Doctoral Thesis

Three-Component Synthesis of Quinolines Based on Radical Cascade Visible-Light Photoredox Catalysis

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This certifies that the thesis/dissertation of Jun-Ho Choi is approved.

06.07.2021 of submission

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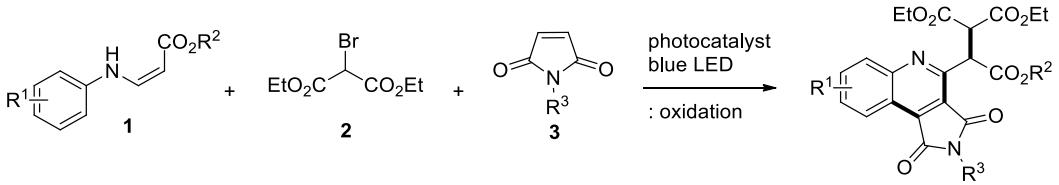
Table of Contents

Abstract

Recently, irradiation of visible light photoredox catalyst has been widely used to drive transformation of organic molecules though the highly desirable processes.[1-5] Absorption of visible light induces the long-lived excited-triplet state of the photocatalyst. The returning from this excited state to the bench state of the catalyst leads single-electron-transfer (SET), transforming the reacting substrates into radical intermediates. The radical cation/anion intermediates show their reactivity which is basically differentiated from those of electronically ground state of molecules.

Multicomponent reaction (MCR) serves as a powerful tool, employing three or more simple building blocks to produce complex molecular frameworks in a single step.[6-9] Given its advantages of rapid access to structural complexity, MCR has been adopted as a valuable means for the discovery of bioactive compounds.[10,11] As such, photoredox catalysis has been explored in the context of MCR.[12-15] However, the limited examples are mostly based on radical-polar crossover mechanisms, in which the process is in operation for initial coupling of two reactants, while a third component is incorporated *via* a polar process.[16-26] Although this approach is useful, quenching of radical processes by redox catalysts entailing the involvement of polar processes poses limitations in the scope of coupling partners. To the best of our knowledge, MCR with three consecutive bond formation based on radical processes *via* visible-light photoredox catalysis has not been reported.

Due to their utilities, significant efforts have been made to develop efficient synthetic methods for quinolines. However, the conventional methods rely on condensation under harsh conditions and more recent developments are limited to transitional metal-catalyzed[27-29] and iodine-mediated synthesis.[30-32] Here, a successful development of a new tandem radical cyclization based on visible-light photoredox catalysis enables the efficient formation of quinolines based on consecutive radical processes.



List of Figures

List of Schemes

List of Tables

Abbreviations

bpy	2,2'-bipyridine
phen	Phenanthroline
ppy	2-phenylpyridine
dF	di-fluoro
dtbbpy	di-*tert*-butyl-2,2'-dipyridyl
LED	Light-emitting diode
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
PhMe	Toluene
MeCN	Acetonitrile
DMF	*N*,*N*-dimethylformamide
DCM	Dichloromethane
1,2-DCE	1,2-dichloroethane
EtOAc	Ethyl acetate
THF	Tetrahydrofuran
DMSO	Dimethyl sulfoxide
NMP	*N*-Methyl-2-pyrrolidone
MeOH	Methanol
PhH	Benzene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DABCO	1,4-diazabicyclo[2.2.2]octane
NMR	Nuclear magnetic resonance
SET	Single-electron-transfer
e^- donor	Electron donor
NaAsc	Sodium ascorbate

DIPEA	*N*,*N*-Diisopropylethylamine
SCE	Saturated calomel electrode
Boc	*tert*-butyloxycarbonyl
Me	Methyl
Et	Ethyl
^{t}Bu	*tert*-Butyl
TBDMS	*tert*-Butyldimethylsilyl
Bn	Benzyl
CN	Cyano
ox	Oxidation
red	Reduction
R^F	Perfluorinated substituent
PR	Photoredox
Cat.	Catalyst
HRMS	High-resolution mass spectrometry
TEMPO	2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TLC	Thin layer chromatography
UV	Ultra-violet
MS	Mass spectroscopy
ESI	Electrospray ionization
Ac	Acetyl
TEA	Triethylamine
RT	Room temperature
TMS	Trimethylsilyl

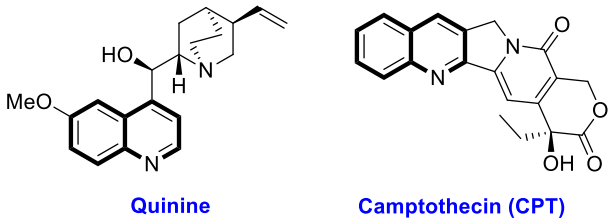
Chapter 1. Background of Quinoline

1.1. Quinolines in natural compounds and drugs

In nature, it is almost impossible to find the biologically active, therapeutic compounds without possession of heterocyclic scaffolds. Among the approximately 20 million natural/synthetic compounds identified by the end of the second millennium, more than half are heterocyclic compounds. Numerous famous natural drugs, including *papaverine*, *theobromine*, *quinine*, *emetine*, *theophylline*, *codeine* and *morphine*, contain heterocyclic scaffolds. Plus, most of important synthetic medications such as *diazepam*, *chlorpromazine*, *isoniazid*, *metronidazole*, are also heterocyclic compounds. Among the diverse heterocycles, nitrogen-containing heterocyclic (*N*-heterocyclic) compounds are especially the most common features in both natural and synthetic drugs. Among the best-selling 200 small molecule pharmaceuticals worldwide, 74% of them are the *N*-heterocyclic compounds.[33] Therefore, seeking the easier way to forming *N*-heterocyclic compounds has been the most important issue in view of synthetic chemistry in a long period.

1.1.1. Quinolines in natural compounds

Quinoline, one of the most important *N*-heterocyclic compounds, has attracted enormous attention when it is discovered 200 years ago because of its significant bioactivity. From 19th century, a number of natural compounds containing quinoline moiety have been isolated from natural sources and studied by worldwide researchers. There are two representatives, *quinine* and *camptothecin* (CPT), which are two of the most famous quinoline-containing compounds. They opened new horizons for drug development in antimalarial and anticancer fields (**Scheme 1-1**).



Scheme 1-1. The most famous quinoline alkaloids, *quinine* and *CPT*

Quinine, which was isolated in 1820 from the bark of Cinchona tree, was the major treatment for malaria before it was replaced by other advanced treatments such as *quinacrine*, *chloroquine* and *primaquine*. It is known that its toxicity against malaria pathogen interferes the ability of malaria parasite, inhibiting the metabolism and ingestion of hemoglobin.

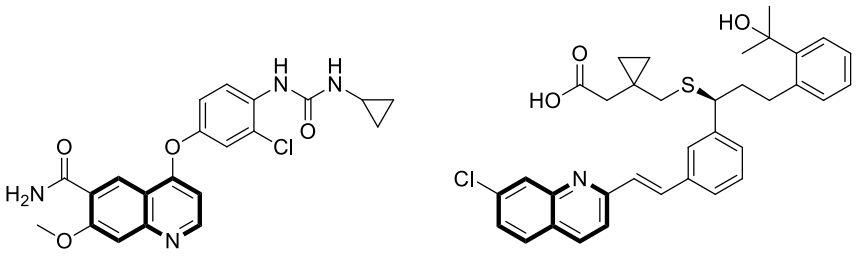
Camptothecin (CPT), which was isolated in 1966 from the bark and stem of Camptotheca acuminate, was widely used as treatment to cancer in China. As a topoisomerase poison, it has been used as preliminary clinical trials for broad range of cancers, including breast, ovarian, colon, lung, and stomach. Due to its poor solubility, numerous analogues of CPT have been developed by synthetic and medicinal chemists.

1.1.2. Quinolines in drugs

Moreover, more than 200 quinoline alkaloids showed expansive range of biological activities on not only antimalarial and anticancer but also antibacterial, antifungal, antiviral and anti-inflammatory effects.[34] The following examples are the famous quinoline-containing medications, which are successfully supplied as treatments of important diseases on a huge scale in the world (**Scheme 1-2**).

Lenvatinib is known to act as a kinase inhibitor, inhibiting the signaling between cancerogenic proteins (VEGFR1, VEGFR2 and VEGFR3 kinases) in thyroid cancer.[35] It is treated for differentiated thyroid cancer, which has not been successful with the treatment of radioactive iodine. In combination with *everolimus*, it is used as treatment to advanced renal cell carcinoma for patient who has experienced anti-angiogenic therapy before. After approval of U.S. FDA in 2016, it is being sold worldwide on a $61.7 million scale.

Montelukast is one of leukotriene receptor antagonists for the treatment of asthma and allergic coryza, opposing the act of leukotriene which is the inflammatory mediator in immune system. Blocking of leukotriene results in the suppressed inflammation and relaxation of smooth muscle in lungs. As a result, *Montelukast* has been a solution for effective prevention and long-term management of asthma. After approval of U.S. FDA in 1998, it is being sold worldwide on a $70.8 million scale.



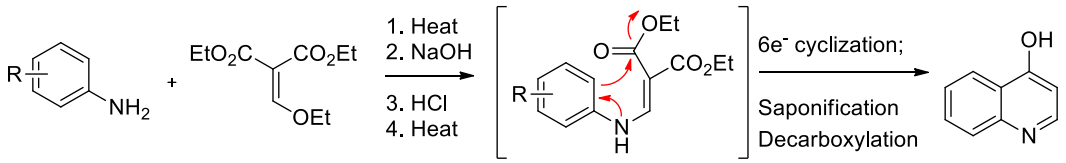
Scheme 1-2. Two of top-selling quinoline-containing medications

1.2. Classical synthesis of quinoline

Classical approaches to synthesis of quinoline generally employed simple aniline, proceeding condensation with carbonyl groups. So far numerous synthetic protocols to quinoline scaffold have been developed. Among them, the most famous named reactions for the synthesis of quinoline are described below.

1.2.1. *Gould–Jacobs* reaction

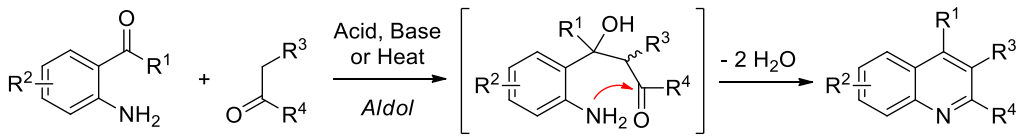
The *Gould-Jacobs* reaction is a named reaction for preparation of 4-hydroxyquinoline derivatives (**Scheme 1-3**). It starts with condensation between aniline and diethyl ethoxymethylenemalonate, followed by substitution. A 6 electron cyclization results in the loss of second ethanol molecule and tautomerization, forming 4-hydroxy-3-carboalkoxyquinoline. Saponification followed by decarboxylation produces 4-hydroxyquinoline. This protocol enables to prepare various drugs containing 4-hydroxyquinoline as a core scaffold.[36]



Scheme 1-3. General scheme of *Gould–Jacobs* reaction

1.2.2. *Friedländer* reaction

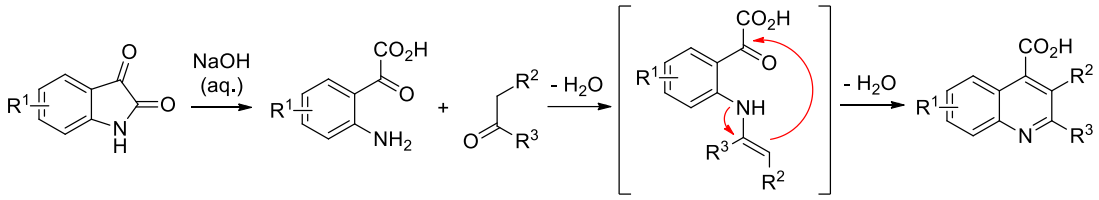
The *Friedländer* reaction is a named reaction between 2-aminobenzaldehyde and ketone for preparation of quinoline (**Scheme 1-4**). It is catalyzed by a base or acid, proceeding *via* condensation and double cyclodehydration. The reactive α-methylene group of ketone undergoes aldol-condensation to produce aldol-adduct, then elimination step results in the loss of water. Another loss of water in formation of imine forms variously functionalized quinoline.[37]



Scheme 1-4. General scheme of *Friedländer* reaction

1.2.3. *Pfitzinger* reaction

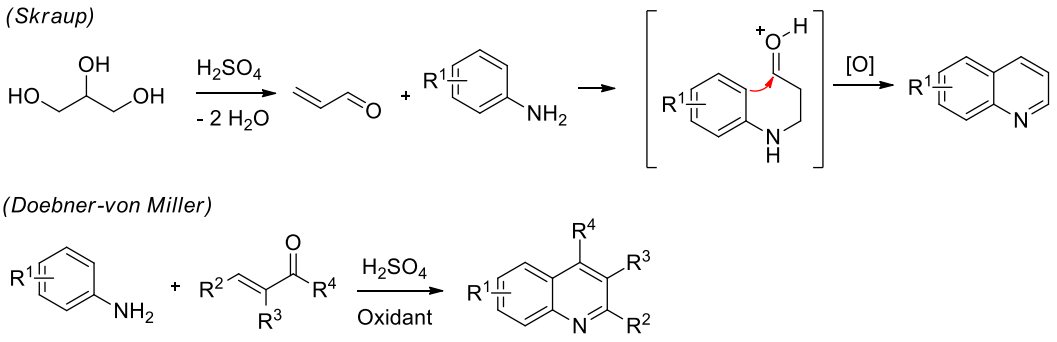
The *Pfitzinger* reaction is a named reaction for preparation of quinoline-4-carboxylic acid from isatin and a carbonyl compound in presence of strong base (**Scheme 1-5**). The hydrolysis of amide bond with base in isatin gives keto-acid, then condensation between resulted aniline and a ketone forms imine intermediate. Enamine, which has come from the imine through tautomerization, cyclizes to from the desired quinoline after dehydration. The *Pfitzinger* reaction is one of extension of the *Friedländer* reaction, but it utilizes the more stable isatin varieties than unstable 2-aminobenzaldehyde.[38]



Scheme 1-5. General scheme of *Pfitzinger* reaction

1.2.4. *Skraup*/*Doebner-von Miller* reaction

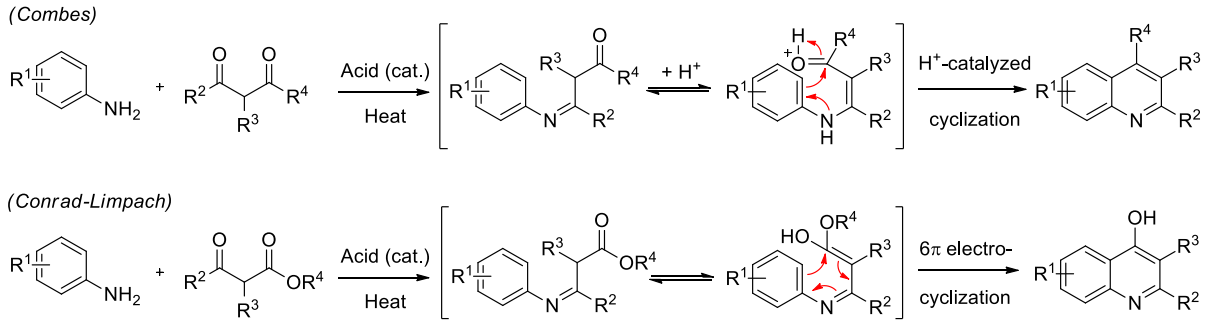
Both the *Skraup* reaction and the *Doebner–von Miller* reaction are organic reactions for formation of quinolines, utilizing an aniline and *α,β*-unsaturated carbonyl compounds (**Scheme 1-6**). In the *Skraup* reaction, the *α,β*-unsaturated carbonyl compound (acrolein) is prepared *in-situ* through dehydration of glycerol in acidic condition. Nucleophilic attack from aniline to acrolein results in propionaldehyde intermediate, then following intramolecular electrophilic attack from aromatic ring to the protonated aldehyde group yields concomitant cyclization.[39] In the *Doebner–von Miller* reaction, 2,3 and 4-substituted quinoline can be prepared when highly substituted *α,β*-unsaturated carbonyl compound is employed in place of the simple acrolein. Both reactions have fundamental drawbacks in that they require strong oxidants and highly acidic reaction conditions.[40]



Scheme 1-6. General scheme of *Skraup*/*Doebner–von Miller* reaction

1.2.5. *Combes*/*Conrad-Limpach* reaction

Both the *Combes* reaction and the *Conrad-Limpach* reaction involve the condensation of aniline with ketones (1,3-diketone and *β*-ketoester; the Combes reaction and the Conrad-Limpach reaction, respectively), forming Schiff bases (**Scheme 1-7**). The Schiff bases undergo acid-catalyzed cyclization from each enamine or imine intermediate (tautomerization). The resulted product in the *Combes* reaction is 2,4-substituted quinoline, which can be differentiated from the substituted 4-hydroxyquinoline in the *Conrad-Limpach* reaction. These reactions also require the use of strong base and high temperature when cyclodehydration is proceeded.[41]



Scheme 1-7. General scheme of *Combes/Conrad–Limpach* reaction

In conclusion, even though there are various modified version of these named reaction, most of them still require harsh conditions such as high reaction temperature, use of hazardous (transitional metal) catalysts, acid or base and solvents, tiresome procedure for work-up, long reaction time, unsatisfactory regioselectivity and involvement of specific functional groups. These are potent burden to environment in aspect of sustainable development of methodology. Therefore, simple and greener route to development of methodology of quinoline is highly desired.

Chapter 2. Photoredox catalysis and Examples in Quinoline Synthesis

2.1. Multicomponent reaction (MCR)

Multicomponent reaction (MCR) is a chemical transformation in which three or more starting materials participate in a single reaction as building blocks to form a product. The newly formed final product contains all or most of the atoms of starting materials, minimizing generation of byproduct. Therefore, MCR is highly ideal methodology in the view of atom economy. Compared with stepwise synthetic route, the target molecule can be achieved faster with much fewer steps in MCR strategy. In other words, MCR enables to access a shortcut to highly-functionalized complex molecule in a one-pot, whereas the sequential synthesis requires the greater effort and resources such as solvent, reagents and catalysts.

2.2. Visible-light-mediated photoredox catalysis

2.2.1. Radical generation from conventional methods to photoredox catalysis

In organic chemistry, radical intermediate indicates the molecule possessing an unpaired electron, which is *in situ* generated during the reaction under specific reaction conditions. The conventional methods depend on the use of toxic regents such as radical initiators and stoichiometric oxidant/reductants. Also, they require harsh conditions involving high reaction temperature or high-energy ultraviolet light for irradiation. Therefore, these methods are usually accompanied by limitations such as chemical wastes from the toxic reagents, the use of specific equipments and generation of undesired radical species.[42]

In modern organic chemistry, development of benign, sustainable and eco-friendly synthetic methodologies has been highly demanded. Recently, photoredox catalysis has received a great attention because of its potential.[43-49] Photocatalysts are excited by visible light, which is mild and abundant in limitless sunlight. The use of visible light does not lead any deleterious side reactions, because most of organic molecules are not excited by visible light. Plus, photoredox catalysis does not require any specific reactor, on the other words, normal glassware is sufficient to carry the reaction under visible light. In the catalytic cycle, it does not require the use of external oxidant and reductant because the photocatalysts act as internal oxidant/reductant themselves. The catalytic reaction usually proceeds at room temperature with a tiny amount of catalyst loading.

2.2.2. General characteristic of photocatalysts

Photoredox catalysts usually consist of a central metal and surrounding polypyridyl ligands. Iridium and ruthenium complexes are frequently used in photoredox catalysis. Their redox potentials of the complexes are determined by the electronic properties of ligands and central metals. The tuning of redox potential, which can be a solution for improvement of reaction efficiency, can be achieved by modification of the structure of the ligands or replacement of central metals.[50] Not only limited to the metallic catalysts, but also organic photoredox catalysts such as eosin Y, rose bengal exhibit the similar reactivity, extending to metal-free photocatalysis.[51]

Among various photocatalysts, $[Ru(bpy)_3]^{2+}$ is the most famous photocatalyst and well-investigated because of its exceptional photochemical properties. The excitation event of $[Ru(bpy)_3]^{2+}$ *via* visible light irradiation can be explained by its orbital energy diagram. (**Figure 2-1**) In the octahedral complex of $[Ru(bpy)_3]^{2+}$, its HOMO is located in d_{t2g}(M) orbital of central Ru^{II} whereas its LUMO is located in π*(L) orbital of its ligands. Under the irradiation of visible light, one electron from the HOMO of Ru^{II} is promoted to the ligand-centered LUMO without conversion of its spin, resulting in excited singlet state (**S1**) of the complex. This promotion is attributed by the absorption of visible light, of which λ_{max} is 452 nm. This transition is named metal-to-ligand charge transfer (MLCT). Subsequently, a rapid spin flipping of the electron in π*(L) orbital is followed, called intersystem crossing (ISC).

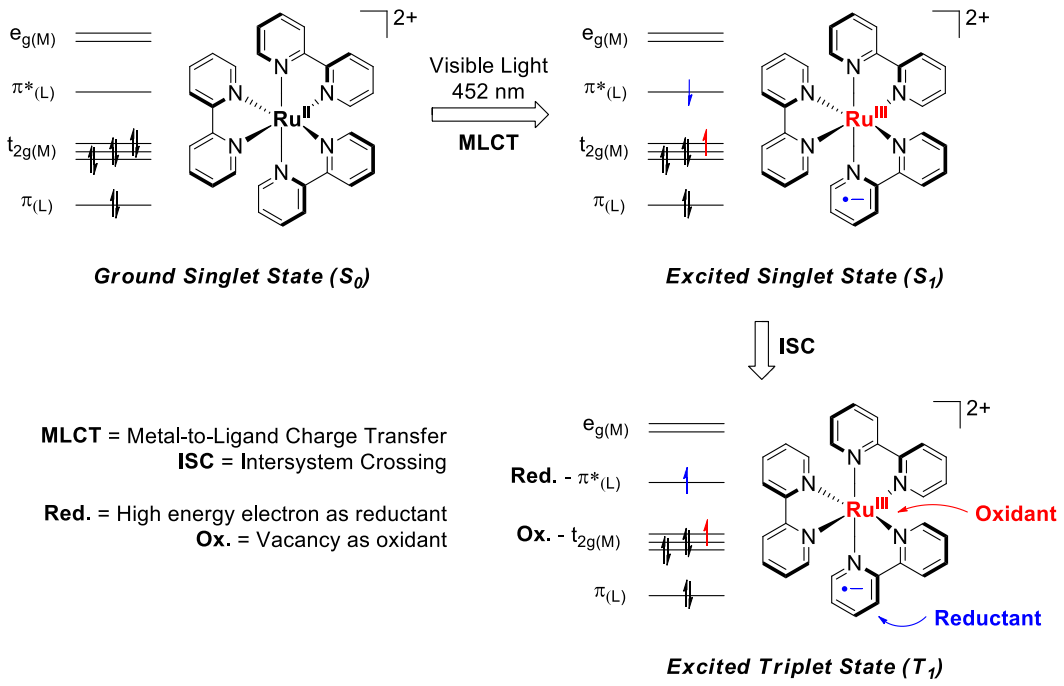


Figure 2-1. Orbital energy diagram for triplet-excited state (T_1) of $*[Ru(bpy)_3]^{2+}$

Finally, the excited triplet state ($\mathbf{T_1}$) of $[Ru(bpy)_3]^{2+}$ possesses both the oxidized Ru^{III} and reduced ligand. The oxidized Ru^{III} has a vacancy to fill one electron, therefore acts as a strong oxidant, on the other hand, the reduced polypyridyl ligand has a high energy electron, which is willing to reduce organic substrates. The excited triplet state of $[Ru(bpy)_3]^{2+}$ has significantly extended lifetime (τ = approximately 1.1 μs), which makes it possible to carry chemical transformations *via* intermolecular single-electron-transfer process.[52-54] It is worthy to note that the overall charge of the excited complex is not changed.

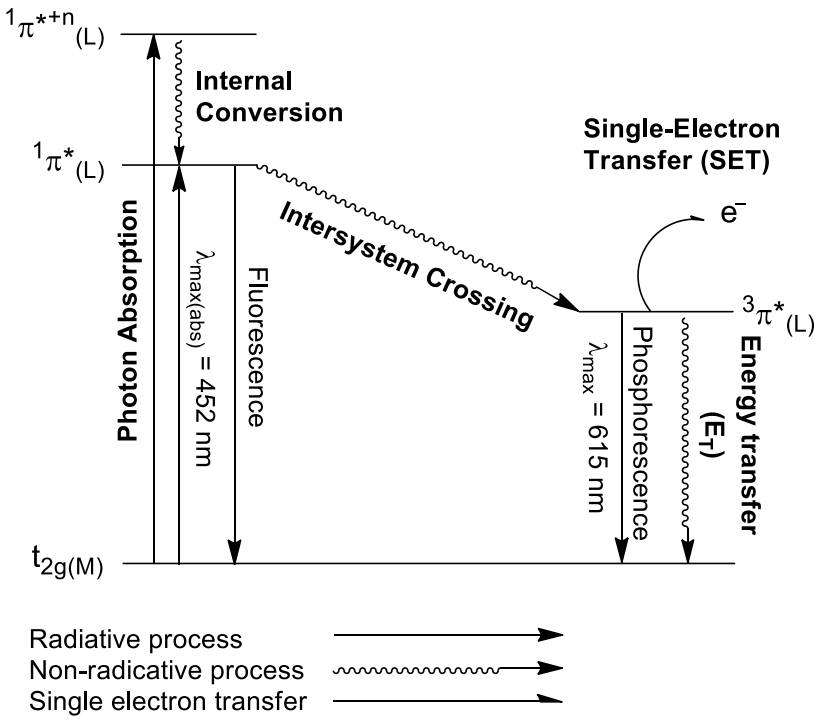


Figure 2-2. Brief Jablonski diagram for a typical photocatalyst

This process can be also explained by the brief *Jablonski* diagram. As described, the transition from the ground to the triplet-excited state is resulted from the absorption of photon from visible light. After MLCT and ISC, the long-lived, stable triplet-excited photocatalyst can be quenched by two possible pathways, including single-electron-transfer (SET) and energy transfer (E_T). In this project, SET was utilized to carry the radical chemistry.

2.2.3. Oxidative/reductive quenching cycles of photoredox catalysts

As noted in section 2.2.2, the ground state of $[Ru(bpy)_3]^{2+}$ (M) can be activated by irradiation of visible light to form its excited triplet state (*M) through MLCT and ISC. The excited photocatalyst is finally able to participate in two opposed quenching cycles; oxidative quenching cycle and reductive quenching cycle. In each quenching process, $*[Ru(bpy)_3]^{2+}$ interacts with organic substrates, either electron donor (***D***) or acceptor (***A***), through single-electron-transfer (SET). $*[Ru(bpy)_3]^{2+}$ can simultaneously act as a strong oxidant or reductant depending on the properties of substrates. (**Figure 2-3**)

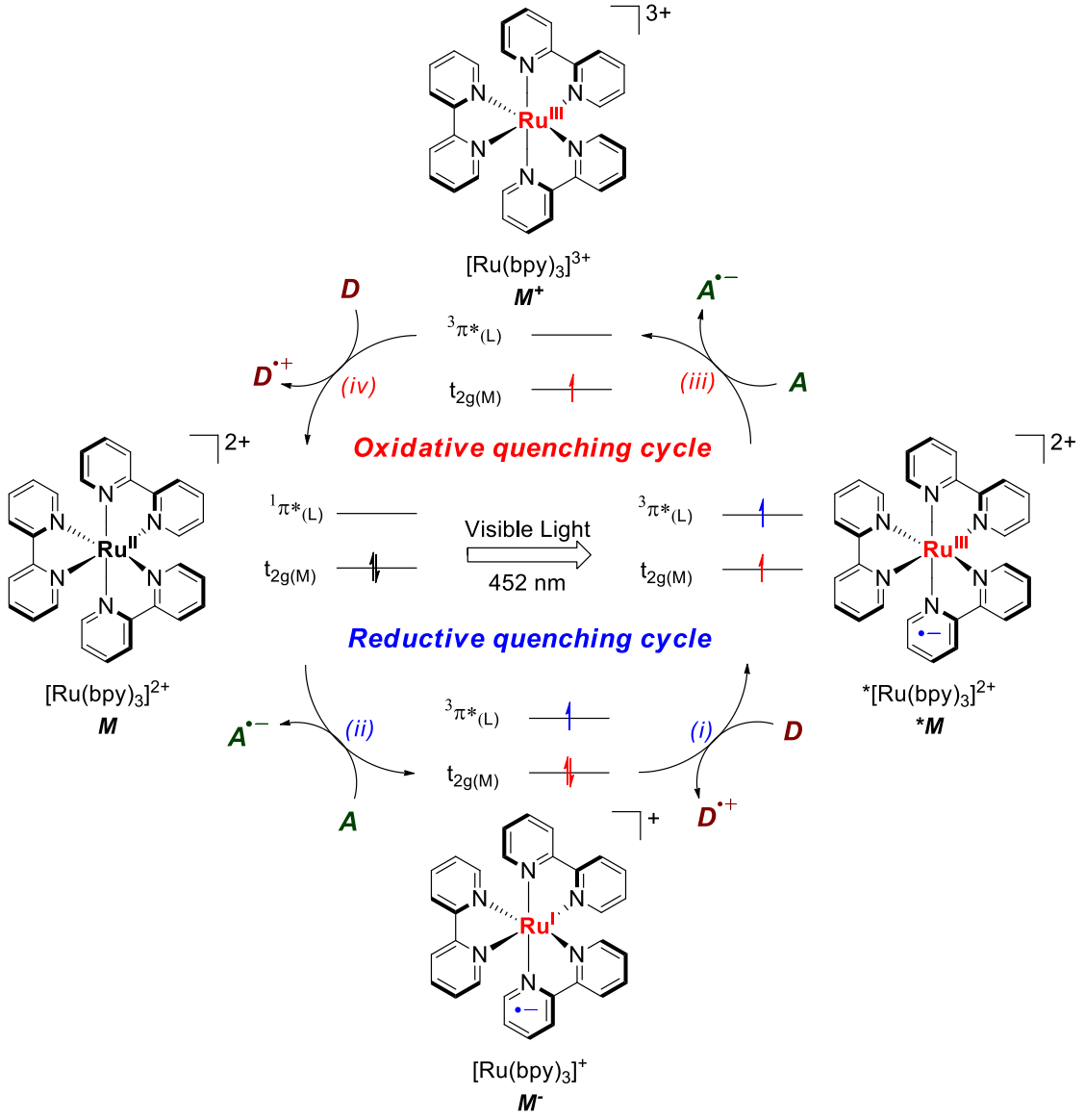


Figure 2-3. Oxidative/reductive quenching cycle of $*[Ru(bpy)_3]^{2+}$

In *reductive* quenching cycle, the excited photocatalyst is reduced first then re-oxidized. (*i*) $^{*}[Ru(bpy)_3]^{2+}$ (***M***) obtains one electron from electron donor (***D***) to fill $t_{2g(M)}$ orbital of ruthenium, resulting in the formation of radical cation ($\boldsymbol{D}^{\bullet+}$) and $[Ru(bpy)_3]^{+}$ ($\boldsymbol{M}^{-}$). (*ii*) Then, the reduced $[Ru(bpy)_3]^{+}$ ($\boldsymbol{M}^{-}$) gives up an electron from $^{3}\pi^{*}_{(L)}$ orbital to the electron acceptor (***A***), resulting in the formation of radical anion ($\boldsymbol{A}^{\bullet-}$) and regeneration of ground-state $[Ru(bpy)_3]^{2+}$ (***M***).

On the other hand, in *oxidative* quenching cycle, the excited photocatalyst is oxidized first then reduced again. (*iii*) $^{*}[Ru(bpy)_3]^{2+}$ (***M***) loses one electron from $^{3}\pi^{*}_{(L)}$ orbital of ligand to electron acceptor (***A***), resulting in the formation of radical anion ($\boldsymbol{A}^{\bullet-}$) and $[Ru(bpy)_3]^{3+}$ ($\boldsymbol{M}^{+}$). (*iv*) Then, the oxidized $[Ru(bpy)_3]^{3+}$ ($\boldsymbol{M}^{+}$) gains an electron from the electron donor (***D***), resulting in the formation of radical cation ($\boldsymbol{D}^{\bullet+}$) and regeneration of ground-state $[Ru(bpy)_3]^{2+}$ (***M***).

The meaning of *oxidative/reductive* can be ambiguous. *Oxidative* originates from the oxidation of $^{*}[Ru(bpy)_3]^{2+}$ (***M***) with reduction of electron donor (***D***). On the contrary, *reductive* originates from the reduction of $^{*}[Ru(bpy)_3]^{2+}$ (***M***) with oxidation of electron acceptor (***A***). It is worthy to note that each of quenching cycles processes its transformation via overall redox-neutral SET pathway.

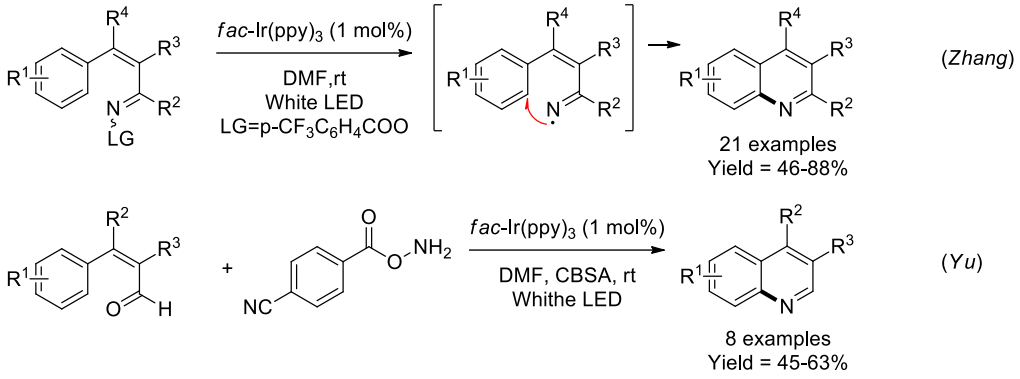
2.3. Synthesis of quinolines based on photoredox catalysis

As discussed in chapter 1, quinoline exhibits an extensive range of its biological activities.[55-60] Moreover, it is often employed to fluorescent agents due to its small size. Also, it is widely applied in DNA, RNA imaging and chemo-sensing because of its tendency not only to coordinate H-bonding of protein and nucleic acid, but also to chelate with metals.[61-64] Considering the potential of quinoline in industry, development of milder, greener and facile synthesis of it has received a great attention. Recently, the development of methodologies based on visible-light-mediated strategy is favored as a greener, sustainable approach. Therefore, a number of quinoline synthesis based on visible-light-mediated photoredox catalysis has been developed and can be categorized as the following sections.[65]

2.3.1. From iminyl or imidoyl radicals

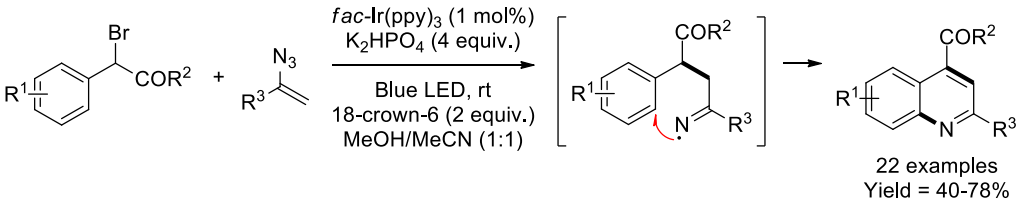
Among *N*-centered radicals in photoredox catalysis, iminyl and imidoyl radicals are usually involved in the synthesis of *N*-heterocycles. They are prepared from distinct methods with particular precursors such as *N*-acyl oximes, vinyl azide and isocyanides. In situ generated such radicals participate in the formation of quinoline under visible light irradiation.

In 2015, *Zhang* and co-workers developed a method for generation of iminyl radical from *N*-acyl oxime. Intramolecular homolytic aromatic substitution (HAS) was achieved by utilization of the radical to form quinoline.[66] In the same manner, *Yu* and co-workers developed the method to form quinoline through *in situ* generation of *N*-acyl oxime and generation of iminyl radical.[67] (**Scheme 2-1**)



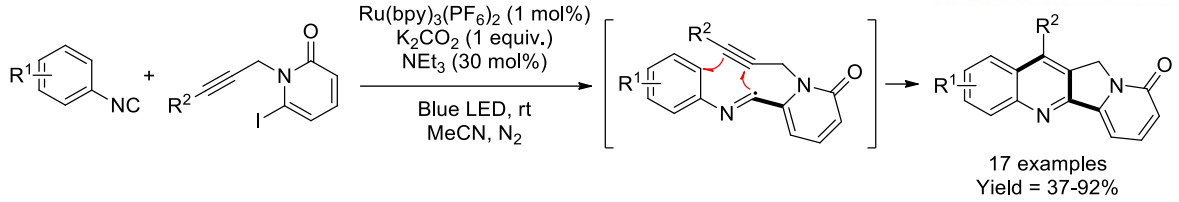
Scheme 2-1. Cyclization of *N*-acyl oximes

In the same year, *Zhou* and co-workers developed the synthesis of quinoline with vinyl azide and α-carbonyl benzyl bromide. Reduction of the bromide by the excited *[*fac*-Ir(ppy)$_3$] results in a radical intermediate and addition of the intermediate into the vinyl azide produces the desired iminyl radical. Subsequently, intramolecular aromatic substitution is followed.[68] (**Scheme 2-2**)



Scheme 2-2. Cross-coupling between vinyl azide and bromide

In 2018, *Zhang* and co-workers developed the synthesis of polycyclic quinoline by cross-coupling and cyclization between isocyanoarenes and *N*-(alkyl-2-yn-1-yl)pyridine-2(1H)-one under visible-light-mediated photoredox catalysis. The uptake of an electron of *N*-(alkyl-2-yn-1-yl)pyridine-2(1H)-one from reductively quenched [Ru(bpy)$_3$]$^+$ produces a radical intermediate, releasing iodide anion. Radical addition to isocyano group yields the desired imidoyl radical and subsequent intramolecular cyclization is followed.[69] (**Scheme 2-3**)

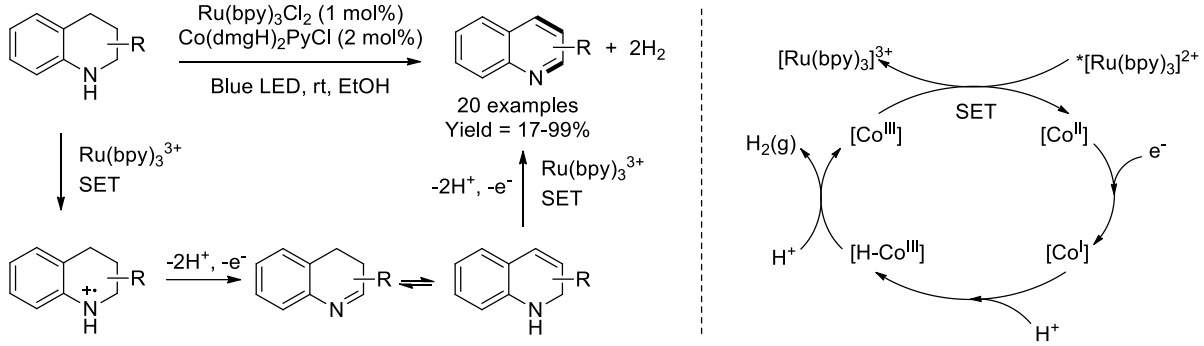


Scheme 2-3. Formation of imidoyl radical from isocyanides

2.3.2. Dehydrogenation of tetrahydroquinolines

Dehydrogenation of H-rich molecules requires quantitative amount of toxic oxidants. Therefore, removal of H atoms as H_2 gas by acceptorless dehydrogenation is highly desired because H_2 gas is non-polluting, valuable energy fuel.

In 2017, *Li* and co-workers developed dehydrogenation of tetrahydroquinolines combining photoredox catalysis with cobalt catalysis. The repetitive generation of H_2 gas can be achieved by single-electron-transfer (SET) from the excited $*[Ru(bpy)_3]^{2+}$ and uptake of protons from intermediates.[70] (**Scheme 2-4**)



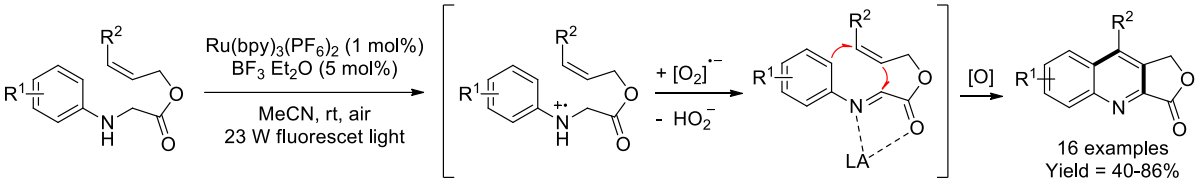
Scheme 2-4. Dehydrogenation in dual photoredox/cobalt catalysis

2.3.3. *Povarov* cyclization

Povarov reaction is a type of [4 + 2] cycloaddition between imines and alkenes, also named aza-Diels-alder reaction, yielding tetrahydroquinoline.[71] The *Povarov* reaction along with dehydrogenation (aromatization to quinoline) usually requires the use of oxidizing agents including metals or quantitative amount of DDQ or peroxides. Employment of photoredox catalysis enables to

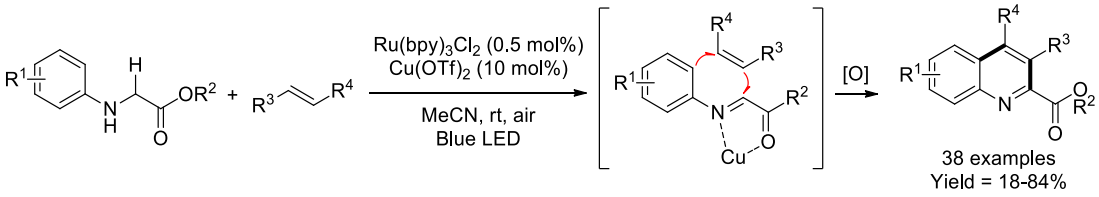
produce imine from radical cation of the electron-rich amines. Then, [4 + 2] cycloaddition between the imine and alkenes in intra/intermolecular manner followed by dehydrogenation results in the formation of quinoline in the way of simpler and cleaner way.

In 2016, *Zhang* and co-workers developed the intramolecular *Povarov* reaction mediated by visible-light-induced photoredox catalysis. The excited *$[Ru(bpy)_3]^{2+}$ oxidizes the amine to its radical cation, then imine formation is achieved by hydrogen atom abstraction by superoxide radical anion. Lewis acid-assisted intramolecular cyclization, followed by aromatization produces the desired quinoline.[72] (**Scheme 2-5**)



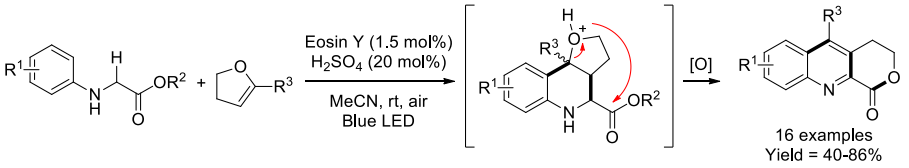
Scheme 2-5. Intramolecular *Povarov* reaction by photoredox catalysis

In the same year, *Li* and co-workers developed the intermolecular version of *Povarov* reaction through coupling between glycine esters and alkenes. The oxidation of glycine is achieved by oxidation of the excited *$[Ru(bpy)_3]^{2+}$ then imine is formed under aerobic condition. The formed imine is not only stabilized but also activated by Cu salt.[73] (**Scheme 2-6.**)



Scheme 2-6. Intermolecular *Povarov* reaction by photoredox catalysis

In 2018, *Zhang* and co-workers developed metal-free visible-light-mediated *Povarov* reaction, which involves coupling between glycine esters and 2,3-dihydrofurans. Instead of metallic photocatalyst, the generation of key intermediate, imine, was achieved by employment of Eosin Y. The resulted quinoline-fused lactone was obtained through intramolecular ester exchange.[74] (**Scheme 2-7**)

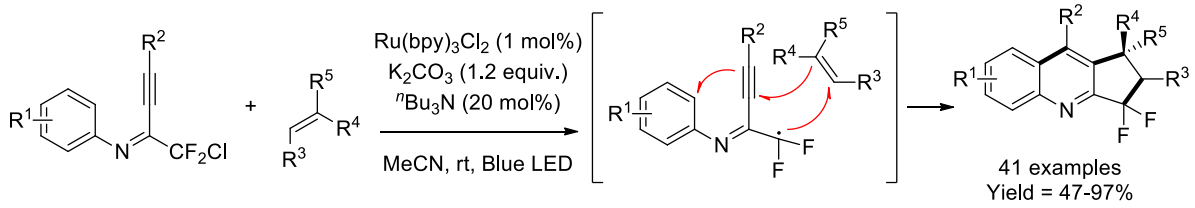


Scheme 2-7. Intermolecular *Povarov* reaction by Eosin Y

2.3.4. *N*-Propargyl aniline/imine

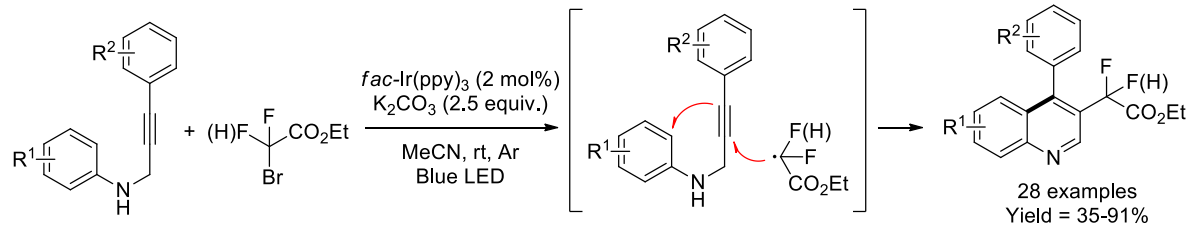
N-Propargyl amines are widely used in the synthesis of important *N*-heterocyclic compounds such as pyridine, pyrrole, 1,4-diazepane and so on.[75] They have been also utilized to the synthesis of highly substituted quinoline via cyclization and aromatization. Especially, the synthesis in photoredox catalysis usually begins with radical addition of in situ generated nucleophilic radicals on the alkyne. Then, the resulted vinyl radical participates in the cyclization, followed by aromatization.

In 2018, *Zhou* and co-workers initially developed the synthesis of quinoline from *N*-propargyl amine. The quinoline was formed by condensation between alkynyl imine and alkene and cascade radical additions. The presence of *gem*-difluorinated ring is characteristic. Due to the electronegativity and lipophilicity, exchange of proton with fluorine is important in drug design.[76] (**Scheme 2-8**)



Scheme 2-8. Synthesis of *gem*-difluorinated quinoline

In the same year, *Liu* and co-workers developed the synthesis of quinoline possessing fluorinated substituents from *N*-propargyl amines. Again, radical addition of *in situ* generated radicals from bromodifluoroacetate or bromofluoroacetate is followed by cyclization to neighboring aromatic ring. Bromodifluoroacetate and bromofluoroacetate are often employed as inexpensive fluorine source for coupling.[77] (**Scheme 2-9**)

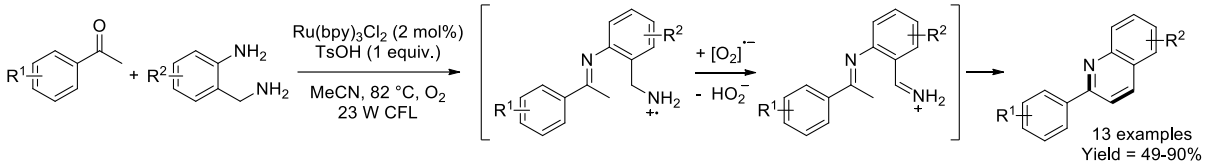


Scheme 2-9. Synthesis of fluorine-substituted quinoline

2.3.5. Aniline derivatives

Anilines have been widely employed as building blocks for construction of *N*-heterocyclic compounds. Also, aniline and its derivatives were explored in photo-catalyzed synthesis of quinolines. The following examples commonly go through the formation of imine/enamine intermediates from anilines, then subsequent oxidation by photocatalyst enables intramolecular radical cyclization.

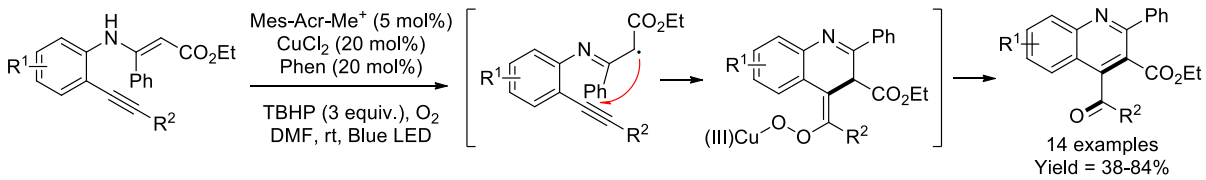
In 2016, *Zhang* and co-workers developed the synthesis of 2-arylquinoline from the coupling between aromatic ketones and 2-aminobenzylamine. Condensation between ketone and aniline results in the formation of amino-imine, which is oxidized by the excited $*[Ru(bpy)_3]^{2+}$. The oxidized radical cation is further oxidized by superoxide ion then followed hydrolysis produces aldehyde-imine. Intramolecular cyclization and elimination of resulted alcohol form 2-arylquinolines.[78] (**Scheme 2-10**)



Scheme 2-10. Synthesis of 2-arylquinoline

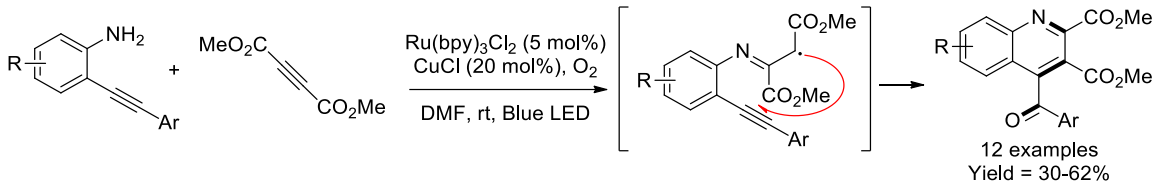
In 2017, *Xia* and co-workers developed the synthesis of 4-carbonyl-quinolines and quinoline-2,3-dicarboxylate via oxidative intramolecular/intermolecular cyclization with photoredox catalysts in the presence of oxygen.[79]

Initially, the intramolecular version of photo-oxidative cyclization was achieved with *ortho*-alkynyl enamine The organic photocatalyst, Mes-Acr-Me^+ is irradiated by visible light, then oxidizes the enamine to form its radical cation intermediate. The resonance form of the radical cation, which is stabilized by the presence of electron-withdrawing group, participates in radical cyclization, followed by deprotonative *O*-*O* cleavage supported by copper to produce 4-carbonyl-quinoline (**Scheme 2-11**)



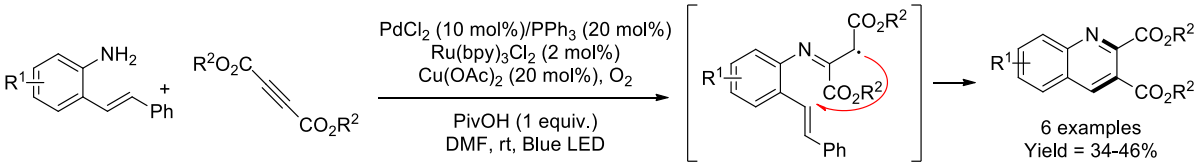
Scheme 2-11. Intramolecular synthesis of 4-carbonyl-quinoline

The concept of oxidative radical cyclization was also tolerated with the intermolecular version between *ortho*-alkynyl aniline and dimethyl acetylenedicarboxylate. The Michael-addition product also gets oxidized by the excited $*[Ru(bpy)_3]^{2+}$ and follows the same mechanism. (**Scheme 2-12**)



Scheme 2-12. Intermolecular synthesis of 4-carbonyl-quinoline

Intermolecular addition/radical cyclization strategy was extended to *o*-alkenyl aniline in the presence of palladium. The addition of amine into the activated alkyne is mediated by palladium, then photo-oxidative radical cyclization is followed. Instead of *O-O* cleavage in the version of *o*-alkynyl aniline, oxidative *C-C* cleavage affords quinoline-2,3-dicarboxylates. (**Scheme 2-13**)



Scheme 2-13. Intermolecular synthesis of quinoline-2,3-dicarboxylate

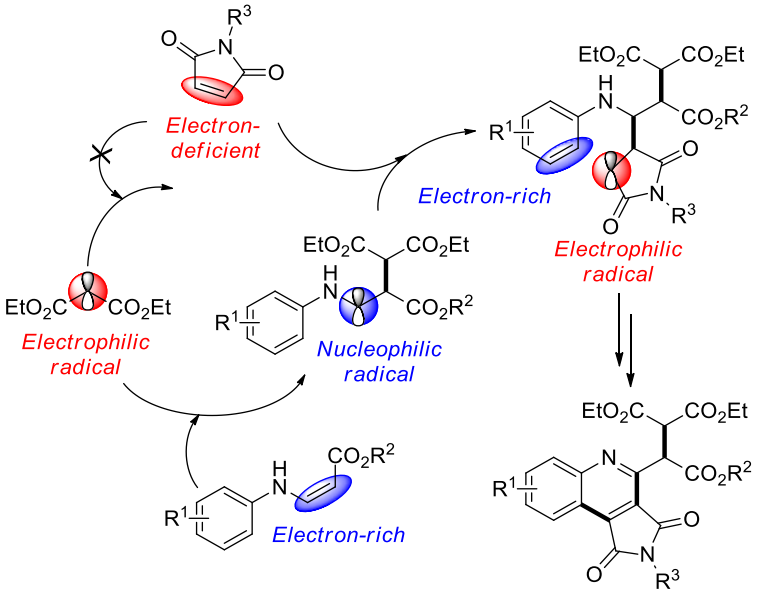
Even though all the developments of synthesis of quinoline in photoredox catalysis are useful in a various aspect, the synthesis in the strategy of multicomponent reaction has not been developed.

Chapter 3. Three-Component Synthesis of Quinolines based on Radical Cascade Visible-light Photoredox Catalysis

3.1. Design of synthesis of quinoline

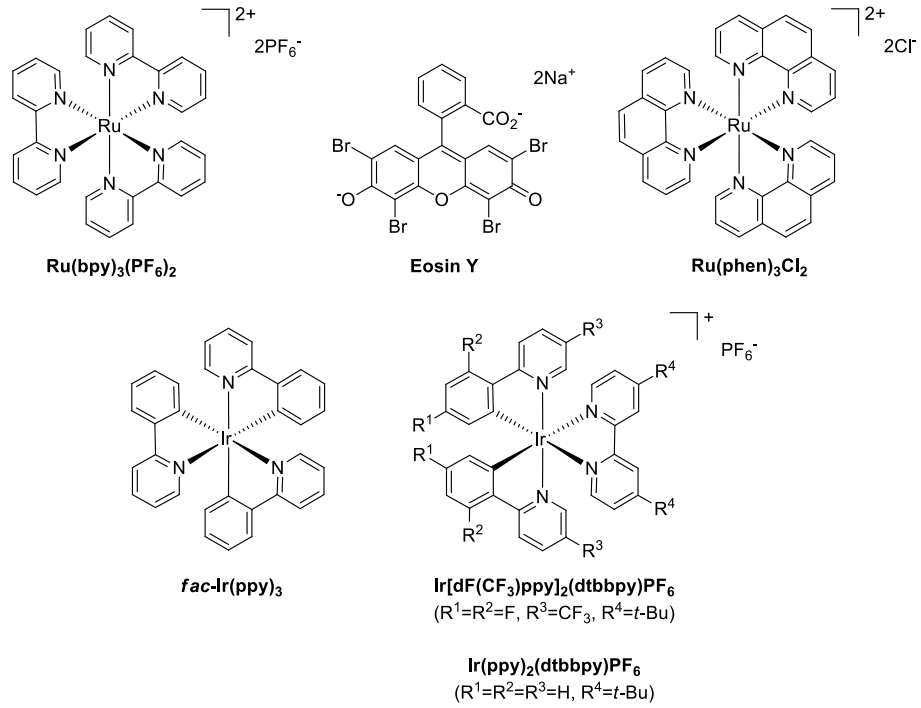
Due to their utilities, significant efforts have been made to develop efficient synthetic methods for quinolines. Conventional synthesis including *Miller*, *Skraup*, *Friedländer*, *Combes*, *Pfitzinger*, and *Conrad-Limpach* reactions typically relies on condensation under harsh conditions and often leads to poor regioselectivity. In order to overcome these limitations, transition metal-catalyzed reactions, iodine-mediated reactions as well as visible-light photoredox reactions have been developed.

In this report, we wish to describe quinoline synthesis based on radical cascade three-component reaction catalyzed by visible-light photoredox catalysis. We envisioned that coordination of the chemoselectivity among reactants may be feasible by the differential electronic properties of radical sources and acceptors such that the tandem cyclization of the three coupling partners smoothly proceeds in order (**Scheme 3-1**). Thus, we reasoned that the combination of *electron-rich β*-aminoacrylates with *electron-deficient* halides and alkenes as the reactants would meet the requirement. Detailed mechanistic studies led us to propose an unexpected reaction mechanism.



