DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF TRICYCLIC PYRONES AND THIOURIDINE NUCLEOSIDES

by

LAXMAN POKHREL
M. Sc., Tribhuvan University, Kathmandu, Nepal, 2001

AN ABSTRACT OF A DISSERTATION

submitted in partial fulfillment of the requirements for the degree

DOCTOR OF PHILOSOPHY

Department of Chemistry
College of Arts and Sciences

KANSAS STATE UNIVERSITY
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2013

Abstract

The first chapter in this thesis includes the design, synthesis, and evaluation of anti-Alzheimer and anti-norovirus activities of tricyclic pyrones (TPs). Alzheimer's disease is a major cause of dementia and sixth leading cause of death; it is a growing problem all over the world. On the other hand, norovirus, a highly contagious agent is responsible for more than 90% of non-bacterial gastroenteritis causing severity mainly in the closed environments. No drugs exist to eradicate the symptoms developed by both of these disorders.

Studies have shown that the development of Alzheimer's disease and the infection of norovirus are dependent on cholesterol metabolism. More specifically, the inhibition of acyl-CoA: cholesterol acyltrasferase (ACAT) led to the reduction of plaques in Alzheimer's disease as well as reduced the infection of norovirus. Mimicking the structure of CP2, a TP with promising anti-Alzheimer activities, a library of tricyclic pyrones containing phenyl, naphthyl, heterocyclic, and dipeptidyl moieties were synthesized and evaluated for their anti-Alzheimer and anti-norovirus efficacies. Several TPs containing phenyl and naphthyl groups showed sub-micromolar to nanomolar potencies for the protection of neuronal MC65 cells from Aβ-oligomers induced death. Similarly, the TPs containing pyrrolyl, imidazolyl, and quinolinyl moieties were effective to inhibit the norovirus replication in low micromolar range. The most effective TPs from MC65 cells protection assay were also effective in the inhibition ACAT and up-regulation ABCA1 gene.

The second chapter in this thesis includes the design, synthesis, and anti-norovirus activity of thiouridine nucleosides. Many nucleosides have demonstrated effective inhibition of viral RNA polymerase, and some are progressing at different level of clinical trials for the treatment of hepatitis C virus. Some of the nucleosides, including 2'-C-methyl and 2'-amino

substituted analogs, were found to effectively inhibit the norovirus replication. In the search of more potent anti-noroviral compounds, two thiouridine nucleosides were synthesized and evaluated as anti-norovirus agents. Both of these analogs were ineffective up to 50 μM for the inhibition of norovirus replication in cell based assay. Proposed work of converting these nucleosides to their phosphoramidate derivatives is also described.

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Approved by:

Major Professor
Dr. Duy H. Hua

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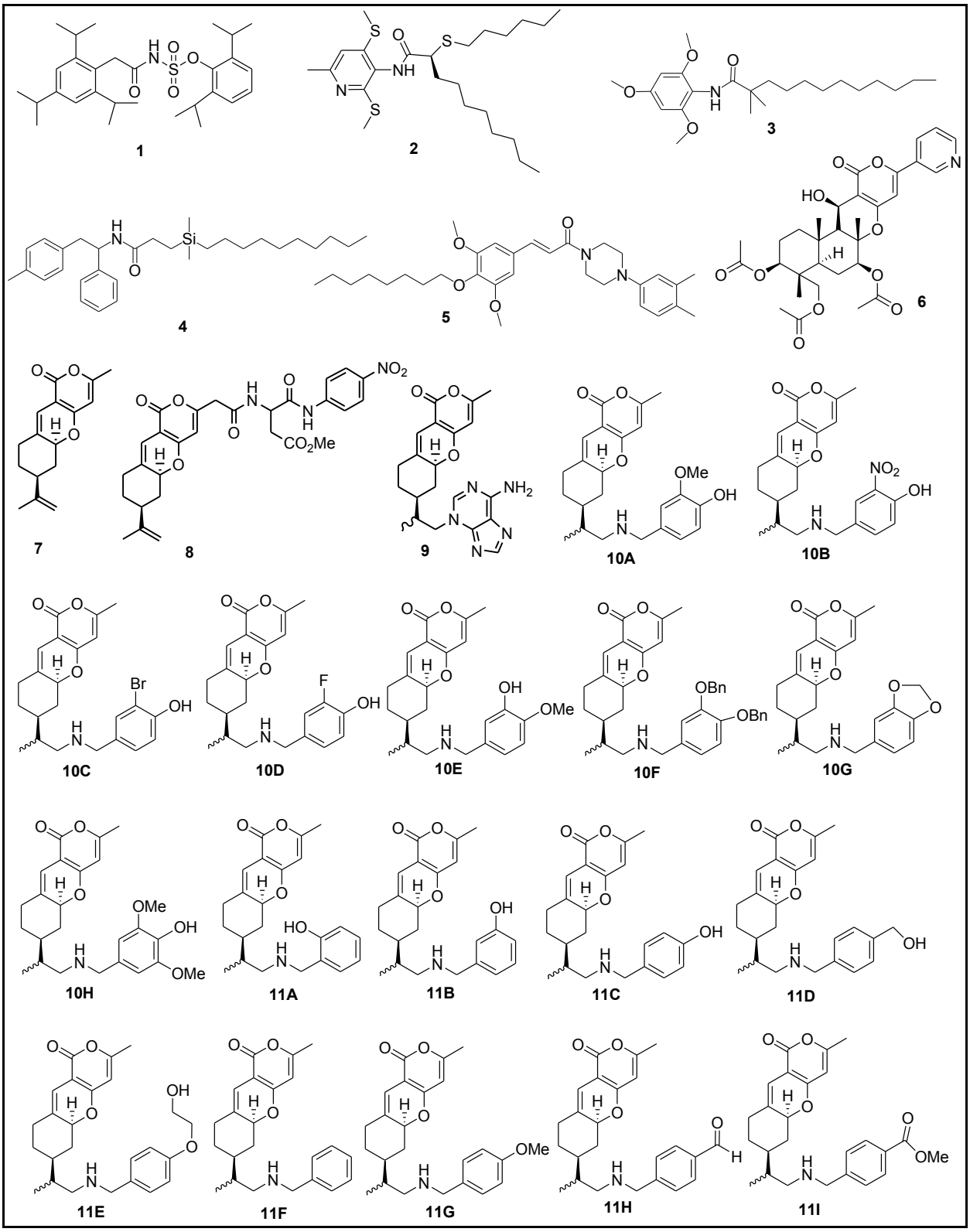

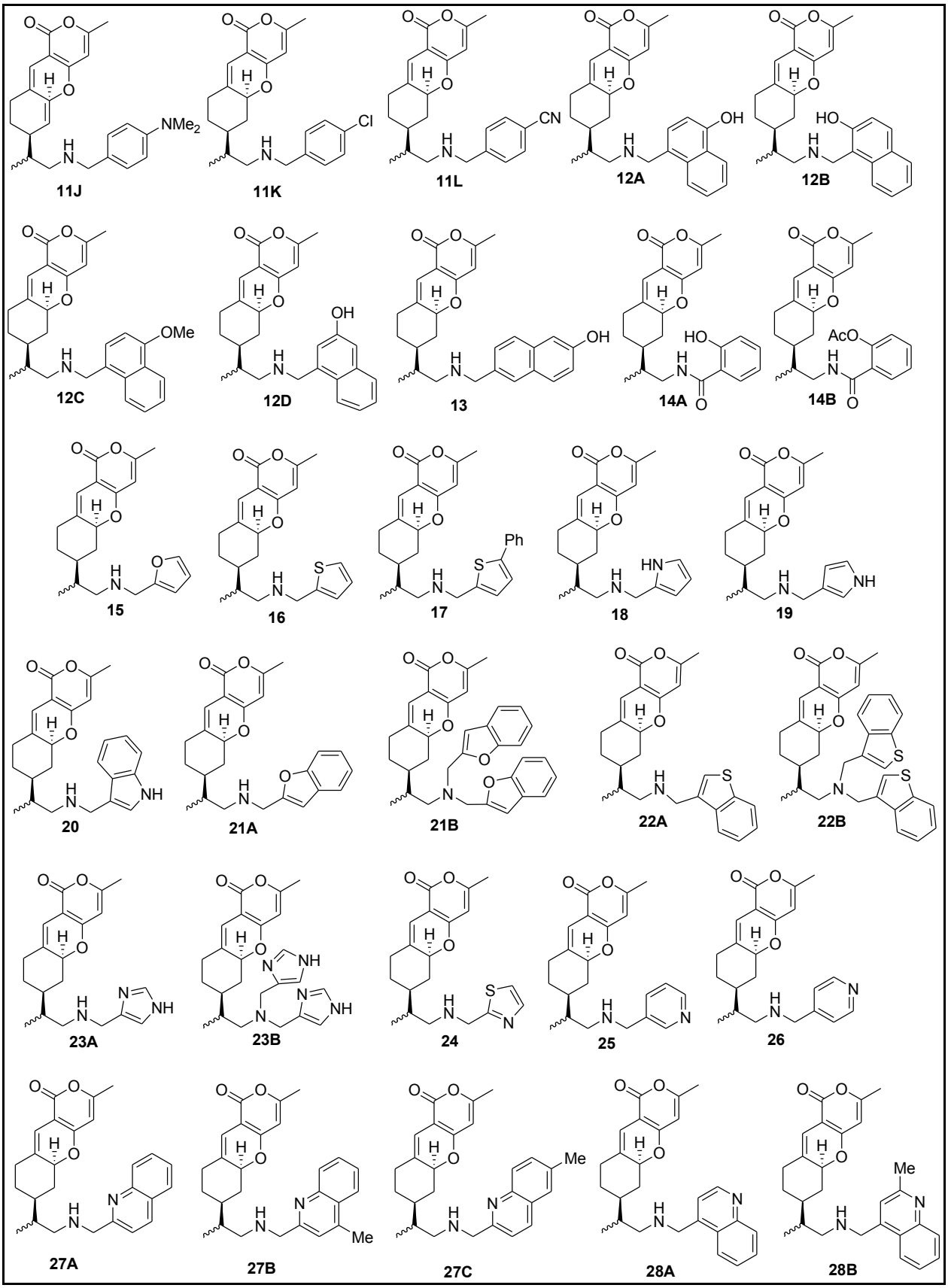
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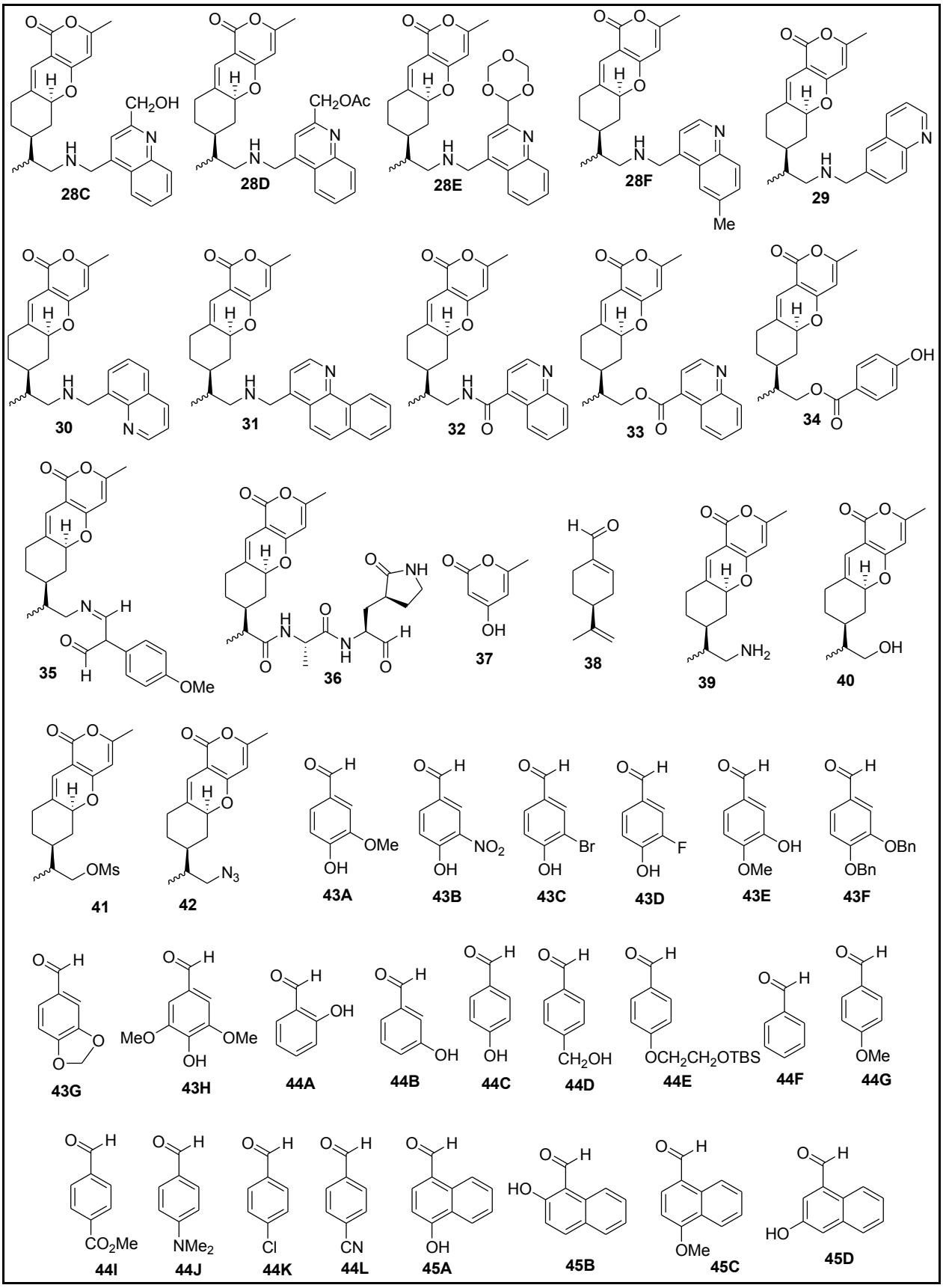
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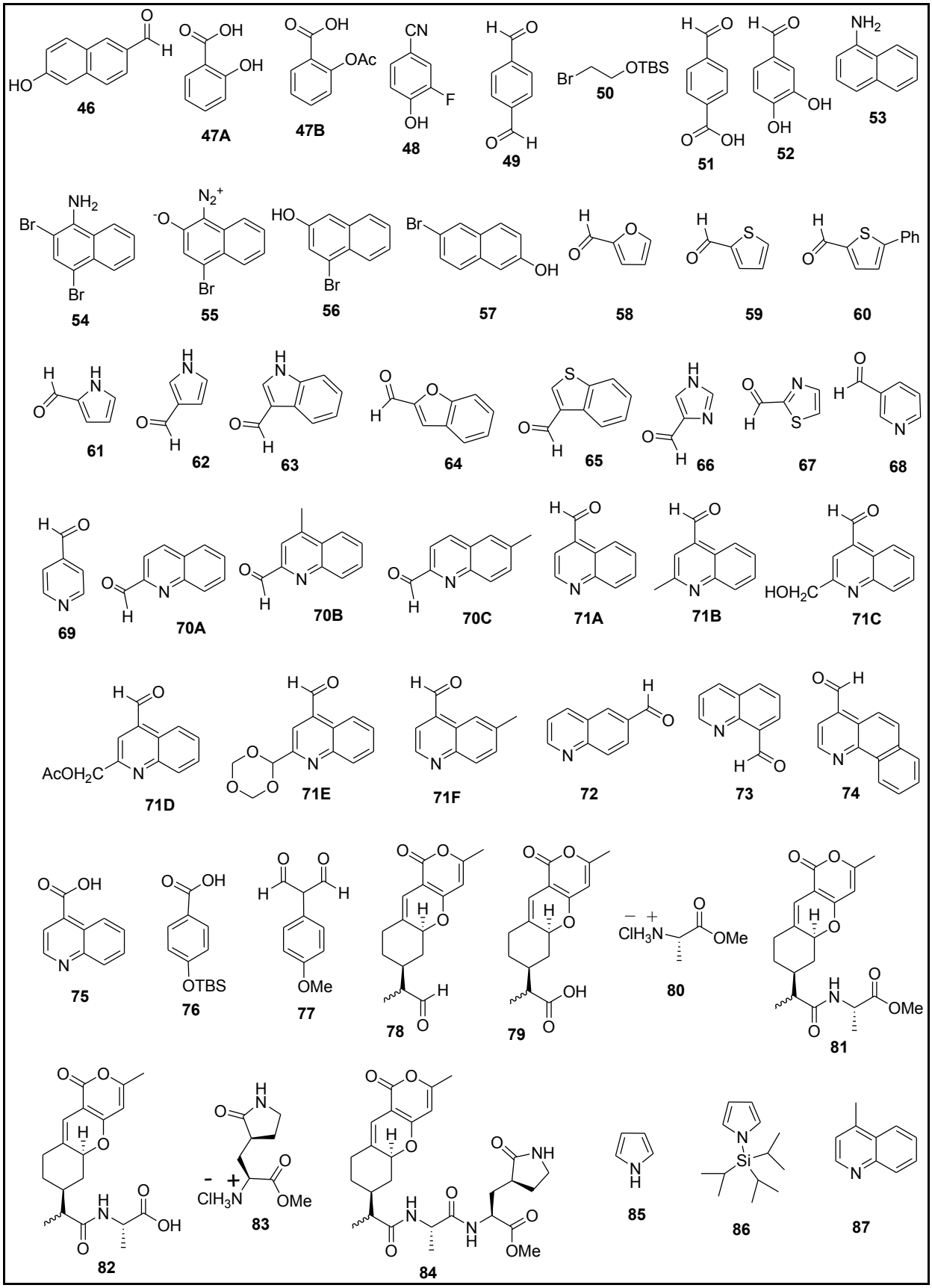
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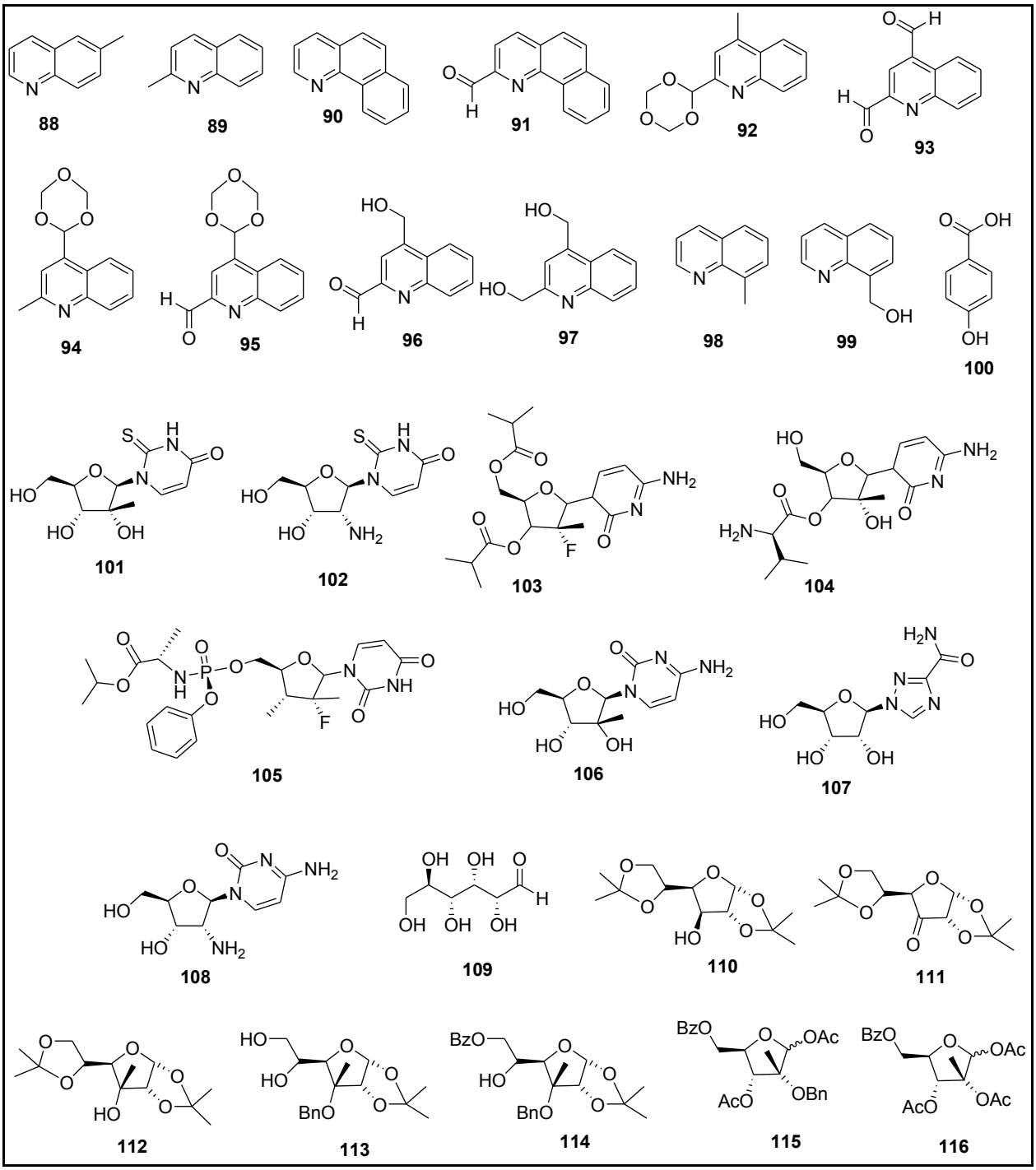
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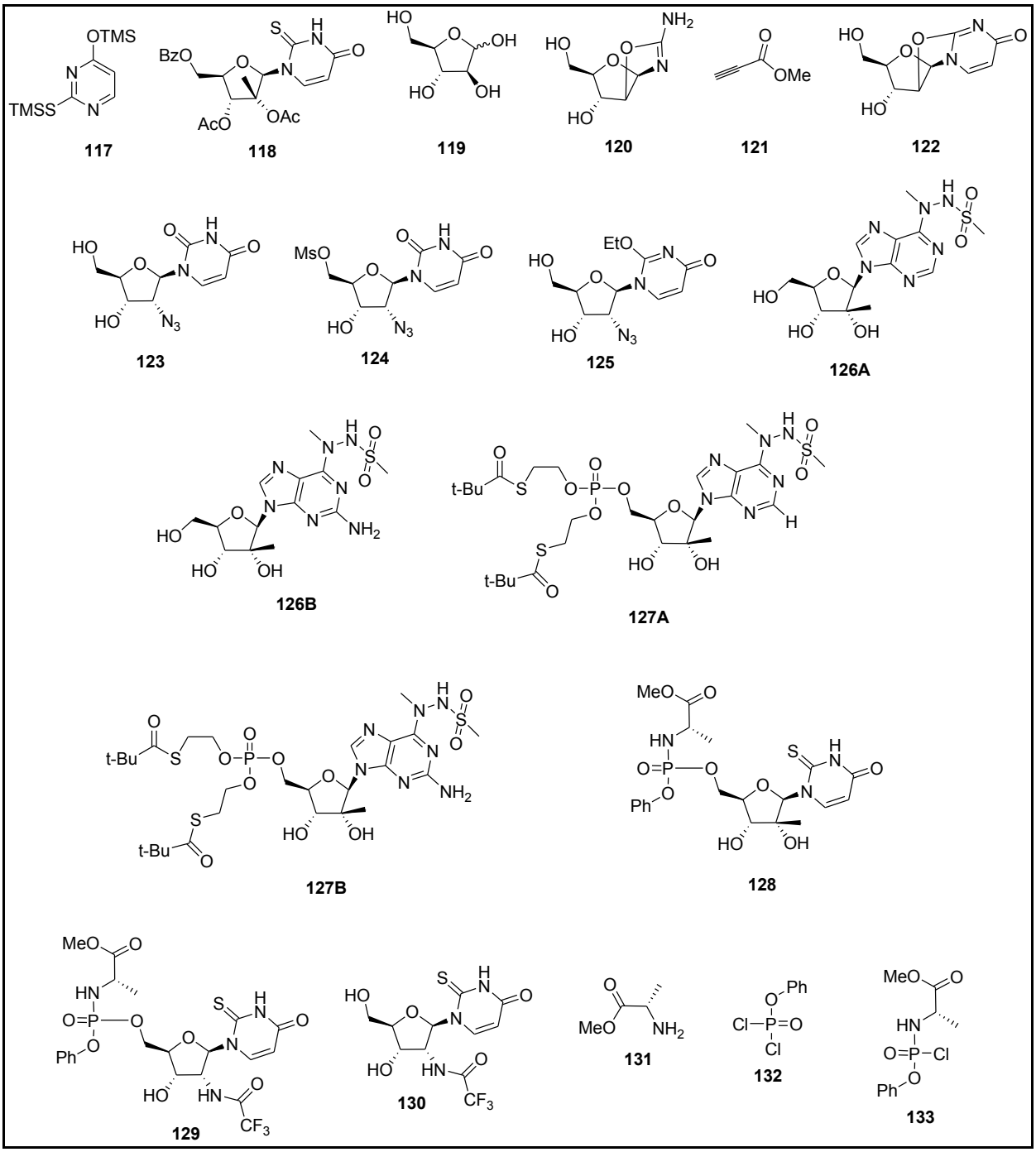
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List of Abbreviations

ABCA1	ATP-binding cassette, sub-family A, member 1
Aβ	Amyloid-beta
ACAT	Acyl-CoA: cholesterol acyltransferase
AD	Alzheimer's disease
Ac_2O	Acetic anhydride
AIBN	Azobisisobutyronitrile
APOE	Apolipoprotein E
APP	Amyloid precursor protein
CE	Cholesterol ester
^{13}C NMR	Carbon 13 nuclear magnetic resonance
DCM	Dichloromethane
DIEA	*N,N*-Di-isopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
EC_{50}	Median effective concentration
EDC	3-(3-dimethylaminopropyl)-1-ethylcarbodiimide
FT-IR	Fourier transform infrared spectroscopy
HCV	Hepatitis C virus
^{1}H NMR	Proton nuclear magnetic resonance
HRMS	High resolution mass spectrometry
HSA	Hydroxylamine-*O*-sulfonic acid
IBX	2-Iodoxybenzoic acid
LXR	Liver X receptor
M. I. N. D.	Medical Investigation of Neurodevelopmental Disorders
MS	Mass spectrometry
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

NBD-cholesterol	22-[*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino]-23,24-bisnor-5-cholen-3-ol
NBS	*N*-bromosuccinimide
NHS	*N*-hydroxysuccinimide
NIs	Nucleosides inhibitors
NNIs	Non-nucleosides inhibitors
NV	Norovirus
ORFs	Open reading frames
PDC	Pyridinium dichromate
Pd/C	Palladium on Carbon
qRT	Quantitative reverse transcription
RdRp	RNA dependent RNA polymerase
RNA	Ribonucleic acid
TBSCl	*t*-Butyldimethylsilyl chloride
TC	Tetracycline
TD_{50}	Median toxic concentration
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TI	Therapeutic index
TLC	Thin layer chromatography
TP	Tricyclic pyrone

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Dedication

To my parents Dilaram Pokhrel and Laxmi Pokhrel

Chapter 1 - Design, synthesis, and biological evaluation of tricyclic pyrones as anti-Alzheimer and anti-norovirus agents

1.1 Introduction

Alzheimer's disease (AD), a neurodegenerative disorder, is a major cause of dementia and sixth leading cause of death affecting around 30 million people all over the world.[1,2] Likewise, norovirus (NV) being a highly contagious agent is responsible for non-bacterial gastroenteritis outbreaks causing 21 million sicknesses, 70,000 hospitalizations and 800 deaths each year in the United States.[3] No drugs or vaccines are available for the treatment of either disorder. Continuous efforts of researches to develop drugs against these disorders are not yet successful.[3,4] Like other cholesterol related disorders,[5,6,7] the beginning and progress of Alzheimer's disease and the replication of norovirus were found to be dependent on the level and distribution of host cholesterol.[8,9] Therefore, the modulation of cholesterol at different stages of its metabolic pathway provides a wide spectrum of targets for the treatment of both disorders. A set of tricyclic pyrones synthesized as acyl-CoA: cholesterol acyltransferase (ACAT) inhibitors in Dr. Hua's lab had shown promising anti-Alzheimer activities.[10] In the search of stronger ACAT inhibitors, several TPs containing phenyl, naphthyl, heterocyclic, and dipeptidyl at C13 position were synthesized and evaluated for their anti-Alzheimer and anti-norovirus activities.

1.2 Background

1.2.1 Alzheimer's disease and its connection with lipid metabolism

Alzheimer's disease (AD) is characterized by cognitive and neuronlogical degradation.[4] The symptoms of AD starts with anatomical change in the parts of brain, unnoticed outwardly until the disease progresses enough to affect the behavior.[11] It may take 10 to 20 years to affect

the physical and mental health of the patients, severely.[11] Cognitive degradation starts with difficulty to remember newly learned things and widens with problems of planning, performing usual work, understanding spatial relations, confusions, change in mood, and personality degradation.[12] Anatomically, extracellular amyloid-β (Aβ) plaques and intracellular hyperphosphorylated tau (**Figure 1.1**) identify the brain of AD patients; both of these hamper communication and flow of nutrients among the neuronal cells leading to their death.[4] The plaques are formed due to over activity of β secretase (**Figure 1.2**) generating Aβ oligomers from amyloid precursor protein (APP).[4] Aβ plaques are made up of amyloid-β 42, amyloid-β 40, astrocytes, microglia, and dystrophic neurides,[13] while the neurofibrilly tangles mainly contained hyper-phosphorylated tau protein.[14] Formation of tangles, including other downstream symptoms, was reported to be the aftermath from the generation of Aβ plaques.[15,16] With the progression of disease, the mental and physical power continuously degrades ultimately leading to the death of AD patients, mainly due to other infections and/or low immunity.[12]

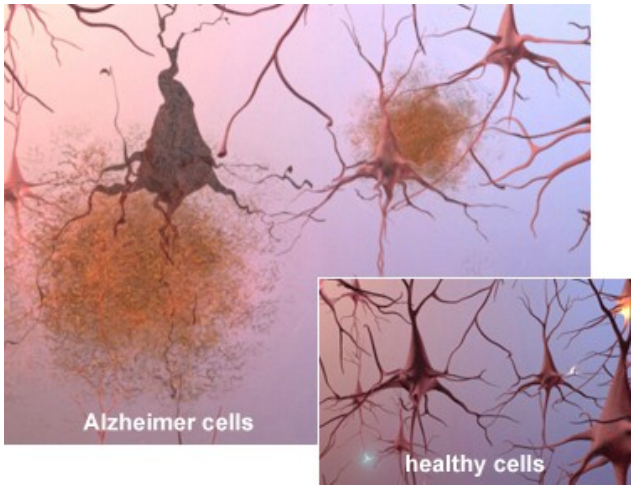

Figure 1.1: Tangles and plaques in Alzheimer affected neurons.
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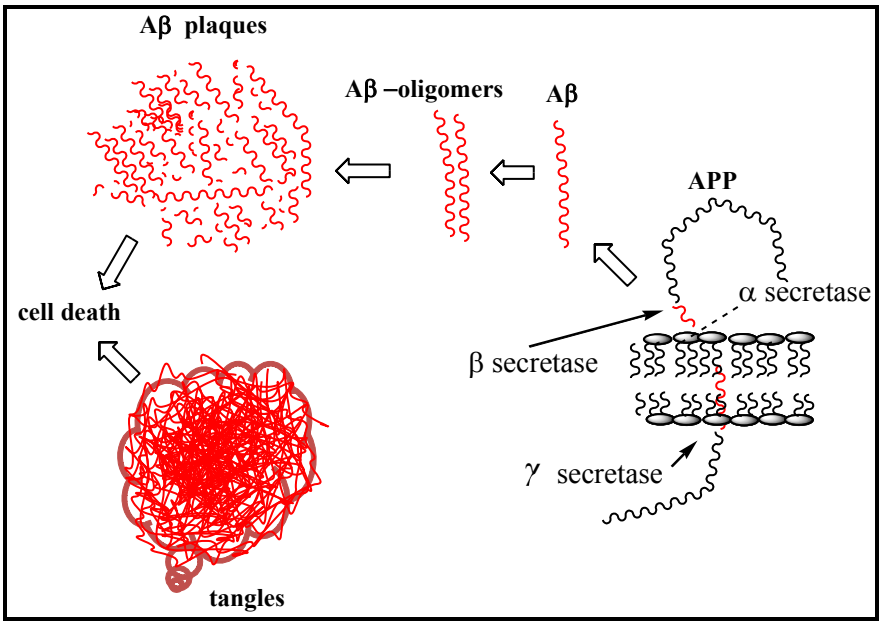

Figure 1.2: Abnormal β-secretase pathway of amyloid precursor protein (APP).
Modified from ref 4

The increasing abundance of AD compared to other disorders (**Figure 1.3**) not only requires more attention to it, but also indicates challenges associated with the treatments.[11] Medications used for Alzheimer's disease only provide temporary comfort dealing with individual symptoms like memory loss, sleep problem, but do not modify the disease.[11]

The mechanism of Alzheimer's disease is yet to be known; however, its development has been reported to be multi-factorial (**Figure 1.4**).[4] In less than 1% of AD patients, the presence of any forms of mutated genes for amyloid precursor protein (APP) or presenilin 1 or presenilin 2 confirmed the early onset of Alzheimer's disease.[4] Other risk factors associated with the development of AD are: age, food, cholesterol,[1,17] head injury,[18] and family's genetic and behavioral history.[19] Several studies have shown strong connection of cholesterol related factors to the development and progression of AD.[4,5,8] Abnormal distribution of cholesterol inside the cells, in the membranes, and outside the cells was found to be responsible for the formation, accumulation, and removal of Aβ peptideds.[4] People with inherited ε4 gene of apolipoprotein E

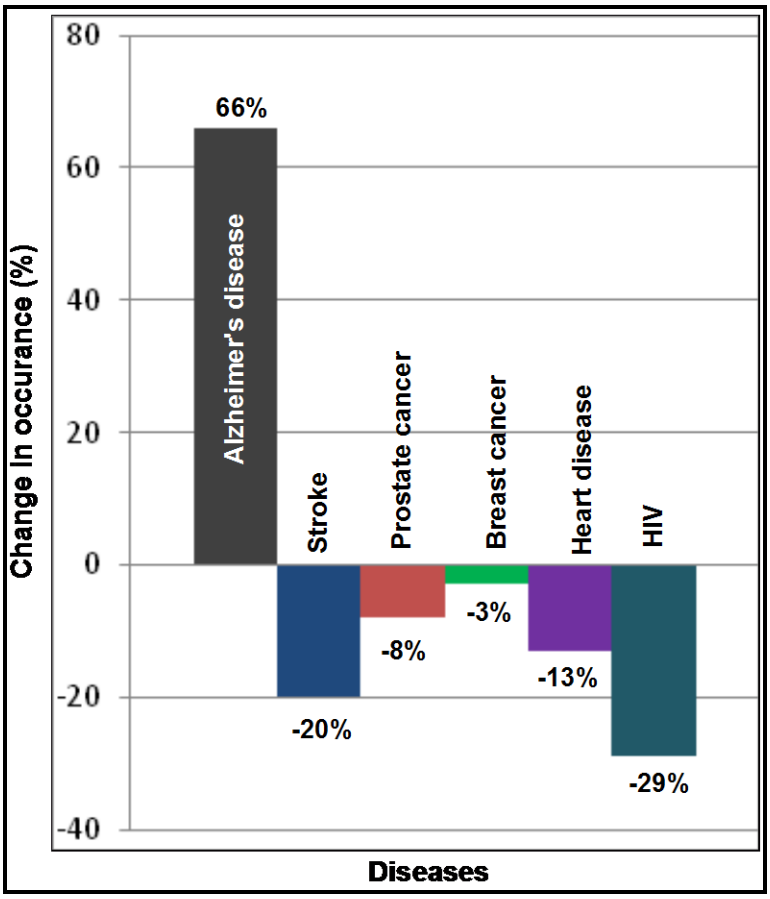

Figure 1.3: Percent change in the abundance of different diseases from 2000 to 2008.
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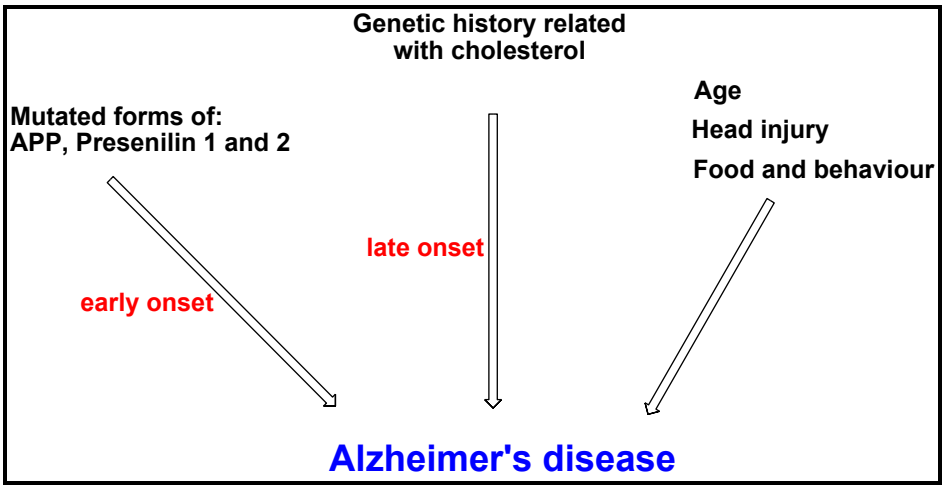

Figure 1.4: Factors associated with the development of Alzheimer's disease.[4,5,8]

(APOE) were found to be at high risk for the development of AD.[20,21] Furthermore, the neurons with tangles were found to have higher level of cholesterol compared to the healthy neurons.[22] Several cholesterol transporters like ABCA1,[23] cholesterol hydroxylase,[24] liver X factor receptors,[25] and ACAT[26] were also found to be connected to the development of Alzheimer's disease. Therefore, the modulation of these factors towards the avoidance or eradication of Alzheimer's disease has been persued.[4]

1.2.2 Norovirus infection and effects of lipid modulation

Norovirus, a category B bioterrorism pathogen, is responsible for more than 90% of non-bacterial gastroenteritis. The outbreaks mainly occurs in the closed environments like dormitories, cruise ships, hospitals, and care facilities.[27,28] Norovirus is mainly transmitted through fecal to oral route and only 10 virions can develop the sickness.[3] The major symptoms of norovirus infection include diarrhea, throwing, nausea, stomach pain, fever, headache, and body aches.[28] In most of the people, it is recovered within 1-3 days; however, it becomes life threatening to children, elderly people, and people with weakened immune system.[3] People with certain histo-blood group antigens receptors were found to be more susceptible to certain strains of norovirus.[29,30]

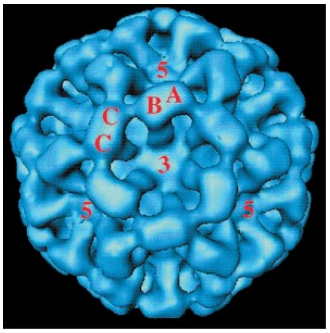

Figure 1.5: X-ray crystallographic structure of Norwalk virus.
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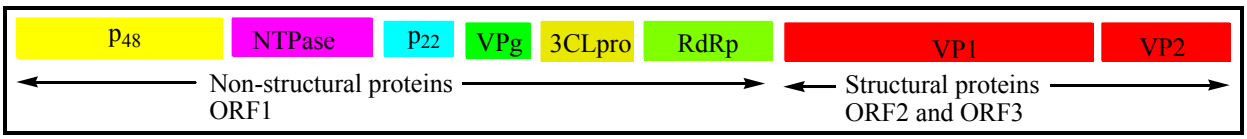


Figure 1.6: Schematic representation of norovirus genome.[32]

Norovirus is one of the four genera in family *caliciviridiae* with an icosahedral shaped capsid (**Figure 1.5**). It contains a non-enveloped, positive sense, single-strand RNA approximately 7.7 kb in length.[31,32] The genome of norovirus (**Figure 1.6**) has three open reading frames (ORFs). The ORF-1 encodes seven non-structural proteins, while ORF-2 and ORF-3 encode a major structural protein VP1 and a minor structural protein VP2 respectively.[33] Depending on the sequence of capsid genes, the norovirus that infects human is classified into main three genogroups (GI, GII, and GIV) and 26 genetic clusters, which further include several strains.[34] The capsid of Norwalk virus contains 90 dimers of casid protein forming S and P domains.[35] The S domain forms the icosahedral pattern and the P domain projects out from the dimeric junctions. The P domain of the NV capsid was found be responsible for its strain variations and virulence.[36,37,38]

Drug or vaccine development for norovirus infection has faced challenges due to its variations in strains, less infective to small animals, and being not able to grow in cell culture.[3] DNA microarray studies of the NV replicon-bearing cells demonstrated a strong dependency of norovirus replication with cellular cholesterol.[9] Moreover, the entry of murine NV in murine macrophages was controlled by host cholesterol.[39,40] These reports indicate the possibility of using cholesterol modulating compounds as anti-noroviral drugs.

1.2.3 Acyl-CoA: cholesterol acyltransferase (ACAT), a target for the treatment of Alzheimer's disease and norovirus infection

Cholesterol is essential for normal body functions; the requirement of cholesterol is fulfilled from both the dietary intake and continuous synthesis in the body.[41] Several enzymes are responsible for the maintenance of cholesterol homeostasis at different stages of its metabolic pathway. Endoplasmic reticulum/cell membrane is the center of intracellular and extracellular cholesterol balance.[42] Acyl-CoA: cholesterol acyltrasferase (ACAT)[43] (**Figure 1.7**) is a membrane bound enzyme, and uses long chain fatty acid as its substrate to convert cholesterol to cholesterol ester maintaining intracellular cholesterol homeostasis.[44]

Well known ACAT inhibitors like avasimibe (**1**) and CP113818 (**2**) (**Figure 1.8**) used for the treatment of atherosclerosis were also found effective to reduce the Aβ plaque formation in AD.[47,45] According to the studies from cell and animal models, the reduction of Aβ plaques was positively correlated with the inhibition ACAT.[45,46] Similarly, genes responsible for ACAT were significantly changed in DNA microarray analysis of the NV replicon cells.[9] Furthermore,

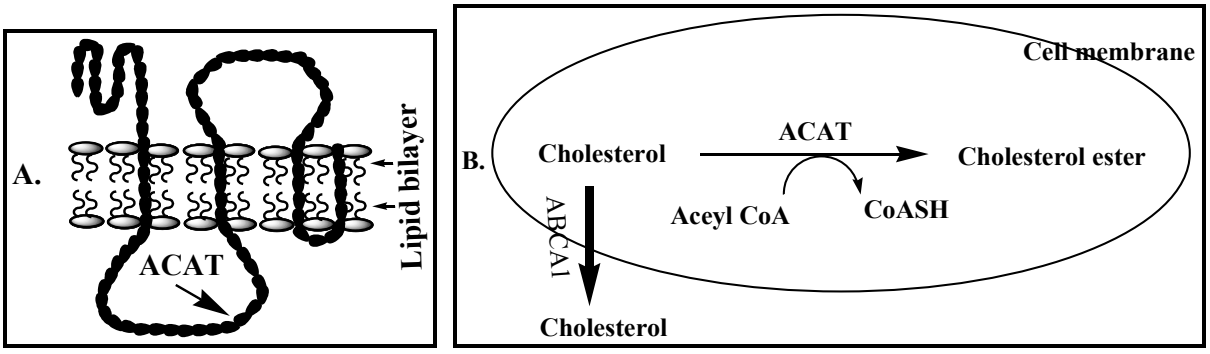


Figure 1.7: A. Schematic representation of enzyme ACAT. B. Role of ACAT and ABCA1 in the maintenance of intracellular cholesterol balance.[43]

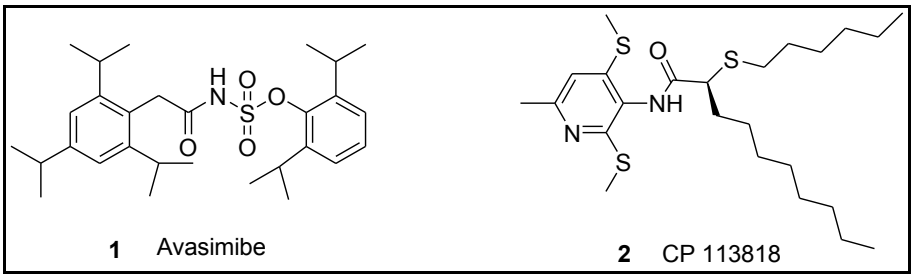


Figure 1.8: ACAT inhibitors effective to reduce Aβ plaques.[47,45]

ACAT inhibitors like CI976 (**3**), Sandoz 58-035 (**4**), and YIC-C8-434 (**5**) (**Figure 1.9**) significantly reduced the replication of norovirus mRNA.[9] Therefore, the modulation of intracellular cholesterol homeostasis by altering the role of ACAT provides an effective pathway for the treatment of Alzheimer's disease and norovirus infection.[9,47]

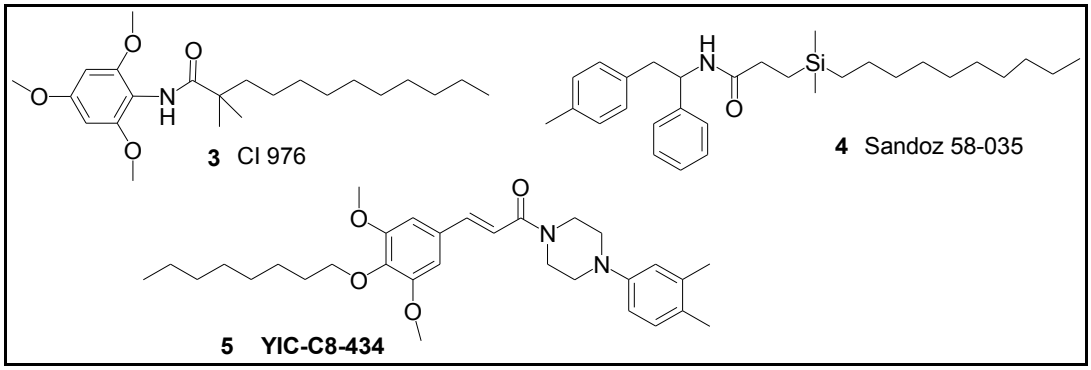


Figure 1.9: ACAT inhibitors effective for NV inhibition.[9]

1.2.4 Motivation to synthesize tricyclic pyrones as ACAT inhibitors

Pyripyropene A (**6**)[48] (**Figure 1.10**), a tetracyclic pyrone, was reported as a strong ACAT inhibitor. Tricyclic pyrone **7**[49] being structurally similar to **6** encouraged for the synthesis of TP analogs as ACAT inhibitors. Among the TP analogs synthesized by modifying different parts in the structure of **7** in Dr. Hua's lab, compounds **8** and **9** (**Figure 1.10**) showed encouraging potency for the protection of MC65 cells.[10] Moreover, compound **9 (**CP2**)** effectively prevented

the formation and enhanced the clearance of Aβ plaques *in vitro* and *in vivo*.[50,51] Therefore, the TPs similar in structure with compound **9** can have better anti-Alzheimer activities. So, the further exploration of similar analogs by modifying C13 position in compound **7** to find more potential candidates was desired.

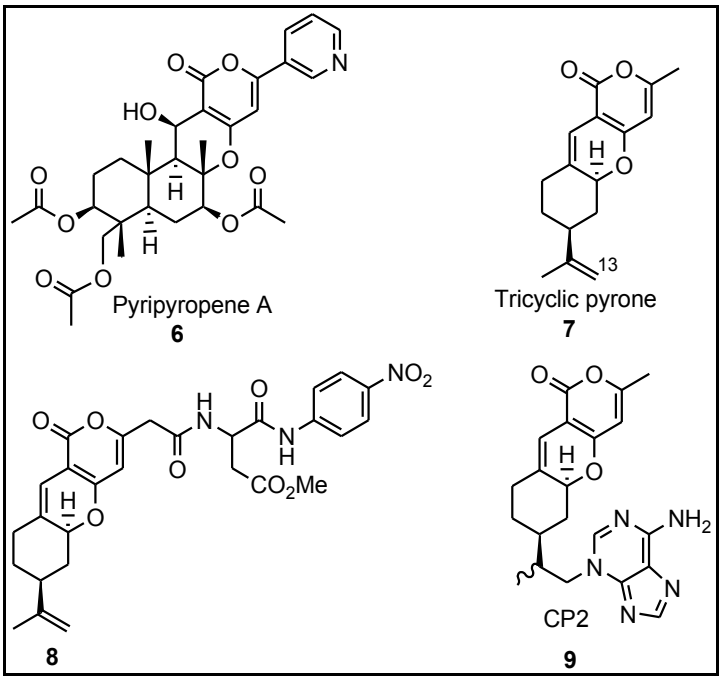


Figure 1.10: Structural resemblance of pyripyropene A and tricyclic pyrones.

1.3 Design and synthesis of tricyclic pyrones (TPs) as anti-Alzheimer and anti-norovirus agents

To find more effective ACAT inhibitors by mimicking the structure of CP2, several analogs (**10 – 36)** of TP (**Figure 1.11 & 1.12**) containing aryl-amino, -amide, -ester, -imine, and -dipeptidyl functionalities at C13 position were synthesized. Compounds **10** – **35** were obtained as a mixture of diastereomers at C12 from the coupling of amine **39** or alcohol **40** with

corresponding aldehydes or acids. The diastereomers were not separable through silica gel column chromatography.

Though initially targeted for anti-Alzheimer activity, tricyclic pyrones were also evaluated for their anti-noroviurs activity as several well known ACAT inhibitors were found to inhibit norovirus.[9] Most of the TP compounds listed here were evaluated for the protection of

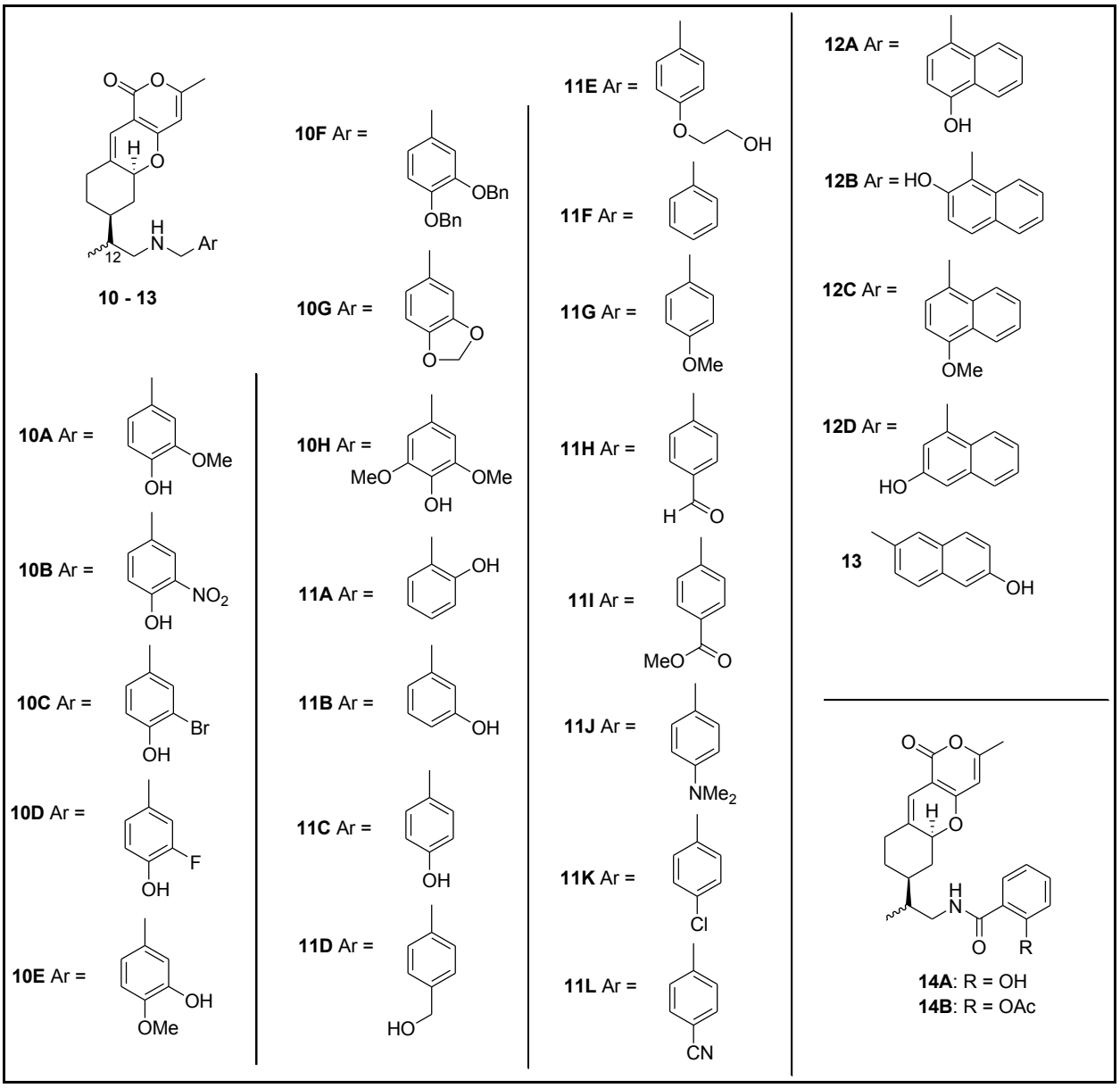


Figure 1.11: Tricyclic pyrones containing phenyl and naphthyl moieties.

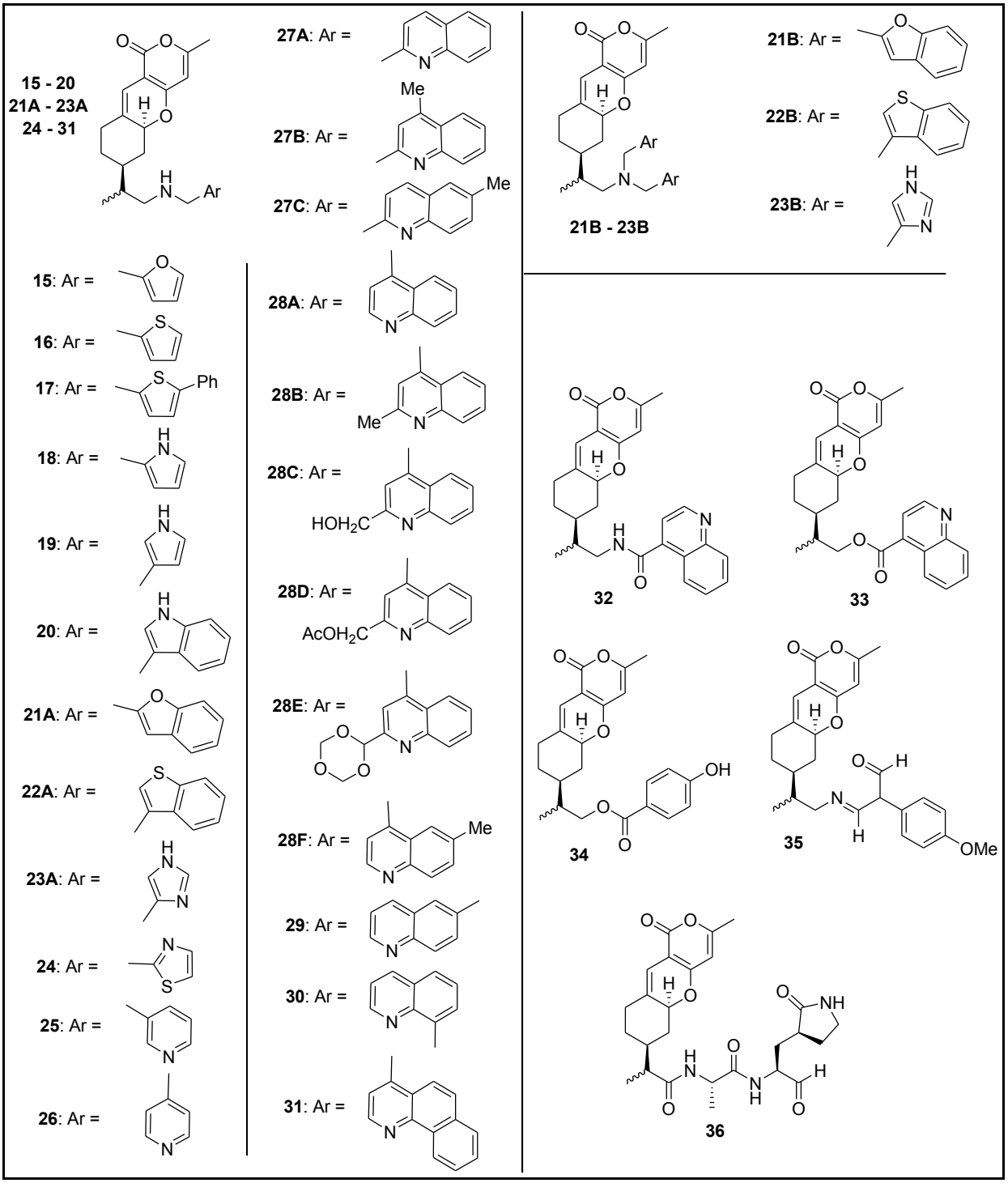


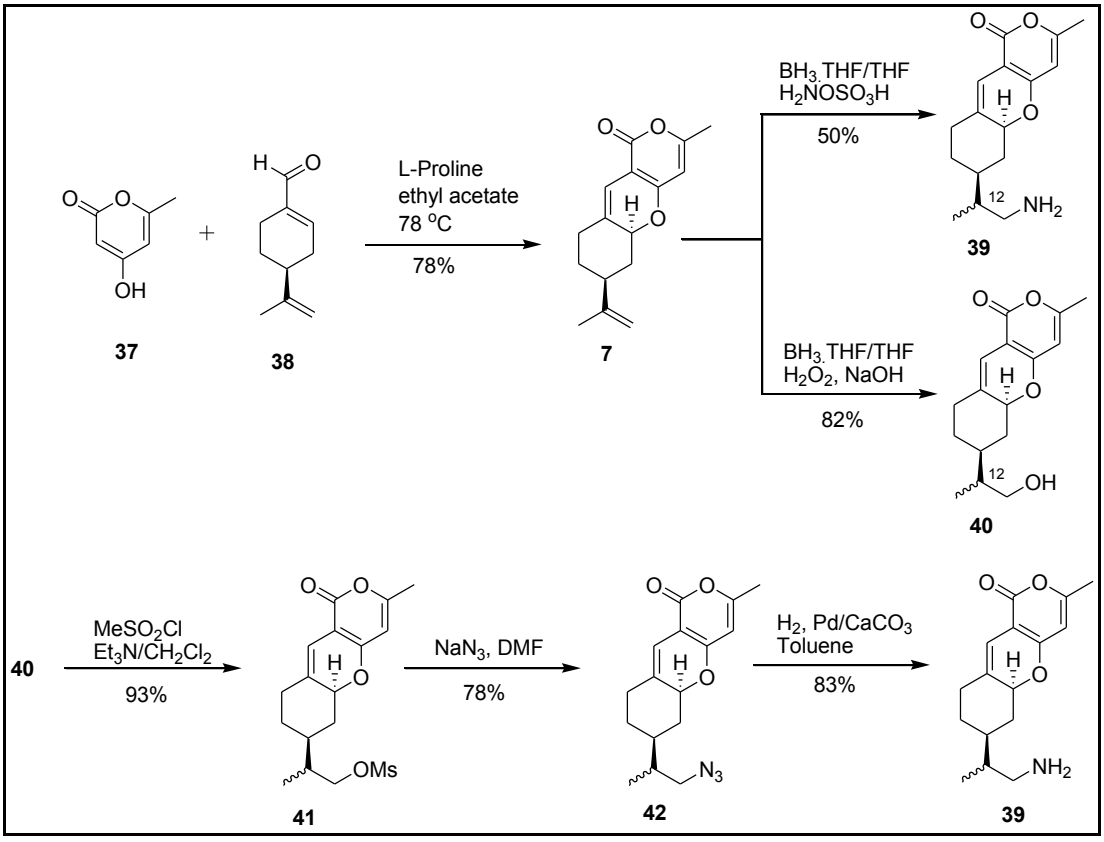
Figure 1.12: Tricyclic pyrones with aryl heterocyclic, phenyl, and dipeptidyl moieties.

neuronal cells as well as for the inhibition of norovirus. However, for the purpose of this dissertation, the compounds containing phenyl and naphthyl moieties are reported for anti-

Alzheimer potencies, while the compounds with aryl heterocylclic functionalities are reported for anti-norovirus activity. Nevertheless, compounds **34** and **35** with phenyl moieties are reported for anti-norovirus activity. Motivated by promising anti-norovirus potency of dipeptidyl aldehydes,[52] the dipeptidyl analog **36** was made through a series of oxidation, hydrolysis and coupling reactions starting from alcohol **40**. Compound **36** could not be obtained with satisfactory purity through silica gel column or from recrystalization. Therefore, compound **36** was not tested for its anti-noroviral efficacy.

1.3.1 Synthesis of tricyclic pyrones amine 39 and alcohol 40

The synthesis of precursors amine **39**[10] and alcohol **40**[10] was performed through a sequence of condensation and hydroboration-amination or hydroboration-hydroxylation (**Scheme 1.1**) reactions respectively, from 4-hydroxypyrone **37** by using reported procedures. Hence, tricyclic pyrone **7** was obtained as a single isomer with excellent yield from condensation of hydroxypyrone **37** with perillaldehyde (**38**) in ethyl acetate at reflux.[49] Then hydroboration-amination[53] of compound **7** by treating with BH_3·THF in dry tetrahydrofuran (THF) at 0 °C followed by refluxing with hydroxylamine-*O*-sulfonic acid (HSA) provided tricyclic pyrone amine **39** in 50% yiled.[54] During basic work up, the treatment of amine **39** with (aq) 1N NaOH gave trace amount of hydrolyzed byproduct, and the problem of hydrolysis was solved by using milder base (aq) K_2CO_3. Similarly, tricyclic pyrone alcohol **40** was obtained in 82% yield via hydroboration-hydroxylation reactions from tricyclic pyrone **7**.[10] Previously, in Dr. Hua's lab, amine **39** was synthesized through a sequence of mesylation, azidation, and reduction reactions (**Scheme 1.1**) starting from alcohol **40**.[10] Both TP amine **39** and alcohol **40** were obtained as a 1:1 mixture of two diastereomers at C12 center.



Scheme 1.1: Synthesis of tricyclic pyrones amine 39 and alcohol 40.[10,54]

1.3.2 Design and synthesis of tricyclic pyrones with phenyl and naphthyl moieties as anti-Alzheimer agents

The synthesis of tricyclic pyrones (TPs) **10 – 14** containing phenylmethyl and naphthylmethyl -amino and -amide functionalities are shown in **Schemes 1.2 & 1.3**. Motivated with the activity of 3-methoxy-4-hydroxybenzylamino analog **10A** for the protection of MC65 cells, several benzyl and naphthylmethyl –amino groups at C13 position of tricyclic pyrone (TP) were synthesized as anti-Alzheimer compounds. 3,4-Disubstituted phenyl analogs with different functionalities (**10B – 10G**) as well as 3,4,5-trisubstituted analog (**10H**) were synthesized. Due to higher efficacy of *p*-hydroxyphenyl analog (**10D**) for the protection of MC65 cells, corresponding monosubstituted aryl analogs with hydroxyl at ortho, meta, and para (**11A – 11C**)

were explored. Superior potency of *p*-hydroxy analog (**11C**) compared to ortho and meta analogs (**11A** – **11B**) led to the synthesis of TPs with varying length of hydroxyl chains (**11D** – **11E**) as well as several other substituents of -methoxy, -formyl, -methyl ester, -chloro, -cyano, and -dimethyl amino (**11G** – **11L**) at para position of aryl moiety. Further derivatization of the potent analog **11C** was done by making differently substituted naphthylmethyl amino analogs (**12 - 13**).

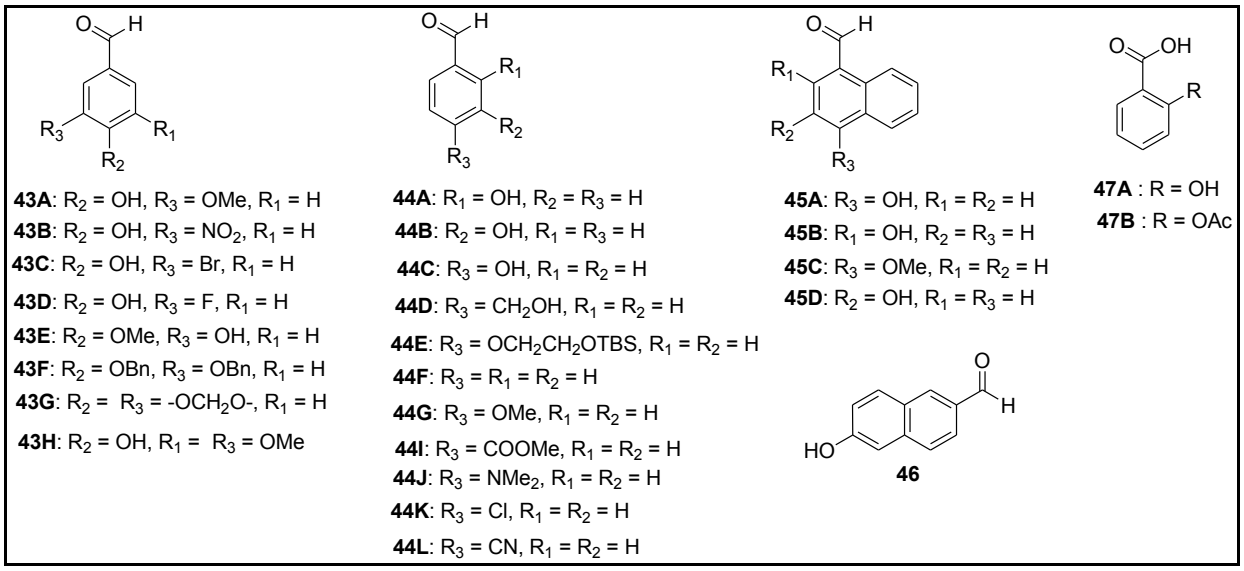
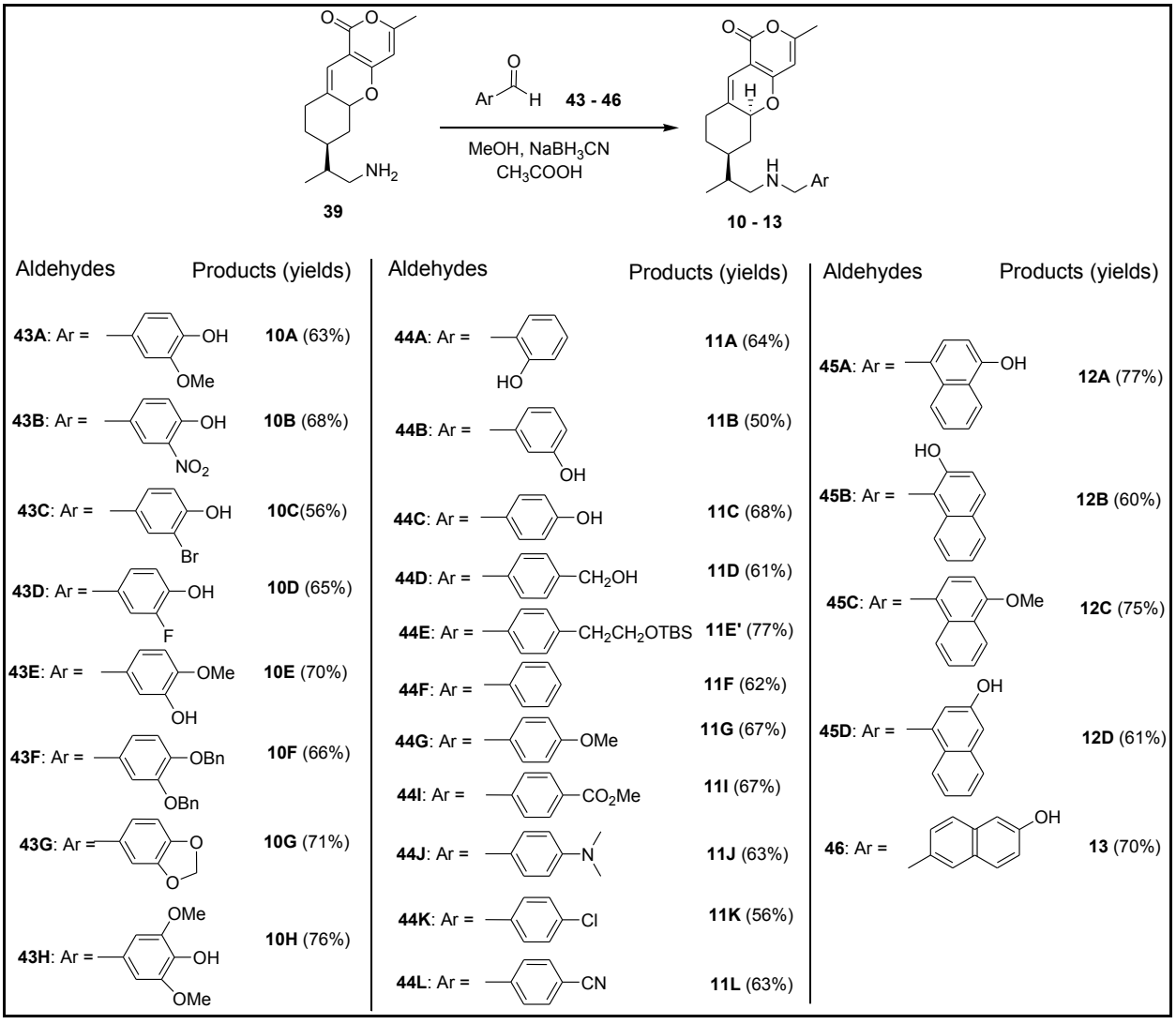


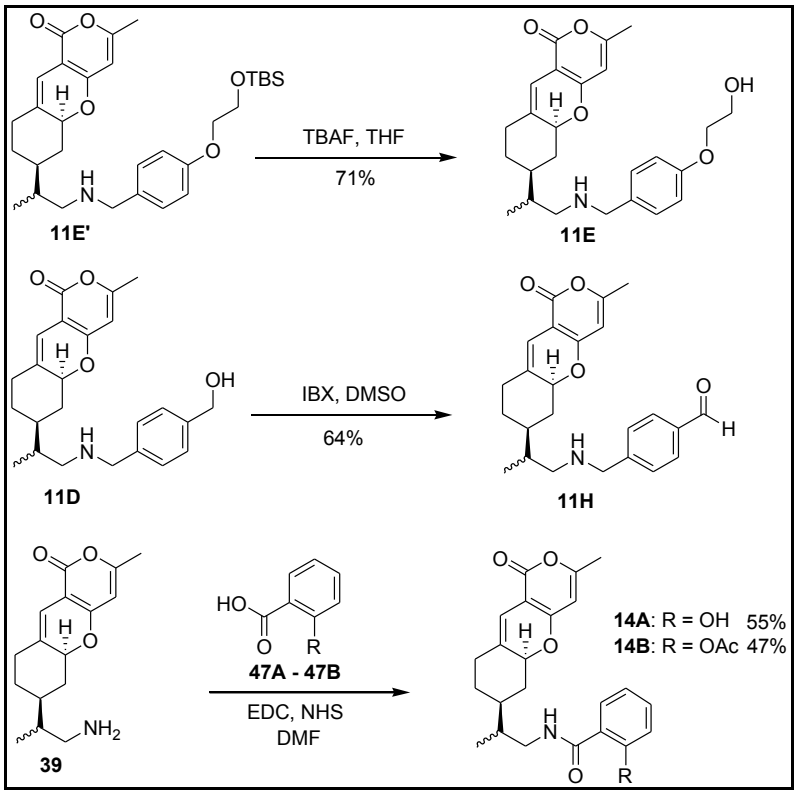
Figure 1.13: Phenyl and naphthyl aldehydes and acids used to synthesize tricyclic pyrones.

Tricyclic pyrone compounds **10A** – **11G**, **11I** – **13** were synthesized (**Scheme 1.2**) by reductive amination[55] of amine **39** with corresponding aldehydes **43** – **46** (**Figure 1.13**) with the yields ranging from 50% to 77%.[56] The reductive amination reaction was conducted in two steps. The formation of imine was achieved by stirring a mixture of amine **39** and an aldehyde in dry MeOH, and then the imine functionality was reduced with $NaBH_3CN$ in the presence of acetic acid. The reaction also proceeded well in EtOH and tetrahydrofuran (THF). The intermediate imine was stable enough to be observed by ^1H NMR, and in some cases was purified through silica gel column. In the absence of CH_3COOH, the reduction was slower and in case of **12B**,

was very reluctant. Higher amounts of $NaBH_3CN$, CH_3COOH, and longer time were needed to complete the reduction to get tricyclic pyrone **12B** from its intermediate imine. Formation of the hydrogen bond between imine functionality and ortho hydroxyl in naphthyl moiety could have made a stable, five or six-membered structure. This intermediate imine was stable enough to be purified through silica gel column. Interestingly, compound **12A** decomposed while



Scheme 1.2: Synthesis of tricyclic pyrones 10 – 13.

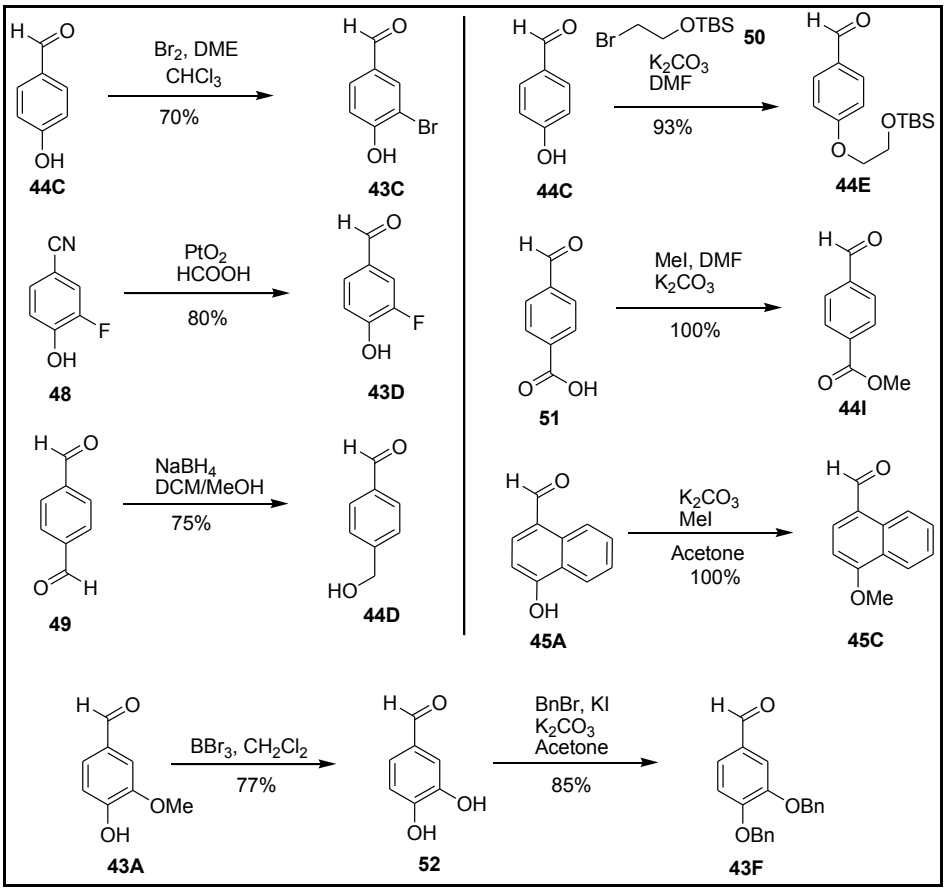


Scheme 1.3: Synthesis of tricyclic pyrones 11E, 11H, and 14.

concentrating the organic layer in reduced pressure, but its trifluoroacetic acid (TFA) salt was found to be more stable. Therefore, 1.2 equivalents TFA was added before concentration of the organic layer, so compound **12A** was obtained in the form of its TFA salt. Synthesis of tricyclic pyrones **11E**, **11H**, and **14** was achieved via desilylation, oxidation, and 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide (EDC) coupling reactions (**Scheme 1.3**). Hence, the *p*-hydroxyethyl ether analog **11E** was obtained after the removal of silyl protecting group from compound **11E'** and the 4-formyl analog **11H** was obtained by benzylic oxidation of compound **11D** with 2-iodoxybenzoic acid (IBX) and dimethyl sulfoxide (DMSO)[57] in 71% and 64% yields, respectively. With encouraging MC65 cells protection results of tricyclic pyrones with 2° amine functionality, the comparison of potency with amide analogs was desired. Therefore, tricyclic pyrone amides **14A** and **14B** were synthesized in reasonable yields from the coupling reaction of

amine **39** with aryl acids **47A** and **47B** in DMF in the presence of EDC and *N*-hydroxysuccinimide (NHS).

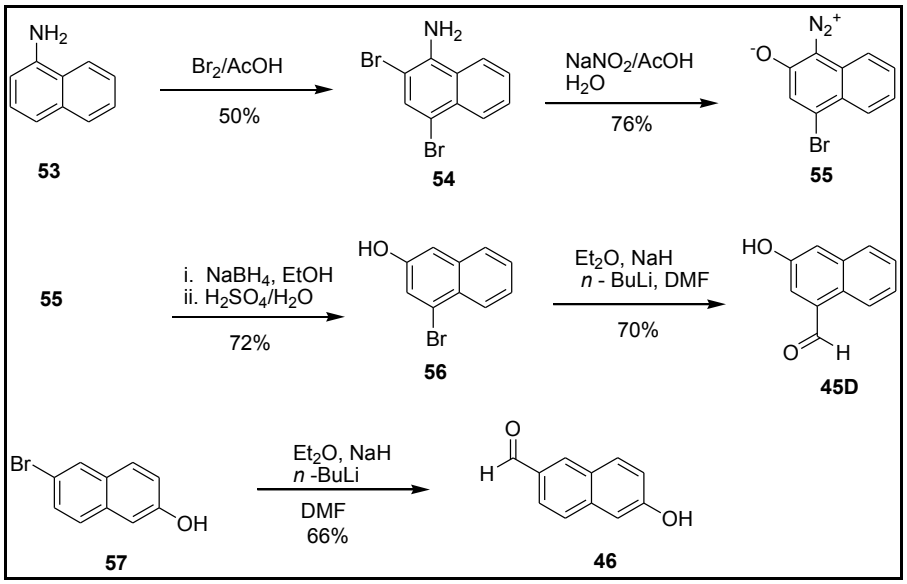
Aryl aldehdydes **43A**, **43B**, **43E**, **43G – 44C**, **44F**, **44G**, **44J – 45B**, and carboxylic acids **47A**, **47B** were obtained from commercial sources. While, aldehydes **43C, 43D, 43F**, **44D**, **44E**, **44I**, **45C**, and **45D** were prepared according to the literature methods (**Schemes 1.4 & 1.5**) with the yields ranging 66% - 100%. Hence, the monobromination of *p*-hydroxybenzaldehyde



Scheme 1.4: Synthesis of aldehydes 43C, **43D, 43F**, **44D**, **44E**, **44I**, and **45C.**[61-69]

(**44C**) with bromine was achieved in 70% yield in a mixture of chloroform and dimethoxyehtane (4:1) to get aldehyde **43C**.[58] The reduction of 4-cyano-2-fluorophenol (**48)** with platinum oxide in formic acid provided 3-fluorinated adehyde **43D**[59] in 80% yield.[60] The reduction of

terephthalaldehyde (**49**) with $NaBH_4$ in a mixture of dichloromethane and methanol at 0 °C gave aldehyde **44D** in 75% yield.[61] Aldehyde **44E** was obtained from the substitution of bromide in (2-bromoehtoxy)(*t*-butly)dimethylsilane (**50**) with phenolic hydroxyl of aldehyde **44C** in the presence of K_2CO_3 in DMF.[62] Esterification of *p*-carboxybenzaldehyde (**51**) with methyl iodide in DMF provided aldehyde **44I**[63] in quantitative yield.[64] Aldehyde **45C**[65] was obtained in quantitative yield by methylation of 4-hydroxy-1-naphthylcarboxaldehyde (**45A**) with methyl iodide in the presence of K_2CO_3.[66] Dibenzylated aldehyde **43F**[67] was obtained from 3-methoxy-4-hydroxybenzaldehyde (**43A**) through a two steps process of demethylation and benzylation.[68] Thus, demethylation of aldehyde **43A** with BBr_3[69] in dichloromethane gave 3,4-dihydroxybenzaldehyde (**52**), which was then benzylated with benzyl bromide and potassium carbonate in acetone to get aldehyde **43F**. Aldehyde **45D** was obtained in 70% yield from metalation/Vilsmeier-Haack reaction of 4-bromo-2-naphthol (**56**) in diethyl ether with NaH, *n*-BuLi and DMF.[70] Compound **56** in turn was obtained from 1-aminonaphthlene (**53**) in a three steps process of bromination, oxidative azotization, and reduction reactions.[71] Thus, the



Scheme 1.5: Synthesis of aldehydes 45D and 46.[70,71]

bromination of compound **53** with bromine in acetic acid provided compound **54**, which then was oxidatively azotized[72] with $NaNO_2$/AcOH to get compound **55**. Finally, compound **55** was reduced with $NaBH_4$ followed by aqueous workup to provide compound **56** in 28% overall yield from compound **53**.[71] Similarly, aldehyde **46** was obtained by metalation/Vilsmeier-Haack reaction of 6-bromo-2-naphthol (**57**) with 66% yield.[70]

1.3.3 Design and synthesis of tricyclic pyrones with heterocyclic, benzyl, and dipeptidyl moieties as anti-norovirus agents

Several TP analogs containing different aryl heterocycles (**15 - 33**), phenyl (**34** , **35**), and dipeptidyl aldehyde (**36**) groups were synthesized (**Schemes 1.6, 1.7, 1.8, & 1.9**) to find potent anti-norovirus compounds. TPs containing 5-membered heterocycles with furanyl, thiophenyl, pyrrolyl, imidadolyl, and thiazolyl groups in mono and bicyclic systems were synthesized. Encouraged with low micromolar efficacy of some of the 5-membered aryl heterocycle containing analogs to inhibit norovirus inhibition, the TPs with six-membered aryl heterocycles were also explored with pyridinyl, quinolinyl, and benzoquinolinyl moieties. Like TPs bearing phenyl analogs, the synthesis of TPs **15 – 31** (**Scheme 1.6 & 1.7**) was achieved via the reductive amination of amine **39** with respective aldehydes **58 – 74** (**Figure 1.14**) in 41% to 75% yields. As in the case of phenyl or naphthylmethyl -amino analogs the reduction of intermediate imine was slower in the absence of acetic acid. Observation of relatively low yields of some heterocyclic TP analogs is due to the loss associated to their higher polarity, during purification through silica gel column. Among the aryl heterocyclic containing TPs, 2-quinolinyl analog **27A** showed improved potency for norovirus inhibition. Therefore, further derivatization of the TPs containing quinolinyl group was carried out by using differently substituted 2-quinolinyl and 4-

quinolinyl aldehydes **70A – 71F** to get their corresponding TP analogs **27A – 28F**. Use of more than one equivalents of aldehydes provided a mixture of monoalkylated and dialkylated products

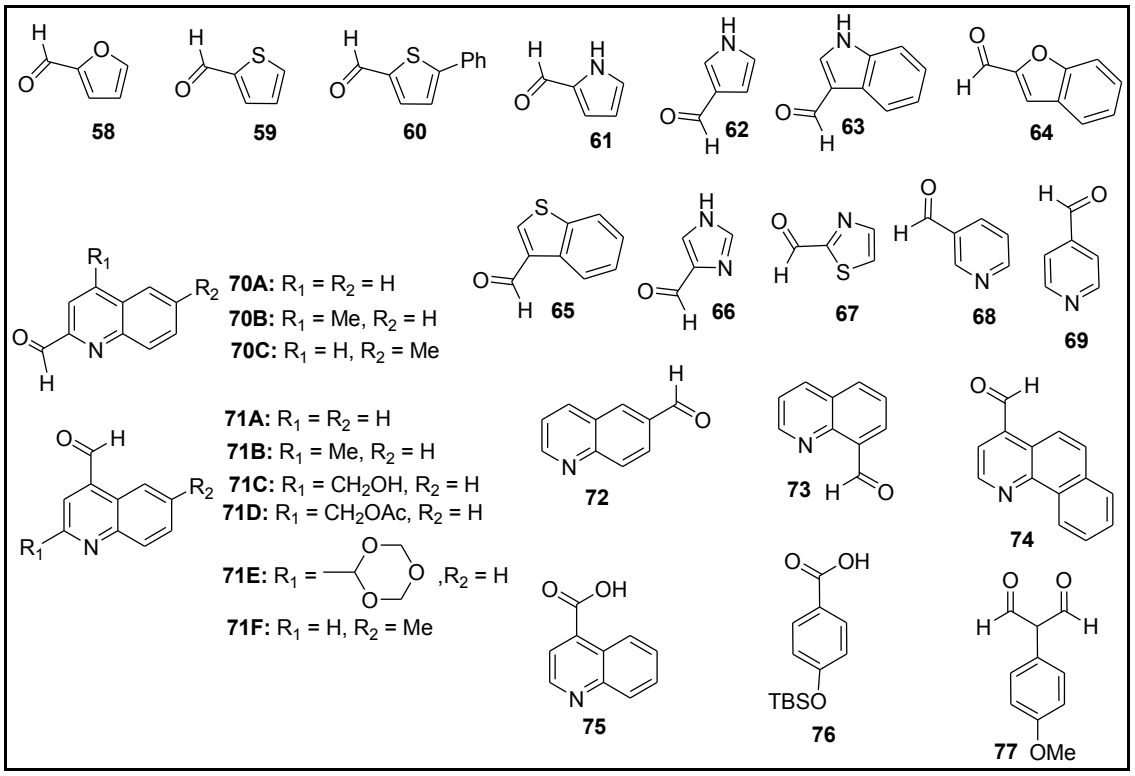
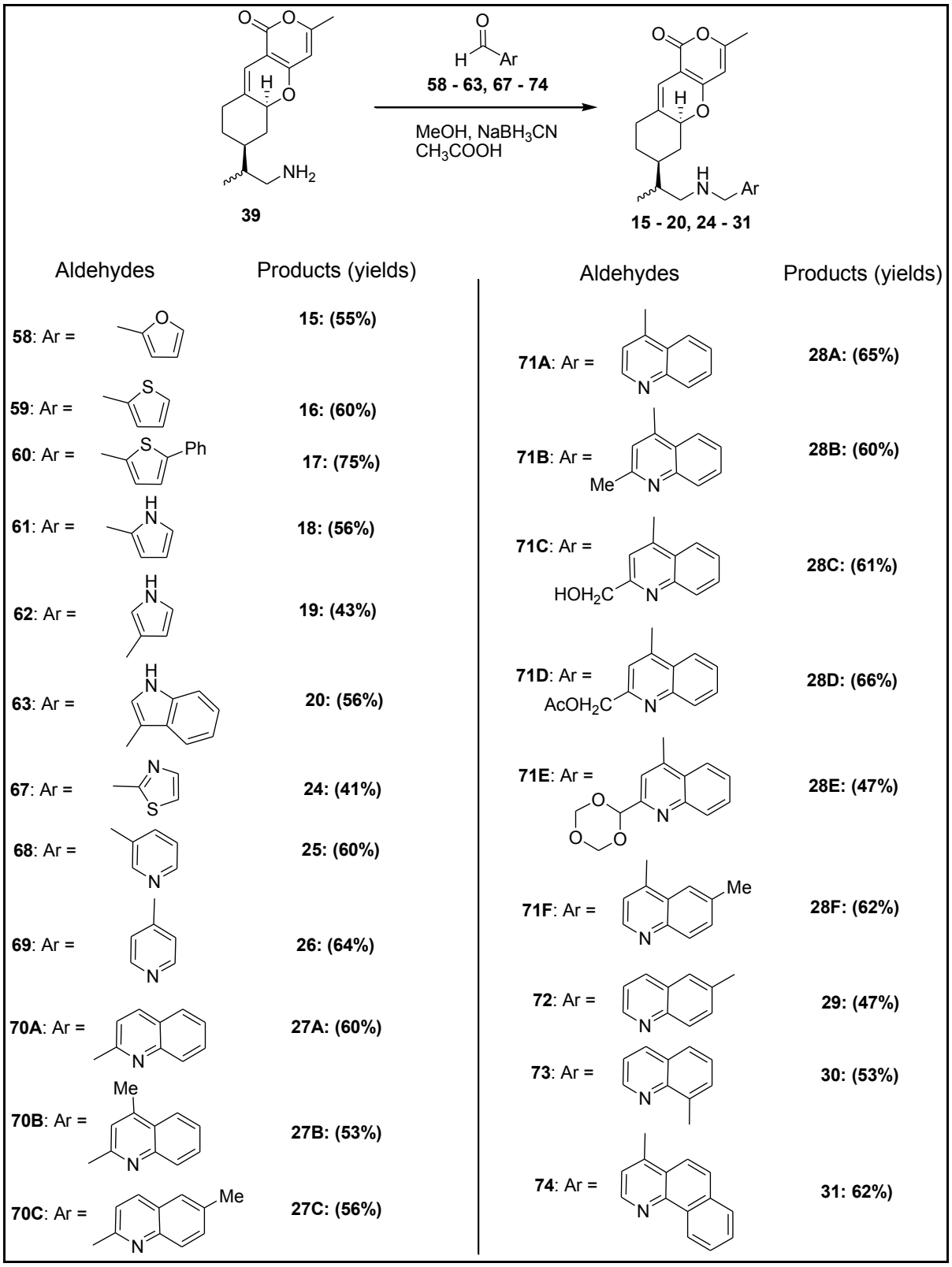
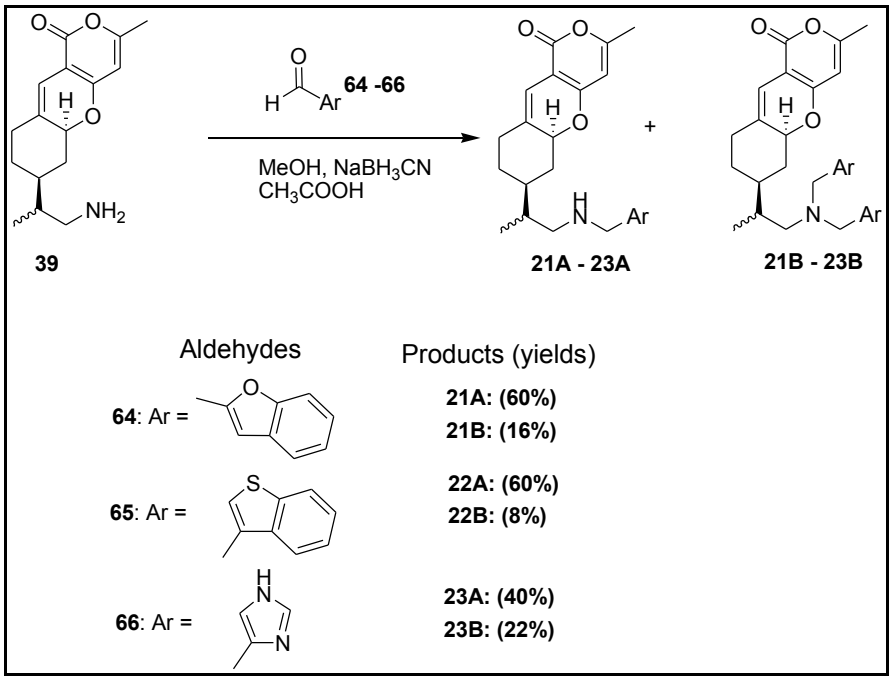


Figure 1.14: Heterocyclic and benzyl, aldehydes and acids used to synthesize tricylic pyrones.

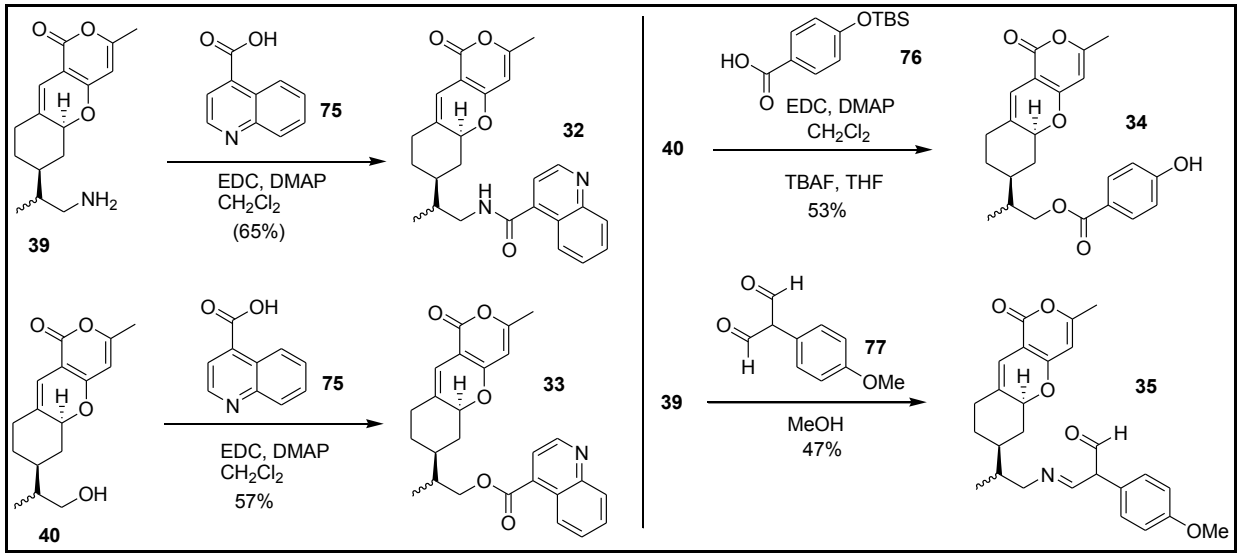
21 - 23 (**Scheme 1.7**), but in the case of analog **23** even the use of less than one equivalent of aldehyde **66** provided a mixture of mono and di-alkylated products **23A** and **23B**. This indicates the possibility of reversal of the reductive amination reaction in some analogs. The formation of dialkylated product was discouraged by addition of higher equivalents of acetic acids, probably due to the protonation of secondary amine lowering its nucleophilicity. Syntheses of the TPs containing quinolinyl -amide **32**, -ester **33**, phenyl ester **34**, and benzyl imine **35** (**Scheme 1.8**) were also performed to further explore the anti-norovirus activity of TPs. By mimicking the structure of the most active TP amine **28A** to inhibit norovirus, the corresponding amide and



Scheme 1.6: Synthesis of tricyclic pyrones 15 – 20 and 24 – 31.



Scheme 1.7: Synthesis of tricyclic pyrones 21 – 23.

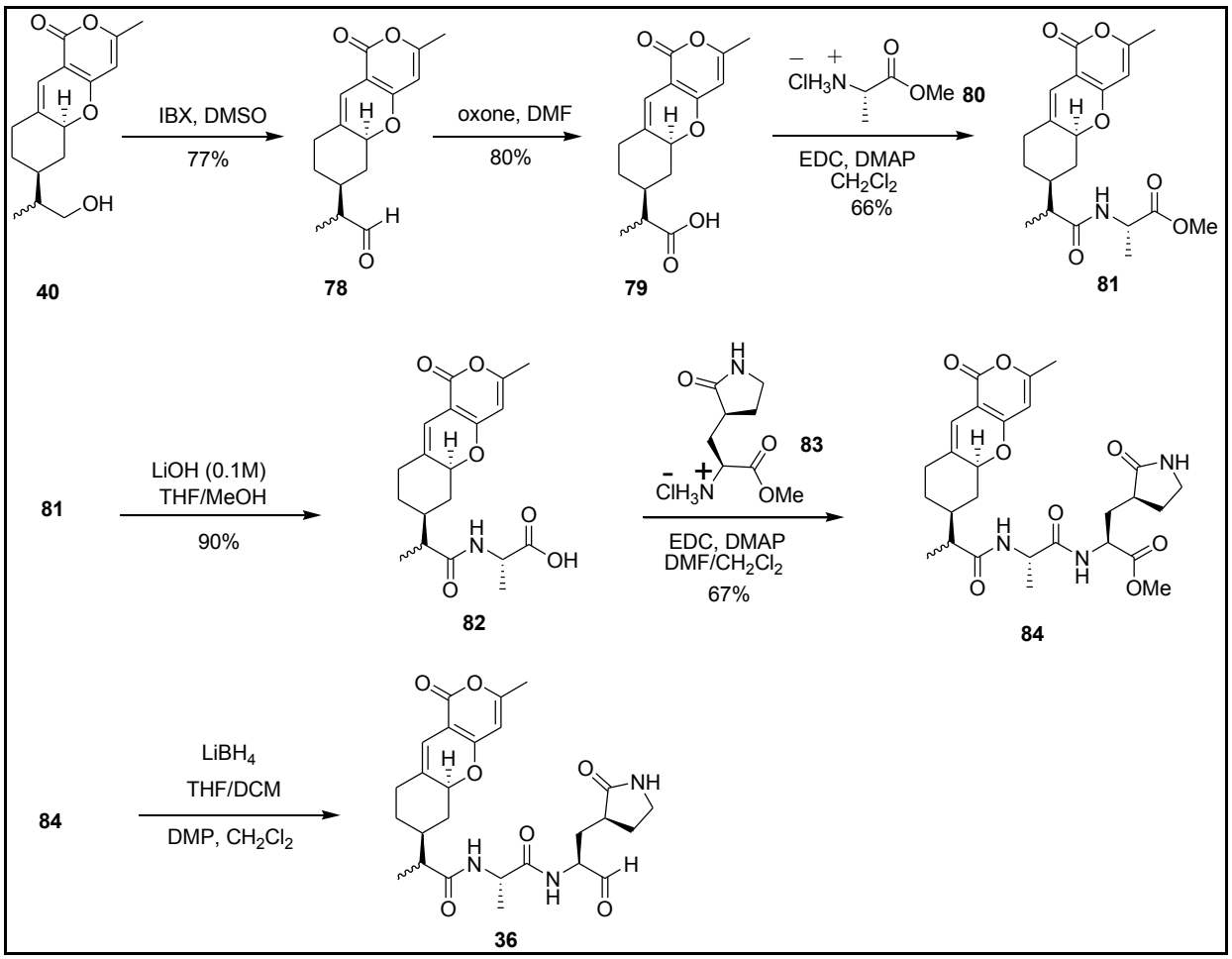


Scheme 1.8: Synthesis of tricyclic pyrones -amide 32, –esters 33, 34, and –imine 35.

ester analogs **32** and **33** were made by EDC coupling reactions of amine **39** and alcohol **40** respectively, with acid **75**. Thus, the treatment of amine **39** and alcohol **40** separately with acid **75** in dichloromethane in the presence of EDC and DMAP provided 62% and 57% yields of

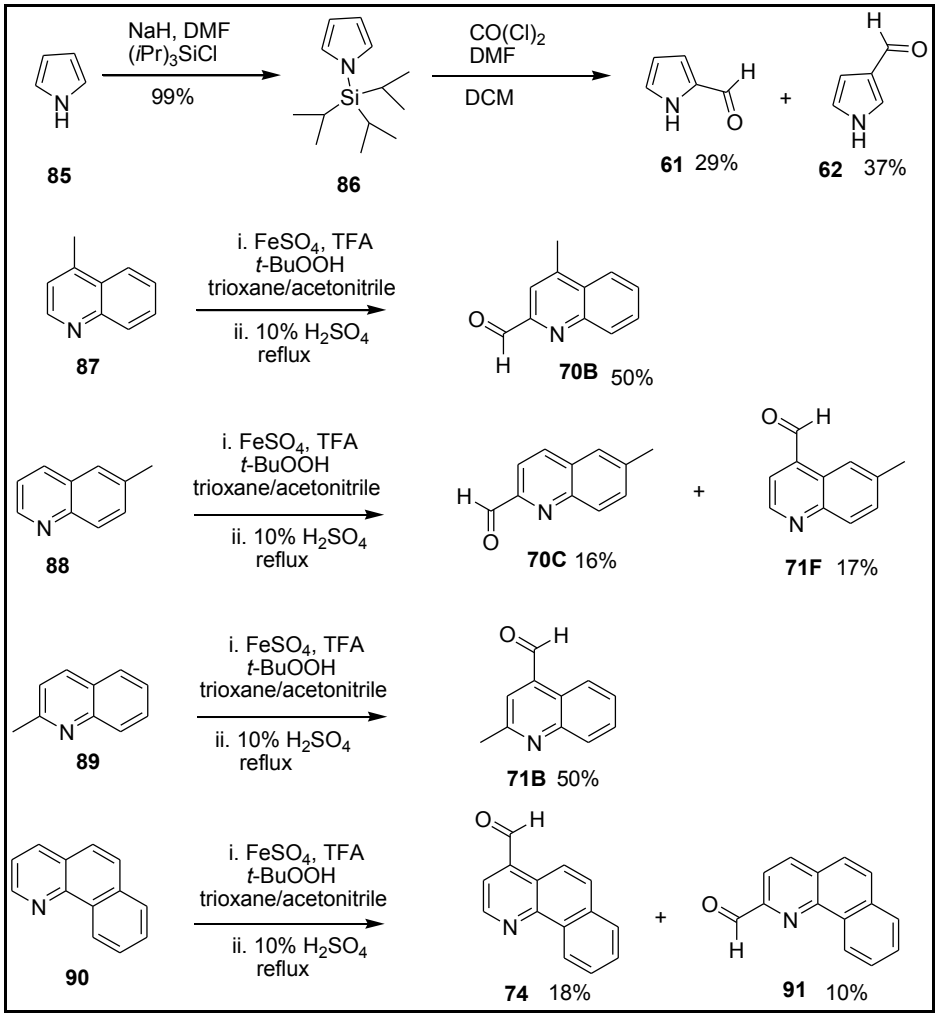
compounds **32** and **33**, respectively. Similarly, TP ester **34** was obtained in 53% overall yield from the EDC coupling of amine **39** and phenyl acid **76** followed by the removal of silyl protecting group. Tricyclic pyrone imine **35** was obtained in an attempt to prepare an analog containing four membered ring analogous to the dialkylated product from the reductive amination of amine **39** and dialdehyde **77**. However, the reduction of imine **35** was not achieved even with higher equivalents of $NaBH_3CN$ and acetic acid. Imine **35** was found stable for the chromatographic separation and purified through silica gel column. It was obtained as a 1:1 mixture of E and Z isomers.

The encouraging anti-norovirus activity of the tricyclic pyrones and the reported NV inhibitory efficacy of dipeptidyl surrogate aldehydes[52] motivated to synthesize the dipeptidyl aldehyde analog **36** as an anti-noroviral agent. The synthesis of compound **36** was achieved through a series of oxidations, coupling, and reduction reactions (**Scheme 1.9**) starting from alcohol **40**. Thus, the treatment of alcohol **40** with IBX/DMSO provided aldehyde **78** with excellent yield. Aldehyde **78** was further oxidized by oxone in DMF to get the corresponding carboxylic acid analog **79** with 80% yield.[73] An attempt to oxidize aldehyde **78** to acid **79** with pyridinium dichromate (PDC)[74] was not successful. The coupling of TP acid **79** with alanine methyl ester (**80**) in the presence of EDC and DMAP in dichloromethane provided the alanine ester analog **81** in 66% yield. The ester functionality in compound **81** was hydrolyzed with (aq) LiOH in a mixture of THF/MeOH (1:1) to get the corresponding carboxylic acid **82** in 90% yield. Similar EDC coupling reaction of acid **82** with glutamine surrogate hydrochloric salt **83**[52] in a mixture of DCM and DMF (10:1) gave dipeptidyl ester analog **84**. Glutamine surrogate HCl salt **83** was synthesized by Dr. Keshar Prasain and Sahani M. Weerasekara by following the literature methods.[52,75] Compound **84** was obtained as a mixture of four isomers indicating the



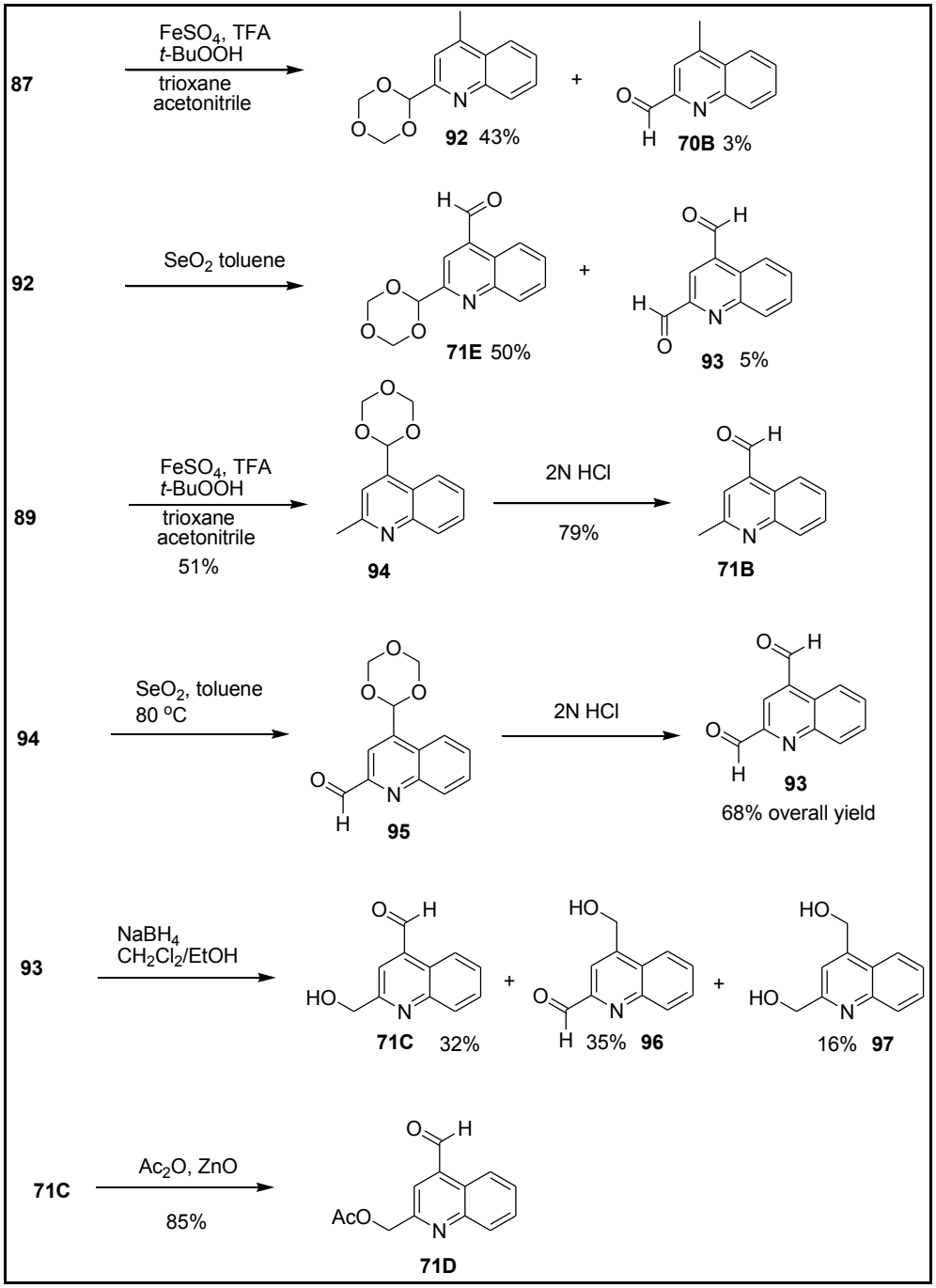
Scheme 1.9: Synthesis of TP 36.

possibility of stable rotational conformations. The origination of four isomers due to epimerization of α-H in compound **82** during hydrolysis with (aq) LiOH is less likely as only two diastereomers were observed by NMRs. The hydrolysis of compound **84** with $LiBH_4$ in a mixture of DCM and THF (1:1) at 0 °C followed by oxidation of the resulted alcohol with Dess-Martin periodinane in DCM provided desired compound **36**. Though the TLC observation of compound **36** from reaction mixture was good, some unidentified problems occurred while purifying the compound **36** through silica gel column and could not be obtained with satisfactory purity.



Scheme 1.10: Synthesis of aldehydes 61, 62, 70B, 70C, 71B, 71F, and 74.[77,78]

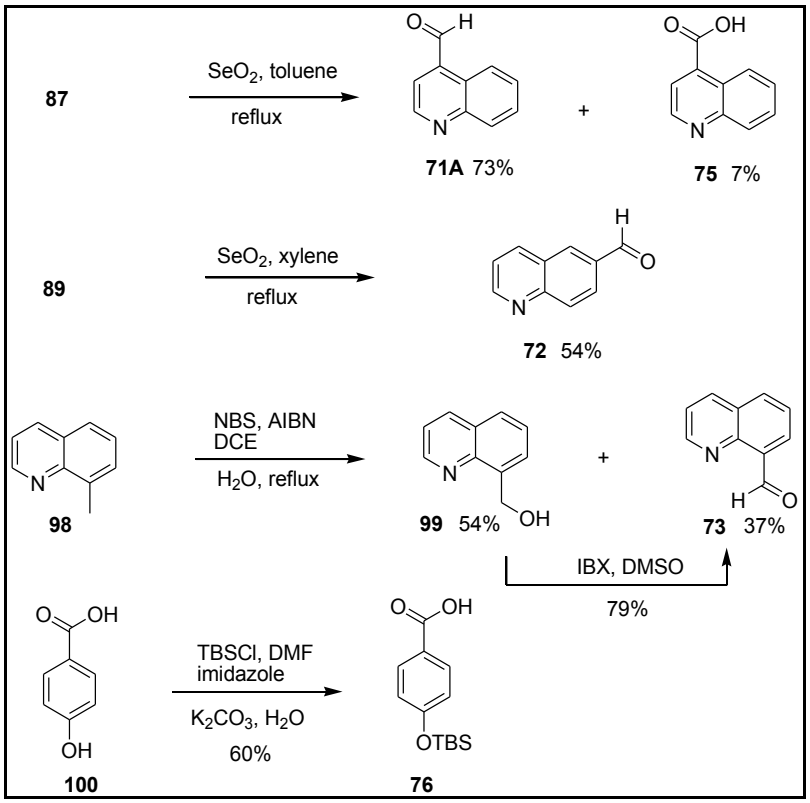
Heterocyclic aldehydes **58** – **60**, **63** – **69**, **70A**, heterocyclic acid **75**, and benzylic dialdehyde **77** were purchased from commercial sources, while heterocyclic aldehydes **61**, **62**, **70B**, **70C**, **71 - 74**, and phenyl acid **76** were prepared in our lab. Synthesis of aldehydes **61**, **62**, **70B**, **70C**, **71B**, **71F**, and **74** was done by aromatic ring formylation of the corresponding heterocycles (**Scheme 1.10**). 2-Formyl pyrrole (**61**)[76] and 3-formyl pyrrole (**62**)[77] were obtained from *N*-silylation followed by formylation reactions. Hence, the treatment of pyrrole (**85**) with NaH and isopropylsilyl chloride in DMF provided intermediate **86**, which was then formylated with oxalyl dichloride and DMF in dichloromethane followed by hydrolysis to get 2-formyl



Scheme 1.11: Synthesis of aldehydes 71B, 71C, 71D, and 71E.[79,82,83]

pyrrole (**61**) and 3-formyl pyrrole (**62**) in 29% and 37% yields, respectively.[77] Aldehydes **70B**, **70C**, **71B**, **71F**, and **74** were obtained through a sequence of oxidation and hydrolysis

reactions.[78,79] Thus, the reflux of protonated forms of the quinolines **87**, **88**, **89** and benzo[*h*]quinoline (**90**) separately, with *t*-butylhydroperoxide and catalytic amount of ferrous



Scheme 1.12: Synthesis of aldehydes 71A, 72, 73, and acid 76.[82,84,85]

sulfate in a mixture of acetonitrile and trioxane (1:1) for 6 h, at 80 °C followed by acidic hydrolysis provided the aldehydes **70B**, **70C**,[80] **71F**, **71B**, and **74**,[81] respectively, with the yields ranging 16% to 50%. A mixture of both 2- and 4-formylated analogs were obtained from 6-methylquinoline (**88**) and benzo[*h*]quinoline (**90**) indicating exclusive formylation only in 2 and 4 positions of the quinoline nitrogen. Synthesis of aldehydes **71C**, **71D**, and **71E** (**Scheme 1.11**) was possible by isolating the intermediates of trioxanylated quinolines **92** and **94**. The trioxanyl moiety in these analogs was found stable enough for the benzlic oxidation of 2- and 4-methyl substituents with SeO_2.[78,82] Thus, the trioxanylation of 4-methylquinoline (**87**) with TFA, $FeSO_4$,

t-butylhydroperoxide, and trioxane provided intermediate **92**[79] in 43% yield along with small amount of hydrolyzed product **70B**. Then the benzylic oxidation of methyl in the intermediate **92** with selenium dioxide, in toluene, at 85 °C gave the aldehyde **71E** in 50% yield.[82] Trace amount of dialdehyde analog **93** was also observed by the hydrolysis of the trioxanyl moiety. Similarly, trioxanylation of 2-methylquinoline (**89**) provided 2-methyl-4-trioxanylquinonline (**94)** in 51% yield. Isolation of intermediate **94** also provided an alternate and stepwise route for the formation of aldehyde **71B**. Benzylic oxidation of intermediate **94** with selenium dioxide at 80 °C followed by acidic hydrolysis provided dialdehyde **93** in 68% overall yield from **94**. The benzylic oxidation of 2-methyl intermediate **94** with selenium dioxide was found more conducive than 4-methyl analog **92**. Reduction of dialdehyde **93** with $NaBH_4$ in a mixture of ethanol and dichloromethane at 0 °C gave desired aldehyde **71C** along with aldehyde **96** and dialcohol **97** with 32%, 35%, and 16% yields, respectively. Acetylation of hydroxyl functionality in aldehyde **71C** with Ac_2O and ZnO provided aldehyde **71D** in 85% yield.[83]

Synthesis of aldehydes **71A**, **72**, **73**, and acid **76** was possible by benzylic oxidation with SeO_2, bromination followed by hydrolysis, and silylation reactions (**Scheme 1.12**). Aldehyde **71A** was obtained in 73% yield along with small amount of quinoline-4-carboxylic acid (**75)** from the oxidation of 4-methylquinoline (**87**) with selenium dioxide in toluene.[82] The oxidation of 6-methylquinoline (**88**) in similar conditions provided very low yield of aldehyde **72**, but refluxing in xylene provided 54% yield.[82] Benzylic oxidation of 8-methylquinoline (**98**) in toluene did not work in above conditions. Therefore, aldehyde **73** was obtained from a two steps process of benzylic bromination followed by hydrolysis.[84] Hence, the bromination of compound **98** with *N*-bromosuccinimide (NBS) and azobisisobutyronitrile (AIBN) in dichloromethane provided a mixture of mono and di –brominated intermediates; then the hydrolysis of these

intermediates by refluxing in water gave a mixture of aldehyde **73** and alcohol **99** in 37% and 54% yields, respectively. The oxidation of alcohol **99** with IBX/DMSO also provided aldehyde **73** in 79% yield. Carboxylic acid **76** was synthesized from *p*-hydroxybenzoic acid (**100**) using silylation followed by hydrolysis reactions by Jianyu Lu, in our lab. So, the treatment of compound **100** with imidazole and TBSCl in DMF followed by hydrolysis with potassium carbonate provided compound **76** in 60% yield.[85]

1.4 Anti-Alzheimer and anti-norovirus activities of tricyclic pyrones

As mentioned earlier, most of the TP compounds were tested for both anti-Alzheimer and anti-norovirus activities. However, for the purpose of this dissertation, TPs **10** – **14** (**Figure 1.11**) with phenyl and naphthyl moieties are reported for anti-Alzheimer activity;[86] while, TPs **15** – **33** (**Figure 1.12**) with heterocyclic moieties and TPs **34**, **35** (**Figure 1.12**) with phenyl moieties are reported for anti-norovirus activity.[87] The most effective compounds (**10D**, **11C**, **11D**, and **12A**) from MC65 cells protection assay were also evaluated for ACAT inhibition and ABCA1 gene modulation potencies.

MC65 cells protection assay was carried out by **Dr. Izumi Maezawa** in **Dr. Lee Way Jin's** lab at M. I. N. D. Institute and the Department of Pathology, University of California Davis Health System. ACAT inhibition, ABCA1 modulation, and Norovirus inhibitory study was performed by **Yungeong Kim** and **Kyeong-Ok**, **Chang** at the Department of Diagnostic Medicine and Pathology, College of Vetenary Medicine, Kansas State University.

1.4.1 Anti-Alzheimer activities of tricyclic pyrones

Anti-Alzheimer activity of TPs was accessed by observing the potency to protect MC65 cells against intracellular amyloid-β oligomers induced toxicity. MC65 cells are neuroblastoma cells[86], which are readily generated in cell culture. In MC65 cells, the generation of intracellular Aβ oligomers from C99 fragment of amyloid precursor protein (APP) leads to cell death after 3 days. Efficacy of TP compounds **10** – **14** to prevent neuronal cell death was observed quantitatively by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Tetracline (TC) prevents the formation of C99 fragment of APP; therefore, it also prevents the death of neuronal cells by supressing the Aβ formation. The efficacy of TPs to protect MC65 cells was determined in the absence of tetracline, while in the presence of tetracline the toxicity of TP compounds was observed. The median effective concentration (EC_{50}), median toxic concentration (TD_{50}), and therapeutic index (TI, ratio of TD_{50} and EC_{50}) of tricyclic pyrones (**10** - **14**) are listed in **Table 1.1**.

The results from MC65 cells protection assay showed that the compounds containing *p*-hydroxy -phenyl, and -naphthyl groups have higher anti-Alzheimer potency than others. 3-Methoxy-4-hydroxy aryl analog **10A** showed submicromolar potency, and the substitution of 3-methoxy in **10A** with nitro or bromo (**10B**, **10C**) led to the reduction of potency, while substitution with fluoro (**10D**) provided a compound with nanomolar activity. Other 3,4-disubstituted (**10E** – **10G**) as well as 3,4,5-trisubstituted (**10H**) analogs were found inferior to compound **10A**. Replacement of 3-methoxy with hydrogen in **10A** also provided a candidate (**11C**) with nanomolar efficacy. Among monosubstituted aryl analogs, TPs with phenolic hydroxyl at ortho and meta (**11A** and **11B**) showed low micromolar potency but were inferior to *p*-hydroxyl analog **11C**. Conversion of the hydroxyl in **11C** to the methyhydroxyl (**11D**) slightly

Table 1.1: MC65 cells protection assay of tricyclic pyrones 10 – 14.

Compounds	EC_{50} (μM)	TD_{50} (μM)	TI	Compounds	EC_{50} (μM)	TD_{50} (μM)	TI
CP2 (9)	**0.120**	39.0	325	**11F**	3.24	37.3	11.5
10A	0.242	26.3	109	**11G**	2.77	>50	>18.1
10B	3.85	>50	>13.0	**11H**	6.41	39.4	6.15
10C	0.639	>50	>78.2	**11I**	0.769	>50	>65.0
10D	**0.067**	>50	>746	**11J**	4.36	38.2	8.76
10E	1.56	>50	>32.1	**11K**	2.79	48	17.2
10F	0.662	9.38	14.2	**11L**	>50	>50	----
10G	1.18	>50	>42.4	**12A**	**0.145**	13.7	94
10H	1.26	>50	>39.7	**12B**	0.198	26.4	133
11A	2.44	30.7	12.6	**12C**	0.621	15.3	24.6
11B	4.66	>50	>10.7	**12D**	0.586	18.2	31.1
11C	**0.070**	49.3	704	**13**	0.459	24.1	52.5
11D	**0.101**	>50	>495	**14A**	6.25	6.69	1.07
11E	24.50	>50	>2.04	**14B**	>50	8.35	----

diminished the potency. While, further lengthening of the hydroxyl in the form of ethyl ether (**11E**) significantly decreased the MC65 cells protection efficiency. Replacing the hydroxyl part in analog **11C** by hydrogen, methoxy, aldehdye, methyl ester, dimethyl amino, and chloro groups (**11F – 11K**) provided less potent analogs. Moreover, placement of cyano group (**11L**) significantly reduced the anti-Alzheimer potency. Analogous to the TPs with phenyl moieties,

the *p*-hydroxyl naphthyl analog **12A** showed highest potency among the compounds **12A – 12D**. Tricyclic pyrone amides **14A** and **14B** were significantly less effective than the amines analogs. Structure activity relationship of TPs indicated the necessity p-hydroxy aryl groups with 2° amine functionality for anti-Alzheimer activity.

Table 1.2: ACAT inhibition and ABCA1 gene modulation activity of tricyclic pyrones.

Compounds	IC_{50} ACAT inhibition (μM)	EC_{50} ABCA1 gene expression (μM)
CP2	1.2 ± 0.2	1.9 ± 0.1
10D	1.8 ± 0.03	2.2 ± 0.2
11C	0.3 ± 0.08	1.1 ± 0.1
11D	1.4 ± 0.2	2.5 ± 0.4
12A	0.8 ± 0.06	1.3 ± 0.1
CI-976	0.2 ± 0.1	0.6 ± 0.07

TP compounds **10D**, **11C**, and **11D** were identified more potent than earlier candidate **CP2** in MC65 cells protection assay, and compound **12A** also showed comparable activity with CP2. The most active analogs to protect MC65 cells along with CI-976, a well known ACAT inhibitor, were evaluated for ACAT inhibitory and ABCA1 modulation activities (**Table 1.2**) in MC65 cells. The ACAT inhibitory activity of the TPs was evaluated by measuring the intensity of fluorescence obtained from staining of cells incubated with mock-medium, TPs, and CI-976 in the presence of 22-[*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino]-23,24-bisnor-5-cholen-3-ol (NBD-cholesterol).[88] NBD-cholesterol fluoresces with lipids containing cholesterol ester (CE); inhibitory activity of the TPs was measured by comparing intensities of fluorescence of the mock

treated cells without the TPs. TP compounds showed low micromolar to submicromolar (0.3 to 1.8 μM) effectiveness, comparable with CI-976 to inhibit ACAT. The inhibition of ACAT will reduce the formation of cholesterol ester increasing the level of free cholesterol inside the cells, which then requires cholesterol efflux by increasing the cholesterol transporter gene ABCA1. Therefore, the observation of ABCA1 gene provides complementary information for the inhibition of ACAT. The modulation of ABCA1 gene by TPs was measured using gene expression assay.[89] TP analogs **10D**, **11C**, **11D**, **12A**, and **CP2** were also effective to upregulate the ABCA1 gene in low micromolar range. The ability of TPs to inhibit ACAT and upregulate ABCA1 gene was correlated with MC65 cells protection activity, but the inability of CI-976 to protect MC65 cells up to 50 μM indicates possibility of other mechanisms. Like **CP2**, other TP compounds may also disaggregate or/and block the formation of Aβ-oligomers leading to the protection of neuronal cells.[51] TPs may also be effective by promoting the efflux of cholesterol increasing the efficiency of cholesterol transporters. Other possible pathways of TPs for the neuronal cells protection are reduction of APOE ε4 or inhibition of β-secratase.

1.4.2 Anti-norovirus activity of tricyclic pyrones

Anti-norovirus activity was performed with quantitative reverse transcription-PCR (qRT-PCR) method with one-step Platinum qRT-PCR kit by observing norovirus genome in norovirus replicon harboring cells.[87,90] One day old norovirus harboring cells (HG23) were treated with different concentrations of each tricyclic pyrone compounds (0 [mock-DMSO] - 10 μM). Effective dose (EC_{50}) for reducing 50% of NV genome was analyzed with real time qRT-PCR after 24 h of treatment. Similarly, the toxic dose (TD_{50}) for for killing 50% of HG23 cells at 48 hours of post treatment was analyzed by using cytotoxicity assay kit (Promega, Madison, WI). The NV inhibitory activity of the TPs **15 – 35** along with their precursor amine **39**,

corresponding toxicities, and therapeutic indexes is listed in **Table 1.3**. Among TPs **15** – **24** containing 5-membered aryl heterocycles, compounds **19** and **23A** with pyrrolyl and imidazolyl moieties, respectively showed higher efficacy in low micromolar range. Similar potency was observed for 3-pyridinly analog **25**, while 4-pyridinyl analog **26** was found less active. Dialkylated analogs **21B – 23B** were found to have similar potency with corresponding mono alkylated analogs **21A – 23A**. 2-Quinolinyl and 4-quinolinyl analogs **27A**, **28A**, and **28F** were found to have increased anti-NV activity, compound **28A** being the most potent. Addition of methyl substituent at 6-position (**28F**) in 4-quinolinyl TP **28A** slightly reduced the activity, while addition of methyl, hydroxymethyl, acetoxymethyl, and trioxanyl moieties at 2-positions (**28B – 28E**) diminished the efficacy significantly. Similarly, addition of the methyl substituents at 4 and 6 -positions (**27B**, **27C**) in 2-quinolinly analog **27A** also lowered the efficacy. Other TPs with 6-quinolinyl analog **29** only showed moderate potency, while 8-quinolinyl analog **30** was found inactive. TP containing benzo[*h*]quinolinyl moiety **31** showed less potency than its quinolinyl analog **28A**. Conversion of the amine functionality in **28A** to its amide or ester analogs also provided the inferior candidates **32** and **33**, respectively. *p*-Hydroxyphenyl ester analog **34** was even inferior to 4-quinolinyl ester analog **33**, while *p*-methoxybenzyl imine analog **35** showed comparable efficacy with ester **33**. Tricyclic pyrone amine **39** was also found ineffective to inhibit NV replication. From structure activity relationships, the TPs containg pyrrolyl, imidazolyl, pyridinly, and quinolinyl moieties showed NV inhibitory activity in low micromolar range. Similar to the case in anti-Alzheimer activity, the 2° amine functionality was found more effective than amide and ester functionalities for anti-norovirus activity. The NV inhibitory activity of TPs may have been effective by inhibiting the cellular ACAT.

Table 1.3: Norovirus inhibitory activity of tricyclic pyrones.

Compounds	EC_{50} (μM)	TD_{50} (μM)	Therapeutic index (TI)	Compounds	EC_{50} (μM)	TD_{50} (μM)	Therapeutic index (TI)
15	5.00	----	----	**27B**	5.3	>200	>40
16	5.00	>200	>40	**27C**	8.1	83.7	10.3
17	7.00	>200	>28.5	**28A**	2.4	96.4	40.2
18	7.00	>200	>28.5	**28B**	8.2	ND	----
19	4.00	>200	>50	**28C**	9.5	ND	----
20	8.00	>200	>25	**28D**	9.7	ND	----
21A	5.00	>200	>40	**28E**	8.4	ND	----
21B	5.00	>200	>40	**28F**	3.4	61.2	18
22A	>10	>200	----	**29**	8.1	ND	----
22B	7.00	>200	>28.5	**30**	>10	>160	----
23A	4.00	>200	>50	**31**	5.3	>200	>40
23B	5.00	>200	>40	**32**	5.5	103.5	18.8
24	7.00	>200	>28.5	**33**	6.00	80	13.3
25	4.1	>200	>50	**34**	8.00	80	10
26	9.6	ND	----	**35**	6.00	>200	>33.3
27A	3.4	>200	>58.8	**39**	>10	>200	----

1.5 Conclusions

Tricyclic pyrones containing phenyl, naphthyl, heterocyclic, and dipeptidyl moieties were synthesized and evaluated for anti-Alzheimer and anti-norovirus activities. Several TPs with *p*-hydroxy -phenyl and -naphthyl showed sub-micromolar to nanomolar efficacy to protect MC65 cells against Aβ oligomers induced toxicity. The most active TPs in MC65 assay were also effective to inhibit ACAT and upregulate ABCA1 gene. Similarly, the tricyclic pyrones containing pyrrolyl, imidazolyl, pyridinyl, and quinolinyl moieties demonstrated effective inhibition of norovirus genome in low micromolar range. The secondary amine functionality was more effective than amide functionality for the efficacy against both disorders. High therapeutic index of tricyclic pyrones indicates higher potentiality of TPs to develop as drugs. Further pharmacokinetic studies or modifications of active TPs could generate drugs with required properties for the treatment of Alzheimer or/and norovirus.

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1.7 Experimental

General Methods: NMR spectra were obtained from 400-MHz and 200-MHz spectrometers (Varian Inc.), in $CDCl_3$, unless otherwise indicated, and reported in ppm. Infrared spectra were taken from a Nicolet 380 FT-IR instrument (Thermo Scientific) in solid forms and reported in cm^{-1}. Low-resolution mass spectra were taken from an API 2000-triple quadrupole ESI-MS/MS mass spectrometer (from Applied Biosystems). High-resolution Mass spectra were obtained from a LCT Premier (Waters Corp., Milford MA) time of flight mass spectrometer. The instrument was operated at 10,000 resolution (W mode) with dynamic range enhancement that attenuates large intensity signals. The cone voltage was 60 eV. Spectra were acquired at 16666 Hz pusher frequency covering the mass range 100 to 1200 μ and accumulating data for 2 seconds per cycle. Mass correction for exact mass determinations was made automatically with the lock mass feature in the MassLynx data system. A reference compound in an auxiliary sprayer is sampled every third cycle by toggling a "shutter" between the analysis and reference needles. The reference mass is used for a linear mass correction of the analytical cycles. Chemicals were purchased from Fisher Scientific, Aldrich Chemical Co., Chem-Impex International, and VWR. CI-976 was purchased from Sigma Chemical Company.

MC65 cell assay:[50] MC65 cells were grown in the presence of 1 μg/mL tetracycline (TC), and cell toxicity was induced via the formation of APP in the absence of tetracycline (TC) by generating C99, a precursor of APP. Cells were washed extensively, and plated at a density of 1.2 to 1.5 x 10^5 cells/cm^2 in Opti-minimal essential medium (MEM; without phenol-red) from Gibco/BRL (Carlsbad, CA, USA) without serum and without TC. Different concentrations of each TP compound were added and cell viabilities were assessed using a colorimetric MTT assay. The cytotoxicity was determined using MTT assay in the presence of TC, the results of

which were comparable with data obtained using counts of viable cells based on trypan blue exclusion and the live/dead assay.

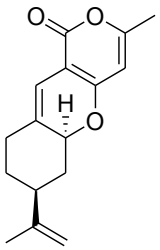
Assay for ACAT activity:[88] Intracellular ACAT activity by the treatment with each compound was measured using staining of lipid droplets with NBD-cholesterol. MC65 or Huh-7 cells grown in 96-well plates were treated with each compound at the concentration ranging 0.01 to 20 μg/ml or mock-medium for 20 min. After initial incubation, the medium was replaced with 200 μl of medium containing 1 μg/ml NBD-cholesterol and the same treatment. Cells were further incubated for 48 hr, the lipid droplets were measured by the intensity of fluorescence on a fluorescent plate reader (FLx800, Bioteck) equipped with 485 nm excitation and 535 nm emission filters. Relative ACAT activity by each treatment was calculated by the comparison of fluorescence signals to mock-medium treatment. **CI-976**, a known ACAT inhibitor, was used as a control.

Detection of ABCA1 mRNA levels:[89] The inhibition of ACAT increases the level of free cholesterol, subsequently induce oxidation of cholesterol (oxycholesterol) and activate the LXR pathway. Therefore, the induction of cholesterol efflux-related proteins such as ABCA1 in MC65 and Huh-7 cells was examined. Cells grown in 6-well plates were incubated with the same compounds or mock-medium as above for 24 hr, and the expression of ABCA1 gene was assessed with the Gene Expression Assay (Applied Biosystems) after total RNA was extracted. The mRNA levels by each treatment were compared to those by mock-medium treatment. The known ACAT inhibitor, CI-976 was also used as a control in this study.

Anti-norovirus activity of tricyclic pyrones:[87,90] The anti-noroviral effects of each compounds were examined in NV replicon-harboring cells (HG23 cells). Briefly, One-day old**,** 80 - 90% confluent HG23 cells were treated with varying concentrations of each compound (0 [mock-

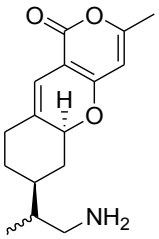
DMSO] - 10 μM) to examine their effects on the replication of NV. At 48 hrs of treatment, the NV genome was analyzed with real time qRT-PCR. The EC_{50} of each compound for NV genome levels was determined at 48 hrs post-treatment. HG23 cells were also treated with varying concentrations (0 [mock-DMSO] - 200 μM) of each compound to assess the cytotoxic effects. Cell cytotoxicity assay kit (Promega, Madison, WI) was used to calculate the median toxic dose (TD_{50}) at 48 hrs of treatment.

(5a*S*,7*S*)-7-Isoprepenyl-3-methyl-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (7)



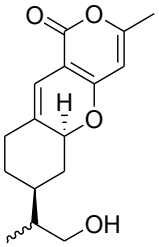
A mixture of 10 g (79.36 mmol) of 4-hydroxypyrone **37** and 4.56 g (39.68 mmol) of L-proline, and 11.9 g (79.36 mmol) of perillaldehyde (**38**) in 500 mL of ethyl acetate was refluxed for 30 h. Then the mixture was diluted with ethyl acetate (400 mL), washed with brine (300 mL x 4), concentrated to 300 mL, and crystallized at -0 °C to get 15.9 g (78%) of compound **7**, whose ^{1}H and ^{13}C NMR spectra are identical to that reported.[49]

(5a*S*,7*S*)-7-[(1*R*) and (1*S*)-2-Amino-1-methylethyl)-3-methyl-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (39)



10 mL (10 mmol) of BH_3•THF complex (1.0 M in THF) was added dropwise to a cold (0 ^oC) solution of 5.0 g (19.4 mmol) of compound **7** in 100 mL of THF, under argon. After stirring the solution at 0 ^oC for 2 h and 25 ^oC for 12 h, the borane solution was added to 3.3 g (29.2 mmol) of hydroxylamine-*O*-sulfonic acid via a cannula followed by the addition of 20 mL of chloroform. The reaction mixture was heated to reflux for 7 h, cooled to 25 ^oC, diluted with 300 mL of ethyl acetate, and extracted with 2 N HCl (100 mL x 2). The combined HCl layer was washed three times with ethyl acetate (100 mL each), basified carefully with 5% sodium carbonate until pH = 9 ~ 10, and extracted three times with dichloromethane. The combined dichloromethane layer was washed with brine, dried (anhydrous Na_2SO_4), and concentrated to give 2.7 g (50% yield) of compound **39**, whose ^1H and ^{13}C NMR spectra are identical to that reported.[10]

(5a*S*,7*S*)-7-[(1*R*) and (1*S*)-2-hydroxy-1-methylethyl)-3-methyl-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (40)

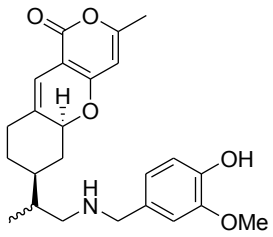


7.5 mL (7.5 mmol) of BH_3•THF complex (1.0 M in THF) was added dropwise to a cold (0 ^oC) solution of 4.1 g (14.8 mmol) of compound **7** in 50 mL of THF, under argon. After stirring the solution at 0 ^oC for 2 h and 25 ^oC for 12 h, solutions of 40 mL of 0.5% NaOH and 15 mL of 30%

H_2O_2 were added at 0 °C. After stirring for 2 h at 0 °C, the mixture was diluted with ethyl acetate (300 mL), washed with a solutions of $NaHCO_3$ and brine, separately; dried with $MgSO_4$, concentrated, and purified through silica gel column eluting with a gradient mixture of hexanes and ethyl acetate to get 3.6 g (82% yield) of alcohol **40**, whose ^1H and ^{13}C NMR spectra are identical to that reported.[10]

General procedure to synthesize tricyclic pyrones 10A – 11G, 11I – 13[56]

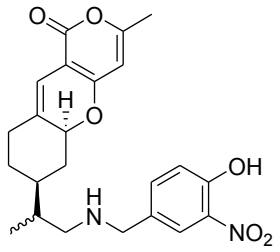
(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(4-hydroxy-3-methoxy)benzylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (10A)



A mixture of 250 mg (0.9 mmol) of amine **39** and 138 mg (0.9 mmol) of aldehyde **43A** in 10 mL of dry methanol was stirred for overnight. To this was added 10 drops of acetic acid followed by a solution of 141 mg (2.25 mmol) of $NaBH_3CN$ in methanol. After stirring for 1 h, the mixture was diluted with 50 mL of 5% NH_4OH and extracted in dichloromethane (100 x 3). The combined organic layer was washed with brine, dried with $MgSO_4$, concentrated, and purified through silica gel column using a gradient mixture of dichloromethane and methanol as eluent to get 236 mg (63% yield) of **10A** as a solid. M.p. 71 – 74 ^oC; FTIR (solid) ν 3600 - 3100 (b, w), 2900, 2866, 1693, 1560, 1506, 1443, 1263, 1224, 1142, 807; ^1H NMR δ 6.81 (s, 1 H), 6.73 (d, *J* = 8.4 Hz, 1 H), 6.68 (d, *J* = 8.4 Hz, 1 H), 5.95 (s, 1 H), 5.64 (s, 1 H), 4.99 – 4.90 (m, 1 H), 3.71 (s, 3 H), 3.67 (s, 2 H), 2.58 (dd, *J* = 11.3, 4.0 Hz, 1 H), 2.47 - 2.37 (m, 1 H), 2.33 (d, *J* = 13.6 Hz, 1 H), 2.10 (s, 3 H), 1.99 – 1.81 (m, 2 H), 1.69 – 1.36 (m, 4 H), 1.20 – 0.95 (m, 1 H), 0.83 and

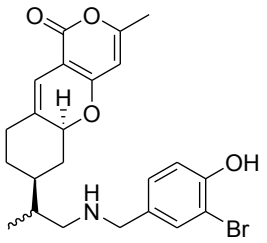
0.82 (2 d, J = 6.6 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.31, 163.29, 162.6, 161.5, 147.1, 145.3, 132.7, 130.3, 121.1, 114.8, 111.3, 108.9, 99.8, 97.2, 79.5, 79.4, 55.6, 55.6, 53.7, 52.6, 52.5, 39.0, 38.5, 38.4, 37.0, 36.9, 36.5, 32.2, 32.1, 30.8, 28.2, 20.0, 14.5, 14.4**;** MS (electrospray ionization) m/z 412.1 ($M+H^+$), 276.5, 137.3; HRMS calcd for $C_{24}H_{30}NO_5^+$ ($M+H^+$) 412.2124, found 412.2124 (100%).

(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(4-hydroxy-3-nitro)benzylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (10B)



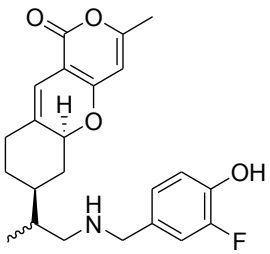
From 85 mg (0.31 mmol) of amine **39** and 52 mg (0.31 mmol) of aldehyde **43B**, 89 mg (68% yield) of **10B** was obtained as a solid. M.p. 76 – 78 ^oC; FTIR (solid) ν 3400 - 3200 (b, w), 2932, 1693, 1615, 1566, 1534, 1509, 1447, 1334, 1232, 1143, 819, 761; ^1H NMR δ 8.04 (d, J = 1.4 Hz, 1 H), 7.56 (dd, J = 8.6, 2.0 Hz, 1 H), 7.09 (d, J = 8.6 Hz, 1 H), 6.02 (s, 1 H), 5.68 (s, 1 H), 5.11 – 4.95 (m, 1 H), 3.74 (s, 2 H), 2.64 – 2.49 (m, 1 H), 2.49 – 2.33 (m, 2 H), 2.16 (s, 3 H), 2.09 – 1.86 (m, 2 H), 1.77 – 1.37 (m, 4 H), 1.33 – 1.02 (m, 1 H), 0.89 and 0.88 (2 d, J = 6.6 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.4, 163.3, 162.7, 161.6, 154.3, 137.7, 133.4, 133.2, 132.8, 123.9, 120.1, 109.2, 99.9, 97.4, 79.7, 79.6, 53.1, 53.0, 52.7, 39.3, 38.7, 38.5, 37.9, 37.7, 36.8, 32.5, 32.3, 31.1, 28.6, 20.2, 14.9, 14.6; MS (electrospray ionization) m/z 427.5 ($M+H^+$), 276.3, 139.1; HRMS calcd for $C_{23}H_{27}N_2O_6^+$ ($M+H^+$) 427.1869, found 427.1880 (100%).

