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Approaches Towards the Synthesis of Ketamine Metabolites

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APPROACHES TOWARDS THE SYNTHESIS OF KETAMINE METABOLITES

By
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A thesis submitted to the faculty of The University of Mississippi in partial fulfillment of the requirements of the Sally McDonnell Barksdale Honors College.

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ABSTRACT

ANN KELLY PATRICK: Approaches Towards the Synthesis of Ketamine Metabolites
(Under the direction of Dr. John Rimoldi)

Major Depressive disorder (MDD) plagues society and stands at the forefront of research as MDD affects approximately 16% of the population. Pharmaceutical drugs including the selective serotonin reuptake inhibitors (SSRIs) have been used for MDD treatment and remain a popular option today. However, current antidepressant treatments have proven to be ineffective in just less than half of the patients. Research continues with the goal to better understand the mechanisms of the pathology of depression and to search for other treatment options. For example, the stress-neurogenesis hypothesis investigates the role of stress and decreased neuroplasticity within MDD.

Supporting the stress-neurogenesis hypothesis, the well-known anesthesia drug, ketamine, has shown antidepressant effects linked to glutamate neurotransmission and the successive downstream effects. However, the positive effects sustain after the rapid hepatic metabolism of ketamine leading scientists to explore key metabolites of ketamine and their effects on depressive symptoms.

One of the ketamine metabolites, (2R, 6R)-hydroxynorketamine (HNK), has shown clinical benefits while decreasing the adverse side effects of ketamine in treatment-resistant MDD. The aim of this thesis research is to explore a simple oxidation protocol for the direct synthesis of hydroxynorketamine from the precursor compound norketamine.

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LIST OF ABBREVIATIONS

MDD	Major Depressive Disorder
HNK	Hydroxynorketamine
FDA	Food and Drug Administration
NMDA	N-methyl-D-aspartate
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
(R)	Receptor
MAOI	Monoamine oxidase inhibitor
SSRI	Selective serotonin reuptake inhibitor
SNRI	Selective norepinephrine reuptake inhibitor
TCA	Tricyclic antidepressant
HPA	Hypothalamic-Pituitary-Adrenal
CRH	Corticotrophin-releasing hormone
ACTH	Adrenocorticotropic hormone
BDNF	Brain-Derived Neurotropic Factor
mTOR	Mammalian target of rapamycin
qEEG	Quantitative EEG
TLC	Thin Layer Chromatography
NMR	Nuclear Magnetic Resonance
TMS	Tetramethylsilane
UV	Ultraviolet
Hz	Hertz
h	Hour

min	Minute
sat.	Saturated
aq.	Aqueous
g	Gram
mL	Milliliter
μL	Microliter
mol	Mole
mmol	Millimole
H_2O	Water
$Pd_2(dba)_3$	Tris(dibenzylideneacetone)dipalladium(0)
$MgSO_4$	Magnesium sulfate
$Cu(OAc)_2$	Copper (II) acetate
$(NH_4)_2Ce(NO_3)_6$; CAN	Ammonium cerium (IV) nitrate; Ceric ammonium nitrate
DCE	Dichloroethane
Et/Ac	Ethyl acetate
AcOH	Acetic acid
Na_2CO_3	Sodium carbonate
DMSO	Dimethyl sulfoxide
I_2	Iodine
$Na_2S_2O_3$	Sodium thiosulfate
TMSI	Trimethylsilyl iodide
$CHCl_3$	Chloroform
HBr	Hydrogen bromide

LIST OF FIGURES AND SCHEMES

INTRODUCTION

Overview of MDD

Major Depressive disorder, commonly known as depression, affects more than 12% of men and 20% of women in the United States and more than 264 million people worldwide. MDD is characterized by significant mood changes associated with extreme sadness or irritability that lasts for longer than two weeks and is followed by psychophysiological changes such as alterations in eating, sleeping patterns, concentration, socialization, and sexual desires that can be accompanied by suicidal thoughts. Within the etiology of MDD lies ambiguity as depression correlates with both environmental and genetic factors. Genetic contribution was tested utilizing a twin study and revealed a 37% heritability; however, no one gene has been linked to MDD.[1] With a lifetime prevalence of 16%, depression stands with the highest prevalence of all mood disorders and the second most common mental illness.[2] Physician office medical records document depression for 9.3% of all patients.[3] According to the World Health Organization, approximately 800,000 people die each year due to suicide.[4] Treatment of depression typically involves pharmacotherapy, psychotherapy, or supportive measures. With depression's high morbidity rates, MDD has significant economic and personal importance within society, guiding immense research efforts to improve the treatment of MDD.

History of Neuropathology, Theories, and Treatment of MDD

The dominant theory throughout the history of MDD remains the monoamine-deficiency hypothesis. The monoamine-deficiency hypothesis targets the norepinephrine and serotonin systems as the basis for depression. Within this hypothesis, the current FDA approved treatments include MAO-Is, TCAs, and SSRIs. These drugs function to increase the concentration of norepinephrine or serotonin at the synaptic cleft.[5] However, these treatments display unimpressive efficacy and therapeutic delays of 2 to 4 weeks. One-third to half of the population is reported to not respond to treatment for MDD, and consequently, this subset of the population is currently left without treatment.[1-2] The prevalence of treatment-resistant depression alongside incomplete data concerning the monoamine hypothesis led to explorations of novel molecular pathways. The latency of clinical benefits directed most researchers to conclude that MDD is not a result of the direct impact of monoaminergic neurotransmitters such as norepinephrine and serotonin, but instead consists of downstream effects.

The Stress Neurogenic Theory

A recent theory concerning the neuropathology of MDD is the stress-neurogenesis hypothesis. This theory involves stress and growth factors within the hypothalamic-pituitary-adrenal (HPA) axis. Stress is processed in the cerebral cortex and relayed in the hypothalamus, causing a release of corticotropin-releasing hormone (CRH) onto anterior pituitary receptors that in response secrete adrenocorticotropic hormone (ACTH) that signal the adrenal cortex to release cortisol into the blood. The increase in cortisol signals the hypothalamus to decrease CRH production as a feedback inhibition to maintain

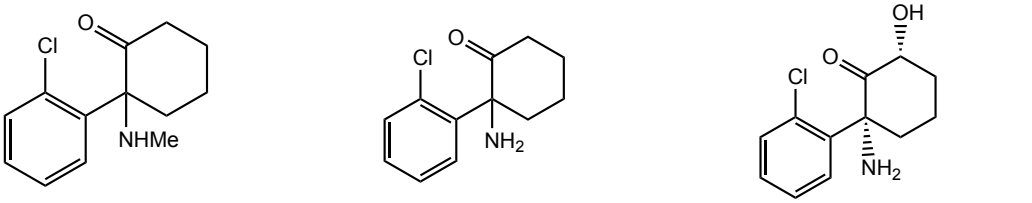
homeostasis. Increased levels of cortisol in the blood and CRH in the cerebral spinal fluid have been reported in individuals with MDD, and disruptions within the feedback inhibition of the HPA axis have been shown in severely depressed individuals. Moreover, an increase in cortisol is linked to a decrease in Brain-Derived Neurotropic Factor (BDNF). BDNF is a neurotrophic peptide that is essential for axonal growth, neuronal survival, and synaptic plasticity. The decrease in BDNF, ultimately caused by stress, stunts neurogenesis in the hippocampus, amygdala, and prefrontal cortex, causing atrophy of these critical limbic structures. The degradation of the critical limbic structures could be accountable for the symptomology of MDD. BDNF appears as a prominent link to MDD as decreased BDNF levels have been found in patients who committed suicide, and increased levels of BDNF have resulted from current antidepressant drugs and electroconvulsive therapies.[1-2]

With the alternate theory of the stress-neurogenesis hypothesis, the major excitatory neurotransmitter, glutamate, has been postulated as an option to offset the neuronal loss. The glutamatergic system induces neuroplasticity with the building of synapses to aid in learning and the retrieval of memories.[5]

Ketamine, Its Metabolites, and Potential Antidepressant Use

Ketamine, a short-acting anesthesia drug, acts as a glutamatergic agent and shows promise in the area of MDD treatment. The drug is commonly used for general anesthesia, especially in pediatric anesthesia cases. At sub-anesthesia doses, the drug generates pain relief, classifying the drug as an analgesic. At high doses, users report out of body experiences sometimes coupled with delirium and symptoms of psychosis. The drug is a noncompetitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist causing

interferences within the glutamatergic system. The drug affects other receptors such as muscarinic, nicotinic, cholinergic, and opioid receptors. A variety of downstream effects commonly associated with antidepressant effects have been reported, including increases in BDNF and mTOR protein levels, a mammalian kinase encoded by the mTOR gene that is the mammalian target of rapamycin. The research proposes that the excitatory neurotransmitter glutamate increases within the synaptic slept due to increased glutamate release and AMPA receptor expression. The increase of glutamate provokes an increase in BDNF and mTOR, triggering extended synaptic growth. The drug shows anti-depressive benefits within two hours, and the effects can continue for a week.[6] The *R* enantiomer is shown to be the source of the sustained antidepressant effects.[7] The proposed signaling cascade links ketamine to antidepressant effects via the stress-neurogenesis hypothesis. However, ketamine's high abuse liability and psychotomimetic (psychotogenic) effects limit its clinical benefits as an antidepressant for everyday use.[6] When researchers examined patients reporting anti-depressive effects of ketamine, they found low concentrations of ketamine and higher concentrations of its metabolites.[8]



Ketamine (**1**) Norketamine (**2**) (2*R*,6*R*)-Hydroxynorketamine (**3**)

Figure I: Molecular structures of ketamine, norketamine, and (2*R*,6*R*)-hydroxynorketamine

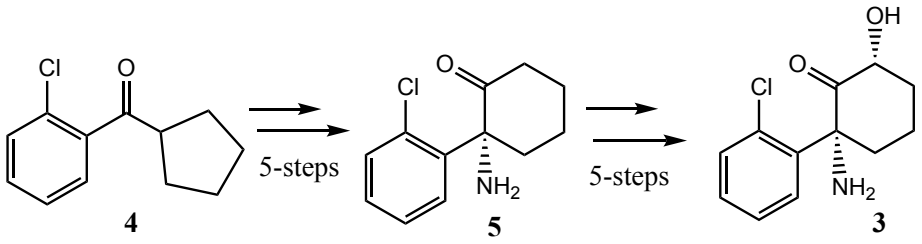
The major metabolites of ketamine are depicted in **Figure I**. Exploring metabolites of ketamine led to promising pharmacotherapies as various metabolites show the same

benefits with ketamine, yet without many of the negative effects. The N-demethylation of ketamine yields norketamine (**2**), which is thereafter hydroxylated to produce multiple hydroxynorketamines. Particularly, the stereoisomer, (2*R*,6*R*)-hydroxynorketamine [(2*R*,6*R*)-HNK: **3**], has shown improved clinical efficacy alongside increased therapeutic windows in multiple animal behavioral tests. The metabolite (2*R*,6*R*)-HNK reduces psychotic effects compared to the parent drug, lowering the abuse liability.[9] Lumsden associates ketamine's abuse liability and adverse behavioral effects to NMDAR inhibition. The metabolite (2*R*,6*R*)-HNK functions differently than ketamine as it does not bind nor inhibit NMDA receptors at antidepressant-relevant concentrations (10 μL).[10] Also, (2*R*,6*R*)-HNK did not inhibit α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Lumsden reported that dissociation effects were experienced with 30 mg/kg doses of ketamine, while doses of up to 375 mg/kg of (2*R*,6*R*)-HNK showed no effect. Also, he reported that unlike ketamine, mice did not self-administer (2*R*,6*R*)-HNK at anti-depressant doses.[10] The exact mechanisms of (2*R*,6*R*)-HNK are unknown, but Fukumoto connected the antidepressant effects to the activity-dependent release of BDNF and mTOR signaling that is mediated by the stimulation of voltage dependent calcium channels.[11] The release of BDNF and mTOR signaling increased synaptogenesis and synaptic function in the medial prefrontal cortex. Zanos revealed group II metabotropic glutamate receptor subtype 2 (mGlu2) inhibition via (2*R*, 6*R*)-HNK to enhance cortical quantitative EEG (qEEG) power in mice, a relevant marker to test antidepressant-relevant actions.[9] The increased AMPA activation, BDNF activity, mGlu2 receptor inhibition, and resulting downstream pathways, including mTOR, are thought to be the source of synaptogenesis, generating the antidepressant effects of (2*R*,6*R*)-HNK. Moreover, not

being processed in the liver, (2*R*,6*R*)-HNK avoids many drug interactions. The metabolite (2*R*,6*R*)-HNK provides a plausible drug of choice to study with promising data in the ongoing search for better treatment of MDD, specifically with treatment-resistant depression. Due to the increased interest surrounding (2*R*,6*R*)-HNK, the objective of this thesis research was to explore a novel route for the synthesis of (2*R*,6*R*)-HNK to improve overall reaction yields and to reduce cost and number of synthetic steps.

