SYNTHESIS AND STRUCTURAL MODIFICATION OF THE MDMA ANTAGONIST NANTENINE: A NATURALLY OCCURRING APORPHINE ALKALOID

by

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Abstract

Synthesis and Structural Modification of the MDMA Antagonist Nantenine: A Naturally Occurring Aporphine Alkaloid

By

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MDMA ("Ecstasy") is a synthetic phenethylamine stimulant which is known to affect the re-uptake of serotonin, dopamine and nor-epinephrine in the brain. Adverse effects of "Ecstasy" in humans include development of hyperthermia, hallucinations, organ failure and in extreme cases, death. There is evidence that the behavioral and physiological effects of MDMA are mediated by α_1-adrenergic and 5-HT_{2A} receptors. Nantenine is a naturally occurring aporphine alkaloid which has been shown to block and reverse behavioral and physiological effects of MDMA in mice via antagonism of the aforementioned receptors. However, the relative role of these receptors in mediating the MDMA antagonizing effects of nantenine *in vivo* is unknown.

The goal of this project is to explore different methods of synthesizing nantenine and nantenine derivatives. These compounds were subjected to *in vitro* testing for antagonistic activity at α_1-adrenergic and 5-HT_{2A} receptors and their ability to block/reverse MDMA-induced effects in mice through *in vivo* drug discrimination assays. This work provided insight into the relative role of these receptors in mediating the antagonistic activity of nantenine. Moreover, the results may provide the foundation for the design and development of potent and selective MDMA antagonists in the future.

Here we present our synthetic studies as well as the results of biological evaluations of nantenine and analogues.

In Memory of April 26th 2008
I miss you more everyday...

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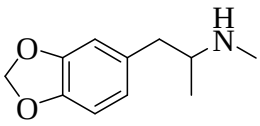
1. INTRODUCTION

1.1. History Discovery of MDMA use in Humans

3,4-Methylenedioxymethamphetamine (MDMA) is an illicit "designer" drug also known as "Ecstasy" (Figure 1). MDMA is a ring-substituted amphetamine that is popular with adolescents at massive parties known as "raves" as well as on college campuses since the mid 1980's.[1] The name "Ecstasy" was first heard on the streets of California in 1984.[2]

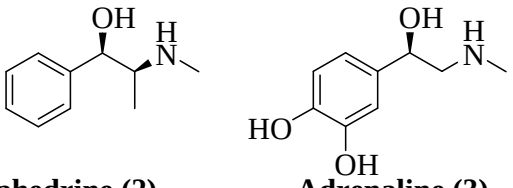


MDMA (1)

Figure 1: 3,4-methylenedioxymethamphetamine

MDMA was first synthesized in 1912 by Köllisch and patented by Merck in Darmstadt Germany as an anorectic drug or appetite suppressant.[2] However, MDMA's patent 274350, has no indications for plans to develop an appetite suppressant.

In 1927, Merck was interested in adrenaline- or ephedrine-like substances and Dr. Max Oberlin noted MDMA's structural similarity to ephedrine and adrenaline (Figure 2).



Ephedrine (2) **Adrenaline (3)**

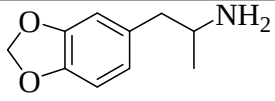
Figure 2: Compounds Structurally Similar to MDMA

Oberlin conducted pharmacological tests on MDMA and determined that it affects blood glucose levels similarly to high doses of ephedrine. MDMA was capable of dilating vascular

smooth muscle and uterine muscle tissue with similar potency to ephedrine, while not affecting the eye muscles.[2] Oberlin concluded that MDMA did not have pure sympathetic effects.

Shulgin reported MDMA as a hallucinogen based on its chemistry, dosage, kinetics and psychotropic effects in humans in 1978.[3,4] MDMA was first detected in tablet size on the streets of Chicago in 1970.[5]

The U.S. Drug Enforcement Administration classified MDMA as a Schedule 1 drug in 1985 due to its high abuse potential, lack of clinical application and lack of accepted safety for use under medical supervision. There was also evidence that 3,4-methylenedioxyamphetamine (MDA), a major MDMA metabolite, caused serotonergic nerve terminal degeneration in rat brain (Figure 3).[6] MDMA was thereafter banned in other countries.



MDA (4)

Figure 3: 3,4-methylenedioxyamphetamine

1.2. Physiological and Behavioral effects of MDMA in Humans

The primary effects of MDMA in humans are similar to that of other amphetamines.[7] Shulgin and Nichols reported that MDMA was psychoactive in humans causing hallucinogenic effects.[4,8] In 1985 Greer and Strassman reported that oral administration of MDMA in 75–175 mg doses increases a patients' self-esteem and promotes open communication during psychotherapy.[9]

MDMA produces a relaxed, euphoric state, including emotional openness, empathy, reduction of negative thoughts, and a decrease in inhibitions.[10-12] MDMA's adverse physiological effects normally occur during the peak period, 20 to 60 minutes after ingestion.

The adverse effects include elevated blood pressure and heart rate, nausea, chills, sweating, tremor, jaw clenching, bruxism, hyperreflexia, urinary urgency, muscle aches or tension, hot and cold flushes, nystagmus, and insomnia.[13,14] Davison and Parrott suggest that individuals who consume MDMA experience sounds and colors more intensely, depression, irritability, panic attacks, visual hallucinations, and paranoid delusions following the initial effects.[11]

Hyperthermia is the second leading cause of death from MDMA abuse and occurs when the core body temperature reaches 104 °F and major organs begin to shut down.[15] Green suggests that MDMA-related hyperthermia occurs as a result of serotonin syndrome, which occurs when serotonin is constantly released into the brain causing its depletion in the presynaptic neuron.[16]

The third most prominent cause of death from MDMA is acute overdose. Walubo has reported the death of a 53-year-old prisoner from a suicidal overdose of MDMA.[17] After becoming severely hyperthermic (107.2 ^{o}F), the prisoner developed acute respiratory distress syndrome, rhabdomyolysis, disseminated intravascular coagulopathy and acute renal failure. At autopsy, the prisoner's blood plasma concentration of MDMA was determined to be 3.05 mg/L. In addition to these studies, Henry has reported similar patterns of toxicity including convulsions and hepatotoxicity among seven fatalities caused by MDMA overdose.[18] In animal studies, the lethal dose of MDMA in rats is sex dependent: LD_{50} for MDMA in males was 18 mg.kg^{-1} sc, significantly lower than that in females at 42.5 mg.kg^{-1} sc.[19] A brief review of the acute and long-term effects of MDMA in humans are listed in Table 1.

Table 1: Effects of MDMA in Humans

Acute Effects	Long-Term Effects
Increase in self-esteem	Serotonin Syndrome
Open communication	Disorganized thinking
Empathy	Depression
Decrease in Inhibition	Panic attacks
Sweating	Visual hallucination
Increase blood pressure	Paranoid delusions
Hyperthermia	Irritability

1.3. How MDMA Affects Neurotransmitters

The roles of neurotransmitters and receptors in mediating the physiological and psychological effects of MDMA in humans are not fully understood. In animals, MDMA mainly releases serotonin by interacting with the serotonin reuptake transporter (SERT) and to a lesser extent, as compared to serotonin, dopamine, via the dopamine reuptake transporter (DAT).[20,21] The effects of MDMA in humans are believed to be greatly dependent on the release of serotonin by the SERT.[21]

Animal studies have shown that 5-HT_2 antagonists can curb several physiological effects of MDMA, including MDMA-induced serotonergic neurotoxicity, acute hyperthermia and disruption of sensorimotor gating. This indicates that 5-HT_2 receptors may be involved in mediating the effects of MDMA.[22-24] In humans, the hallucinogen-like effects of MDMA may be due to stimulation of the 5-HT_{2A} receptor given that this receptor mediates the visual and psychological effects of indole hallucinogens.[25,26] Pretreatment with a 5-HT_2 antagonist can reduce the MDMA-induced visual and psychological effects.[27]

The role of dopamine in mediating responses to MDMA in humans is also not fully understood. *In vivo* micro-dialysis and *in vitro* studies using brain tissue slices have shown that MDMA rapidly increases dopamine release from cerebral tissue.[28] Classical stimulants such as

D-amphetamine and cocaine cause euphoria which is believed to be mediated in part by dopamine.[29,30] Increases in dopaminergic activity may also contribute to MDMA-induced euphoria.

There have been recent reports stating that 5-HT_2 antagonists can increase the levels of dopamine. Ruiu has determined that ritanserin (**5a**), a 5-HT_{2A} and 5-HT_{2C} receptor antagonist, affects the reuptake and efflux of dopamine in rat frontal cortex synaptosomes (Figure 4).[31] Ritanserin (**5a**) blocks the DAT with a K_i of 0.18 μM, which is similar to cocaine (K_i = 0.11 μM). When compared to other serotonin and dopamine antagonists such as ketanserin and haloperidol, ritanserin proved to be more potent.

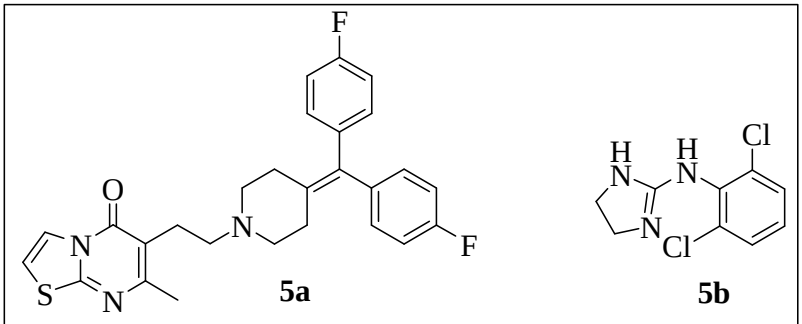


Figure 4: Strucutre of Ritanserin (**5a**) and Clonidine (**5b**)

MDMA has been shown to produce complex effects on body temperature including hypo- and hyperthermia as well as increased locomotor activity in rats, activities which are mediated by the α-adrenoceptors.[32-36]

Bexis has previously reported that MDMA is a α_2-adrenoceptor agonist and has also conducted studies to determine the specific involvement of the α_2 receptor in MDMA-induced core body temperatures variations using wild-type and α_{2A}-knockout mice.[34] As a control, clonidine (**5b**), a direct-acting α_2 adrenergic agonist, was used to activate the α_2 receptor. Clonidine (**5b**) produced a hypothermic response in wild-type mice but did not significantly

affect body temperature in α_{2A}-knockout mice. MDMA produced a significant hyperthermia in wild-type mice but produced a biphasic response, hypothermia followed by hyperthermia, in α_{2A}-knockout mice. Therefore, these findings provide evidence that MDMA's α_2-adrenoceptor agonistic activity affects core body temperature in a biphasic manner.[34]

Selken has reported *in vitro* studies that suggest MDMA releases norepinephrine with equal potency as the release of serotonin.[36] Selken determined that MDMA-induced stimulation of the α_1-adrenoceptor causes an increase in locomotor activity in rats, which is attenuated by blockade of α_1-adrenoceptors with systemic or local administration of prazosin.[36]

Trigo has reported the effects of MDMA in SERT-knockout mice.[37] In this study, the goal was to determine the contribution of the SERT in mediating MDMA responses. Knockout and wild-type mice were trained to acquire intravenous self-administration of MDMA at various doses. Microdialysis was used to determine the extracellular levels of dopamine and serotonin in the prefrontal cortex and the nucleus accumbens. The results of this study showed that in SERT knockout mice, none of the MDMA doses maintained intravenous self-administration and operant responding for food and water were also delayed, while wild-type mice acquired MDMA response. MDMA increased the extracellular levels of dopamine in the nucleus accumbens for both the wild-type and knockout mice. Extracellular concentration of serotonin in the prefrontal cortex was increased following MDMA self-administration only in wild-type mice. Therefore, these findings provide evidence for the involvement of the SERT in MDMA's reinforcing properties.[37]

1.4. Long-term effects of MDMA ingestion

Single or multiple doses of MDMA administered to rats results in long-term depletion of serotonin and 5-Hydroxyindoleacetic acid (5-HIAA), the main metabolite of serotonin. Low levels of 5-HIAA in the cerebrospinal fluid have been associated with aggressive behavior and suicide by violent means.[38-40] Schmidt states that MDMA-induced serotonin release initially decreases the amount of serotonin in the brain with concentrations returning to pretreatment levels within 24 h.[41]

1.5. Effects of MDMA-induced Serotonin Depletion in Animal Models

Serotonin is known to be involved in the regulation of body heat and MDMA-induced serotonin depletion is attributed to rats' inability to thermally regulate.[42] O'Callaghan and Stone have reported that MDMA has a different pharmacology in mice as compared to rats.[43,44] O'Callaghan argues that in mice, MDMA does not affect the concentration of serotonin in the brain but is a selective dopamine neurotoxin.[44] Ricaurte claims that MDMA-induced serotonin depletion and neural damage in primates is more pronounced than the observed effects in rodents.[45,46] In primates, the effects of MDMA-induced serotonin depletion are dose dependent while MDMA does not affect the levels of dopamine.[47] MDMA effects in primates may suggest a similar effect occurs in humans.

2. PHARMACOKINETICS OF MDMA

2.1. MDMA Metabolites in Humans

MDMA reaches the highest concentration in the blood between 1.5 and 3 hours after ingestion and is then slowly metabolized and excreted with a half-life of approximately 8 hours. Several metabolites of MDMA have been identified in humans (Figure 5).

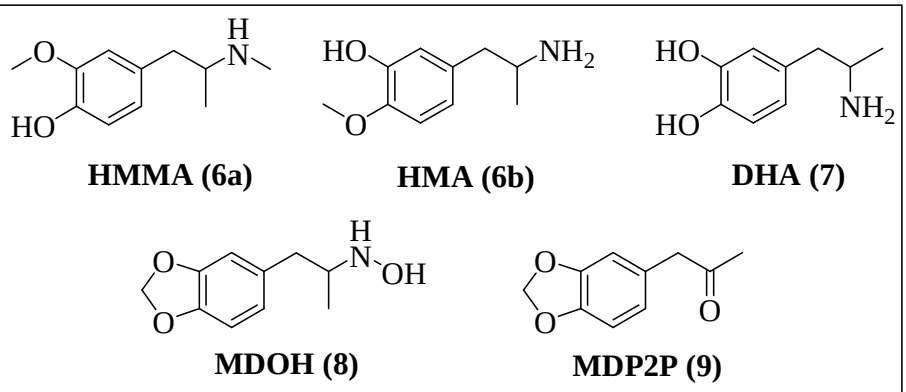


Figure 5: Metabolites of MDMA

These compounds include: MDA, **4**, 4-hydroxy-3-methoxy-methamphetamine (**6a**), 4-hydroxy-3-methoxyamphetamine (**6b**), 3,4-dihydroxyamphetamine (**7**), N-hydroxy-3,4-methylenedioxyamphetamine (**8**) and 3,4-methylenedioxyphenylacetone (**9**).[48] Verebey has reported the 65% of MDMA is excreted unchanged in the urine during the 24 h after ingestion, while 7% is metabolized as MDA.[48] MDA causes serotonin and dopamine release by acting on the SERT and DAT, respectively. MDA tends to cause more psychedelic-like effects than MDMA given that *R*-MDA has a higher efficacy in stimulating the 5-HT_{2A} receptor than *R*-MDMA.[48]

3. MECHANISM OF MDMA NEUROTOXICITY

Several groups have reported *in vitro* studies that suggest MDMA induces neuronal death in cortical and cerebella granule neurons.[49-52] MDMA-induced neurotoxicity occurs predominantly from apoptotic cell death of serotonergic and dopaminergic neurons.[53] The activation of caspase 3, a protein that plays a major role in the execution-phase of cell apoptosis, occurs with MDMA-induced apoptotic neuronal death in a concentration dependent manner.[54] Under normal temperatures, activity of caspase-3 increases as the concentration of MDMA increases (Figure 6).

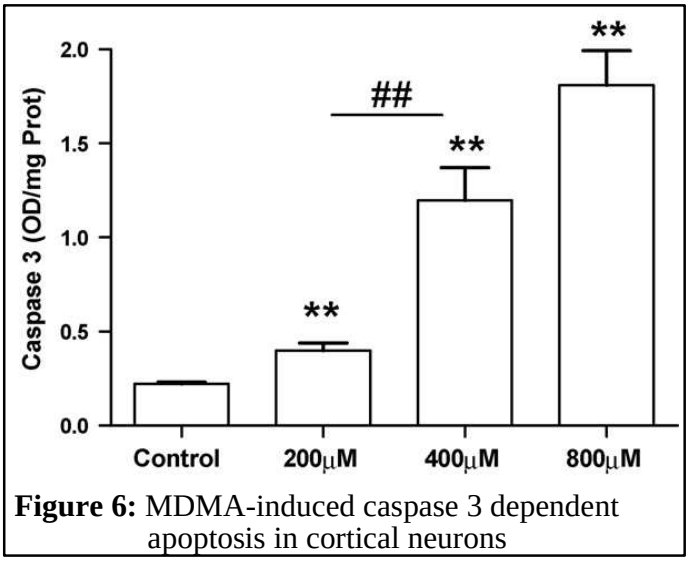
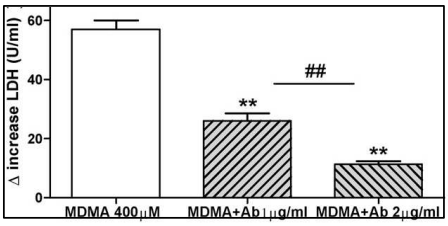


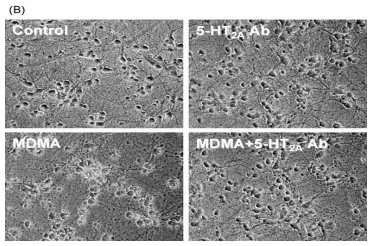
Figure 6: MDMA-induced caspase 3 dependent apoptosis in cortical neurons

Animal studies were conducted to determine the discrete brain regions affected by MDMA-induced degeneration. *In vivo* studies on rats have provided evidence that neural degeneration occurs throughout the entire brain including the parietal cortex, which is important for integrating sensory information from various parts of the body, knowledge of numbers and in the manipulation of objects.[55-57] MDMA affect in the parietal cortex can explain the long-term effect causing disorganized thinking.

In vivo studies also show that 5-HT_{2A}-receptor antagonists are effective in preventing MDMA-induced neuronal damage in rats, indicating that the 5-HT_{2A}-receptor is involved in MDMA-induced serotonin degeneration.[58-60] Capele argues that agonism of the 5-HT_{2A}-receptor mediates MDMA-induced neurotoxicity.[53] To test this hypothesis, Capele pre-incubated cultured cortical neurons with the 5-HT_{2A}-receptor antibody, an irreversible non-competitive antagonist, under hyperthermic conditions. Results of the study show that 5-HT_{2A}-receptor antibodies prevent the neurotoxic effects of MDMA in a dose dependent manner as measured by the decrease in the production of lactate dehydrogenase (LDH), increased levels of LDH would indicate tissue breakdown, (Figure 7A). The protective effect of the 5-HT_{2A}-receptor antibody was dependent on its concentration. Under hyperthermic conditions, MDMA-induced apoptotic neurodegeneration in cortical neurons are prevented by antibody pre-treatment (Fig. 7B).[53]



(A) 2 mg/ml of the 5-HT_{2A}-receptor antibody prevented MDMA-induced neurotoxicity, as evaluated by LDH release into the medium.



(B) Cortical neurons, 48 h after 400 mM MDMA stimulation, undergo neurodegeneration with a loss of axons and dendrites with typical features of apoptosis. The use of the 5-HT2A-receptor antibody blocked this event

Figure 7: MDMA-induced cortical neurotoxicity is mediated by 5-HT_{2A}-receptor stimulation

3.1. Neurotransmitter Release and Reuptake Process

In the normal signal pathway, the concentration of serotonin, norepinephrine and dopamine in the brain is regulated following a similar process depicted in Figure 8: (1) Serotonin being released from the pre-synaptic neuron (2) Serotonin receptor in the post-synaptic neuron (3) Serotonin reuptake via the reuptake transporter as well as degraded and oxidized via Catechol-O-

Methyl Transferase (COMT) and Monoamine Oxidase (MAO) respectively.[61] For example, serotonin is released from the vesicles into the synapse and is received by receptors in the postsynaptic neuron thus activating secondary messenger pathways.[62] Once a critical concentration of serotonin in reached in the synapse, removal of serotonin can occur through one of these processes: *i*) enzymes may inactivate or metabolize serotonin in the synapse *ii*) the re-uptake pump may pump serotonin back into the presynaptic neuron to be recycled or degraded or *iii*) serotonin may bind to a serotonin receptor thus effecting chemical neurotransmission across the synaptic cleft.

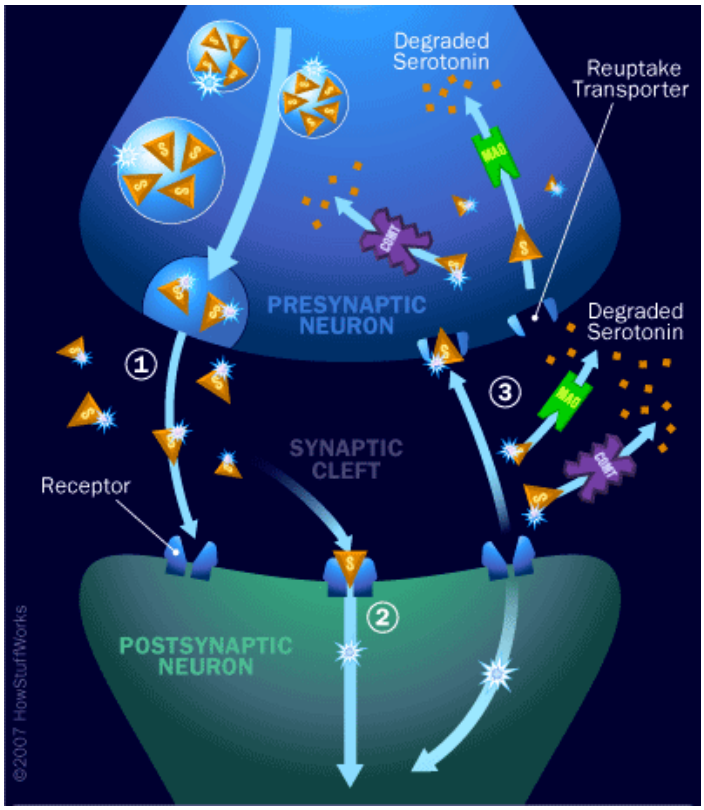


Figure 8: Cross Section of Synapse[61]

3.2. MDMA as a Reuptake Inhibitor

MDMA is classified as a monoamine, specifically serotonin, norepinephrine and dopamine, reuptake inhibitor as well as a releasing agent.[63] Once ingested, MDMA enters neurons via the monoamine reuptake transporter.[64] MDMA then inhibits the function of the respective monoamine reuptake transporter.[65]

3.3. MDMA as a Neurotransmitter Releasing Agent

MDMA causes the release of neurotransmitters into the synapse via the reuptake transporters. Through *in vitro* analysis, Fitzgerald determined the mechanism of MDMA-induced neurotransmitter release is mediated by the reuptake transporter given that these effects are blocked by neuronal uptake inhibitors such as cocaine and fluoxetine.[64]

In addition to Fitzgerald's study, Bogen studied the mechanism for MDMA-induced neurotransmitter release through *in vitro* and *ex vivo* experiments.[65] Bogen determined that MDMA reduced both synaptosomal and vesicular uptake of serotonin and dopamine in a dose dependent manner *in vitro*. The *ex vivo* studies involved adult male Wistar rats that were treated with MDMA over 66 h followed by decapitation. These experiments showed that MDMA affects the reuptake of dopamine after short-term exposure while long-term exposure affects the reuptake of serotonin.[65]

4. POTENTIAL TREATMENT STRATEGIES FOR MDMA ABUSE

The adrenergic receptors (α-receptors) are a class of G-protein-coupled receptors that are targets of the catecholamines, specifically noradrenaline and adrenaline. Activation of these receptors causes a sympathetic (fight-or-flight) response. α-Receptors have several functions including vasoconstriction of coronary arteries and veins as well as decreasing the motility of smooth muscle in the gastrointestinal tract.[66-68]

Serotonin receptors (5-HT receptors) are also a group of G-protein-coupled receptors and ligand-gated ion channels found in the central and peripheral nervous system.[69] These receptors mediate both excitatory and inhibitory neurotransmission. Serotonin receptors influence various biological and neurological processes such as aggression, anxiety, appetite, cognition, learning, memory, mood, nausea, sleep and thermoregulation.[70]

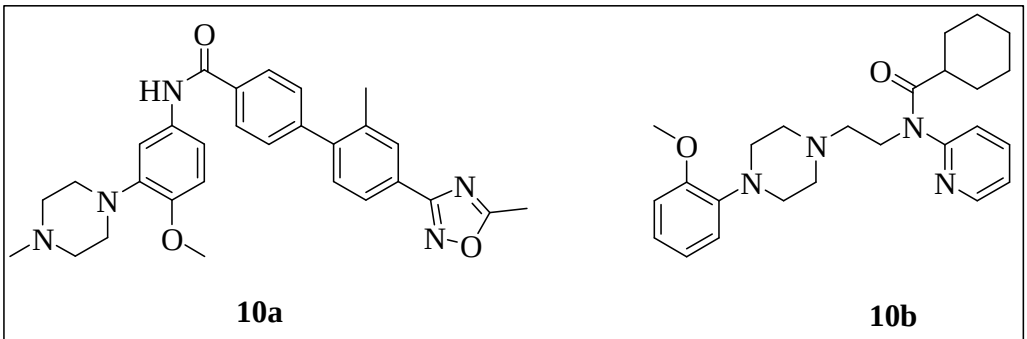
The effects of MDMA are believed to be mediated by both the 5-HT_{2A} and α_1 receptors. As previously stated, 5-HT_{2A} antibodies can prevent MDMA-induced neurodegeneration and neurotoxicity. Selective 5-HT_{2A} or α_1 receptor antagonists can potentially be used to treat MDMA abuse and overdose. While, MDMA is classified as a serotonin re-uptake inhibitor, it is uniquely different from classical SSRI's in its ability to also release serotonin into the brain. Therefore, it is important to develop a potential therapeutic that can address both the inhibitor and releasing properties of MDMA.

4.1. Serotonin and Dopamine Antagonists

The effects of MDMA in humans are believed to be largely dependent on the SERT-mediated efflux of serotonin. While it is unclear which specific postsynaptic serotonin receptor

mediates the effects of the MDMA-induced serotonin released, there have been several reports linking the 5-$HT_{1A/1B/1D/2A/2C}$ receptors to the physiological and psychological effects of MDMA.[23,27,71-77]

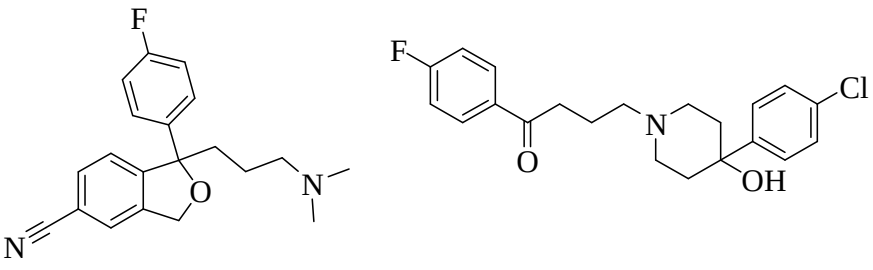
Cunningham has shown that GR-127935 (**10a**), a selective antagonist at the 5-HT_{1B} and 5-HT_{1D} receptors, and WAY-100635 (**10b**), a selective 5-HT_{1A} receptor antagonist, are able to block acute MDMA-induced hyperactivity in rats in a dose dependent manner (Figure 9).[77]



10a **10b**

Figure 9: Strucutre of GR-127,935 (**10a**) and WAY-100,635 (**10b**)

Prepulse inhibition (PPI) of the acoustic startle response is an operational measure of sensorimotor gating that can be assessed in animals and in humans**.** MDMA disrupts PPI and reduce startle habituation in rodents.[78] Pretreatment with SSRI's can prevent these effects which indicate that the effect of MDMA on startle plasticity is largely due to the release of serotonin from presynaptic neuron. Citalopram (**11a**), a selective serotonin reuptake inhibitor, and the dopamine D_2 antagonist haloperidol (**11b**), have been used as pretreatments for MDMA administration in healthy human subjects (Figure 10).[78] Citalopram attenuated the MDMA-induced increase in PPI and all the MDMA-induced psychological effects.[78-80] Haloperidol did not affect the MDMA-induced PPI increases but partially attenuated some MDMA-induced psychological effects.[78]

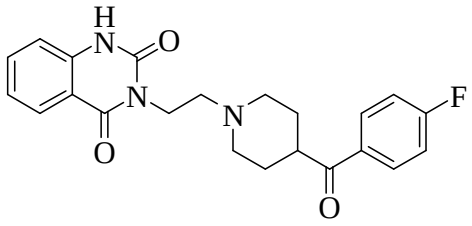


Citalopram (11a) **Haloperidol (11b)**

Figure 10: 5-HT reuptake inhibitor and Dopamine D2 antagonist

Citalopram (**11a**) was shown to reduce the subjective and physiological effects of MDMA.[81] Haloperidol (**11b**) reduced MDMA-induced positive mood but had no affect on cardiovascular stimulation or other physiological effects.[82]

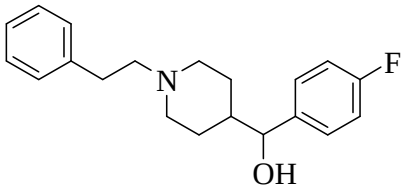
Ketanserin (**12**), a 5-$HT_{2A/C}$ antagonist, was shown to significantly reduce MDMA-induced perceptual changes, emotional excitation, and acute adverse effects, while having little effect on positive mood and well-being in humans (Figure 11).[27]



Ketanserin (12)

Figure 11: Structure of Ketanserin

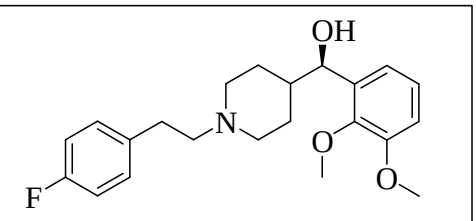
The active and inactive stereoisomers of MDL 11,939 (**13**), a 5-HT_2 antagonist, were used to examine the relationship between the acute effects of MDMA on the dopaminergic system and long-term effects on the serotonergic system (Figure 12). Only the *R*-(+) stereoisomer of MDL 11,939 (**13**) both reversed the acute stimulation of striatal dopamine synthesis by MDMA and prevented the deficit in forebrain serotonin concentrations measured one week post adminsitration.[83]



MDL 11,939 (13)

Figure 12: Structure of MDL 11,939

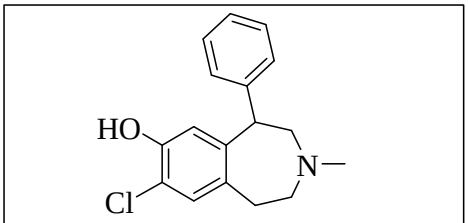
MDMA releases dopamine and serotonin in vivo which stimulates locomotor activity. MDL 100,907 (**14**), a selective 5-HT_{2A} receptor antagonist, is believed to reduce the MDMA-stimulated release of dopamine (Figure 13). Kehne has provided evidence that MDL 100,907 (**14**) significantly reduced MDMA-stimulated locomotion without affecting basal levels of locomotion.[71]



MDL 100,907 (14)

Figure 13: Structure of MDL 100,907

SCH 23390 (**15**), a D_1-like receptor antagonist, was studied by Daniela to determine whether dopaminergic mechanisms also mediate the reinforcing effects of MDMA (Figure 14).[84] At low doses, **15** attenuated the reinforcing effects of MDMA.



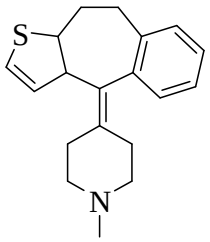
SCH 23390 (15)

Figure 14: Structure of SCH 23390

SCH 23390 (**15**) was also examined to determine its effect on MDMA-induced hyperactivity through self-administration.[84] SCH 23390 attenuated MDMA-produced hyperactivity in a dose-dependent manner.

4.1. Broad Spectrum Treatments for MDMA

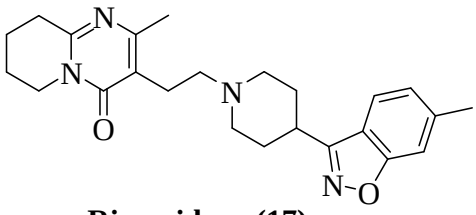
Pizotyline (**16**), is known to bind at multiple serotonin and dopamine receptor subtypes, was used as an MDMA therapeutic (Figure 15).[72,85] MDMA-antagonistic studies show that **16** effectively reduces MDMA-induced responses as compared to saline (AD_{50}=2.5 mg/kg).[86]



Pizotyline (16)

Figure 15: Structure of Pizotyline

Risperidone (**17**) has been shown to weakly block the dopamine D_1 and possibly the D_2 and 5-HT_{2A} receptors.[87] Nisijima has shown that **17** also prevent hyperthermia and death in animal models with serotonin syndrome (Figure 16). [88]



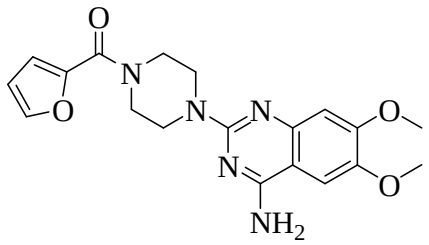
Risperidone (17)

Figure 16: Structure of Risperidone

Further animal studies conducted by Shioda showed that **17** attenuates and reverses MDMA-induced hyperthermia in rats. These results suggest that risperidone's mechanism of action occurs by blocking activity at the 5-HT_{2A} receptor and partially at the D_1 receptor.[89]

4.3. α_1 Receptor Antagonist as Potential anti-MDMA Treatments Modalities

Sprague has shown that α_1 receptors are involved in the hyperthermic response of MDMA in rats.[90] α_1 Receptor antagonist, Prazosin (**18**), is a sympatholytic drug used to treat high blood pressure and affects the vascular smooth muscles, which reduces blood pressure (Figure 17).[91] MDMA-induced increased rectal temperature in rats was reduced with prazosin pretreatment.



Prazosin (18)

Figure 17: Structure of Prazosin

Prazosin (**18**) was also used to treat the physiological effects caused by MDMA by Fantegrossi.{Fantegrossi, 2004 #439} Prazosin was examined in animal models for its ability to reverse MDMA-induced hyperthermia.[92] Prazosin completely blocked the onset of MDMA-induced hyperthermia without altering the core body temperature. However, **18** was not able to reverse MDMA-induced hyperthermia when administered 30-minutes after treatment with MDMA. In rodents, head-twitch response is a selective behavioral model for 5-HT_2 receptor activity; Prazosin was not able to block MDMA-induced head-twitch response.[93] As previously

stated, prazosin can also antagonize MDMA-induced locomotor activity, a selective behavioral model for α_1 receptor activity.[36]

A wide variety of receptor antagonists have been used to block and/or reverse MDMA-induced effects. MDMA-induced hyperthermia and neurotoxicity are two major concerns resulting from MDMA-ingestion. Serotonin and adrenergic receptors affect various biological and neurological processes including memory, vasoconstriction and thermoregulation.[66,75,76,94] 5-HT_{2A} and α_1 receptor antagonists have been shown to block and/or reverse MDMA-induced hyperthermia and neurodegeneration.

Currently, there are no specific treatments for MDMA abuse or overdose. Based on the preceding, the development of a selective dual 5-HT_{2A} and α_1 antagonist is likely to be an appropriate strategy to combat MDMA-induced hyperthermia and neurotoxicity. The following chapters will detail our work towards synthesis and evaluation of such antagonists. In chapter 2 we will discuss the emergence, use of and synthesis of aporphines as possible antagonist for MDMA-induced responses. In chapters 3 and 4 we will discuss approaches to an optimized synthesis of the aporphine nantenine (**32**) and analogues. In chapter 5 we will discuss the biological evaluation, *in vitro* examination (K_i and K_e) and *in vivo* examination (behavioral suppression assay), of nantenine and its analogues. A summary of nantenine's past and present SAR results will also be presented.

CHAPTER II: APORPHINES

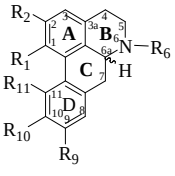
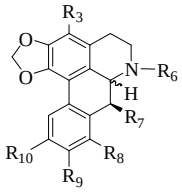
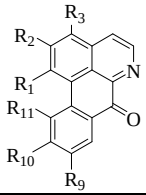
1. INTRODUCTION

With more than 500 reported structures, aporphines are one of the largest groups of isoquinoline alkaloids. Several derivatives of aporphines have been isolated from different plant families including Annonaceae, Monimiaceae, Lauraceae, Menispermaceae, Hernandiaceae and Ranunculaceae.[95] Aporphine alkaloids have been isolated from the leaves, stem barks, roots and branches of trees grown in Thailand: *Polyalthia cerasoides*, Australia: *Doryphora sassafras*, Taiwan: *Cassytha filiformis* Linn, South America: *Guatteriopsis friesiana*, and Indonesia: *Mitrephora glabra*.[96-100]

1.1. Aporphine Structural Diversity

The aporphine core is derived by a biaryl bond connection between the A and D aromatic rings of a benzylisoquinoline framework. Naturally occurring aporphines exist as one of two enantiomers (*R* or *S*) and contain hydroxy, methoxy or a methylenedioxy group at positions 1 and 2. The tetracyclic core can also be substituted at positions 9, 10 and 11. In a few cases, position 7 is oxygenated.[101] The structural variations of aporphines are presented in Table 2.

Table 2: Structural Variation of Aporphines

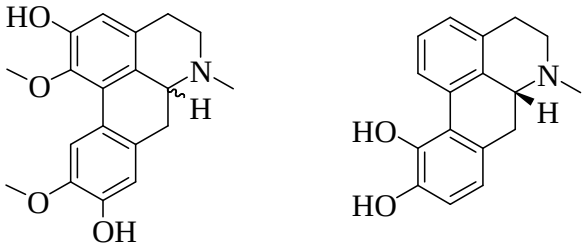
A	**B**	**C**
		

Entry	Aporphine	R_1	R_2	R_3	R_6	R_7	R_8	R_9	R_{10}	R_{11}
1	**A**	O-CH_2-O		H	H	H	H	OH	OCH_3	H
2	**B**			H	CH_3	OH	H	CH_3	H	H
3	**C**	OCH_3	OCH_3	H	--	--	--	OCH_3	OCH_3	H

1.2. Biological Activity of Aporphines

Aporphinoids exhibit a wide range of pharmacological activities, including antioxidant, antiplatelet, antitumor, anticonvulsant, anti-plasmodial, antineoplastic, anti-malarial, antiprotozoal, antipoliovirus, cytotoxic, and antiparkinsonian effects.[16,102-105] Structure activity relationship (SAR)-studies of substituted aporphines suggest they have potential to increase the affinity and selectivity for the dopamine D_2, serotonin 5-HT_{1A} and α_1 adrenergic receptors.[106,107]

Two aporphines are currently available on the market as pharmaceutical products.[95] Isolated from the leaves and bark of the South American tree *Peumus boldus*, boldine (**19**) is considered an antioxidant and a choleretic because it possesses well-established free radical scavenger properties and increases bile secretion (Figure 18).[95] *R*-(⁻)-Apomorphine (**20**) is a well-documented non-selective dopamine receptor agonist and is marketed as a treatment for Parkinson's disease in Europe since the 1990s and in the US since 2004 (Figure 18).[108]



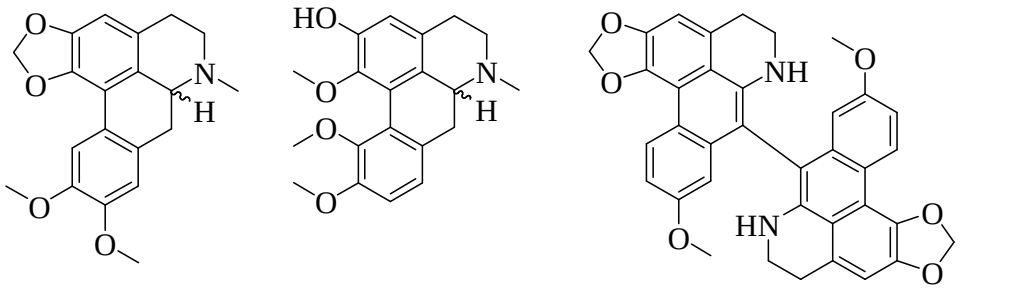
Boldine (19) ***R*-(-)-Apomorphine (20)**

Figure 18: Structure of Boldine and *R*-(-)-Apomorphine

1.2.1. Non-CNS Activity

Aporphines show signs of cytotoxic and antitumor properties.[101] *S*-dicentrine (**21**), isolated from *Lindera megaphylla*, was evaluated against human tumor cells and shows cytotoxic (*in vitro*) and anti-tumor (*in vivo*) effects (Figure 19).[109] Dicentrine (**21**) significantly inhibits the

growth of the human hepatoma cell line HuH-7. Woo has also suggested that **21** behaves as a DNA targeted adaptive interchelating agent.[110] Corydine (**22**) has shown DNA-damaging activity in yeast bioassays. The IC_{50} values against YCp50 gal, pRAD52 gal, pRAD52 glu are 27.5, >73.9, and 22.5 μg/mL (Figure 19).[111] Bis-7,7′-dehydro-9,9′-dimethoxyanonaine (**23**) exhibits antimalarial activity *in vitro* against *P. falciparum* (IC_{50} = 4.2 μg/mL) as well as antimycobacterial activity against *M. tuberculosis* (MIC = 6.25 μg/mL) (Figure 19).[96]



Dicentrine (21) **Corydine (22)** **Bis-7,7'-dehydro-9,9'-dimethoxyanonaine (23)**

Figure 19: Structure of Selected Aporphines

1.2.2. CNS Activity

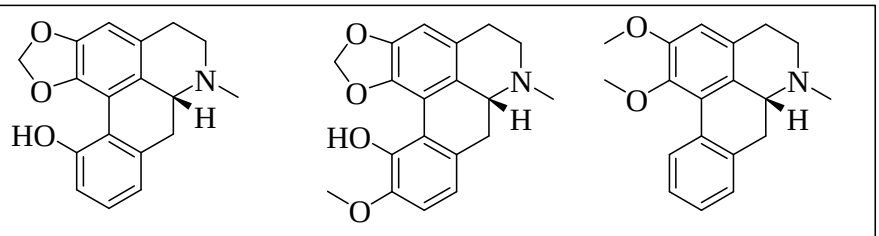
Changing the substituents on the core structure of apomorphine (**20**) can lead to major changes in its pharmacological profile.[112] C2- or C3-substituted 11-hydroxyaporphine or 10,11-dihydroxyaporphine derivatives are highly potent at dopamine D_2 receptors.[112] Replacing the C10-hydroxyl group of (**20**) with a methyl group introduces 5-HT_{1A} receptor agonism.[113]

Pukateine (**24**) is an aporphine alkaloid isolated from the bark of the New Zealand tree *Laurelia novae-zelandiae* and is used in traditional Māori herbal medicine as an analgesic. Pukateine has multiple mechanisms of action, with the most prominent effects being

an antagonist at the α_1 adrenergic receptor as a vasorelaxant against noradrenaline or KCl-induced contraction and an agonist at the D_2 dopamine receptor, (Figure 20).[114,115]

Bulbocapnine (**25**) is an aporphine alkaloid isolated from species of the *Corydalis* and *Dicentra* genera that acts as an acetylcholinesterase inhibitor and inhibits biosynthesis of dopamine via inhibition of the enzyme tyrosine hydroxylase (Figure 20).[116-118]

Nuciferine (**26**) is an aporphine alkaloid isolated from the plants *Nymphaea caerulea* and *Nelumbo nucifera*.[119] Nuciferine shows dopamine receptor blocking activity and induces catalepsy, inhibits spontaneous motor activity, conditioned avoidance response, amphetamine toxicity and stereotypy (Figure 20).[119]

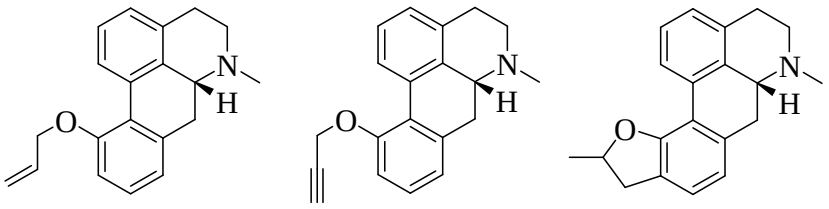


Pukateine (24) **Bulbocapnine (25)** **Nuciferine (26)**

Figure 20: Structure of Aporphines

1.3. SAR Studies at 5-HT$_{1A}$, α_1, and D$_1$

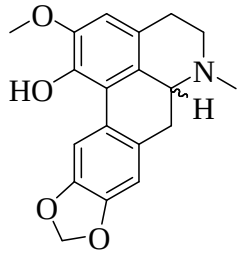
SAR-studies conducted by Liu show that position C11 plays a major role in the binding affinity at 5-HT$_{1A}$. Aporphines with an ether bridge at C11 such as **27**, **28**, and **29** display 5-HT$_{1A}$ affinity with K_i values of 12.0, 14.0 and 6.7 nM, respectively (Figure 21).[74]



27 **28** **29**

Figure 21: Structure of Aporphines with 5-HT_{1A} Affinity

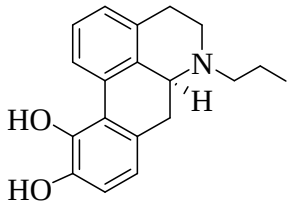
Aporphine alkaloids also show α_1-adrenoceptor antagonistic properties in vascular smooth muscle.[120,121] Indra has determined that (+/-)-domesticine, (**30**), is a selective α_{1D} adrenergic receptor antagonist that is highly selective over the 5-HT_{1A} and other receptors in animals and humans (Figure 22).[122]



Domesticine (30)

Figure 22: Sturcture of (+/-)-Domesticine

Kula conducted SAR-studies at the D_3 receptor aimed at discovering new leads for atypical antipsychotic agents that possess limited extrapyramidal side effects.[123] Kula determined that *R*-(-)-*N*-propylnorapomorphine (**31**) showed a substantial D_3 affinity but no D_3/D_2 selectivity (Figure 23).



31

Figure 23: Structure of *R*-(-)-*N*-propylnorapomorphine

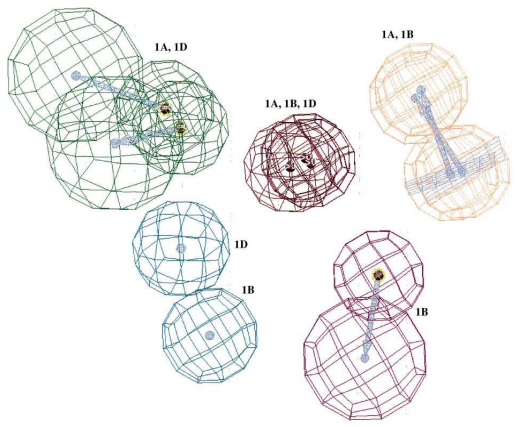
Given that aporphines can be structurally modified to be selective for individual receptors, the question is; can we discover or develop an aporphine derivative that is capable of dual antagonism of 5-HT_{2A} and α_1 receptors and may therefore be capable of attenuating and/or reversing the physiological and psychological effects of MDMA?

1.4. CNS-related Activity: Pharmacophore receptor models

Kołaczkowski used homology models to show that the aporphine core structure can be used as a possible pharmacophore template for development of selective antagonists for the 5-HT_7 receptor.[124] Kołaczkowski determined that the presence and geometry of aromatic and H-bond accepting moieties are necessary for binding at the 5-HT_7 receptor providing selectivity over other monoamine receptors. Varying the rigidity of the aporphine core can increase its affinity for the 5-HT_7 or the 5-HT_{1A} receptors.[125,126]

Previously, a pharmacophore model has been described for antagonists at the α_1 adrenergic receptor, which includes three features: an aromatic region, a basic nitrogen and a semi-polar or a bulky lipophilic area.[106] Using this information, Bremner developed pharmacophores based on the aporphine skeleton for selective antagonists at the α_{1A} and α_{lB} receptors and a preliminary pharmacophore for the α_{lD} adrenergic receptor.[106]

Bremner determined that all α_1 receptor substypes have a 3-point pharmacophore (Figure 24). The α_{1B} pharmacophore must include a hydrogen bond acceptor group, which is a feature unique to the α_{1B} pharmacophore, an aromatic ring system and a hydrophobic group. The α_{1A} pharmacophore requires a positive charge in the middle of the system, a hydrogen bond acceptor group and an aromatic ring system at opposite end. The requirements for the α_{1D} pharmacophore are similar to that of the α_{1A} with the exception that distance between the hydrogen bond acceptor and the positive ion is much smaller and the need for a hydrophobic group.



Mesh spheres represent the location constraints for the feature on the receptor and are color coded according to feature: red - positive ion, green-hydrogen bond acceptor, light brown - aromatic ring system, the light blue square denotes the position of the plane of the aromatic system, purple - hydrogen bond donor feature and blue - a hydrophobic group.

