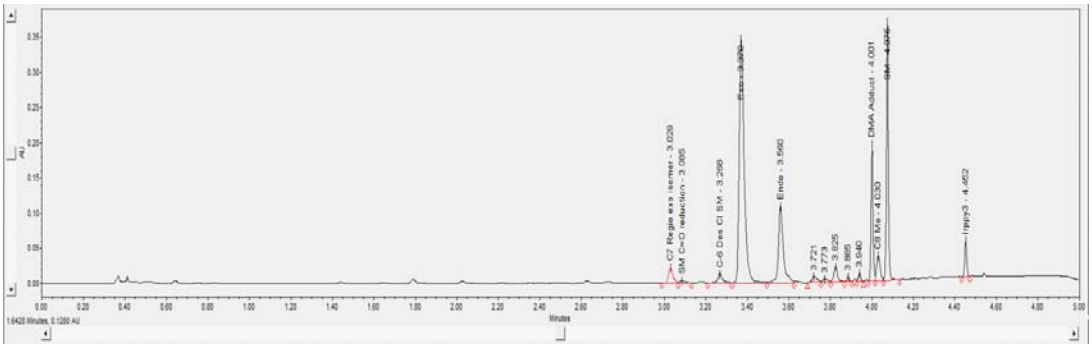


Figure S10. 0.22 mmol scale in a 27 mm diameter vial (26 cm^2/mmol)

2.2 Variation of light source

Calculated yields of **1** and **2**. Known compounds are the total of crude % a/a. 35 W LED corresponds a LED puck (http://www.luxeonstar.com/Royal-Blue-447-5nm-7-LED-40mm-Round-Assembly-p/sr-02-r0425.htm)

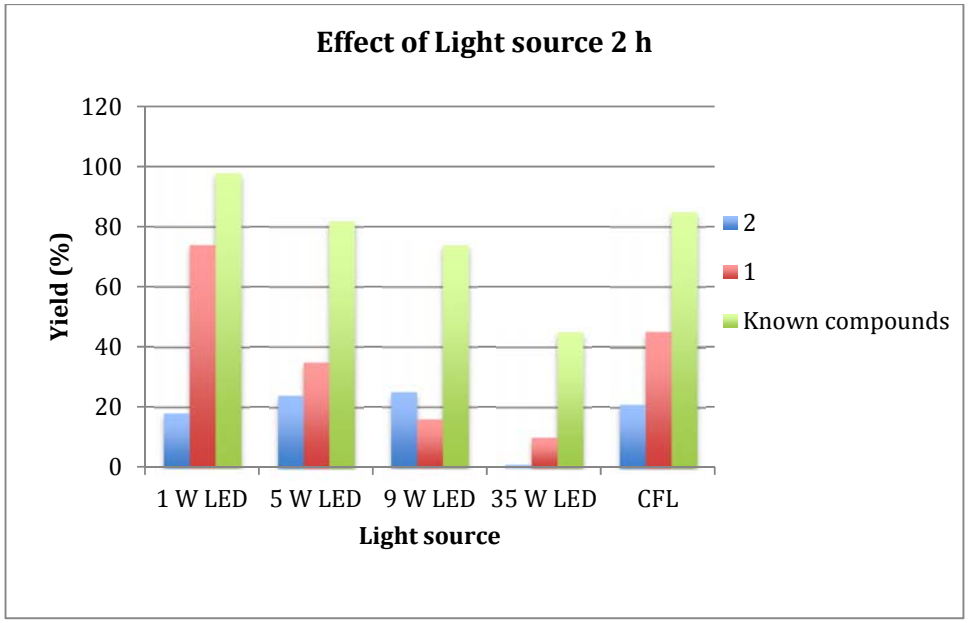


Figure S11. Showing the effect of light source after 2 h.

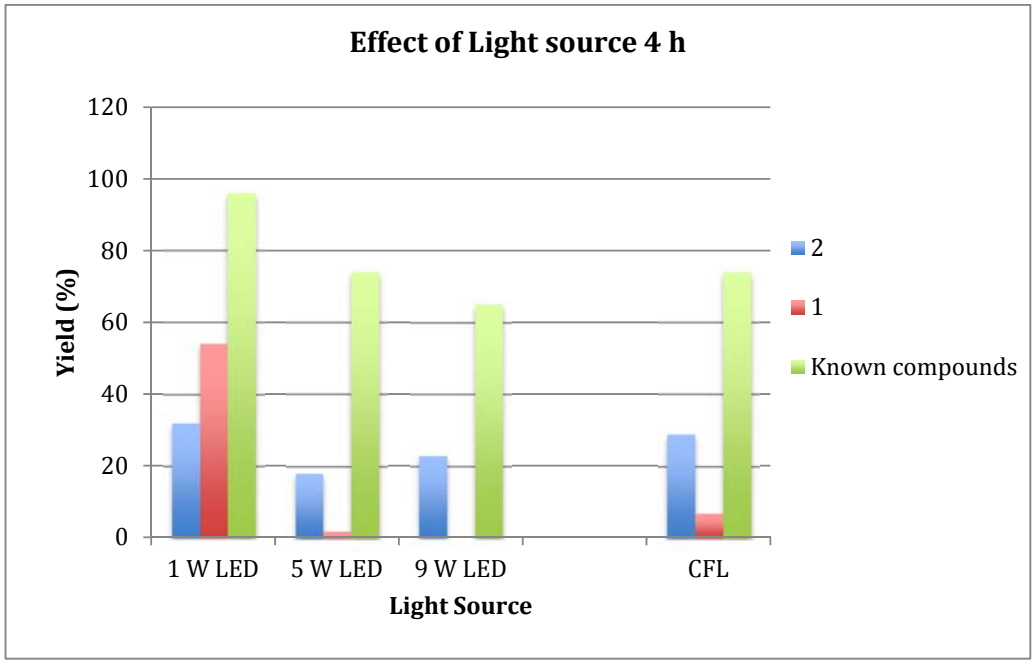
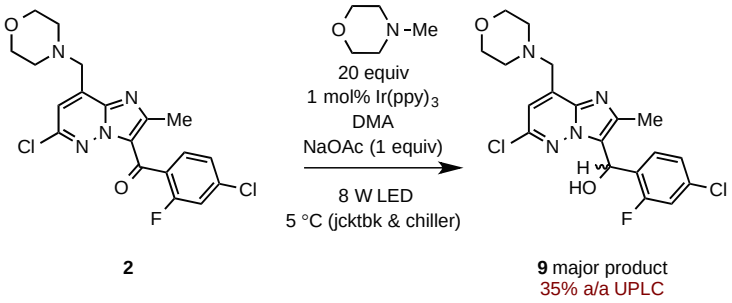


Figure S12. Showing the effect of light source after 4 h.

3.0 Exo degradation studies.



2

9 major product
35% a/a UPLC

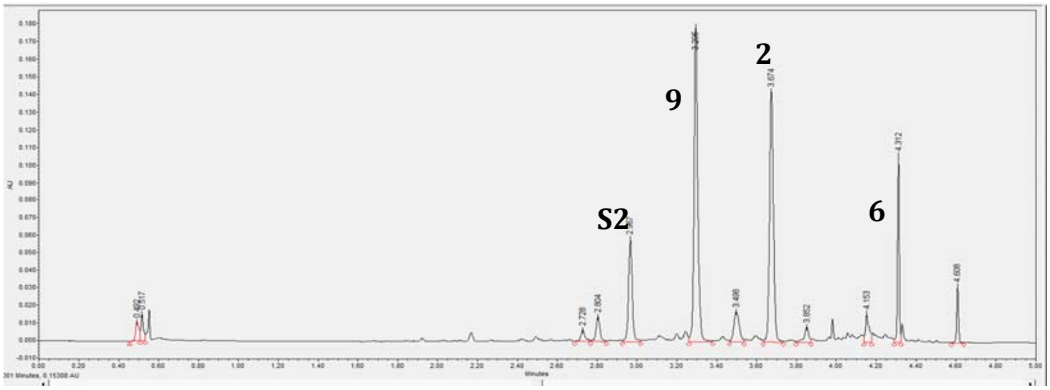
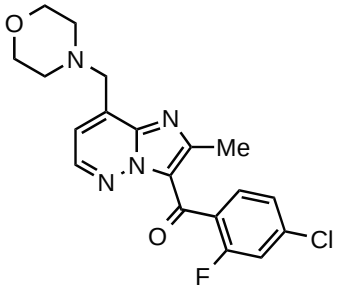


Figure S13. Crude UPLC trace showing **9** as the major product of degradation of **2**.

(4-chloro-2-fluorophenyl)(2-methyl-8-(morpholinomethyl)imidazo[1,2-*b*]pyridazin-3-yl)methanone S2



S2

S2 was identified via UPLC mass spec and ^{1}H NMR spectroscopy analysis of the crude reaction mixture. The high polarity of **S2** and **9** made isolation difficult.

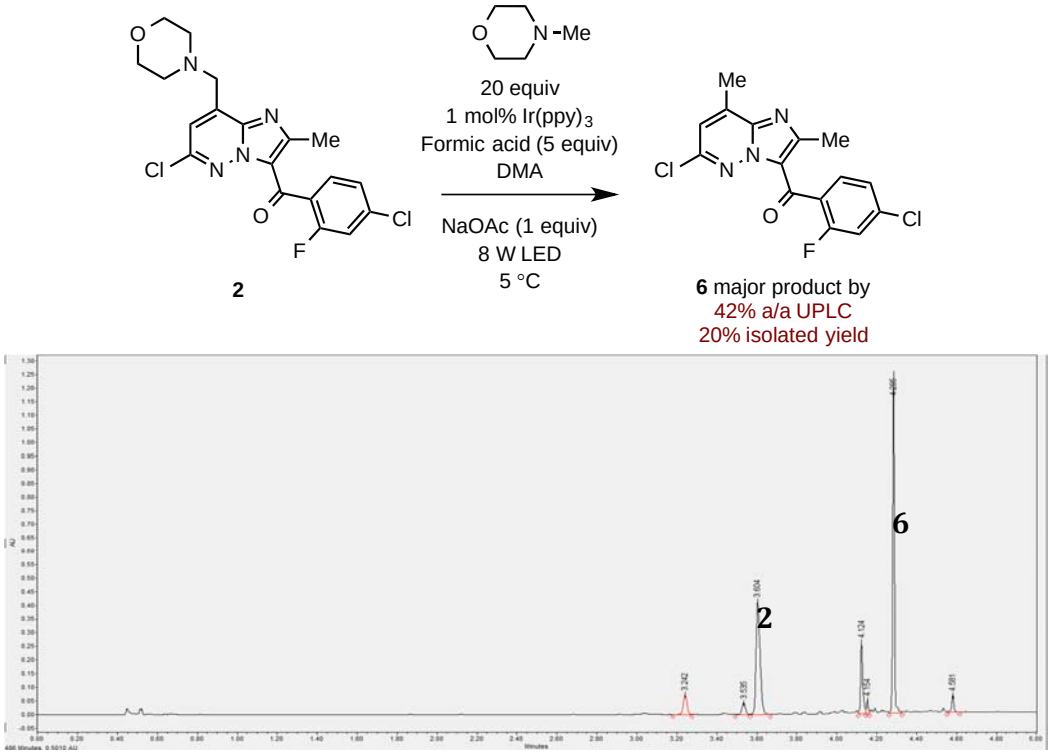


Figure S14. Crude UPLC trace showing **6** as the major product of degradation of **2**.

4.0 Effect of base

Table S1: Effect of base

Entry	Base	NMM (equiv)	Yield of **2**[a]	Yield of **1**[a]	*exo*:*endo* ratio[a]
1	NaOAc	20	53	<5	5.1:1
2	None	20	41	17	3.8:1
3	K_2HPO_4	20	36	30	3.2:1
4	2,6-lutidine	20	33	30	2.9:1
5	Imidazole	20	22	48	2.1:1
6	DBU	20	<5	>95	N/A
7	$NaHCO_3$	20	33	27	3.6:1
8	K_2CO_3	20	39	17	3.8:1

[a]Reactions performed at a 0.231 mmol scale, at 5 °C with 1.0 mol% $Ir(ppy)_3$, 1.0 equiv of base, 20 equiv of NMM for 8 h unless otherwise stated. [a]Calculated by UPLC (PDA).

The use of NaOMe or KO^{t}Bu as base caused an instant black color and the reaction was not attempted. It is likely that those bases are not compatible with **1**.

5.0 Variation of photocatalyst

Table S2: Variation of photocatalyst

Entry	Photocataylst	Yield of **2**[a]	Yield of **1**[a]	*exo*:*endo* ratio[a]
1[b]	$[Ru(bpy)_3]Cl_2$	<5	86	N/A
2[b]	$[Ru(bpz)_3](PF_6)_2$	<5	86	N/A
3	$Ru(Phen)_3Cl_2$	<5	82	N/A
4	$Ru(bpm)_3Cl_2$	<5	85	N/A
5[c,d]	$Cu(dap)_2$ Cl (2 mol%)	<5 [e]	92 [e]	N/A
6[c]	Fukuzumi Acridinium[f] (2mol%)	8[e]	82	3.9:1
3[c]	Eosin Y (5 mol%)	22	48	3.7:1
4	$Ir(Fppy)_3$	21	48	3.6:1
5	$[Ir(py)_2(dtbbpy)]PF_6$	11	71	2.3:1
6	$[Ir\{(dF(CF_3)ppy)_2(dtbbpy)\}]PF_6$	17	58	2.9:1

[a]Reactions performed at a 0.231 mmol scale, at 5 °C with 1.0 mol% $Ir(ppy)_3$, 1.0 equiv of base, 20 equiv of NMM for 8 h unless otherwise stated. [a]Calculated by UPLC (PDA). [b]Reaction time of 10 h. [c] Reaction time of 15 h. [d] Tested in CH_2Cl_2 and DMA [e]Crude% a/a. [f]See *J. Am. Chem. Soc.*, 2004, **126**, 1600-1601

6.0 Solvent additives effects and the use of DMPU

Reactions were conducted at 22 °C for 16 h on a 0.231 mmol scale using 1 mol% $Ir(ppy)_3$, NaOAc (1.0 equiv) and 10:1 DMA:additive (6.5 mL/mmol).