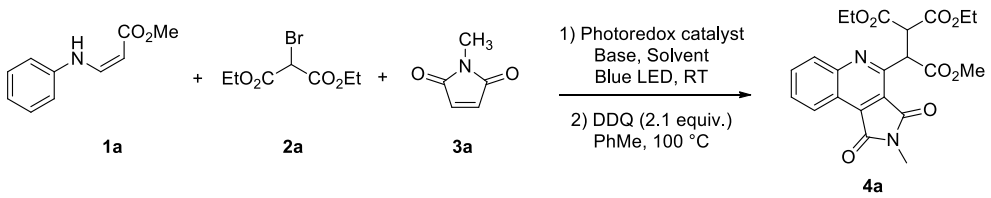
Scheme 3-1. Three-Component synthesis of quinolines based on radical cascade visible-light photoredox catalysis

3.2. Reaction optimization for synthesis of quinoline



Scheme 3-2. Photoredox catalysts used in **Table 3-1.**

Table 3-1. First optimization of reaction condition in absence of electron donor [a, b]



Entry	**2a** (equiv.)	**3a** (equiv.)	Photoredox catalyst (mol %)	Base (equiv.)	Solvent (M)	Time (hour)	Yield (%)
1	1	2	$Ru(bpy)_3(PF_6)_2$ (2)	$NaHCO_3$ (2)	MeCN (0.2)	18	Trace
2	1	2	Eosin Y (2)	$NaHCO_3$ (2)	MeCN (0.2)	18	14%
3	1	2	$Ru(phen)_3Cl_2$ (2)	$NaHCO_3$ (2)	MeCN (0.2)	18	20%
4	1	2	$Ir(ppy)_3$ (2)	$NaHCO_3$ (2)	MeCN (0.2)	18	45%
5	1	2	$Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$ (2)	$NaHCO_3$ (2)	MeCN (0.2)	18	47%
6	1	2	$Ir(ppy)_2(dtbbpy)PF_6$ (2)	$NaHCO_3$ (2)	MeCN (0.2)	18	58%
7	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (2)	MeCN (0.2)	18	66%
8	1.5	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (3)	MeCN (0.2)	18	45%
9	2	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (3)	MeCN (0.2)	18	40%

10	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (2)	Acetone (0.2)	18	63%
11	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (2)	DMF (0.2)	18	65%
12	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (2)	DCM (0.2)	18	38%
13	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (2)	$CHCl_3$ (0.2)	18	45%
14	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (2)	1,2-DCE (0.2)	18	31%
15	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (2)	EtOAc (0.2)	18	38%
16	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (2)	THF (0.2)	18	36%
17	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (2)	DMSO (0.2)	18	Trace
18	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (2)	NMP (0.2)	18	Trace
19	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (2)	MeOH(0.2)	18	Trace
20	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (2)	PhH (0.2)	18	Trace
21	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (2)	MeCN (0.4)	18	43%
22	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (2)	MeCN (0.1)	18	73%
23	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$NaHCO_3$ (2)	MeCN (0.05)	18	76%
24	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	$KHCO_3$ (2)	MeCN (0.05)	18	76%
25	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	Na_2HPO_4 (2)	MeCN (0.05)	18	78%
26	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	K_2HPO_4 (2)	MeCN (0.05)	18	72%
27	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	NaH_2PO_4(2)	MeCN (0.05)	18	43%
28	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	KH_2PO_4 (2)	MeCN (0.05)	18	33%
29	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	NaOAc (2)	MeCN (0.05)	18	71%
30	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	KOAc (2)	MeCN (0.05)	18	Trace
31	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	Na_3PO_4 (2)	MeCN (0.05)	18	73%
32	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	K_3PO_4 (2)	MeCN (0.05)	18	Trace
33	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	Cs_2CO_3 (2)	MeCN (0.05)	18	Trace
34	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	CsOAc (2)	MeCN (0.05)	18	Trace
35	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	CsF (2)	MeCN (0.05)	18	Trace
36	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	DBU (2)	MeCN (0.05)	18	Trace
37	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	DABCO (2)	MeCN (0.05)	18	Trace
38	**1**	**3**	**$Ir(ppy)_2(dtbbpy)PF_6$ (3)**	**Na_2HPO_4 (1)**	**MeCN (0.05)**	**18**	**81%**
39	1	3	$Ir(ppy)_2(dtbbpy)PF_6$ (3)	Na_2HPO_4 (3)	MeCN (0.05)	18	79%

[a] Reactions were conducted under argon atmosphere with 0.05 mmol scale.

[b] Yields were calculated based on NMR yield; 1,1,2-trichloroethene used as internal standard.

Our initial attempts commenced with the reaction of β-aminoacrylate **1a** (1 equiv.) with diethyl bromomalonate **2a** (1 equiv.) and *N*-methyl maleimide **3a** (2 equiv.) in MeCN (0.2 M) in the presence of $NaHCO_3$ (2 equiv.) under blue irradiation of blue light from LED stripe at room temperature. Upon completion of the reaction under visible light, teterhydroquinoline intermediate was directly oxidized to quinoline **4a** with with 2,3- Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). All yields in **Table 3-1** were calculated based on ^{1}H NMR spectroscopic analysis in the presence of stoichiometric amount of 1,1,2-trichloroethene as an internal standard.

We started the optimization with the survey of various photoredox catalysts. The use of $Ru(bpy)_3(PF_6)_2$ gave a trace amount of the three-component coupling product **4a** (Entry 1). While an improved but low yield (20%) of **4a** was obtained with $Ru(phen)_3Cl_2$ (Entry 3), iridium-based complexes provided more promising results with $Ir(ppy)_2(dtbbpy)PF_6$ giving a highest yield (58%) among other iridium-based complexes (Entries 4~6). On the other hand, organic dye Eosin Y turned out to be much less effective than the iridium catalysts (Entry 2). To examine the influence of catalyst loading and the equivalence of alkene **3a** on the efficiency of the reaction, increased amounts of $Ir(ppy)_2(dtbbpy)PF_6$ (3 mol%) and **3a** (3 equiv.) were employed, which resulted in a slightly improved yield (66%) (Entry 7). In contrast, the increased amount of radical source **2a** led to diminished yields; 1.5 equiv. and 2 equiv. gave 45% and 40%, respectively (Entries 8, 9).

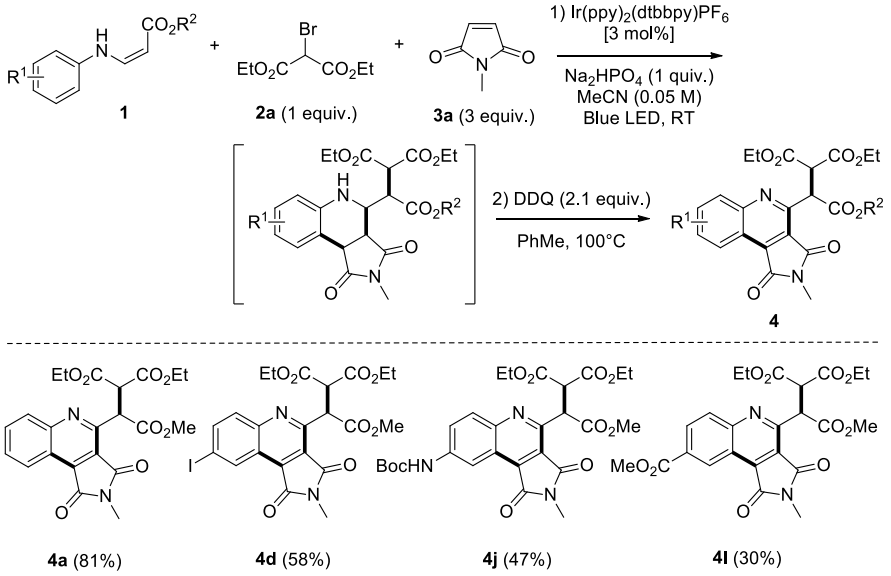
Next, we observed the significant solvent effects when a variety of solvents were tested. Acetonitrile, acetone and DMF gave comparable yields (68%, 65%, and 63%, respectively) (Entries 7, 10, 11), while other chlorinated solvents, EtOAc and THF gave quinoline **4a** in moderate yields (Entries 12~16). Interestingly, trace amounts of quinoline **4a** were obtained when other polar solvents (DMSO, NMP and MeOH) were employed (Entries 17~19). Also, the use of nonpolar solvent such as benzene afforded a poor result (Entry 20). Since the reaction involves tandem intermolecular reaction followed by intramolecular cyclization, we anticipated that reaction concentration would play an important role. It turned out that high reaction concentration (0.4 M) is detrimental to the reaction efficiency as yield decreased to 43% as opposed to 66% with 0.2 M concentration. (Entry 21). On the contrary to this, dilution of reaction mixture to lower concentration (0.1 M and 0.05 M) gave the improved yields (73% and 76%, respectively) (Entries 22 and 23).

With the optimal reaction concentration identified, we became intrigued by the effect of base. It appeared that no such counter ion effect was observed for bases including bicarbonate, mono and dibasic phosphates, affording comparable yields with both sodium and potassium cations ($NaHCO_3$ vs. $KHCO_3$, 76% vs. 76%; Na_2HPO_4 vs. K_2HPO_4, 78% vs. 72%; NaH_2PO_4 vs. KH_2PO_4, 43% vs. 33%) (Entries 23~28). On the other hand, for certain inorganic bases including acetates and

phosphates, counter cations have the crucial impact for the efficient transformation (NaOAc vs. KOAc, 71% vs. trace; Na_3PO_4 vs. K_3PO_4, 73% vs. trace) (Entries 29~32). None of cesium salts (Cs_2CO_3, CsOAc, and CsF) and amine bases (DBU and DABCO) gave the coupling product (Entries 33-37). Finally, the equivalence of base could be reduced without affecting the reaction efficiency (Entry 38 vs Entries 25 and 39).

3.3. Preliminary result

Table 3-2. Preliminary result with optimized reaction condition in **Table 3-1**. [a, b]

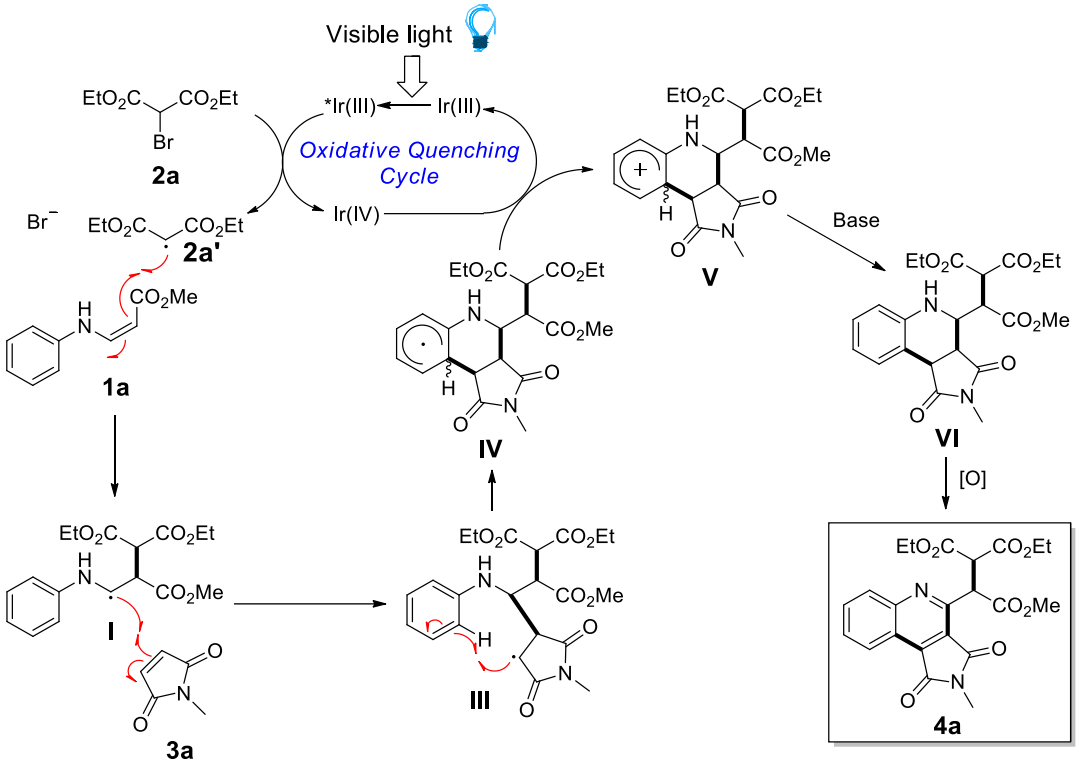


[a] Reaction conditions: **1** (0.1 mmol), **2a** (0.1 mmol), **3a** (0.3 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (3 mol%), Na_2HPO_4 (0.1 mmol), MeCN (0.05 M), DDQ (0.21 mmol), toluene (0.1 M).

[b] isolated yield.

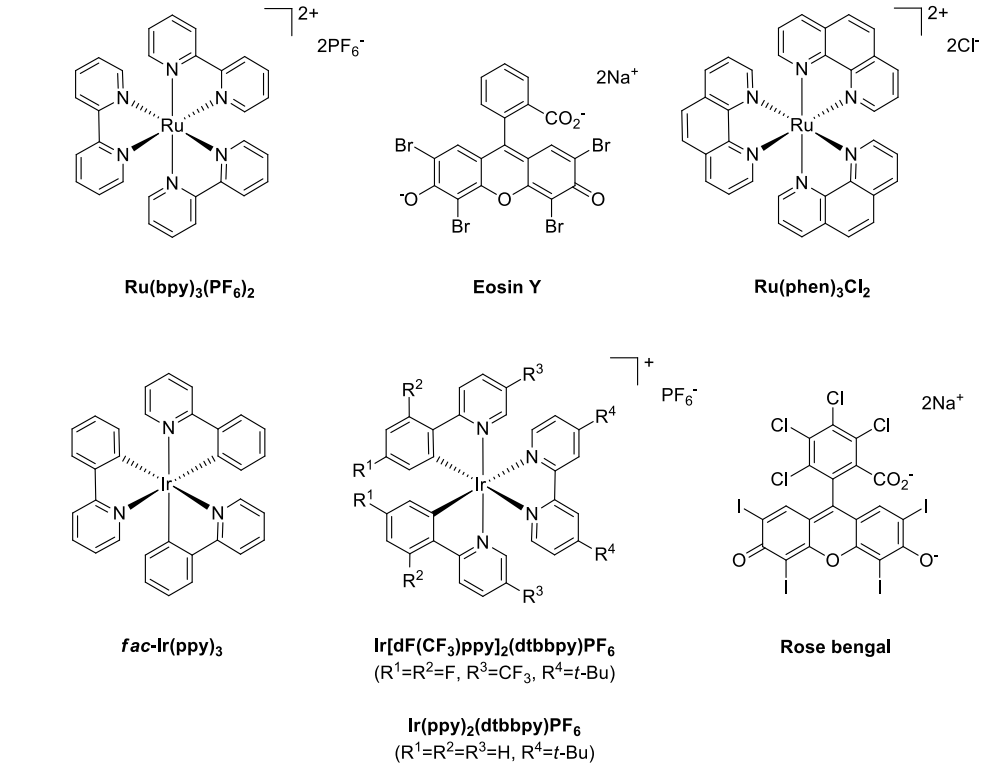
With the optimized conditions in hand, we turned our attention to the scope of this reaction, in which various β-aminoacrylates **1** have been investigated for their reactivity in this three-component reaction. However, the reaction conditions turned out to be unsatisfactory in that β-aminoacrylates **1** containing functionalized aryl groups such as **1d**, **1j** and **1l** gave poor to moderate yields with extended reaction time for completion (30 h) (**Table 3-2**).

In this stage, we mechanistically propose that oxidative quenching of the excited photocatalyst $Ir^{(III)*}$ by a single electron transfer (SET) process to electron-deficient bromide **2a** initiates the reaction by the generation of the corresponding *electrophilic* radical **2a'**, which reacts with *electron-rich* β-aminoacrylate **1a** to give α-amino radical **I**. Subsequent intercept of the *nucleophilic* α-amino radical **I** by *electron-deficient* alkene **3a** leads to the formation of another *electron-deficient* radical species **III**, which undergoes annulation by addition to the aryl group of **III**. Finally, oxidation of aryl radical intermediate **IV** by the photocatalyst affords tetrahydroquinoline **VI**. Formation of quinoline **4a** is achieved by one-pot oxidation of the tetrahydroquinoline with DDQ (**Scheme 3-3**).



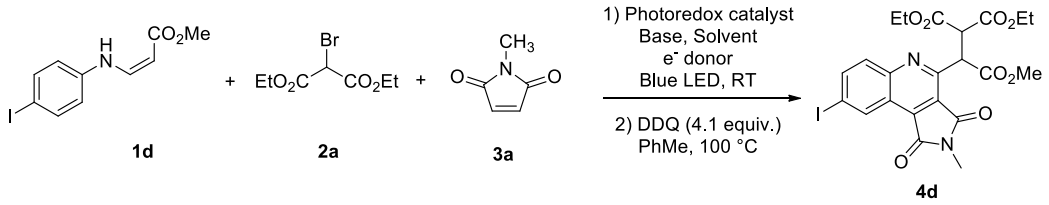
Scheme 3-3. Initially proposed reaction mechanism with preliminary result

3.4. Second reaction optimization



Scheme 3-4. Photoredox catalysts used in **Table 3-3**

Table 3-3. Second optimization of reaction condition in presence of electron donor [a, b]



Entry	**2a** (equiv.)	**3a** (equiv.)	Photoredox catalyst (mol%)	e^- donor (equiv.)	Base (equiv.)	Solvent (M)	Time (hour)	Yield (%)
1	1	3	$Ru(phen)_3Cl_2$ (3)	NaAsc (2)	Na_2HPO_4 (1)	Acetone (0.05)	18	17
2	1	3	$Ru(bpy)_3(PF_6)_2$ (3)	NaAsc (2)	Na_2HPO_4 (1)	Acetone (0.05)	18	30
3	1	3	$Ir[dF(CF_3)ppy]_2$ (dtbbpy)PF_6 (3)	NaAsc (2)	Na_2HPO_4 (1)	Acetone (0.05)	18	67
4	1	3	$Ir(ppy)_2$(dtbbpy) PF_6 (3)	NaAsc (2)	Na_2HPO_4 (1)	Acetone (0.05)	18	75
5	1	3	*fac*-$Ir(ppy)_3$ (3)	NaAsc (2)	Na_2HPO_4 (1)	Acetone (0.05)	18	77
6	1	3	Eosin Y (3)	NaAsc (2)	Na_2HPO_4 (1)	Acetone (0.05)	18	38

7	1	3	Rose Bengal (3)	NaAsc (2)	Na_2HPO_4 (1)	Acetone (0.05)	18	33
8	1	3	$Ir(ppy)_3$ (3)	DIPEA (2)	Na_2HPO_4 (1)	Acetone (0.05)	18	19
9	1	3	$Ir(ppy)_3$ (3)	$^iPr_2NH$ (2)	Na_2HPO_4 (1)	Acetone (0.05)	18	18
10	1	3	$Ir(ppy)_3$ (3)	(4-MeO-Ph) Ph_2N (2)	Na_2HPO_4 (1)	Acetone (0.05)	18	74
11	1	3	$Ir(ppy)_3$ (3)	DABCO (2)	Na_2HPO_4 (1)	Acetone (0.05)	18	Trace
12	1	3	$Ir(ppy)_3$ (3)	Hantzsch ester (2)	Na_2HPO_4 (1)	Acetone (0.05)	18	17
13	1	3	$Ir(ppy)_3$ (3)	Ascorbic acid (2)	Na_2HPO_4 (1)	Acetone (0.05)	18	63
14	**1.2**	**3**	**$Ir(ppy)_3$ (3)**	**NaAsc (2)**	**Na_2HPO_4 (1.2)**	**Acetone (0.05)**	**18**	**84**
15	1.5	3	$Ir(ppy)_3$ (3)	NaAsc (2)	Na_2HPO_4 (1.5)	Acetone (0.05)	18	75
16	2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	Na_2HPO_4 (2)	Acetone (0.05)	18	71
17	1.2	2	$Ir(ppy)_3$ (3)	NaAsc (2)	Na_2HPO_4 (1.2)	Acetone (0.05)	18	69
18	1.2	4	$Ir(ppy)_3$ (3)	NaAsc (2)	Na_2HPO_4 (1.2)	Acetone (0.05)	18	81
19	1.2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	NaOAc (1.2)	Acetone (0.05)	18	31
20	1.2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	KOAc (1.2)	Acetone (0.05)	18	trace
21	1.2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	$NaHCO_3$ (1.2)	Acetone (0.05)	18	80
22	1.2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	$KHCO_3$ (1.2)	Acetone (0.05)	18	50
23	1.2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	K_2HPO_4 (1.2)	Acetone (0.05)	18	72
24	1.2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	Na_2CO_3 (1.2)	Acetone (0.05)	18	59
25	1.2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	Cs_2CO_3 (1.2)	Acetone (0.05)	18	trace
26	1.2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	DBU (1.2)	Acetone (0.05)	18	trace
27	1.2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	Na_2HPO_4 (1.2)	MeCN (0.05)	18	74
28	1.2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	Na_2HPO_4 (1.2)	DMF (0.05)	18	49
29	1.2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	Na_2HPO_4 (1.2)	DMSO (0.05)	18	19
30	1.2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	Na_2HPO_4(1.2)	CH_2Cl_2 (0.05)	18	trace
31	1.2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	Na_2HPO_4 (1.2)	$CHCl_3$ (0.05)	18	41
32	1.2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	Na_2HPO_4 (1.2)	EtOAc (0.05)	18	trace
33	1.2	3	$Ir(ppy)_3$ (3)	NaAsc (2)	Na_2HPO_4 (1.2)	MeOH (0.05)	18	trace
34	1.2	3	-	NaAsc (2)	Na_2HPO_4 (1.2)	Acetone (0.05)	18	trace
35	1.2	3	$Ir(ppy)_3$ (3) **<dark>**	NaAsc (2)	Na_2HPO_4 (1.2)	Acetone (0.05)	18	trace

[a] Reactions were conducted under argon atmosphere with 0.05 mmol scale.

[b] Yields were calculated based on NMR yield; 1,1,2-trichloroethene used as internal standard.

We envisaged that addition of an external electron donor may increase the efficiency of the catalytic cycle. The results on the combination of various catalysts and reducing agents are summarized in **Table 3-3**.

By employing **1d** as a benchmark along with sodium ascorbate (NaAsc) as an external electron donor, we surveyed various photoredox catalysts. **4d** was obtained in poor yields after *in-situ* oxidation of the tetrahydroquinoline when ruthenium-based catalysts including $Ru(phen)_3Cl_2$ and $Ru(bpy)_3(PF_6)_2$ were used (Entries 1 and 2; 17%, and 30%, respectively). Iridium-based complexes provided more promising results with *fac*-$Ir(ppy)_3$ giving an improved yield (77%, Entry 5). On the other hand, organic dyes including Eosin Y and Rose Bengal turned out to be inferior to iridium catalysts (Entries 6 and 7).

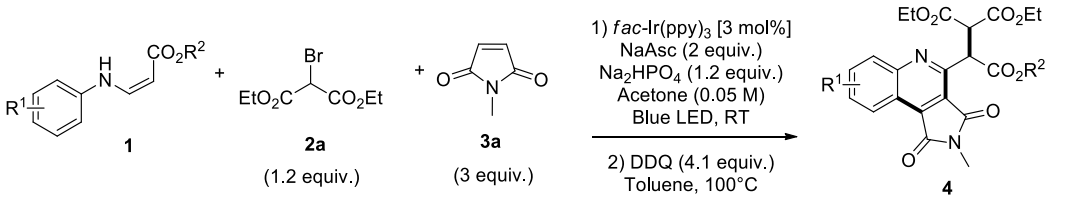
Next, with *fac*-$Ir(ppy)_3$ as an optimal photocatalyst, we examined the effects of various electron donors. Alkyl amines including diisopropylethylamine (DIPEA) ($E_{p/2}^{ox}$ = + 0.65 V vs SCE in MeCN at 25 ℃)[80] and diisoproylamine ($E_{p/2}^{ox}$ = + 1.09 V vs SCE in MeCN at 25 ℃)[81] gave low yields (19% and 18%, respectively) (Entries 8 and 9), while 74% of quinoline **4d** was obtained when 4-methoxy-*N*,*N*-diphenylaniline ($E_{p/2}^{ox}$ = + 0.82 V vs Ag/AgCl in MeCN at 25 ℃, see experimental data) was employed (Entry 10). Widely used electron donors including DABCO ($E_{p/2}^{ox}$ = + 0.69 V vs SCE in MeCN at 25 ℃)[82] and Hantzsch ester ($E_{p/2}^{ox}$ = + 0.72 V vs SCE in MeCN at 25 ℃)[83] proved to be ineffective (trace and 17%, Entries 11 and 12, respectively). Replacement of NaAsc ($E_{p/2}^{ox}$ = + 0.33 V vs Ag/AgCl in MeCN at 25 ℃)[84] to ascorbic acid resulted in a decrease in yield (77% to 63%, Entries 5 and 13, respectively).

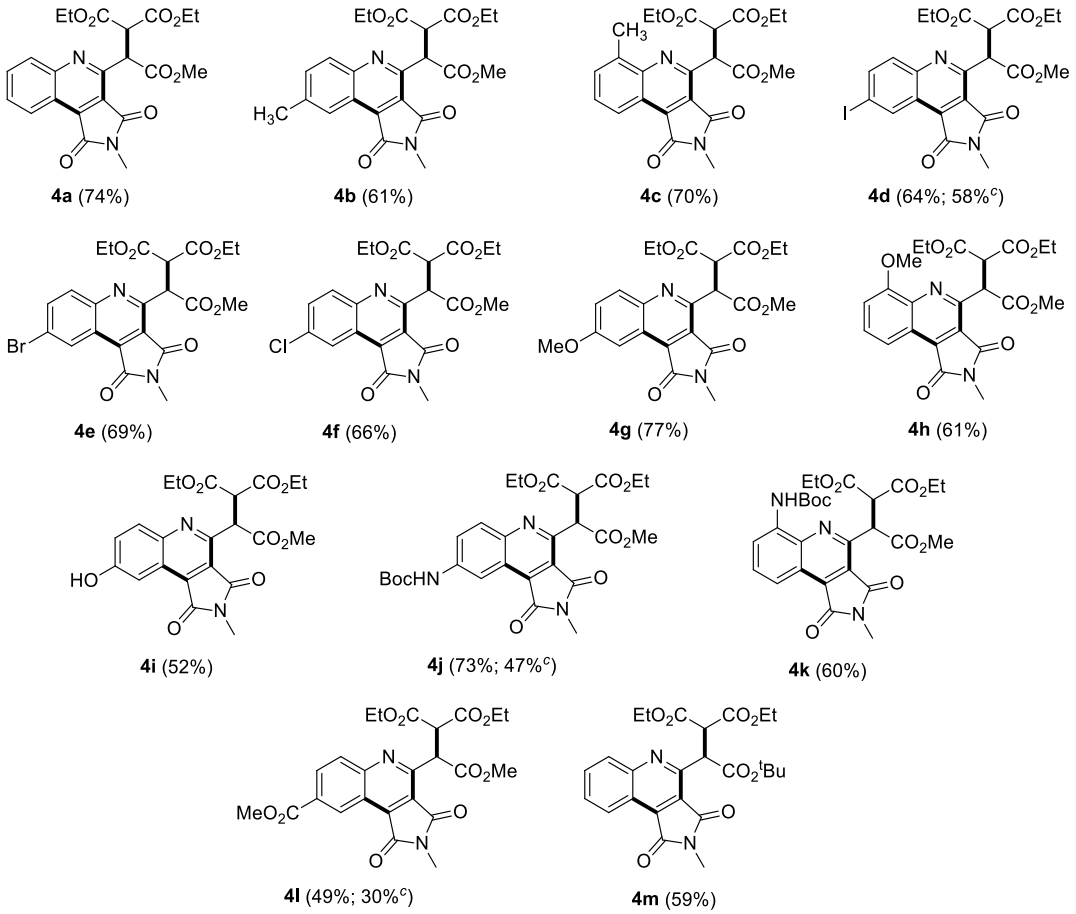
With NaAsc as the optimized electron donor in hand, the stoichiometric control of reactants (radical source **2a** and coupling partner **3a**) was followed. The minor increase of **2a** (1.2 equiv.) along with the equal amount of base (1.2 equiv.) leaded the improvement of yield up to 84% (Entry 14), while further increase of both showed the tendency of decrease in yield (75% and 71%, Entries 15 and 16, respectively). Plus, the reduced amount of **3a** to 2 equiv. and increased amount of **3a** to 4 equiv. was not effective, indicating 3 equiv. of **3a** was the optimal amount (Entries 17 and 18).

The detailed investigation on bases and solvents was conducted in the same manner of **Table 3-1**, indicating that the use of Na_2HPO_4 (1.2 equiv.) was still helpful, while the optimal solvent was changed from acetonitrile to acetone (Entries 19~33). Finally, control experiments performed in the absence of either catalyst or visible light showed no product formation, which supported that the reaction is indeed mediated by visible light photoredox catalysis (entries 34 and 35).

3.5. Substrate scope in β-aminoacrylate

Table 3-4. Substrate scope in β-aminoacrylate **1** [a, b]





[a] Reaction conditions: **1** (0.1 mmol), **2a** (0.12 mmol), **3a** (0.3 mmol), *fac*-Ir(ppy)$_3$ (3 mol%), sodium ascorbate (0.2 mmol), Na_2HPO_4 (0.12 mmol), acetone (0.05 M) then, 2,3- Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.41 mmol), toluene (0.1 M).

[b] All isolated yield.

[c] Isolated yield with reaction condition described in **Table 3-2**.

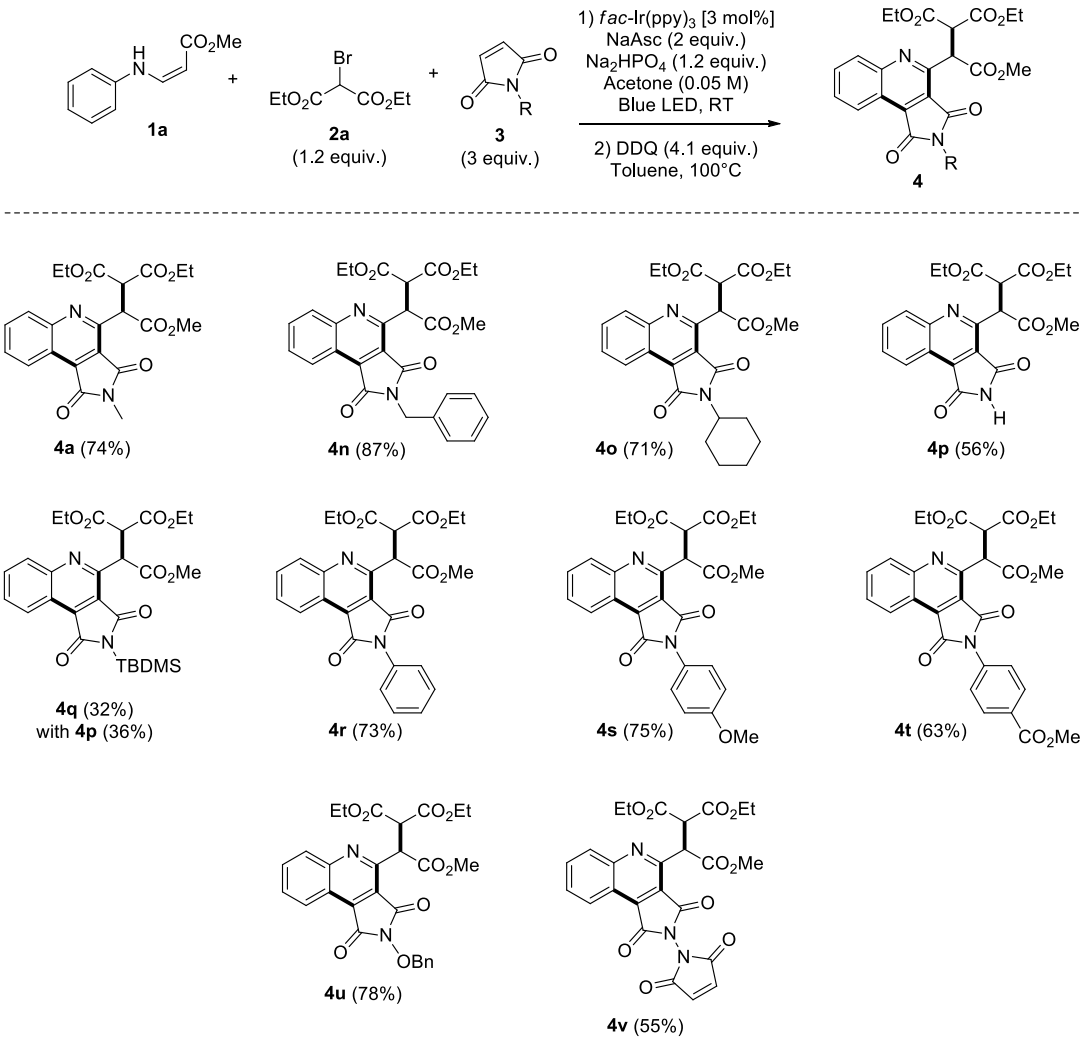
With the newly optimized conditions in hand, we turned our attention to the scope of the developed reaction, in which various β-aminoacrylates **1** have been investigated for their reactivity in this three-component coupling (**Table 3-4**).

We began by examining the influence of various substituents on the aromatic ring on the reaction. Substitution with a methyl group on the *para* or *ortho* position was tolerated to afford the corresponding quinolines **4b** and **4c** after oxidation with DDQ. Even though one of the two positions available in annulation step was blocked by the *ortho*-methyl group, substitution on *ortho* position did not affect the formation of quinolines **4c**. We also examined the tolerability of different halides under the reaction condition and found that iodo, bromo, and chloro- substituted quinolines **4d**, **4e**, **4f** could be prepared in good yields. The reaction with the substrates bearing electron-donating groups such as methoxy group proceeded smoothly to give **4g** and **4h**, while that with a free hydroxy group gave the corresponding quinoline **4i** in a moderate yield. Aminoquinolines **4j** and **4k** were successfully synthesized by employing substrates containing Boc-protected amine **1j** and **1k**. Also, that bearing electron-deficient aryl group **1l** gave the corresponding quinoline **4l** in moderate yield. β-aminoacrylate **1m** containing a bulky *tert*-butyl ester, instead of methyl ester, successfully participated in the reaction to give **4m**.

3.6. Substrate scope in C-C unsaturated bonds and halides

3.6.1. Substrate scope in maleimide

Table 3-5. Substrate scope in maleimide **3** [a, b]



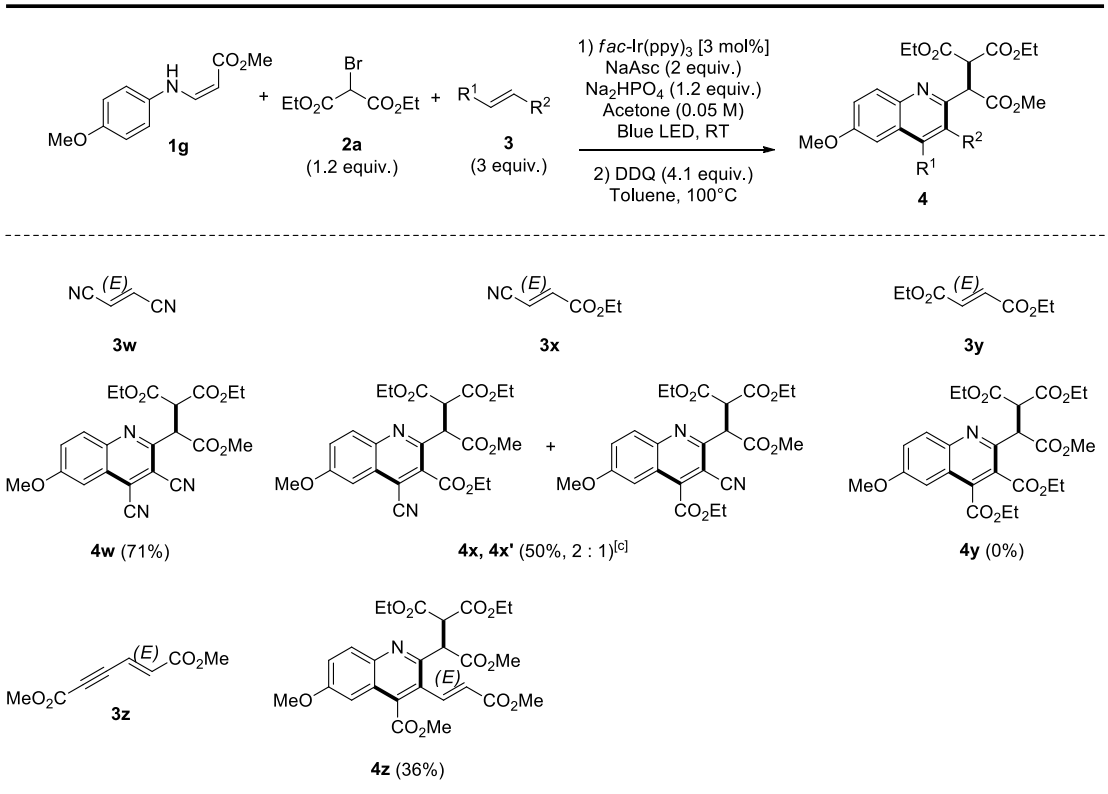
[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), **3** (0.3 mmol), *fac*-Ir(ppy)$_3$ (3 mol%), sodium ascorbate (0.2 mmol), Na_2HPO_4 (0.12 mmol), acetone (0.05 M) then, 2,3- Dichloro-5,6-dicyano-1,4-benzoquinone (0.41 mmol), toluene (0.1 M).
[b] All isolated yield.

Next, we examined the effect of substituents on maleimide **3** (**Table 3-5**). The use of maleimides with *N*-alkyl groups including methyl, benzyl and cyclohexyl groups provided the corresponding quinolines **4a**, **4n** and **4o** in good yields. While the maleimide lacking a *N*-substituent **3p** furnished **4p** in moderate yield (56%), TBDMS-protected maleimide **3q** provided the corresponding quinoline **4q** along with the deprotected quinoline **4p** in 68% yield (almost 1:1).

In order to investigate electronic effects, maleimides **3r**, **3s** and **3t** bearing aryl groups with different electronic properties were subjected to the reaction. Whereas phenyl substituted **3r** and electron-rich **3s** respectively provided quinoline **4r** and **4s** in similar yields, the use of the maleimide bearing an electron-deficient aryl group **3t** resulted in relatively lower yield (63%). We also examined the compatibility of maleimide containing *N*-alkoxy group, which is known to be labile under photoredox conditions.[85] Gratifyingly, **3u** with a benzyloxy group gave **4u** in 78% yield. With the anticipation of *bis*-quinoline formation, we employed [1,1'-bipyrrole]-2,2',5,5'-tetraone **3v** as a coupling partner, however, it gave only mono-annulated product **4v** in 55% yield. Interestingly, when **4v** was re-subjected to the reaction as a coupling partner, the second annulation did not proceed.

3.6.2. Substrate scope in activated unsaturated C-C bonds

Table 3-6. Substrate scope in activated unsaturated bond [a, b]

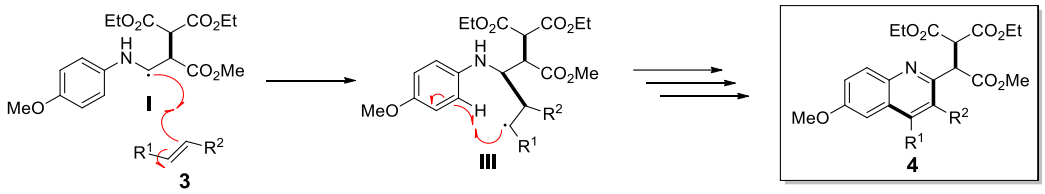


[a] Reaction conditions: **1g** (0.1 mmol), **2a** (0.12 mmol), **3** (0.3 mmol), *fac*-Ir(ppy)$_3$ (3 mol%), sodium ascorbate (0.2 mmol), Na_2HPO_4 (0.12 mmol), acetone (0.05 M) then, 2,3- Dichloro-5,6-dicyano-1,4-benzoquinone (0.41 mmol), toluene (0.1 M).

[b] All isolated yield.

[c] 5 equiv. of **3x** was used.

In addition to maleimides, we turned our attention to the scope of unsaturated carbon-carbon bonds, which are activated by neighboring electron-withdrawing groups (**Table 3-6**). Fumaronitrile **3w,** which is highly electron-deficient, turned out to be a good coupling partner affording quinoline **4w** in 71% yield. While a moderate yield of **4x** and **4x'** was obtained with 2:1 ratio when less activated 1,2-cyanoacrylate **3x** was employed, no product corresponding to **4y** formed when diethyl fumarate **3y** was used.



Scheme 3-5. Radical addition to activated alkene

We rationalized these results based on the electrophilicity of alkenes **3**, as radical acceptors toward nucleophilic radical intermediates **I** at the annulation step. The electrophilicity of alkenes was deduced from their relative redox potentials. The redox potentials were measured by cyclic voltammetry. ($E_{p/2}^{red}$ of **3w** = - 1.22 V vs Ag/AgCl in MeCN at 25 °C, $E_{p/2}^{red}$ of **3x** = - 1.29 V vs Ag/AgCl in MeCN at 25 °C and $E_{p/2}^{red}$ of **3y** = - 1.40 V vs Ag/AgCl in MeCN at 25 °C, **Figure 3-1**).

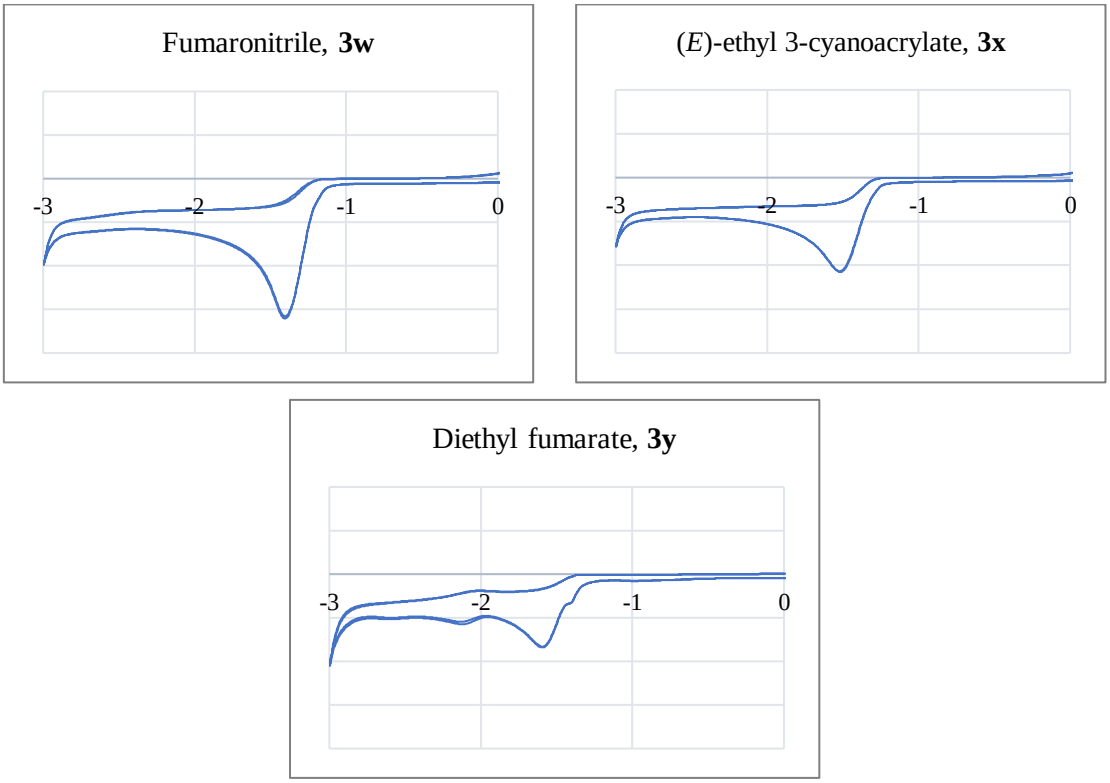
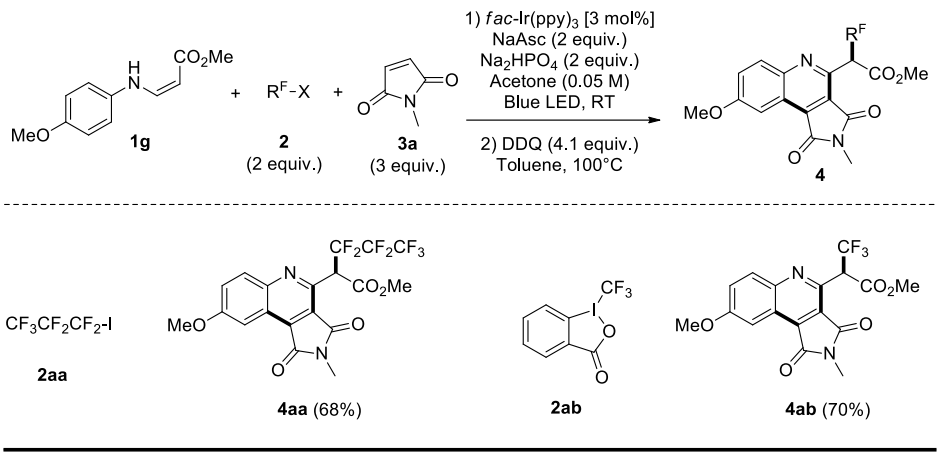


Figure 3-1. Reduction potentials of activated alkenes **3w**, **3x** and **3y**

The higher the relative reduction potential of alkene is, the more it is readily to accept an electron. Therefore, fumaronitrile **3w** showed the highest yield among alkenes because of its highest reduction potential indicating strong electrophilicity, whereas no product was observed with fumarate **3y**. Plus, the ratio of **4x** and **4x'** can be explained by the location of radical and the stability of radical at intermediate **III**. We also examined the reactivity of alkyne vs. alkene by employing (*E*)-dimethyl hex-2-en-4-ynedioate **3z** as a coupling partner, and found that the reaction proceeds selectively on the alkyne to give **4z** in moderate yield.

3.6.3. Substrate scope with Perfluorinated substituents

Table 3-7. Substrate scope with fluorinated substituents [a, b]



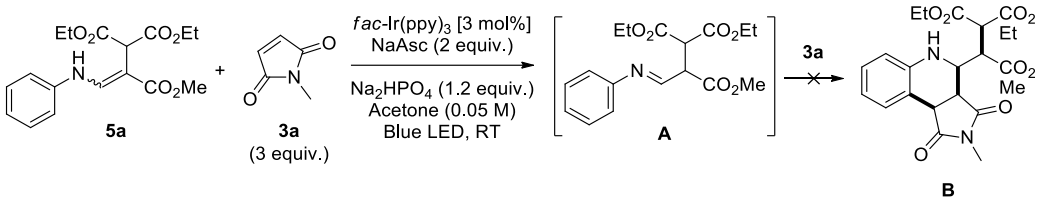
[a] Reaction conditions: **1g** (0.1 mmol), **2a** (0.2 mmol), **3** (0.3 mmol), *fac*-Ir(ppy)$_3$ (3 mol%), sodium ascorbate (0.2 mmol), Na_2HPO_4 (0.2 mmol), acetone (0.05 M) then, 2,3- Dichloro-5,6-dicyano-1,4-benzoquinone (0.41 mmol), toluene (0.1 M).
[b] All isolated yield.

Given that fluorination is an important tactic to modulate the physicochemical properties of drugs, we have shown that perfluorinated substituents can be readily introduced by using the corresponding coupling partners. Thus, quinolines **4aa** and **4ab** with fluorinated substituents were prepared in good yields by using *n*-heptafluoropropyl iodide **2aa** and Togni's reagent II **2ab**, respectively (**Table 3-7**).

3.7. Mechanistic studies

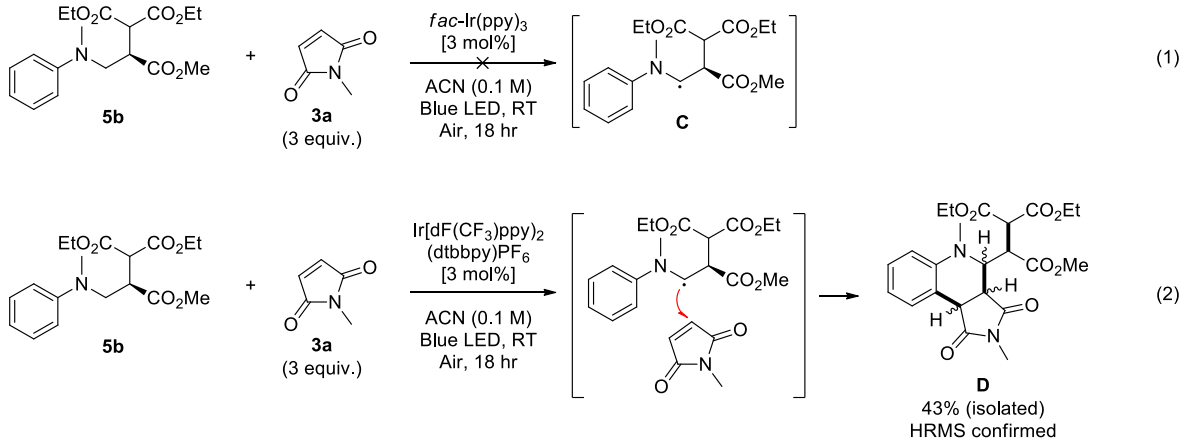
3.7.1. Control experiments

In order to probe the reaction mechanism, we have performed several experiments described in this section.



Scheme 3-6. Control experiments (1)

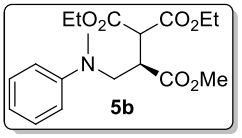
During the survey of substrate scope, the formation of isomeric mixture of enamine **5a** was often observed as by-products, which led us to examine the intermediacy of **5a** in the course of reaction. In place of radical mechanism, the incorporation of maleimide **3a** may proceed through *Diels-Alder* reaction after tautomerization to intermediate **A**. However, this could be ruled out based on the observation that desired tetrahydroquinoline **B** did not form when enamine **5a** and maleimide **3a** were subjected to the standard reaction conditions (**Scheme 3-6**). In other words, the possibility of intermediacy of **5a** could be excluded.



Scheme 3-7. Control experiments (2)

This led us to the postulation that successful coupling of **5b** and **3a** under photoredox conditions would provide an evidence for the intermediacy of α-amino radical **C** derived from **5b** (Eq. 1, **Scheme 3-7**). An initial attempt by using *fac*-Ir(ppy)$_3$ as a catalyst failed to give **C**, which is consistent with the result from a fluorescence quenching experiment and redox potentials; **5b** ($E_{p/2}^{ox}$ = + 0.98 V vs Ag/AgCl in MeCN at 25 °C, **Figure 3-2**) vs. *fac*-Ir(ppy)$_3$ ($E^{III*/II}$ = + 0.31 V vs SCE in

MeCN at 25 ℃). In terms of oxidation potentials, the excited *fac*-Ir(ppy)$_3$ has insufficient oxidative potential for oxidation of **5b** to produce α-amino radical **C** (**Figure 3-3**). In other words, the coincidence between the normalized intensity of the solution containing only photocatalyst (Blue, **Figure 3-3**) and that of the solution containing both photocatalyst and **5b** (orange, **Figure 3-3**) proved that the interaction in redox between them did not take place.



$E_{p/2}^{ox}$ = + 0.98 V
(vs SCE in MeCN at 25°C)

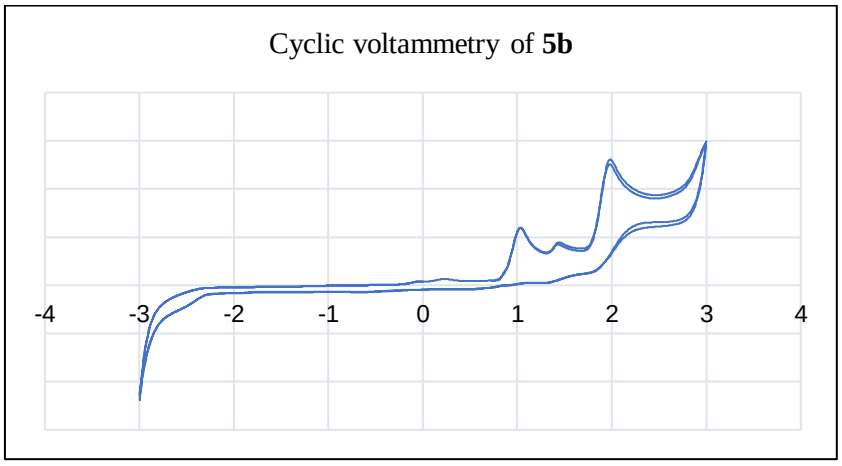


Figure 3-2. Measurement of oxidation potential of **5b**

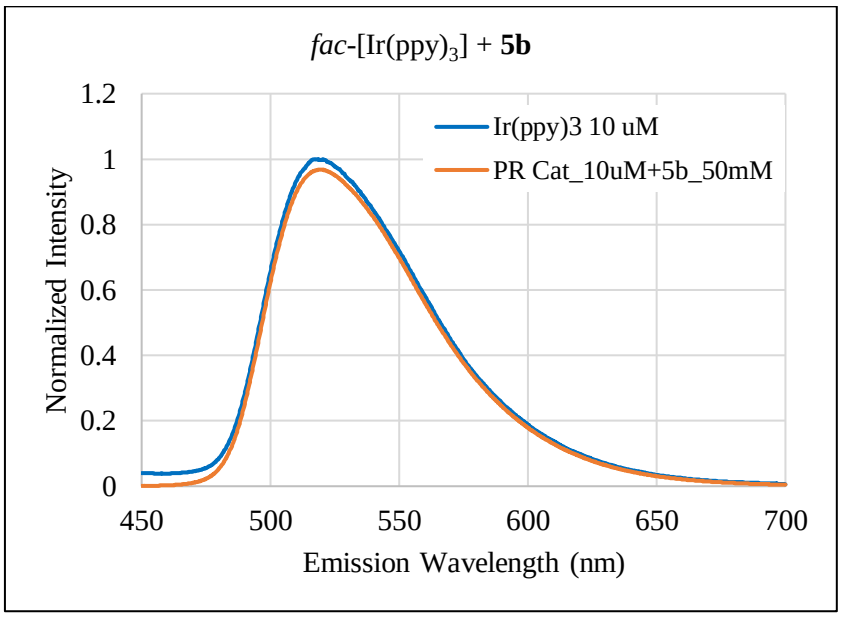


Figure 3-3. Fluorescence quenching between **5b** and *fac*-Ir(ppy)$_3$

Meanwhile, as the oxidation potential of **5b** was known by measurement of cyclic voltammetry, $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ was chosen because of its higher oxidation potential ($E^{III*/II}$ = + 1.21 V vs SCE in MeCN at 25 °C). So, we were able to observe the clear interaction between photocatalyst and **5b** in fluorescence quenching study, when $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ was employed instead of *fac*-$Ir(ppy)_3$ (**Figure 3-4**). Again, the blue line indicated the normalized intensity of the solution containing the photocatalyst only and orange line showed that of the solution containing both photocatalyst and **5b**. The fully diminished graph in orange proved that the excited photocatalyst was readily quenched by **5b** through redox interaction. Therefore, replacement of photocatalyst from *fac*-$Ir(ppy)_3$ to $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ enabled to oxidize **5b** to produce α-amino radical **C**, forming the isomeric mixture of **D** in 43 % yield. The characterization of the isomeric mixture in **D** was confirmed based on HRMS analysis due to the complexity of isomers in NMR. These results strongly suggest the coupling of maleimide **3a** proceeds via radical mechanism.[86, 87]

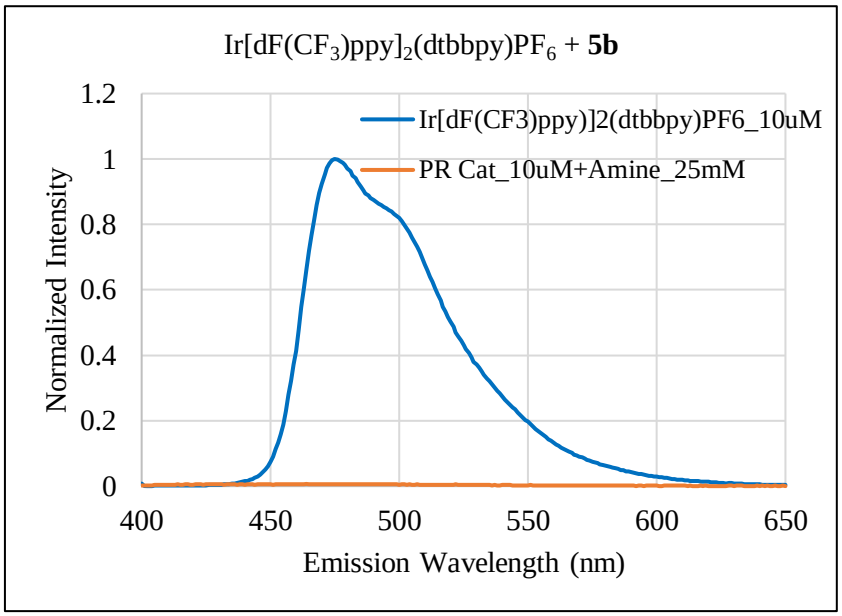
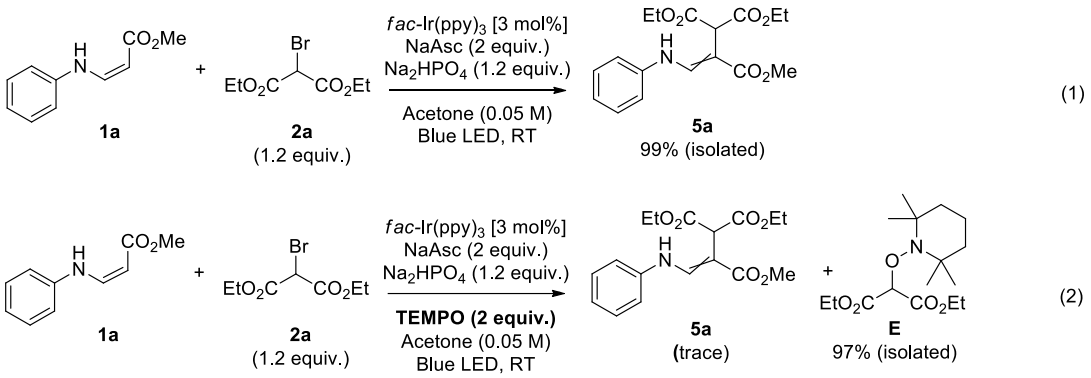


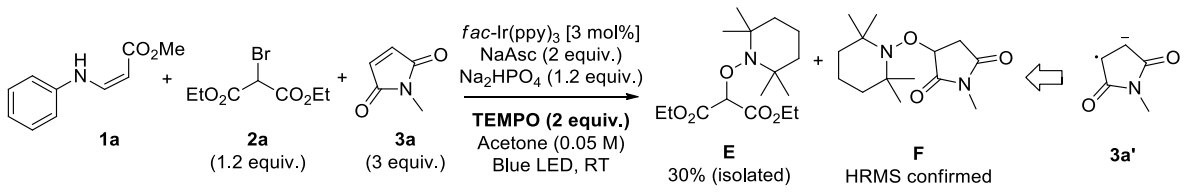
Figure 3-4. Fluorescence quenching between **5b** and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$

Next, we turned our attention to the mechanism, tracing the origin of radical species by employing 2,2,6,6-Tetramethylpiperidin-1-yl)oxyl, TEMPO, which is widely used as a radical scavenger.



Scheme 3-8. Control experiments (3)

In the absence of maleimide **3a**, reaction between β-aminoacrylate **1a** and bromomalonate **2a** under standard condition produced the isomeric mixture of enamine **5a** in 99 % yield (Eq. 1, **Scheme 3-8**). Meanwhile, when 2 equimolar amount of TEMPO was injected, the formation of enamine **5a** was completely suppressed and a large amount of malonate-TEMPO adduct **E** was obtained in 97 % after isolation (Eq. 2, **Scheme 3-8**). This is consistent with the hypothesis that the generation of malonyl radical **2a'** proceeds through oxidative quenching of photoexcited $[Ir^{III}]$*.

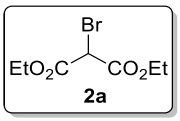


Scheme 3-9. Control experiments (4)

On the other hand, when the reaction of **1a** and **2a** was performed in the presence of **3a** and TEMPO, the maleimide-TEMPO adduct **F**, which was unstable for isolation, was observed by HRMS along with **4a** and **E** (trace and 30% isolated yield, respectively) (**Scheme 3-9**). We were perplexed by the observation of **F**, which suggests the formation of maleimide radical **3a'** in the reaction.