Figure 24: Overlap of the three α_1-Subtype Pharmacophores based on Catalyst Program. Letters indicate subtype

2. NANTENINE

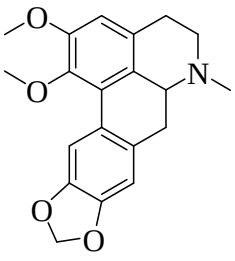
2.1. The Occurrence and Biological Activity of Nantenine

The fruit of *Nandina domestica* commonly known as "heavenly or sacred bamboo" is a shrub of the Barberry family, Berberidaceae. In Japan *Nandina domestica* is known as nantenjitsu and has been used to treat respiratory diseases such as asthma, whooping cough and pharynx tumor.[127] Little is known about the mechanism of the plant's pharmacological action.

Shoji studied the crude methanol extracts of *Nandina domestica* and found that it strongly inhibits serotonin-induced contractions of rabbit aorta and rat stomach.[128] The major alkaloid and active compound from the extract was identified as *O*-methyldomesticine or nantenine (**32**) (Figure 25).

Nantenine has also been isolated from the young leaves, stems and fruits of *Guatteria dumetorum, Platycapnos spicata, Ocotea macrophylla H.B.K., Stephania tetrandra, Siparuna tonduziana, Siparuna pauciflora, Corydalis slivenesis, Corydalis bulbosa, Corydalis marschalliana, Papaver armeniacum, Papaver fugax, Papver tauricola, Cassytha filiformis and Cassytha racemosa* in yields ranging from 3-17 mg.[129-140]

Other than being a serotonergic receptor antagonist, nantenine also shows different pharmacological benefits depending on its concentration and method of administration.[141] At 0.3-3μM, nantenine shows antagonistic properties at the α_1-adrenergic and 5-HT_{2A} receptors by competitively inhibiting phenylephrine-induced contraction in rat aorta.[142,143]



Nantenine (32)

Figure 25: Structure of Nantenine

At higher concentrations, 2.35 and $4.7x10^{-4}$ M, nantenine inhibits KCl-induced increase in intracellular Ca^{2+} concentration and contraction in rat vas deferens, which suggests that it is also a Ca^{2+} antagonist.[144] In anesthetized rats, intravenous administration of 3-6 mg/kg of nantenine produces a dose-dependent decrease in the average arterial blood pressure and heart rate, a 5-

HT_{2A} response.[145,146] Intraperitoneal administration of nantenine at 20-50 mg/kg inhibits pentylenetetrazol- and electroshock-induced seizures in mice.[147]

The chemical structure of nantenine is similar to that of MDMA. Fantegrossi has argued that the MDMA-induced physiological and psychological effects can be weakened or completely stopped by antagonists acting at the 5-HT_{2A} and α_1 receptors.[92] This data suggests that nantenine acts at the 5-HT_{2A} and α_1 receptors.

Fantegrossi also found that nantenine blocked and reversed the development of MDMA-induced hyperthermia, death, locomotor stimulation, and head-twitch response in mice.[92] Nantenine's ability to act as both a 5-HT_{2A} and α_1 receptor antagonist, receptors that influence vasoconstriction and thermoregulation, may explain why it can attenuate MDMA-induced hyperthermia pre- and post administration of MDMA. Nantenine is a promising lead molecule in the development of a potent and selective MDMA antagonist. Our approach in this regard (detailed later) will involve synthesis of nantenine analogues as well as *in vitro* (5-HT_{2A} and α_{1A}) and *in vivo* SAR studies.

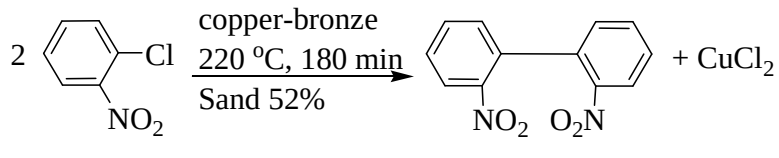
3. BIARYL COUPLING METHODS AND SYNTHESIS OF APORPHINES

A major challenge in the synthesis of aporphines is the construction of the biaryl bond. Developing a synthetic pathway with an efficient biaryl coupling strategy is an important first step in the synthesis and SAR-study of nantenine. Metal catalyzed cross coupling reactions have been widely used for this purpose. Several different strategies can be incorporated in the synthesis of aporphines.

3.1. Biaryl coupling Methods

Over the past three decades, there has been a great improvement in the methods to prepare biaryl bonds.[148] Initially, syntheses of biologically active aporphines alkaloids were plagued by low yields due to inefficient methods to prepare the biaryl bond.

Fritz Ullmann was the first to introduce biaryl coupling reactions using aryl halides and copper (Figure 26).[149] While the Ullmann reaction was successful for homo-coupled products, the reaction required electron deficient aryl halides and gave erratic yields, which limited the scope of the reaction.[150]



33 **34**

Figure 26: Ullman Reaction

Due to the limitations, the Ullmann reaction has been replaced by palladium catalyzed reactions such as Negishi, Heck, Suzuki, Stille and Hiyama couplings.[151-154] However, they all have specific limitations. Palladium catalyzed reactions require milder reaction conditions than the Ullmann reaction. Coupling using aryl halides in the presence of reducing agents such as formic acid, amines, alcohol or zinc can diminish the selectivity in some cases due to competitive chemisorptions and hydride formation, which leads to competing reduction reaction such as hydrodehalogenation.[150]

In the Negishi and Hiyama coupling reactions the aryl halide or silane must be first converted to an activated species. For the Negishi reaction, this is an organozinc and in the Hiyama reaction base is used to activate the organosilane (Figure 27).

Although a pre-activation step is required, the Hiyama reaction is considered more practical than the Stille and Suzuki reaction because the siloxane methodology eliminates the purification difficulties associated with organo-boron and tin by-products in the Suzuki and Stille couplings (*vide infra*) (Figure 28).[151] While useful for synthesis of various homo- and cross-coupled biaryl compounds, the Hiyama reaction is highly dependent on the catalyst to ligand ratio.

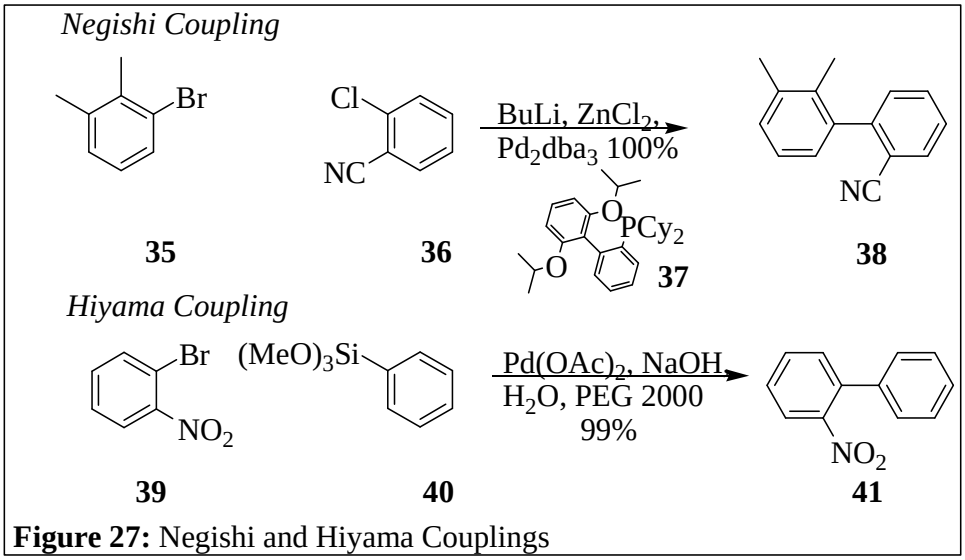


Figure 27: Negishi and Hiyama Couplings

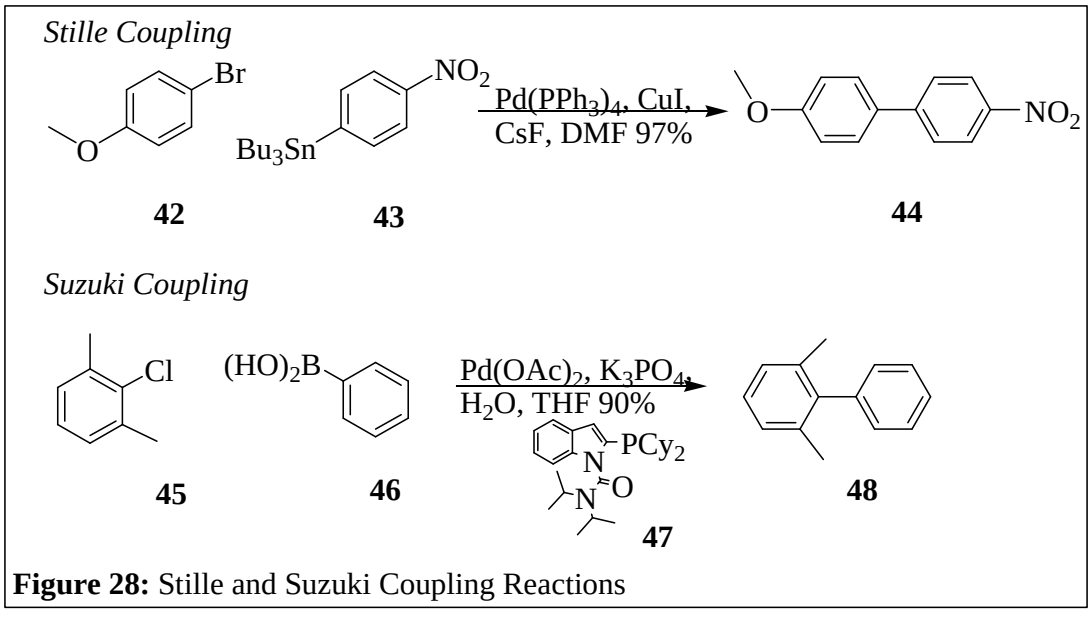


Figure 28: Stille and Suzuki Coupling Reactions

Nucleophilic arenes can also engage in cross coupling without the need for prior functionalization as an organometallic species.[152] Researchers have utilized Heck reaction of aryl halide with activated alkenes to synthesize a variety of stilbene compounds, which can be used as a building block for biaryl compounds (Figure 29).

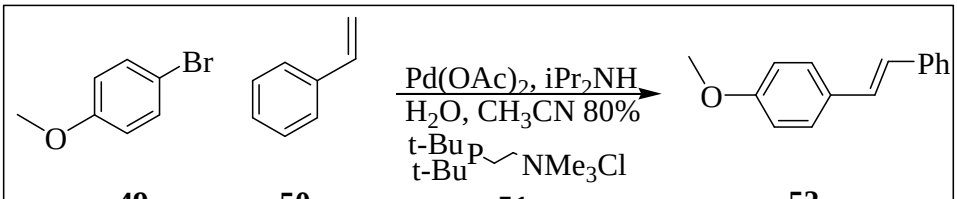


Figure 29: Heck Coupling Reaction

A comparison of the stated biaryl coupling methods is listed in Table 3.

Table 3: Biaryl Coupling Comparison

Entry	Reaction	Date of Discovery	Catalyst	Substrate		Coupling	Requirements
1	Ullmann	1901	Cu	Aryl Halide		Homo	
2	Heck	1972	Pd	Alkene	Halide[a], OTs	Cross	Requires base
3	Negishi	1977	Pd or Ni	R^b-Zn-X	Halide[a], OTs	Cross	
4	Stille	1978	Pd	R^b-Sn-R_3	Halide[a]	Cross	
5	Suzuki	1979	Pd	R-$B(OR)_2$	Halide[a], OTf, OTs	Cross	Requires base
6	Hiyama	1988	Pd	R^b-SiR_3	Halide[a], OMs, OTs	Cross	Requires base

a: Aryl, alkyl or allyl halides b: aryl, alkyl, or allyl

3.2. Approaches to Aporphine Synthesis via Biaryl Coupling

3.2.1. Typical Aporphine Synthesis

Synthesis of aporphines usually occurs by formation of an amide (eg **55**) followed by synthesis of the corresponding tetrahydroisoquinoline (eg **56**). Biaryl coupling of the tetrahydroisoquinoline prepares the aporphine (eg **57**) (Figure 30).

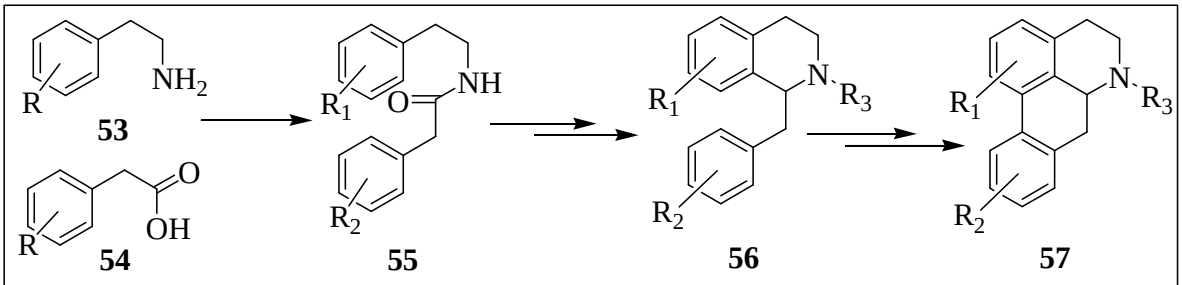


Figure 30: General Aporphine Synthesis Strategy

3.2.2. Pschorr Cyclization

The Pschorr cyclization is an intramolecular variation of the Gomberg-Bachmann reaction that provides higher yields of the coupled product.[155] Typically, the Pschorr reaction involves reaction of arenediazonium salts, which acts as a precursor to the aryl cation or the aryl radical (or both), and an aryl group (Figure 31).

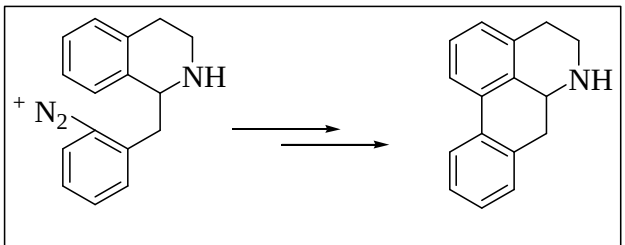


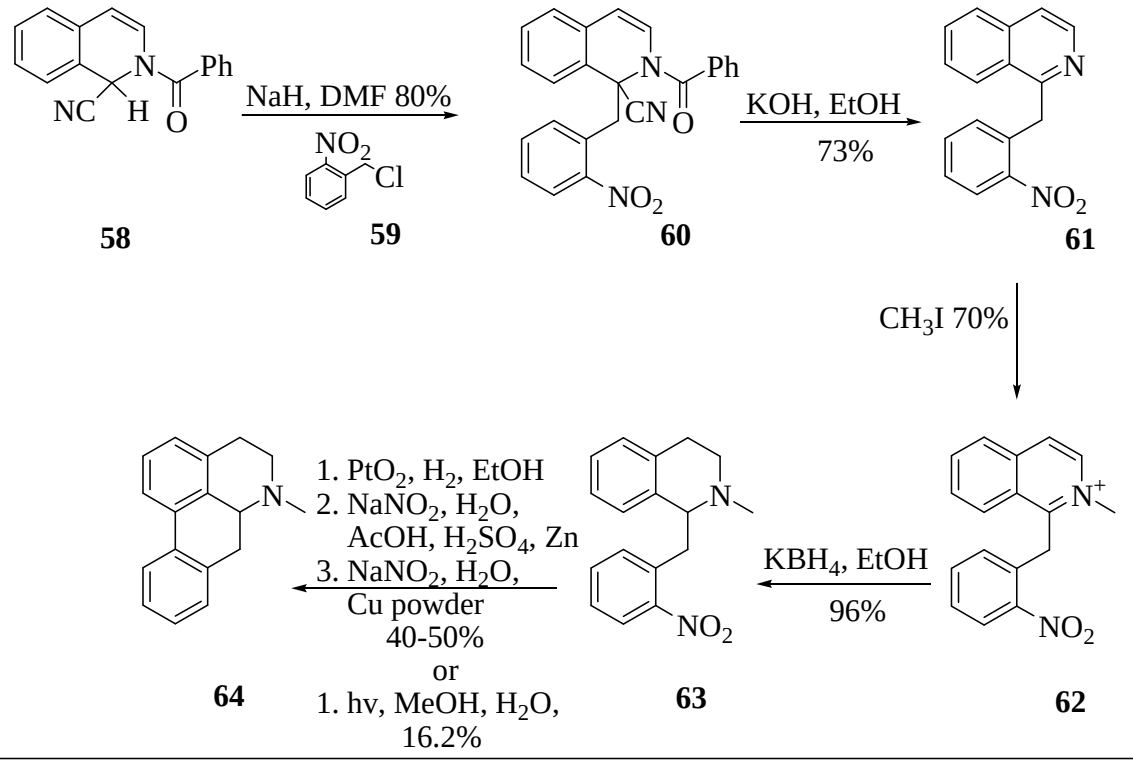
Figure 31: Pschorr Biaryl Coupling

Due to their interesting biological activities, the synthesis of aporphine alkaloids has been of interest for many years. However these syntheses generally give very poor yields.[156]

Neumeyer has reported the first synthesis of aporphines **64** following Scheme 1. The Reissert compound **58** was reacted with *o*-nitrobenzyl chloride **59** to give the

dihydroisoquinoline **60**. Compound **60** was then oxidized under basic conditions to afford **61** in good yield. Quaternization of **61** afforded **62**, which was reduced to **63**. Compound **63** was then subjected to the Pschorr protocol yielding aporphine **64** in moderate yield.[156,157]

Scheme 1: First Moderate Yield Synthesis of Aporphines



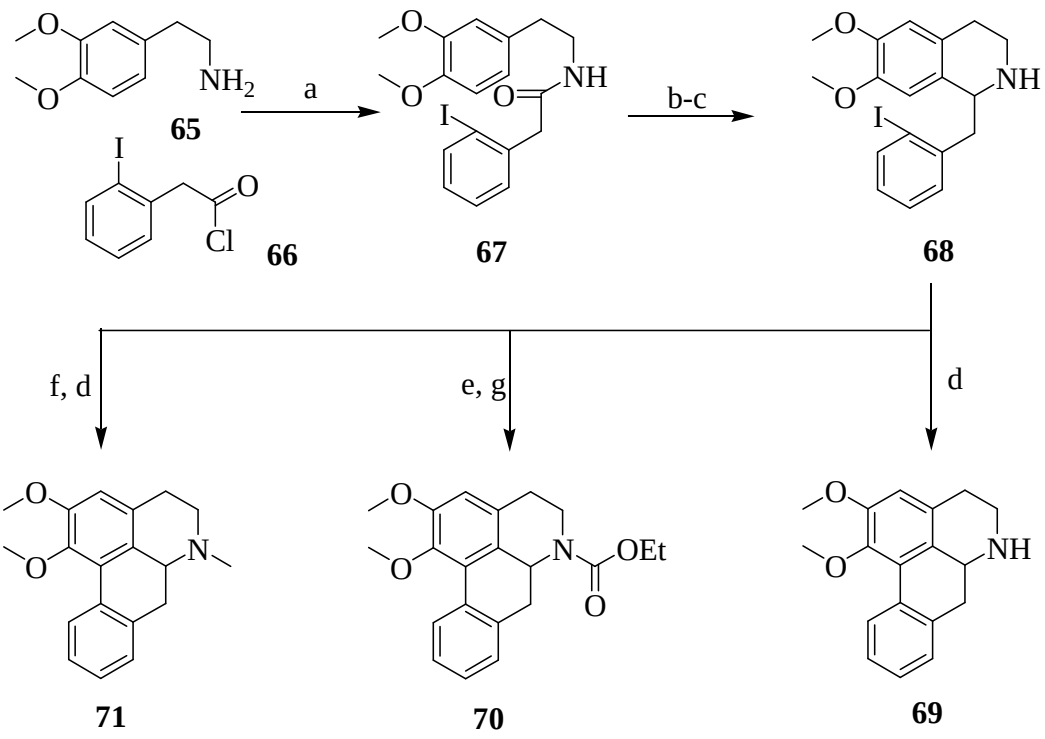
3.3. Photochemical Methods

Photochemical biaryl cyclization on **63** was also performed. Irradiation of **63** in methanol and water for 12 h at 70 ^{o}C afforded the desired aporphine albeit in very low yields, 10-16%.[156] Attempts to optimize the photochemical cyclization were unsuccessful.

Further investigation into the use of photochemical cyclization in the synthesis of aporphines was conducted by Kupchan et al.[158] Kupchan developed an improved method for the synthesis of *N*-acyl and *N*-carbamoyl noraporphines and aporphines utilizing the

photocyclization of iodobenzyltetrahydroisoquinolines. Condensing dimethoxy phenethylamines, **65** with *o*-iodophenylacetyl chloride, **66**, gave the corresponding amide, **67** (Scheme 2). Subjecting the amide **10** to the Bischler-Napieralski cyclization afforded the quaternized iminyl chloride in high yield followed by reduction with sodium borohydride to give secondary amine **68**. Kupchan argued that the free electron pair on the secondary nitrogen was not compatible with the photocyclization reaction conditions and formation of a salt should solve the problem.[158] The hydrochloride salt of amine **68** was then photolyzed to give noraporphine **69** in 21% yield.

Scheme 2: Imporved Photochemical Synthesis of Aporphines



Reagents and conditions:
a. Et_3N, DCM b. $POCl_3$, DCM, 90% c. $NaBH_4$, MeOH, 70%
d. hv, sodium bisulfate, benzene, 13-20% e. Ethyl chloroformate f. MeI, 60%
g. hv, benzene, sodium thiosulfate 45%

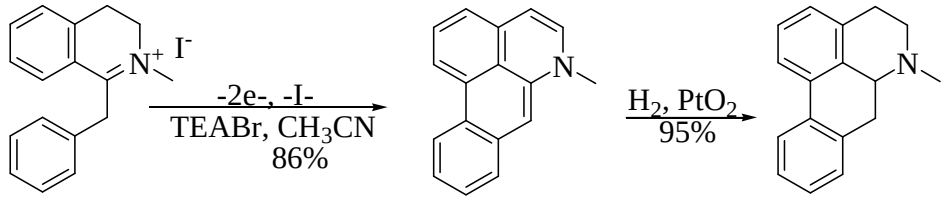
Alkylating secondary amine **68** with methyl iodide yielded the corresponding tertiary amine which was then photolyzed in the presence of sodium bisulfate gave the desired

aporphines **71** in 20% yield. The low yield of the reaction was attributed to the formation of a phenanthrene derivative resulting from a Hofmann type nitrogen-carbon bond cleavage. To avoid the Hofmann elimination, the nitrogen was protected as *N*-ethyl carbamate followed by photolysis in benzene with sodium thiosulfate to afford the substituted noraporphine **70** in 45% yield.

3.4. Voltammetric Methods

Gottlieb has shown that *o*-iodobenzyl isoquinolinium methyiodides can be converted to the corresponding aporphines via cathodic cyclization.[159] Cathodic cyclization involves a two-compartment electrolysis cell, an anodic compartment and a cathodic compartment held together with a silver wire. Using voltammetry, Gottlieb reduced *o*-iodobenzyl isoquinolinium methyiodides, **72**, to the corresponding aporphines using tetraethylazanium bromide (TEABr), dry acetonitrile with -1500 millivolts under a nitrogen atmosphere at room temperature. The two-electron reduction yielded 86% of the corresponding aporphine, **73** (Scheme 3).

Scheme 3: Cyclic Voltammetric Synthesis of Aporphines



72 **73** **74**

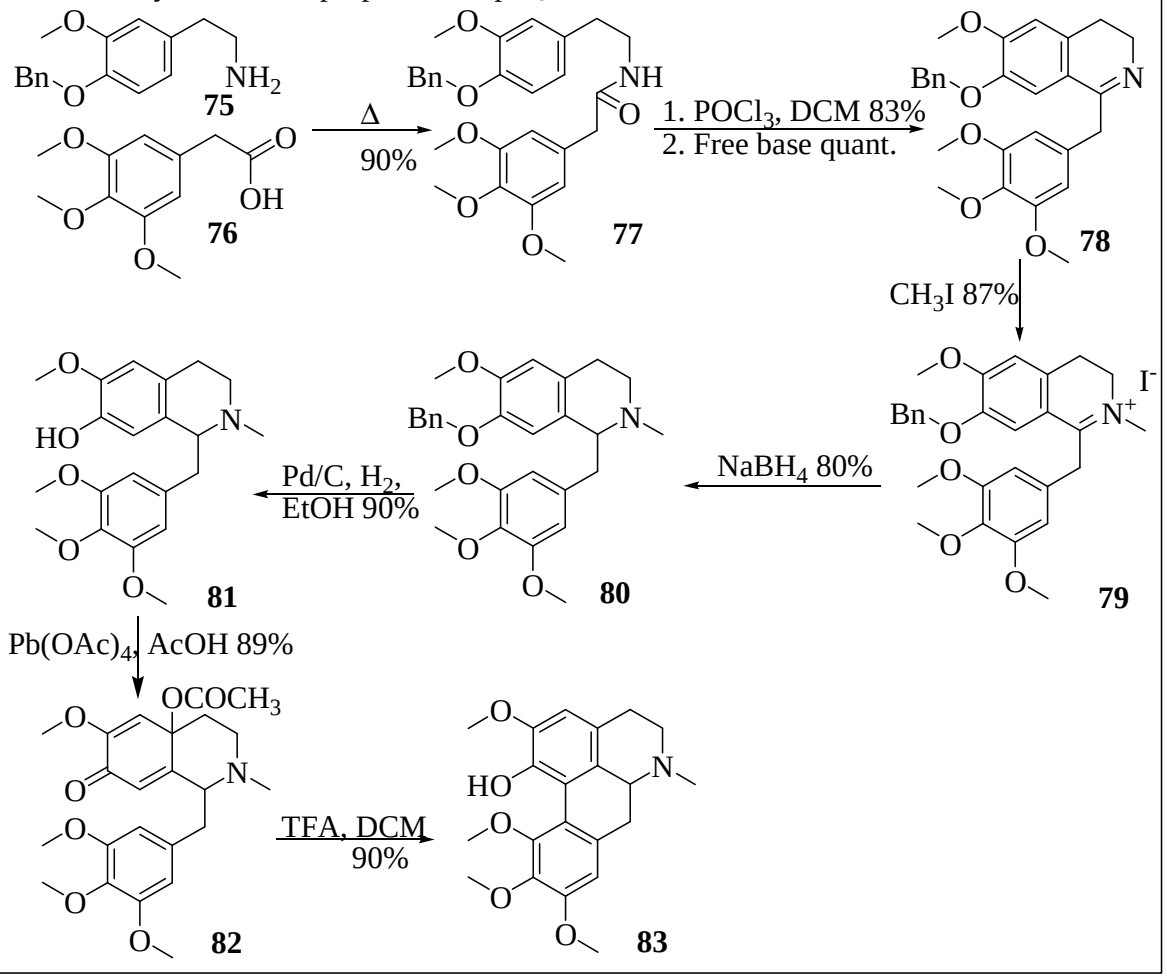
Catalytic hydrogenation of **73** in methanolic HCl with PtO_2 gave aporphine **74** in quantitative yield. This represents the first intramolecular cathodic cyclization of a benzylisoquinolinium salt involving an aryl radical that was generated from an aryl halide.

Gottlieb also demonstrated that electrooxidative coupling of nonphenolic benzylisoquinolines showed promise as effective synthetic methods for synthesis of aporphines; however attempts to repeat these reactions were unsuccessful.[159]

3.5. Wessely Acetoxylation

Hara applied a unique method, the Wessely Acetoxylation, to synthesize aporphines using lead tetraacetate as an oxidizing agent to ultimately achieve the biaryl coupling.[160,161] Following a procedure similar to Scheme 2, Hara prepared C1 benzyl-protected tetrahydroisoquinoline, **80**, in 4 quantitative steps (Scheme 4). Oxidation of phenol **81** using lead tetraacetate in acetic acid afforded the corresponding *p*-quinol acetate, **82**. The corresponding aporphine, **83**, was prepared by acid treatment of the crude acetate (Scheme 4).

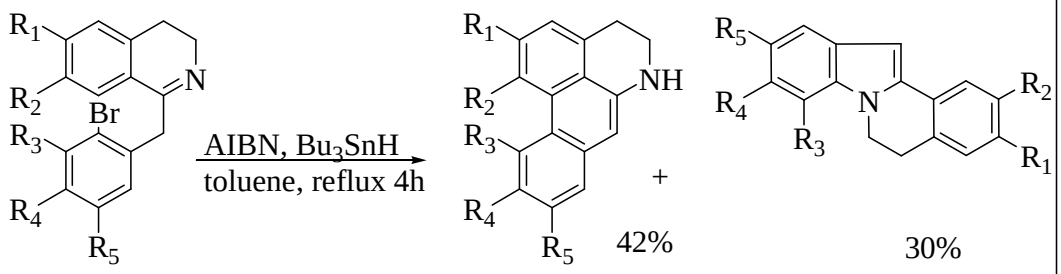
Scheme 4: Synthesis of Aporphines via *p*-Quinol Acetates



3.6. Radical Cyclization

Radical cyclization of bromo substituted dihydroisoquinolines with AIBN-Bu_3SnH have been used to prepare the corresponding aporphines (Scheme 5).[162] Orito claims that the substitution pattern of **85** governs the formation of aporphine **86**. Substituted noraporphines are formed via a 6-*exo* transition state, while the indole derivative **87** is formed via a 5-*endo* transition state.

Scheme 5: Aporphine Synthesis with AIBN-Bu_3SnH



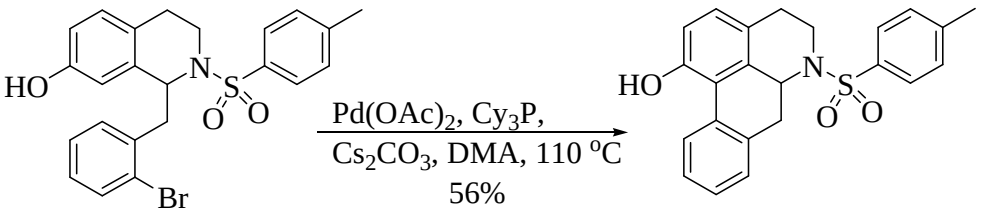
84 **85** **86**

3.7. Transition-metal Catalyzed Methods

3.7.1. Biaryl Coupling to Prepare Aporphines

Aporphines can be prepared using direct intramolecular carbon-hydrogen arylation or the Suzuki coupling.[163,164] A non-basic nitrogen is required with palladium catalyzed arylation to avoid homo-coupling.[165] Cuny has shown that direct arylation of activated *ortho*-phenol substrates can be used to prepare aporphines (Scheme 6).[166] However, high catalyst loading gave only moderate yields. LaFrance and Zhang have implemented a Heck-type direct biaryl coupling using an aryl halide with an aromatic ring in the synthesis of aporphine alkaloids with high overall yield.[153,154]

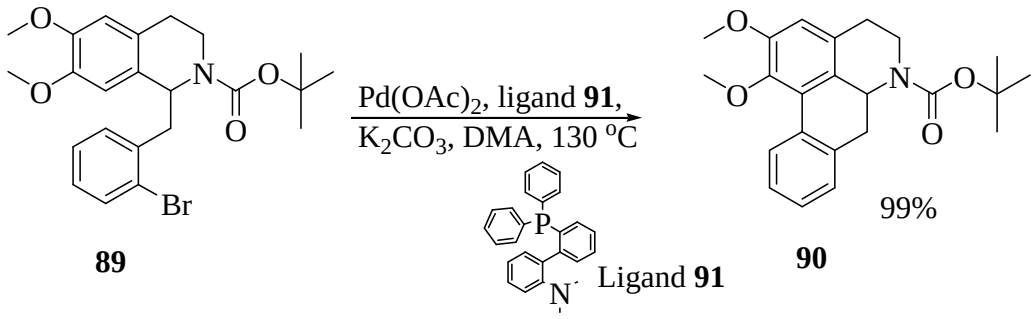
Scheme 6: Direct Arylation of Activated Arenes



87 **88**

Lafrance employed palladium catalyzed direct intramolecular arylation of unactivated arenes to prepare aporphines in moderate to high yields (Scheme 7).[163]

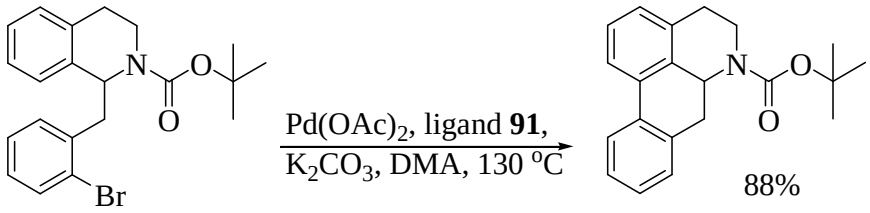
Scheme 7: Direct Arylation of Unactivated Arenes



89 **90**

Lafrance synthesized various substituted bromo-tetrahydroisoquinolines based on compound **92** to determine the substrate scope of the direct arylation. Using direct arylation prepared aporphine **93** from the unsubstituted tetrahydroisoquinoline **92** showed that direct arylation can tolerate various substitution patterns (Scheme 8).[153]

Scheme 8: Direct Arylation of Unsubstituted Arenes



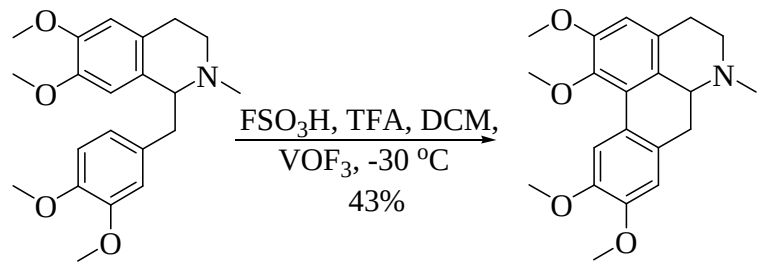
92 **93**

3.8. Other metal-catalyzed Methods

Intramolecular coupling of nonphenolic benzylisoquinolines using vanadium oxytrifluoride (VOF_3) in trifluoroacetic acid (TFA) have been shown to proceed through morphinandienone intermediates to give aporphines.[167] Kupchan reported that treating tetrahydroisoquinoline

laudanosine (**94**) dissolved in fluorosulfonic acid, dichloromethane, and TFA with a solution of VOF_3 in TFA at -30 ^oC, yielded the aporphine (+/-)-glaucine (**95**) in 43% yield (Scheme 9).[168]

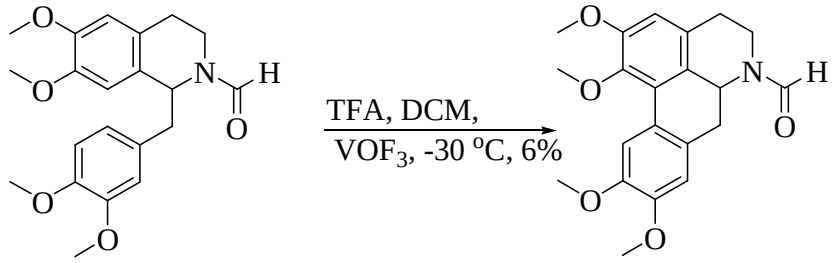
Scheme 9: Nonphenolic Oxidative Cyclization of Laudanosine



94 **95**

To examine the scope of the oxidative reaction, compound **94a** was prepared and treated with VOF_3 in TFA at -30 ^oC. *N*-formylnorglaucine, **95b**, was isolated in 6% yield (Scheme 10).[168]

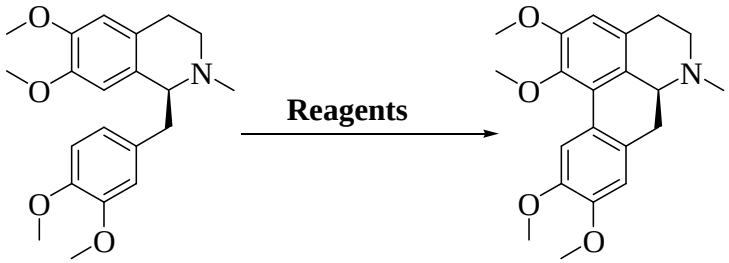
Scheme 10: Nonphenolic Oxidative Cyclization of *N*-formylnorlaudanosine



94a **95b**

Anakabe reported the synthesis of (+)-glaucine using Ruthenium (IV) oxide hydrate, and Cerium hydroxide, Scheme 11.[169]

Scheme 11: Transition Metal Conditions for the Synthesis of (+)-Glaucine

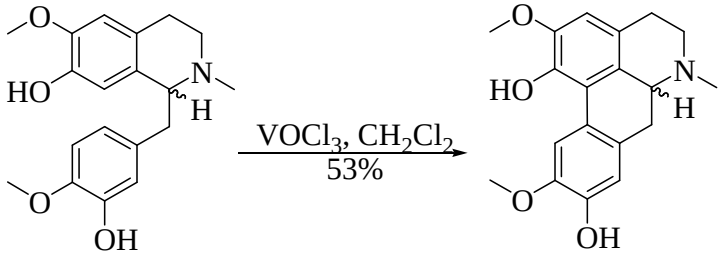


(+)-**94** (+)-**95**

Entry	Reagents	T(°C)	Yield(%)	ee(%)
1	$Ce(OH)_4$/TFAA/TFA/$BF_3{\cdot}OEt_2$	0 °C	60	93
2	RuO_2/TFAA/TFA/$BF_3{\cdot}OEt_2$	-10 °C	75	91

Schwartz has also employed Vanadium oxytrichloride to synthesize isoboldine (Scheme 12).[170]

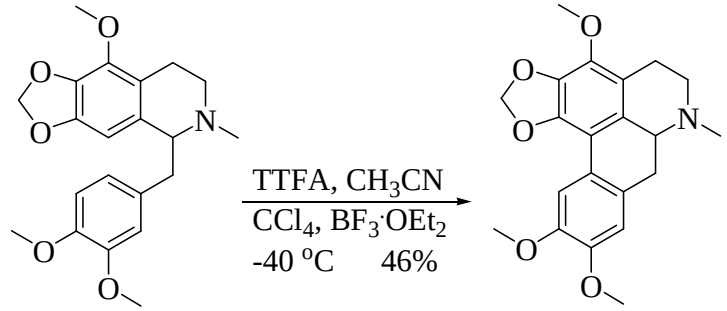
Scheme 12: Vanadium Oxytrichloride Aporphine Synthesis



96a **96b**

Taylor has incorporated Thallium(III) trifluoroacetate into the synthesis of ocoteine (Scheme 13).[171]

Scheme 13: Thallium(III) Trifluoroacetate Aporphine Synthesis



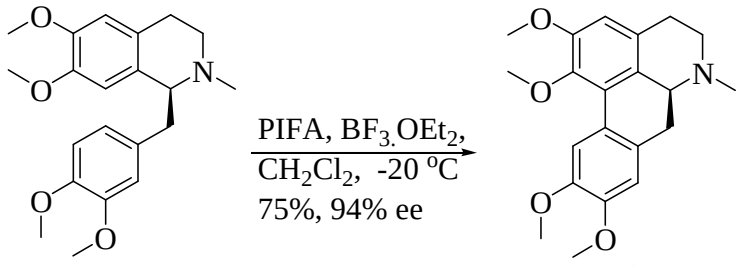
97a **97b**

3.9. Hypervalent Iodine Methods

Oxidative inter- and intramolecular aryl-aryl coupling has been investigated using phenyliodine (III) bis (trifluoroacetate) (PIFA).[172,173] Kita claims that *para*-subsitituted phenol ethers and aromatic compounds undergo nucleophilic substitution reactions in the presence of PIFA with poorly nucleophilic polar solvents such as trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP).[174] Hamamoto provided further evidence that PIFA can achieve biaryl coupling. Hamamoto showed that at low temperature (-40 °C) PIFA can be used to convert laudanosine (**94**) to the corresponding aporphine **95**.

Anakabe reported the stereoselective synthesis of (+)-glaucine using PIFA (Scheme 14).[169]

Scheme 14: Reagent conditions for the Synthesis of (+)-Glaucine



(+)-94 **(+)-95**

4. PREVIOUS SYNTHESES OF NANTENINE

There are no clinical treatments for MDMA overdose; Nantenine presents as a possible treatment. *In vitro* and *in vivo* SAR studies of nantenine should be conducted in order to lay the groundwork for the preparation of a more potent and selective MDMA antagonist.

As mentioned previously, extraction from the fruits, leaves and stems of plants such as the *Nandina domestica* only yield a small amount of the nantenine.[175] Chemical synthesis of nantenine is necessary for several reasons: 1) provides access to both the natural (*S*) and unnatural (*R*) enantiomer 2) facilitates the acquisition of significant amounts of the compound for *in vivo* testing 3) synthetic methods pursued may allow access to analogues by structural modification. Developing a chemical synthesis of nantenine provides a route to gain further insight into nantenine's mechanism of action and development of a more potent antagonist.

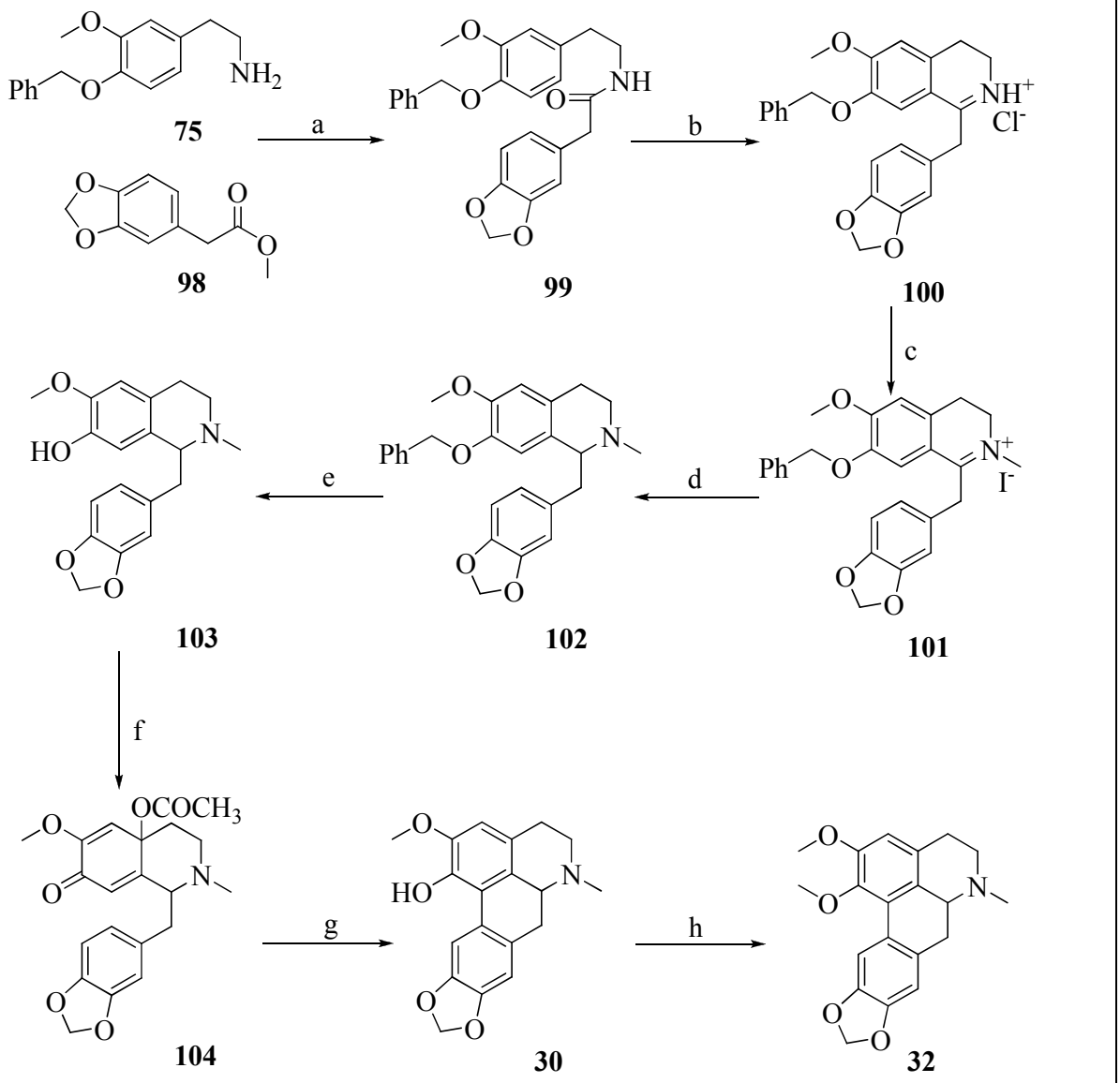
4.1. Synthesis of Nantenine

Nantenine has been prepared using three approaches: *O*-methylation of domesticine with diazomethane through the Wessely Acetoxylation methodology, AIBN radical cyclization, and [3C + 3C] annulation involving ethylthiopropanone and Mannich bases.[153,169,176-181]

4.2. Synthesis of Nantenine: via Wessely Acetoxylation route

Hoshino prepared Nantenine following the Wessely Acetoxylation (Scheme 15).[176,177]

Scheme 15: Synthesis of Nantenine by Methylation of Domesticine

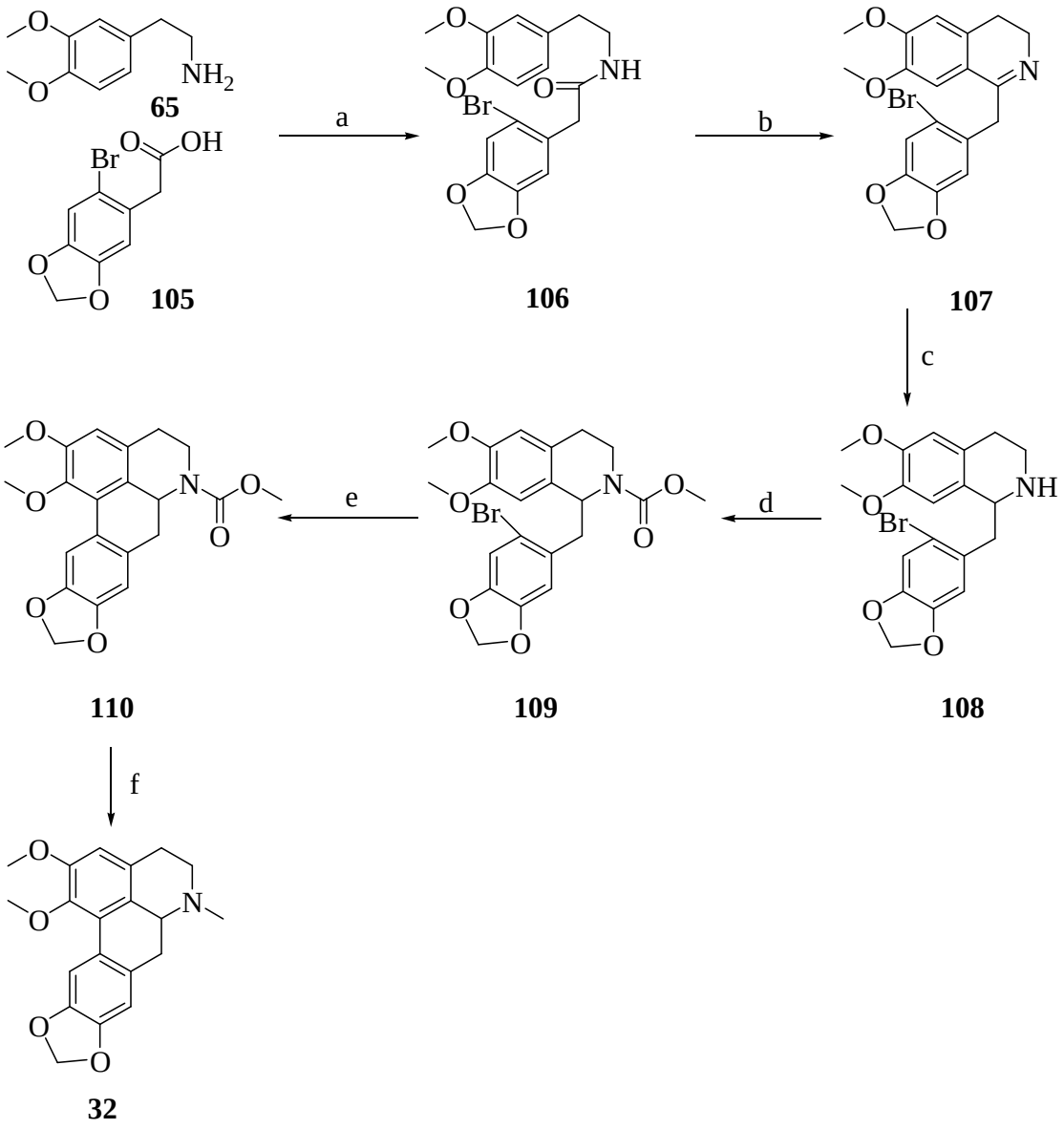


Reagents and conditions:
a. Δ 71% b. $POCl_3$, CH_2Cl_2 57% c. Free base, MeI 89% d. $NaBH_4$, MeOH 97%
e. Pd/C, H_2 99% f. $Pb(OAc)_4$, AcOH g. *i.* Ac_2O, H_2SO_4 18% *ii.* 4N HCl, dioxane 83%
h. diazomethane, CH_2Cl_2 95%

4.3. Synthesis of Nantenine: Radical Cyclization

Nantenine can be prepared using AIBN and tributyltin hydride to construct the biaryl bond following the methodology reported by Nimgirawath (Scheme 16).[179]

Scheme 16: Synthesis of Nantenine using Radical Cyclization



Reagents and conditions:

a. Δ 180-185 ^{o}C, 2 h. 58% b. $POCl_3$, Benzene, reflux, 3 h, 80%

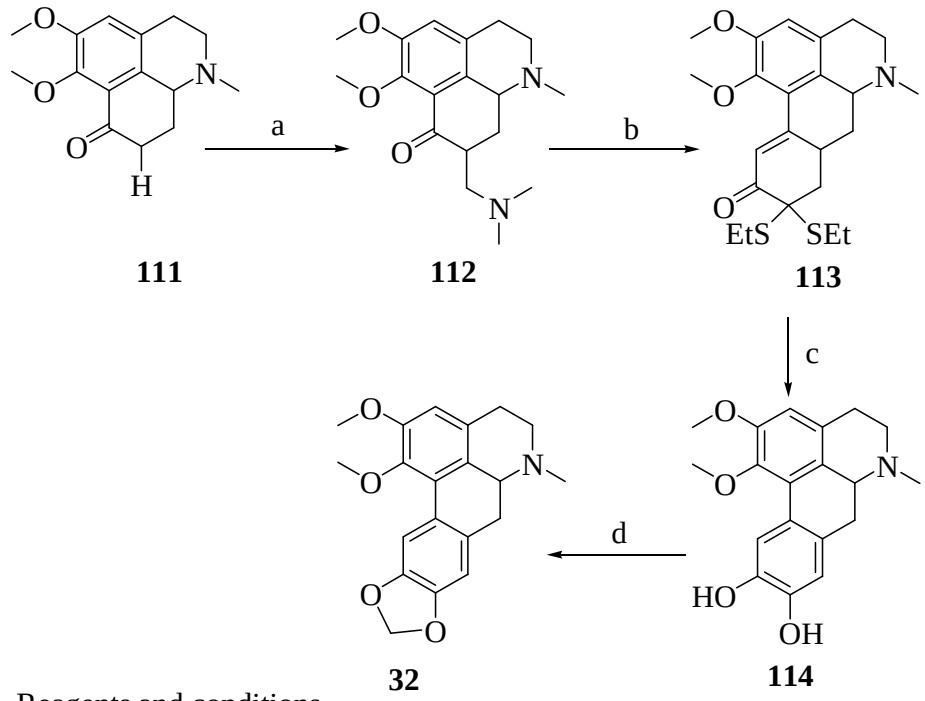
c. $NaBH_4$, MeOH, reflux, 1 h, 83% d. Methyl Chloroformate, Et_3N, $CHCl_3$, 0-5 ^{o}C, 3 h, 91%

e. AIBN, $SnHBu_3$, $PhCH_3$, reflux, 24 h, 21% f. LAH, THF, reflux 3 h, 64%

4.4. Synthesis of Nantenine: [3C + 3C] Annulation

Ozaki has reported the application of [3C + 3C] annulation to prepare the D-ring of nantenine (Scheme 17).[181]

Scheme 17: Synthesis of Nantenine using [3C + 3C] Annulation



Reagents and conditions
a. $Me_2NH.HCl$, HCHO (aq), MeOH, 78%
b. 1,1-bis(ethylthio)-2-propanone, DME, NaH, reflux, 10 min, 47%
c. NBS, AcOH-H_2O-MeCH, 0 ^oC, 38% d. KOH, CH_2Cl_2, DMSO, 80 ^oC, 1 h, 43%

Nantenine was prepared following these three pathways; Wessely acetoxylation in 9 steps with 5% overall yield, the radical cyclization in 6 steps with 5% overall yield and the annulation 4 steps with 6% overall yield. The Wessely acetoxylation and the radical cyclization protocols are not sufficient methods to prepare large quantities of nantenine or analogues due to the low yield of the biaryl coupling, however the wessely acetoxylation can provide access to C1 alkoxy analogues. The annulation protocol can possibly provide C1 or C2 alkoxy analogues via the substitution pattern of the starting material.