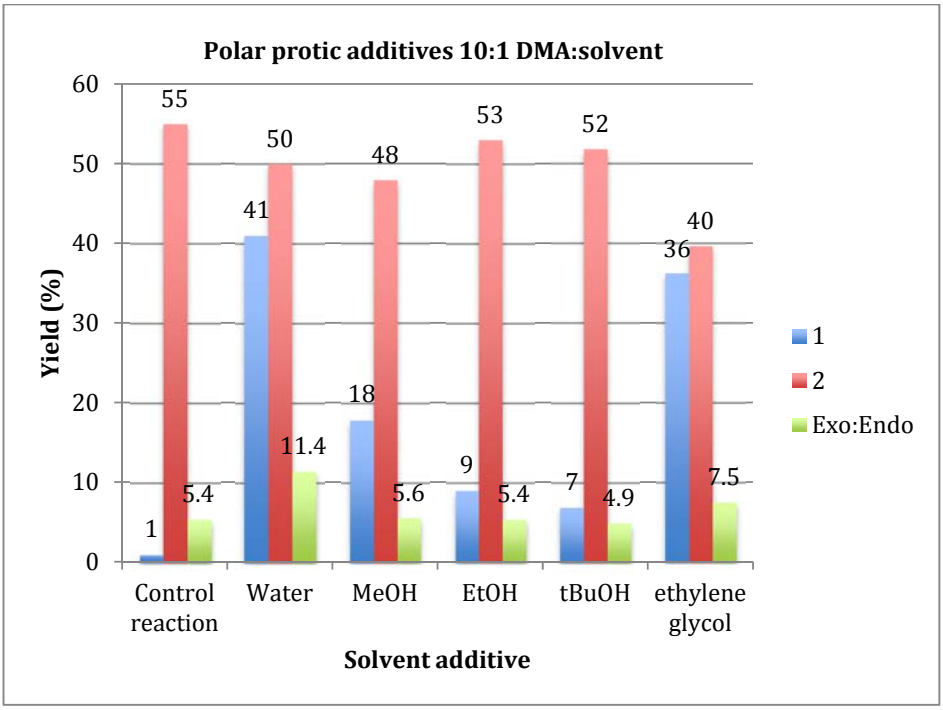
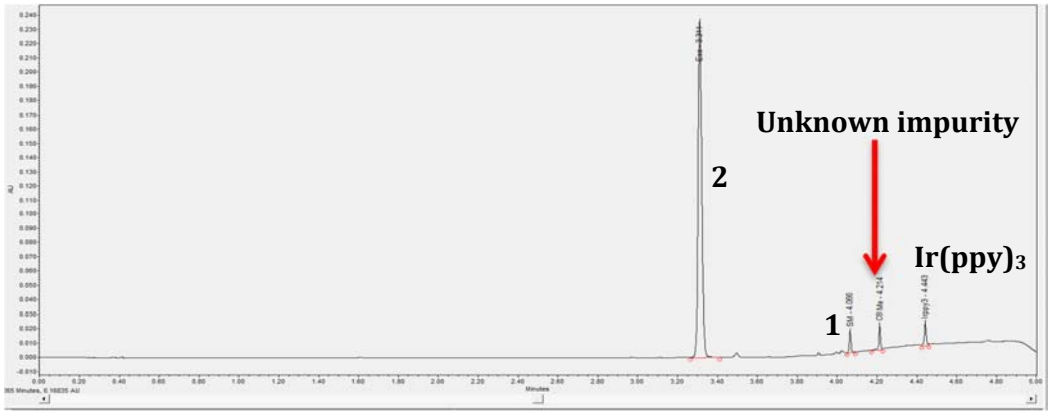
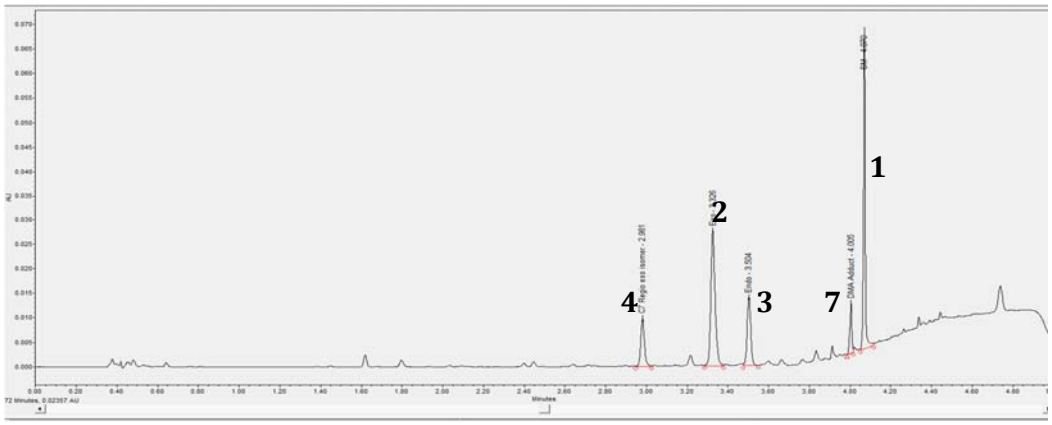


Figure S15. Effect of polar protic solvent additives.

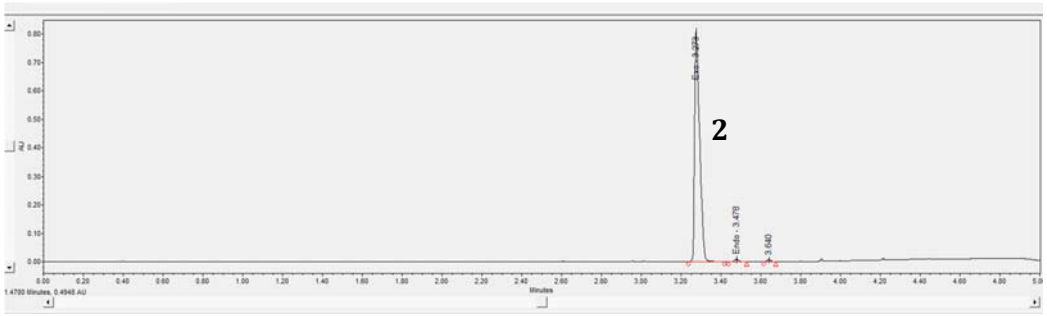
7.0 Final reaction conditions



S16. UPLC trace of solids after filtration.

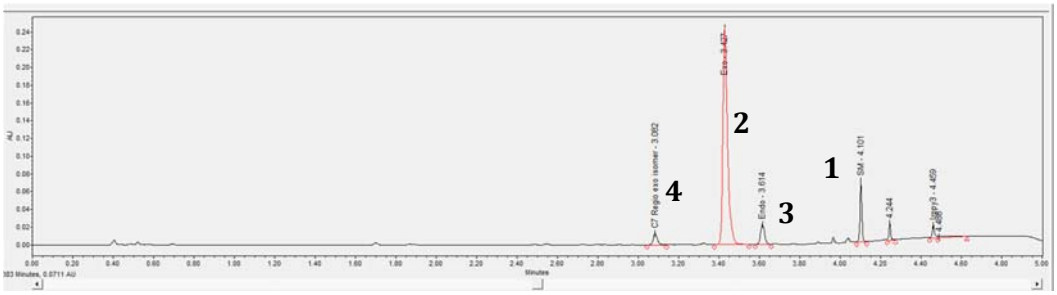


S17. UPLC trace of filltrate after filtration.



S18. UPLC trace of solids after acid base purification.

In one isolated instance using 1.0 mol% $Ir(ppy)_3$ **2** failed to precipitate from the reaction mixture giving an estimate of conversion after 28 h.



S19. UPLC trace of crude reaction mixture that failed to precipitate **2**.

8.0 Chiral HPLC trace for 21

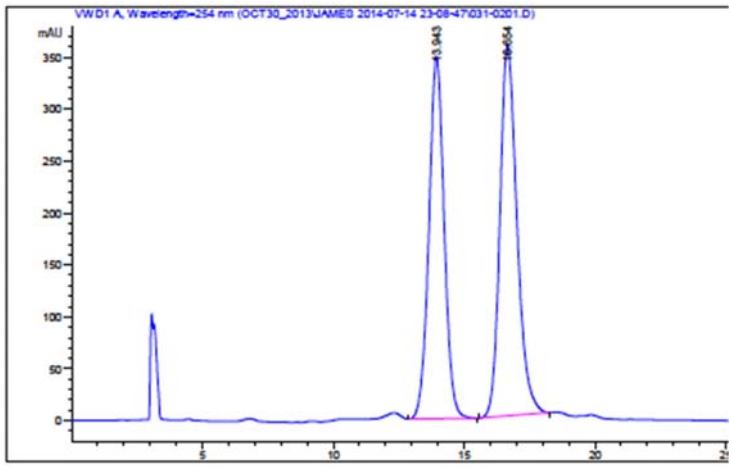
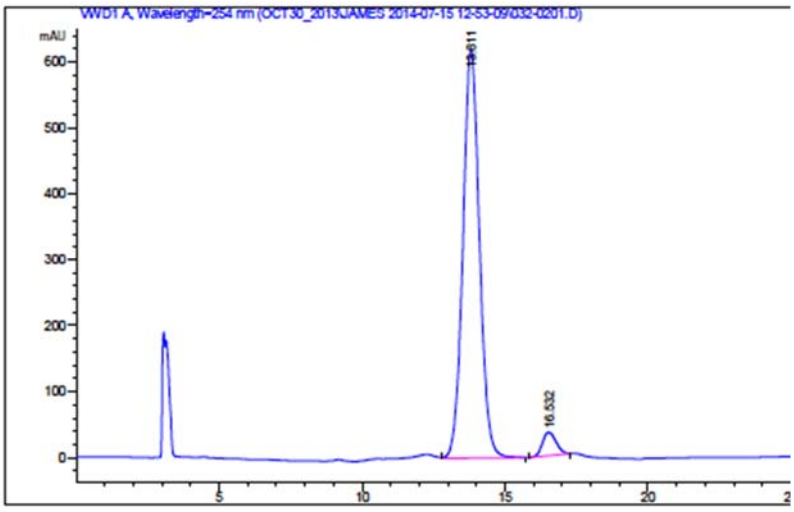


Figure S20. HPLC trace of racemic **21**



Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.811	VB	0.6150	2.48618e4	619.72040	95.5499
2	16.532	BB	0.5183	1157.91333	35.33810	4.4501

Figure S21. HPLC trace of enantioenriched **21**

9.0 Attempted expansion to other heterocycles.

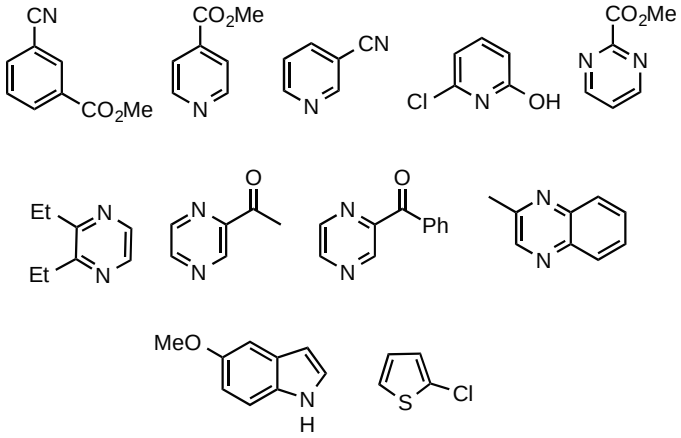


Figure S22. Other arenes and heteroarenes that failed to react.

The use of 3,6-dichloropyridazine with TMEDA led to incomplete conversion and low isolated crude mass recovery. ^{1}H spectroscopic analysis of the crude reaction mixture indicated the formation of the addition product and the formal methylation product. The isolation of these products, and the corresponding NMM addition products was hampered by hydrolysis of one of the chlorines leading to increased aqueous solubility.

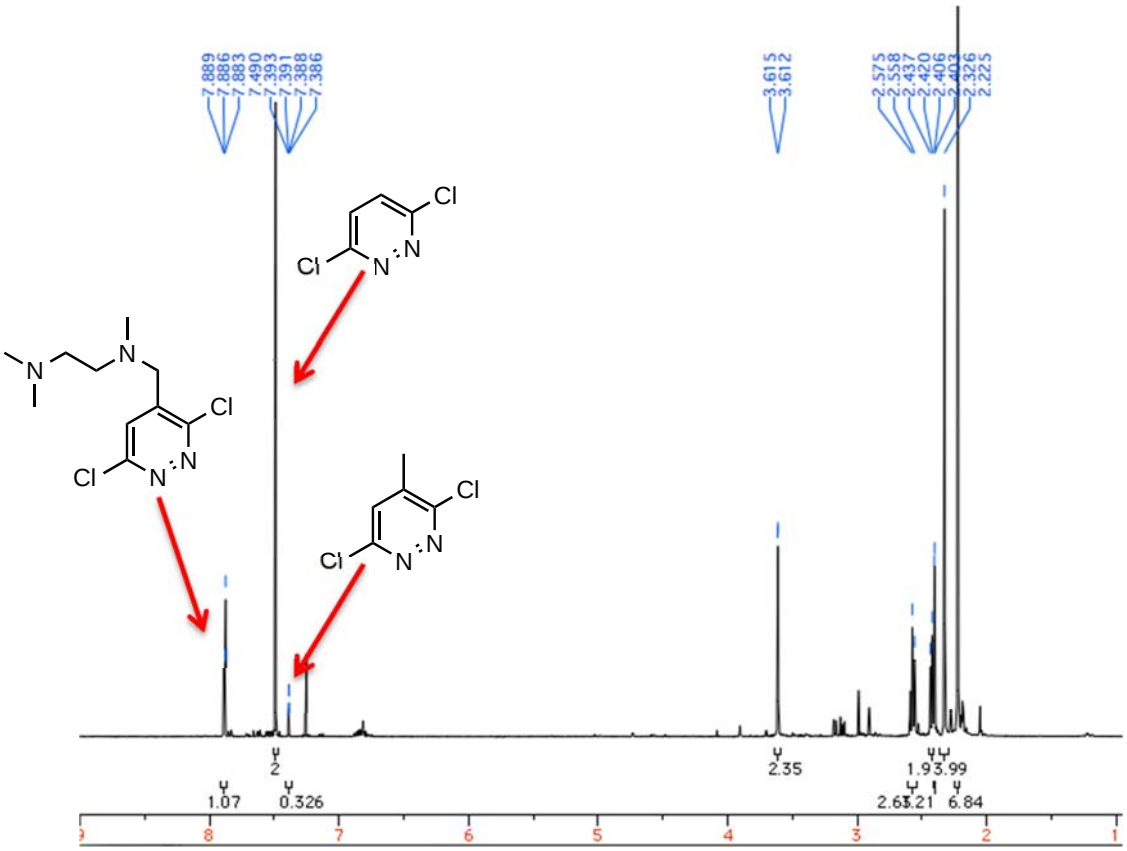


Figure S23. ^{1}H NMR spectrum of the crude reaction of 3,6-dichloropyridazine with TMEDA.

