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# Quinolines: Novel Synthesis and Derivatives of Heterocyclic Bioactive Agents

## Abstract

Tuberculosis is a pulmonary disease that has ravaged the world throughout history. Even today, many developed and developing countries are experiencing this plight, made worse by the scourge of antibiotic-resistant bacteria.

*Mycobacterium tuberculosis's* class II fructose-1,6-bisphosphate aldolase presents an interesting target in the design of new therapies against this disease. Previous attempts to construct an inhibitor to this enzyme fell short due to poor selectivity or poor cellular uptake. However a new class of noncompetitive inhibitor based on 8-hydoxyquinoline-2-carboxylic acid presents a fresh approach. Preliminary studies indicate various modifications to this scaffold could be beneficial to its inhibitory efficacy.

Modifications made to the phenol ring of the quinoline included small hydrophobic moieties such as methyl groups and fluorine. Additionally various carboxylic acid derivatives were installed next to the nitrogen of the heteroring. These derivatives included esters, amides, carbamates and ureas, and heterocycles. Biochemical testing of these compounds is ongoing but is already showing promising results.

Many methods exist for the construction of quinoline rings systems, which can be utilized based on the pattern of substitution desired. Synthesis of heteroring-unsubstituted quinolines, however, has historically presented more of a challenge. Herein is described a novel method of cyclizing anilines with acrolein diethyl acetal to form these desired structures. This method produces quinolines with various substitutions on the phenyl ring in moderate to high yields without the use of harsh oxidants, extended reaction times, or organic solvents.

The Lewis base-catalyzed annulation of allenoates with alkene acceptors in [3+2] cycloadditions is a new but burgeoning field. Many acceptors have been used in these reactions, but the use of quinones is unprecedented. Due to the highly reactive nature of quinones, it became necessary to screen various Lewis bases that would catalyze the reaction without being oxidized by the quinone. This is an ongoing investigation but is promising in the production of novel carbocycles that have potential benefits in medicinal chemistry.

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# QUINOLINES: NOVEL SYNTHESIS AND DERIVATIVES OF HETEROCYCLIC BIOACTIVE AGENTS

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A Dissertation

Presented to

The Faculty of Natural Sciences and Mathematics

University of Denver

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In Partial Fulfillment

of the Requirements for the Degree

Doctor of Philosophy

---

by

Ginelle A. Ramann

June 2016

Advisor: Dr. Bryan J. Cowen

Author: Ginelle A. Ramann
Title: QUINOLINES: NOVEL SYNTHESIS AND DERIVATIVES OF HETEROCYCLIC BIOACTIVE AGENTS
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# LIST OF ABBEVIATIONS AND ACRONYMS

| | |
|---|---|
| Å | Ångstrom |
| $\alpha$ | alpha |
| $\beta$ | beta |
| $\delta$ | delta |
| $\Delta$ | delta (heat) |
| $\gamma$ | gamma |
| $\pi$ | pi |
| $\sigma$ | sigma |
| °C | degrees Celcius |
| AcOH | Acetic acid |
| ALS | Amyotrophic Lateral Sclerosis |
| aq. | aqueous |
| ATP | Adenosine triphosphate |
| $BBr_3$ | Boron tribromide |
| BINOL | 1,1'-Bi-2-naphthol |
| cat. | Catalytic amount |
| $CCl_4$ | Carbon tetrachloride |
| $CDCl_3$ | Deuterated chloroform |
| $CH_2Cl_2$ | Dichloromethane |
| $(CH_3)_2CO$ | Acetone |
| $CH_3CN$ | Acetonitrile |
| CO | Carbon monoxide |
| $CO_2$ | Carbon dioxide |
| $(COCl)_2$ | Oxalyl chloride |
| $Cs_2CO_3$ | Cesium carbonate |
| CuCN | Copper cyanide |
| DABCO | 1,4-diazabicyclo[2.2.2]octane |
| DCM | Dichloromethane |
| DDQ | 2,3-dichloro-5,6-dicyano-p-benzoquinone |
| DIPEA | Diisopropylethylamine |
| DMAP | 4-dimethylaminopyridine |
| DMF | N,N-dimethylformamide |
| DMSO | Dimethylsulfoxide |

| | |
|---|---|
| DMSO-$d^6$ | Deuterated DMSO |
| DNA | Deoxyribonucleic acid |
| DVM | Doebner-Von Miller quinoline synthesis |
| eq | equivalent |
| $Et_2O$ | Diethyl ether |
| EtOAc | Ethyl acetate |
| EtOH | Ethanol |
| g | gram |
| Glu | Glutamate |
| $H_2O$ | Water |
| $H_2SO_4$ | Sulfuric acid |
| HCl | Hydrochloric acid |
| His | Histidine |
| HIV | Human Immunodeficiency Virus |
| $HNEt_2$ | Diethylamine |
| Hz | Hertz |
| $IC_{50}$ | Inihibitory Concentration inhibiting 50% of growth |
| $K_2CO_3$ | Potassium carbonate |
| kcal | kilocalorie |
| KOH | Potassium hydroxide |
| $KO^tBu$ | Potassium tert-butoxide |
| $K_m$ | Substrate concentration at ½ maximum rate ($V_{max}$) |
| Leu | Leucine |
| $LiAlH_4$ | Lithium aluminum hydride |
| Lys | Lysine |
| m-CPBA | meta-chloroperoxybenzoic acid |
| MHz | Megahertz |
| μM | micromolar |
| mL | milliliter |
| mM | millimolar |
| M | molar |
| $Me_2SO_4$ | Dimethyl sulfate |
| MeOH | Methanol |
| mg | milligram |
| mmol | millimole |
| mol | mole |
| MRSA | Methicillin-resistant Staphylococcus aureus |
| MS | Molecular sieves |
| Mt | Mycobacterium tuberculosis |

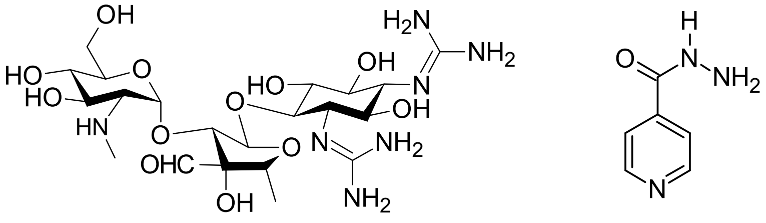
| | |
|---|---|
| MtFBA | Mycobacterium tuberculosis fructose-1,6-bisphosphate aldolase |
| $Na_2SO_4$ | Sodium sulfate |
| $NaBH_4$ | Sodium borohydride |
| NaCl | Sodium chloride |
| NaCN | Sodium cyanide |
| $NaHCO_3$ | Sodium bicarbonate |
| $NaN_3$ | Sodium azide |
| NaOH | Sodium hydroxide |
| $NBu_4Cl$ | Tetrabutylammonium chloride |
| $NEt_3$ | Triethylamine |
| $NH_3$ | Ammonia |
| $NH_4Cl$ | Ammonium chloride |
| NMR | Nuclear Magnetic Resonance |
| [O] | Oxidant |
| Pd/C | Palladium on Carbon |
| PG | Protecting group |
| $PPh_3$ | Triphenylphosphine |
| RNA | Ribonucleic acid |
| r.t. | Room temperature |
| SaFBA | MRSA fructose-1,6-bisphosphate aldolase |
| $SeO_2$ | Selenium (IV) oxide |
| $S_N2$ | Bimolecular nucleophilic substitution |
| $S_NAr$ | Aromatic nucleophilic substitution |
| $SO_2$ | Sulfur dioxide |
| $SOCl_2$ | Thionyl chloride |
| TBAI | Tetrabutylammonium iodide |
| t-BuOH | tert-Butyl alcohol |
| $Tf_2O$ | Trifluoromethanesulfonic anhydride |
| THF | Tetrahydrofuran |
| Thr | Threonine |
| TLC | Thin-layer chromatography |
| TsCl | para-toluenesulfonyl chloride |
| TsOH | para-toluenesulfonic acid |
| Val | Valine |
| $V_{max}$ | Maximum rate of reaction of an enzyme |

# 1 INTRODUCTION TO TUBERCULOSIS AND ANTI-TUBERCULOSIS DRUG RESEARCH

## 1.1 The problem of tuberculosis

Tuberculosis (TB) is a pulmonary disease that affects millions of people and is a leading cause of death worldwide. According to the most recent World Health Organization report, an estimated 9.6 million new cases of active tubercular disease were reported in 2014, and 1.5 million deaths were attributed to this illness [1]. In fact, TB has overtaken HIV as the leading cause of death due to infectious disease [2]. In addition, an estimated two billion people harbor an asymptomatic form of tuberculosis known as latent TB infection which poses a risk for subsequent emergence of the disease in the infectious form [3].

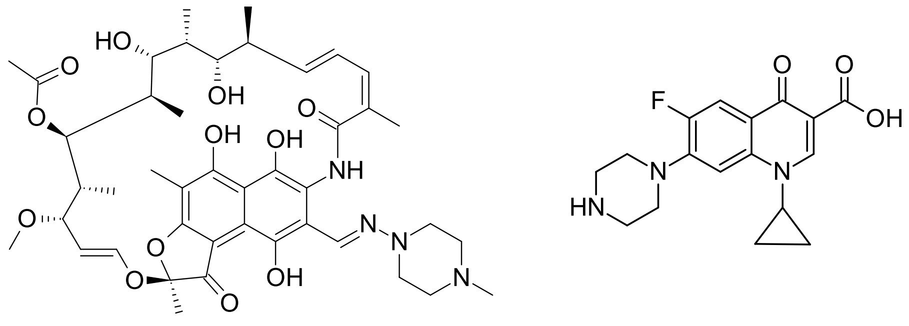
The German physician Robert Koch identified the bacillus *Mycobacterium tuberculosis* as the causative agent of tuberculosis disease in 1882 [4]. However it was not until the 1940s that the earliest chemotherapies against the bacterium were developed. The first of these, the aminoglycoside streptomycin (**I**, *Figure 1.1.1*) which was isolated from the bacterium *Streptomyces griseus* in 1944 [3], was shown to cause cell death by inhibiting protein synthesis on the ribosome [5]. Then in 1952, the pyridine-based isoniazid (**II**) was shown to have antitubercular activity via inhibition of mycolic acid production which is needed for structural integrity of the cell wall [6].



I II

*Figure 1.1.1 Anti-TB drugs Streptomycin and Isoniazid*

However, these therapies were shown to quickly lose efficacy due to development of bacterial resistance, necessitating the expansion of available treatments. This led to the identification of dozens of drug candidates, many of which are used regularly today. These therapeutics are organized into five groups, based on factors such as efficacy, potency, and drug class. First-line anti-TB drugs, including the two most potent drugs [7] isoniazid and rifampin (**III**, *Figure 1.1.2*), a semisynthetic compound that inhibits RNA synthesis [8], are used to treat drug-susceptible bacteria. The current TB treatment regimen, designed in the 1970s and termed Direct Observed Therapy (DOT), involves a six-month course of several of these first-line drugs.



III IV

*Figure 1.1.2 Current TB drugs Rifampin and Ciprofloxacin*

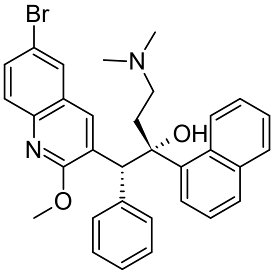
Adding to the problem of global tuberculosis incidence is the rapid upswing in prevalence of multidrug-resistant TB. MDR-TB is defined as resistance to the first-line drugs isoniazid and rifampin. When a case of TB is diagnosed as multidrug-resistant, the use of second-line drugs is indicated [3]. These second-line treatments include streptomycin and fluoroquinolones such as ciprofloxacin (**IV**, *Figure 1.1.2*), which inhibits bacterial DNA replication [9]. Even more concerning is the increasing prevalence of extensively drug resistant TB (XDR-TB), which is defined as resistance to any fluoroquinolone and an injectable second-line drug in addition to all first-line drugs [7]. An estimated 3.3% of all newly reported TB cases and 20% of previously treated cases are determined to be multidrug resistant; of those, 9.7% are considered extensively drug resistant [1].

While the occurrence of drug resistance has been acknowledged since the advent of streptomycin therapy, the sources and mechanisms of this phenomenon have only been amply studied in the last decade or so [10]. A few of the underlying elements that contribute to resistance stem from intrinsic features of *M. tuberculosis*. For instance, mycobacteria possess thick hydrophobic cell walls that impede pharmacological molecules from entering the cell. Also, these bacteria are able to essentially conceal themselves from the host immune response by hiding out within the host's own macrophages and phagocytes [2]. As opposed to intrinsic resistance, acquired resistance is due to genetic changes that result in deactivation of the drug or modification of the drug target [11]. As an example, mutations that deactivate efflux pump restrictor genes can cause overexpression of these pumps [12], which are used by the bacteria for general detoxification purposes, including the extrusion of foreign drug molecules [13]. Interestingly, the probability of a spontaneous mutation that confers this type of drug resistance is abysmally small; however, this probability is amplified by inappropriate drug prescription and inadequate patient adherence to the treatment regimen [10].

## 1.2 Current research into new drugs

The expense, duration, and complexity of the current tuberculosis treatment regimen, as well as the global problem of drug resistance, has spurred a profusion of research into new possible anti-tuberculosis therapies [4]. These investigations encompass diverse structural designs, ranging from small heterocyclic molecules to larger polysaccharides and polypeptides, with a range of bacterial targets.

Publication of the full sequence of the *M. tuberculosis* genome by Barrell and coworkers in 1998 [14] greatly expanded the opportunity for research into new anti-TB drugs via direct targeting of specific bacterial metabolic pathways. A comprehensive review by Mdluli and Spigelman in 2006 [15] summed up the known targets that were actively being addressed at the time. These targets included amino acid and fatty acid biosynthesis, DNA synthesis, regulatory proteins, the glyoxylate shunt, and the stringent response enzyme. More recently, Zumla, Nahid, and Cole published a review in 2013 [3] describing the progress made in the search for new drug candidates. One such candidate was the diarylquinoline referred to as bedaquiline (**V**, *Figure 1.2.1*), which had been introduced by Andries and coworkers in 2005 [16]. While this compound showed promising inhibitory activity against the *Mycobacterium tuberculosis* ATP synthase, it also presented challenges including accumulation in tissues and potential to induce arrhythmia [3].



**V**

*Figure 1.2.1 Potential Mt ATP synthase inhibitor Bedaquiline*

In addition, the *M. tuberculosis* flavoenzyme DprE1[*], which catalyzes the production of the arabinose precursor that is necessary for proper cell wall assembly, was determined to be a vulnerable target for several classes of inhibitory compounds [3]. In 2009, Makarov and coworkers [17] developed BTZ038[†] (**VI**, *Figure 1.2.2*), a benzothiazinone that exhibited promising antimycobacterial activity by inhibiting this enzyme. Also in 2009, Brodin *et al.* [18] reported the anti-DprE1 activity of various nitrobenzamides, of which *N*-[2-(4-methoxyphenoxy)ethyl]-3,5-dinitrobenzamide (**VII**) gave encouraging inhibitory results. In 2010, two other candidates emerged which took advantage of the susceptibility of DprE1. One of these, described by Reddy and coworkers

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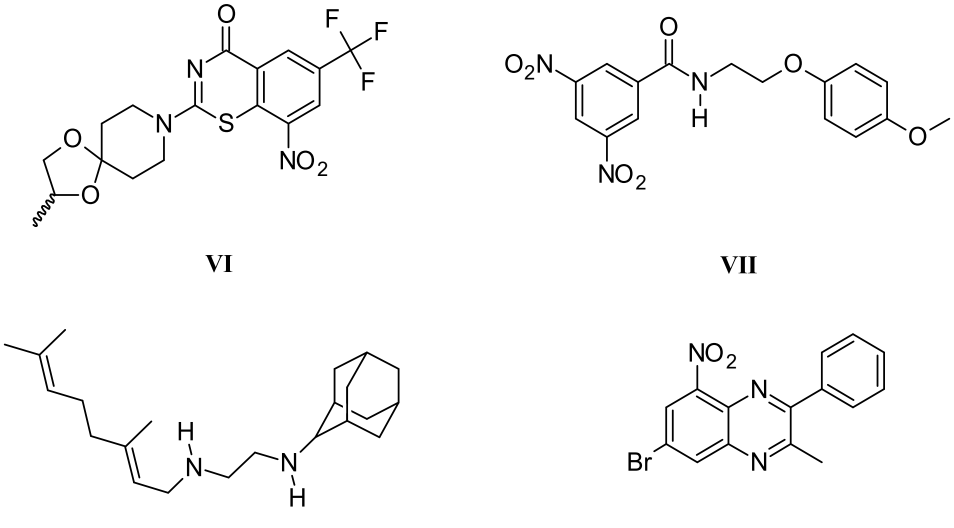
[*] Decaprenylphosphoryl-β-D-ribose 2′-epimerase

[†] 2-(2-methyl-1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-8-nitro-6-(trifluoromethyl)-4H-benzo[e][1,3]thiazin-4-one

[19], is known as SQ109[*] (**VIII**). The other was identified by Cole *et al.* [20] and termed VI-9376[†] (**IX**).



**VI** **VII**

**VIII** **IX**

*Figure 1.2.2 Potential Mycobacterium tuberculosis DprE1 inhibitors*

Chibale and coworkers have been particularly industrious in the search for small molecules with anti-Mt properties. In 2012, they disclosed a series of nitroimidazooxazine derivatives that displayed sub-micromolar $MIC_{99}$[‡] values against *M. tuberculosis* strain H37Rv, the most potent being a benzaldehyde derivative[§] (**X**, *Figure 1.2.3*). Then in 2014 they introduced an assortment of 2-amino-4-(2-pyridyl)thiazole compounds, the most potent of which included a bromobenzamide moiety[**] (**XI**). However, despite their promising activity against *M. tuberculosis*, these latter compounds also exhibited poor solubility, high cytotoxicity, and metabolic instability.

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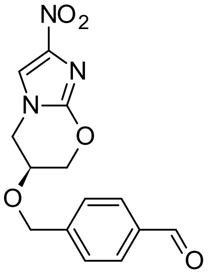
[*] *N*-geranyl-*N*'-(2-adamantyl) ethane-1,2-diamine

[†] 7-bromo-2-methyl-5-nitro-3-phenylquinoxaline

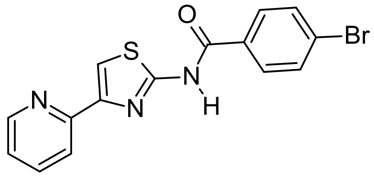
[‡] Minimum Inhibitory Concentration inhibiting > 99% of bacterial growth.

[§] 4-({[(6*S*)-2-nitro-6,7-dihydro-5*H*-imidazo[2,1-*b*][1,3]oxazin-6-yl]oxy}methyl)benzaldehyde

[**] 4-bromo-*N*-[4-(pyridin-2-yl)-1,3-thiazol-2-yl]benzamide



**X**



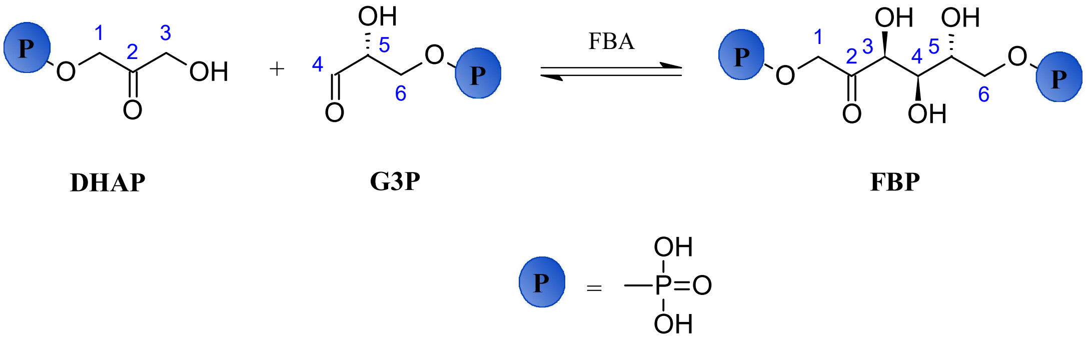
**XI**

*Figure 1.2.3 Potential anti-Mycobacterium tuberculosis compounds*

This theme of novel tuberculosis drug research has grown exponentially just in the last year, with several such studies published in 2015, each identifying small molecules that are directed at highly diverse targets. One representative example came from Carroll and coworkers who used high-throughput screening to find model substrates that inhibit sulfur metabolism in mycobacteria [21]. In addition, Yogeeswari *et al.* performed computational studies to identify potent inhibitors of N-acetylglucosamine-1-phosphate uridyltransferase (glmUMtb), an enzyme required for cell wall integrity [22]. Also, Sririam and coworkers reported on a series of aminoquinoline derivatives that showed potency against the *M. tuberculosis* DNA gyrase (GyrB), which relieves strain during DNA unwinding [23]. Zhang, Lu, and Ding, among others, introduced a group of pyridine-3-carboxamides with promising anti-tubucular activity; however, the mode of action and specific target of these compounds remain unknown [24]. As a final example, Das and coworkers disclosed a series of azatidinone derivatives that exhibit dual functionality as both β-ketoacyl CoA reductase (FabG4) and 3(R)-hydroxyacyl CoA dehydratase (HtdX) inhibitors [25]. While not exhaustive, this list shows the scope of research being conducted on this issue.

## 1.3 Class II fructose-1,6-bisphosphate aldolase as a drug target

Energy gains and expenditures via various metabolic pathways are fundamental to the vitality of *Mycobacterium tuberculosis*. These pathways involve many steps and enzymes, all of which are potential targets for directed drug research. One such enzyme is the class II fructose-1,6-bisphosphate aldolase (FBA) that catalyzes the reversible aldol addition of dihydroxyacetone phosphate (DHAP) with glyceraldehyde-3-phosphate (G3P) to give fructose-1,6-bisphosphate (FBP, *Scheme 1.3.1*), a process that is present in the glycolysis and gluconeogenesis pathways of these bacteria [26].



*Scheme 1.3.1 Reversible aldol addition of dihydroxyacetone phosphate with glyceraldehyde-3-phosphate to give fructose-1,6-bisphosphate*[*]

FBA has been shown to be expressed to higher levels by *M. tuberculosis* under hypoxic conditions, such as within necrotic pulmonary lesions [27], and the requirement of this enzyme for Mt viability was demonstrated with a series of elegant experiments by

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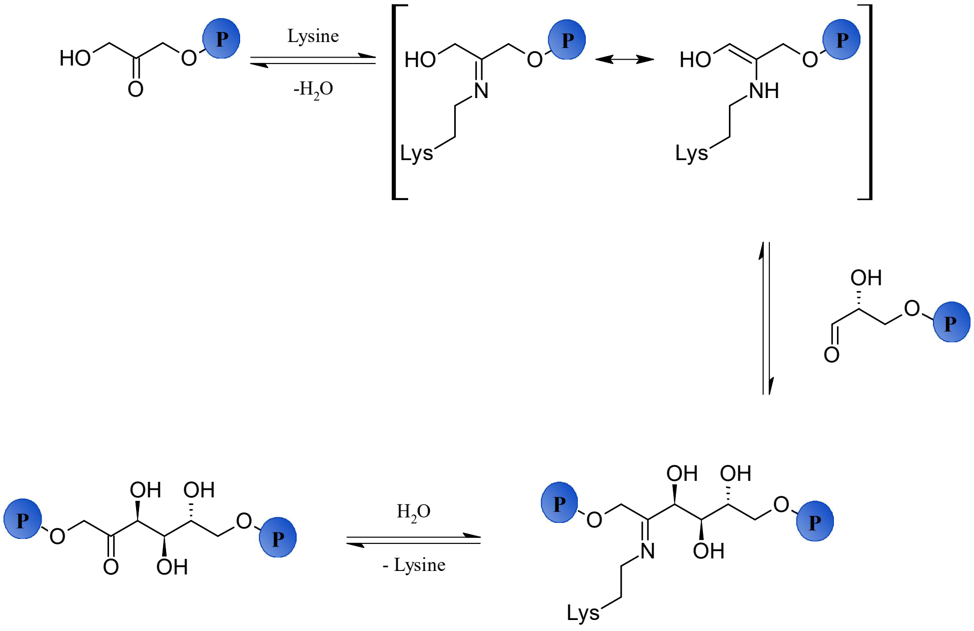
[*] Phosphate ($H_2PO_3$) moiety depicted as a P inside a blue circle.

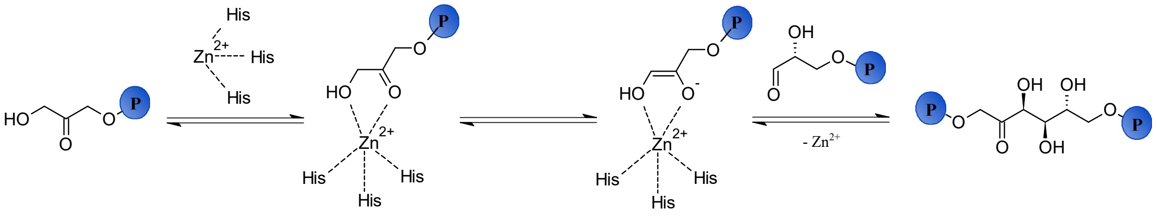
Ehrt and coworkers in 2014 [26]. By engineering a strain of *M. tuberculosis* in which FBA is depleted, they observed a loss of viability *in vitro* when the bacteria were cultured with a single carbon source; they also detected the eradication of both acute and chronic infection in mouse models. While this phenomenon has yet to be demonstrated in humans, it is highly likely that depletion of FBA in human mycobacterial infection would have similar consequences.

Two classes of aldolase occur in nature – class I and class II. While the two classes catalyze the same process, they perform the task in mechanistically divergent ways [27]. The class I aldolase initiates the catalysis by forming an intermediate Schiff base between DHAP and an active site lysine residue. Through tautomerization, an enamine is formed, which then attacks G3P. A water molecule then reforms the carbonyl, producing FBP and regenerating the lysine side chain (*Scheme 1.3.2)* [28].



*Scheme 1.3.2 Mechanism of the class I FBA*

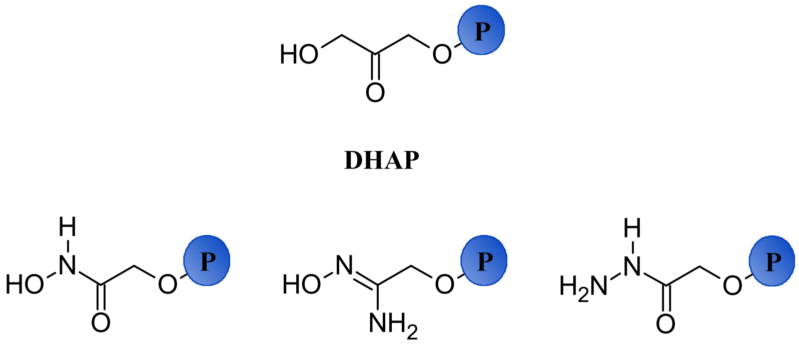
Conversely, class II aldolases utilize a zinc ion to achieve catalysis. Histidine-linked $Zn^{2+}$ acts as a Lewis acid and coordinates with both the carbonyl and hydroxyl oxygens of DHAP, stabilizing the base-assisted enolate formation. This intermediate then attacks G3P, and formation of FBP allows the zinc ion to dissociate and reenter the catalytic cycle (*Scheme 1.3.3*) [28].



*Scheme 1.3.3 Mechanism of the class II FBA*

Class I and class II aldolases exhibit almost no similarity in amino acid sequence and are assumed to have evolved independently. In addition to their mechanistic and sequence divergence, these two enzymes differ in their distribution among species. While class I aldolases are present in “higher” organisms such as animals (including humans), plants, and some prokaryotes, class II aldolases are exclusively found in bacteria, fungi, and protozoa [29]. This dichotomy is fundamental to the success of this enzyme as a potential drug target; a small molecule specific to inhibition of the bacterial class II aldolase would be less likely to be toxic to the human host. Furthermore, the amino acid sequence of the class II aldolase is 100% conserved among all strains of *M. tuberculosis*, including MDR- and XDR-TB strains [27].

Taken together, these characteristics make this enzyme extremely attractive as a potential drug target. This has not gone unnoticed; over the last few decades several prospective inhibitors have been introduced. Initially, these potential inhibitors were targeted to be mimics of DHAP (*Figure 1.3.1*), designed to competitively impede substrate binding in the active site of FBA. The first such mimic, phosphoglycolohydroxymate (PGH, **XII**), was introduced in 1973 by Lewis and Lowe, who envisioned it as a broad inhibitor of both classes of aldolase as well as triosephosphate isomerase [30]. Therisod and coworkers [31] expanded on this theme with the introduction of amidoxime (**XIII**) and hydrazide (**XIV**) derivatives of PGH. These latter two were shown to be less potent inhibitors than PGH, but they proved to be more selective for the class II aldolase active site.

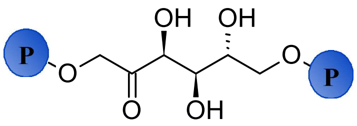


**DHAP**

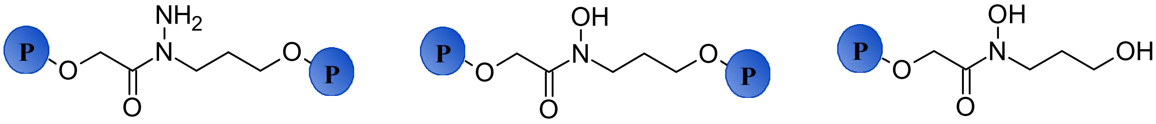
**XII** **XIII** **XIV**

*Figure 1.3.1 Hydroxamide, hydrazine, and hydrazide DHAP mimics*

Then in 2008 Therisod looked at inhibitors targeting the downstream FBP product (*Figure 1.3.2*). These included hydrazide and hydroxamide derivatives (**XV**, **XVI**, **XVII**). Compound **XVI** showed promising activity with high selectivity for class II over class I aldolases and low-nanomolar inhibitory concentrations in biological assays. However, *in vitro* tests showed significantly reduced activity.



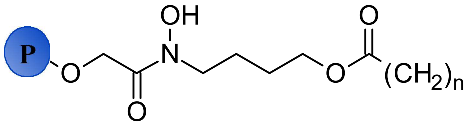
**FBP**



**XV** **XVI** **XVII**

*Figure 1.3.2 Hydrazide and hydroxamide FBP mimics*

In 2010 [32] this group attempted to improve the *in vitro* inhibition of these FBP mimics by replacing one phosphate group with a lipophilic moiety (**XVIII**, *Figure 1.3.3*). However, it showed no advantage over their previous analogs for *in vitro* inhibitory efficacy. This indicates that the phosphate moiety, while essential for potent active-site inhibition, interferes with the compound’s ability to cross the lipophilic barrier into the cell’s interior.

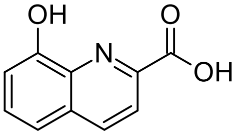


**XVIII**

*Figure 1.3.3 Hydroxamide FBP mimic with alkyl ester*

All aldolases exhibit high substrate specificity for DHAP, and only a select few substitutions of the phosphate ester moiety are tolerated in the active site [33]. This severely limits the number and type of DHAP and FBP mimics that would be able to bind in the active site and provide competitive inhibition. However, there is significantly more tolerance for compounds to bind out of the active site, thereby providing uncompetitive or noncompetitive inhibition.

In 2013, through extensive enzymatic and structure-based screening, Pegan and coworkers [27] identified 8-hydroxyquinoline-2-carboxylic acid (HCA, **XIX**, *Figure 1.3.4*) as a prospective scaffold for a class II FBA inhibitor. While biochemical assays showed HCA to reduce MtFBA activity by 95% at a concentration of 1 mM, kinetic studies of HCA interaction clearly showed a decreased $V_{max}$, as compared to substrate binding, while $K_m$ remained constant, indicating a noncompetitive interaction.



**XIX**

*Figure 1.3.4 MtFBA-inhibitor lead compound 8-hydroxyquinoline-2-carboxylic acid*

Once the binding mechanism of HCA with the class II FBA was determined, this group further explored the specifics of this interaction by capturing the enzyme with HCA in its binding site and deciphering the crystal structure of the complex. From this crystal structure they ascertained several interesting features of HCA binding. Not only does this molecule bind at a site outside of – but adjacent to – the substrate-binding pocket, it also alters the conformation of the active site (*Figure 1.3.5,* **A** and **B**). By forming a trident coordination with zinc and displacing the so-called "Z-loop" which contains the histidine residues that coordinate the $Zn^{2+}$, HCA accomplishes two tasks: it blocks natural substrates (DHAP or FBP) from accessing the active site and also sequesters the zinc ion, disallowing its coordination with those substrates (**C**). In addition the crystal structure showed supplementary stabilization of HCA by hydrogen bonding interactions with nearby glutamic and aspartic acid residues (**D**) [27].

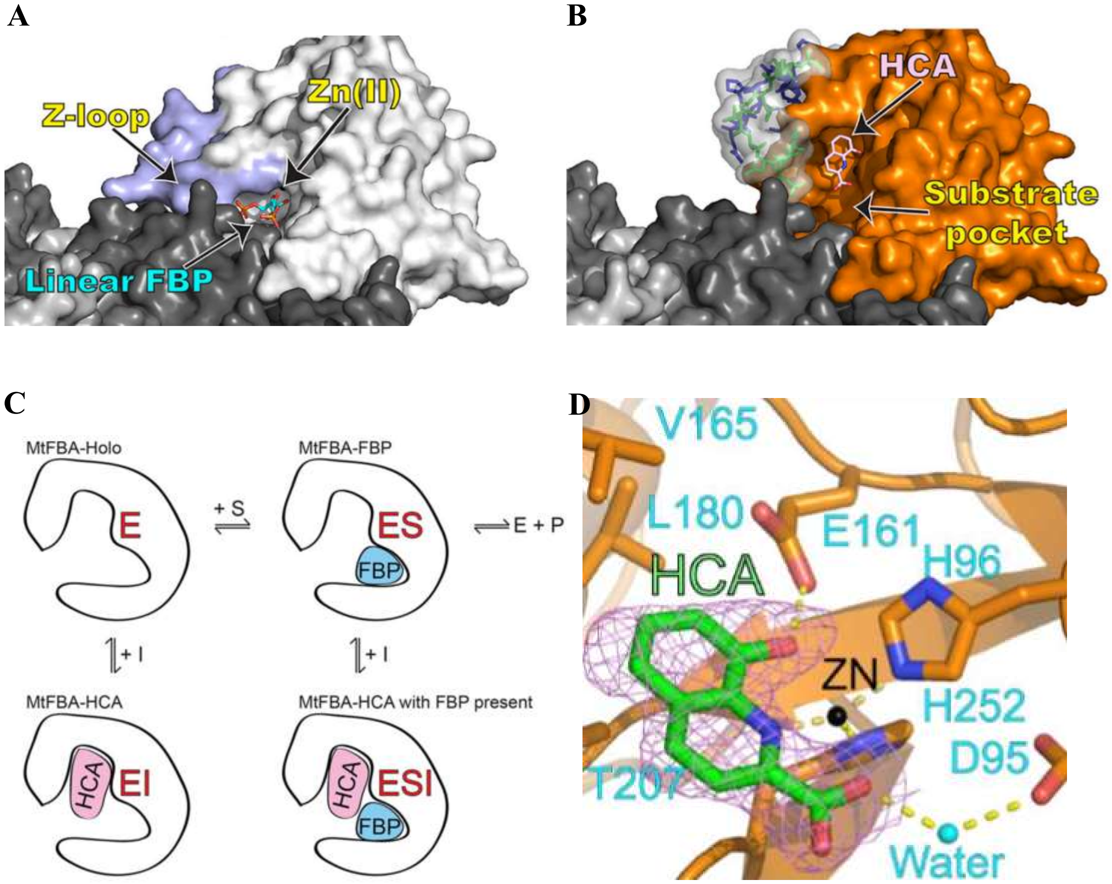

A
Z-loop
Zn(II)
Linear FBP
B
HCA
Substrate pocket
C
MtFBA-Holo
E
+ S
MtFBA-FBP
ES
FBP
E + P
+ I
+ I
MtFBA-HCA
HCA
EI
MtFBA-HCA with FBP present
HCA
ESI
FBP
D
V165
L180
E161
H96
HCA
ZN
H252
D95
T207
Water

*Figure 1.3.5*[*] *A. Substrate binding pocket of MtFBA with linear fructose-1,6-bisphosphate bound. B. Substrate binding pocket of MtFBA with 8-hydroxyquinoline-2-carboxylic acid bound. C. Cartoon of non-competitive inhibition of HCA with MtFBA. D. HCA bound to MtFBA, showing specific interactions with Zn*$^{2+}$*, water, and amino acid side chains*

Verification that HCA did not inhibit class I FBAs was achieved by performing assays with aldolases isolated from both rabbit and human muscle. As was expected due to the mechanistic divergence of the two classes, these assays resolutely showed no activity against the class I aldolase (**D** and **E**, *Figure 1.3.6*). Encouragingly, they saw that HCA had the potential to be a broad-spectrum antibacterial agent; it also exhibited promising inhibition against the structurally similar *E. coli* (EcFBA, **B**) and MRSA (SaFBA, **C**) aldolases.

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[*] Images courtesy of Capodagli, *et al*., Biochemistry (2014) 53, 202−213.

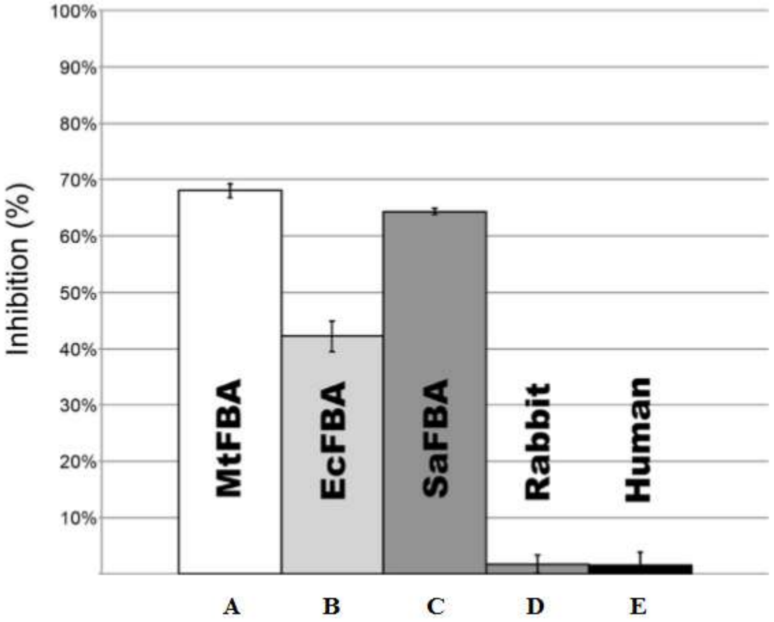

*Figure 1.3.6*[*] *Inhibition of aldolase activity measured in vitro using 25 µM HCA. Aldolases tested include Mycobacterium tuberculosis (A), E. coli (B), MRSA (C), Rabbit muscle (D), and Human muscle (E)*

Overall, HCA possesses many characteristics that make it interesting from a medicinal chemistry standpoint. Its low molecular weight (189 g/mol) and potential for functionalization are extremely desirable features for a lead compound. In addition, the lack of highly-charged phosphate groups indicates an increased likelihood for it to be capable of crossing the hydrophobic bacterial membrane, an essential feature for the successful inhibition of MtFBA. Finally, with an MIC of 600 µM, HCA shows extraordinary potential for optimization-induced inhibition in the low nanomolar range.

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[*] Image courtesy of Capodagli, *et al*., Biochemistry (2014) 53, 202−213.

# 2 QUINOLINES AS POTENT NONCOMPETITIVE INHIBITORS OF MTFBA

## 2.1 Introduction: Building diversity into HCA scaffold.

After Pegan and coworkers identified 8-hydroxyquinoline-2-carboxylic acid as a candidate small molecule to induce noncompetitive inhibition of MtFBA, the next objective was to introduce functionality onto the scaffold that would increase its inhibitory efficacy. Optimally, functionalization of the HCA skeleton would attain nanomolar affinity for the binding site – representing a 1-2 order of magnitude improvement – and low-micromolar MIC values against Mt – an enhancement of 2-3 orders of magnitude.

With this objective in mind, PyMOL molecular imaging was used to evaluate the most significant areas of potential functionalization and optimization of HCA. Based on the data obtained, several features were identified where diversity could be introduced into the quinoline scaffold.

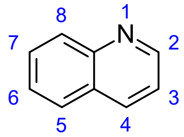


*Figure 2.1.1 Quinoline numbering system*

The aforementioned trident coordination of a $Zn^{2+}$ ion with the lone pair electrons of the carbonyl oxygen at position 2 (see *Figure 2.1.1* and **A** and **B**, *Figure 2.1.2*), the hydroxyl oxygen at position 8, and the in-ring nitrogen is central to the affinity of HCA for the protein. This was confirmed by substitution of one or more of these features by other moieties. For instance, removal of the carboxylic acid group resulted in over 50% drop in inhibitory efficacy. Similarly, substitution of the hydroxyl for an amine or nitro group reduced the inhibition by over 70%. This also supports the vital hydrogen-bonding interaction of this hydroxyl with Glu161 (**B**, *Figure 2.1.2*).

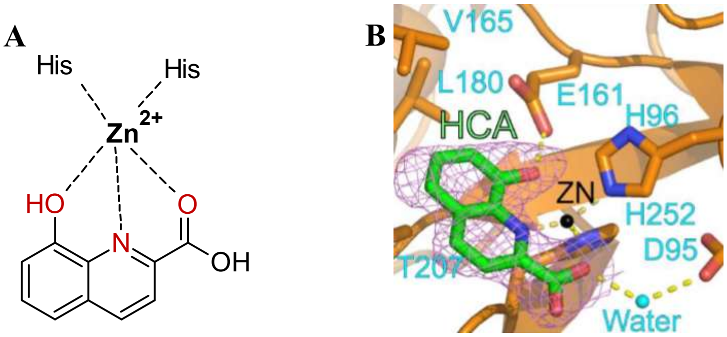


*Figure 2.1.2 A. Trident coordination of HCA with Zn$^{2+}$. B. Interactions of HCA within the binding site of MtFBA*

Within the site where the small molecule binds, three nonpolar amino acid residues (Val165, Leu180, and Thr207, **B**, *Figure 2.1.2*) form a small hydrophobic pocket surrounding the 5-, 6-, and 7-positions on the quinoline ring. This pocket, which is estimated to be about 15 Å$^3$, would be able to accommodate a small hydrophobic substitution. Suitable substituents for this pocket include halogens such as fluorine or alkyl groups such as methyl.

In addition, the region near the carboxylic acid at position 2 could accommodate a variety of substitutions. These could include small aromatic rings, heterocycles, or alkyl chains, on condition that the metal-binding capability of the oxygen is not impeded. For instance, oxazoles, esters, and amides would be appropriate functionalities.

Finally, the in-ring nitrogen of quinoline could potentially be substituted for an exo-ring primary amine. This could hypothetically displace the zinc ion and directly interact with the side chains of the protein.

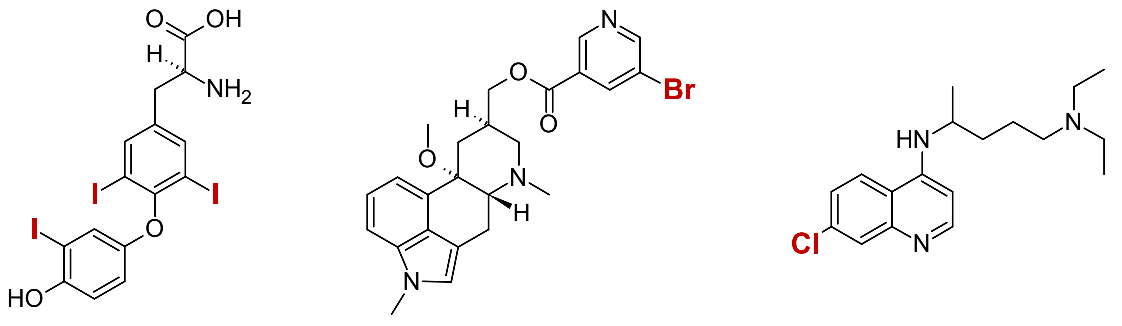
## 2.2 Substitutions on phenol ring of quinoline

Due to the hydrophobic pocket accommodating the 5-, 6-, and 7-positions of the quinoline ring system, the first analogs of 8-hydroxyquinoline-2-carboxylic acid to be explored contained various small hydrophobic substitutions at these positions. These substitutions included assorted halogens and methyl groups.

### 2.2.1 Halogen-substituted quinoline target molecules

The identification of halogens in biologically active molecules has increased exponentially in the last decade. Once thought a rarity, halogens are now accepted as commonplace in biological systems, particularly within protein-bound ligands. This is evidenced by the surge in hits of halogenated ligands in the Protein Data Bank in recent years. It was historically presumed that any specificity observed in the interaction between a protein and its halogenated ligand stemmed from the interaction of other moieties in the molecule, leaving the role of the halogen to be a general lipophilic area of electron density: In essence, an inactive, electron-withdrawing globule. However, recent analysis has determined that halogens – particularly the larger three: chlorine, bromine, and iodine – are actively involved in the binding of a ligand to the active site of its protein, providing unique and robust electrostatic interactions with Lewis acidic atoms within the protein [34]. This insight has led to new research into small molecule inhibitors that exploit halogen interactions with target proteins.

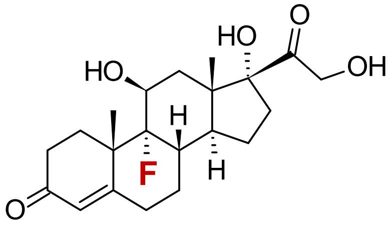
Halogen moieties are present in several biological compounds and currently-used therapeutics. These include three iodo groups in the thyroid hormone triiodothyronine (**XX**, *Figure 2.2.1*), brominated nicergoline (**XXI**), a vasodilator, and a chlorine in the widely used – and aptly named – antimalarial drug chloroquine (**XXII**).



**XX** **XXI** **XXII**

*Figure 2.2.1 Structures of triiodothyronine, nicergoline, and chloroquine, common halogenated therapeutics*

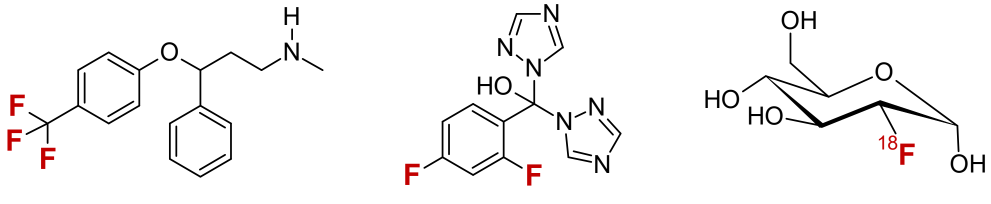
Fluorine has a more intriguing history in pharmaceutical compounds than its larger halogen cousins. Due to the highly reactive nature of elemental fluorine, it was relegated to military and other specialized uses through the 1940s; it was considered abiotic and its use in pharmaceuticals inconceivable. However in 1953 Fried and Sabo recognized the increased mineralocorticoid potency of 9α-fluoro-17α-hydroxycorticosterone acetate (**XXIII**, *Figure 2.2.2*) over other halogen substitutions, and thus began the age of fluorinated biological compounds.



**XXIII**

*Figure 2.2.2 Structure of 9α-fluoro-17α-hydroxycorticosterone acetate (fludrocortisone), a fluorine-containing therapeutic*

Now fluorine moieties are abundant in biologically active molecules including the antidepressant fluoxetine, better known as Prozac (**XXIV**, *Figure 2.2.3)* and the antifungal fluconazole (**XXV**) [35]. Fluorine-substituted compounds are also essential to medical technology, particularly in the form of the positron emission topography tracer 2-deoxy-2-($^{18}$F)fluoro-D-glucose (**XXVI**) [36].



**XXIV** **XXV** **XXVI**

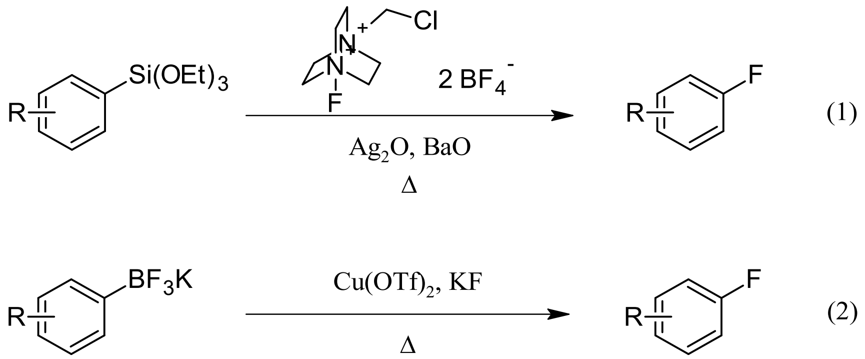
*Figure 2.2.3 Structures of fluorinated compounds fluoxetine, ciprofloxacin, and 2-deoxy-2-(18F)fluoro-D-glucose*

The source of increased activity of fluorinated compounds in biological systems diverges from the electrostatic interactions seen in the more polarizable halogens. While substitution of hydrogen with fluorine in a molecule does not significantly change steric interactions, the substantial increase in electronegativity has the potential to modulate acid/base properties, conformational aspects, and lipophilicity of the parent molecule. In addition, fluorine substitutions on pharmaceutically active molecules have the added benefit of reducing the metabolic deactivation of such compounds via Cytochrome P450 monooxygenases, resulting in a longer lifetime of these molecules in the biological system [35].

### 2.2.1.1 Results and Discussion

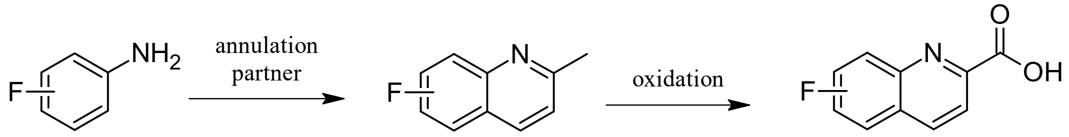
The first set of quinoline analogs targeted were designed to take advantage of the enzyme's small hydrophobic pocket by having fluorine substitutions on the phenol ring of the quinoline system. The selection of fluorine was not designed to exploit the previously mentioned electrostatic Lewis acid/base-type interactions of the larger, more polarizable halogens. Instead, fluorine was chosen due to its metabolic stability, small size, and lipophilicity.

There are two general routes to obtain quinolines with fluorine substituents on the aromatic ring. The first is introduction of fluorine onto the premade quinoline ring via aromatic substitution. The inefficiency of fluoride as a nucleophile means a direct $S_NAr$-type mechanism is impractical. However, several methods of aryl fluorination involving transition metals have been developed recently. These include silver-mediated fluorination of aryl silanes (eq 1, *Scheme 2.2.1*) [37] and copper triflate-mediated fluorination of aryl borates (eq 2) [36].



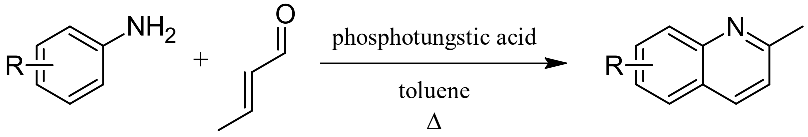
*Scheme 2.2.1 Fluorination options via aromatic substitution.*

The second route toward fluorinated quinolines is cyclization of a pre-fluorinated aniline with an appropriate coupling partner to form the quinaldine, which can then be oxidized to the desired carboxylic acid (*Scheme 2.2.2*). The ready availability of fluorinated aniline starting materials for this approach makes it much more attractive than the former.



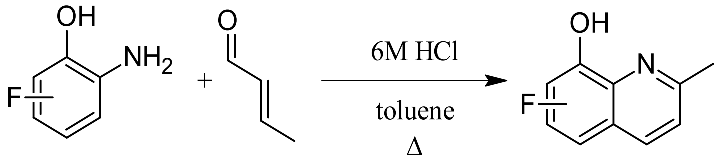
*Scheme 2.2.2 Fluorinated quinoline synthesis starting from fluorinated aniline*

The latter cyclization approach to the fluorinated quinaldine precursor was first attempted through the route described by Perumal and coworkers [38] in which anilines are heated with α,β-unsaturated aldehydes or ketones in a biphasic system of toluene and phosphotungstic acid (*Scheme 2.2.3*). The use of phosphotungstic acid presents advantages over the more common hydrohalide and mineral acids due to its stability, relative non-toxicity, and highly acidic nature. However, while the Perumal lab was able to obtain their desired quinaldines in good yield, it was decidedly less successful under the current conditions. No desired product was obtained using this method.



*Scheme 2.2.3 Quinoline cyclization via phosphotungstic acid*

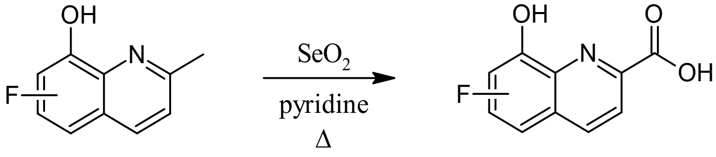
Therefore a more traditional two-phase Doebner-Von Miller method was utilized to obtain the quinaldine precursors. The cyclization step was performed by heating the aniline with crotonaldehyde in a biphasic mixture of toluene and aqueous hydrochloric acid (*Scheme 2.2.4*) [39]. This method proved to be much more viable, resulting in isolation of the products (**1**) in very good yield. Pleasingly, purification of these compounds was not necessary; a simple neutralization and extraction workup procedure was sufficient to obtain the crude quinaldines with less than 5% starting material contamination.[*]



**1**

*Scheme 2.2.4 Biphasic Doebner-Von Miller quinoline synthesis*

The second step was an oxidation by selenium (IV) oxide. This reaction easily oxidized the benzylic methyl group to a carboxylic acid (**2**, *Scheme 2.2.5*) [39]. Acidification of the crude carboxylate allowed precipitation of the product from the aqueous solution.



**1** **2**

*Scheme 2.2.5 Oxidation of benzylic methyl to carboxylic acid*

Notably, cooling on ice during the acidification process improved isolation of the precipitated product drastically; in the case of the 6-fluoroquinoline product, the yield was increased from 18% to 74%. This could be due to two separate factors. The first is the decreased solubility of the product in cold solution, hence a more vigorous precipitation.

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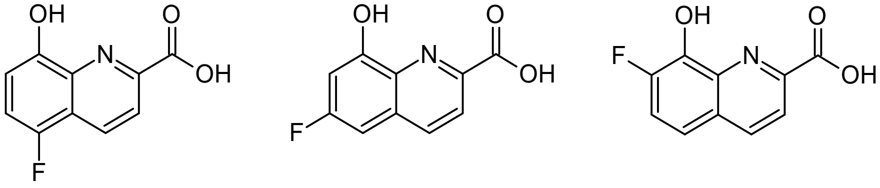
[*] As seen by NMR.

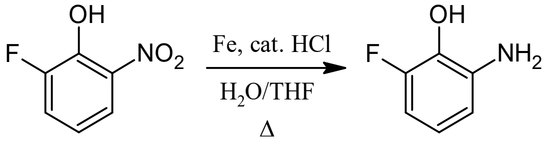
The second is the prevention of decarboxylation; the acidification process is highly exothermic, and the excess heat could spur this degradation mechanism. Using this method, three quinoline analogs with fluorine substitutions at the 5-, 6-, and 7-positions were achieved (**2a**, **2b**, **2c**, *Figure 2.2.4*).



**2a** **2b** **2c**

*Figure 2.2.4 Fluorinated quinoline target compounds*

The synthesis of analog **2c**, with fluorine in the 7-position, included an additional step. Since the starting aniline (2-amino-6-fluorophenol) was not commercially available, the analogous nitro compound was used instead. This required reduction of the nitro group to an amine before cyclization could occur. While there are many reagents available to perform the task of reduction, it was noted that using iron powder with a catalytic amount of concentrated aqueous HCl [40] was the simplest, most efficient route, giving the aniline in excellent yield (**3a**, *Scheme 2.2.6*).

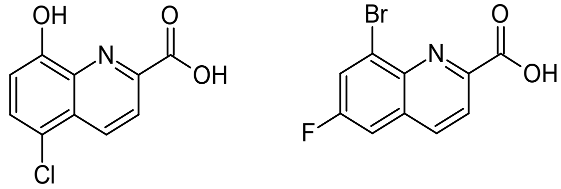


**3a**

*Scheme 2.2.6 Reduction of aryl nitro to primary aryl amine.*

In order to probe the size of the hydrophobic pocket within the binding site of the protein, a 5-chloroquinoline analog (**2d**, *Figure 2.2.5*) was synthesized. Starting from 2-

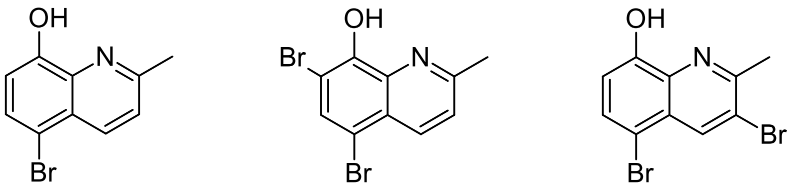
amino-4-chlorophenol and using the same synthetic method, this analog was isolated in excellent yield. Furthermore, due to an unforeseen circumstance (details of which will be discussed in Section 2.3.1.1), synthesis of an analog bearing a bromine at the 8-position and fluorine at the 6-position (**2e**) was desired. The standard cyclization of 2-bromo-4-fluoroaniline with crotonaldehyde and subsequent oxidation to the 2-carboxylic acid were easily accomplished.



**2d** **2e**

*Figure 2.2.5 Other halogen-substituted quinoline analogs*

Finally, a quinoline analog containing a bromine in addition to the hydroxyl group (**1f**, *Figure 2.2.6*) was considered interesting, even though a bromine would most likely be too large to fit into the hydrophobic pocket of the aldolase. Since the brominated aminophenol was not immediately available, a different route was sought. Imperiali and coworkers [41] described an electrophilic bromination of the aryl ring using the hydroxyl at the 8-position as a directing group in order to perform the substitution selectively in the 5-position. Therefore 8-hydroxyquinaldine was reacted with molecular bromine, giving an exceedingly interesting mixture of products that were inseparable by chromatography. According to NMR analysis, the mixture consisted of nearly equal amounts of two doubly-brominated quinaldines (**1g** and **1h**), the structures of which were assigned based on the electrophilic aromatic substitution reactivity patterns of phenol and pyridine. Unfortunately not enough product was isolated to advance to the oxidation step.

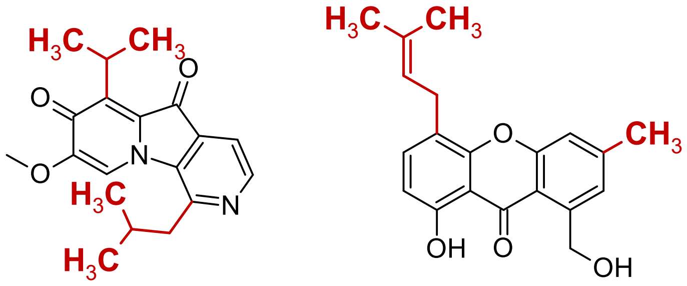


**1f** **1g** **1h**

*Figure 2.2.6 Target bromine-substituted analog and doubly-brominated compounds actually isolated*

### 2.2.2 Methyl-substituted quinoline target molecules

Precisely placed alkyl substituents play an important role in pharmaceutically active compounds. These nonpolar groups can be of highly variable size and can be placed in specific locations on a molecule to optimize hydrophobic interactions with a binding site [42]. Aromatic alkyl groups can be found in many natural products and biologically active compounds such as the metabolite Pterocellin D (**XXVII**, *Figure 2.2.7*), isolated from bryozoans and exhibiting strong activity against *B. subtilis*, and a paeciloxanthone (**XXVIII**) that is found in mangrove bark and demonstrates a broad range of activity against tumor cells, bacteria, and acetylcholinesterase [43].



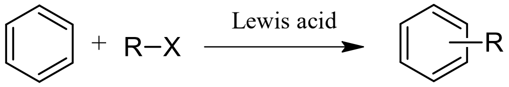
**XXVII** **XXVIII**

*Figure 2.2.7 Biologically active compounds with aromatic alkyl groups*

#### 2.2.2.1 Results and Discussion

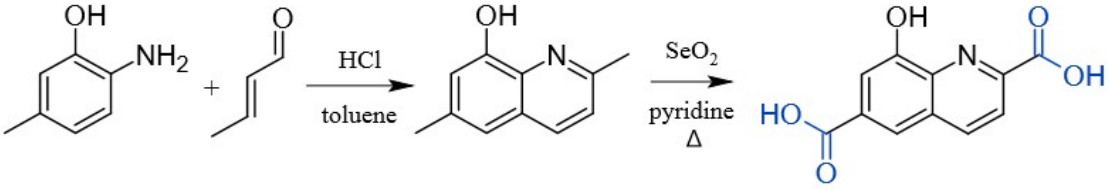
Similar to the previous halogen substitutions, the next target molecules also sought to take advantage of the hydrophobic pocket by employing an alkyl substitution at the 5- or 6-position of the quinoline ring. Since the pocket could only tolerate small substitutions, only methyl groups were considered at this stage.

Alkyl-substituted quinolines can be achieved by methods similar to the previously discussed halide derivatives, namely through aromatic substitution or cyclization of a pre-functionalized aniline. One of the oldest and most widely used methods of introducing alkyl groups onto an aromatic ring is the Friedel-Crafts alkylation. Known since 1877, this procedure proceeds through electrophilic substitution on the aromatic ring by an alkyl halide via Lewis-acid catalysis (*Scheme 2.2.7*). Many variations have been introduced over the intervening years. These include a variety of electrophiles such as alcohols and alkenes and an assortment of Lewis acids that display a wide range of activities. While this method has historically been a powerful tool for the purpose of aromatic alkylation, it also has several weaknesses; it is prone to alkyl-group rearrangements and polyalkylation, and it is unsuccessful with aromatic rings containing electron-withdrawing substituents [44].



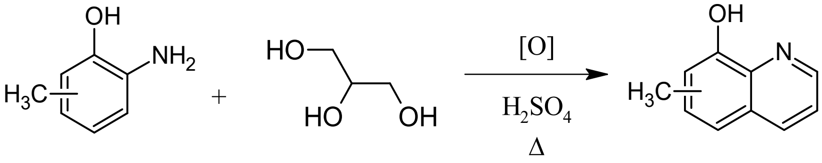
*Scheme 2.2.7 Friedel-Crafts alkylation of an aromatic ring*

Due to the difficulties presented by the Friedel-Crafts alkylation and the ready availability of methyl-substituted aminophenols, a methylquinoline synthesis via cyclization of anilines – analogous to the synthesis used to obtain the halogenated quinolines – was deemed to be more accessible. However, initial trials showed the Doebner-Von Miller quinoline cyclization to be an impractical method to synthesize these molecules. After coupling of the methyl aniline with crotonaldehyde to obtain the dimethyl-substituted quinoline, reaction with selenium (IV) oxide resulted in oxidation of both methyl groups, forming the dicarboxylic acid(*Scheme 2.2.8*).



*Scheme 2.2.8 Undesired formation of quinoline dicarboxylic acid from DVM synthesis*

Therefore an alternative approach was explored. Ideally, installation of the carboxylic acid group at position 2 would be orthogonal to oxidation of the existing methyl in position 5 or 6. An often-used synthetic route developed by Krasavin *et al.* [45] toward quinoline-2-carboxylic acids starts with a quinoline unsubstituted at position 2 of the ring. Initially a classical Skraup reaction [46] was used to obtain this compound, in which the appropriate methyl-substituted aminophenol was refluxed with glycerol and an oxidant[*] in concentrated sulfuric acid (*Scheme 2.2.9*). However, the desired product was difficult to



*Scheme 2.2.9 Skraup quinoline synthesis*

extract from the thick tarry reaction mixture, and an extremely low yield of product was obtained. On the other hand, when acrolein diethyl acetal was utilized as the cyclization partner and refluxed with the starting aniline in dilute HCl, the yield of methylquinoline was greatly improved (*Scheme 2.2.10*) [47].

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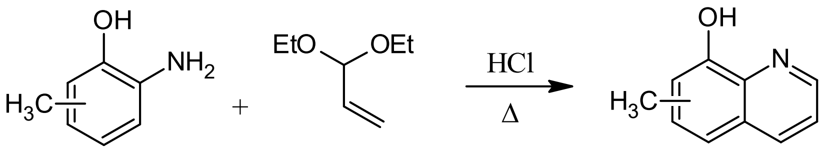
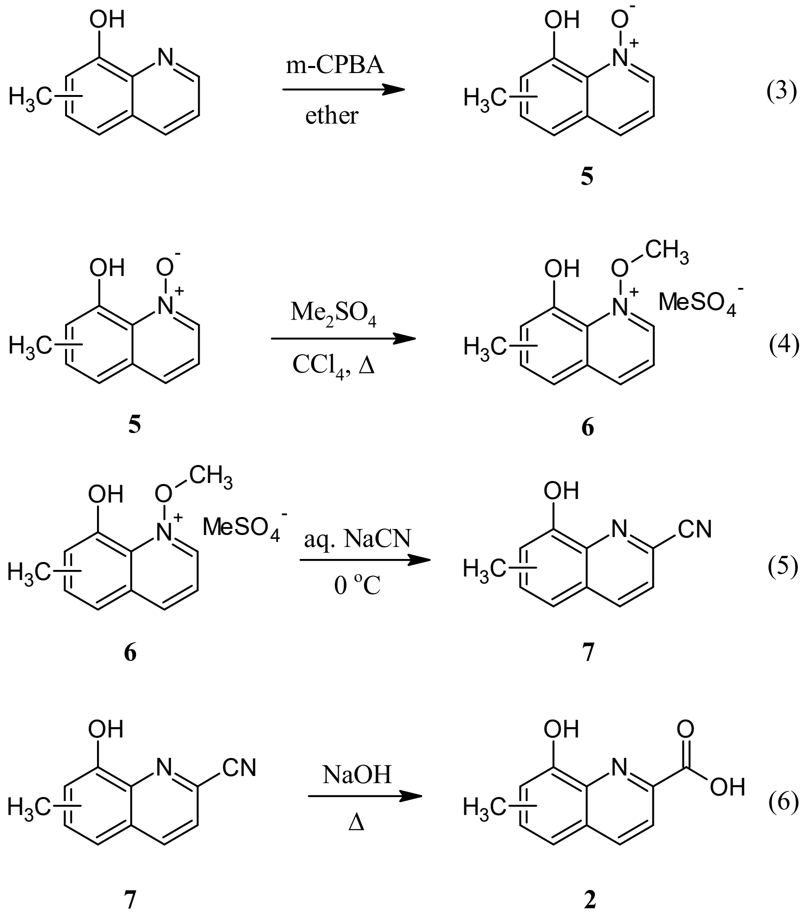
[*] Oxidants used include nitrobenzene and sodium 3-nitrobenzene sulfonate.



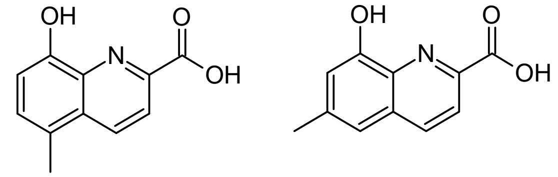
*Scheme 2.2.10 Synthesis of methylquinolin-8-ols*

Subsequent oxidation of the ring nitrogen was easily accomplished with m-CPBA (eq 3, *Scheme 2.2.11*). The quinoline-*N*-oxide was then methylated with dimethyl sulfate (eq 4), and treatment with sodium cyanide afforded the quinoline-2-carbonitrile (eq 5). Finally, hydrolysis of the nitrile by refluxing in aqueous sodium hydroxide gave the desired carboxylic acid (**2**, eq 6) [45].



*Scheme 2.2.11 Synthesis of methylquinolin-8-ol-2-carboxylic acids*

The aforementioned procedural change proved advantageous in the formation of the 5- and 6-methyl quinoline-2-carboxylic acids. Over the course of five synthetic steps, the overall yield of the 6-methyl analog (**2f**, *Figure 2.2.8*) increased from 0.01% (obtained via the Skraup method) to 12.6%, a difference of greater than 1000-fold. Similarly, the 5-methyl analog (**2g**), which had not been carried through to the final step under the original procedure, was produced in an overall yield of 3.5% via the modified version. However, complete isolation of the 5-methyl analog proved difficult; several trials all resulted in a final product contaminated with one of the intermediates. Therefore, while it was considered an interesting compound, it was not determined to be pure enough for biochemical testing.



**2f** **2g**

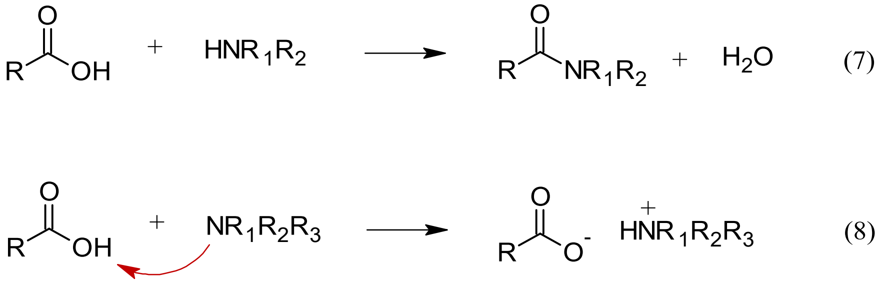
*Figure 2.2.8 Methyl-substituted quinoline products*

## 2.3 Carboxylic acid alternatives at position 2

Investigation of modifications to the carboxylic acid at position 2 of the quinoline ring system were designed to probe the unique properties of HCA's binding site within the enzyme. These derivatives included amides, esters, alcohols, carbamates and ureas, amines, and heterocycles, each of which took individual advantage of the space and binding properties within that region. As will be discussed in Section 2.5, the HCA analog which contained a fluorine in the 6-position quinoline ring system showed the most promising inhibition of MtFBA, so from this point forward that scaffold was used in all derivatization probes.

### 2.3.1 Amides

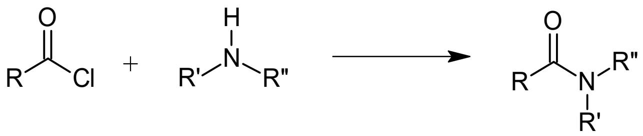
Synthesis of amides has historically been accomplished by many methods. One prominent and straightforward scheme is the coupling of carboxylic acids with amines. However, direct coupling of the acid with amine via nucleophilic acyl substitution, and the necessary elimination of a water molecule (eq 7, *Scheme 2.3.1*), does not occur spontaneously at room temperature, instead forming undesirable ammonium carboxylate salts (eq 8) [48]. The preferred process of nucleophilic attack requires extremely high temperatures, often resulting in decomposition of the starting materials. Therefore several alternative techniques have been developed in recent years, including the use of organometallic catalysis, oxidation/reduction-assisted coupling [49], and conversion of the acid into a derivative with enhanced electrophilicity [50].



*Scheme 2.3.1 Reactions of amines with carboxylic acids: the desired substitution and the undesired acid/base*

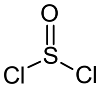
Representing a simple, straight-forward method of coupling carboxylic acids with amines, derivatization is one of the foremost routes in amide synthesis. Acid halides, activated esters, mixed anhydrides, and carbodiimides are among the most frequently used activation intermediates [51]. The choice of coupling agent in a particular amidation reaction is highly dependent on the inherent reactivity of the substrates and the need to restrict the formation of undesired side reactions [50].

Exploiting the principle of enhanced carbonyl reactivity by introduction of a weakly basic leaving group, acid halides are the most reactive carboxylic acid derivatives and thus ideal for nucleophilic acyl substitution reactions with amines. In particular, owing to their practicality, simplicity, and relatively mild reaction conditions, acyl chlorides are the most common halide derivatives used in these coupling reactions (*Scheme 2.3.2*) [51].

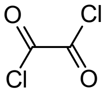


*Scheme 2.3.2 Reaction of amine with acyl chloride to give amide product*

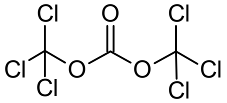
Introduced by Emil Fischer who, in 1901, first applied acyl chloride intermediates to the coupling of amino acids [50], this method has seen numerous modifications over the last 115 years, particularly in the variety of chlorinating reagents used; these include, in their simplest forms, thionyl chloride, oxalyl chloride, and triphosgene (**XXIX**, **XXX**, **XXXI**, *Figure 2.3.1*).



**XXIX**



**XXX**

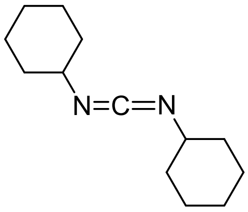


**XXXI**

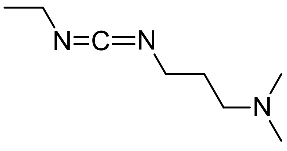
*Figure 2.3.1 Chlorinating reagents thionyl chloride, oxalyl chloride, triphosgene*

While there is no shortage of "designer" halogenating agents, developed for specific purposes such as increased reactivity with hindered substrates and functional-group compatibility [50], the ready availability and low cost of the more common reagents, as well as the depth of published experiments using them, make these attractive for use in the formation of reactive coupling partners.

Peptide coupling reagents such as carbodiimides are commonly used to create amide bonds between the free amine of one amino acid and the carboxyl group of another amino acid. In 1955 Sheehan [52] introduced N,N'-dicyclohexylcarbodiimide (DCC, **XXXII**, *Figure 2.3.2*) as a moderately reactive, reasonably inexpensive peptide coupling agent; since then, this has been the single most important carboxylic acid activating agent in peptide synthesis. This method is particularly useful due to the easy separation of the main byproduct, dicyclohexylurea, which is insoluble in most reaction solvents and can be removed by filtration [51]. Another peptide coupling reagent is 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC, **XXXIII**, *Figure 2.3.2*). The amenability of this reagent to mild reaction conditions, and its convenient solubility in a variety of solvents including water and dichloromethane, make it highly practical. Also, the main urea byproduct is water-soluble, and thus can be removed by simple aqueous extraction [53].



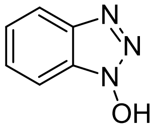
**XXXII**



**XXXIII**

*Figure 2.3.2 Peptide coupling reagents DCC and EDC*

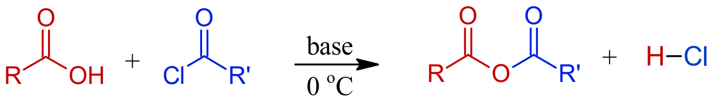
Despite the numerous advantages of using carbodiimides as activating agents in the acylation of amines, this method is also subject to several drawbacks, including racemization, slow reaction rates [52], and possible formation of multiple side products [50]. These shortcomings can be controlled or completely negated by the addition of additives to the reaction mixture. In 1970, Koenig and Geiger introduced 1-hydroxy-1-*H*-benzotriazole (HOBt, **XXXIV**, *Figure 2.3.3*) as an epimerization-reducing agent; consequently they recorded a substantial drop in epimerization for their model peptide coupling reaction from 35% to 1.5%. It is proposed that HOBt initially reacts with the previously formed *O*-acylurea to give the activated OBt ester. This ester increases the reactivity of the carbonyl by stabilizing and directing the approach of the nucleophilic amine via hydrogen bonding interactions [50].



**XXXIV**

*Figure 2.3.3 HOBt: Activating agent for peptide coupling reactions*

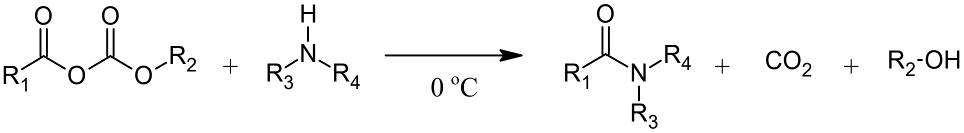
The formation of mixed anhydride intermediates represents a third route toward amide synthesis (*Scheme 2.3.3*). Proposed independently by three separate groups in 1951, formation of mixed anhydrides by reaction with a chloroformate or acyl chloride provides a fast and simple method of activating a carboxylic acid for nucleophilic attack by an amine [54].



*Scheme 2.3.3 Formation of mixed anhydride by reaction of a carboxylic acid with an acyl chloride*

In contrast to peptide coupling reagents which are uneconomical, producing large amounts of wasted byproducts – especially when used in stoichiometric amounts and with additional additives – this method is more compliant with green chemistry techniques due to its superior atom economy. Additionally, the formation of acyl halide intermediates produces toxic sulfur dioxide (from thionyl chloride) or carbon monoxide (from oxalyl chloride), and the acyl halides themselves are relatively unstable and hydrolyze easily under atmospheric conditions. In comparison, the use of mixed anhydrides represents a relatively non-toxic alternative; the only byproducts being $CO_2$ and an alcohol (*Scheme*

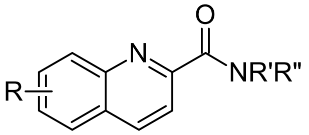
*2.3.4*) [55]. This is particularly attractive since the lack of byproducts gives a relatively clean crude product that is easily isolated in high yields [54]. It is also advantageous in that the formation of the mixed anhydride is easily identifiable by TLC analysis, so that the amine can be added as soon as all the carboxylic acid is converted.



*Scheme 2.3.4 Formation of amide by reaction of amine with mixed anhydride*

### 2.3.1.1 Results and Discussion

Amide functional groups were the first carboxylic acid derivatives to be considered for functionalization at the 2-position of the quinoline (**8**, *Figure 2.3.4*). The amide was attractive due to the retention of the zinc-coordinating carbonyl oxygen while altering the electronics and sterics of the attached group. Resonance of the lone pair of electrons on the amide nitrogen into the carbonyl group could result in interesting interactions of the molecule within the binding pocket. In addition, the groups attached to the nitrogen could possibly utilize the space inside that pocket in advantageous ways.

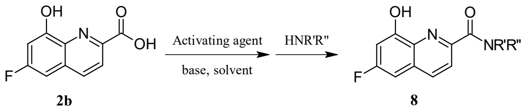


**8**

*Figure 2.3.4 Amide quinoline derivative*

Several of the aforementioned methods were applied to the installation of amide functional groups at the 2-position of the quinoline scaffold. Acyl chloride intermediates were first utilized in an attempt to produce a diethyl amide. Unfortunately, neither thionyl chloride nor oxalyl chloride were effective agents in this regard, even when used in large excess. Under various reaction conditions, including addition of a catalytic amount of DMF, this method either resulted in no product formation, or extremely poor yield of unclean product. The results are summarized in *Table 1*.

*Table 1 Attempted amide formation via acyl chloride derivative.*



| *Entry* | *Amine* | *Activating agent* | *Additive* | *Base* | *Solvent* | *Yield*[*] *(%)* |
|---|---|---|---|---|---|---|
| *1* | $HNEt_2$ | $(COCl)_2$ | None | $NEt_3$ | $(CH_3)_2CO$ | NP |
| *2* | $HNEt_2$ | $(COCl)_2$ | DMF | $NEt_3$ | $CH_2Cl_2$ | Trace |
| *3* | $HNEt_2$ | $SOCl_2$ | None | $NEt_3$ | $CH_3CN$ | NP |

Subsequently, this reaction was attempted via peptide coupling reagents. Readily-available EDC was used as the activating agent, and HOBt was initially utilized as additive. This reaction produced a trace of desired product, but it proved inseparable from the HOBt byproduct. Therefore HOBt was replaced with a catalytic amount of DMAP, but this resulted in no product formation. These results can be seen in *Table 2*.

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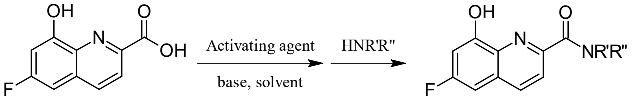
[*] NP = No product obtained.

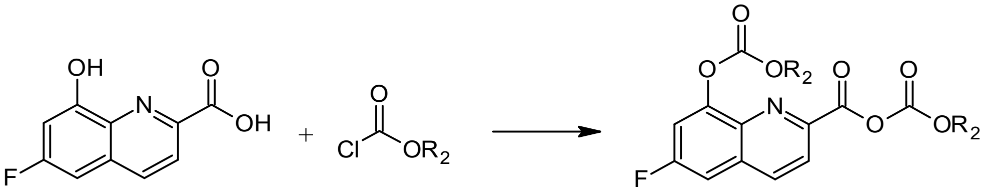
*Table 2 Attempted amide formation via peptide coupling reagents.*



**2b** **8**

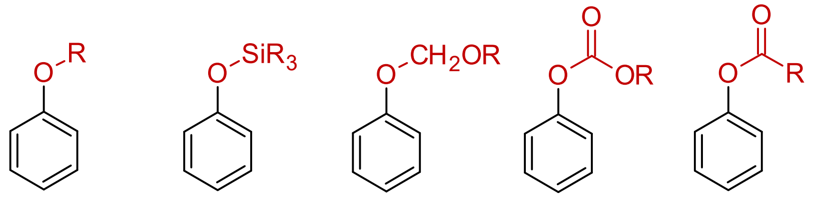
| *Entry* | *Amine* | *Activating Agent* | *Additive* | *Base* | *Solvent* | *Yield (%)* |
|---|---|---|---|---|---|---|
| *4* | $HNEt_2$ | EDC | HOBt | DIPEA | DMF/DCM | Trace |
| *5* | $HNEt_2$ | EDC | DMAP | DIPEA | DMF/DCM | NP |

A final attempt to produce the desired amides was conducted via mixed anhydride derivatives. An additional consideration that required attention, however, was the formation of carbonate esters on the phenolic oxygen upon reaction with chloroformate esters (*Scheme 2.3.5*). This carbonate ester could then compete with the anhydride for nucleophilic attack by the amine, producing undesired side products and reducing yield of the desired amide.