CHAPTER III: APPROACHES TO AN OPTIMIZED SYNTHESIS OF NANTENINE AND NANTENINE ANALOGUES

1. INTRODUCTION

Synthesizing nantenine is the first step in the development of a potent and selective nantenine-based MDMA antagonist. While there are several reported methods to prepare nantenine, developing a high yielding synthetic method is of great importance.

Our major goals were to: 1) develop a high-yielding synthesis of nantenine, 2) explore methods to prepare nantenine analogues for SAR studies and to 3) explore methods to prepare both enantiomers of nantenine. Therefore, our group decided to investigate the PIFA, Wessely acetoxylation and the direct arylation methods to prepare nantenine.

Synthesis of aporphines have been plagued by one major challenge; construction of the biaryl bond. When compared to oxidants such as Chromium or Ruthenium (IV), the PIFA-mediated biaryl coupling has provided a less toxic method to construct biaryl bonds.[182] The Wessely acetoxylation was chosen because we envisioned that it may be used to prepare nantenine as well as C1 analogues. Nantenine as well as several classes of analogues can be prepared by using direct arylation.

To determine the effects of structural modification on nantenine's *in vitro* (5-HT_{2A} and α_1 antagonism) and *in vivo* (MDMA antagonism) antagonistic activity, a panel of target analogues was envisioned (Figure 32). Varying the length of the C1, C2 and C3-alkoxy chain as well as the *N*6-alkyl chain in compounds **115-118**, will help determine the effect increasing nantenine's lipophilicity has on the *in vivo* anti-MDMA activity. C1, C2 and C3-alkyl analogues will determine the significance of the oxygen in nantenine's anti-MDMA activity. The amino analogues will determine the effect increasing the number of possible protonation sites has on

nantenine's antagonistic effects. Compound **119** will determine how flexibility of the aporphine core affects nantenine's MDMA antagonism. Studying nantenine's enantiomers, *R*- and *S*-**32**, will provide insight into the significance of nantenine's chiral center in its MDMA antagonistic activity. Additionally, SAR studies of these analogues at 5-HT_{2A} and α_1 receptors will shed light on the importance of particular structural elements for nantenine's activity at these receptors. As mentioned before, these *in vivo* and *in vitro* SAR-studies are a necessary first step in the development of a more potent and selective MDMA antagonist.

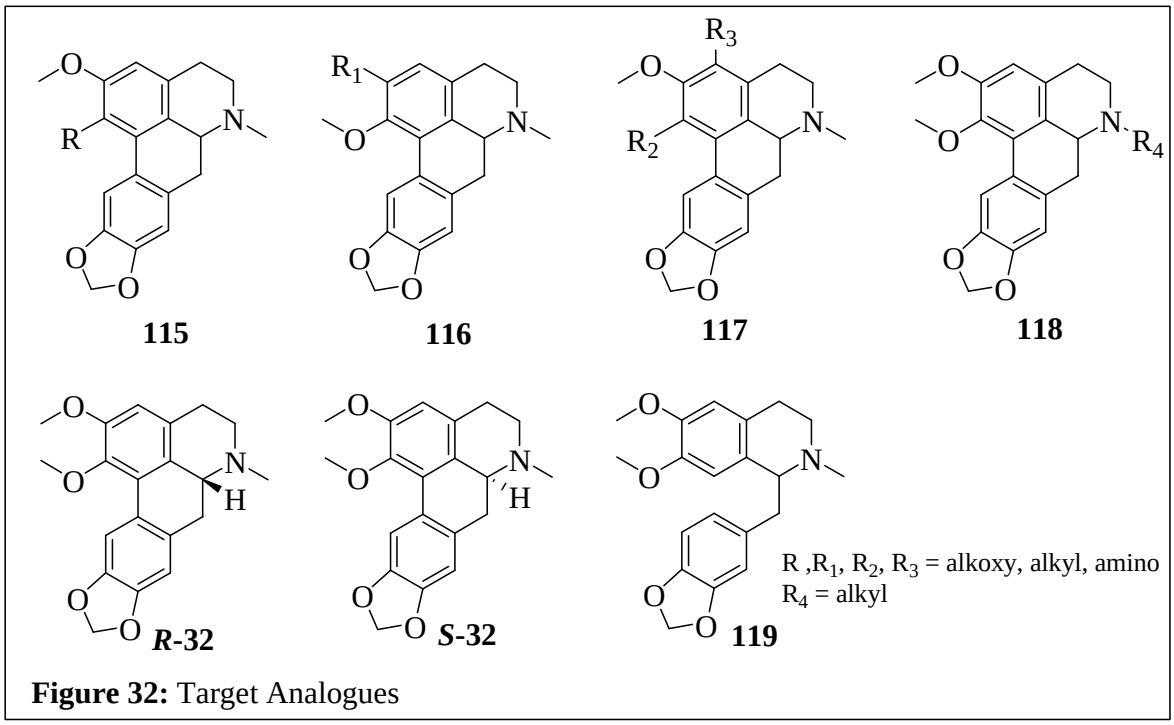


Figure 32: Target Analogues

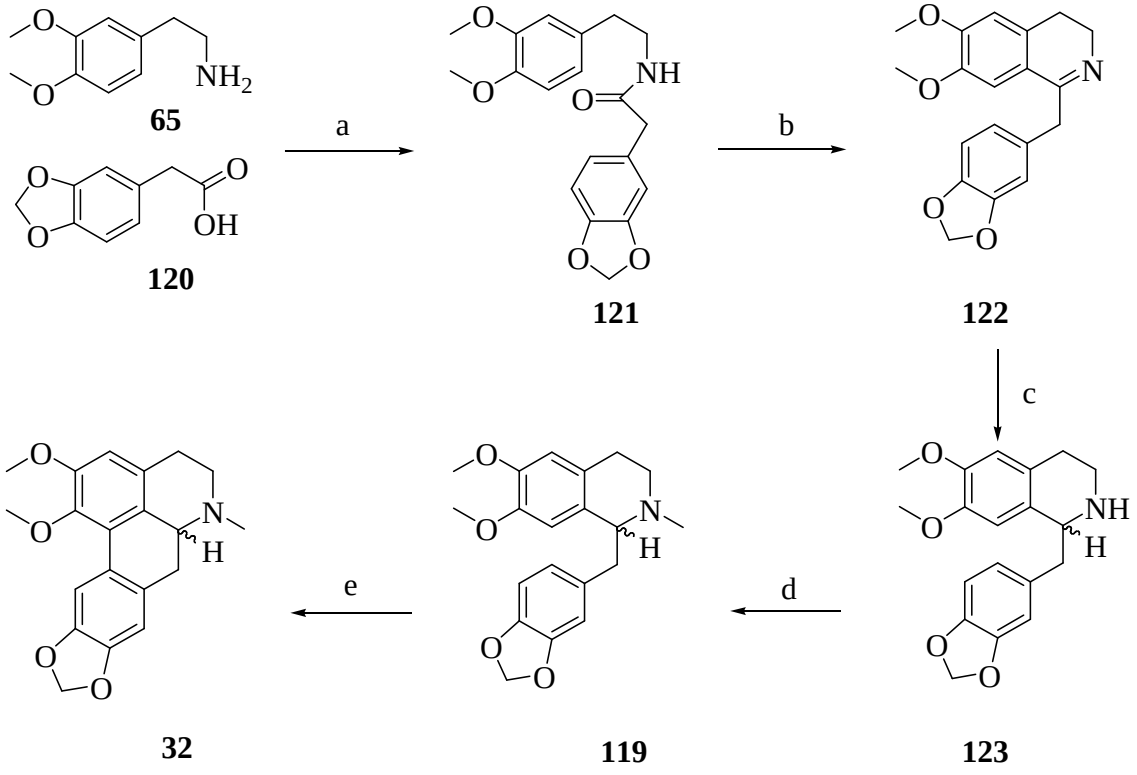
RESULTS

2. SYNTHESIS OF NANTENINE VIA PIFA-MEDIATED BIARYL COUPLING

2.1. Synthesis of Racemic Nantenine

Racemic nantenine was prepared using the PIFA-mediated cyclization (Scheme 18). Steps a-d of the protocol gave high yields; however, the oxidative coupling of compound **119** gave low yields and irreproducible results.

Scheme 18: Synthesis of Racemic Nantenine via PIFA-mediated cyclization



Reagents and conditions

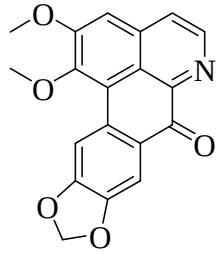
a. CDI, THF, 99% b. $POCl_3$, CH_2Cl_2, 87% c. $NaBH_4$, MeOH, -78 ^oC 77%

d. DCM, HCHO, $Na(OAc)_3BH$, 1.5h, 95%, e. PIFA, $BF_3.OEt_2$, DCM, -20 ^oC, 30 min, 25%

Amide **121** was prepared by CDI peptide coupling of 3,4-methylenedioxyphenylacetic acid **120** and 3,4-dimethoxyphenethyl amine **65**.[183] Bischler-Napieralski cyclization with phosphorus oxychloride converted amide **121** to the cyclic imine **122**.[184] Reduction of imine **122** with sodium borohydride at -78 ^{o}C afforded secondary amine **123**.[185] Subjecting amine **123** to reductive amination conditions (formaldehyde with sodium triacetoxy borohydride as the reducing agent) afforded the tertiary amine **119**. Nantenine precursor **119** was prepared in 64% yield over four steps. Subjecting **119** to oxidative cyclization using PIFA, $BF_3.OEt_2$, in DCM at -20 ^{o}C afforded nantenine (**32**) in 25% yield.[186] However the reaction was not reproducible and no other identifiable compounds were isolated. Attempts to improve the yield of nantenine from the PIFA cyclization reaction by purging with argon under vacuum and protecting from light did not increase the yield of nantenine.

2.1.1. By-products of PIFA oxidation reaction

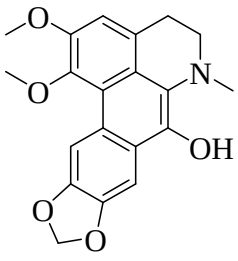
After the PIFA reaction with HFIP, there was difficulty isolating nantenine from a slightly more polar compound, which was identified as an oxidized derivative of nantenine, compound **A** (Figure 33).



Compound A

Figure 33: Structure of Oxidized Product

Aporphine alkaloids have been recrystallized from cyclohexane.[187] Therefore, attempts were made to re-crystallize nantenine from *n*-hexane. After several minutes of heating in a water bath, a solid substance began to precipitate: this substance was identified as compound **B** using ^{1}HNMR and mass spectroscopy (Figure 34).

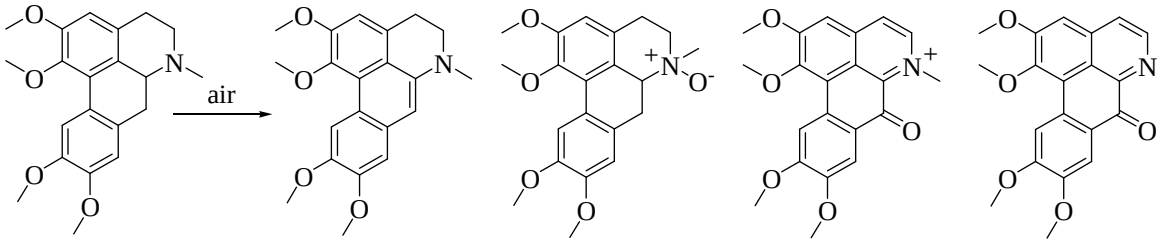


Compound B

Figure 34: Structure of Compound **B**

According to Chervenkova and Hidalgo, alkaloids such as glaucine (**95**) can be oxidized in air, light or heat.[188,189] When dissolved in ethanol, **95** is unstable in air and can lead to several oxidized compounds (Scheme 19).

Scheme 19: Glaucine air oxidized products



Glaucine (95) **124** **125** **126** **127**

Therefore, a possible explanation for the low yield of nantenine in the PIFA reaction is oxidation. It is possible that during the cyclization reaction, work up and/or purification steps, nantenine is formed in a significant yield but is then oxidized to these side products. To test this assumption, a solution of methylene chloride and pure nantenine was left standing over 48h. TLC analysis showed trace amounts of compound **A** but no evidence of compound **B**.

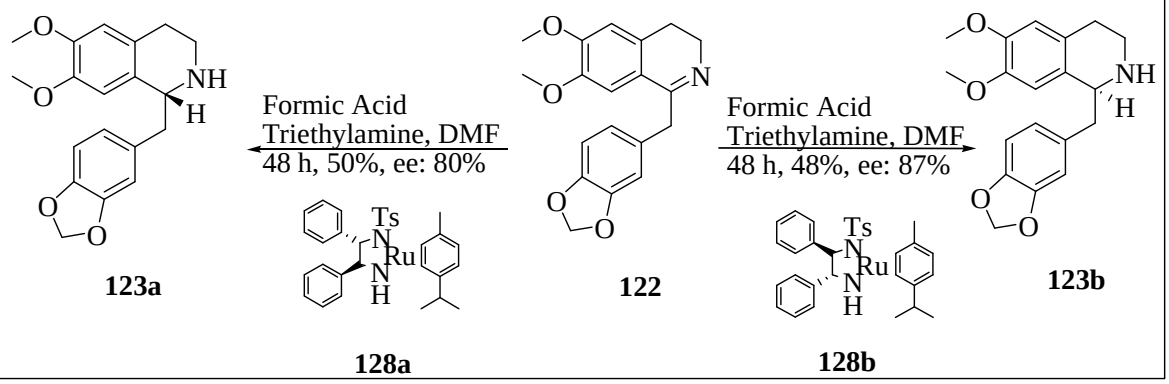
Demethylation of tertiary to secondary amines by UV light can occur through the Polonovsky reaction forming first the *N*-oxide then undergoing deoxygenative demethylation.[188, 190,191] Therefore, trace amounts of compound **A** in the test solution suggests that a solution of nantenine may undergo demethylation to form oxidized products in the presence of light. There were also a number of by-products from the PIFA reaction which have not yet been identified.

2.1.2. Enantioselective synthesis of tetrahydroisoquinoline substrate for PIFA cyclization

2.1.2.1. Via enantioselective reduction of a dihydroisoquinoline substrate

Once a route to prepare racemic nantenine was established our focus then turned to the synthesis of both nantenine enantiomers via this route. Using Noyori catalyst **128**, cyclic imine **122** was enantioselectively reduced to the chiral secondary amine **123a** and **123b** (Scheme 20).[192,193]

Scheme 20: Asymmetric Reduction of Cyclic Imine **122**



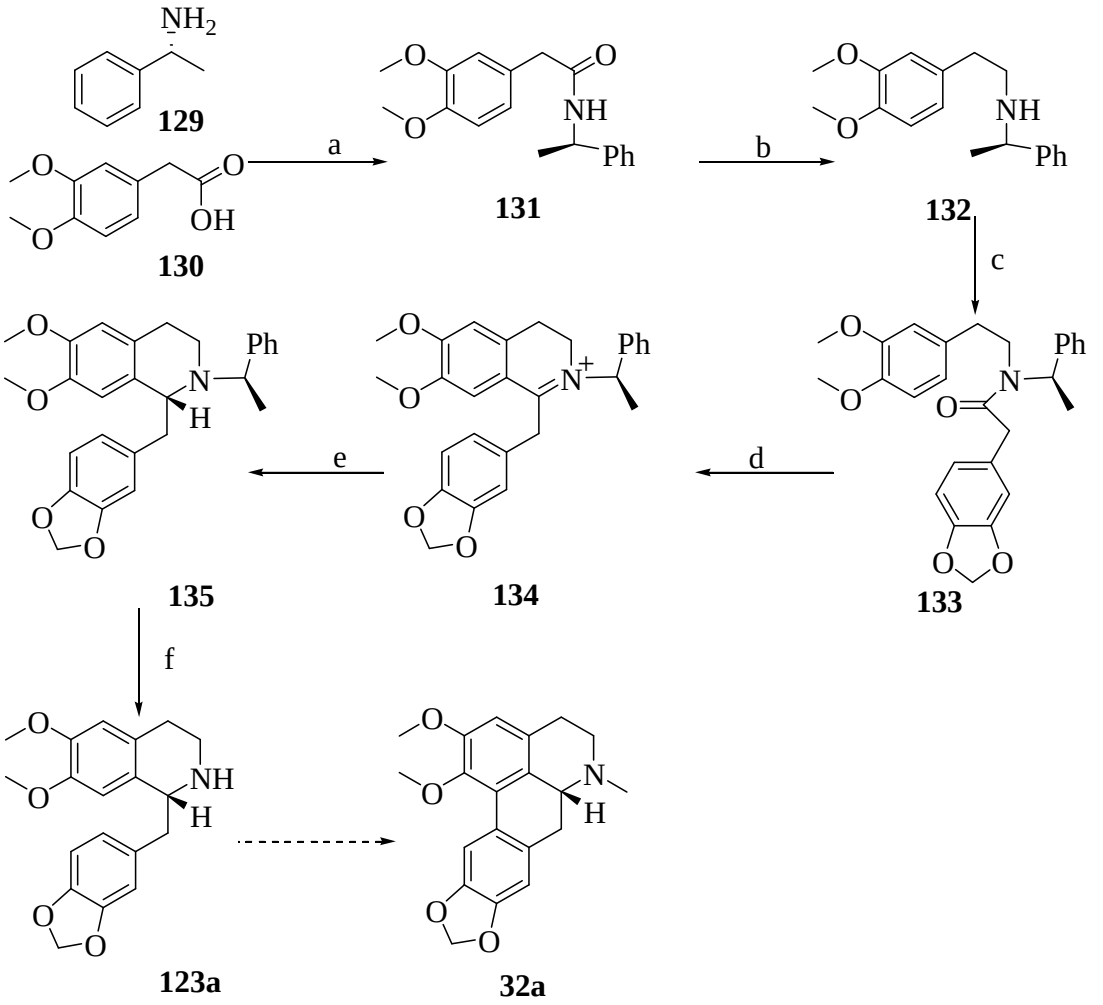
While the imine reduction occurred with an 87% and 80% ee for **123b** and **123a** respectively, complete conversion took 48h with a moderate 48% and 50% isolated yield,

respectively.[194] Determination of the enantiomeric excess (ee) was conducted using ^{1}HNMR analysis with (*R*)-(+)-α-methylbenzyl isocyanate. The ^{1}HNMR peak corresponding to the methylenedioxy CH_2 at 5.95 ppm was used as the reference peak for the ee determination. Once the Isocyanate was added to the sample, the reference peak was split into two distinct peaks with chemical shifts at 5.86 ppm as a doublet and 5.95 ppm as a singlet. In the racemic mixture, these peaks are a one-to-one mixture, while in the chiral mixture the peaks are a major and minor peak based on the enantiomer being tested. The integrations of the corresponding peaks were used to determine the ee of the major and minor enantiomer.

2.1.2.2. Via a chiral auxiliary

The moderate ee's obtained led us to consider alternative methods for introducing the chiral center in nantenine. Thus, an attempt to prepare **123a** and **123b** via chiral phenethyl amine **132** was conducted (Scheme 21). Compound **135** was prepared in 39% yield over five steps.[192,195,196]

Scheme 21: Synthesis of **123a** en route to *R*-Nantenine (**32a**)

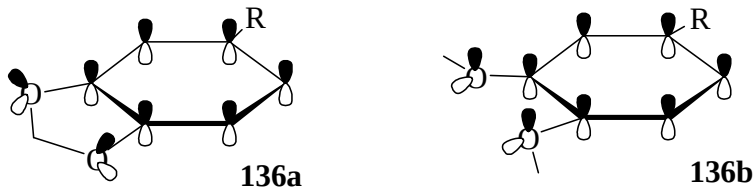


Reagents and conditions:
a. CH_2Cl_2, Et_3N, EDCI, 92% b. THF, BF_3OEt, BH_3THF, 92% c. CDI or EDCI, THF, 95%
d. $POCl_3$, CH_2Cl_2, 70% e. $NaBH_4$, MeOH, -78 ^oC, 70%
f. H_2, Pd/C, EtOH, 10% HCl (aq), 10% ee = 73%

N-deprotection through hydrogenolysis resulted in poor yields of the desired secondary amine with only moderate ee's. We also employed a similar pathway as in Scheme 21 to prepare compound **123b**, but the yield and ee were also poor. Due to the low yield and ee obtained, this method was not further investigated.

2.1.3. Evaluation of Reaction Parameters and Substrate Scope in PIFA Biaryl Coupling

Sha has reported that the rigid methylenedioxy substituent on the phenyl ring does not allow complete orbital overlap between the oxygen lone pairs and the π-system of the phenyl ring (Figure 35).[197]

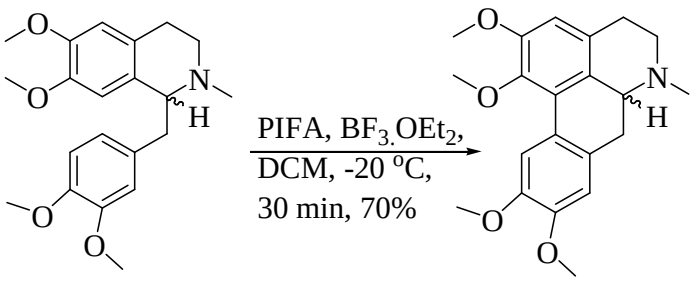


136a **136b**

Figure 35: The orientation of lone pairs of electrons of oxygen atoms

Compounds bearing two methoxy groups on the phenyl ring (**136b**) have better orbital overlap with the π-system of the phenyl ring as a result of their free rotation. The stereoelectronic effects of the methoxy groups causes a higher electron density on the phenyl ring making it more nucleophilic.[197] It is possible that low yields in the PIFA cyclization reaction to prepare nantenine are as a result of similar stereoelectronic effects involving the methylenedioxy ring of **123**. To determine the validity of this assumption, Laudanosine (**94**) was subjected to the PIFA-mediated cyclization (Scheme 22). Glaucine (**95**) was isolated in 70% yield.

Scheme 22: PIFA-mediated Cyclization of Laudanosine*



Laudanosine (94) **Glaucine (95)**

* Obtainted from Professor Jack Rosazza:
University of Iowa College of Pharmacy

2.1.4. Effect of Solvent

To determine solvent effects on the cyclization, we attempted the PIFA reaction at room temperature using methylene chloride, 1,4-dioxane, acetonitrile, isopropanol, 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) as solvents, Table 4.

Table 4: PIFA Cyclization: Solvent Study

Entry	Precursor	Coupling Reagent	$BF_3{\cdot}OEt_2$	Solvent	Temp	Reaction Time	Yield (32)
1	**119**	PIFA	Yes	HFIP	rt	30 min	16%
2	**119**	PIFA	Yes	DCM[a]	-20 °C	30 min	--
3	**119**	PIFA	Yes	1,4-Dioxane[a]	-20 °C	30 min	--
4	**119**	PIFA	Yes	Acetonitrile[a]	-20 °C	30 min	--
5	**119**	PIFA	Yes	Isopropanol[b]	-20 °C	30 min	--
6	**119**	PIFA	Yes	TFE[a]	-20 °C	30 min	--

a: Decomposition observed
b: Starting material recovered

Subjecting **119** to PIFA-mediated cyclization in DCM, 1,4-dioxane, isopropanol, acetonitrile or TFE did not afford nantenine. Starting material was recovered when isopropanol was used as solvent. Unidentified products were isolated from the dioxane, acetonitrile and TFE

reactions. Kita has reported that cyclization is facilitated when a polar, poorly nucleophilic protic solvent such as HFIP, is used in the PIFA reaction. HFIP promotes cyclization by stabilizing the radical cation generated by PIFA.[198] HFIP proved to be the only solvent to afford nantenine, albeit in a low yield of 16%.

2.1.5. Effect of $BF_3{\cdot}OEt_2$

With the best solvent in hand (HFIP), we then looked to determine the effect of $BF_3{\cdot}OEt_2$ on the biaryl cyclization. The PIFA-mediated cyclization was conducted in HFIP at room temperature without $BF_3{\cdot}OEt_2$; neither nantenine nor starting material was isolated. Kita has reported that $BF_3{\cdot}OEt_2$ acts as an activating agent for PIFA by coordinating to the trifluoroacetoxy ligands.[199] The activated PIFA would then generate the radical cation on the aromatic ring through a charge transfer complex. Without $BF_3{\cdot}OEt_2$, PIFA is unable to afford the biaryl coupled product.

2.1.6. Examination of Other Oxidants in the Biaryl Cyclization of **119**

Cyclization of **119** was attempted using stronger reagents such as ruthenium dioxide, cerium hydroxide, manganese (III) acetate dihydrate and vanadium oxytrifluoride in DCM. Anakabe and Moreno have reported the use of ruthenium oxide, vanadium oxytrifluoride (VOF_3) and cerium hydroxide as oxidative biaryl coupling reagents to prepare aporphines.[169,182,200] However, attempts to prepare nantenine from precursor **119** using $RuO_2.xH_2O$, RuO_2 and VOF_3

were unsuccessful. Starting material was recovered from the ruthenium oxide reaction and unidentified products were isolated from the vanadium oxytrifluoride reaction.

The limited success observed when using HFIP as the solvent to cyclize **119** to give nantenine (**32**) encouraged us to repeat the previously attempted cyclization using $RuO_2.xH_2O$ and cerium (IV) hydroxide. Unfortunately, changing the oxidant did not lead to the cyclized product (Table 5, entry 1 and 2). Kita claims that addition of a catalytic amount of magnesium perchlorate ($Mg(ClO_4)_2$) enhances the stability of the radical cation generated by PIFA.[198] However, addition of $Mg(ClO_4)_2$ to the PIFA-mediated reaction in HFIP did not increase the yield of the nantenine; 2% of nantenine was isolated.

Table 5: Attempted Cyclization Reactions on **119**

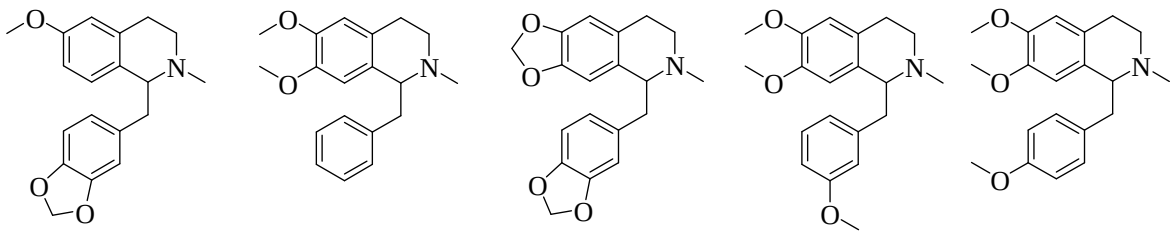
Entry	Cyclization Reagent	Solvent	Temperature	Reaction Time	Yield (32)
1	$RuO_2.xH_2O$[b]	HFIP	rt	30 min	--
2	$Ce(OH)_4$[c]	HFIP	rt	30 min	--
3	$Ce(OH)_4$[c]	DCM	0 $^oC \rightarrow$ rt	30 min	--
4	$Mn(OAc)_3.2H_2O$[c]	TFA	0 ^oC	20 min	--
5	VOF_3[c]	DCM	0 ^oC	30 min	--
6	PIFA[a]	HFIP	rt	30 min	2%

a: $Mg(Cl_4)_2$ used as a additive
b: Starting material recovered
c: Decomposition observed

2.1.7. Substrate scope

2.1.8. Examination of the substrate scope of the PIFA Biaryl Cyclization in the Synthesis of Aporphines

To examine the substrate scope of the PIFA cyclization, tetrahydroisoquinolines **137-141** was prepared following the methodology in Scheme 18 (Figure 36).



137 **138** **139** **140** **141**

Figure 36: PIFA cyclization substrates

Compounds **137-141** were subjected to the PIFA reaction conditions (Table 6).

Table 6: PIFA-mediated biaryl cyclization on **137-141**

Entry	Precursor	Aporphine Yield	Starting Material Recovered
1	**137**	1.1%	0%
2	**138**	0%	30.3%
3	**139**	0.71%	0%
4	**140**	8%	0%
5	**141**	0%	18.3%

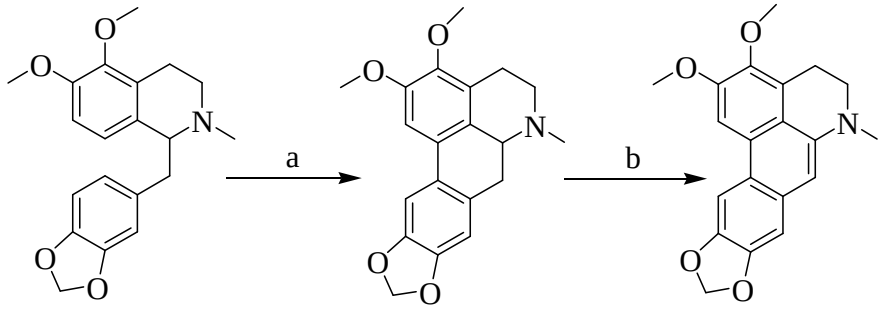
Reaction conditions: PIFA, $BF_3{\cdot}OEt_2$, HFIP, rt, 30 min

The aporphine core was isolated for compounds **137**, **139** and **140** (Table 6, entry 1, 3 and 4, respectively), while starting material was recovered for compounds **138** and **141** (Table 6, entry 2 and 5m respectively). From these results, it seems that having an electron-donating group *para* to the site of ring closure on the D-ring is necessary for biaryl coupling via the PIFA-mediated cyclization. Also, compound **140** (Table 6, entry 4), which has a free methoxy group on the D-ring, provided the highest yield for the corresponding aporphine. This result supports Sha's assumption for the stereoelectronic effects of methoxy groups as compared to methylenedioxy groups on phenyl rings.

In attempts to further probe the substrate tolerance in the PIFA reaction, compound **144** was prepared in 33% yield over four steps (Scheme 23). Subjecting amine **142** to the PIFA-

mediated cyclization conditions yielded compound **143** in 86% yield with incomplete conversion; **142** was recovered in 5% yield (Scheme 23).

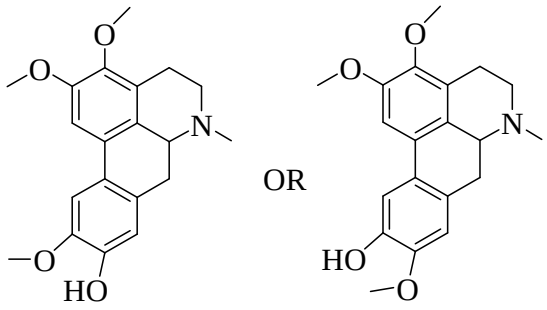
Scheme 23: C-3 Analogue Synthesis



142 **143** **144**

Reagents and conditions
a. PIFA, $BF_3.OEt_2$, HFIP, rt, 30 min 86%, b. Left standing in air

The instability of these aporphines also presented in compound **143**. Exposing compound **143** to light over 12h results in an oxidized product isolated in 31% yield. ^{1}HNMR analysis identified the structure as **144**.[171,201-206] Conversion of **144** to **143** is possible following Gao's procedure (sodium cyanoborohydride at pH 3).[207]



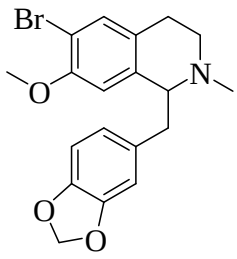
145 **146**

Figure 37: Possible Structure of Ring Opened Products

Attempting to drive the cyclization of **142** to completion by doubling the equivalents of PIFA and $BF_3.OEt_2$ resulted in cleavage of the methylenedioxy ring. ^{1}HNMR and mass spectroscopy analysis identified the product as **145** or **146** (Figure 37). Identifying the actual

structure of the ring-opened product was not of high importance; therefore no further characterization experiments were conducted. Tomar has reported that methylenedioxy rings are unstable in excess $BF_3{\cdot}OEt_2$ leading to ring opening, giving a catechol or a phenol.[208]

In addition to the above six compounds, we also attempted to prepare compound **147** for our substrate scope study (Figure 38).

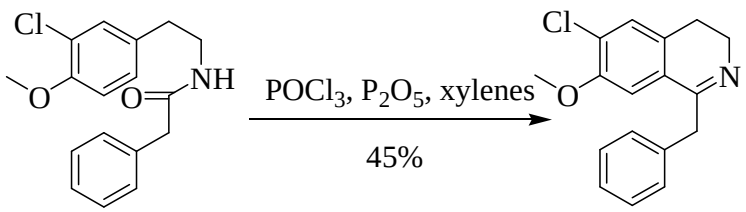


147

Figure 38: Bromo Substituted Tetrahydroisoquinoline

Charifson reported the synthesis of tetrahydroisoquinolines with a chloride atom as a substituent on the A-ring (Scheme 24).[209]

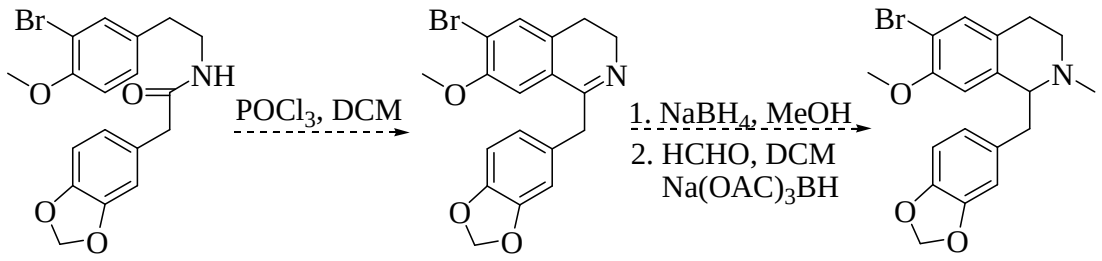
Scheme 24: Charifson protocol for synthesis of Imine **149**



148 **149**

Against this precedence it was anticipated that compound **147** could be prepared in a three step procedure involving Bischler-Napieralski cyclization on compound **150** followed by reduction of the dihydroisoquinoline formed and subsequent *N*-methylation (Scheme 25).

Scheme 25: Proposed Intermediate to Synthesize Compound **147**



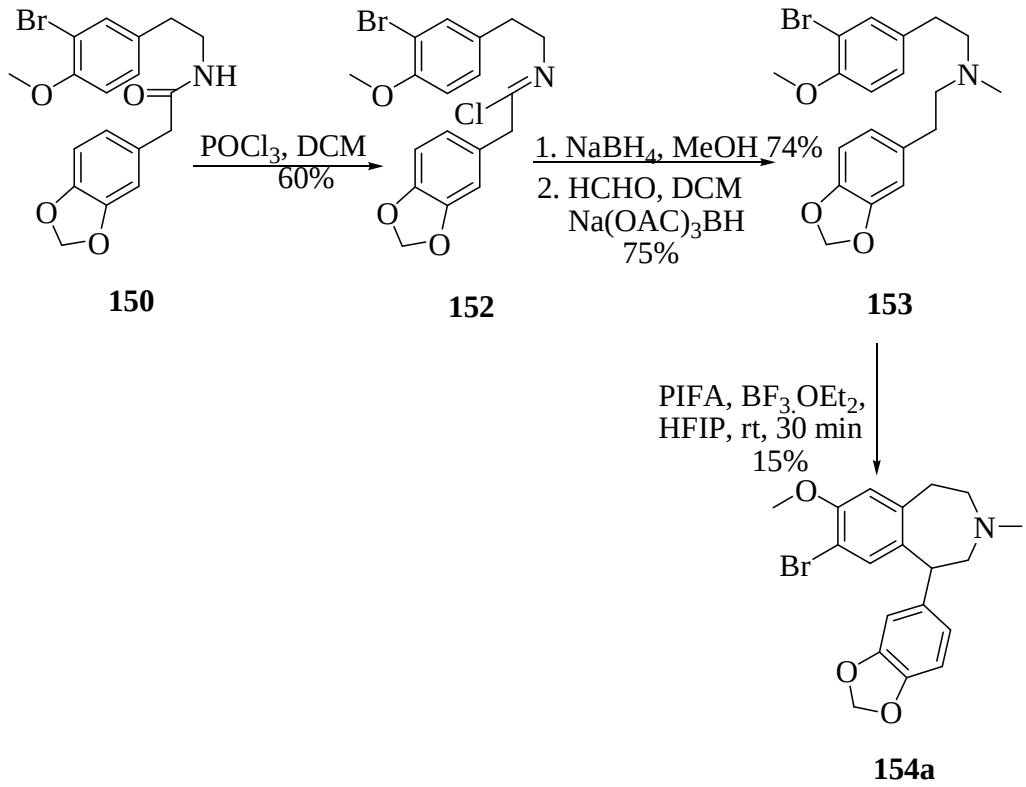
150 **151** **147**

However the product of this three-step sequence was not identified as compound **147**, as we later discovered. After subjecting what was believed to be compound **147** to the PIFA cyclization conditions, a compound possessing a benzazepine core was obtained. Upon careful inspection of spectral data for intermediates in the potential synthesis of **147** it became clear that the sequence had not gone as expected.[210-212]

Analysis of the intermediates via NMR and mass spectroscopy, the resulting imine was identified as compound **152**. It is believed that compound **153** was prepared following treatment of amide **150** with phosphorus oxychloride. Reduction of **152** with sodium borohydride followed by methylation of the resulting secondary amine gave tertiary amine **153** (Scheme 26).

Subjecting amine **153** to the PIFA reactions conditions resulted in the formation of a benzazepine core structure. There are two possible regiochemistries for the bromine of the benzazepine structure. A possible mechanism for the formation of **154a** and the other possible benzazepine is depicted in Figure 39.

Scheme 26: Synthesis of compound **151**



150 **152** **153** **154a**

PIFA initially forms radical cation **155**, which then rearranges to form the benzylic cation **156**. Nucleophilic attack from the A-ring forms the spiro intermediate **157**. Formation of compound **154a** occurs by CH_2 bond migration following the red arrows, while formation of compound **154b** occurs by CH bond migration following the blue arrows. 2D NMR: HMQC, HMBC, NOESY, and COSY, was utilized to determine the substitution pattern of the A-ring. To determine the compound's structure, HMQC (Heteronuclear Multiple Quantum Coherence) is selective for determining the hydrogen a particular carbon is directly bonded; HMBC (Heteronuclear Multiple Bond Coherence) is specific for determining the bonding pattern of carbons 2-4 bond lengths away; NOESY (Nuclear Overhauser Effect Spectroscopy) is used to determine the spacial environment of a particular functional group. COSY (Correlation

Spectroscopy) is used to show how a hydrogen correlates with another hydrogen in the molecule to determine is symmetry is present.

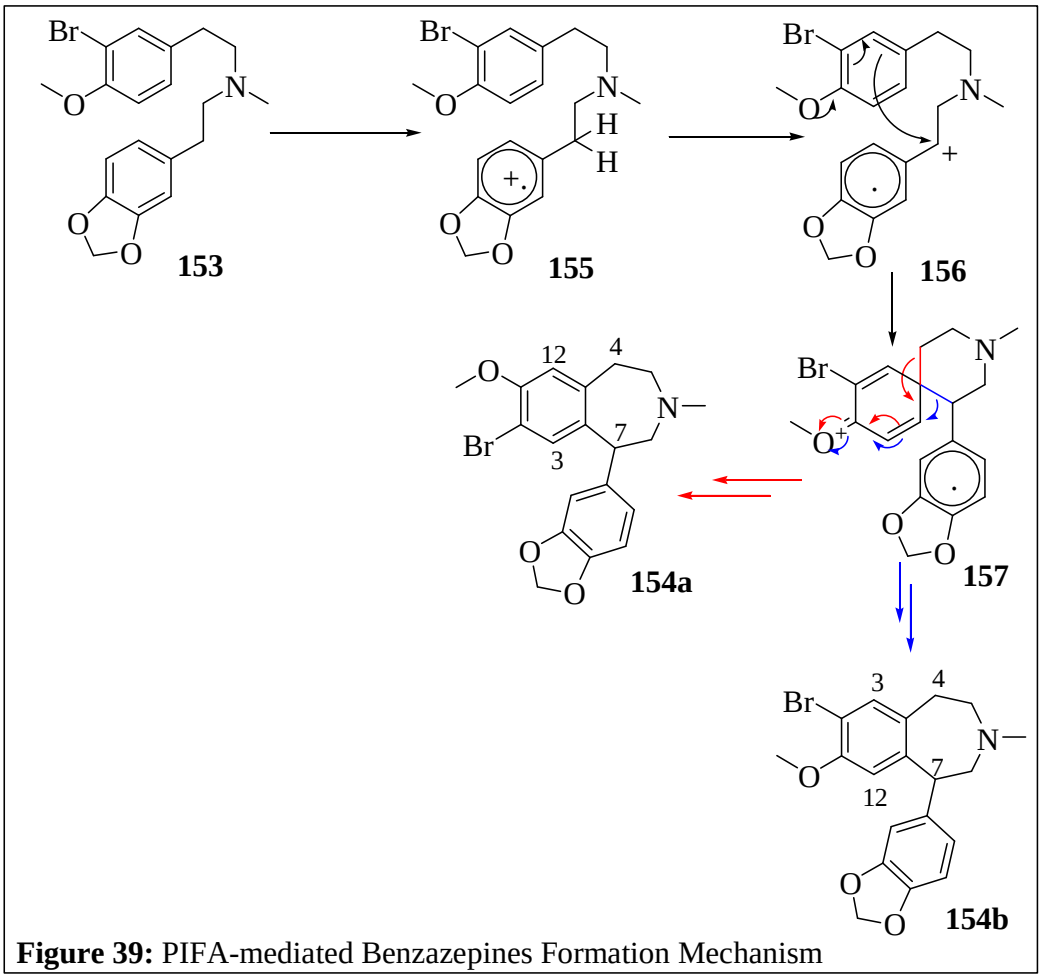


Figure 39: PIFA-mediated Benzazepines Formation Mechanism

Table 7: HMBC NMR Analysis: ^{1}H (500 MHz) and ^{13}C (150 MHz) NMR Data for Compounds **154a** in $CDCl_3$ (δ in ppm)

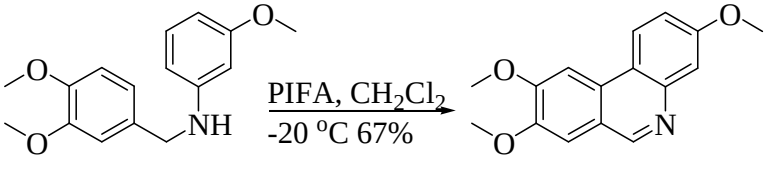
	Proton: Carbon		**HMBC Correlation**
	154a		**154a**
Position	δH	δC	δC
12	6.64 CH (s, 1H)	109.3	36.3
3	7.35 CH (s, 1H)	128.5	48.6
4	3.01 CH_2 (m, 2H)	36.3	109.3
7	4.19 CH (m, 1H)	48.6	128.5

Identification of the benzazepine structure began with labeling the aromatic protons H_{12} and H_3 by performing ^{1}H, ^{13}C NMR, and HMQC experiments and the C_4 and C_7 carbon using ^{1}H,

^{13}C NMR, COSY and HMQC experiments on **154a**. Aromatic proton H_3 was labeled as such because the high electronegativity of the bromine substituent reduces the electron density on the *ortho* carbon, deshielding the proton and shifting the peak downfield. Therefore, the ^{1}HNMR singlet furthest downfield at 7.35 ppm with ^{13}CNMR peak at 128.5 ppm corresponds to H_3. The only other ^{1}HNMR singlet at 6.64 ppm with ^{13}CNMR peak at 109.3 ppm was therefore labeled as H_{12}. Carbon 7 is bonded to the only peak which integrates for 1 H in ^{1}HNMR with chemical shift 4.19 ppm and ^{13}CNMR chemical shift at 48.6 ppm. Carbon 4 is bonded to multiplet with ^{1}HNMR chemical shift at 3.01 ppm and ^{13}CNMR at 36.3 ppm. Once identified, analysis using HMBC showed a correlation between H_{12} and C_4 as well as H_3 and C_7. Therefore, the structure of the benzazepine was identified as compound **154a**.

2.1.9. Further examination of the substrate Scope of the PIFA reaction: Attempted Synthesis of Anilino Aporphines

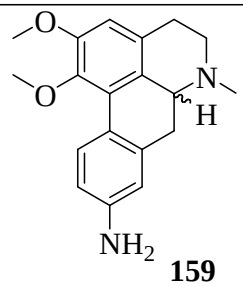
Moreno has shown the utility of PIFA to prepare compounds with the benzophenanthridine skeleton in high yields by formation of a radical cation which is trapped by an internal arylic nucleophile (Scheme 27).[182]



158a **158b**

Scheme 27: PIFA-mediated Synthesis of Phenanthridines

It was envisioned that a similar method could be used to synthesize anilino aporphines. Therefore the PIFA-mediated cyclization was examined to prepare anilino substituted aporphine **159** (Figure 40).