10.0 Quenching studies

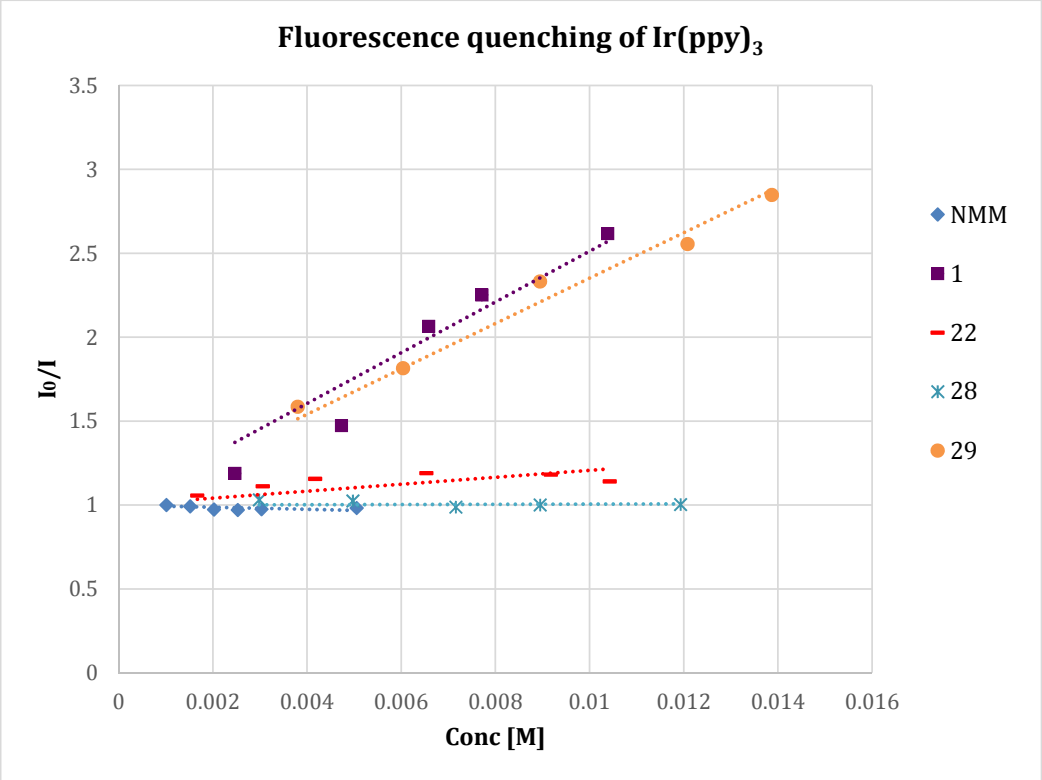


Figure S24. Fluorescence quenching of $Ir(ppy)_3$

All quenching data was recorded in a quartz cuvette with a stir bar at 25 °C with DMA as the solvent with no action taken to exclude oxygen. Excitation was at 450 nm (NMM) or 350 nm (**1**, **22**, **28** and **29**) with emission at 520 nm. At 450 nm fluorescence was observed for **1** and **22**. All values are the average of 3 measurements. It is interesting to note that **22** is reactive but does not quench $Ir(ppy)_3$ under the same concentration as **1.** This may be indicative of different mechanisms available for **1** and **22**.

11.0 Lights-on-lights-off experiment

1 (75.0 mg, 0.231 mmol, 1.0 equiv), sodium acetate (19.0 mg, 0.231 mmol, 1.0 equiv), $Ir(ppy)_3$ (1.50 mg, 2.31 μmol, 0.01 equiv), DMA (1.50 mL) and *N*-methylmorpholine (510 μL, 4.63 mmol, 20 equiv). In periods of the dark the reaction was wrapped in foil to exclude all light. The lights-on-lights-off data is an average of two reactions vs a control run identically at the same time. Data is quoted in crude area/area% UPLC.

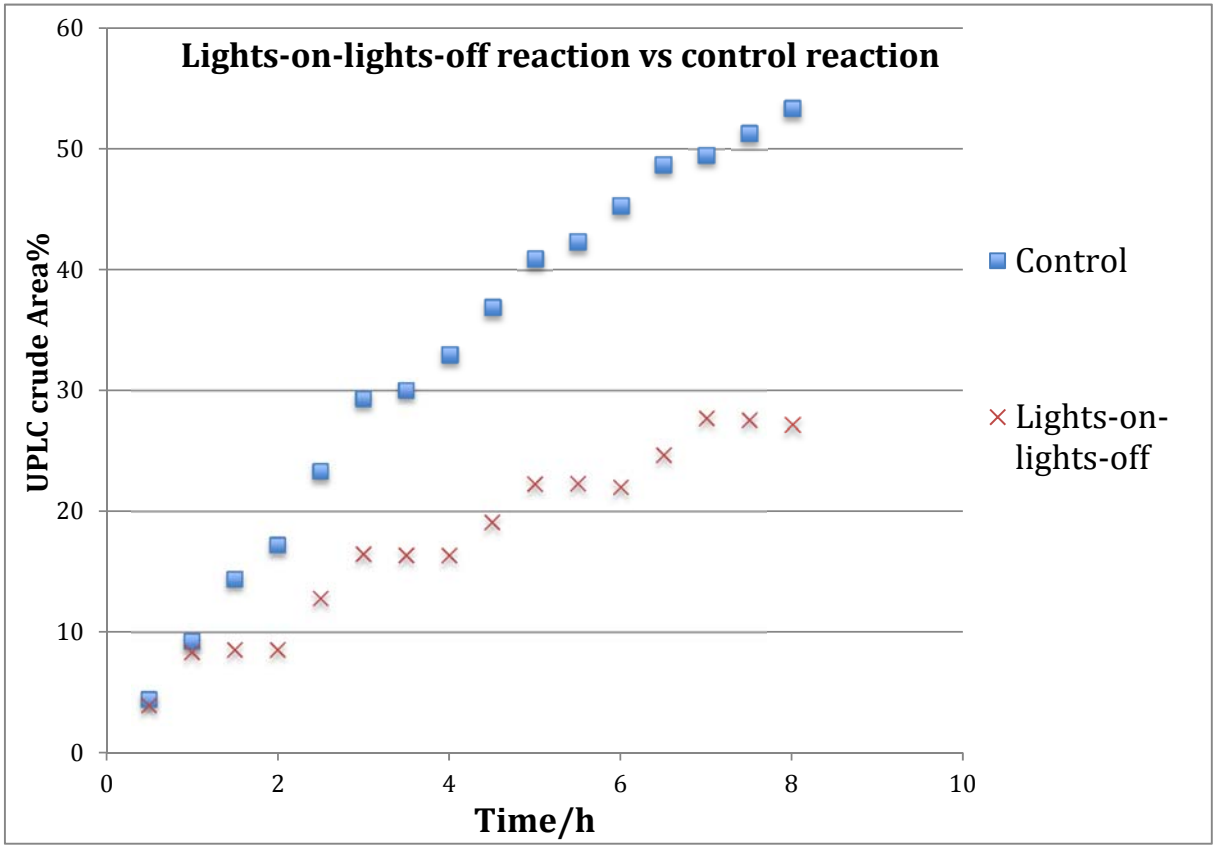
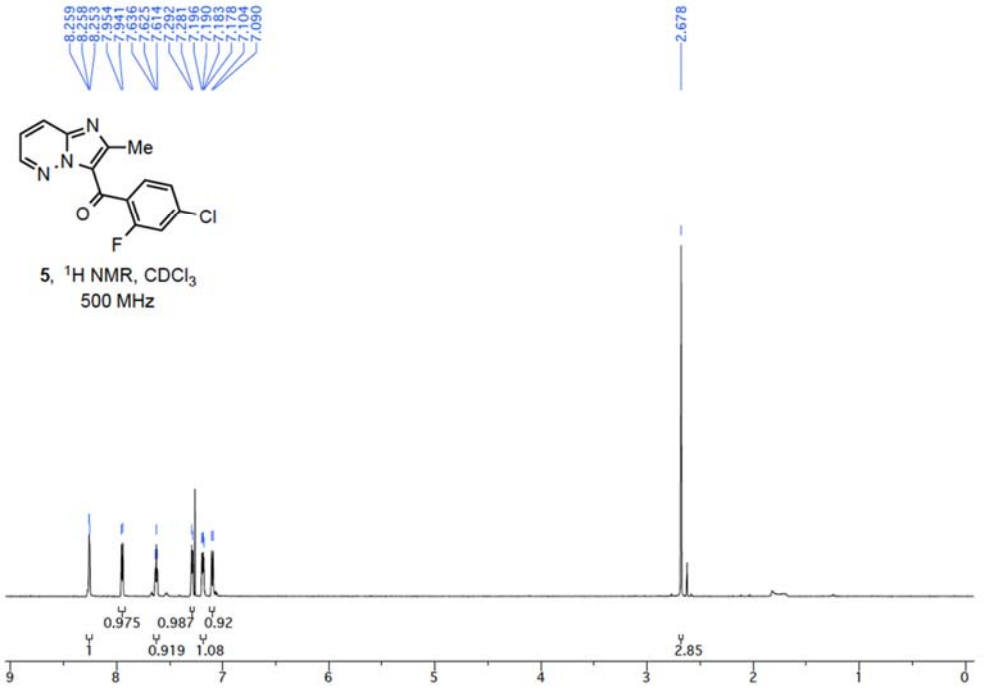
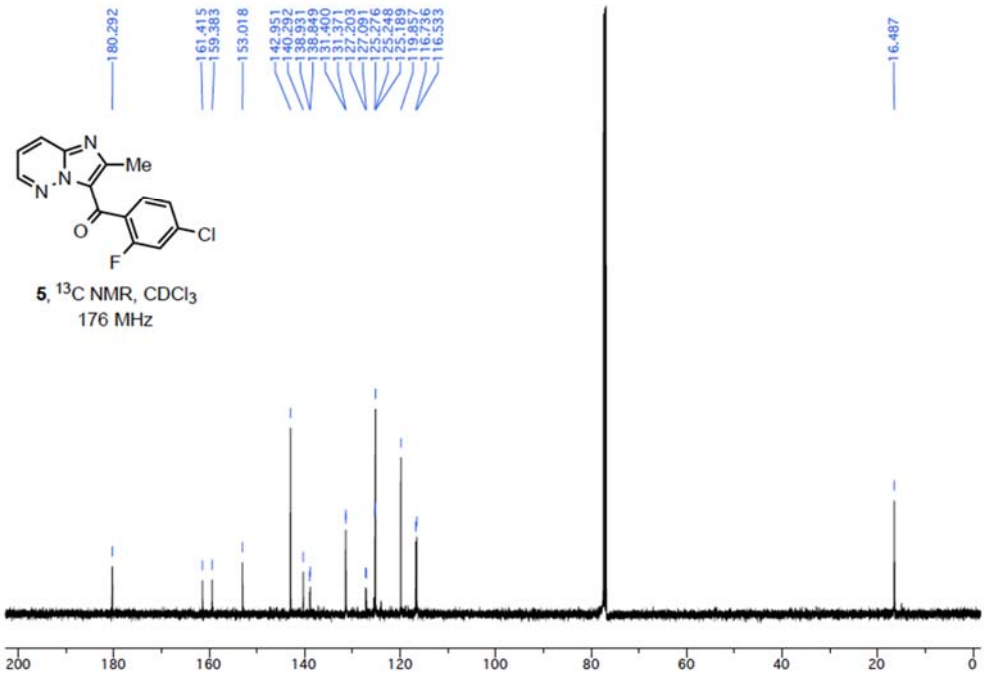


Figure S25. Graph showing UPLC area% Vs time in periods of light irradiation and dark.