3.7.2. Fluorescence quenching study

Our initial mechanistic hypothesis was that the excited $[Ir^{III}]^*$ would undergo oxidative quenching by **2a** to give **2a'**, however, the presence of **3a'** prompted us to investigate the competitive oxidative quenching of the excited catalyst between **2a** and **3a**.



$\mathbf{E_{p/2}^{2a/2a^{\bullet-}} = -1.42\ V}$

(vs SCE in MeCN at 25°C)

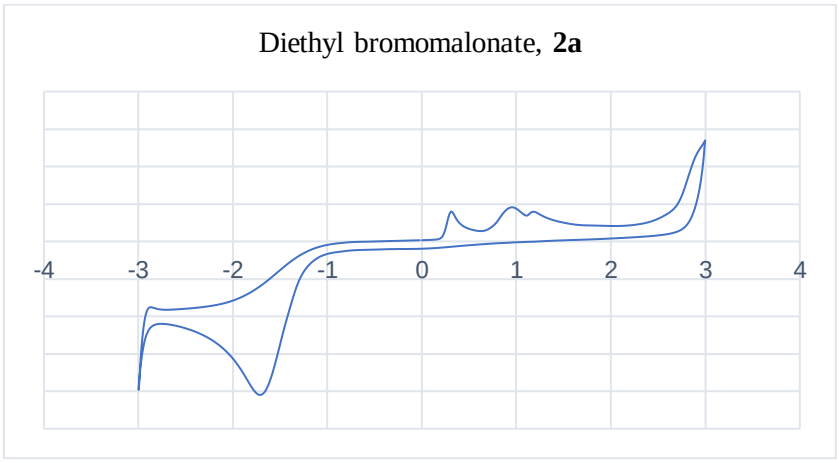


Figure 3-5. Measurement of reduction potential of **2a**

In order to identify *the radical species forming first in the catalytic cycle*, Stern-Volmer quenching studies were performed. The redox potential of *fac*-Ir(ppy)$_3$ ($E^{III*/IV}$ = - 1.73 V vs SCE in MeCN at 25 °C) indicates that oxidative quenching of $[Ir^{III}]^*$ by both **2a** and **3a** would be feasible ($E_{p/2}^{2a/2a^{\bullet-}}$ = - 1.42 V vs Ag/AgCl in MeCN at 25 °C, **Figure 3-5** and $E_{p/2}^{3a/3a^{\bullet-}}$ = - 1.21 V vs SCE in MeCN at 25 °C,[88] respectively). Fluorescence quenching study of **2a** and **3a** with phased concentrations was independently conducted with a fixed amount of *fac*-Ir(ppy)$_3$ (**Figure 3-6**). In the case of both **2a** and **3a**, the normalized intensity of excited *fac*-Ir(ppy)$_3$ was inversely proportional to the concentration of **2a** or **3a**, indicating that they did participate in the quenching of the excited *fac*-Ir(ppy)$_3$ in the redox interaction. Then, this result was converted into Stern-Volmer plot for the direct comparison about the preference of quenching between **2a** and **3a**. Based on the slope of each trend curve, the Stern-Volmer plot clearly suggested that **3a** was the preferred electron acceptor over **2a**.

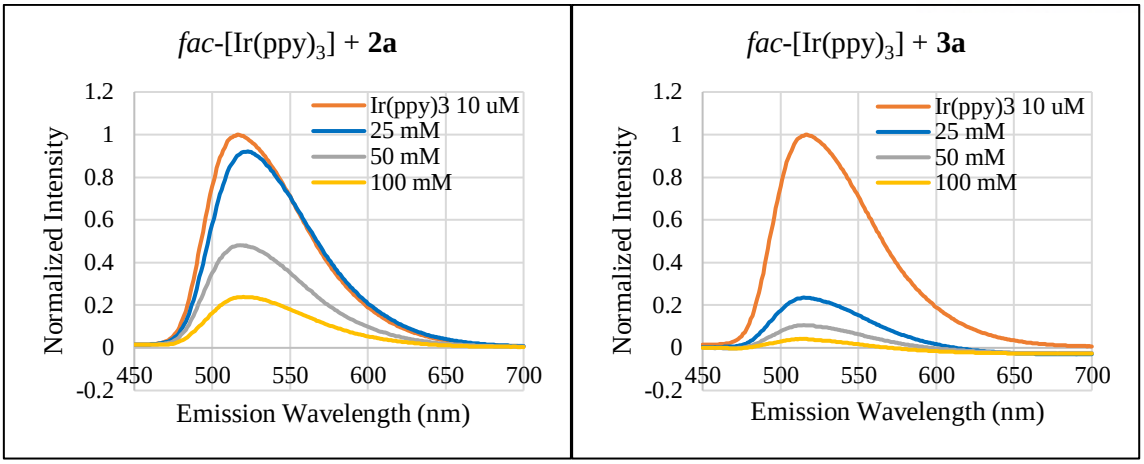


Figure 3-6. Fluorescence quenching study of **2a** (left) and **3a** (right) with *fac*-Ir(ppy)$_3$

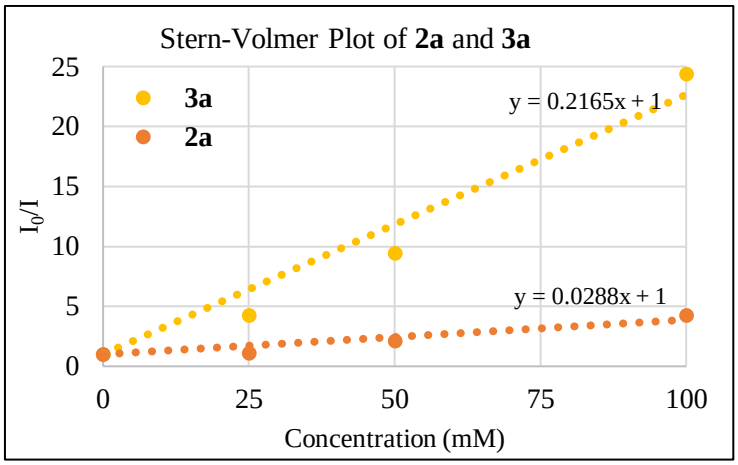


Figure 3-7. Comparison of Stern-Volmer Plots of **2a** and **3a**

This result of the preferential reduction of **3a** over **2a** raises the question of identification of the counterpart reacting with radical anion **3a'** derived from **3a**. We speculated that the radical anion **3a'** is responsible for the reduction of **2a** to **2a'**. Therefore, additional fluorescence quenching experiments were performed on equimolar mixtures of **2a** and **3a** at varying concentrations (**Figure 3-8**).

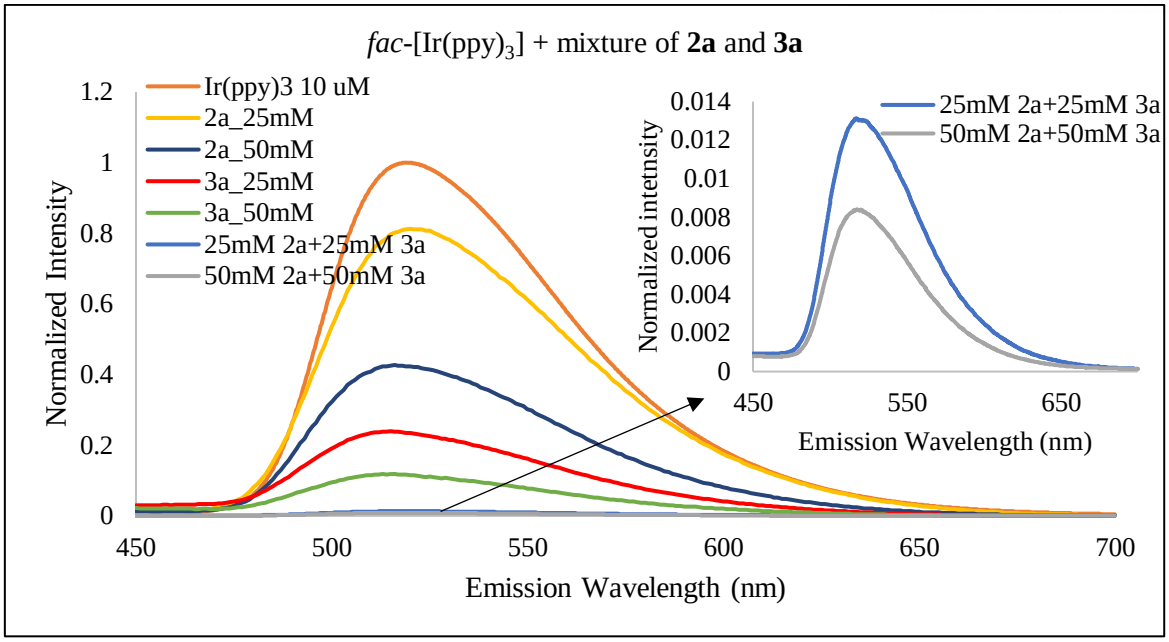
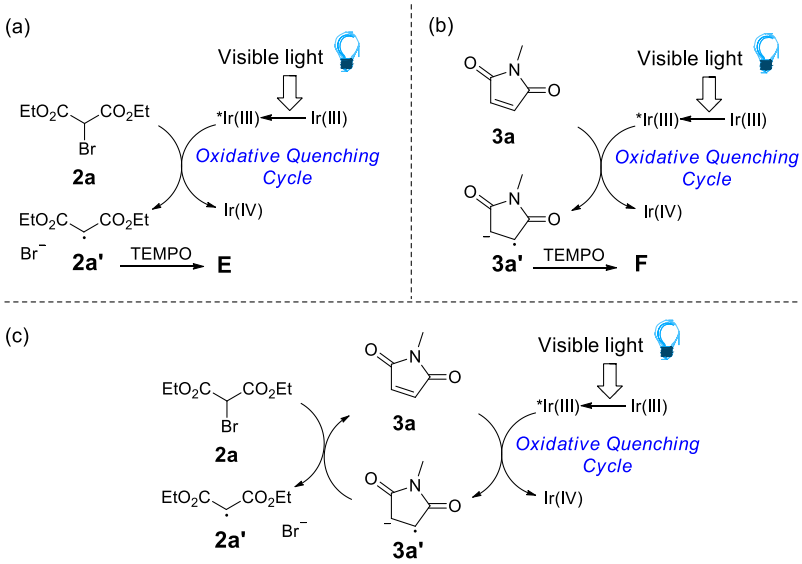


Figure 3-8. Fluorescence quenching study of mixture of **2a** and **3a**

To our surprise, much greater extent of fluorescence quenching was observed in comparison to those taken separately (Expanded graph, blue and grey, **Figure 3-8**). Again, the increase of concentration of mixture also leaded stronger quenching of the photocatalyst. This synergistic effect could be reasoned that the reversible quenching of the excited $[Ir^{III}]^*$ in the presence of **3a** alone becomes irreversible when both **3a** and **2a** are present, in which **2a** is irreversibly reduced to **2a'** by **3a'**. This result could also account for the presence of the radical species derived from **3a** evidenced by **3a**-TEMPO adduct **F** (**Scheme 3-10**).



Scheme 3-10. Synergetic effect of **2a** and **3a**

3.7.3. Visible-light on/off experiment

We have performed an experiment with light-on/off to investigate whether the reaction involves *radical chain propagation*. However, this could be ruled out as the conversion comes to a halt as shown in **Figure 3-9**. The recorded yields were determined by ^{1}H NMR spectroscopy with the addition of trichloroethylene as an internal standard.

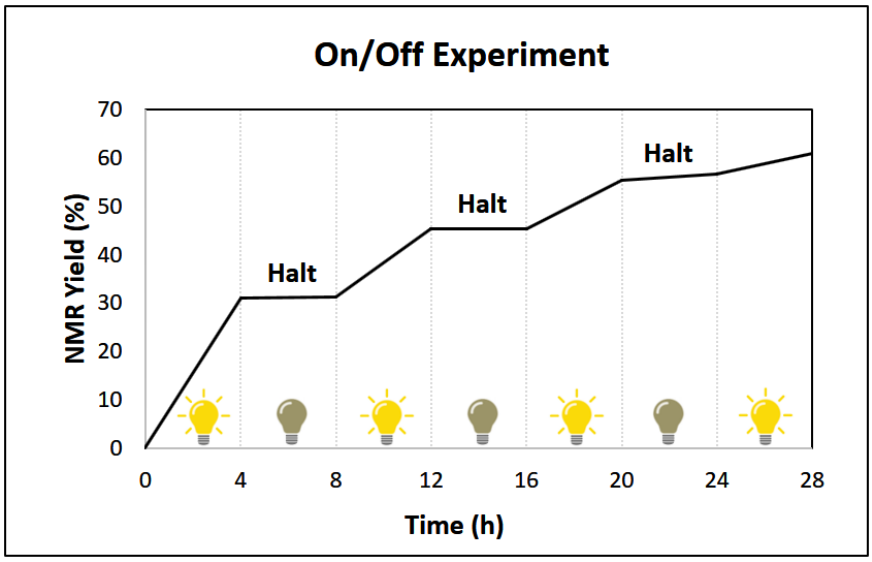
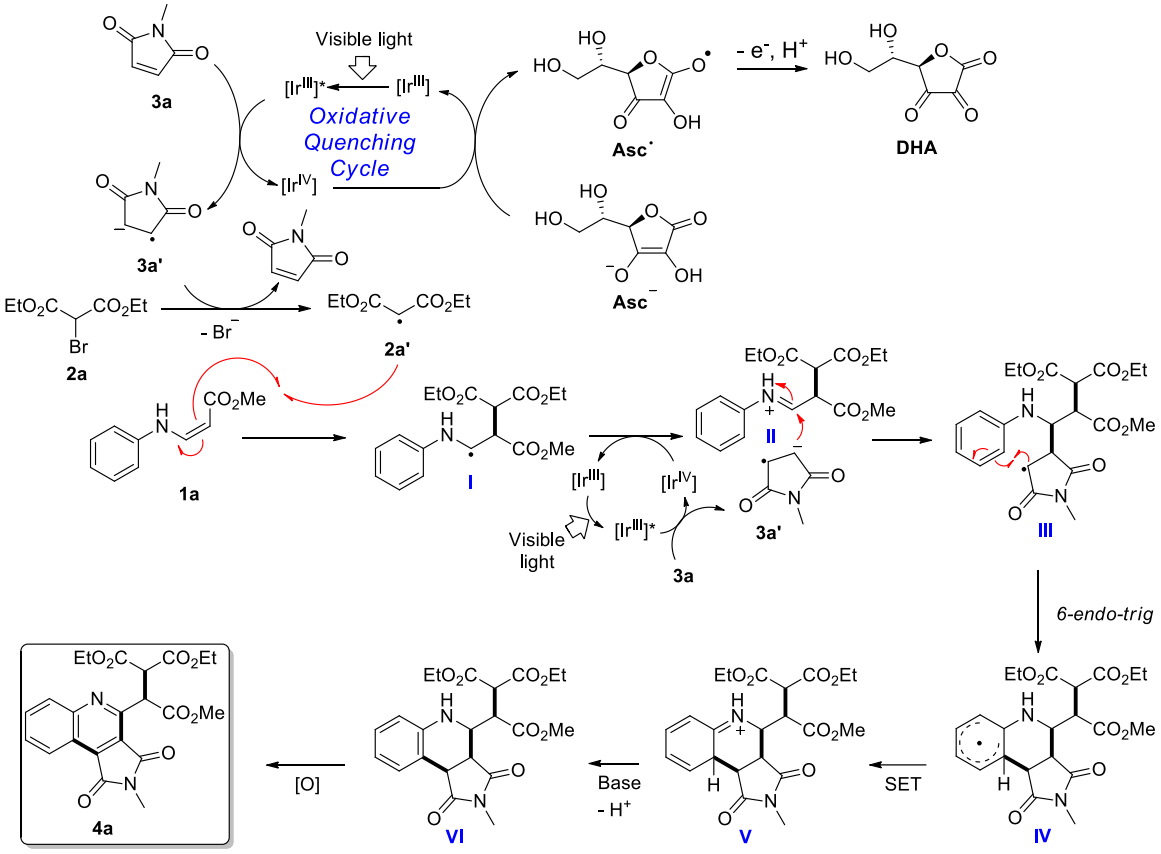


Figure 3-9. On/off experiment at 4 hour intervals

3.7.4. Plausible Mechanism

Based on the mechanistic studies, we propose a plausible mechanism shown in **Scheme 3-11**. The reaction is initiated with oxidative quenching of the excited [Ir^{III}]* by **3a** to form radical anion **3a'**, which allows the reduction of **2a** resulting in the formation of malonyl radical **2a'**. Selective coupling of the *electron-deficient* radical **2a'** with *electron-rich* β-aminoacrylate **1a** over *electron-deficient* alkene **3a** leads to the formation of α-amino radical species **I**. Concomitant redox reaction of **I** and **3a** catalyzed by the catalyst provides iminium species **II** and radical anion **3a'**, which undergoes coupling to afford radical species **III**. Subsequently, intramolecular cyclization of the resulting *electron-deficient* radical **III** with the *electron-rich* aryl group furnishes **IV**, which proceeds to form tetrahydroquinoline **VI** by oxidation followed by aromatization. Lastly, one pot oxidation with DDQ provides quinoline **4**.



Scheme 3-11. Plausible Mechanism

In sum, we have developed an efficient three-component radical cascade reaction for the synthesis of highly substituted quinolines based on visible-light photoredox catalysis. This method, which involves three consecutive radical-mediated bond formations, allows chemoselective incorporation of coupling partners. Detailed mechanistic studies were performed by various spectroscopic methods.

3.8. Experimental procedures and data

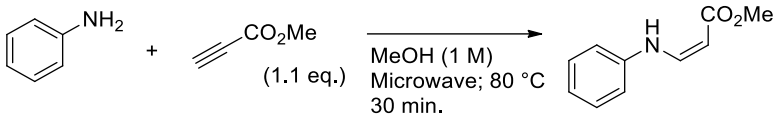
3.8.1. General methods

All the reactions were carried out in oven dried glassware under nitrogen atmosphere with freshly distilled dry solvents under anhydrous conditions unless otherwise indicated. Solvents for the key step and optimization table are dried by drying agents (appropriate for each solvent, for example, acetonitrile was distilled from P_2O_5) and distilled out. Then they were degassed by bubbling of nitrogen gas for 30 minutes with cooling bath. All key step reactions were set under nitrogen atmosphere in glovebox. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using water bath. Analytical thin layer chromatography (TLC) was performed using Merck TLC Silica gel 60 F254 precoated plate (0.2 mm thickness). After elution, plates were visualized using UV radiation (254 nm) on Spectroline Model ENF-240C/FE 254 nm. Further visualization was possible by staining with basic solution of potassium permanganate or acidic solution of ceric molybdate. Flash column chromatography was performed with Silica Flash P60 silica gel (230-400 mesh). All reagents were obtained from commercial sources (Alfa Aesar, Sigma Aldrich, TCI Chemicals) and were used without further purification.

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on a 400/100 MHz Agilent 400M FT-NMR spectrometer or 400/100 MHz Bruker Advance III FT-NMR spectrometer. NMR solvents were obtained from Cambridge Isotope Laboratories and the residual solvent signals were taken as the reference (0.0 ppm for ^{1}H NMR spectra and 77.0 ppm for ^{13}C NMR spectra in $CDCl_3$). The signals observed are described as: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Coupling constants are reported as *J* value in Hz. High resolution mass analysis (HRMS) was performed with Bruker HCT Basic System coupled with Agilent 1200 Series. Cyclic voltammetry spectra were recorded on WizMAC WizECM – 1200 Premium. Luminescence quenching studies were performed with Varian Cary Eclipse. The reaction mixture of key steps was irradiated with a 12 W blue LED lamp (5 cm away, 25 ℃ maintained with a cooling fan). For reactions irradiated by microwave, Biotage Initiator$^+$ was used. Systematic nomenclature for the compounds follows the numbering system as defined by IUPAC with assistance from CS Chemdraw® software.

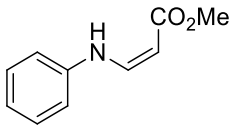
3.8.2. Synthetic procedures for β-aminoacrylates

3.8.2.1. General procedure A (for **1a** ~ **1l**)



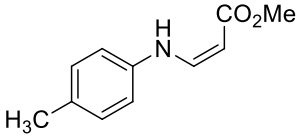
To a solution of aniline (1 equiv.) in MeOH (1 M) was added methyl propiolate (1.1 equiv.). The reaction was stirred and irradiated in microwave synthesizer for 30 minutes at 80 ℃. Upon completion (monitored by TLC analysis), the solution was concentrated under reduced pressure. The residue was purified by flash chromatography.

Methyl 3-(phenylamino)acrylate (1a): Prepared according to *General Procedure A* from aniline and methyl propiolate. Yield 70%.



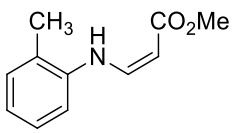
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (d, 1H, J = 10.4 Hz) δ 7.28 – 7.21 (m, 3H) δ 7.00 – 6.94 (m, 3H) δ 4.83 (d, 1H, J = 8.4 Hz) δ 3.70 (s, 3H). NMR data is consistent with the reported data.

Methyl 3-(p-tolylamino)acrylate (1b): Prepared according to *General Procedure A* from *p*-toluidine and methyl propiolate. Yield 57%



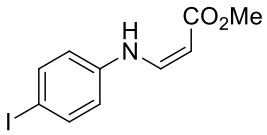
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (d, 1H, J = 12.0 Hz) δ 7.22 (dd, 1H, J = 8.3 Hz, 12.8 Hz) δ 7.10 (d, 2H, J = 8.0 Hz) δ 6.87 (d, 2H, J = 7.8 Hz) δ 4.81 (d, 1H, J = 8.3 Hz) δ 3.72 (s, 3H) δ 2.30 (s, 3H). NMR data is consistent with the reported data.

Methyl 3-(*o*-tolylamino)acrylate (1c): Prepared according to *General Procedure A* from *o*-toluidine and methyl propiolate and methyl propiolate. Yield 85%



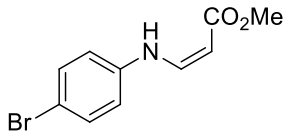
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.0 (d, 1H, J = 11.4 Hz) δ 7.32 (dd, 1H, J = 8.3 Hz, 12.5 Hz) δ 7.19 (m, 2H) δ 7.04 (d, 1H, J = 7.9 Hz) δ 6.94 (m, 1H) δ 4.89 (d, 1H, J = 8.2 Hz) δ 3.74 (s, 3H) δ 2.34 (s, 3H) NMR data is consistent with the reported data.

Methyl 3-((4-iodophenyl)amino)acrylate (1d): Prepared according to *General Procedure A* from 4-iodo aniline and methyl propiolate. Yield 57%.



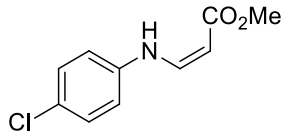
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (d, 1H, J = 12.7 Hz) δ 7.58 (d, 2H, J = 8.8 Hz) δ 7.18 (dd, 1H, J = 8.4 Hz, 12.6 Hz) δ 6.73 (d, 2H, J = 8.8 Hz) δ 4.89 (d, 1H, J = 8.4 Hz) δ 3.72 (s, 3H) NMR data is consistent with the reported data.

methyl 3-((4-bromophenyl)amino)acrylate (1e): Prepared according to *General Procedure A* from 4-bromo aniline and methyl propiolate. Yield 60%.



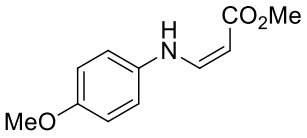
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (d, 1H, J = 12.3 Hz) δ 7.40 (d, 2H, J = 8.9 Hz) δ 7.18 (dd, 1H, J = 8.4 Hz, 12.3 Hz) δ 6.84 (d, 2H, J = 8.9 Hz) δ 4.88 (d, 1H, J = 8.4 Hz) δ 3.72 (s, 3H) NMR data is consistent with the reported data.

Methyl 3-((4-chlorophenyl)amino)acrylate (1f): Prepared according to *General Procedure A* from 4-chloro aniline and methyl propiolate. Yield 40%



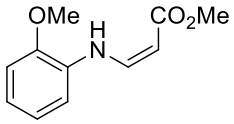
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.88 (d, 1H, J = 11.4 Hz) δ 7.26 (d, 2H, J = 8.8 Hz) δ 7.17 (dd, 1H, J = 12.6 Hz, 8.4 Hz)) δ 6.89 (d, 2H, J = 8.8 Hz) δ 4.88 (d, 1H, J = 8.4 Hz) δ 3.72 (s, 3H) NMR data is consistent with the reported data.

Methyl 3-((4-methoxyphenyl)amino)acrylate (1g): Prepared according to *General Procedure A* from 4-methoxyaniline and methyl propiolate. Yield 56%.



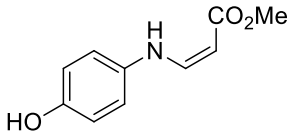
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (d, 1H, J = 13.6 Hz) δ 7.15 (dd, 1H, J = 8.25 Hz, 12.84 Hz) δ 6.92 (d, 2H, J = 9.02 Hz) δ 6.85 (d, 2H, J = 9.02 Hz) δ 4.79 (d, 1H, J = 8.25 Hz) δ 3.78 (s, 3H) δ 3.71 (s, 3H). NMR data is consistent with the reported data.

Methyl 3-((2-methoxyphenyl)amino)acrylate (1h): Prepared according to *General Procedure A* from 2-methoxyaniline and methyl propiolate. Yield 66%



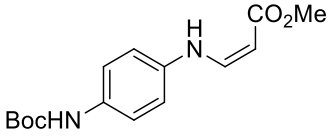
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.14 (d, 1H, J = 11.9 Hz) δ 7.28 (dd, 1H, J = 8.3 Hz, 13.1 Hz) δ 7.03 (dd, 1H, J = 1.8 Hz, 7.4 Hz) δ 6.93 (dqd, 3H, J = 1.8 Hz, 7.4 Hz, 14.9 Hz) δ 4.88 (d, 1H, J = 8.3 Hz) δ 3.92 (s, 3H) δ 3.73 (s, 3H). NMR data is consistent with the reported data.

Methyl 3-((4-hydroxyphenyl)amino)acrylate (1i): Prepared according to *General Procedure A* from 4-hydroxyaniline and methyl propiolate. Yield 60%



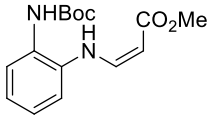
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (d, 1H, J = 11.1 Hz) δ 7.14 (dd, 1H, J = 8.3 Hz, 12.8 Hz) δ 6.86 (d, 2H, J = 8.9 Hz) δ 6.79 (d, 2H, J = 8.9 Hz) δ 4.78 (d, 1H, J = 8.2 Hz) δ 3.71 (s, 3H). MS (ESI) m/z calcd. for $C_{10}H_{11}NO_3$ ($[M+H]^+$) 194.07, found 194.1.

Methyl 3-((4-((tert-butoxycarbonyl)amino)phenyl)amino)acrylate (1j): Prepared according to *General Procedure A* from tert-butyl (4-aminophenyl)carbamate and methyl propiolate. Yield 78%.



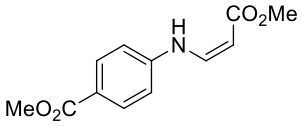
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.82 (d, 1H, J = 12.6 Hz) δ 7.29 (d, 2H, J = 8.7 Hz) δ 7.18 (dd, 1H, J = 8.3 Hz, 12.6 Hz) δ 6.90 (m, 2H) δ 6.38 (br s, 1H) δ 4.81 (d, 1H, J = 8.3 Hz) δ 3.71 (s, 3H) δ 1.51 (s, 9H). MS (ESI) m/z calcd. for $C_{15}H_{21}N_2O_4$ ($[M+H]^+$) 293.15, found 293.2

Methyl 3-((2-((tert-butoxycarbonyl)amino)phenyl)amino)acrylate (1k): Prepared according to *General Procedure A* from tert-butyl (2-aminophenyl)carbamate and methyl propiolate. Yield 44%.



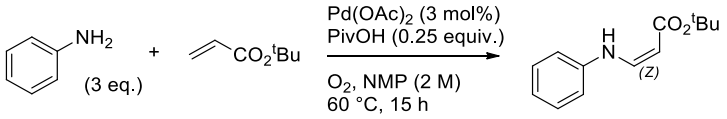
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (d, 1H, J = 12.0 Hz) δ 7.47 (d, 1H, J = 7.8 Hz) δ 7.10 (m, 4H) δ 6.26 (br s, 1H) δ 4.89 (d, 1H, J = 8.3 Hz) δ 3.71 (s, 3H) δ 1.53 (s, 9H). MS (ESI) m/z calcd. for $C_{15}H_{21}N_2O_4$ ($[M+H]^+$) 293.15, found 293.2

Methyl 4-((3-methoxy-3-oxoprop-1-en-1-yl)amino)benzoate (1l): Prepared according to *General Procedure A* from methyl 4-aminobenzoate and methyl propiolate. Yield 42%.



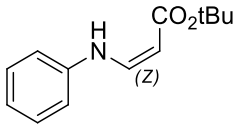
^{1}H NMR (400 MHz, $CDCl_3$): δ 10.07 (d, 1H, J = 12.5 Hz) δ 7.98 (d, 2H, J = 8.8 Hz) δ 7.29 (dd, 1H, J = 8.4 Hz, 12.5 Hz) δ 6.97 (d, 2H, J = 8.8 Hz) δ 4.96 (d, 1H, J = 8.4 Hz) δ 3.88 (s, 3H) δ 3.73 (s, 3H). NMR data is consistent with the reported data.

3.8.2.2. General procedure B (for **1m**)



To a solution of aniline (3 equiv.), tert-butyl acrylate (1 equiv.), $Pd(OAc)_2$ (3 mol%) and pivalic acid (0.25 equiv.) in NMP (2 M) was stirred for 15 hours at 60 ℃ under oxygen atmosphere. The solution was diluted with EtOAc and filtered through Celite. The solution was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel.

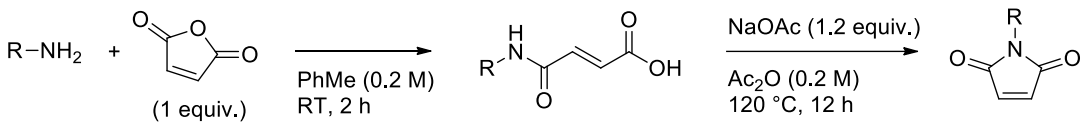
***tert*-butyl 3-(phenylamino)acrylate (1m):** Prepared according to *General Procedure B* from aniline and *tert*-butyl acrylate. Yield = 40%.



^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (d, 1H, J = 12.8 Hz) δ 7.31 – 7.27 (m, 2H) δ 7.18 (dd, 1H, J = 8.4 Hz, 12.8 Hz) δ 7.01 – 6.92 (m, 3H) δ 4.75 (d, 1H, J = 8.4 Hz) δ 1.51 (s, 9H) MS (ESI) m/z calcd. for $C_{13}H_{18}NO_2$ ($[M+H]^+$) 220.1, found 220.2.

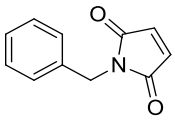
3.8.3. Synthetic procedures for maleimide

3.8.3.1. General Procedure C (for **3n**, **3o**, **3r**, **3s** and **3t**)



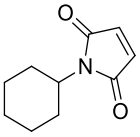
To a solution of maleic anhydride (1 equiv.) in anhydrous toluene (0.2 M) was added amine (1 equiv.) in anhydrous toluene dropwise while stirring at room temperature. The solution was stirred for 2 hours at room temperature, the precipitate was filtered and washed with diethyl ether several time. The collected precipitate was dried under reduced pressure and used without further purification. To a solution of maleic acid (1 equiv.) in acetic anhydride (0.2 M) was added sodium acetate (1.2 equiv.) and the solution was stirred at 120 ℃ overnight. The mixture was concentrated under reduced pressure and purified by flash chromatography on silica gel.

1-benzyl-1H-pyrrole-2,5-dione (3n): Prepared according to *General Procedure C* from benzyl amine and maleic anhydride. Two-step yield 56%.



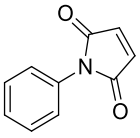
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (m, 5H) δ 6.71 (s, 2H) δ 4.68 (s, 2H). NMR data is consistent with the reported data.

1-cyclohexyl-1H-pyrrole-2,5-dione (3o): Prepared according to *General Procedure C* from cyclohexyl amine and maleic anhydride. Two-step yield 63%.



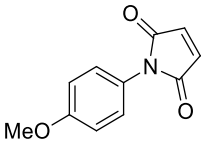
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.62 (s, 2H) δ 3.91 (tt,1H, J = 3.93 Hz, 12.43 Hz) δ 2.05 (qd, 2H, J = 3.20 Hz, 12.43 Hz) δ 1.83 (d, 2H, J = 13.38 Hz) δ 1.66 (dd, 3H, J = 2.7, J = 12.2 Hz) δ 1.37 – 1.19 (m, 3H). NMR data is consistent with the reported data.

1-phenyl-1H-pyrrole-2,5-dione (3r): Prepared according to the *General Procedure C* from aniline and maleic anhydride. Two-step Yield 57%.



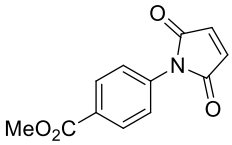
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (t, 2H, J = 7.7 Hz) δ 7.36 (m, 3H) δ 6.85 (s, 2H). NMR data is consistent with the reported data.

1-(4-methoxyphenyl)-1H-pyrrole-2,5-dione (3s): Prepared according to the *General Procedure C* from 4-methoxyaniline and maleic anhydride. Two-step Yield 59%.



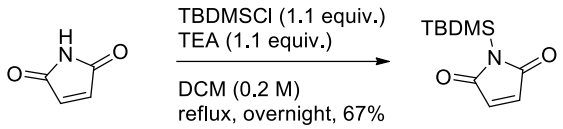
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (d, J = 9.1 Hz, 2H), δ 6.98 (d, J = 9.1 Hz, 1H), δ 6.83 (s, 2H), δ 3.83 (s, 3H) NMR data is consistent with the reported data.

methyl 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoate (3t): Prepared according to the *General Procedure C* from methyl 4-aminobenzoate and maleic anhydride. Two-step Yield 69%



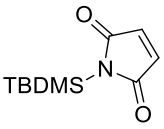
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, 2H, J = 8.8 Hz) δ 7.50 (d, 2H, J = 8.8 Hz) δ 6.89 (s, 2H) δ 3.94 (s, 3H). NMR data is consistent with the reported data.

3.8.3.2. General procedure D (for **3q**)



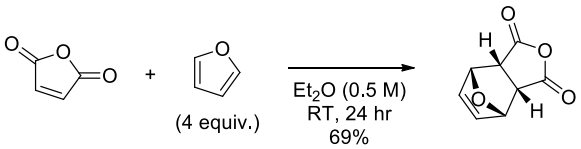
To a stirred and cooled mixture of maleimide (1 equiv.) and TBDMS-Cl (1.1 equiv.) in DCM (0.2 M) was slowly added triethylamine (1.1 equiv.). The solution was refluxed and stirred overnight. The precipitated triethylammonium chloride was filtered and the filtrate was washed successively with 5% HCl solution, H_2O and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography.

1-(tert-butyldimethylsilyl)-1H-pyrrole-2,5-dione (3q): Prepared according to the *General Procedure D* from maleimide. Yield 67%



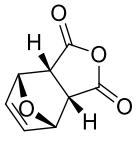
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.67 (s, 2H), δ 0.93 (s, 9H), δ 0.44 (s, 6H). NMR data is consistent with the reported data.

3.8.3.3. General procedure E (for **3u**)

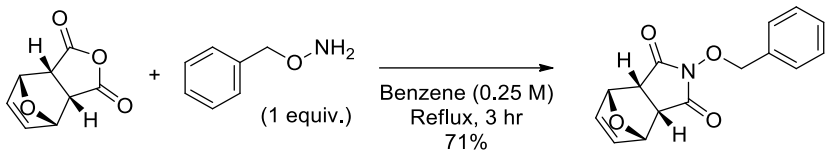


Step 1: To a solution of maleic anhydride (1 equiv.) in anhydrous diethyl ether (0.5 M) was added furan (4 equiv.) while stirring at room temperature. The reaction was stirred for 24 hours at room temperature. The product was precipitated out and was collected by vacuum filtration. The colorless precipitation was used without further purification.

(3aR,4R,7S,7aS)-3a,4,7,7a-tetrahydro-4,7-epoxyisobenzofuran-1,3-dione

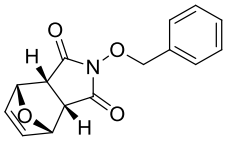


^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (s, 2H), δ 5.46 (s, 2H), δ 3.18 (s, 2H), NMR data is consistent with the reported data.

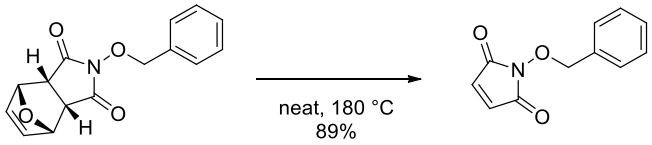


Step 2: To a solution of (3aR,4R,7S,7aS)-3a,4,7,7a-tetrahydro-4,7-epoxyisobenzofuran-1,3-dione (1 equiv.) in anhydrous benzene (0.25 M) was added solution of *N*-benzyloxyamine (1 equiv.) in benzene while stirring at room temperature. The reaction was stirred and refluxed for 3 hours. After completion (monitored by TLC analysis), the solution was cooled and concentrated under reduced pressure. The crude material was purified by flash chromatography.

(3aR,4R,7S,7aS)-2-(benzyloxy)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione

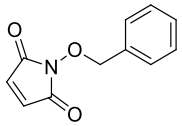


^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (m, 2H), δ 7.37 (m, 3H), δ 6.49 (s, 2H), δ 5.25 (s, 2H) δ 5.07 (s, 2H) δ 2.72 (s, 2H). MS (ESI) m/z calcd. for $C_{15}H_{14}NO_4$ ($[M+H]^+$) 272.09, found 272.2



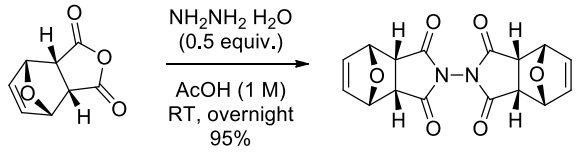
Step 3: (3aR,4R,7S,7aS)-2-(benzyloxy)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione (1 equiv.) was heated in an oil bath at 170-180 ℃ under reduced pressure. The solid slowly melted with vigorous furan evolution. After completion of furan evolution (monitored by TLC analysis), the yellowish liquid was cooled to room temperature. The crude material was purified by flash chromatography.

1-(benzyloxy)-1H-pyrrole-2,5-dione (3u)



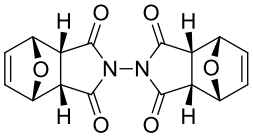
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (m, 2H), δ 7.38 (m, 3H), δ 6.58 (s, 2H), δ 5.10 (s, 2H). MS (ESI) m/z calcd. for $C_{11}H_{10}NO_3$ ($[M+H]^+$) 204.6, found 204.8

3.8.3.4. General procedure F (for **3v**)

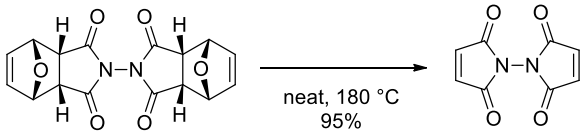


Step 1: To a solution of (3aR,4R,7S,7aS)-3a,4,7,7a-tetrahydro-4,7-epoxyisobenzofuran-1,3-dione (1 equiv.) in glacial acetic acid (1 M) was added hydrazine hydrate (0.5 equiv.) dropwise while stirring at RT. The reaction was stirred at RT for 1 hour and 50-60 ℃ for 1 hour then at RT for overnight. The product was precipitated out and was collected by vacuum filtration. The colorless precipitation was used without further purification.

(4R,4'R,5R,5'R,8S,8'S,9S,9'S)-4,5,8,8',9,9'-hexahydro-[2,2'-bi(4,7-epoxyisoindole)]-1,1',3,3'(4'H,5'H)-tetraone

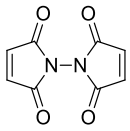


^{1}H NMR (400 MHz, $CDCl_3$): δ 6.55 (s, 4H), δ 5.39 (s, 4H), δ 3.00 (s, 4H). NMR data is consistent with the reported data.



Step 2: (4R,4'R,5R,5'R,8S,8'S,9S,9'S)-4,5,8,8',9,9'-hexahydro-[2,2'-bi(4,7-epoxyisoindole)]-1,1',3,3'(4'H,5'H)-tetraone (1 equiv.) was heated in an oil bath at 170-180 ℃ under reduced pressure. The solid slowly melted with vigorous furan evolution. After completion of furan evolution (monitored by TLC analysis), the residue was cooled to RT. The crude material was purified by flash chromatography.

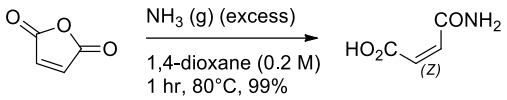
[1,1'-bipyrrole]-2,2',5,5'-tetraone (3v)



^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (s, 4H). NMR data is consistent with the reported data.

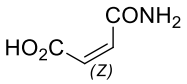
3.8.4. Synthetic procedures for other coupling partners

3.8.4.1. (Z)-ethyl 3-cyanoacrylate (**3x**)

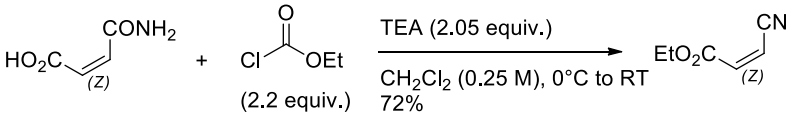


Step 1: A solution of maleic anhydride (1 equiv.) in anhydrous 1,4-dioxane (0.2 M) was preheated to 80 ℃. When the maleic anhydride had melted, ammonium hydroxide solution was heated to 40 ℃ to generate ammonia gas. The stream of ammonia gas was introduced to the maleic anhydride solution for 1 hour. White precipitate was collected by vacuum filtration.

(Z)-4-amino-4-oxobut-2-enoic acid



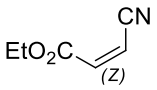
^{1}H NMR (400 MHz, MeOH-d4): δ 6.31 (d, 2H, J = 12.9 Hz), δ 6.05 (d, 2H, J = 12.9 Hz). MS (ESI) m/z calcd. for $C_4H_6NO_3$ ($[M+H]^+$) 116.03, found 116.1



Step 2: To a solution of (Z)-4-amino-4-oxobut-2-enoic acid (1 equiv.) in anhydrous CH_2Cl_2 (0.25 M) was cooled to 0 ℃ under nitrogen atmosphere. To the solution was added trimethylamine (2.05 equiv.) dropwise followed by addition of ethyl chloroformate (2.2 equiv.) dropwise. After completion of addition, the solution was allowed to warm to RT and stirred for 24 h. After completion, a 10% aqueous NaOH solution was added to the reaction mixture and the organic layer was separated. The aqueous layer was extracted with dichloromethane three times and the combined organic layers was

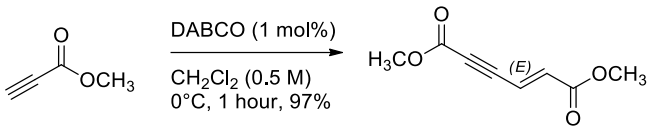
dried over anhydrous $MgSO_4$. The solution was concentrated under reduced pressure. The crude material was purified by flash chromatography.

(Z)-ethyl 3-cyanoacrylate (3x):



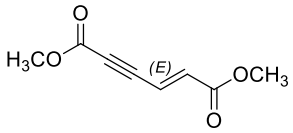
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.57 (d, 2H, J = 11.5 Hz), δ 5.95 (d, 2H, J = 11.5 Hz), δ 4.33 (q, 2H, J = 7.1 Hz) δ 1.36 (t, 3H, J = 7.1 Hz). NMR data is consistent with the reported data.

3.8.4.2. (E)-dimethyl hex-2-en-4-ynedioate (**3z**)



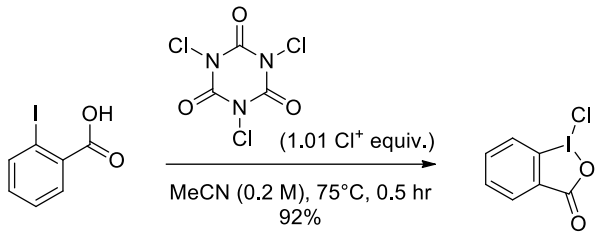
To a solution of methyl propiolate (1 equiv.) in CH_2Cl_2 (0.5 M) at 0 ℃ was added DABCO (1 mol%) in CH_2Cl_2. The reaction immediately turned dark and was stirred for 1 hour. The solution was concentrated under reduced pressure. The crude material was purified by flash chromatography.

(E)-dimethyl hex-2-en-4-ynedioate (3z)



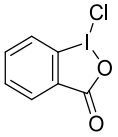
^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (d, 2H, J = 16.0 Hz), δ 6.47 (d, 2H, J = 16.0 Hz), δ 3.83 (s, 3H), δ 3.79 (s, 3H). NMR data is consistent with the reported data.

3.8.4.3. Togni's reagent II (**2ab**)

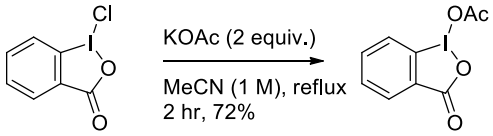


Step 1: To a solution of 2-iodobenzoic acid (1 equiv.) in MeCN (0.2 M) at 75 ℃ was added a solution of trichloroisocyanuric acid (1.01 Cl^+ equiv.) in MeCN in one portion. The solution was stirred and heated at 75 ℃ for 30 minutes. After completion, the solution was diluted with MeCN and the precipitated product was filtered on vacuum filtration. The filter cake was rinsed with additional amount of hot MeCN two times.

1-chloro-1λ^3 -benzo[d][1,2]iodaoxol-3(1H)-one

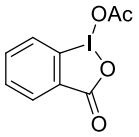


^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (dd, 1H, J = 7.5, 1.5 Hz), δ 8.21 (d, 1H, J = 8.5 Hz), δ 8.00 (m, 1H), δ 7.80 (t, 1H, J = 7.3 Hz). NMR data is consistent with the reported data.

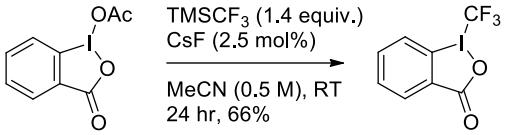


Step 2: To a solution of 1-chloro-1λ^3 -benzo[d][1,2]iodaoxol-3(1H)-one (1 equiv.) in MeCN (1 M) was added potassium acetate (2 equiv.) under nitrogen atmosphere. The resulting suspension was stirred for 2 hours during refluxing. The solution was cooled to RT. and diluted with $CHCl_3$ then filtered on Celite to remove KCl salt. The filtrate was concentrated under reduced pressure. The crude material was purified by flash chromatography.

1-acetoxy-1,2-benziodoxol-3-one

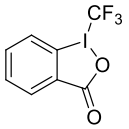


^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, 1H, J = 7.6 Hz), δ 8.01 (d, 1H, J = 8.3 Hz), δ 7.93 (ddd, 1H, J = 8.3, 7.2, 1.6 Hz), δ 7.72 (t, 1H, J = 7.4 Hz). NMR data is consistent with the reported data.



Step 3: To a solution of 1-acetoxy-1,2-benziodoxol-3-one (1 equiv.) in MeCN (0.5 M) was added anhydrous CsF (2.5 mol%), $TMSCF_3$ (1.4 equiv.) under nitrogen atmosphere. The solution was stirred at RT for 24 hours (reaction turns brown). The white precipitation was collected by vacuum filtration. The white solid was dissolved in $CHCl_3$ and insoluble materials were removed by filtration through a cotton plug. The colorless filtrate was washed with water and saturated Na_2CO_3 solution. The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford pure product.

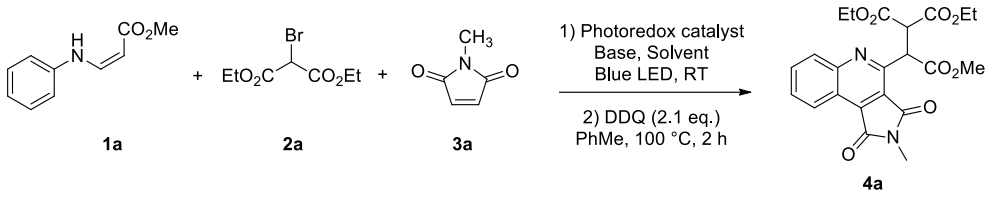
Togni's reagent II (2ab)



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.48 (dd, 1H, J = 7.1, 1.9 Hz), δ 7.86 – 7.74 (m, 3H). NMR data is consistent with the reported data.

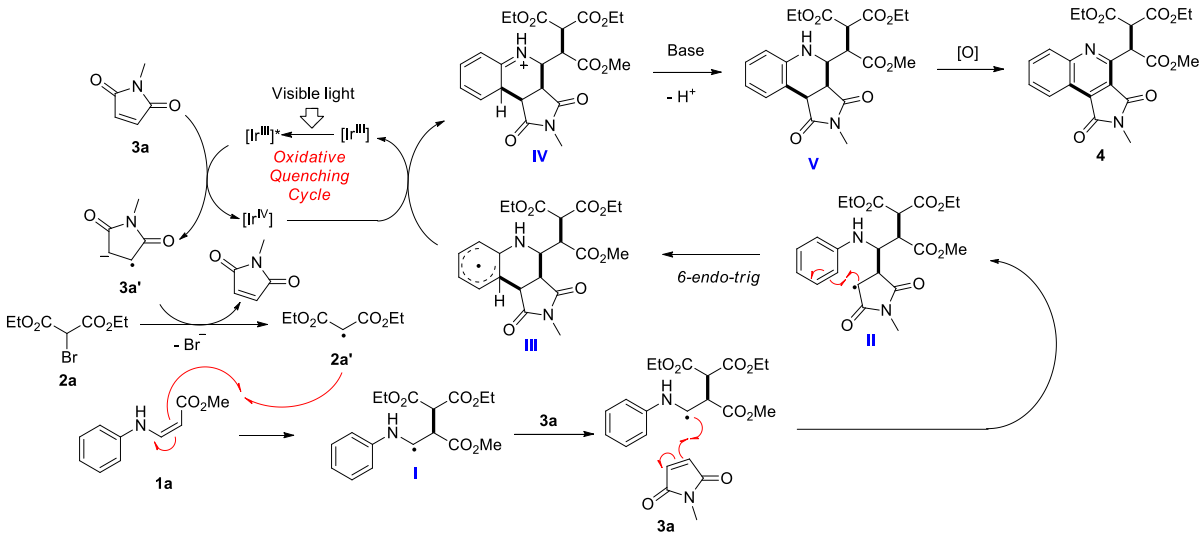
3.8.5. Procedure for optimization studies

3.8.5.1. First optimized reaction condition

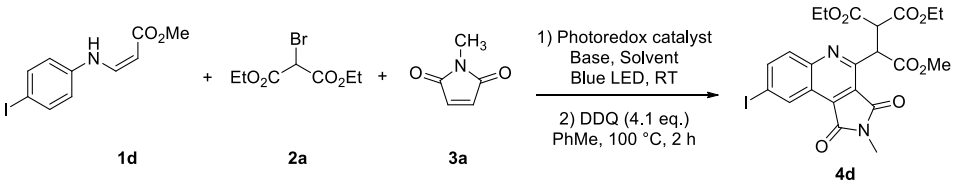


To an oven-dried 4 mL vial equipped with a stir bar was added photocatalyst $Ir(ppy)_2(dtbbpy)PF_6$ (1.4 mg, 1.5 μmol, 0.03 equiv.), anhydrous sodium phosphate dibasic (powder) (7.1 mg, 0.05 mmol, 1 equiv.), methyl 3-(phenyl amino) acrylate **1a** (8.9 mg, 0.05 mmol, 1 equiv.) and *N*-methyl maleimide **3a** (16.7 mg, 0.15 mmol, 3 equiv.). Required amounts of anhydrous acetonitrile (1 mL) and diethyl bromomalonate **2a** (90 % purity, 9.5 μL, 0.05 mmol, 1 equiv.) were added under argon atmosphere in glovebox. The reaction mixture was irradiated with a 12 W blue LED lamp (5 cm away, 25 ℃ maintained with a cooling fan) for 18 h. After evaporating the solvent under reduced pressure, the crude material was dissolved in toluene (1 mL) and treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (23.8 mg, 0.105 mmol, 2.1 equiv.). The mixture was heated at 100 ℃ for 2 h. NMR yields were calculated by using 1,1,2-trichloroethene as an internal standard.

Proposed reaction mechanism – Preliminary result

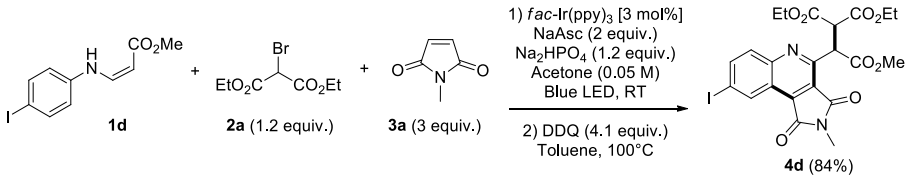


3.8.5.2. Second optimized reaction condition



To an oven-dried 4 mL vial equipped with a stir bar was added photocatalyst *fac*-Ir(ppy)$_3$ (1.0 mg, 1.5 μmol, 0.03 equiv.), sodium ascorbate (19.8 mg, 0.1 mmol, 2 equiv.), anhydrous sodium phosphate dibasic (powder) (8.5 mg, 0.06 mmol, 1.2 equiv.), methyl 3-((4-iodophenyl) amino) acrylate **1d** (15.2 mg, 0.05 mmol, 1 equiv.) and *N*-methyl maleimide **3a** (16.7 mg, 0.15 mmol, 3 equiv.). Required amounts of anhydrous acetone (1 mL) and diethyl bromomalonate **2a** (90 % purity, 11.35 μL, 0.06 mmol, 1.2 equiv.) were added under argon atmosphere in glovebox. The reaction mixture was irradiated with a 12 W blue LED lamp (5 cm away, 25 ℃ maintained with a cooling fan) for 18 h. After evaporating the solvent under reduced pressure, the crude material was dissolved in toluene (1 mL) and treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (46.5 mg, 0.205 mmol, 4.1 equiv.). The mixture was heated at 100 ℃ for 2 h. NMR yields were calculated by using 1,1,2-trichloroethene as an internal standard.

3.8.6. Procedures for Three-Component Synthesis of Quinolines based on Radical Cascade Visible-Light Photoredox Catalysis

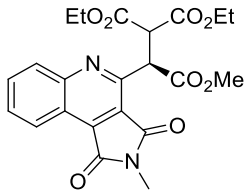


To an oven-dried 4 mL vial equipped with a stir bar was added photocatalyst *fac*-Ir(ppy)$_3$ (2.0 mg, 3 μmol, 0.03 equiv.), sodium ascorbate (39.6 mg, 0.2 mmol, 2 equiv.), anhydrous sodium phosphate dibasic (powder) (17 mg, 0.12 mmol, 1.2 equiv.), methyl 3-((4-iodophenyl) amino) acrylate **1d** (30.3 mg, 0.1 mmol, 1 equiv.) and *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.). Required amounts of anhydrous acetone (2 mL) and diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.) were added under argon atmosphere in glovebox. The reaction mixture was irradiated with a 12 W blue LED lamp (5 cm away, 25 ℃ maintained with a cooling fan) for 18 h. After evaporating the solvent under reduced pressure, the crude material was dissolved in toluene (2 mL) and treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (93 mg, 0.41 mmol, 4.1

equiv.). The mixture was heated at 100 ℃ for 2 h. Aromatization reaction was monitored by TLC analysis. The solution was filtered on Celite and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, 20 – 50% EtOAc in hexanes), yielding the corresponding final product.

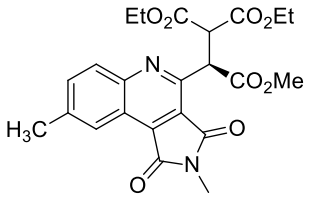
3.8.7. Characterization data of Quinolines **4**

1,1-diethyl 2-methyl 2-(2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (4a): Prepared following the general procedure outlined above using methyl 3-(phenyl amino) acrylate, **1a** (17.7 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 µL, 0.12 mmol, 1.2 equiv.), *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (74 % yield).



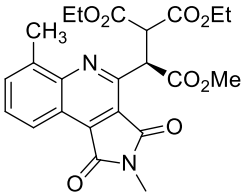
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.82 (d, 1H, J = 8.4 Hz) δ 8.10 (d, 1H, J = 8.6 Hz) δ 7.87 (t, 1H, J = 7.73 Hz) δ 7.85 (t, 1H, J = 7.6 Hz) δ 5.81 (d, 1H, J = 9.75 Hz) δ 4.77 (d, 1H, J = 9.75 Hz) δ 4.32 (q, 2H, J = 7.1 Hz) δ 4.02 (m, 2H) δ 3.65 (s, 3H) δ 3.25 (s, 3H) δ 1.35 (t, 3H, J = 7.12 Hz) δ 1.08 (t, 3H, J = 7.11 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 168.1, 167.9, 167.7, 167.5, 151.6, 150.9, 136.4, 132.6, 129.8, 129.6, 124.8, 122.5, 120.9, 61.8, 61.6, 52.8, 52.6, 48.1, 24.1, 14.0, 13.8.
HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{22}N_2NaO_8$ ($[M+Na]^+$) 465.1268, found 465.1269.

1,1-diethyl 2-methyl 2-(2,8-dimethyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (4b): Prepared following the general procedure outlined above using methyl 3-(*p*-tolyl amino) acrylate, **1b** (19.1 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 µL, 0.12 mmol, 1.2 equiv.), *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (61 % yield).



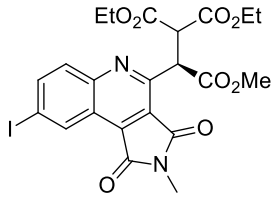
^{1}H NMR (400 MHz, CDCl3): δ 8.58 (s, 1H) δ 7.98 (d, 1H, J = 8.7 Hz) δ 7.69 (dd, 1H, J = 1.9 Hz, 8.8 Hz) δ 5.78 (d, 1H, J = 9.8 Hz) δ 4.75 (d, 1H, J = 9.8 Hz) δ 4.32 (qd, 2H, J = 0.9 Hz, 7.1 Hz) δ 4.01 (m, 2H) δ 3.65 (s, 3H) δ 3.24 (s, 3H) δ 1.34 (t, 3H, J = 7.1 Hz) δ 1.06 (t, 3H, J = 7.1 Hz).
^{13}C NMR (100 MHz, CDCl3): δ 170.2, 168.2, 167.9, 167.8, 167.5, 150.5, 149.8, 140.4, 135.4, 135.0, 129.4, 123.3, 122.4, 121.1, 61.7, 61.6, 52.8, 52.6, 47.9, 24.0, 21.9, 14.0, 13.8;
HRMS (ESI-TOF) m/z calcd. for $C_{23}H_{24}N_2NaO_8$ ([M+Na]+) 479.1425, found 479.1426.

