

SYNTHESIS OF NEW HALOGENATED AND BENZYLATED QUINOLONES

by

Lawrence Ammann
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of
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Committee:

_____	Dr. Suzanne Slayden, Committee Chair
_____	Dr. Robert Honeychuck, Committee Co-Chair
_____	Dr. Deborah Polayes, Committee Member
_____	Dr. Pritha Roy, Committee Member
_____	Dr. Gerald Weatherspoon, Department Chairperson
_____	Dr. Donna M. Fox, Associate Dean, Office of Student Affairs & Special Programs, College of Science
_____	Dr. Ali Andalibi, Dean, College of Science

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Director: Robert V. Honeychuck

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Dedication

To my grandfather
Prof. Dr. Wolfgang Bäseler

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List of Abbreviations and Symbols

bp	boiling point
CaSO ₄	calcium sulfate
CDCl ₃	deuterated chloroform, an NMR solvent
-CH ₂ C ₆ H ₅	benzyl group
cm ⁻¹	reciprocal wavelength, a unit of measurement in infrared spectroscopy
-CO	carbonyl group
-COOH	carboxyl group
° C	degrees Celsius
DMSO	dimethyl sulfoxide
DMSO-d ₅	partially deuterated dimethyl sulfoxide, impurity in NMR solvent
DMSO-d ₆	deuterated dimethyl sulfoxide, NMR solvent
DNA	deoxyribonucleic acid
EtOH	ethyl alcohol
FTIR	Fourier-transform infrared spectroscopy
g	gram(s)
HIV-1	human immunodeficiency virus type 1
HOD	partially deuterated water
H ₂ O	water
IR	infrared
KBr	potassium bromide
mg	milligram(s)
MHz	megahertz
mL	milliliter(s)
mp	melting point
mmol	millimole(s)
NaH	sodium hydride
-NO ₂	nitro group
NMR	nuclear magnetic resonance
N ₂	nitrogen gas
-OCH ₃	methoxy group
-OH	hydroxyl group
-Ph	phenyl group
Ph ₂ O	diphenyl ether
ppm	parts per million (NMR)
PTSA	<i>p</i> -toluenesulfonic acid

-SO ₃ H	a sulfonic acid group
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
THF	tetrahydrofuran
TMS	tetramethylsilane
μg	microgram(s)
μL	microliter(s)
δ	chemical shift in ppm (NMR)
Δ	heat in a reaction diagram
¹⁹ F NMR	nuclear magnetic resonance with respect to the fluorine-19 nucleus
¹ H NMR	nuclear magnetic resonance with respect to the hydrogen-1 nucleus
¹³ C NMR	nuclear magnetic resonance with respect to the carbon-13 nucleus

Abstract

SYNTHESIS OF NEW HALOGENATED AND BENZYLATED QUINOLONES

Lawrence M. Ammann, Ph.D.

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Dissertation Director: Dr. Robert V. Honeychuck

Quinolone derivatives have been used as antibiotics since the introduction of nalidixic acid in the 1960s. Antibiotic quinolone drugs are thought to bind to DNA, inhibiting the action of topoisomerase II, an enzyme which cuts both strands of DNA during replication, unwinds them, and then rejoins them. Without this enzyme's action, no cell division is possible. Some antibiotic quinolone drugs are fluorinated and many contain a carboxyl group to facilitate aqueous solubility. At least one quinolone drug has been used to treat muscular dystrophy. The new quinolone derivatives described do not follow the existing template for quinolone drugs, but are similar. Some of these new quinolones were nitrated in order to enhance their solubility in water, and all were fluorinated or chlorinated. The quinolone derivatives described here were tested against three common bacteria, *S. saprophyticus*, *E. coli*, and *P. stutzeri*. None was found to be effective against any of these three bacteria.

Background

Most quinolone drugs are based on 4-quinolone (**1**), which is composed of two fused rings, a benzene ring on the left, and a 4-pyridone ring on the right, as shown in Figure 1. Eight of the quinolone atoms are shown numbered according to convention in this bond line structure.

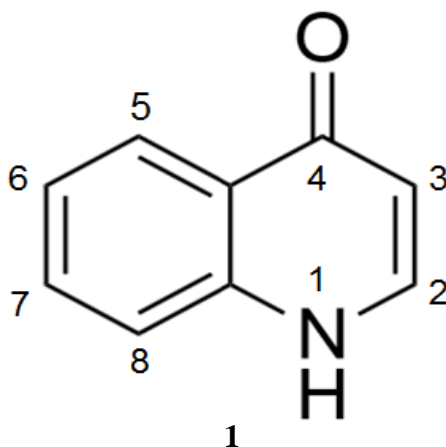


Figure 1 4-Quinolone structure

Current quinolone drugs (2) commonly contain a fluorine atom at position 6 on the quinolone ring, and a carboxyl group at position 3 on the ring (1). Various other organic groups (R), as shown in Figure 2, are commonly attached to the quinolone ring (2).

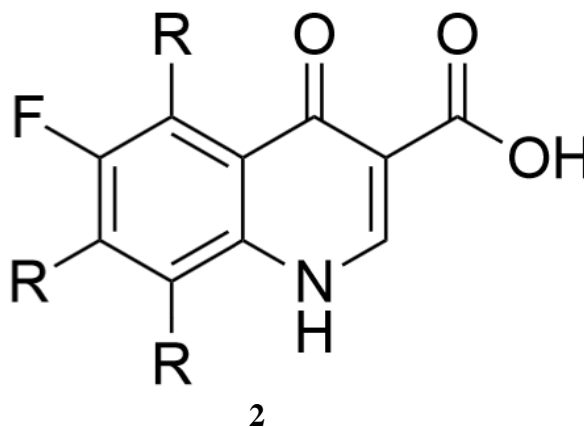


Figure 2 Structure of many common quinolone drugs

Fluoroquinolone drugs are completely synthetic; they do not come from bacteria, fungi or plants (3). Without additions such as a carboxyl group (-COOH), a hydroxyl group (-OH), a sulfonic acid group (-SO₃H), or a nitro group (-NO₂), fluoroquinolone drugs are not very soluble in aqueous solutions, and therefore not always effective as oral drugs. Most relatively new fluoroquinolone drugs contain one or more of these groups, and are therefore sufficiently water soluble to be administered orally. Many early fluoroquinolones were considered to be more effective against Gram-negative bacteria than against Gram-positive bacteria, but newer fluoroquinolones are often found to be

effective against Gram-positive bacteria as well (4). Some common current fluoroquinolone drugs are:

- Ciprofloxacin
- Perfloxacin
- Norfloxacin
- Enoxacin
- Ofloxacin
- Moxifloxacin
- Gatifloxacin

Upon review of the pharmacore of common quinolone drugs, it becomes apparent that many variants of this pharmacore have already been tried. Most current fluoroquinolone drugs have a fluorine atom at position 6 and a carboxyl group at position 3 as shown in Figure 2; there are only so many organic groups that may be attached to positions 2, 5, 7, and 8 of the ring to make new variants. According to a study by de Brito (5), newer generations of quinolone drugs contain ever bigger or longer hydrocarbon chains, making them more lipophilic - a trend which can only go so far before water solubility falls below acceptable levels for an orally administered drug.

Since common quinolone drugs seem to follow this common pattern, synthesis in this proposal has been focused on some quinolone variants not seen in the drugs mentioned above. In addition, according to Marchant (6), many of the newer quinolone drugs are suspected of toxic side effects, such as muscle and tendon pain, sometimes quite severe.

For instance, an FDA review has found that fluoroquinolone antibiotics can increase the occurrence of serious “ruptures or tears in the main artery of the body, called the aorta” and has recommended the use of fluoroquinolone antibiotics only when “no other treatment options are available” (7). Also, in a recent safety announcement, the FDA warned that, “fluoroquinolone antibiotics may cause significant decreases in blood sugar and certain mental health side effects. The low blood sugar levels can result in serious problems, including coma, particularly in older people and patients with diabetes who are taking medicines to reduce blood sugar.” (8).

All of the synthesized variants described in this paper contain a benzyl group at position 3 on the quinolone ring. This benzyl group is always either fluorinated or chlorinated at position 3 or 4 on the benzyl ring. In addition to the variable halogenation on the benzyl ring, the quinolone derivatives contain one of the following substitution patterns on the quinolone ring:

- A nitro group at position 6
- A chlorine atom at position 6
- Two chlorine atoms, at positions 5 and 7
- A chlorine atom at position 8
- No substituents at any of the positions 5, 6, 7, or 8

Quinolone Drugs

Common quinolone drugs function as topoisomerase II inhibitors in bacteria by blocking DNA replication (9). During DNA replication, DNA strands must be unwound. However, this leads to increasing tension in the remainder of the DNA strand, as it is wound tighter. Without relief of this tension, DNA replication fails, leading to cell death. Type II topoisomerases cut both strands of the DNA helix simultaneously ahead of the replication site, unwind them, and then rejoin them (10). This relieves tension in the DNA strand and allows replication to continue. Quinolone derivatives can apparently bind to DNA, and prevent topoisomerase II from unwinding it. Wohlkonig et al. (11) have shown that moxifloxacin, a 3rd generation fluoroquinolone, binds to DNA with the intermediation of a magnesium ion.

According to Mascaretti (12), there are three generations of quinolone drugs. Nalidixic acid (3), approved by the FDA in 1964 for urinary infections, and shown in Figure 3, is an example of a first generation quinolone drug. Nalidixic acid has a carboxyl group attached to the ring at position 3, a common feature of most following generations of quinolone drugs as well. Actually, this drug is not a quinolone derivative, but rather a naphthyridone derivative, due to the two nitrogen atoms in the fused rings (13).

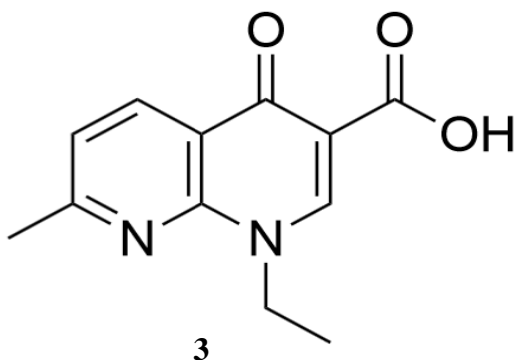


Figure 3 Nalidixic Acid

Ciprofloxacin (**4**), approved by the FDA in 1981 and shown in Figure 4, is an example of a second generation quinolone (*14*). By the time of this drug, a cyclopropyl ring at position 1, a fluorine atom at position 6, and a complex organic group at position 7 (in this case a piperazine ring) were very common. Second generation fluoroquinolones tend to be more effective against Gram-(-) than Gram-(+) bacteria.

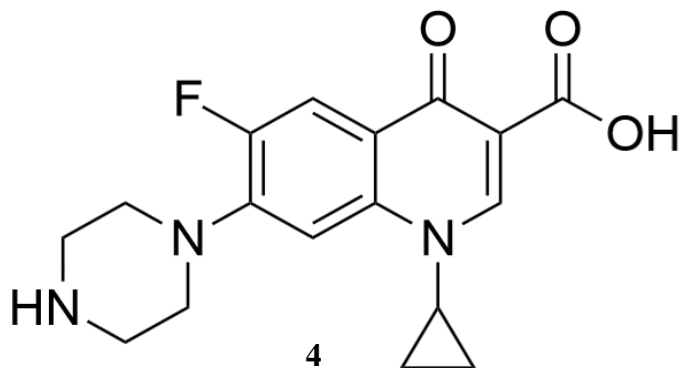


Figure 4 Ciprofloxacin

Moxifloxacin (**5**), approved by the FDA in 1999 and shown in Figure 5, is an example of a third generation quinolone drug (15). Identical to ciprofloxacin at positions 1, 3, and 6, it adds a more complex bridged ring at position 7, and a methoxy group at position 8.

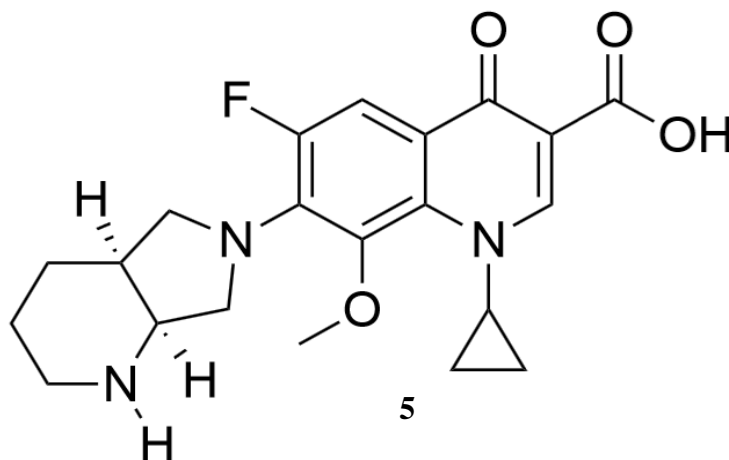


Figure 5 Moxifloxacin

Quinolone drugs have also been developed for purposes other than antibiotic. Laquinimod (**6**), approved by the FDA in 2007 and shown in Figure 6, is a quinolone drug approved for use in the treatment of multiple sclerosis, although it was withdrawn in 2011, due to adverse side effects (16). Note that laquinimod, is a 2-quinolone, meaning the carbonyl group is at the 2 position on the quinolone ring, not the 4 position, which is normal for almost all other quinolone drugs. Also, laquinimod contains a phenylated amide group in place of the carboxyl group at position 3.

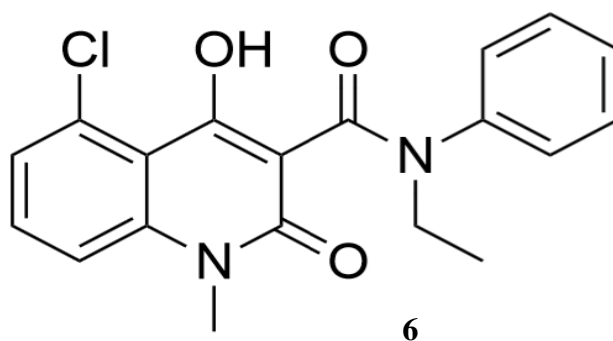


Figure 6 Laquinimod

Quinolone derivatives have also been used as antiviral drugs. Elvitegravir (7), approved by the FDA in 2012 and shown in Figure 7, is a quinolone drug approved for use in the first time treatment of HIV.

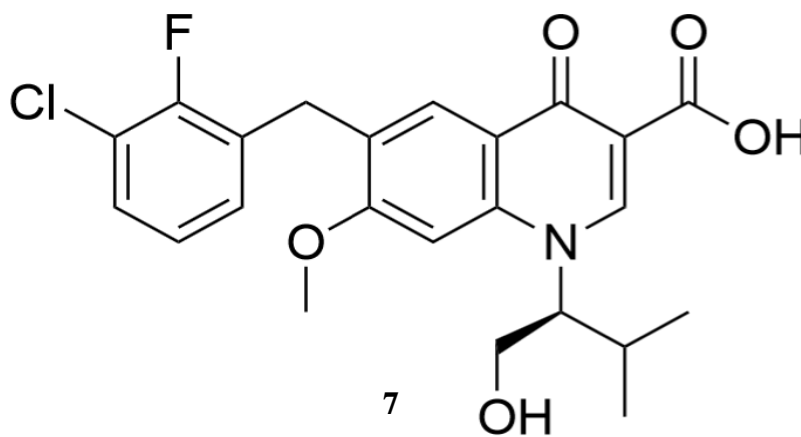


Figure 7 Elvitegravir

Elvitegravir is a complex quinolone derivative with a fluorinated and chlorinated benzyl group at position 6, a methoxy group at position 7, as well as the common carboxyl group at position 3. Elvitegravir is an HIV-1 integrase strand transfer inhibitor which prevents the integration of HIV-1 DNA into a host's DNA (17). It is typically used as one part of a cocktail of several drugs in order to increase its effectiveness.

Objectives and Aims

- 1) The major objective of this project was to synthesize new halogenated (fluorinated or chlorinated) and / or nitrated quinolone derivatives. A secondary objective of this project was to test, where possible, the antibacterial effectiveness of the new compounds.
- 2) Most of the current quinolone drugs are fluorinated at position 6 on the quinolone ring. However, fluorination of the quinolones described in this paper is limited to the benzyl group, attached at position 3 on the quinolone ring.
- 3) Nitration is desirable, if possible, to increase solubility in water. The $-\text{NO}_2$ group has a +1 charge on the nitrogen atom; depending on pH, a -1 charge is distributed over the two oxygen atoms. Therefore, some of the newly synthesized quinolone derivatives include a nitro group on the quinolone ring.

Research Design and Methods

Numerous methods of synthesizing quinolones have been attempted and documented. Hu et al. (18) described a synthesis of 2-aryl-4-quinolones (9) from *N*-arylmethyl-2-aminophenylketones (8) with high yields, shown in Figure 8.

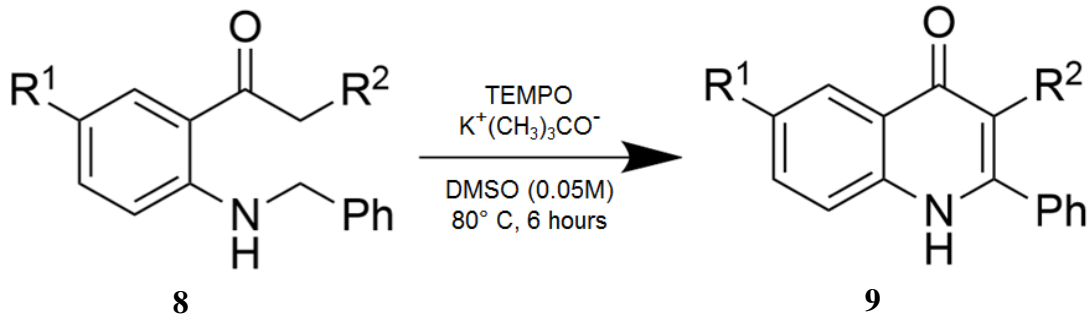


Figure 8 Hu's synthesis of 2-aryl-4-quinolones

While quinolones with an aryl (phenyl or similar) group at the 2 position are unusual and interesting, this synthesis required complex aromatic starting compounds, and always results in the placement of an aromatic group at the 2 position of the resulting 4-quinolone.

Barbe et al. (19) described a synthesis using toluidine (2-methylaniline) (**10**) and ethyl acetoacetate to make imines (**11**) which then formed 2,8-dimethyl-4-quinolones (**12**), upon heating as shown in Figure 9. Methyl acetoacetate derivatives can result in more complicated 2,8-dimethyl-4-quinolones, but the drawback of this reaction is that methyl groups at the 2 and 8 positions are always present in the resulting quinolone.

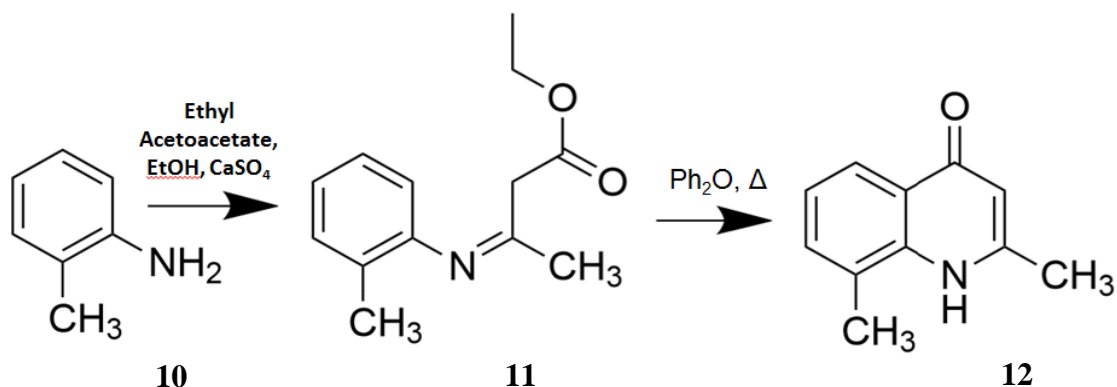


Figure 9 Barbe's synthesis of 2,8-dimethyl-4-quinolones

There are many more, but most have some deficiency in a university lab setting. One problem is safety – some chemicals are simply too dangerous to use. Another problem is cost – many compounds and catalysts, especially those of very high purity, are extremely expensive, and university budgets are very limited. Finally, many reactions require specialized equipment that is simply not available in a university laboratory. The

Conrad-Limpach synthesis (20) appears to provide a better general pathway to quinolone synthesis in a university lab setting.

The Conrad-Limpach synthesis, shown in Figure 10, can be used to synthesize 2,3-alkyl-4-quinolones (**16**), starting with aniline (**13**) and a β -ketoester (**14**). These reactants undergo a condensation reaction to form an imine or Schiff base (**15**). When heated, the Schiff base undergoes cyclization to form the desired 2,3-alkyl-4-quinolone. This is also a condensation reaction; an alkoxy group ($-\text{R}^3\text{OH}$) is lost in the formation of the quinolone derivative, as shown in Figure 10.

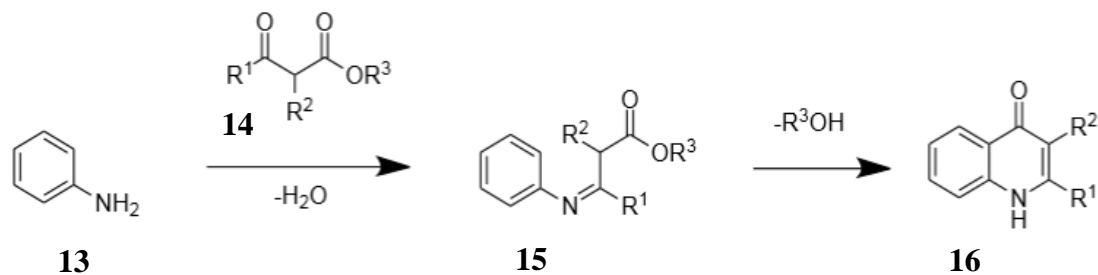


Figure 10 Conrad-Limpach quinolone synthesis

Smith and Somanathan (21) described a modified Conrad-Limpach quinolone synthesis, condensing aniline (**13**) with a β -ketoester (**14**), followed by cyclization of the resulting Schiff's base (**15**) to form a 4-quinolone derivative (**16**), as shown in Figure 11. This method used benzene as a solvent and PTSA (*p*-toluenesulfonic acid) as a catalyst

for the formation of the imine. The imine was then refluxed in diphenyl ether to form the desired substituted 4-quinolone.

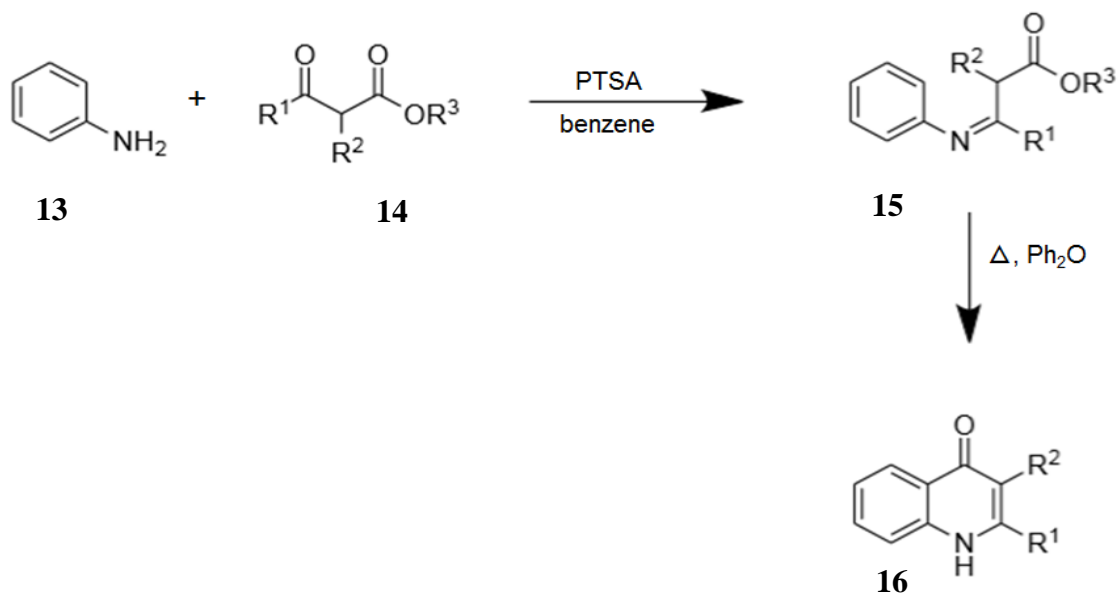


Figure 11 Smith and Somanathan quinolone synthesis

Pant (22) summarized many other methods, but found the most useful method to be that of Somanathan and Smith. Initial attempts to use a version of the Smith and Somanathan synthesis to produce the desired compounds for this research failed at first. The failure resulted from an initial step consisting of producing and alkylating a methyl acetoacetate dianion, resulting in a troublesome by-product which proved impossible to separate from the desired product. Therefore clean NMRs could not be obtained, and the method had to be modified. The problem proved to be in the formation of the dianion.

Removal of the first proton from methyl acetoacetate by sodium hydride (NaH) to make an anion proved easy – NaH cannot act as a nucleophile. However, removal of a second proton to form a dianion by a stronger base, butyl lithium, was problematic because butyl lithium can also act as a nucleophile and add to a carbonyl carbon, forming a by-product. This by-product could not be eliminated by low temperatures – even that of dry ice (-78° C).

The solution adopted was to form only the single anion of methyl acetoacetate, using NaH. This allowed a pure product to be formed upon alkylation. It had the side effect of alkylating the yet to be formed quinolone at a different location on the quinolone ring. Toluene was tried several times as a substitute solvent for benzene, due to the known carcinogenic effects of benzene. However, poor yield and poor purity of the resulting quinolones was found to be a problem with toluene as a solvent. As a result, benzene was used as a solvent.

Perhaps the most important reason for using the Smith and Somanathan synthesis was that it produced very high purity precipitates when the final reaction vessel contents were poured over a cheap solvent (hexanes). No further purification was required. The importance of this advantage is almost impossible to overstate. Many reactions will produce a desired compound given enough time and effort. However, if that compound is difficult or expensive or impossible to purify, the reaction is of little use. The Smith and Somanathan synthesis had one more important benefit – it produced relatively high yields. When reactants, solvents, and catalysts are expensive, then yield becomes even

more important. The average yield of the compounds synthesized via the Smith and Somanathan method was 50%.

According to a study by Brouet et al. (23), the ideal temperature for the ring closure step in this type of synthesis is above 250° C. Since the boiling point of diphenyl ether is between 258° C to 260° C, it forms an ideal solvent for the ring closure step.

The new quinolone derivatives were synthesized in three major steps:

1) Formation of a methyl 2-benzylacetoacetate derivative.

Equimolar amounts of sodium hydride (NaH) and methyl acetoacetate (**17**) were combined in a 100 mL round bottom flask, along with 20 mL of tetrahydrofuran (THF) solvent, (bp 66° C) and a stir bar, at room temperature and under an N₂ atmosphere. The NaH removed a proton from the acidic carbon atom between the carbonyls of the methyl acetoacetate to form a methyl acetoacetate anion (**18**) as shown in Figure 12.

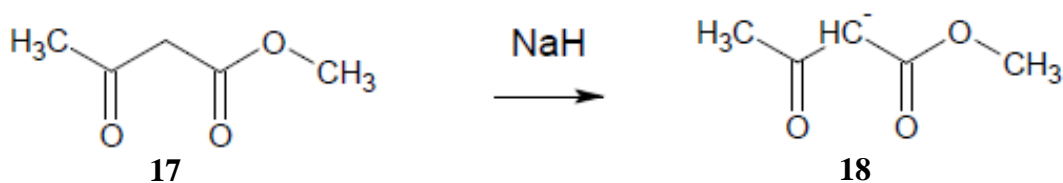


Figure 12 Deprotonation of methyl acetoacetate

After the mixture was heated to about 50° C, a benzyl bromide derivative (**19**) was added dropwise to methyl acetoacetate anion (**18**), as shown in Figure 13. (Solid benzyl bromide derivatives were dissolved in THF before addition.) The mixture was then stirred under N₂ for about an hour. An ISCO CombiFlash Separation System Sg 100c was used to separate the product, methyl 2-halobenzylacetoacetate (**20**), a viscous liquid, from other reactants. This is a flash chromatography system which separates liquids based on polarity using a UV detector.

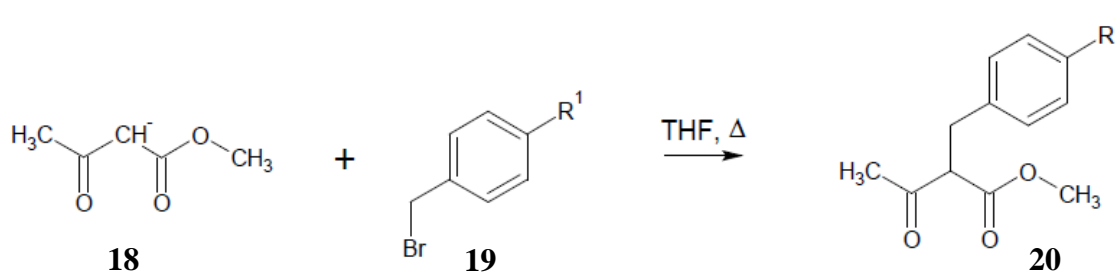


Figure 13 Formation of a methyl 2-benzyl acetoacetate derivative

- 2) Formation of an imine between an aniline derivative and the methyl 2-benzylacetoacetate derivative.

Equimolar amounts of a methyl 2-benzylacetoacetate (**20**) and an aniline derivative (**21**) were combined in a 100 mL round bottom flask, along with 25 mL

of benzene solvent (bp 80° C), a *p*-toluenesulfonic acid catalyst, and a stir bar. The round bottom flask was topped with a Dean Stark trap and condenser, and refluxed for 24 hours. After removal from the heat, the resultant mixture was cooled and the excess benzene was evacuated by means of a Buchi Rotavapor R-114, leaving a viscous liquid for the next step. This intermediate product, an imine, (**22**) is shown in Figure 14.

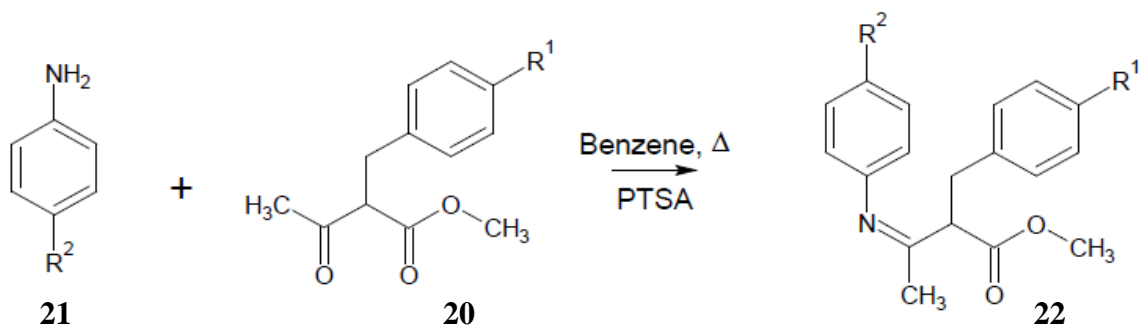


Figure 14 Imine formation between aniline and methyl acetoacetate derivatives

3) Ring closure to form a substituted quinolone.

About 30 mL of the diphenyl ether solvent (bp 258° C), and a stir bar were added to a 3-necked 100 mL round bottom flask. The top neck was fitted with a condenser, the left neck with a 250° C thermometer, and right neck was left open. After the diphenyl ether was heated to its boiling point, the imine product (**22**) of step 2, still containing some PTSA, was added dropwise over about ten minutes, flashing off the remaining benzene at the moment of addition of each drop.

Dropwise addition proceeded slowly enough to keep the solvent at its boiling point. The mixture was then refluxed for about 1 hour, cooled to room temperature, and poured over about 30 mL of hexane isomers. The desired quinolone product (**23**) formed as a precipitate in the hexane isomers, and was vacuum filtered and then washed with more hexanes for purification. Formation of the quinolone derivative is shown in Figure 15. The quinolone derivative in this figure corresponds to the following para-derivatives in Table 1: LA 41-2, LA 45-2, and LA 75-2.

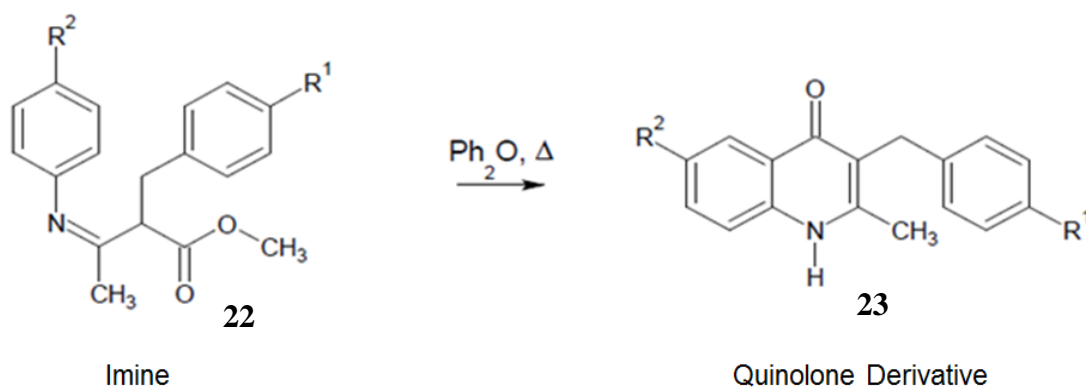


Figure 15 Ring closure to form a substituted quinolone

Results and Analysis

Properties of the New Quinolone Compounds

The new quinolone derivatives can be categorized by means of a table with the benzyl derivative as the column and the aniline derivative as the row as shown in Table 1. All of the quinolones contain methyl acetoacetate, so this is not included in the table, but it becomes part of the benzyl derivative in the first step of synthesis.

Table 1 Synthetic Components of Newly Synthesized Quinolones

	4-Fluorobenzyl bromide	3-Chlorobenzyl bromide	3-Fluorobenzyl bromide	4-Chlorobenzyl bromide
4-Chloroaniline	LA 41-2	Already existed	LA 61-2	Not Analyzed
3,5-Dichloroaniline	LA 42-2	LA 52-2	LA 62-2	LA 72-2
Aniline	LA 44-2	LA 54-2	LA 64-2	LA 74-2
4-Nitroaniline	LA 45-2	LA 55-2	LA 65-2	LA 75-2
2-Chloroaniline	LA 46-2	LA 56-2	LA 66-2	Impure Result

Lab names, chemical names, formulas, melting points, yields, and colors of the new quinolone compounds are shown in Table 2. Melting points were measured on a Stanford Research Systems DigiMelt, which has a maximum temperature of 260° C; as a consequence many melting points are known only to be greater than 260° C.

Table 2 Properties of New Quinolone Compounds

Lab Name	Formula	Chemical Name	MP°C	Yield	Color
LA 41-2	C ₁₇ H ₁₃ NOClF	6-Chloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone	> 260	50.3%	Pale Yellow
LA 61-2	C ₁₇ H ₁₃ NOClF	6-Chloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone	> 260	55.0%	Ivory
LA 42-2	C ₁₇ H ₁₂ NOCl ₂ F	5,7-Dichloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone	> 260	45.0%	Light tan
LA 52-2	C ₁₇ H ₁₂ NOCl ₃	5,7-Dichloro-3-(3-chlorobenzyl)-2-methyl-4-quinolone	> 260	48.9%	Light tan
LA 62-2	C ₁₇ H ₁₂ NOCl ₂ F	5,7-Dichloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone	> 260	58.0%	Light tan
LA 72-2	C ₁₇ H ₁₂ NOCl ₃	5,7-Dichloro-3-(4-chlorobenzyl)-2-methyl-4-quinolone	> 260	58.0%	Tan
LA 44-2	C ₁₇ H ₁₄ NOF	3-(4-Fluorobenzyl)-2-methyl-4-quinolone	> 260	47.3%	Light tan
LA 54-2	C ₁₇ H ₁₄ NOCl	3-(3-Chlorobenzyl)-2-methyl-4-quinolone	> 260	36.3%	Ivory
LA 64-2	C ₁₇ H ₁₄ NOF	3-(3-Fluorobenzyl)-2-methyl-4-quinolone	> 260	65.0%	Light tan
LA 74-2	C ₁₇ H ₁₄ NOCl	3-(4-Chlorobenzyl)-2-methyl-4-quinolone	> 260	57.8%	Light tan
LA 45-2	C ₁₇ H ₁₃ N ₂ O ₃ F	3-(4-Fluorobenzyl)-2-methyl-6-nitro-4-quinolone	> 260	45.3%	Brown
LA 55-2	C ₁₇ H ₁₃ N ₂ O ₃ Cl	3-(3-Chlorobenzyl)-2-methyl-6-nitro-4-quinolone	> 260	48.5%	Brown
LA 65-2	C ₁₇ H ₁₃ N ₂ O ₃ F	3-(3-Fluorobenzyl)-2-methyl-6-nitro-4-quinolone	> 260	50.7%	Brown
LA 75-2	C ₁₇ H ₁₃ N ₂ O ₃ Cl	3-(4-Chlorobenzyl)-2-methyl-6-nitro-4-quinolone	> 260	48.8%	Brown
LA 46-2	C ₁₇ H ₁₃ NOClF	8-Chloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone	220	35.7%	Light tan
LA 56-2	C ₁₇ H ₁₃ NOCl ₂	8-Chloro-3-(3-chlorobenzyl)-2-methyl-4-quinolone	248	43.8%	Light tan
LA 66-2	C ₁₇ H ₁₃ NOClF	8-Chloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone	231	51.5%	Ivory

Structures of the new quinolone derivatives are shown in Appendix A – Bond Line Structures.

Solubility of the new nitrated quinolone derivatives varies from about one to two mg/mL in water and from about 15 to 20 mg/mL in DMSO. Solubility of the new non-nitrated quinolone derivatives varies from about 1/2 to one mg/mL in water and from about five to ten mg/mL in DMSO. Solubility of all of the new quinolone derivatives in CDCl_3 is negligible; therefore all NMR spectra were run using DMSO-d_6 as a solvent.

The synthesis of many more analogs of the above quinolone derivatives was attempted by using other substituted anilines. Most failed to produce any meaningful product. However some failed due to inseparable impurities, usually isomers. Below are some of the aniline derivatives which were used in failed syntheses:

- 3-Nitroaniline – produced a mix of two inseparable isomers by recrystallization, due to two different ring closures
- 2,4-Dinitroaniline – failed to produce a meaningful amount of product
- 4-Aminobenzoic acid – failed to produce a meaningful amount of product
- Sulfanilic acid (4-aminobenzenesulfonic acid) – failed to produce a meaningful amount of product
- Sulfanilamide (4-Aminobenzenesulfonamide) – failed to produce a meaningful amount of product
- 2-Methoxyaniline (o-anisidine) – failed to produce a meaningful amount of product
- 4-Methoxyaniline (p-anisidine) – failed to produce a meaningful amount of product

¹H NMR spectra

¹H NMR spectra of all the new quinolones are shown in Appendix B – ¹H NMR Spectra. All ¹H NMR spectra were run on a Bruker DRX 400 spectrometer. An annotated example of a ¹H NMR spectrum is shown in Figure 16.

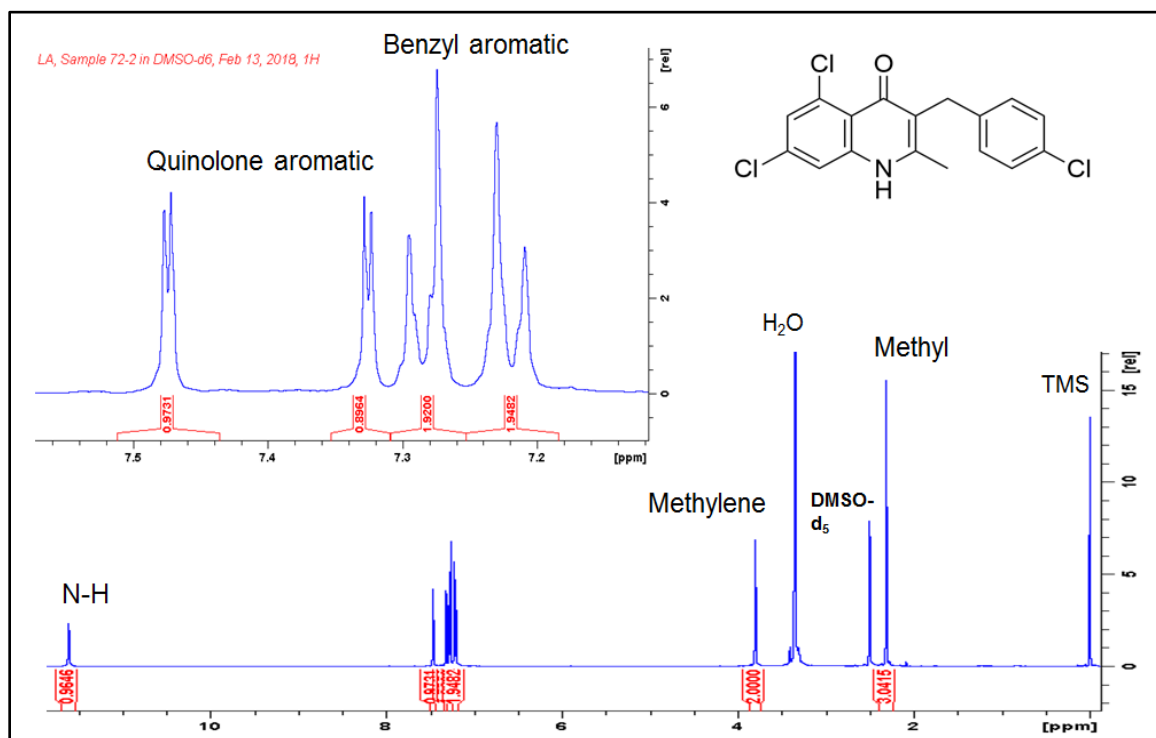


Figure 16 ¹H NMR spectrum of LA 72-2 and detail

The peaks in the above figure appear in all of the ^1H NMR spectra of the new compounds:

- N-H singlet between 11 to 12 ppm.
- Aromatic peaks from the quinolone ring above about 7.3 ppm.
- Aromatic peaks from the benzyl ring between 6.8 and 7.3 ppm.
- Methylene singlet at a shift of about 3.8 ppm
- H_2O singlet (impurity) at a shift of about 3.36 ppm. According to Gottlieb et al. (25), in DMSO-d_6 solvent, a broad singlet at a shift of about 3.33 ppm is water not HOD, which is a triplet at a shift of about 3.30 ppm.
- DMSO-d_5 quintet (impurity) at a shift of about 2.51 ppm.
- Methyl singlet (on the quinolone ring) at a shift of about 2.3 ppm.