RESULTS AND DISCUSSION

With the promise of progress in antidepressant pharmacotherapy, novel approaches for the synthesis of (2*R*,6*R*)-HNK (**3**) were considered based on prior synthesis. Two chemical syntheses of compound **3** have been reported to date. The first synthesis was reported by Morris et. al in 2017 and relied on a modification of an original route for ketamine synthesis (**Figure II**).[12] Commercially available ketone **4** was converted in a 5-step sequence to enantiopure *R*-norketamine (**5**) through initial bromination of the ketone, subsequent condensation with ammonium hydroxide, and a thermal rearrangement to afford racemic norketamine in 44% overall yield. Chiral resolution using pyroglutamic acid provided **5** in gram scale, which was subjected to a Rubottom oxidation to install the α-keto-alcohol with the desired stereochemistry and an excellent diastereoselective ratio. A series of amine protection/deprotection protocols were also included in the synthesis.



4 **5** **3**

Figure II: Morris synthesis of (2*R*,6*R*)-HNK (**3**)

In 2017, the Corey group reported an alternate synthesis of **3** employing as a key step the enantioselective epoxidation of 1-*ortho*-chlorophenylcyclohexene **6** using a modified

Jacobsen's salen-type catalyst (catalyst B, **Figure III**) and NaOCl as oxidant.[13] Regioselective ring opening of the epoxide with titanium isopropoxide and trimethylsilylazide followed by a Dess−Martin periodinane oxidation afforded enantiopure **7** which was reduced to the corresponding amine and converted to **3** utilizing a Rubottom oxidation and similar reaction sequences as first reported by Morris.

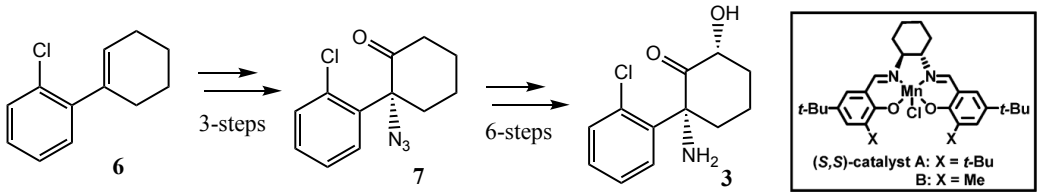


Figure III: Corey's synthesis of (2*R*,6*R*)-HNK (**3**)

Each reported synthesis relies on a late-stage Rubottom oxidation of key intermediate norketamine (**2**), with this oxidation method requiring the use of an alkylithium, low reaction temperatures, peroxybenzoic acid and a fluoride source. Our approach was to synthesize sufficient quantities of racemic norketamine and to use this intermediate to explore an inexpensive oxidation protocol for the synthesis of hydroxynorketamine metabolites, namely, the α-hydroxylation reaction of ketones with dimethyl sulfoxide catalyzed by iodine or N-bromosuccinimide.

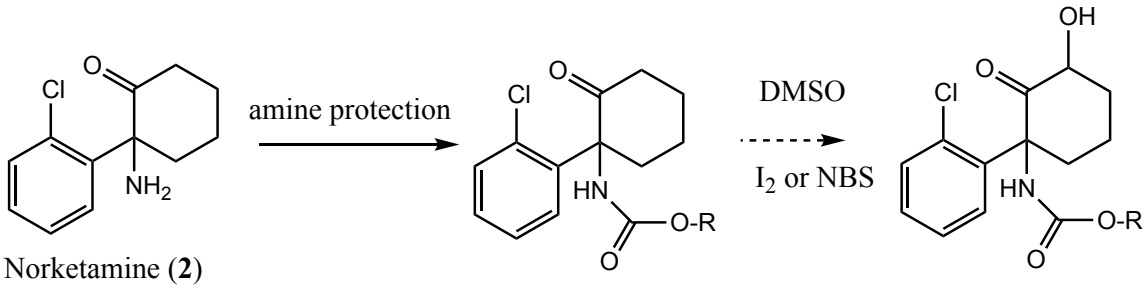
Synthetic Approach and Specific Aims

The specific aims of this thesis research project are:

1) To synthesize sufficient quantities of norketamine (**2**) using established procedures.

2) To explore the potential utility of the I_2- or NBS-catalyzed α-hydroxylation reaction of norketamine with dimethylsulfoxide (DMSO).[14]

This oxidation protocol is attractive insofar as DMSO acts as an oxidant, oxygen source, and solvent. Moreover, the reaction conditions are mild and reagents are inexpensive, in comparison the Rubottom oxidation protocol. This sequence would provide direct access to hydroxylated norketamine analogs (stereochemistry notwithstanding).

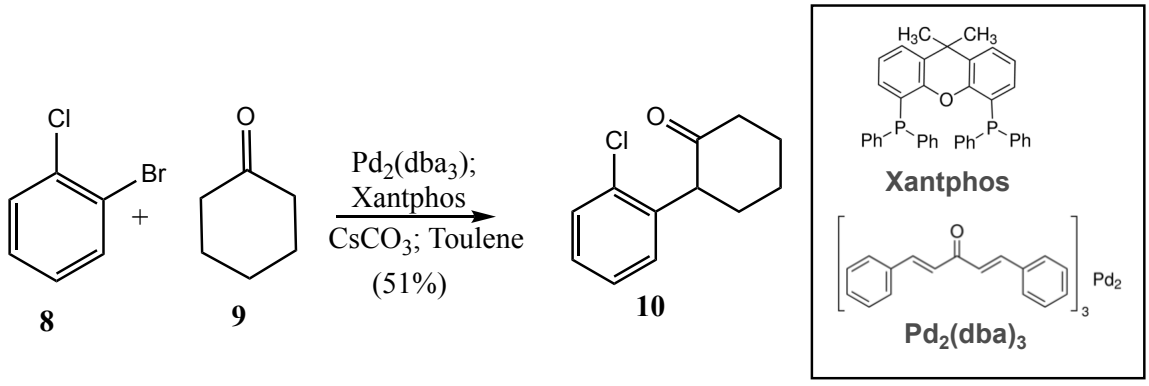


Norketamine (**2**)

Figure IV: Proposed scheme for the synthesis of hydroxynorketamine

Specific Aim 1: 3-Step Synthesis of Norketamine (2)

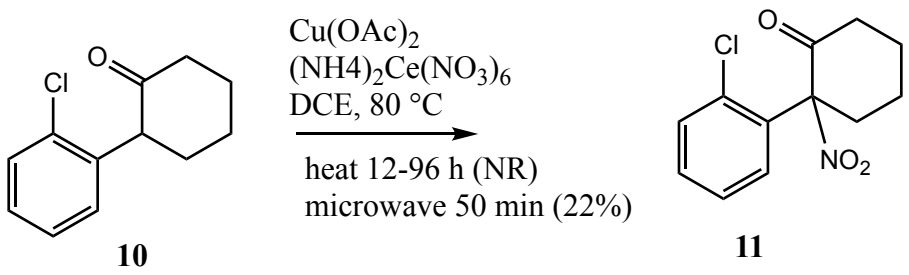
Step 1 (Palladium Catalyzed Arylation Reaction): We initiated the synthesis by using a palladium-catalyzed ketone arylation reaction between 1-bromo-2-chlorobenene (**8**) and cyclcohexanone (**9**) to afford the desired product, 2-(2-chlorophenyl)cyclohexan-1-one (**10**; **Scheme 1**). This specific reaction was reported by Willis in 2004 as an adaptation of the Buchwald arylation reaction and represents an efficient method for the creation of alpha-arylated ketones.[15] The reaction was performed in toluene at 80 ^{o}C using 0.5 mol % of Pd_2-$(dba)_3$, 1.2 mol % of Xantphos, and Cs_2CO_3 affording product **10** in 51% yield (unoptimized). The spectroscopic data (^{1}H NMR, ^{13}C NMR, MS) matched the literature reported values and the product yields were consistent when repeated reactions were performed.



Scheme 1: Synthesis of 2-(2-chlorophenyl)-cyclohexan-1-one (**10**)

Step 2 (Aliphatic Nitration Reaction): In 2017, Zhang et al reported a 4-step synthesis of ketamine (**1**), employing as a key step, a copper-assisted direct nitration of aryl and alkyl substituted cyclic ketones with ceric ammonium nitrate [$(NH_4)_2Ce(NO_3)_6$: CAN] (**Scheme 2**).[16] In this reaction prototype, it was speculated that CAN serves three important

functions: as a Lewis acid (promoting enolization of ketone starting material), an oxidant, and a nitrating reagent. Although the role of copper had not been fully elucidated for this reaction, it is believed to stabilize an intermediate radical species. This reaction was conducted using the reported reaction conditions (conventional heating in oil bath) in addition to performing the reaction using an alternative method of heating, microwave irradiation.



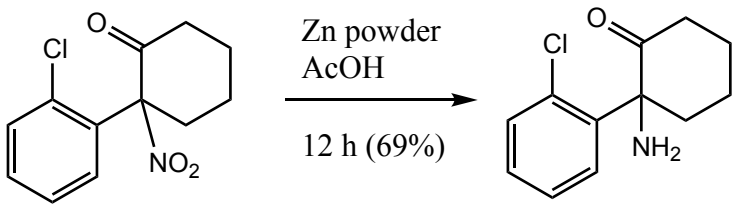
10 **11**

Scheme 2: Synthesis of 2-(2-chlorophenyl)-2-nitrocyclohexan-1-one (**11**)

We utilized identical experimental conditions for the nitration reaction using the conventional heating method as reported by Zhang, who optimized reaction conditions for the synthesis of nitrated products from a small library of alpha-substituted cyclic ketone precursors. It is important to note Zhang's reported yields of nitrated products (using 14 different substrates) were modest and varied with an average yield of approximately 55%. The reaction conditions for the synthesis of **11** used 1, 2-dichloroethane (DCE) as a solvent with the addition of **10**, $Cu(OAc)_2$ and $(NH_4)_2Ce(NO_3)_6$ in a sealed tube under an argon atmosphere and heating in an oil bath at 80 ^oC. When the reaction was repeated using these conditions, the desired product of the reaction, 2-(2-chlorophenyl)-2-nitrocyclohexan-1-one (**11**) was not observed, even after repeated attempts, prolonged reaction times (up to 4

days), and higher reaction temperatures (100 ^{o}C). Alternate commercial sources of CAN were also used in separate reactions to rule out reagent quality issues, but without success. It is not clear why the nitration reaction failed in our hands when conducted using identical reaction conditions as reported in the literature. Notwithstanding, the literature yield for the conversion of **10** to **11** was reported to be 51% after product purification by silica gel column chromatography. We then turned our efforts to using microwave irradiation rather than conventional heating to provide some insight. We utilized a Biotage Initiator Microwave Synthesizer (2.45 GHz) and performed the nitration reaction using similar reaction conditions reported under conventional heating. Since microwave irradiation allows reaction times to exponentially decrease, we anticipated 10-20 minutes of microwave heating would suffice. Using DCE as a solvent was appropriate for conducting the microwave heating (The heating performance of a solvent under microwave irradiation is dependent on its ability to convert electromagnetic energy into heat and is related to the solvent dielectric constant). In initial experiments, microwave irradiation was applied to the reaction mixture in 10-minute intervals with reaction monitoring and required 50 minutes of microwave heating at 80 °C. Each 10-minute interval was preceded with pre-stirring (2 min) due to a concern with inconsistency of stirring throughout the microwave irradiation timeframe, based on visual inspection of the reaction mixture. Although not fully optimized, reactions performed under these conditions afforded the nitration product **11**, albeit in low yields (average yield 22%).