(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(3-bromo-4-hydroxy)benzylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (10C)



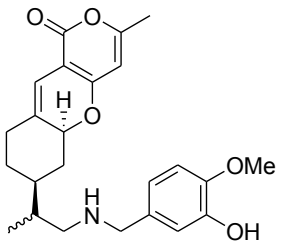
From 85 mg (0.31 mmol) of amine **39** and 62 mg (0.31 mmol) of aldehyde **43C**, 80 mg (56% yield) of **10C** was obtained as a solid. M.p. 67 – 68 ^{o}C; FTIR (solid) ν 3550 - 3150 (b, w), 2925, 1681, 1564, 1513, 1447, 1422, 1293, 1232, 1147, 1047, 822, 763, 669; ^{1}H NMR δ 7.45 (s, 1 H), 7.16 (d, *J* = 8.0 Hz, 1 H), 6.95 (d, *J* = 8.2 Hz, 1 H), 6.07 (s, 1 H), 5.71 (s, 1 H), 5.10 – 5.02 (m, 1 H), 3.71 (s, 2 H), 2.64 – 2.56 (m, 1 H), 2.50 – 2.41 (m, 2 H), 2.19 (s, 3 H), 2.08 – 1.93 (m, 2 H), 1.74 – 1.46 (m, 4 H), 1.30 – 1.05 (m, 1 H), 0.91 and 0.90 (2 d, *J* = 6.8 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.50, 163.47, 162.8, 161.7, 151.9, 133.0, 132.0, 129.1, 116.4, 110.5, 109.3, 100.0, 97.6, 79.8, 79.7, 53.2, 53.1, 39.4, 38.8, 38.7, 37.8, 37.7, 36.9, 32.6, 32.4, 31.2, 28.6, 20.3, 14.9, 14.7; MS (electrospray ionization) m/z 462.1 (M+2), 459.9 ($M+H^+$), 276.3, 115.1; HRMS calcd for $C_{23}H_{27}NO_4Br^+$ ($M+H^+$) 460.1123, found 460.1146.

(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(3-fluoro-4-hydroxy)benzylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (10D)



From 85 mg (0.31 mmol) of amine **39** and 44 mg (0.31 mmol) of aldehyde **43D**, 80 mg (65% yield) of **10D** was obtained as a solid. M.p. 90 – 92 ^{o}C; FTIR (solid) ν 3500 - 3100 (b, w), 2929, 1686, 1566, 1517, 1447, 1289, 1233, 1203, 1146, 1007, 860, 763; ^{1}H NMR δ 6.98 (dd, *J* = 11.6, 1.6 Hz, 1 H), 6.94 – 6.84 (m, 2 H), 6.07 (s, 1 H), 5.71 (s, 1 H), 5.10 – 4.99 (m, 1 H), 3.67 (s, 2 H), 2.66 – 2.59 (m, 1 H), 2.51 – 2.41 (m, 2 H), 2.19 (s, 3 H), 2.08 – 1.92 (m, 2 H), 1.73 – 1.44 (m, 4 H), 1.30 – 1.06 (m, 1 H), 0.92 and 0.91 (2 d, *J* = 6.8 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.52, 163.49, 162.8, 161.8, 152.9, 150.5, 143.9, 143.7, 132.9, 124.8, 118.4, 116.1, 115.9, 109.4, 100.0, 97.6, 79.8, 79.7, 53.5, 53.2, 53.1, 39.3, 38.9, 38.8, 37.5, 37.4, 36.9, 32.5, 32.4, 31.1, 28.5, 20.3, 14.8, 14.7; MS (electrospray ionization) m/z 400.1 ($M+H^+$), 276.2, 147.4, 139.0; HRMS calcd for $C_{23}H_{27}NO_4F^+$ ($M+H^+$) 400.1924, found 400.1924 (100%).

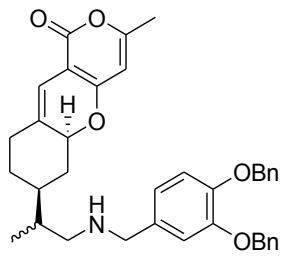
(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(3-hydroxy-4-methoxy)benzylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (10E)



From 85 mg (0.31 mmol) of amine **39** and 47 mg (0.31 mmol) of aldehyde **43E**, 89 mg (70% yield) of **10E** was obtained as a solid. M.p. (TFA salt) 85 – 87 ^{o}C; FTIR (TFA salt; solid) ν 3500 - 3200 (b, w), 2939, 1671, 1567, 1513, 1444, 1278, 1198, 1181, 1134, 1028, 810, 720; ^{1}H NMR δ 6.95 (s, 1 H), 6.82 – 6.72 (m, 2 H), 6.00 (s, 1 H), 5.67 (d, *J* = 4.4 Hz, 1 H), 5.01 (td, *J* = 10.4, 4.7 Hz, 1 H), 3.82 (s, 3 H), 3.74 (s, 2 H), 2.62 (dd, *J* = 11.9, 6.0 Hz, 1 H), 2.51 – 2.43 (m, 1 H), 2.38 (d, *J* = 14.4 Hz, 1 H), 2.15 (s, 3 H), 2.03 – 1.88 (m, 2 H), 1.78 – 1.37 (m, 4 H), 1.31 – 0.99 (m, 1 H), 0.88 and 0.87 (2 d, *J* = 6.4 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.4,

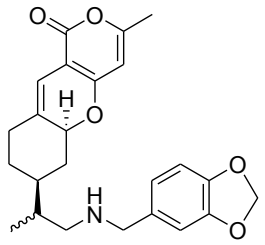
162.7, 161.6, 146.6, 146.1, 132.8, 130.9, 120.2, 115.3, 110.9, 109.1, 99.9, 97.4, 79.6, 79.5, 56.0, 55.98, 53.0, 52.1, 52.0, 39.2, 38.4, 38.2, 36.9, 36.8, 36.4, 32.4, 32.2, 31.0, 28.0, 20.2, 14.5, 14.4; MS (electrospray ionization) m/z (negative Mode) 410.3 (M-1), 274.3, 121.3; HRMS calcd for $C_{24}H_{30}NO_5^+$ ($M+H^+$) 412.2124, found 412.2115 (100%).

(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(3,4-di(benzyloxy)benzylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (10F)



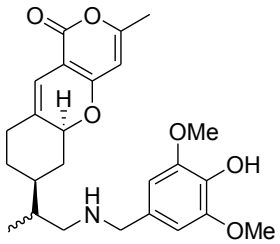
From 85 mg (0.31 mmol) of amine **39** and 99 mg (0.31 mmol) of aldehyde **43F**, 117 mg (66% yield) of **10F** was obtained as a solid. M.p. (TFA salt) 83 – 85 ^oC; FTIR (solid) ν 3400 (b, w), 2870, 1674, 1530, 1405, 1265, 1200, 1173, 1008, 821, 797, 719, 737, 696; ^1H NMR δ 7.46 (d, *J* = 7.6 Hz, 2 H), 7.43 (d, *J* = 7.6 Hz, 2 H), 7.39 - 7.26 (m, 6 H), 7.09 (d, *J* = 6.4 Hz, 1 H), 690 – 683 (m, 2 H), 6.05 (s, 1 H), 5.66 and 5.62 (2d, 1 H, two diastereomers), 5.18 (s, 2 H), 5.11 (s, 2 H), 5.09 – 4.99 (m, 1 H), 381 - 3.71 (m, 2 H), 2.63 – 2.53 (m, 1 H), 2.49 – 2.35 (m, 2 H), 2.13 (s, 3 H), 2.04 – 1.88 (m, 2 H), 1.78 – 1.40 (m, 4 H), 1.27 – 1.00 (m, 1 H), 0.90 and 0.88 (2 d, *J* = 6.8 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.3, 263.3, 162.6, 161.6, 149.0, 148.4, 148.37, 137.3, 132.6, 128.5, 128.5, 127.8, 127.4, 127.3, 121.7, 115.2, 115.1, 114.8, 109.2, 99.8, 97.3, 79.5, 79.4, 71.2, 71.1, 53.1, 53.0, 52.0, 39.1, 38.4, 38.1, 36.9, 36.7, 36.3, 32.3, 32.1, 30.9, 28.2, 20.1, 14.6, 14.3; MS (electrospray ionization) m/z 578.7 ($M+H^+$), 181.2; HRMS calcd for $C_{37}H_{40}NO_5^+$ ($M+H^+$) 578.2906, found 578.2921 (100%).

(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(benzo[d][1,3]dioxol-5-ylmethylamino)benzylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (10G)



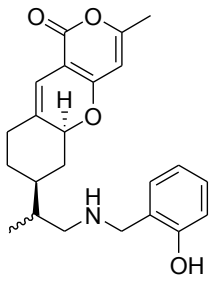
From 85 mg (0.31 mmol) of amine **39** and 46.5 (0.31 mmol) of aldehyde **43G**, 90 mg (71% yield) of **10G** was obtained as a solid. M.p. (HCl salt) 107 – 110 ^{o}C; FTIR (HCl salt; solid) ν 3367 (b, w), 2928, 1682, 1564, 1446, 1250, 1035, 923, 810, 723; ^{1}H NMR δ 6.84 (s, 1 H), 6.75 (s, 2 H), 6.05 (s, 1 H), 5.93 (s, 2 H), 5.69 (s, 1 H), 5.08 – 4.99 (m, 1 H), 3.69 (s, 2 H), 2.62 – 2.54 (m, 1 H), 2.48 – 2.38 (m, 2 H), 2.18 (s, 3 H), 2.06 – 1.87 (m, 2 H), 1.73 – 1.44 (m, 4 H), 1.37 - 1.03 (m, 1 H), 0.89 and 0.88 (2 d, *J* = 7.0 Hz, 3 H, CH_3 for two diastereomers); ^{13}C NMR δ 163.4, 163.36, 162.7, 161.6, 147.9, 146.7, 134.1, 133.0, 132.93, 121.42, 121.41, 109.3, 108.8, 108.2, 101.1, 99.9, 97.5, 79.8, 79.7, 54.0, 52.93, 52.85, 39.4, 38.8, 38.6, 37.8, 37.7, 36.8, 32.5, 32.4, 31.2, 28.5, 20.3, 14.8, 14.7; MS (electrospray ionization) m/z 410.3 ($M+H^+$), 315.0, 214.4, 115.1; HRMS calcd for $C_{24}H_{28}NO_5^+$ ($M+H^+$) 410.1967, found 410.1958 (100%).

(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(4-hydroxy-3,5-dimethoxy)benzylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (10H)



From 85 mg (0.31 mmol) of amine **39** and 56 mg (0.31 mmol) of aldehyde **43H**, 103 mg (76% yield) of **10H** was obtained as a solid. M.p. (TFA salt) 108 – 110 ^{o}C; FTIR (TFA salt; solid) ν 3500 - 314 (b, w), 2836, 1677, 1566, 1521, 1450, 1431, 1332, 1200, 1115, 831, 720; ^{1}H NMR δ 6.59 (s, 2 H), 6.01 (s, 1 H), 5.67 (s, 1 H), 5.02 (d, *J* = 9.4 Hz, 1 H), 3.83 (s, 6 H), 3.73 (s, 2 H), 2.72 – 2.55 (m, 1 H), 2.55 – 2.29 (m, 2 H), 2.15 (s, 3 H), 2.07 – 1.80 (m, 2 H), 1.80 – 1.36 (m, 4 H), 1.32 – 1.00 (m, 1 H), 0.89 (d, *J* = 6.2 Hz, 3 H, CH_3); ^{13}C NMR δ 163.33, 163.32, 162.6, 161.6, 147.3, 134.2, 132.7, 129.4, 109.2, 105.3, 99.9, 97.4, 79.6, 79.5, 56.4, 54.0, 52.5, 39.2, 38.7, 38.5, 37.1, 37.0, 36.7, 32.4, 32.2, 31.0, 28.4, 20.2, 14.8, 14.6; MS (electrospray ionization) m/z (Negative Mode) 440.3 (M-1), 274.3, 230.2; HRMS calcd for $C_{25}H_{32}NO_6^+$ ($M+H^+$) 442.2230, found 442.2236 (100%).

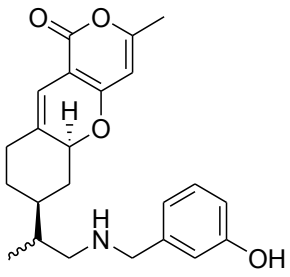
(5a*S*,7*S*)-3-Methyl-7-[(1*R*) and (1*S*)-1-(2-hydroxybenzylamino)propan-2-yl]-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (11A)



From 85 mg (0.31 mmol) of amine **39** and 38 mg (0.31 mmol) of aldehyde **44A**, 75 mg (64% yield) of **11A** was obtained as a solid. M.p. 73 – 75 ^{o}C; FTIR (solid) ν 3500 - 3090 (b, w), 2852, 1701, 1638, 1566, 1448, 1419, 1256, 1232, 1146, 817, 754; ^{1}H NMR δ 7.18 (t, *J* = 7.6 Hz, 1 H), 7.00 (d, *J* = 7.2 Hz, 1 H), 6.84 (d, *J* = 8.4 Hz, 1 H), 6.79 (t, *J* = 7.4 Hz, 1 H), 6.08 (s, 1 H), 5.71 (t, *J* = 0.8 Hz, 1 H), 5.11 – 5.02 (m, 1 H), 3.99 (s, 2 H), 2.73 - 2.64 (m, 1 H), 2.60 – 2.51 (m, 1 H), 2.46 (d, *J* = 14.0 Hz, 1 H), 2.19 (s, 3 H), 2.09 – 1.92 (m, 2 H), 1.73 – 1.45 (m, 4 H), 1.31 – 1.05 (m, 1H), 0.95 and 0.94 (2 d, *J* = 6.8 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.4,

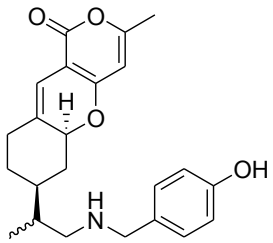
162.7, 161.7, 158.3, 132.6, 129.0, 128.5, 122.7, 119.2, 116.5, 109.5, 99.9, 97.5, 79.6, 79.5, 53.2, 52.9, 52.9, 39.3, 38.8, 38.7, 37.6, 37.57, 36.8, 32.4, 32.3, 31.1, 28.5, 20.3, 14.8, 14.7; MS (electrospary ionization) m/z 382.4 ($M+H^+$), 276.5, 247.4, 139.1; HRMS calcd for $C_{23}H_{28}NO_4^+$ ($M+H^+$) 382.2018, found 382.2033 (100%).

(5a*S*,7*S*)-3-Methyl-7-[(1*R*) and (1*S*)-1-(3-hydroxybenzylamino)propan-2-yl]-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (11B)



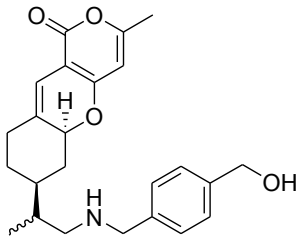
From 85 mg (0.31 mmol) of amine **39** and 38 mg (0.31 mmol) of aldehyde **44B**, 59 mg (50% yield) of **11B** was obtained as a solid. M.p. (TFA salt) 55 - 57°C; FTIR (TFA salt; solid) ν 3500 - 3100 (b, w), 2941, 2871, 1671, 1590, 1564, 1450, 1197, 1134, 797, 720, 695; ^{1}H NMR δ 7.14 (t, *J* = 8.0 Hz, 1 H), 6.78 (d, *J* = 7.2 Hz, 1 H), 6.77 (s, 1 H), 6.73 (d, *J* = 8.8 Hz, 1 H), 6.03 (s, 1 H), 5.71 (d, *J* = 2 Hz, 1 H), 5.05 – 4.96 (m, 1 H), 3.71 (s, 2 H), 2.68 – 2.60 (m, 1 H), 2.52 – 2.44 (m, 1 H), 2.40 (d, *J* = 13.2 Hz, 1 H), 2.18 (s, 3 H), 2.05 - 1.87 (m, 2 H), 1.74 – 1.40 (m, 4 H), 1.34 - 1.02 (m, 1 H), 0.88 (d, *J* = 6.6, Hz, 3 H, CH_3); ^{13}C NMR δ 163.62, 163.60, 163.0, 161.8, 157.2, 140.7, 132.9, 129.8, 120.0, 115.7, 115.0, 109.2, 100.1, 97.5, 79.8, 79.7, 53.9, 53.0, 52.9, 39.3, 38.7, 38.6, 37.3, 37.2, 36.7, 32.5, 32.3, 31.1, 28.3, 20.3, 14.7, 14.6; MS (electrospray ionization) m/z 404.3 ($M+Na^+$), 382.2 ($M+H^+$), 139.1, 107.1; HRMS calcd for $C_{23}H_{28}NO_4^+$ ($M+H^+$) 382.2018, found 382.2000 (100%).

(5a*S*,7*S*)-3-Methyl-7-[(1*R*) and (1*S*)-1-(4-hydroxybenzylamino)propan-2-yl]-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (11C)



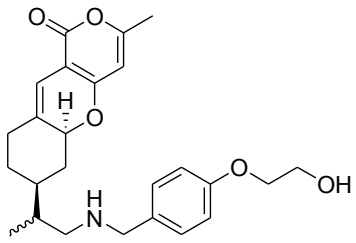
From 85 mg (0.31 mmol) of amine **39** and 38 mg (0.31 mmol) of aldehyde **44C**, 80 mg (68% yield) of **11C** was obtained as a solid. M.p. 75 – 78 ^{o}C; FTIR (solid) ν 3276 (b, w), 1682, 1637, 1565, 1514, 1446, 1231, 1146, 879, 762; ^{1}H NMR δ 7.16 (d, *J* = 8.0 Hz, 2 H), 6.76 (d, *J* = 8.4 Hz, 2 H), 6.06 (s, 1 H), 5.71 (s, 1 H), 5.09 – 4.99 (m, 1 H), 3.70 (s, 2 H), 2.66 – 2.57 (m, 1 H), 2.51 – 2.39 (m, 2 H), 2.19 (s, 3 H), 2.07 – 1.90 (m, 2 H), 1.73 – 1.47 (m, 4 H), 1.29 – 1.08 (m, 1 H), 0.90 and 0.89 (2 d, *J* = 6.4 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.7, 163.6, 163.0, 161.8, 156.5, 133.0, 129.9, 129.7, 115.9, 109.1, 100.1, 97.5, 79.7, 79.65, 53.5, 52.8, 52.7, 39.2, 38.8, 38.7, 37.2, 37.1, 36.8, 32.4, 32.3, 31.0, 28.4, 20.2, 14.7, 14.6; MS (electrospray ionization) m/z 382.4 ($M+H^+$), 276.5; HRMS calcd for $C_{23}H_{28}NO_4^+$ ($M+H^+$) 382.2018, found 382.2013.

(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(4-hydroxymethyl)benzylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (11D)



From 170 mg (0.62 mmol) amine **39** and 84 mg (0.62 mmol) of aldehyde **44D**, 150 mg (61% yield) of **11D** was obtained as a solid. M.p. (TFA salt) 85 – 87 ^{o}C; FTIR (TFA salt; solid) ν 3376 (b, w), 2909, 1670, 1563, 1443, 1424, 1197, 1172, 1134, 797, 719, 702; ^{1}H NMR δ 7.36 – 7.28 (m, 4 H), 6.05 (s, 1 H), 5.70 (s, 1 H), 5.08 – 4.98 (m, 1 H), 4.67 (s, 2 H), 3.77 (s, 2 H), 2.65 – 2.54 (m, 1 H), 2.49 – 2.39 (m, 2 H), 2.18 (s, 3 H), 2.06 – 1.90 (m, 2 H), 1.72 – 1.44 (m, 4 H), 1.36 – 1.04 (m, 1 H), 0.89 and 0.88 (2 d, J = 6.8 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.4, 163.4, 162.8, 161.7, 140.1, 139.6, 133.0, 132.95, 128.5, 128.5, 127.3, 109.3, 100.0, 97.6, 79.9, 79.7, 65.2, 54.0, 53.9, 53.1, 53.1, 39.4, 38.9, 38.7, 37.8, 37.7, 36.9, 32.6, 32.4, 31.2**,** 28.5, 20.3, 14.8, 14.7; MS (electrospray ionization) m/z 418.5 ($M+Na^+$), 396.3 ($M+H^+$), 378.6, 245.2; HRMS calcd for $C_{24}H_{30}NO_4^+$ ($M+H^+$) 396.2175, found 396.2183 (100%).

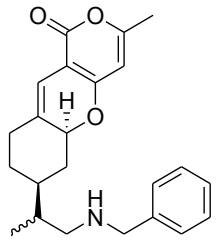
(5aS,7S)-3-Methyl-7-{(1*R*) and (1*S*)-1-[4-(2-hydroxyethoxy)benzylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (11E)



From 85 mg (0.31 mmol) of amine **39** and 87 mg (0.31 mmol) of aldehyde **44E**, 72 mg (55% overall yield in two steps) of **11E** was obtained as a solid. (Note: To product **11E'** obtained from reductive amination, deprotection of TBDMS with n-Bu_4NF was done in THF at 25 ^{o}C). M.p. (TFA salt) 68 – 72 ^{o}C; FTIR (TFA salt; solid) ν 3370 (b, w), 1668, 1559, 1508, 1417, 1253, 1197, 1173, 1136, 831, 798, 720; ^{1}H NMR δ 7.19 (d, J = 8.4 Hz, 2 H), 6.83 (d, J = 8.4 Hz, 2 H), 6.01 (s, 1 H), 5.68 (s, 1 H), 5.06 – 4.95 (m, 1 H), 4.02 (t, J = 4.4 Hz, 2 H), 3.89 (t, J = 4.2 Hz, 2 H), 3.67 (s, 2 H), 2.62 – 2.50 (m, 1 H), 2.46 – 2.34 (m, 2 H), 2.14 (s, 3 H), 2.03 – 1.87 (m, 2 H),

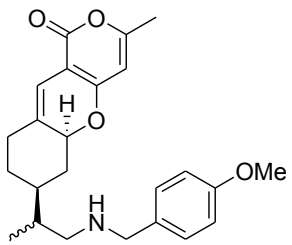
1.69 – 1.42 (m, 4 H), 1.33 – 1.01 (m, 1 H), 0.85 (d, J = 6.8 Hz, 3 H, CH_3); ^{13}CNMR δ 163.4, 163.3, 162.6, 161.5, 157.9, 132.9, 132.7, 129.4, 114.5, 109.1, 99.9, 97.4, 79.7, 79.6, 69.4, 61.2, 53.5, 53.0, 52.9, 39.2, 38.7, 38.6, 37.6, 37.5, 36.8, 32.4, 32.3, 31.0, 28.4, 20.1, 14.7, 14.6; MS (electrospray ionization) m/z 427.2 (M+2), 426.3 ($M+H^+$), 151.1, 107.1; HRMS calcd for $C_{25}H_{32}NO_5^+$ ($M+H^+$) 426.2280, found 426.2260.

(5a*S*,7*S*)-3-Methyl-7-[(1*R*) and (1*S*)-1-(benzylamino)propan-2-yl]-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (11F)



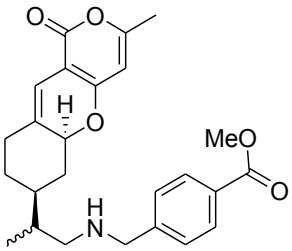
From 85 mg (0.31 mmol) of amine **39** and 33 mg (0.31 mmol) of aldehyde **44F**, 70 mg (62% yield) of **11F** was obtained as a solid. M.p. (TFA salt) 86 – 90 ^{o}C; FTIR (solid) ν 3340 (w), 1658, 1572, 1161 (s), 1133, 719, 702; ^{1}H NMR δ 7.45 – 7.20 (m, 5 H), 6.05 (s, 1 H), 5.70 (s, 1 H), 5.15 – 4.95 (m, 1 H), 3.78 (s, 2 H), 2.65 – 2.55 (m, 1 H), 2.52 – 2.38 (m, 2 H), 2.18 (s, 3 H), 2.08 – 1.89 (m, 2 H), 1.77 – 1.45 (m, 4 H), 1.37 – 1.05 (m, 1 H), 0.89 (d, J = 7.2 Hz, 3 H, CH_3); ^{13}C NMR δ 163.4, 163.4, 162.8, 161.6, 140.5, 133.0, 132.97, 128.6, 128.2, 127.1, 109.2, 100.0, 97.5, 79.8, 79.7, 54.3, 53.3, 53.2, 39.4, 38.8, 38.6, 37.8, 37.7, 36.8, 32.5, 32.4, 31.1, 28.4, 20.3, 14.8, 14.7; MS (electrospray ionization) m/z 388.4 ($M+Na^+$), 366.4 ($M+H^+$), 139.1; HRMS calcd for $C_{23}H_{28}NO_3^+$ ($M+H^+$) 366.2069, found 366.2078 (100%).

(5a*S*,7*S*)-3-Methyl-7-[(1*R*) and (1*S*)-1-(4-methoxybenzylamino)propan-2-yl]-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (11G)



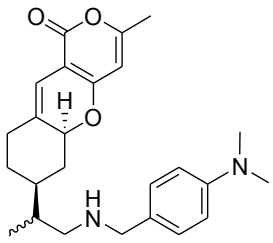
From 85 mg (0.31 mmol) of amine **39** and 42 mg (0.31 mmol) of aldehyde **44G**, 82 mg (67% yield) of **11G** was obtained as a solid. M.p. (TFA salt) 90 - 92°C; FTIR (TFA salt; solid) ν 3350 (w), 1667, 1563, 1252, 1197, 1177, 1135, 829, 798, 719; ^{1}H NMR δ 7.23 (d, *J* = 8.4 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 6.04 (s, 1 H), 5.69 (d, *J* = 0.8 Hz, 1 H), 5.08 – 4.96 (m, 1 H), 3.79 (s, 3 H), 3.71 (s, 2 H), 2.62 – 2.51 (m, 1 H), 2.48 – 2.36 (m, 2 H), 2.17 (s, 3 H), 2.05 – 1.86 (m, 2 H), 1.71 – 1.44 (m, 4 H), 1.27 – 1.04 (m, 1 H), 0.88 and 0.87 (2 d, *J* = 6.6 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.4, 163.37, 162.7, 161.6, 158.8, 132.9, 132.2, 129.5, 113.9, 109.1, 99.9, 97.4, 79.8, 79.7, 55.4, 53.6, 53.0, 52.9, 39.3, 38.7, 38.6, 37.7, 37.6, 36.8, 32.5, 32.4, 31.1, 28.4, 20.3, 14.8, 14.6; MS (electrospray ionization) m/z 396.4 ($M+H^+$), 121.1; HRMS calcd for $C_{24}H_{30}O_4N^+$ ($M+H^+$) 396.2175, found 396.2180 (100%).

(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(4-methoxycarbonyl)benzylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (11I)



From 85 mg (0.31 mmol) of amine **39** and 51 mg (0.31 mmol) of aldehyde **44I**, 88 mg (67% yield) of **11I** was obtained as a solid. M.p. (HCl salt) 117 – 120 ^{o}C; FTIR (HCl salt; solid) ν 3329 (b, w), 2925, 1716, 1566, 1434, 1280, 1107, 761; ^{1}H NMR δ 7.98 (d, *J* = 8.0 Hz, 2 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 6.04 (s, 1 H), 5.69 (s, 1 H), 5.07 – 4.98 (m, 1 H), 3.90 (s, 3 H), 3.82 (s, 2 H), 2.62 – 2.53 (m, 1 H), 2.48 – 2.38 (m, 2 H), 2.17 (s, 3 H), 2.06 – 1.89 (m, 2 H), 1.72 – 1.44 (m, 4 H), 1.35 – 1.04 (m, 1 H), 0.89 and 0.88 (2 d, *J* = 6.6 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 167.2, 163.4, 163.35, 162.7, 161.6, 146.1, 132.9, 129.8, 129.0, 128.0, 109.3, 99.9, 97.5, 79.8, 79.7, 53.9, 53.3, 53.2, 52.2, 39.3, 38.8, 38.7, 37.9, 37.8, 36.9, 32.5, 32.4, 31.1, 28.6, 20.2, 14.8, 14.7; MS (electrospray ionization) m/z 424.4 ($M+H^+$), 139.1; HRMS calcd for $C_{25}H_{30}NO_5^+$ ($M+H^+$) 424.2124, found 424.2114 (100%).

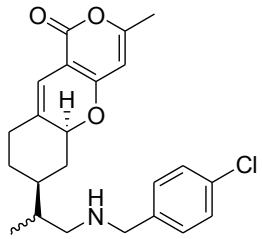
(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(4-dimethylamino)benzylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (11J)



From 85 mg (0.31 mmol) of amine **39** and 46 mg (0.31 mmol) of aldehyde **44J**, 80 mg (63% yield) of **11J** was obtained as a solid. M.p. (HCl salt) 132 – 136 ^{o}C; FTIR (HCl salt; solid) ν 3398 (b, w), 2928, 1701, 1635, 1560, 1439, 1236, 1138, 825, 669; ^{1}H NMR δ 7.29 (d, *J* = 8.4 Hz, 2 H), 6.69 (d, *J* = 8.4 Hz, 2 H), 6.05 (s, 1 H), 5.68 (s, 1 H), 5.16 – 4.98 (m, 1 H), 3.81 (s, 2 H), 2.92 (s, 6 H), 2.72 – 2.60 (m, 1 H), 2.58 – 2.46 (m, 1 H), 2.41 (d, *J* = 14.0 Hz, 1 H), 2.18 (s, 3 H), 2.06 – 1.92 (m, 2 H), 1.88 – 1.67 (m, 2 H), 1.67- 1.40 (m, 2 H), 1.35 – 1.03 (m, 1 H), 0.93 and 0.92 (2 d, *J* = 6.4 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.4, 162.7, 161.7, 150.5,

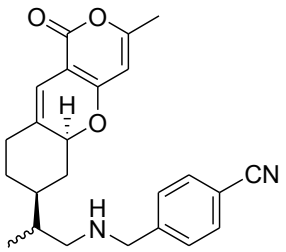
132.7, 130.3, 112.7, 109.4, 99.9, 97.5, 79.6, 79.5, 52.6, 51.3, 40.7, 40.4, 39.3, 38.3, 38.1, 36.5, 36.3, 32.4, 32.2, 31.1, 28.0, 20.3, 14.5, 14.4; MS (electrospray ionization) m/z 409.6 ($M+H^+$), 365.3, 207.1; HRMS calcd for $C_{25}H_{33}N_2O_3^+$ ($M+H^+$) 409.2491, found 409.2510 (100%).

(5a*S*,7*S*)-3-Methyl-7-[(1*R*) and (1*S*)-1-(4-chlorobenzylamino)propan-2-yl]-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (11K)



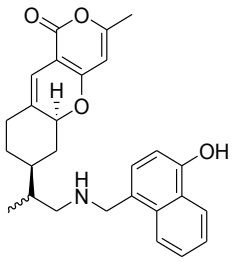
From 85 mg (0.31 mmol) of amine **39** and 43.5 mg (0.31 mmol) of aldehyde **44K**, 69 mg (56% yield) of **11K** was obtained as a solid. ^{1}H NMR δ 7.32 – 7.24 (m, 4 H), 6.06 (s, 1 H), 5.71 (s, 1 H), 5.09 - 5.00 (m, 1 H), 3.75 (s, 2 H), 2.62 – 2.54 (m, 1 H), 2.49 – 2.39 (m, 2 H), 2.19 (s, 3 H), 2.06 – 1.91 (m, 2 H), 1.71 – 1.46 (m, 4 H), 1.30 – 1.05 (m, 1 H), 0.90 and 0.89 (2 d, J = 6.6 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.43, 163.40, 162.7, 161.7, 139.0, 132.9, 132.8, 132.2, 129.6, 128.7, 109.3, 100.0, 97.6, 79.9, 79.7, 53.6, 53.2, 53.1, 39.4, 38.9, 38.7, 37.9, 37.8, 36.9, 32.6, 32.4, 31.2, 28.6, 20.3, 14.9, 14.7; MS (electrospray ionization) m/z 400.1 ($M+H^+$), 139.2, 124.9; HRMS calcd for $C_{23}H_{27}NO_3Cl^+$ ($M+H^+$) 400.1679, found 400.1667 (100%).

(5a*S*,7*S*)-3-Methyl-7-[(1*R*) and (1*S*)-1-(4-cyanobenzylamino)propan-2-yl]-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (11L)



From 85 mg (0.31 mmol) amine **39** and 41 mg (0.31 mmol) of aldehyde **44L**, 76 mg (63% yield) of **11L** was obtained as a solid. M.p. (TFA salt) 127 – 129 ^{o}C; FTIR (TFA salt; solid) ν 3300 (b, w), 2930, 2848, 2231, 1712, 1655, 1562, 1446, 1420, 1195, 1169, 1137, 827, 798, 719; ^{1}H NMR δ 7.58 (d, *J* = 8.2 Hz, 2 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 6.02 (s, 1 H), 5.69 (s, 1 H), 5.06 – 4.97 (m, 1 H), 3.82 (s, 2 H), 2.60 – 2.51 (m, Hz, 1 H), 2.45 – 2.37 (m, 2 H), 2.16 (s, 3 H), 2.04 – 1.89 (m, 2 H), 1.70 – 1.45 (m, 4 H), 1.26 – 1.06 (m, 1 H), 0.89 and 0.88 (2 d, *J* = 6.8 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.3, 163.3, 162.6, 161.6, 146.5, 132.8, 132.2, 128.7, 119.1, 110.7, 109.2, 99.9, 97.4, 79.7, 79.6, 53.7, 53.7, 53.3, 53.2, 39.2, 38.8, 38.6, 37.9, 37.8, 36.8, 32.5, 32.3, 31.1, 28.6, 20.2, 14.9, 14.6; MS (electrospray ionization) m/z 413.2 ($M+Na^+$), 391.5 ($M+H^+$), 247.3, 139.0; HRMS calcd for $C_{24}H_{27}N_2O_3^+$ ($M+H^+$) 391.2022, found 391.2031 (100%).

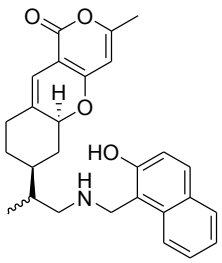
(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(4-hydroxynaphthalen-1-yl)methylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran•TFA salt (12A)



From 85 mg (0.31 mmol) of amine **39** and 53.5 mg (0.31 mmol) of aldehyde **45A**, 130 mg (77% yield) of **12A•TFA** was obtained as a solid. (Note: compound **12A** decomposes during concentration (removal of solvents), therefore 1.2 equivalents of trifluoroacetic acid was added to make the stable salt before concentration). M.p. (TFA salt) 80 – 82 ^{o}C; FTIR (TFA salt; solid) ν 3440 - 3100 (b, w), 2958, 1667, 1564, 1446, 1198, 1177, 1131, 824, 762, 719; ^{1}H NMR **(**Acetone–d6**)** δ 8.30 (d, *J* = 8.4 Hz, 1 H), 8.17 (d, *J* = 8.4 Hz, 1 H), 7.64 (d, *J* = 7.2 Hz, 1 H), 7.56 (t, *J* = 7.6 Hz 1 H), 7.49 (t, *J* = 7.6 Hz 1 H), 7.00 (d, *J* = 7.2 Hz, 1 H), 5.88 (s, 1 H), 5.82 (s,

1 H), 512 – 4.98 (m, 1 H), 4.71 (s, 2 H), 3.36 – 3.22 (m, 1 H), 3.14 – 3.00 (m, 1 H), 2.38 (d, *J* = 14.0 Hz, 1 H), 2.15 (s, 3 H), 2.11 – 1.40 (m, 6 H), 1.30 – 1.02 (m, 1 H), 0.98 and 0.97 (2 d, *J* = 6.8 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR **(**Acetone–d6**)** δ 164.0, 163.0, 162.4, (161.4, 161.0, 160.7, 160.3 are from TFA), 155.9, 134.0, 133.7, 132.0, 128.0, 126.1, 125.8, 124.0, 123.9, (121.9, 119.0 are from TFA), 118.7, (116.1, 113.2 are from TFA), 109.7, 108.4, 100.1, 97.7, 97.6, 79.9, 79.8, 51.9, 49.2, 39.6, 38.7, 38.6, 36.7, 35.7, 35.65, 32.7, 32.4, 31.4, 28.5, 20.0, 14.1, 14.0; MS (electrospray ionization) 432.2 ($M+H^+$), 276.2; HRMS calcd for $C_{27}H_{30}NO_4^+$ ($M+H^+$) 432.2175, found 432.2165.

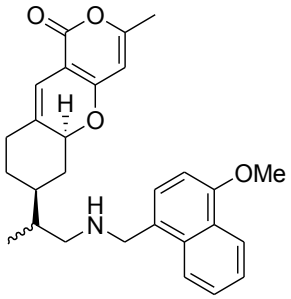
(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(2-hydroxynaphthalen-1-yl)methylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (12B)



From 790 mg (2.87 mmol) of amine **39** and 495 mg (2.87 mmol) of aldehyde **45B**, 750 mg (61% yield) of **12B** was obtained as a solid. (Note: the reduction of intermediate imine required higher amounts of CH_3COOH and $NaBH_3CN$ and the product decomposed gradually during column chromatographic purification, but its intermediate imine was stable; therefore, the imine was purified through silica gel column and reduced to get the pure product.) M.p. (TFA salt) 113 – 115 ^oC; FTIR (TFA salt; solid) ν 3400 - 3070 (b, w), 2933, 1674, 1629, 1566, 1442, 1199, 1135, 818, 720; ^1H NMR δ 7.80 (d, *J* = 8.4 Hz, 1 H), 7.77 (d, *J* = 8.0 Hz, 1 H), 7.69 (d, *J* = 9.2 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 1 H), 7.29 (t, *J* = 7.6 Hz, 1 H), 7.10 (d, *J* = 9.2 Hz, 1 H), 6.06 (s, 1 H), 5.69 (s, 1 H), 5.10 – 5.02 (m, 1 H), 4.44 (s, 2 H), 2.80 – 2.72 (m, 1 H), 2.67 – 2.58 (m, 1 H), 2.45

(d, J = 14.4 Hz, 1 H), 2.18 (s, 3 H), 2.09 – 1.93 (m, 2 H), 1.76 – 1.46 (m, 4 H), 1.33 – 1.06 (m, 1 H), 0.98 and 0.97 (2 d, J = 6.8 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.3, 162.6, 161.6, 156.9, 132.5, 132.47, 129.2, 128.9, 128.4, 126.4, 122.5, 121.0, 119.4, 112.1, 109.2, 99.8, 97.3, 79.4, 79.3, 53.2, 53.1, 47.9, 39.1, 38.7, 38.6, 37.5, 37.4, 36.6, 32.3, 32.1, 30.9, 28.3, 20.1, 14.7, 14.6; MS (electrospray ionization) m/z 432.2 ($M+H^+$), 276.2; HRMS calcd for $C_{27}H_{30}NO_4^+$ ($M+H^+$) 432.2175, 432.2184.

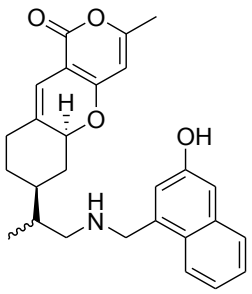
(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(4-methoxynaphthalen-1-yl)methylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (12C)



From 110 mg (0.4 mmol) of amine **39** and 75 mg (0.4 mmol) of aldehyde **45C**, 134 mg (75% yield) of **12C** was obtained as a solid. M.p. 76 – 78 ^{o}C; FTIR (solid) ν 3300 (b, w), 2927, 1681, 1583, 1568, 1448, 1390, 1273, 1231, 1155, 1091, 816, 760; ^{1}H NMR δ 8.30 (d, J = 8.0, Hz, 1 H), 8.08 (d, J = 8.4 Hz, 1 H), 7.53 (t, J = 7.2 Hz, 1 H), 7.47 (t, J = 7.2 Hz, 1 H), 7.33 (d, J = 7.6 Hz, 1 H), 6.73 (d, J = 7.6 Hz, 1 H), 6.03 (s, 1 H), 5.68 (s, 1 H), 5.02 – 4.87 (m, 1 H), 4.12 (s, 2 H), 3.98 (s, 3 H), 2.71 – 2.62 (m, 1 H), 2.60 – 2.51 (m, 1 H), 2.39 (dd, J = 13.9, 1.9 Hz, 1 H), 2.17 (s, 3 H), 2.02 – 1.82 (m, 2 H), 1.71 – 1.42 (m, 4 H), 1.35 – 1.02 (m, 1 H), 0.88 and 0.87 (2 d, J = 6.6 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.4, 163.3, 162.7, 161.5, 155.1, 133.0, 132.98, 132.8, 128.0, 126.6, 126.5, 126.1, 125.1, 123.8, 122.7, 109.02, 109.00, 103.0, 99.9, 97.4, 79.79, 79.75, 79.67, 79.63, 55.6, 55.5, 53.5, 53.1, 52.0, 39.3, 38.5, 38.4, 37.7, 37.6,

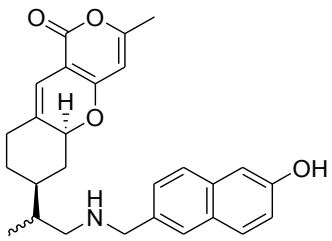
36.6, 32.5, 32.3, 31.1, 28.3, 20.2, 14.8, 14.6; MS (electrospray ionization) m/z 446.3 ($M+H^+$), 171.1; HRMS calcd for $C_{28}H_{32}NO_4^+$ ($M+H^+$) 446.2331, found 446.2343 (100%).

(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(3-hydroxynaphthalen-1-yl)methylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (12D)



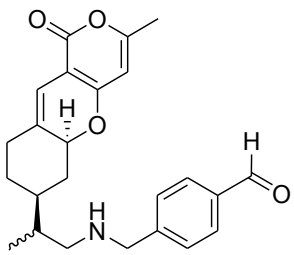
From 85 mg (0.31 mmol) of amine **39** and 53 mg (0.31 mmol) of aldehyde **45D**, 80 mg (60% yield) of **12D** was obtained as a solid. M.p. (TFA salt) 115 – 117 ^oC; FTIR (TFA salt; solid) ν 3500 - 3200 (b, w), 2927, 1672, 1604, 1565, 1449, 1236, 1199, 1136, 829, 720; ^1H NMR δ 7.92 (d, *J* = 8.0 Hz, 1 H), 7.62 (d, *J* = 7.6 Hz, 1 H), 7.38 (t, *J* = 7.6 Hz, 1 H), 7.31 (t, *J* = 7.6 Hz, 1 H), 7.16 (s, 1 H), 7.05 (s, 1 H), 6.02 (s, 1 H), 5.68 (s, 1 H), 5.01 – 4.90 (m, 1 H), 4.18 (s, 2 H), 2.75 (dd, *J* = 11.6, 5.6 Hz, 1 H), 2.66 – 2.55 (m, 1 H), 2.37 (d, *J* = 13.6 Hz, 1 H), 2.17 (s, 3 H), 2.05 – 1.80 (m, 2 H), 1.76 – 1.42 (m, 4 H), 1.33 – 1.02 (m, 1 H), 0.89 (d, *J* = 6.6 Hz, 3 H, CH_3); ^{13}C NMR δ 163.64, 163.62, 163.0, 161.7, 154.1, 136.8, 135.7, 133.0, 127.5, 126.8, 126.4, 123.6, 123.2, 119.3, 109.7, 109.1, 100.1, 97.5, 79.8, 79.7, 53.6, 53.5, 51.3, 39.3, 38.6, 38.5, 37.4, 37.3, 36.7, 32.5, 32.3, 31.1, 28.2, 20.3, 14.72, 14.66; MS (electrospray ionization) m/z 432.6 ($M+H^+$), 157.1; HRMS calcd for $C_{27}H_{30}NO_4^+$ ($M+H^+$) 432.2175, 432.2170 (100%).

(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(6-hydroxynaphthalen-2-yl)methylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (13)



From 85 mg (0.31 mmol) of amine **39** and 53.5 (0.31 mmol) of aldehyde **46**, 98 mg (70% yield) of **13** was obtained as a solid. M.p. 100 – 102 ^{o}C; FTIR (solid) ν 3500 - 3100 (b, w), 2924, 2867, 1681, 1639, 1605, 1565, 1447, 1232, 1147, 860, 811, 763; ^{1}H NMR δ 7.63 (s, 1 H), 7.62 (d, *J* = 7.6 Hz 1 H), 7.57 (d, *J* = 8.6 Hz, 1 H), 7.37 (d, *J* = 8.2 Hz, 1 H), 7.05 (s, 1 H), 7.04 (d, *J* = 8.0 Hz, 1 H), 6.06 (s, 1 H), 5.70 (s, 1 H), 5.09 – 4.99 (m, 1 H), 3.91 (s, 2 H), 2.68 (dd, *J* = 11.1, 4.9 Hz, 1 H), 2.58 – 2.49 (m, 1 H), 2.43 (d, *J* = 13.3 Hz, 1 H), 2.19 (s, 3 H), 2.09 – 1.90 (m, 2 H), 1.75 – 1.43 (m, 4 H), 1.30 – 1.06 (m, 1 H), 0.93 and 0.92 (2 d, *J* = 6.4 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.68, 163.65, 163.0, 161.7, 154.9, 134.2, 134.0, 133.02, 133.00, 129.3, 128.4, 127.0, 126.8, 119.0, 109.6, 109.1, 100.1, 97.5, 79.8, 79.7, 54.3, 53.1, 53.0, 39.2, 38.9, 38.8, 37.5, 37.4, 36.9, 32.5, 32.3, 31.0, 28.5, 20.2, 14.8, 14.7; MS (electrospray ionization) m/z 432.1 ($M+H^+$); HRMS calcd for $C_{27}H_{30}NO_4^+$ ($M+H^+$) 432.2175, found 432.2163 (100%).

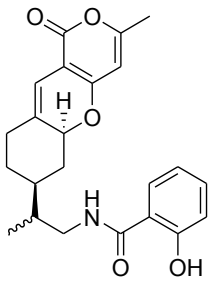
(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[(4-formyl)benzylamino]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (11H)



A solution of 100 mg (0.25 mmol) of **11D** and 84 mg (0.30 mmol) of IBX in 2 mL of DMSO was stirred at 25 ^{o}C for 2 h. The reaction mixture was poured into water (300 mL) and extracted twice with CH_2Cl_2 (200 mL). The combined organic layer was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of CH_2Cl_2 and MeOH as eluant to get 64 mg (64% yield) of **11H** as a solid. M.p. (HCl salt) 140 – 142 ^{o}C; FTIR (HCl salt; solid) ν 3407 (b, w), 2930, 1686 (s), 1566, 1448, 1418, 1215, 1002, 821, 764; ^{1}H NMR δ 9.99 (s, 1 H), 7.84 (d, J = 8.0 Hz, 2 H), 7.49 (d, J = 8.0 Hz, 2 H), 6.05 (s, 1 H), 5.69 (s, 1 H), 5.07 – 4.99 (m, 1 H), 3.86 (s, 2 H), 2.63 - 2.56 (m, 1 H), 2.49 – 2.40 (m, 2 H), 2.18 (s, 3 H), 2.06 – 1.91 (m, 2 H), 1.72 – 1.45 (m, 4 H), 1.33 – 1.06 (m, 1 H), 0.91 and 0.90 (2 d, J = 6.8 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 192.1, 163.4, 163.35, 162.7, 161.7, 148.0, 135.6, 132.8, 130.1, 128.7, 109.3, 99.9, 97.5, 79.8, 79.7, 54.0, 53.4, 53.3, 39.3, 38.9, 38.7, 38.0, 37.9, 36.9, 32.5, 32.4, 31.1, 28.7, 20.3, 14.9, 14.7; MS (electrospray ionization) m/z 394.6 ($M+H^+$), 242.6; HRMS calcd for $C_{24}H_{28}NO_4^+$ ($M+H^+$) 394.2018, found 394.2006 (100%).

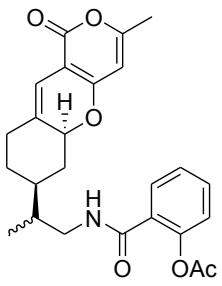
General procedure for the synthesis of amides 14A and 14B

2-Hydroxy-N-{(2*R*) and (2*S*)-2-[(5a*S*,7*S*)-3-methyl-(*N*-(2-(1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran-7-yl]propyl}benzamide (14A)



A mixture of 45 mg (0.33 mmol) of salicylic acid (**47A**), 100 mg (0.36 mmol) of amine **39**, 56 mg (0.36 mmol) of EDC, and 13 mg (0.1 mmol) of NHS in 2 mL of dry DMF, under argon, was stirred for 16 h at 25 ^{o}C. Then the reaction solution was diluted with 50 mL of ethyl acetate, washed twice with water (10 mL each) followed by brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluent to give 78 mg (55% yield) of compound **14A** as a solid. M.p. 110 – 112 ^{o}C; FTIR (solid) ν 3336 (b, w), 2929, 2850, 1686, 1638, 1591, 1566, 1543, 1491, 1447, 1365, 1232, 1147, 818, 754; ^{1}H NMR δ 12.33 (s, 1 H), 7.42 - 7.37 (m, 2 H), 7.00 (d, *J* = 7.8 Hz, 1 H), 6.85 (t, *J* = 7.4 Hz, 1 H), 6.46 (br s, 1 H), 6.08 (s, 1 H), 5.72 (s, 1 H), 5.06 (t, *J* = 5.2 Hz, 1 H), 3.58 - 3.47 (m, 1 H), 3.33 - 3.25 (m, 1 H), 2.47 (d, *J* = 8.0 Hz, 1 H), 2.20 – 2.11 (m, 1 H), 2.19 (s, 3 H), 2.10 – 1.95 (m, 1 H), 1.86 – 1.54 (m, 4 H), 1.36 – 1.14 (m, 1 H), 0.98 and 0.97 (2 d, *J* = 7.2 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 170.3, 163.6, 163.5, 162.8, 161.8, 161.7, 134.5, 132.5, 125.4, 118.9, 118.8, 114.4, 109.6, 100.0, 97.5, 79.6, 79.4, 43.5, 43.47, 39.3, 38.7, 38.5, 38.1, 38.0, 36.7, 32.4, 32.3, 31.2, 28.5, 20.3, 14.4, 14.3. MS (electrospray ionization) m/z 418.6 ($M+Na^+$, 100%); HRMS calcd for $C_{23}H_{25}NO_5Na^+$ ($M+Na^+$) 418.1630, found 418.1613 (100%).

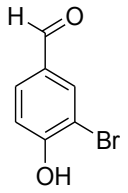
2-Acetoxy-N-{(2*R*) and (2*S*)-2-[(5a*S*,7*S*)-3-methyl-(*N*-(2-(1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran-7-yl]propyl}benzamide (14B)



From 65 mg (0.36 mmol) of acetylsalicylic acid **47B** and 0.10 g (0.36 mmol) of amine **39**, 75 mg (47 % yield) of **14B** was obtained as a solid. M.p. 98 – 100 ^{o}C; FTIR (solid) ν 3297 (b, w),

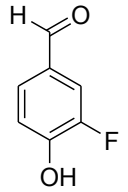
2928, 2862, 1766, 1696, 1640, 1567, 1532, 1447, 1367, 1193, 1008, 816, 752; ^{1}H NMR δ 7.70 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.48 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.32 (td, *J* = 7.6, 1.2 Hz, 1 H), 7.11 (dd, *J* = 8.2, 1.2 Hz, 1 H), 6.23 (br. s, 1 H), 6.08 (s, 1 H), 5.71 (s, 1 H), 5.07 (t, *J* = 6.2 Hz, 1 H), 3.56 - 3.45 (m, 1 H), 3.31 - 3.19 (m, 1 H), 2.48 (dd, *J* = 14.0, 2.2 Hz, 1 H), 2.34 (s, 3 H), 2.22 - 2.10 (m, 1 H), 2.19 (s, 3 H), 2.08 – 1.95 (m, 1 H), 1.84 - 1.53 (m, 4 H), 1.35 - 1.12 (m, 1 H), 0.96 and 0.95 (2 d, *J* = 6.8 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 169.5, 166.2, 163.5, 162.8, 161.8, 148.0, 132.5, 132.0, 129.6, 128.9, 126.6, 123.4, 109.5, 100.0, 97.5, 79.5, 79.4, 43.83, 43.80, 39.4, 38.6, 38.4, 38.1, 38.1, 36.7, 32.4, 32.3, 31.2, 28.5, 21.4, 20.3, 14.4, 14.2; MS (electrospray ionization) m/z 460.2 ($M+Na^+$; 100%), 400.1; HRMS calcd for $C_{25}H_{27}NO_6Na^+$ ($M+Na^+$) 460.1736, found 460.1729 (100%).

3-bromo-4-hydroxybenzaldehyde (43C)



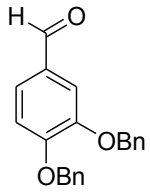
To a solution of 500 mg (4.1 mmol) of aldehyde **44C** in 15 mL of a mixture of chloroform and dimethoxyethane (4:1) at -40 °C was added 159.8 mg (4.1 mmol) of bromine through a syringe. After stirring for 4 h, the mixture was diluted with dichloromethane (300 mL), washed with water (100 mL x 4) followed by brine, dried ($MgSO_4$), and concentrated to get 595 (70% yield) of aldehyde **43C** as a solid whose ^{1}H spectrum was in agreement to that reported.[58]

3-fluoro-4-hydroxybenzaldehyde (43D)



A mixture of 300 mg (2.19 mmol) of 4-cyano-2-fluorophenol (**48**), 50 mg (0.22 mmol) of PtO_2, and 10 mL of 88% formic acid was stirred at 75 °C, for 5 h. The mixture was diluted with water (200 mL) and extracted in dichloromethane. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to get 240 mg (80% yield) of aldehyde **43D** as a solid, whose ^1H spectrum was in agreement to that reported.[59]

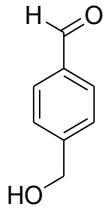
3,4-bis(benzyloxy)benzaldehyde (43F)



Step 1: 1.81 g (7.23 mmol) of BBr_3 was added to a solution of 1 g (6.57 mmol) of aldehyde **43A** in 50 mL of dichloromethane at 0 °C. After stirring for 0.5 h at 0 °C and 4 h at 25 °C, diluted with MeOH (40 mL) and concentrated in reduced vacuum. This process of dilution and concentration with methanol was repeated for 3 times. Diluted with dichloromethane, filtered and the residue was washed with dichloromethane to get 3,4-dihydroxybenzaldehyde (**52**) as a solid.

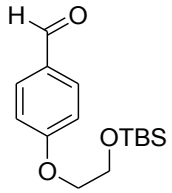
Step 2: To a mixture of 300 mg (2.17 mmol) of aldehyde **52**, and 138.21 mg (6.5 mmol) of K_2CO_3 in 20 mL of acetone was added 928.5 mg (5.42 mmol) of benzyl bromide followed by 108 mg (0.65 mmol) of potassium iodide. After refluxing for 25 h, the mixture was filtered through celite, concentrated, and purified through silica gel column using a gradient mixture of hexanes and ether to get 605 mg (85% yield) of compound **43F**, whose ^1H and ^{13}C NMR were in agreement with that of reported.[67]

(hydroxymethyl)benzaldehyde (44D)



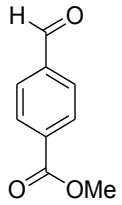
To a solution of 1g (7.45 mmol) of terepthaldehyde (**49**), in a mixture of 10 mL of dichloromethane and 5 mL of methanol, at 0 °C was added 70 mg (1.86 mmol) of $NaBH_4$. After stirring for 4 h, diluted with dichloromethane (200 mL), washed with brine, dried ($MgSO_4$), concentrated, and purified through silica gel column using a gradient mixture of hexanes and ether as eluent to get 750 mg (75% yield) of aldehyde **44D**, whose ^1H and ^{13}C NMR spectra were in agreement to that reported.[61]

4-(2-(*t*-butyldimethylsilyloxy)ethoxy)benzaldehyde (44E)



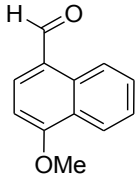
A mixture of 300 mg (2.6 mmol) of aldehyde **44C**, 750 mg (3.4 mmol) of (2-bromoethoxy) (*t*-butyl)dimethylsilane (**50**), and 1 g (7.8 mmol) of K_2CO_3 in 10 mL of dry DMF was stirred at 100 °C for 12 h. The mixture was acidified with 2N HCl and extracted with dichloromethane. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to get 612.8 mg (93% yield) of aldehyde **44E**, whose ^1H and ^{13}C NMR spectra were in agreement to that reported.[62]

Methyl 4-formylbenzoate (44I)



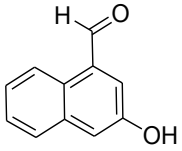
To a mixture of 150 mg (0.99 mmol) of *p*-carboxybenzaldehyde (**51**), and 413.6 mg (2.99 mmol) of K_2CO_3 in 5 mL of dry DMF was added 425.4 mg (2.99 mmol) of MeI. After stirring for 12 h, the mixture was diluted with dichloromethane (300 mL), washed with brine, dried ($MgSO_4$), and concentrated to get 274.5 mg (100% yield) of compound **44I**, whose ^1H and ^{13}C NMR spectra were in agreement to that reported.[63]

4-methoxy-1-naphthaldehyde (45C)



185 mg (1.3 mmol) of MeI was added to a mixture of 150 mg (0.87 mmol) aldehyde **12A**, and 180 mg (1.3 mmol) of K_2CO_3, in 5 mL of acetone. After stirring for 10 h, the mixture was diluted with water (30 mL) and extracted in diethyl ether. The ether layer was washed with brine, dried with $MgSO_4$, and concentrated to get 140 mg (100% yield) of aldehyde **45C** whose ^1H NMR spectrum was in agreement to that reported.[65]

3-hydroxy-1-naphthaldehyde (45D)



Step 1:[71]: A solution of 5 g (34.91 mmol) of 1-aminonaphthalene (**53**) in 20 mL of AcOH, was added to a solution of 12.3 g (76.8 mmol) of Br_2 in AcOH at 0 °C. The mixture was stirred at 60 °C for 45 min and filtered; the residue was mixed with 1N NaOH and filtered. The residue was

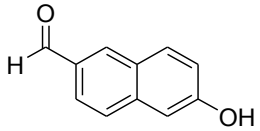
washed with water and recrystalized from ethanol to get 5.2 g (50% yield) of 2,4-dibromo-1-aminonaphthalene (**54**).

Step 2:[71]: 1.27 g (18.48 mmol) of $NaNO_2$ (solid) was added to a solution of 4 g (13.2 mmol) of 2,4-dibromo-1-aminonaphthalene (**54**) in a mixture of 200 mL of acetic acid and 20 mL of propanoic acid at 0 °C. After stirring for 1 h at 0 °C, the mixture was poured into 300 mL of ice water and filtered. To the filtrate, 3 L of water was added and filtered again; the residue was washed with water and recrystalized from ethanol to get 2.5 g (76% yield) of compound **55**.

Step 3:[71]: 189 mg (4.99 mmol) of $NaBH_4$ (solid) was added to a solution of 2.5 g (9.99 mmol) of intermediate **55** in 150 mL of EtOH at 0 °C. After stirring for 3.5 h at 0 °C, the mixture was diluted with water (300 mL) and conc. H_2SO_4 (4 mL), basified with 10% NaOH and extracted with dichloromethane. This organic portion was discarded. Aqueous layer was acidified with 4N HCl and extracted with dichloromethane. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to get 1.6 g (72% yield) of 4-bromo-2-naphthol (**56**).

Step 4[70]: 1 g (4.48 mmol) of 4-bromo-2-naphthol (**56**) in 15 mL of diethyl ether was added to a slurry of 140 mg (5.82 mmol) of NaH in 10 mL of diethyl ether, under argon, at 0 °C. After stirring for 1.5 h at 0 °C, 5 mL (8.96 mmol) of *n*-BuLi (1.6 M in hexanes) was added dropwise. After stirring for 1 h, 556 mg (8.96 mmol) of DMF was added and stirring was continued for 3 h. The mixture was acidified with 2N HCl and extracted with diethyl ether. The organic layer was washed with brine, dried ($MgSO_4$), concentrated, and purified through silica gel column using a gradient mixture of hexanes and ether to get 325 mg (70% yield, on the basis of recovered starting material) of aldehyde **12D** as a solid. 400 mg of starting material **56** was also recovered. ^1H and ^{13}C spectra of aldehyde **12D** were in agreement to that reported.[70]

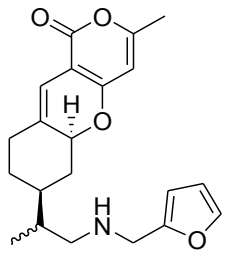
6-hydroxy-1-naphthaldehyde (46)



A solution of 1 g (4.48 mmol) of 6-bromo-2-hydroxynaphthlene (**57**) in 35 mL of diethyl ether, under argon, at 0 °C was added to slurry of 140 mg (5.82 mmol) of NaH in 15 mL of diethyl ether. After stirring for 2 h, at °C, 4.7 mL (7.62 mmol) of *n*-BuLi (1.6 M, in hexanes) was added dropwise and stirred for 1 h. To this mixture was added 556 mg (7.62 mmol) of DMF and the stirring was continued for 2 h. Then the mixture was cooled to 0 °C, acidified with 2N HCl and extracted with diethyl ether. The ether layer was washed with brine, dried with $MgSO_4$, concentrated, and purified through silica gel column to get 278 mg (66% yield on the basis of recovered **57**) of aldehye **46** and 450 mg of starting material **57** was also recovered. ^{1}H and ^{13}C spectra of aldehyde **46** were in agreement to that reported.[70]

General procedure for the syntheses of tricyclic pyrones 15 -31

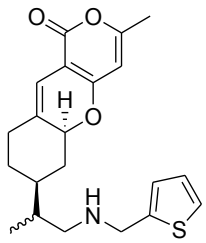
(5a*S*,7*S*)-3-Methyl-7-(1-(furan-2-ylmethylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (15)



A mixture of 50 mg (0.18 mmol) of amine **39**, 17.5 mg (0.18 mmol) of aldehyde **58**, in 5 mL of distilled MeOH, under argon was stirred for 12 h. Acetic acid (5 drops) was added followed by a solution of 34 mg (0.54 mmol) of $NaBH_3CN$ in MeOH. After stirring for 1 h, the mixture was diluted with 30 mL of 5% NH_4OH solution and extracted in dichloromethane. The organic layer

was washed with brine, dried ($MgSO_4$), concentrated, and purified through silica gel column using a gradient mixture of dichloromethane and methanol as eluent to get 35.5 mg (55% yield) of compound **15**, as a solid. ^{1}H NMR δ 7.36 (s, 1 H), 6.32 (d, *J* = 2.1 Hz, 1 H), 6.17 (d, *J* = 2.7 Hz, 1 H), 6.06 (s, 1 H), 5.70 (s, 1 H), 5.10 – 4.99 (m, 1 H), 3.77 (s, 2 H), 2.63 – 2.55 (m, 1 H), 2.48 - 2.40 (m, 2 H), 2.18 (s, 3 H), 2.08 - 1.92 (m, 2 H), 1.70 - 1.46 (m, 4 H), 1.28 - 1.05 (m, 1 H), 0.89 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR δ 163.42, 163.38, 162.72, 161.65, 154.10, 141.96, 132.96, 110.30, 109.29, 107.10, 99.94, 97.55, 79.85, 79.72, 53.01, 52.93, 46.61, 39.39, 38.80, 38.69, 37.84, 37.76, 36.91, 32.56, 32.43, 31.18, 28.48, 20.28, 14.79, 14.71; MS (electrospray ionization) m/z 356.4 ($M+H^+$), 100%).

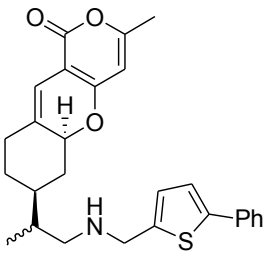
(5a*S*,7*S*)-3-Methyl-7-(1-(thiophen-2-ylmethylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (16)



From 100 mg (0.36 mmol) of amine **39** and 41 mg (0.36 mmol) of aldehyde **59**, 81 mg of compound **16** (60% yield) was obtained as a solid. ^{1}H NMR δ 7.21 (d, *J* = 5.1 Hz, 1 H), 6.95 (t, *J* = 4.0 Hz, 1 H), 6.91 (d, *J* = 3.1 Hz, 1 H), 6.06 (s, 1 H), 5.70 (s, 1 H), 5.05 (dt, *J* = 10.7, 5.2 Hz, 1 H), 3.98 (s, 2 H), 2.63 (ddd, *J* = 11.7, 6.1, 3.7 Hz, 1 H), 2.53 – 2.41 (m, 2 H), 2.18 (s, 3 H), 2.09 – 1.91 (m, 2 H), 1.73 – 1.47 (m, 4 H), 1.28 – 1.06 (m, 1 H), 0.90 and 0.89 (2 d, *J* = 6.8 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.43, 163.41, 162.74, 161.65, 144.66, 133.00, 126.78, 124.91, 124.51, 109.26, 99.96, 97.56,

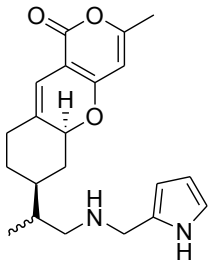
79.88, 79.55, 53.03, 52.94, 48.82, 39.43, 38.75, 38.64, 37.88, 37.80, 36.91, 32.58, 32.45, 31.23, 2 8.49, 20.27, 14.79, 14.69; MS (electrospray ionization) m/z 372.5 ($M+H^+$, 100%).

(5a*S*,7*S*)-3-Methyl-7-(1-(5-phenylthiophen-2-ylmethylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (17)



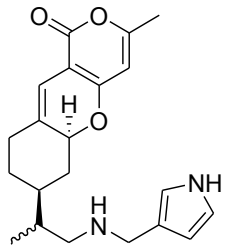
From 80 mg (0.29 mmol) of amine **39** and 55 mg (0.29 mmol) of aldehyde **60**, 98 mg (75% yield) of compound **17** was obtained as a solid. ^{1}H NMR (200 MHz) δ 7.62 - 7.52 (m, 2 H), 7.42 - 7.24 (m, 3 H), 7.16 (d, *J* = 3.7 Hz, 1 H), 6.89 (d, *J* = 3.7 Hz, 1 H), 6.06 (s, 1 H), 5.67 and 5.65 (2 s, 1 H, two diastereomers), 3.99 (s, 2 H), 2.73 – 2.61 (m, 1 H), 2.59 – 2.38 (m, 2 H), 2.17 (s, 3 H), 2.11 – 1.96 (m, 2 H), 1.76 – 1.40 (m, 4 H), 1.31 – 1.05 (m, 1 H), 0.91 and 0.90 (2 d, *J* = 7.0 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR (200 MHz) δ 163.44, 162.77, 161.62, 144.15, 143.41, 134.17, 133.00, 132.98, 129.16, 129.02, 127.45, 126.07, 126.01, 125.72, 122.70, 109.23, 99.96, 97.52, 79.87, 79.72, 52.91, 52.83, 49.05, 39.39, 38.74, 38.52, 37.83, 37.72, 36.78, 32.56, 32.42, 31.20, 28.56, 20.26, 14.85, 14.63; MS (electrospray ionization) m/z 448.3 ($M+H^+$).

(5a*S*,7*S*)-3-Methyl-7-(1-(1*H*-pyrrol-2-ylmethylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (18)



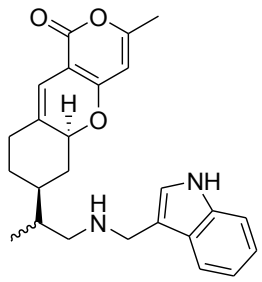
From 80 mg (0.29 mmol) of amine **39** and 28 mg (0.29 mmol) of aldehyde **61**, 58 mg (56% yield) of compound **18** was obtained as a solid. ^{1}H NMR (200 MHz) δ 10.44 (br. s, 1 H, NH), 6.84 (s, 1 H), 6.20 (s, 1 H), 6.10 (s, 1 H), 6.01 (s, 1 H), 5.68 (s, 1 H), 5.24 – 4.85 (m, 1 H), 4.17 (s, 2 H), 2.98 - 2.52 (m, 2 H), 2.39 (d, *J* = 12.5 Hz, 1 H), 2.16 (s, 3 H), 2.07 - 1.05 (m, 7 H), 0.96 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR δ 163.50, 162.75, 161.88, 132.15, 120.85, 120.29, 112.04, 109.51, 108.38, 99.96, 97.35, 79.09, 79.05, 49.28, 44.63, 38.85, 37.79, 37.65, 35.88, 35.17, 35.08, 32.10, 31.85, 30.76, 27.60, 20.25, 14.21, 14.10; MS m/z (electrospray ionization) 355.5 ($M+H^+$).

(5a*S*,7*S*)-3-Methyl-7-(1-(1*H*-pyrrol-3-ylmethylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (19)



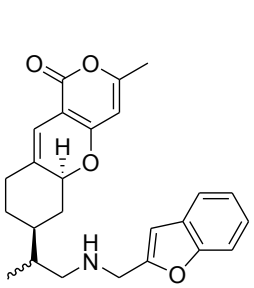
From 80 mg (0.29 mmol) of amine **39** and 28 mg (0.29 mmol) of aldehyde **62**, 44 mg (43% yield) of compound **19** was obtained as a solid. ^{1}H NMR δ 8.60 (br. s, 1 H, NH), 6.73 (d, *J* = 2.3 Hz, 1 H), 6.70 (s, 1 H), 6.17 (s, 1 H), 6.05 (s, 1 H), 5.70 (s, 1 H), 5.10 - 4.98 (m, 1 H), 3.68 (s, 2 H), 2.64 (ddd, *J* = 11.6 5.6 3.9 Hz, 1 H), 2.55 – 2.37 (m, 2 H), 2.18 (s, 3 H), 2.11 – 1.90 (m, 2 H), 1.75 – 1.38 (m, 4 H), 1.32 – 1.05 (m, 1 H), 0.89 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR δ 163.46, 143.43, 162.77, 161.62, 133.09, 133.07, 122.66, 118.23, 116.16, 109.14, 109.13, 108.31, 99.97, 97.51, 79.88, 79.75, 53.38, 53.29, 46.90, 46.89, 39.39, 38.89, 38.78, 37.75, 37.67, 36.91, 32.56, 32.43, 31.17, 28.47, 20.22, 14.82, 14.73; MS (electrospray ionization) m/z 355.5 ($M+H^+$).

(5a*S*,7*S*)-3-Methyl-7-(1-(1*H*-indol-3-ylmethylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (20)

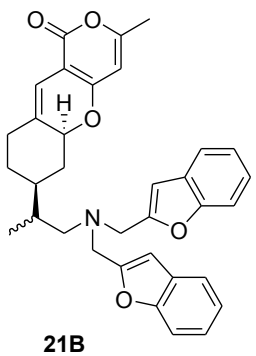


From 80 mg (0.29 mmol) of amine **39** and 42 mg (0.29 mmol) of aldehyde **63**, 66 mg (56% yield) of compound **20** was obtained as a solid. ^{1}H NMR δ 9.53 (br. s, 1 H, NH), 7.71 (s, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.21 – 7.11 (m, 2 H), 5.93 (s, 1 H), 5.63 and 5.60 (2 s, 1 H, two diastereomers), 5.11 – 5.03 and 4.99 – 4.91 (2 m, 1 H, two diastereomers), 4.33 (s, 2 H), 2.98 – 2.86 (m, 1 H), 2.81 – 2.71 (m, 1 H), 2.32 (d, *J* = 12.4 Hz, 1 H), 2.16 and 2.15 (2 s, 3 H), 2.12 – 1.03 (m, 7 H), 0.95 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR δ 163.58, 163.54, 162.90, 161.82, 136.09, 132.29, 127.63, 127.28, 122.72, 120.64, 118.05, 112.18, 109.45, 104.71, 100.02, 97.48, 79.09, 79.05, 50.06, 42.65, 38.93, 37.61, 37.50, 35.71, 35.06, 32.13, 31.80, 30.79, 27.29, 20.28, 14.14.

(5a*S*,7*S*)-3-Methyl-7-(benzofuran-2-ylmethylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (21A) and **(5a*S*,7*S*)-3-Methyl-7-(bis(benzofuran-2-ylmethyl)amino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (21B)**



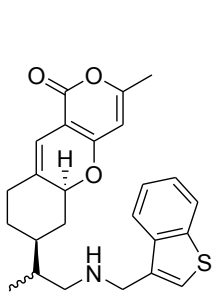
21A



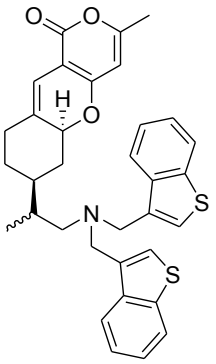
21B

From 100 (0.36 mmol) of amine **39** and 69.1 mg (0.47 mmol) of aldehyde **64**, 89 mg (60% yield) of compound **21A** and 32 mg (16% yield) of compound **21B** were obtained as solids. Compound **21A:** ^{1}H NMR δ 7.53 (d, *J* = 7.8 Hz, 1 H), 7.45 (d, *J* = 8.2 Hz, 1 H), 7.28 – 7.18 (m, 2 H), 6.57 (s, 1 H), 6.06 (s, 1 H), 5.69 (s, 1 H), 5.10 – 4.97 (m, 1 H), 3.93 (s, 2 H), 2.69 – 2.60 (m, 1 H), 2.54 – 2.47 (m, 1 H), 2.43 (d, *J* = 14.0 Hz, 1 H), 2.18 (s, 3 H), 2.07 – 1.92 (m, 2 H), 1.70 - 1.46 (m, 4 H), 1.31 – 1.06 (m, 1 H), 0.91 and 0.90 (2 d, *J* = 6.4 Hz, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.43, 163.40, 162.75, 161.66, 156.85, 155.09, 132.92, 128.58, 123.99, 122.85, 120.90, 111.23, 109.30, 104.05, 99.96, 97.54, 79.81, 79.69, 53.06, 52.96, 47.04, 39.37, 38.79, 38.66, 37.88, 37.79, 36.87, 32.53, 32.39, 31.17, 28.52, 20.27, 14.81, 14.67; MS (electrospray ionization) m/z 406.3 ($M+H^+$, 100%). Compound **21B:** ^{1}H NMR δ 7.61 - 7.42 (m, 4 H), 7.37 – 7.17 (m, 4 H), 6.61 (s, 2 H), 6.01 (s, 1 H), 5.70 and 5.59 (2 s, 1 H, two diastereomers), 5.17 – 5.00 and 4.88 – 4.80 (2 m, 1H), 4.01 – 3.79 (m, 4 H), 2.61 – 2.41 (m, 1 H), 2.40 – 2.23 (m, 2H), 2.20 (s, 3 H), 2.17 – 1.45 (m, 5 H), 1.54 – 1.19 (m, 2 H), 0.84 and 0.83 (2 d, 3 H, CH_3 of two diastereomers); ^{13}C NMR δ 163.43, 162.79, 161.58, 161.52, 155.54, 155.20, 155.19, 133.16, 128.48, 128.46, 124.13, 122.89, 120.95, 120.92, 111.37, 111.31, 109.15, 105.76, 99.99, 99.96, 97.58, 79.91, 79.79, 56.93, 51.36, 39.70, 37.83, 37.43, 35.69, 35.39, 35.18, 32.66, 32.34, 31.48, 27.47, 20.31, 14.31, 14.02; MS (electrospray ionization) 536.5 m/z ($M+H^+$, 100%).

(5a*S*,7*S*)-3-Methyl-7-(benzo[*b*]thiophen-3-ylmethylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (22A) and **(5a*S*,7*S*)-3-Methyl-7-(bis(benzo[*b*]thiophen-3-ylmethyl)amino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (22B)**



22A

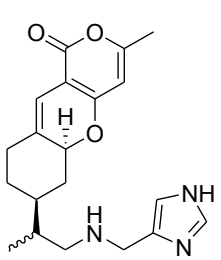


22B

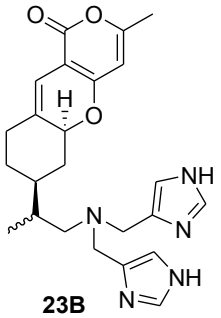
From 110 mg (0.4 mmol) of amine **39**, and 84 mg (0.52 mmol) of aldehyde **65**, 100 mg (60% yield) of compound **22A** and 19 mg of (8% yield) of **22B** were obtained as solids. Compound **22A:** ^{1}H NMR (200 MHz) δ 7.92 - 7.80 (m, 2 H), 7.41 - 7.33 (m, 2 H), 7.30 (s, 1 H), 6.04 (s, 1 H), 5.70 (s, 1 H), 5.09 – 4.89 (m, 1 H), 4.03 (s, 2 H), 2.77 – 2.27 (m, 3 H), 2.18 (s, 3 H), 2.10 - 1.80 (m, 2 H), 1.76 – 1.40 (m, 4 H), 1.36 – 1.04 (m, 1 H), 0.90 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR (200 MHz) δ 163.43, 162.76, 161.64, 140.87, 138.55, 135.40, 132.97, 124.53, 124.11, 123.15, 123.06, 122.05, 109.18, 99.96, 97.50, 79.82, 79.70, 53.55, 53.49, 48.14, 39.40, 38.66, 38.53, 37.86, 37.76, 36.81, 32.53, 32.38, 31.17, 28.43, 20.27, 14.85, 14.72; MS (electrospray ionization) m/z 422.4 ($M+H^{+}$). Compound **22B:** ^{1}H NMR δ 7.91 - 7.81 (m, 2 H), 7.61 (t, *J* = 8.6 Hz, 2 H), 7.45 – 7.28 (m, 4 H), 7.23 – 7.14 (m, 2 H), 5.90 and 5.86 (2 s, 1 H, two diastereomers), 5.70 and 5.64 (2 s, 1 H), 4.96 (d, *J* = 4.8 Hz, 1 H), 4.74 and 3.38 (2 dd, *J* = 11.2, 4.2 Hz, 1 H), 4.07 – 3.96 (m, 2 H), 4.65 – 3.56 (m, 2 H), 2.59 – 2.49 (m, 1 H), 2.36 – 2.10 (m, 2 H), 2.18 (s, 3 H), 1.89 – 0.53 (m, 6 H), 0.69 and 0.67 (2 d, *J* = 6.8 Hz, 3 H, CH_3 of two diastereomers); ^{13}C

NMR δ 163.42, 163.30, 162.78, 162.75, 161.48, 161.44, 140.88, 140.86, 138.99, 134.50, 133.41, 133.18, 125.31, 125.20, 124.58, 123.75, 123.19, 123.12, 122.99, 122.95, 108.74, 108.67, 100.02, 99.97, 97.55, 97.36, 79.84, 79.28, 58.33, 58.25, 53.94, 40.40, 36.42, 36.34, 35.76, 35.56, 34.36, 32.62, 32.10, 31.44, 26.07, 20.28, 20.26, 13.73, 13.49; MS (electrospray ionization) m/z 568.5 ($M+H^+$).

(5a*S*,7*S*)-3-Methyl-7-(1*H*-imidazol-4-ylmethylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (23A) and **(5a*S*,7*S*)-3-Methyl-7-(bis(1*H*-imidazol-4-ylmethyl)amino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (23B)**



23A

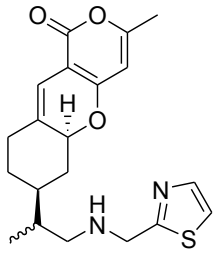


23B

From 217 mg (0.79 mmol) of amine **39** and 83 mg (0.86 mmol) of aldehyde **66**, 112 mg (40% yield) of compound **23A** and 75 mg (22% yield) of compound **23B** were obtained as solids. Compound **23A:** ^{1}H NMR δ 7.56 (s, 1 H), 6.89 (s, 1 H), 6.02 (s, 1 H), 5.70 (s, 1 H), 5.06 – 4.98 (m, 1 H), 3.77 (s, 2 H), 2.64 (dd, *J* = 11.1, 4.9 Hz, 1 H), 2.51 – 2.43 (m, 1 H), 2.40 (d, *J* = 14.1 Hz, 1 H), 2.17 (s, 3 H), 2.11 – 1.86 (m, 2 H), 1.72 – 1.42 (m, 4 H), 1.41 – 1.02 (m, 1 H), 0.88 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR δ 163.54, 163.53, 162.84, 161.73, 135.39, 132.95, 117.85, 109.17, 104.93, 100.03, 97.47, 79.74, 79.64, 53.09, 53.00, 46.14, 39.26, 38.80, 38.69, 37.57, 37.50, 36.85, 32.48, 32.34, 31.09, 28.45, 20.24, 14.81, 14.71; MS (electrospray ionization) m/z 356.5 ($M+H^+$). Compound **23B:** ^{1}H NMR δ 9.09 (br. s, 2 H, NH), 7.62 (s, 2 H), 6.91 (s, 2 H), 5.97 (s, 1

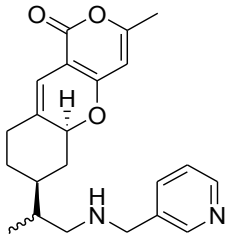
H), 5.70 and 5.69 (2 s, 1 H, two diastereomers), 5.07 – 4.93 (m, 1 H), 3.64 – 3.42 (m, 4 H), 2.46 – 2.26 (m, 2 H), 2.19 – 2.09 (m, 1 H), 2.15 and 2.14 (2 s, 3 H), 2.04 – 1.82 (m, 2 H), 1.81 – 0.85 (m, 5 H), 0.77 (d, J = 6.0 Hz, 3 H); ^{13}C NMR δ 163.76, 163.72, 163.04, 161.72, 161.67, 135.12, 133.45, 132.51, 121.36, 108.81, 100.19, 97.44, 97.40, 80.04, 79.82, 58.29, 58.14, 49.10, 39.62, 37.88, 37.72, 35.93, 35.11, 35.01, 32.62, 32.42, 31.45, 27.49, 20.22, 14.42, 14.26; MS (electrospray ionization) m/z 458.5 (M+Na$^+$, 100%), 436.5 (M+H$^+$).

(5a*S*,7*S*)-3-Methyl-7-(thiazol-2-ylmethylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (24)



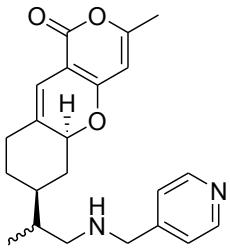
From 80 mg (0.29 mmol) of amine **39** and 33 mg (0.29 mmol) of aldehyde **67**, 44 mg (41% yield) of compound **24** was obtained as a solid. ^{1}H NMR (200 MHz) δ 7.72 (d, J = 3.3 Hz, 1 H), 7.28 (d, J = 3.3 Hz, 1 H), 6.06 (s, 1 H), 5.71 (s, 1 H), 5.14 - 5.00 (m, 1 H), 4.13 (s, 2 H), 2.77 – 2.52 (m, 2 H), 2.52 – 2.39 (m, 1 H), 2.19 (s, 3 H), 2.13 – 1.89 (m, 2 H), 1.79 – 1.42 (m, 4 H), 1.36 – 1.07 (m, 1 H), 0.92 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 172.38, 163.41, 163.39, 162.72, 161.65, 142.63, 132.87, 119.03, 109.27, 99.93, 97.50, 79.79, 79.67, 53.51, 53.42, 51.30, 39.38, 38.60, 38.47, 37.97, 37.90, 36.82, 32.53, 32.29, 31.18, 28.42, 20.27, 14.69, 14.58; MS (electrospray ionization) m/z 373.5 (M+H$^+$), 100%).

(5a*S*,7*S*)-3-Methyl-7-(1-(pyridin-3-ylmethylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (25)



From 85 mg (0.31 mmol) of amine **39** and 33 mg (0.31 mmol) of aldehyde **68**, 68 mg (60% yield) of compound **25** was obtained as a solid. ^{1}H NMR δ 8.57 (s, 1 H), 8.51 (d, *J* = 4 Hz, 1 H), 7.70 (d, *J* = 7.5 Hz, 1 H), 7.28 (dd, *J* = 7.5, 4 Hz, 1 H), 6.05 (s, 1 H), 5.71 (s, 1 H), 5.11 – 4.98 (m, 1 H), 3.81 (s, 2 H), 2.67 – 2.57 (m, 1 H), 2.53 – 2.38 (m, 2 H), 2.19 (s, 3 H), 2.08 – 1.91 (m, 2 H), 1.74 – 1.46 (m, 4 H), 1.29 – 1.06 (m, 1 H), 0.91 (d, *J* = 5.0 Hz, 3 H); ^{13}C NMR δ 163.3, 162.6, 161.6, 149.7, 148.5, 136.0, 135.6, 132.8, 123.5, 109.1, 99.9, 97.4, 79.7, 79.5, 53.1, 53.05, 51.5, 39.2, 38.7, 38.5, 37.7, 37.6, 36.7, 32.4, 32.3, 31.0, 28.4, 20.2, 14.7, 14.6; MS (electrospray ionization) m/z 367.2 ($M+H^+$); HRMS calcd for $C_{22}H_{27}N_2O_3^+$ ($M+H^+$) 367.2022, found 367.2017 (100%).

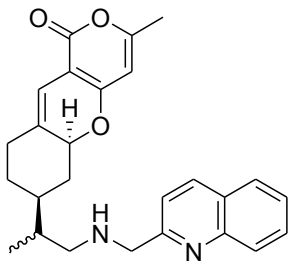
(5aS,7S)-3-Methyl-7-(1-(pyridin-4-ylmethylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (26)



From 85 mg (0.31 mmol) of amine **39** and 33 mg (0.31 mmol) of aldehyde **69**, 72 mg (64% yield) of compound **26** was obtained as a solid. ^{1}H NMR δ 8.54 (d, *J* = 4.5 Hz, 2 H), 7.26 (d, *J* = 4.7 Hz, 2 H), 6.06 (s, 1 H), 5.70 (s, 1 H), 5.11 – 4.98 (m, 1 H), 3.80 (s, 2 H), 2.63 – 2.55 (m, 1

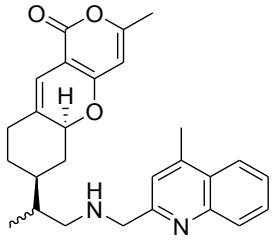
H), 2.50 – 2.39 (m, 2 H), 2.18 (s, 3 H), 2.09 – 1.91 (m, 2 H), 1.75 – 1.47 (m, 4 H), 1.35 – 1.05 (m, 1 H), 0.92 (d, J = 6.6 Hz, 3 H); ^{13}C NMR δ 163.3, 163.3, 162.6, 161.6, 149.8, 132.8, 123.1, 109.3, 99.9, 97.4, 79.7, 79.6, 53.4, 53.3, 53.0, 39.3, 38.8, 38.7, 38.0, 37.9, 36.9, 32.5, 32.4, 31.1, 28.6, 20.2, 14.8, 14.7; MS (electrospray ionization) m/z 367.2 ($M+H^+$), 139.0, 121.2; HRMS calcd for $C_{22}H_{26}N_2O_3Na^+$ ($M+Na^+$) 389.1841, found 389.1844 (100%).

(5aS,7S)-3-Methyl-7-(1-(quinolin-2-ylmethylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (27A)



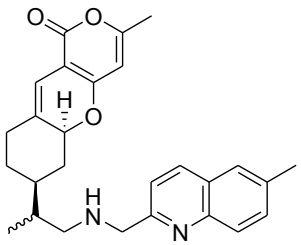
From 60 mg (0.22 mmol) of amine **39** and 35 mg (0.22 mmol) of aldehyde **70A**, 54 mg (60% yield) of **27A** was obtained as a solid. ^{1}H NMR δ 8.11 (d, J = 8.6 Hz, 1 H), 8.04 (d, J = 8.2 Hz, 1 H), 7.79 (d, J = 8.2 Hz, 1 H), 7.69 (t, J = 7.4 Hz, 1 H), 7.50 (t, J = 7.4 Hz, 1 H), 7.43 (d, J = 8.6 Hz, 1 H), 6.04 (s, 1 H), 5.67 (s, 1 H), 5.08 – 5.00 (m, 1 H), 4.09 (s, 2 H), 2.69 (dd, J = 11.7, 5.8 Hz, 1 H), 2.59 – 2.50 (m, 1 H), 2.41 (d, J = 14 Hz, 1 H), 2.16 (s, 3 H), 2.10 – 1.91 (m, 2 H), 1.78 – 1.45 (m, 4 H), 1.27 – 1.04 (m, 1 H), 0.93 and 0.92 (2 d, J = 6.2 Hz, 3 H, CH_3 of diastereomers at C_{12}); ^{13}C NMR δ 163.4, 163.4, 162.7, 161.6, 160.1, 147.8, 136.6, 133.0, 132.9, 129.7, 129.0, 127.7, 127.5, 126.3, 120.7, 109.2, 99.9, 97.5, 79.8, 79.7, 55.9, 53.7, 53.6, 39.3, 38.7, 38.6, 37.9, 37.8, 36.8, 32.5, 32.4, 31.1, 28.5, 20.2, 14.8, 14.7; MS (electrospray ionization) m/z 417.3 ($M+H^+$); HRMS calcd for $C_{26}H_{29}N_2O_3^+$ ($M+H^+$) 417.2178, found 417.2164 (100%).

(5aS,7S)-3-Methyl-7-(1-((4-methylquinolin-2-yl)methylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (27B)



From 43 mg (0.15 mmol) of amine **39** and 26 mg (0.15 mmol) of aldehyde **70B**, 35 mg (53% yield) of compound **27B** was obtained as a solid. Note: Ethanol was used as solvent in the reaction. ^{1}H NMR δ 8.03 (d, *J* = 8.1 Hz, 1 H), 7.96 (d, *J* = 8.2 Hz, 1 H), 7.67 (t, *J* = 7.4 Hz, 1 H), 7.51 (t, *J* = 7.4 Hz, 1 H), 7.27 (s, 1 H), 6.03 (s, 1 H), 5.67 (s, 1 H), 5.12 – 4.97 (m, 1 H), 4.02 (s, 2 H), 2.75 - 2.60 (m, 1 H), 2.68 (s, 3 H), 2.59 – 2.31 (m, 2 H), 2.16 (s, 3 H), 2.11 – 1.86 (m, 2 H), 1.78 – 1.39 (m, 4 H), 1.31 – 1.04 (m, 1 H), 0.92 and 0.91 (2 d, *J* = 6.4, Hz, 3 H, CH_3 of two diastereomers at C_{12}); ^{13}C NMR δ 163.4, 162.7, 161.6, 156.0, 147.7, 144.7, 133.0, 129.6, 129.3, 127.5, 126.0, 123.9, 121.4, 109.2, 99.9, 97.5, 79.9, 79.7, 56.0, 53.8, 53.7, 39.4, 38.7, 38.5, 38.0, 37.8, 36.8, 32.6, 32.4, 31.2, 28.5, 20.2, 18.9, 14.9, 14.7; MS (electrospray ionization) 429.1 (M-1); HRMS calcd for $C_{27}H_{31}N_2O_3^+$ ($M+H^+$) 431.2335, found 431.2308 (100%).

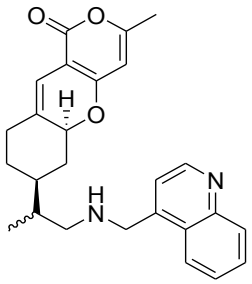
(5aS,7S)-3-Methyl-7-(1-((6-methylquinolin-2-yl)methylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (27C)



From 43 mg (0.15 mmol) of amine **39** and 26 mg (0.15 mmol) of aldehyde **70C**, 37 mg of compound **27C** (56% yield) was obtained as a solid. Note: Ethanol was used as a solvent in the

reaction. ^{1}H NMR δ 8.04 (d, *J* = 8.2 Hz, 1 H), 7.94 (d, *J* = 8.6 Hz, 1 H), 7.57 (s, 1 H), 7.53 (dd, *J* = 8.6, 1.6 Hz, 1 H), 7.40 (d, *J* = 8.6 Hz, 1 H), 6.05 (s, 1 H), 5.69 (s, 1 H), 5.10 – 5.02 (m, 1 H), 4.08 (s, 2 H), 2.73 – 2.65 (m, 1 H), 2.59 – 2.49 (m, 1 H), 2.53 (s, 3 H), 2.43 (d, *J* = 14.4 Hz, 1 H), 2.18 (s, 3 H), 2.10 – 1.93 (m, 2 H), 1.77 – 1.46 (m, 4 H), 1.29 – 1.07 (m, 1 H), 0.94 and 0.93 (2 d, *J* = 6.6 Hz, 3 H, CH_3, 2 diastereomers at C_{12}); ^{13}C NMR δ 163.5, 163.4, 162.8, 161.6, 159.1, 146.4, 136.2, 136.1, 133.0, 132.99, 132.0, 128.7, 127.5, 126.7, 120.7, 109.2, 100.0, 97.5, 79.9, 79.7, 55.9, 53.7, 53.6, 39.4, 38.7, 38.5, 37.9, 37.8, 36.8, 32.6, 32.4, 31.2, 28.4, 21.7, 20.3, 14.9, 14.7; MS (electrosprary ionization) 431.4 (M+1), 156.1, 129.2; HRMS calcd for $C_{27}H_{31}N_2O_3^+$ ($M+H^+$) 431.2335, found 431.2309 (100%).

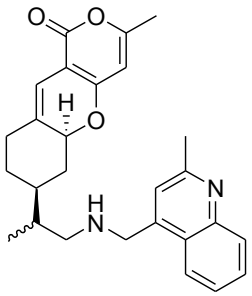
(5aS,7S)-3-Methyl-7-(1-(quinolin-4-ylmethylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (28A)



From 1.28 g (4.65 mmol) of amine **39** and 0.73 g (4.65 mmol) of aldehyde **71A**, 1.25 g (65% yield) of **28A** was obtained as a solid. ^{1}H NMR δ 8.88 (d, *J* = 4.3 Hz, 1 H), 8.14 (d, *J* = 7.4 Hz, 1 H), 8.12 (d, *J* = 7.0 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 7.58 (t, *J* = 7.8 Hz, 1 H), 7.45 (d, *J* = 4.3 Hz, 1 H), 6.07 (s, 1 H), 5.70 (s, 1 H), 5.06 – 4.95 (m, 1 H), 4.27 (s, 2 H), 2.75 – 2.67 (m, 1 H), 2.63 – 2.55 (m, 1 H), 2.44 (d, *J* = 14.4 Hz, 1 H), 2.19 (s, 3 H), 2.07 – 1.88 (m, 2 H), 1.75 – 1.47 (m, 4 H), 1.30 – 1.08 (m, 1 H), 0.94 and 0.93 (2 d, *J* = 6.6 Hz, 3 H, CH_3, 2 diastereomers at C_{12}); ^{13}C NMR δ 163.4, 163.37, 162.7, 161.7, 150.4, 148.4, 146.0, 132.8, 130.3, 129.3, 127.3, 126.6, 123.6, 120.1, 109.3, 99.9, 97.5, 79.8, 79.7, 53.9, 53.8, 50.7, 50.7, 39.3, 38.8, 38.6, 38.0, 37.9,

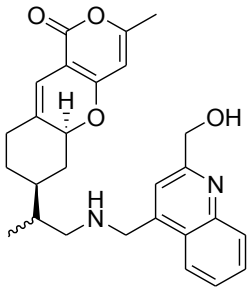
36.9, 32.5, 32.4, 31.1, 28.6, 20.3, 14.9, 14.8; MS (electrospray ionization) m/z 417.5 ($M+H^+$),139.1; HRMS calcd for $C_{26}H_{29}N_2O_3^+$ ($M+H^+$) 417.2178, found 417.2162 (100%).

(5aS,7S)-3-Methyl-7-(1-((2-methylquinolin-4-yl)methylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (28B)



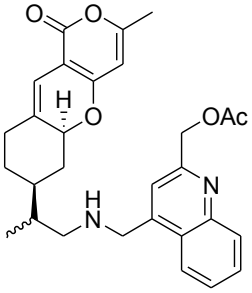
From 43 mg (0.15 mmol) of amine **39** and 26 mg (0.15 mmol) of aldehyde **71B**, 40 mg (60% yield) of **28B** was obtained as a solid. ^{1}H NMR δ 8.01 (d, *J* = 8.6 Hz, 2 H), 7.65 (t, *J* = 7.6 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 1 H), 7.31 (s, 1 H), 6.03 (s, 1 H), 5.68 (s, 1 H), 5.04 – 4.94 (m, 1 H), 4.18 (s, 2 H), 2.73 – 2.63 (m, 1 H), 2.71 (s, 3 H), 2.59 – 2.52 (m, 1 H), 2.41 (d, *J* = 14.5 Hz, 1 H), 2.16 (s, 3 H), 2.05 – 1.86 (m, 2 H), 1.75 – 1.44 (m, 4 H), 1.26 – 1.05 (m, 1 H), 0.91 and 0.90 (2 d, *J* = 6.6 Hz, 3 H, CH_3, two diastereomers); ^{13}C NMR δ 163.4, 163.3, 162.7, 161.6, 158.9, 148.0, 145.8, 132.81, 132.80, 129.3, 129.3, 125.7, 125.4, 123.3, 120.9, 109.2, 99.9, 97.4, 79.7, 79.6, 53.8, 53.79, 50.64, 50.61, 39.3, 38.7, 38.5, 37.9, 37.8, 36.8, 32.5, 32.3, 31.1, 28.5, 25.5, 20.2, 14.9, 14.7; MS (electrospray) m/z 431.4 ($M+H^+$), 144.2; HRMS calcd for $C_{27}H_{31}N_2O_3^+$ ($M+H^+$) 431.2335, found 431.2320 (100%).

(5aS,7S)-7-(1-((2-(Hydroxymethyl)quinolin-4-yl)methylamino)propan-2-yl)-3-methyl-6,7,8,9-hexahydropyrano[4,3-b]chromen-1(5aH)-one (28C)



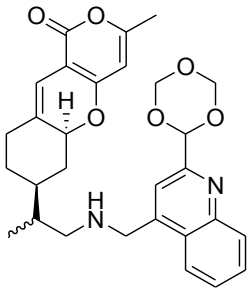
From 43 mg (0.15 mmol) of amine **39** and 29 mg (0.15 mmol) of aldehyde **71C**, 42 mg (61% yield) of **28C** was obtained as a solid. Note: Ethanol was used as a solvent in the reaction. ^{1}H NMR δ 8.09 (d, *J* = 8.2 Hz, 1 H), 8.07 (d, *J* = 7.8 Hz, 1 H), 7.72 (t, *J* = 7.6 Hz, 1 H), 7.56 (t, *J* = 7.6 Hz, 1 H), 7.35 (s, 1 H), 6.06 (s, 1 H), 5.70 (s, 1 H), 5.06 – 4.97 (m, 1 H), 4.91 (s, 2 H), 4.25 (s, 2 H), 2.76 – 2.66 (m, 1 H), 2.63 – 2.54 (m, 1 H), 2.43 (d, *J* = 14.0 Hz, 1 H), 2.19 (s, 3 H), 2.08 – 1.88 (m, 2 H), 1.77 – 1.47 (m, 4 H), 1.33 – 1.06 (m, 1 H), 0.94 and 0.93 (2 d, *J* = 6.6 Hz, 3 H, CH_3, two diastereomers); ^{13}C NMR δ 163.4, 163.37, 162.7, 161.7, 159.0, 146.9, 146.7, 132.8, 132.79, 129.6, 129.5, 126.5, 126.4, 123.5, 117.1, 109.3, 99.9, 97.5, 79.8, 79.6, 64.3, 53.9, 53.86, 50.7, 50.65, 39.3, 38.8, 38.6, 38.0, 37.9, 36.8, 32.5, 32.4, 31.1, 29.9, 28.6, 20.3, 14.9, 14.8; MS (electrospray ionization) m/z 469.3 ($M+Na^+$), 447.3 ($M+H^+$), 142; HRMS calcd for $C_{27}H_{31}N_2O_4^+$ ($M+H^+$) 447.2284, found 447.2284.

4-((2-((5aS,7S)-Methyl-1-oxo-1,5a,6,7,8,9-hexahydropyrano[4,3-b]chromen-7-yl)propylamino)methyl)quinolin-2-yl)methyl acetate (28D)



From 43 mg (0.15 mmol) of amine **39** and 34 mg (0.15 mmol) of aldehyde **71D**, 50 mg (66% yield) of **28D** was obtained as a solid. A mixture of ethanol and THF (2:1) was used as a solvent in the reaction. ^{1}H NMR δ 8.09 (dd, *J* = 8.2, 3.1 Hz, 2 H), 7.71 (t, *J* = 7.6 Hz, 1 H), 7.56 (t, *J* = 7.6 Hz, 1 H), 7.52 (s, 1 H), 6.05 (s, 1 H), 5.70 (s, 1 H), 5.37 (s, 2 H), 5.06 – 4.96 (m, 1 H), 4.25 (s, 2 H), 2.75 – 2.67 (m, 1 H), 2.61 – 2.54 (m, 1 H), 2.43 (d, *J* = 14.0 Hz, 1 H), 2.19 (s, 3 H), 2.18 (s, 3 H), 2.07 – 1.88 (m, 2 H), 1.73 – 1.48 (m, 4 H), 1.31 – 1.06 (m, 1 H), 0.94 and 0.93 (2 d, *J* = 6.6 Hz, 3 H, CH_3, 2 diastereomers at C_{12}); ^{13}C NMR δ 170.9, 163.4, 163.4, 162.7, 161.7, 156.0, 147.9, 147.0, 132.8, 130.1, 129.7, 126.8, 126.5, 123.5, 118.5, 109.3, 99.9, 97.5, 79.8, 79.6, 67.8, 53.9, 53.9, 50.8, 50.8, 39.3, 38.8, 38.7, 38.0, 37.9, 36.9, 32.5, 32.4, 31.1, 28.6, 21.2, 20.3, 15.0, 14.8; MS (electrospray ionization) 511.2 ($M+Na^+$), 489.2 ($M+H^+$); HRMS calcd for $C_{29}H_{32}N_2O_5Na^+$ ($M+Na^+$) 511.2209, found 511.2184 (100%).

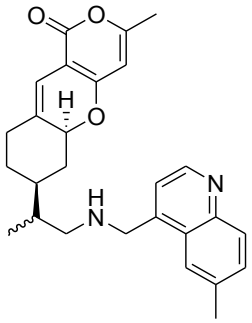
(5aS,7S)-7-(1-((2-(1,3,5-Trioxan-2-yl)quinolin-4-yl)methylamino)propan-2-yl)-3-methyl-6,7,8,9-tetrahydropyrano[4,3-b]chromen-1(5aH)-one (28E)



From 102 mg (0.37 mmol) of amine **39** and 91 mg (0.37 mmol) of aldehyde **71E**, 88 mg (47% yield) of compound **28E** was obtained as a solid. Note: Ethanol was used as a solvent in the reaction. ^{1}H NMR δ 8.16 (d, *J* = 8.2 Hz, 1 H), 8.14 (d, *J* = 7.6 Hz, 1 H), 7.84 (d, *J* = 1.6 Hz, 1 H), 7.72 (t, *J* = 7.6 Hz, 1 H), 7.59 (t, *J* = 8.1 Hz, 1 H), 6.11 (s, 1 H), 6.05 (s, 1 H), 5.69 (s, 1 H), 5.46 – 5.39 (m, 4 H), 5.07 – 4.98 (m, 1 H), 4.27 (s, 2 H), 2.75 – 2.66 (m, 1 H), 2.63 - 2.54 (m, 1 H), 2.43 (d, *J* = 14.1 Hz, 1 H), 2.18 (s, 3 H), 2.07 – 1.87 (m, 2 H), 1.78 – 1.46 (m, 4 H), 1.33 –

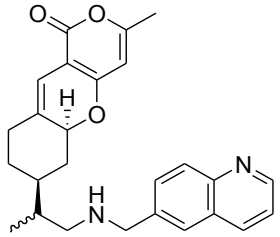
1.06 (m, 1 H), 0.92 and 0.92 (2 d, J = 6.8 Hz, 3 H, CH_3, 2 diastereomers at C_{12}); ^{13}C NMR δ 163.4, 163.37, 162.7, 161.7, 155.2, 147.7, 147.5, 133.0, 130.5, 129.7, 127.5, 127.3, 123.7, 117.3, 117.2, 109.3, 102.3, 99.9, 97.5, 93.9, 79.8, 79.7, 54.0, 53.9, 51.0, 51.0, 39.4, 38.6, 38.5, 38.0, 37.9, 36.8, 32.6, 32.4, 31.2, 28.5, 20.3, 14.9, 14.8; MS (electrospray ionization) 527.4 ($M+Na^+$), 505.6 ($M+H^+$), 445.1, 199.3, 139.0**;** HRMS calcd for $C_{29}H_{33}N_2O_6^+$ ($M+H^+$) 505.2339, found 505.2340.

(5aS,7S)-3-Methyl-7-(1-((6-methylquinolin-4-yl)methylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (28F)



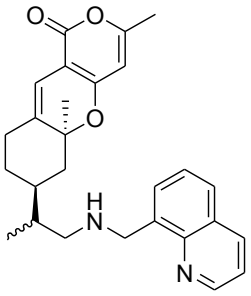
From 85 mg (0.31 mmol) of amine **39** and 53 mg (0.31 mmol) of aldehyde **71F**, 82 mg (62% yield) of compound **28F** was obtained as a solid. Note: A mixture of ethanol and THF (2:1) was used as a solvent in the reaction. ^1H NMR δ 8.78 (d, J = 4.3 Hz, 1 H), 8.01 (d, J = 8.6 Hz, 1 H), 7.85 (s, 1 H), 7.53 (d, J = 8.6 Hz, 1 H), 7.39 (d, J = 4.3 Hz, 1 H), 6.05 (s, 1 H), 5.69 (s, 1 H), 5.05 – 4.94 (m, 1 H), 4.21 (s, 2 H), 2.75 – 2.66 (m, 1 H), 2.62 – 2.54 (m, 1 H), 2.56 (s, 3 H), 2.43 (d, J = 14.0 Hz, 1 H), 2.17 (s, 3 H), 2.07 – 1.88 (m, 2 H), 1.74 – 1.47 (m, 4 H), 1.31 – 1.07 (m, 1 H), 0.94 and 0.93 (2 d, J = 7.0 Hz, 3 H, CH_3, 2 diastereomers at C_{12}); ^{13}C NMR δ 163.4, 163.35, 162.7, 161.6, 149.5, 147.0, 145.2, 136.5, 132.8, 131.5, 130.0, 127.2, 122.4, 120.0, 109.3, 99.9, 97.5, 79.8, 79.7, 53.9, 53.8, 50.7, 39.3, 38.8, 38.7, 38.0, 37.9, 36.9, 32.5, 32.4, 31.2, 28.6, 22.1, 20.2, 14.9, 14.8; MS (electrospray ionization) 431.4 (M+1), 156.2, 144.3; HRMS calcd for $C_{27}H_{30}N_2O_3Na^+$ ($M+Na^+$) 453.2154, found 453.2151.

(5aS,7S)-3-Methyl-7-(1-(quinolin-6-ylmethylamino)propan-2-yl)-6,7,8,9-tetrahydropyrano[4,3-b]chromen-1(5aH)-one (29)



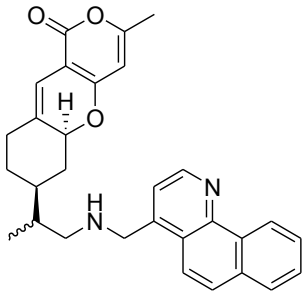
From 0.15 g (0.53 mmol) of amine **39** and 83 mg (0.53 mmol) of aldehyde **72**, 104 mg (47% yield) of **29** was obtained as a solid. ^{1}H NMR 8.87 δ (d, *J* = 3.9 Hz, 1 H), 8.12 (d, *J* = 8.2 Hz, 1 H), 8.06 (d, *J* = 8.6 Hz, 1 H), 7.76 (s, 1 H), 7.71 (d, *J* = 9.0 Hz, 1 H), 7.38 (dd, *J* = 8.4, 4.1 Hz, 1 H), 6.02 (s, 1 H), 5.66 (s, 1 H), 5.01 (dd, *J* = 10.9, 4.7 Hz, 1 H), 3.99 (s, 2 H), 2.70 – 2.62 (m, 1 H), 2.55 – 2.46 (m, 1 H), 2.40 (d, *J* = 14.1 Hz, 1 H), 2.15 (s, 3 H), 2.05 – 1.88 (m, 2 H), 1.74 – 1.42 (m, 4 H), 1.26 – 1.01 (m, 1 H), 0.90 and 0.89 (2 d, *J* = 6.3 Hz, 3 H, CH_3, 2 diastereomers at C_{12}); ^{13}C NMR δ 163.4, 163.36, 162.7, 161.6, 150.3, 147.7, 137.4, 136.2, 132.7, 132.7, 130.4, 129.6, 128.3, 126.9, 121.5, 109.2, 99.9, 97.4, 97.4, 79.7, 79.5, 53.5, 52.7, 52.7, 39.2, 38.7, 38.5, 37.4, 37.3, 36.7, 32.4, 32.3, 31.0, 28.4, 20.2, 14.7, 14.6; MS (electrospray ionization) m/z 417.5 ($M+H^+$), 142.0; HRMS calcd for $C_{26}H_{29}N_2O_3^+$ ($M+H^+$) 417.2178, found 417.2174 (100%).

(5aS,7S)-3-Methyl-7-(1-(quinolin-8-ylmethylamino)propan-2-yl)-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (30)



From 43 mg (0.15 mmol) of amine **39** and 24 mg (0.15 mmol) of aldehyde **73**, 34 mg (53% yield) of **30** was obtained as a solid. Note: A mixture of ethanol and THF (2:1) was used as a solvent in the reaction. In the column chromatographic separation, the column was deactivated with 2% triethylamine in hexane prior to the loading of the crude product. ^{1}H NMR δ 8.87 – 8.83 (m, 1 H), 8.12 (d, *J* = 8.2 Hz, 1 H), 7.69 (d, *J* = 8.2 Hz, 1 H), 7.61 (d, *J* = 7.0 Hz, 1 H), 7.44 (t, *J* = 7.4 Hz, 1 H), 7.37 (dd, *J* = 8.2, 3.9 Hz, 1 H), 5.99 (s, 1 H), 5.65 (s, 1 H), 5.01 – 4.91 (m, 1 H), 4.30 (s, 2 H), 2.58 (dd, *J* = 11.7, 5.8 Hz, 1 H), 2.50 – 2.42 (m, 1 H), 2.35 (d, *J* = 12.9 Hz, 1 H), 2.13 (s, 3 H), 2.02 – 1.82 (m, 2 H), 1.69 – 1.38 (m, 4 H), 1.30 – 0.99 (m, 1 H), 0.82 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR δ 163.4, 163.35, 162.7, 161.6, 149.5, 147.0, 136.8, 133.0, 132.9, 129.6, 128.6, 127.5, 126.5, 121.3, 109.2, 109.14, 99.9, 97.5, 79.8, 79.7, 53.1, 53.0, 51.7, 51.67, 39.4, 38.5, 38.45, 37.5, 37.4, 36.7, 32.5, 32.4, 31.1, 28.2, 20.3, 14.7, 14.63; MS (electrospray ionization) 439.5 (M+Na^{+}), 417.3 (M +H^{+}), 142.1; HRMS calcd for $C_{26}H_{29}N_2O_3^{+}$ (M+H^{+}) 417.2178, found 417.2173 (100%).

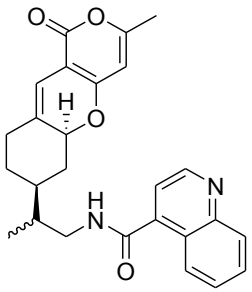
5aS,7S)-7-(1-(Benzo[h]quinolin-4-ylmethylamino)propan-2-yl)-3-methyl-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (31)



From 51 mg (0.18 mmol) of amine **39** and 38 mg (0.18 mmol) of aldehyde **74**, 54 mg (62% yield) of compound **31** was obtained as a solid. Note: Ethanol was used as a solvent in the reaction. ^{1}H NMR δ 9.32 (d, *J* = 7.4 Hz, 1 H), 8.96 (d, *J* = 4.3 Hz, 1 H), 8.03 (d, *J* = 9.0 Hz, 1 H), 7.92 (d, *J* = 7.4 Hz, 1 H), 7.85 (d, *J* = 9.4 Hz, 1 H), 7.78 – 7.68 (m, 2 H), 7.56 (d, *J* = 4.7 Hz,

1 H), 6.05 (s, 1 H), 5.64 (s, 1 H), 5.05 – 4.94 (m, 1 H), 4.30 (s, 2 H), 2.76 – 2.66 (m, 1 H), 2.64 – 2.56 (m, 1 H), 2.43 (d, J = 14.4 Hz, 1 H), 2.18 (s, 3 H), 2.04 – 1.89 (m, 2 H), 1.76 – 1.46 (m, 4 H), 1.43 – 1.06 (m, 1 H), 0.95 and 0.93 (2 d, J = 7.0 Hz, 3 H, CH_3, two diastereomers); ^{13}C NMR δ 163.4, 162.8, 161.6, 148.8, 146.7, 145.7, 133.4, 132.9, 132.0, 128.3, 127.9, 127.8, 127.3, 125.1, 124.9, 121.3, 121.1, 109.2, 99.9, 97.5, 79.8, 79.6, 53.8, 53.7, 51.1, 39.2, 38.8, 38.6, 38.0, 37.8, 36.8, 32.5, 32.4, 31.1, 28.7, 20.3, 15.0, 14.8; MS (electrospray ionization) m/z 467.6 ($M+H^+$), 192.3; HRMS calcd for $C_{30}H_{31}N_2O_3^+$ ($M+H^+$) 467.2335, found 467.2335 (100%).

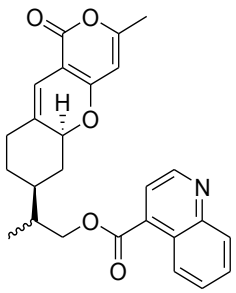
N-(2-((5aS,7S)-3-Methyl-1-oxo-1,5a,6,7,8,9-hexahydropyrano[4,3-b]chromen-7-yl)propyl)quinolie-4-carboxamide (32)



A mixture of 43 mg (0.15 mmol) of amine **39**, 42 mg (0.24 mmol) of acid **75**, 56 mg (0.36 mmol) of EDC.HCl, and 2 mg (0.02 mmol) of DMAP in 5 mL of dry dichloromethane was stirred under argon, at 25 ^{o}C, for 12 h. The reaction mixture was diluted with 100 mL of dichloromethane, washed with water and brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluant to give 43 mg (65% yield) of compound **32** as a solid. ^{1}H NMR δ 8.82 (d, J = 4.3 Hz, 1 H), 8.16 (d, J = 8.6 Hz, 1 H), 8.08 (d, J = 8.6 Hz, 1 H), 7.73 (t, J = 7.6 Hz, 1 H), 7.57 (t, J = 7.6 Hz, 1 H), 7.34 (d, J = 4.3 Hz, 1 H), 6.72 (br. s, 1 H, NH), 5.97 (s, 1 H), 5.68 (s, 1 H), 5.09 – 4.98 (m, 1 H), 3.63 – 3.52 (m, 1 H), 3.42 – 3.29 (m, 1 H), 2.43 (d, J = 13.3 Hz, 1 H), 2.14 (s, 4 H), 2.06 – 1.90 (m, 1 H), 1.87 – 1.71 (m, 2 H), 1.71 – 1.51 (m, 2 H), 1.43 – 1.11 (m, 1 H), 0.99 and 0.98 (2 d, J =

6.6 Hz, 3 H, CH_3, 2 diastereomers at C_{12}); ^{13}C NMR δ 167.7, 163.5, 162.7, 161.8, 149.9, 148.7, 142.4, 132.4, 130.2, 129.9, 127.8, 125.4, 124.6, 118.5, 109.4, 99.9, 97.4, 79.6, 79.4, 43.9, 39.2, 38.8, 38.7, 38.0, 36.9, 32.4, 32.3, 31.1, 28.6, 20.2, 14.5, 14.4; MS (electrospray ionization) m/z 453.3 (M + Na^+), 431.1 (M+H^+); HRMS calcd for $C_{26}H_{27}N_2O_4^+$ (M+H^+) 431.1971, found 431.1957 (100%).

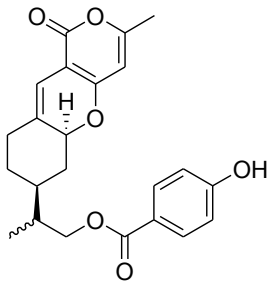
N-(2-((5aS,7S)-3-Methyl-1-oxo-1,5a,6,7,8,9-hexahydropyrano[4,3-b]chromen-7-yl)propyl)quinolie-4-carboxylate (33)



A mixture of 50 mg (0.18 mmol) of alcohol **40**, 32 mg (0.18 mmol) of acid **75**, 47.7 mg (0.3 mmol) of EDC.HCl, and 5 mg (0.04 mmol) of DMAP in 5 mL of dry dichloromethane was stirred for 24 h. The mixture was dilute with 120 mL of dry dichloromethane, washed with 0.5N HCl followed by brine, dried with $MgSO_4$, concentrated, and purified through a silica gel column using a mixture of hexanes and ethyl acetate (1:2) to get 27 mg (57% yield) of compound **33**, as a solid. 20 mg of alcohol **40** was also recovered. ^1H NMR δ 9.08 – 9.04 (m, 1 H), 8.78 – 8.74 (m, 1 H), 8.51 (d, *J* = 6.2 Hz, 1 H), 7.96 (d, *J* = 6.6 Hz, 1 H), 7.83 – 7.73 (m, 2 H), 6.09 (s, 1 H), 5.70 (s, 1 H), 5.11 – 5.03 (m, 1 H), 4.44 – 4.38 (m, 1 H), 4.32 – 4.23 (m, 1 H), 2.54 – 2.46 (m, 1 H), 2.18 (s, 4 H), 2.10 – 1.92 (m, 2 H), 1.89 – 1.55 (m, 3 H), 1.43 – 1.17 (m, 1 H), 1.06 and 1.07 (2 d, *J* = 6.6 Hz, 3 H, CH_3, two diastereomers); ^{13}C NMR δ 164.78, 163.35, 163.33, 162.60, 161.86, 142.53, 134.57, 132.18, 130.63, 130.40, 128.84, 126.90, 124.35, 123.10, 120.02, 109.73, 99.85,

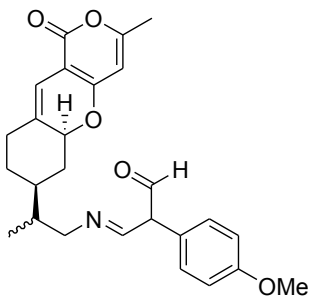
97.51, 79.40, 79.30, 68.57, 68.55, 39.10, 38.36, 38.28, 37.44, 37.25, 37.20, 32.36, 32.27, 30.90, 29.10, 20.29, 14.14, 14.05; MS (electrospray ionization) m/z 470.3 ($M+K^+$).

N-(2-((5aS,7S)-3-Methyl-1-oxo-1,5a,6,7,8,9-hexahydropyrano[4,3-b]chromen-7-yl)propyl)4-hydroxy benzoate (34)



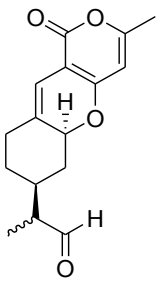
A mixture of 100 mg (0.36 mmol) of alcohol **40** and 91.5 mg (0.36 mmol) of acid **76**, 96 mg (0.61 mmol) of EDC.HCl, and 6 mg (0.05 mmol) of DMAP in 7 mL of dry dichloromethane was stirred for 20 h. The mixture was diluted with 250 mL of dichloromethane and washed with 0.5N HCl and brine, dried ($MgSO_4$), and concentrated. To this crude in 10 mL of THF was added 1.1 mL (1.1 mmol) of TBAF (1M in THF), and the mixture was stirred for 2 h. The mixture was diluted with dichloromethane (200 mL), washed with water and brine, dried with $MgSO_4$, concentrated, and purified through silica gel column to get 60 mg (53% yield) of compound **34** as a solid. 21 mg of alcohol **40** was also recovered. ^{1}H NMR δ 7.93 (d, *J* = 8.9 Hz, 2 H), 6.92 (d, *J* = 8.6 Hz, 2 H), 6.08 (s, 1 H), 5.75 (s, 1 H), 5.12 – 5.03 (m, 1 H), 4.29 - 4.21 (m, 1 H), 4.21 - 4.13 (m, 1 H), 2.48 (d, *J* = 14.0 Hz, 1 H), 2.20 (s, 4 H), 2.08 – 1.88 (m, 2 H), 1.87 - 1.55 (m, 3 H), 1.35 - 1.14 (m, 1 H), 1.01 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR δ 166.83, 164.00, 163.97, 163.38, 161.97, 161.09, 132.90, 131.97, 122.20, 115.61, 109.24, 100.32, 97.62, 79.74, 79.65, 65.50, 67.47, 39.11, 38.34, 38.21, 37.44, 37.21, 37.21, 32.48, 32.40, 30.95, 29.20, 20.28, 14.05, 13.90; MS (electrospray ionization) m/z 419.3 ($M+Na^+$, 100%).

(5a*S*,7*S*)-3-Methyl-7-{(1*R*) and (1*S*)-1-[3-imino-2(4-methoxyphenyl)propanal]propan-2-yl}-1*H*,7*H*-5a,6,8,9-tetrahydro-1-oxopyrano[4,3-b][1]benzopyran (35)



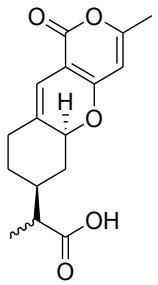
A mixture of 85 mg (0.31 mg) of amine **39** and 64.8 mg (0.36 mmol) of dialdehyde **77**, in 5 mL of dry MeOH was stirred for 12 h. Diluted with dichloromethane, washed with brine, dried ($MgSO_4$), concentrated, and purified through silica gel column to get 63 mg (47% yield) of compound **35** as a solid. (NOTE: The attempt to reduce imine **35** with $NaBH_3CN$ in the presence of acetic acid was not successful and the product was obtained as a mixture of E and Z conformational isomers). ^{1}H NMR (200 MHz) 10.59 - 10.35 and 5.57 – 5.28 (2 m, 1 H, CHO, E and Z isomers), 9.42 (d, *J* = 3.7 Hz, 0.5 H, CHO-aldehyde), 9.06 (s, 0.5 H, CHO-aldehyde), 7.24 – 7.10 (m, 2 H), 7.07 and 7.00 (2 d, *J* = 3.8 Hz, 1 H, imine), 6.99 – 6.82 (m, 2 H), 6.07 (s, 1 H), 5.71 (s, 1 H) 5.06 (br. s, 1 H), 3.80 (s, 3 H), 3.46 – 3.23 (m, 1 H), 3.23 – 1.96 (m, 1 H), 2.47 (d, *J* = 13.6 Hz, 1 H), 2.18 (s, 3 H), 2.15 – 1.88 (m, 2 H), 1.83 – 1.42 (m, 4 H), 1.36 – 1.08 (m, 1 H), 0.96 and 0.91 (2 d, *J* = 6.6 Hz, 3 H, CH3 of two diastereomers); ^{13}C NMR 189.25, 163.41, 163.36, 162.69, 161.95, 161.85, 157.99, 153.41, 132.20, 132.18, 130.72, 130.68, 127.46, 114.81, 114.37, 109.85, 109.68, 99.91, 99.85, 97.47, 79.35, 79.22, 77.44, 55.56, 55.54, 53.64, 39.17, 39.14, 39.10, 38.50, 38.18, 37.01, 32.28, 32.18, 30.98, 28.48, 20.32, 14.29, 14.20; MS (electrospray ionization) m/z 458.6 ($M+Na^+$, 100%).

2-{(5aS, 7S)-3-methyl-1-oxo-1,5a,6,7,8,9-hexahydropyrano[4,3-b]chromen-7-yl}propanal (78)



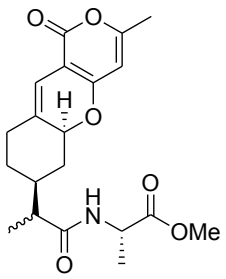
To a solution of 500 mg (1.81 mmol) of TP alcohol **40** in 10 mL of DMSO was added 608.7 mg (2.17 mmol) of IBX. After stirring for 3 h, the mixture was diluted with water (100 mL), and extracted in dichloromethane (75 x 3 mL). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to get 380 mg (77% yield) of aldehyde **78** as a solid. ^{1}H NMR δ 9.68 and 9.67 (2 s, 1 H, 2 diastereomers), 6.10 (s, 1 H), 5.70 (s, 1 H), 5.14 – 5.05 (m, 1 H), 2.53 – 2.44 (m, 1 H), 2.40 – 2.28 (m, 1 H), 2.19 (s, 3 H), 2.16 – 1.98 (m, 2 H), 1.81 – 1.52 (m, 3 H), 1.35 – 1.15 (m, 1 H), 1.11 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR δ 204.15, 204.11, 163.24, 163.21, 162.44, 161.77, 131.69, 109.70, 99.74, 78.95, 78.78, 50.69, 50.64, 39.11, 37.16, 36.15, 36.01, 32.08, 31.96, 31.11, 29.05, 20.16, 10.08, 9.96; MS (electrospray ionization) m/z 297.3 ($M+Na^+$), 275.2 ($M+H^+$).

2-{(5aS, 7S)-3-methyl-1-oxo-1,5a,6,7,8,9-hexahydropyrano[4,3-b]chromen-7-yl}propanoic acid (79)



To a solution of 200 mg (0.73 mmol) of aldehyde **78** in 7 mL of DMF was added 278 mg (1.82 mmol) of oxone, and the mixture was stirred for 5 h. Basified with K_2CO_3 (aq) and some impurities are extracted in dichloromethane. Acidified with 2N HCl and extracted in dichloromethane. The dichloromethane layer was washed with brine, dried ($MgSO_4$), and concentrated to get 170 mg (80% yield) of carboxylic acid **79**, as a solid. ^{1}H NMR δ 6.09 (s, 1 H), 5.71 (s, 1 H), 5.12 – 5.04 (m, 1 H), 2.52 – 2.38 (m, 2 H), 2.27 - 2.13 (m, 1 H), 2.19 (s, 3 H), 2.11 – 1.52 (m, 4 H), 1.28 – 1.12 9 (m, 1 H), 1.19 and 1.18 (2 d, *J* = 7.2 Hz, 3 H, two diastereomers); ^{13}C NMR δ 181.36, 181.29, 163.48, 163.46, 162.80, 161.90, 132.01, 132.00, 109.72, 109.71, 99.94, 97.50, 79.17, 79.01, 44.47, 44.32, 39.22, 38.64, 38.56, 37.70, 32.10, 32.03, 31.11, 29.62, 20.30, 13.96, 13.65; MS (electrospray ionization) m/z (negative mode) 289.3 (M-1, 100%).

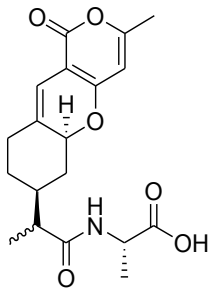
(S)-methyl 2-{2-{(5aS, 7S)-3-methyl-1-oxo-1,5a,6,7,8,9-hexahydropyrano[4,3-b]chromen-7-yl}proanamido}propanoate (81)



A mixture of 175 mg (0.6 mmol) tricyclic pyrone acid **79**, 110 mg (0.78 mmol) of alanine methyl ester (**80**), 186 mg (1.2 mmol) of EDC.HCl, and 80 mg of DMAP (0.6 mmol) in 8 mL of dry dichloromethane was stirred for 12 h. The mixture was diluted with dichloromethane (250 mL) and washed with 0.5N HCl followed by brine, dried with $MgSO_4$, concentrated, and purified through silica gel column eluting with a gradient mixture of DCM and MeOH to get 150 mg (66%) of compound **81**, as a solid. ^{1}H NMR δ 6.27 and 6.17 (2 d, *J* = 7.6 Hz, 1 H, two

diastereomers), 6.06 (s, 1 H), 6.71 – 5.68 (m, 1 H), 5.10 – 5.05 (m, 1 H), 4.63 – 4.52 (m, 1 H), 3.75 and 3.74 (2 s, 3 H), 2.49 – 2.37 (m, 1 H), 2.28 – 1.94 (m, 3 H), 2.18 and 2.17 (2 s, 3 H), 1.93 – 1.77 (m, 2 H), 1.57 – 1.44 (m, 1 H), 1.43 and 1.40 (2 d, J = 7.6 Hz, 3 H), 1.15 (d, J = 6.4 Hz, 3 H), 1.13 – 1.00 (m, 1 H); ^{13}C NMR δ 175.15, 174.92, 173.69, 163.46, 163.43, 162.76, 162.71, 161.74, 161.71, 132.64, 132.32, 109.42, 109.26, 99.96, 97.43, 97.40, 79.33, 79.00, 52.66, 52.59, 48.06, 47.99, 46.51, 46.39, 39.52, 39.08, 39.06, 38.20, 32.08, 31.65, 30.14, 20.25, 18.65, 18.29, 15.18, 15.10; MS (electrospray ionization) m/z 376.1 ($M+H^+$, 100%).

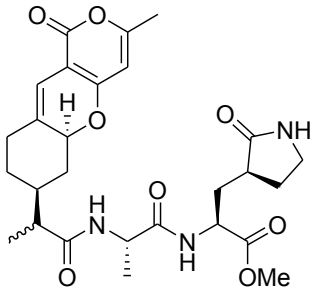
(S)-2-{2-{(5aS, 7S)-3-methyl-1-oxo-1,5a,6,7,8,9-hexahydropyrano[4,3-b]chromen-7-yl}proanamido}propanoic acid (82)



To a solution of 90 mg (0.32 mmol) of compound **81** in a mixture of 5 mL of MeOH and THF (1:1), at 0 °C was added 6 mL of 0.1 N (aq) LiOH solution. After stirring for 5 h at 0 °C, acidified with 0.1 N HCl and extracted in dichloromethane (50 mL x 3). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to get 78 mg (90% yield) of compound **82** as a solid. ^{1}H NMR δ 8.05 – 7.39 (br. s, 1 H, COOH), 7.05 and 6.65 (2 d, J = 7.2 Hz, 1 H, NH, two diastereomers), 6.08 and 6.06 (2 s, 1 H), 5.74 and 5.72 (2 s, 1 H), 5.10 – 5.00 (m, 1 H), 4.63 – 4.51 (m, 1 H), 2.52 – 2.31 (m, 1 H), 2.29 – 1.70 (m, 5 H), 2.19 and 2.18 (2 d, 3 H), 1.60 – 1.34 (m, 1 H), 1.47 and 1.45 (2 d, J = 7.2 Hz, 3 H), 1.30 – 0.81 (m, 1 H), 1.15 and 1.14 (2 d, J = 6.8 Hz, 3 H); ^{13}C NMR δ 176.53, 176.51, 176.11, 175.97, 175.81, 163.91, 163.82, 163.30, 163.29, 163.09, 161.91, 161.89, 133.23, 133.21, 132.57, 109.17, 108.83, 100.29, 100.18, 97.41, 97.33

79.49, 79.05, 48.29, 48.24, 46.21, 39.48, 39.14, 38.94, 38.44, 32.02, 31.80, 30.08, 20.20, 18.16, 17.64, 15.36, 15.34, 15.01; MS (electrospray ionization) m/z (negative mode) 260.4 (M-1, 100%).

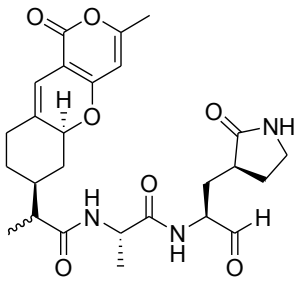
(S)-methyl 2- 2-((S)-2-(2-((5aS, 7S)-3-methyl-1-oxo-1,5a,6,7,8,9-hexahydropyrano[4,3-b]chromen-7-yl)proanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanoate (84)



A mixture of mixture of 60 mg (0.16 mmol) of compound **82**, 48 mg (0.216 mmol) of glutamine surrogate salt **83**, 51.5 mg (0.33 mmol) of EDC.HCl, and 41 mg (0.33 mmol) of DMAP in dry dichloromethane was stirred for 12 h. The mixture was diluted with dichloromethane (100 mL), washed with 0.5N HCl followed by brine, dried ($MgSO_4$), concentrated, and purified through silica gel column to get 59 mg (67% yield) of compound **84** (solid) as a mixture of four isomers. Note: indication of further two isomers may be from rotational conformations. ^{1}H NMR δ 8.21 – 8.09 (m, 1 H, NH), 6.56 (br. s, 2 H, NHs), 6.04 (s, 1 H), 5.71 – 5.67 (m, 1 H), 5.10 – 4.99 (m, 1 H), 4.65 – 4.52 (m, 1 H), 4.51 – 4.40 (m, 1 H), 3.74 – 3.69 (m, 3 H), 3.41 – 3.29 (m, 2 H), 2.54 – 2.33 (m, 3 H), 2.32 – 1.68 (m, 10 H), 1.65 – 1.32 (m, 5 H), 1.31 – 0.98 (m, 4 H); ^{13}C NMR δ 180.03, 179.87, 179.81, 175.20, 175.16, 175.11, 175.04, 173.21, 173.10, 173.07, 172.34, 172.30, 172.24, 163.48, 163.46, 163.44, 163.42, 162.73, 161.78, 161.76, 161.72, 132.49, 132.43, 132.33, 109.42, 109.37, 109.32, 109.29, 99.96, 99.93, 97.44, 97.41, 79.28, 79.25, 79.10, 79.00, 52.65, 51.91, 51.78, 48.73, 48.70, 48.67, 48.65, 46.49, 46.40, 40.76, 40.70, 39.57, 39.51, 39.18, 39.13, 39.02, 38.96, 38.77, 38.75, 38.65, 38.61, 38.30, 38.11, 33.30, 33.15, 33.12, 33.06, 32.08, 32.04,

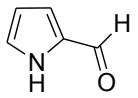
31.74, 31.64, 31.55, 30.19, 29.57, 28.59, 28.51, 22.81, 20.27, 19.34, 19.16, 19.08, 18.85, 15.17, 15.06, 15.03; MS (electrospray ionization) m/z 552.3 ($M+Na^+$, 100%).

(S)-2-((S)-2-(2-((5aS, 7S)-3-methyl-1-oxo-1,5a,6,7,8,9-hexahydropyrano[4,3-b]chromen-7-yl)proanamido)propanamido)-3-((S)-2-oxopyrrolidin-3-yl)propanal (36)

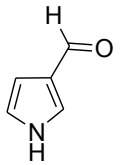


To 30 mg (0.06 mmol) of compound **84** in a mixture of THF and DCM (1:1), at 0 °C was added 12.5 mg (0.6 mmol) of $LiBH_4$ and stirred for 3 h. The reaction was quenched with sat. NH_4Cl solution (1 mL), diluted with brine (20 mL), and extracted with dichloromethane (30 x 3 mL). The combined organic layer was dried ($MgSO_4$) and concentrated. To 20 mg (0.04 mmol) of this residue in 5 mL of dry dichloromethane, under argon was added 25.4 mg (0.06 mmol) of Dess-Martin periodinane (solid). After stirring for 2 h, 3 drops of water were added and stirred for 5 min and filtered. The filtrate was concentrated and purified through silica gel column using a gradient mixture of dichloromethane and acetone as eluent to get 10 mg of tricyclic pyrone-dipeptidyl aldehyde **36** (solid), as a mixture of four isomers. ^1H NMR δ 9.57 and 9.49 (2d, J = 3.2 Hz, 1 H, aldehyde), 8.79 – 8.44 (m, 1 H, NH), 6.85 – 6.39 (m, 2 H, NHs), 6.05 and 6.04 (2d, 1 H, two diastereomers), 5.83 – 5.66 (m, 1 H), 5.04 (br. s, 1 H), 4.71 – 4.41 (m, 2 H), 4.32 (br. s, 1 H), 4.50 – 4.22 (m, 3 H), 2.72 – 0.95 (m, 17 H), 2.18 (s, 3 H); MS (electrospray ionization) m/z 522.1 ($M+Na^+$, 100%), 500.2 ($M+H^+$).

Pyrrole-2-corboxaldehyde (61) and pyrrole-3-carboxaldehyde (62)



61



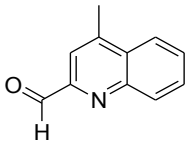
62

Step 1: To a slurry of 357 mg (14.9 mmol) of NaH in 15 mL of dry DMF, at 0 °C was added 1 g (14.9 mmol) of pyrrole (**85**) dropwise. After stirring for 30 min at 0 °C, 3.18 mL (14.9 mmol) of triisopropylsilyl chloride was added. After stirring for 1.5 h at 0 °C to room temperature, the mixture was concentrated to get 3.2 g (99% yield) of viscous oil **86**.

Step 2: To a solution of 1.3 g (17.8 mmol) of DMF in 5 mL of dichloromethane, at 0 °C, under argon was added 2.3 g (17.8 mmol) of oxalyl chloride. After stirring for 0.5 h, at 25 °C, a solution of 3.2 g (14.3 mmol) of compound **86** in 7 mL of dichloromethane was added dropwise at 0 °C. After stirring for 45 min, 40 ml of 5% NaOH was added and stirring was continued at room temperature for 4 h. Extracted in dichloromethane (125 x 3), washed with brine, dried ($MgSO_4$), concentrated, and purified through silica gel column using a gradient mixture of hexane and ethyl acetate to get 410 mg (29% yield) of 2-formylpyrrole **61**[76] and 530 mg (37% yield) of 3-formylpyrrole **62**[77] as solids. ^{1}H NMR spectra of both aldehydes were in agreement with reported in corresponding literatures.[76,77]

General procedure for the syntheses of aldehydes 70B, 70C, 71B, 71F, and 74

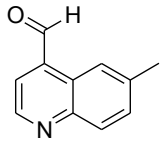
4-Methylquinoline-2-carboxaldehyde (70B)



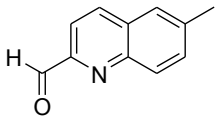
To a mixture of 0.95 g (8.4 mmol) of trifluoroacetic acid and 1.0 g (7.0 mmol) of 4-methylquinoline (**87**) were added 3.6 mL (28 mmol) of 70% *tert*-butyl hydroperoxide, 78 mg (0.28 mmol) of $FeSO_4 \bullet 7H_2O$, 20 mL of acetonitrile, and 20 g of trioxane. The reaction mixture

was heated to reflux for 12 h, cooled to 25 °C, basified with 5% NaOH, and extracted three times with diethyl ether. The combined organic layer was washed with brine, and concentrated. The residue was diluted with 100 mL of 10% H_2SO_4, heated to reflux for 5 h, cooled to 25 °C, basified with 10% NaOH, and extracted three times with diethyl ether. The combined organic layer was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluant to give 0.38 g (50% yield based on recovered **87**) of **70B** as a solid. 0.37 g of **87** was also recovered. ^{1}H NMR δ 10.19 (s, 1 H), 8.24 (d, *J* = 8.2 Hz, 1 H), 8.06 (d, *J* = 8.2 Hz, 1 H), 7.86 (s, 1 H), 7.81 (ddd, *J* = 8.4, 6.8, 1.2 Hz, 1 H), 7.70 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1 H), 2.78 (s, 3 H); ^{13}C NMR δ 194.3, 152.4, 147.9, 146.2, 131.2, 130.3, 130.25, 129.1, 124.2, 118.1, 19.1; MS (electrospray ionization) m/z 172.0 (100%) ($M+H^+$).

6-Methylquinoline-4-carboxaldehyde (71F) and 6-methylquinoline-2-carboxaldehyde (70C)



71F

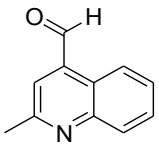


70C

From 1.5 g (10.5 mmol) of 6-methylquinoline (**88**), 0.24 g (17% yield, based on recovered **88**) of **71F** and 0.23 g (16% yield, based on recovered **88**) of **70C**[80] were obtained as solids, and 0.31 g of **88** was also recovered. Compound **71F**: ^{1}H NMR δ 10.51 (s, 1 H), 9.14 (d, *J* = 4.3 Hz, 1 H), 8.83 (s, 1 H), 8.12 (d, *J* = 8.6 Hz, 1 H), 7.77 (d, *J* = 4.3 Hz, 1 H), 7.67 (dd, *J* = 8.6, 1.9 Hz, 1 H), 2.63 (s, 3 H); ^{13}C NMR δ 192.8, 149.2, 147.7, 139.6, 135.8, 132.2, 129.4, 125.8, 123.7, 123.1, 22.0; MS (electrospray ionization) m/z 172.0 (100%) ($M+H^+$), 144.1. Compound **70C**: ^{1}H NMR δ 10.21 (s, 1 H), 8.21 (d, *J* = 8.2 Hz, 1 H), 8.14 (d, *J* = 9.4 Hz, 1 H), 8.00 (d, *J* = 8.6 Hz, 1 H), 7.67 (s, 1 H), 7.66 (dd, *J* = 8.0, 2.0 Hz, 1 H), 2.59 (s, 3 H); ^{13}C NMR δ 194.0, 152.2, 146.8,

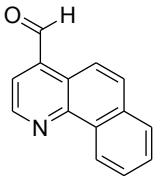
139.9, 136.8, 133.1, 130.4, 130.3, 126.9, 117.7, 22.1; MS (electrospray ionization) m/z 172.0 (100%) ($M+H^+$).