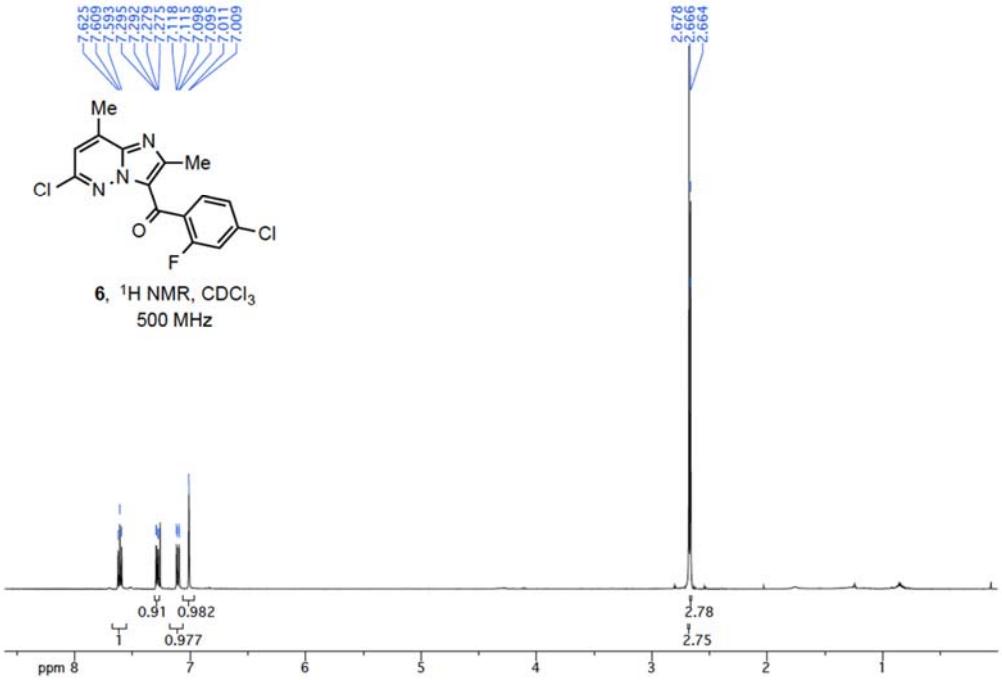
12.0 NMR Spectra



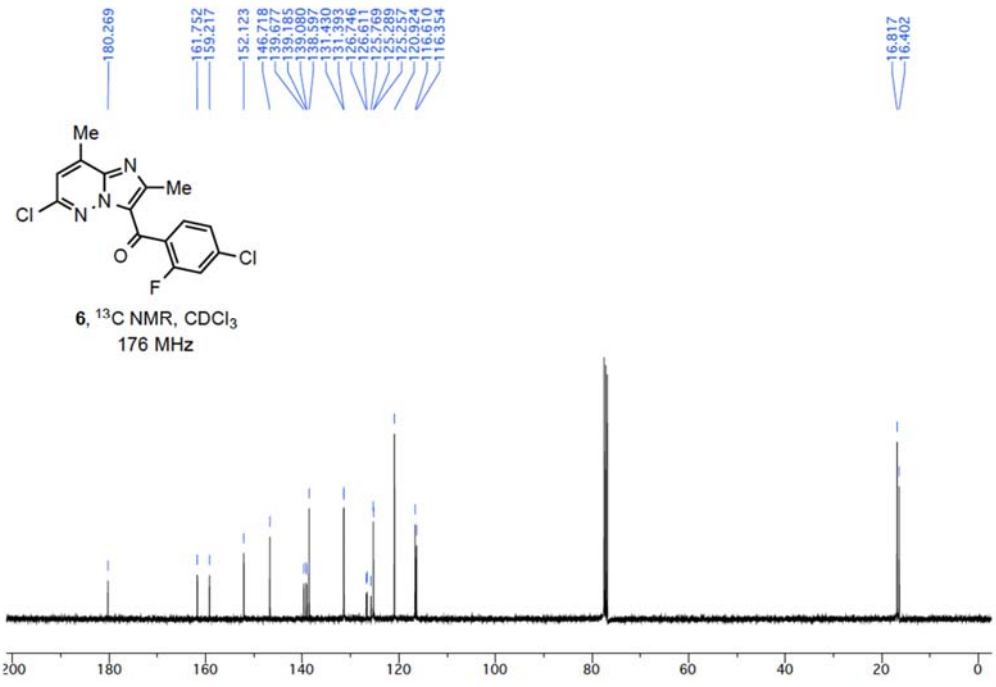
5, ^{1}H NMR, $CDCl_3$
500 MHz



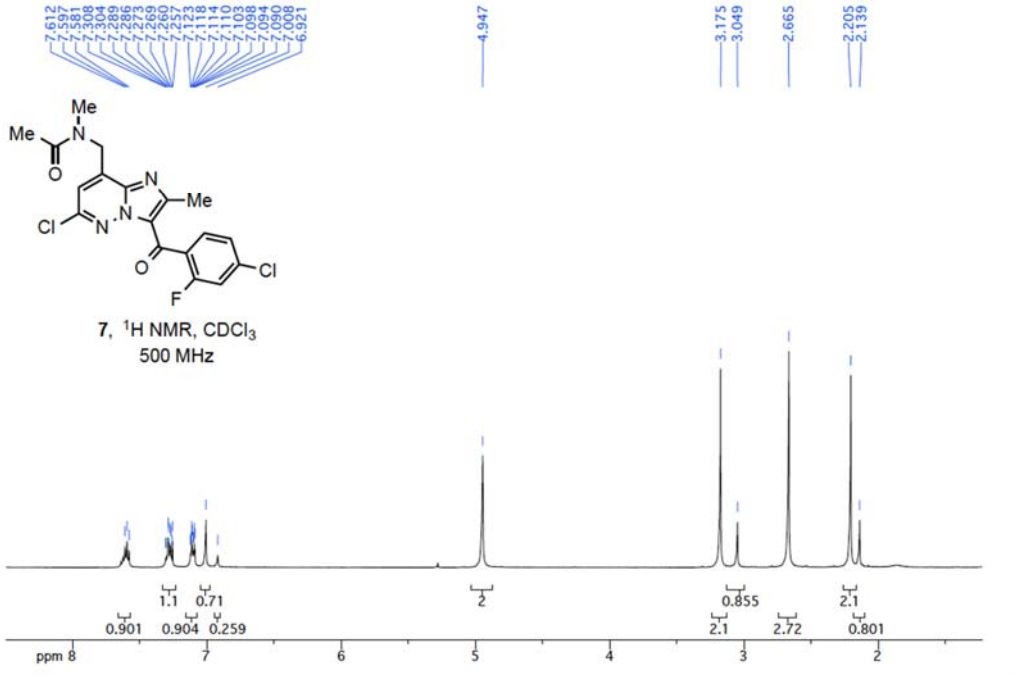
5, ^{13}C NMR, $CDCl_3$
176 MHz



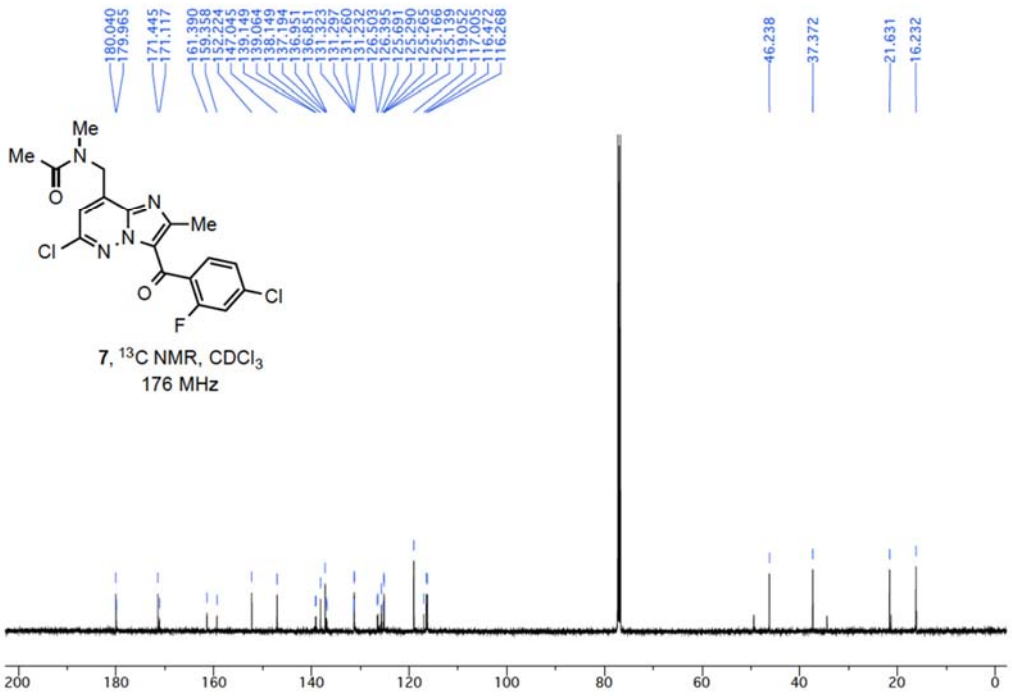
6, ^{1}H NMR, $CDCl_3$
500 MHz



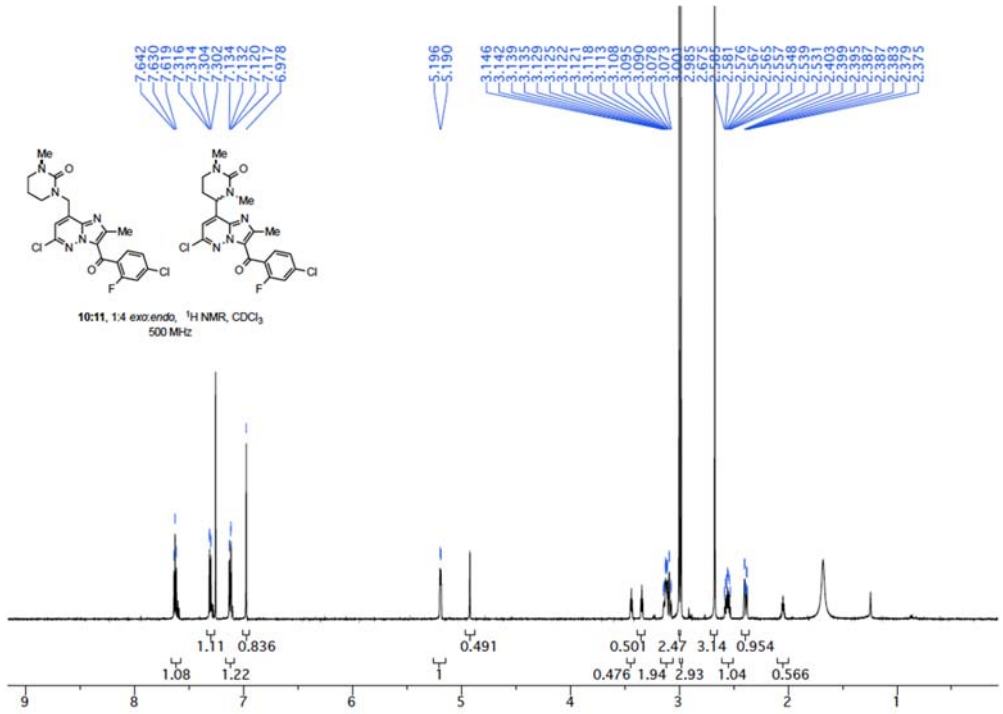
6, ^{13}C NMR, $CDCl_3$
176 MHz



7, ^{1}H NMR, $CDCl_3$
500 MHz



7, ^{13}C NMR, $CDCl_3$
176 MHz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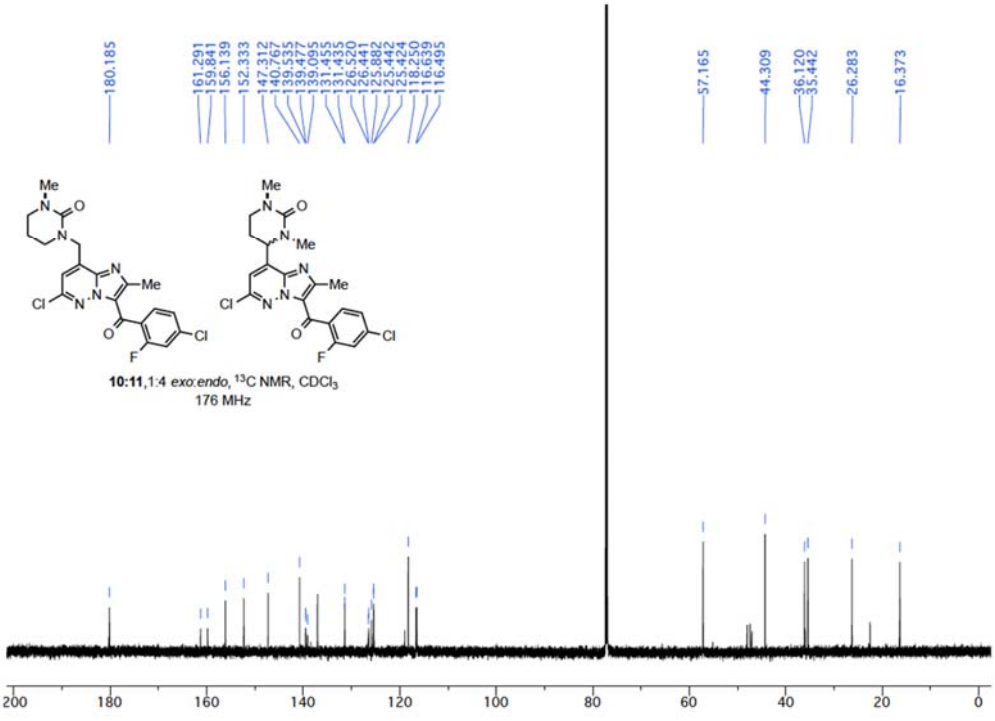
7.630
7.619
7.316
7.314
7.304
7.302
7.134
7.132
7.120
7.117
6.978
5.196
5.190
3.146
3.142
3.139
3.135
3.129
3.125
3.122
3.121
3.118
3.113
3.108
3.095
3.090
3.078
3.073
3.001
2.985
2.675
2.661
2.581
2.576
2.567
2.565
2.557
2.548
2.539
2.531
2.403
2.399
2.395
2.387
2.383
2.379
2.375
Me
N
O
Me
Cl
Me
Cl
F
Cl
10:11, 1:4 exo:endo, 1H NMR, CDCl3
500 MHz
1.11
0.836
0.491
0.501
2.47
3.14
0.954
1.08
1.22
1
0.476
1.94
2.93
1.04
0.566
9
8
7
6
5
4
3
2
1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159.841
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147.312
140.767
139.535
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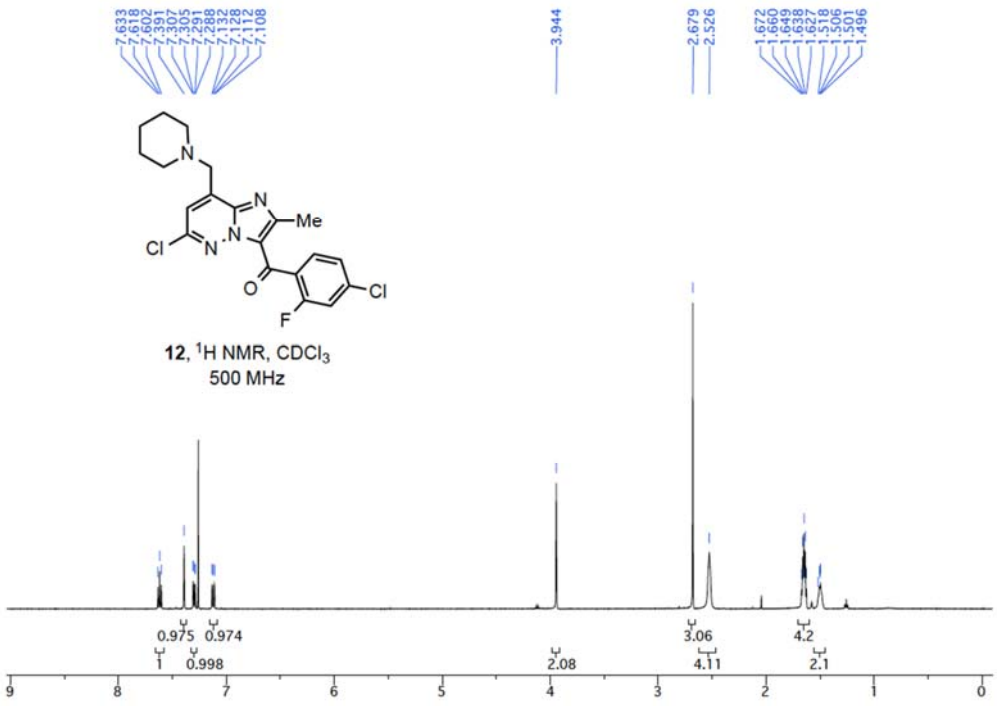
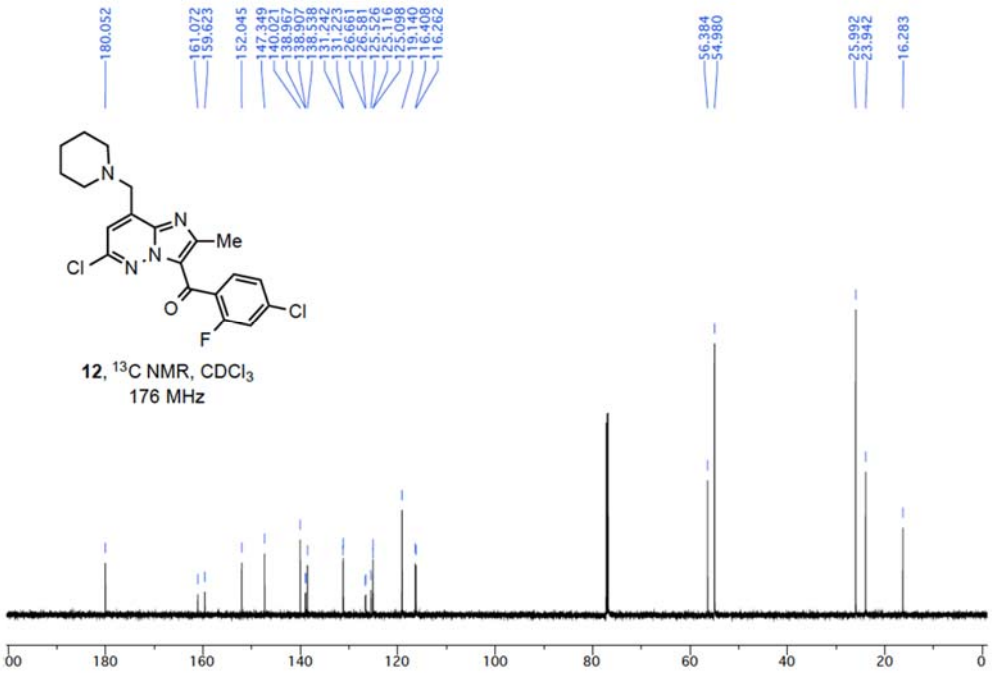
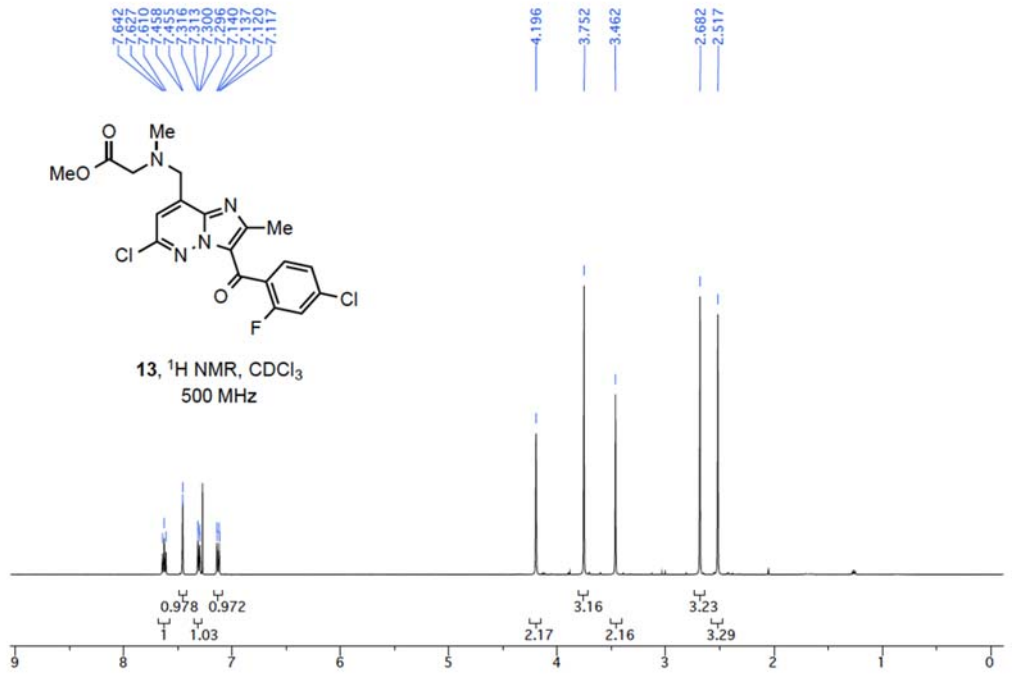
139.065
131.455
131.435
126.520
126.441
125.882
125.442
125.424
118.250
116.639
116.495
57.165
44.309
36.120
35.442
26.283
16.373
Me
N
O
Me
Cl
Me
Cl
F
Cl
10:11,1:4 exo:endo, 13C NMR, CDCl3
176 MHz
200
180
160
140
120
100
80
60
40
20
0