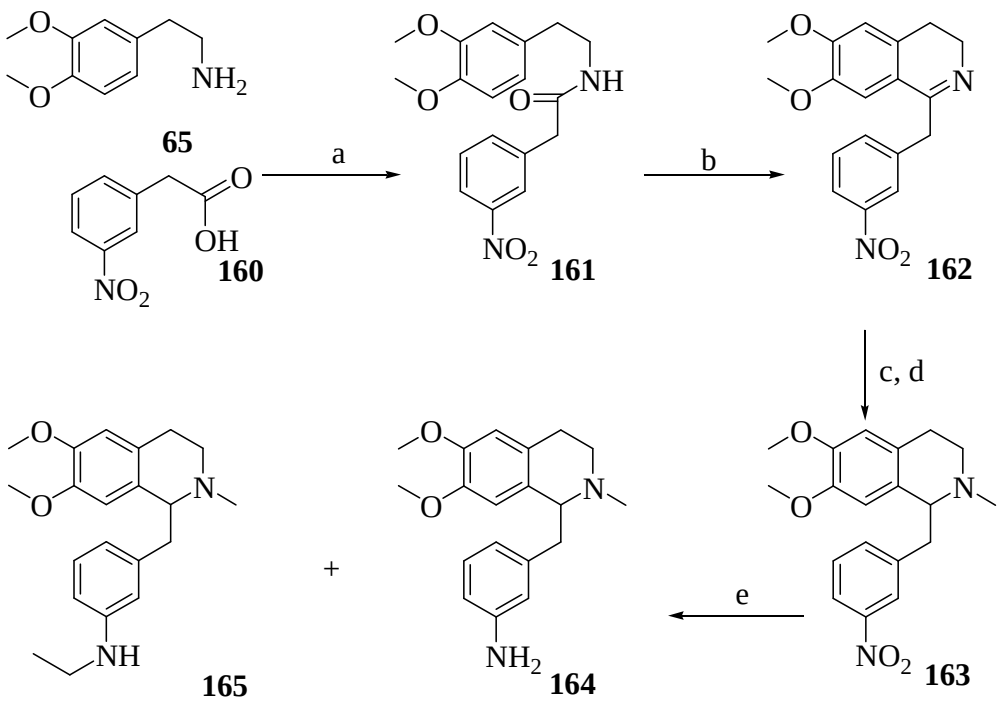


159

Figure 40: Anilino Aporphine

Starting from *m*-nitrophenylacetic acid, **160**, compound **163** was prepared in 69% yield over four steps (Scheme 28). Converting the nitro substituent to an anilino group using a standard procedure (H_2/Pd/C in ethanol) gave an almost 1:1 mixture of two compounds.[213] ^{1}H NMR, ^{13}C NMR and mass spectroscopy were used to identify the structure of compounds **164** and **165.**

Scheme 28: Synthesis of Amino derivative



Reaction Conditions:
a) CDI, THF, 24h, 78% b) $POCl_3$, DCM, reflux, 24h c) $NaBH_4$, MeOH, rt, 2h d)HCHO, DCM, $Na(OAc)_3BH$, 24h, 88% over 3 steps e) H_2, Pd/C, EtOH, **164** (53%) & **165** (47%)

In attempts to avoid the alkylated by-product and increase the yield of the aniline derivative **164**, a series of reduction methods were investigated. Table 8 summarizes our results.

Table 8: Attempts at Nitro Reduction of Compound **163**

Entry	Solvent	Temperature	Time	Reducing Agent	Yield 164 (%)
1	EtOH	rt	24h	H_2/Pd/C	50
2	EtOH	rt	2h	H_2/Pd/C	50
3	DCM	rt	24h	H_2/Pd/C	0[a]
4	THF	rt	24h	H_2/Pd/C	0[a]
5	THF	reflux	18h	$LiBH_4$/TMSCl[214]	0[a]
6	Acetone/H_2O	rt	45min	Zn-NH_4Cl[215]	29

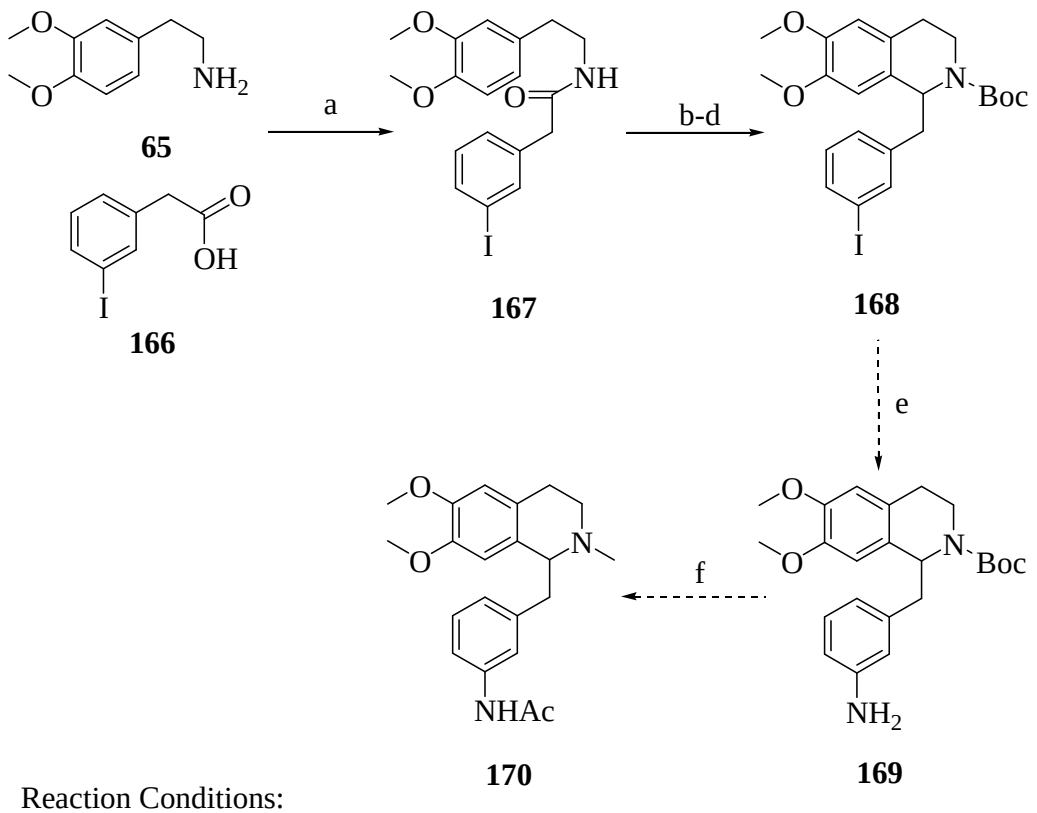
a: Starting material recovered

Changing the reaction time did eliminate the formation of compound **165** (Table 8, entry 2); however the change did not lead to an increase in yield of the desired aniline derivative **164**. The synthesized anilino substrate, **164**, was subsequently subjected to the PIFA reaction. However the reaction was not successful at producing the desired aporphine core; no identifiable products or starting materials were isolated.

At this juncture it was contemplated that the unprotected $-NH_2$ group of **164** may be causing undesired side reactions. Therefore we attempted to prepare the acetamide of **164**. However, several attempts to protect the aniline **164** as an acetamide using acetic anhydride or acetyl chloride with triethylamine in dichloromethane were unsuccessful.

A copper-catalyzed synthesis of primary aryl amines was then attempted to prepare the acetamide derivative of **164** (Scheme 29).[216] Compound **168** was prepared in 77% yield from **167** over three steps. Attempts to convert **168** to **169** were unsuccessful yielding only starting material.

Scheme 29: Synthesis of Amino derivative from Iodo Starting Material

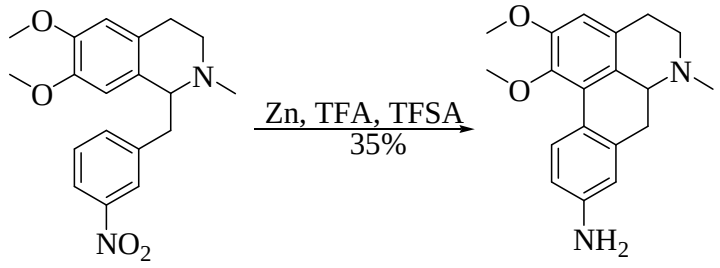


Reaction Conditions:
a) CDI, THF, 24h 76% b) $POCl_3$, DCM, reflux, 24hr c) $NaBH_4$, MeOH, rt, 2h
d) $(Boc)_2O$, iPr_2EtN, DMAP, DCM, 24h, 77% over 3 steps e) CuI, L-Proline, Cs_2CO_3, Benzamidine HCl, 120 ^oC, 24h f) i. Acetic Anhydride, Et_3N, DCM ii. $ZnBr_2$, DCM iii. HCHO, $Na(OAc)_3BH$, DCM

2.1.10. Reductive Phenylation: Attempted Synthesis of Anilino Aporphines

An alternative method to prepare anilino aporphine is the reductive phenylation of nitro substituted tetrahydroisoquinolines (Scheme 30).[217] Nitro-tetrahydroisoquinoline **163** was converted to the C9-amino aporphine **159** in 35% yield following Scheme 26; starting material was recovered.

Scheme 30: Synthesis of Amino Aporphine

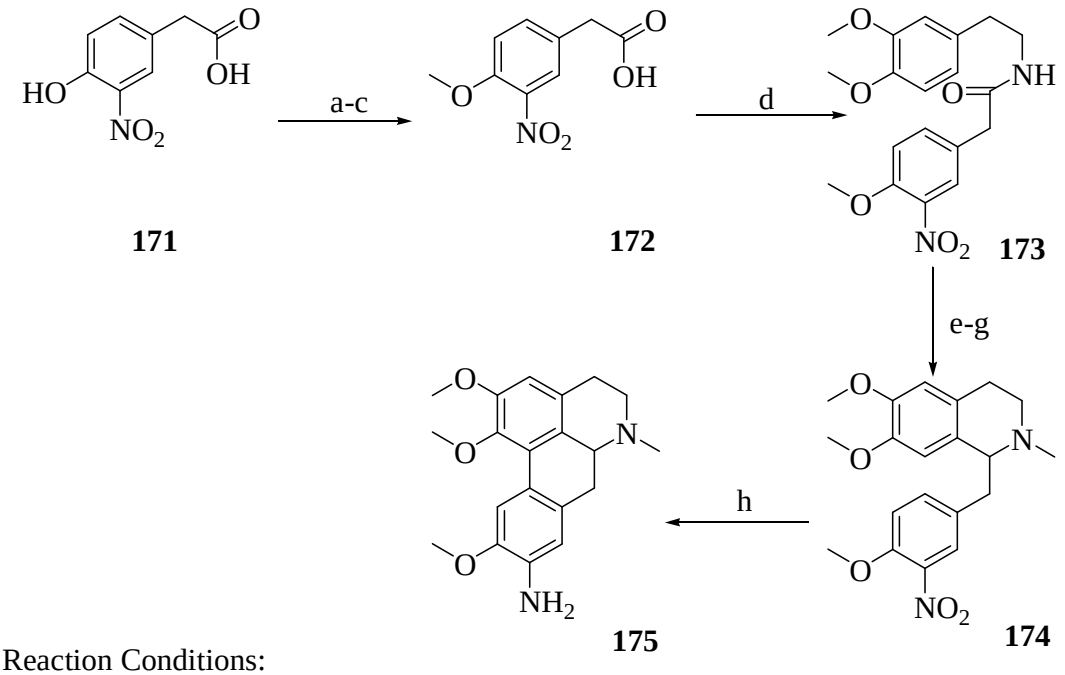


163 **159**

2.1.10.1. Reductive Phenylation: Synthesis of Anilino Aporphines Analogues

The reductive phenylation was subsequently used to prepare the C10-methoxy-C9 amino aporphine analogue **175** (Scheme 31). Compound **174** was prepared in 17% over 7 steps. From **174**, compound **175** was obtained in 38% yield.

Scheme 31: C-10 methoxy C-9 amino analogues Synthesis

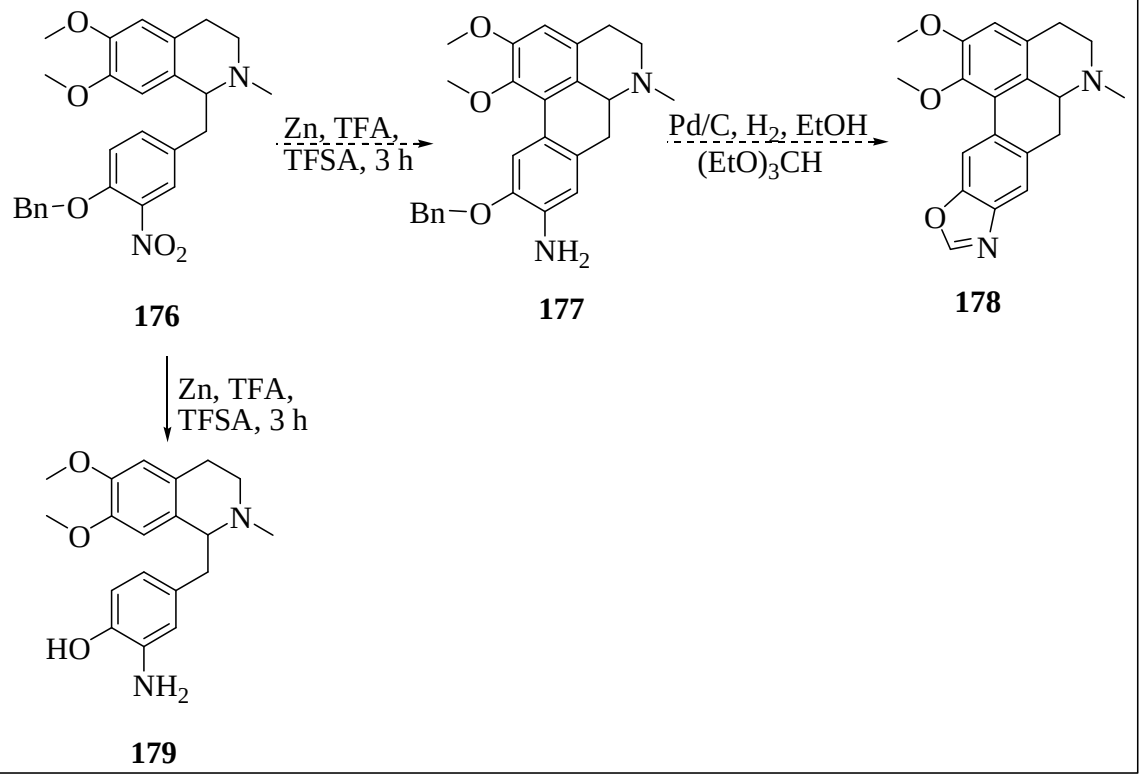


171 **172** **173** **174** **175**

Reaction Conditions:
a) H_2SO_4, MeOH, reflux 96% b) K_2CO_3, MeI, Acetone, reflux, 24 h, 93%
c) 2N NaOH, MeOH, 88% d) 8, CDI, THF, 50% e) $POCl_3$, DCM, reflux, 24h 90%
f) $NaBH_4$, MeOH, rt, 2 h, 56% g) HCHO, DCM, $Na(OAc)_3BH$, 24 h, 88%
h) Zn, TFA, TFSA, 3 h, 38%

Compound **177** is an intermediate required for preparation of oxazolidine **178**. Oxazolidine **178** is interesting to study from an SAR perspective since the molecule contains a bioisosteric replacement of the methylenedioxy functionality of nantenine. An attempt to prepare compound **177** using reductive phenylation was unsuccessful (Scheme 32).

Scheme 32: Attempted Synthesis of C-10 Benzyloxy C-9 Amino Aporphine



176 **177** **178** **179**

Subjecting compound **176** to reductive phenylation conditions did not afford the desired aporphine **177**. ^{1}H NMR analysis identified the isolated product as the C10-hydroxyl-C9-aniline tetrahydroisoquinoline, **179**.

The acidic conditions of the reductive phenylation are tolerated well by methoxy ethers; however, benzyloxy ethers are not tolerated. The benzyloxy protecting group appears to be labile under the acidic conditions of the reductive phenylation. Debenzylation probably occurs

before the reductive phenylation forming a phenol which presumably interferes with the expected biaryl coupling.

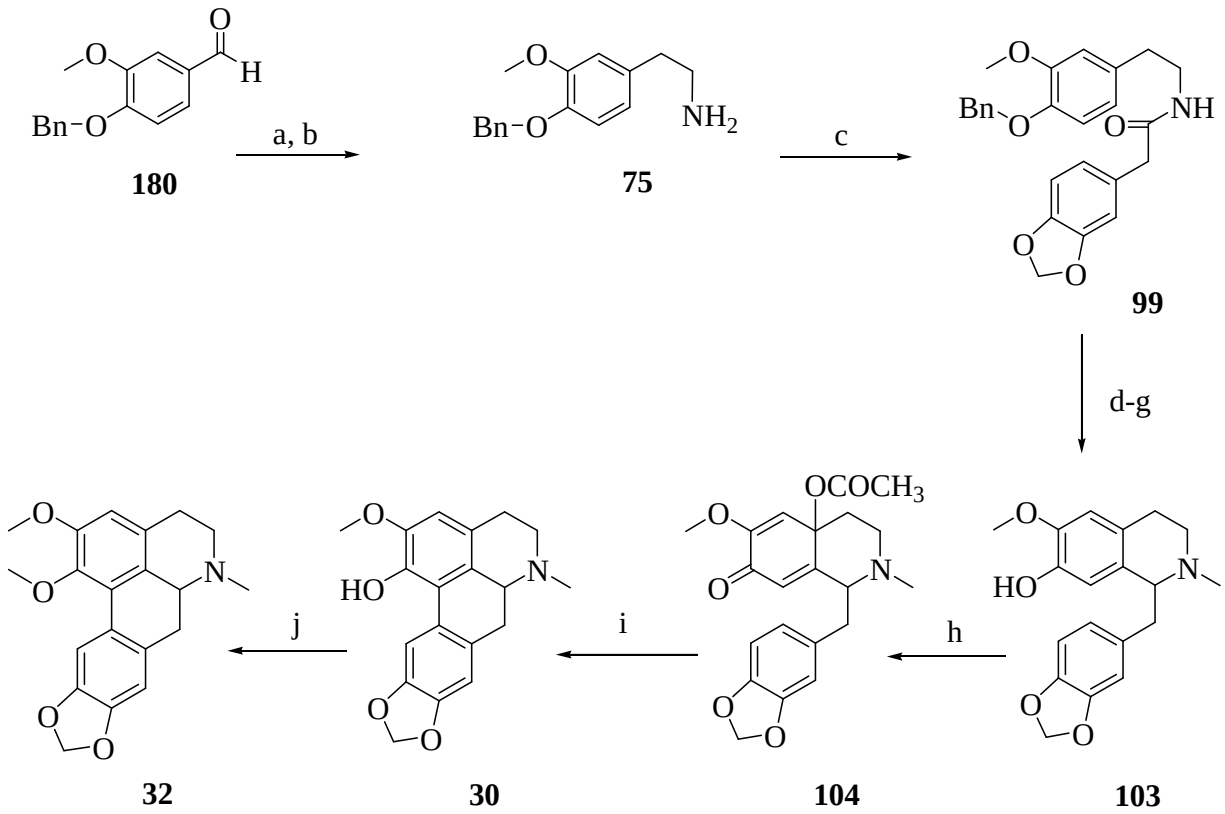
2.2. SYNTHESIS OF NANTENINE VIA THE WESSELY ACETOXYLATION

2.2.1. Synthesis of Nantenine

Our attention was then directed to a phenolic synthesis of nantenine using lead tetraacetate ($Pb(OAc)_4$), to prepare aporphines as reported by Hara.[161,218] $Pb(OAc)_4$ oxidation of phenolic tetrahydroisoquinolines (**103**) was used to prepare the corresponding *p*-quinol acetate (**104**). Subsequent acid treatment converted the quinol (**104**) to the corresponding aporphine (**30**). *O*-methylation afforded (+/-)-nantenine (**32**) in 8% yield over ten steps (Scheme 33).

Overall, the phenolic synthesis of nantenine was a success. However, we did encounter a few problems; using phosphorus oxychloride ($POCl_3$) as the dehydrating agent to prepare the required cyclic imine also caused debenzylation; *O*-methylation of (+/-)-domesticine, **30**, gave very low yields: 30%. Solution of the former problem was achieved by modification of the reaction conditions: phosphorus pentachloride (PCl_5) was used as the dehydrating agent instead of $POCl_3$.[160,161,219]

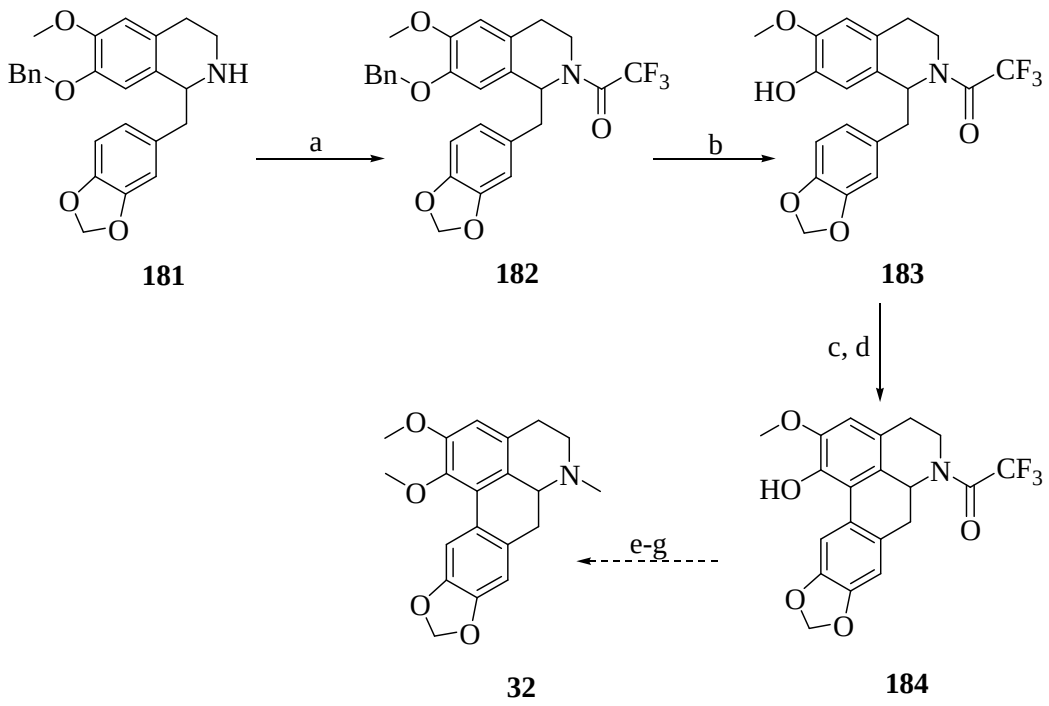
Scheme 33: Synthesis of Nantenine via Wessely Acetoxylation



Reagents and conditions:
a. NO_2CH_3, NH_4OAc, AcOH, 100 ^oC 2h, 99% b. TMSCl, $LiBH_4$, THF, 97%
c. **70**, CDI, THF, 95% d. PCl_5, DCM, 80% e. $NaBH_4$, MeOH, -78 ^oC, 74%
f. HCHO, DCM, $Na(OAc)_3BH$, 78% g. H_2, Pd/C, 90% h. AcOH, $Pb(OAc)_4$
i. TFA, DCM, 73% over 2 steps j. DMF, Toluene, PhenylTrimethyl-Ammonium Chloride, Potassium ^{t}Butoxide, 30%

We contemplated that solving the latter problem could be achieved via synthesis of compound **182** (Scheme 34). This is because the basic conditions required for *O*-methylation of **30** may also cause quaternization of the basic nitrogen of **30** thereby reducing the yield of nantenine. Compound **183** was prepared and subjected to the Wessely acetoxylation (Scheme 34).

Scheme 34: Attempted Synthesis of Nantenine via *N*-acyl Aporphine



Reagents and conditions:
a. K_2CO_3, Trifluoroacetic anhydride, DCM, 90% b. H_2, Pd/C, 95% c. AcOH, $Pb(OAc)_4$, 90% d. TFA, DCM, 26% e. NaH, MeI, Hexane f. 5% K_2CO_3, MeOH g. $Na(OAc)_3BH$, HCHO, DCM

N-acyl domesticine (**184**) was isolated in 26% yield from the corresponding quinol. The Wessely acetoxylation was not pursued to prepare nantenine and a variety of C1 analogues given the low isolated yield of the acid cyclization step.

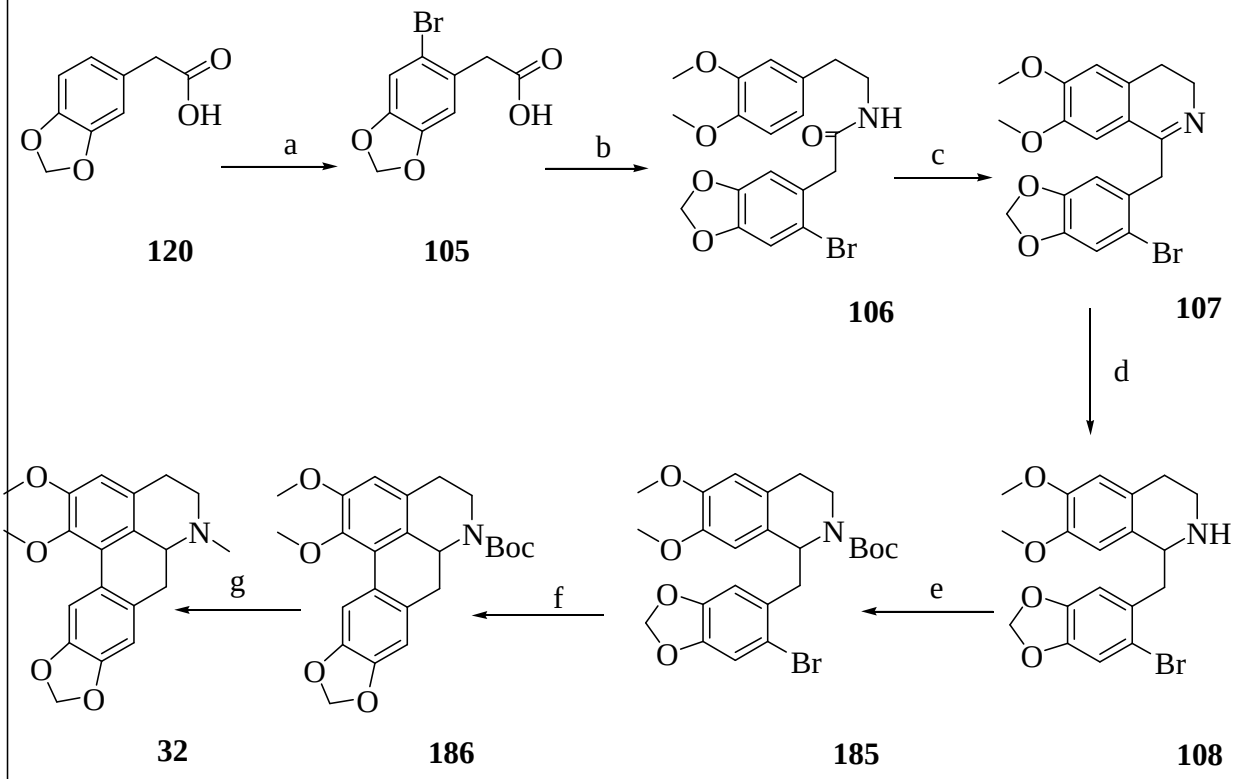
2.3. SYNTHESIS OF NANTENINE VIA DIRECT ARYLATION

2.3.1. Initial Synthesis of Nantenine via Direct Arylation

As an alternative non-phenolic synthesis, the direct arylation protocol was employed (Scheme 35). The key step in this sequence is the biaryl bond formation. Following the protocol

reported by Fagnou, the aporphine core, **186**, was isolated in 40% yield. Optimization of the biaryl coupling and N-deprotection steps of this sequence is important for developing this protocol.

Scheme 35: Direct Arylation Synthesis of Nantenine



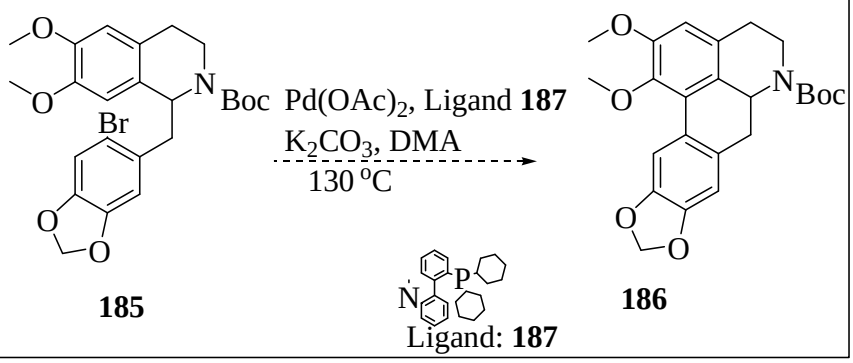
Reagents and conditions:
a. Br_2, AcOH, 77% b. CDI, THF, **65**, THF, 95% c. $POCl_3$, CH_2Cl_2, 88%
d. $NaBH_4$, MeOH, -78^oC, 62% e. $(Boc)_2O$, DMAP, iPr_2EtN, CH_2Cl_2 62%
f. $Pd(OAc)_2$, ligand **91**, K_2CO_3, DMA, 130 ^oC, 40% g. 1. TFA, DCM, rt, 50%
2. HCHO, DCM, $Na(OAc)_3BH$, rt, 85%

2.3.2. Attempts at optimizing the Direct Biaryl Coupling

2.3.2.1. Evaluation of the Fagnou Method

An attempt to cyclize tetrahydroisoquinoline **185** to the aporphine **186** using 2-(dicyclohexylphosphanyl)-2'-(dimethylamino) biphenyl (**187**) as the ligand was unsuccessful. Only starting material was recovered (Scheme 36). It was envisioned that ligand **187** would be an adequate substitute for the ligand used by Fagnou given their structural similarity.

Scheme 36: Direct Arylation with dicyclohexyl ligand



Given that **187** is less expensive and more readily available that the reported ligand **91**, attempts were made to optimize the biaryl coupling reaction conditions using ligand **187**. Table 9 summarizes our attempts. All attempts to prepare compound **186** using ligand **187** were unsuccessful.

Table 9: Biaryl coupling conditions with Ligand **187**

Entry	Precursor	Ligand	Reaction Time	Temperature	Yield: 186
1			24h	130 °C	--
2	**185**	**187**	48h	130 °C	--
3			24h	168 °C	--

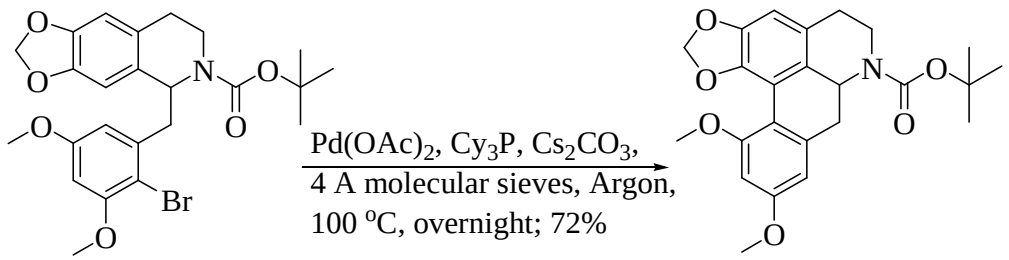
Employing the reported ligand 2-(diphenylphosphanyl)-2'-(dimethylamino) biphenyl (**91**) as the phosphine ligand, **186** was isolated as the major product in 40% yield.

Unfortunately, after three successful trials of this methodology, the reaction was not repeatable. Even after purchasing new reagents and repeating the reaction under the given literature conditions, only starting material was recovered.

2.3.3. Evaluation of the Zhang Biaryl Coupling Protocol for the synthesis of Nantenine

The lack of success using the Fagnou protocol for synthesis of compound **186** could be due to possible oxidation of the phosphine ligand. Zhang has reported the use of tricyclohexylphosphine in the synthesis of substituted aporphine alkaloid (Scheme 37).[154]

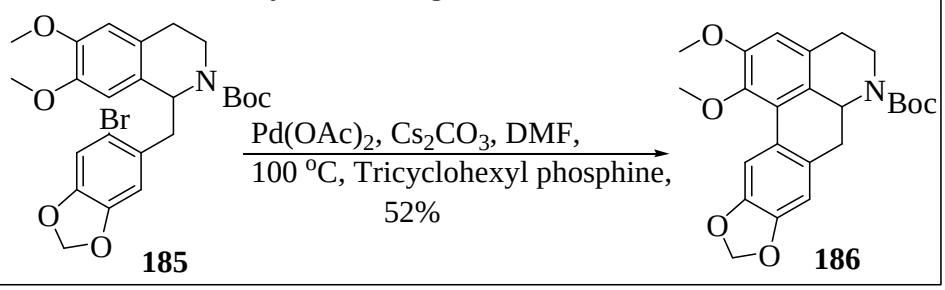
Scheme 37: Synthesis of Aporphine Alkaloids via Zhang Methodology



188 **189**

Changing the reagent cocktail and following the Zhang protocol **186** was isolated in 52% yield consistently (Scheme 38). The Zhang protocol was continued thereafter for the synthesis of a number of nantenine analogues.

Scheme 38: Direct Arylation Zhang Protocol

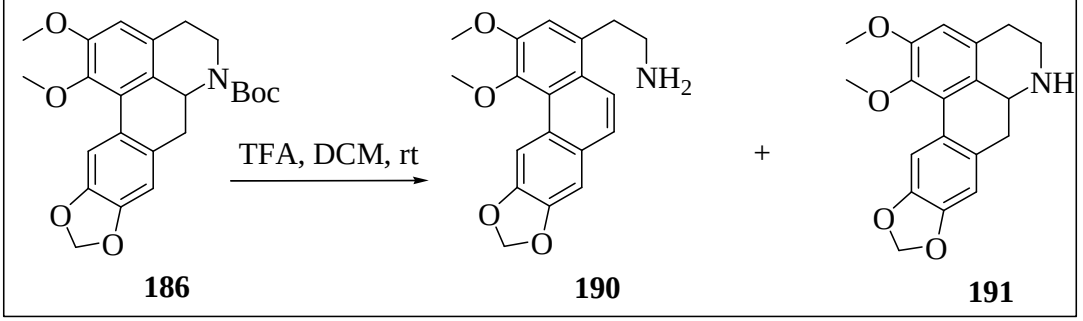


185 **186**

*2.3.4. Conversion of **186** to Nantenine*

Deprotection of aporphine **186** using trifluoroacetic acid (TFA) in dichloromethane at room temperature proved to be problematic: the reaction yielded two major compounds in a 1:1 ratio. NMR and mass spectroscopy analysis identified the products as the desired secondary amine **191** and phenanthrene derivative **190 (**Scheme 39).[154,189,215,216]

Scheme 39: Products of Boc-Deprotection

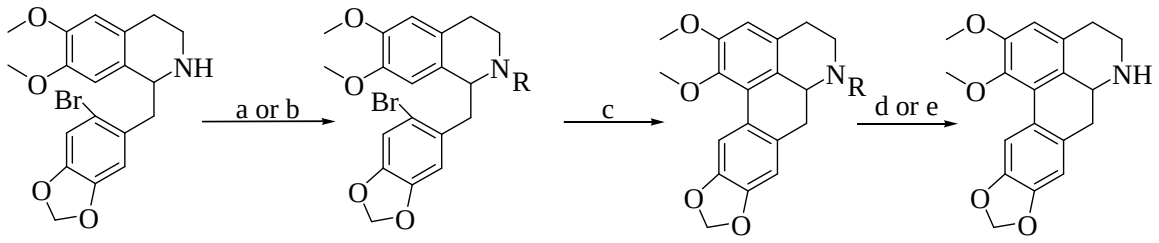


The reaction leading to undesired phenanthrene **190** most likely proceeds through an acid promoted Hofmann-type elimination of a quaternized nitrogen compound.[215] Due to the decreased basicity of the Boc-protected nitrogen, quaternization is unlikely to occur with the nitrogen still protected. Therefore, it is probable that compound **191** first forms in the reaction and is then quaternized by the acid leading to ring opening. Attempts to eliminate compound **190** by decreasing or increasing the amount of TFA used in the reaction was fruitless. Changing the deprotecting agent to 1.0 M HCl in diethyl ether also did not afford **191**. TLC analysis showed only **186** after 24h.

Given the apparent acid sensitivity of **191**, the next step was to prepare *N*-acyl and *N*-Cbz derivatives, which can be deprotected under basic and hydrogenolytic conditions,

respectively.[220-223] Compound **192** and **193** were prepared and subjected to direct arylation to prepare aporphines **194** and **195** (Scheme 40).

Scheme 40: *N*-acyl and *N*-Cbz Tetrahydroisoquinoline synthesis and Zhang Biaryl Coupling



108 | **192** R = $COCF_3$, **193** R = CO_2Bn | **194** R = $COCF_3$, **195** R = CO_2Bn | **191**

Reagents and conditions:
a. K_2CO_3, DCM, 30 min, Trifluoroacetic anhydride, 87% b. CbzCl, Et_3N, DCM, rt, 80%
c. $Pd(OAc)_2$, PCy_3, Cs_2CO_3, 4 A molecular sieves, Ar, DMF, 100 ^oC, overnight, **192**: 33.1%, **193**: 38% d. K_2CO_3, MeOH, 0 % e. H_2, Pd/C, MeOH, rt, 10 %

Following the Zhang protocol, the *N*-Cbz and *N*-acyl substrates provided the corresponding aporphine core in lower yields as compared to the *N*-Boc substrate. Results of the subsequent deprotection steps are presented in Table 10.

Table 10: Direct Biaryl Coupling and De-protection methods

Entry	Compound	Coupling Method	Aporphine: Yield	De-protection Method	% Yield: 191
1	**193**	**A**	**195 :** 38%	H_2 and Pd/C	10
2	**192**	**A**	**194 :** 33%	K_2CO_3/MeOH	0[b]
3	**185**	**A**	**186 :** 52%	$ZnBr_2$	97
4				TFA	50
5				AcCl/MeOH	30
6				TFA/H_20	40
7				TFA/TFAA	50
8				HCl in Dioxane	0[c]

a: $Pd(OAc)_2$, Cs_2CO_3, DMF, 100 ^oC, Triphenylphosphine
b: Phenanthrene isolated
c: Starting material recovered

While changing the protecting group and the coupling method did afford the aporphine core, deprotection did not afford significant amount of the desired secondary amine. Using a

trifluoroacetamide protecting group afforded 33% of the aporphine core (Table 10, entry 2). Using Cbz as the protecting group afforded 38% of the aporphine core, while deprotection with palladium on carbon afforded only 10% of the desired secondary amine (Table 10, entry 1).

Due to the lack of positive results for deprotection of *N*-acyl and *N*-Cbz aporphines, deprotection of the *N*-Boc group was reinvestigated.[154,224-226] Implementing a Lewis acid based deprotection of carbamates using $ZnBr_2$, the desired secondary amine, **191**, was isolated as the only product in high yield, 92-97%.[227] This was a significant accomplishment since **191** could allow us to prepare nantenine as well as N-analogues.

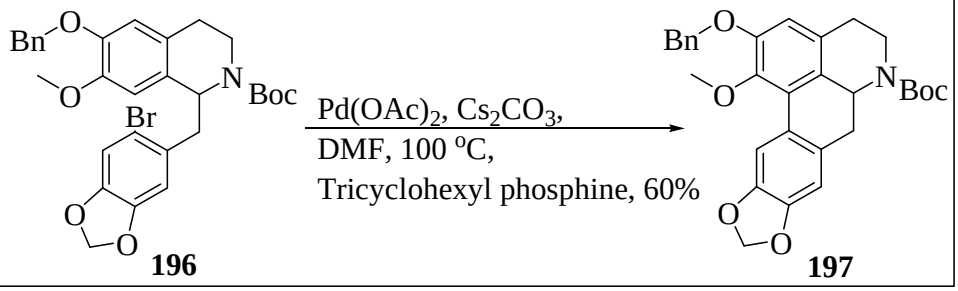
2.3.5. Evaluation of the Use of Microwaves for Direct Biaryl Coupling

Optimizing the synthesis of the key intermediate aporphinoid **186** was essential. Two main methods which utilize direct arylation to prepare aporphines are those developed by the Fagnou group and the Zhang group.[228,229] As mentioned earlier, these methods differ in the cocktail of reagents used for the arylation process. A protocol developed in our lab to synthesize nantenine and C1 analogues by application of a microwave-assisted direct arylation procedure, provided high yields of the aporphine core based on Fagnou's method.[230] This protocol required the use of di-*tert*-butyl phosphine tetrafluoroborate and $Pd(OAc)_2$ in DMA. It was found in these studies that addition of pivalic acid enhanced the isolated yields. Lafrance has determine that the pivalic acid is converted to a pivalate that acts as an intramolecular base by the palladium metal or through an intermolecular deprotonation to create a concerted palladation-deprotonation pathway.[231] The *N*-ethyl carbamate derivative of compound **185** was used as the substrate for the microwave-assisted arylation. While similar to the arylation method developed by the Zhang

group, the biggest disadvantage for the Fagnou protocol is the cost of the phosphine ligand; $101/g. Changing the ligand to the less expensive tricyclohexyl phosphine ($20/g) provided a more economical arylation protocol with similar yields.

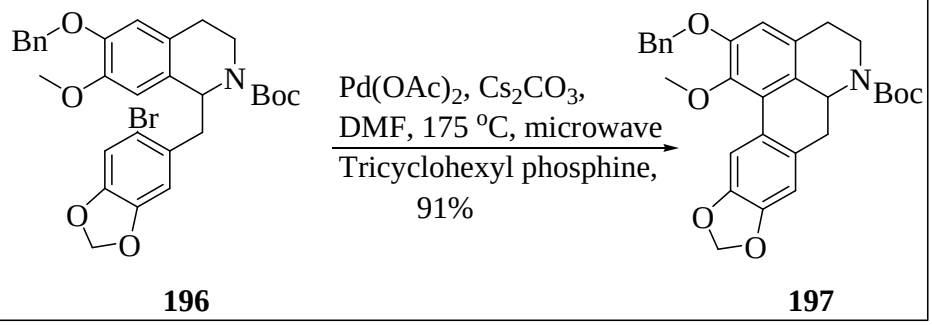
Therefore we decided to investigate the alternative Zhang protocol and to optimize this method if necessary. In attempts to prepare C2 analogues of nantenine, compound **196** was prepared. Subjecting compound **196** to the Zhang cyclization conditions will also determine the substrate scope of the biaryl coupling reaction. Under thermal conditions, the Zhang protocol afforded moderate yield of aporphine **197** from the C2-Benzyloxy tetrahydroisoquinoline, **196**, Scheme 41.[228]

Scheme 41: Synthesis of C2-Benzyloxy Aporphine using Zhang Protocol



Application of the microwave-assisted variation of the Zhang protocol to the synthesis of compound **197** provided consistently high yields of the C2-benxyloxy aporphine core without the need for pivalic acid (Scheme 42).

Scheme 42: Microwave-assisted Synthesis of C2-Benzyloxy Aporphine



DISCUSSION

During the course of our work in studying the PIFA reaction, Pingeaw published findings on his study of the reaction.[232] This aspect of the project was thus discontinued. Reactions involving *para*-substituted phenol ethers with PIFA in HFIP are known to successfully attain biaryl coupling.[198,199] Pingeaw studied the oxidative biaryl coupling of various *N*-substituted 1-benzyltetrahydroisoquinolines to the corresponding aporphines by PIFA. They have suggested that the *p-p* coupling via a six-membered transition state is a required first step in the mechanism.

Pingeaw claims that the PIFA-mediated biaryl coupling mechanism depends on the substituted pattern of the tetrahydroisoquinoline. Radical cations bearing alkoxy substitution *para* to the site of ring closure in the A-ring as in (Figure 41). **C** then leads to a direct *p-p* mechanism via a six-membered transition state, **D**.

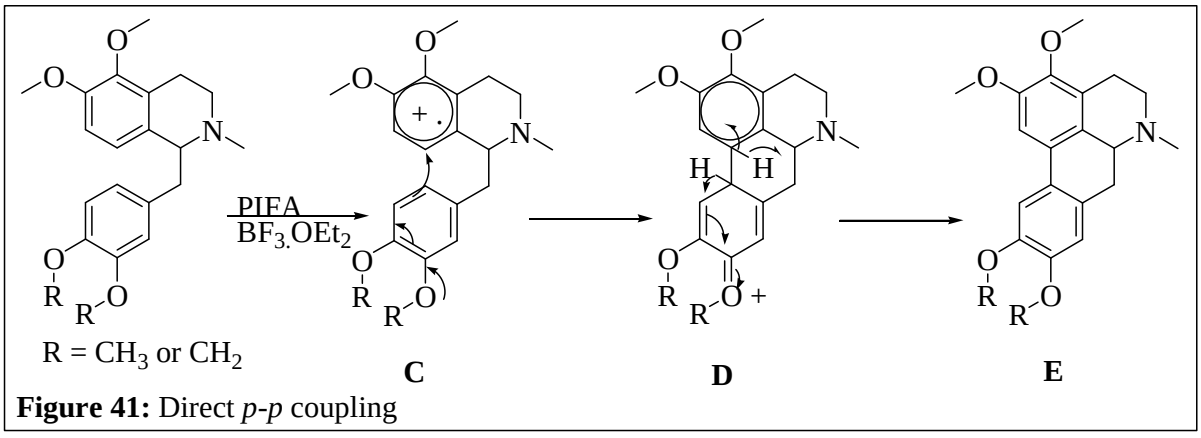


Figure 41: Direct *p-p* coupling

Alkoxy substitution *meta* to the site of ring closure on the A-ring leads to a bridgehead *p-p* mechanism (Figure 42). More complex than the direct *p-p* coupling mechanism, the bridgehead *p-p* coupling mechanism also occurs through a six-membered transition state to form a

morphinandienone intermediate, **H**. The first aryl migration leads to a proerythrinadienone intermediate **I**. A second aryl migration affords the aporphine, **K**.

Pingeaw has concluded that the PIFA reaction mechanism occurs through *p–p* coupling involving a six-membered transition state in the initial step and depends on the substitution pattern of the methoxy groups on the aromatic ring and the nature of the substituents on the nitrogen.

Our brief study on the PIFA-mediated biaryl coupling suggests that having an electron-donating group *para* to the site of biaryl coupling is essential for adequate cyclization. Substrates bearing substituents *para* to the site of ring closure on the A-ring provides significantly higher yields of the corresponding aporphine. Our results are in line with and add support to Pingeaw's conclusions. Given the substrate limitation of the PIFA-mediated biaryl coupling, this method was not further pursued to prepare analogues of nantenine.

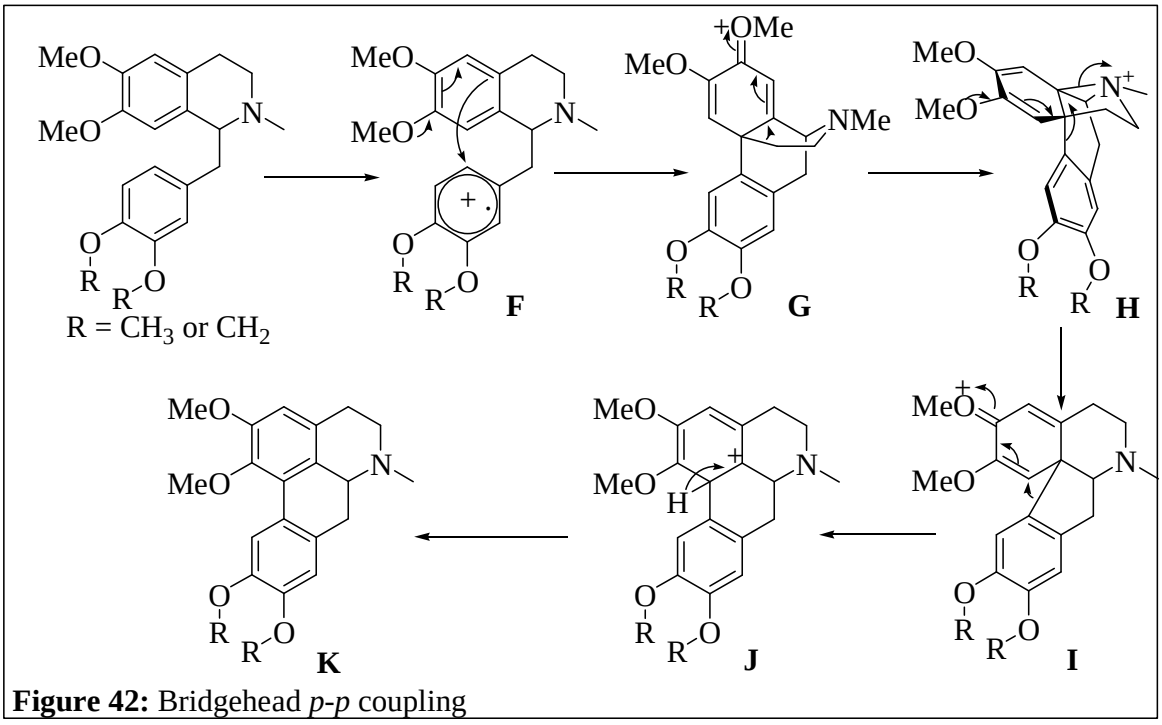


Figure 42: Bridgehead *p-p* coupling

The Wessely Acetoxylation is a successful method to prepare domesticine. However, due the basic nitrogen the reagent conditions used for *O*-methylation to prepare nantenine do not provide a significant yield. While protecting the nitrogen as an *N*-acyl provides a way to *O*-methylate using standard methylation condition, low yields for the conversion of the *N*-protected quinol to the corresponding aporphine forced us to consider alternative methods to prepare nantenine and C1-analogues. A plausible mechanism for the Wessely Acetoxylation is depicted in Figure 43.