*Scheme 2.3.5 Undesired phenolic carbonate formation from reaction of phenol with ethyl chloroformate*

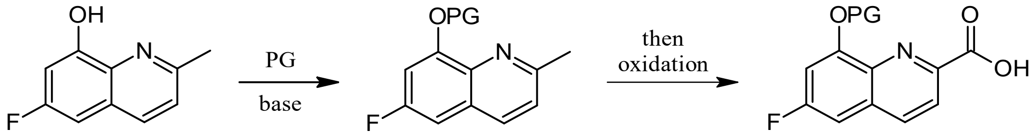
Therefore, it was desired to put a protecting group on the phenol to deactivate it from attacking the chloroformate. Numerous phenol protecting groups are available, and several factors must be taken into consideration when choosing one. Introduction of the protecting group must be selective for the functional group intended to be protected. It must also be stable to all subsequent reaction conditions, and it must be able to be taken off without compromising any other functional groups. Some of the more common phenol protecting groups include ethers (**XXXV**, *Figure 2.3.5*), silyl ethers (**XXXVI**), acetals (**XXXVII**), carbonates (**XXXVIII**), and esters (**XXXIX**).



**XXXV** **XXXVI** **XXXVII** **XXXVIII** **XXXIX**

*Figure 2.3.5 Phenol protecting groups*

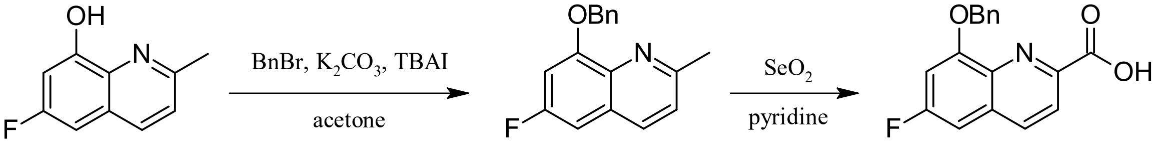
For the intended quinoline amide synthesis, it was necessary to establish the protecting group on the phenol before the carboxylic acid was introduced. Since the general mechanism of phenol protection involves nucleophilic attack by oxygen on the protecting group, usually via $S_N2$ substitution, a carboxylic acid moiety would compete with the phenol in this attack. This would necessitate several equivalents of the protecting group and would also deactivate the carboxylic acid against subsequent reactions, essentially defeating the purpose. Therefore it was decided that the phenol should be protected directly after cyclization of the quinoline (*Scheme 2.3.6*).



*Scheme 2.3.6 Preferred order of quinoline cyclization, phenol protection, and oxidation*

As previously mentioned, the choice of protecting group must take into account its durability through the subsequent oxidation and amidation reaction conditions. For the oxidation of the pyridyl methyl to a carboxylic acid via $SeO_2$, both acidic and alkaline conditions are used. Acetate and ester protecting groups would therefore be unsuitable due to their lability under basic conditions; similarly, silyl ethers and methoxymethyl ethers would be unusable due to their instability in acidic media. Furthermore, carbonates were ruled out since the protecting group was being installed to prevent their formation in the first place, and methyl ethers were not considered due to their difficulty in removal [44].

A benzyl ether protecting group was consequently determined to be the most appropriate for the situation. The tolerance of the benzyl group to acidic and basic conditions, its stability against nucleophilic attack, and its mode of removal orthogonal to amide hydrolysis made it attractive for the given reaction. Installation of the benzyl group was easily achieved in very high yield by reacting 6-fluoro-8-hydroxyquinaldine with benzyl bromide, potassium carbonate, and a catalytic amount of tetrabutylammonium iodide in acetone (**1i**, *Scheme 2.3.7*). Subsequent oxidation of the benzylic methyl group to a carboxylic acid (**2h**) was also a smooth process. In fact, the benzyloxy group enhanced the yield of this step over that of the free phenol; due to its hydrophobic nature, it precipitated from the acidified aqueous solution much more robustly.

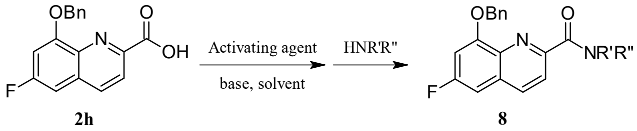


**1b** **1i** **2h**

*Scheme 2.3.7 Installation of benzyl protecting group on quinoline phenol and subsequent oxidation*

With the benzyl-protected quinoline-2-carboxylic acid in hand, the mixed-anhydride-assisted amidation reaction was performed. The carboxylic acid was first activated by addition of ethyl chloroformate and triethylamine in THF; upon TLC confirmation of the consumption of starting material, the amine was added. This process proved amenable to formation of the diethyl, morpholine, and free[*] amides in moderate yields, the results of which can be seen in *Table 3*.

*Table 3 Attempted amide formation via mixed anhydride intermediate.*



| *Entry* | *Amine* | *Activating agent* | *Additive* | *Base* | *Solvent* | *Yield (%)* |
|---|---|---|---|---|---|---|
| *6* | $HNEt_2$ | Ethyl Chloroformate | None | $NEt_3$ | THF | 58 |
| *7* | Morpholine | Ethyl Chloroformate | None | $NEt_3$ | THF | 41 |
| *8* | $NH_3$ | Ethyl Chloroformate | None | $NEt_3$ | THF | ND[†] |

The final step to obtain the desired amide products was deprotection of the phenol. Removal of a benzyl protecting group can be accomplished through reaction with boron tribromide, and this method was applied to the three benzyloxyquinoline amide products. Deprotection of the diethyl amide gave the expected product (**8a**, *Figure 2.3.6)* in moderate yield.

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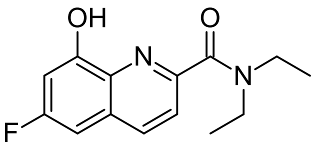
[*] "Primary" amide with formula $CONH_2$.

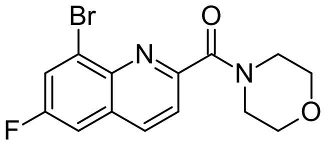
[†] ND: Yield not determined.



**8a**

*Figure 2.3.6 Desired diethyl amide*

However, the morpholine and free amides gave unexpected results under these conditions. Following deprotection of the free amide, no desired product was obtained. In contrast, NMR analysis of the purified morpholine amide indicated a mixture of two similar but distinct compounds. Analysis by mass spectroscopy clearly showed that in addition to the expected morpholino quinoline amide, there was a second product, also with a morpholine amide in the 2-position of the quinoline ring, but with a bromine in place of the phenolic oxygen in the 8-position (**8d**). These two products proved inseparable by chromatography.



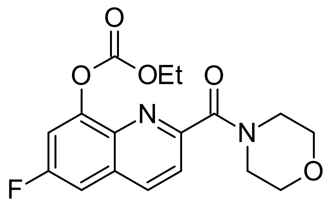
**8d**

*Figure 2.3.7 Unexpected quinoline product from attempted amide syntheses*

Mechanistically, the most likely scenario for this substitution occurred during the deprotection stage. It is conceivable that upon mixture of boron tribromide with the quinoline amide, free bromides in solution, rather than attacking the methylene carbon of the benzyl group, attacked the aromatic ring and displaced the benzyloxide in an $S_NAr$ fashion. This process could be catalyzed by the boron coordinating with oxygen as a Lewis acid.

Since this 8-bromo quinoline morpholine amide derivative represented an interesting analog in and of itself, it was prepared in pure form, starting from 2-bromo-4-fluoroaniline. The final amide was obtained in acceptable yield through the same general procedure as previously described.

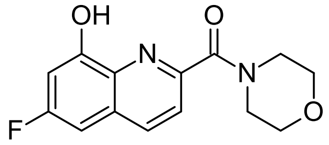
Additionally, it was desired to obtain a pure sample of the 8-hydroxyquinoline morpholine amide. Since the removal of the benzyl protecting group had proven to be problematic, a different approach was considered. The unprotected 6-fluoro-8-hydroxyquinoline-2-carboxylic acid was subjected to the same reaction conditions. However in an attempt to selectively deprotonate and activate the more acidic carboxylic acid over the phenol, less basic imidazole was used in place of triethylamine. Upon purification, NMR analysis indicated the amide had been successfully created; however, despite the precaution taken with the base, the phenol had also reacted with ethyl chloroformate to form an ethyl carbonate ester (**8b**, *Figure 2.3.8*).



**8b**

*Figure 2.3.8 Unexpected product from ethyl chloroformate addition to phenol*

This new analog was interesting with regard to its potential interaction with MtFBA: it could either enhance or detract from the molecule's binding capability. The addition of two extra electron-rich oxygens at the 8-position of the molecule presented additional opportunity for coordination with the $Zn^{2+}$; on the other hand it could be too sterically demanding to fit into the narrow binding site of the enzyme. Regardless, a sample was reserved for biochemical analysis. The remaining portion was subjected to deprotection under basic conditions, resulting in the desired 8-hydroxyquinoline amide in fair yield (**8c**, *Figure 2.3.9*).



**8c**

*Figure 2.3.9 Desired morpholine amide*

With two of the three intended amide products successfully created, the focus then shifted to synthesis of the free amide. The first two attempts used the benzyl-protected quinoline-2-carboxylic acid as precursor, with ethyl chloroformate as activating agent. However, neither $NH_3$ nor $NH_4Cl$ were suitable reagents in this process; only the intermediate ethyl anhydride was recovered. Another trial was conducted using an aqueous $NH_4Cl$ solution as the ammonia source with ethyl quinoline-2-carboxylate as the activated carbonyl component. After 48 hours of stirring at room temperature with only minimal conversion of starting material to product[*], the temperature was increased to 50°C for an additional 48 hours. However, upon purification of the reaction mixture and NMR analysis only starting material was identifiable.

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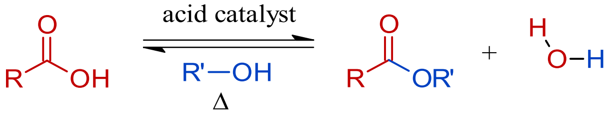
[*] As seen by TLC analysis.

### 2.3.2 Esters

Similar to amide synthesis, an abundance of methods are available to convert carboxylic acids into esters. These include common and mechanistically simple approaches such as the eponymous Fischer esterification, nucleophilic acyl substitution via activated carboxylic acid intermediates, and nucleophilic substitution on an alkyl halide. Though not an exhaustive list, a few of the more complex routes include the Mitsunobu, Yamaguchi, and Steglich reactions.

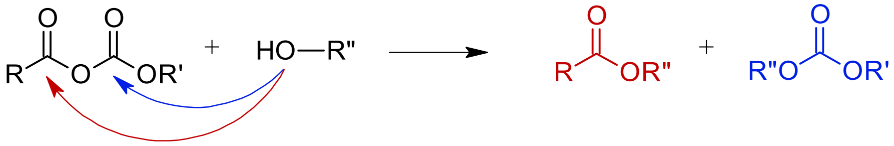
One of the most straightforward and widely-used synthetic routes to esters is the Fischer-Speier esterification. Announced by these two gentlemen in 1895, it is usually performed by refluxing a carboxylic acid in a large excess of the nucleophilic alcohol with an acid catalyst (*Scheme 2.3.8*). This method is advantageous for its simplicity and superior atom economy, but the unfavorable equilibrium of the reaction diminishes its utility. This poor equilibrium is due to the nearly identical basicity of the hydroxide and alkoxide leaving groups so that one is not heavily favored over the other, and similarly the ester is not substantially more stable than the carboxylic acid. However, this can be countered by passing dry HCl gas through the solution or removal of the water byproduct via addition of molecular sieves or Dean-Stark distillation [46].



*Scheme 2.3.8: Fischer-Speier esterification*

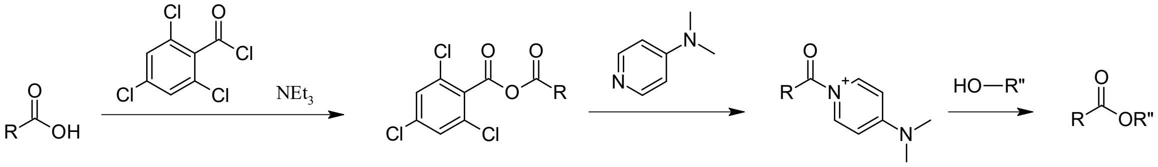
Nucleophilic acyl substitution reactions are powerful and simple methods of ester synthesis. As with amide synthesis, acid halides and mixed anhydrides are commonly employed as electrophilic coupling partners with alcohols or alkoxides to form esters. A wealth of variations on this method exist that counter inherent shortcomings of the substrates or accord with specific reaction requirements.

A particular shortcoming that frequently accompanies the use of mixed anhydride coupling partners is the propensity for the nucleophilic alcohol to attack the carbonyl of the anhydride, rather than the desired substrate carbonyl. This leads to the varied production of carbonate side products, and a decreased yield of the desired product (*Scheme 2.3.9*).



*Scheme 2.3.9 Dual products possible from nucleophilic attack on mixed anhydride*

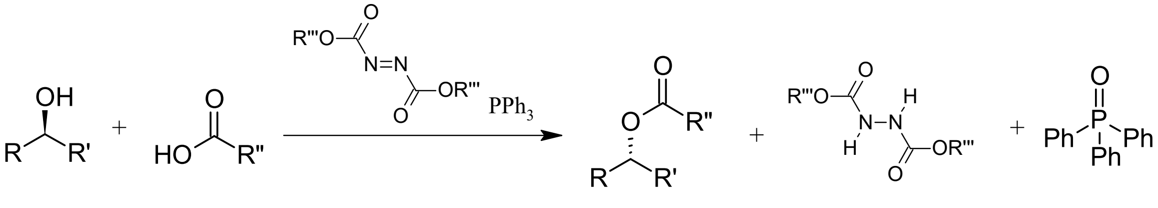
As a counter to this obstacle, Yamaguchi and coworkers [56] devised a reagent for use with aliphatic carboxylic acids that would encourage nucleophilic attack of the alcohol on the appropriate carbonyl. In 1979, they disclosed 2,4,6-trichlorobenzoyl chloride (*Scheme 2.3.10*) as a sterically-hindering carbonyl activator. The addition of triethylamine allows the deprotonation of the aliphatic carboxylic acid, which then couples with the activating agent. A catalytic amount of DMAP is added to the reaction, which then selectively attacks at the less-hindered carbonyl. The Yamaguchi reagent is sufficiently sterically encumbering to ensure that only the desired substrate carbonyl is attacked. The resultant dimethylaminopyridinium analog is then attacked by the alcohol, restoring the catalyst and forming the ester.



*Scheme 2.3.10 Esterification using the Yamaguchi reagent*

The Yamaguchi method has been used extensively in recent years, including in the total synthesis of (-)-decarestrictine D by Victor and coworkers in 1998 [57] and the synthesis of a Lux-S aspartic acid enzyme inhibitor by SantaLucia in 2006 [58].

In a divergent approach, Mitsunobu and Yamada introduced a procedure in 1967 using triphenylphosphine and azodicarboxylates to form esters with a high degree of stereoselectivity (*Scheme 2.3.11*) [59]. While this approach is generally high-yielding, it also comes with drawbacks. For instance, in terms of green chemistry, the Mitsunobu reaction falls short. The byproducts in the reaction, hydrazodicarboxylate and triphenylphosphine oxide, are highly atom uneconomical and cannot be reused. In addition, the large amount of byproducts necessitates extensive workup and purification procedures.



*Scheme 2.3.11 Mitsunobu method of stereoselective ester formation*

This latter disadvantage prompted Pelletier and Kincaid to devise a bypass [60]. In 2000 they reported the use of resin-bound triphenylphosphine in the Mitsunobu reaction. This modification allowed for a simplified workup procedure in which filtration, evaporation, and an aqueous wash were sufficient to remove most contaminants and obtain over 80% purity. This was advantageous for their high-throughput molecular screening process.

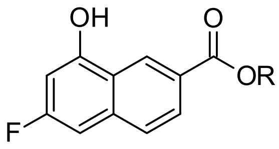
Innumerable other examples of the Mitsunobu reaction have appeared in the literature. Three groups, including that of Barry Trost, independently used this reaction in the synthesis of morphine [61]. In addition, Stork and coworkers exploited this reaction in the first entirely stereoselective synthesis of (-)-quinine [62]. As a final example, Stephen Hanessian and coworkers applied the Mitsunobu reaction to the total syntheses of Dysinosin A [63] and Malayamycin A [64].

Wolfgang Steglich introduced another ester synthesis method in 1978 [65]. Analogous to peptide coupling reactions, it utilizes DCC (see *Figure 2.3.2*) to combine carboxylic acids and alcohols. However, due to the less nucleophilic nature of alcohols compared to amines, this reaction tends to occur slowly which leads to the formation of side products such as *N*-acylureas. This obstacle can be overcome by addition of a catalytic amount of DMAP; this additive speeds up the reaction to such an extent that even sterically demanding esters can be formed in very high yields. As proof of this, Ghosh and coworker [66] applied this technique to an extraordinarily sterically challenging step in the total synthesis of (-)-Doliculide.

Finally, esters can be formed by nucleophilic attack of carboxylate anions on alkyl halides. While this approach looks good on paper, for decades it was considered synthetically futile, mainly due to the solvent incompatibility of the carboxylate salt and alkyl halide. However, in 1968 Thompson and colleagues disclosed a valuable set of conditions that bypassed this obstacle. By heating the carboxylate salt and alkyl chloride with catalytic amounts of triethylamine and sodium iodide in 2-butanone, they were able to achieve very high yields of several diverse esters [67].

### 2.3.2.1 Results and Discussion

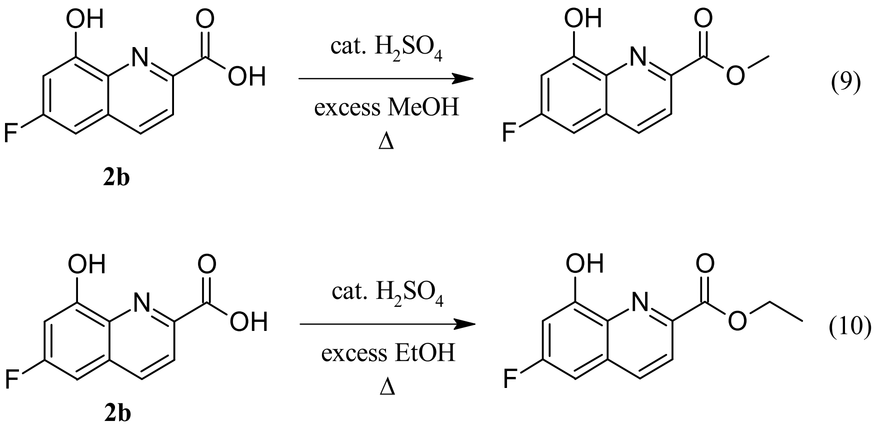
Similar to the amide derivatives, esters were desirable HCA analogs (**9**, *Figure 2.3.10*) due to the retention of the zinc-coordinating carbonyl moiety and the utilization of the extra space in the binding pocket around the 2-position of the quinoline ring.



**9**

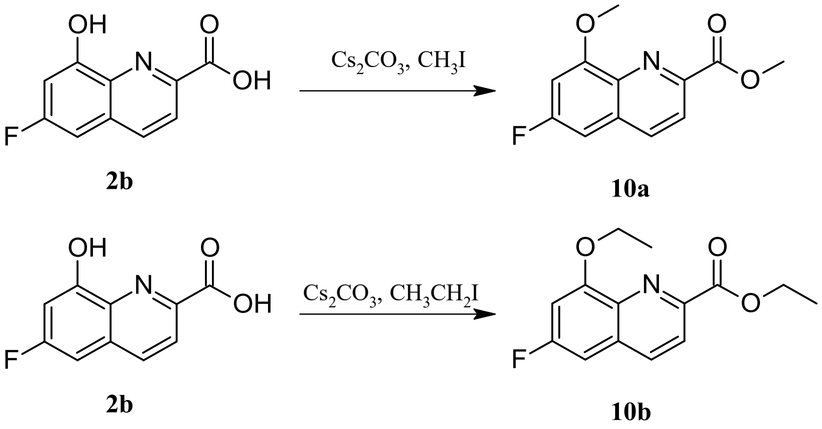
*Figure 2.3.10 Ester quinoline derivative*

Due to its simplicity and economy – both in terms of atoms and expense – the Fischer-Speier esterification was the first to be tried. Refluxing the quinoline-2-carboxylic acid **2b** in methanol with a catalytic amount of concentrated sulfuric acid resulted in the desired methyl carboxylate; however, after workup and purification only 11% yield of product was obtained (eq 9, *Scheme 2.3.12*). Of greater concern, the same reaction in ethanol did not produce any ethyl ester (eq 10).


OH
O
N
OH
F
2b
cat. H2SO4
excess MeOH
Δ
OH
O
N
O
F
(9)
OH
O
N
OH
F
2b
cat. H2SO4
excess EtOH
Δ
OH
O
N
O
F
(10)

*Scheme 2.3.12 Fischer-Speier esterification of quinoline-2-carboxylic acid*

Therefore an alternative approach was considered. As previously mentioned, reaction of the carboxylic acid with alkyl halides presented a feasible course of action with comparable atom economy. After deprotonation of the quinoline carboxylic acid by cesium carbonate, the alkyl halide (either methyl iodide or ethyl iodide) was added. However, this method resulted in alkylation of not only the acid, but also the phenol (**10a** and **10b**, *Scheme 2.3.13*). Since removal of the alkyl group from the phenol would certainly have also hydrolyzed the ester, it was decided to preserve these samples as they were for biochemical analysis.

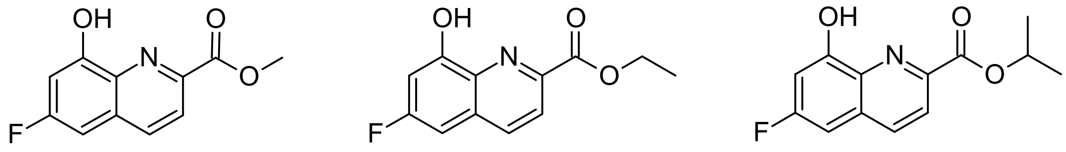


*Scheme 2.3.13 Esterification of quinoline-2-carboxylic acids by nucleophilic attack on an alkyl halide, resulting in alkylation of the phenol*

Therefore, it was desired to introduce a protecting group to the phenol in order to prevent ether formation. However, this proved more difficult than anticipated. In order to selectively protect the phenol without also affecting the carboxylic acid, installation of the protecting group must occur before the acid is formed by $SeO_2$ oxidation. As was the case with phenol protection during amide synthesis (see Section 2.3.1.1), that means the protecting group must be resilient to both the basic conditions of the oxidation reaction and the highly acidic conditions of the subsequent workup and isolation. In addition, the protecting group must be durable under the conditions of the ester synthesis, and the newly formed ester must be stable to the ensuing deprotection of the phenol. This multitude of requirements drastically reduced the number of viable protecting groups.

For instance, while silyl ethers are easily introduced to phenols, they are extremely acid labile and would not survive the low pH required for isolation of the carboxylic acid after oxidation. Conversely, methyl and benzyl ethers are extremely stable to both acidic and basic conditions, but removal of these protecting groups requires harsh conditions such as $BBr_3$ which would destroy the ester. Acetal, carbonate, and ester protecting groups all pose similar difficulties. Therefore ester synthesis via nucleophilic substitution of the carboxylate on alkyl halides did not appear to be a viable option.

Rather than resort to some of the more complex ester synthesis techniques, it was then decided to revisit the method of Fischer esterification. The standard reaction was again run with a large excess of alcohol and a catalytic amount of sulfuric acid, but instead of a workup procedure after the reaction had finished, the crude reaction mixture was immediately purified via flash chromatography over silica gel. In this way the methyl, ethyl, and isopropyl esters (**9a**, **9b**, **9c**, *Figure 2.3.11*) were obtained in fair to good yields.



**9a** **9b** **9c**

*Figure 2.3.11 Desired ester quinoline derivatives*

### 2.3.3 Alcohols

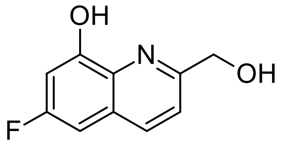
Primary alcohols can be obtained by several methods of carbonyl reduction. These range from the mild reduction of aldehydes by $NaBH_4$ to the extremely harsh Superhydride[*] reduction of nearly any carbonyl it encounters, including relatively stable amides. The choice of reducing agent is highly dependent on the substrate and other functional groups [44].

---

[*] Lithium triethylborohydride

#### 2.3.3.1 Results and Discussion

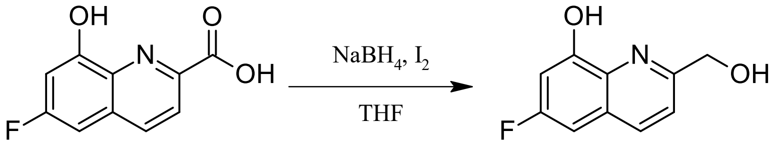
A primary alcohol on the 2-position of the quinoline ring (specifically a hydroxymethyl group) was considered an attractive analog to explore (**12,** *Figure 2.3.12*). While it did not present any additional advantages over carboxylic acid derivatives in terms of extra zinc-coordinating lone pair electrons or space-consuming alkyl groups, the supplemental flexibility inherent in the sp$^3$-hybridized methylene carbon presented interesting binding opportunities.



**12**

*Figure 2.3.12 Hydroxymethyl quinoline derivative*

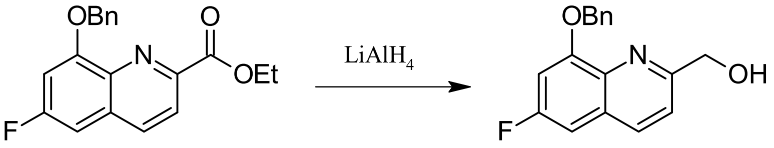
Initially synthesis of this analog was attempted through reduction of the previously synthesized quinoline-2-carboxylic acid. Although sodium borohydride is generally not strong enough to reduce carboxylic acids, addition of a substoichiometric amount of $I_2$ can catalyze the reaction to completion (*Scheme 2.3.14*) [68]. Disappointingly, these conditions did not produce any of the desired reduction product.



**2b**

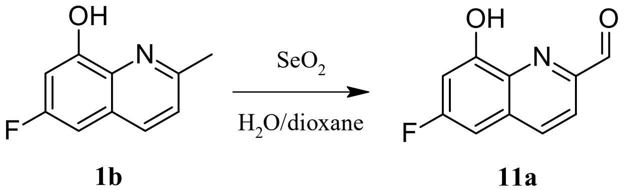
*Scheme 2.3.14 Reduction of carboxylic acid to hydroxymethyl using sodium borohydride and molecular iodine*

Next a more aggressive reducing agent was used. Lithium aluminum hydride was combined with the quinoline methyl ester in diethyl ether, but even after several days no reaction occurred; only starting material was present in the reaction mixture. After careful consideration, it seemed likely that the slightly acidic phenol had deactivated the borohydride reagent. This would occur when the basic hydride ions deprotonate the phenol, thereby releasing hydrogen gas and precluding these ions from performing the desired reduction. Therefore the next iteration of this approach involved protection of the phenol with a benzyl group. The benzyl-protected quinoline ethyl ester was subjected to lithium aluminum hydride reduction (*Scheme 2.3.15*) [69]; however, despite the more reactive reducing agent and extended reflux, the desired product was not discernable in the reaction mixture.



*Scheme 2.3.15 Reduction of ethyl ester to hydroxymethyl using lithium aluminum hydride*

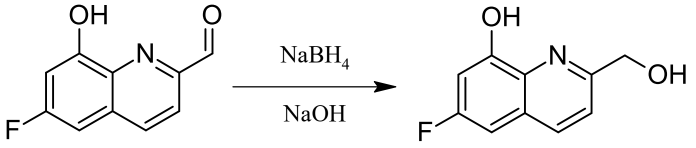
The final attempts to create this analog occurred through reduction of an aldehyde. The aldehyde itself was easily obtained through selenium (IV) oxidation. By simply changing the oxidation reaction solvent from pyridine to a 5:1 mixture of 1,4-dioxane in water, an aldehyde can be obtained rather than a carboxylic acid (**11a**, *Scheme 2.3.16*).



**1b** **11a**

*Scheme 2.3.16 Oxidation of benzylic methyl to aldehyde using selenium (IV) oxide in $H_2O$/dioxane*

Since aldehydes are significantly more reactive than esters or carboxylic acids, use of a milder reducing agent is acceptable. Initially the quinoline-2-carbaldehyde was stirred with sodium borohydride in methanol. However, the acidic phenol once again most likely deactivated the hydride ions, resulting in no formation of the reduction product. To prevent this from occurring again, in the next attempt the quinoline aldehyde was first dissolved in aqueous sodium hydroxide then afterwards combined with sodium borohydride. Promisingly NMR analysis of the crude reaction mixture showed the disappearance of the signature aldehyde peak, and after purification there appeared to be a new methylene peak. While these observations indicated the formation of the desired hydroxymethyl product (**12**, *Scheme 2.3.17*), it was too impure to analyze biochemically and isolated in too small an amount to purify again. The appearance of a successful reaction was encouraging, and in the future this technique could be attempted again, perhaps with a larger excess of reducing agent to ensure enough hydride ions are available for the reduction process.

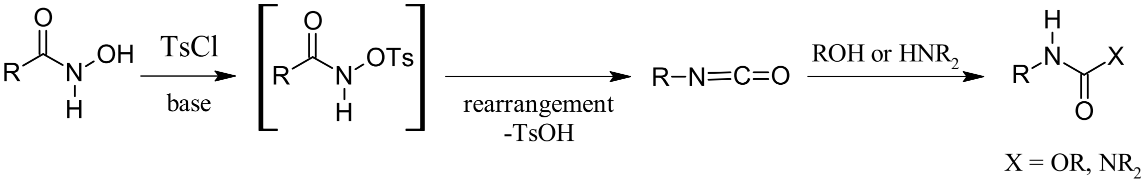


**11a** **12**

*Scheme 2.3.17 Reduction of quinoline-2-carbaldehyde by sodium borohydride in sodium hydroxide to give 2-hydroxymethylquinoline*

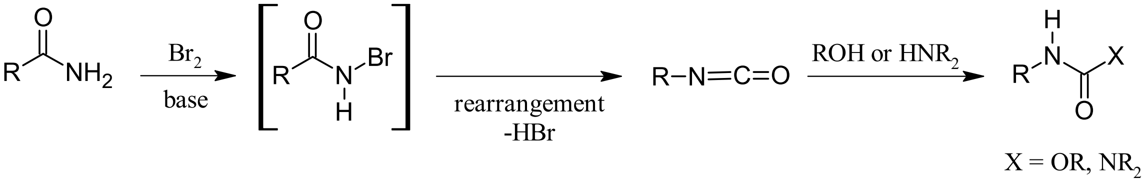
### 2.3.4 Carbamates and Ureas

The latter third of the nineteenth century brought several correlated methods for the preparation of carbamate and urea functional groups from carboxylic acids (or derivatives thereof), generally by way of isocyanate intermediates. The first of these was disclosed by Wilhelm Lossen in 1872 [70] in which hydroxamic acid is converted to an *O*-acyl, sulfonyl, or phosphoryl intermediate, which then undergoes rearrangement to an isocyanate under thermal or alkaline conditions. Upon reaction with an alcohol or amine, the isocyanate is then converted to a carbamate or urea (*Scheme 2.3.18*). However, due to the tendency of the hydroxamic acid to condense with the newly formed isocyanate, this reaction has not seen much synthetic use recently.



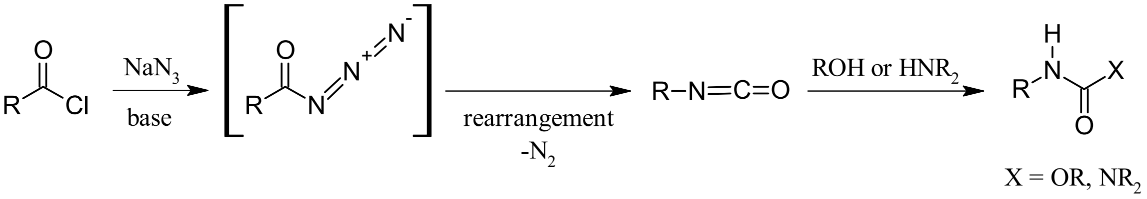
*Scheme 2.3.18 Isocyanate formation by Lossen rearrangement. The isocyanate can then be combined with an alcohol or amine to form a carbamate or urea*

Then in 1881, August Wilhelm von Hofmann reported that halogenated amides also undergo rearrangement to the isocyanate under basic conditions, a process that has come to be known as the Hofmann degradation or Hofmann rearrangement (*Scheme 2.3.19*). This reaction is generally amenable to most aliphatic, aromatic, and heterocyclic amides, but the necessity for strong base precludes its use with compounds containing base-labile functional groups [71].



*Scheme 2.3.19 Isocyanate formation by Hofmann rearrangement. The isocyanate can then be combined with an alcohol or amine to form a carbamate or urea.*

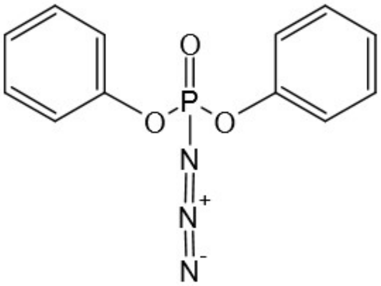
The third installment in this series came in 1890 when Theodor Curtius reported the formation of acyl azides – from the reaction of acyl halides with sodium azide – which then decomposed under thermal conditions with loss of $N_2$ to give the isocyanate intermediate [46]. As with the Lossen and Hofmann rearrangements previously mentioned, carbamates and ureas can be formed from the addition of alcohol or amine to the isocyanate (*Scheme 2.3.20*).



*Scheme 2.3.20 Isocyanate formation by Curtius rearrangement. The isocyanate can then be combined with an alcohol or amine to form a carbamate or urea*

The Curtius method is nearly universally effective with its tolerance to a wide scope of functionality. With $N_2$ and NaCl as the only major byproducts, it also represents an improvement in green chemistry techniques over the atom-uneconomical loss of sulfonic or phosphoric acid with the Lossen procedure and the extrusion of toxic HBr with the Hofmann. Despite these advantages, this procedure also poses a significant risk due to the acute toxicity and explosive danger of sodium azide [72].

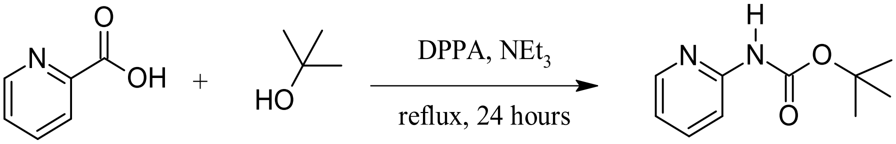
Therefore the most significant modification made to this procedure was the advent of diphenylphosphoryl azide (DPPA, **XXXIV**, *Figure 2.3.13)* as a substitute azidation agent.



**XXXIV**

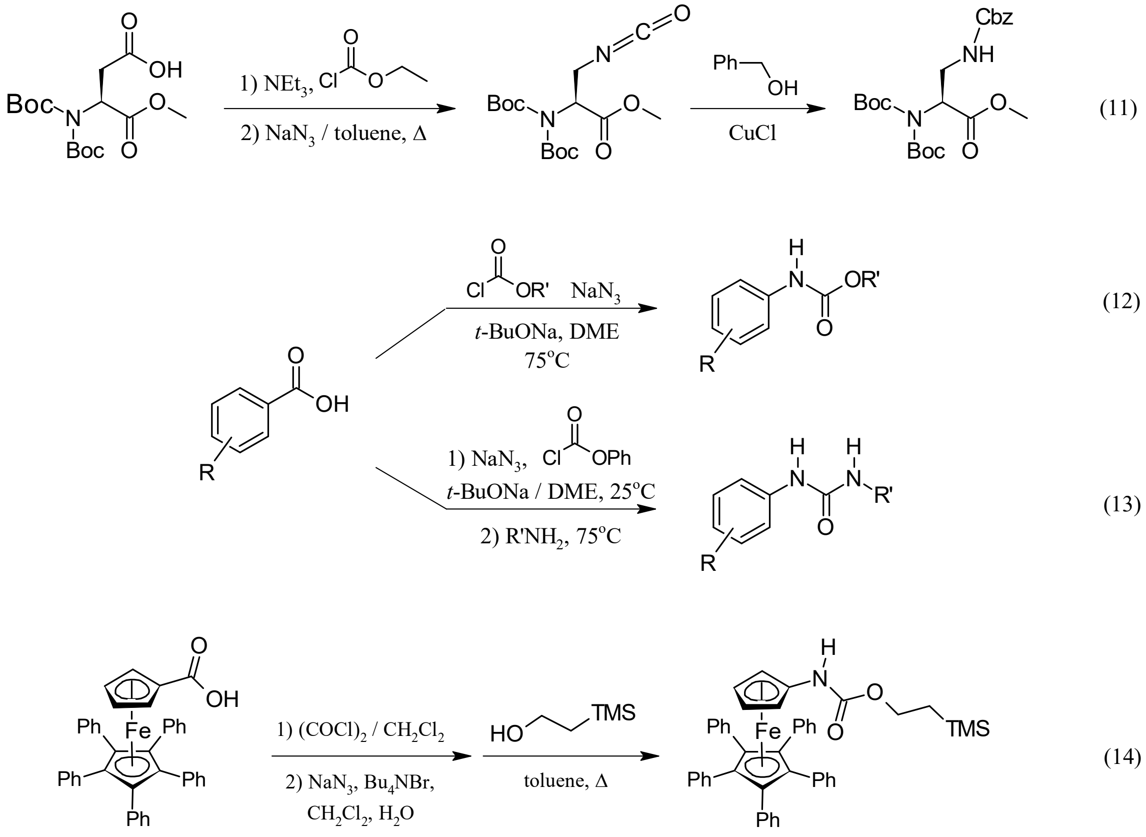
*Figure 2.3.13 Diphenylphosphoryl azide*

Introduced by Shioiri, Ninomiya, and Yamada in 1972 [73] and reportedly first used in a Curtius reaction in 1974 by the same group [74], this modification increased the convenience and efficacy of the reaction. Treating benzoic acid with a variety of alcohols in the presence of DPPA and triethylamine, they obtained the corresponding carbamates in good yield. Moreover, they were purportedly able to expand the scope of the rearrangement to include previously elusive products. For instance, they found the reaction of pyridine-2-carboxylic acid with *tert*-butyl alcohol, which had given poor yield of the rearrangement product under standard Curtius conditions, to be facile with DPPA, giving 73% yield of the *tert*-butyl carbamate (*Scheme 2.3.21*) [74].



*Scheme 2.3.21 Curtius rearrangement using Shioiri reagent modification*

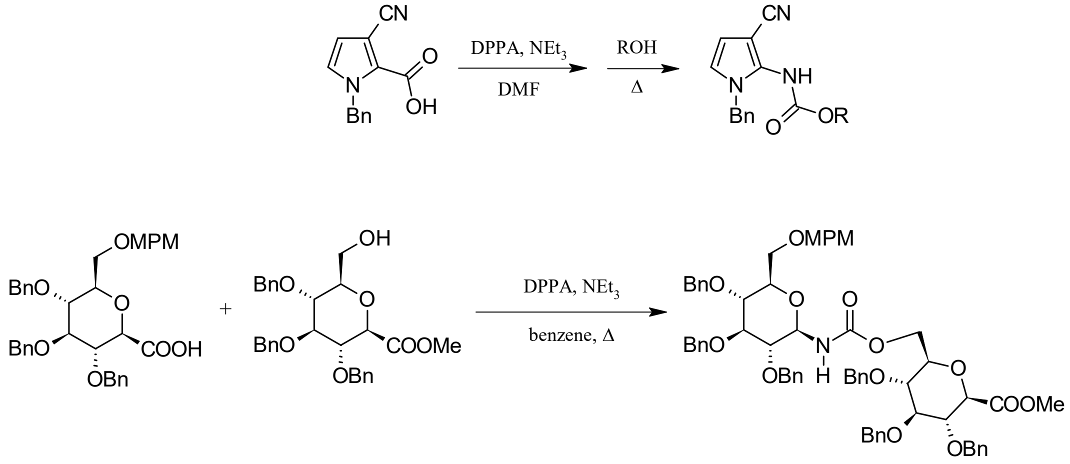
The standard Curtius rearrangement and its variations have recently been widely utilized. For instance, Appella and coworkers [75] synthesized peptide probes containing benzyl carbamate side chains via this method (eq 11, *Scheme 2.3.22*). Lebel and coworker [76] used a similar technique in order to access protected anilines and ureas (eq 12 and 13). Utilizing chloroformates as carboxylic acid activators and heating the resulting mixed anhydride with sodium azide and sodium *tert*-butoxide in 1,2-dimethoxyethane (DME), they were conveniently able to exploit the inherent nucleophilicity of the extruded alkoxide toward the isocyanate, thus forming carbamates in a one-pot procedure. In order to achieve the desired urea compounds, they employed phenyl chloroformate as the acid activator, which extrudes the less nucleophilic phenoxide upon reaction with sodium azide. Subsequent addition of amine provided the desired ureas.


1) NEt3,
2) NaN3 / toluene, Δ
CuCl
(11)
NaN3
t-BuONa, DME
75°C
(12)
1) NaN3,
t-BuONa / DME, 25°C
2) R'NH2, 75°C
(13)
1) (COCl)2 / CH2Cl2
2) NaN3, Bu4NBr,
CH2Cl2, H2O
toluene, Δ
(14)

*Scheme 2.3.22 Various reactions using the Curtius rearrangement to form carbamates and ureas*

Interestingly, Richards and coworker [77] applied this method to the functionalization of organometallic substrates (eq 14, *Scheme 2.3.22*). As part of a larger scheme to obtain 1,2,3,4,5-pentaphenyl-1′-aminoferrocene, they were able to achieve the (trimethylsilyl)ethylcarbamate via Curtius rearrangement in excellent yield.

A wealth of procedures using the DPPA modification can also be found in the literature. These range from simple alkyl and aryl starting carboxylic acids to highly intriguing heterocyclic and glycosidic substrates. Townsend *et al.* [78] described the reaction of 1-benzyl-3-cyanopyrrole-2-carboxylic acids with DPPA, to which was added various alcohols to give the corresponding carbamates (eq 15, *Scheme 2.3.23*). These were then further reacted to obtain biologically interesting pyrimidine compounds.



(15)

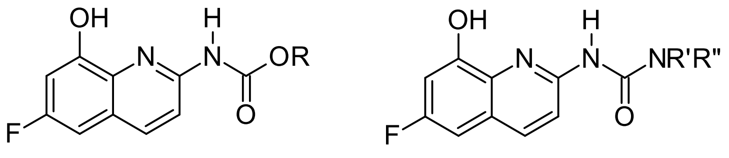
(16)

*Scheme 2.3.23 Various reactions to form carbamates and ureas via Curtius rearrangement using DPPA*

Also, Ikegami *et al.* [79] applied this modification to the synthesis of carbamate- and urea-linked oligosaccharides (eq 16, *Scheme 2.3.23*). These compounds are attractive targets because while they mimic natural oligosaccharides with enhanced stability due to the carbamate or urea linkages, they also present unique biological properties. One of the most important features of the Curtius rearrangement in this situation is the complete retention of stereochemistry at both the carboxylic acid and hydroxymethyl groups.

### 2.3.4.1 Results and Discussion

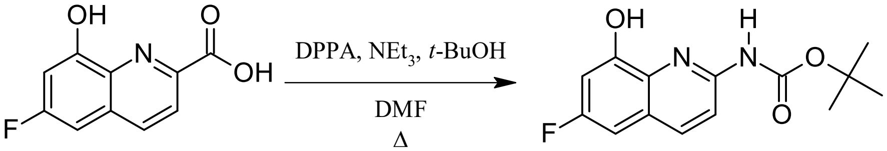
The structurally and electronically similar carbamate and urea derivatives of 6-fluoro-8-hydroxyquinoline were the next functional groups to be explored (**13** and **14**, *Figure 2.3.14*). With multiple nitrogen and oxygen moieties, these analogs provide abundant opportunity for electronic coordination with the $Zn^{2+}$ ion while utilizing the space within the binding pocket.



**13** **14**

*Figure 2.3.14 Carbamate and urea quinoline analogs*

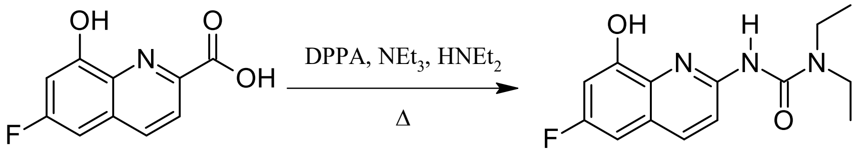
To begin, the aforementioned Curtius rearrangement modification using the so-called Shioiri reagent DPPA was utilized in the attempted synthesis of the *tert*-butyl carbamate derivative. The first trial involved reflux of the quinoline carboxylic acid with DPPA, triethylamine, and *tert*-butyl alcohol in DMF to form the *tert*-butyl carbamate (**13**, *Scheme 2.3.24*). Unfortunately, despite the appearance of a completed reaction on TLC, no product was isolated after chromatographic purification.



**13**

*Scheme 2.3.24 Attempted synthesis of quinoline-2-tert-butyl carbamate*

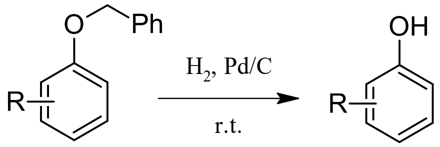
However, when DMF was omitted and the alcohol was used as solvent [74], the desired product was produced, albeit in small yield and with inseparable impurities. Similarly, the reaction was run with diethylamine in place of the alcohol; in this way the diethyl urea derivative was produced in very small quantity (**14**, *Scheme 2.3.25*).



**2b** **14**

*Scheme 2.3.25 Attempted synthesis of quinoline-2-diethylurea*

Despite the attractiveness of performing this reaction with an unprotected phenol, the low yields were unsatisfactory. Therefore further attempts to obtain the carbamate and urea products were executed with the phenol of the starting quinoline-2-carboxylic acid protected with a benzyl group. Under these conditions, isolation of the products was much more productive. Removal of the benzyl ether protecting group was achieved via catalytic hydrogenolysis (*Scheme 2.3.26*) as opposed to the problematic $BBr_3$ method. This mild room temperature alternative proved to be highly effective, affording the desired carbamate **13** and urea **14** relatively cleanly and in good yield.

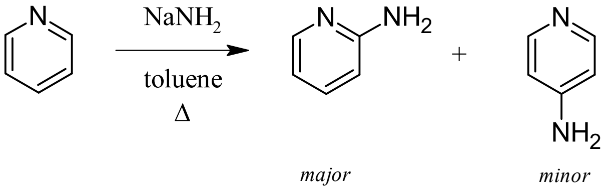


*Scheme 2.3.26 Catalytic hydrogenolysis of benzyl ether protecting group*

### 2.3.5 Amines

Installation of aromatic amines has historically been accomplished by several methods, some of which are particular to aromatic nitrogen heterocycles, and others that are more general. These routes include, among others, the Chichibabin reaction, the mechanistically related Lossen, Hofmann, and Curtius rearrangements, and amination from the *N*-oxide.

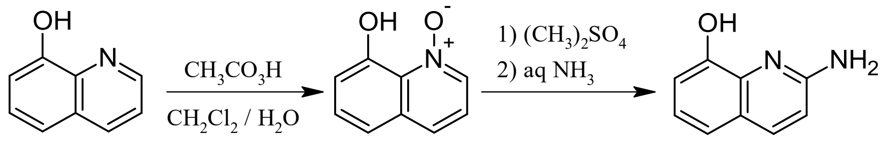
Aleksei Chichibabin reported the first direct amination of pyridine in 1914 [80]. By reacting the heterocycle with sodium amide in toluene, he produced mainly 2-aminopyridine in very good yield with a small amount of 4-aminopyridine as side product (*Scheme 2.3.27*). Applicable to a wide variety of electron-deficient aromatic heterocycles such as quinolines, imidazoles, and pyrimidines, this methodology has proven to be extremely useful over the last hundred years. However, the exceedingly aggressive and highly basic sodium amide reagent significantly decreases the synthetic utility of this procedure, particularly as it relates to functional group compatibility.



*Scheme 2.3.27 Chichibabin amination of pyridine*

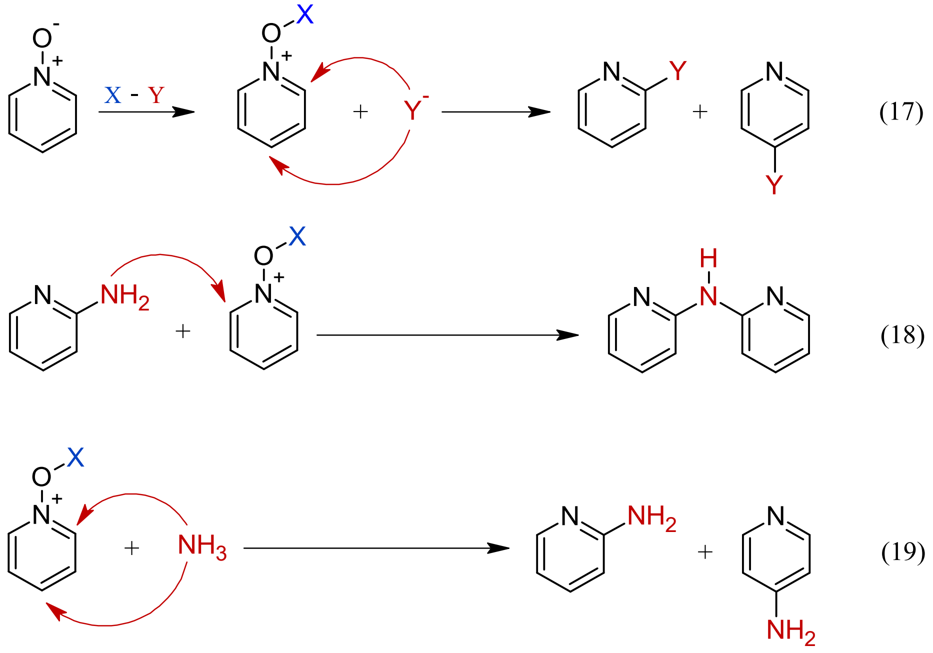
While the Chichibabin reaction exhibits a high degree of regioselectivity in the amination of nitrogen heterocycles, it is still subject to formation of a mixture of products. Alternatively, substitution of a halide by amine at the 2-position of the heterocycle would give only the single 2-amino product. Yet installation of the halide in the first place is itself beset by poor regioselectivity and low yields [81].

A recent development in the direct amination of nitrogen heterocycles came from Storz and associates in 2004 [82] when they desired a scalable route to 2-amino-8-hydroxyquinoline. After a set of unsuccessful trials with the Chichibabin reaction and an outright rejection of the use of toxic chloramines, they developed a new protocol in which the quinoline-*N*-oxide was initially formed by oxidation with peracetic acid. This was then activated by methylation with dimethyl sulfate, and the resultant salt was quenched in aqueous ammonia (*Scheme 2.3.28*). By this method they obtained the desired 2-amino-8-hydroxyquinoline without the need for phenol protection.


OH
N
$CH_3CO_3H$
$CH_2Cl_2$ / $H_2O$
OH
O
N
1) $(CH_3)_2SO_4$
2) aq $NH_3$
OH
N
$NH_2$

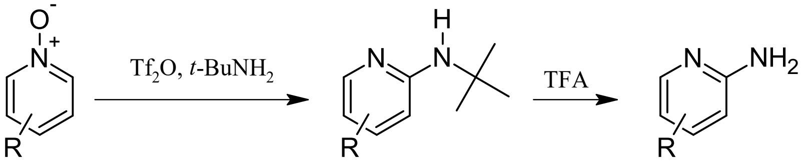
*Scheme 2.3.28 Amination of 8-hydroxyquinoline via N-oxide intermediate*

Despite the perceived ease, this and similar approaches are generally subject to poor yields due to various side-processes occurring simultaneously. These include attack of the activating agent's counterion on the ring (eq 17 *Scheme 2.3.29*), amine-induced dimerization (eq 18), and poor regioselectivity of the amine (eq 19) [81].


O
N
X - Y
O
X
N
+
Y
N
Y
+
N
Y
(17)
N
$NH_2$
+
O
X
N
H
N
N
N
(18)
O
X
N
+
$NH_3$
N
$NH_2$
+
N
$NH_2$
(19)

*Scheme 2.3.29 Side reactions that can occur during amination reaction via N-oxide intermediate.*

These observations induced Yin and coworkers at Merck to attempt a related approach to these pharmaceutically interesting pyridine derivatives. In 2007 [81], they reported 100% conversion of the starting pyridine-*N*-oxide by combining it with *tert*-butylamine and triflic anhydride (trifluoromethanesulfonic anhydride, $Tf_2O$) as activating agent. After formation of the 2-*tert*-butylaminopyridine, the *tert*-butyl group was removed by heating in trifluoroacetic acid (TFA) to give the unprotected 2-aminopyridine (*Scheme 2.3.30*).



*Scheme 2.3.30 Primary aryl amine formation by acid hydrolysis of aryl tert-butylamine*

These conditions served to minimize the formation of unwanted 4-aminopyridine[*] while maximizing overall yield of desired product. However, this was accomplished mainly through saturation of the reaction mixture with superstoichiometric amounts of $Tf_2O$ and *tert*-butylamine, thereby ensuring that even if the amine was deactivated by attack on the triflic anhydride, there would be enough of both remaining in the mixture to react with the pyridine-*N*-oxide. Therefore, although the high yield and selectivity of this method are favorable, the atom economy is less so.

This method was also used by the team of Cheng and Judd at Amgen. In 2011 [83] they reported on the synthesis of a library of potent small molecule inhibitors of BACE1[†] towards a novel treatment of Alzheimer's disease. Fragment screening identified the 2-aminoquinoline moiety as a starting point, and one approach used to obtain these molecules was essentially that of Yin *et al.* As part of a broader synthetic strategy, they obtained several diversely substituted 2-aminoquinolines, mostly in fair to excellent yields (eqs 20, 21, 22, *Scheme 2.3.31*).

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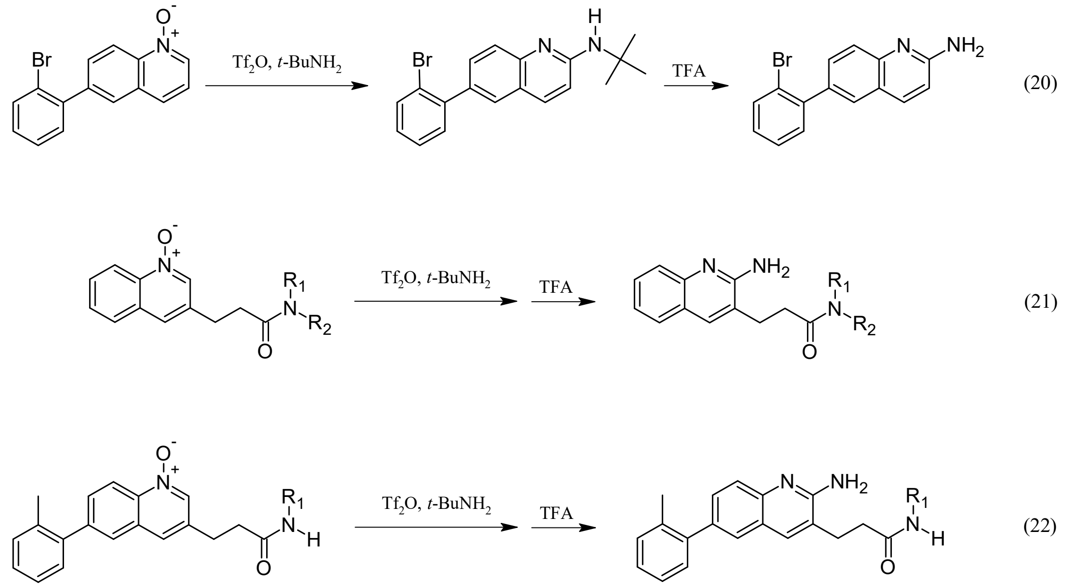
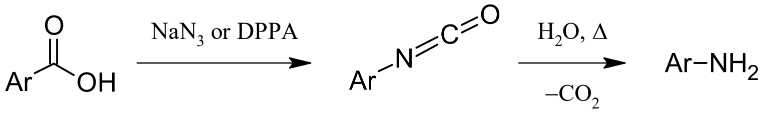
[*] 59:1 ratio of 2- to 4-aminopyridine was observed.

[†] Beta-site amyloid precursor protein cleaving enzyme 1



*Scheme 2.3.31 Reactions to form amines utilizing tert-butylamine and Tf2O*

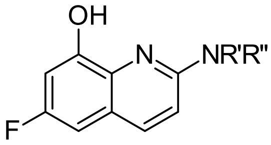
As previously discussed in section 2.3.4, the Lossen, Hofmann, and Curtius rearrangements are mechanistically related strategies toward the formation of isocyanates. In addition to the ureas and carbamates that are produced upon introduction of amines or alcohols to the isocyanate intermediate, this reaction can also be used to form primary aryl amines. Addition of water to the isocyanate results in the carbamic acid, which is significantly less stable than the associated carbamate and spontaneously decomposes upon heating to carbon dioxide and the aryl amine (*Scheme 2.3.32*).



*Scheme 2.3.32 Primary aryl amine formation by Curtius rearrangement*

#### 2.3.5.1 Results and Discussion

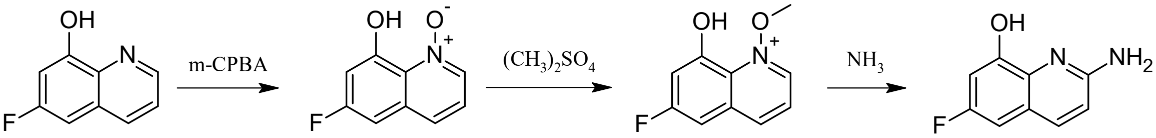
Amine functional groups at the 2-position of the quinoline ring were also considered desirable HCA analogs (**15**, *Figure 2.3.15*). Similar to amides, resonance of the nitrogen lone pair electrons into the quinoline ring would present interesting interactions within the enzyme while imparting diverse space-exploiting alkyl groups.



**15**

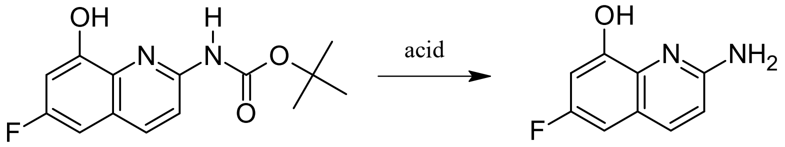
*Figure 2.3.15 Quinoline with amine functional group*

Building off the work of Storz and associates, it was first attempted to obtain the amine-substituted quinolines by activating the 2-position of the heterocycle by methoxylation of the ring nitrogen (*Scheme 2.3.33*). The *N*-oxide was formed through reaction with *m*-CPBA and subsequently methylated by dimethyl sulfate. Once activated, a solution of $NH_3$ in dioxane was added and the reaction was stirred at room temperature. Unfortunately two trials of this reaction did not produce any discernible product.



*Scheme 2.3.33 Attempted amination on 2-position of quinoline by methoxylation of ring nitrogen and addition of ammonia*

It was then noted that the previous formation of the *tert*-butyl carbamate could be an advantageous alternative to a direct amination reaction. Since a *tert*-butyl carbamate is essentially a Boc[*]-protected amine, acid hydrolysis of the *tert*-butoxy protecting group by acid would result in the primary amine (*Scheme 2.3.34*) [84]. This was attempted through stirring the carbamate in a mixture of trifluoroacetic acid (TFA) and $CH_2Cl_2$ at room temperature. NMR analysis indicated a very small conversion of the carbamate to an amine; however, it was not isolable.



*Scheme 2.3.34 Acid hydrolysis of tert-butylcarbamate to form primary amine on 2-position of quinoline*

### 2.3.6 Heterocycles

Heterocycles represent one of the largest categories of compounds within organic chemistry and account for the majority of pharmaceutically and industrially significant compounds [85]. There are innumerable heterocyclic components that have countless combinations of nitrogens, oxygens, and sulfurs in a broad range of ring sizes and arrangements. Since an exhaustive accounting of these various permutations would be impractical, only a few will be highlighted.

Indoles are one of the most important and widely used structural motifs in organic chemistry and chemical biology. Among the most plentiful heterocycles in nature, indoles account for over 3000 characterized biological compounds including the amino acid tryptophan (**XXXV**, *Figure 2.3.16*) and the neurotransmitter serotonin (**XXXVI**). In addition, indoles are often integral parts of powerful pharmacophores such as in the statin drug Fluvastatin (**XXXVII**) [86].

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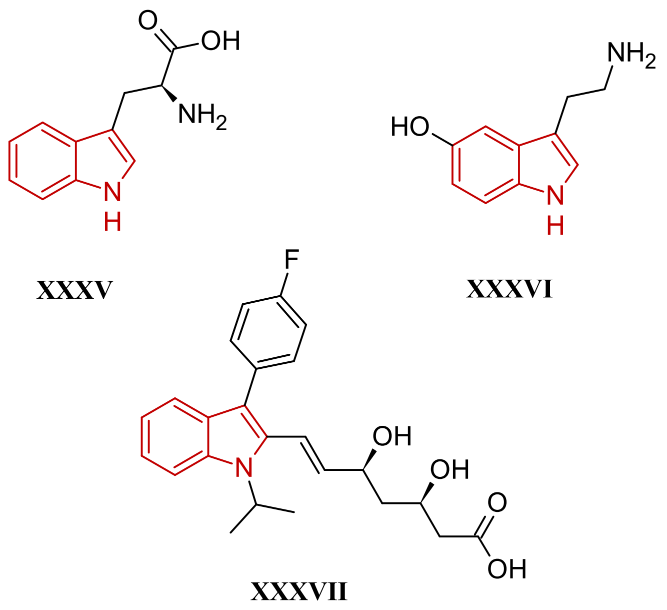
[*] Boc = *tert*-butyloxycarbonyl

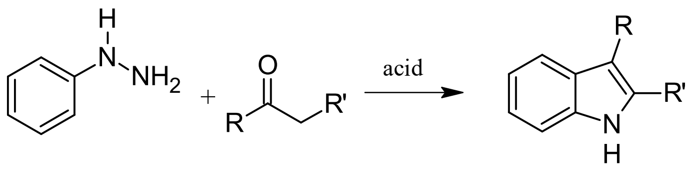

**XXXV**

**XXXVI**

**XXXVII**

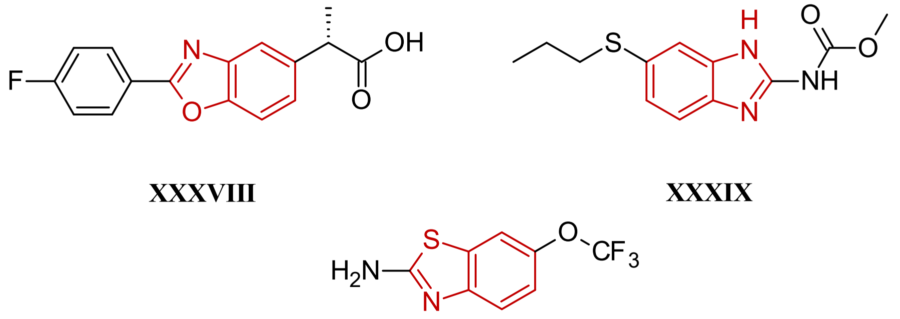
*Figure 2.3.16 Naturally-occurring and biologically active indole-based compounds*

While there are nearly as many routes to synthesize indoles as there are indole compounds in nature, a few are more widely used than the others. The Fischer indole synthesis, introduced in 1884 by Emil Fischer – whom we have encountered a few times before – is one of the oldest, simplest, and most ubiquitous means to obtain this heterocycle. This method involves the reaction of phenylhydrazine with a ketone under acid catalysis (*Scheme 2.3.35*) [87]. The pliability of this reaction rests in its tolerance to a wide variety of substitution on both the aryl and ketone components.



*Scheme 2.3.35 Fischer indole synthesis*

Structurally related benzoxazoles, benzimidazoles, and benzothiazoles are biologically and industrially important isosteres of indole. While precedent has been set over the last 35 years for the production and use of these structures scaffolds for compounds with light-emitting properties [88], there are also many examples of their use in biologically active compounds. These include the benzoxazole-based anti-inflammatory drug flunoxaprofen (**XXXVIII**, *Figure 2.3.17*), the benzimidazole-based anti-parasitic albendazole (**XXXIX**), and the benzothiazole-based ALS therapy riluzole (**XL**).



**XXXVIII**

**XXXIX**

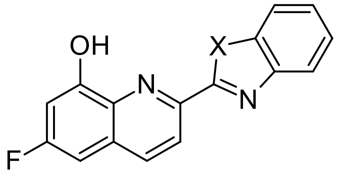
**XL**

*Figure 2.3.17 Structures of benzoxazole, benzimidazole, and benzothiazole compounds that show biological activity*

The most common synthetic route toward these heterocycles is a cyclization reaction between a functionalized aldehyde and an appropriately substituted aniline. While this general method is useful for all three heterocycles, the specifics of each individual reaction vary greatly. The benzothiazole can be synthesized by simply refluxing the aldehyde and 2-aminothiophenol in DMSO, but the benzimidazole needs the more acidic mixture of thionyl chloride and silica gel in order to cyclize. The benzoxazole requires a multi-step process involving functional-group protection [89], Schiff base formation, and DDQ oxidation [90].

### 2.3.6.1 Results and Discussion

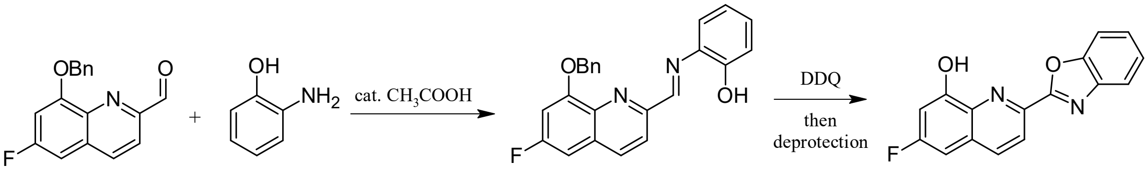
An additional approach to introducing an $sp^2$-hybridized metal coordination site at the 2-position of the quinoline ring came in the form of heterocyclic moieties (**16**, *Figure 2.3.18*). In fact, there is ample precedent for the use of 8-hydroxyquinolines with heterocyclic substituents at the 2-position as tridentate metal chelators. While Bünzli and associates found 8-hydroxyquinolines with benzoxazole substituents to be excellent lanthanide chelators for use in near-infrared luminescent materials [90], Hwang and coworkers complexed benzothiazole-based compounds with iridium (III) to exploit the heavy metal's phosphorescent properties [91]. Most intriguingly, Zhou *et al.* used benzimidazole-substituted 8-hydroxyquinolines as novel $Zn^{2+}$ chelate ligands in order to take advantage of their electroluminescent properties in organic light-emitting diodes [89]. This directly demonstrates these compounds' ability to tightly coordinate with a zinc ion, which is highly advantageous for the present study.



**16**

*Figure 2.3.18 Heterocyclic quinoline derivatives: X can be CH, NH, O, or S*

To begin, the benzoxazole derivative was considered the most promising insofar as metal-chelating ability was concerned. In order to access the benzyl-protected quinoline-8-ol-2-carbaldehyde precursor, 8-benzyloxy-6-fluoro-quinaldine was subjected to the same oxidation as described in Section 2.3.3.1. The intermediate Schiff base was formed by combination of the aldehyde with 2-aminophenol under acid catalysis, and the subsequent cyclization was achieved under reflux with DDQ [90]. Upon phenol deprotection, the final benzoxazole compound (**16a,** *Scheme 2.3.36*) was isolated in good yield.

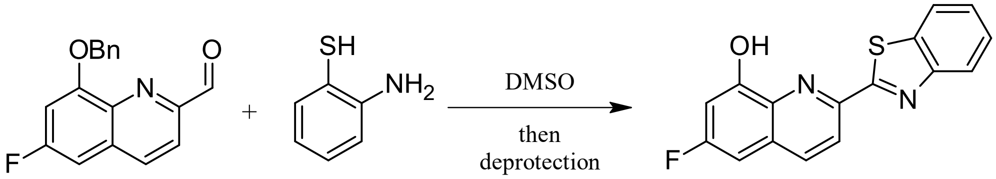


**11b**

**16a**

*Scheme 2.3.36 Formation of quinoline benzoxazole derivative*

The relatively straightforward synthesis of the benzothiazole derivative was attempted next. Although protection of the phenol was not strictly necessary [90], this precaution was taken and the benzyl-protected quinoline-2-carbaldehyde was refluxed with 2-aminothiophenol in DMSO (*Scheme 2.3.37*). Upon deprotection, the desired analog was obtained in poor yield. In an attempt to bypass loss of product due to the extra protection/deprotection steps, the unprotected aldehyde was subjected to the same reaction conditions. However, no product was isolated from this attempt.



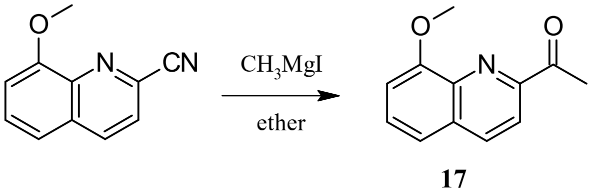
**11b**

**16b**

*Scheme 2.3.37 Formation of quinoline benzothiazole derivative*

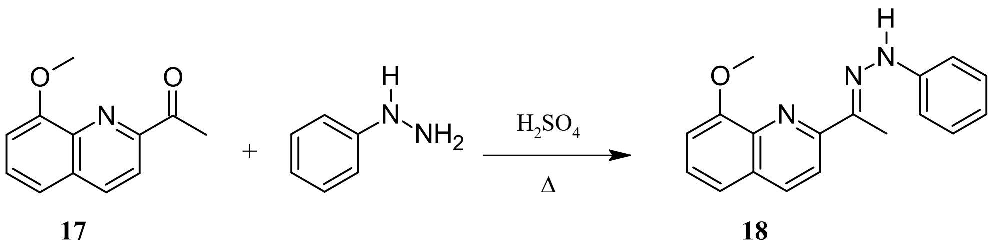
In order to obtain the benzimidazole analog, the benzyl-protected aldehyde was combined with *o*-phenylenediamine in a dichloromethane solution of oxalyl chloride and silica gel [89]. Under these conditions, no product was formed and only the original aldehyde was recovered. Simply refluxing in DMSO, though, appeared to be more successful. NMR analysis indicated the consumption of aldehyde starting material and the apparent formation of product. Upon deprotection and purification, the product had appeared to be present, but was impure and in too small a quantity to pursue further.

The final heterocyclic derivative attempted was an indole substitution on the 2-position of the quinoline ring. The model reaction began with preparation of quinoline-2-methylketone (**17**, *Scheme 2.3.38*) by a Grignard reaction of methyl magnesium iodide with the commercially available 8-hydroxyquinoline-2-carbonitrile. Protection of the phenol was performed in order to avoid deactivation of the Grignard reagent.



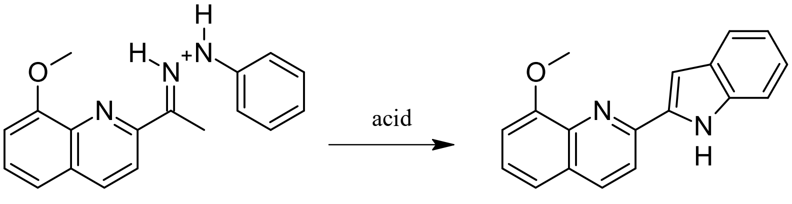
*Scheme 2.3.38 Grignard reaction of quinoline-2-carbonitrile to give quinoline-2-methylketone*

Under standard Fischer conditions of refluxing the quinoline-2-methylketone with phenyl hydrazine under acidic conditions [92], the indole cyclization did not go to completion. Instead, despite extended reaction times and high reflux temperatures, the reaction stopped at the intermediate hydrazone (**18**, *Scheme 2.3.39*).



*Scheme 2.3.39 Attempted Fischer indole synthesis under acid reflux*

In an attempt to force the hydrazone to cyclize into an indole (**19**, *Scheme 2.3.40*), the intermediate was refluxed in acids of varying strengths. While trifluoroacetic acid [93], *p*-toluenesulfonic acid [94], and methanesulfonic acid [95] were ineffective in prompting the cyclization, acetic acid actually caused the hydrazone to revert back to the methyl ketone.

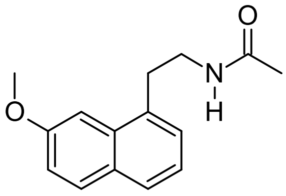


**18** **19**

*Scheme 2.3.40 Attempted cyclization of hydrazone to indole by acid catalysis*

## 2.4 Exo-ring nitrogen

Naphthalenes are important building blocks of biologically active compounds, especially within antidepressant therapeutics such as Agomelatine (**XLIV**, *Figure 2.4.1*) [96]. Naphthalenes with *ortho*-amino esters are less well known; therefore although there are innumerable means to obtain variously substituted naphthalenes, not many involve direct routes to this interesting derivative.

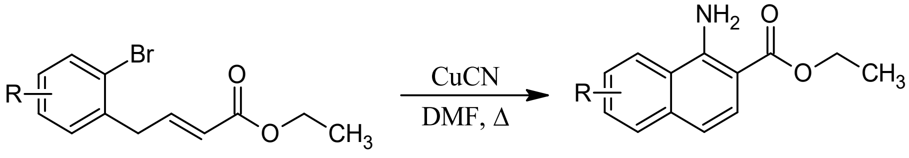


**XLIV**

*Figure 2.4.1 Agomelatine, naphthalene-containing biologically active compound*

Amino naphthalene compounds are generally constructed one of two ways: through placement of the amine on a previously assembled naphthalene via substitution reaction, or through cyclization of an aromatic precursor that already contains the amine functionality. It is generally preferred to proceed through the annulation route, since substitution on the naphthalene core is tedious and requires preexisting directing groups [97].

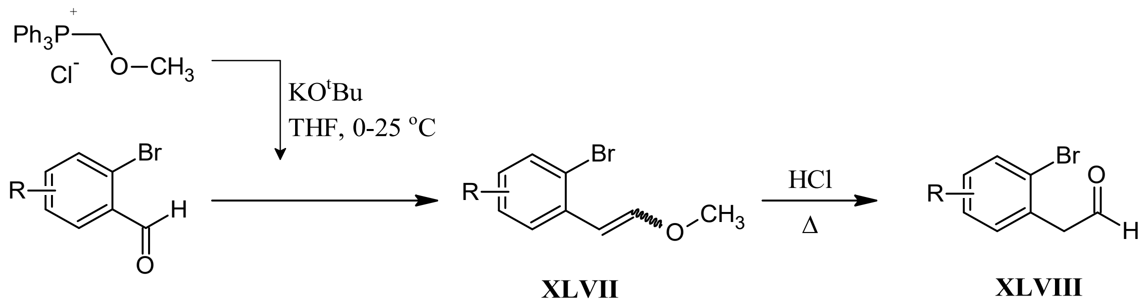
A review of the literature indicates numerous routes toward cyclization of an aromatic precursor into a naphthalene with an amino group in the 1-position. However, these methods generally suffer from highly variable yields and poor atom economy. Therefore Sudalai and coworkers explored a simple synthetic process toward these molecules. This method affords ethyl 1-aminonaphthalene-2-carboxylates by copper-mediated substitution of a bromine for cyanide ortho to an α,β-unsaturated ester on an aromatic ring (**XLV**, *Scheme 2.4.1*), which then spontaneously cyclizes and rearomatizes to the naphthalene (**XLVI**) [97].



**XLV** **XLVI**

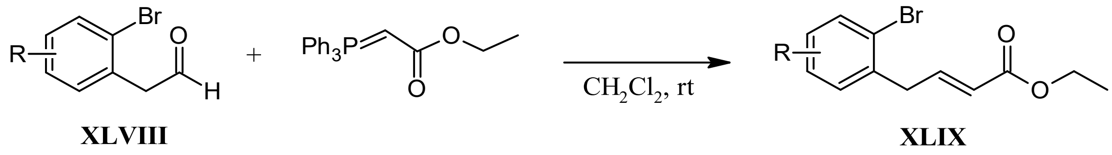
*Scheme 2.4.1 CuCN-mediated cyclization to aminonaphthalenes*

Sudalai also described the synthetic route to the *o*-bromo-α,β-unsaturated ester precursor whereby, starting with the appropriate *o*-bromoacetaldehyde, Wittig olefination affords the corresponding enol ether (**XLVII**, *Scheme 2.4.2*). Acid hydrolysis of the ether then gives the bromophenylacetaldehyde (**XLVIII**).


Ph3P
Cl-
O—CH3
KOtBu
THF, 0-25 °C
Br
R
H
O
CH3
HCl
Δ
XLVII
XLVIII

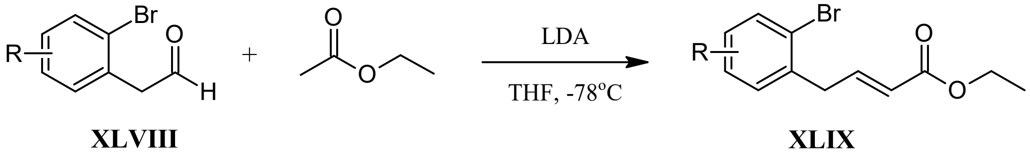
*Scheme 2.4.2 Synthetic scheme to phenylacetaldehyde*

The desired ethyl 4-(2-bromophenyl)-2-butenoate (**XLIX**) could then conceivably be prepared by two methods. The first approach, used by Sudalai, subjects the bromophenylacetaldehyde to Wittig conditions (*Scheme 2.4.3*).


Br
R
O
H
+
Ph3P
O
CH2Cl2, rt
XLVIII
XLIX

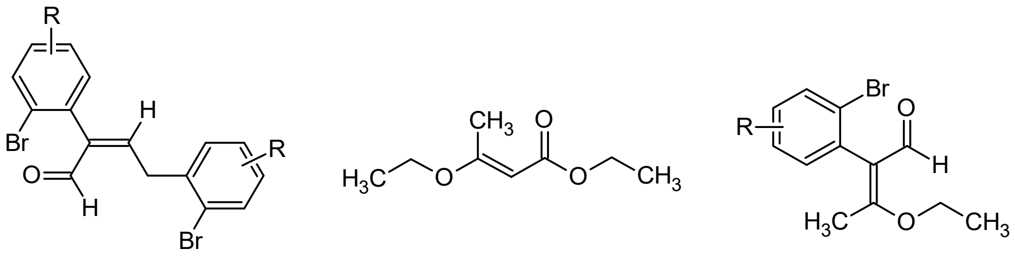
*Scheme 2.4.3 Synthesis of ethyl 4-(2'-bromophenyl)-2-butenoate by Wittig Synthesis*

Alternatively, the aldehyde could undergo aldol condensation with ethyl acetate under highly basic conditions to give the same product (*Scheme 2.4.4*) [98].


Br
R
O
H
+
O
LDA
THF, -78°C
XLVIII
XLIX

*Scheme 2.4.4: Synthesis of ethyl 4-(2'-bromophenyl)-2-butenoate by Aldol Condensation*

The aldol route would plausibly be of greater synthetic value since it uses more cost-effective reagents (ethyl acetate vs. pre-made or synthesized ethyl phosphorylidene) and has much improved atom economy with less wasteful byproducts ($H_2O$ vs. triphenylphosphine oxide). However, conventional mixed aldol condensations often suffer from poor regioselectivity [99], meaning the yield of the desired product could be decreased by several undesired alternative reactions: self-condensation of the aldehyde (**L**, *Figure 2.4.2*) or ester (**LI**), or cross-condensation of the alpha carbon of the aldehyde with the carbonyl of ethyl acetate (**LII**).



**L** **LI** **LII**

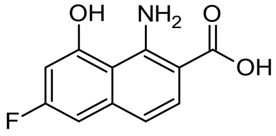
*Figure 2.4.2 Undesired side reaction products of Aldol Condensation*

Formation of these undesired side products could be alleviated by directed aldol synthesis [99]. Preliminary deprotonation of the alpha carbon of ethyl acetate with an equimolar amount of lithium diisopropylamide (LDA) would ensure the ethyl acetate is fully deprotonated (and thus further resistant to self-aldol) before it is mixed with the aldehyde. This directed aldol synthesis circumvents the undesirable formation of the aldehyde enolate, and since it is performed at -78°C, it exerts kinetic control over the development of crossed-aldol products.

This method of forming 4-(2-bromophenyl)-2-butenoate via aldol condensation is not without drawbacks. For one, any relatively acidic functional group would have to be protected before being combined with the enolate. Also lithium diisopropylamide is a highly reactive base [100], and use of a full equivalent would certainly create waste in the form of lithium chloride and diisopropylamine. However, from a green chemistry point of view, aldol condensation would be far more atom-economical than Wittig synthesis for this reaction.