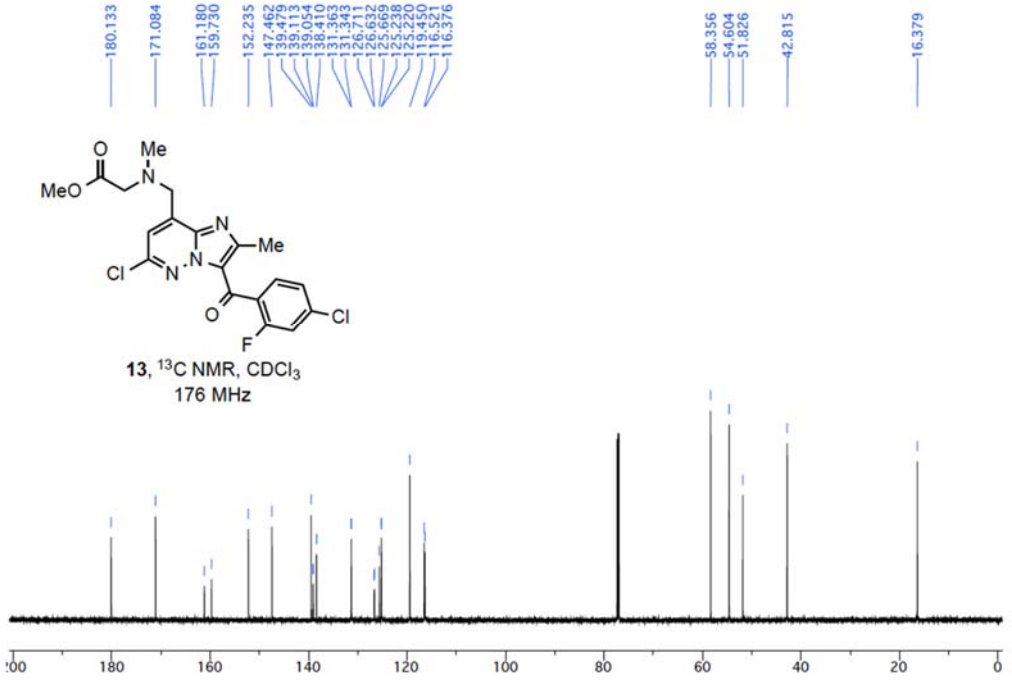
12, ^{1}H NMR, $CDCl_3$
500 MHz



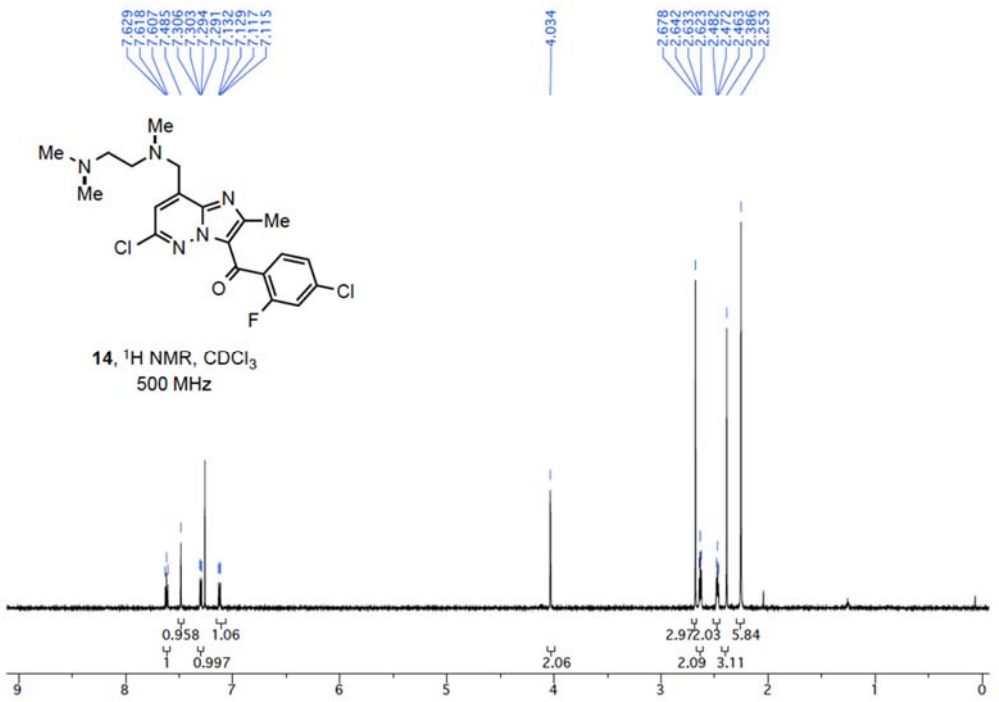
12, ^{13}C NMR, $CDCl_3$
176 MHz



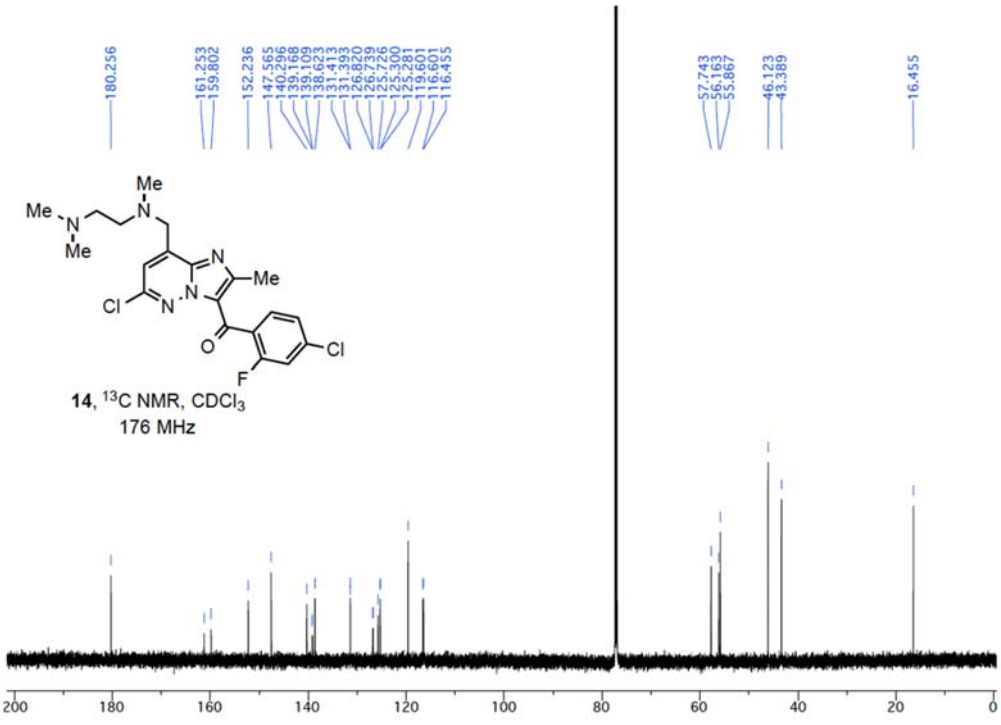
13, ^{1}H NMR, $CDCl_3$
500 MHz



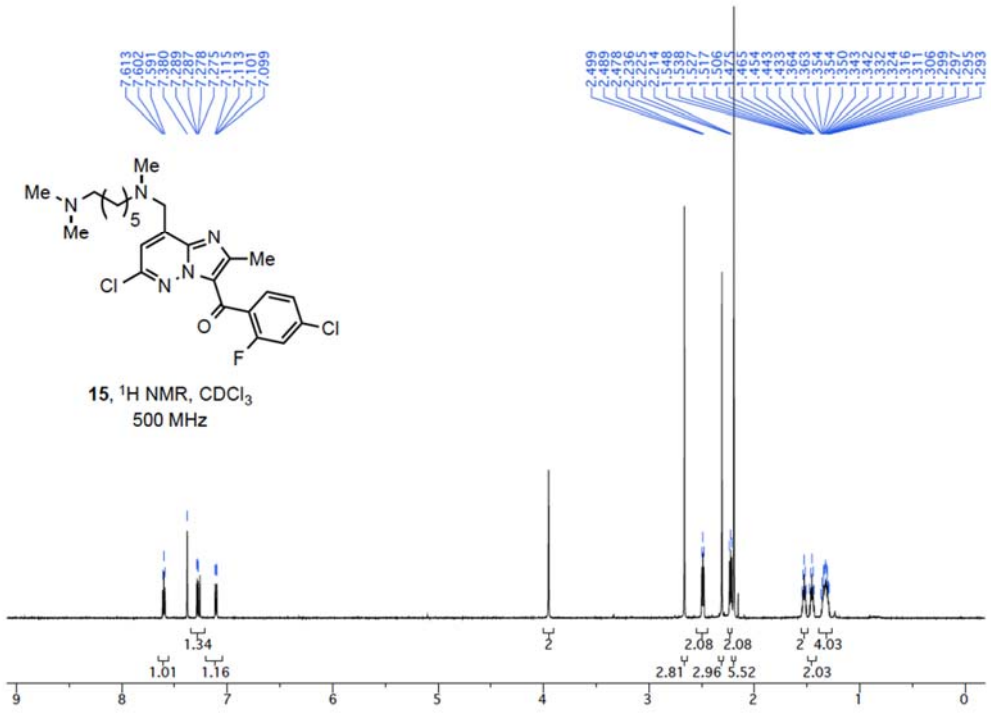
13, ^{13}C NMR, $CDCl_3$
176 MHz



14, ^{1}H NMR, $CDCl_3$
500 MHz



14, ^{13}C NMR, $CDCl_3$
176 MHz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7.591
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7.287
7.278
7.275
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7.113
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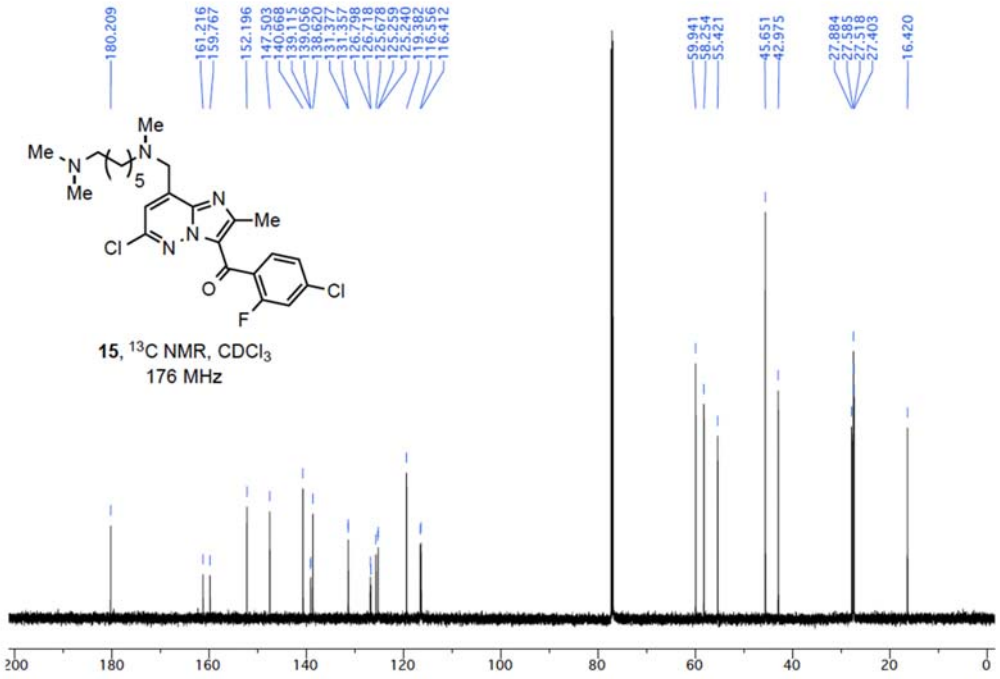
2.489
2.478
2.466
2.225
2.214
1.548
1.538
1.527
1.517
1.506
1.475
1.465
1.454
1.443
1.433
1.364
1.363
1.354
1.354
1.350
1.343
1.342
1.324
1.316
1.311
1.306
1.299
1.297
1.295
1.293
Me
Me
N
Me
5
N
N
Me
Cl
N
N
O
Cl
F
15, 1H NMR, CDCl3
500 MHz
1.34
1.01
1.16
2
2.08
2.08
2.81
2.96
5.52
2
4.03
2.03
9
8
7
6
5
4
3
2
1
0