2-Methylquinoline-4-carboxaldehyde (71B)



From 0.50 g (2.2 mmol) of 2-methylquinoline (**89**), 0.29 g (50% yield) of **71B** was obtained as a solid. ^1H NMR δ 10.49 (s, 1 H), 8.97 (dd, *J* = 8.6, 1.2 Hz, 1 H), 8.13 (d, *J* = 8.6 Hz, 1 H), 7.80 (ddd, *J* = 8.3, 7.0, 1.6 Hz, 1 H), 7.70 (s, 1 H), 7.68 (ddd, *J* = 8.5, 6.8, 1.2 Hz, 1 H), 2.88 (s, 3 H); ^{13}C NMR δ 193.0, 159.2, 149.0, 137.0, 130.2, 129.2, 128.3, 127.2, 124.3, 122.2, 25.3; MS (electrospray ionization) m/z 172.0 (100%) ($M+H^+$).

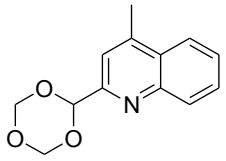
Benzo[*h*]quinoline-4-carboxaldehyde (74)



From 0.50 g (2.79 mmol) of benzo[*h*]quinoline (**90**), 90 mg (18% yield based on recovered **90**) of **74** was obtained as a solid and 85 mg of **90** was also recovered. Note: 10% of 2-formylated analog **91** was also formed. ^1H NMR δ 10.50 (s, 1 H), 9.26 (d, *J* = 7.8 Hz, 1 H), 9.16 (d, *J* = 4.3 Hz, 1 H), 8.74 (d, *J* = 9.4 Hz, 1 H), 7.94 – 7.84 (m, 2 H), 7.80 – 7.68 (m, 3 H); ^{13}C NMR δ 192.9, 148.9, 147.8, 136.5, 133.3, 131.2, 130.9, 129.0, 127.9, 127.7, 125.0, 124.9, 122.9, 120.8; MS (electrospray ionization) m/z 208 ($M+H^+$), 186.2.

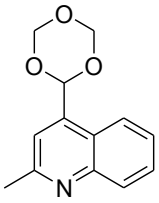
Syntheses of intermediates 92 and 94

4-Methyl-2-(1,3,5-trioxan-2-yl)quinoline (92)



To a mixture of 5.0 g (35 mmol) of 4-methylquinoline (**87**) and 4.75 g (42 mmol) of TFA was added 18 mL (140 mmol) of 70% *tert*-butyl hydroperoxide, 390 mg (1.4 mmol) of $FeSO_4 \bullet 7H_2O$, 80 mL of acetonitrile, and 80 g of trioxane. The reaction mixture was heated to reflux for 12 h, cooled to 25 °C, basified with 5% NaOH, and extracted three times with diethyl ether. The combined organic layer was washed with brine, concentrated, and purified through silica gel column using a gradient mixture of hexanes and ethyl acetate to get 3.0 g (43% yield based on recovered **87**) of **92** and 0.18 g (3% yield) of **70B** as solids. 0.70 g of starting material **87** was also recovered. ^{1}H NMR δ 8.11 (d, *J* = 8.2 Hz, 1 H), 7.92 (d, *J* = 8.5 Hz, 1 H), 7.67 (t, *J* = 7.6 Hz, 1 H), 7.61 (s, 1 H), 7.52 (t, *J* = 7.6 Hz, 1 H), 6.04 (s, 1 H), 5.41 – 5.33 (m, 4 H), 2.66 (s, 3 H); ^{13}C NMR δ 154.9, 147.0, 145.9, 130.1, 129.5, 128.4, 127.0, 123.7, 118.9, 102.2, 93.7, 18.9; MS (electrospray ionization) m/z 270.2 ($M+K^+$), 254.1 ($M+Na^+$), 232.2 ($M+H^+$), 172.0.

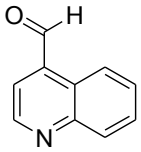
2-Methyl-4-(1,3,5-trioxan-2-yl)quinoline (94)



From 10.0 g (70 mmol) of 2-methylquinoline (**89**), 5.3 g (51% yield based on recovered **89**) of **94** was obtained as a solid. 3.5 g of starting material **89** was recovered. ^{1}H NMR δ 8.05 (d, *J* = 8.6 Hz, 2 H), 7.66 (t, *J* = 7.8 Hz, 1 H), 7.55 (s, 1 H), 7.49 (t, *J* = 7.8 Hz, 1 H), 6.33 (s, 1 H), 5.44 – 5.36 (m, 4 H), 2.73 (s, 3 H); ^{13}C NMR δ 159.0, 148.4, 140.4, 129.4, 129.39, 126.1, 123.6, 123.3, 119.5, 98.8, 93.8, 25.5; MS (electrospray ionization) m/z 232.2 ($M+H^+$), 172.0, 144.1.

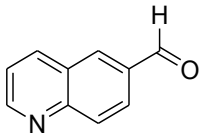
General procedure for the syntheses of compounds 71A, 71E, 72, and 95

Quinoline-4-carboxaldehyde (71A)



A solution of 5.0 g (35 mmol) of 4-methylquinoline (**87**) and 5.0 g (45 mmol) of SeO_2 in toluene, under argon, was heated to reflux for 24 h. The reaction mixture was diluted with dichloromethane, washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexanes and ethyl acetate as eluent to give 4.0 g (73% yield) of compound **71A**, as a solid. ^{1}H NMR δ 10.54 (s, 1 H), 9.22 (d, J = 4.3 Hz, 1 H), 9.04 (d, J = 8.6 Hz, 1 H), 8.24 (d, J = 8.2 Hz, 1 H), 7.84 (t, J = 7.6 Hz, 1 H), 7.81 (d, J = 4.3 Hz, 1 H), 7.76 (t, J = 8.0 Hz, 1 H); ^{13}C NMR δ 193.1, 150.7, 149.5, 137.0, 130.4, 130.3, 129.6, 126.0, 124.7, 124.1; MS (electrospray ionization) m/z 158.0 (100%) ($M+H^+$), 130.2.

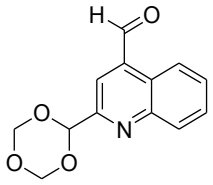
Quinoline-6-carboxaldehyde (72)



The benzylic oxidation of 6-methylquinoline **88** with SeO_2 was found to be reluctant; only trace amount of product **72** was obtained while refluxing in toluene. But the use of xylene as a solvent gave satisfactory yield. From 0.50 g (3.5 mmol) of 6-methylquinoline (**88**), 0.12 g (54% yield based on recovered compound **88**) of **72** was obtained as a solid. 0.30 g of starting material **88** was also recovered. ^{1}H NMR δ 10.20 (s, 1 H), 9.05 (dd, J = 4.3, 1.6 Hz, 1 H), 8.35 (s, 1 H), 8.32 (dd, J = 8.2, 1.9 Hz, 1 H), 8.23 – 8.17 (m, 2 H), 7.52 (dd, J = 8.2, 4.3 Hz, 1 H); ^{13}C NMR δ

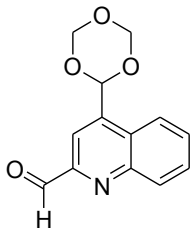
191.6, 153.3, 151.1, 137.6, 134.5, 133.8, 131.0, 127.9, 126.9, 122.4; MS (electrospray ionization) m/z 157.9 (100%) ($M+H^+$).

2-(1,3,5-Trioxan-2-yl)quinoline-4-carboxaldehyde (71E)



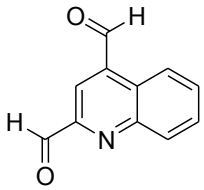
From 0.30 g (1.3 mmol) of **92**, 130 mg (50% yield based on recovered **92**) of compound **71E** was obtained as a solid and 40 mg of **92** was also recovered. ^{1}H NMR δ 10.53 (s, 1 H), 9.08 (dd, *J* = 8.0, 1.2 Hz, 1 H), 8.26 (dd, *J* = 7.8, 0.8 Hz, 1 H), 8.25 (s, 1 H), 7.86 (ddd, *J* = 7.8, 7.0, 1.6 Hz, 1 H), 7.78 (ddd, *J* = 7.8, 7.0, 1.6 Hz, 1 H), 6.21 (s, 1 H), 5.49 – 5.45 (m, 4 H); ^{13}C NMR δ 193.0, 155.8, 148.3, 138.0, 130.7, 130.2, 130.1, 124.7, 124.3, 124.0, 101.3, 93.8; MS (electrospray ionization) m/z 268.3 (100%) ($M+Na^+$).

4-(1,3,5-Trioxan-2-yl)quinoline-2-carboxaldehyde (95)



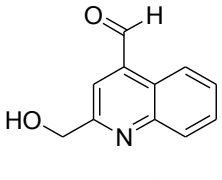
From 0.70 g (3.0 mmol) of **94**, 0.60 g (81% yield) of **95** was obtained as a solid. Note: the reaction was conducted at 80 °C for 15 h. ^{1}H NMR δ 10.24 (s, 1 H), 8.32 (d, *J* = 9.0 Hz, 2 H), 8.31 (s, 1 H), 7.85 (ddd, *J* = 8.5, 7.1, 1.2 Hz, 1 H), 7.75 (ddd, *J* = 8.4, 6.6, 1.2 Hz, 1 H), 6.47 (s, 1 H), 5.51 – 5.46 (m, 4 H); ^{13}C NMR δ 193.5, 152.5, 148.6, 142.1, 131.3, 130.6, 129.8, 127.0, 124.6, 115.5, 99.1, 93.9; MS (electrospray ionization) m/z 267.9 (100%) ($M+Na^+$), 245.9 ($M+H^+$).

Quinoline-2,4-dicarboxaldehyde (93)

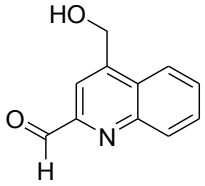


Hydrolysis of 0.60 g (3.0 mmol) of **95** by refluxing with 2N hydrochloric acid provided 0.38 g (98% yield) of dialdehyde **93**, as a solid. ^{1}H NMR δ 10.53 (s, 1 H), 10.28 (s, 1 H), 9.11 (dd, *J* = 8.2, 1.2 Hz, 1 H), 8.40 (s, 1 H), 8.35 (dd, *J* = 8.0, 1.4 Hz, 1 H), 7.92 (ddd, *J* = 8.2, 7.0, 1.6 Hz, 1 H), 7.87 (ddd, *J* = 8.4, 7.0, 1.6 Hz, 1 H); ^{13}C NMR δ 192.9, 192.7, 153.0, 149.2, 138.1, 132.3, 131.3, 131.2, 125.6, 125.2, 122.8; MS (electrospray ionization) m/z 186.1 ($M+H^+$), 172.0.

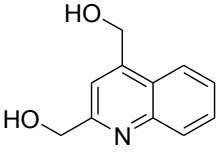
2-(Hydroxymethyl)quinoline-4-carboxaldehyde (71C), **4-(Hydroxymethyl)quinoline-2-carboxaldehyde (96),** and **2,4-dihydroxymethylquinoline (97)**



71C



96

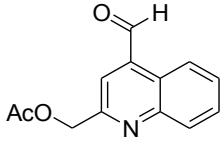


97

To a solution of 0.30 g (1.62 mmol) of dialdehyde **93** in a mixture of 15 mL of dichloromethane and ethanol (3:1) at 0 °C, under argon, was added 15 mg (0.40 mmol) of $NaBH_4$, and the mixture was stirred for 1 h. The reaction mixture was diluted with 50 mL of brine, extracted twice with dichloromethane, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and ethyl acetate as eluant to give 73 mg (32% yield) of **71C**, 81 mg (35% yield) of **96**, and 38 mg (16% yield) of **97** along with 72 mg of recovered **93**. Compound **71C**: ^{1}H NMR δ 10.53 (s, 1 H), 9.00 (dd, *J* = 8.4, 1.0 Hz, 1 H), 8.20 (d, *J* = 8.2 Hz, 1 H), 7.84 (ddd, *J* = 8.6, 7.0, 1.6 Hz, 1 H), 7.75 (s, 1 H), 7.73 (ddd, *J* = 8.6, 7.0, 1.6 Hz, 1 H), 5.06 (s, 2 H); ^{13}C NMR δ 192.8, 159.7, 148.1, 137.8, 130.7, 129.4, 129.1, 124.7, 123.8, 123.5, 64.5; MS (electrospray ionization) m/z 188.3 ($M+H^+$), 128.2, 115.2. Compound **96**: ^{1}H NMR δ 10.24

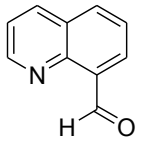
(s, 1 H), 8.30 (d, J = 8.6 Hz, 1 H), 8.19 (s, 1 H), 8.05 (dd, J = 8.2, 0.8 Hz, 1 H), 7.85 (ddd, J = 8.5, 6.9, 1.4 Hz, 1 H), 7.73 (ddd, J = 8.4, 7.0, 1.4 Hz, 1 H), 5.29 (d, J = 0.8 Hz, 2 H); ^{13}C NMR δ ($CDCl_3$ and DMSO-d_6) δ 193.1, 151.6, 148.9, 146.7, 130.1, 129.2, 128.3, 126.8, 122.5, 113.4, 59.7; MS (electrospray ionization) m/z 188.3 (100%) ($M+H^+$), 115.1. Compound **97**: ^{1}H NMR δ 8.12 (d, J = 9.0 Hz, 1 H), 7.94 (d, J = 8.2 Hz, 1 H), 7.75 (ddd, J = 8.4, 6.8, 1.2 Hz, 1 H), 7.58 (ddd, J = 8.4, 7.0, 1.2 Hz, 1 H), 7.46 (s, 1 H), 5.25 (d, J = 3.5 Hz, 2 H), 4.93 (d, J = 3.9 Hz, 2 H); ^{13}C NMR (DMSO-d_6) δ 162.2, 148.0, 146.5, 129.1, 128.9, 125.8, 124.6, 123.3, 115.7, 65.0, 59.8; MS (electrospray ionization) m/z 190.2 (100%) ($M+H^+$).

(4-Formylquinolin-2-yl)methyl acetate (71D)[83]

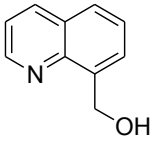


To a mixture of 50 mg (0.27 mmol) of **71C** and 5 mg (0.05 mmol) of ZnO in 8 mL of dichloromethane, under argon, was added 0.28 g (2.7 mmol) of acetic anhydride. The reaction mixture was stirred at 25 ^{o}C for 2 h, diluted with 100 mL of dichloromethane, washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel to get 52 mg (85% yield) of compound **71D** as a solid. ^{1}H NMR δ 10.53 (s, 1 H), 8.99 (d, J = 8.2 Hz, 1 H), 8.18 (d, J = 8.6 Hz, 1 H), 7.87 (s, 1 H), 7.82 (t, J = 7.6 Hz, 1 H), 7.73 (t, J = 8.2 Hz, 1 H), 5.48 (s, 2 H), 2.23 (s, 3 H); ^{13}C NMR δ 192.9, 170.8, 156.8, 149.0, 137.8, 130.7, 130.0, 129.6, 124.5, 124.5, 123.5, 67.2, 21.1; MS (electrospray ionization) m/z 230.1 ($M+H^+$), 216.5.

Quinoline-8-carboxaldehyde (73), 8-hydroxymethylquinoline (99)



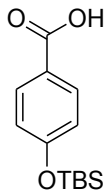
73



99

A solution of 0.50 g (3.5 mmol) of 8-methylquinoline (**98**), 1.87 g (10.5 mmol) of *N*-bromosuccinamide (NBS), and 50 mg (0.3 mmol) of azobisisobutyronitrile (AIBN) in 25 mL of dry dichloroethane was refluxed, under argon, for 30 h. The reaction mixture was diluted with 150 mL of dichloromethane, washed three times with 2 N NaOH followed by brine, dried ($MgSO_4$), and concentrated. The residue was refluxed in 50 mL of water for 4 h, cooled to 25 °C, diluted with 50 mL of 2 N NaOH, and extracted three times with diethyl ether. The combined organic layer was washed with brine, dried ($MgSO_4$), concentrated, and column chromatographed on silica gel using a gradient mixture of hexane and diethyl ether as eluant to give 205 mg (37% yield) of **73** and 298 mg (54% yield) of **99** as solids. Compound **99** was converted to compound **73** in 79% yield by treating with IBX and DMSO. Compound **73**: ^{1}H NMR δ 11.45 (s, 1 H), 9.04 (dd, *J* = 4.3, 1.9 Hz, 1 H), 8.32 (dd, *J* = 7.0, 1.6 Hz, 1 H), 8.24 (dd, *J* = 8.4, 1.8 Hz, 1 H), 8.08 (dd, *J* = 8.2, 1.6 Hz, 1 H), 7.67 (t, *J* = 7.6 Hz, 1 H), 7.51 (dd, *J* = 8.4, 4.1 Hz, 1 H); ^{13}C NMR δ 192.8, 151.5, 147.8, 136.5, 134.4, 131.9, 129.5, 128.5, 126.4, 122.0; MS (electrospray ionization) m/z 158.0 ($M+H^+$), 128.1.Compound **99**: ^{1}H NMR δ 8.77 (dd, *J* = 3.9, 1.2 Hz, 1 H), 8.07 (dd, *J* = 8.2, 1.2 Hz, 1 H), 7.65 (d, *J* = 8.2 Hz, 1 H), 7.55 (d, *J* = 7.0 Hz, 1 H), 7.40 (t, *J* = 7.6 Hz, 1 H), 7.32 (dd, *J* = 8.2, 4.3 Hz, 1 H), 5.20 (s, 2 H); ^{13}C NMR δ 149.0, 146.8, 138.2, 136.7, 128.3, 127.5, 127.3, 126.4, 121.1, 64.2; MS (electrospray ionization) m/z 160.3 ($M+H^+$), 142.0, 141.1.

6-(*t*-butyldimethylsilyloxy)benzoic acid (76)



To a mixture 200 mg (1.45 mmol) of *p*-hydroxybenzoicacid (**100**) and 295.8 mg (4.35 mmol) of imidazole in 6 mL of dry DMF was added 437.1 mg (2.9 mmol) of *t*-butyldimethylsilylchloride, under argon. After stirring for 5 h, diluted with dichloromethane (200 mL), washed with 0.1N HCl followed by brine, and concentrated to get viscous oil. To this oil, in a mixture 6 mL of MeOH and THF (1:1), was added a solution of 2 mL of 1M K_2CO_3 (aq) and stirred for 3 hours. Then the mixture was acidified with 1N HCl, filtered, and the residue was washed with water to get 220 mg (60 % yield) of compound **76**, whose ^{1}H NMR was in agreement with that of reported.[85]

Chapter 2 - Design, synthesis, and anti-norovirus activity of thiouridine nucleosides

2.1 Introduction

RNA dependent RNA polymerase (RdRp) is one of the non-structural proteins present in viruses.[1] Because of its unique nature and essentiality for the replication of viral particles,[2] it has been an attractive and selective target for antiviral drugs development.[3] Several nucleosides have been reported as strong inhibitors of viral RdRp polymerase, and some are progressing at different levels of clinical trials mainly for the treatment of hepatitis C virus (HCV).[4] Use of nucleosides for the treatment of norovirus has been less explored, yet few of the nucleosides tested against norovirus had shown effective inhibition.[5,6] The severity of norovirus infection and the problems associated with its treatments are explained in chapter one (**1.2.2**). In this chapter, the design, synthesis, and anti-norovirus activity of 2'-C-methylthiouridine (**101**) and a reported 2'-amino-2'-deoxythiouridine (**102**)[7] (**Figure 2.1**) along with the proposed future work of making phosphoramidate derivatives of these nucleosides is described.

2.2 Background

Two main categories of RdRp inhibitors: nucleosides inhibitors (NIs) and non-nucleosides inhibitors (NNIs) have been used for viral inhibition.[8] The nucleosidic analogs substitute natural nucleoside in polymerase substrate terminating the RNA elongation, while the non-nucleosidic analogs bind to the allosteric site of the polymerase converting it inactive.[9,10] Modification of nucleosides by establishing the methyl substituent at C2' led to the enhancement of potency against hepatitis C virus (HCV).[11,12] Many of such 2'-C-methyl analogs (**Figure 2.2**) are at different levels of clinical trials.[4] Like other viral RdRps, the structural features of finger,

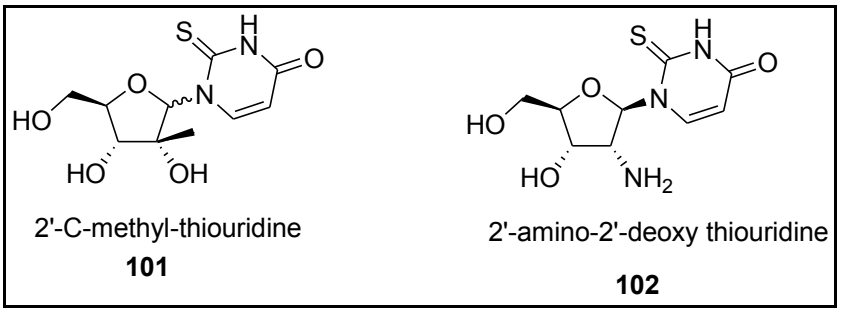


Figure 2.1: Thiouridine nucleosides synthesized as anti-norovirus agents.

palm, and thumb (**Figure 2.3 B**) are also common in norovirus, but the C-terminus active site is highly specific.[13] Moreover, the active form of norovirus RdRp was found to exist as homodimer.[14] Binding of 5-nitrocytidine triphosphate, a norovirus inhibitor, with NV RdRp revealed the possibility using nucleosides as NV RdRp inhibitors.[15] 2'-C-methyl cytidine (**106**) and ribavirin (**107**) (**Figure 2.4**) were found to effectively inhibit the replication of murine NV and human NV, respectively.[5,6] Similarly, the triphosphate derivative of amino analog 2'-C-amino-2'-C-deoxy-cytidine (**108**) was effective to cause rearrangement of the active site in NV RdRp.[16] The practice of substituting natural base pairs with thiolated analogs while modifying

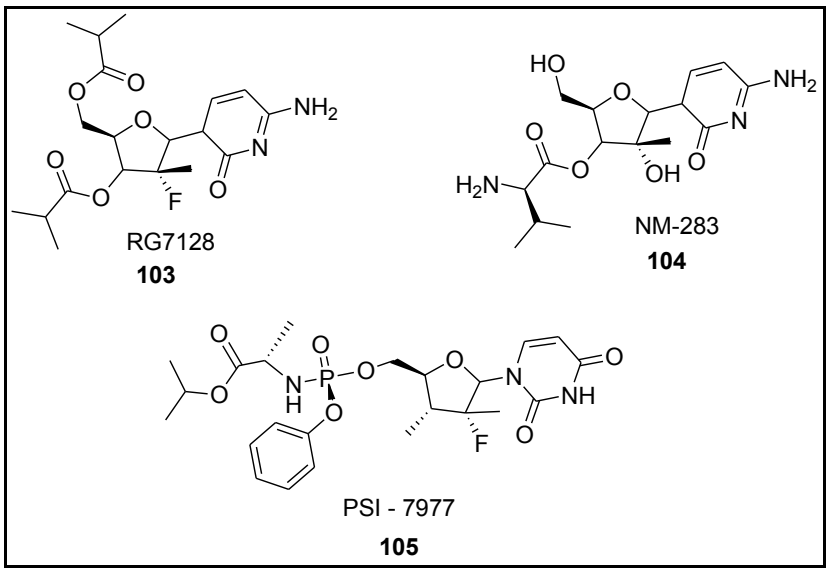


Figure 2.2: Nucleosides effective for the inhibition of HCV virus.

nucleosides was found beneficial; significant enhancement in the potency of nucleosides with thiolated uracil was observed as P2Y2 receptors.[7,17] Crystal structures of murine NV RdRp with ribavirin and thiouridine have been revealed and stronger inhibition of murine NV was observed by thiouridine.[18] All these studies encourage for the exploration of synthetic nucleosides as NV RdRp inhibitors towards the development potent anti-noroviral agents.

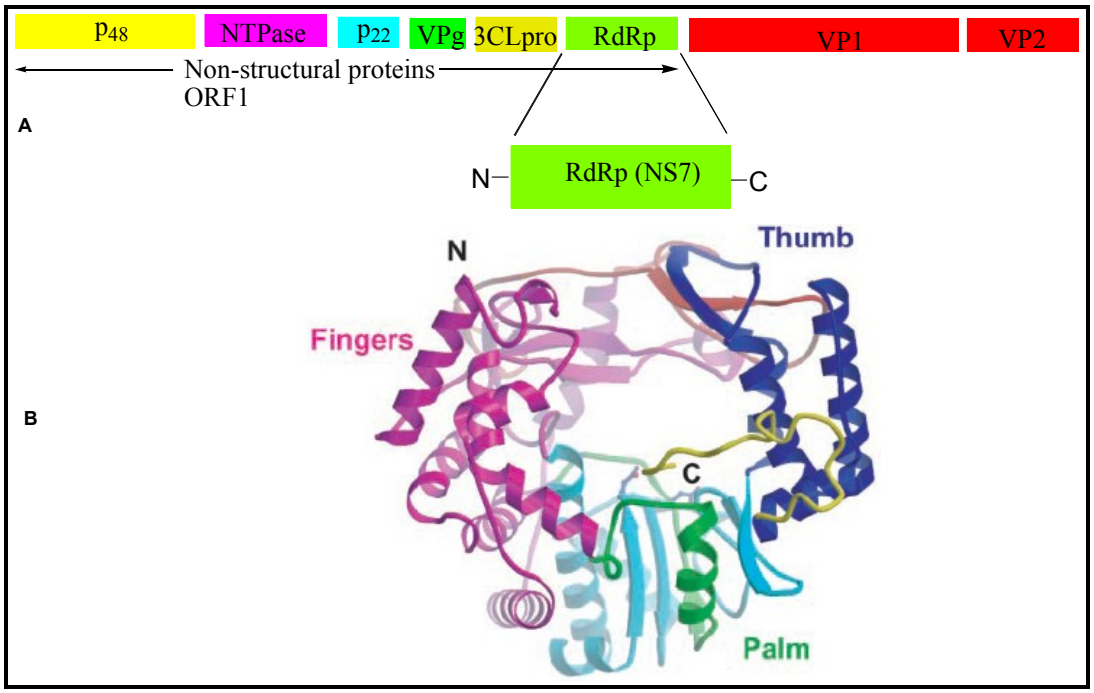


Figure 2.3: A- Schematic representation of NV genome (RdRp encoding is highlighted). B-X-ray structure of NV RdRp.[13]

Taken from ref 13 with permission

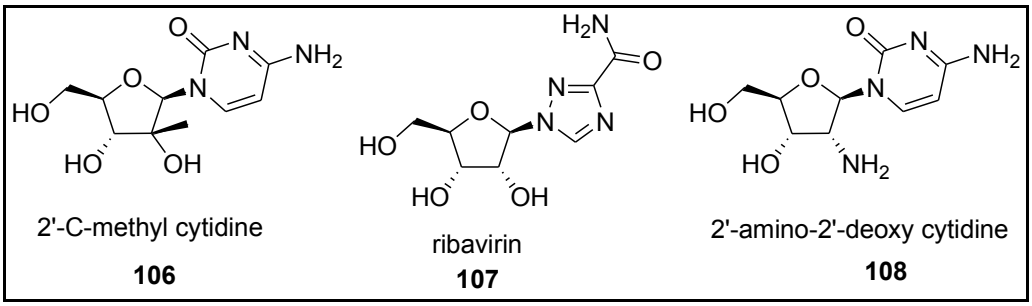


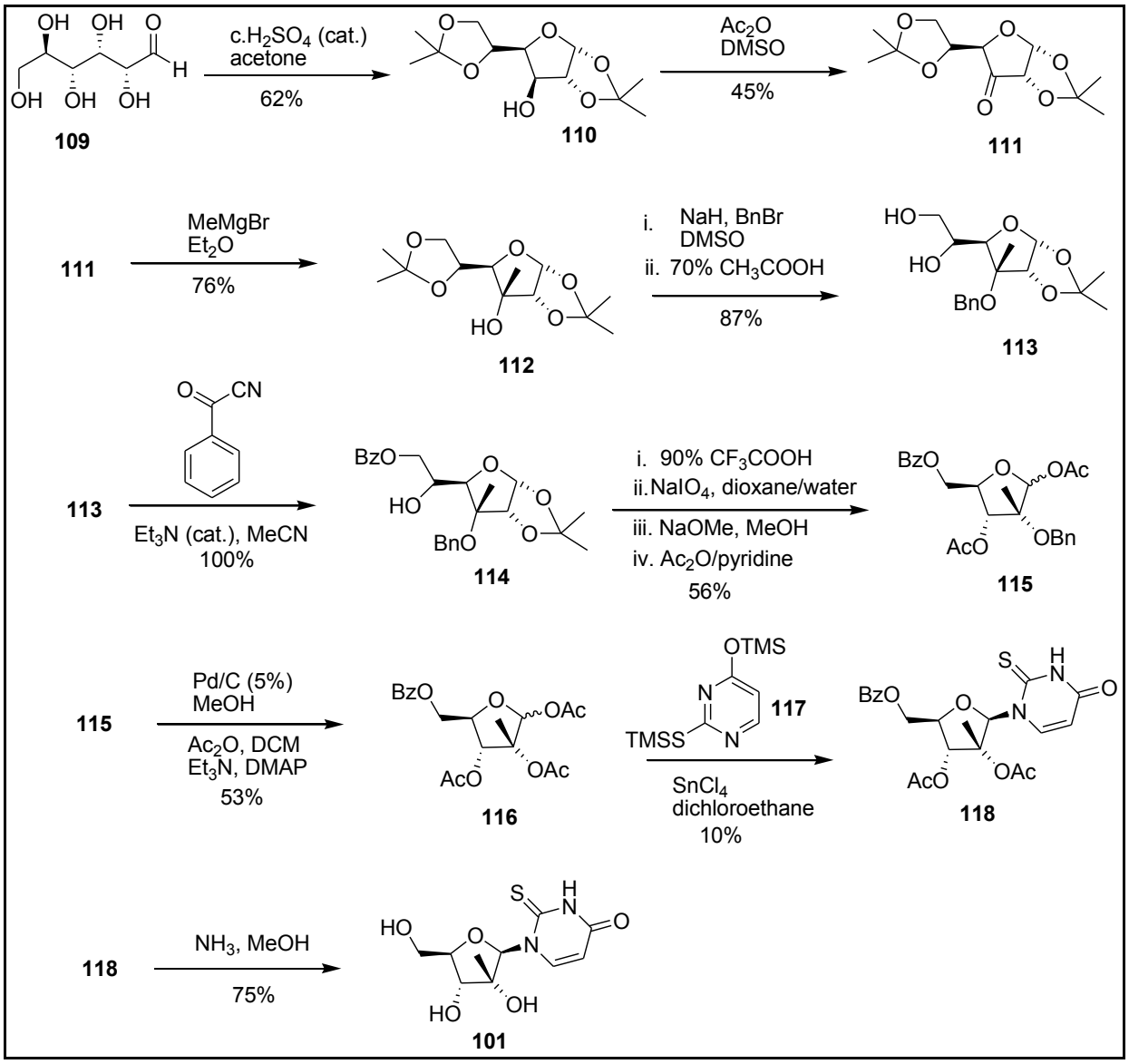
Figure 2.4: Nucleosides effective for the inhibiton of norovirus.

2.3 Design and synthesis of thiouridine nucleosides

Based on above literature studies, the modification of natural nucleosides by establishing 2'-C-methyl or 2'-amino as well as the substitution with thio analogs in base pairs can provide potential anti-norovirus compounds. Therefore, a novel 2'-C-methylthiouridine (**101**) and a reported 2'-amino-2'-deoxythiouridine (**102**)[7] were synthesized to evaluate the norovirus inhibition activity.

2.3.1 Synthesis of 2'-C-methylthiouridine (101)

The synthesis of 2'-C methylated thiouridine **101** was accomplished through a series reactions (**Scheme 2.1**) reported in different literatures starting from dextrose (**109**). Thus, the isopropylidene protection of diols in compound **109** was easily achieved by treating with a catalytic amount of conc. H_2SO_4 in acetone to get **110**.[19] The oxidation of hydroxyl in compound **110** with a mixture of acetic anhydride and dimethyl sulfoxide gave ketone **111** in 45% yield.[20] Then the treatment of compound **111** with methylmagnesisum bromide in ether provided compound **112** in 76% yield.[21] The benzyl protection of hydroxyl in compound **112** followed by selective removal of less hindered isopropylidene with 70% (aq) acetic acid provided dihydroxy analog **113** in 87% overall yield.[22] Selective benzoylation of primary hydroxyl in compound **113** was achieved by treating with benzoyl cyanide in acetonitrile using triethylamine as a base to get quantitative yield of compound **114**. Compound **115** was obtained as a mixture of epimers at C1 through a series of of hydrolysis, oxidative cleavage, cyclization, and acetylation reactions from compound **114**. Thus, after the removal of isopropylidene in the compound **114** with 90% (aq) TFA, the oxidation with $NaIO_4$ in a mixture of dioxane and water followed by cyclization using sodium methoxide as a base in methanol gave 5'-*O*-benzoylated-2'-C-methylribofuranose. Then the treatment of this 1',3' dihydroxyl intermediate with acetic



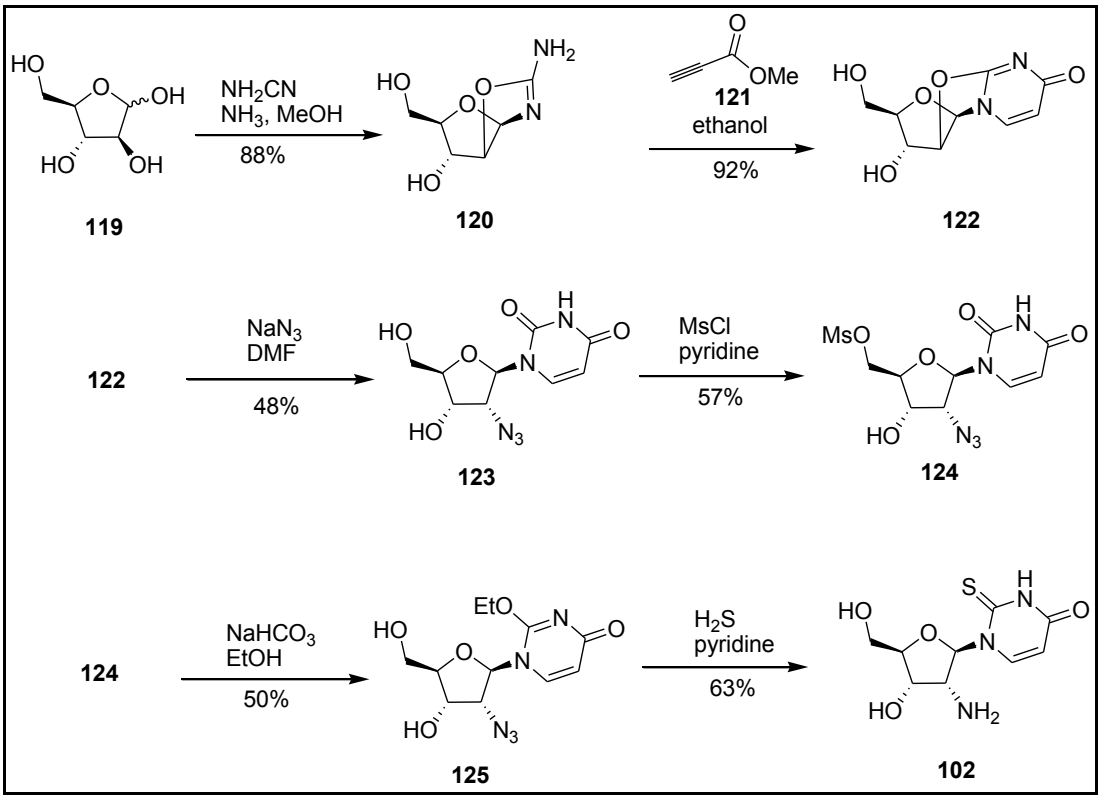
Scheme 2.1: Synthesis of 2'-C-methylthiouridine.

anhydride in pyridine gave compound **115** in 56% overall yield, as a mixture of epimers (4:1) at C1.[23] Attempt to remove C-2'-*O*-benzyl with Pd/C at 1 atmospheric pressure of H_2 at 25 °C did not work well, and the reaction at 50 °C gave a mixture of 2'-hydroxyl, 3',4'-dihydroxyl, and C1 methoxy substituted analogs. Then the acetylation with acetic anhydride in dichloromethane by treating with acetic anhydride in the presence of Et_3N and DMAP gave compound **116** in 53% overall yield. Treatment of compound **116** with silylated uracil **117** in dichloroethane in the

presence of tin-tetrachloride provided compound **118**, in 10% yield.[24,25] The α-anomer was only detected in trace amount. The methyl substituent at C2 must have caused some steric hindrance to upcoming thiouracil nucleophile leading to low yield. Similar Lewis acid catalyzed condensations of silylated thiouracil **117** were found to be very sensitive to reaction conditions and suffered with low yields.[26,27] The silylated thiouracil **117** was made by following the literature reported procedure.[17,24] The treatment of compound **118** with methanolic ammonia provided desired compound **101** in 75% yield. An attempt to make compound **101** by treating compound **118** with sodium methoxide in methanol followed by the neutralization with acidic resin was not fruitful.[28]

2.3.2 Synthesis of 2'-amino-2'-deoxythiouridine (102)

Motivated from the results that 2'-amino analog was effective to cause rearrangement of NV RdRp,[16] a reported 2'-amimo analog compound **102**[7] was synthesized (**Scheme 2.2**) by using literature methods, starting from D-arabinose (**119)**. Hence, the treatment of compound **119** with cyanamide in methanol at reflux in the presence of concentrated ammonia provided compound **120**[29] in 88% yield.[30] Then the stirring of compound **120** with methyl propiolate (**121**) in ethanol, at 78 °C, provided compound **122**[31] in 92% yield.[30,32] Nucleophilic substitution at C2 was achieved by refluxing compound **122** with excess amount of sodium azide in DMF to get compound **123** in 48% yield.[31] Selective mesylation of the 5'-hydroxyl was achieved by treating compound **123** with methanesulfonyl chloride in pyridine at 0 °C providing 57% yield of compound **124**.[7] The mesylated analog **124** was refluxed in ethanol in the presence of excess sodium bicarbonate to give compound **125** in 50% yield, which then was heated to 70 °C in pyridine, saturated with hydrogen sulfide, to get desired product **102** in 63% yield.[7]



Scheme 2.2: Synthesis of 2'-amino-2'-deoxythiouridine.

2.4 Anti-norovirus activity of thiouridine nucleosides

Anti-norovirus activity of thiouridine nucleosides was performed by **Yungeong Kim** and **Kyeong-Ok**, **Chang** at the Department of Diagnostic Medicine and Pathology, College of Vetenary Medicine, Kansas State University. The same protocol of quantitative reverse transcription-PCR (qRTPCR) that was used to evaluate anti-norovirus activity of tricyclic pyrones, mentioned in chapter one, was also used for the evaluation of thiouridine nucleosides.

Both the thiouridine nucleosides were found ineffective up to 50 μM for the inhibition of norovirus replication in HG23 cells (**Table 2.1**). Because of inactivity of these analogs the cytotoxicity was not measured. One of the reasons for their low efficacy may be inabitility of cellular kinase to initiate phosphorylation inside the cells.[10] Therefore, in this project, we have

planned to make phosphoramidate derivatives of these analogs hoping to get increased potency against norovirus.

Table 2.1: Anti-norovirus activity of thiouridine nucleosides.

Compounds	EC_{50} (μM)
2'-deoxy-2'-C-methylthiouridine (**101**)	> 50
2'-amino-2'-deoxythiouridine (**102**)	> 50

2.5 Future works

As both the nucleosides were found ineffective to inhibit norovirus, the future work of this project is to modify them to phosphoramide derivatives. The phosphoramidate analogs were found more effective and less toxic as anti-viral compounds to their corresponding free nucleosides, probably due to the increased lipophilicity and avoidance of kinase-mediated activation.[33,34,35] Sub-micromolar to nanomolar efficacy against HCV was achieved (**Figure 2.5**) by converting inactive nucleosides to corresponding phosphoramidate derivatives.[12,36,37] *In vivo* bioavailability of active triphosphate derivatives of nucleosides in liver was high when the compounds were administered as their phosphoramidates.[38] In this regard, the synthesis of phosphoramidate derivatives **128** and **129** (**Figure 2.6**) of nucleosides **101** and **102** has been proposed. The synthesis of compounds **128** and **129** will be executed (**Scheme 2.3**) by following the methods reported in literatures. Acetyl protection of amino group in nucleoside **102** will allow phosphorylation at *O*-5'. Therefore, the compound **102** will be treated with ethyl trifluoroacetate in DMF in the presence of *N,N*-di-isopropylethylamine (DIEA) to get compound

130.[7] Then the phosphorylation of compounds **101** and **130** will be achieved by treating them separately with compound **133** in THF in the presence of Et_3N.[33] Compound **133** will be prepared by reacting alanine methyl ester (**131**) with phenyl phosphoryl chloride (**132**) in THF using Et_3N as a base.[38]

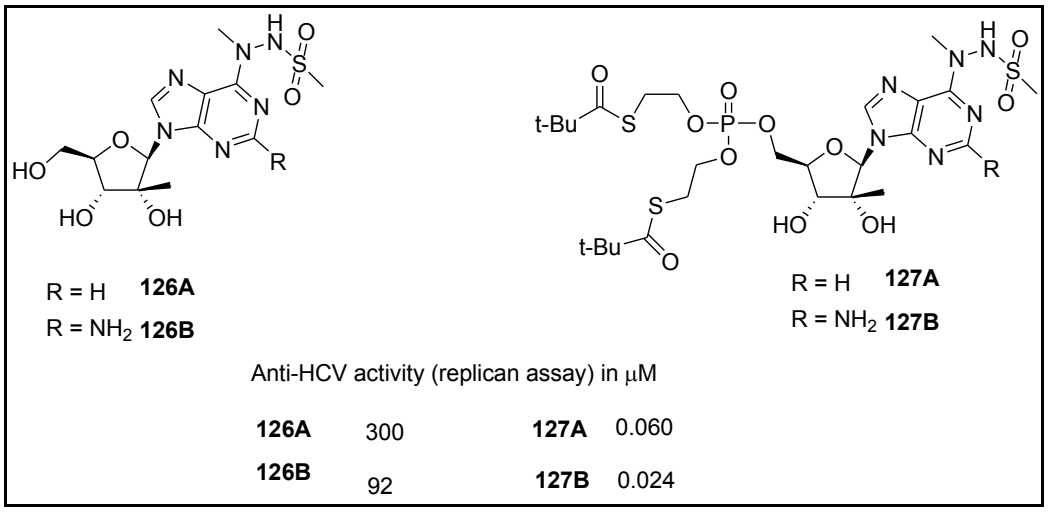


Figure 2.5: Increased efficacy of phosphoramidate analogs compared to corresponding free nucleosides against HCV.[12]

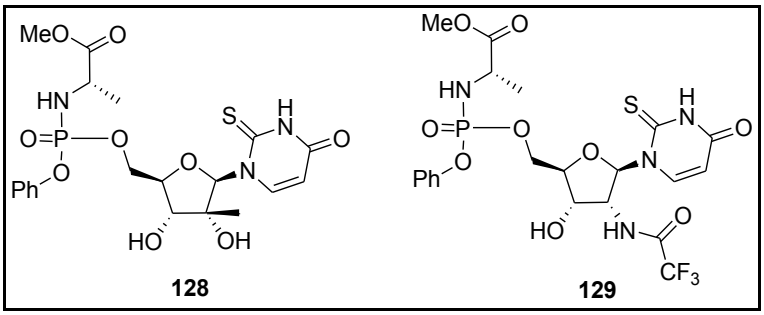
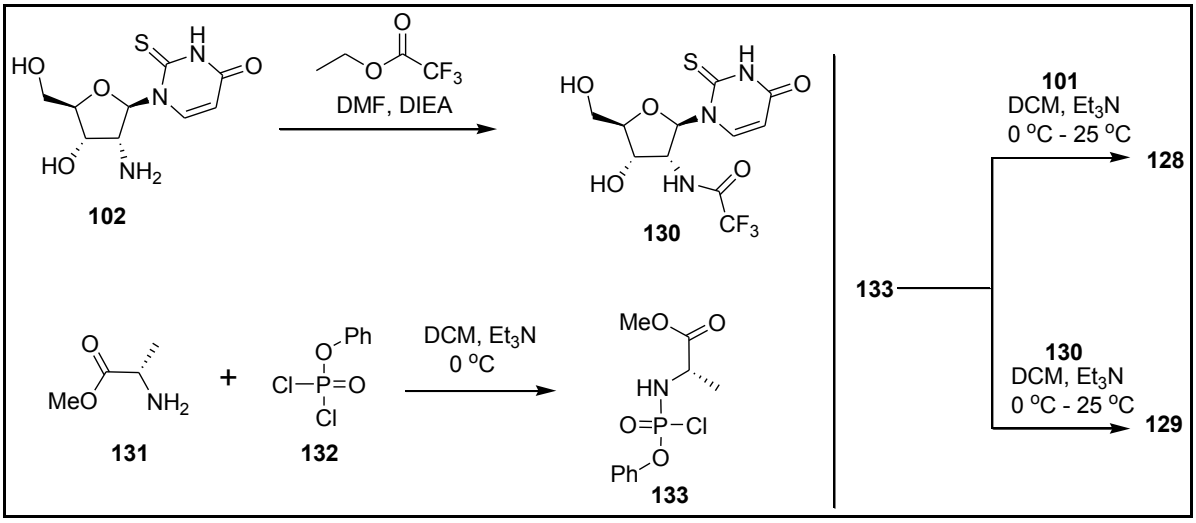


Figure 2.6: Proposed phosphoramidate analogs.



Scheme 2.3: Proposed synthesis of phosphoramidate analogs 128 and 129.[7,33,38]

2.6 Conclusions

Nucleosides 2'-C-methylthiouridine and 2'-amino-2'-deoxythiouridine were synthesized and found ineffective for the inhibition of norovirus replication in cell based assay. The inactivity may be due to low cell permeability or inability of cellular kinase to convert the nucleosides into active triphosphates inside the cells. Derivatization of these nucleosides to their corresponding phosphoramidate analogs may enhance anti-norovirus activity.

2.7 References

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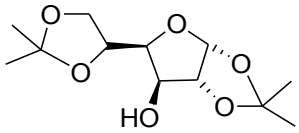
2.8 Experimental

General Methods. NMR spectra were obtained from a 400-MHz spectrometer (Varian Inc.), in $CDCl_3$, unless otherwise indicated, and reported in ppm. Low-resolution mass spectra were taken from an API 2000-triple quadrupole ESI-MS/MS mass spectrometer (from Applied Biosystems). Chemicals were purchased from Fisher Scientific, Aldrich Chemical Co., Chem-Impex International, and VWR.

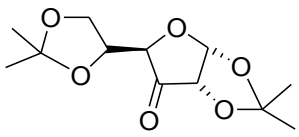
Anti-norovirus activity of thiouridines: The anti-noroviral effects of each compound were examined in NV replicon-harboring cells (HG23 cells) using Real-time qRT-PCR method as described in chapter one.

1,2;5,6-Di-*O*-isopropylidene-α-D-glucofuranose (110)



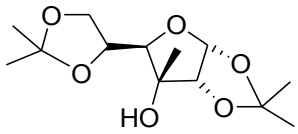
To 50 g (277 mmol) of dextrose (**109**) in 500 mL of acetone was added 6 drops of conc. H_2SO_4 and the mixture was stirred for 30 h. 40 g of the unreacted dextrose was recovered as residue by filtering the mixture. The filtrate was concentrated to 150 mL, diluted with dichloromethane (500 mL), washed with brine, dried with $MgSO_4$, and concentrated to get 9 g (62% yield) of compound **110** as a solid. ^{1}H NMR δ 5.95 (d, *J* = 3.5 Hz, 1 H), 4.54 (d, *J* = 3.5 Hz, 1 H), 4.37 – 4.31 (m, 2 H), 4.18 (dd, *J* = 8.6, 6.3 Hz, 1 H), 4.08 (dd, *J* = 7.4, 2.7 Hz, 1 H), 3.99 (dd, *J* = 8.6, 5.5 Hz, 1 H), 2.56 (d, *J* = 3.9 Hz, 1 H, OH), 1.51 (s, 3 H), 1.45 (s, 3 H), 1.37 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR δ 111.94, 109.73, 105.37, 85.27, 81.37, 75.00, 73.28, 67.75, 26.97, 26.92, 26.32, 25.31; MS (electrospray ionization) 543.2 (dimer + Na^+, 100%), 283.2 (M + Na^+).

1,2;5,6-Di-*O*-isopropylidene-α-D-*ribo*-hexofuranos-3-ulose (111)



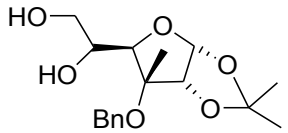
8.5 g (32.7 mmol) of compound **110**, in a mixture of 50 mL of DMSO and 25 mL of Ac_2O was stirred for 20 h. The mixture was diluted with diethyl ether (500 mL), washed with water followed by brine, dried ($MgSO_4$), concentrated, and purified through silica gel column using a gradient mixture of hexanes and ether as eluent to obtain 3.8 g (45% yield) of compound **111**. ^{1}H NMR δ 6.14 (d, *J* = 4.30 Hz, 1 H), 4.43 – 4.31 (m, 3 H), 4.03 (d, *J* = 6.3 Hz, 2 H), 1.46 (s, 3 H), 1.44 (s, 3 H), 1.34 (s, 6 H); ^{13}C NMR δ 209.02, 114.46, 110.54, 103.28, 79.12, 77.43, 76.54, 64.46, 27.73, 27.33, 26.15, 25.46; MS (electrospray ionization) 381.4 ($M + Na^+$).

1,2;5,6-Di-*O*-isopropylidene-3-C-methyl-α-D-allofuranose (112)



To 3.5 g (13.56 mmol) of ketone **111**, in 110 mL of dry diethyl ether at 0 °C was added 6 mL (17.63 mmol) methyl magnesium bromide (3M in diethyl ether). After stirring the mixture at room temperate for 4 h, diluted with water (100 mL), and extracted with diethyl ether. The ether layer was washed with brine, dried ($MgSO_4$), and concentrated to get 2.8 g (76% yield) of compound **112** as a solid. ^{1}H NMR δ 5.71 (d, *J* = 3.9 Hz, 1 H), 4.18 (d, *J* = 3.5 Hz, 1 H), 4.14 – 4.08 (m, 2 H), 3.97 – 3.90 (m, 1 H), 3.79 (d, *J* = 7.8 Hz, 1 H), 2.68 (s, 1 H, OH), 1.60 (s, 3 H), 1.46 (s, 3 H), 1.37 (s, 3 H), 1.36 (s, 3 H), 1.29 (s, 3 H); ^{13}C NMR δ 113.05, 109.80, 103.81, 84.96, 81.63, 77.63, 73.97, 68.00, 26.97, 26.95, 26.64, 25.50, 19.73; MS (electrospray ionization) 297.2 ($M + Na^+$, 100%).

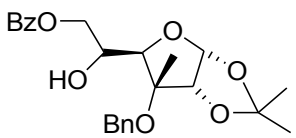
3-*O*-Benzyl-1,2-*O*-isopropylidene-3-C-methyl-α-D-allofuranose (113)



Step 1: 2.8 gm (10.2 mmol) of alcohol **112**, in 50 mL of DMSO was transferred to a slurry of 294 (12.26 mmol) NaH in 15 mL of DMSO. After stirring for 1 h, 1.8 mL (15.31 mmol) of BnBr was added dropwise. After stirring for 2 more hours, the mixture was diluted with water (300 mL) and extracted in diethyl ether. The ether layer was washed with brine, dried with $MgSO_4$, concentrated, and purified through silica gel column using a gradient mixture of hexanes and ether to get 2.8 g (91% yield) of benzylated analog and 0.5 g of recovered alcohol **112**.

Step 2: 2.8 g (7.7 mmol) of the benzylated product obtained from earlier step was stirred in 100 mL of 70% CH_3COOH (aq) for 18 h. Then the mixture was diluted with brine (100 mL) and extracted in dichloromethane (150 mL x 3). The organic layer was dried with $MgSO_4$ and concentrated to get 2.4 g (96% yield) of compound **113** as a solid. ^{1}H NMR δ 7.42 – 7.28 (m, 5 H), 5.75 (d, *J* = 3.9 Hz, 1 H), 4.69 – 4.61 (m, 2 H), 4.40 (d, *J* = 3.9 Hz, 1 H), 4.05 (d, *J* = 8.6 Hz, 1 H), 3.85 (dt, *J* = 8.6, 4.3 Hz, 1 H), 3.79 (dd, *J* = 12.0, 4.3 Hz, 1 H), 3.68 (dd, *J* = 12.0, 4.3 Hz, 1 H), 1.62 (s, 3 H), 1.41 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR δ 137.99, 128.61, 127.98, 113.53, 104.52, 83.58, 82.76, 78.58, 70.18, 67.40, 64.70, 27.00, 26.84, 16.64; MS (electrospray ionization) 346.9 (M + Na^+, 100%).

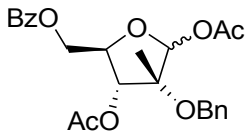
3-*O*-Benzyl-1,2-di-*O*-isopropylidene-3-C-methyl-6-*O*-benzoyl-α-D-allofuranose (114)



To a mixture of 2.4 g (7.4 mmol) of compound **113**, and 1380 mg (10.52 mmol) of benzoyl cyanide in 60 mL of dry acetonitrile was added 2 drops of triethylamine and the mixture was stirred for 16 h. The mixture was dilute with dichloromethane, washed with water followed by

brine, dried ($MgSO_4$), and concentrated to provide 3.2 g (100% yield) of compound **114** as a solid. ^{1}H NMR δ 8.13 – 8.05 (m, 2 H), 7.59 – 7.51 (m, 1 H), 7.49 – 7.28 (m, 7 H), 5.77 (d, *J* = 3.5 Hz, 1 H), 4.70 – 4.63 (m, 3 H), 4.42 (d, *J* = 3.5 Hz, 1 H), 4.36 (dd, *J* = 11.7, 5.1 Hz, 1 H), 4.17- 4.08 (m, 2 H), 1.61 (s, 3 H), 1.43 (s, 3 H), 1.38 (s, 3 H); ^{13}C NMR δ 166.76, 138.11, 133.08, 129.92, 128.55, 128.46, 127.93, 127.85, 113.46, 104.44, 83.58, 82.88, 78.06, 68.82, 67.33, 67.09, 26.95, 26.86, 16.41; MS (electrospray ionization) 451.8 (M + Na^+, 100%).

1,3-Di-*O*-acetyl-2-*O*-benzyl-2-C-methyl-5-*O*-benzoyl-β-D-ribofuranose (115)



Step 1: 3 g (7.0 mmol) of compound **114** in 30 mL of 90% trifluoroacetic acid (aq), at 0 °C to 25 °C, was stirred for 0.5 h. The mixture was diluted with 300 mL of dichloromethane, washed with water, 10% $NaHCO_3$ followed by brine, dried with $MgSO_4$, and concentrated.

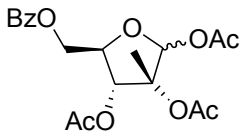
Step 2: To the residue obtained in step 1, in a mixture of 50 mL of dioxane and 20 mL of water, was added a solution of 10 mL of 1M $NaIO_4$ and the mixture was stirred for 12 h. Diluted with 30 mL of EtOH, filtered, the filtrate was concentrated in reduced vacuum. To this residue was added 30 mL of $CHCl_3$ and concentrated again in reduced pressure.

Step 3: To the residue obtained in step 2, in 50 mL of dry MeOH, was added 0.2 mL of 1M NaOMe in MeOH. After stirring for 45 min at 25 °C, the mixture was neutralized with Dowex resin, filtered, and the filtrate was concentrated under reduced pressure.

Step 4: To the residue obtained in step 3, in 30 mL of dry pyridine, was added 5 mL of acetic anhydride. After stirring for 5 h at 25 °C, the mixture was acidified with 2N HCl and extracted in dichloromethane. The organic layer was washed with brine, dried with $MgSO_4$, concentrated, and purified through silica gel column using a gradient mixture of hexanes and ethyl acetate to

get 1.75 g (56% overall yield in 4 steps) of compound **115** as a mixture of two epimers (4:1) at C1 center. ^{1}H NMR δ 8.13 - 8.03 (m, 2 H), 7.62 – 7.54 (m, 1 H), 7.50 – 7.26 (m, 7 H), 7.32 and 6.28 (2 s, 1 H), 5.54 and 5.42 (2 d, *J* = 8.2, 1 H), 4.69 – 4.33 (m, 5 H), 2.13 (s, 3 H), 1.98 and 1.96 (2 s, 3 H), 1.47 and 1.43 (2 s, 3 H); ^{13}C NMR δ 170.60, 169.72, 166.28, 160.32, 138.49, 133.38, 129.96, 128.59, 127.81, 127.24, 98.51, 98.47, 98.07, 83.38, 78.81, 75.95, 75.30, 66.23, 64.00, 63.61, 21.37, 21.29, 21.05, 15.72, MS (electrospray ionization) 465.1 (M + Na^+, 100%).

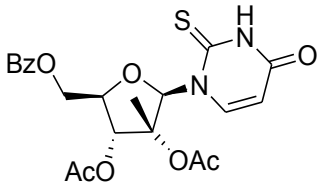
1,2,3-Tri-*O*-acetyl-2-C-methyl-5-*O*-benzoyl-β-D-ribofuranose (116)



Step 1: A mixture of 1 g (2.26 mmol) of compound **115**, 300 mg of (5%) Pd/C in 30 mL of MeOH was stirred at 50 °C for 18 h. The mixture was filtered through celite and concentrated to get a mixture of 2'-hydroxy, 2',3'-dihydroxy, and C1 methoxy substituted analogs.

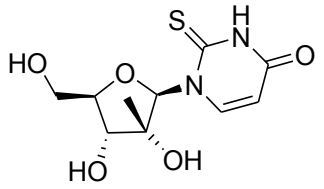
Step 2: To the crude mixture obtained in first step, in 25 mL of dry DCM, was added 100 mg (0.82 mmol) of DMAP and 1.2 mL of triethylamine followed by 2.5 mL of acetic anhydride. After stirring for 12 h, diluted with water (30 mL), acidified with 1N HCl, and extracted in dichloromethane (80 x3). The combined organic layer was washed with brine, dried with $MgSO_4$, concentrated, and purified through silica gel column to get 472 mg (53% yield in two steps) of compound **116**. ^{1}H NMR δ 8.14 – 7.97 (m, 2 H), 7.63 – 7.53 (m, 1 H), 7.50 – 7.40 (m, 2 H), 6.53 (s, 1 H), 5.45 (d, *J* = 8.2 Hz, 1 H), 4.61 (dd, *J* = 11.7, 3.5 Hz, 1 H), 4.47 – 4.41 (m, 1 H), 4.40 – 4.34 (m, 1 H), 2.13 (s, 3 H), 2.11 (s, 3 H), 2.00 (s, 3 H), 1.64 (s, 3 H); ^{13}C NMR δ 170.33, 169.80, 169.09, 166.23, 133.47, 129.93, 128.64, 97.45, 78.38, 75.21, 64.01, 22.02, 21.18, 20.91, 16.52; MS (electrospray ionization) 416.9 (M + Na^+, 100%).

1-(2,3-Di-*O*-acetyl-2-C-methyl-5-*O*-benzoyl-β-D-ribofuranosyl)thiouracil (118)



To a solution of 200 mg (0.5 mmol) comound **116** in 6 mL of dichloroethane was added silylated thiouracil **117**. After stirring for 5 min, 145 mg (0.55 mmol) of tin tetrachloride was added and the mixture was stirred for 4h. 5 mL of sat. $NaHCO_3$ solution was added, stirred for 1 h, and left to stand for 3h. The mixture was filtered through silica pad; the filtrate was diluted with 15 mL of water and extracted in dichloromethane. The organic layer was washed with brine, dried with $MgSO_4$, concentrated, and purified through silica gel column to get 31 mg (10% yield) of compound **118**. ^{1}H NMR δ 8.08 – 8.00 (m, 2 H), 7.91 (d, *J* = 6.6 Hz, 1 H), 7.62 – 7.54 (m, 1 H), 7.50 – 7.40 (m, 2 H), 6.75 (s, 1 H), 6.26 (d, *J* = 6.6 Hz, 1 H), 5.23 (d, *J* = 3.9 Hz, 1 H), 4.71 – 4.56 (m, 2 H), 4.54 – 4.49 (m, 1 H), 2.16 (s, 3 H), 2.09 (s, 3 H), 1.85 (s, 3 H); ^{13}C NMR δ 169.85, 169.12, 166.31, 164.19, 160.07, 154.99, 133.52, 129.90, 129.66, 128.69, 112.15, 92.31, 82.24, 81.28, 75.71, 63.37, 22.86, 21.57, 20.93; MS (electrospray ionization) 485.3 (M + Na^+, 100%).

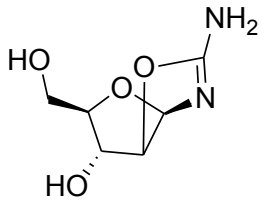
2'-C-methylthiouridine (101)



20 mg (0.04 mmol) of compound **118** in 5 mL of 7M methanolic ammonia was stirred for overnight. The mixture was concentrated and purified through silica gel column using a gradient mixture of dichloromethane and methanol as eluent to get 8.9 mg (75% yield) of compound **101**. ^{1}H NMR (D_2O) δ 7.82 (d, *J* = 8.2 Hz, 1 H), 5.9 (d, *J* = 7.8 Hz, 1 H), 5.16 (s, 1 H, H-1), 3.94 –

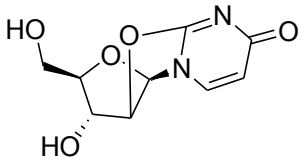
3.87 (m, 2 H), 3.75 – 3.68 (m, 1 H), 3.44 (d, J = 8.2 Hz, 1 H), 1.07 (s, 3 H, Me); MS (electrospray ionization) negative mode, 273.4 (M - 1).

2-Amino-β-D-arabinofurano[1',2';4,5]-2-oxazoline (120)



2 mL of ammonia (28% aqueous) was added to a mixture of 5 g (33.3 mmol) of D-arabinose (**119**) and 2.8 g (66.6 mmol) of cyanamide in 20 mL of MeOH. After stirring for 4.5 h at 45 °C, the mixture was concentrated to 15 mL, cooled to 0 °C, and filtered to get 5.1 g (88% yield) of compound **120** as a white solid. ^{1}H NMR (DMSO-d_6) δ 6.30 (br. s., 2 H), 5.66 (d, J = 5.5 Hz, 1 H), 5.40 (br. s., 1 H), 4.70 (br. s., 1 H), 4.52 (d, J = 5.5 Hz, 1 H), 4.00 (d, J = 3.1 Hz, 1 H), 3.71 – 3.58 (m, 1 H), 3.32 – 3.20 (m, 2 H); ^{13}C NMR (DMSO-d_6) δ 162.21, 99.95, 88.05, 84.61, 75.61, 61.54; MS (electrospray ionization) 174.9 (M + Na^+, 100%).

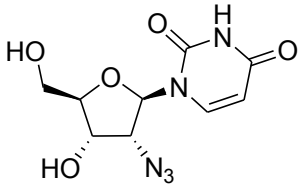
2,2'-Anhydro-1-(D-arabinofuranosyl)uracil (122)



A mixture of 1 g (5.7 mmol) of compound **120** and 1 mL (11.5 mmol) of methyl propiolate (**121**) in 12 mL of 96% EtOH was refluxed for 2 h. Then the mixture was diluted with dichloromethane (50 mL), cooled to 0 °C, and filtered to get 1.2 g (92% yield) of compound **122** as a white solid. ^{1}H NMR (DMSO-d_6) δ 7.83 (d, J = 7.4 Hz, 1 H), 6.30 (d, J = 5.9 Hz, 1 H), 5.88 (d, J = 4.3 Hz, 1 H), 5.84 (d, J = 7.4 Hz, 1 H), 5.20 (d, J = 5.5 Hz, 1 H), 4.97 (t, J = 5.1 Hz, 1 H), 4.38 (d, J = 3.5 Hz, 1 H), 4.07 (t, J = 5.1 Hz, 1 H), 3.32 – 3.24 (m, 1 H), 3.23 – 3.15 (m, 1 H); ^{13}C NMR

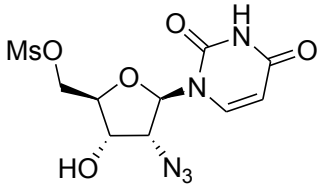
(DMSO-d_6) δ 171.18, 159.79, 136.83, 108.61, 90.01, 89.21, 88.75, 74.73, 60.83; MS (electrospray ionization) 249.0 (M + Na^+, 100%).

2'-Azido-2'-deoxyuridine (123)



A mixture of 0.7 g (3.1 mmol) of compound **122** and 1.6 g (24.77 mmol) of sodium azide was stirred in 20 mL of DMF at 115 °C for 16 h. The mixture was diluted with 150 mL of a mixture of dichloromethane and methanol (15:1) and filtered. The filtrate was concentrated, and purified through silica gel column using a gradient mixture of dichloromethane and methanol to get 0.4 g (48% yield) of compound **123**, as a solid. ^{1}H NMR (DMSO-d_6) δ 11.40 (br. s, 1 H), 7.87 (dd, J = 8.2, 1.2 Hz, 1 H), 5.95 (d, J = 5.5 Hz, 1 H), 5.88 (d, J = 5.5 Hz, 1 H), 5.67 (d, J = 8.20 Hz, 1 H), 5.17 (t, J = 4.7 Hz, 1 H), 4.30 (q, J = 4.7 Hz, 1 H), 4.05 (t, J = 5.5 Hz, 1 H), 3.92 – 3.87 (m, 1 H), 3.70 – 3.62 (m, 1 H), 3.61 – 3.54 (m, 1 H); ^{13}C NMR (DMSO-d_6) δ 163.00, 150.43, 140.01, 102.06, 85.57, 85.22, 70.44, 64.58, 60.21; MS (electrospray ionization) 292.0 (M + Na^+, 100%).

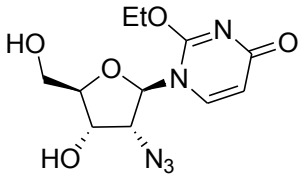
2'-Azido-2'-deoxy-5'-*O*-methanesulfonyluridine (124)



To a mixture of 0.4 g (1.49 mmol) of compound **123** in 8 mL of pyridine at -30 °C was added 0.15 mL (1.63 mmol) of methanesulfonyl chloride and temperature was increased to 0 °C and stirred for 1 h. Reaction was quenched with sat. $NaHCO_3$ (20 mL) and extracted with dichloromethane. The organic layer was washed with brine, dried with $MgSO_4$, concentrated,

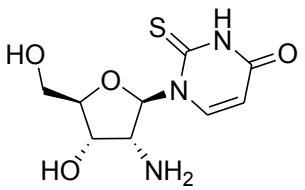
and purified through silica gel column using a gradient mixture of dichloromethane and methanol as eluent to get 295 mg (57% yield) of compound **124**, as a solid. ^{1}H NMR (DMSO-d_6) δ 11.46 (s, 1 H), 7.62 (d, J = 8.2 Hz, 1 H), 6.19 (d, J = 5.5 Hz, 1 H), 5.82 (d, J = 5.1 Hz, 1 H), 5.68 (d, J = 7.8 Hz, 1 H), 4.54 – 4.20 (m, 4 H), 4.13 – 4.00 (m, 1 H), 3.23 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 162.92, 150.33, 140.43, 102.36, 86.77, 81.20, 70.20, 68.70, 63.51, 36.86.

2'-Azido-2'-deoxy-2-*O*-ethyluridine (125)



A mixture of 160 mg (0.46 mmol) of compound **124** and 386 mg (4.6 mmol) of $NaHCO_3$ in 10 mL of absolute ethanol was refluxed for 36 h. Diluted with ethyl acetate (100 mL), and filtered. The filtrate was concentrated and purified through silica gel column using a gradient mixture of dicholoromethane and methanol as eluent to get 69 mg (50% yield) of compound **125**, as a solid. ^{1}H NMR DMSO-d_6) δ 7.97 (d, J = 7.6 Hz, 1 H), 6.01 (d, J = 5.9 Hz, 1 H), 5.86 (d, J = 7.6 Hz, 1 H), 5.84 (d, J = 4.9 Hz, 1 H), 5.24 (t, J = 5.1 Hz, 1 H), 4.43 – 4.25 (m, 3 H), 4.12 (t, J = 5.2 Hz, 1 H), 3.95 – 3.88 (m, 1 H), 3.74 – 3.66 (m, 1 H), 3.63 – 3.56 (m, 1 H), 1.33 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (DMSO-d_6) δ 169.52, 154.72, 137.62, 107.94, 87.27, 85.44, 70.05, 65.29, 64.49, 59.86, 13.84; MS (electrospray ionization) 320.1 (M + Na^+, 100%).

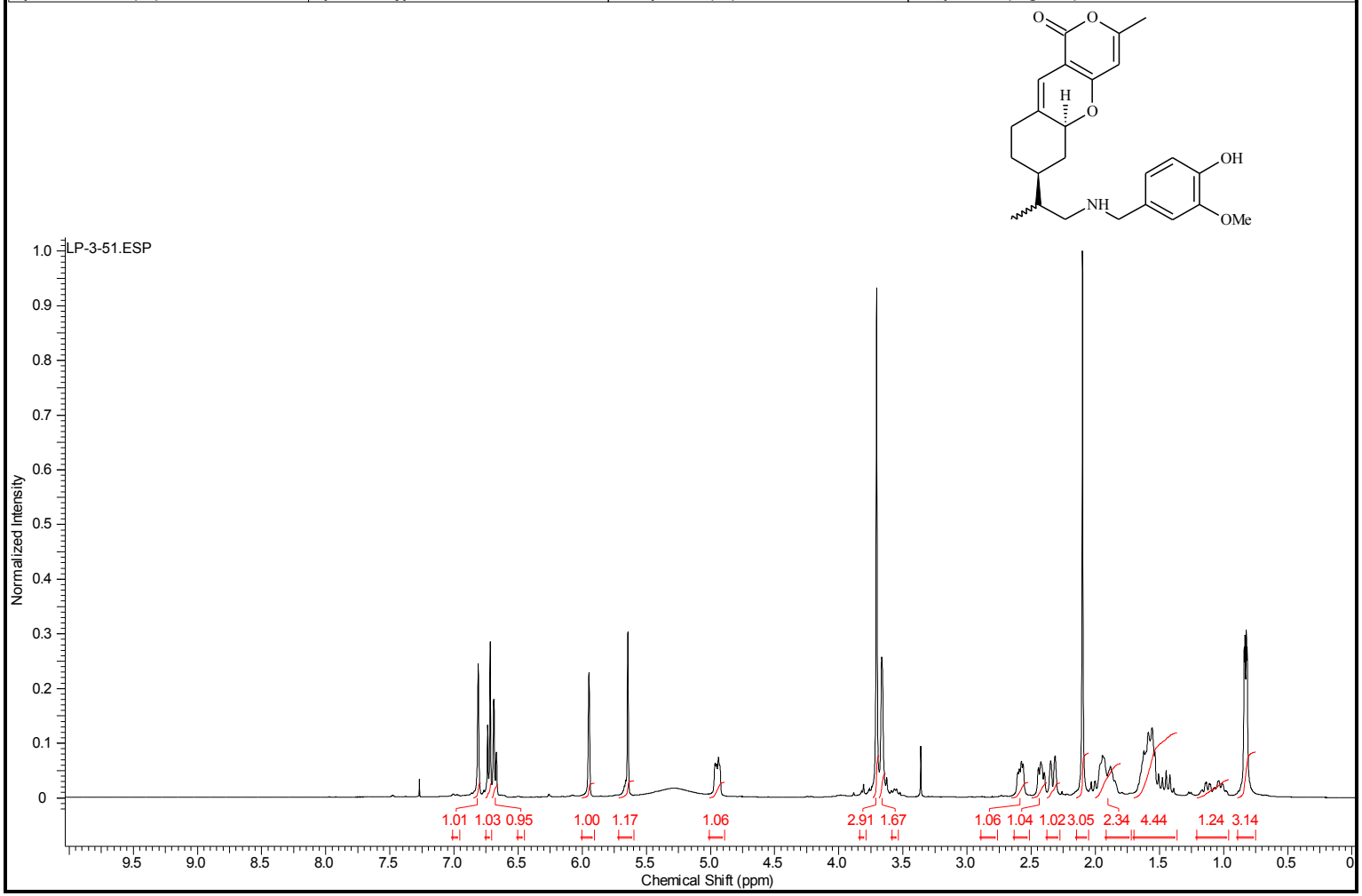
2'-Amino-2'-deoxythiouridine (102)



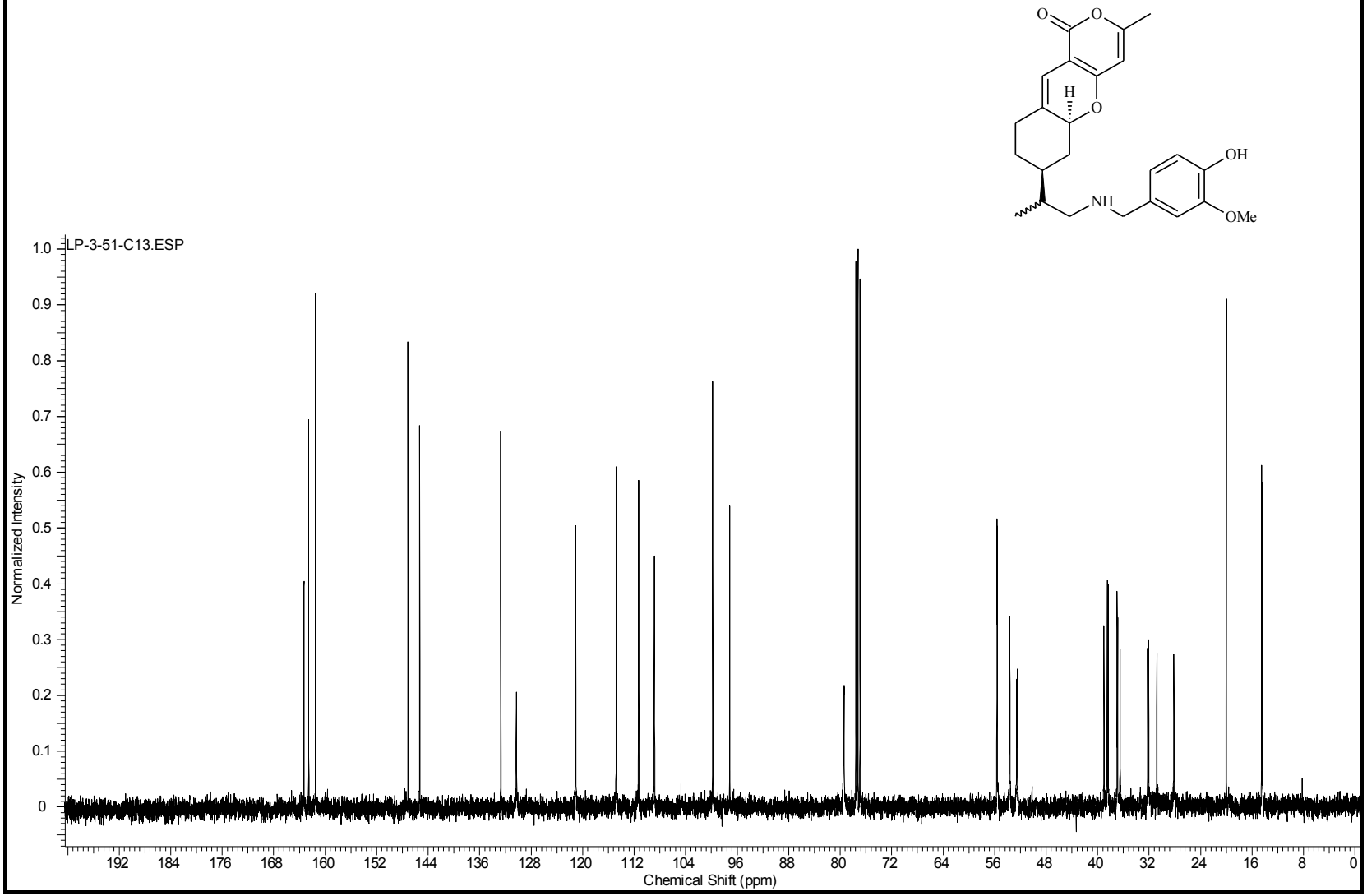
H_2S gas was bubbled into a solution of 40 mg (0.13 mmol) compound **125** in 8 mL of pyridine, at 0 °C for 0.5 h in a sealed tube, and the tube was closed. After stirring at 75 °C for 3 days, the solution was concentrated, and purified through silica gel column using a gradient mixture of dichloromethane and methanol as eluent to get 20 mg (63% yield) of compound **102**, as a solid. ^{1}H NMR (DMSO-d_6) δ 8.09 (d, J = 8.2 Hz, 1 H), 6.56 (d, J = 6.3 Hz, 1 H), 6.00 (d, J = 8.2 Hz, 1 H), 5.24 (br. s., 1 H), 4.05 – 3.87 (m, 2 H), 3.69 – 3.54 (m, 2 H), 3.43 – 3.26 (m, 4 H); ^{13}C NMR (DMSO-d_6) δ 176.90, 159.51, 140.97, 106.67, 92.43, 85.90, 70.08, 60.65, 58.80; MS (electrospray ionization) 260.1 ($M + Na^+$, 100%).

Appendix: ^{1}H and ^{13}C spectra

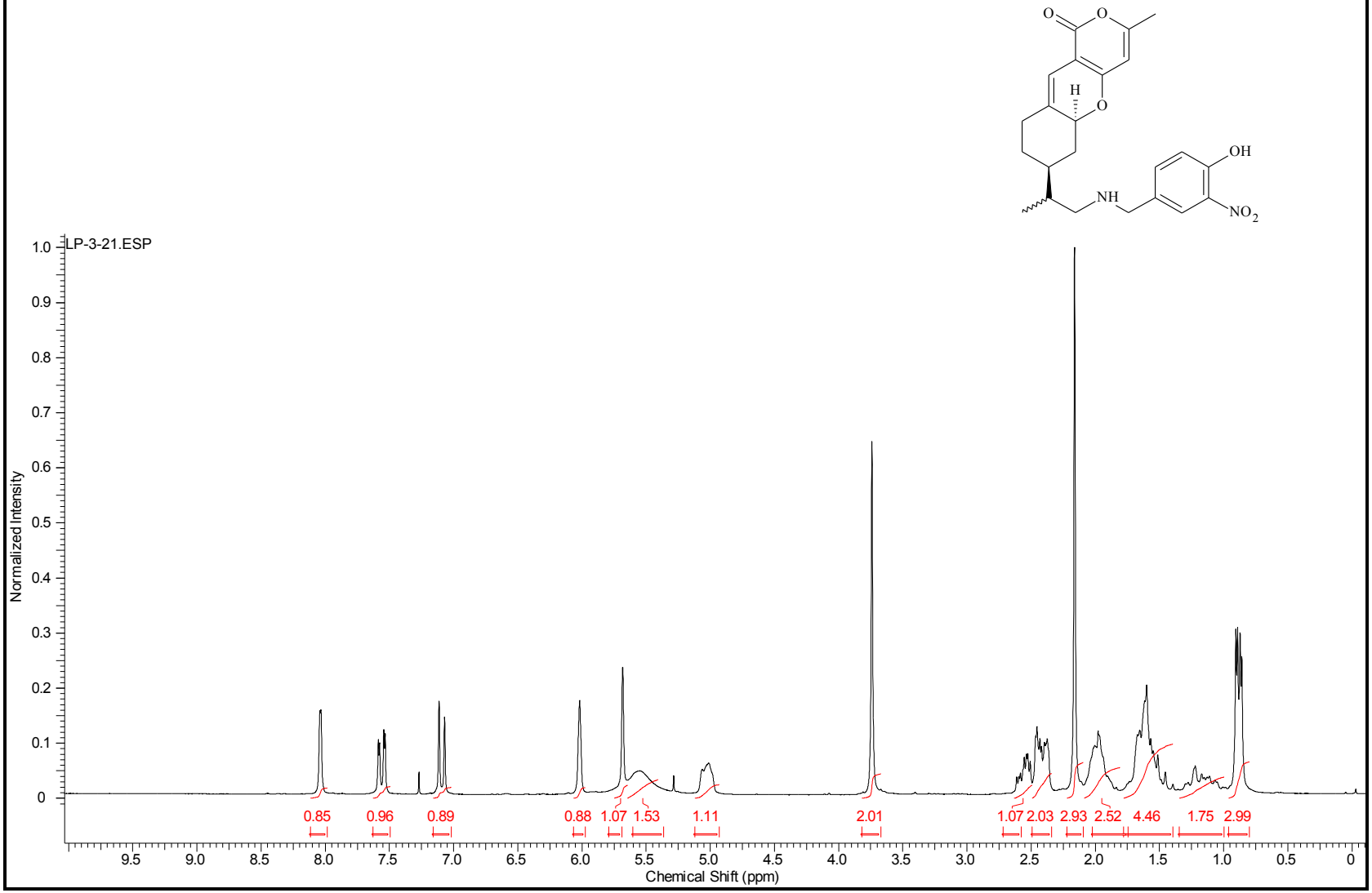
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Dec 23 2009	***Date Stamp***	Dec 23 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\400 MHZ\LP-3-VANILINEALDEHYDE-AMINE.FID\FID					***Frequency (MHz)***	399.75
Nucleus	1H	***Number of Transients***	44	***Original Points Count***	13103	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2403.5376	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	30.000



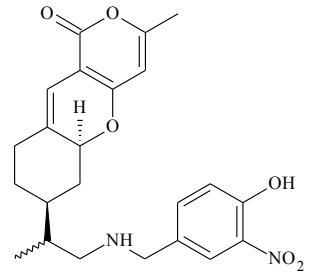
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Dec 23 2009	***Date Stamp***	Dec 23 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\400 MHZ\LP-3-51C13.FID\FID					***Frequency (MHz)***	100.53
Nucleus	13C	***Number of Transients***	472	***Original Points Count***	31375	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10528.0313	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	30.000

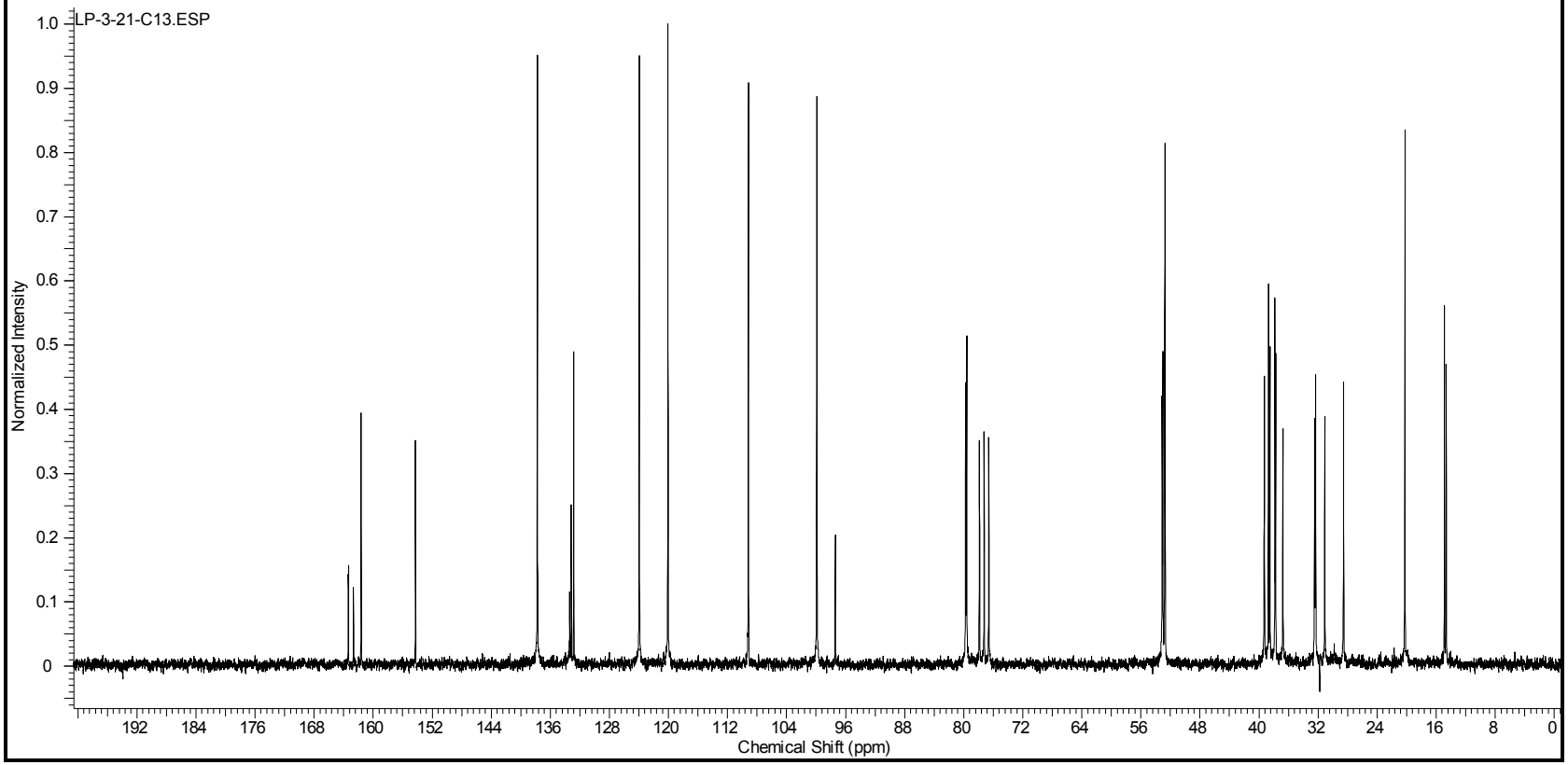


Acquisition Time (sec)	1.9945	***Comment***	STANDARD 1H OBSERVE□lp-3-21fr7-21			***Date***	Nov 1 2009
Date Stamp	Nov 1 2009	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LPOKHREL\LP-3-21FR7-21.FID\FID				
Frequency (MHz)	199.98	***Nucleus***	1H	***Number of Transients***	80	***Original Points Count***	5984
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	16.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	1002.8743	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	3000.30	***Temperature (degree C)***	AMBIENT TEMPERATURE

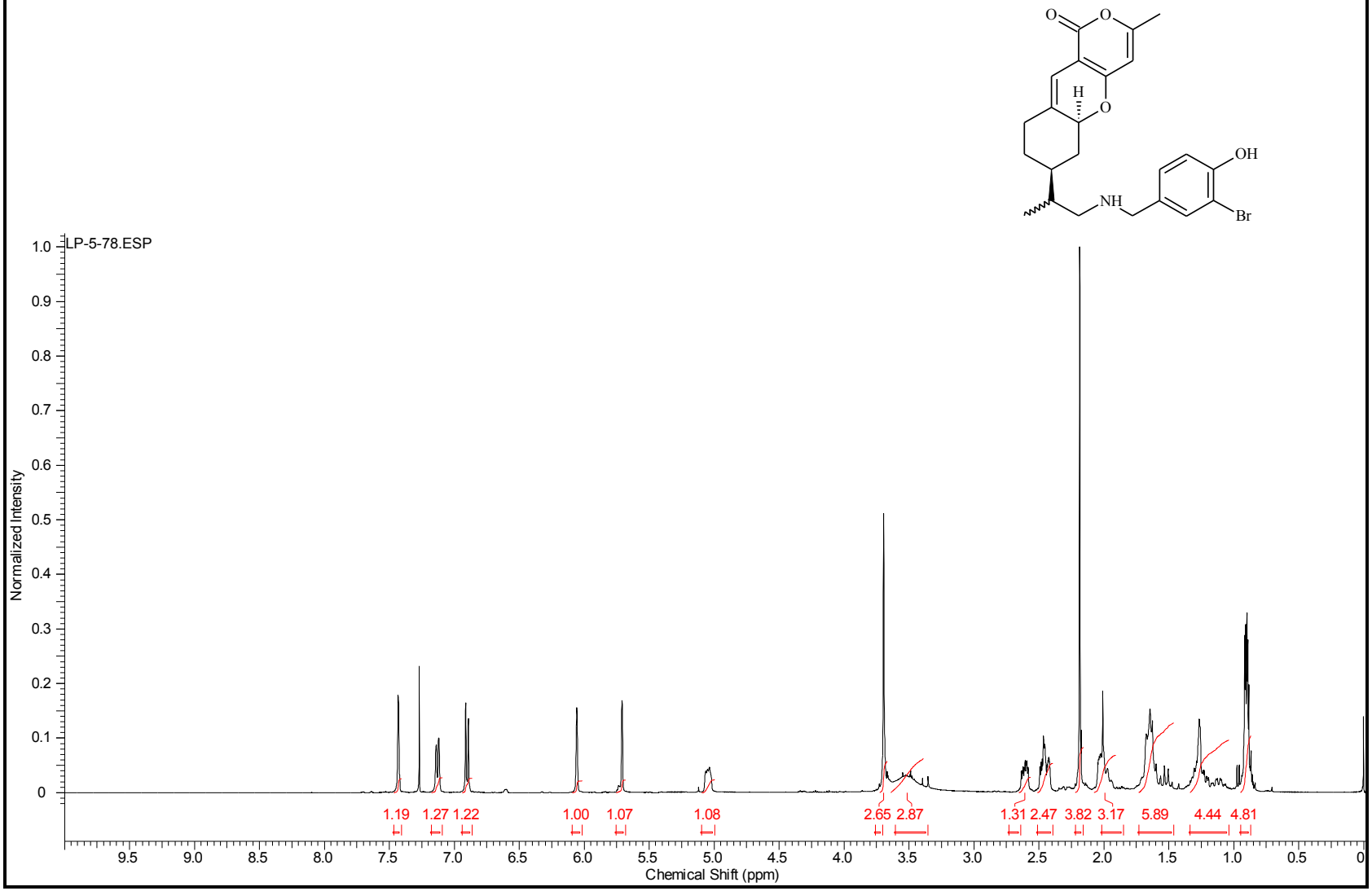


Acquisition Time (sec)	1.4976	***Comment***	13C OBSERVE□lp-3-21fr7-21			***Date***	Nov 1 2009
Date Stamp	Nov 1 2009	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LPOKHREL\LP-3-21FR7-21-C13.FID\FID				
Frequency (MHz)	50.29	***Nucleus***	13C	***Number of Transients***	4320	***Original Points Count***	18720
Points Count	65536	***Pulse Sequence***	s2pul	***Receiver Gain***	40.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	4876.9170	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	12500.00	***Temperature (degree C)***	AMBIENT TEMPERATURE

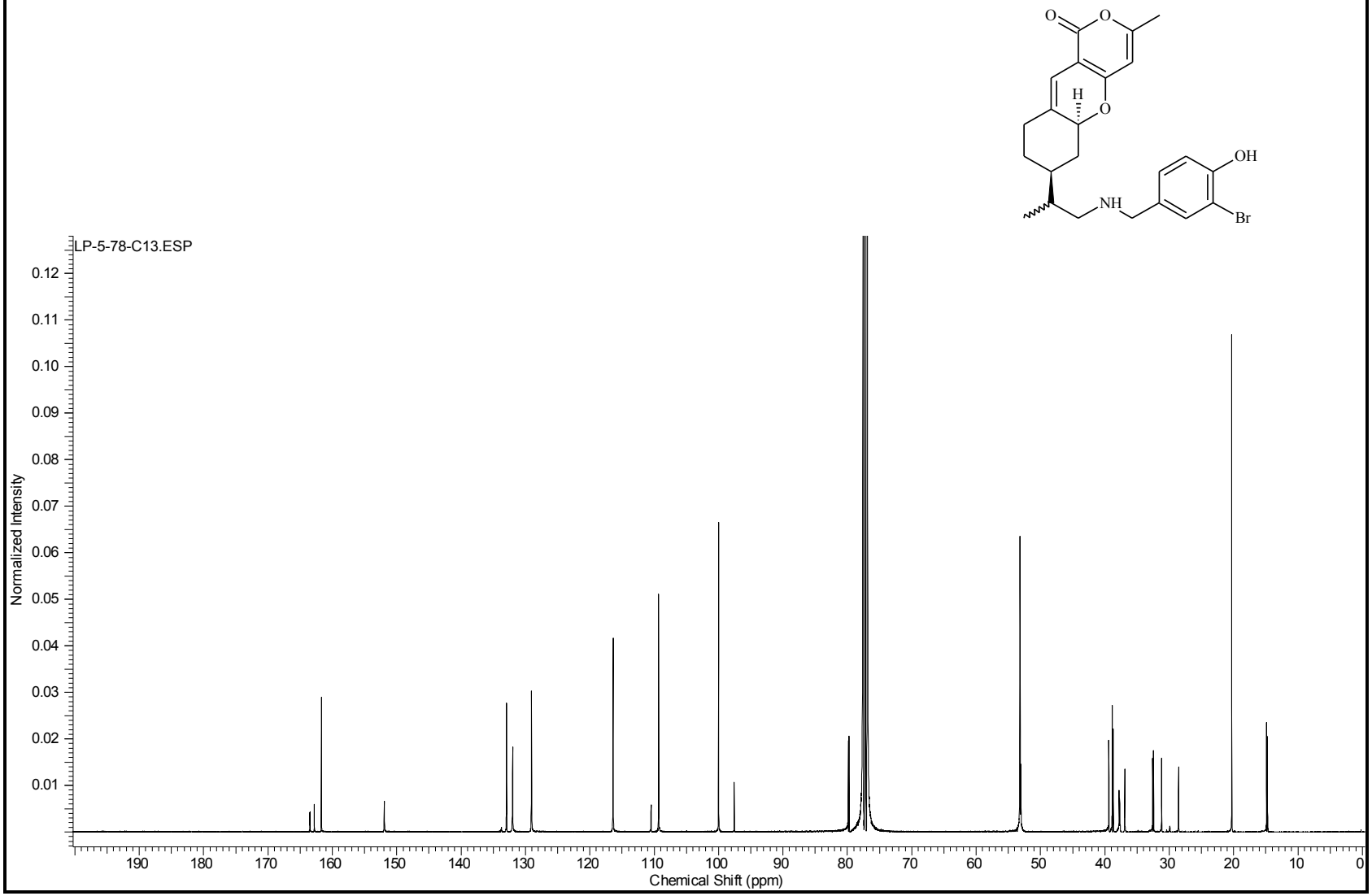




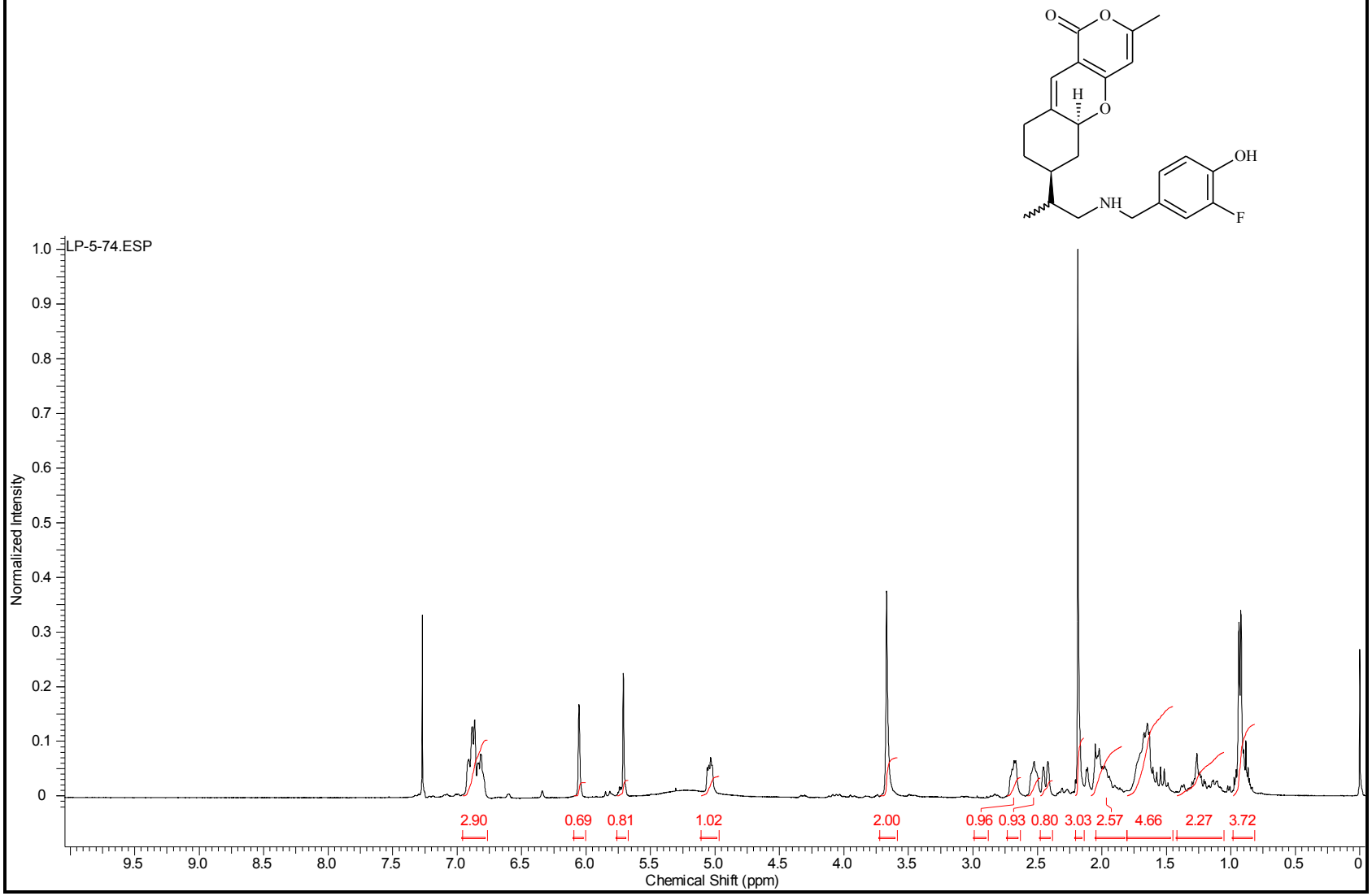
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Apr 14 2011
Date Stamp	Apr 14 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-78.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	40	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	28.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2403.3633	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



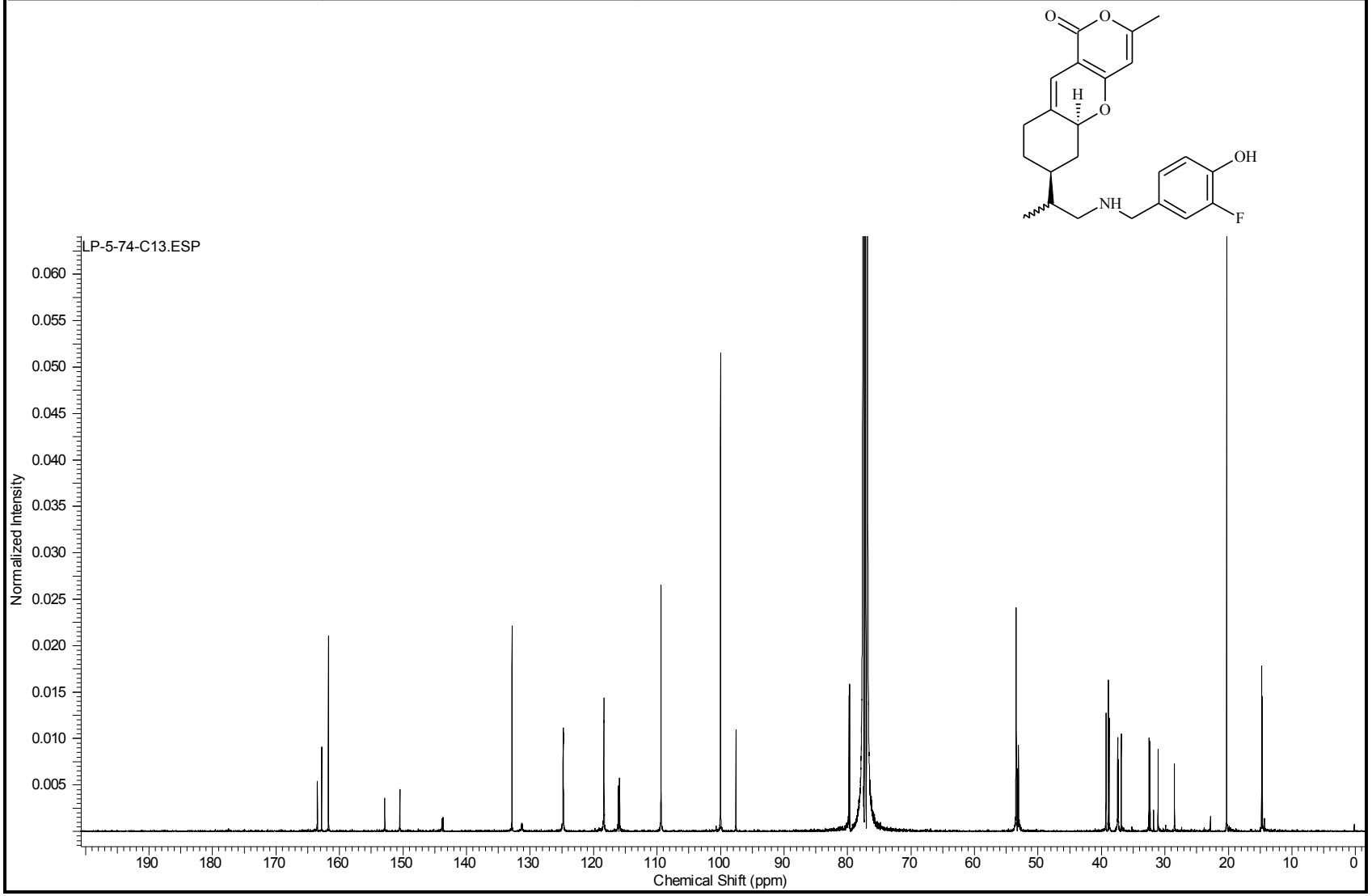
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Apr 14 2011
Date Stamp	Apr 14 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-78-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	21208	***Original Points Count***	31413
Points Count	65536	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10557.7637	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



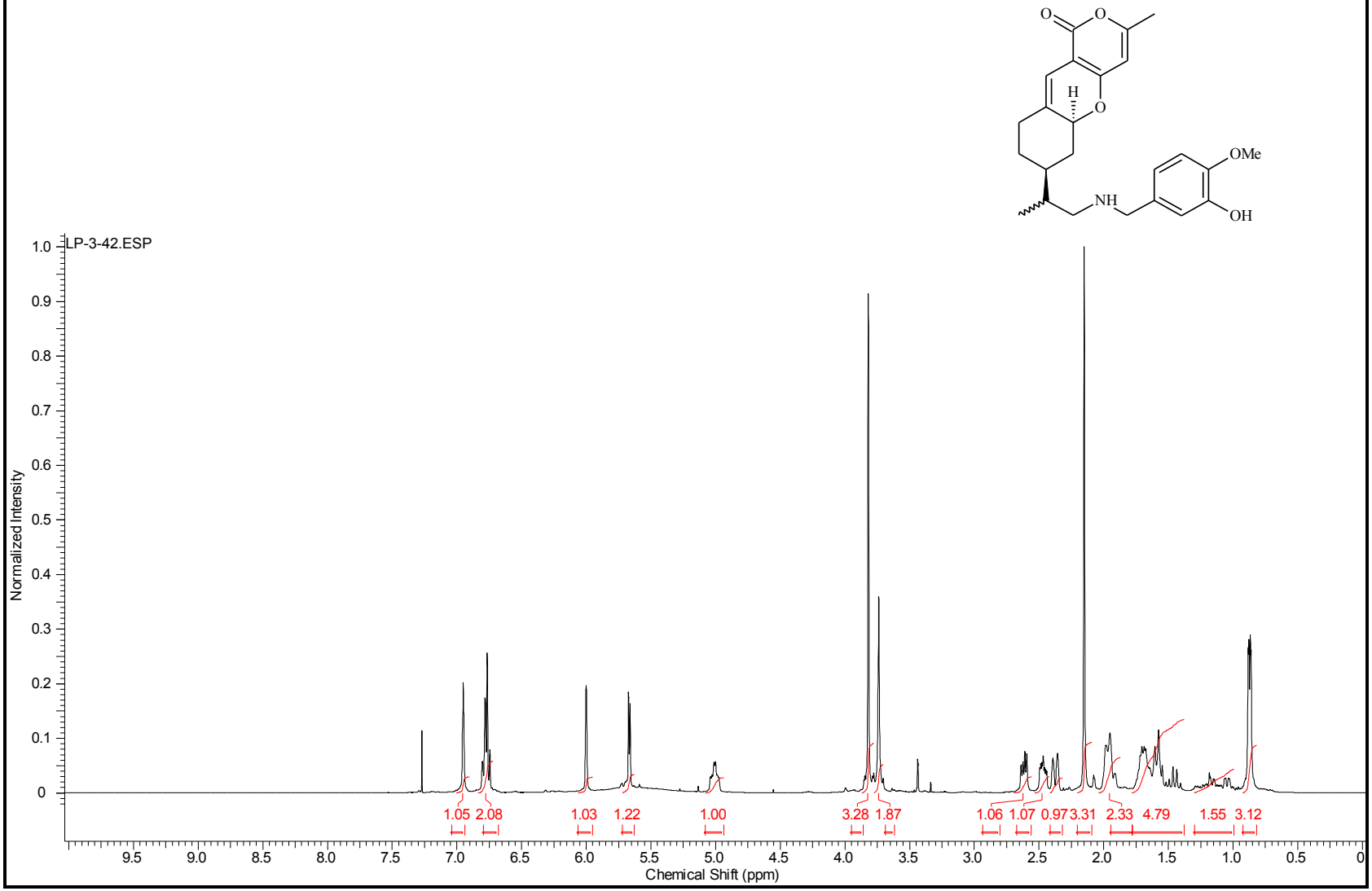
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Apr 10 2011
Date Stamp	Apr 10 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-74.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	28	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	28.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2403.7539	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



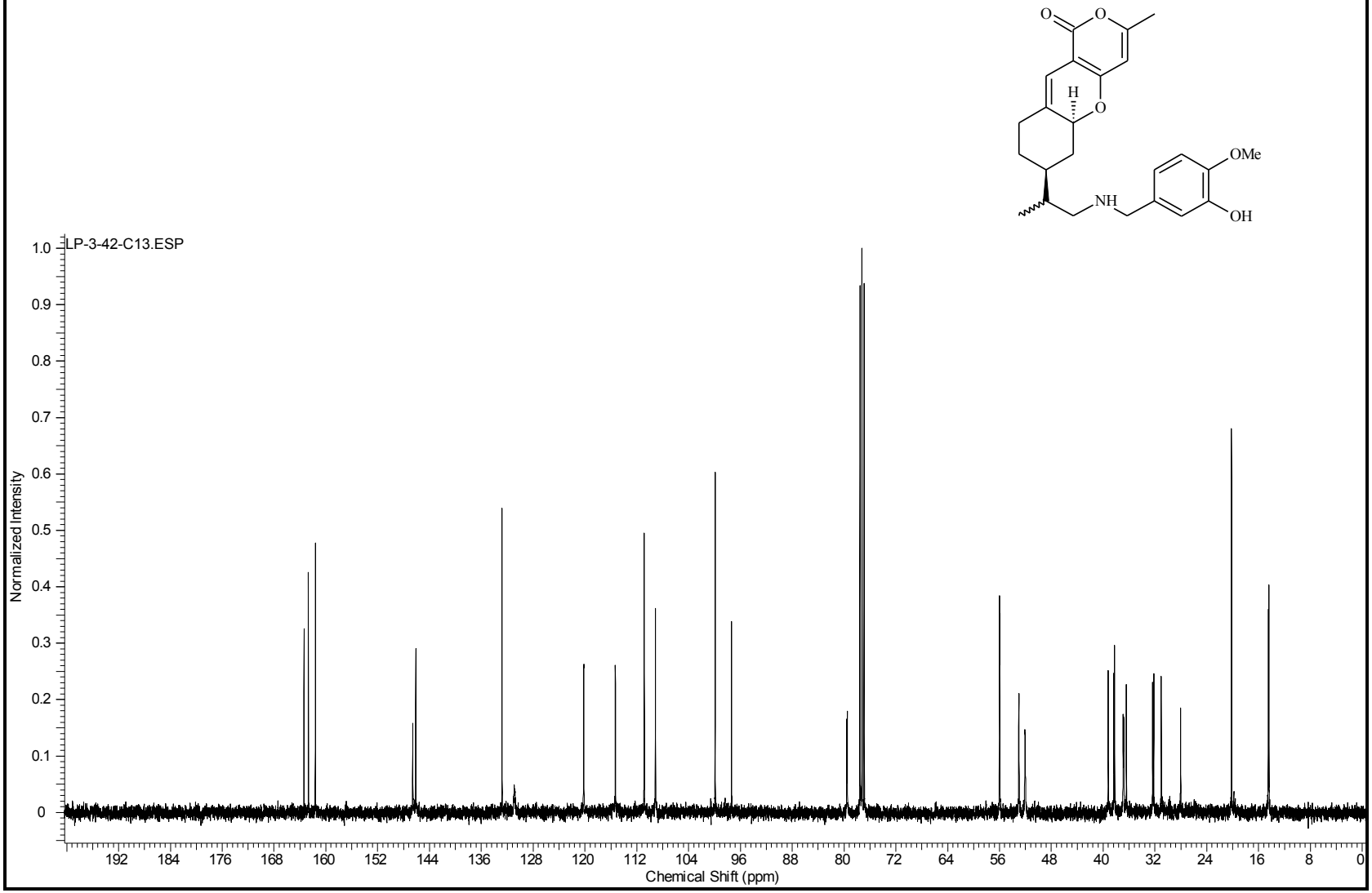
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Apr 10 2011
Date Stamp	Apr 10 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-74-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	8804	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10558.3594	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



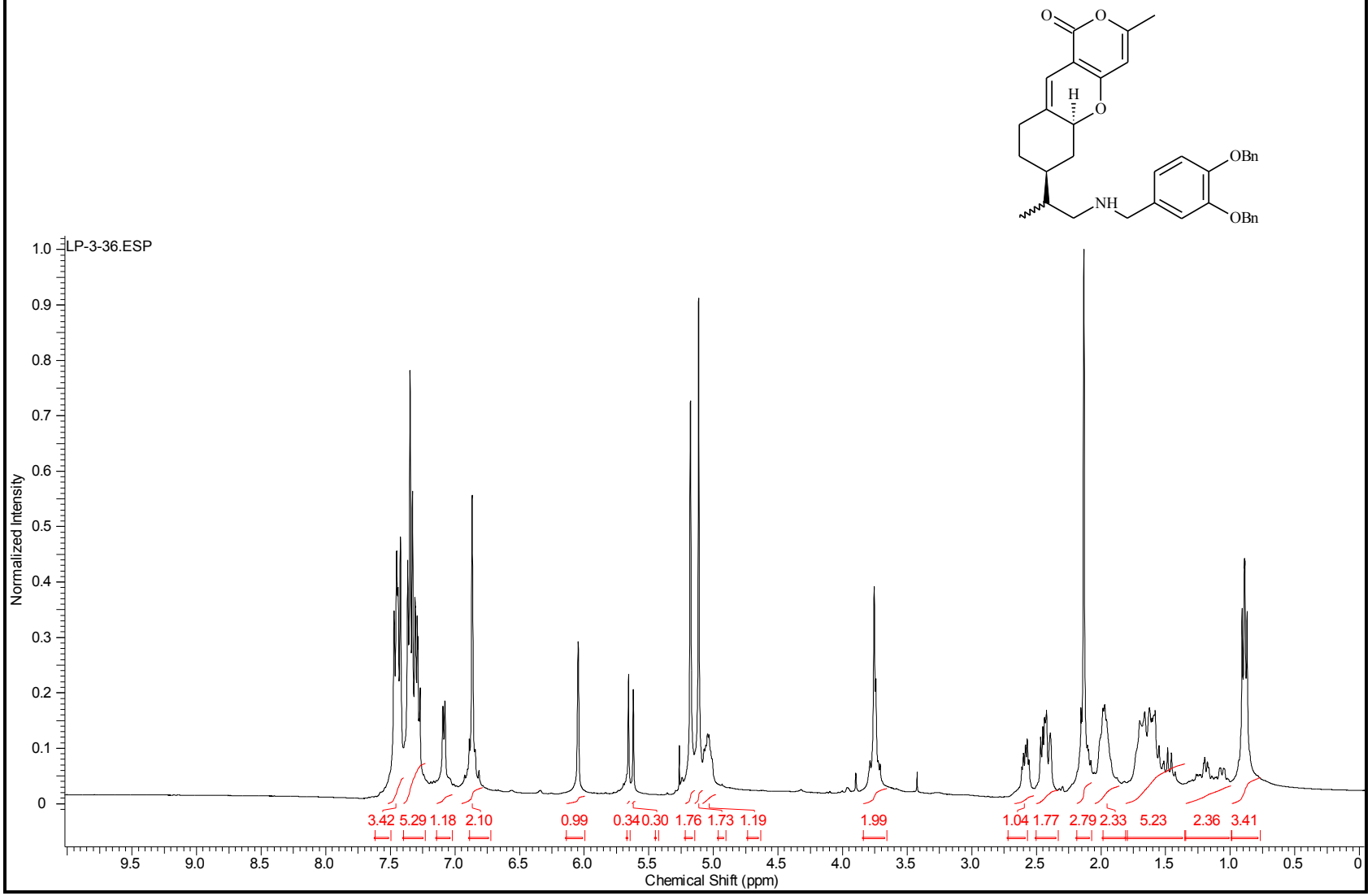
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Dec 13 2009	***Date Stamp***	Dec 13 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-3-42COLUMN.FID\FID						
Frequency (MHz)	399.75	***Nucleus***	1H	***Number of Transients***	48	***Original Points Count***	13103
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	26.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2403.9280	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	25.000



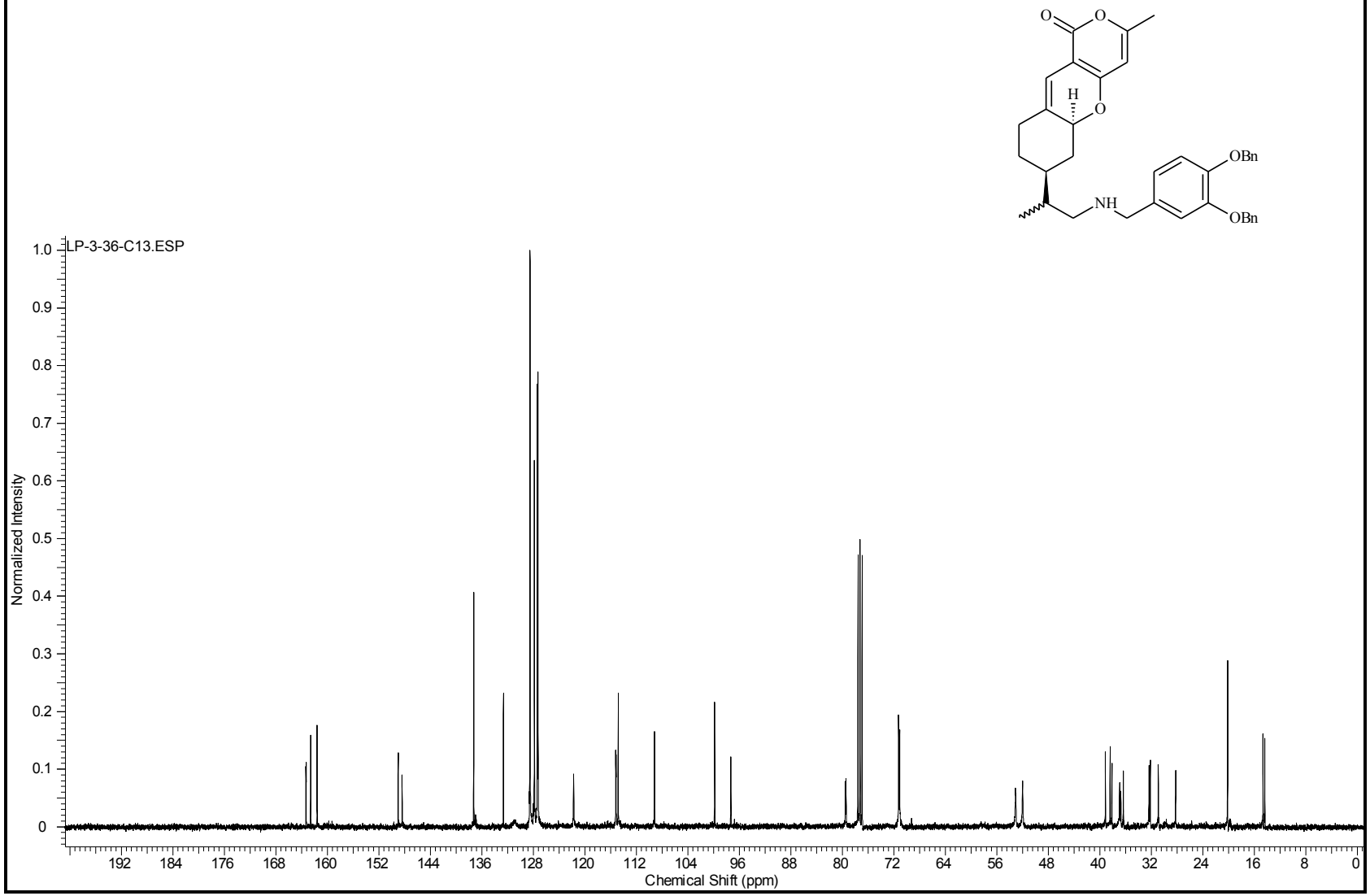
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Dec 13 2009	***Date Stamp***	Dec 13 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-3-42C13.FID\FID						
Frequency (MHz)	100.53	***Nucleus***	13C	***Number of Transients***	2540	***Original Points Count***	31375
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10542.0205	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	25.000



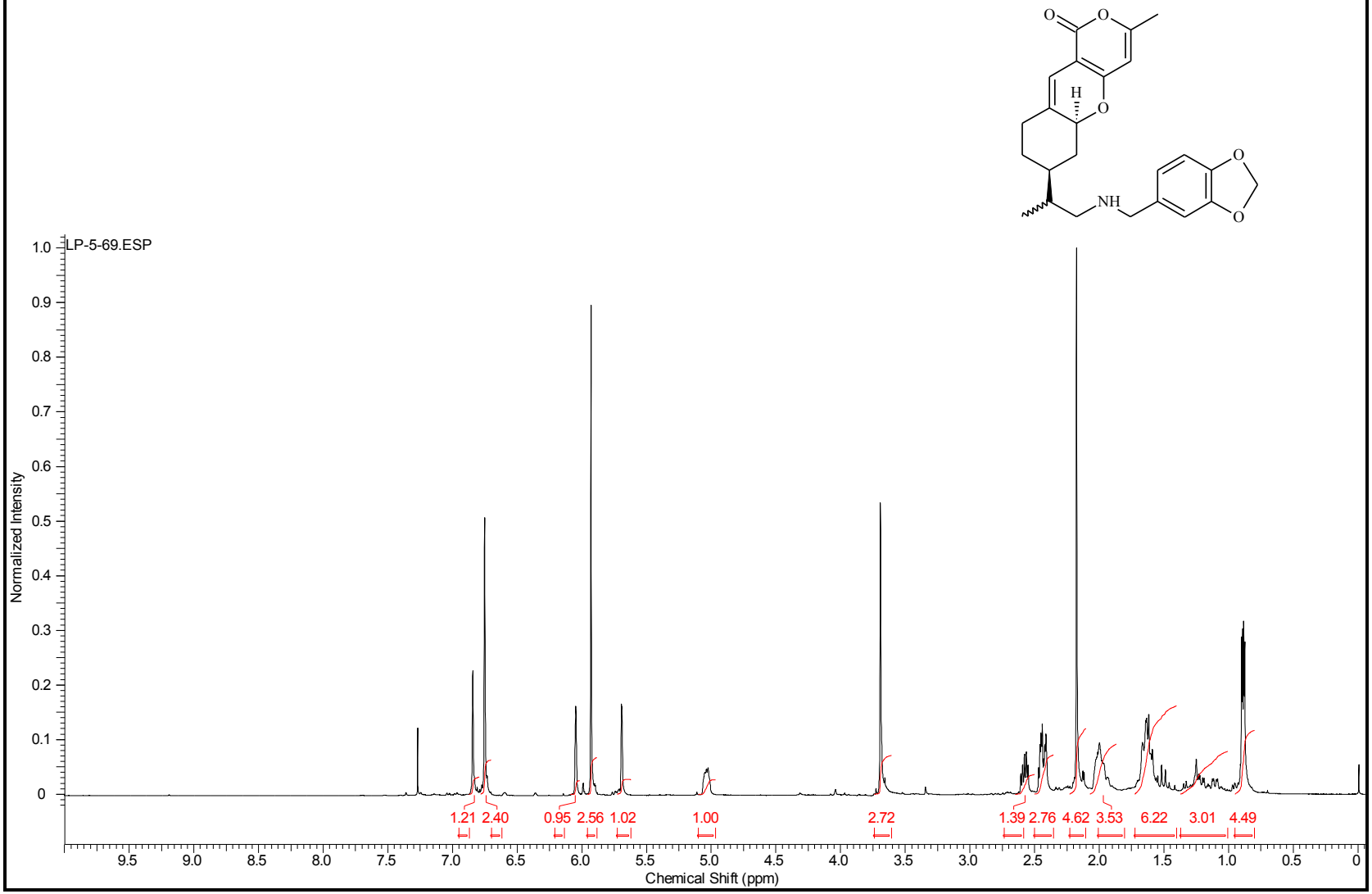
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Dec 3 2009	***Date Stamp***	Dec 3 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\400 MHZ\LP-3-36COLUMN.FID\FID					***Frequency (MHz)***	399.75
Nucleus	1H	***Number of Transients***	72	***Original Points Count***	13103	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	26.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2404.3184	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	25.000



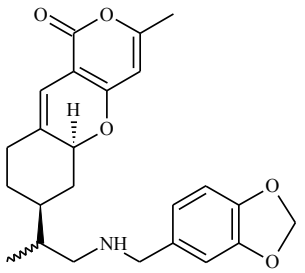
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Dec 3 2009	***Date Stamp***	Dec 3 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-3-36-C13.FID\FID						
Frequency (MHz)	100.53	***Nucleus***	13C	***Number of Transients***	4804	***Original Points Count***	31375
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10536.1299	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	25.000

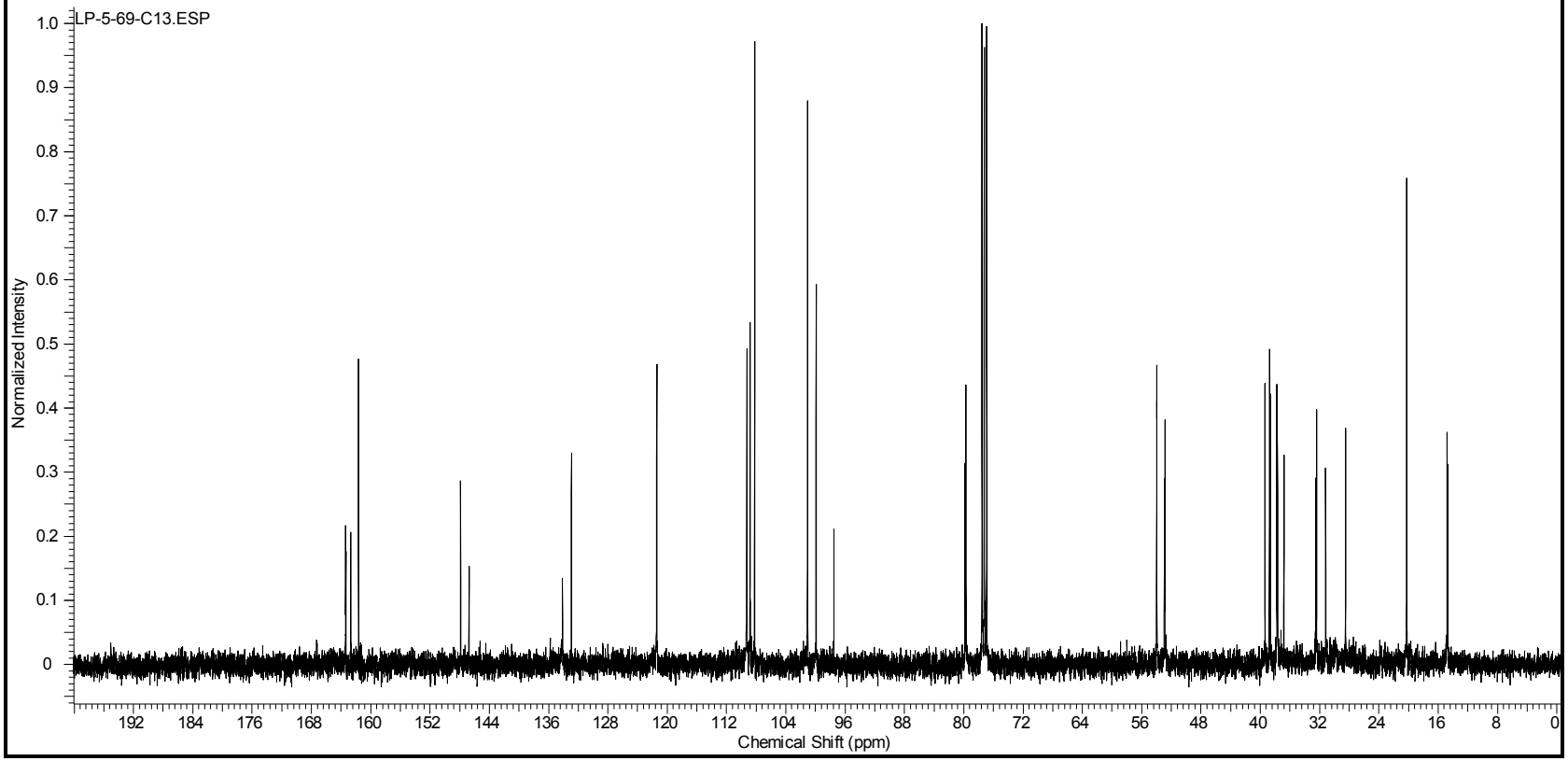


Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Mar 31 2011
Date Stamp	Mar 31 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-69.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	24	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2402.9727	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000

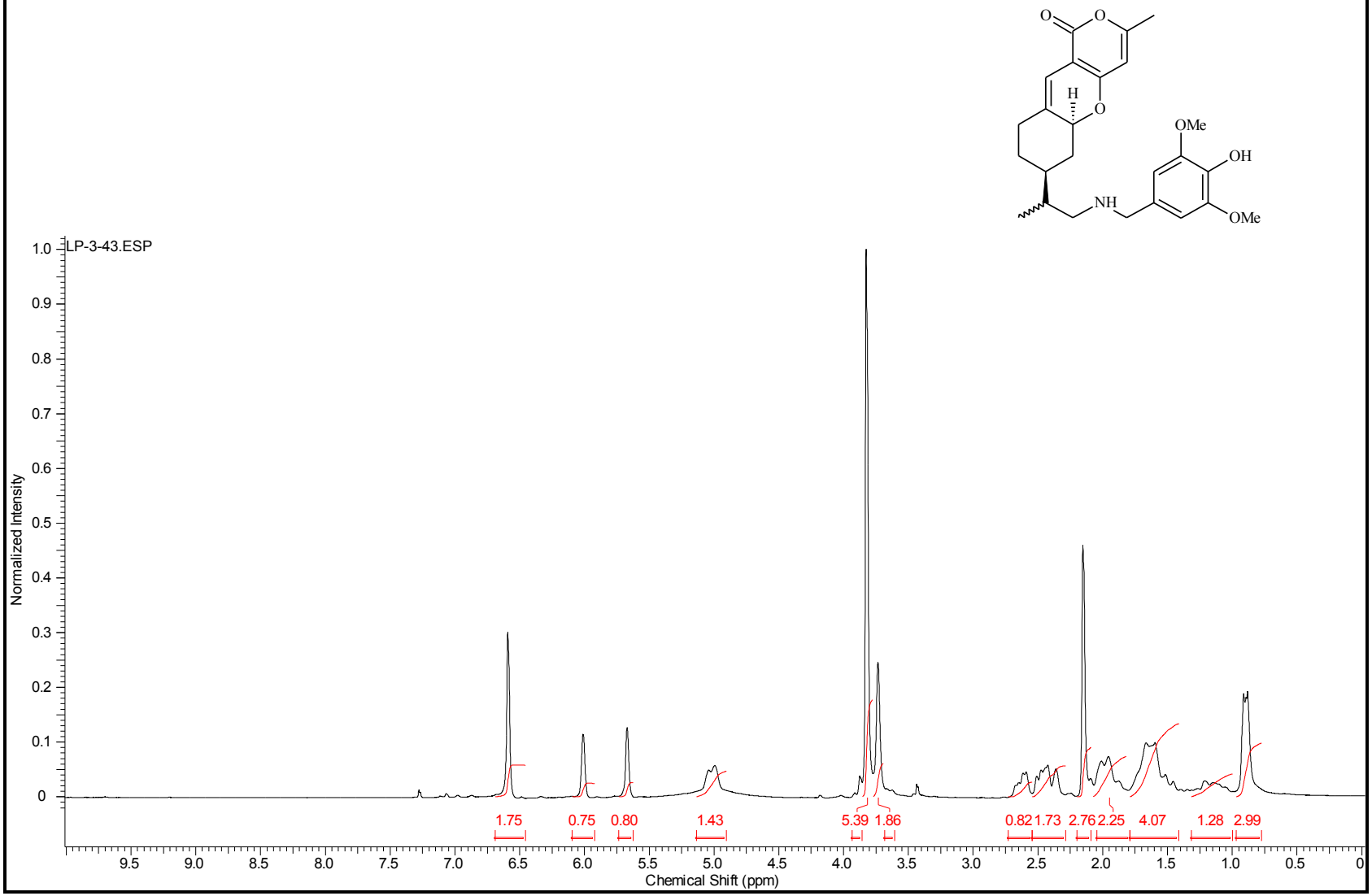


Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Mar 31 2011
Date Stamp	Mar 31 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-69-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	956	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10553.9355	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000

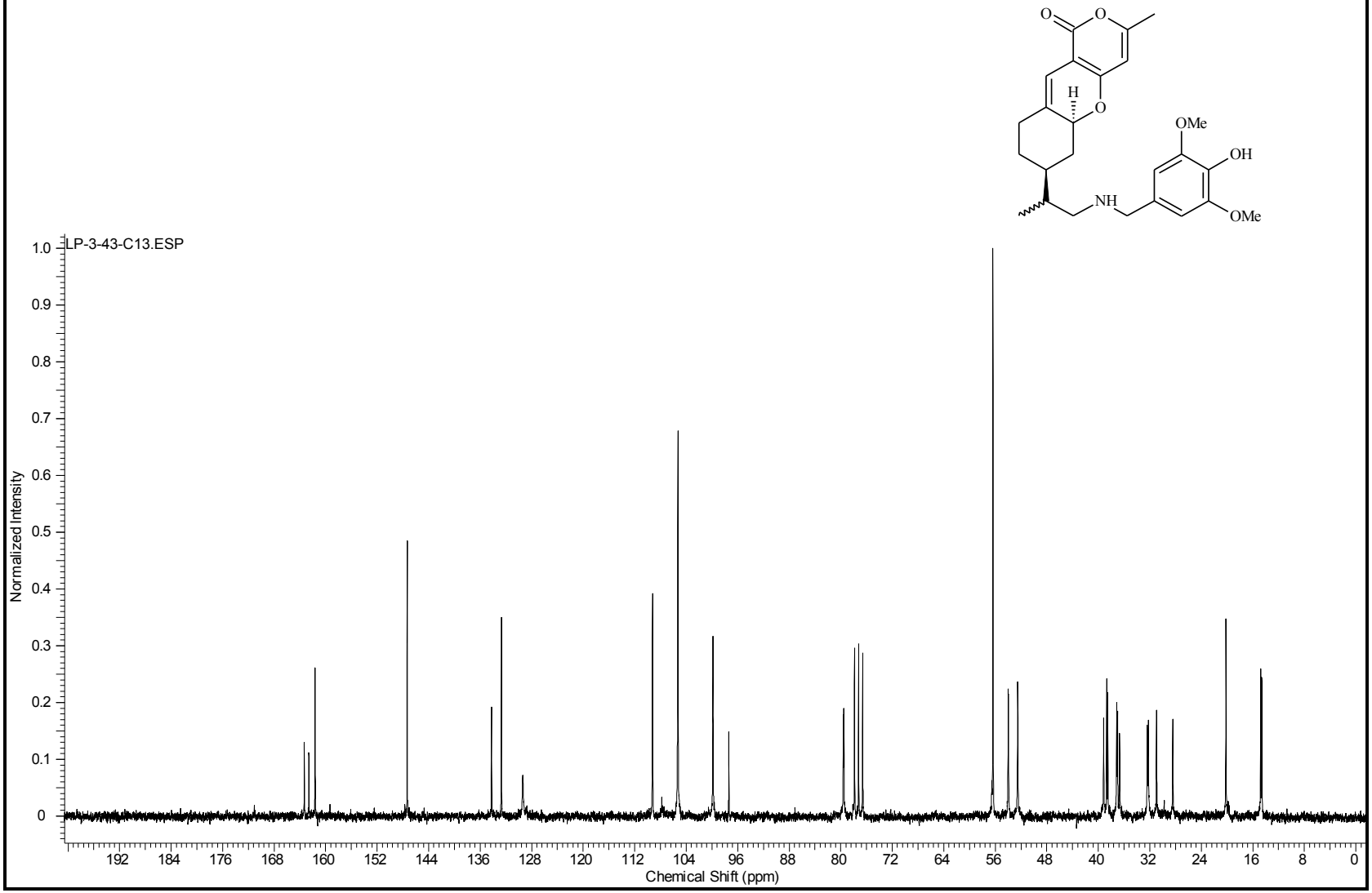




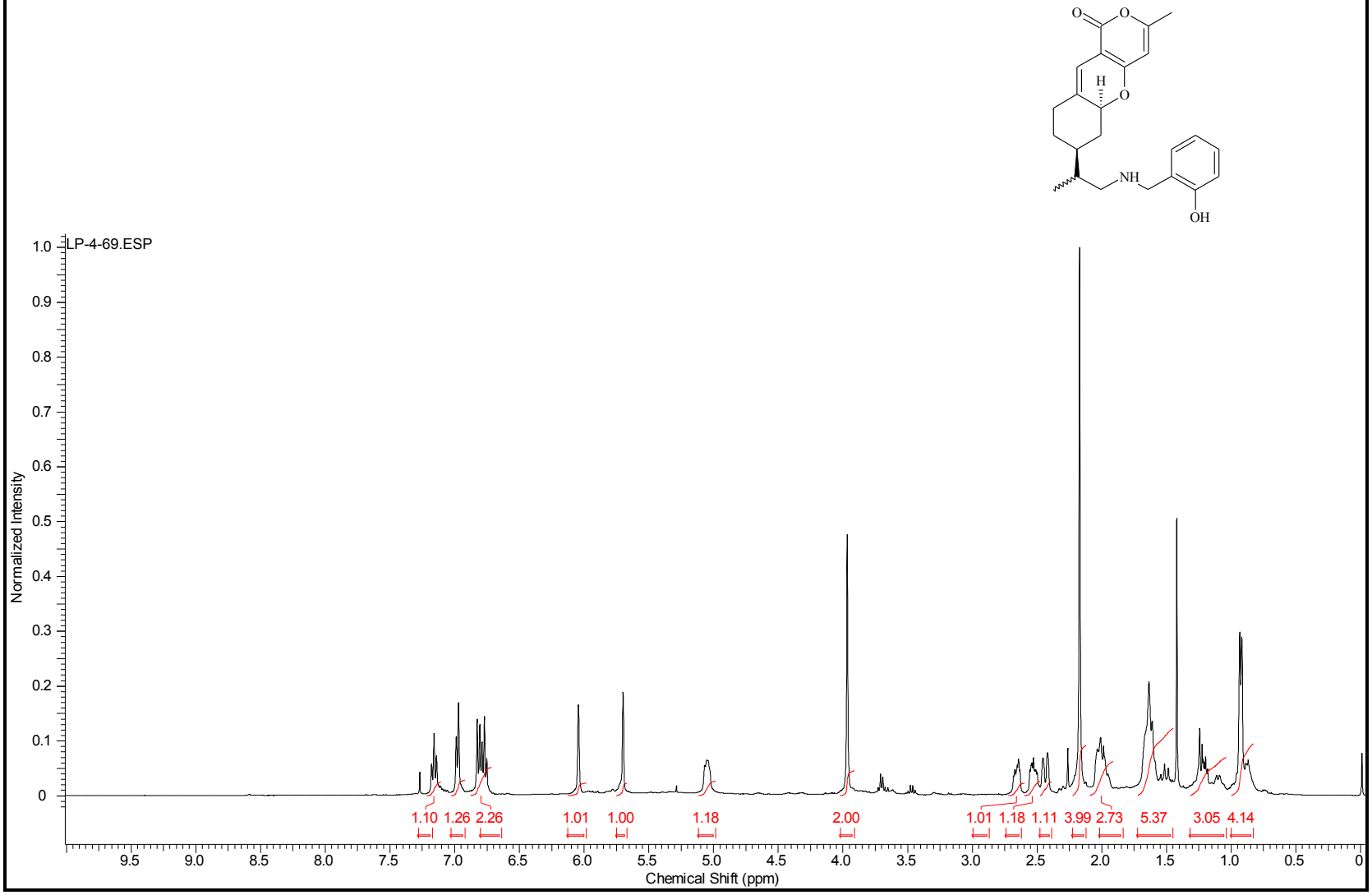
Acquisition Time (sec)	1.9945	***Comment***	STANDARD 1H OBSERVE□lp-3-43			***Date***	Dec 16 2009
Date Stamp	Dec 16 2009	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LPOKHREL\LP-3-43.FID\FID				
Frequency (MHz)	199.98	***Nucleus***	1H	***Number of Transients***	68	***Original Points Count***	5984
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	16.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	1003.7899	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	3000.30	***Temperature (degree C)***	AMBIENT TEMPERATURE



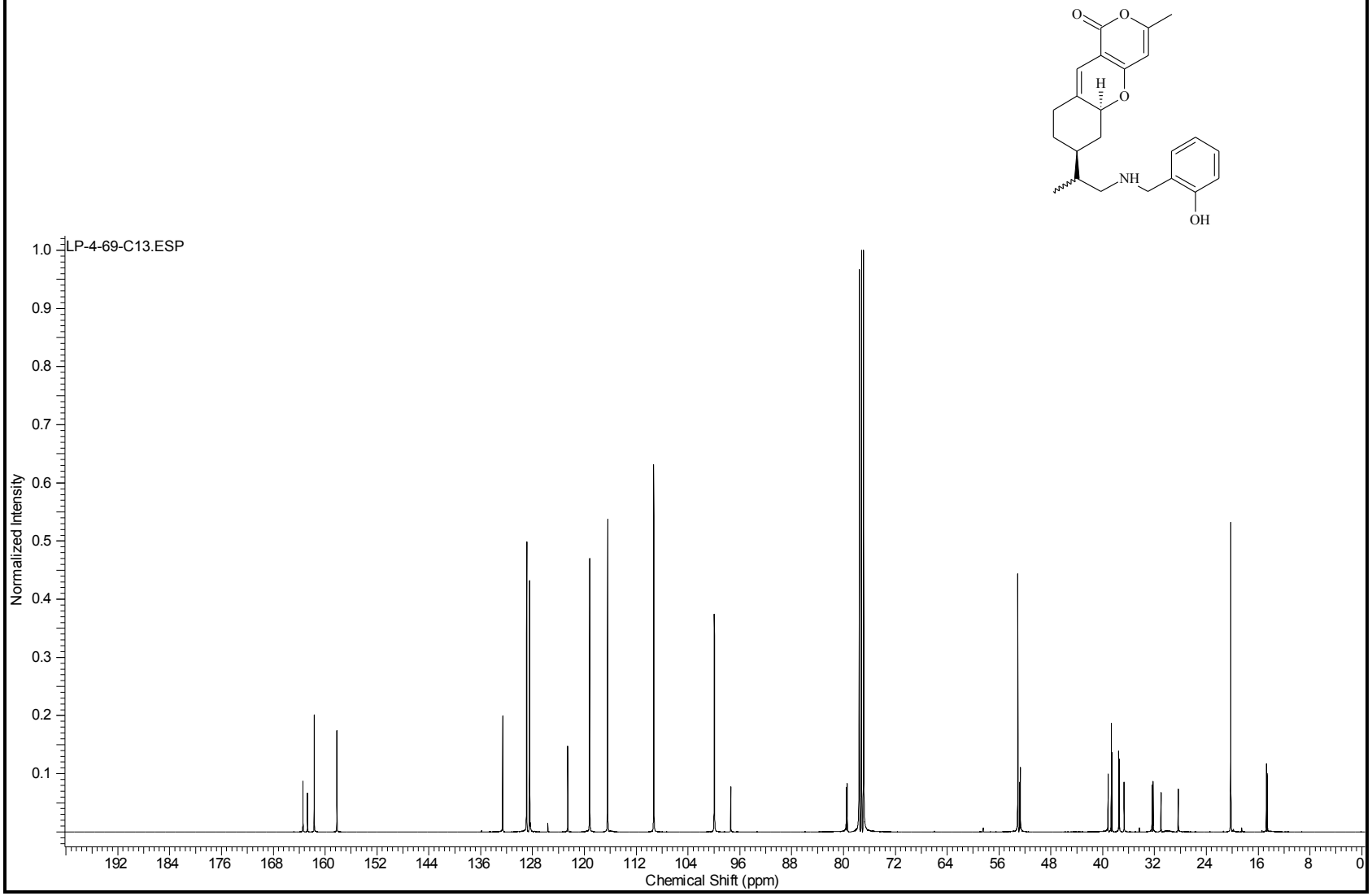
Acquisition Time (sec)	1.4976	***Comment***	13C OBSERVE	***Date***	Dec 16 2009	***Date Stamp***	Dec 16 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LPOKHREL\LP-3-43-C13.FID\FID					***Frequency (MHz)***	50.29
Nucleus	13C	***Number of Transients***	2976	***Original Points Count***	18720	***Points Count***	65536
Pulse Sequence	s2pul	***Receiver Gain***	40.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	4876.7261	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	12500.00	***Temperature (degree C)***	AMBIENT TEMPERATURE