Step 3 (Nitro Reduction)



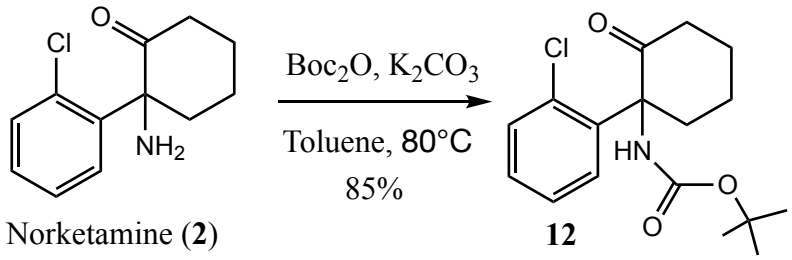
11 **2**

Scheme 3: Synthesis of 2-(2-chlorophenyl)-2-aminocyclohexan-1-one (norketamine; **2**)

This final step involved the reduction of the nitro group to an amine group with zinc powder and the weak acid solvent acetic acid (**Scheme 3**). This resulted in a 69% product yield (isolated as free base), and the spectroscopic data matched the literature reported values for norketamine. Around the time the three-step synthesis of norketamine was completed, a commercial vendor (Advanced ChemBlocks Inc.) began to offer this rare compound in gram quantities at a reasonable price, and one gram was purchased in order to explore the novel oxidation reaction.

Specific Aim 2: Exploring the potential of the DMSO oxidation of norketamine

In order to evaluate the potential of applying the DMSO oxidation to the substrate norketamine, initial amine group protection was warranted. Treatment of **2** with di-*tert*-butyl dicarbonate and potassium carbonate in toluene yielded N-Boc protected amine derivative **12** in 85% yield (**Scheme 4**), with spectroscopic data consistent with the data reported by Corey for the same compound produced as an intermediate in his synthesis.[13]

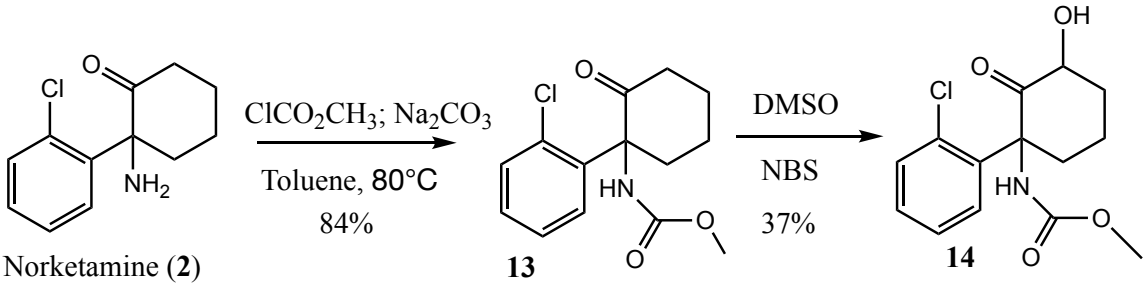


Norketamine (**2**) **12**

Scheme 4: Synthesis of *tert*-butyl (1-(2-chlorophenyl)-2-oxocyclohexyl)carbamate (**12**)

Preliminary DMSO oxidation studies were performed on compound **12** using either I_2 or N-bromosuccinimide (NBS) as catalysts. Standard reaction conditions reported for this conversion were optimized for α-methine carbonyl containing substrates and include the following: ketone (0.5 mmol), NBS or I_2 (20 mol %), DMSO (1 mL), at 100 °C, under air for 24 h.[14] When the reaction was performed using either NBS or I_2, only norketamine **2** was isolated, suggesting the instability of the N-Boc protecting group under these reaction conditions. In order to circumvent this problem, a more stable amine protecting group was selected, namely a methylcarbamate group. Treatment of **2** with methylchloroformate and sodium carbonate in toluene yielded carbamate **13** in an 84% yield, Reaction of **13** with I_2 (20 mol %) in DMSO at 100 °C, under air for as long as 96 hours did not result in conversion to the oxidized product (only starting material remained), while reaction of **13**

with NBS (20 mol %) in DMSO at 100 °C, under air for 4 days afforded a hydroxylated product **14** in 37% yield (**Scheme 5**).



Norketamine (**2**)

Scheme 5: Synthesis of carbamate **13** and its subsequent DMSO oxidation

The mechanism of DMSO oxidation of ketones catalyzed by iodine or NBS has been proposed and is believed to operate by way of an initial electrophilic halogenation of the substrate ketone yielding an α-halogen carbonyl **A** followed by an S_N2 reaction with the nucleophilic oxygen atom of DMSO yielding an intermediate **B/C** (**Figure V**). Protonation affords the hydroxylation product concomitant with the release of dimethyl sulfide and regeneration of the halogen catalyst for the next cycle.

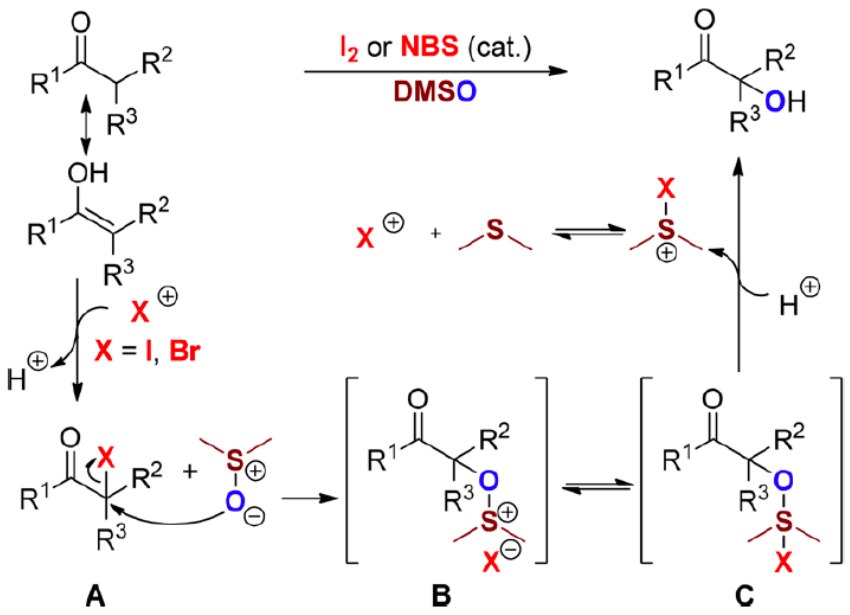


Figure V: Proposed mechanism of NBS or I_2 catalyzed DMSO oxidation of ketones[14]

Due to unforeseen circumstances related to Covid-19, this oxidation reaction was only performed once. The purified product was analyzed by ^{1}H -NMR, and the data appear encouraging. But the NMR data is more complex than anticipated, which is suggestive of a product containing a diastereomeric mixture of 6-hydroxy isomers. Further NMR analysis needs to be conducted on the product from the reaction.

Conclusions

A three-step synthesis of norketamine (2) was accomplished in order to produce starting material for exploring its subsequent I_2- or NBS-catalyzed DMSO oxidation. Although the results of the DMSO oxidation reaction of carbamate protected norketamine was encouraging, further studies are warranted to optimize reaction conditions and to confirm both the regiochemistry of hydroxylation, and the relative stereochemistry of the hydroxylated product. The use of microwave irradiation may be beneficial in the DMSO oxidation reaction, based on the positive results obtained from the nitration experiments described using CAN.

MATERIALS AND METHODS

General Methods:

Commercially available solvents and reagents were purchased from either Sigma Aldrich Inc., Fisher Scientific, or Alfa Aesar Chemicals. Glassware used for anhydrous reactions was flame or oven dried and placed under vacuum and purged with argon gas.

Chromatographic Purification:

Thin layer chromatography and UV light source was used to monitor the reaction progress with references to the starting materials and products using aluminum plates coated with silica gel and a phosphor. Phosphomolybdic acid was used to stain the TLC plates when non-UV active compounds were analyzed.

Silica gel column chromatography was performed using 220-440 mesh and appropriate mobile phase solvents. Fractions were collected and monitored by comparing sample from test tubes to crude and reference materials using TLC.

Mass Spectrometry:

After TLC confirmed the presence of the desired product, mass spectroscopy data was obtained to confirm the desired molecular weight of the product. A Waters ZQ single quadrupole mass spectrometer was employed using an ESI source to monitor MH^+ parent ions or their associated MNa^+ adducts.

NMR Analysis:

NMR spectral data was obtained using a Bruker Ascend™ 400 MHz NMR spectrometer, and samples were prepared using deuterated chloroform ($CDCl_3$) as the solvent. Each signal is defined relative to TMS. Proton (^1H), carbon (^{13}C), and DEPT-135 NMR spectra were acquired. The TOPSHIM function was utilized to adjust the probe to the sample. Mestrelab software (MNova) was utilized to analyze raw data. The baseline correction, peak picking, and integration functions were utilized.

Experimental

2-(2-chlorophenyl)-cyclohexan-1-one (10)

Cesium carbonate (9.10 mg, 27.94 mmol) was added to a 100 mL oven dried round bottom flask charged with $Pd_2(dba)_3$ (59 mg, 0.064 mmol) and Xantphos (88.6 mg, 0.153 mmol) under a blanket of argon gas. The flask was vacuum purged and refilled with argon gas three times. Anhydrous 1,4-dioxane (15 mL) was added to the flask, and under argon gas, freshly redistilled cyclohexanone (**9**, 2.50 mg, 2.64 mL, 25.48 mmol) and 1-bromo-2-chlorobenzene (**8**, 2.439 g, 1.49 mL, 12.74 mmol) were added. The reaction was heated at 100 °C for 24 hours. In the first 10 minutes of heating, the reaction mixture changed from a red to a yellow color, and after 25 minutes, it changed to a green color. The final color was a dark brown. After 24 hours, the sample was cooled to room temperature and then diluted with diethyl ether (50 mL) and washed with distilled H_2O (100 mL). Using a separation funnel, the organic layer containing the product was extracted with diethyl ether (3 x 100 mL). The organic layer was washed with brine solution (100 mL), dried over

$MgSO_4$, filtered using gravity filtration, and concentrated under vacuum. The catalyst created a sticky product that was slightly water soluble. The product was purified using a silica gel column and a mobile phase of 10% ethyl acetate/hexanes as an eluent to afford the purified product of **10** as a white solid (1.4 g, Yield: 51%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.32 – 7.20 (m, 3H), 4.14 (dd, *J* = 12.6, 5.4 Hz, 1H), 2.63 – 2.49 (m, 2H), 2.36 – 2.15 (m, 2H), 2.13 – 1.98 (m, 2H), 1.98 – 1.76 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.72, 136.80, 134.21, 129.46, 129.38, 128.13, 126.78, 77.45, 77.14, 76.82, 54.05, 42.39, 33.94, 27.69, 25.69. (ESI) *m/z* calculated for $C_{12}H_{14}ClO$ $(M+H)^+$ 209.06, found: 209.10 m/z.