A ^1H NMR spectrum of a sample consisting of pure DMSO- d_6 was run to demonstrate that the H_2O impurity found in all NMR spectra was inherent to the process of making up a sample. The H_2O singlet near 3.33 and the DMSO- d_5 impurity near 2.51 ppm appeared in this ^1H NMR spectrum, as in all of the ^1H NMR spectra containing quinolone derivative samples. Neither impurity peak impinged significantly on any quinolone derivative peak. The juxtaposition of two NMRS, each showing the aligned impurities, the top solvent only, the bottom LA 72-2, is shown in Figure 17.

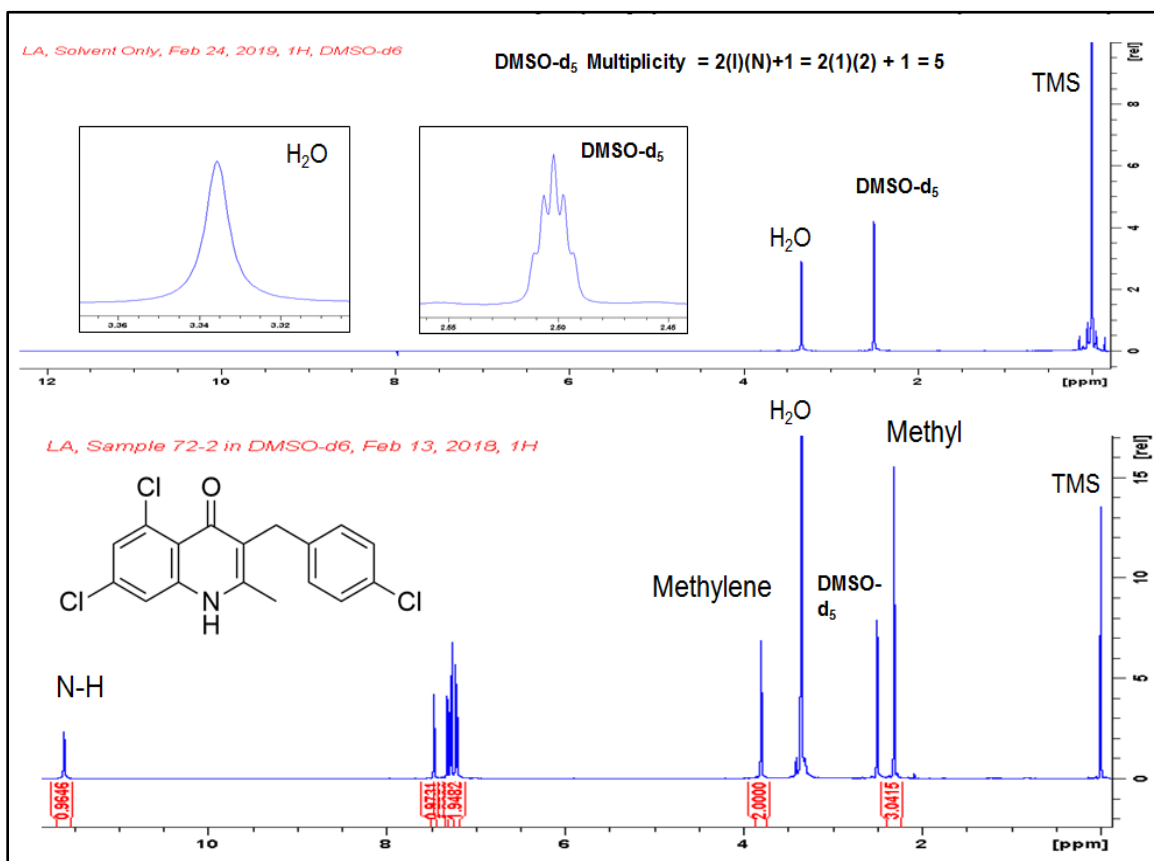


Figure 17 Juxtaposition of two NMRS showing H_2O and DMSO- d_5 impurities

¹³C NMR spectra of compounds without fluorine

¹³C NMR spectra of the all new quinolones, with and without fluorine, are shown in Appendix C – ¹³C NMR Spectra. All ¹³C NMR spectra were run on a Bruker DRX 400 spectrometer.

All of the quinolone compounds described have 17 carbon atoms. Therefore, if no carbon atoms are chemically equivalent and none is split, 17 peaks should be present. However, in the spectrum shown in Figure 18, two sets of two carbon atoms on the benzyl ring are chemically equivalent causing there to be only 15 signals from the compound. Two of these 15 are aliphatic, one is from the carbonyl carbon, and the rest are aromatic. The prominent septet centered near 39 is from the solvent, DMSO-d₆. Details of the peaks above 100 ppm are shown in the bottom half of Figure 18.

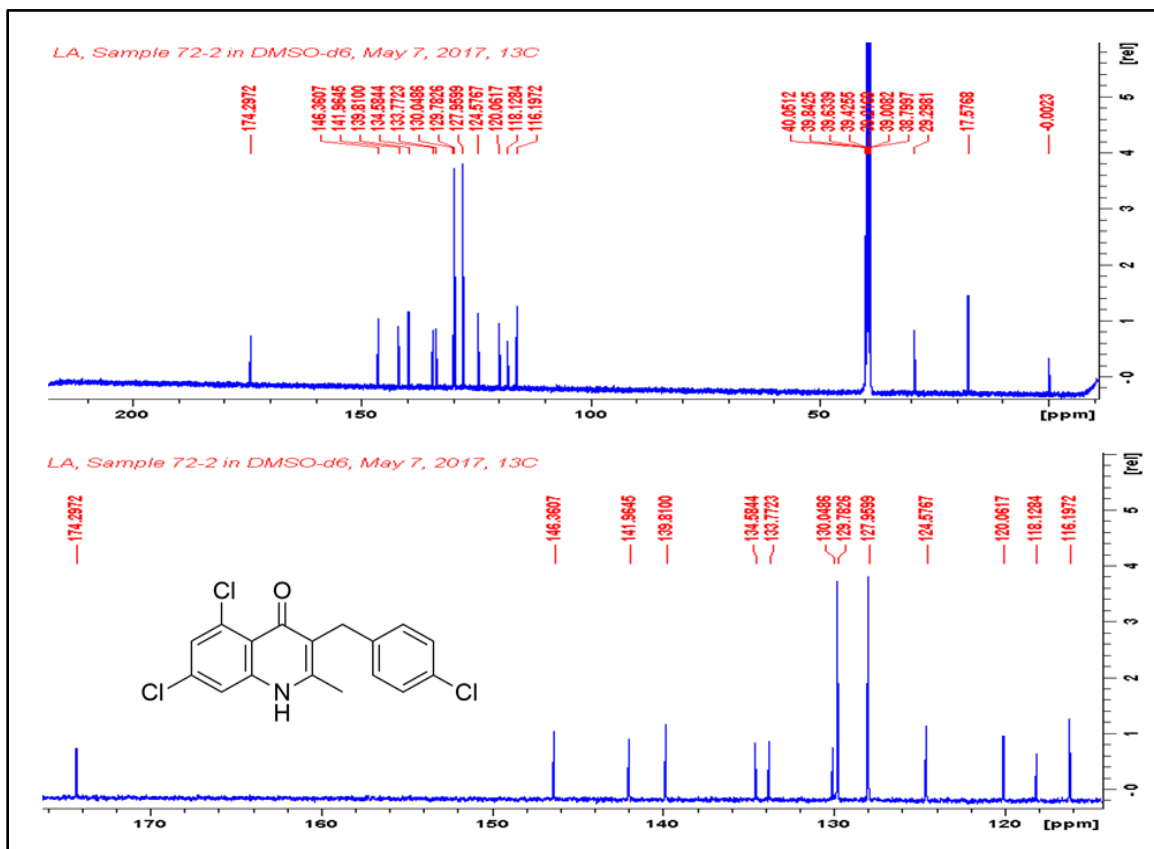


Figure 18 ¹³C NMR spectrum of LA 72-2 showing 15 peaks

In the spectrum shown in Figure 19, no carbon atom is chemically equivalent to any other, and no carbon peak is split. Therefore, 17 signals (from 17 carbon atoms) are expected and present. Two of the 17 signals are aliphatic, one is from the carbonyl carbon, and the rest are aromatic. The prominent septet centered near 39 is from the solvent, DMSO-d₆. The signal at 0 is TMS. Details of the peaks above 100 ppm are shown in the bottom half of Figure 19.

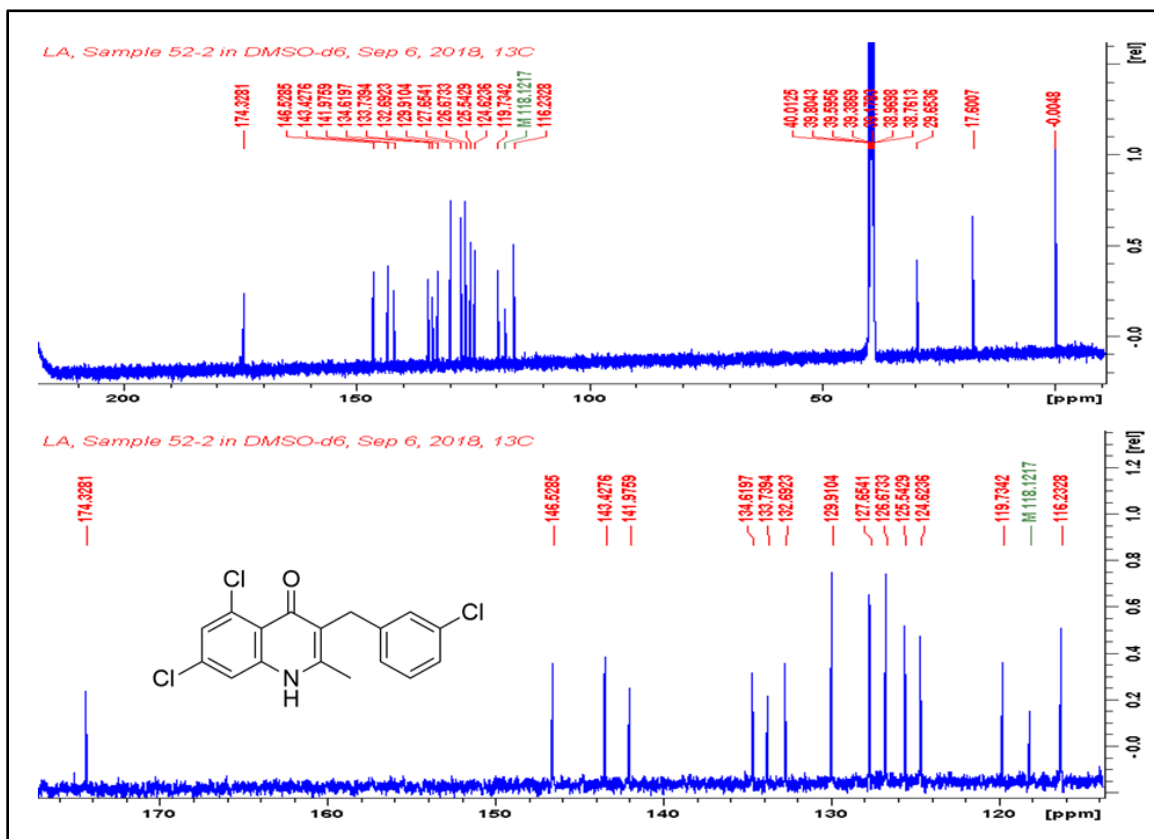


Figure 19 ¹³C NMR spectrum of LA 52-2 showing 17 peaks

^{13}C NMR spectra of fluorine containing compounds

For those compounds with a para-substituted fluorine atom on the benzyl ring, each of the four equivalent aromatic carbon atoms is expected to be split. Splitting of carbon peaks can extend beyond the aromatic ring, but often does not, as shown in the ^{13}C NMR spectrum of 4-fluorotoluene in Figure 20, from the Spectral Database for Organic Compounds (24). In this figure, the four equivalent aromatic carbons of toluene are split by the fluorine substituent as shown by the different colors of the numbers marking the peaks, but the aliphatic carbon is not split, and shows up as a single peak.

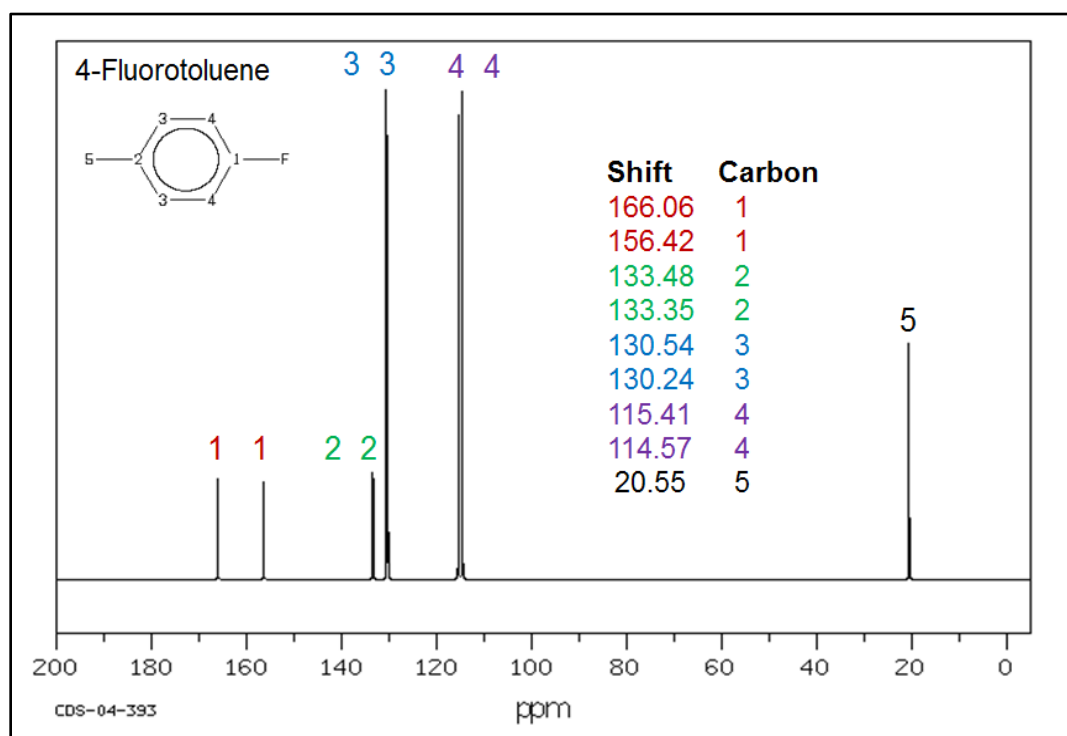


Figure 20 ^{13}C NMR Spectrum of 4-fluorotoluene

For those compounds with a meta-substituted fluorine atom on the benzyl ring, each of the six aromatic carbon atoms is expected to be split. Splitting of carbon peaks can extend one atom beyond the aromatic ring, as shown in the ^{13}C spectrum of 3-fluorotoluene in Figure 21, from the Spectral Database for Organic Compounds (24). In this figure, the six aromatic carbons and the aliphatic carbon of toluene are each split by the fluorine substituent as shown by the different colors of the numbers marking the peaks.

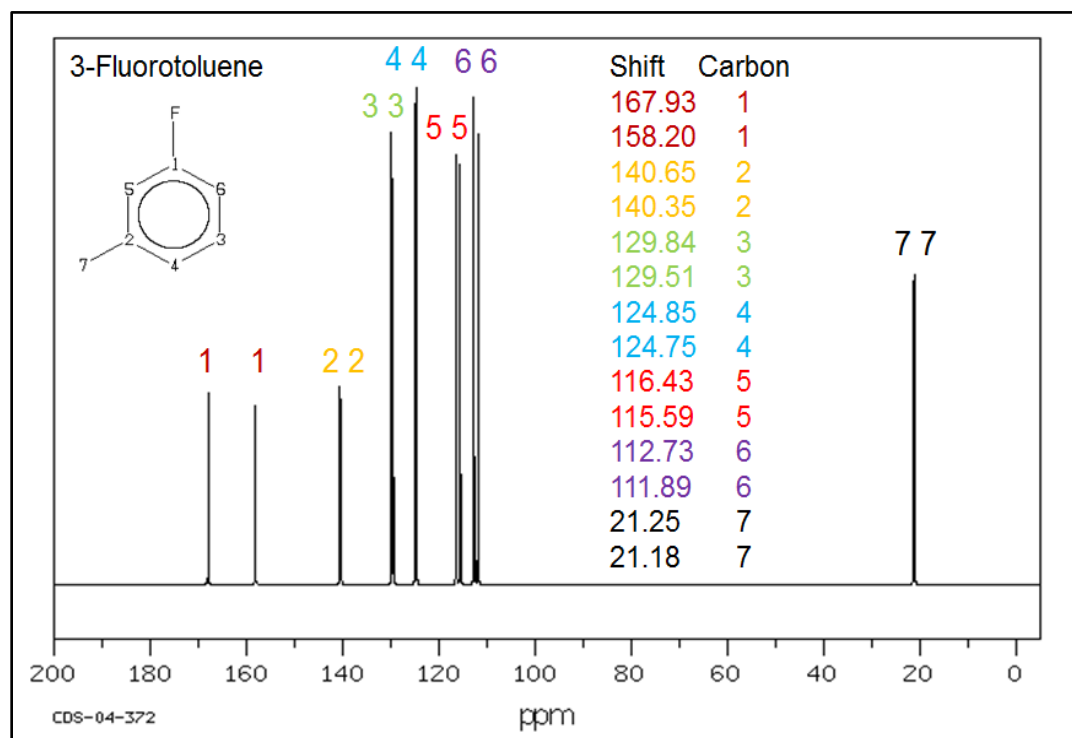


Figure 21 ^{13}C NMR Spectrum of 3-fluorotoluene

Since all of the compounds described in this paper contain at most one fluorine atom, and since that atom is always a substituent on a benzyl ring if present, ^{13}C NMR spectra make clear the presence and location of a fluorine atom if present.

In the spectrum shown in Figure 22, two sets of two carbon atoms are chemically equivalent. In the absence of any splitting, 15 signals would be expected. However, a fluorine atom is present on the benzyl ring, and it causes all carbon atoms on the ring to be split. Therefore, $(17 - 2) + (6 - 2)$ or 19 signals are expected and present. Two of the signals are aliphatic, one is from the carbonyl carbon, and the rest are aromatic. The prominent septet centered near 39 is from the solvent, DMSO- d_6 . The signal at 0 is TMS. Details of the peaks above 100 ppm are shown in the bottom half of Figure 22. The four split carbon signals are near 160, 136, 129, and 114 ppm.

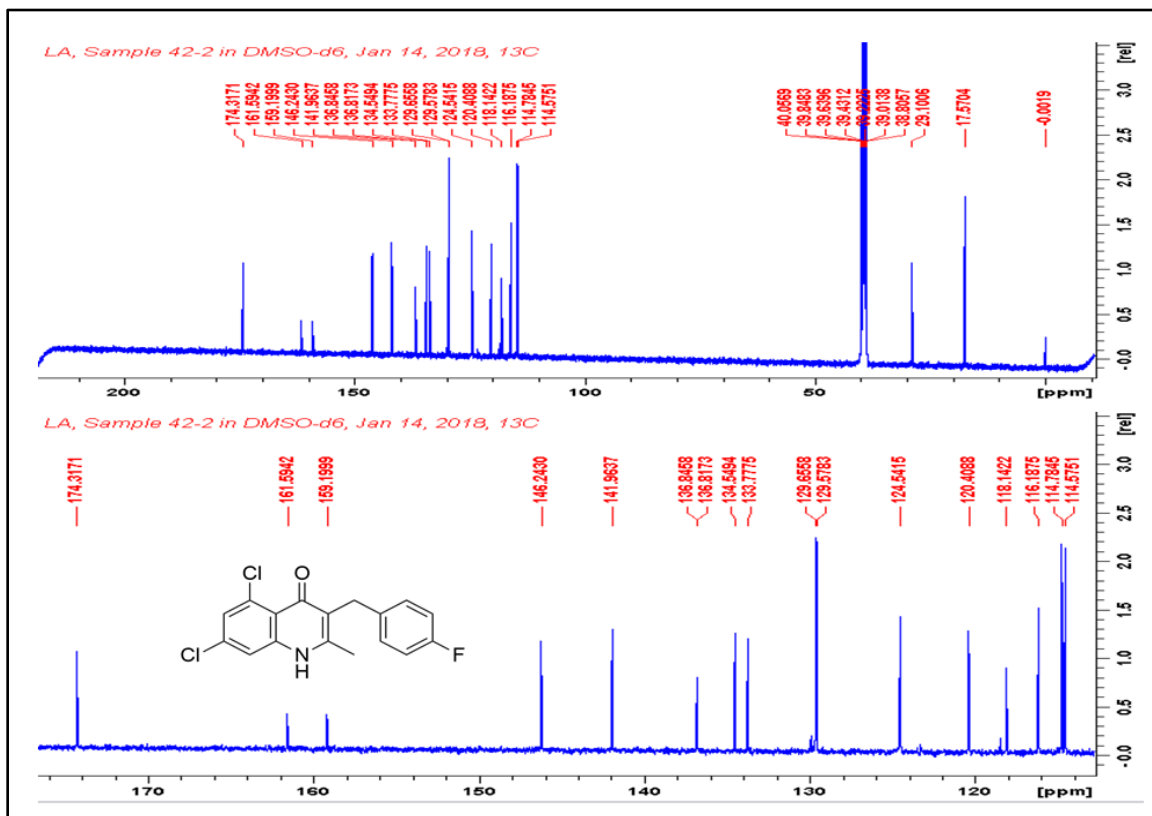


Figure 22 ^{13}C NMR spectrum of LA 42-2 showing 19 peaks

In the spectrum shown in Figure 23, no carbon atom is chemically equivalent to any other. In the absence of any splitting, 17 signals (from 17 carbon atoms) would be expected. However, a fluorine atom is present on the benzyl ring, and it causes all carbon atoms on the ring to be split. Therefore, 17 + 6 or 23 signals are expected and present. Two of the signals are aliphatic, one is from the carbonyl carbon, and the rest are aromatic. The prominent septet centered near 39 is from the solvent, DMSO-d₆. The signal at 0 is TMS. Details of the peaks above 100 ppm are shown in the bottom half of Figure 23. The six split carbon signals are near 161, 142, 129, 124, 114, and 112 ppm.

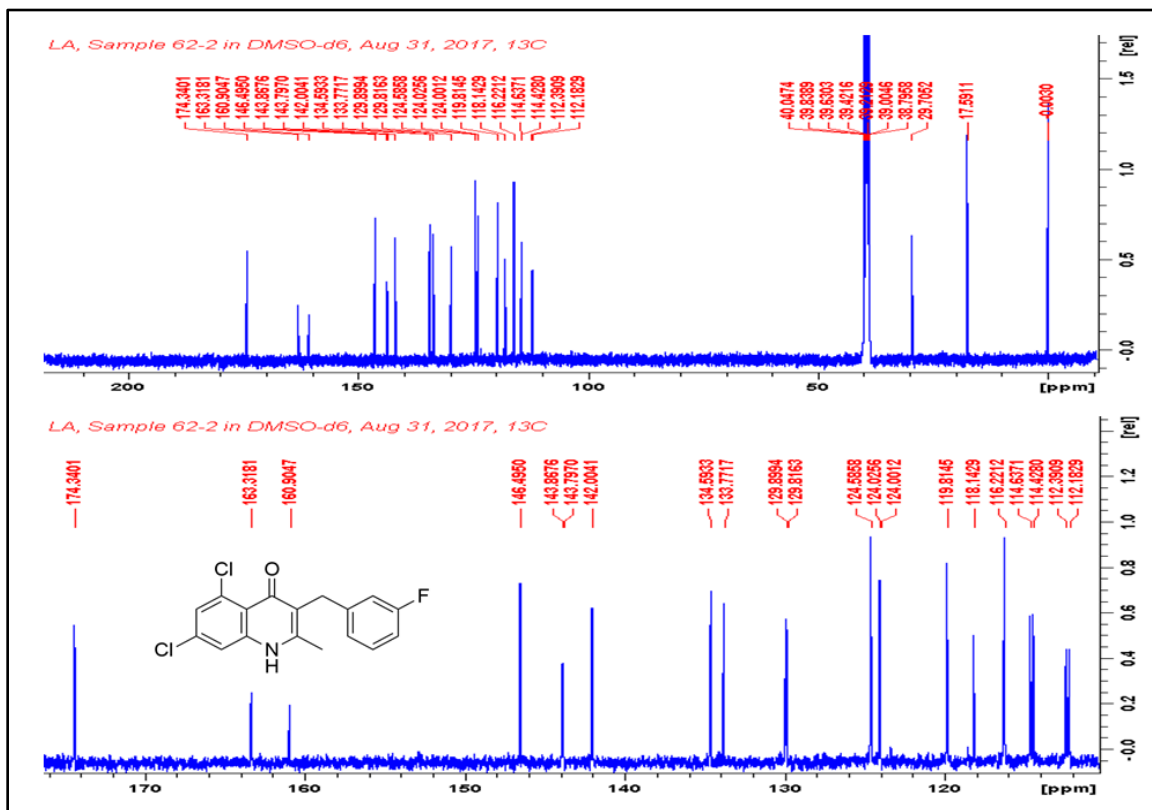


Figure 23 ¹³C NMR spectrum of LA 62-2 showing 23 peaks

The one apparent exception to 23 peaks in compounds with a 3-fluorobenzyl derivative is LA 61-2; it has only 22 peaks, instead of 23. However, this is due to an overlap of two peaks at 124.04 ppm, so counting this overlap, LA 61-2 also has 23 peaks. Its ^{13}C NMR spectrum (full and detail) is shown in Table 22.

¹⁹F NMR Spectra

A ¹⁹F NMR spectrum was run on each of the ten compounds containing fluorine. ¹⁹F NMR spectra of these quinolones are shown in Appendix D – ¹⁹F NMR Spectra. All ¹⁹F NMR spectra were run on a Bruker Avance III HD 400 spectrometer. Fluorobenzene was used as a standard to calibrate the NMR spectra, since its ¹⁹F peak at a known shift of -113.10 ppm was assumed to be close to the ¹⁹F peaks of the compounds in question (26). ¹⁹F NMR spectra of the all new quinolones are shown in Appendix D – ¹⁹F NMR Spectra.

Elemental Analysis

An elemental analysis by Atlantic Microlabs for C, H, N, and F or Cl was run on each of the quinolone derivatives. The results are summarized in Table 3, which shows the percentage errors between computed percentages of elements in the compounds and measured ones as well as the percentage errors in the synthetic components.

Table 3 Elemental Analysis of Quinolone Derivatives

Compound	Formula	C Error	N Error	H Error	Cl Error	F Error	Avg Error	Aniline Derivative Impurity	Benzyl Derivative Impurity
LA 41-2	C ₁₇ H ₁₃ NOClF	0.28%	1.38%	0.43%	0.68%	0.16%	0.53%	2%	3%
LA 61-2	C ₁₇ H ₁₃ NOClF	0.21%	1.38%	0.00%	0.26%	0.32%	0.43%	2%	5%
LA 42-2	C ₁₇ H ₁₂ NOCl ₂ F	0.18%	2.70%	1.12%	0.76%	0.53%	1.06%	2%	3%
LA 52-2	C ₁₇ H ₁₂ NOCl ₃	0.26%	2.91%	1.51%	0.63%	N/A	1.33%	2%	3%
LA 62-2	C ₁₇ H ₁₂ NOCl ₂ F	0.12%	1.67%	1.20%	0.71%	0.53%	0.85%	2%	5%
LA 72-2	C ₁₇ H ₁₂ NOCl ₃	0.12%	1.17%	1.76%	0.56%	N/A	0.90%	2%	2%
LA 44-2	C ₁₇ H ₁₄ NOF	0.20%	1.33%	1.34%	N/A	0.00%	0.72%	2%	3%
LA 54-2	C ₁₇ H ₁₄ NOCl	0.17%	1.81%	0.00%	2.10%	N/A	1.02%	2%	3%
LA 64-2	C ₁₇ H ₁₄ NOF	0.13%	1.70%	0.76%	N/A	1.55%	1.04%	2%	5%
LA 74-2	C ₁₇ H ₁₄ NOCl	0.33%	3.22%	0.61%	0.88%	N/A	1.26%	2%	2%
LA 45-2	C ₁₇ H ₁₃ N ₂ O ₃ F	0.43%	0.00%	2.45%	N/A	3.29%	1.54%	2%	3%
LA 55-2	C ₁₇ H ₁₃ N ₂ O ₃ Cl	0.45%	1.50%	1.41%	2.23%	N/A	1.40%	2%	3%
LA 65-2	C ₁₇ H ₁₃ N ₂ O ₃ F	0.44%	0.71%	1.45%	N/A	1.33%	0.98%	2%	5%
LA 75-2	C ₁₇ H ₁₃ N ₂ O ₃ Cl	0.31%	0.50%	2.82%	2.70%	N/A	1.58%	2%	2%
LA 46-2	C ₁₇ H ₁₃ NOClF	0.38%	2.53%	4.31%	2.38%	3.33%	2.59%	2%	3%
LA 56-2	C ₁₇ H ₁₃ NOCl ₂	0.33%	3.16%	0.91%	0.85%	N/A	1.31%	2%	3%
LA 66-2	C ₁₇ H ₁₃ NOClF	0.07%	3.23%	1.51%	1.36%	0.48%	1.33%	2%	5%

The impurities in the compounds are likely from three sources:

- 1) The aniline derivatives used in synthesis were all 98% pure according to the labels. It is likely that some of the 2% of impurities would have been compatible with the purification step of the quinolone syntheses, and would have led to impurities in the final compounds.
- 2) The benzyl bromide derivatives combined with methyl acetoacetate in the syntheses varied from 95% to 98% pure (therefore from 2% to 5% impure), according to the labels. Since all of these compounds were supposed to be singly halogenated, any instances of double halogenation or lack of halogenation would have led directly to elemental analysis errors in the final compounds, and would almost certainly not have been eliminated during the purification step of recrystallization.
- 3) The compounds were not dried by Atlantic Microlabs before elemental analysis. Therefore, there may have been some water in the compounds analyzed. For instance if LA 45-2 ($C_{17}H_{13}N_2O_3F$, FW = 312.426) included one molecule of water for every one hundred molecules of compound, its H content would be in error by about $[(2 * 1.008) / 18.015] / [(13 * 1.008) / 312.426 * 100]$ or about 2.7%. In this case the measured error was 2.45%. So a tiny amount of water content could easily account for all of the errors in H content.

Infrared Spectra

Infrared spectra were run on all the samples. Each sample was mixed with potassium bromide (KBr) in a ratio of about 1 mg sample to about 200 mg KBr. The resulting powder was crushed with an agate mortar and pestle, and then pressed to make a translucent plate. An Agilent Cary 630 FTIR spectrometer was then used to make an infrared spectrum in percent transmittance mode. All the FTIR spectra are shown in Appendix E – Infrared Spectra.

Quinolones can be viewed as keto-enol tautomers as shown in Figure 24. Although the keto form (**24**) appears in ^1H and ^{13}C NMR spectra of the quinolone compounds when dissolved in DMSO- d_6 solvent, the enol form (**25**), appears in infrared spectra when the quinolone compounds are compressed into KBr pellets.

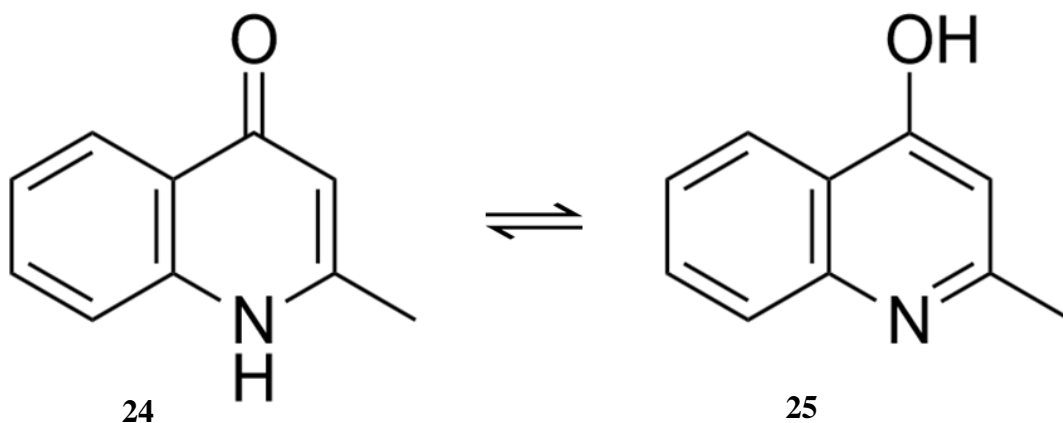


Figure 24 Keto-enol tautomerism in quinolones

Some general assignments for the IR spectra follow (27):

- $3200 - 3600 \text{ cm}^{-1} \Rightarrow$ O-H stretching of the enol form
- $3300 - 3400 \text{ cm}^{-1} \Rightarrow$ N-H stretching
- $1450 - 1600 \text{ cm}^{-1} \Rightarrow$ C-C ring stretching
- $1100 - 1250 \text{ cm}^{-1} \Rightarrow$ C-F stretching
- Near $1100 \text{ cm}^{-1} \Rightarrow$ C-Cl stretching

Anti-bacterial Testing

The quinolone compounds were tested at two concentrations on the following three bacteria, in a study conducted by a George Mason student (28).

- *Staphylococcus saprophyticus*
- *Escherichia coli*
- *Pseudomonas stutzeri*

Staphylococcus saprophyticus, a Gram-positive coccus, is a common cause of urinary infections. Most strains of *Escherichia coli*, a Gram-negative rod-shaped bacterium commonly found in the gut, are harmless. However, some strains can cause food poisoning. *Pseudomonas stutzeri*, a Gram-negative bacterium commonly found in soil, does not generally cause infections in humans.

All three strains of bacteria used in testing are Biological Safety Level 1 (BSL 1) safe. These BSL 1 derivatives are relatively harmless to humans, but each of these strains has a pathological strain that can cause harm to humans.

A spectrophotometer was used to measure the absorbance of each bacterium, and each was normalized to a McFarland Standard. For each combination of a quinolone compound and a bacterium, 0.25 mL of an absorbance standardized bacterial solution was plated on a Mueller-Hinton plate and dried for a few minutes. Each plate was then inoculated with 0.5 µg (micrograms) of one of the quinolone compounds dissolved in

DMSO and then incubated at 37° C overnight. In addition, three control plates were used in testing: one was inoculated with DMSO, one with triple sulfa (a mix of three sulfa drugs: sulfathiazole, sulfacetamide, and sulfabenzamide), and one with bacitracin (a mix of cyclic peptides produced by *Bacillus subtilis*). DMSO, as expected, had no zone of inhibition on any plate. Bacitracin, as expected, had a zone of inhibition only on the *Staphylococcus saprophyticus* (Gram-positive) plate. Triple sulfa, as expected, had a zone of inhibition on all of the plates.

None of the quinolone compounds at a dose of 0.5 µg had any effect (zone of inhibition) on any of the three bacteria. The dose of each quinolone compound was therefore increased to ten times its previous level. For each combination of a quinolone compound and a bacterium, 0.25 mL of an absorbance standardized bacterial solution was plated on a Mueller-Hinton plate and dried for a few minutes. Each plate was then inoculated with 5.0 µg of one of the quinolone compounds dissolved in DMSO and then incubated at 37° C overnight. Once again, none of the compounds had any effect (zone of inhibition) on any of the bacteria.

No testing of any of the quinolone compounds was performed on viruses, so it is unknown if any of the compounds has any antiviral properties. However, Elvitegravir (shown earlier in Figure 7) demonstrates quinolone derivatives can be highly effective as antiviral agents.

Conclusions

The major objective of this project was to synthesize new halogenated (fluorinated or chlorinated) and / or nitrated quinolone derivatives. This objective was met, although in a slightly modified form. The original purpose was to create as many nitrated quinolones as possible, but the only successful nitrated compounds created used 4-nitroaniline as the aniline derivative.

Attempts to use 3-nitroaniline failed due to a mixture of two isomeric products. An example of the two isomers that result when 3-nitroaniline (**26**) is condensed with methyl 2-(4-chlorobenzyl)-acetoacetate (**27**) is shown in Figure 25. The isomers result because it is possible for the new ring to form either at the 2 position or the 6 position in the 3-chloroaniline ring. (The -NH₂ group is at the 1 position on the 3-chloroaniline ring.) Based on ¹H NMR analysis, the predominant isomer (**28**) forms about 2/3 of the product due its less crowded configuration, while the more crowded isomer (**29**) forms the remaining 1/3 of the product. While is it possible to separate these isomers by chromatography, it is expensive, time consuming, and decreases yield. For this reason, aniline derivatives with a substituent at the 3 position were rejected.

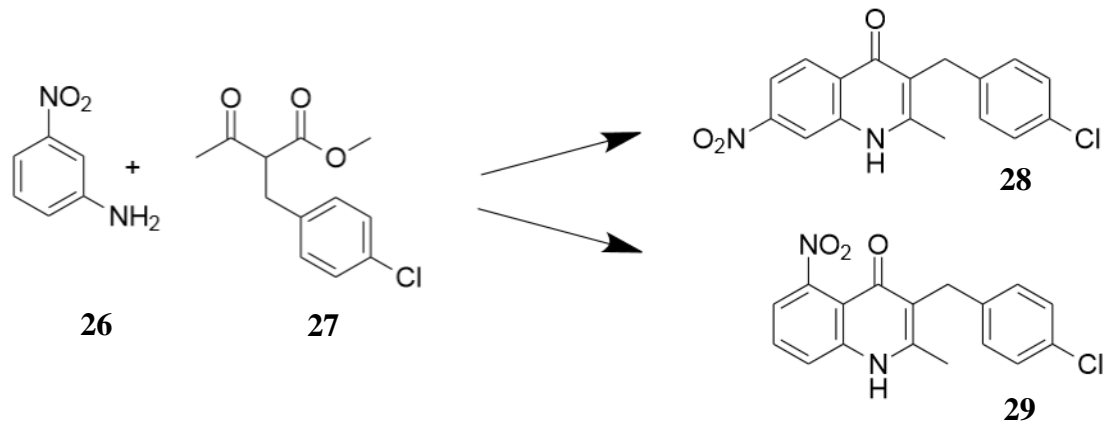


Figure 25 Twin isomers resulting from 3-nitroaniline

Aniline derivatives with acid substituents were considered due to the fact that an acid substituent in the final product would increase water solubility in a manner similar to a nitro substituent. However, attempts to use anilines with acid substituents, namely 4-aminobenzoic acid and sulfanilic acid, failed. This was probably due to the fact that these aniline derivatives were in the form of zwitter ions, with a positive charge on the nitrogen. An aniline derivative in this form would have been ineffective in an imine reaction.

Attempts to use sulfanilamide, an aniline derivative with an amide substituent, also failed. Attempts to use aniline derivatives containing multiple substituents such as 2-chloro-4-nitroaniline failed. Finally, attempts to use 2-methoxyaniline, and 3-methoxyaniline, (anilines with ether substituents) failed. Had a synthesis using 3-

methoxyaniline worked, it almost certainly would have failed due to the production of isomers as detailed above for 3-nitroaniline.

Attempts to use 2,4-dinitroaniline failed to produce a measurable amount of product. This was likely due to the weakening and or deactivation of the benzene ring caused by the dual nitro substituents. The reaction requires that the imine formed from the aniline derivative (2,4-dinitroaniline) undergo a condensation reaction at a temperature of more than 250° C for more than one hour, and it is possible that the 2,4-dinitroaniline ring was simply unequal to the stress induced by these conditions.

The aniline derivatives which worked well were 2-chloroaniline, 4-chloroaniline, 3,5-dichloroaniline, 4-nitroaniline, and aniline itself. Aniline, and 3,5-dichloroaniline derivatives produced both excellent proton and ¹³C NMR spectra. Of the four compounds produced with 4-chloroaniline, the one with a 3-chlorobenzyl group was found to exist already, and was excluded from analysis. The one with a 4-chlorobenzyl was incorrectly believed to exist already as well, and consequently was not analyzed. Spectra of compounds using 2-chloroaniline were not as good as those derived from other chloroaniline derivatives. One reason could be the crowding this derivative engendered – the large chlorine substituent is adjacent to the amino substituent, probably making the reaction of the amino group more difficult. The 4-nitroaniline derivatives produced very good NMR spectra, although not quite as good as the other chloroaniline derivatives, probably due to weakening of the aromatic ring caused by the nitro substituent. This could

have resulted in degradation of the ring in the experimental procedure, in which high temperatures (~250° C) were used for an hour or more.

The halogenated benzyl bromides used in the synthesis of the compounds varied in purity from 95% to 98%. This almost certainly caused some breakdown in the purity of the synthetic results, since the recrystallization method used to purify those results could not have distinguished synthetic products containing improperly substituted benzyl rings from those containing properly substituted benzyl rings. Given purities of 95% to 98%, it was almost certainly the case that improperly halogenated benzyl bromides were present. The expected outcome of this would be unexpected minor variations in the hydrogen, fluorine, and chlorine percentages found in the compounds by elemental analysis, which was the case.