1,1-diethyl 2-methyl 2-(2,6-dimethyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (4c): Prepared following the general procedure outlined above using methyl 3-(*o*-tolyl amino) acrylate, **1b** (19.1 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 µL, 0.12 mmol, 1.2 equiv.), *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.), *fac*-$Ir(ppy)_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (70 % yield).



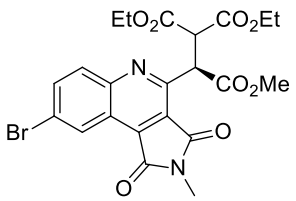
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, 1H, J = 8.3 Hz) δ 7.70 (d, 1H, J = 7.0 Hz) δ 7.62 (m, 1H) δ 5.75 (d, 1H, J = 9.3 Hz) δ 4.76 (d, 1H, J = 9.3 Hz) δ 4.31 (dddd, 2H, J = 3.6 Hz, 7.1 Hz, 10.8 Hz, 17.8 Hz) δ 4.04 (dddd, 2H, J = 3.6 Hz, 7.1 Hz, 10.8 Hz, 17.8 Hz) δ 3.66 (s, 3H) δ 3.23 (s, 3H) δ 2.74 (s, 3H) δ 1.33 (t, 3H, J = 7.1 Hz) δ 1.09 (t, 3H, J = 7.1 Hz);
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 168.1, 167.9, 167.8, 167.6, 149.99, 149.97, 138.1, 136.5, 132.7, 129.6, 122.5, 122.3, 121.1, 61.8, 61.6, 52.7, 52.6, 48.5, 24.0, 18.1, 14.0, 13.8.
HRMS (ESI-TOF) m/z calcd. for $C_{23}H_{24}N_2NaO_8$ ($[M+Na]^+$) 479.1425, found 479.1427.

1,1-diethyl 2-methyl 2-(8-iodo-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl)ethane-1,1,2-tricarboxylate (4d): Prepared following the general procedure outlined above using methyl 3-((4-iodophenyl) amino) acrylate, **1d** (30.3 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.), *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (64 % yield).



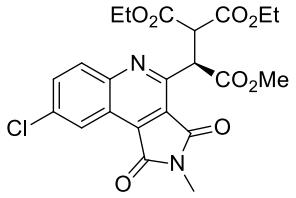
^{1}H NMR (400 MHz, $CDCl_3$): δ 9.20 (d, 1H, J = 1.80 Hz) δ 8.09 (dd, 1H, J = 2.0, 9.0 Hz) δ 7.79 (d, 1H, J = 9.0 Hz) δ 5.77 (d, 1H, J = 9.8 Hz) δ 4.72 (d, 1H, J = 9.8 Hz) δ 4.31 (qd, 2H, J = 1.4 Hz, 7.1 Hz) δ 4.01 (m, 2H) δ 3.64 (s, 3H) δ 3.24 (s, 3H) δ 1.33 (t, 3H, J = 7.14 Hz) δ 1.07 (t, 3H, J = 7.14 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 167.7, 167.5, 167.4, 167.3, 152.3, 149.7, 141.4, 134.9, 133.6, 131.0, 123.0, 122.2, 96.4, 61.8, 61.7, 52.7, 52.6, 48.0, 24.2, 14.0, 13.8.
HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{21}IN_2NaO_8$ ($[M+Na]^+$) 591.0235, found 591.0234.

1,1-diethyl 2-methyl 2-(8-bromo-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl)ethane-1,1,2-tricarboxylate (4e): Prepared following the general procedure outlined above using methyl 3-((4-bromophenyl) amino) acrylate, **1e** (25.6 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.), *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (69 % yield).



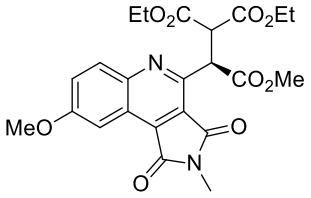
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (s, 1H) δ 7.94 (m, 2H) δ 5.78 (d, 1H, J = 9.76 Hz) δ 4.73 (d, 1H, J = 9.76 Hz) δ 4.32 (q, 2H, J = 6.7 Hz) δ 4.02 (m, 2H) δ 3.65 (s, 3H) δ 3.25 (s, 3H) δ 1.34 (t, 3H, J = 7.12 Hz) δ 1.08 (t, 3H, J = 7.12 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 167.8, 167.5, 167.4, 167.3, 152.1, 149.4, 136.2, 135.3, 131.2, 129.1, 126.9, 124.5, 123.2, 121.8, 61.9, 61.7, 52.7, 48.0, 24.2, 14.0, 13.8.
HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{21}BrN_2NaO_8$ ($[M+Na]^+$) 543.0373, found 543.0376.

1,1-diethyl 2-methyl 2-(8-chloro-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (4f): Prepared following the general procedure outlined above using methyl 3-((4-chlorophenyl) amino) acrylate, **1f** (21.2 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.), *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (66 % yield).



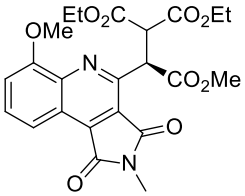
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, 1H, J = 2.0 Hz) δ 8.03 (d, 1H, J = 9.2 Hz) δ 7.79 (dd, 1H, J = 2.3 Hz, 9.2 Hz) δ 5.78 (d, 1H, J = 9.8 Hz) δ 4.73 (d, 1H, J = 9.8 Hz) δ 4.31 (q, 2H, J = 6.8) δ 4.02 (m, 2H) δ 3.65 (s, 3H) δ 3.25 (s, 3H) δ 1.34 (t, 3H, J = 7.1 Hz) δ 1.08 (t, 3H, J = 7.1 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 167.7, 167.5, 167.4, 167.3, 152.0, 149.2, 136.2, 135.5, 133.6, 131.2, 129.6, 127.5, 123.6, 121.4, 61,8, 61.7, 52.7, 48.0, 24.2, 14.0, 13.8.
HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{21}ClN_2NaO_8$ ($[M+Na]^+$) 499.0879, found 499.0880.

1,1-diethyl 2-methyl 2-(8-methoxy-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl)ethane-1,1,2-tricarboxylate (4g): Prepared following the general procedure outlined above using methyl 3-((4-methoxyphenyl) amino) acrylate, **1g** (20.7 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.), *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (77 % yield).



^{1}H NMR (400 MHz, DMSO): δ 7.98 (d, 1H, J = 9.4 Hz) δ 7.96 (d, 1H, J = 2.8 Hz) δ 7.63 (dd, 1H, J = 2.9 Hz, 9.3 Hz) δ 5.58 (d, 1H, J = 9.8 Hz) δ 4.49 (d, 1H, J = 9.8 Hz) δ 4.21 (q, 2H, J = 7.1 Hz) δ 3.94 (s, 3H) δ 3.89 (q, 2H, J = 7.1 Hz) δ 3.54 (s, 3H) δ 3.09 (s, 3H) δ 1.22 (t, 3H, J = 7.1 Hz) δ 0.87 (t, 3H, J = 7.1 Hz).
^{13}C NMR (100 MHz, DMSO): δ 170.0, 168.2, 168.0, 167.8, 167.1, 160.4, 148.3, 147.1, 134.7, 131.3, 126.5, 122.9, 122.4, 101.7, 61.9, 61.8, 56.4, 53.02, 53.00, 47.6, 24.3, 14.3, 13.9.
HRMS (ESI-TOF) m/z calcd. for $C_{23}H_{24}N_2NaO_9$ ([M+Na]$^+$) 495.1374, found 495.1375.

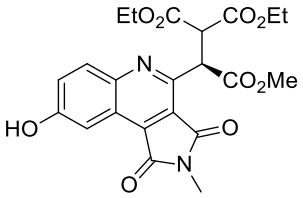
1,1-diethyl 2-methyl 2-(6-methoxy-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (4h): Prepared following the general procedure outlined above using methyl 3-((2-methoxyphenyl) amino) acrylate, **1h** (20.7 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.), *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (61 % yield).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.58 (s, 1H) δ 7.98 (d, 1H, J = 8.7 Hz) δ 7.69 (d, 1H, J = 8.8 Hz) δ 5.78 (d, 1H, J = 9.8 Hz) δ 4.75 (d, 1H, J = 9.8 Hz) δ 4.31 (q, 2H, J = 7.1 Hz) δ 4.01 (m, 2H) δ 3.64 (s, 3H) δ 3.24 (s, 3H) δ 2.60 (s, 3H) δ 1.34 (t, 3H, J = 7.1 Hz) δ 1.06 (t, 3H, J = 7.1 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 168.2, 167.9, 167.8, 167.5, 150.5, 149.8, 140.4, 135.4, 135.0, 129.4, 123.3, 122.4, 121.1, 61.7, 61.6, 52.8, 52.6, 47.9, 24.0, 21.9, 14.0, 13.8.
HRMS (ESI-TOF) m/z calcd. for $C_{23}H_{24}N_2NaO_9$ ([M+Na]$^+$) 495.1374, found 495.1376.

1,1-diethyl 2-methyl 2-(8-hydroxy-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (4i): Prepared following the general procedure outlined above using

methyl 3-((4-hydroxyphenyl) amino) acrylate, **1i** (19.3 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 µL, 0.12 mmol, 1.2 equiv.), *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (52 % yield).

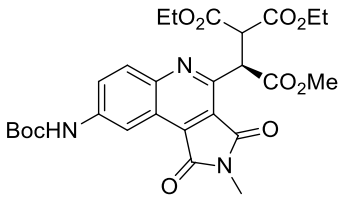


^{1}H NMR (400 MHz, DMSO): δ 10.85 (s, 1H) δ 7.94 (dd, 2H, J = 6.1 Hz, 7.7 Hz) δ 7.52 (dd, 1H, J = 2.7 Hz, 9.2 Hz) δ 5.56 (d, 1H, J = 9.9 Hz) δ 4.47 (d, 1H, J = 9.9 Hz) δ 4.21 (dd, 2H, J = 6.6 Hz, 13.7 Hz) δ 3.88 (q, 2H, J = 7.0 Hz) δ 3.53 (s, 3H) δ 3.08 (s, 3H) δ 1.22 (t, 3H, J = 7.1 Hz) δ 0.86 (t, 3H, J = 7.0 Hz)

^{13}C NMR (100 MHz, DMSO): δ 170.19, 168.3, 168.1, 167.8, 167.1, 159.2, 147.2, 146.4, 134.1, 131.5, 126.6, 122.7, 122.6, 104.8, 61.8, 61.7, 53.0, 52.9, 47.5, 24.3, 14.3, 13.9.

HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{22}N_2NaO_9$ ($[M+Na]^+$) 481.1218, found 481.1220.

1,1-diethyl 2-methyl 2-(8-((tert-butoxycarbonyl)amino)-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)ethane-1,1,2-tricarboxylate (4j): Prepared following the general procedure outlined above using methyl 3-((4-((tert-butoxycarbonyl)amino)phenyl)amino)acrylate, **1j** (29.2 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 µL, 0.12 mmol, 1.2 equiv.), *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (73 % yield).



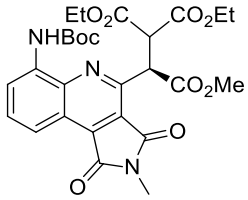
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, 1H, J = 1.74 Hz) δ 8.17 (d, 1H, J = 8.8 Hz) δ 7.98 (d, 1H, J = 9.3 Hz) δ 7.17 (s, 1H) δ 5.75 (d, 1H, J = 10.0 Hz) δ 4.76 (d, 1H, J = 10.0 Hz) δ 4.32 (m, 2H) δ 4.05

(m, 2H) δ 3.65 (s, 3H) δ 3.19 (s, 3H) δ 1.58 (s, 9H) δ 1.34 (t, 3H, J = 7.1 Hz) δ 1.09 (t, 3H, J = 7.1 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.29, 167.93, 167.88, 167.74, 167.70, 152.27, 149.39, 147.87, 139.94, 134.78, 130.68, 125.26, 122.84, 121.66, 109.56, 81.6, 61.79, 61.75, 52.86, 52.68, 47.95, 28.26, 24.01, 14.06, 13.8

HRMS (ESI-TOF) m/z calcd. for $C_{27}H_{31}N_3NaO_{10}$ ($[M+Na]^+$) 580.1902, found 580.1903.

1,1-diethyl 2-methyl 2-(6-((tert-butoxycarbonyl)amino)-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)ethane-1,1,2-tricarboxylate (4k): Prepared following the general procedure outlined above using methyl 3-((2-((tert-butoxycarbonyl)amino)phenyl)amino)acrylate, **1k** (29.2 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.), *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (60 % yield).



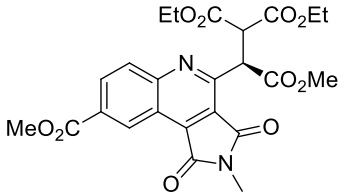
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, 1H, J = 7.6 Hz) δ 8.60 (s, 1H) δ 8.40 (dd, 1H, J = 8.4, 11 Hz) δ 7.71 (t, 1H, J = 8.2 Hz) δ 5.72 (d, 1H, J = 8.6 Hz) δ 4.65 (d, 1H, J = 8.6 Hz) δ 4.32 (m, 2H) δ 4.10 (m, 2H) δ 3.69 (s, 3H) δ 3.23 (s, 3H) δ 1.60 (s, 9H) δ 1.30 (t, 3H, J = 7.1 Hz) δ 1.13 (t, 3H, J = 7.1 Hz)

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.94, 167.81, 167.69, 167.67, 167.54, 152.66, 149.19, 140.52, 136.57, 135.82, 131.01, 123.19, 121.19, 118.00, 117.16, 81.16, 61.98, 61.85, 52.79, 52.58, 48.45, 28.37, 24.18, 13.99, 13.84.

HRMS (ESI-TOF) m/z calcd. for $C_{27}H_{31}N_3NaO_{10}$ ($[M+Na]^+$) 580.1902, found 580.1903.

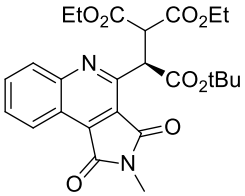
1,1-diethyl 2-methyl 2-(8-(methoxy carbonyl)-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo [3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (4l): Prepared following the general procedure outlined above using methyl 4-((3-methoxy-3-oxoprop-1-en-1-yl) amino) benzoate, **1l** (19.3 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.), *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4

(17 mg, 0.12 mmol, 1.2 equiv.), Acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (49 % yield).



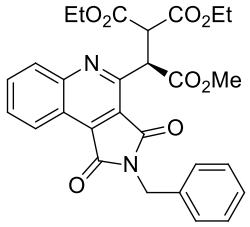
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (d, 1H, J = 8.7 Hz) δ 8.79 (d, 1H, J = 1.5 Hz) δ 8.31 (dd, 1H, J = 1.5, 8.7 Hz) δ 5.81 (d, 1H, J = 9.7 Hz) δ 4.76 (d, 1H, J = 9.7 Hz) δ 4.33 (q, 2H, J = 7.1 Hz) δ 4.09-4.00 (m, 5H) δ 3.66 (s, 3H) δ 3.26 (s, 3H) δ 1.36 (t, 3H, J = 7.1 Hz) δ 1.10 (t, 3H, J = 7.1 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 167.8, 167.6, 167.5, 167.4, 166.0, 152.9, 150.4, 136.3, 133.6, 131.9, 129.0, 125.2, 124.0, 123.2, 61.9, 61.8, 52.82, 52.80, 48.1, 24.2, 14.1, 13.8.
HRMS (ESI-TOF) m/z calcd. for $C_{24}H_{24}N_2NaO_{10}$ ($[M+Na]^+$) 523.1323, found 523.1325.

2-tert-butyl 1,1-diethyl 2-(2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (4m): Prepared following the general procedure outlined above using *tert*-butyl 3-(phenyl amino) acrylate, **1m** (22 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.), *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.), *fac*-$Ir(ppy)_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (59 % yield).



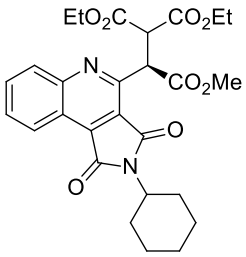
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, 1H, J = 8.4 Hz) δ 8.07 (d, 1H, J = 8.5 Hz) δ 7.85 (ddd, 1H, J = 1.4 Hz, 7.4 Hz, 8.5 Hz) δ 7.72 (m, 1H) δ 5.64 (d, 1H, J = 9.1 Hz) δ 4.66 (d, 1H, J = 9.1 Hz) δ 4.32 (m, 2H) δ 4.04 (pd, J = 3.7 Hz, 6.9 Hz) δ 3.23 (s, 3H) δ 1.37 – 1.32 (m, 12H) δ 1.10 (t, 3H, J = 7.1 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 168.1, 167.9, 167.8, 167.7, 152.3, 150.8, 136.1, 134.1, 132.4, 129.7, 124.8, 122.7, 120.8, 82.5, 61.59, 61.58, 52.6, 49.2, 27.7, 24.0, 14.1, 13.8.
HRMS (ESI-TOF) m/z calcd. for $C_{25}H_{28}N_2NaO_8$ ($[M+Na]^+$) 507.1738, found 507.1741.

1,1-diethyl 2-methyl 2-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (4n): Prepared following the general procedure outlined above using methyl 3-(phenyl amino) acrylate, **1a** (17.7 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 µL, 0.12 mmol, 1.2 equiv.), *N*-benzyl maleimide **3n** (56.2 mg, 0.3 mmol, 3 equiv.), *fac*-$Ir(ppy)_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (87 % yield).



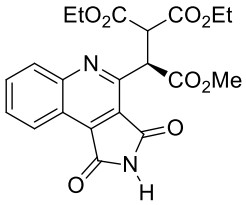
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (dd, 1H, J = 0.7 Hz, 8.4 Hz) δ 8.09 (d, 1H, J = 8.5 Hz) δ 7.86 (ddd, 1H, J = 1.4 Hz, 6.9 Hz, 8.5 Hz) δ 7.73 (ddd, 1H, J = 1.1 Hz, 7.0 Hz, 8.2 Hz) δ 7.47 (d, 2H, J = 6.9 Hz) δ 7.39 – 7.28 (m, 3H) δ 5.79 (d, 1H, J = 9.7 Hz) δ 4.90 (d, 2H, J = 3.3 Hz) δ 4.73 (d, 1H, J = 9.7 Hz) δ 4.32 (qd, 2H, J = 1.3 Hz, 7.1 Hz) δ 3.98 (qd, 2H, J = 2.2 Hz, 7.1 Hz) δ 3.63 (s, 3H) δ 1.34 (t, 3H, J = 7.1 Hz) δ 1.03 (t, 3H, J = 7.1 Hz);
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 167.9, 167.6, 167.4, 167.3, 151.6, 151.0, 136.2, 135.9, 132.6, 129.8, 129.7, 128.75, 128.71, 128.0, 124.8, 122.4, 121.0, 61.8, 61.6, 52.8, 52.6, 48.1, 41.8, 14.0, 13.8.
HRMS (ESI-TOF) m/z calcd. for $C_{28}H_{26}N_2NaO_8$ ($[M+Na]^+$) 541.1581, found 541.1582.

1,1-diethyl 2-methyl 2-(2-cyclohexyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (4o): Prepared following the general procedure outlined above using methyl 3-(phenyl amino) acrylate, **1a** (17.7 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 µL, 0.12 mmol, 1.2 equiv.), 1-cyclohexyl-1H-pyrrole-2,5-dione, **3o** (53.8 mg, 0.3 mmol, 3 equiv.), *fac*-$Ir(ppy)_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (71 % yield).



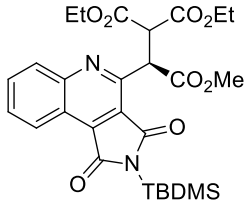
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (d, 1H, J = 7.9) δ 8.08 (d, 1H, J = 8.6 Hz) δ 7.85 (ddd, 1H, J = 1.3 Hz, 7.0 Hz, 8.5 Hz) δ 7.75 – 7.70 (m ,1H) δ 5.78 (d, 1H, J = 9.7 Hz) δ 4.74 (d, 1H, J = 9.7 Hz) δ 4.31(qd, 2H, J = 1.9 Hz, 7.1 Hz) δ 4.20 – 4.12 (m, 1H) δ 4.01 (qd, 2H, J = 3.0 Hz, 7.1 Hz) δ 2.24 (ddd, 2H, J = 8.7 Hz, 12.8 Hz, 16.7 Hz) δ 1.89 (d, 2H, J = 13.0 Hz) δ 1.79 (d, 2H, J = 11.3 Hz) δ 1.72 (d, 1H, J = 12.1 Hz) δ 1.45 – 1.36 (m, 2H) δ 1.33 (t, 3H, J = 7.1 Hz) δ 1.07 (t, 3H, J = 7.1 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 168.0, 167.9, 167.7, 167.5, 151.5, 150.9, 136.0, 132.4, 129.7, 129.5, 124.8, 122.1, 121.0, 61.7, 61.6, 52.8, 52.6, 51.2, 48.0, 29.9, 29.8, 26.0, 14.0, 13.8.
HRMS (ESI-TOF) m/z calcd. for $C_{27}H_{30}N_2NaO_8$ ($[M+Na]^+$) 533.1894, found 533.1896.

1,1-diethyl 2-methyl 2-(1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (4p): Prepared following the general procedure outlined above using methyl 3-(phenyl amino) acrylate, **1a** (17.7 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.), maleimide **3p** (29.3 mg, 0.3 mmol, 3 equiv.), *fac*-$Ir(ppy)_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (56 % yield).



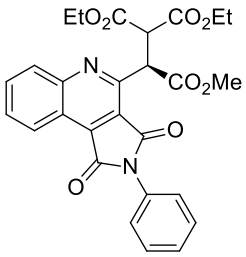
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.81 (ddd, 1H, J = 0.6 Hz, 1.4 Hz, 8.4 Hz) δ 8.14 – 8.10 (m, 1H) δ 7.89 (ddd, 1H, 1.5 Hz, 6.9 Hz, 8.5 Hz) δ 7.76 (ddd, 1H, J = 1.2 Hz, 6.9 Hz, 8.2 Hz) δ 5.77 (d, 1H, J = 9.7 Hz) δ 4.77 (d, 1H, J = 9.7 Hz) δ 4.33 (qd, 2H, J = 0.8 Hz, 7.1 Hz) δ 4.07 – 4.00 (m, 2H) δ 3.66 (s, 3H) δ 1.35 (t, 3H, J = 7.1 Hz) δ 1.09 (t, 3H, J = 7.1 Hz)
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 167.9, 167.5, 167.4, 167.0, 152.0, 151.0, 136.6, 135.1, 132.8, 129.9, 124.8, 122.9, 121.1, 61.8, 61.7, 52.8, 52.7, 48.1, 14.0, 13.8.
HRMS (ESI-TOF) m/z calcd. for $C_{21}H_{20}N_2NaO_8$ ($[M+Na]^+$) 451.1112, found 451.1112.

1,1-diethyl 2-methyl 2-(2-(tert-butyldimethylsilyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)ethane-1,1,2-tricarboxylate (4q): Prepared following the general procedure outlined above using methyl 3-(phenyl amino) acrylate, **1a** (17.7 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 µL, 0.12 mmol, 1.2 equiv.), 1-(tert-butyldimethylsilyl)-1H-pyrrole-2,5-dione **3q** (63.3 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (32 % yield).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (ddd, J = 8.3, 1.3, 0.5 Hz, 1H), δ 8.10 (d, J = 8.2 Hz, 1H), δ 7.85 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), δ 7.72 (ddd, J = 8.3, 6.9, 1.2 Hz, 1H), δ 5.77 (d, J = 9.5 Hz, 1H), δ 4.73 (d, J = 9.5 Hz, 1H), δ 4.32 (q, J = 6.9 Hz, 1H), δ 4.04 (qq, J = 7.0, 3.7 Hz, 1H), δ 3.64 (s, 3H), δ 1.34 (t, J = 7.1 Hz, 2H), δ 1.09 (t, J = 7.1 Hz, 2H), δ 1.01 (s, 9H), δ 0.57 (s, 6H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 173.4, 172.8, 170.16, 167.9, 167.59, 151.8, 150.7, 137.8, 132.3, 129.7, 129.5, 125.0, 121.1, 115.9, 61.7, 61.6, 52.7, 52.6, 48.2, 26.2, 25.2, 14.0, 13.8, -4.23.
HRMS (ESI-TOF) m/z calcd. for $C_{27}H_{34}N_2NaO_8Si$ ($[M+Na]^+$) 565.1977, found 565.1980.

1,1-diethyl 2-methyl 2-(1,3-dioxo-2-phenyl-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (4r): Prepared following the general procedure outlined above using methyl 3-(phenyl amino) acrylate, **1a** (17.7 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 µL, 0.12 mmol, 1.2 equiv.), 1-phenyl-1H-pyrrole-2,5-dione, **3r** (52 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (73 % yield).

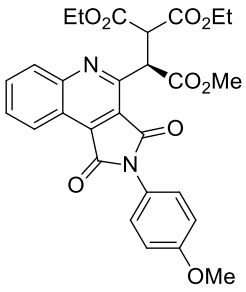


^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (d, 1H, J = 8.3 Hz) δ 8.14 (d, 1H, J = 8.5 Hz) δ 7.91 (ddd, 1H, J = 1.4 Hz, 7.0 Hz, 8.4 Hz) δ 7.77 (m, 1H) δ 7.57 – 7.32 (m, 5H) δ 5.85 (d, 1H, J = 9.5 Hz) δ 4.78 (d, 1H, J = 9.5 Hz) δ 4.32 (qd, 2H, J = 1.6 Hz, 7.1 Hz) δ 4.06 (qd, 2H, J = 3.0 Hz, 7.1 Hz) δ 3.67 (s, 3H) δ 1.34 (t, 3H, J = 7.1 Hz) δ 1.11 (t, 3H, J = 7.1 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 167.9, 167.6, 166.9, 166.6, 152.0, 151.1, 135.8, 134.1, 132.8, 131.1, 129.9, 129.1, 128.3, 127.9, 126.5, 126.0, 125.0, 121.9, 121.0, 61.8, 61.7, 52.8, 52.7, 48.2, 14.0, 13.8.

HRMS (ESI-TOF) m/z calcd. for $C_{27}H_{24}N_2NaO_8$ ($[M+Na]^+$) 527.1425, found 527.1425.

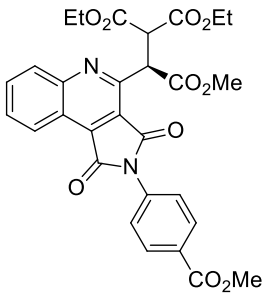
1,1-diethyl 2-methyl 2-(2-(4-methoxyphenyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)ethane-1,1,2-tricarboxylate (4s): Prepared following the general procedure outlined above using methyl 3-(phenyl amino) acrylate, **1a** (17.7 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.), 1-(4-methoxyphenyl)-1H-pyrrole-2,5-dione, **3s** (60.9 mg, 0.3 mmol, 3 equiv.), *fac*-$Ir(ppy)_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (75 % yield).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (d, J = 8.4 Hz, 1H), δ 8.13 (d, J = 8.6 Hz, 1H), δ 7.90 (ddt, J = 8.3, 6.9, 1.3 Hz, 1H), δ 7.77 (ddt, J = 8.4, 6.9, 1.4 Hz, 1H), δ 7.40 (d, J = 8.7 Hz, 1H), δ 7.04 (d, J = 9.1 Hz, 1H), δ 5.84 (d, J = 9.5 Hz, 1H), δ 4.78 (d, J = 9.5 Hz, 1H), δ 4.32 (qd, J = 7.1, 1.6 Hz, 2H), δ 4.05 (qd, J = 7.1, 2.4 Hz, 2H), δ 3.86 (s, 3H), δ 3.66 (s, 3H), δ 1.34 (t, J = 7.1 Hz, 2H), δ 1.11 (t, J = 7.1 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.09, 167.9, 167.1, 166.8, 159.3, 151.9, 151.0, 135.9, 132.78, 129.8, 127.9, 125.0, 123.7, 122.0, 121.08, 114.4, 61.79, 61.70, 55.52, 52.8, 52.7, 48.2, 14.07, 13.87.
HRMS (ESI-TOF) m/z calcd. for $C_{28}H_{26}N_2NaO_9$ ($[M+Na]^+$) 557.1531, found 557.1533.

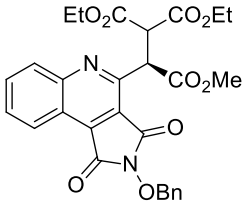
1,1-diethyl 2-methyl 2-(2-(4-(methoxycarbonyl)phenyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)ethane-1,1,2-tricarboxylate (4t): Prepared following the general procedure outlined above using methyl 3-(phenyl amino) acrylate, **1a** (17.7 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 µL, 0.12 mmol, 1.2 equiv.), methyl 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoate, **3t** (69.3 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (63 % yield).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.89 (d, *J* = 8.4 Hz, 1H), δ 8.21 (d, *J* = 8.7 Hz, 2H), δ 8.15 (d, *J* = 8.5 Hz, 1H), δ 7.93 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), δ 7.80 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), δ 7.66 (d, *J* = 8.7 Hz, 2H), δ 5.85 (d, *J* = 9.6 Hz, 1H), δ 4.79 (d, *J* = 9.6 Hz, 1H), δ 4.33 (qd, *J* = 7.1, 1.7 Hz, 2H), δ 4.10 – 4.01 (m, 2H), δ 3.96 (s, 3H), δ 3.67 (s, 3H), δ 1.35 (t, *J* = 7.1 Hz, 3H), δ 1.11 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 167.8, 167.6, 166.4, 166.2, 166.1, 152.1, 151.1, 135.6, 135.3, 133.0, 130.4, 130.1, 129.9, 129.5, 125.9, 124.9, 121.8, 121.0, 61.86, 61.77, 52.81, 52.78, 52.33, 48.21, 14.07, 13.87.
HRMS (ESI-TOF) m/z calcd. for $C_{29}H_{26}N_2NaO_{10}$ ($[M+Na]^+$) 585.1480, found.585.1483.

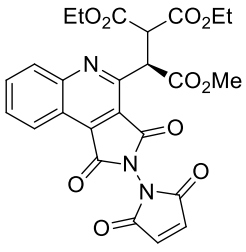
1,1-diethyl 2-methyl 2-(2-(benzyloxy)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)ethane-1,1,2-tricarboxylate (4u): Prepared following the general procedure outlined above using methyl 3-(phenyl amino) acrylate, **1a** (17.7 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 µL, 0.12 mmol, 1.2 equiv.), 1-(benzyloxy)-1H-pyrrole-2,5-dione, **3u** (60.9 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.),

acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (78 % yield).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, *J* = 7.8 Hz, 1H), δ 8.08 (d, *J* = 8.5 Hz, 1H), δ 7.91 – 7.85 (m, 1H), δ 7.74 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), δ 7.60 – 7.54 (m, 2H), δ 7.39 (m, 3H), δ 5.71 (d, *J* = 9.6 Hz, 1H), δ 5.27 (s, 2H), δ 4.74 (d, *J* = 9.6 Hz, 1H), δ 4.32 (q, *J* = 6.4 Hz, 2H), δ 4.03 (qd, *J* = 7.1, 5.7 Hz, 2H), δ 3.64 (s, 3H), δ 1.35 (t, *J* = 7.1 Hz, 3H), δ 1.08 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 167.8, 167.4, 163.2, 163.0, 151.4, 151.1, 133.5, 132.99, 132.98, 131.6, 129.96, 129.96, 129.91, 129.8, 129.4, 128.6, 124.8, 120.5, 119.1, 80.1, 61.8, 61.7, 52.75, 52.73, 48.1, 14.0, 13.8.
HRMS (ESI-TOF) m/z calcd. for $C_{28}H_{26}N_2NaO_9$ ($[M+H]^+$) 535.1711, found 535.1708.

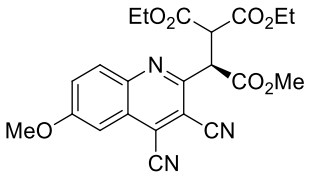
1,1-diethyl 2-methyl 2-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)ethane-1,1,2-tricarboxylate (4v): Prepared following the general procedure outlined above using methyl 3-(phenyl amino) acrylate, **1a** (17.7 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.), [1,1'-bipyrrole]-2,2',5,5'-tetraone, **3v** (57.6 mg, 0.3 mmol, 3 equiv.), *fac*-$Ir(ppy)_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (55 % yield).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (ddd, *J* = 8.4, 1.5, 0.7 Hz, 1H), δ 8.16 (ddd, *J* = 8.6, 1.3, 0.7 Hz, 1H), δ 7.93 (ddd, *J* = 8.6, 6.9, 1.5 Hz, 1H), δ 7.80 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), δ 7.73 (s, 2H), δ 5.87 (d, *J* = 9.6 Hz, 1H), δ 4.80 (d, *J* = 9.6 Hz, 1H), δ 4.34 (qd, *J* = 7.1, 1.7 Hz, 2H), δ 4.07 (qt, *J* = 7.2, 3.7 Hz, 2H), δ 3.69 (s, 3H), δ 1.36 (t, *J* = 7.1 Hz, 3H), δ 1.13 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 167.8, 167.6, 166.6, 166.3, 152.1, 151.1, 135.7, 132.9, 130.8, 130.0, 129.9, 126.9, 125.0, 121.9, 121.0, 61.8, 61.7, 52.8, 52.7, 48.2, 14.0, 13.8.
HRMS (ESI-TOF) m/z calcd. for $C_{25}H_{21}N_3NaO_{10}$ ($[M+Na]^+$) 546.1119, found 546.1116.

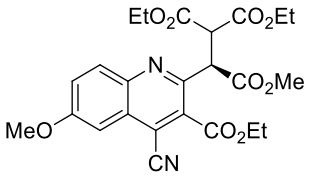
1,1-diethyl 2-methyl 2-(3,4-dicyano-6-methoxyquinolin-2-yl) ethane-1,1,2-tricarboxylate (4w): Prepared following the general procedure outlined above using methyl 3-((4-methoxyphenyl) amino) acrylate, **1g** (20.7 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.), fumaronitrile **3w** (23.3 mg, 0.3 mmol, 3 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (71 % yield).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, 1H, J = 9.3 Hz) δ 7.59 (dd, 1H, J = 2.7 Hz, 9.3 Hz) δ 7.36 (d, 1H, J = 2.7 Hz) δ 5.19 (d, 1H, J = 10.4 Hz) δ 4.74 (d, 1H, J = 10.4 Hz) δ 4.31 (qd, 2H, J = 2.4 Hz, 7.1 Hz) δ 4.08 – 3.97 (m, 5H) δ 3.68 (s, 3H) δ 1.33 (t, 3H, J = 7.1 Hz) δ 1.09 (t, 3H, J = 7.1 Hz)
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 167.3, 166.8, 161.2, 152.6, 144.4, 131.7, 127.8, 125.9, 122.2, 114.0, 113.2, 111.3, 102.0, 62.1, 62.0, 56.2, 53.1, 53.0, 50.4, 14.0, 13.8.
HRMS (ESI-TOF) m/z calcd. for $C_{22}H_{21}N_3NaO_7$ ($[M+Na]^+$) 462.1272, found 462.1275.

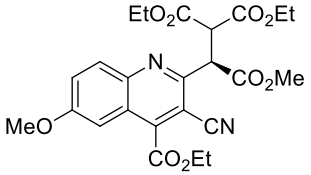
1,1-diethyl 2-methyl 2-(4-cyano-3-(ethoxycarbonyl)-6-methoxyquinolin-2-yl)ethane-1,1,2-tricarboxylate (4x) and **1,1-diethyl 2-methyl 2-(3-cyano-4-(ethoxycarbonyl)-6-methoxyquinolin-2-yl)ethane-1,1,2-tricarboxylate (4x')** Prepared following the general procedure outlined above using methyl 3-((4-methoxyphenyl) amino) acrylate, **1g** (20.7 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.), (Z)-ethyl 3-cyanoacrylate **3x** (62.5 mg, 0.5 mmol, 5 equiv.), *fac*-Ir(ppy)$_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (50 % yield, **4x** : **4x'** = 2 : 1).

1,1-diethyl 2-methyl 2-(4-cyano-3-(ethoxycarbonyl)-6-methoxyquinolin-2-yl) ethane-1,1,2-tricarboxylate (4x)



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, J = 9.2 Hz, 1H), δ 7.51 (dd, J = 9.2, 2.7 Hz, 1H), δ 7.44 (d, *J* = 2.7 Hz, 1H), δ 5.53 (d, *J* = 9.5 Hz, 1H), δ 4.71 (d, *J* = 9.5 Hz, 1H), δ 4.60 (qd, *J* = 7.2, 2.4 Hz, 2H), δ 4.29 (qd, *J* = 7.1, 0.9 Hz, 2H), δ 4.05 (q, *J* = 7.0 Hz, 2H), δ 4.01 (s, 3H), δ 3.65 (s, 3H), δ 1.53 (t, *J* = 7.2 Hz, 3H), δ 1.33 (t, *J* = 7.1 Hz, 3H), δ 1.07 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 168.1, 167.5, 164.6, 160.5, 150.3, 143.6, 131.4, 128.7, 126.4, 125.9, 117.9, 114.3, 102.4, 63.1, 61.7, 61.6, 56.0, 53.1, 52.6, 49.3, 14.0, 13.88, 13.85.
HRMS (ESI-TOF) m/z calcd. for $C_{24}H_{26}N_2NaO_9$ ($[M+Na]^+$) 509.1531, found 509.1530.

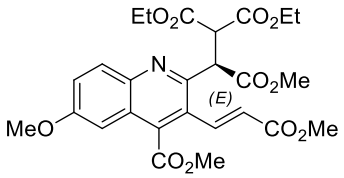
1,1-diethyl 2-methyl 2-(3-cyano-4-(ethoxycarbonyl)-6-methoxyquinolin-2-yl) ethane-1,1,2-tricarboxylate (4x')



^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (d, *J* = 9.3 Hz, 1H), δ 7.50 (dd, *J* = 9.3, 2.8 Hz, 1H), δ 7.39 (d, *J* = 2.7 Hz, 1H), δ 5.26 (d, *J* = 10.4 Hz, 1H), δ 4.77 (d, *J* = 10.4 Hz, 1H), δ 4.64 (qd, *J* = 7.1, 1.4 Hz, 2H), δ 4.31 (qd, *J* = 7.1, 1.0 Hz, 2H), δ 4.01 (qd, *J* = 7.1, 5.9 Hz, 2H), δ 3.94 (s, 3H), δ 3.68 (s, 3H), δ 1.54 (t, *J* = 7.2 Hz, 3H), δ 1.34 (t, *J* = 7.1 Hz, 3H), δ 1.06 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 167.6, 166.9, 164.4, 159.8, 152.6, 144.7, 141.8, 131.4, 126.1, 123.5, 115.1, 106.5, 102.6, 63.3, 61.9, 61.8, 55.7, 53.4, 52.9, 50.2, 14.06, 14.01, 13.78.
HRMS (ESI-TOF) m/z calcd. for $C_{24}H_{26}N_2NaO_9$ ($[M+Na]^+$) 509.1531, found 509.1530.

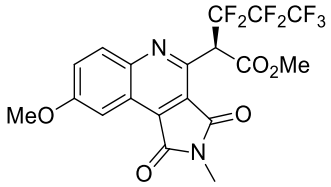
(E)-1,1-diethyl 2-methyl 2-(6-methoxy-3-(3-methoxy-3-oxoprop-1-en-1-yl)-4-(methoxycarbonyl)quinolin-2-yl)ethane-1,1,2-tricarboxylate (4z): Prepared following the general procedure outlined above using methyl 3-((4-methoxyphenyl) amino) acrylate, **1g** (20.7 mg, 0.1 mmol, 1 equiv.), diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.), (E)-dimethyl hex-2-en-4-ynedioate, **3z** (50.4 mg, 0.3 mmol, 3 equiv.), *fac*-$Ir(ppy)_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1

equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (36 % yield).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 16.2 Hz, 1H), δ 7.93 (d, *J* = 9.2 Hz, 1H), δ 7.39 (dd, *J* = 9.2, 2.7 Hz, 1H), δ 7.11 (d, *J* = 2.7 Hz, 1H), δ 6.26 (d, *J* = 16.2 Hz, 1H), δ 5.11 (d, *J* = 10.4 Hz, 1H), δ 4.81 (d, *J* = 10.4 Hz, 1H), δ 4.27 (qd, *J* = 7.1, 1.0 Hz, 2H), δ 4.00 (q, *J* = 7.1 Hz, 2H), δ 3.94 (s, 3H), δ 3.90 (s, 3H), δ 3.85 (s, 3H), δ 1.31 (t, *J* = 7.1 Hz, 3H), δ 1.01 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 168.3, 167.6, 167.5, 165.7, 158.8, 149.0, 143.3, 140.0, 139.8, 131.4, 126.4, 125.6, 125.3, 123.5, 102.6, 61.7, 61.4, 55.7, 53.3, 52.7, 52.5, 52.1, 49.6, 14.0, 13.8.
HRMS (ESI-TOF) m/z calcd. for $C_{26}H_{29}NNaO_{11}$ ($[M+Na]^+$) 554.1633, found 554.1635.

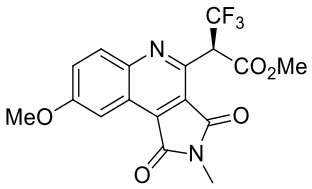
methyl 3,3,4,4,5,5,5-heptafluoro-2-(8-methoxy-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) pentanoate (4aa): Prepared following the general procedure outlined above using methyl 3-((4-methoxyphenyl) amino) acrylate, **1g** (20.7 mg, 0.1 mmol, 1 equiv.), heptafluoropropyl iodide, **2aa** (28.8 μL, 0.2 mmol, 2 equiv.), *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.), *fac*-$Ir(ppy)_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (68 % yield).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, 1H, J = 9.4 Hz) δ 8.07 (d, 1H, J = 1.9 Hz) δ 7.56 (dd, 1H, J = 9.4 Hz, 1.7 Hz) δ 6.13 (dd, 1H, J = 11.7 Hz, 16.9 Hz) δ 4.02 (s, 3H) δ 3.74 (s, 3H) δ 3.25 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.9, 167.8, 164.4, 161.2, 148.4, 134.1, 132.0, 127.0, 123.15, 122.5, 101.0, 56.06, 52.9, 48.9, 48.7, 48.5, 29.2, 24.1, 23.6.
^{19}F NMR (376 MHz, $CDCl_3$): δ -80.43 (t, J = 10.5 Hz, 3F) δ -110.45 (d, J = 301.1 Hz, 1F) δ -112.85 (d, J = 301.1 Hz, 1F) δ -123.71 (ddd, J = 287.7 Hz, 10.6 Hz, 1.8 Hz, 1F) δ -124.72 (ddd, J = 287.7 Hz, 10.5 Hz, 1.2 Hz, 1F)

HRMS (ESI-TOF) m/z calcd. for $C_{19}H_{13}F_7N_2NaO_5$ ($[M+Na]^+$) 505.0605, found 505.0606.

methyl 3,3,3-trifluoro-2-(8-methoxy-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)propanoate (4ab): Prepared following the general procedure outlined above using methyl 3-((4-methoxyphenyl) amino) acrylate, **1g** (20.7 mg, 0.1 mmol, 1 equiv.), Togni's reagent II, **2ab** (63.2 μL, 0.2 mmol, 2 equiv.), *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.), *fac*-$Ir(ppy)_3$ (2 mg, 0.003 mmol, 0.03 equiv.), Na_2HPO_4 (17 mg, 0.12 mmol, 1.2 equiv.), Acetone (2 mL), DDQ (93 mg, 0.41 mmol, 4.1 equiv.) and toluene (2 mL). Purification by column chromatography yielded the pure product. (70 % yield).



^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 9.4 Hz, 1H), δ 8.07 (d, *J* = 2.8 Hz, 1H), δ 7.56 (dd, *J* = 9.4, 2.9 Hz, 1H), δ 5.94 (q, *J* = 8.2 Hz, 1H), δ 4.03 (s, 3H), δ 3.78 (s, 3H), δ 3.26 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 167.8, 161.1, 148.4, 142.3, 134.2, 131.8, 126.9, 124.6, 123.2, 122.4, 121.8, 101.1, 56.0, 52.9, 52.4-51.6 (q), 24.1
^{19}F NMR (376 MHz, $CDCl_3$): δ -65.08 (d, *J* = 8.2 Hz, 3F).
HRMS (ESI-TOF) m/z calcd. for $C_{17}H_{13}F_3N_2NaO_5$ ($[M+H]^+$) 383.0849, found 383.0851

3.8.8. Control experiments

3.8.8.1. Control experiment (2)

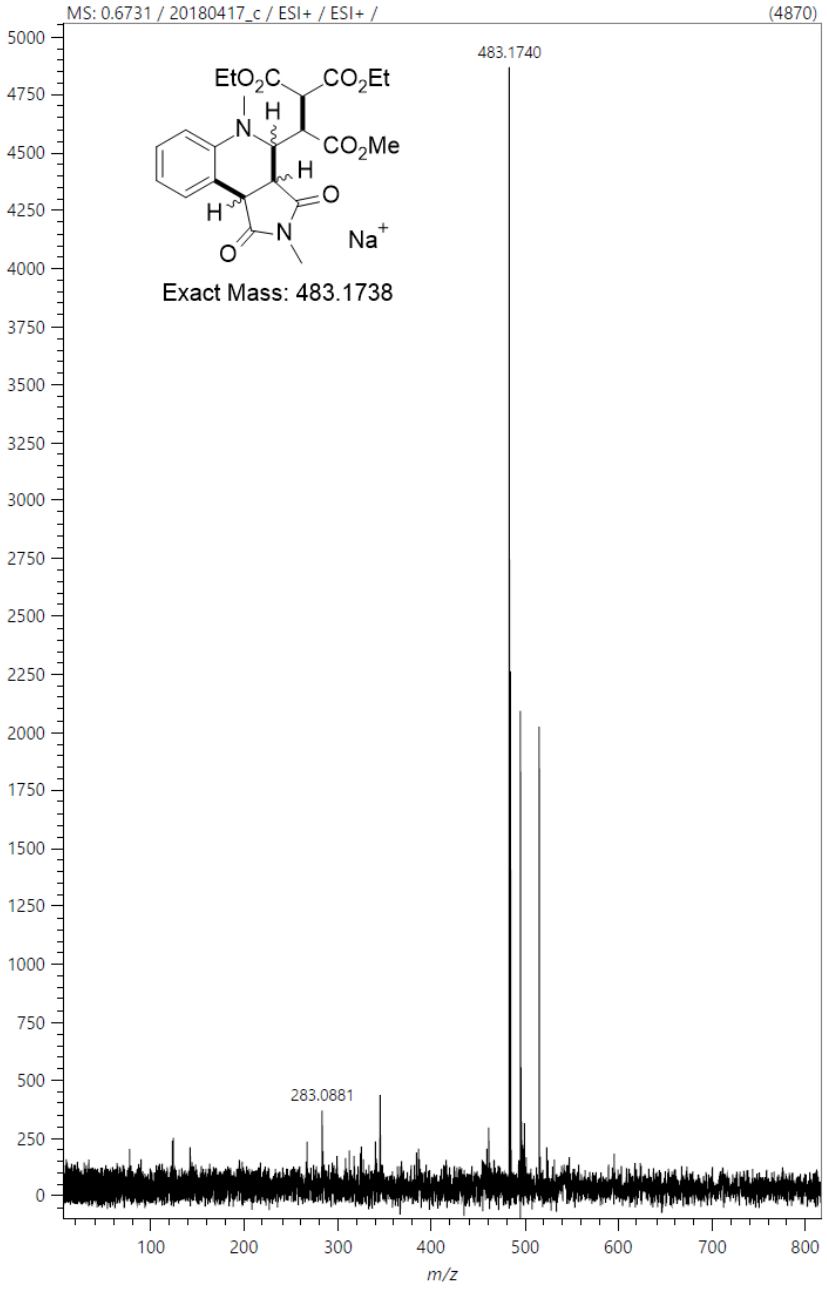
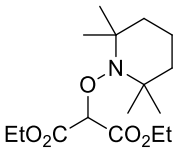


Figure 3-10. HRMS data of **D**

3.8.8.2. Control experiment (3)



^{1}H NMR (400 MHz, $CDCl_3$): δ 4.92 (s, 1H), δ 4.25 (q, J = 7.1 Hz, 4H), δ 1.65 – 1.38 (m, 6H), δ 1.29 (t, *J* = 7.1 Hz, 6H), δ 1.20 (s, 6H), δ 1.08 (s, 6H). NMR data is consistent with the reported data.

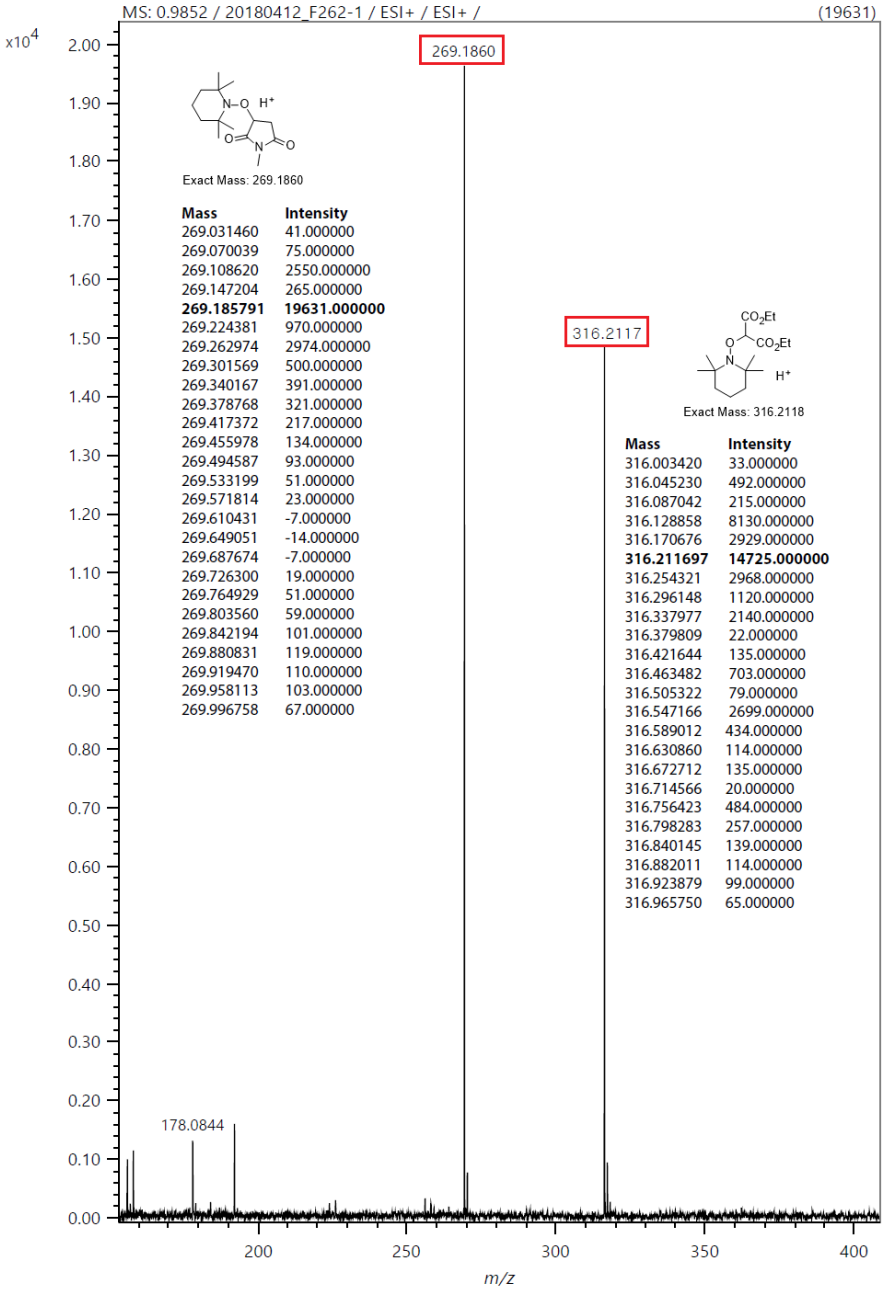
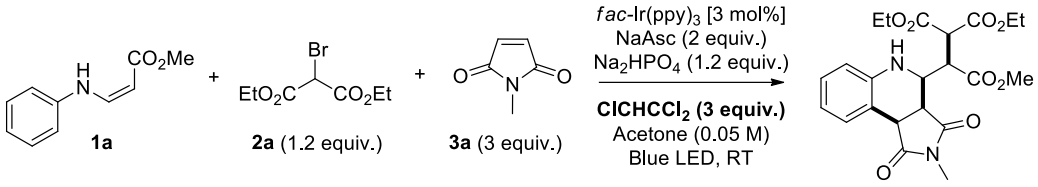


Figure 3-11. HRMS data of **E** and **F**.

3.8.9. Procedure for visible-light on/off experiment



To an oven-dried 4 mL vial equipped with a stir bar was added photocatalyst *fac*-Ir(ppy)$_3$ (2.0 mg, 3 μmol, 0.03 equiv.), sodium ascorbate (39.6 mg, 0.2 mmol, 2 equiv.), anhydrous sodium phosphate dibasic (powder) (17 mg, 0.12 mmol, 1.2 equiv.), methyl 3-(phenyl amino) acrylate **1a** (17.7 mg, 0.1 mmol, 1 equiv.) and *N*-methyl maleimide **3a** (33.3 mg, 0.3 mmol, 3 equiv.). Required amounts of anhydrous acetone (2 mL) and diethyl bromomalonate **2a** (90 % purity, 22.7 μL, 0.12 mmol, 1.2 equiv.) were added under argon atmosphere in glovebox. *Trichloroethylene (27 uL, 0.3 mmol, 3 equiv.) was added as internal standard.* The reaction mixture was irradiated with a 12 W blue LED lamp (5 cm away, 25 ℃ maintained with a cooling fan). Yields were determined by ^{1}H NMR spectroscopy with trichloroethylene as an internal standard at every 4 hours.