### 2.4.1 Results and Discussion

As previously mentioned, PyMol analysis of the site within MtFBA where the quinoline analogs bind indicated that a $Zn^{2+}$ ion coordinates with several atoms on the structure through donated lone pair electrons. This included the nitrogen within the quinoline ring. It was postulated that converting that nitrogen to an exo-cyclic primary amine could displace the zinc at the active site, thereby allowing that nitrogen, as well as the two oxygens of the carboxylic acid and phenol, to directly interact with the side chains of the protein. Therefore, as proof of concept, it was proposed to create 1-amino-6-fluoro-8-hydroxynaphthalene-2-carboxylic acid (**24**, *Figure 2.4.3*).



**24**

*Figure 2.4.3 Proposed analog 1-amino-6-fluoro-8-hydroxynaphthalene-2-carboxylic acid*

To begin, it was decided that 2-bromophenol-3-carbaldehyde (*Figure 2.4.4*) would act as model substrate for this reaction since the fluorinated analogs of the desired starting compound were prohibitively difficult to obtain.

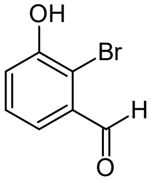
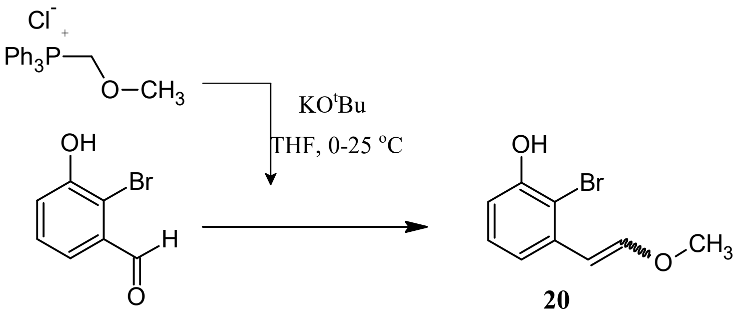


*Figure 2.4.4 Starting aldehyde*

This substrate was first subjected to the conditions of the Wittig olefination, wherein (methoxymethylene)triphenylphosphonium chloride was deprotonated by potassium *tert*-butoxide at 0°C to give the ylide, which was then combined with the aldehyde to give the enol ether (**20**, *Scheme 2.4.5*). However, several trials of this reaction consistently gave only partial conversion of the aldehyde to the enol ether[*], despite variations in reaction time. After some consideration, it was hypothesized that two variables could be at play to cause the low conversion. First, since the phosphonium chloride and butoxide were added together at 0°C and remained at that temperature while the aldehyde was added, it is possible that ylide formation was incomplete. Second, the relatively acidic phenol on the benzaldehyde could easily be deprotonated by the ylide, thus deactivating this reagent and prohibiting further reaction.



*Scheme 2.4.5 Wittig olefination to obtain enol ether*

In order to counteract these effects, the reaction was performed again, but the phosphonium-butoxide mixture was allowed to warm to room temperature for an hour before cooling again prior to aldehyde addition. This initially appeared to facilitate the reaction, as evidenced by the robust formation of white precipitate, presumably triphenylphosphine oxide. However, after 24 hours of stirring at room temperature, the precipitate had dissolved back into solution. At this point, another equivalent of butoxide was added to the reaction mixture and allowed to stir overnight. Vigorous formation of precipitate, along with positive TLC analysis, indicated the success of this tactic. Subsequent NMR analysis confirmed the absence of aldehyde starting material. However, the isolated yield of enol ether was disappointingly low. Most likely, the factor responsible for this phenomenon was the aforementioned deprotonation of the phenol by either KO$^t$Bu or the ylide. This would complicate isolation of the product since the phenoxide salt would not be as amenable to extraction by an organic solvent, instead remaining at least partially in the aqueous medium.

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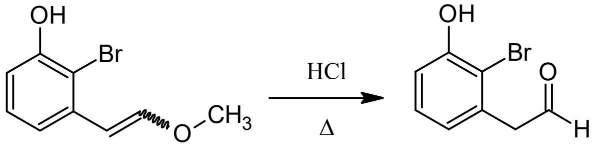
[*] As seen by NMR.

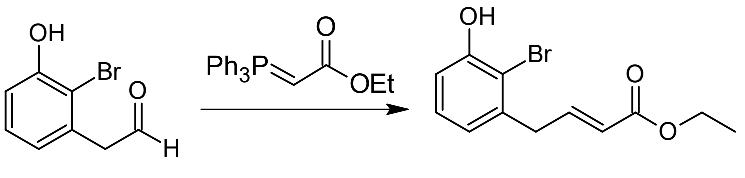
Nevertheless acid hydrolysis of the enol ether was performed, and the intended (2-bromo-3-hydroxyphenyl)acetaldehyde was obtained (**21**, *Scheme 2.4.6*).



**20** **21**

*Scheme 2.4.6 Acid hydrolysis of aryl enol ether to aryl acetaldehyde*

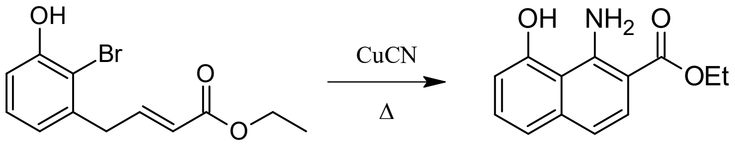
Next the aldehyde was converted to an α,β-unsaturated ester by Wittig reaction; (carbethoxymethylene)triphenylphosphorane was combined with the aldehyde to form the intended cyclization precursor (**22**, *Scheme 2.4.7*).



**21** **22**

*Scheme 2.4.7 Wittig reaction to form α,β-unsaturated ester*

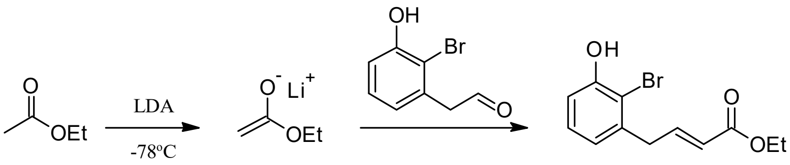
Finally, reflux with CuCN gave the cyclized ethyl 1-amino-8-hydroxynaphthalene-2-carboxylate (**23**, *Scheme 2.4.8*). However, the yield and purity of the isolated product were subpar. Multiple trials consistently resulted in a very small amount of product that was contaminated with the uncyclized α,β-unsaturated ester intermediate; unfortunately the amount of aminonaphthalene recovered was not enough to attempt hydrolysis of the ester into the carboxylic acid. While this synthetic method appeared promising, it required some adjustments.



**22** **23**

*Scheme 2.4.8 CuCN-mediated cyclization to form naphthylamine*

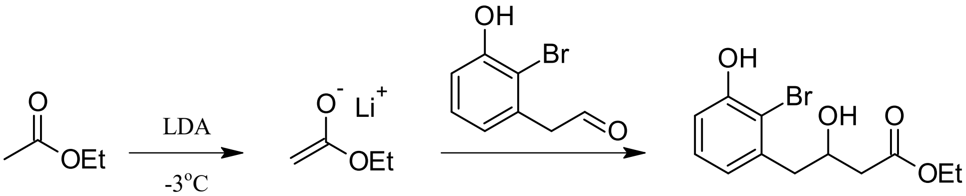
In a subsequent attempt to obtain this product, the alternative aldol method of α,β-unsaturated ester formation was utilized. Lithium diisopropyl amide was first combined with ethyl acetate at -78°C to form the enolate, which was then added to the acetaldehyde (*Scheme 2.4.9*). Despite several observed color changes and the disappearance of acetaldehyde starting material on TLC, no desired product was recovered.



**22**

*Scheme 2.4.9 Aldol condensation method of obtaining α,β-unsaturated ester*

A second attempt was performed, this time at a more moderate -3°C. After workup and purification, NMR analysis indicated the aldol addition β-hydroxy ester product had likely been formed (**22**, *Scheme 2.4.10*); however, the subsequent attempt at dehydration by heating in acid was unsuccessful.

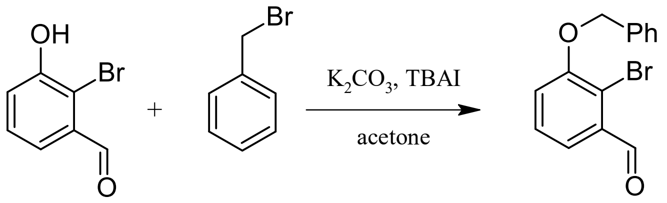


**22**

*Scheme 2.4.10 Aldol addition reaction that resulted in β-hydroxy ester*

Since it was possible that the commercial LDA reagent was degraded, a final trial was conducted in which LDA was generated *in situ* via deprotonation of diisopropylamine by butyllithium. This was then combined with ethyl acetate at -78°C, and after an hour the aldehyde was added. However, this procedure also resulted in no isolated product.

As with the previous problems encountered in this series of reactions, it was hypothesized that the highly basic conditions of this step were incompatible with an unprotected phenol. The difficulty this situation posed was an unprecedented circumstance since Sudalai had not used any substrates with even marginally acidic functional groups. Therefore, as a preventive measure against this problem, it was decided that a protecting group on the phenol would be beneficial. As previously mentioned, benzyl ether protecting groups are stable to both acidic and basic conditions, so this was decidedly the best choice to use on the phenol of the starting aldehyde (*Scheme 2.4.11*).



*Scheme 2.4.11 Benzyl ether protection of starting aldehyde*

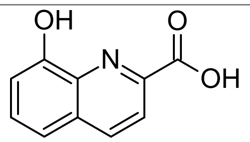
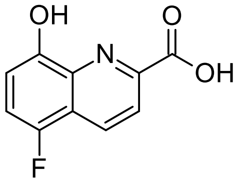
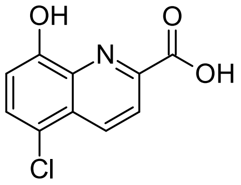
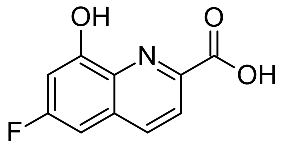
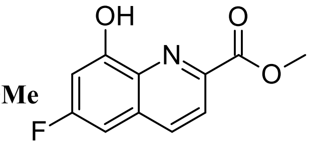
While the protection itself was a facile process, the subsequent reactions were disturbingly ineffective. Formation of the enol ether was partially successful, but the following acid hydrolysis gave only starting material and an unidentifiable product. Therefore this derivative was tabled for further synthetic analysis.

## 2.5 Biochemical analysis, future directions, and conclusion

Pegan and coworkers utilized various assays to analyze the inhibitory capability of the synthesized quinoline-2-carboxylic acid analogs against MtFBA. Initially they utilized the Resazurin Blue Assay to analyze cell viability when exposed to the inhibitors [27]. This assay measures the fluorescence change seen when metabolically active cells reduce the non-fluorescent dye resazurin to the strongly-fluorescent dye resorufin. Since nonliving cells are not able to perform this reduction, it is possible to use the fluorescence output to detect the percentage of nonliving cells among those that have been exposed to the inhibitors [101]. In this way the $IC_{50}$ values and percentages of inhibition of each potential inhibitory compound can be calculated. In addition, this assay can be used to determine MIC values by visually inspecting the nutrient broth for cell growth [27].

Using these techniques, Pegan tested a selection of the HCA derivatives for percent inhibition and minimum inhibitory concentration. However, it was found that many of the compounds exhibit intrinsic fluorescence, which muddles the results of the assay. Therefore all inhibitory values are preliminary and await further analysis. The results are summarized in *Table 4*.

*Table 4 Preliminary biochemical data for inhibition of MtFBA.*

| *Substrate* | *% Inhibition*[*] | *MIC* |
|---|---|---|
| **HCA**  | 95 (1 mM) | 1.2 mM |
| **5-F-HCA**  | ND | 2.4 mM |
| **5-Cl-HCA**  | ND | 1.2 mM |
| **6-F-HCA**  | 31.1 (25 μM) | 2.4 mM |
| **6-F-HCA-OMe**  | 24.1 (25 μM) | 600 μM |

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[*] ND = value not determined.

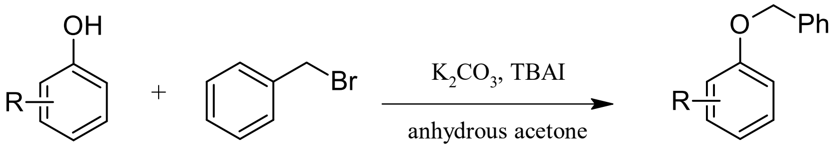
With these initial results, it still remains to be seen which analogs are promising inhibitors of MtFBA. However, the introduction of new analytical techniques such as isothermal calorimetry (ITC) could resolve some of the issues experienced with the fluorescence assays and present more solid data. At that point it would be possible to expand the catalog of derivatives that are specifically engineered to build on the most potent inhibitors and design a compound that is highly effective against MtFBA.

On the synthetic side, it would be beneficial to continue to pursue a few of the more elusive compounds. This is especially true for the naphthylamine derivatives, for which an improved synthetic process is highly desirable. Future plans to streamline the formation of these derivatives include a one-pot process to both form and hydrolyze the enol ether and refinements to an aldol condensation alternative to the Wittig reaction step.

In conclusion, a small library of novel compounds were prepared as potential inhibitors of the *Mycobacterium tuberculosis* fructose-1,6-bisphosphate aldolase. These compounds encompassed many variations on the 8-hydroxyquinoline-2-carboxylic acid scaffold, including alkyl and halogen substitutions on the phenol ring and many carboxylic acid derivatives in the 2-position. While it is as of yet unclear which, if any, of these analogs have the potential to become therapeutic agents against this global disease, it is clear that a new therapy is desperately needed and these compounds represent a promising new direction.

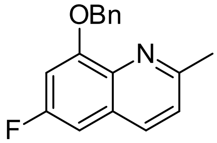
## 2.6 Experimental Details

*Experimental procedure for benzyl protection of phenol* [102]



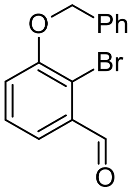
Acetone (5 mL), dried over 3Å MS, was added to the phenol (1 mmol). To this was added $K_2CO_3$ (2 eq), TBAI (0.1 eq), and benzyl bromide (1 eq). The mixture was stirred at room temperature overnight. The reaction mixture was filtered through a frit, and the solids were washed with EtOAc. The filtrate was washed with $H_2O$ and a saturated NaCl solution. The organic layer was dried over $Na_2SO_4$ and evaporated under reduced pressure to give the desired product (1.6g, quantitative yield).

***8-(benzyloxy)-6-fluoro-2-methylquinoline (1i)***



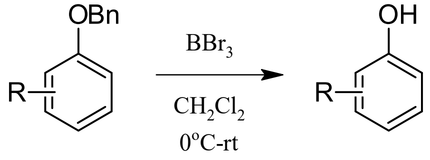
**1.6g, quantitative yield.**

***3-(benzyloxy)-2-bromobenzaldehyde***



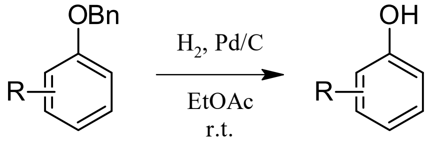
**620.3 mg, 73%.**

*Experimental procedure for benzyl deprotection of phenol by* $BBr_3$ [103]



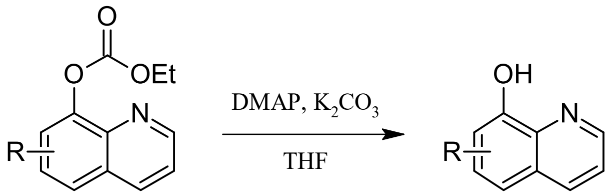
Anhydrous $CH_2Cl_2$ (10 mL) was added to the benzyl-protected phenol (1 mmol) under $N_2$ atmosphere. The reaction flask was placed in an ice-water bath, and the mixture was stirred while cooling for 20 minutes. $BBr_3$ (14.5 eq, 1M solution in $CH_2Cl_2$) was then added and the mixture was stirred over ice. The ice was allowed to melt, and the mixture was stirred at room temperature overnight. The reaction was quenched by dropwise addition of MeOH (15 mL), and the mixture was stirred an additional 2 hours. The solvent was then evaporated, and the residue was dissolved in $CH_2Cl_2$. The organic layer was washed with 1M NaOH then dried over anhydrous $Na_2SO_4$ and evaporated. The crude product was purified by flash chromatography over silica gel by elution of hexanes/ethyl acetate.

*Experimental procedure for benzyl deprotection by catalytic hydrogenolysis* [44]



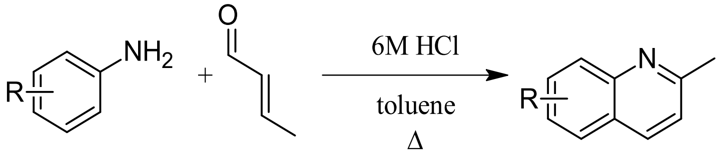
The benzyl-protected phenol (1 mmol) and palladium on carbon (0.2 eq) were combined in a round bottom flask. The flask was air-purged, and ethyl acetate (5 mL, dried over 3Å MS) was added. A hydrogen balloon was attached to the flask, and the reaction was stirred at room temperature under $H_2$ atmosphere for 2 hours. After completion the solids were filtered through a frit and washed with EtOAc. The filtrate was evaporated and the crude residue was purified by flash chromatography with silica gel by elution of hexanes/ethyl acetate.

*Experimental procedure for carbonate deprotection of phenol*



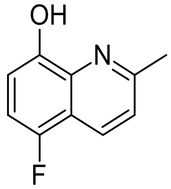
The carbonate-protected quinoline (1 mmol) and DMAP (2 eq) were dissolved in THF (5.5 mL). To this was added a 1M solution of $K_2CO_3$ in $H_2O$ (5 eq), and the mixture was stirred at room temperature overnight. The reaction was quenched with 1M HCl and the product was extracted into ethyl acetate. The organic layer was washed with a saturated solution of $NH_4Cl$, dried over anhydrous $Na_2SO_4$, and evaporated to give the product.

*Experimental procedure for modified DVM quinoline synthesis* [39]



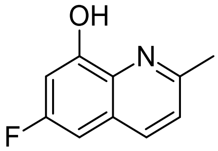
6M HCl (13.75 mL) was added to the aminophenol (1 mmol) under ambient atmosphere. To this was added toluene (2 mL), then crotonaldehyde (2 mmol). The reaction mixture was refluxed for 3 hours then cooled to room temperature. The organic layer was removed, and the aqueous layer was adjusted to pH 7-8 by addition of a saturated solution of $Na_2CO_3$. The aqueous mixture was extracted with $CH_2Cl_2$ (3x30 mL), and the combined organic layers were dried over anhydrous $Na_2SO_4$ then evaporated under reduced pressure. The crude product was used without purification in the next step.

***5-fluoro-2-methylquinolin-8-ol (1a)***



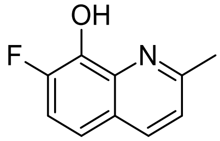
Brown solid. **133.4 mg, 95%.** $^1$H NMR (500 MHz, CDCl$_3$) δ 8.24 (d, $J_{3\text{-}4}$ = 8.56 Hz, 1H, H-4), 8.05 (s, 1H, OH), 7.33 (d, 1H, H-3), 7.05 (m, 2H, H-6, H-7), 2.73 (s, 3H, *CH$_3$*). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 157.90, 150.73 (*J* = 245.32 Hz), 147.89 (*J* = 3.45 Hz), 137.30 (*J* = 3.55 Hz), 129.76 (*J* = 2.67 Hz), 122.67 (*J* = 2.51 Hz), 116.98 (*J* = 19.00 Hz), 109.63 (*J* =20.73 Hz), 108.48 (*J* =7.82 Hz), 24.96.

***6-fluoro-2-methylquinolin-8-ol (1b)***



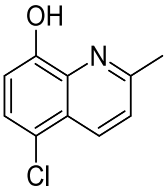
Brown solid. **268mg, 95%.** $^1$H NMR (500 MHz, CDCl$_3$) δ 8.00 (d, $J_{3\text{-}4}$ = 8.47 Hz, 1H, H-4), 7.35 (d, 1H, H-3), 6.94 (m, 2H, H-5, H-7), 2.73 (s, 3H, *CH$_3$*). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 160.98 (*J* = 244.94 Hz), 156.01 (*J* = 2.82 Hz), 153.31 (*J* = 13.80 Hz), 135.65 (*J* = 5.77 Hz), 135.03, 126.59 (*J* = 12.22 Hz), 123.80, 100.81 (*J* = 4.80 Hz), 100.60 (*J* = 2.27 Hz), 24.71.

***7-fluoro-2-methylquinolin-8-ol (1c)***



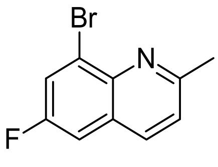
Brown solid. **194.0mg, 91%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.03 (d, $J$ = 8.14 Hz, 1H), 7.29 (m, 3H), 2.73 (s, 3H, $CH_3$). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 158.00, 147.57 ($J$ = 243.91 Hz), 138.92 ($J$ = 7.30 Hz), 137.80 ($J$ = 10.49 Hz), 136.17 ($J$ = 1.58 Hz), 123.16, 121.85 ($J$ = 2.61 Hz), 117.36 ($J$ = 7.93 Hz), 117.04 ($J$ = 21.34 Hz), 24.91.

***5-chloro-2-methylquinolin-8-ol (1d)***



Tan solid. **251.7mg, 93%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.36 (d, $J_{3\text{-}4}$ = 8.62 Hz, 1H, H-4), 7.44 (d, $J_{6\text{-}7}$ = 8.23 Hz, 1H, H-7), 7.40 (d, 1H, H-3), 7.08 (d, 1H, H-6), 2.75 (s, 3H, $CH_3$). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 157.64, 150.76, 138.02, 133.36, 126.35, 124.46, 123.46, 120.29, 109.87, 24.77.

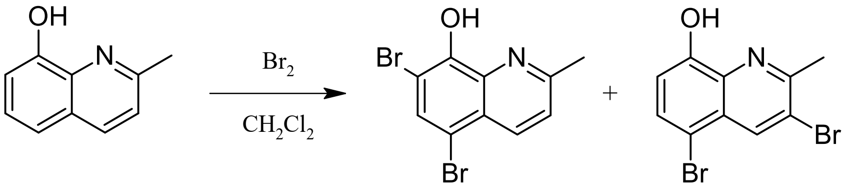
***8-bromo-6-fluoro-2-methylquinoline (1e)***



Off-white solid, **588.1mg, 94%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.84 (d, $J_{3\text{-}4}$ = 8.43 Hz, 1H, H-4), 7.72 (dd, $J_{5\text{-}7}$ = 2.78 Hz, 1H, H-7), 7.25 (dd, 1H, H-5), 7.22 (d, 1H, H-3), 2.72 (s, 3H, $CH_3$). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 159.52 ($J$ = 2.75 Hz), 158.68 ($J$ = 248.9

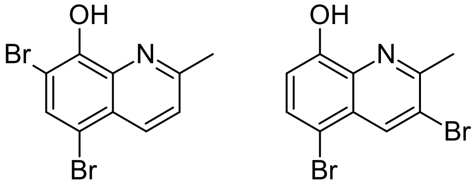
Hz), 141.98, 135.82 (*J* = 5.31 Hz), 127.21 (*J* =10.07 Hz), 125.36 (*J* = 10.45 Hz), 123.43, 122.98 (*J* = 28.04 Hz), 110.49 (*J* =20.98 Hz), 25.45.

*Experimental procedure for the bromination of 8-hydroxyquinaldine* [41]



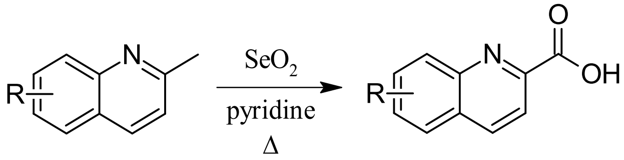
$CH_2Cl_2$ (6 mL) was added to 8-hydroxyquinaldine (1 mmol). To this was added bromine ($Br_2$, 1eq, in 1 mL $CH_2Cl_2$) over the course of 40 minutes. The mixture was stirred at room temperature overnight, then washed with $H_2O$. The aqueous layer was extracted with $CH_2Cl_2$, the combined organic layers were dried over $Na_2SO_4$, and the solvent was evaporated under reduced pressure. The crude residue was purified by flash chromatography over silica gel by elution of hexanes/ethyl acetate.

***5,7-dibromo-2-methylquinolin-8-ol (1g) and 4,5-dibromo-2-methylquinoline-8-ol (1h)***



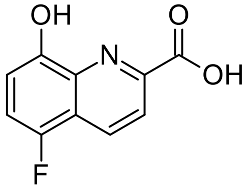
Inseparable mixture (~0.83:1). White solid. **16.2 mg, 7%**. $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.31 Hz, 1H), 8.28 (*J* = 8.65 Hz, 1H), 7.97 (s, 1H), 7.80 (d, *J* = 1.07 Hz, 1H), 7.55 (d, *J* = 8.33 Hz, 1H), 7.41 (d, *J* = 8.63 Hz, 1H), 2.76 (s, 3H), 2.74 (s, 3H).

Experimental procedure for the oxidation of benzylic methyl to carboxylic acid [39]



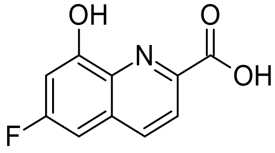
The 2-methylquinoline (1 mmol) and $SeO_2$ (1.2 eq) were dissolved in pyridine (5 mL) and refluxed for 24 hours. The reaction mixture was then cooled to room temperature, and the solids were filtered through a celite frit and washed on the frit with ethyl acetate. The filtrate was evaporated, giving a dark brown filmy residue, which was redissolved in a 10% solution of KOH (20 mL). The remaining solids were filtered off and washed with a small amount of $H_2O$. The filtrate was adjusted to pH 2 by addition of 6M HCl while cooling on ice then cooled in the refrigerator for at least two hours. The resulting precipitate was filtered, washed with $H_2O$, and air-dried to give the clean product.

***5-fluoro-8-hydroxyquinoline-2-carboxylic acid (2a)***



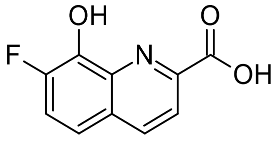
Brown solid. **77.3 mg, 95%**. $^1$H NMR (500 MHz, DMSO-d$^6$) δ 8.66 (dd, *J* = 4.27, 8.65 Hz, 1H), 8.23 (t, *J* = 8.36 Hz, 1H), 7.49 (dd, *J* = 8.56, 10.06 Hz, 1H), 7.16 (dd, *J* = 4.66, 8.58 Hz, 1H).

### *6-fluoro-8-hydroxyquinoline-2-carboxylic acid (2b)*



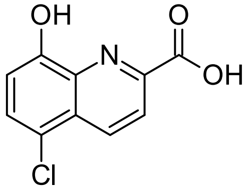
Brown solid. **273 mg, 74%.** $^1$H NMR (500 MHz, DMSO-d$^6$) δ 8.51 (d, $J_{3\text{-}4}$ = 8.59 Hz, 1H, H-3), 8.15 (d, 1H, H-4), 7.32 (dd, $J_{5\text{-}7}$ = 2.69 Hz, 1H, H-7), 7.11 (dd, 1H, H-5). $^{13}$C NMR (126 MHz, DMSO-d$^6$) δ 165.51, 162.83 ($J$ = 246.82 Hz), 156.64 ($J$ = 14.89 Hz), 144.29 ($J$ = 2.90 Hz), 138.33 ($J$ = 6.19 Hz), 134.75, 130.83 ($J$ = 13.51 Hz), 121.52, 102.89 ($J$ = 29.12 Hz), 101.52 ($J$ = 23.02 Hz).

### *7-fluoro-8-hydroxyquinoline-2-carboxylic acid (2c)*



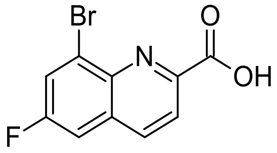
Brown solid. **16.2 mg, 30%**. $^1$H NMR (500 MHz, DMSO-d$^6$) δ 10.56 (br s, 1H, OH), 8.62 (d, $J$ = 8.47 Hz, 1H), 8.12 (d, $J$ = 8.48 Hz, 1H), 7.73 (dd, $J$ = 8.97, 11.07 Hz, 1H), 7.61 (dd, $J$ = 5.06, 9.04 Hz, 1H). $^{13}$C NMR (126 MHz, DMSO-d$^6$) δ 165.46, 148.66 ($J$ = 243.13 Hz), 145.59, 140.41 ($J$ = 10.56 Hz), 139.16, 138.38 ($J$ = 7.81 Hz), 127.05, 120.84 ($J$ = 21.78 Hz), 119.57 (2.58 Hz), 118.21 ($J$ = 8.18 Hz).

***5-chloro-8-hydroxyquinoline-2-carboxylic acid (2d)***



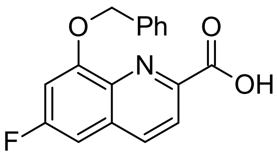
Tan solid. **123.2 mg, 92%**. $^1$H NMR (500 MHz, DMSO-d$^6$) δ 8.63 (d, $J_{3\text{-}4}$ = 8.72 Hz, 1H, H-3), 8.25 (d, 1H, H-4), 7.74 (d, $J_{6\text{-}7}$ = 8.35 Hz, 1H, H-7), 7.18 (d, 1H, H-6). $^{13}$C NMR (126 MHz, DMSO-d$^6$) δ 165.29, 153.93, 145.63, 137.56, 135.33, 130.66, 127.49, 121.77, 119.05, 112.78.

***8-bromo-6-fluoroquinoline-2-carboxylic acid (2e)***



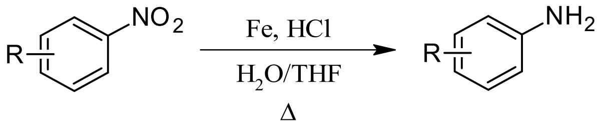
Beige solid. **96.8 mg, 82%**. $^1$H NMR (500 MHz, DMSO-d$^6$) δ 7.84 (d, $J_{3\text{-}4}$ = 8.43 Hz, 1H, H-4), 7.72 (dd, $J_{5\text{-}7}$ = 2.78 Hz, 1H, H-7), 7.25 (dd, 1H, H-5), 7.22 (d, 1H, H-3), 2.72 (s, 3H, *CH$_3$*). $^{13}$C NMR (126 MHz, DMSO-d$^6$) δ 166.37, 161.23, 152.90 (d, *J* = 149.72 Hz), 141.78, 138.61 (d, *J* = 5.67 Hz), 130.76 (d, *J* = 11.32 Hz), 127.11 (d, *J* = 11.07 Hz), 124.93 (d, *J* = 28.94 Hz), 122.95, 111.77 (d, *J* = 21.65 Hz).

***8-benzyloxy-6-fluoroquinoline-2-carboxylic acid (2h)***



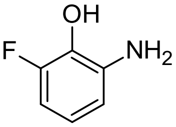
Brown solid. **1.2g, 95%.**

Experimental procedure for the reduction of nitro to amine [40]



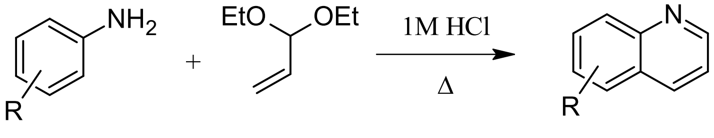
The nitrobenzene (1 mmol) and iron powder (10 eq) were added to a round bottom flask. $H_2O$ (5 mL) and THF (15 mL) were added to the flask, then 6 drops of 6M HCl. The reaction mixture was refluxed for 3 hours then cooled to room temperature. The mixture was diluted with saturated NaCl (25 mL), and the solids were filtered off. The solids were rinsed on the filter with ethyl acetate. The organic layer of the filtrate was extracted off, and the aqueous was extracted with EtOAc. The combined organic layers were dried over anhydrous $Na_2SO_4$ and evaporated under reduced pressure to give the product.

***2-amino-6-fluorophenol (3a)***



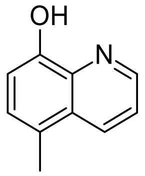
**159.8 mg, 94%.** $^1H$ NMR (500 MHz, $CDCl_3$) δ 6.69 (m, 1H), 6.54 (m, 2H), 3.90 (br s, 2H, $NH_2$). $^{13}C$ NMR (126 MHz, $CDCl_3$) δ 151.56 (d, $J$ = 233.93 Hz), 136.42 (d, $J$ = 4.03 Hz), 131.34 (d, $J$ = 16.64 Hz), 120.29 (d, $J$ = 9.00 Hz), 111.49 (d, $J$ = 2.40), 105.27 (d, $J$ = 18.68 Hz).

Experimental procedure for heteroring-unsubstituted quinoline synthesis [47]



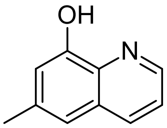
1M HCl (82.5 mL) was added to the methyl aminophenol in a round bottom flask. To this was added acrolein diethyl acetal (2.5 eq). The reaction was refluxed for 24 hours, then cooled to room temperature. The solution was neutralized to pH 7-8 by addition of solid $Na_2CO_3$ then extracted into $CH_2Cl_2$. The organic layers were combined and dried over $Na_2SO_4$ then concentrated by rotary evaporation. The crude residue was purified by column chromatography by elution of EtOAc/hexanes to give the pure product.

***5-methylquinolin-8-ol (39)***



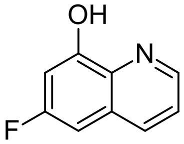
**1.5 g, 58%**. Characterization in Section 3.3.

***6-methylquinolin-8-ol (38)***



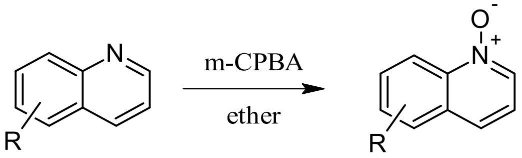
**66.3 mg, 50%**. Characterization in Section 3.3.

***6-fluoroquinolin-8-ol (41)***



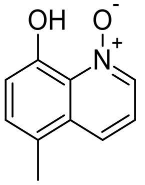
**40.0 mg, 42%.** Characterization in Section 3.3.

*Experimental procedure for preparation of quinoline-N-oxides* [104]



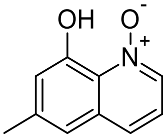
The quinoline (1 mmol) was dissolved in $Et_2O$ (15 mL) and stirred at room temperature. Then m-CPBA (1.5 eq) was added slowly to the mixture. The reaction mixture was stirred at room temperature for 24 hours. After TLC analysis indicated full conversion of starting material, the solvent was evaporated, and the resultant solid residue was dissolved in ethyl acetate. This mixture was extracted with saturated $NaHCO_3$ (3x30 mL). The aqueous layers were washed with ethyl acetate, then the combined organic layers were dried over anhydrous $Na_2SO_4$ then evaporated to give the quinoline-*N*-oxide which was used in the next step without purification.

***5-methylquinolin-8-ol-N-oxide (5a)***



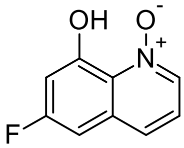
**355.1 mg, 77%**.

***6-methylquinolin-8-ol-N-oxide (5b)***



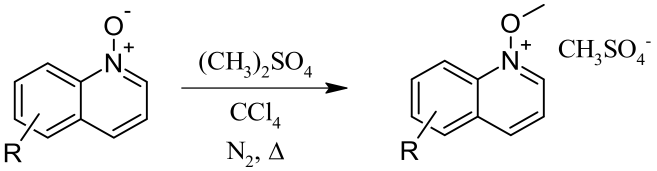
**256.1 mg, 94%**.

***6-fluoroquinolin-8-ol-N-oxide (5c)***



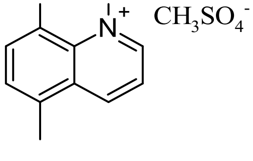
**24 mg, 45%.**

*Experimental procedure for methylation of quinoline-N-oxide* [45]



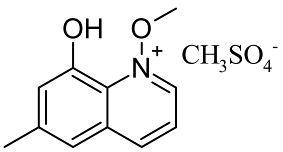
In a round bottom flask, the quinoline-N-oxide (0.25 mmol) was degassed and flushed with $N_2$. To this was added dimethyl sulfate (1 eq) in $CCl_4$ (2 mL). The reaction was refluxed for 24 hours under $N_2$ atmosphere. Upon full conversion of starting material to product, as seen by TLC analysis, the mixture was cooled to room temperature, then the solvent was removed by rotary evaporation. The crude residue was washed with diethyl ether and evaporated under reduced pressure to give the *N*-methoxyquinolinium methylsulfate salt, which was used in the next step without purification.

***8-hydroxy-1-methoxy-5-methylquinolin-1-ium methylsulfate (6a)***



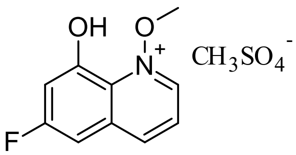
Crude product used in subsequent reaction.

***8-hydroxy-1-methoxy-6-methylquinolin-1-ium methylsulfate (6b)***



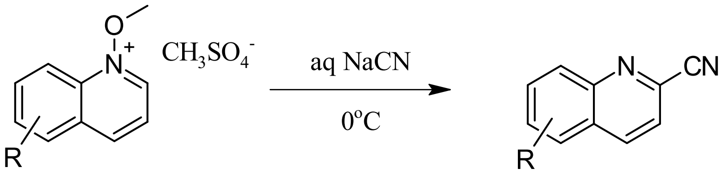
Crude product used in subsequent reaction.

***6-fluoro-8-hydroxy-1-methoxyquinolin-1-ium methylsulfate (6c)***



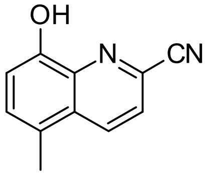
Crude product used in subsequent reaction.

Experimental procedure for cyanation of N-methoxyquinoline [45]



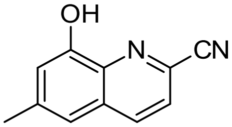
The *N*-methoxyquinoline (0.13 mmol) was combined with sodium cyanide (3 eq) and dissolved in $H_2O$ (0.2 mL). The reaction was stirred on ice for 4 hours, until the starting material was no longer visible by TLC. The pH of the mixture was reduced to 4-5 by addition of AcOH, then the solids were filtered off and washed with $H_2O$. The crude solid was used without purification in the following step.

***8-hydroxy-5-methylquinoline-2-carbonitrile (7a)***



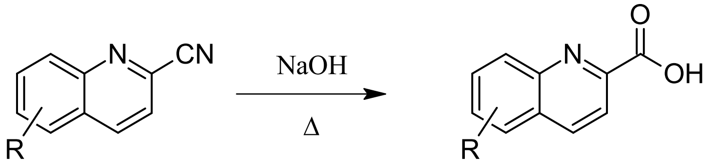
Crude product used in subsequent reaction.

***8-hydroxy-6-methylquinoline-2-carbonitrile (7b)***



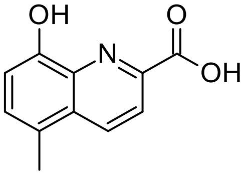
Crude product used in subsequent reaction.

*Experimental procedure for hydrolysis of cyano to carboxylic acid* [45]



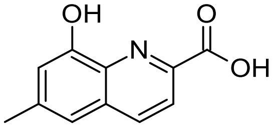
A solution of 6M NaOH (6 mL) was added to the quinoline-2-carbonitrile (0.13 mmol) and refluxed for 5 hours. The reaction mixture was cooled to room temperature then washed with ethyl acetate. The pH of the aqueous layer was reduced to 2 by addition of 6M HCl then extracted with EtOAc. The combined organic layers were dried over anhydrous $Na_2SO_4$ then evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel by elution of ethyl acetate-hexanes to give the final product.

***8-hydroxy-5-methylquinoline-2-carboxylic acid (2f)***



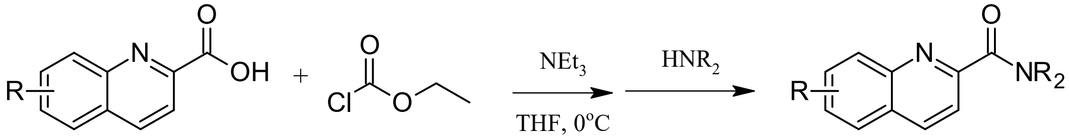
Tan solid. **17.8 mg**, **8%** (over three steps). $^1$H NMR (500 MHz, DMSO-d$^6$) δ 10.06 (br s, 1H), 8.64 (d, *J* = 8.70 Hz, 1H), 8.18 (d, *J* = 8.66 Hz, 1H), 7.47 (d, *J* = 7.78 Hz, 1H), 7.11 (d, *J* = 7.78 Hz, 1H), 2.59 (s, 3H).

***8-hydroxy-6-methylquinoline-2-carboxylic acid (2g)***



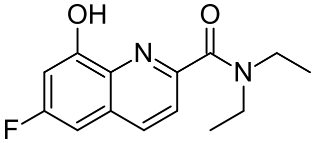
Yellow solid. **428.8 mg, 27%** (over three steps). $^1$H NMR (500 MHz, DMSO-d$^6$) δ 8.45 (d, *J* = 8.51 Hz, 1H), 8.10 (d, *J* = 8.50 Hz, 1H), 7.33 (m, 1H), 7.08 (d, *J* = 1.66 Hz), 1.92 (s, 3H).

*Experimental procedure for amide formation* [55]



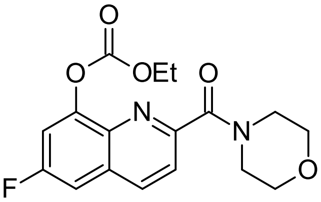
The quinoline-2-carboxylic acid (1 mmol) was dissolved in THF (5.5 mL) and stirred in an ice bath. $NEt_3$ (2 eq) was added to the mixture, then ethyl chloroformate (1.1 eq). The reaction was stirred at 0°C for one hour, then the amine was added dropwise. The mixture was stirred at 0°C until the ice melted naturally, then was allowed to stir at room temperature overnight. The solvent was evaporated, and the crude residue was dissolved in EtOAc and washed with saturated $NaHCO_3$ and $H_2O$. The organic layer was dried over $Na_2SO_4$, the solvent was evaporated under reduced pressure, and the crude residue was purified by flash chromatography on silica gel by elution of hexanes/ethyl acetate.

***N,N-diethyl-6-fluoro-8-hydroxyquinoline-2-carboxamide (8a)***



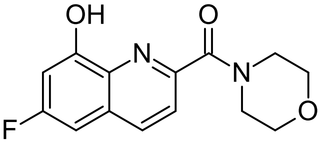
Brown solid. **24.5 mg, 53%** (after amide formation and benzyl deprotection). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.70 (d, *J* = 8.49 Hz, 1H), 7.85 (d, *J* = 8.49 Hz, 1H), 7.31 (dd, *J* = 2.59, 8.91 Hz, 1H), 7.13 (dd, *J* = 2.55, 10.22 Hz, 1H), 3.67 (q, *J* = 7.20 Hz, 2H), 3.38 (q, *J* = 7.15 Hz, 2H), 1.34 (t, *J* = 7.23 Hz, 3H), 1.21 (t, *J* = 7.12 Hz, 3H).

***Ethyl 6-fluoro-2-(morpholine-4-carbonyl)quinolin-8-yl carbonate (8b)***



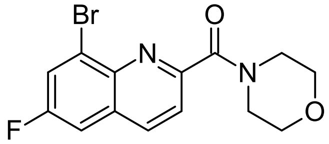
Tan solid. **22.7 mg, 27%.** $^1$H NMR (500 MHz, CDCl$_3$) δ 8.28 (d, *J* = 8.57 Hz, 1H), 7.95 (m, 1H), 7.44 (m, 2H), 4.39 (q, *J* = 7.16 Hz, 2H), 3.88 (m, 6H), 3.76 (m, 2H), 1.46 (t, *J* = 7.12 Hz, 3H).

***(6-fluoro-8-hydroxyquinolin-2-yl)(morpholin-4-yl)methanone (8c)***



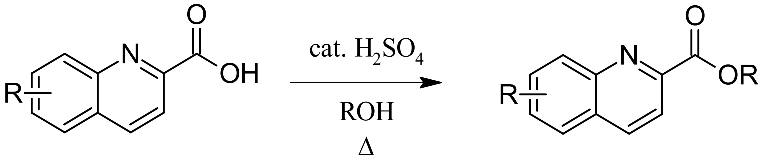
**11.8 mg, 25%** (after amide formation and carbonate deprotection). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.25 (d, *J* = 8.52 Hz, 1H), 8.05 (s, 1H, OH), 7.79 (d, *J* = 8.54 Hz, 1H), 7.05 (m, 2H), 3.90 (m, 4H), 3.70 (m, 4H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 166.93, 162.40 (*J* = 248.94 Hz), 154.04 (*J* = 14.54 Hz), 150.16 (*J* = 3.04 Hz), 137.07 (*J* = 6.04 Hz), 133.77, 128.81 (*J* = 12.42 Hz), 122.68, 102.25, 102.02, 101.49, 101.31, 99.99, 66.90 (*J* = 16.80 Hz), 47.85, 42.73.

***(8-bromo-6-fluoroquinolin-2-yl)(morpholin-4-yl)methanone (8d)***



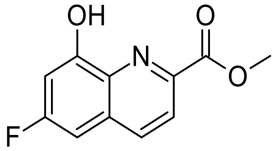
Beige solid. **34.1 mg**, **36%.** $^1$H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, *J* = 8.51 Hz, 1H), 8.02 (d, *J* = 8.47 Hz, 1H), 7.93 (dd, *J* = 2.69, 8.03 Hz, 1H), 7.50 (dd, *J* = 2.69, 8.20 Hz, 1H), 4.13 (m, 2H), 3.91 (m, 6H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.85, 160.25 (*J* = 253.78 Hz), 152.72 (*J* = 3.03 Hz), 140.48, 137.16 (*J* = 5.60 Hz), 129.38 (*J* = 10.61 Hz), 127.00 (*J* = 10.54 Hz), 124.22 (*J* = 28.41 Hz), 123.44, 110.60 (*J* = 21.49 Hz), 67.47, 67.01, 48.36, 43.55.

*Experimental procedure for Fischer ester synthesis* [46]



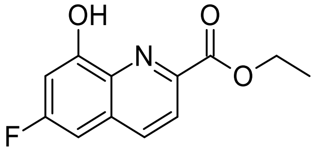
6-fluoro-8-hydroxyquinoline-2-carboxylic acid (0.72 mmol) was dissolved in the appropriate alcohol (5 mL) in a round bottom flask. Five drops of concentrated sulfuric acid was added, and the reaction was refluxed 16 hours. After cooling to room temperature, the alcohol was evaporated off under reduced pressure, and the crude product was purified by flash chromatography over silica gel by elution of 10% ethyl acetate-hexanes to give the quinoline-2-carboxylate ester.

### *Methyl 6-fluoro-8-hydroxyquinoline-2-carboxylate (9a)*



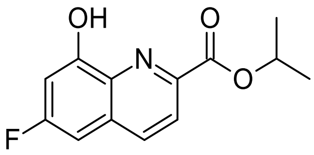
Peach-colored solid **113.7mg**, **70%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.86 (br s, 1H, OH), 8.20 (m, 2H), 7.02 (m, 2H), 4.07 (s, 3H, CH$_3$). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 165.28, 163.24 ($J$ = 250.37 Hz), 155.35 ($J$ = 14.81 Hz), 144.49 ($J$ = 3.02 Hz), 136.64 ($J$ = 6.27 Hz), 135.30, 130.22 ($J$ = 12.77 Hz), 122.56, 101.06 ($J$ = 22.98 Hz), 102.24 ($J$ = 29.69 Hz), 52.95.

### *Ethyl 6-fluoro-8-hydroxyquinoline-2-carboxylate (9b)*



Off-white solid **56.0mg**, **33%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.93 (br s, 1H, OH), 8.21 (m, 2H), 7.03 (m, 2H), 4.54 (q, $J$ = 7.14 Hz, 2H), 1.50 (t, $J$ = 7.15 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 164.83, 163.20 ($J$ = 250.26 Hz), 155.31 ($J$ = 14.90 Hz), 144.84 ($J$ = 3.04 Hz), 136.60 ($J$ = 6.30 Hz), 135.30, 130.17 ($J$ = 12.80 Hz), 122.60, 102.15 ($J$ = 29.85 Hz), 101.05 ($J$ = 22.98 Hz), 62.18, 14.31.

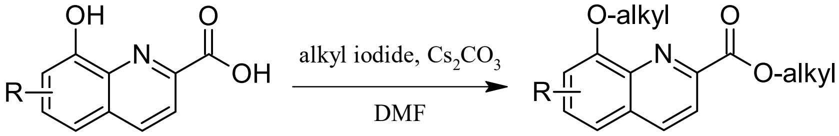
### *Isopropyl 6-fluoro-8-hydroxyquinoline-2-carboxylate (9c)*



Off-white solid **58.7mg**, **33%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.94 (br s, 1H, OH), 8.21 (m, 2H), 7.03 (m, 2H), 5.40 (hept, $J$ = 6.29 Hz, 1H), 1.48 (d, $J$ = 6.27 Hz, 6H). $^{13}$C

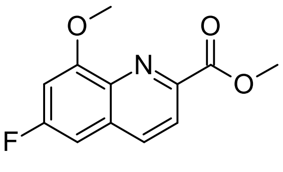
NMR (126 MHz, $CDCl_3$) δ 164.32, 163.16 ($J = 250.10$ Hz), 155.30 ($J = 14.96$ Hz), 145.20 ($J = 3.05$ Hz), 136.54 ($J = 6.28$ Hz), 135.31, 130.12 ($J = 12.68$ Hz), 122.61, 102.09 ($J = 29.74$ Hz), 101.02 ($J = 22.89$ Hz), 70.00, 21.91.

*Experimental procedure for dual ester/phenol ether synthesis* [67]



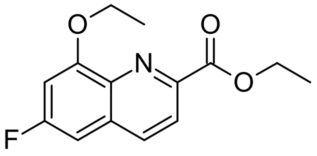
The 8-hydroxyquinoline-2-carboxylic acid (1 mmol) was dissolved in DMF. Cesium carbonate (2 eq) and the appropriate alkyl iodide (2 eq) were added, and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with $H_2O$ and extracted into EtOAc. The organic layer was washed with saturated $NaHCO_3$, $H_2O$, and 1M HCl. The organic layer was then dried over $Na_2SO_4$, the solvent was evaporated, and the crude product was purified by flash chromatography over silica gel by elution with hexanes/ethyl acetate.

***Methyl 6-fluoro-8-methoxyquinoline-2-carboxylate (10a)***



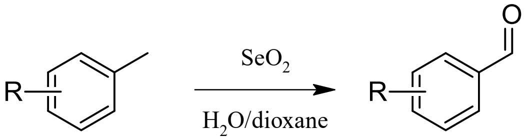
Dark brown viscous oil. **11.5 mg, 28%**. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.26 (q, $J = 8.56$ Hz, 2H), 7.10 (dd, $J = 2.55$, 8.65 Hz, 1H), 6.92 (dd, $J = 2.54$, 10.61 Hz, 1H), 4.13 (s, 3H), 4.08 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.79, 162.44 ($J = 250.54$ Hz), 136.96, 136.67, 136.62, 130.92 ($J = 12.60$ Hz), 122.55, 102.12 ($J = 22.21$ Hz), 99.83 ($J = 30.27$ Hz), 56.57, 53.11.

***Ethyl 6-fluoro-8-ethoxyquinoline-2-carboxylate (10b)***



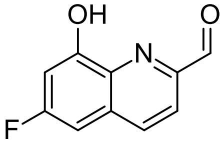
Dark brown viscous oil. **18.8 mg, 25%**. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.23 (m, 2H), 7.07 (dd, *J* = 2.56, 8.65 Hz, 1H), 6.89 (dd, *J* = 2.58, 10.84 Hz, 1H), 4.54 (q, *J* = 7.15 Hz, 2H), 4.32 (q, *J* = 7.03 Hz, 2H), 1.70 (t, *J* = 6.99, 3H), 1.52 (t, *J* = 7.14, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 165.35, 162.37 (*J* = 250.36 Hz), 146.27, 137.08, 136.58 (*J* = 6.10 Hz), 130.88 (*J* = 12.54 Hz), 122.42, 101.90 (*J* = 22.05 Hz), 100.46 (*J* = 29.96 Hz), 65.19, 62.20, 14.34, 14.25.

*Experimental procedure for benzylic oxidation to aldehyde* [88]



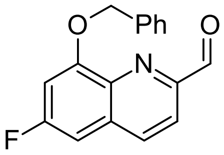
$SeO_2$ (1.5 eq) was dissolved in $H_2O$ (0.2 mL) and 1,4-dioxane (2 mL) and placed in a 105°C oil bath. Once reflux had begun, the 2-methylquinoline (1 mmol) in 1,4-dioxane (1.5 mL) was added to it. The reaction was refluxed for 5 hours then removed from heat and cooled to room temperature. The reaction mixture was diluted with $H_2O$, extracted into $CH_2Cl_2$, and dried over $Na_2SO_4$. The crude residue was purified by flash chromatography on silica gel by elution of hexanes/ethyl acetate.

***6-fluoro-8-hydroxyquinoline-2-carbaldehyde (11a)***



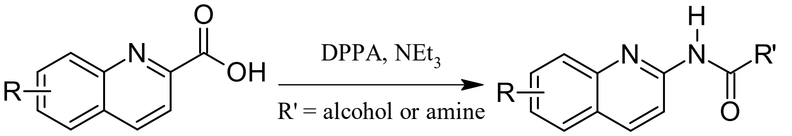
**302.0 mg**, **72%.**

***8-(benzyloxy)-6-fluoroquinoline-2-carbaldehyde (11b)***



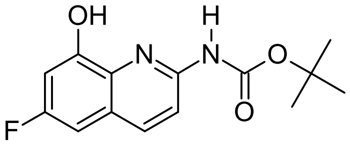
**803.0 mg**, **95%.**

*Experimental procedure for synthesis of carbamates and ureas* [74]



The quinoline-2-carboxylic acid (1 mmol) and NEt$_3$ (1 eq) were placed in a round bottom flask. To this was added DPPA (1 eq) and the alcohol or amine (10 mL). The mixture was refluxed for 8 hours then cooled to room temperature. The crude reaction mixture was purified over silica gel by elution of hexanes/ethyl acetate.

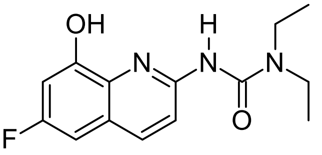
***tert-butyl (6-fluoro-8-hydroxyquinolin-2-yl)carbamate (13)***



Yellow solid. **29.2 mg**, **22%** (after carbamate formation and benzyl deprotection). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.25 (d, *J* = 8.99 Hz, 1H), 8.08 (d, *J* = 9.06 Hz, 1H), 7.76

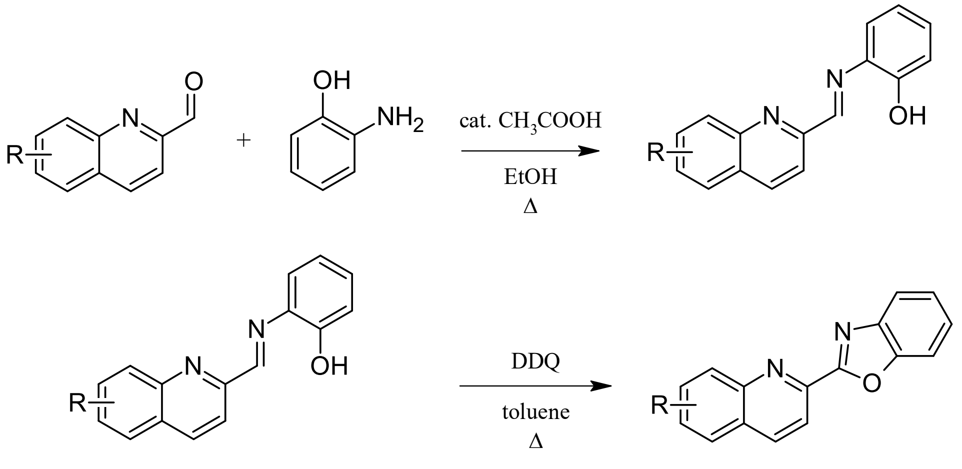
(br s, 1H), 7.42 (br s, 1H), 6.94 (m, 2H), 1.59 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 160.19 (*J* = 244.05 Hz), 152.13, 149.19 (*J* = 2.31 Hz), 137.98 (*J* = 5.53 Hz), 133.48, 125.52 (*J* = 11.93 Hz), 114.47, 101.56, 101.27 (*J* = 12.90 Hz), 101.04, 81.68, 28.25.

***N,N-diethyl-N'-(6-fluoro-8-hydroxyquinolin-2-yl)urea (14)***



**9.8 mg**, **7%.** $^1$H NMR (500 MHz, CDCl$_3$) δ 8.22 (d, *J* = 8.48 Hz, 1H), 8.11 (br s, 1H), 7.74 (d, *J* = 8.48 Hz, 1H), 7.04 (m, 2H), 3.66 (q, *J* = 7.14 Hz, 2H), 3.42 (q, *J* = 7.08 Hz, 2H), 1.35 (t, *J* = 7.15 Hz, 3H), 1.27 (t, *J* = 7.09 Hz, 3H).

Experimental procedure for synthesis of benzoxazole derivative [90]



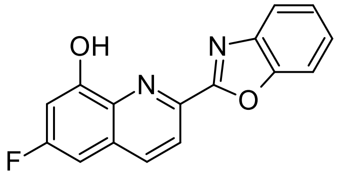
(1)

(2)

(1) Under N$_2$ atmosphere, the aldehyde (1 mmol) was added to a round bottom flask. 2-aminophenol (1.1 eq) was dissolved in absolute ethanol (10 mL) and added to the flask along with glacial acetic acid (5 drops). The mixture was refluxed under N$_2$ overnight. The solvent was evaporated, and the crude residue was used directly in the subsequent reaction.

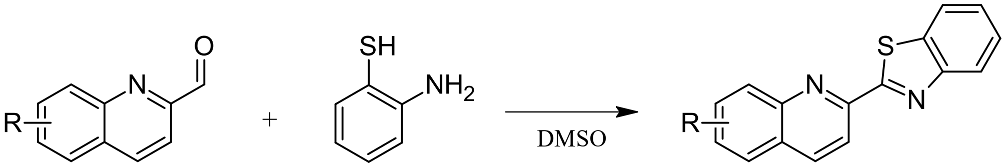
(2) The crude product from the first reaction was dissolved in anhydrous toluene (33 mL). DDQ (2 eq) was added in portions, and the mixture was refluxed for 3 hours. The solvent was evaporated, the crude residue was dissolved in $CH_2Cl_2$, and the residual solids were filtered off. The filtrate was evaporated onto silica gel and the product purified with flash chromatography by elution of hexanes/ethyl acetate.

***2-(1,3-benzoxazol-2-yl)-6-fluoroquinolin-8-ol (16a)***



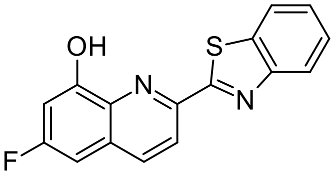
**90.5 mg, 70%** (after (1), (2), and benzyl deprotection). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, *J* = 8.60 Hz, 1H), 8.34 (d, *J* = 8.59 Hz, 1H), 7.84 (d, *J* = 7.67 Hz, 1H), 7.78 (d, *J* = 8.00 Hz, 1H), 7.51 (dt, *J* = 7.35, 19.55 Hz, 2H), 7.13 (dd, *J* = 2.61, 9.20 Hz, 1H), 6.98 (dd, *J* = 2.55, 10.54 Hz, 1H).

Experimental procedure for synthesis of benzothiazole derivative [90]



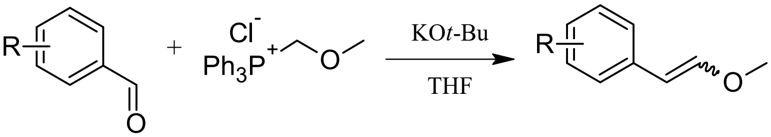
The quinoline-2-carbaldehyde (1 mmol) and 2-aminothiophenol (1 eq) were added to a round bottom flask with DMSO (2 mL). The mixture was refluxed for 4.5 hours then cooled to room temperature. The crude mixture was diluted with $H_2O$ and extracted into $CH_2Cl_2$. The organic layer was washed with saturated NaCl and dried over $Na_2SO_4$. The crude product was purified by flash chromatography over silica gel by elution with hexanes/ethyl acetate.

***2-(1,3-benzothiazol-2-yl)-6-fluoroquinolin-8-ol (16b)***



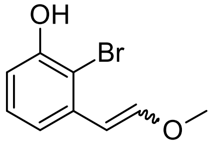
**5.8 mg, 3.2%** (after benzothiazole formation and benzyl deprotection). $^1$H NMR (500 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 0.75, 8.71 Hz, 1H), 8.28 (d, *J* = 8.61 Hz, 1H), 8.17 (dt, *J* = 0.85, 8.29 Hz, 1H), 8.01 (ddd, *J* = 0.61, 1.23, 8.02 Hz, 1H), 7.57 (ddd, *J* = 1.28, 7.19, 8.32 Hz, 1H), 7.50 (ddd, *J* = 1.20, 7.21, 8.18 Hz, 1H), 7.07 (d, *J* = 9.47 Hz, 2H).

*Experimental procedure for Wittig olefination* [97]



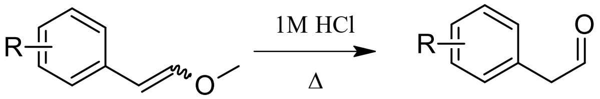
THF (5 mL) was added to (methoxymethyl)triphenylphosphonium chloride (2.5 mmol) and placed in an ice-water bath. KO*t*-Bu (2.5 mmol) was added, and the mixture was stirred on ice. After one hour, the mixture was removed from the ice, allowed to stir at room temperature for 30 minutes, then placed back on ice. The aldehyde (1 mmol) was added to the reaction mixture, which was stirred on ice until the ice melted naturally, and it was then stirred at room temperature overnight. The reaction was quenched with $H_2O$ and extracted into EtOAc. The organic layer was washed with saturated NaCl then dried over $Na_2SO_4$. The solvent was evaporated to give the crude product, as seen by NMR analysis.

***2-bromo-3-(2-methoxyethenyl)phenol (20)***



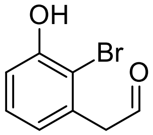
Crude product used in subsequent reaction.

*Experimental procedure for acid hydrolysis of enol ether to aldehyde* [97]



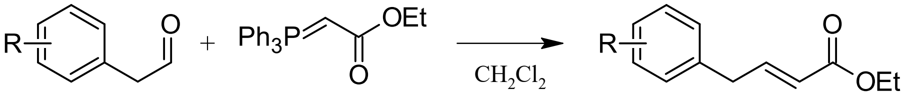
THF (2 mL) was added to the enol ether (1 mmol), then 1M HCl (2 mL) was added. The mixture was refluxed for 2.5 hours, then cooled to room temperature. The product was extracted into EtOAc, then the organic layer was dried over $Na_2SO_4$ and evaporated to give the crude product, as seen by NMR analysis.

***(2-bromo-3-hydroxyphenyl)acetaldehyde (21)***



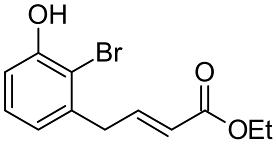
Crude product used in subsequent reaction.

*Experimental procedure for Wittig synthesis of aryl butenoate* [97]



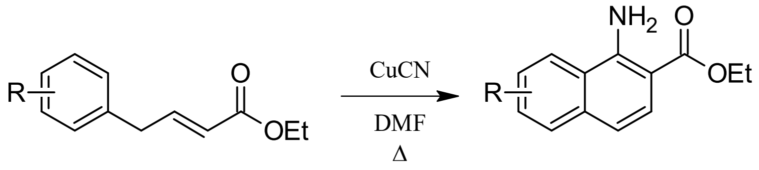
$CH_2Cl_2$ (1 mL) was added to the phenyl acetaldehyde (1 mmol), and the phosphorylidene (1.1 eq) was then added. The mixture was stirred at room temperature for 2 hours, then the solvent was evaporated and the crude residue was purified by flash chromatography over silica gel by elution of hexanes/ethyl acetate.

***Ethyl 4-(2-bromo-3-hydroxyphenyl)but-2-enoate (22)***



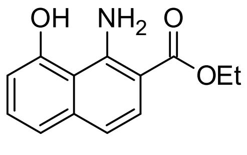
Gray/white solid. **204.8 mg, 72.8%.**

Experimental procedure for CuCN-mediated cyclization to aminonaphthalene [97]



The reaction flask containing the α,β-unsaturated ester (1 mmol) was air-purged and saturated with $N_2$. Anhydrous DMF (10 mL) was added, then CuCN (3 eq) was added. The mixture was refluxed 24 hours, cooled to room temperature, and diluted with $H_2O$. The product was extracted into EtOAc, then the organic layer was washed with saturated NaCl and dried over $Na_2SO_4$. The crude product was purified by flash chromatography over silica gel by elution of hexanes/ethyl acetate.

***Ethyl 1-amino-8-hydroxynaphthalene-2-carboxylate (23)***

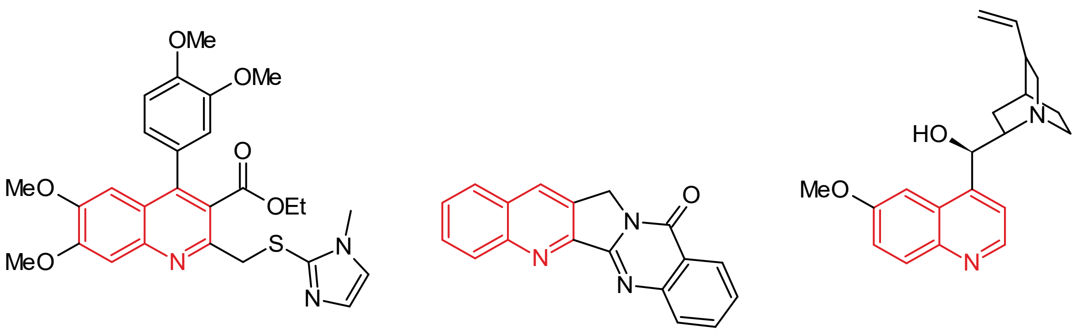


Yellow solid. **27.8 mg, 27%.** $^1H$ NMR (500 MHz, DMSO-$d^6$) δ 11.34 (s, 1H), 7.74 (d, *J* = 15.91 Hz, 1H), 7.51 (m, 2H), 7.08 (dd, *J* = 1.22, 7.95 Hz, 1H), 6.82 (d, *J* = 15.90 Hz, 1H), 4.23 (q, *J* = 7.10 Hz, 2H), 1.27 (t, *J* = 7.11 Hz, 3H).

# 3 IMPROVED SKRAUP-DOEBNER-VON MILLER QUINOLINE SYNTHESIS

## 3.1 Introduction to quinoline synthesis

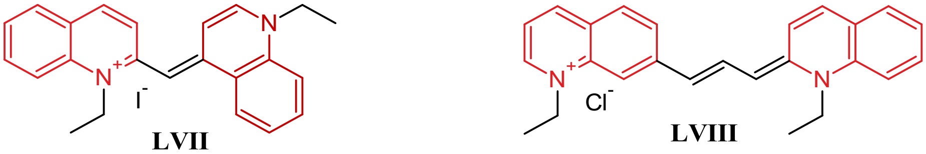
The quinoline ring system is ubiquitous in the areas of medicinal and industrial chemistry [105]. Several promising anti-inflammatory (**LIV**, *Figure 3.1.1*) [106] and antitumor (**LV**) [107] agents that have been recently developed contain the quinoline scaffold. Prominently, the first and most widely used antimalarial agent [108], quinine (**LVI**), is also based on the quinoline framework [109].



**LIV** **LV** **LVI**

*Figure 3.1.1 Quinoline-based therapeutics*

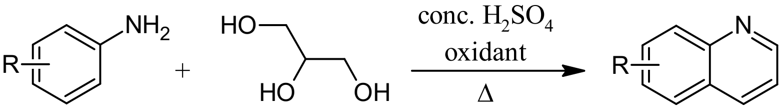
In addition, quinoline-based dyes such as ethyl red iodide (**LVII**, *Figure 3.1.2*) and pinacyanol (**LVIII**) have been used since the beginning of the nineteenth century in photographic plates, and quinolines provide frameworks for other industrial uses including organic light-emitting diodes (OLEDs), photovoltaic cells [110], and as solvent for terpenes and resins [111].



**LVII** **LVIII**

*Figure 3.1.2 Quinoline-based dyes*

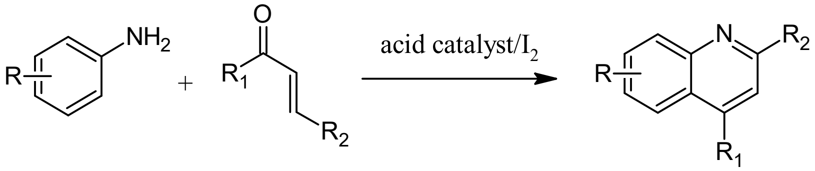
The synthesis of quinolines has been practiced since Koenigs published the first in 1879, in which he passed allylaniline over heated lead (II) oxide [112]. Soon afterwards, in 1880, Czech chemist Zdenko Hans Skraup developed one of the most well-known syntheses of quinolines: heating anilines and glycerol with an oxidant in concentrated sulfuric acid (*Scheme 3.1.1*) [105].



*Scheme 3.1.1 Classical Skraup quinoline synthesis*

For nearly a century and a half, numerous modifications of the Skraup quinoline synthesis have been developed in an attempt to improve product yield, introduce various functional groups, and minimize harsh reaction conditions. The beginning of the last century saw various attempts at improving the efficiency of this method. In the late 1920s and early 1930s, Essie White Cohn of the University of Denver introduced acetic and boric acid modifications in order to reduce the violence of the reaction [113]. Around the same time, Clarke and Davis introduced the addition of ferrous sulfate; and Darzens, Delaby, and Hiron implemented a thorium-vanadium oxide modification. Employing the generally held belief that acrolein is the active intermediate in the cyclization mechanism, in 1947 Yale reacted this component with 3-nitro-4-aminoanisole in a mixture of concentrated sulfuric acid and arsenic pentoxide [114]. This group also found success with 85% phosphoric acid and arsenic acid in place of the previously used acid catalyst and oxidant [115]. However, none of these modifications completely addressed or alleviated the problems inherent in the method, namely low yield, violent reactions, toxic reagents, and inconvenient isolation processes [113]. More recently, microwave-assisted Skraup reactions have provided a means of decreasing reaction time and slightly increasing yield, but these methods still required large amounts of sulfuric acid [111] or toxic arsenic oxide as an oxidant [116].

In 1881, Doebner and Von Miller conducted similar quinoline synthesis experiments; they replaced the glycerol component of the reaction with ethylene glycol and produced 2-methylquinoline. They also heated aniline with paraldehyde (the cyclic trimer of acetaldehyde) in sulfuric acid and again obtained 2-methylquinoline. Through these experiments they determined that crotonaldehyde was the key reactive intermediate, signifying that the use of any α,β-unsaturated aldehyde or ketone as the annulation partner to aniline would similarly result in quinoline (*Scheme 3.1.2*) [117].

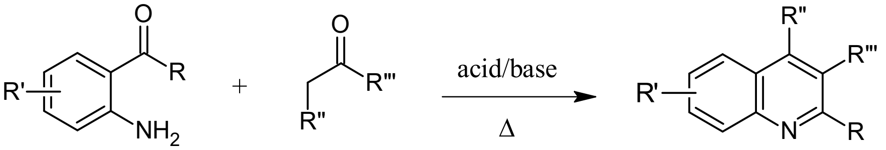


*Scheme 3.1.2 Doebner-Von Miller quinoline synthesis*

With omission of the oxidant and replacement of the concentrated acid with an acid catalyst or iodine ($I_2$) [105], this modification represents an important step forward in the practicality of quinoline synthesis, particularly for quinolines bearing a substituent on C-2 or C-4 of the nitrogen ring. However, there are several serious drawbacks to this method in its classical form. Tedious isolation and purification procedures and acid-catalyzed polymerization of the α,β-unsaturated aldehyde or ketone are detrimental to the yield and purity of quinoline product [118]. In addition, this method is not compatible with the synthesis of heteroring-unsubstituted quinolines, as acrolein would be the obligatory annulation partner; the propensity of acrolein to quickly polymerize in acidic environments makes this an unsuitable procedure [47].

An important modification to this technique was the introduction by Matsugi and coworkers in 2000 of a two-phase solvent system in the cyclization of various substituted anilines with crotonaldehyde [118]. Introducing toluene to the reaction mixture in addition to the aqueous hydrochloric acid ensured crotonaldehyde would remain in the organic layer, thereby avoiding acid-catalyzed self-condensation. The actual cyclization, then, would necessarily occur on the interface of the two layers. This modification resulted in a significant increase in yield (80% in the two-phase reaction versus 47% in HCl alone) and also simplified the isolation of product.

Of the other quinoline syntheses regularly performed, the Friedländer reaction is one of the simplest and most well-established [119]. Traditionally, a Friedländer annulation combines a 2-amino aryl carbonyl with another carbonyl compound containing an active α-carbon; these two components are either refluxed in acid or base or subjected to microwave heating to perform the cyclization (*Scheme 3.1.3*) [119].

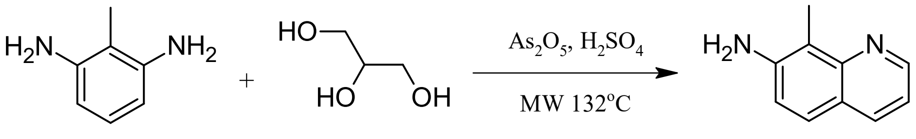


*Scheme 3.1.3 Friedlander quinoline synthesis*

The synthetic utility of this reaction lies in its remarkable compatibility with a wide variety of functional groups, as long as those groups are stable to the acidic or basic reaction conditions or intense heating. However, this method is not without its limitations. Unsymmetrical ketone annulation partners exhibit poor regioselectivity, thereby significantly reducing yield of the desired product.

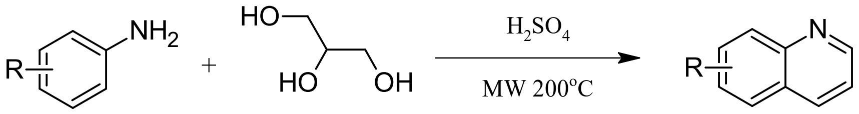
Advances in quinoline syntheses continue to be highly desirable. Recently, several groups have published alternative routes to these structures that utilize various methods to obtain diversely-substituted quinolines. These methods range from microwave irradiation to one-pot cascade reactions, oxidative annulations, and numerous metal-catalyzed syntheses.

In 2007 Silberg *et al.* [120] described a procedure in which they obtained 7-amino-8-methylquinoline from 2,6-diaminotoluene and glycerol (*Scheme 3.1.4*). Using 132°C microwave irradiation, they were able to achieve the desired product in 33 minutes reaction time. While this showed a marked improvement in reaction time (conventional heating at 140°C took 270 minutes), product yield was significantly decreased. The use of super-stoichiometric amounts of arsenic (V) oxide and sulfuric acid also reduced the scalability of this procedure.



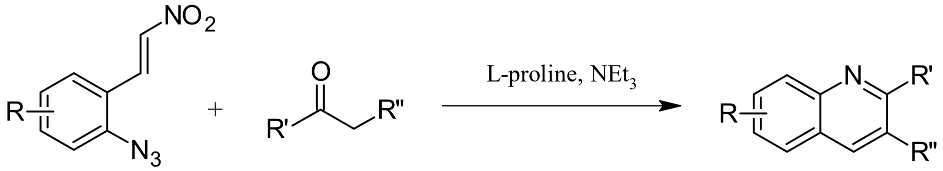
*Scheme 3.1.4 Synthesis of 7-amino-8-methylquinoline using 2,6-diaminotoluene and glycerol in arsenic (V) oxide and sulfuric acid via microwave irradiation*

Then, in 2014 Len and coworkers [121] published a novel Skraup-like cyclization of anilines with glycerol to give various quinolines (*Scheme 3.1.5*). They accomplished this in sulfuric acid (three equivalents) by 200°C microwave irradiation. While on the surface their method appeared promising, including the use of "green" solvent-free conditions and the elimination of toxic oxidizing agents such as arsenic oxide and nitrobenzene that had been used by other groups, it presented several challenges. The high concentration and volume of sulfuric acid made the workup procedure difficult (presumably because of the thick tar that surrounds the crude product), and although this method was amenable to both electron-donating and electron-withdrawing substitutions on the 2-, 3-, and 4-positions of the aniline, their yields only ranged from fair to moderate.



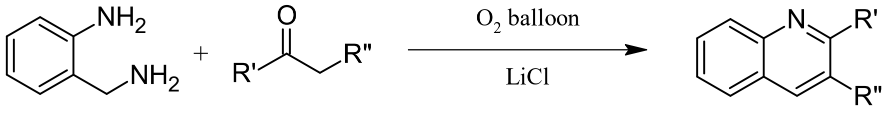
*Scheme 3.1.5 Quinoline synthesis from anilines and glycerol using sulfuric acid and microwave irradiation*

Skraup-like procedures are convenient for the synthesis of heteroring-unsubstituted quinolines, but since the glycerol annulation partner cannot contain functional groups, this procedure is not amenable to divergent functionality on the nitrogen ring. Other methods resolve this issue. The Shi group [122] introduced a one-pot cascade route in 2013 in which various carbonyl compounds were cyclized and aromatized with *ortho*-azido-β-nitro-styrenes to give functionalized quinolines (*Scheme 3.1.6*). Using a catalytic amount of L-proline and an equimolar amount of triethylamine in dichloromethane, they were able to obtain various heteroring-substituted quinolines in good to excellent yield. The mild, short, room temperature reaction conditions make this an interesting route toward quinolines. However, it is unclear whether this method is amenable to diverse substitutions on the phenyl ring; only two trials were conducted with chlorine para to the azide group on the starting styrene.



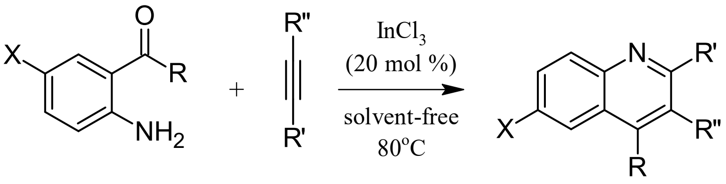
*Scheme 3.1.6 One-pot cascade synthesis of substituted quinolines*

Another interesting and novel approach came from the group of Lei and coworkers [123] who, in 2014, disclosed an aerobic C-N bond activation in the formation of quinolines. Reacting 2-(aminomethyl)aniline with various ketones and an equimolar addition of lithium chloride under one atmosphere of molecular oxygen afforded 2-substituted quinolines in very good yields (*Scheme 3.1.7*). Their reaction appeared adaptable, tolerating both electron-donating and electron-withdrawing aryl rings on the ketone annulation partner, but they did not conduct any trials with aliphatic ketones or substitutions on the aniline. In addition, the reaction required very high temperatures and extended reaction times.



*Scheme 3.1.7 Aerobic C-N activation synthesis of substituted quinolines*

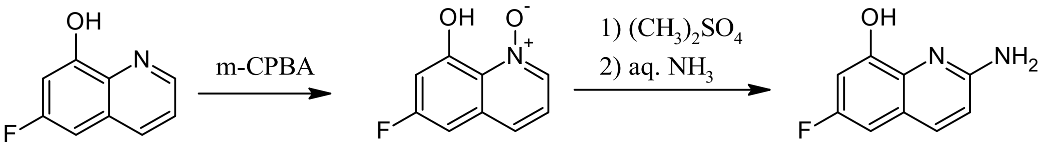
Metal catalysis has become a highly desirable method recently due to the reduction in waste achieved by using sub-stoichiometric reagents [124]. Several recent publications have utilized this strategy toward the synthesis of quinolines. One such paper from Singh and coworkers in 2012 described indium (III) chloride as an efficient Lewis acid catalyst in the solvent-free cyclization of *ortho*-amino aryl ketones with alkynes (*Scheme 3.1.8*) [110].



*Scheme 3.1.8 InCl₃-catalyzed cyclization of ortho-carbonyl anilines with alkynes*

## 3.2 Heteroring-unsubstituted quinoline synthesis

As mentioned in Section 2.3.5.1, an analog of 8-hydroxyquinoline-2-carboxylic acid bearing an amine group in the 2-position was desired as a potential inhibitor against the class II *Mycobacterium tuberculosis* fructose-1,6-bisphosphate aldolase. The proposed synthetic scheme toward this 2-amino quinoline commenced with the heteroring-unsubstituted quinoline, which would subsequently be converted to the quinoline-*N*-methoxide then reacted with ammonia to form the desired product (*Scheme 3.2.1*).