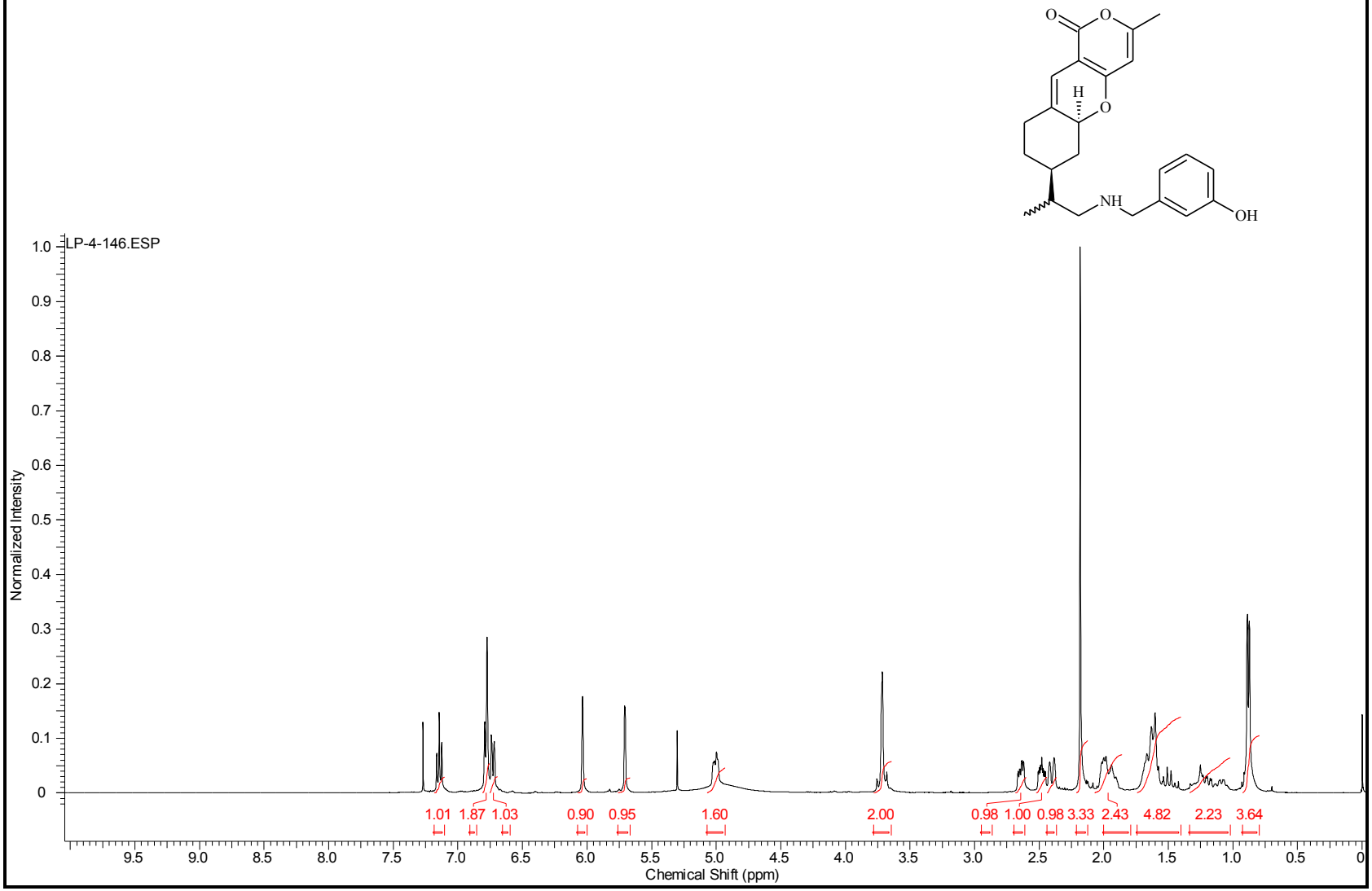
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Sep 2 2010	***Date Stamp***	Sep 2 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-69.FID\FID						
Frequency (MHz)	399.74	***Nucleus***	1H	***Number of Transients***	52	***Original Points Count***	13103
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2416.7397	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	30.000



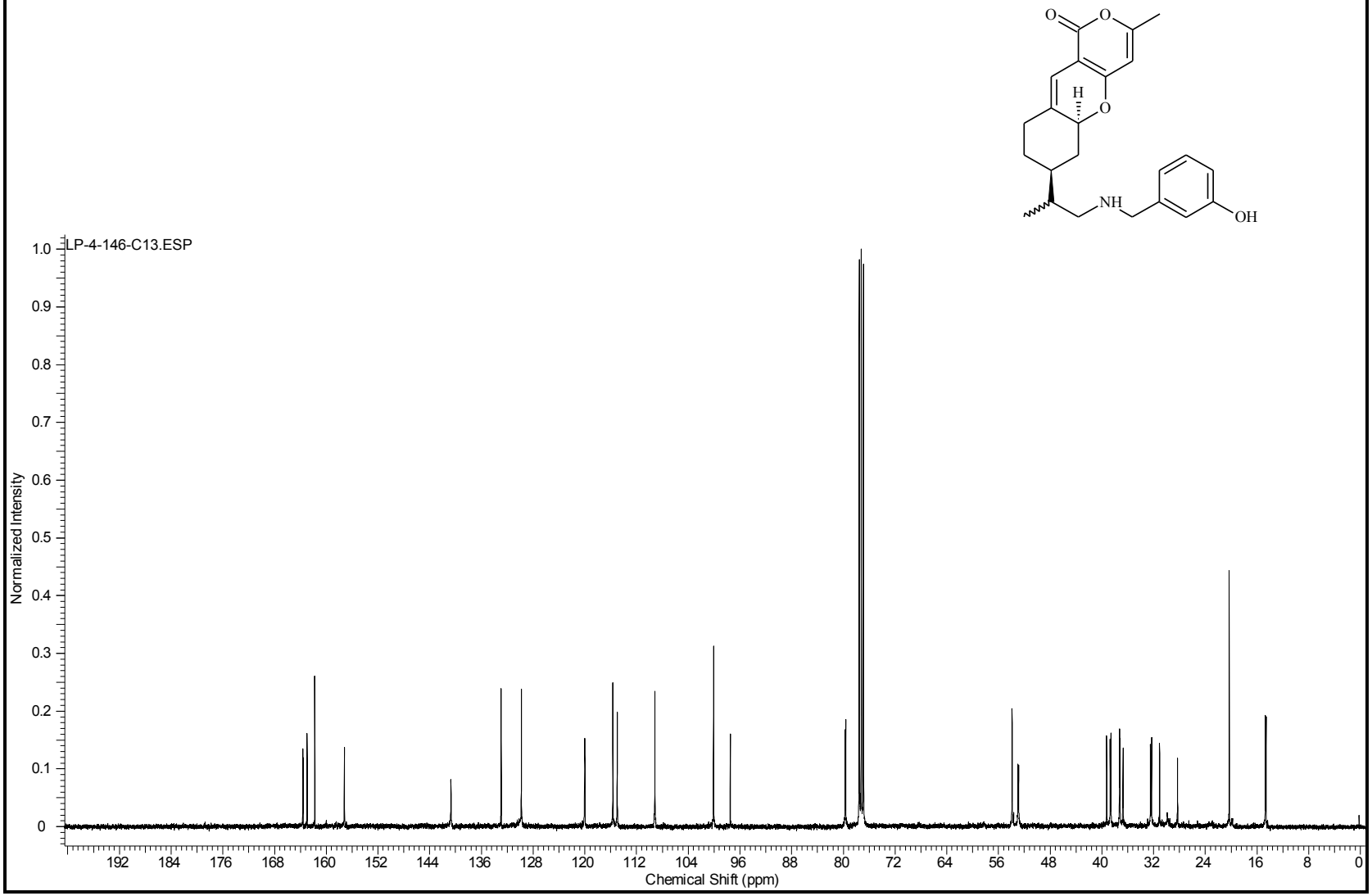
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Sep 2 2010	***Date Stamp***	Sep 2 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-69-C13.FID\FID						
Frequency (MHz)	100.52	***Nucleus***	13C	***Number of Transients***	16832	***Original Points Count***	31375
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10545.5117	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	30.000



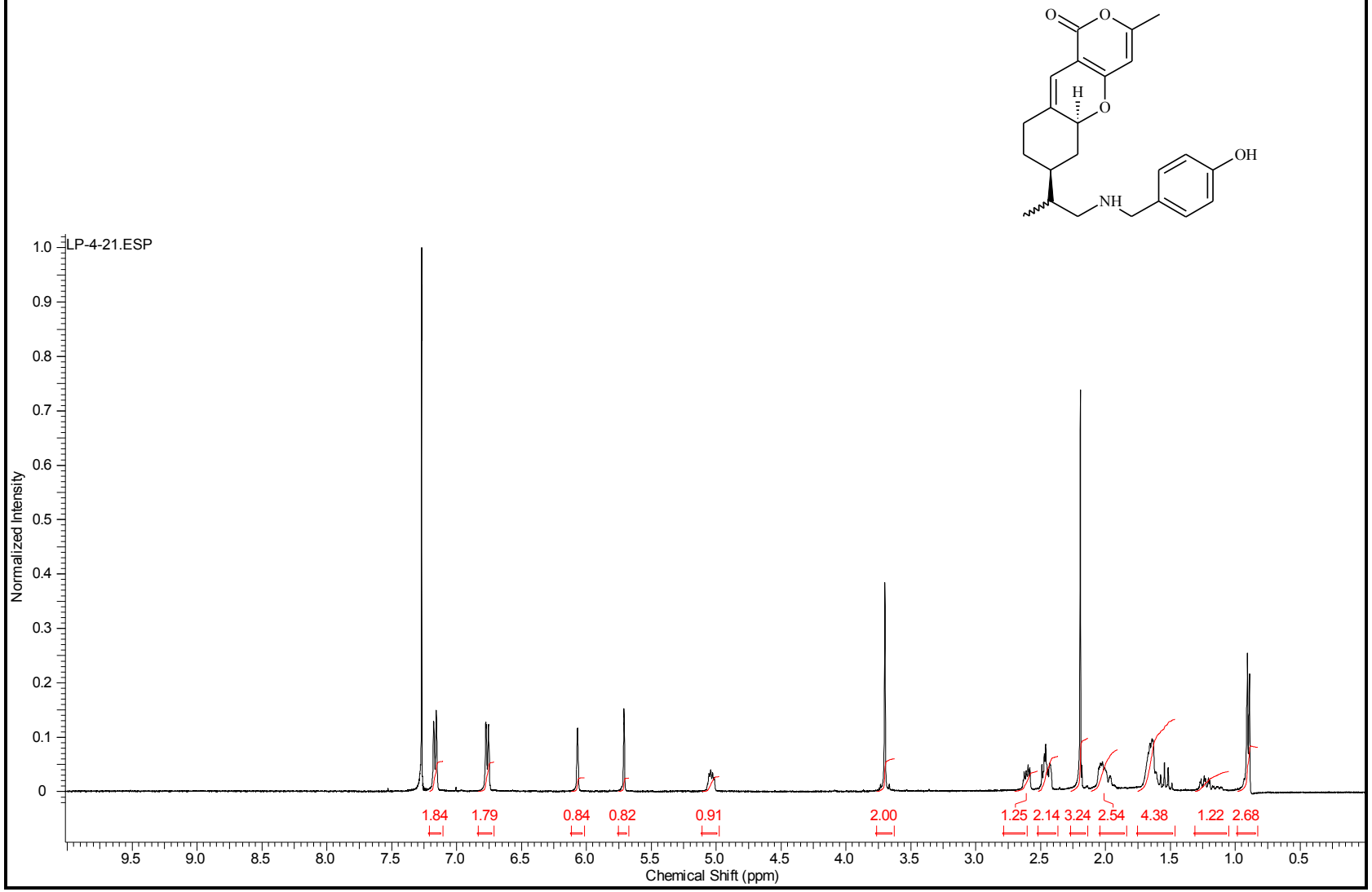
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Dec 23 2010	***Date Stamp***	Dec 23 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-146.FID\FID						
Frequency (MHz)	399.73	***Nucleus***	1H	***Number of Transients***	32	***Original Points Count***	13103
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	36.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2413.9363	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	25.000



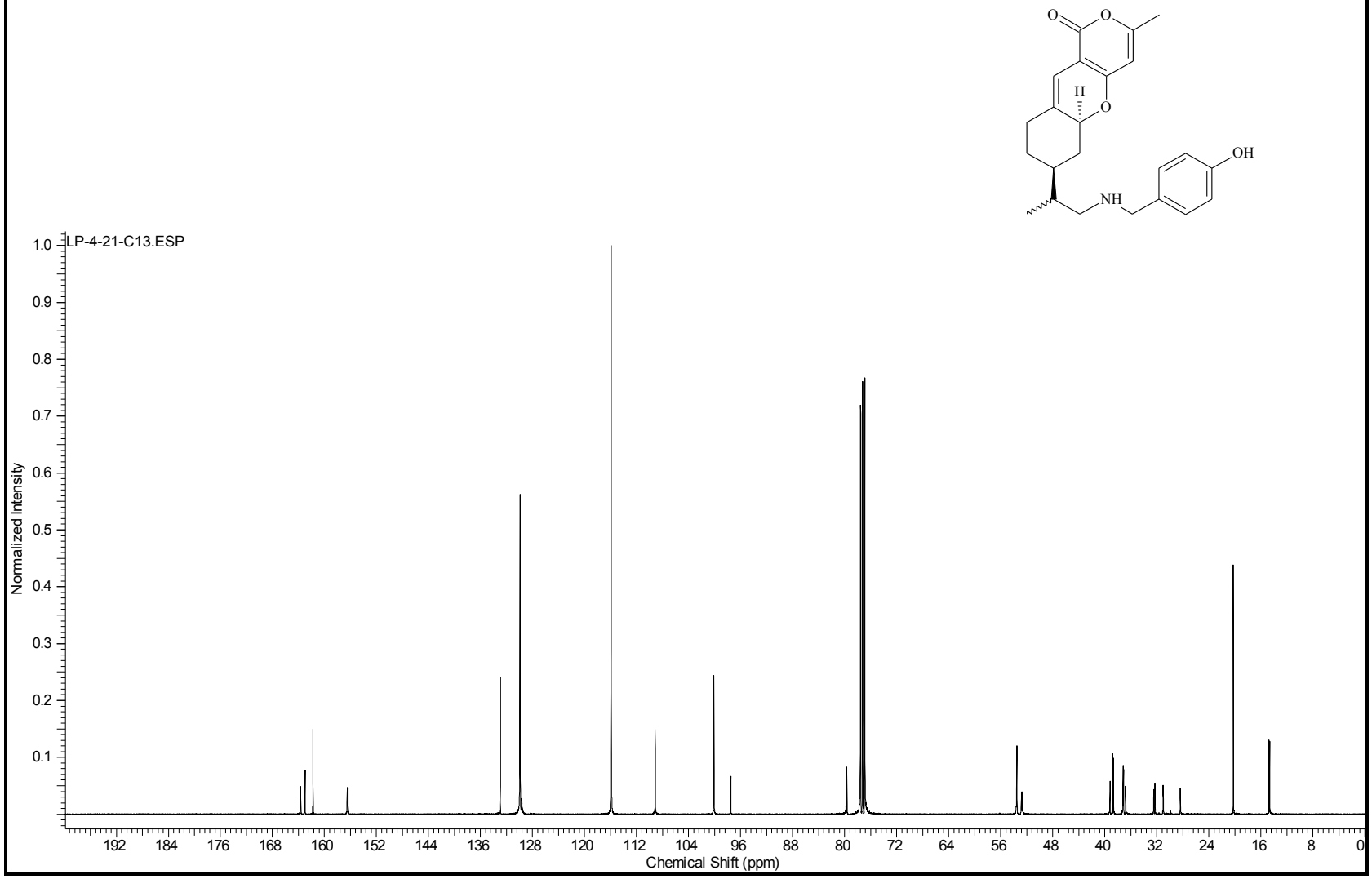
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Dec 23 2010
Date Stamp	Dec 23 2010	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-4-146-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	24948	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10553.9365	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



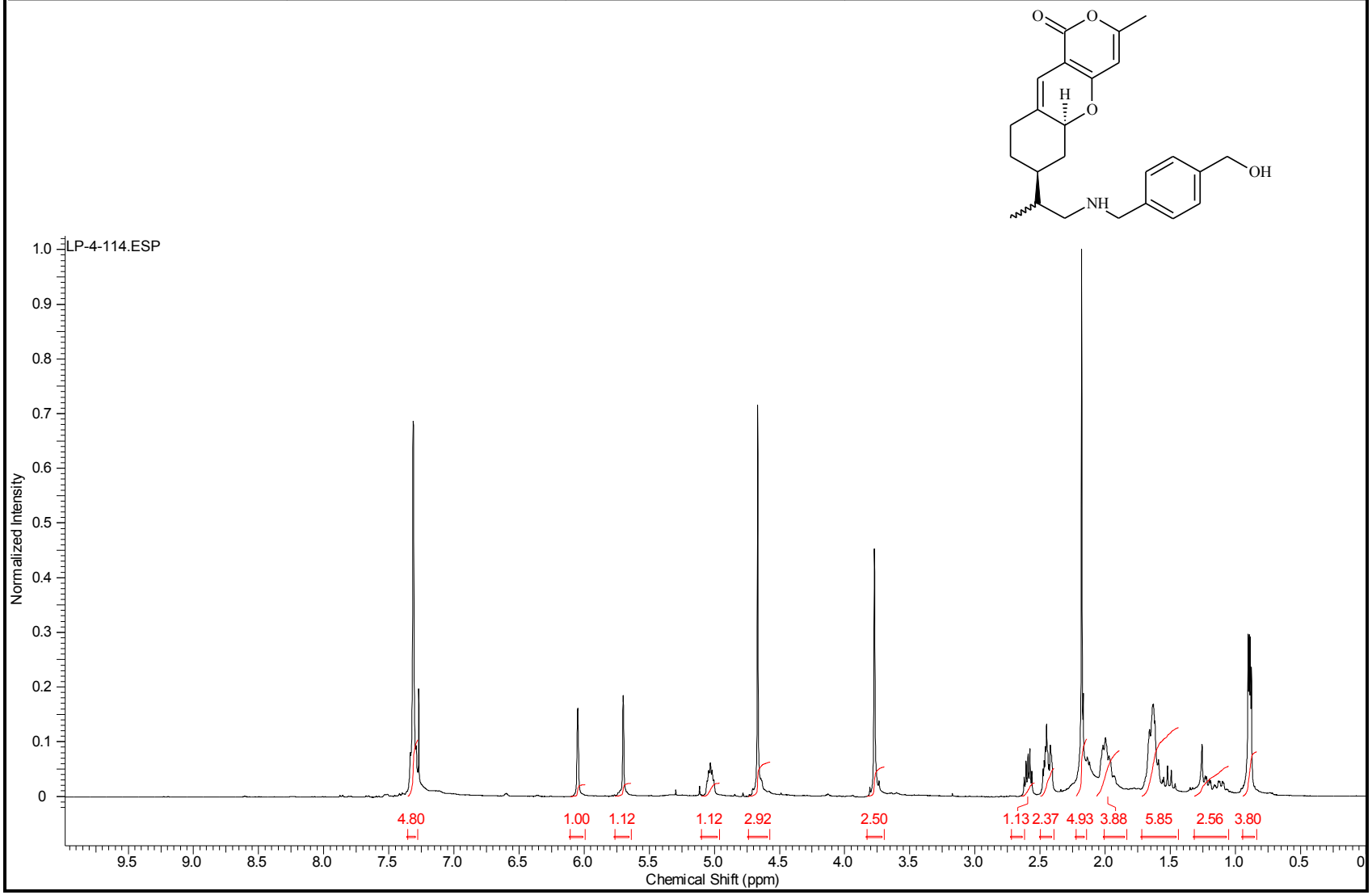
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Aug 21 2011
Date Stamp	Aug 21 2011	***File Name***	F:\NMR-MERCURY-02012\TP70-08-22.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	80	***Original Points Count***	12783	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	38.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2404.1443	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



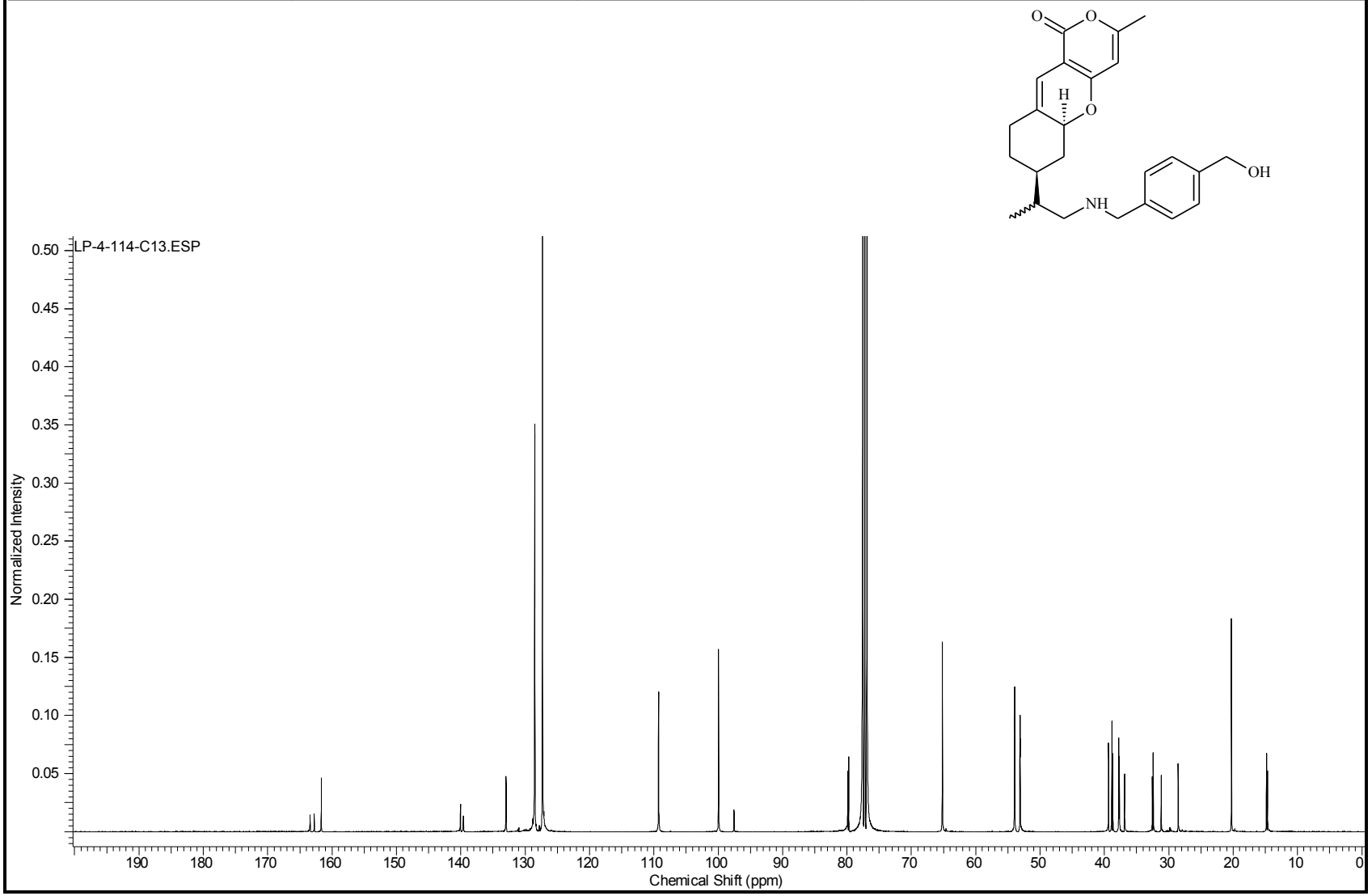
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jul 26 2011
Date Stamp	Jul 26 2011	***File Name***	F:\TP70-07-25-C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	1904	***Original Points Count***	31413	***Points Count***	65536
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10553.7100	***Spectrum Type***	STANDARD			***Sweep Width (Hz)***	24154.59
Temperature (degree C)	25.000						



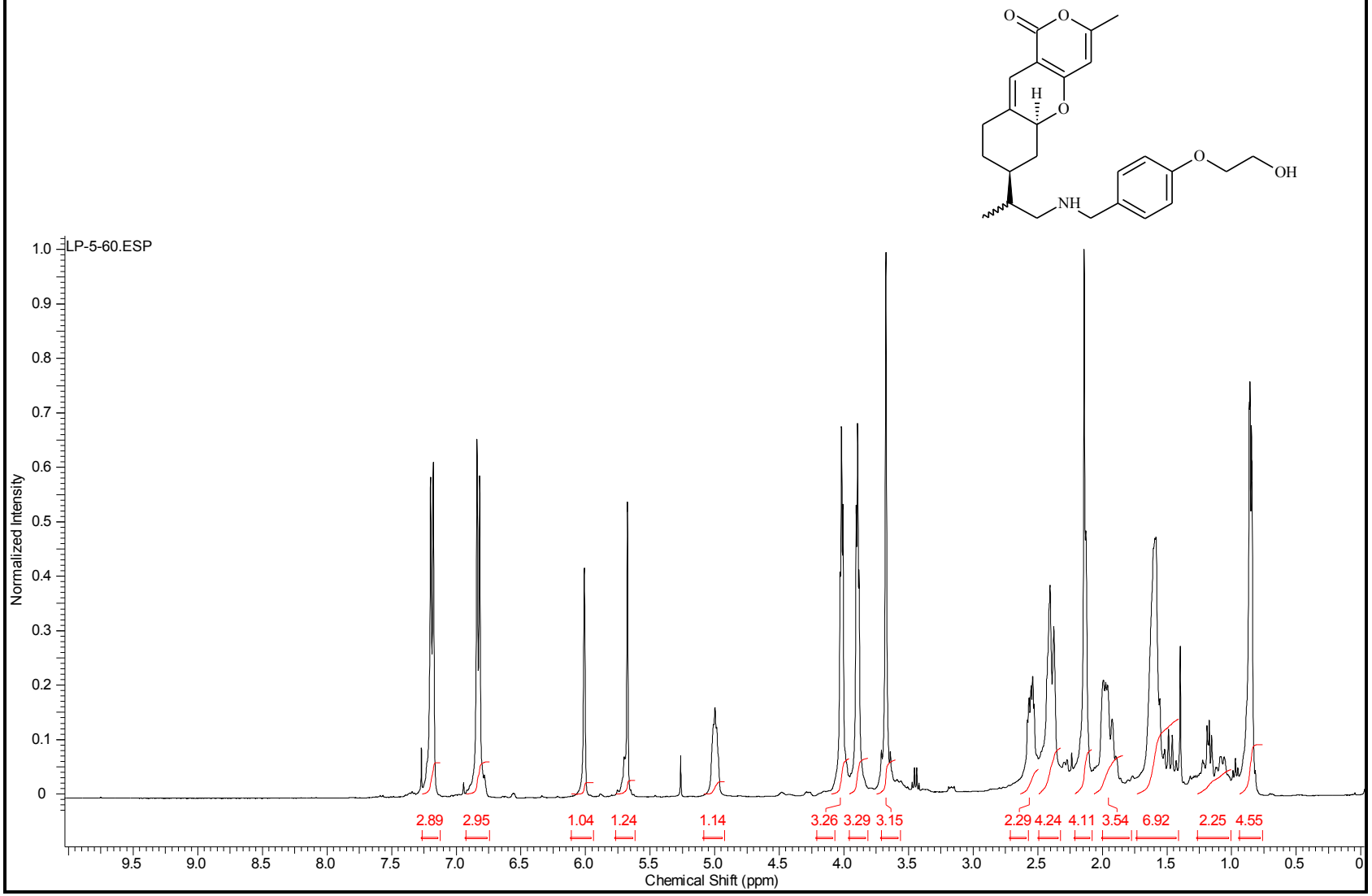
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Aug 9 2011
Date Stamp	Aug 9 2011	***File Name***	F:\NMR-MERCURY-02012\LP-4-114-2.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	44	***Original Points Count***	12783	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	24.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2403.3633	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



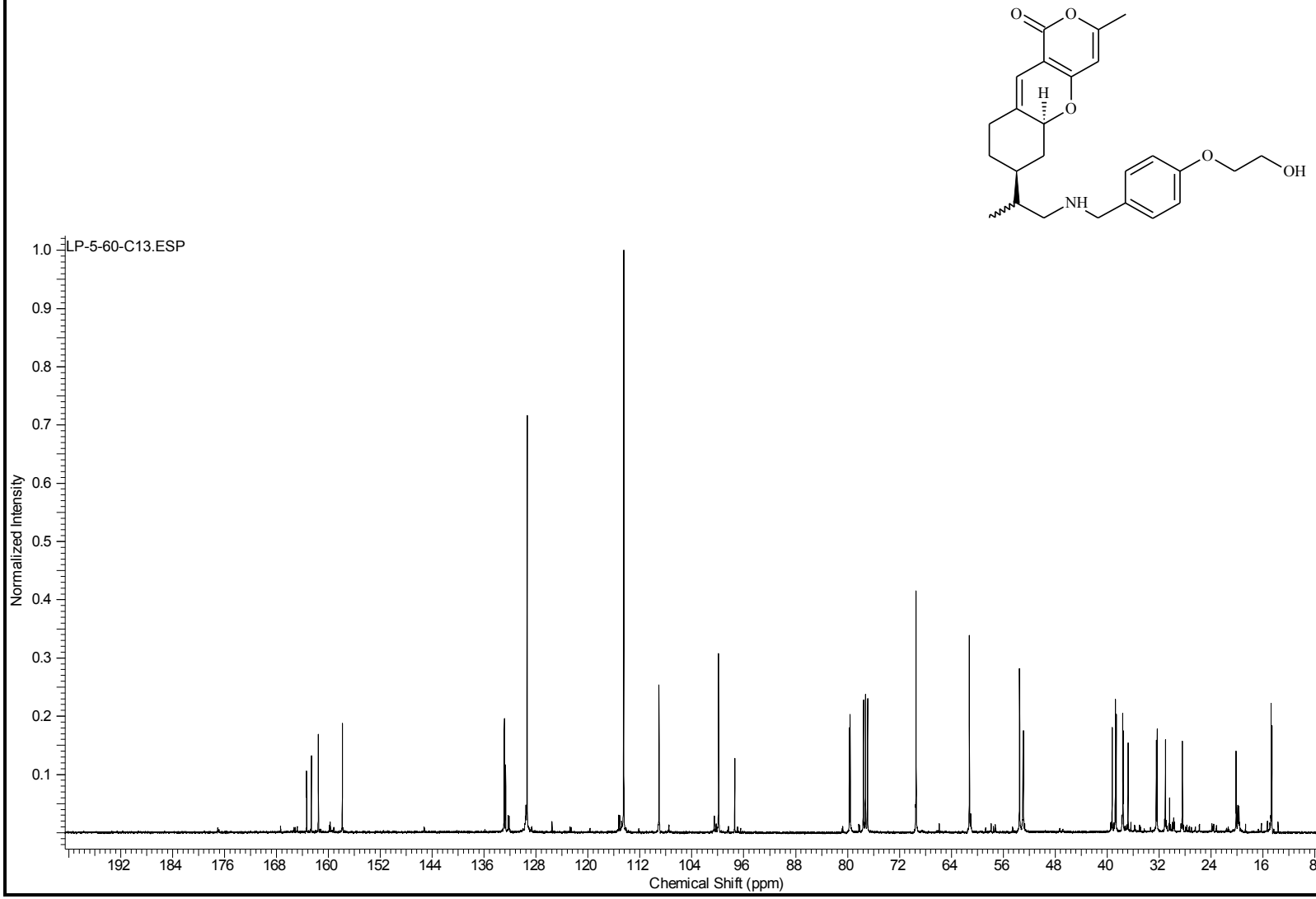
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Aug 9 2011
Date Stamp	Aug 9 2011	***File Name***	F:\NMR-MERCURY-02012\LB-4-114-2-C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	15228	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10555.4111	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



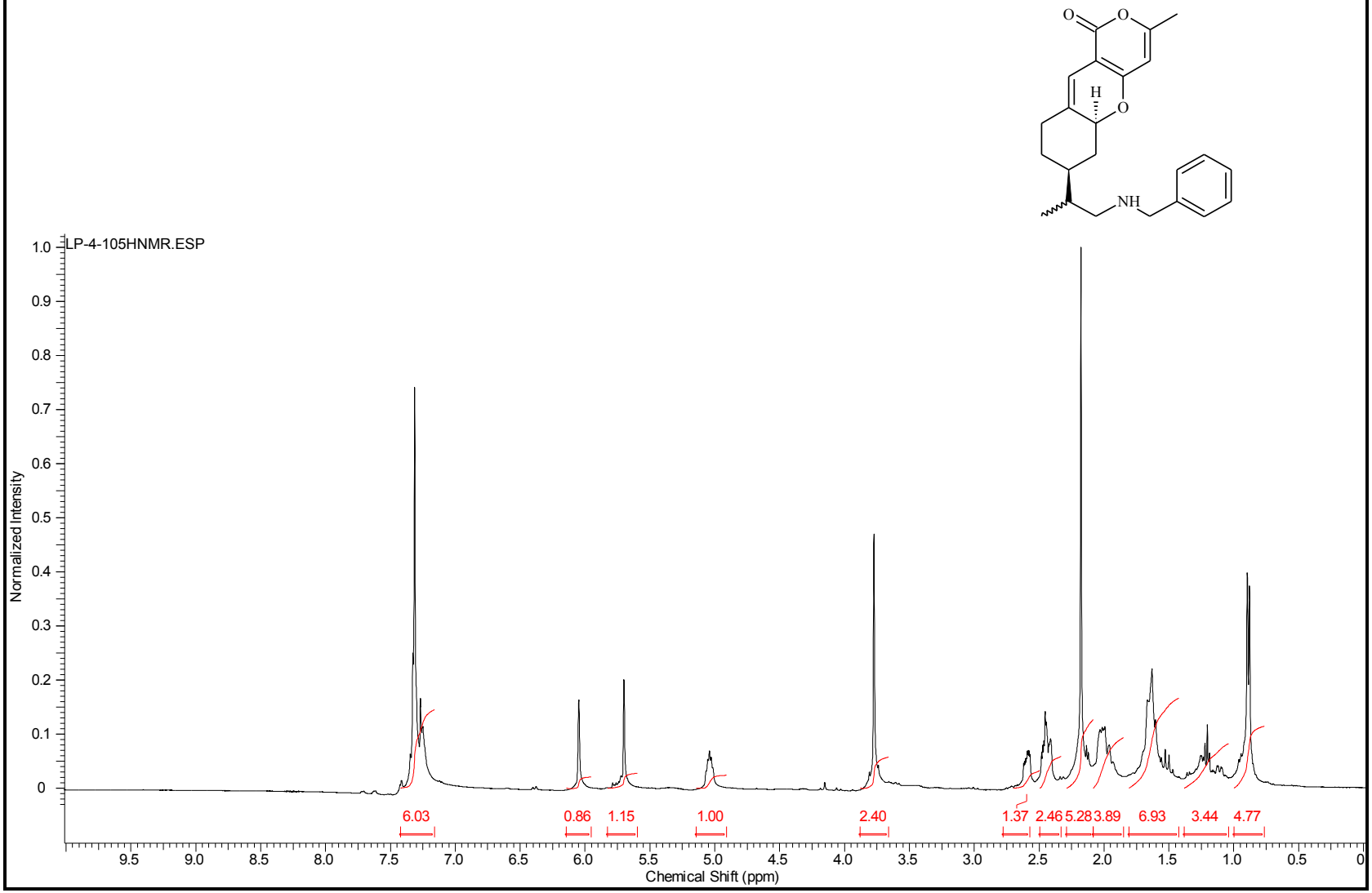
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Mar 16 2011
Date Stamp	Mar 16 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-60.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	12	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	12.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2404.1443	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



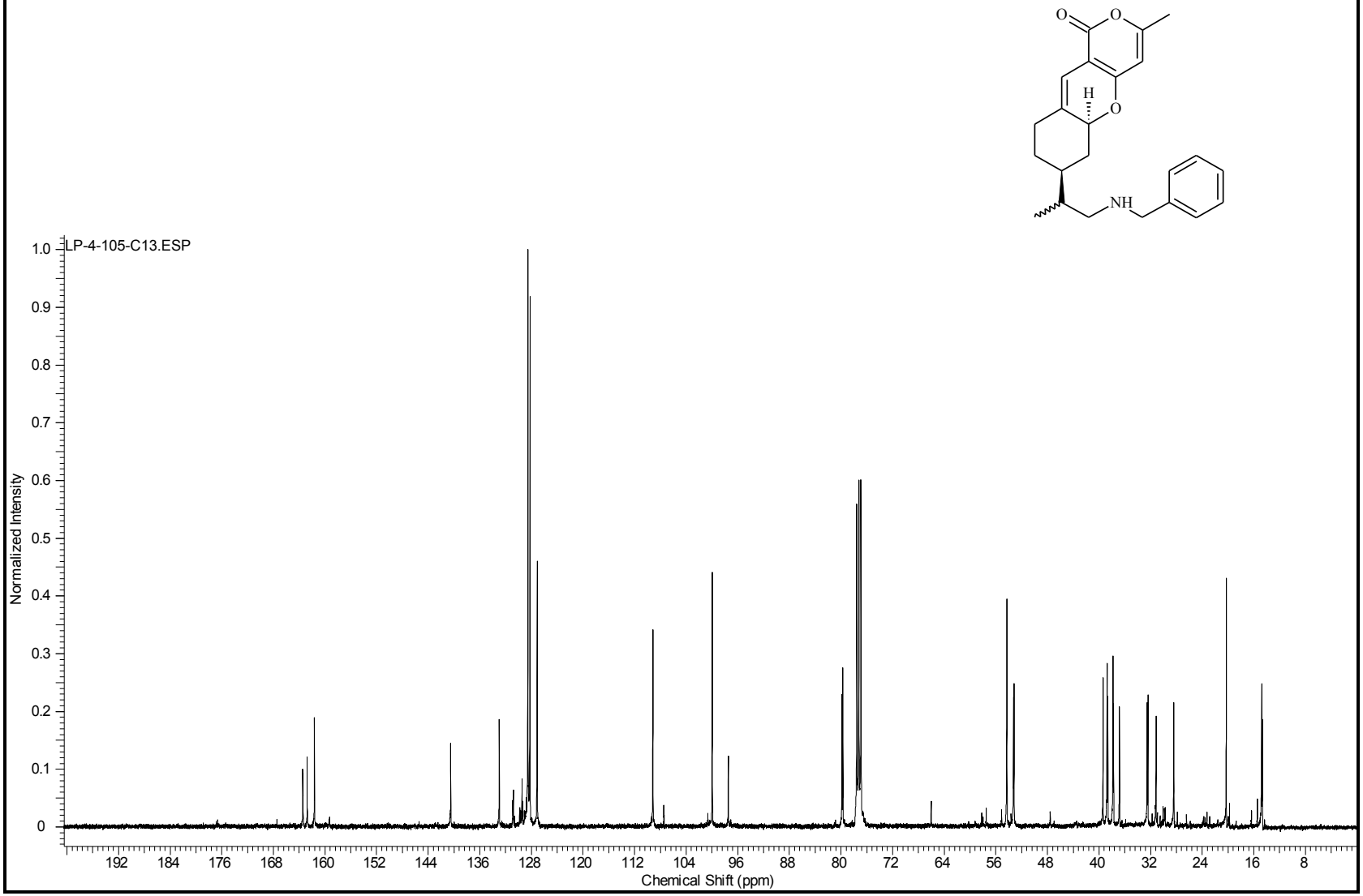
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Mar 16 2011
Date Stamp	Mar 16 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-60-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	16396	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10544.3525	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



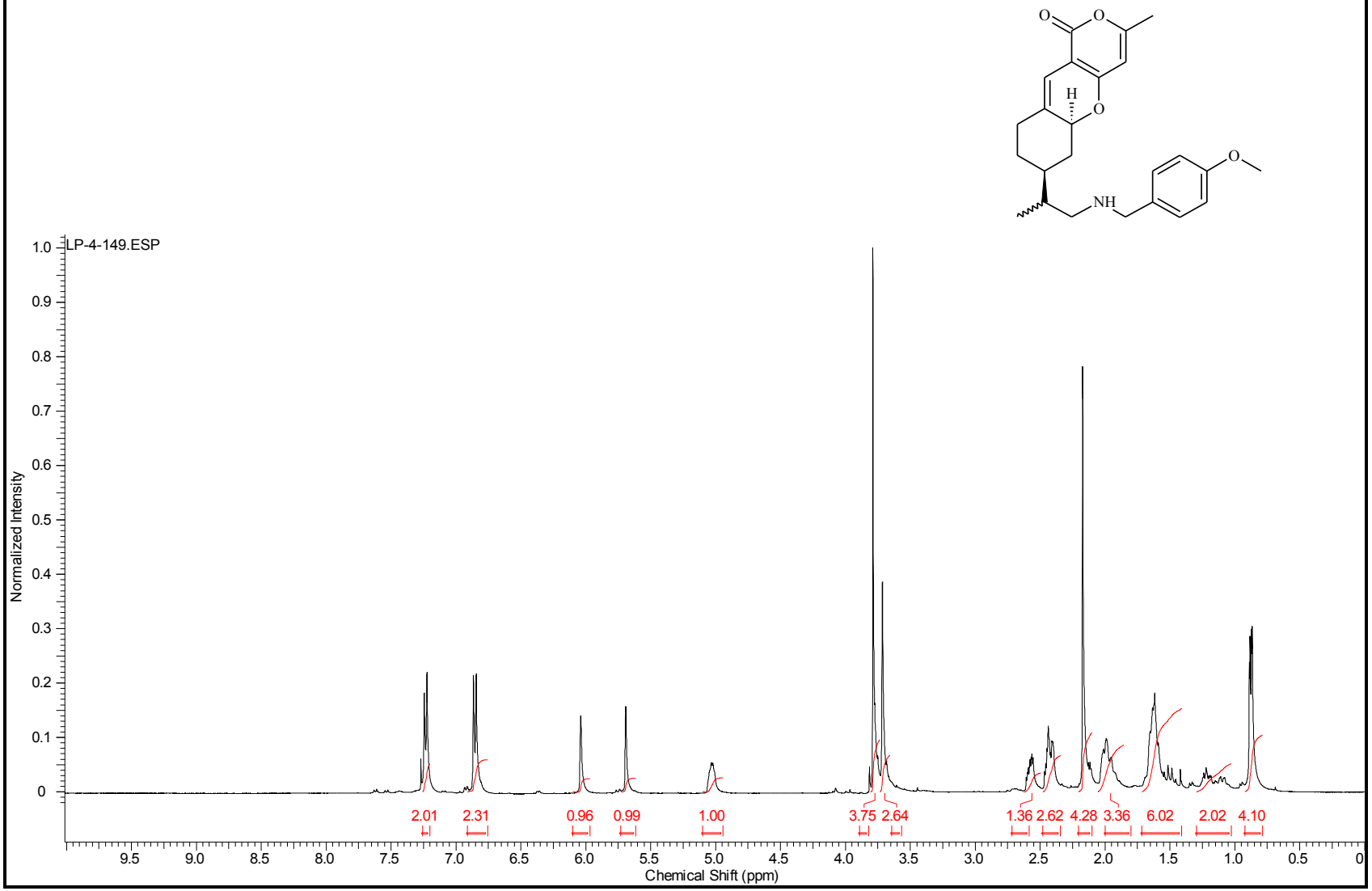
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Sep 14 2010
Date Stamp	Sep 14 2010	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-4-105.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	84	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2402.5823	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



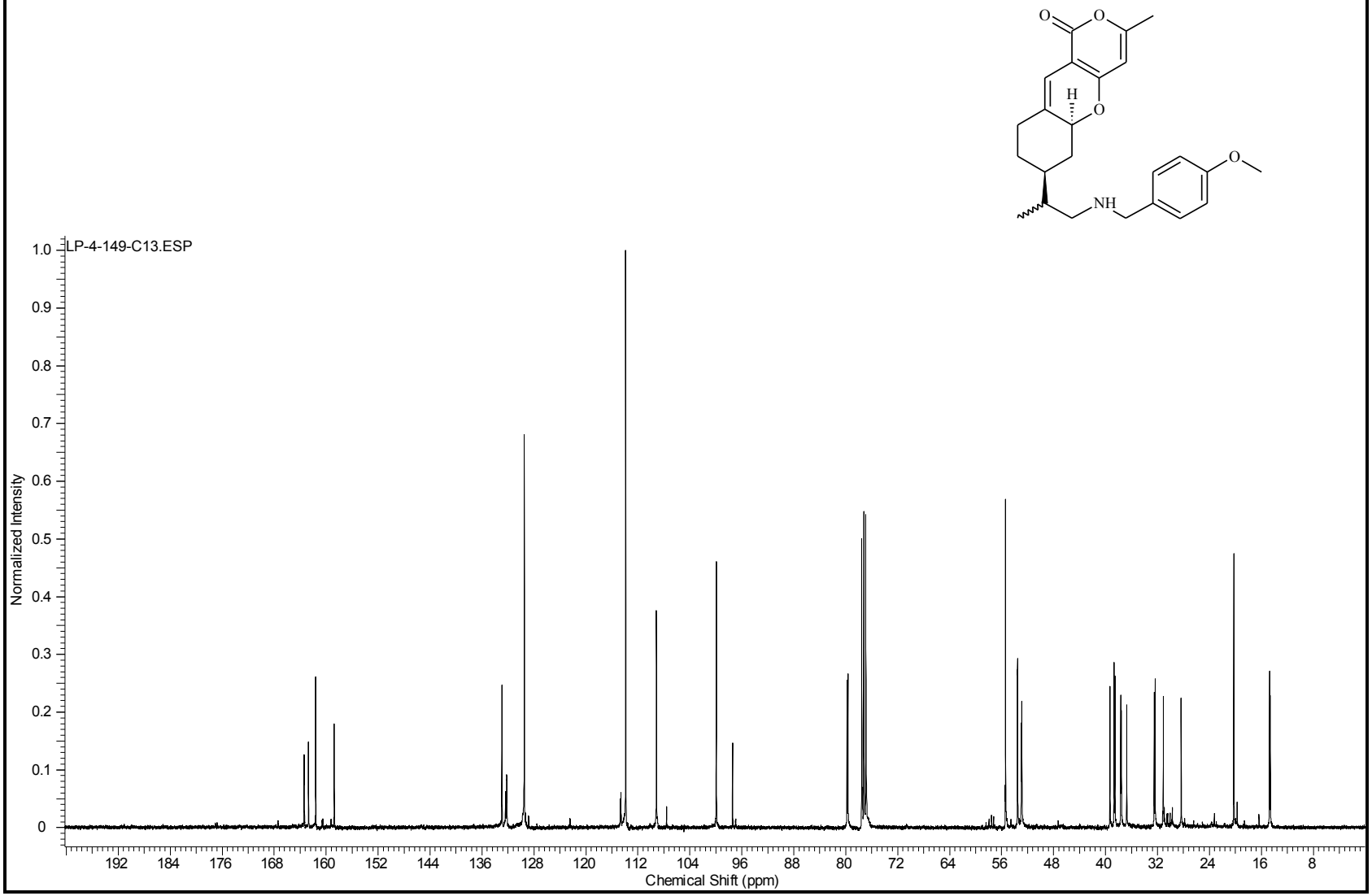
Date Stamp	Sep 14 2010	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-4-105-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	23628	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10550.9873	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



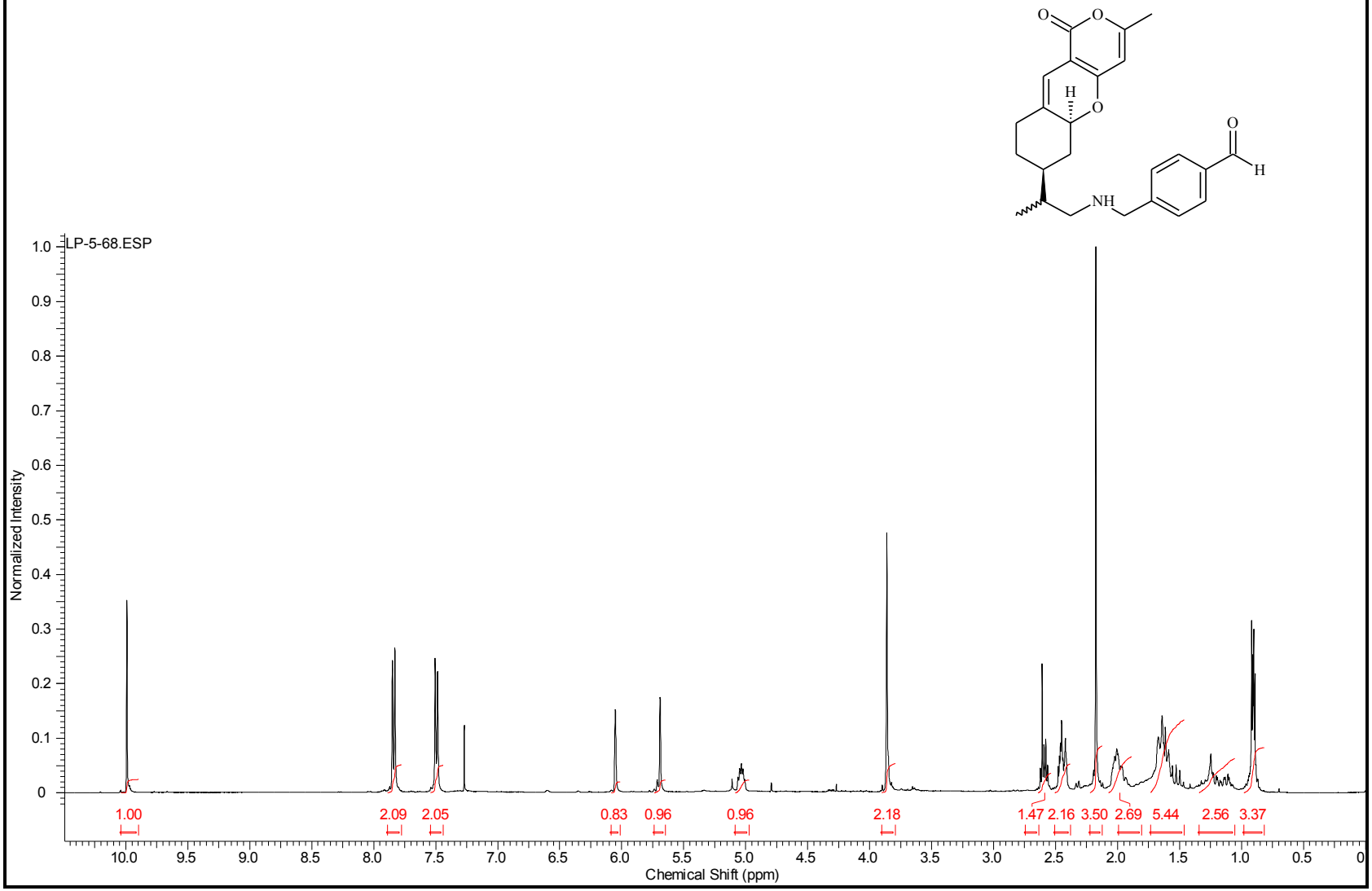
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Dec 28 2010
Date Stamp	Dec 28 2010	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-4-149.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	36	***Original Points Count***	12783
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	18.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2403.4763	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



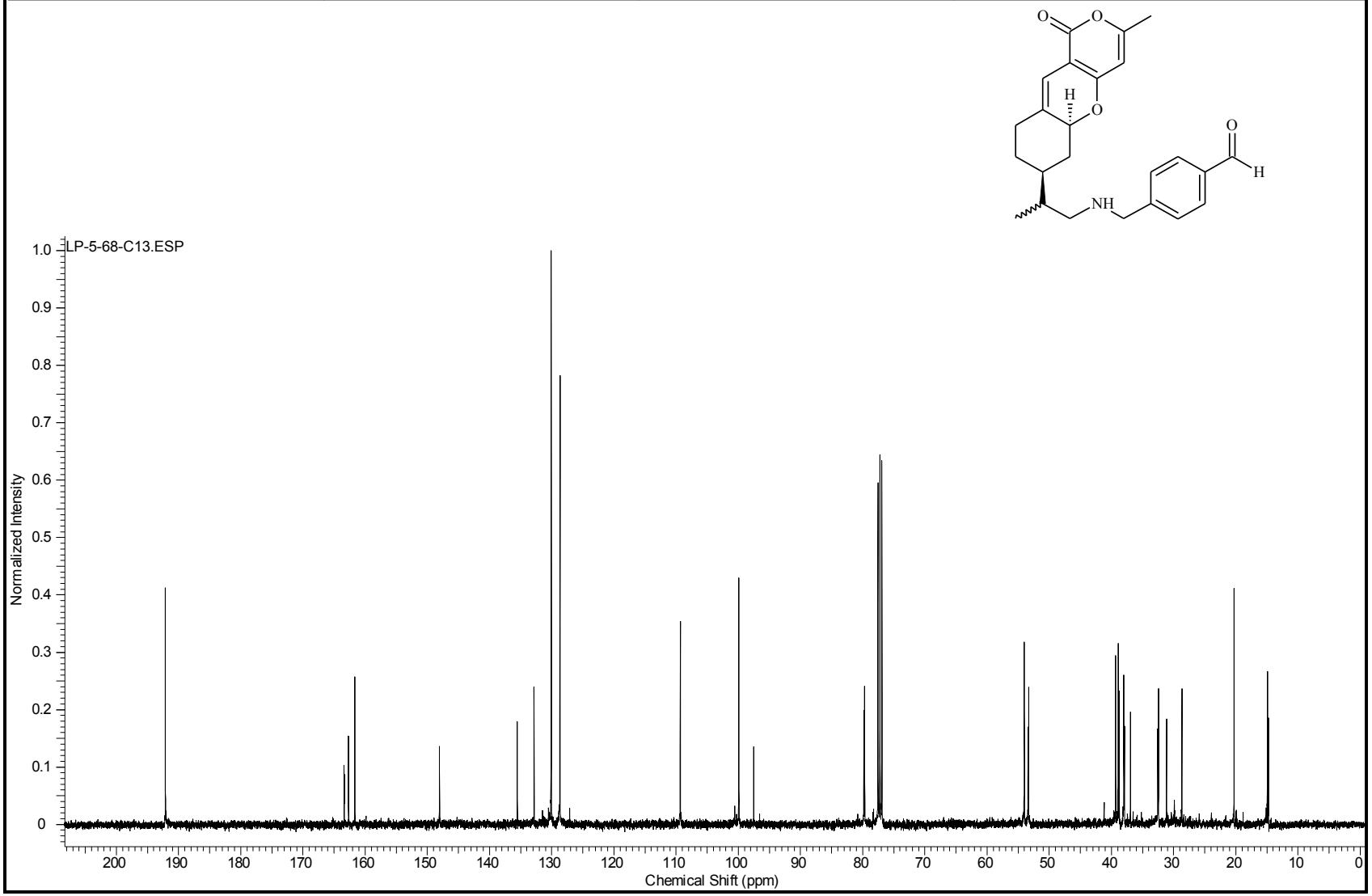
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Dec 28 2010
Date Stamp	Dec 28 2010	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-4-149-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	23844	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10550.2510	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



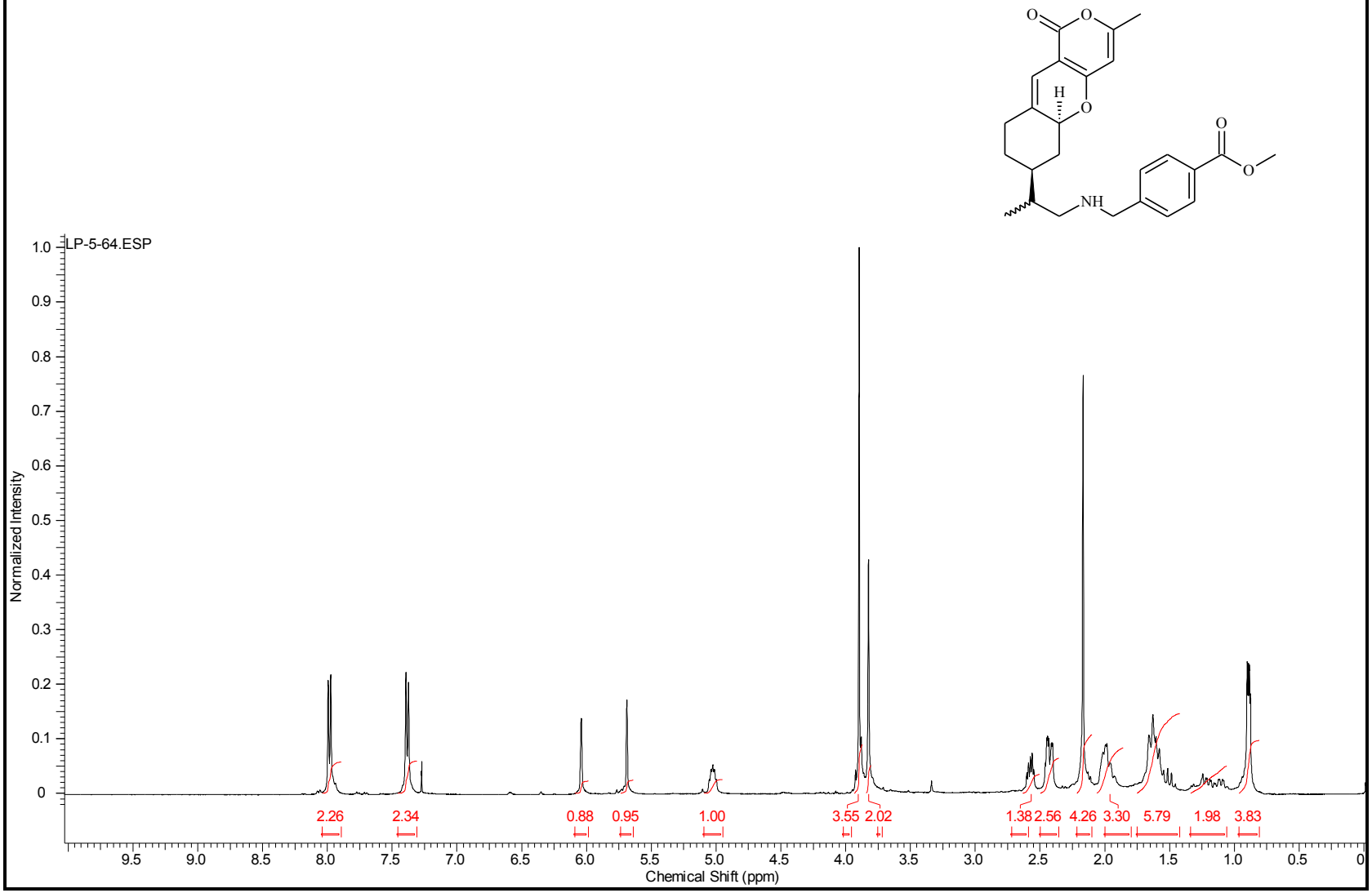
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Mar 31 2011
Date Stamp	Mar 31 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-68.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	48	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2403.3633	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



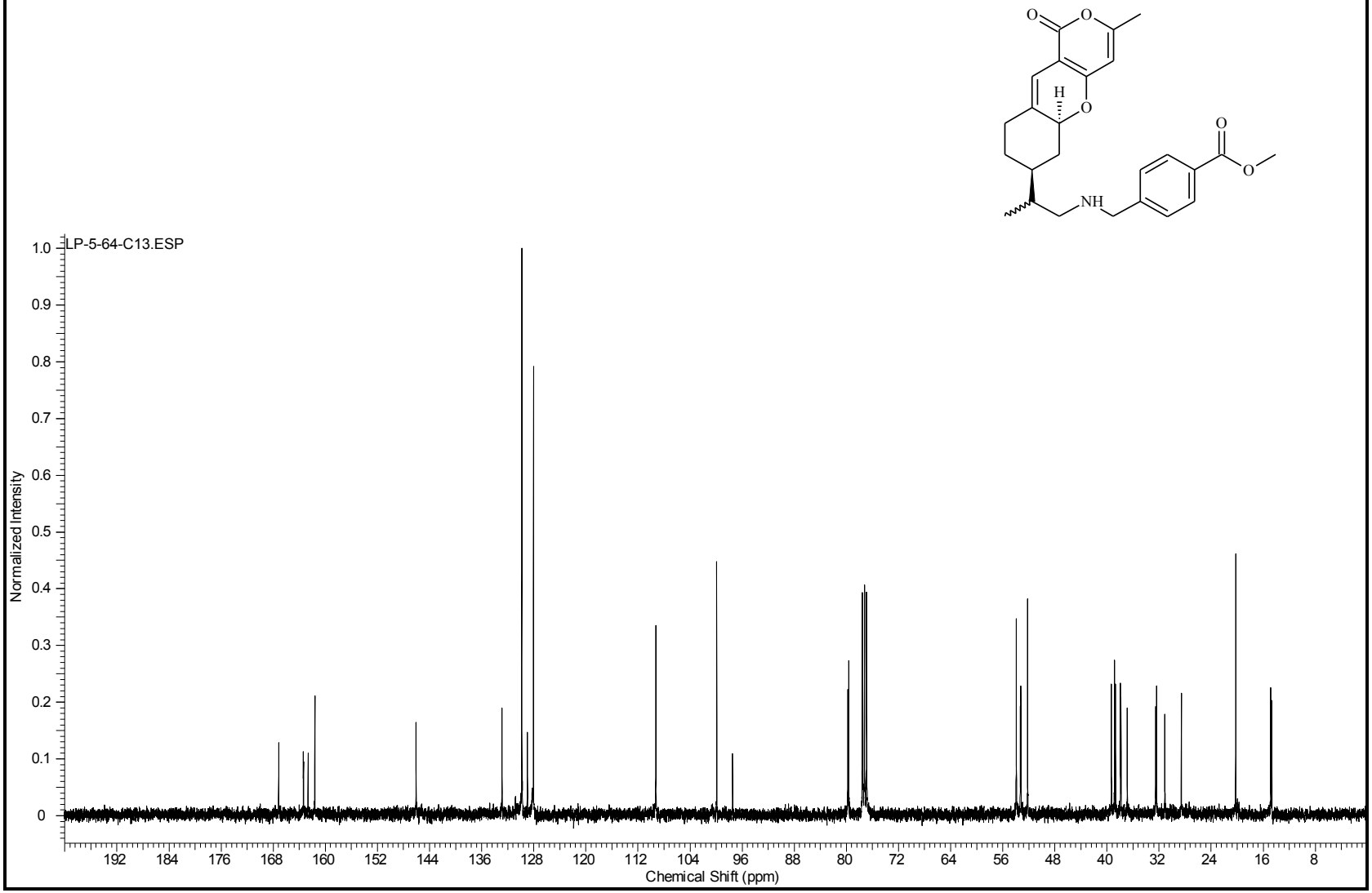
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Mar 31 2011
Date Stamp	Mar 31 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-68-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	4036	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10555.4111	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



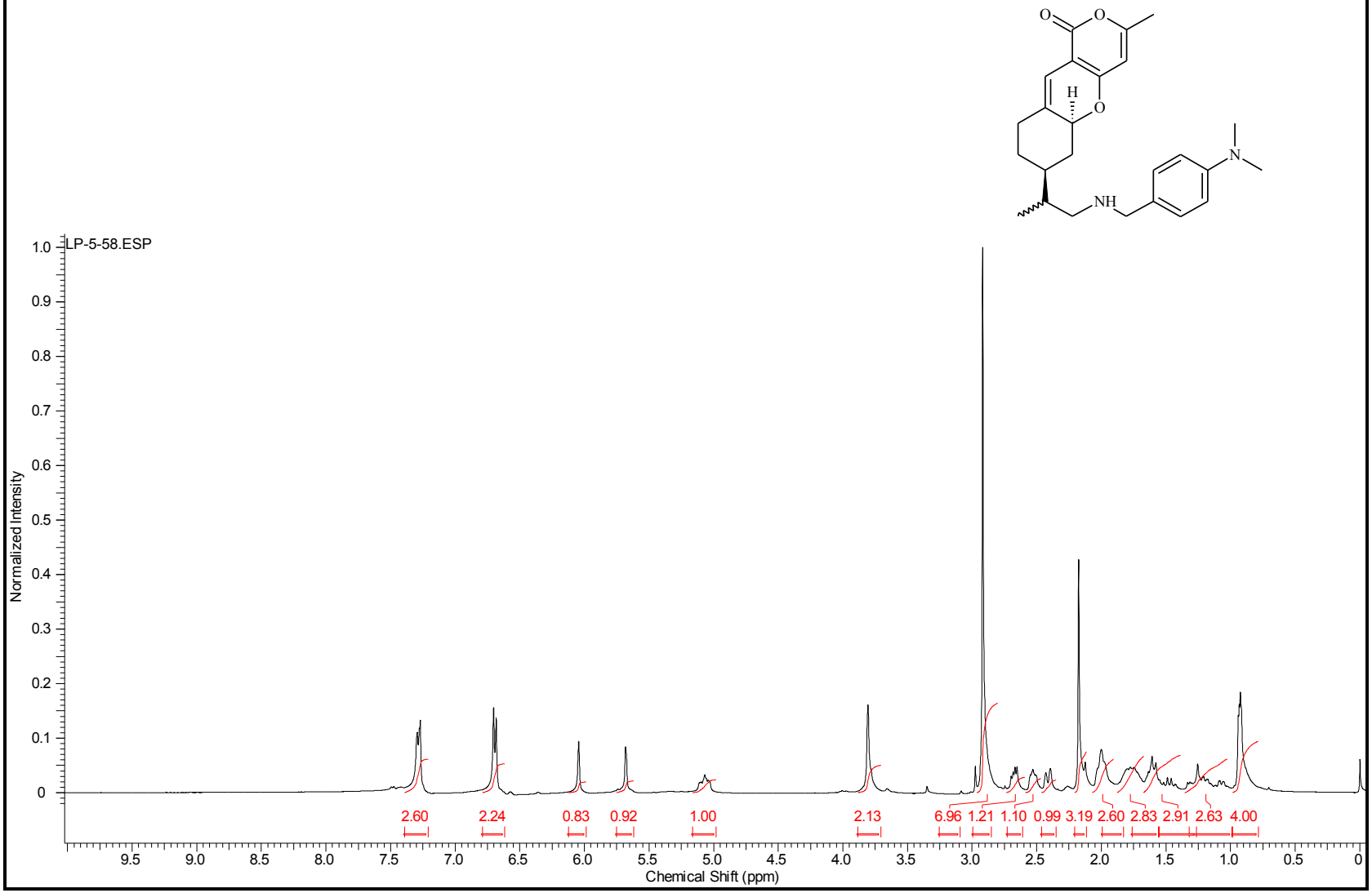
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Mar 25 2011
Date Stamp	Mar 25 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-64.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	20	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2403.7539	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



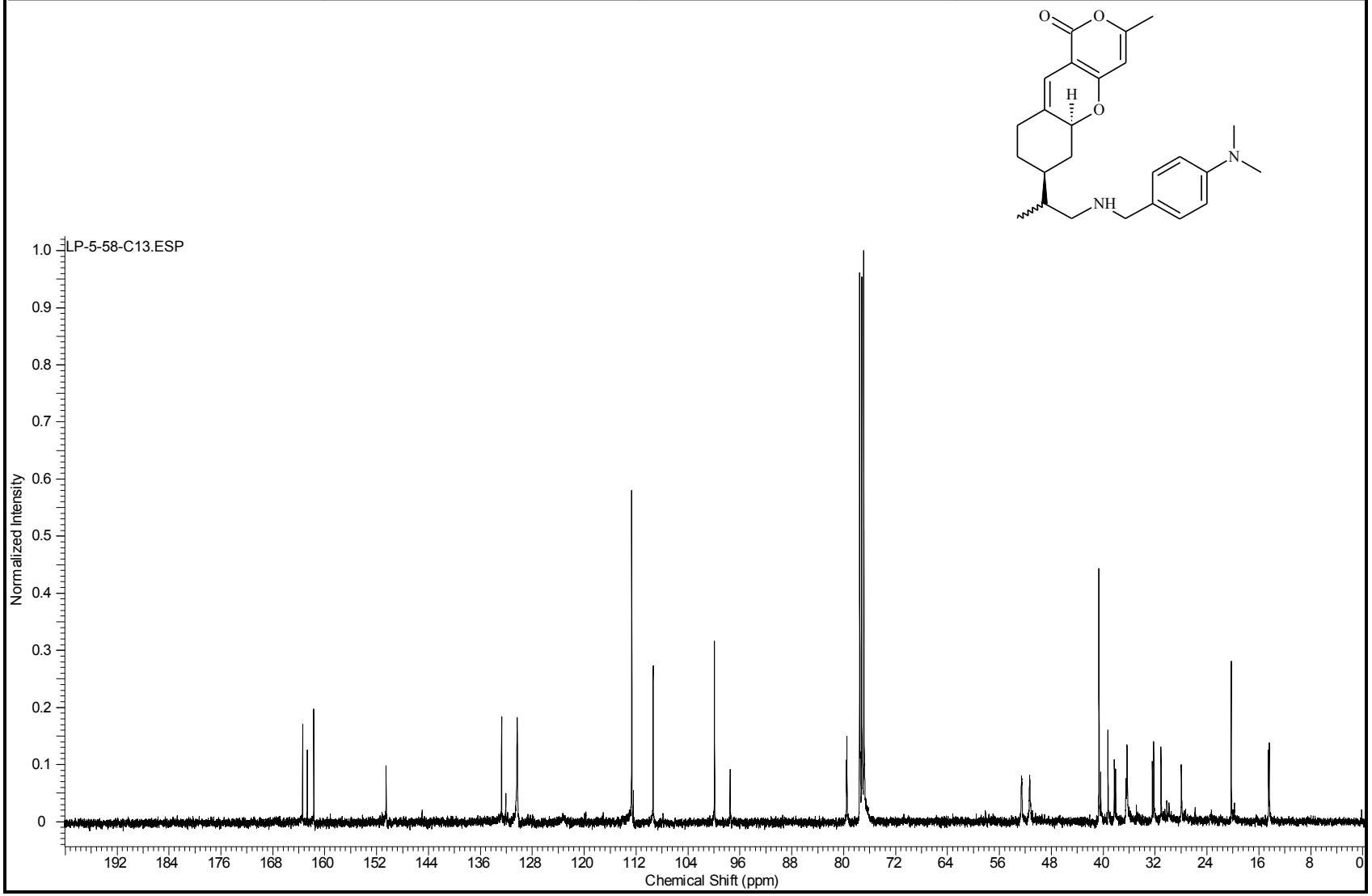
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Mar 25 2011
Date Stamp	Mar 25 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-64-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	880	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10552.4619	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



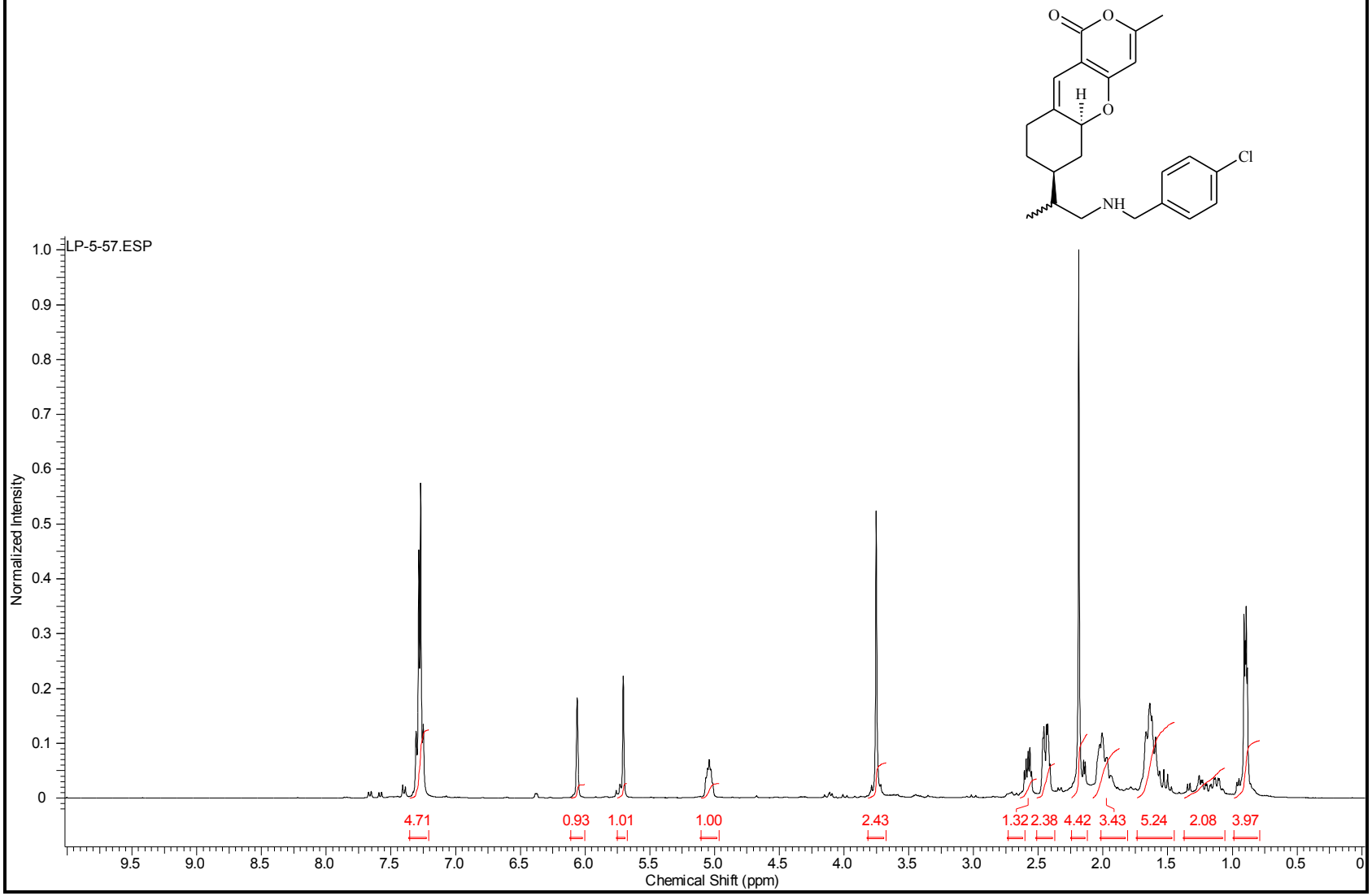
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Mar 30 2011
Date Stamp	Mar 30 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-58.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	44	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	24.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2401.8013	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



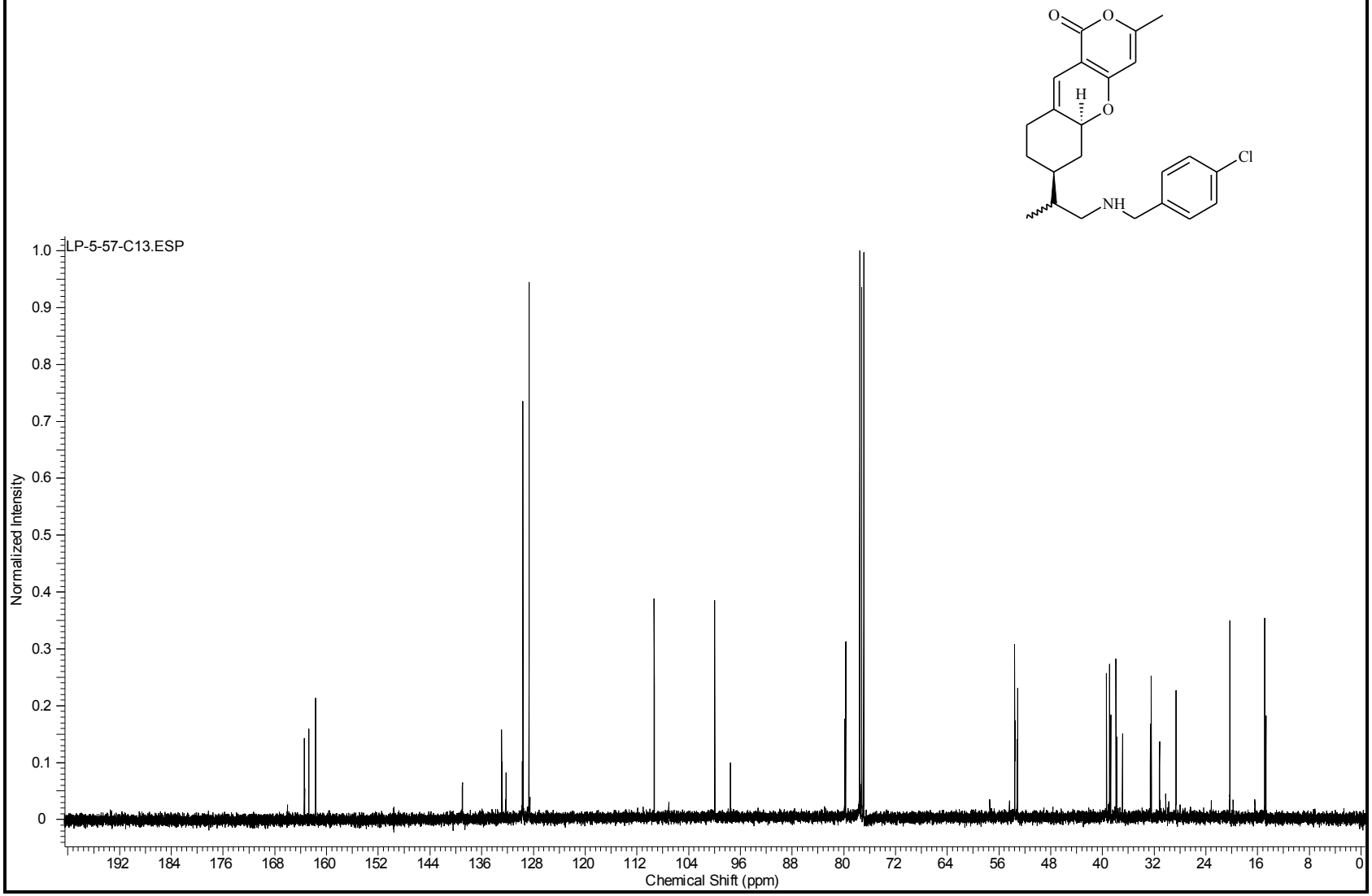
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Mar 30 2011
Date Stamp	Mar 30 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-58-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	10432	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10555.4102	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



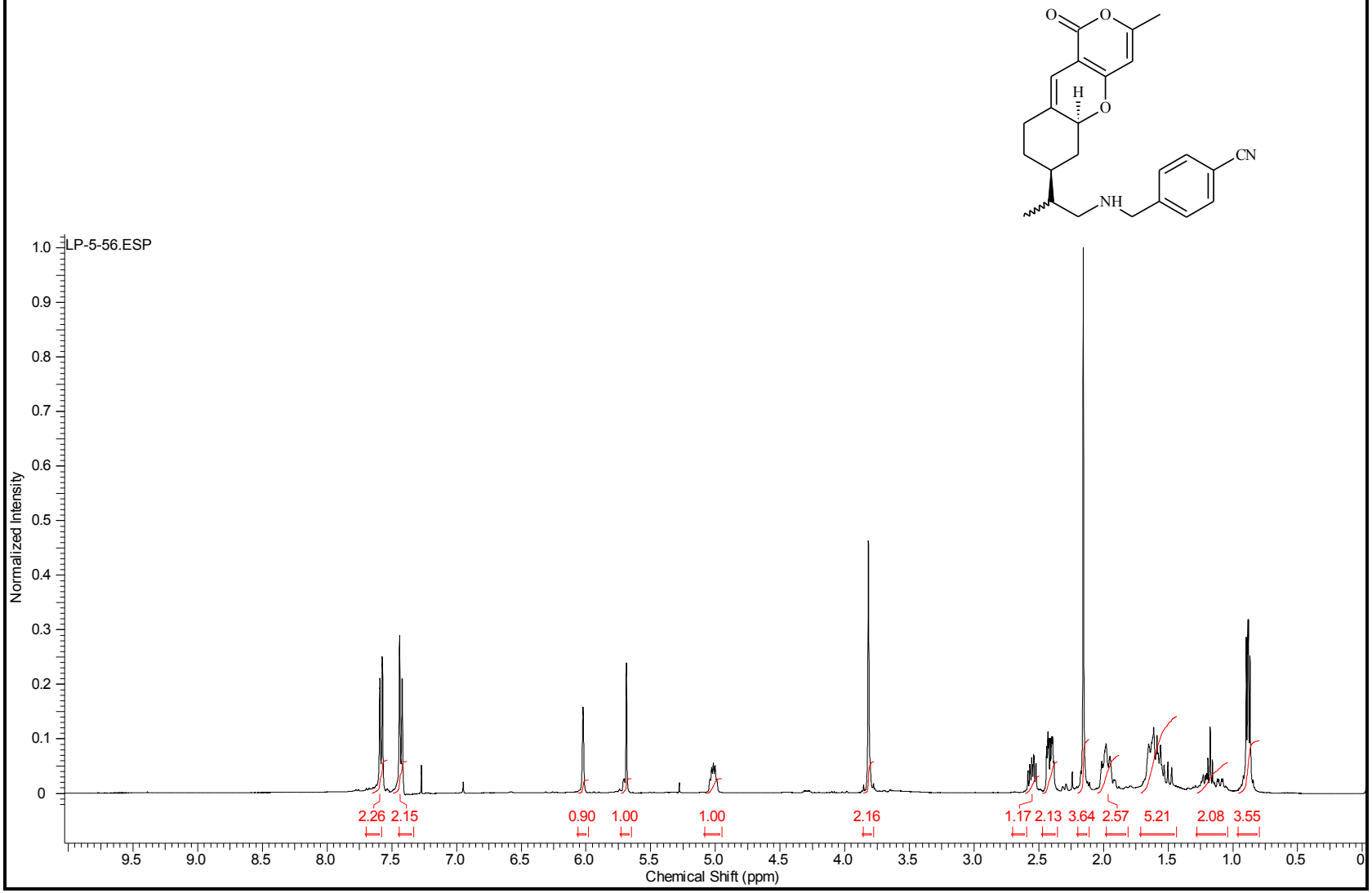
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Jul 1 2011	***Date Stamp***	Jul 1 2011		
File Name	F:\NMR-NOVA-02-12\LP-5-57-2.FID\FID			***Frequency (MHz)***	399.73	***Nucleus***	1H	***Number of Transients***	44
Original Points Count	13102	***Points Count***	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	36.00		
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	2414.7563	***Spectrum Type***	STANDARD		
Sweep Width (Hz)	6395.40	***Temperature (degree C)***	25.000						



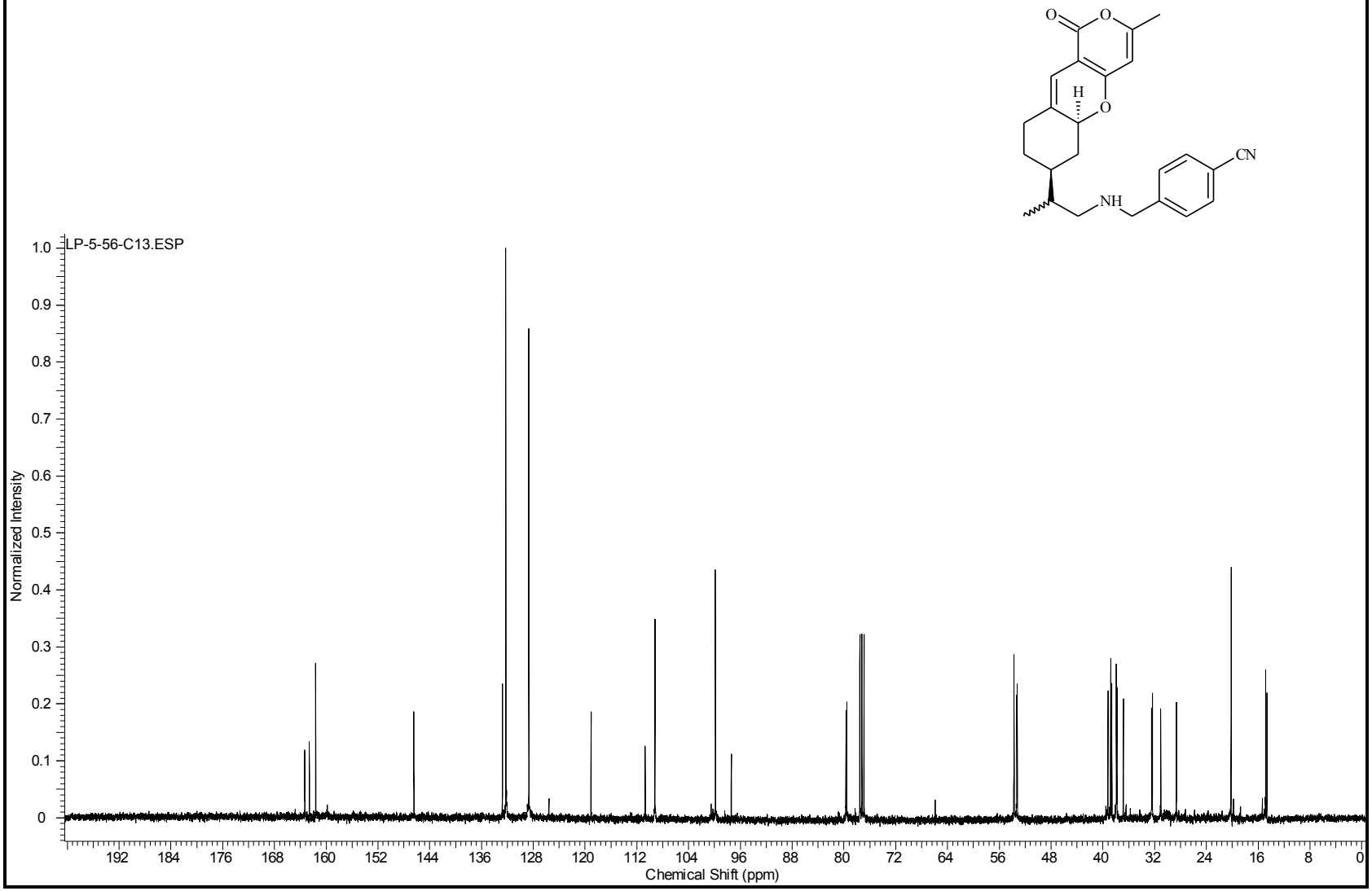
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Jul 1 2011	***Date Stamp***	Jul 1 2011
File Name	F:\NMR-NOVA-02-12\LP-5-57-2-C13.FID\FID			***Frequency (MHz)***	100.52	***Nucleus***	13C
Number of Transients	22968	***Original Points Count***	31375	***Points Count***	32768	***Pulse Sequence***	s2pul
Receiver Gain	30.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	10553.6523
Spectrum Type	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	25.000		



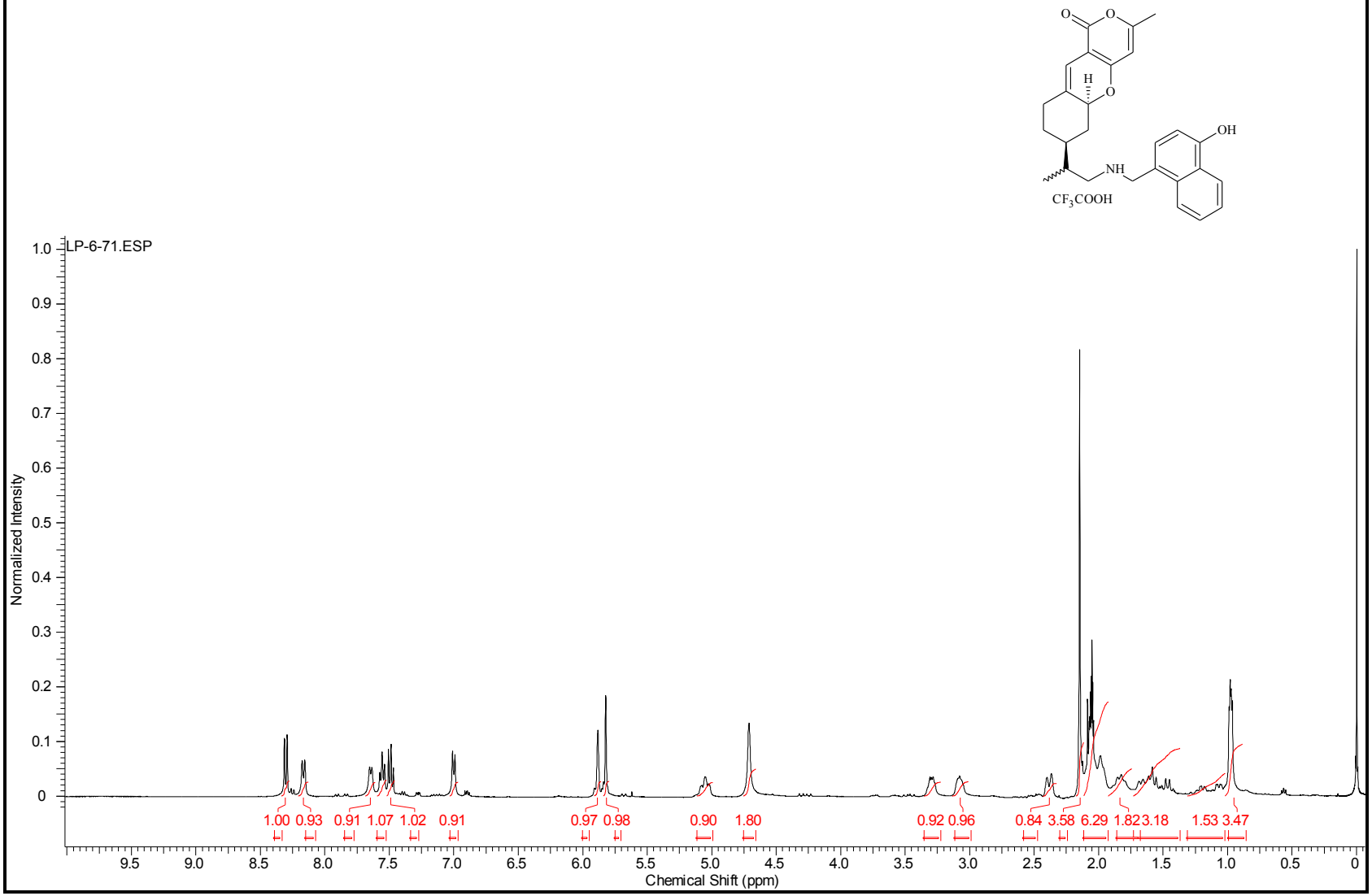
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Mar 17 2011
Date Stamp	Mar 17 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-56.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	28	***Original Points Count***	12783
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	16.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2404.2573	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



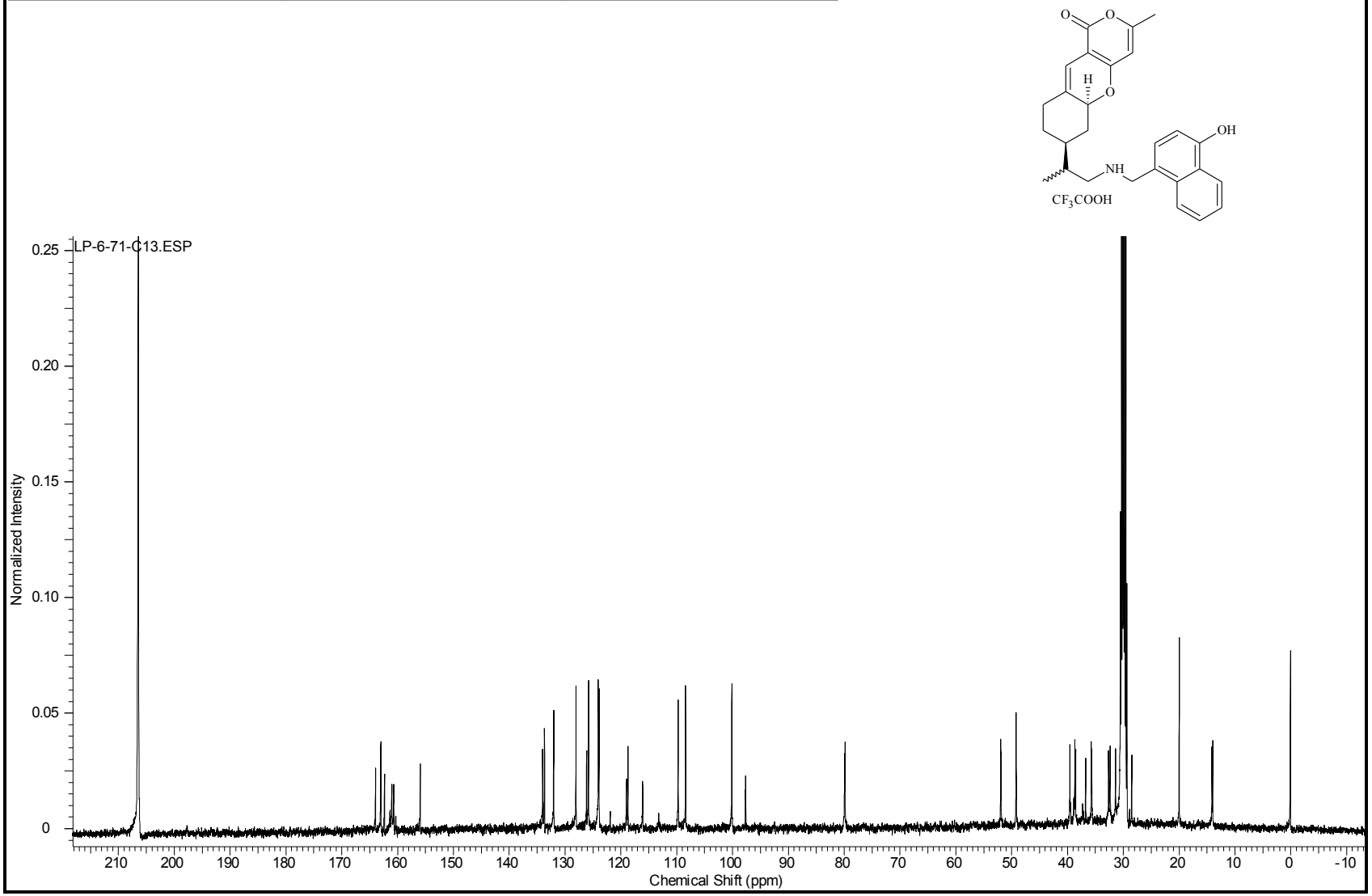
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Mar 17 2011
Date Stamp	Mar 17 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-56-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	828	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10548.0381	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



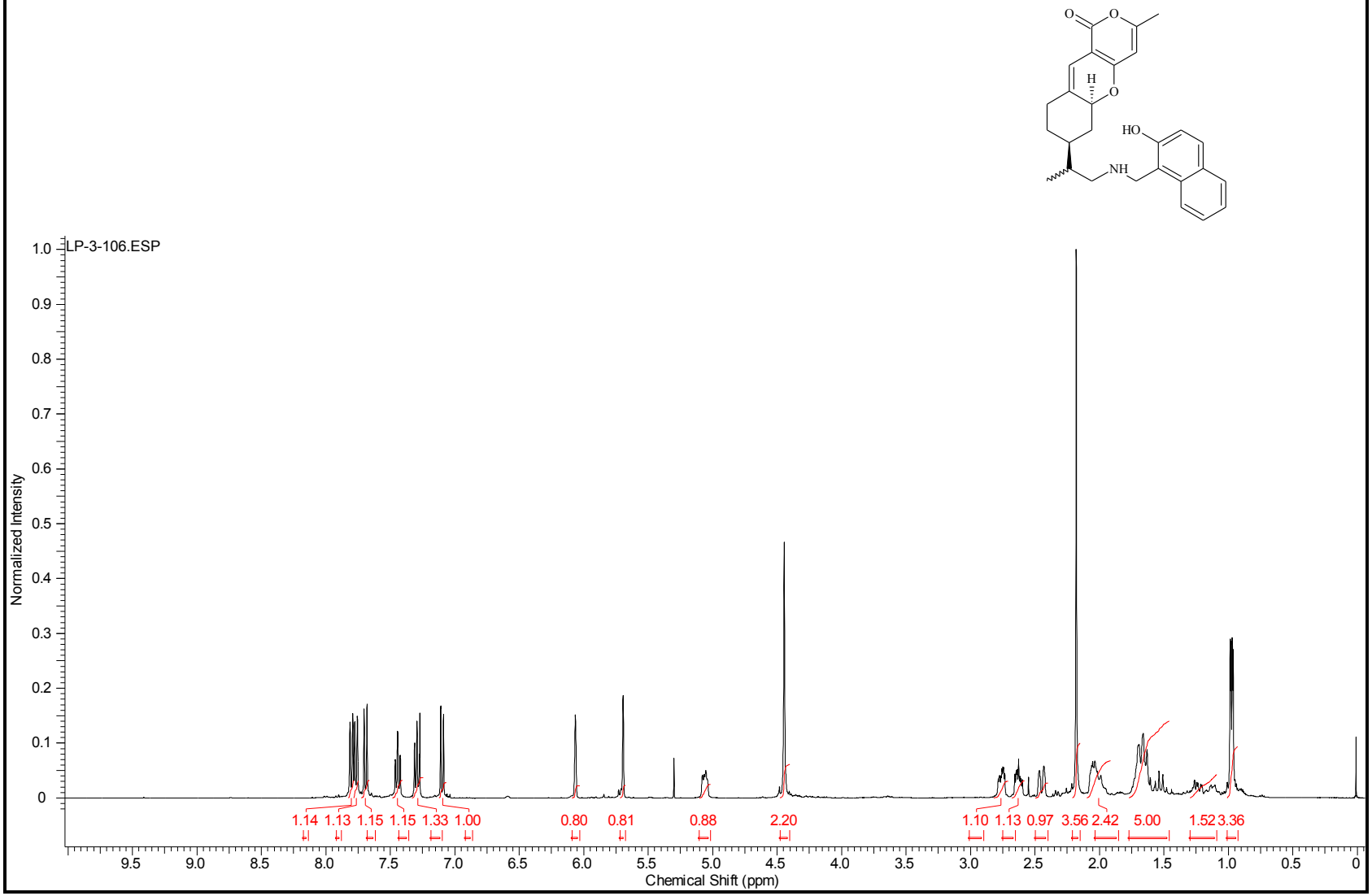
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Mar 6 2012
Date Stamp	Mar 6 2012	***File Name***	F:\MERCURY03-2-2012\LP-6-71-LAST.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	112	***Original Points Count***	12783	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	26.00	***Solvent***	acetone	***Spectrum Offset (Hz)***	2399.0100
Spectrum Type	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000		



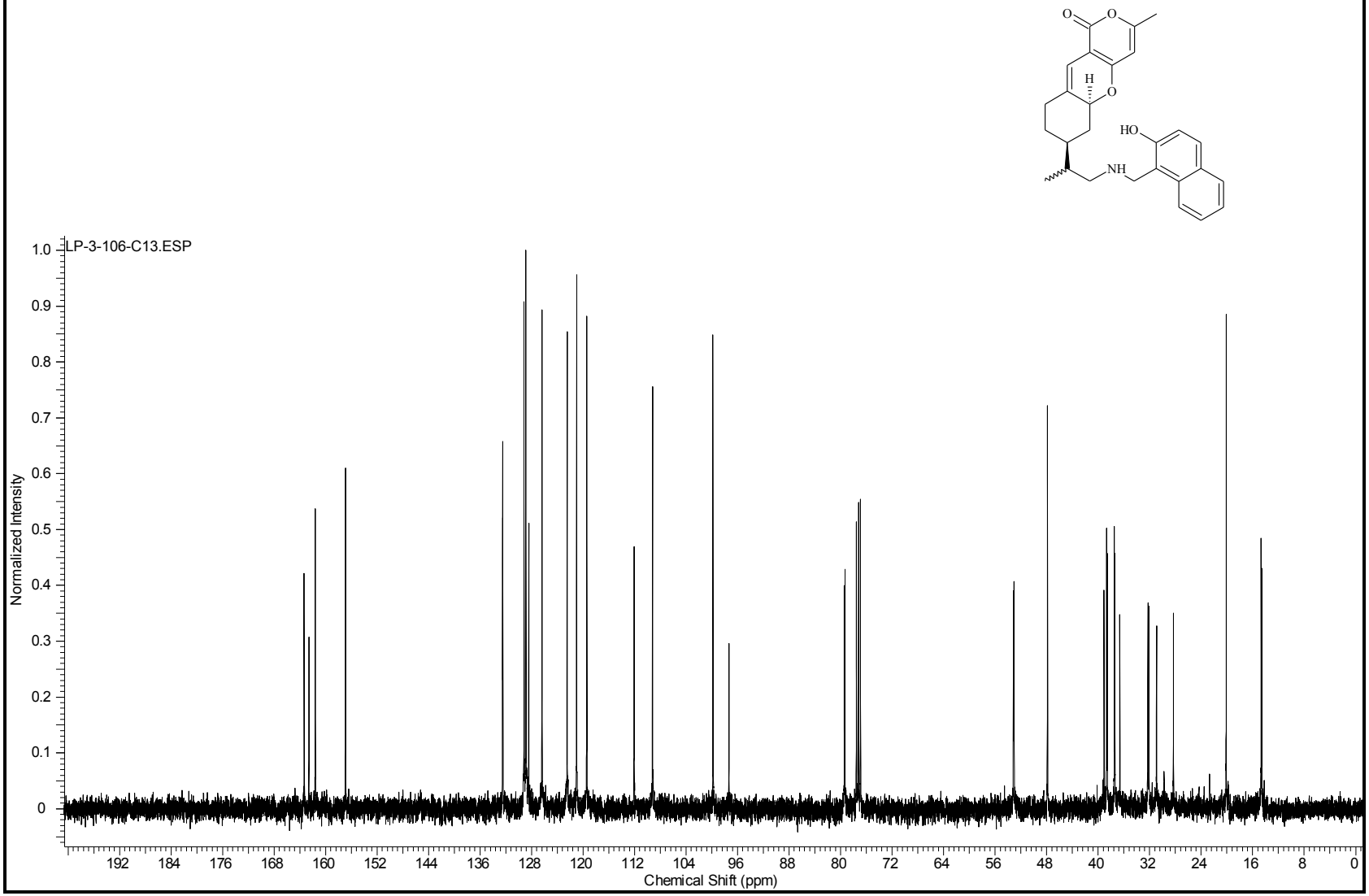
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Mar 1 2012
Date Stamp	Mar 1 2012	***File Name***	F:\MERCURY03-2-2012\LP-6-71-C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	20136	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	acetone	***Spectrum Offset (Hz)***	10633.4824
Spectrum Type	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000		



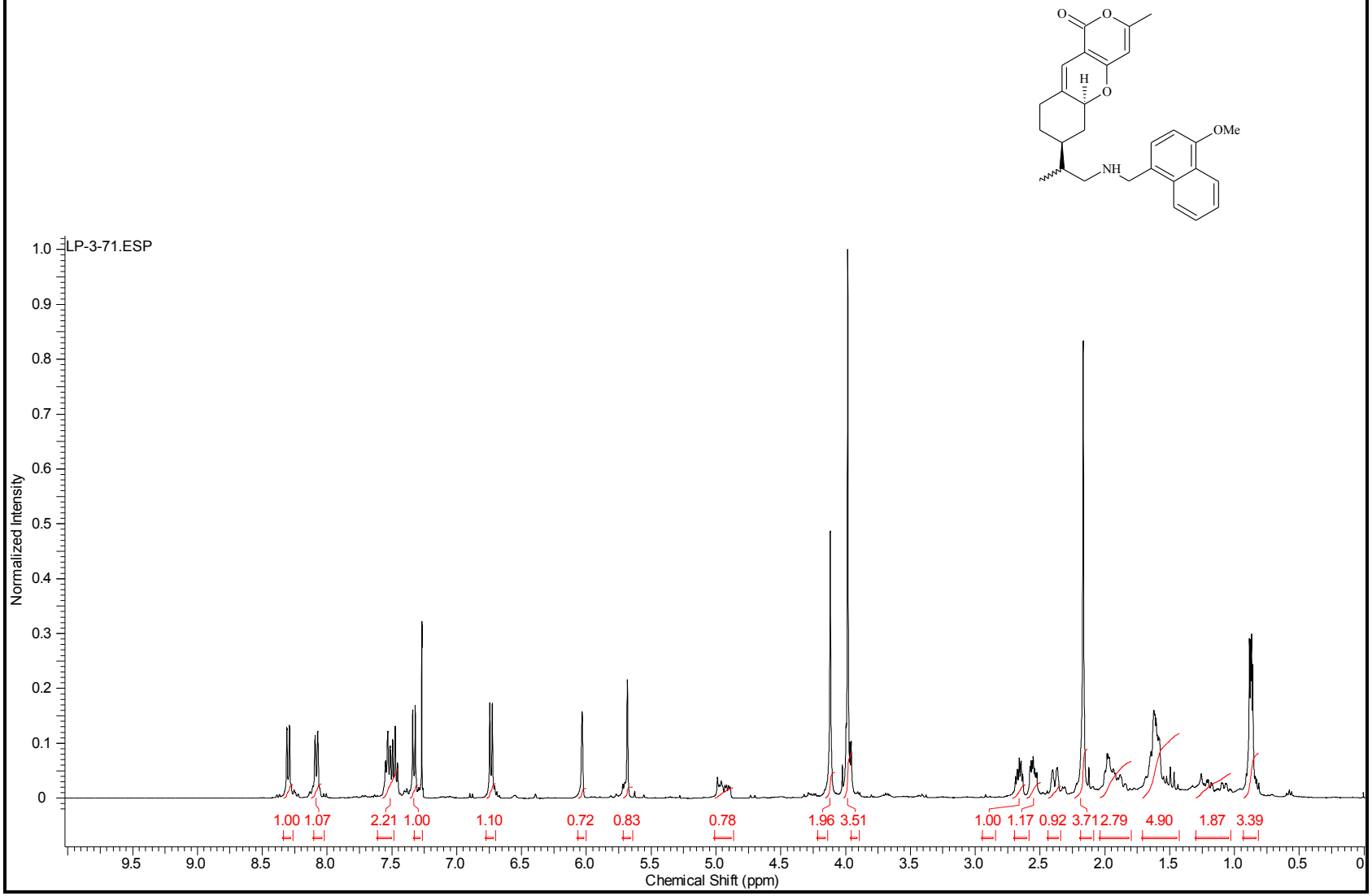
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Mar 25 2010	***Date Stamp***	Mar 25 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-3-106.FID\FID						
Frequency (MHz)	399.74	***Nucleus***	1H	***Number of Transients***	28	***Original Points Count***	13103
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	36.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2417.1301	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	25.000



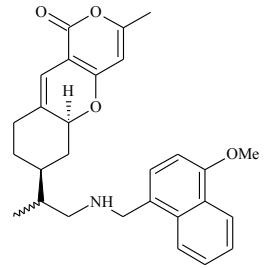
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jul 11 2011
Date Stamp	Jul 11 2011	***File Name***	F:\LAXMAN POKHREL\LAXMAN-MERCURY-07-15-2011\TP61-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	376	***Original Points Count***	31413
Points Count	65536	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10541.1777	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000

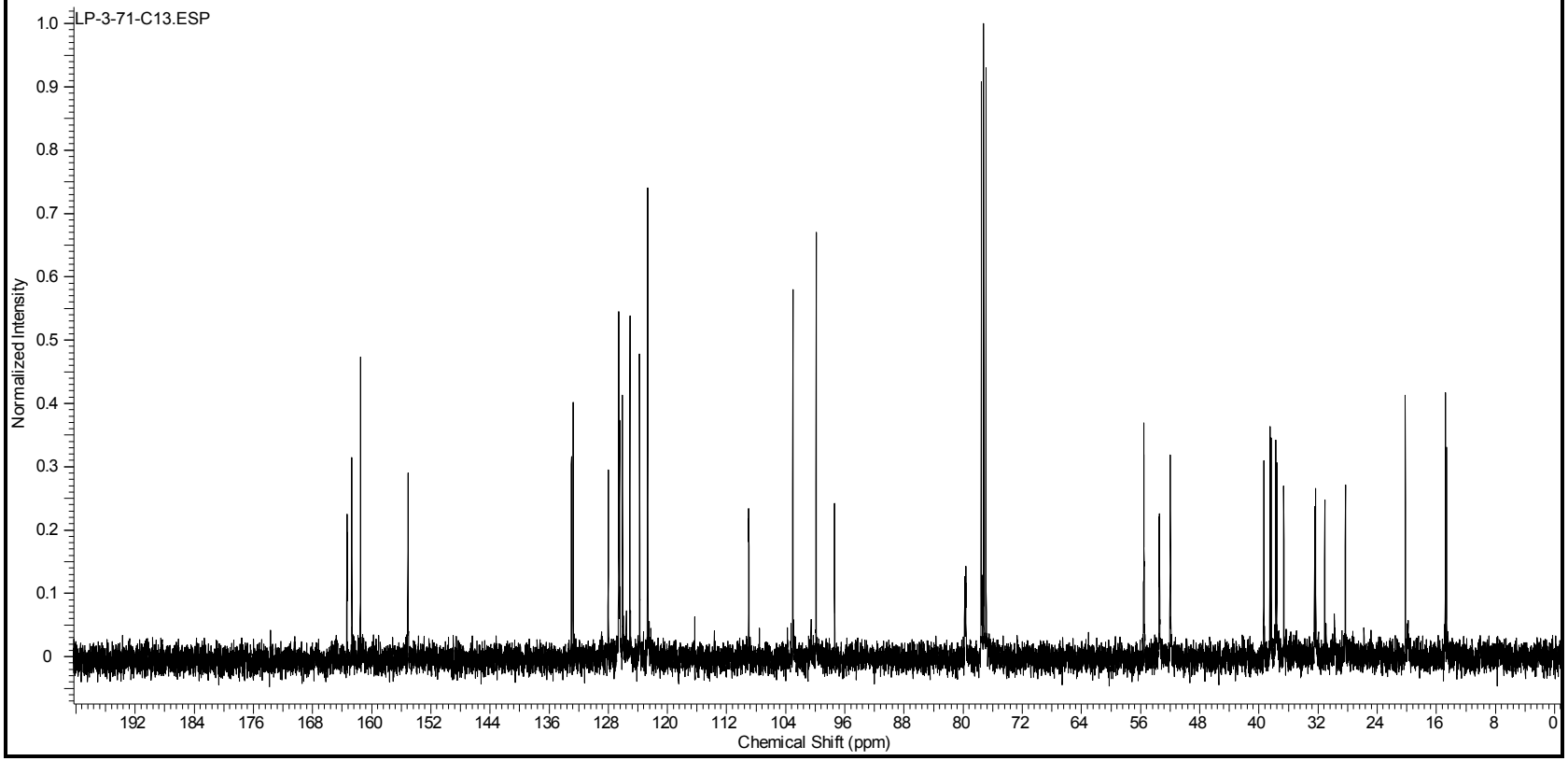


Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Feb 5 2010	***Date Stamp***	Feb 5 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-3-71-2.FID\FID						
Frequency (MHz)	399.74	***Nucleus***	1H	***Number of Transients***	52	***Original Points Count***	13103
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	26.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2416.4619	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	30.000

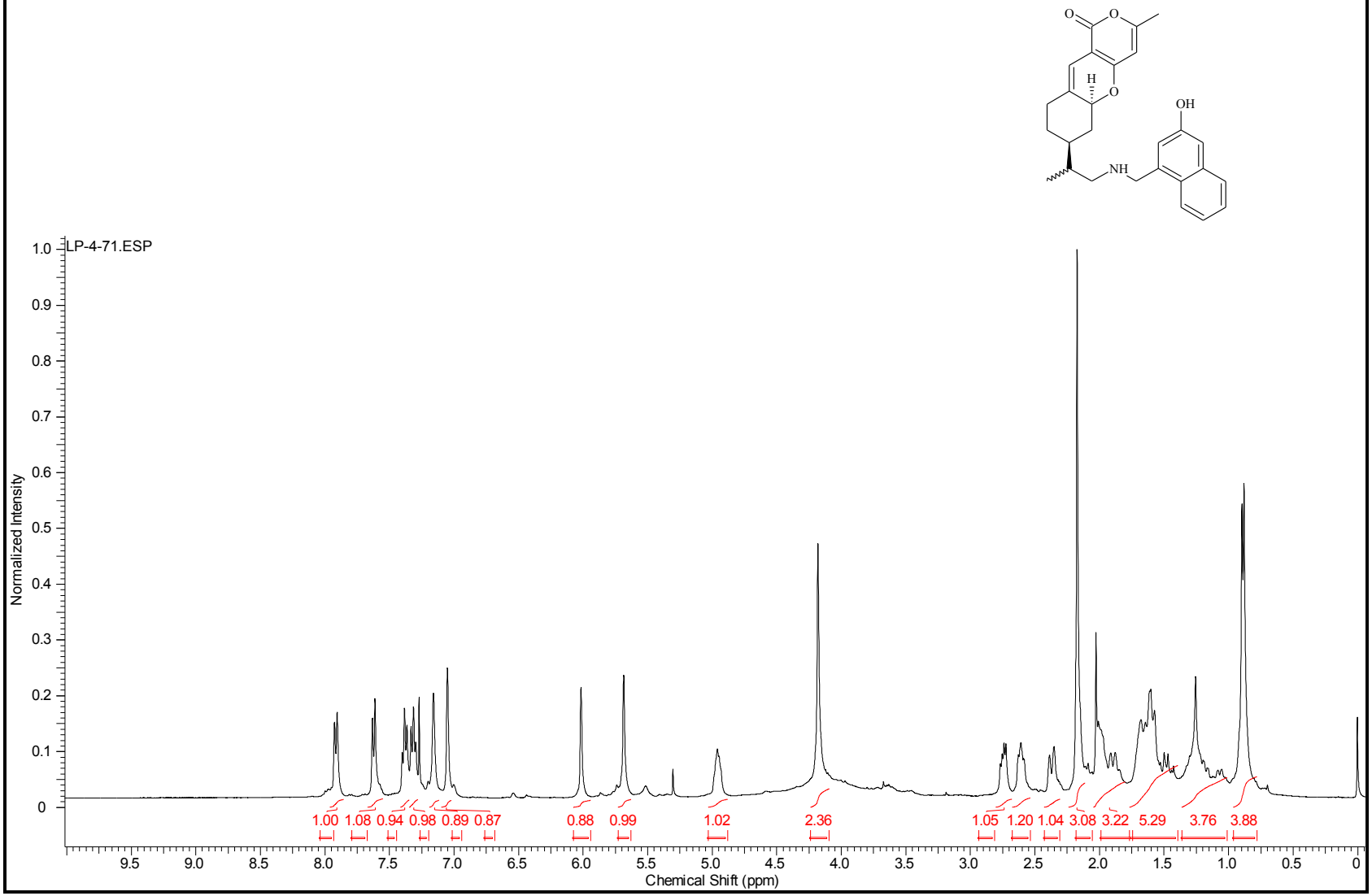


Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Feb 5 2010	***Date Stamp***	Feb 5 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-3-71-2C13.FID\FID						
Frequency (MHz)	100.52	***Nucleus***	13C	***Number of Transients***	628	***Original Points Count***	31375
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10542.5674	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	30.000

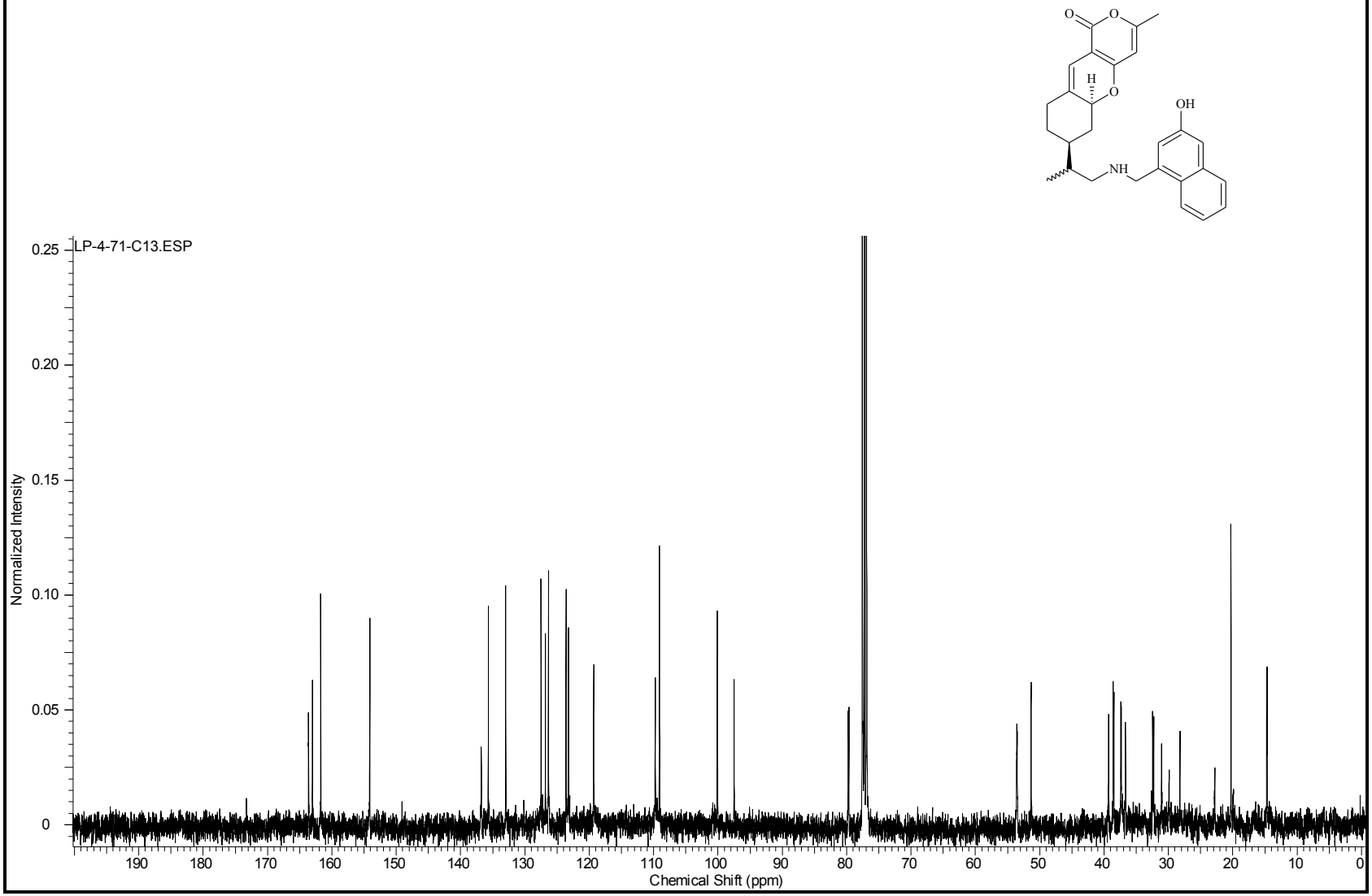




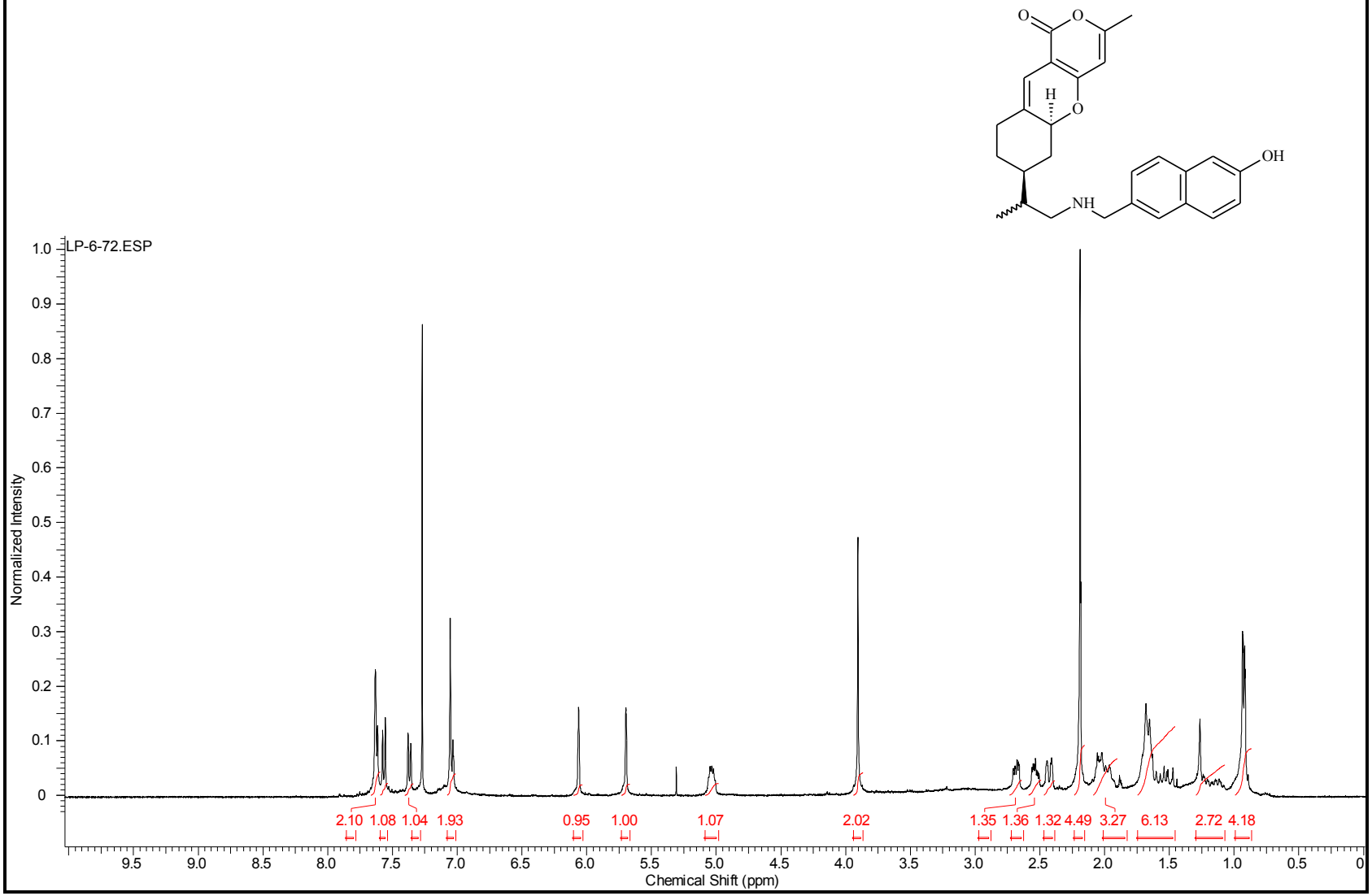
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Aug 17 2010	***Date Stamp***	Aug 17 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-71.FID\FID						
Frequency (MHz)	399.74	***Nucleus***	1H	***Number of Transients***	44	***Original Points Count***	13103
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	32.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2418.5090	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	30.000



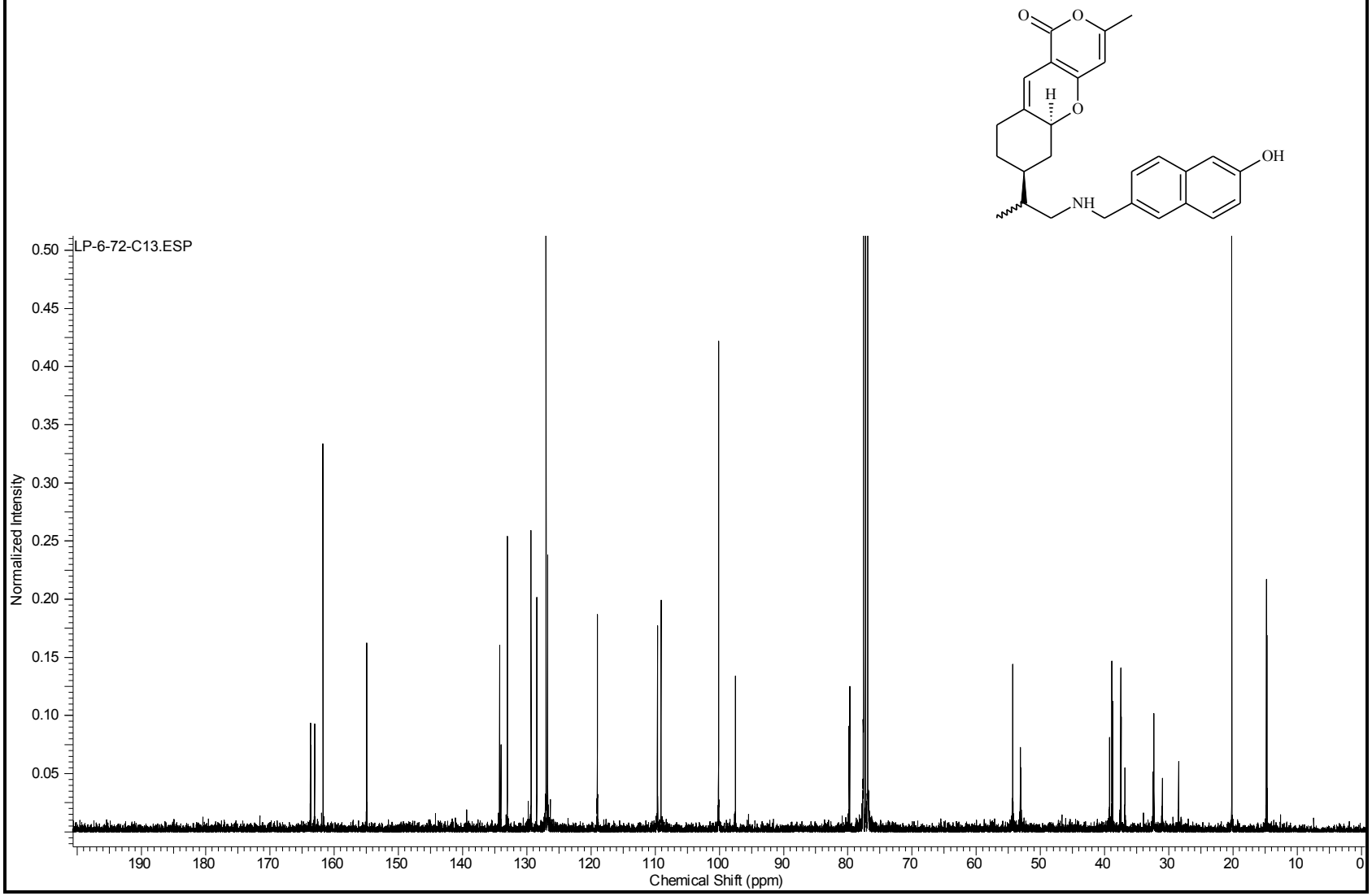
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Aug 17 2010	***Date Stamp***	Aug 17 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-71-C13.FID\FID						
Frequency (MHz)	100.52	***Nucleus***	13C	***Number of Transients***	7800	***Original Points Count***	31375
Points Count	65536	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10552.2803	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	30.000



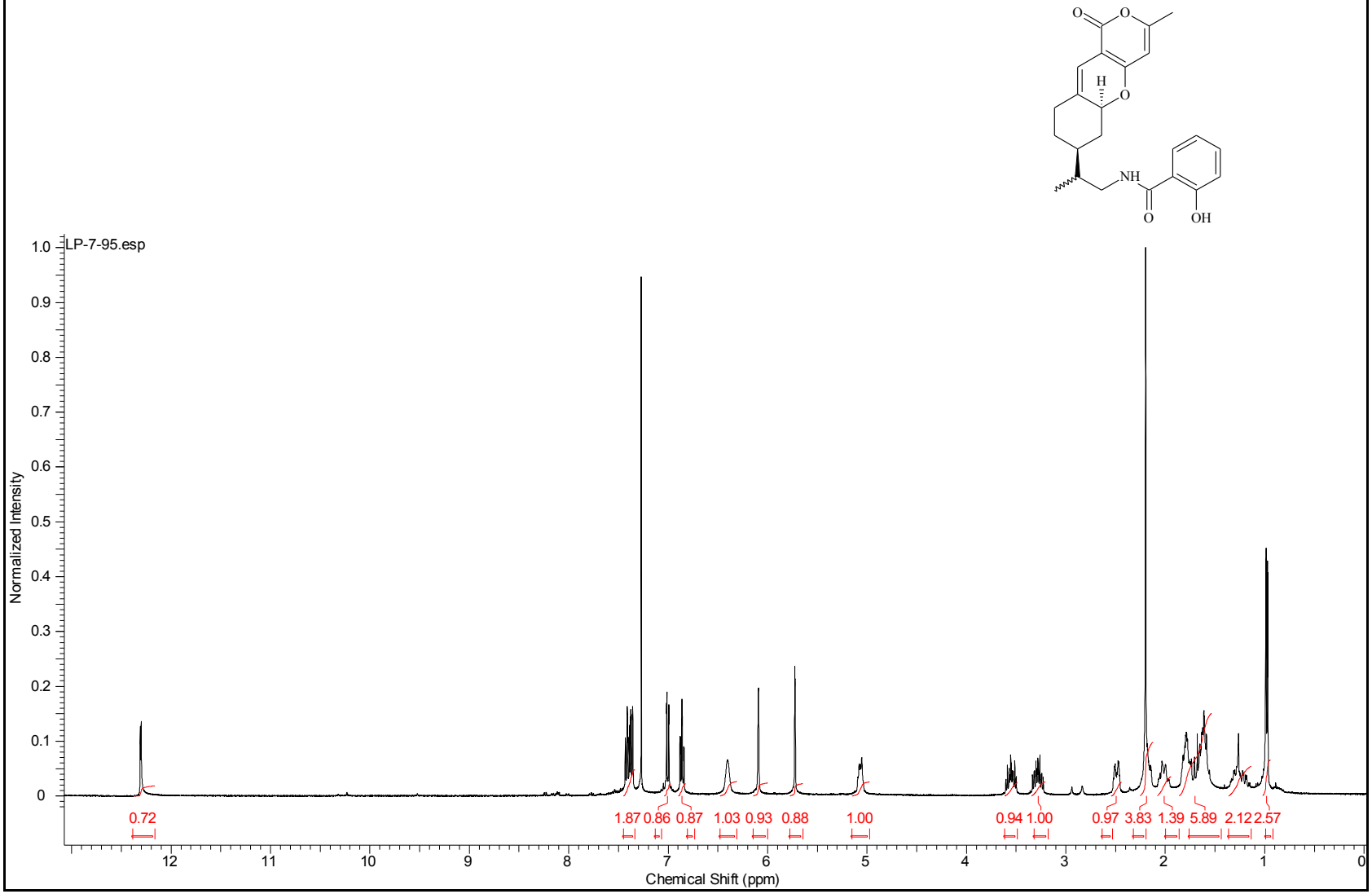
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Mar 1 2012
Date Stamp	Mar 1 2012	***File Name***	F:\MERCURY03-2-2012\LP-6-72-LAST.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	52	***Original Points Count***	12783	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	36.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2404.5349	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



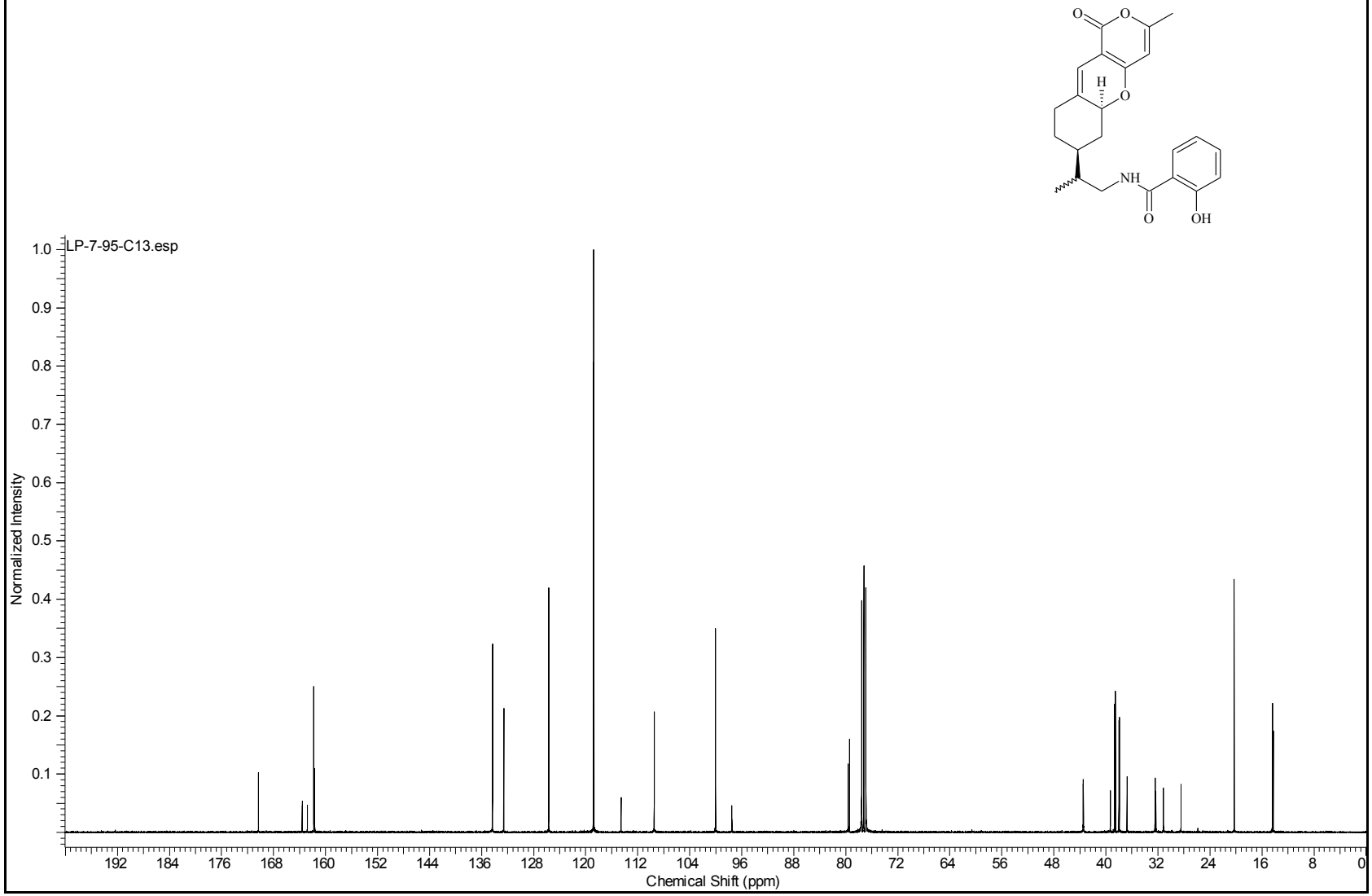
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Feb 29 2012
Date Stamp	Feb 29 2012	***File Name***	F:\MERCURY03-2-2012\LP-6-72-C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	500	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10552.4619	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



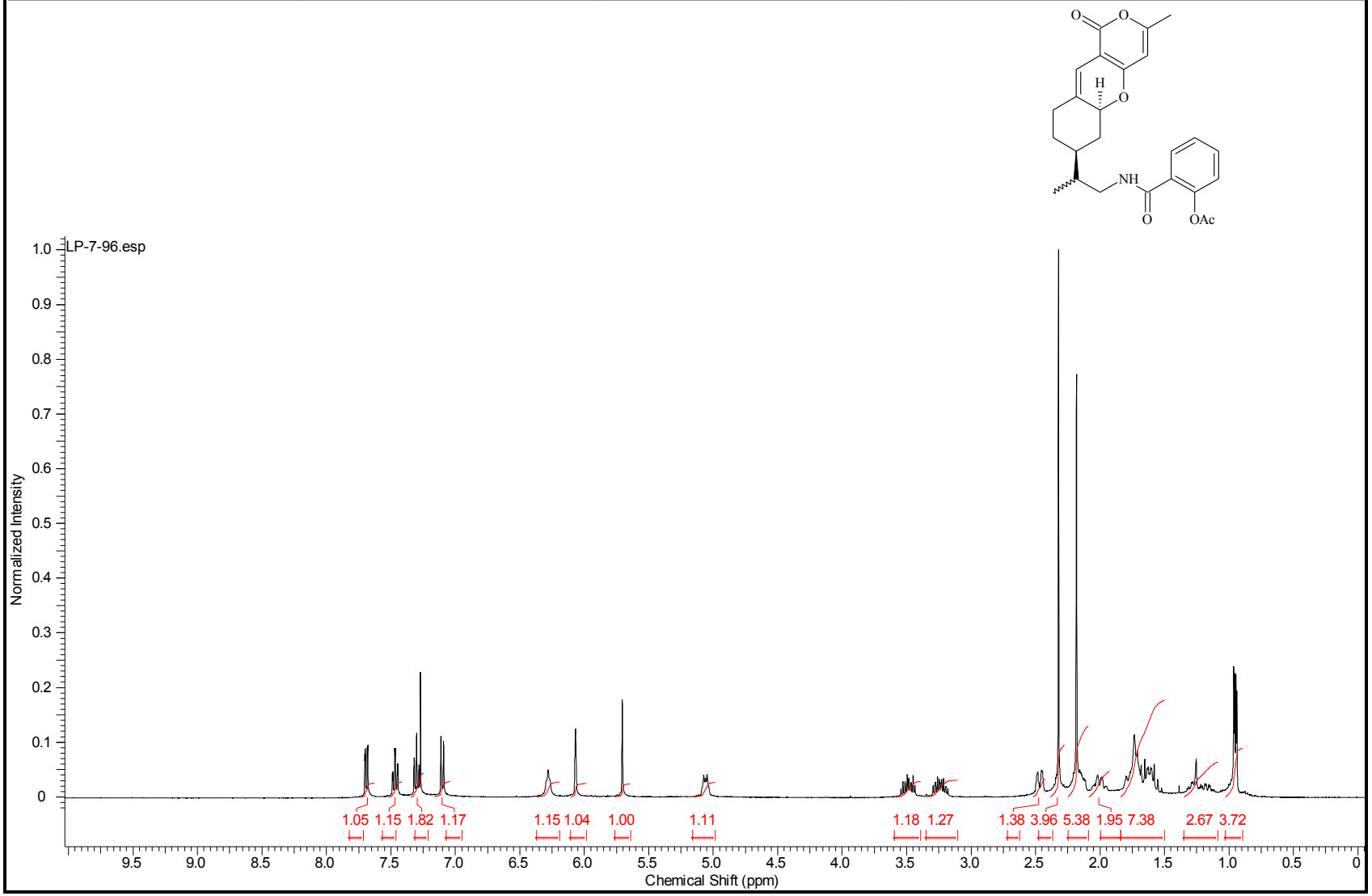
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Aug 16 2012
Date Stamp	Aug 16 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\LP-7-95.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	100	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	36.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2404.3528	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