Aniline and the aniline derivatives used in the syntheses were all 98% pure. This almost certainly also contributed to minor errors found in elemental analysis. If the impure aniline input was able to participate in the required reactions, but had unexpected substituents, then once again the recrystallization used to purify the resulting final compounds might easily have failed to distinguish between the intended product and a slight variant thereof. This could have contributed to unexpected minor variations in the carbon and nitrogen percentages found in the elemental analyses.

The reason for the use of inputs with impurities in the range of 95% to 98% was simply cost. High purity inputs cost very much more, and were simply not affordable.

A secondary objective of this project was to test, where possible, the antibacterial effectiveness of the new compounds. DMSO was used as a solvent for the compounds, due to a roughly tenfold increase in solubility of those compounds in DMSO compared to water.

Unfortunately, the compounds did not produce any noticeable effect on the three types of bacteria against which they were tested. In retrospect, benzyl bromides with substituents other than fluorine or chlorine should probably have been tried. This could have resulted in compounds which might have proven more effective as antibacterial agents.

Experimental

Synthesis of LA 34-2: Methyl 2-(4-fluorobenzyl)-acetoacetate

To a 250 mL round bottom flask were added 75 mmol of NaH (sodium hydride, 60% in mineral oil), 50 mL of THF (tetrahydrofuran), and a stir bar. After sealing with a rubber cap, the flask was flushed with nitrogen gas and stirred for 20 minutes in a water ice bath at 0° C. The color at this point was milky white. Next, 75 mmol of methyl acetoacetate were added to the flask through the rubber cap with a syringe, dropwise over ten minutes, after which the flask was stirred under nitrogen gas at 0° C for another 20 minutes. During this time the color changed from milky white to a clear, pale yellow. Then 75 mmol of 4-fluorobenzyl bromide were added dropwise over ten minutes, and the mixture was stirred under nitrogen gas at 0° C for another 20 minutes. After being warmed to 50° to 60° C in order to speed the S_N2 reaction, the mixture was stirred under nitrogen gas for 40 minutes. During this time the color changed to darker, but still clear, yellow.

After cooling, ten mL of water were added to lessen the viscosity, and then the very basic mixture was neutralized with 1 M HCl until the pH reached 7.0. The product, LA

34-2, methyl 2-(4-fluorobenzyl)-acetoacetate, was extracted twice with 20 mL of diethyl ether, washed twice with 20 mL of diethyl ether, then poured over MgSO₄ to remove any remaining water. After filtration to remove the MgSO₄, LA 34-2 was separated from any remaining reactants and solvents by an ISCO CombiFlash Separation System Sg 100c. LA 34-2 was then evacuated on a Buchi Rotavapor R-114 for several hours at 80° C. The yield was found to be 79.3%.

LA 34-2, methyl 2-(4-fluorobenzyl)-acetoacetate, was used as an intermediate in the synthesis of the compounds LA 41-2, LA 42-2, LA 44-2, LA 45-2, and LA 46-2.

Synthesis of LA 35-2: Methyl 2-(3-chlorobenzyl)-acetoacetate

To a 250 mL round bottom flask were added 75 mmol of NaH (sodium hydride, 60% in mineral oil), 50 mL of THF (tetrahydrofuran), and a stir bar. After sealing with a rubber cap, the flask was flushed with nitrogen gas and stirred for 20 minutes in a water ice bath at 0° C. The color at this point was milky white. Next, 75 mmol of methyl acetoacetate were added to the flask through the rubber cap with a syringe, dropwise over ten minutes, after which the flask was stirred under nitrogen gas at 0° C for another 20 minutes. During this time the color changed from milky white to a clear, pale yellow. Then 75 mmol of 3-chlorobenzyl bromide were added dropwise over ten minutes, and the mixture was stirred under nitrogen gas at 0° C for another 20 minutes. After being warmed to 50° to 60° C in order to speed the S_N2 reaction, the mixture was stirred under nitrogen gas for 40 minutes. During this time the color changed to darker, but still clear, yellow.

After cooling, ten mL of water were added to lessen the viscosity, and then the very basic mixture was neutralized with 1 M HCl until the pH reached 7.0. The product, LA 35-2, methyl 2-(3-chlorobenzyl)-acetoacetate, was extracted twice with 20 mL of diethyl ether, washed twice with 20 mL of diethyl ether, then poured over MgSO₄ to remove any remaining water. After filtration to remove the MgSO₄, LA 35-2 was separated from any remaining reactants and solvents by an ISCO CombiFlash Separation System Sg

100c. LA 35-2 was then evacuated on a Buchi Rotavapor R-114 for several hours at 80°

C. The yield was found to be 68.4%.

LA 35-2, methyl 2-(3-chlorobenzyl)-acetoacetate, was used as an intermediate in the synthesis of the compounds LA 52-2, LA 54-2, LA 55-2, and LA 56-2.

Synthesis of LA 36-2: Methyl 2-(3-fluorobenzyl)-acetoacetate

To a 250 mL round bottom flask were added 75 mmol of NaH (sodium hydride, 60% in mineral oil), 50 mL of THF (tetrahydrofuran), and a stir bar. After sealing with a rubber cap, the flask was flushed with nitrogen gas and stirred for 20 minutes in a water ice bath at 0° C. The color at this point was milky white. Next, 75 mmol of methyl acetoacetate were added to the flask through the rubber cap with a syringe, dropwise over ten minutes, after which the flask was stirred under nitrogen gas at 0° C for another 20 minutes. During this time the color changed from milky white to a clear, pale yellow. Then 75 mmol of 3-fluorobenzyl bromide were added dropwise over ten minutes, and the mixture was stirred under nitrogen gas at 0° C for another 20 minutes. After being warmed to 50° to 60° C in order to speed the S_N2 reaction, the mixture was stirred under nitrogen gas for 40 minutes. During this time the color changed to darker, but still clear, yellow.

After cooling, ten mL of water were added to lessen the viscosity, and then the very basic mixture was neutralized with 1 M HCl until the pH reached 7.0. The product, LA 36-2, methyl 2-(3-fluorobenzyl)-acetoacetate, was extracted twice with 20 mL of diethyl ether, washed twice with 20 mL of diethyl ether, then poured over MgSO₄ to remove any remaining water. After filtration to remove the MgSO₄, LA 36-2 was separated from any remaining reactants and solvents by an ISCO CombiFlash Separation System Sg

100c. LA 36-2 was then evacuated on a Buchi Rotavapor R-114 for several hours at 80°

C. The yield was found to be 66.4%.

LA 36-2, methyl 2-(3-fluorobenzyl)-acetoacetate, was used as an intermediate in the synthesis of the compounds LA 61-2, LA 62-2, LA 64-2, LA 65-2, and LA 66-2.

Synthesis of LA 37-2: Methyl 2-(4-chlorobenzyl)-acetoacetate

To a 250 mL round bottom flask were added 75 mmol of NaH (sodium hydride, 60% in mineral oil), 50 mL of THF (tetrahydrofuran), and a stir bar. After sealing with a rubber cap, the flask was flushed with nitrogen gas and stirred for 20 minutes in a water ice bath at 0° C. The color at this point was milky white. Next, 75 mmol of methyl acetoacetate were added to the flask through the rubber cap with a syringe, dropwise over ten minutes, after which the flask was stirred under nitrogen gas at 0° C for another 20 minutes. During this time the color changed from milky white to a clear, pale yellow. Then 75 mmol of 4-chlorobenzyl bromide were added dropwise over ten minutes, and the mixture was stirred under nitrogen gas at 0° C for another 20 minutes. After being warmed to 50° to 60° C in order to speed the S_N2 reaction, the mixture was stirred under nitrogen gas for 40 minutes. During this time the color changed to darker, but still clear, yellow.

After cooling, ten mL of water were added to lessen the viscosity, and then the very basic mixture was neutralized with 1 M HCl until the pH reached 7.0. The product, LA 37-2, methyl 2-(4-chlorobenzyl)-acetoacetate, was extracted twice with 20 mL of diethyl ether, washed twice with 20 mL of diethyl ether, then poured over MgSO₄ to remove any remaining water. After filtration to remove the MgSO₄, LA 37-2 was separated from any remaining reactants and solvents by an ISCO CombiFlash Separation System Sg

100c. LA 37-2 was then evacuated on a Buchi Rotavapor R-114 for several hours at 80°

C. The yield was found to be 52.4%.

LA 37-2, methyl 2-(4-chlorobenzyl)-acetoacetate, was used as an intermediate in the synthesis of the compounds LA 72-2, LA 74-2, LA, and 75-2.

Synthesis of LA 41-2: 6-Chloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

Five mmol of methyl 2-(4-fluorobenzyl)-acetoacetate, five mmol of 4-chloroaniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 41-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 41-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 41-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 75 minutes at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy to black over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was a light tan precipitate with a yield of 50%.

The compound has a melting point > 260° C. IR: 3400, 2800 – 2900, 1400 – 1600, 1220, 1150, 820 cm⁻¹. Elemental Analysis (C₁₇H₁₃NOCIF): C = 67.48%, H = 4.40%, N = 4.66%, Cl = 11.83%, F = 6.29%. ¹H NMR (DMSO-d₆) δ: 2.36 (singlet, 3H, methyl), 3.87 (singlet, 2H, methylene), 7.04 (triplet, J = 9.0 Hz, 2H, Aromatic), 7.24 (triplet, J = 7.2 Hz, 2H, Aromatic), 7.54 (doublet, J = 8.8 Hz, 1H, Quinolone), 7.64 (doublet, J = 8.8 Hz, 1H, Quinolone), 8.02 (doublet, J = 2.5 Hz, 1H, Quinolone), 11.74 (singlet, 1H, N-H).

^{13}C NMR (DMSO- d_6) δ : 17.78, 29.06, 114.57, 114.78, 118.48, 120.03, 124.01, 124.43, 127.10, 129.57, 129.65, 131.23, 137.01, 137.04, 137.67, 147.60, 159.18, 161.57, 174.35.

^{19}F NMR (DMSO- d_6) δ : -117.96.

Synthesis of LA 61-2: 6-Chloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

Five mmol of methyl 2-(3-fluorobenzyl)-acetoacetate, five mmol of 4-chloroaniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 61-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 61-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 61-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 60 minutes, at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was an ivory precipitate with a yield of 55%.

The compound has a melting point > 260° C. IR: 3400, 2950, 1600, 1450 – 1520, 1350, 1250 cm⁻¹. Elemental Analysis (C₁₇H₁₃NOClF): C = 67.53%, H = 4.40%, N = 4.64%, Cl = 11.78%, F = 6.32%. ¹H NMR (DMSO-d₆) δ: 2.37 (singlet, 3H, methyl), 3.92 (singlet, 2H, methylene), 7.01 (complex, 3H, Aromatic), 7.27 (quartet, J = 7.4 Hz, 1H, Aromatic), 7.55 (doublet, J = 8.9 Hz, 1H, Quinolone), 7.64 (doublet, J = 8.8 Hz, 1H, Quinolone), 8.04 (doublet, J = 2.1 Hz, 1H, Quinolone), 11.76 (singlet, 1H, N-H). ¹³C

NMR (DMSO-d₆) δ : 17.82, 29.69, 112.19, 112.39, 114.45, 114.66, 117.92, 120.06, 124.02, 124.04, 124.43, 127.18, 129.83, 129.92, 131.27, 137.71, 144.00, 144.07, 147.81, 160.92, 163.33, 174.40. There is a hidden peak in the 124.0x range – the resolution of the 400 MHz NMR is incapable of showing it. ¹⁹F NMR (DMSO-d₆) δ : -113.97.

Synthesis of LA 42-2: 5,7-Dichloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

Five mmol of methyl 2-(4-fluorobenzyl)-acetoacetate, five mmol of 3,5-dichloroaniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 42-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 42-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 42-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 75 minutes at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was a light tan precipitate with a yield of 45%.

The compound has a melting point > 260° C. IR: 3420, 3100, 2980, 1650, 1550, 1500, 1330, 850 cm^{-1} . Elemental Analysis ($\text{C}_{17}\text{H}_{12}\text{NOCl}_2\text{F}$): C = 60.85%, H = 3.70%, N = 4.12%, Cl = 20.93%, F = 5.62%. ^1H NMR (DMSO-d_6) δ : 2.32 (singlet, 3H, methyl), 3.80 (singlet, 2H, methylene), 7.05 (triplet, J = 8.9, 2H, Aromatic), 7.23 (triplet, J = 7.2 Hz, 2H, Aromatic), 7.31 (doublet, J = 2.0 Hz, 1H, Quinolone), 7.46 (doublet, J = 2.1 Hz, 1H, Quinolone), 11.59 (singlet, 1H, N-H). ^{13}C NMR (DMSO-d_6) δ : 17.57, 29.10,

114.58, 114.78, 116.19, 118.14, 120.41, 124.54, 129.58, 129.66, 133.78, 134.55, 136.82,
136.85, 141.96, 146.24, 159.20, 161.59, 174.32. ^{19}F NMR (DMSO- d_6) δ : -117.93.

Synthesis of LA 52-2: 5,7-Dichloro-3-(3-chlorobenzyl)-2-methyl-4-quinolone

Five mmol of methyl 2-(3-chlorobenzyl)-acetoacetate, five mmol of 3,5-dichloroaniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 52-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 52-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 52-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 75 minutes at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was an ivory precipitate with a yield of 49%.

The compound has a melting point > 260° C. IR: 3420, 3100, 2980, 1500 – 1630, 1330, 780 cm⁻¹. Elemental Analysis (C₁₇H₁₂NOCl₃): C = 58.05%, H = 3.53%, N = 3.91%, Cl = 29.97%. ¹H NMR (DMSO-d₆) δ: 2.33 (singlet, 3H, methyl), 3.83 (singlet, 2H, methylene), 7.21 (complex, 4H, Aromatic), 7.33 (doublet, J = 2.1 Hz, 1H, Quinolone), 7.48 (doublet, J = 2.1 Hz, 1H, Quinolone), 11.63 (singlet, 1H, N-H). ¹³C

NMR (DMSO-d₆) δ : 17.60, 29.65, 116.23, 118.12, 119.73, 124.62, 125.54, 126.67,
127.65, 129.91, 132.69, 133.74, 134.62, 141.98, 143.43, 146.53, 174.33.

Synthesis of LA 62-2: 5,7-Dichloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

Five mmol of methyl 2-(3-fluorobenzyl)-acetoacetate, five mmol of 3,5-dichloroaniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 62-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 62-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 62-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 75 minutes at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was an ivory precipitate with a yield of 58%.

The compound has a melting point > 260° C. IR: 3420, 3280, 3120, 2980, 1650, 1550, 1500, 1350, 1240 cm^{-1} . Elemental Analysis ($\text{C}_{17}\text{H}_{12}\text{NOCl}_2\text{F}$): C = 60.67%, H = 3.66%, N = 4.12%, Cl = 20.94%, F = 5.68%. ^1H NMR (DMSO-d_6) δ : 2.33 (singlet, 3H, methyl), 3.84 (singlet, 2H, methylene), 7.00 (complex, 3H, Aromatic), 7.27 (quartet, J = 7.4 Hz, 1H, Aromatic), 7.32 (doublet, J = 2.1 Hz, 1H, Quinolone), 7.48 (doublet, J = 2.1 Hz, 1H, Quinolone), 11.63 (singlet, 1H, N-H). ^{13}C NMR (DMSO-d_6) δ : 17.59, 29.71,

112.18, 112.39, 114.43, 114.64, 116.22, 118.14, 119.81, 124.00, 124.03, 124.59, 129.82,
129.90, 133.77, 134.59, 142.00, 143.80, 143.87, 146.49, 160.90, 163.32, 174.34. ¹⁹F

NMR (DMSO-d₆) δ : -113.97.

Synthesis of LA 72-2: 5,7-Dichloro-3-(4-chlorobenzyl)-2-methyl-4-quinolone

Five mmol of methyl 2-(4-chlorobenzyl)-acetoacetate, five mmol of 3,5-dichloroaniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 72-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 72-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 72-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 75 minutes at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was a light reddish tan precipitate with a yield of 58%.

The compound has a melting point > 260° C. IR: 3420, 3280, 3050 – 3150, 2980, 1650, 1550, 1480, 1320, 1100, 800 cm⁻¹. Elemental Analysis (C₁₇H₁₂NOCl₃): C = 57.83%, H = 3.47%, N = 3.90%, Cl = 29.99%. ¹H NMR (DMSO-d₆) δ: 2.32 (singlet, 3H, methyl), 3.81 (singlet, 2H, methylene), 7.22 (doublet, J = 8.4 Hz, 2H, Aromatic), 7.28 (doublet, J = 8.4 Hz, 2H, Aromatic), 7.33 (doublet, J = 2.0 Hz, 1H, Quinolone), 7.47 (doublet, J = 2.1 Hz, 1H, Quinolone), 11.62 (singlet, 1H, N-H). ¹³C NMR (DMSO-d₆) δ:

17.58, 29.30, 116.20, 118.13, 120.06, 124.58, 127.96, 129.78, 130.05, 133.77, 134.58,
139.81, 141.96, 146.36, 174.30.

Synthesis of LA 44-2: 3-(4-Fluorobenzyl)-2-methyl-4-quinolone

Five mmol of methyl 2-(4-fluorobenzyl)-acetoacetate, five mmol of aniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 44-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 44-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 44-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 60 minutes at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was an ivory precipitate with a yield of 47%.

The compound has a melting point $> 260^{\circ}\text{C}$. IR: 3420, 3330, 3050 – 3150, 2920, 1650, 1600, 1550, 1360, 1210, 770 cm^{-1} . Elemental Analysis ($\text{C}_{17}\text{H}_{14}\text{NOF}$): C = 76.24%, H = 5.21%, N = 5.17%, F = 7.11%. ^1H NMR (DMSO-d_6) δ : 2.36 (singlet, 3H, methyl), 3.88 (singlet, 2H, methylene), 7.04 (triplet, J = 8.9 Hz, 2H, Aromatic), 7.26 (complex, 3H, Aromatic + Quinolone), 7.50 (doublet, J = 8.2 Hz, 1H, Quinolone), 7.60 (triplet, J = 7.6 Hz, 1H, Quinolone), 8.10 (doublet, J = 7.9 Hz, 1H, Quinolone), 11.55 (singlet, 1H, N-H). ^{13}C NMR (DMSO-d_6) δ : 17.73, 29.08, 114.53, 144.73, 117.50, 118.04, 122.47,

123.51, 125.12, 129.56, 129.64, 131.07, 137.34, 137.37, 139.13, 146.99, 159.14, 161.53,
175.51. ^{19}F NMR (DMSO- d_6) δ : -116.11.

Synthesis of LA 54-2: 3-(3-Chlorobenzyl)-2-methyl-4-quinolone

Five mmol of methyl 2-(3-chlorobenzyl)-acetoacetate, five mmol of aniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 54-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 54-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 54-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 60 minutes at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was an ivory precipitate with a yield of 36%.

The compound has a melting point > 260° C. IR: 3450, 2800 – 2950, 1650, 1600, 1550, 1500, 1360 cm^{-1} . Elemental Analysis ($\text{C}_{17}\text{H}_{14}\text{NOCl}$): C = 72.08%, H = 5.06%, N = 4.94%, Cl = 12.23%. ^1H NMR (DMSO-d_6) δ : 2.37 (singlet, 3H, methyl), 3.91 (singlet, 2H, methylene), 7.19 (complex, 2H, Aromatic), 7.27 (complex, 3H, Aromatic + Quinolone), 7.52 (doublet, J = 8.2 Hz, 1H, Quinolone), 7.62 (triplet, J = 7.7 Hz, 1H, Quinolone), 8.11 (doublet, J = 8.1 Hz, 1H, Quinolone), 11.60 (singlet, 1H, N-H). ^{13}C

NMR (DMSO-d₆) δ : 17.76, 29.63, 117.40, 117.56, 122.62, 123.44, 125.10, 125.45,
126.69, 127.67, 129.90, 131.19, 132.69, 139.12, 143.94, 147.29, 175.54.

Synthesis of LA 64-2: 3-(3-Fluorobenzyl)-2-methyl-4-quinolone

Five mmol of methyl 2-(3-fluorobenzyl)-acetoacetate, five mmol of aniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 64-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 64-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 64-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 60 minutes at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was an ivory precipitate with a yield of 65%.

The compound has a melting point > 260° C. IR: 3420, 3380, 2950, 1650, 1550, 1450 – 1500, 1350, 1240, 760 cm⁻¹. Elemental Analysis (C₁₇H₁₄NOF): C = 76.49%, H = 5.19%, N = 5.20%, F = 7.00%. ¹H NMR (DMSO-d₆) δ: 2.37 (singlet, 3H, methyl), 3.93 (singlet, 2H, methylene), 6.96 (triplet, J = 8.6 Hz, 1H, Aromatic), 7.05 (complex, 2H, Aromatic), 7.27 (complex, 2H, Aromatic + Quinolone), 7.52 (doublet, J = 8.2 Hz, 1H, Quinolone), 7.62 (triplet, J = 7.7 Hz, 1H, Quinolone), 8.11 (doublet, J = 8.1 Hz, 1H, Quinolone), 11.59 (singlet, 1H, N-H). ¹³C NMR (DMSO-d₆) δ: 17.75, 29.69, 112.10,

112.31, 114.42, 114.63, 117.49, 117.55, 122.60, 123.46, 124.01, 124.03, 125.12, 129.80,
129.88, 131.17, 139.13, 144.31, 144.38, 147.30, 160.91, 163.32, 175.57. ^{19}F NMR
(DMSO- d_6) δ : -114.05.

Synthesis of LA 74-2: 3-(4-Chlorobenzyl)-2-methyl-4-quinolone

Five mmol of methyl 2-(4-chlorobenzyl)-acetoacetate, five mmol of aniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 74-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 74-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 74-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 75 minutes at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was a nearly white precipitate with a yield of 58%.

The compound has a melting point > 260° C. IR: 3420, 3380, 3120, 2950, 1650, 1550, 1460 – 1520, 1350, 1240, 760 cm⁻¹. Elemental Analysis (C₁₇H₁₄NOCl): C = 72.20%, H = 5.13%, N = 4.91%, Cl = 12.38%. ¹H NMR (DMSO-d₆) δ: 2.35 (singlet, 3H, methyl), 3.88 (singlet, 2H, methylene), 7.26 (complex, 5H, Aromatic + Quinolone), 7.50 (doublet, J = 8.3 Hz, 1H, Quinolone), 7.61 (triplet, J = 7.6 Hz, 1H, Quinolone), 8.09 (doublet, J = 8.2 Hz, 1H, Quinolone), 11.55 (singlet, 1H, N-H). ¹³C NMR (DMSO-d₆) δ:

17.75, 29.29, 117.53, 117.71, 122.53, 123.49, 125.13, 127.94, 129.80, 129.95, 131.13,
139.15, 140.35, 147.11, 175.51.

Synthesis of LA 45-2: 3-(4-Fluorobenzyl)-2-methyl-6-nitro-4-quinolone

Five mmol of methyl 2-(4-fluorobenzyl)-acetoacetate, five mmol of 4-nitroaniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 45-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 45-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 45-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 75 minutes at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy to black over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was a medium brown precipitate with a yield of 45%.

The compound has a melting point > 260° C. IR: 3380, 3250, 3110, 1650, 1550, 1500, 1330, 1220 cm⁻¹. Elemental Analysis (C₁₇H₁₃N₂O₃F): C = 65.10%, H = 4.20%, N = 9.19%, F = 5.86%. ¹H NMR (DMSO-d₆) δ: 2.40 (singlet, 3H, methyl), 3.89 (singlet, 2H, methylene), 7.05 (triplet, J = 8.9 Hz, 2H, Aromatic), 7.26 (triplet, J = 7.1 Hz, 2H, Aromatic), 7.66 (doublet, J = 9.1 Hz, 1H, Quinolone), 8.37 (doublet, J = 9.3 Hz, 1H, Quinolone), 8.86 (doublet, J = 2.6 Hz, 1H, Quinolone), 12.08 (singlet, 1H, N-H). ¹³C NMR (DMSO-d₆) δ: 17.81, 28.96, 114.66, 114.87, 119.36, 119.86, 121.97, 122.33,

125.36, 129.62, 129.70, 136.53, 136.56, 142.16, 142.72, 148.54, 159.26, 161.65, 175.27.

^{19}F NMR (DMSO- d_6) δ : -117.76.

Synthesis of LA 55-2: 3-(3-Chlorobenzyl)-2-methyl-6-nitro-4-quinolone

Five mmol of methyl 2-(3-chlorobenzyl)-acetoacetate, five mmol of 4-nitroaniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 55-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 55-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 55-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 75 minutes at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy to black over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was a medium brown precipitate with a yield of 48%.

The compound has a melting point > 260° C. IR: 3380 – 3480, 3100, 2910, 2860, 1650, 1550, 1500, 1340 cm^{-1} . Elemental Analysis ($\text{C}_{17}\text{H}_{13}\text{N}_2\text{O}_3\text{Cl}$): C = 61.83%, H = 4.05%, N = 8.64%, Cl = 10.54%. ^1H NMR (DMSO-d_6) δ : 2.41 (singlet, 3H, methyl), 3.92 (singlet, 2H, methylene), 7.24 (complex, 4H, Aromatic), 7.67 (doublet, J = 9.1 Hz, 1H, Quinolone), 8.38 (doublet, J = 9.1 Hz, 1H, Quinolone), 8.86 (singlet, 1H, Quinolone), 12.12 (singlet, 1H, N-H). ^{13}C NMR (DMSO-d_6) δ : 17.86, 29.51, 119.19,

119.41, 121.97, 122.32, 125.40, 125.67, 126.71, 127.71, 129.98, 132.78, 142.20, 142.74,
143.12, 148.78, 175.29.

Synthesis of LA 65-2: 3-(3-Fluorobenzyl)-2-methyl-6-nitro-4-quinolone

Five mmol of methyl 2-(3-fluorobenzyl)-acetoacetate, five mmol of 4-nitroaniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 65-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 65-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 65-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 75 minutes at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy to black over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was a medium brown precipitate with a yield of 51%.

The compound has a melting point > 260° C. IR: 3400 – 3480, 3110, 2910, 2860, 1650, 1550, 1500, 1330 cm^{-1} . Elemental Analysis ($\text{C}_{17}\text{H}_{13}\text{N}_2\text{O}_3\text{F}$): C = 65.09%, H = 4.23%, N = 9.10%, F = 6.00%. ^1H NMR (DMSO-d_6) δ : 2.41 (singlet, 3H, methyl), 3.93 (singlet, 2H, methylene), 7.03 (complex, 3H, Aromatic), 7.28 (quartet, $J = 7.4$ Hz, 1H, Aromatic), 7.66 (doublet, $J = 9.2$ Hz, 1H, Quinolone), 8.37 (doublet, $J = 9.2$ Hz, 1H, Quinolone), 8.86 (doublet, $J = 2.5$ Hz, 1H, Quinolone), 12.11 (singlet, 1H, N-H). ^{13}C NMR (DMSO-d_6) δ : 17.59, 29.70, 112.19, 112.40, 114.43, 114.64, 116.21, 118.13,

119.82, 124.01, 124.03, 124.60, 129.83, 129.91, 133.76, 134.61, 141.99, 143.79, 143.86,
146.51, 160.90, 163.32, 174.35. ^{19}F NMR (DMSO- d_6) δ : -113.85.

Synthesis of LA 75-2: 3-(4-Chlorobenzyl)-2-methyl-6-nitro-4-quinolone

Five mmol of methyl 2-(4-chlorobenzyl)-acetoacetate, five mmol of 4-nitroaniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 65-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 65-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 65-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 75 minutes at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy to black over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was a medium brown precipitate with a yield of 51%.

The compound has a melting point > 260° C. IR: 3380 – 3440, 3100, 2950, 2860, 1650, 1560, 1500, 1330, 830 cm^{-1} . Elemental Analysis ($\text{C}_{17}\text{H}_{13}\text{N}_2\text{O}_3\text{Cl}$): C = 61.92%, H = 4.01%, N = 8.76%, Cl = 10.49%. ^1H NMR (DMSO-d_6) δ : 2.39 (singlet, 3H, methyl), 3.90 (singlet, 2H, methylene), 7.27 (quartet, J = 8.4 Hz, 4H, Aromatic), 7.66 (doublet, J = 9.2 Hz, 1H, Quinolone), 8.38 (doublet, J = 9.1 Hz, 1H, Quinolone), 8.85 (doublet, J = 2.4 Hz, 1H, Quinolone), 12.10 (singlet, 1H, N-H). ^{13}C NMR (DMSO-d_6) δ : 17.82, 129.14,

119.38, 119.50, 121.96, 122.31, 125.39, 128.03, 129.80, 130.18, 139.50, 142.18, 142.72,
148.65, 175.25.

Synthesis of LA 46-2: 8-Chloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

Five mmol of methyl 2-(4-fluorobenzyl)-acetoacetate, five mmol of 2-chloroaniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 46-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 46-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 46-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 75 minutes at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy to black over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was a light reddish tan precipitate with a yield of 36%.

The compound has a melting point of about 220° C. 3400 – 3450, 3120, 2860, 1640, 1550, 1500, 1330, 750, 980 cm^{-1} . Elemental Analysis ($\text{C}_{17}\text{H}_{13}\text{NOClF}$): C = 67.41%, H = 4.45%, N = 4.44%, Cl = 11.47%, F = 6.09%. ^1H NMR (DMSO-d_6) δ : 2.48 (singlet, 3H, methyl), 3.89 (singlet, 2H, methylene), 7.04 (triplet, J = 8.9 Hz, 2H, Aromatic), 7.24 (triplet, J = 7.1 Hz, 2H, Aromatic), 7.30 (triplet, J = 7.8 Hz, 1H, Quinolone), 7.80 (doublet, J = 7.6 Hz, 1H, Quinolone), 8.11 (doublet, J = 7.6 Hz, 1H, Quinolone), 10.61

(singlet, 1H, N-H). ^{13}C NMR (DMSO- d_6) δ : 17.70, 29.15, 114.63, 114.84, 119.16, 120.77, 122.97, 124.59, 125.08, 129.58, 129.66, 131.45, 135.73, 136.81, 136.84, 148.46, 159.22, 161.61, 175.11. ^{19}F NMR (DMSO- d_6) δ : -117.90.

Synthesis of LA 56-2: 6-Chloro-3-(3-chlorobenzyl)-2-methyl-4-quinolone

Five mmol of methyl 2-(3-chlorobenzyl)-acetoacetate, five mmol of 2-chloroaniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 56-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 56-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 56-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 60 minutes at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy to black over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was an ivory precipitate with a yield of 44%.

The compound has a melting point of about 248° C. IR: 3380 – 3450, 3100, 1640, 1550, 1500, 1330, 1170, 980, 770 cm^{-1} . Elemental Analysis ($\text{C}_{17}\text{H}_{13}\text{NOCl}_2$): C = 63.96%, H = 4.25%, N = 4.36%, Cl = 22.47%. ^1H NMR (DMSO-d_6) δ : 2.49 (singlet, 3H, methyl), 3.92 (singlet, 2H, methylene), 7.25 (complex, 5H, Aromatic + Quinolone), 7.81 (doublet, J = 7.6 Hz, 2H, Aromatic), 8.11 (doublet, J = 8.0 Hz, 1H, Quinolone), 10.64 (singlet, 1H, N-H). ^{13}C NMR (DMSO-d_6) δ : 17.71, 29.67, 118.48, 120.78, 123.05,

124.56, 125.02, 125.57, 126.65, 127.65, 129.95, 131.52, 132.73, 135.73, 143.40, 148.66,
175.09.

Synthesis of LA 66-2: 8-Chloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

Five mmol of methyl 2-(3-fluorobenzyl)-acetoacetate, five mmol of 2-chloroaniline, a stir bar, a tiny amount of PTSA, and 30 mL of benzene solvent were added to a 100 mL round bottom flask, topped with a Dean Stark trap containing another ten mL of benzene, topped with a condenser. This mixture was refluxed for 24 hours, producing LA 66-1, an imine. Excess benzene was then evacuated, leaving about five mL of LA 66-1. 30 mL of diphenyl ether was heated to boiling in a 100 mL three neck round bottom flask, containing a stir bar, topped with a condenser in the middle neck, and a 250° C thermometer in the left neck. LA 66-1 was added dropwise over ten minutes through the right neck, then the mixture was refluxed for 60 minutes, at a temperature just above 250° C. The color changed from pale yellow to gold to red to burgundy to black over this time. After cooling to room temperature, the mixture was poured over 30 mL of hexanes, then vacuum filtered, then washed three times with another 20 mL of hexanes each time. The result was an ivory precipitate with a yield of 51%.

The compound has a melting point of about 231° C. IR: 3380 – 3450, 3120, 1640, 1550, 1500, 1320, 1150, 980 cm^{-1} . Elemental Analysis ($\text{C}_{17}\text{H}_{13}\text{NOClF}$): C = 67.62%, H = 4.48%, N = 4.57%, Cl = 11.91%, F = 6.27%. ^1H NMR (DMSO-d_6) δ : 2.49 (singlet, 3H, methyl), 3.93 (singlet, 2H, methylene), 7.01 (complex, 3H, Aromatic), 7.29 (complex, 2H, Aromatic + Quinolone), 7.81 (doublet, J = 7.8 Hz, 1H, Quinolone), 8.11 (doublet, J = 8.0 Hz, 1H, Quinolone), 10.64 (singlet, 1H, N-H). ^{13}C NMR (DMSO-d_6) δ :

17.71, 29.74, 112.23, 112.44, 114.44, 114.65, 118.57, 120.78, 123.03, 123.98, 124.01,
124.59, 125.06, 129.87, 129.96, 131.50, 135.75, 143.78, 143.85, 148.66, 160.92, 163.34,
175.12. ^{19}F NMR (DMSO- d_6) δ : -113.93.

Appendix A – Bond Line Structures

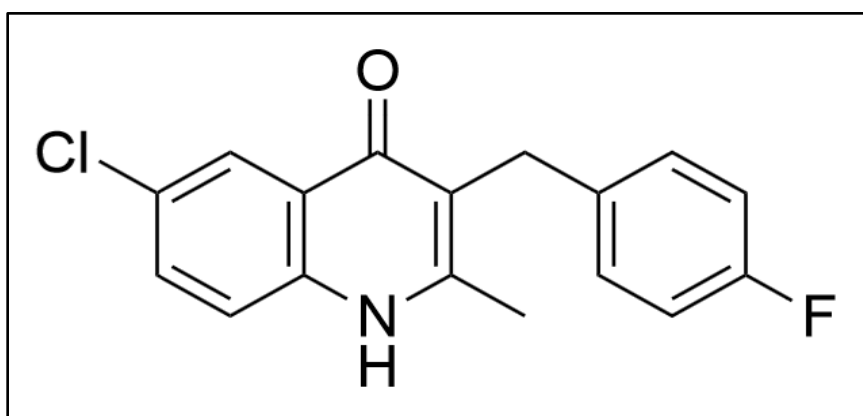


Figure 26 LA 41-2: 6-Chloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

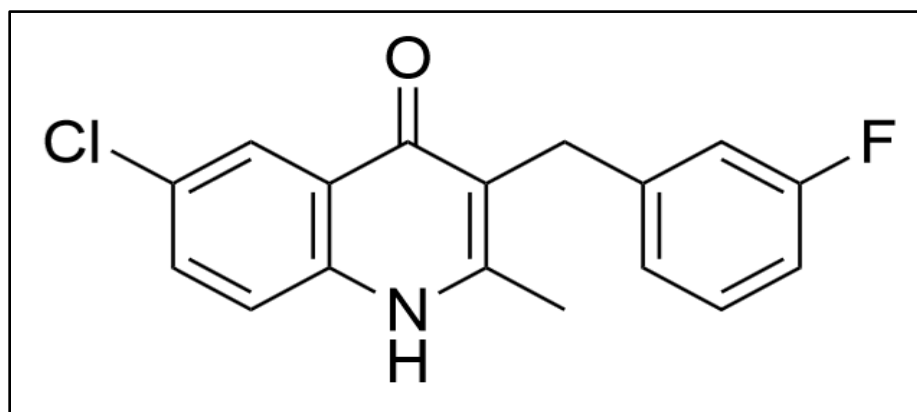


Figure 27 LA 61-2: 6-Chloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

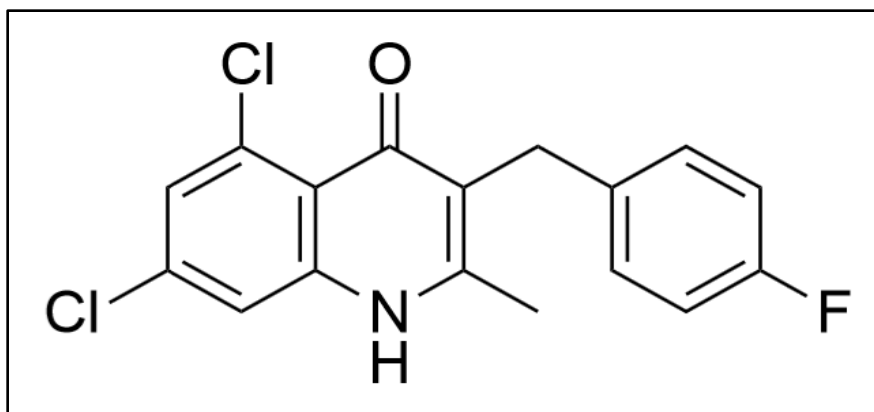


Figure 28 LA 42-2: 5,7-Dichloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

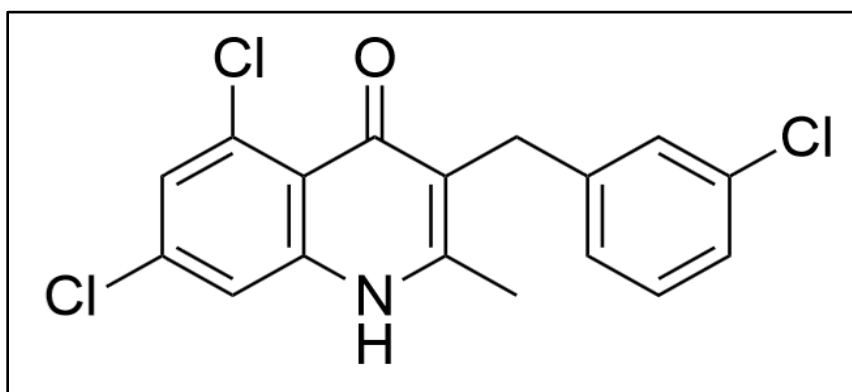


Figure 29 LA 52-2: 5,7-Dichloro-3-(3-chlorobenzyl)-2-methyl-4-quinolone

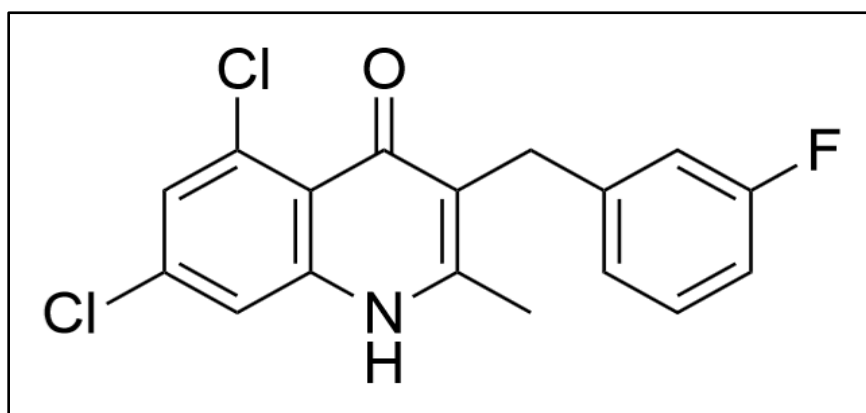


Figure 30 LA 62-2: 5,7-Dichloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