*Scheme 3.2.1 Synthetic scheme toward amination of 2-position of quinoline, necessitating the use of heteroring-unsubstituted quinoline*

As the go-to reaction for the assembly of a heteroring-unsubstituted quinoline, the Skraup reaction was first attempted to obtain this precursor. 2-amino-5-fluorophenol was refluxed with glycerol in concentrated sulfuric acid, using sodium 3-nitrobenzene sulfonate as the oxidizing agent; this resulted in a thick tarry crude product. Extraction and purification of the quinoline from this tar proved to be prohibitively difficult; only 4% yield of the quinoline was attained. Since this method was not feasible as the first step of a multi-step synthetic scheme, it was necessary to investigate an alternative route to synthesize this heterocycle.

Mechanistically related to the Skraup quinoline synthesis, the Doebner-Von Miller protocol is attractive due to the relatively simple workup procedure and the omission of harsh oxidizing agents. However, since the desired quinoline product required the 2-, 3-, and 4-positions of the heterocyclic ring to be unsubstituted, the α,β-unsaturated carbonyl annulation partner would have to be acrolein. As previously mentioned, under the standard DVM reaction conditions of refluxing in acid, acrolein has a high propensity to oligomerize, complicating the purification procedure and requiring a large excess of this relatively costly reagent. Tellingly, Yale's investigation into the use of acrolein as the enal partner in the cyclization with aniline produced only a trace of unsubstituted quinoline [114].

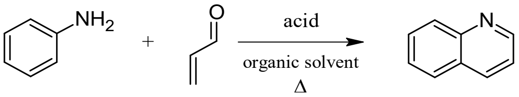
Previous success with the biphasic DVM method of Matsugi *et al.* in the cyclization of anilines with crotonaldehyde (Section 2.2.1) recommended the application of this procedure to the analogous cyclization with acrolein. Therefore, 2-amino-5-fluorophenol was refluxed with acrolein in a mixture of toluene and 6M HCl, giving 26% yield of the desired product, an increase of more than six-fold over the same reaction run under Skraup conditions. Encouraged by these results, it was decided to explore the optimization of this reaction [47].

### 3.2.1 Optimization Studies

Investigations into the validity of this method began with the reaction of unsubstituted aniline with acrolein in a biphasic mixture of equal volumes of 6M HCl and toluene. This reaction mixture was refluxed for 24 hours, but aniline concentrations of both 0.50M and 0.25M yielded less than 10% of the desired quinoline.

While substitution of HCl with either a Lewis acid (aluminum trichloride, $AlCl_3$), or ten mole percent of a phase-transfer catalyst (tetrabutylammonium chloride, $NBu_4Cl$), resulted in only a trace amount of product formation, dilution of the reaction mixture and reduction of the ratio of organic cosolvent proved advantageous. A 28% yield of quinoline was obtained from a 3.4:1 mixture of HCl/toluene at 0.06M aniline concentration, and the yield was increased to 35% with a 6.9:1 ratio of solvents at the same concentration. Both were allowed to react for 24 hours. Even though lower ratios of organic cosolvent were beneficial to the success of the reaction, complete elimination of the organic layer was decidedly detrimental; as had been expected, only a trace of quinoline was observed. The results are summarized in *Table 5*.

*Table 5 Optimization of quinoline synthesis using acrolein.*



| *Entry* | *Acid* | *Organic Solvent* | *Ratio Acid: Organic* | *Concentration*[*] *(M)* | *Yield*[†] *(%)* |
|---|---|---|---|---|---|
| *1* | 6M HCl | Toluene | 1:1 | 0.50 | 2 |
| *2* | 6M HCl | Toluene | 1:1 | 0.25 | 9 |
| *3* | 6M HCl | Xylenes | 3.4:1 | 0.06 | 20 |
| *4* | 6M HCl | Xylenes | 6.9:1 | 0.06 | 23 |
| *5* | 6M HCl | Toluene | 3.4:1 | 0.06 | 28 |
| *6* | 6M HCl | Toluene | 6.9:1 | 0.06 | 35 |
| *7* | $AlCl_3$ | $CH_2Cl_2$ | - | 0.20 | Trace |
| *8* | $NBu_4Cl$ (0.1 eq) | Toluene | - | 0.25 | Trace |
| *9* | 6M HCl | - | - | 0.06 | Trace |

Modification of other variables did not improve the reaction outcome. Under the most efficient reaction conditions of a 6.9:1 ratio of 6M HCl to toluene with an aniline concentration of 0.06M, a decreased reaction time from 24 hours to either three or six hours caused the yield to drop into the single digits.

---

[*] Aniline concentration.

[†] Isolated yields.

The moderate product yields seen under these conditions indicated that, even with super-stoichiometric amounts of acrolein and an organic cosolvent to reduce acid-catalyzed self-condensation of this reagent, oligomerization was still a problem.

Therefore an alternative annulation partner was sought that would be resistant to this process. Acrolein diethyl acetal (ADA, *Figure 3.2.1*) was used in lieu of acrolein due to its increased stability in acidic media, and a comparable yield of quinoline was obtained from reaction conditions identical to those that had produced 35% yield with acrolein. Although this did not initially represent much of an advantage, it was encouraging enough to continue with optimization.

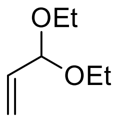


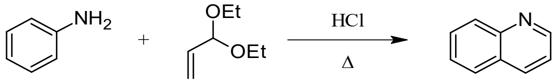
*Figure 3.2.1 Acrolein diethyl acetal*

While conducting optimization of this reaction, it was hypothesized that the organic cosolvent would not be necessary. In fact, it may even hinder the efficiency of the reaction. Since hydrolysis of one ethoxy group of the diethyl acetal would initially need to occur for the reaction to proceed, sequestration of this reagent in the organic layer would only allow the acid-mediated hydrolysis and the subsequent annulation to take place on the interface of the two layers. However, omission of the organic layer would likely allow the desired hydrolysis to occur without incurring undesired oligomerization.

This hypothesis was substantiated when the reaction was performed without an organic cosolvent. Initial conditions of refluxing aniline with acrolein diethyl acetal in 6M HCl at a concentration of 0.07M for 24 hours gave a very encouraging 54% yield of quinoline. Even on a larger scale the reaction was relatively efficient, producing 45% of the expected product. However, attempts to decrease the reflux time to three or six hours reduced the yield by more than half. Increasing the aniline concentration to 0.1M and 0.2M proved even more detrimental, producing only traces of product.

On the other hand when the reaction mixture was diluted to 0.01M, nearly the same efficiency was achieved after 24 hours of reflux. Increasing the reaction time to 67 hours marginally improved the outcome, but not enough to outweigh the inconvenience and extra energy usage resulting from the extended reaction time. Pleasingly, it was noted that under the more dilute conditions isolation of quinoline was significantly simplified, giving a much cleaner crude product. The results can be seen in *Table 6*.

*Table 6 Optimization of quinoline synthesis using acrolein diethyl acetal.*



| *Entry* | *Acid* | *Time (h)* | *Concentration*[*] *(M)* | *Yield*[†] *(%)* |
|---|---|---|---|---|
| *1*[‡] | 6M HCl | 24 | 0.06 | 25 |
| *2* | 6M HCl | 24 | 0.07 | 54 |
| *3*[§] | 6M HCl | 24 | 0.07 | 45 |
| *4* | 6M HCl | 3 | 0.07 | 22 |
| *5* | 6M HCl | 6 | 0.07 | 25 |
| *6* | 6M HCl | 24 | 0.10 | Trace |
| *7* | 6M HCl | 24 | 0.20 | Trace |
| *8* | 1M HCl | 67 | 0.01 | 63 |
| *9* | 1M HCl | 24 | 0.01 | 56 |

This procedure represents a marked improvement in terms of yield and purity and is equally efficient with both 6M and 1M HCl, meaning the amount of acid can be adjusted based on the scale of the reaction. It is also an advancement over previous methods – such as that of Yale – in terms of green chemistry practices. The omission of organic cosolvent, highly concentrated acids, harsh oxidizing agents, and extremely high reflux temperatures greatly increases the synthetic utility of this reaction. Also, exchanging acrolein for the more stable acrolein diethyl acetal drastically improved the reaction outcome. It is interesting to note that Yale and coworker also investigated the use of ADA in place of acrolein in a modified version of their quinoline synthesis [115]. However, they actually observed a decrease in efficiency with this reagent and decided it was not a necessary substitution.

---

[*] Aniline concentration.

[†] Isolated yields.

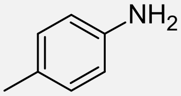
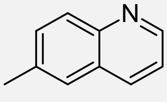
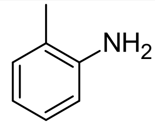
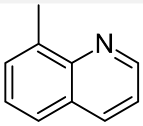
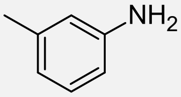
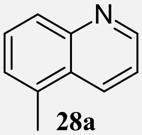
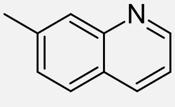
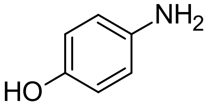
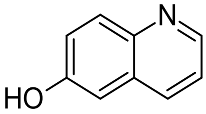
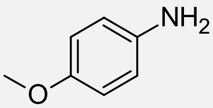
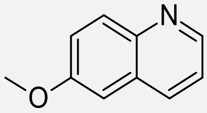
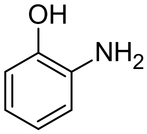
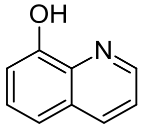
[‡] Reaction run with 3.4:1 ratio of 6M HCl to toluene.

[§] Reaction run on 500 mg scale.

### 3.2.2 Scope of the Reaction

Once the optimal reaction conditions were determined, the scope of the reaction was then probed with regard to various starting anilines. Initially, a variety of moderately electron-donating methyl substitutions on this substrate were investigated. While reaction of *p*-toluidine under these conditions gave a modest yield of 6-methylquinoline, *o*-toluidine was much more efficient, giving 83% of 8-methylquinoline. When *m*-toluidine was used, both 5- and 7-methylquinoline were produced in nearly equal amounts, showing no preference for cyclization one way or the other; these were produced as an inseparable mixture. Along the same lines, more vigorously electron-donating substituents gave similar results. While *p*-aminophenol and *p*-anisidine were only modestly successful, *o*-aminophenol gave a more robust yield of 8-hydroxyquinoline. These series clearly show that electron-donating substituents *ortho* to nitrogen in the starting aniline assist the cyclization process more than other positions. The results are shown in *Table 7.*

*Table 7 Singly-substituted quinoline products.*

| *Entry* | *Starting Aniline* | *Quinoline Product(s)* | *Yield (%)** |
|---|---|---|---|
| *1* |  |  **26** | 36 |
| *2* |  |  **27** | 83 |
| *3* |  |  **28a**  **28b** | 26 |
| *4* |  |  **29** | 23 |
| *5* |  |  **30** | 27 |
| *6* |  |  **31** | 41 |

However, electron-withdrawing substituents in the *ortho* position of the starting aniline were slightly detrimental to the reaction efficiency. Under the same reaction conditions, 2-bromoaniline gave a relatively poor yield of 8-bromoquinoline. In addition, other halogenated starting anilines were similarly ineffective. 3,4-difluoroaniline only gave 16% yield of the single 6,7-difluoroquinoline product. Similarly, 4-iodoaniline produced only 9% of the desired 6-iodoquinoline. The low yield in this reaction, though, was partially due to extrusion of the iodine from the final product; initial purification gave a mixture of 6-iodoquinoline and unsubstituted quinoline. Careful separation by chromatography allowed for isolation of the desired product. An outlier in this series was 2-bromo-4-fluoroaniline, which produced the desired 8-bromo-6-fluoroquinoline in 55% yield.

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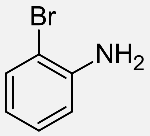
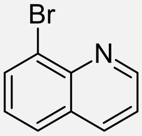
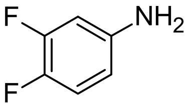
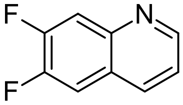
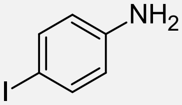
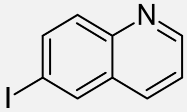
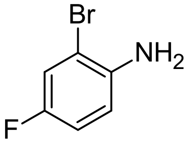
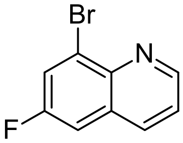
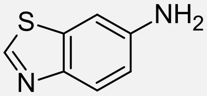
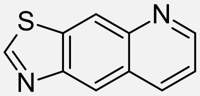
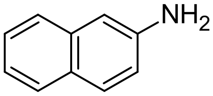
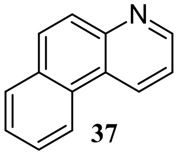
* Purified yields.

Aromatic and heterocyclic substituents on the aniline were also moderately successful but surprisingly regioselective. 6-aminobenzothiazole cyclized with ADA exclusively at the 5-position to give the corresponding tricyclic product in modest yield. The reaction with 2-aminonaphthalene was more fruitful under these conditions. The single product from this reaction, isolated in 46% yield, was benzo[*f*]quinoline, implicating the preference for cyclization closer to the aromatic ring rather than at the symmetric 3 position. These results are summarized in *Table 8.*

*Table 8 Variously-substituted quinoline products.*

| *Entry* | *Starting Aniline* | *Quinoline Product* | *Yield* * *(%)* |
|---|---|---|---|
| *1* |  |  **32** | 32 |
| *2* |  |  **33** | 16 |
| *3* |  |  **34** | 9 |
| *4* |  |  **35** | 55 |
| *5* |  |  **36** | 21 |
| *6* |  |  **37** | 46 |

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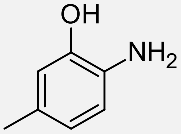
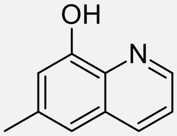
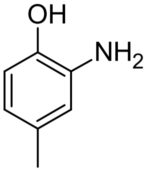
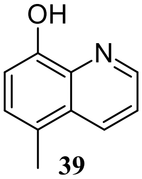
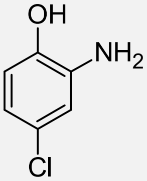
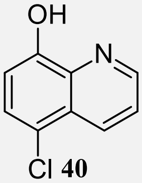
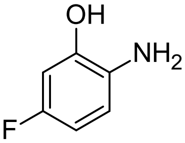
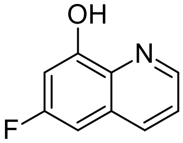
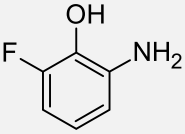
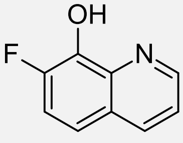
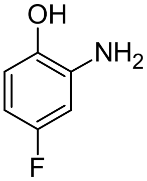
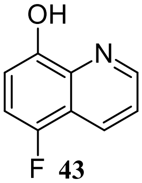
* Purified yields.

In a final sequence of investigations into the scope of this reaction, a series of substituted *ortho*-aminophenols were tested. These aminophenols, featuring a variety of both electron-donating and electron-withdrawing substituents at the 4-, 5-, or 6- positions on the aromatic ring, underwent the reaction with widely varying success.

To begin, the reaction was performed on aminophenols with an electron-donating substituent. 2-amino-5-methylphenol and 2-amino-4-methylphenol were similarly amenable to this reaction, giving the appropriate quinoline products in 50% and 58% yields, respectively. With a combination of electron-donating and electron-withdrawing substituents, 2-amino-4-chlorophenol gave equally robust results with 49% yield of the quinoline product. While some of the fluorine-substituted 8-hydroxyquinoline products were easily obtained – 6-fluoro-8-hydroxyquinoline and 7-fluoro-8-hydroxyquinoline were isolated in 42% and 43% yields, respectively – others were less so. 5-fluoro-8-hydroxyquinoline was substantially less successful, representing the least productive cyclization of the aminophenol series. These results are shown in *Table 9*.

*Table 9 Doubly-substituted hydroxyquinoline products.*

| *Entry* | *Starting Aniline* | *Quinoline Product* | *Yield (%)*[*] |
|---|---|---|---|
| *1* |  | <br>**38** | 50 |
| *2* |  | <br>**39** | 58 |
| *3* |  | <br>**40** | 49 |
| *4* |  | <br>**41** | 42 |
| *5* |  | <br>**42** | 43 |
| *6* |  | <br>**43** | 18 |

In addition to these successful results, there were a few unexpected outcomes. Subjecting 4-ethynylaniline to the previous reaction conditions in 6M HCl resulted in the cyclization product, but it also caused oxidation of the aryl alkyne to a methyl ketone (*Scheme 3.2.2*). It was determined that the kinetics of the acid-mediated oxidation of an alkyne is first-order in acid concentration; therefore, lowering the acid concentration could potentially allow the cyclization to occur more rapidly than the oxidation. However, it was also necessary to maintain a minimum molar ratio of acid to aniline, since it had been determined that lowering this molar ratio was detrimental to the cyclization. With this in mind, the concentration of HCl was reduced to 1M while the volume was increased accordingly to maintain the molar ratio. While this tactic did not result in the desired 6-ethynylquinoline, it did proceed smoothly with a much more straightforward workup, providing the basis for the eventually adopted procedure.

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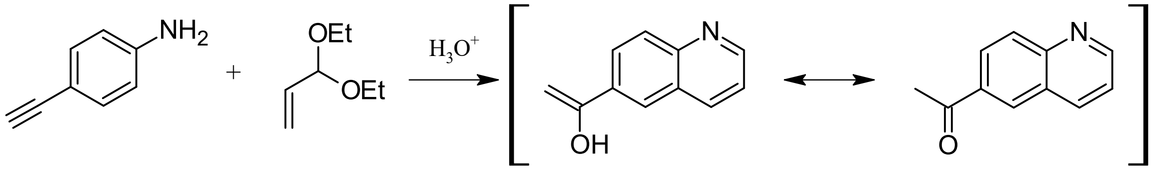
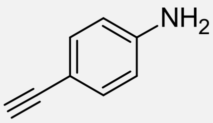
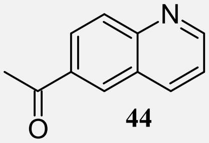
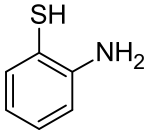
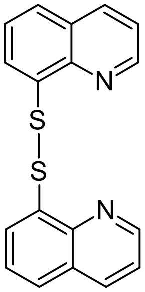
[*] Purified yields.



*Scheme 3.2.2 Acid-catalyzed oxidation of ethyne group to methyl ketone during quinoline cyclization*

In addition, attempts to subject 2-aminothiophenol to these reaction conditions gave similarly surprising results. Initial investigation into the product structure by NMR seemed to support product formation. However, mass spectral analysis indicated the sole product to be a disulfide dimer of two quinolines. These results can be seen in *Table 10.*

*Table 10 Unexpected quinoline products.*

| *Entry* | *Starting Aniline* | *Quinoline Product* | *Yield (%)*[*] |
|---|---|---|---|
| *1* |  | <br>**44** | 32 |
| *2* |  | <br>**45** | 3 |

### 3.2.3 Mechanism

Ever since Skraup published his synthesis of quinoline via the acid-catalyzed annulation of aniline with glycerol over a century ago, various groups have endeavored to evaluate and establish a reasonable mechanism for this reaction. While it is generally accepted that the initial step involves acid-mediated dehydration of glycerol to acrolein (*Scheme 3.2.3*), the subsequent annulation with aniline has been a source of contention [105].

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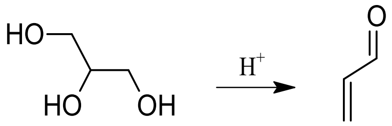
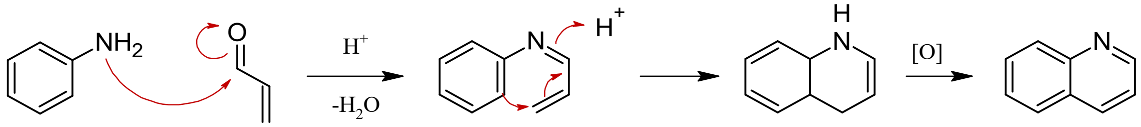
[*] Purified yields.



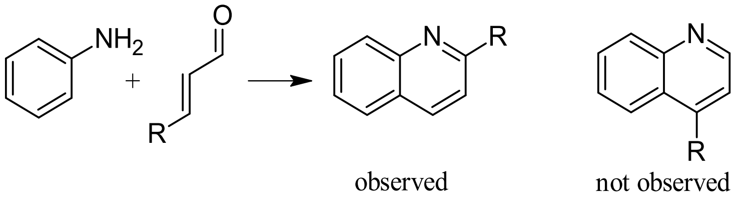
*Scheme 3.2.3 In situ acid-catalyzed dehydration of glycerol to acrolein*

Skraup himself postulated a direct carbonyl addition and subsequent condensation of the aniline with acrolein, forming an intermediate Schiff base. Attack of π electrons from the aromatic ring on the terminal end of the alkene would result in cyclization, and the dihydroquinoline intermediate would rearomatize upon oxidation (*Scheme 3.2.4*).



*Scheme 3.2.4 Mechanism of quinoline cyclization postulated by Skraup*

However, this was quickly disproven by the observation that anilines react with β-substituted α,β-unsaturated aldehydes to give exclusively 2-substituted quinolines[*] rather than the 4-substituted products expected from the Schiff base mechanism Skraup proposed (*Scheme 3.2.5*) [125].

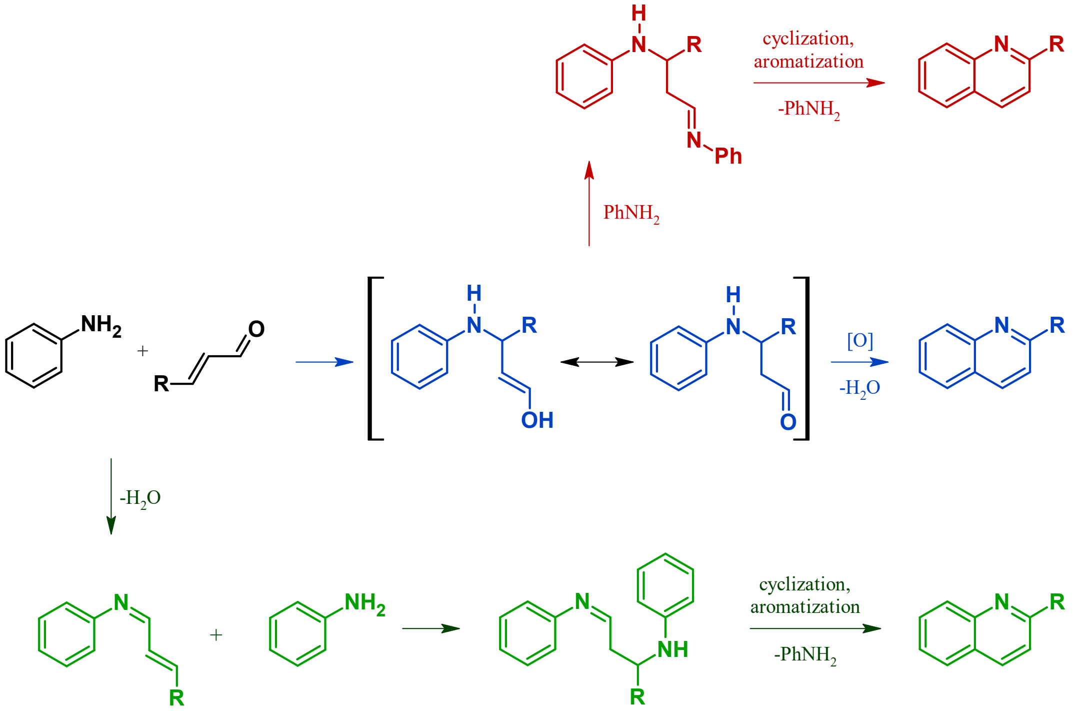


*Scheme 3.2.5 Observed 2-substituted quinoline and not observed 4-substituted quinoline products of cyclization of aniline with β-substituted α,β-unsaturated aldehydes*

---

[*] As seen experimentally in section 2.2.1.1.

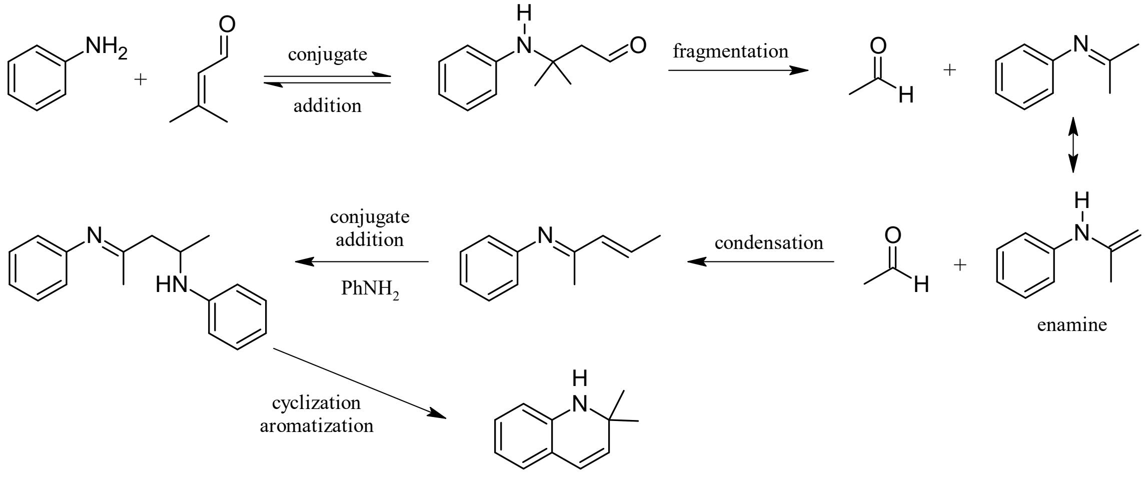
In order to justify this observation, Bischler soon after proposed an alternative pathway. Taking into account Skraup's contention that the intermediate Schiff base is central to the mechanism, he conceived a dual pathway, whereby the reaction could proceed through a direct 1,4-addition of the aniline with either the aldehyde (blue route, *Scheme 3.2.6*) or the preformed Schiff base (green route). Elimination of water or aniline would then provide the observed 2-substituted quinoline [125]. Koenig expanded on Bischler's proposal by suggesting the product of 1,4-addition undergoes condensation with a second molecule of aniline (red route), thereby forming the highly electrophilic imine, which then undergoes ring closure and expulsion of aniline to give the 2-substituted quinoline [105].



H
N
R
cyclization,
aromatization
-PhNH$_2$
N
R
N
Ph
PhNH$_2$
NH$_2$
+
R
O
H
N
R
OH
H
N
R
O
[O]
-H$_2$O
N
R
-H$_2$O
N
R
+
NH$_2$
N
NH
R
cyclization,
aromatization
-PhNH$_2$
N
R

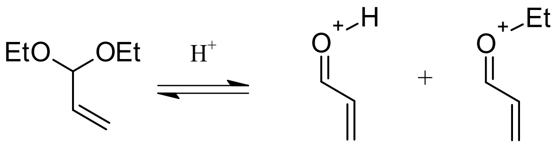
*Scheme 3.2.6 Three possible mechanistic routes for the formation of 2-substituted quinolines from the cyclization of aniline with β-substituted α,β-unsaturated aldehydes*

In a series of ingenious experiments, several groups have independently attempted to determine which (if any) of these mechanistic proposals is at play in the synthesis of quinolines. Prominently, Denmark and coworker published a review of these studies and also conducted their own research on the matter. Through extensive carbon-13 labeling experiments, they determined that β-disubstituted carbonyls underwent a conjugate addition-fragmentation mechanism when combined with anilines under Skraup conditions (*Scheme 3.2.7*). This mechanism then proceeds through enamine formation, condensation with the carbonyl fragment, conjugate addition of a second molecule of aniline, and finally cyclization and aromatization.



*Scheme 3.2.7 Conjugate addition-fragmentation mechanism of quinoline synthesis proposed by Denmark*

Under the novel conditions of employing acrolein diethyl acetal as the annulation partner, the proposed Denmark mechanism would be unproductive since the intermediate enamine fragment could not form. Therefore, a more traditional pathway was proposed, initiated by the acid-catalyzed hydrolysis of the diethyl acetal, giving the reactive protonated acrolein or oxocarbenium species (*Scheme 3.2.8*). Subsequently, any of the three mechanistic routes proposed by Bischler and Koenig (blue, green, and red routes, *Scheme 3.2.6*) could conceivably occur.



*Scheme 3.2.8 Protonated acrolein or oxocarbenium reactive species*

## 3.3 Conclusion

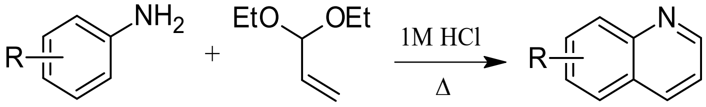
The synthesis of quinolines has been studied for well over a century, and there are a wealth of procedural options for nearly any substitution pattern desired. However, an efficient and "green" synthesis of heteroring-unsubstituted quinolines has been elusive, forcing chemists to resort to procedures that use toxic reagents or result in extremely poor yields.

Therefore, the new procedure reported herein, which uses aqueous media and results in decent to very good yields, represents a significant step in this direction. This method is amenable to a broad range of substitutions on the aniline, including many different electron-withdrawing and electron-donating groups.

As a highly desirable framework for building biologically active molecules, including a potent inhibitor of *Mycobacterium tuberculosis* fructose-1,6-bisphosphate aldolase, the quinoline moiety is an important scaffold in the field of synthetic medicinal chemistry. This new procedure adds to the arsenal of processes that can be used to obtain functionally diverse quinolines and will prove to be highly valuable in this regard.

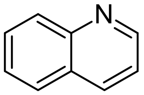
## 3.4 Experimental Details

*Experimental procedure for synthesis of heteroring-unsubstituted quinolines*



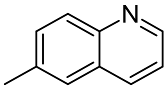
1M HCl (82.5 mL) was added to the aniline in a round bottom flask. To this was added acrolein diethyl acetal (2.5 eq). The reaction was refluxed for 24 hours, then cooled to room temperature. The solution was neutralized to pH 7-8 by addition of solid $Na_2CO_3$ then extracted into $CH_2Cl_2$. The organic layers were combined and dried over $Na_2SO_4$ then concentrated by rotary evaporation. The crude residue was purified by column chromatography by elution of EtOAc/hexanes to give the pure product.

***Quinoline (25)*** *Compound known in literature.*



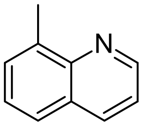
**82.2 mg, 56%** (isolated yield). $^1$H NMR (500 MHz, $CDCl_3$) δ 9.24 (dd, *J* = 1.41, 5.40 Hz, 1H), 9.05 (d, *J* = 8.23 Hz, 1H), 8.84 (d, *J* = 8.62 Hz, 1H), 8.24 (m, 1H), 8.10 (m, 2H), 7.93 (ddd, *J* = 1.07, 6.98, 8.23 Hz, 1H).

***6-methylquinoline (26)*** *Compound known in literature.*



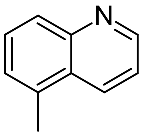
**55.4 mg, 36%**. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.87 (dd, *J* = 1.75, 4.24 Hz, 1H), 8.09 (m, 1H), 8.03 (d, *J* = 8.56 Hz, 1H), 7.60 (dt, *J* = 1.02, 2.03 Hz, 1H), 7.57 (dd, *J* = 2.01, 8.59 Hz, 1H), 7.38 (dd, *J* = 4.20, 8.27 Hz, 1H), 2.56 (s, 3H).

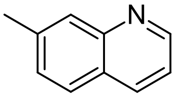
***8-methylquinoline (27)*** *Compound known in literature.*



**115.9 mg, 83%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.97 (dd, *J* = 1.81, 4.19 Hz, 1H), 8.90 (s, 1H), 8.16 (dd, *J* = 1.83, 8.22 Hz, 1H), 7.69 (m, 1H), 7.59 (m, 1H), 7.47 (m, 1H), 7.42 (dd, *J* = 4.20, 8.22 Hz, 1H), 2.85 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 149.26, 137.06, 136.38, 129.67, 128.34, 126.32, 125.89, 120.85, 18.18.

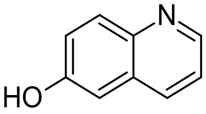
***5-methylquinoline (28a) and 7-methylquinoline (28b)*** *Compounds known in literature.*





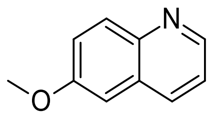
**34.7 mg, 26%** (mixture inseparable by chromatography). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.96 (dd, *J* = 1.70, 4.23 Hz, 1H), 8.91 (dd, *J* = 1.76, 4.30 Hz, 1H), 8.37 (ddd, *J* = 0.91, 1.71, 8.50 Hz, 1H), 8.15 (m, 1H), 8.00 (m, 1H), 7.92 (m, 1H), 7.74 (d, *J* = 8.29 Hz, 1H), 7.63 (dd, *J* = 7.02, 8.56 Hz, 1H), 7.47 (dd, *J* = 4.21, 8.50 Hz, 1H), 7.41 (m, 1H), 7.37 (dd, *J* = 4.29, 8.23 Hz, 1H), 2.72 (m, 3H), 2.60 (d, *J* = 0.95 Hz, 3H).

***Quinoline-6-ol (29)*** *Compound known in literature.*



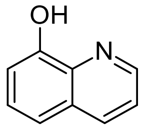
**35.5 mg, 23%**. $^1$H NMR (500 MHz, MeOD) δ 8.62 (dd, *J* = 1.67, 4.30 Hz, 1H), 8.15 (m, 1H), 7.89 (d, *J* = 9.11 Hz, 1H), 7.42 (dd, *J* = 4.29, 8.35 Hz, 1H), 7.37 (dd, *J* = 2.69, 9.11 Hz, 1H), 7.16 (d, *J* = 2.72 Hz, 1H). $^{13}$C NMR (126 MHz, MeOD) δ 155.95, 146.48, 142.62, 135.19, 130.00, 128.97, 122.13, 121.12, 108.19.

***6-methoxyquinoline (30)*** *Compound known in literature.*



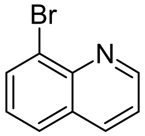
**44.1 mg, 27%**. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 1.70, 4.25 Hz, 1H), 8.08 (m, 1H), 8.03 (d, *J* = 9.21 Hz, 1H), 7.39 (ddd, *J* = 3.54, 8.77, 10.54 Hz, 2H), 7.10 (d, *J* = 2.82 Hz, 1H), 3.96 (s, 3H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 157.73, 147.95, 144.46, 134.76, 130.88, 129.30, 122.26, 121.36, 105.12, 55.54.

***Quinoline-8-ol (31)*** *Compound known in literature.*



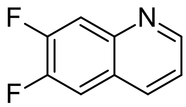
**58.9 mg, 41%**. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.82 (dd, $J_{2\text{-}3}$ = 4.21 Hz, $J_{2\text{-}4}$ = 1.62 Hz, 1H, H-2), 8.42 (br s, 1H, OH), 8.18 (dd, $J_{3\text{-}4}$ = 8.39 Hz, 1H, H-4), 7.47 (m, 2H, H-3, H-6), 7.36 (dd, $J_{5\text{-}6}$ = 8.39 Hz, $J_{5\text{-}7}$ = 1.19 Hz, 1H, H-5), 7.23 (dd, $J_{6\text{-}7}$ = 7.69 Hz, 1H, H-7). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 152.3, 147.9, 138.4, 136.1, 128.6, 127.7, 121.8, 117.9, 110.1.

***8-bromoquinoline (32)*** *Compound known in literature.*



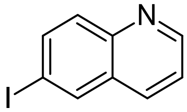
**41.0 mg, 32%**. $^{1}$H NMR (500 MHz, $CDCl_3$) δ 9.08 (dd, *J* = 1.72, 4.23 Hz, 1H), 8.19 (dd, *J* = 1.72, 8.26 Hz, 1H), 8.08 (dd, *J* = 1.34, 7.51 Hz, 1H), 7.82 (dd, *J* = 1.33, 8.21 Hz, 1H), 7.49 (dd, *J* = 4.22, 8.25 Hz, 1H), 7.43 (t, *J* = 7.78 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 151.28, 145.32, 136.63, 133.21, 129.60, 127.80, 124.82, 121.93.

***6,7-difluoroquinoline (33)***



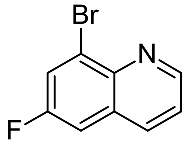
Light brown powder, **23.1 mg, 16%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.92 (dd, $J_{2\text{-}3}$ = 4.34 Hz, $J_{2\text{-}4}$ = 1.67 Hz, 1H, H-2), 8.12 (dd, $J_{3\text{-}4}$ = 8.35 Hz, 1H, H-4), 7.88 (dd, 1H, H-8), 7.57 (dd, 1H, H-5), 7.44 (dd, 1H, H-3). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 153.3 ($J$ = 16.2 Hz), 151.2 ($J$ = 11.9 Hz, 16.1 Hz), 150.6 ($J$ = 2.9 Hz), 149.2 ($J$ = 16.0 Hz), 145.5 ($J$ = 10.6 Hz), 135.2 ($J$ = 2.0 Hz, 5.3 Hz), 125.2 ($J$ = 8.1 Hz), 121.2 ($J$ = 2.5 Hz), 115.8 ($J$ = 16.4 Hz), 112.9 ($J$ = 1.7 Hz, 17.4 Hz).

***6-iodoquinoline (34)***



Light tan powder, **11.2 mg, 9%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.95 (dd, $J_{2\text{-}3}$ = 4.09 Hz, $J_{2\text{-}4}$ = 1.61 Hz, 1H, H-2), 8.24 (d, $J_{5\text{-}7}$ = 1.95, 1H, H-5), 8.07 (dd, $J_{3\text{-}4}$ = 8.28 Hz, 1H, H-4), 7.97 (dd, $J_{7\text{-}8}$ = 8.91, 1H, H-7), 7.86 (d, 1H, H-8), 7.44 (dd, 1H, H-3). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 150.9, 147.2, 138.2, 136.5, 134.8, 131.2, 129.9, 121.7, 92.1.

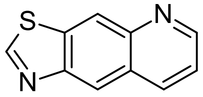
***8-bromo-6-fluoroquinoline (35)***



Off-white powder, **68.0 mg, 55%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 9.00 (dd, $J_{2\text{-}3}$ = 4.26 Hz, $J_{2\text{-}4}$ = 1.65 Hz, 1H, H-2), 8.12 (dd, $J_{3\text{-}4}$ = 8.30 Hz, 1H, H-4), 7.87 (dd, $J_{5\text{-}7}$ = 2.75 Hz, 1H, H-7), 7.48 (dd, 1H, H-3), 7.43 (dd, 1H, H-5). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 159.4

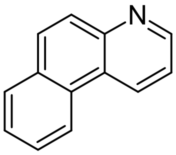
($J$ = 251.6 Hz), 150.5 ($J$ = 2.8 Hz), 142.6, 136.0 ($J$ = 5.6 Hz), 129.3 ($J$ = 10.3 Hz), 126.6 ($J$ = 10.7 Hz), 123.6 ($J$ = 28.3 Hz), 122.5, 110.7 ($J$ = 21.1 Hz).

***[1,3]thiazolo[4,5-g]quinoline (36)***



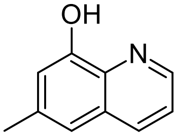
Light orange-brown powder, **40.6 mg, 21%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 9.16 (s, 1H, H-9), 9.03 (dd, $J_{2\text{-}3}$ = 4.30 Hz, $J_{2\text{-}4}$ = 1.69 Hz, 1H, H-2), 8.42 (m, 2H, H-4, H-8), 8.20 (d, $J_{5\text{-}8}$ = 9.04, 1H, H-5). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 153.5, 151.7, 150.1, 146.8, 133.2, 130.9, 129.0, 125.3, 123.4, 121.6.

***Benzo[f]quinoline (37)*** *Compound known in literature.*



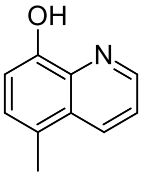
**63.3 mg, 46%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.99 (dd, $J$ = 1.62, 4.36 Hz, 1H), 8.96 (dd, $J$ = 1.64, 8.33 Hz, 1H), 8.64 (dd, $J$ = 1.30, 8.16 Hz, 1H), 8.01 (m, 2H), 7.96 (dd, $J$ = 1.51, 7.92 Hz, 1H), 7.70 (dddd, $J$ = 1.39, 7.06, 8.15, 21.48 Hz, 2H), 7.58 (dd, $J$ = 4.37, 8.38 Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 149.74, 148.25, 131.70, 130.86, 130.68, 129.66, 128.72, 128.23, 127.10, 127.33, 125.44, 122.59, 121.31.

***6-methylquinolin-8-ol (38)***



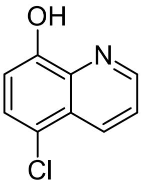
Light brown powder, **59.0 mg, 50%**. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.74 (dd, $J_{2\text{-}3}$ = 4.25 Hz, $J_{2\text{-}4}$ = 1.59 Hz, 1H, H-2), 8.50 (br s, 1H, OH), 8.06 (dd, $J_{3\text{-}4}$ = 8.32 Hz, 1H, H-4), 7.40 (dd, 1H, H-3), 7.11 (m, 2H, H-5, H-7), 2.52 (s, 3H, $CH_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 151.9, 147.0, 138.0, 137.1, 135.4, 128.6, 121.8, 116.9, 112.2, 22.2.

***5-methylquinolin-8-ol (39)***



Off-white powder, **1.5g, 58%**. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.81 (dd, $J_{2\text{-}3}$ = 4.20 Hz, $J_{2\text{-}4}$ = 1.57 Hz, 1H, H-2), 8.30 (dd, $J_{3\text{-}4}$ = 8.51 Hz, 1H, H-4), 7.48 (dd, 1H, H-3), 7.29 (dd, $J_{6\text{-}7}$ = 7.67 Hz, 1H, H-7), 7.11 (d, 1H, H-6), 2.61 (s, 3H, $CH_3$). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 150.6, 147.3, 138.6, 133.0, 127.64, 127.61, 124.3, 121.3, 109.3, 17.8.

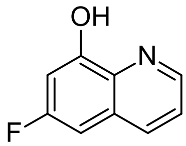
***5-chloroquinolin-8-ol (40)*** *Compound known in literature.*



**61.2 mg, 49%**. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.86 (dd, $J$ = 1.56, 4.22 Hz, 1H), 8.55 (dd, $J$ = 1.56, 8.61 Hz, 1H), 8.30 (br s, 1H, OH), 7.58 (dd, $J$ = 4.22, 8.53 Hz, 1H), 7.55

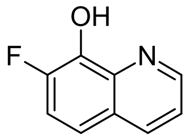
(d, $J$ = 8.24 Hz, 1H), 7.14 (d, $J$ = 8.23 Hz, 1H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 151.39, 148.36, 138.69, 133.38, 127.48, 126.32, 122.55, 120.38, 109.95.

***6-fluoroquinolin-8-ol (41)***



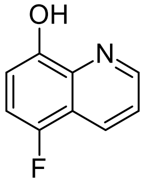
Off-white powder, **40.0 mg, 42%**. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.75 (dd, $J_{2\text{-}3}$ = 4.28 Hz, $J_{2\text{-}4}$ = 1.53 Hz, 1H, H-2), 8.55 (br s, 1H, OH), 8.12 (dd, $J_{3\text{-}4}$ = 8.34 Hz, 1H, H-4), 7.48 (dd, 1H, H-3), 6.99 (m, 2H, H-5, H-7). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 161.6 ($J$ = 246.6 Hz), 154.0 ($J$ = 14.6 Hz), 147.0 ($J$ = 2.8 Hz), 135.8, 135.6 ($J$ = 5.9 Hz), 128.7 ($J$ = 12.2 Hz), 122.8, 101.1 ($J$ = 12.8 Hz), 100.9 ($J$ = 5.7 Hz).

***7-fluoroquinolin-8-ol (42)***



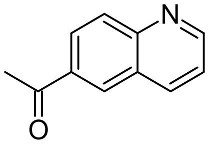
Beige powder, **25.4 mg, 42%**. $^1$H NMR (500 MHz, $CDCl_3$) δ 8.86 (dd, $J_{2\text{-}3}$ = 4.30 Hz, $J_{2\text{-}4}$ = 1.59 Hz, 1H, H-2), 8.19 (dd, $J_{3\text{-}4}$ = 8.33 Hz, 1H, H-4), 7.43 (m, 2H, H-5, H-6), 7.34 (dd, 1H, H-3). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 148.8, 147.6 ($J$ = 244.9 Hz), 139.5 ($J$ = 7.2 Hz), 138.4 ($J$ = 10.6 Hz), 136.2 ($J$ = 1.8 Hz), 125.1, 120.9 ($J$ = 2.7 Hz), 118.3 ($J$ = 21.5 Hz), 117.7 ($J$ = 7.8 Hz).

***5-fluoroquinolin-8-ol (43)***



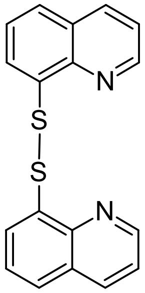
Off-white powder, **23.0 mg, 18%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.86 (dd, $J_{2\text{-}3}$ = 4.33 Hz, $J_{2\text{-}4}$ = 1.61 Hz, 1H, H-2), 8.43 (dd, $J_{3\text{-}4}$ = 8.53 Hz, 1H, H-4), 8.03 (br s, 1H, OH), 7.53 (dd, 1H, H-3), 7.13 (m, 2H, H-6, H-7). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 150.5 ($J$ = 245.9 Hz), 148.7, 148.5 ($J$ = 3.6 Hz), 137.8 ($J$ = 3.6 Hz), 129.8 ($J$ = 3.0 Hz), 121.8 ($J$ = 2.7 Hz), 119.0 ($J$ = 18.9 Hz), 110.7 ($J$ = 20.8 Hz), 108.6 ($J$ = 7.7 Hz).

***1-(quinolin-6-yl)ethan-1-one (44)***



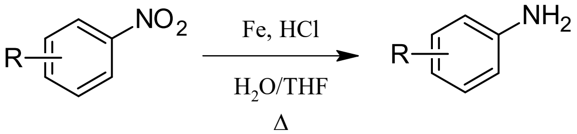
**110.1 mg, 37%.** $^1$H NMR (500 MHz, DMSO-d$^6$) δ 9.04 (m, 1H), 8.75 (s, 1H), 8.58 (d, $J$ = 8.29 Hz, 1H), 8.17 (m, 2H), 7.65 (dd, $J$ = 4.20, 8.20 Hz, 1H), 2.74 (s, 3H). $^{13}$C NMR (126 MHz, DMSO-d$^6$) δ 197.98, 153.33, 149.92, 138.19, 134.85, 131.14, 129.82, 127.69, 122.81, 27.29.

***8,8'-disulfanediyldiquinoline (45)***



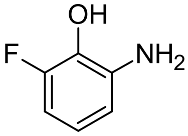
**10 mg, 3%.** $^1$H NMR (500 MHz, CDCl$_3$) δ 9.04 (dd, *J* = 1.74, 4.29 Hz, 1H), 8.23 (dd, *J* = 1.74, 8.35 Hz, 1H), 7.94 (dd, *J* = 1.25, 7.48 Hz, 1H), 7.66 (dd, *J* = 1.25, 8.15 Hz, 1H), 7.53 (dd, *J* = 4.25, 8.31 Hz, 1H), 7.44 (dd, *J* = 7.48, 8.11 Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 149.46, 145.95, 136.31, 135.51, 128.36, 126.94, 125.24, 124.71, 121.78.

*Experimental procedure for reduction of nitrobenzenes to anilines.*



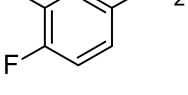
Procedure detailed in Section 2.6.

***2-amino-6-fluorophenol (3a)***



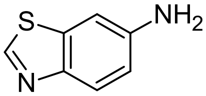
**159.8 mg, 94%**. Characterization in Section 2.6.

***3,4-difluoroaniline (3b)***



**163.1 mg, 98%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.78 (m, 2H), 7.36 (m, 1H).

### *1,3-benzothiazol-6-amine (3c)*



**147.4 mg, 94%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.68 (s, 1H), 7.88 (d, *J* = 8.70 Hz, 1H), 7.11 (d, *J* = 2.35 Hz, 1H), 6.84 (dd, *J* = 2.31, 8.69 Hz, 1H), 3.96 (s, 2H).

# 4 PHOSPHINE-CATALYZED [3+2]-CYCLOADDITION OF ALLENOATES WITH NAPHTHOQUINONE

## 4.1 Introduction to Lewis-base catalysis and allenoate chemistry

Heterocyclic compounds such as quinolines play an important role in medicinal chemistry, and as has been discussed, there are a multitude of methods through which they are synthesized. Equally important are aromatic carbocycles, in which the main polycyclic skeleton is made up of only carbon atoms. This chapter will focus on the synthesis of a series of carbocycles via Lewis-base catalyzed [3+2] cycloadditions.

### 4.1.1 Lewis-base catalysis

The Lewis theory of acids and bases was advanced by G.N. Lewis at the beginning of the twentieth century. He proposed that all acids are simply electron acceptors, and bases are electron donors; therefore all reactions between atoms and molecules can be described as acid-base interactions [126]. Take for example the nucleophilic addition of a phosphorus ylide to a carbonyl compound (*Figure 4.1.1*); here the carbanion nucleophile of the Wittig reagent acts as the Lewis base (electron pair donator) while the carbonyl carbon electrophile acts as the Lewis acid (electron pair acceptor).

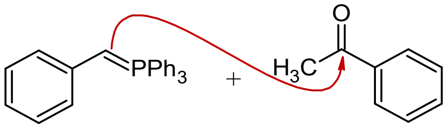


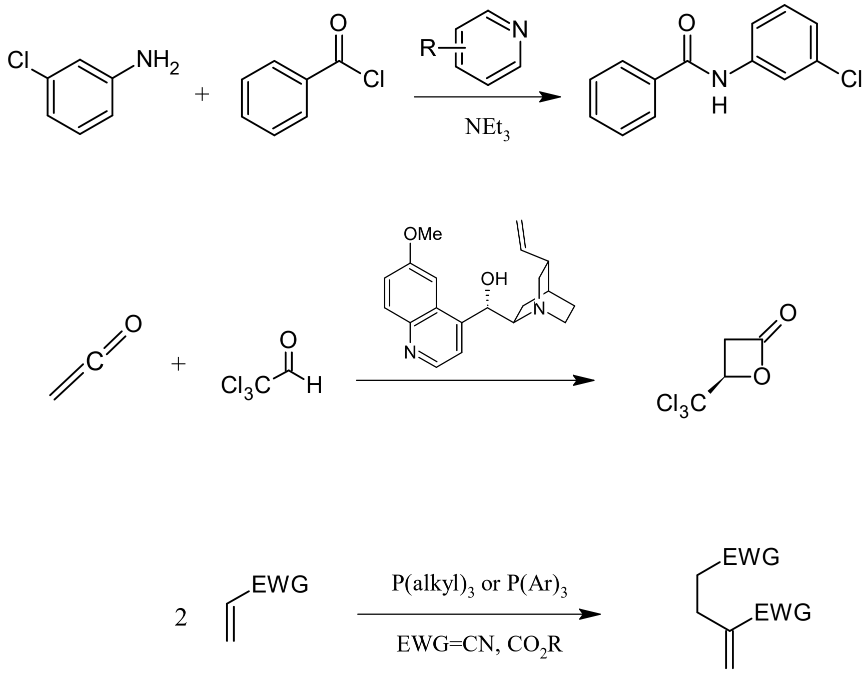
*Figure 4.1.1 Lewis base/acid interaction*

In addition to acting as reagents in their own right, Lewis acids and bases can also act as catalysts in reactions by either drawing electron density away from (acids) or pushing electron density toward (bases) the substrate. Historically, Lewis acids have been the more popular of the two for catalytic usage. Until recently, Lewis base catalysis was underrepresented in the literature; generally these reagents were used instead as ligands in transition metal catalysts [126]. However, the last two decades have seen an influx of tertiary amines and phosphines as activating agents in organic syntheses [127].

Lewis base catalysis can very succinctly be defined, in the words of Denmark and Beutner, as "the process by which an electron-pair donor increases the rate of a given chemical reaction by interacting with an acceptor atom" with the ever-important caveat that the catalyst "should not be consumed or altered during the course of the reaction". Lewis base catalysis takes two general forms: catalysis by nucleophilic addition and catalysis by polarization. Catalysis by nucleophilic addition is defined as the interaction of a nonbonding pair of electrons – termed "n" in molecular orbital theory – and a pi antibonding orbital – termed "π*". This type of interaction is exemplified by the addition of an oxygen, nitrogen, or phosphorus to an alkyne, alkene, or carbonyl. Conversely, the interaction of a lone pair of electrons ("n") with a sigma antibonding orbital ("σ*") or n-antibonding orbital ("n*") is termed catalysis by polarization. The σ* orbital is generally found in organometallic species containing main-group elements, while the n* orbital is present in Group 13 elements such as boron and aluminum which are able to expand their valence shells. Of these two forms of catalysis, nucleophilic addition is by far the more prominent [126].

This type of catalysis represents a powerful mode of enhancing reactions and building complex structures from simple components [128], and it presents several key advantages over other forms. For instance, substrate activation by Lewis bases can be achieved by a wide range of modes, including enhancement of either the nucleophilicity or electrophilicity – or both – of the substrate [126]. In addition, Lewis base catalysts are highly versatile, allowing a high degree of tunability to specific requirements of reactions, including enantio- and regioselectivity [129]. Similarly, altering substituents on a Lewis base catalyst will promote varying degrees of nucleophilicity, which can be finely tuned depending on the needs of the reaction [130]. Finally, this method does not rely on transition metals to provide catalysis. This offers several advantages: metal impurities, which are difficult and costly to remove from compounds such as polymers, are not present to hinder their application in biomaterials and electronics [131]; it also eliminates heavy metal waste that can be toxic and expensive [130]. Indeed, Lewis base catalysts can often be recovered and reused.

During the latter half of the twentieth century, Lewis base catalysis emerged as a new and exciting method to achieve various reactions that previously were either prohibitively slow or unattainable. Tertiary and aromatic amines dominated the field in the beginning, catalyzing reactions such as the acylation of anilines (eq. 23, *Scheme 4.1.1*) and [2+2] cycloadditions of ketenes with aldehydes (eq 24). Phosphine catalysis emerged as viable method of carbon-carbon bond formation in 1962 when Price used triphenylphosphine as a catalyst in the hexamerization of acrylonitrile [128]. However, a patent from Rauhut and Currier one year later describing the phosphine-catalyzed dimerization of alkenes solidified the widespread dissemination of this method (eq 25) [127].


Cl
NH2
O
Cl
R
N
NEt3
O
N
H
Cl
OMe
OH
N
N
O
C
O
Cl3C
H
O
O
Cl3C
2
EWG
P(alkyl)3 or P(Ar)3
EWG=CN, CO2R
EWG
EWG

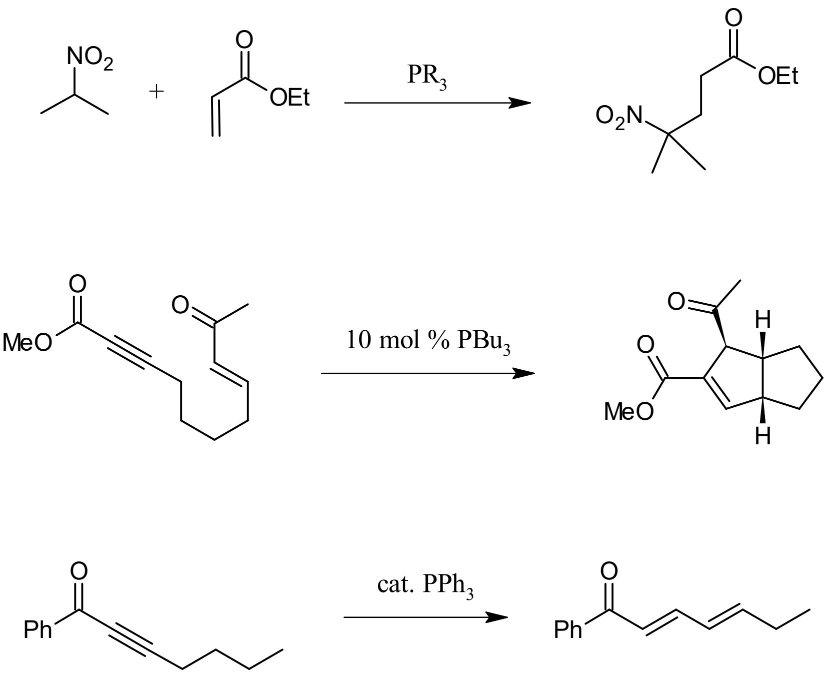
(23)

(24)

(25)

*Scheme 4.1.1 Examples of Lewis-base catalysis*

Less than a decade later, the eponymous Morita-Baylis-Hillman coupling of an activated alkene with an aldehyde built on this theme. In 1968 Morita used a phosphine catalyst, while four years later Baylis and Hillman used tertiary amines, but subsequent studies have generally shown phosphines to be the superior reagent [127]. Since then, phosphine catalysts have been used in Michael additions of alkenes (eq 26, *Scheme 4.1.2*) [127], cycloadditions of alkynes (eq 27) [132], and even isomerizations of alkynes to dienes (eq 28) [133].


PR$_3$
10 mol % PBu$_3$
cat. PPh$_3$

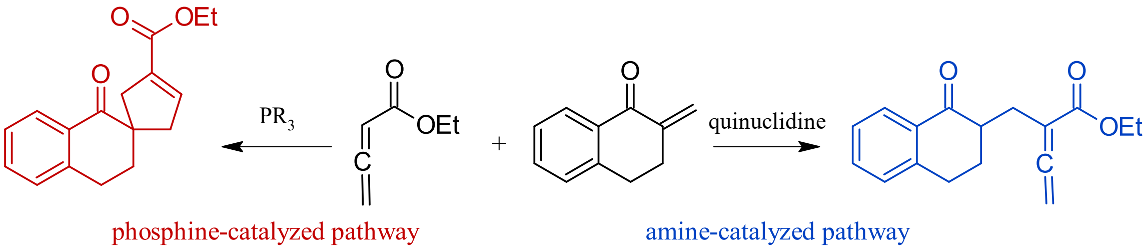
(26)

(27)

(28)

*Scheme 4.1.2 Examples of phosphine-catalyzed reactions*

Notably, tertiary amines and phosphines often exhibit disparate catalytic reactivities and efficiencies; therefore the outcome of a reaction can be modified by switching between these two classes of catalyst (*Scheme 4.1.3*) [129]. The reasoning behind these differences encompasses various characteristics such as polarizability, geometry, and orbital availability.


PR$_3$
quinuclidine
phosphine-catalyzed pathway
amine-catalyzed pathway

*Scheme 4.1.3 Divergent products from phosphine and amine-catalyzed reactions*

For instance, amines and phosphines display disparate reactivity in terms of basicity versus nucleophilicity. In the 1960s, several studies were conducted that support the general tendency of amines to act predominantly as bases and phosphines to be more nucleophilic. The overarching theme in these trends is related to the hard/soft acid-base theory (HSAB). Since phosphorus, as a more polarizable atom, is a softer base than nitrogen, it will be less reactive toward a Brønsted acid, as protons are considered hard [134]. Alternatively, phosphines are more nucleophilic toward soft Lewis acids than otherwise comparable amines.

These assertions are evidenced by several notable studies conducted over the last half-century. The aforementioned Rauhut-Currier dimerization (See eq 25, *Scheme 4.1.1*) involved conjugate addition of the phosphine catalyst to an α,β-unsaturated carbonyl, taking advantage of the soft phosphine nucleophile preferring addition at the similarly soft β carbon, rather than the harder carbonyl carbon. In fact, subsequent studies using amine catalysts were unable to match the catalytic power of the phosphines, and the intramolecular version was similarly indisposed to amine catalysis. Perhaps unsurprisingly, the related Morita-Baylis-Hillman reaction, in which catalysis occurs by conjugate addition, was also more successful using phosphines. This includes the intramolecular, asymmetric, and sulfinimine variants [127].

In addition, although tertiary amines and phosphines both have pyramidal geometry, the inversion barriers at room temperature are quite different [127]. With an inversion barrier of six kcal/mol [135], amines rapidly invert (the “umbrella flip”). However, at 35 kcal/mol [136], the activation energy for phosphine inversion is high enough to consider these compounds configurationally stable at room temperature. For this reason, tertiary phosphines are more useful than amines in controlling stereochemistry.

### 4.1.2 Allene Chemistry and Reactivity

Cumulated dienes, commonly known as allenes, are an interesting class of molecules in which both double bonds are connected to the same carbon atom (*Figure 4.1.2*). They exhibit characteristics similar to both alkenes and alkynes while displaying reactivity greater than either [137].

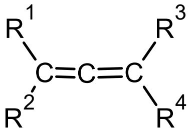


*Figure 4.1.2 Cumulated diene, also known as allene*

Allenes have been known and synthesized since before the 1880s – clearly a highly productive era in the history of organic chemistry – but only in the last several decades have they been recognized for their versatility and synthetic utility. The peculiar reactivity patterns of these molecules can be at least partially attributed to their unconventional geometry. Since a single sp-hybridized carbon atom unites both double bonds, the three carbons of the allene are laid out in a straight line, but the two pi bonds are necessarily orthogonal [138]. This means that the molecule is not planar and the substituents on either end of the allene moiety are perpendicular to each other. This confers potential chirality on the molecule – even if there are no stereocenters – when the substituents at each end are distinct (*Figure 4.1.3*) [139].

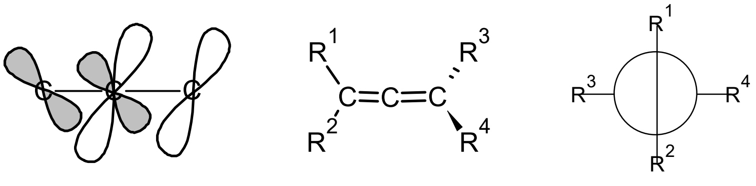


*Figure 4.1.3 Perpendicular π orbital arrangement of allenes and stereochemical consequences*

Variations in substituents on the ends of the allene moiety drastically affect the reactivity of the molecule. For instance, electron-donating groups push electron density toward the central carbon, making it nucleophilic. On the other hand, electron-withdrawing groups confer electrophilicity on the central carbon, favoring addition reactions [138]. In particular, allenoates – a unique class of allenes in which an ester is connected to the α-carbon – display a distinctive electrophilicity due to the strongly electron-withdrawing group.

With that being said, the diverse reactivity of allenoates render them apt for Lewis base-catalyzed reactions. Upon contact, a Lewis base will add to the β-carbon of the allene, resulting in a zwitterionic intermediate which can be depicted as an enolate, α-centered anion, γ-centered anion, or 1,3-dipole (*Figure 4.1.4*). The predominant form the zwitterionic intermediate takes is highly dependent on the type of Lewis base used [129]. In this way, switching the class of catalyst can vastly alter the resultant reactive species, thus altering its interaction with other substrates [140].

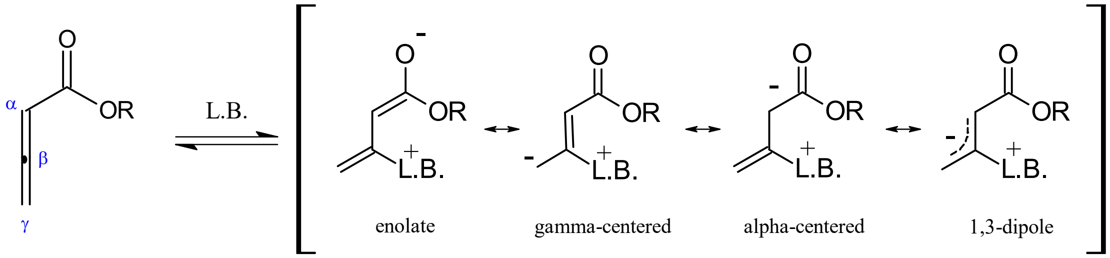
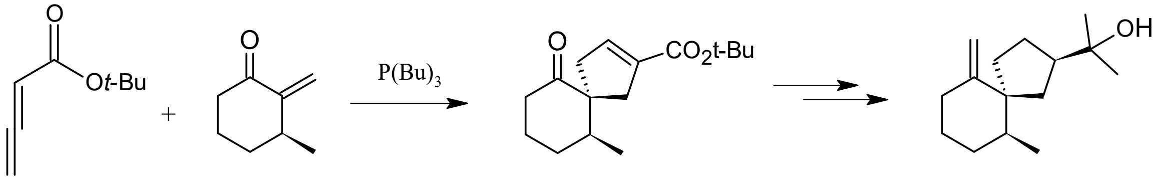


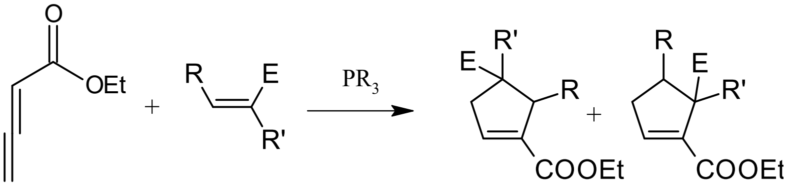
*Figure 4.1.4 Zwitterion intermediates from Lewis base addition: enolate, gamma-centered anion, alpha-centered anion, and 1,3-dipole*

Allenoates undergo several intriguing processes in the presence of Lewis bases, including coupling reactions with a variety of annulation partners. These include formal [3+2], [4+2], [4+3], [3+3], and [3+2+3] cycloadditions. The ability of allenoates to form cyclization products is directly related to the zwitterionic intermediate. In the α-centered anion resonance form, the intermediate possesses both nucleophilic (at the α-carbon) and electrophilic (at the γ-carbon) character (see *Figure 4.1.4*) [141]. Therefore the single molecule has the ability to both donate and accept electron density, facilitating a cyclization reaction. Many products of these annulations have seen use as building blocks in the synthesis of natural products such as Lu's total synthesis of (-)-hinesol in 2005 (*Scheme 4.1.5*) [142].



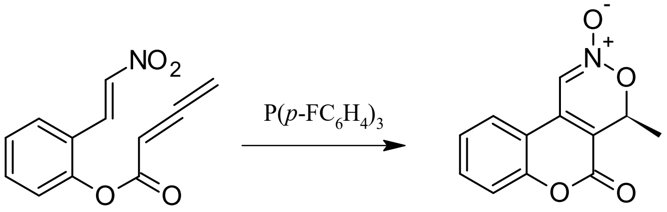
*Scheme 4.1.4 Synthesis of (-)-hinesol via [3+2] cycloaddition*

One decade earlier, the same Lu had reported the first phosphine-catalyzed [3+2] annulation of allenoates with electron-deficient olefins to obtain cyclopentene derivatives. While the reaction was generally facile, furnishing the cyclization product in good yield under substoichiometric amounts of phosphine, the regioselectivity was minimal (*Scheme 4.1.6*) [143].



*Scheme 4.1.5 Lu's intermolecular [3+2] cycloaddition between allenoates and olefins to give two regioisomeric products*

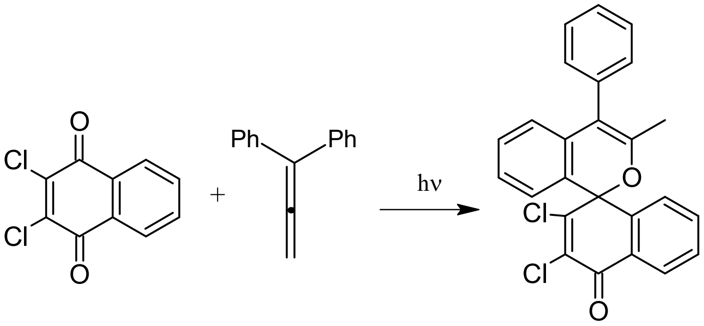
Since then many modifications have emerged, including intramolecular variants. Kwon *et al.* disclosed a simple procedure to obtain highly complex coumarins in good yield with high regio- and stereoselectivity by the annulation of intramolecular allenoates and nitro olefins (*Scheme 4.1.7*) [130].



*Scheme 4.1.6 Intramolecular phosphine-catalyzed [3+2] cycloaddition*

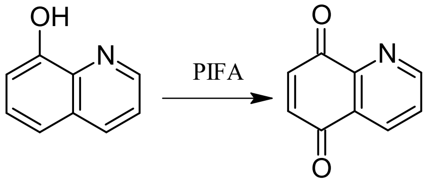
## 4.2 Lewis Base Catalyzed [3+2]-Cycloaddition Reactions of Allenoates with Naphthoquinone

As previously mentioned, α-allenic esters activated by Lewis base catalysis can display both nucleophilic and electrophilic activity. If the anion formed from Lewis base attack on the central carbon is captured by an α,β-unsaturated carbonyl compound, a cycloaddition reaction can occur. While many reactions of this type have been reported, examples in the literature of quinones as the electrophilic partner are unknown. Rather, the only report citing the use of this reagent, by Maruyama in 1988, described the production of spiro compounds via photochemical [2+4] cyclizations of allene with the carbonyl of a quinone (*Scheme 4.2.1*) [144].



*Scheme 4.2.1 Photochemical [2+4] cyclization of quinone and allene*

Exploration of this reaction began during the investigation into new quinoline derivatives as frameworks for biologically active molecules. Quinoline-5,8-dione, formed by the oxidation of 8-hydroxyquinoline (*Scheme 4.2.2*), was originally produced for use in a subsequent cyclopropanation reaction. It was noted, however, that this compound's α,β-unsaturated carbonyl moiety could be a suitable electrophile for attack by an allenoate anion.



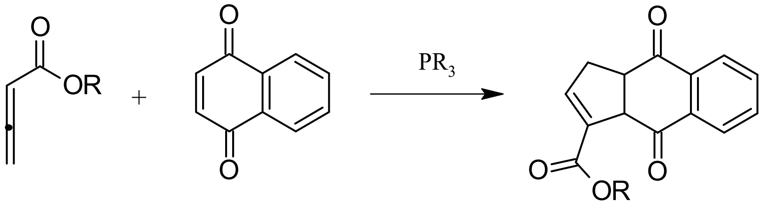
*Scheme 4.2.2 Oxidation of 8-hydroxyquinoline to quinoline-5,8-dione*

Initial attempts to perform the cyclization reaction with the quinoline derivative gave complex but promising results. It was decided that a simpler symmetrical analog would be ideal for investigating and optimizing the reaction before more complex substrates were employed. Therefore 1,4-naphthoquinone was identified as a possible replacement.

Naphthoquinones are an intriguing class of molecules with dichotomous biological reactivities. On one hand, they are prevalent components of fuel combustion and tobacco smoke; conversely, they are important moieties in anti-inflammatory and anti-cancer therapeutics [145]. It is this second set of properties that make these molecules interesting from a medicinal chemistry perspective.

Since quinones are responsive acceptors for conjugate addition reactions, it was hypothesized that a Lewis base-catalyzed reaction between allenoates and 1,4-

naphthoquinone would result in polycyclic [3+2]-cycloaddition products (*Scheme 4.2.3*), which could potentially have interesting biological or therapeutic applications.



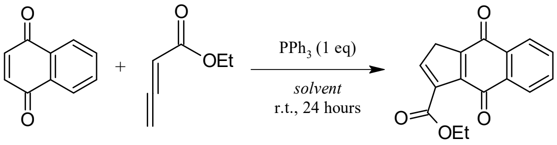
*Scheme 4.2.3 Hypothesized [3+2] cycloaddition of 1,4-naphthoquinone with allenoates*

### 4.2.1 Optimization Studies

Due to the aforementioned simplicity and commercial availability of the reagents, 1,4-naphthoquinone and ethyl-2,3-butadienoate were used as model substrates to determine the optimal conditions of the reaction. Using a full molar equivalent of triphenylphosphine as the Lewis base activator, the first variable studied was the solvent.

To begin, in a few of the solvents that are more commonly used in this class of cycloaddition reaction were tested with the model substrates on a 50 mg scale. Stirring at room temperature under ambient atmosphere, all the trials with solvent variations gave encouraging results. Among the most successful trials were the reactions run under highly polar acetonitrile and the nearly nonpolar dichloromethane. The full results can be seen in *Table 11*. Since the reaction in dichloromethane was so efficient, giving a quantitative yield of product in as little as 30 minutes, it was decided to continue with the rest of the optimization using this solvent.

*Table 11 Solvent variation in optimization reaction.*



| *Entry* | *Solvent* | *Yield*[*] *(%)* |
|---|---|---|
| *1* | Toluene | 58 |
| *2* | Dichloromethane | >99 |
| *3* | Chlorobenzene | 54 |
| *4* | 1,2-Dichloroethane | 65 |
| *5* | Tetrahydrofuran | 53 |
| *6* | Acetonitrile | 91 |

Next the catalyst loading was explored. While the reaction proceeded robustly with a full equivalent of triphenylphosphine, lower ratios of the Lewis base were detrimental. Although a slightly reduced amount of phosphine did not seriously hinder the reaction – lowering the yield from 99% to 76% – further reductions were more significant. Because of this, further reactions were run with a full equivalent of Lewis base. The results can be seen in *Table 12*.

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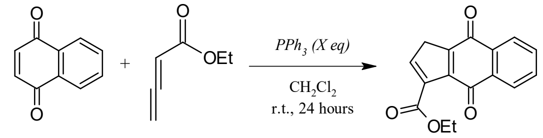
[*] Purified yield.

*Table 12 Phosphine catalyst loading trials.*



| *Entry* | *Phosphine equivalent* | *Yield[*] (%)* |
|---|---|---|
| *1* | 1 | >99 |
| *2* | 0.75 | 76 |
| *3* | 0.5 | 31 |
| *4* | 0.2 | NP[†] |

Though the outcome of the reaction using a full equivalent of triphenylphosphine was no doubt outstanding, it was troubling that substoichiometric amounts of the catalyst gave such poor results. After all, the reagent was expected to act as a “catalyst”, meaning it should be regenerated after each cycle and available to perform its duty again. Most literature examples of similar cyclization reactions use no more than ten mole percent of the phosphine catalyst [146, 147], therefore it was perplexing that the current reaction could not tolerate low phosphine loading.

One clue as to the source of this phenomenon was the appearance of triphenylphosphine oxide as a byproduct of the reaction. Unlike the Wittig or Mitsunobu reactions in which triphenylphosphine oxide is an expected byproduct of the normal

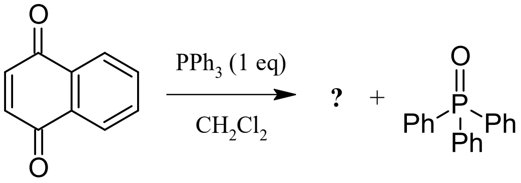
---

[*] Purified yield.

[†] NP = No product obtained.

progress of the reaction, when used as a catalyst the phosphine should never oxidize but instead remain in its original form to participate in several catalytic cycles.

Since ethyl-2,3-butadienoate is an extremely common coupling reagent in Lewis base-catalyzed reactions, it was assumed that this compound was not the cause of the unwelcome oxidation. Instead the highly reactive quinone was considered the more likely source. To probe the validity of this insight, a trial was run in which just the naphthoquinone and triphenylphosphine were stirred together in DCM. As expected, TLC analysis of the mixture showed that in as few as ten minutes triphenylphosphine oxide had begun to appear. NMR analysis after chromatography of the reaction mixture showed definitive triphenylphosphine oxide formation as well as an unidentifiable quinone byproduct (*Scheme 4.2.4*).



*Scheme 4.2.4 Oxidation of triphenylphosphine by 1,4-naphthoquinone*

With the deactivation of triphenylphosphine under these conditions confirmed, the next priority was to screen various Lewis base catalysts for resistance to oxidation by the quinone. As it was alluded to previously, alteration of the substituents on a phosphine or amine greatly affects its nucleophilicity. For instance, in the scale devised by Pearson *et al.* triethylphosphine and tributylphosphine – in which the phosphorus is attached to three electron-donating alkyl groups – are several orders of magnitude more nucleophilic than triphenylphosphine [148]. Similar trends are seen with amines.

Although it was assumed that alkyl substituents would make the phosphine catalyst too reactive, in the interest of thoroughness triethylphosphine was the first alternative Lewis base catalyst to be tested. It was no surprise that this resulted in almost instantaneous oxidation of the phosphine and no product formation. Tri(*para*-tolyl)phosphine gave similar results, as did methyldiphenylphosphine and the amine DABCO.

In a divergent approach, it was hypothesized that an adjustment to either the steric or electronic properties of the catalyst would be advantageous. In response to the former, it was noted that Buchwald and Barder [149] had extensively studied the oxidation of various phosphines with molecular oxygen. During the course of their study, they determined the phosphine X-Phos* (*Figure 4.2.1*) to be extraordinarily resistant to oxidation.

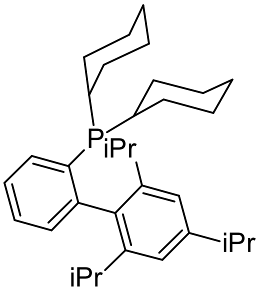


*Figure 4.2.1 X-Phos*

Intrigued by the possible application to the current reaction, this reagent was utilized as the Lewis base catalyst in the cyclization of naphthoquinone with allenoate. The phosphine proved to be as resistant to oxidation as hoped; however, after 24 hours of reaction no product had formed. The excess steric hindrance of the catalyst had not only prevented the unwanted interaction with the quinone, it had also prevented the desired interaction with the allenoate.

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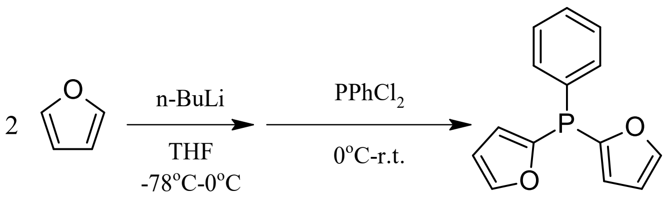
* 2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

After the inefficacy of the sterically hindered phosphine, it was conjectured that a modification to the electronic properties of the catalyst would be more efficient. Therefore, a phosphine containing three of the more electron-withdrawing furyl groups was utilized. Again, oxidation of the phosphine was minimal, but after seven days of stirring only a trace amount of product was formed.

Under the assumption that a catalyst with electronic properties midway between triphenylphosphine and tri(2-furyl)phosphine would be ideal, a hybrid of these two compounds was sought. Di(2-furyl)phenylphosphine was synthesized easily from dichlorophenylphosphine and 2-lithiated furan (**58,** *Scheme 4.2.5*) [150].

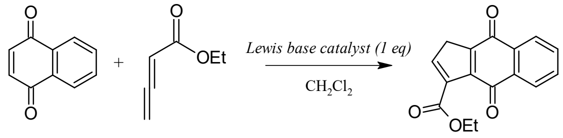


**58**

*Scheme 4.2.5 Synthesis of di(2-furyl)phenylphosphine*

This novel reagent was applied in equimolar amount to the model reaction. However, it showed much the same reactivity as the tri(2-furyl)phosphine catalyst; it gave very little product, with mostly naphthoquinone recovered. The full results of these trials can be seen in *Table 13*.

*Table 13 Lewis-base catalyst optimization.*



| *Entry* | *Lewis base (1 eq)* | *Reaction time* | *Yield[*] (%)* |
|---|---|---|---|
| *1* | Triphenylphosphine | 30 min | >99 |
| *2* | Methyldiphenylphosphine | 1.5 hr | NP |
| *3* | Triethylphosphine | 1.5 hr | NP |
| *4* | Tri(*p*-tolyl)phosphine | 24 hr | NP |
| *5* | X-Phos | 24 hr | NP |
| *6* | Tri(2-furyl)phosphine | 7 days | Trace |
| *7* | Di(2-furyl)phenylphosphine | 2 days | Trace |
| *8* | DABCO | 1.5 hr | NP |

Interestingly, throughout the trials it was noted that two products were formed from the cyclization. Upon careful scrutiny of the NMR spectra from these reactions, it appeared that neither of the two products were actually identical to the expected product, in which both carbonyls of the quinone remained intact. The proposed structures of the actual products can be seen in *Figure 4.2.2* (**59a** and **59b**).

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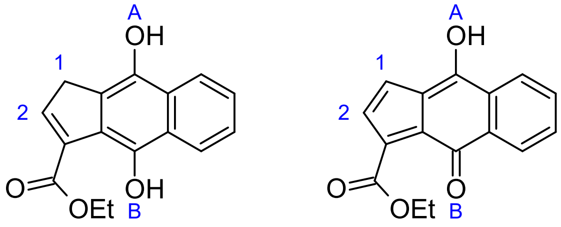
[*] NP = No product formed.



**59a** **59b**

*Figure 4.2.2 Observed products of [3+2] cyclization*

These proposals initially came from the detection of a singlet at 5.49 ppm, indicating a phenolic OH. This led to the identification of A on compound **59a**. A second singlet at 7.56 ppm was indicative of another phenolic OH, particularly one that is hydrogen-bonded, due to the downfield shift. This implied the presence of B on **59a**, which could be hydrogen bonding with the carbonyl oxygen of the nearby ester.

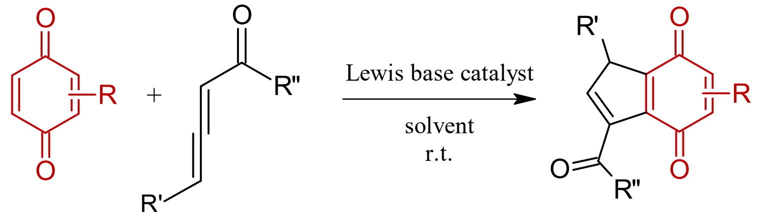
In contrast to the observed doublet and triplet resulting from the coupling of the protons on carbons 1 and 2 on **59a**, the appearance of two sets of doublets at 7.15 and 7.2 ppm suggested the existence of a second molecule. These doublets indicated the presence both carbon 1 and carbon 2 each had a single proton, which were necessarily on a double bond and coupling with each other, as in compound **59b**.