2-(2-chlorophenyl)-2-nitrocyclohexan-1-one (11)

For the conventional heating reaction, 2-(2-chlorophenyl)-cyclohexan-1-one (**10**, 59.3 mg, 0.284 mmol), anhydrous $Cu(OAc)_2$ (99% purity, 11.1 mg, 0.061 mmol), and $(NH_4)_2Ce(NO_3)_6$ (290 mg, 0.529 mmol) were added into a tube with 1, 2-dichloroethane (4 mL). The reaction mixture was vortexed, then a stir bar was added, the cap was sealed, and finally, the reaction mixture was stirred in a preheated oil bath at 80°C for 24 hours. The reaction was monitored by TLC with a mobile phase consisting of 20% ethyl acetate/hexanes and no product was observed even with prolonging the reaction time for 4 days and also by increasing the reaction temperature to 100°C.

Alternatively, we attempted a microwave irradiation reaction using a 2.45 GHz Biotage Microwave Initiator employing the same combination of reagents described above. Microwave radiation was applied to the reaction mixture in 10 minute intervals for 50 minutes at 80°C. Each 10-minute interval was preceded with pre-stirring (2 min). The

reaction was monitored by TLC with a 20% ethyl acetate/hexanes solvent system. After 50 minutes of the reaction, the reaction mixture was diluted with 30 mL of ethyl acetate, dried over anhydrous sodium sulfate and the organic portion was filtered one more time, evaporated under a reduced pressure using a rotary evaporator and the resultant crude viscous dark yellow residue was purified, using preparative TLC (silica gel, 500-micron thickness) with 20:80 ethyl acetate/hexanes as an eluent, to afford 16 mg of the desired product **11** as a pale yellow solid (yield: 22%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.10 (m, 4H), 3.14 – 2.55 (m, 3H), 2.03 – 1.50 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.15, 135.08, 132.04, 131.77, 131.01, 129.04, 127.42, 101.40, 40.62, 36.51, 27.16, 21.92. (ESI) *m/z* calculated for $C_{12}H_{12}NO_3ClNa$ [M+Na]+ 276.04, found 276.05.

2-(2-chlorophenyl)-2-aminocyclohexan-1-one (norketamine; 2)

Zinc powder (4 x 20 mg; 0.3 mmol; in 30 min intervals) was added to a solution of 2-(2-chlorophenyl)-2-nitrocyclohexan-1-one (13 mg, 0.05 mmol) in AcOH (1.0 mL) under a blanket of argon. The reaction mixture was stirred for 12 hours and filtered. The filtrate was concentrated and the residue diluted with dichloromethane and washed with a saturated aqueous sodium bicarbonate solution (5.0 mL). The aqueous phase was extracted with dichloromethane (3×4 mL) and the combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent was removed under vacuum yield 8 mg (69%) of product. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.70 (d, *J* = 7.8 Hz, 1H), 7.41 – 7.30 (m, 2H), 7.30 – 7.22 (m, 1H), 2.81 (d, *J* = 11.7 Hz, 2H), 2.64 – 2.53 (m, 1H), 2.47 (dd, *J* = 9.2, 3.9 Hz, 1H), 2.02 (d, *J* = 6.2 Hz, 1H), 1.89 – 1.59 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.46, 139.66, 133.14, 131.07, 129.19, 128.57, 127.29, 77.39, 77.08,

76.76, 66.62, 41.08, 39.03, 28.54, 22.17. (ESI) *m/z* calculated for $C_{12}H_{13}NO_3Cl$ [M+H]+ 224.08, found 224.0.

tert-Butyl (1-(2-chlorophenyl)-2-oxocyclohexyl)carbamate (12)

To a solution of norketamine (**2**; 100 mg, 0.39 mmol) in toluene (3 mL) was added potassium carbonate (160 mg, 1.2 mmol) and di-*tert*-butyl dicarbonate (126 mg, 0.58 mmol). The reaction was heated to 80 °C and stirred for 20 hours. The reaction was cooled, extracted with ethyl acetate and washed with water. The organic layer dried over anhydrous sodium sulfate, filtered, and the solvent removed to afford a crude white solid. Purification by silica gel chromatography (20% ethyl acetate in hexanes) gave 124 mg (Yield: 85%) of **12** as a crystalline white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.36 (dt, *J* = 7.9, 2.0 Hz, 2H), 7.31 – 7.24 (m, 1H), 6.64 (s, 1H), 3.86 (d, *J* = 14.4 Hz, 1H), 2.50 – 2.26 (m, 2H), 2.07 (td, *J* = 5.7, 2.7 Hz, 1H), 1.91 – 1.57 (m, 4H), 1.33 (s, 9H). (ESI) *m/z* calculated for $C_{17}H_{23}ClO_3N$ [M+H]+ 324.14; found, 324.10.

Methyl (1-(2-chlorophenyl)-2-oxocyclohexyl)carbamate (13)

To a mixture of norketamine (**2**; 100 mg; 0.45 mmol) in anhydrous toluene (3 mL) and anhydrous Na_2CO_3 (150 mg), a solution of methyl chloroformate (100 µL) in anhydrous toluene (300 µL) was added. After heating under reflux for 3 h, the reaction mixture was cooled to room temperature and washed subsequently with water, 10% Na_2CO_3, and water. The product was diluted with ethyl acetate, dried with anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to yield 106 mg (yield 84%) of **13** as a white solid. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 – 6.64 (m, 5H), 3.44 (s,

3H), 2.48 – 1.43 (m, 8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.87, 154.49, 134.67, 133.88, 131.66, 131.03, 129.54, 126.21, 77.37, 77.05, 76.73, 67.17, 51.63, 39.35, 38.38, 30.80, 22.33. (ESI) *m/z* calculated for $C_{14}H_{17}ClNO_3$ [M+H]+ 282.08 found, 282.14.

Methyl (1-(2-chlorophenyl)-3-hydroxy-2-oxocyclohexyl)carbamate (14)

Compound **13** (28 mg, 0.1 mmol), iodine crystals (6 mg, 0.02 mmol; 20 mol%), and DMSO (1 mL) were added to a 5 mL reaction flask fitted with an air-condenser. The mixture was stirred at 60 °C for 24 hours and monitored by TLC. There was no change in the reaction even after 3 days and also at higher temperatures of up to 100 °C. After cooling to room temperature, the solution was diluted with ethyl acetate (10 mL) and washed with 0.1 M $Na_2S_2O_3$ (5 mL) aqueous solution to quench the unreacted iodine, extracted with ethyl acetate (3×5 mL), and evaporated under vacuum and unreacted starting material collected. Substituting iodine crystals for N-bromosuccinimide (5 mg, 0.02 mmol; 20 mol%) and performing the reaction under the same conditions resulted a reaction showing the formation of a new product by TLC which showed a lower R_f value compared to the starting material. The reaction was cooled, diluted with ethyl acetate and washed with water. The organic layer was dried over sodium sulfate, the solvent removed under reduced pressure to yield a white solid. Purification by silica gel column chromatography (30% ethyl acetate in hexanes) afforded 11 mg (Yield: 37%) of compound tentatively identified as **14**. ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 – 7.01 (m, 5H), 5.77 (s, 1H), 4.04 (s, 1H), 3.57 (s, 3H), 2.98 – 1.39 (m, 6H).

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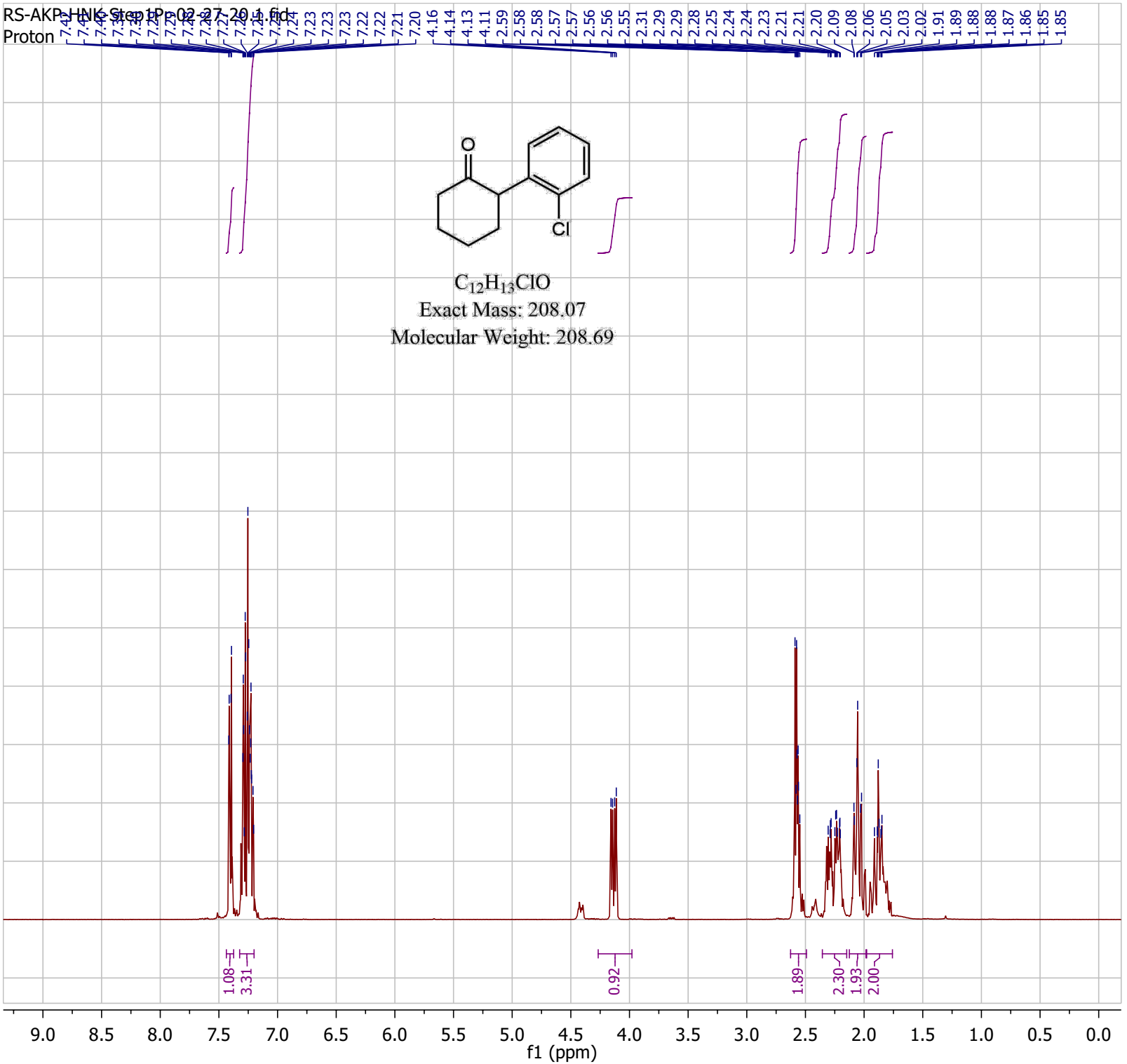
SUPPORTING INFORMATION