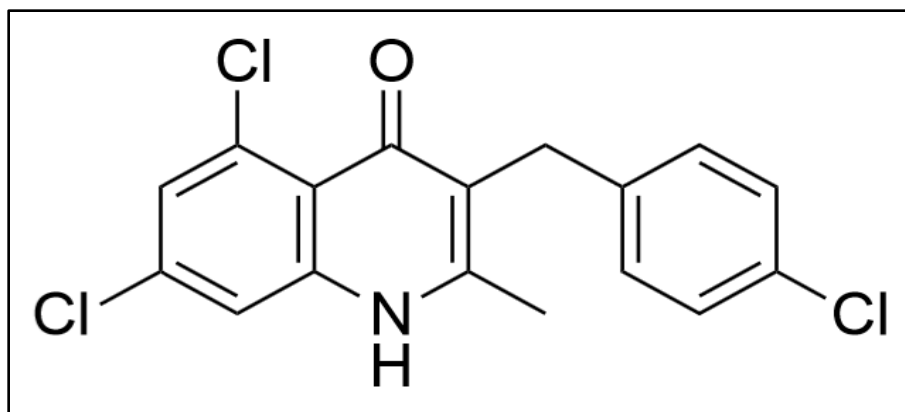


Figure 31 LA 72-2: 5,7-Dichloro-3-(4-chlorobenzyl)-2-methyl-4-quinolone

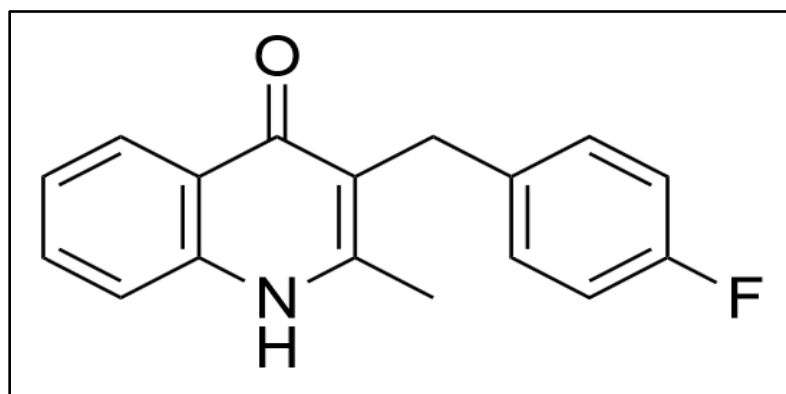


Figure 32 LA 44-2: 3-(4-Fluorobenzyl)-2-methyl-4-quinolone

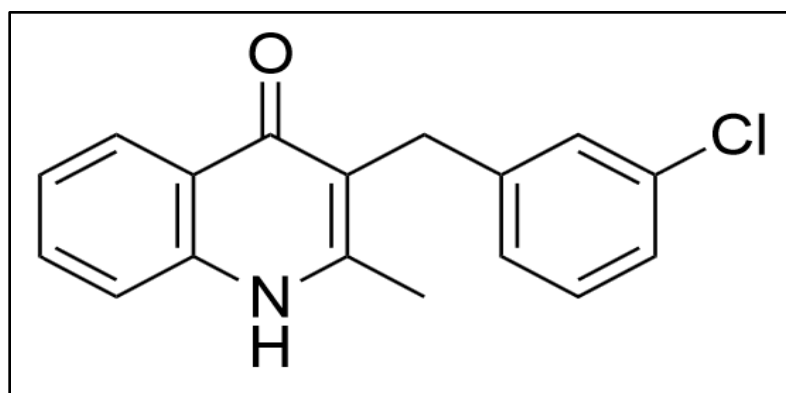


Figure 33 LA 54-2: 3-(3-Chlorobenzyl)-2-methyl-4-quinolone

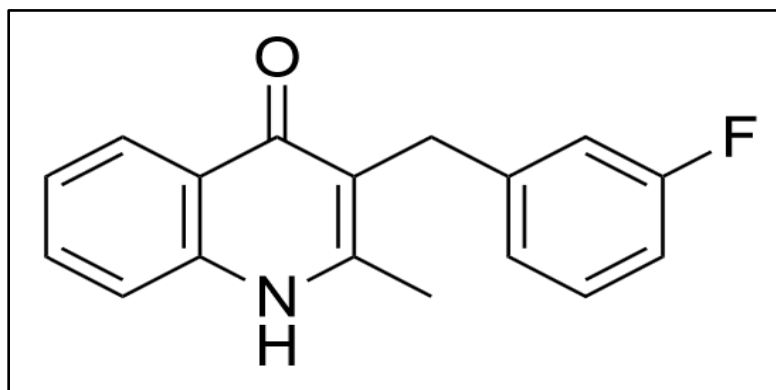


Figure 34 LA 64-2: 3-(3-Fluorobenzyl)-2-methyl-4-quinolone

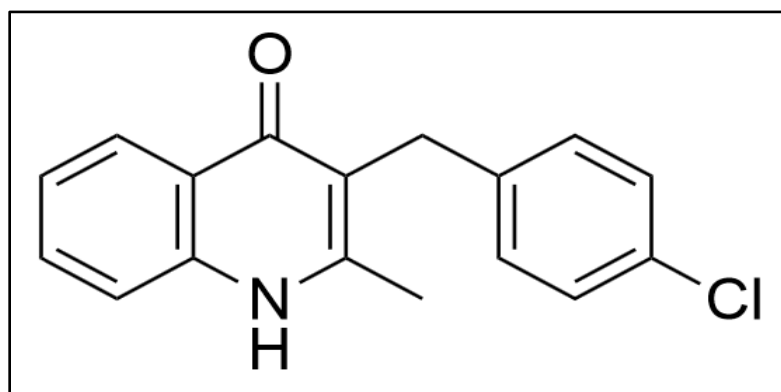


Figure 35 LA 74-2: 3-(4-Chlorobenzyl)-2-methyl-4-quinolone

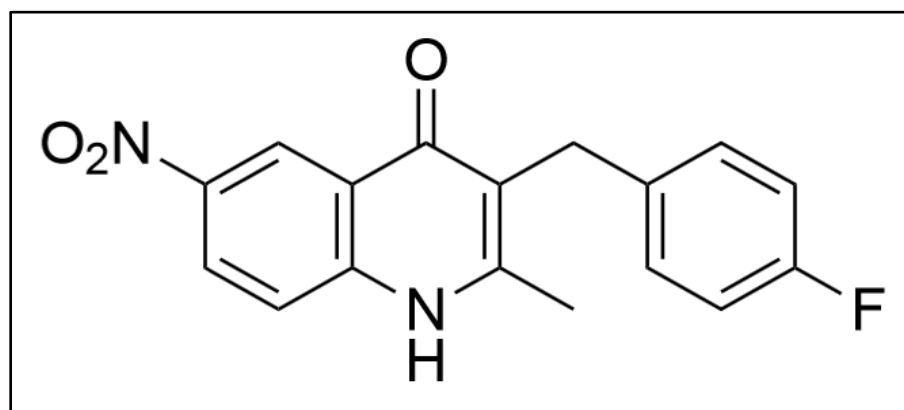


Figure 36 LA 45-2: 3-(4-Fluorobenzyl)-2-methyl-6-nitro-4-quinolone

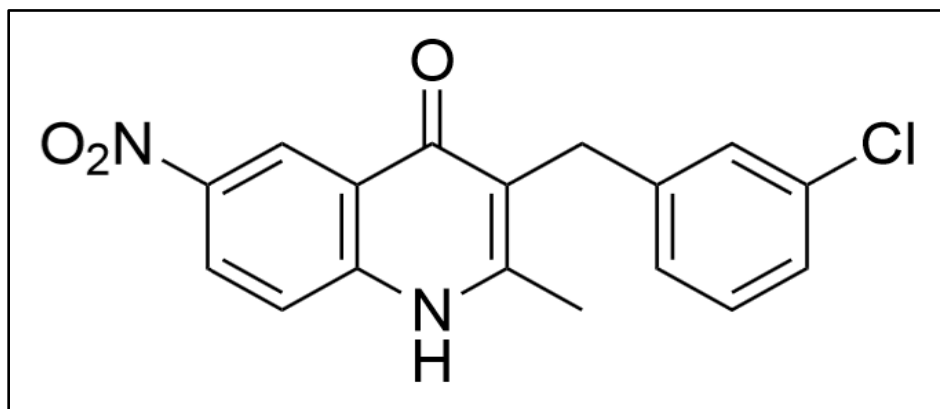


Figure 37 LA 55-2: 3-(3-Chlorobenzyl)-2-methyl-6-nitro-4-quinolone

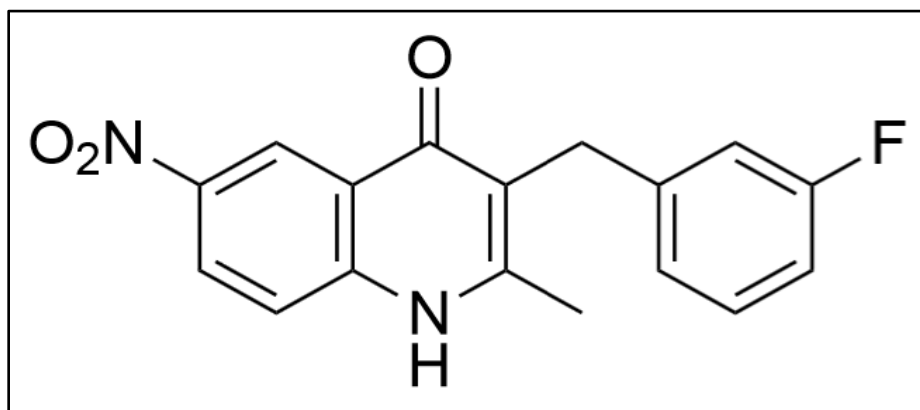


Figure 38 LA 65-2: 3-(3-Fluorobenzyl)-2-methyl-6-nitro-4-quinolone

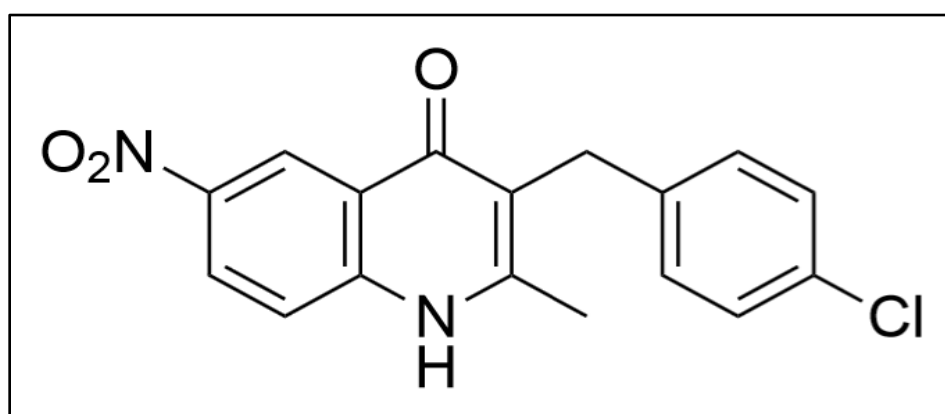


Figure 39 LA 75-2: 3-(4-Chlorobenzyl)-2-methyl-6-nitro-4-quinolone

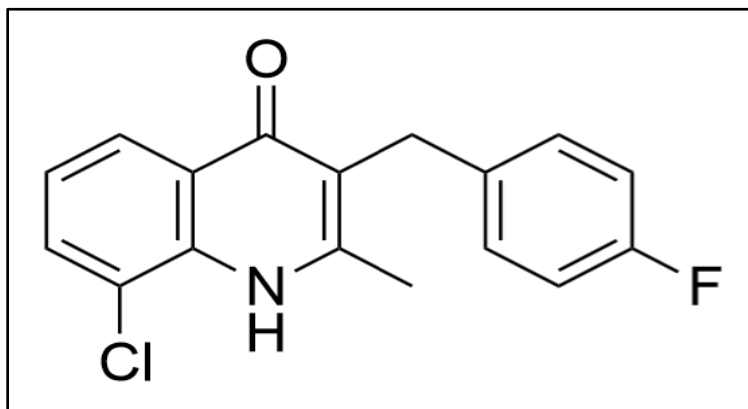


Figure 40 LA 46-2: 8-Chloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

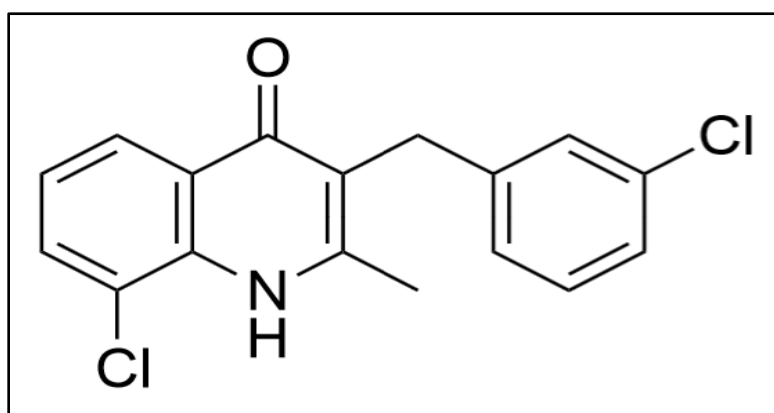


Figure 41 LA 56-2: 8-Chloro-3-(3-chlorobenzyl)-2-methyl-4-quinolone

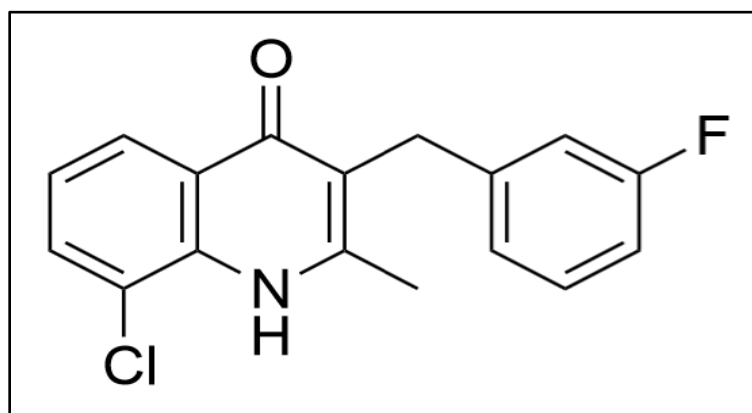


Figure 42 LA 66-2: 8-Chloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

Appendix B – ^1H NMR Spectra

Table 4 ¹H NMR of 6-Chloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

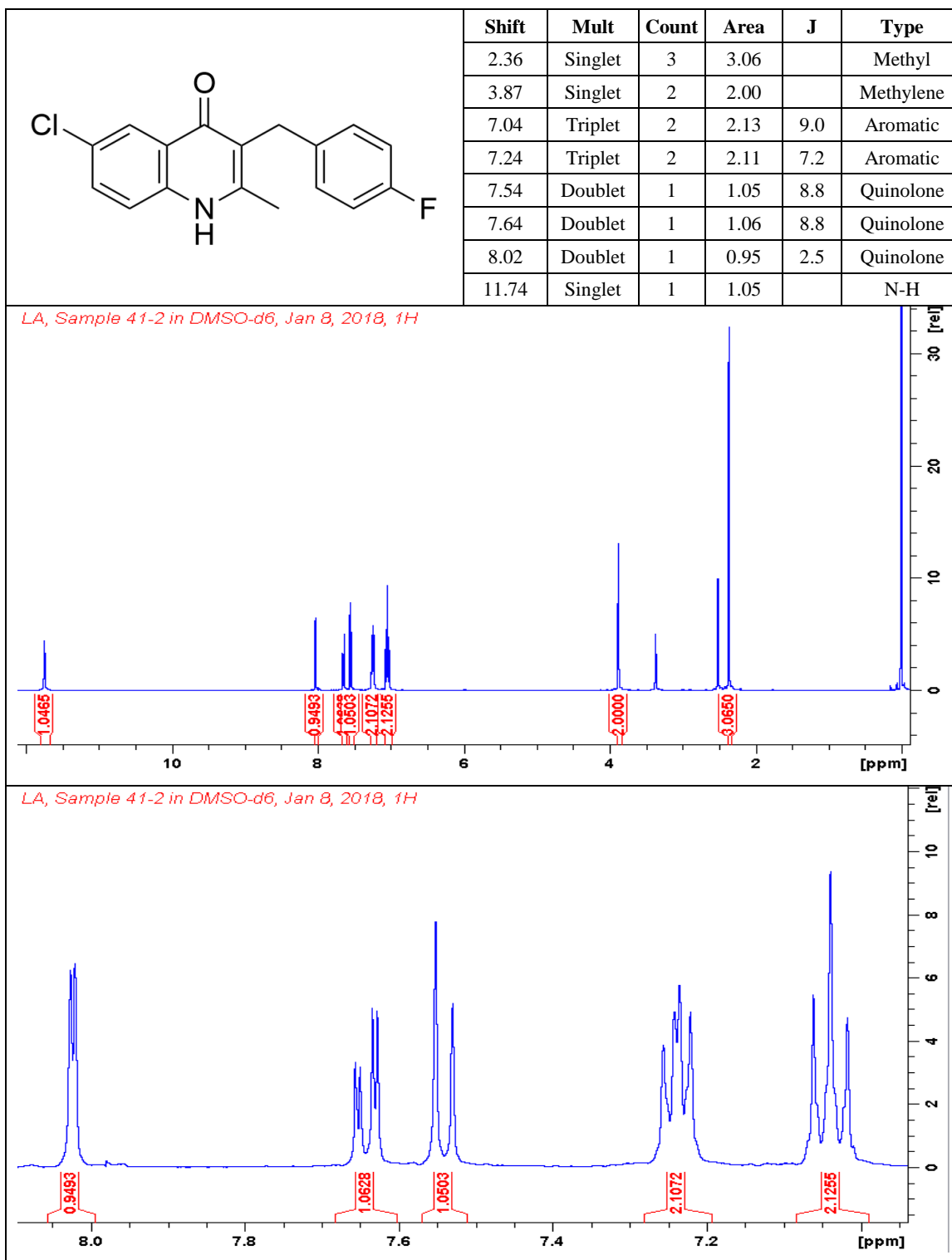


Table 5 ¹H NMR of 6-Chloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

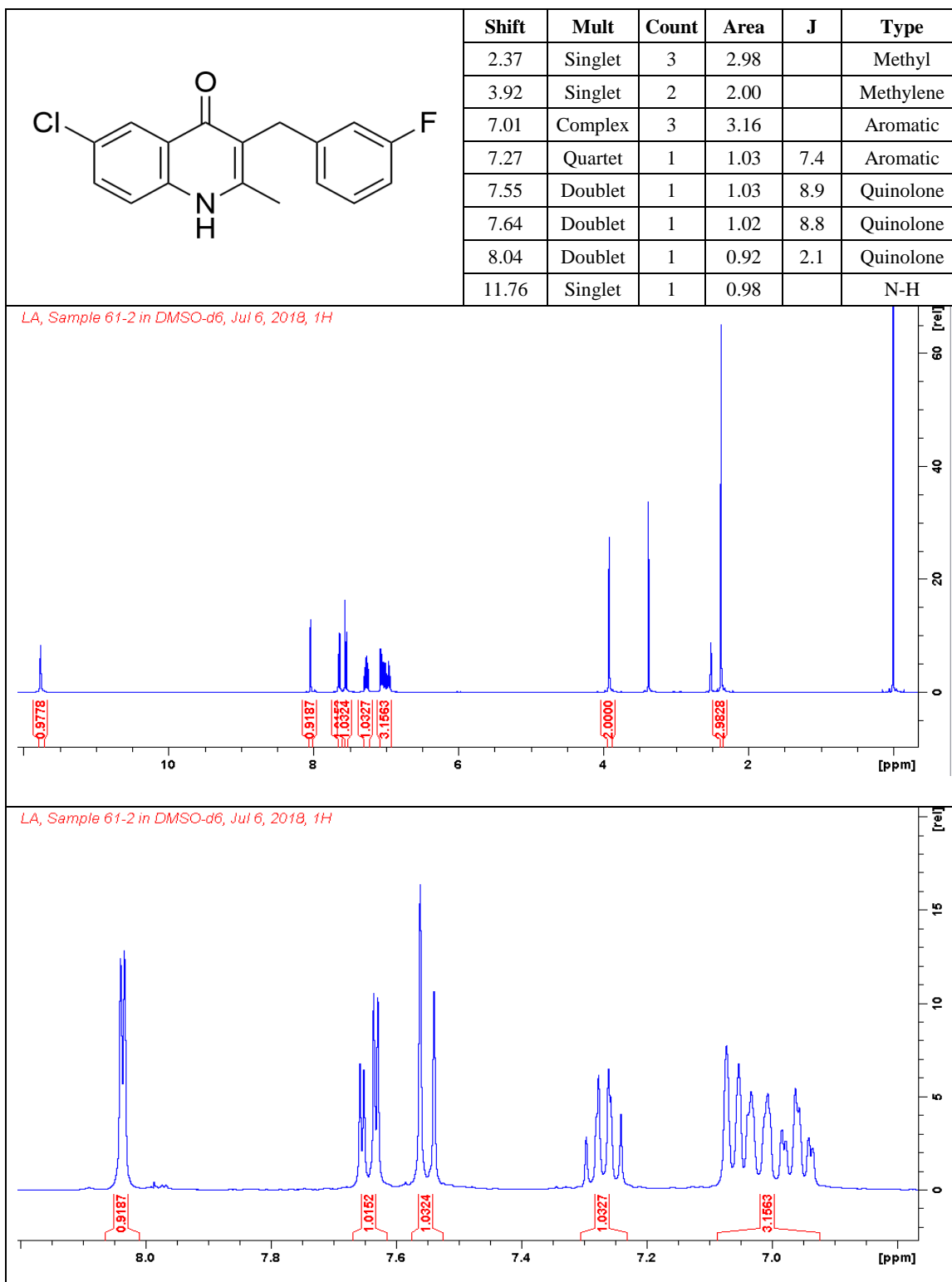


Table 6 ¹H NMR of 5,7-Dichloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

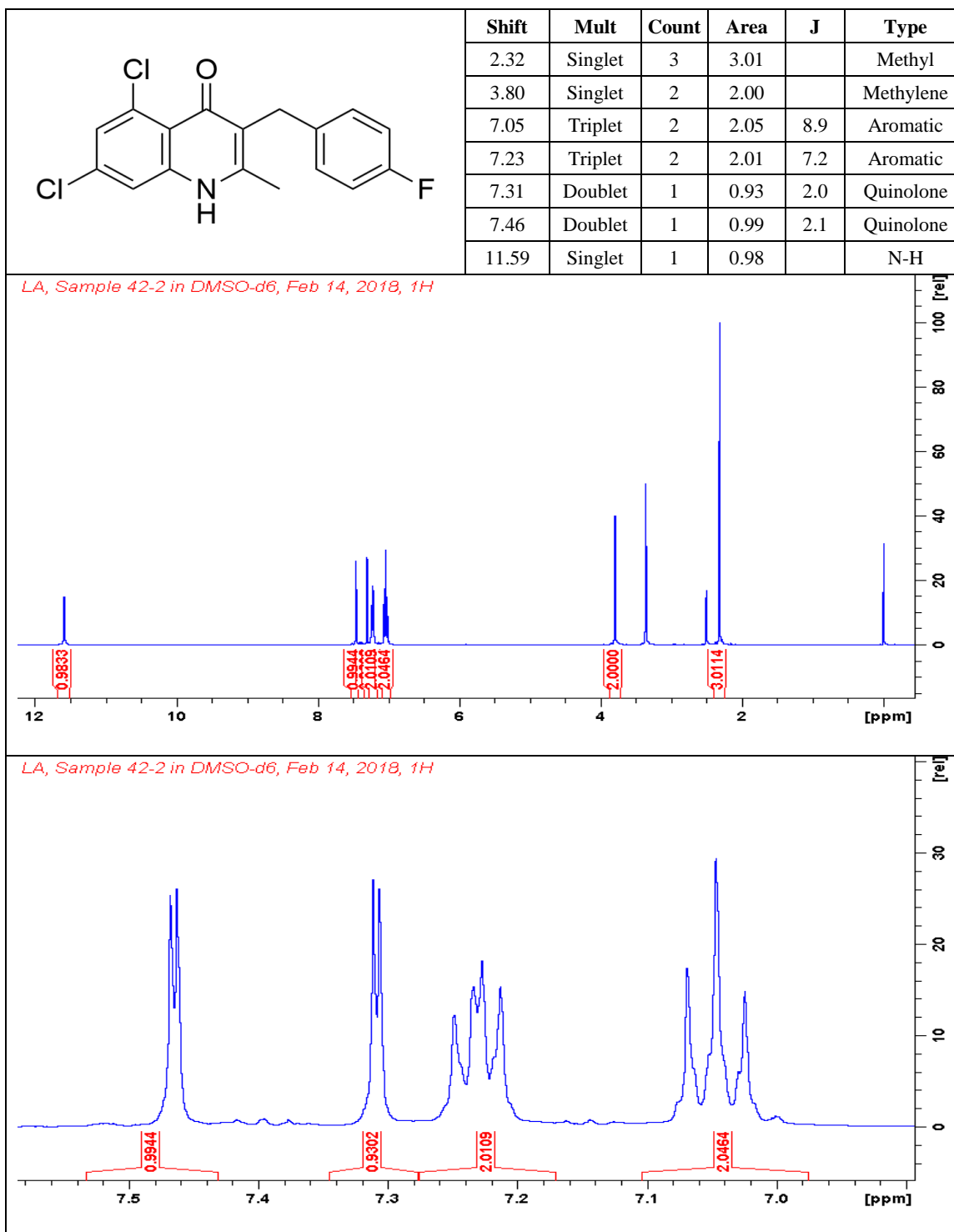


Table 7 ^1H NMR of 5,7-Dichloro-3-(3-chlorobenzyl)-2-methyl-4-quinolone

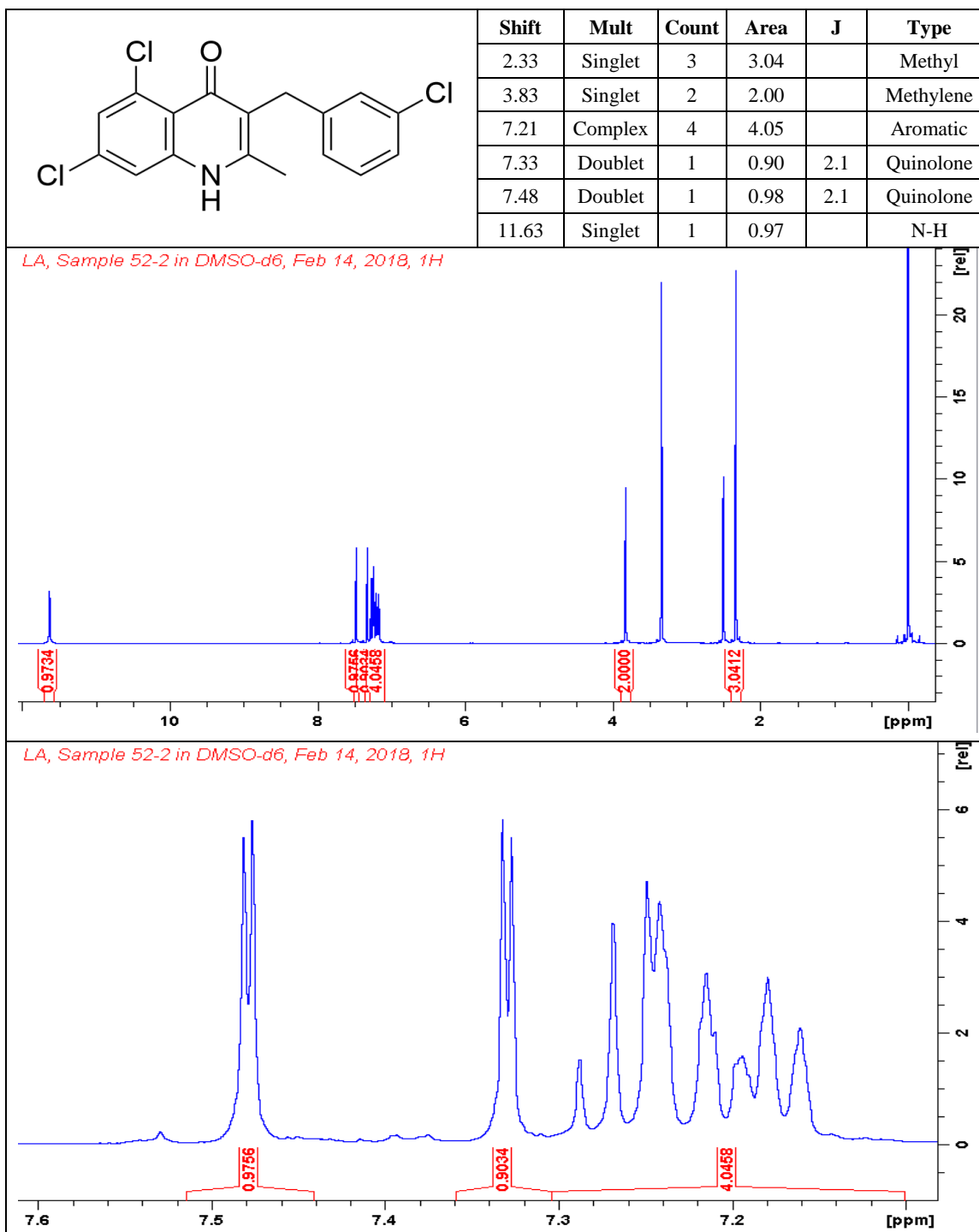


Table 8 ¹H NMR of 5,7-Dichloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