All reactions executed during the optimization stage resulted in a nearly equivalent mixture of these two products. It has not been determined what causes the additional oxidative step from **59a** to **59b**, although it is clear that the oxidation is not caused by atmospheric oxygen – since a sample that was left exposed to air for several weeks appeared unchanged in the NMR spectrum. Attempts to force the conversion to **59b** by stirring the crude reaction mixture on silica gel were also unsuccessful.

Despite the uncertainty of the product mixture and the unproductive oxidation of the phosphine catalyst, this is undoubtedly an interesting reaction that has the potential to produce very high yields of polycyclic products that are appealing in a medicinal chemistry perspective.

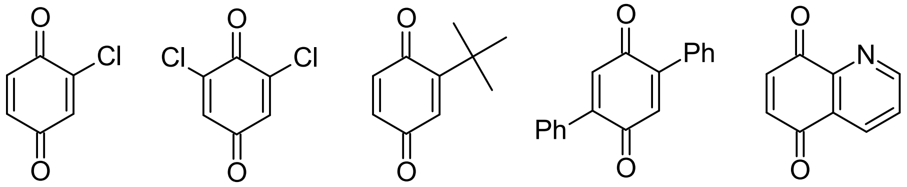
### 4.2.2 Scope of the Reaction

With the most favorable reaction conditions in hand, the focus then shifted to the substrate scope of the reaction. Since there are two possible ways to introduce diversity into the reaction – by modifying the quinone or the allenoate annulation partner – both were addressed in this stage.



*Scheme 4.2.6 Exploring the scope of quinone substrate*

To begin, several diversely-substituted quinones with varying electronic and steric characteristics were investigated (*Scheme 4.2.6*). These included chloro (**LIX** and **LX**, *Figure 4.2.4*), *tert*-butyl (**LXI**), and phenyl (**LXII**) substituents, as well as another trial with quinoline-5,8-dione (**LXIII**). Surprisingly, none of these attempted reactions resulted in identifiable cyclization products.

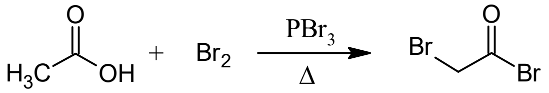


**LIX** **LX** **LXI** **LXII** **LXIII**

*Figure 4.2.3 Variously substituted quinones tested in [3+2] cyclization reaction*

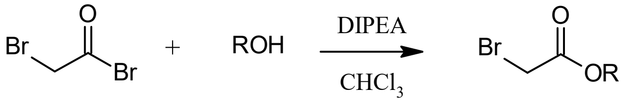
Therefore it was decided to concentrate on variations in the allenoate partner of the cycloaddition. Several simple modifications can result in interestingly diverse products, so a few of these were explored, including an assortment of ester and γ-carbon substitutions.

Many non-commercially available allenoates can be synthesized through a series of reactions starting with the production of bromoacetyl bromide by refluxing acetic acid and molecular bromine with phosphorus tribromide (*Scheme 4.2.7*). However, due to the harsh conditions and the difficulty in removing excess bromine from the product, it was found to be much more productive to use commercial bromoacetyl bromide.



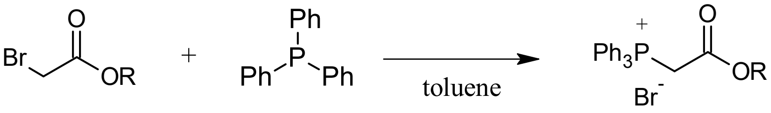
*Scheme 4.2.7 Production of bromoacetyl bromide by reaction of acetic acid with bromine*

The formation of α-bromo esters [147] from bromoacetyl bromide was a straightforward process by which the bromide and the desired alcohol were combined under anhydrous conditions and stirred at room temperature (*Scheme 4.2.8*). The esters were generally formed in very high yield, although a few – such as the isopropyl and *tert*-butyl esters – were less facile due to steric complications.



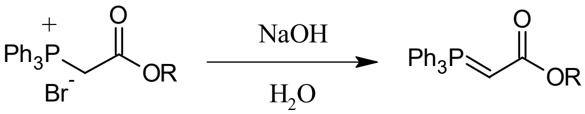
*Scheme 4.2.8 Formation of alpha-bromo esters by reaction of bromoacetyl bromide with alcohols*

Next the α-bromo esters were easily converted to their corresponding triphenylphosphonium salts by addition of triphenylphosphine in universally high yields (*Scheme 4.2.9*) [147]. This procedure was aided by the use of toluene as solvent, which ensured that the salts would precipitate out of solution, enabling a smooth isolation.



*Scheme 4.2.9 Formation of triphenylphosphonium bromide esters*

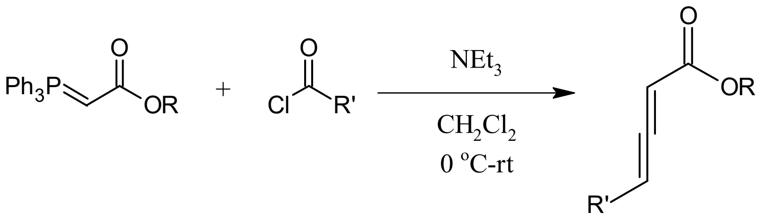
In order to form the ylide esters that would subsequently be converted into the allenoates by Wittig reaction, the triphenylphosphonium bromide esters were vigorously stirred in sodium hydroxide (*Scheme 4.2.10*) [147]. It was noted that the deprotonation at the α-carbon was nearly instantaneous – the insoluble ylide clumped around the stirbar within seconds. Therefore a small volume of DCM was added to the reaction mixture, allowing the ylide esters to dissolve and facilitating their isolation.



*Scheme 4.2.10 Formation of ylide ester by NaOH deprotonation at the alpha-carbon*

Finally the allenoates were prepared by a method similar to that of MacMillan [151], whereby the ylide was combined with an acyl chloride under basic conditions

(*Scheme 4.2.11*). It was noted that the use of triethylamine and DCM that had been dried over molecular sieves increased the yield of allenoate product.



*Scheme 4.2.11 Formation of allenoates by reaction of ylide esters with acyl chlorides*

However, isolation of some allenoates proved extraordinarily difficult. Smaller allene esters – especially those unsubstituted at the γ-carbon – are predicted to have boiling points in the vicinity of many common solvents such as hexane and ethyl acetate, meaning the same conditions used to isolate the allenoates from these solvents would also cause at least partial evaporation of the products. This effect was not as pronounced with the larger alkyl and aromatic esters – and those with substitutions on the γ-carbon – so the range of yields was broad. Even with modifications to the procedure such as cooling during filtration, liquid injection of the crude product into the chromatography column, and heatless evaporation of solvent from the product fractions, several attempted allenoates proved too difficult to obtain.

The allenoates that were isolated in acceptable quantity were then subjected to the previously described conditions of [3+2]-cycloaddition with 1,4-naphthoquinone. Much like the model reagent ethyl-2,3-butadienoate, the γ-unsubstituted allenoates proved amenable to the phosphine-assisted cyclization process. However, despite the disappearance of the starting quinone on TLC, the isolated yields of these products were not as impressive as the initial trial during the optimization phase.

In addition, the ratio of products (analogous to **59a** and **59b**, see *Figure 4.2.2*) were inconsistent for these trials. While the butyl and isopentyl derivatives produced only the diphenol product (**60** and **62**, respectively, *Figure 4.2.5*), the n-pentyl allenoate cyclized to give only the monophenol product (**61**).

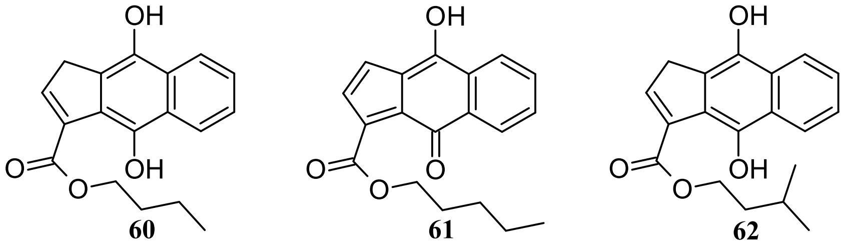
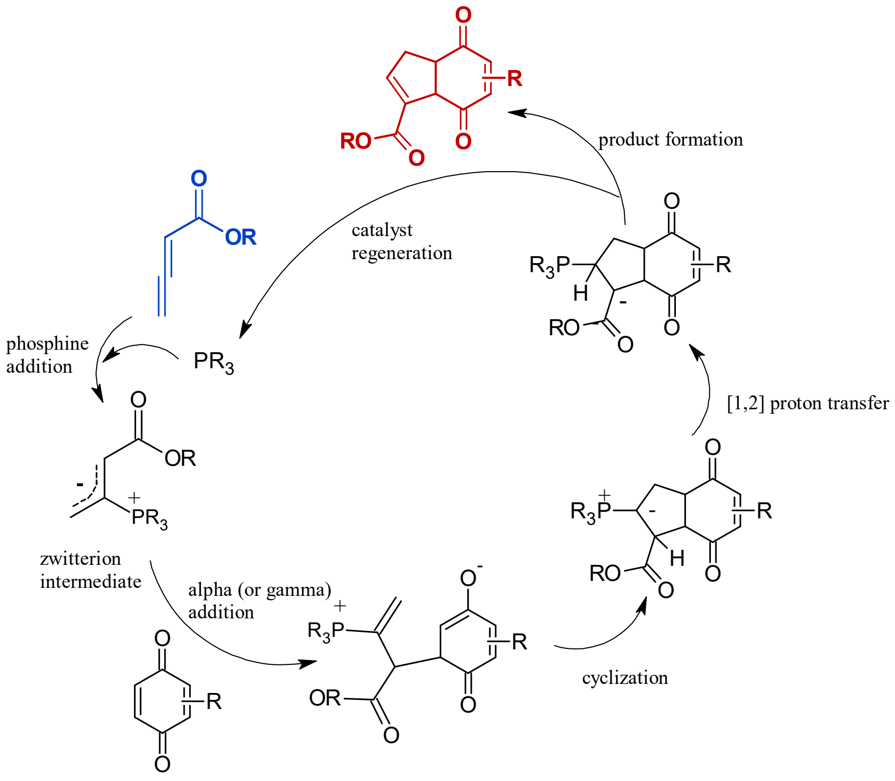


*Figure 4.2.4 [3+2] cycloaddition products of butyl, pentyl, and isopentyl allene esters with 1,4-naphthoquinone*

Even more perplexing were the products of γ-substituted allenoate cyclization. While NMR analysis indicated a successful cyclization, the form the products took is yet to be determined. There may be other as-of-yet unidentified mechanistic factors at play in these cases. Also, because of the inherent chirality of γ-substituted allenoates, the increased complexity of the reaction due to enantiomeric product formation is a matter that should be taken into account.

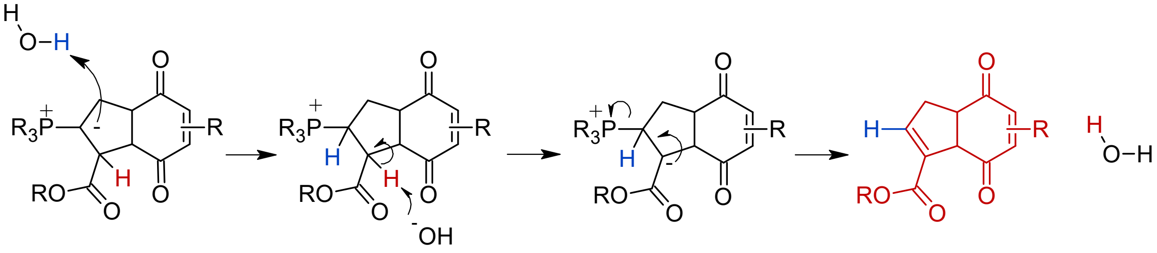
### 4.2.3 Mechanism

Lu was the first to report the phosphine-catalyzed [3+2] cycloaddition reaction of allenoates with olefins and was also the first to propose a mechanism for the process, which is applicable to the current conditions of using quinones as the olefin acceptor. Very simply, the mechanism begins with nucleophilic attack of the phosphine on the electrophilic β-carbon of the allene (*Scheme 4.2.12*). This leads to a zwitterionic intermediate. The anion then attacks the double bond of the olefin via either the α- or γ-carbon, displacing the π electrons, which then attack the nearby electrophilic center on the allene, generating an ylide intermediate. Proton transfer and elimination of the phosphine to form the double bond complete the process and result in product formation [143].


product formation
catalyst regeneration
phosphine addition
PR3
zwitterion intermediate
alpha (or gamma) addition
cyclization
[1,2] proton transfer
OR
RO
R3P
R

*Scheme 4.2.12 Mechanism of [3+2] cycloaddition of allenoate with quinone*

Several groups have undertaken mechanistic studies to more thoroughly elucidate this elegant process. Specifically, through a joint effort of experiment and computation, Yu and coworkers [152] concluded the reaction proceeded as indicated through the [3+2] cycloaddition process. However, at the proton transfer stage, they determined that the activation energy of an intramolecular [1,2] proton shift was prohibitively high (39.6 kcal/mol) and could not be accomplished. However if a trace amount of water is available to act as a catalyst (*Scheme 4.2.13*), the activation energy of this transfer is substantially decreased (7.7 kcal/mol). Deuterium-labeling experiments confirmed the exchange of deuterium for a proton (from $H_2O$) in the final product (blue H in red molecule, *Scheme 4.2.13*). This insight could have interesting implications in the experimental procedure of this type of reaction.



*Scheme 4.2.13 [1,2] proton transfer assisted by a molecule of water*

## 4.3 Future directions and conclusion

The [3+2] cycloaddition of allenoates with quinones is appealing on both a mechanistic and functional level. While the mechanism of the reaction is elegantly straightforward, the carbocycles achieved by these annulations are inherently interesting on a medicinal basis. These details enhance the synthetic practicality of this reaction.

However, there are still many challenges to overcome. The inconsistency of annulation products is one area that needs to be addressed. Since the reaction mixture most often produces an equal amount of the oxidized and unoxidized products, this decreases the yield of each. Finding a method to force the product into one or the other form is a top priority of future research in this area.

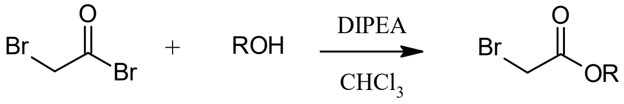
Also, the current loading of a full equivalent of phosphine is problematic. The increased reactivity of quinones over other α,β-unsaturated carbonyls means the phosphine catalyst needs to be specifically tuned to prevent its interaction with the quinone. Further investigation into hybrid phosphines that present an intermediate reactivity pattern would be beneficial to the efficiency of the process.

Stereochemical tuning is also an interesting direction for research in this area. The enantiomeric resolution of allenoates and their cyclization products would be intriguing. In addition, the successful use of asymmetric quinones would lend additional insight into the mechanistic tendencies and regioselectivity of the reaction.

In all, while a lot has been accomplished on this front, including the synthesis of interesting new allenoates and their novel cyclizations with 1,4-naphthoquinone, there remains a multitude of areas to explore. This process, while new and not fully developed, possesses a great amount of potential, and it will be interesting to see where it leads.

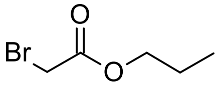
## 4.4 Experimental Details

*Experimental procedure for the synthesis of alpha-bromo acetates* [147]



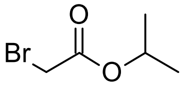
Anhydrous $CHCl_3$ (5 mL) was added to bromoacetyl bromide (25 mmol). The appropriate alcohol (2 eq, dried over 3Å MS), and anhydrous diisopropylethylamine (1 eq) were combined, and this mixture was added to the flask dropwise at room temperature, via addition funnel, over the course of 30 minutes. This mixture was stirred at room temperature overnight, then purified by flash chromatography over silica gel by elution of 5% ethyl acetate/hexanes.

***Propyl bromoacetate (46a)***



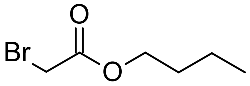
**2.67g, 60%**.

***Isopropyl bromoacetate (46b)***



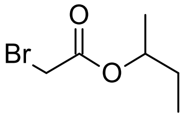
**2.02g, 45%**.

***Butyl bromoacetate (46c)***



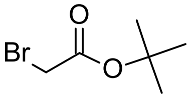
**15.79g, 82%.**

***Butan-2-yl bromoacetate (46d)***



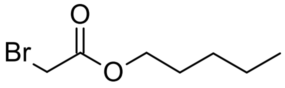
**4.32g, 89%**.

***tert-Butyl bromoacetate (46e)***



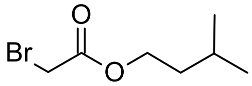
**1.57g, 33%**.

***Pentyl bromoacetate (46f)***



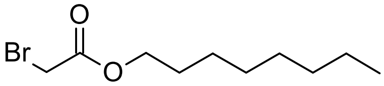
**5.09g, 99%**.

***Isopentyl bromoacetate (46g)***



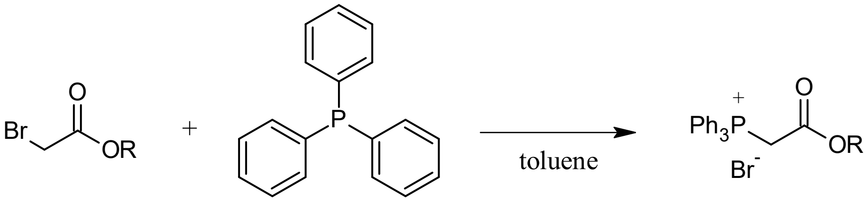
**4.12g, 80%**.

***Octyl bromoacetate (46h)***



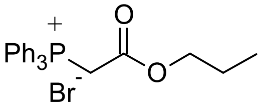
**5.76g, 92%**.

*Experimental procedure for triphenylphosphonium bromide esters* [147]



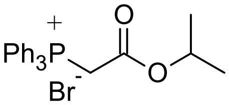
Toluene (3 mL) was added to the alpha-bromo ester from the previous reaction (1 mmol). To this was added triphenylphosphine (1 eq). The reaction was stirred at room temperature overnight. The solid precipitate was then filtered off, washed on the filter with toluene, and air-dried to give the triphenylphosphonium bromide ester.

***(Propoxycarbonylmethyl)triphenylphosphonium bromide (47a)***



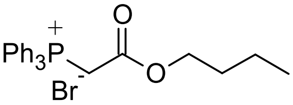
**4.58g, 70%**.

***(Isopropoxycarbonylmethyl)triphenylphosphonium bromide (47b)***



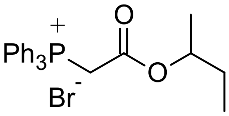
**3.8g, 88%**.

***(Butoxycarbonylmethyl)triphenylphosphonium bromide (47c)***



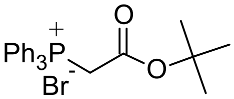
**31.64g, 85%**.

***(sec-Butoxycarbonylmethyl)triphenylphosphonium bromide (47d)***



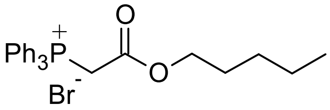
**2.85g, 74%**.

***(tert-Butoxycarbonylmethyl)triphenylphosphonium bromide (47e)***



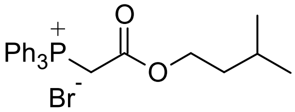
**521.9mg, 74%**.

***(Pentoxycarbonylmethyl)triphenylphosphonium bromide (47f)***



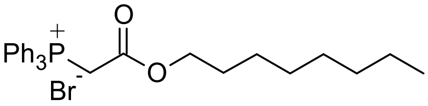
**9.02g, 79%**.

***(Isopentoxycarbonylmethyl)triphenylphosphonium bromide (47g)***



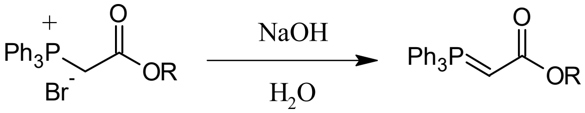
**8.59g, 93%**.

***(Octoxycarbonylmethyl)triphenylphosphonium bromide (47h)***



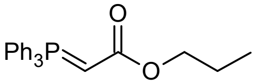
**10.53g, 89%**.

Experimental procedure to produce ylide esters [147]



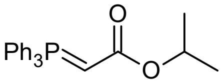
$H_2O$ (16 mL) was added to the triphenylphosphonium bromide ester from the previous reaction (6 mmol). This mixture was stirred at room temperature for 10 minutes, then 6M NaOH was added (10 mL). This was stirred at room temperature for an additional 10 minutes. Dichloromethane (30 mL) was added and stirred an another 30 minutes. The aqueous layer was separated and extracted with dichloromethane (3x30mL). The combined organic layers were dried over $Na_2SO_4$ then evaporated to give the ylide ester.

*Propyl (triphenylphosphoranylidene)acetate (48a)*



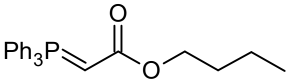
**2.41g, 99%**.

*Isopropyl (triphenylphosphoranylidene)acetate (48b)*



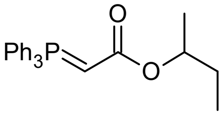
**2.26g, 93%**.

*Butyl (triphenylphosphoranylidene)acetate (48c)*



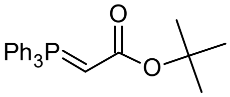
**26.39g, quantitative yield**.

*sec-Butyl (triphenylphosphoranylidene)acetate (48d)*



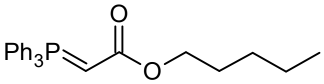
**2.04g, quantitative yield**.

*tert-Butyl (triphenylphosphoranylidene)acetate (48e)*



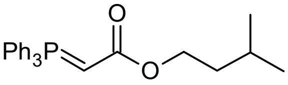
**656.0mg, 78%**.

*Pentyl (triphenylphosphoranylidene)acetate (48f)*



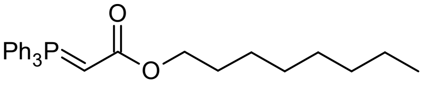
**3.98g, 96%**.

***Isopentyl (triphenylphosphoranylidene)acetate (48g)***



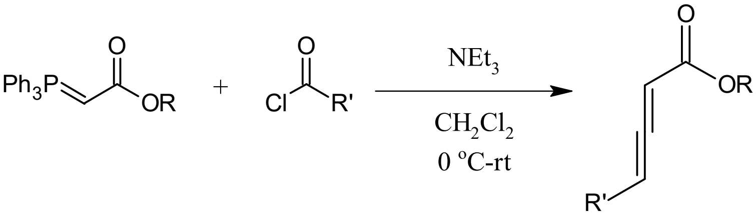
**3.5g, 85%**.

***Octyl (triphenylphosphoranylidene)acetate (48h)***



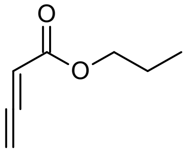
**4.0g, 95%**.

Experimental procedure for the synthesis of allenoates [151]



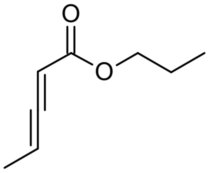
Anhydrous dichloromethane (3 mL) was added to the phosphorus ylide (1 mmol). To this was added triethylamine (2 eq, dried over 3Å MS), and the mixture was stirred on ice. After 20 minutes, the acyl chloride (2 eq) was added dropwise. After addition, the mixture was stirred on ice for 1.5 hours, then taken off ice and stirred at room temp for an additional 1-2 hours. The solvent was evaporated from the reaction mixture under reduced pressure. Diethyl ether was added to the crude oil, and the solids were filtered off. The ether was partially evaporated from the filtrate, and the crude product was purified by flash chromatography over silica gel by elution with hexanes-ethyl acetate.

***Propyl buta-2,3-dienoate (49a)***



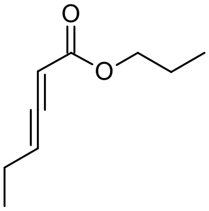
Colorless oil **8.6 mg, 10%**.

***Propyl penta-2,3-dienoate (49b)***



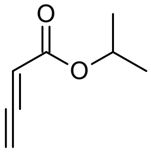
Colorless oil **30.5 mg, 27%**.

***Propyl hexa-2,3-dienoate (49c)***



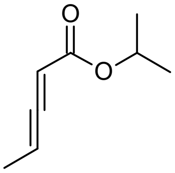
Colorless oil **12.5 mg, 10%.**

***Isopropyl buta-2,3-dienoate (50a)***



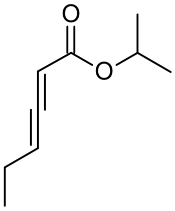
Colorless oil **3.4 mg, 8%**.

***Isopropyl penta-2,3-dienoate (50b)***



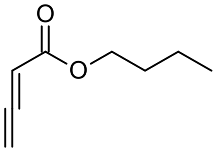
Colorless oil **12.9 mg, 19%**.

***Isopropyl hexa-2,3-dienoate (50c)***



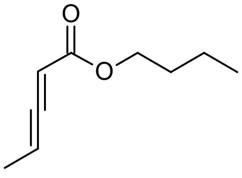
Colorless oil **41.6 mg, 58%**.

***Butyl buta-2,3-dienoate (51a)***



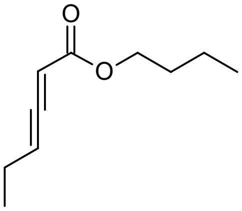
Colorless oil, **560.1 mg, 36%**. $^{1}$H NMR (500 MHz, CDCl$_3$) δ 5.65 (t, *J* = 6.55 Hz, 1H), 5.23 (d, *J* = 6.56 Hz, 2H), 4.16 (t, *J* = 6.73 Hz, 2H), 1.65 (m, 2H), 1.40 (m, 2H), 0.95 (t, *J* = 7.41 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 215.72, 165.79, 88.03, 79.16, 64.85, 30.65, 19.08, 13.68.

***Butyl penta-2,3-dienoate (51b)***



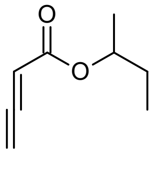
Colorless oil, **1.35g, 86%**. $^{1}$H NMR (500 MHz, CDCl$_3$) δ 5.58 (m, 2H), 4.15 (t, *J* = 6.70 Hz, 2H), 1.80 (dd, *J* = 3.32, 7.23 Hz, 3H), 1.65 (m, 2H), 1.41 (m, 2H), 0.95 (t, *J* = 7.41 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 212.94, 166.31, 90.14, 87.67, 64.67, 30.68, 19.11, 13.70, 12.77.

***Butyl hexa-2,3-dienoate (51c)***



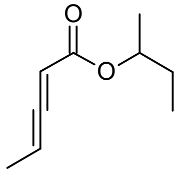
Colorless oil, **4.07g, 83%**. $^{1}$H NMR (500 MHz, CDCl$_3$) δ 5.68 (q, *J* = 6.33 Hz, 1H), 5.61 (dt, *J* = 3.29, 3.29, 6.32 Hz, 1H), 4.14 (qt, *J* = 6.67, 10.83 Hz, 2H), 2.15 (m, 2H), 1.64 (ddt, *J* = 6.50, 7.91, 8.87 Hz), 1.40 (m, 2H), 1.08 (t, *J* = 7.41 Hz, 3H), 0.94 (t, *J* = 7.40 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 212.12, 166.37, 96.99, 88.81, 64.59, 30.67, 20.32, 19.10, 18.03, 13.67.

***sec-Butyl buta-2,3-dienoate (52a)***



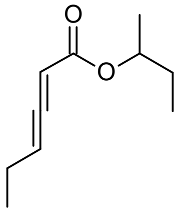
Colorless oil **56.4 mg, 19%**.

***sec-Butyl penta-2,3-dienoate (52b)***



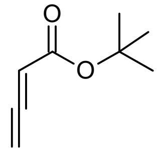
Colorless oil **203.7 mg, 63%.**

***sec-Butyl hexa-2,3-dienoate (52c)***



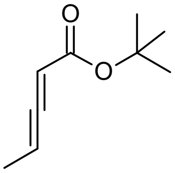
Colorless oil **222.1 mg, 63%.** $^1$H NMR (500 MHz, CDCl$_3$) δ 5.69 (qd, *J* = 2.07, 6.36 Hz, 1H), 5.61 (dt, *J* = 3.27, 6.35 Hz, 1H), 4.91 (hd, *J* = 1.13, 6.27 Hz, 1H), 2.17 (m, 2H), 1.61 (m, 2H), 1.25 (dd, *J* = 4.59, 6.28 Hz, 3H), 1.09 (t, *J* = 7.42 Hz, 3H), 0.93 (td, *J* = 3.13, 7.45 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 212.04 (*J* = 4.02 Hz), 166.04, 96.96, 89.22 (*J* = 3.80 Hz), 72.55, 28.84, 20.85, 19.46 (*J* = 13.35 Hz), 13.10 (*J* = 6.50 Hz), 9.62 (*J* = 2.14 Hz).

***tert-Butyl buta-2,3-dienoate (53a)***



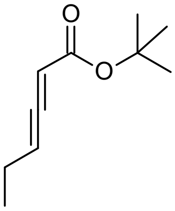
Colorless oil **2.4 mg, 4%**.

***tert-Butyl penta-2,3-dienoate (53b)***



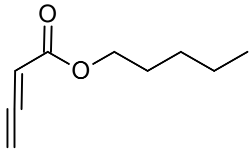
Colorless oil **7 mg, 15%**.

***tert-Butyl hexa-2,3-dienoate (53c)***



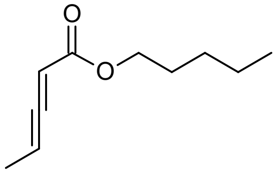
Colorless oil **55.5 mg, 90%**.

***Pentyl buta-2,3-dienoate (54a)***



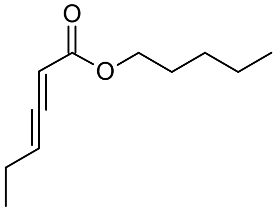
Colorless oil **195.4 mg, 50%**. $^{1}$H NMR (500 MHz, CDCl$_3$) δ 5.64 (t, *J* = 6.54 Hz, 1H), 5.22 (d, *J* = 6.55 Hz, 2H), 4.14 (t, *J* = 6.80 Hz, 2H), 1.66 (m, 2H), 1.34 (m, 4H), 0.91 (m, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 215.72, 165.78, 88.03, 79.16, 65.13, 28.29, 27.99, 22.29, 13.92.

***Pentyl penta-2,3-dienoate (54b)***



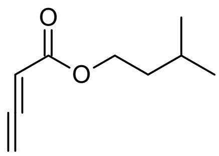
Colorless oil **310.8mg, 51%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.49 (m, 2H), 4.05 (m, 2H), 1.71 (dd, *J* = 3.31, 7.28 Hz, 3H), 1.58 (m, 2H), 1.27 (m, 4H), 0.83 (t, *J* = 1.76 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 212.94, 166.32, 90.15, 87.68, 64.96, 28.31, 28.04, 22.30, 13.95, 12.78.

***Pentyl hexa-2,3-dienoate (54c)***



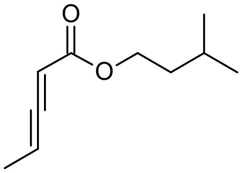
Colorless oil **462.0mg, 69%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.65 (dq, *J* = 1.10, 6.29 Hz, 1H), 5.58 (dtd, *J* = 1.13, 3.29, 6.34 Hz, 1H), 4.10 (m, 2H), 2.13 (m, 2H), 1.63 (p, *J* = 6.45 Hz, 3H), 1.32 (m, 3H), 1.05 (td, *J* = 1.05, 7.39 Hz, 3H), 0.88 (m, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 212.14, 166.42, 97.02, 88.84, 64.91, 28.31, 28.05, 22.30, 20.84, 13.95, 13.05.

***Isopentyl buta-2,3-dienoate (55a)***



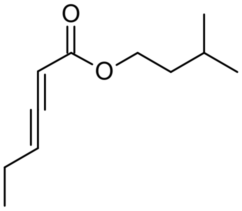
Colorless oil **80.8mg, 17%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.63 (t, *J* = 6.56 Hz, 1H), 5.21 (d, *J* = 6.62 Hz, 2H), 4.18 (t, *J* = 6.92 Hz, 2H), 1.69 (m, 1H), 1.55 (q, *J* = 6.90, 6.85 Hz, 2H), 0.92 (d, *J* = 8.07 Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 215.72, 165.75, 88.01, 79.13, 63.65, 37.29, 25.07, 22.43.

***Isopentyl penta-2,3-dienoate (55b)***



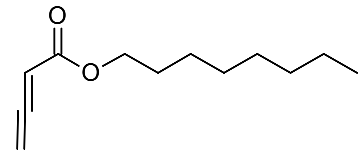
Colorless oil **156.4mg, 58%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.57 (m, 2H), 4.17 (t, *J* = 6.87 Hz, 2H), 1.79 (dd, *J* = 3.29, 7.27 Hz, 3H), 1.70 (m, 1H), 1.55 (q, *J* = 6.87, 6.88 Hz, 2H), 0.93 (d, *J* = 6.68 Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 212.94, 166.29, 90.13, 87.68, 63.50, 37.32, 25.15, 22.47.

***Isopentyl hexa-2,3-dienoate (55c)***



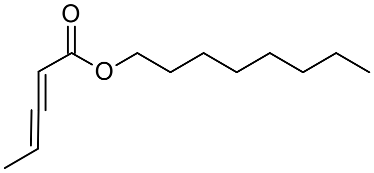
Colorless oil **285.4 mg, 65%**. $^1$H NMR (500 MHz, CDCl$_3$) δ 5.67 (q, *J* = 6.34 Hz, 1H), 5.60 (dt, *J* = 3.29, 6.36 Hz, 1H), 4.16 (m, 2H), 2.15 (m, 2H), 1.70 (dp, *J* = 6.72, 13.44 Hz, 1H), 1.55 (m, 2H), 1.07 (t, *J* = 7.41 Hz, 3H), 0.93 (dd, *J* = 1.18, 6.67 Hz, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 212.12, 166.33, 96.98, 88.82, 63.42, 37.32, 25.13, 22.47, 22.43, 20.82, 13.03.

***Octyl buta-2,3-dienoate (56a)***



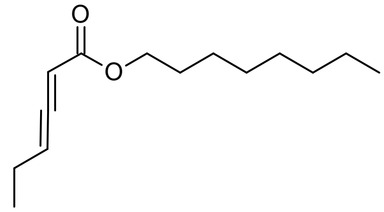
Colorless oil **276 mg, 44%**. $^{1}$H NMR (500 MHz, CDCl$_3$) δ 5.62 (t, *J* = 6.56 Hz, 1H), 5.20 (d, *J* = 6.54 Hz, 2H), 4.12 (t, *J* = 6.80 Hz, 2H), 1.64 (dq, *J* = 6.75, 6.75, 6.73, 8.14 Hz, 2H), 1.29 (m, 10H), 0.87 (t, *J* = 6.87 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 215.70, 165.67, 87.99, 79.06, 65.09, 31.74, 29.14 (*J* = 3.43 Hz), 28.58, 25.82, 22.59, 14.00.

***Octyl penta-2,3-dienoate (56b)***



Colorless oil **299 mg, 69%**. $^{1}$H NMR (500 MHz, CDCl$_3$) δ 5.52 (m, 2H), 4.08 (t, *J* = 6.78 Hz, 2H), 1.73 (dd, *J* = 3.35, 7.26 Hz, 2H), 1.60 (m, 2H), 1.26 (m, 11H), 0.84 (t, *J* = 6.86 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 212.86, 166.09, 89.99, 87.59, 64.81, 31.71, 29.13 (*J* = 1.68 Hz), 28.57, 25.82, 22.57, 13.97, 12.67.

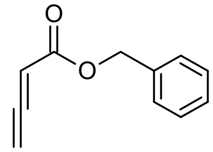
***Octyl hexa-2,3-dienoate (56c)***



Colorless oil **527 mg, 80%**. $^{1}$H NMR (500 MHz, CDCl$_3$) δ 5.68 (q, *J*= 6.33 Hz, 1H), 5.62 (dt, *J* = 3.29, 3.29, 6.30 Hz, 1H), 4.13 (m, 2H), 2.17 (m, 2H), 1.66 (dq, *J* = 6.70, 8.34 Hz, 2H), 1.32 (m, 10H), 1.09 (t, *J* = 7.40 Hz, 3H), 0.89 (t, *J* = 6.88 Hz, 3H). $^{13}$C NMR

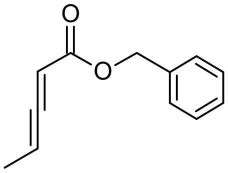
(126 MHz, $CDCl_3$) δ 212.12, 166.34, 96.98, 88.84, 64.89, 31.75, 29.17 ($J$ = 1.71 Hz), 28.63, 25.88, 22.62, 20.83, 14.04, 13.05.

***Benzyl buta-2,3-dienoate (57a)***



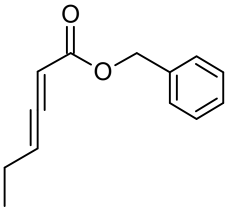
Colorless oil. **90.2mg, 42%**. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.69, (t, $J$ = 6.53 Hz, 1H), 5.24 (d, $J$ = 6.55 Hz, 2H), 5.20 (s, 2H). $^{13}$C NMR (126 MHz, $CDCl_3$) δ 216.02, 165.54, 135.90, 87.88, 79.44, 77.36, 77.10, 76.85, 66.64.

***Benzyl penta-2,3-dienoate (57b)***



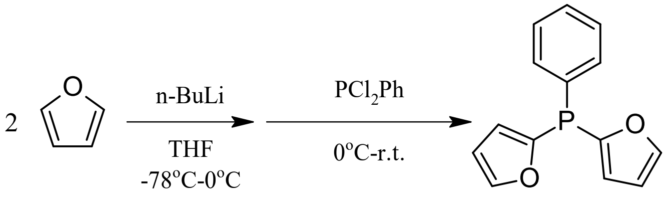
Colorless oil. **12.0 mg, 2%.**

***Benzyl hexa-2,3-dienoate (57c)***



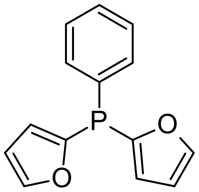
Colorless oil. **156.5 mg, 63%.**

*Experimental procedure for the synthesis of di(2-furyl)phenylphosphine* [150]



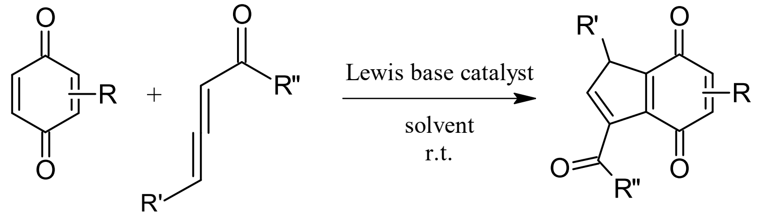
THF (5 mL) was added to furan (2.2 mmol) at -78°C. n-Butyl lithium (2.2 mmol) was cooled to -78°C and added to the mixture. This was stirred at -78°C for 30 minutes, then placed in an ice bath. After 30 minutes in the ice bath, dichlorophenylphosphine (1 mmol) was added slowly. The reaction was allowed to slowly warm to room temperature, and was stirred at that temperature overnight. It was then diluted with $NH_4Cl$ and extracted into EtOAc. The organic layers were washed with saturated NaCl, dried over $Na_2SO_4$, and purified by flash chromatography over silica gel by elution of hexanes/ethyl acetate.

***Di(2-furyl)phenylphosphine (58)***



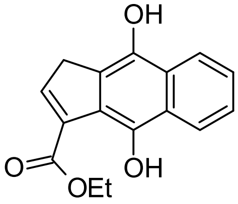
Yellow oil, **313.4 mg, 22%.**

*Experimental procedure for the [3+2] cyclization of allenoates with quinones*



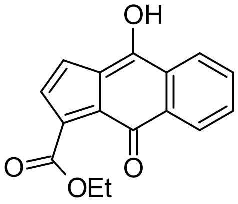
The quinone (1 mmol) was dissolved in $CH_2Cl_2$ (3 mL). To this was added the allenoate (2 eq) then the Lewis base (0.2, 0.5, 0.75. or 1.0 eq, depending on the reaction). The reaction was stirred at room temperature for the specified amount of time, then the solvent was evaporated and the crude product was purified by flash chromatography over silica gel via elution of hexanes/ethyl acetate.

***Ethyl 4,9-dihydroxy-1H-cyclopenta[b]naphthalene-3-carboxylate (59a)***



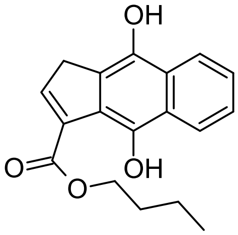
**29.3 mg, 32%.** $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.14 (ttd, *J* = 2.05, 3.29, 3.90, 5.64 Hz, 2H), 7.58 (s, 1H, OH), 7.50 (m, 2H), 6.92 (t, *J* = 4.31 Hz, 1H), 5.49 (s, 1H, OH), 4.96 (d, *J* = 4.31 Hz, 2H), 4.37 (q, *J* =7.13 Hz, 2H), 1.41 (t, *J* = 7.13 Hz, 3H).

### *Ethyl 9-hydroxy-4-oxo-4H-cyclopenta[b]naphthalene-3-carboxylate (59b)*



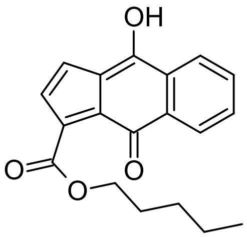
**62.7 mg, 68%.** $^1$H NMR (500 MHz, CDCl$_3$) δ 8.15 (m, 1H), 8.07 (m, 1H), 7.61 (m, 2H), 7.21 (d, *J* = 3.29 Hz, 1H), 7.14 (d, *J* = 3.29 Hz, 1H), 4.47 (q, *J* = 7.14 Hz, 2H), 1.46 (t, *J* = 7.14 Hz, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 179.93, 169.30, 166.80, 134.45, 134.39, 133.83, 133.17, 132.96, 132.72, 127.94, 127.69, 126.61, 124.03, 118.60, 62.69, 14.20.

### *Butyl 4,9-dihydroxy-1H-cyclopenta[b]naphthalene-3-carboxylate (60)*



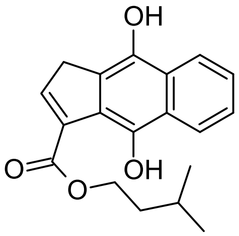
**18.3 mg, 24%.** $^1$H NMR (500 MHz, DMSO-d$^6$) δ 9.78 (s, 1H, OH), 8.06 (m, 1H), 8.00 (m, 1H), 7.48 (m, 2H), 7.39 (s, 1H, OH), 6.90 (t, *J* = 4.24 Hz, 1H), 4.92 (d, *J* = 4.27 Hz, 2H), 4.25 (t, *J* = 6.57 Hz, 2H), 1.69 (m, 2H), 1.42 (m, 2H), 0.95 (m, 3H).

***Pentyl 9-hydroxy-4-oxo-4H-cyclopenta[b]naphthalene-3-carboxylate (61)***



**1.6 mg, 2%.** $^1$H NMR (500 MHz, $CDCl_3$) δ 8.16 (m, 1H), 8.08 (m, 1H), 7.61 (m, 2H), 7.21 (d, *J* = 3.29 Hz, 1H), 7.15 (d, *J* = 3.29 Hz, 1H), 4.41 (t, *J* = 6.67 Hz, 2H), 1.83 (m, 2H), 1.45 (dddd, *J* = 4.18, 6.85, 12.39, 13.98 Hz, 4H), 0.97 (m, 3H).

***3-methylbutyl 4,9-dihydroxy-1H-cyclopenta[b]naphthalene-3-carboxylate (62)***



**33.9 mg, 46%.** $^1$H NMR (500 MHz, $CDCl_3$) δ 8.14 (m, 2H), 7.58 (s, 1H, OH), 7.50 (m, 2H), 6.89 (t, *J* = 4.30 Hz, 1H), 5.55 (s, 1H, OH), 4.95 (d, *J* = 4.32 Hz, 2H), 4.34 (t, *J* = 6.85 Hz, 2H), 1.69 (m, 1H), 1.55 (q, *J* = 6.90, 6.85 Hz, 2H), 0.92 (d, *J* = 8.07 Hz, 6H).

# 5 FINAL THOUGHTS

The three projects I have participated in over the last three years may seem disparate on the surface, but their commonality runs deep. My initial work on the MtFBA project was exciting and generally gratifying, and it expanded my knowledge of diversification and synthesis exponentially. But one of the most rewarding aspects of this endeavor was the chance it gave me to develop my second project, the novel quinoline synthesis procedure. This presented my first solo plunge into the depths of organic chemistry, and I reveled in the chance to make my own way in this area. The allenoate project was a recent addition that merged the process of reaction optimization with the construction of diverse polycyclic compounds, requiring skills and knowledge earned from the previous two projects. As with the quinoline synthesis, this project was also borne out of circumstances related to finding analogs for the MtFBA project, expanding the thread that connects these three stories.

My hopes for the future are that both the MtFBA and allenoate projects continue to be fruitful. These ventures have granted me moments of both intense joy and intense frustration, and I hope whoever carries them on can find some of the answers that have so far been elusive. After all: *It is good to have an end to journey toward; but it is the journey that matters, in the end.* ~Ernest Hemingway

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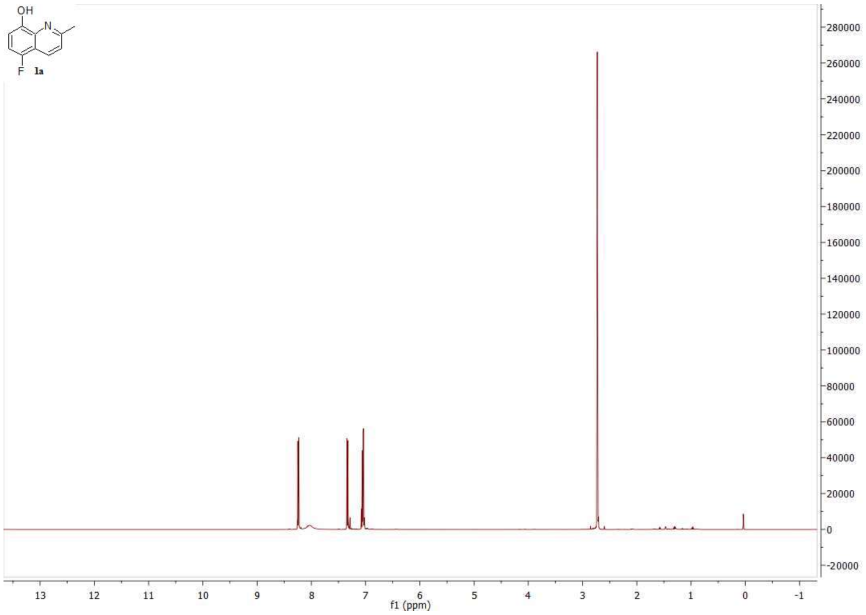
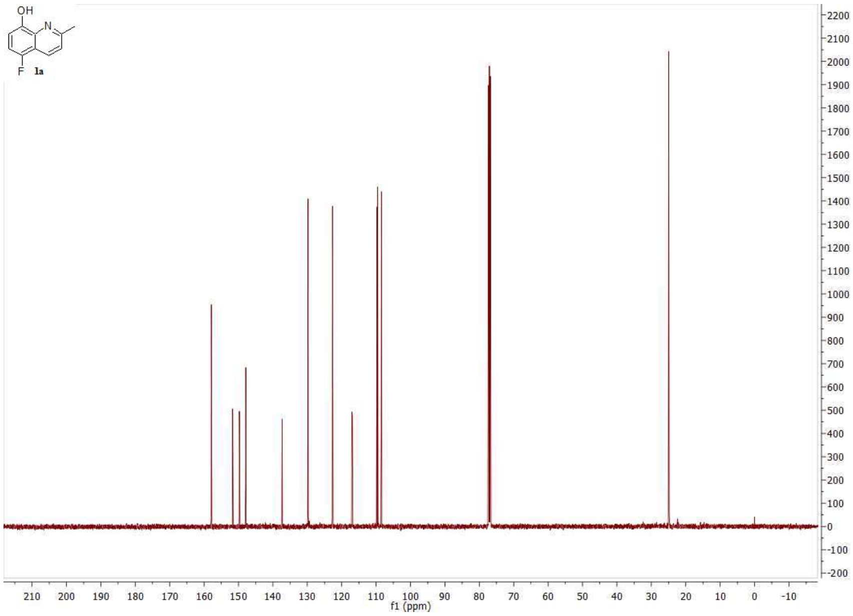
## APPENDIX A: LITERATURE

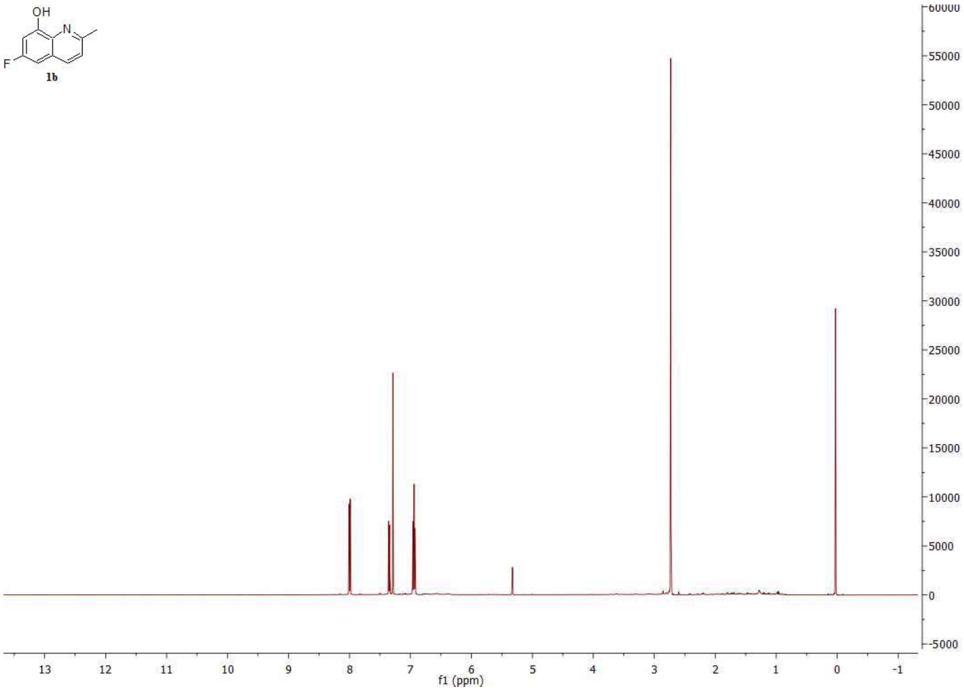
**Ramann, G.**, Cowen, B. Phosphine-promoted [3+2]-Cycloadditions of Allenoates and Naphthoquinones. Manuscript in preparation.

**Ramann, G.**, Cowen, B. Quinoline synthesis by improved Skraup–Doebner–Von Miller reactions utilizing acrolein diethyl acetal. *Tetrahedron Lett.* **2015,** *56*, 6436-6439.