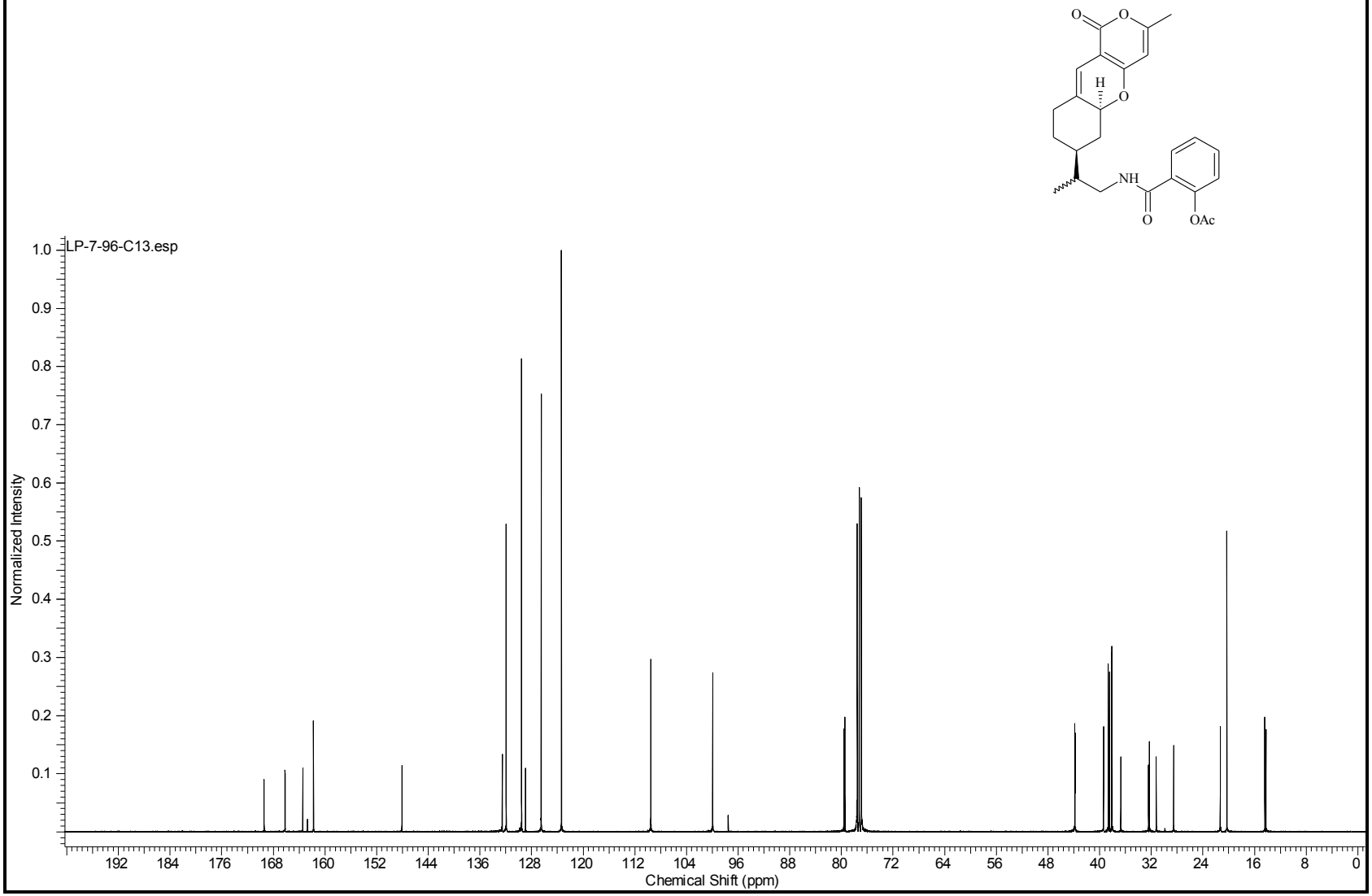
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Aug 15 2012
Date Stamp	Aug 15 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\LP-7-95-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	2000	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10556.1475	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



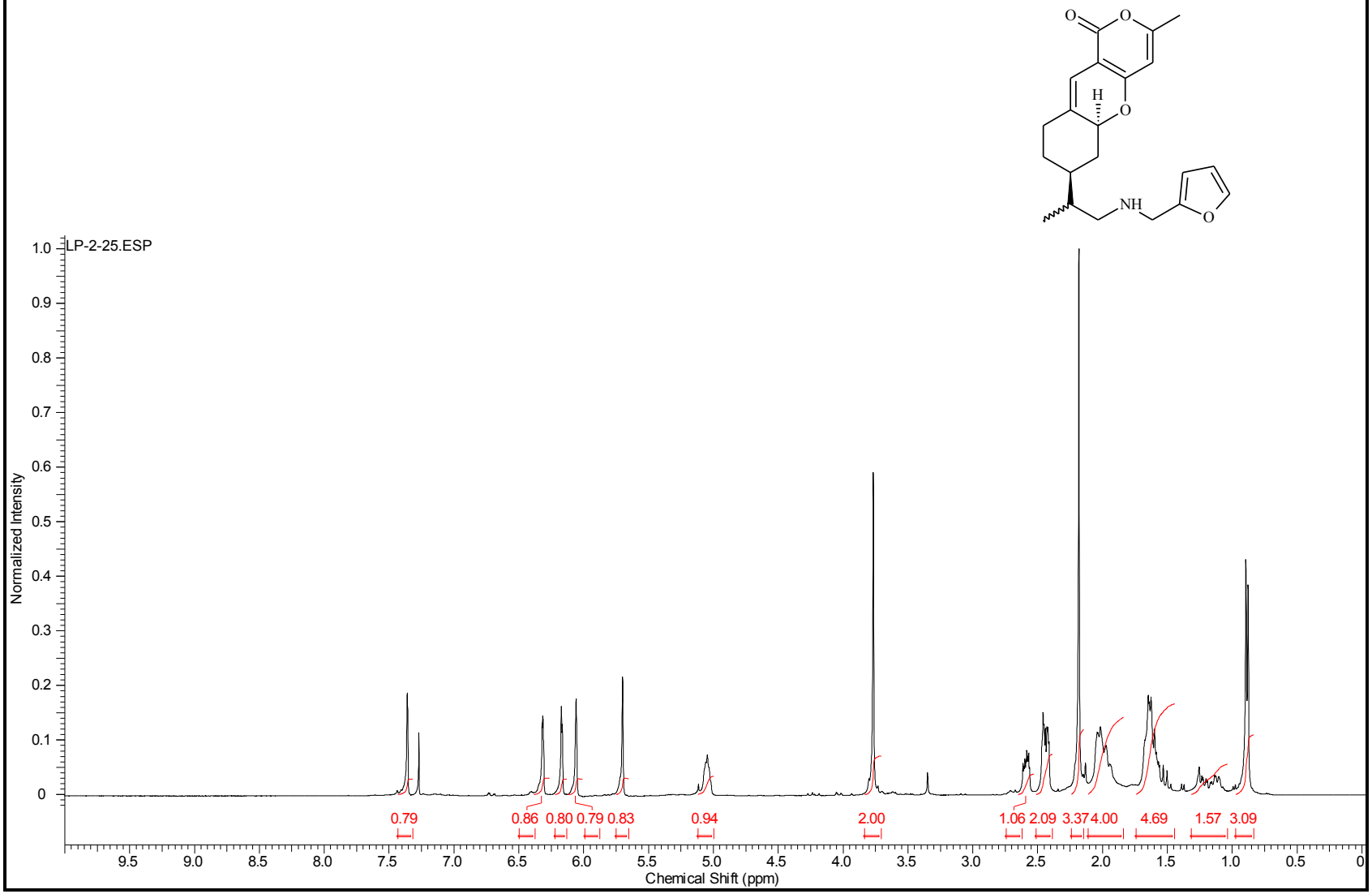
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Aug 15 2012
Date Stamp	Aug 15 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\LP-7-96.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	40	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	26.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2404.3528	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



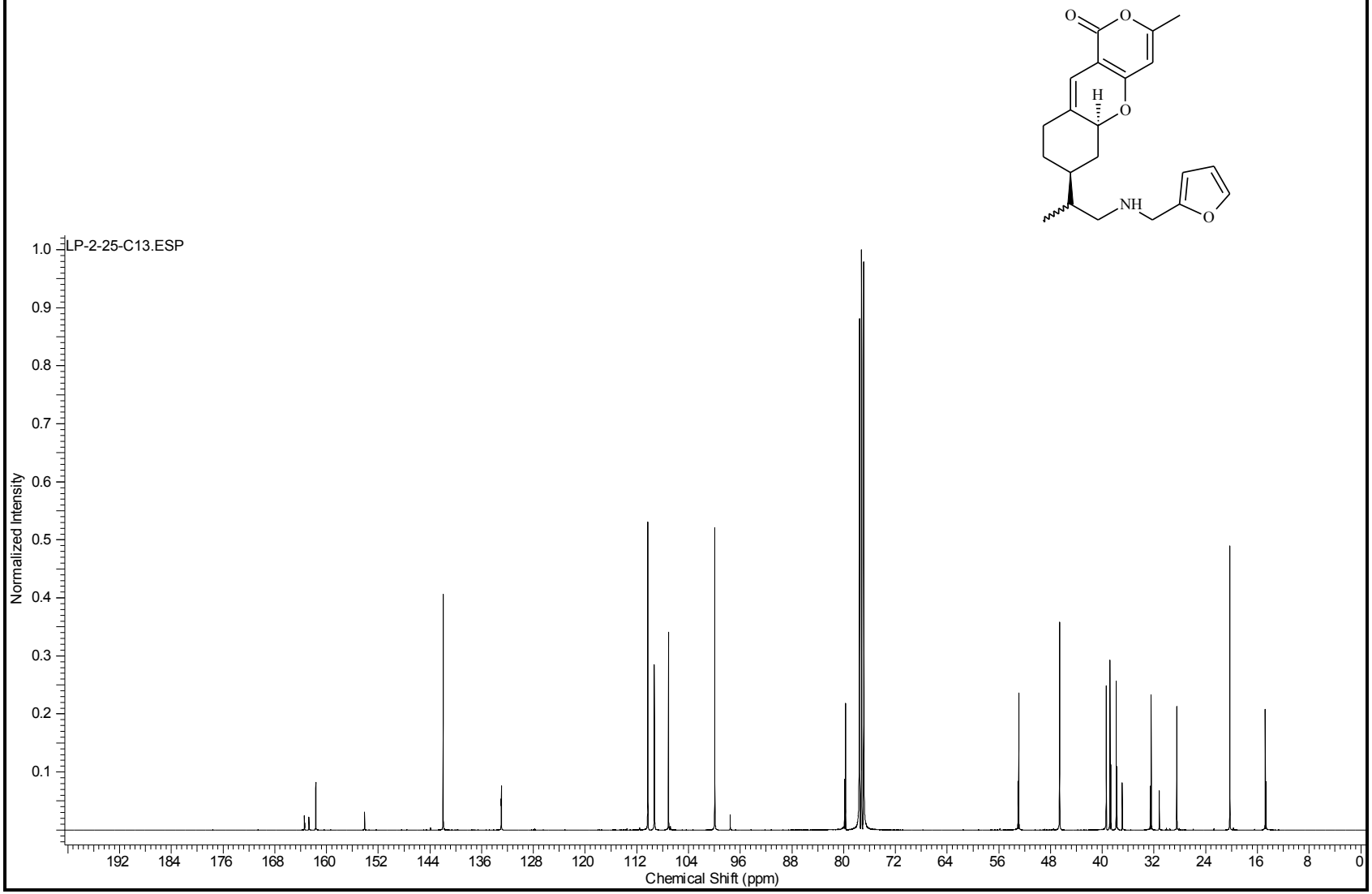
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Aug 15 2012
Date Stamp	Aug 15 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\LP-7-96-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	14984	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10557.6221	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



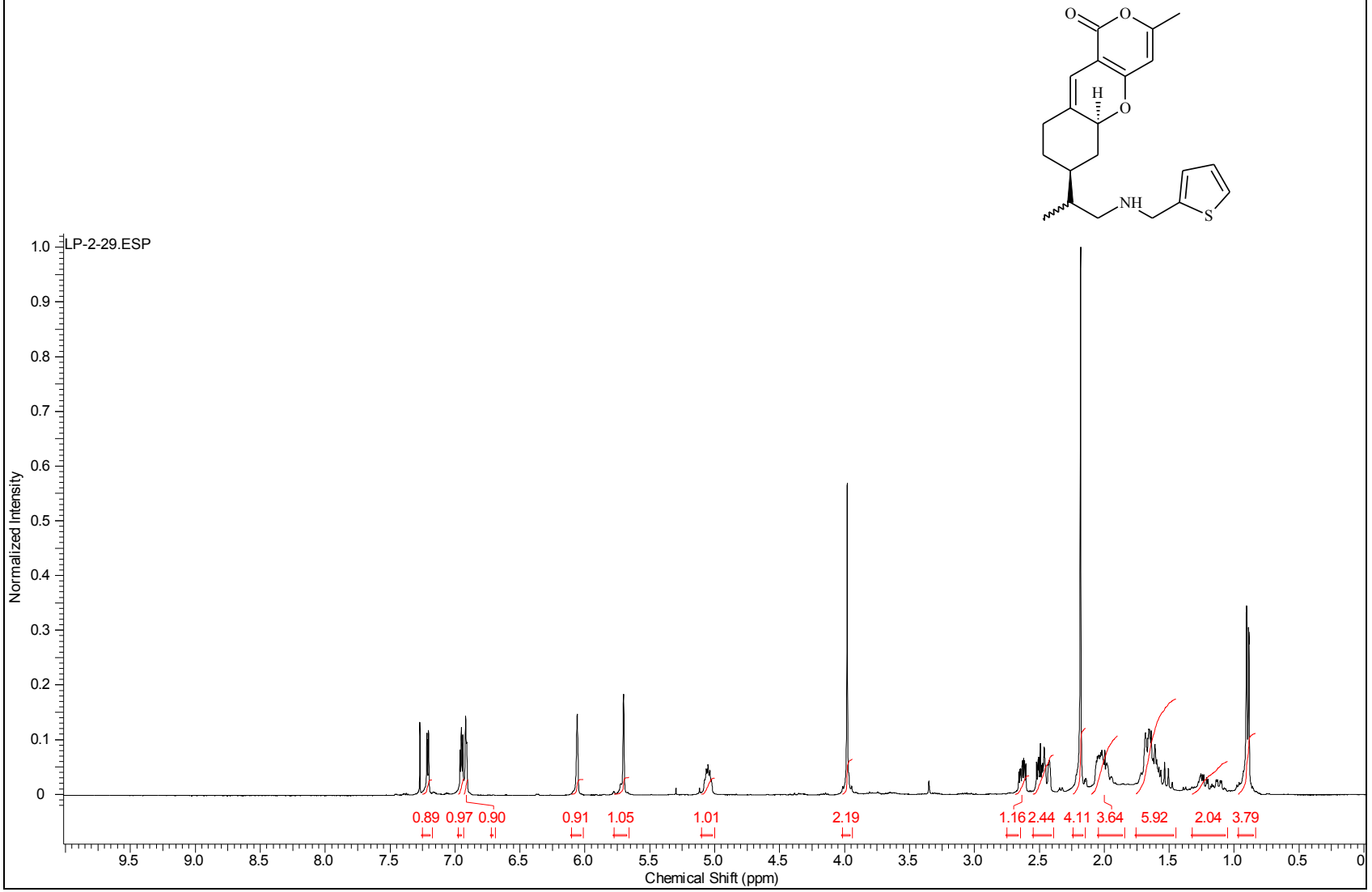
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Jul 11 2011
Date Stamp	Jul 11 2011	***File Name***	F:\LAXMAN POKHREL\LAXMAN-MERCURY-07-15-2011\LP-2-25.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	44	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	26.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2403.7539	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



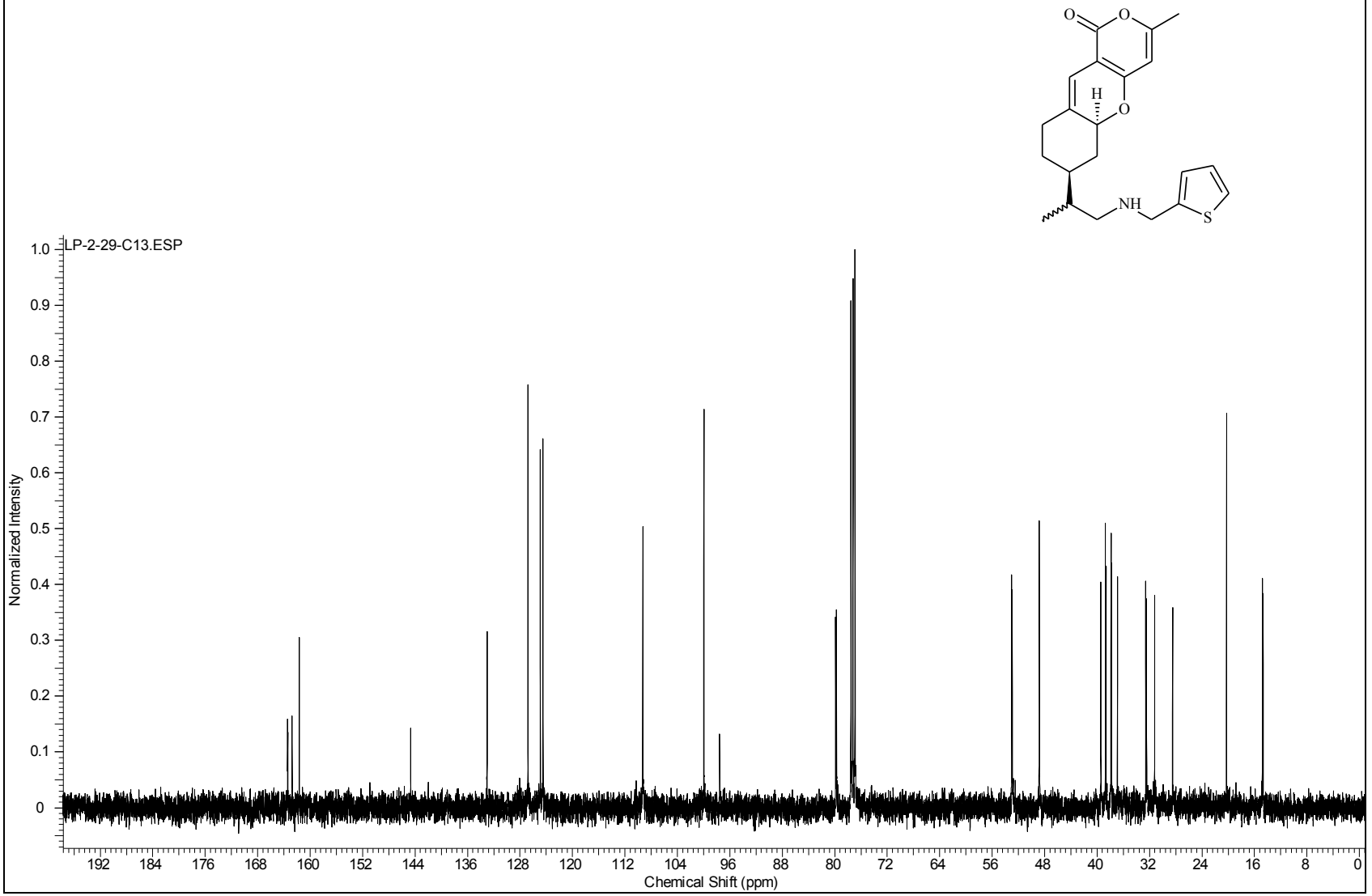
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jul 11 2011
Date Stamp	Jul 11 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKH\.TRASH-LAXMAN\LP-2-25-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	16224	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10556.3525	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



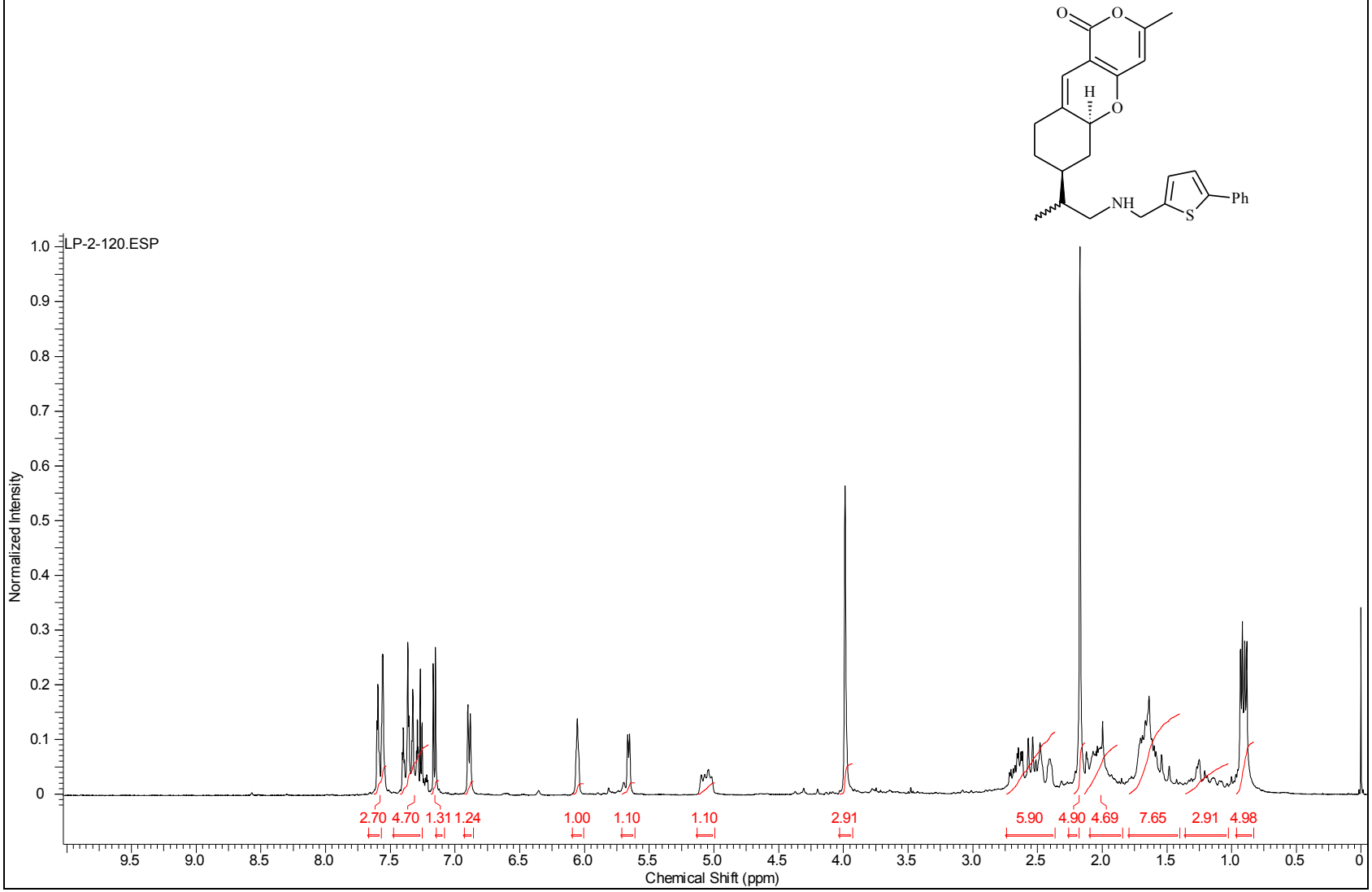
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Jul 7 2011
Date Stamp	Jul 7 2011	***File Name***	F:\LAXMAN POKHREL\LAXMAN-MERCURY-07-15-2011\LP-2-29-2.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	24	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2403.9622	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



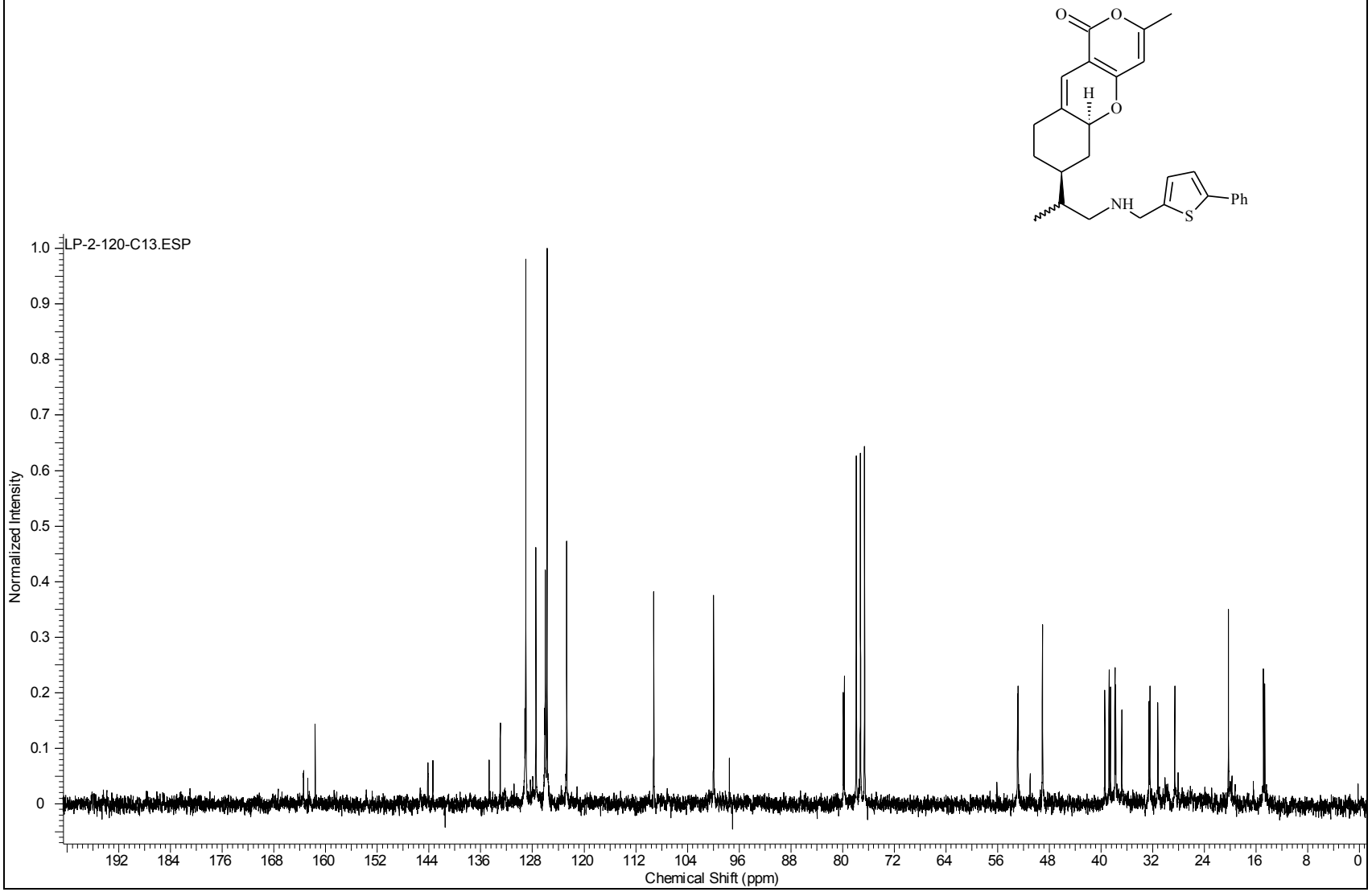
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jul 7 2011
Date Stamp	Jul 7 2011	***File Name***	F:\LAXMAN POKHREL\LAXMAN-MERCURY-07-15-2011\LP-2-29-2-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	824	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10556.1475	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



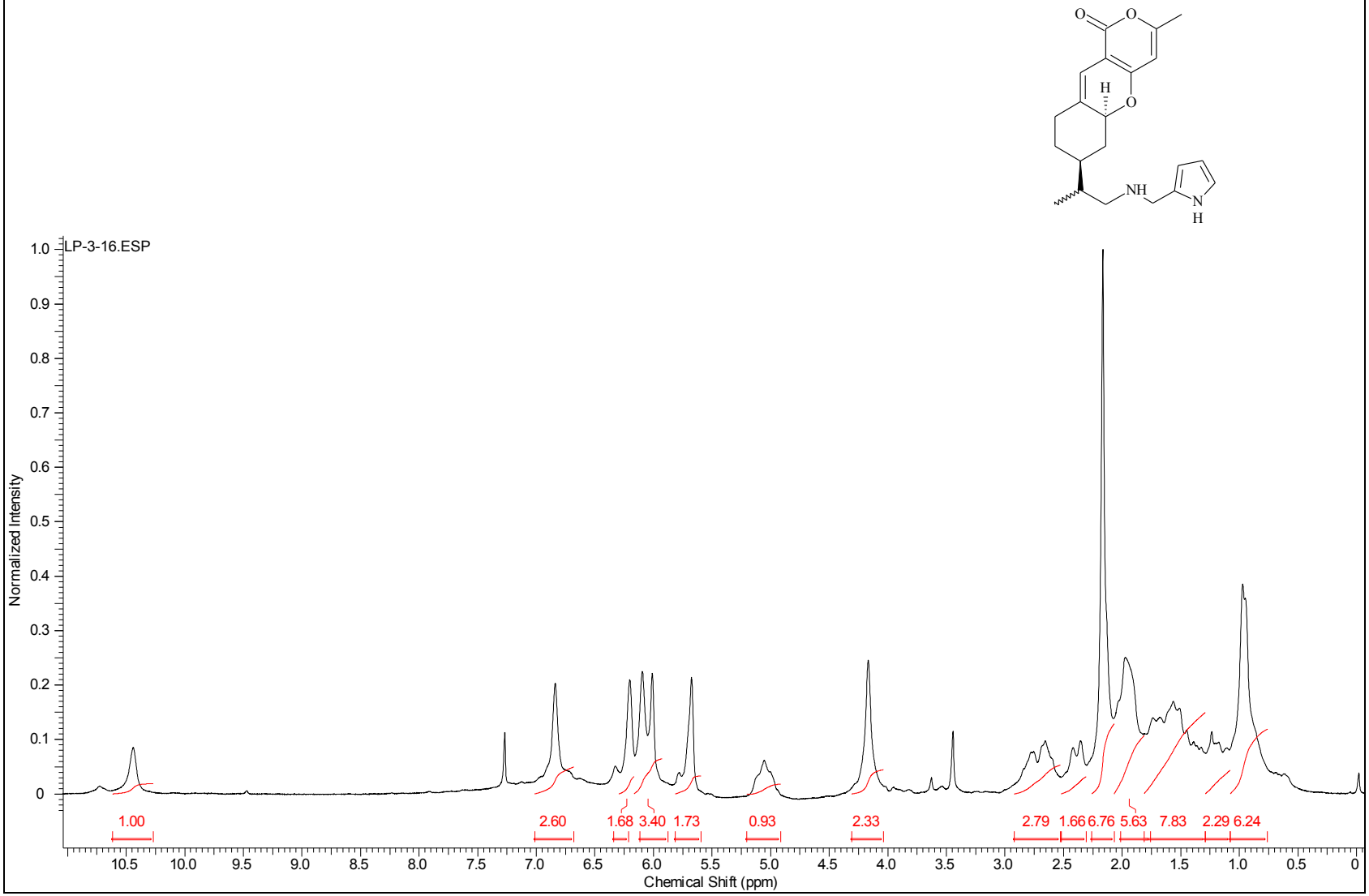
Acquisition Time (sec)	1.9945	***Comment***	STANDARD 1H OBSERVE□lp-2-120fr22-24			***Date***	Oct 4 2009
Date Stamp	Oct 4 2009	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\200MHZ\LP-2-120FR22-24.FID\FID				
Frequency (MHz)	199.98	***Nucleus***	1H	***Number of Transients***	48	***Original Points Count***	5984
Points Count	8192	***Pulse Sequence***	s2pul	***Receiver Gain***	22.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	1001.9926	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	3000.30	***Temperature (degree C)***	AMBIENT TEMPERATURE



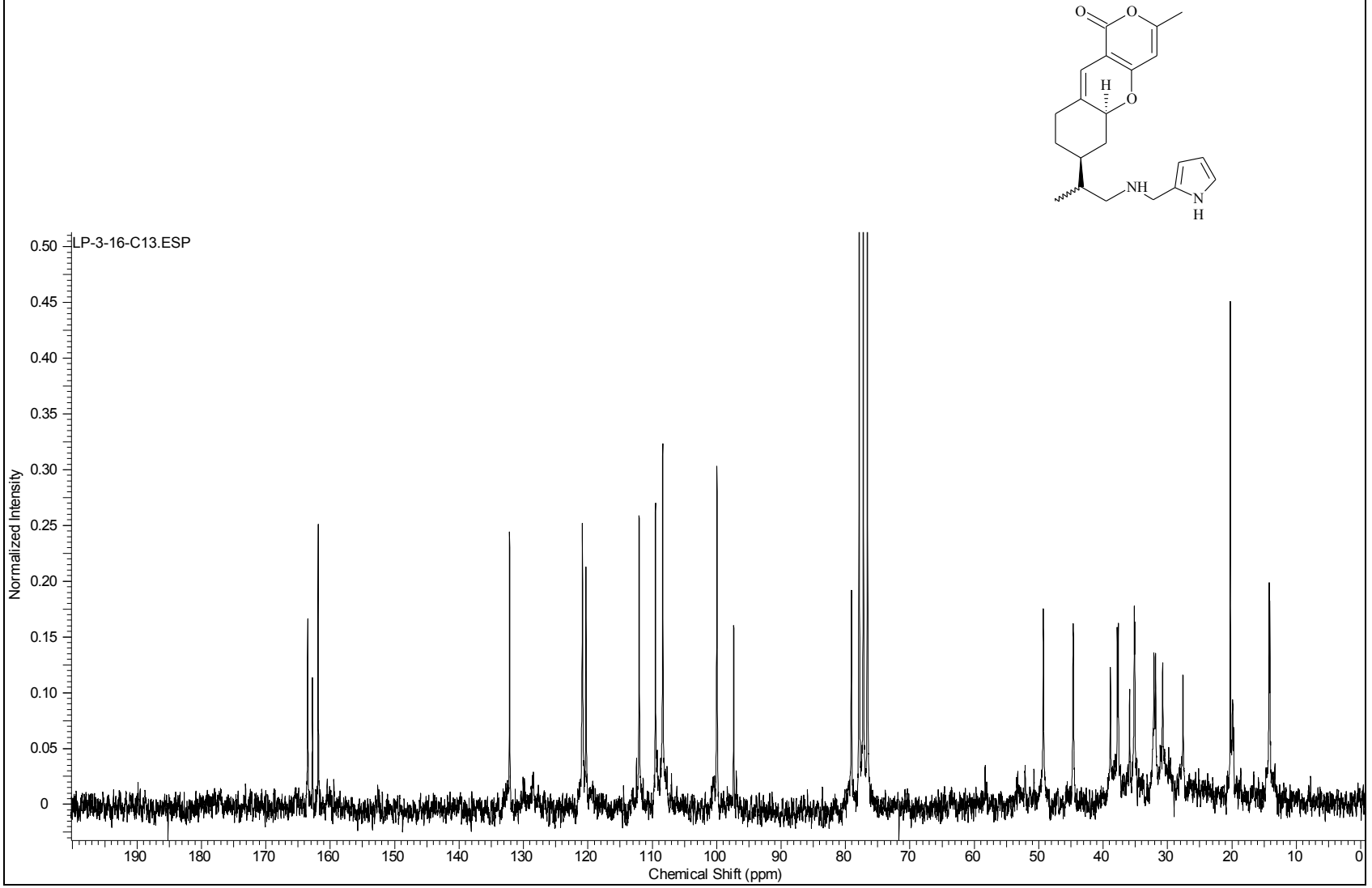
Acquisition Time (sec)	1.4976	***Comment***	13C OBSERVE	***Date***	Oct 7 2009	***Date Stamp***	Oct 7 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\200MHZ\LP-2-120-C13.FID\FID					***Frequency (MHz)***	50.29
Nucleus	13C	***Number of Transients***	4928	***Original Points Count***	18720	***Points Count***	65536
Pulse Sequence	s2pul	***Receiver Gain***	40.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	4879.2056	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	12500.00	***Temperature (degree C)***	AMBIENT TEMPERATURE



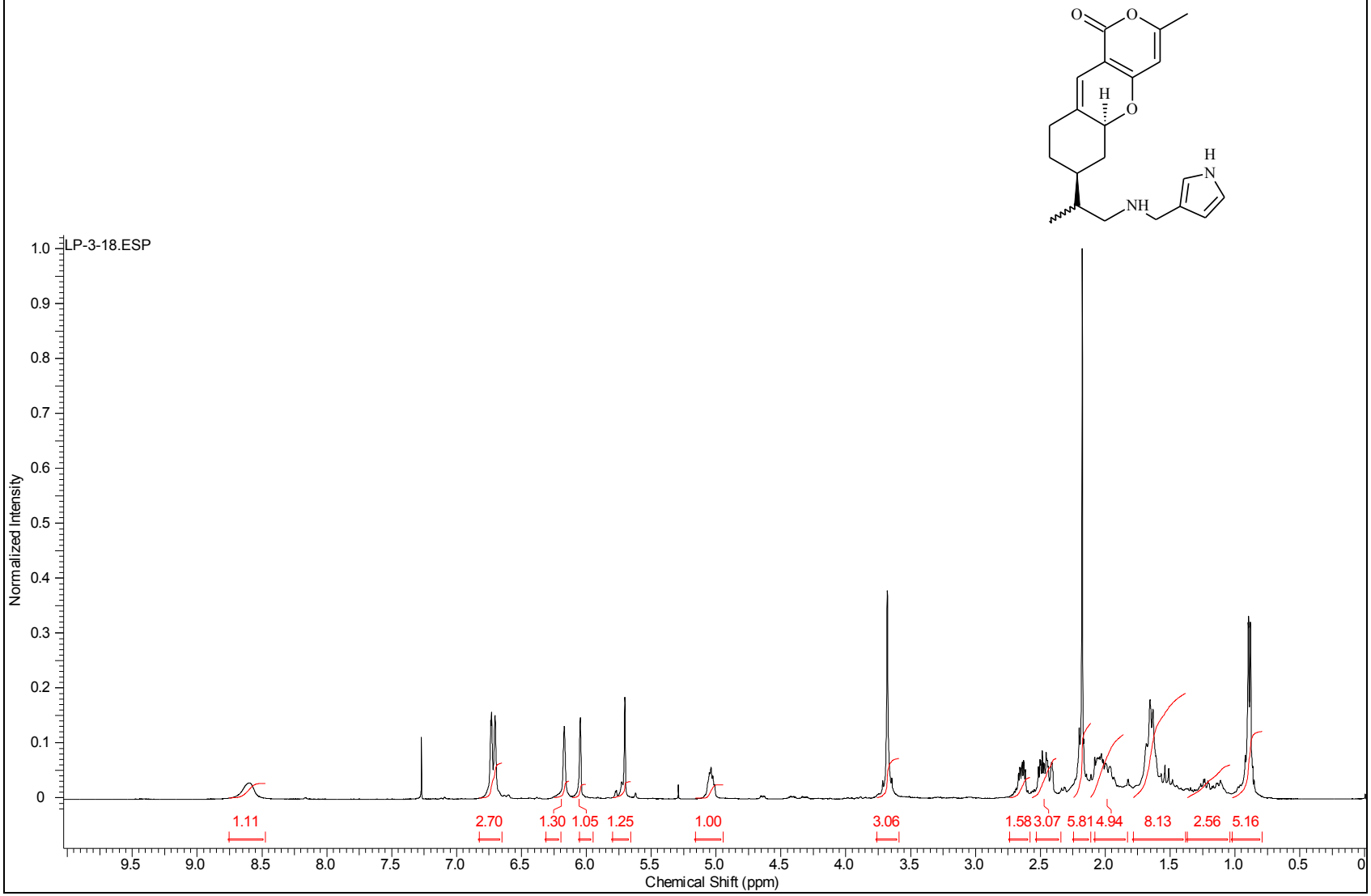
Acquisition Time (sec)	1.9945	***Comment***	STANDARD 1H OBSERVE			***Date***	Oct 21 2009
Date Stamp	Oct 21 2009	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\200MHZ\LP-3-16PURE.FID\FID				
Frequency (MHz)	199.98	***Nucleus***	1H	***Number of Transients***	64	***Original Points Count***	5984
Points Count	8192	***Pulse Sequence***	s2pul	***Receiver Gain***	18.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	1003.4878	***Sweep Width (Hz)***	3000.30	***Temperature (degree C)***	AMBIENT TEMPERATURE		



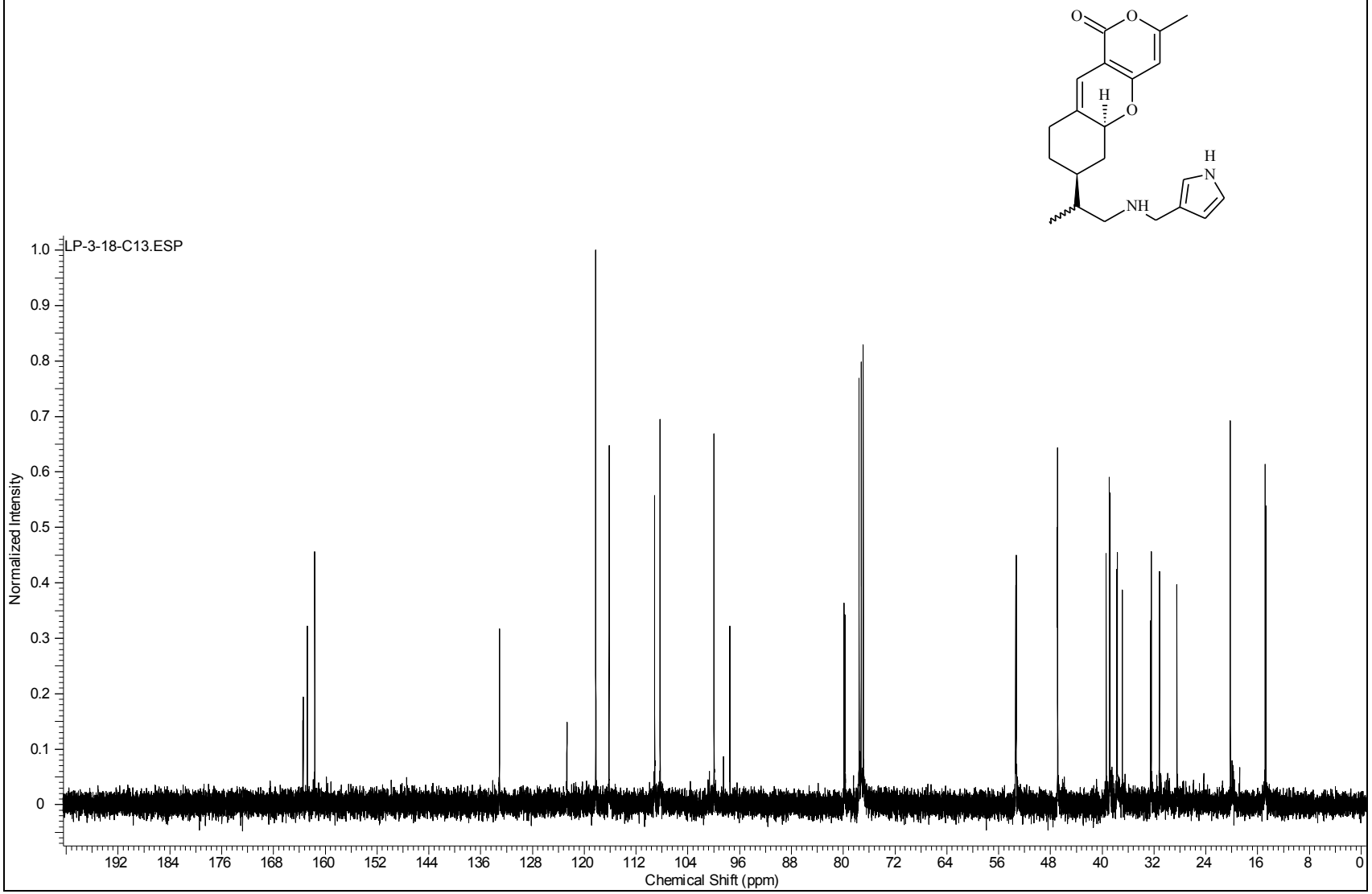
Acquisition Time (sec)	1.4976	***Comment***	13C OBSERVE lp-3-16pure-c13			***Date***	Oct 21 2009
Date Stamp	Oct 21 2009	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\200MHZ\LP-3-16-C13.FID\FID				
Frequency (MHz)	50.29	***Nucleus***	13C	***Number of Transients***	5024	***Original Points Count***	18720
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	40.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	4877.7900	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	12500.00	***Temperature (degree C)***	AMBIENT TEMPERATURE



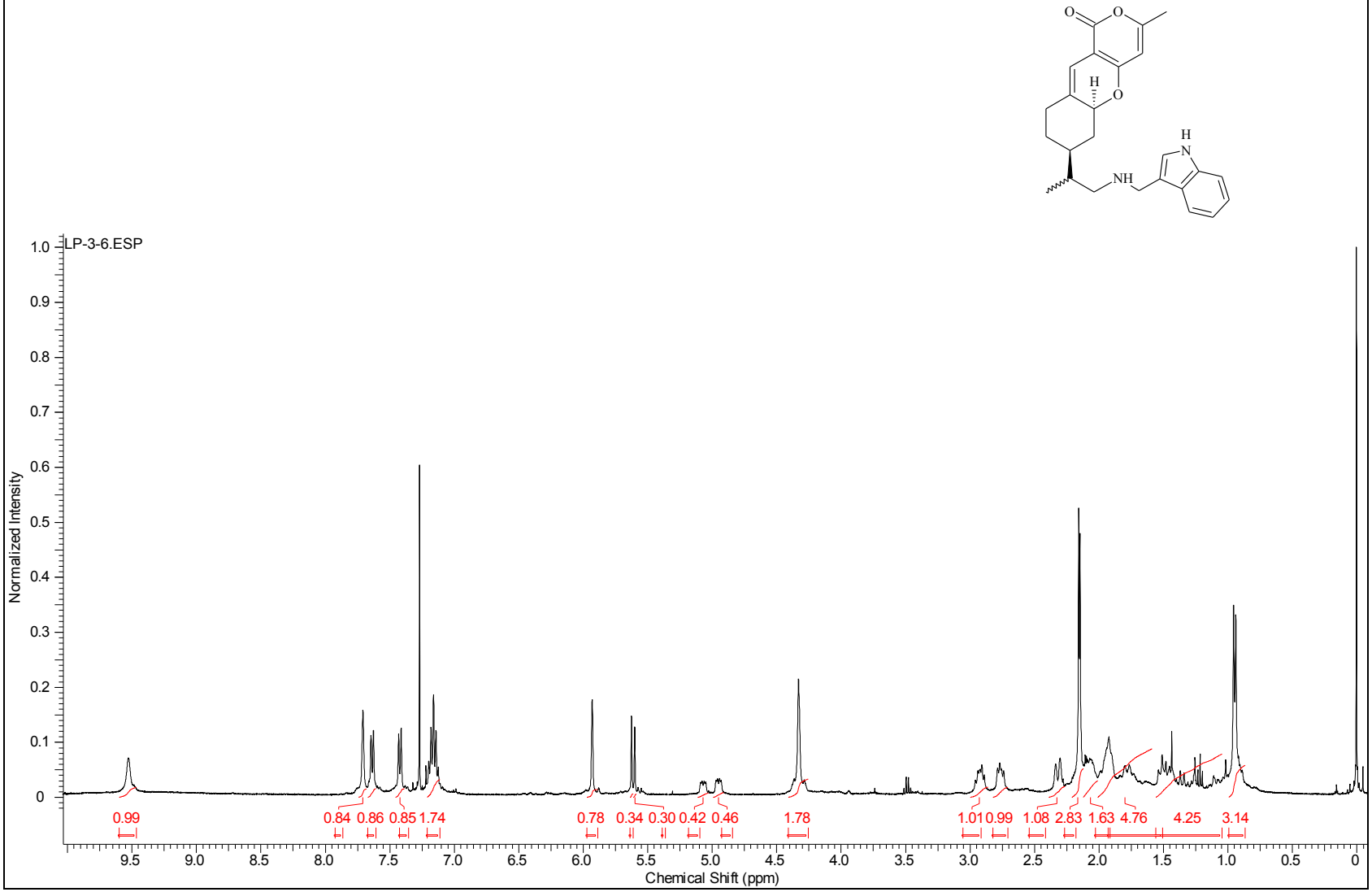
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Jul 21 2011		
Date Stamp	Jul 21 2011			***File Name***	F:\LP-3-18.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	40	***Original Points Count***	12783	***Points Count***	16384	***Pulse Sequence***	s2pul
Receiver Gain	22.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	2404.3528	***Spectrum Type***	STANDARD
Sweep Width (Hz)	6397.95	***Temperature (degree C)***	25.000						



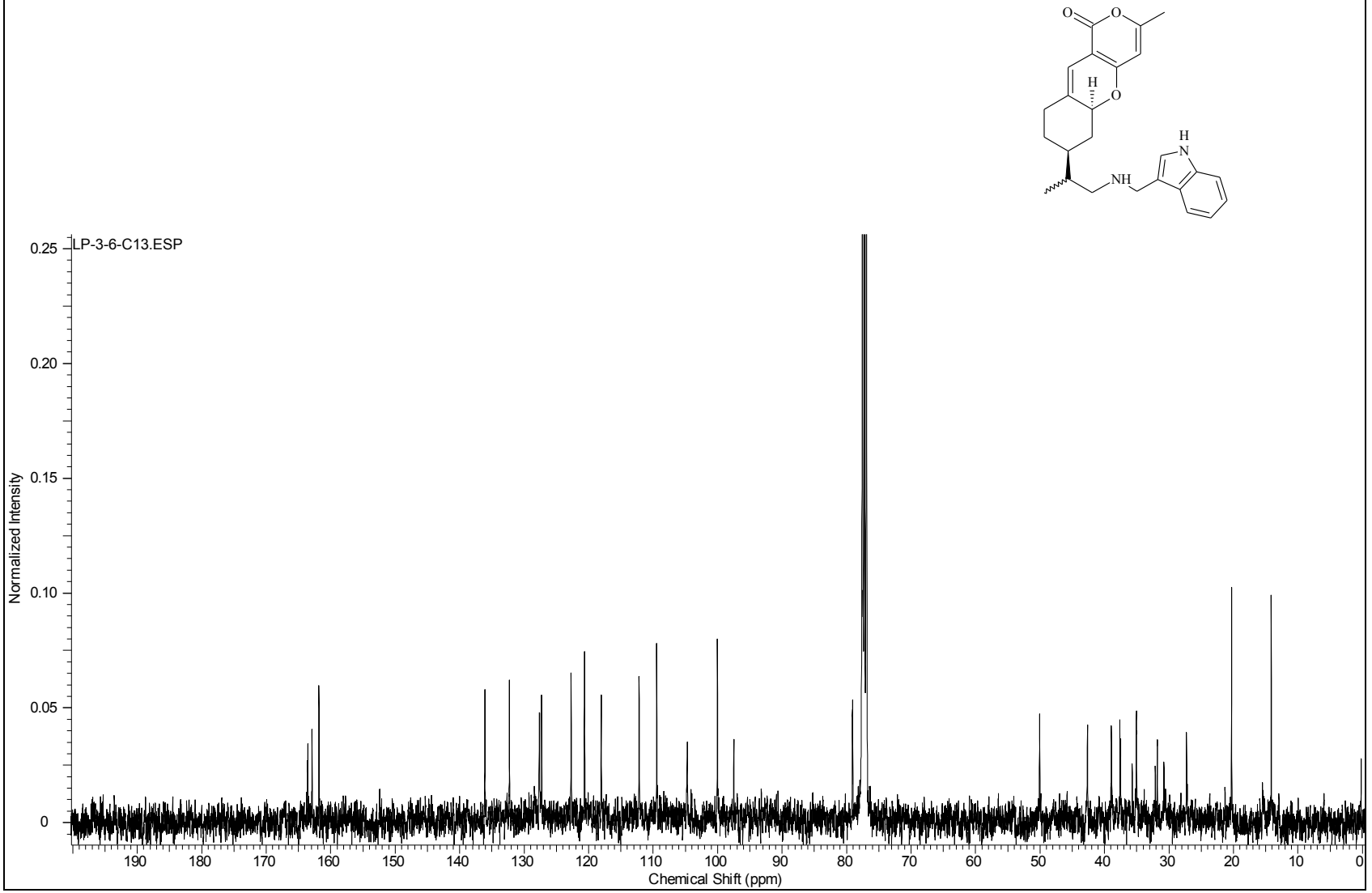
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jul 21 2011	***Date Stamp***	Jul 21 2011
File Name	F:\LP-3-18-C13.FID\FID			***Frequency (MHz)***	100.58	***Nucleus***	13C	***Number of Transients***	2800
Original Points Count	31413	***Points Count***	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00		
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	10552.4619	***Spectrum Type***	STANDARD		
Sweep Width (Hz)	24154.59	***Temperature (degree C)***	25.000						



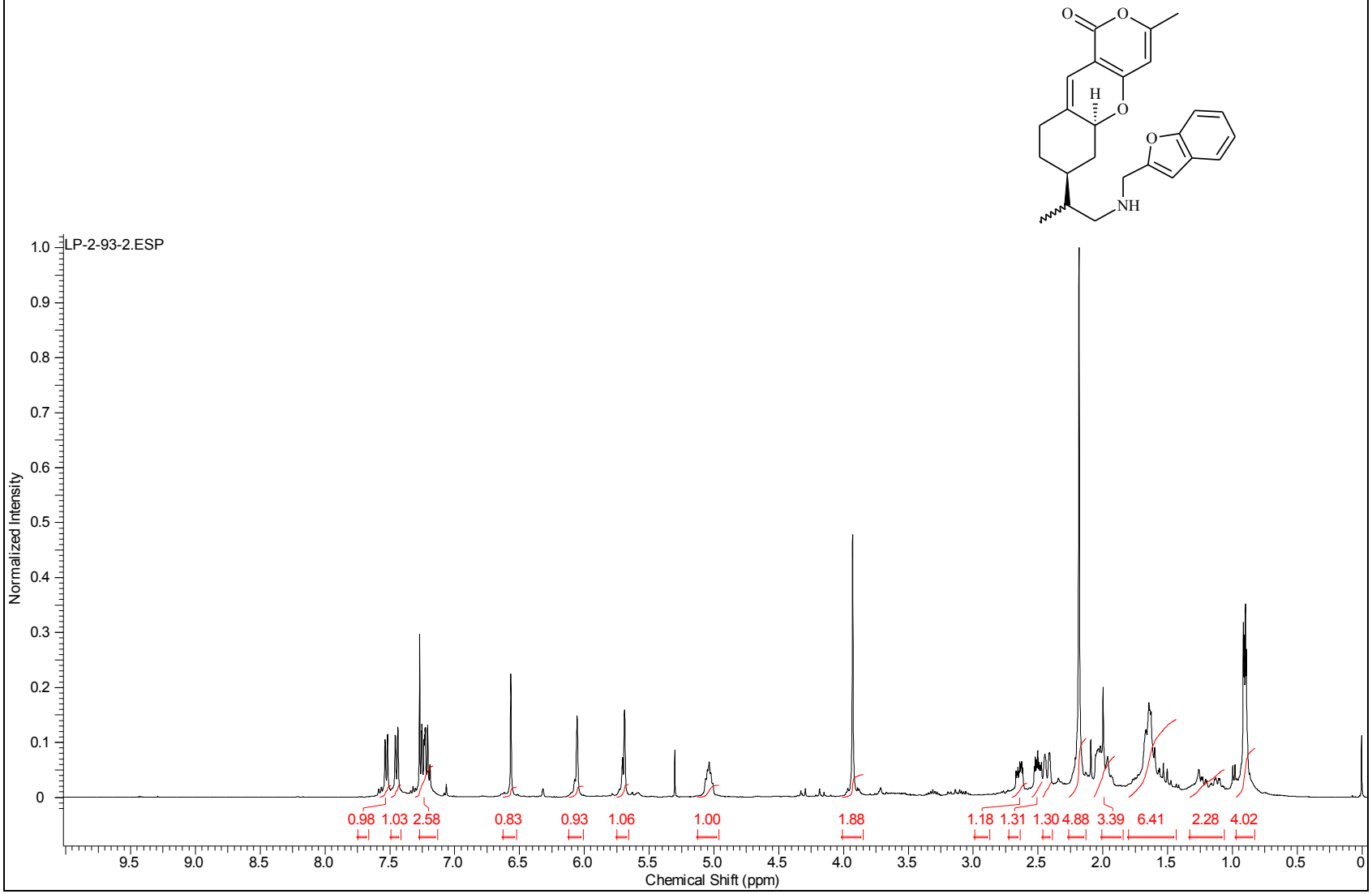
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Oct 12 2009	***Date Stamp***	Oct 12 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKH\LAXMAN POKHREL\400 MHZ\LP-3-06PURE.FID\FID					***Frequency (MHz)***	399.75
Nucleus	1H	***Number of Transients***	100	***Original Points Count***	13103	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	54.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2404.1362	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	25.000



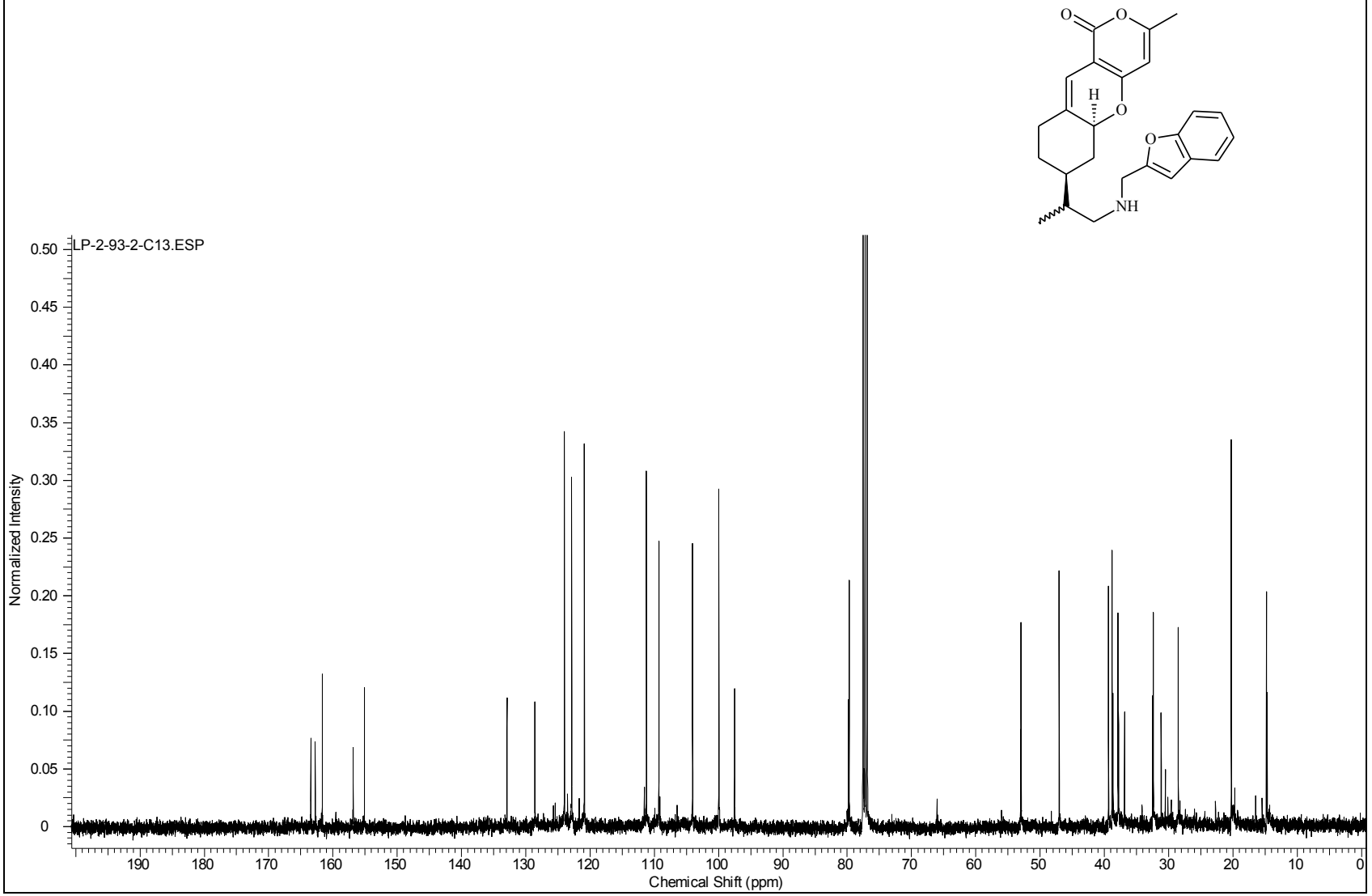
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Oct 12 2009	***Date Stamp***	Oct 12 2009
File Name	C:\USERS\LAXMAN\DESKTOP\NMR\LAXMAN POKHREL\400 MHZ\LP-3-6-C13.FID\FID					***Frequency (MHz)***	100.53
Nucleus	13C	***Number of Transients***	3032	***Original Points Count***	31375	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10551.5918	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	25.000

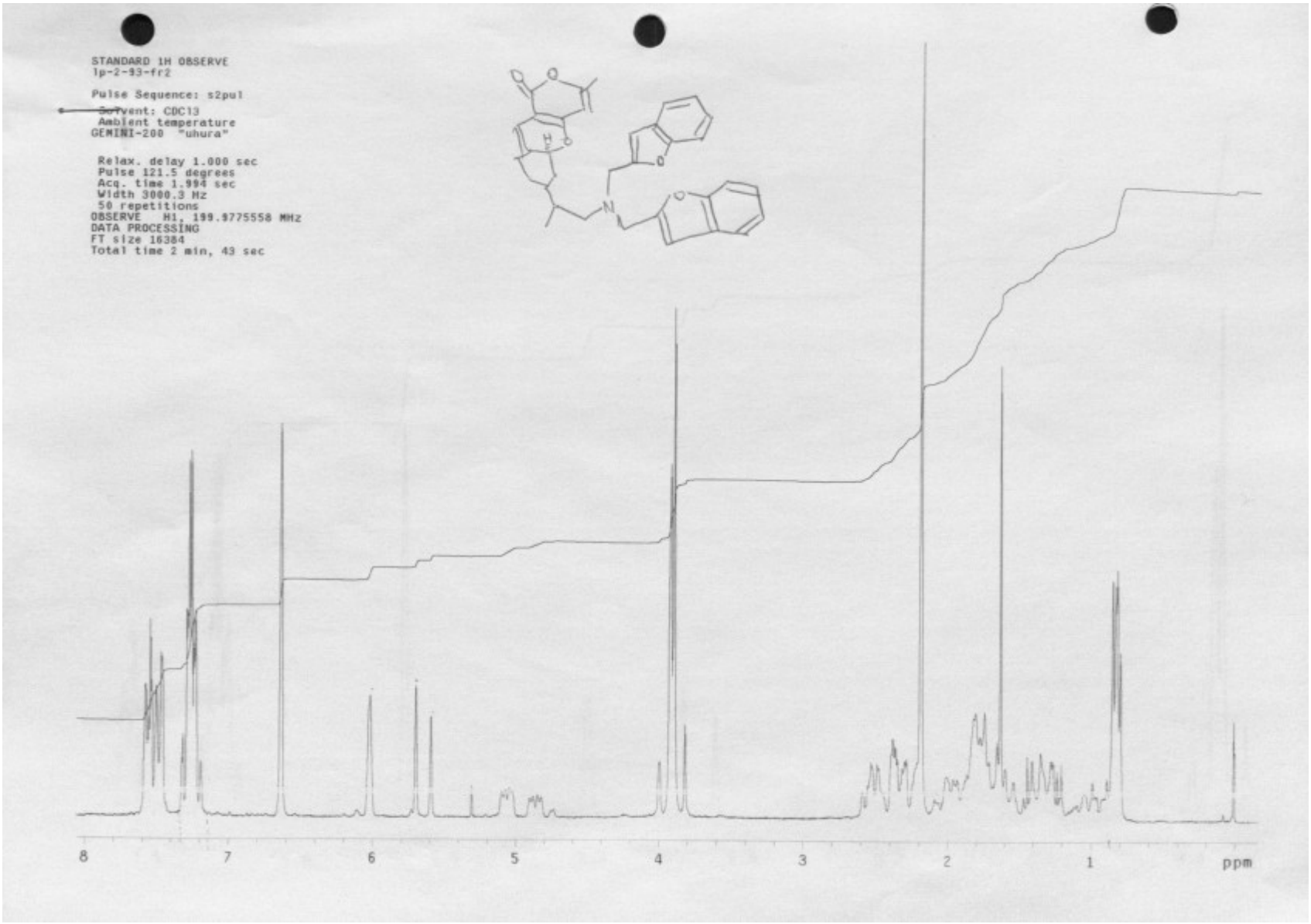


Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Aug 11 2009	***Date Stamp***	Aug 11 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\400 MHZ\LP-2-93-FR41.FID\FID					***Frequency (MHz)***	399.75
Nucleus	1H	***Number of Transients***	50	***Original Points Count***	13103	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	36.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2403.9280	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	25.000

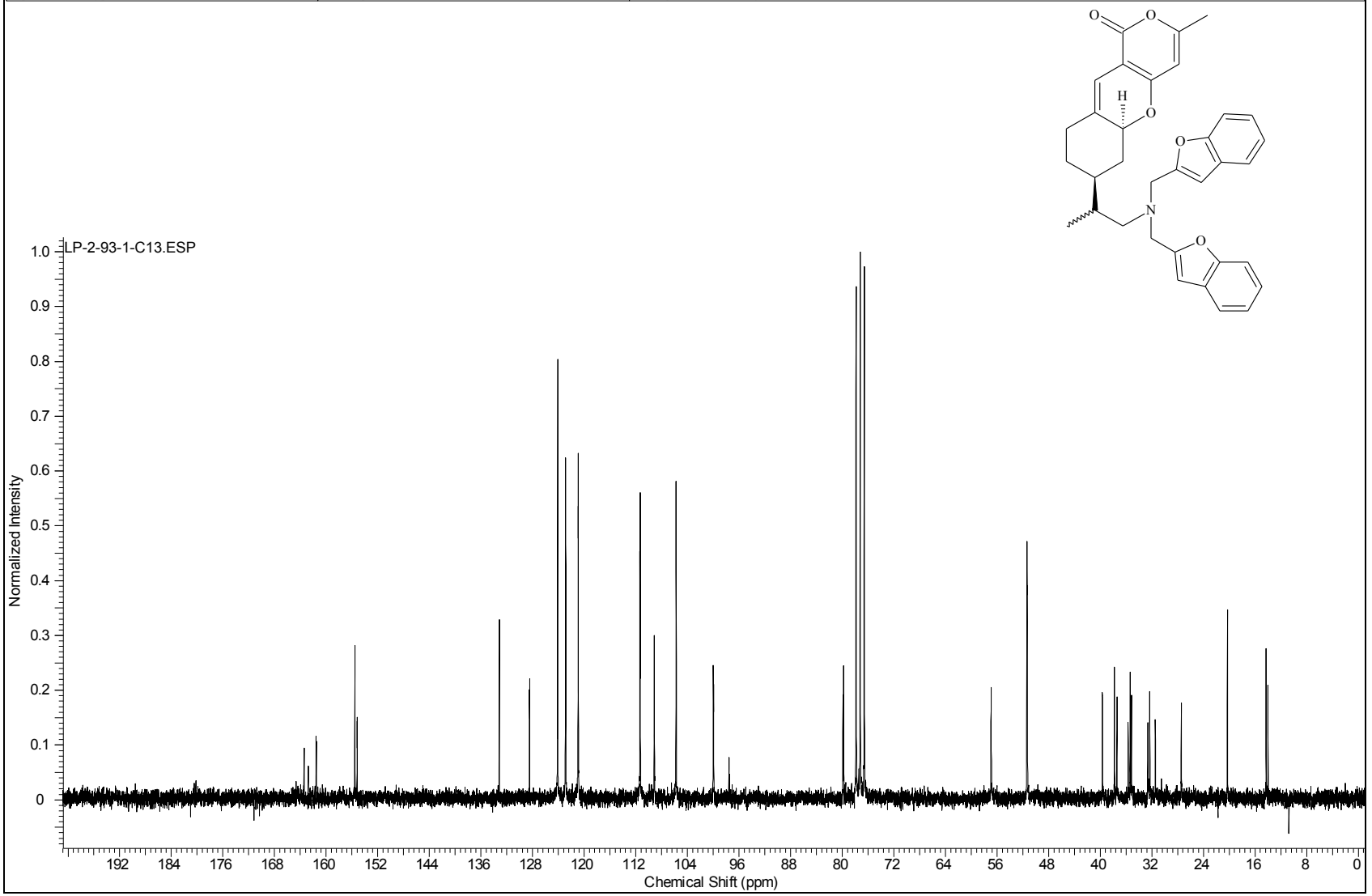


Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Aug 11 2009	***Date Stamp***	Aug 11 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\400 MHZ\LP-2-93-FR40-C13.FID\FID					***Frequency (MHz)***	100.53
Nucleus	13C	***Number of Transients***	21284	***Original Points Count***	31375	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10550.8555	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	25.000

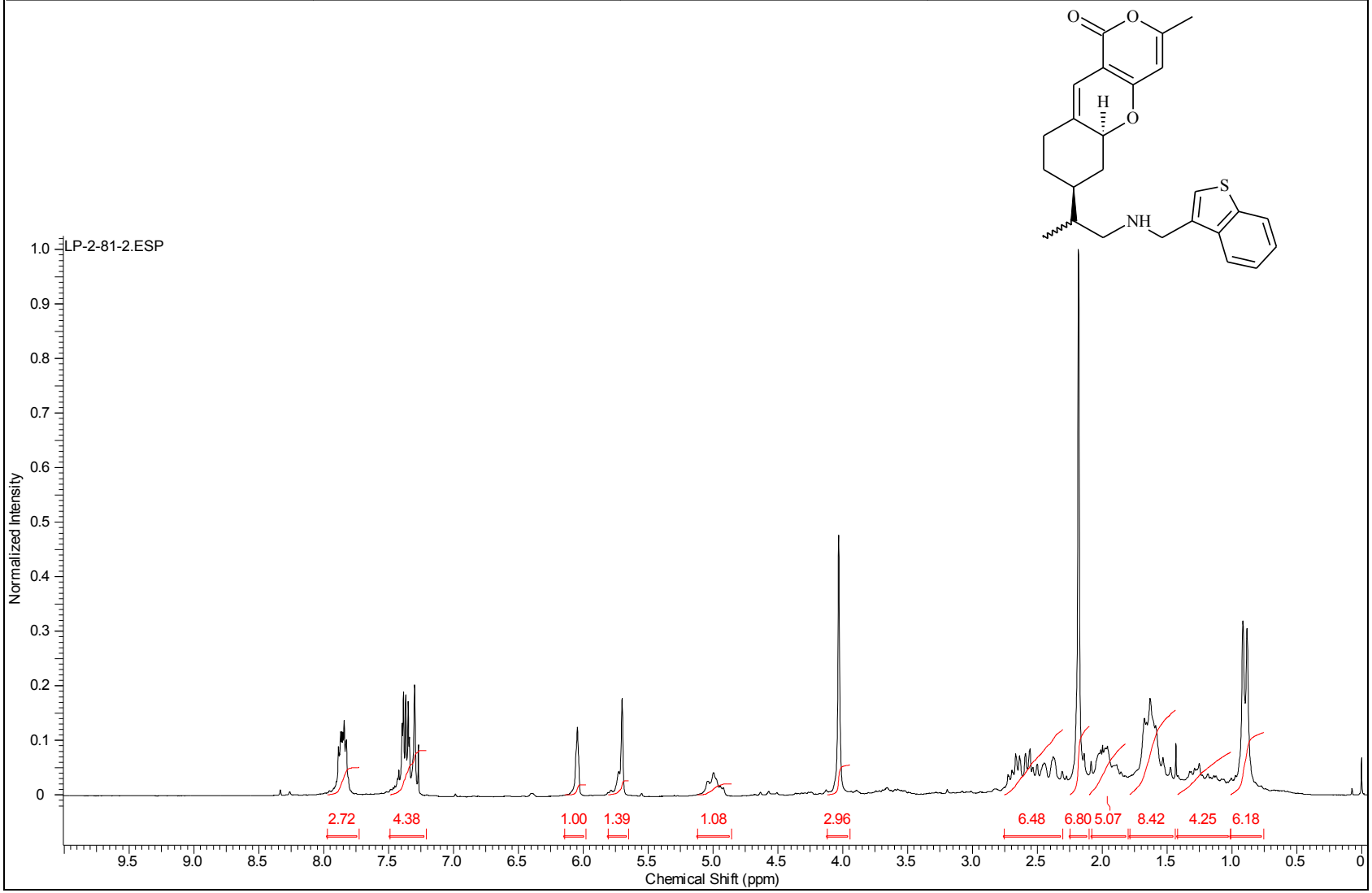



STANDARD 1H OBSERVE
lp-2-93-fr2
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-200 "uhura"
Relax. delay 1.000 sec
Pulse 121.5 degrees
Acq. time 1.994 sec
Width 3000.3 Hz
50 repetitions
OBSERVE H1, 199.9775558 MHz
DATA PROCESSING
FT size 16384
Total time 2 min, 43 sec
8
7
6
5
4
3
2
1
ppm

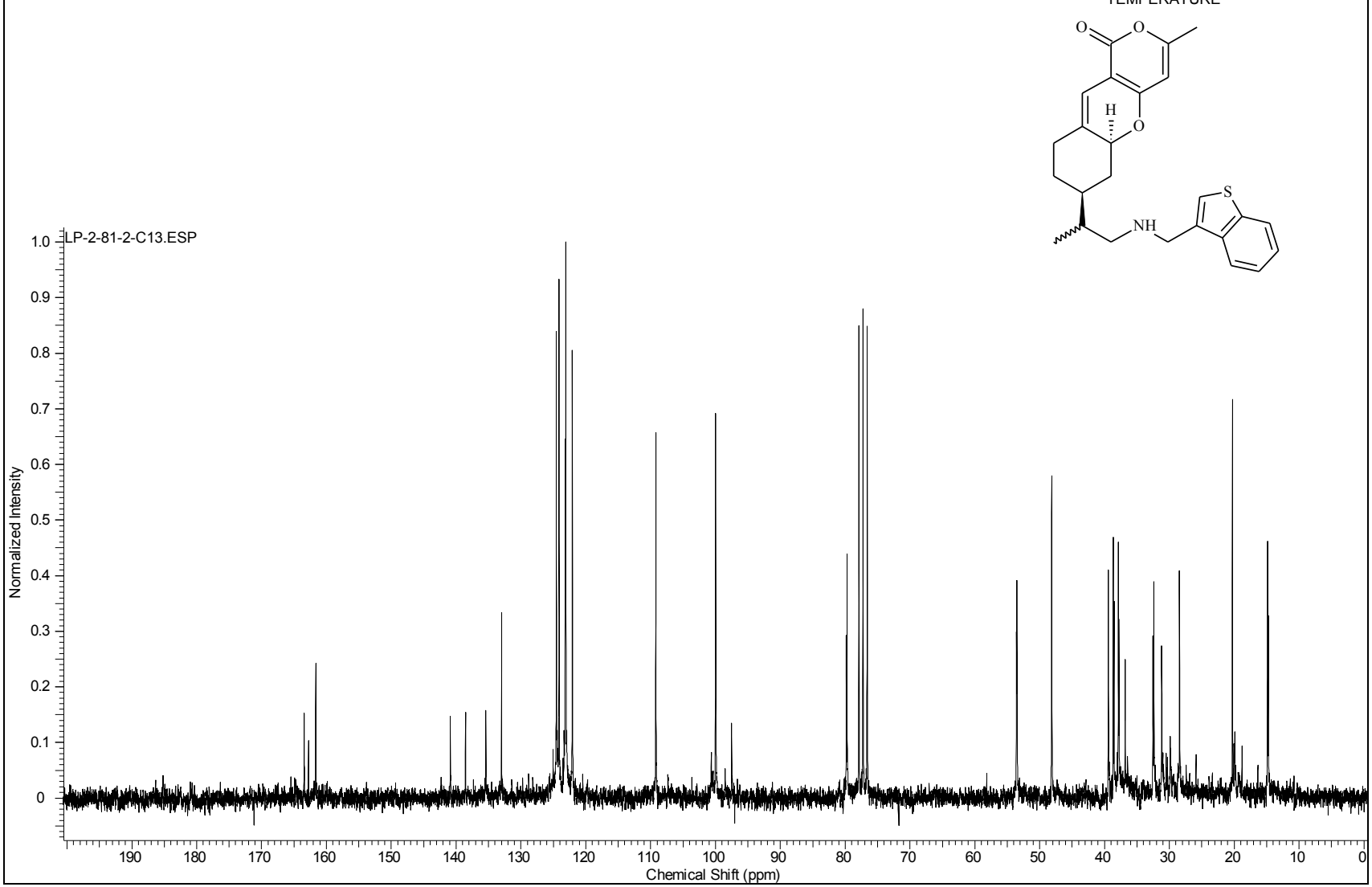
Acquisition Time (sec)	1.4976	***Comment***	lp-2-93-fr2	***Date***	Aug 10 2009	***Date Stamp***	Aug 10 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKH\LAXMAN POKHREL\200MHZ\LP-2-93-FR2.FID\FID					***Frequency (MHz)***	50.29
Nucleus	13C	***Number of Transients***	13080	***Original Points Count***	18720	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	40.00	***Solvent***	CHLOROFORM-d	***Spectrum Offset (Hz)***	4880.4604
Spectrum Type	STANDARD	***Sweep Width (Hz)***	12500.00	***Temperature (degree C)***	AMBIENT TEMPERATURE		



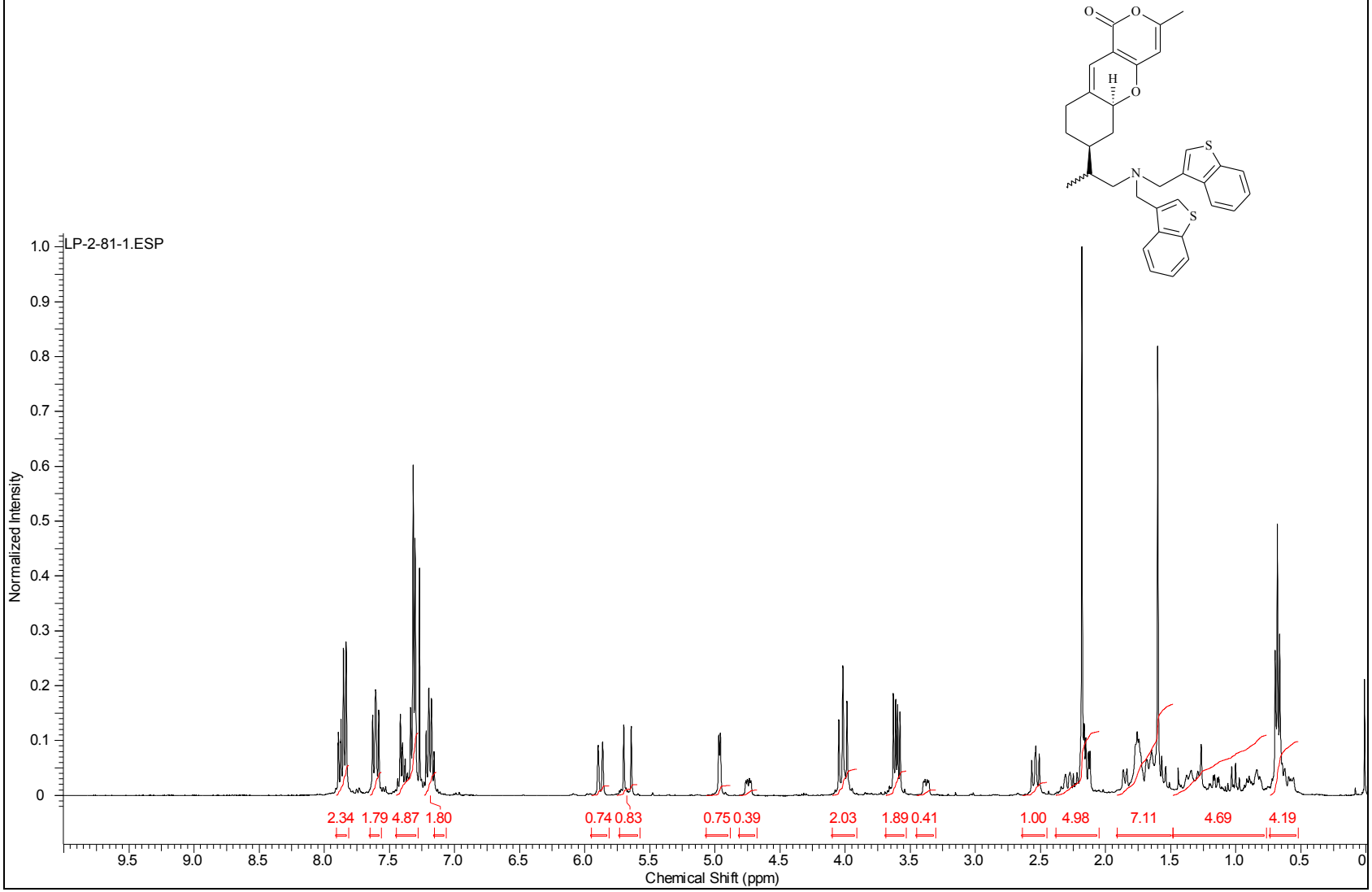
Acquisition Time (sec)	1.9945	***Comment***	STANDARD 1H OBSERVE			***Date***	Jul 27 2009
Date Stamp	Jul 27 2009	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\200MHZ\LP-2-81-2.FID\FID				
Frequency (MHz)	199.98	***Nucleus***	1H	***Number of Transients***	200	***Original Points Count***	5984
Points Count	8192	***Pulse Sequence***	s2pul	***Receiver Gain***	22.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	1003.1215	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	3000.30	***Temperature (degree C)***	AMBIENT TEMPERATURE



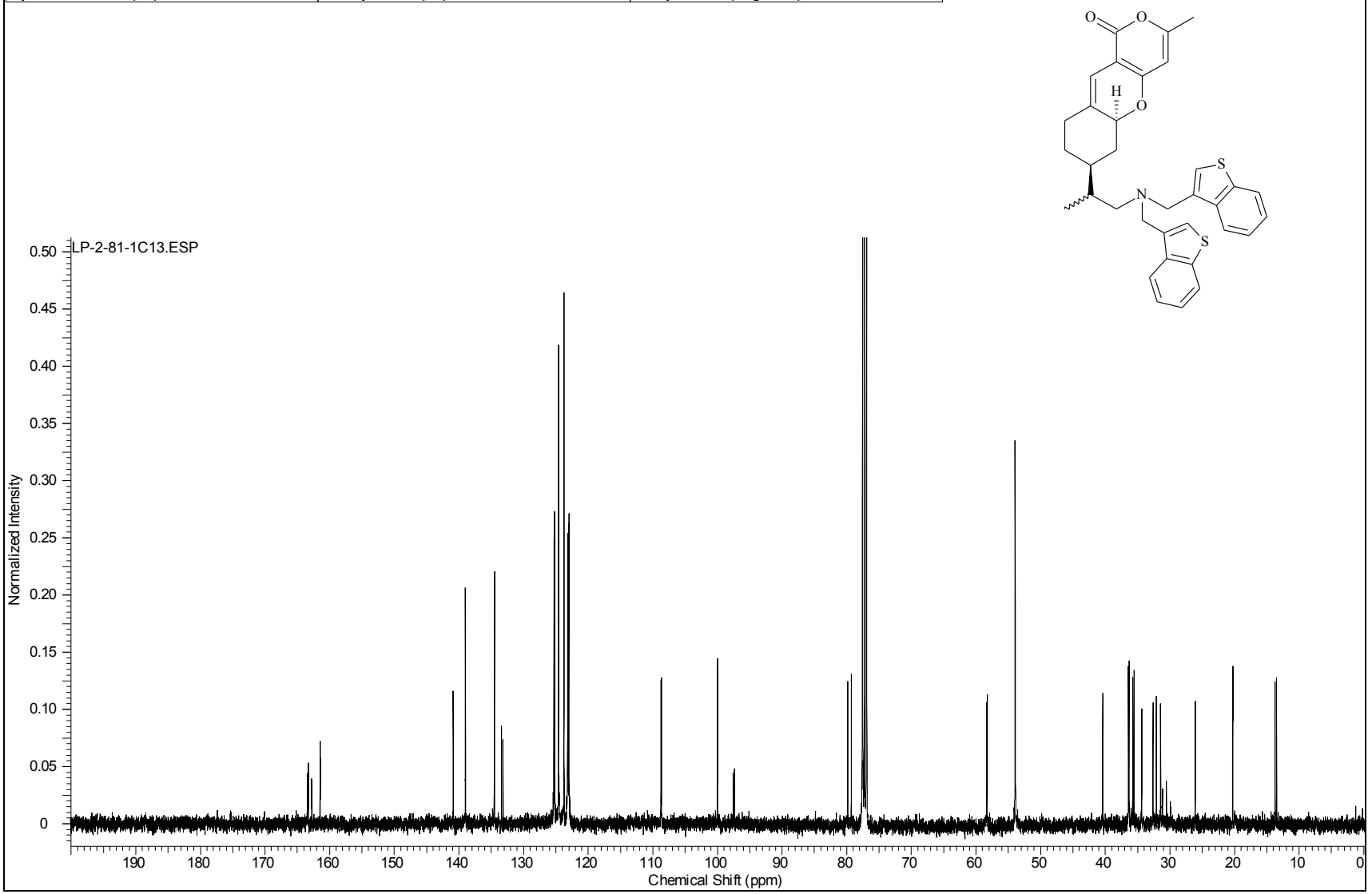
Acquisition Time (sec)	1.4976	***Comment***	13C OBSERVE	***Date***	Jul 27 2009	***Date Stamp***	Jul 27 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\200MHZ\LP-2-81-2-C13-FID\FID					***Frequency (MHz)***	50.29
Nucleus	13C	***Number of Transients***	5720	***Original Points Count***	18720	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	40.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	4878.9351	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	12500.00	***Temperature (degree C)***	AMBIENT TEMPERATURE



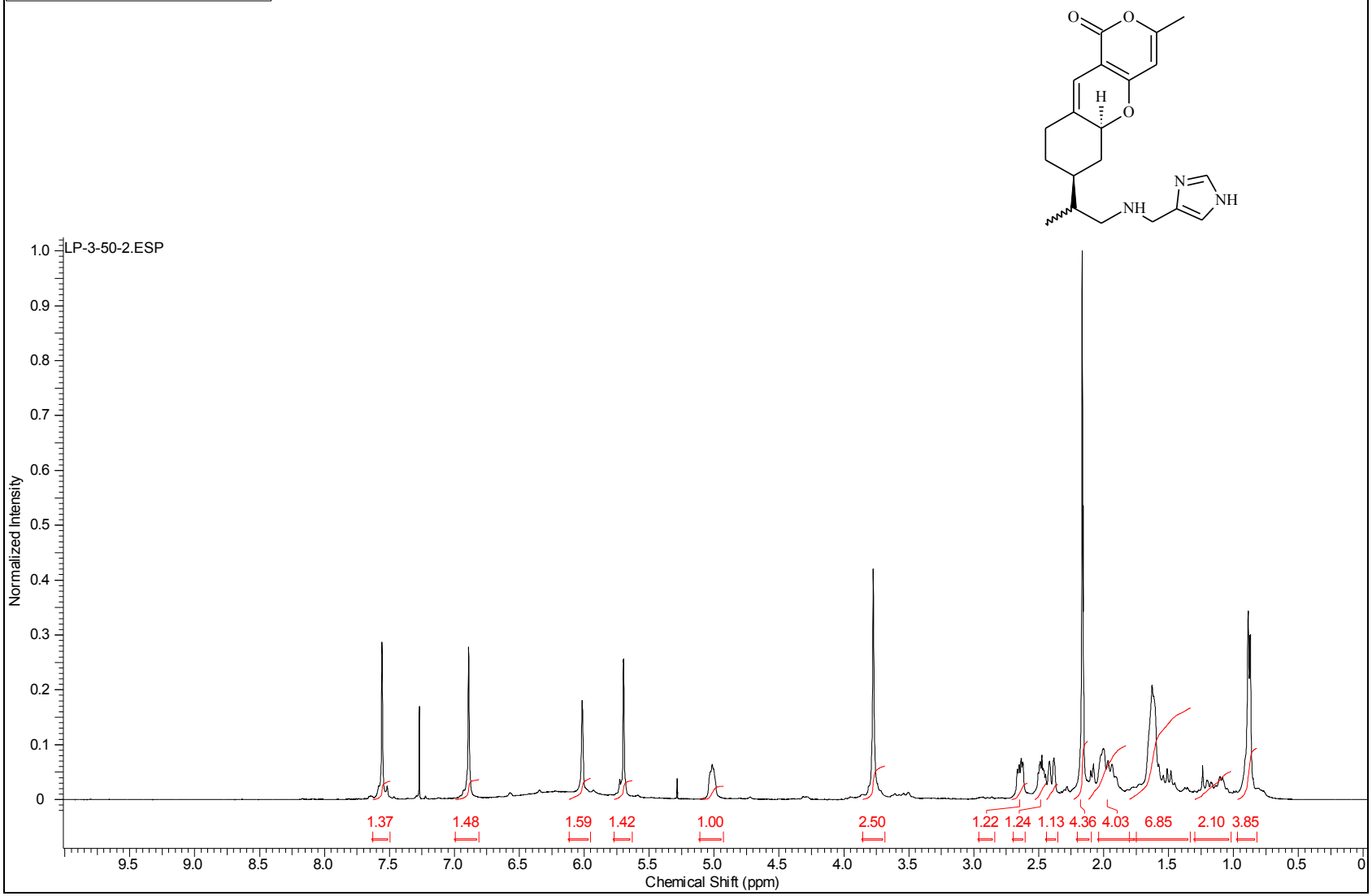
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Jul 29 2009	***Date Stamp***	Jul 29 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-2-81-1.FID\FID						
Frequency (MHz)	399.75	***Nucleus***	1H	***Number of Transients***	100	***Original Points Count***	9357
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	42.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	1900.3818	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	4567.25	***Temperature (degree C)***	25.000



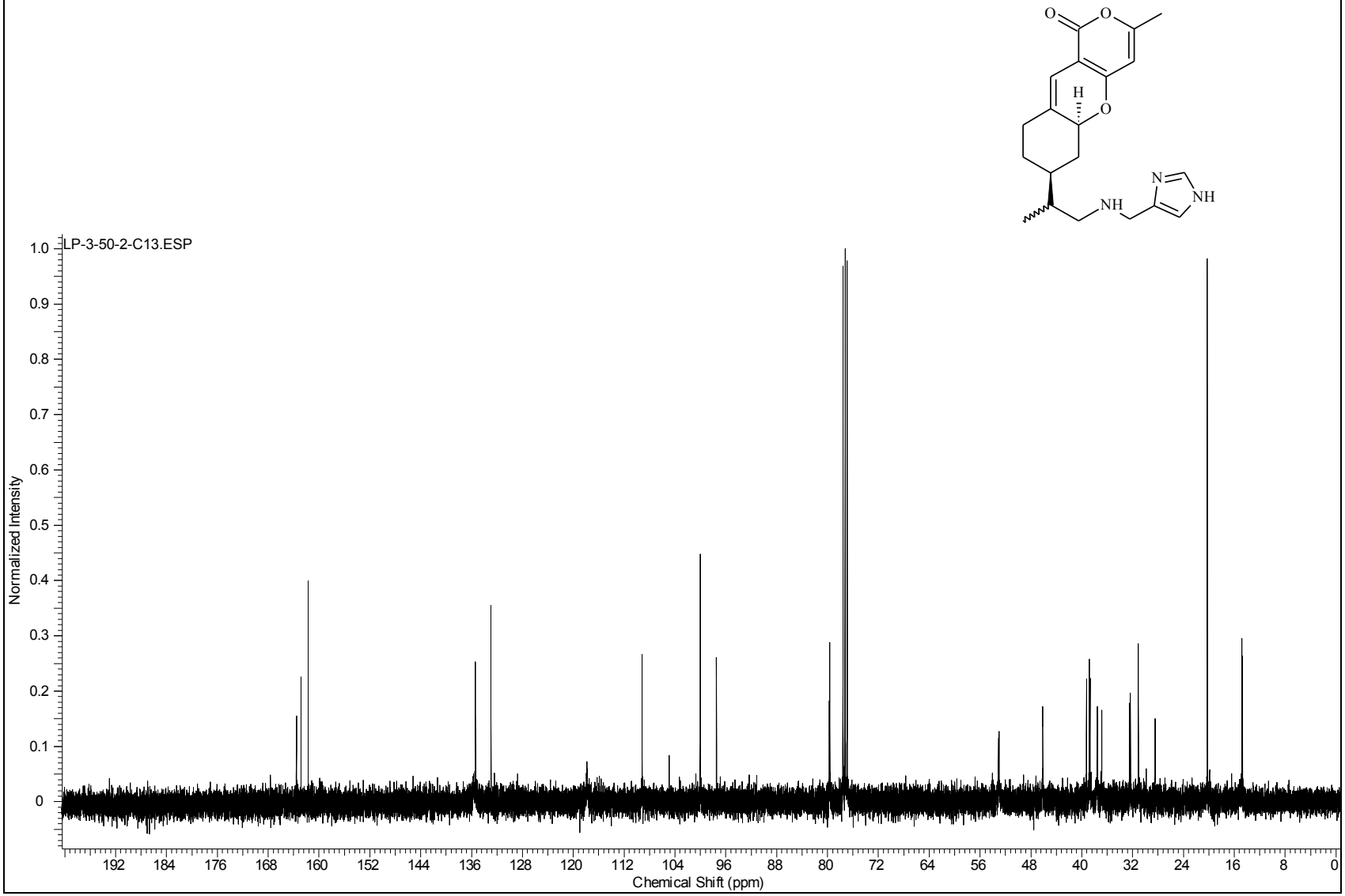
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Aug 2 2009	***Date Stamp***	Aug 2 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-2-81-1-1-C13.FID\FID						
Frequency (MHz)	100.53	***Nucleus***	13C	***Number of Transients***	22288	***Original Points Count***	31375
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10553.0645	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	25.000		



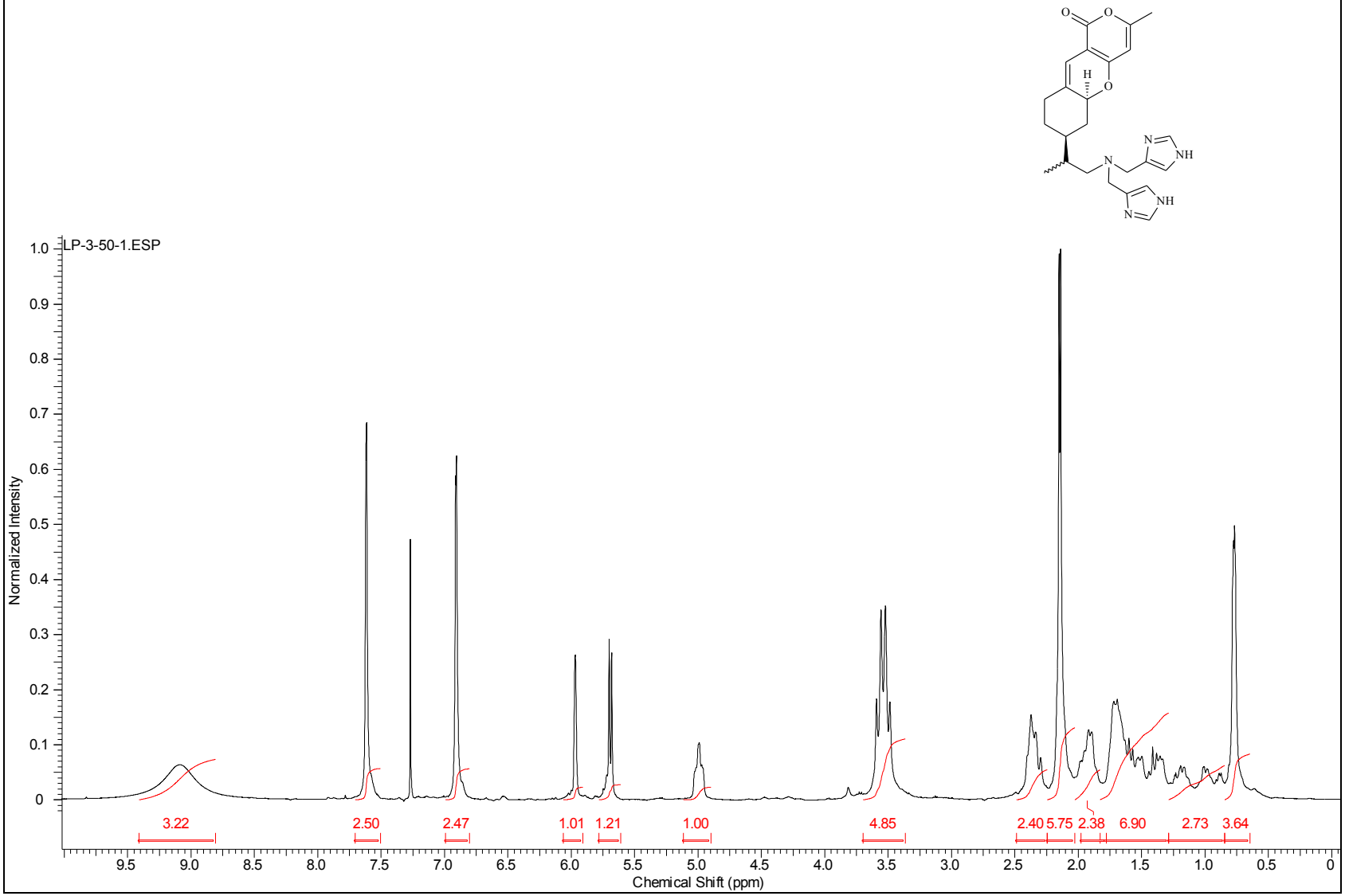
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Aug 9 2011		
Date Stamp	Aug 9 2011			***File Name***	G:\TP36-08-10-11			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	100	***Original Points Count***	12783	***Points Count***	16384	***Pulse Sequence***	s2pul
Receiver Gain	22.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	2402.9727	***Sweep Width (Hz)***	6397.95
Temperature (degree C)	25.000								



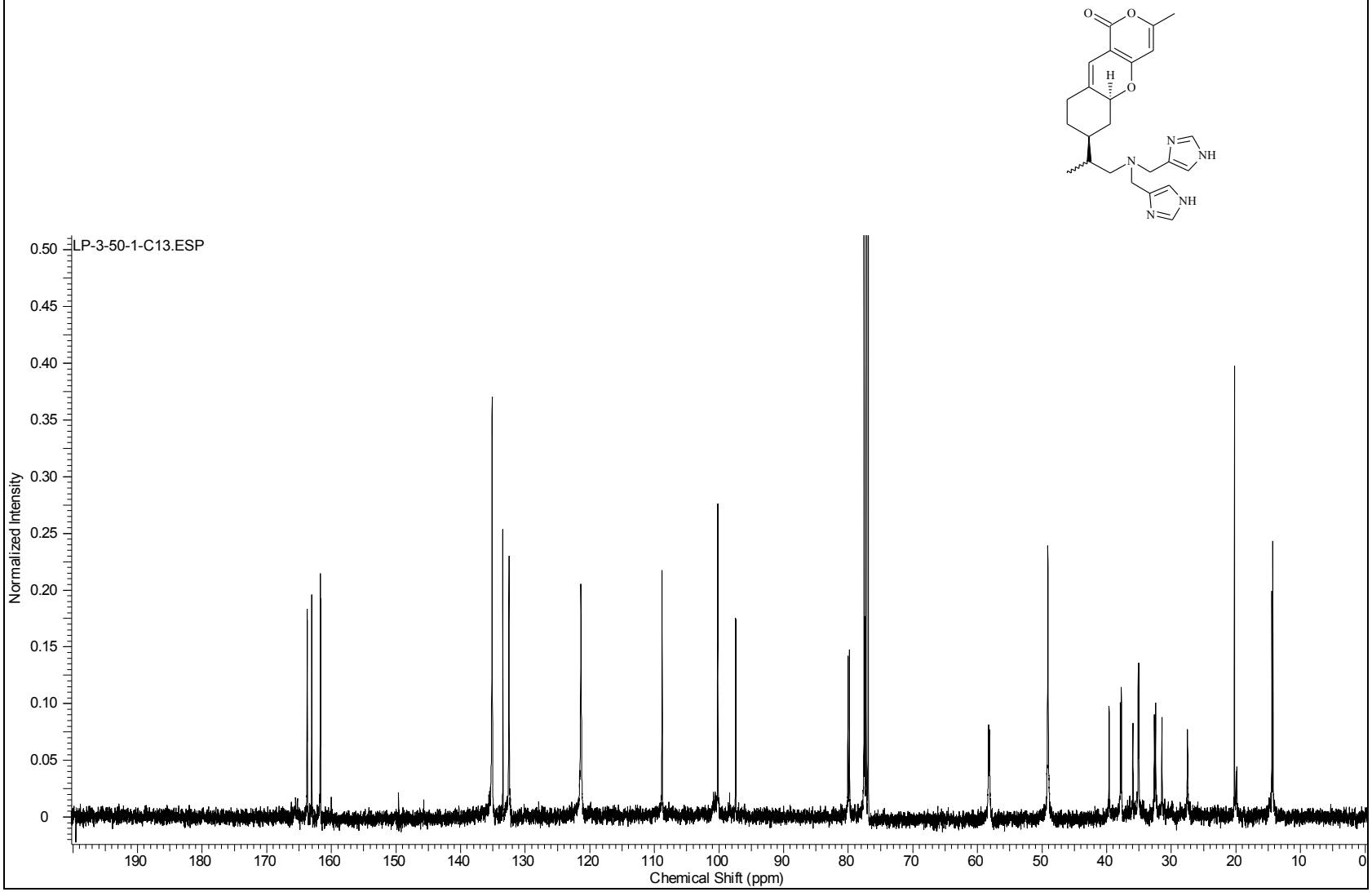
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Aug 9 2011	***Date Stamp***	Aug 9 2011
File Name	G:\TP36-08-10-11-C13			***Frequency (MHz)***	100.58	***Nucleus***	13C	***Number of Transients***	30000
Original Points Count	31413	***Points Count***	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00		
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	10553.9365	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



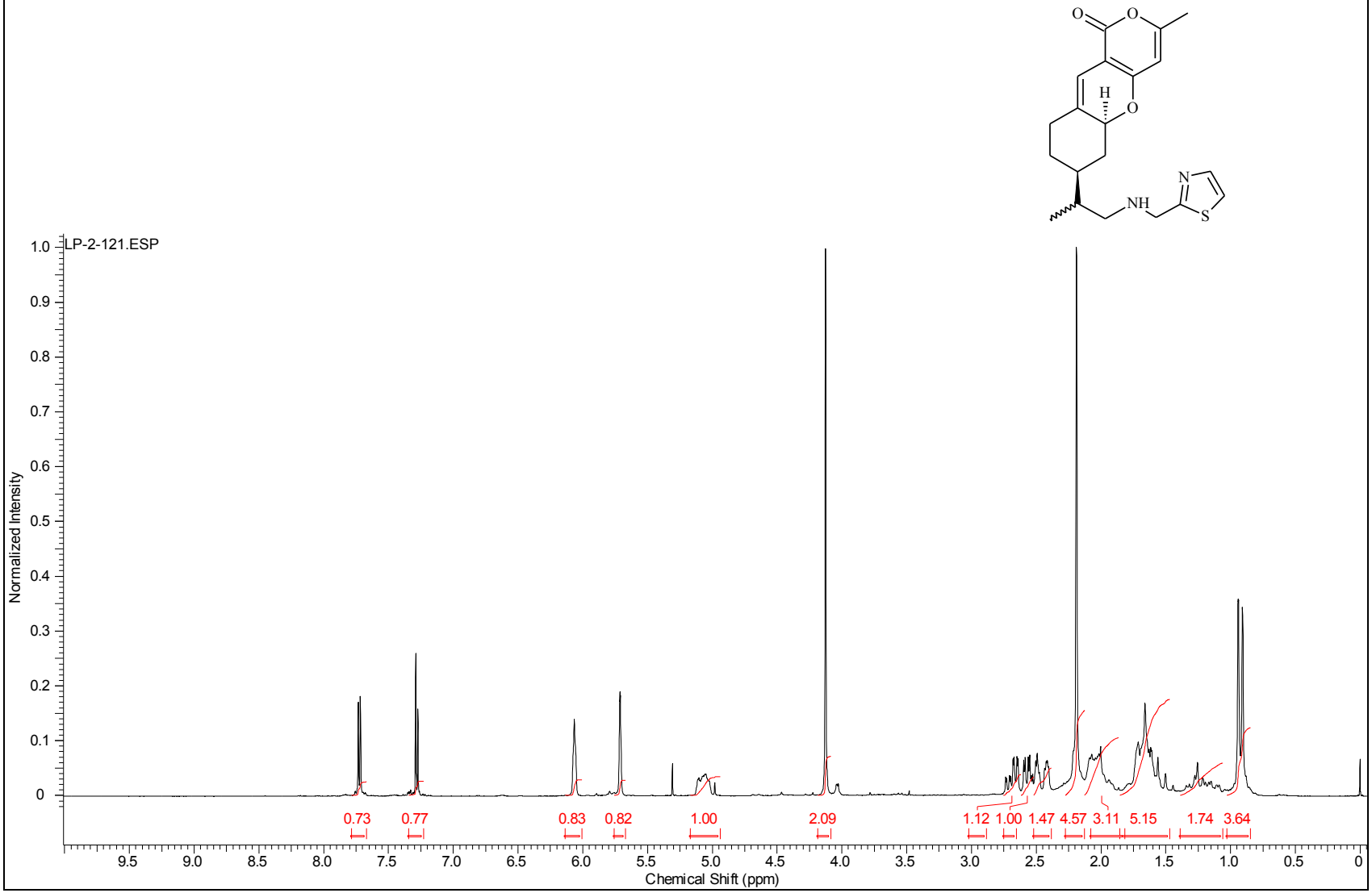
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Jun 17 2011			***Date Stamp***	Jun 17 2011
File Name	F:\LAXMAN POKHREL\TP36-DI2.FID\FID			***Frequency (MHz)***	399.73	***Nucleus***	1H	***Number of Transients***	28
Original Points Count	13102	***Points Count***	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00		
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	2414.5737	***Sweep Width (Hz)***	6395.40	***Temperature (degree C)***	25.000



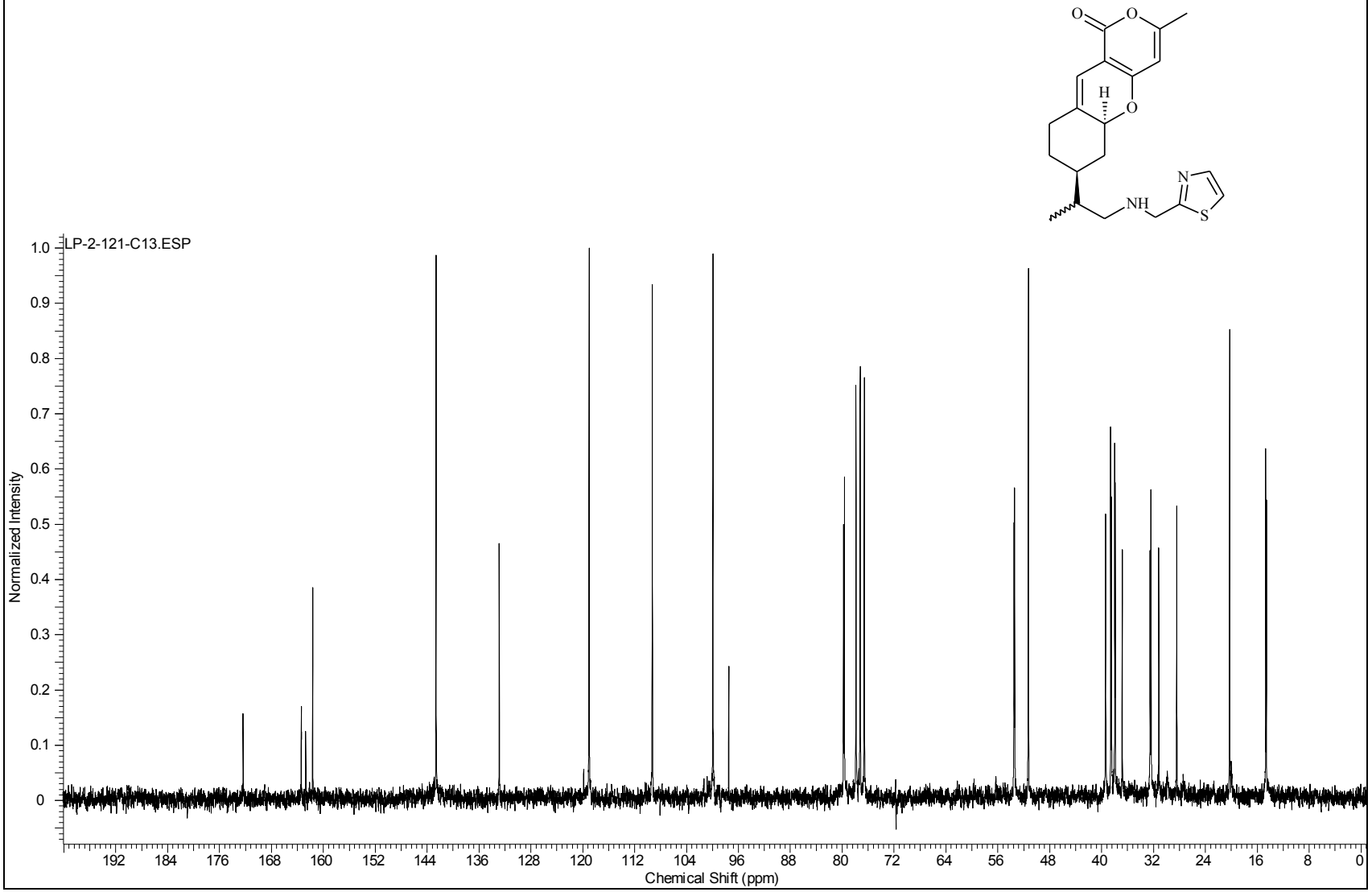
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Jun 17 2011	***Date Stamp***	Jun 17 2011
File Name	F:\LAXMAN POKHREL\TP36DI2.FID\FID			***Frequency (MHz)***	100.52	***Nucleus***	13C
Number of Transients	20000	***Original Points Count***	31375	***Points Count***	32768	***Pulse Sequence***	s2pul
Receiver Gain	30.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	10549.7402
Spectrum Type	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	25.000		



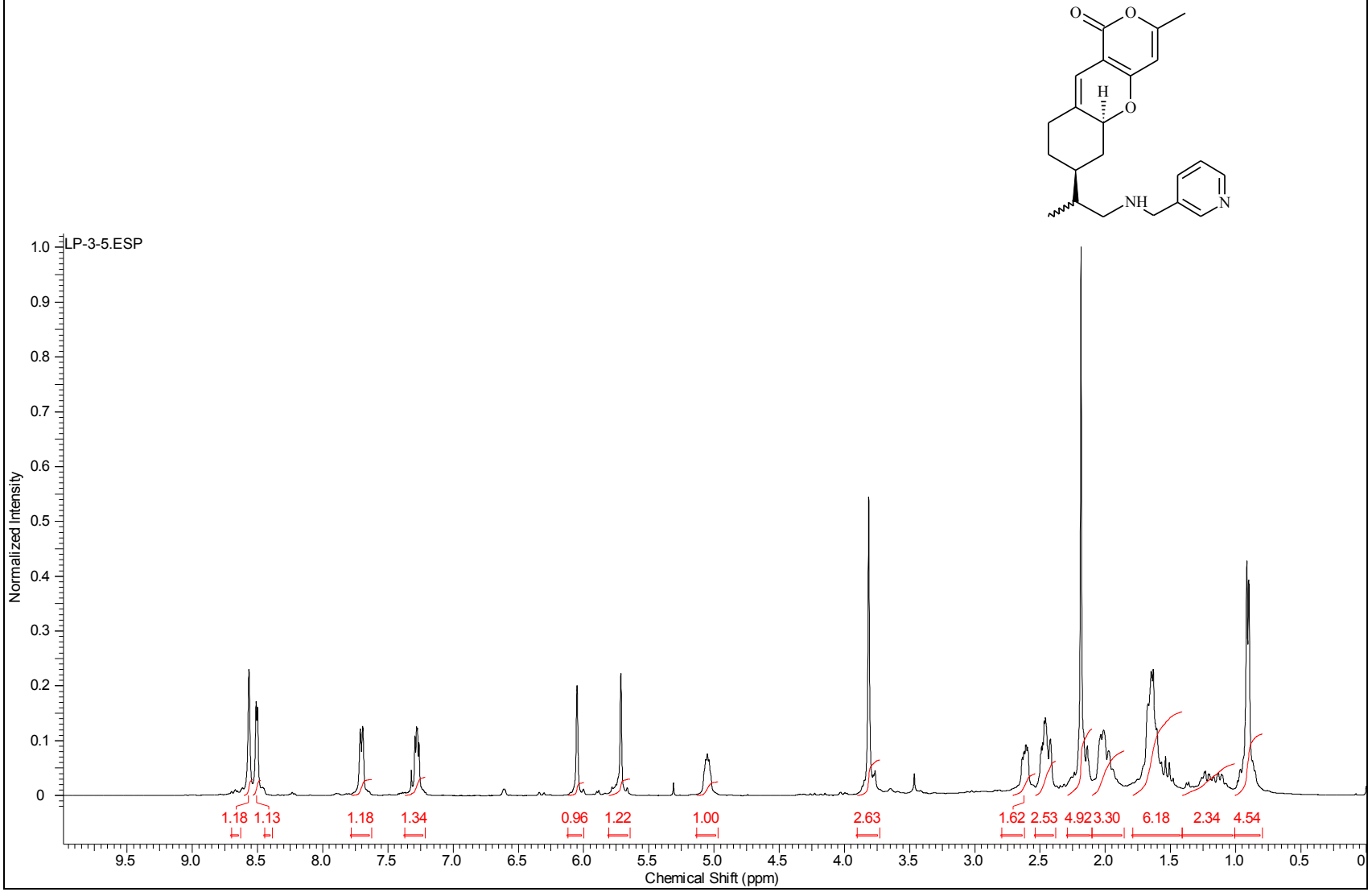
Acquisition Time (sec)	1.9945	***Comment***	STANDARD 1H OBSERVE□lp-2-121fr4-6			***Date***	Oct 4 2009
Date Stamp	Oct 4 2009	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\200MHZ\LP-2-121FR4-6.FID\FID				
Frequency (MHz)	199.98	***Nucleus***	1H	***Number of Transients***	100	***Original Points Count***	5984
Points Count	8192	***Pulse Sequence***	s2pul	***Receiver Gain***	22.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	1006.0217	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	3000.30	***Temperature (degree C)***	AMBIENT TEMPERATURE



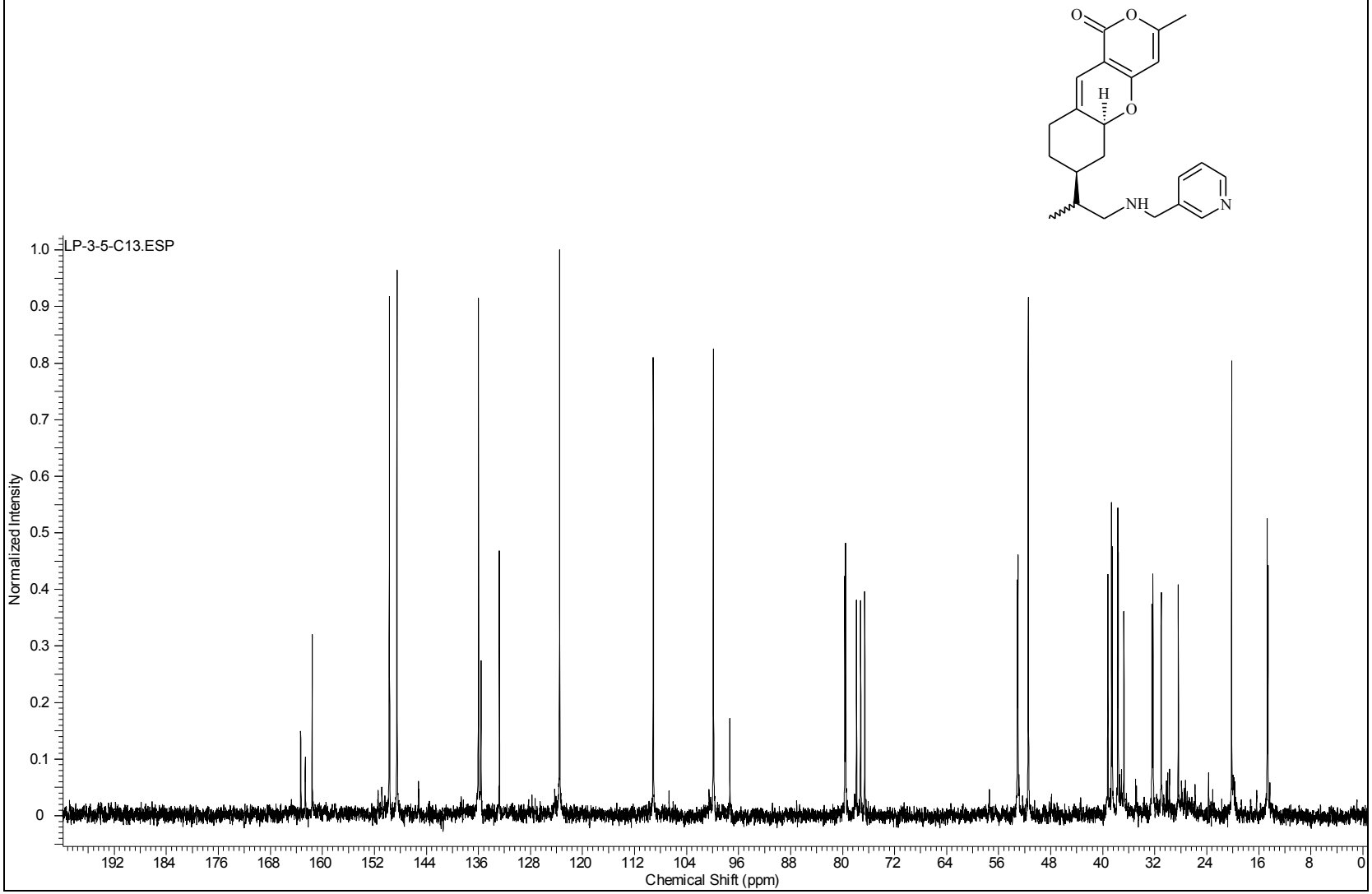
Acquisition Time (sec)	1.4976	***Comment***	13C OBSERVE	***Date***	Oct 4 2009	***Date Stamp***	Oct 4 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\200MHZ\LP-2-121FR4-6-C13.FID\FID					***Frequency (MHz)***	50.29
Nucleus	13C	***Number of Transients***	5532	***Original Points Count***	18720	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	40.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	4878.9351	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	12500.00	***Temperature (degree C)***	AMBIENT TEMPERATURE



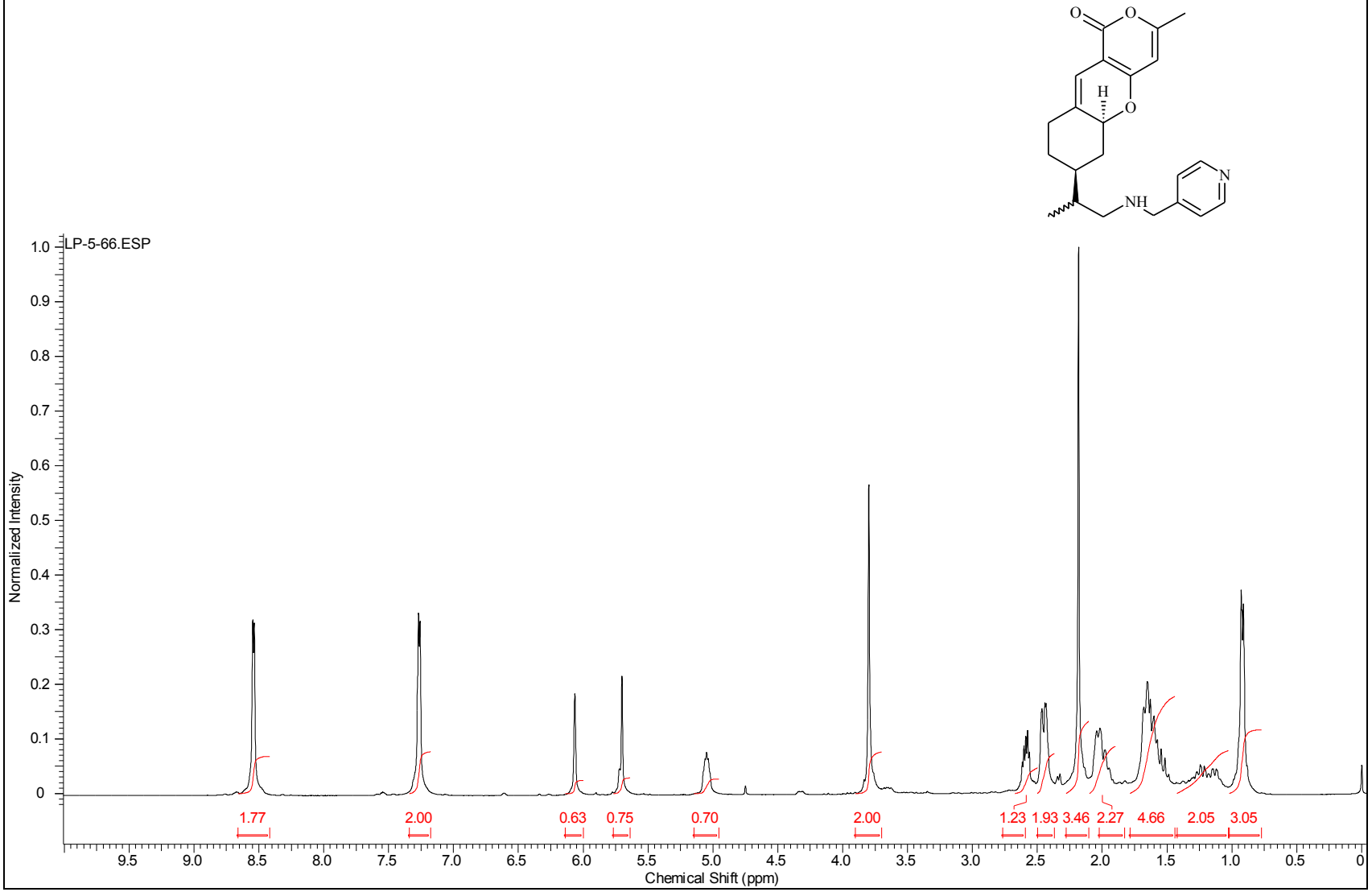
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Oct 9 2009	***Date Stamp***	Oct 9 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-3-5PURE.FID\FID						
Frequency (MHz)	399.75	***Nucleus***	1H	***Number of Transients***	50	***Original Points Count***	13103
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	36.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2424.8154	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	25.000



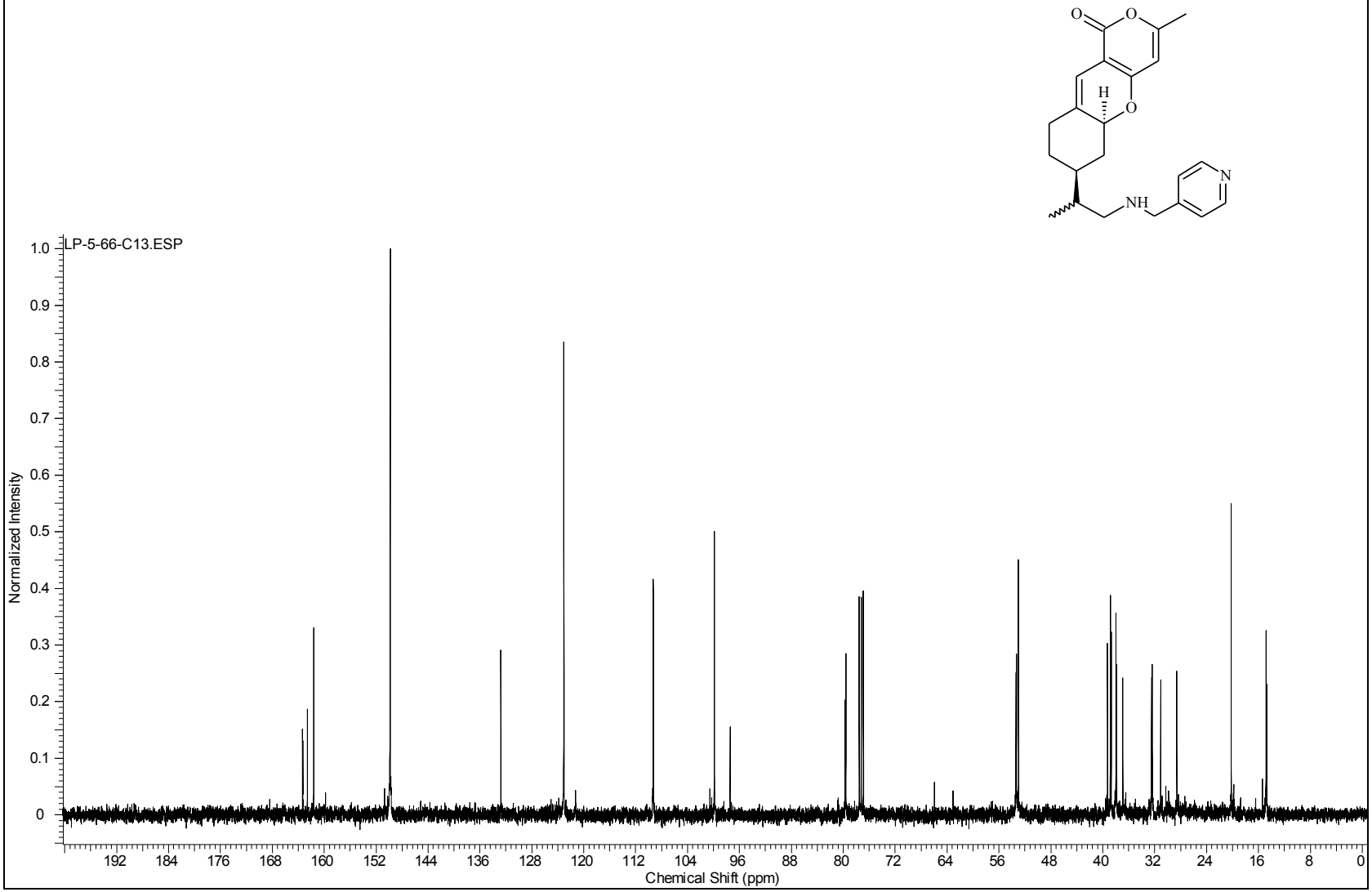
Acquisition Time (sec)	1.4976	***Comment***	13C OBSERVE	***Date***	Oct 9 2009	***Date Stamp***	Oct 9 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LPOKHREL\LP-3-05PURE-C13.FID\FID					***Frequency (MHz)***	50.29
Nucleus	13C	***Number of Transients***	3848	***Original Points Count***	18720	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	40.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	4875.5015	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	12500.00	***Temperature (degree C)***	AMBIENT TEMPERATURE



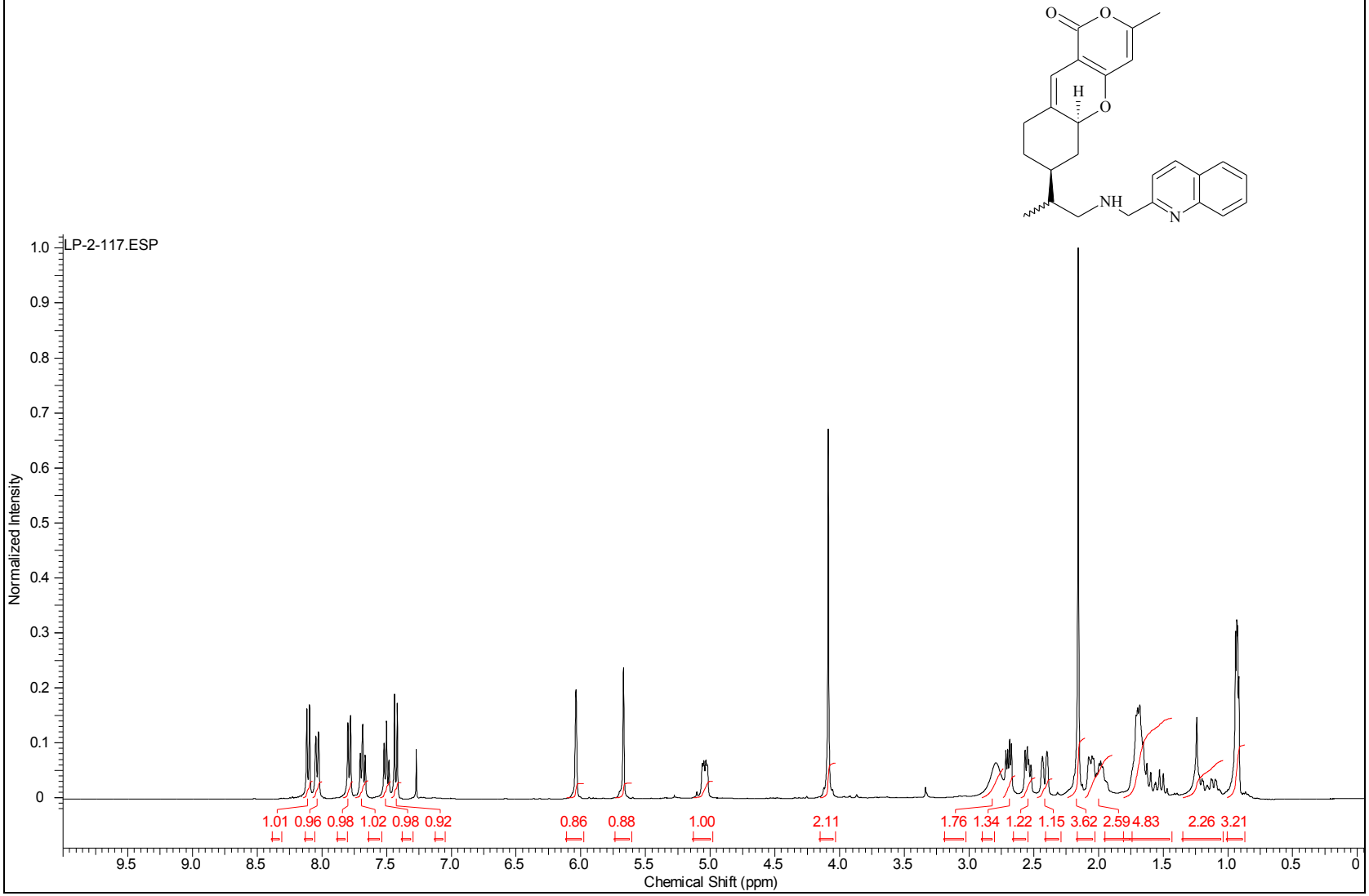
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Mar 25 2011
Date Stamp	Mar 25 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\NEW FOLDER\LP-5-66-REC.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	48	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2406.2129	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



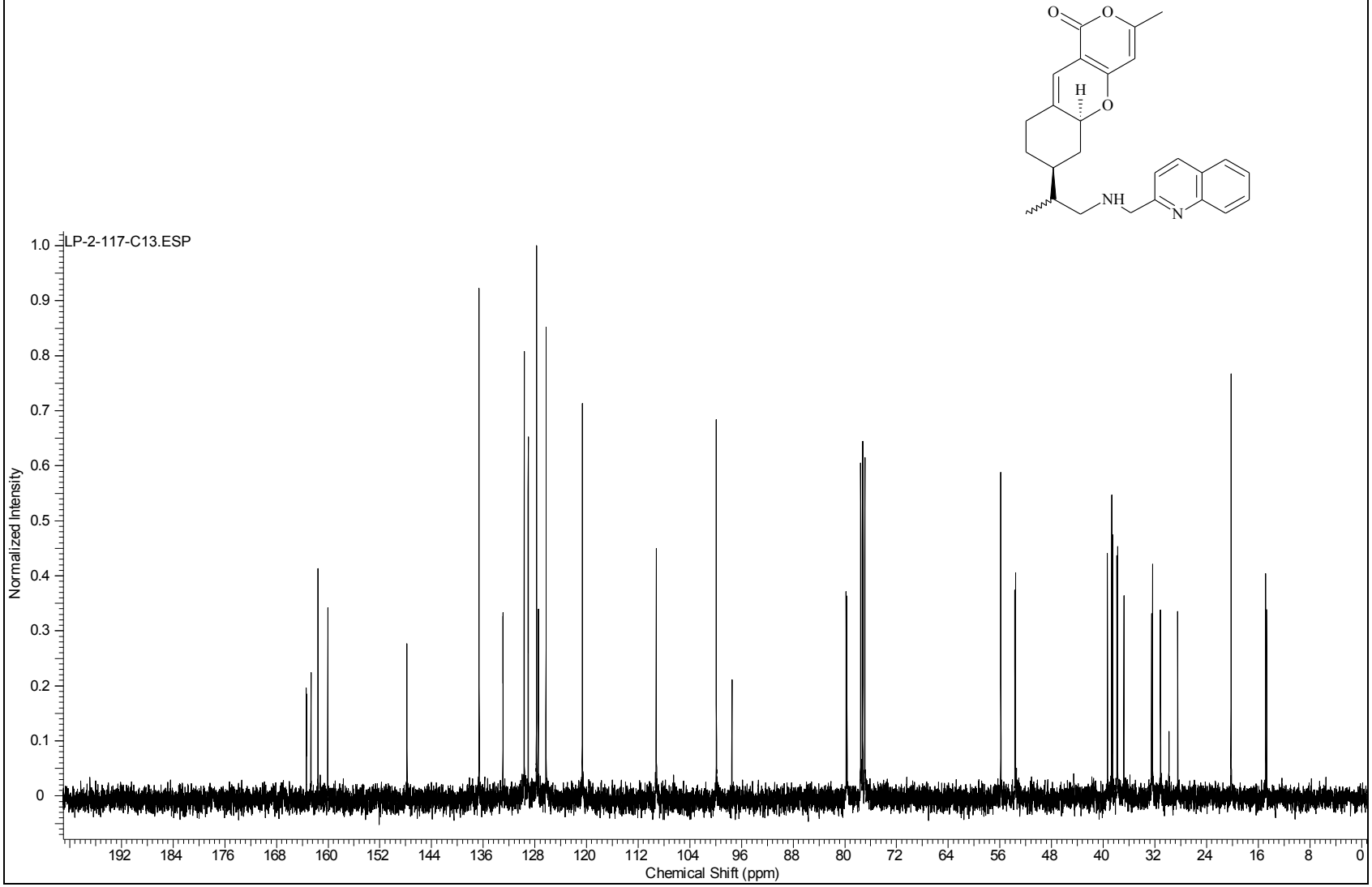
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Mar 24 2011
Date Stamp	Mar 24 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-66-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	544	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10551.7246	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



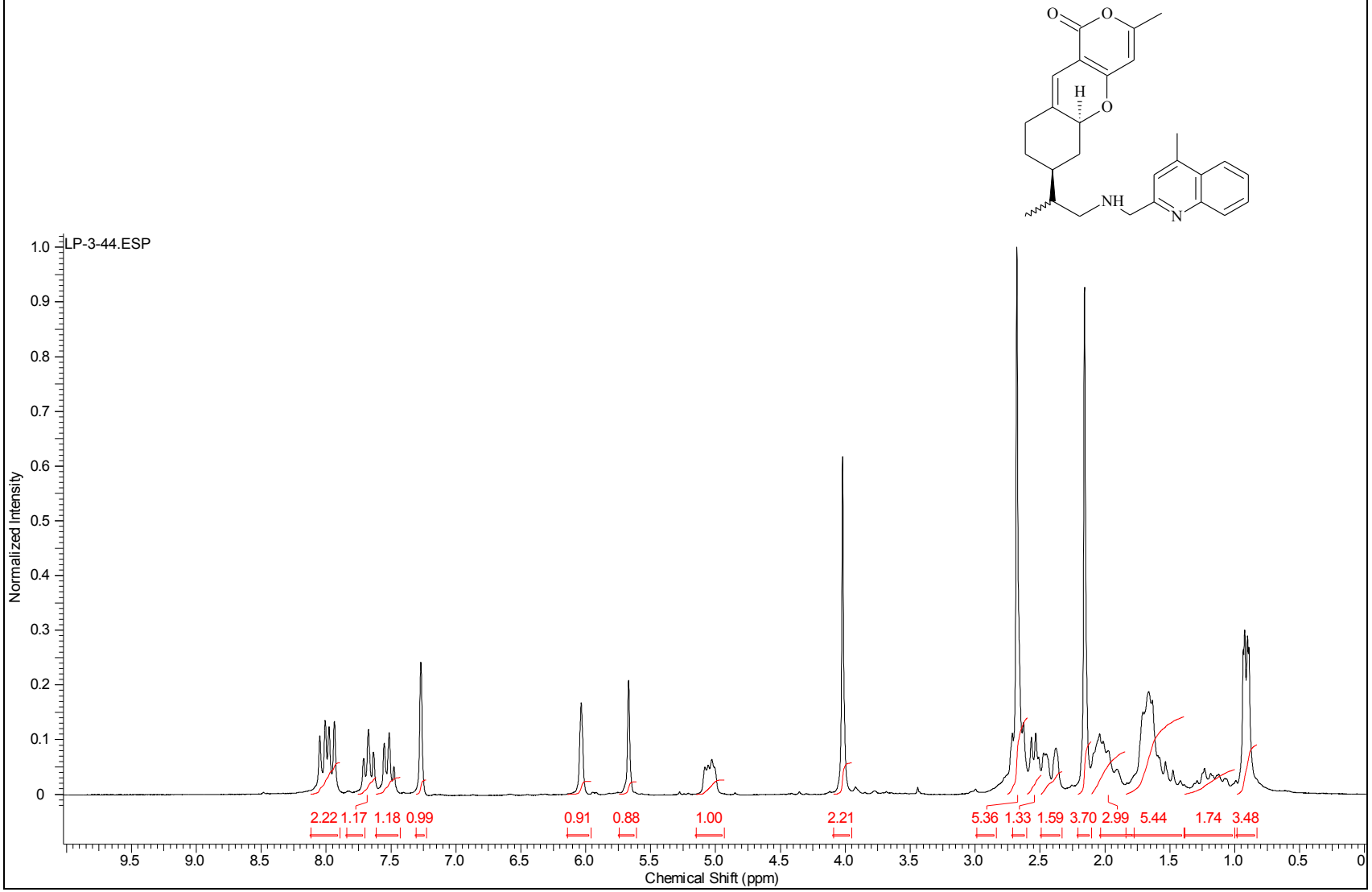
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Jul 7 2011
Date Stamp	Jul 7 2011	***File Name***	F:\LAXMAN POKHREL\LAXMAN-MERCURY-07-15-2011\LP-2-117-2.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	40	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2403.9622	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



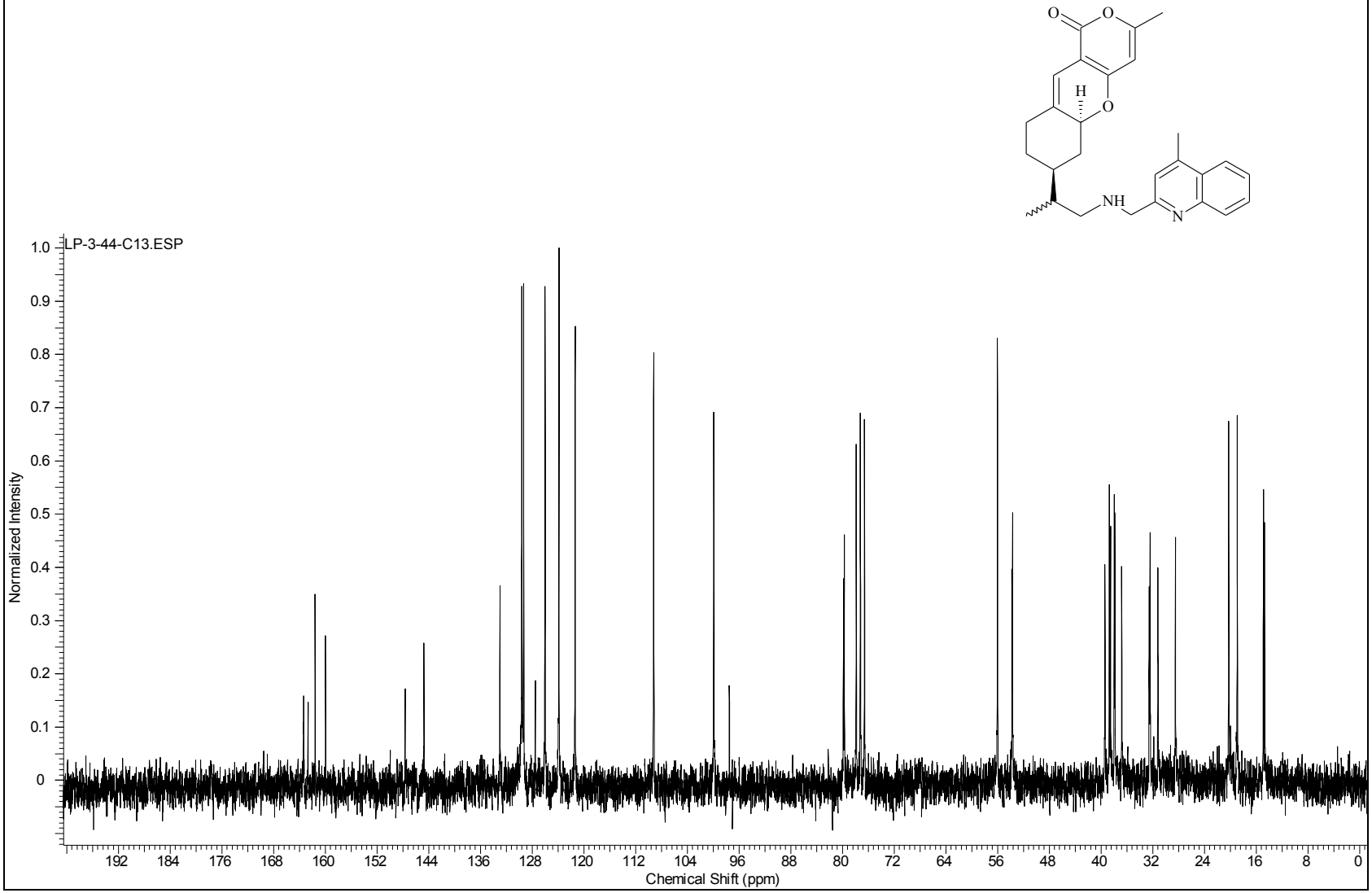
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jul 7 2011
Date Stamp	Jul 7 2011	***File Name***	F:\LAXMAN POKHREL\LAXMAN-MERCURY-07-15-2011\LP-2-117-2-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	324	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10551.7246	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