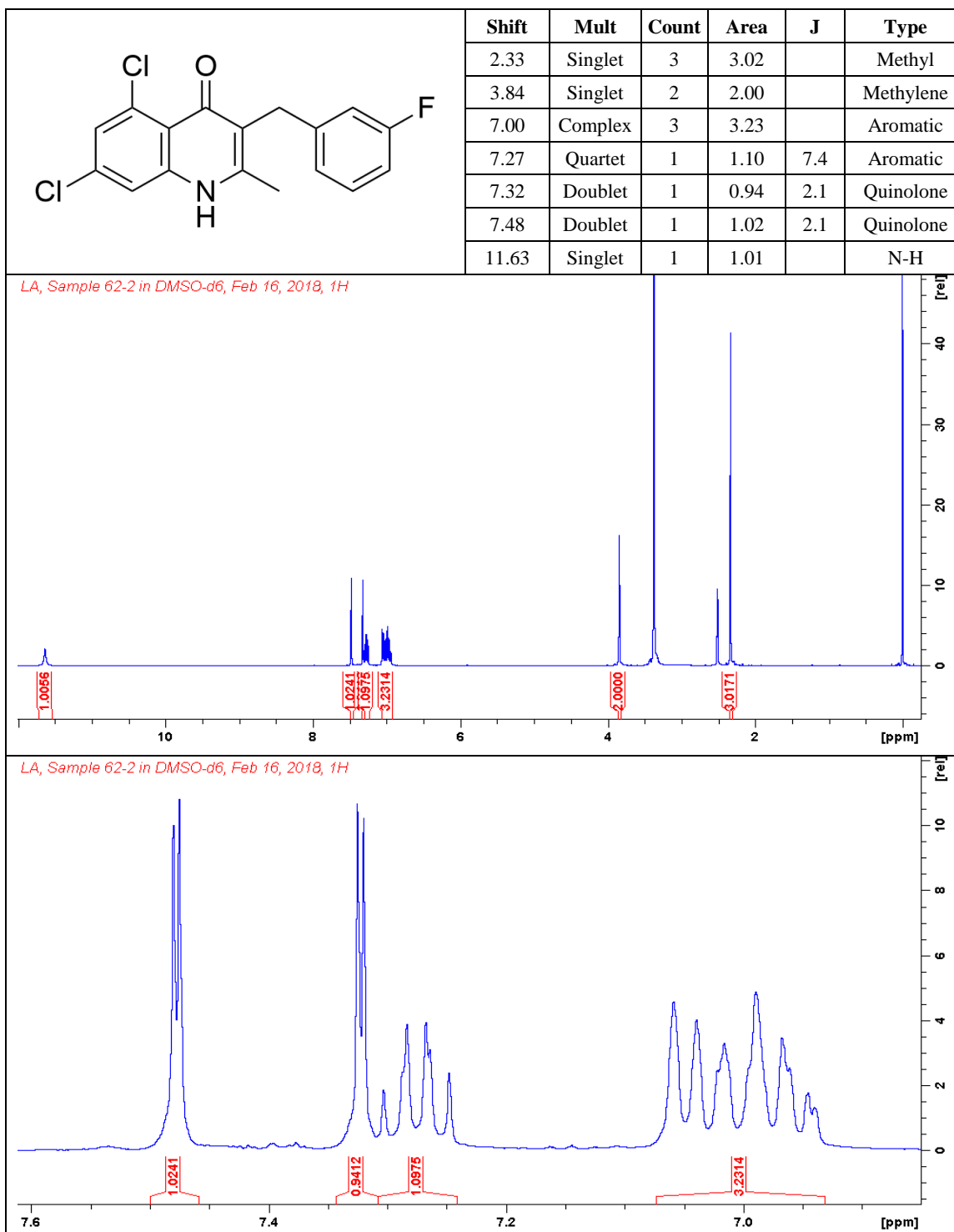


Table 9 ¹H NMR of 5,7-Dichloro-3-(4-chlorobenzyl)-2-methyl-4-quinolone

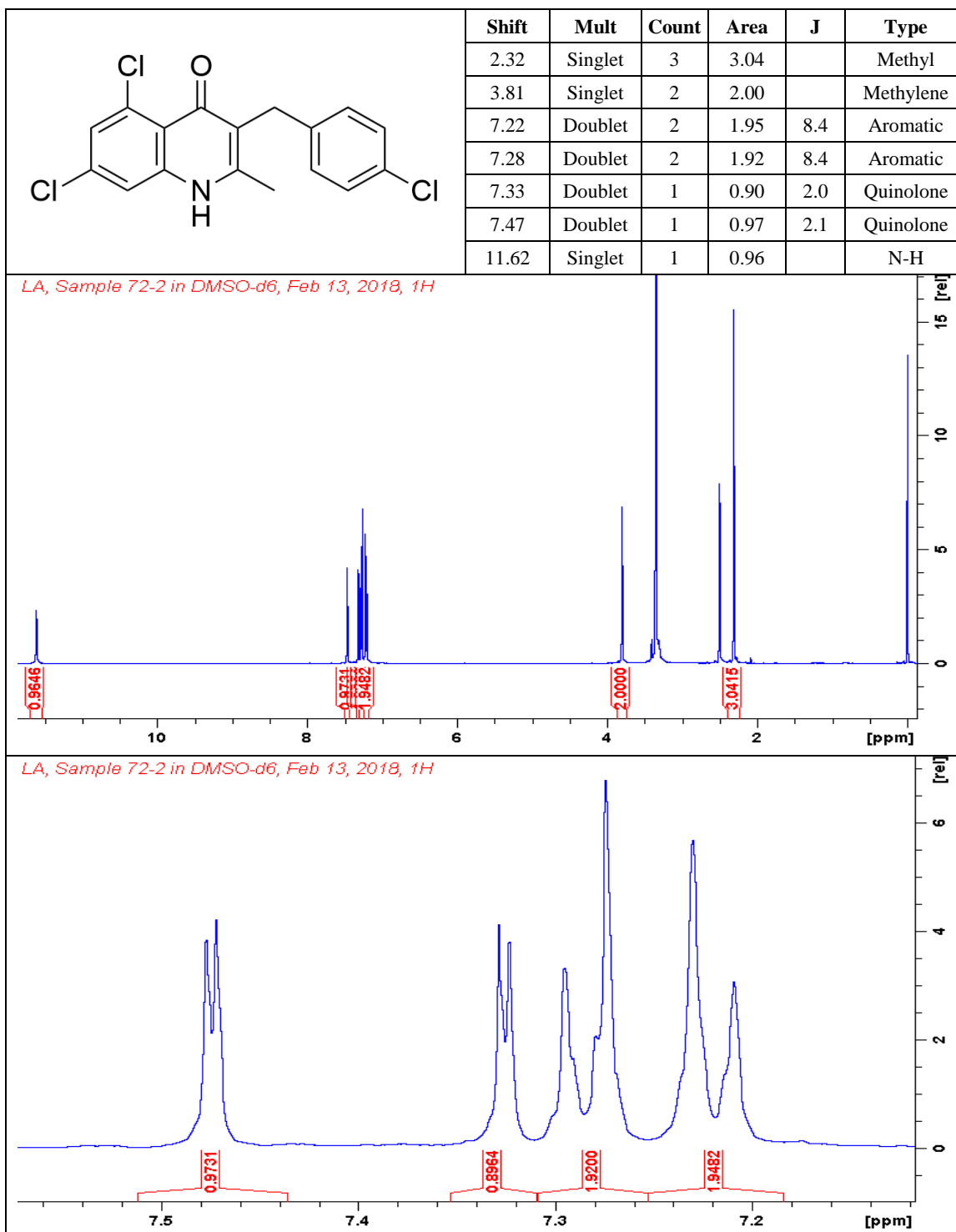


Table 10 ¹H NMR of 3-(4-Fluorobenzyl)-2-methyl-4-quinolone

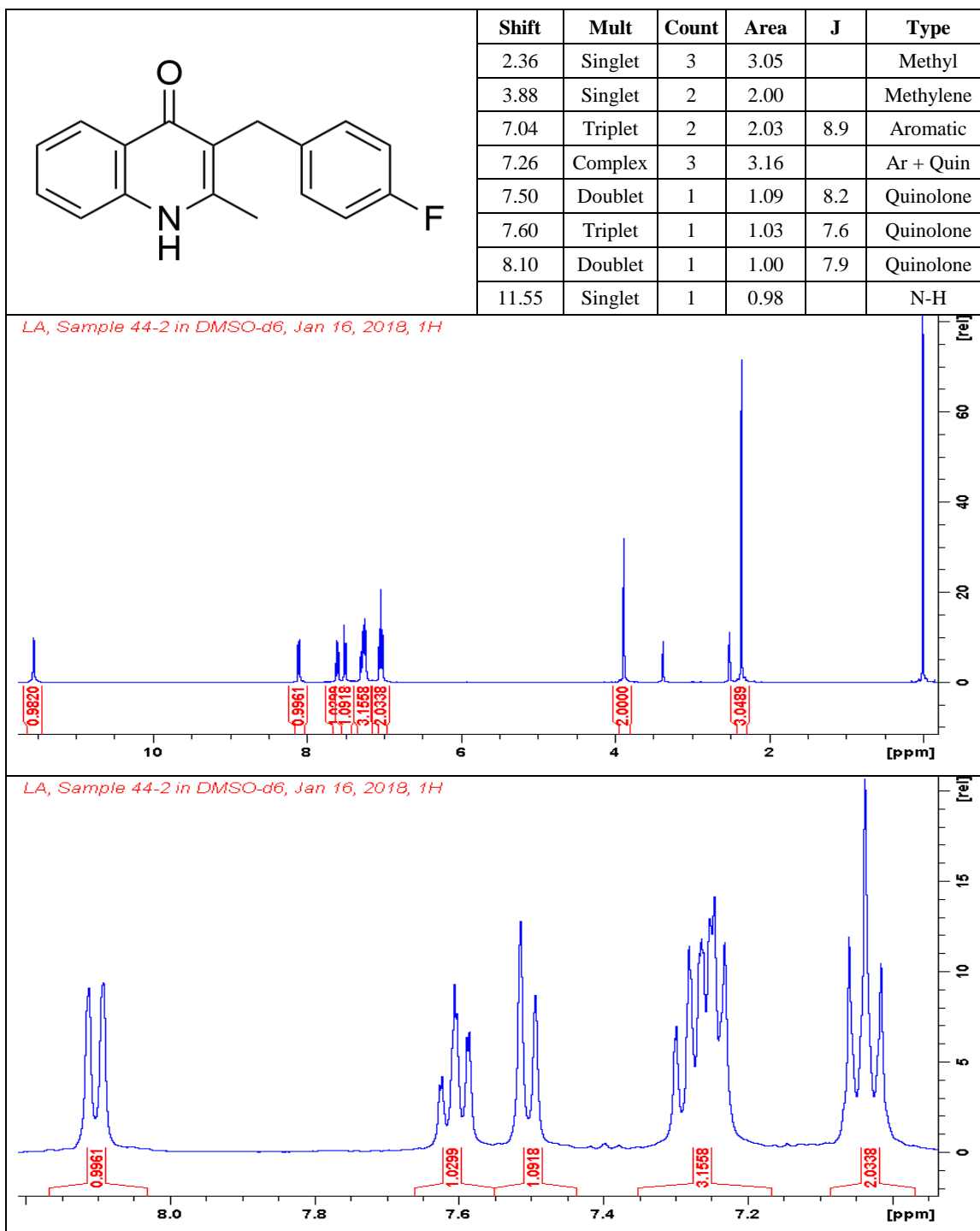


Table 11 ¹H NMR of 3-(3-Chlorobenzyl)-2-methyl-4-quinolone

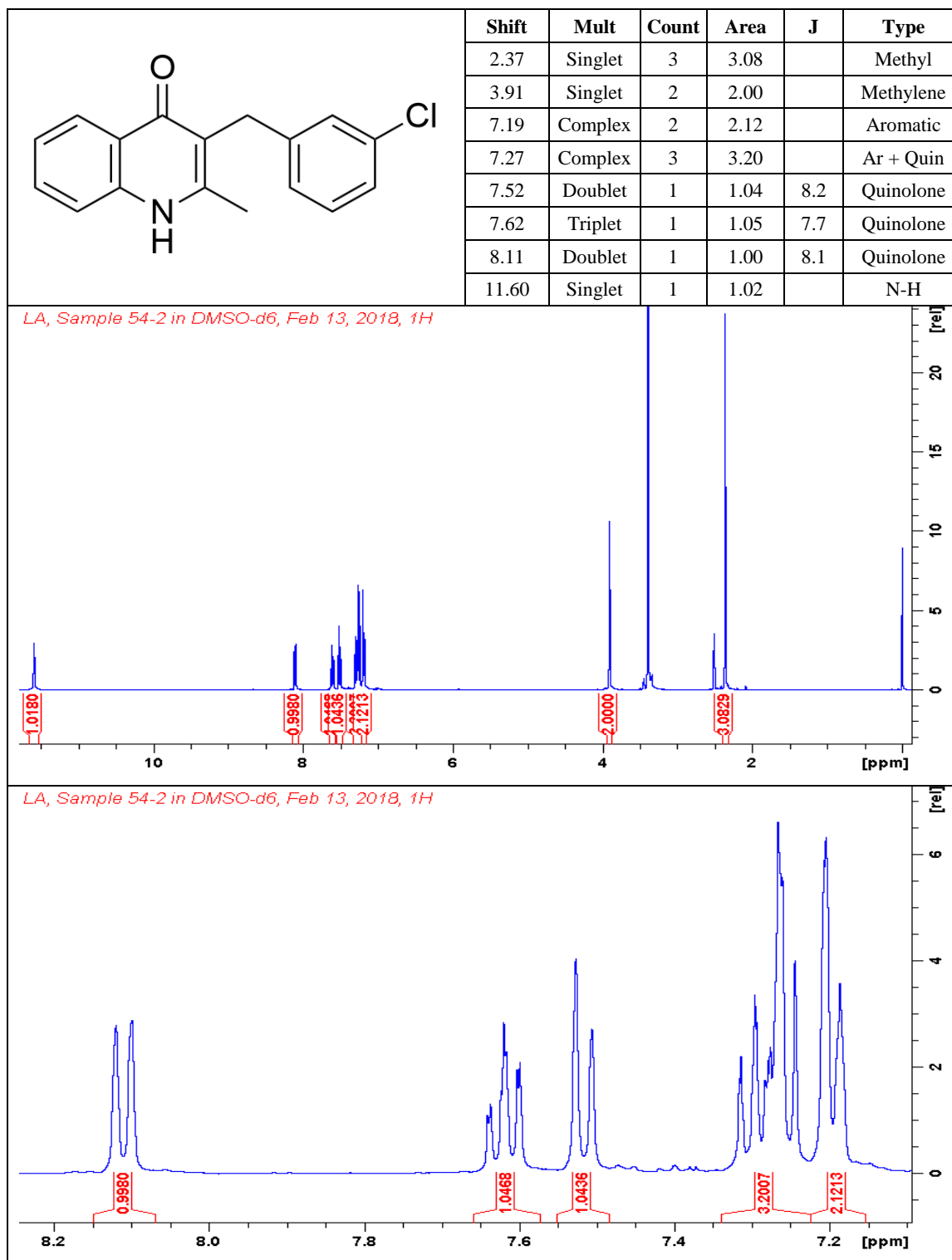


Table 12 ¹H NMR of 3-(3-Fluorobenzyl)-2-methyl-4-quinolone

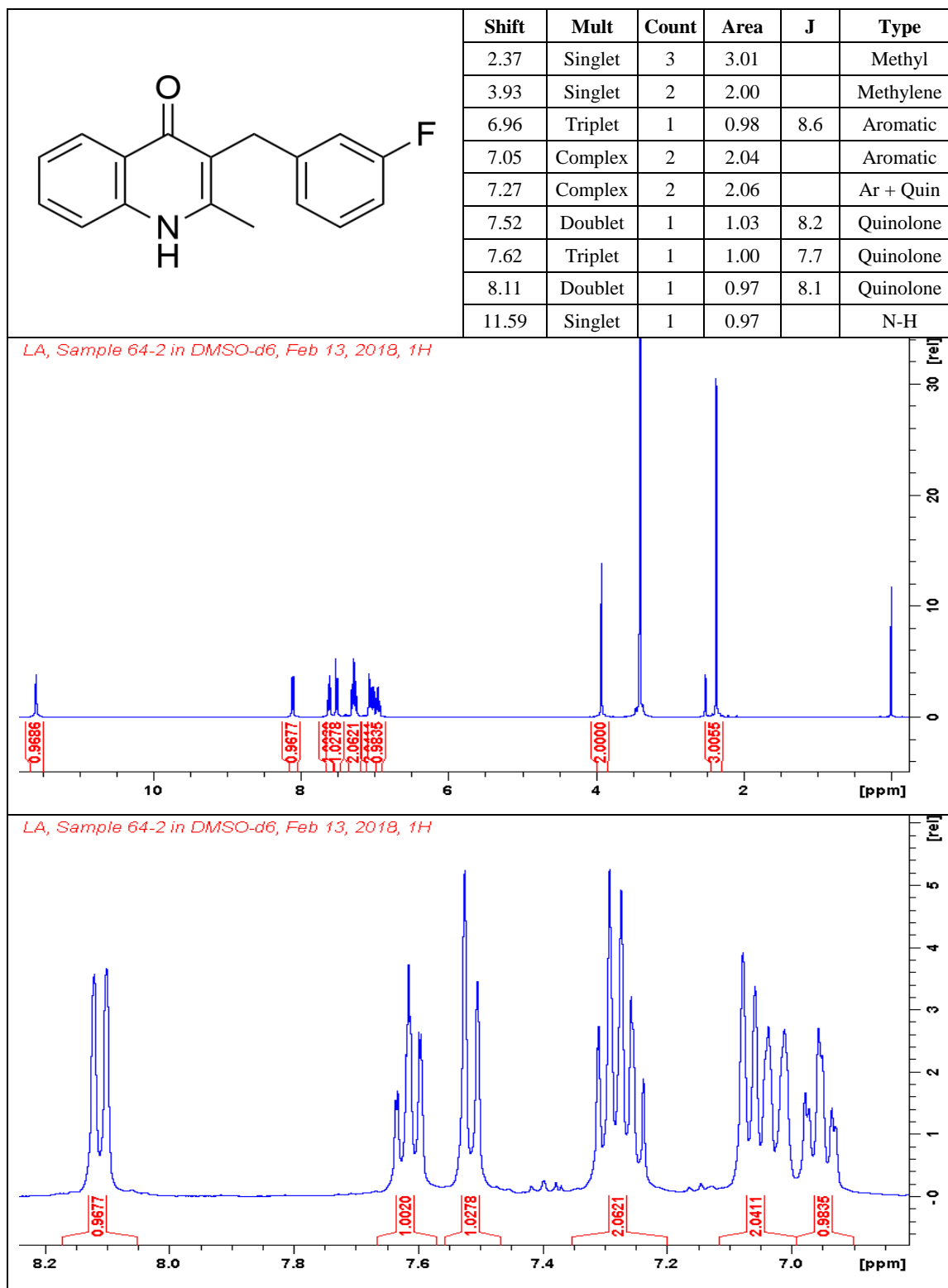


Table 13 ¹H NMR of 3-(4-Chlorobenzyl)-2-methyl-4-quinolone

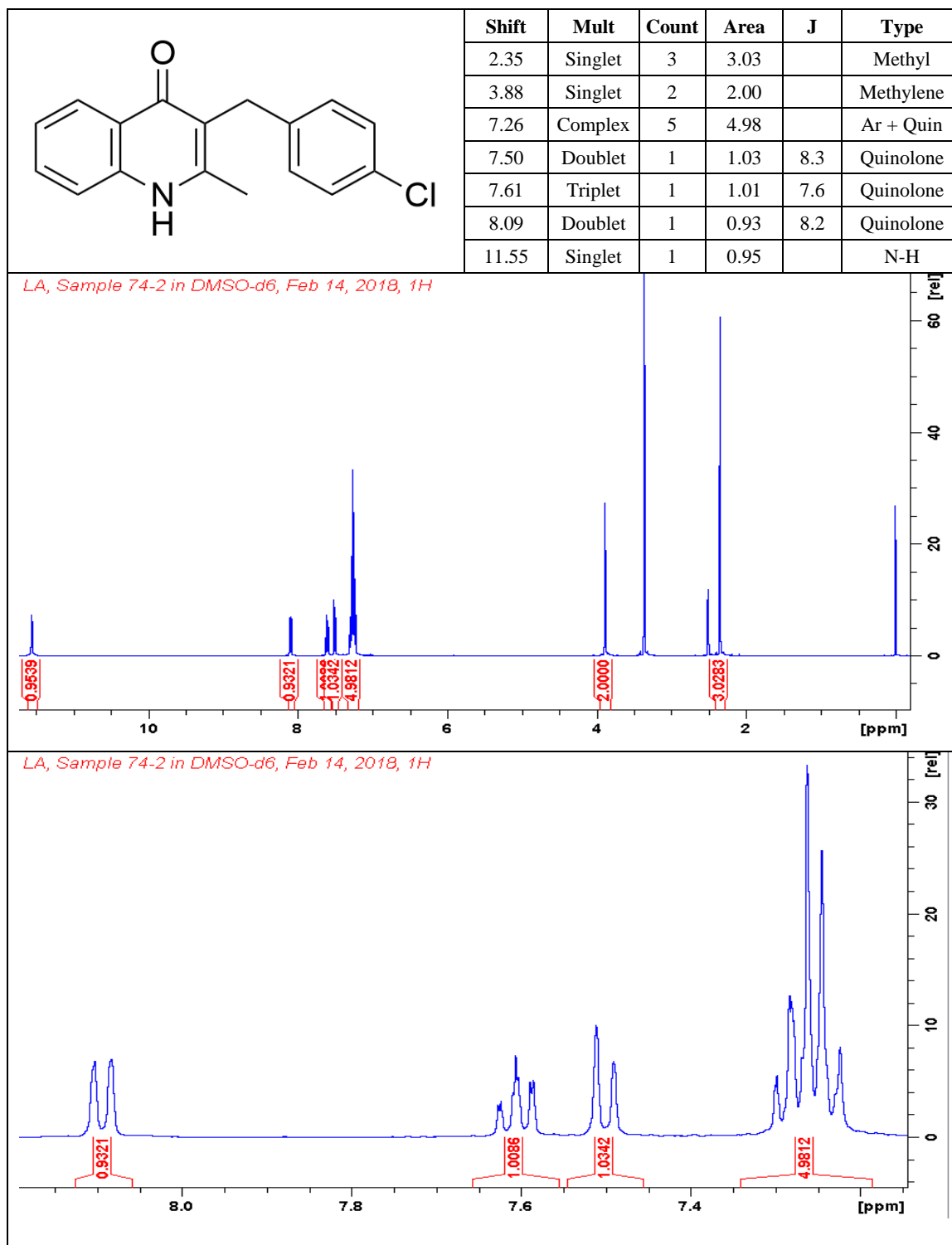


Table 14 ¹H NMR of 3-(4-Fluorobenzyl)-2-methyl-6-nitro-4-quinolone

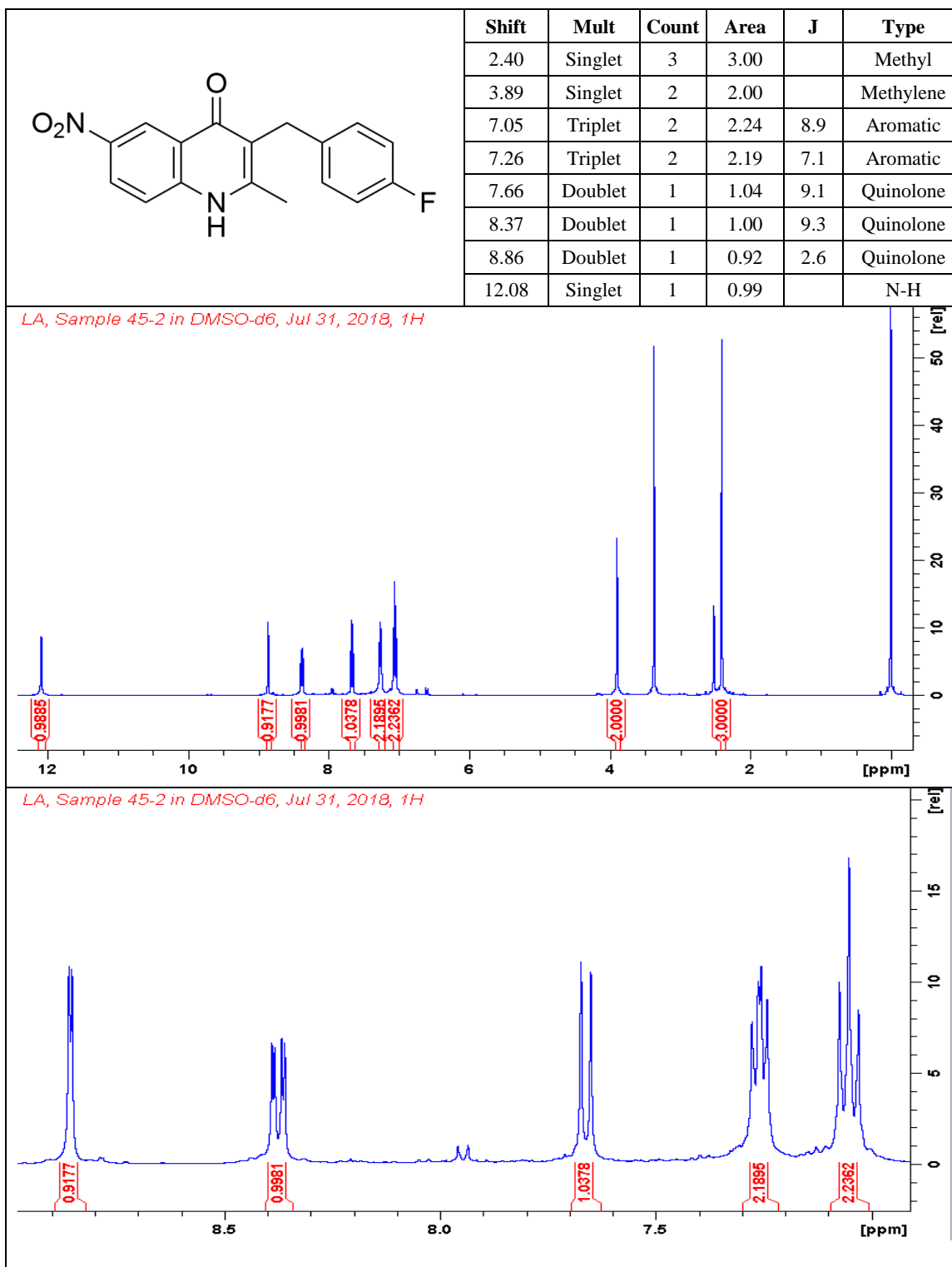


Table 15 ¹H NMR of 3-(3-Chlorobenzyl)-2-methyl-6-nitro-4-quinolone

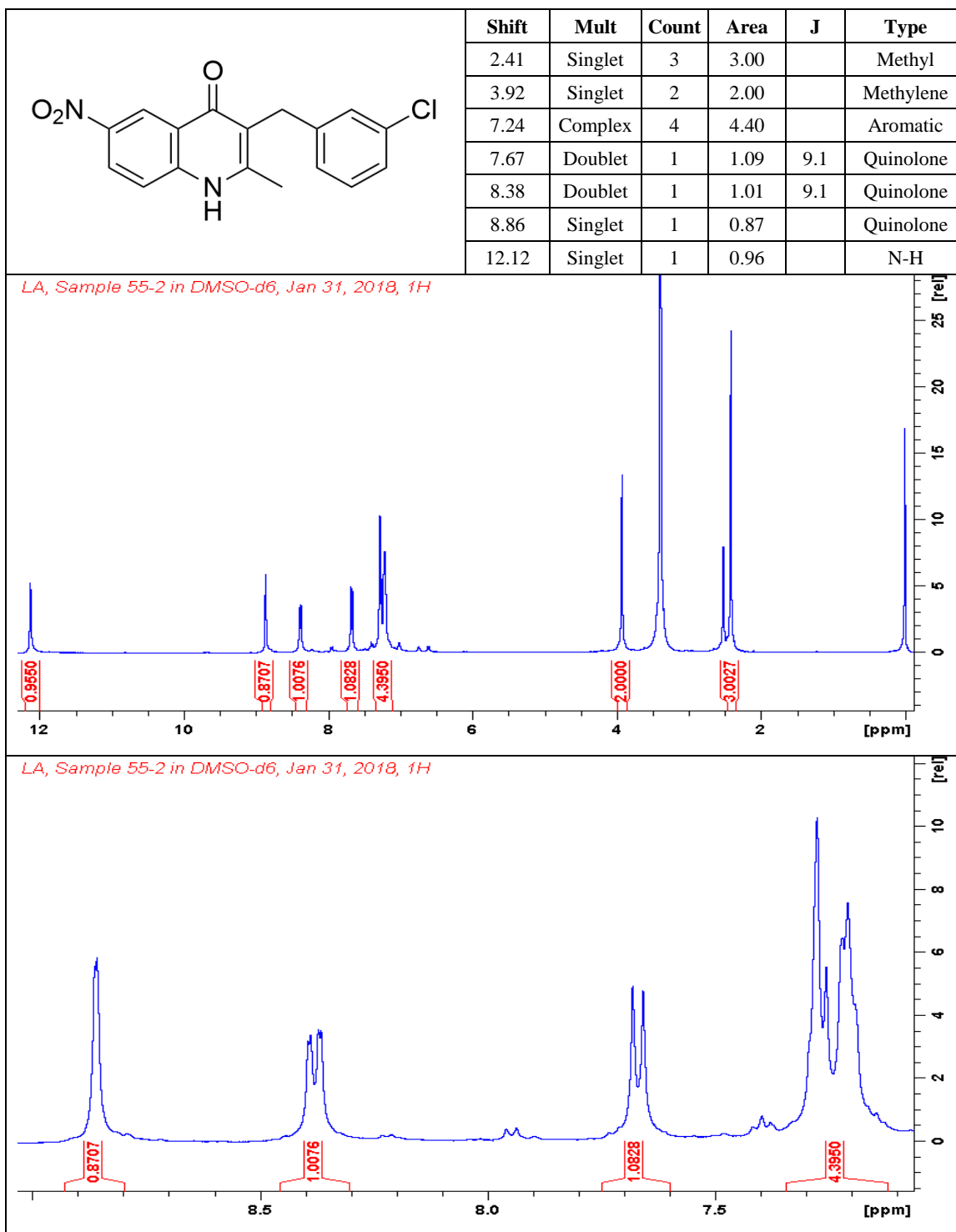


Table 16 ¹H NMR of 3-(3-Fluorobenzyl)-2-methyl-6-nitro-4-quinolone

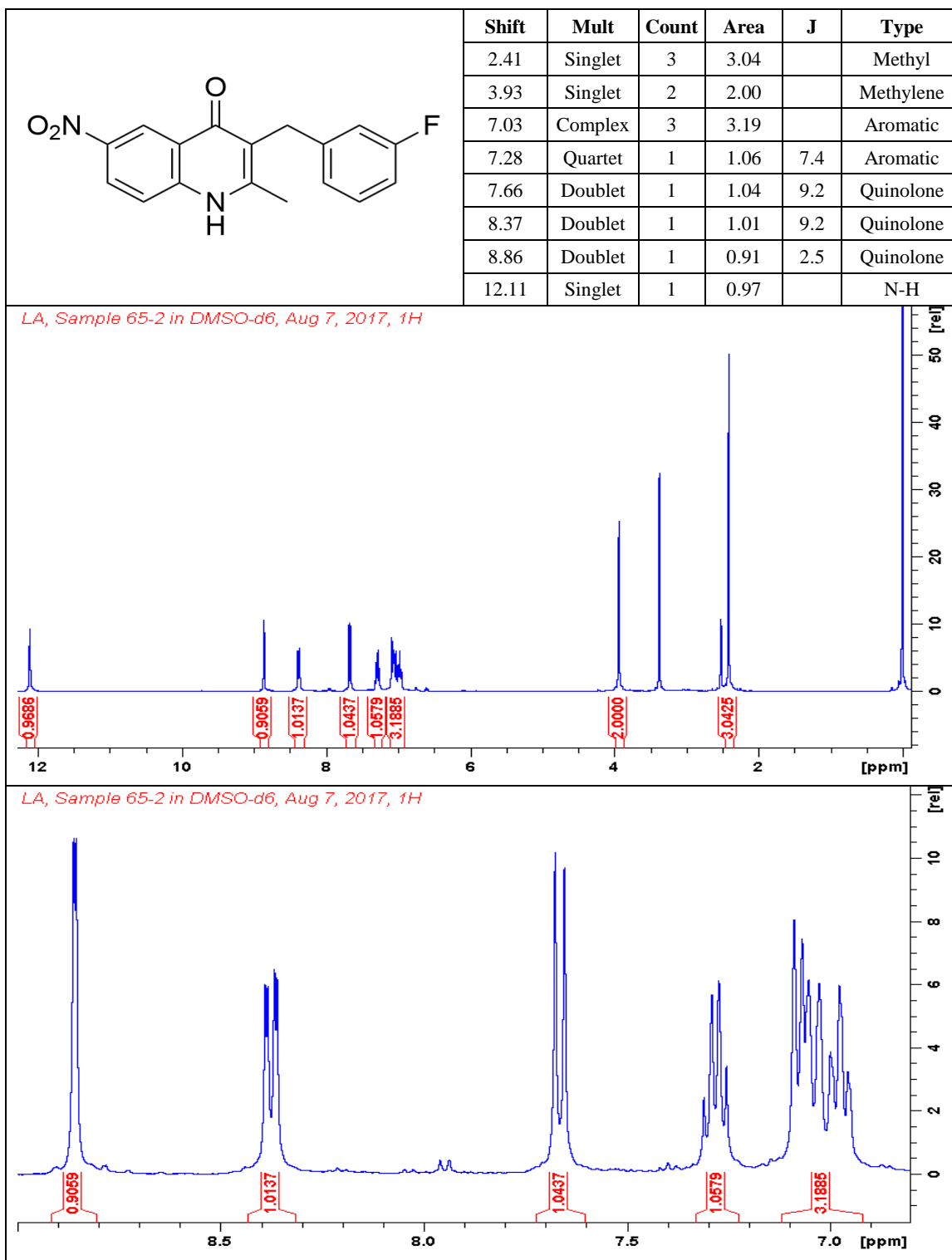


Table 17 ¹H NMR of 3-(4-Chlorobenzyl)-2-methyl-6-nitro-4-quinolone

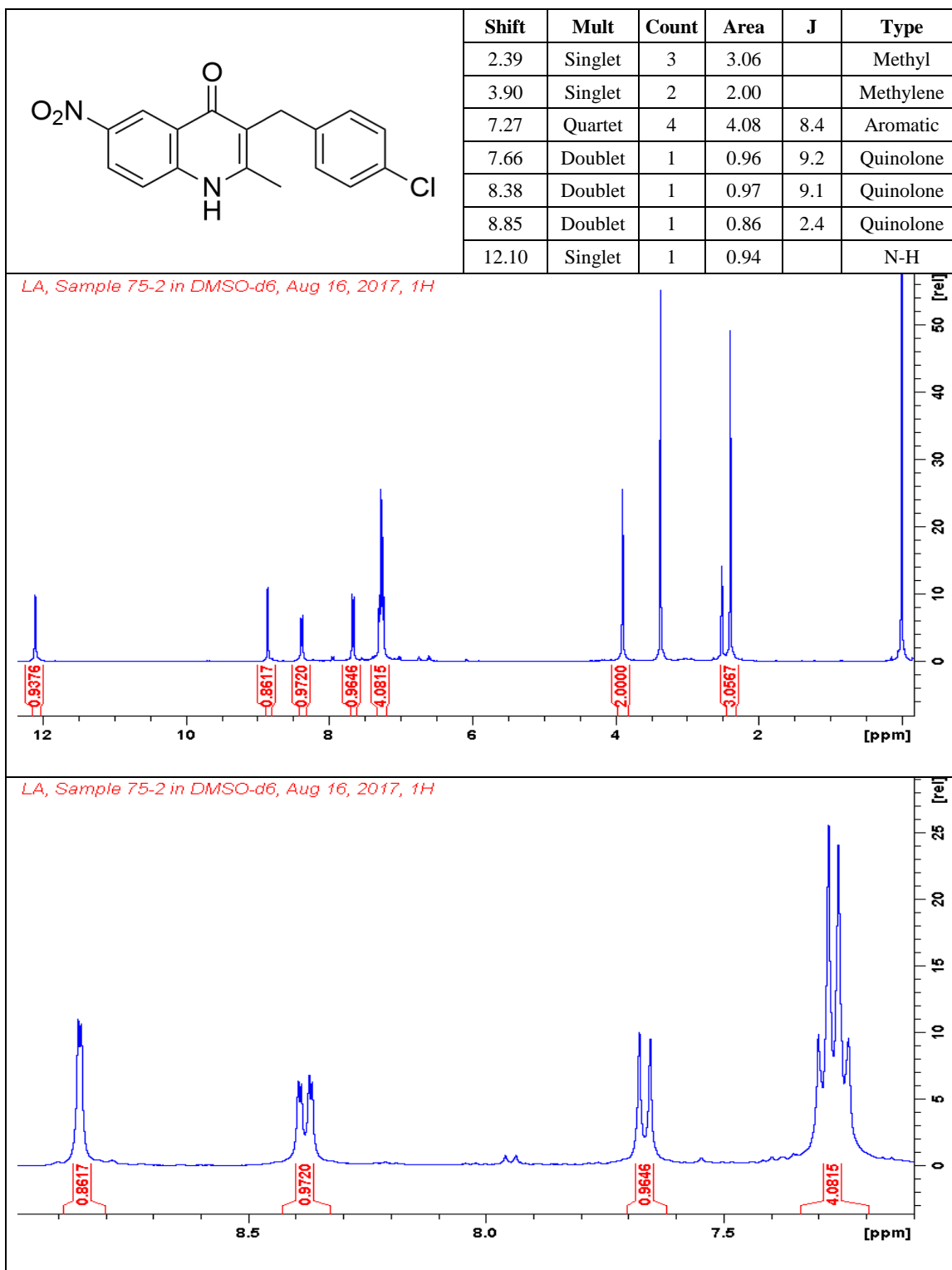


Table 18 ¹H NMR of 8-Chloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

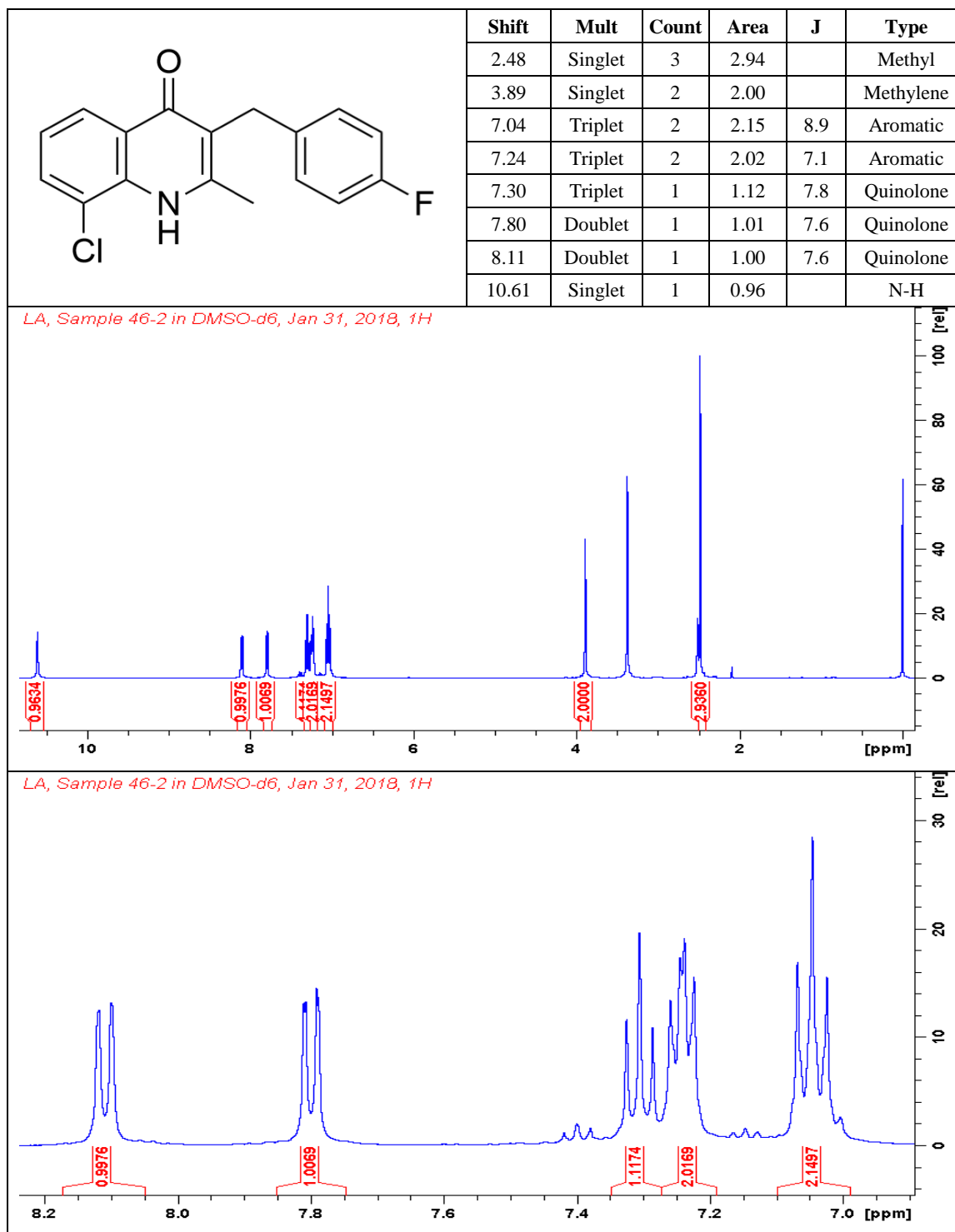


Table 19 ¹H NMR of 8-Chloro-3-(3-chlorobenzyl)-2-methyl-4-quinolone

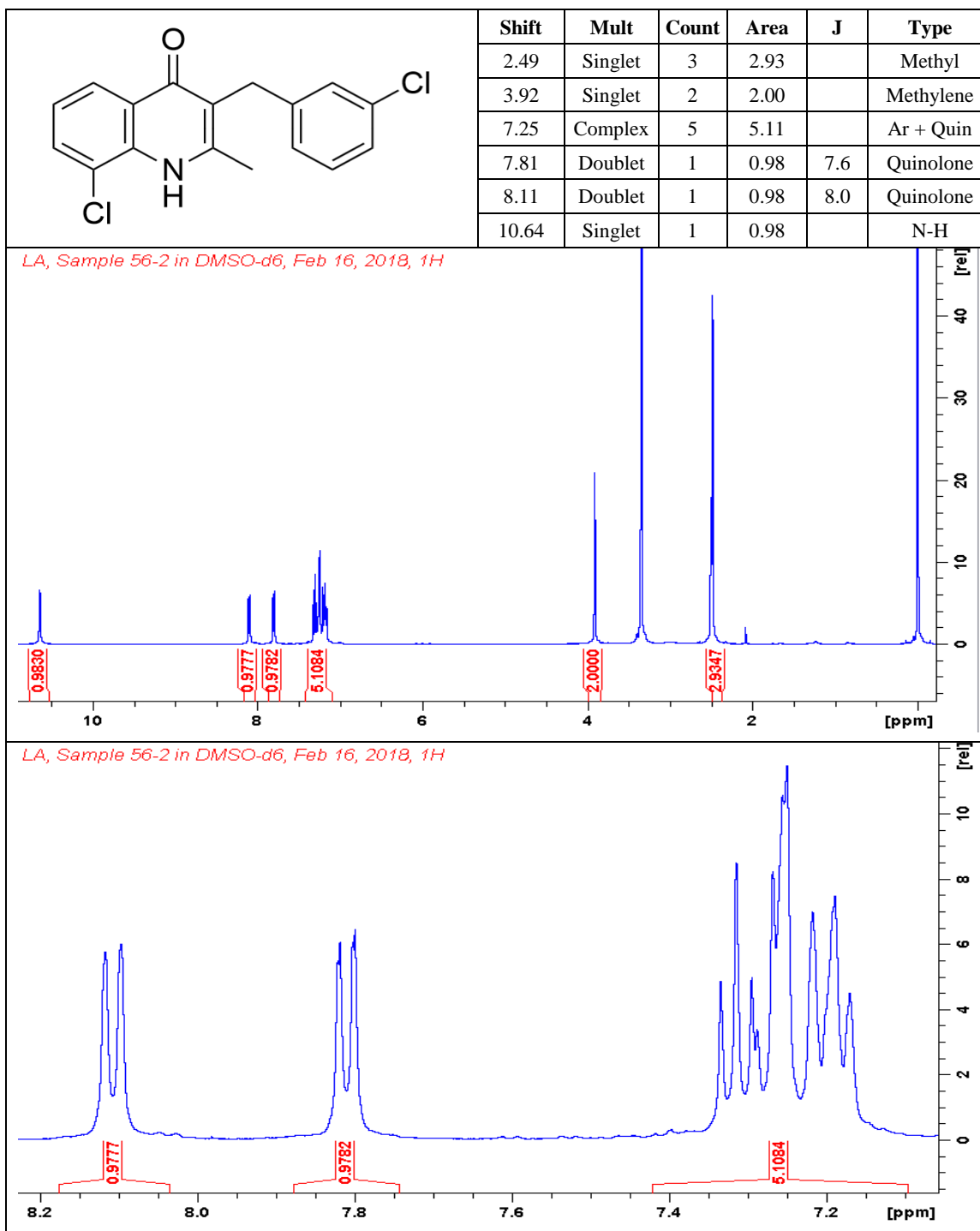
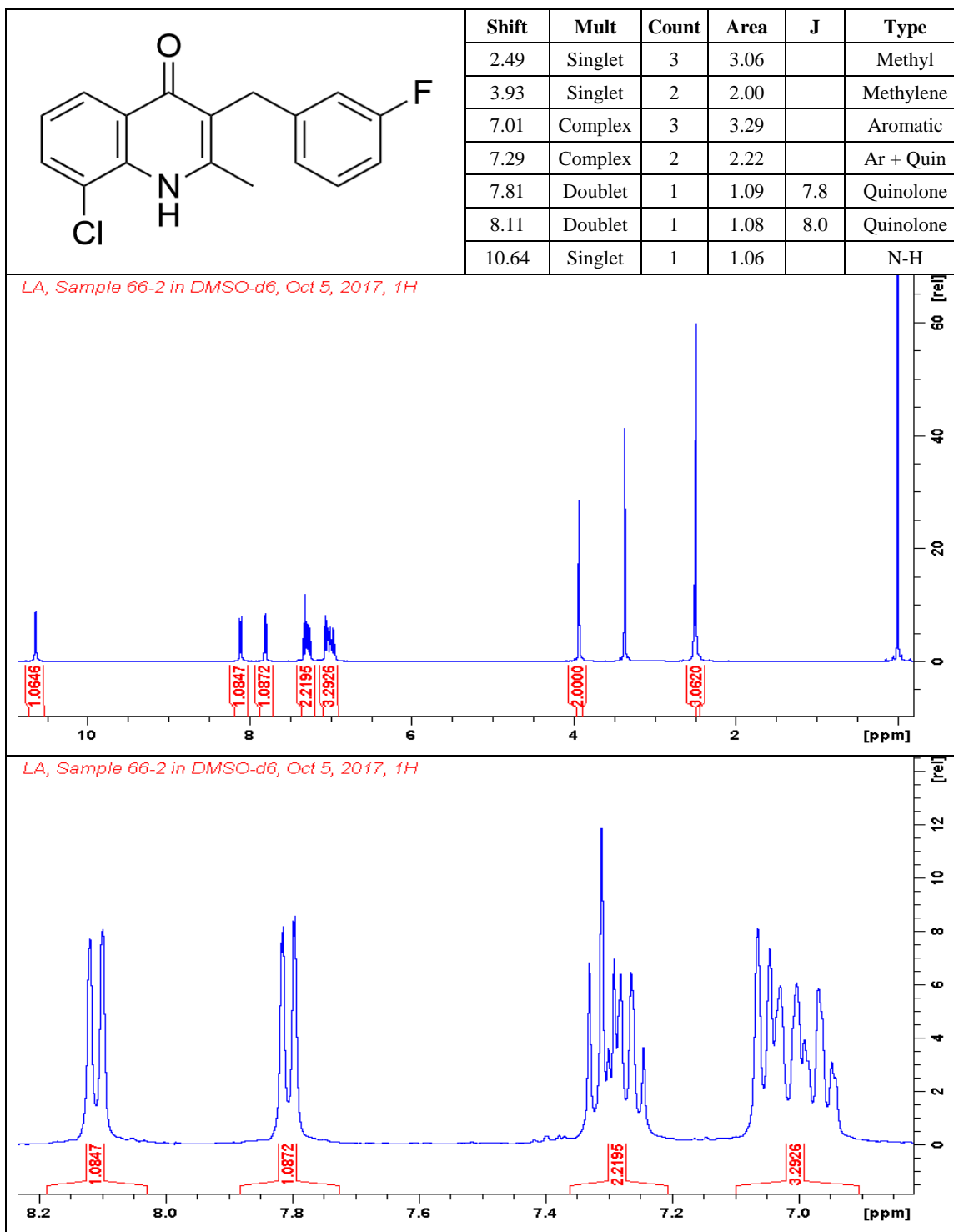


Table 20 ^1H NMR of 8-Chloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone



Appendix C – ^{13}C NMR Spectra

Table 21 ^{13}C NMR of 6-Chloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

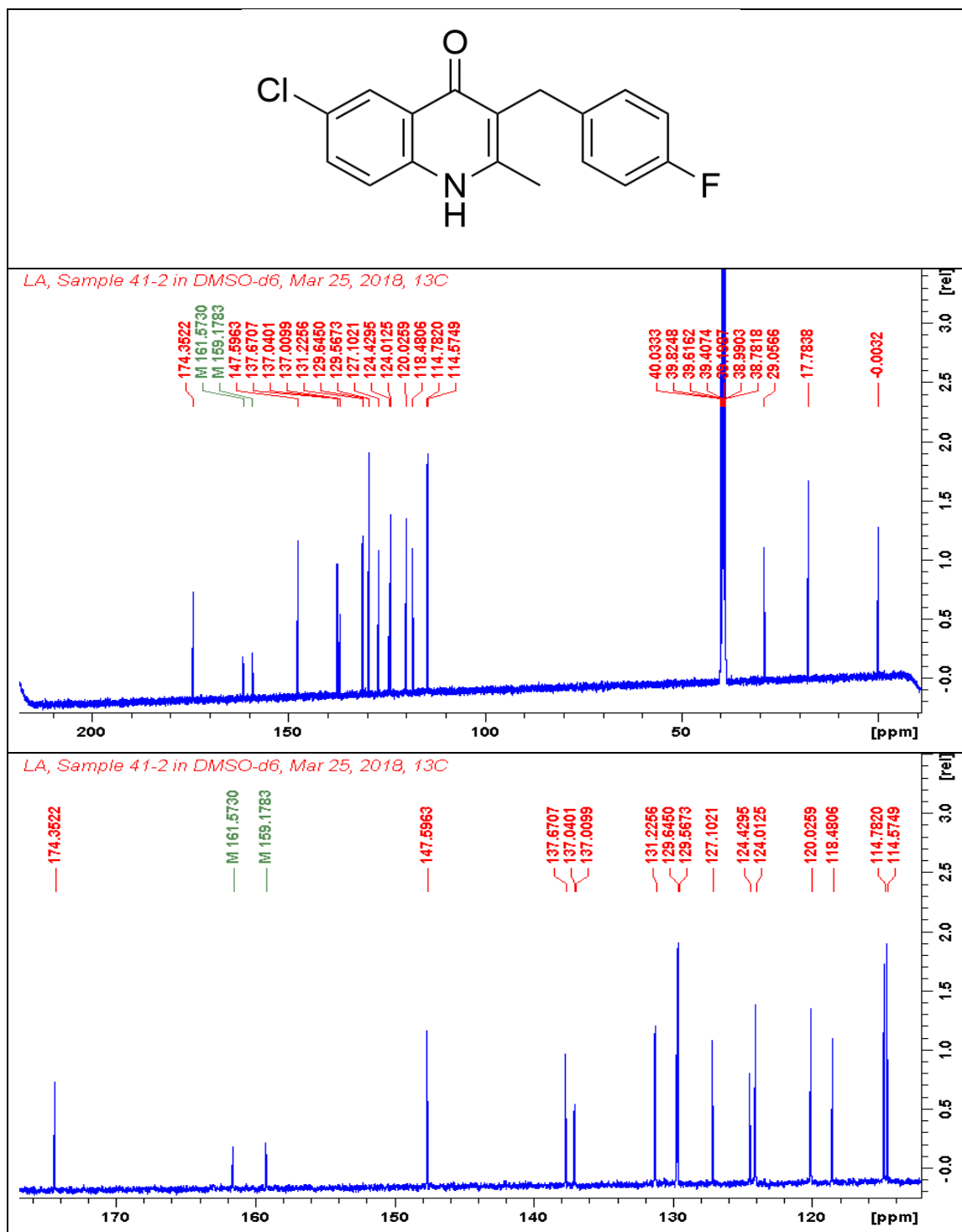


Table 22 ^{13}C NMR of 6-Chloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

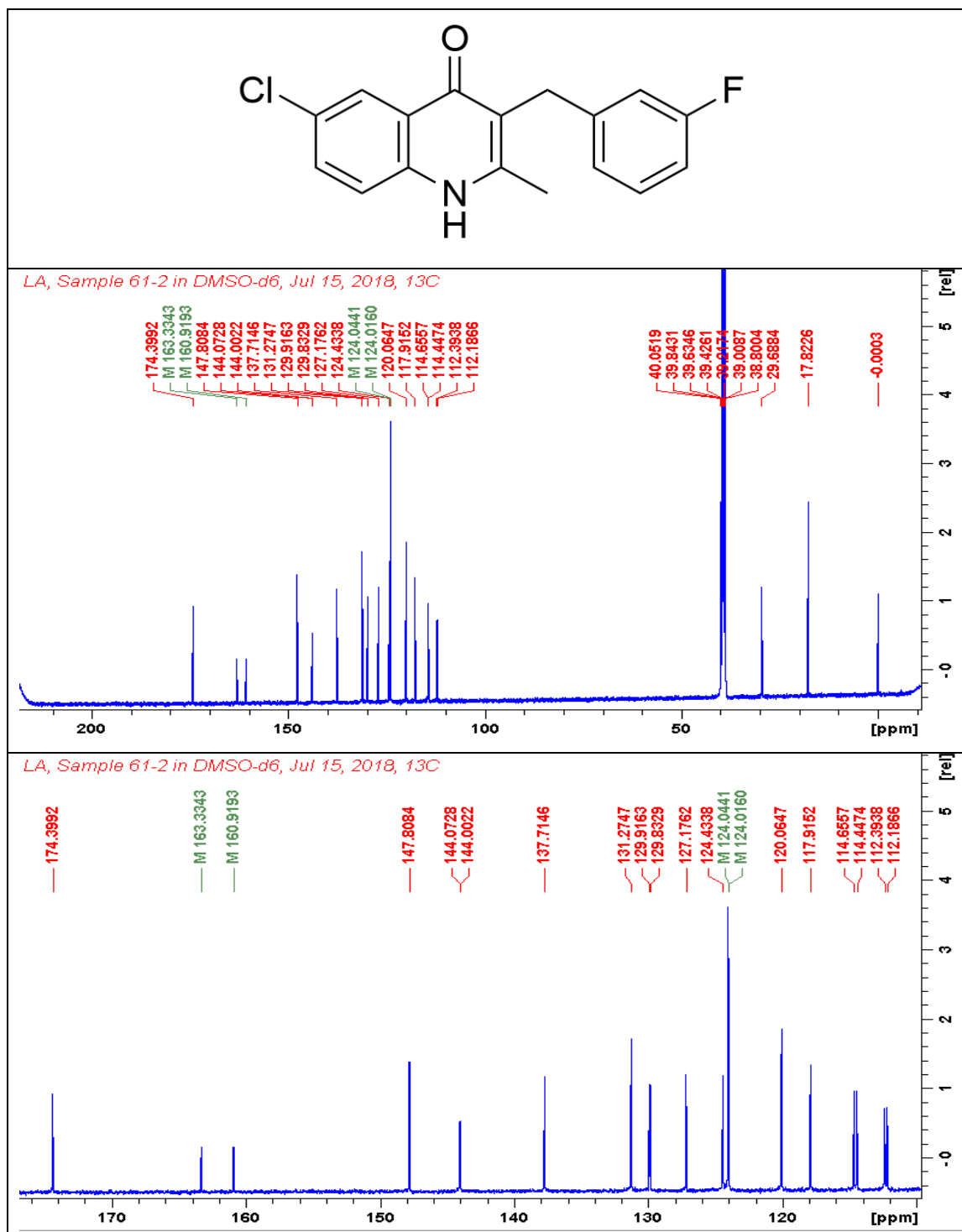


Table 23 ^{13}C NMR of 5,7-Dichloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