# APPENDIX B: NMR SPECTRA



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4
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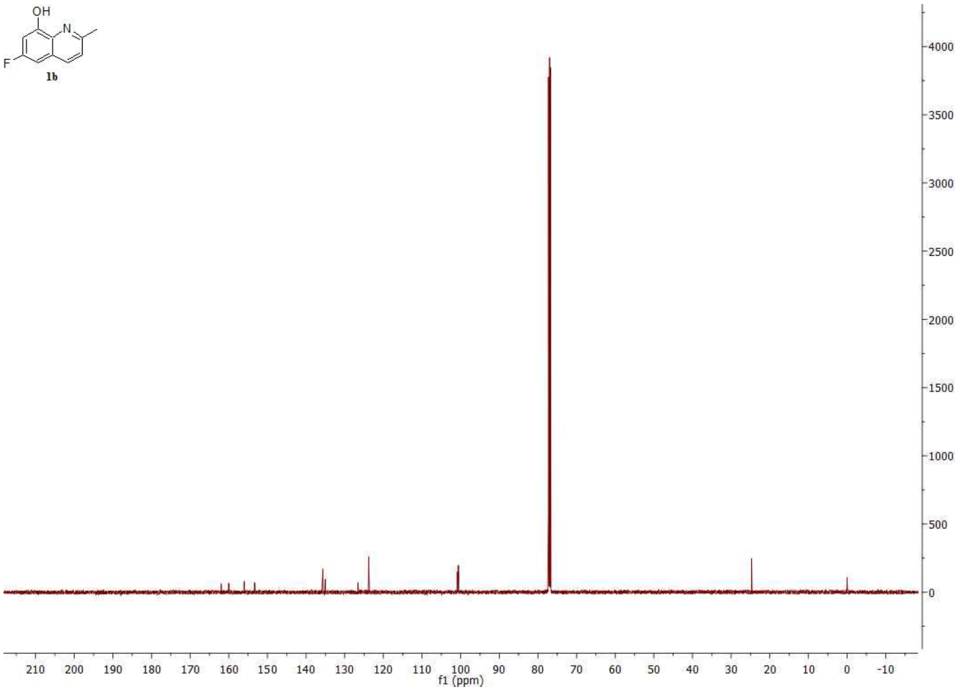
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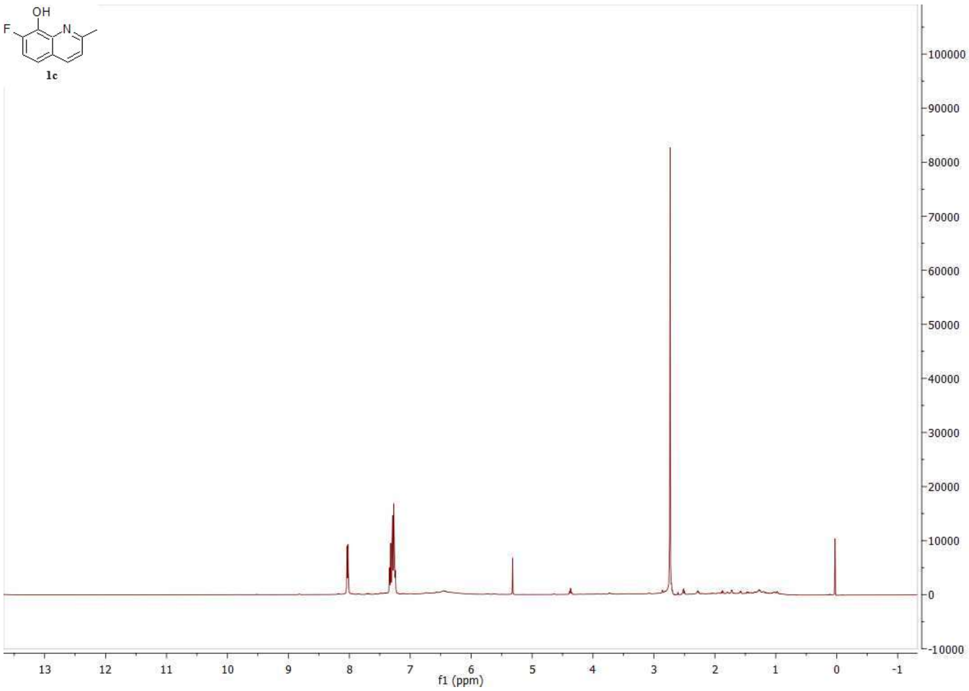
f1 (ppm)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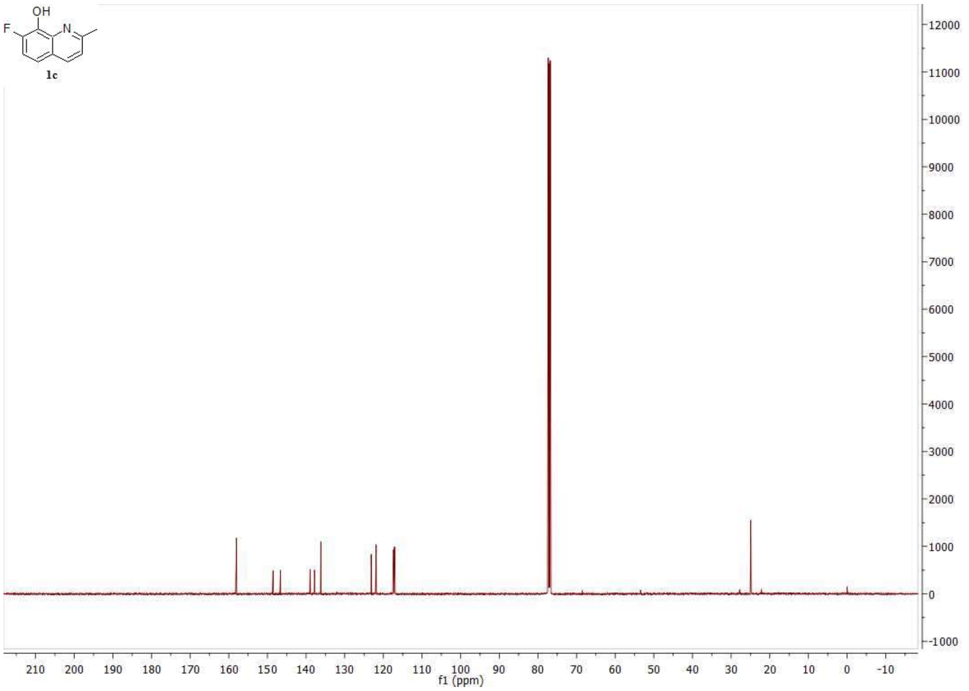
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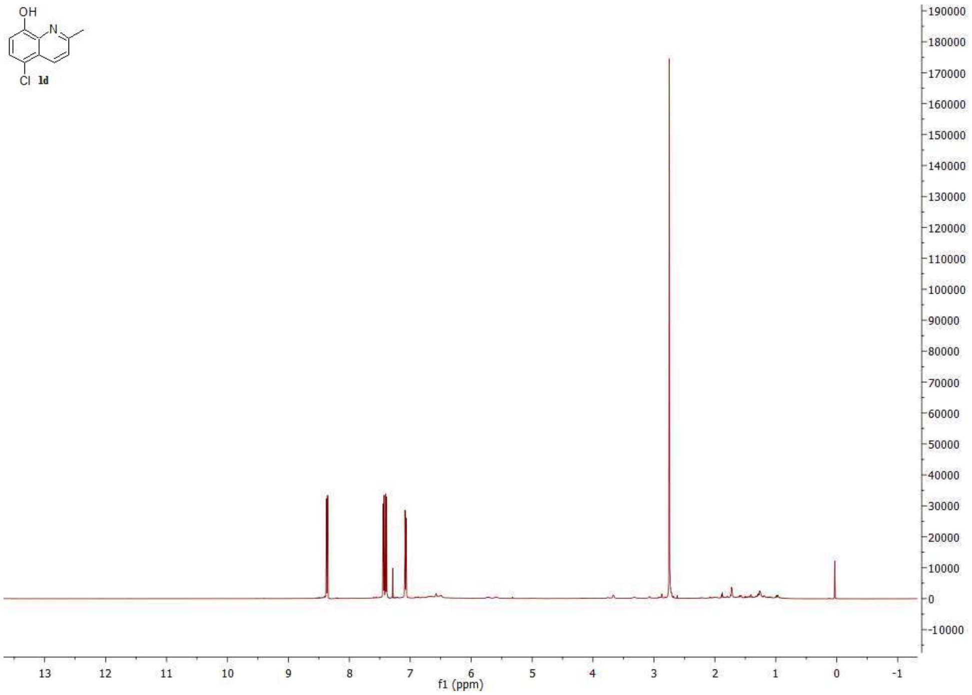
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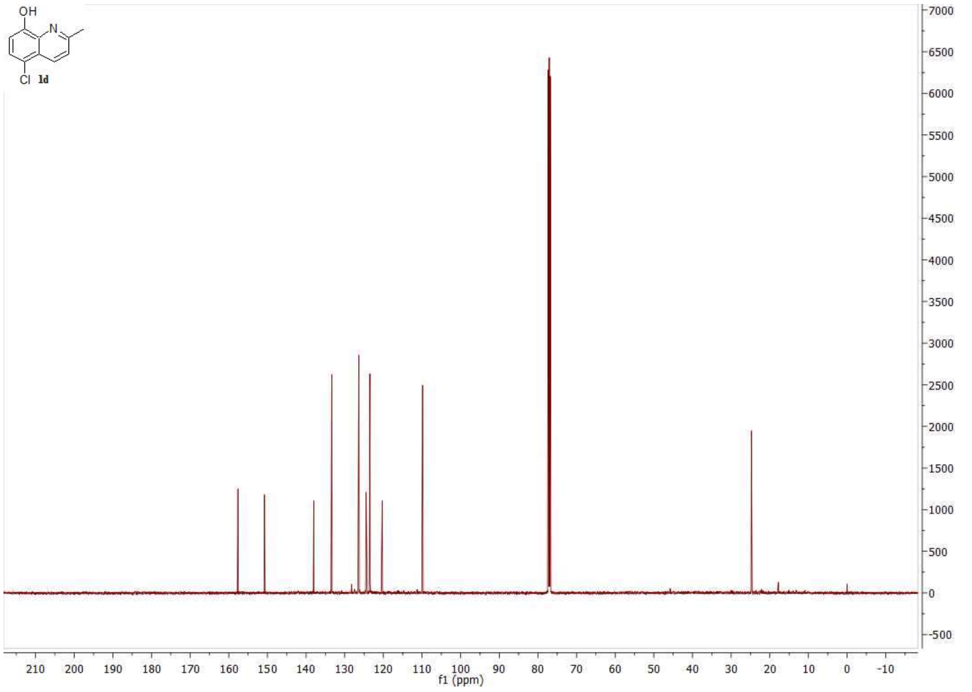
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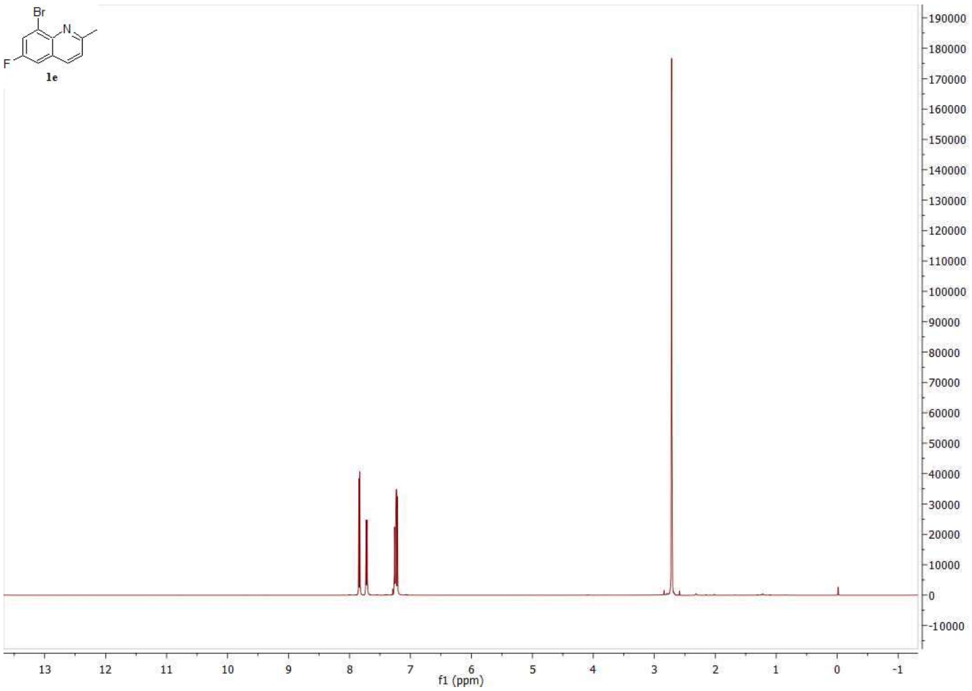
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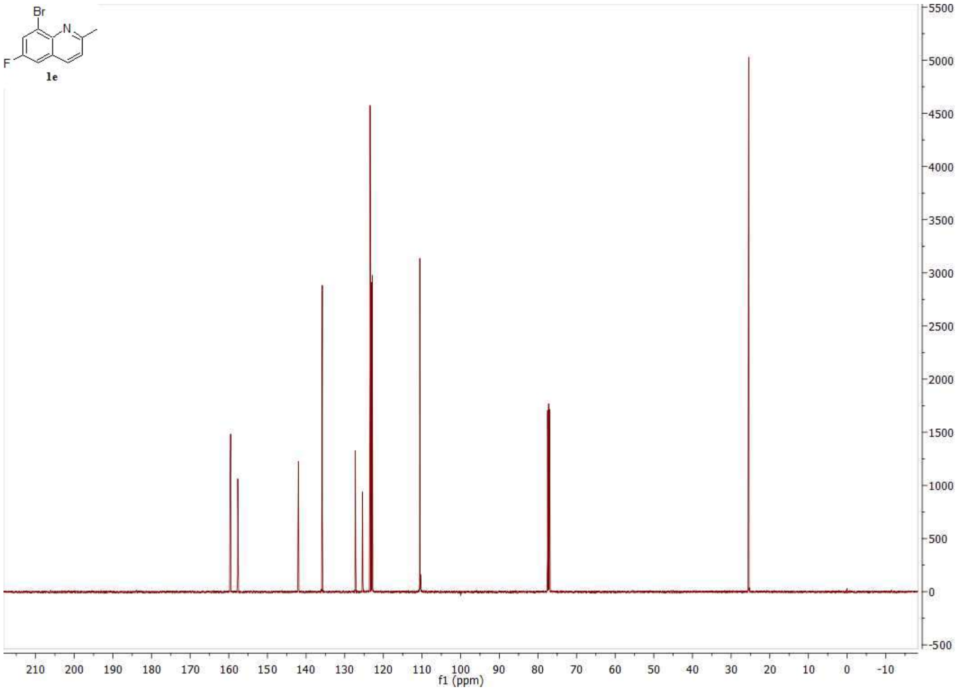
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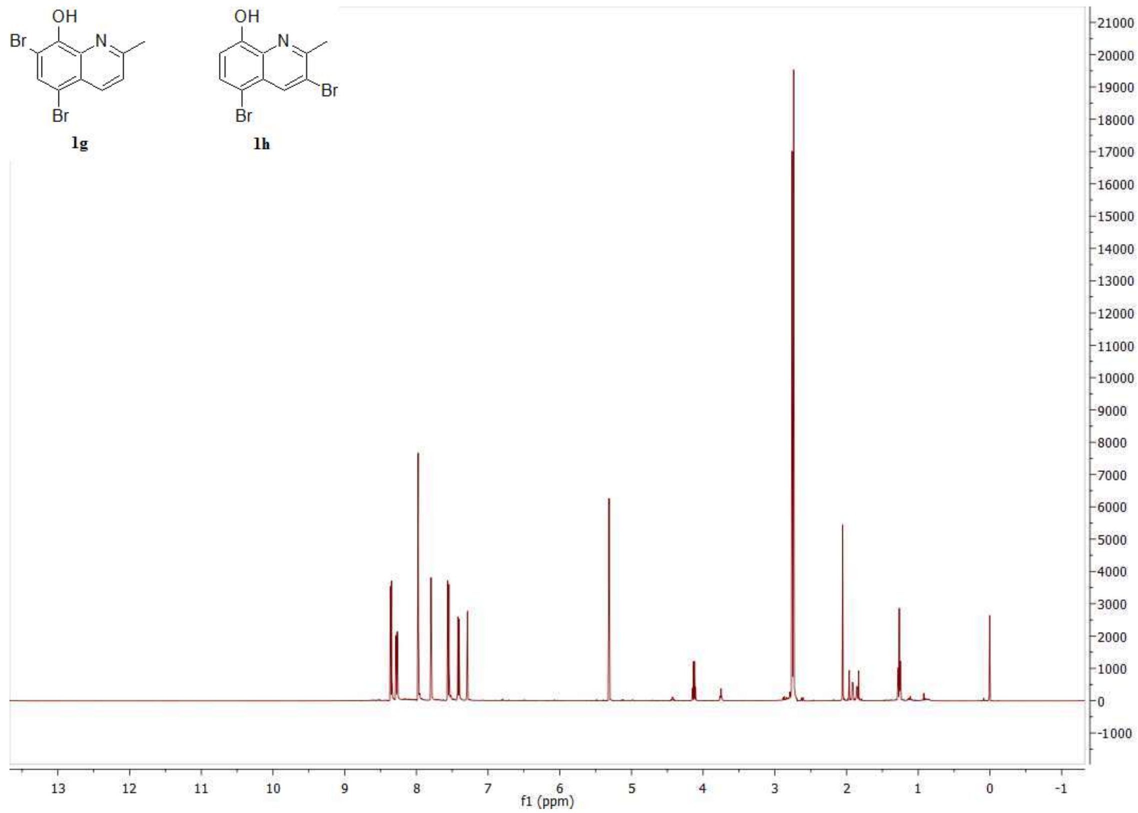
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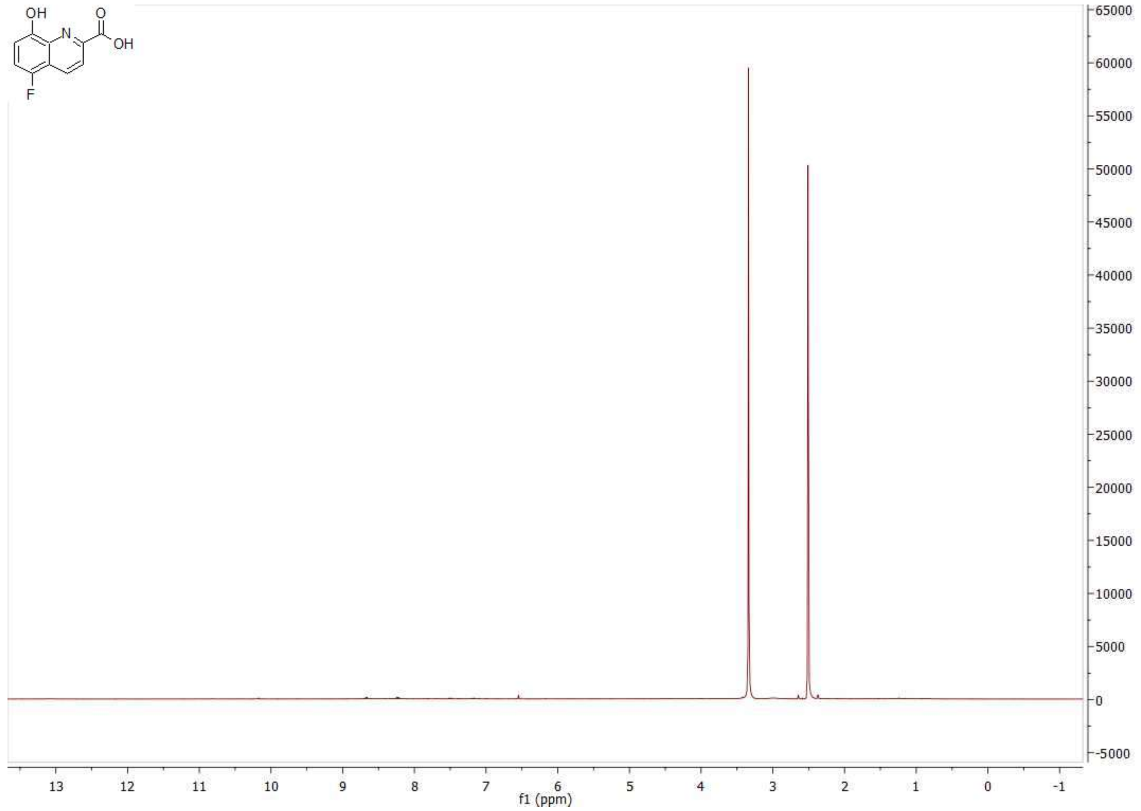
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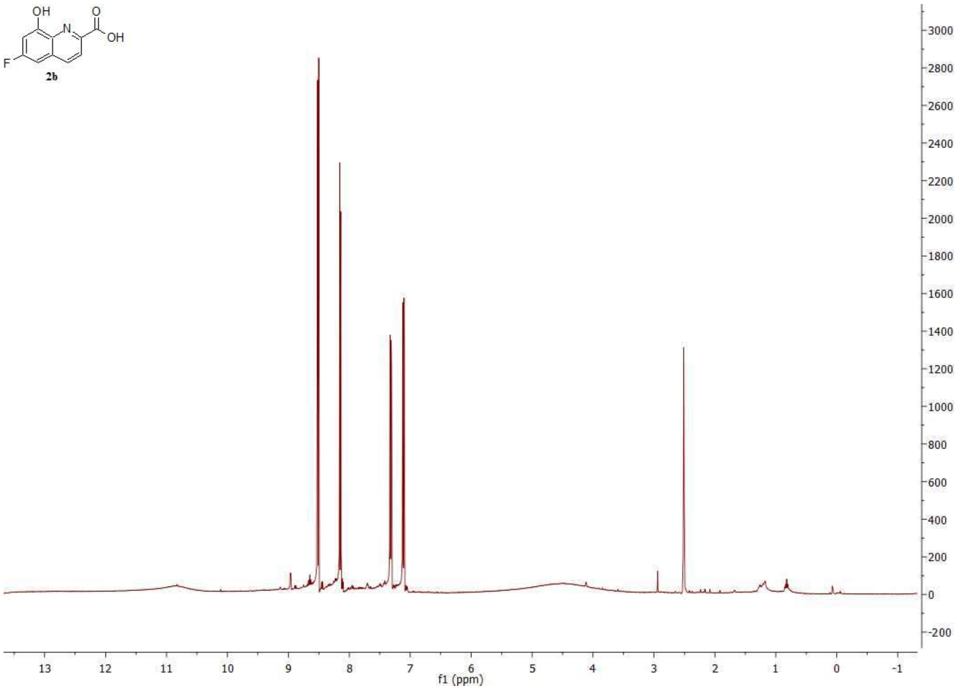
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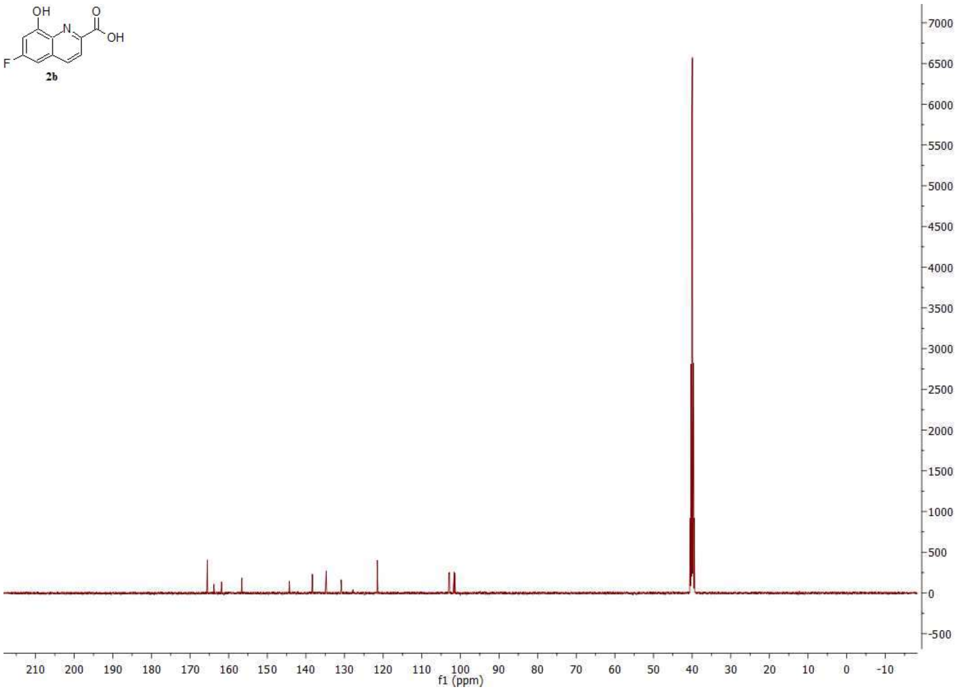
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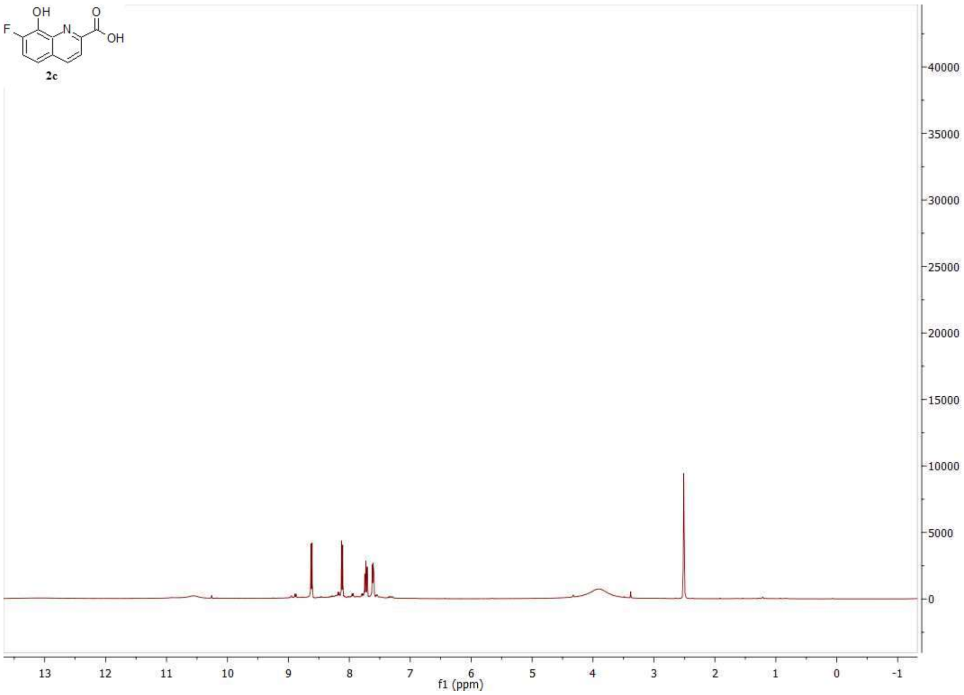
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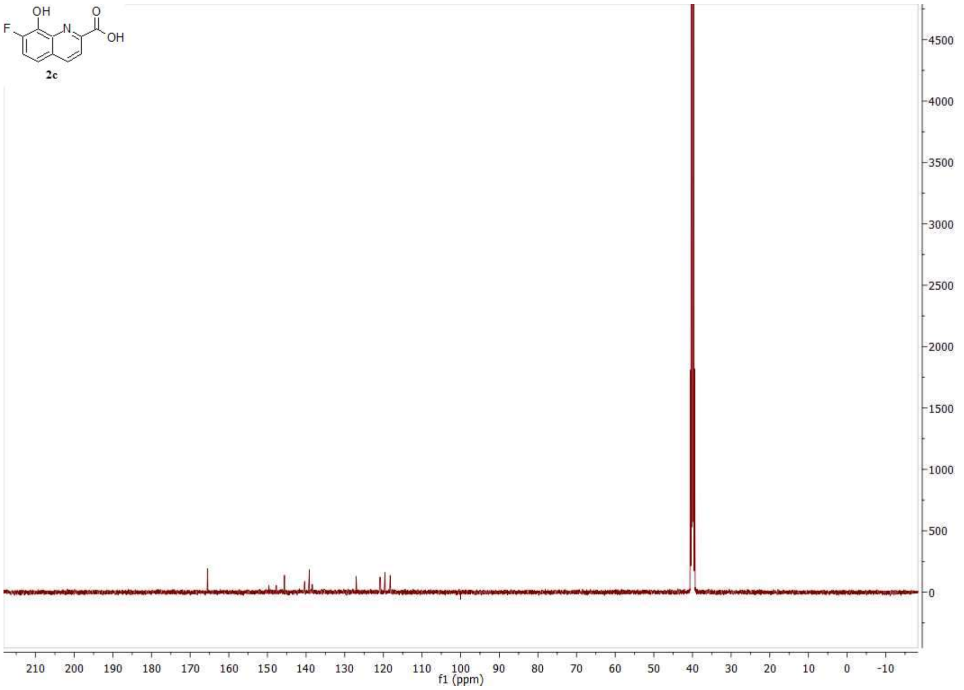
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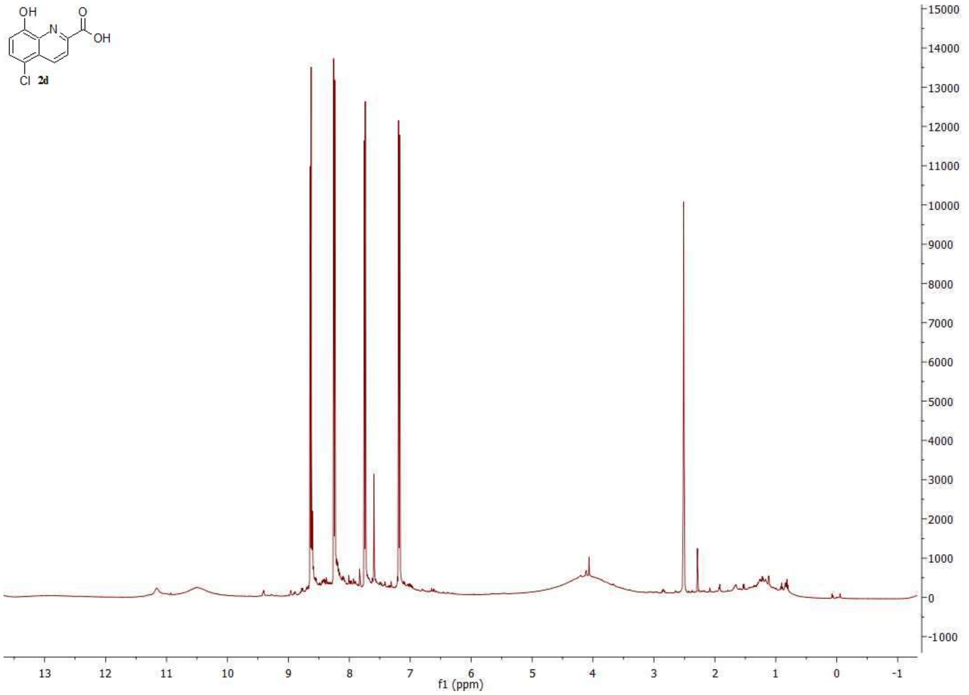
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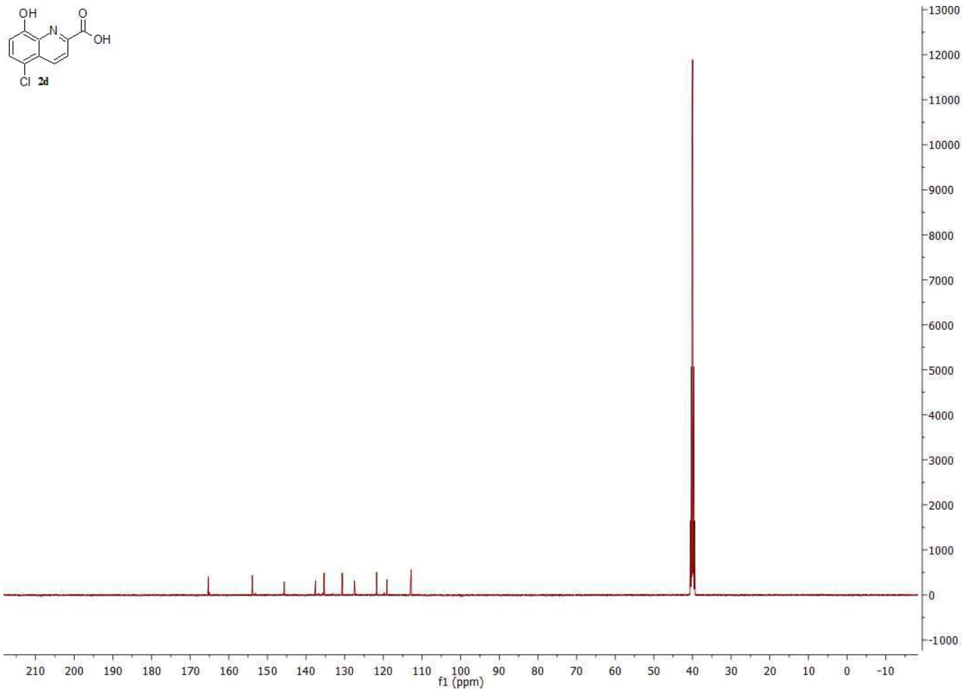
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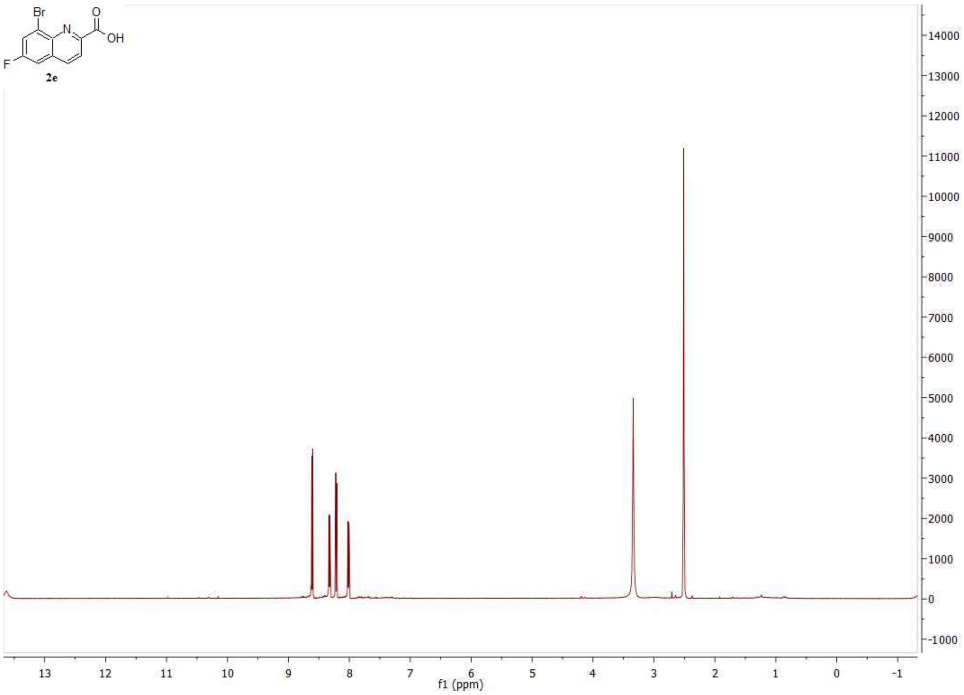
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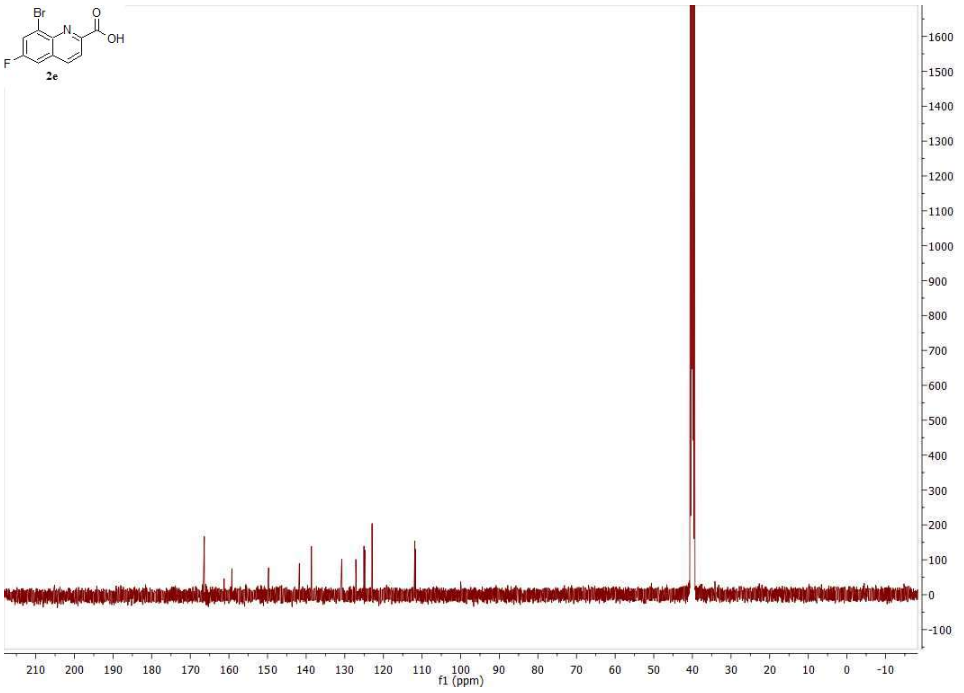
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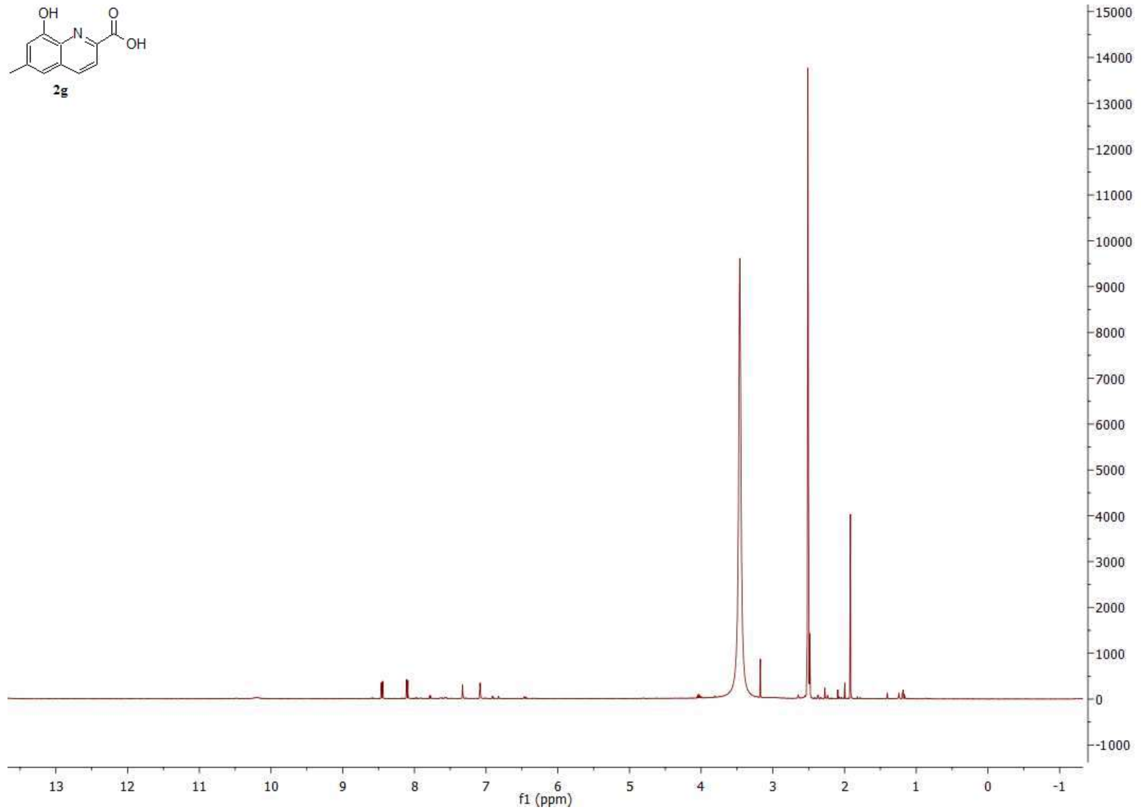
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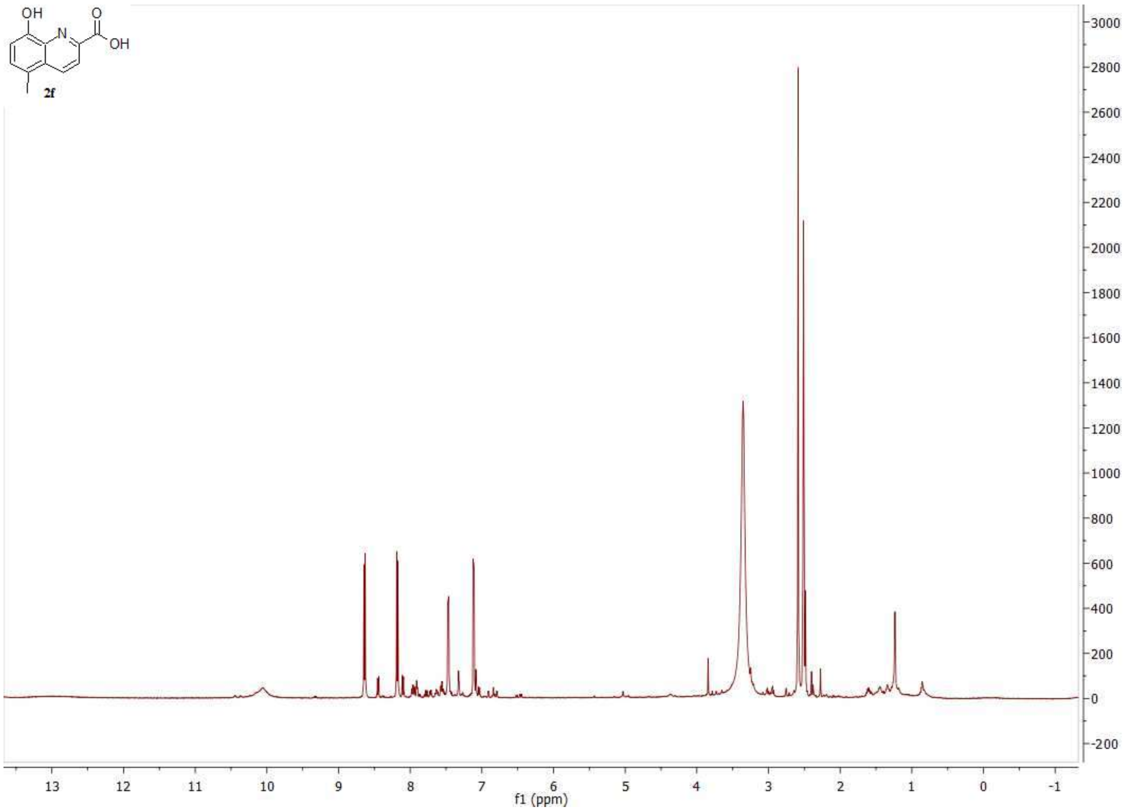
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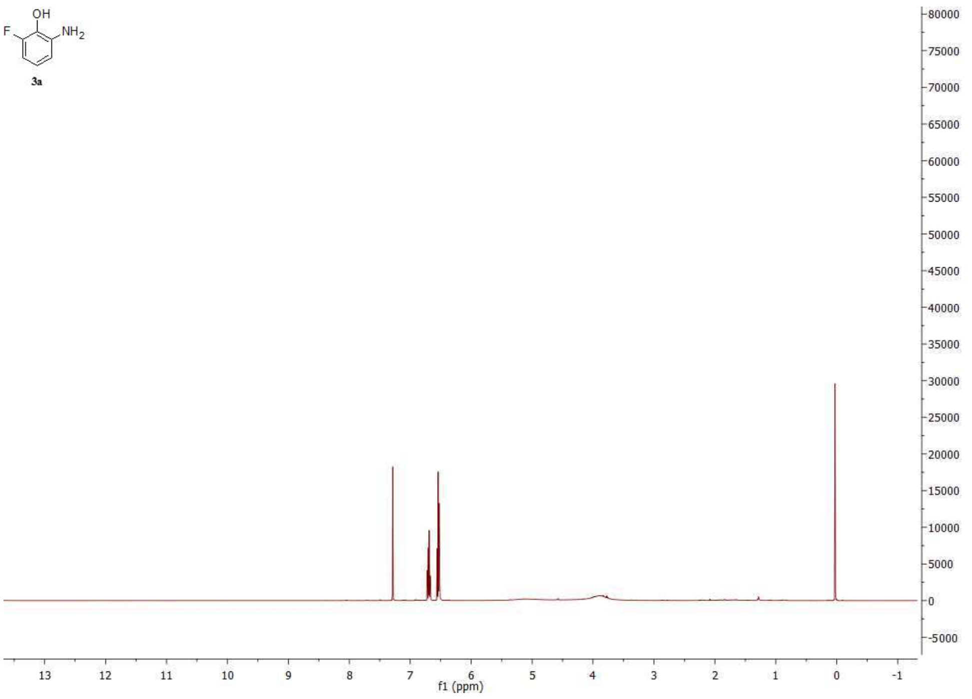
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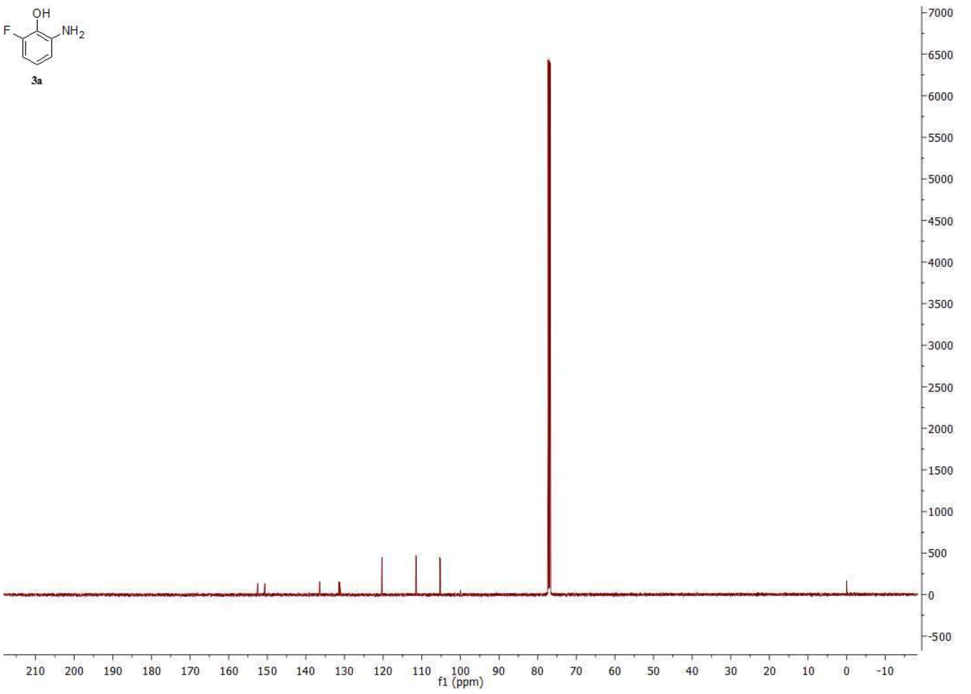
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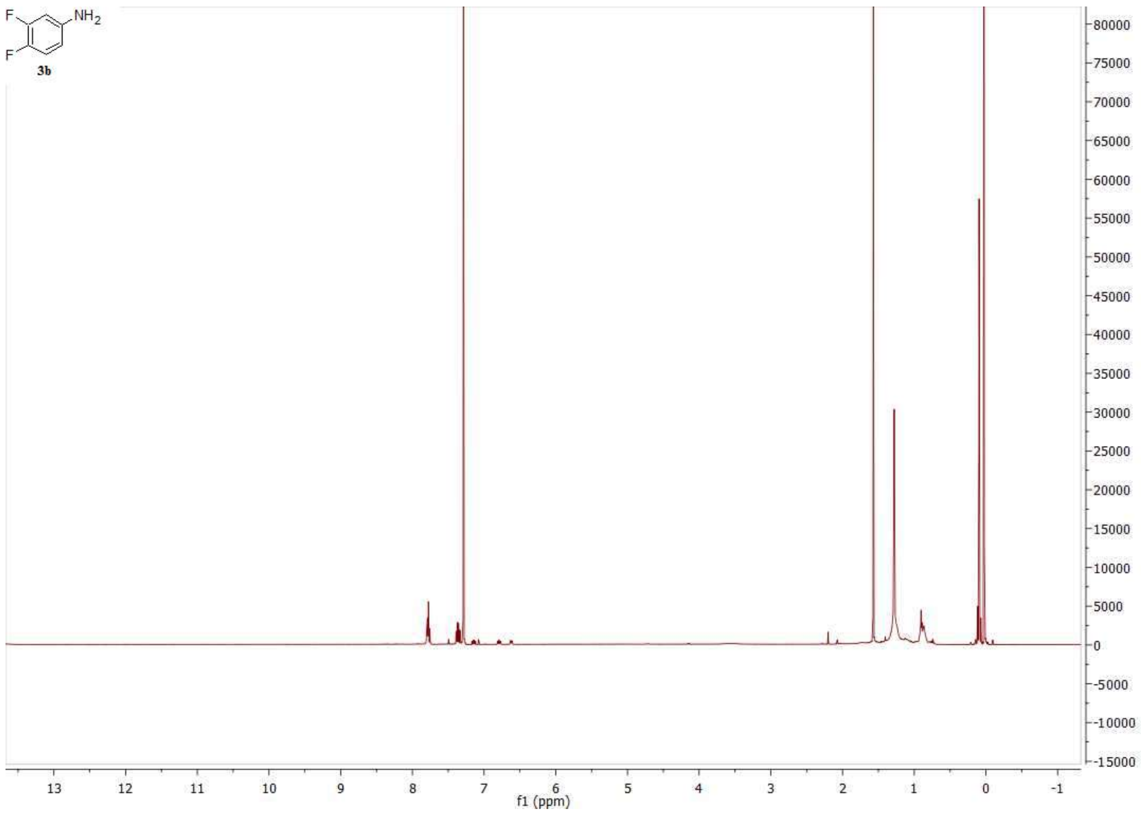
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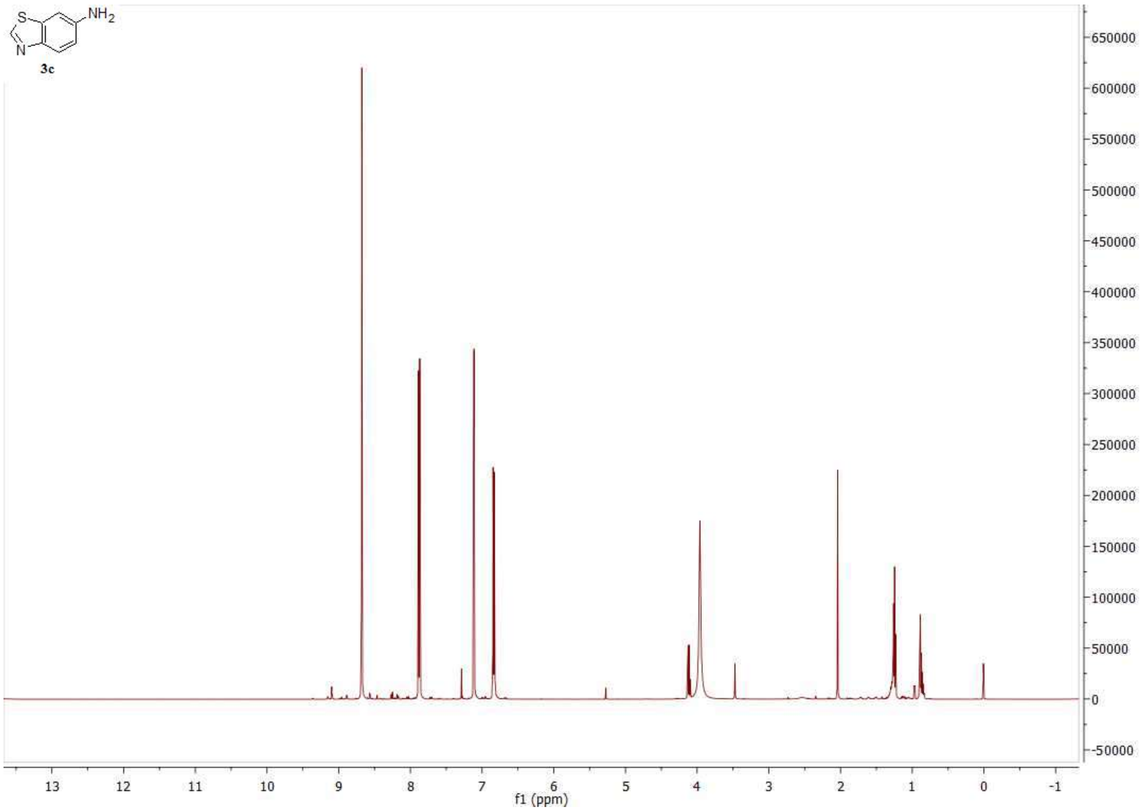
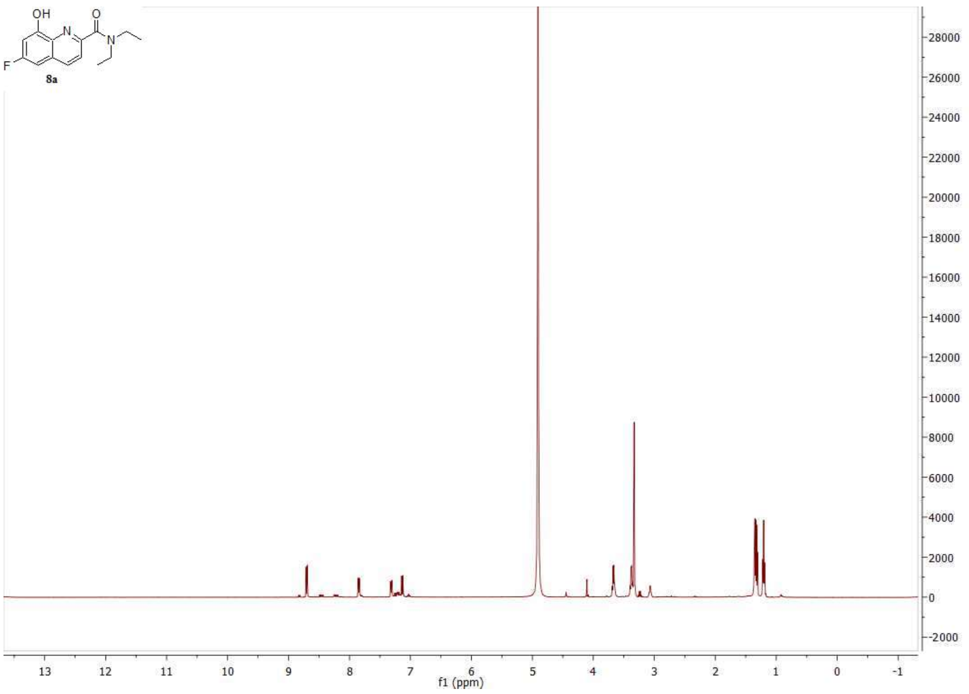
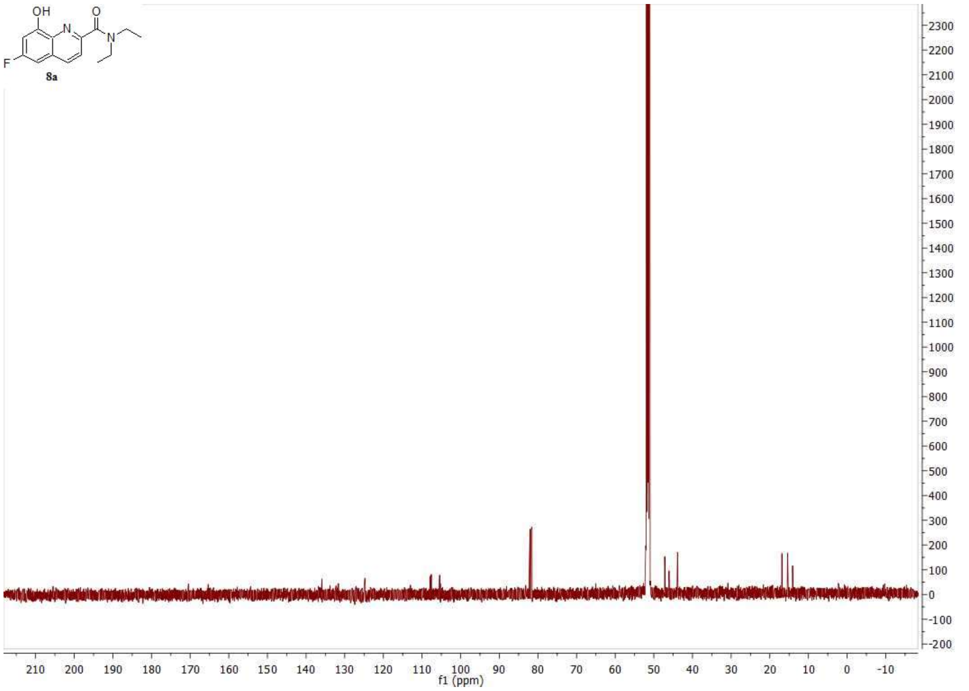
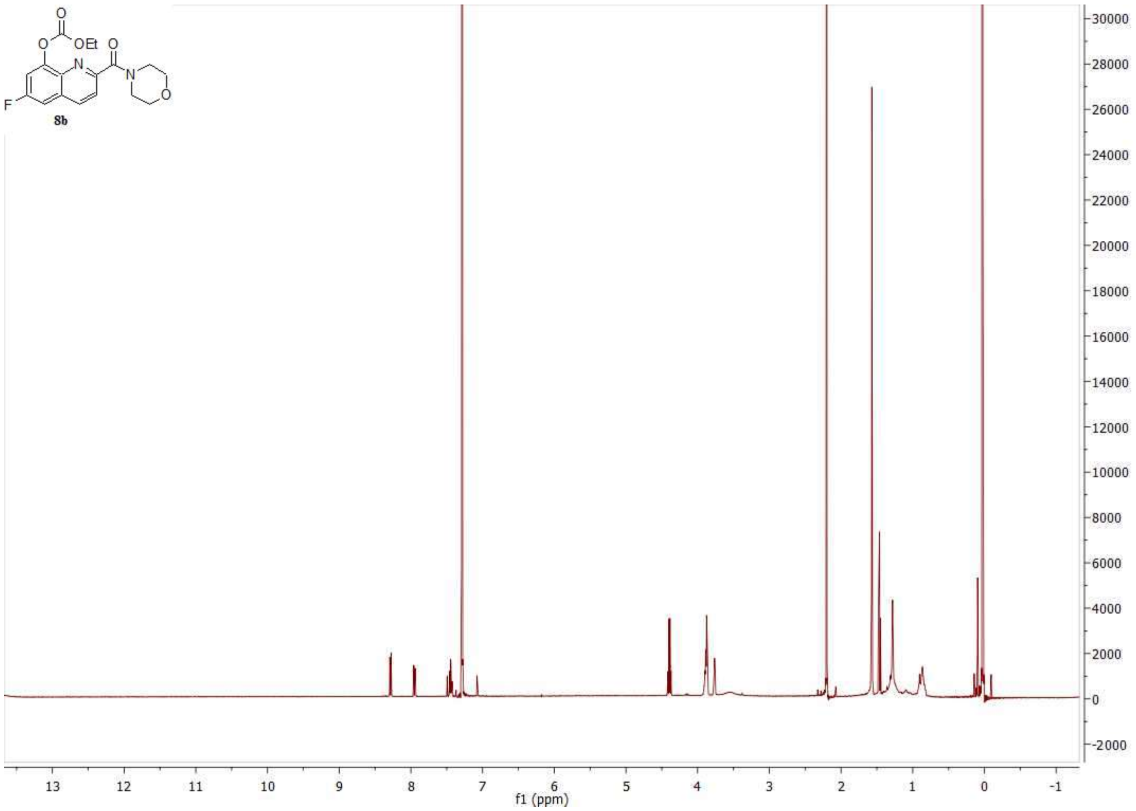
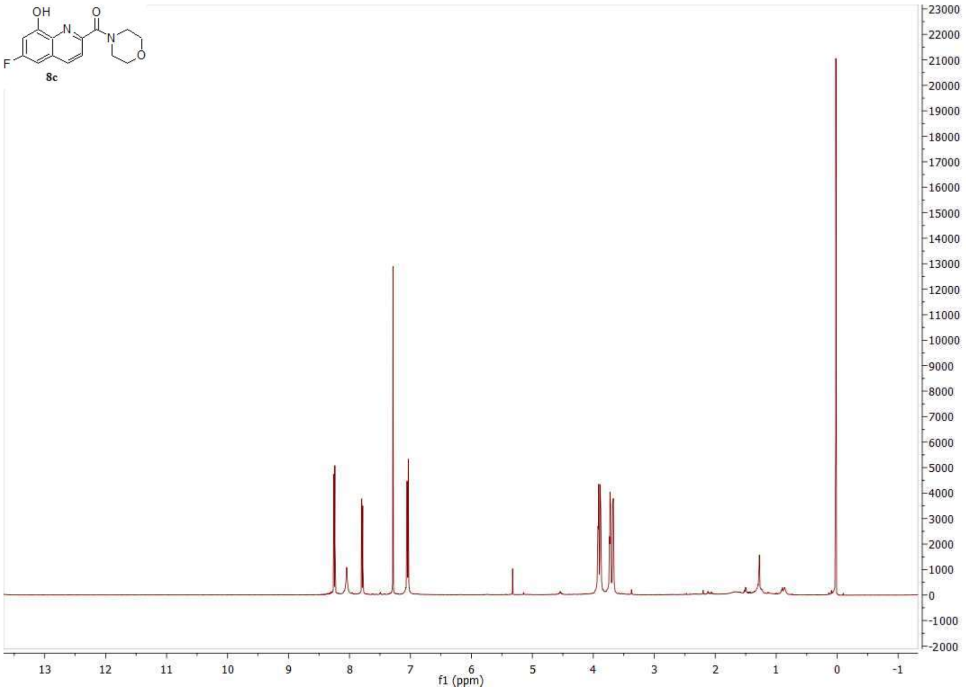
-1
f1 (ppm)

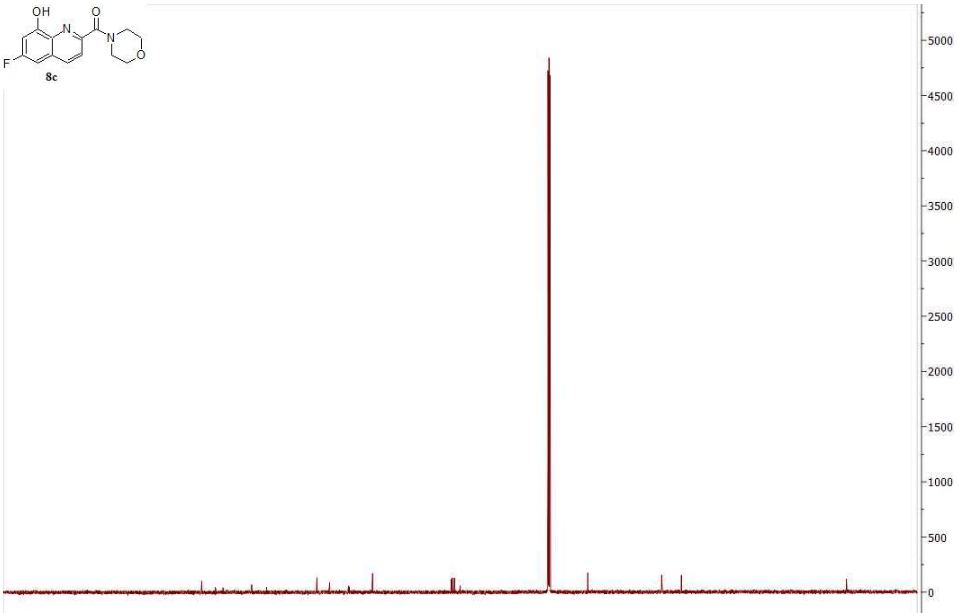

S
N
NH2
3c
650000
600000
550000
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
-50000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

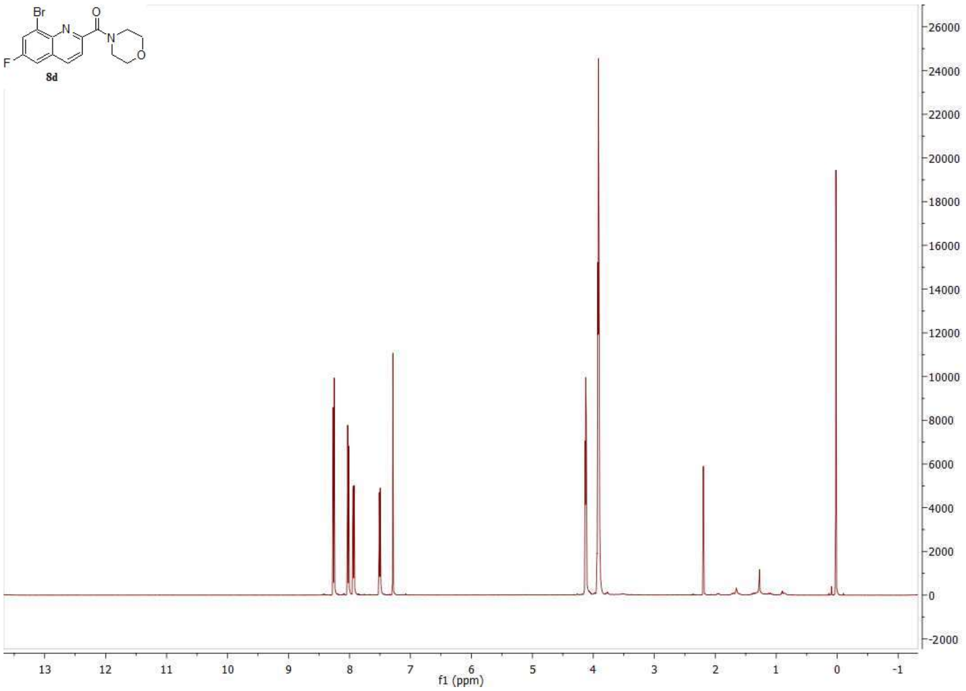

OH
O
N
N
F
8a
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

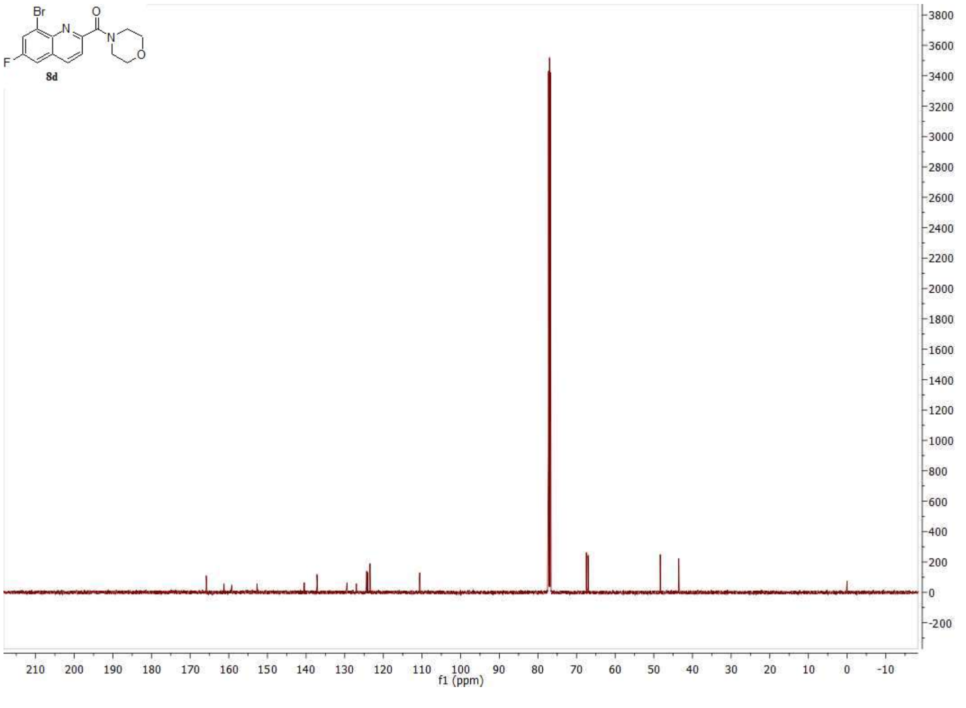

OH
O
N
N
F
8a
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

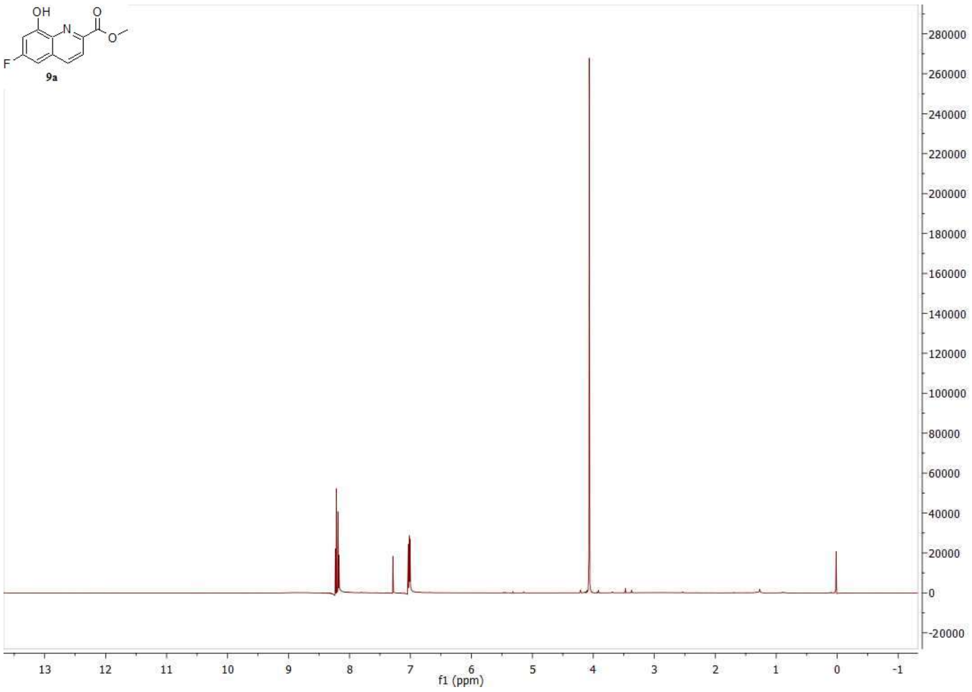

O
O
OEt
N
O
N
O
F
8b
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

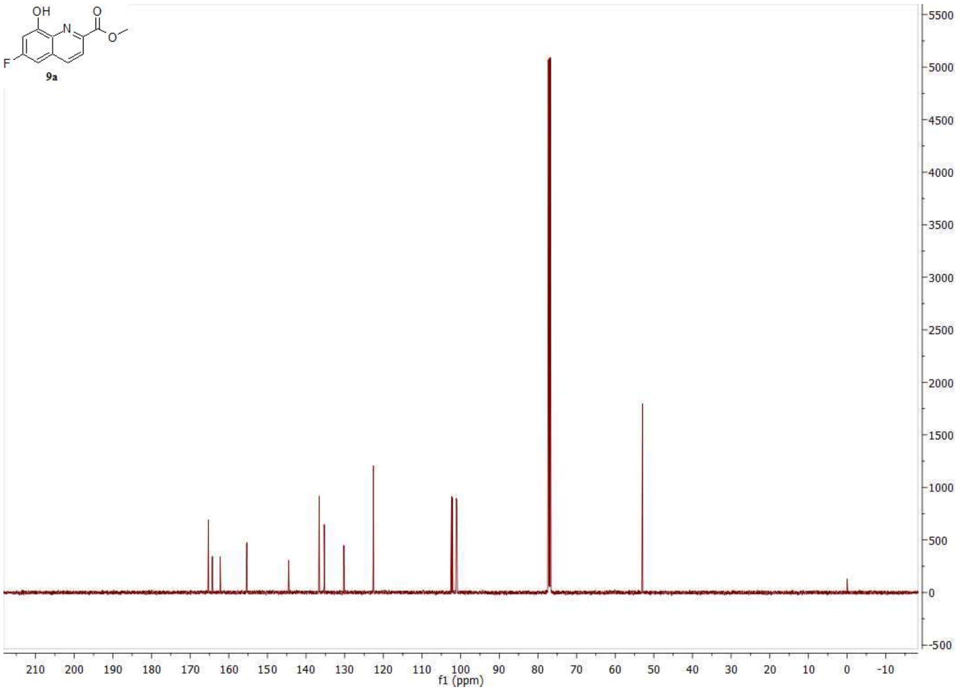

OH
O
N
N
O
F
8c
23000
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

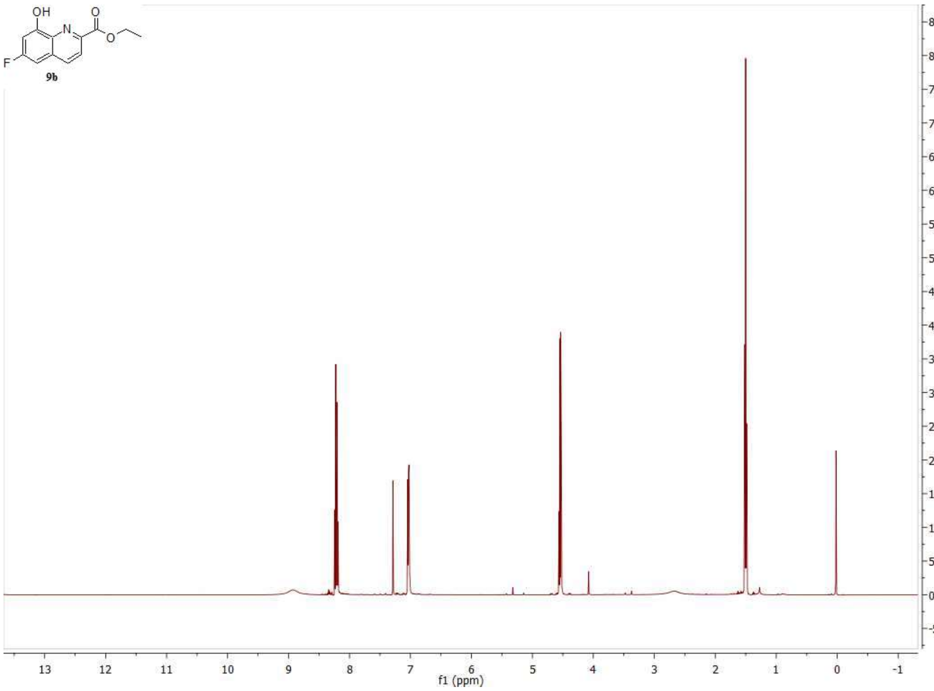

OH
O
N
N
O
F
8c
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

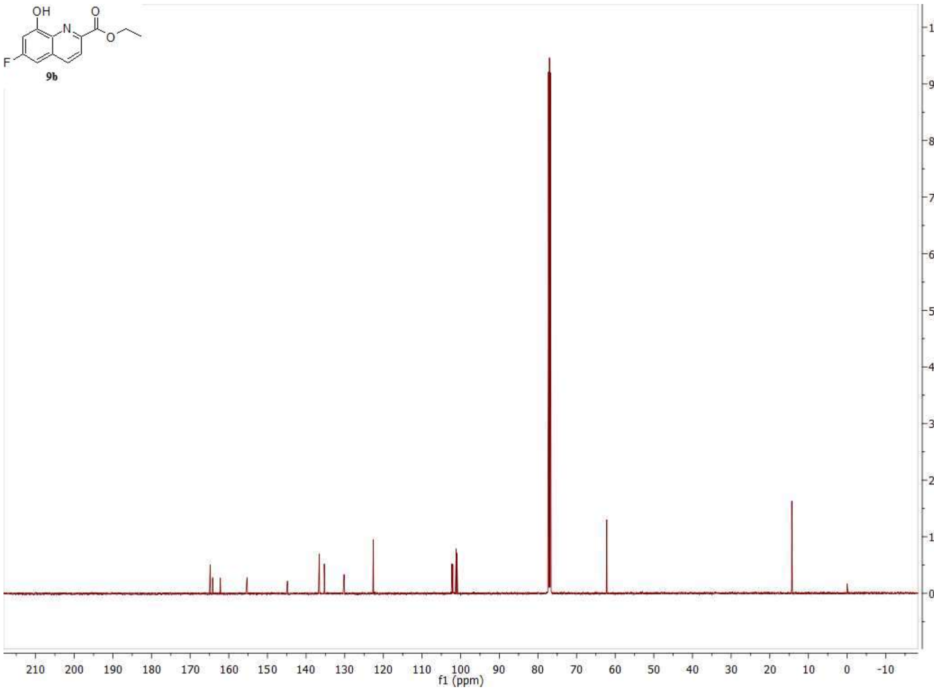

Br
O
N
N
O
F
8d
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

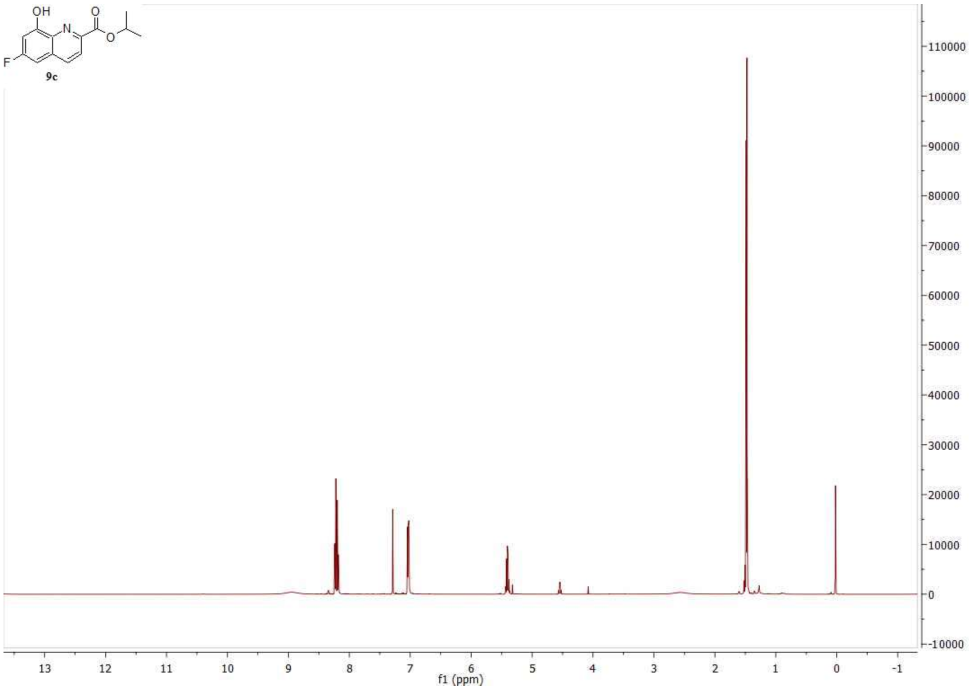

Br
O
N
N
O
F
8d
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

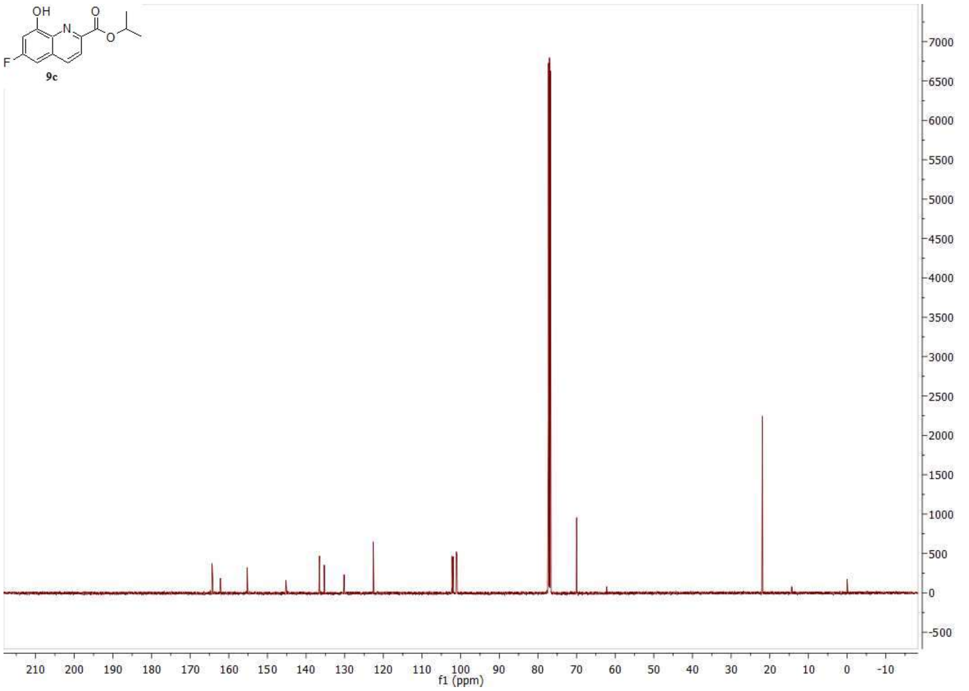

OH
N
O
O
F
9a
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

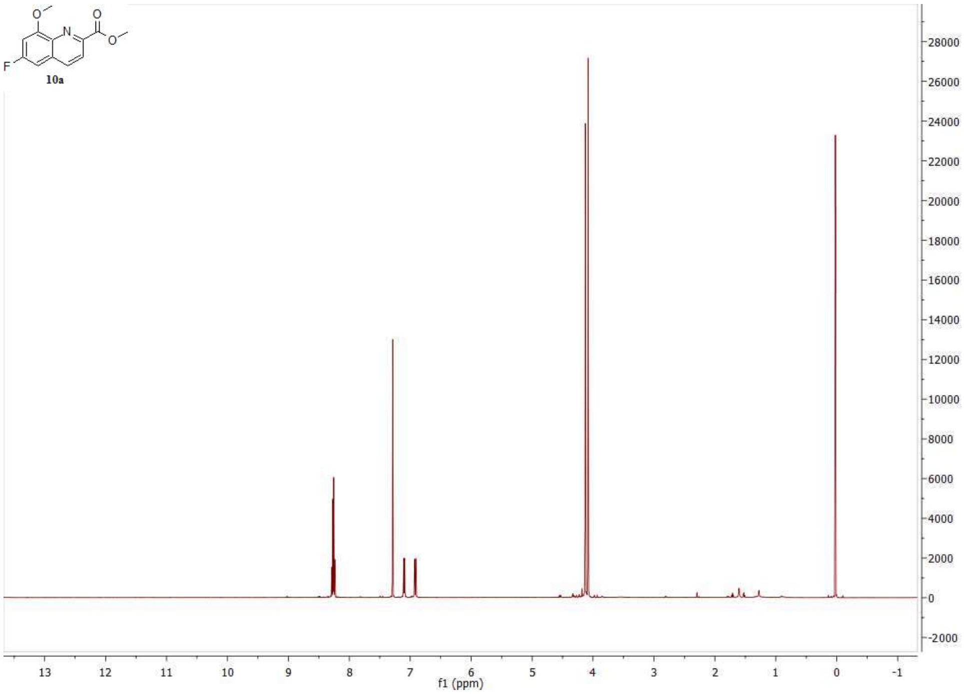

OH
N
O
O
F
9a
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

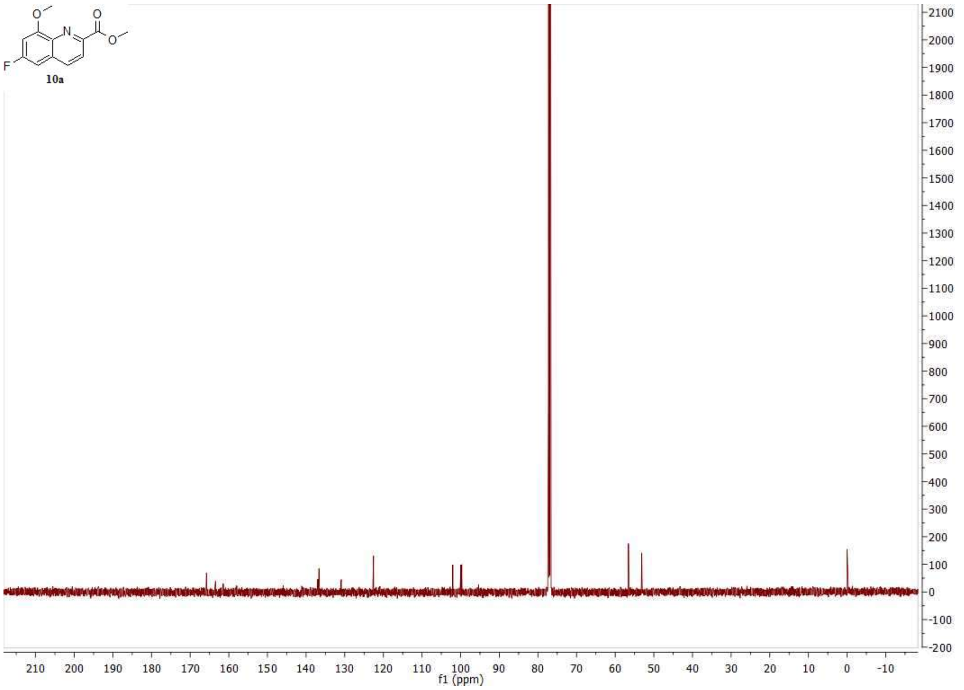

OH
N
O
O
F
9b
85000
80000
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

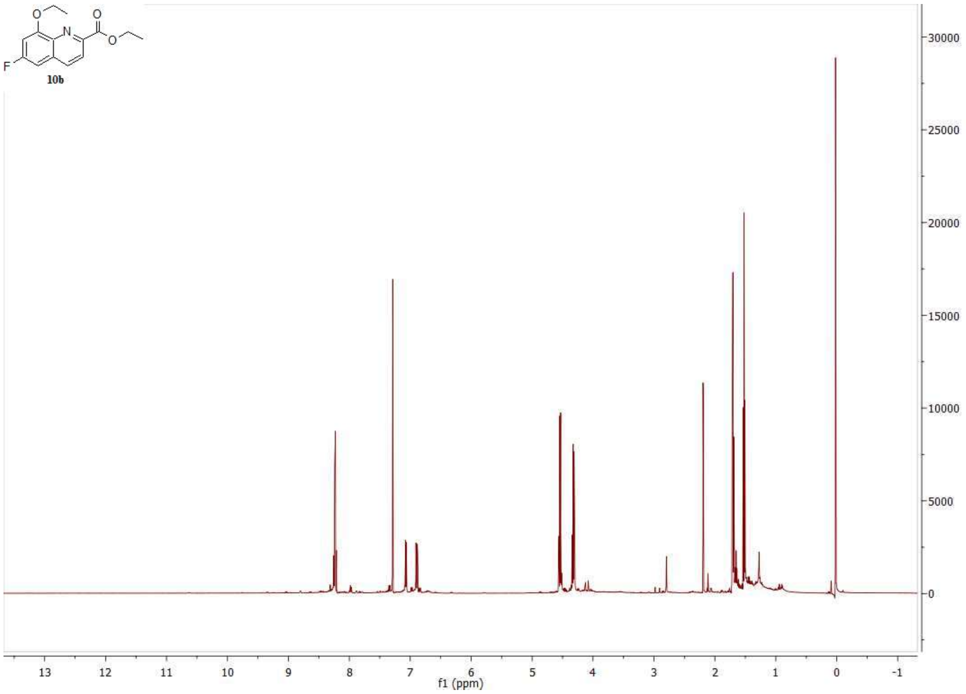

OH
N
O
O
F
9b
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

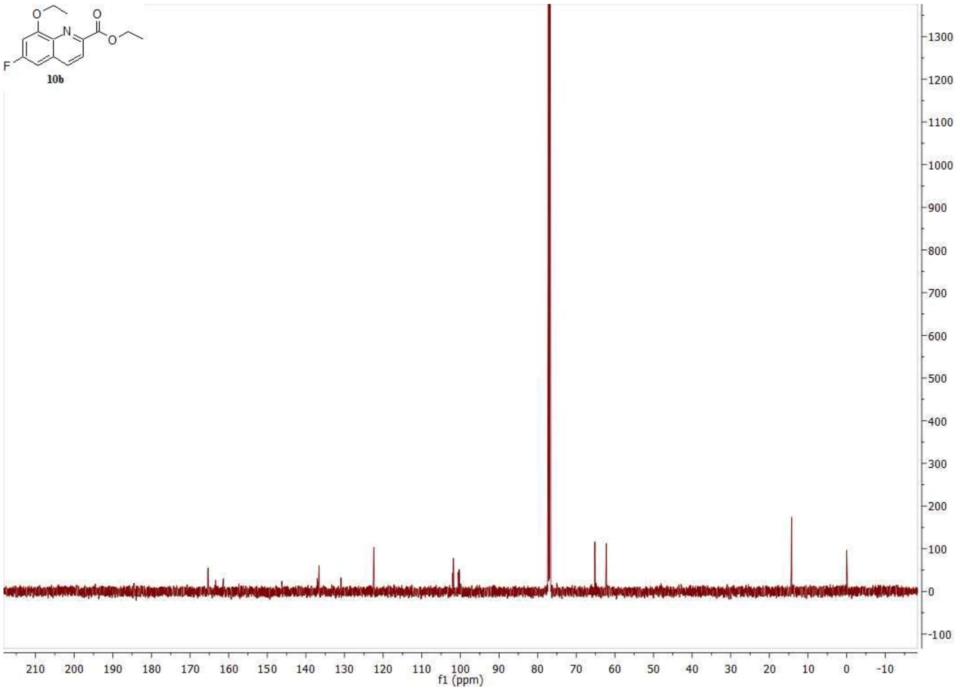

OH
N
O
O
F
9c
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

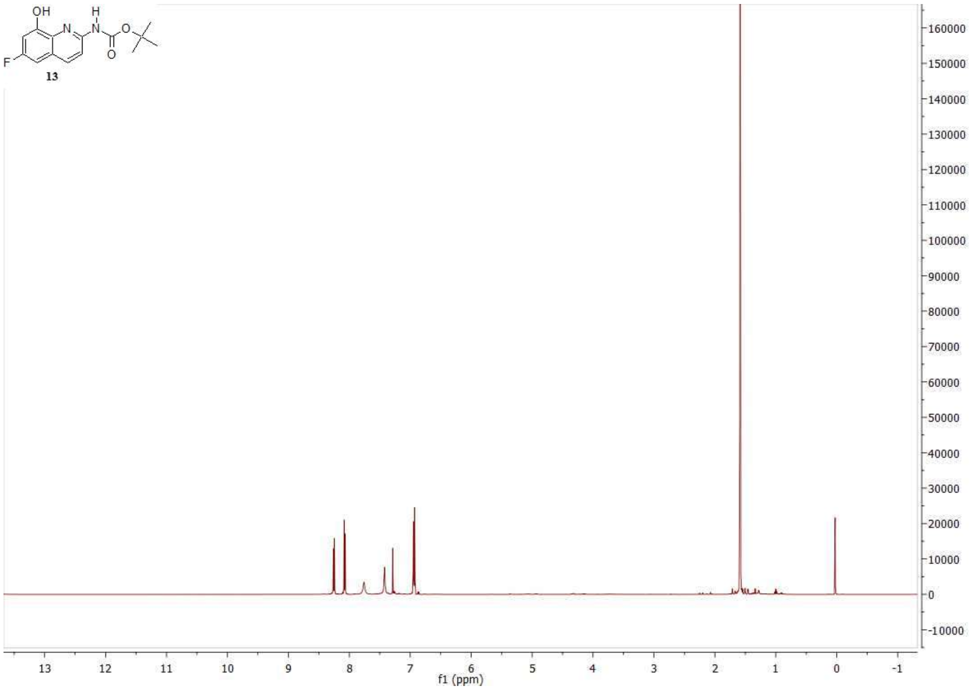

OH
N
O
O
F
9c
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

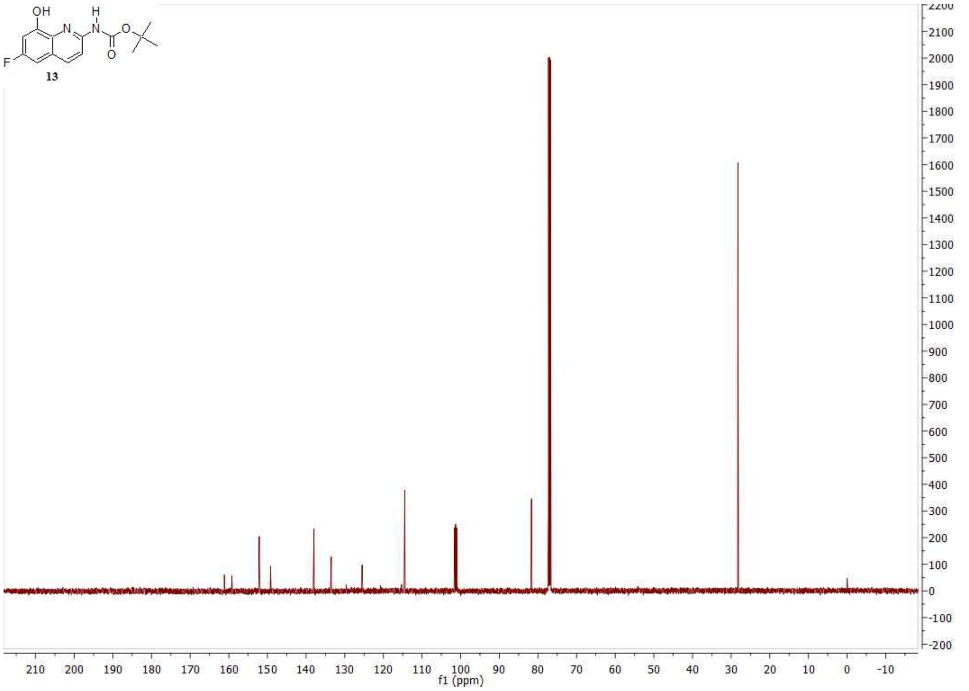

O
O
N
O
F
10a
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

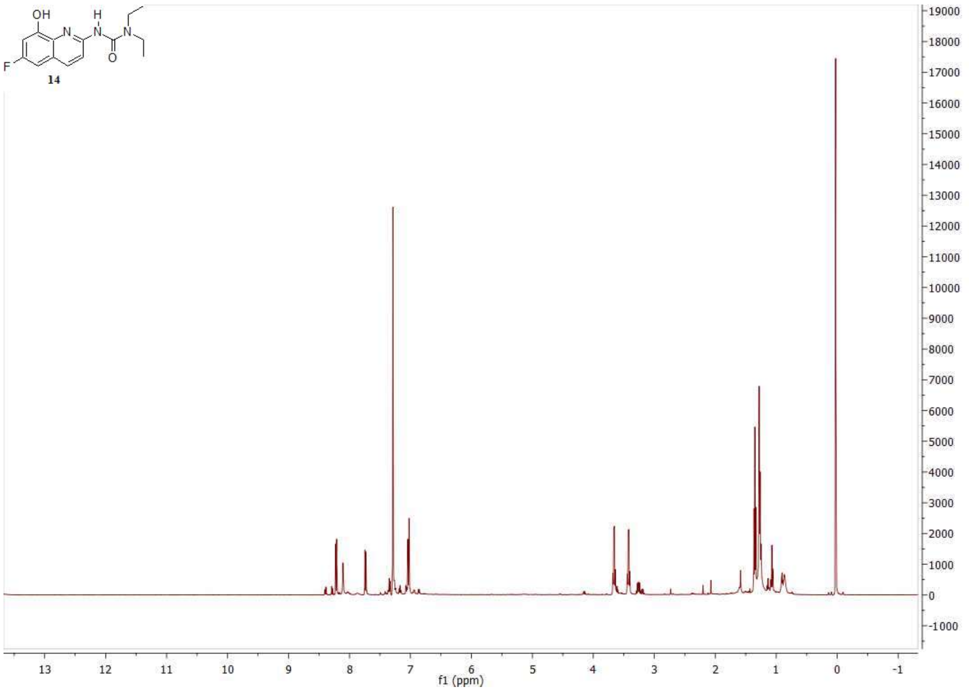

O
O
N
O
F
10a
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

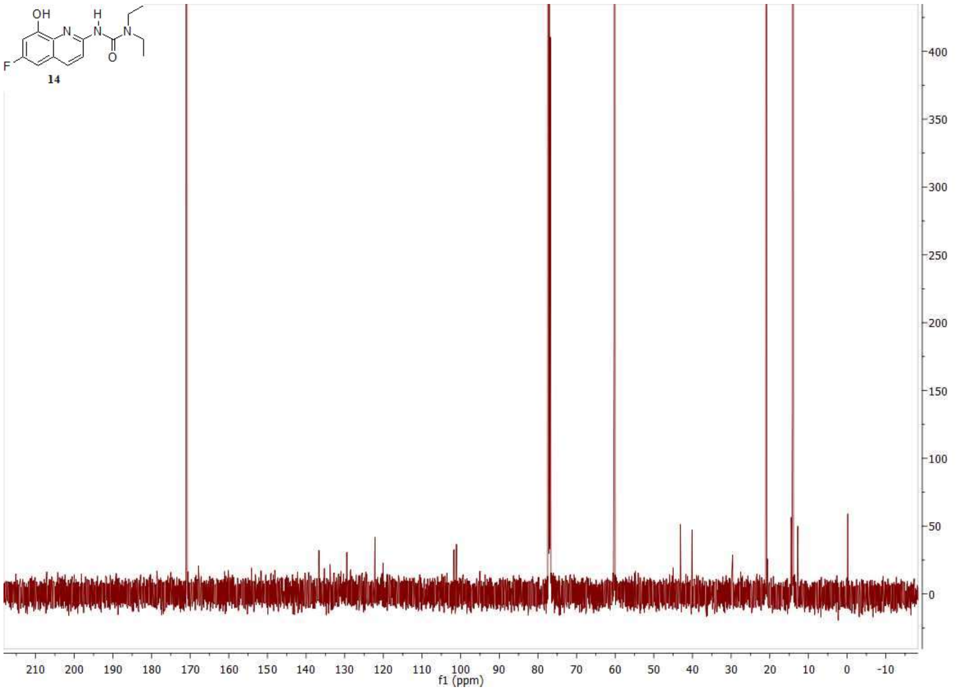

O
N
O
O
F
10b
30000
25000
20000
15000
10000
5000
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

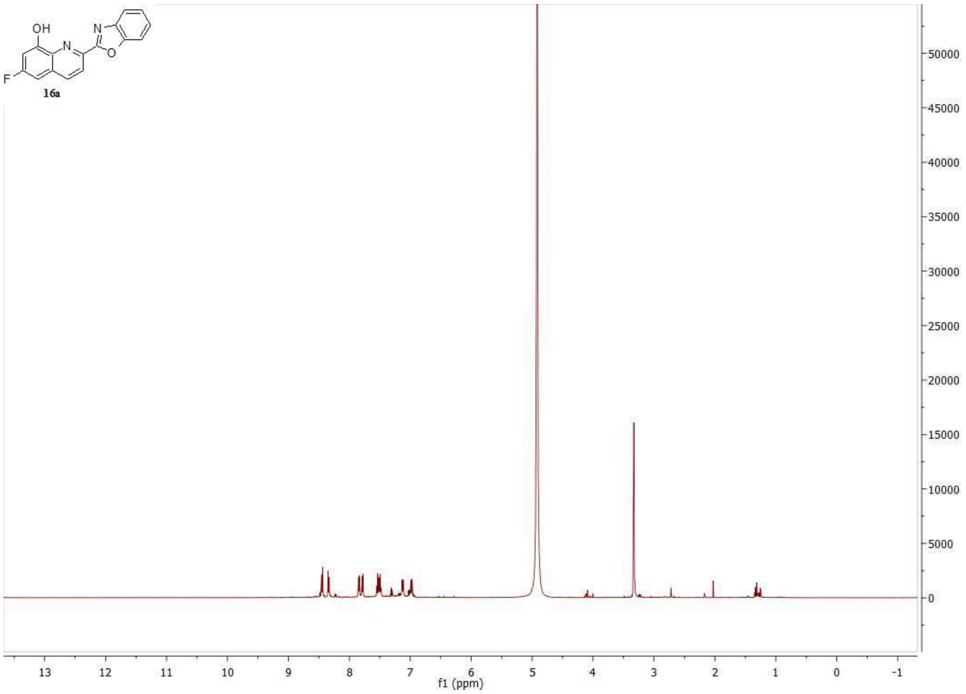

O
N
O
O
F
10b
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

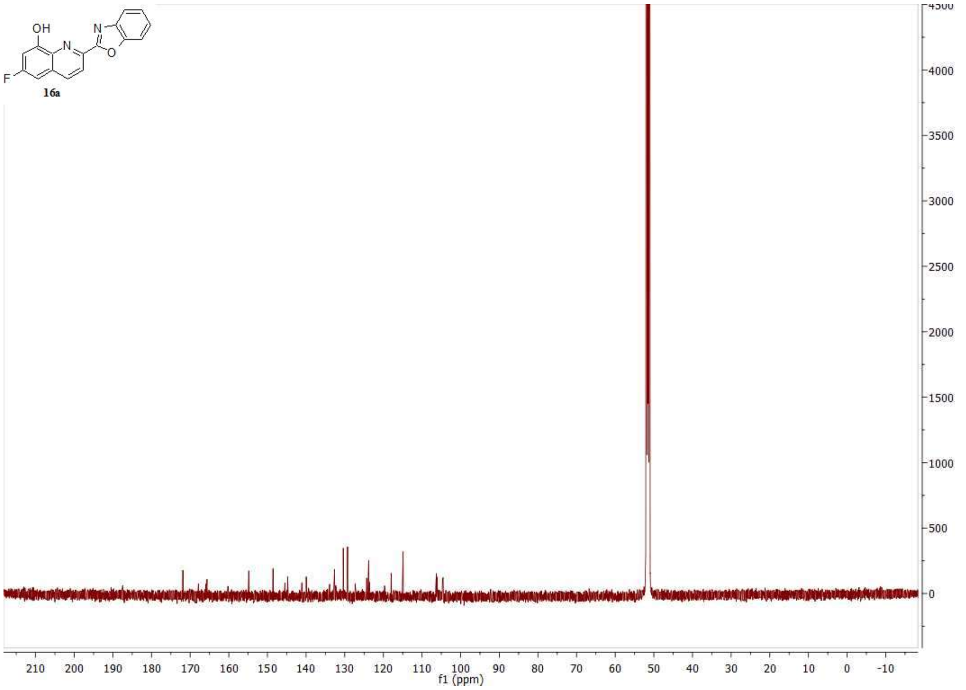

OH
H
N
N
O
O
F
13
160000
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

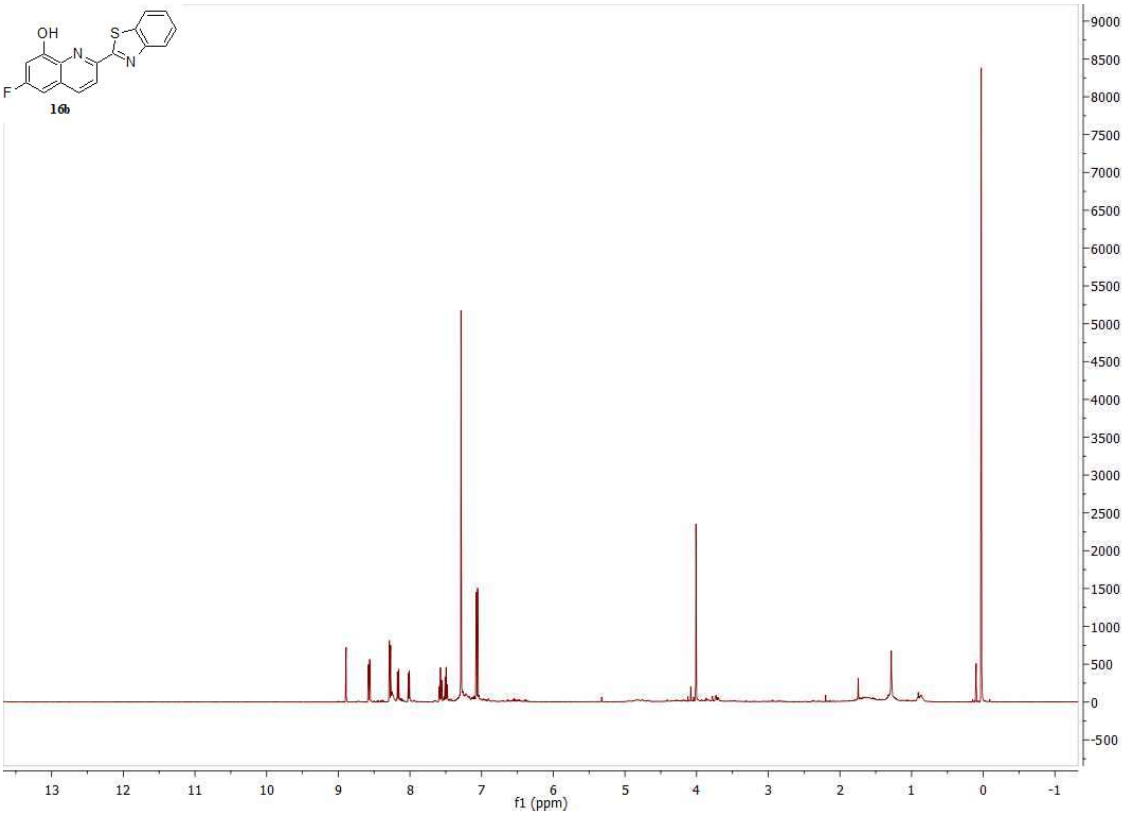

OH
H
N
N
O
O
F
13
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
H
N
N
N
O
F
14
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

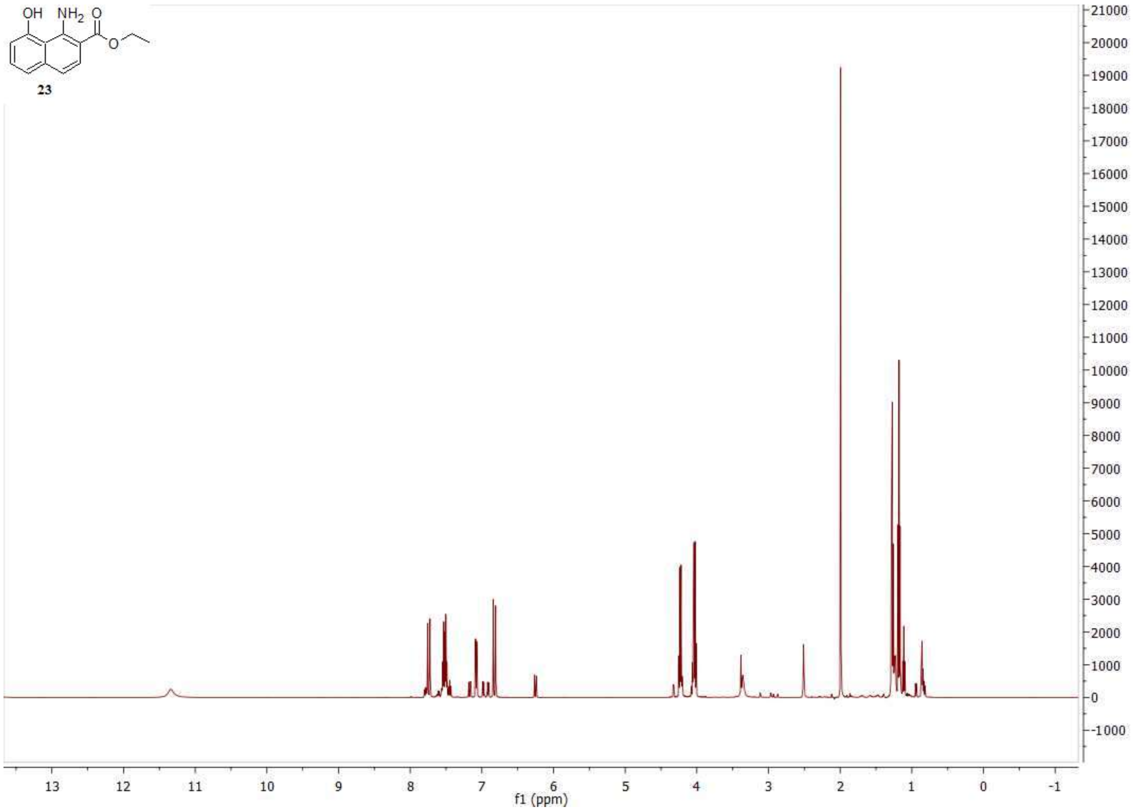

OH
H
N
N
N
O
F
14
400
350
300
250
200
150
100
50
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
N
N
O
F
16a
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

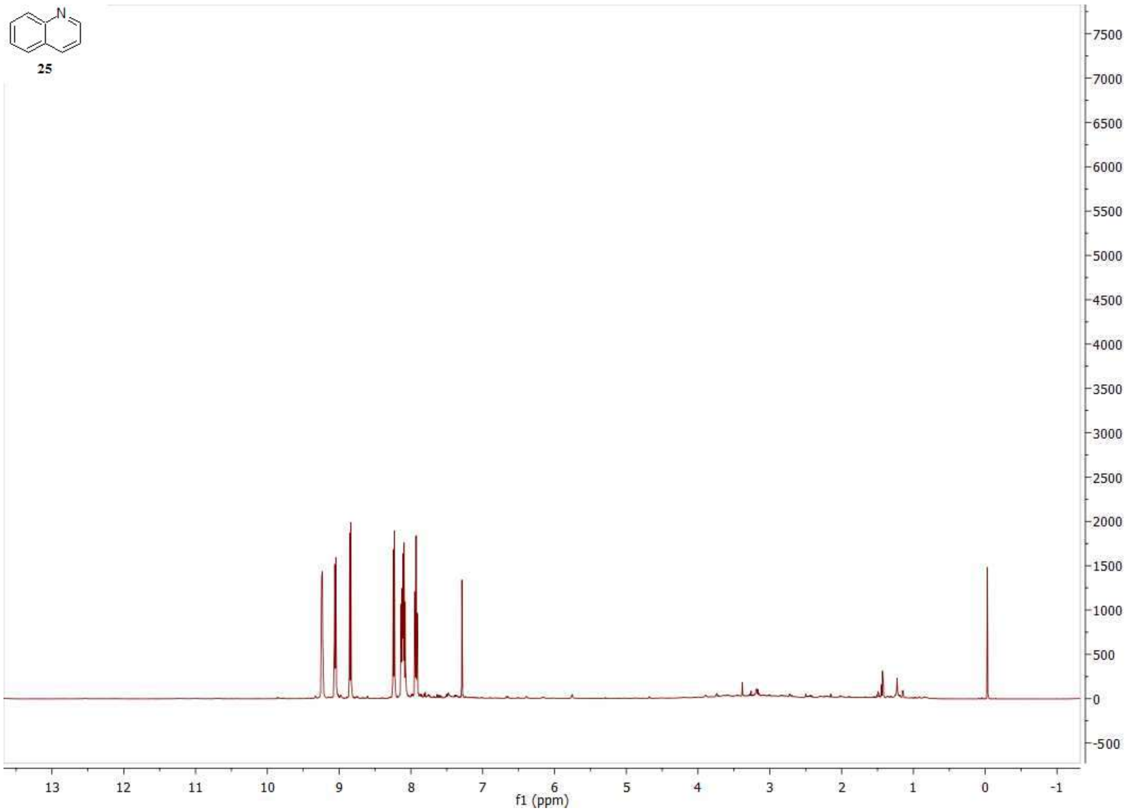

OH
N
N
O
F
16a
4500
4000
3500
3000
2500
2000
1500
1000
500
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)