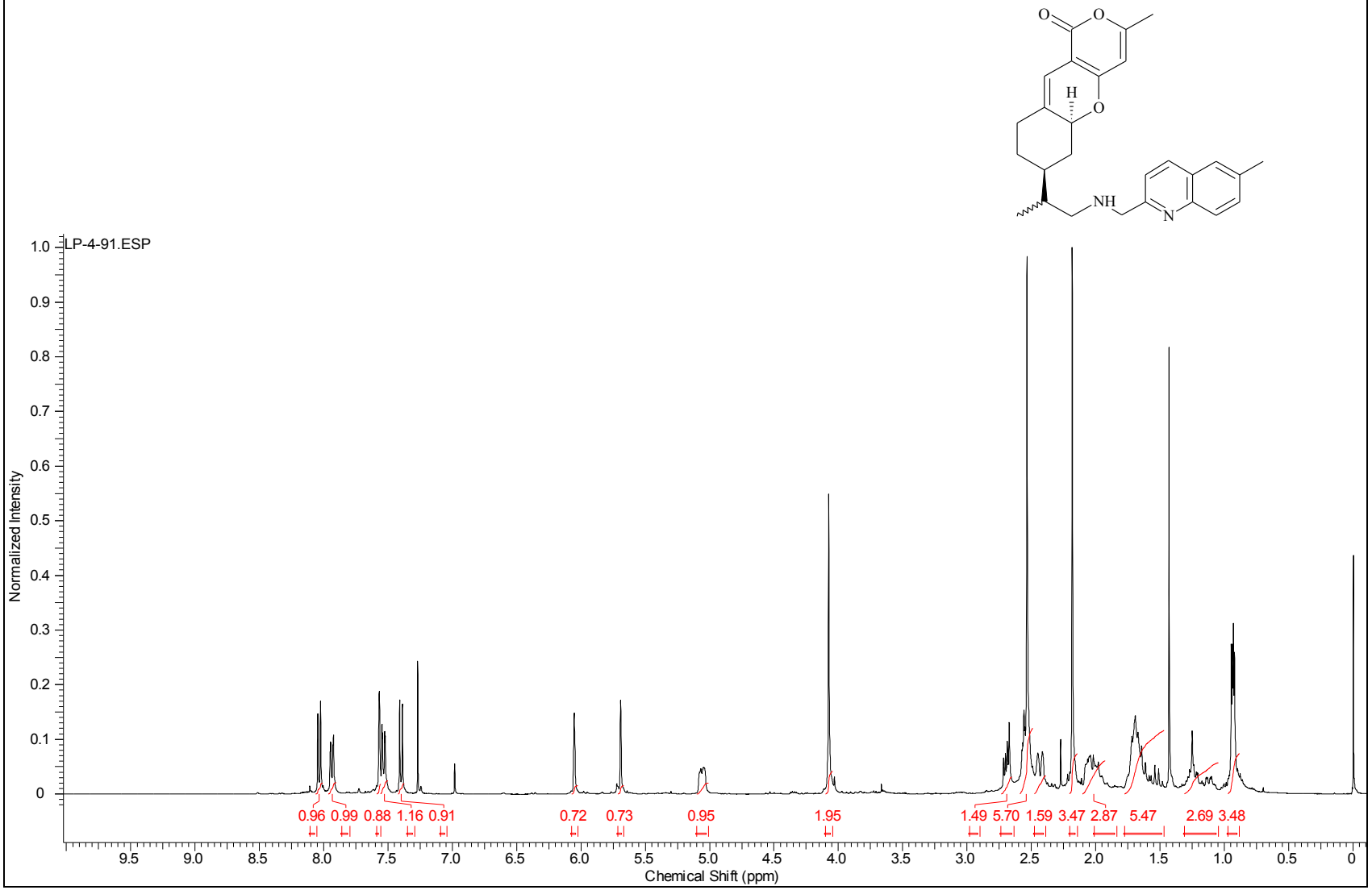
Acquisition Time (sec)	1.9945	***Comment***	STANDARD 1H OBSERVE□lp-3-44fr2			***Date***	Dec 16 2009
Date Stamp	Dec 16 2009	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LPOKHREL\LP-3-44.FID\FID				
Frequency (MHz)	199.98	***Nucleus***	1H	***Number of Transients***	56	***Original Points Count***	5984
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	22.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	1001.2827	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	3000.30	***Temperature (degree C)***	AMBIENT TEMPERATURE



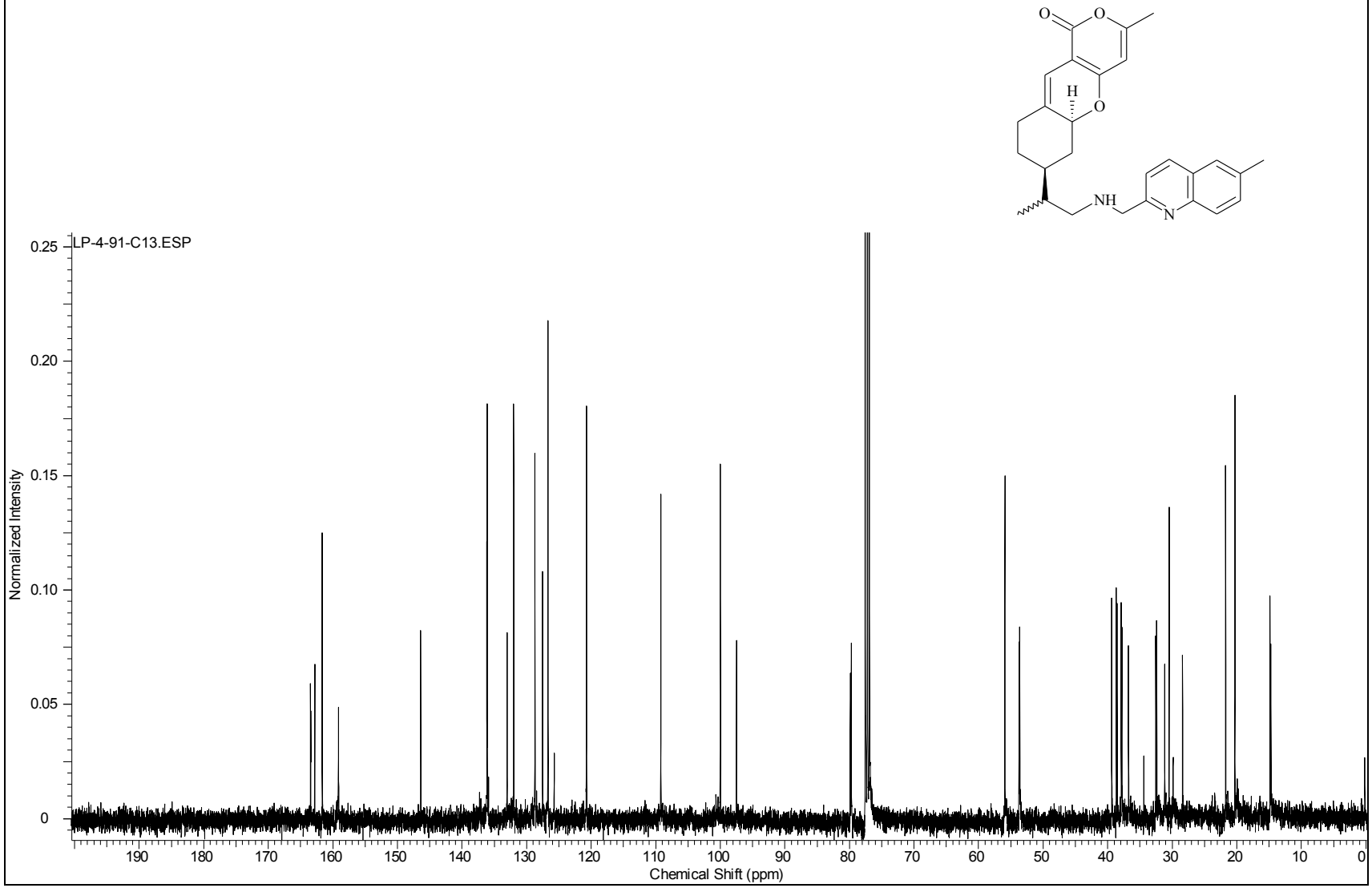
Acquisition Time (sec)	1.4976	***Comment***	13C OBSERVE	***Date***	Dec 16 2009	***Date Stamp***	Dec 16 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LPOKHREL\LP-3-44C13.FID\FID					***Frequency (MHz)***	50.29
Nucleus	13C	***Number of Transients***	1008	***Original Points Count***	18720	***Points Count***	65536
Pulse Sequence	s2pul	***Receiver Gain***	40.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	4878.8242	***Sweep Width (Hz)***	12500.00	***Temperature (degree C)***	AMBIENT TEMPERATURE		



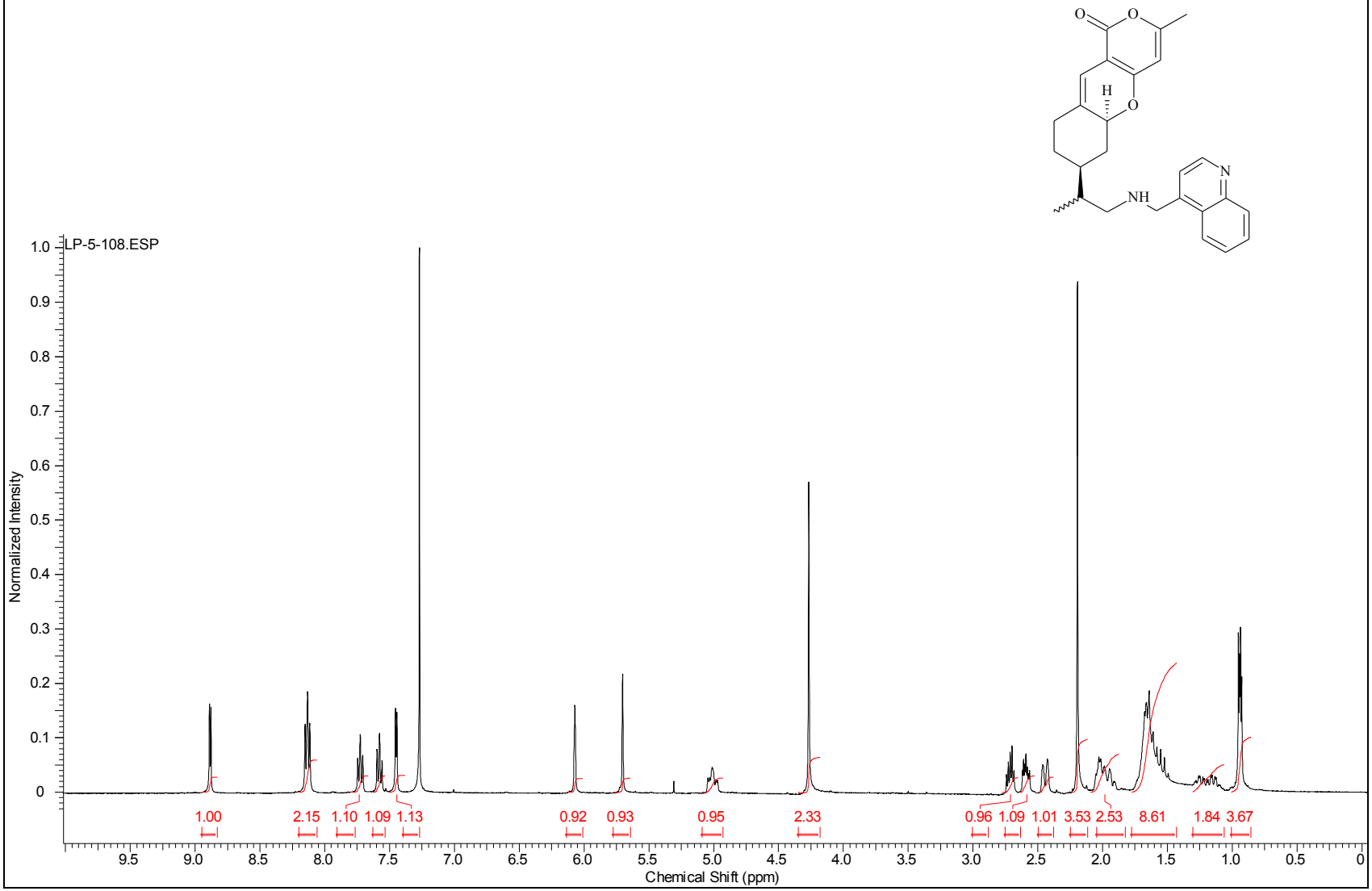
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Aug 27 2010	***Date Stamp***	Aug 27 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-91FR3.FID\FID						
Frequency (MHz)	399.74	***Nucleus***	1H	***Number of Transients***	64	***Original Points Count***	13103
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2416.7397	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	30.000



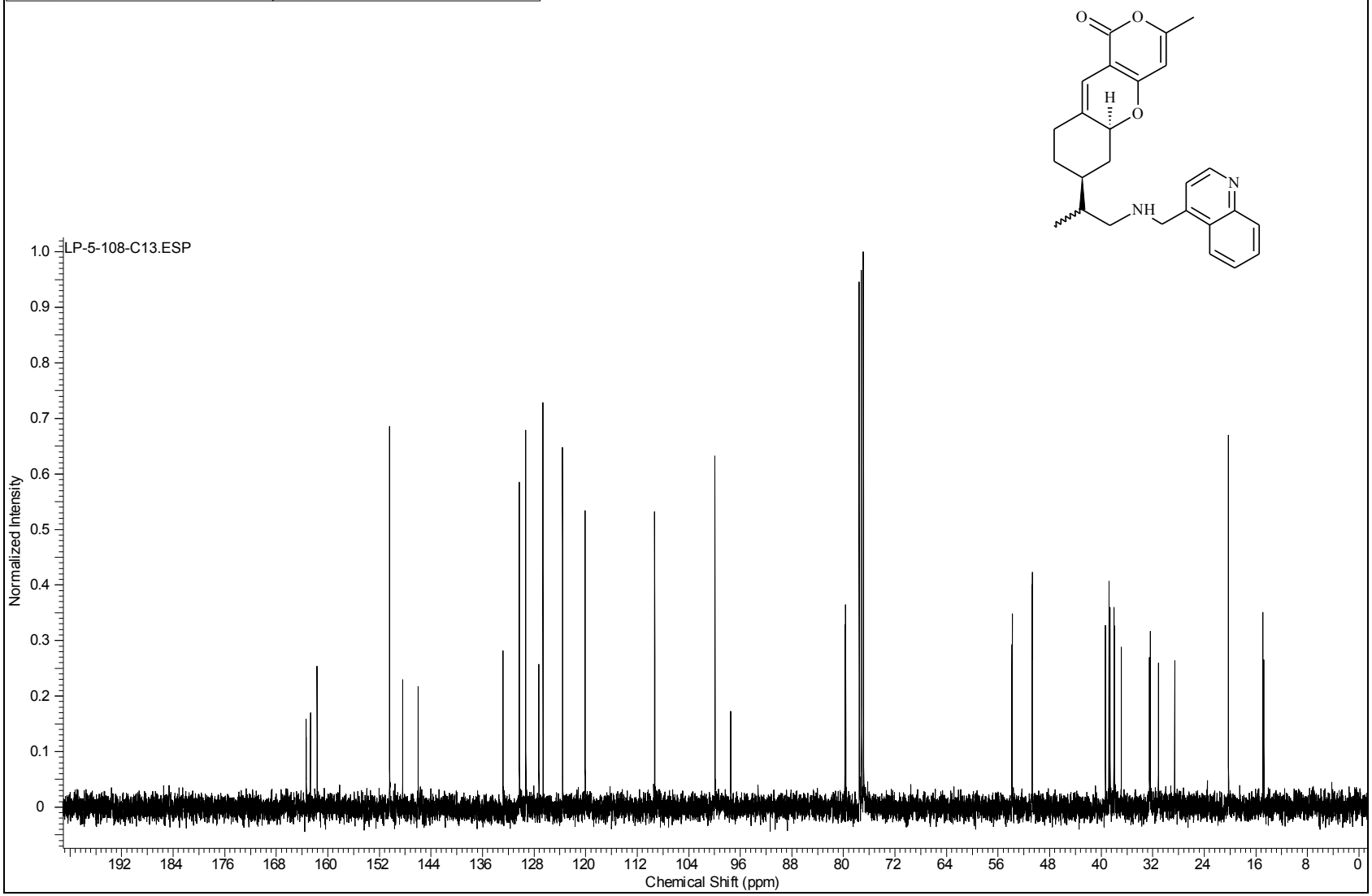
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Aug 27 2010	***Date Stamp***	Aug 27 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-91-C13.FID\FID						
Frequency (MHz)	100.52	***Nucleus***	13C	***Number of Transients***	20000	***Original Points Count***	31375
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10552.1387	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	30.000



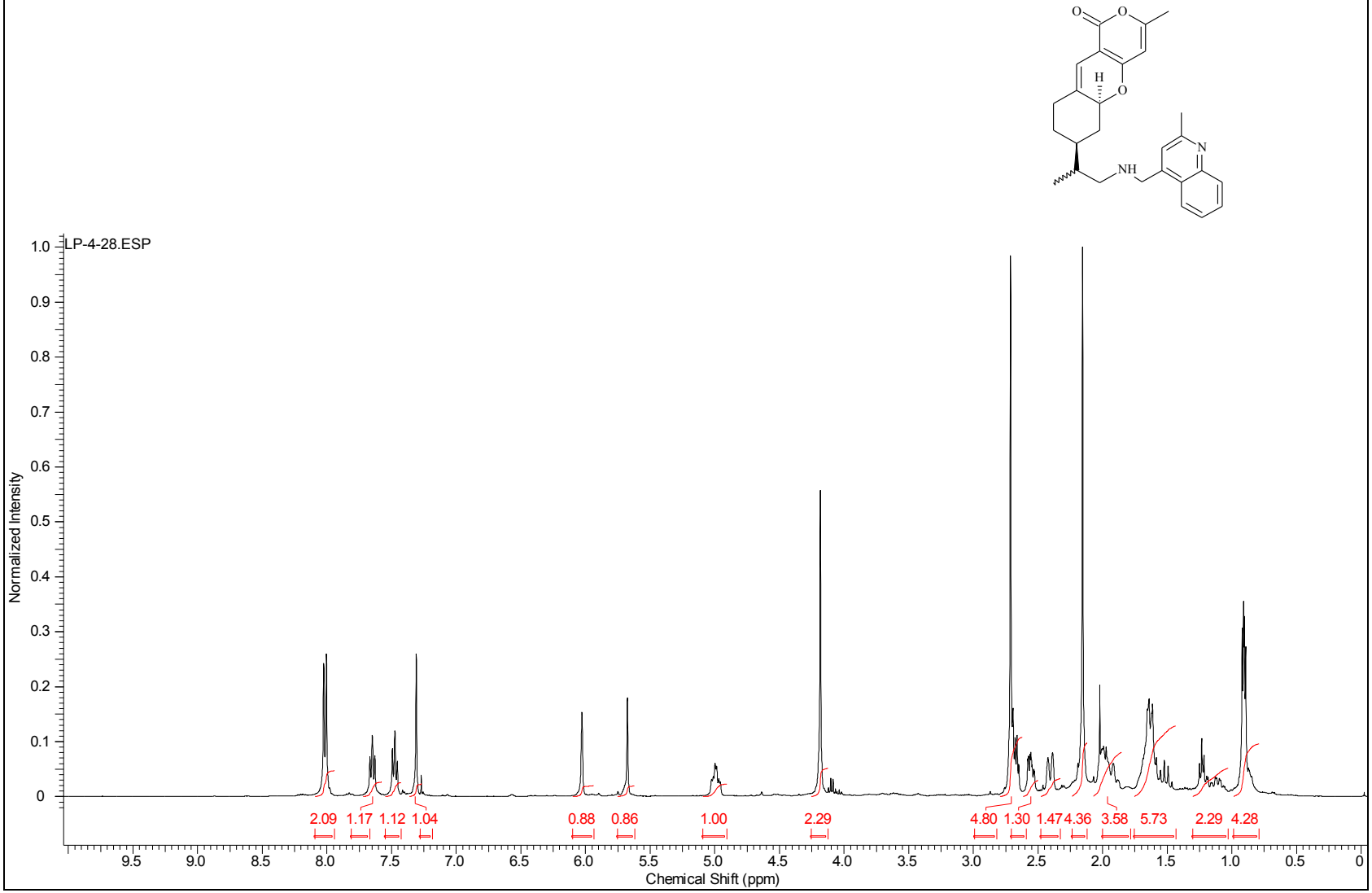
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Sep 29 2011
Date Stamp	Sep 29 2011	***File Name***	F:\NMR-MERCURY-02012\TP63-HCL-CON-2.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	100	***Original Points Count***	12783	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	39.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2404.5349	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



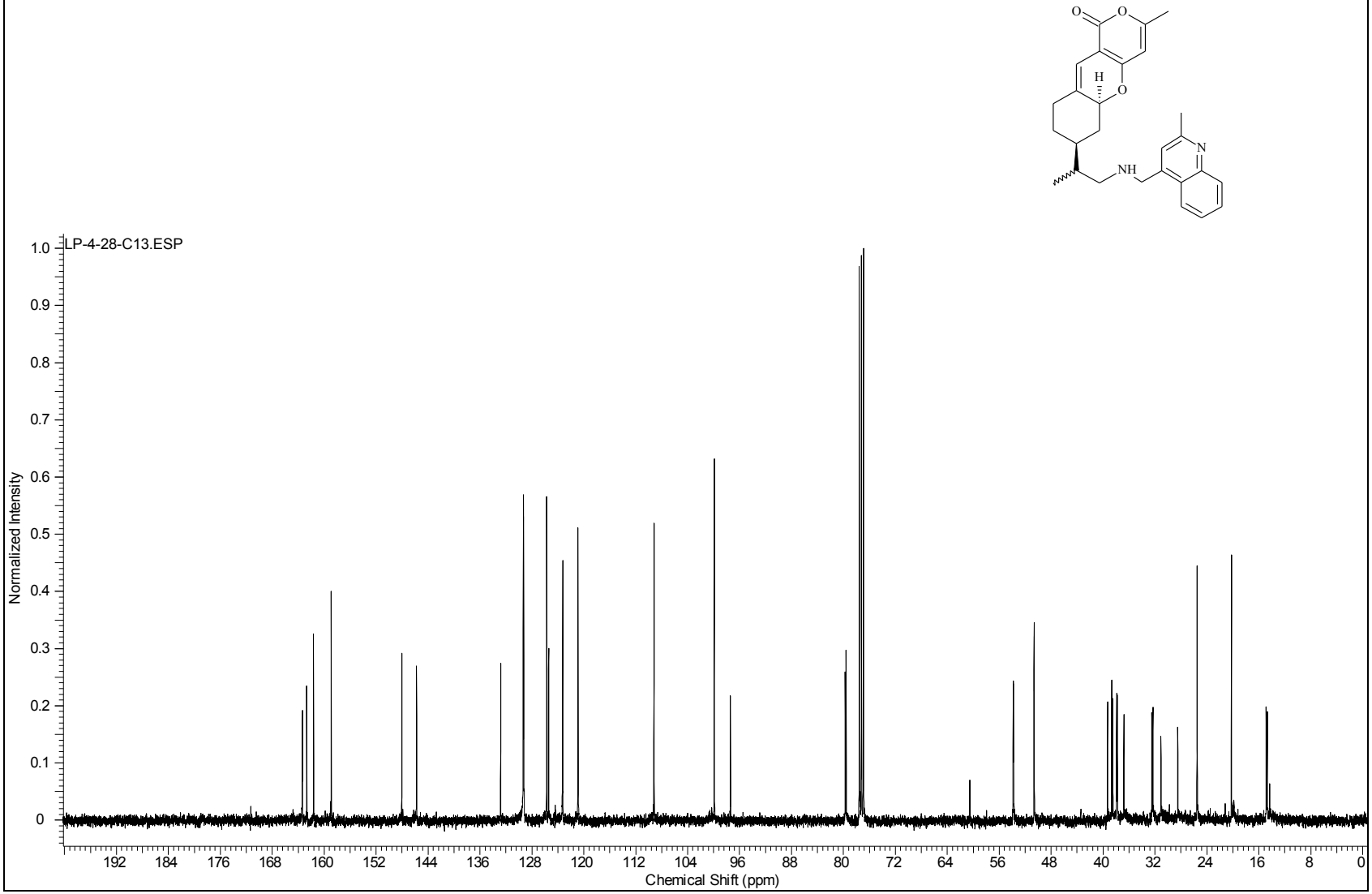
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Jun 29 2011			***Date Stamp***	Jun 29 2011
File Name	F:\LP-5-108-C13.FID\FID			***Frequency (MHz)***	100.52	***Nucleus***	13C	***Number of Transients***	1628
Original Points Count	31375	***Points Count***	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00		
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	10551.2129			***Spectrum Type***	STANDARD
Sweep Width (Hz)	24125.45	***Temperature (degree C)***	25.000						



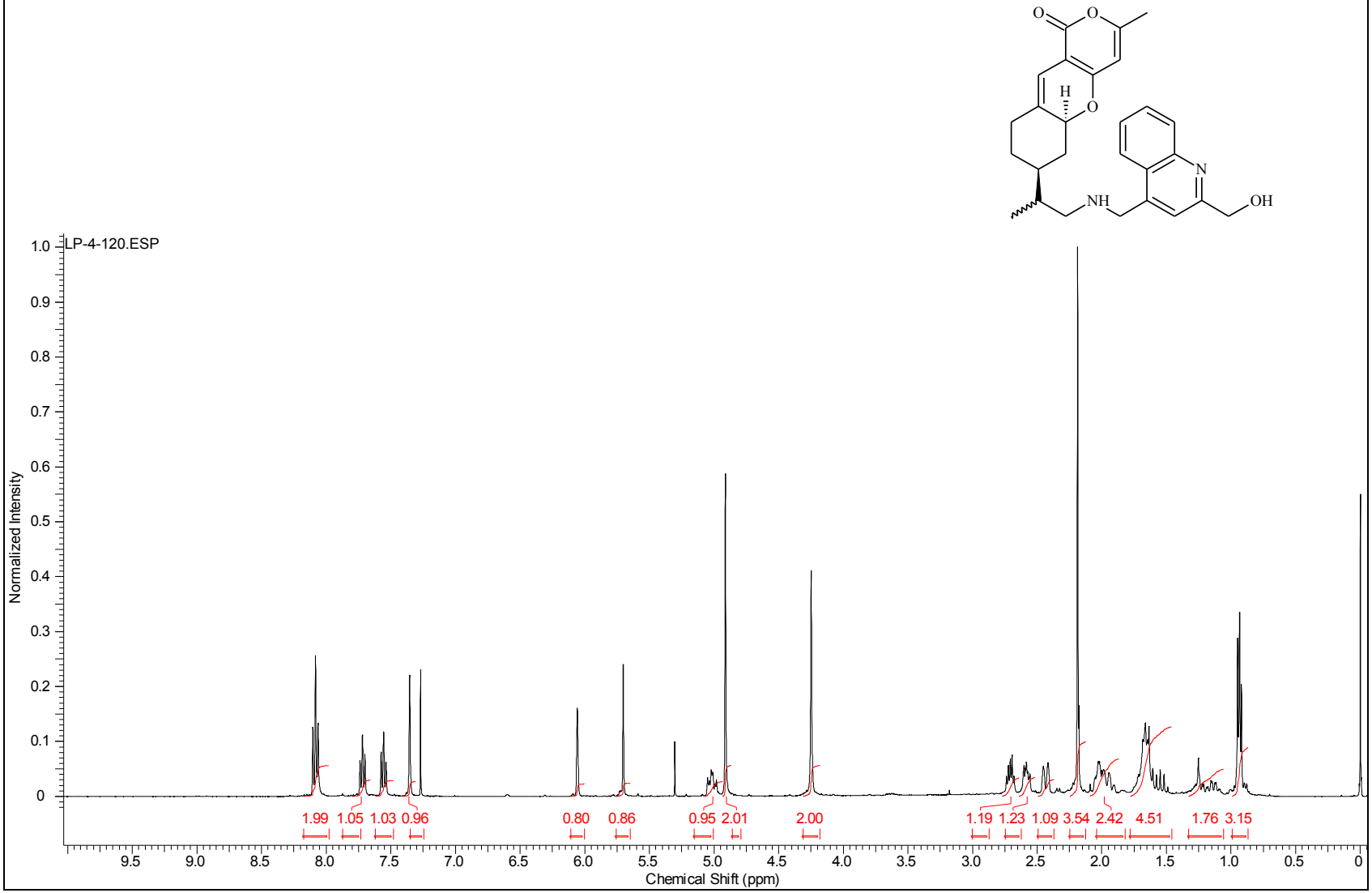
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	May 14 2010	***Date Stamp***	May 14 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-28.FID\FID						
Frequency (MHz)	399.74	***Nucleus***	1H	***Number of Transients***	48	***Original Points Count***	13103
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2416.7397	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	40.000



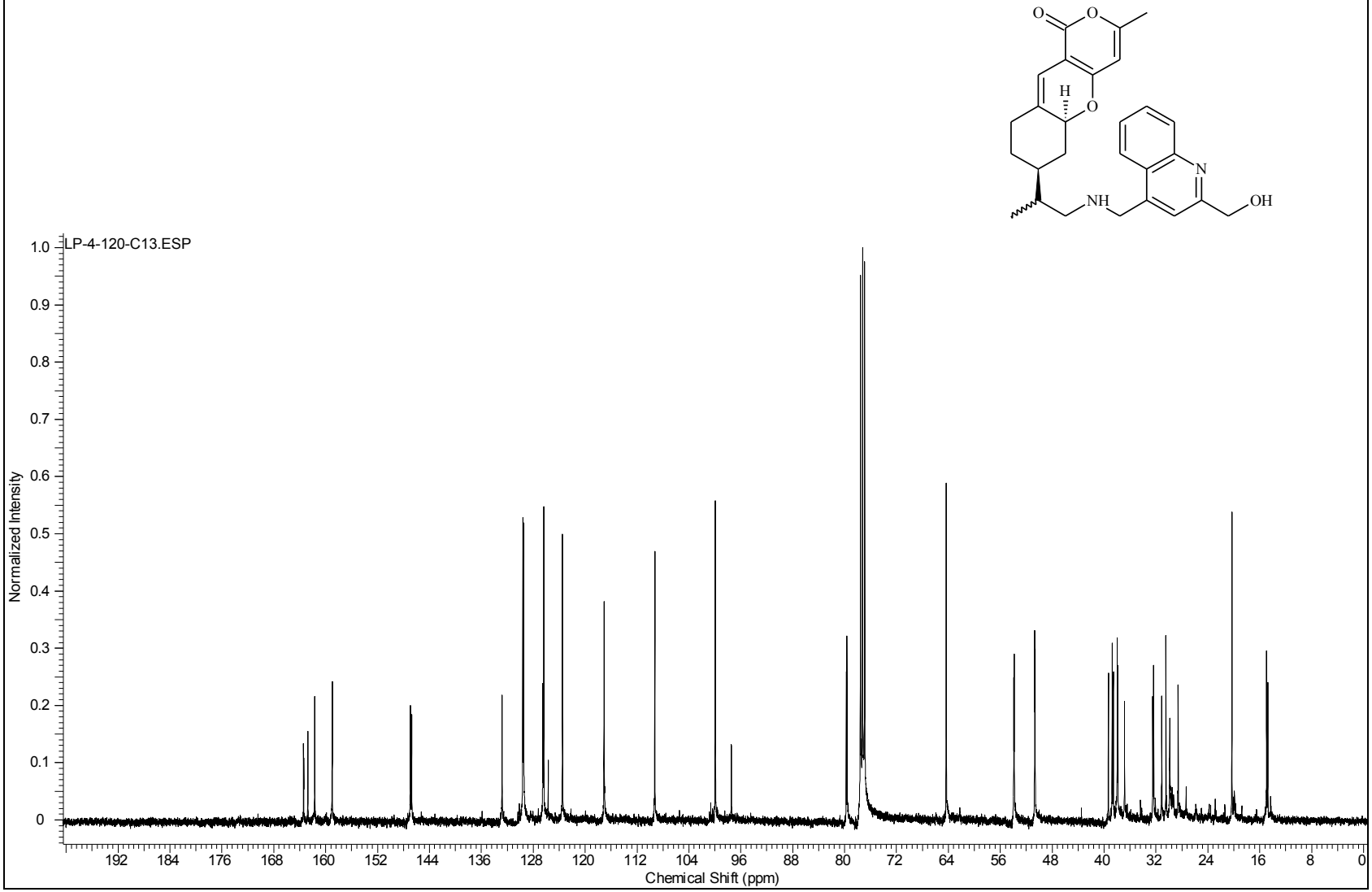
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	May 14 2010	***Date Stamp***	May 14 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-28C13.FID\FID						
Frequency (MHz)	100.52	***Nucleus***	13C	***Number of Transients***	5400	***Original Points Count***	31375
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10546.9844	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	40.000



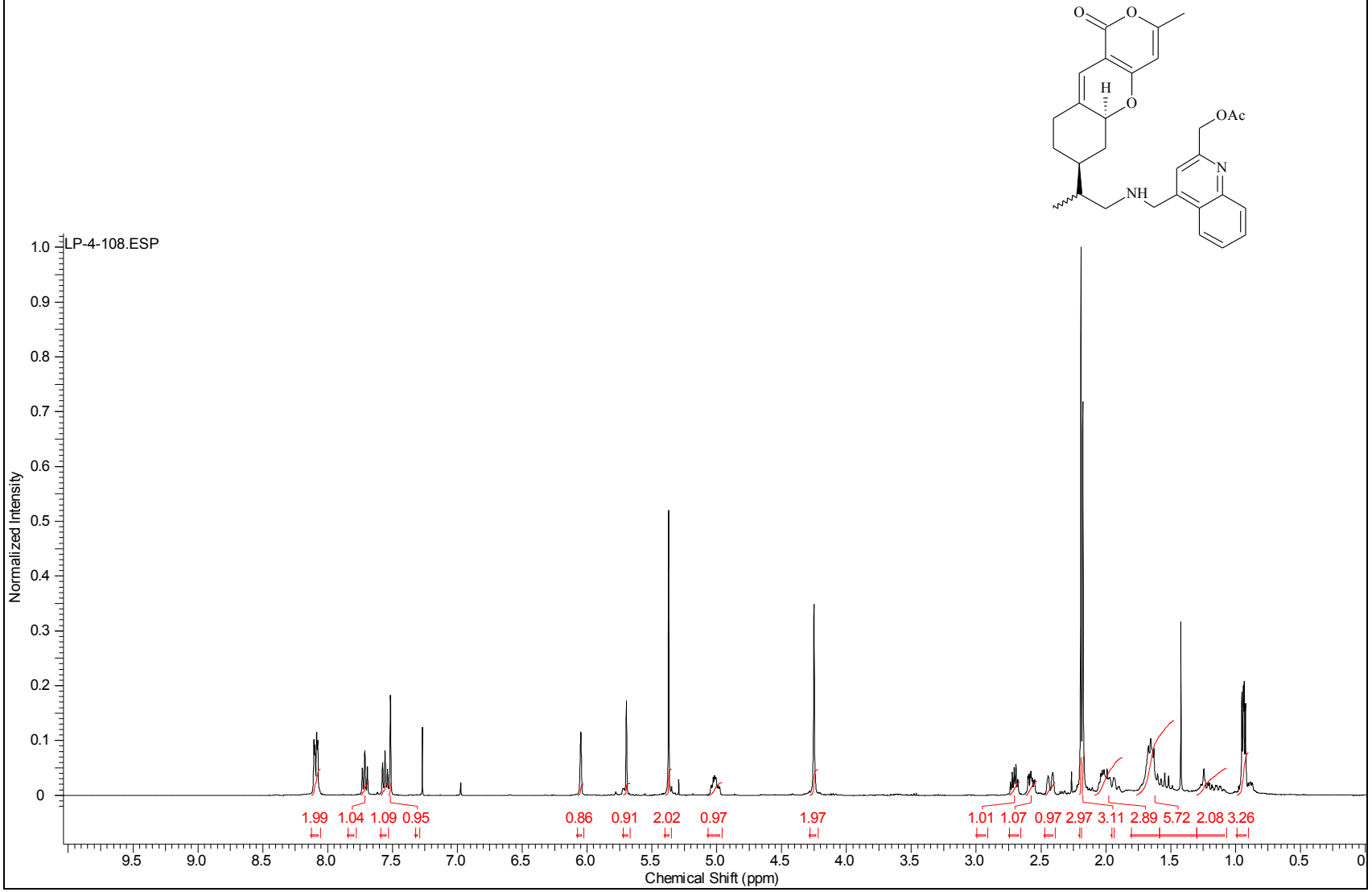
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Dec 19 2010	***Date Stamp***	Dec 19 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-120COL.FID\FID						
Frequency (MHz)	399.73	***Nucleus***	1H	***Number of Transients***	20	***Original Points Count***	13103
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	38.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2414.2439	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	25.000



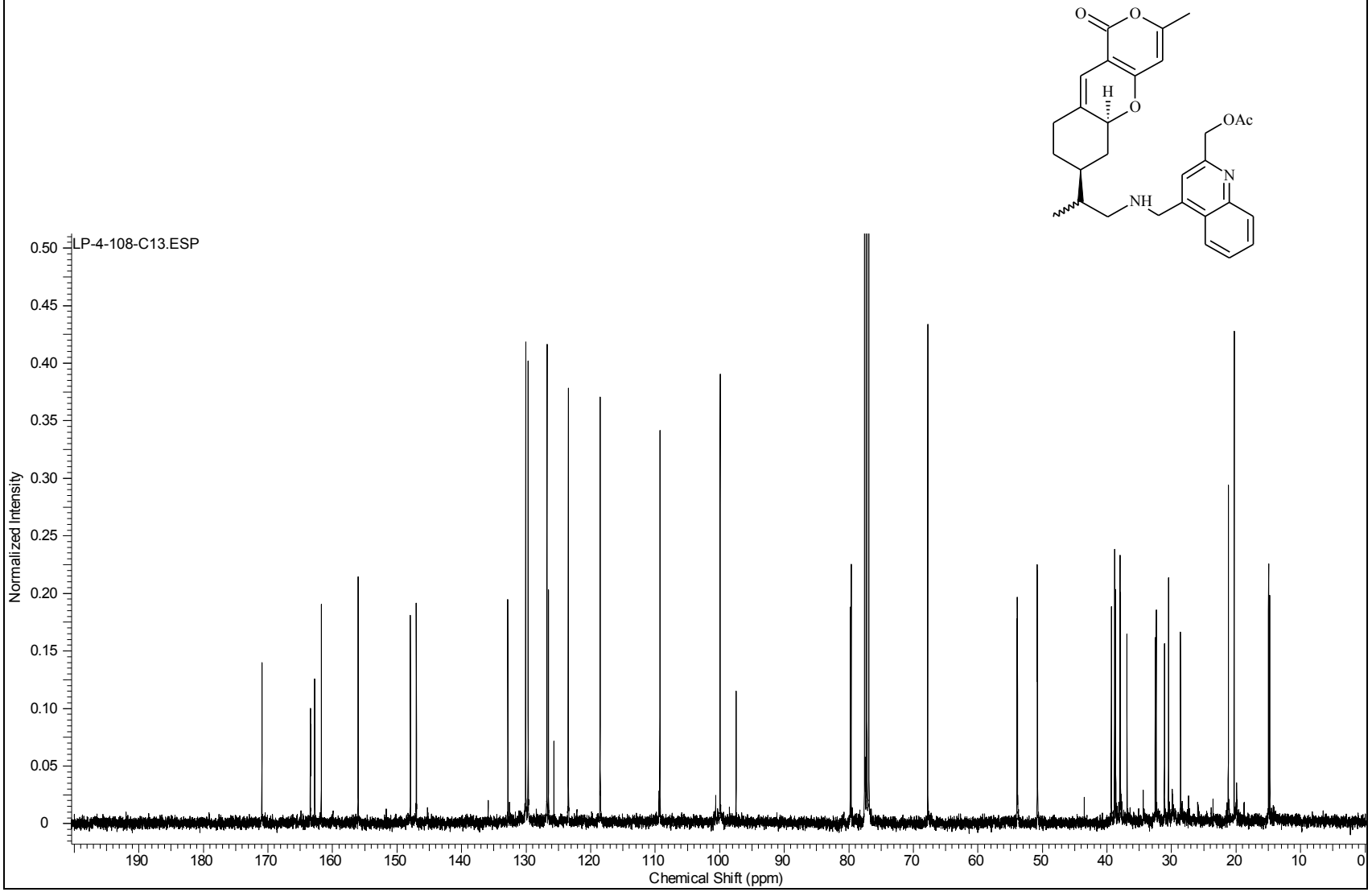
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Oct 5 2010
Date Stamp	Oct 5 2010	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-4-120-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	22992	***Original Points Count***	31413
Points Count	65536	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10552.6035	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



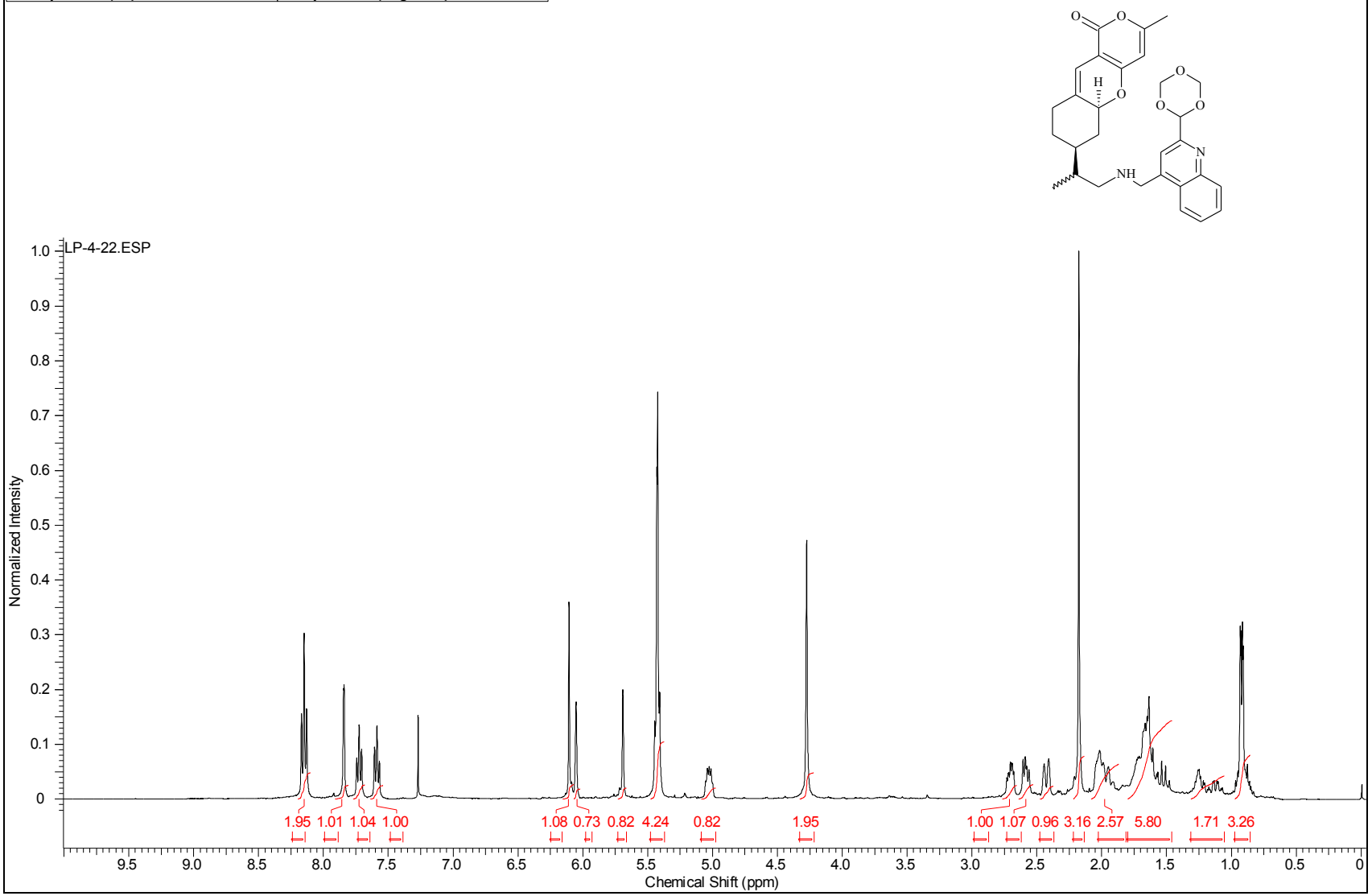
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Oct 1 2010	***Date Stamp***	Oct 1 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-108FR2.FID\FID						
Frequency (MHz)	399.74	***Nucleus***	1H	***Number of Transients***	32	***Original Points Count***	13103
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	32.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2416.7397	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	25.000



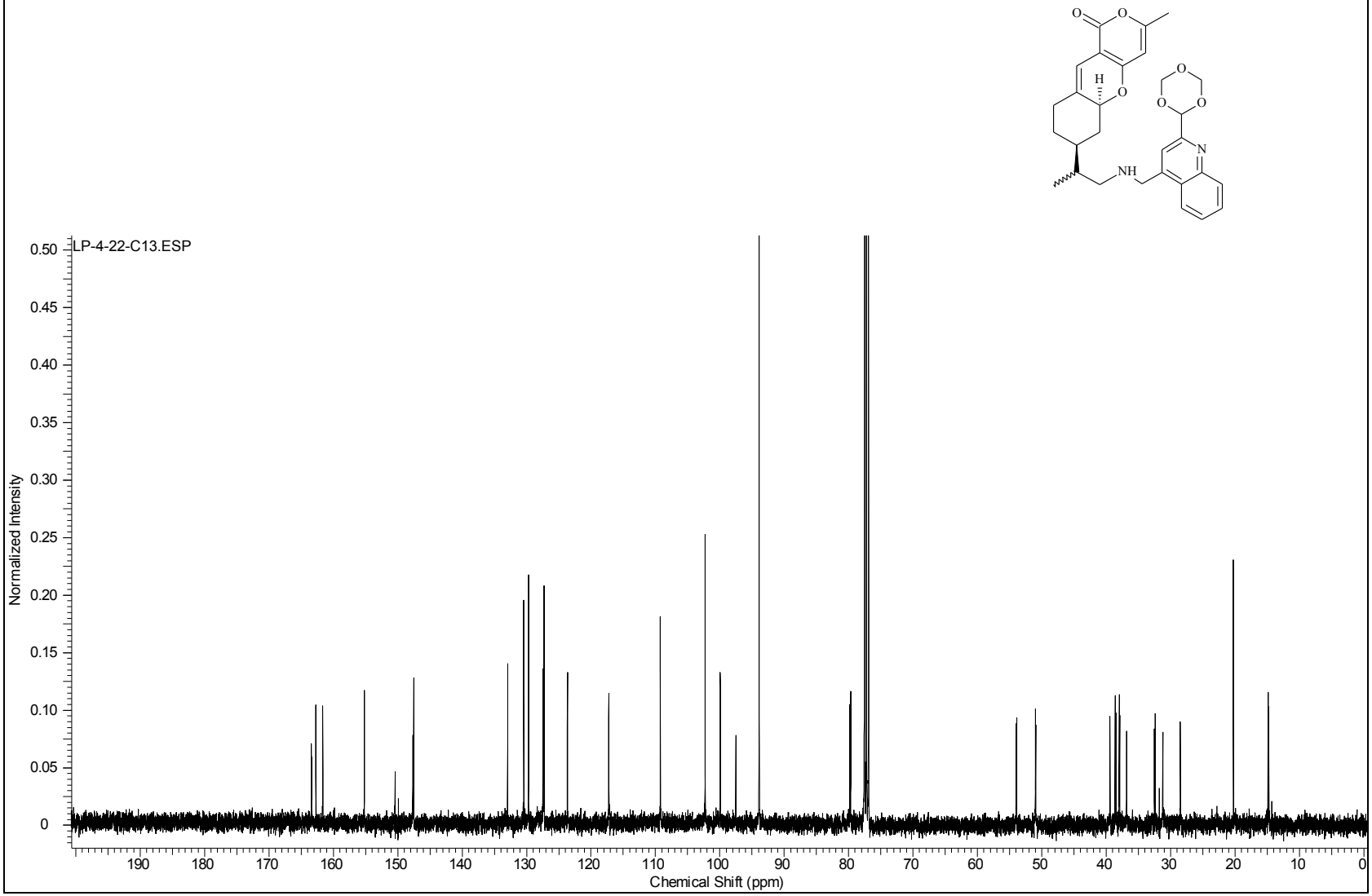
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Oct 1 2010	***Date Stamp***	Oct 1 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-108FR1-C13.FID\FID						
Frequency (MHz)	100.52	***Nucleus***	13C	***Number of Transients***	20000	***Original Points Count***	31375
Points Count	65536	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10550.8076	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	25.000



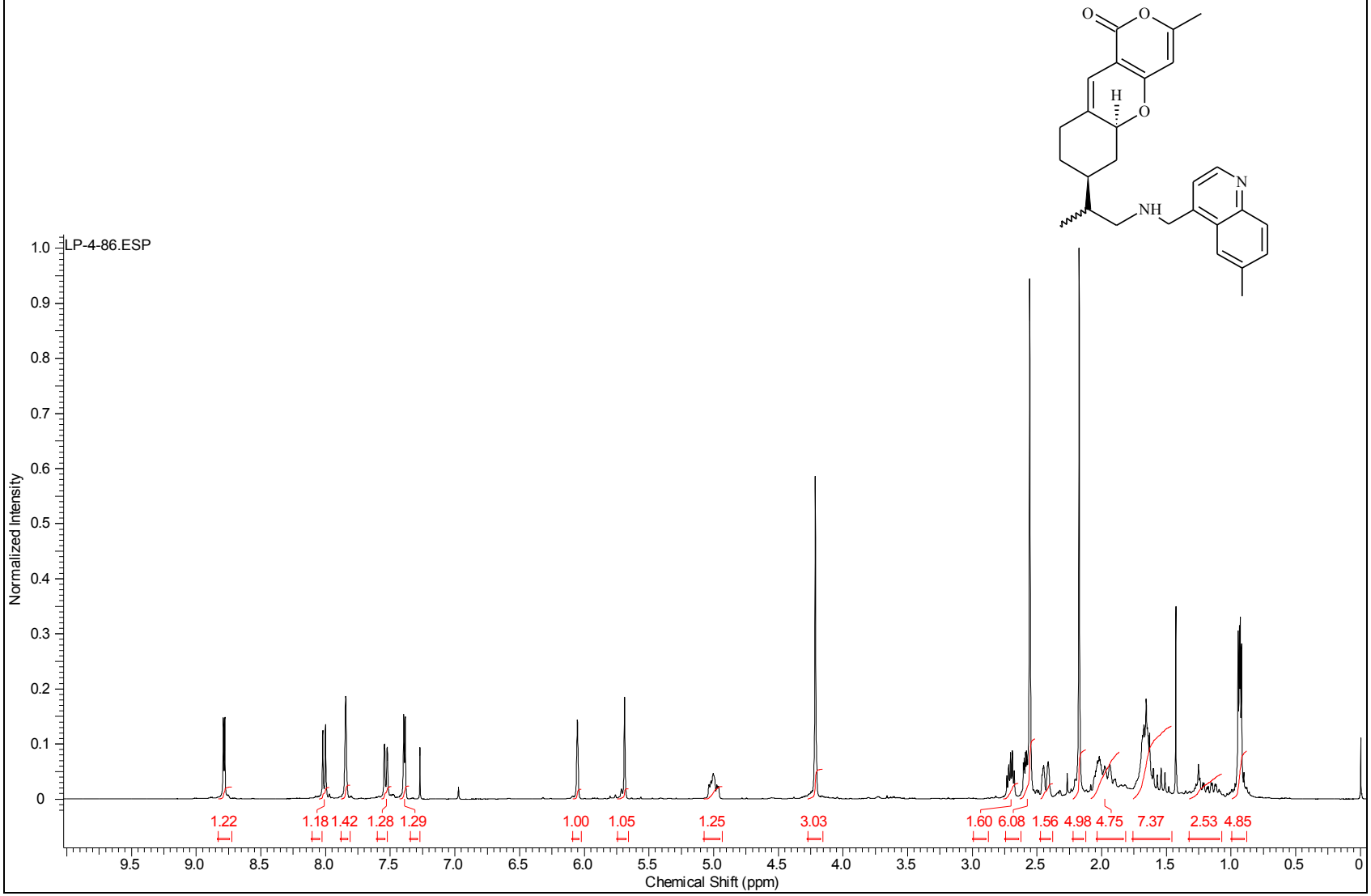
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Jun 15 2011			***Date Stamp***	Jun 15 2011
File Name	F:\LAXMAN POKHREL\LP-4-22.FID\FID			***Frequency (MHz)***	399.73	***Nucleus***	1H	***Number of Transients***	32
Original Points Count	13102	***Points Count***	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	34.00		
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	2414.6738	***Spectrum Type***	STANDARD		
Sweep Width (Hz)	6395.40	***Temperature (degree C)***	25.000						



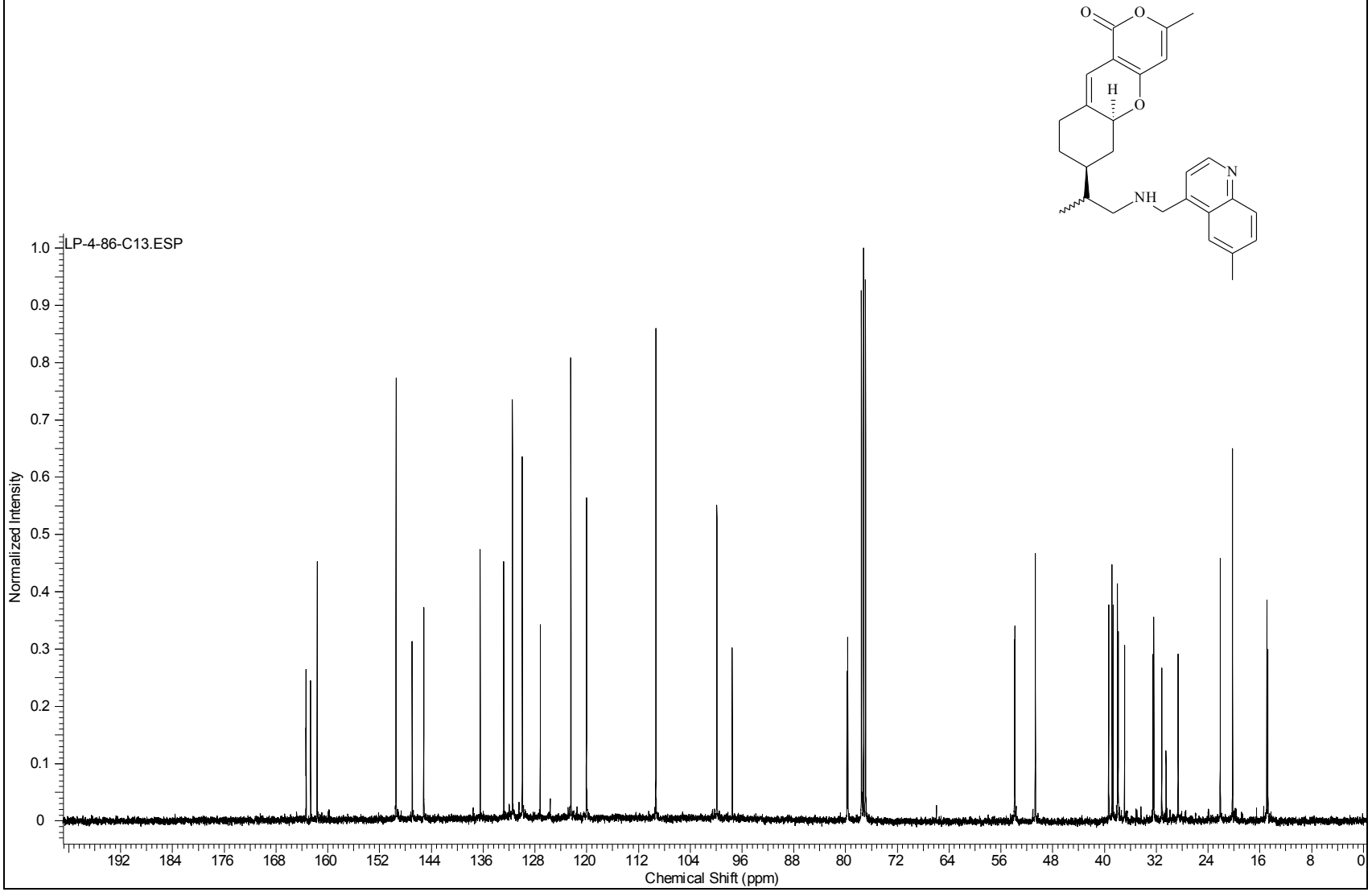
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Jun 15 2011	***Date Stamp***	Jun 15 2011
File Name	F:\LAXMAN POKHREL\LP-4-22-C13.FID\FID			***Frequency (MHz)***	100.52	***Nucleus***	13C
Number of Transients	2396	***Original Points Count***	31375	***Points Count***	65536	***Pulse Sequence***	s2pul
Receiver Gain	30.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	10551.7217
Spectrum Type	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	25.000		



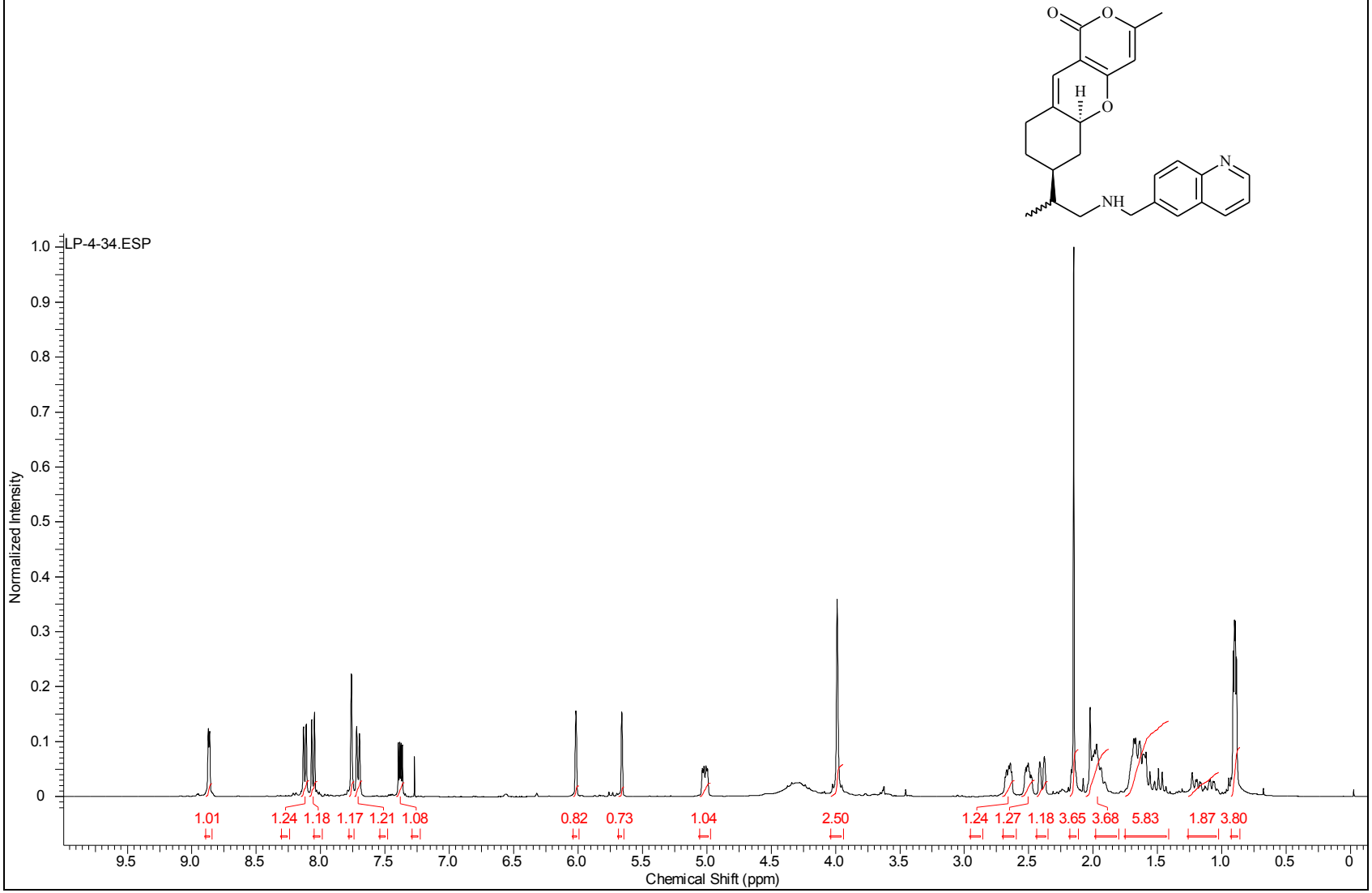
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Aug 21 2010	***Date Stamp***	Aug 21 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-86FR2.FID\FID						
Frequency (MHz)	399.74	***Nucleus***	1H	***Number of Transients***	100	***Original Points Count***	13103
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	26.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2417.5210	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	30.000



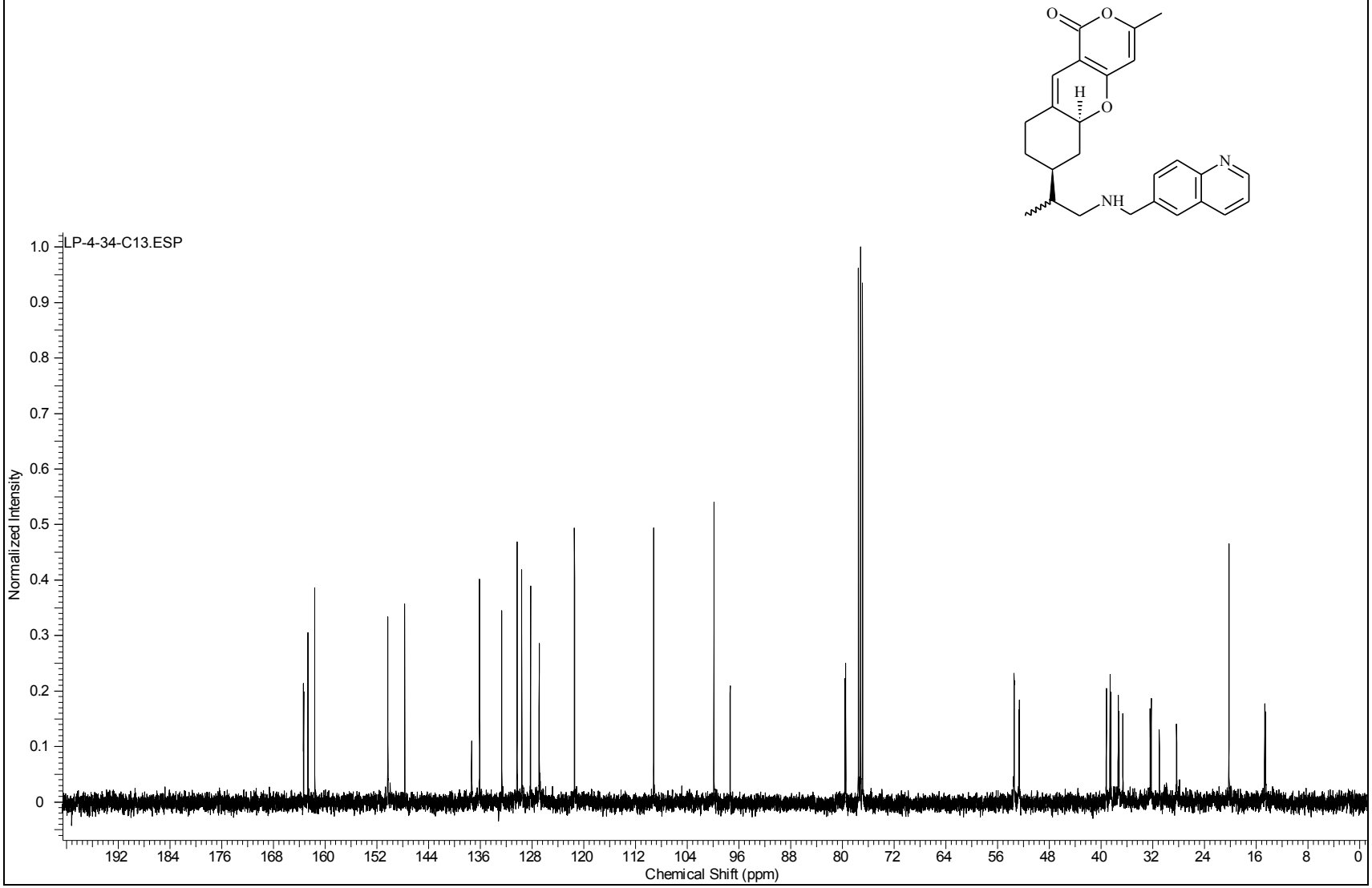
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Aug 21 2010	***Date Stamp***	Aug 21 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-86-C13.FID\FID						
Frequency (MHz)	100.52	***Nucleus***	13C	***Number of Transients***	20912	***Original Points Count***	31375
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10552.1377	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	30.000



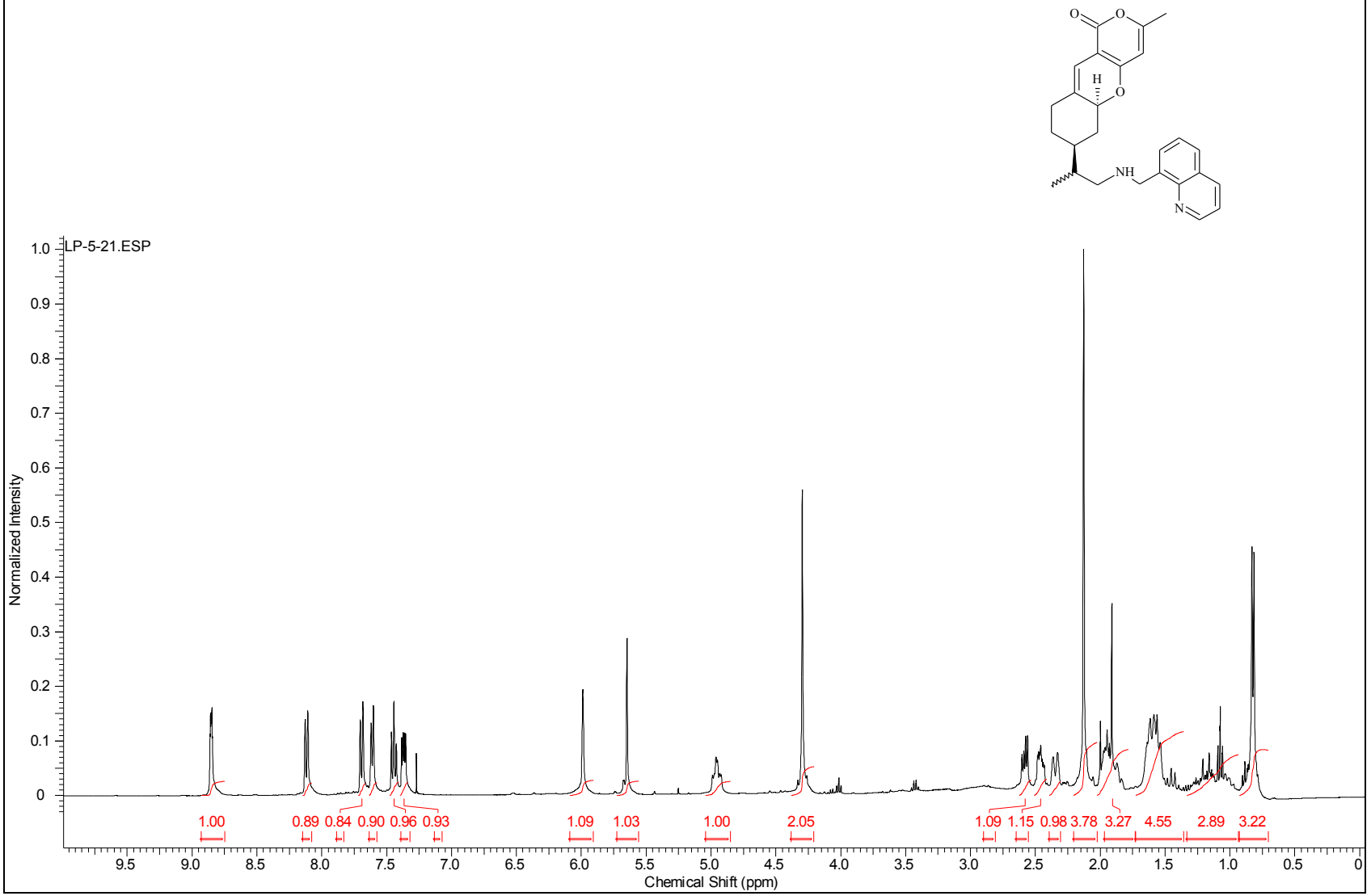
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	May 25 2010	***Date Stamp***	May 25 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-34.FID\FID						
Frequency (MHz)	399.74	***Nucleus***	1H	***Number of Transients***	44	***Original Points Count***	13103
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	26.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2416.7397	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	40.000



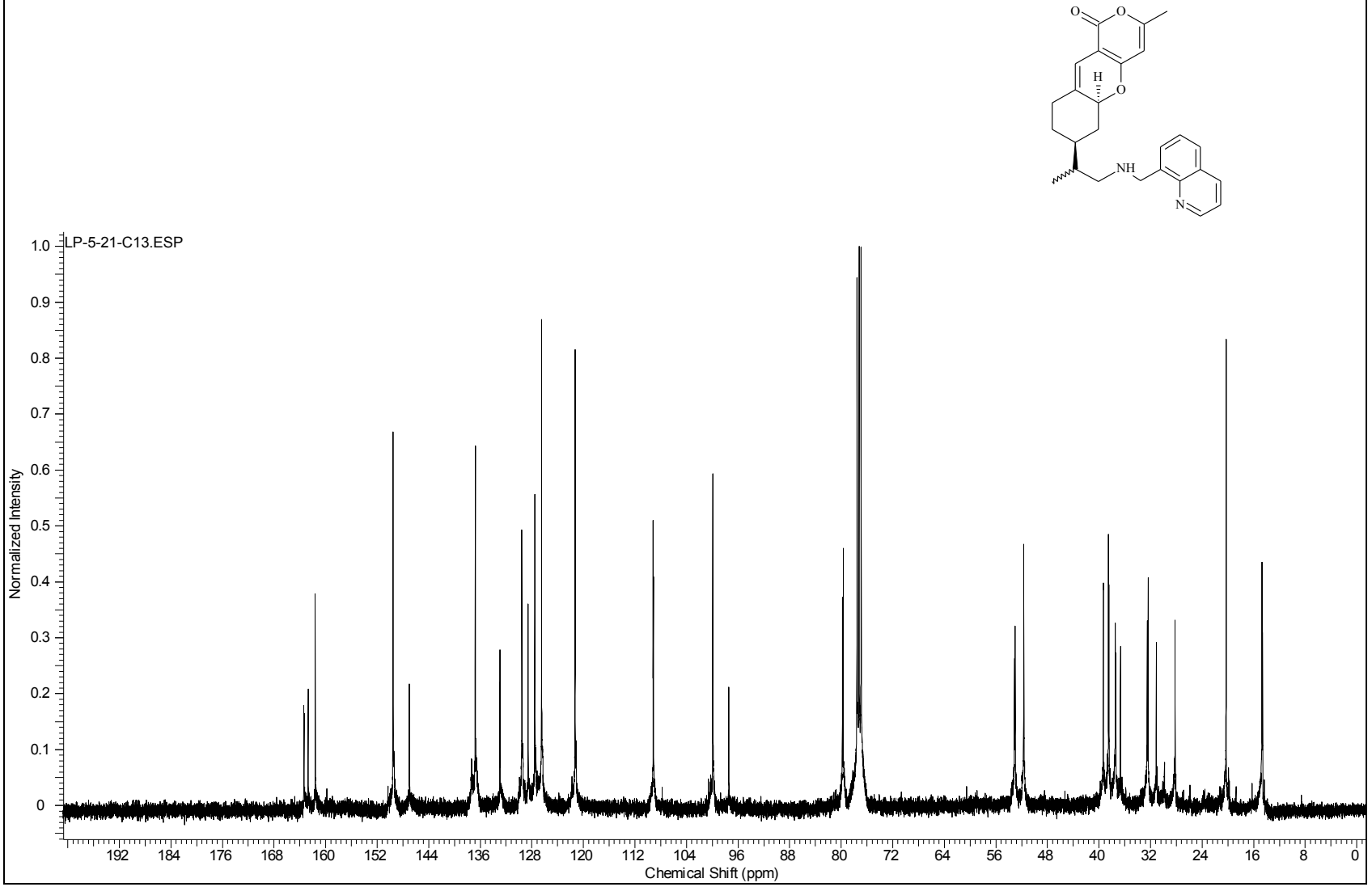
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	May 25 2010	***Date Stamp***	May 25 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-34C13.FID\FID						
Frequency (MHz)	100.52	***Nucleus***	13C	***Number of Transients***	1816	***Original Points Count***	31375
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10547.7207	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	40.000



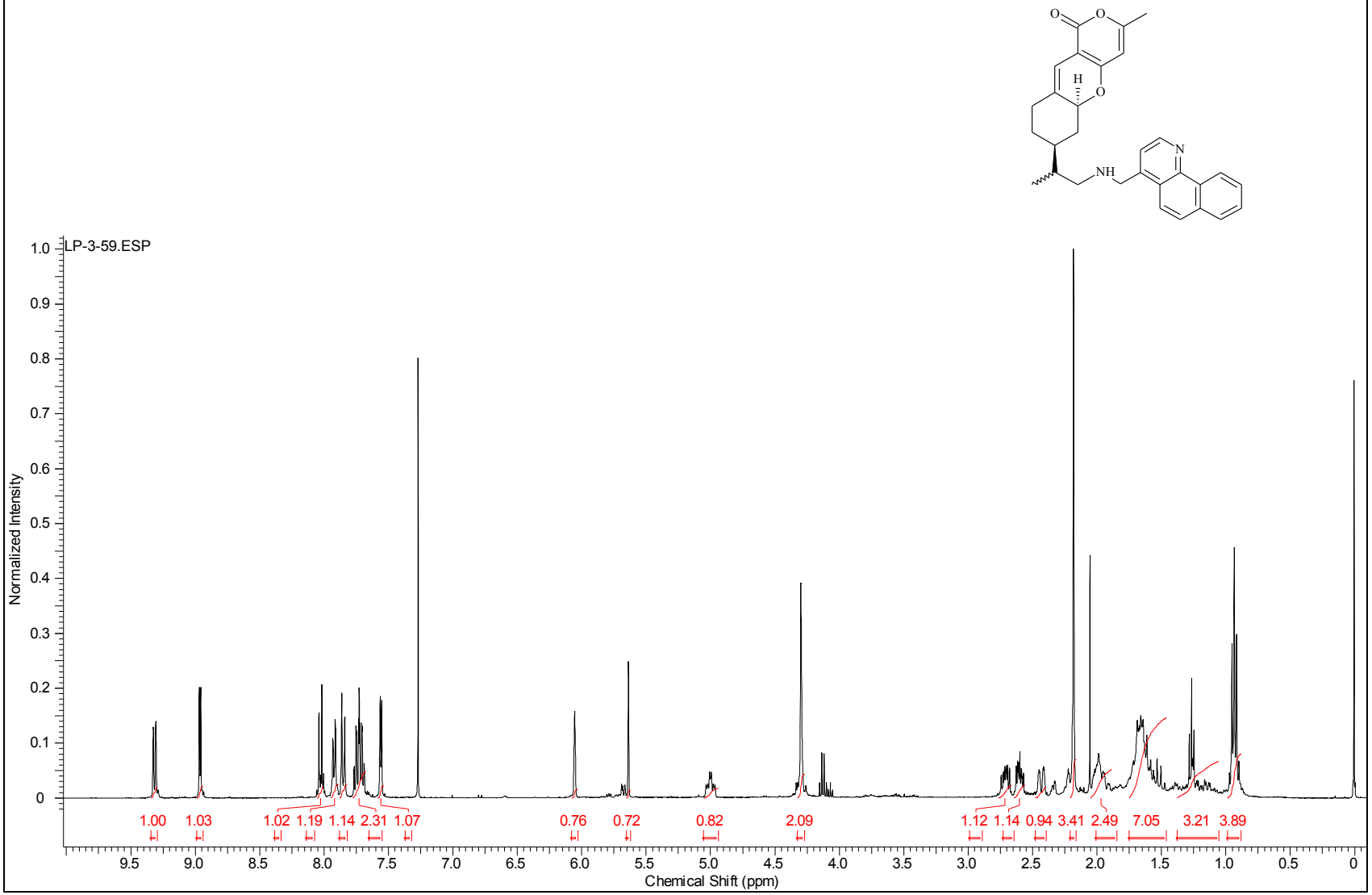
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Jan 21 2011	***Date Stamp***	Jan 21 2011
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-5-11.FID\FID						
Frequency (MHz)	399.73	***Nucleus***	1H	***Number of Transients***	56	***Original Points Count***	13102
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	24.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2414.7561	***Sweep Width (Hz)***	6395.40	***Temperature (degree C)***	25.000		



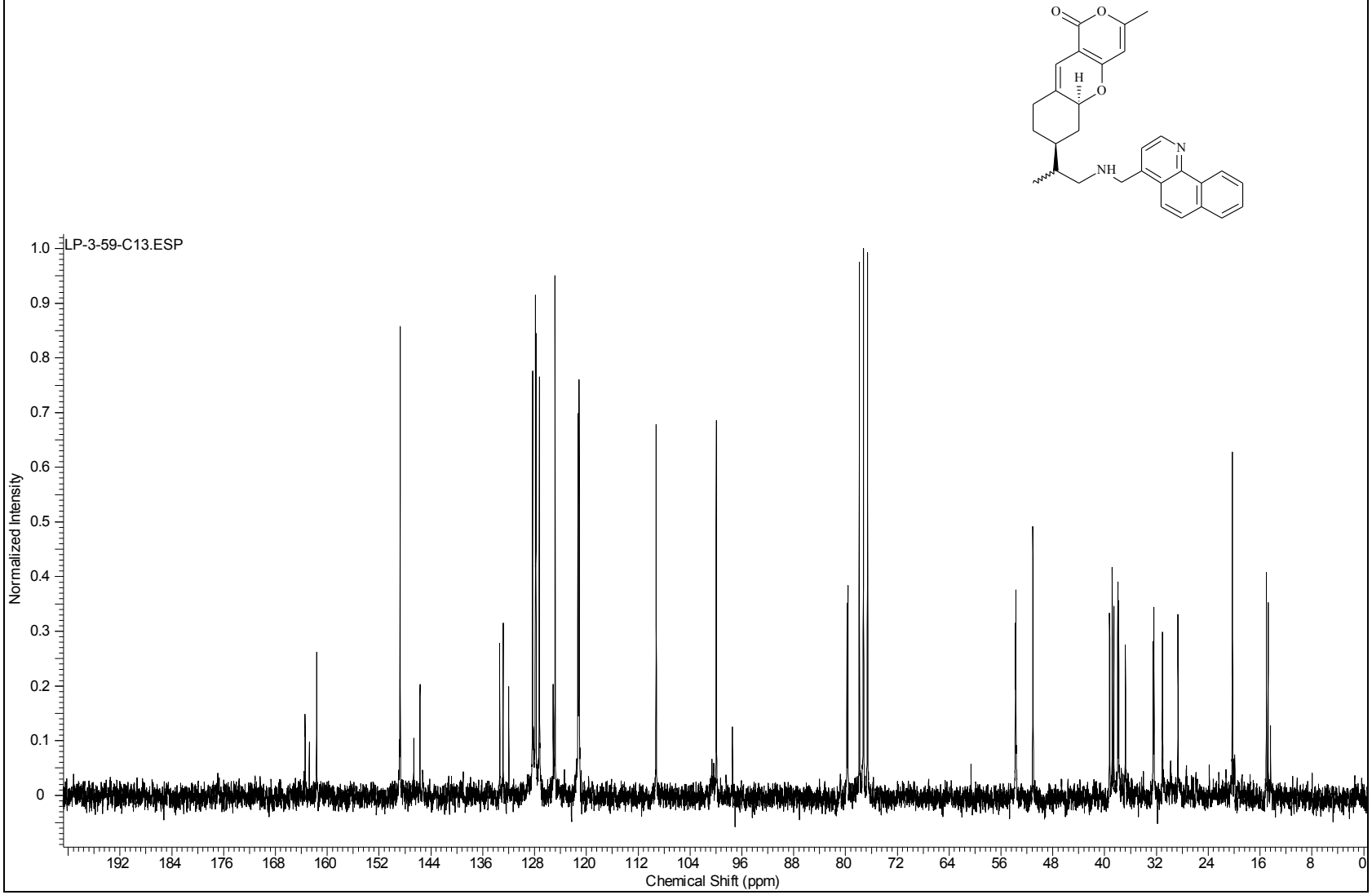
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jan 22 2011
Date Stamp	Jan 22 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-11C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	25900	***Original Points Count***	31413
Points Count	65536	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10552.6035	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



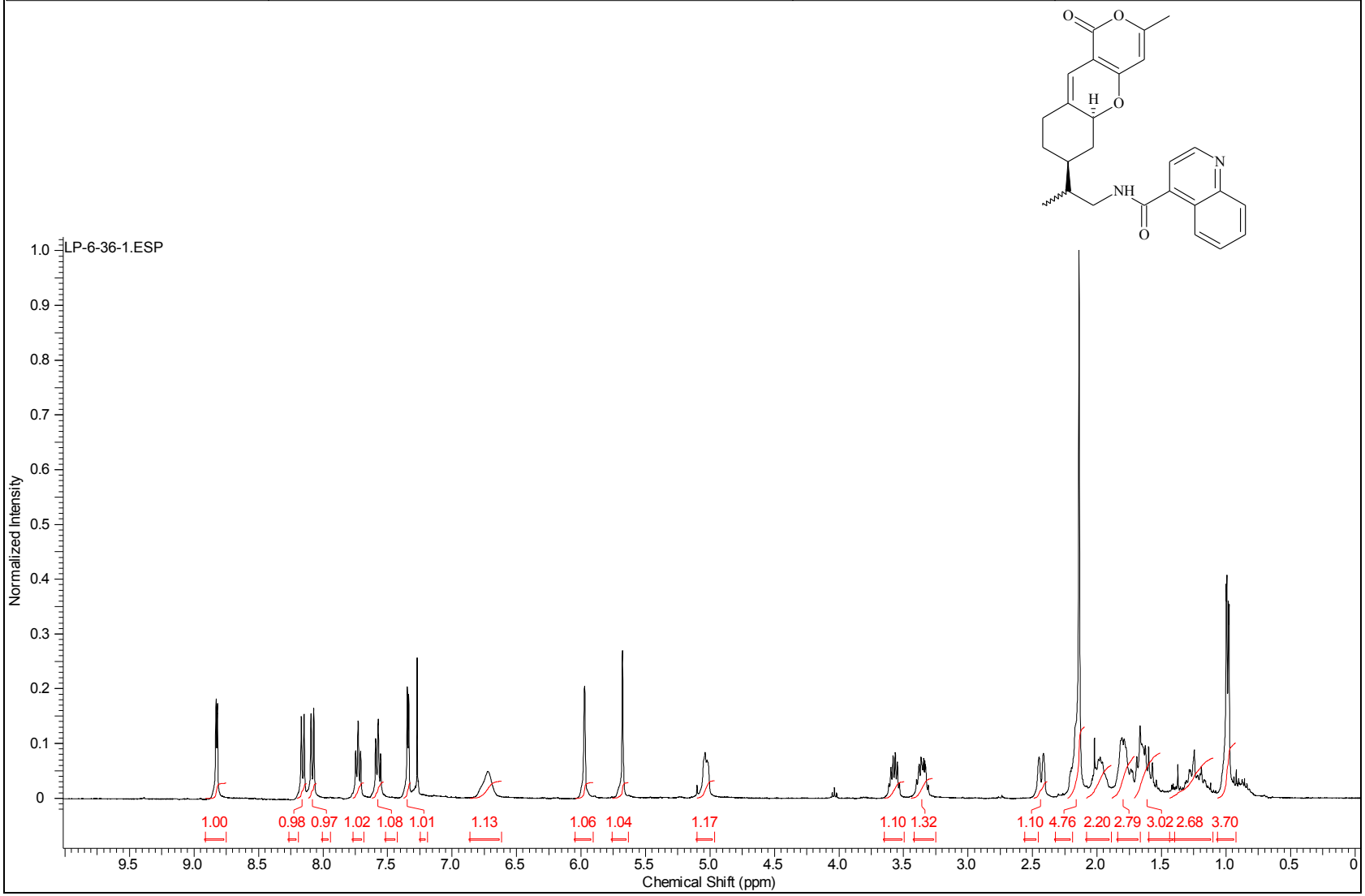
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Jan 14 2010	***Date Stamp***	Jan 14 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\400 MHZ\LP-3-59COL2FR1.FID\FID					***Frequency (MHz)***	399.74
Nucleus	1H	***Number of Transients***	44	***Original Points Count***	13103	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	48.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2416.7397	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	30.000



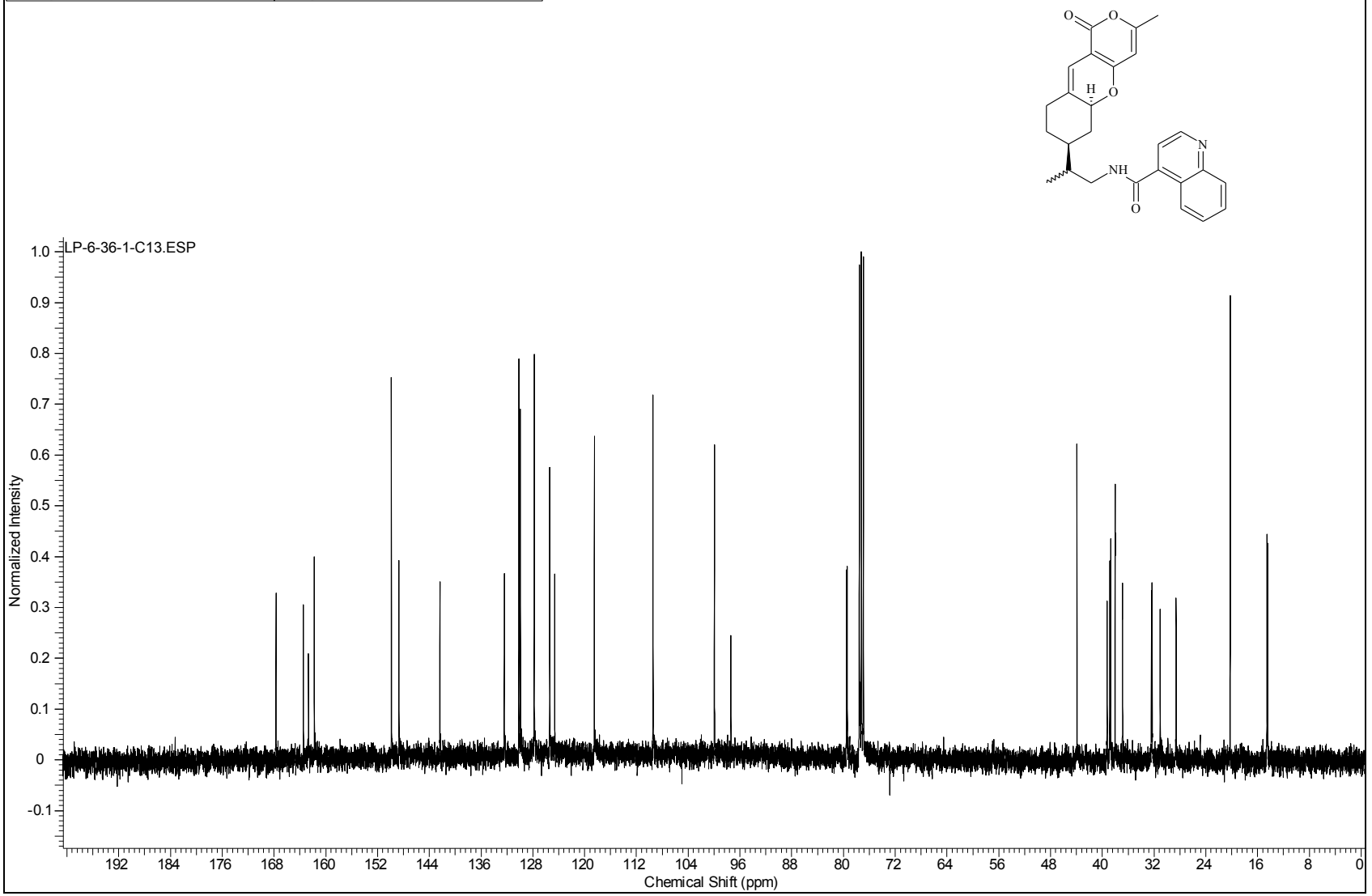
Acquisition Time (sec)	1.4976	***Comment***	13C OBSERVE	***Date***	Jan 14 2010	***Date Stamp***	Jan 14 2010
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\200MHZ\LP-3-59C13.FID\FID					***Frequency (MHz)***	50.29
Nucleus	13C	***Number of Transients***	5004	***Original Points Count***	18720	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	40.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	4878.9346	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	12500.00	***Temperature (degree C)***	AMBIENT TEMPERATURE



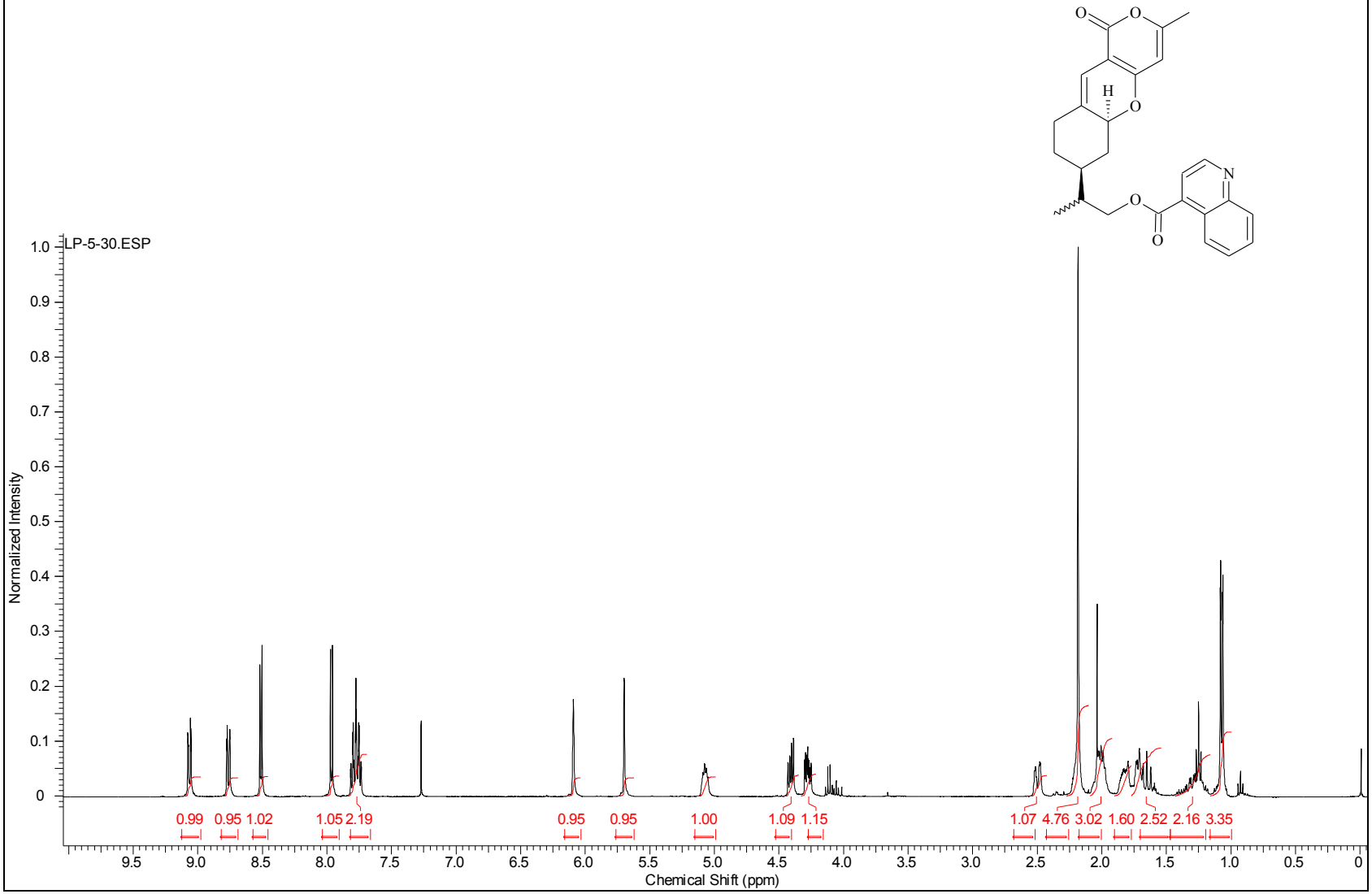
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Dec 30 2011			***Date Stamp***	Dec 30 2011
File Name	F:\LP-6-36FR1.FID\FID			***Frequency (MHz)***	399.72	***Nucleus***	1H	***Number of Transients***	16
Original Points Count	13102	***Points Count***	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	42.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2407.6953	***Spectrum Type***	STANDARD			***Sweep Width (Hz)***	6395.40	***Temperature (degree C)***	25.000



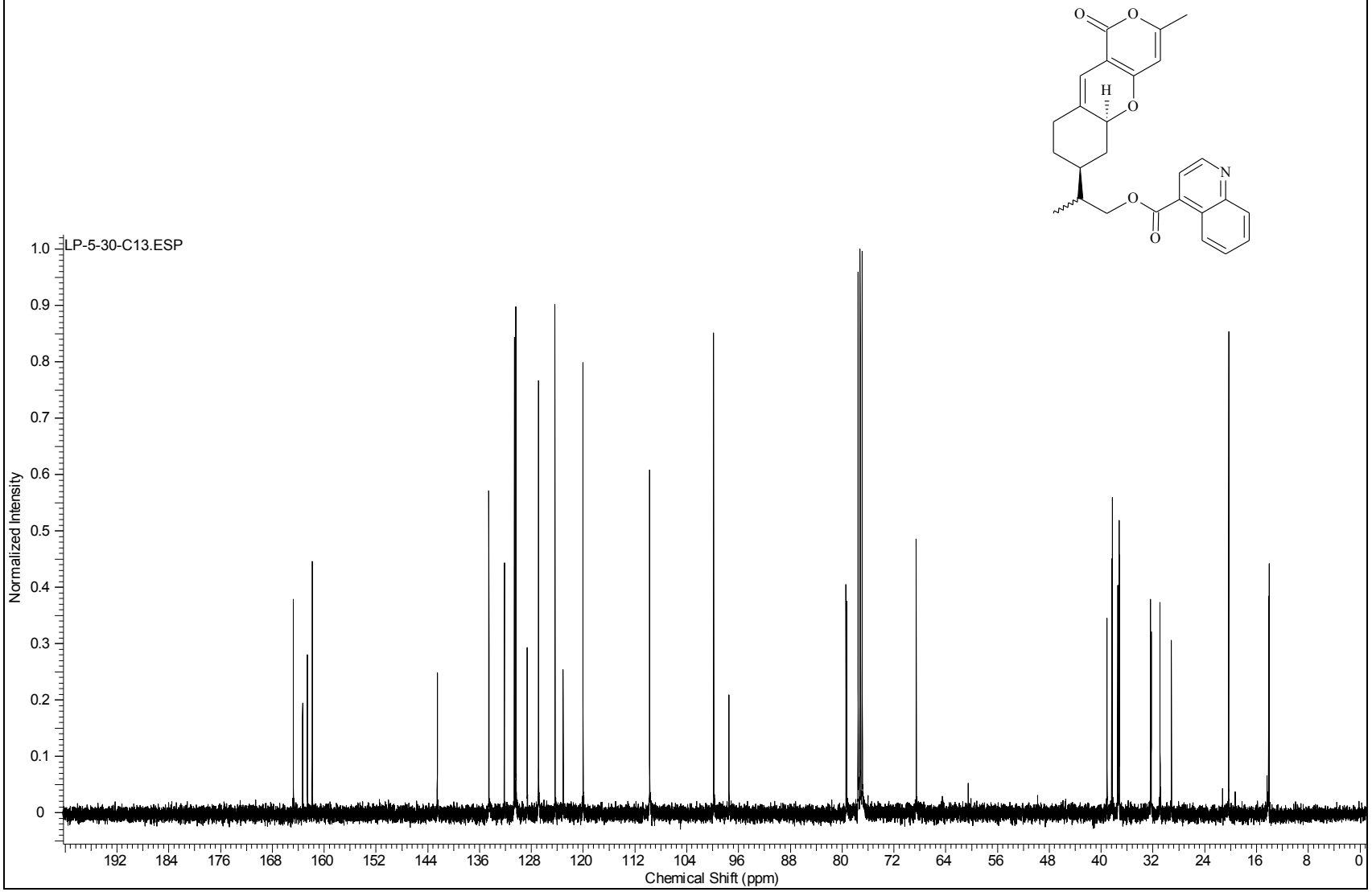
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Dec 30 2011			***Date Stamp***	Dec 30 2011
File Name	F:\LP-6-36FR1-C13.FID\FID			***Frequency (MHz)***	100.52	***Nucleus***	13C	***Number of Transients***	2088
Original Points Count	31375	***Points Count***	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00		
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	10549.6133	***Spectrum Type***	STANDARD		
Sweep Width (Hz)	24125.45	***Temperature (degree C)***	25.000						



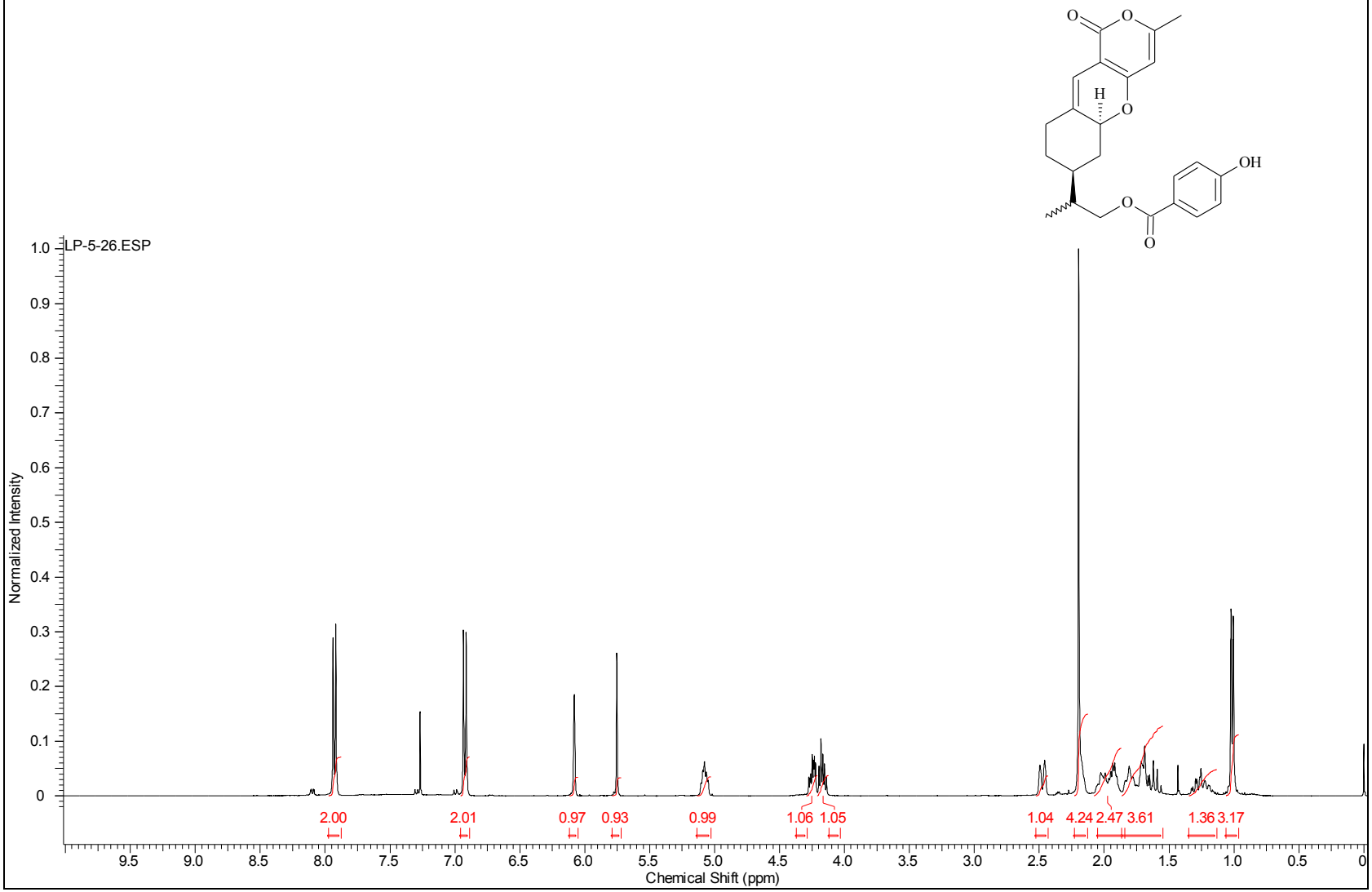
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Feb 7 2011
Date Stamp	Feb 7 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-30.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	100	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	22.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2403.7539	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



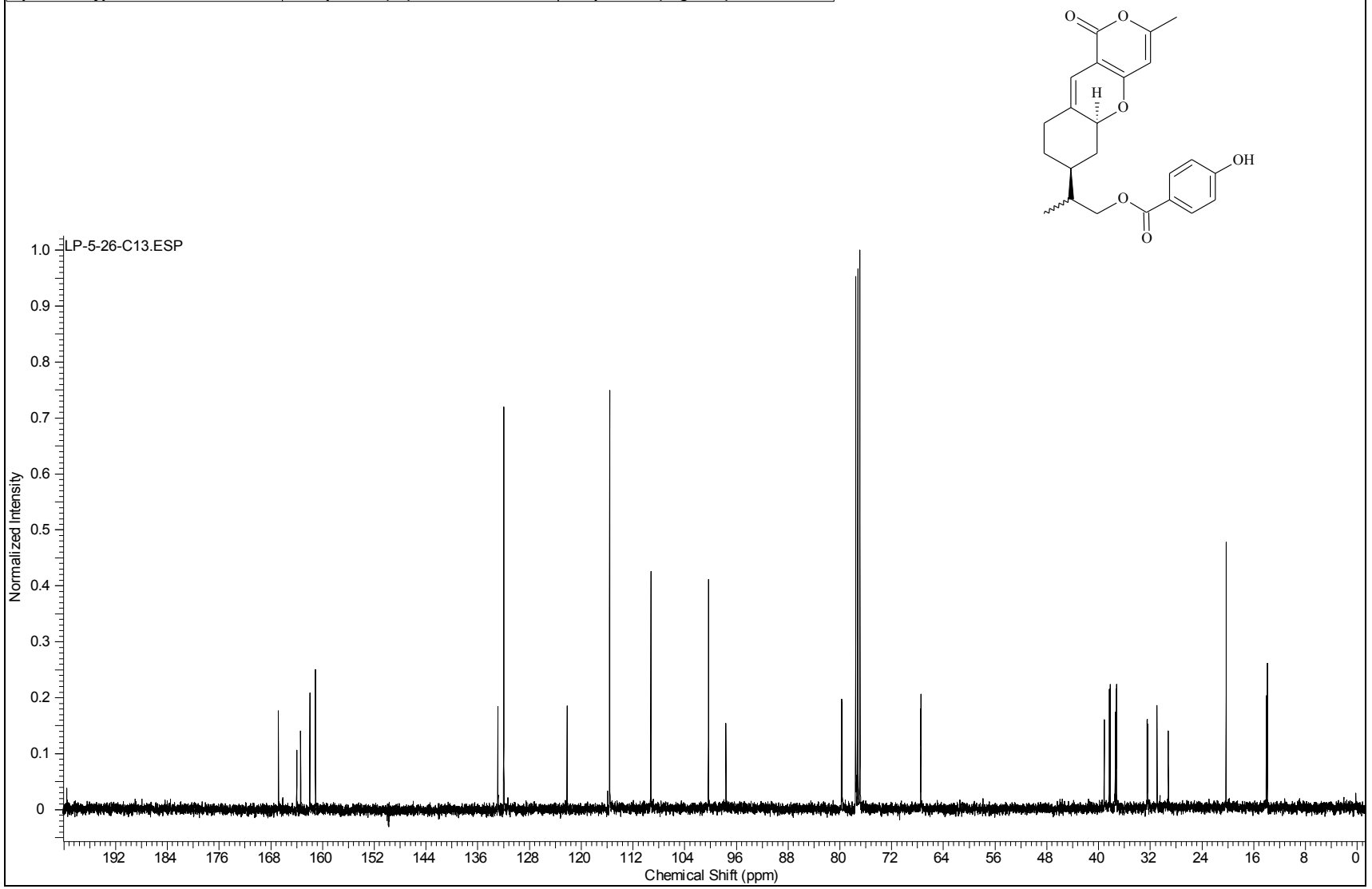
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Feb 7 2011
Date Stamp	Feb 7 2011	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN-MERCURY04-15-11\LPOKHREL\LP-5-30-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	3820	***Original Points Count***	31413
Points Count	65536	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10555.9209	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000		



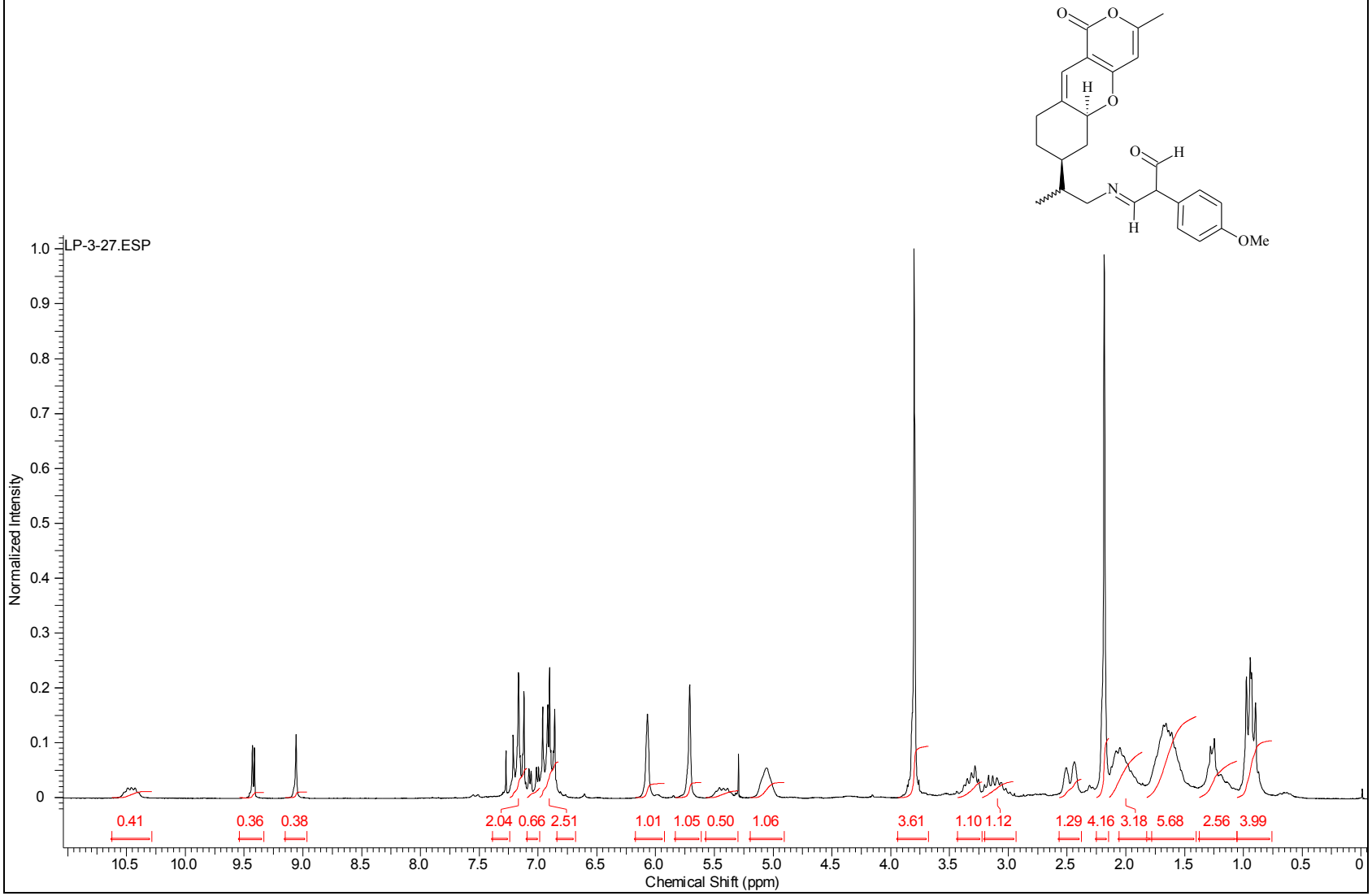
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Jun 14 2011			***Date Stamp***	Jun 14 2011
File Name	F:\LAXMAN POKHREL\LP-5-26.FID\FID			***Frequency (MHz)***	399.73	***Nucleus***	1H	***Number of Transients***	28
Original Points Count	13102	***Points Count***	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	10.00		
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	2413.4968	***Spectrum Type***	STANDARD		
Sweep Width (Hz)	6395.40	***Temperature (degree C)***	25.000						



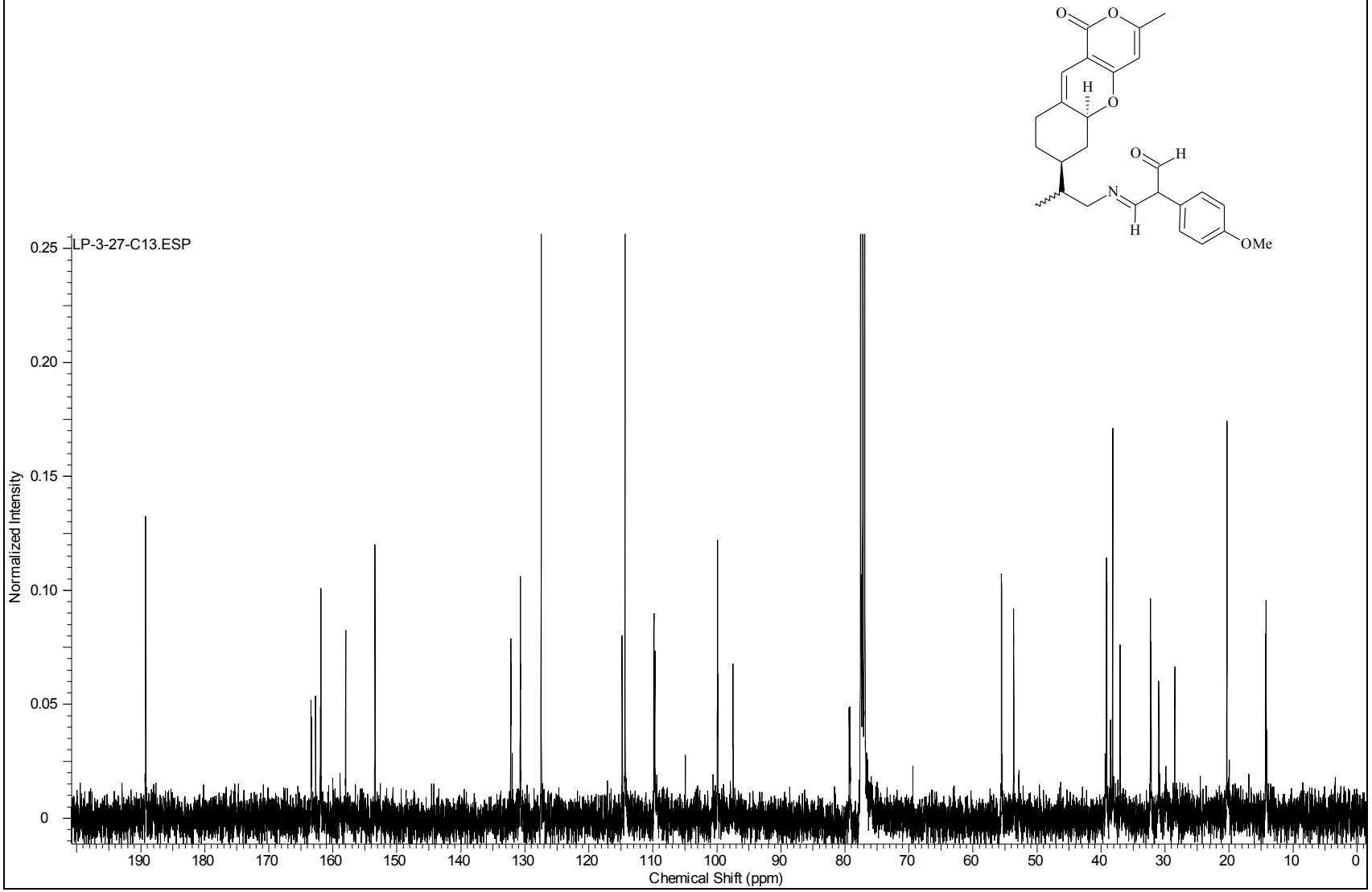
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Jun 14 2011	***Date Stamp***	Jun 14 2011
File Name	F:\LAXMAN POKHREL\LP-5-26-C13.FID\FID			***Frequency (MHz)***	100.52	***Nucleus***	13C
Number of Transients	5776	***Original Points Count***	31375	***Points Count***	32768	***Pulse Sequence***	s2pul
Receiver Gain	30.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	10554.1582
Spectrum Type	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	25.000		



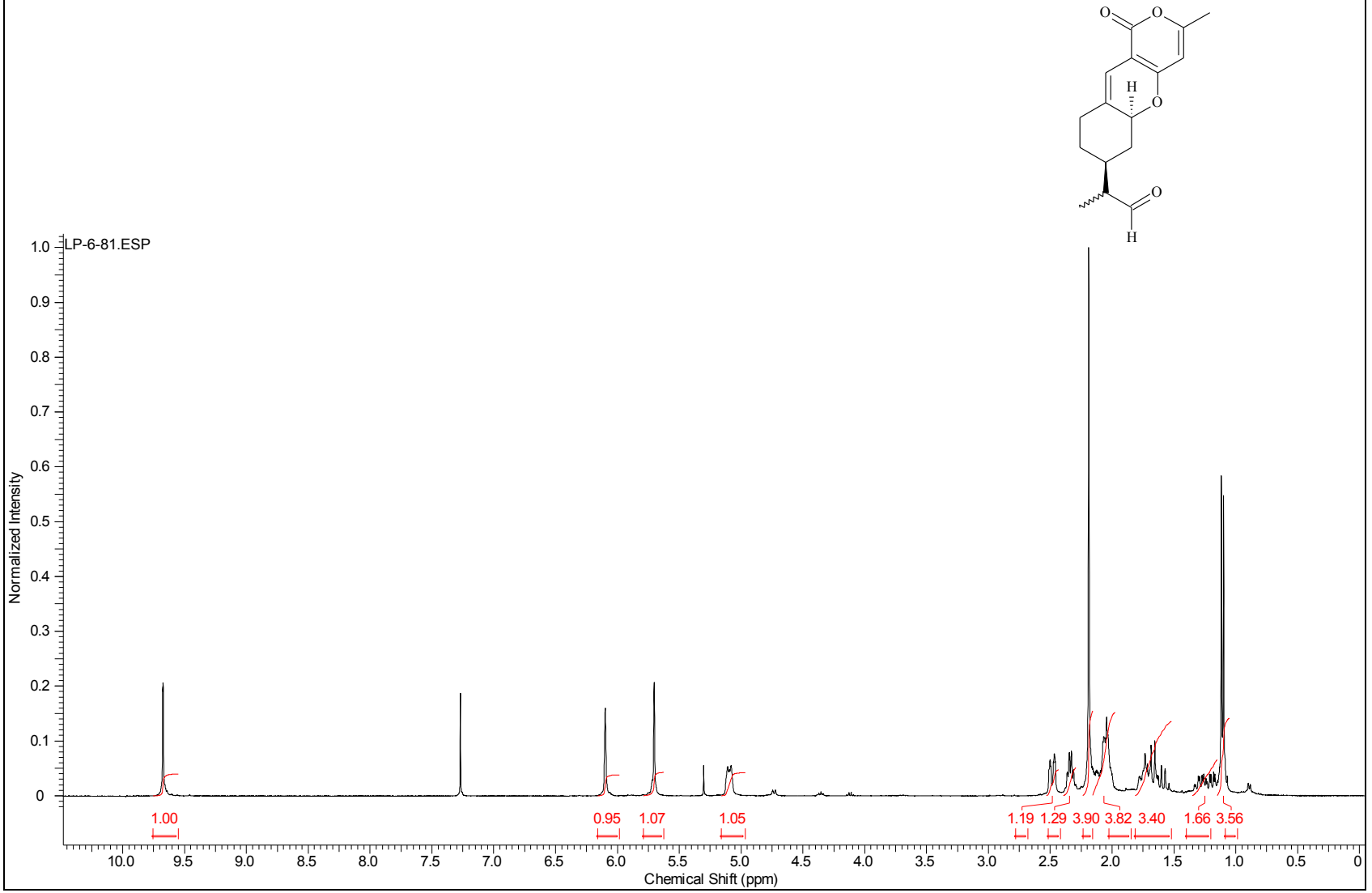
Acquisition Time (sec)	1.9945	***Comment***	STANDARD 1H OBSERVE			***Date***	Nov 15 2009
Date Stamp	Nov 15 2009	***File Name***	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\200MHZ\LP-3-27FR18-19.FID\FID				
Frequency (MHz)	199.98	***Nucleus***	1H	***Number of Transients***	76	***Original Points Count***	5984
Points Count	8192	***Pulse Sequence***	s2pul	***Receiver Gain***	22.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	1003.4805	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	3000.30	***Temperature (degree C)***	AMBIENT TEMPERATURE



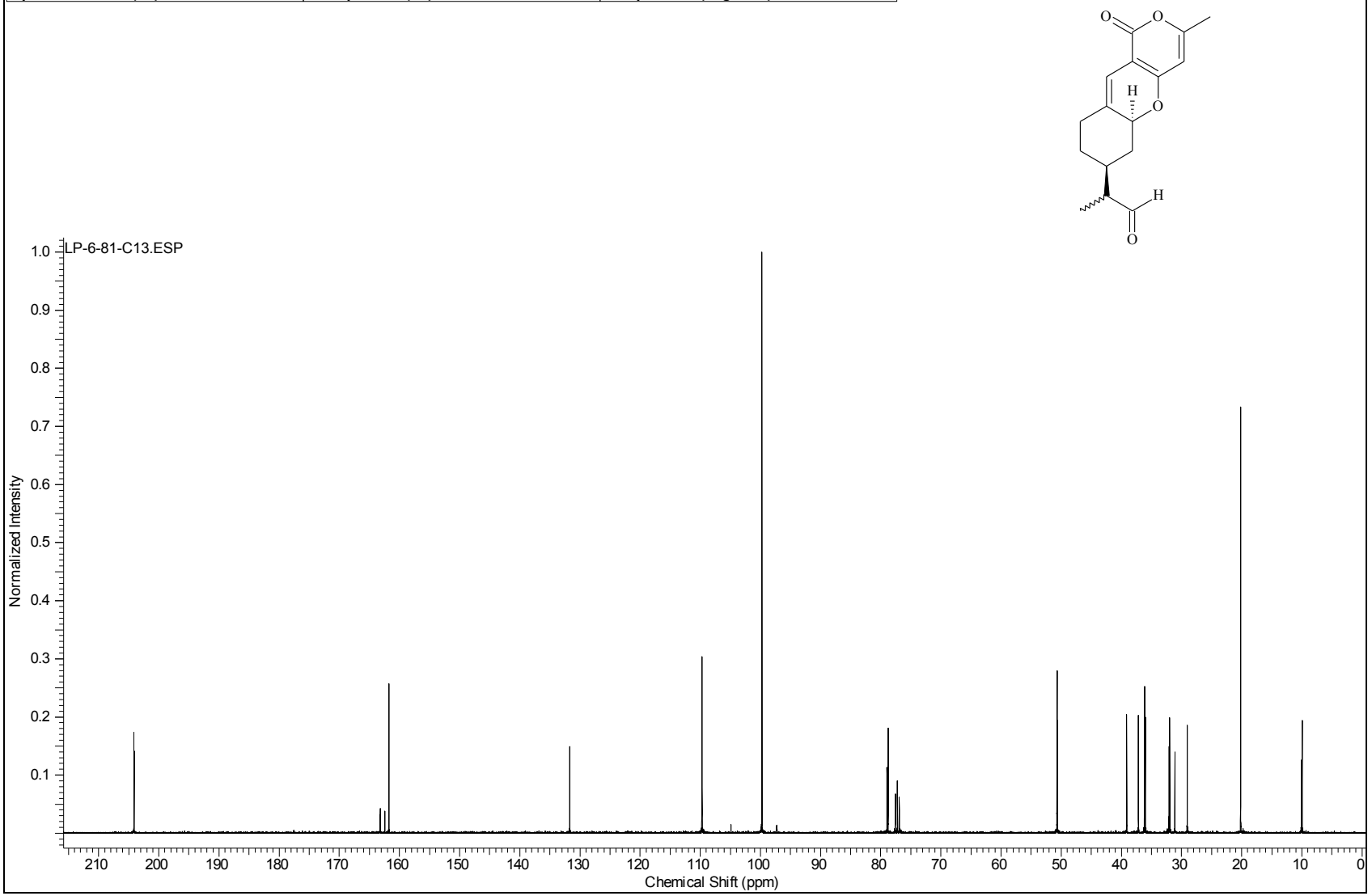
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Dec 4 2009	***Date Stamp***	Dec 4 2009
File Name	C:\USERS\LAXMAN\DESKTOP\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-3-27C13.FID\FID						
Frequency (MHz)	100.53	***Nucleus***	13C	***Number of Transients***	6504	***Original Points Count***	31375
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10549.3828	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	25.000



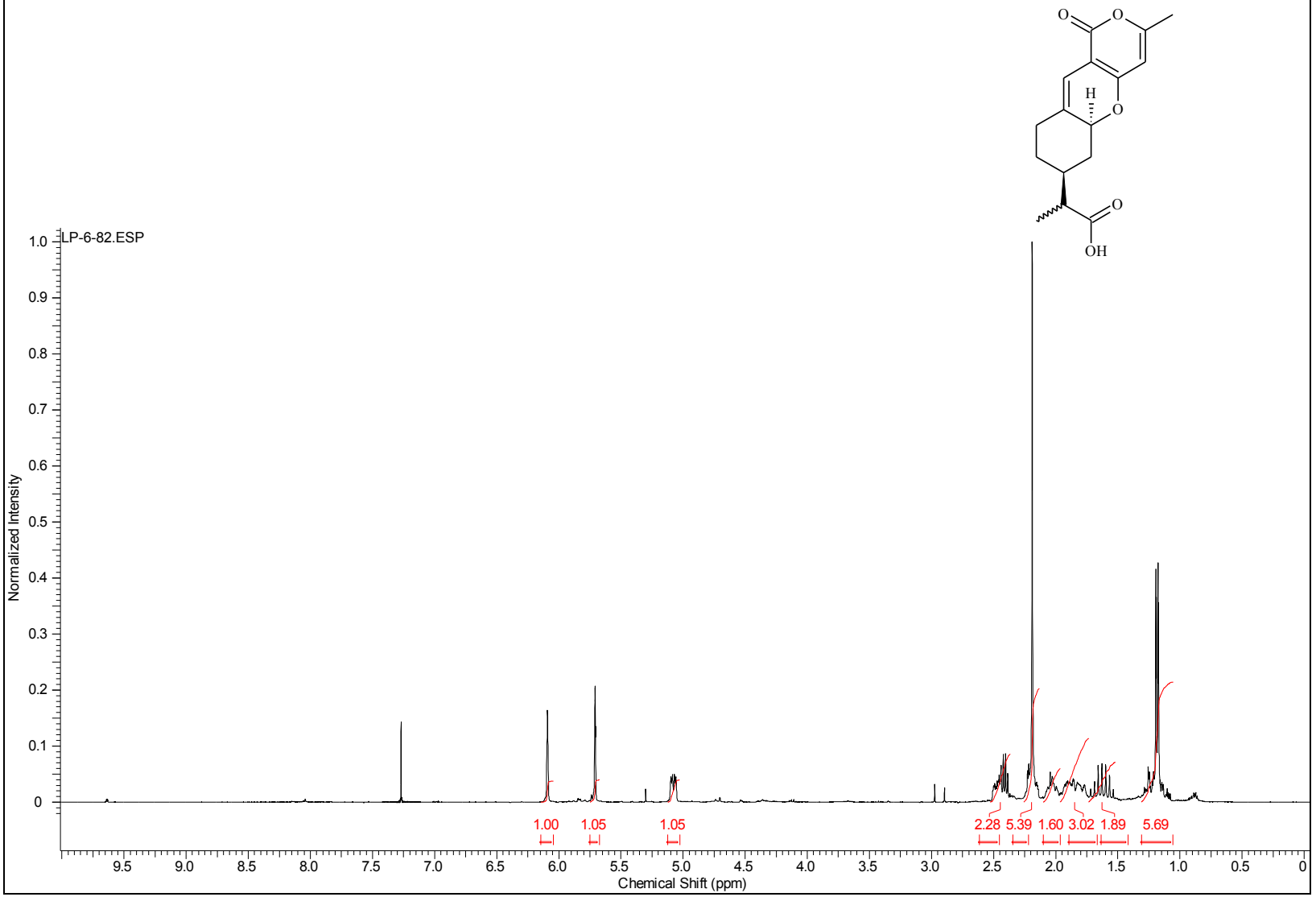
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Mar 19 2012	***Date Stamp***	Mar 19 2012
File Name	C:\USERS\LAXMAN\DESKTOP\INOVA-03-27-2013\MARCH\LP-6-81.FID\FID					***Frequency (MHz)***	399.72
Nucleus	1H	***Number of Transients***	48	***Original Points Count***	13102	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	44.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2407.6824	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.40	***Temperature (degree C)***	25.000



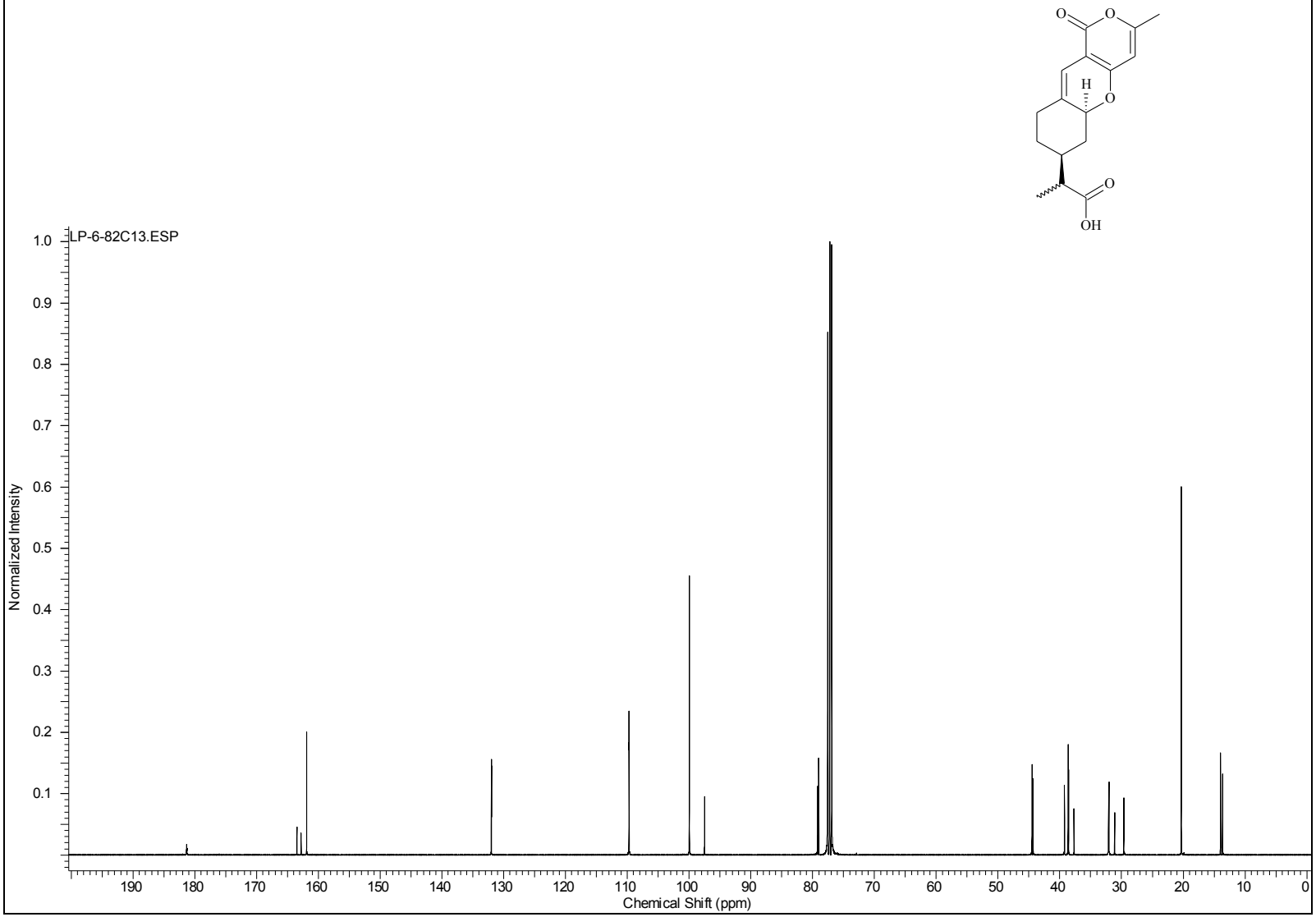
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Mar 19 2012
Date Stamp	Mar 19 2012	***File Name***	E:\LAXMAN POKHREL-NMRS\LP-NMR-02-15-2013-MERCURY\LP-6-81-C13				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	500	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10546.5645	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	20.000		



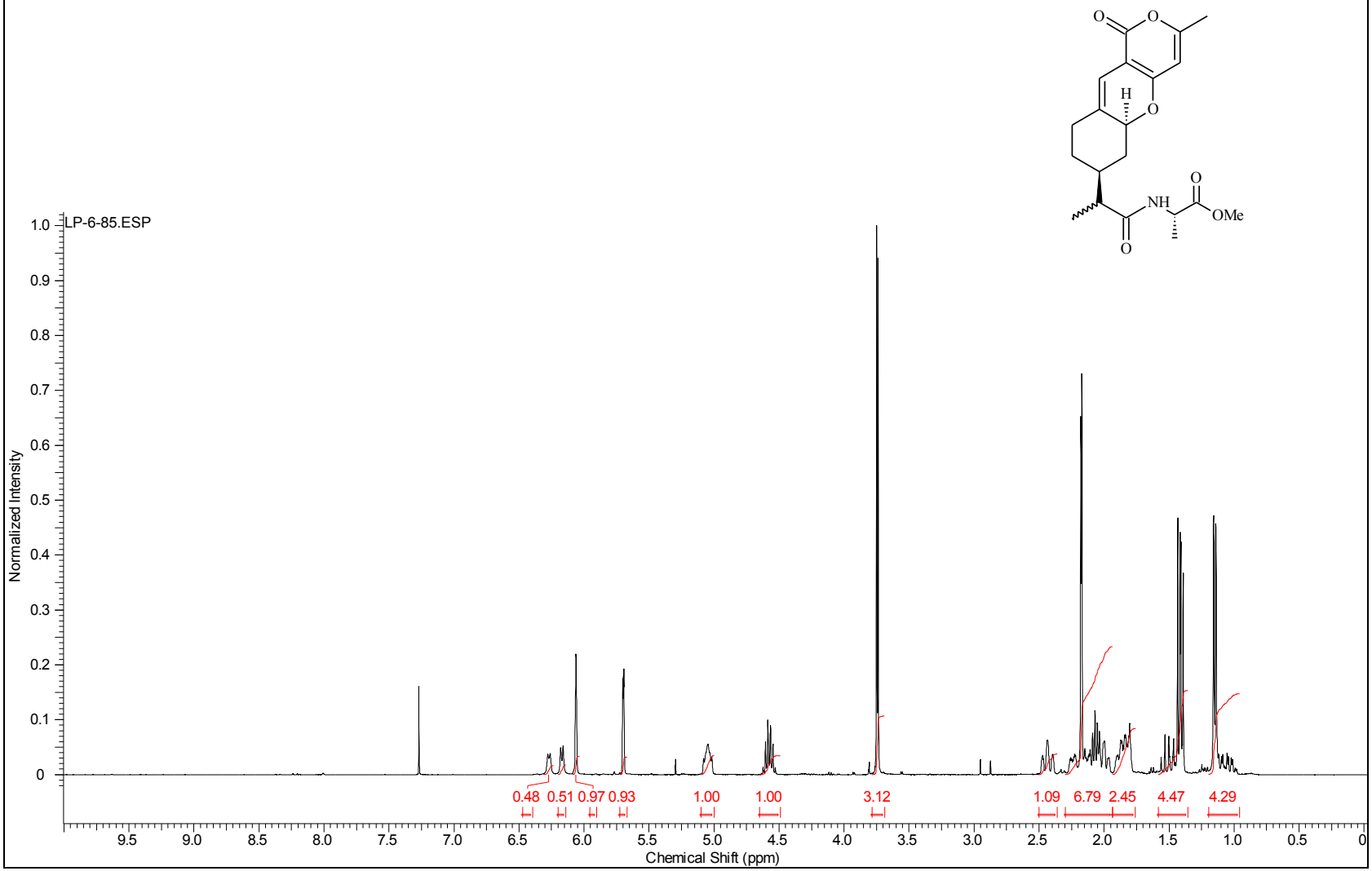
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Mar 21 2012	***Date Stamp***	Mar 21 2012
File Name	C:\USERS\LAXMAN\DESKTOP\INOVA-03-27-2013\MARCH\LP-6-82.FID\FID					***Frequency (MHz)***	399.72
Nucleus	1H	***Number of Transients***	52	***Original Points Count***	13102	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	44.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2406.9146	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.40	***Temperature (degree C)***	25.000



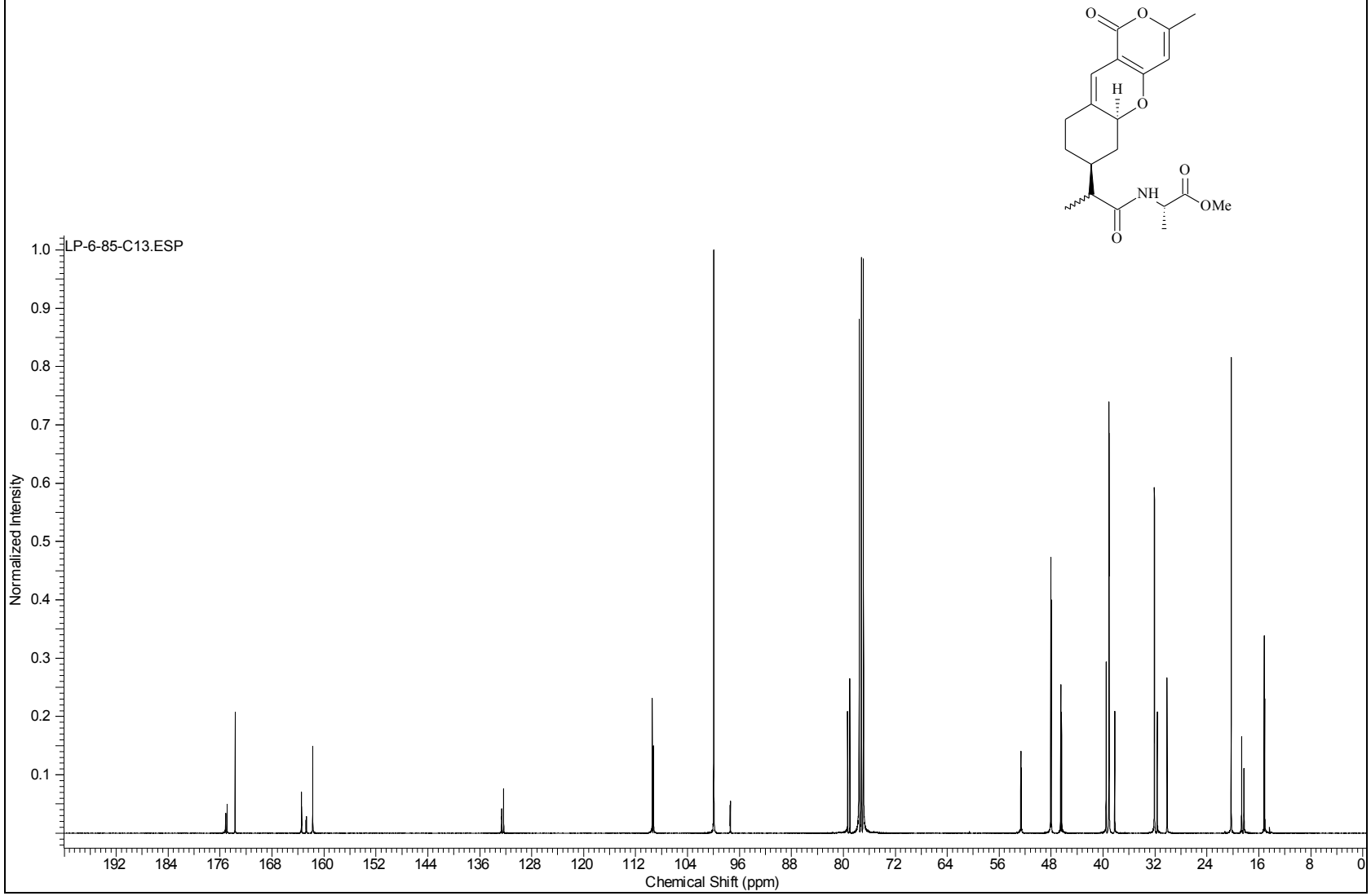
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Mar 21 2012	***Date Stamp***	Mar 21 2012
File Name	C:\USERS\LAXMAN\DESKTOP\INOVA-03-27-2013\MARCH\LP-6-82C13.FID\FID					***Frequency (MHz)***	100.52
Nucleus	13C	***Number of Transients***	19844	***Original Points Count***	31375	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10550.3496	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	25.000