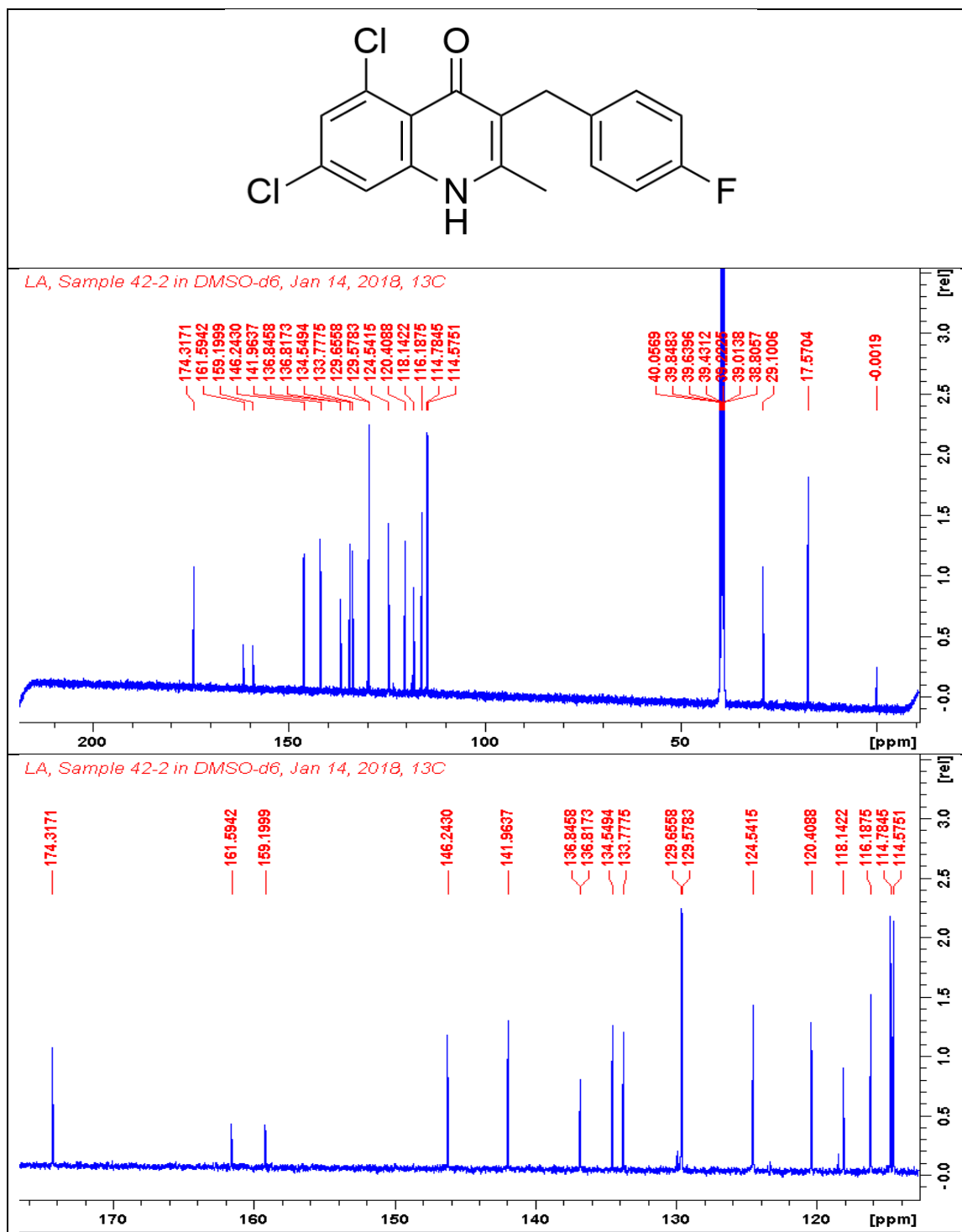


Table 24 ^{13}C NMR of 5,7-Dichloro-3-(3-chlorobenzyl)-2-methyl-4-quinolone

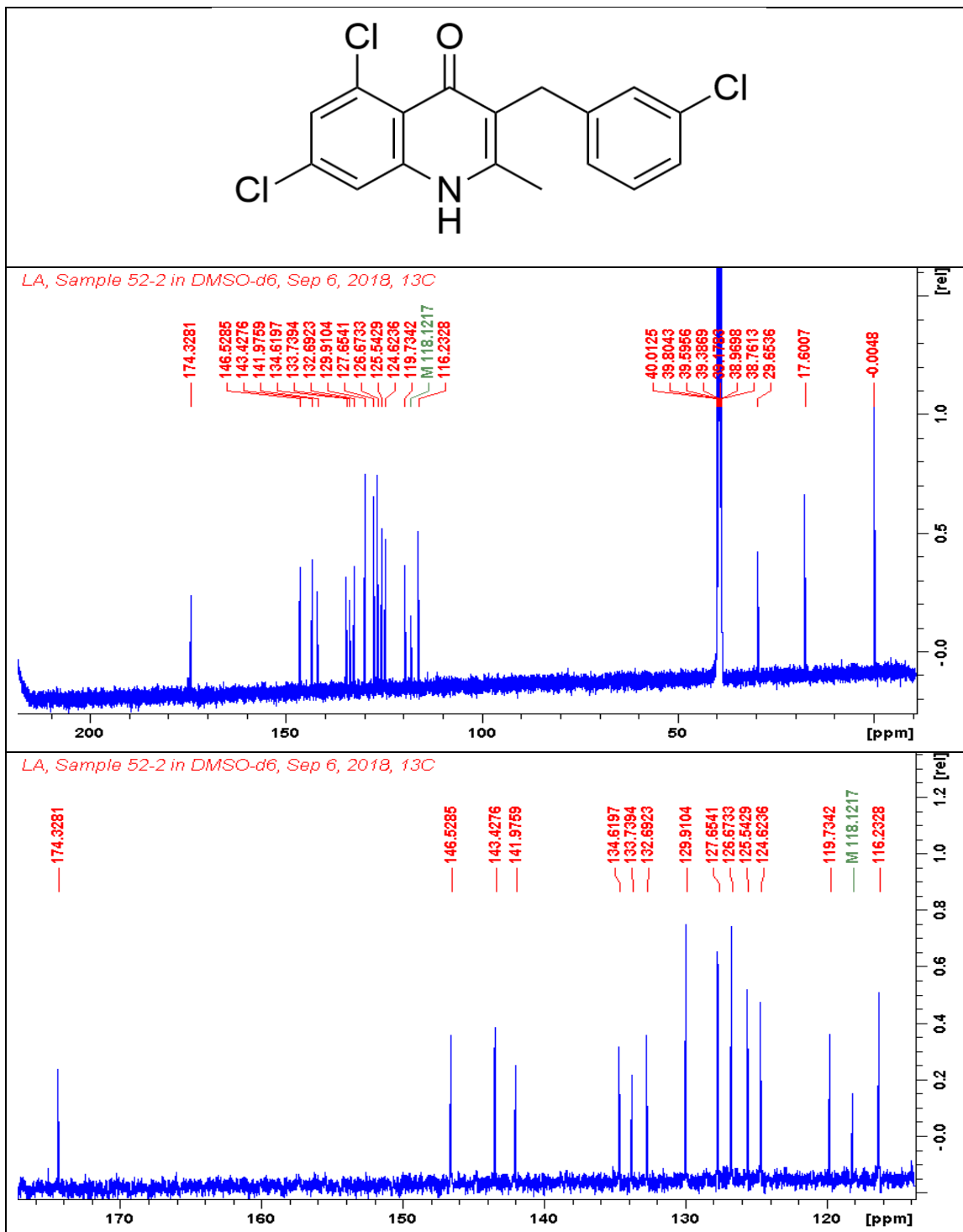


Table 25 ^{13}C NMR of 5,7-Dichloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

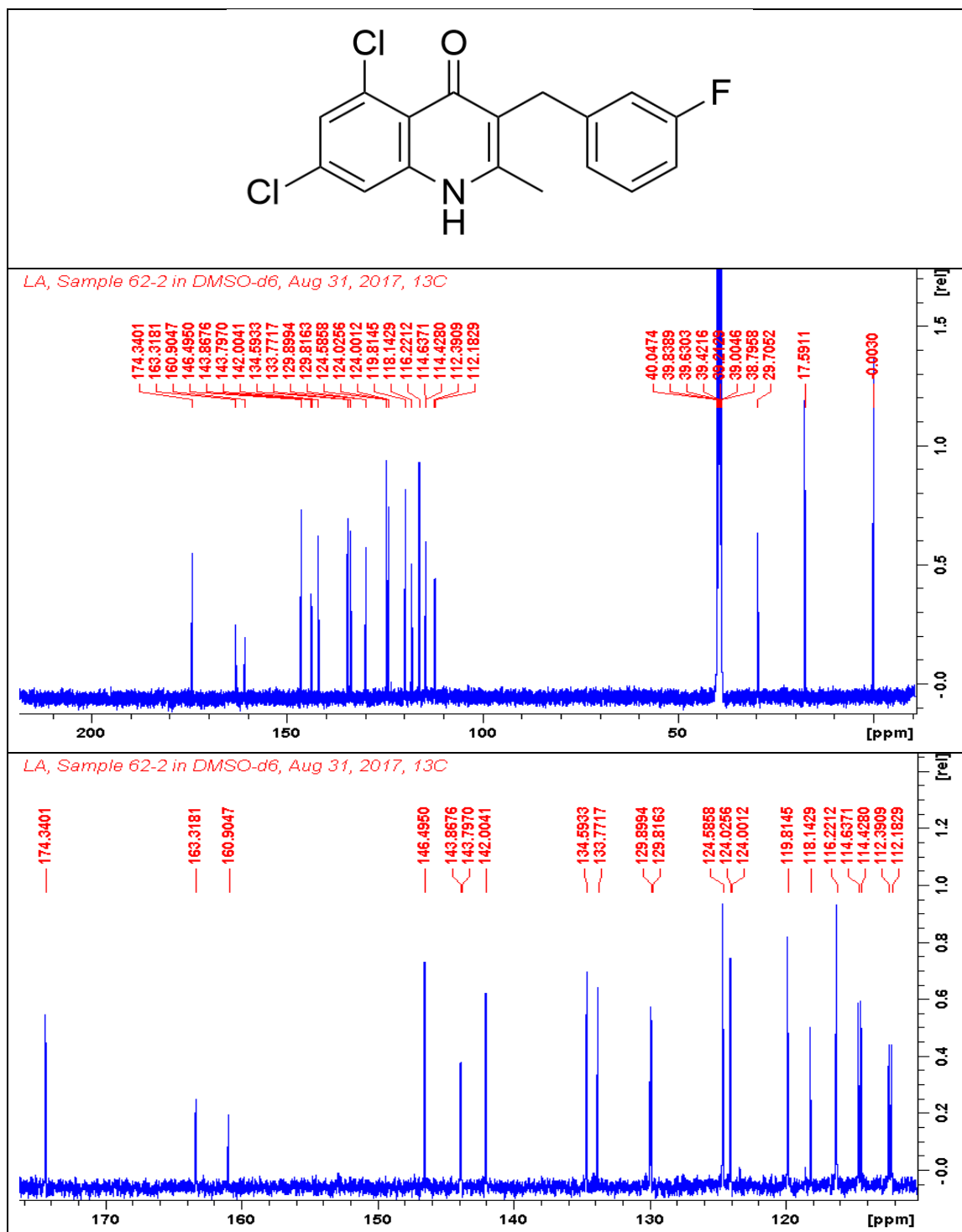


Table 26 ^{13}C NMR of 5,7-Dichloro-3-(4-chlorobenzyl)-2-methyl-4-quinolone

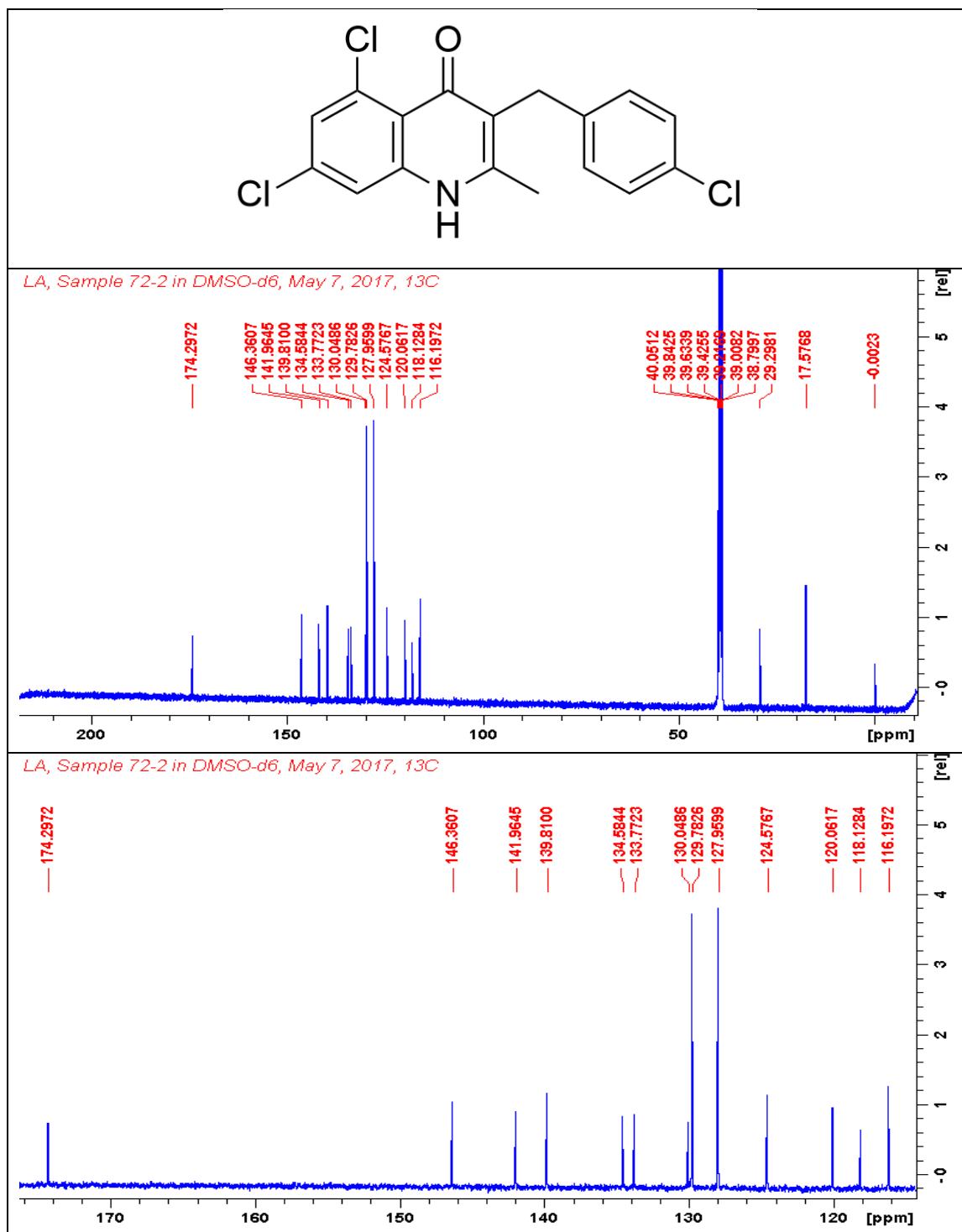


Table 27 ^{13}C NMR of 3-(4-Fluorobenzyl)-2-methyl-4-quinolone

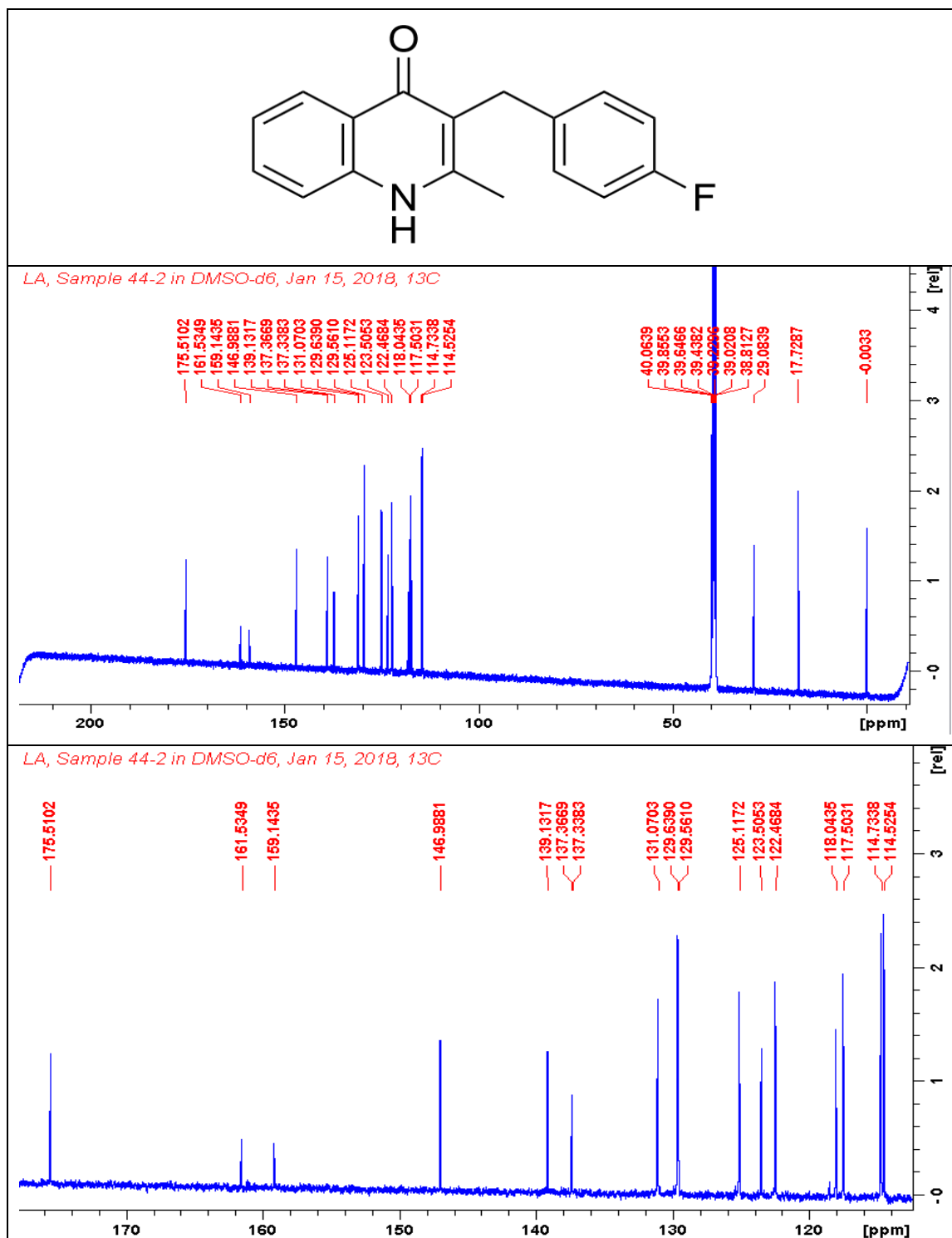


Table 28 ^{13}C NMR of 3-(3-Chlorobenzyl)-2-methyl-4-quinolone

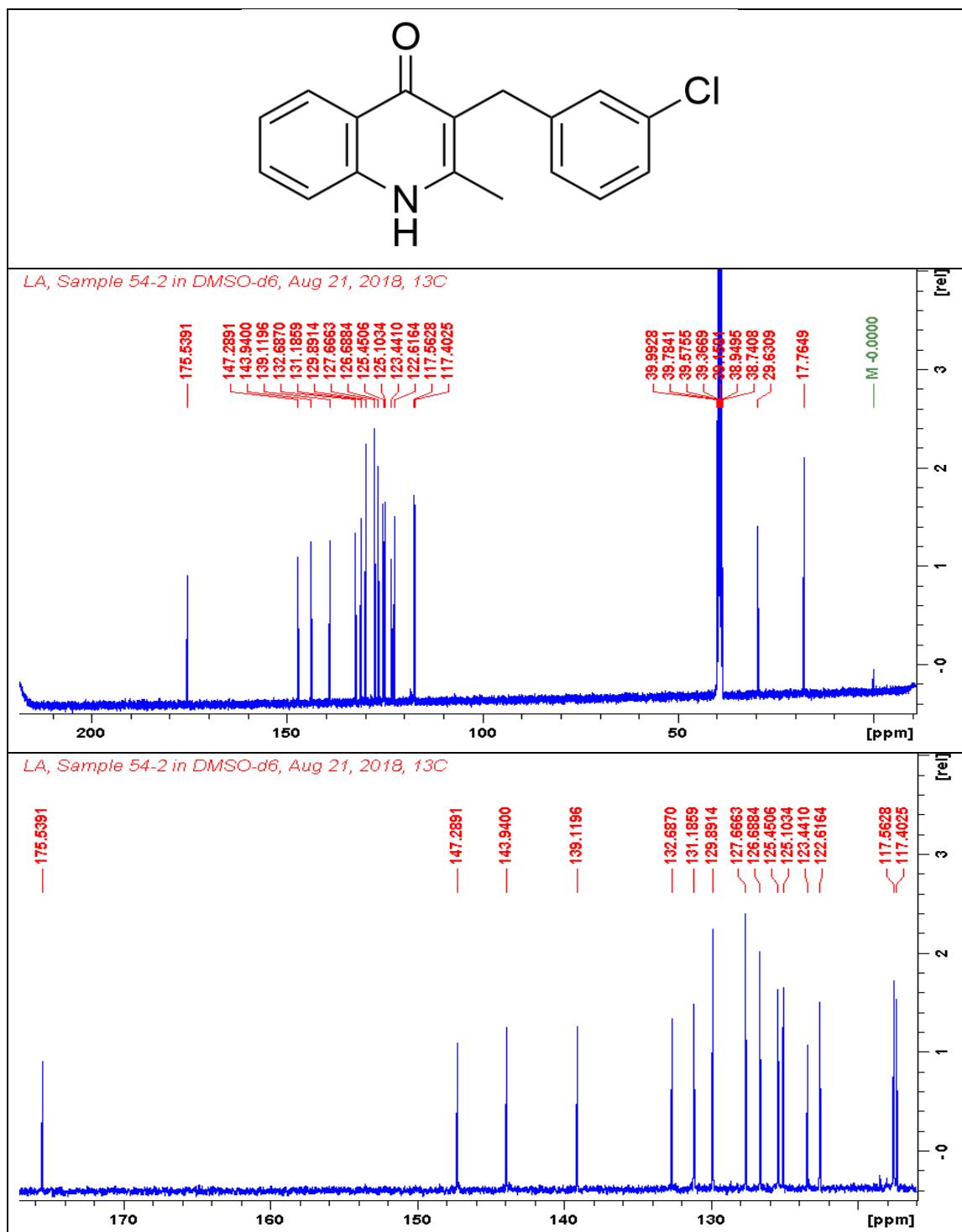


Table 29 ^{13}C NMR of 3-(3-Fluorobenzyl)-2-methyl-4-quinolone

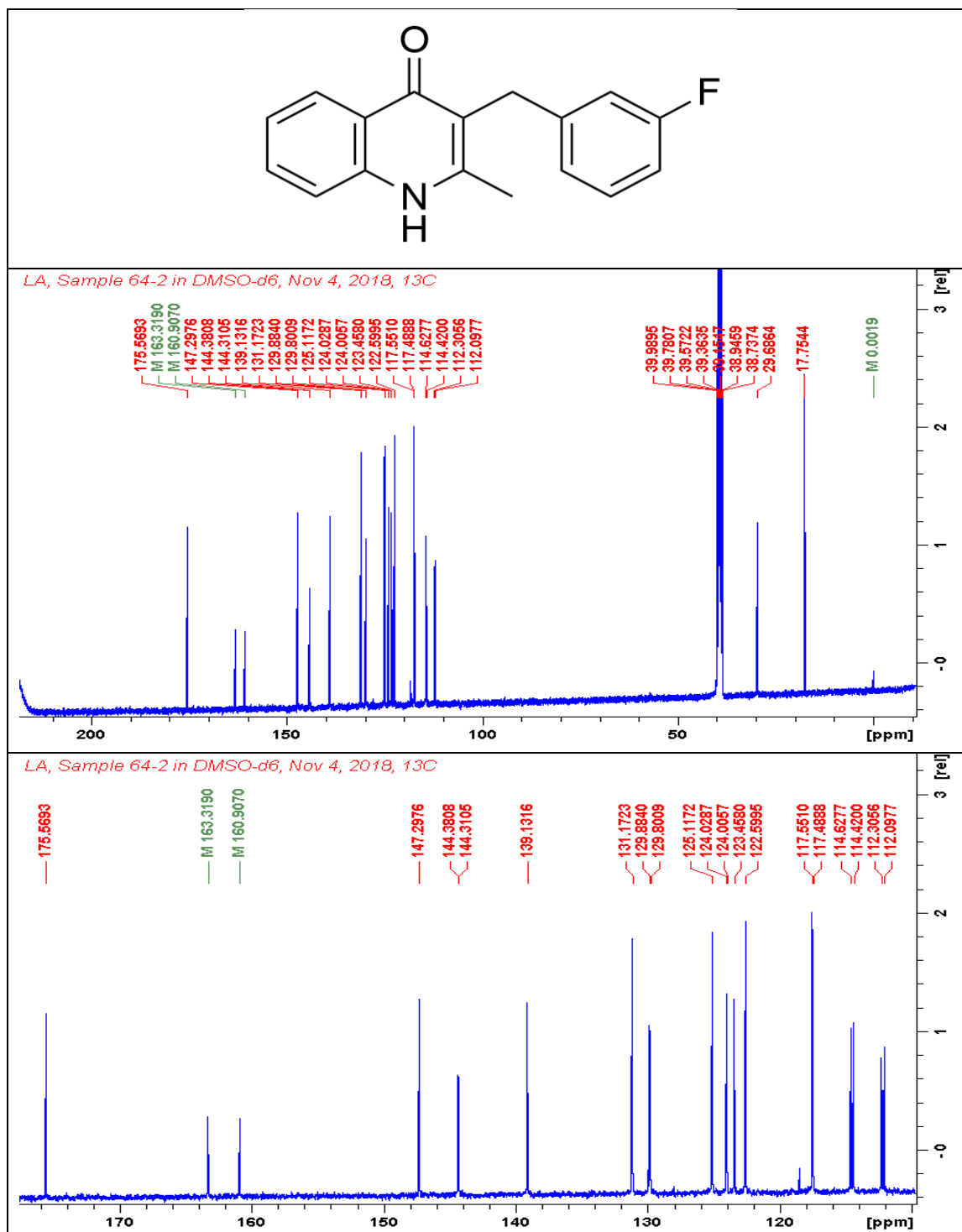


Table 30 ^{13}C NMR of 3-(4-Chlorobenzyl)-2-methyl-4-quinolone

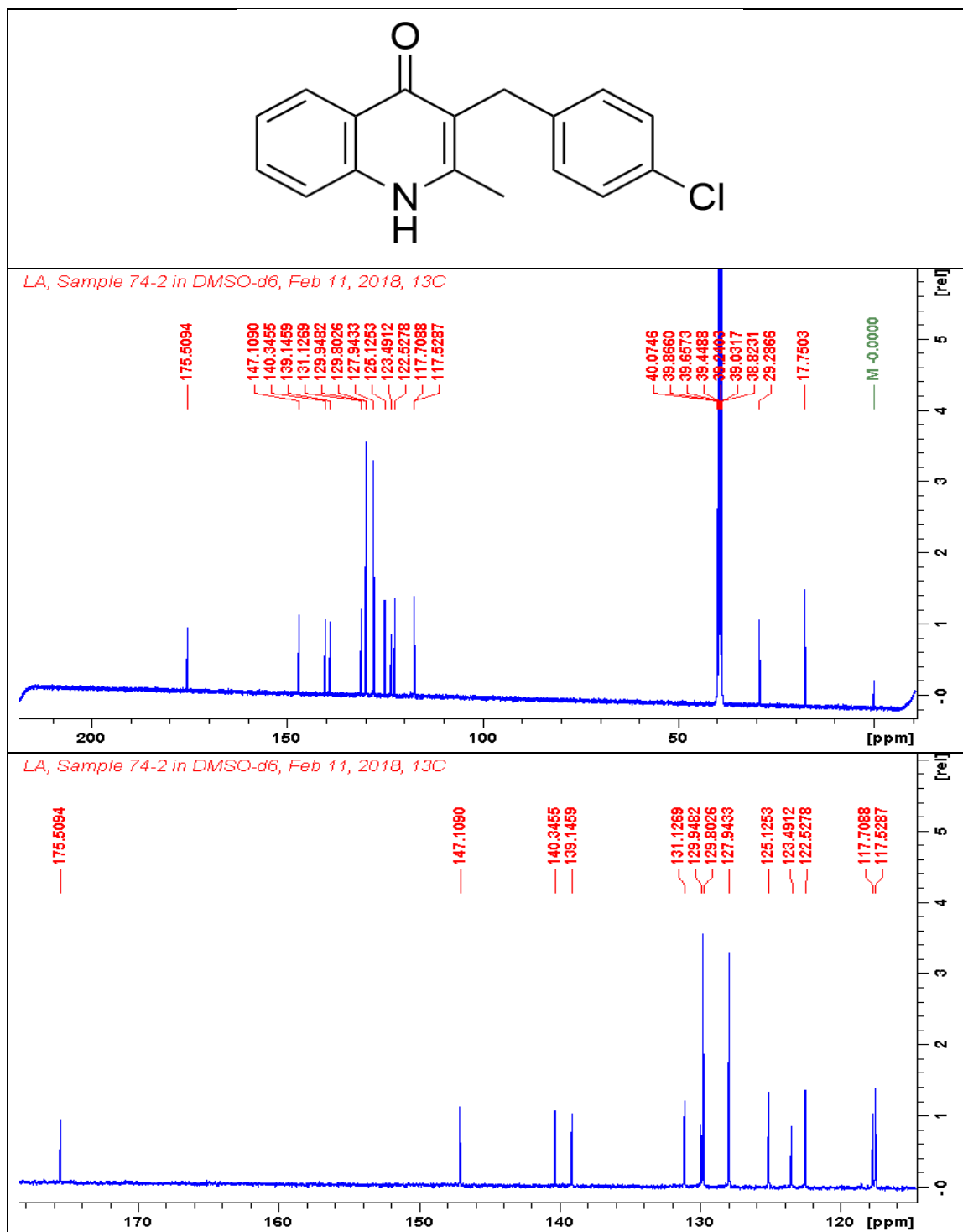


Table 31 ^{13}C NMR of 3-(4-Fluorobenzyl)-2-methyl-6-nitro-4-quinolone

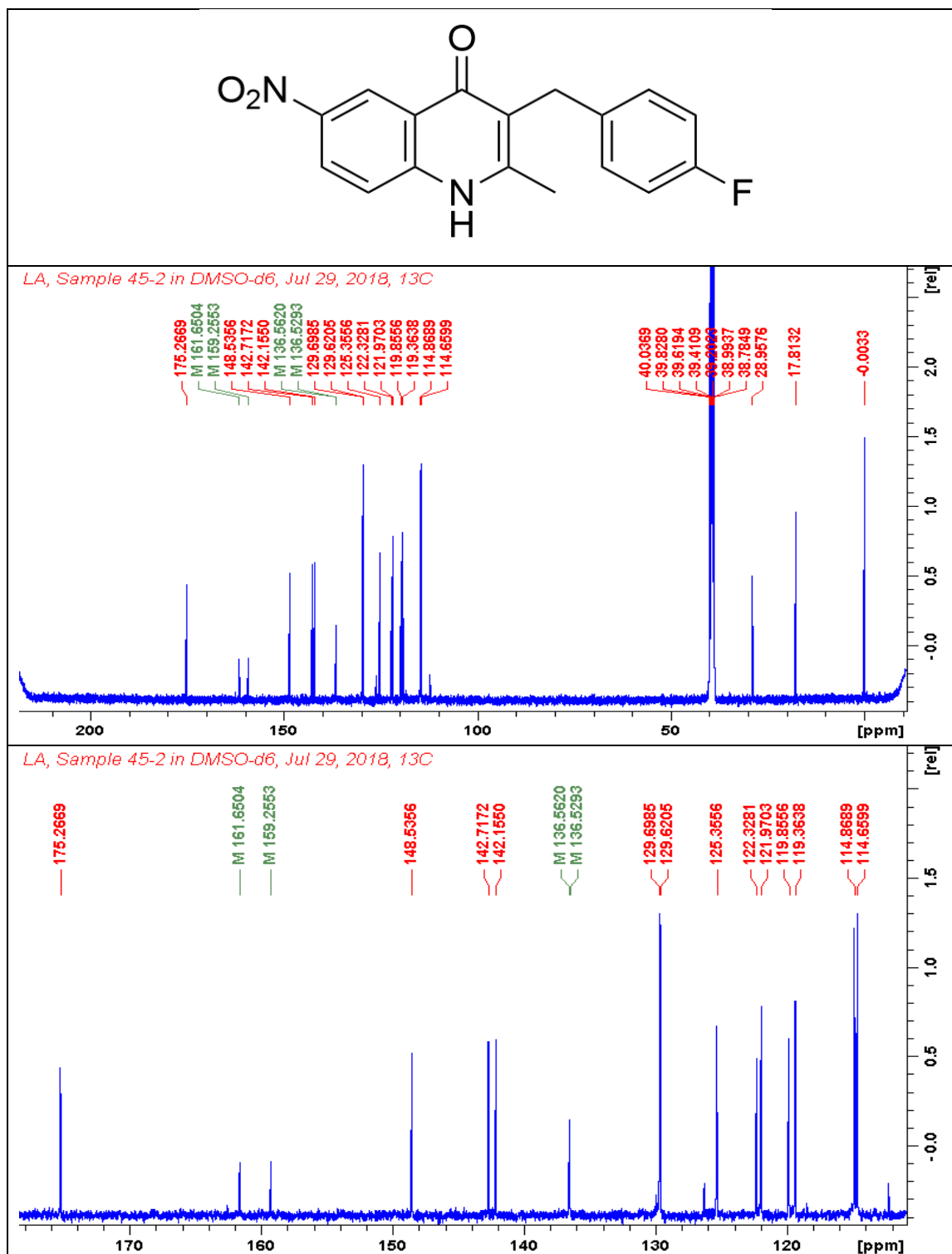
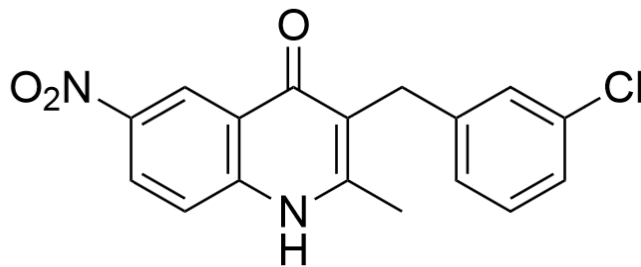
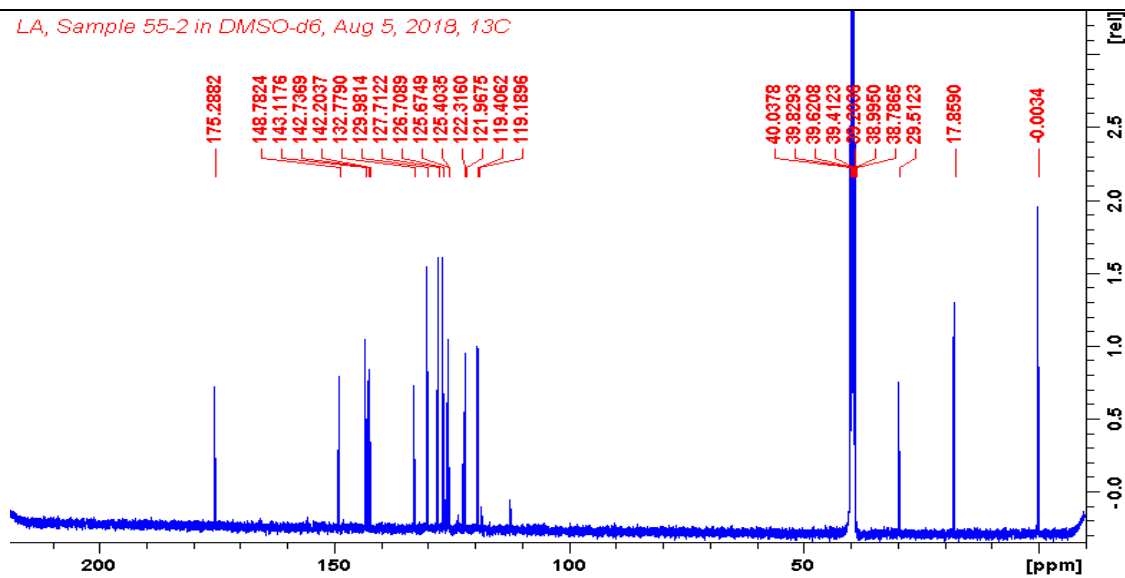