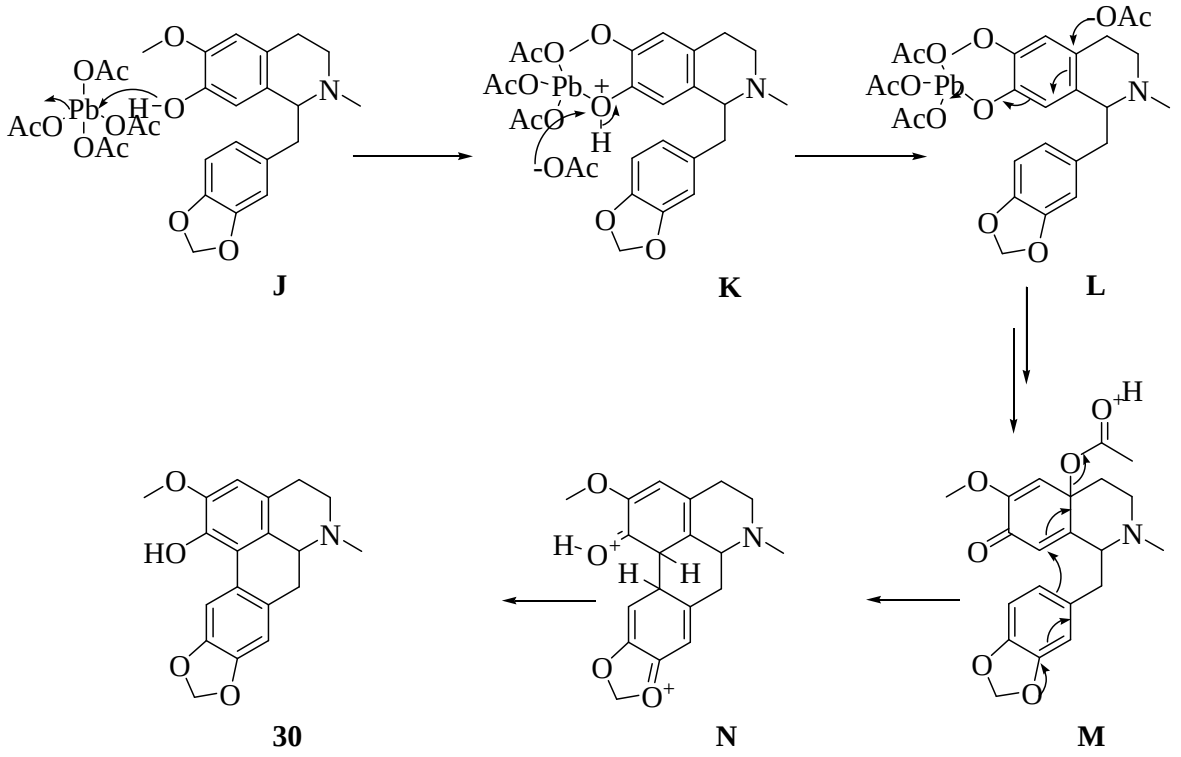


Figure 43: Possible Wessely Acetoxylation Mechanism

Direct arylation has proven to be the most versatile synthetic pathway to prepare nantenine and several classes of structural analogues. Incorporating microwaves to the biaryl coupling have provided a novel method to prepare the aporphine core in high yields.

Direct arylation was widely believed to occur through an electrophilic aromatic substitution, S_EAr. However, recent reports have claimed that palladium-catalyzed arylation reactions are facilitated by electron-withdrawing substituents on the aromatic ring, which is inconsistent with an S_EAr mechanism.[233]

Studies conducted by Garcia-Cuadrado on the intramolecular palladium-catalyzed arylation of bromobenzyldiarylmethane systems have determined that the mechanism of direct arylation occurs through a proton-abstraction.[234] The key feature of the proton abstraction mechanism is the concerted bond forming and bond breaking of a metal—carbon bond and the carbon—hydrogen bond, respectively, with the hydrogen being transferred to a basic ligand (Figure 44). Three possible mechanistic pathways can occur to form the organopalladium complex and preference for one mechanism is substrate dependent.[235]

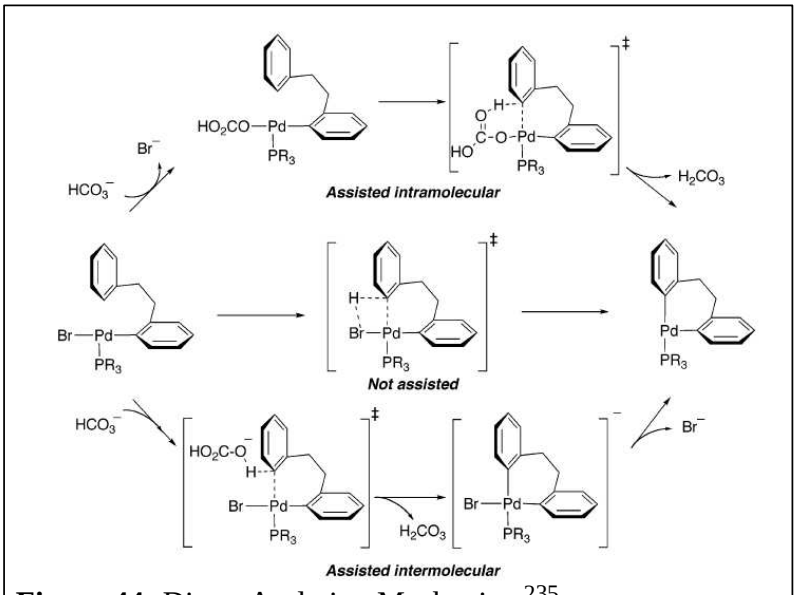


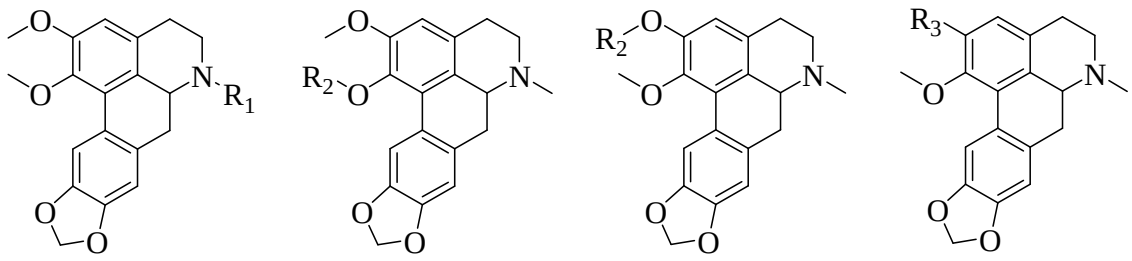
Figure 44: Direct Arylation Mechanism[235]

We have successfully achieved goal (1) (stated on page 47) using the direct arylation protocol to prepare nantenine in consistent yields. In the upcoming chapters, I will describe the approach taken to achieve goals (2) and (3).

CHAPTER IV: SYNTHESIS OF NANTENINE ANALOGUES

1. INTRODUCTION

SAR studies of nantenine require the synthesis of various structural analogues. These analogues will determine the relative role and tolerance of each position in nantenine's anti-MDMA activity. For this study, modification of the *N*-, C1- and C2-positions was conducted to determine the roles of each position. Four classes of target analogues are depicted in Figure 45.



198 **199** **200** **201**

R_1 = Et, Propyl, Butyl, Pentyl, CypMe
R_2 = H, Et, Propyl, Butyl, Pentyl, CypMe. Benzyl
R_3 = Et, Propyl, Butyl, Pentyl, Anilino, Cyclohexyl Amine, BenzylAmine

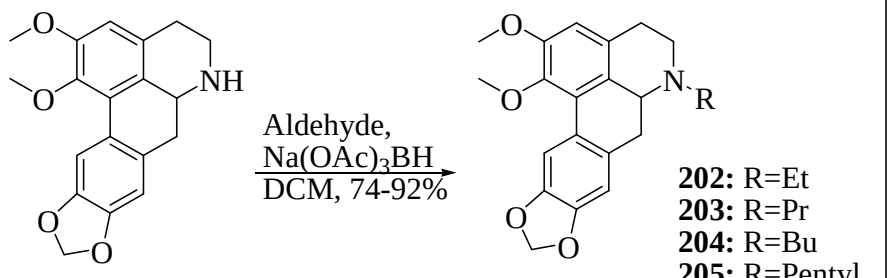
Figure 45: Target Analogue via Direct Arylation Protocol

Having optimized the direct arylation protocol to prepare nantenine, the next step was to prepare various structural derivatives of nantenine. Using direct arylation to prepare nornantenine (**191**) provided access to various *N*-analogues. Given that the C2-benzyloxy tetrahydroisoquinoline substrate was stable in the microwave-assisted Zhang biaryl coupling protocol, this method was utilized to prepare various C1 and C2 analogues.

2. SYNTHESIS OF ANALOGUES: N-ALKYL ANALOGUES

Using reductive amination with the appropriate aldehydes, several *N*-analogues were prepared in 74-92% yield (Scheme 43).

Scheme 43: Synthesized Nantenine *N*6 Analogues



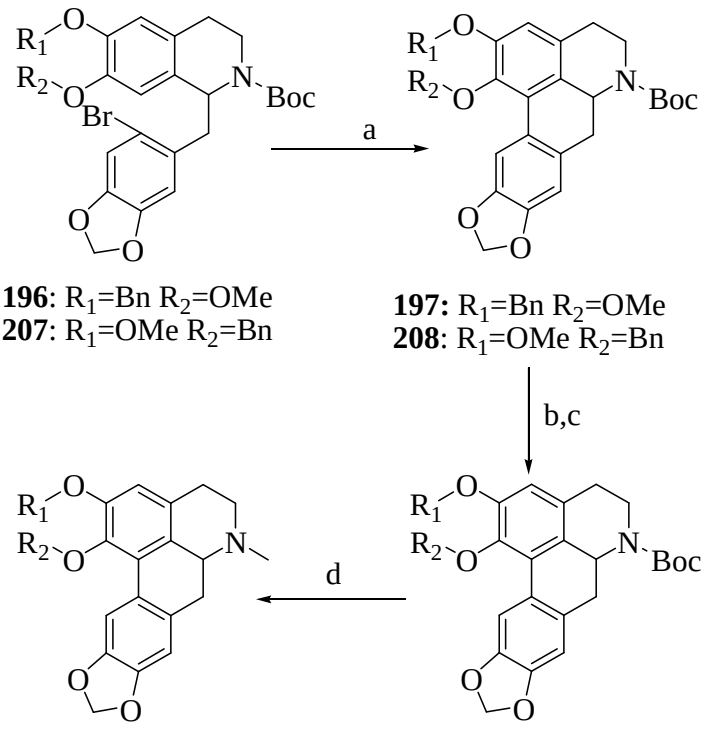
191

202: R=Et
203: R=Pr
204: R=Bu
205: R=Pentyl
206: R=CypMe

2.1. SYNTHESIS OF ANALOGUES: ALKOXY ANALOGUES

Using benzyloxy protected C1 phenethylamine **75** and the C2 variation, tetrahydroisoquinolines **207** and **196** were prepared (Scheme 44). Using microwaves, **208** and **197** were isolated in 90% and 92% yield, respectively. C1 and C2-alkoxy analogues, **211**-**223**, were prepared in 24-59% yield over three steps by etherification of the corresponding phenols, **210** and **209** using the appropriate alkyl bromide, potassium iodide and potassium carbonate in acetone refluxing overnight followed by deprotection and methylation (Scheme 44).[236,237]

Scheme 44: Synthesis of C1 and C2 analogues



196: R_1=Bn R_2=OMe
207: R_1=OMe R_2=Bn

197: R_1=Bn R_2=OMe
208: R_1=OMe R_2=Bn

209: R_1=H R_2=OMe
210: R_1=OMe R_2=H

211: R_1=Et; R_2=Me
212: R_1=Pr; R_2=Me
213: R_1=Bu; R_2=Me
214: R_1=Pen; R_2=Me
215: R_1=MeCyp; R_2=Me
216: R_1=OH; R_2=Me
217: R_1=Bn; R_2=Me
218: R_1=Me; R_2=Et
219: R_1=Me; R_2=Pr
220: R_1=Me; R_2=Bu
221: R_1=Me; R_2=Pen
222: R_1=Me; R_2=Bn
223: R_1=Me; R_2=MeCyp

Reagents and conditions:
a. $Pd(OAc)_2$, Cs_2CO_3, DMF, 175 ^oC, Tricyclohexyl phosphine **196**: 92%, **207**: 90%
b. Pd/C, H_2, EtOH **209**: 90%, **210**: 95% c. 1. Alkyl bromide, KI, K_2CO_3, Acetone,
d 1. $ZnBr_2$, DCM, 2. HCHO, $Na(OAc)_3BH$, DCM, 24-59% over three steps

2.2. SYNTHESIS OF ANALOGUES: C2-ALKYL AND AMINO ANALOGUES

C2-aryl triflate, **231** (Scheme 45), is an integral intermediate in the synthesis of C2-alkyl and amino analogues. It was envisioned that various coupling methods may be employed to prepare alkyl and amino target analogues in Figure 46. These analogues will provide

information concerning the effect of increasing the lipophilicity at C2 as well as the tolerance for alkyl and amino substituents at the C2 position.

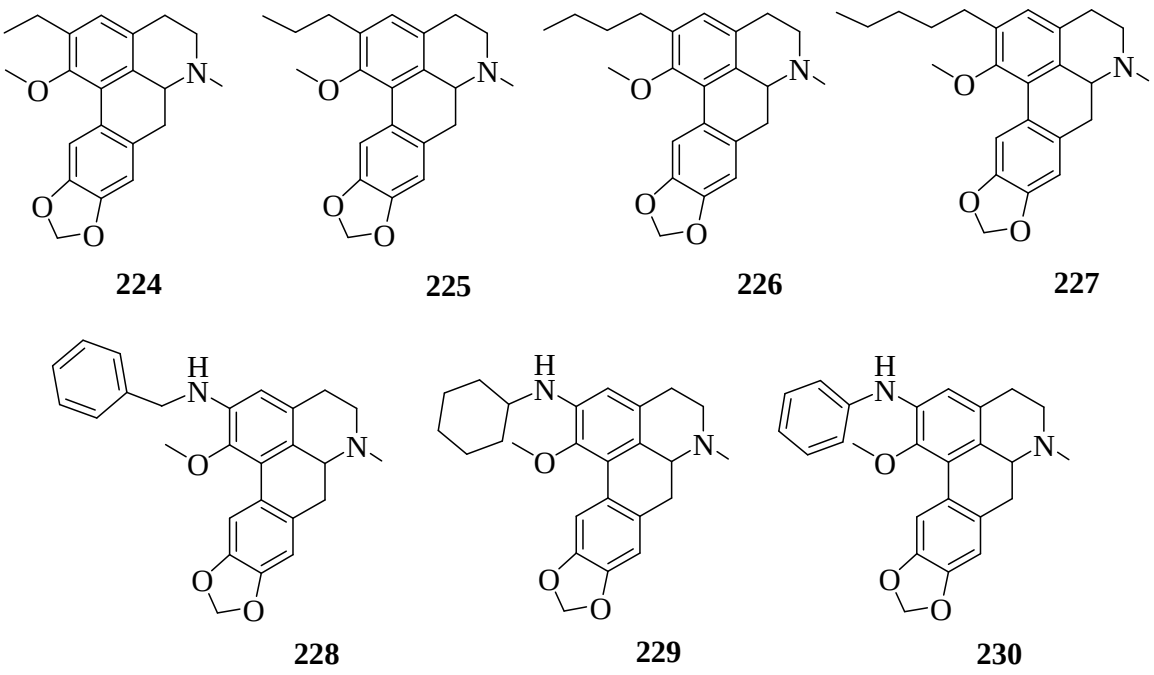


Figure 46: C2 Target Analogues

2.2.1. Suzuki Reaction

The Suzuki reaction has been used to construct biaryl bonds in high yields using an aryl halide with an aryl boronic acid.[164,238] However, using the Suzuki reaction to add alkyl groups to an aryl ring are more difficult and substrate dependent. Recently, there have been reports using Nickel-catalyzed Suzuki coupling with alkyl halides and aryl boronic acids.[239]

Kirchhoff has demonstrated that when using a palladium-catalyzed Suzuki coupling use of a Lewis basic additive such as potassium *tert*-butoxide in *tert*-amyl alcohol gives high yields of the alkylated product.[240] Also, the structure of the phosphine ligand affects the outcome of the reaction; the lower the steric demand of the phosphine, the higher the yield. Hedberg has shown

that palladium-catalyzed Stille coupling of vinylstannanes with aporphine aryl triflates can be utilized to prepare alkylated aporphine analogues via hydrogenation of the corresponding vinyl substituent.[241]

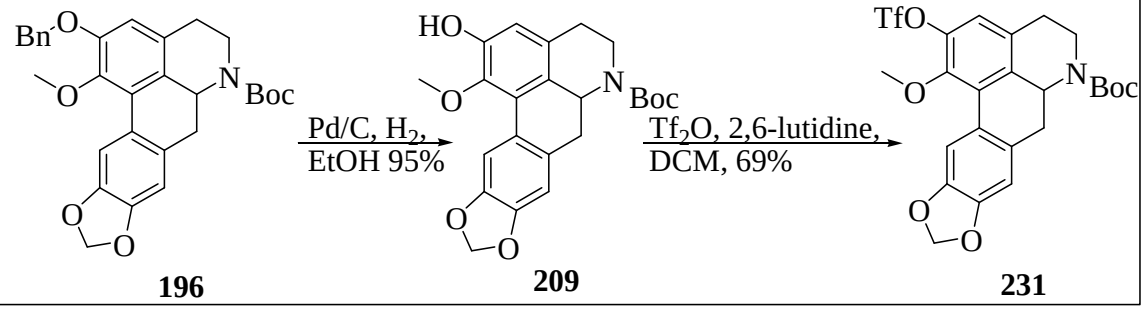
Currently there are no reported Suzuki reactions using alkyl boronic acid with aporphines aryl triflates. The result of this portion of our project may present an area of novelty in structural modification of aporphine alkaloids.

2.2.2. Synthesis of Alkyl Analogues via the Suzuki Reaction

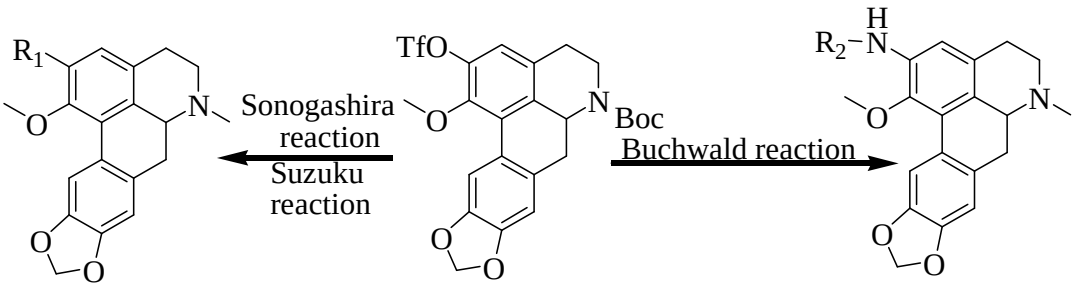
It was envisioned that the C2 triflate **231** could be used to prepare C2 alkyl nantenine analogues via a Suzuki reaction. A modification of the Suzuki coupling reported by Sondergaard, using an aryl triflate instead of an aryl halide, was the starting point for this undertaking.[242]

Preparation of the C2 analogues began by hydrogenolysis of compound **196** to prepare the corresponding phenol **209**, which was isolated in 95% yield. Compound **209** was then converted to the triflate **231** (Scheme 45).[243] Triflate **231** was isolated in 69% yield.

Scheme 45: Synthesis of Triflate



Compound **231** is a required intermediate in the preparation of several classes of C2 analogues (Figure 47).

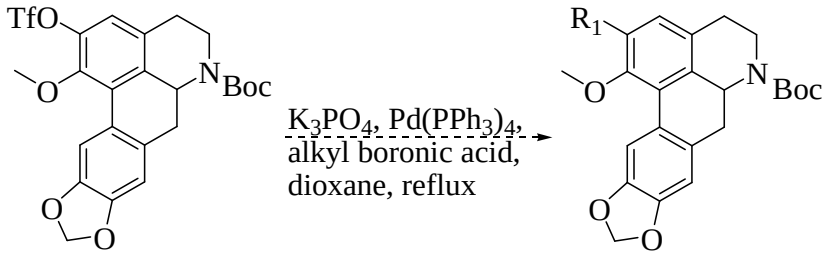


224-227 **231** **228-230**

Figure 47: C2 Analogues Prepared from Aryl Triflate

The Suzuki reaction was employed in an attempt to prepare C2-ethyl, -propyl and -isopropyl analogues (Scheme 46). Only starting material was isolated under these conditions.

Scheme 46: Synthesis of Alkyl Analogues by Suzuki Reaction

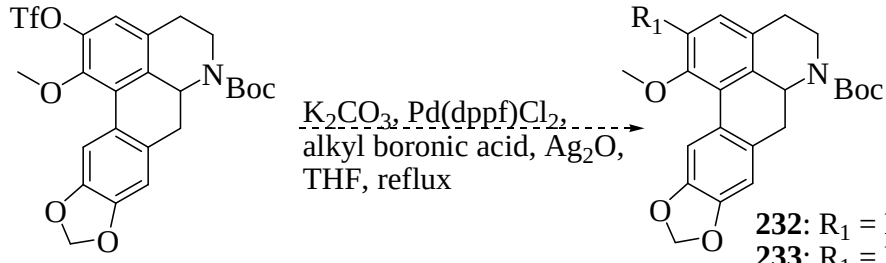


231

232: R_1 = Et
233: R_1 = Propyl
234: R_1 = Isopropyl

Zou has claimed that addition of silver (I) oxide can promote Suzuki coupling reactions with alkyl boronic acids.[244] Scheme 47 was therefore attempted. The desired alkyl products were not prepared.

Scheme 47: Synthesis of Alkyl Analogues by Suzuki Reaction with Silver (I) Oxide



231

232: R_1 = Et
233: R_1 = Propyl
234: R_1 = Isopropyl

In hopes of improving the outcome of the Suzuki reaction, microwaves were applied to the reaction protocol in Schemes 46 and 47 (Table 11, entry 1 and 3, respectively). Changing the solvent to toluene or DMF and reaction temperature to refluxing conditions or microwaves did not afford the alkylated compounds **232-234** (Table 11, entry 2, 4 and 5, respectively). Reaction conditions undertaken for the Suzuki reaction are summarized in Table 11. Alternative methods for preparing alkyl analogues **232-234** via **231** were therefore considered.

Table 11: Suzuki reaction attempts with alkyl boronic acids

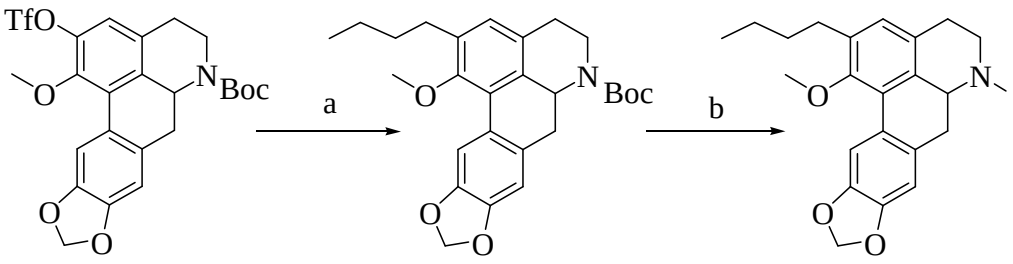
Entry	Triflate	Catalyst	Additive	Tempt	Boronic Acid	Solvent	% Yield
1	**231**	$Pd(PPh_3)_4$	--	Reflux	Et, Pr, *i*Pr	Dioxane	0
2		$Pd(PPh_3)_4$	--	Reflux	Et, Pr, *i*Pr	Toluene	0
3		$Pd(dppf)Cl_2$	Ag_2O	Reflux	Et, Pr, *i*Pr	THF	0
4		$Pd(dppf)Cl_2$	Ag_2O	Reflux	Et, Pr, *i*Pr	DMF	0
5		$Pd(dppf)Cl_2$	--	μwave	Pr	DMF	0

a: K_3PO_4 used in each reaction

Wang reported the use cesium acetate (CsOAc) to promote the Suzuki–Miyaura cross-coupling reaction under anhydrous conditions with similar effectiveness as stronger bases. The use of aryl triflates also exhibited reaction rates comparable to that of bromoarenes.[150,245]

Compound **226** was prepared using a modified Suzuki reaction reported by Wang (Scheme 48).[245] The reaction did not go to completion with the initial condition attempted. Adjusting the reagent equivalents and the reaction time afforded higher yields of **226**. Under microwave conditions, compound **226** was prepared in 89% yield based on recovered starting material. Subsequent *N*-deprotection and *N*-methylation of **235** gave the C2 butyl analogue **226**. Optimization of the modified Suzuki reaction is presented in Table 12.

Scheme 48: C2 Butyl Synthesis



231 **235** **226**

Reagents and conditions:

a. $Pd(dppf)Cl_2$, CsOAc, Bu_3B, DMF, mwave, 10 min 175 ^oC, 89%

b. 1. $ZnBr_2$, DCM, 97% 2. HCHO, $Na(OAc)_3BH$, DCM, 70%

Table 12: Optimization Conditions for the Suzuki reaction with Tributyl Borane

Entry	Compound	Temperature	Time (min)	Equivalents Base	Catalyst	n-Bu_3B	Yield
1	**231**	120	10	2	0.2	2	38%
2		120	30	2	0.2	2	38%
3		175	60	6	0.6	6	89%

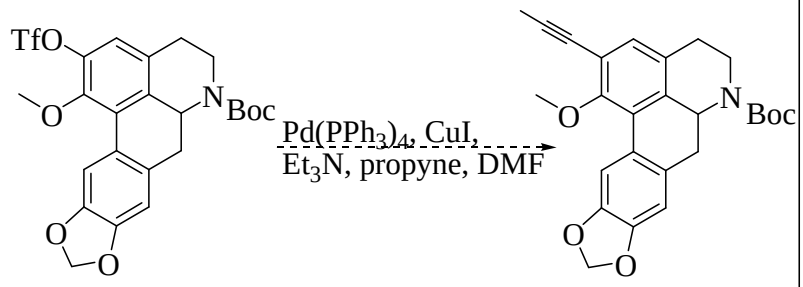
All reactions conducted using microwave conditions

The limited success using the Suzuki reaction to prepare C2 alkyl analogues prompted us to consider other options such as the Sonogashira route described henceforth.

2.2.3. Sonogashira reaction

Ortar has shown that the Sonogashira reaction can be utilized to prepare alkylated aromatics from aryl triflates.[246] Triflate **231** was subjected to the Sonogashira reaction with propyne (Scheme 49).

Scheme 49: Attempted Sonogashira reaction with propyne

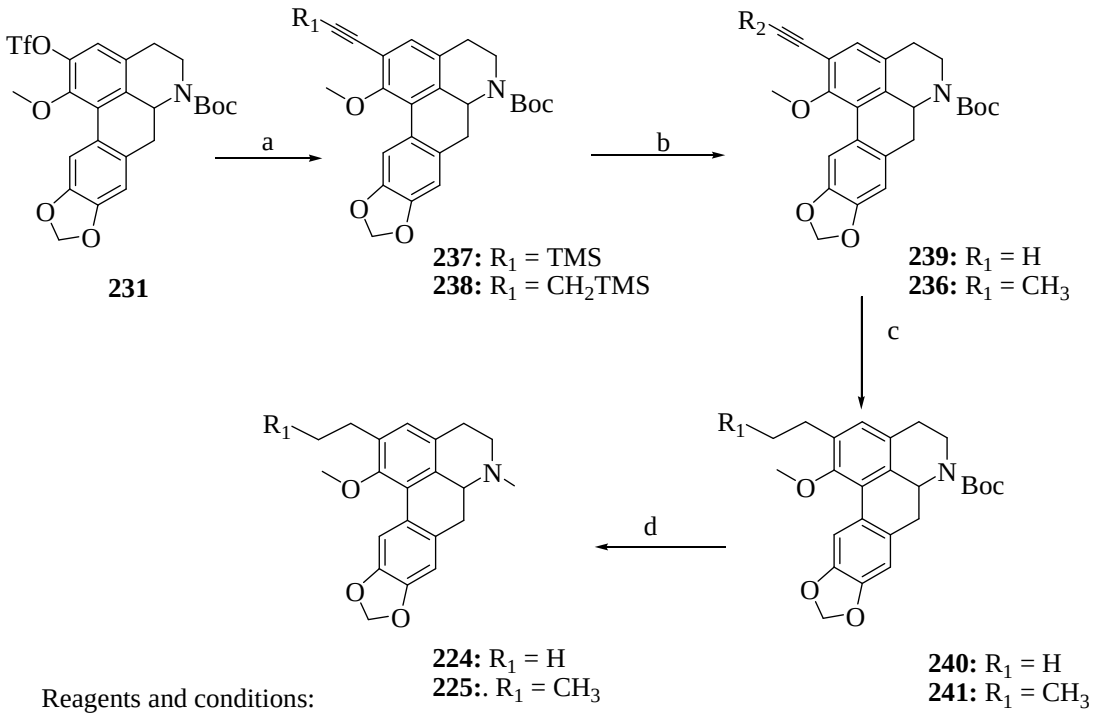


231 **236**

Since propyne is a gas, there were initial concerns the reaction would not give the desired product due to the heterogeneous reaction mixture. There are current literature reports that indicate DMSO can be saturated with propyne.[247] Crisp has also showed the feasibility of using DMF as the solvent in the Sonogashira reaction.[248,249] Unfortunately, only starting material was isolated using these conditions. To deal with the solubility of propyne in DMF, TMS-substituted acetylene was used to prepare a homogeneous reaction mixture.[250-252] The reaction was conducted under microwave conditions to prepare compounds **237** and **238** (Scheme 50).

Employing microwaves provided access to the TMS-acetylene and TMS-propargyl products in good yield. Removing the silyl group using TBAF in THF afforded the acetylene **239** and propyne **236** in 69% and 80% yield, respectively. Hydrogenation afforded the Boc-protected alkyl products **240** and **241**. Boc-deprotection and methylation afforded the C2-ethyl and propyl analogues **224** and **225** respectively.

Scheme 50: Sonogashira reaction with TMSacetylene and TMSpropragyl: TMS deprotection



Reagents and conditions:

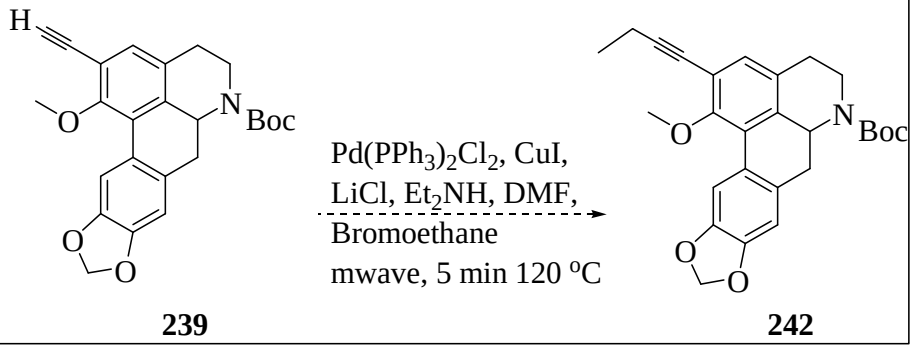
a. $Pd(PPh_3)_2Cl_2$, CuI, LiCl, Et_2NH, DMF, µwave, 5 min 120 ^oC **237**: 76% **238** : 73%

b. TBAF, THF, 5 min **239** : 69% **236**: 80% c. Pd/C, H_2, EtOH **240** : 88% **241** : 90%

d. 1. $ZnBr_2$, DCM 2. HCHO, $Na(OAc)_3BH$, DCM, **224** : 46% over two steps **225** : 52% over 2 steps

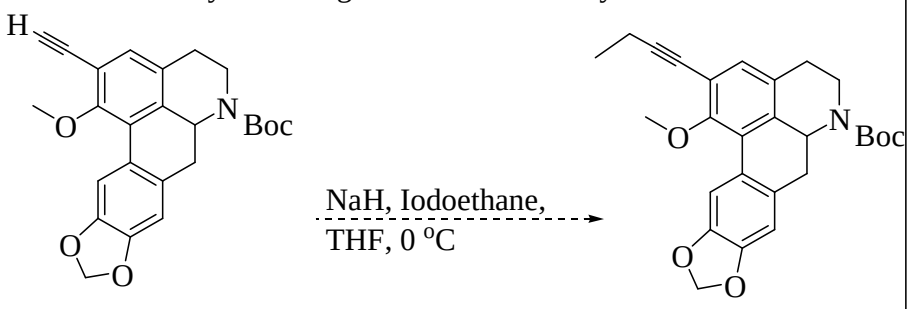
We anticipated that **239** could serve as a substrate to prepare higher alkyl homologues at C2. In attempts to prepare the C2 n-butyl analogue, we first subjected compound **239** to the Sonogashira reaction with bromoethane (Scheme 51).

Scheme 51: Acetylene homo-elongation



The ^{1}H NMR spectrum of the compound isolated was not in agreement with expected data. While the peak for the acetylene proton was absent, there were no peaks that were attributable to the ethyl group. Thus, a different method to prepare the n-butyl analogue via formation of the acetylide anion with sodium hydride was attempted (Scheme 52).

Scheme 52: Acetylene elongation with sodium hydride



239 **242**

Compound **242** was not prepared using Scheme 48; only starting material was isolated after 24h reaction time. Caubere has argued that adding HMPTA (hexamethylphosphorotriamide) to sodium hydride reactions can accelerate acetylene deprotonation to promote coupling reactions by stabilizing the charged intermediate.[253] Incorporating the additive HMPTA and changing the solvent to DMF did not afford the alkylated product; only starting material was isolated. Results of the alkylation attempts are listed in Table 13.

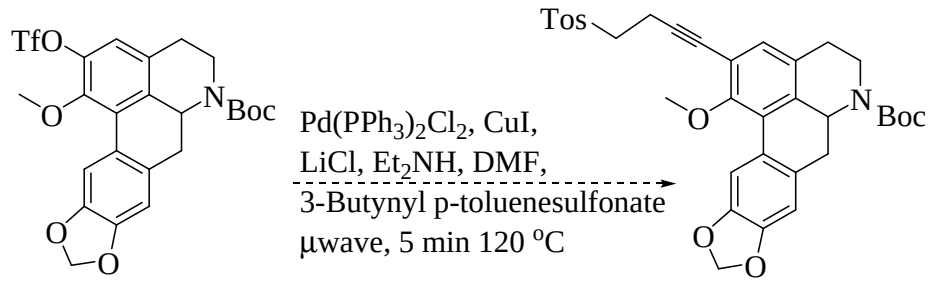
Table 13: Alkylation of Acetylene

Entry	Compound	Conditions	Solvent	Additive	Alkyl Halide	Temp	%Yield 242
1	**239**	Sonogashira	DMF	--	EtBr	μwave	0
2		NaH	THF	--	EtI	0 °C—rt	0
3		NaH	THF	HMPTA	EtI	0 °C—rt	0
4		NaH	DMF	--	EtI	0 °C—rt	0

Due to the inability to alkylate the acetylene with standard condition, the Sonogashira reaction was then attempted on triflate **231** using 3-Butynyl p-toluenesulfonate to prepare **243**

(Scheme 52). It was anticipated that solvolysis of the tosyl group would afford the butynynyl derivative.[254]

Scheme 52: Alternative Butyne Synthesis

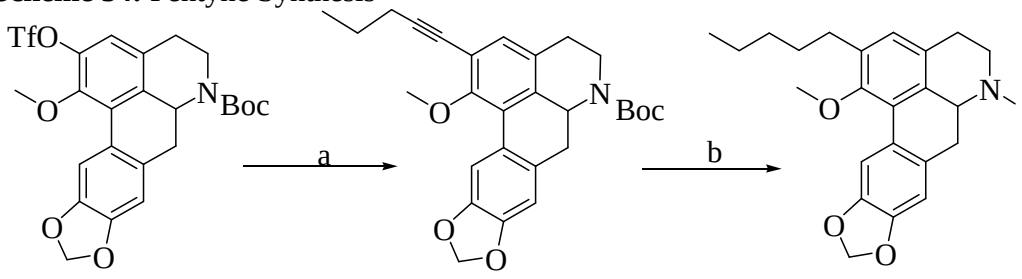


231 **243**

Subjecting triflate **231** to the Sonogashira conditions did not result in the coupled product **243**: only starting material was recovered (Scheme 53).

The pentyne analogue, **244**, was also prepared using the Sonogashira reaction in 81% yield (Scheme 54). Boc deprotection with $ZnBr_2$ and reductive amination afforded the C2 pentyl analogue, **227**, in 20% yield.

Scheme 54: Pentyne Synthesis



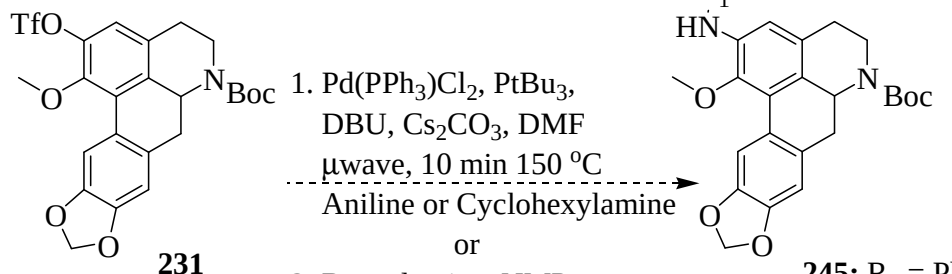
231 **244** **227**

Reagents and conditions:
a. $Pd(PPh_3)_2Cl_2$, CuI, LiCl, Et_2NH, DMF, 1-Pentyne, μwave, 60 min 120 °C, 81 %
b. 1. $ZnBr_2$, DCM, overnight 2. HCHO, $Na(OAc)_3BH$, DCM, overnight, 20 % over two steps

2.2.4. Buchwald-Hartwig Reaction

While microwave-assisted Buchwald-Hartwig reaction has been conducted with aryl triflates, there is currently no literature showing this reaction on aporphine alkaloids. Synthesis of C2 amino analogues was conducted under microwave conditions following a protocol published by Huang and Xu (Scheme 55).[255,256]

Scheme 55: Buchwald-Hartwig Amino Synthesis



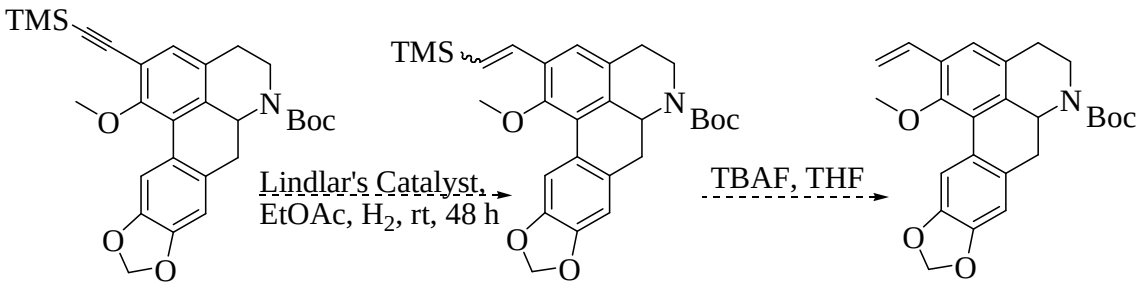
The high polarity of these amino compounds gave problems with purification. An attempt to convert the product to the hydrochloride salt using 1M HCl in diethyl ether was unsuccessful. Converting the amino compounds to oxalate salts as an alternative method of purification was also unsuccessful. ^{1}H NMR of the resulting oxalate showed no peaks corresponding to the aporphine core. No further purification methods were attempted.

2.2.5. Selective Alkyne Reduction and Alkyne Oxidative Cleavage

As an alternative method to prepare structural analogues at the C2-position, we attempted to selectively reduce compound **237** to the TMS-vinyl derivative using Lindlar's catalyst (Scheme 56).[257] The C2-vinyl derivative, **248**, can subsequently be used to prepare analogues

via the Heck reaction. Unfortunately after 48 h, only starting material was isolated from the hydrogenolysis.

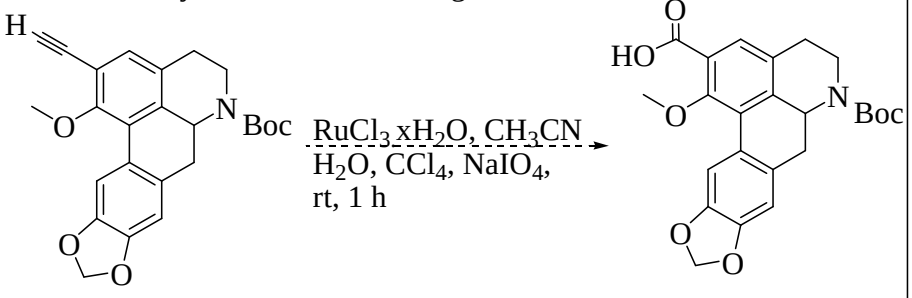
Scheme 56: Selective Alkyne Reduction



237 **248** **249**

Having a carboxylic acid at position C2 also presents the possibility for a biologically interesting class of analogues. Following the published protocol by Griffith, Scheme 57 was employed.[258] Unfortunately, no identifiable compounds were isolated from the reaction. No peaks corresponding to the aporphine core were identified.

Scheme 57: Alkyne Oxidative Cleavage



239 **250**

2.3. PREPARATION OF *R*- AND *S*-NANTENINE

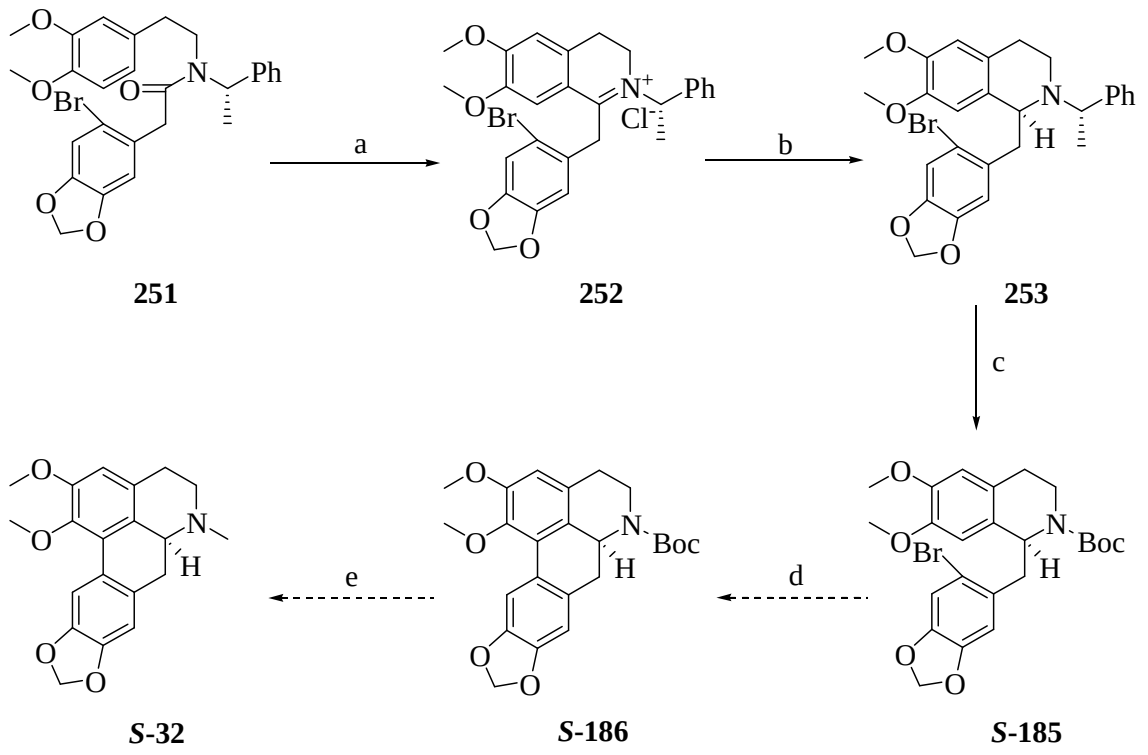
Enantiomers of a biologically active compound may possess different *in vivo* and *in vitro* effects. It is possible that enantiomers can have either a synergistic or dysnergistic biological

effect. Having access to each enantiomer will enable us to determine the biological effect of each enantiomer as well as the racemic mixture. Previously both enantiomers of nantenine were synthesized employing a chiral auxiliary.[169]

2.3.1. Via Chiral Isoquinolinium

An attempt to prepare the *R*- and *S*-enantiomer using a chiral phenethylamine acetamide with the direct arylation protocol was investigated following Scheme 58.

Scheme 58: Enantioselective synthesis via chiral isoquinolinium



Reaction Conditions:
a) $POCl_3$, DCM, 48 h, 83% b) $NaBH_4$, MeOH, -78 ^oC, 77% c) i. Pd/C, H_2, 10% HCl, rt
ii. Boc anhydride, iPr_2EtN, DMAP, DCM, rt d) $Pd(OAc)_2$, Cs_2CO_3, Ms 4A, DMF, PCy_3, 100 ^oC
e) i. $ZnBr_2$, DCM ii. $Na(OAc)_3BH$, DCM

Chiral secondary amine *S*-**132** was prepared in 80% yield over two steps and used to prepare amide **251** in 70% yield.[259] Treatment of **251** with phosphorus oxychloride under reflux

conditions gave the iminium salt **252** in 83% yield. Sodium borohydride reduction of **252** yielded **253**.[196,260] Polniaszek conducted a similar study on the use of chiral auxiliaries to prepare enantiospecific tetrahydroisoquinolines.[196,260] Polniaszek argues that reducing iminium ions similar to **253** at low temperature allows for stereoselective addition of a hydride to the electrophilic carbon. Therefore it is possible to obtain a high enantiomer excess. Also, Polniaszek claims that at low temperature the hydride predominantly add to the least hindered face (the methyl) of the molecule producing a single enantiomer. Stereochemistry of **253** was assigned following this methodology and confirmed using chiral HPLC.

Hydrogenolysis of **253** with Pd/C in slightly acidic ethanol gave very low yields (< 10%) of the corresponding chiral secondary amine: predominantly starting material was recovered. Attempts to optimize the hydrogenolysis by changing the reaction conditions were unsuccessful (Table 14).

Table 14: Hydrogenolysis Optimization

Entry	Compound	Time (h)	Catalyst (equivalents)	Acid (10%. HCl)	Yield
1	**253**	24	0.1	10 drops	8%
2		24	0.2	10 drops	8%
3		48	0.2	15 drops	10%

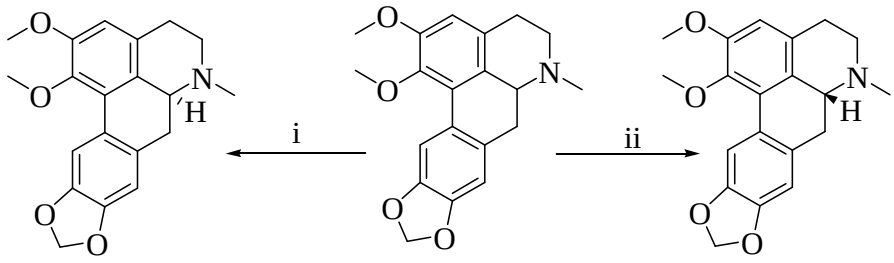
The enantiomeric excess was determined (ee = 58%) using chiral HPLC at 360 nM using methanol and hexanes as the solvent and via a (*R*)-(+)-α-methylbenzyl isocyanate as previously described with ^{1}H NMR from the isolated secondary amine *S*-**191**. Similar methods were used to prepare the *R*-enantiomer secondary amine (ee = 73%), which also gave very low yields. This protocol was not continued.

2.3.2. Via Resolution of (+/-)-Nantenine

Shi has reported the use of (+)-Dibenzoyl-D-Tartaric acid ((+)-DBTA) chirally resolve aporphines and apomorphine via a recycle process of resolution.[261] Resolution via a recycle process can be achieved by racemizing the undesired enantiomer and resolving the racemate to prepare the desired enantiomer.

Cannon also reported resolution of aporphines using (+)-di-*p*-toluoyl tartaric acid.[262] Following Cannon's methodology, L- and D-2,3-di-*p*-toluoyl-tartaric acid, was used to chirally resolve nantenine (**32**). *R*-(**32**) was obtained in enantiomer in 32% yield with 97% ee, while *S*-(**32**) was obtained in 30% yield with 96% ee (Scheme 59).

Scheme 59: Chiral Resolution of Nantenine



***(S)*-(+)-32** **32** ***(R)*-(-)-32**

Reagent and conditions:
(i) (-)-2,3-di-p-toluoyl-L-tartaric acid, EtOH then 10% aq NaOH, 30%, 96% ee
(ii) (+)-2,3-di-p-toluoyl-D-tartaric acid, EtOH then 10% aq NaOH, 32%, 97% ee

DISCUSSION

Subjecting nornantenine to reductive amination condition afforded N-alkyl analogues in moderate to high yields. Various C1- and C2-alkoxy analogues were prepared by subjecting the

corresponding phenol to etherification conditions. While high yielding, the etherification required the use of excess potassium salts under refluxing condition.

Initial attempts to prepare C2-alkyl analogues via the Suzuki reaction with alkyl boronic acids with or without the use of a silver additive were unsuccessful. Following a modified Suzuki reaction reported by Wang using cesium acetate and tributyl borane to promote the reaction allowed for the preparation of the C2-butyl analogue under microwave conditions. This method to prepare C2-alkyl analogues can be utilized to synthesize various alkyl analogues. Using hydroboration with various alkenes to prepare the desired alkylated borane, it is possible to prepare a wide variety of analogues using this modified Suzuki coupling.