3.8.10. Cyclic voltammetry data

3.8.10.1. 4-methoxy-*N*,*N*-diphenylaniline

($E_{1/2}^{ox}$ = + 0.78 V vs SCE in MeCN at 25°C)

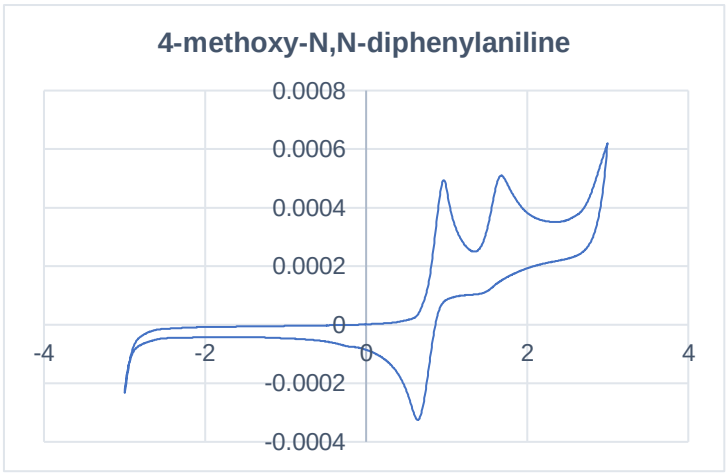
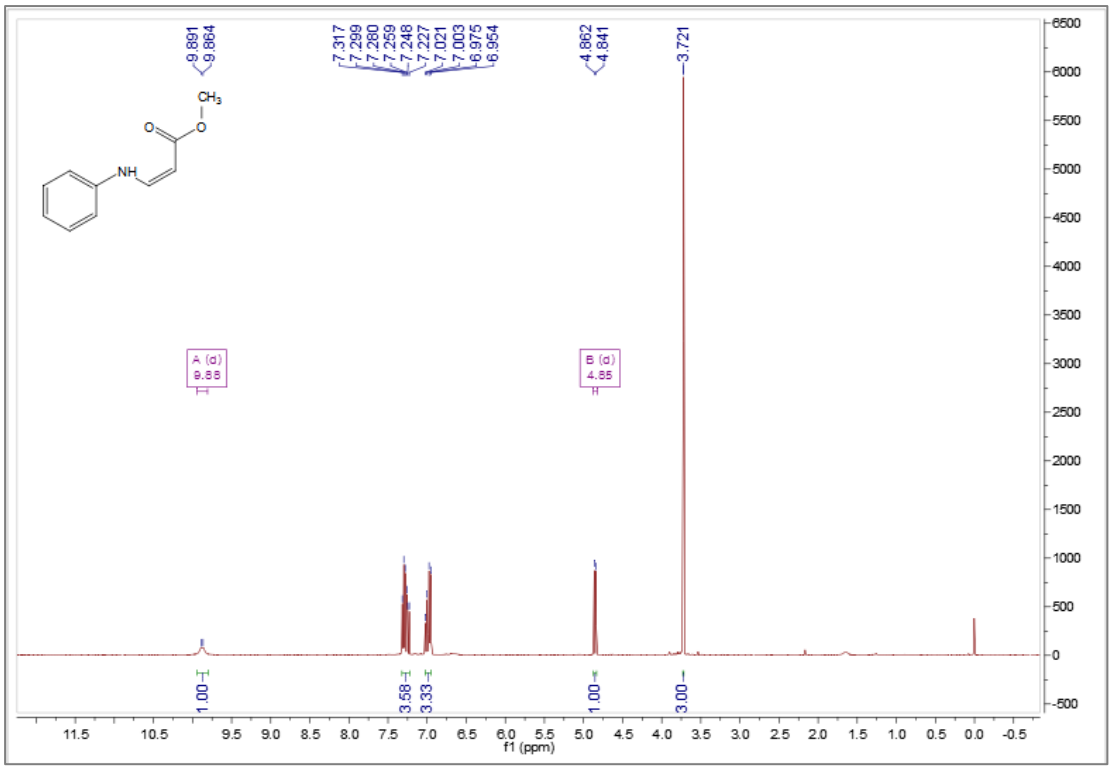


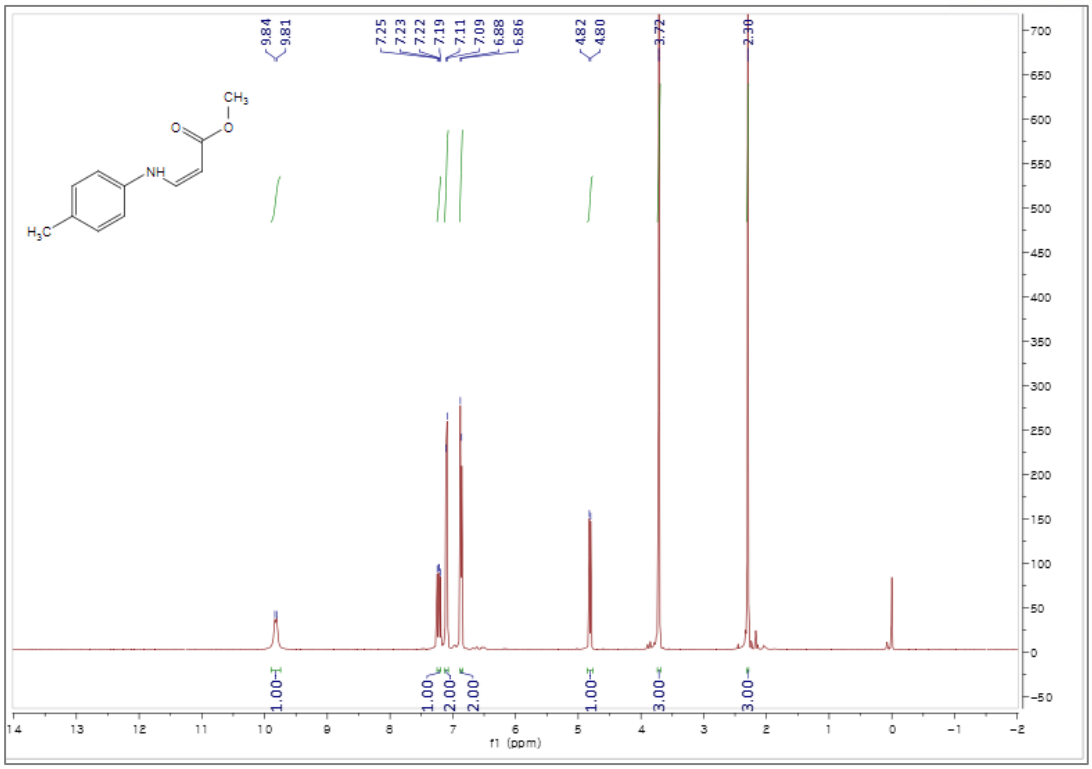
Figure 3-11. Measurement of oxidation potential of 4-methoxy-N,N-diphenylaniline

3.8.11. NMR spectra

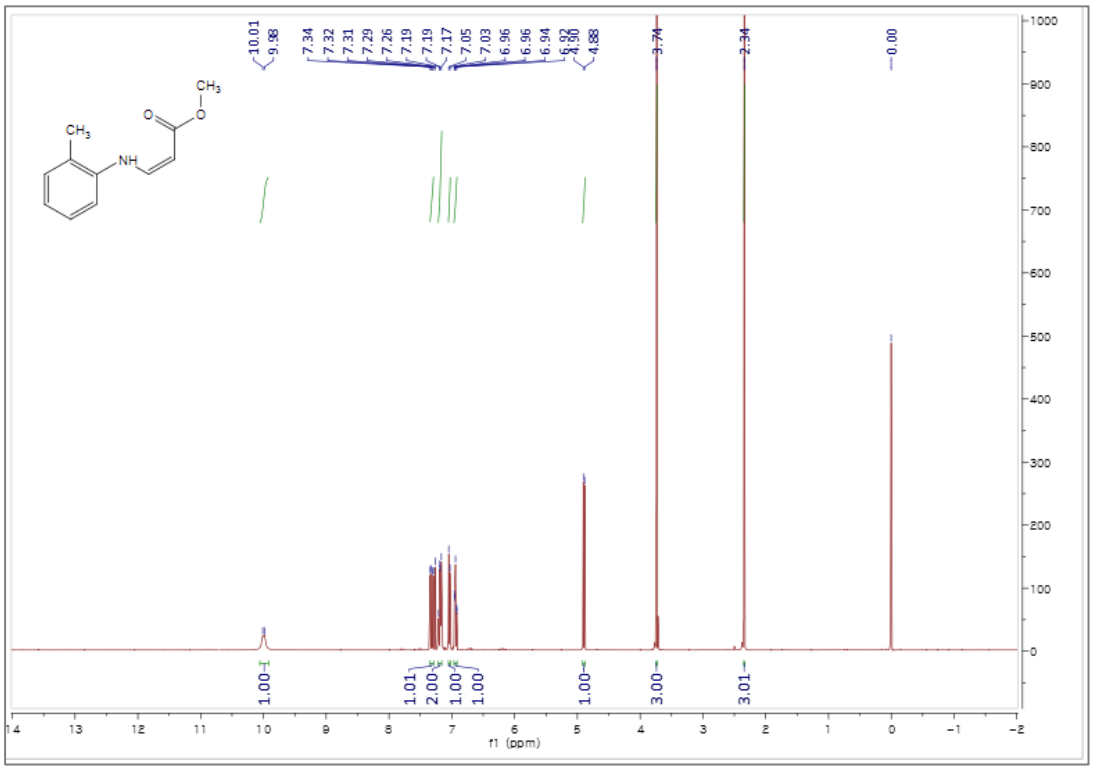
methyl 3-(phenylamino)acrylate (**1a**)



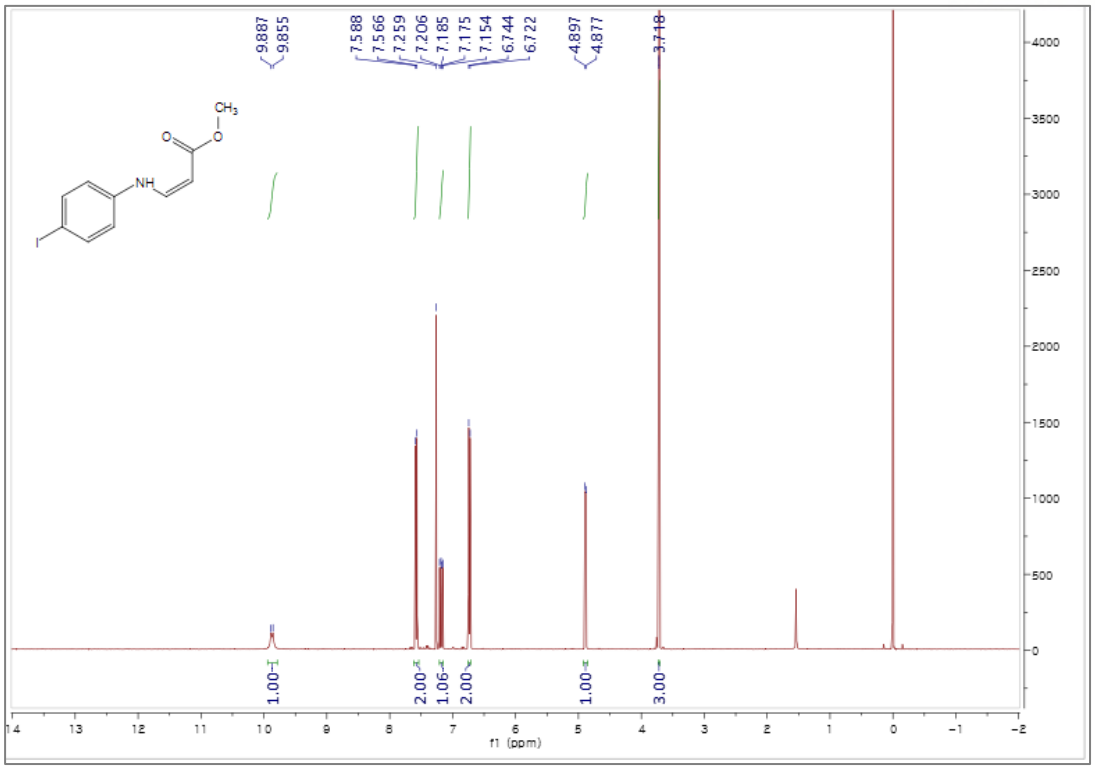
methyl 3-(*p*-tolyl amino) acrylate (**1b**)



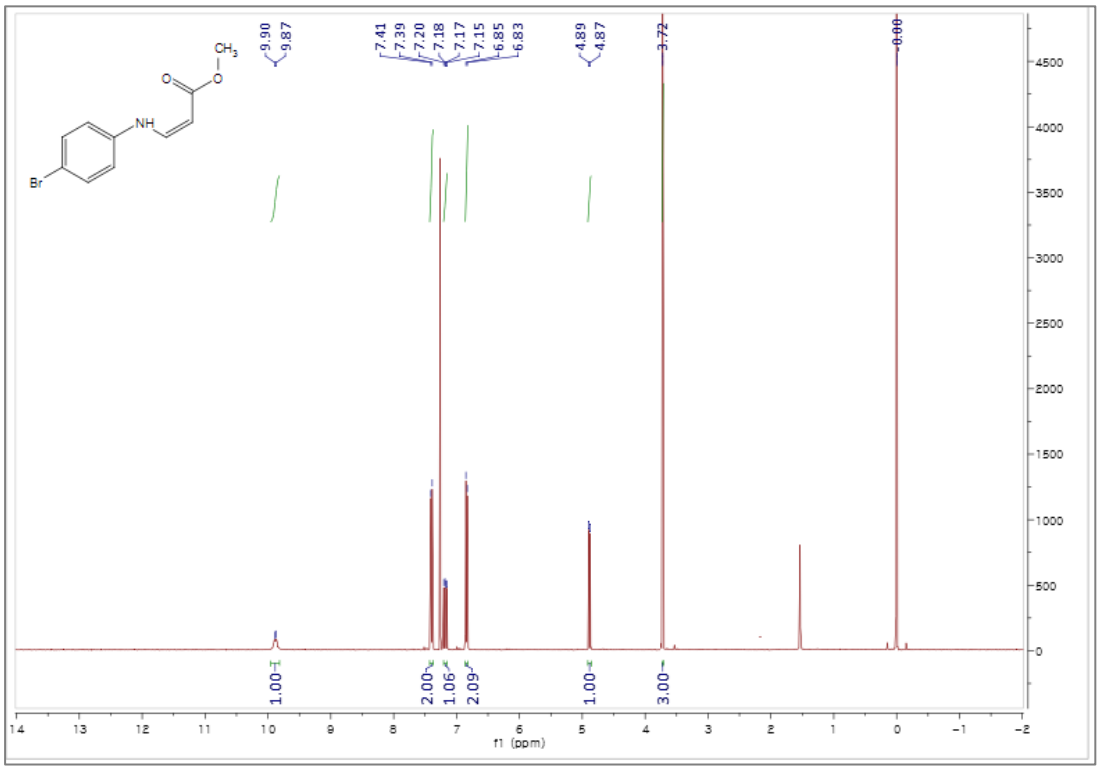
methyl 3-(*o*-tolyl amino) acrylate (**1c**)



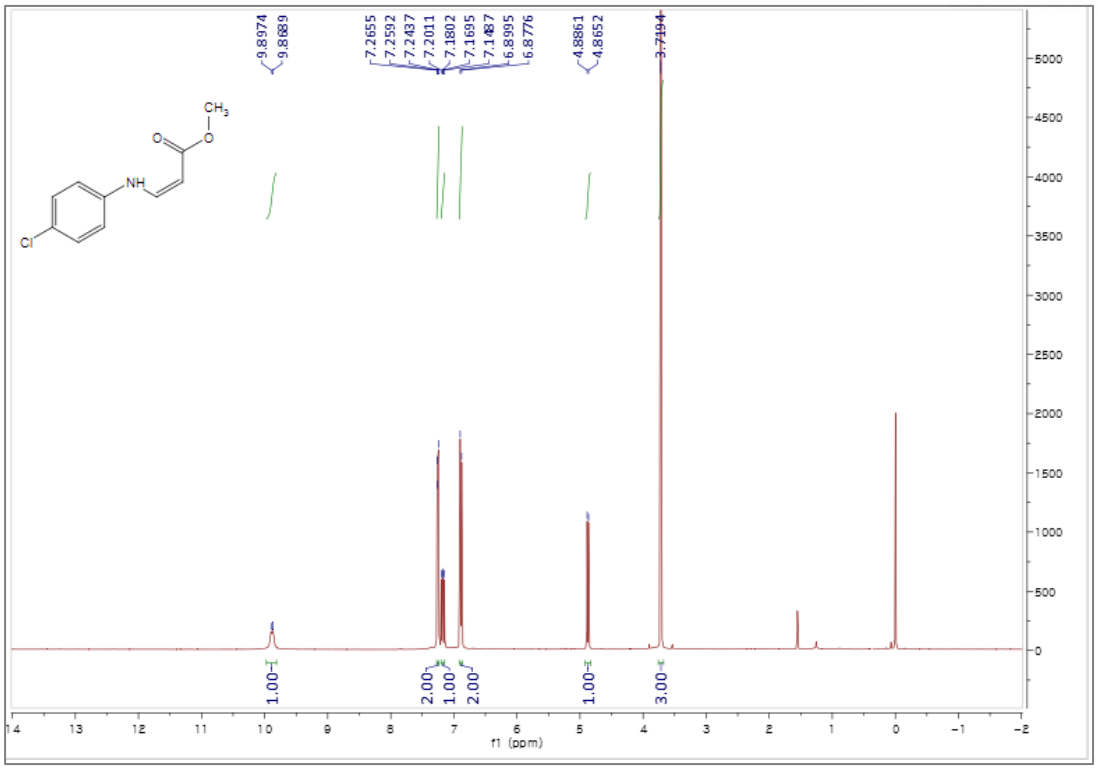
methyl 3-((4-iodophenyl) amino) acrylate (**1d**)



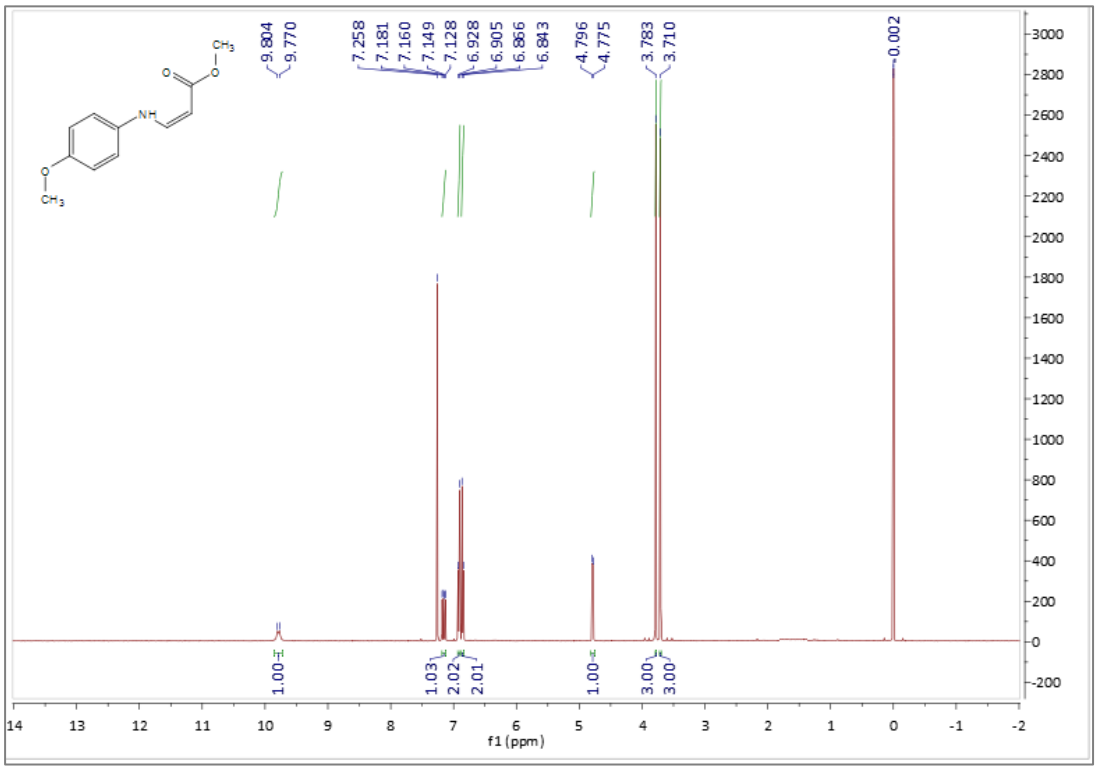
methyl 3-((4-bromophenyl) amino) acrylate (**1e**)



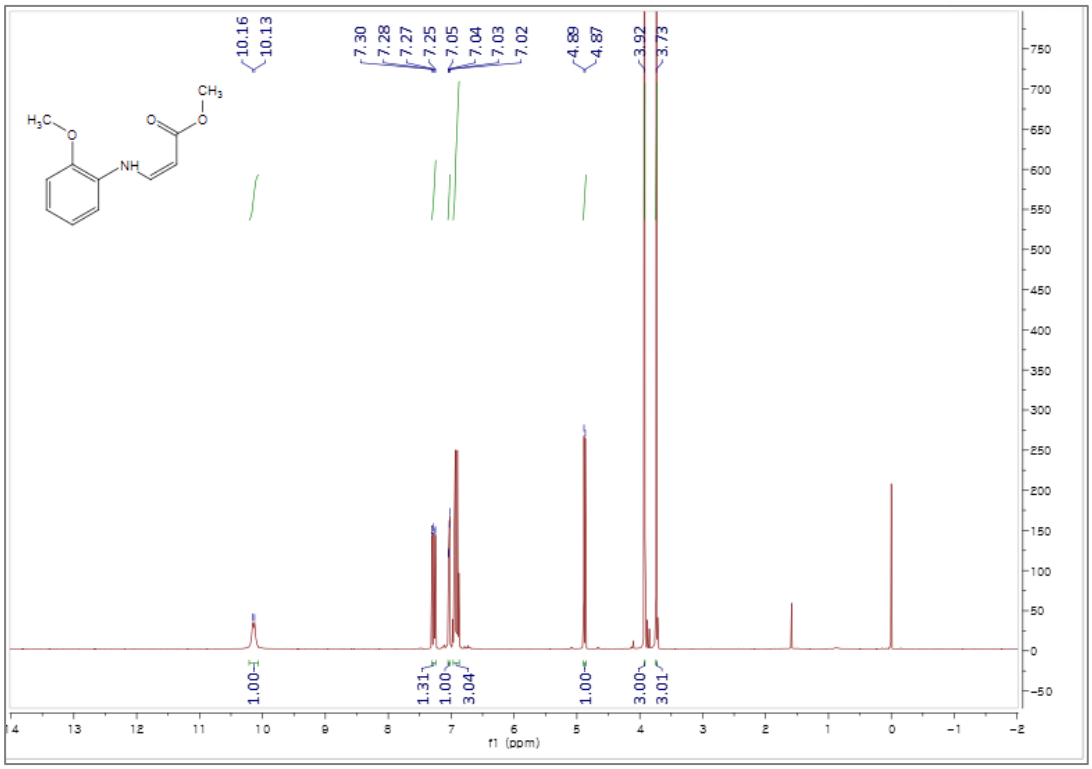
methyl 3-((4-chlorophenyl) amino) acrylate (**1f**)



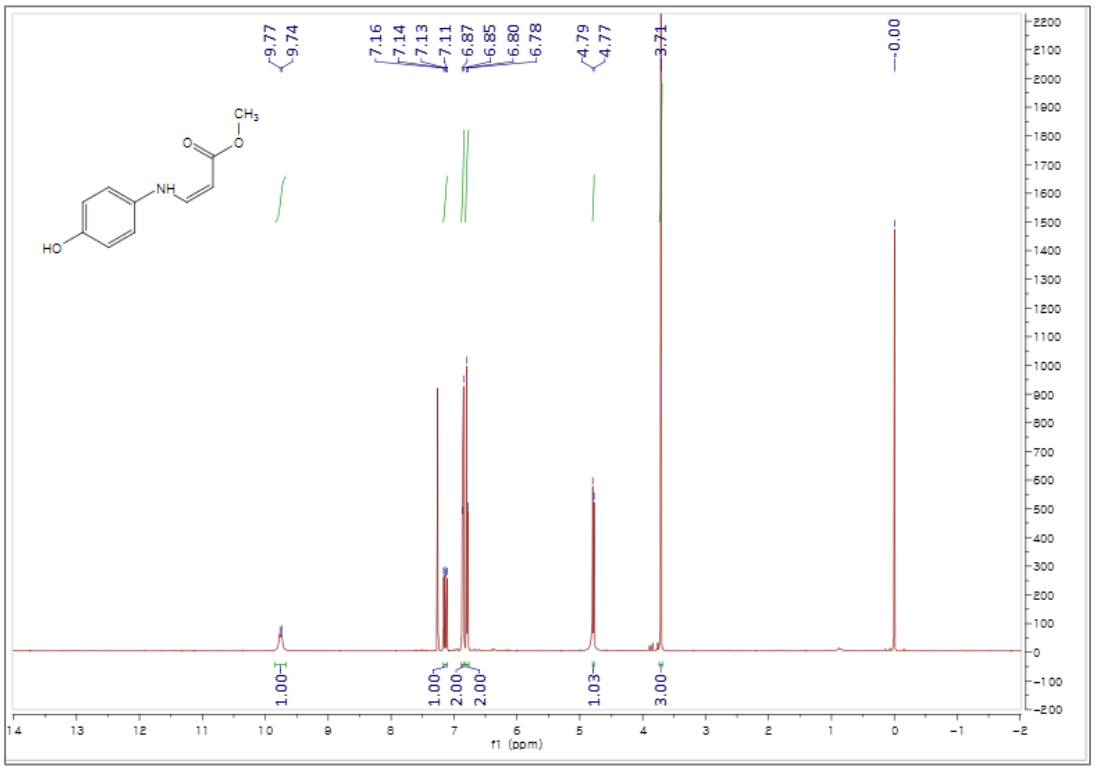
methyl 3-((4-methoxyphenyl) amino) acrylate (**1g**)



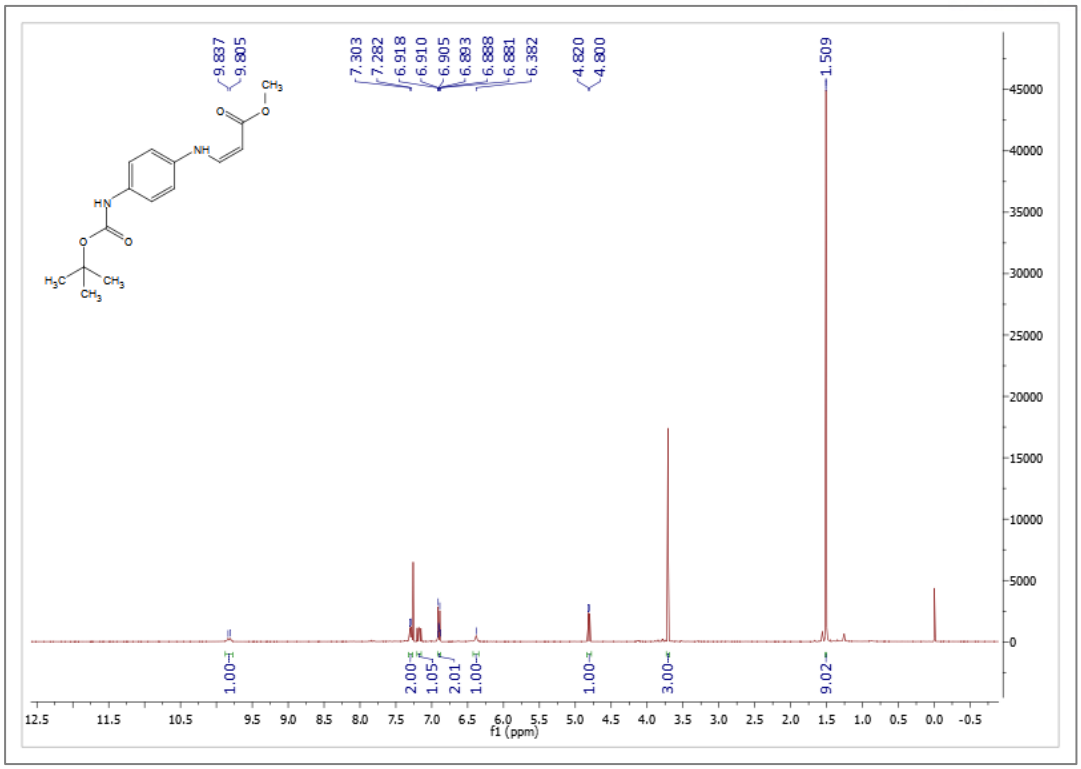
methyl 3-((2-methoxyphenyl) amino) acrylate (**1h**)



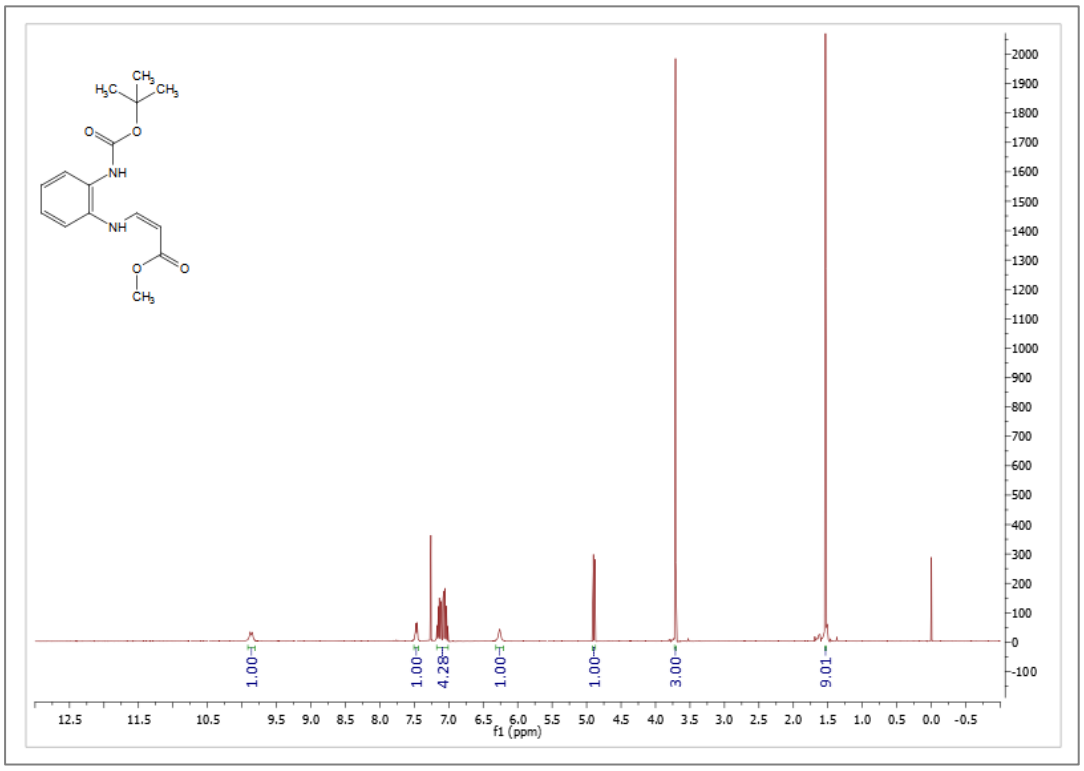
methyl 3-((4-hydroxyphenyl) amino) acrylate (**1i**)



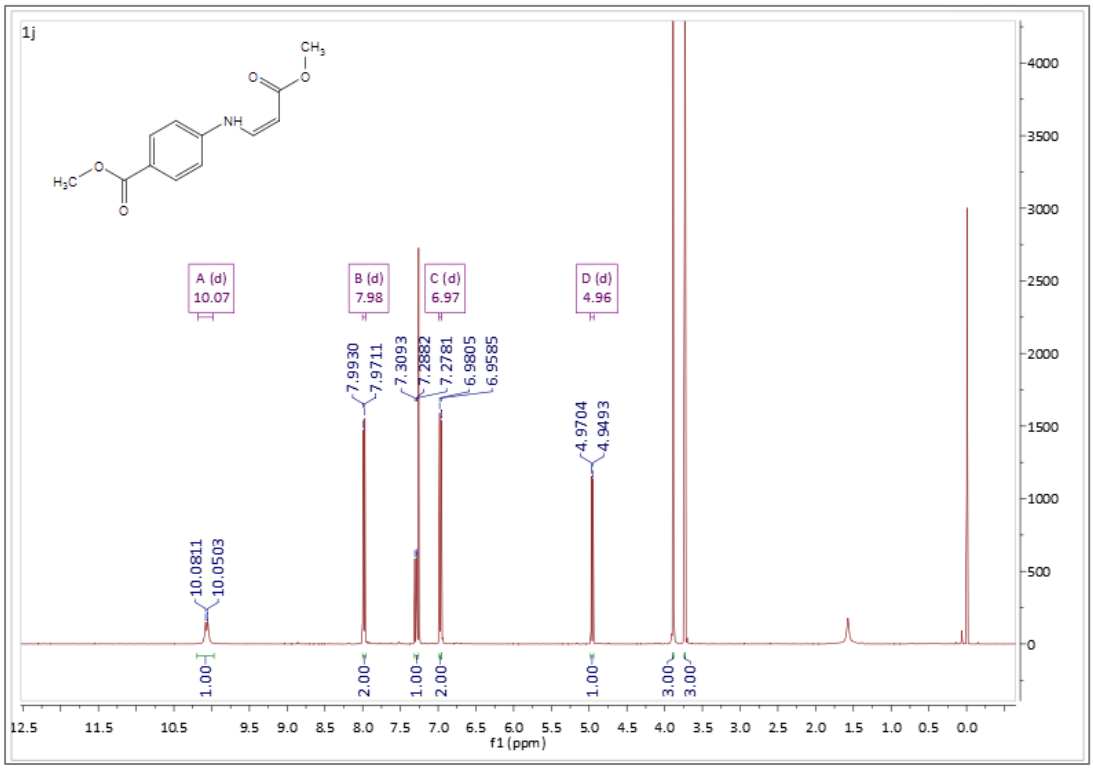
methyl 3-((4-((tert-butoxycarbonyl)amino)phenyl)amino)acrylate (**1j**)



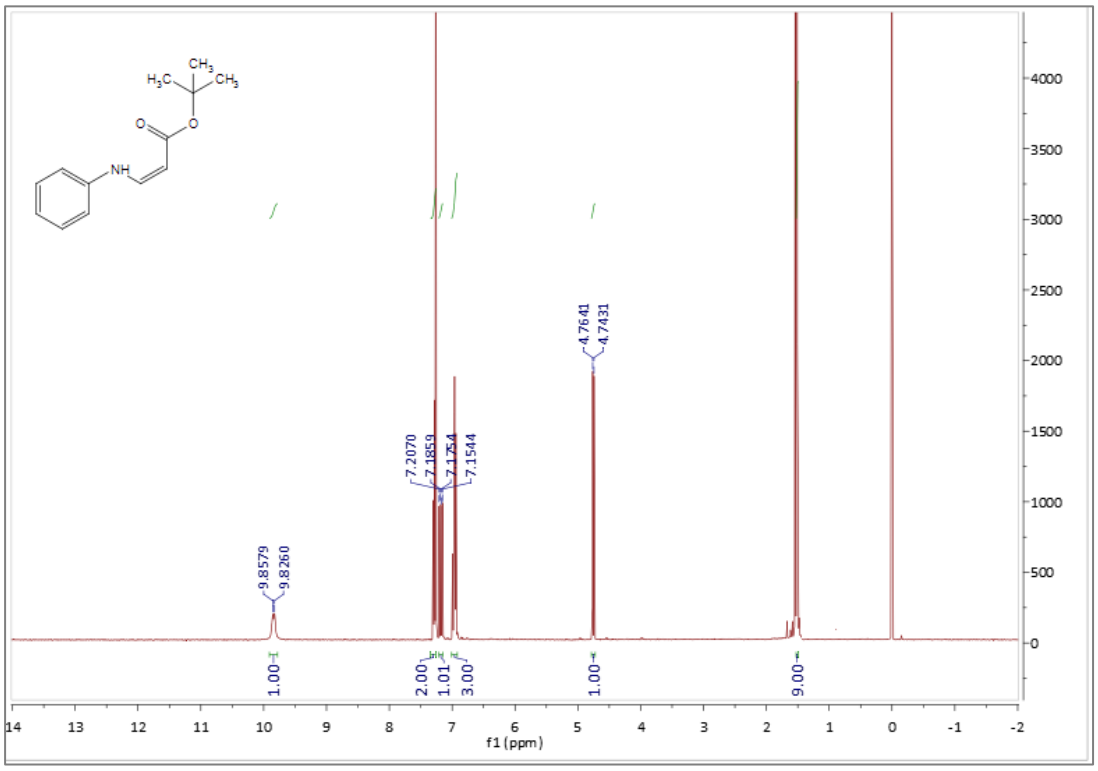
methyl 3-((2-((tert-butoxycarbonyl)amino)phenyl)amino)acrylate (**1k**)



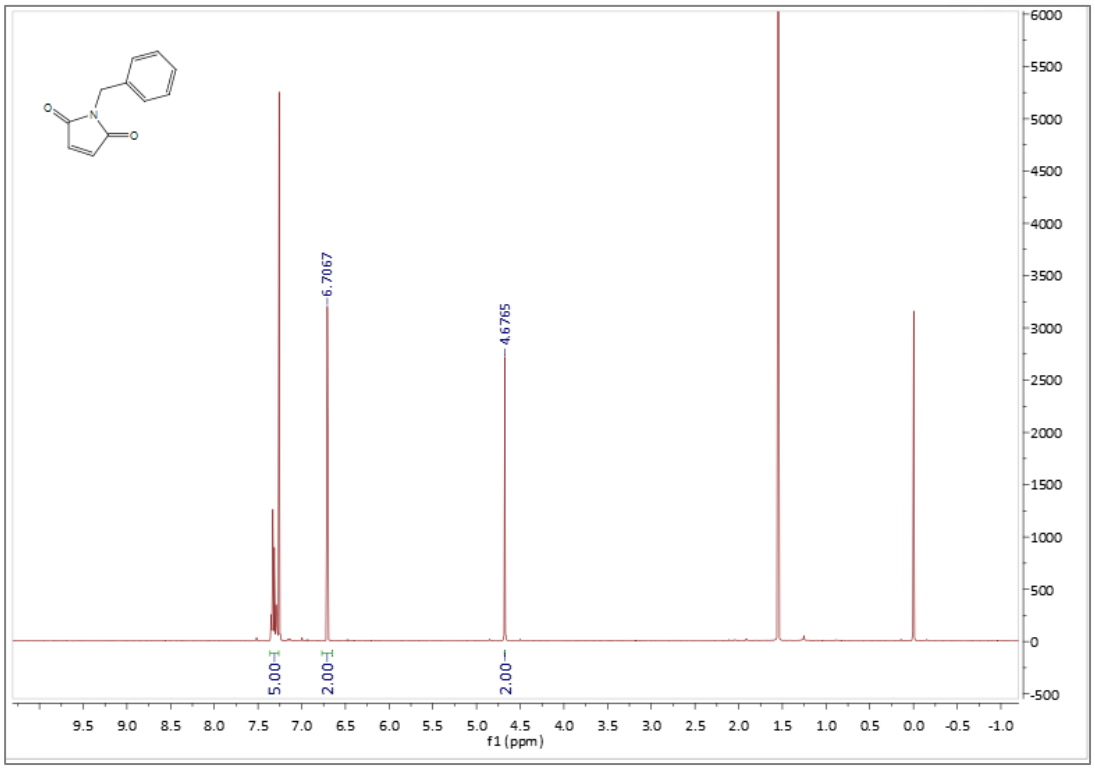
methyl 4-((3-methoxy-3-oxoprop-1-en-1-yl) amino) benzoate (**1l**)



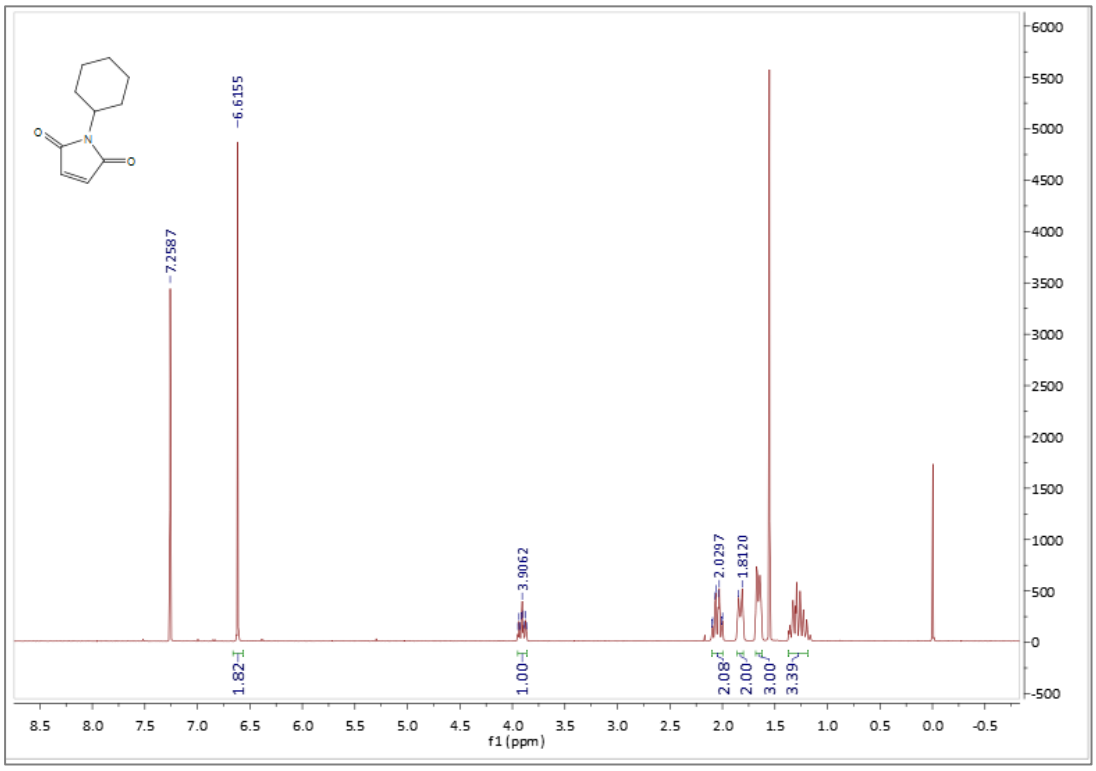
tert-butyl 3-(phenyl amino) acrylate (**1m**)



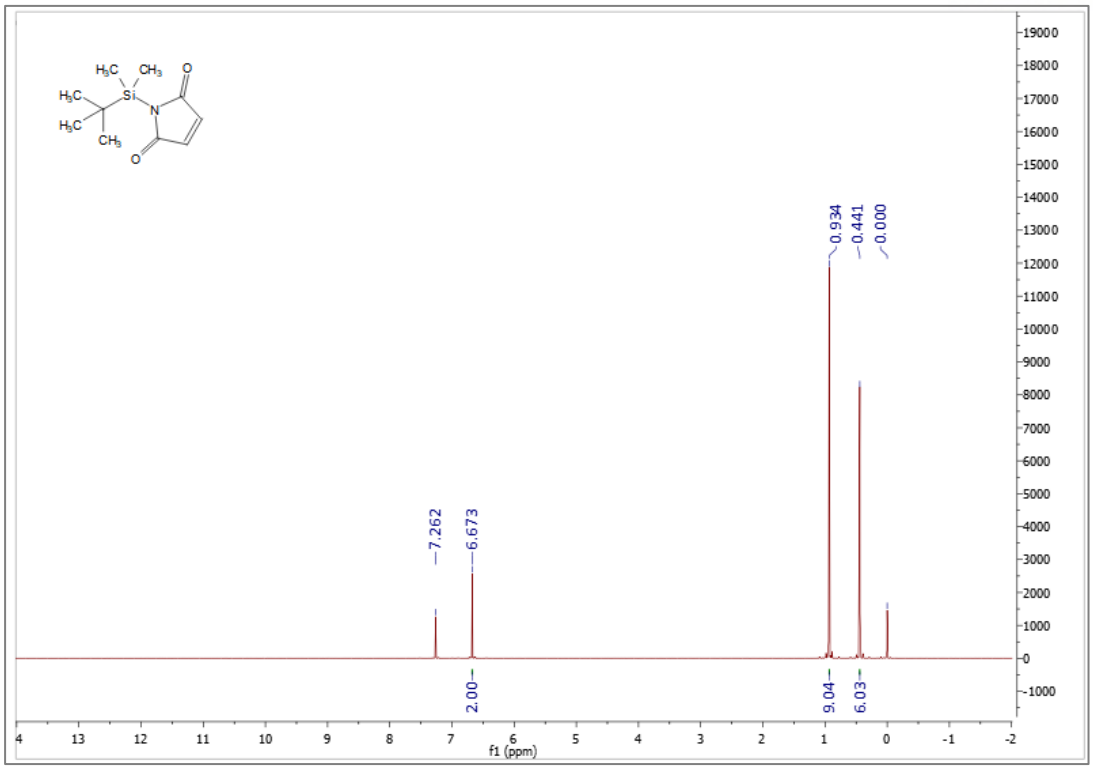
1-benzyl-1H-pyrrole-2,5-dione (**3n**)



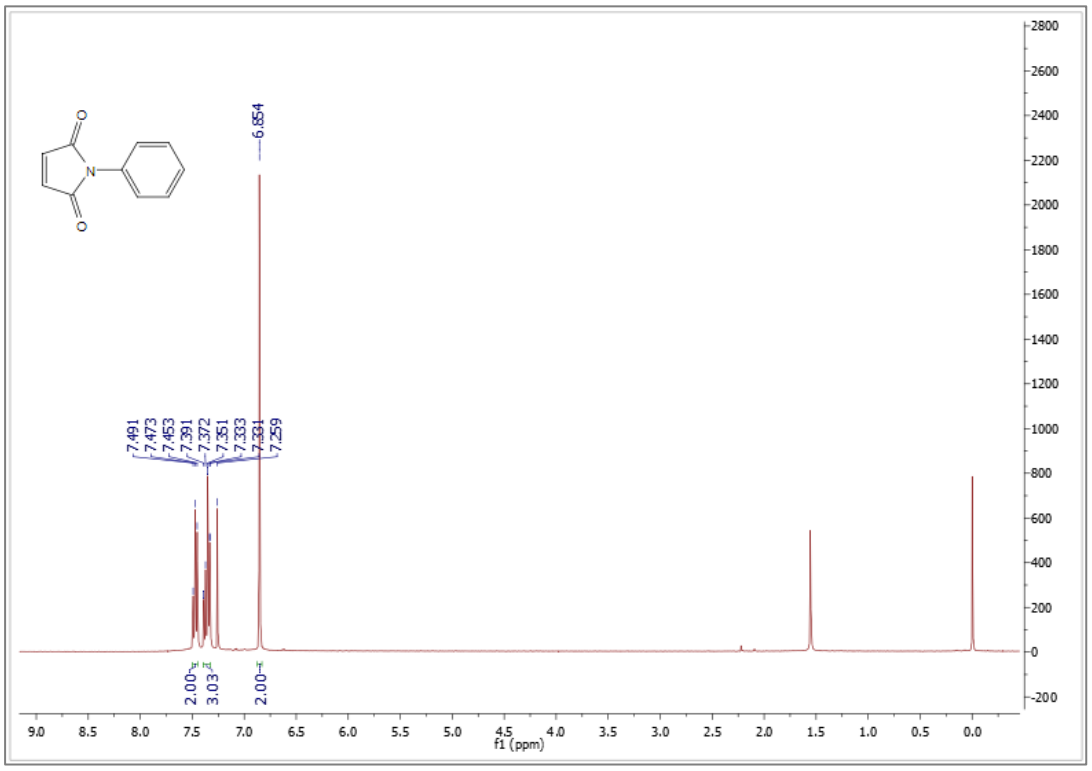
1-cyclohexyl-1H-pyrrole-2,5-dione (**3o**)



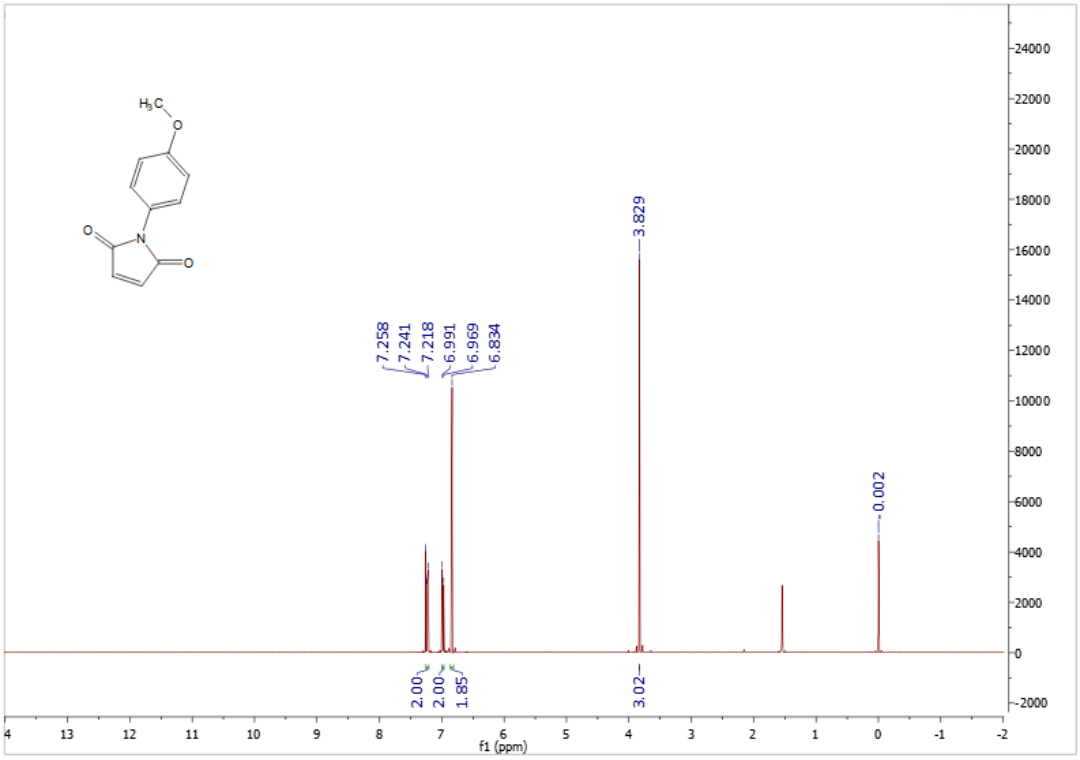
1-(tert-butyldimethylsilyl)-1H-pyrrole-2,5-dione (**3q**)



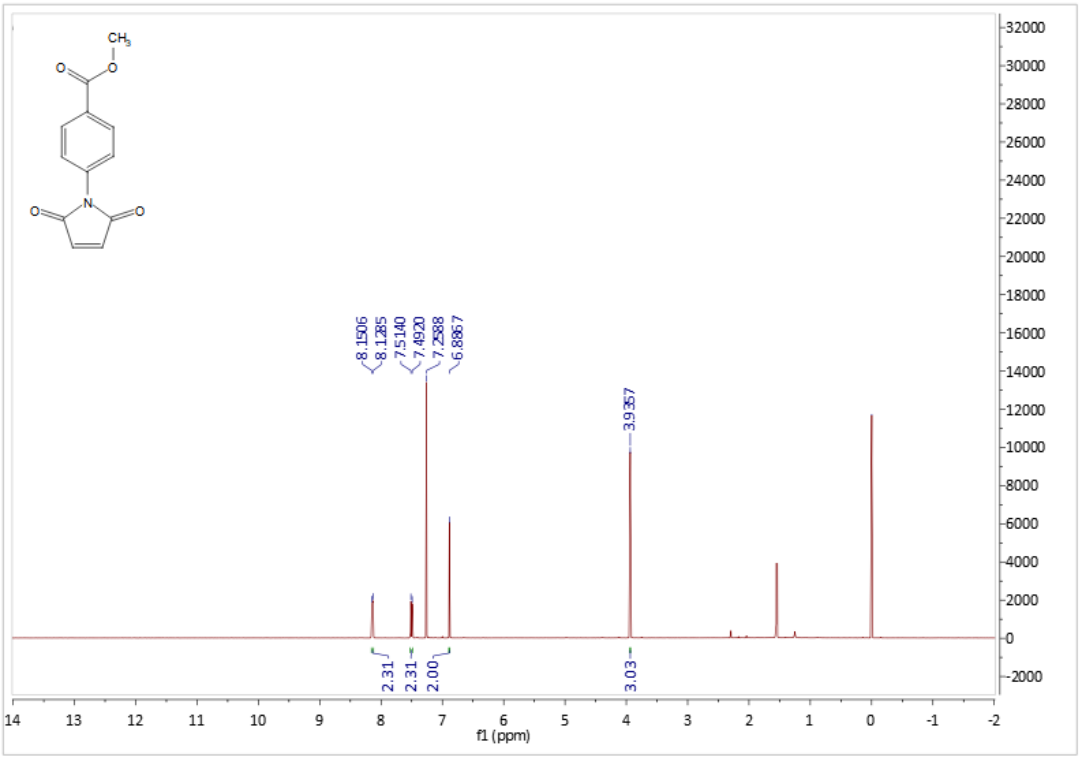
1-phenyl-1H-pyrrole-2,5-dione (**3r**)



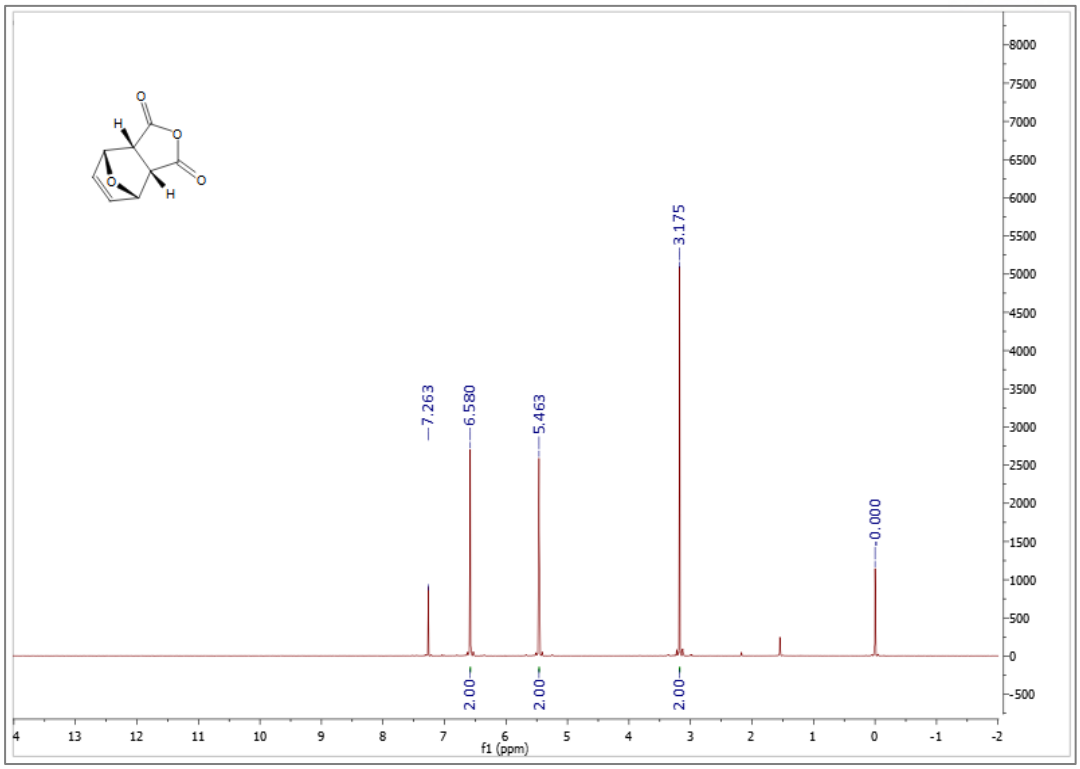
1-(4-methoxyphenyl)-1H-pyrrole-2,5-dione (**3s**)



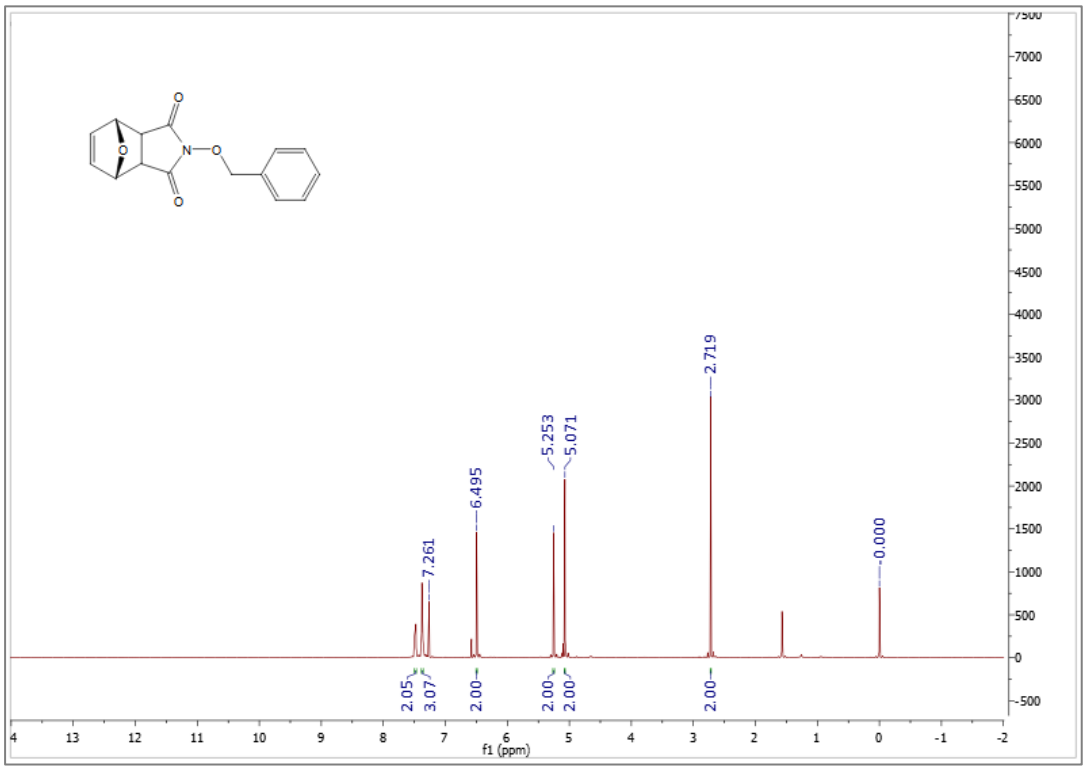
methyl 4-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)benzoate (**3t**)



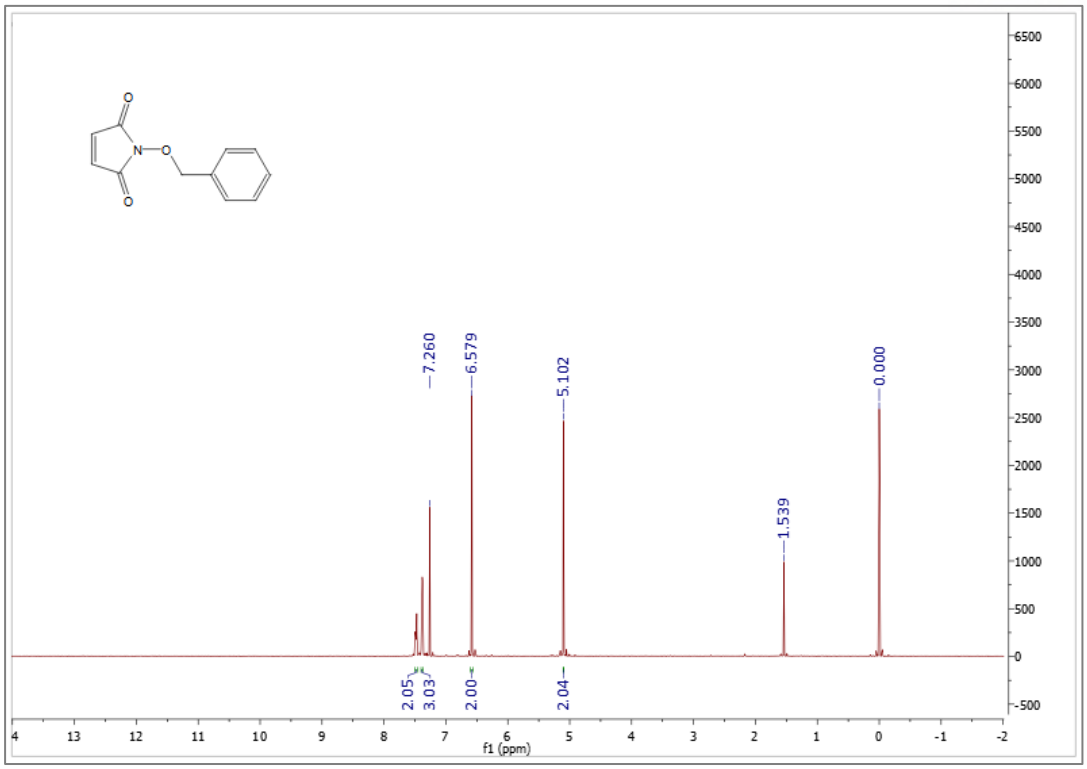
(3aR,4R,7S,7aS)-3a,4,7,7a-tetrahydro-4,7-epoxyisobenzofuran-1,3-dione



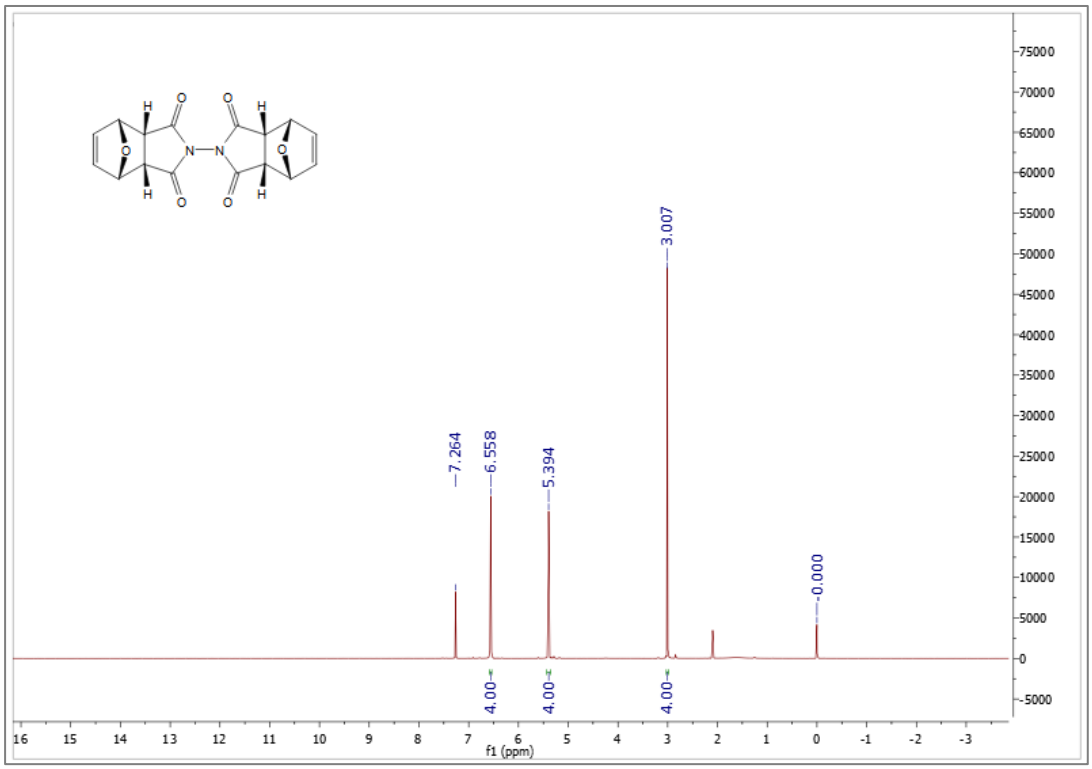
(3aR,4R,7S,7aS)-2-(benzyloxy)-3a,4,7,7a-tetrahydro-1H-4,7-epoxyisoindole-1,3(2H)-dione