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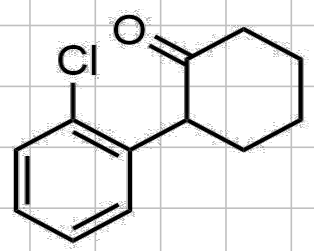

$C_{12}H_{13}ClO$
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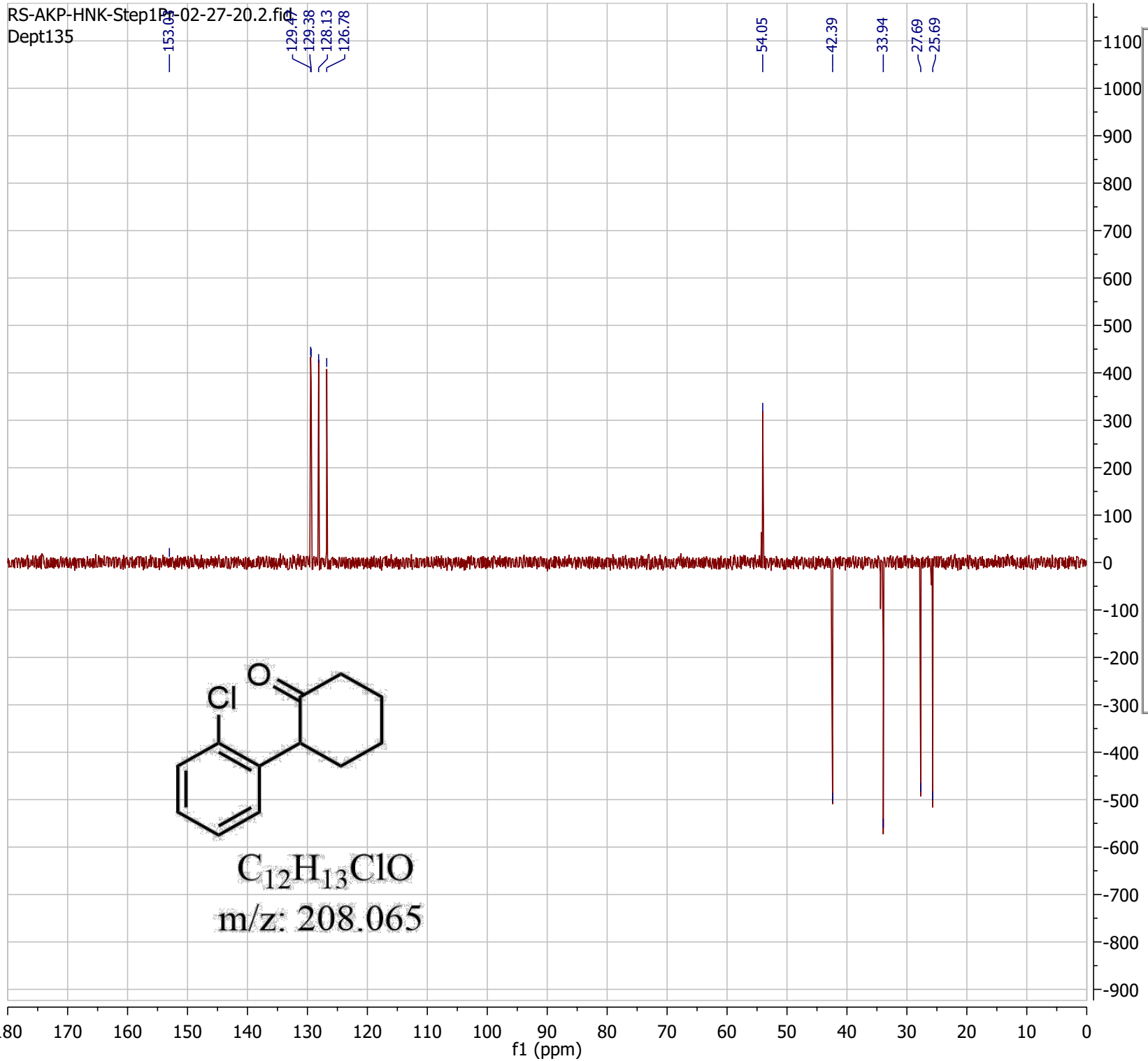

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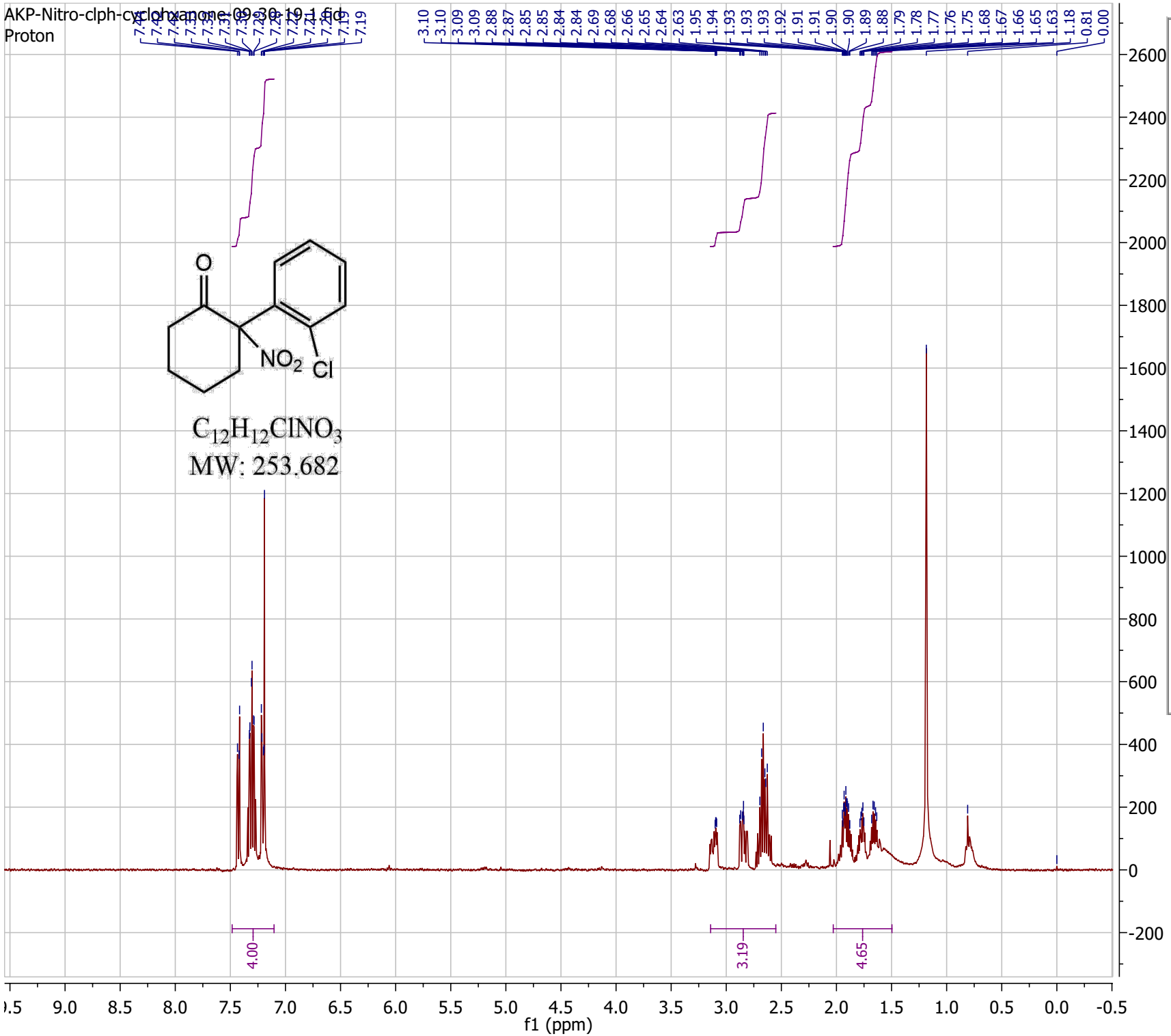

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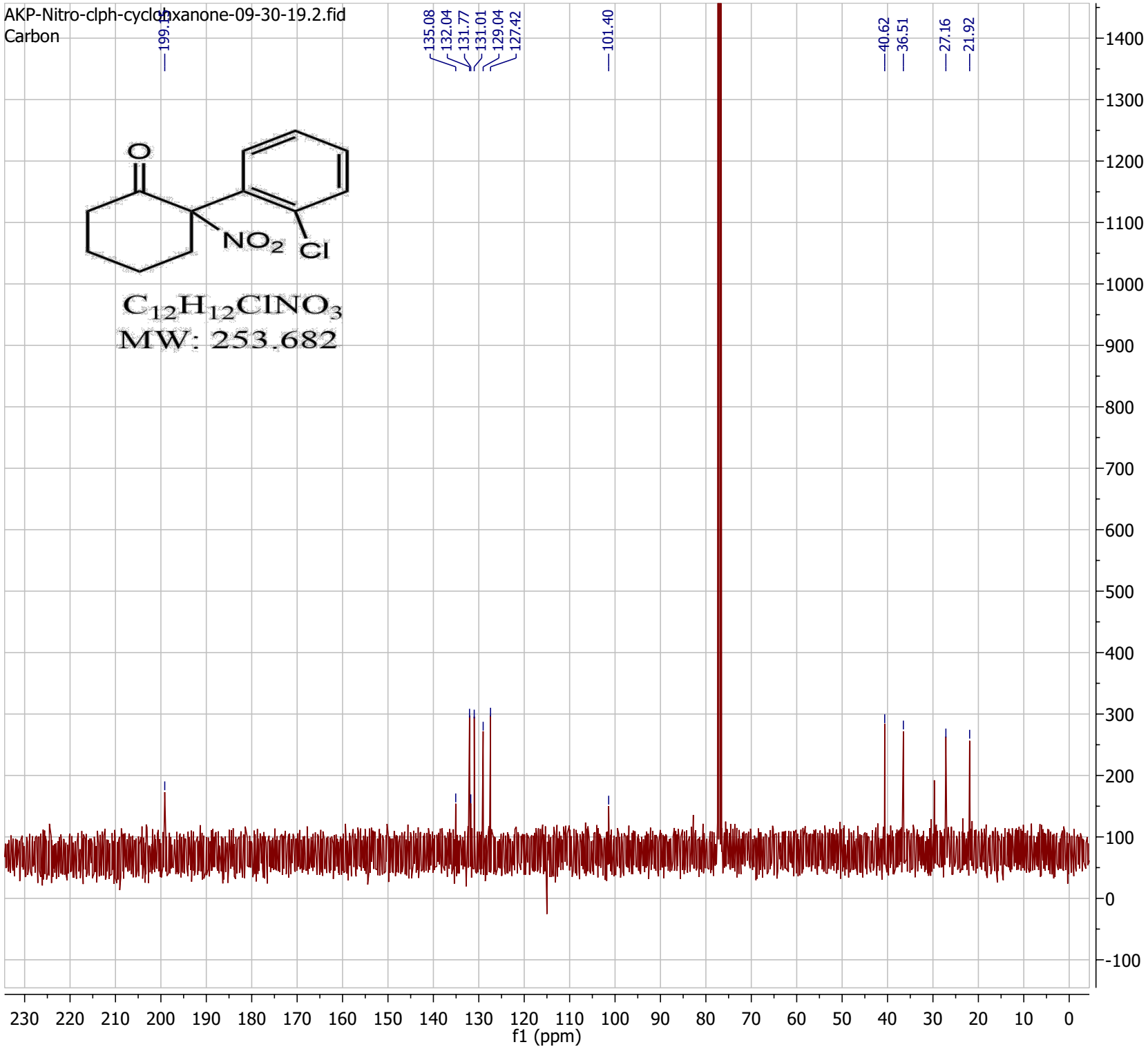