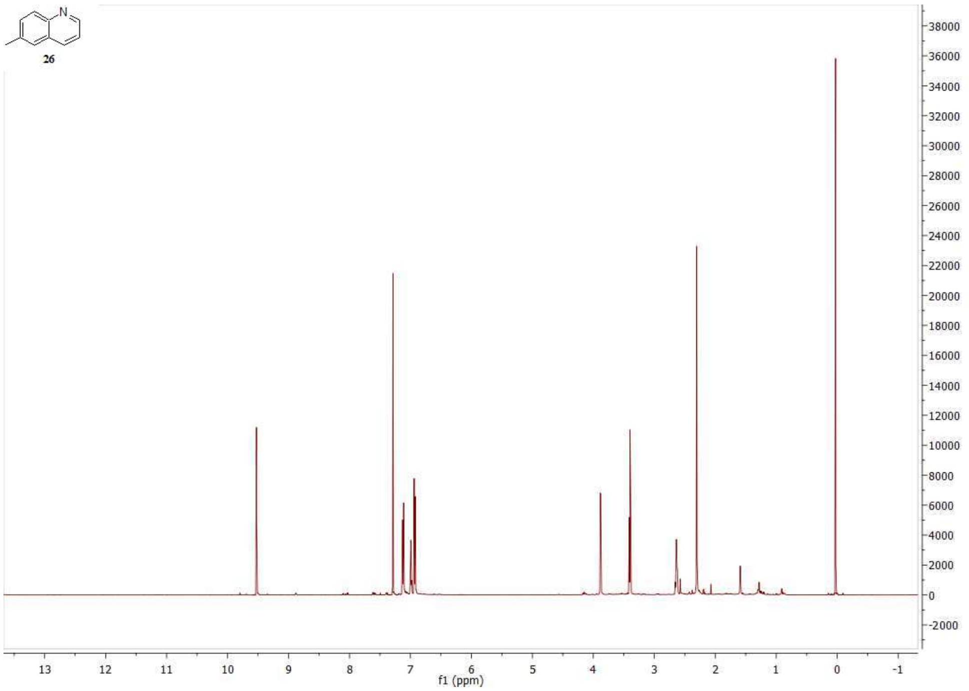
OH
N
S
N
F
16b
9000
8500
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

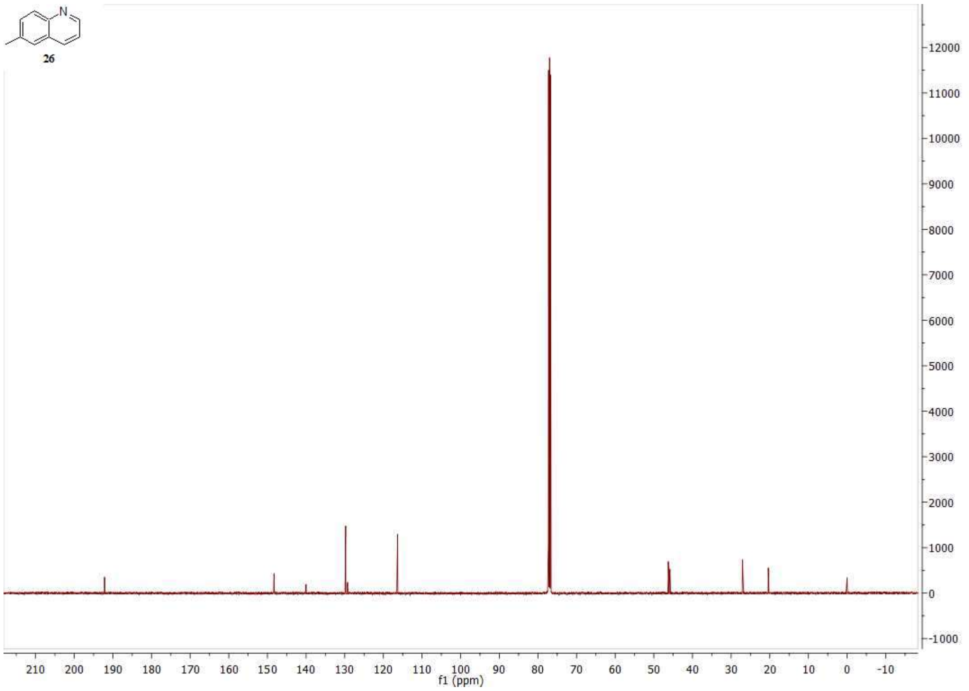


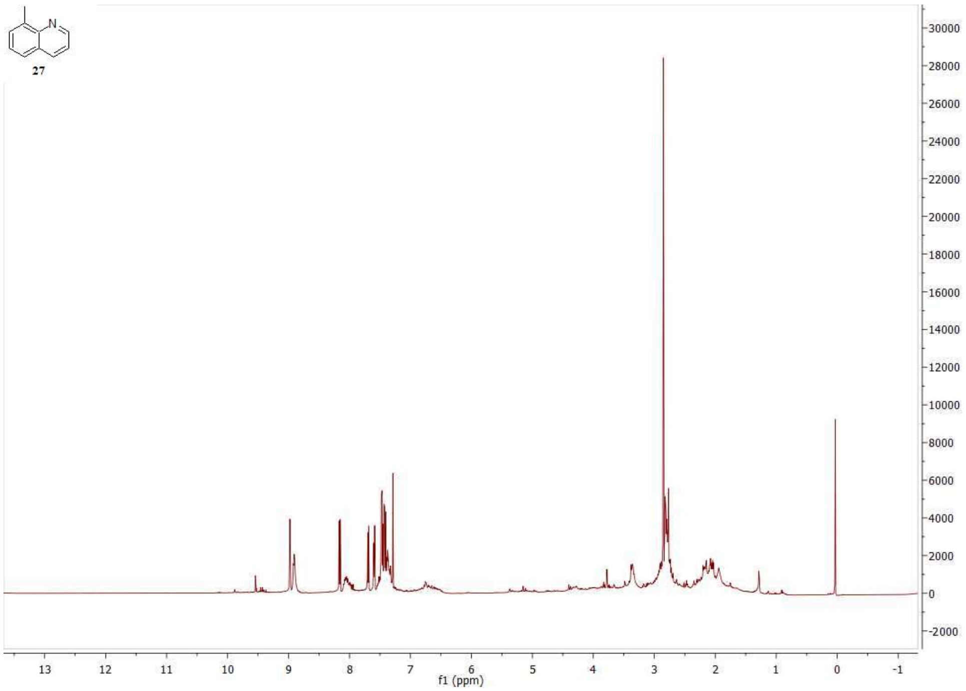
OH
NH2
O
O
23
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

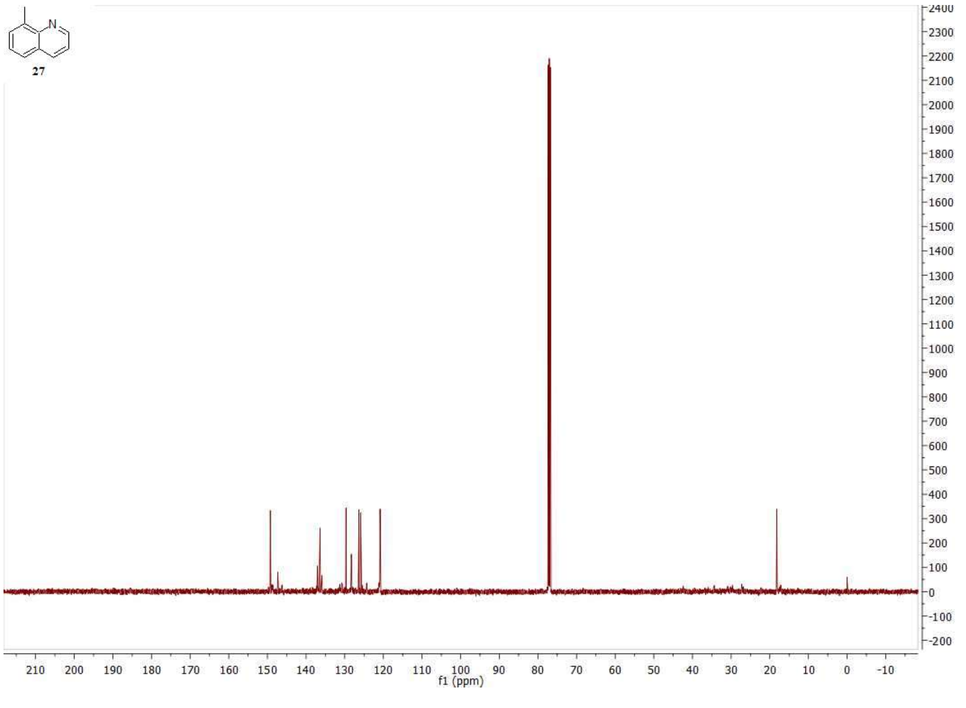

25

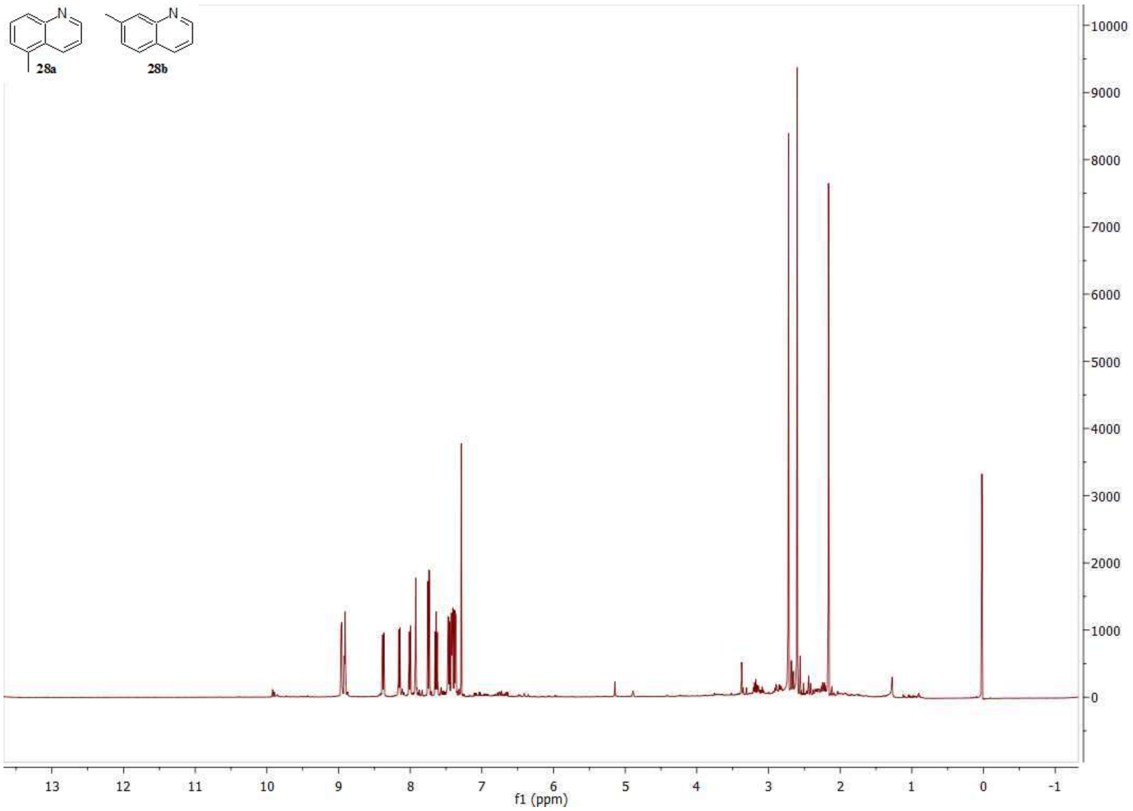
N
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

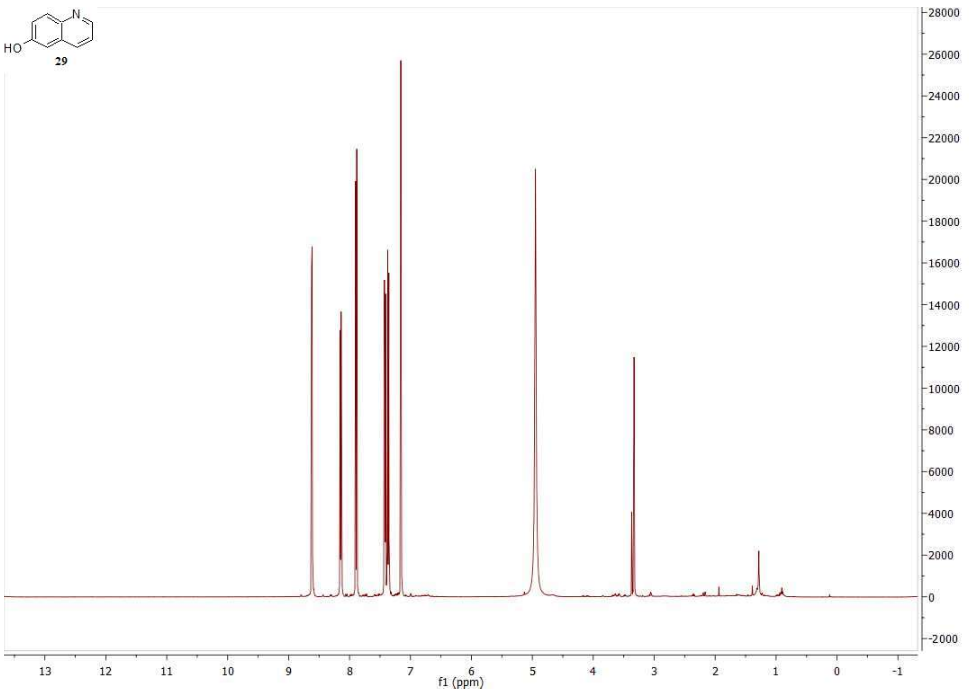

N
26
38000
36000
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


N
26
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

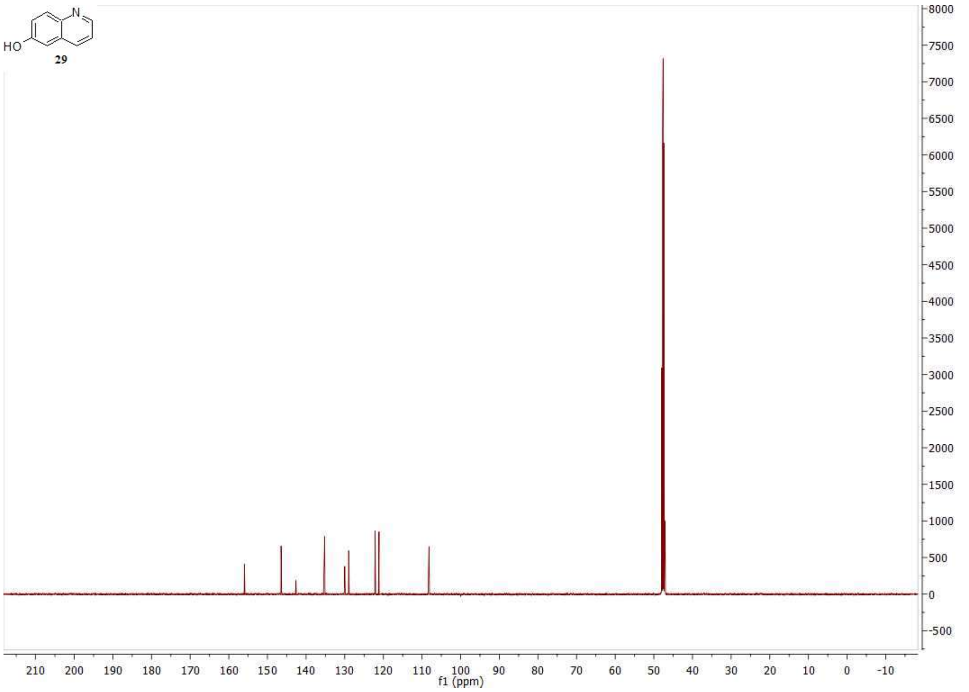

N
27
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


N
27
2400
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


N
N
28a
28b
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


29

HO
N
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


29

HO
N
8000
7500
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
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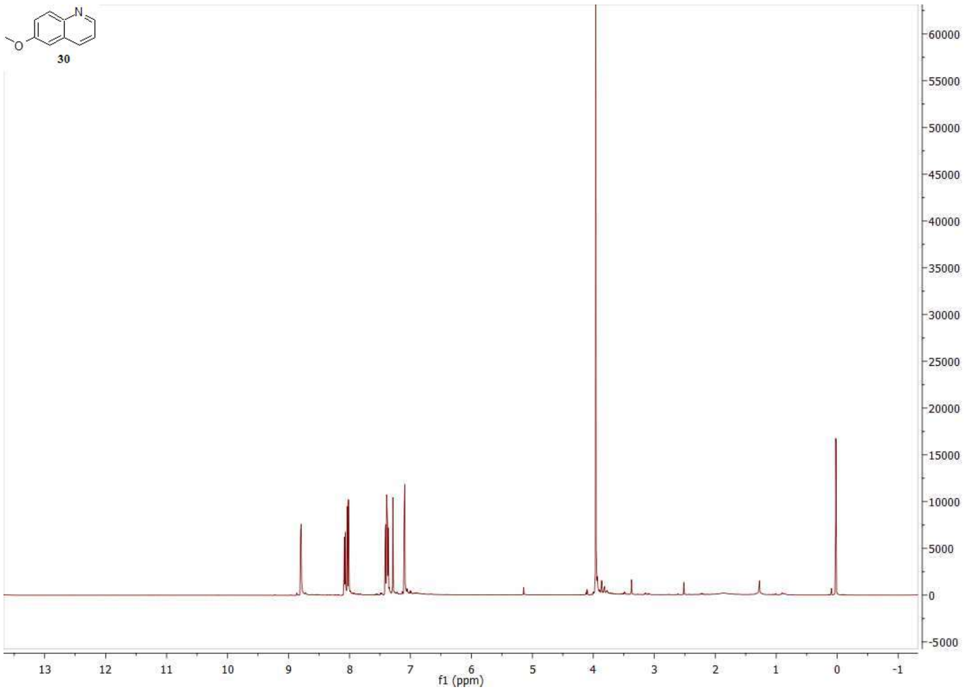
0
-10
f1 (ppm)


N
O
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55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
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-5000
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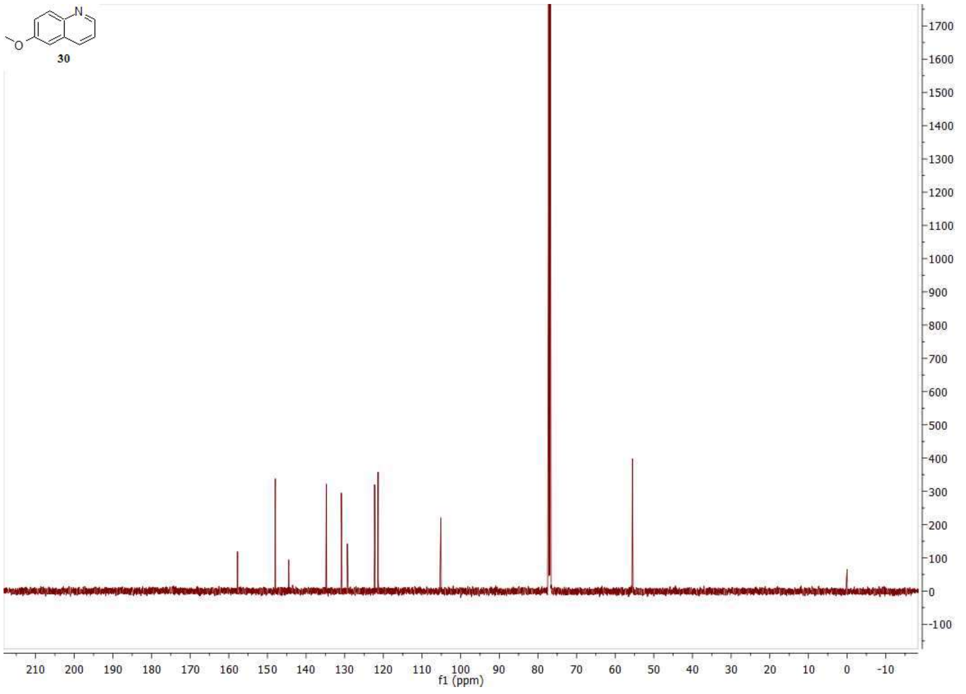
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)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1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
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140
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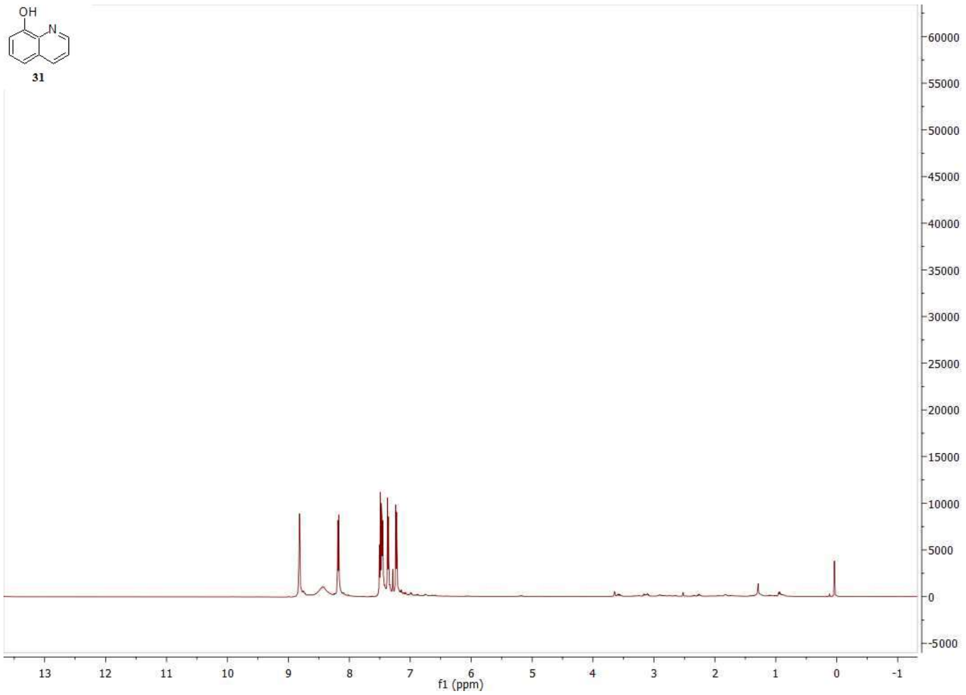
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
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31
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55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
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-5000
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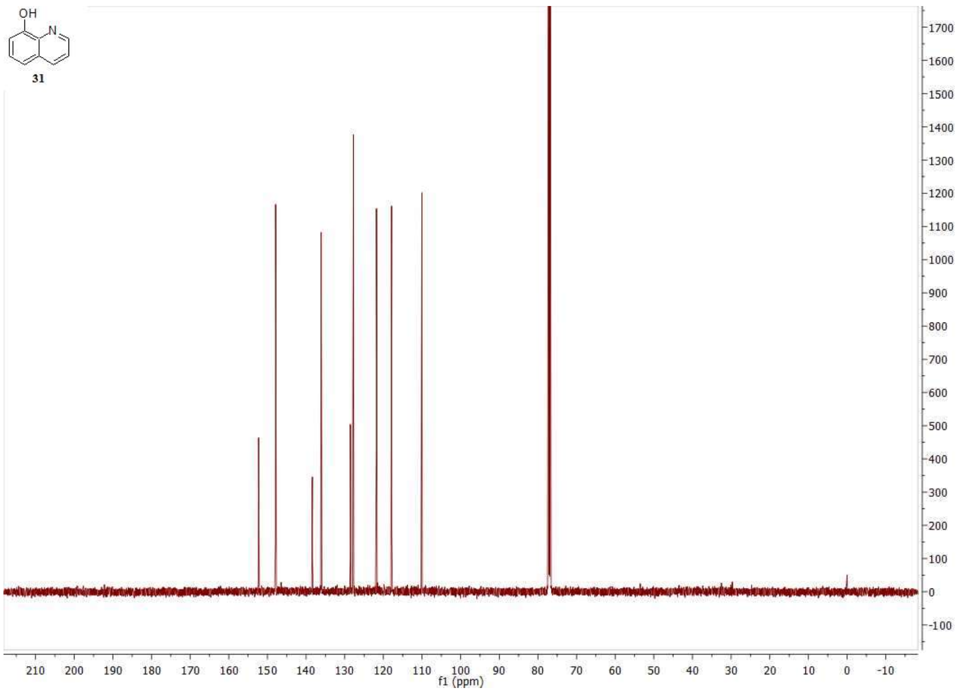
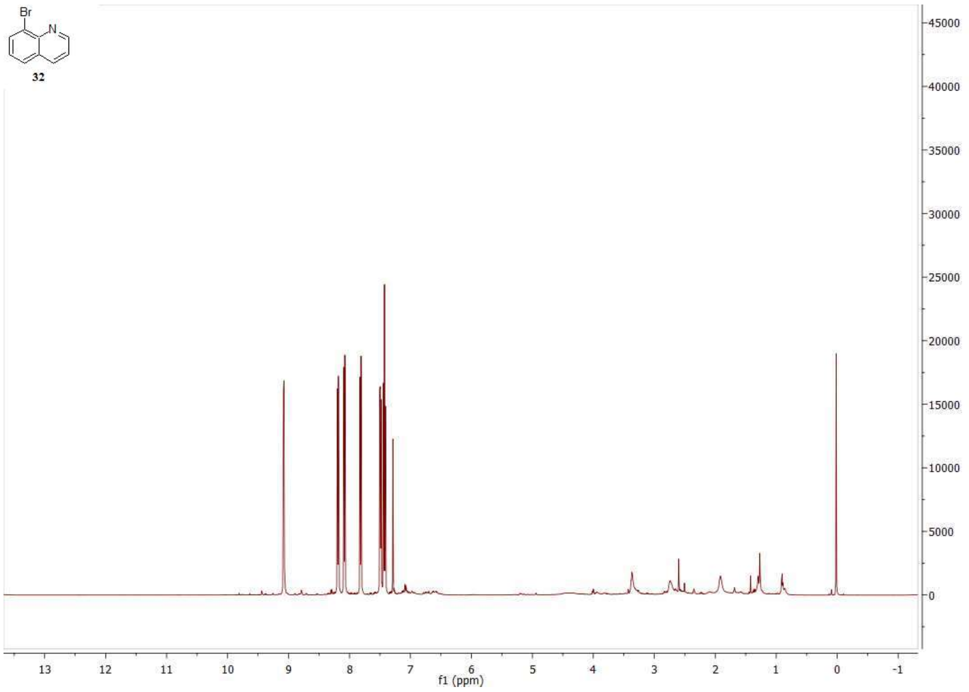
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


OH
N
31
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


Br
N
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40000
35000
30000
25000
20000
15000
10000
5000
0
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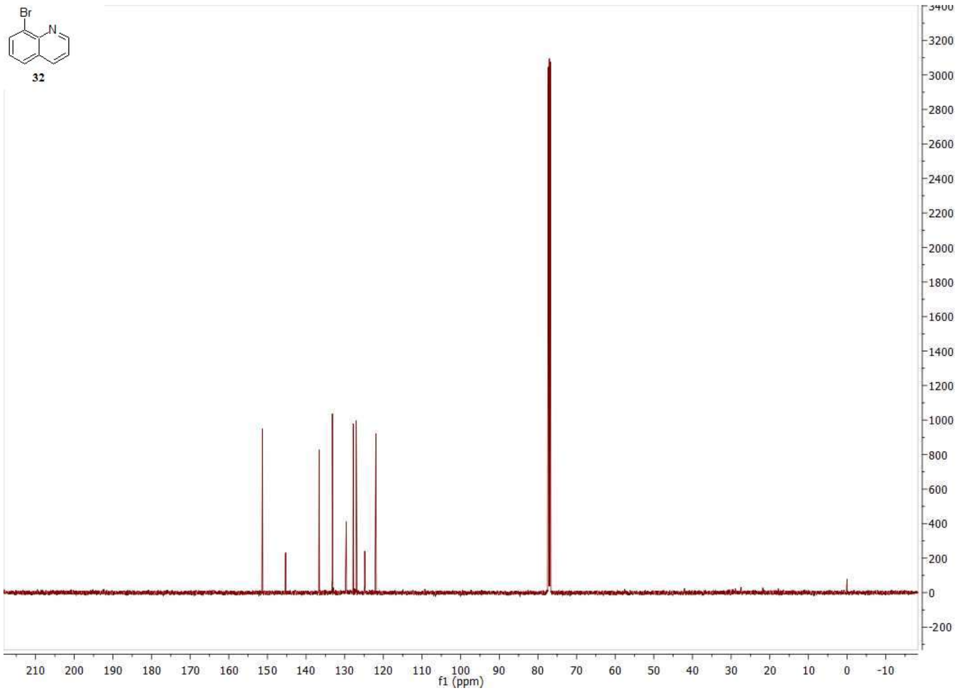
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


Br
N
32
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210
200
190
180
170
160
150
140
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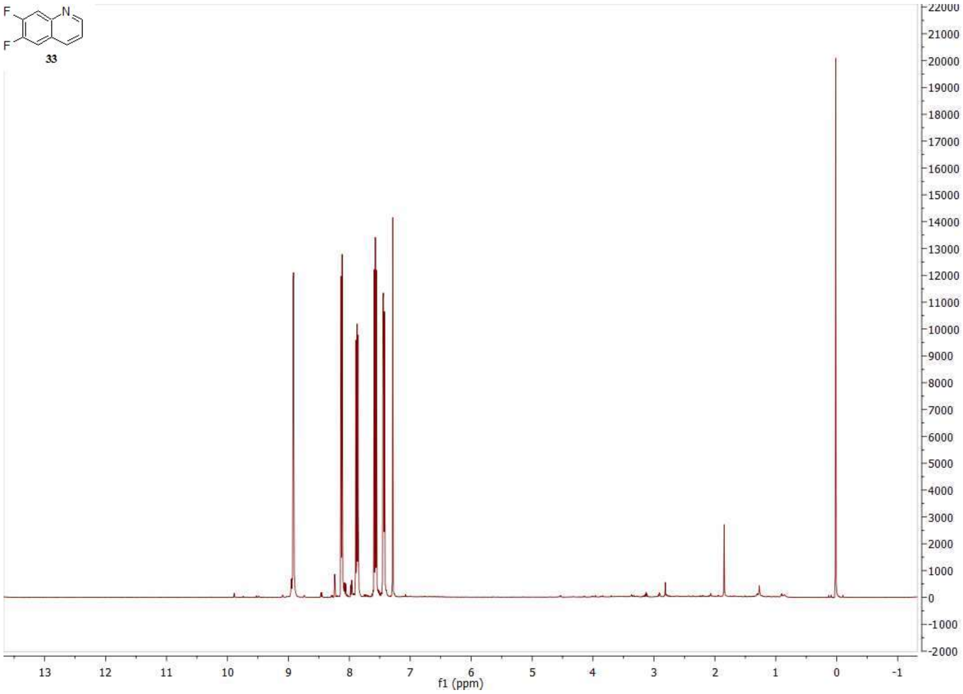
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


F
F
N
33
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
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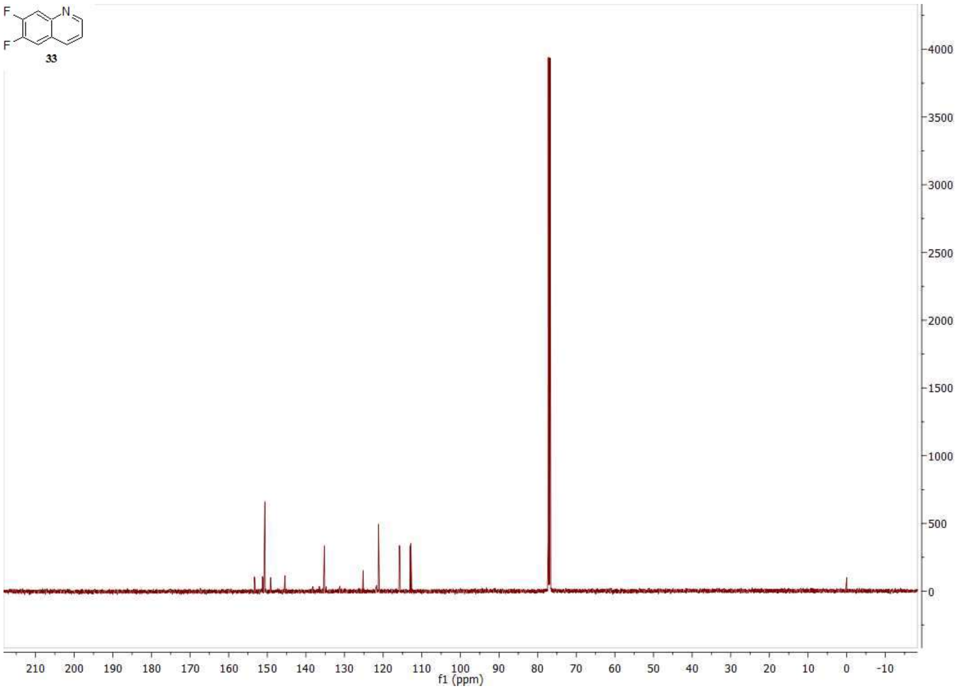
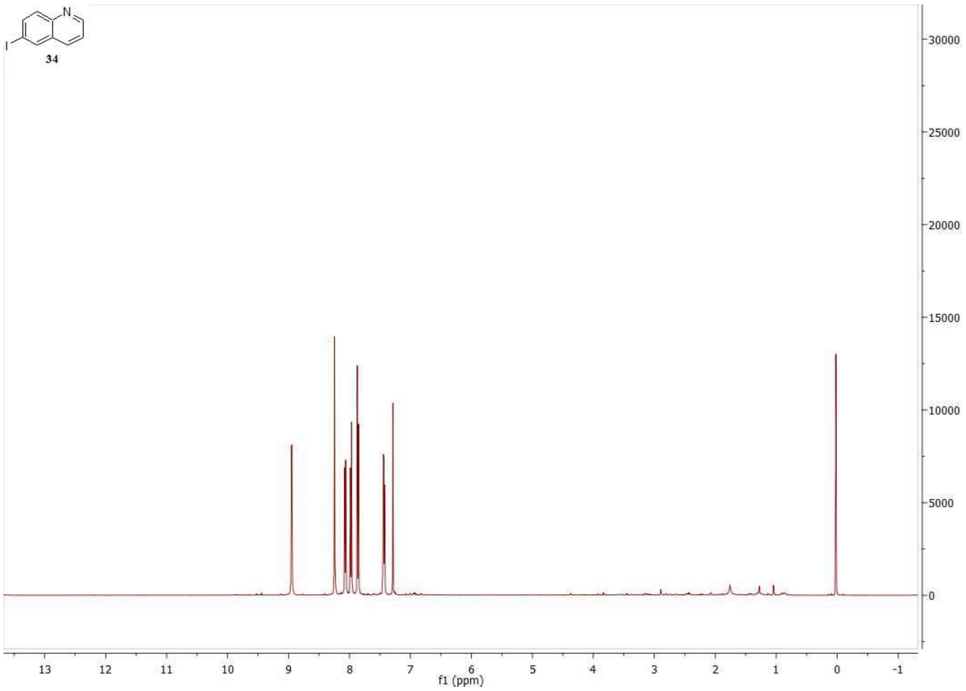
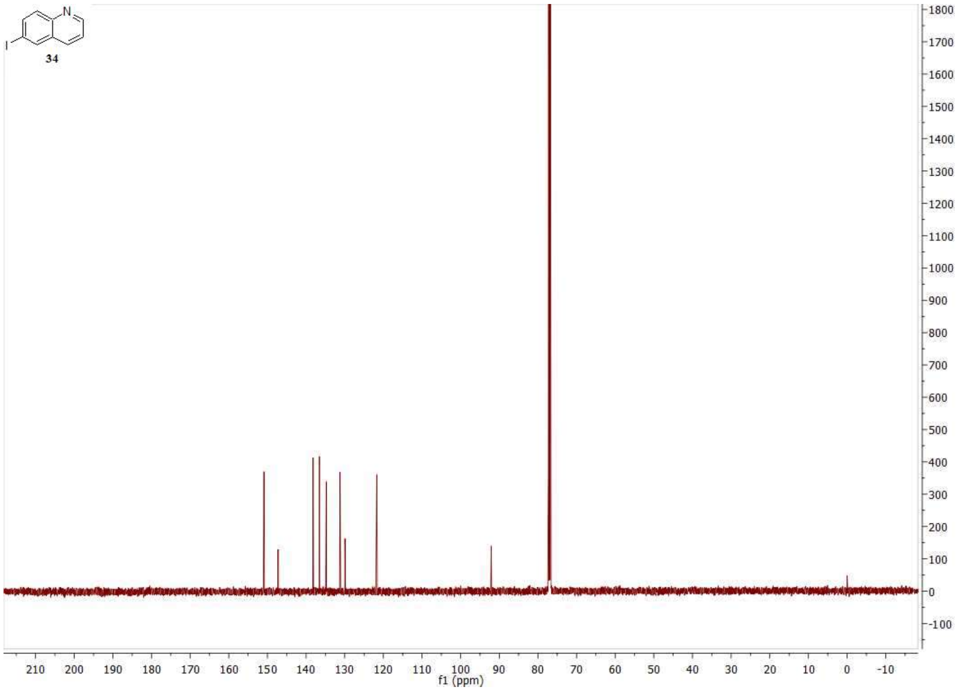
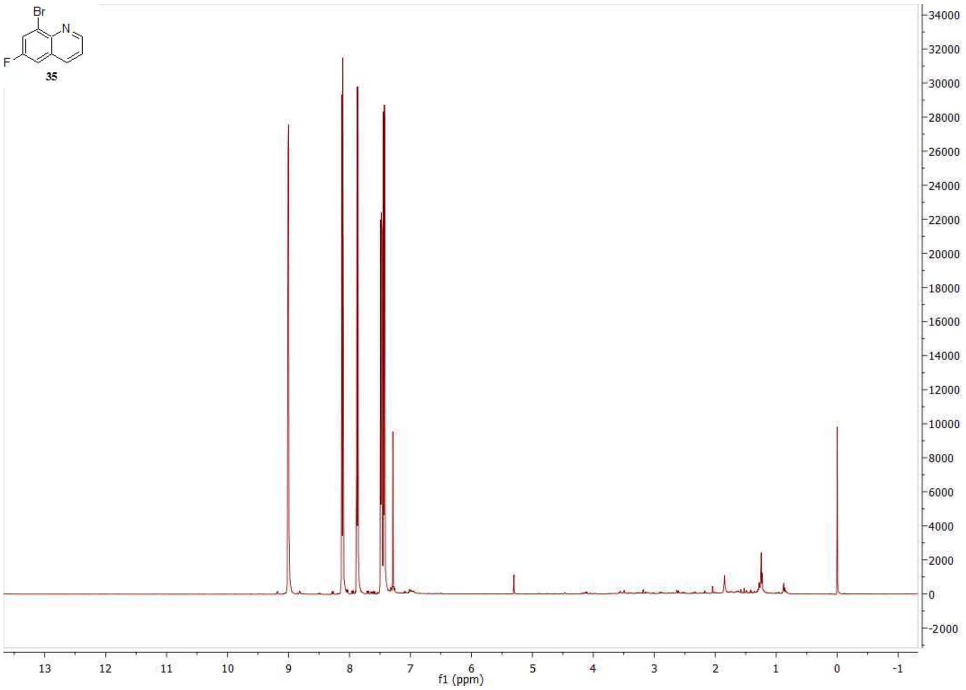
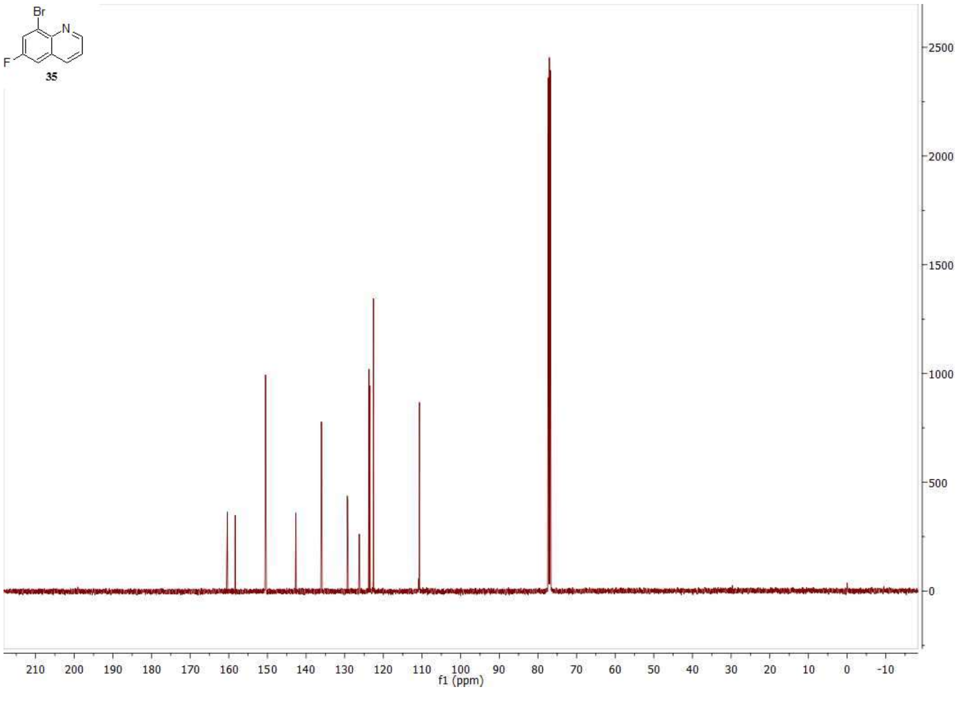
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

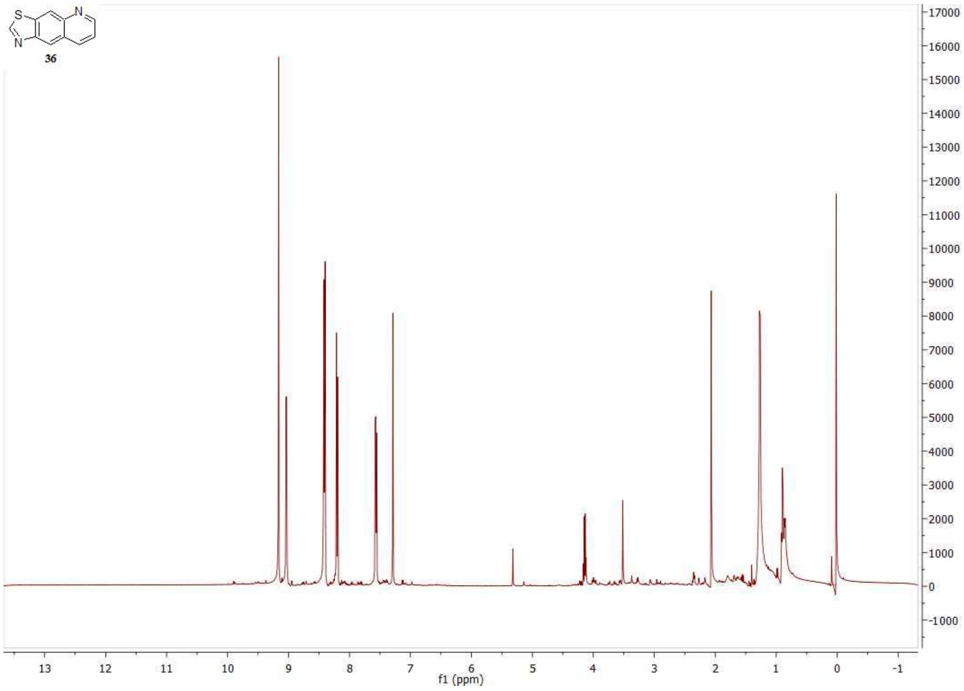

F
F
N
33
4000
3500
3000
2500
2000
1500
1000
500
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

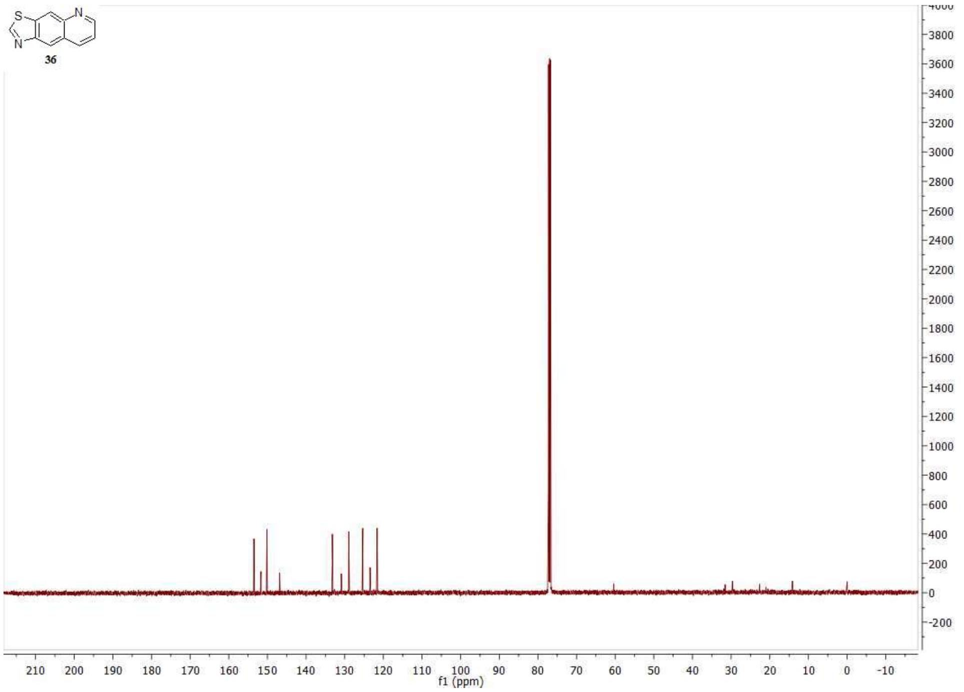

N
I
34
30000
25000
20000
15000
10000
5000
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

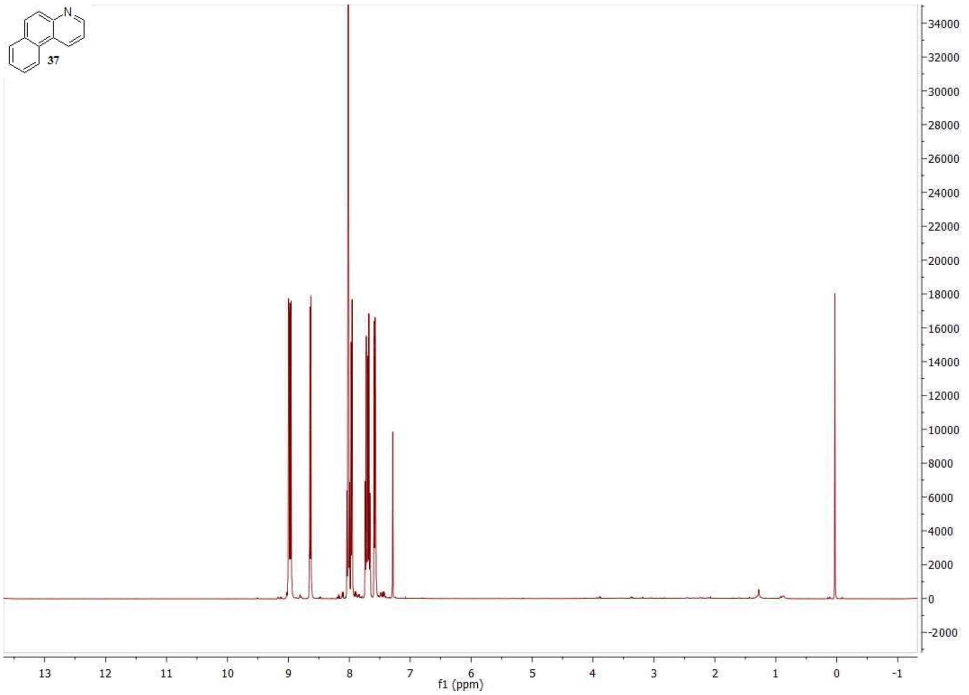

N
I
34
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

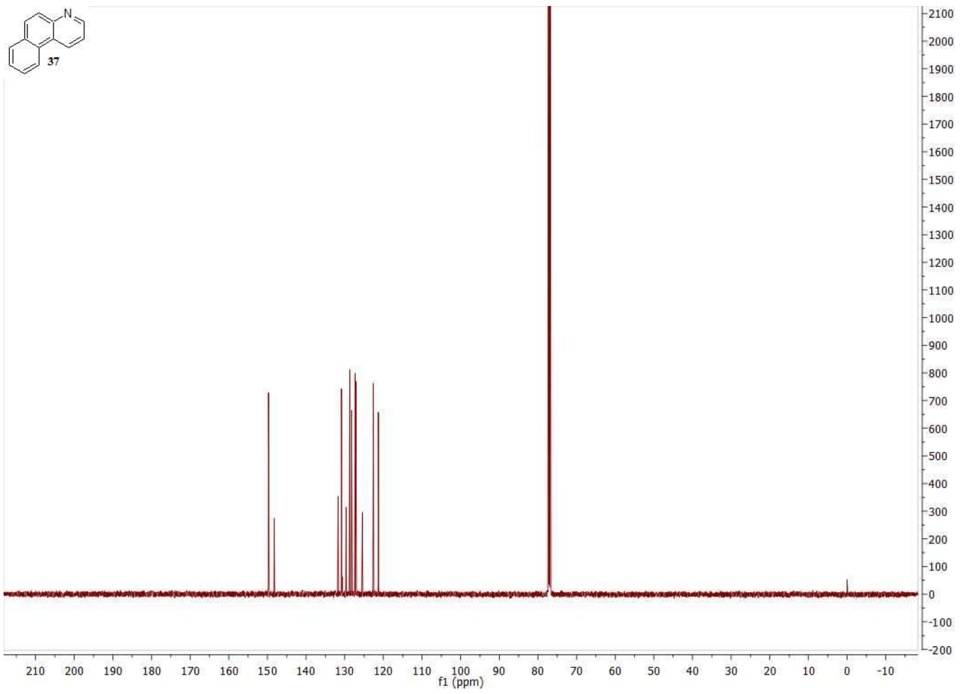

Br
N
F
35
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

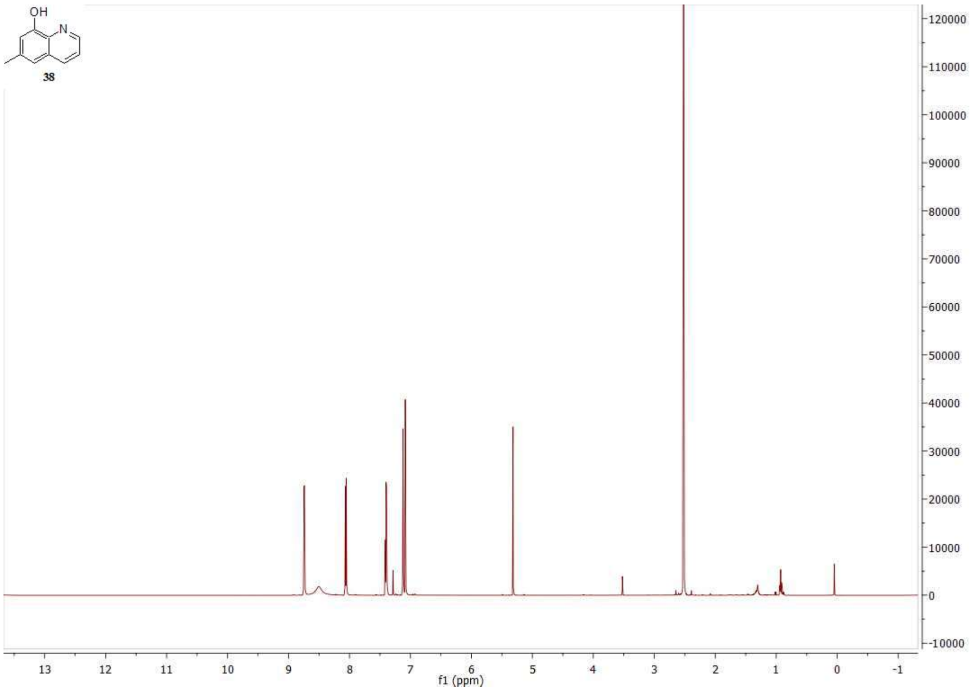

Br
N
F
35
2500
2000
1500
1000
500
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


S
N
36
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


S
N
36
4000
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


37
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


37
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
N
38
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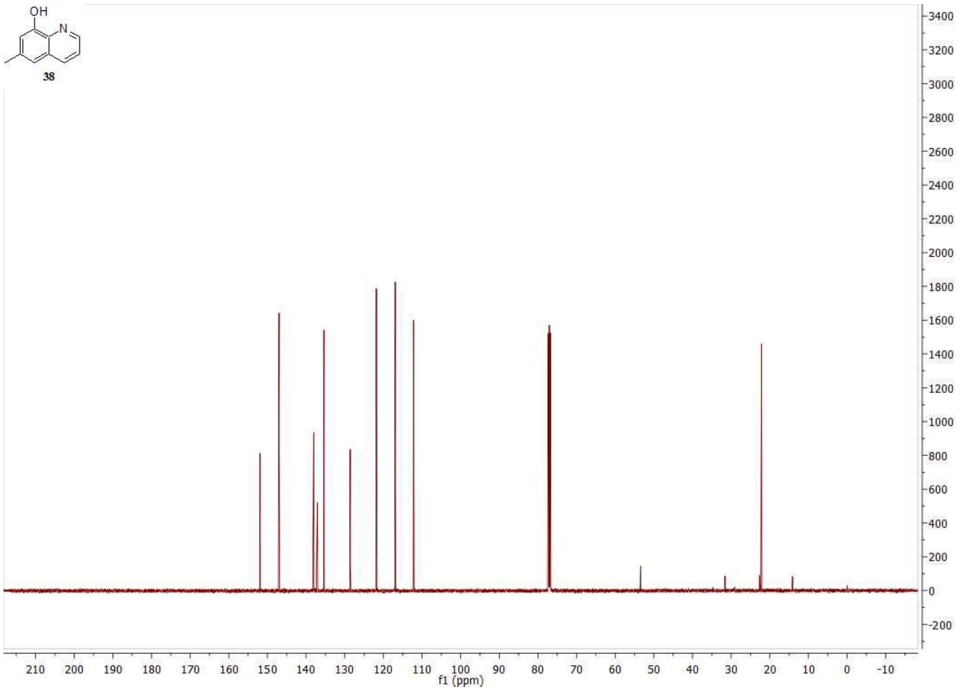
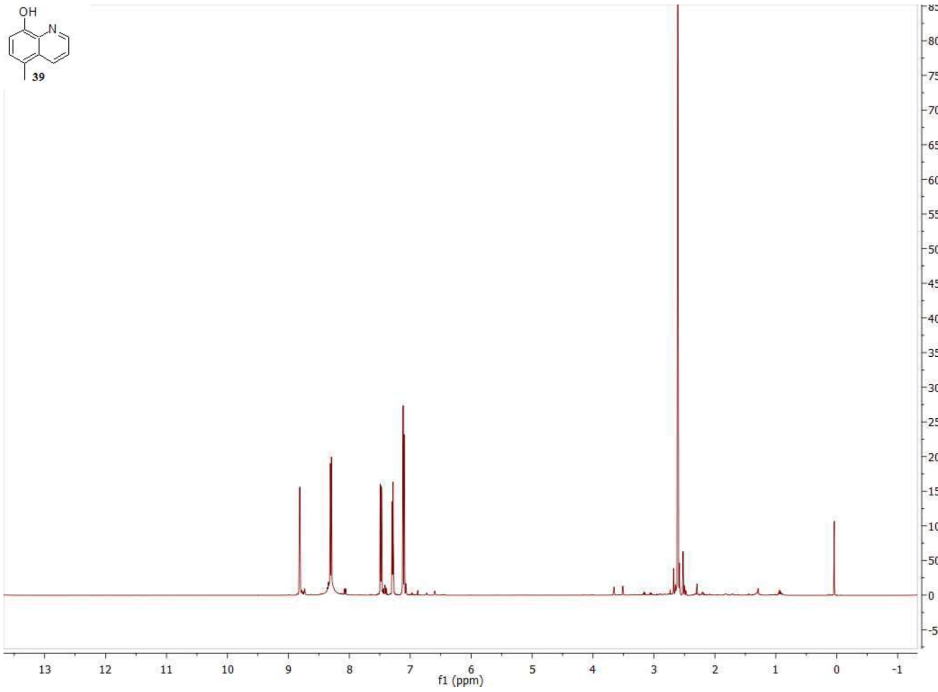
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


OH
N
38
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
N
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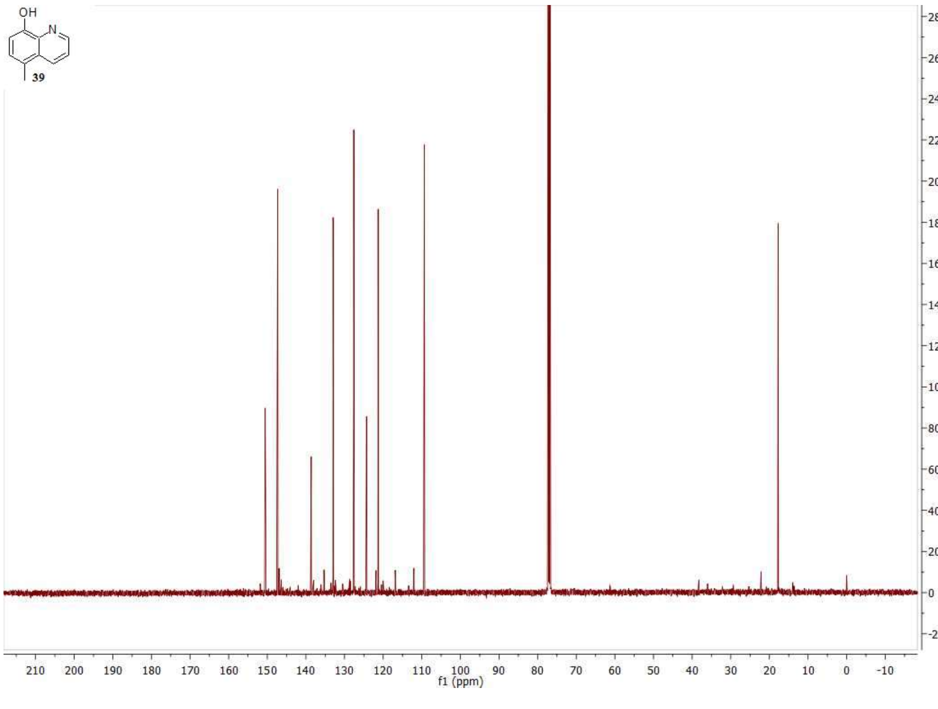
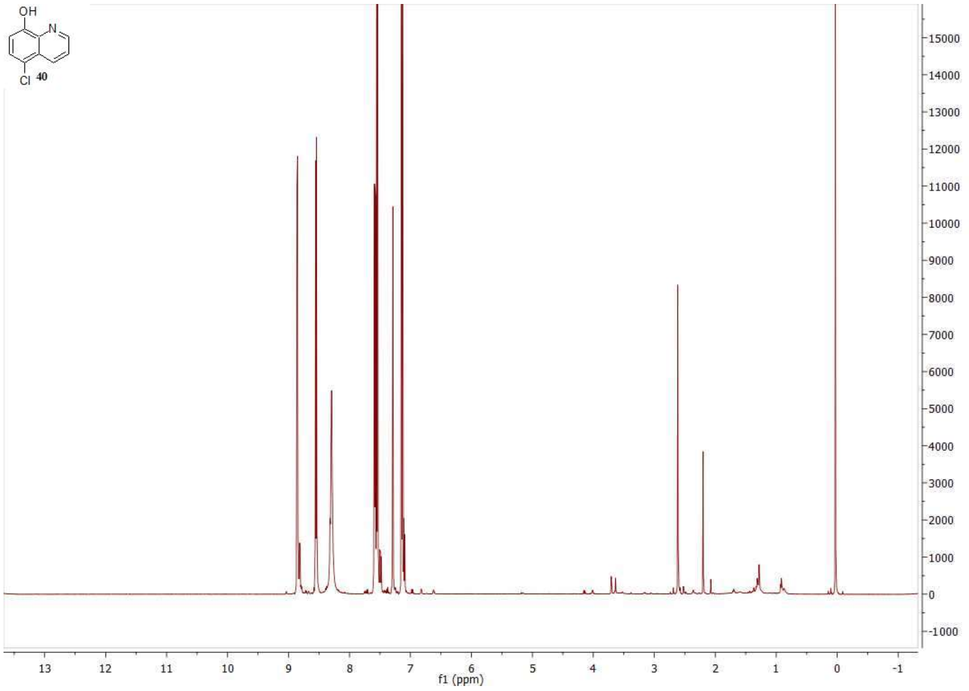
80000
75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


OH
N
39
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
N
Cl
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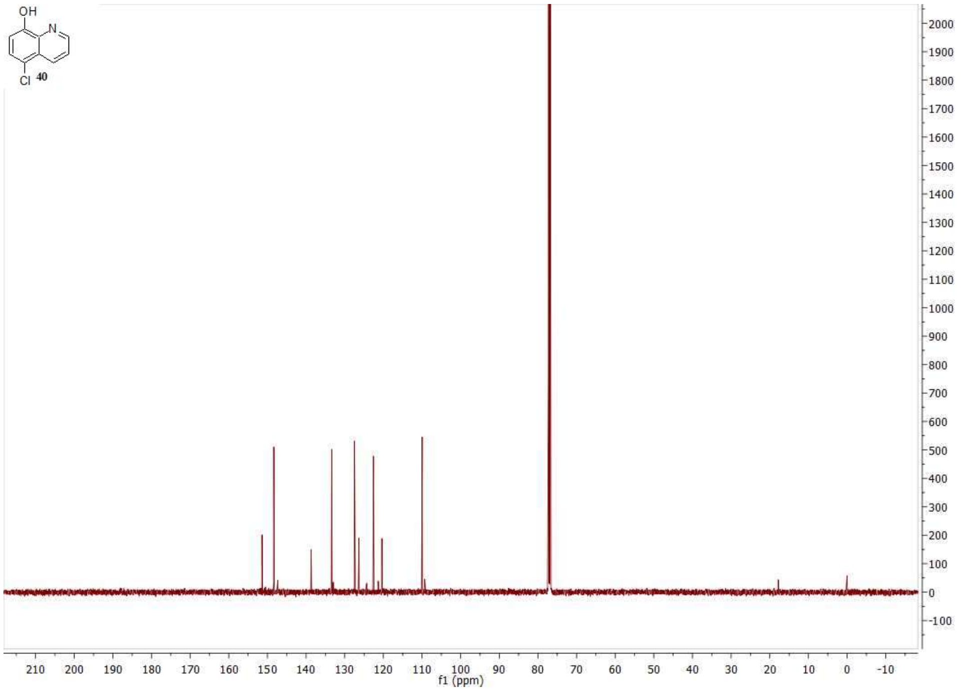
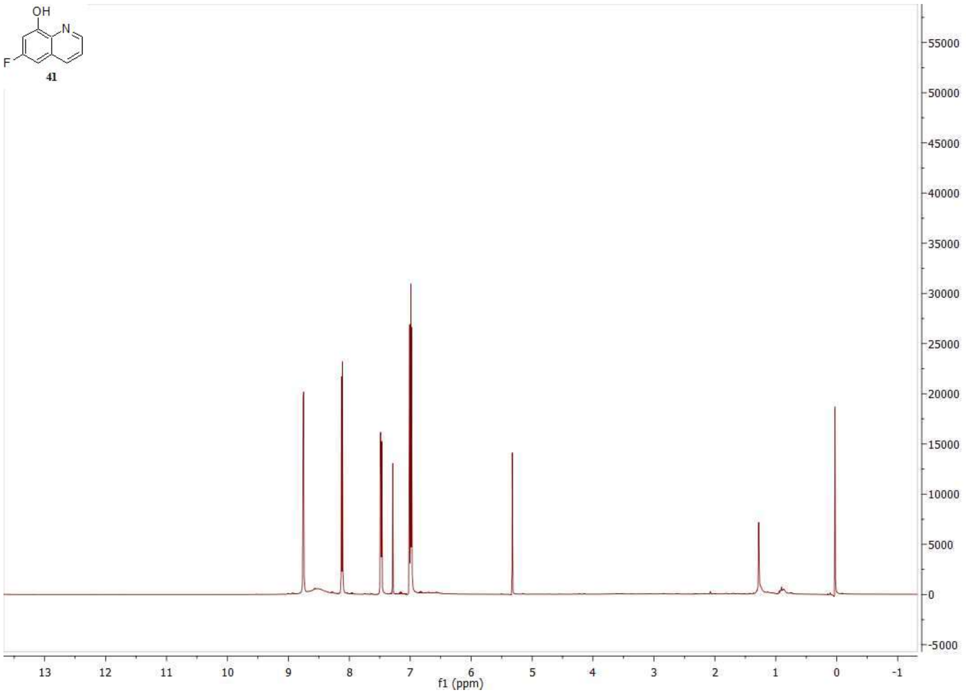
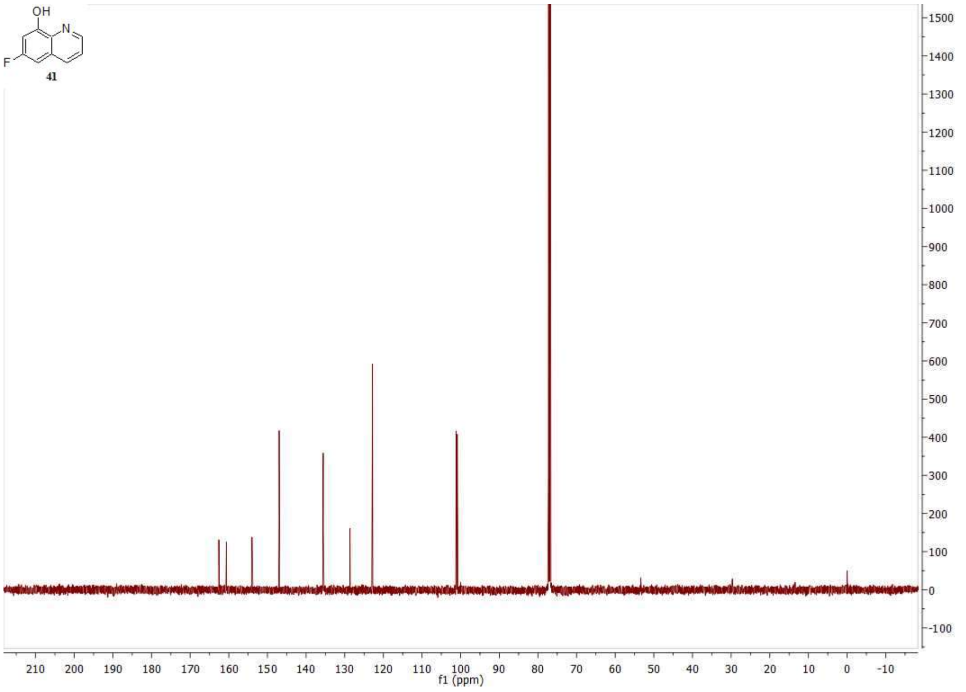
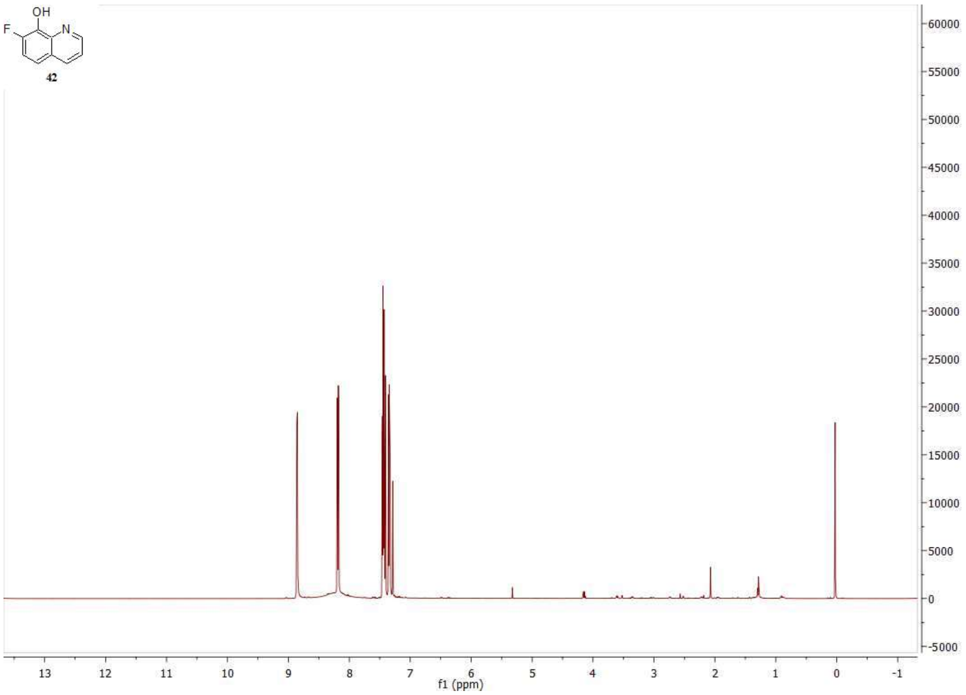
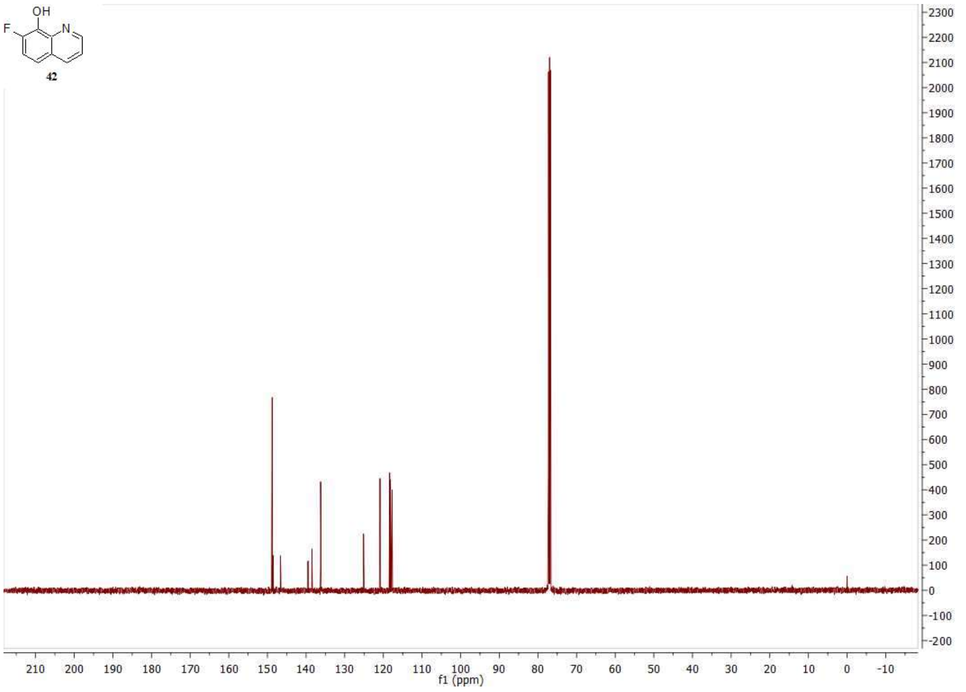
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


OH
N
Cl
40
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
N
F
41
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


OH
N
F
41
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


OH
F
N
42
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


OH
F
N
42
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
210
200
190
180
170
160
150
140
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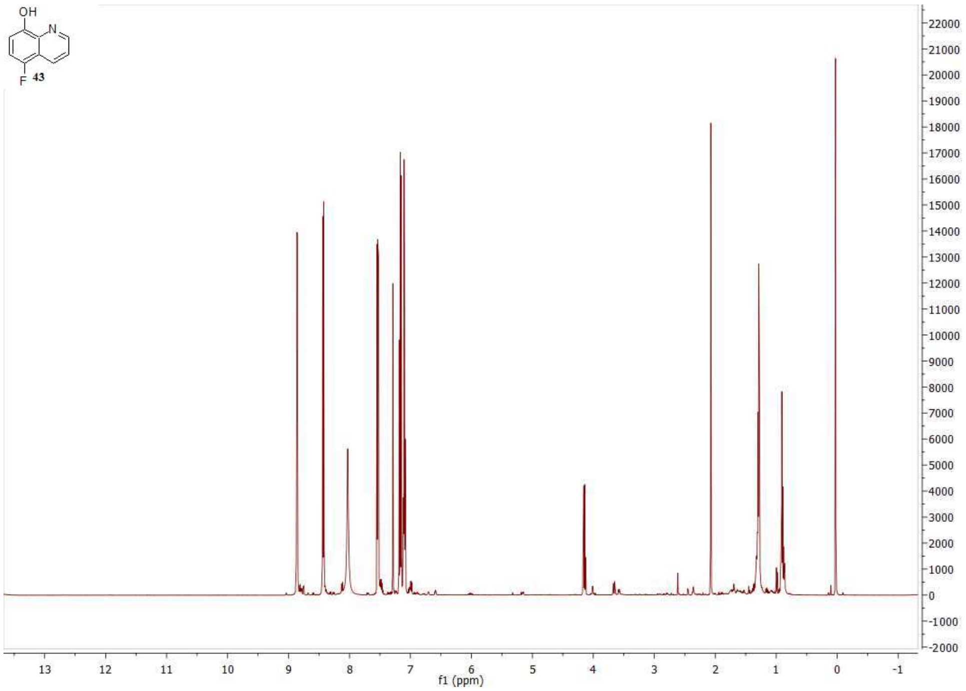
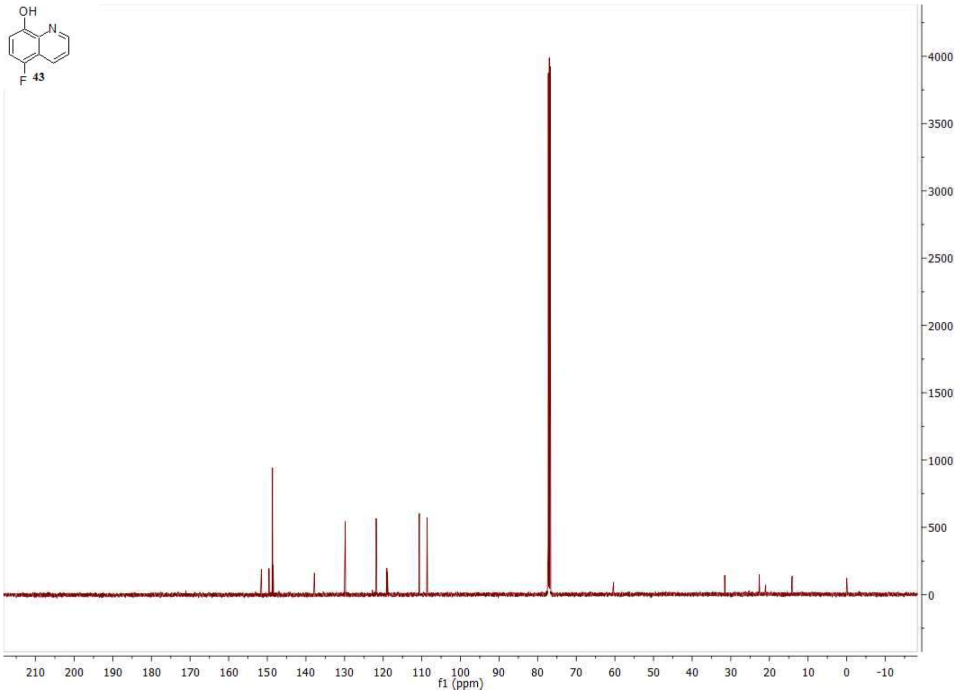
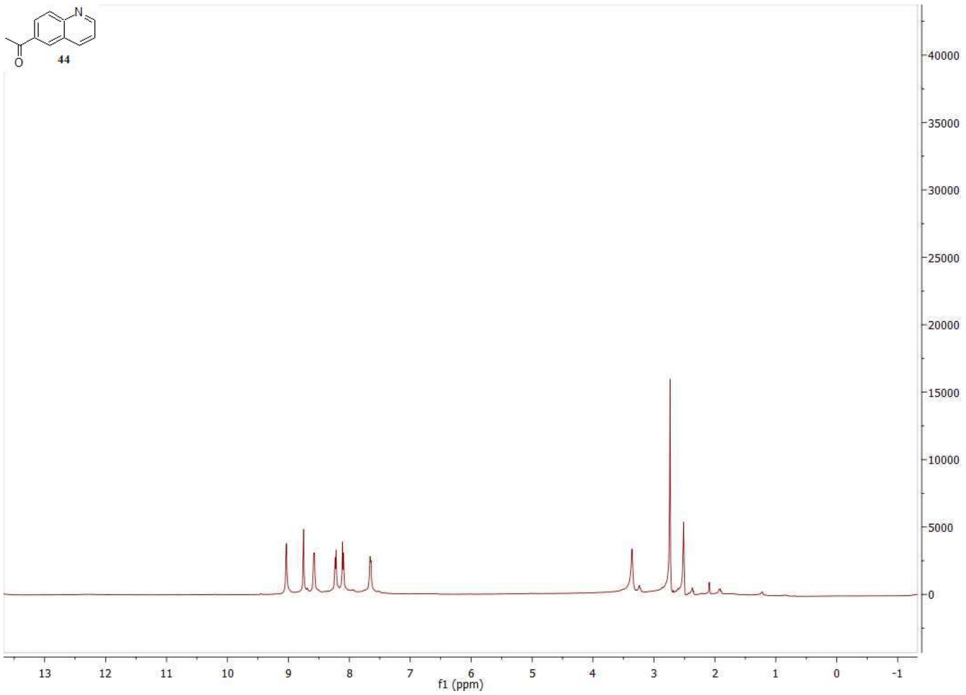
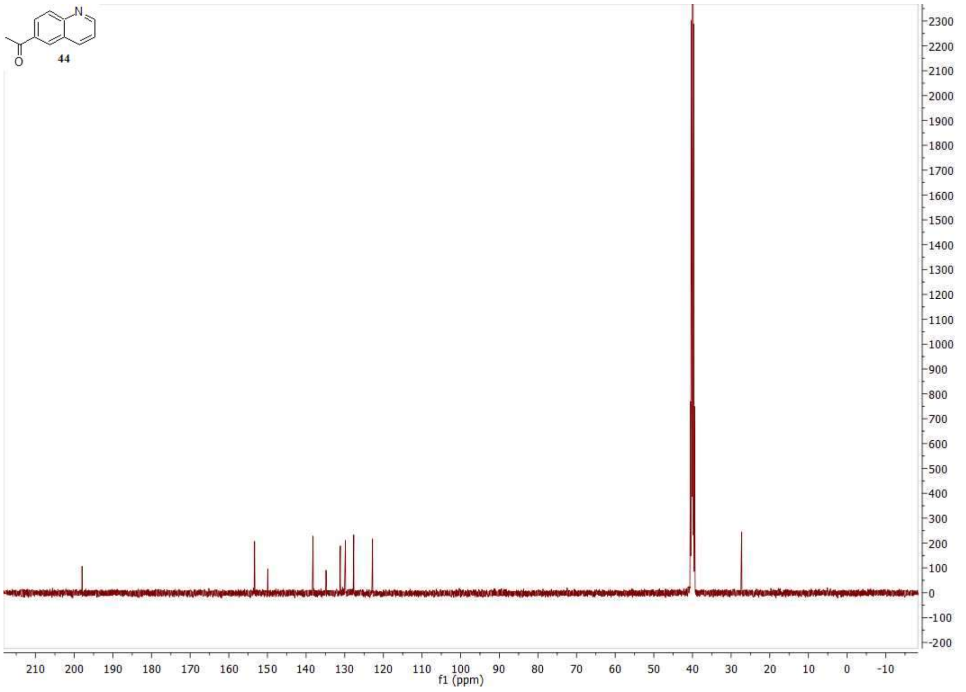
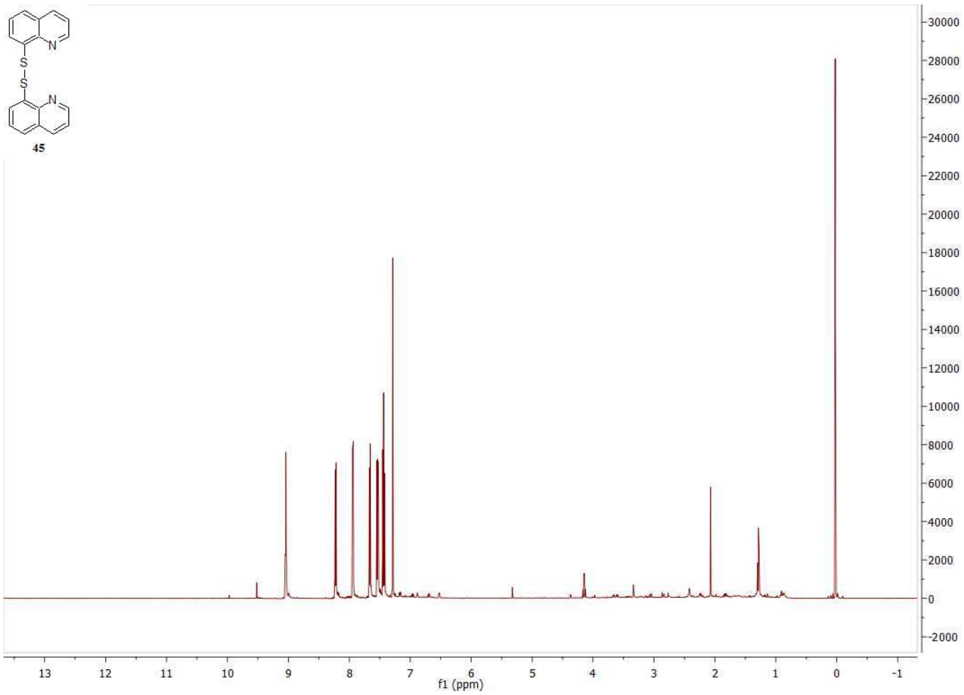
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