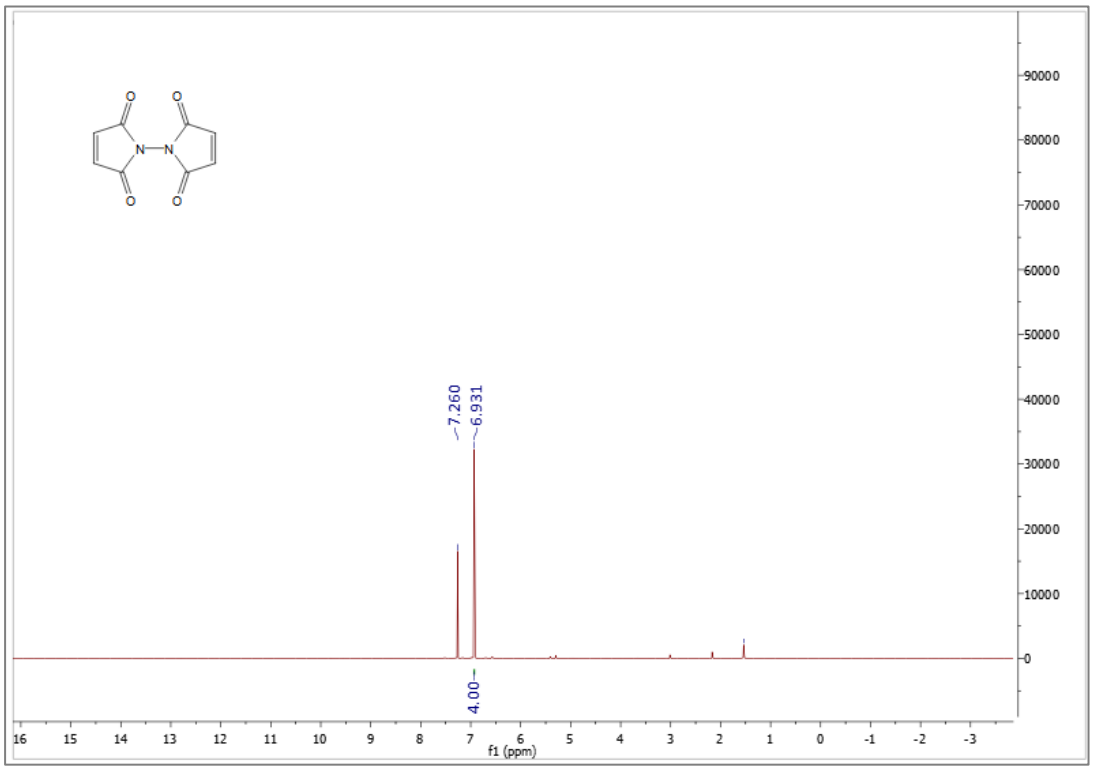
1-(benzyloxy)-1H-pyrrole-2,5-dione (**3u**)



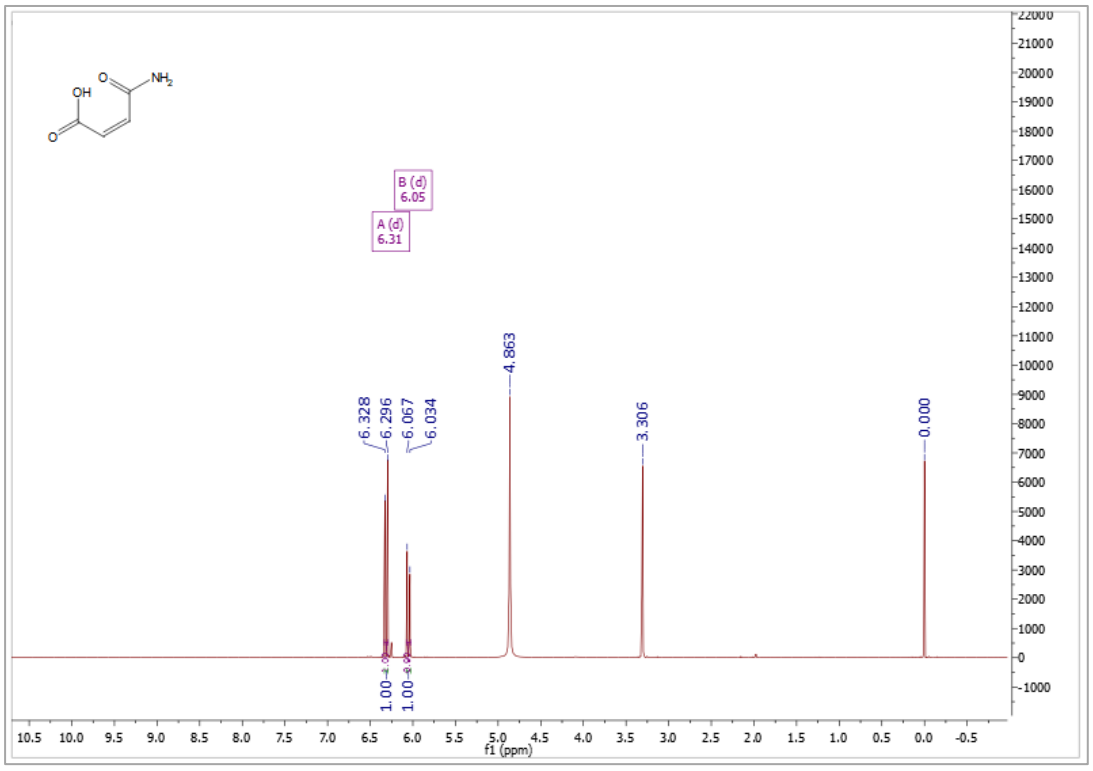
(4R,4'R,5R,5'R,8S,8'S,9S,9'S)-4,5,8,8',9,9'-hexahydro-[2,2'-bi(4,7-epoxyisoindole)]-1,1',3,3'(4'H,5'H)-tetraone



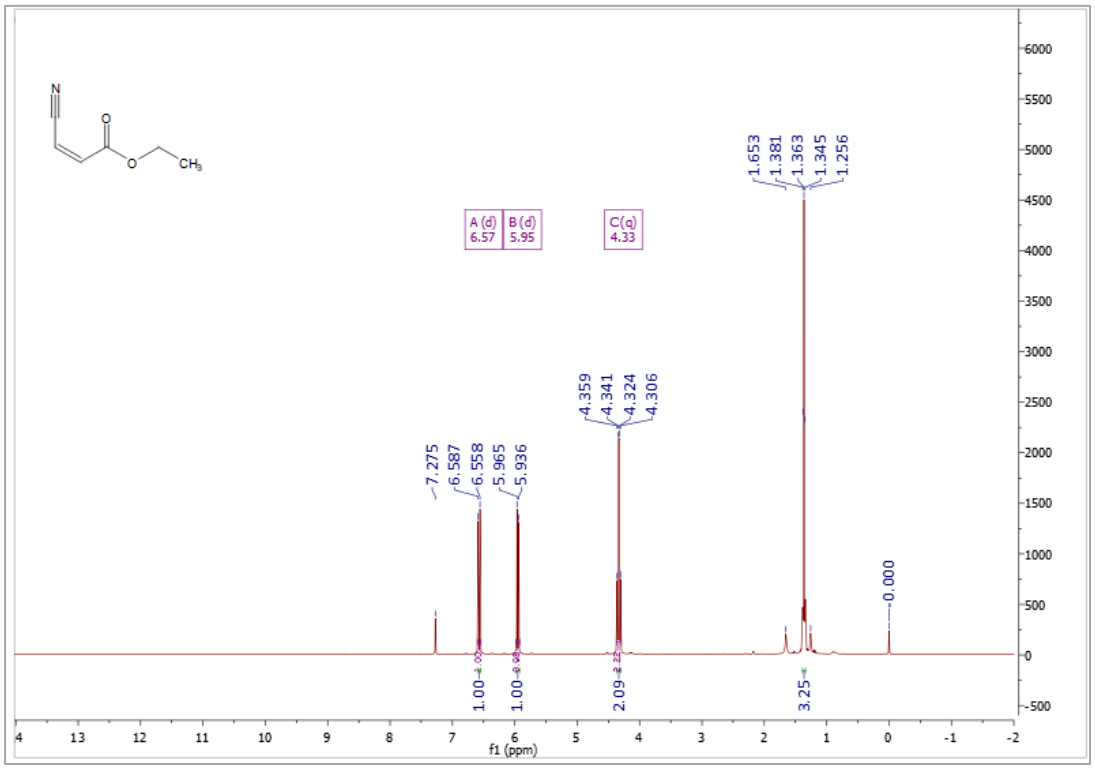
[1,1'-bipyrrole]-2,2',5,5'-tetraone (**3v**)



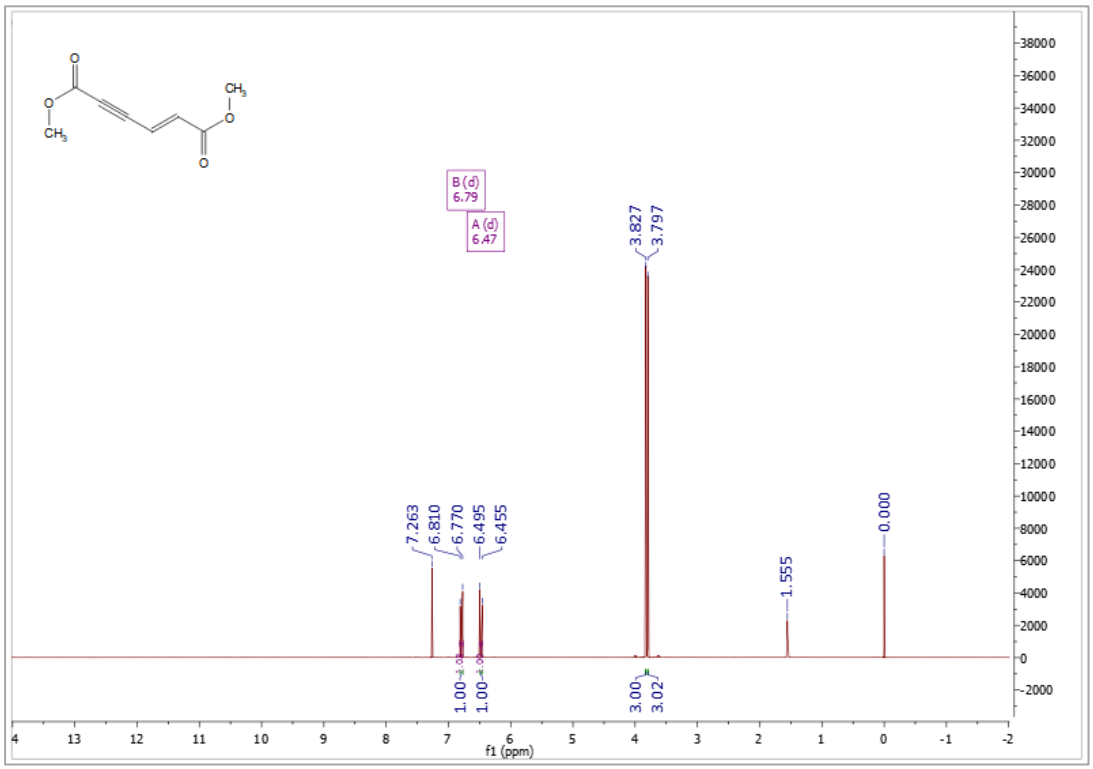
(Z)-4-amino-4-oxobut-2-enoic acid



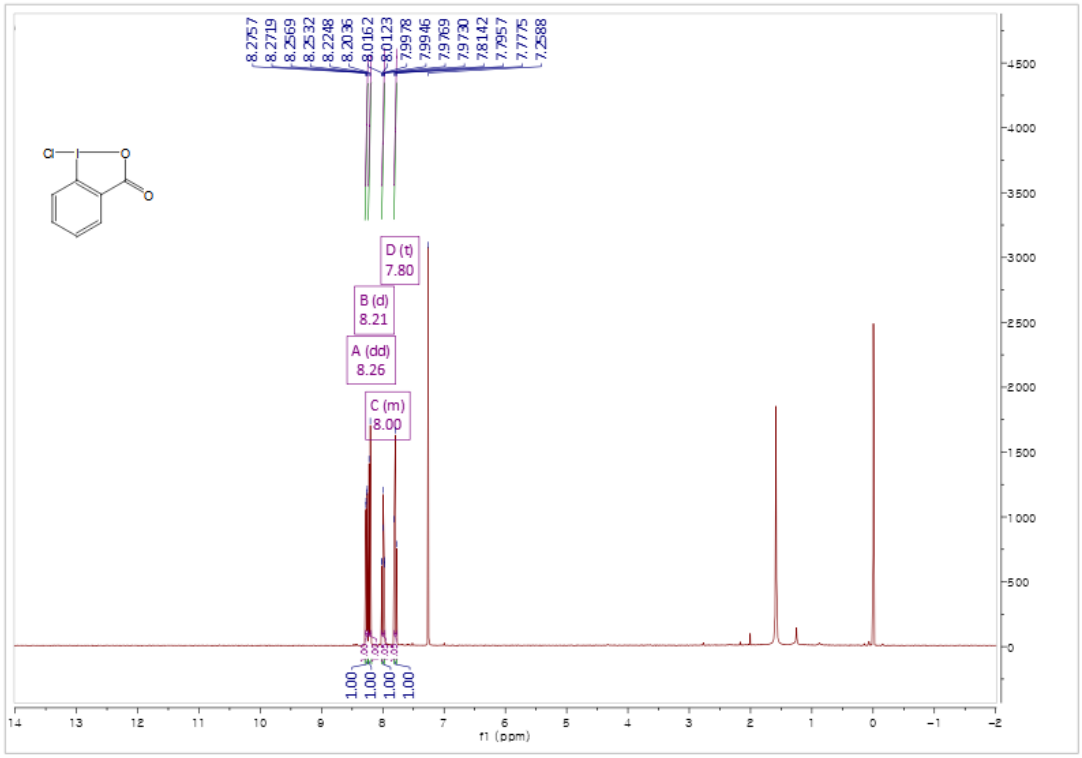
(Z)-ethyl 3-cyanoacrylate (**3x**)



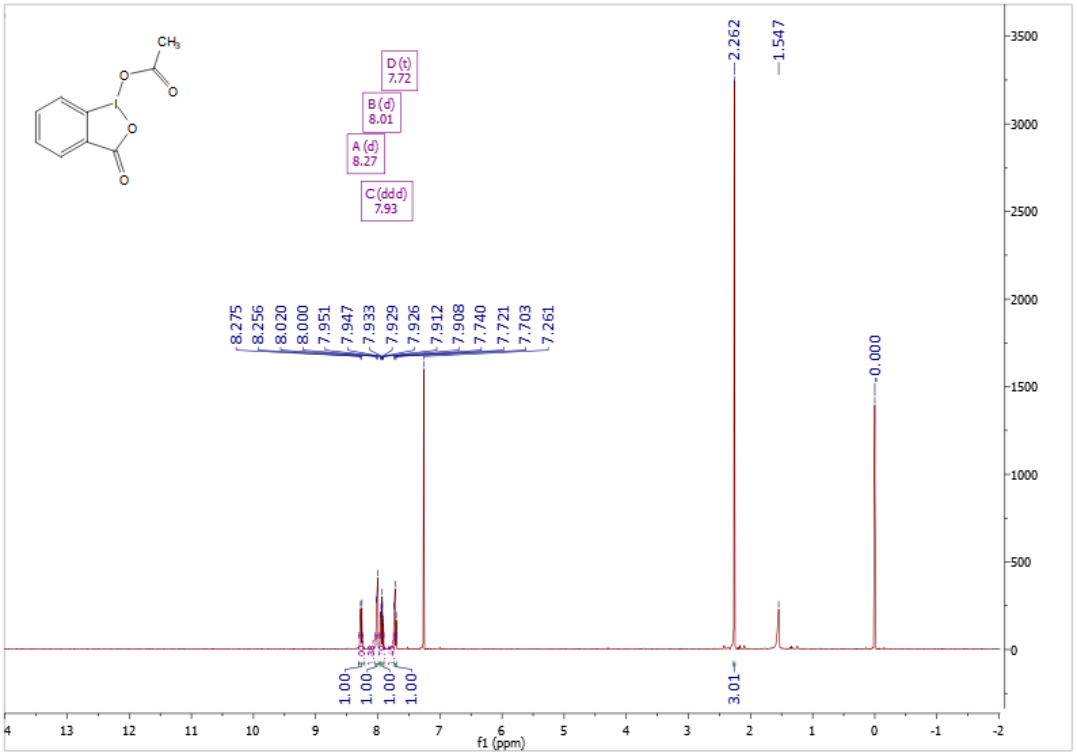
(E)-dimethyl hex-2-en-4-ynedioate (**3z**)



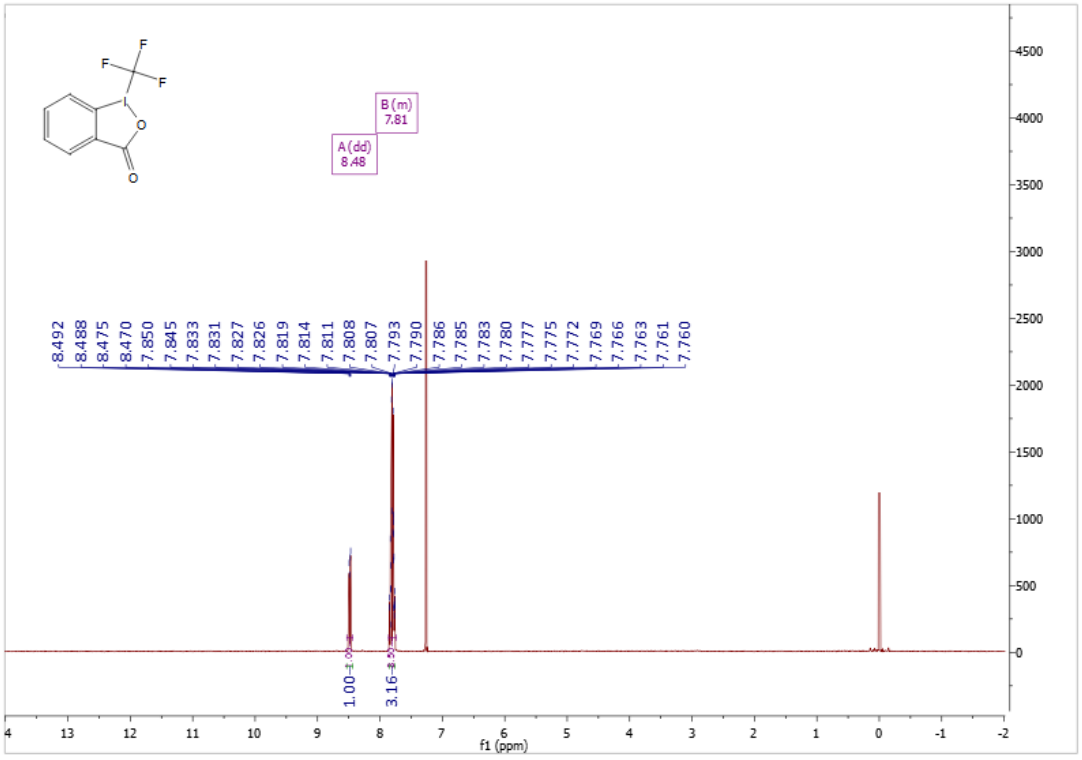
1-chloro-1λ^3 -benzo[d][1,2]iodaoxol-3(1H)-one



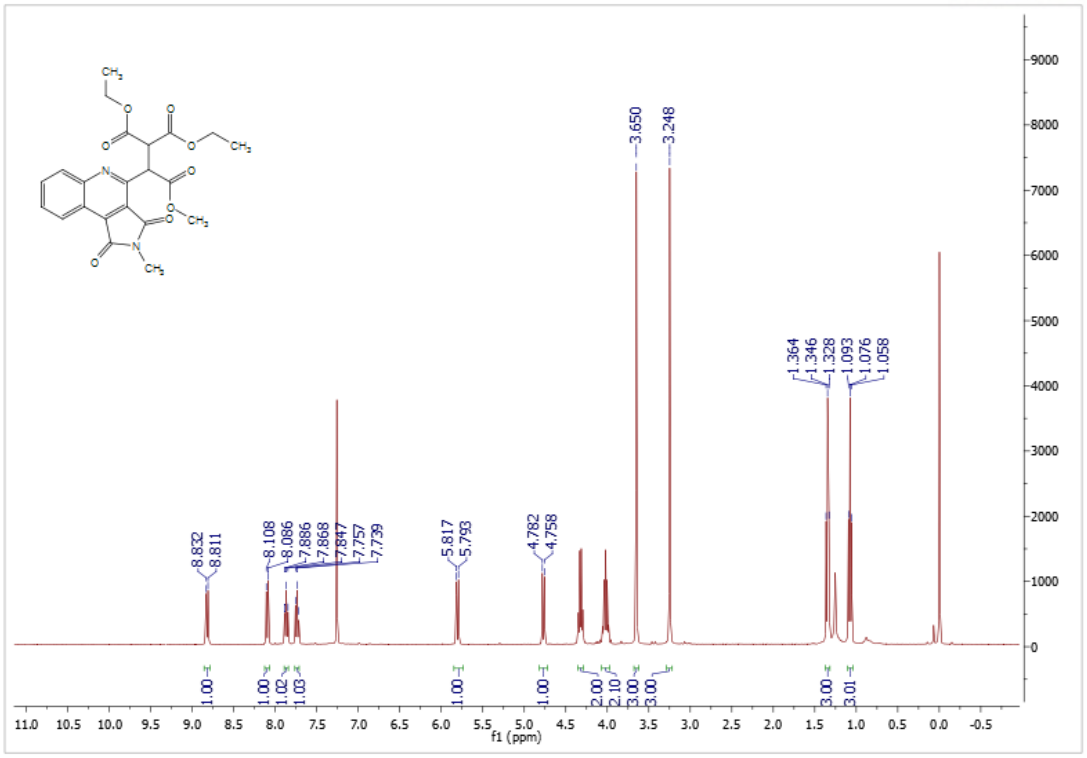
1-acetoxy-1,2-benziodoxol-3-one

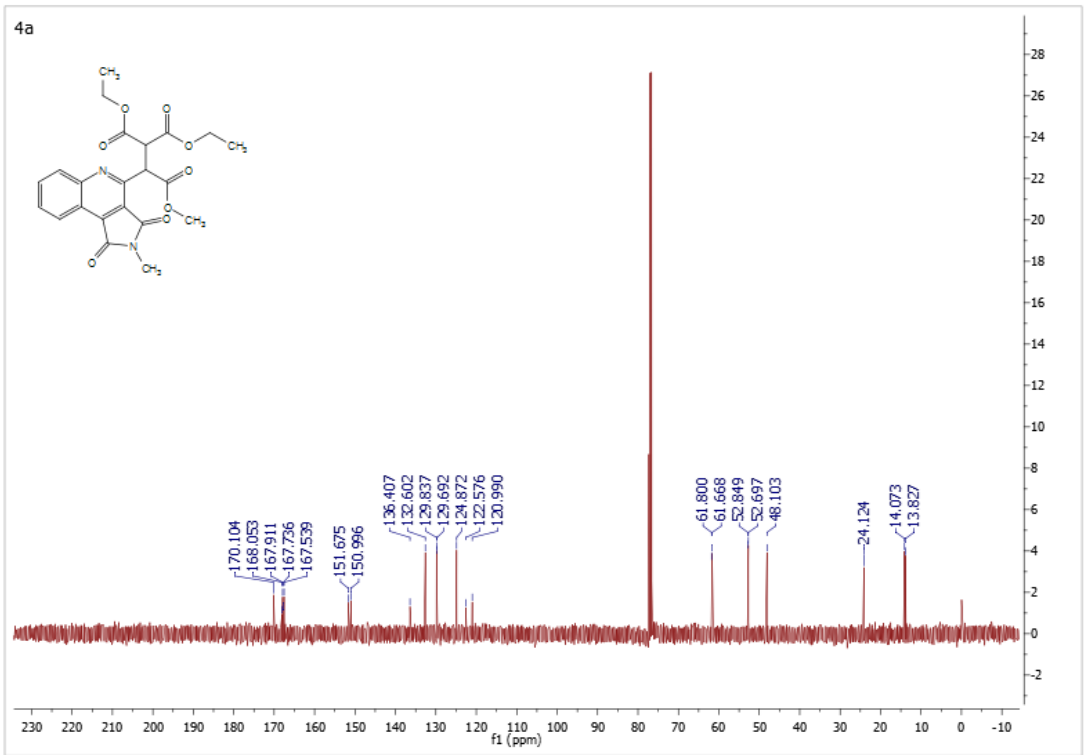


Togni's reagent II (**2ab**)

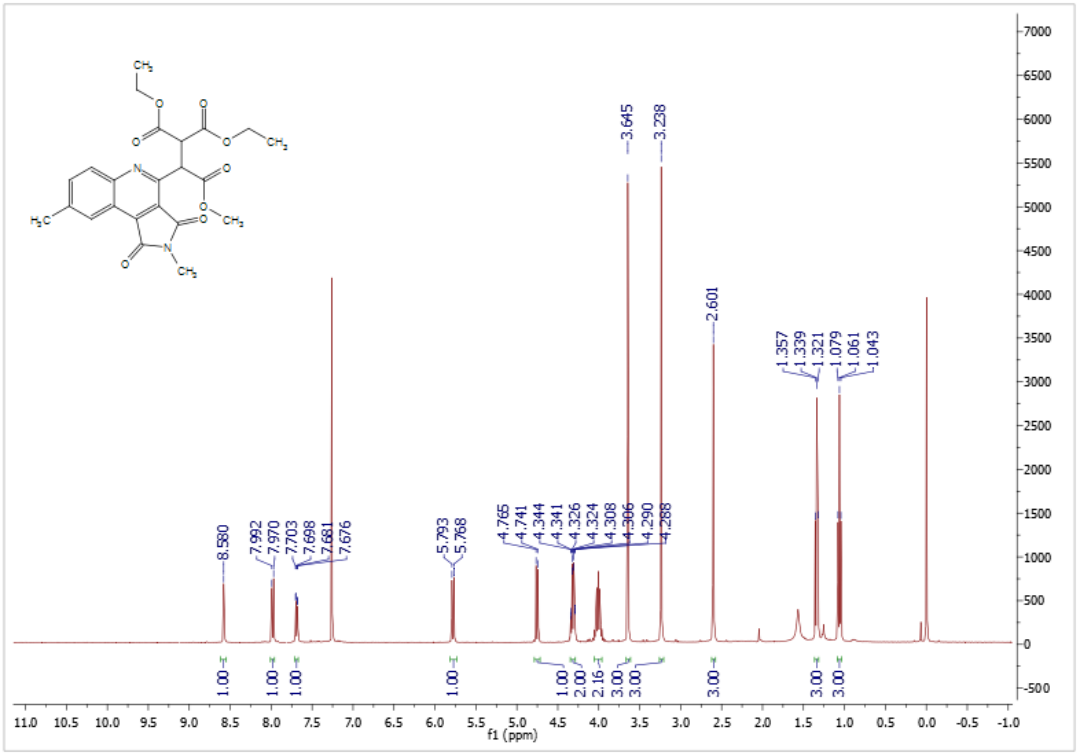


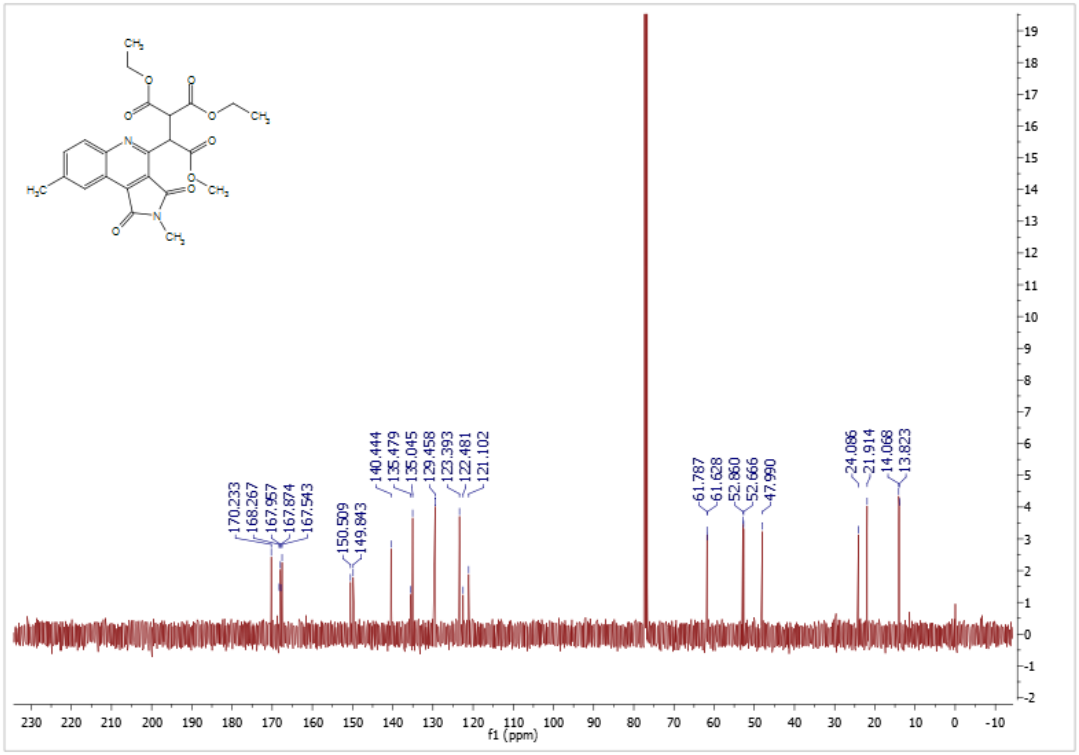
1,1-diethyl 2-methyl 2-(2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4a**)



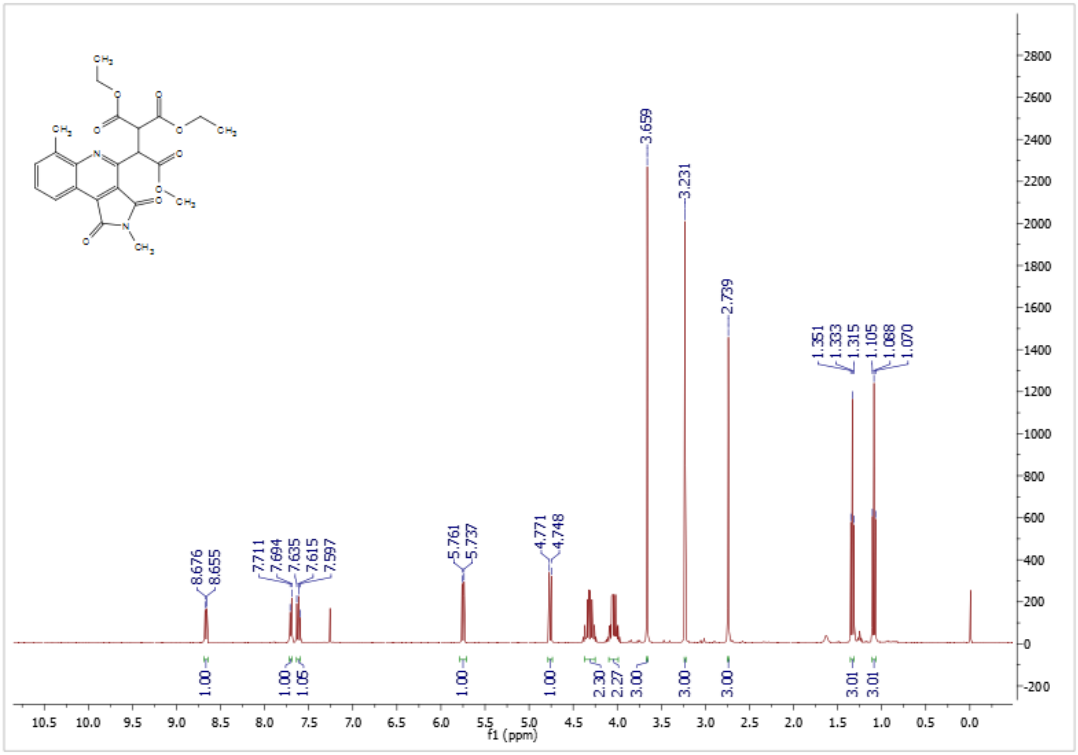


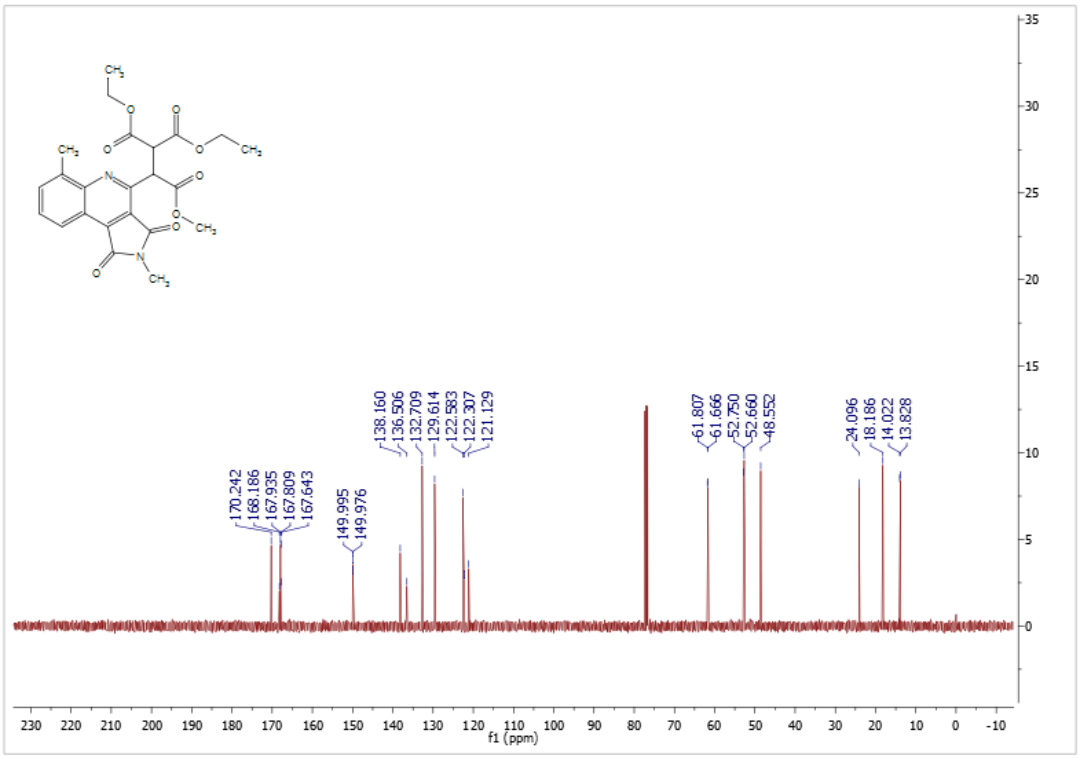
1,1-diethyl 2-methyl 2-(2,6-dimethyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4b**)



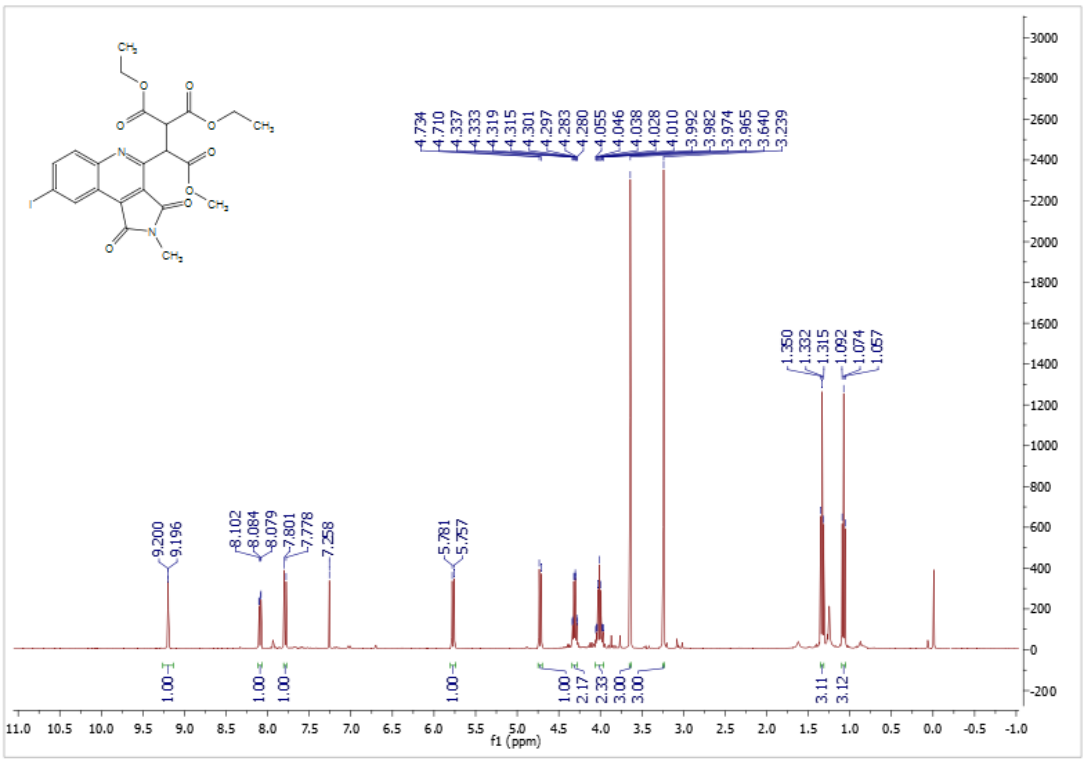


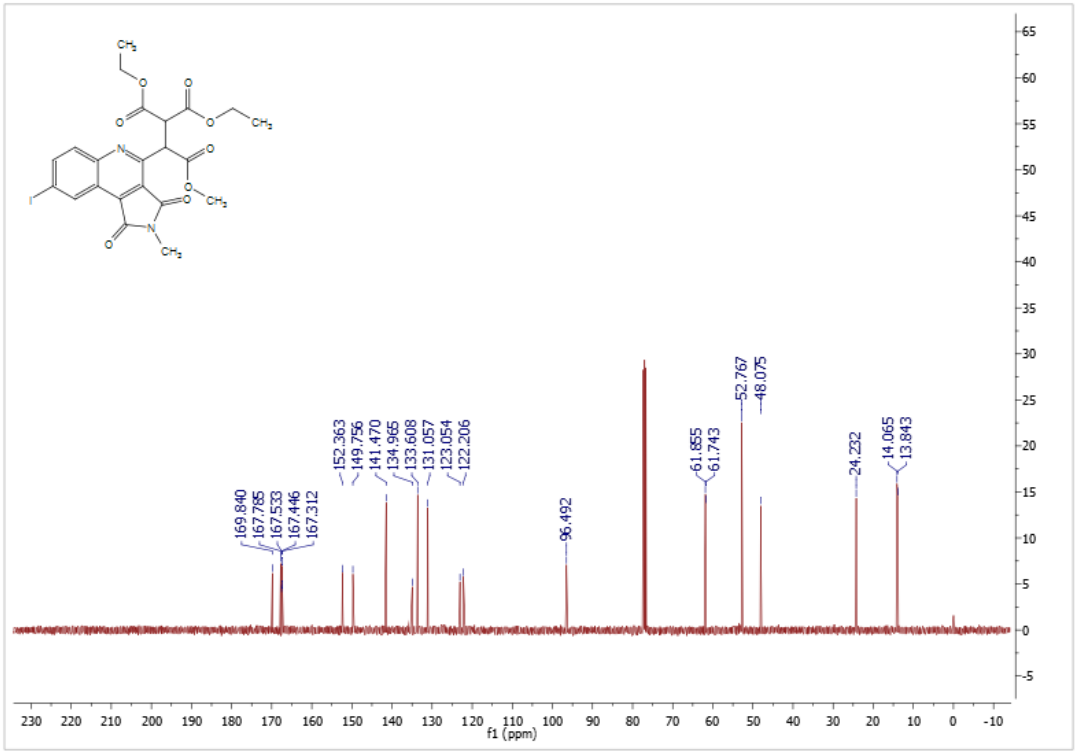
1,1-diethyl 2-methyl 2-(2,6-dimethyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4c**)



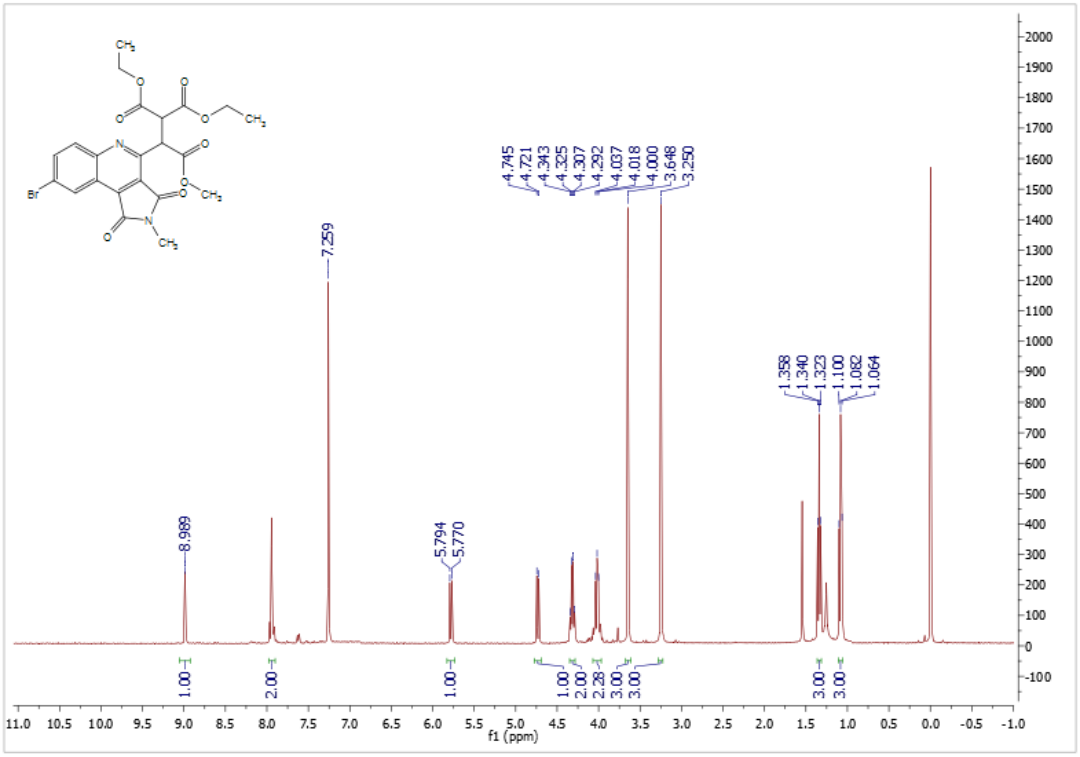


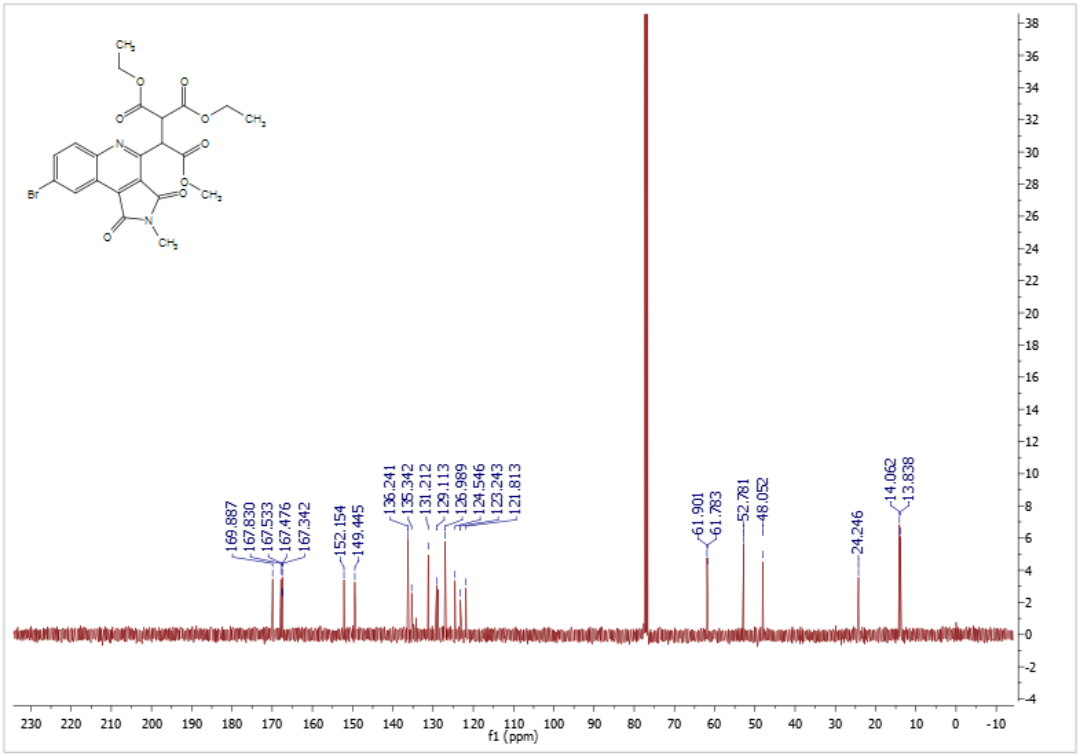
1,1-diethyl 2-methyl 2-(8-iodo-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4d**)



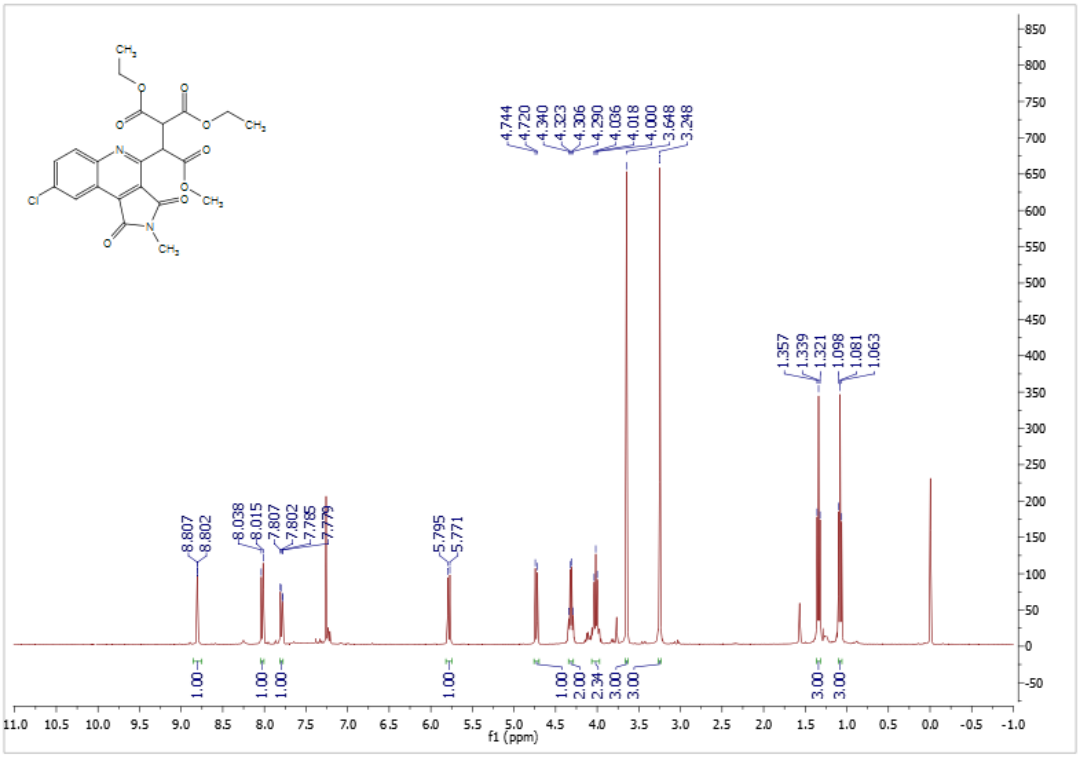


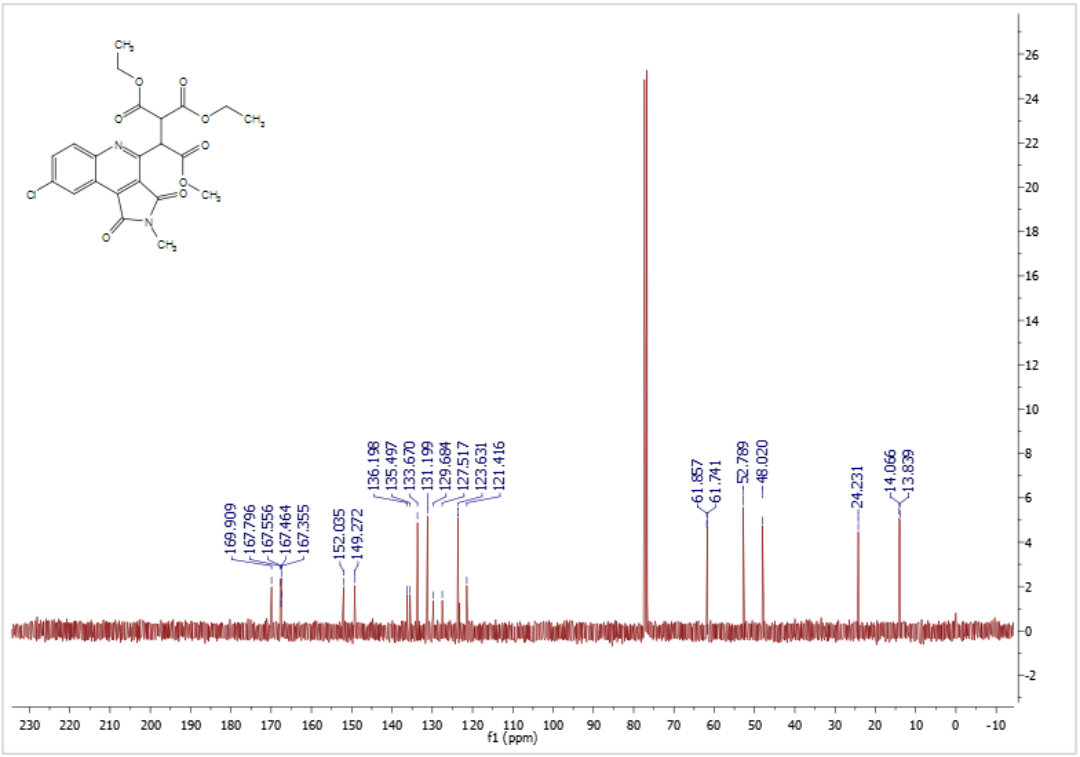
1,1-diethyl 2-methyl 2-(8-bromo-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4e**)



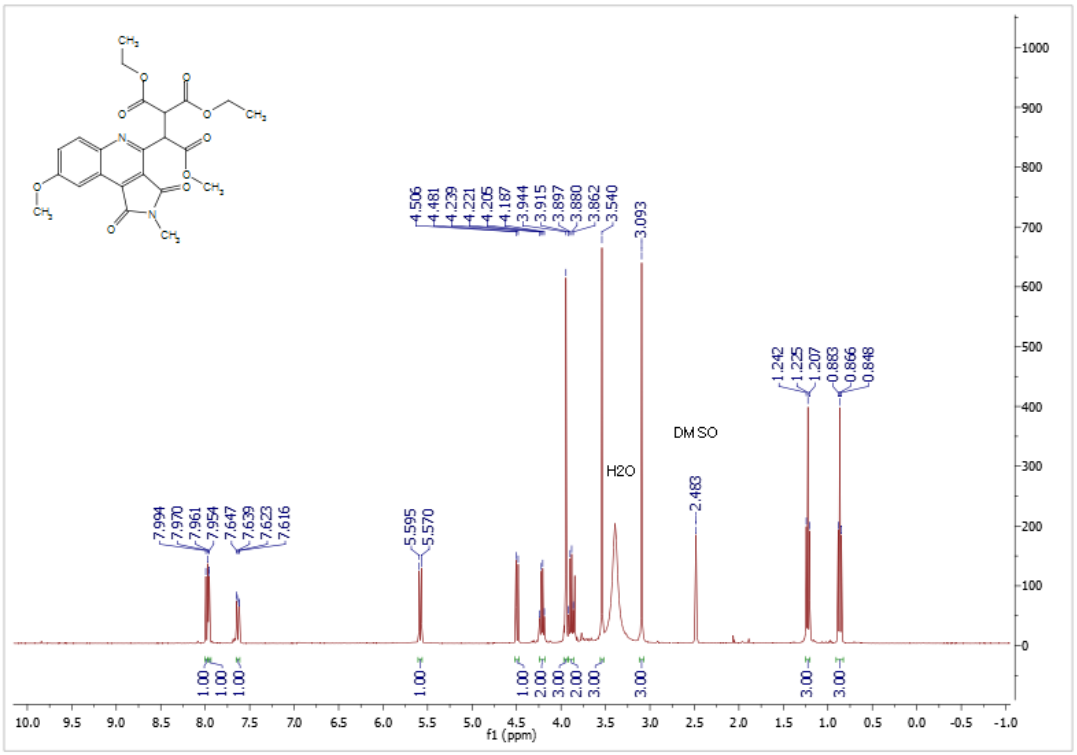


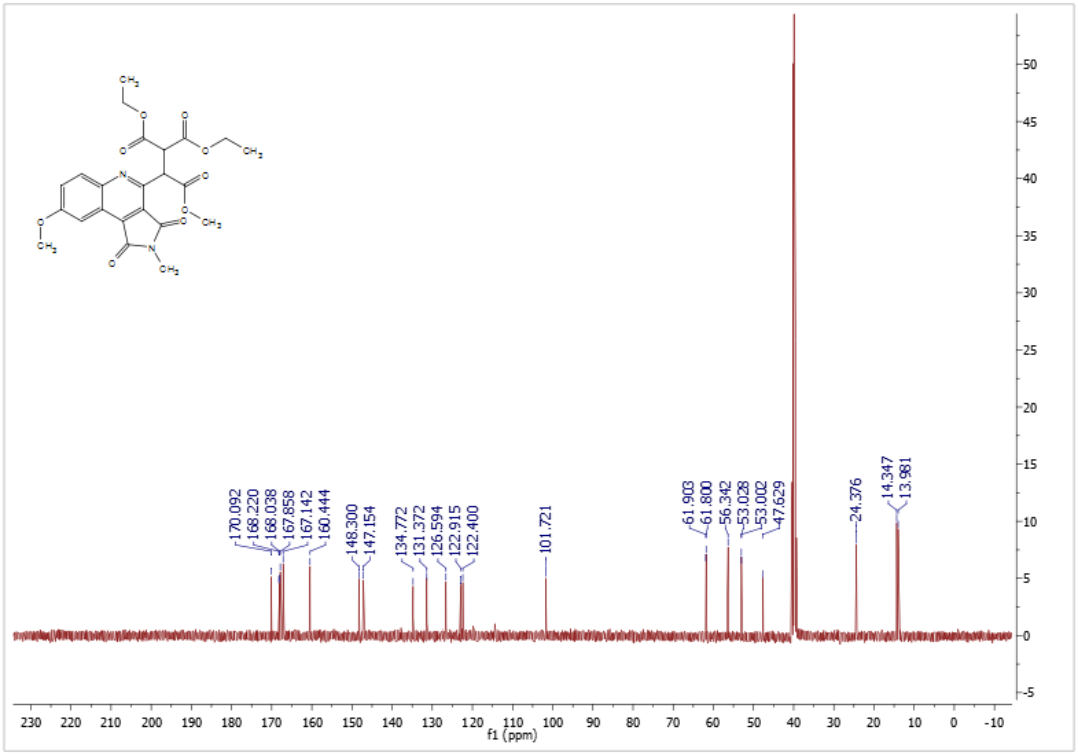
1,1-diethyl 2-methyl 2-(8-chloro-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4f**)



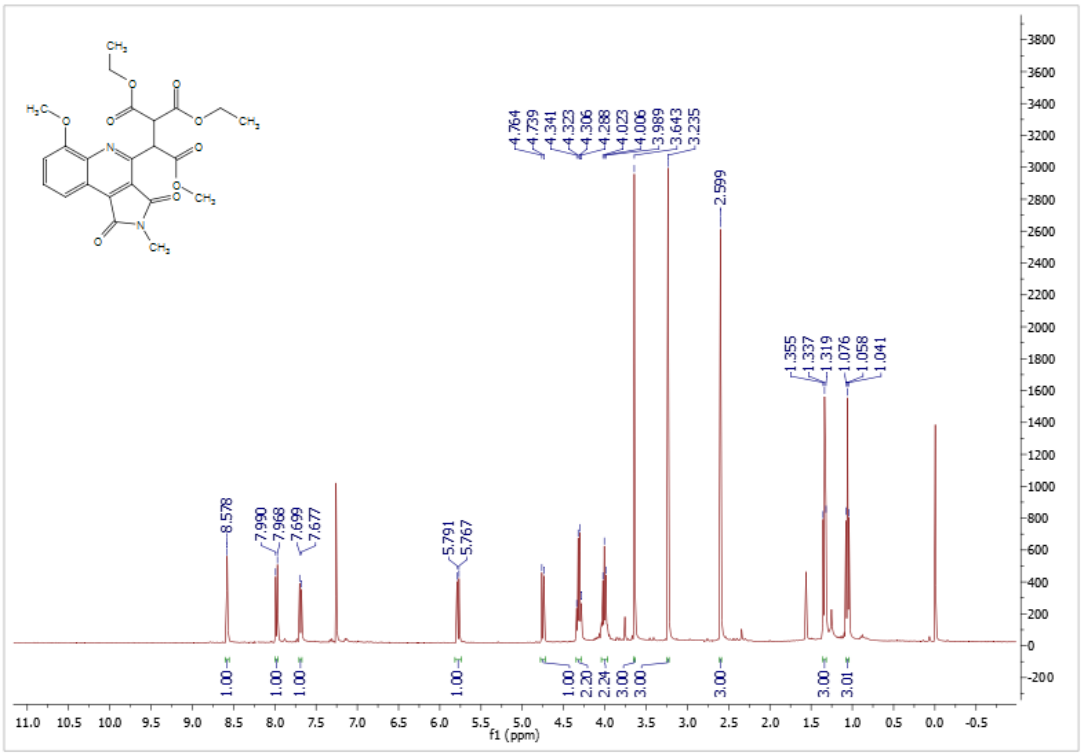


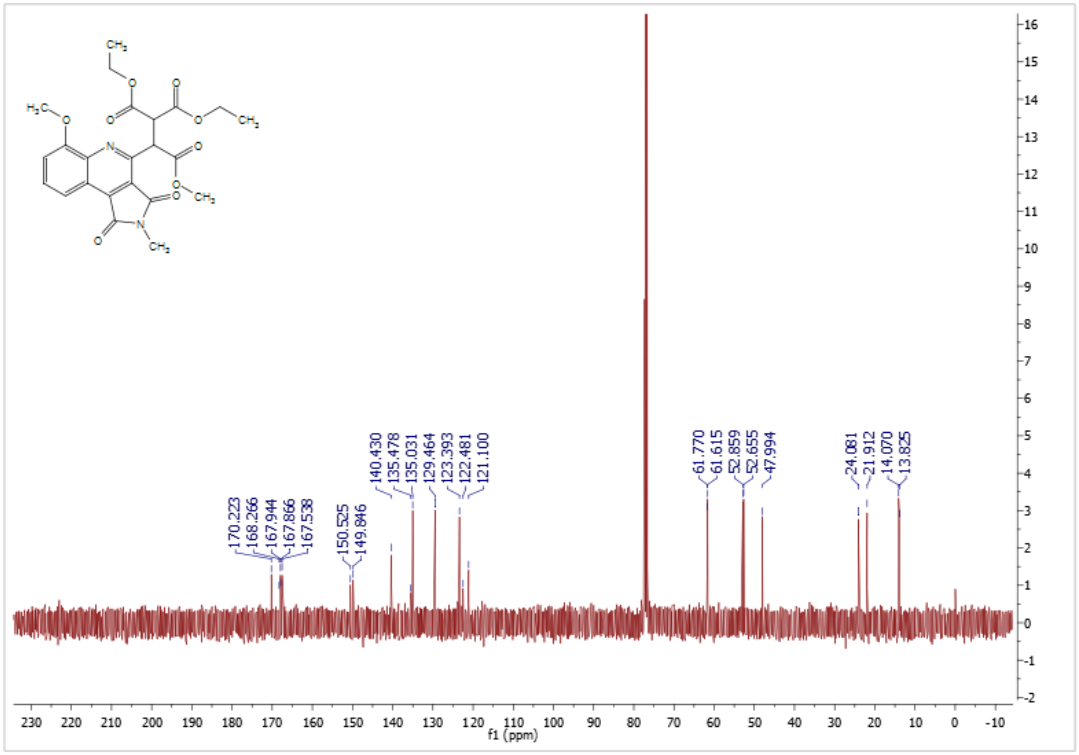
1,1-diethyl 2-methyl 2-(8-methoxy-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4g**)