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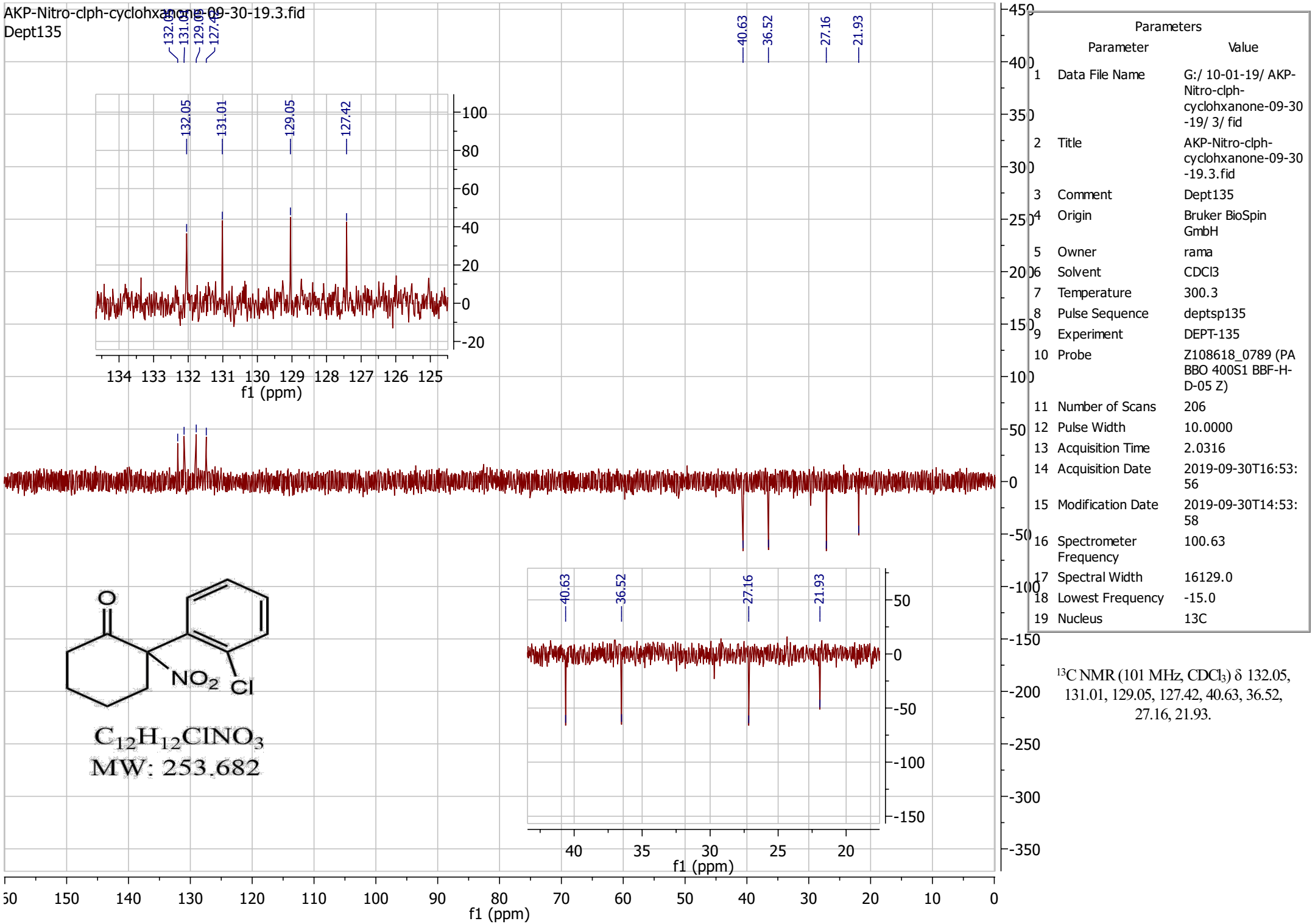
^{13}C NMR (101 MHz, $CDCl_3$) δ 199.15, 135.08, 132.04, 131.77, 131.01, 129.04, 127.42, 101.40, 40.62, 36.51, 27.16, 21.92.



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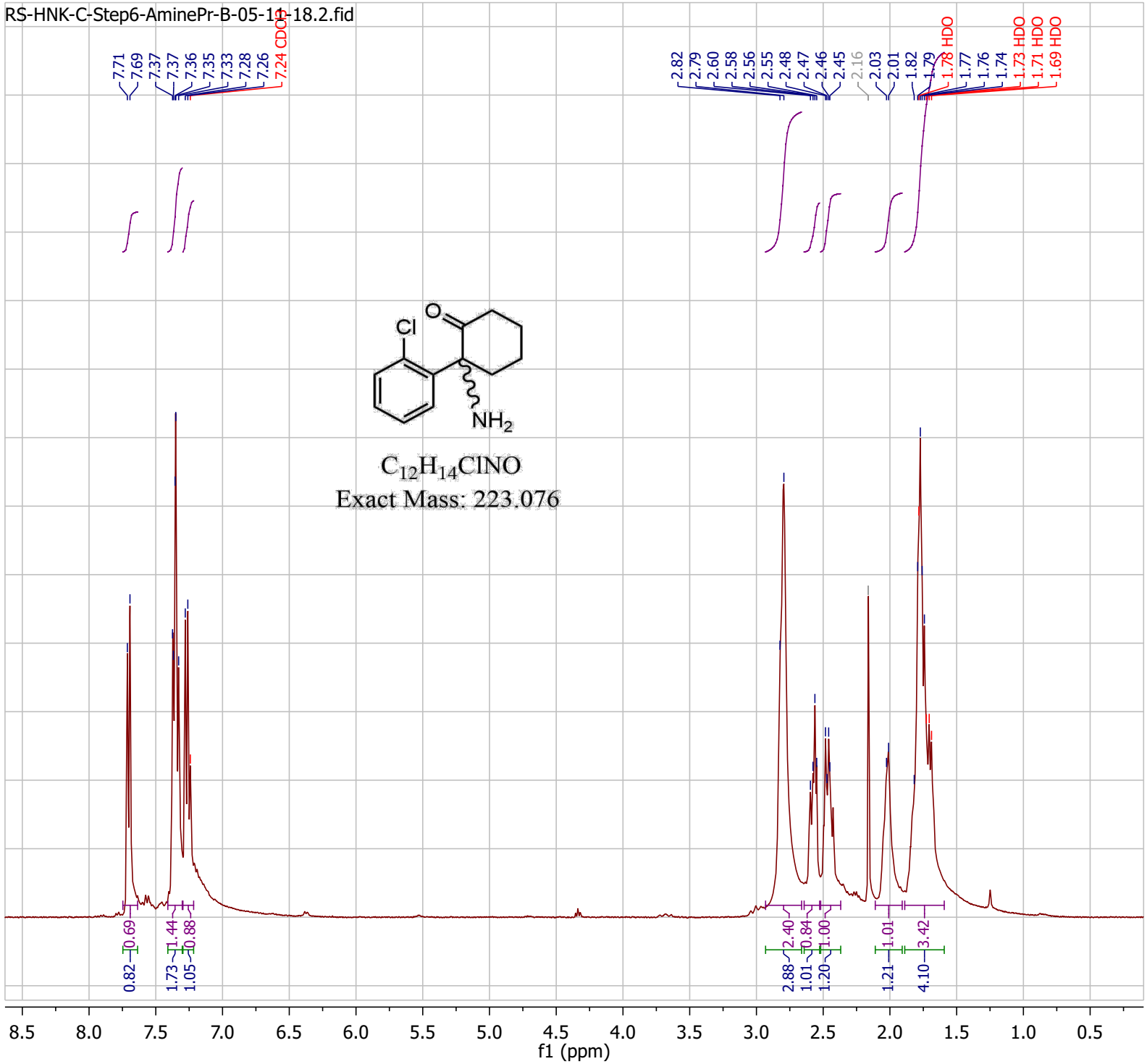

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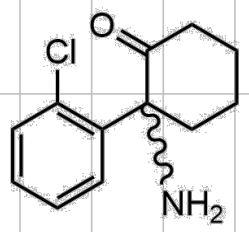

$C_{12}H_{14}ClNO$

Exact Mass: 223.076

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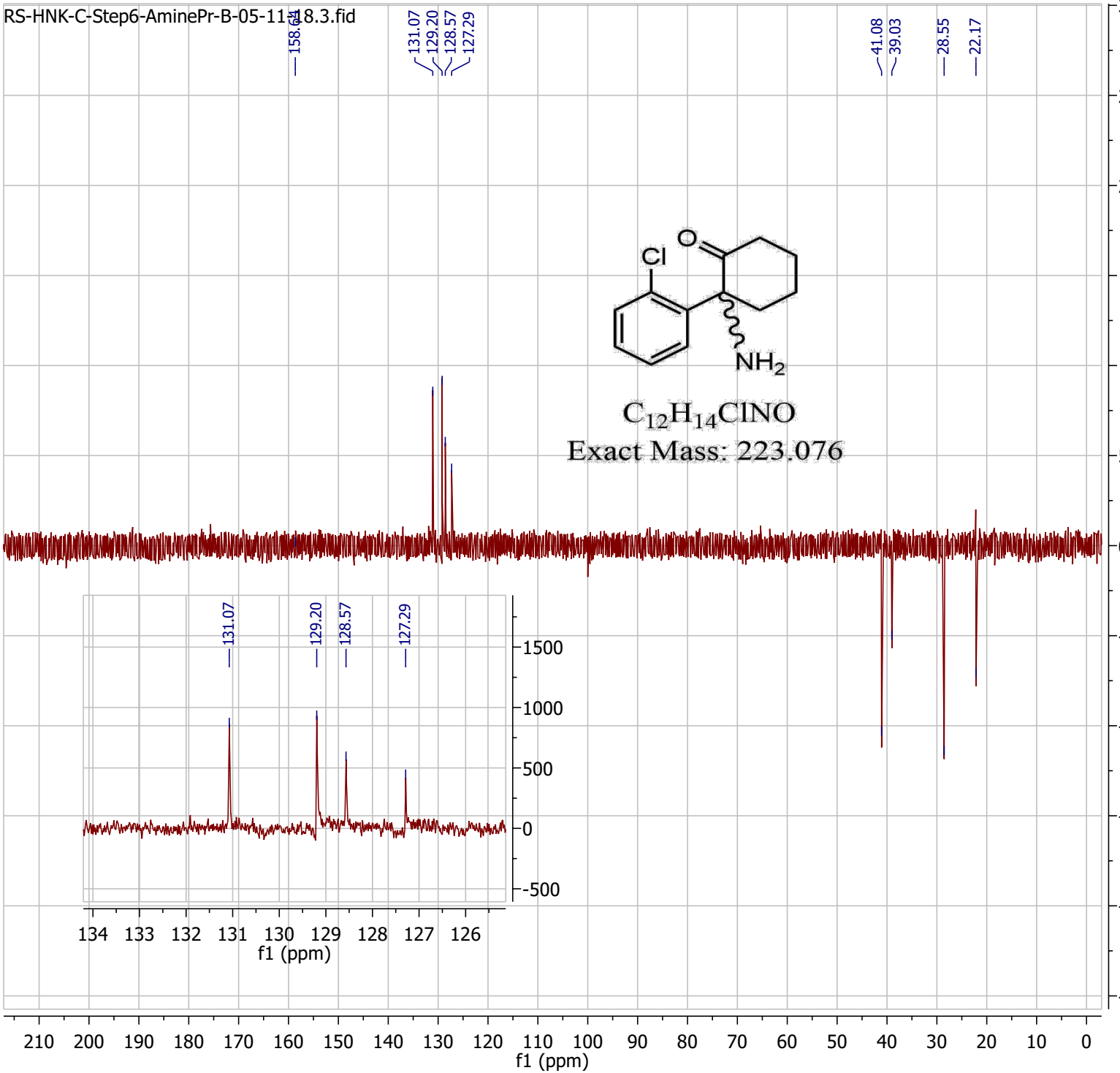
18	Lowest Frequency	-1928.6
19	Nucleus	13C

^{13}C NMR (101 MHz, $CDCl_3$) δ 212.46, 139.66, 133.14, 131.07, 129.19, 128.57, 127.29, 77.39, 77.08, 76.76, 66.62, 41.08, 39.03, 28.54, 22.17.