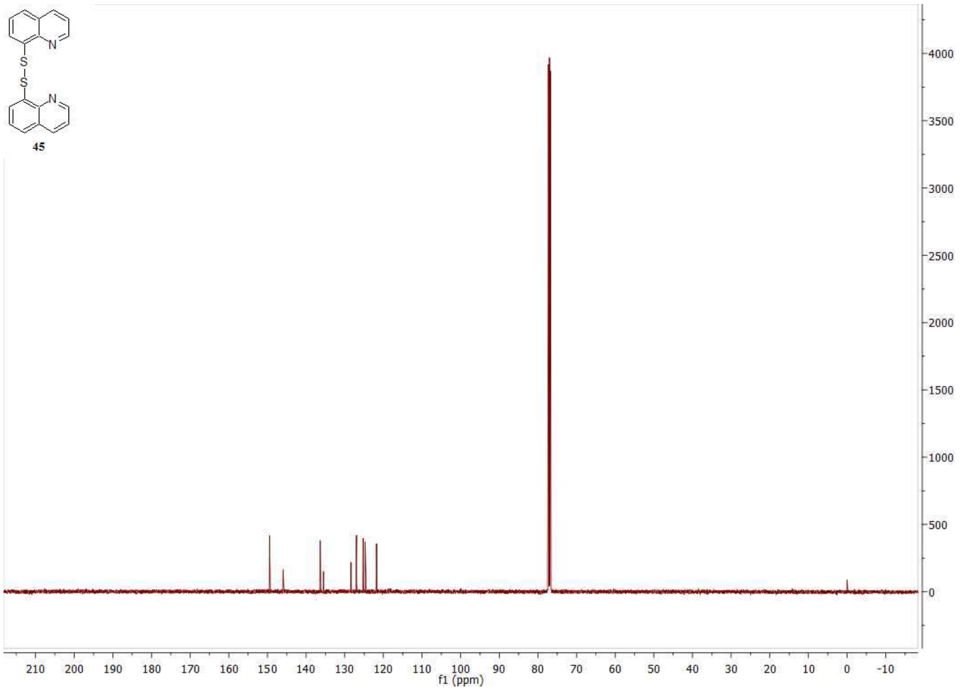

OH
N
F
43
22000
21000
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
-2000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)

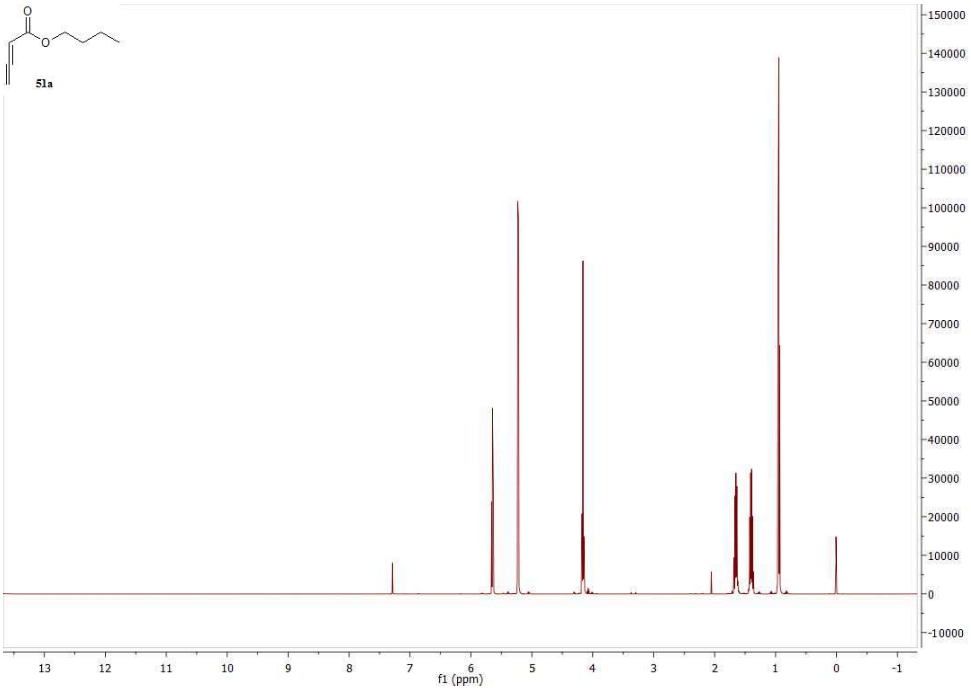

OH
N
F
43
4000
3500
3000
2500
2000
1500
1000
500
0
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

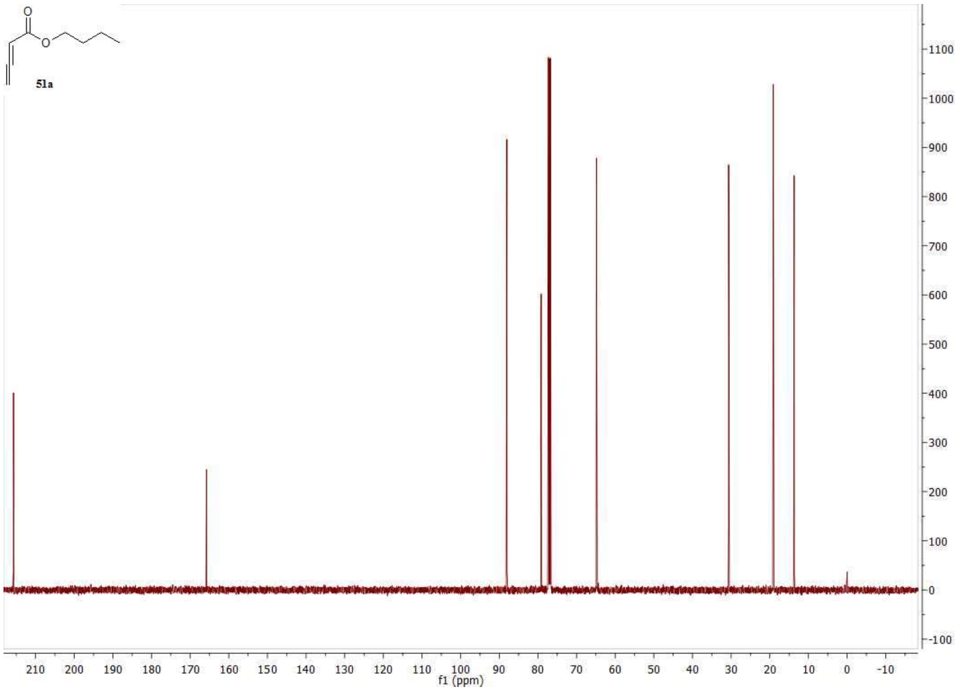

N
O
44
40000
35000
30000
25000
20000
15000
10000
5000
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


N
O
44
2300
2200
2100
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


N
S
S
N
45
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
-2000


N
S
S
N
45
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
4000
3500
3000
2500
2000
1500
1000
500
0


51a
f1 (ppm)
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
150000
140000
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000


51a
f1 (ppm)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
1100
1000
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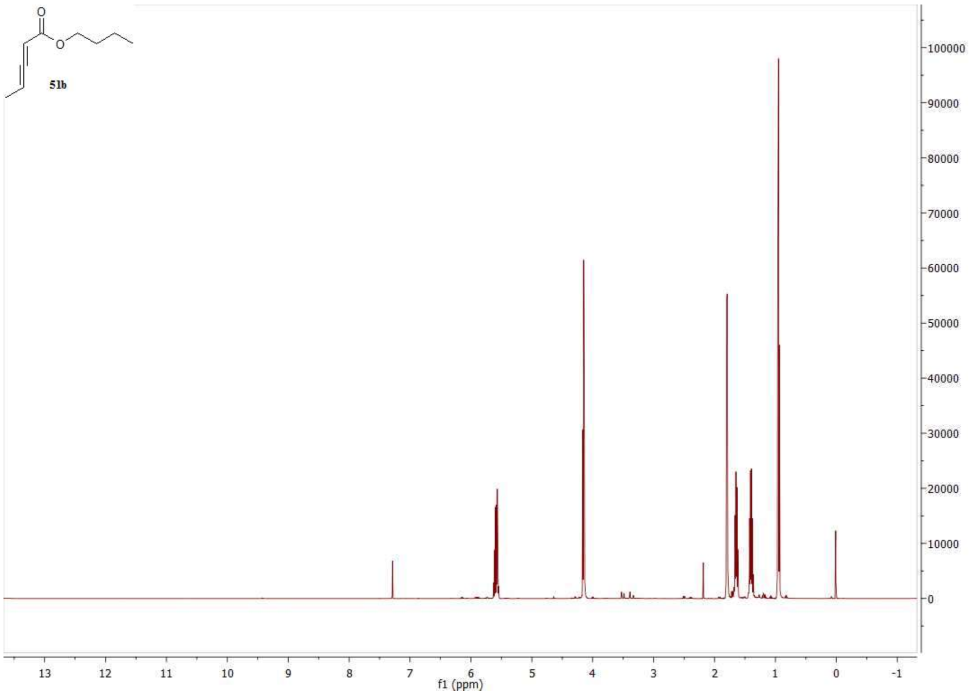
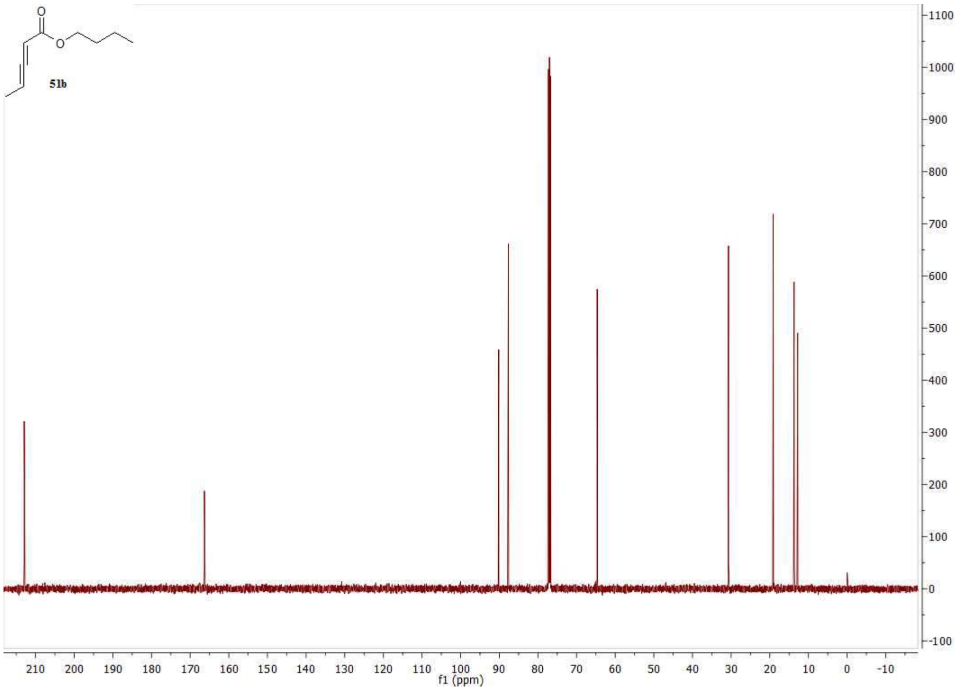
600
500
400
300
200
100
0
-100


O
O
51b
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)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O
51b
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900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
160
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140
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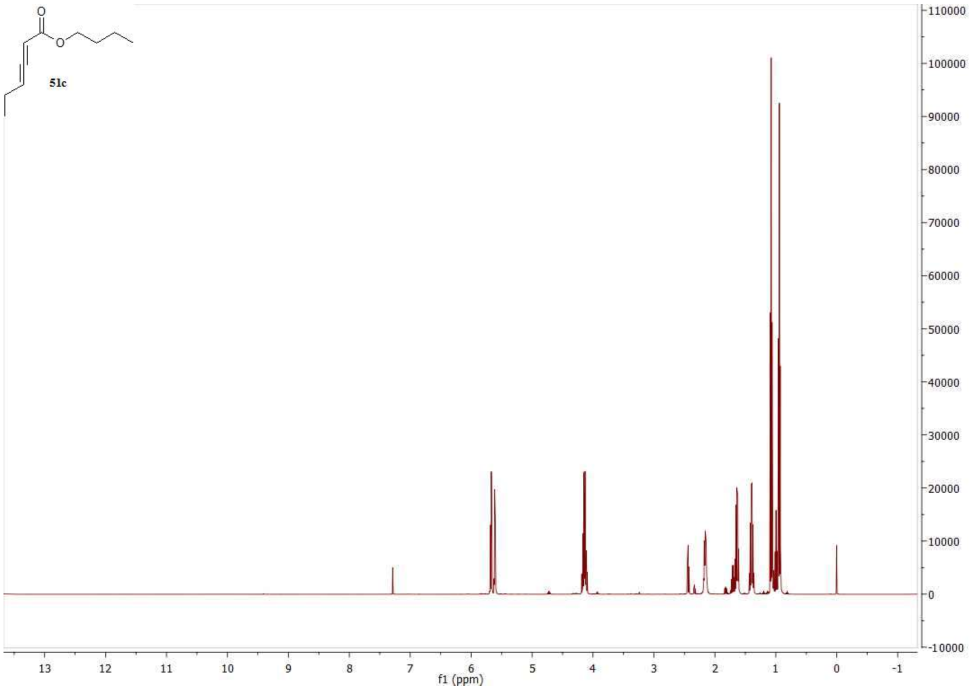
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


51c
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60000
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40000
30000
20000
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8
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6
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4
3
2
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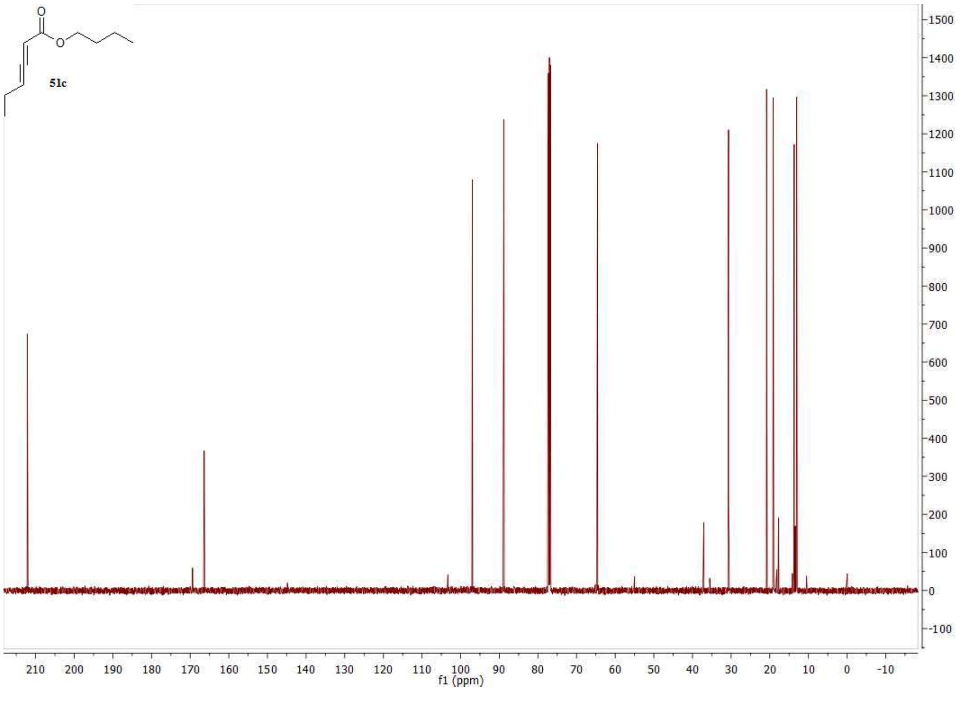
0
-1
f1 (ppm)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1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
210
200
190
180
170
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140
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120
110
100
90
80
70
60
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40
30
20
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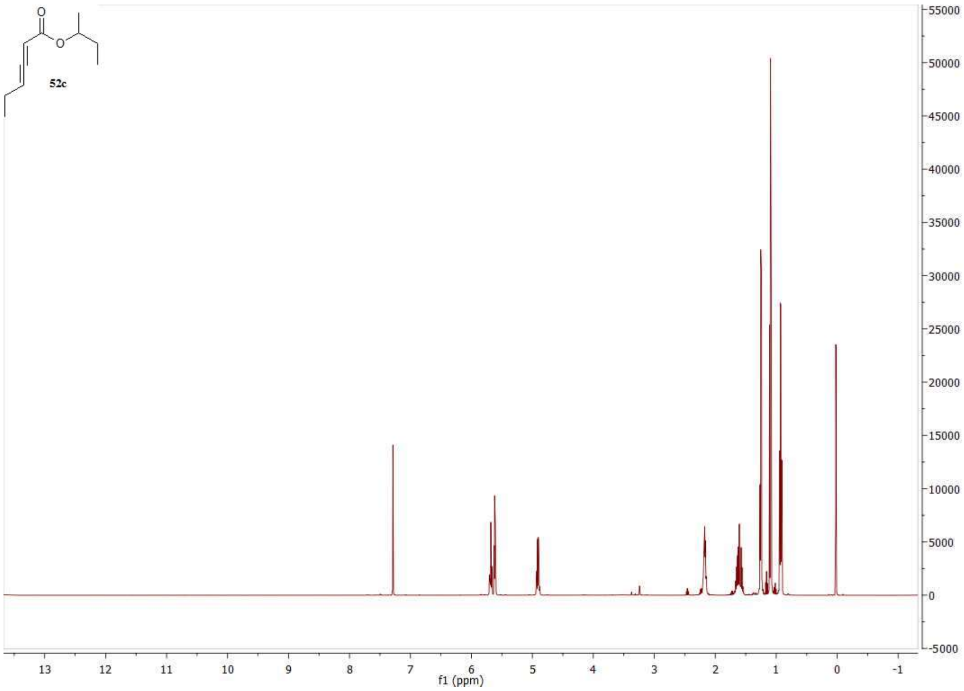
0
-10
f1 (ppm)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52c
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40000
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10000
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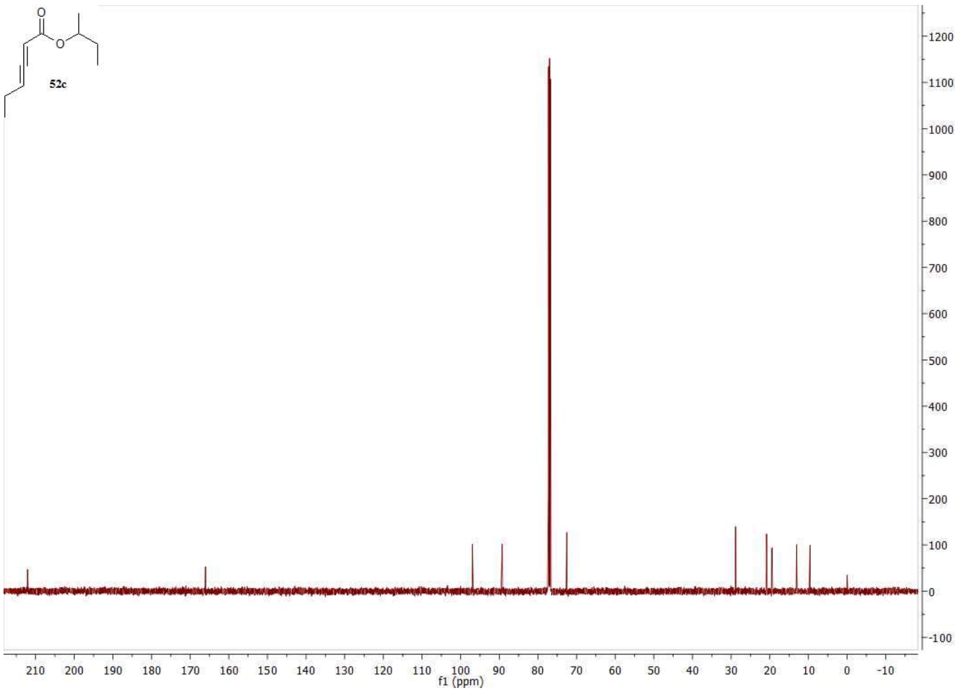
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


O
O
52c
1200
1100
1000
900
800
700
600
500
400
300
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100
0
-100
210
200
190
180
170
160
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140
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120
110
100
90
80
70
60
50
40
30
20
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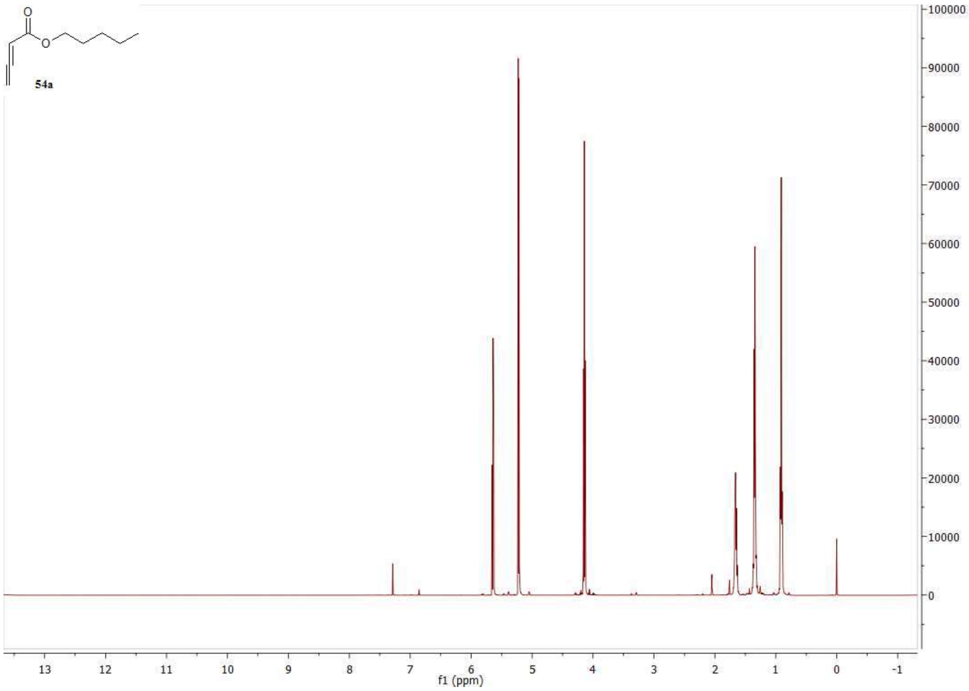
0
-10
f1 (ppm)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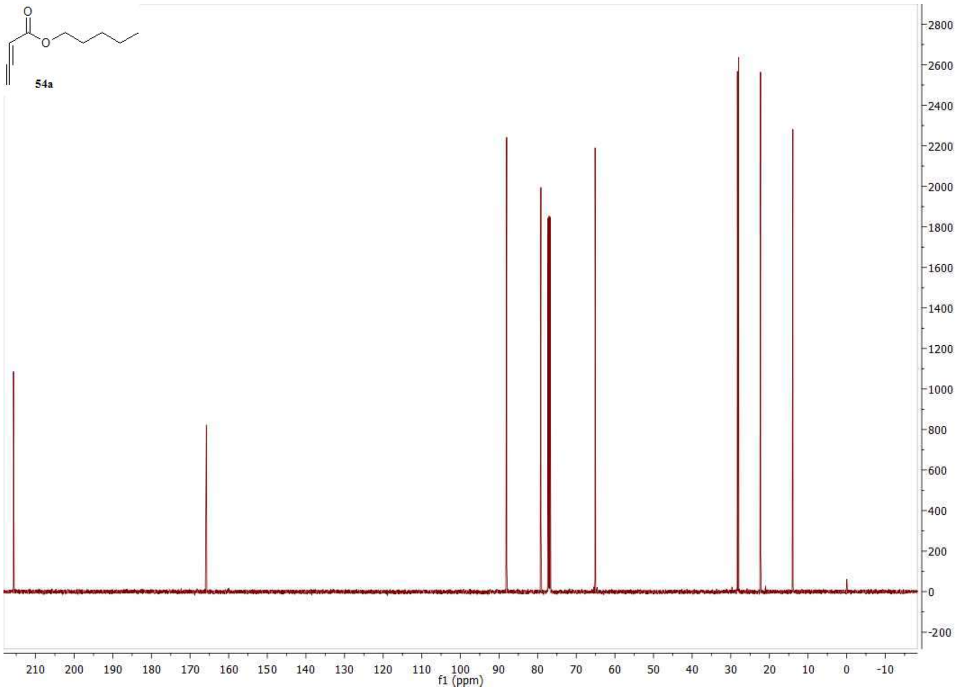
70000
60000
50000
40000
30000
20000
10000
0
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)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2400
2200
2000
1800
1600
1400
1200
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800
600
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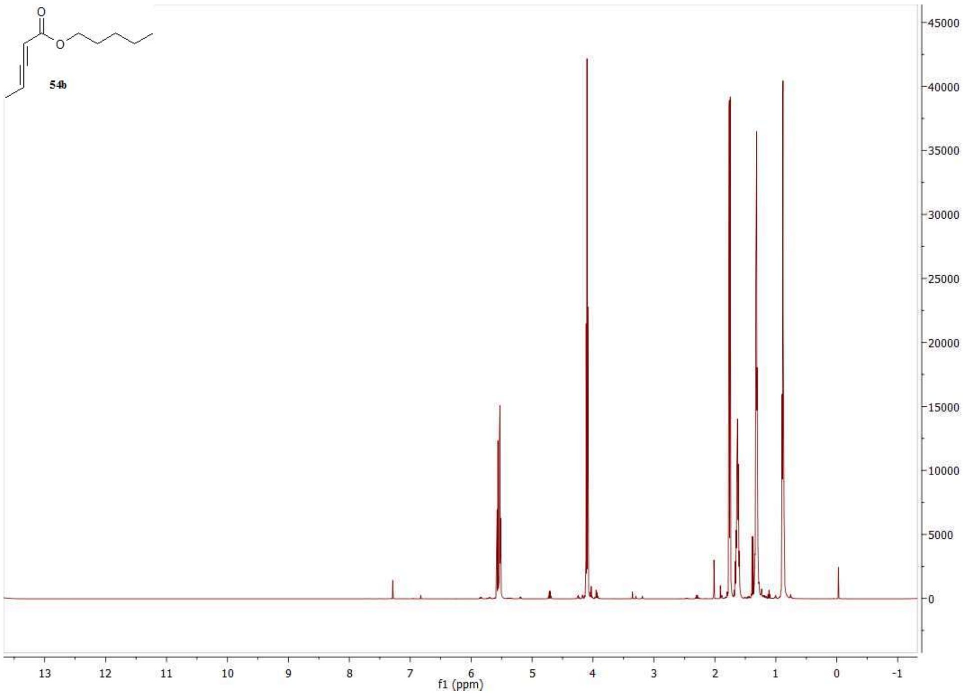
200
0
-200
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)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O
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35000
30000
25000
20000
15000
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10
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8
7
6
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4
3
2
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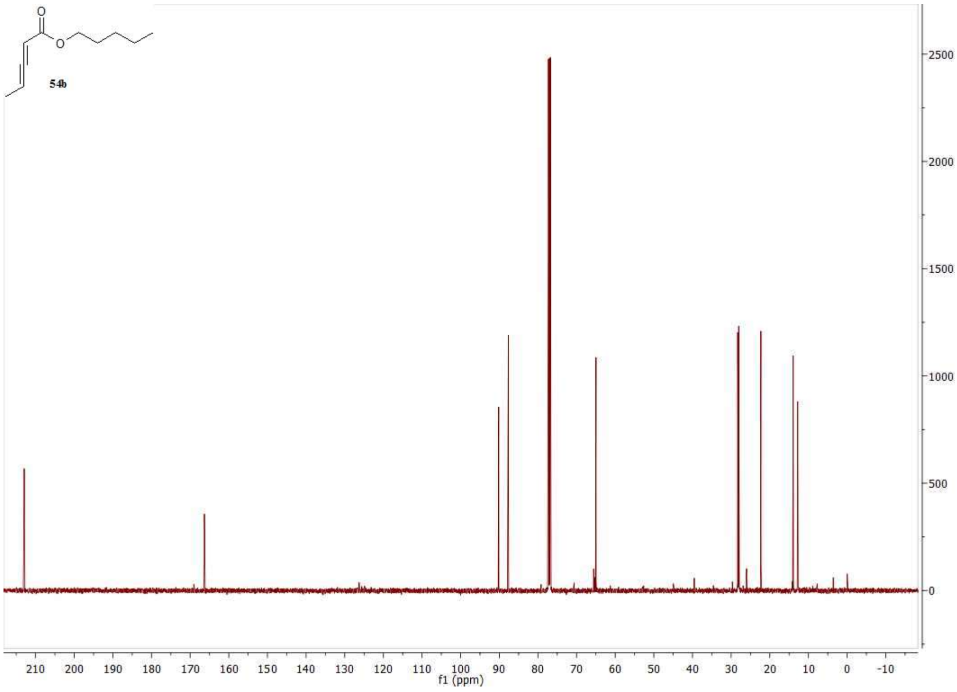
0
-1
f1 (ppm)


O
O
54b
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2000
1500
1000
500
0
210
200
190
180
170
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140
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100
90
80
70
60
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40
30
20
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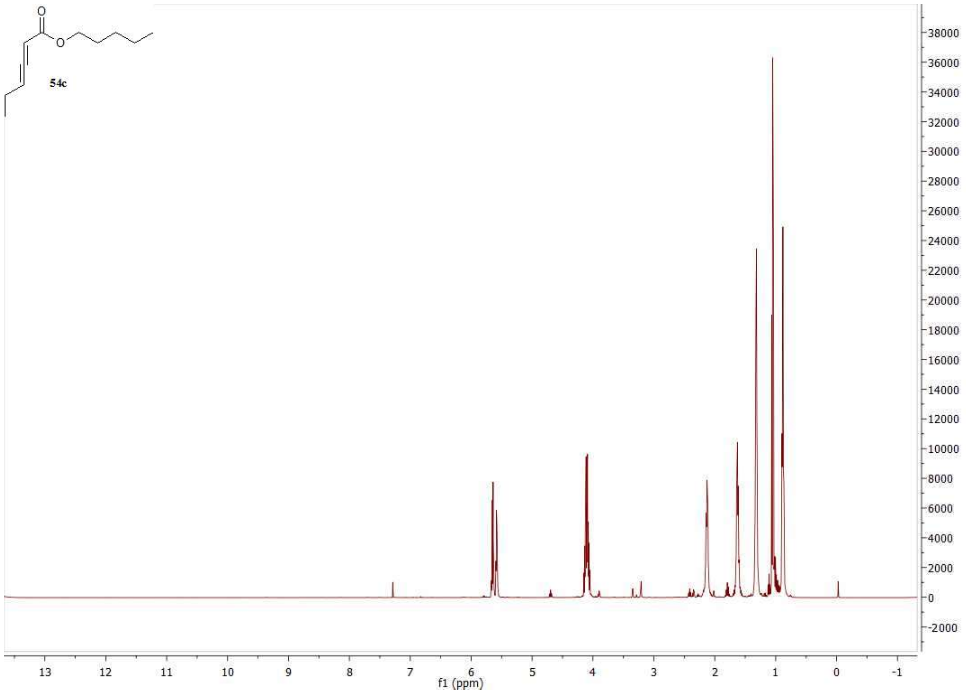
0
-10
f1 (ppm)



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30000
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26000
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20000
18000
16000
14000
12000
10000
8000
6000
4000
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-2000
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10
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4
3
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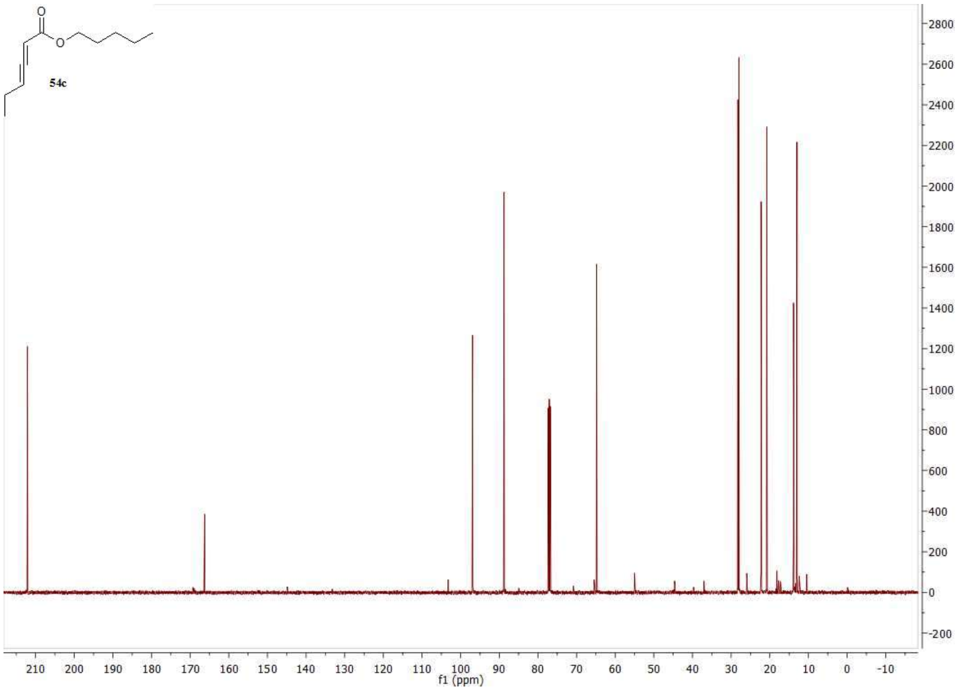
0
-1
f1 (ppm)



O
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2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
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-200
210
200
190
180
170
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100
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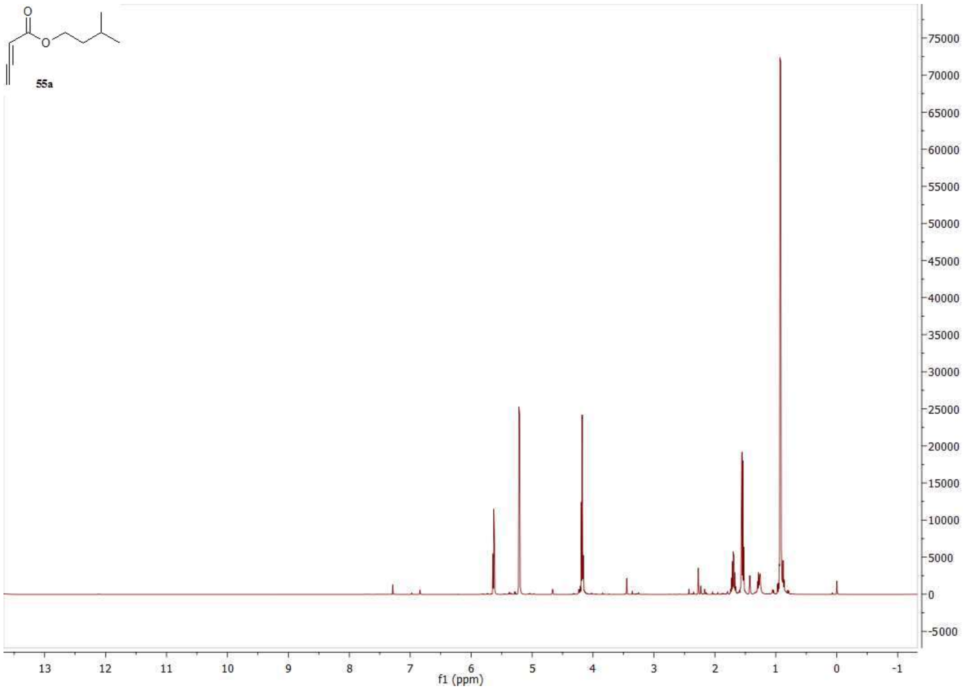
0
-10
f1 (ppm)


55a

75000
70000
65000
60000
55000
50000
45000
40000
35000
30000
25000
20000
15000
10000
5000
0
-5000
13
12
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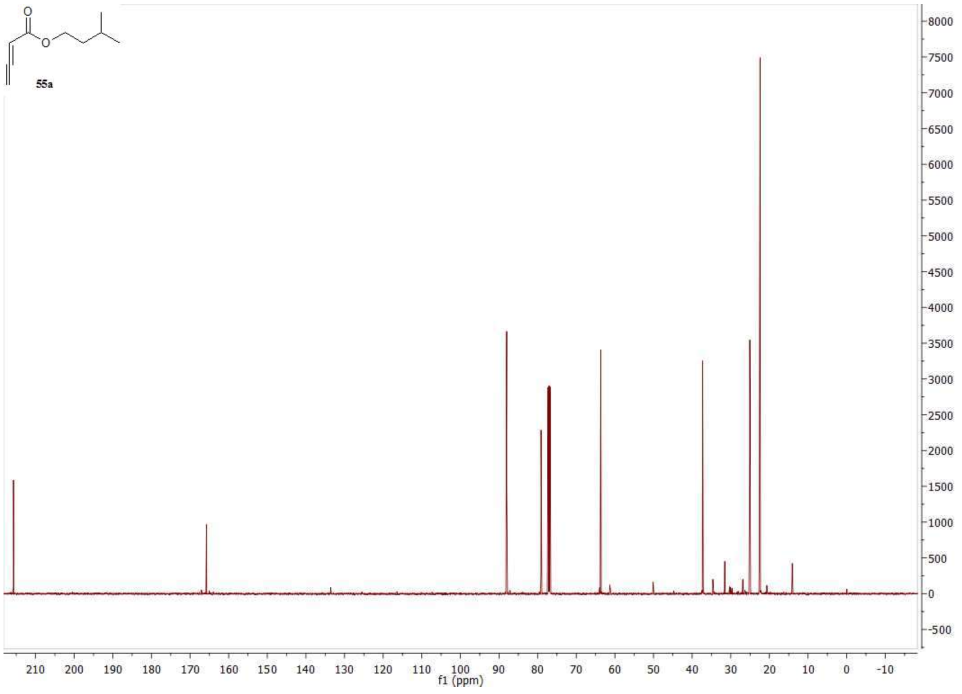
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)
O
O


55a

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6000
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5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
150
140
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120
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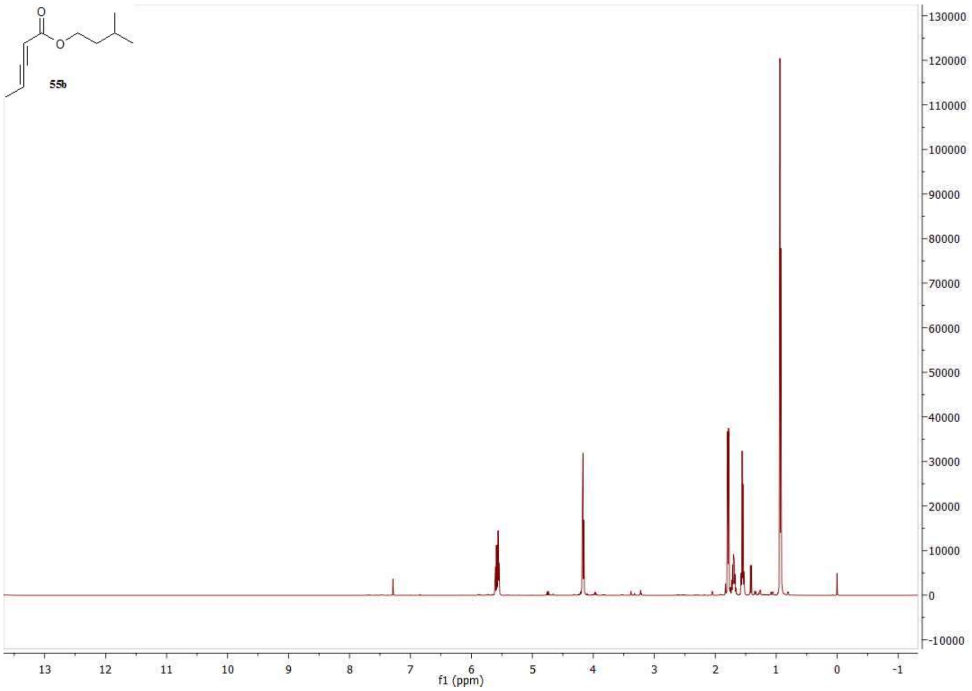
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)
O
O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O
O
130000
120000
110000
100000
90000
80000
70000
60000
50000
40000
30000
20000
10000
0
-10000
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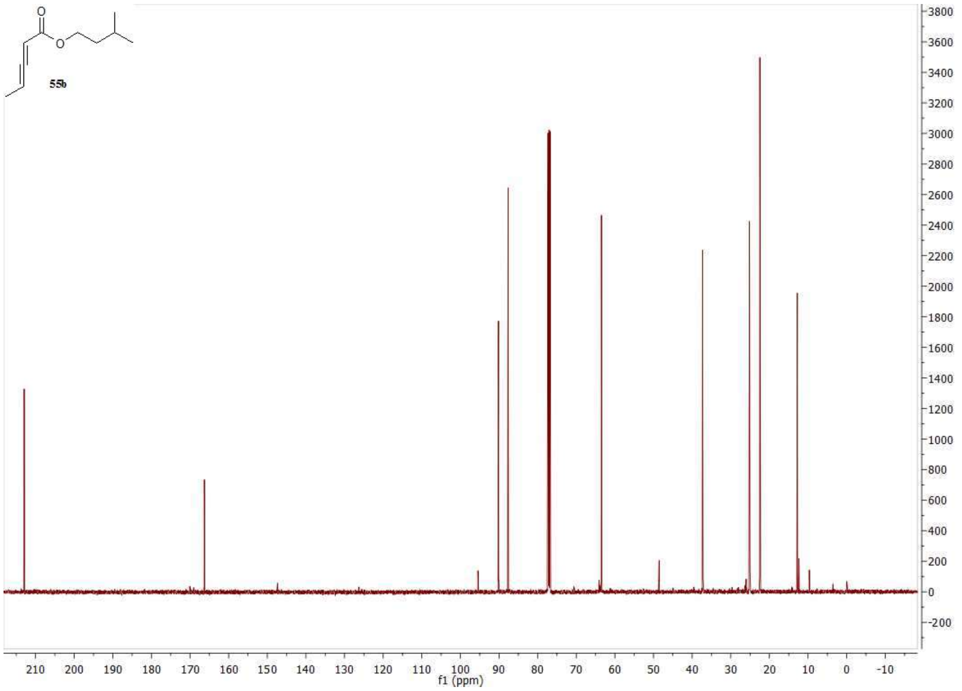
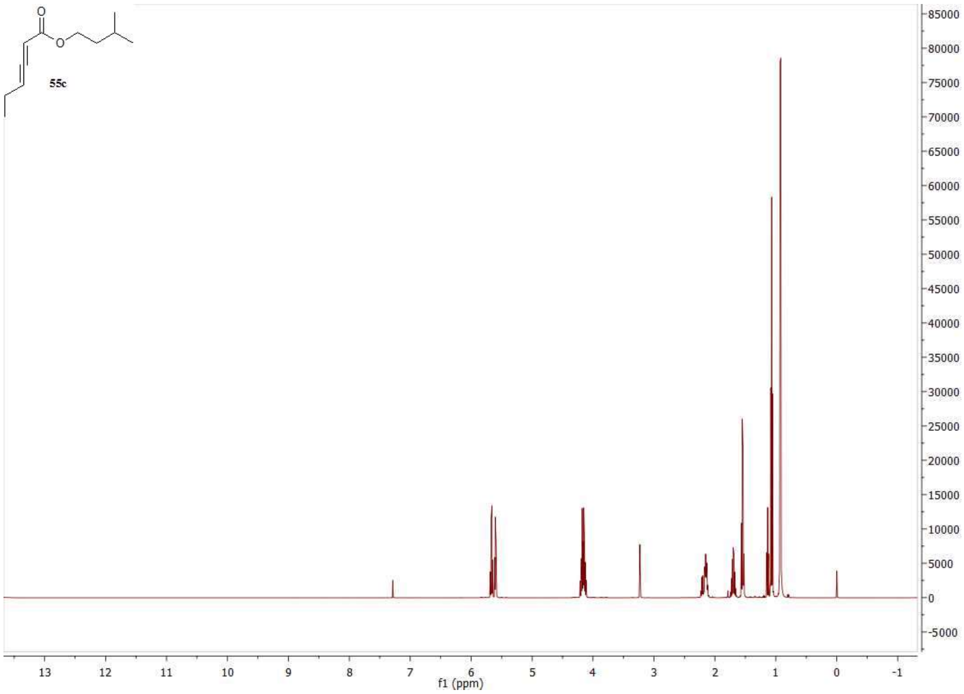
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


55b
O
O
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)


55c
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75000
70000
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60000
55000
50000
45000
40000
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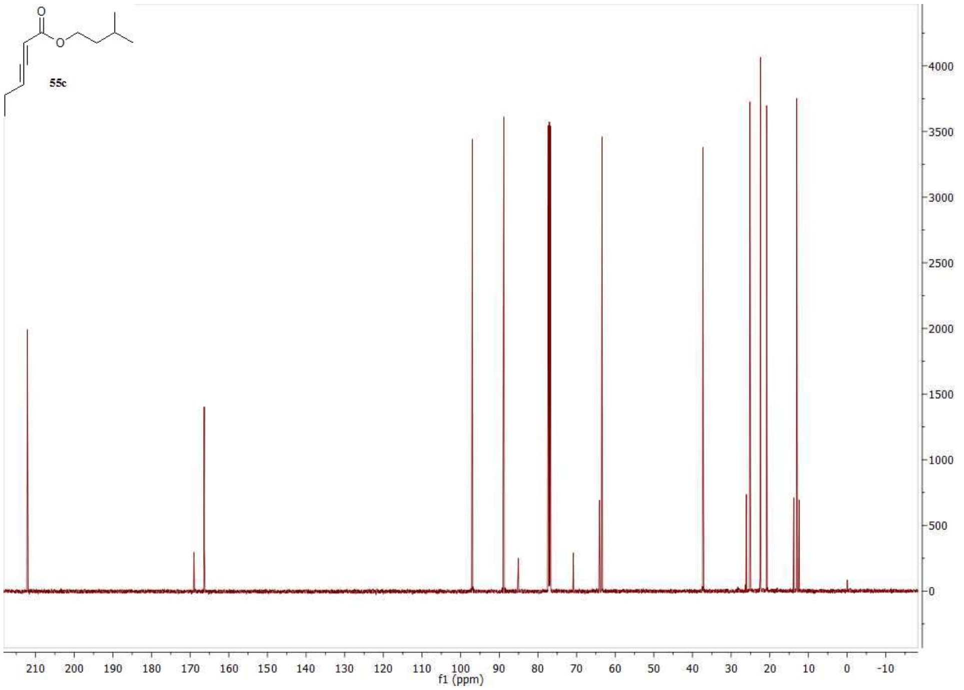
25000
20000
15000
10000
5000
0
-5000
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


55c
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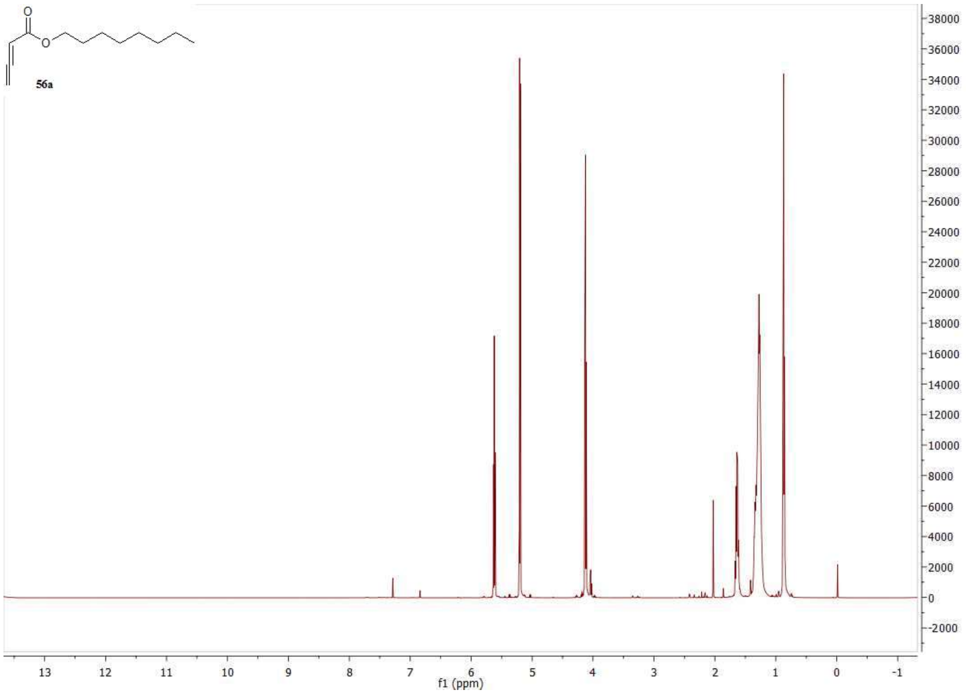
2000
1500
1000
500
0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
56a
38000
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34000
32000
30000
28000
26000
24000
22000
20000
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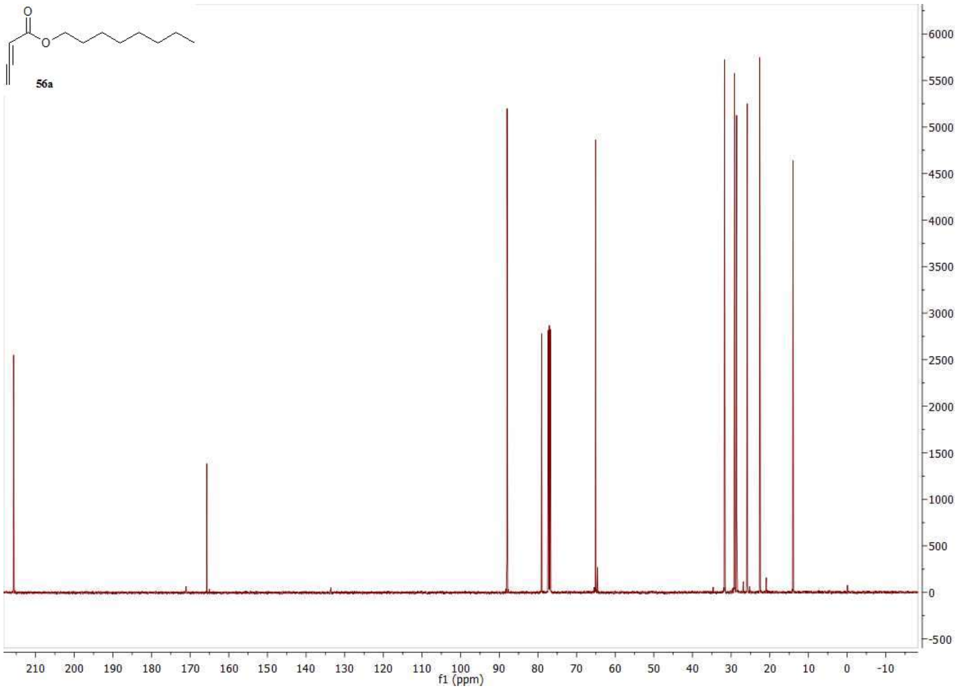
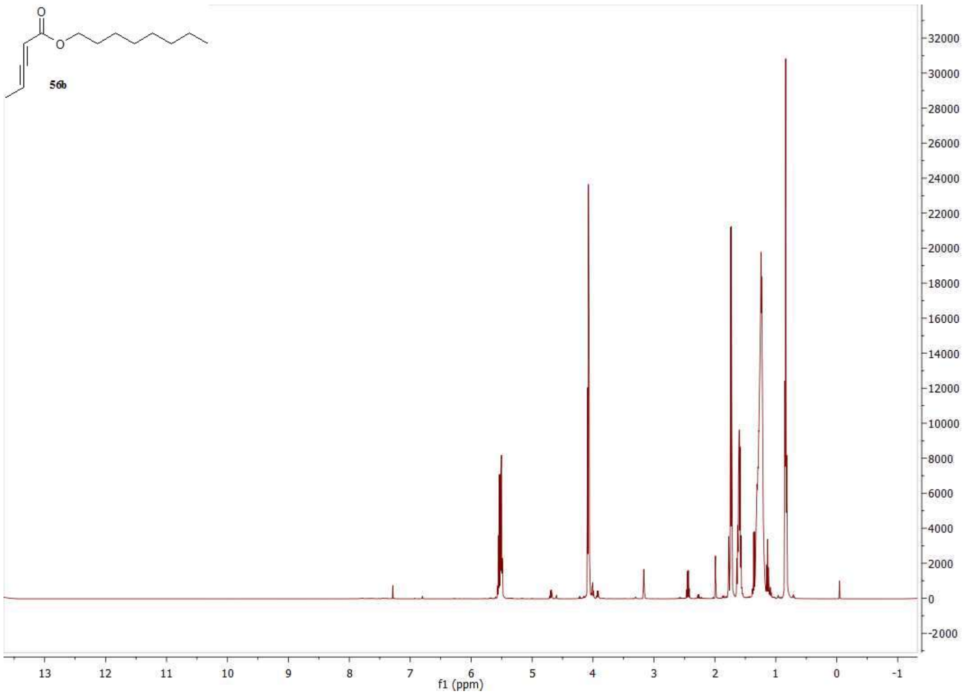
10000
8000
6000
4000
2000
0
-2000
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


O
O
56a
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


56b
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30000
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26000
24000
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20000
18000
16000
14000
12000
10000
8000
6000
4000
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10
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3
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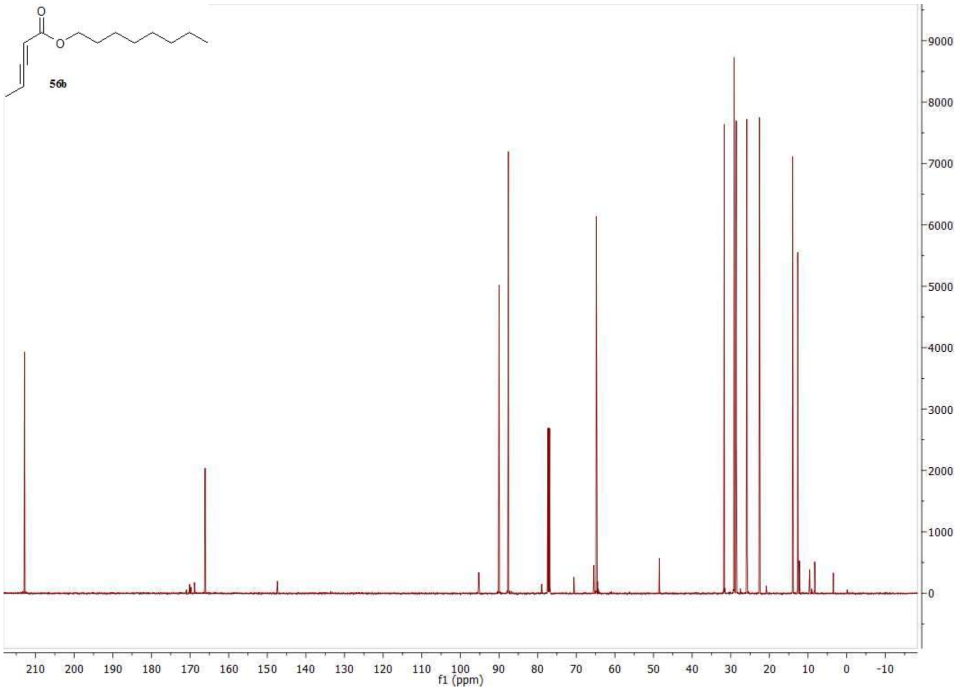
0
-1
f1 (ppm)


56b
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
210
200
190
180
170
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100
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80
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30
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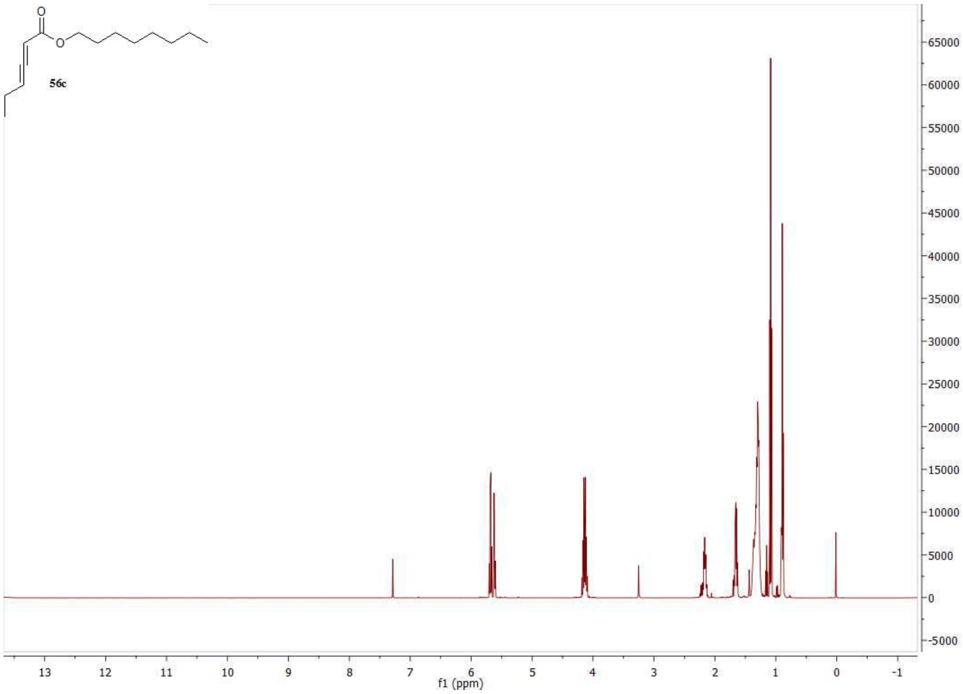
0
-10
f1 (ppm)



O
O
56c
65000
60000
55000
50000
45000
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35000
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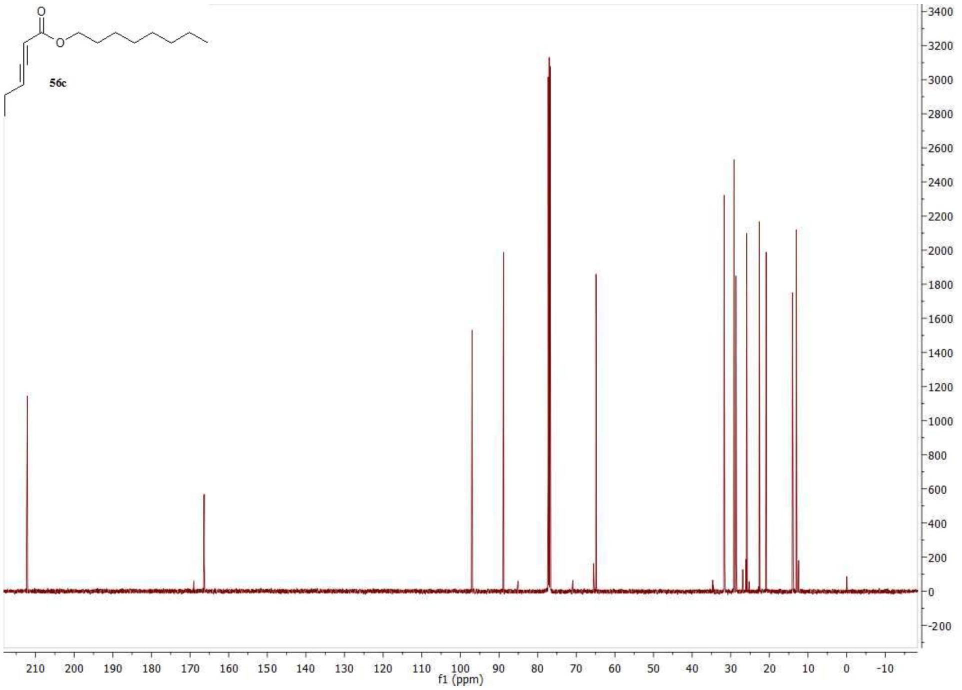
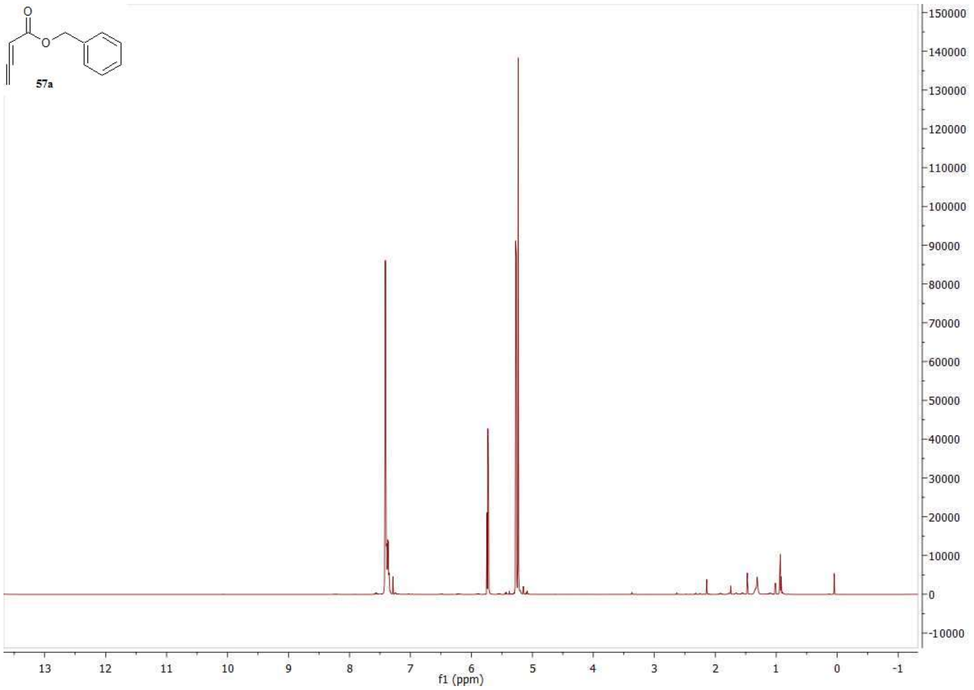
25000
20000
15000
10000
5000
0
-5000
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)



O
O
56c
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


O
O
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110000
100000
90000
80000
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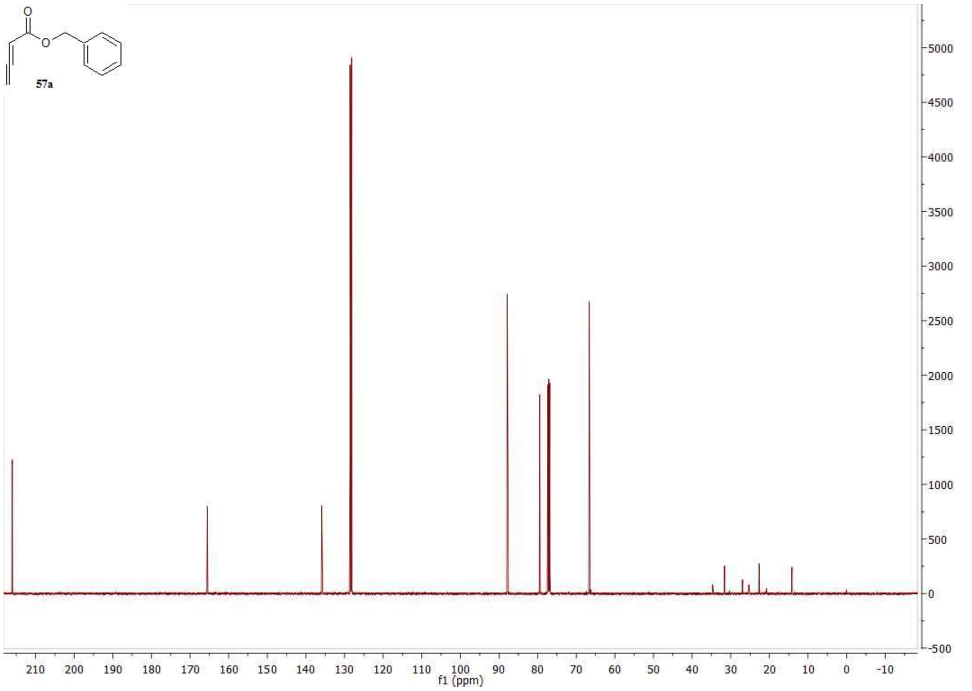
20000
10000
0
-10000
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)


O
O
57a
5000
4500
4000
3500
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2000
1500
1000
500
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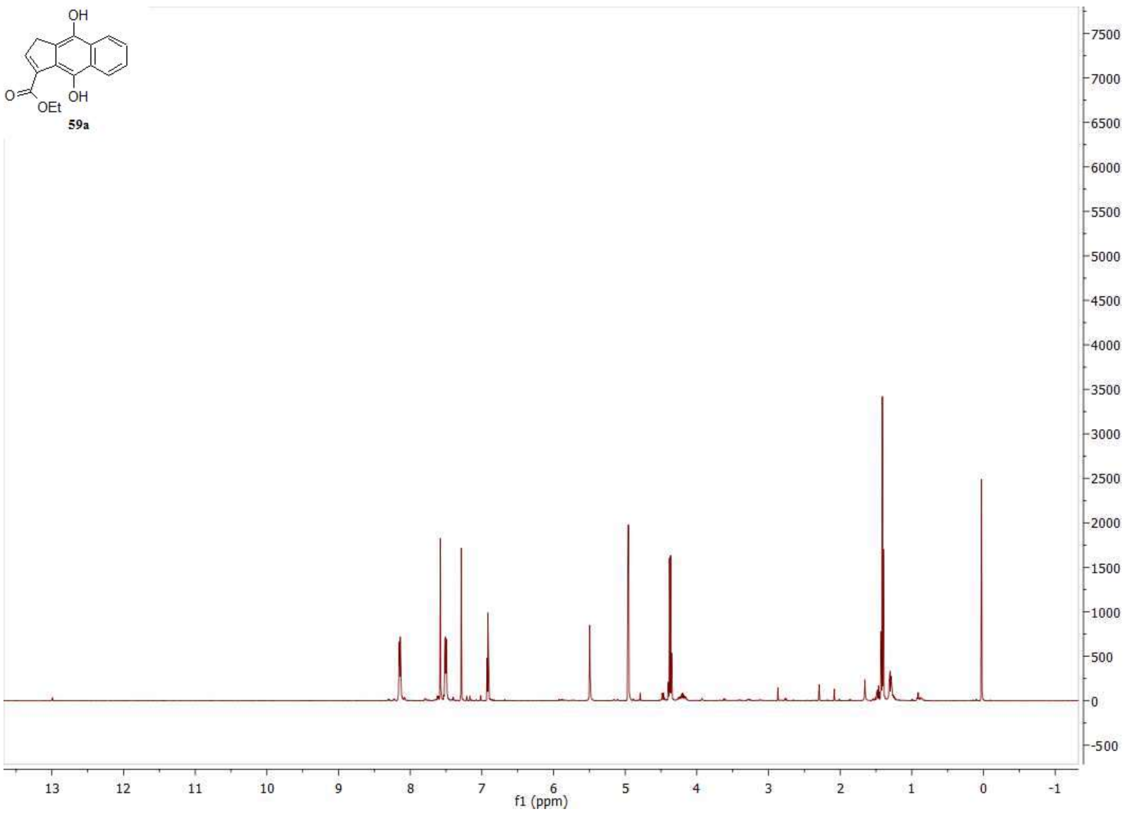
-500
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OH
O
OEt
OH
59a
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6500
6000
5500
5000
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4000
3500
3000
2500
2000
1500
1000
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-500
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10
9
8
7
6
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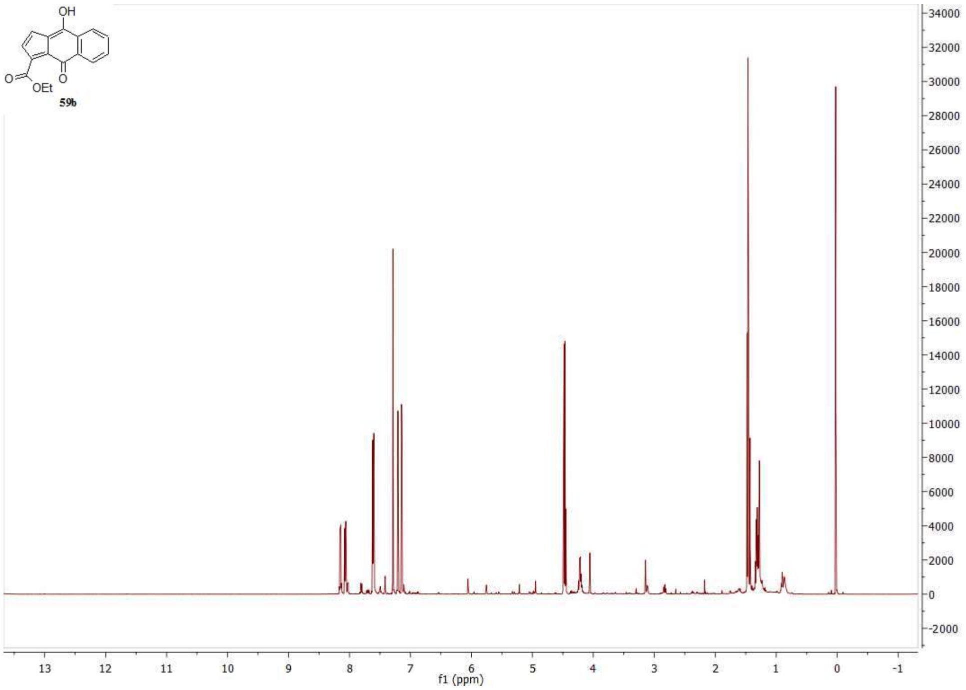
4
3
2
1
0
-1
f1 (ppm)


OH
O
O
OEt
59b
34000
32000
30000
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
2000
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-2000
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11
10
9
8
7
6
5
4
3
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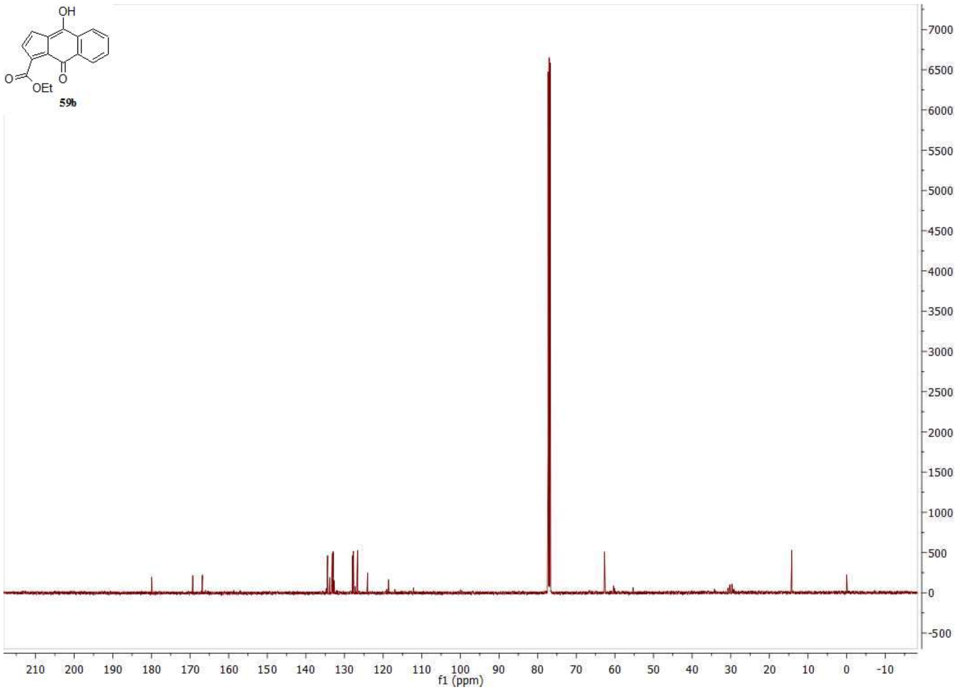
1
0
-1
f1 (ppm)


OH
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O
OEt
59b
7000
6500
6000
5500
5000
4500
4000
3500
3000
2500
2000
1500
1000
500
0
-500
210
200
190
180
170
160
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140
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100
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80
70
60
50
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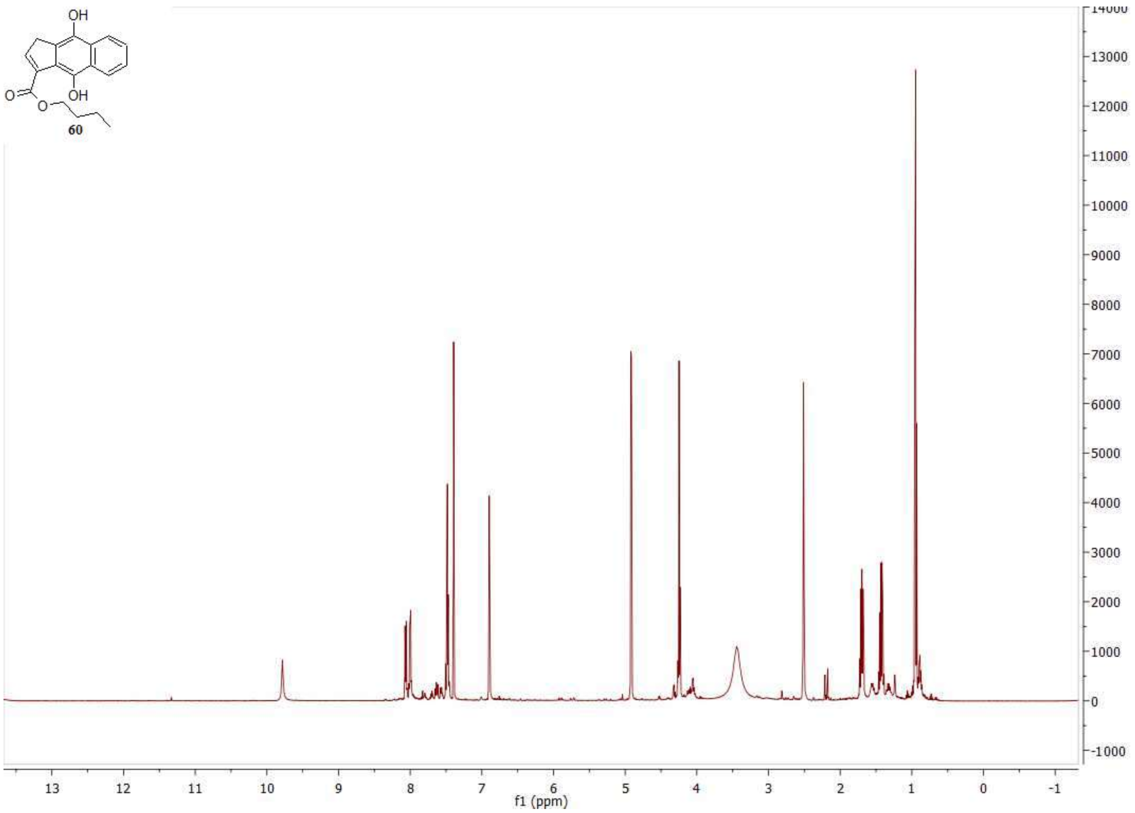
30
20
10
0
-10
f1 (ppm)


OH
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OH
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12000
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10000
9000
8000
7000
6000
5000
4000
3000
2000
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-1000
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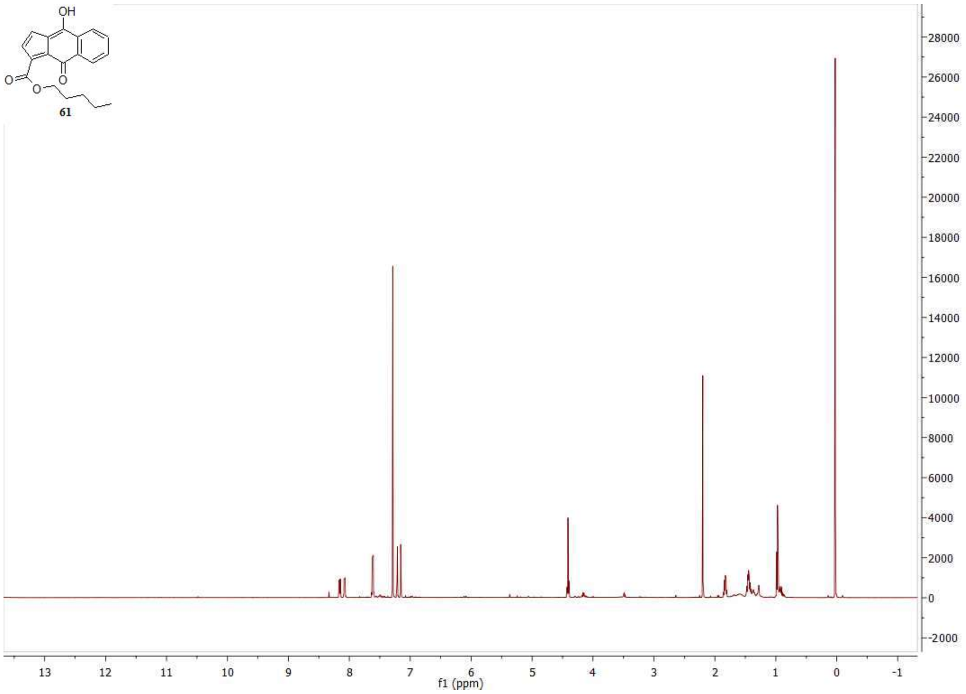
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


61

OH
O
O
O
28000
26000
24000
22000
20000
18000
16000
14000
12000
10000
8000
6000
4000
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-2000
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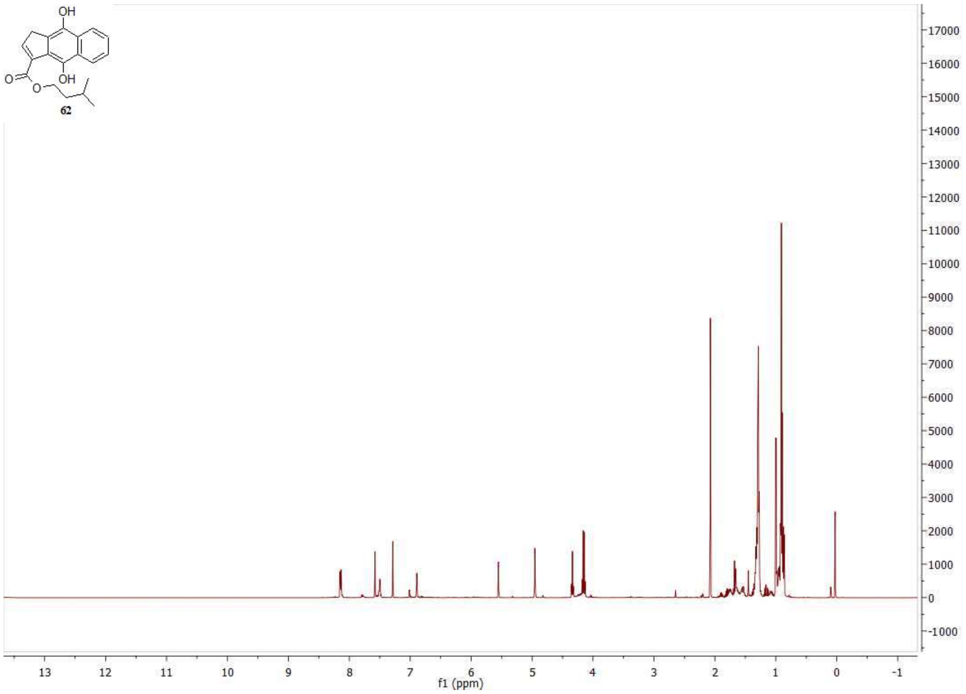
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


62

OH
OH
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O
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12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
-1000
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)