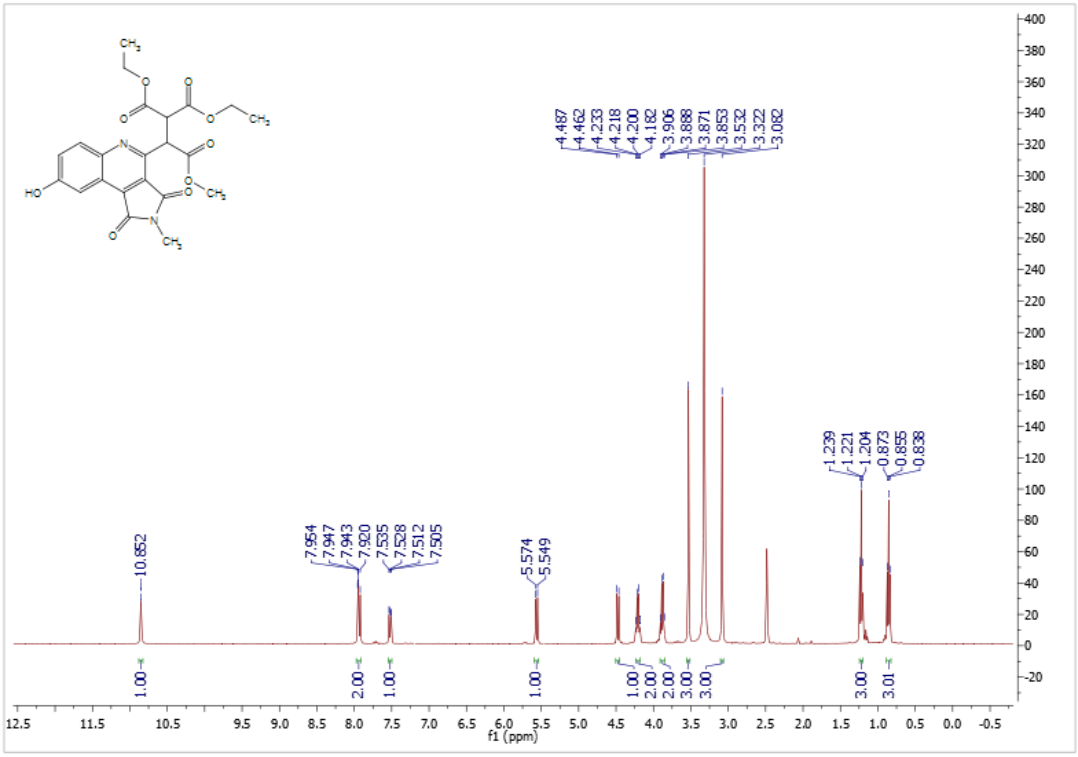


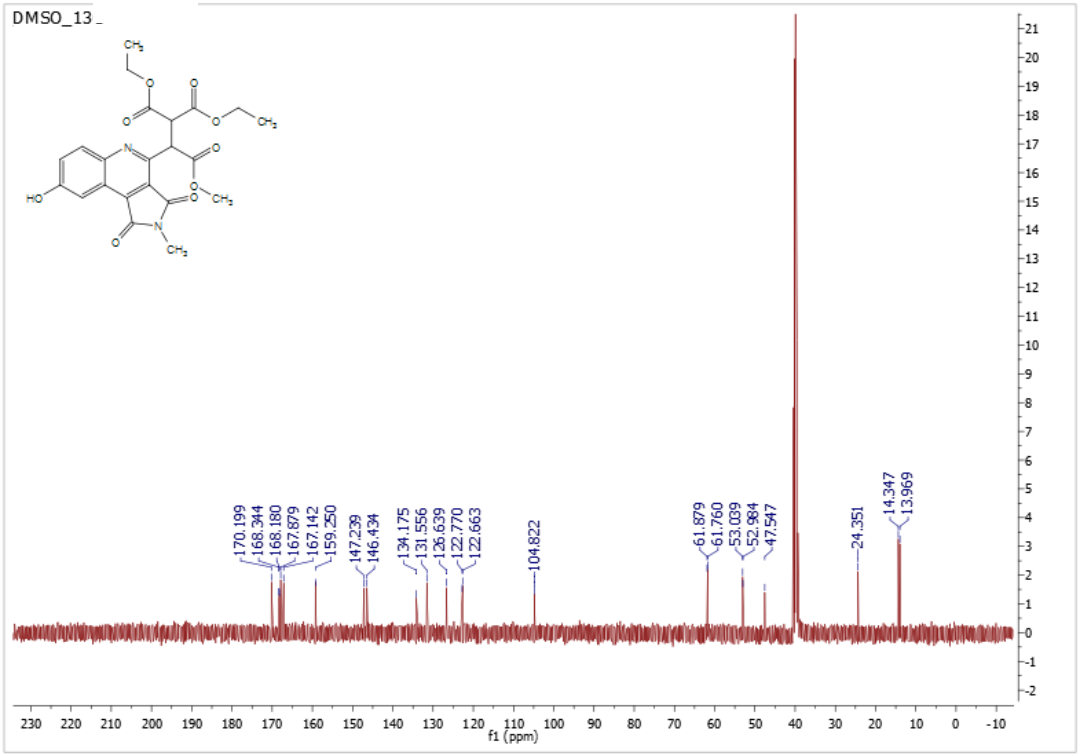
1,1-diethyl 2-methyl 2-(6-methoxy-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4h**)



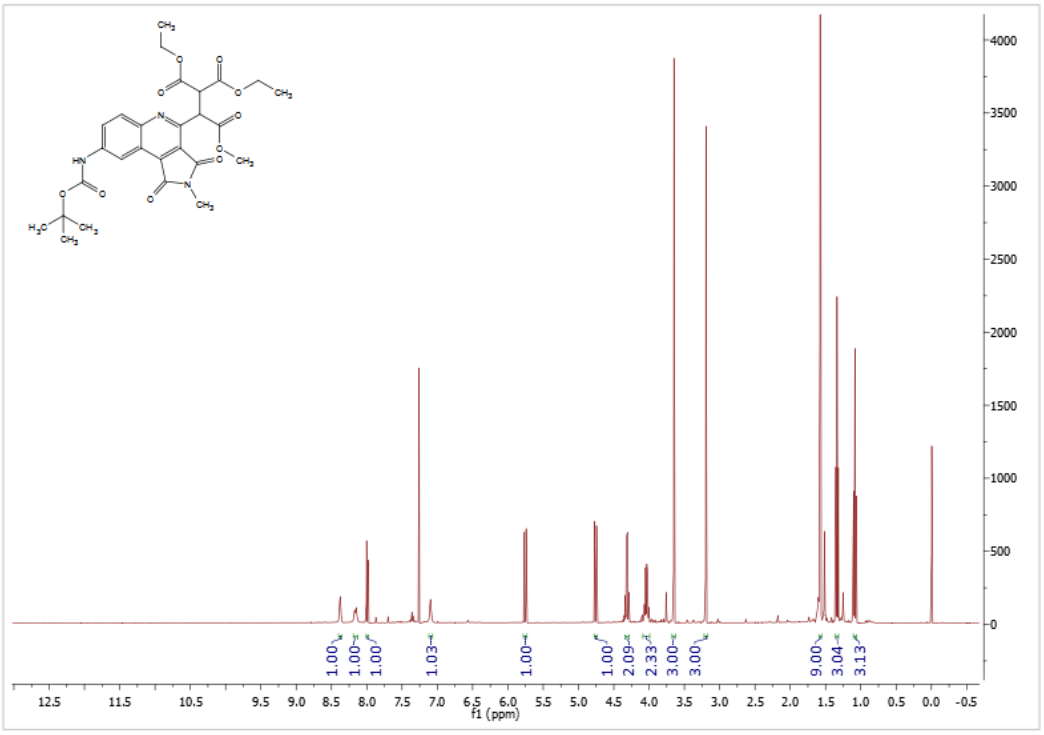


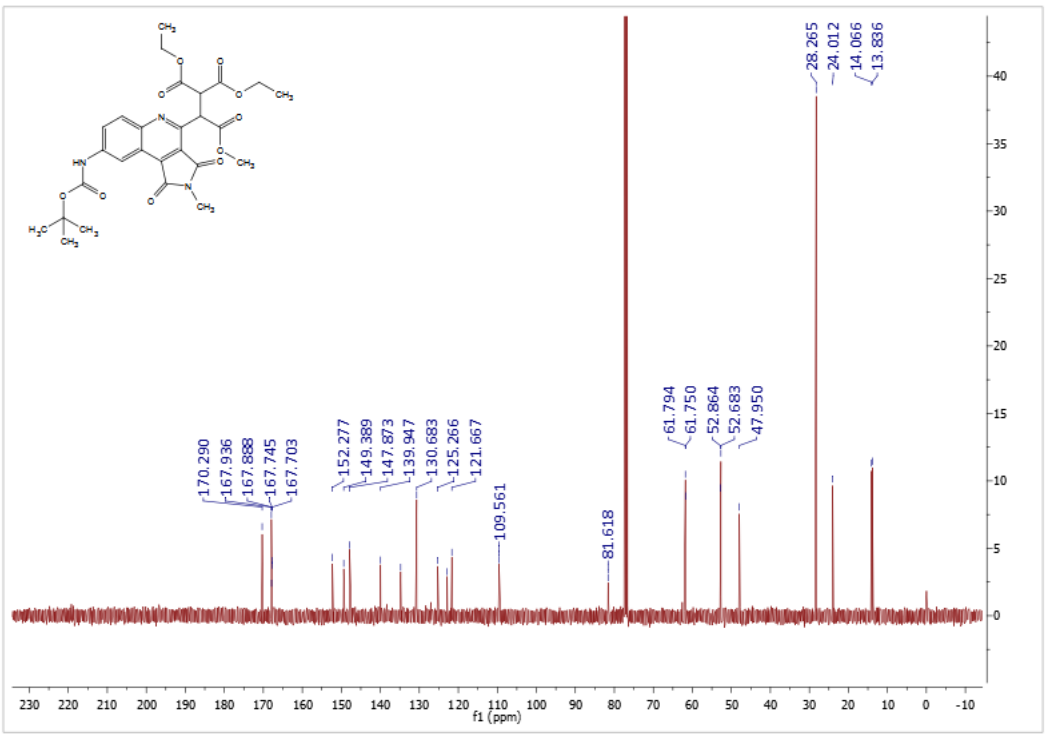
1,1-diethyl 2-methyl 2-(8-hydroxy-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4i**)



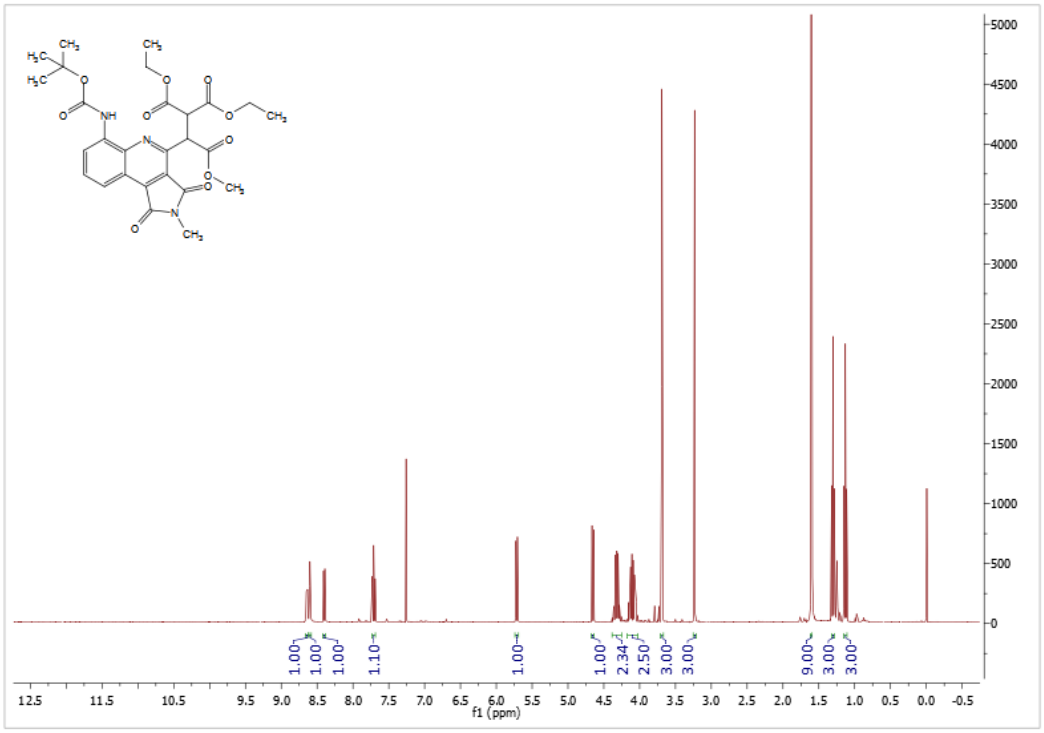


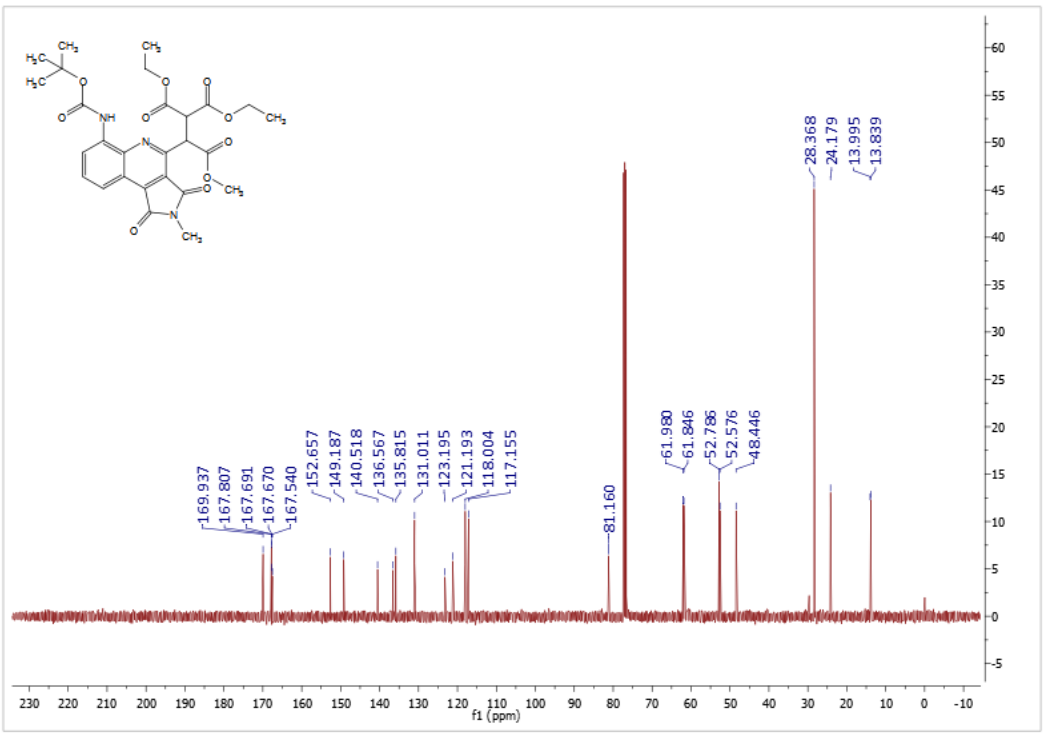
1,1-diethyl 2-methyl 2-(8-((tert-butoxycarbonyl)amino)-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)ethane-1,1,2-tricarboxylate (**4j**)



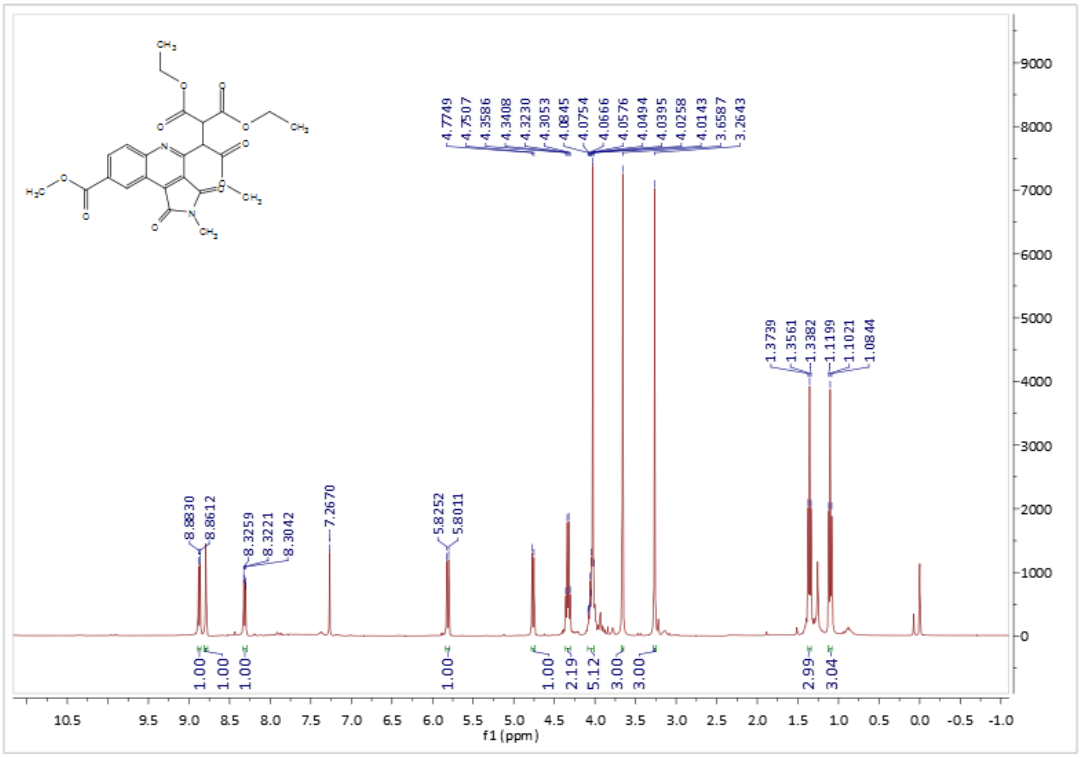


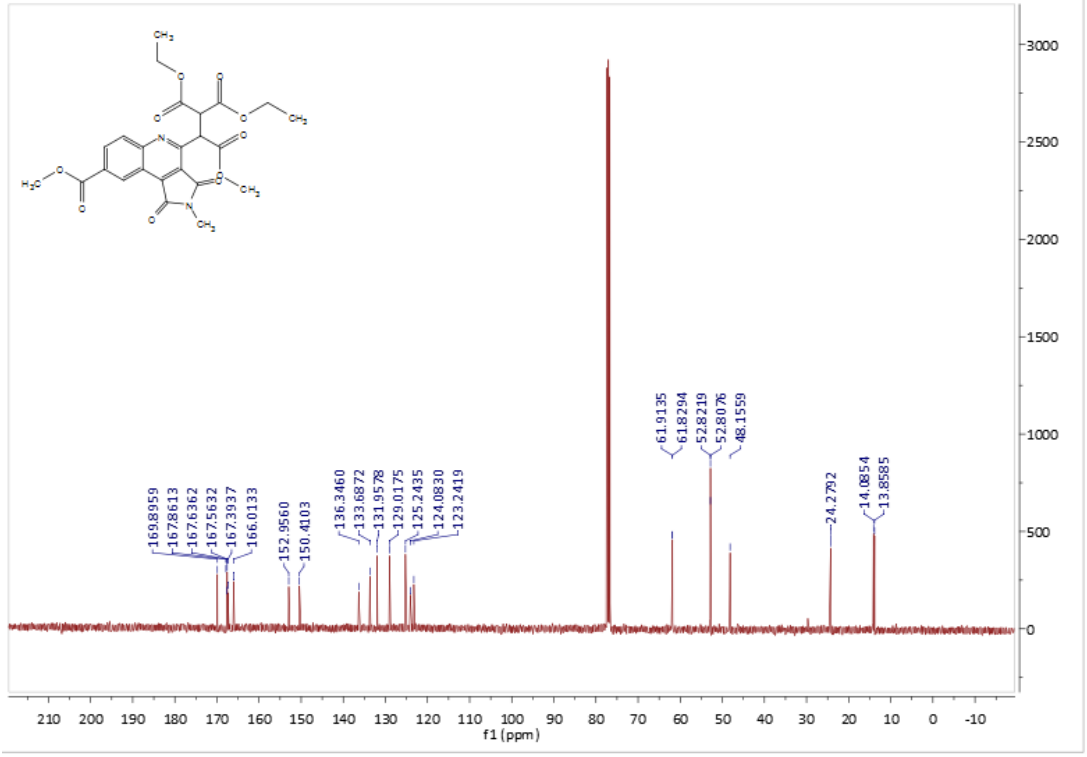
1,1-diethyl 2-methyl 2-(6-((tert-butoxycarbonyl)amino)-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)ethane-1,1,2-tricarboxylate (**4k**)



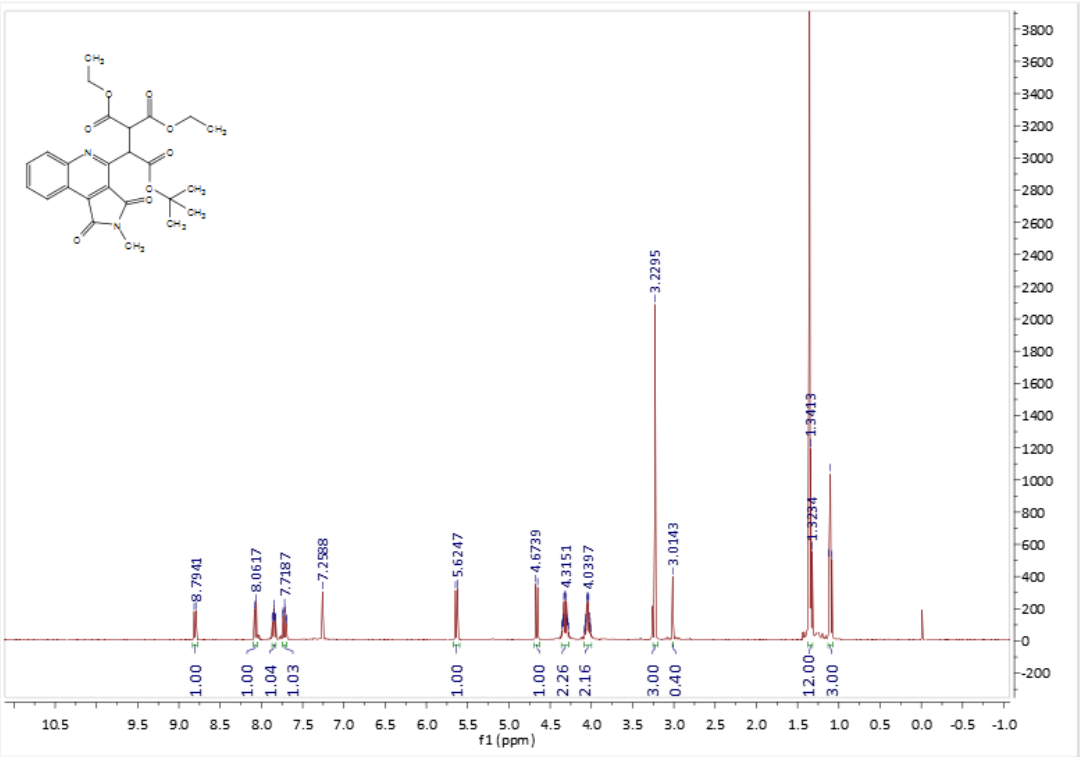


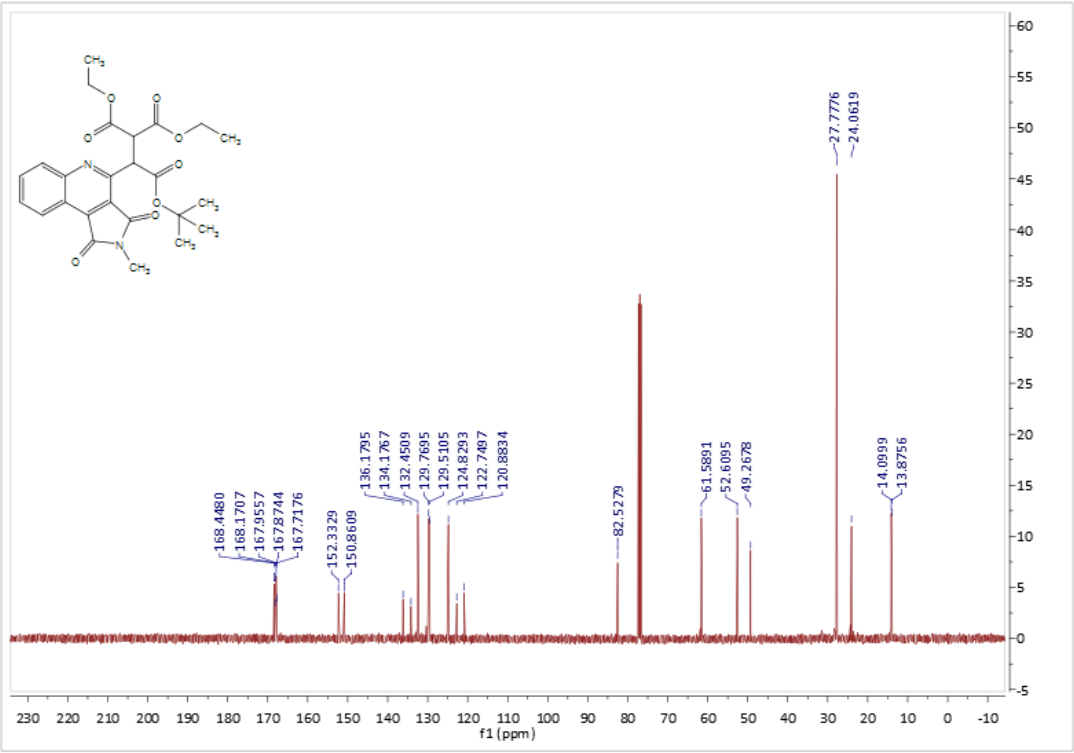
1,1-diethyl 2-methyl 2-(8-(methoxy carbonyl)-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo [3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4l**)



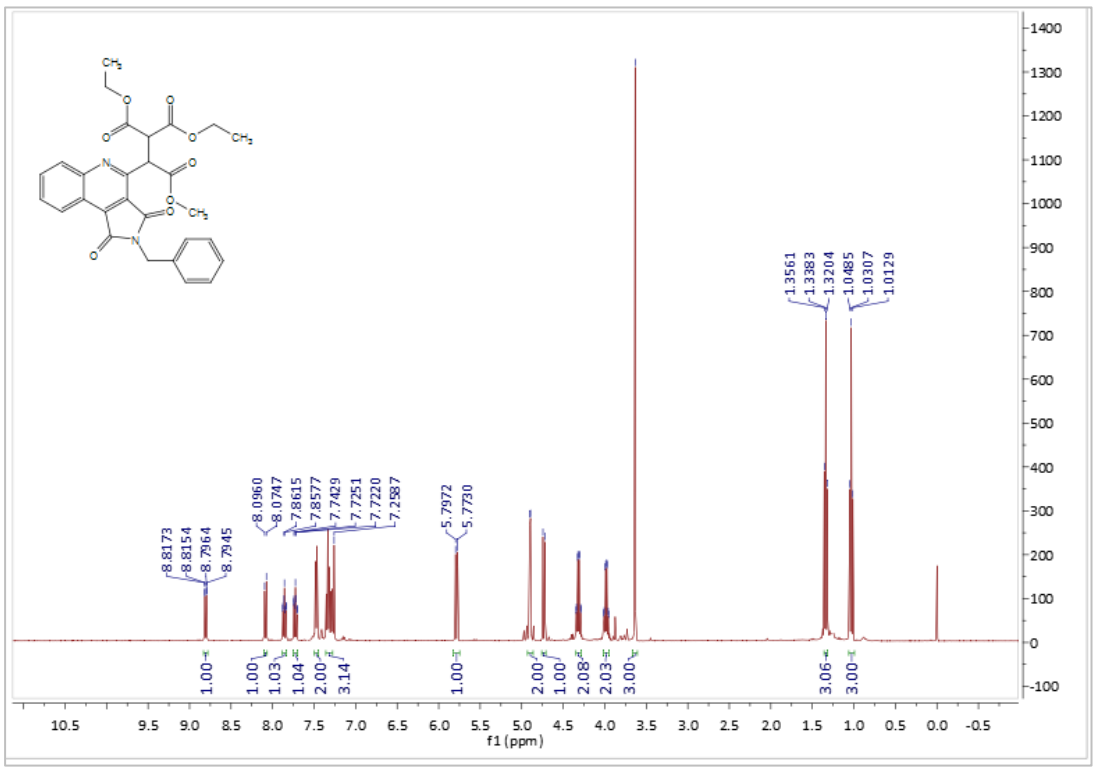


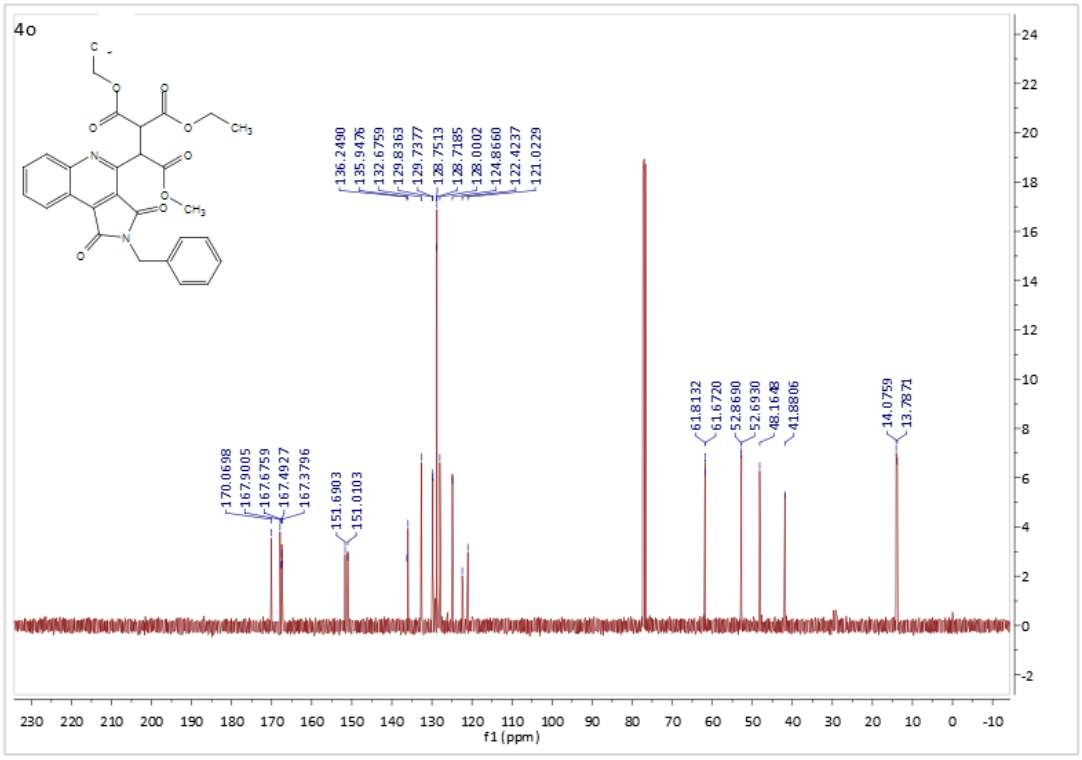
2-tert-butyl 1,1-diethyl 2-(2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4m**)



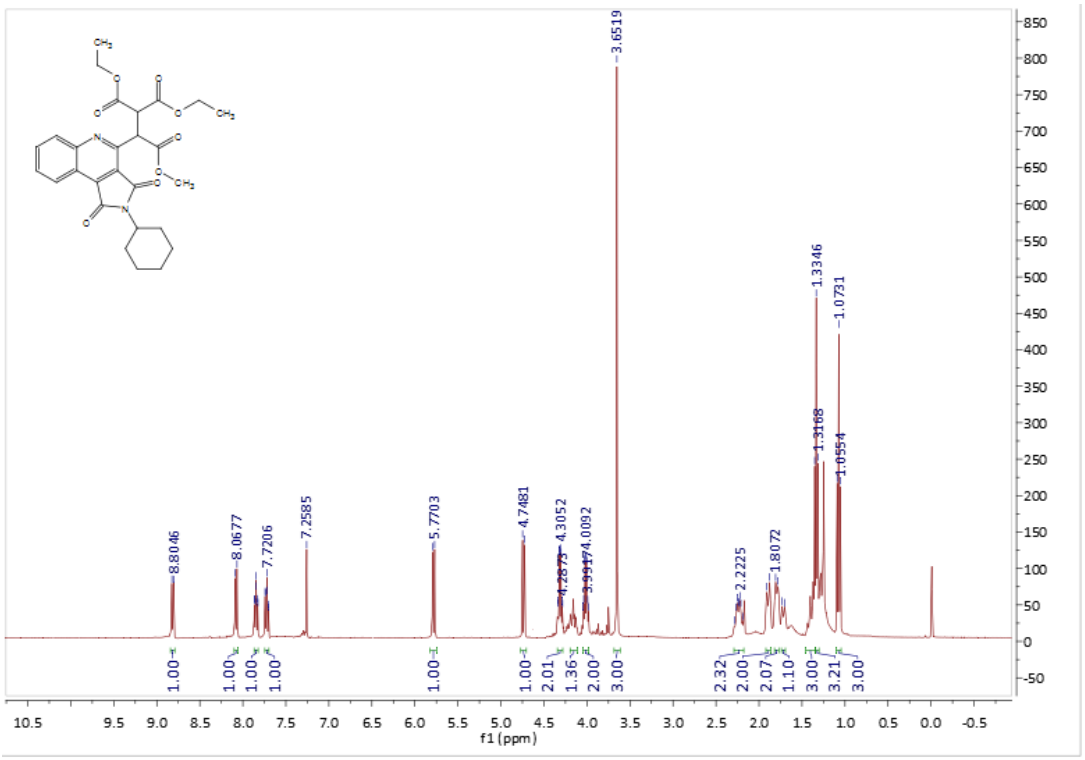


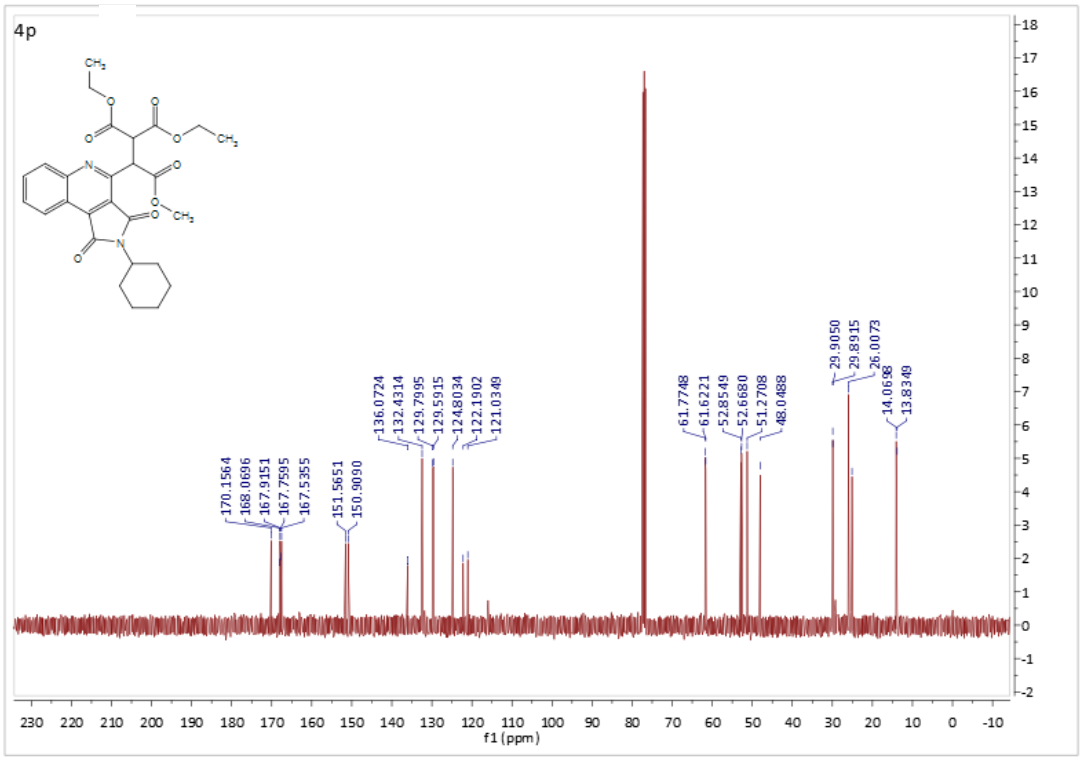
1,1-diethyl 2-methyl 2-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4n**)



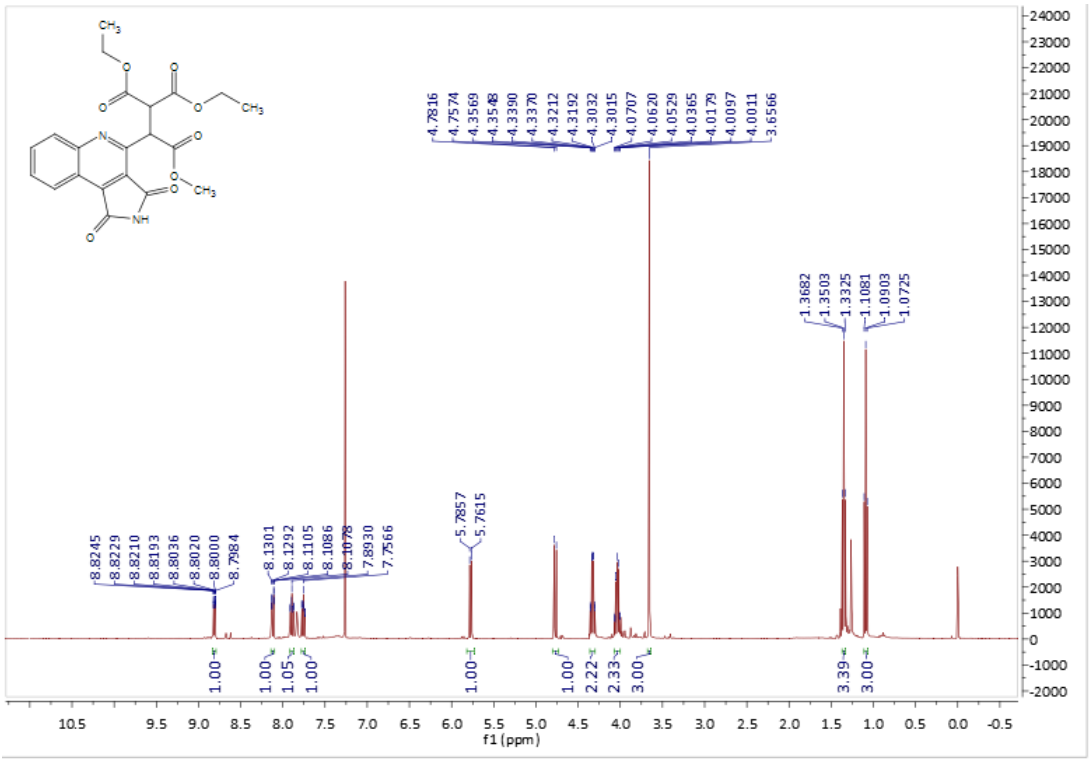


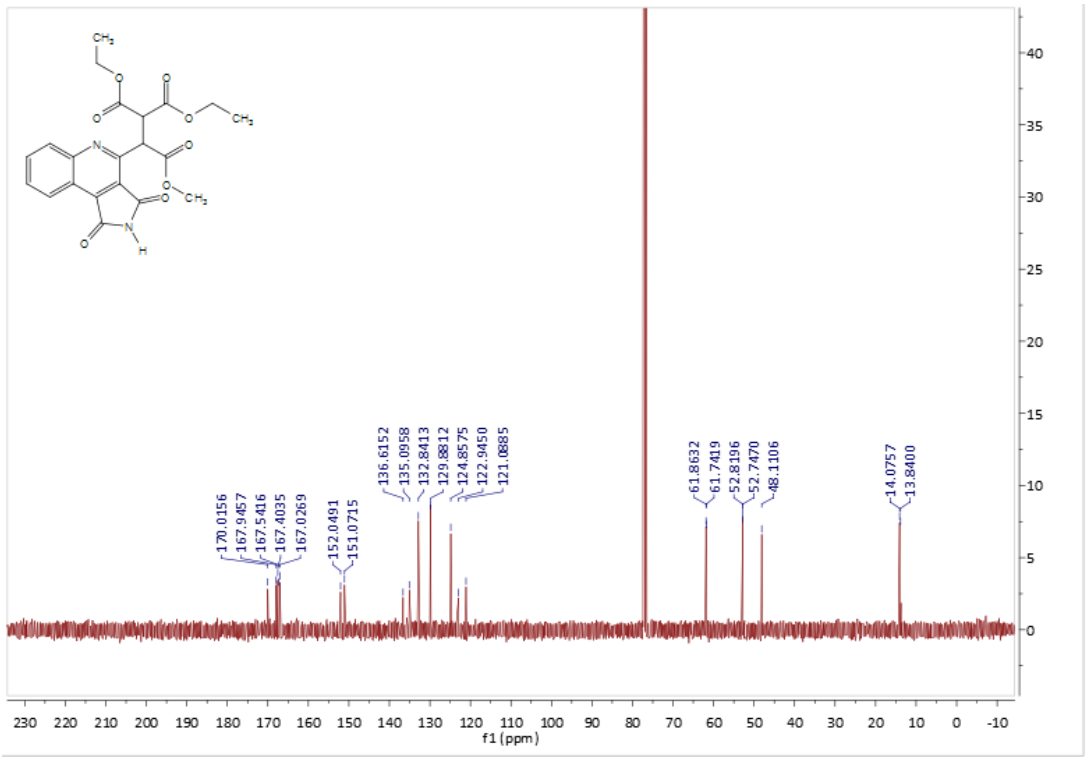
1,1-diethyl 2-methyl 2-(2-cyclohexyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4o**)



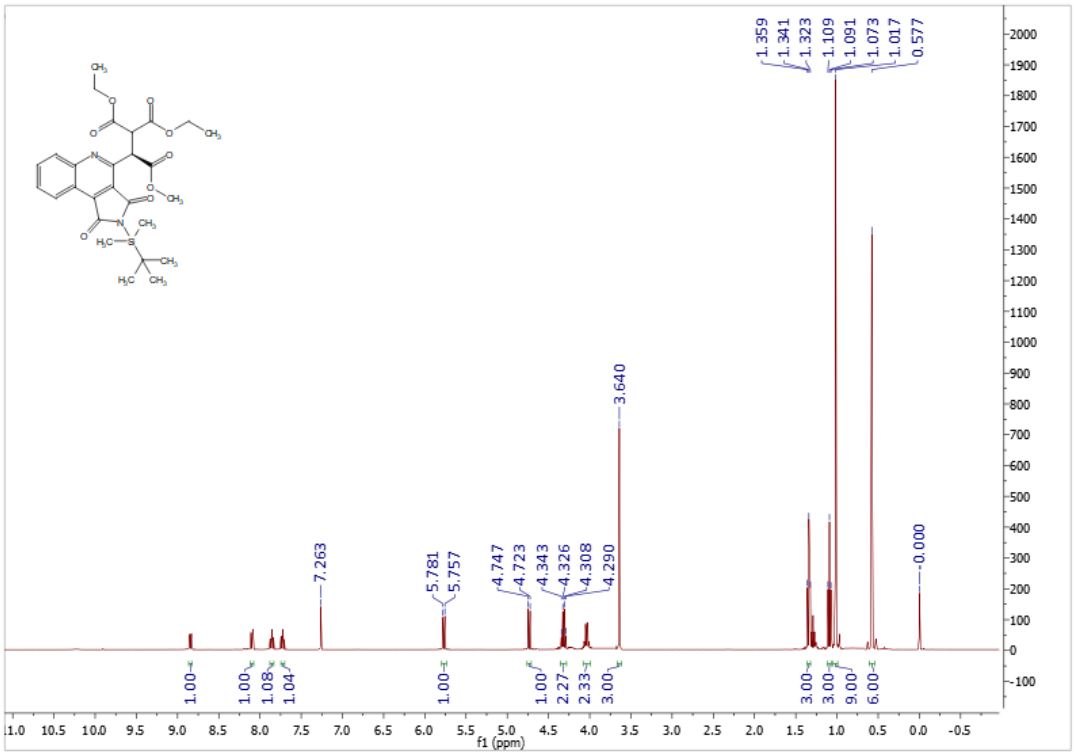


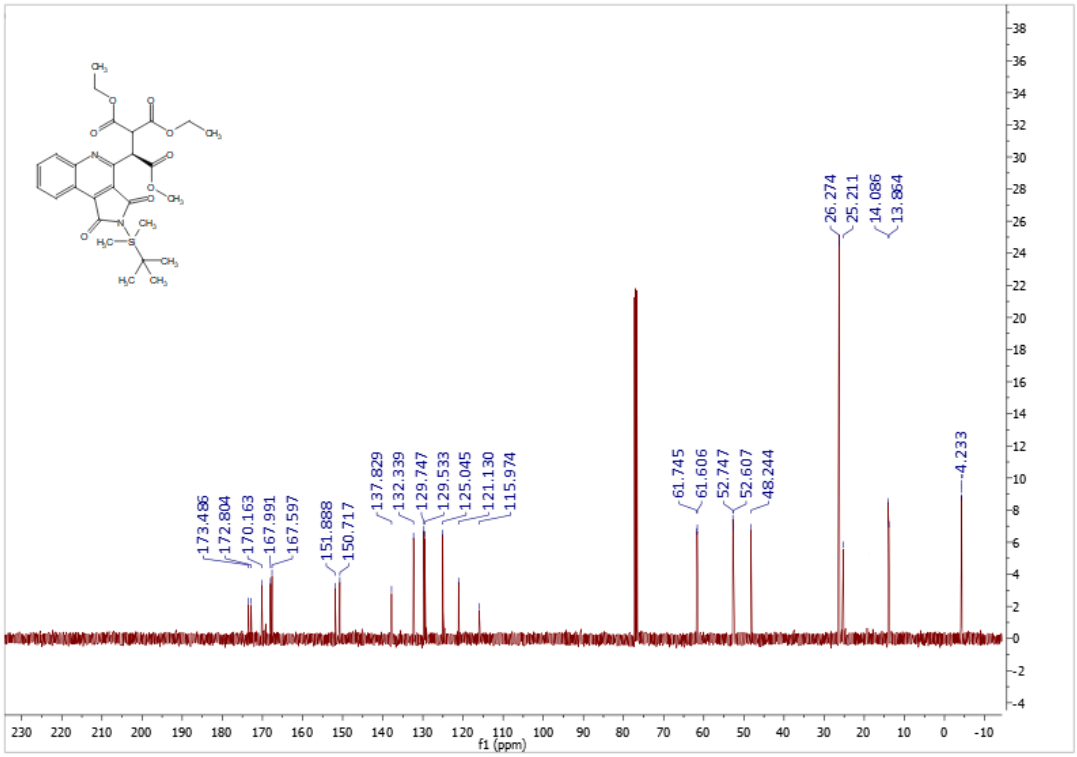
1,1-diethyl 2-methyl 2-(1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4p**)



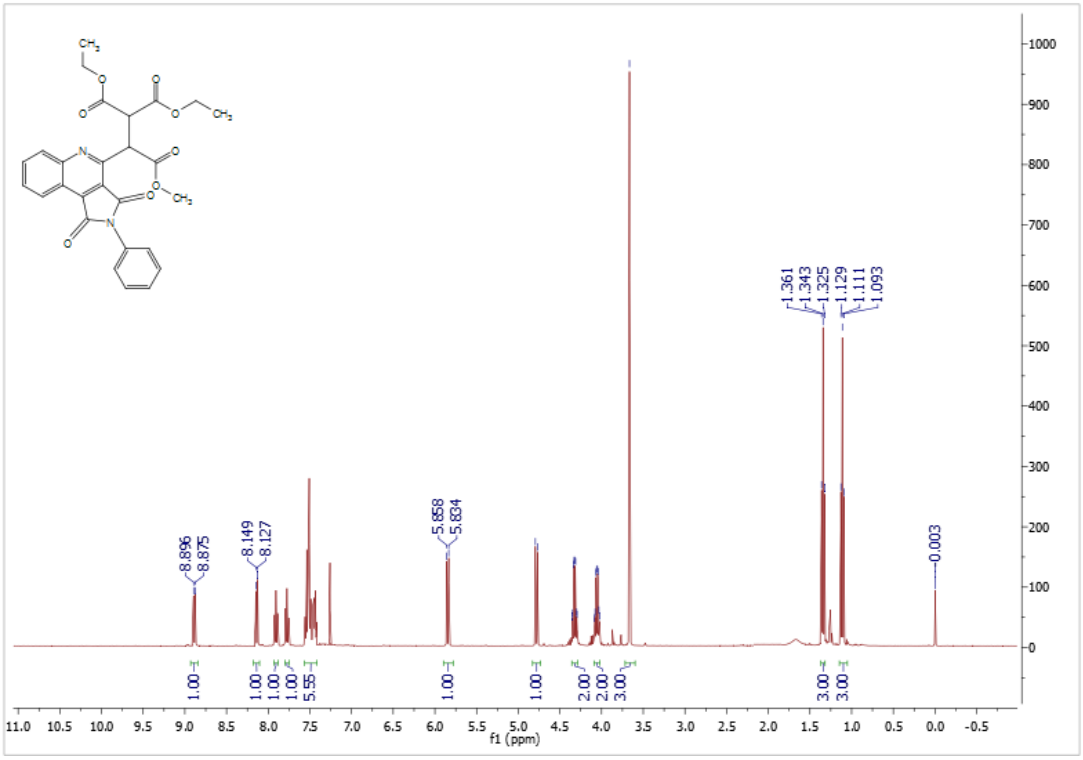


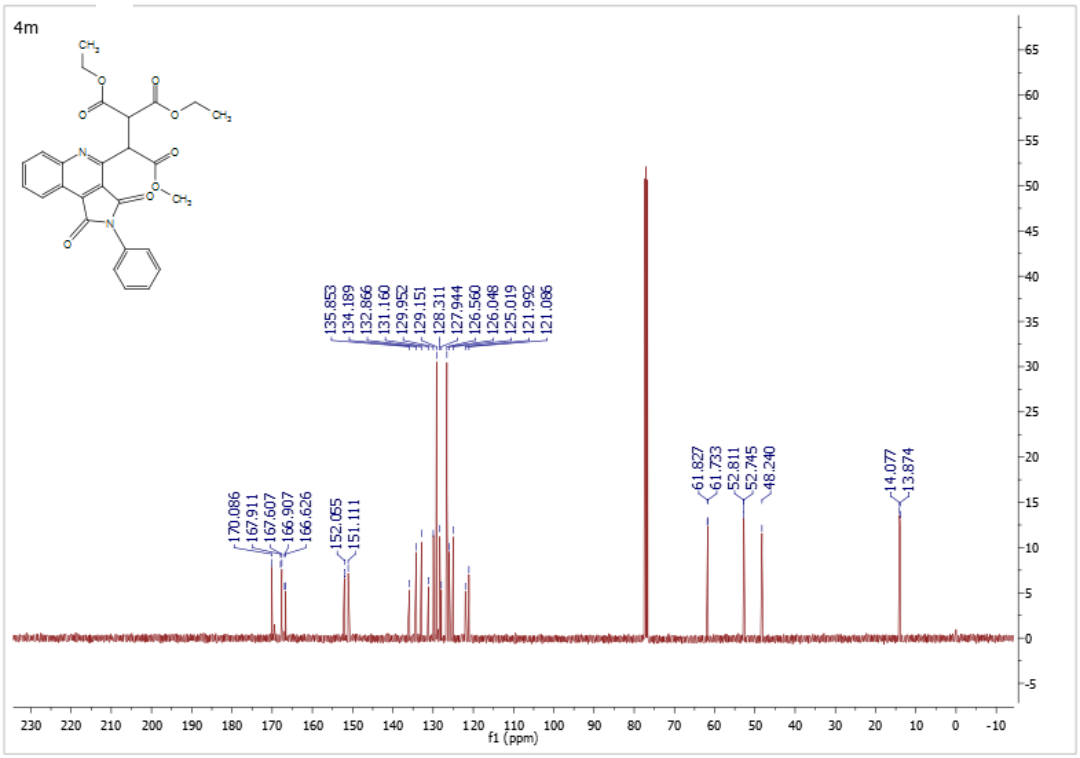
1,1-diethyl 2-methyl 2-(2-(tert-butyldimethylsilyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)ethane-1,1,2-tricarboxylate (**4q**)



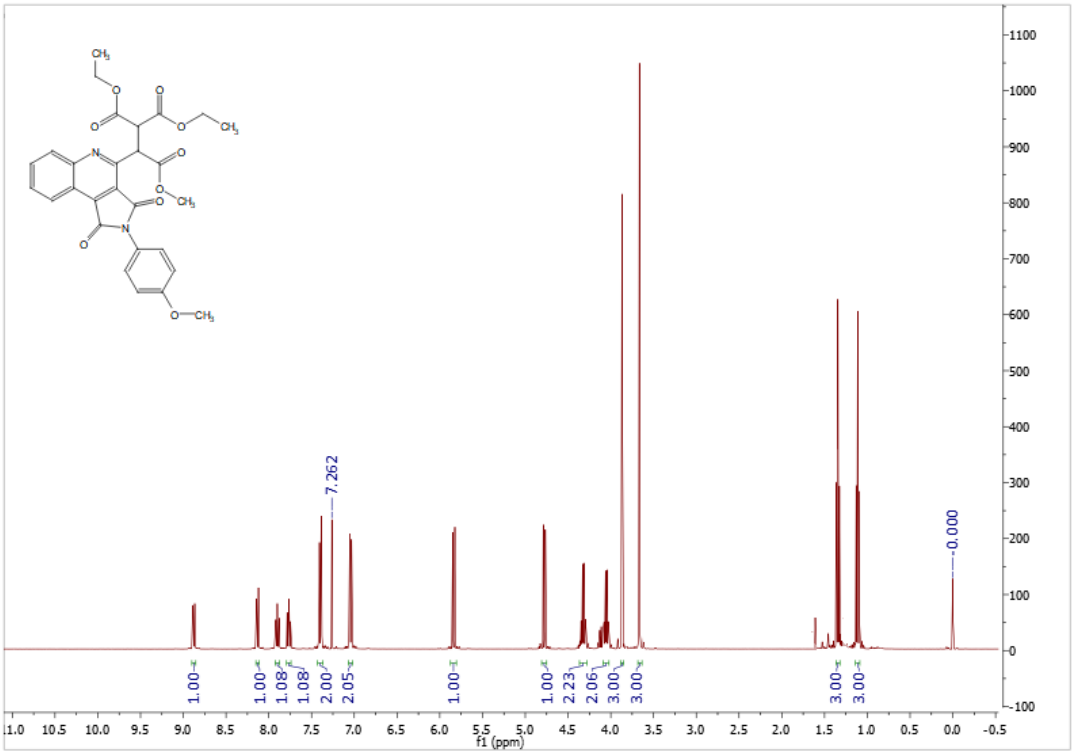


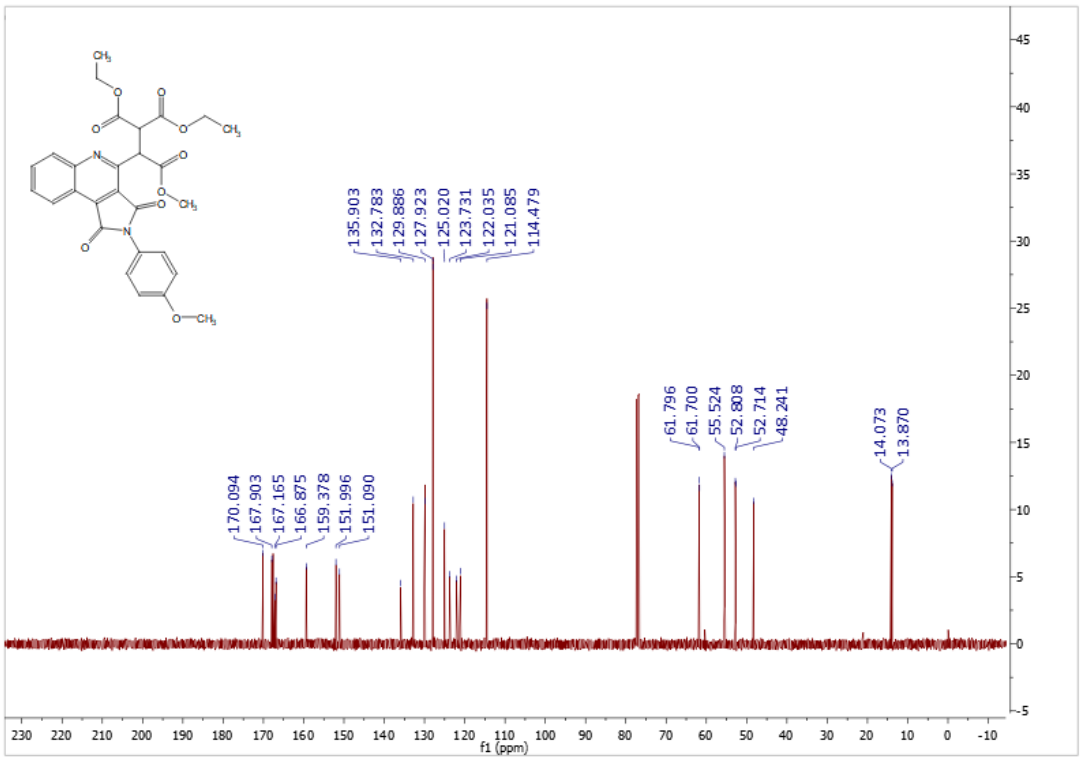
1,1-diethyl 2-methyl 2-(1,3-dioxo-2-phenyl-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4r**)