Microwave-assisted Sonogashira reaction provided access to C2-ethyl, -propyl and –pentyl analogues. Using the Sonogashira reaction as a method to couple aporphine aryl triflate with substituted acetylenes has not been previously reported. Therefore, the versatility of aporphines has been demonstrated by this study. However, elongation of the carbon chain by alkylating the acetylene analogue was not successful using sodium hydride. Stronger deprotonation reagents may possibly provide access to analogues via this route.

Using chiral methyl benzyl amine as a chiral auxiliary to selectively prepare both enantiomers of nantenine was problematic. Low temperature reduction of the iminium salt afforded low to moderate ee’s and hydrogenolysis of the methylbenzyl auxiliary was inadequate. Chiral resolution of nantenine using a chiral tartaric acid proved to be an efficient method to isolate both enantiomers with high ee’s.

CONCLUSION

Using the PIFA-mediated biaryl coupling with HFIP as the solvent allowed for the preparation of a limited number of aporphines. The substitution pattern of the reacting tetrahydroisoquinoline governs the product formed and its yield. Electron donating group *para* to the site of ring closure favor the formation of the aporphine core.

Employing the reductive phenylation cyclization condition to the C9-nitro tetrahydroisoquinoline prepared the desired C9-anilino analogue in low yield. Increasing the equivalents of the zinc afforded a slightly higher yield of the aporphine product. The acidic conditions of the reductive phenylation are not well-tolerated by benzyloxy ethers. Debenzylation occurs before the reductive phenylation therefore preventing biaryl coupling from occurring.

Applying microwaves for the construction of aporphines using the Zhang protocol afforded the aryl coupled product in consistently high yields. While previous reports have stated the microwave-mediated arylation requires the use of pivalic acid to enhance the biaryl coupling, using the modified Zhang protocol avoided the need for this additive. Also, the previous method requires a relatively expensive, charged, less sterically demanding phosphine ligand: di-*tert*-butyl phosphine tetrafluoroborate, while the Zhang protocol is conducted using a significantly less expensive neutral, bulky phosphine ligand: tricyclohexyl phosphine. Therefore, the Zhang microwave-mediated direct arylation protocol is more economical, costing $265 per reaction, than the previously reported microwave-mediated arylation, costing $385 per reaction.

Initially, attempts to prepare the alkyl analogues using classic Suzuki reaction conditions with an aryl triflate and alkyl boronic acids were unsuccessful. Possible causes for the unsuccessful results are the reactivity of the aryl triflates or the alkyl boronic acids. Aryl triflates

are more reactive than aryl halide towards palladium catalyzed arylation; therefore the problem is likely to be the alkyl boronic acids. Alkyl boronic acids undergo elimination faster than the coupling reaction. Addition of a silver additive can promote Suzuki reactions with alkyl boronic acids.[244] Under thermal and microwave conditions, using silver oxide did not afford the desired alkylated product. Alternative methods to prepare the C2-ethyl and -propyl analogues were developed.

Treating triflate **231** with a modified Suzuki reaction with cesium acetate acting as a weak base prepared the C2-butyl analogue. Adjusting the reaction temperature, time and reagents equivalent improve the yield of the desired product.

C2-ethyl, propyl and pentyl analogues were prepared using the Sonogashira reaction. Using TMS-protected acetylene and propargyl eliminated the need to saturate the corresponding gas in the reaction solvent.

C2-benzylamine, -cyclohexyl amine and -aniline derivatives were not prepared using palladium and non-palladium catalyzed Buchwald-Hartwig reaction conditions under microwave assisted conditions. Due to the polarity of these amino compounds, purification by column chromatography on silica gel was challenging. Purification using oxalic acid was also unsuccessful.

Modifying the starting substrates of the direct arylation protocol to use chiral *N*-(1-phenylethyl) acetamides to prepare enantiomerically pure tetrahydroisoquinolines is not an efficient method to prepare *R*- and *S*-nantenine. Polniaszek have reported high yields of the hydrogenolysis and the enantiomer excess. However, in our hands very low yields of the chiral tetrahydroisoquinolines were isolated with only moderate enantiomeric excess.

This series of investigations provided insight into all three synthetic routes proposed to synthesize nantenine and its analogues, from which we were able to prepare 32 compounds (Figure 48). For the PIFA-mediated biaryl coupling, we have learned that optimal orbital overlap between the *para*-substituted alkoxy substituent and the aromatic D-ring is necessary for adequate cyclization. Cyclization can also be enhanced by *meta* and *para*-alkoxy substituents on the A-ring. We have also learned that PIFA can be used to prepare benzazepine derivatives with electron withdrawing substituents on the A-ring. Reductive phenylation is a useful method to prepare C9 anilino aporphine analogues.

While successful to synthesis domesticine in relatively good yields, the Wessely acetoxylation methodology is an inefficient protocol to synthesize C1 analogues due to the low yield of intermediates.

The direct biaryl coupling is a very versatile synthetic methodology, affording the synthesis of a variety of substituted aporphines. Varying the substitution patterns of the starting phenethylamine or the phenylacetic acid afforded the desired material for preparation of nantenine analogues. Microwave-assisted direct arylation using the Zhang protocol provided access to large quantities of the aporphine core. The microwave-assisted direct arylation protocol in combination with the Sonogashira, and Suzuki reactions have been used to prepare C2-alkyl analogues, further showing the versatility of microwave-assisted variations of these reactions.

Resolution of nantenine and its analogues using a chiral tartaric acid appears to be the best method to prepare both enantiomers with high ee's.

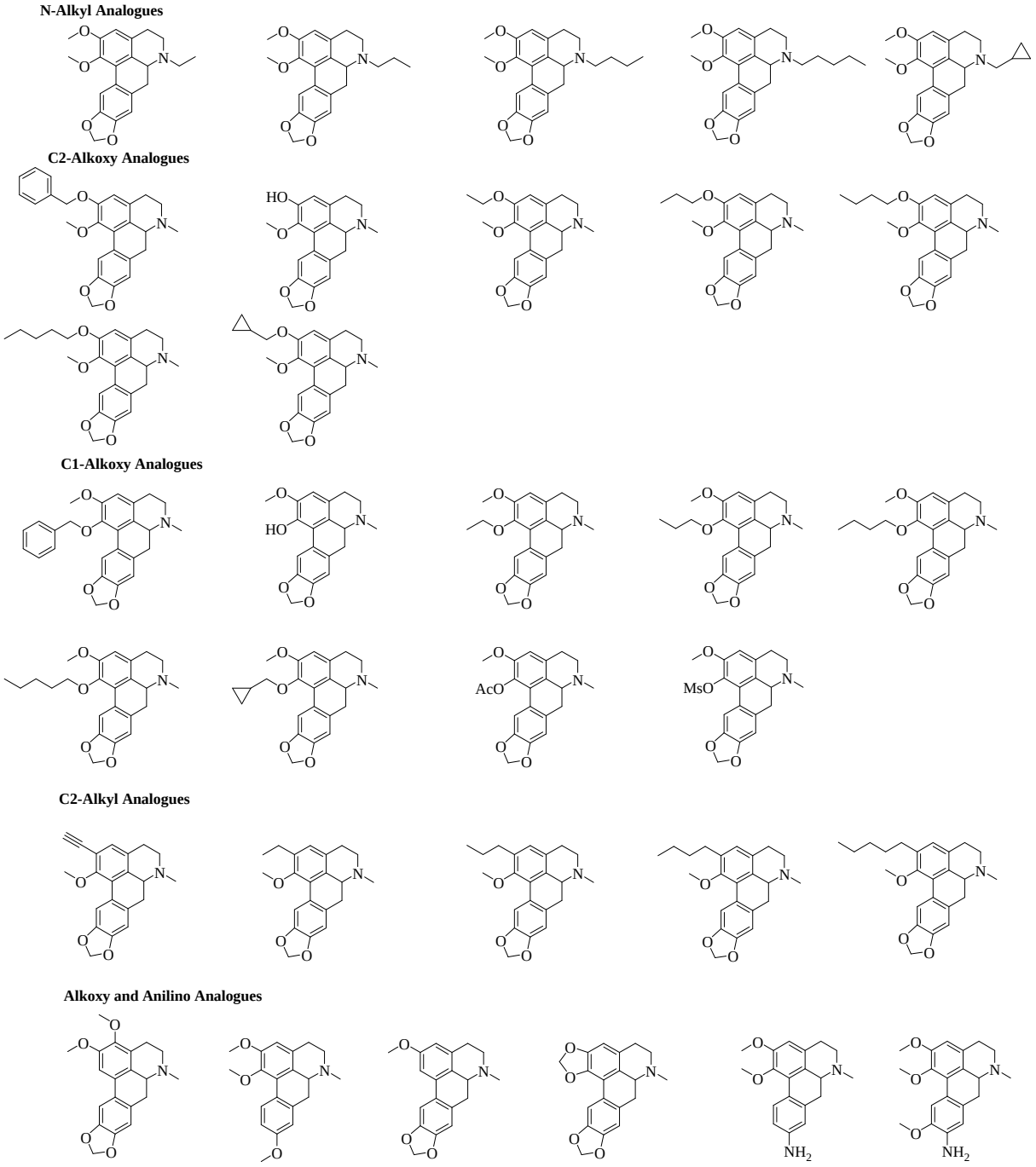


Figure 48: Analogues Synthesized

CHAPTER V: BIOLOGICAL ACTIVITY

1. INTRODUCTION

The physiological and psychological effects of MDMA are believed to be mediated by the 5-HT_{2A} and the α_1 receptors. Antagonist at both of these receptors can block or reverse the effects of MDMA. Fantegrossi and Indra have shown that nantenine can antagonize the 5-HT_{2A} and the α_1 receptors. While nantenine has been shown to antagonize the psychological and behavioral effect of MDMA in mice, no report of the receptor binding profile of nantenine has been published.

2. IN VITRO STUDIES

Nantenine, **32**, was therefore screened by the Psychoactive Drug Screening Program, (PDSP) for affinity at cloned human CNS receptors, channels, and transporters. The results of these experiments are listed in Table 15.

Table 15: PDSP K_i Data for Compound **32**

Receptor	K_i(nM)	Receptor	K_i(nM)	Receptor	K_i(nM)	Receptor	K_i(nM)
5-HT_{1B}	na[1]	**α_{1A}-AR**	**2.2**	D1	895	DOR	>10,000
5-HT_{1B}	100	α_{1B}-AR	1,191	D2	858	MOR	>10,000
5-HT_{1D}	49	α_{1D}-AR	340	D3	309	KOR	7,265
5-HT_{2A}	**832**	α_{2A}-AR	1,288	D4	262	H1	>10,000
5-HT_{2B}	543	α_{2B}-AR	252	D5	2.397	H2	672
5-HT_{2C}	1,069	α_{2c}-AR	181	H2	672	H3	>10,000
5-HT_{5A}	2,224	β_1-AR	8,565	DAT	895	H4	>10,000
5-HT_6	257	β_2-AR	>10,000	SERT	858	Sigma 2	>10,000
5-HT_7	67	β_3-AR	>10,000	NET	>10,000		

1. data not available

Interestingly, racemic nantenine is subtype selective for the α_{1A} receptor and 380-fold more selective for the α_{1A} over the 5-HT_{2A} receptor. It can be inferred that the mechanism of nantenine's anti-MDMA activity is largely governed by its ability to block the α_{1A} receptor. Nantenine also shows greater selectivity for the 5-HT_{1D} and 5-HT_7 receptors over the 5-HT_{2A} receptor. There is no reported literature stating that these receptors are involved in mediating the effects of MDMA. However, SAR studies of nantenine can determine the function of the 5-HT_{1D} and 5-HT_7 receptors in its MDMA antagonistic activity.

For development of a more potent and selective MDMA antagonist, it is important to understand how nantenine's selectivity ratio for the α_{1A}/5-HT_{2A} receptors affects its antagonistic activity. SAR-studies must be conducted to gain insight into nantenine's mechanism of action. Also, the binding profile for each enantiomer of nantenine needs to be conducted to determine how they individually affect nantenine's antagonistic activity.

Nantenine (**32**), as well as several C1-analogues and N-alkyl analogues were subjected to *in vitro* testing at the 5-HT_{2A} receptor.[263] The apparent affinity (K_e) of these compounds was determined. The results of these experiments are stated in Table 16.

Table 16: Apparent affinity of Nantenine and analogues at human 5-HT_{2A} receptor

Entry	**Compound**	**C1**	**K_e(nM)**
1	**32**	Methyl	850
2	**222**	Benzyl	4600
3	**218**	Ethyl	890
4	**219**	Propyl	297
5	**220**	Butyl	274
6	**221**	Pentyl	171
7	**223**	Methylcyclopropyl	68
8		Mesyl	>10,000
9		Acetyl	>10,000
Entry	**Compound**	***N*6**	**K_e(nM)**
10	**202**	Ethyl	>10,000
11	**203**	Propyl	>10,000
12	**204**	Butyl	>10,000
13	**205**	Pentyl	>10,000
14	**206**	MethylCyclopropyl	>10,000

The data in Table 15 shows the effect structural modification of the nantenine scaffold has on binding and activity at the α_{1A} and the 5-HT_{2A} receptors. 5-HT_{2A} antagonistic activity increases as the length of the C1 alkoxy chain is increased beyond two carbon atoms. For example, compound **223** (Table 14, entry 7) was the most active compound tested, showing a 12-fold increase in activity compared to nantenine. Compound **223** will also be tested for α_{1A} antagonist activity. The C2-alkoxy and the C9-anilino analogues were also examined for activity at α_1, (Table 17).

Table 17: Apparent affinity of Nantenine and analogues at human α_1 receptor

Entry	Compound	C2	C9	C10	K_e(nM)
1	**211**	Ethyl	O- CH_2- O		52
2	**212**	Propyl	O- CH_2- O		133
3	**213**	Butyl	O- CH_2- O		234
4	**214**	Pentyl	O- CH_2- O		449
5	**215**	MethylCyclopropyl	O- CH_2- O		195
6	**216**	Benzyl	O- CH_2- O		1917
7	**159**	Methyl	NH_2	H	293

Further structural modifications at C1 will be conducted to develop a compound with greater activity at the 5-HT_{2A} and α_{1A} receptors.

3. IN VIVO STUDIES

Both enantiomers of nantenine (**32)** were subjected to *in vivo* analysis for their ability to reverse MDMA-induced behavioral suppression.[264] Ketanserin has been shown to block a range of behavioral and physiological effects of MDMA in various mammalian systems. When compared to Ketanserin, both (*R*)- and (*S*)-nantenine completely blocked MDMA-induced

behavioral suppression in rats.[265-269] The unnatural (*R*)-isomer was slightly more active than the natural (*S*)-isomer in this behavioral assay (Figure 48). Further investigation is needed to fully understand the importance of the chiral center of nantenine in its antagonism of MDMA's behavioral and physiological effects.

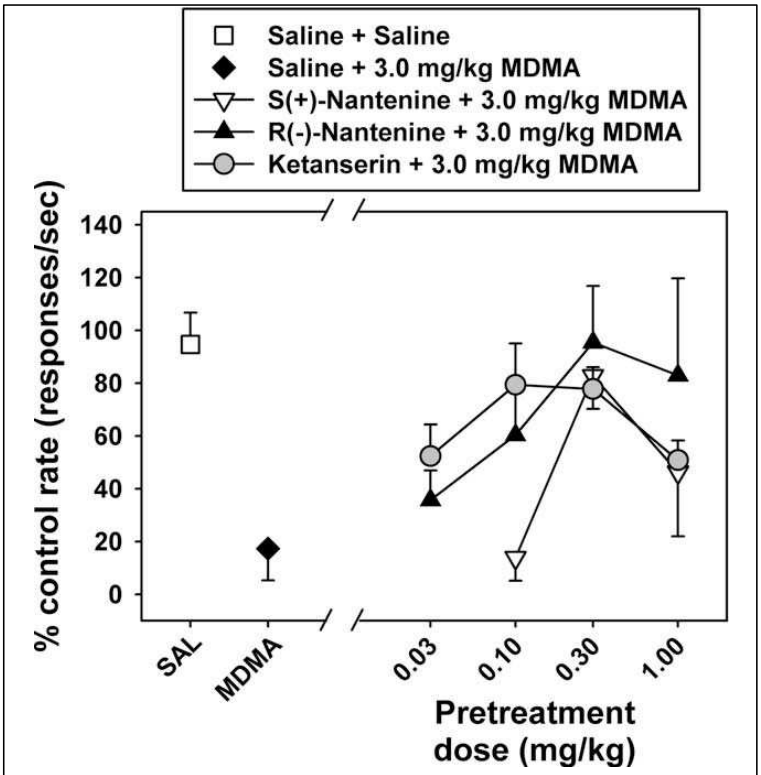


Figure 49: MDMA-Induced Behavioral Suppression Assay

DISCUSSION

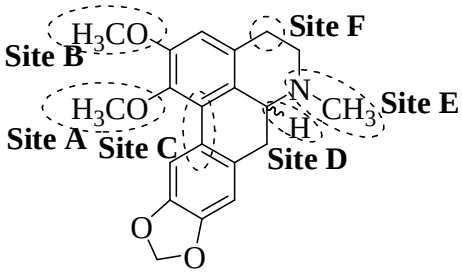
Chiral resolution presented an alternate method for isolating the enantiomers of nantenine. Using chiral toluoyl tartaric acid, chiral nantenine was isolated in moderate yield with high ee's: *R* = 32% yield, 97% ee; *S* = 30% yield, 96% ee. Previous reports by Fantegrossi have stated that the naturally occurring enantiomer *S*-**32** antagonizes various MDMA-induced effects including

locomotor stimulation, head-twitch response, lethality and hyperthermia.[270] However, the unnatural *R*-enantiomer has not been evaluated as an MDMA antagonist.

In a food-reinforced operant assay, the *R*- and *S*-enantiomer was tested for antagonizing activity against MDMA-induced effects. The results indicate that both *R*- and *S*-nantenine can be used as antagonist for behavioral suppression induced by MDMA.

A summary of nantenine's past and present SAR results are stated in Table 18 and 19.

Table 18: Previous SAR Results of Nantenine



Entry	Site	Substituent	Effect
1	A	OH	Lower 5-HT_{2A} Increases α_1
2	B	--	--
3	C	--	--
4	D	--	--
5	E	H or Et	Reduces α_1 and 5-HT_{2A} activity
6	F	α or β-OH	Reduces α_1 and 5-HT_{2A} activity

Table 19: Current SAR Results of Nantenine

Entry	Site	Substituent	Effect
1	A	Methylcyclopropyloxy	12-fold increase at 5-HT_{2A}
2	B	Increased the carbon chain	Reduces α_1 activity
3	C	--	Required for activity at the 5-HT_{2A} receptor
4	D	--	Plays a minor role for *in vivo* antagonism
5	E	Longer carbon chains	Reduces the 5-HT_{2A} activity
6	F	--	--

FUTURE ASPECTS FOR THE PROJECT

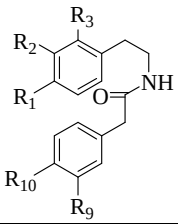
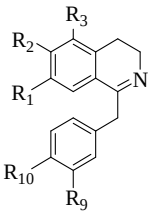
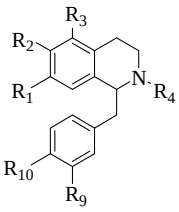
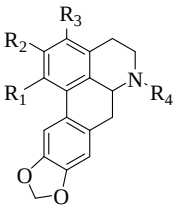
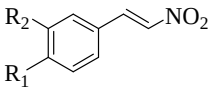
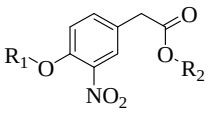
The main focus of this project was to potentially design a potent MDMA antagonist based on the structure of nantenine. The completion of *in vitro* analysis for compounds currently synthesized is important for the continuation and progress of the SAR design of an MDMA antagonist. Currently there are many gaps in the *in vitro* SAR results. The apparent affinity (K_e) of our compounds at 5-HT_{2A} and α_{1A} receptors is an important test which will aid in the development of an MDMA antagonist. In efforts to design a compound with affinity for both the 5-HT_{2A} and α_{1A} receptors, analyzing the structural requirements for each receptor is necessary.

We currently have information that gives us insight into the structural requirements for 5-HT_{2A} receptor antagonism at position C1 and *N*6 as well as structural requirements for α_1 receptor antagonism at position C2. Compound **223**, C1 = Methylcyclopropyloxy, shows high apparent affinity at 5-HT_{2A} receptor, We also know that elongation of the C2 alkoxy chain to an ethoxy chain and beyond reduces the apparent affinity at the α_1 receptor. Once all *in vitro* results are collected, the next step would be to modify each position according to the receptor requirements. For example, compound **223** can be used as a lead compound for the design of α_{1A} antagonist which also possesses 5-HT_{2A} antagonism.

In order to develop nantenine into a potentially useful agent the following gaps in our knowledge must be filled: 1) The effect C1 methylcyclopropyloxy has on the apparent affinity at α_{1A} receptor 2) How carbon chain elongation at C2 affects the apparent affinity at 5-HT_{2A} and the specific α_{1A} subtype 3) The apparent affinity for nantenine at the α_1 receptor and 4) Determine the role of the oxygen at the C1 and C2 positions.

EXPERIMENTAL SECTION

Table 20: Compounds Intermediates

A	B	C	D	E	F
					

Entry	Compound	R_1	R_2	R_3	R_4	R_9	R_{10}
1	A	H	OMe	OMe	H	O-CH_2-O	
2	A	OMe	OMe	H	H	H	H
3	A	OMe	OMe	H	H	H	OMe
4	A	OMe	OMe	H	H	OMe	H
5	A	OBn	OMe	H	H	O-CH_2-O	
6	A	O-CH_2-O		H	H	O-CH_2-O	
7	A	OMe	OMe	H	H	H	NO_2
8	A	OMe	OMe	H	H	NO_2	OBn
9	B	OMe	OMe	H	H	OMe	H
10	B	OMe	OMe	H	H	H	OMe
11	B	OBn	OMe	H	H	O-CH_2-O	
12	B	OMe	OMe	H	H	I	H
13	B	OMe	OMe	H	H	NO_2	OBn
14	B	OMe	OMe	H	H	NO_2	OMe
15	C	OMe	OMe	H	H	H	H
16	C	OMe	OMe	H	H	H	OMe
17	C	OMe	OMe	H	H	OMe	H
18	C	OMe	OMe	H	H	NO_2	OBn
19	C	OMe	OMe	H	Me	H	NO_2
20	C	OMe	OMe	H	Me	H	NH_2
21	C	OMe	OMe	H	Me	H	NHEt
22	C	OMe	OMe	H	Me	NH_2	H
23	D	OMe	Et	H	Boc	--	--
24	D	OAc	OMe	H	Me	--	--
25	D	OMs	OMe	H	Me	--	--
26	D	OMe	OEt	H	Boc	--	--
27	D	OMe	OPr	H	Boc	--	--
28	D	OMe	OBu	H	Boc	--	--
29	D	OMe	OPen	H	Boc	--	--
30	D	OMe	OCypMe	H	Boc	--	--
31	D	OEt	OMe	H	Boc	--	-
32	D	OPr	OMe	H	Boc	--	--
33	D	OBu	OMe	H	Boc	--	--
34	D	OPen	OMe	H	Boc	--	--
35	D	OCypMe	OMe	H	Boc	--	--
36	E	OBn	OMe	--	--	--	--
37	E	OMe	OBn	--	--	--	--
38	F	Bn	Me	--	--	--	--
39	F	Me	Me	--	--	--	--
40	F	Bn	H	--	--	--	--
41	D	OMe	OH	H	H	--	--
42	D	Acetyl	OMe	H	Me	--	--

GENERAL EXPERIMENTAL PROCEDURES

All reactions were carried out in oven-dried reaction vessels, under argon. Thermal reaction temperatures are reported as the temperature of the reaction mixture. Microwave reaction temperatures are reported as the set temperature. All new compounds were fully characterized. All anhydrous solvents and reagents were purchased from Sigma Aldrich and Fisher Scientific and used as received. HR-MS Spectra were recorded on an Agilent 6520 Q-TOF complete with Agilent 1200 capillary HPLC system.

^{1}H NMR spectra were recorded on a Bruker Advance 500 equipped with a ^{13}C-^{1}H cryoprobe at 500 MHz in $CDCl_3$. Chemical shifts are reported relative to $CDCl_3$ (7.24 ppm for 1H NMR) or $CDCl_3$ (77.23 ppm for 13C NMR). ^{13}C NMR spectra were recorded at the corresponding frequency on the same instrument at 125 MHz. Chemical shifts are in ppm and coupling constants, *J*, are in Hz.

All melting points were carried out in a MEL-TEMP capillary melting point apparatus using melting point capillary tubes for MEL-TEMP apparatus. Enantiomeric excess was determined by chiral Agilent HPLC analysis, performed on a Chiralcel OD-H column, eluting with MeOH/hexane at 360 nM. Microwave irradiation was carried out with CEM Discover microwave oven in microwave safe vials.

1.2. In vitro Methodology: K_i Bioassay

The Psychoactive Drug Screening Program (PDSP) uses a Radioligand Binding Assays to determine the affinity the compounds has for a subset of receptors, transporters and ion channels.[271] Radioligand bound cells are treated with a reference and test compound to a dilution 5x the final assay concentration in the appropriate radioligand binding buffer. Pure radioligand

bound cells were used as a control. The total bound radioactivity is estimated from comparing the cells with and without the test and reference compound. The percent inhibition of radioligand binding is calculated using the following equation:

Equ 1: % inhibition = 100% - % radioactivity bound

1.3. Determination of K_e

For the apparent affinity, compounds are screened at 10 nM for agonist and antagonist activity at the human 5-HT_{2A} using FLIPR-based functional assays that detect receptor-mediated mobilization of internal calcium with a calcium sensitive florescent dye, and at the α_{1A}-AR for their ability to inhibit the binding of the α_{1A}-AR antagonist, [3H]-prazosin using CHO-K1 membrane preparations that express the human α_{1A}-AR.

1.4. In vivo Methodology

Experiments were conducted in Med Associates, Inc. modular operant chambers for rats or mice enclosed within sound attenuating cubicles. Chambers are equipped with exhaust fans, house lights, two retractable levers and associated stimulus lights, and a liquid dipper which delivers specific columns of palatable liquid in order to reinforce operant responding. During training, rodents are injected with saline or the training dose (3.0 mg/kg) of MDMA and placed in the chambers. Ten minutes later, house lights are illuminated, levers are extended and responding on the injection-appropriate lever is reinforced under an FR10 schedule. Following 3 consecutive days of at least 80% injection appropriate performance, the generalization of the

training drug to itself will be tested using a cumulative dosing procedure under extinction conditions. In these sessions, subjects will be injected with 0.1 mg/kg, 0.2 mg/kg, 0.7 mg/kg, and 2.0 mg/kg in ascending order. Ten minutes after each injection, house lights will be illuminated, levers will be extended and components will last for 2 minutes or end when either lever registers 10 total responses. Rodents will be immediately injected with the next dose and returned to the chamber, and the process will repeat until all doses are tested. Percent drug-appropriate response and response rates will be quantified for each component. Failure to emit 10 responses in 10 minutes will indicate behavioral disruption by the drug and no higher doses will be tested. This entire procedure will be repeated three times per animal. For antagonism studies, nantenine or one of it s analogues will be administered 15 min prior to the first injection of the training drug. Three independent antagonism sessions will be conducted per animal.

1.5. Chiral Resolution

At 0 ^{o}C, **32** was dissolved in absolute ethanol. The mixture was treated with (-)-2,3-p-toluoyl-L-tartaric acid and allowed to stir for 30 minutes. The corresponding salt crashed out of solution as a white precipitate. The precipitate was filtered through a Buchner funnel. The compound was recrystallization (2 x) from hot ethanol and free based using 10% aq NaOH to afforded *S*-**32** in 30% and 96% ee. The resulting filtrates were combined and concentrated under vacuum. The residue was dissolved in absolute ethanol at 0 ^{o}C and treated with (+)-2,3-p-toluoyl-D-tartaric acid and allowed to stir for 30 minutes. The solvent was then removed under vacuum. The residue was recrystallized (2 x) from hot ethanol and free based using 10% aq NaOH to afford *R*-**32** in 32% yield and 97% ee.

General Procedure for Peptide Coupling: Synthesis of (*R*)-2-(3,4-dimethoxyphenyl)-N-(1-phenylethyl)acetamide (***R*-131**) To a solution of **130** (5.0 g, 24.8 mmol, 1.5 eq) dissolved in DCM (50 mL) was added ***R*-129** (2.1 mL, 16.5 mmol, 1 eq), triethylamine (6.0 mL, 41.3 mmol, 2.5 eq), and EDCI (8.0 g, 41.3 mmol, 2.5 eq). The reaction was stirred at room temperature overnight. 2N HCl (25 mL) was added to the reaction mixture. The reaction was then basified with saturated sodium bicarbonate. The organic layer was washed with brine then dried over sodium sulfate. The solvent was removed under vacuum. The residue was recrystallized from acetone and hexanes yielding ***R*-131** (84%) as a white solid, mp: 60-61 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{18}H_{21}NO_3$ 299.1521, found 299.1521
^{1}HNMR: (500 MHz, $CDCl_3$) δ 1.41 (d, 3H, *J* = 7.0 Hz), 3.53 (s, 2H), 3.85 (s, 3H), 3.89 (s, 3H), 5.11-5.16 (m, 1H), 5.78 (bs, 1H), 6.79-6.86 (m, 3H), 7.30-7.20 (m, 5H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 21.9, 43.5, 48.7, 55.9, 55.9, 111.3, 112.1, 121.7, 126.1, 127.3, 127.4, 128.7, 143.2, 148.2, 149.1, 170.6

(*S*)-2-(3,4-dimethoxyphenyl)-N-(1-phenylethyl)acetamide (***S*-131**) By a procedure identical with that described for the synthesis of the amide ***R*-131** the amide ***S*-131** was prepared in 80% yield as a white solid. mp: 71-72 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{18}H_{21}NO_3$ 299.1521, found 299.1521
^{1}HNMR: (500 MHz, $CDCl_3$) δ 1.41 (d, 3H, *J* = 7.0 Hz), 3.53 (s, 2H), 3.85 (s, 3H), 3.89 (s, 3H), 5.11-5.16 (m, 1H), 5.78 (bs, 1H), 6.79-6.86 (m, 3H), 7.30-7.20 (m, 5H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 21.9, 43.5, 48.7, 55.9, 55.9, 111.3, 112.1, 121.7, 126.2, 127.3, 127.4, 128.7, 143.2, 148.2, 149.1, 170.6

2-Benzo[1,3]dioxol-5-yl-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide (121) A mixture of **120** (0.5 g, 2.8 mmol, 1eq) and CDI (0.5 g, 2.8 mmol, 1eq) dissolved in THF (30 mL) was stirred at 0 ^{o}C for 1 h then at room temperature for 1 h. At 0 ^{o}C **65** (0.5 mL, 2.8 mmol, 1.0 eq) was added to the reaction mixture. The reaction was then stirred at 0 ^{o}C for 4 h then overnight at room temperature. The solvent was removed under vacuum. The resulting residue was dissolve in DCM (50 mL) washed with 1N HCl, water, 5% $NaHCO_3$, and water. The organic layer was dried over sodium sulfate. The solvent was removed solvent under vacuum. **121** was isolated in 99% yield as a white solid after recrystallization from ethyl acetate. mp: 126.7-128 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{19}H_{21}NO_5$ 343.1423, found 343.1420
^{1}HNMR*:* (500 MHz, $CDCl_3$) 2.69 (t, 2H *J* = 7.0 Hz), 3.44 (s, 2H), 3.46 (t, 2H, *J* = 7.0 Hz), 3.83 (s. 3H), 3.87 (s, 3H), 5.38 (bs, 1H), 5.95 (s, 2H), 6.59-6.65 (m, 4H), 6.73-6.76 (m, 2H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 35.6, 40.8, 42.7, 45.9, 55.9, 56.1, 101.3, 108.8, 109.9, 111.4, 111.9, 120.8, 122.8, 131.3, 147.0 148.5, 149.1, 152.3, 171.2

2-Benzo[1,3]dioxol-5-yl-N-[2-(2,3-dimethoxy-phenyl)-ethyl]-acetamide (Table 20, entry 1) By a procedure identical with that described for the synthesis of the amide **121** this compound was prepared in 95% yield as a cream solid with mp 90-93 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{19}H_{21}NO_5$ 343.1423, found 343.1420
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.77 (t, 2H, *J* = 7.0 Hz), 3.42 (s, 2H), 3.45 (t, 2H, *J* = 7.0 Hz), 3.78 (s. 3H), 3.87 (s, 3H), 5.71 (bs, 1H), 5.95 (s, 2H), 6.64-6.81 (m, 5H), 6.94 (t, 1H, *J* = 8 Hz)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 29.8, 40.7, 43.7, 55.9, 60.8, 101.3, 108.7, 110.1, 111.1, 122.6, 122.9, 124.3, 128.7, 132.8, 146.9, 147.3, 148.2, 152.9, 174.4

N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2-phenyl-acetamide (Table 20, entry 2) By a procedure identical with that described for the synthesis of the amide **121** this compound was prepared in 80% yield as a white solid mp: 104.9-106.4 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{18}H_{21}NO_3$ 299.1524, found 299.1521

^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.68 (t, 2H, *J* = 7.0 Hz), 3.44 (q, 2H, *J* = 6.0 Hz), 3.53 (s, 2H), 3.81 (s, 3H), 3.85 (s, 3H), 5.37 (bs, 1H), 6.56 (d, 1H, *J* = 7.0 Hz), 6.60 (s, 1H), 6.71 (d, 1H, *J* = 7.0 Hz), 7.16 (d, 2H, *J* = 8.0 Hz), 7.26-7.31 (m, 3H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 35.2, 40.9, 44.1, 56.0, 56.1, 111.5, 111.9, 120.8, 127.5, 129.2, 129.6, 131.3, 134.9, 147.8, 149.2, 171.1

N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2-(4-methoxy-phenyl)-acetamide (Table 20, entry 3) By a procedure identical with that described for the synthesis of the amide **121** this compound was prepared in 79% yield as a white solid, mp: 124.9-126.3 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{19}H_{23}NO_4$ 329.1631, found 329.1627

^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.68 (t, 2H, *J* = 7.0 Hz), 3.44 (q, 2H, *J* = 7.0 Hz), 3.48 (s, 2H), 3.81 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 5.37 (bs, 1H), 6.56 (d, 1H, *J* = 6.0 Hz), 6.61 (s, 1H), 6.72 (d, 1H, *J* = 8.0 Hz), 6.84 (d, 2H, *J* = 8.0 Hz), 7.07 (d, 2H, *J* = 8.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 35.3, 40.9, 43.2, 55.5, 56.0, 56.1, 111.5, 111.9, 114.6, 120.8, 126.9, 130.8, 131.3, 147.8, 149.2, 159.0, 171.5

N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2-(3-methoxy-phenyl)-acetamide (Table 20, entry 4) By a procedure identical with that described for the synthesis of the amide **121** this compound was prepared in 81% yield as a white solid mp: 114-115 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{19}H_{23}NO_4$ 329.1631, found 329.1627

^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.68 (t, 2H, *J* = 7.0 Hz), 3.44 (q, 2H, *J* = 7.0 Hz), 3.50 (s, 2H), 3.78 (s, 3H), 3.83 (s, 3H), 3.86 (s, 3H), 5.43 (bs, 1H), 6.54 (d, 1H, *J* = 8.0 Hz), 6.61 (s, 1H), 6.72-6.76 (m, 3H), 6.83 (d, 1H, *J* = 8.0 Hz), 7.23 (t, 1H, *J* = 8.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 35.2, 40.9, 44.1, 55.3, 55.9, 56.0, 111.4, 111.8, 113.0, 115.1, 120.7, 121.8, 130.2, 131.2, 136.4, 147.8, 149.1, 160.1, 170.9

2-(benzo[d][1,3]dioxol-5-yl)-N-(4-(benzyloxy)-3-methoxyphenethyl)acetamide (Table 20, entry 5) By a procedure identical with that described for the synthesis of the amide **121** this compound was prepared in 82% yield as an orange oil. HRMS calcd for $[M]^{+}$ $C_{25}H_{25}NO_5$ 419.1733, found 419.1733

^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.68 (t, 2H, *J* = 7.0 Hz), 3.43 (s, 2H), 3.45 (t, 2H, *J* = 7.0 Hz), 3.85 (s, 3H), 5.13 (s, 2H), 5.40 (bs, 1H), 5.95 (s, 2H), 6.50 (d, 1H, *J* = 5.0 Hz), 6.55 (d, 1H, *J* = 5.0 Hz), 6.64 (s, 2H), 6.71 (d, 1H, *J* = 8.0 Hz), 6.77 (d, 1H, *J* = 8.0 Hz), 7.30 (t, 1H, *J* = 8.0 Hz), 7.38 (t, 2H, *J* = 8.0 Hz), 7.45 (d, 2H, *J* = 7.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 35.2, 40.8, 43.6, 56.1, 71.3, 101.3, 108.8, 109.9, 112.5, 114.3, 120.8, 122.8, 127.4, 128.0, 128.5, 128.7, 131.9, 137.4, 147.0, 147.0, 148.2, 149.9, 171.1

2-(6-Bromo-benzo[1,3]dioxol-5-yl)-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide (106) By a procedure identical with that described for the synthesis of the amide **121**, compound **106** was prepared in 95% yield as a solid mp: 161-164 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{19}H_{20}BrNO_5$ 421.0526, found 421.0525

^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.75 (t, 2H, *J* = 15.0 Hz), 3.50 (q, 2H, *J* = 15.0Hz), 3.63 (s, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 5.40 (bs, 1H), 6.00 (s, 2H), 6.63-6.66 (m, 2H), 6.75-6.77 (m, 2H) 7.01 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 37.7, 39.4, 43.6, 56.0, 56.1, 101.2, 108.8, 112.8, 112.2, 114.7, 120.8, 122.8, 130.4, 131.0, 147.0, 147.0, 148.3, 149.7, 171.1

2-Benzo[1,3]dioxol-5-yl-N-(2-benzo[1,3]dioxol-5-yl-ethyl)-acetamide (Table 20, entry 6) By a procedure identical with that described for the synthesis of the amide **121** this compound was prepared in 63% yield as a solid mp: 113.7-117.7 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{18}H_{17}NO_5$ 327.1107, found 327.1107

^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.65 (t, 2H, *J* = 7.0 Hz), 3.42 (q, 2H, *J* = 6.0 Hz), 3.44 (s, 2H) 5.34 (bs, 1H) 5.94 (s, 2H) 5.97 (s, 2H) 6.48 (d, 1H, *J* = 2.0 Hz) 6.55 (s, 1H) 6.63 (d, 1H, *J* = 10.0 Hz), 6.65 (s, 1H), 6.68 (d, 1H, *J* = 8.0 Hz) 6.75 (d, 1H, *J* = 8.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 35.2, 40.8, 43.6, 101.3, 112.5, 114.3, 115.2, 115.8, 120.8, 122.8, 128.7, 131.9, 146.0, 147.0, 148.2, 149.9, 171.1

N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2-(4-nitro-phenyl)-acetamide (Table 20, entry 7) By a procedure identical with that described for the synthesis of the amide **121** this compound was prepared in 35% yield as a solid mp: 79-80 ^{o}C. HRMS calcd for $[M + H]^{+}$ $C_{18}H_{20}N_2O_5$ 344.1375, found 344.1372

^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.73 (t, 2H, *J* = 7.0 Hz), 3.51 (q, 2H, *J* = 6.0 Hz), 3.50 (s, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 5.38 (bs, 1H), 6.58 (d, 1H, *J* = 8.0 Hz), 6.65 (s, 1H), 6.73 (d, 1H, *J* = 8.0Hz), 7.38 (d, 2H, *J* = 9.0 Hz), 8.18 (d, 2H, *J* = 9.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 35.1, 40.9, 43.5, 56.0, 56.1, 111.2, 111.8, 120.7, 124.1, 130.3, 130.9, 142.4, 147.3, 148.0, 149.3, 169.2

N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2-(3-nitro-phenyl)-acetamide (161) By a procedure identical with that described for the synthesis of the amide **121**, compound **161** was prepared in 86% yield as a solid mp: 130-132 ^{o}C. HRMS calcd for $[M + H]^{+}$ $C_{18}H_{20}N_2O_5$ 344.1375, found 344.1372

^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.71 (t, 2H, *J* = 7.0 Hz), 3.48 (q, 2H, *J* = 6.0 Hz), 3.56 (s, 2H), 3.79 (s, 3H), 3.81 (s, 3H), 5.94 (bs, 1H), 6.59 (m, 1H), 6.63 (s, 1H), 6.71 (d, 1H, *J* = 8.0 Hz), 7.46 (t, 1H, *J* = 8.0 Hz), 7.56 (d, 1H, *J* = 8.0 Hz), 8.05-8.09 (d, 2H, *J* = 13.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 35.0, 40.9, 42.9, 55.8, 55.9, 111.1, 111.7, 120.7, 122.2, 124.1, 129.7, 131.0, 135.6, 137.1, 147.7, 148.2, 149.0, 169.5

N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2-(3-iodo-phenyl)-acetamide (167) By a procedure identical with that described for the synthesis of the amide **121**, compound **167** was prepared in 76% yield as a solid mp: 133-134 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{18}H_{20}INO_3$ 425.0488, found 425.0487

^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.71 (t, 2H, *J* = 7.0 Hz), 3.46-3.49 (m, 4H), 3.85 (s, 3H), 3.88 (s, 3H), 5.34 (bs, 1H), 6.55-6.63 (d, 1H, *J* = 8.0 Hz), 6.63 (s, 1H), 6.77 (d, 1H, *J* = 8.0 Hz), 7.05 (t, 1H, *J* = 8.0 Hz), 7.16 (d, 1H, *J* = 8.0 Hz), 7.57 (s, 1H), 7.62 (d, 2H, *J* = 13.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 35.2, 40.9, 43.4, 56.0, 56.1, 95.0, 111.4, 111.8, 120.8, 128.8, 130.7, 13.1, 136.6, 137.3, 138.4, 147.9, 149.2, 170.1

2-(6-Bromo-benzo[1,3]dioxol-5-yl)-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-N-(1-phenyl-ethyl)-acetamide (*R*-251) By a procedure identical with that described for the synthesis of the amide **121**, compound ***R*-251** was prepared in 65% yield as a yellow oil. HRMS calcd for $[M + H]^{+}$ $C_{27}H_{28}BrNO_5$ 526.1151, found 526.1151 (Major Rotamer)

^{1}HNMR: (500 MHz, $CDCl_3$) δ 1.55 (m, 3H), 2.29-2.35 (m, 1H), 2.69-2.75 (m, 1H), 3.18-3.29 (m, 2H), 3.76 (s, 3H), 3.77 (s, 3H), 3.88 (s, 2H), 5.16-5.24 (m, 1H), 5.92 (d, 2H, *J* = 7.0 Hz), 6.34 (s, 1H), 6.66-6.71 (m, 2H), 6.83 (s, 1H), 6.87 (s, 1H), 6.99 (d, 1H, *J* = 8.0 Hz), 7.23-7.49 (m, 4H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 18.2, 34.6, 36.8, 45.9, 55.9, 56.0, 60.0, 101.9, 112.7, 114.9, 115.1, 116.8 , 117.9, 119.1, 120.6, 127.1, 127.3, 128.4, 130.9, 132.3, 140.7, 147.4, 148.8, 149.0, 170.2

2-(6-Bromo-benzo[1,3]dioxol-5-yl)-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-N-(1-phenyl-ethyl)-acetamide (*S*-251) By a procedure identical with that described for the synthesis of the amide **121**, compound ***S*-251** was prepared in 45% yield as a yellow oil. HRMS calcd for $[M + H]^{+}$ $C_{27}H_{28}BrNO_5$ 526.1151, found 526.1151 (Major Rotamer)

^{1}HNMR: (500 MHz, $CDCl_3$) δ 1.55 (m, 3H), 2.29-2.35 (m, 1H), 2.69-2.75 (m, 1H), 3.18-3.29 (m, 2H), 3.76 (s, 3H), 3.77 (s, 3H), 3.88 (s, 2H), 5.16-5.24 (m, 1H), 5.92 (d, 2H, *J* = 7.0 Hz), 6.34 (s, 1H), 6.66-6.71 (m, 2H), 6.83 (s, 1H), 6.87 (s, 1H), 6.99 (d, 1H, *J* = 8.0 Hz), 7.23-7.49 (m, 4H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 18.2, 34.6, 36.8, 45.9, 55.9, 56.0, 60.0, 101.9, 112.7, 114.9, 115.1, 116.8 , 117.9, 119.1, 120.6, 127.1, 127.3, 128.4, 130.9, 132.3, 140.7, 147.4, 148.8, 149.0, 170.2

2-(4-Benzyloxy-3-nitro-phenyl)-N-[2-(3,4-dimethoxy-phenyl)-ethyl]-acetamide (Table 20, entry 8) By a procedure identical with that described for the synthesis of the amide **121** this compound was prepared in 38% yield as an oil. HRMS calcd for $[M + H]^{+}$ $C_{25}H_{26}N_2O_6$ 450.1791, found 450.1791

^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.73 (t, 2H, *J* = 7.0 Hz), 3.46 (s, 2H), 3.48 (q, 2H, *J* = 13.0 Hz), 3.84 (s, 3H), 3.86 (s, 3H), 5.23 (s, 2H), 5.44 (bs, 1H), 6.58 (d, 1H, *J* = 8.0 Hz), 6.65 (s, 1H), 6.75 (d, 1H, *J* = 8.0 Hz), 6.98 (s, 1H), 7.05 (d, 1H, *J* = 8.0 Hz), 7.32-7.41 (m, 5H), 7.80 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 35.1, 40.9, 42.3, 56.0, 56.1, 71.4, 111.9, 115.7, 120.8, 125.7, 126.4, 127.1, 127.7, 128.4, 128.5, 128.9, 131.0, 135.1, 135.6, 135.9, 140.1, 147.9, 149.3, 151.3, 169.8

N-[2-(3,4-Dimethoxy-phenyl)-ethyl]-2-(4-methoxy-3-nitro-phenyl)-acetamide (173) By a procedure identical with that described for the synthesis of the amide **121**, compound **173** was prepared in 50% yield as a yellow solid mp: 99-101 ^{o}C. HRMS calcd for $[M + H]^{+}$ $C_{19}H_{22}N_2O_6$ 374.1478, found 374.1778

^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.73 (t, 2H, *J* = 7.0 Hz), 3.48 (s, 2H), 3.50 (q, 2H, *J* = 13.0 Hz), 3.84 (s, 3H), 3.87 (s, 3H), 3.97 (s, 3H), 5.42 (bs, 1H), 6.60 (d, 1H, *J* = 2.0 Hz), 6.65 (s, 1H), 6.76 (d, 1H, *J* = 8.0 Hz), 7.03 (d, 1H, *J* = 8.0 Hz), 7.39 (d, 1H *J* = 8.0 Hz), 7.70 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 35.1, 40.9, 42.3, 54.8, 56.0, 56.1, 111.4, 111.9, 114.1, 120.8, 126.4, 127.3, 131.0, 135.0, 135.3, 147.9, 149.3, 151.3, 169.9

General procedure for Imine synthesis: Synthesis of 1-(6-Bromo-benzo[1,3]dioxol-5-ylmethyl)-6,7-dimethoxy-3,4-dihydro-isoquinoline (**107**) To a solution of amide **108** (1.0 g, 2.4 mmol, 1.0 eq) dissolved in dry DCM (30 mL) was added PCl_5 (2.0 g, 7.2 mmol, 3eq) was added in three portions at 0 ^{o}C over 30 minutes. The reaction was stirred for 30 minutes at 0 ^{o}C then overnight at room temperature. The reaction was poured onto saturated sodium bicarbonate and allowed to stir for 1 h. The product was extracted with DCM (2 x 20mL) and washed with 5% sodium bicarbonate. The organic layer was dried over sodium sulfate. The solvent was removed under vacuum yielding **107** as a brown oil in 80% yield. The crude product was used in the following step.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.67 (t, 2H, *J* = 7.0 Hz), 3.74 (t, 2H, *J* = 7.0 Hz), 3.84 (s, 3H), 3.90 (s, 3H), 4.09 (s, 2H), 5.92 (s, 2H), 6.67 (s, 1H), 6.78 (s, 1H), 6.94 (s, 1H), 7.03 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 165.3, 150.8, 147.8, 147.6, 147.3, 131.7, 130.9, 121.9, 114.6, 112.7, 110.4, 109.7, 109.2, 101.8, 56.4, 56.1, 47.6, 42.7, 25.9

6,7-Dimethoxy-1-(3-methoxy-benzyl)-3,4-dihydro-isoquinoline (Table 20, entry 9) By a procedure identical with that described for the synthesis of imine **107**, this compound was prepared in 90% yield as a yellow oil.