180.209
161.216
159.767
152.196
147.503
140.668
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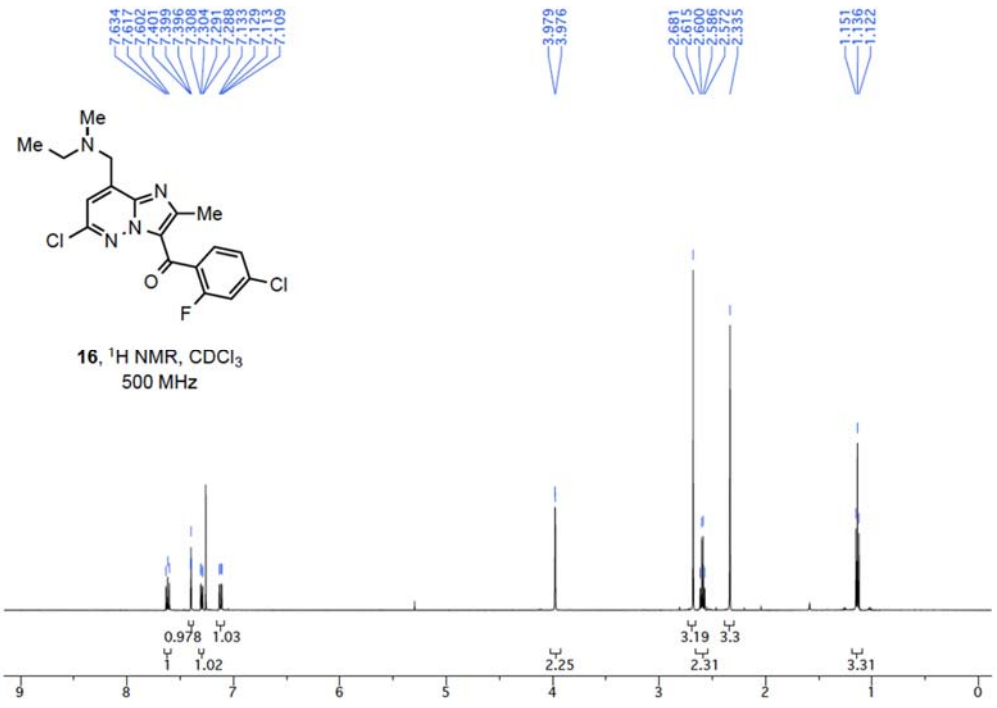
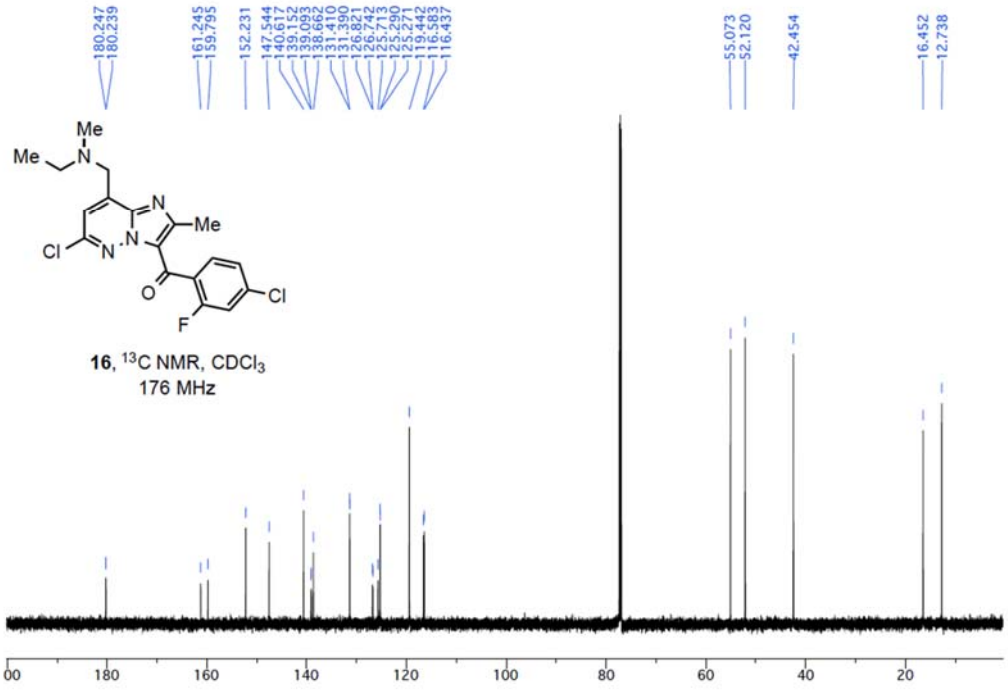
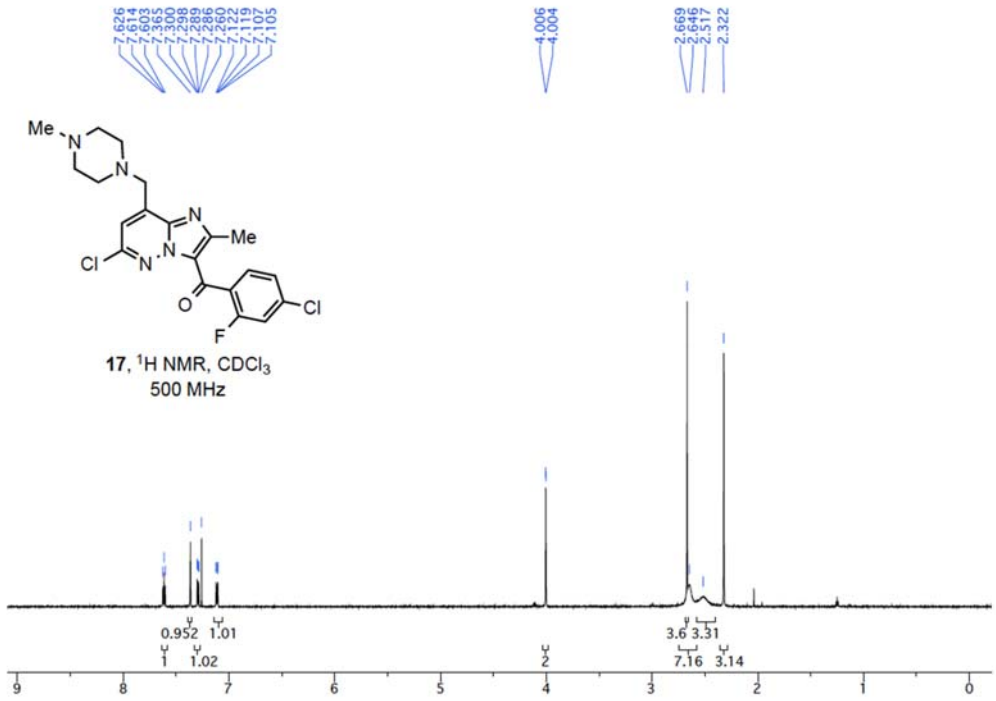
139.056
138.820
138.627
131.357
126.798
126.718
125.678
125.259
125.240
119.382
116.556
116.412
59.941
58.254
55.421
45.651
42.975
27.884
27.585
27.518
27.403
16.420
Me
Me
N
Me
5
N
N
Me
Cl
N
N
O
Cl
F
15, 13C NMR, CDCl3
176 MHz
200
180
160
140
120
100
80
60
40
20
0