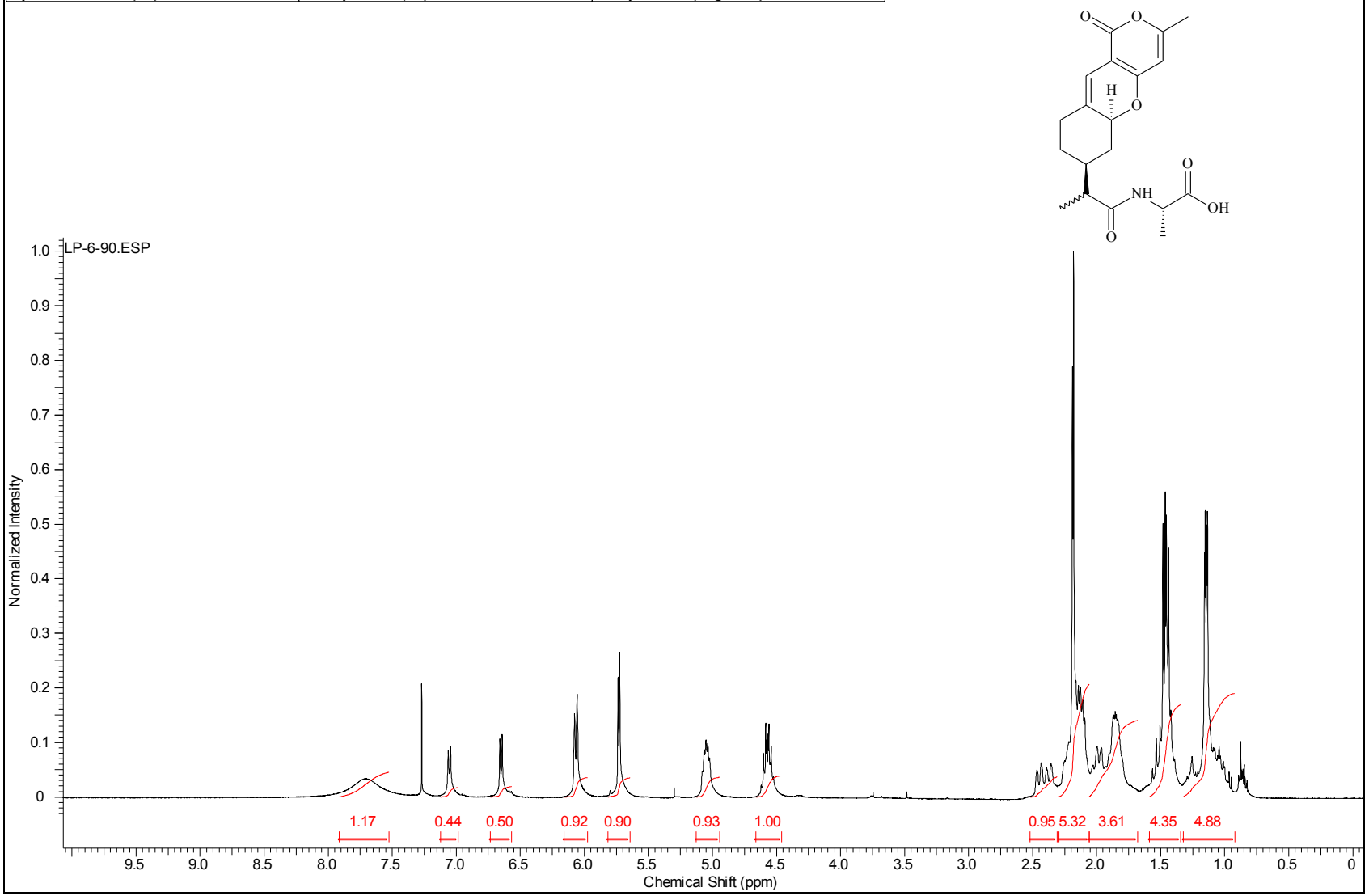
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Mar 22 2012	***Date Stamp***	Mar 22 2012
File Name	C:\USERS\LAXMAN\DESKTOP\INOVA-03-27-2013\MARCH\LP-6-85.FID\FID					***Frequency (MHz)***	399.72
Nucleus	1H	***Number of Transients***	40	***Original Points Count***	13102	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	42.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2408.8535	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.40	***Temperature (degree C)***	25.000



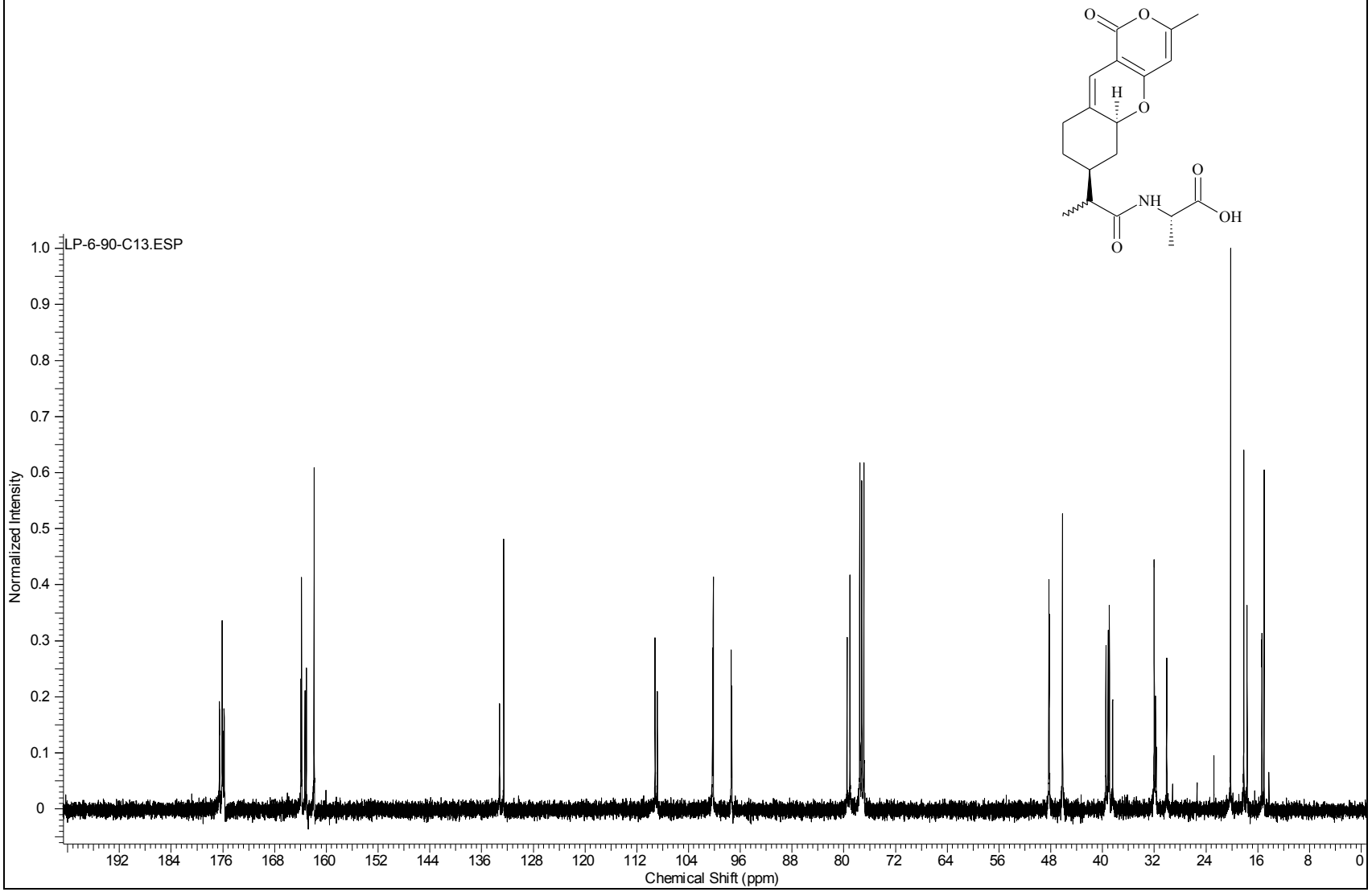
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Mar 22 2012
Date Stamp	Mar 22 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\LP-6-85-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	5944	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10553.9365	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



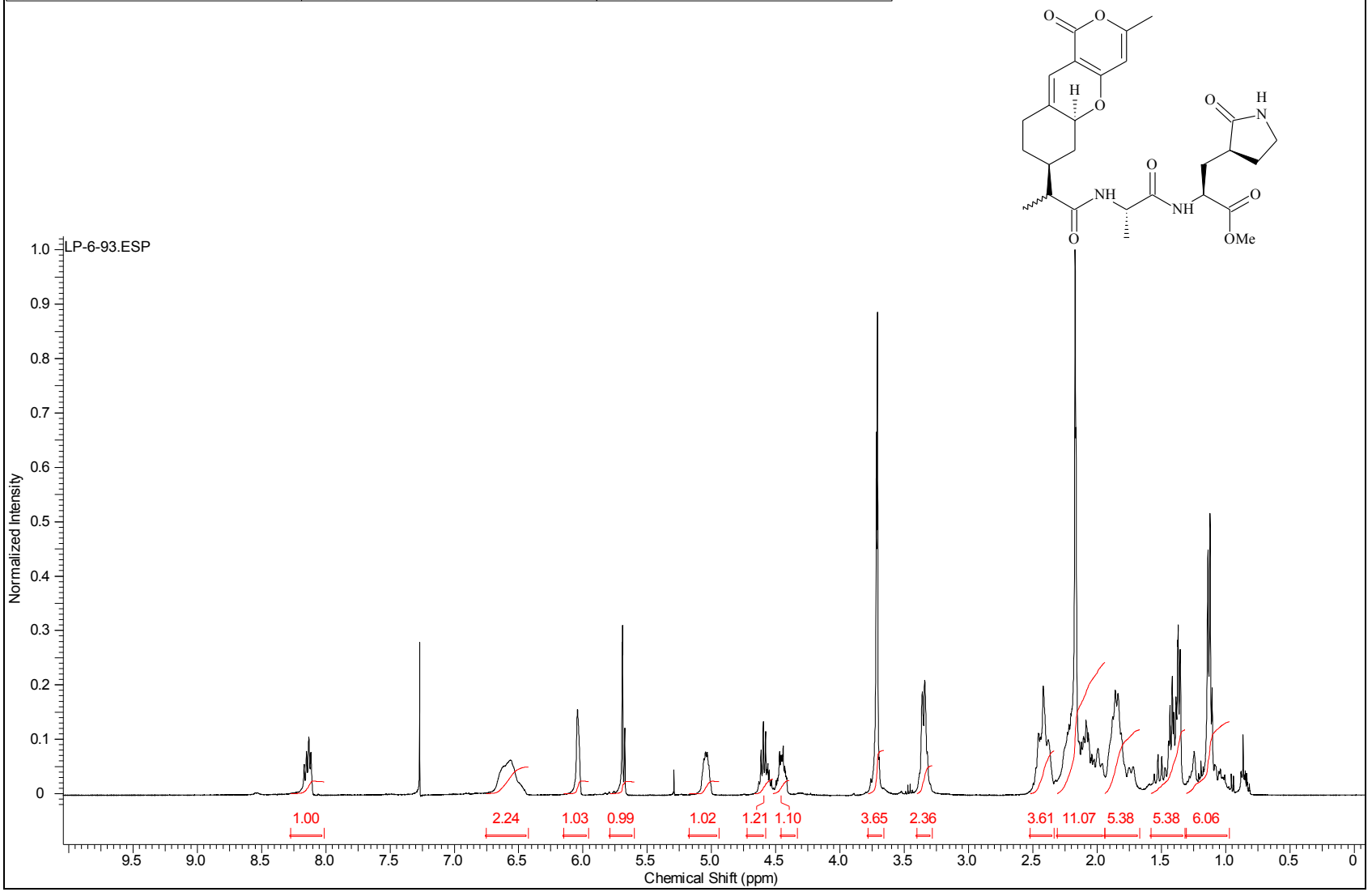
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Mar 27 2012
Date Stamp	Mar 27 2012	***File Name***	E:\LAXMAN POKHREL-NMRS\LP-NMR-02-15-2013-MERCURY\LP-6-90-2				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	100	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	22.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2403.7539	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000		



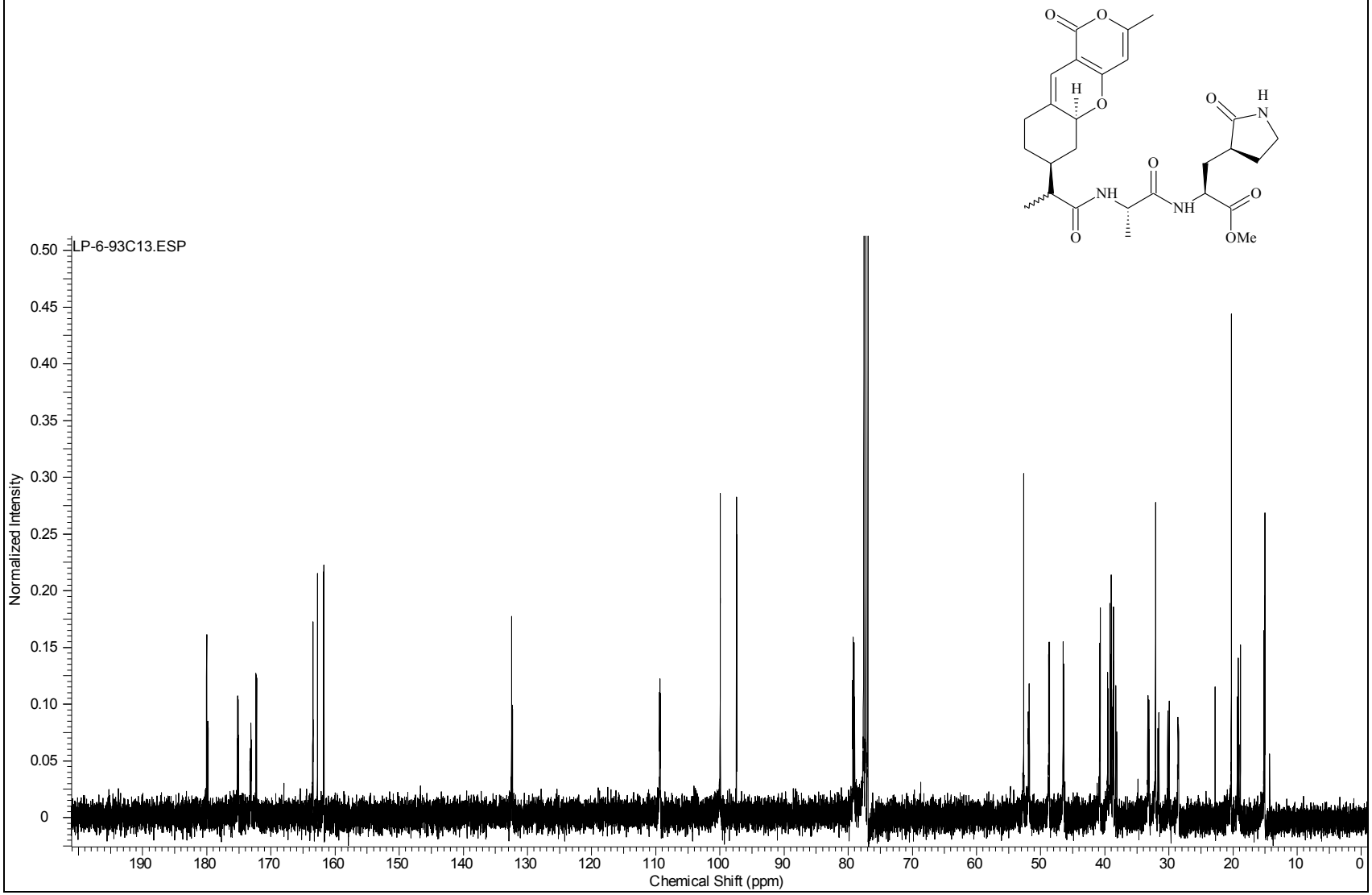
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Mar 27 2012
Date Stamp	Mar 27 2012	***File Name***	E:\LAXMAN POKHREL-NMRS\LP-NMR-02-15-2013-MERCURY\LP-6-90-C13				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	20000	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10552.4619	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000		



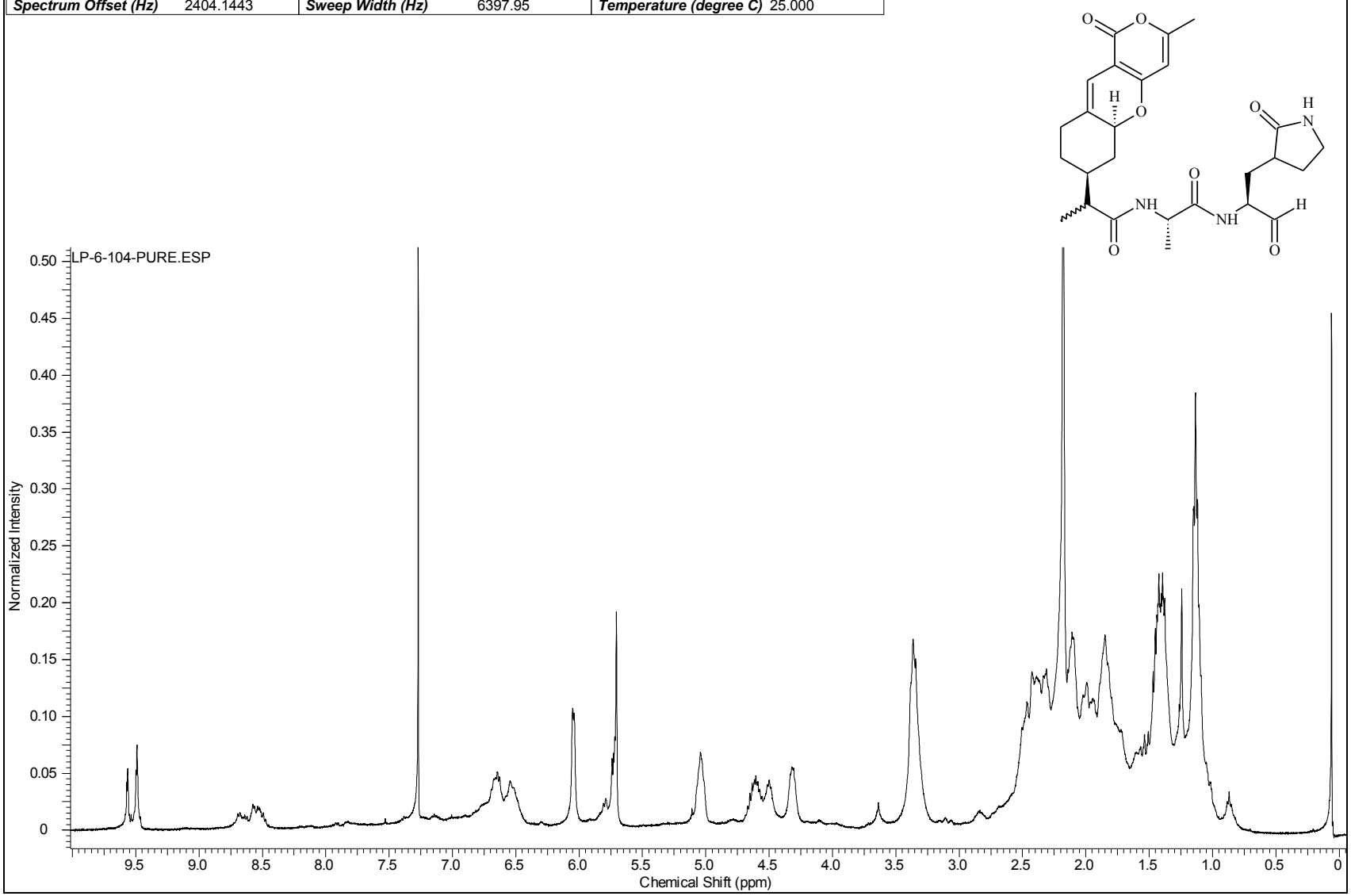
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Mar 29 2012
Date Stamp	Mar 29 2012	***File Name***	E:\LAXMAN POKHREL-NMRS\LP-NMR-02-15-2013-MERCURY\LP-6-93FR2-2				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	100	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2404.1443	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000		



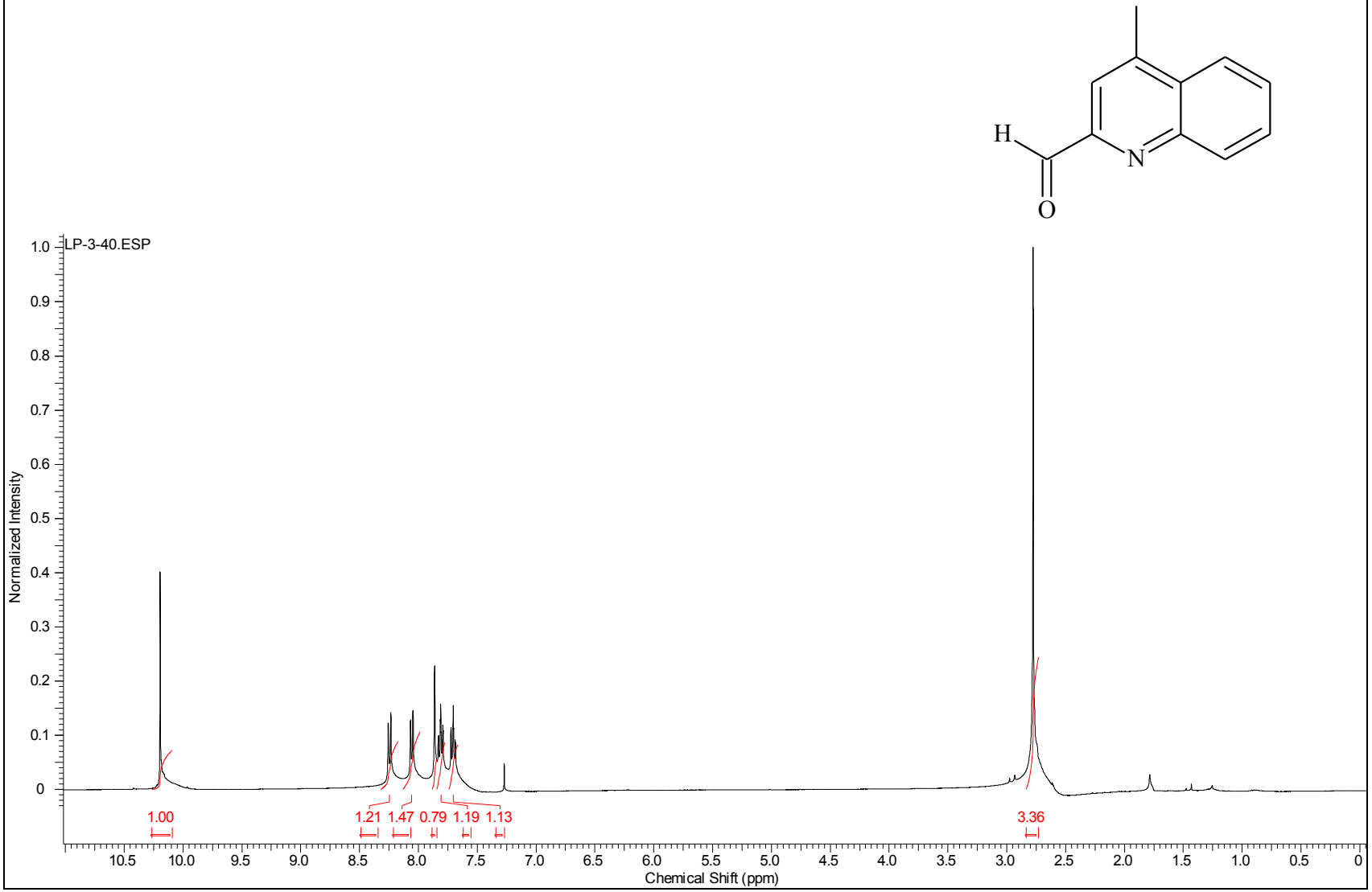
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Mar 29 2012
Date Stamp	Mar 29 2012	***File Name***	E:\LAXMAN POKHREL-NMRS\LP-NMR-02-15-2013-MERCURY\LP-6-93FR2C13				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	30000	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10553.9365	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000		



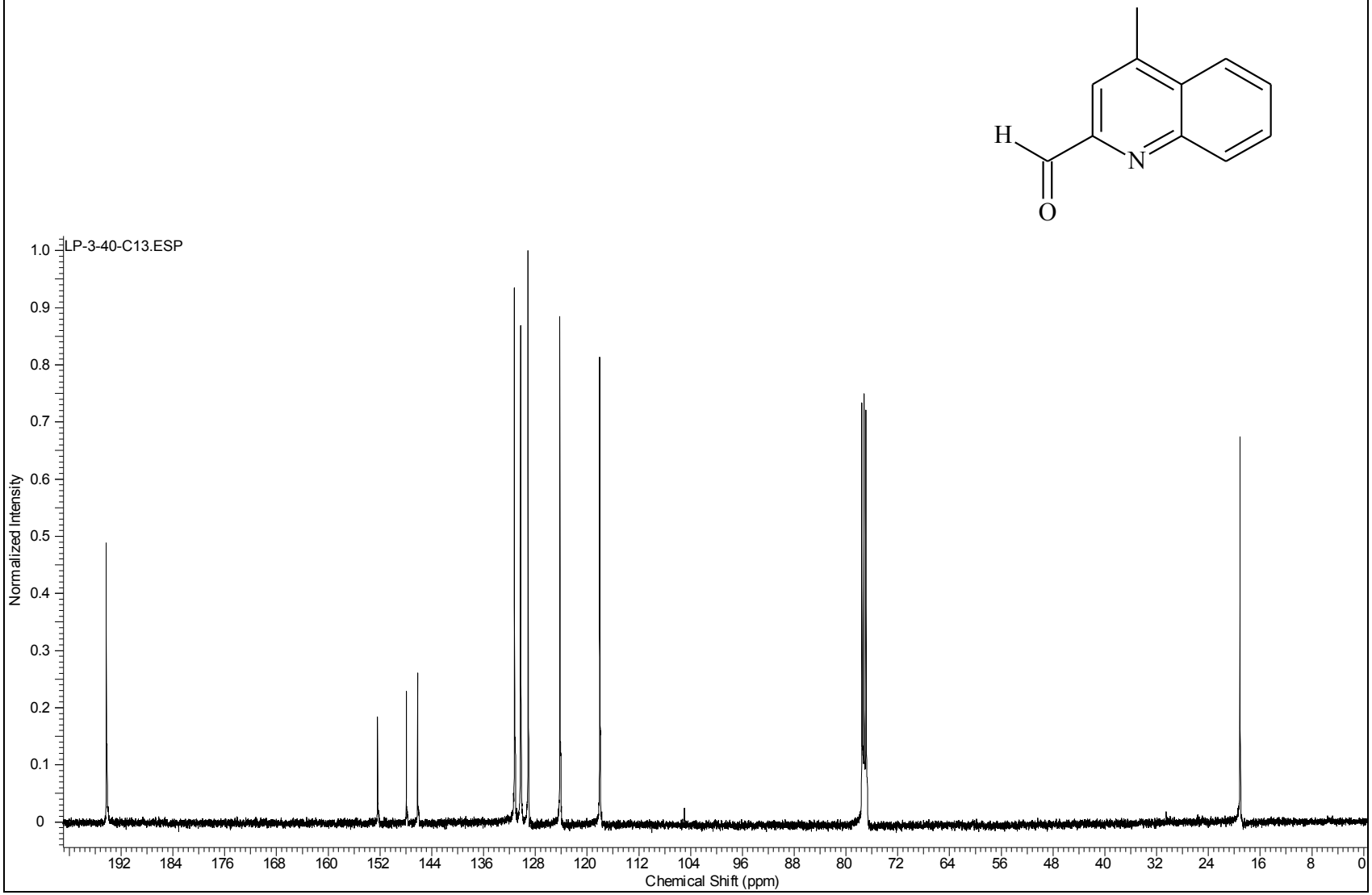
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	May 24 2012
Date Stamp	May 24 2012	***File Name***	E:\LAXMAN POKHREL-NMRS\LP-NMR-02-15-2013-MERCURY\LP-6-104-PURE				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	100	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	28.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2404.1443	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000		



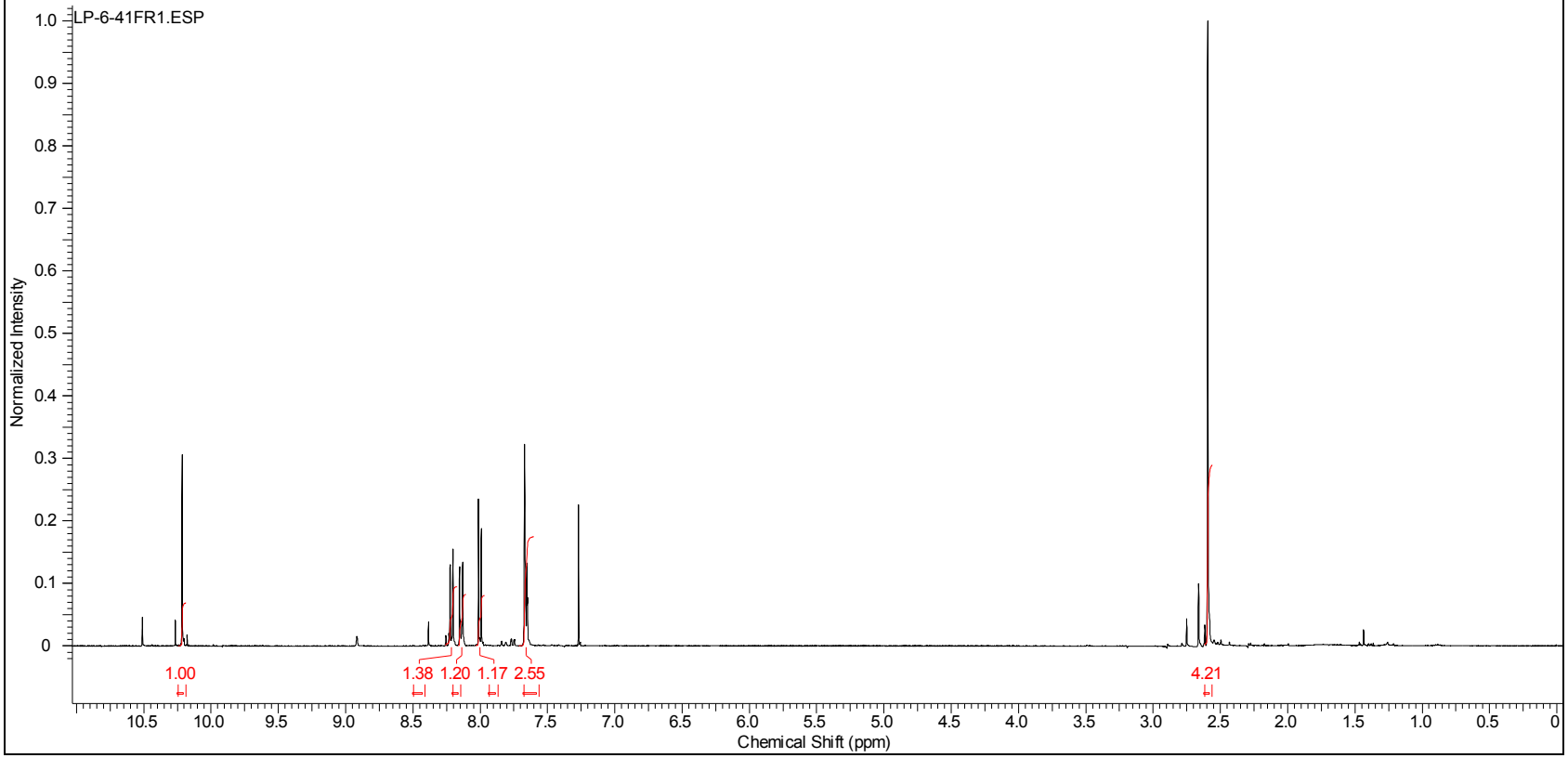
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Jan 26 2012
Date Stamp	Jan 26 2012	***File Name***	F:\NMR-MERCURY-02012\LP-3-40.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	40	***Original Points Count***	12783	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	22.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2404.1443	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



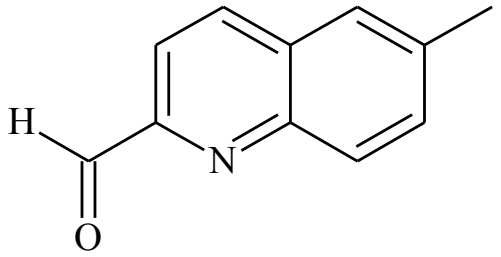
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jan 26 2012
Date Stamp	Jan 26 2012	***File Name***	F:\NMR-MERCURY-02012\LP-3-40C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	17788	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10557.6221	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000

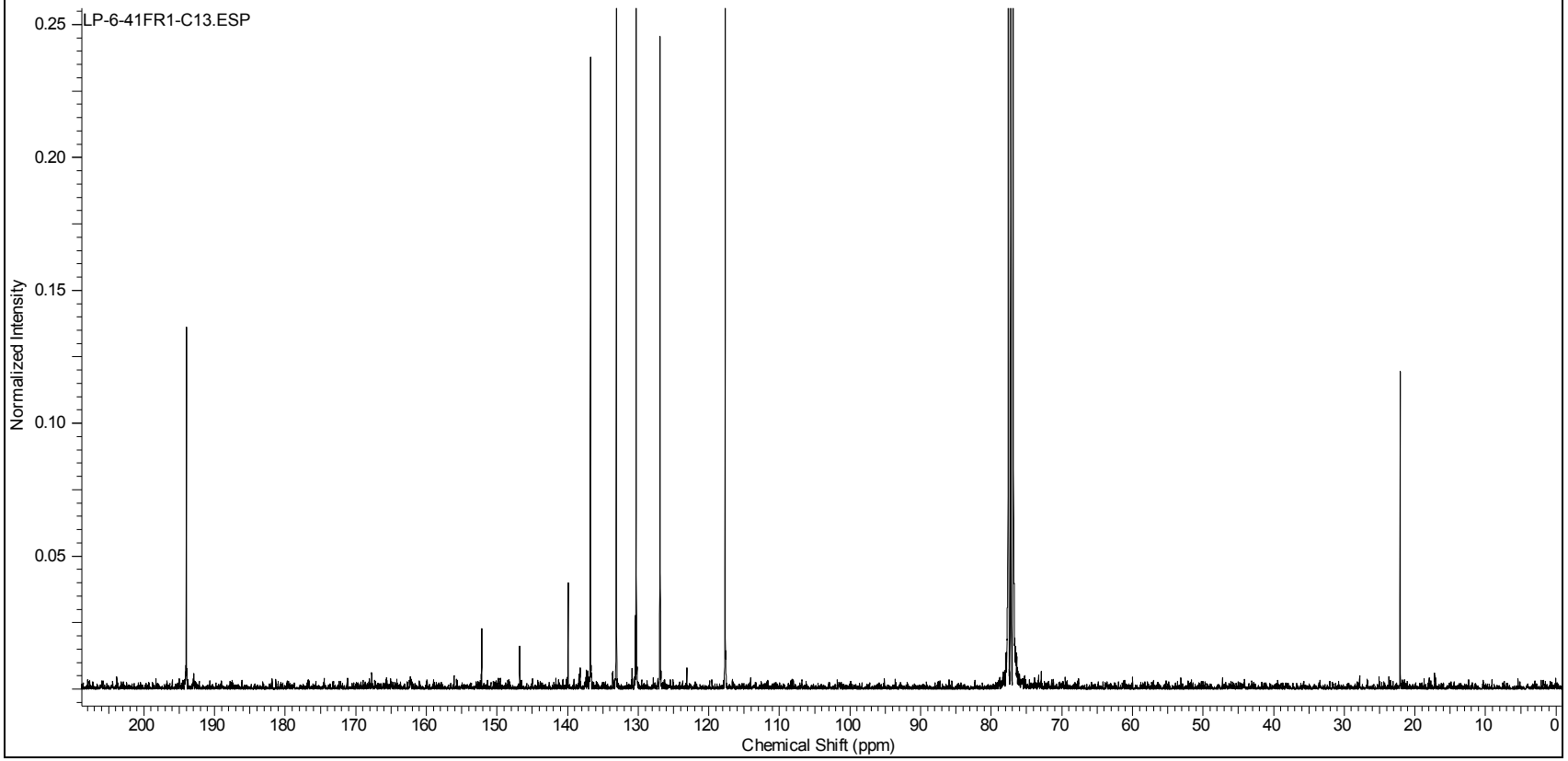


Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Jan 9 2012	***Date Stamp***	Jan 9 2012		
File Name	F:\NMR-NOVA-02-12\LP-6-41FR1.FID\FID			***Frequency (MHz)***	399.72	***Nucleus***	1H	***Number of Transients***	32
Original Points Count	13102	***Points Count***	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	50.00		
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	2408.0728	***Spectrum Type***	STANDARD		
Sweep Width (Hz)	6395.40	***Temperature (degree C)***	25.000						

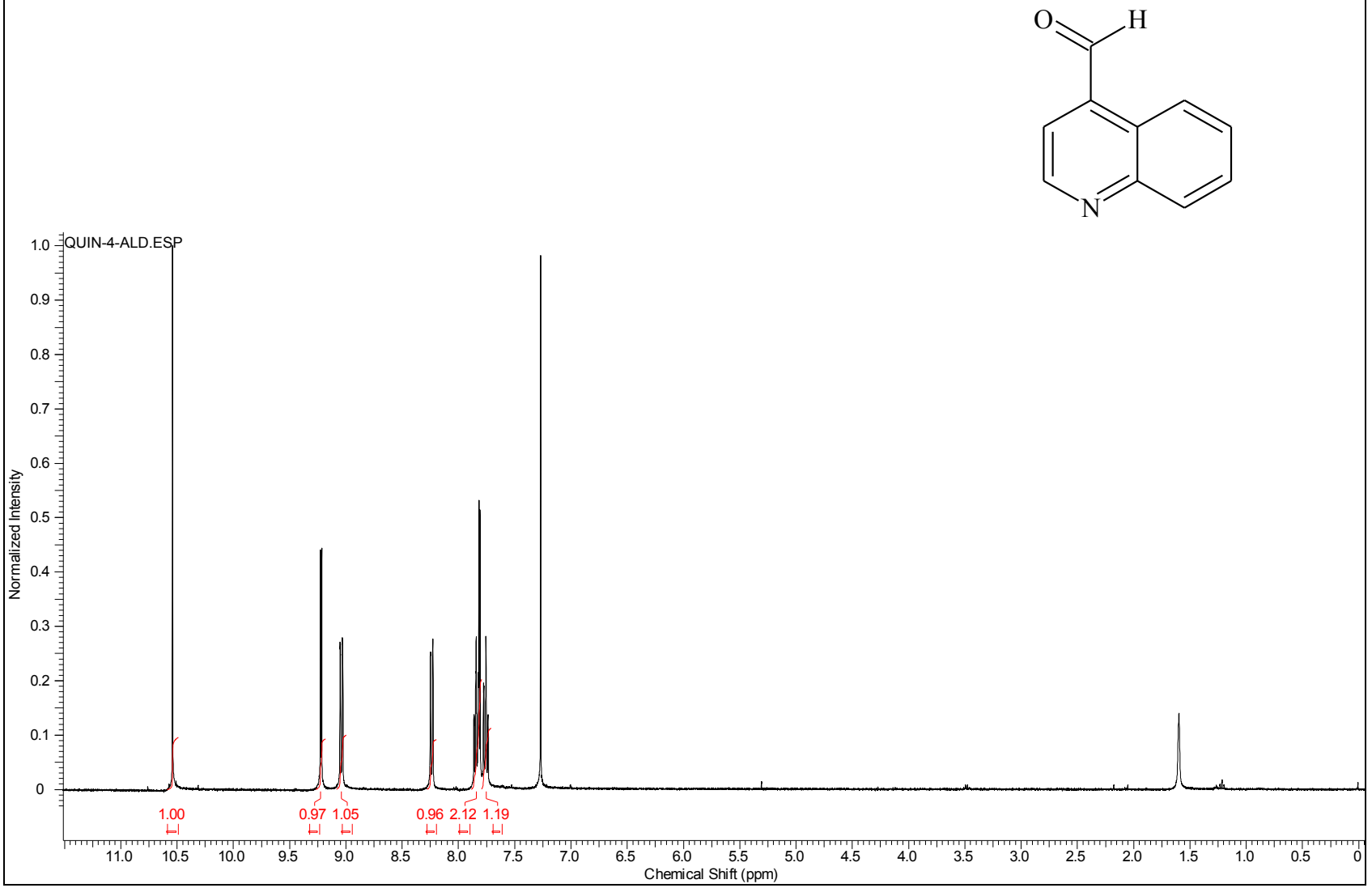


Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Jan 9 2012	***Date Stamp***	Jan 9 2012
File Name	F:\NMR-NOVA-02-12\LP-6-41FR1-C13.FID\FID			***Frequency (MHz)***	100.52	***Nucleus***	13C
Number of Transients	400	***Original Points Count***	31375	***Points Count***	32768	***Pulse Sequence***	s2pul
Receiver Gain	30.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	10554.0303
Spectrum Type	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	25.000		

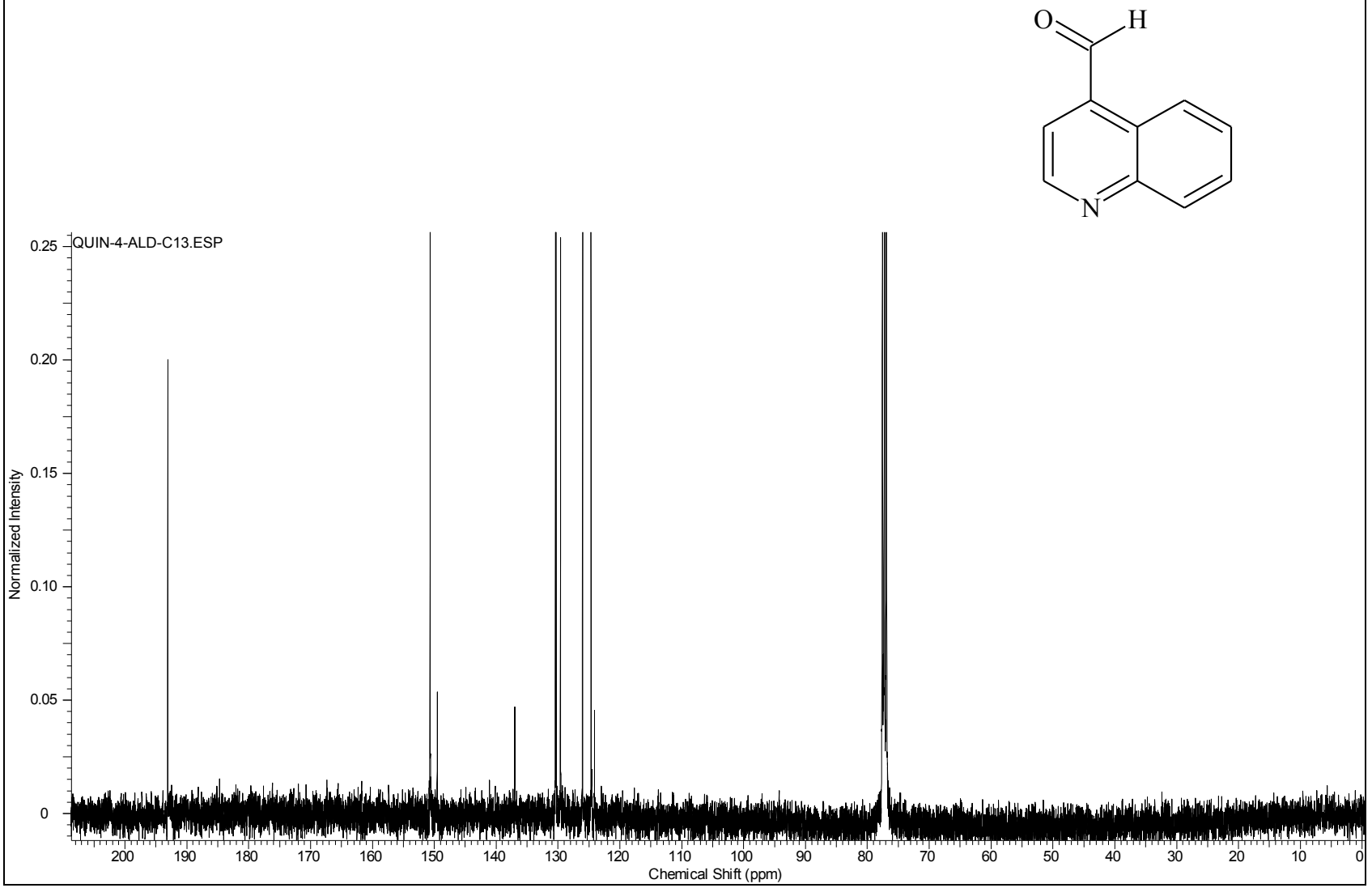




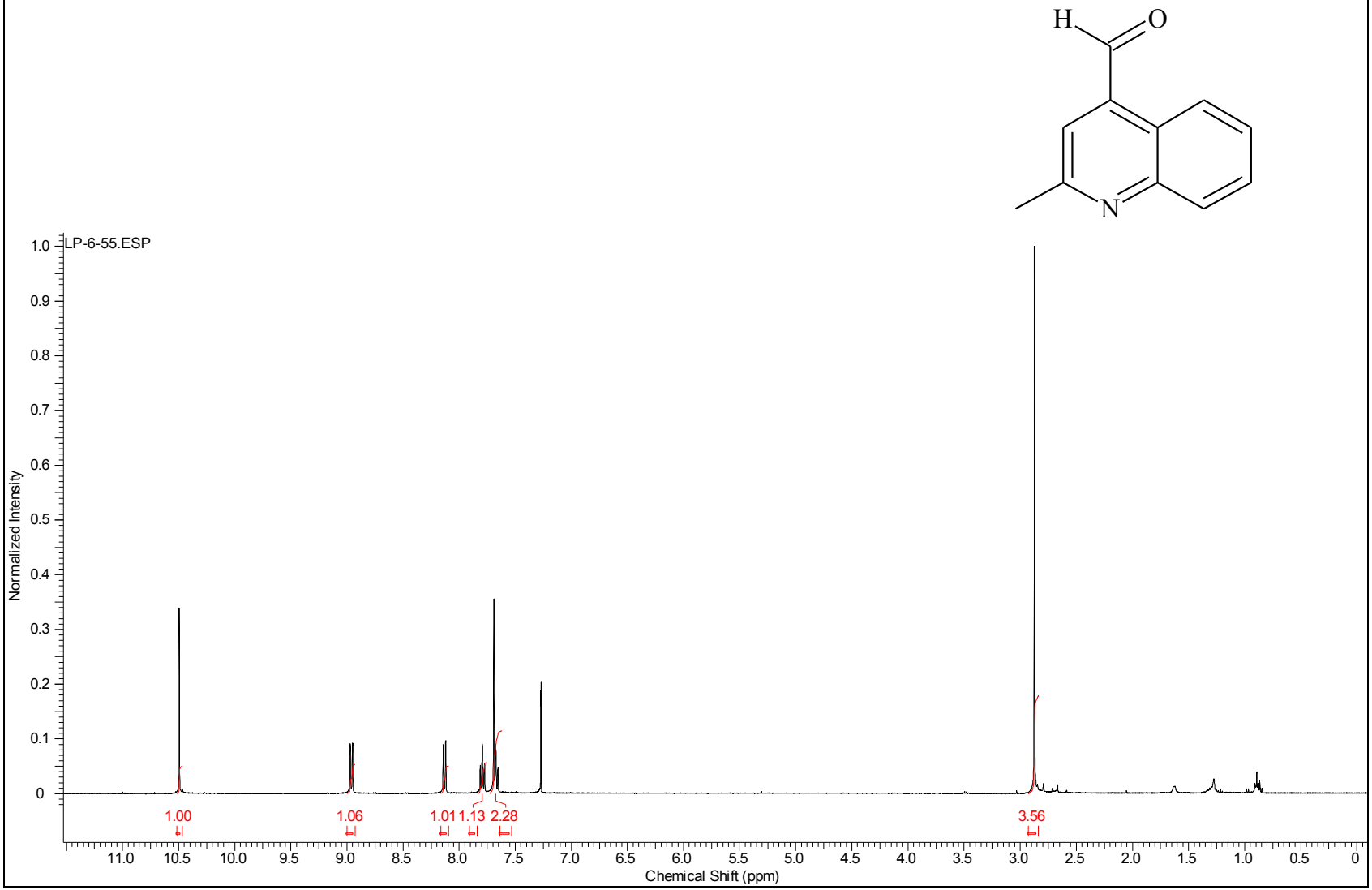
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Jan 15 2012
Date Stamp	Jan 15 2012	***File Name***	F:\NMR-MERCURY-02012\QUIN-4-ALD.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	24	***Original Points Count***	12783	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	39.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2404.5349	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



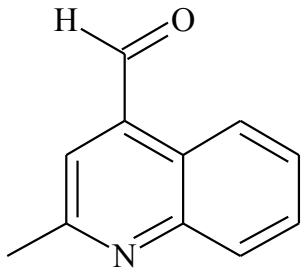
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jan 15 2012
Date Stamp	Jan 15 2012	***File Name***	F:\NMR-MERCURY-02012\QUINOLINE-4-ALD-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	10000	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10559.8330	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000

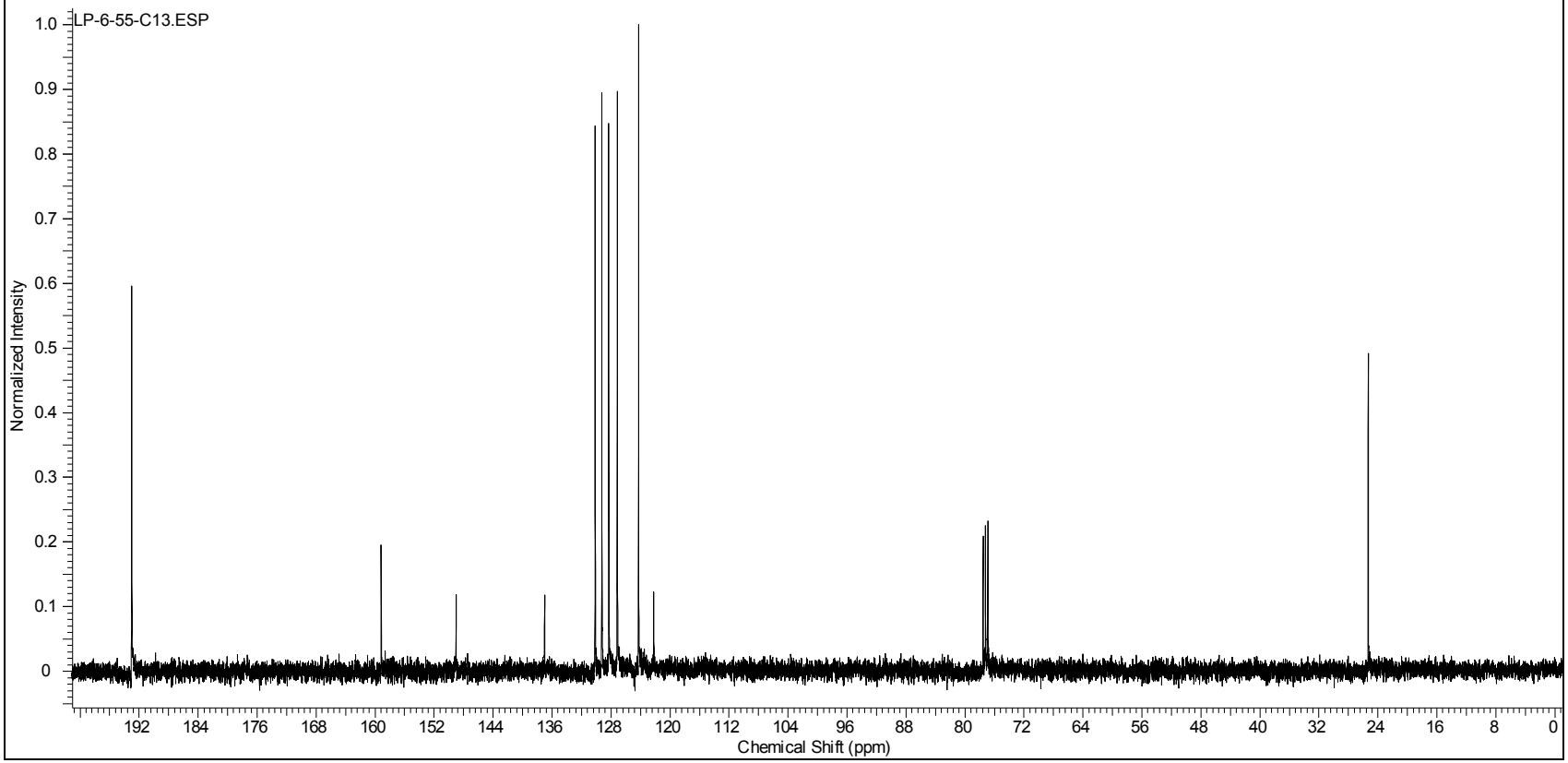


Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Jan 31 2012
Date Stamp	Jan 31 2012	***File Name***	F:\NMR-MERCURY-02012\LP-6-55.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	36	***Original Points Count***	12783	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	38.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2405.5242	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000

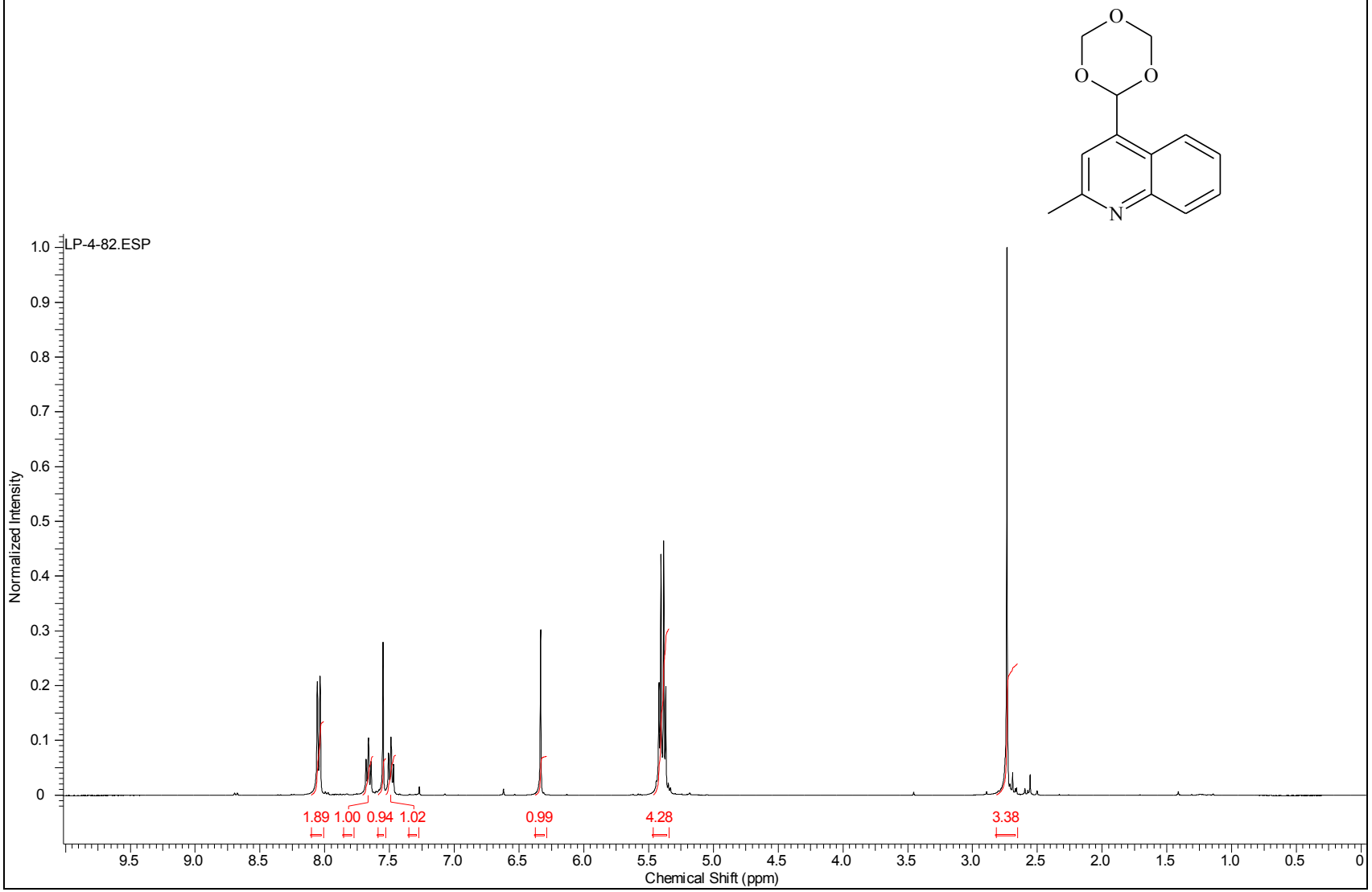


Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jan 31 2012
Date Stamp	Jan 31 2012	***File Name***	F:\NMR-MERCURY-02012\LP-6-55C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	100	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10549.5137	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000

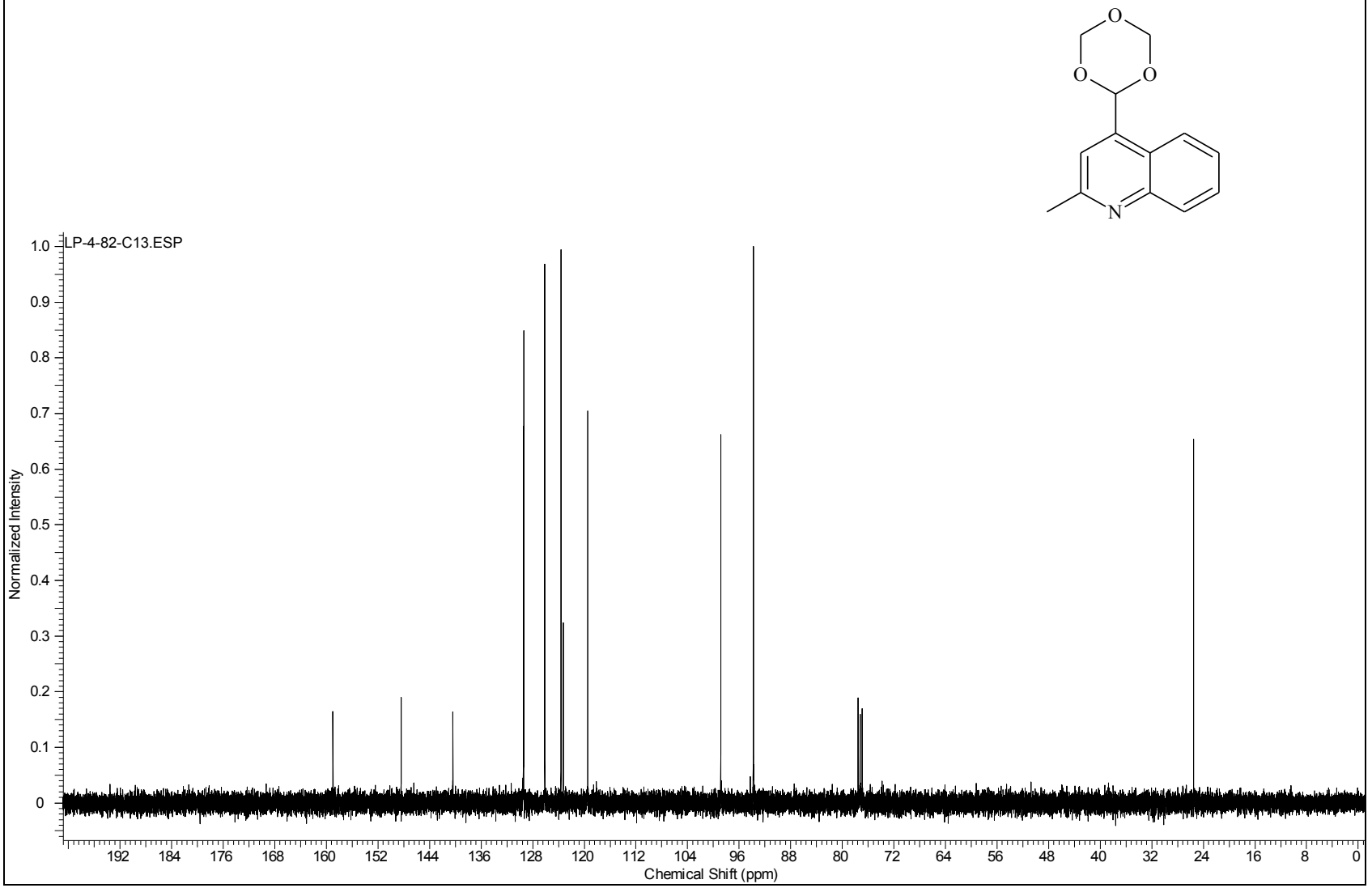




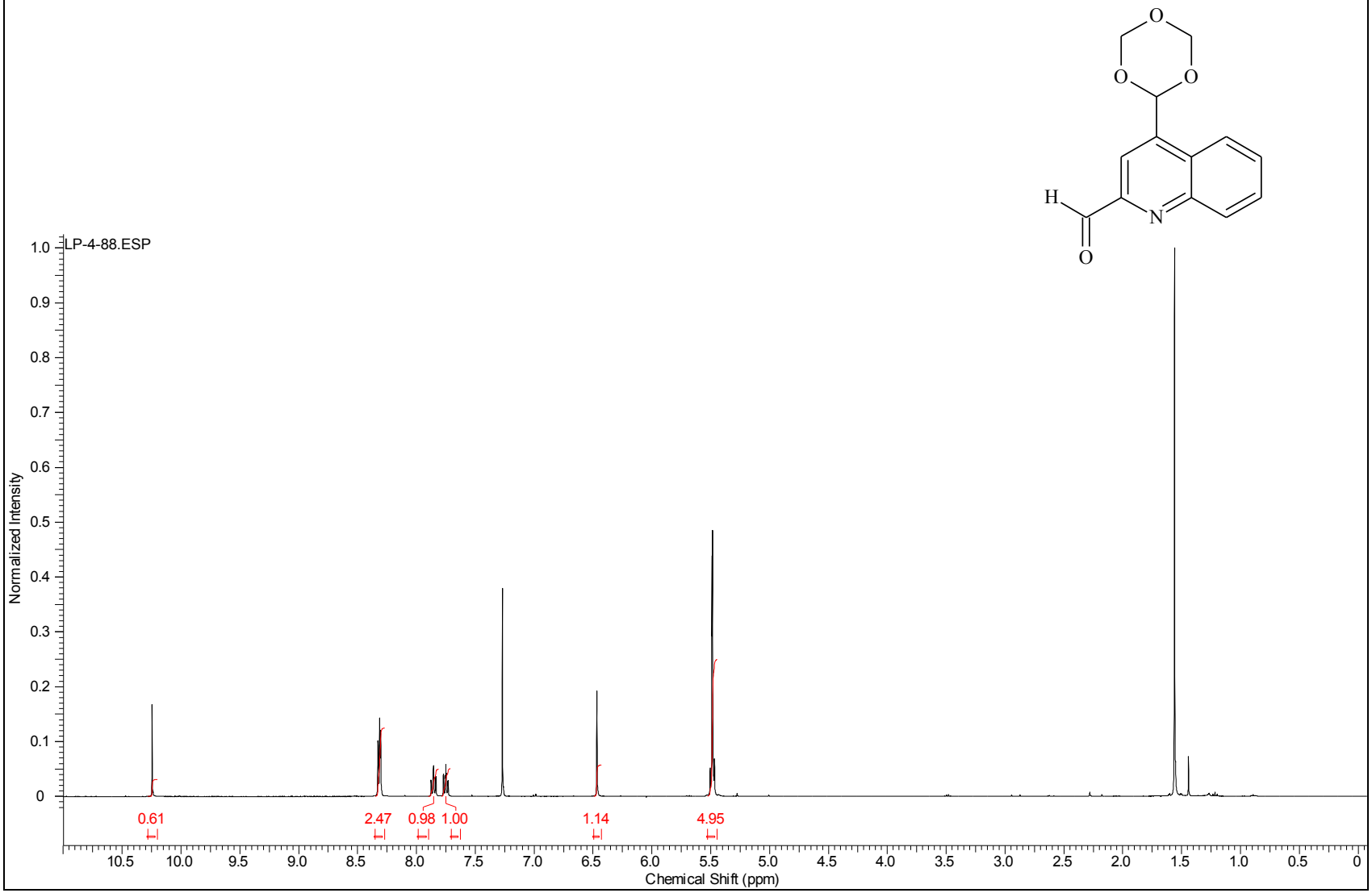
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Dec 26 2011
Date Stamp	Dec 26 2011	***File Name***	F:\NMR-MERCURY-02012\LP-4-82.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	16	***Original Points Count***	12783	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	16.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2404.9253	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



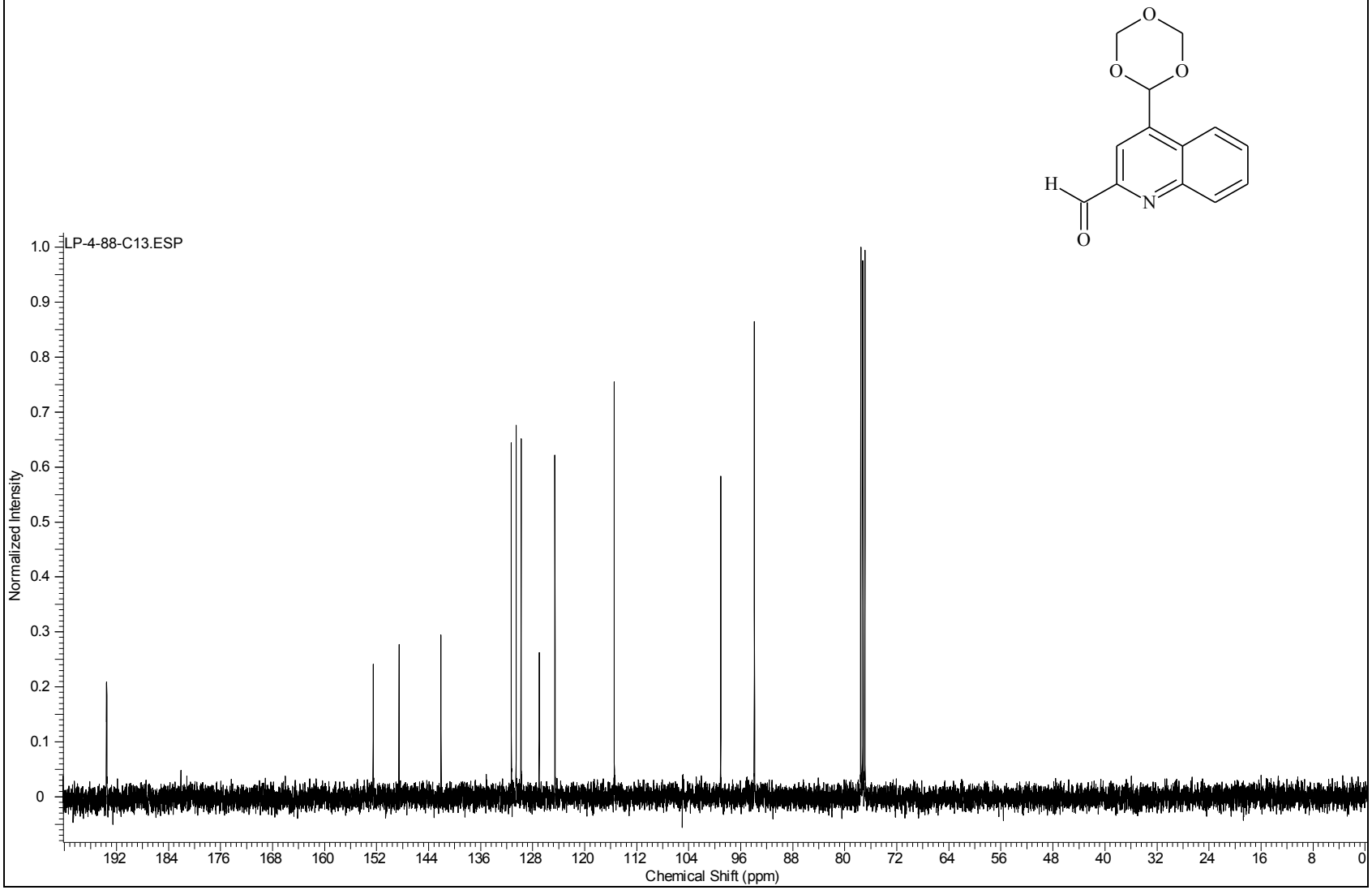
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Dec 26 2011
Date Stamp	Dec 26 2011	***File Name***	F:\NMR-MERCURY-02012\LP-4-82-C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	72	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10547.3018	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



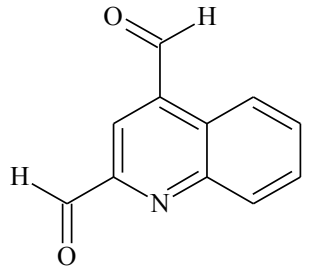
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Aug 23 2010	***Date Stamp***	Aug 23 2010
File Name	C:\USERS\LAXMAN\DESKTOP\NMR\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-88FR1.FID\FID						
Frequency (MHz)	399.74	***Nucleus***	1H	***Number of Transients***	52	***Original Points Count***	13103
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	50.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2417.1301	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	30.000

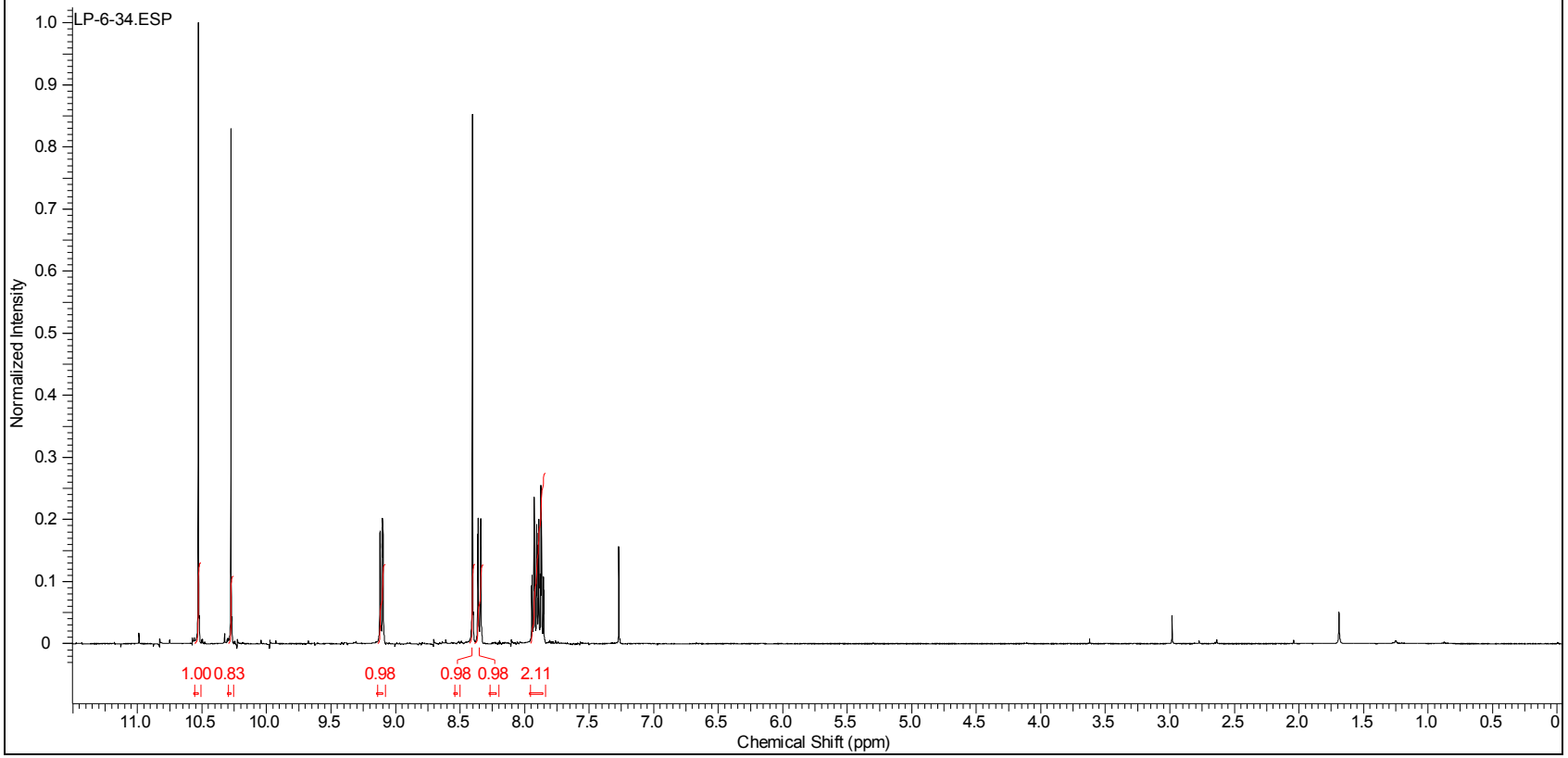


Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Aug 26 2010	***Date Stamp***	Aug 26 2010
File Name	C:\USERS\LAXMAN\DESKTOP\NMR\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-88-C13.FID\FID						
Frequency (MHz)	100.52	***Nucleus***	13C	***Number of Transients***	984	***Original Points Count***	31375
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10552.1377	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	30.000

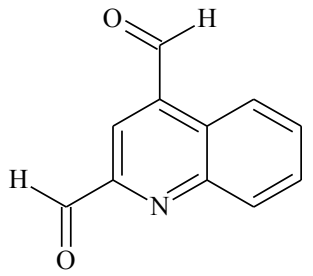


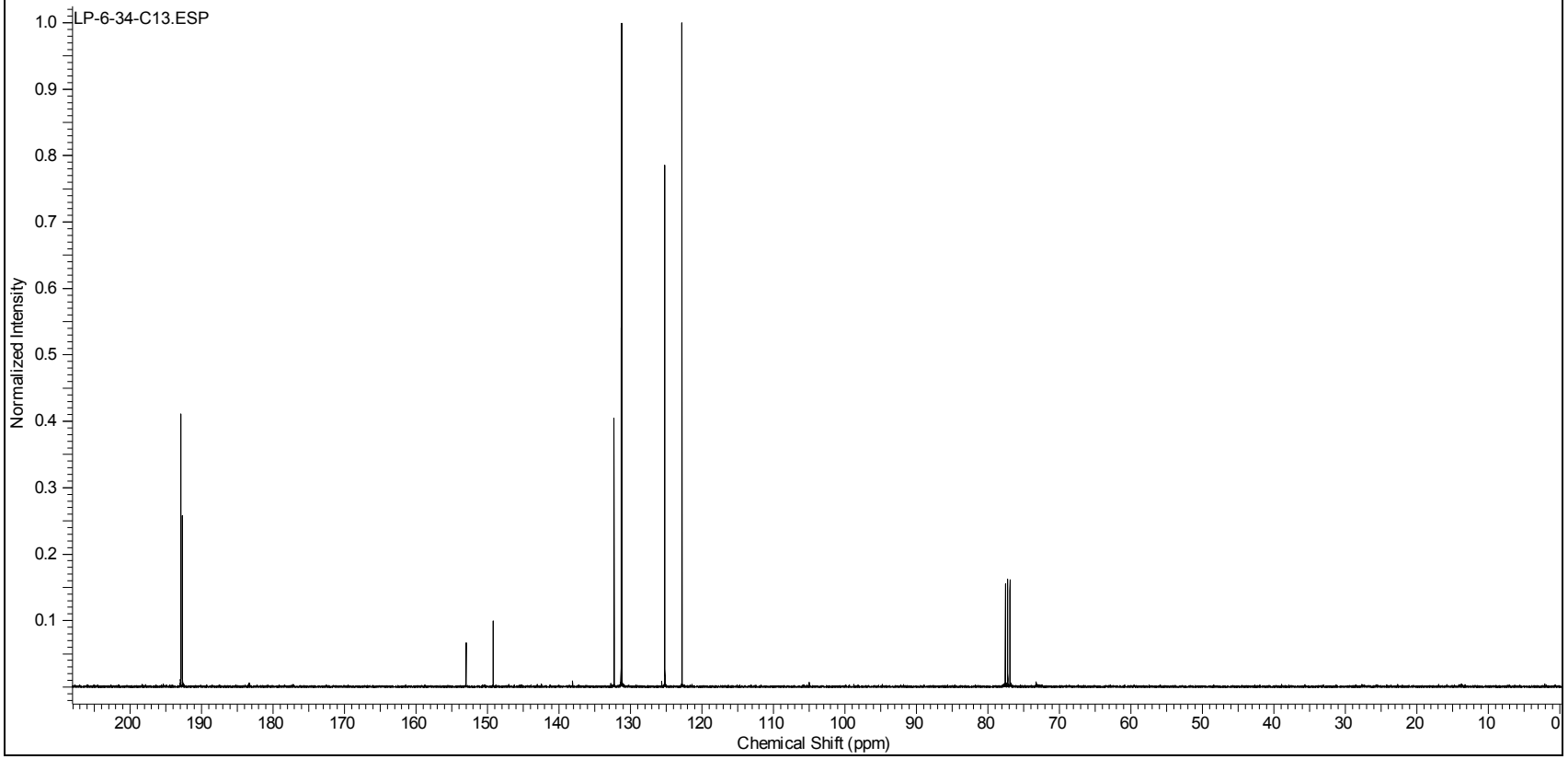
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Jan 1 2012	***Date Stamp***	Jan 1 2012		
File Name	F:\NMR-NOVA-02-12\LP-6-34.FID\FID			***Frequency (MHz)***	399.72	***Nucleus***	1H	***Number of Transients***	24
Original Points Count	13102	***Points Count***	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	48.00		
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	2405.3401	***Spectrum Type***	STANDARD		
Sweep Width (Hz)	6395.40	***Temperature (degree C)***	25.000						



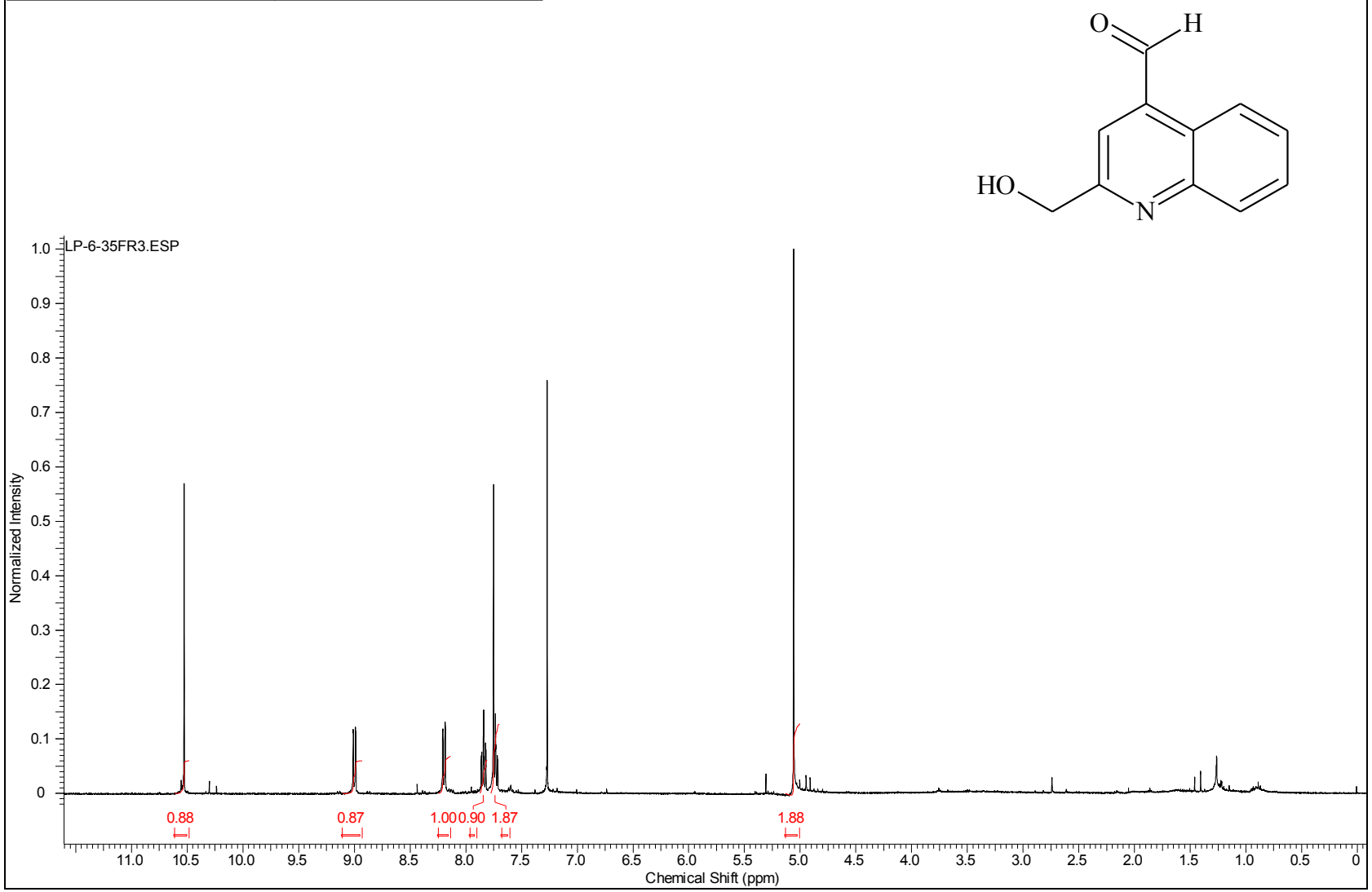


Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Jan 1 2012	***Date Stamp***	Jan 1 2012
File Name	F:\NMR-NOVA-02-12\LP-6-34C13.FID\FID			***Frequency (MHz)***	100.52	***Nucleus***	13C
Number of Transients	252	***Original Points Count***	31375	***Points Count***	32768	***Pulse Sequence***	s2pul
Receiver Gain	30.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	10551.8213
Spectrum Type	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	25.000		

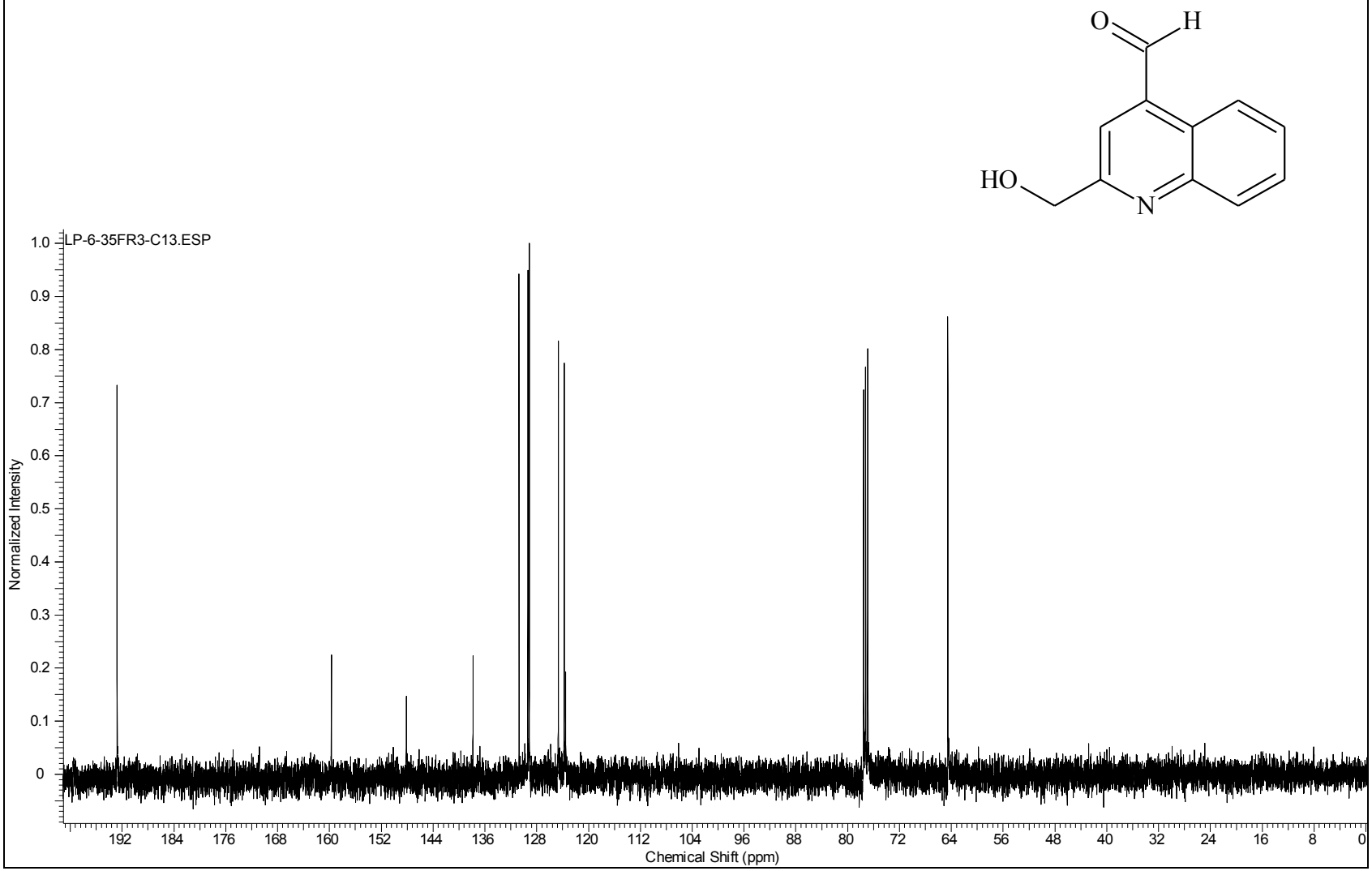




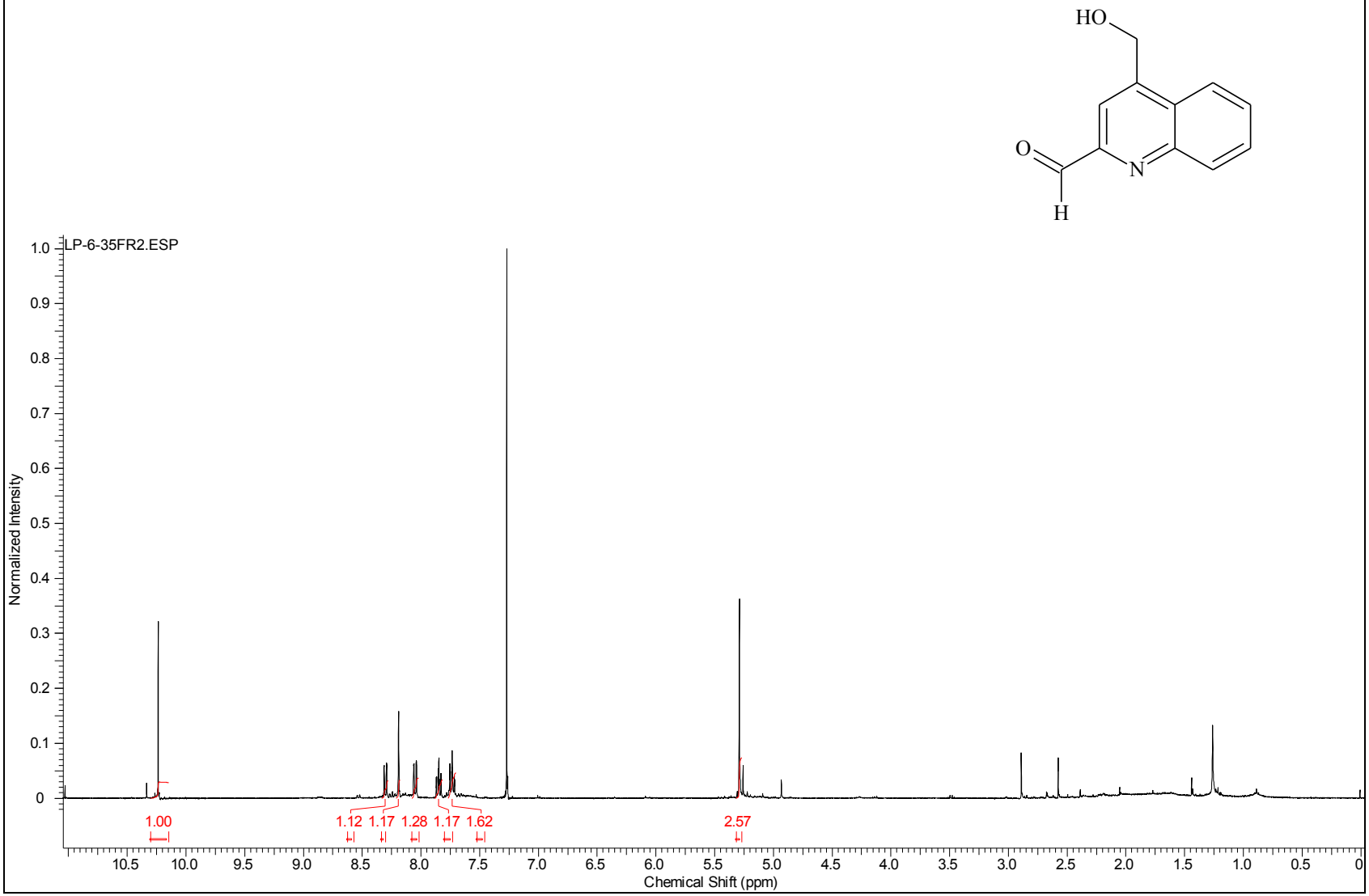
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Jan 2 2012	***Date Stamp***	Jan 2 2012
File Name	F:\LP-6-35FR3.FID\FID			***Frequency (MHz)***	399.96	***Nucleus***	1H	***Number of Transients***	16
Original Points Count	12783	***Points Count***	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	39.00		
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	2404.1443	***Spectrum Type***	STANDARD		
Sweep Width (Hz)	6397.95	***Temperature (degree C)***	25.000						



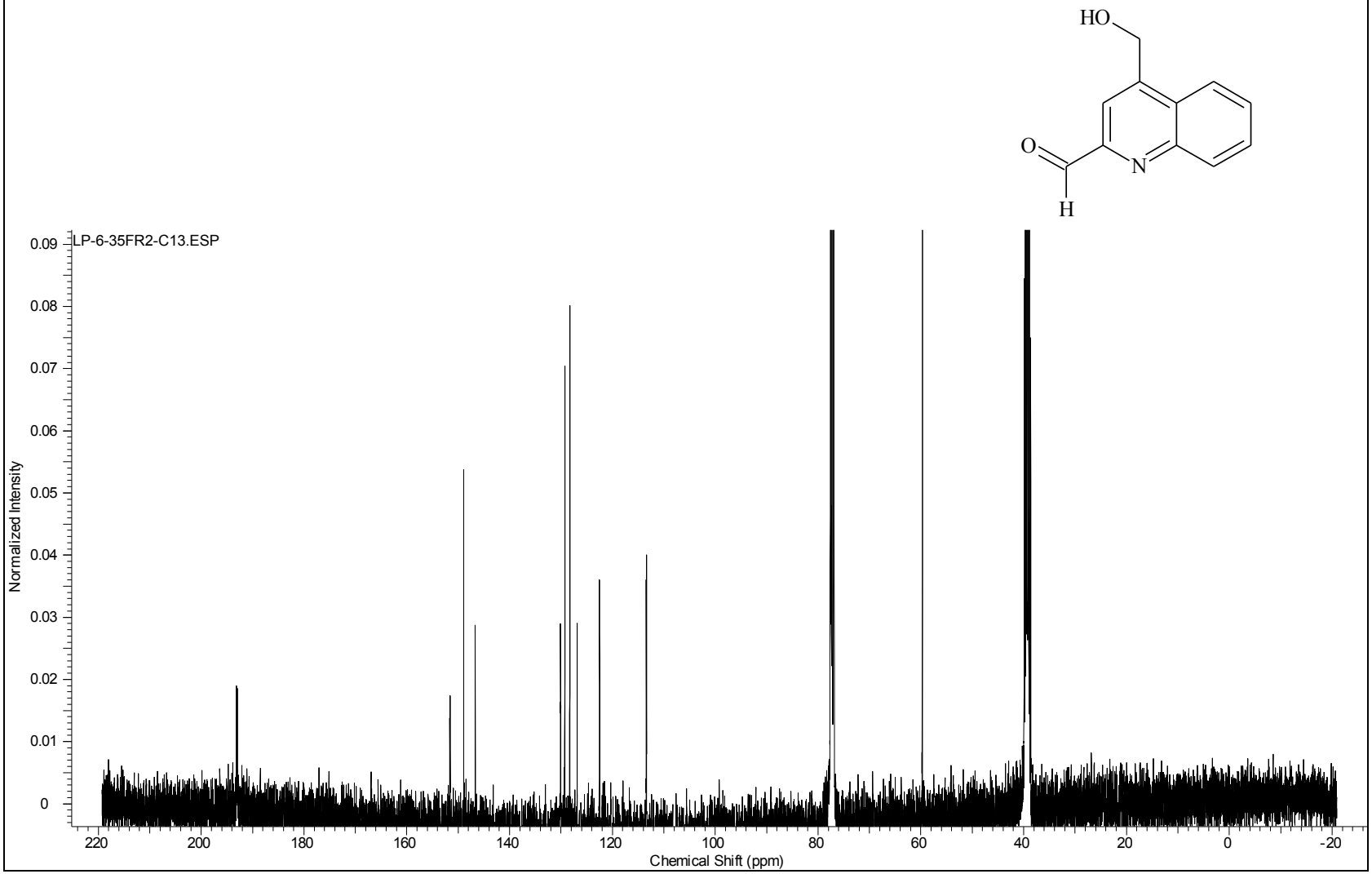
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jan 2 2012
Date Stamp	Jan 2 2012	***File Name***	F:\LP-6-35FR3-C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	632	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10558.3594	***Spectrum Type***	STANDARD			***Sweep Width (Hz)***	24154.59
Temperature (degree C)	25.000						



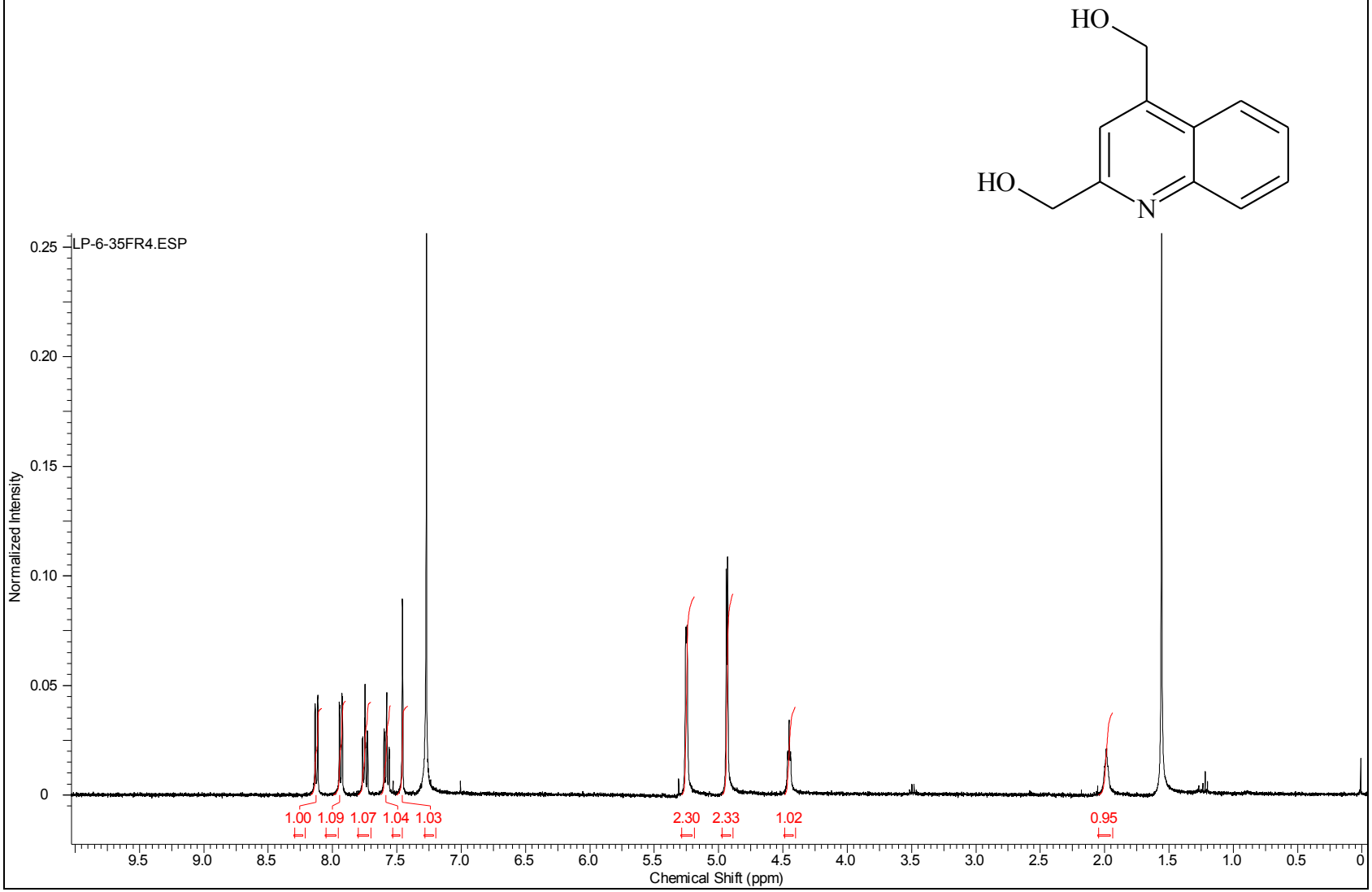
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Jan 2 2012			***Date Stamp***	Jan 2 2012
File Name	F:\LP-6-35FR2.FID\FID			***Frequency (MHz)***	399.72	***Nucleus***	1H	***Number of Transients***	32
Original Points Count	13102	***Points Count***	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	60.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2408.0728	***Spectrum Type***	STANDARD			***Sweep Width (Hz)***	6395.40	***Temperature (degree C)***	25.000



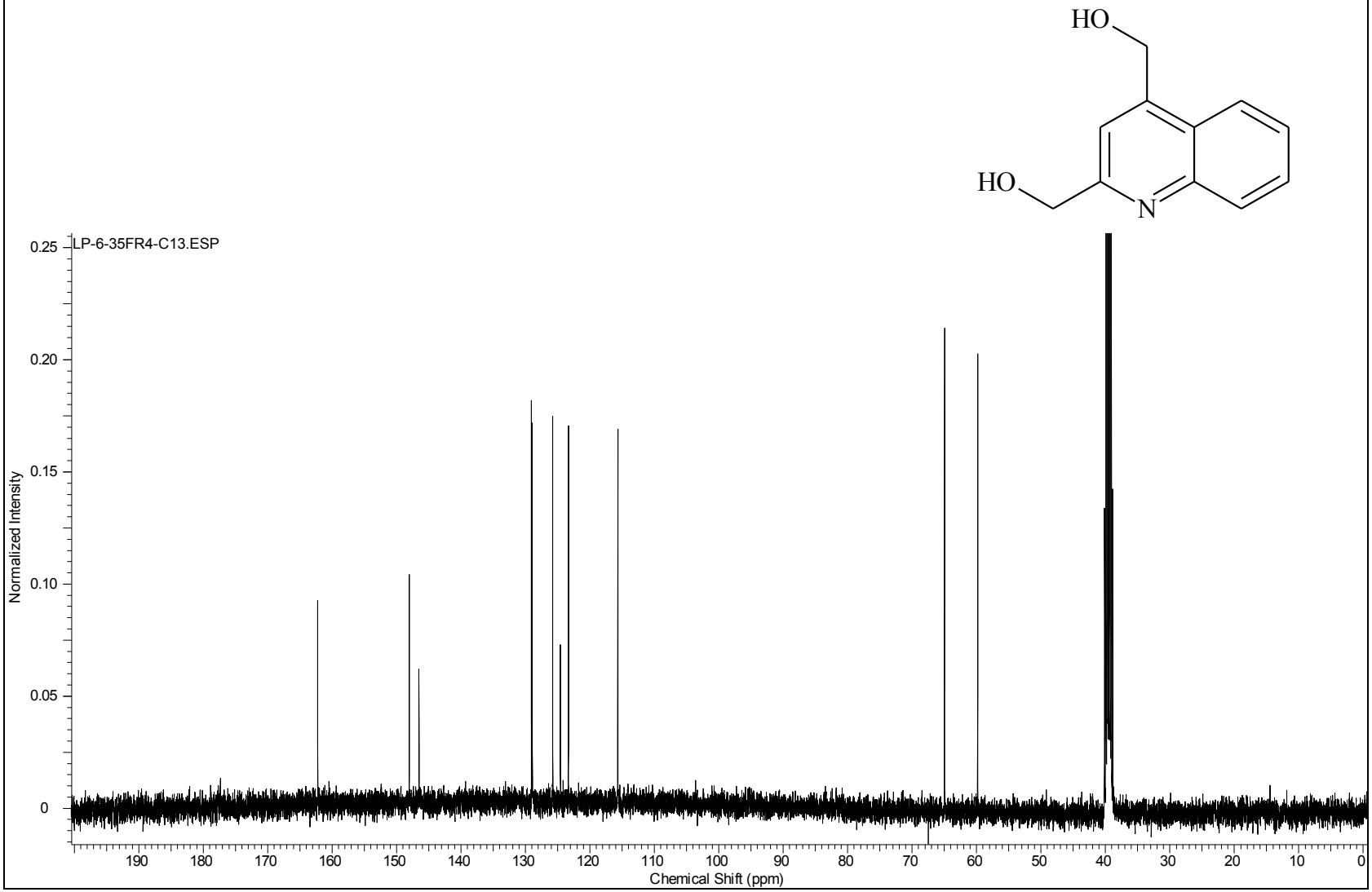
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jan 5 2012
Date Stamp	Jan 5 2012	***File Name***	F:\LP-6-35FR2-C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	22480	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	9976.0010	***Spectrum Type***	STANDARD			***Sweep Width (Hz)***	24154.59
Temperature (degree C)	25.000						



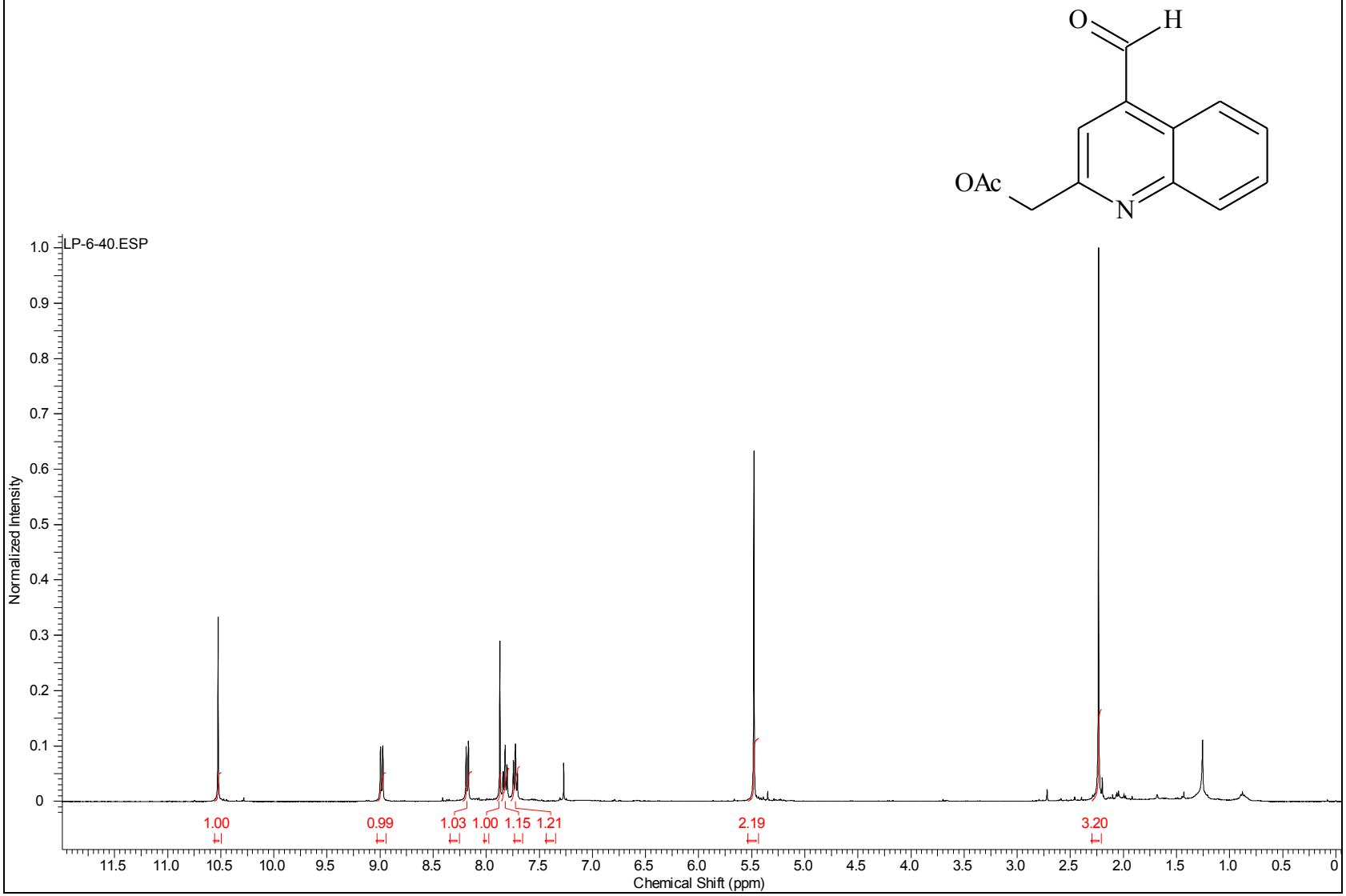
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Jan 2 2012	***Date Stamp***	Jan 2 2012
File Name	F:\LP-6-35FR4.FID\FID			***Frequency (MHz)***	399.96	***Nucleus***	1H	***Number of Transients***	72
Original Points Count	12783	***Points Count***	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	39.00		
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	2404.1443	***Spectrum Type***	STANDARD		
Sweep Width (Hz)	6397.95	***Temperature (degree C)***	25.000						



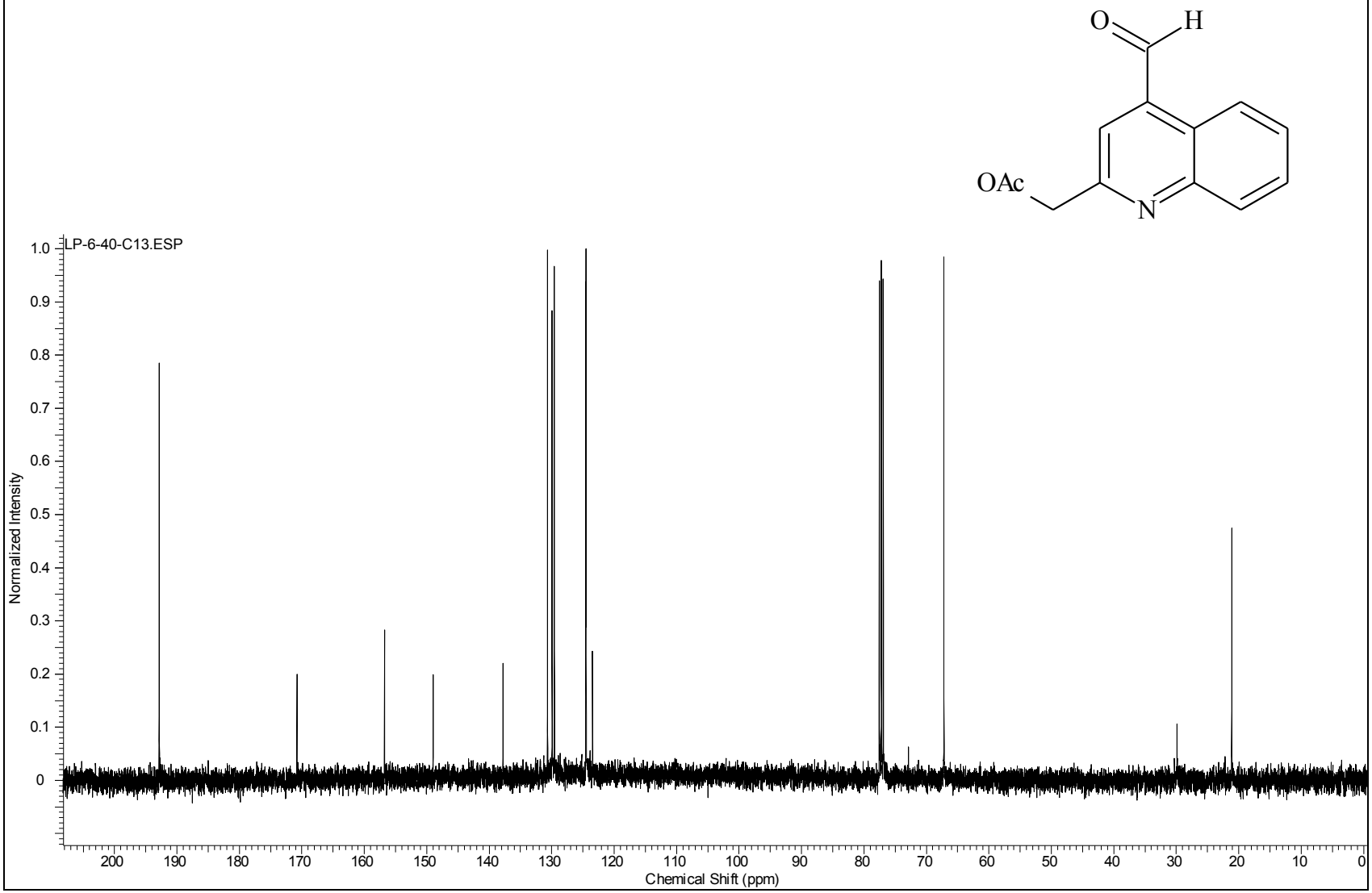
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Jan 2 2012			***Date Stamp***	Jan 2 2012
File Name	F:\LP-6-35FR4-C13.FID\FID			***Frequency (MHz)***	100.52	***Nucleus***	13C	***Number of Transients***	4020
Original Points Count	31375	***Points Count***	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	DMSO-d6
Spectrum Offset (Hz)	10486.9805			***Spectrum Type***	STANDARD			***Sweep Width (Hz)***	24125.45
Temperature (degree C)	25.000								



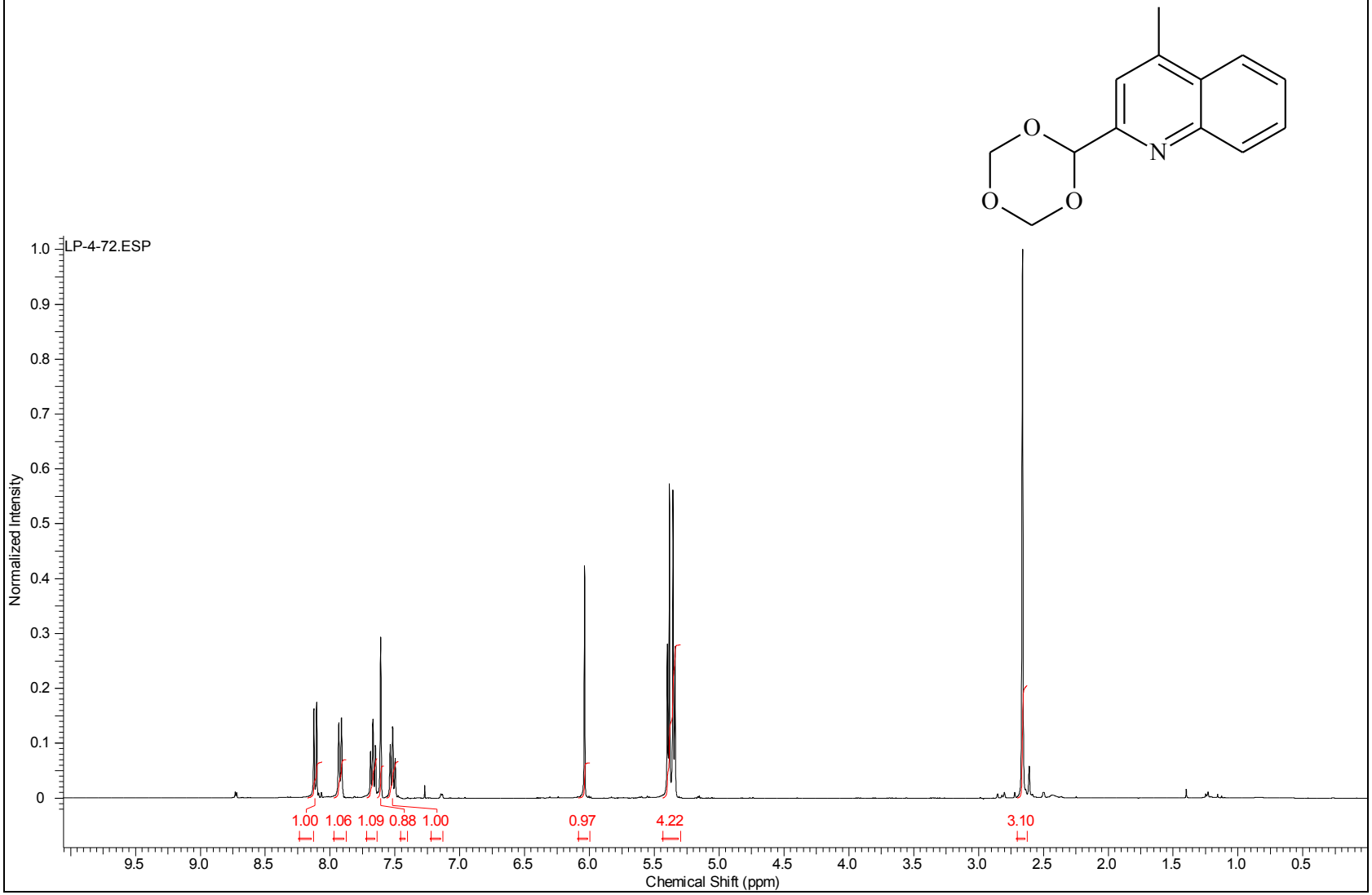
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Jan 2 2012			***Date Stamp***	Jan 2 2012
File Name	F:\LP-6-40.FID\FID			***Frequency (MHz)***	399.72	***Nucleus***	1H	***Number of Transients***	56
Original Points Count	13102	***Points Count***	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	48.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2408.4761	***Spectrum Type***	STANDARD			***Sweep Width (Hz)***	6395.40	***Temperature (degree C)***	25.000



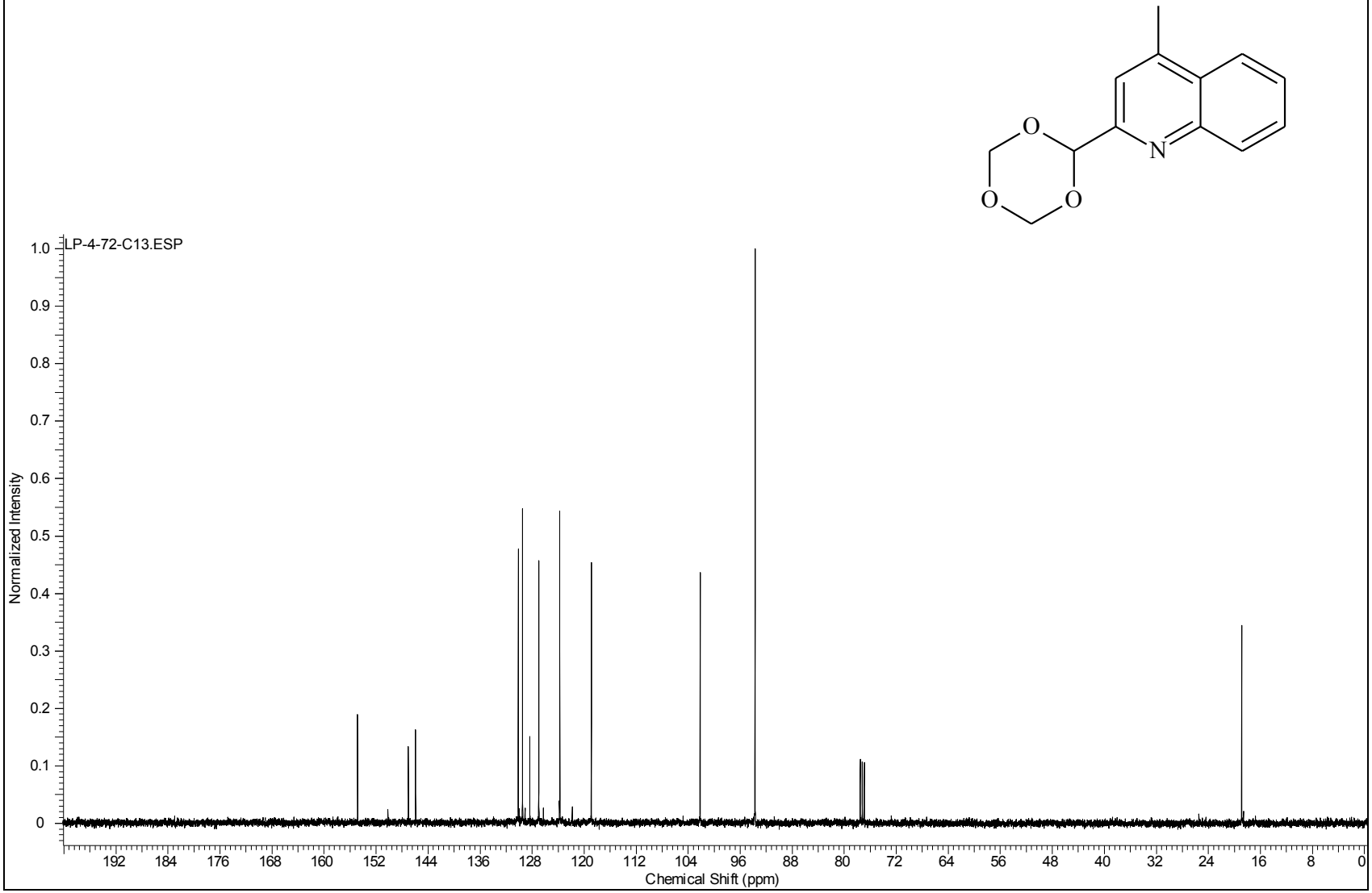
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Jan 2 2012			***Date Stamp***	Jan 2 2012
File Name	F:\LP-6-40-C13.FID\FID			***Frequency (MHz)***	100.52	***Nucleus***	13C	***Number of Transients***	1168
Original Points Count	31375	***Points Count***	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00		
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	10551.8213			***Spectrum Type***	STANDARD
Sweep Width (Hz)	24125.45	***Temperature (degree C)***	25.000						



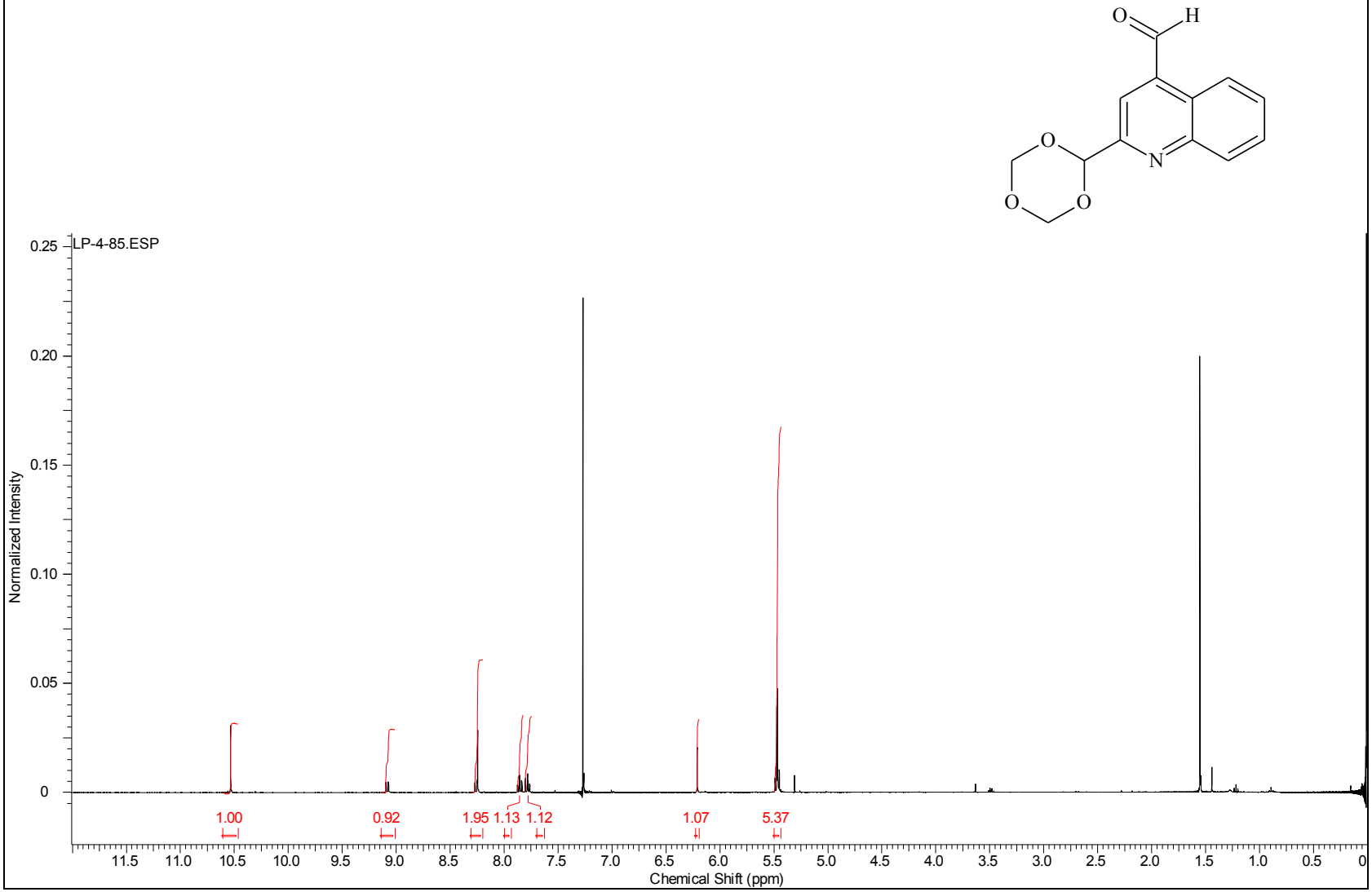
Acquisition Time (sec)	2.0500	***Comment***	Std proton	***Date***	Jan 25 2012			***Date Stamp***	Jan 25 2012
File Name	F:\NMR-NOVA-02-12\LP-4-72.FID\FID			***Frequency (MHz)***	399.72	***Nucleus***	1H	***Number of Transients***	40
Original Points Count	20485	***Points Count***	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00		
Solvent	CHLOROFORM-d			***Spectrum Offset (Hz)***	2409.0603	***Spectrum Type***	STANDARD		
Sweep Width (Hz)	9992.51	***Temperature (degree C)***	25.000						



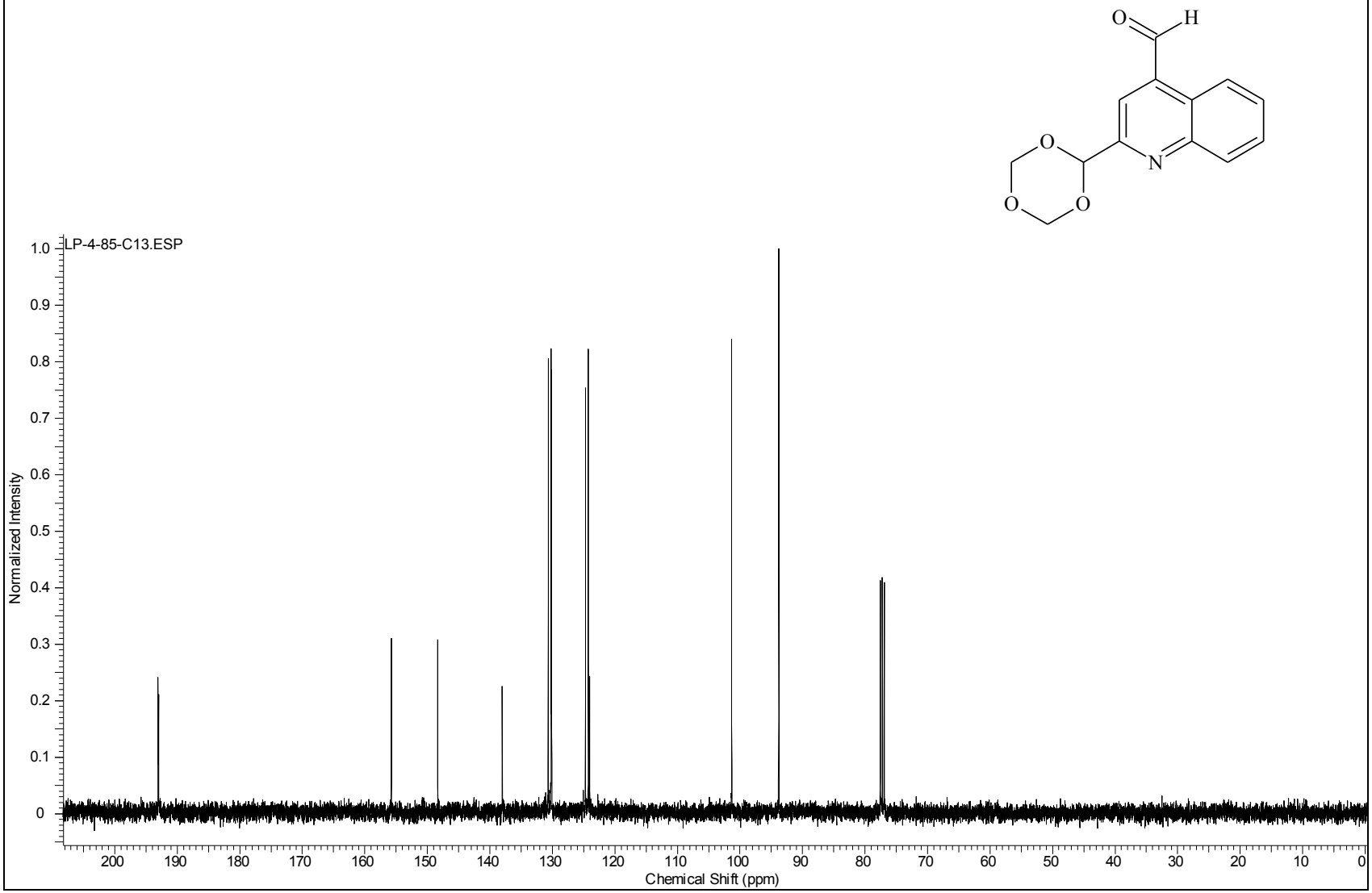
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Jan 25 2012	***Date Stamp***	Jan 25 2012
File Name	F:\NMR-NOVA-02-12\LP-4-72C13.FID\FID			***Frequency (MHz)***	100.52	***Nucleus***	13C
Number of Transients	108	***Original Points Count***	31375	***Points Count***	32768	***Pulse Sequence***	s2pul
Receiver Gain	30.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	10535.6240
Spectrum Type	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	25.000		



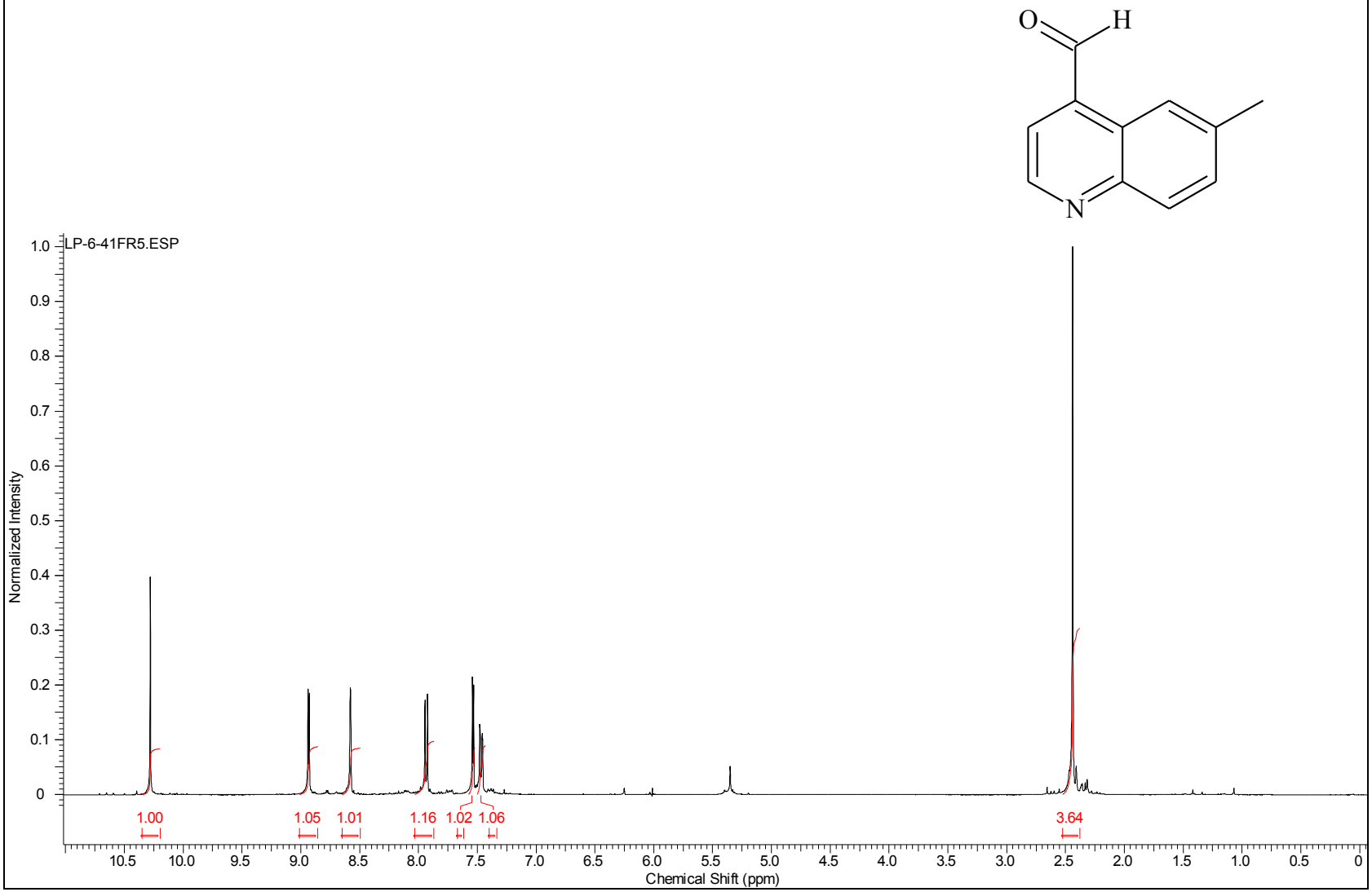
Acquisition Time (sec)	2.0487	***Comment***	Std proton	***Date***	Aug 19 2010	***Date Stamp***	Aug 19 2010
File Name	C:\USERS\LAXMAN\DESKTOP\NMR\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-85FR3.FID\FID						
Frequency (MHz)	399.74	***Nucleus***	1H	***Number of Transients***	76	***Original Points Count***	13103
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	52.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2417.1301	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6395.91	***Temperature (degree C)***	25.000



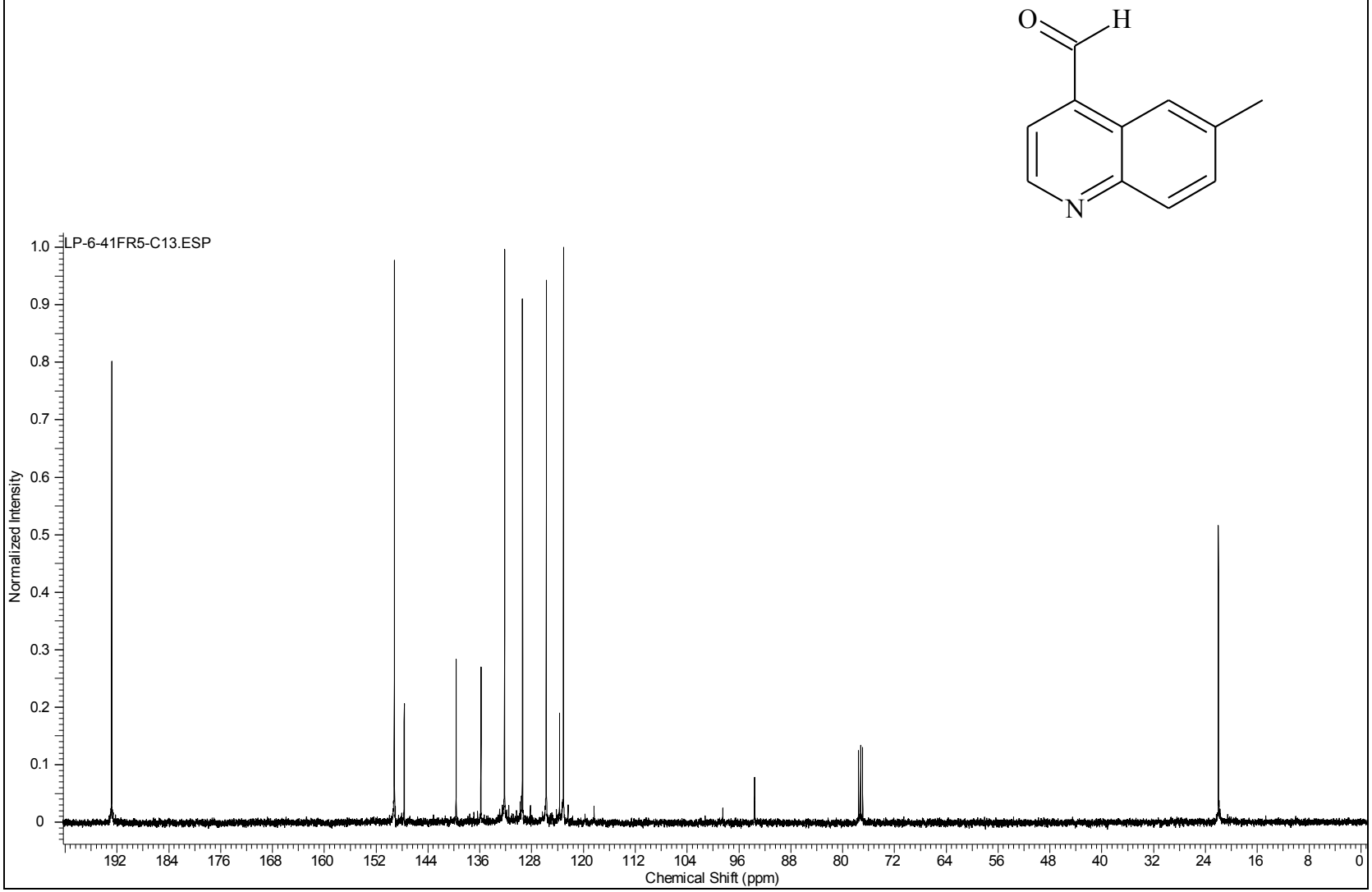
Acquisition Time (sec)	1.3005	***Comment***	Std proton	***Date***	Aug 26 2010	***Date Stamp***	Aug 26 2010
File Name	C:\USERS\LAXMAN\DESKTOP\NMR\LAXMAN POKHREL\LAXMAN(NOVA)-03-15-11\LPOKHREL\LP-4-85-C13.FID\FID						
Frequency (MHz)	100.52	***Nucleus***	13C	***Number of Transients***	300	***Original Points Count***	31375
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10546.2480	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24125.45	***Temperature (degree C)***	30.000



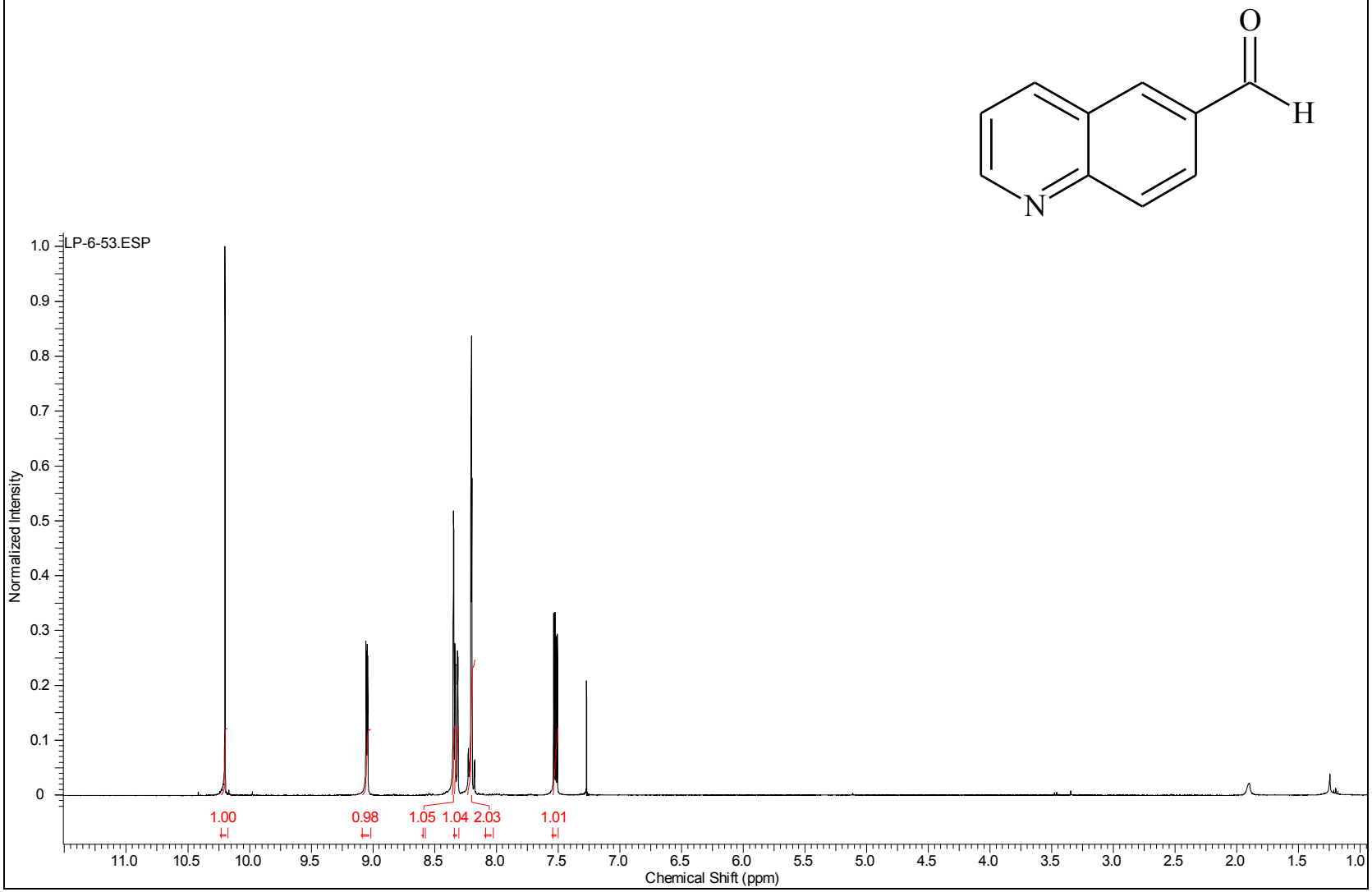
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Jan 24 2012
Date Stamp	Jan 24 2012	***File Name***	F:\NMR-MERCURY-02012\LP-6-41FR5.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	10	***Original Points Count***	12783	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	12.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2404.5349	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