Parameters		
	Parameter	Value
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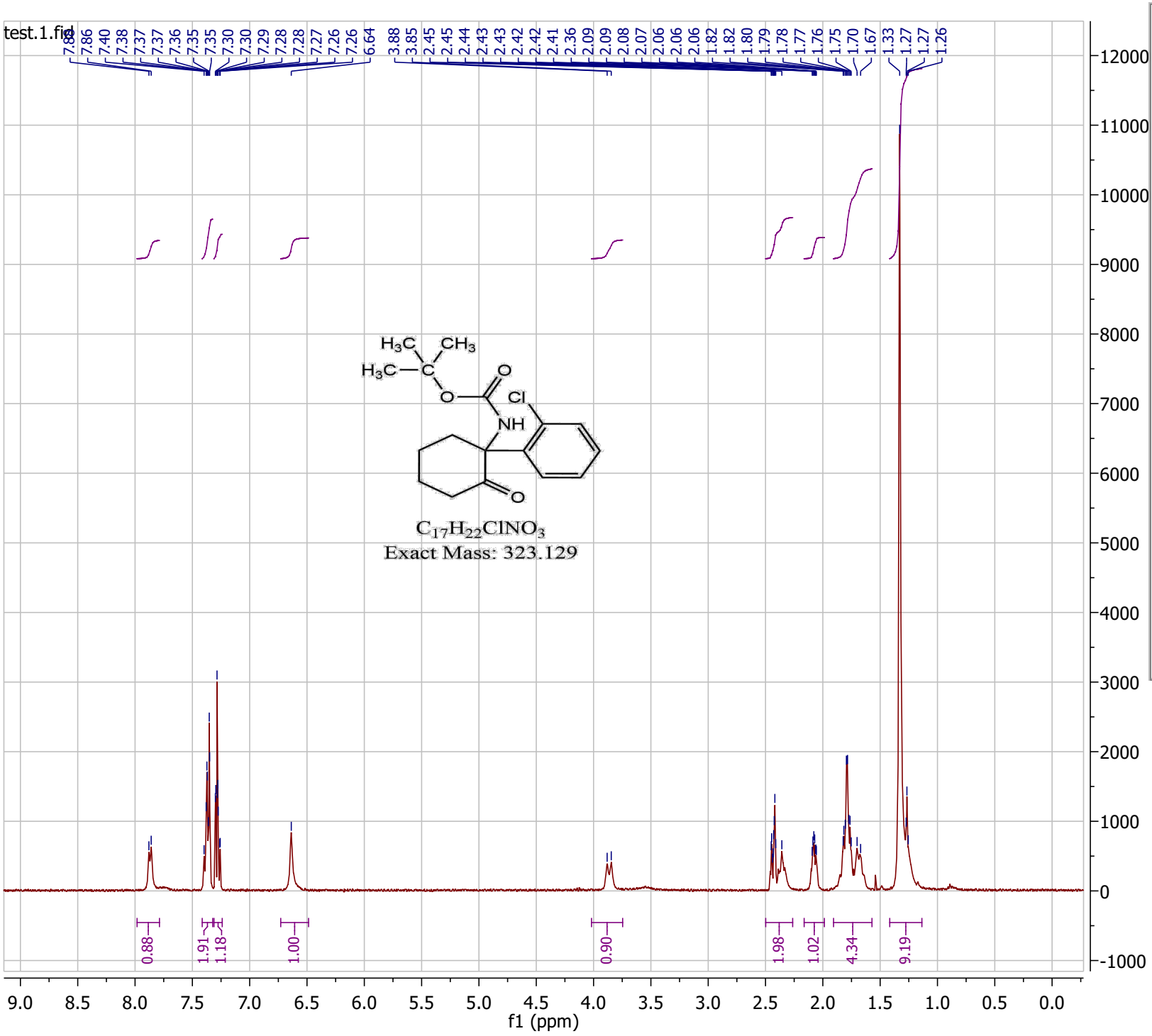
2	Title	RS-HNK-C-Step6-AminePr-B-05-11-18.3.fid
3	Comment	
4	Origin	Bruker BioSpin GmbH
5	Owner	rama
6	Solvent	CDCl3
7	Temperature	296.0
8	Pulse Sequence	dept135
9	Experiment	DEPT-135
10	Probe	5 mm PABBO BB-1H/ D Z-GRD Z108618/ 0813
11	Number of Scans	237
12	Pulse Width	9.0000
13	Acquisition Time	1.3664
14	Acquisition Date	2018-05-11T12:43:22
15	Modification Date	2018-05-11T12:53:22
16	Spectrometer Frequency	100.63
17	Spectral Width	23980.8
18	Lowest Frequency	-1928.6
19	Nucleus	13C

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.64, 131.07, 129.20, 128.57, 127.29, 41.08, 39.03, 28.55, 22.17.

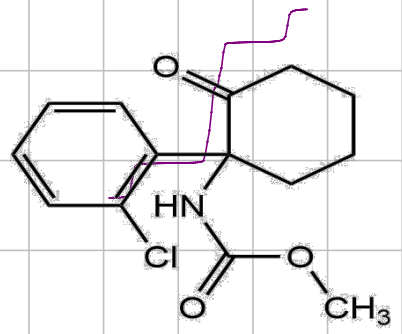


Parameters

	Parameter	Value
1	Data File Name	C:/ Users/ Rama/ Desktop/ Desktop Folders/ Sufka's new RR-OH-Norketamine/ AKP-HNK/ test/ 1/ fid
2	Title	test.1.fid
3	Comment	
4	Origin	Bruker BioSpin GmbH
5	Owner	rama
6	Solvent	CDCl3
7	Temperature	300.0
8	Pulse Sequence	zg30
9	Experiment	1D
10	Probe	Z108618_0813 (PA BBO 400S1 BBF-H-D-05 Z)
11	Number of Scans	16
12	Pulse Width	14.0000
13	Acquisition Time	4.0894
14	Acquisition Date	2020-01-29T13:55:11
15	Modification Date	2020-01-29T13:55:12
16	Spectrometer Frequency	400.15
17	Spectral Width	8012.8
18	Lowest Frequency	-1535.5
19	Nucleus	1H

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.87 (d, *J* = 8.0 Hz, 1H), 7.36 (dt, *J* = 7.9, 2.0 Hz, 2H), 7.31 – 7.24 (m, 1H), 6.64 (s, 1H), 3.86 (d, *J* = 14.4 Hz, 1H), 2.50 – 2.26 (m, 2H), 2.07 (td, *J* = 5.7, 2.7 Hz, 1H), 1.91 – 1.57 (m, 4H), 1.33 (s, 9H).

RS-Meo-CO-NH-Nork-03-10-20.1.fid
Proton

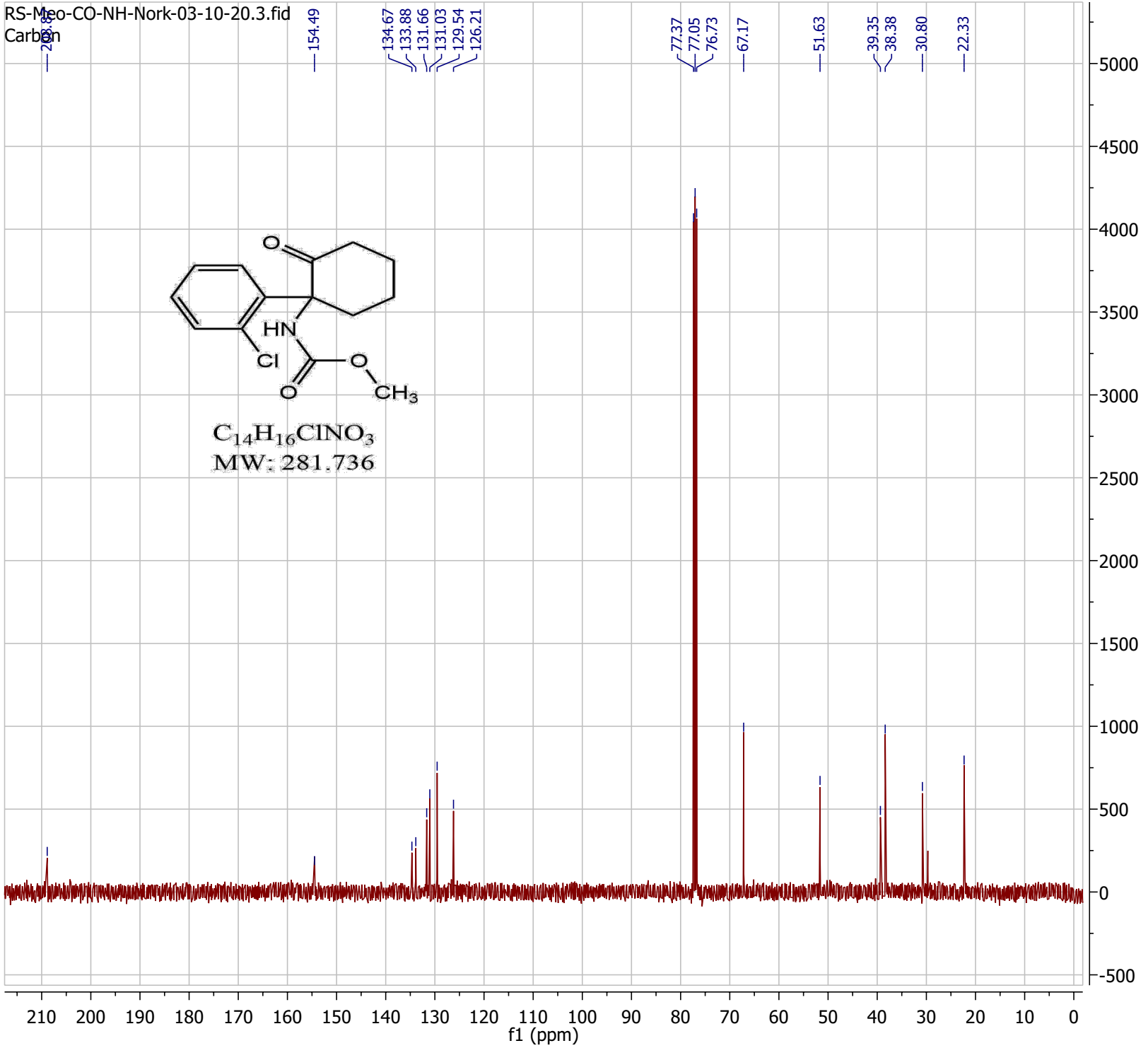


$C_{14}H_{16}ClNO_3$
MW: 281.736

Parameters		
	Parameter	Value
1	Data File Name	C:/ Users/ Rama/ Desktop/ Desktop Folders/ Sufka's new RR-OH-Norketamine/ AKP-HNK/ RS-Meo-CO-NH-Nork-03-10-20/ 1/ fid
2	Title	RS-Meo-CO-NH-Nork-03-10-20.1.fid
3	Comment	Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	rimolldi
6	Solvent	CDCl3
7	Temperature	298.2
8	Pulse Sequence	zg30
9	Experiment	1D
10	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0795
11	Number of Scans	16
12	Pulse Width	10.0000
13	Acquisition Time	4.0894
14	Acquisition Date	2020-03-10T15:06:51
15	Modification Date	2020-03-10T15:06:54
16	Spectrometer Frequency	400.13
17	Spectral Width	8012.8
18	Lowest Frequency	-405.2
19	Nucleus	1H