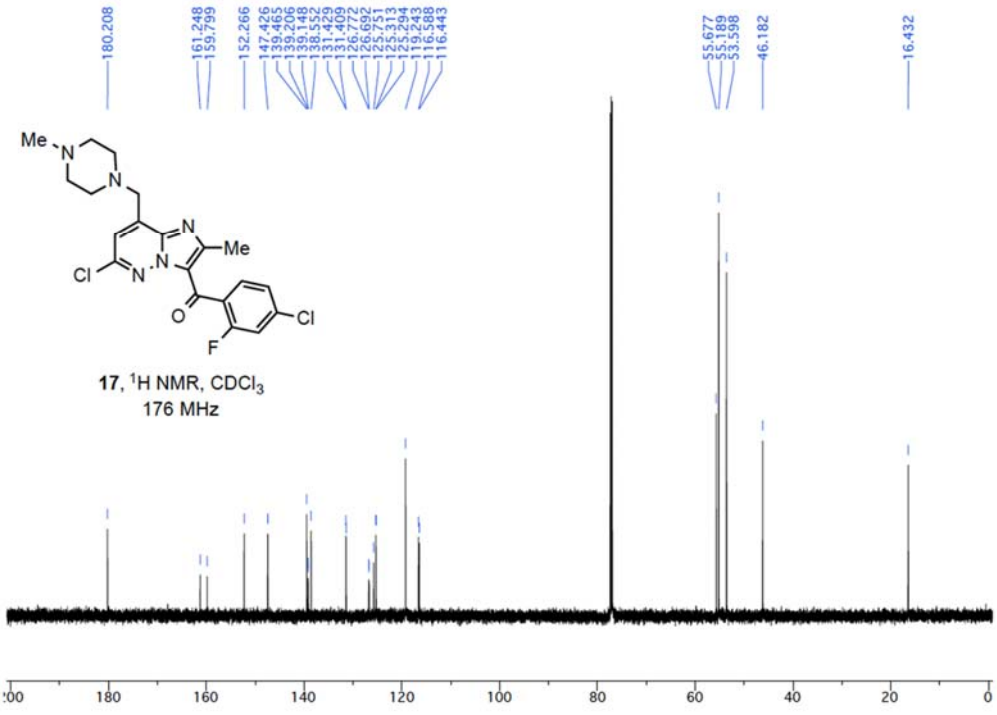
16, ^{1}H NMR, $CDCl_3$
500 MHz



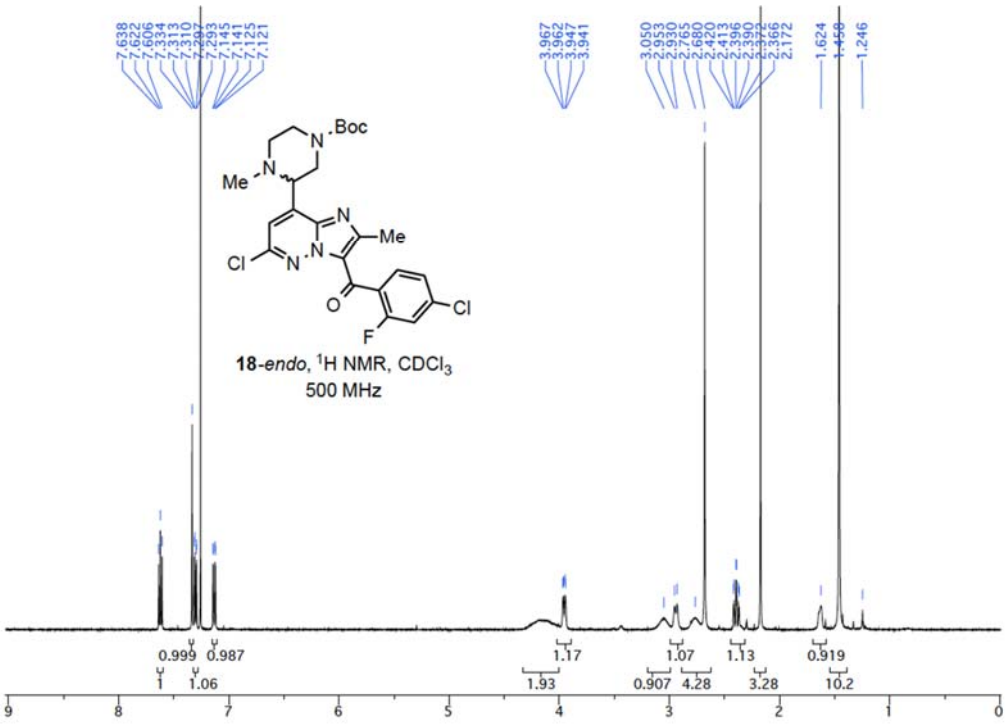
16, ^{13}C NMR, $CDCl_3$
176 MHz



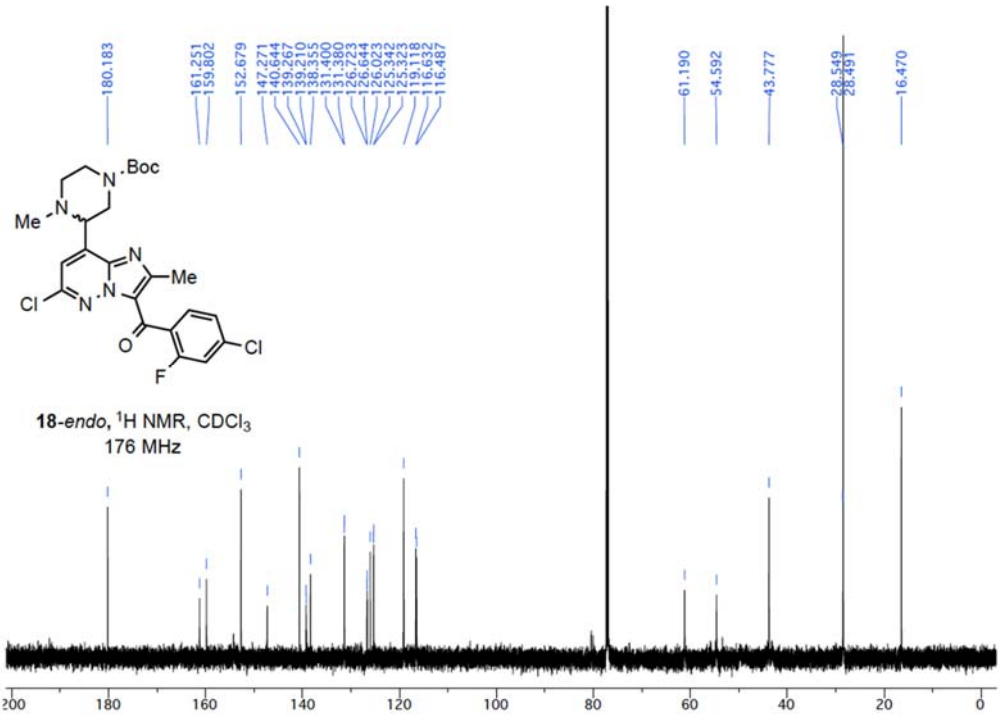
17, ^{1}H NMR, $CDCl_3$
500 MHz



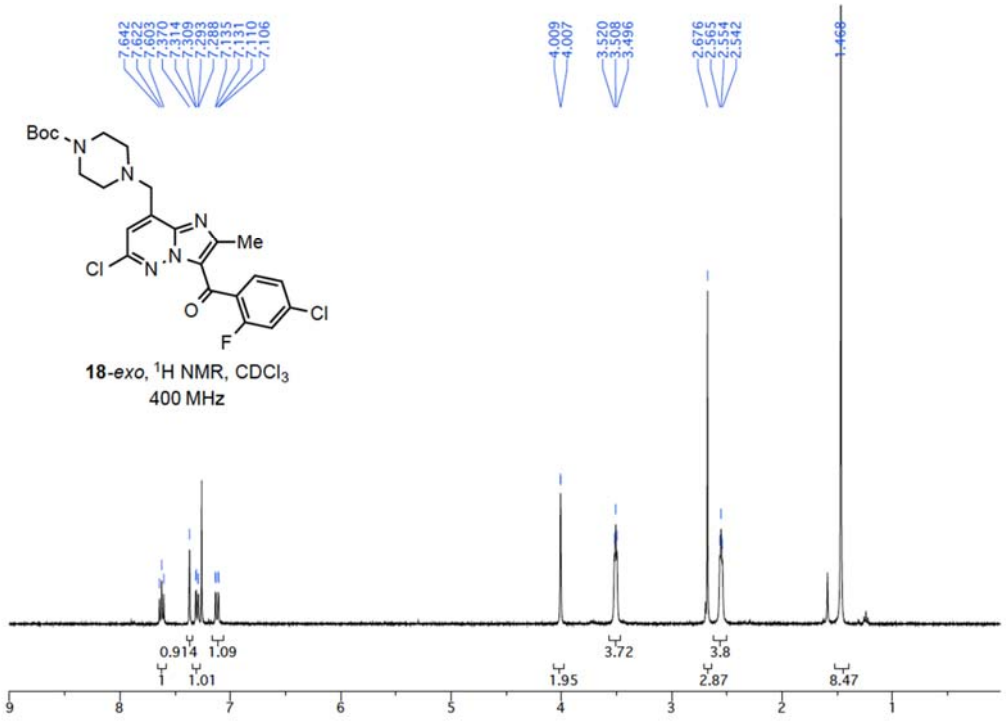
17, ^{1}H NMR, $CDCl_3$
176 MHz



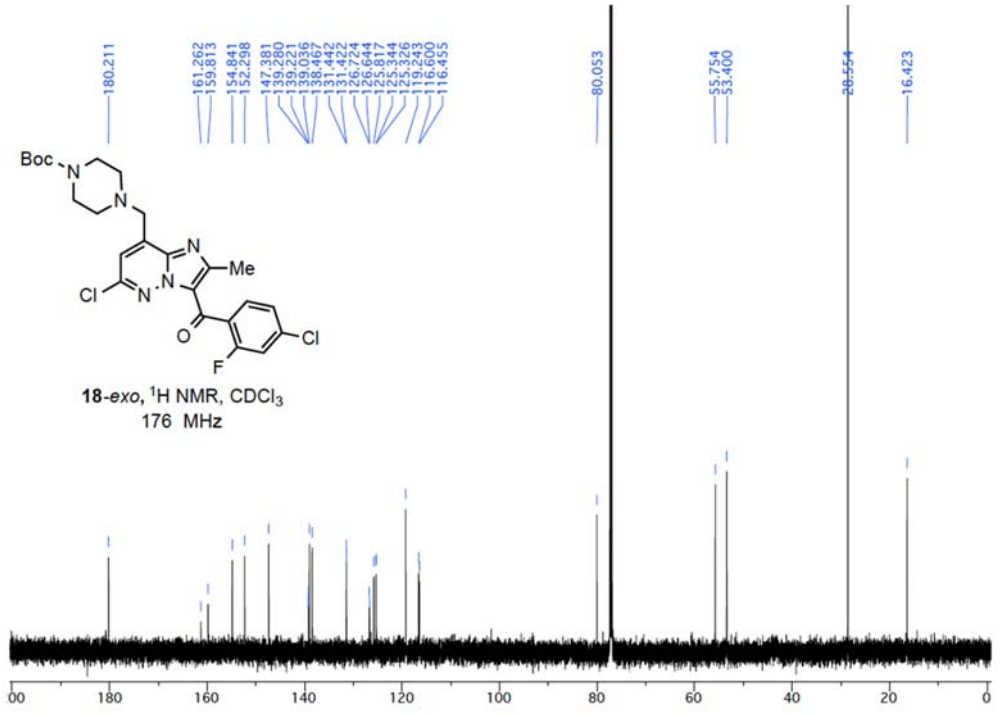
18-*endo*, ^{1}H NMR, $CDCl_3$
500 MHz



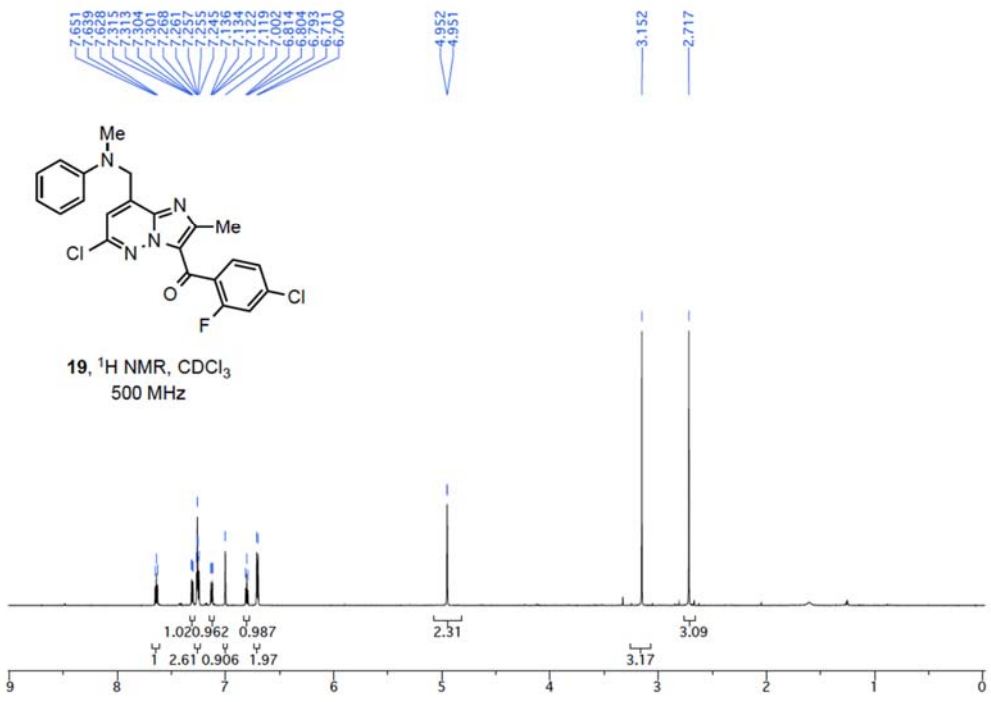
18-*endo*, ^{1}H NMR, $CDCl_3$
176 MHz



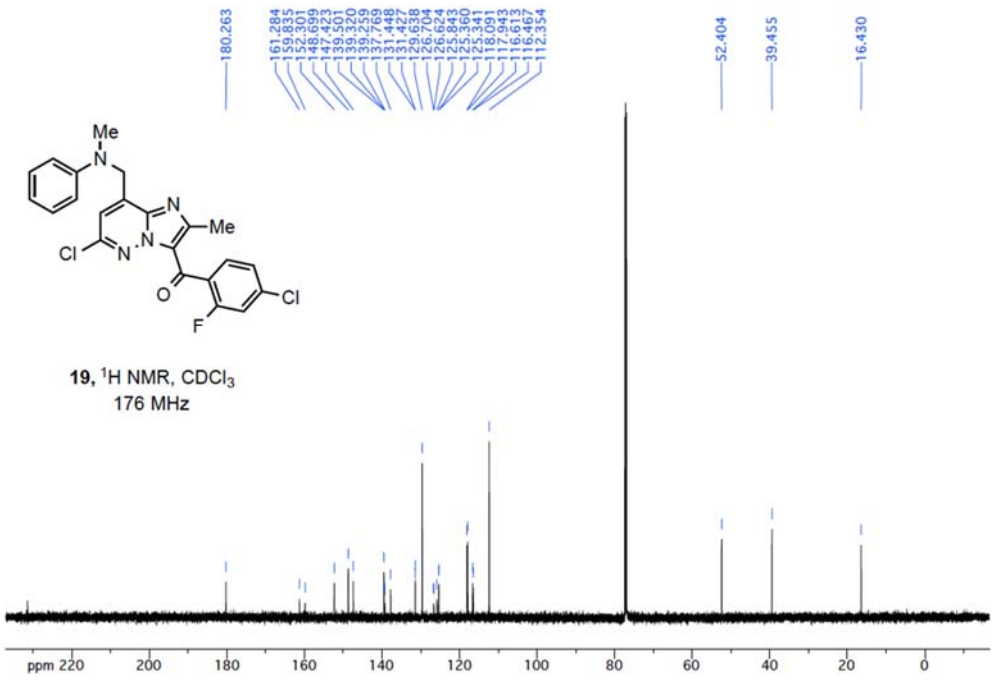
18-*exo*, ^{1}H NMR, $CDCl_3$
400 MHz



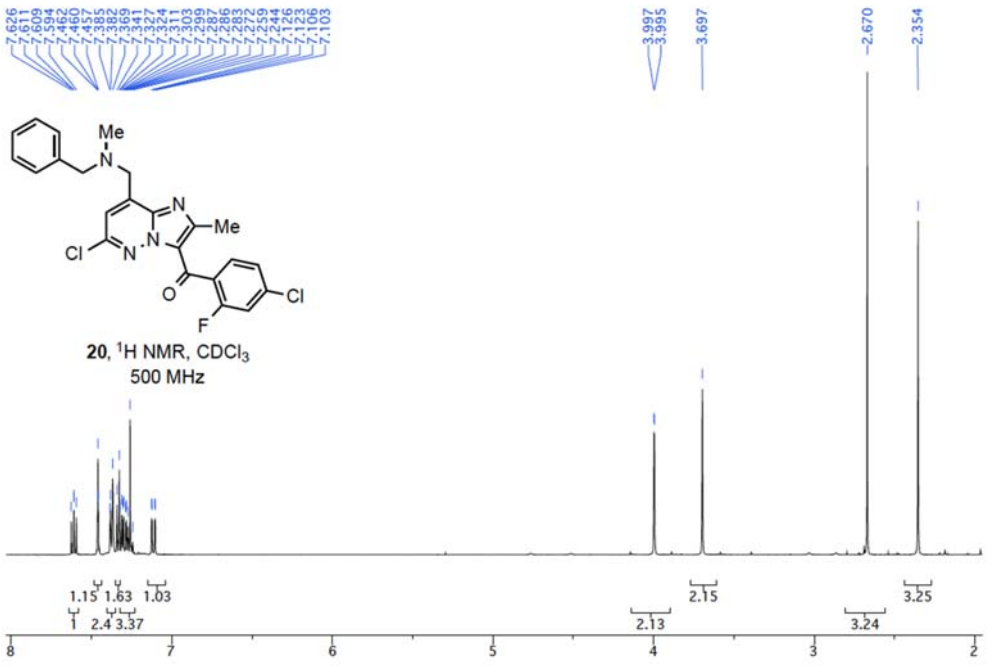
18-*exo*, ^{1}H NMR, $CDCl_3$
176 MHz



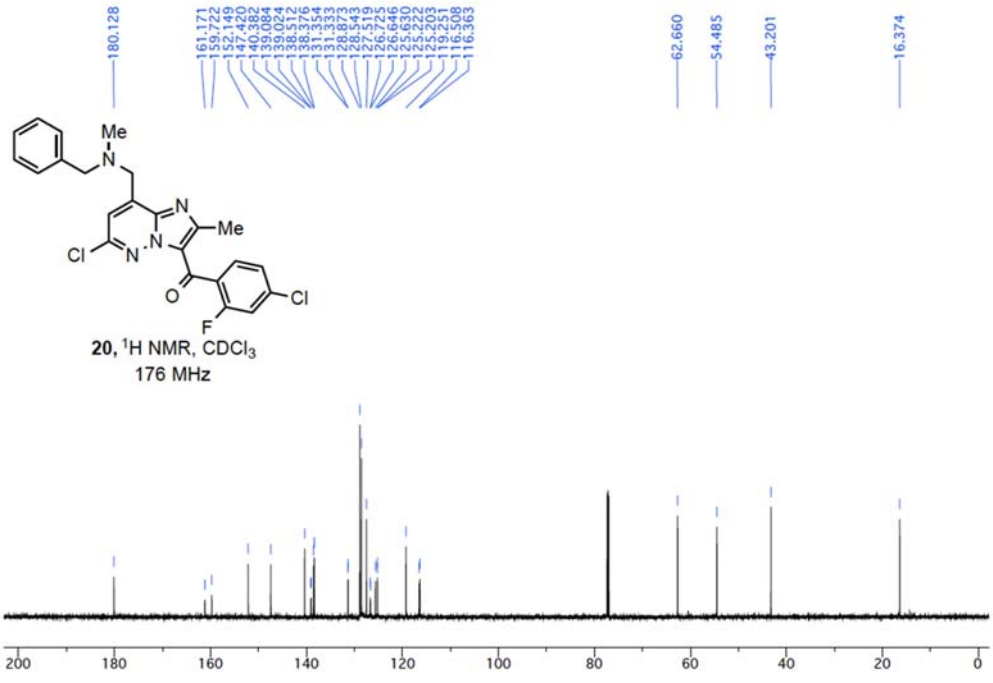
19, ^{1}H NMR, $CDCl_3$
500 MHz



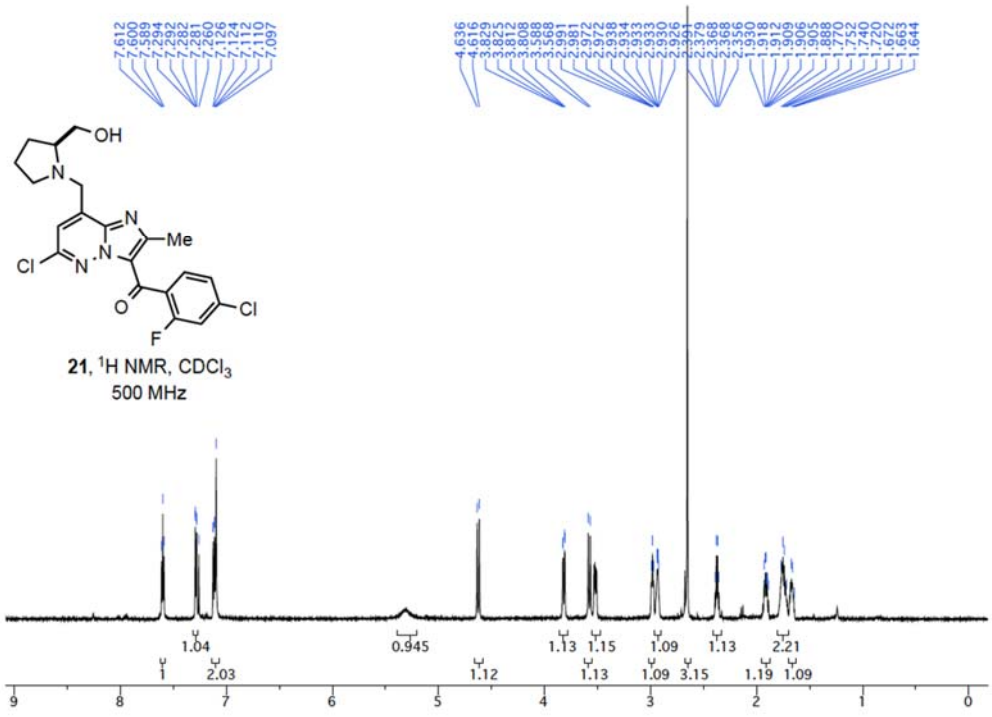
19, ^{1}H NMR, $CDCl_3$
176 MHz



20, ^{1}H NMR, $CDCl_3$
500 MHz



20, ^{1}H NMR, $CDCl_3$
176 MHz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7.110
7.097
4.636
4.616
3.829
3.825
3.812
3.808
3.588
3.588
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1.770