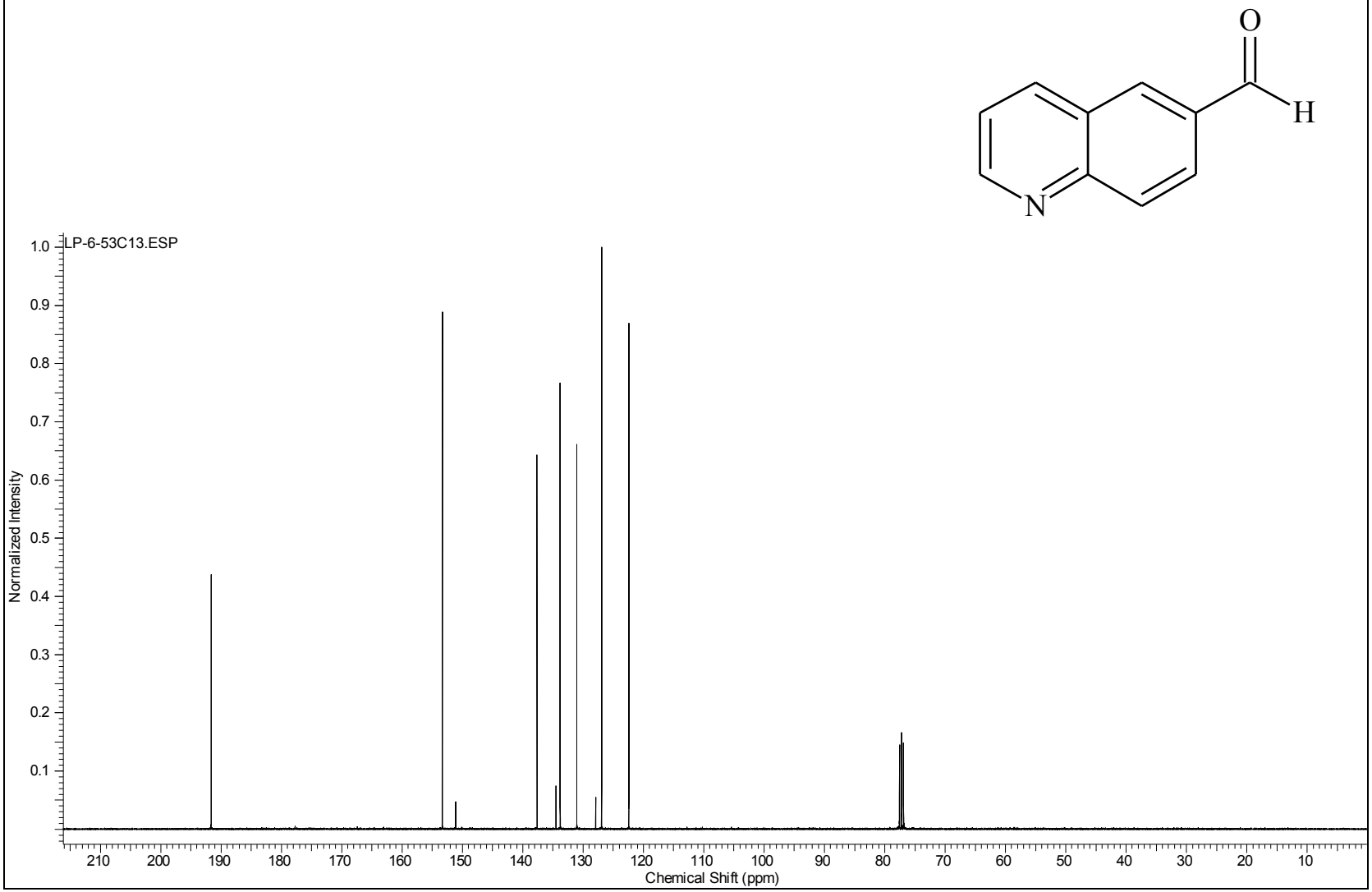
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jan 24 2012
Date Stamp	Jan 24 2012	***File Name***	F:\NMR-MERCURY-02012\LP-6-41FR5-C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	216	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10536.9814	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



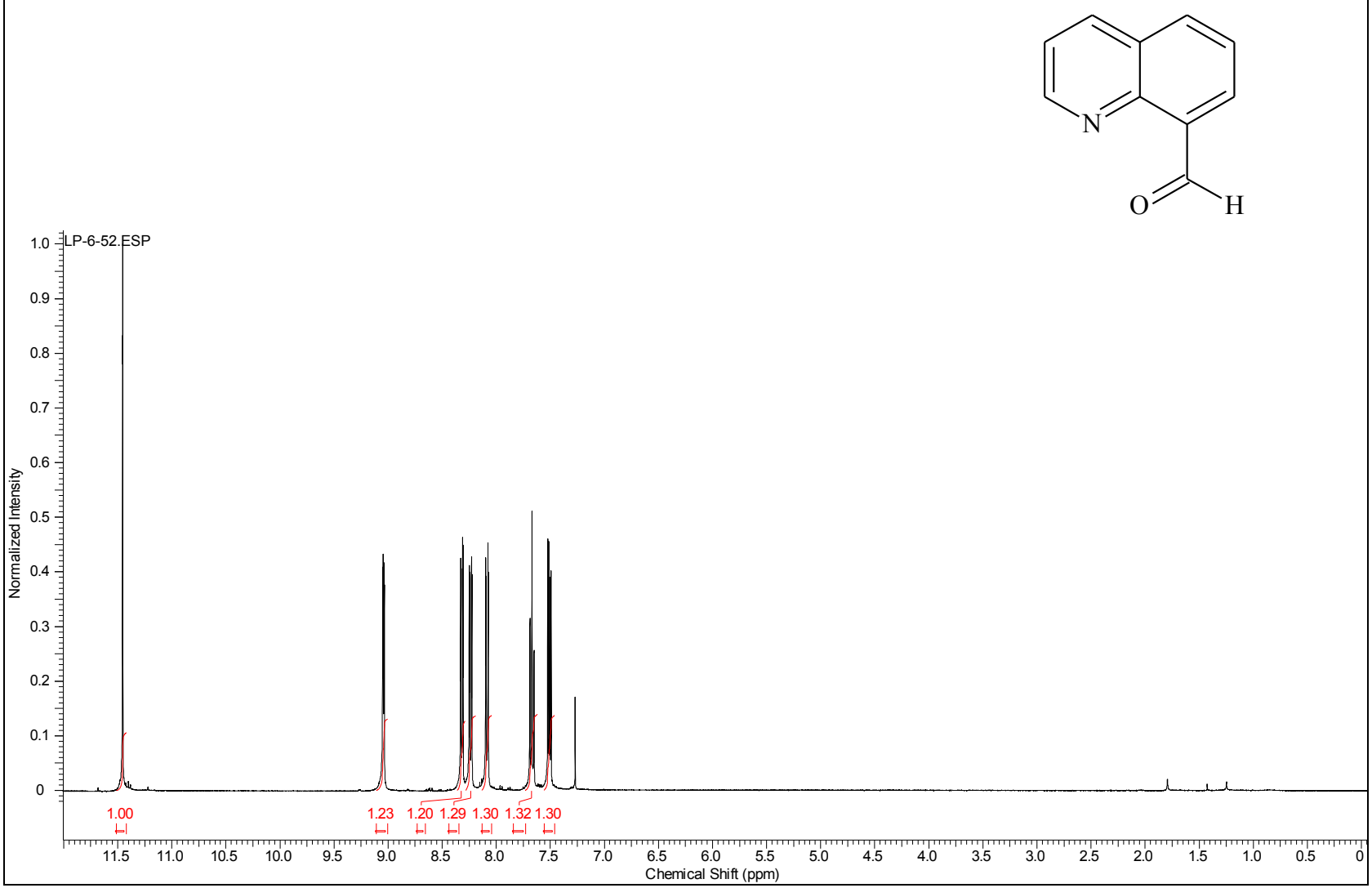
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Jan 26 2012
Date Stamp	Jan 26 2012	***File Name***	F:\NMR-MERCURY-02012\LP-6-53.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	20	***Original Points Count***	12783	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2403.7539	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



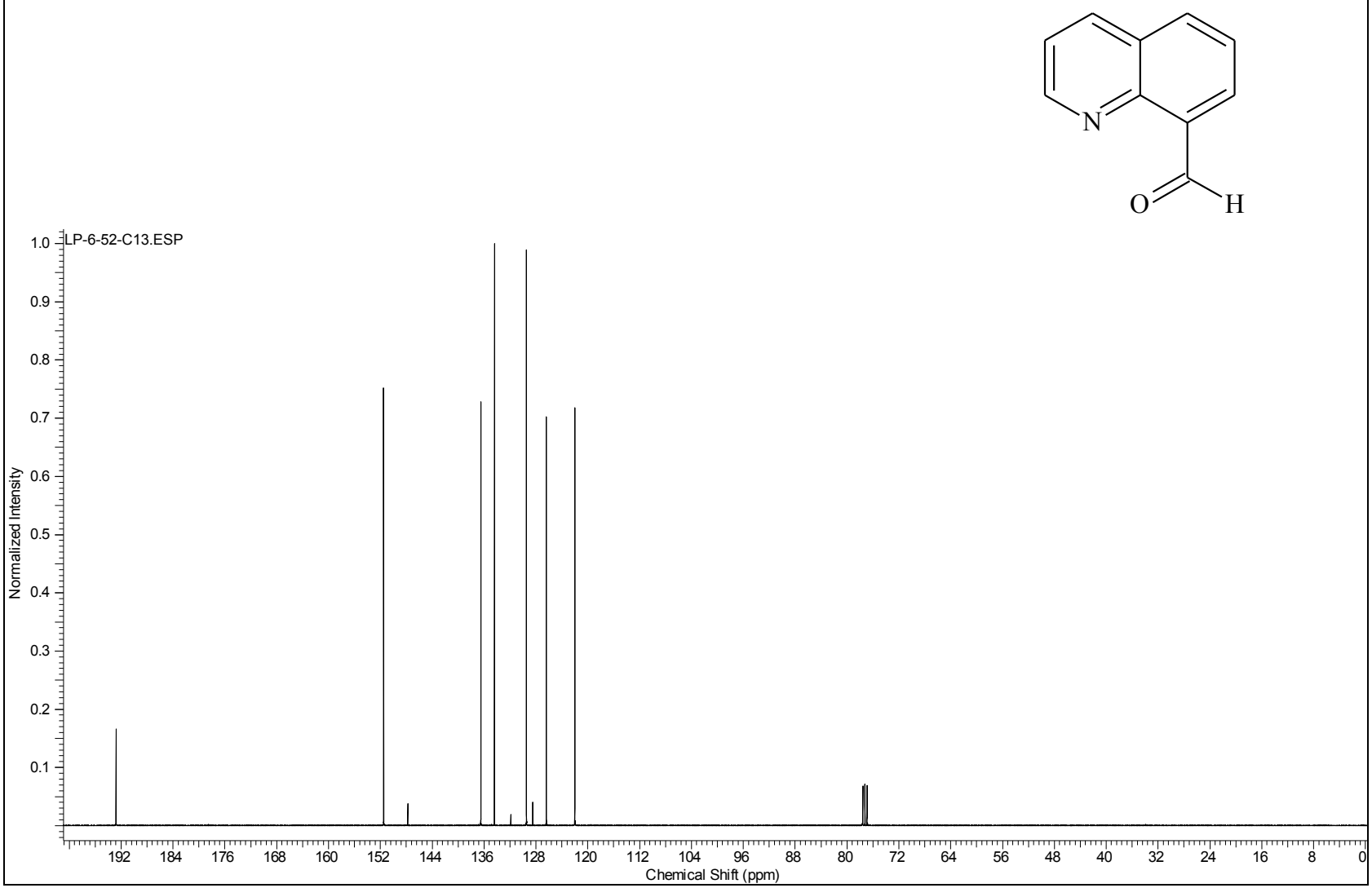
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jan 26 2012
Date Stamp	Jan 26 2012	***File Name***	F:\NMR-MERCURY-02012\LP-6-53C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	252	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10556.8848	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



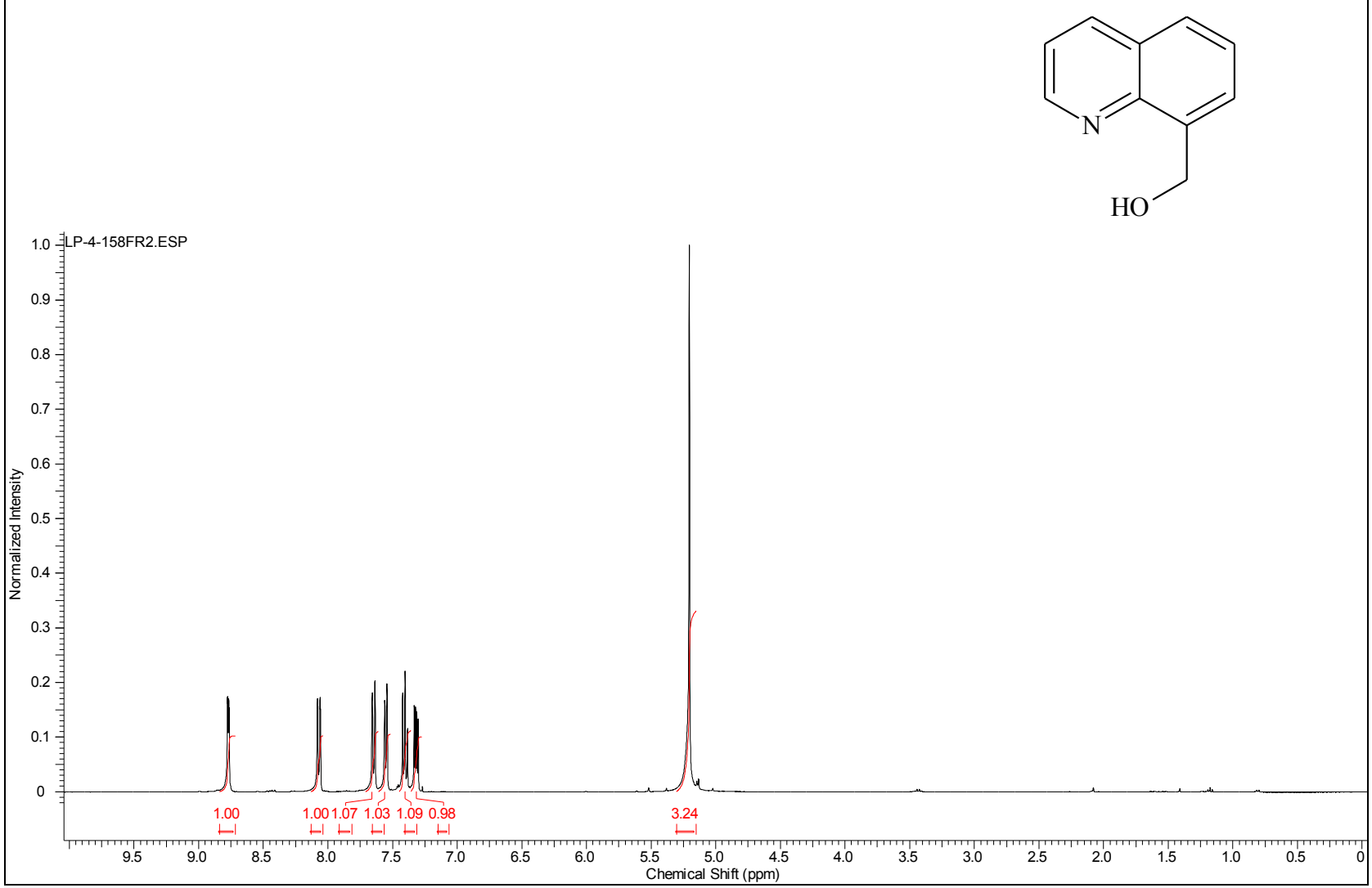
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Jan 24 2012
Date Stamp	Jan 24 2012	***File Name***	F:\NMR-MERCURY-02012\LP-6-52.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	8	***Original Points Count***	12783	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	24.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2404.1443	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



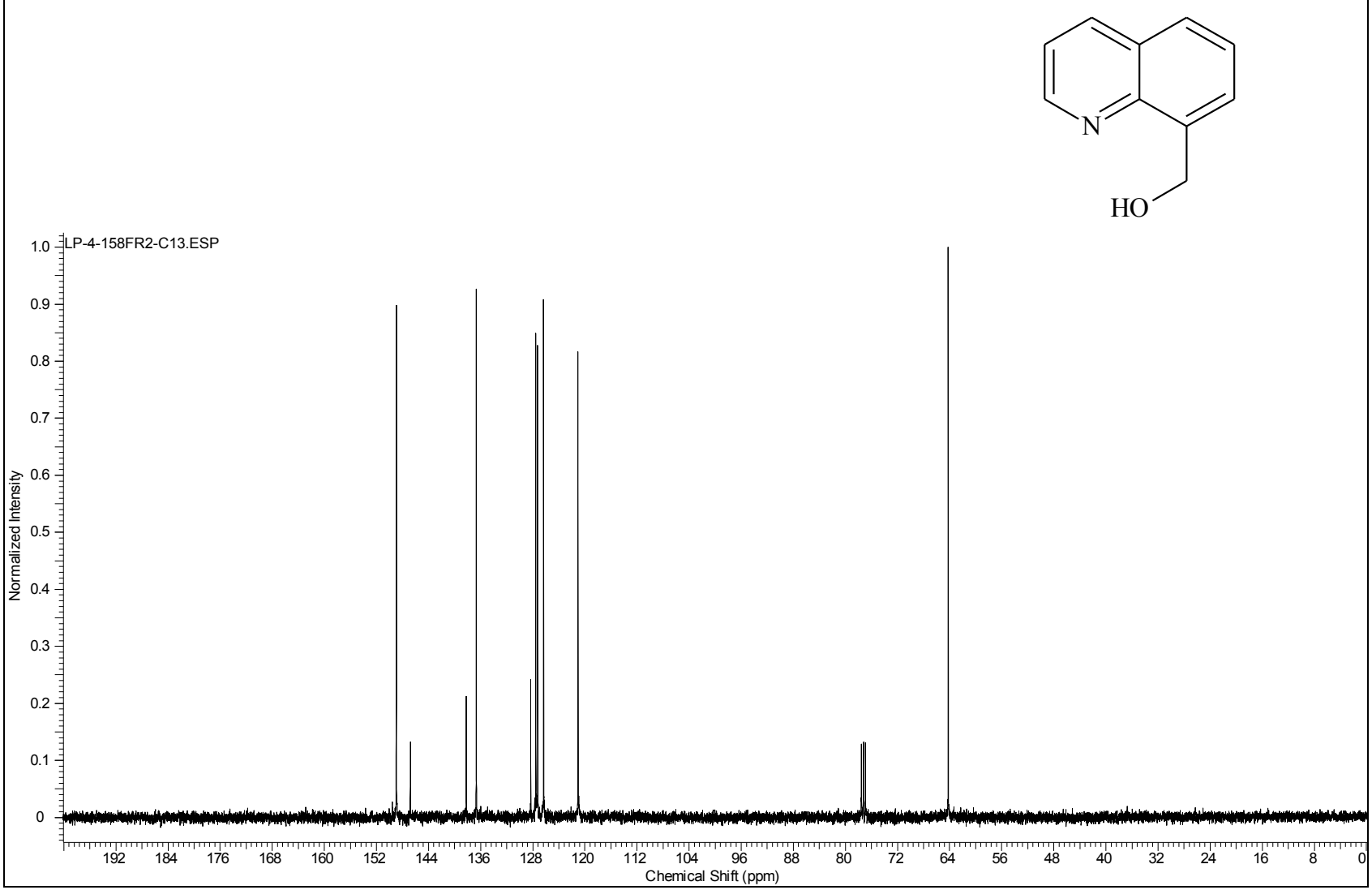
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jan 24 2012
Date Stamp	Jan 24 2012	***File Name***	F:\NMR-MERCURY-02012\LP-6-52C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	316	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10556.1475	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



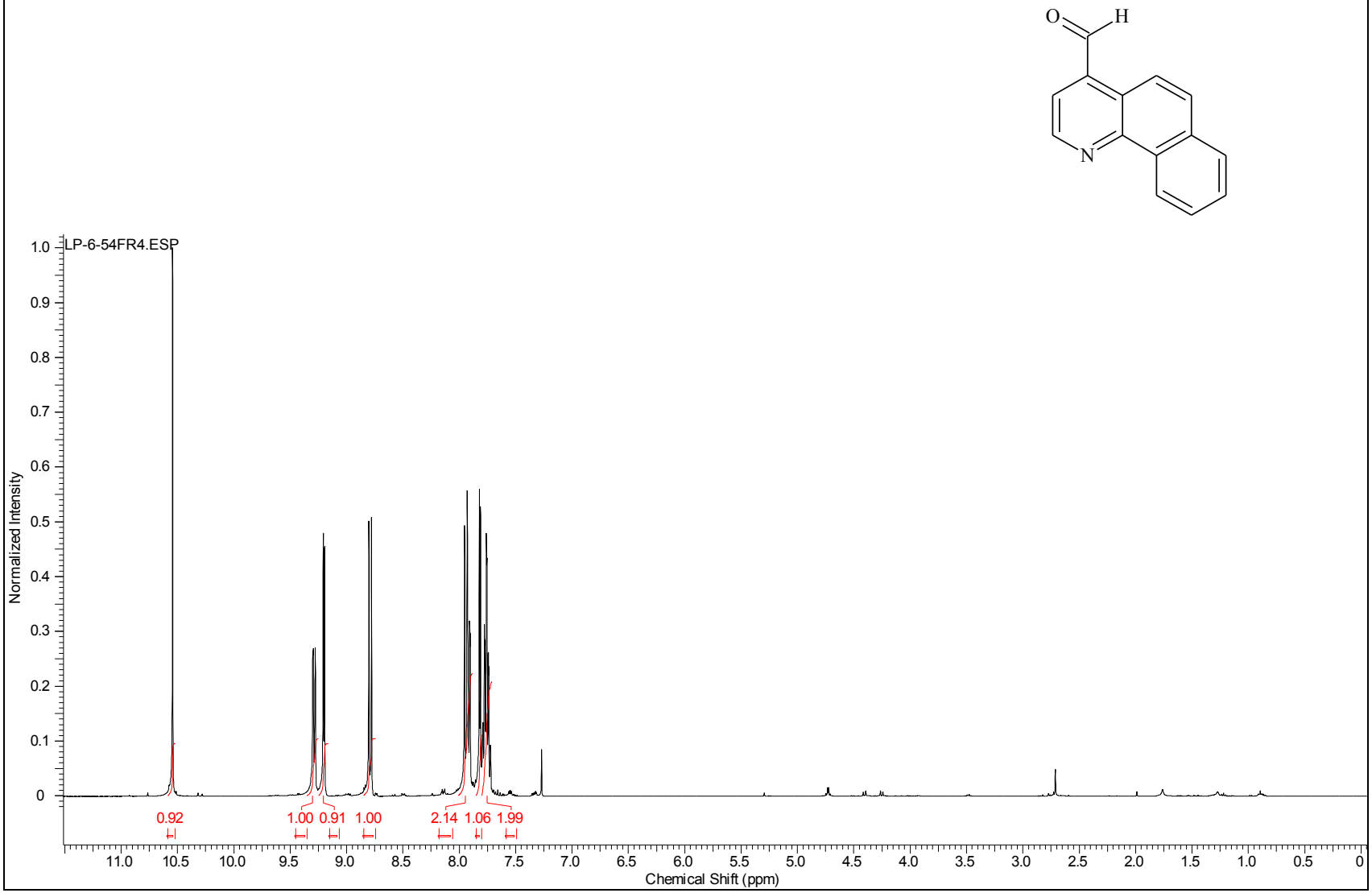
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Jan 24 2012
Date Stamp	Jan 24 2012	***File Name***	F:\NMR-MERCURY-02012\LP-4-158FR2.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	20	***Original Points Count***	12783	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	12.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2404.1443	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



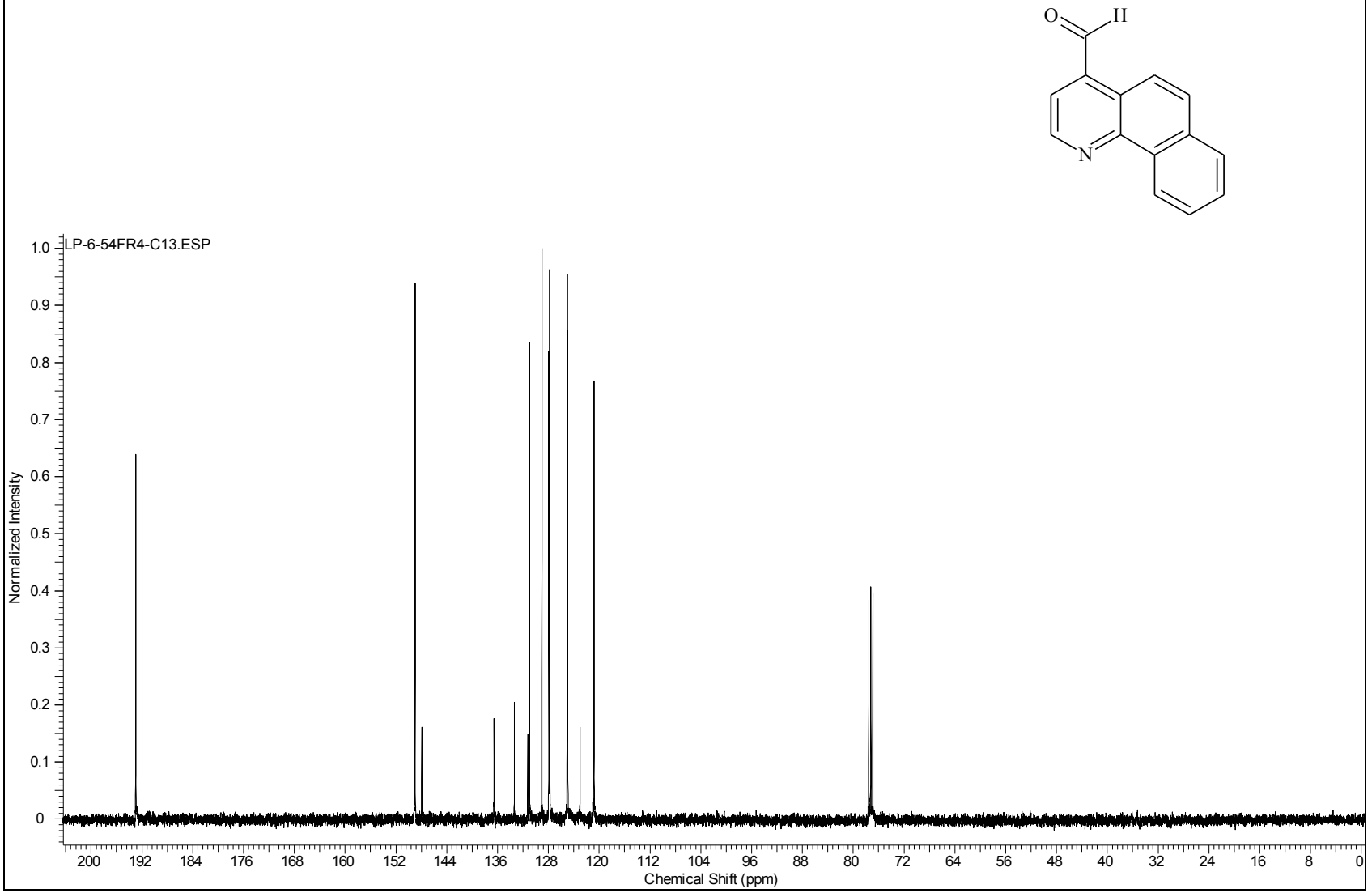
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jan 24 2012
Date Stamp	Jan 24 2012	***File Name***	F:\NMR-MERCURY-02012\LP-4-158FR2C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	56	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10535.5068	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



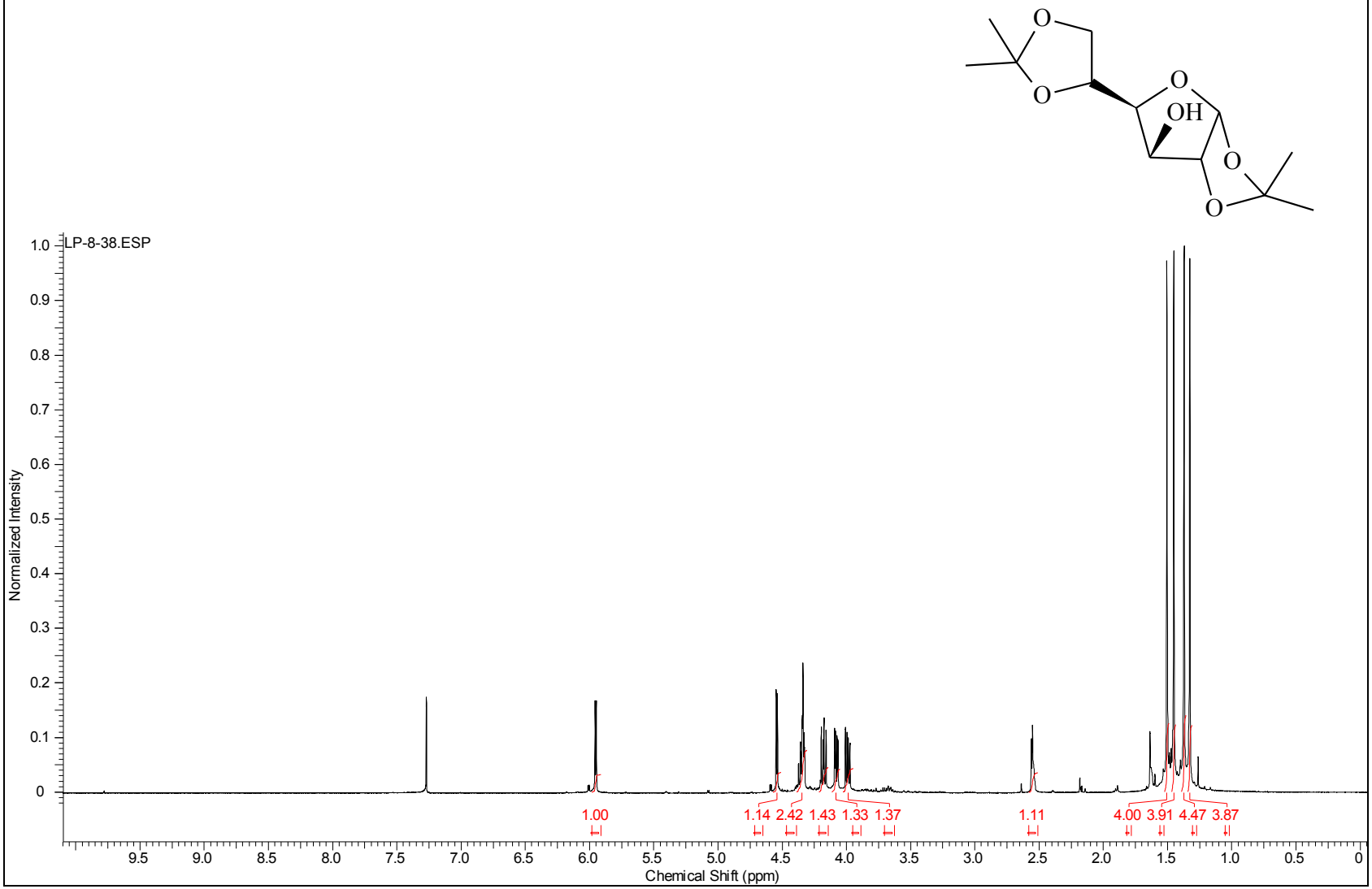
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Jan 27 2012
Date Stamp	Jan 27 2012	***File Name***	F:\NMR-MERCURY-02012\LP-6-54FR4-DP.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	40	***Original Points Count***	12783	***Points Count***	16384
Pulse Sequence	s2pul	***Receiver Gain***	24.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	2404.7432	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



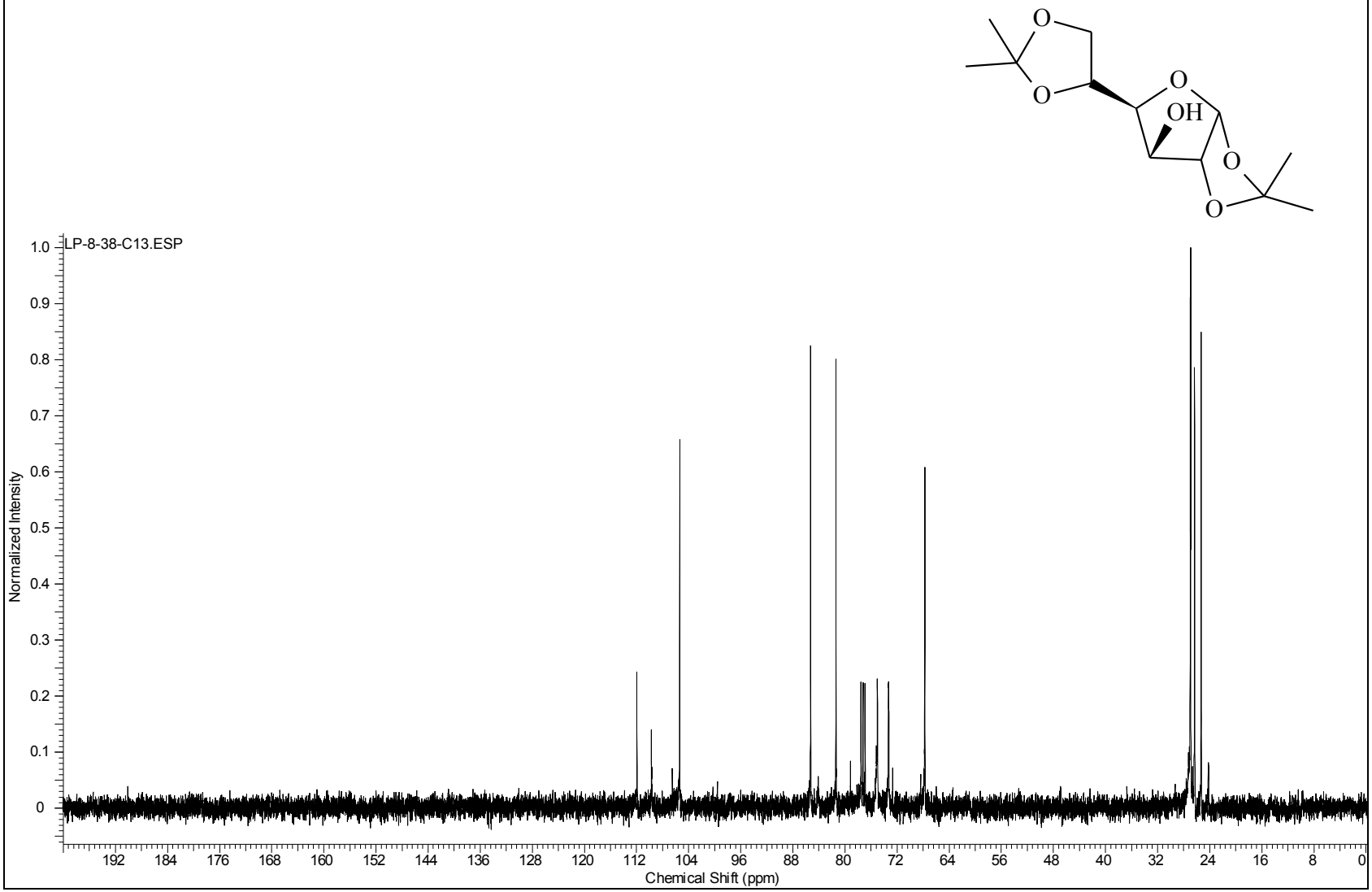
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Jan 27 2012
Date Stamp	Jan 27 2012	***File Name***	F:\NMR-MERCURY-02012\LP-6-54FR4-C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	848	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10554.6738	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



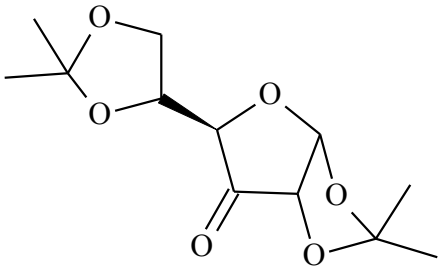
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Oct 17 2012
Date Stamp	Oct 17 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-38DP.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	32	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	28.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2404.1443	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000

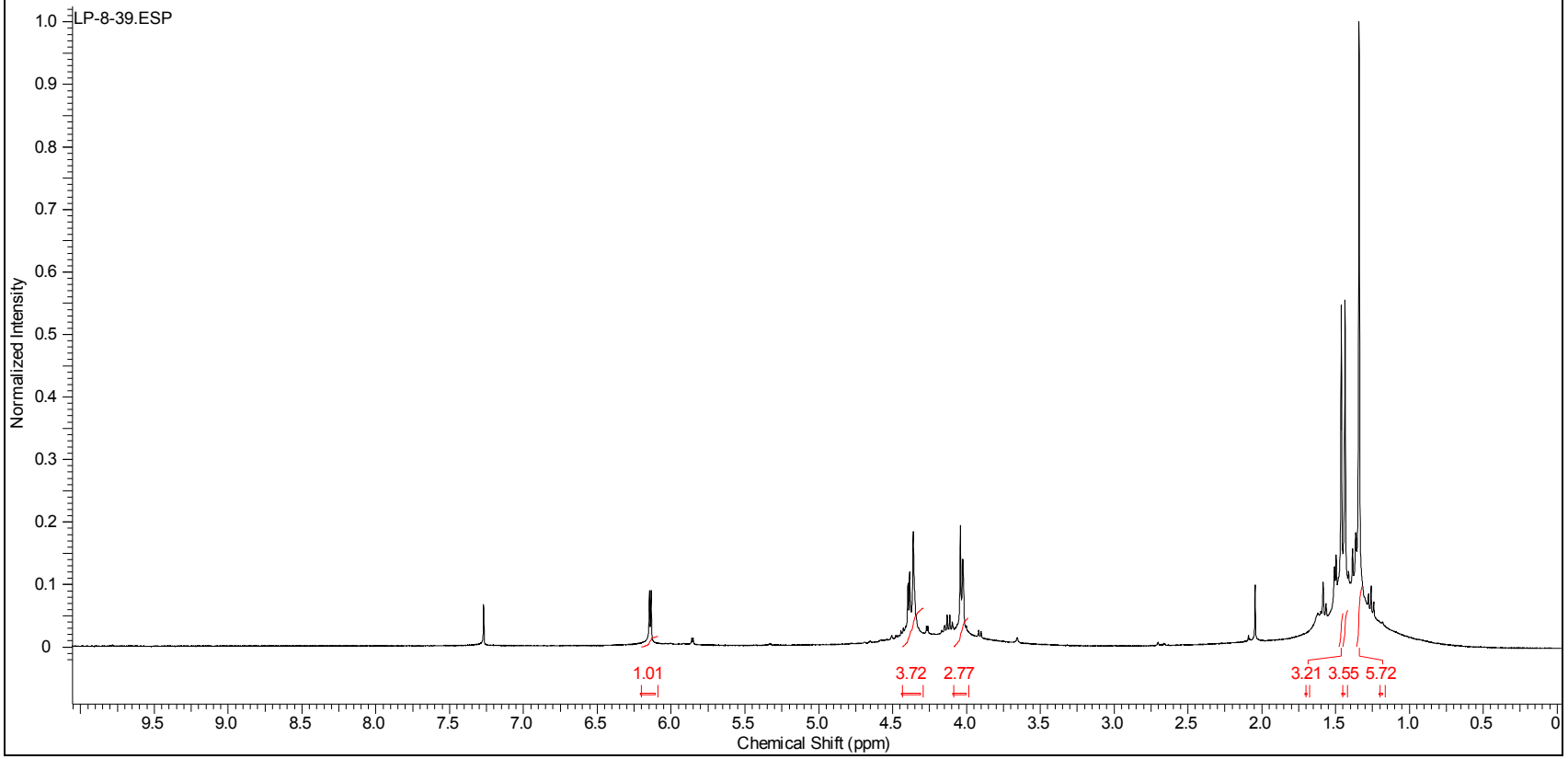


Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Oct 17 2012
Date Stamp	Oct 17 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-38C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	100	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	9243.8975	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000

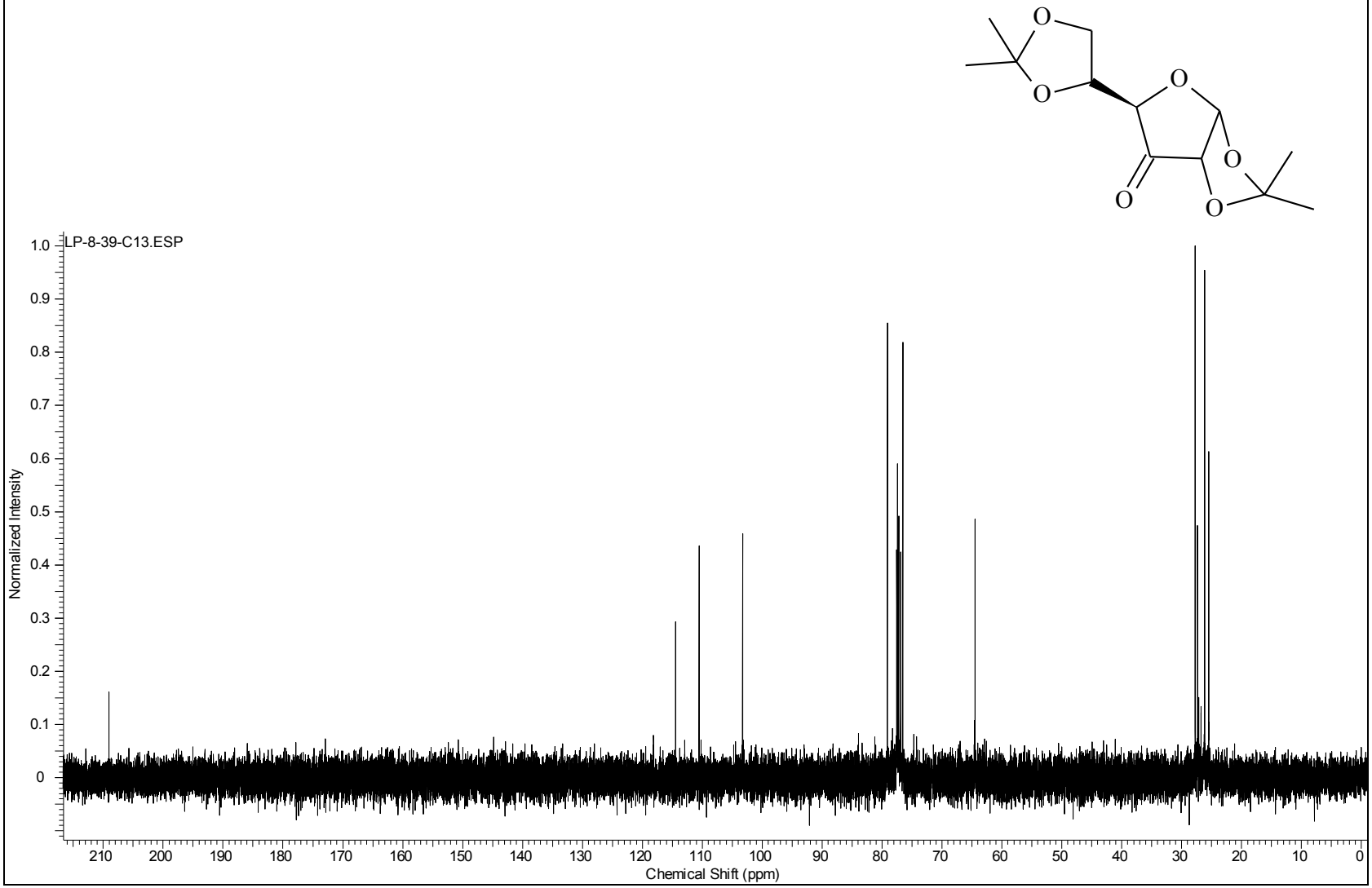


Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Oct 21 2012
Date Stamp	Oct 21 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-39FR3.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	32	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	28.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2403.3633	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000

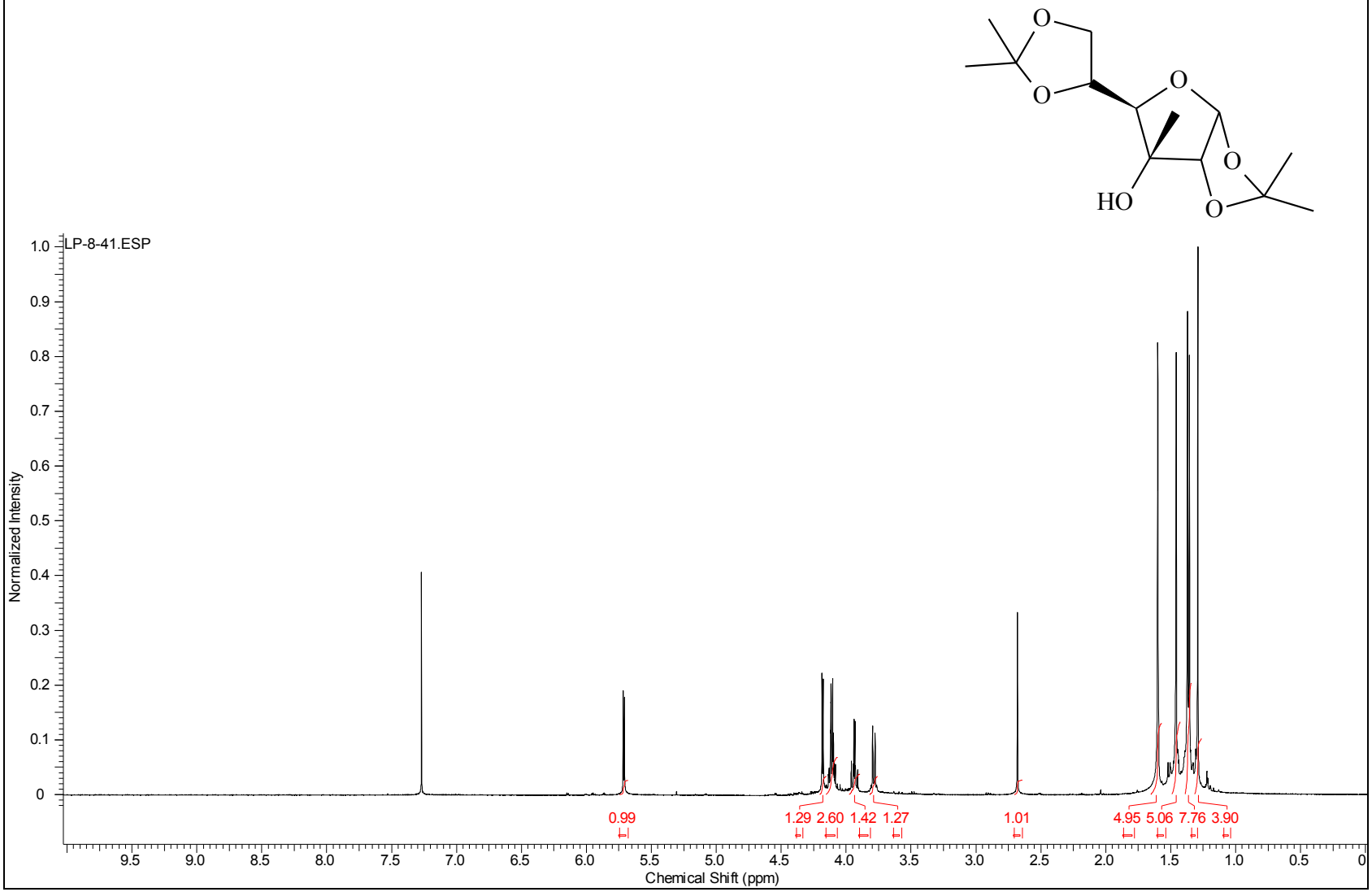




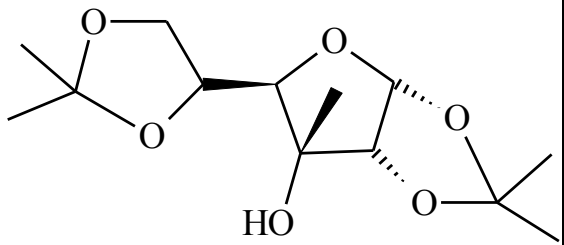
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Oct 21 2012
Date Stamp	Oct 21 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-39FR3C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	248	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10556.8848	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000

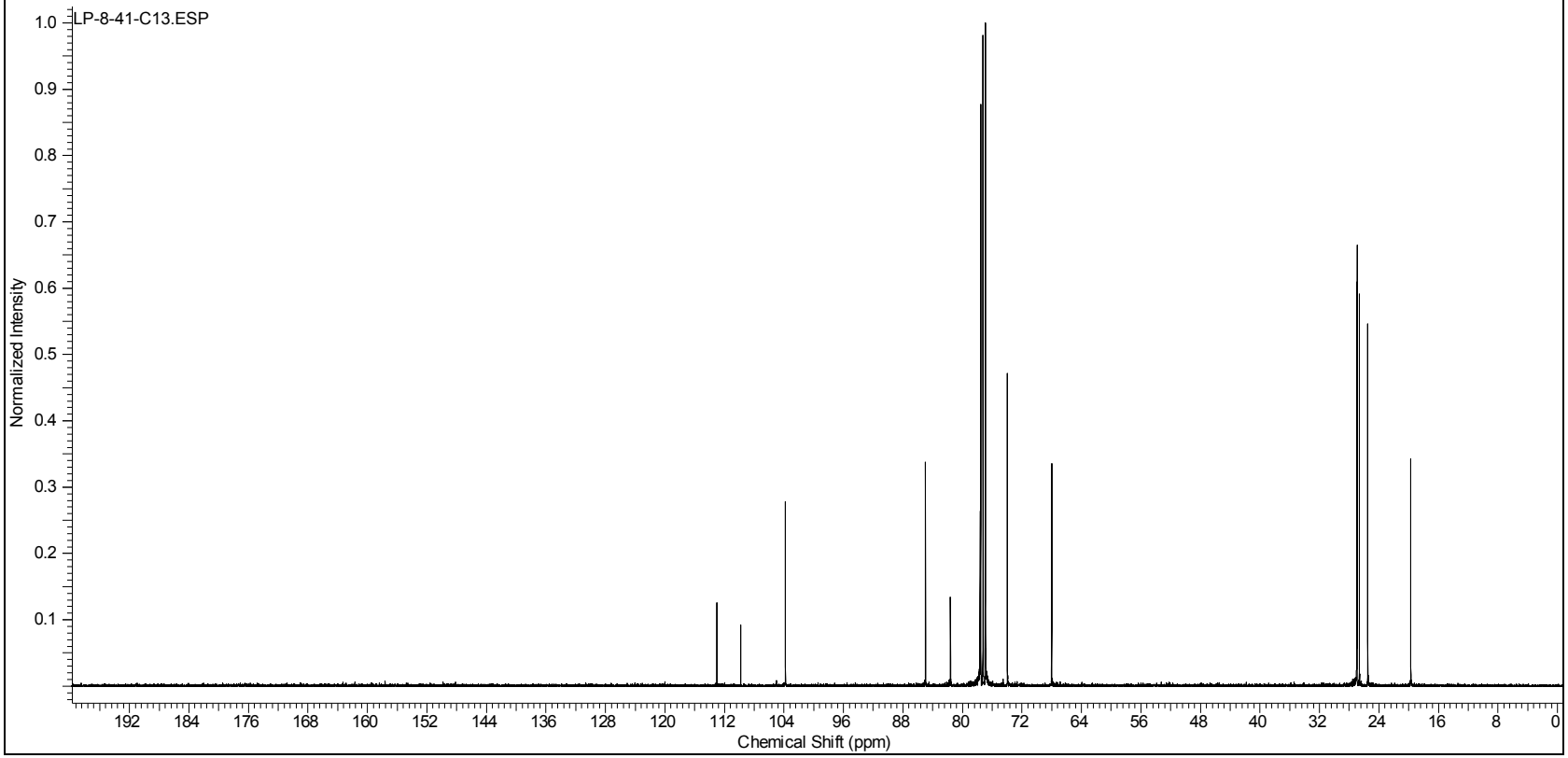


Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Oct 23 2012
Date Stamp	Oct 23 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-41.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	36	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	34.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2404.1443	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000

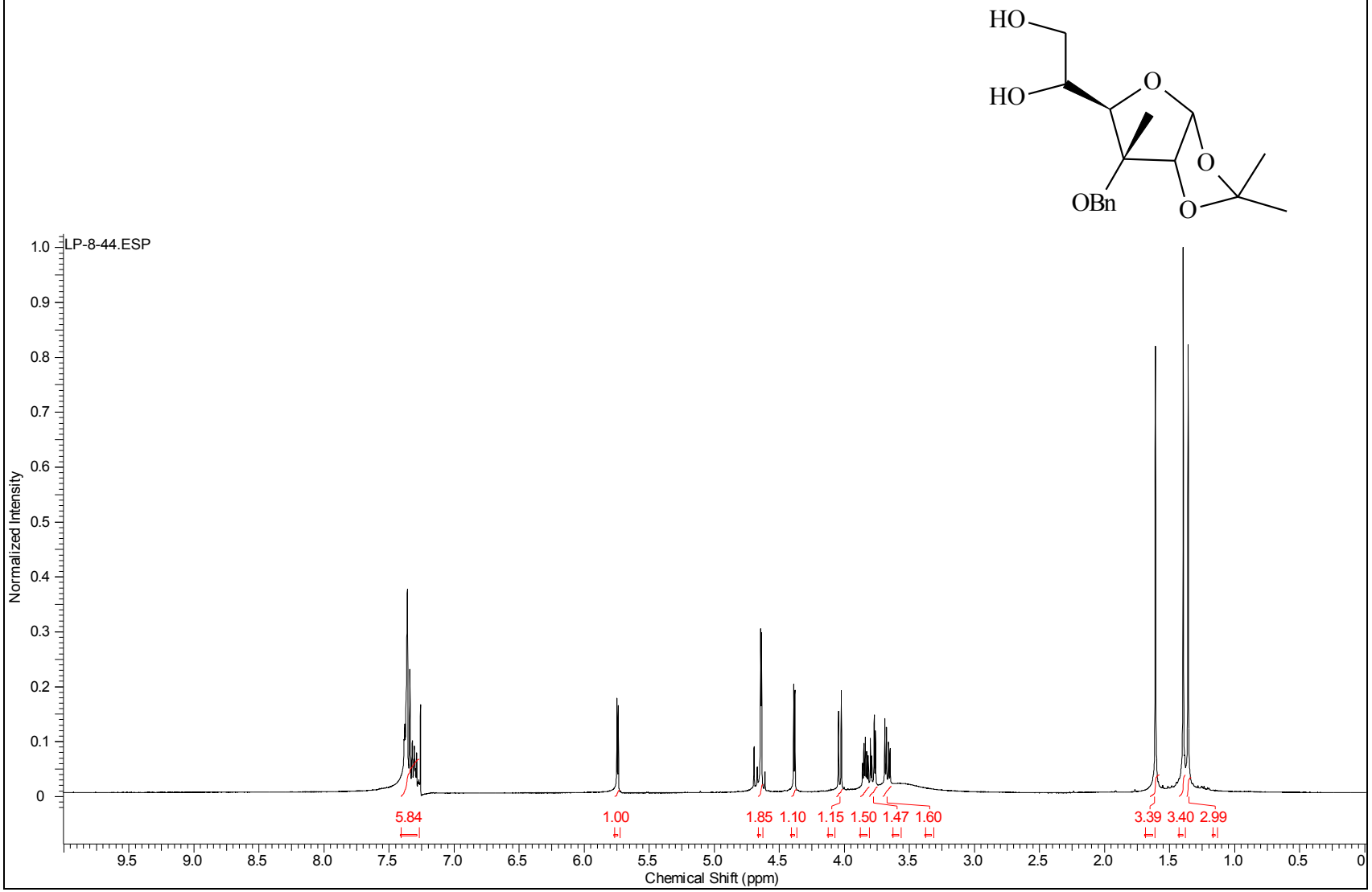


Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Apr 7 2013
Date Stamp	Apr 7 2013	***File Name***	G:\LP-8-41AGAINC13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	3244	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10559.8340	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000

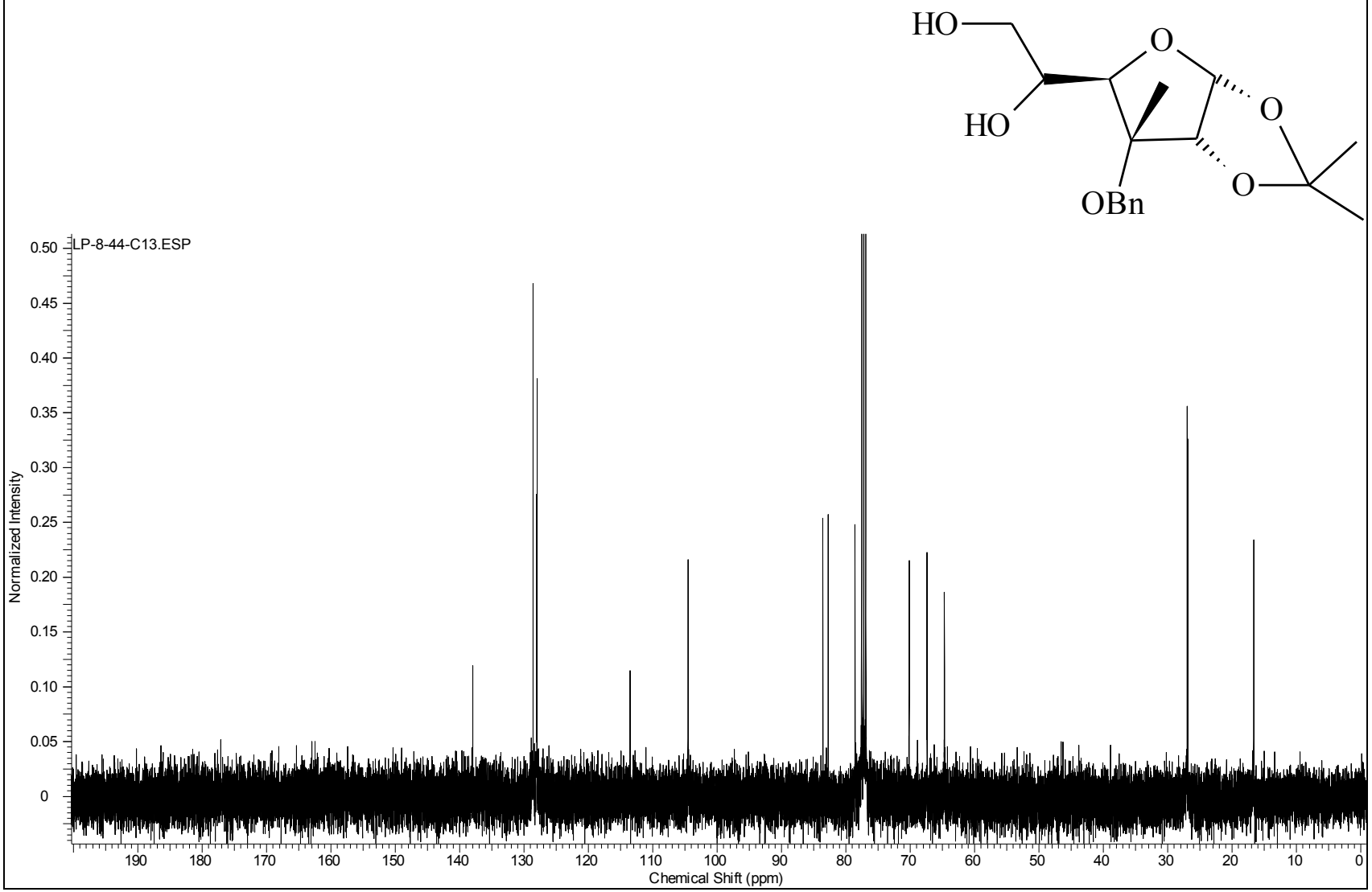




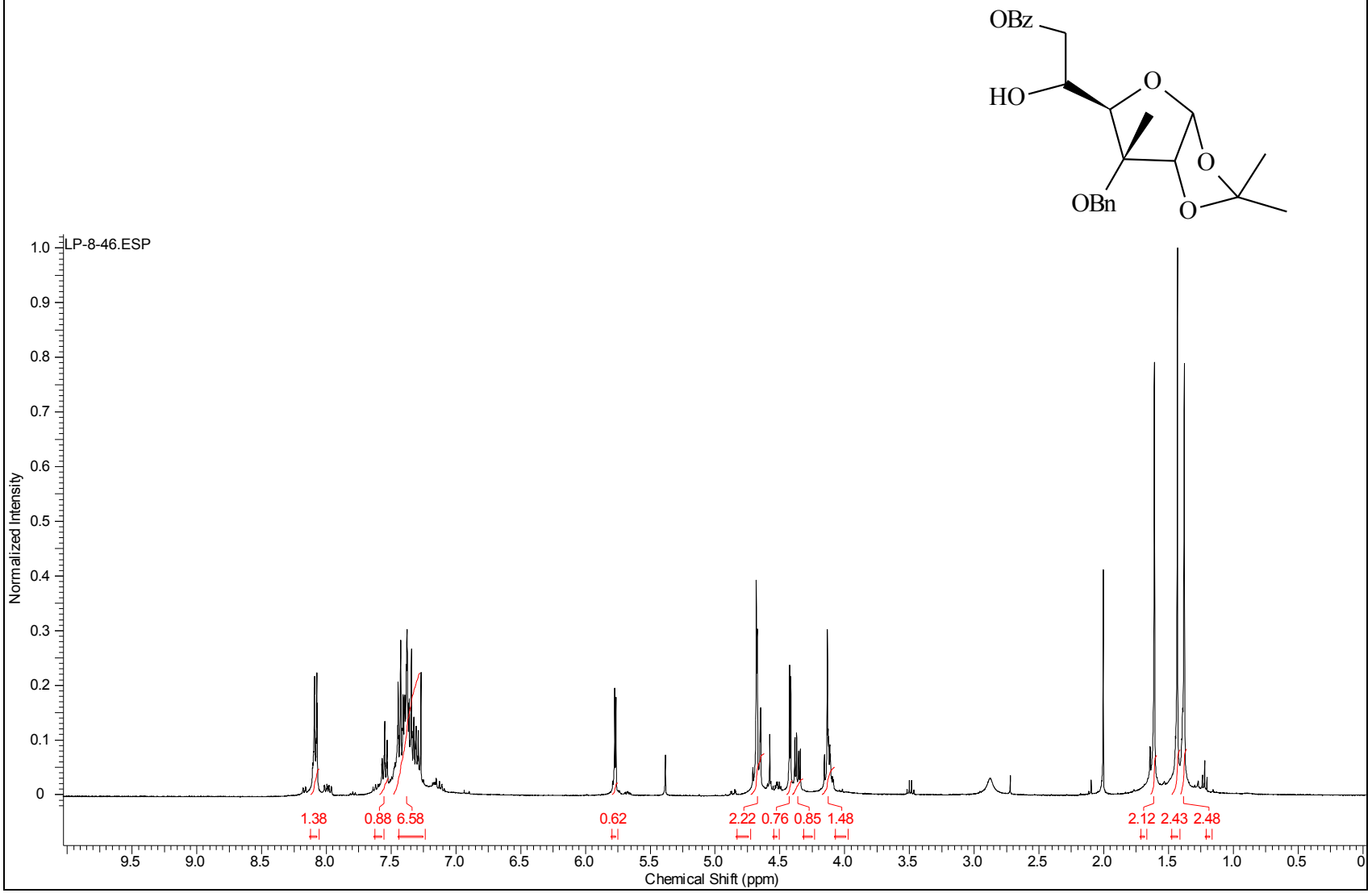
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Nov 1 2012
Date Stamp	Nov 1 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-44.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	52	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2399.7554	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



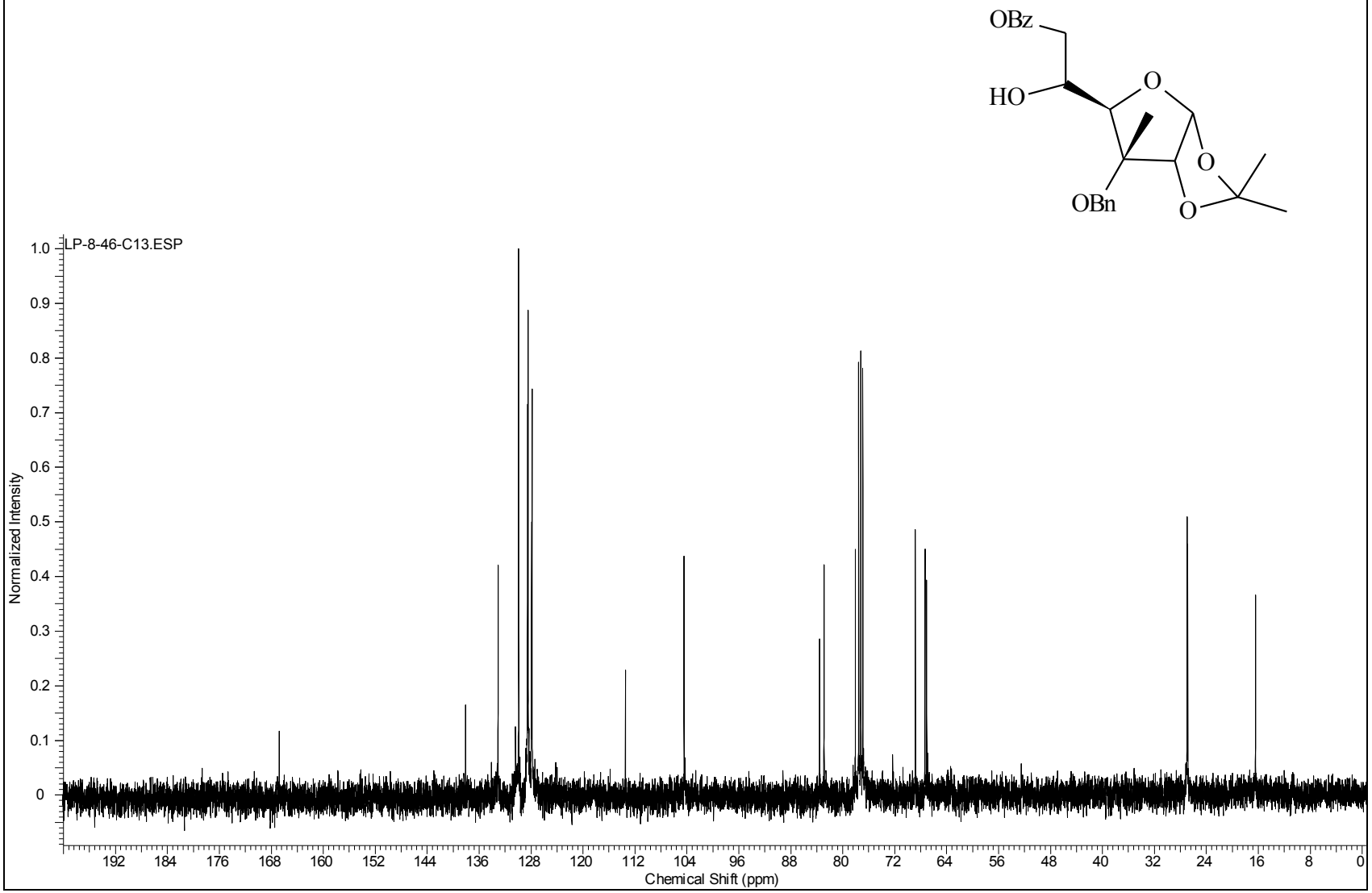
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Apr 7 2013
Date Stamp	Apr 7 2013	***File Name***	G:\LP-8-44AGAINC13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	4484	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10559.8330	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



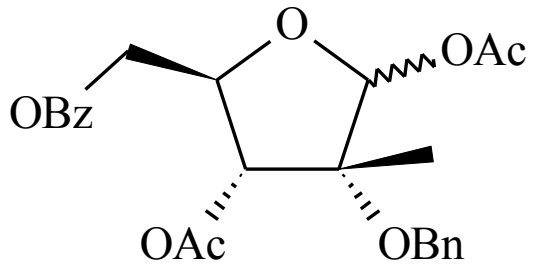
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Nov 2 2012
Date Stamp	Nov 2 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-46.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	28	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	26.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2404.5349	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000

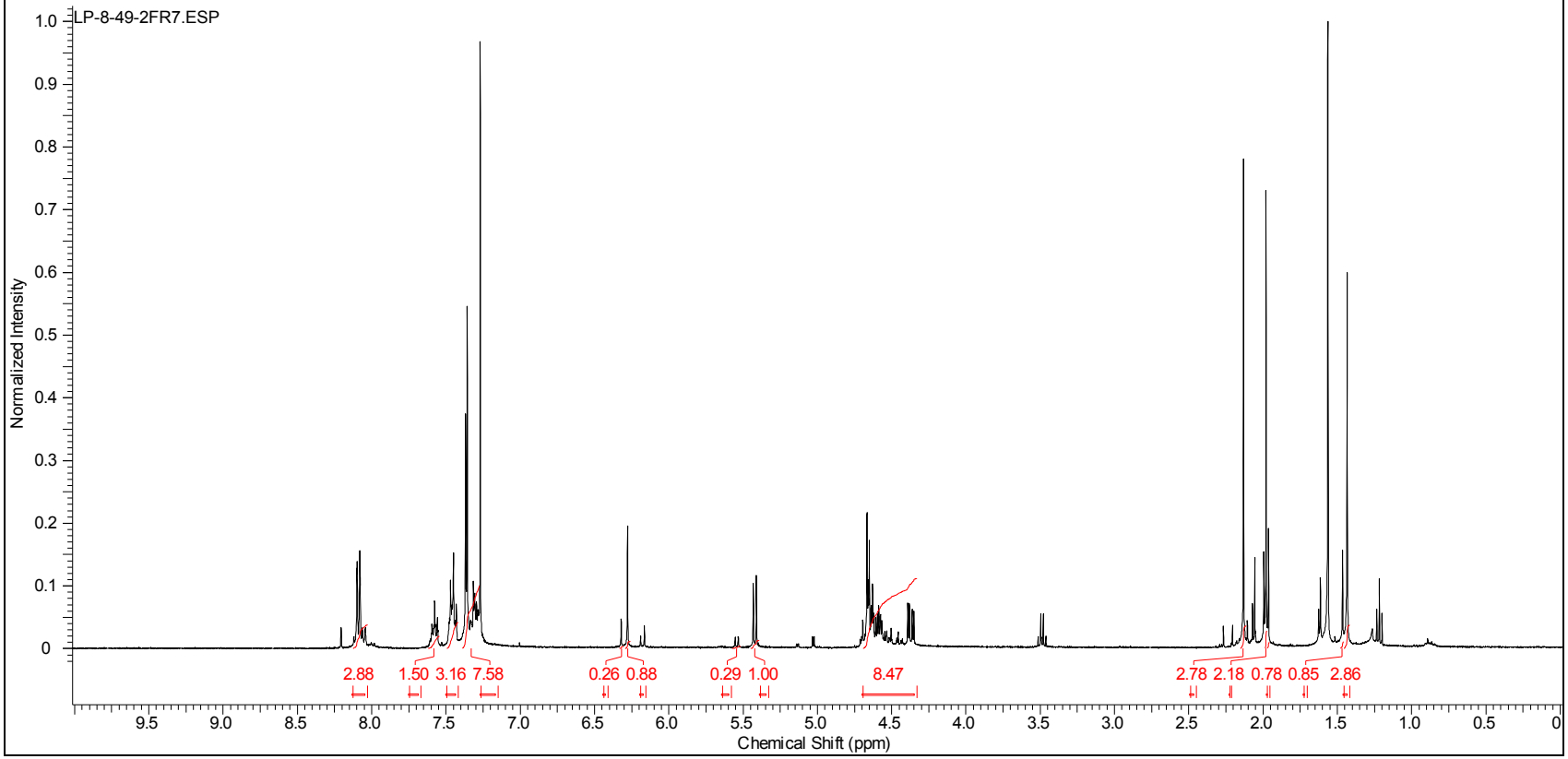


Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Nov 2 2012
Date Stamp	Nov 2 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-46-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	440	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10556.8848	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000

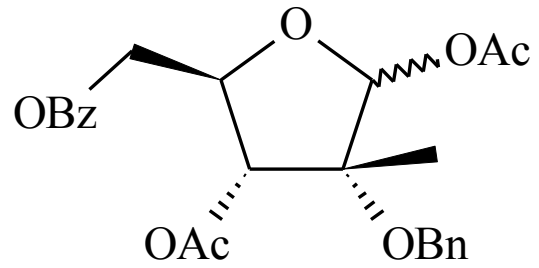


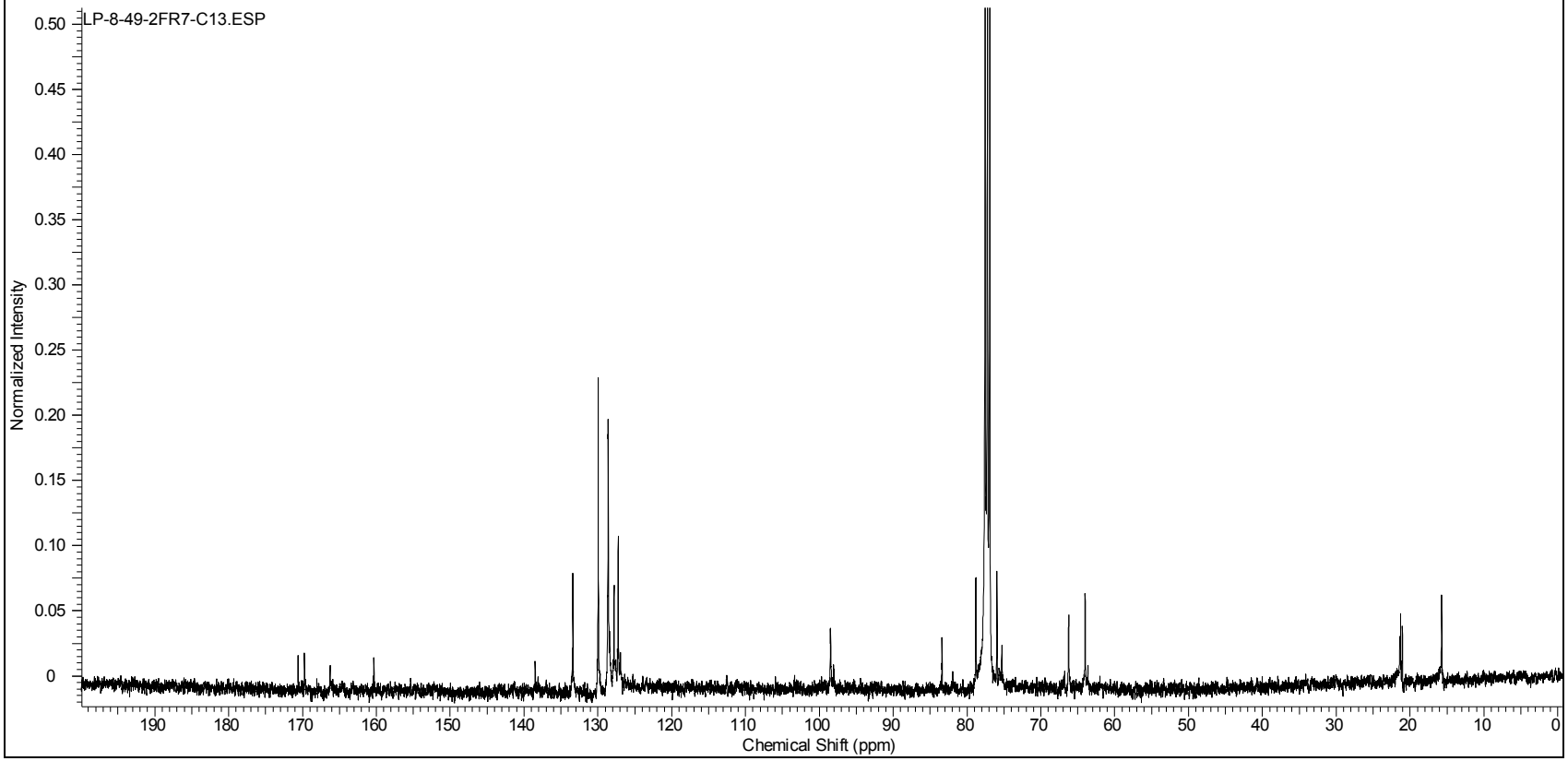
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters		***Date***	May 24 2013	
Date Stamp	May 24 2013			***File Name***	G:\LP-8-49-2FR7.FID\FID	***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	100	***Original Points Count***	12783	***Points Count***	16384	***Pulse Sequence***	s2pul
Receiver Gain	39.00	***Solvent***	CHLOROFORM-d			***Spectrum Offset (Hz)***	2403.7539	***Spectrum Type***	STANDARD
Sweep Width (Hz)	6397.95	***Temperature (degree C)***	25.000						



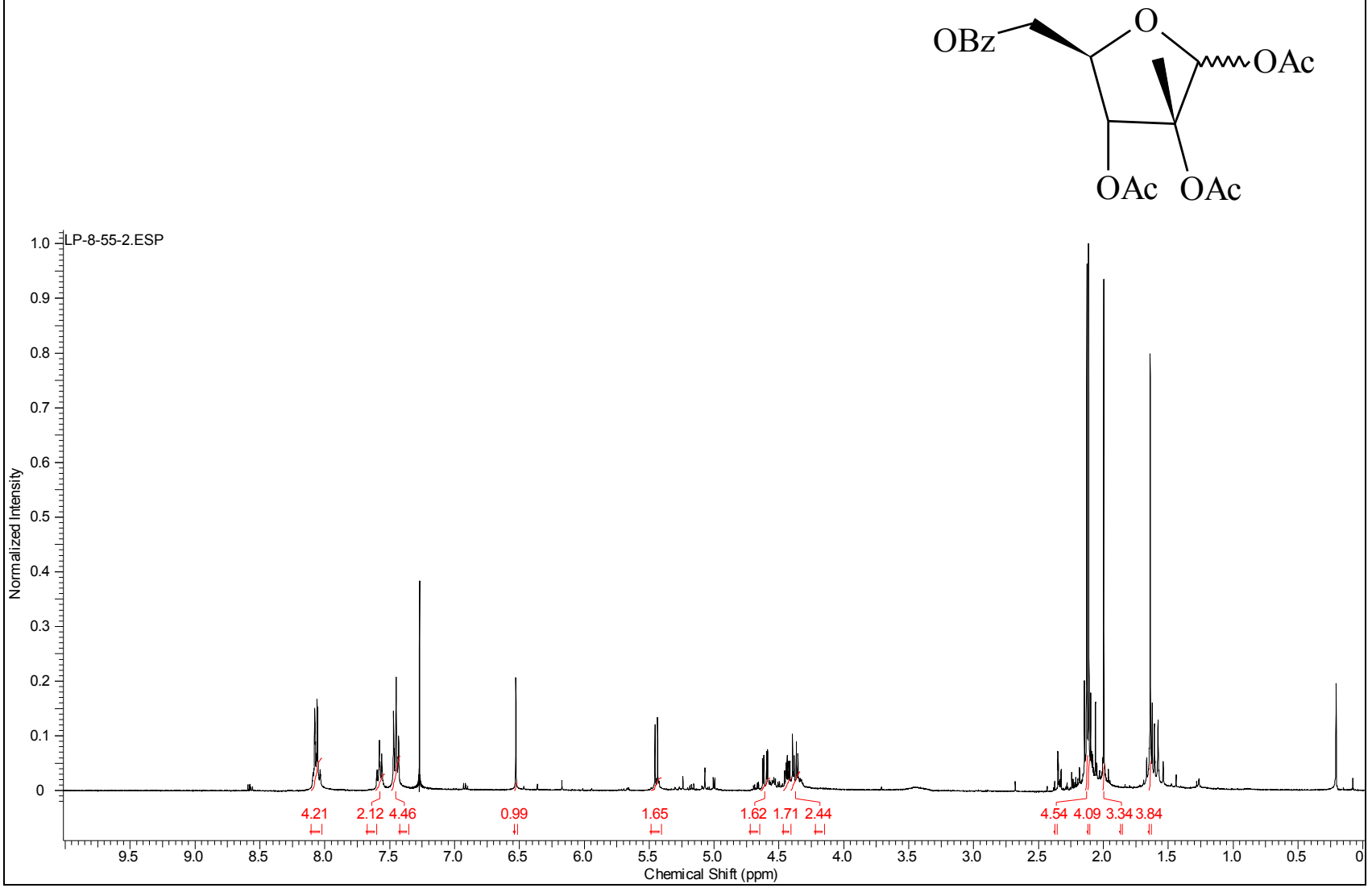


Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	May 24 2013
Date Stamp	May 24 2013	***File Name***	G:\LP-8-49-2FR7-C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	30816	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d		
Spectrum Offset (Hz)	10559.8418	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000

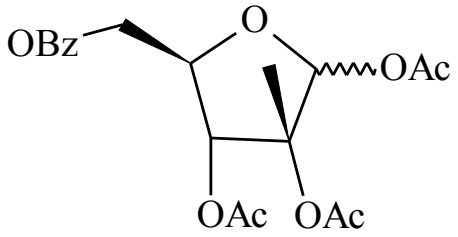


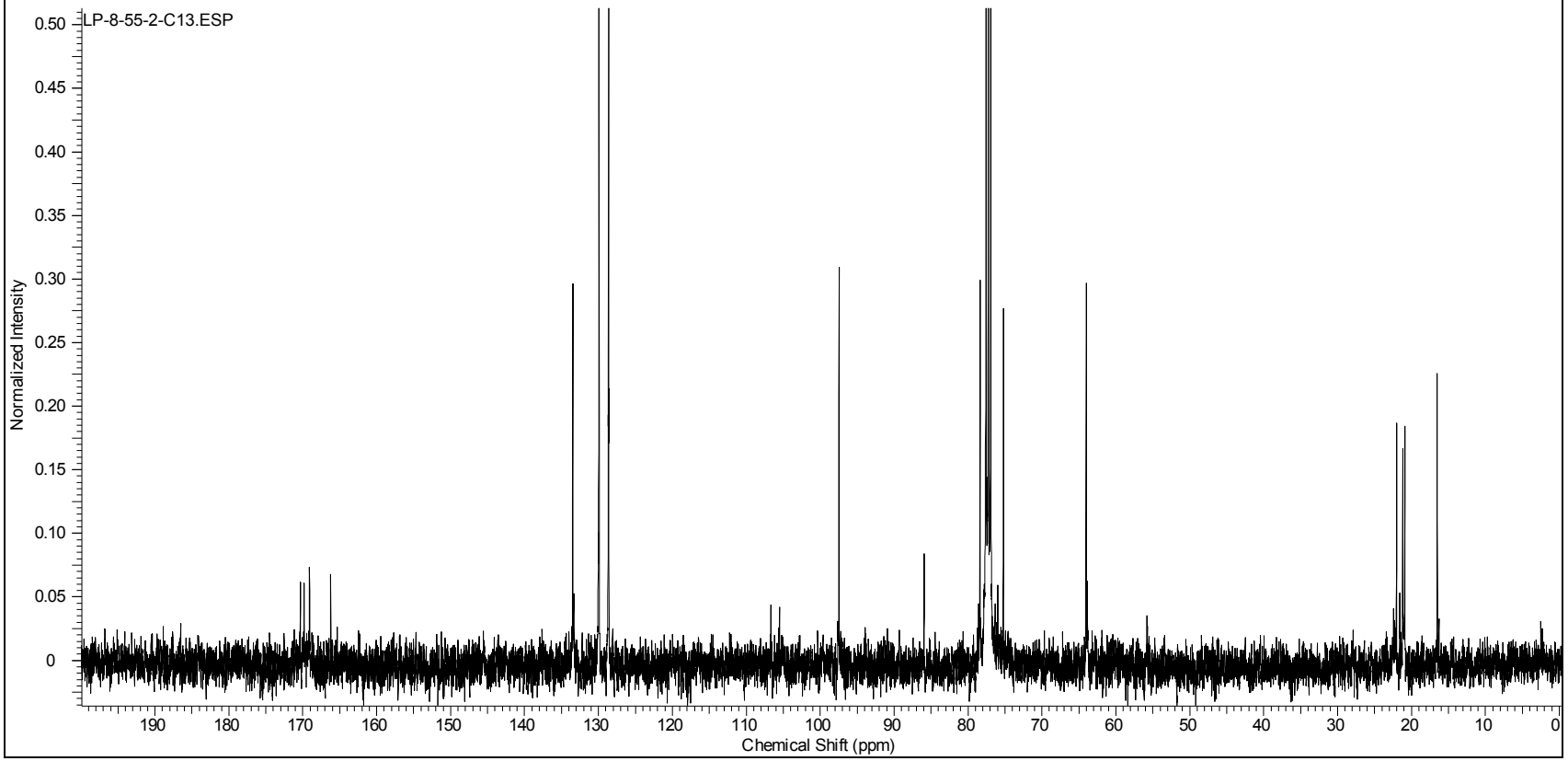


Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Nov 24 2012
Date Stamp	Nov 24 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-55DP2.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	28	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2404.1443	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000

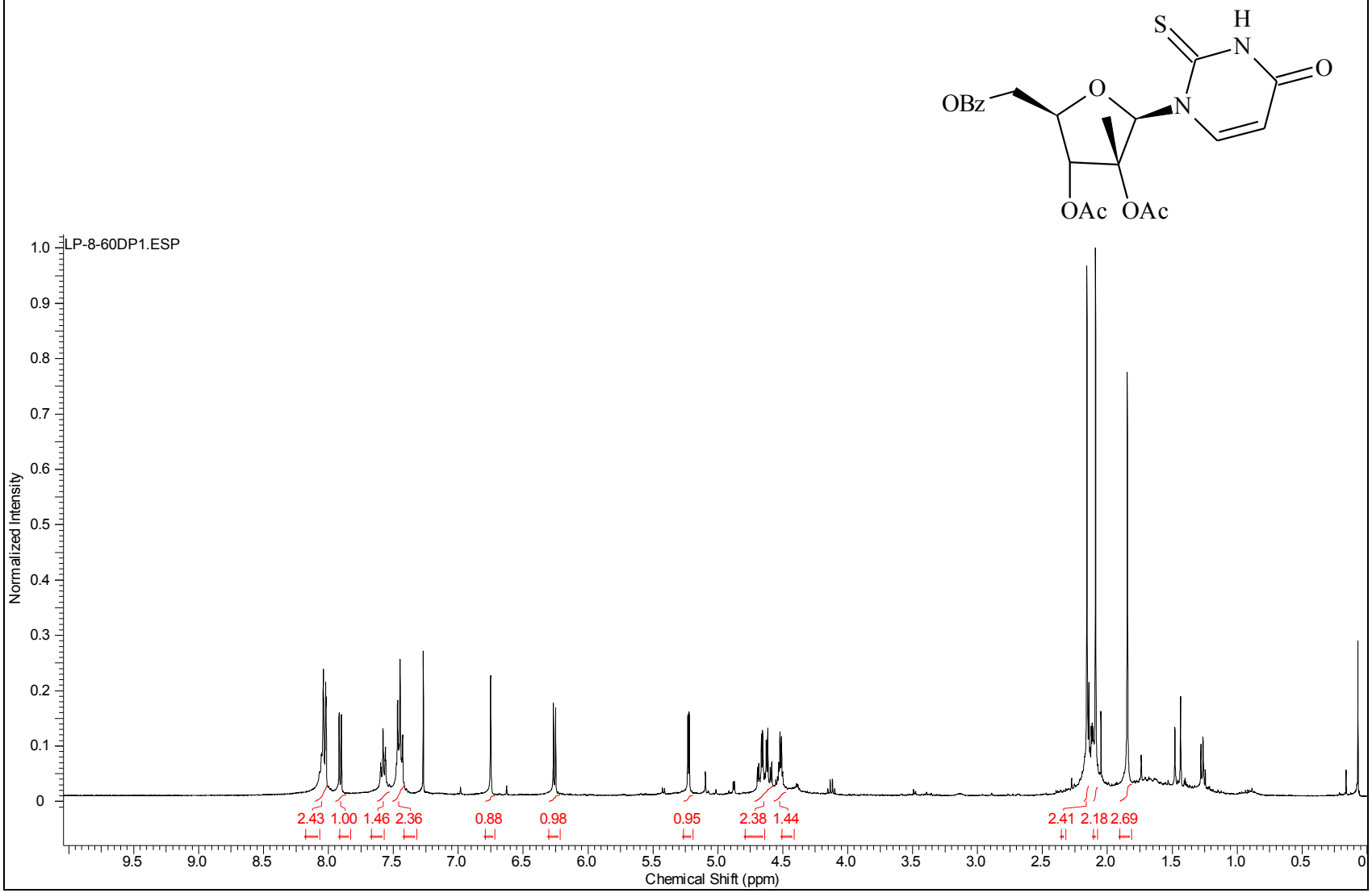


Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Nov 24 2012
Date Stamp	Nov 24 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-55DP2C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	2724	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10559.8330	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000

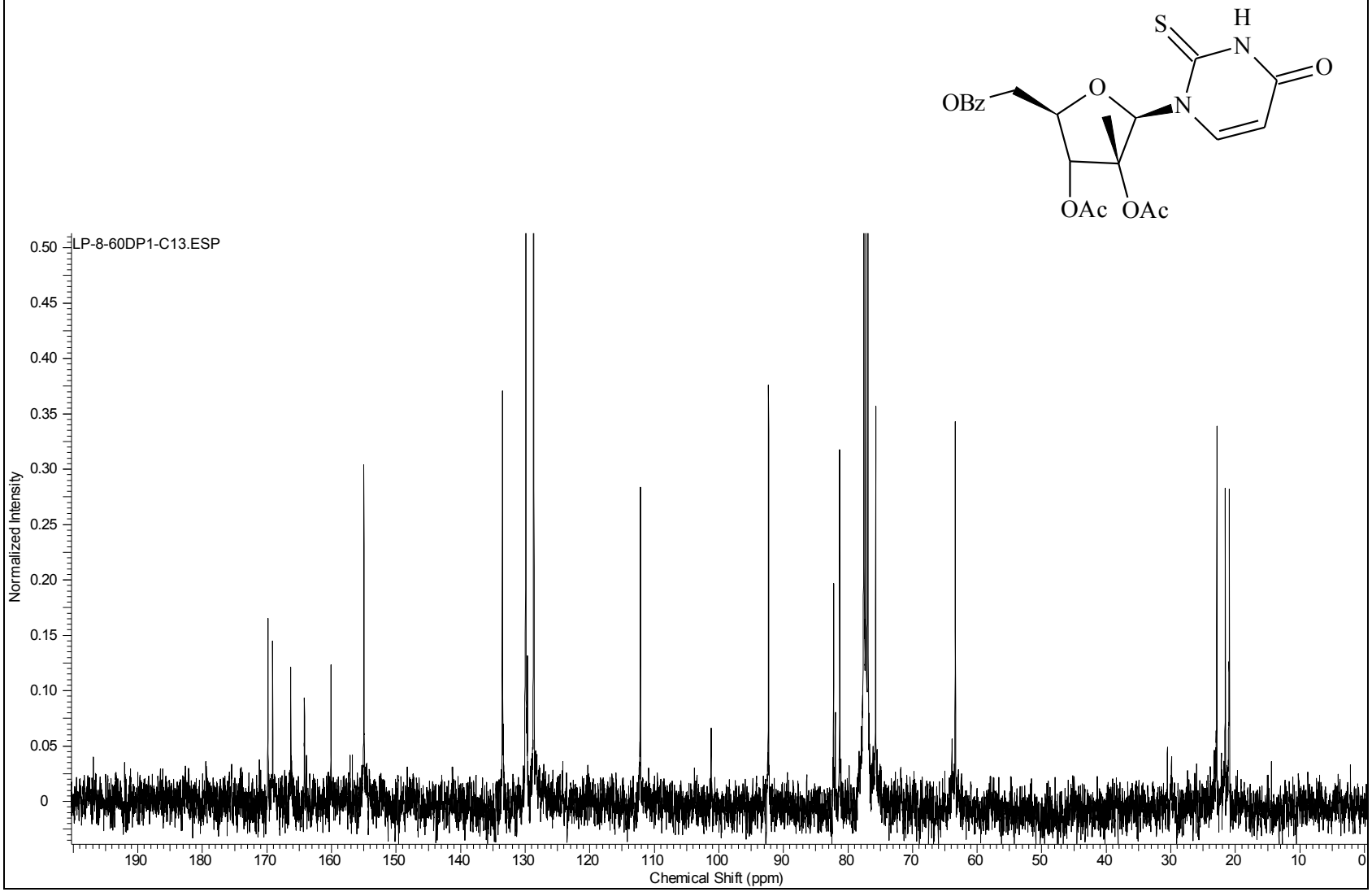




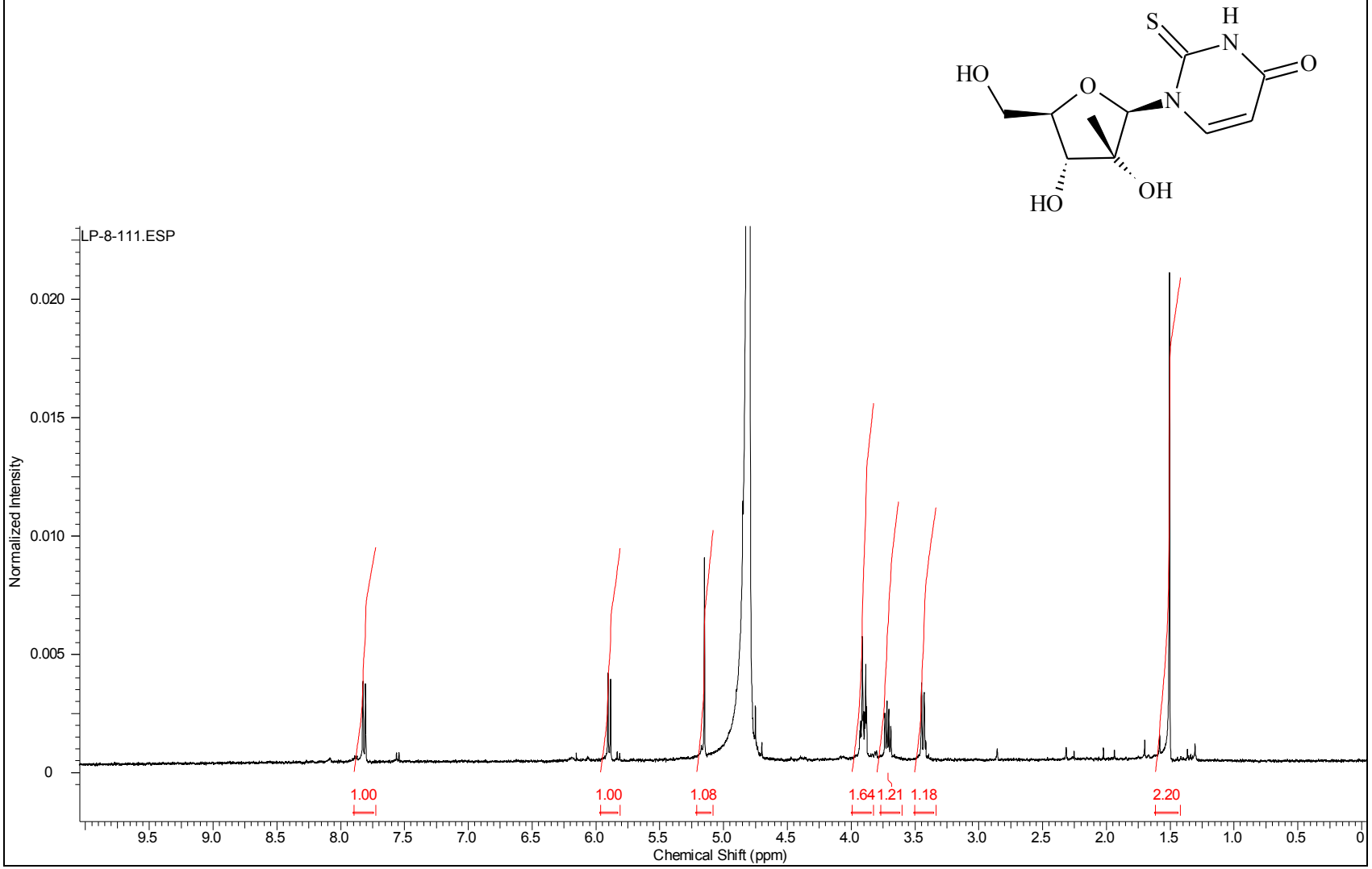
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Nov 25 2012
Date Stamp	Nov 25 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-60DP1.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	60	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	30.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	2403.7539	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



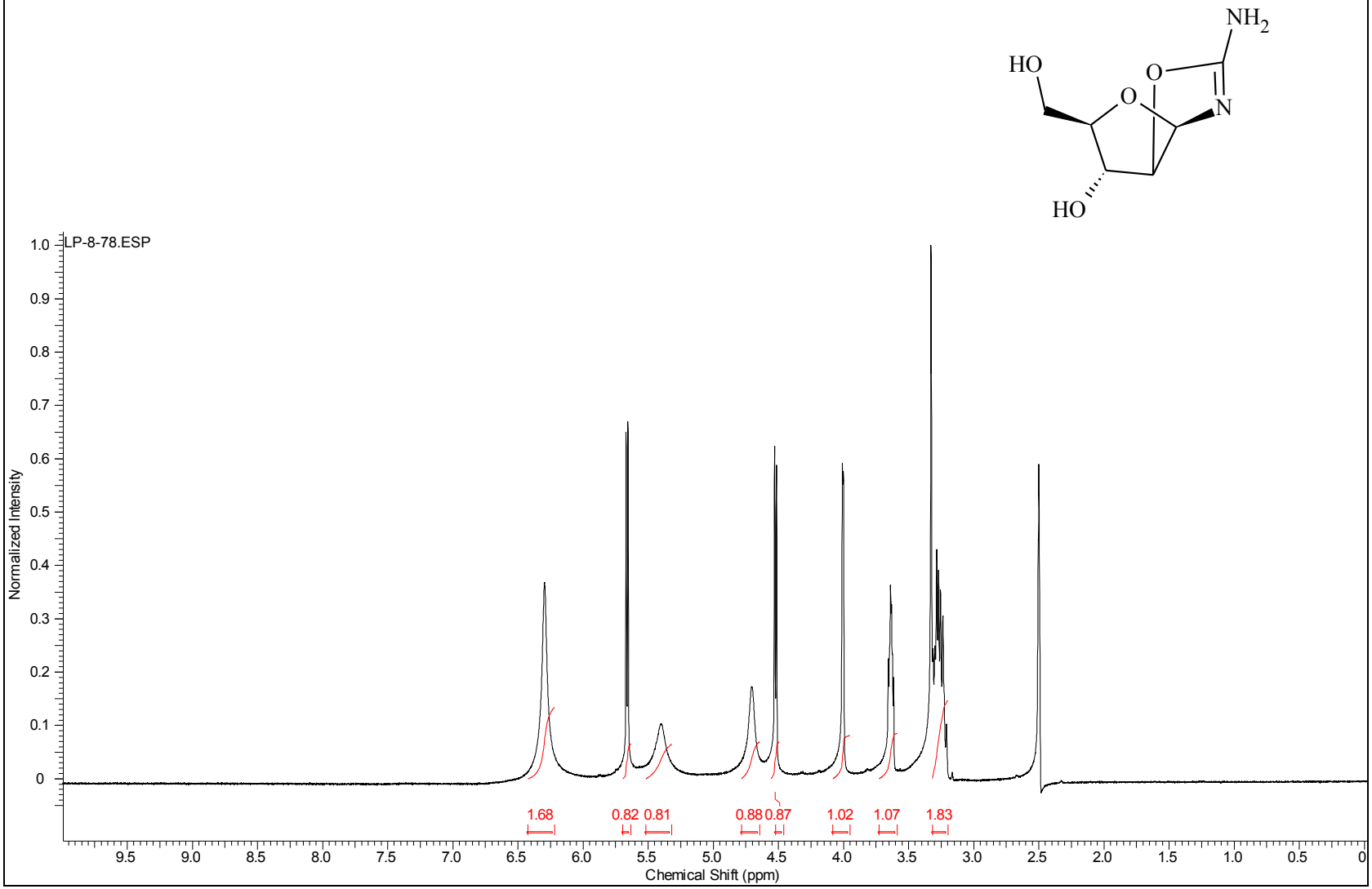
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Nov 25 2012
Date Stamp	Nov 25 2012	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-60DP1-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	2160	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	CHLOROFORM-d
Spectrum Offset (Hz)	10558.3594	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



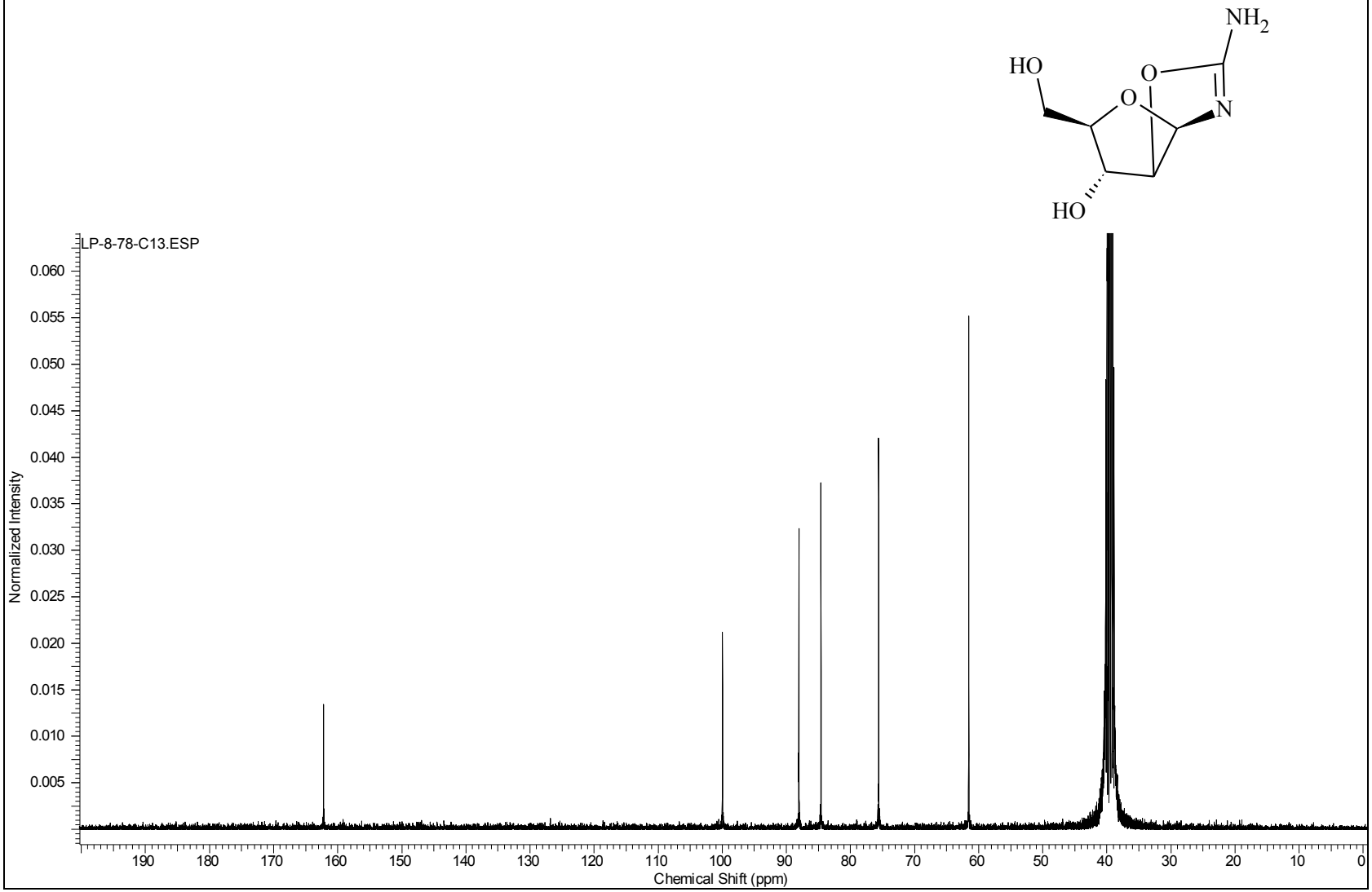
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	May 30 2013
Date Stamp	May 30 2013			***File Name***	G:\THIOURIDINE.FID\FID		
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	192	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	39.00	***Solvent***	DEUTERIUM OXIDE
Spectrum Offset (Hz)	2460.8940	***Spectrum Type***	STANDARD			***Sweep Width (Hz)***	6397.95
Temperature (degree C)	25.000						



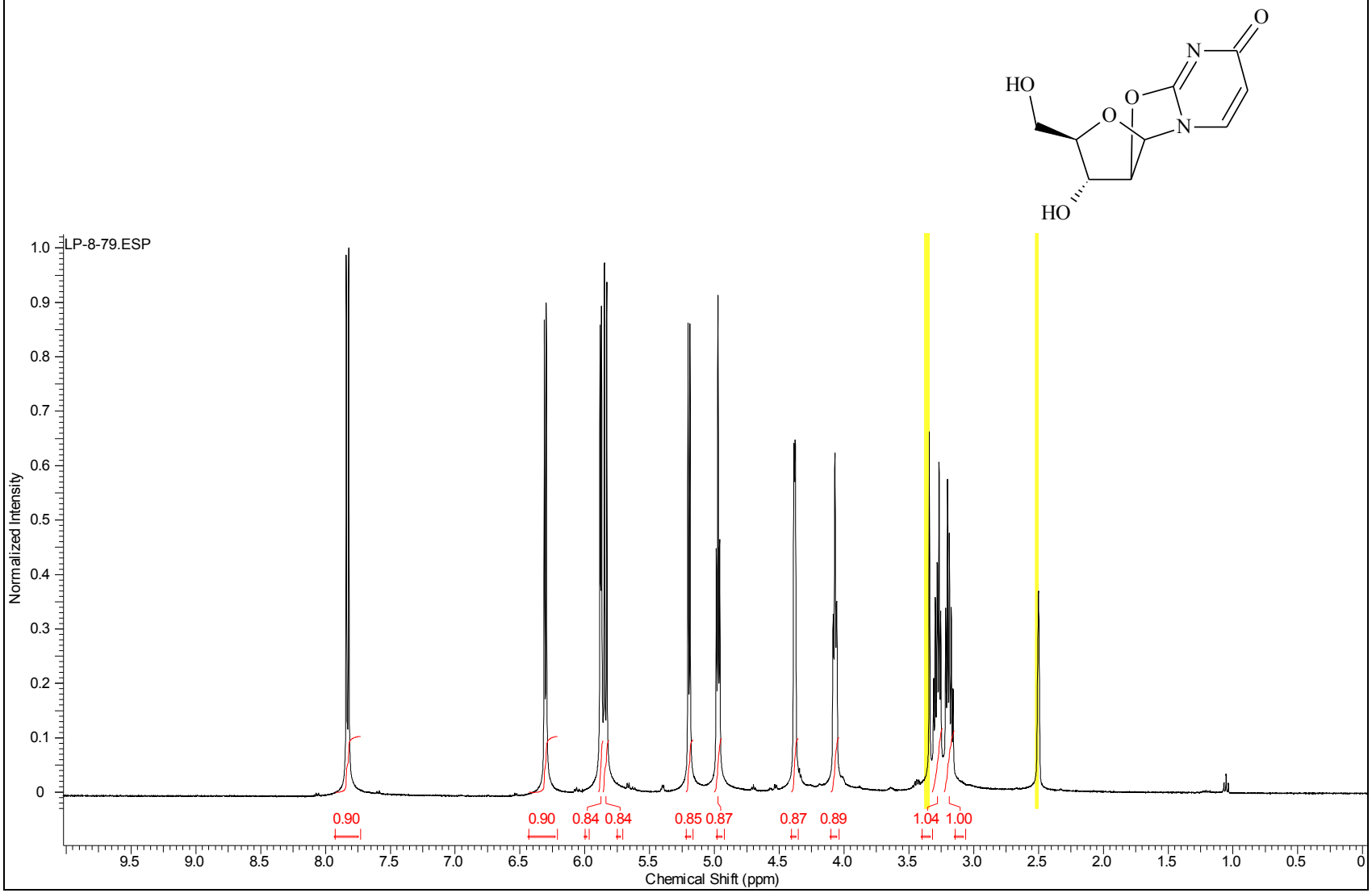
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Feb 12 2013
Date Stamp	Feb 12 2013	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-78-DMSO.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	24	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	32.00	***Solvent***	DMSO-d6
Spectrum Offset (Hz)	2405.9915	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



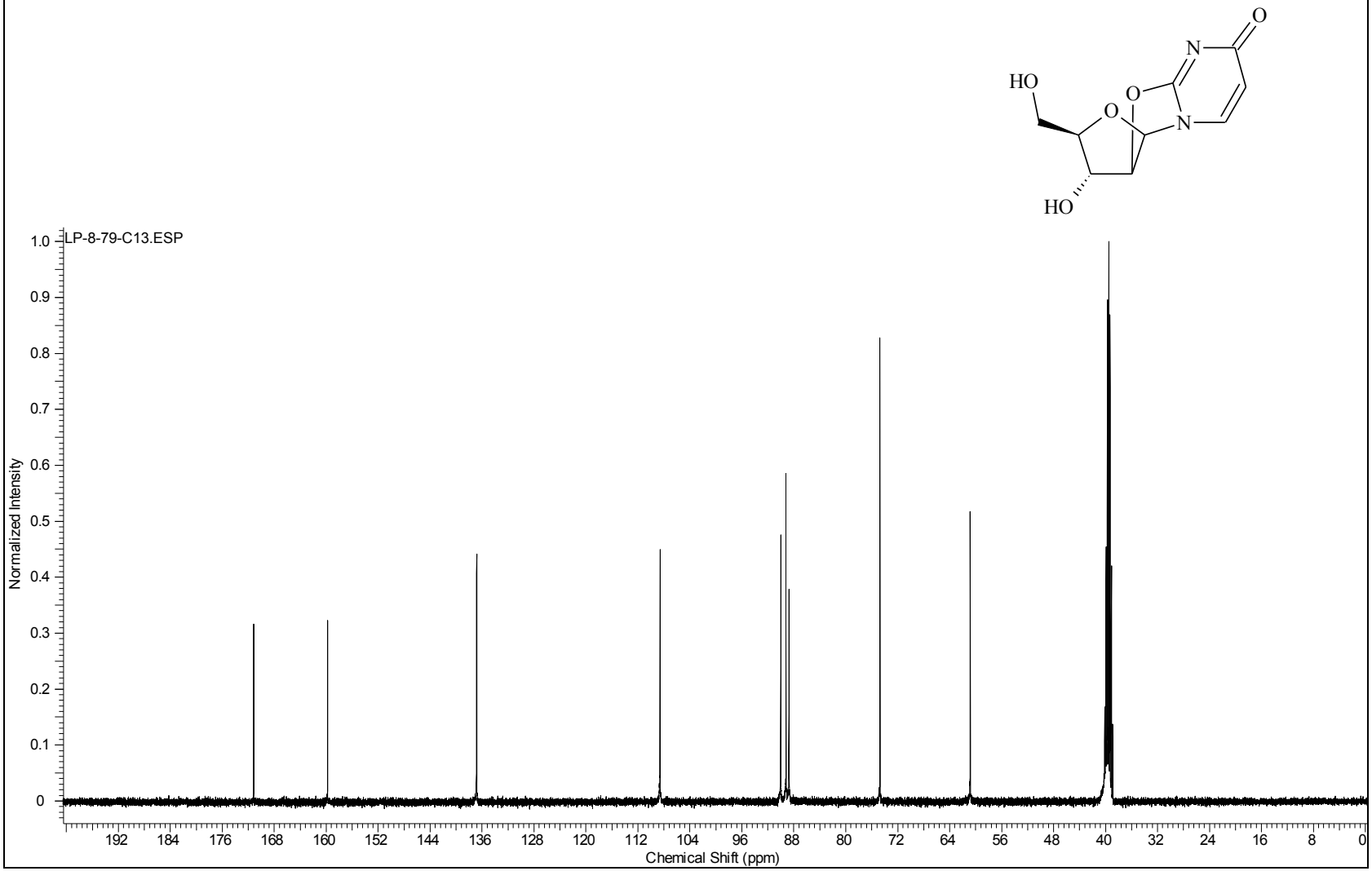
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Feb 12 2013
Date Stamp	Feb 12 2013	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-78C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	2172	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	DMSO-d6
Spectrum Offset (Hz)	10490.8350	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



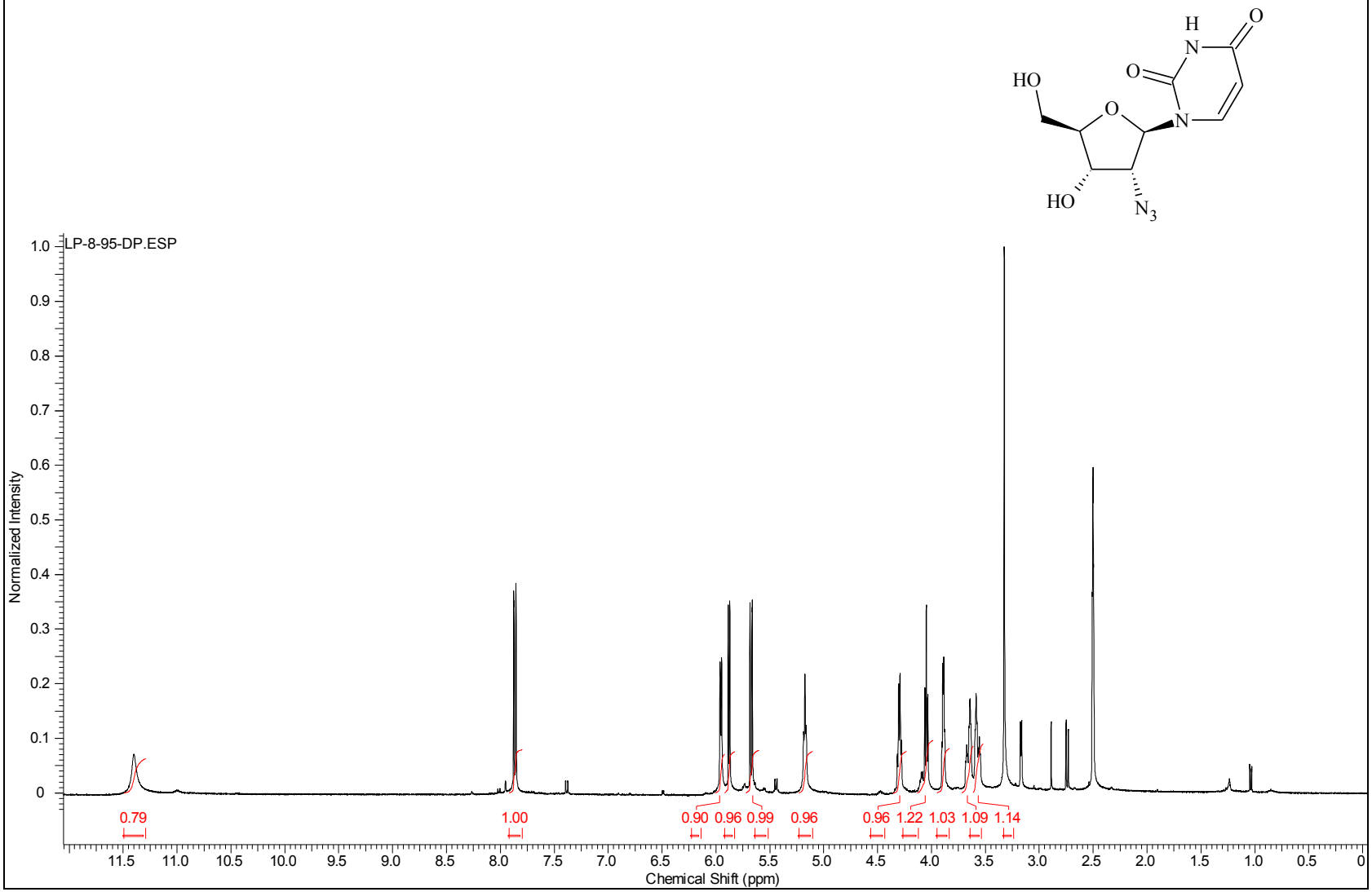
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Feb 12 2013
Date Stamp	Feb 12 2013	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-ARABINOSE-PROPIOLATE.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	24	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	26.00	***Solvent***	DMSO-d6
Spectrum Offset (Hz)	2406.7725	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



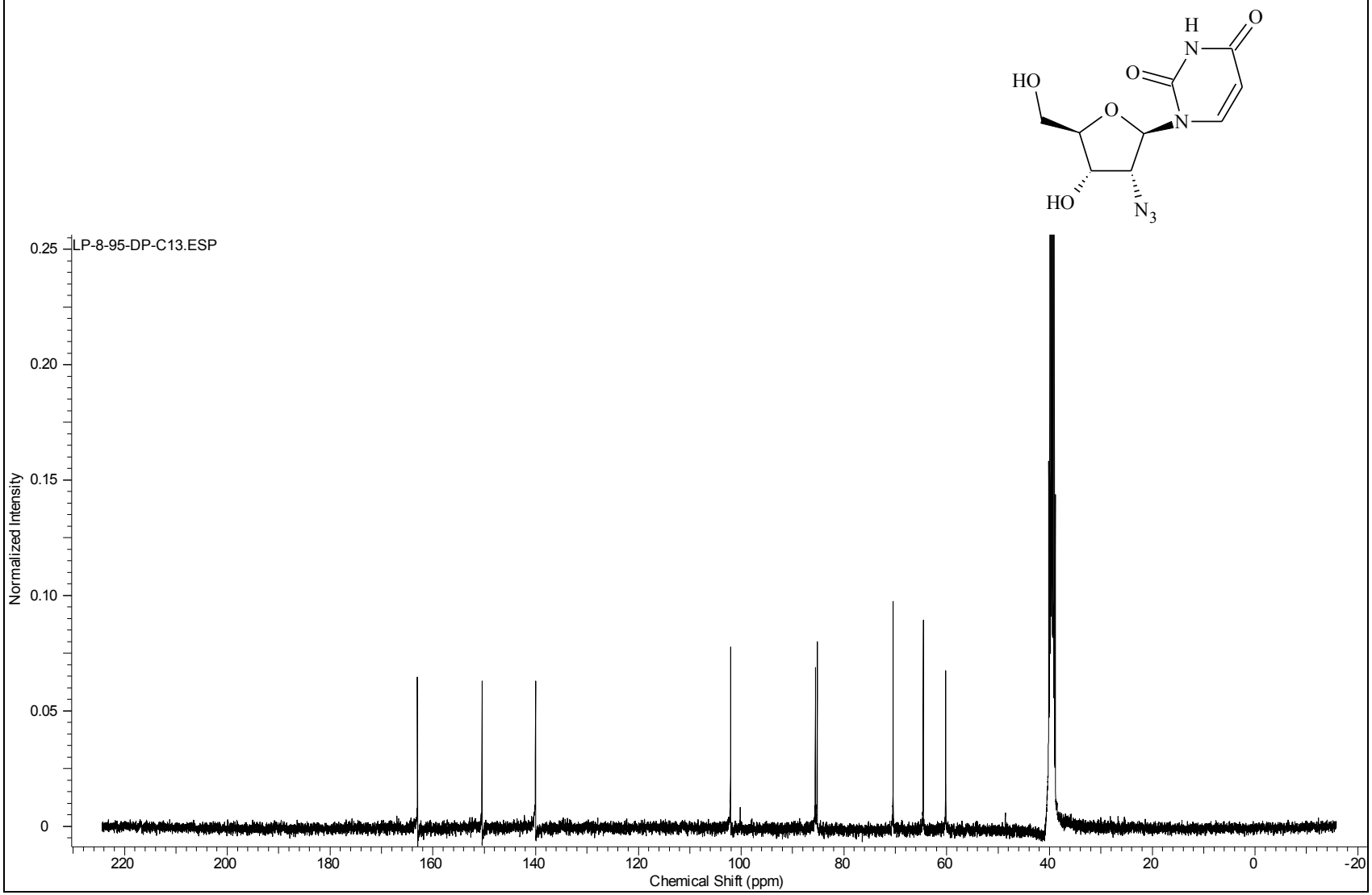
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Feb 12 2013
Date Stamp	Feb 12 2013						
File Name	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-ARABINOFURANOSE-PROPIOLATE-C13.FID\FID						
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	15000	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	DMSO-d6
Spectrum Offset (Hz)	10491.5723	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



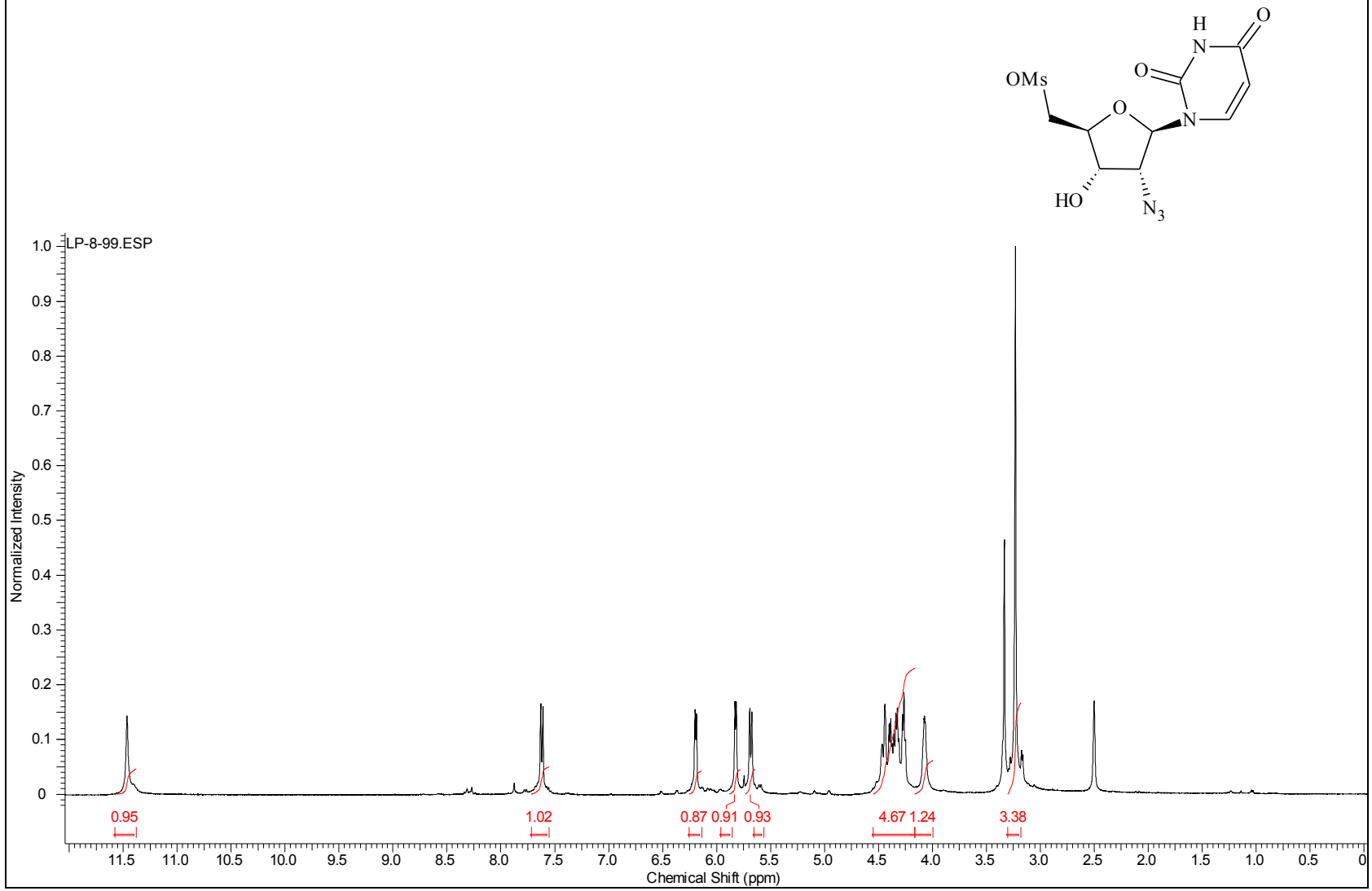
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Feb 16 2013
Date Stamp	Feb 16 2013	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-95-DP.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	48	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	36.00	***Solvent***	DMSO-d6
Spectrum Offset (Hz)	2407.5535	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



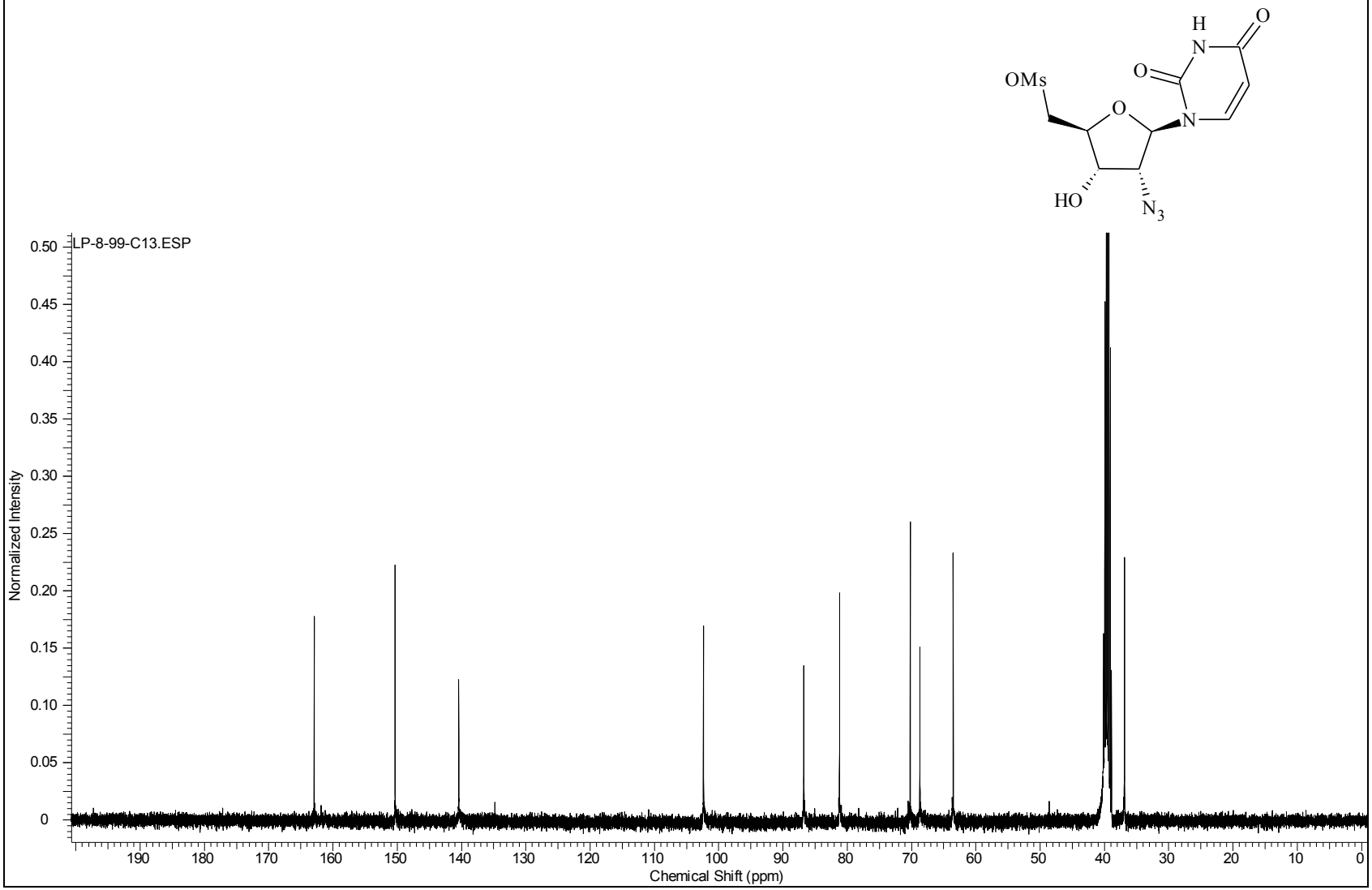
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Feb 16 2013
Date Stamp	Feb 16 2013	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-95-DP-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	18172	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	DMSO-d6
Spectrum Offset (Hz)	10490.0986	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



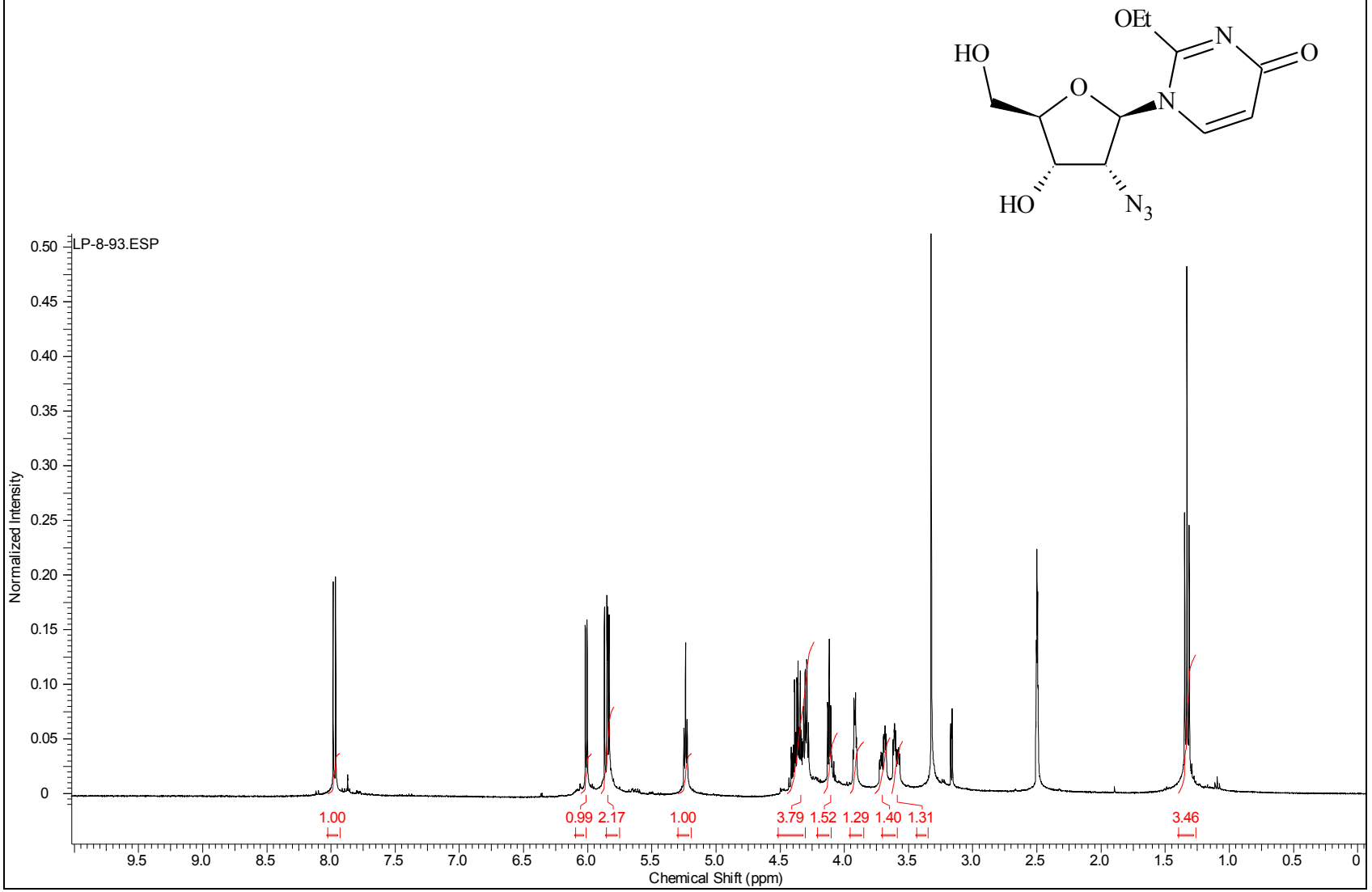
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Feb 26 2013		
Date Stamp	Feb 26 2013			***File Name***	G:\LP-8-99-MESYLATE.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	36	***Original Points Count***	12783	***Points Count***	16384	***Pulse Sequence***	s2pul
Receiver Gain	26.00	***Solvent***	DMSO-d6	***Spectrum Offset (Hz)***	2407.1628	***Spectrum Type***	STANDARD		
Sweep Width (Hz)	6397.95	***Temperature (degree C)***	25.000						



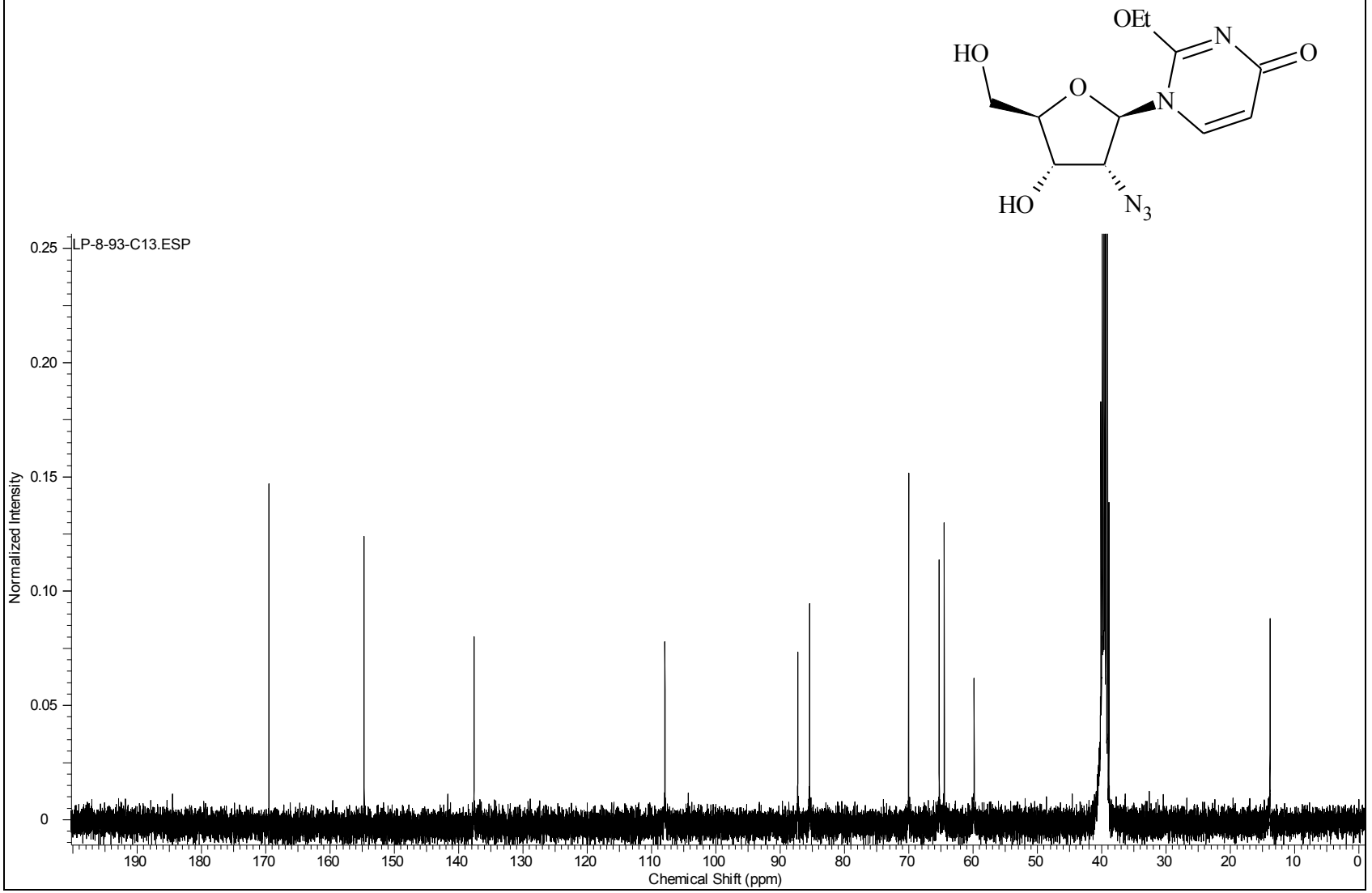
Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Feb 26 2013
Date Stamp	Feb 26 2013	***File Name***	G:\LP-8-99-MESYLATE-C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	18656	***Original Points Count***	31413	***Points Count***	32768
Pulse Sequence	s2pul	***Receiver Gain***	20.00	***Solvent***	DMSO-d6	***Spectrum Offset (Hz)***	10491.5723
Spectrum Type	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000		



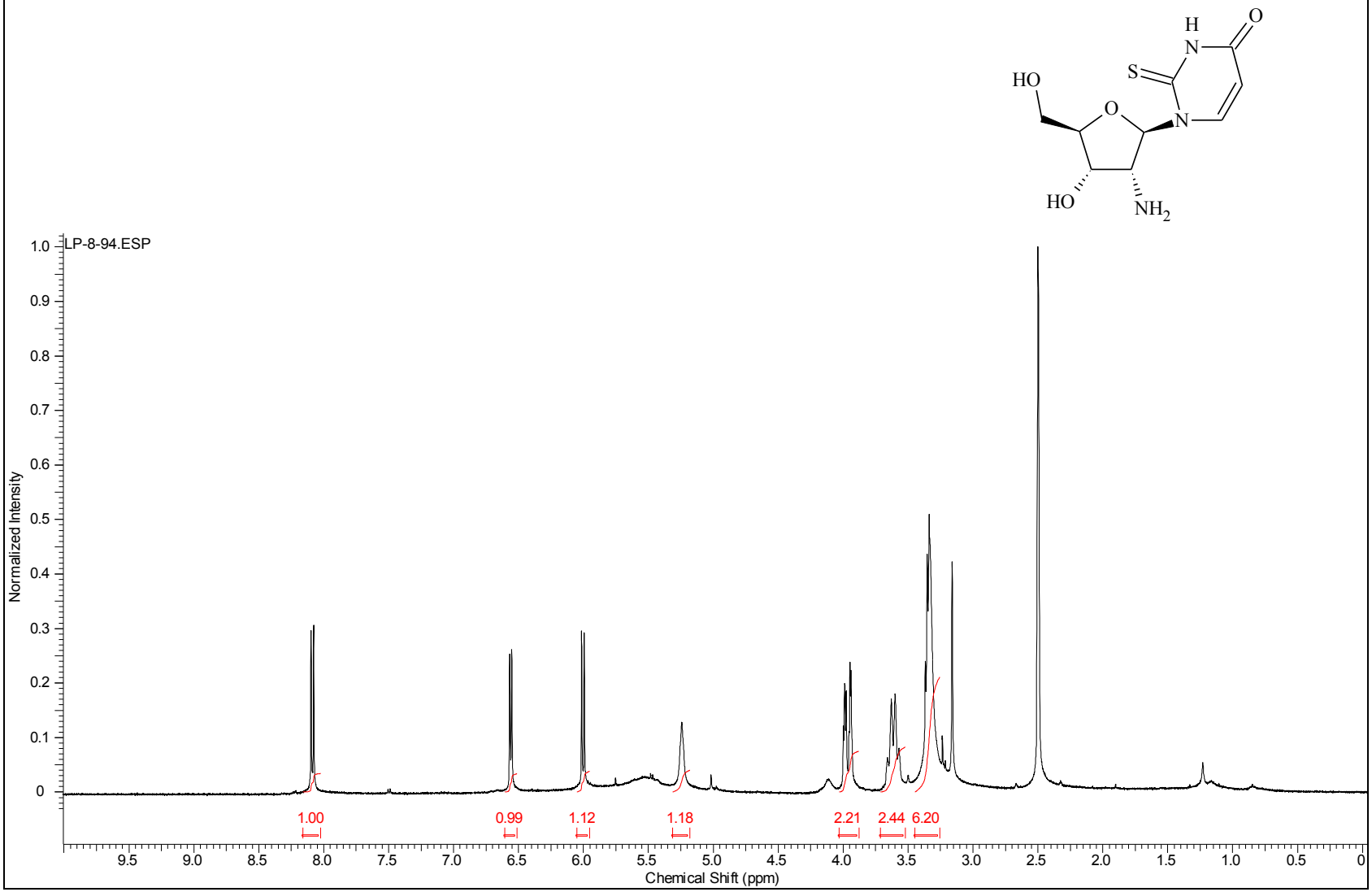
Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Feb 13 2013
Date Stamp	Feb 13 2013	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-93-ETHOXY.FID\FID				
Frequency (MHz)	399.96	***Nucleus***	1H	***Number of Transients***	32	***Original Points Count***	12783
Points Count	16384	***Pulse Sequence***	s2pul	***Receiver Gain***	36.00	***Solvent***	DMSO-d6
Spectrum Offset (Hz)	2406.3818	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	6397.95	***Temperature (degree C)***	25.000



Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Feb 13 2013
Date Stamp	Feb 13 2013	***File Name***	C:\USERS\LAXMAN\DESKTOP\LP-NMR-02-15-2013-MERCURY\SUGAR ANALOGS\LP-8-93-ETHOXY-C13.FID\FID				
Frequency (MHz)	100.58	***Nucleus***	13C	***Number of Transients***	14468	***Original Points Count***	31413
Points Count	32768	***Pulse Sequence***	s2pul	***Receiver Gain***	20.00	***Solvent***	DMSO-d6
Spectrum Offset (Hz)	10490.0986	***Spectrum Type***	STANDARD	***Sweep Width (Hz)***	24154.59	***Temperature (degree C)***	25.000



Acquisition Time (sec)	1.9980	***Comment***	Std Proton parameters			***Date***	Feb 27 2013		
Date Stamp	Feb 27 2013			***File Name***	G:\LP-8-94-AGAIN.FID\FID			***Frequency (MHz)***	399.96
Nucleus	1H	***Number of Transients***	60	***Original Points Count***	12783	***Points Count***	16384	***Pulse Sequence***	s2pul
Receiver Gain	36.00	***Solvent***	DMSO-d6	***Spectrum Offset (Hz)***	2405.9915	***Spectrum Type***	STANDARD		
Sweep Width (Hz)	6397.95	***Temperature (degree C)***	25.000						



Acquisition Time (sec)	1.3005	***Comment***	Std Carbon experiment			***Date***	Feb 27 2013		
Date Stamp	Feb 27 2013			***File Name***	G:\LP-8-94C13.FID\FID			***Frequency (MHz)***	100.58
Nucleus	13C	***Number of Transients***	14024	***Original Points Count***	31413	***Points Count***	32768	***Pulse Sequence***	s2pul
Receiver Gain	20.00	***Solvent***	DMSO-d6	***Spectrum Offset (Hz)***	10489.3613	***Spectrum Type***	STANDARD		
Sweep Width (Hz)	24154.59	***Temperature (degree C)***	25.000