^{1}HNMR: (500 MHz, $CDCl_3$) δ 3.03 (t, 2H, *J* = 8.0 Hz), 3.79 (s, 3H), 3.82 (s, 3H), 3.97 (s, 5H), 4.56 (s, 2H), 6.77 (s, 1H), 6.78-6.80 (d, 1H, *J* = 8.0 Hz), 6.94-6.96 (d, 1H, *J* = 8.0 Hz), 6.99 (s, 1H), 7.23 (t, 1H, *J* = 8.0 Hz), 7.26 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 25.5, 39.0, 41.2, 55.6, 56.4, 56.7, 111.1, 112.3, 113.7, 114.8, 117.4, 121.2, 130.5, 134.0, 135.1, 148.8, 156.4, 160.5, 174.5

6,7-Dimethoxy-1-(4-methoxy-benzyl)-3,4-dihydro-isoquinoline (Table 20, entry 10) By a procedure identical with that described for the synthesis of imine **107**, this compound was prepared in 95% yield as a yellow oil.

^{1}HNMR: (500 MHz, $CDCl_3$) δ 3.01 (t, 2H, *J* = 8.0 Hz), 3.76 (s, 3H), 3.82 (s, 3H), 3.98 (s, 5H), 4.58 (s, 2H), 6.76 (s, 1H), 6.83-6.86 (d, 2H, *J* = 9.0 Hz), 7.24 (s, 1H) 7.35-7.37 (d, 2H, *J* = 9.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 25.5, 37.9, 41.0, 55.5, 56.4, 56.7, 111.0, 112.2, 115.0, 117.4, 125.5, 130.3, 134.0, 148.8, 156.2, 159.4, 174.4

1-Benzo[1,3]dioxol-5-ylmethyl-7-benzyloxy-6-methoxy-3,4-dihydro-isoquinoline (Table 20, entry 11) By a procedure identical with that described for the synthesis of imine **107**, this compound was prepared in 98% yield as a brown oil.

^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.98 (t, 2H, *J* = 8.0 Hz), 3.90 (t, 2H, *J* = 8.0Hz), 3.99 (s, 3H), 4.37 (s, 2H), 5.13 (s, 2H), 5.91 (s, 2H), 6.62-6.65 (m, 2H), 6.70 (s, 1H), 6.79 (s, 1H), 7.22 (s, 1H), 7.37-7.42 (m, 5H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 25.6, 38.0, 40.9, 56.7, 71.6, 101.5, 109.1, 109.4, 111.4, 115.0, 117.2, 122.6, 126.8, 127.0, 128.7, 128.7, 129.1, 134.3, 136.0, 147.5, 147.7, 148.5, 157.0, 174.3

1-(3-Iodo-benzyl)-6,7-dimethoxy-3,4-dihydro-isoquinoline (Table 20, entry 12) By a procedure identical with that described for the synthesis of imine **107**, this compound was prepared in 42% yield as a yellow oil.

^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.69 (t, 2H, *J* = 8.0 Hz), 3.79 (t, 2H, *J* = 8.0 Hz), 3.78 (s, 3H), 3.90 (s, 3H), 4.04 (s, 2H), 6.68 (s, 1H), 6.94 (s, 1H), 7.02 (t, 1H, *J* = 8.0 Hz), 7.29 (d, 1H, *J* = 8.0 Hz), 7.54 (d, 1H, *J* = 8.0 Hz), 7.71 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 25.9, 42.7, 46.9, 53.6, 56.2, 56.3, 94.8, 109.7, 110.5, 128.1, 130.5, 132.2. 135.9, 137.9, 147.6

1-(4-(benzyloxy)-3-nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (Table 20, entry 13) By a procedure identical with that described for the synthesis of imine **107**, this compound was prepared in 90% yield as a yellow solid mp: 60-62 ^{o}C.

^{1}HNMR: (500 MHz, $CDCl_3$) δ 3.04 (t, 2H, *J* = 8.0 Hz), 3.92 (s, 3H), 3.78 (t, 2H, *J* = 8.0 Hz), 4.00 (s, 3H), 4.49 (s, 2H), 5.22 (s, 2H), 6.81 (s, 1H), 7.18 (d, 1H, *J* = 9.0 Hz), 7.23 (s, 1H), 7.34-7.45 (m, 5H), 7.79 (d, 1H, *J* = 9.0 Hz) 7.85 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 25.5, 37.4, 41.4, 56.6, 56.9, 71.5, 111.4, 111.7, 116.8, 125.5, 126.2, 127.2, 128.6, 129.0, 134.5, 135.2, 135.5, 149.2, 152.1, 157.2

6,7-dimethoxy-1-(4-methoxy-3-nitrobenzyl)-3,4-dihydroisoquinoline (Table 20, entry 14) By a procedure identical with that described for the synthesis of imine **107**, this compound was prepared in 90% yield as a yellow solid mp: 42-45 ^{o}C.

^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.91 (t, 2H, *J* = 8.0 Hz), 3.88 (t, 2H, *J* = 8.0 Hz), 3.84 (s, 3H), 3.87 (s, 3H), 3.96 (s, 3H), 4.49, (s, 2H), 6.60 (d, 1H, *J* = 8.0 Hz), 6.65 (s, 1H), 6.76 (d, 1H, *J* = 8.0 Hz), 7.02 (d, 1H, *J* = 8.0 Hz), 7.39 (d, 1H, *J* = 8.0 Hz), 7.70 (s, 1H),

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 33.1, 40.4, 51.9, 55.0, 56.6, 56.9, 114.4, 114.7, 115.9, 125.3, 130.0, 130.9, 133.9, 134.5, 144.9, 149.8, 154.0, 164.0

General Procedure for Imine Reduction: Synthesis of 1-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (**123**) Imine **122** (0.4 g, 1.7 mmol, 1.0 eq) was dissolved in MeOH (40mL) and treated with $NaBH_4$ (1.3 g, 24.0 mmol, 5.0 eq) at 0 ^oC. The reaction was stirred at room temperature for 2 h. 5% HCl was slowly added to the reaction mixture. The solvent was removed under vacuum. The reaction was basified with 5% NH_4OH and extracted with DCM (2 x 30 mL). The organic layer was then washed with brine then water and dried over sodium sulfate. The solvent was evaporated under vacuum to yield (**123**) in 74% yield as a yellow solid mp: 163–165 ^oC. The crude product was used in following step.
^{1}**HNMR***:* (500 MHz, $CDCl_3$) δ 2.72-2.85 (m, 3H), 2.91-2.94 (m, 1H), 3.12-3.15 (m, 1H), 3.20-3.22 (m, 1H), 3.85 (s, 3H), 3.87 (s, 3H), 4.08-4.10 (m, 1H), 5.95 (s, 2H), 6.60 (s, 1H), 6.65 (s, 1H), 6.71-6.73 (m, 1H), 6.77-6.79 (m, 2H)
^{13}**CNMR***:* (125 MHz, $CDCl_3$) δ 29.6, 29.7, 40.5, 42.3, 55.9, 56.0, 56.8, 100.9, 108.4, 109.5, 109.6, 111.9, 122.4, 127.3, 130.2, 132.7, 146.2, 147.1, 147.6, 147.9

1-(6-Bromo-benzo[1,3]dioxol-5-ylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline By a procedure identical with that described for the synthesis of amine **123**, compound **108** was prepared in 26% yield as a brown oil.
^{1}**HNMR***:* (500 MHz, $CDCl_3$) δ 2.76-2.74 (m, 2H), 2.91-2.87 (m, 1H), 3.00-2.96 (m, 1H), 3.29-3.23 (m, 2H), 3.83 (s, 3H), 3.86 (s, 3H), 4.22-4.19 (bs, 1H), 5.98 (s, 2H), 6.60 (s, 1H), 6.67 (s, 1H), 6.79 (s, 1H), 7.06 (s, 1H)
^{13}**CNMR***:* (125 MHz, $CDCl_3$) δ 29.6, 40.2, 43.1, 55.3, 56.0, 56.1, 101.9, 109.8, 111.5, 111.9, 113.1, 115.1, 127.4, 130.8, 132.0, 147.3, 147.5, 147.7

1-Benzyl-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (Table 20, entry 15) By a procedure identical with that described for the synthesis of amine **123**, this compound was prepared in 75% yield as a cream oil.
^{1}**HNMR***:* (500 MHz, $CDCl_3$) δ 2.78-2.80 (m, 2H), 2.98-3.03 (m, 2H), 3.19-3.26 (m, 2H), 3.79 (s, 1H), 3.87 (s, 3H), 4.21-4.23 (m, 1H), 6.56 (s, 1H), 6.60 (s, 1H), 7.25-7.36 (m, 5H)
^{13}**CNMR***:* (125 MHz, $CDCl_3$) δ 29.2, 40.6, 42.7, 56.0, 56.0, 56.9, 109.5, 111.8, 126.7, 127.0, 128.8, 129.6, 138.9, 147.1, 147.7

6,7-Dimethoxy-1-(4-methoxy-benzyl)-1,2,3,4-tetrahydro-isoquinoline (Table 20, entry 16) By a procedure identical with that described for the synthesis of amine **123**, this compound was prepared in 65% yield as a yellow oil.
^{1}**HNMR***:* (500 MHz, $CDCl_3$) δ 2.77-2.79 (m, 2H), 2.94-2.98 (m, 2H), 3.14-3.19 (m, 1H), 3.22-3.24 (m, 1H), 3.80 (s, 3H), 3.86 (s, 3H), 4.16 (m, 1H), 6.57 (s, 1H), 6.60 (s, 1H), 6.67 (d, 2H, J = 9.0 Hz), 7.17 (d, 2H, J = 9.0 Hz)
^{13}**CNMR***:* (125 MHz, $CDCl_3$) δ 29.1, 40.6, 41.7, 55.4, 56.0, 56.0, 56.9, 109.5, 111.8, 114.2, 127.0, 129.7, 130.6, 130.7, 147.1, 147.7, 158.5

6,7-Dimethoxy-1-(3-methoxy-benzyl)-1,2,3,4-tetrahydro-isoquinoline (Table 20, entry 17) By a procedure identical with that described for the synthesis of amine **123**, this compound was prepared in 72% yield as a yellow oil.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.76-2.79 (m, 2H), 2.93-2.97 (m, 2H), 3.18-3.24 (m, 2H), 3.81 (s, 4H), 3.87 (s, 3H), 4.21 (m, 1H), 6.60 (s, 2H), 6.80-6.82 (m, 1H), 6.86 (m, 1H), 7.24-7.26 (m, 2H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 29.3, 40.7, 42.8, 55.4, 56.0, 56.1, 56.8, 109.5, 111.8, 112.1, 115.2, 121.9, 127.1, 129.8, 140.6, 147.1, 147.7, 159.9

1-(6-Bromo-benzo[1,3]dioxol-5-ylmethyl)-6,7-dimethoxy-2-(1-phenyl-ethyl)-1,2,3,4-tetrahydro-isoquinoline (*S*-253) By a procedure identical with that described for the synthesis of amine **123**, compound ***S*-253** was prepared in 82% yield yellow solid mp: 51-53 ^{o}C. HRMS calcd for $[M]^+$ $C_{27}H_{28}BrNO_4$ 509.1207, found 509.1202.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 1.35 (d, 3H, *J* = 7.0 Hz), 2.43-2.47 (m, 1H), 2.80-2.88 (m, 1H), 2.91-3.01 (m, 2H), 3.34-3.45 (m, 2H), 3.69 (s, 3H), 3.70-3.82 (m, 1H), 3.88 (s, 3H), 5.95 (s, 1H), 6.00 (s, 1H), 6.31 (s, 1H), 6.53 (s, 1H), 6.62 (s, 1H), 6.90 (s, 1H), 6.92-6.93 (d, 2H, *J* = 7.0 Hz), 7.09-7.17 (m, 3H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 22.3, 23.2, 39.5, 42.8, 55.8, 55.9, 58.2, 59.1, 101.6, 111.3, 111.4, 112.3, 112.4, 115.4, 126.6, 126.9, 127.4, 128.1, 129.6, 132.6, 146.2, 146.7, 146.8, 146.9. 147.3

1-(6-Bromo-benzo[1,3]dioxol-5-ylmethyl)-6,7-dimethoxy-2-(1-phenyl-ethyl)-1,2,3,4-tetrahydro-isoquinoline *(R*-253) By a procedure identical with that described for the synthesis of amine **123**, compound ***R*-253** was prepared in 63% yield as a yellow solid mp: 55-57 ^{o}C. HRMS calcd for $[M]^+$ $C_{27}H_{28}BrNO_4$ 509.1207, found 509.1202.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 1.34 (m, 3H), 2.43-2.47 (m, 1H), 2.83-2.87 (m, 1H), 2.92-3.00 (m, 2H), 3.36-3.45 (m, 2H), 3.69 (s, 3H), 3.78-3.80 (m, 1H), 3.88 (s, 3H), 5.97 (s, 1H), 6.02 (s, 1H), 6.31 (s, 1H), 6.55 (s, 1H), 6.62 (s, 1H), 6.90 (s, 1H), 6.91 (s, 2H), 7.09-7.16 (m, 3H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 22.4, 22.9, 39.3, 42.8, 55.8, 55.9, 58.0, 59.0, 101.6, 111.0, 111.5, 112.3, 112.4, 115.4, 126.6, 126.8, 127.3, 128.2, 129.4, 132.5, 146.2, 146.7, 146.8, 146.9, 147.3

1-(4-Benzyloxy-3-nitro-benzyl)-6,7-dimethoxy-1,2,3,4-tetrahydro-isoquinoline (Table 20, entry 18) By a procedure identical with that described for the synthesis of amine **123**, this compound was prepared in 77% yield as a yellow oil.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.66-2.78 (m, 2H), 2.88-2.98 (m, 2H), 3.15-3.21 (m, 2H), 3.84 (s, 3H), 3.87 (s, 3H), 4.11-4.15 (m, 1H), 5.24 (s, 2H), 6.60 (d, 2H, *J* = 8.0 Hz), 7.07 (d, 1H, *J* = 8.0 Hz), 7.33-7.40 (m, 6H), 7.80 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$)
δ 29.6, 40.7, 41.7, 56.0, 56.2, 56.7, 71.4, 109.4, 112.1, 115.4, 126.4, 127.1, 127.2, 127.6, 128.4, 128.9, 130.0, 132.3, 135.2, 135.8, 140.2, 147.3, 147.8, 150.7

General Procedure for *N*-Alkylation: Synthesis of 1-Benzo[1,3]dioxol-5-ylmethyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinoline (**119**) To a solution of amine **123** (0.5 g, 0.2 mmol, 1.0 eq) dissolved in DCM (30mL) was added 37% formaldehyde (0.5 mL, 0.2 mmol, 1.0 eq) and sodium triacetoxyborohydride (0.1 g, 0.2 mmol, 1.4 eq). The reaction was allowed to stir overnight at room temperature. The reaction was quenched with 5% sodium bicarbonate. The product was extracted with ethyl acetate (2 x 15 mL). The organic layers were combined and dried over sodium sulfate. The solvent was removed under vacuum and the residue was purified by column chromatography: 3% MeOH : DCM. **119** was isolated as a yellow solid in 77% yield. mp 91-99^{o}C. HRMS calcd for $[M]^+$ $C_{20}H_{23}NO_4$ 341.1627, found 341.1627.
^{1}**HNMR***:* (500 MHz, $CDCl_3$) δ 2.52 (s, 3H), 2.59-2.62 (m, 1H), 2.74-2.80 (m, 3H), 3.09-3.13 (m, 1H), 3.19 (m, 1H), 3.63 (s, 3H), 3.68 (m, 1H), 3.85 (s, 3H), 5.91 (s, 1H), 5.92 (s, 1H), 6.12 (s, 1H), 6.54-6.57 (m, 1H), 6.70 (s, 1H), 6.70-6.71 (m, 1H)
^{13}**CNMR***:* (125 MHz, $CDCl_3$) δ 22.5, 23.2, 40.4, 40.4, 44.7, 64.3, 100.9, 108.1, 110.4, 111.1, 111.3, 123.1, 123.3, 125.5, 131.8, 146.2, 146.6, 147.6, 148.1, 176.4

1-Benzo[1,3]dioxol-5-ylmethyl-5,6-dimethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinoline (142) By a procedure identical with that described for the synthesis of amine **119**, compound **142** was prepared in 71 % yield as a yellow oil. HRMS calcd for $[M]^+$ $C_{20}H_{23}NO_4$ 341.1627, found 341.1627.
^{1}**HNMR***:* (500 MHz, $CDCl_3$) δ 2.49 (s, 3H), 2.63-2.66 (m, 1H), 2.76-2.80 (m, 2H), 2.84-2.88 (m, 1H), 3.05 (m, 1H), 3.14 (m, 1H), 3.72 (t, 1H, *J* = 6.0 Hz), 3.80 (s, 3H), 3.84 (s, 3H), 5.92 (s, 1H), 5.93 (s, 1H), 6.49-6.55 (m, 2H), 6.64-6.71 (m, 3H)
^{13}**CNMR***:* (125 MHz, $CDCl_3$) δ 20.4, 41.1, 42.8, 46.6, 55.9, 60.2, 62.8, 100.9, 108.1, 110.0, 110.1, 115.2, 122.7, 123.5, 127.7, 128.7, 145.9, 146.3, 147.5, 150.7

1-Benzyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinoline (138) By a procedure identical with that described for the synthesis of amine **119**, compound **138** was prepared in 37% yield as a yellow oil. HRMS calcd for $[M]^+$ $C_{19}H_{23}NO_2$ 297.1729, found 297.1729.
^{1}**HNMR***:* (500 MHz, $CDCl_3$) δ 2.57 (s, 3H), 2.62-2.65 (m, 1H), 2.78-2.88 (m, 3H), 3.23-3.27 (m, 2H), 3.49 (s, 3H), 3.75-3.78 (m, 1H), 3.84 (s, 3H), 5.92 (s, 1H) 6.57 (s, 1H), 7.10-7.28 (m, 5H)
^{13}**CNMR***:* (125 MHz, $CDCl_3$) δ 25.4, 41.3, 42.6, 46.7, 55.5, 55.8, 65.0, 111.0, 111.2, 125.6, 126.1, 128.3, 128.9, 130.0, 140.0, 146.3, 147.4

6,7-Dimethoxy-1-(4-methoxy-benzyl)-2-methyl-1,2,3,4-tetrahydro-isoquinoline (141) By a procedure identical with that described for the synthesis of amine **119**, compound **141** was prepared in 89% yield as a yellow oil. HRMS calcd for $[M]^+$ $C_{20}H_{25}NO_3$ 327.1834, found 327.1834.
^{1}**HNMR***:* (500 MHz, $CDCl_3$) δ 2.56 (s, 3H), 2.61 (m, 1H), 2.75-2.86 (m, 3H), 3.16-3.20 (m, 2H), 3.55 (s, 3H), 3.70-3.78 (m, 1H), 3.79 (s, 3H), 5.85 (s, 3H), 5.98 (s, 1H), 6.57 (s, 1H), 6.80-6.83 (d, 2H, *J* = 11.0 Hz) 7.01 (d, 2H, *J* = 11.0 Hz)
^{13}**CNMR***:* (125 MHz, $CDCl_3$) δ 25.5, 40.4, 42.8, 46.8, 55.4, 55.6, 55.8, 65.0, 111.1, 111.2, 113.7, 125.9, 130.3, 130.9, 132.1, 146.3, 147.3, 156.0

6,7-Dimethoxy-1-(3-methoxy-benzyl)-2-methyl-1,2,3,4-tetrahydro-isoquinoline (140) By a procedure identical with that described for the synthesis of amine **119**, compound **140** was prepared in 99% yield as a yellow oil HRMS calcd for $[M]^+$ $C_{20}H_{25}NO_3$ 327.1834, found 327.1834.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.55 (s, 3H), 2.60-2.63 (m, 1H), 2.75-2.79 (m, 2H), 2.81-2.82 (m, 1H), 3.17-3.21 (m, 2H), 3.54 (s, 3H), 3.72-3.75 (m, 1H), 3.76 (s, 3H), 3.84 (s, 3H), 6.01 (s, 1H) 6.57 (s, 1H), 6.67 (s, 1H), 6.68-6.76 (m, 2H), 7.19 (t, 1H, *J* = 8.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 25.6, 41.4, 42.8, 46.8, 55.3, 55.6, 55.9, 64.9, 111.1, 111.2, 111.5, 115.6, 122.4, 125.8, 129.3, 129.3, 141.9, 146.3, 147.3, 159.6

5-Benzo[1,3]dioxol-5-ylmethyl-6-methyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]isoquinoline (139) By a procedure identical with that described for the synthesis of amine **119**, compound **139** was prepared in 79% yield as a yellow oil. HRMS calcd for $[M]^+$ $C_{19}H_{19}NO_4$ 325.1314, found 325.1228.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.47 (s, 3H), 2.54 (m, 1H), 2.72-2.81 (m, 3H), 2.99 (m, 1H), 3.15 (m, 1H), 3.65 (t, 1H, *J* = 6.0 Hz), 5.87 (m, 2H), 5.93 (m, 2H), 6.28 (s, 1H), 6.54 (s, 1H), 6.56 (d, 1H, *J* = 8.0 Hz), 6.68 (s, 1H), 6.70(d, 1H, *J* = 8.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 25.8, 41.5, 42.8, 46.8, 65.4, 100.7, 100.9, 107.9, 108.1, 108.6, 110.0, 122.6, 127.5, 130.7, 133.8, 145.5, 145.9, 146.0, 147.5

1-Methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracen-2-ol (216) By a procedure identical with that described for the synthesis of amine **119**, compound **216** was prepared in 50% yield as a yellow solid mp: 145-147 ^oC. HRMS calcd for $[M]^+$ $C_{19}H_{19}NO_4$ 325.1316, found 325.1314.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.45-2.56 (m, 5H), 2.62-2.66 (m, 2H), 2.94-3.13 (m, 4H), 3.58 (s, 3H), 5.97 (s, 1H), 5.99 (s, 1H), 6.65 (s, 1H), 6.77 (s, 1H), 7.83 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 29.1, 35.1, 44.2, 53.5, 60.6, 62.6, 101.1, 107.9, 108.7, 113.5, 125.3, 125.9, 127.0, 129.9, 131.0, 142.4, 146.7, 147.0, 148.2

2-Ethoxy-1-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (211) By a procedure identical with that described for the synthesis of amine **119**, compound **211** was prepared in 62% yield as a yellow solid mp: 101-104 ^oC. HRMS calcd for $[M]^+$ $C_{21}H_{23}NO_4$ 353.1627, found 353.1628.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 1.47 (t, 3H, *J* = 7.0 Hz), 2.45-2.54 (m, 5H), 2.62-2.66 (m, 1H), 2.94-3.02 (m, 3H), 3.08-3.15 (m, 1H), 3.67 (s, 3H), 4.02-4.12 (m, 2H), 5.95 (s, 1H), 5.96 (s, 1H), 6.57 (s, 1H), 6.74 (s, 1H), 7.92 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 15.1, 29.3, 35.3, 44.2, 53.4, 60.2, 62.5, 64.2, 100.9, 108.4, 109.1, 111.8, 125.8, 127.1, 127.3, 128.6, 130.9, 144.7, 146.4, 146.5, 151.4

1-Methoxy-6-methyl-2-propoxy-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (212) By a procedure identical with that described for the synthesis of amine **119**, compound **212** was prepared in 24% yield as a yellow solid mp: 76-77 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{22}H_{25}NO_4$ 367.1784, found 367.1785.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 1.09 (t, 3H, *J* = 7.0 Hz), 1.85-1.93 (m, 3H), 2.48-2.55 (m, 4H), 2.65 (m, 1H), 2.96-3.04 (m, 3H), 3.10-3.17 (m, 1H), 3.69 (s, 3H), 3.90-4.04 (m, 2H), 5.96 (s, 1H), 5.98 (s, 1H), 6.59 (s, 1H), 6.76 (s, 1H), 7.95 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 10.9, 22.9, 29.4, 35.3, 44.2, 53.4, 60.3, 62.6, 70.3, 101.0, 108.4, 109.1, 111.8, 125.8, 127.1, 127.5, 128.6, 131.0, 144.2, 146.4, 146.6, 151.6

2-Butoxy-1-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (213) By a procedure identical with that described for the synthesis of amine **119**, compound **213** was prepared in 26% yield as a yellow solid mp: 95-97 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{23}H_{27}NO_4$ 381.1940, found 381.1940.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 1.01 (t, 3H, *J* = 7.0 Hz), 1.47-1.63 (m, 3H), 1.78-1.92 (m, 2H), 2.46-2.55 (m, 4H), 2.64-2.68 (m, 1H), 2.95-3.04 (m, 3H), 3.10-3.17 (m, 1H), 3.69 (s, 3H), 3.90-4.04 (m, 2H), 5.96 (s, 1H), 5.98 (s, 1H), 6.60 (s, 1H), 6.76 (s, 1H), 7.95 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 14.0, 19.5, 29.4, 31.6, 35.3, 44.2, 53.4, 60.3, 62.6, 68.4, 100.9, 108.4, 109.1, 111.7, 125.8, 127.1, 127.3, 128.6, 130.9, 144.7, 146.4, 146.5, 151.6

1-Methoxy-6-methyl-2-pentyloxy-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (214) By a procedure identical with that described for the synthesis of amine **119**, compound **214** was prepared in 59% yield as a yellow oil. HRMS calcd for $[M]^{+}$ $C_{24}H_{29}NO_4$ 395.2097, found 395.2099.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 0.96 (t, 3H, *J* = 7.0 Hz), 1.37-1.55 (m, 4H), 1.81-1.92 (m, 2H), 2.46-2.55 (m, 5H), 2.63-2.67 (m, 1H), 2.95-3.03 (m, 3H), 3.09-3.15 (m, 1H), 3.68 (s, 3H), 3.94-4.05 (m, 2H), 5.96 (s, 1H), 5.97 (s, 1H), 6.59 (s, 1H), 6.75 (s, 1H), 7.94 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 14.2, 22.6, 28.5, 29.2, 29.4, 35.3, 44.2, 53.4, 60.3, 62.6, 68.7, 100.9, 108.4, 109.1, 111.8, 125.8, 127.1, 127.3, 128.6, 130.9, 144.7, 146.4, 146.5, 151.6

2-Cyclopropylmethoxy-1-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (215) By a procedure identical with that described for the synthesis of amine **119**, compound **215** was prepared in 61% yield as a yellow solid mp: 91-92 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{23}H_{25}NO_4$ 379.1784, found 379.1781.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 036-0.39 (m, 2H), 0.67-0.60 (m, 2H), 1.24-1.37 (m, 1H), 2.45-2.54 (m, 5H), 2.61-2.65 (m, 1H), 2.94-3.02 (m, 3H), 3.07-3.14 (m, 1H), 3.70 (s, 3H), 3.75-3.79 (m, 1H), 3.90-3.94 (m, 1H), 5.95 (s, 1H), 5.97 (s, 1H), 6.56 (s, 1H), 6.74 (s, 1H), 7.93 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 3.3, 3.4, 10.6, 29.3, 35.3, 44.2, 53.4, 60.3, 62.6, 73.7, 100.9, 108.4, 109.1, 112.3, 125.8, 127.1, 127.5, 128.6, 130.9, 144.9, 146.4, 146.5, 151.5

6,7-Dimethoxy-2-methyl-1-(4-nitro-benzyl)-1,2,3,4-tetrahydro-isoquinoline (Table 20, entry 19) By a procedure identical with that described for the synthesis of amine **119**, this compound was prepared in 86% yield as an orange oil. HRMS calcd for $[M + H]^+$ $C_{19}H_{22}N_2O_4$ 342.1580, found 342.1581.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.45-2.49 (m, 1H), 2.50 (s, 3H), 2.71-2.74 (m, 2H), 3.04-3.20 (m, 3H), 3.70 (s, 3H), 3.78 (t, 1H, *J*=6.0 Hz), 3.84 (s, 3H), 6.28 (s, 1H), 6.54 (s, 1H), 7.23 (d, 2H, *J* = 9.0 Hz), 8.07 (d, 2H, *J* = 9.0 Hz)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 25.6, 41.2, 42.9, 47.5, 55.9, 64.5, 110.4, 111.4, 123.2, 126.9, 128.5, 130.7, 146.5, 146.9, 147.6, 148.1

6,7-Dimethoxy-2-methyl-1-(3-nitro-benzyl)-1,2,3,4-tetrahydro-isoquinoline (163) By a procedure identical with that described for the synthesis of amine **119**, compound **163** was prepared in 85% yield as a yellow solid mp: 83-84 ^oC. HRMS calcd for $[M + H]^+$ $C_{19}H_{22}N_2O_4$ 342.1580, found 342.1581.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.46-2.47 (m, 1H), 2.50 (s, 3H), 2.73-2.76 (m, 2H), 3.04-3.08 (m, 1H), 3.15-3.19 (m, 2H), 3.71 (s, 3H), 3.76 (t, 1H, *J* = 6.0 Hz), 3.85 (s, 3H), 6.30 (s, 1H), 6.55 (s, 1H), 7.37-7.38 (m, 2H), 8.03-8.05 (m, 2H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 25.5, 41.0, 42.9, 47.3, 55.9, 56.0, 64.4, 110.5, 111.5, 121.3, 124.7, 126.9, 128.5, 128.7, 136.3, 142.0, 147.0, 147.6, 148.1

1-(4-Benzyloxy-3-nitro-benzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinoline (176) By a procedure identical with that described for the synthesis of amine **119**, compound **176** was prepared in 80% yield as a yellow oil. HRMS calcd for $[M + H]^+$ $C_{26}H_{28}N_2O5$ 448.1789, found 448.1791.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.46-2.50 (m, 2H), 2.51 (s, 3H), 2.70-2.77 (m, 2H), 2.90-2.94 (m, 1H), 3.04-3.16 (m, 2H), 3.69 (s, 3H), 3.84 (s, 3H), 5.20 (s, 2H), 6.27 (s, 1H), 6.53 (s, 1H), 6.94 (d, 1H, *J* = 9.0 Hz), 7.14 (d, 1H, *J* = 9.0 Hz), 7.31-7.38 (m, 5H), 7.80 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 25.6, 40.1, 42.9, 47.5, 56.0, 56.1, 64.5, 67.6, 71.4, 110.7, 111.6, 114.8, 126.8, 127.2, 128.4, 128.6, 128.9, 129.1, 130.6, 135.6, 135.9, 147.1, 147.7, 150.4

6,7-Dimethoxy-1-(4-methoxy-3-nitro-benzyl)-2-methyl-1,2,3,4-tetrahydro-isoquinoline (174) By a procedure identical with that described for the synthesis of amine **119**, compound **174** was prepared in 56% yield as an orange oil. HRMS calcd for $[M + H]^+$ $C_{20}H_{24}N_2O_5$ 372.1685, found 372.1685.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.46-2.52 (m, 1H), 2.50 (s, 3H), 2.69-2.77 (m, 2H), 2.92-2.96 (m, 1H), 3.03-3.08 (m, 1H), 3.11-3.17 (m, 1H), 3.69 (t, 1H, *J* = 6.0 Hz), 3.73 (s, 3H), 3.84 (s, 3H), 3.91 (s, 3H), 6.31 (s, 1H), 6.54 (s, 1H), 6.91 (d, 1H, *J* = 9.0 Hz), 7.19 (d, 1H *J* = 9.0 Hz), 7.67 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 25.6, 40.1, 42.9, 47.4, 56.0, 57.2, 64.5, 110.7, 111.5, 114.8, 126.3, 126.4, 128.7, 133.6, 135.9, 139.9, 147.1, 147.7, 152.3

2-Acetylene-1-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (Table 20, entry 42) By a procedure identical with that described for the synthesis of amine **119**, this compound was prepared in 72% yield as a clear oil. HRMS calcd for $[M]^+$ $C_{21}H_{19}NO_3$ 333.1367, found 333.1365.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.42-2.48 (m, 1H), 2.50 (s, 3H), 2.63-2.67 (m, 1H), 2.94-3.10 (m, 5H), 3.24 (s, 1H), 3.68 (s, 3H), 5.94 (s, 1H), 5.96 (s, 1H), 6.73 (s, 1H), 7.14 (s, 1H), 7.89 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 28.7, 34.7, 44.2, 53.1, 60.9, 63.1, 80.4, 80.8, 101.2, 108.4, 108.9, 115.9, 125.1, 126.8, 129.2, 130.8, 132.7, 137.5, 146.8, 146.9, 156.8

2-Ethyl-1-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (224) By a procedure identical with that described for the synthesis of amine **119**, compound **224** was prepared in 62% yield as a yellow solid mp: 48-50^{o}C. HRMS calcd for $[M]^+$ $C_{21}H_{23}NO_3$ 337.1684, found 337.1678.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 1.24 (t, 3H *J* = 7.0 Hz), 2.50 (s, 3H), 2.45-2.55 (m, 2H), 2.57-2.76 (m, 3H), 2.92-3.12 (m, 4H), 3.47 (s, 3H), 5.94 (s, 1H), 5.96 (s, 1H), 6.73 (s, 1H), 6.86 (s, 1H), 7.92 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 15.3, 23.0, 28.8, 29.9, 35.0, 44.2, 53.5, 60.4, 63.1, 101.0, 108.4, 108.6, 126.0, 126.1, 128.2, 128.6, 130.7, 136.6, 146.4, 146.9, 153.7

2-Propyl-1-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (225) By a procedure identical with that described for the synthesis of amine **119**, compound **225** was prepared in 20% yield as a yellow oil. HRMS calcd for $[M]^+$ $C_{22}H_{25}NO_3$ 351.1834, found 351.1834.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 1.24 (t, 3H *J* = 7.0 Hz), 1.59-1.68 (m, 2H), 2.46-2.49 (m, 3H), 2.52 (s, 3H), 2.64-2.71 (m, 2H), 2.93-3.11 (m, 4H), 3.47 (s, 3H), 5.94 (s, 1H), 5.96 (s, 1H), 6.74 (s, 1H), 6.85 (s, 1H), 7.92 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 14.6, 24.2, 28.9, 29.9, 32.2, 44.1, 53.5, 60.5, 63.1, 101.1, 108.4, 108.6, 126.0, 126.2, 128.7, 128.8, 128.9, 132.3, 132.4, 146.4, 146.9, 153.8,

2-Butyl-1-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (226) By a procedure identical with that described for the synthesis of amine **119**, compound **226** was prepared in 62% yield as a yellow solid mp: 48-50^{o}C. HRMS calcd for $[M]^+$ $C_{23}H_{27}NO_3$ 365.1994, found 365.1991.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 0.93 (t, 3H *J* = 6.0 Hz), 1.36-1.44 (m, 2H), 1.51-1.65 (m, 2H), 2.47-2.53 (m, 3H), 2.50 (s, 3H), 2.62-2.71 (m, 2H), 2.91-3.10 (m, 4H), 3.46 (s, 3H), 5.95 (s, 1H), 5.98 (s, 1H), 6.72 (s, 1H), 6.84 (s, 1H), 7.91 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 14.2, 23.1, 29.8, 33.4, 44.2, 53.4, 53.5, 60.4, 63.1, 64.5, 66.1, 101.0, 108.4, 108.6, 126.0, 126.1, 128.7, 128.9, 129.9, 132.8, 146.4, 146.9, 153.8

2-Pentyl-1-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (227) By a procedure identical with that described for the synthesis of amine **119**, compound **227** was prepared in 42% yield as a yellow oil. HRMS calcd for $[M]^+$ $C_{24}H_{29}NO_3$ 379.2152, found 379.2147.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 0.89 (t, 3H *J* = 6.0 Hz), 1.42 (m, 4H), 1.57-1.67 (m, 2H), 2.49 (s, 3H), 2.47-2.51 (m, 3H), 2.63-2.69 (m, 2H), 2.93-3.11 (m, 4H), 3.46 (s, 3H), 5.94 (s, 1H), 5.96 (s, 1H), 6.73 (s, 1H), 6.84 (s, 1H), 7.92 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 14.3, 22.8, 28.8, 30.1, 30.9, 32.2, 35.0, 44.1, 45.9, 53.5, 60.4, 63.1, 101.1, 108.4, 108.6, 126.0, 126.2, 128.5, 128.9, 130.6, 135.4, 146.4, 146.9, 153.8

6-Ethyl-1,2-dimethoxy-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (202) By a procedure identical with that described for the synthesis of amine **119**, compound **202** was prepared in 87% yield as a solid mp: 220-222 ^oC. HRMS calcd for $[M + H]^+$ $C_{21}H_{23}NO_4$ 353.1627, found 353.1630.
^{1}HNMR: (500 MHz, $CDCl_3$) δ1.15 (t, 3H, *J* = 7.0 Hz), 2.48-2.71 (m, 4H), 2.96-2.99 (m, 1H), 3.08-3.12 (m, 2H), 3.17-3.19 (m, 1H), 3.27 (m, 1H), 3.65 (s, 3H), 3.88 (s, 3H), 5.97 (s, 1H), 5.98 (s, 1H), 6.60 (s, 1H), 6.76 (s, 1H), 7.92 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 10.8, 29.4, 35.0, 47.9, 48.4, 55.9, 59.3, 60.4, 101.0, 108.4, 109.1, 110.8, 125.8, 127.3, 129.1, 131.1, 144.6, 146.5, 146.7, 152.0

1,2-Dimethoxy-6-propyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (203) By a procedure identical with that described for the synthesis of amine **119**, compound **203** was prepared in 92% yield as a yellow oil. HRMS calcd for $[M]^+$ $C_{22}H_{25}NO_4$ 367.1786, found 367.1784.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 0.97 (t, 3H, *J* = 7.0 Hz), 1.57-1.60 (m, 2H), 2.41-2.54 (m, 3H), 2.66-2.69 (m, 1H), 2.81-2.89 (m, 1H), 2.95-2.99 (m, 1H), 3.01-3.09 (m, 1H), 3.15-3.25 (m, 2H), 3.65 (s, 3H), 3.88 (s, 3H), 5.97 (s, 1H), 5.98 (s, 1H), 6.59 (s, 1H), 6.77 (s, 1H), 7.92 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 12.2, 19.7, 29.5, 35.3, 49.3, 55.9, 56.4, 60.0, 60.3, 101.0, 108.4, 109.0, 110.7, 125.7, 127.3, 128.1, 129.2, 131.2, 144.5, 146.4, 146.6, 151.9

6-Butyl-1,2-dimethoxy-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (204) By a procedure identical with that described for the synthesis of amine **119**, compound **204** was prepared in 84% yield as a yellow oil. HRMS calcd for $[M]^+$ $C_{23}H_{27}NO_4$ 381.1944, found 381.1944.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 0.98(t, 3H, *J* = 7.0 Hz), 1.38-1.42 (m, 2H), 1.59-1.55 (m, 2H), 2.43-2.55 (m, 3H), 2.70 (m, 1H), 2.96-3.12 (m, 3H), 3.15-3.25 (m, 2H), 3.66 (s, 3H), 3.89 (s, 3H), 5.98 (s, 1H), 5.99 (s, 1H), 6.60 (s, 1H), 6.78 (s, 1H), 7.92 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 14.3, 21.0, 28.7, 29.6, 35.3, 49.3, 54.2, 56.0, 60.0, 60.4, 101.0, 108.1, 109.0, 110.7, 125.8, 127.3, 128.2, 129.3, 131.3, 144.5, 146.4, 146.6, 151.9

1,2-Dimethoxy-6-pentyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (205) By a procedure identical with that described for the synthesis of amine **119**, compound **205** was prepared in 74% yield as a yellow oil. HRMS calcd for $[M]^+$ $C_{24}H_{29}NO_4$ 395.2102, found 395.2097.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 0.93 (t, 3H, *J* = 7.0 Hz), 1.37-1.42 (m, 2H), 1.56-1.59 (m, 2H), 2.43-2.55 (m, 4H), 2.62-2.69 (m, 2H), 2.95-2.97 (m, 2H), 2.98.2.99 (m, 1H), 3.15-3.17 (m, 2H), 3.65 (s, 3H), 3.88 (s, 3H), 5.97 (s, 1H), 5.99 (s, 1H), 6.59 (s, 1H), 6.77 (s, 1H), 7.92 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 14.3, 22.9, 26.2, 29.6, 30.1, 35.3, 49.3, 54.5, 56.0, 60.0, 60.4, 101.0, 108.4, 109.0, 110.7, 125.8, 127.3, 128.1, 129.2, 131.3, 144.5, 146.4, 146.6, 151.9

6-Cyclopropylmethyl-1,2-dimethoxy-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (206) By a procedure identical with that described for the synthesis of amine **119**, compound **206** was prepared in 74% yield as a yellow oil. HRMS calcd for $[M]^+$ $C_{23}H_{25}NO_4$ 379.1789, found 379.1784.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 0.19-0.20 (m, 2H), 0.52-0.59 (m, 2H), 0.96-1.02 (m, 1H), 2.36-2.41 (m, 1H), 2.48-2.57 (m, 2H), 2.71-2.27 (m, 1H), 2.93-2.99 (m, 2H), 3.03-3.12 (m, 1H), 3.31-3.35 (m, 1H), 3.77-3.89 (m, 1H), 3.65 (s, 3H), 3.88 (s, 3H), 5.97 (s, 1H), 5.99 (s, 1H), 6.60 (s, 1H), 6.76 (s, 1H), 7.92 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 3.1, 5.2, 7.7, 29.5, 35.2, 49.5, 56.0, 59.2, 59.5, 60.4, 101.0, 108.3, 109.0, 110.7, 125.8, 127.2, 128.0, 129.2, 131.2, 144.5, 146.4, 146.6, 151.9

General Procedure for PIFA-mediated Biaryl coupling: Synthesis of 1,2-Dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (**32**) A solution of PIFA (1.7 g, 4.0 mmol, 1.2 eq) in HFIP (5 mL) was added to a solution of amine **119** (1.2 g, 3.3 mmol, 1.0 eq) and $BF_3{\cdot}OEt$ (1.0 mL, 7.9 mmol, 2.4 eq) in HFIP (10mL). The reaction was stirred at room temperature for 30 minutes. The reaction was quenched with MeOH. The solvent was evaporated under vacuum. The resulting residue was purified by column chromatography yielding **32** in 16% yield as a cream solid mp: 135 ^oC. HRMS calcd for $[M]^+$ $C_{20}H_{21}NO_4$ 339.1472, found 339.1471.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.47-2.55 (m, 5H), 2.66 (m, 1H), 2.95-3.02 (m, 3H), 3.12-3.24 (m, 1H), 3.65 (s, 3H), 3.87 (s, 3H), 5.94 (s, 1H), 5.96 (s, 1H), 6.59 (s, 1H), 6.75 (s, 1H), 7.93 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 29.5, 35.4, 44.2, 53.4, 56.0, 60.4, 62.7, 101.0, 108.4, 109.1, 110.8, 125.8, 127.1, 127.6, 128.8, 131.1, 142.7, 146.5, 146.6, 152.1

2,3-Dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (143) By a procedure identical with that described for the synthesis of aporphine **32**, compound **143** was prepared in 86% yield as an orange oil. HRMS calcd for $[M]^+$ $C_{20}H_{21}NO_4$ 339.1472, found 339.1471.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.44-2.48 (m, 1H), 2.53-2.59 (m, 4H), 2.92-3.12 (m, 5H), 3.83 (s, 3H), 3.91 (s, 3H), 5.94 (s, 1H), 5.96 (s, 1H), 6.73 (s, 1H), 6.99 (s, 1H), 7.13 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 24.0, 34.5, 43.9, 53.3, 56.0, 60.2, 62.0, 101.0, 104.0, 106.2, 108.9, 126.7, 128.0, 128.1, 129.2, 129.4, 145.6, 146.7, 147.2, 151.3

1,2,9-Trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline (140A) By a procedure identical with that described for the synthesis of aporphine **32**, compound **140A** was prepared in 8% yield as an orange oil. HRMS calcd for $[M]^+$ $C_{20}H_{23}NO_3$ 325.1678, found 325.1678.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.64 (s, 3H), 2.66-2.77 (m, 3H), 3.07-3.12.(m, 1H), 3.19-3.26 (m, 3H), 3.65 (s, 3H), 3.85 (s, 3H), 3.88 (s, 3H), 6.59 (s, 1H), 6.61 (s, 1H), 6.86 (d, 1H, *J* = 9.0 Hz), 8.31 (d, 1H, *J* = 9.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 28.5, 29.9, 35.0, 53.3, 55.4, 56.0, 60.2, 62.4, 110.5, 112.7, 113.5, 124.8, 127.1, 128.1, 129.8, 129.9, 137.6, 144.9, 152.5, 158.9

1,2-methylenedioxy-6-methyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (139A) By a procedure identical with that described for the synthesis of aporphine **32**, compound **139A** was prepared in 6% yield as an orange oil. HRMS calcd for $[M]^+$ $C_{19}H_{17}NO_4$ 323.1158, found 323.1155.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.51-2.65 (m, 6H), 3.04-3.13 (m, 4H), 5.93 (s, 1H), 5.96 (s, 1H), 5.98 (s, 1H), 6.07 (s, 1H), 6.53 (s, 1H), 6.76 (s, 1H), 7.62 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 29.4, 34.8, 44.1, 53.7, 62.4, 100.8, 101.1, 107.0, 107.6, 108.8, 116.8, 124.7, 126.7, 126.7, 129.9, 142.0, 146.7, 146.7, 149.8

General Procedure for Synthesis of Nitrostyrenes: Synthesis of 4-Benzyloxy-3-methoxy-β-nitrostyrene (Table 20, entry 36) Nitromethane (33.0 mL, 7.5 mmol, 3.0 eq) was added to a mixture of benzylated vanillin **180** (1.0 g, 6.6 mmol, 1.0 eq), ammonium acetate (1.5 g, 20.0 mmol, 0.3 eq) dissolved in acetic acid (150mL). The reaction was refluxed for 2 h. The reaction was cooled to room temperature. The product crashed out of solution as yellow crystals in 95% yield mp: 122-123 ^oC. HRMS calcd for $[M]^+$ $C_{16}H_{15}NO_4$ 285.1002, found 285.1001.

^{1}HNMR: (500 MHz, $CDCl_3$) δ 3.94 (s, 3H), 5.22 (s, 2H), 6.92 (d, 1H *J* = 8.0 Hz), 7.03 (s, 1H), 7.12 (d, 1H, *J* = 8.0 Hz), 7.38 (d, 1H J=7.1 Hz), 7.39 (t, 3H *J* = 7.1 Hz), 7.43 (d, 1H *J* = 7.1 Hz), 7.51 (d, 1H *J* = 14.0 Hz), 7.95 (d, 1H *J* = 14.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 56.3, 71.1, 110.9, 113.6, 124.5, 127.4, 128.4, 128.9, 135.4, 136.2, 139.5, 150.2, 152.1

3-Benzyloxy-4-methoxy-β-nitrostyrene (Table 20, entry 37) By a procedure identical with that described for the previous nitrostyrene synthesis, this compound was prepared in 90% yield as a yellow solid mp: 126-128 ^oC. HRMS calcd for $[M]^+$ $C_{16}H_{15}NO_4$ 285.1002, found 285.1001.