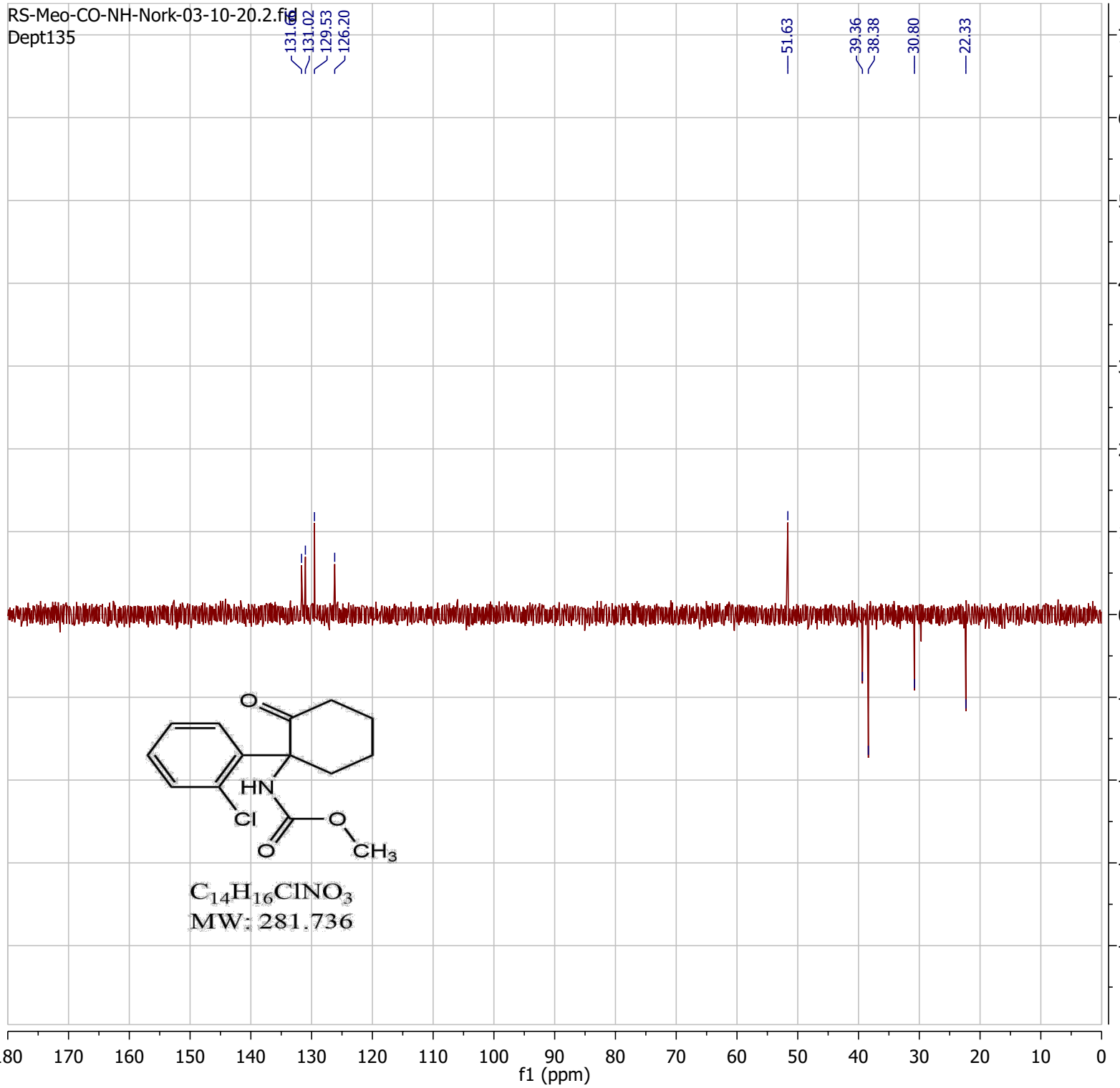
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.96 – 6.64 (m, 5H), 3.44 (s, 3H), 2.48 – 1.43 (m, 8H).

f1 (ppm)



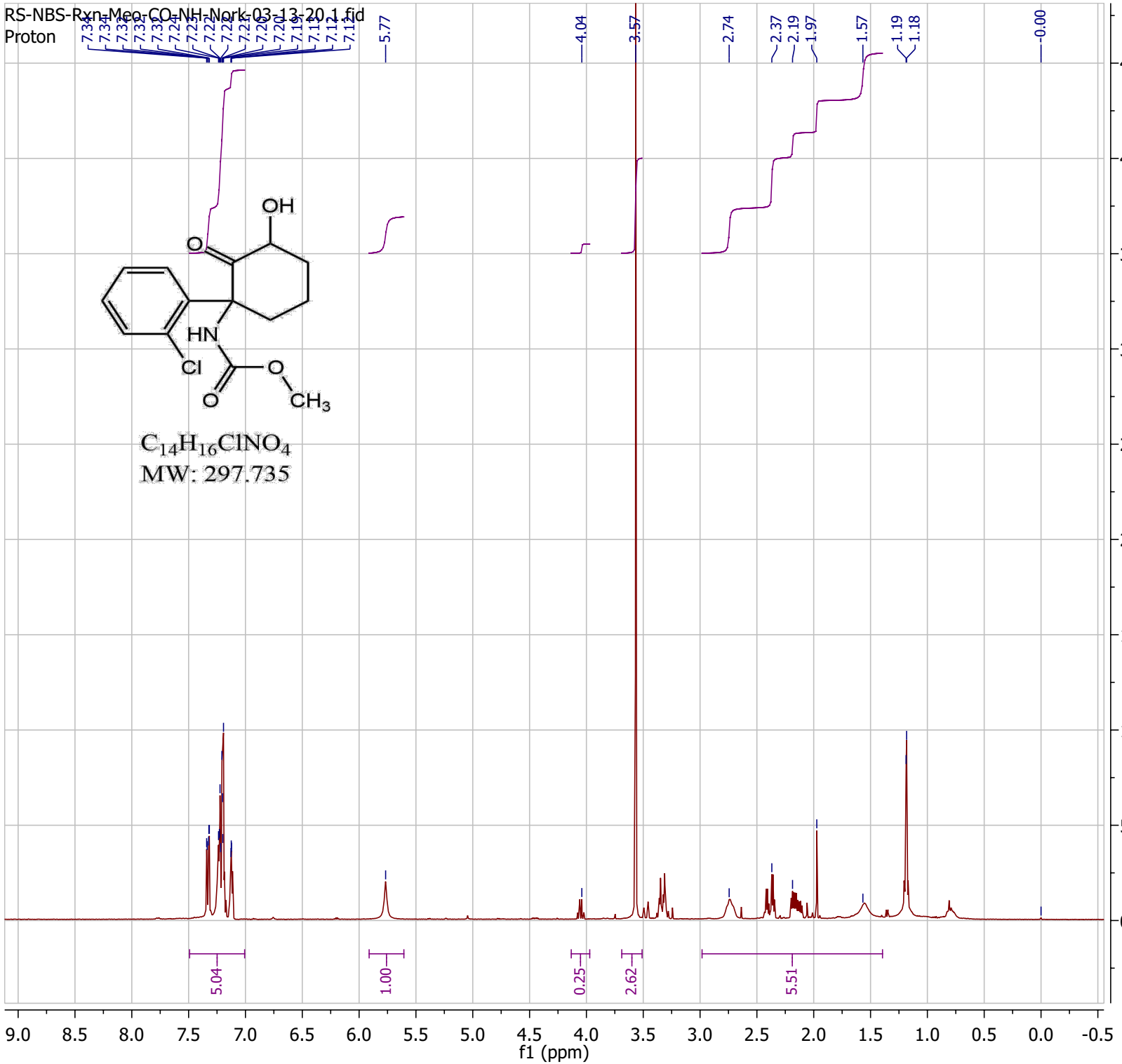
Parameters		
	Parameter	Value
1	Data File Name	C:/ Users/ Rama/ Desktop/ Desktop Folders/ Sufka's new RR-OH-Norketamine/ AKP-HNK/ RS-Meo-CO-NH-Nork-03-10-20/ 3/ fid
2	Title	RS-Meo-CO-NH-Nork-03-10-20.3.fid
3	Comment	Carbon
4	Origin	Bruker BioSpin GmbH
5	Owner	rimolldi
6	Solvent	CDCl3
7	Temperature	297.3
8	Pulse Sequence	zgpg30
9	Experiment	1D
10	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0795
11	Number of Scans	1869
12	Pulse Width	10.0000
13	Acquisition Time	1.3631
14	Acquisition Date	2020-03-10T16:24:19
15	Modification Date	2020-03-10T17:42:54
16	Spectrometer Frequency	100.62
17	Spectral Width	24038.5
18	Lowest Frequency	-951.8
19	Nucleus	13C

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.87, 154.49, 134.67, 133.88, 131.66, 131.03, 129.54, 126.21, 77.37, 77.05, 76.73, 67.17, 51.63, 39.35, 38.38, 30.80, 22.33.



Parameters		
	Parameter	Value
1	Data File Name	C:/ Users/ Rama/ Desktop/ Desktop Folders/ Sufka's new RR-OH-Norketamine/ AKP-HNK/ RS-Meo-CO-NH-Nork-03-10-20/ 2/ fid
2	Title	RS-Meo-CO-NH-Nork-03-10-20.2.fid
3	Comment	Dept135
4	Origin	Bruker BioSpin GmbH
5	Owner	rimolldi
6	Solvent	CDCl3
7	Temperature	298.5
8	Pulse Sequence	deptsp135
9	Experiment	DEPT-135
10	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0795
11	Number of Scans	202
12	Pulse Width	10.0000
13	Acquisition Time	1.8088
14	Acquisition Date	2020-03-10T15:10:07
15	Modification Date	2020-03-10T15:21:54
16	Spectrometer Frequency	100.62
17	Spectral Width	18115.9
18	Lowest Frequency	-2.8
19	Nucleus	13C

^{13}C NMR (101 MHz, $CDCl_3$) δ 131.66, 131.02, 129.53, 126.20, 51.63, 39.36, 38.38, 30.80, 22.33.



Parameters

	Parameter	Value
1	Data File Name	C:/ Users/ Rama/ Desktop/ Desktop Folders/ Sufka's new RR-OH-Norketamine/ AKP-HNK/ RS-NBS-Rxn-Meo-CO-NH-Nork-03-13-20/ 1/ fid
2	Title	RS-NBS-Rxn-Meo-CO-NH-Nork-03-13-20.1.fid
3	Comment	Proton
4	Origin	Bruker BioSpin GmbH
5	Owner	rimolldi
6	Solvent	CDCl3
7	Temperature	298.0
8	Pulse Sequence	zg30
9	Experiment	1D
10	Probe	5 mm PABBO BB/ 19F-1H/ D Z-GRD Z108618/ 0795
11	Number of Scans	112
12	Pulse Width	10.0000
13	Acquisition Time	4.0894
14	Acquisition Date	2020-03-13T14:15:59
15	Modification Date	2020-03-13T14:16:02
16	Spectrometer Frequency	400.13
17	Spectral Width	8012.8
18	Lowest Frequency	-405.2
19	Nucleus	1H

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.49 – 7.01 (m, 5H), 5.77 (s, 1H), 4.04 (s, 1H), 3.57 (s, 3H), 2.98 – 1.39 (m, 6H).