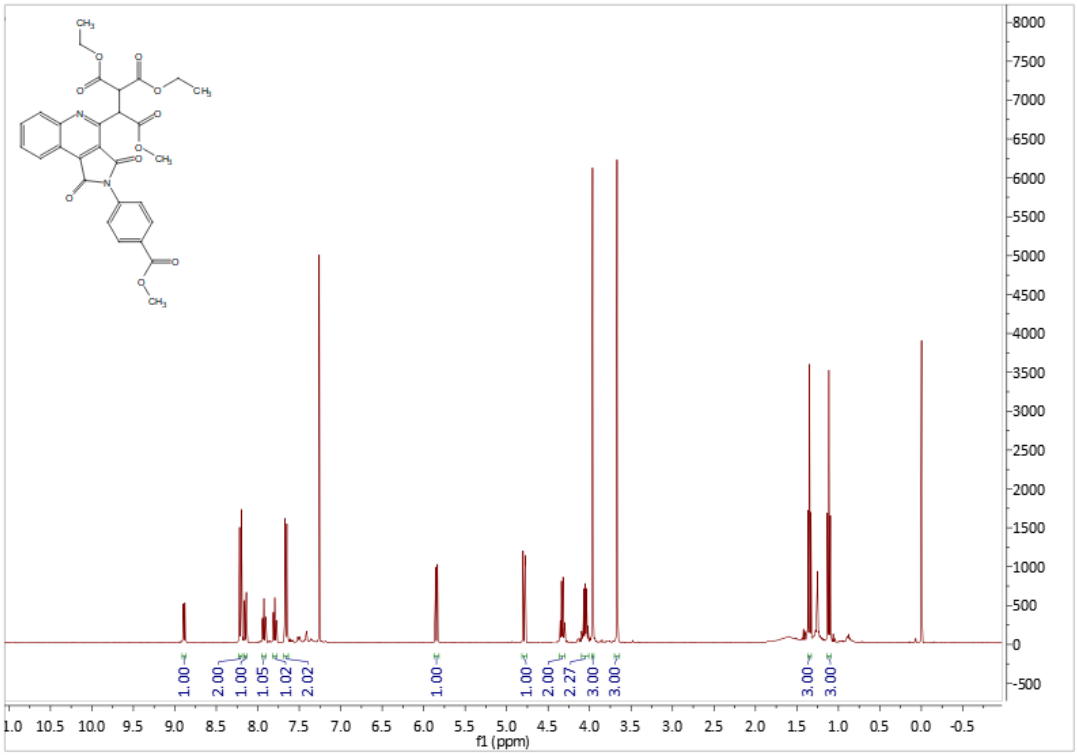


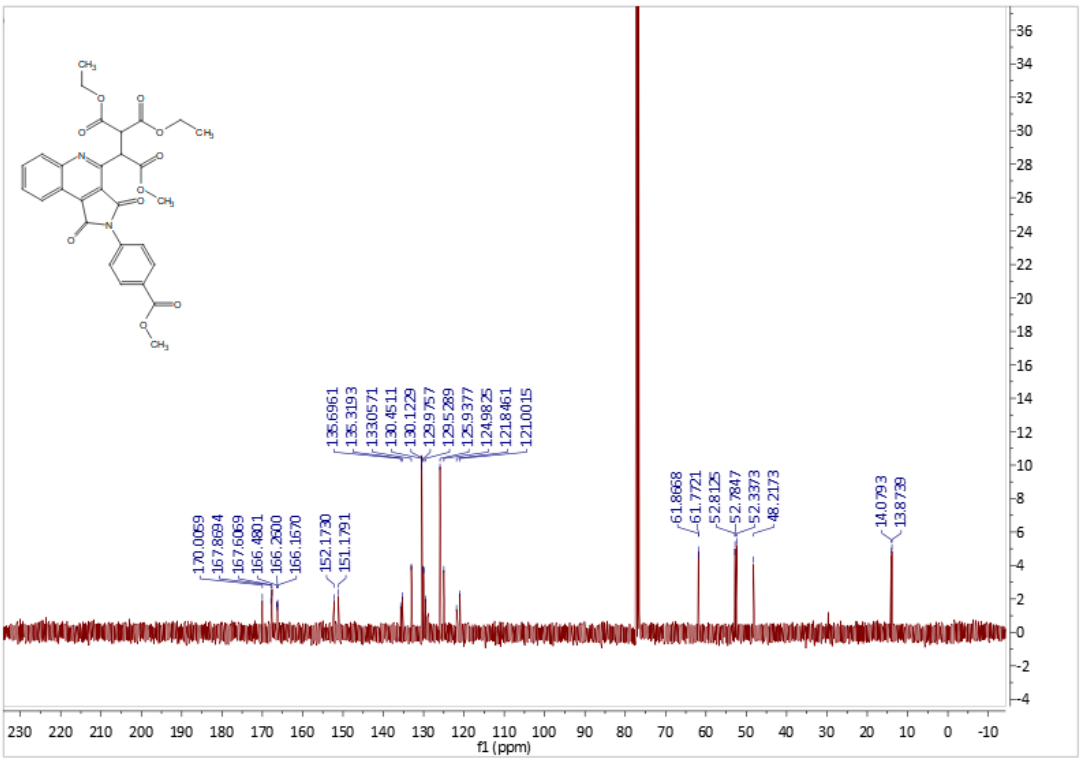
1,1-diethyl 2-methyl 2-(2-(4-methoxyphenyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)ethane-1,1,2-tricarboxylate (**4s**)



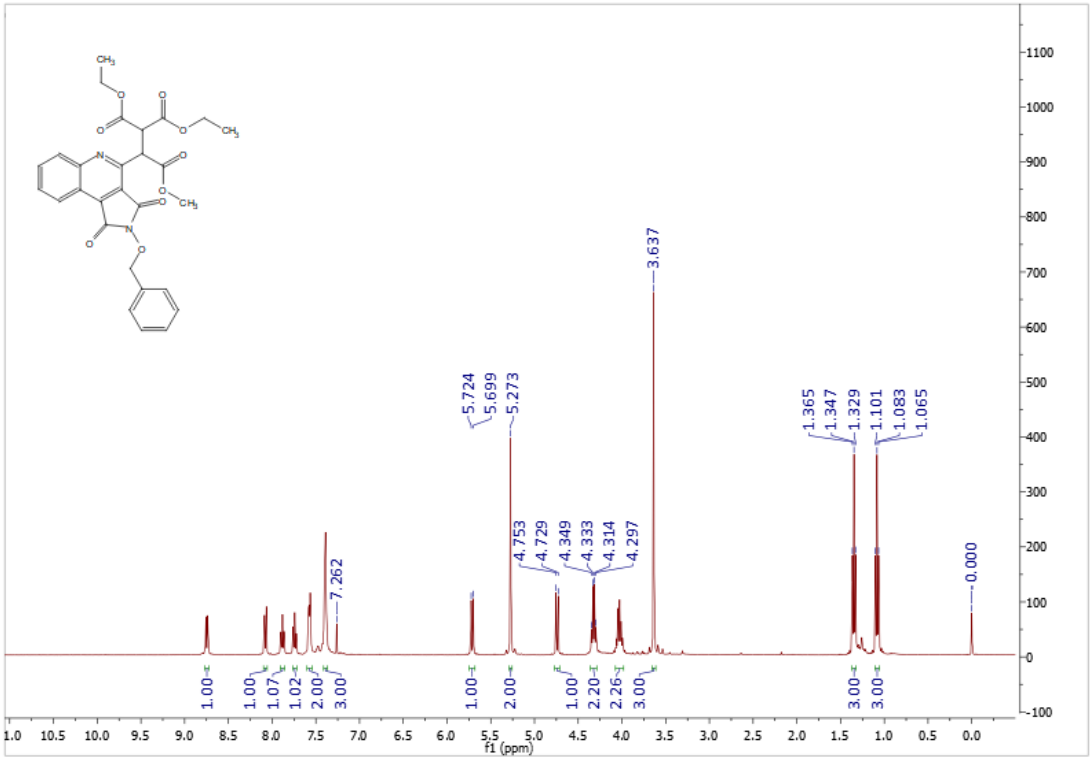


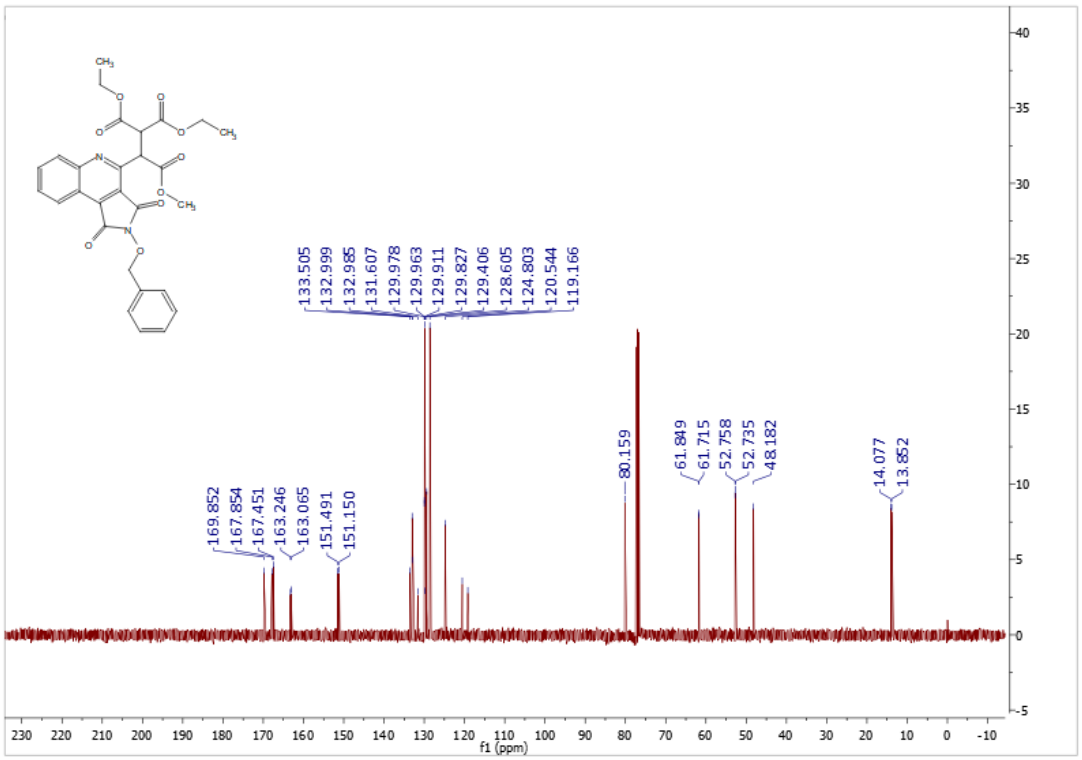
1,1-diethyl 2-methyl 2-(2-(4-(methoxycarbonyl)phenyl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)ethane-1,1,2-tricarboxylate (**4t**)



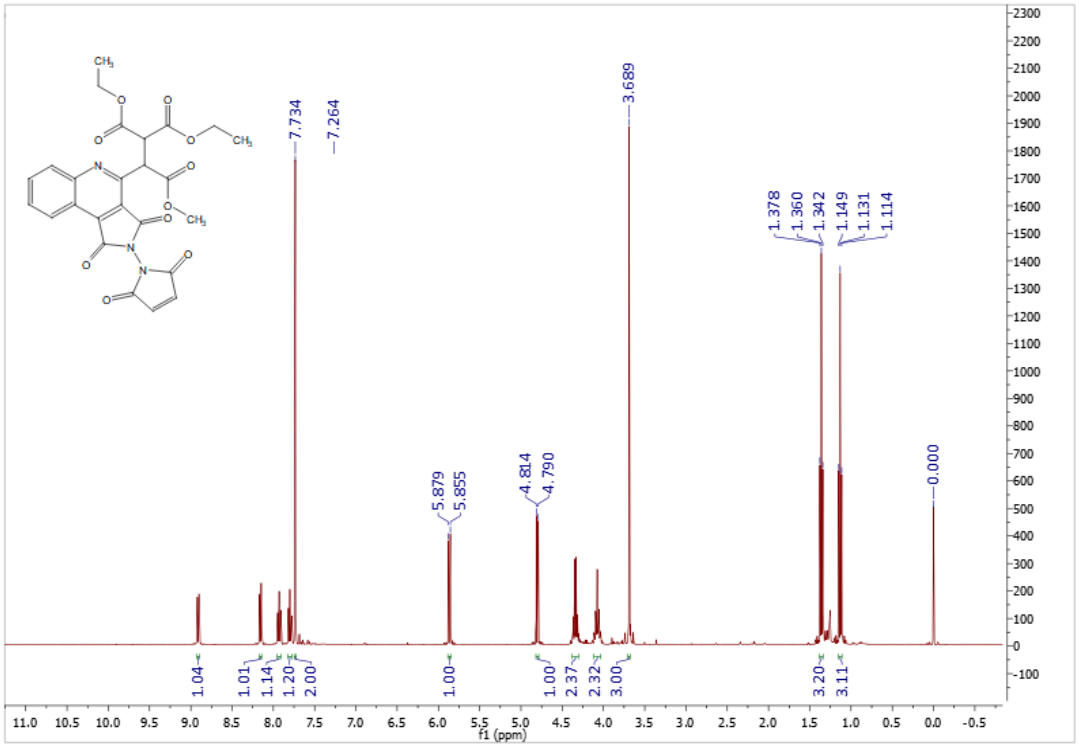


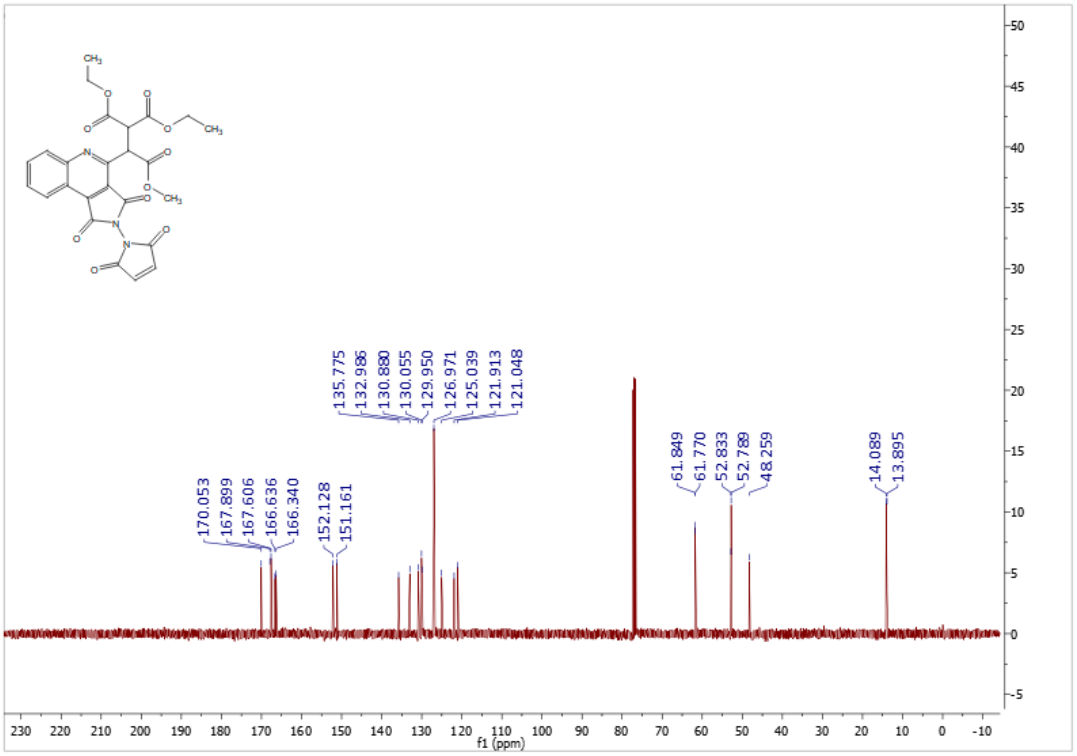
1,1-diethyl 2-methyl 2-(2-(benzyloxy)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)ethane-1,1,2-tricarboxylate (**4u**)



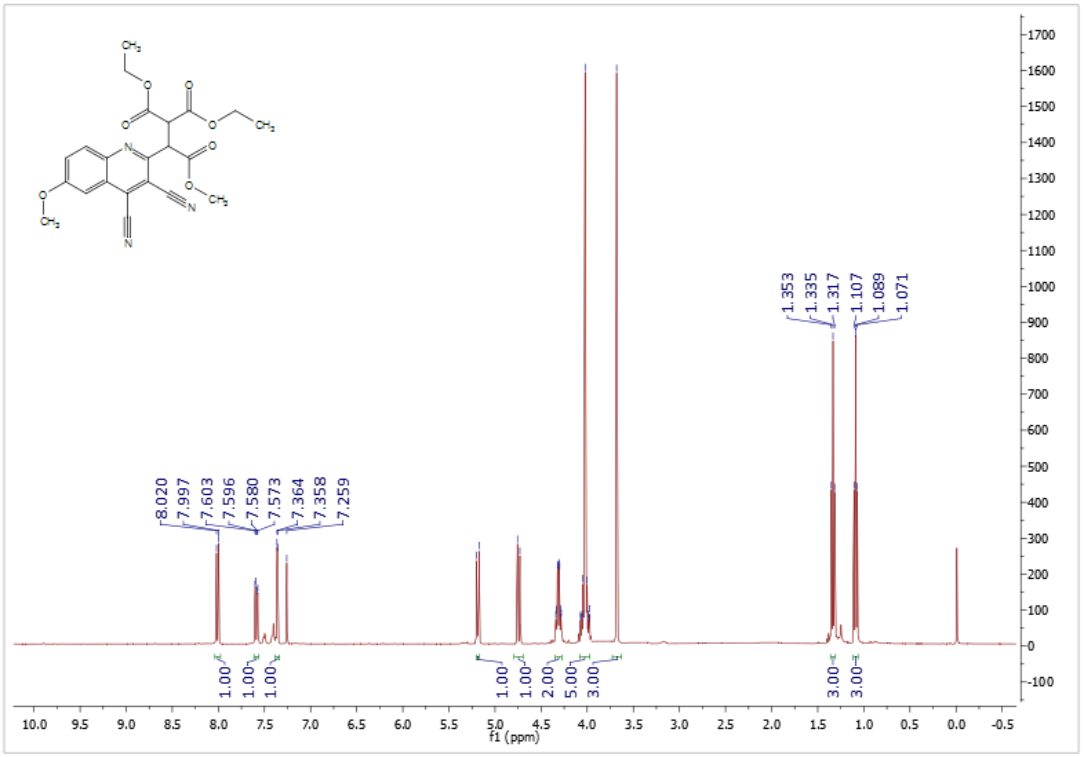


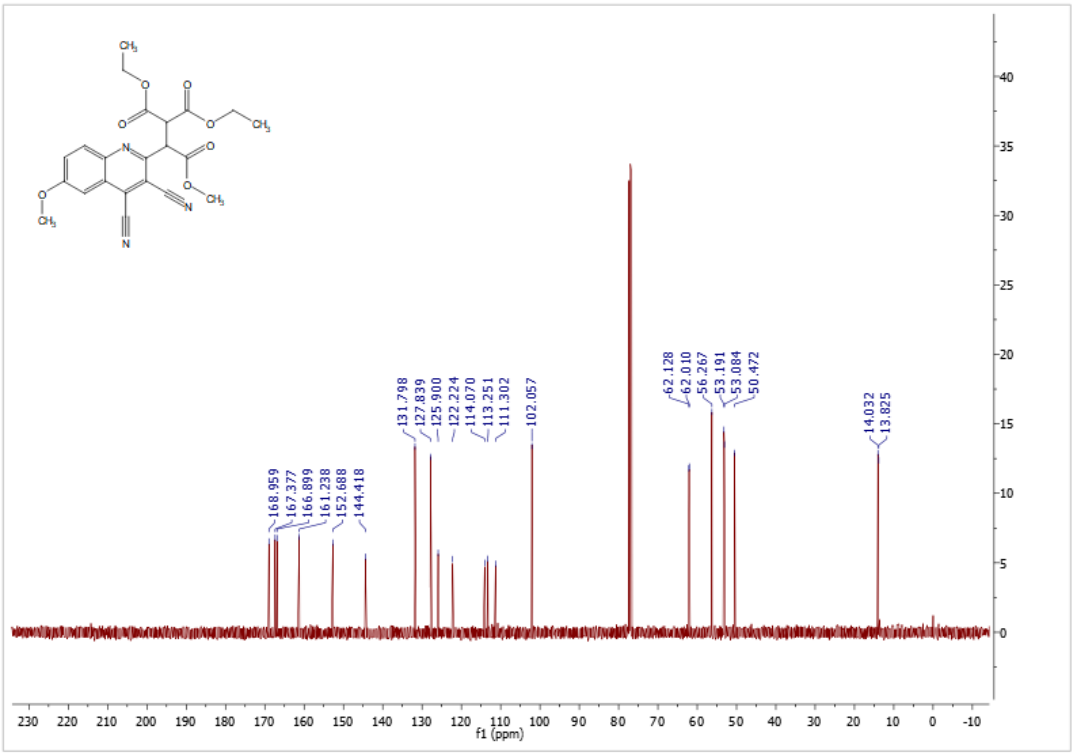
1,1-diethyl 2-methyl 2-(2-(2,5-dioxo-2,5-dihydro-1H-pyrrol-1-yl)-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)ethane-1,1,2-tricarboxylate (**4v**)



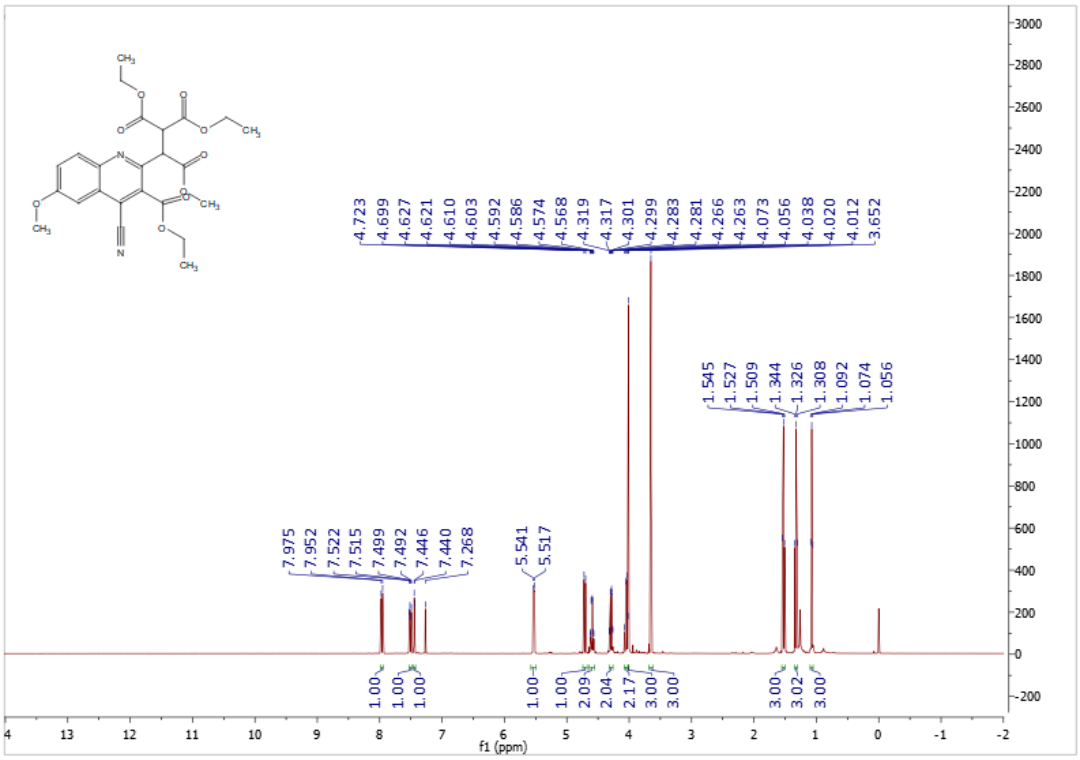


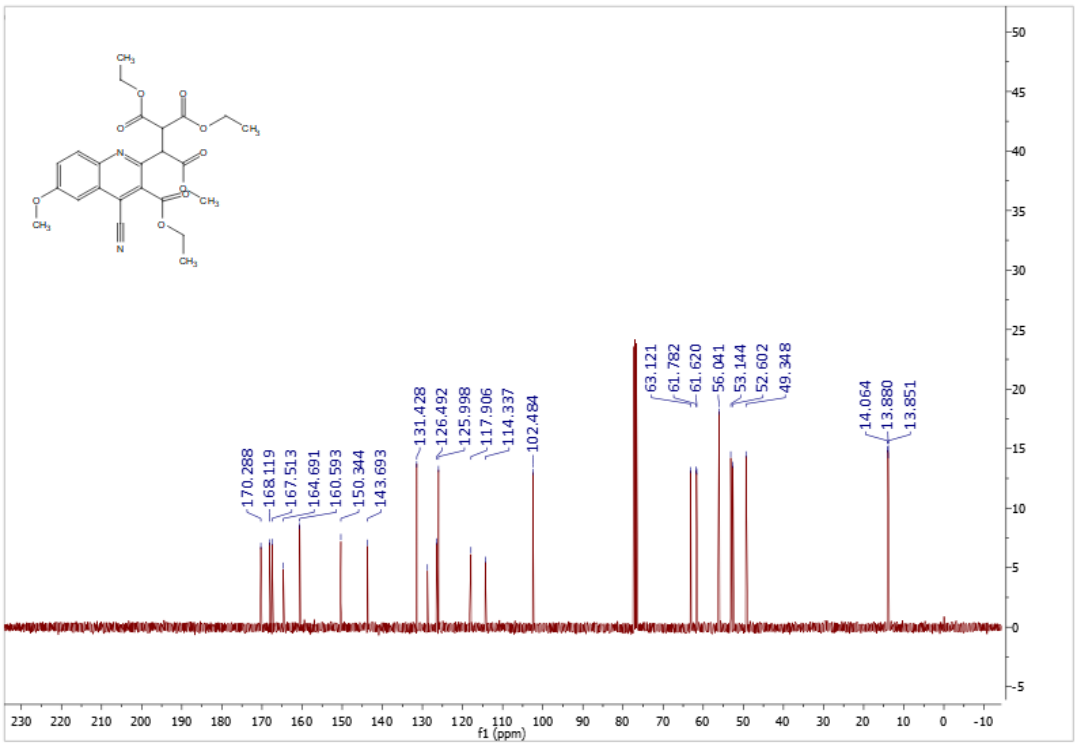
1,1-diethyl 2-methyl 2-(2-cyclohexyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) ethane-1,1,2-tricarboxylate (**4w**)



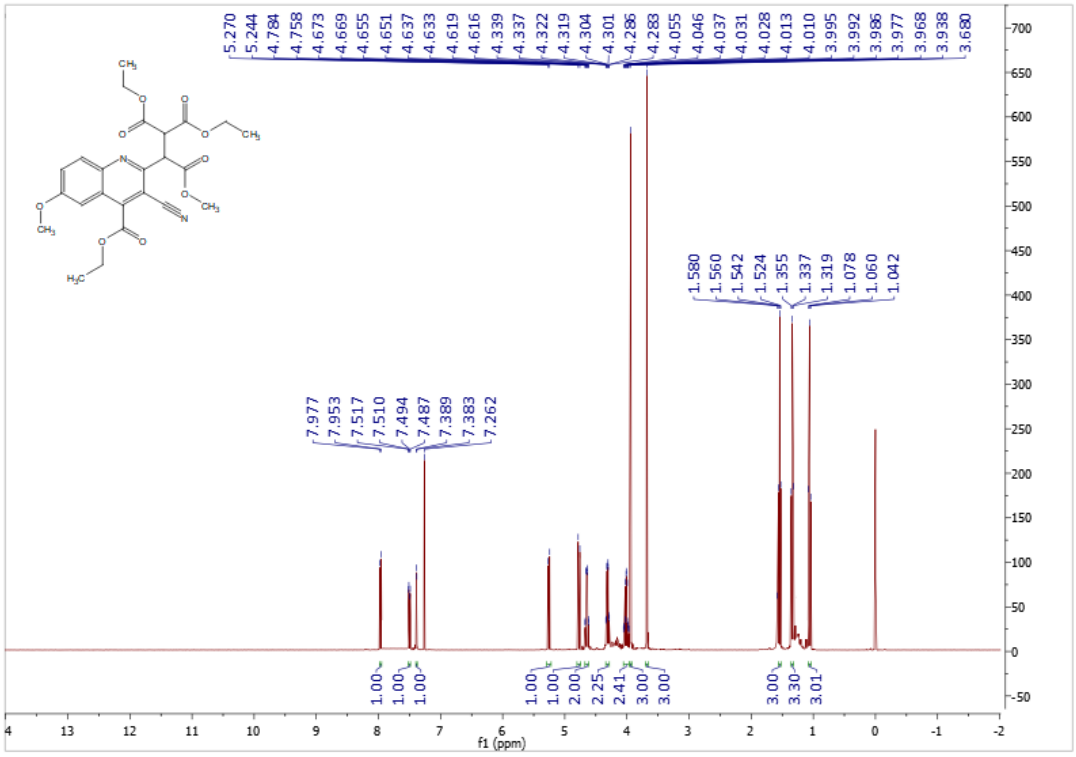


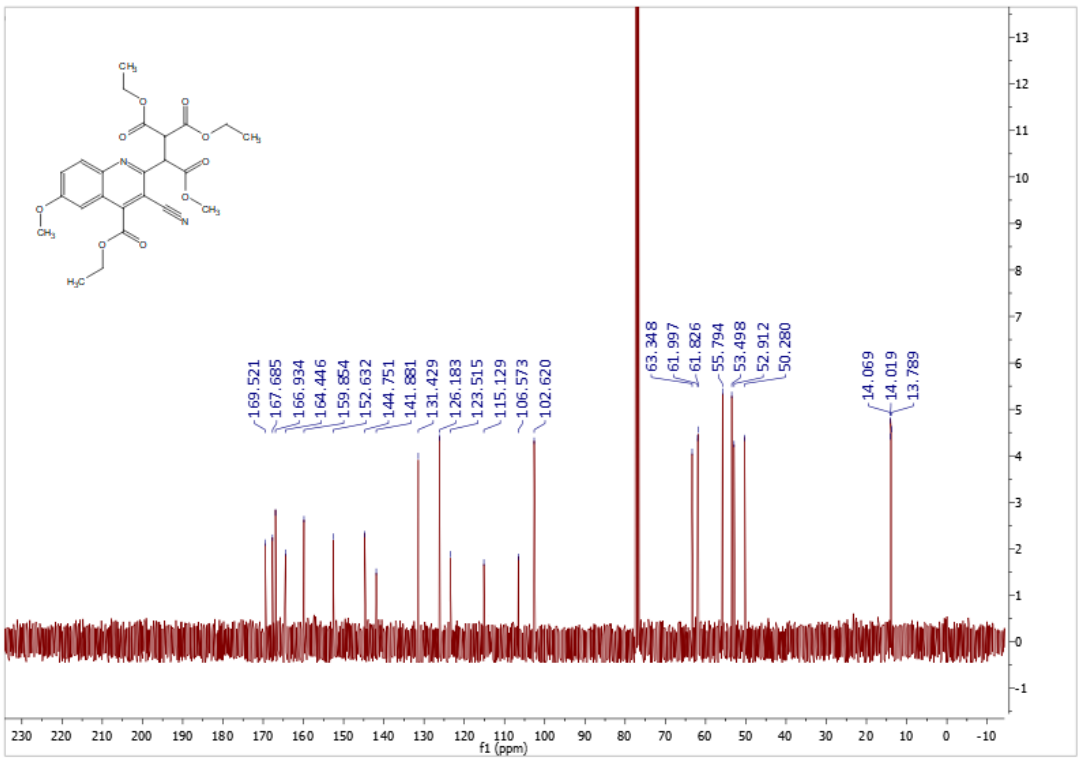
1,1-diethyl 2-methyl 2-(4-cyano-3-(ethoxycarbonyl)-6-methoxyquinolin-2-yl) ethane-1,1,2-tricarboxylate (**4x**)



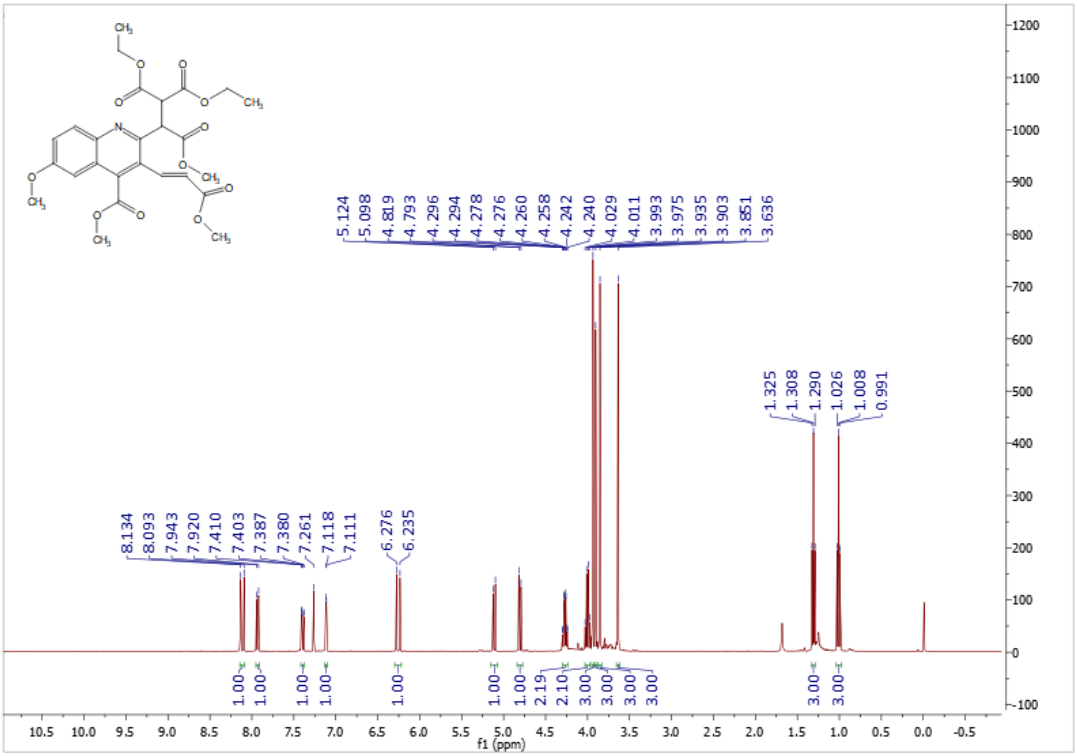


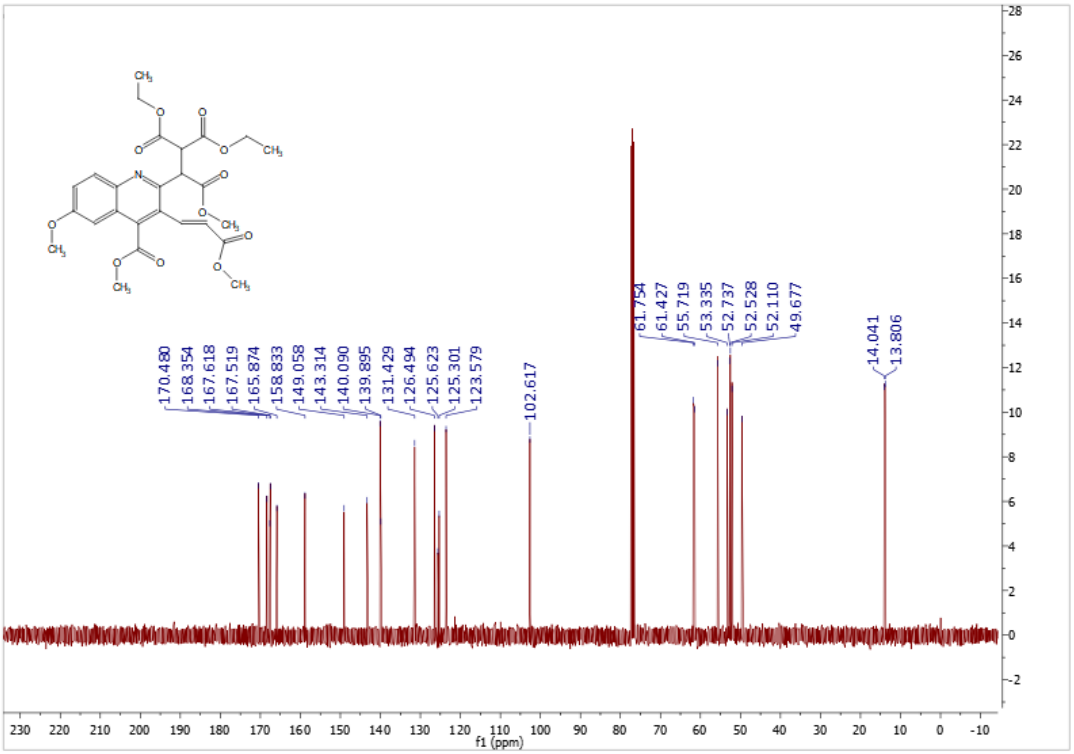
1,1-diethyl 2-methyl 2-(3-cyano-4-(ethoxycarbonyl)-6-methoxyquinolin-2-yl) ethane-1,1,2-tricarboxylate (**4x'**)



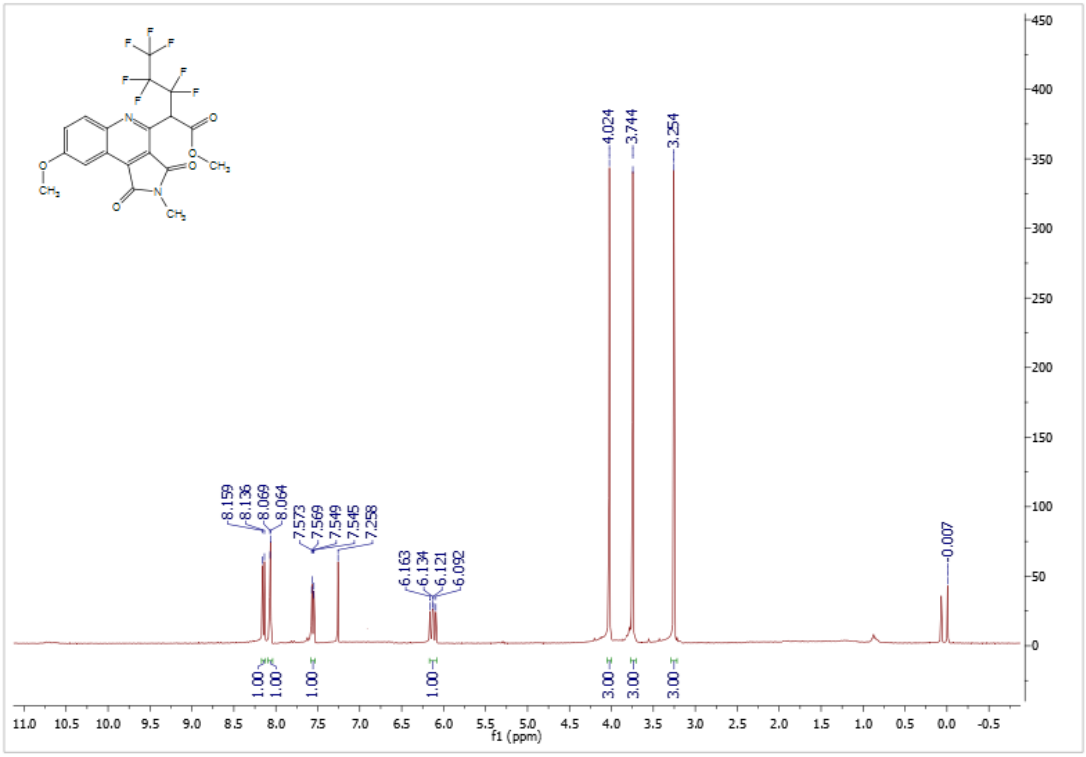


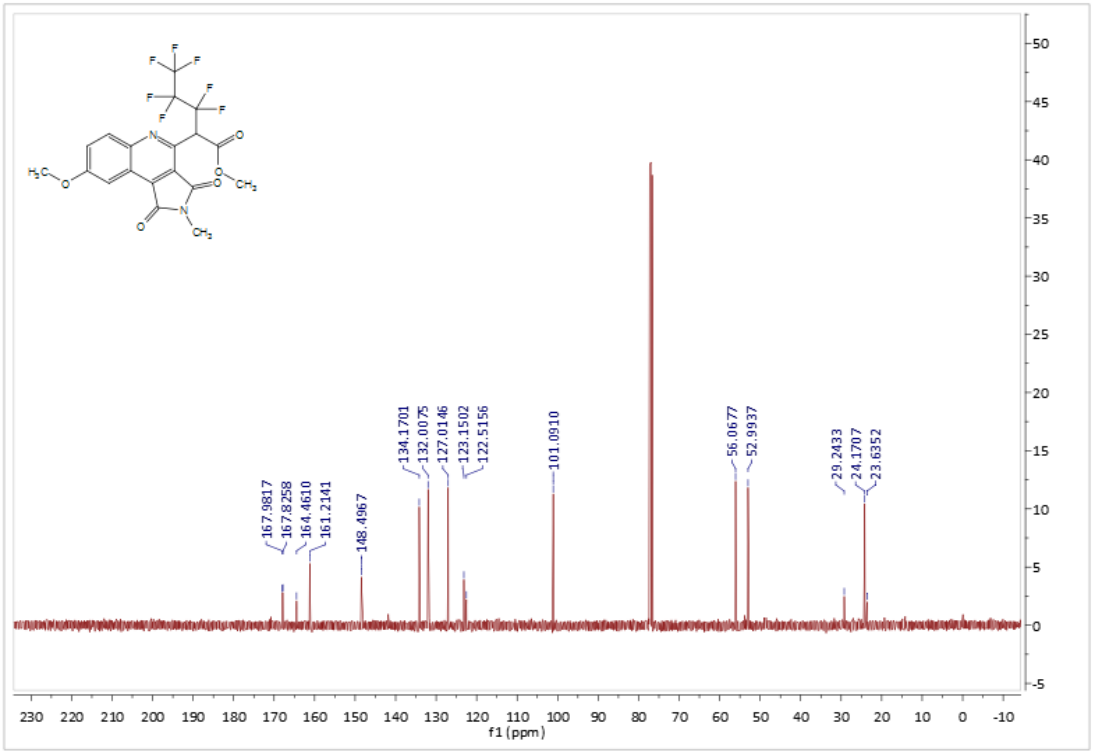
(E)-1,1-diethyl 2-methyl 2-(6-methoxy-3-(3-methoxy-3-oxoprop-1-en-1-yl)-4-(methoxycarbonyl) quinolin-2-yl)ethane-1,1,2-tricarboxylate (**4z**)

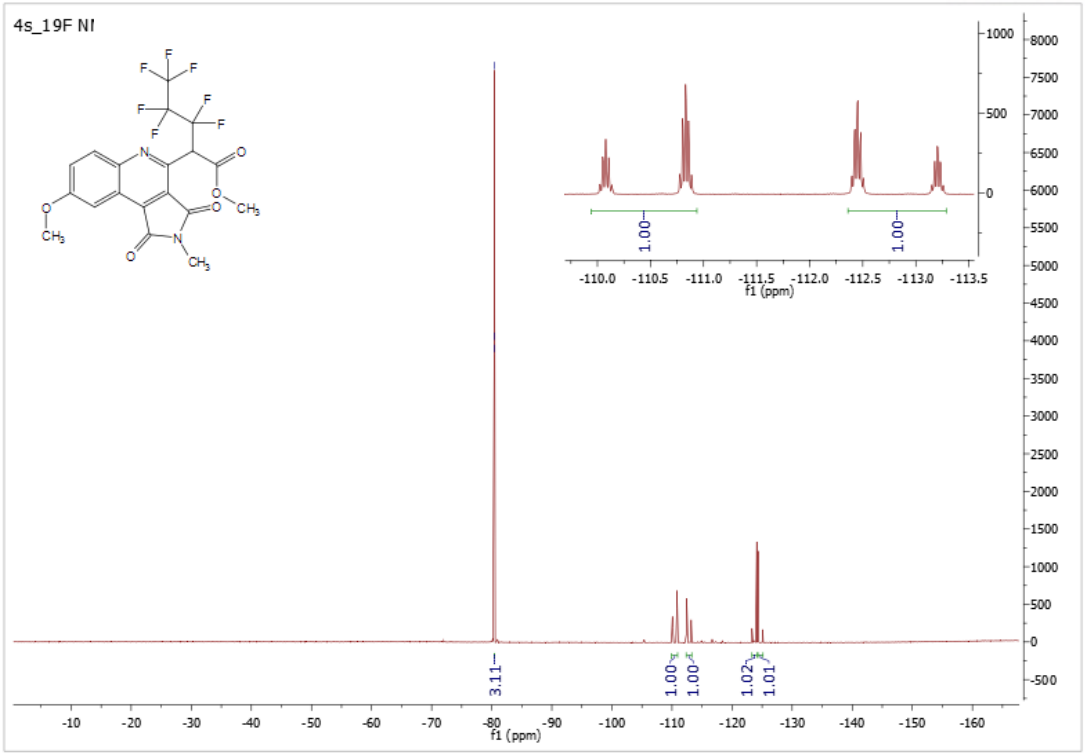




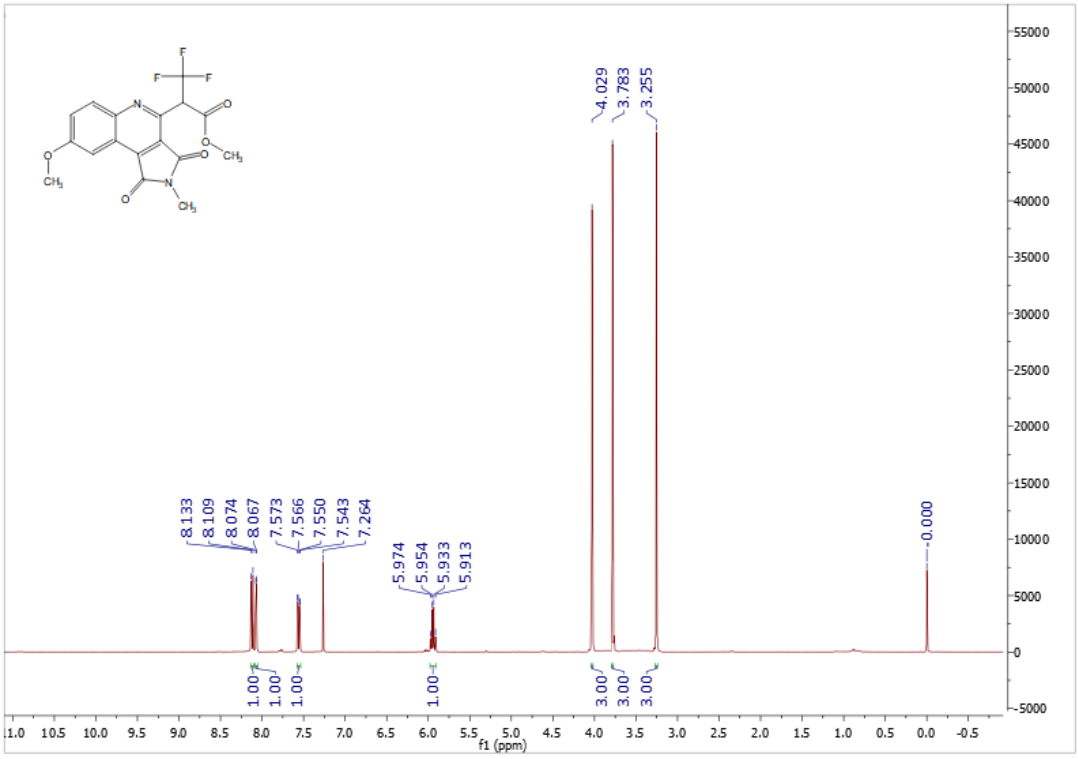
methyl 3,3,4,4,5,5,5-heptafluoro-2-(8-methoxy-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c] quinolin-4-yl) pentanoate (**4aa**):

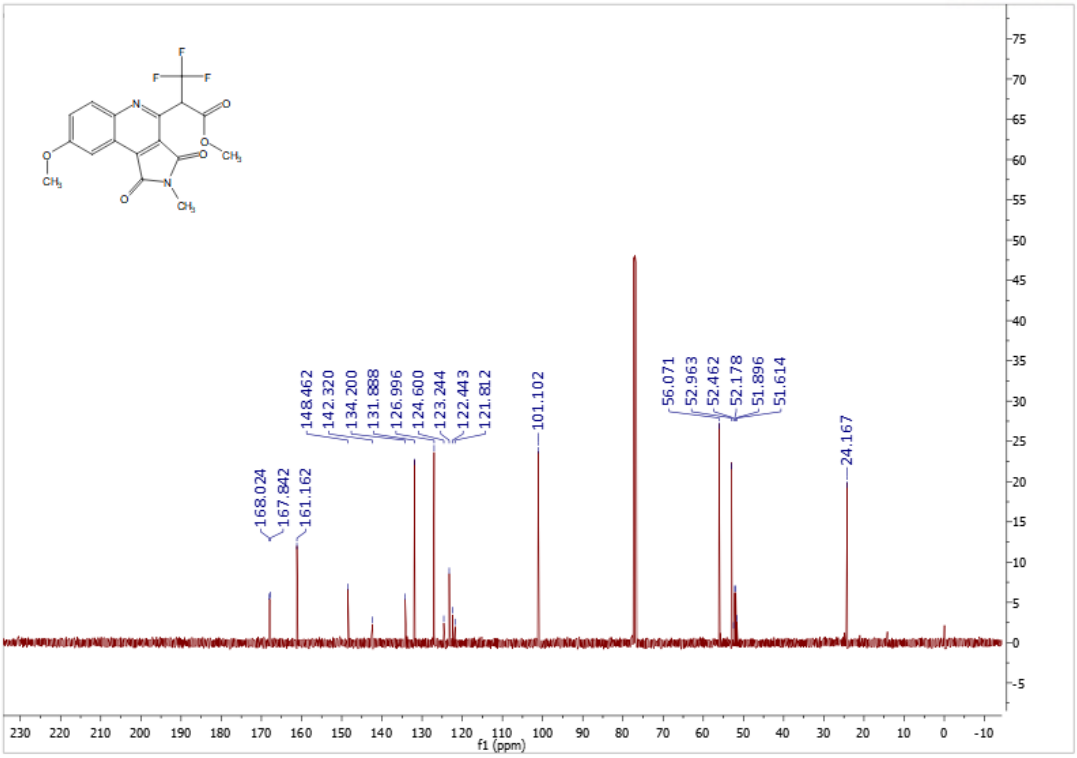


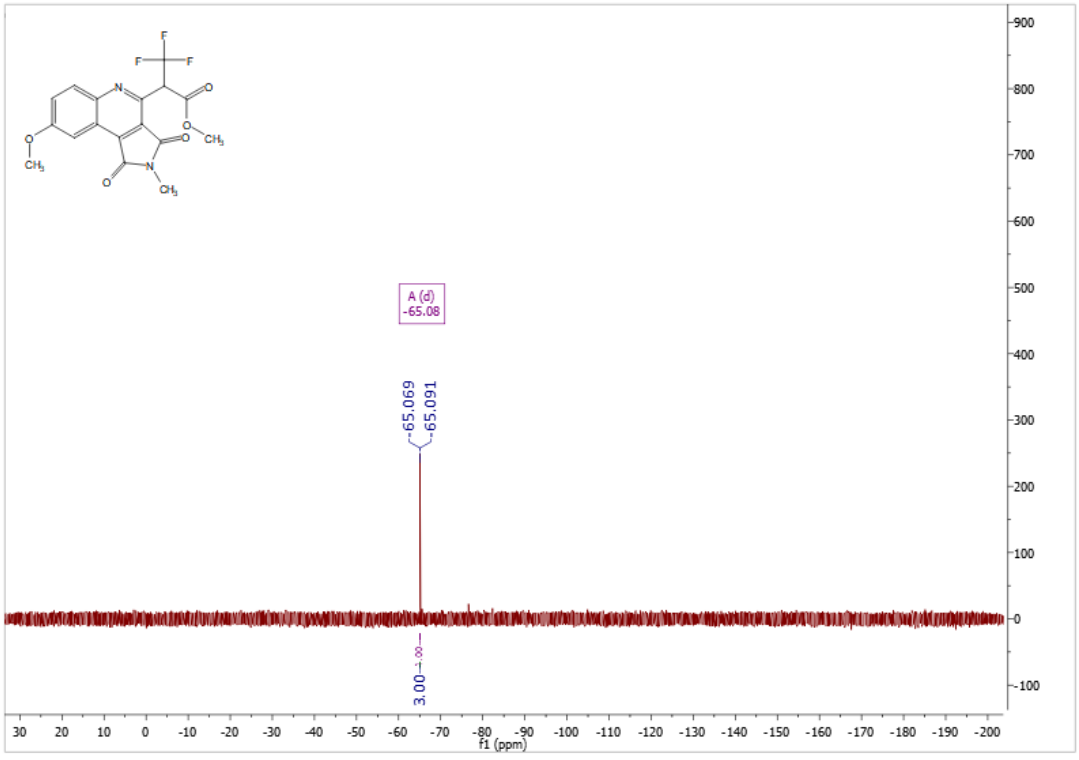




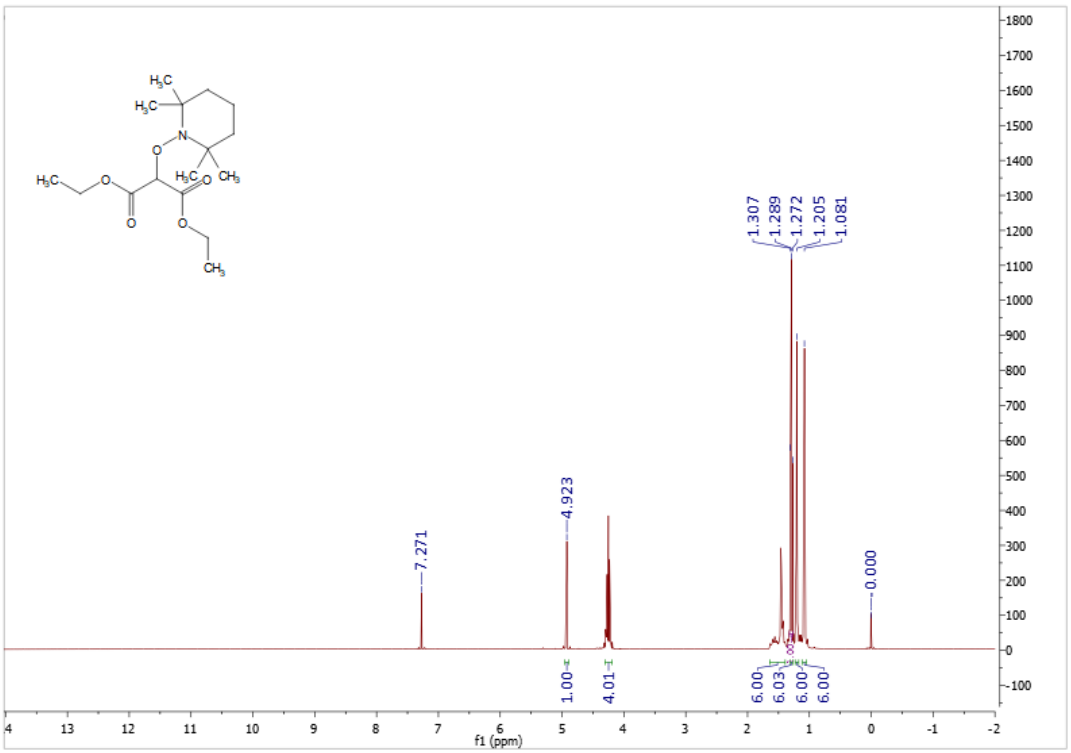
methyl 3,3,3-trifluoro-2-(8-methoxy-2-methyl-1,3-dioxo-2,3-dihydro-1H-pyrrolo[3,4-c]quinolin-4-yl)propanoate (**4ab**)







Diethyl 2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)malonate



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우선, 학부 3 학년때부터 인턴십을 시작으로, 대학원에 진학하여 학위를 마칠 때까지 아낌없는 가르침과 따끔한 지도로 저를 이끌어주신 저의 지도 교수님 박철민 교수님께 무한한 감사의 말씀을 올립니다. 처음 연구실에 발을 들이고 스포이드 하나 쉽게 쥐지 못하는 저를, 한 명의 연구자로 키워주셔서 감사드립니다. 부족한 면이 너무나도 많아 많은 실망과 더불어 심려를 끼쳐드려서 죄송합니다. 포기할 수 있었던 많은 순간에도 저를 제자로서 아껴주시고 끝까지 이끌어주신 것에 깊은 감사의 말씀을 드립니다. 정직하고 성실하지 못했던 모습은 반성하고 교수님의 가르침을 따라 교수님의 명성에 누가 되지 않도록 명심하며 노력하며 살겠습니다. 지도 교수로서 교수님의 헌신적인 지원을 은혜로 생각하며 발전하는 연구자가 되도록 열정을 다해 임하도록 하겠습니다.

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그리고, 형제자매와 같이 입학하기 전부터 졸업하는 순간까지 동병상련을 느끼며 옆에서 응원해준 많은 친구들에게 감사의 인사를 전합니다. 비록 이제 캠퍼스를 떠나 각자의 길로 나아가겠지만, 함께했던 우리의 지난 날들은 평생 잊지못한 순간들로 충만하였음을 기억합니다.

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