Table 32 ^{13}C NMR of 3-(3-Chlorobenzyl)-2-methyl-6-nitro-4-quinolone



LA, Sample 55-2 in DMSO-d₆, Aug 5, 2018, ^{13}C



LA, Sample 55-2 in DMSO-d₆, Aug 5, 2018, ^{13}C

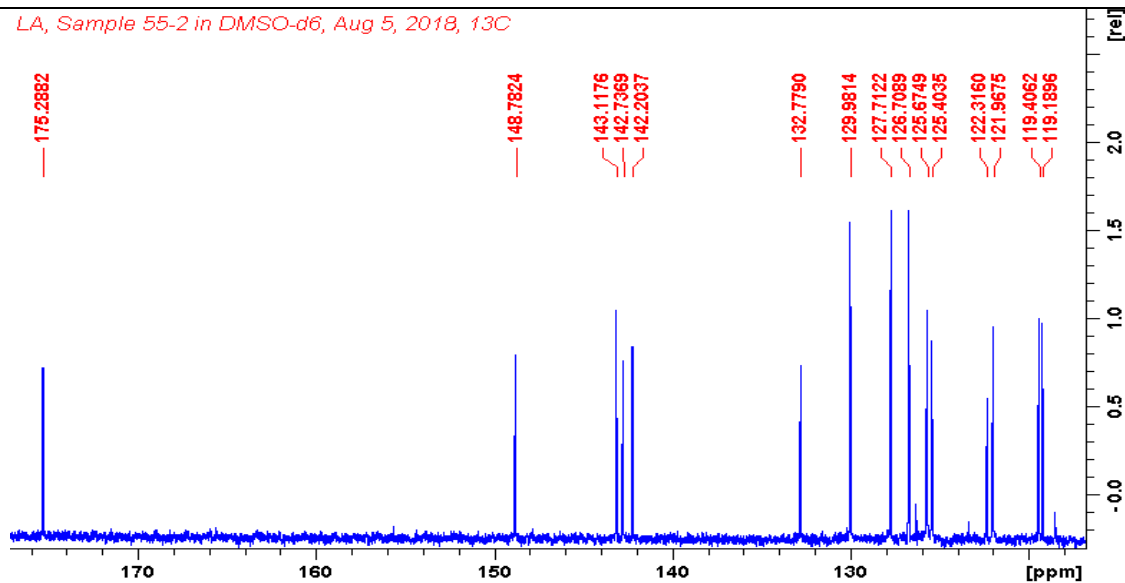


Table 33 ^{13}C NMR of 3-(3-Fluorobenzyl)-2-methyl-6-nitro-4-quinolone

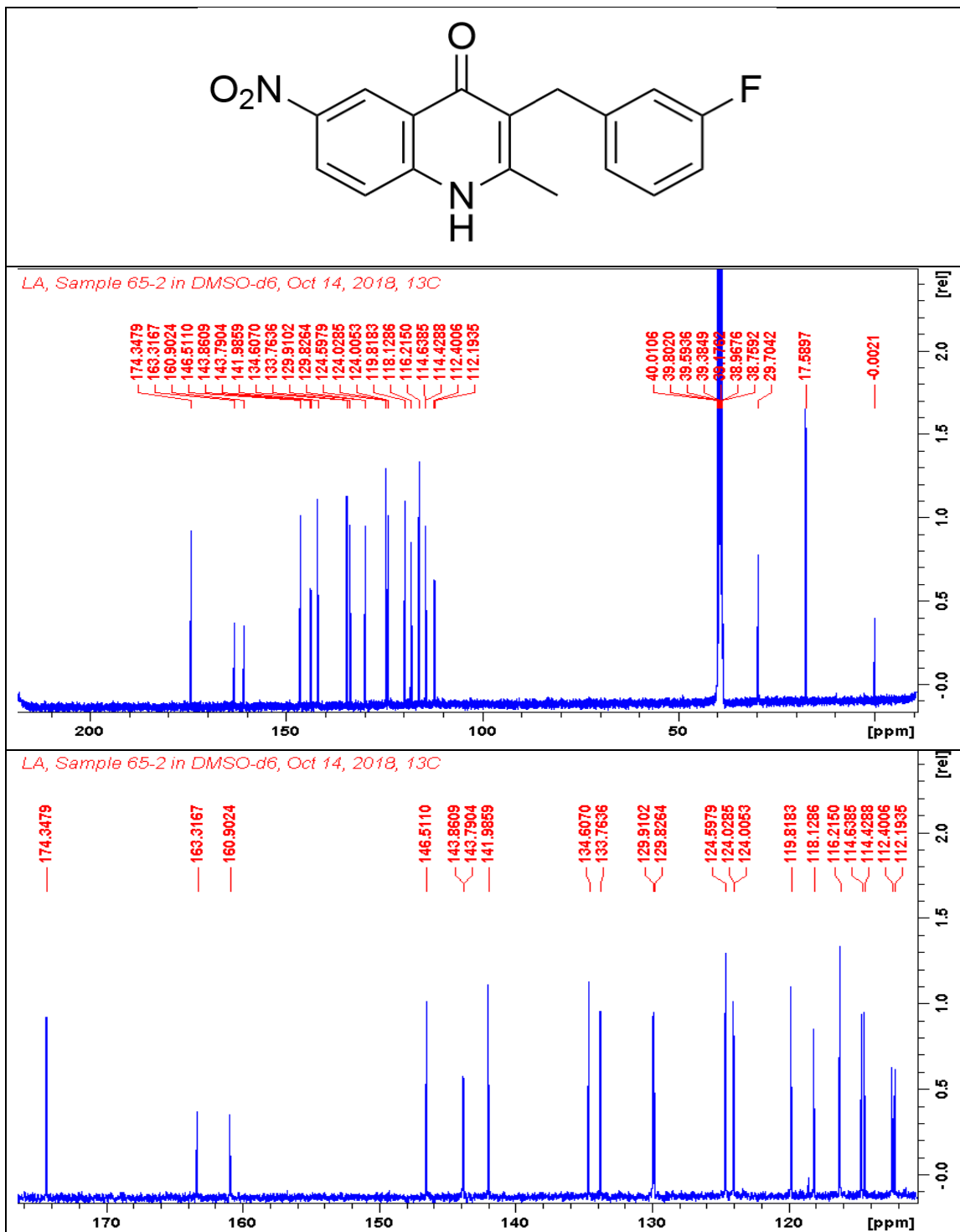


Table 34 ^{13}C NMR of 3-(4-Chlorobenzyl)-2-methyl-6-nitro-4-quinolone

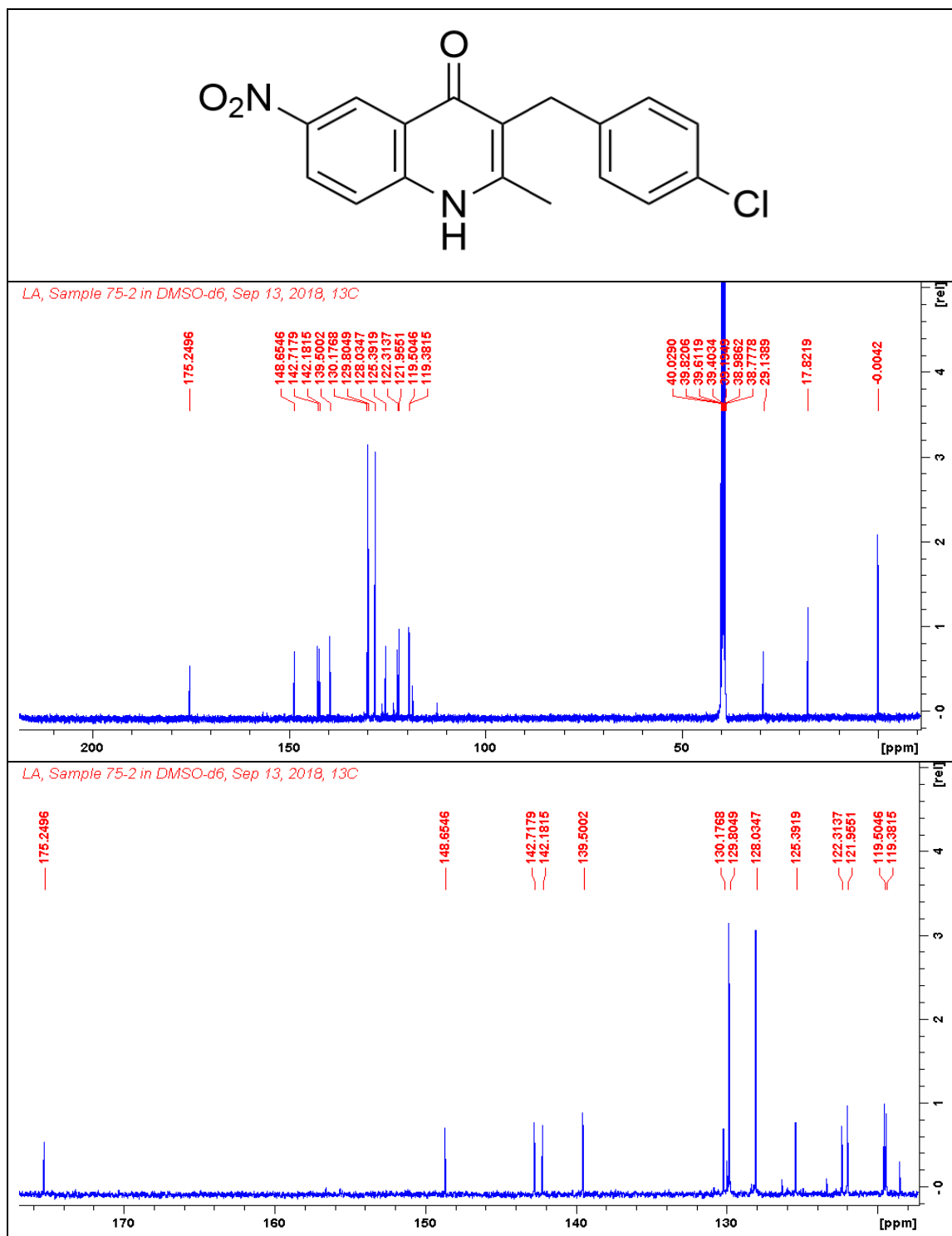


Table 35 ¹³C NMR of 8-Chloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

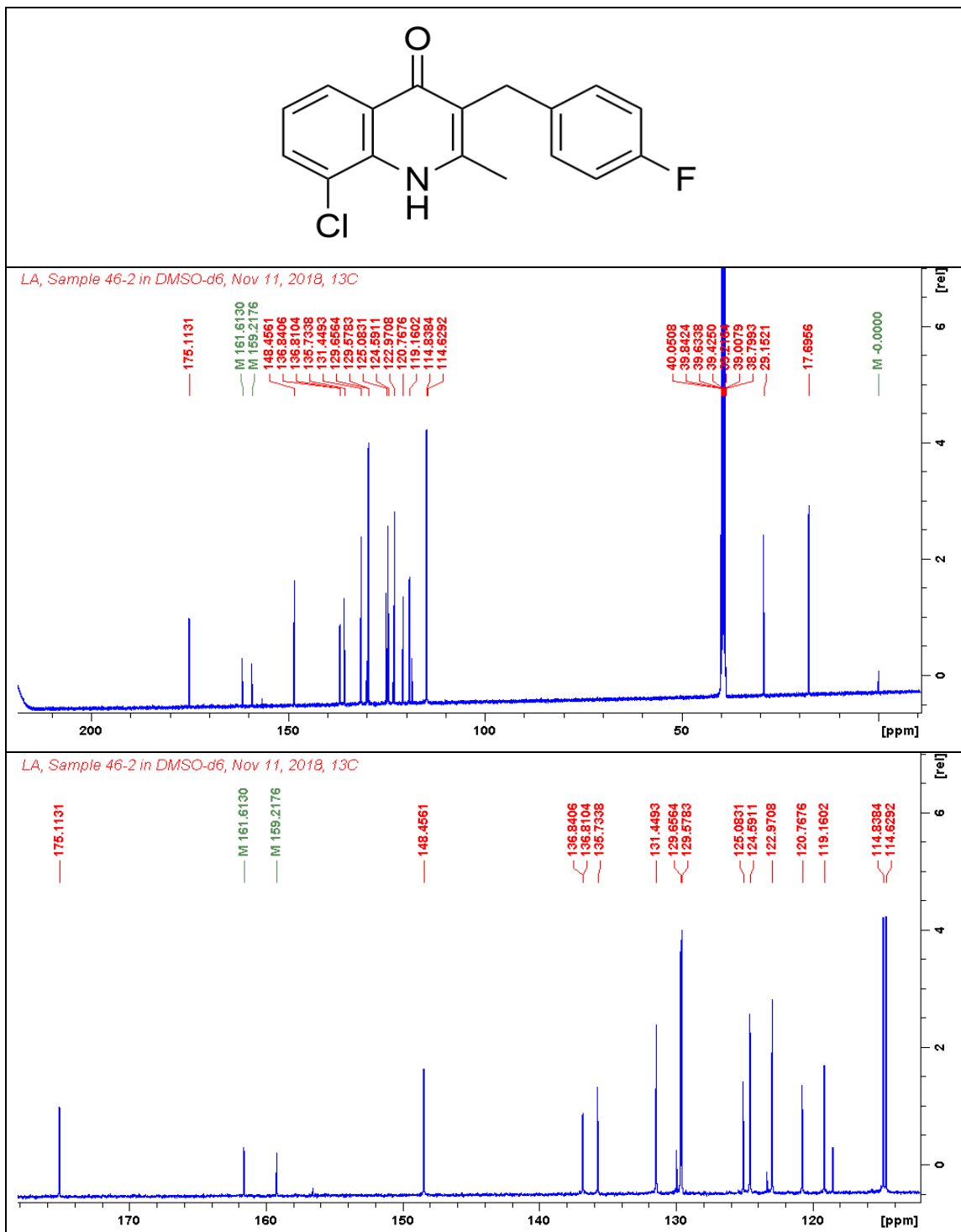


Table 36 ^{13}C NMR of 8-Chloro-3-(3-chlorobenzyl)-2-methyl-4-quinolone

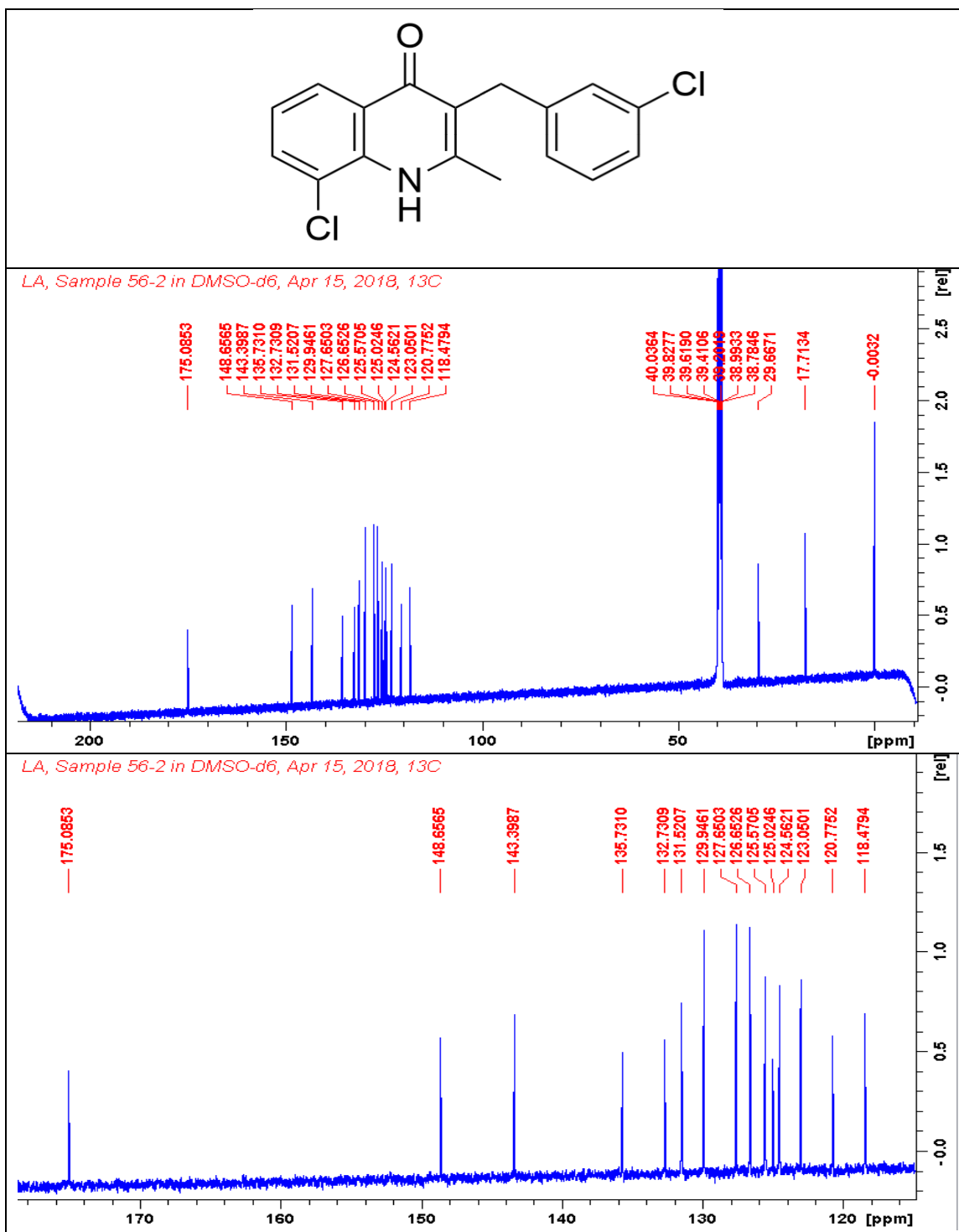
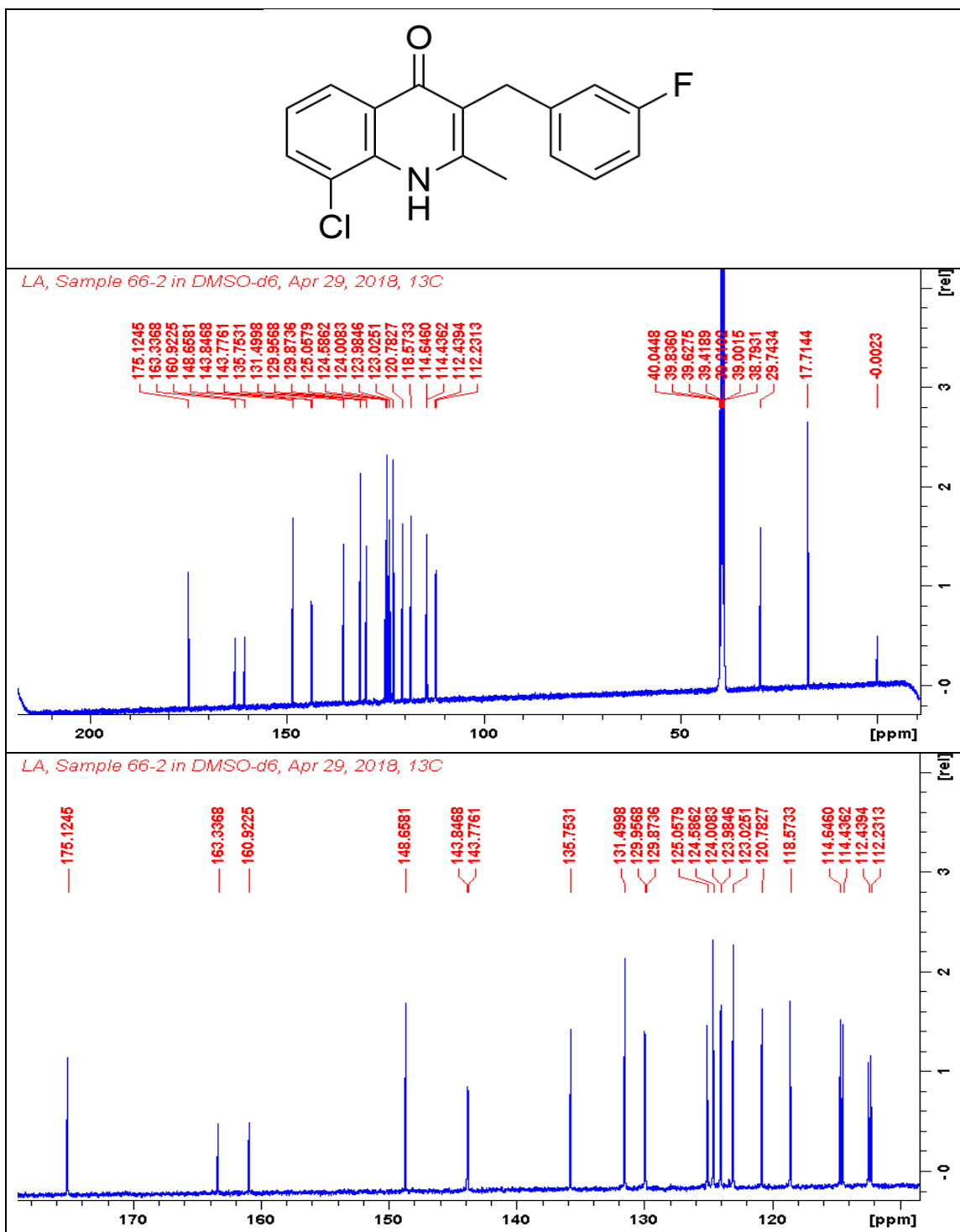


Table 37 ^{13}C NMR of 8-Chloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone



Appendix D – ^{19}F NMR Spectra

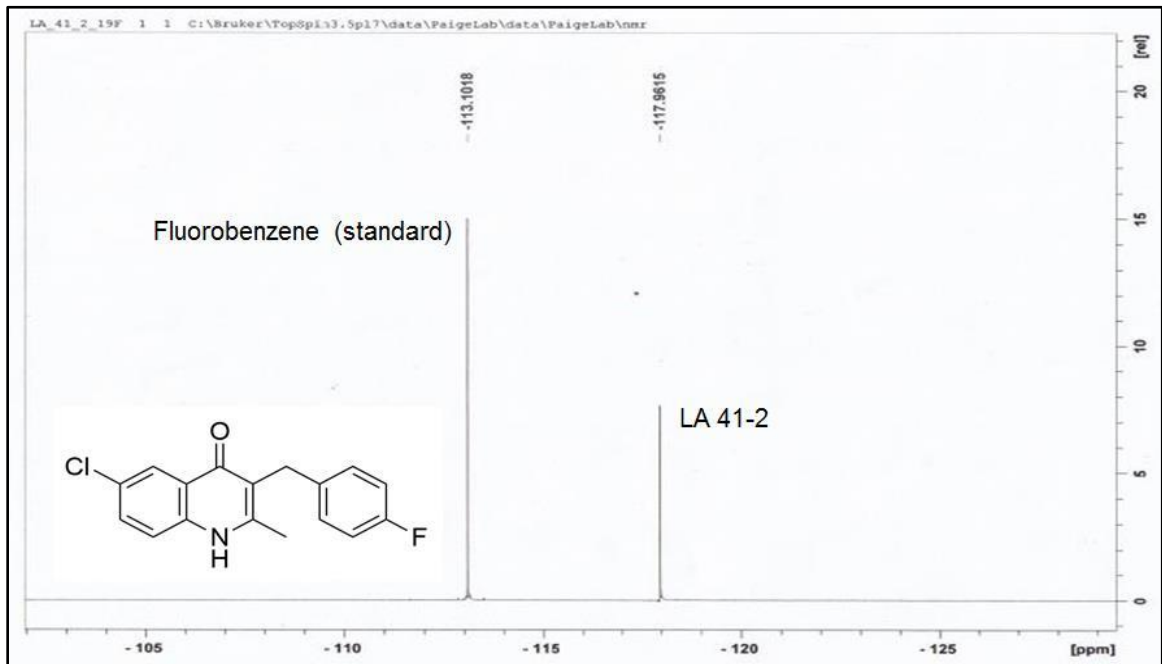


Figure 43 ^{19}F NMR of 6-Chloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

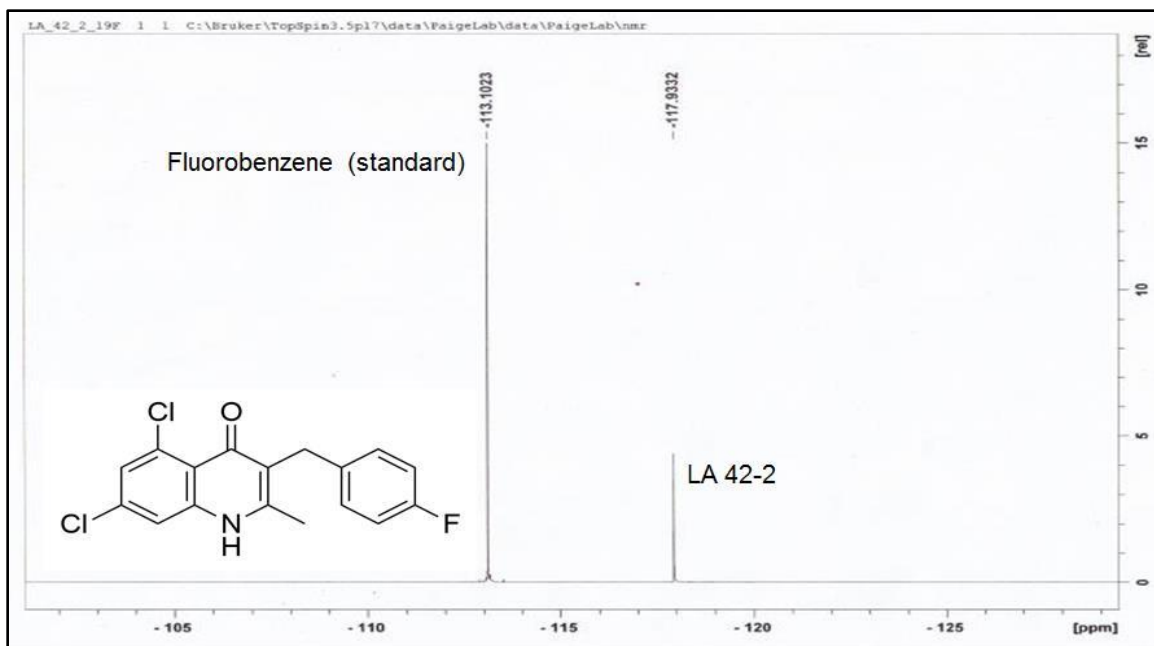


Figure 44 ^{19}F NMR of 5,7-Dichloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

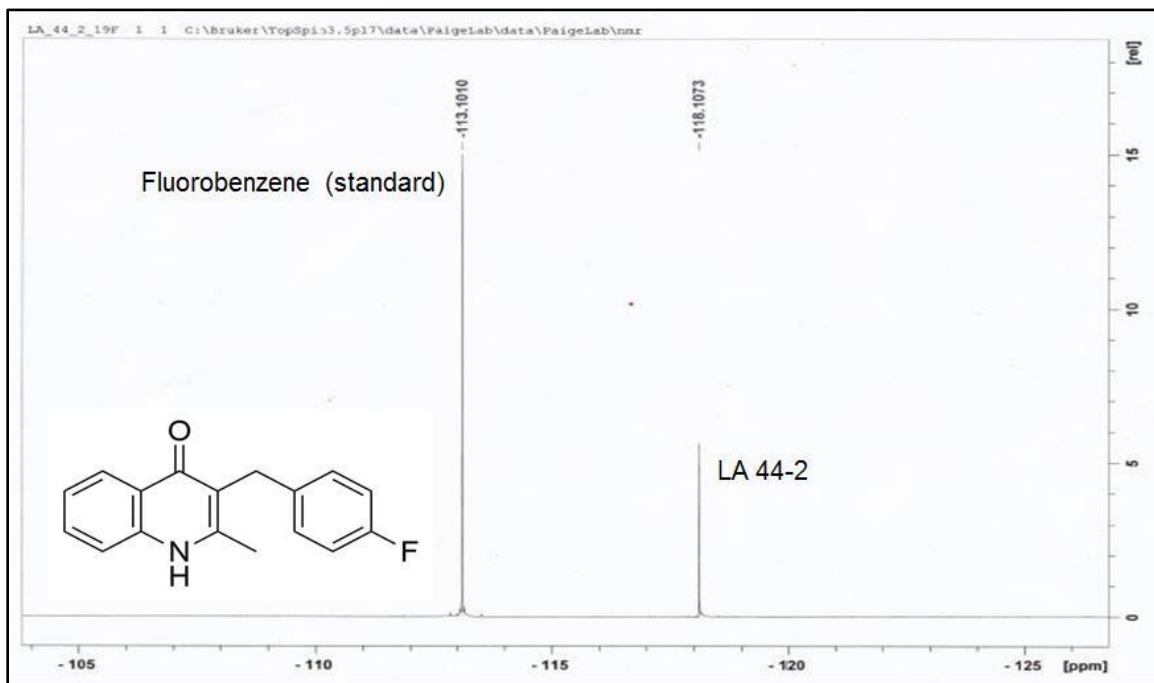


Figure 45 ^{19}F NMR of 3-(4-Fluorobenzyl)-2-methyl-4-quinolone

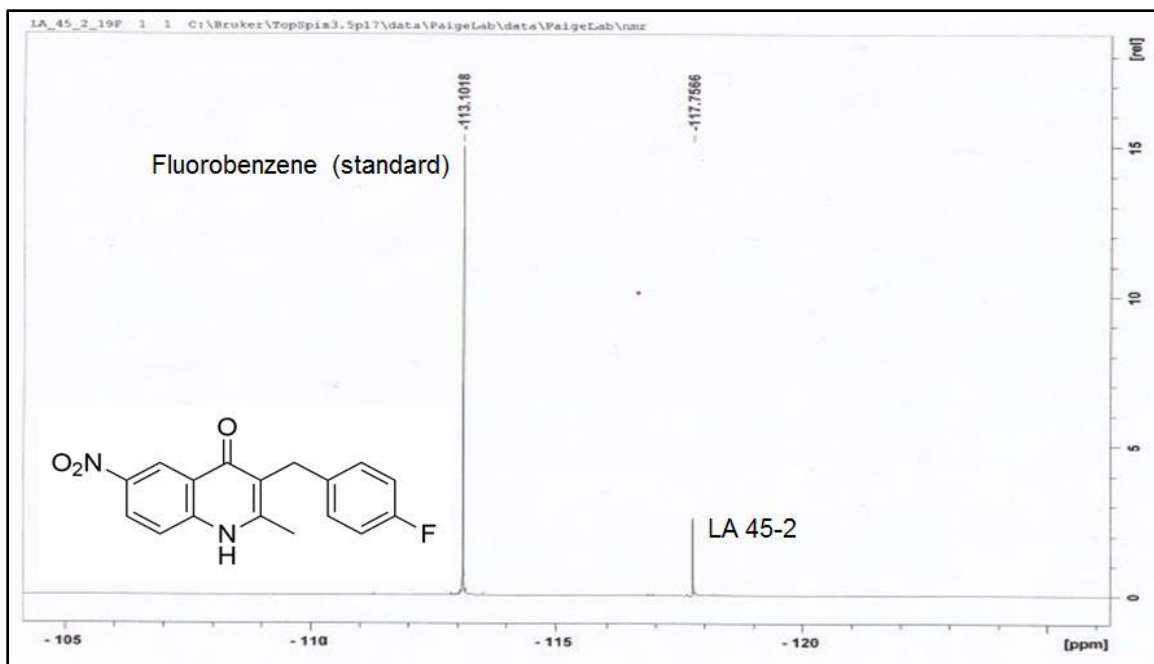


Figure 46 ^{19}F NMR of 3-(4-Fluorobenzyl)-2-methyl-6-nitro-4-quinolone

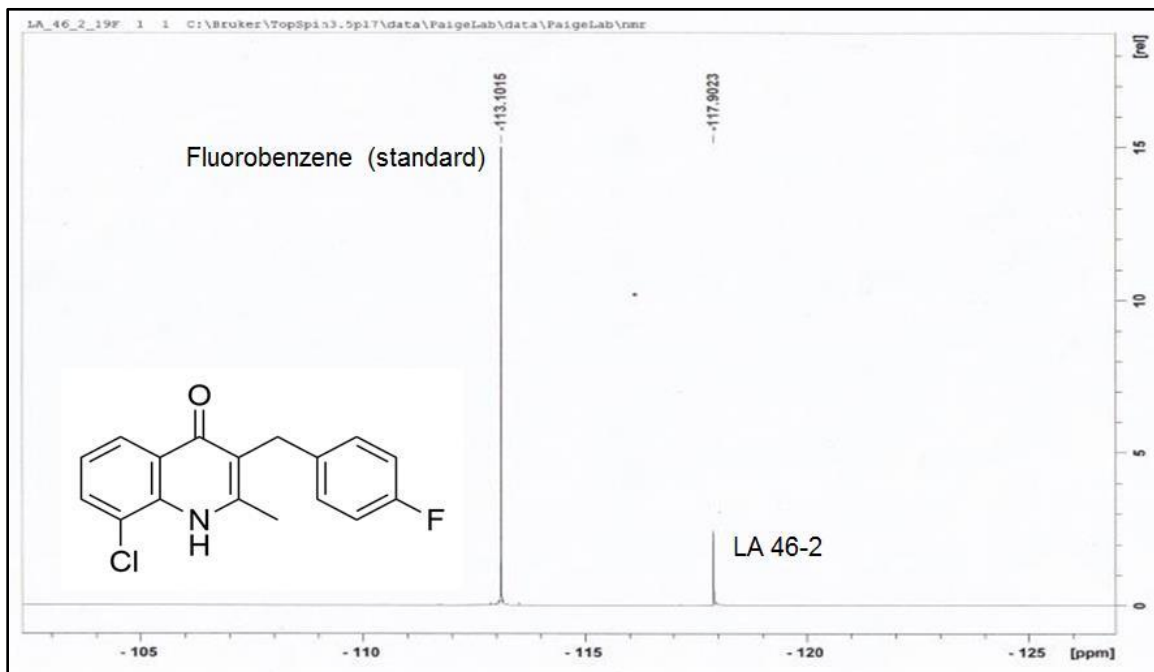


Figure 47 ^{19}F NMR of 8-Chloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

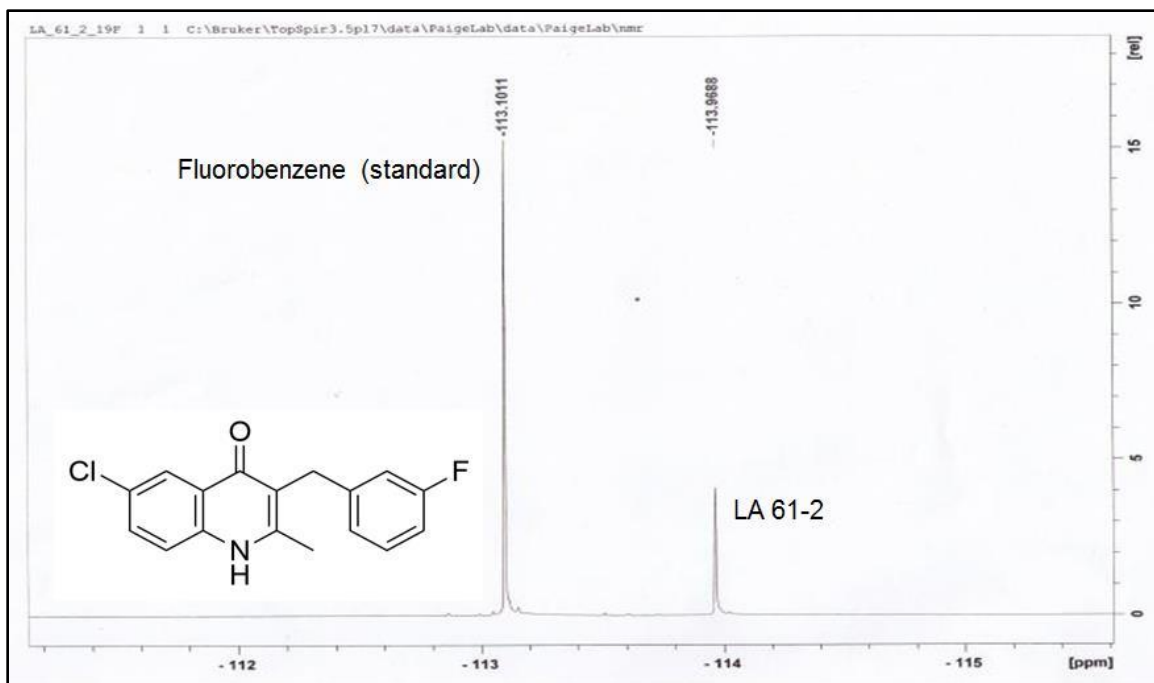


Figure 48 ^{19}F NMR of 6-Chloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

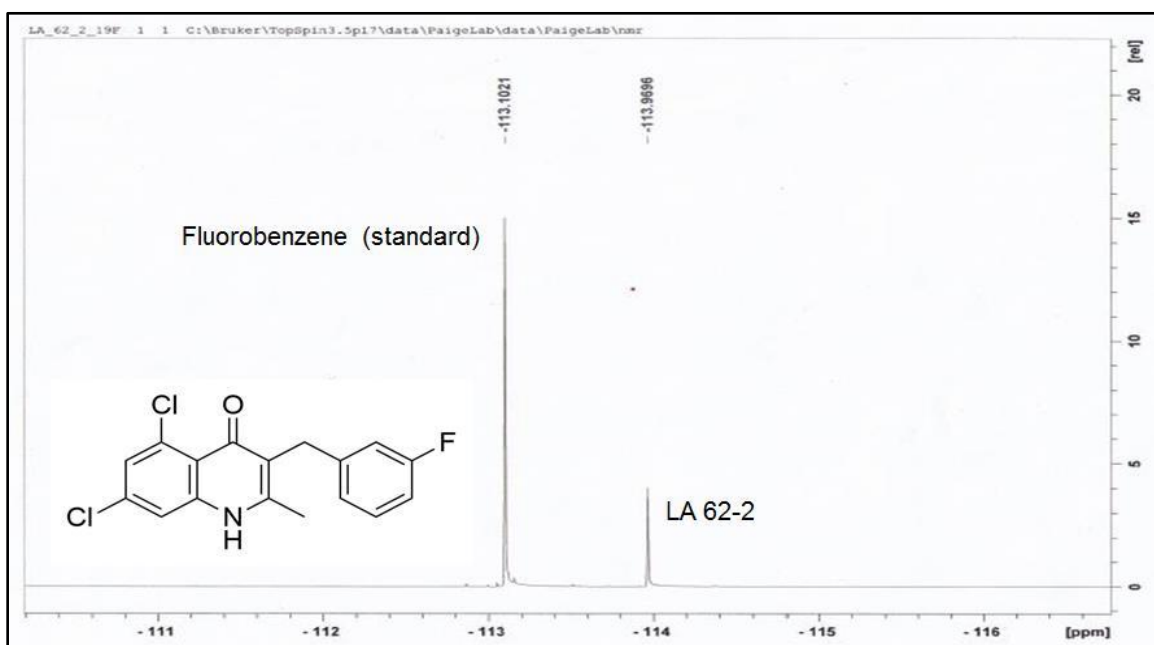


Figure 49 ^{19}F NMR of 5,7-Dichloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

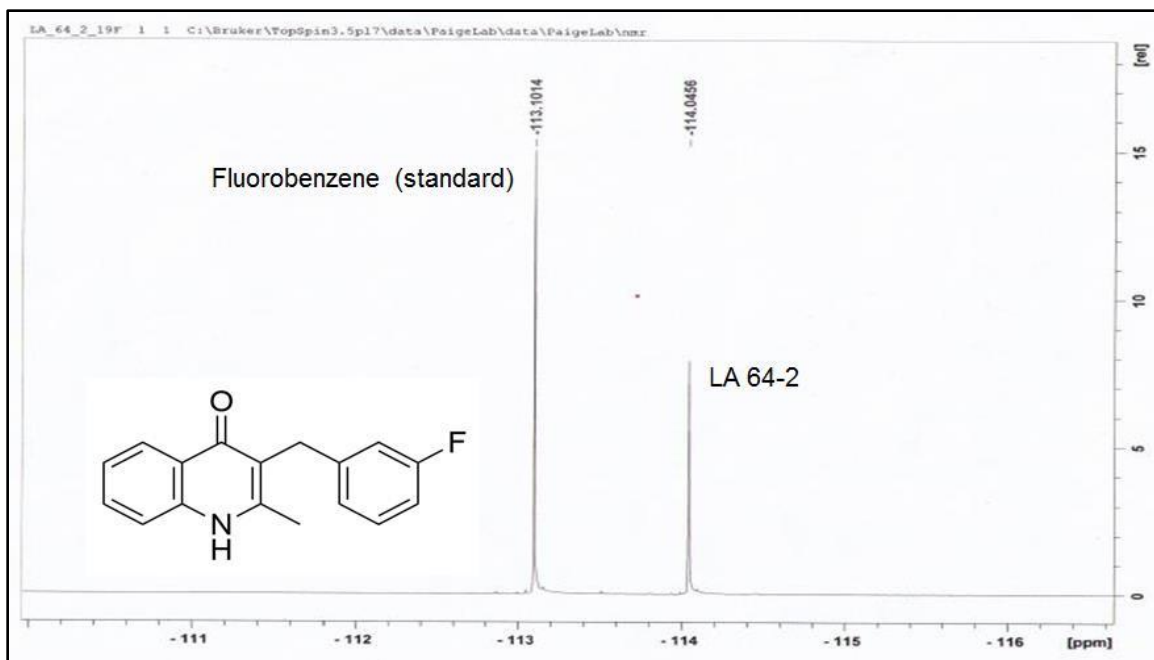


Figure 50 ^{19}F NMR of 3-(3-Fluorobenzyl)-2-methyl-4-quinolone

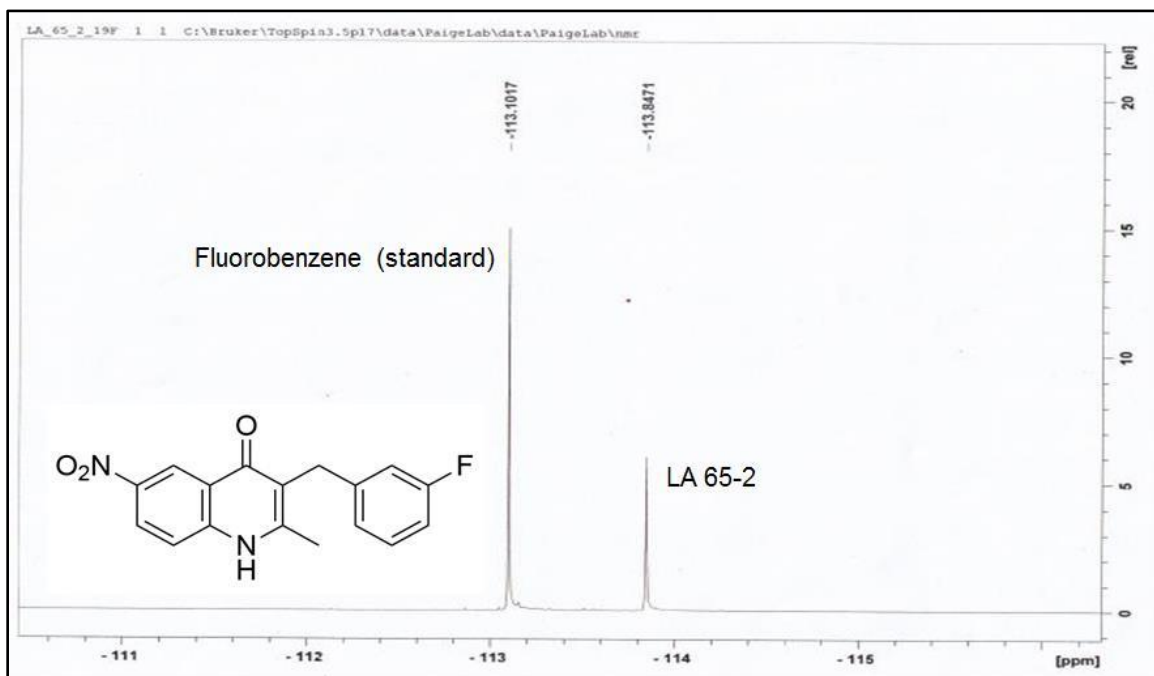


Figure 51 ^{19}F NMR of 3-(3-Fluorobenzyl)-2-methyl-6-nitro-4-quinolone

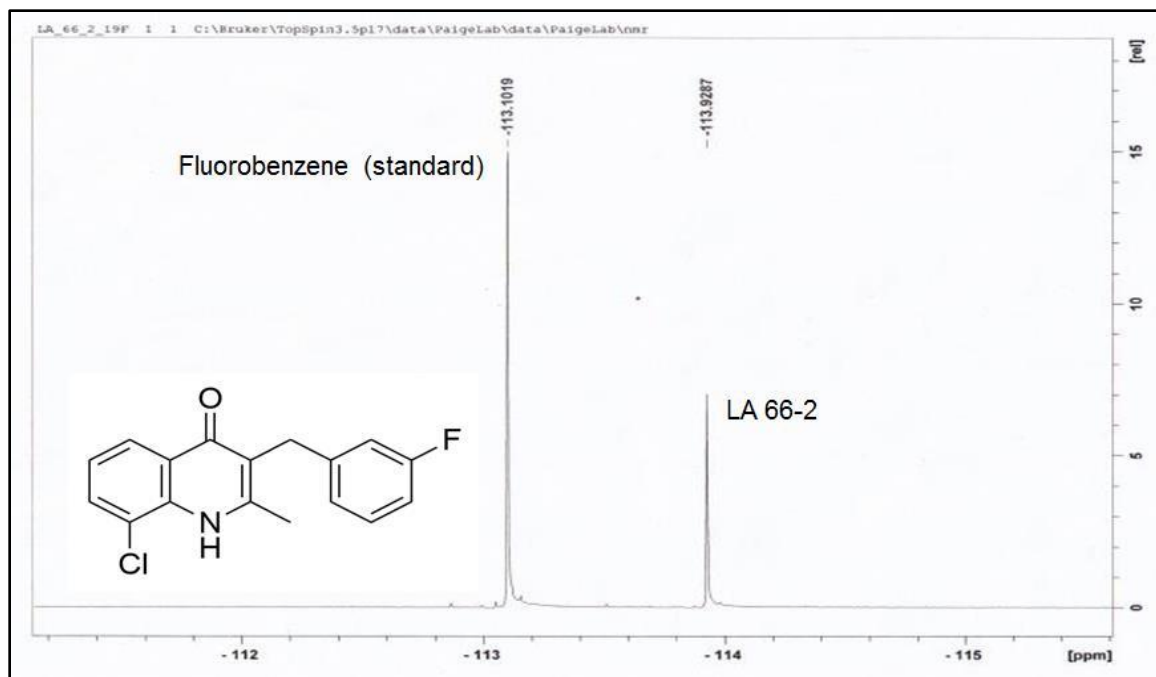


Figure 52 ^{19}F NMR of 8-Chloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