1.752
1.740
1.720
1.672
1.663
1.644
OH
N
N
Me
Cl
N
N
O
Cl
F
21, 1H NMR, CDCl3
500 MHz
1.04
2.03
0.945
1.12
1.13
1.15
1.13
1.09
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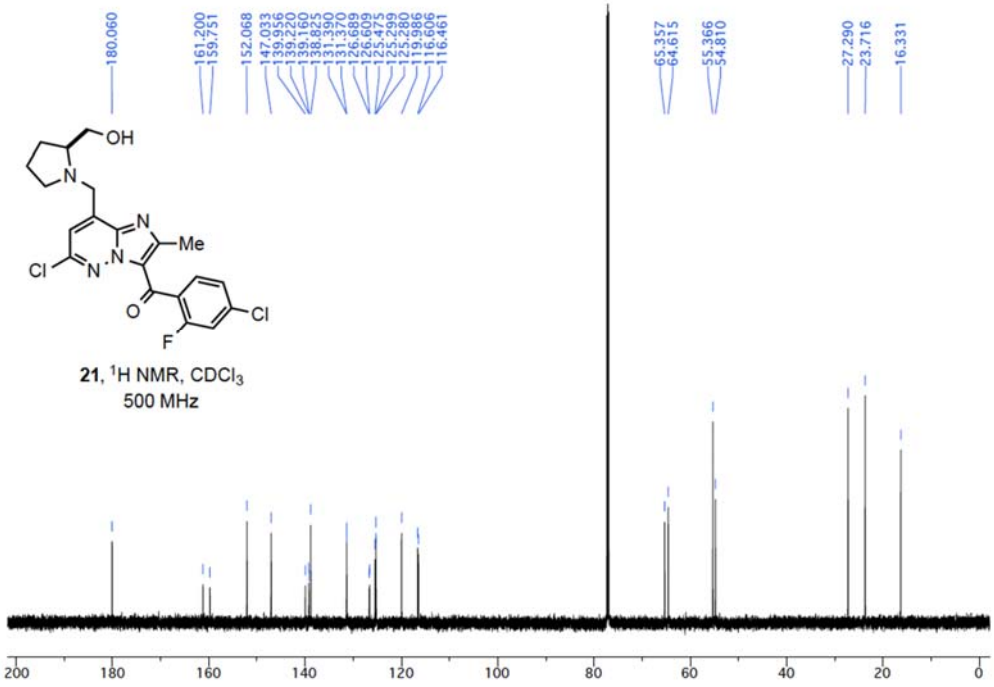
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125.280
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116.606
116.461
65.357
64.615
55.366
54.810
27.290
23.716
16.331
OH
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N
Me
Cl
N
N
O
Cl
F
21, 1H NMR, CDCl3
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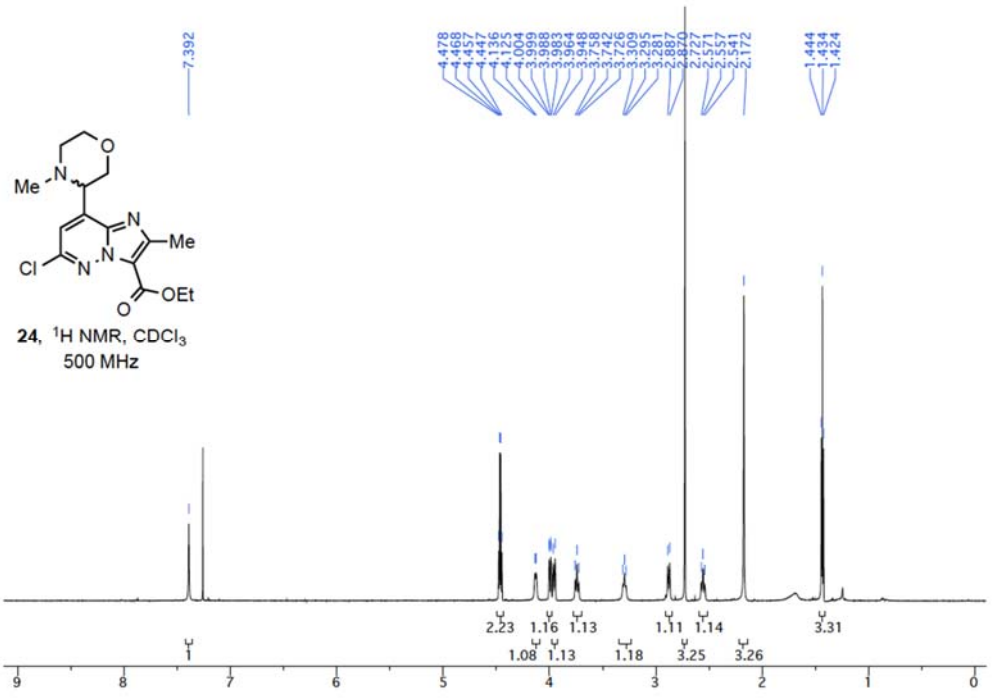
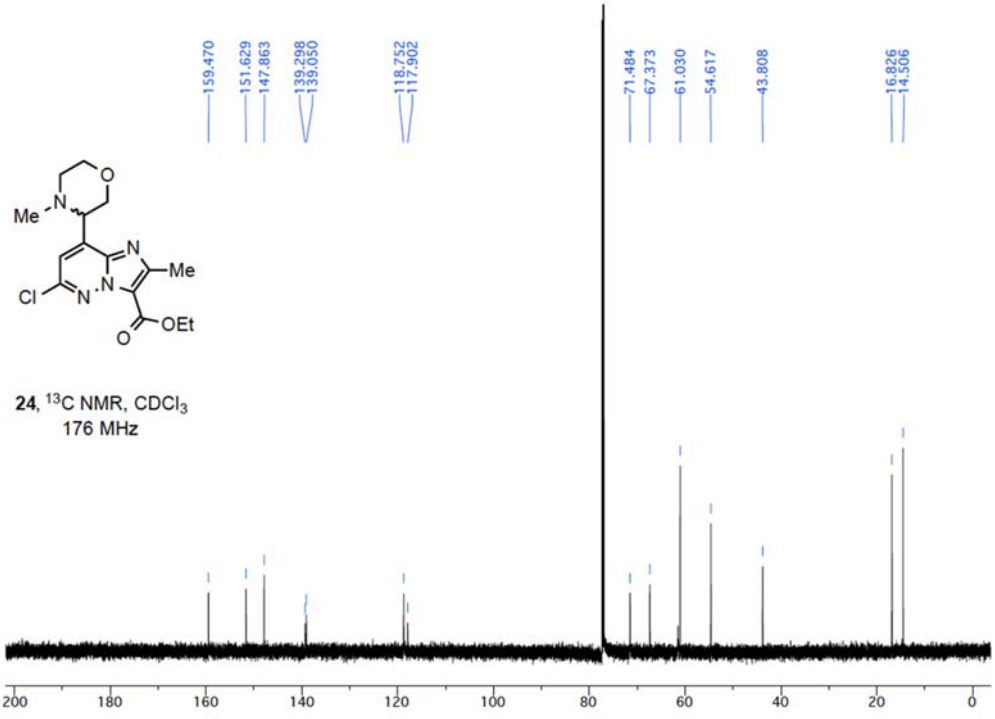
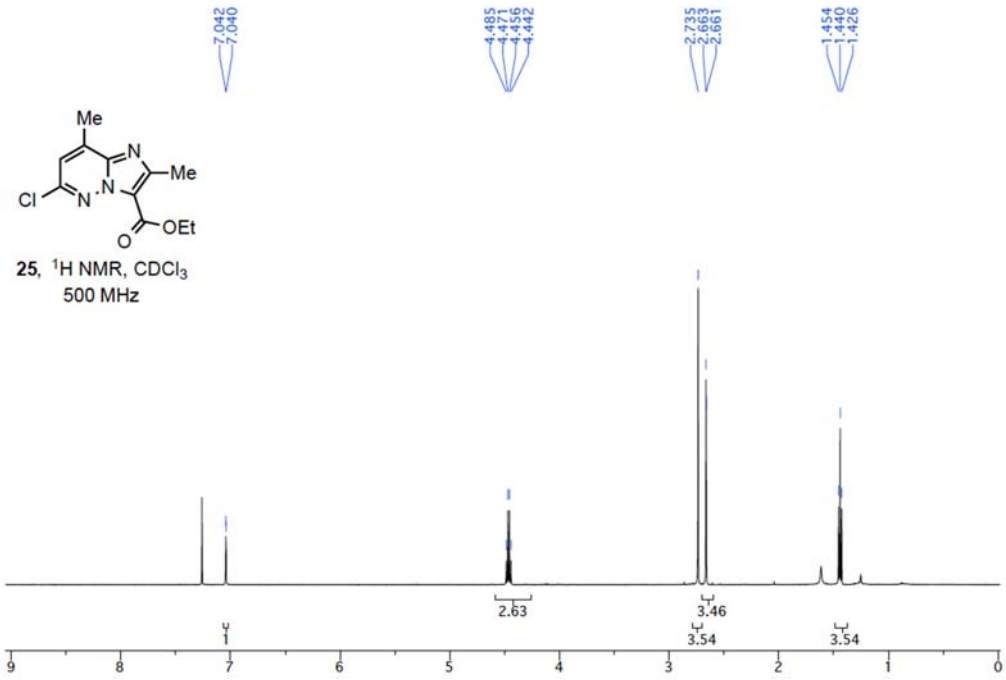
20
0



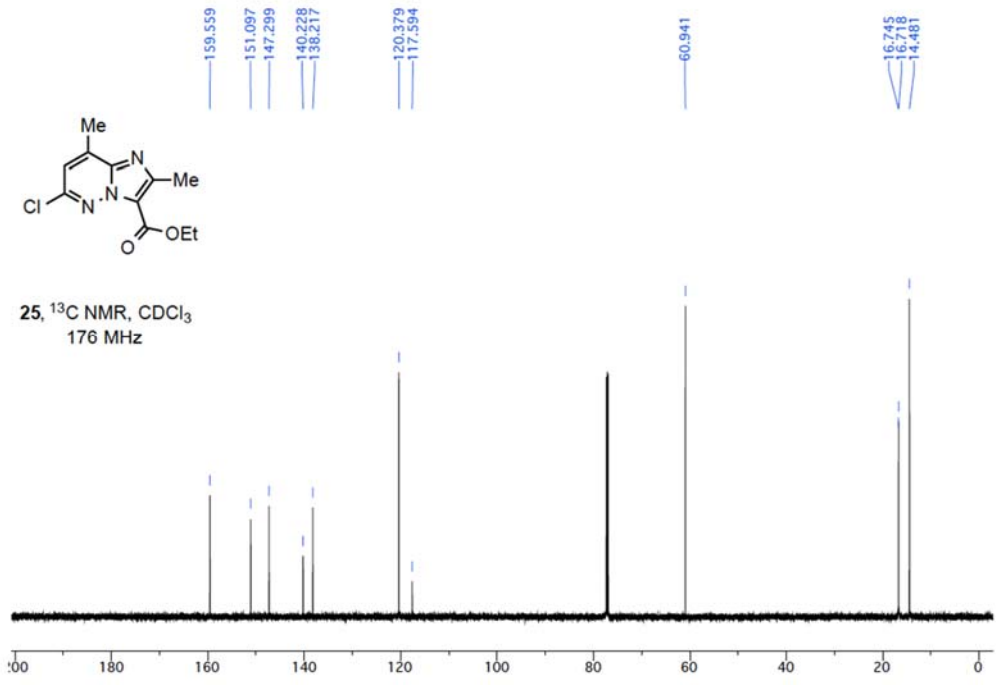
24, ^{1}H NMR, $CDCl_3$
500 MHz



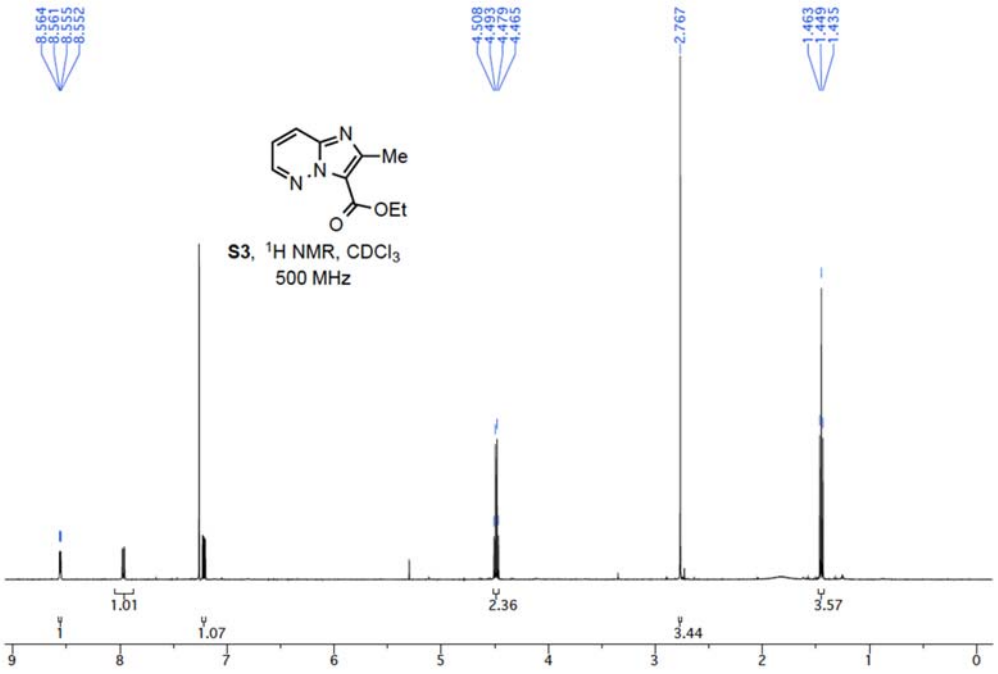
24, ^{13}C NMR, $CDCl_3$
176 MHz



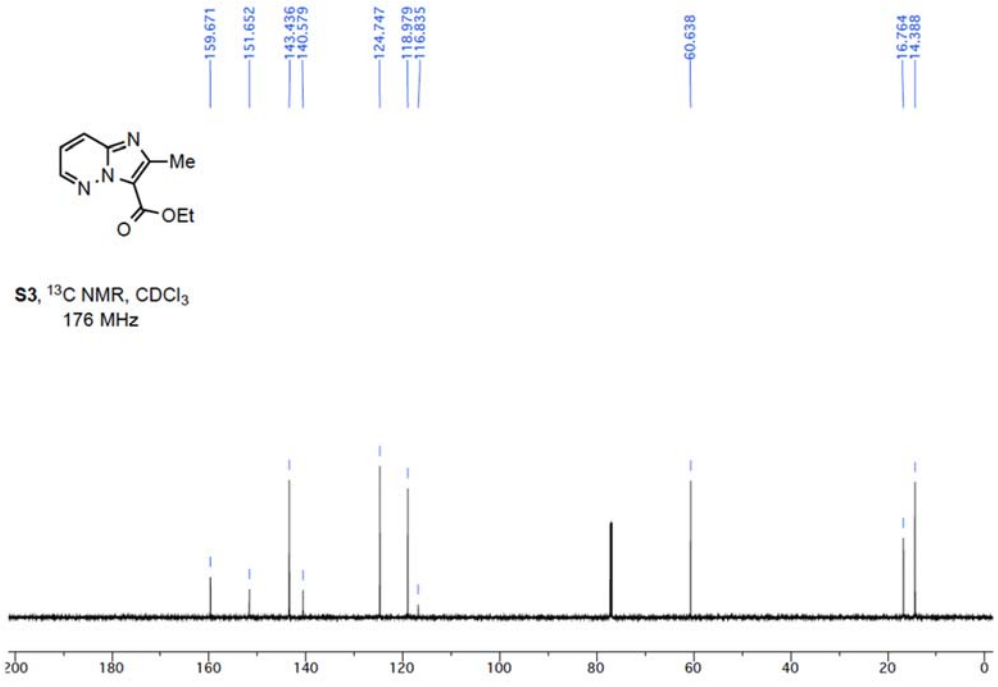
25, ^{1}H NMR, $CDCl_3$
500 MHz



25, ^{13}C NMR, $CDCl_3$
176 MHz



S3, ^{1}H NMR, $CDCl_3$
500 MHz



S3, ^{13}C NMR, $CDCl_3$
176 MHz