Appendix E – Infrared Spectra

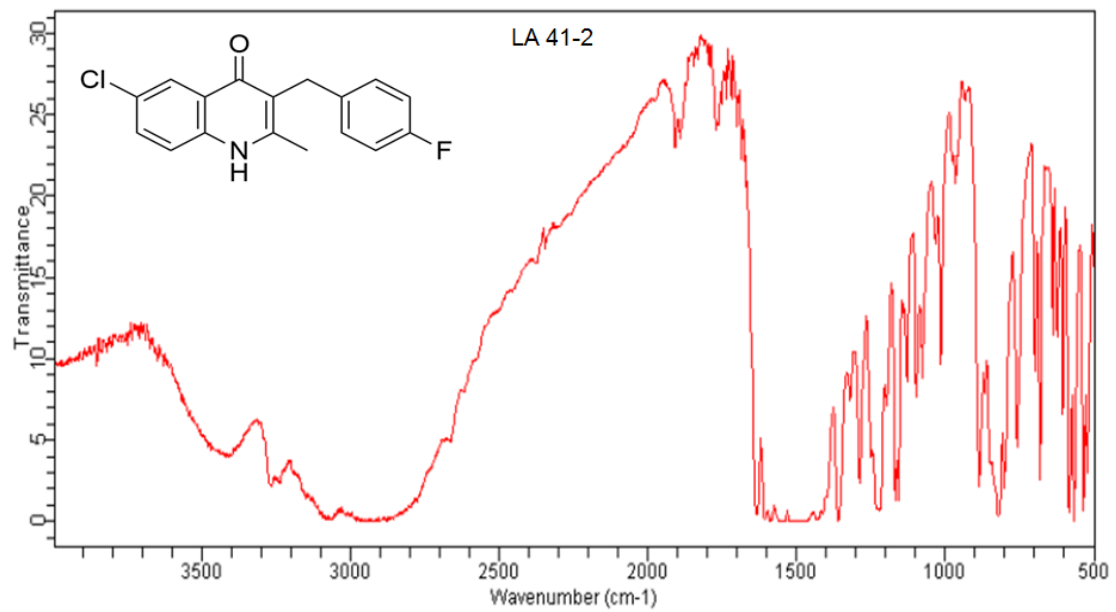


Figure 53 FTIR of 6-Chloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

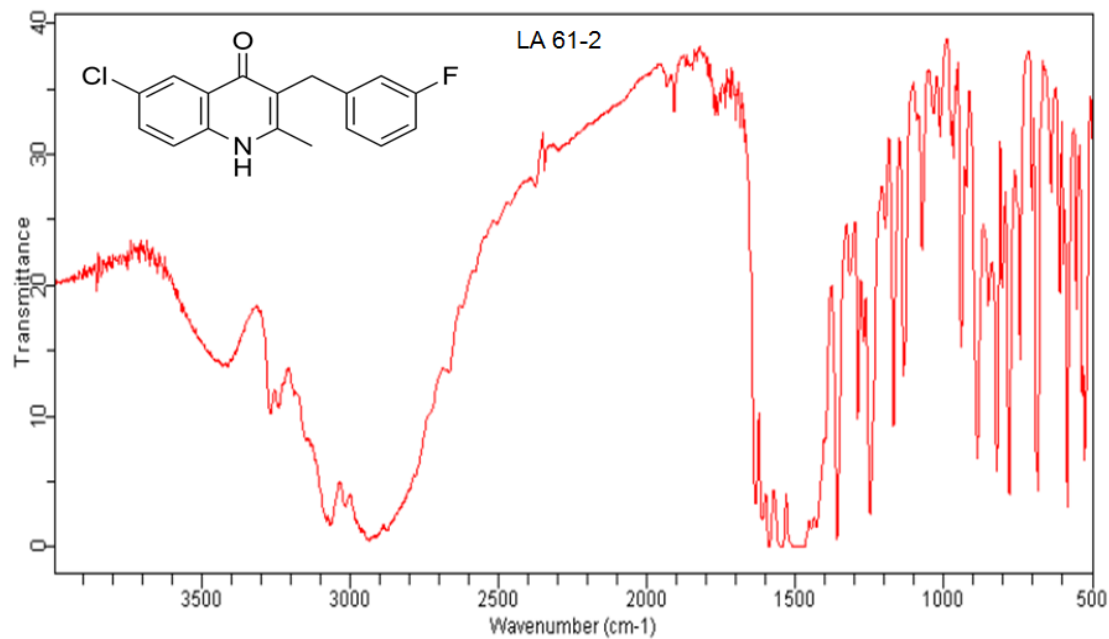


Figure 54 FTIR of 6-Chloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

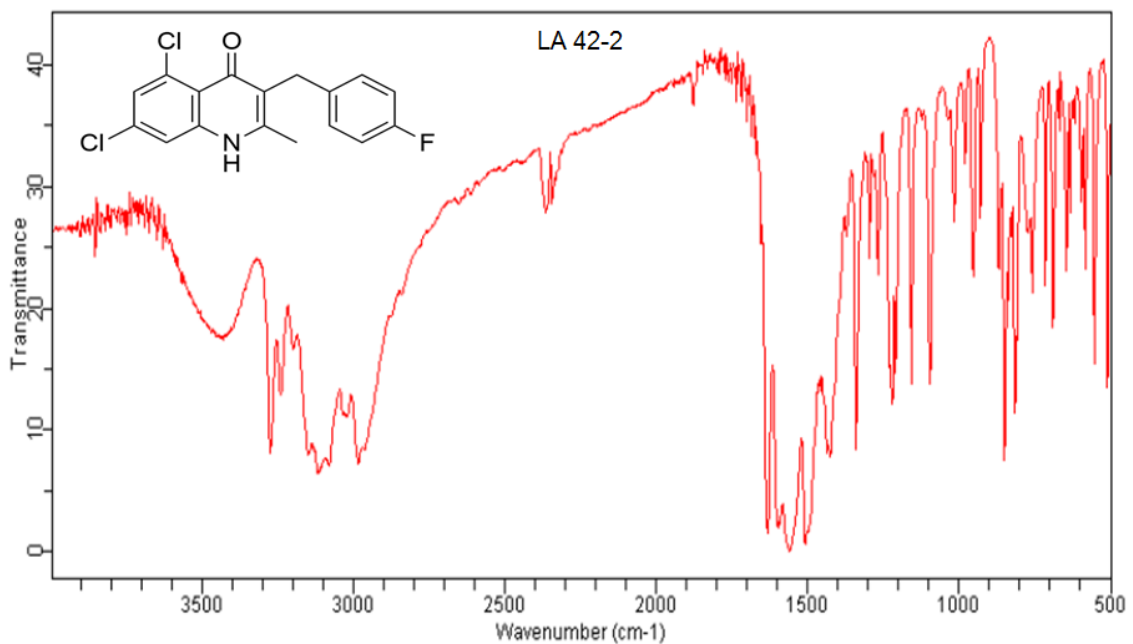


Figure 55 FTIR of 5,7-Dichloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

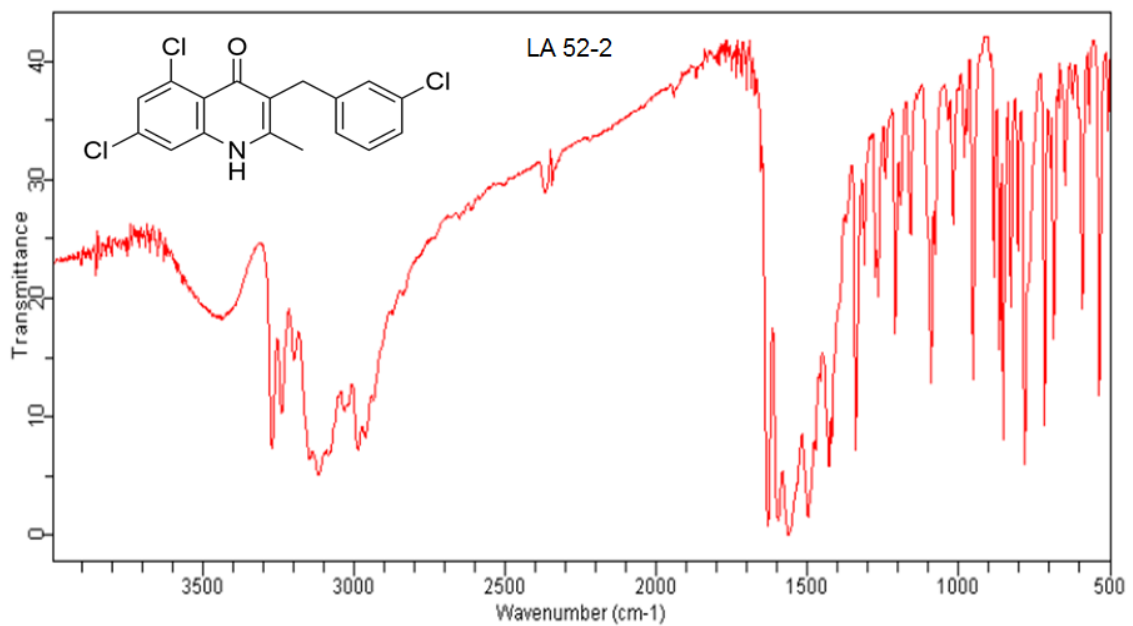


Figure 56 FTIR of 5,7-Dichloro-3-(3-chlorobenzyl)-2-methyl-4-quinolone

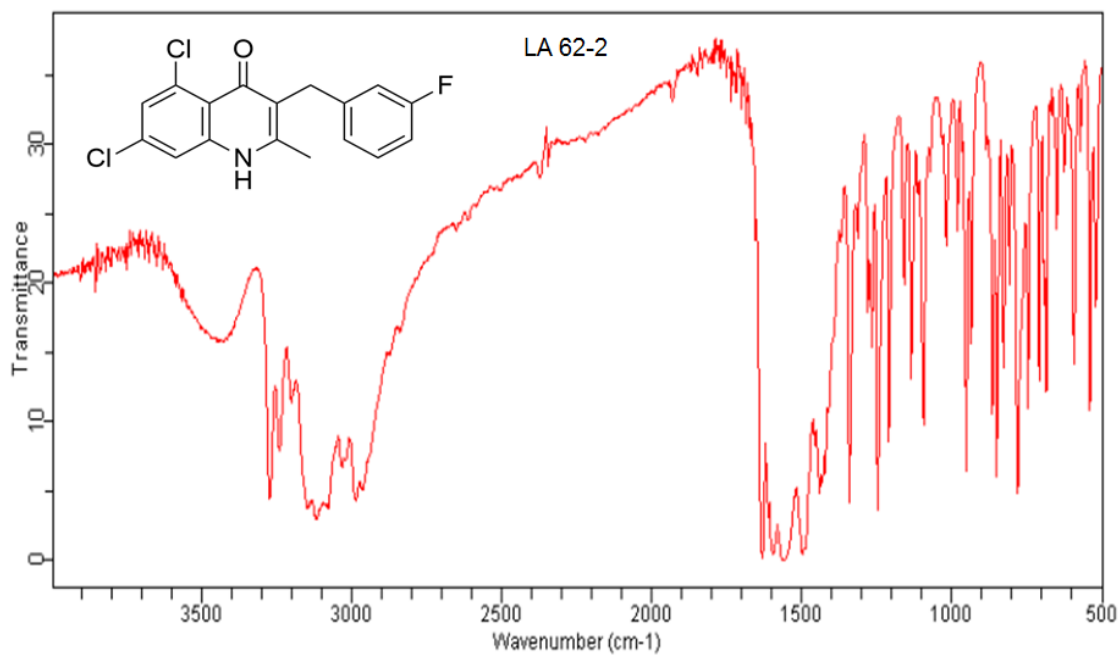


Figure 57 FTIR of 5,7-Dichloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

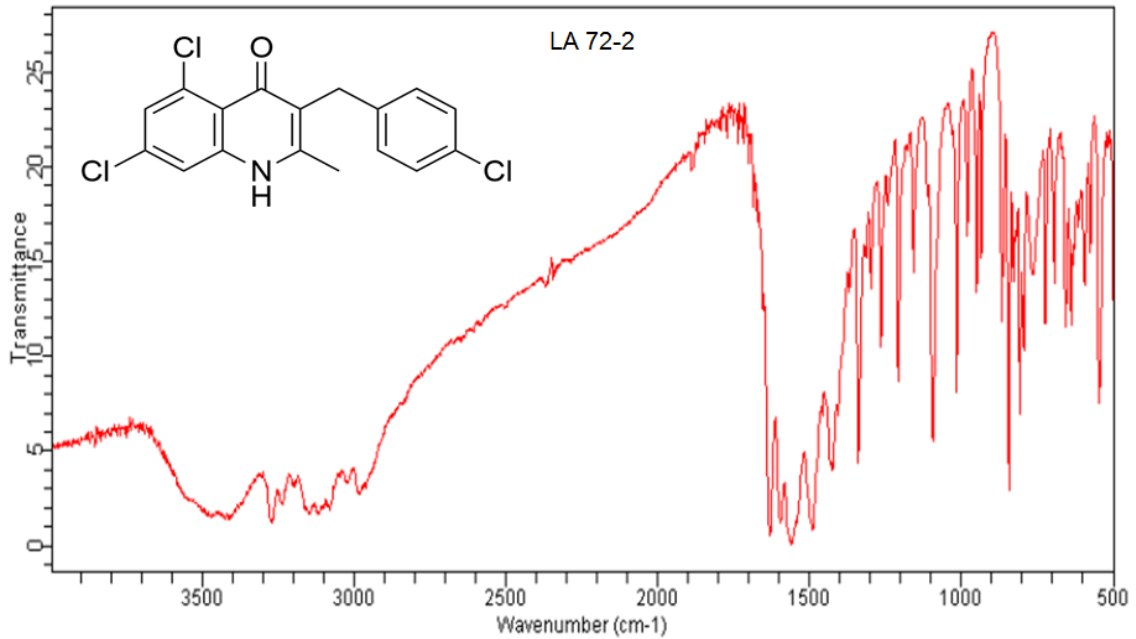


Figure 58 FTIR of 5,7-Dichloro-3-(4-chlorobenzyl)-2-methyl-4-quinolone

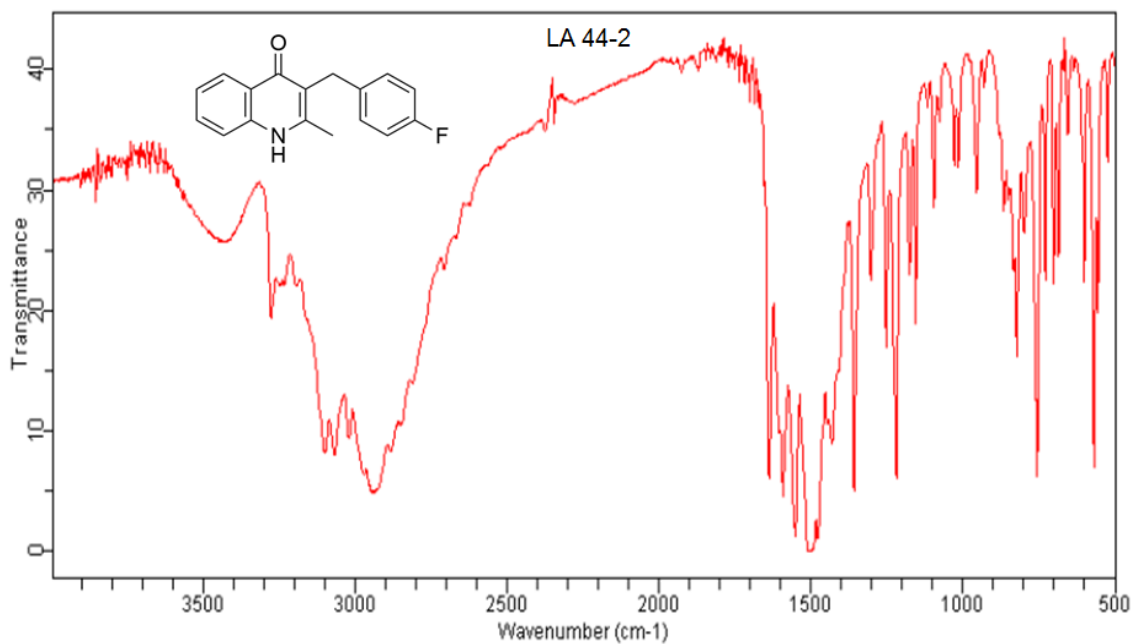


Figure 59 FTIR of 3-(4-Fluorobenzyl)-2-methyl-4-quinolone

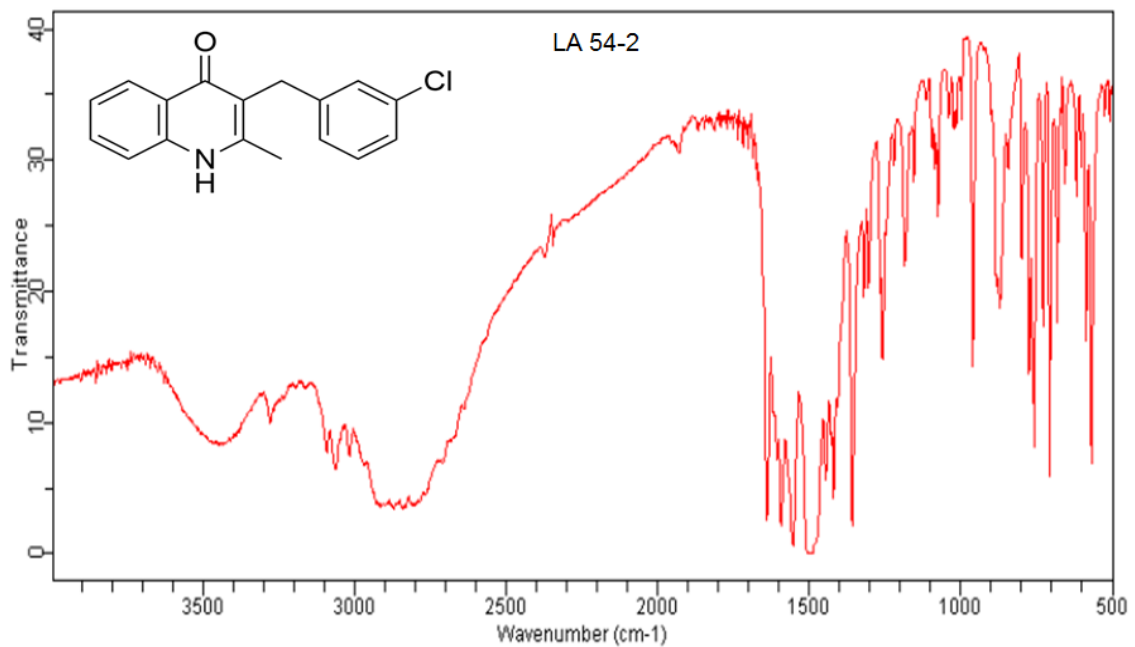


Figure 60 FTIR of 3-(3-Chlorobenzyl)-2-methyl-4-quinolone

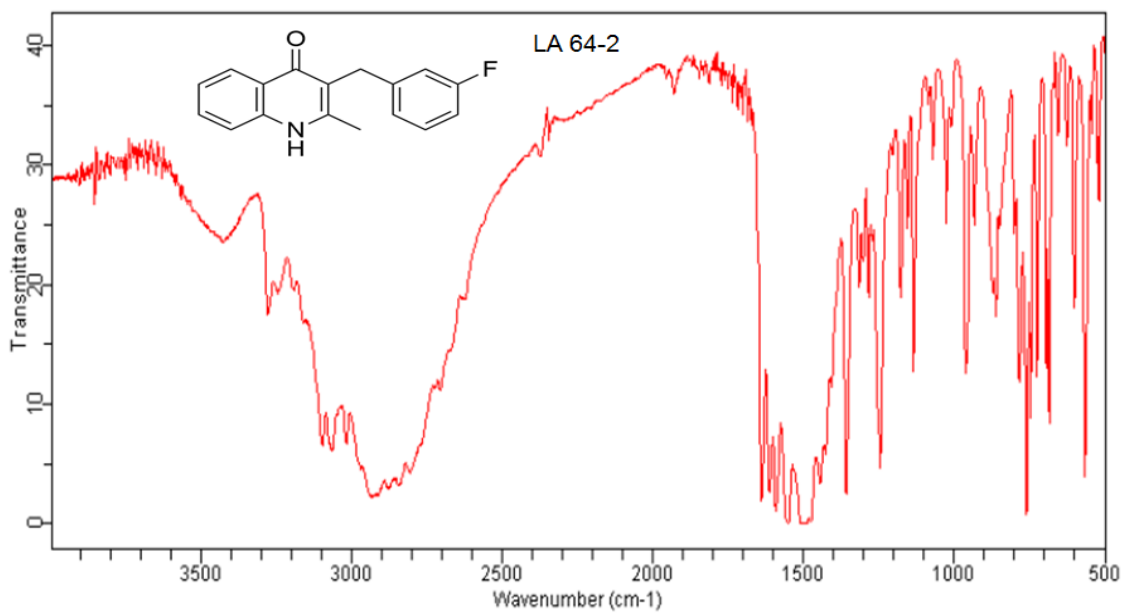


Figure 61 FTIR of 3-(3-Fluorobenzyl)-2-methyl-4-quinolone

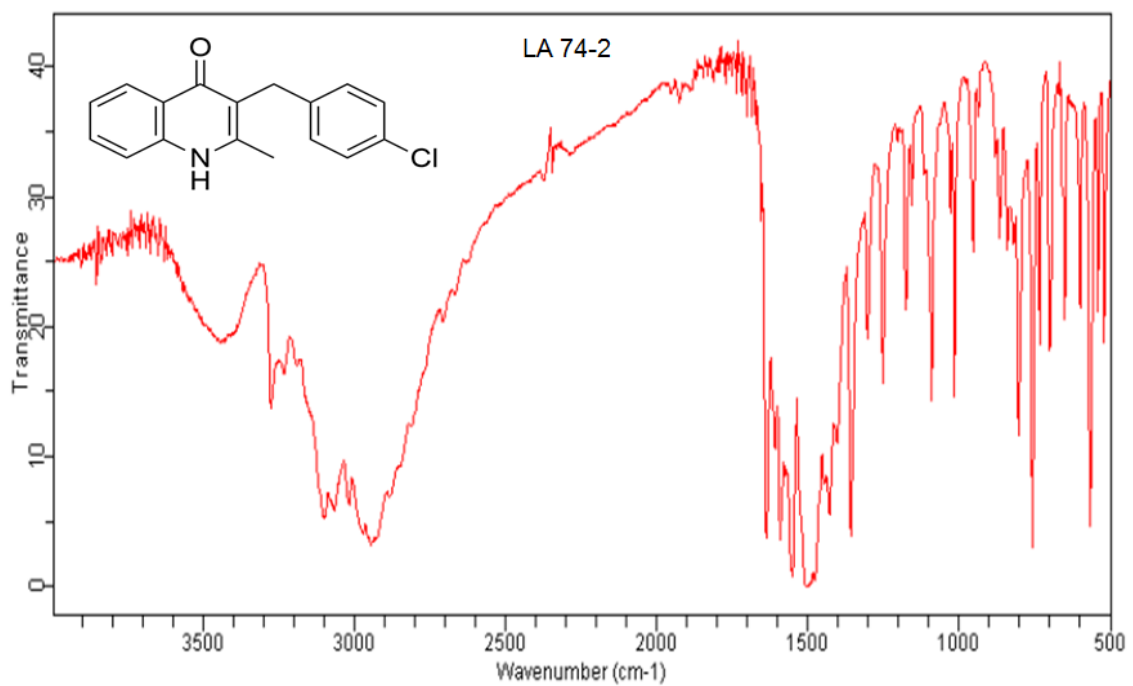


Figure 62 FTIR of 3-(4-Chlorobenzyl)-2-methyl-4-quinolone

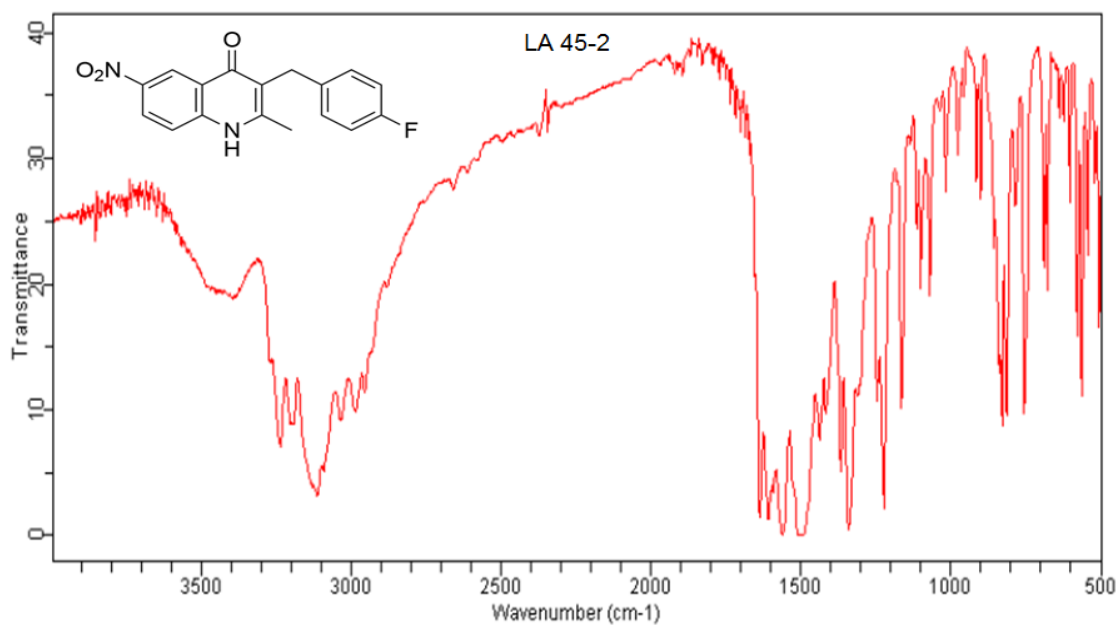


Figure 63 FTIR of 3-(4-Fluorobenzyl)-2-methyl-6-nitro-4-quinolone

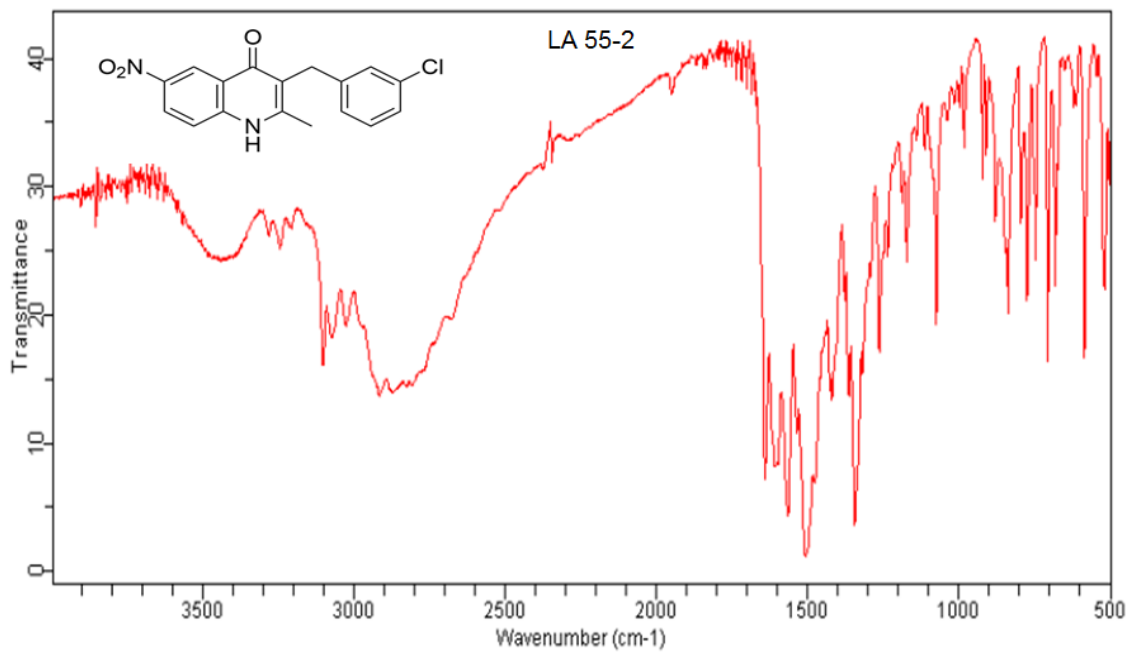


Figure 64 FTIR of 3-(3-Chlorobenzyl)-2-methyl-6-nitro-4-quinolone

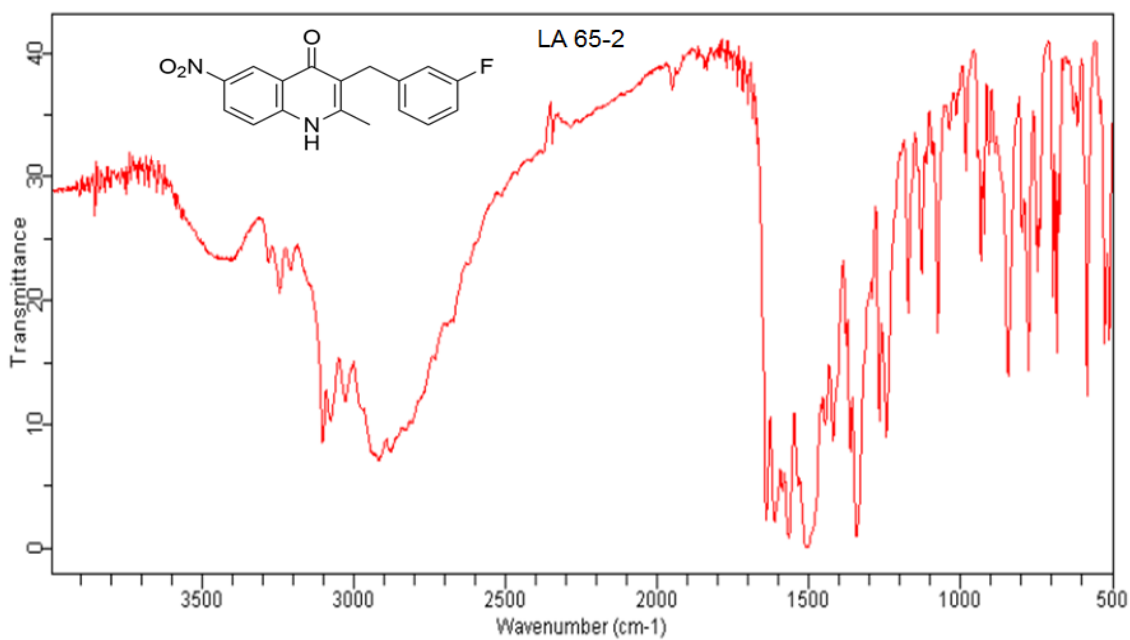


Figure 65 FTIR of 3-(3-Fluorobenzyl)-2-methyl-6-nitro-4-quinolone

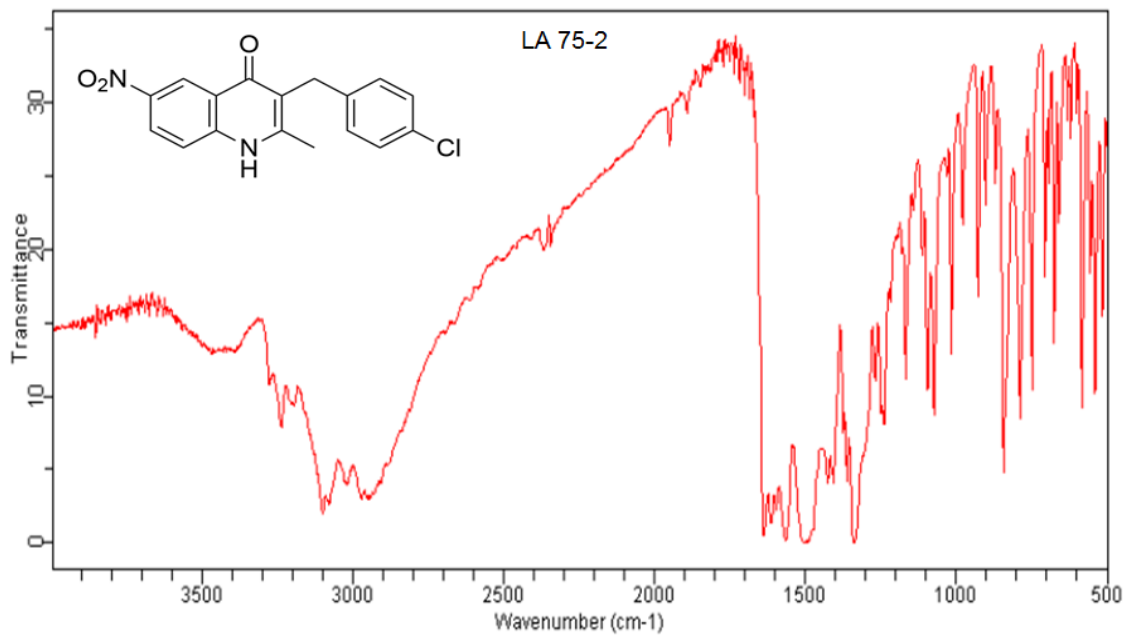


Figure 66 FTIR of 3-(4-Chlorobenzyl)-2-methyl-6-nitro-4-quinolone

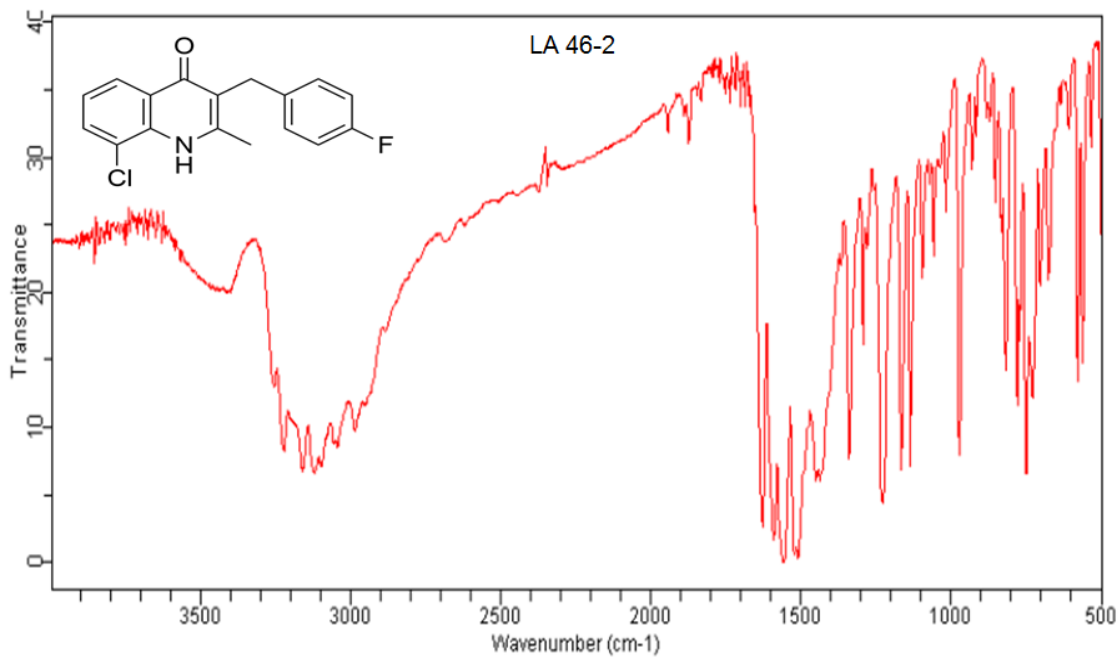


Figure 67 FTIR of 8-Chloro-3-(4-fluorobenzyl)-2-methyl-4-quinolone

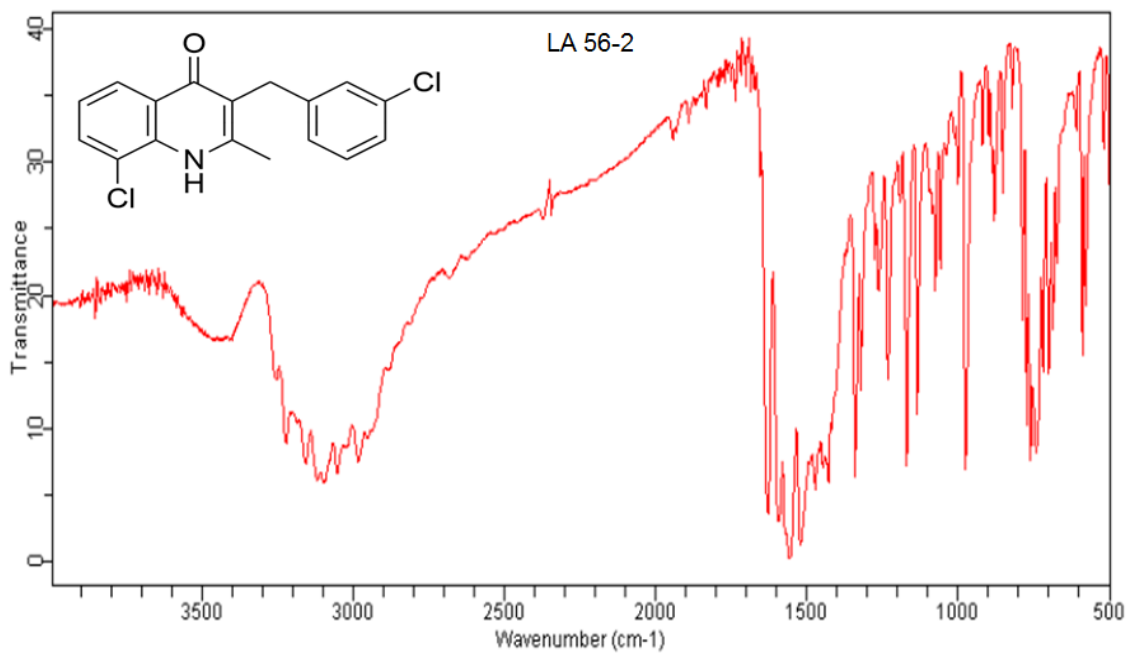


Figure 68 FTIR of 8-Chloro-3-(3-chlorobenzyl)-2-methyl-4-quinolone

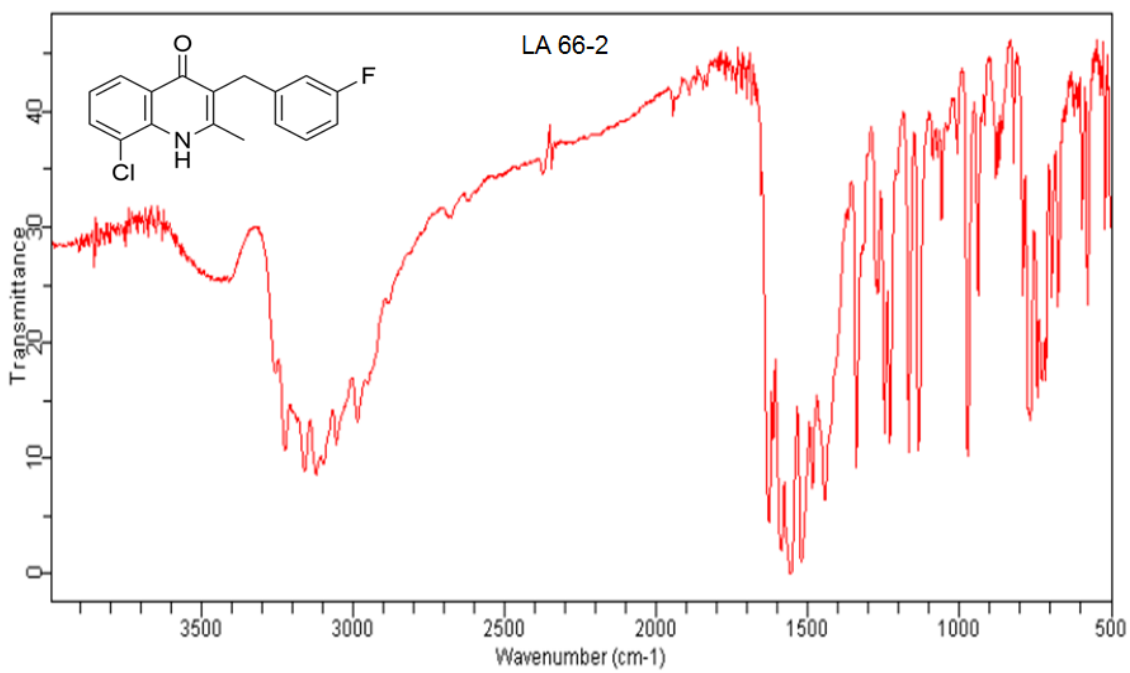


Figure 69 FTIR of 8-Chloro-3-(3-fluorobenzyl)-2-methyl-4-quinolone

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Biography

Lawrence Ammann received a Bachelor of Science degree from the University of Notre Dame in 1976, and a Master's degree in computer science from the University of Colorado in 1984. He worked for more than two decades as a computer programmer for several companies including IBM, Lockheed Martin, and Freescale Semiconductor, a chip manufacturing division of Motorola. His work for those firms included both commercial and defense tasks. He is married to a medical doctor and has lived in the Washington DC metro area for many years. He and his wife have two sons, each with an advanced degree.