^{1}HNMR: (500 MHz, $CDCl_3$) δ 3.94 (s, 3H), 5.17 (s, 2H), 6.93 (d, 1H *J* = 8.0 Hz), 7.03 (s, 1H), 7.12 (d, 1H, *J* = 8.0 Hz), 7.38 (d, 1H *J* = 7.0 Hz), 7.39 (t, 3H *J* = 7.0 Hz), 7.43 (d, 1H *J* = 7.0 Hz), 7.51 (d, 1H *J* = 14.0 Hz), 7.90 (d, 1H *J* = 14.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 56.3, 71.4, 111.9, 113.4, 125.1, 127.5, 127.7, 128.4, 128.9, 135.3, 136.4, 139.5, 148.8, 153.6

General Procedure for the Reduction of Nitrostyrenes: Synthesis of 2-(4-Benzyloxy-3-methoxy-phenyl)-ethylamine (75) TMS-Cl (7.0 mL, 53.8 mmol, 8.5 eq) was slowly added to a vigorously stirring suspension of $LiBH_4$ (0.6 g, 25.3 mmol, 4.0 eq) in dry THF (30 mL) under argon. A solution of the nitrostyrene **(Table 17, entry 36)** (1.1 g, 6.3 mmol, 1.0 eq) in dry THF (20 mL) was added dropwise to the mixture and heated at reflux for 18 h. The reaction was cooled to room temperature then quenched with methanol. The reaction mixture was removed under reduced pressure. The residue was dissolved in 20% aqueous KOH and extracted with DCM (3 x 25 mL). The organic layers were then dried over sodium sulfate and concentrated under vacuum. The product **75** was isolated as a cream oil in 95% yield and was used in the following step without purification.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.69 (t, 2H *J* = 7.0 Hz), 2.95 (t, 2H *J* = 7.0 Hz), 3.89 (s, 3H), 5.14 (s, 2H), 6.68 (d, 1H *J* = 8.0 Hz), 6.75 (s, 1H), 6.83 (d, 1H, *J* = 8.0 Hz), 7.33 (t, 2H *J* = 7.0 Hz), 7.37 (d, 2H *J* = 7.0 Hz)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 40.2, 44.43, 56.3, 78.0, 114.5, 115.0, 121.2, 127.3, 127.4, 127.7, 128.2, 128.3, 133.6, 140.9, 144.8, 147.5

2-(3-Benzyloxy-4-methoxy-phenyl)-ethylamine (C3-OBn-75) By a procedure identical with that described for the synthesis of **18**, this compound was prepared in 90% yield as a cream oil.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.63 (t, 2H *J* = 7.0 Hz), 2.88 (t, 2H *J* = 7.0 Hz), 3.87 (s, 3H), 5.15 (s, 2H), 6.76 (d, 2H *J* = 8.0 Hz), 6.83 (s, 1H), 7.30 (d, 1H, *J* = 8.0 Hz), 7.36 (t, 2H *J* = 7.0 Hz), 7.44 (d, 2H *J* = 7.0 Hz)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 39.5, 43.6, 56.2, 71.2, 114.1, 115.3, 121.6, 127.5, 127.4, 127.7, 128.0, 128.7, 132.4, 137.3, 148.1, 148.4

General Procedure of N-Protection: Synthesis of 1-(6-Bromo-benzo[1,3]dioxol-5-ylmethyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid *tert*-butyl ester (**185**) To a solution of the amine **108** (1.0 g, 2.0 mmol, 1.0 eq) dissolved in DCM (50mL) was added diisopropyl ethylamine (0.4 mL, 4.0 mmol, 2.0 eq) and 3mg of DMAP, and Boc anhydride (0.5 mL, 2.4 mmol, 1.2 eq). The reaction mixture was stirred overnight at room temperature. The reaction was quenched with aq. NH_4Cl. The product was extracted with DCM (3x 20mL). The organic layers were combined and dried over sodium sulfate. The solvent was then removed under vacuum. The product **185** was purified by column chromatography (10% EtOAc: Hexanes) yielding a white solid in 68% yield mp: 139-141 ^{o}C. HRMS calcd for $[M]^+$ $C_{24}H_{28}BrNO_6$ 505.1102, found 505.1100.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 1.21 (s, 9H), 2.67 (m, 2H), 2.91 (m, 2H), 3.18 (m, 2H), 3.87 (s, 6H), 4.32 (m, 1H), 5.91 (s, 1H), 5.96 (s, 1H), 6.59 (s, 1H), 6.62 (s, 1H), 6.78 (s, 1H), 7.05 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 28.0, 28.1, 28.2, 42.5, 53.8, 55.8, 55.8, 55.9, 55.9, 79.5, 101.7, 109.3, 111.1, 111.4, 112.4, 115.2, 126.4, 128.7, 13.19, 147.2, 147.2, 147.2, 147.6, 154.3

1-[1-(6-Bromo-benzo[1,3]dioxol-5-ylmethyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl]-2,2,2-trifluoro-ethanone (192) By a procedure identical with that described for the synthesis of **185**, compound **192** was prepared in 95% yield as a white solid mp: 115-116 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{21}H_{19}BrF_3NO_5$ 501.0402, found 501.0399 (Major Rotamer).
^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.79-2.83 (m, 1H), 2.97 (m, 1H), 3.07-3.11 (m, 1H), 3.29-3.33 (d, 1H, *J* = 14.0 Hz), 3.75 (m, 1H), 3.78 (s, 3H), 3.87 (s, 3H), 4.04 (d, 1H, *J* = 3.0 Hz), 5.72 (t, 1H, *J* = 3.0 Hz), 5.98 (s, 1H), 5.95 (s, 1H), 6.53 (s, 1H), 6.61 (s, 1H), 6.65 (s, 1H), 7.00 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 28.7, 40.1, 41.4, 54.0, 55.8, 55.9, 101.7, 110.0, 110.6, 110.7, 112.7, 115.6, 117.6, 124.8, 126.5, 129.4, 147.3, 147.5, 147.7, 148.3, 155.9

6-Benzyloxy-1-(6-bromo-benzo[1,3]dioxol-5-ylmethyl)-7-methoxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (196) By a procedure identical with that described for the synthesis of **185**, compound **196** was prepared in 52% yield as a white solid mp: 58-68 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{30}H_{32}BrNO_6$ 581.1413, found 581.1413 (Major Rotamer).
^{1}HNMR: (500 MHz, $CDCl_3$) δ 1.18 (s, 9H), 2.57-2.61 (m, 1H) 2.84-2.90 (m, 1H), 3.18-3.21 (m, 2H). 3.90 (s, 3H), 4.36 (bs 1H), 5.14 (s, 2H), 5.30 (bs, 1H), 5.98 (s, 1H), 6.01 (s, 1H), 6.58-6.65 (m, 2H), 6.84 (s, 1H), 7.00 (s, 1H), 7.06 (s, 1H), 7.32 (s, 1H), 7.39 (s, 2H), 7.45 (s, 2H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 27.6, 28.44, 36.2, 38.5, 42.6, 53.9, 56.2, 70.9, 79.6, 101.8, 110.1, 110.9, 111.5, 112.6, 113.6, 115.4, 126.4, 127.9, 128.0, 128.7, 128.8, 129.4, 131.3, 137.0, 146.9, 147.3, 147.9, 154.4

Benzyl-1-((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)-6,7-dimethoxy-3,4-dihydroisoquinoline-2(1H)-carboxylate (193) By a procedure identical with that described for the synthesis of **185**, compound **193** was prepared in 60% yield as a white solid mp: 100-103 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{27}H_{26}BrNO_6$ 539.0950, found 539.0944 (Major Rotamer).
^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.64-2.68 (m, 1H) 2.88-2.96 (m, 1H), 3.12-3.18 (m, 2H). 3.31-3.37 (m, 1H), 3.78 (s, 3H), 3.84 (m, 1H), 4.29-4.34 (d, 1H, *J* = 12.0 Hz), 4.77-4.89 (d, 2H, *J* = 12.0 Hz), 5.32-5.35 (m, 1H), 5.88 (s, 1H), 5.90 (s, 1H), 6.48 (s, 1H), 6.60 (d, 2H, *J* = 4.0 Hz), 6.57 (s, 1H), 7.25 (d, 2H, *J* = 4.0 Hz), 7.30-7.45 (m, 5H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 28.1, 37.8, 39.0, 42.1, 54.4, 56.1, 67.4, 101.7, 110.0, 111.1, 111.5, 112.7, 115.7, 126.4, 127.9, 128.1, 128.3, 128.4, 128.5, 128.6, 130.9, 136.4, 147.2, 147.4, 155.2

1-(3-Iodo-benzyl)-6,7-dimethoxy-3,4-dihydro-1H-isoquinoline-2-carboxylic acid tert-butyl ester (168) By a procedure identical with that described for the synthesis of **185**, compound **168** was prepared in 67% yield as a yellow oil. HRMS calcd for $[M]^{+}$ $C_{23}H_{28}INO_4$ 509.1071, found 509.1063 (Major Rotamer).
^{1}HNMR: (500 MHz, $CDCl_3$) δ 1.31 (s, 9H), 2.74-2.80 (m, 1H), 2.85-3.08 (m, 3H), 3.24-3.29 (m, 1H), 3.78 (s, 3H), 4.90 (s, 5H), 4.20-4.22 (m, 1H), 5.08-5.11 (m, 1H), 6.38 (s, 1H), 6.63 (s, 1H), 6.97-7.10 (m, 2H), 7.45-7.60 (m, 2H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 28.1, 28.6, 29.9, 37.2, 39.5, 42.7, 55.9, 56.4, 79.8, 80.0, 94.5, 110.7, 111.7, 126.7, 128.5, 129.3, 130.3, 135.6, 138.8, 141.4, 147.4, 148.0, 154.8

General Procedure for Direct Arylation: Synthesis of 1,2-Dimethoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (**186**) Ce_2CO_3 (0.6 g, 2.0 mmol, 3.0 eq), Tricyclohexylphosphine (0.1 g, 0.3 mmol, 0.4 eq), palladium acetate (0.1 g, 0.1 mmol, 0.02 eq), and **185** (0.3 g, 0.7 mmol, 1.0 eq) was placed in a round bottom flask with a stir bar. The flask was purged with argon (3 x). DMF was then added to the flask. The reaction mixture was then heated to 100 ^oC and stirred overnight. The reaction was cooled to room temperature, and treated with 1N HCl. The product was extracted in ethyl acetate and dried over sodium sulfate. The solvent was removed under vacuum. The product was purified by column chromatography (10% EtOAc : Hexanes) yielding **186** in 52% yield as a white solid mp: 179-178 ^oC. HRMS calcd for $[M]^+$ $C_{24}H_{27}NO_6$ 425.1858, found 425.1858.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.66-2.84 (m, 7H), 3.67 (s, 3H), 3.90 (s, 3H), 5.99 (s, 2H), 6.64 (s, 1H), 6.76 (s, 1H), 8.01 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 14.3, 28.5, 30.3, 35.0, 51.7, 55.9, 60.0, 60.4, 79.9, 100.9, 108.3, 108.9, 110.73, 125.1, 125.8, 127.6, 129.7, 131.5, 144.8, 146.5, 146.6, 151.9

1,2-Dimethoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid benzyl ester (195) By a procedure identical with that described for the synthesis of **186**, compound **195** was prepared in 38% yield as a white solid mp: 139-141 ^oC. HRMS calcd for $[M]^+$ $C_{27}H_{25}NO_6$ 459.1690, found 459.1682.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.73-2.94 (m, 5H), 3.65 (s, 3H), 3.87 (s, 3H), 4.40 (m, 1H), 4.64-4.68 (m, 1H), 5.17 (m, 2H), 6.02 (s, 2H), 6.79 (bs, 1H), 6.82 (s, 1H), 7.32-7.44 (m, 5H), 7.90 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 31.3, 38.7, 40.0, 53.1, 56.6, 60.5, 67.8, 102.5, 109.7, 109.9, 112.8, 126.4, 126.5, 128.5, 129.1, 129.2, 129.8, 131.0, 132.7, 138.7, 146.4, 148.0, 148.1, 153.6

General Procedure for N-Deprotection: Synthesis of 1,2-Dimethoxy-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene (191) A round bottom flask containing a stir bar and zinc bromide (0.4 g, 1.9 mmol, 4.0 eq) was first heated under vacuum using Bunsen burner to remove all moister. The flask was cooled to room temperature then placed under nitrogen. A solution of **186** (0.2 g, 0.5 mmol, 1.0 eq) dissolved in DCM was then added to the zinc bromide and allowed to stir overnight. Saturated sodium bicarbonate was added to the mixture. The product was extracted in the organic layer using DCM then dried over sodium sulfate. The solvent was removed under vacuum. **191** was isolated in 97% yield as a yellow oil. The compound was used in the next step without further purification. HRMS calcd for $[M]^+$ $C_{19}H_{19}NO_4$ 325.1318, found 325.1314.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.18 (bs, 2H), 2.64-2.77 (m, 2H), 3.01 (m, 2H), 3.37-3.39 (m, 1H), 3.68 (s, 3H), 3.79-3.83 (m, 1H), 3.89 (s, 3H), 5.97 (s, 1H), 5.98 (s, 1H), 6.62 (s, 1H), 6.74 (s, 1H), 7.97 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 30.4, 39.1, 51.9, 56.0, 60.1, 60.5, 67.2, 101.0, 109.0, 110.8, 125.4, 128.1, 128.7, 129.7, 131.2, 136.8, 145.0, 146.7, 152.1

1-Methoxy-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracen-2-ol (Table 20, entry 41) By a procedure identical with that described for the synthesis of **191**, this compound was prepared in 90% yield as a yellow oil.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.62-2.74 (m, 4H), 2.89-3.01 (m, 2H), 3.32-3.36 (m, 2H), 3.60 (s, 3H), 3.74-3.77 (m, 1H), 5.98 (s, 1H), 6.00 (s, 1H), 6.67 (s, 1H), 6.75 (s, 1H), 7.84 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 29.2, 37.7, 43.4, 53.9, 60.6, 101.1, 107.9, 108.6, 114.0, 125.4, 125.6, 128.3, 130.2, 130.8, 142.3, 146.7, 146.9, 148.3

General Procedures for Hydrogenation: Synthesis of 1-(benzo[d][1,3]dioxol-5-ylmethyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinolin-7-ol (103) Benzyloxy tertiary amine **102** (1.7 g, 4.1 mmol, 1.0 eq) was added to a round bottom flask and flushed with argon (3 x). Then 10% palladium on activated carbon (0.2 g, 0.1 eq) and a stir bar was added over the amine. Flush again with argon (3 x). Slowly add ethanol (60mL) to the flask to cover the catalyst. Evacuate the flask and flush with H_2 (3 x). Allow stirring overnight. The reaction was filtered through a soxhlet thimble. The solvent want removed under vacuum to yield **103** in 80% yield as a yellow oil. HRMS calcd for $[M]^+$ $C_{19}H_{21}NO_4$ 327.1471, found 327.1471.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.47 (s, 3H), 2.56-2.59 (m, 2H), 2.74-2.84 (m, 3H), 3.01-3.05 (m, 2H), 3.16-3.17 (m, 1H), 3.85 (s, 3H), 5.91 (s, 2H), 6.39 (s, 1H), 6.54-6.57 (m, 2H), 6.67 (s, 1H), 6.69 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 25.4, 41.5, 42.8, 47.2, 58.6, 64.8, 100.8, 110.0, 110.7, 113.5, 113.7, 122.5, 125.8, 130.5, 134.0, 143.5, 145.2, 145.8, 147.5

2-Hydroxy-1-methoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (209) By a procedure identical with that described for the synthesis of amine **103**, compound **209** was prepared in 95% yield as a clear oil. HRMS calcd for $[M]^+$ $C_{23}H_{25}NO_6$ 411.1688, found 411.1682.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.63-2.89 (m, 4H), 3.59 (s, 3H), 3.72-3.74 (m, 2H), 4.30 (bs, 1H), 4.60 (bs, 1H), 5.83 (s, 1H), 6.01 (s, 2H), 6.71 (s, 1H), 6.77 (s, 1H), 7.88 (s, 1H),
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 18.6, 28.7, 30.3, 42.7, 51.9, 58.7, 60.4, 80.1, 101.2, 107.9, 109.0, 113.5, 124.9, 125.5, 131.2, 131.7, 142.6, 146.9, 147.0, 148.2, 155.5

1-Hydroxy-2-methoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (210) By a procedure identical with that described for the synthesis of amine **103**, compound **210** was prepared in 95% yield as a white solid mp: 216 ^{o}C. HRMS calcd for $[M]^+$ $C_{23}H_{25}NO_6$ 411.1688, found 411.1682.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.63-2.89 (m, 6H), 3.73 (s, 3H), 3.72-3.74 (m, 2H), 4.30 (bs, 1H), 4.60 (bs, 1H), 5.83 (s, 1H), 6.00 (s, 2H), 6.71 (s, 1H), 6.77 (s, 1H), 7.88 (s, 1H),
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 18.6, 29.9, 33.7, 38.7, 42.7, 56.5, 62.0, 79.8, 101.2, 108.8, 109.0, 109.5, 109.8, 123.7, 124.2, 125.2, 130.0, 146.7, 148.5, 149.1, 152.3

4-(6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-phenylamine (Table 20, entry 20) By a procedure identical with that described for the synthesis of amine **103**, this compound was prepared in 48% yield as a yellow oil. HRMS calcd for $[M + H]^+$ $C_{19}N_{24}N_2O_2$ 312.1832, found 312.1832.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.51 (s, 3H), 2.59-2.85 (m, 4H), 3.11-3.23 (m, 4H), 3.58 (s, 3H), 3.65-3.68 (m, 1H), 3.83 (s, 3H), 6.02 (s, 1H), 6.56 (s, 1H), 6.56-6.62 (d, 2H, *J* = 9.0 Hz), 6.88 (d, 2H, *J* = 9.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 25.5, 40.6, 42.7, 46.8, 55.6, 55.9, 65.1, 111.1, 111.2, 115.2, 125.7, 129.3, 129.9, 130.8, 144.6, 146.3, 147.3

[4-(6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-phenyl]-ethyl-amine (Table 20, entry 21) By a procedure identical with that described for the synthesis of amine **103**, this compound was prepared in 52% yield as a yellow oil. HRMS calcd for $[M + H]^+$ $C_{21}H_{28}N_2O_2$ 340.2151, found 340.2147.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 1.23 (t, 3H, *J* = 4.0 Hz), 1.25-1.27 (m, 1H), 2.55 (s, 3H), 2.61-2.71 (m, 2H), 2.80-2.86 (m, 2H), 3.11-3.25 (m, 4H), 3.56 (m, 3H), 3.66-3.68 (m, 1H), 3.84 (s, 3H), 6.01 (s, 1H), 6.53 (d, 2H, *J* = 8.0 Hz), 6.56 (s, 1H), 6.90 (d, 2H, *J* = 8.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 15.1, 25.5, 38.8, 40.5, 42.7, 46.8, 55.6, 55.8, 65.2, 111.1, 111.3, 112.9, 125.5, 128.4, 129.3, 130.7, 146.2, 146.9, 147.2

3-(6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydro-isoquinolin-1-ylmethyl)-phenylamine (Table 20, entry 22) By a procedure identical with that described for the synthesis of amine **103**, this compound was prepared in 53% yield as a yellow oil. HRMS calcd for $[M + H]^+$ $C_{19}N_{24}N_2O_2$ 312.1832, found 312.1832.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.55 (s, 3H), 2.60-2.69 (m, 4H), 2.76-2.90 (m, 2H), 3.13-3.22(m, 2H), 3.55-3.59 (m, 3H), 3.70-3.73 (m, 1H), 3.84 (s, 3H), 6.03 (s, 1H), 6.46 (s, 1H), 6.52-6.56 (m, 3H), 7.05 (t, 1H, *J* = 8.0 Hz)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 25.6, 41.4, 42.8, 46.8, 55.6, 55.9, 64.9, 111.1, 111.2, 113.0, 116.8, 120.3, 125.7, 129.3, 129.6, 141.5, 146.3, 146.5, 147.3

2-Ethyl-1-methoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (Table 20, entry 23) By a procedure identical with that described for the synthesis of amine **103**, this compound was prepared in 87% yield as a white solid mp: 52-72 ^oC. HRMS calcd for $[M]^+$ $C_{25}H_{29}NO_5$ 423.2049, found 423.2046.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 1.24 (t, 3H *J* = 7.0 Hz), 1.46 (s, 9H), 2.55-2.64 (m, 2H), 2.69-2.90 (m, 5H), 3.47 (s, 3H), 4.38 (bs, 1H), 4.69 (bs 1H), 5.96 (s, 2H), 6.73 (s, 1H), 6.90 (s, 1H), 7.98 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 15.0, 22.9, 28.7, 29.8, 38.7, 44.6, 58.5, 60.2, 80.0, 101.0, 108.6, 109.0, 123.5, 125.6, 126.7, 128.1, 130.0, 131.4, 132.4, 136.6, 146.6, 146.9, 153.9

General Procedure for the Acid cyclization of *O*-Quinols: Synthesis of 1-Hydroxy-2-methoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-2,2,2-trifluoro-ethanone (184) *N*-$COCF_3$-**104** (0.3 g, 0.7 mmol, 1.0 eq) was dissolved in dry DCM (10 mL) then treated with TFA (2 mL, 24.5 mmol, 41.0 eq). The reaction was stirred for 1 h at room temperature. The reaction was quenched with saturated sodium bicarbonate. The product was extracted with DCM (3x 20 mL). The organic layer was washed with saturated sodium bicarbonate, dried over Na_2SO_4 and the solvent was removed under vacuum. The product was purified by column chromatography 10% EtOAc: Hexanes to yield **184** in 26 % yield as a white solid mp: > 250 ^oC. HRMS calcd for $[M]^+$ $C_{20}H_{16}F_3NO_5$ 407.0984, found 407.0981.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.69-2.80 (m, 2H), 2.88-2.96 (m, 1H), 3.31 (t, 2H, *J* = 13.1 Hz), 3.92 (s, 3H), 4.18 (d, 1H, *J* = 13 Hz), 5.00 (d, 1H, *J* = 13.1 Hz), 5.66 (s, 1H), 5.68 (s, 1H) 6.17 (s, 1H), 6.56 (s, 1H) 6.73 (s, 1H), 7.99 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 25.6, 41.4, 42.8, 46.8, 55.6, 55.9, 64.9, 101.0, 111.1, 111.2, 113.0, 116.8, 120.3, 125.7, 129.3, 129.6, 141.5, 146.3, 146.5, 147.3

General Procedure for Phenol Acylation: Synthesis of Acetic acid 2-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracen-1-yl ester (Table 20, entry 24) To a mixture of **30** (13.7 mg, 0.042 mmol, 1.0 eq) dissolved in DCM (10 mL) was added triethylamine (0.018 mL, 0.126 mmol, 3 eq), DMAP (13 mg, 0.12 mmol, 2.5 eq), and acetyl chloride (0.009 mL, 0.13 mmol, 3.0 eq). The reaction was stirred at room temperature for 4h. Water (5 mL) was added to the reaction mixture. The organic layer was separated and the aqueous layer was extracted with DCM (3 x 10 mL). The organic layers were combined and dried over sodium sulfate. The solvent was removed under vacuum to give the compound in 56% yield as an oil. HRMS calcd for $[M]^+$ $C_{21}H_{21}NO_5$ 367.1423, found 367.1420.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.49-2.57 (m, 5H), 2.69-2.71 (m, 2H), 2.94-3.05 (m, 3H), 3.14-3.25 (m, 1H), 3.83 (s, 3H) 5.99 (s, 2H), 6.64 (s, 1H), 6.76 (s, 1H), 7.42 (bs, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 21.2, 29.8, 32.1, 35.0, 44.2, 53.1, 56.2, 62.5, 101.1, 107.8, 108.9, 110.5, 124.7, 127.3, 131.4, 131.8, 134.7, 146.6, 146.8, 150.3, 169.0

Methanesulfonic acid 2-methoxy-6-methyl-5,6,6a,7-tetrahydro-4H-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracen-1-yl ester (Table 17, entry 25) By a procedure similar to the synthesis of **(Table 20, entry 24)** this compound was prepared in 70 % yield as a white solid mp: 71-75 ^oC. HRMS calcd for $[M]^+$ $C_{20}H_{21}NO_6S$ 403.1092, found 403.1090,
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.49-2.55 (m, 5H), 2.69-2.72 (m, 1H), 2.92-3.05 (m, 6H), 3.15-3.25 (m, 1H), 3.90 (s, 3H) 5.97 (s, 1H), 5.99 (s, 1H), 6.66 (s, 1H), 6.77 (s, 1H), 7.63 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 29.4, 35.0, 39.9, 44.1, 53.1, 56.3, 62.6, 101.3, 108.8, 109.1, 111.1, 124.2, 128.2, 128.9, 131.7, 132.9, 134.1, 146.7, 147.2, 151.4

General Procedure for Acid Bromination: Synthesis of (6-Bromo-benzo[1,3]dioxol-5-yl)-acetic acid (105) To a solution of acid **130** (5.0 g, 27.8 mmol, 1.0 eq) dissolved in acetic acid was added Br_2 (1.6 mL, 30.5 mmol, 1.1 eq). The reaction was stirred at room temperature overnight. The solvent was removed under vacuum. The product was recrystallized from acetone and hexane to yield **105** in 82% yield as a cream solid mp: 185-187 ^oC. HRMS calcd for $[M]^+$ $C_9H_7BrO_4$ 257.9527, found 257.9528.

^{1}HNMR: (500 MHz, $CDCl_3$) δ 3.59 (s, 2H), 5.85 (s, 2H), 6.69 (s, 1H), 6.88 (s, 1H)

^{13}CNMR: (125 MHz, $CDCl_3$) δ 40.9, 101.8, 111.0, 112.5, 115.3, 127.1, 147.4, 147.6, 172.1

General Procedure for O-Alkylation: Synthesis of 2-Ethoxy-1-methoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (Table 20, entry 26) To a stirring solution of **209** (0.1 g, 0.3 mmol, 1.0 eq) in acetone (20 mL) K_2CO_3 (0.3 g, 2.5 mmol, 10.0 eq), KI (0.4 g, 2.5 mmol, 10.0 eq), and ethyl bromide (0.4 mL, 5 mmol, 20.0 eq) was added. The reaction was allowed to stir overnight under refluxing conditions. The reaction mixture was quenched with saturated ammonium chloride. The resulting solution was extracted with ethyl acetate. The organic extract was washed with brine and dried over sodium sulfate. The solvent was removed under vacuum. The product was purified by column chromatography (10% ethyl acetate: Hexanes) in 96% yield as a yellow oil.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 1.47-1.49 (m, 9H), 1.50 (t, 3H, *J* = 7.0 Hz), 2.59-2.93 (m, 5H), 3.68 (s, 3H), 4.05-4.12 (m, 2H), 4.39 (bs, 1H), 4.62 (bs, 1H), 5.97 (s, 2H), 6.62 (s, 1H), 6.74 (s, 1H), 7.99 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 15.1, 28.7, 29.8, 30.5, 44.6, 51.9, 60.1, 64.3, 80.1, 101.0, 108.4, 109.2, 112.0, 125.4, 125.8, 127.7, 129.8, 131.6, 145.2, 146.6, 146.8, 151.3, 154.8

1-Methoxy-2-propoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (Table 20, entry 27) By a procedure identical for the synthesis of **(Table 20, entry 26)** this compound was prepared in 97% yield as a white solid mp: 161-163 ^oC.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 1.09 (t, 3H, *J* = 7.0 Hz), 1.49 (s, 9H), 1.84-1.95 (m, 2H), 2.60-2.94 (m, 5H), 3.69 (s, 3H), 3.91-4.03 (m, 2H), 4.40 (bs, 1H), 4.61 (bs, 1H), 5.98 (s, 2H), 6.63 (s, 1H), 6.74 (s, 1H), 8.01 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 10.9, 22.9, 28.7, 30.0, 44.6, 51.9, 60.2, 70.4, 80.0, 101.0, 108.4, 108.5, 109.2, 111.9, 125.4, 125.8, 127.7, 129.8, 131.6, 145.2, 146.7, 151.6, 154.8, 154.9

2-Butoxy-1-methoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (Table 20, entry 28) By a procedure identical to the synthesis of **(Table 20, entry 26)** this compound was prepared in 96% yield as a white solid mp: 65-67 ^oC.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 1.00 (t, 3H, *J* = 7.0 Hz), 1.43-1.45 (m, 2H), 1.46-1.61 (s, 9H), 1.79-1.89 (m, 2H), 2.60-2.91 (m, 5H), 3.68 (s, 3H), 3.96-4.06 (m, 2H), 4.40 (bs, 1H), 4.61 (bs, 1H), 5.98 (s, 2H), 6.63 (s, 1H), 6.74 (s, 1H), 8.01 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 14.0, 19.5, 28.7, 30.5, 31.6, 38.7, 44.6, 51.9, 60.1, 68.5, 80.0, 101.0, 108.5, 109.2, 111.9, 125.4, 125.8, 127.7, 129.8, 131.6, 145.2, 146.6, 146.6, 151.6, 154.8

1-Methoxy-2-pentyloxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (Table 20, entry 29) By a procedure identical to the synthesis of **(Table 20, entry 26)** this compound was prepared in 82% yield as a clear oil.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 0.84-0.94 (m, 2H), 0.95 (t, 3H, *J* = 7.0 Hz), 1.25-1.49 (s, 9H), 1.51-1.52 (m, 2H), 1.80-1.90 (m, 2H), 2.59-2.93 (m, 5H), 3.68 (s, 3H), 3.96-4.03 (m, 2H), 4.39 (bs, 1H), 4.62 (bs, 1H), 5.96 (s, 2H), 6.62 (s, 1H), 6.74 (s, 1H), 8.00 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 14.2, 22.6, 28.4, 28.7, 29.2, 30.5, 31.7, 38.7, 44.6, 56.4, 60.1, 68.8, 79.9, 101.0, 108.4, 109.2, 111.9, 125.7, 127.7, 129.7, 131.6, 145.2, 146.6, 146.7, 151.5, 154.8

2-Cyclopropylmethoxy-1-methoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (Table 20, entry 30) By a procedure identical to the synthesis of **(Table 20, entry 26)** this compound was prepared in 86% yield as a white solid: mp: 184-187 ^{o}C.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 0.37 (m, 2H), 0.66 (m, 2H), 1.34-1.36 (m, 1H), 1.49 (s, 9H), 2.60-2.94 (m, 5H), 3.72 (s, 3H), 3.92-3.95 (m, 2H), 4.41 (bs, 1H), 4.62 (bs, 1H), 5.99 (s, 2H), 6.62 (s, 1H), 6.75 (s, 1H), 8.02 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 3.4, 3.5, 10.6, 28.7, 30.4, 51.9, 60.1, 73.8, 80.0, 101.0, 108.3, 108.4, 108.5, 108.6, 109.2, 112.5, 125.4, 126.0, 127.8, 129.7, 131.1, 145.4, 146.7, 151.5, 154.8

1-Ethoxy-2-methoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (Table 20, entry 31) By a procedure identical to the synthesis of **(Table 20, entry 26)** this compound was prepared in 98% yield as an oil.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 1.32 (t, 3H, *J* = 7.0 Hz), 1.50 (s, 9H), 2.62-2.92 (m, 5H), 3.67-3.73 (m, 1H), 3.88 (s, 3H), 3.90-3.96 (m, 1H), 4.40 (bs, 1H), 4.61 (bs, 1H), 5.98 (s, 1H), 6.00 (s, 1H), 6.62 (s, 1H), 6.74 (s, 1H), 8.08 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 15.1, 28.7, 29.8, 30.5, 51.9, 55.0, 69.38, 80.1, 101.0, 108.4, 109.2, 112.0, 125.4, 125.8, 127.7, 129.8, 131.6, 145.2, 146.6, 146.8, 151.3, 154.8

2-Methoxy-1-propoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (Table 20, entry 32) By a procedure identical to the synthesis of **(Table 20, entry 26)** this compound was prepared in 37% yield as an oil.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 0.97 (t, 3H, *J* = 7.0 Hz) 1.49 (s, 9H), 1.71-1.76 (m, 2H), 2.60-2.94 (m, 5H), 3.54-3.59 (m, 1H), 3.78-3.87 (m, 1H), 3.87 (s, 3H), 4.40 (bs, 1H), 4.60 (bs, 1H), 5.97 (s, 1H), 5.99 (s, 1H), 6.62 (s, 1H), 6.74 (s, 1H), 8.05 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 10.7, 23.6, 28.7, 29.9, 30.5, 44.6, 52.0, 56.1, 62.0, 74.8, 80.0, 101.1, 108.4, 109.6, 111.0, 125.6, 126.0, 128.1, 129.7, 131.5, 144.3, 146.5, 146.7, 152.2

1-Butoxy-2-methoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (Table 20, entry 33) By a procedure identical to the synthesis of **(Table 20, entry 26)** this compound was prepared in 86% yield as an oil.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 0.90 (t, 3H, *J* = 7.0 Hz), 1.40-1.49 (s, 9H), 1.66-1.73 (m, 2H), 2.61-2.94 (m, 5H), 3.58-3.63 (m, 2H), 3.80-3.85 (m, 2H), 3.87 (s, 3H), 4.39 (bs, 1H), 4.60 (bs, 1H), 5.97 (s, 1H), 5.99 (s, 1H), 6.62 (s, 1H), 6.74 (s, 1H), 8.04 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 14.0, 19.4, 28.7, 30.5, 32.5, 38.7, 44.6, 52.0, 56.1, 72.8, 80.0, 101.1, 108.4, 109.5, 111.0, 125.6, 125.0, 128.1, 129.0, 129.7, 131.5, 144.4, 146.5, 146.7, 152.2

2-Methoxy-1-pentyloxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (Table 20, entry 34) By a procedure identical to the synthesis of **(Table 20, entry 26)** this compound was prepared in 82% yield as a clear oil.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 0.84-0.94 (m, 2H), 0.95 (t, 3H, *J* = 7.0 Hz), 1.48 (s, 9H), 1.49 (s, 9H), 1.51-1.52 (m, 2H), 1.80-1.90 (m, 2H), 2.59-2.93 (m, 5H), 3.68 (s, 3H), 3.96-4.03 (m, 2H), 4.39 (bs, 1H), 4.62 (bs, 1H), 5.96 (s, 2H), 6.62 (s, 1H), 6.74 (s, 1H), 8.00 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 14.2, 22.6, 28.4, 28.7, 29.2, 30.5, 31.7, 44.6, 56.1, 60.1, 68.8, 79.9, 101.0, 108.4, 109.2, 111.9, 125.4, 125.7, 127.7, 129.7, 131.6, 145.2, 146.6, 146.8, 151.5, 154.8

1-Cyclopropylmethoxy-2-methoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (Table 20, entry 35) By a procedure identical to the synthesis of **(Table 20, entry 26)** this compound was prepared in 70% yield as an oil.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 0.37 (m, 2H), 0.66 (m, 2H), 1.34-1.36 (m, 1H), 1.49 (s, 9H), 2.60-2.94 (m, 5H), 3.72 (s, 3H), 3.92-3.95 (m, 2H), 4.41 (bs, 1H), 4.62 (bs, 1H), 5.99 (s, 2H), 6.62 (s, 1H), 6.75 (s, 1H), 8.02 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 3.4, 3.5, 10.6, 28.7, 30.4, 38.7, 44.6, 51.9, 60.1, 73.8, 80.0, 101.0, 108.3, 109.2, 112.5, 125.4, 126.0, 127.8, 129.7, 131.1, 145.4, 146.6, 146.7, 151.5, 154.8

3-Nitro-4-Benxyloxy-phenylacetic methyl ester (Table 20, entry 38) By a procedure identical to the synthesis of **(Table 20, entry 26)** this compound was prepared in 52% yield as a yellow solid mp: 72-73 ^{o}C.

^{1}HNMR: (500 MHz, $CDCl_3$) δ 3.62 (s, 2H), 3.71 (s, 3H), 5.23 (s, 2H), 7.08 (d, 1H *J* = 9.0 Hz), 7.31-7.46 (m, 6H), 7.80 (s, 1H)

^{13}CNMR: (125 MHz, $CDCl_3$) δ 39.8, 52.5, 71.4, 115.5, 126.7, 126.8, 128.4, 128.9, 135.1, 135.7, 140.1, 151.3, 171.3

3-Nitro-4-Methoxy-phenylacetic methyl ester (Table 20, entry 39) By a procedure identical to the synthesis of **(Table 20, entry 26)** this compound was prepared in 93% yield as a yellow solid mp: 90-92 ^{o}C.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 3.62 (s, 2H), 3.72 (s, 3H), 3.96 (s, 3H), 7.06 (d, 1H *J* = 9.0 Hz), 7.48 (d, 1H *J* = 9.0 Hz), 7.79 (s, 1H)
^{13}CNMR: (125 MHz, $CDCl_3$) δ 39.7, 52.5, 56.8, 113.9, 126.4, 126.7, 135.3, 136.8, 152.3, 171.4

General Procedure for Reductive Phenylation: Synthesis of 1,2-Dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolin-9-ylamine (159) To a solution of **163** (114.0 mg, 0.3 mmol, 1 eq) dissolved in TFA (0.7 mL, 10.0 mmol, 30.0 eq) and TFSA (0.9 mL, 10.0 mmol, 30.0 eq) was added zinc dust (108.9 mg, 1.7 mmol, 5.0 eq) at 0 ^{o}C. The reaction was stirred at 0 ^{o}C for 3 h. The reaction was basified with saturated sodium bicarbonate. The product was extracted with DCM (3 x 15mL). The organic layers were combined and dried over sodium sulfate. The solvent was removed under vacuum. The product was column purified on deactivated silica yielding **159** in 35% yield as a white solid mp: 80-82 ^{o}C. HRMS calcd for **[**M + H]$^{+}$ $C_{19}H_{22}N_2O_2$ 310.1981, found 310.2510.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 2.46-2.59 (m, 5H), 2.64-2.68 (m, 1H), 2.95-3.04 (m, 3H), 3.10-3.18 (m, 1H), 3.64 (s, 3H), 3.73 (bs, 2H), 3.87 (s, 3H), 6.55 (s, 1H), 6.59 (s, 1H), 6.63-6.65 (d, 1H, *J* = 8.0 Hz), 8.19 (d, 1H, *J* = 8.0 Hz)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 29.5, 35.5, 44.2, 53.5, 56.0, 60.1, 62.6, 110.0, 113.8, 114.4, 123.0, 127.4, 127.6, 128.7, 129.8, 138.2, 144.5, 145.8, 152.1

1,2,10-Trimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinolin-9-ylamine By a procedure identical with that described for the synthesis of **159**, compound **175** was prepared in 38% yield as a yellow oil. HRMS calcd for [M + H]$^{+}$ $C_{20}H_{24}N_2O_3$ 340.1790, found 340.1787.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 2.47-2.54 (m, 2H), 2.50 (s, 3H), 2.63-2.68 (m, 1H), 2.91-2.97 (m, 1H), 3.00-3.04 (m, 2H), 3.11-3.18 (m, 1H), 3.69 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 6.55 (s, 1H), 6.60 (s, 1H), 8.00 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 29.5, 34.5, 44.2, 53.5, 55.8, 55.9, 60.2, 62.9, 109.9, 114.2, 122.4, 127.3, 127.7, 128.9, 129.9, 135.6, 144.1, 146.1, 152.1

General Triflation Procedure: Synthesis of 1-Methoxy-2-trifluoromethanesulfonyloxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (231) To a solution of **209** (0.4 g, 0.9 mmol, 1.0 eq) dissolved in DCM (20 mL) was added, trifilic anhydride (0.2 mL, 1.1 mmol, 1.2 eq) and 2,6-lutidine (0.2 mL, 1.7 mmol, 2.0 eq) at 0 ^{o}C. The reaction was allowed to stir for 30 minutes at 0 ^{o}C. Water (10mL) was added to the reaction mixture. The product was then extracted with DCM (3 x 20 mL). The organic layers were combined and then washed with brine and dried over anhydrous sodium sulfate. The solvent was removed under vacuum. The residue was purifed by column chromatography: 10% EtOAc:Hexanes yielding **231** in 69% yield as a white solid, mp: 80-82 ^{o}C. HRMS calcd for $[M]^+$ $C_{24}H_{24}F_3NO_8S$ 543.1176, found 543.1175.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.66-2.90 (m, 5H), 3.66 (s, 3H), 4.43 (bs, 1H), 4.68 (bs 1H), 6.01 (s, 2H), 6.77 (s, 1H), 6.69 (s, 1H), 7.93 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 28.7, 30.2, 38.7, 44.6, 56.4, 60.9, 80.5, 101.4, 108.7, 109.2, 112.5, 117.6, 120.3, 123.9, 128.2, 131.4, 131.6, 134.7, 142.5, 147.1, 147.5, 147.6

General Procedure for Microwave-assisted Sonogashira Reaction: Synthesis of 1-Methoxy-2-trimethylsilanylethynyl-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (237) 231 (12.5 mg, 0.1 mmol, 1.0 eq), $Pd(PPh_3)_2Cl_2$ (0.4 mg, 0.02 eq), CuI (0.19 mg, .001 mmol, 0.04 eq), TMS acetylene (0.004 mL, 0.1 mmol, 1.1 eq), LiCl (1.5 mg, 0.1 mmol, 1.5 eq), Et_2NH (0.4mL, 0.04 mmol, 15.0 eq) and DMF were placed in a microwave vial under nitrogen and stirred at 120 ^{o}C for 5 minutes in a CEM microwave. The mixture was then poured into 1N HCl (10 mL) and extracted with diethyl ether (3 x 10 mL). The organic layer was then washed with saturated sodium bicarbonate (10 mL) and water (10 mL). The aqueous layer was extracted with diethyl ether (10 mL). The organic layers were combined and dried over sodium sulfate. The solvent was removed under vacuum and purified by column chromatography with 10% EtOAc : Hexanes yielding **237** in 76% yield as a yellow solid mp: 85-90 ^{o}C. HRMS calcd for $[M]^+$ $C_{28}H_{33}NO_5Si$ 491.2132, found 491.2128.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 0.25 (s, 9H), 1.47 (s, 9H), 2.59-2.63 (m, 1H) 2.69-2.87 (m, 4H), 3.72 (s, 3H), 4.38 (bs, 1H), 4.67 (bs 1H), 5.96 (s, 1H), 5.97 (s, 1H), 6.72 (s, 1H), 7.16 (s, 1H), 7.97 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 3.4, 28.7, 29.9, 35.2, 38.5, 52.4, 60.3, 80.2, 98.7, 100.1, 101.2, 101.1, 109.1, 116.8, 124.8, 127.3, 130.0, 131.4, 132.4, 135.6, 146.8, 147.9, 154.6, 156.9

1-Methoxy-2-(3-trimethylsilanyl-prop-1-ynyl)-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester By a procedure identical with that described for the synthesis of the **237,** compound **238** was prepared in 73% yield as a yellow solid mp: 145-149 ^{o}C. HRMS calcd for $[M]^+$ $C_{29}H_{35}NO_5Si$ 505.2284, found 505.2284.

^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 0.17 (s, 9H), 1.47 (s, 9H), 1. 76 (s, 2H), 2.59-2.93 (m, 5H), 3.66 (s, 3H), 4.37 (bs, 1H), 4.63 (bs 1H), 5.95 (s, 1H), 5.96 (s, 1H), 6.72 (s, 1H), 7.07 (s, 1H), 7.98 (s, 1H)

^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 0.2, 8.6, 28.7, 29.9, 35.2, 38.5, 52.4, 60.3, 80.2, 92.6, 100.1, 101.1, 109.1, 116.8, 118.5, 125.1, 127.3, 129.9, 131.4, 132.1, 133.9, 146.8, 147.9, 154.6, 156.3

General TMS-Deprotection Procedure: Synthesis of 2-Ethynyl-1-methoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (239) To a solution of **237** (12.6 mg, 0.03 mmol, 1.0 eq) dissolved in THF (5mL) was added TBAF (0.05 mL, 0.03 mmol, 1.1 eq). The reaction was stirred at room temperature for 5 minutes. The solvent was removed under vacuum. The product was purified by column chromatography. 10% EtOAc: Hexanes yielding **239** in 69% yield as a yellow solid mp: 166-170 ^{o}C. HRMS calcd for $[M]^{+}$ $C_{25}H_{25}NO_5$ 419.1740, found 419.1733.
^{1}HNMR*:* (500 MHz, $CDCl_3$) δ 1.47 (s, 9H), 2.58-2.88 (m, 5H), 3.26 (s, 1H), 3.70 (s, 3H), 4.39 (bs, 1H), 4.67 (bs 1H), 5.97 (s, 2H), 6.73 (s, 1H), 7.19 (s, 1H), 7.95 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 28.7, 29.8, 35.2, 38.5, 52.4, 60.7, 80.2, 80.3, 81.1, 100.2, 108.5, 108.9, 115.9, 124.7, 127.4, 130.3, 131.4, 132.6, 136.0, 143.4, 146.9, 147.0, 157.1

General Procedure for Microwave-assisted Modified Suzuki Reaction: Synthesis of 2-Butyl-1-methoxy-4,5,6a,7-tetrahydro-9,11-dioxa-6-aza-benzo[fg]cyclopenta[b]anthracene-6-carboxylic acid tert-butyl ester (226) 231 (147.7 mg, 0.3 mmol, 1 eq), $Pd(dppf)Cl_2$ (13.3 mg, 0.02 mmol, 0.02 eq), CsOAc (300 mg, 1.6 mmol, 2.0 eq), nBu_3B (400 mg, 1.6 mmol, 2.0 eq), and DMF were placed in a microwave vial under nitrogen and stirred at 175 ^{o}C for 1 h in a CEM microwave reactor. The reaction was poured over 1N HCl. The product was extracted with diethyl ether (3 x 10 mL). The organic layer was then washed with saturated sodium bicarbonate (10 mL) and brine (10 mL). The organic layer was then dried over sodium sulfate. The solvent was removed under vacuum and purified by column chromatography 10% EtOAc : Hexanes yielding **226** in 89% yield (yield based on recovered starting material) as a white solid mp: 35-41 ^{o}C.

General Esterification Procedure: Synthesis of 3-Nitro-4-Hydroxyl-phenylacetic methyl ester Nitro Acid **171** (400 mg, 1.9 mmol, 1.0 eq) dissolved in MeOH was treated with a catalytic amount of sulfuric acid. The reaction was refluxed for 3 h. The reaction was cooled to room temperature and the solvent was evaporated under vacuum yielding the ester in 96% yield as a yellow solid mp: 61-62 ^{o}C.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.75 (s, 2H), 7.17 (d, 1H *J* = 9.0 Hz), 7.64 (d, 1H *J* = 9.0Hz), 8.07 (s, 1H)
^{13}CNMR*:* (125 MHz, $CDCl_3$) δ 39.5, 52.3, 120.6, 126.4, 128.0, 139.7, 151.9, 172.0

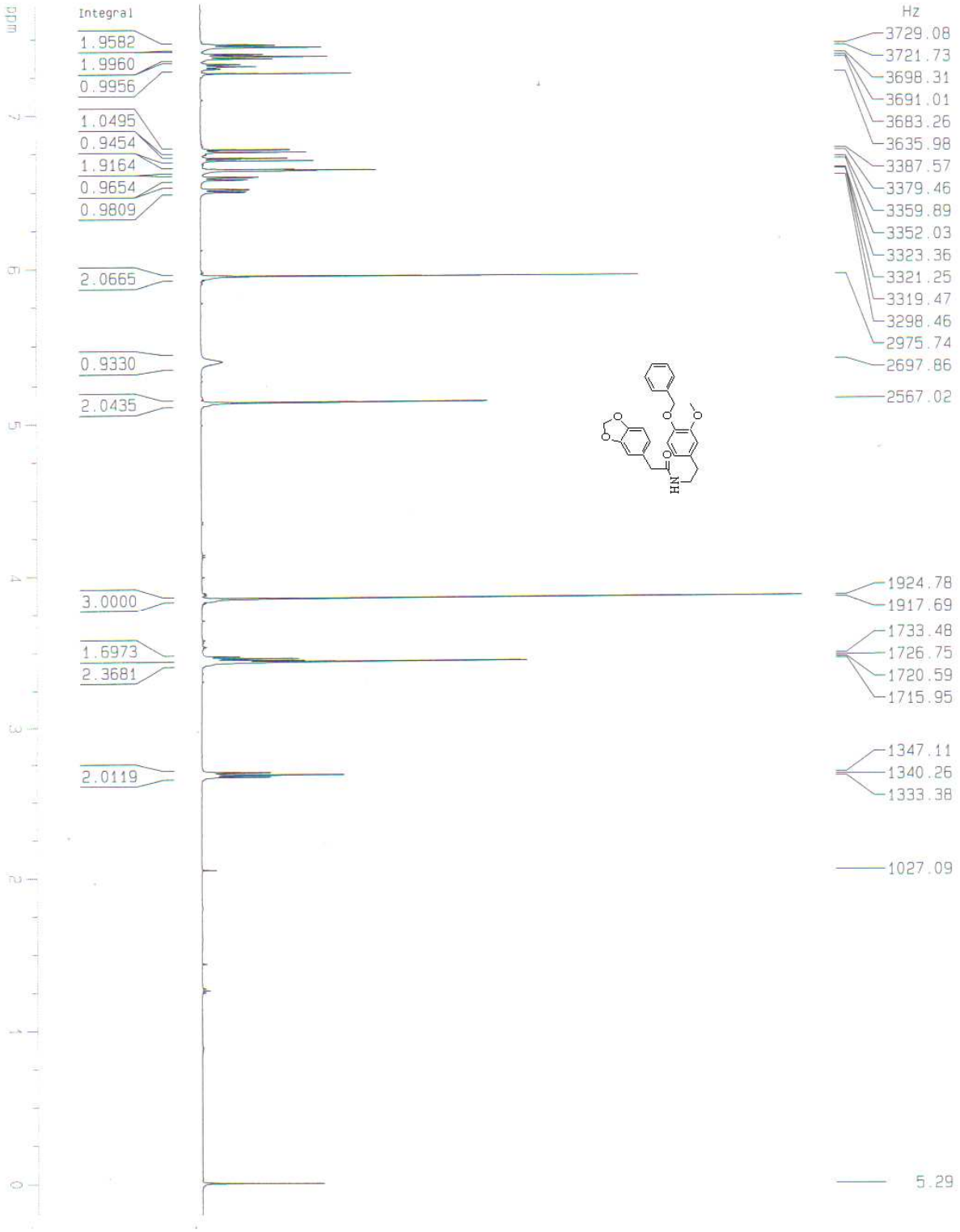
General Procedure for Ester Reduction: Synthesis of (4-Methoxy-3-nitro-phenyl)-acetic acid (172) To a solution of the appropriate ester (0.3 g, 1.0 mmol, 1.0 eq) was dissolved in anhydrous MeOH (20 mL) 2N NaOH (0.5 mL, 4.7 mmol, 5.0 eq) was added. The reaction was allowed to stir for 2 h. The solvent was removed under vacuum. The resulting residue was dissolved in water and acidified with 2N HCl. The product was extracted with DCM (3 x 20 mL). The organic layers were combined and dried over sodium sulfate. The solvent was removed under vacuum. The product was recrystallized from EtOAc: Hexanes yielding **124** in 88% yield as a yellow solid mp: 127-129 ^{o}C.
^{1}HNMR: (500 MHz, $CDCl_3$) δ 3.66 (s, 2H), 3.96 (s, 3H), 7.07 (d, 1H *J* = 9.0 Hz),
7.48 (d, 1H *J* = 9.0 Hz), 7.80 (s, 1H)
^{13}CNMR: (125 MHz, $CDCl_3$) δ 39.5, 56.8, 113.9, 125.7, 126.8, 132.6, 135.4, 152.5, 176.1

3-Nitro-4-Benzyloxy-phenylacetic acid (Table 20, entry 40) By a procedure identical with that described for the synthesis of **173**, this compound was prepared in 80% yield as a white solid mp: 148-149 ^{o}C (lit mp: 142-144 ^{o}C).[272]

^{1}HNMR: (500 MHz, $CDCl_3$) δ 3.66 (s, 2H), 5.25 (s, 2H), 7.10 (d, 1H *J* = 9.0 Hz), 7.33-7.45 (m, 6H), 7.80 (s, 1H)

^{13}CNMR: (125 MHz, $CDCl_3$) δ 39.2, 71.4, 115.6, 126.6, 127.1, 128.9, 135.2, 135.6, 151.4, 171.9

Appendix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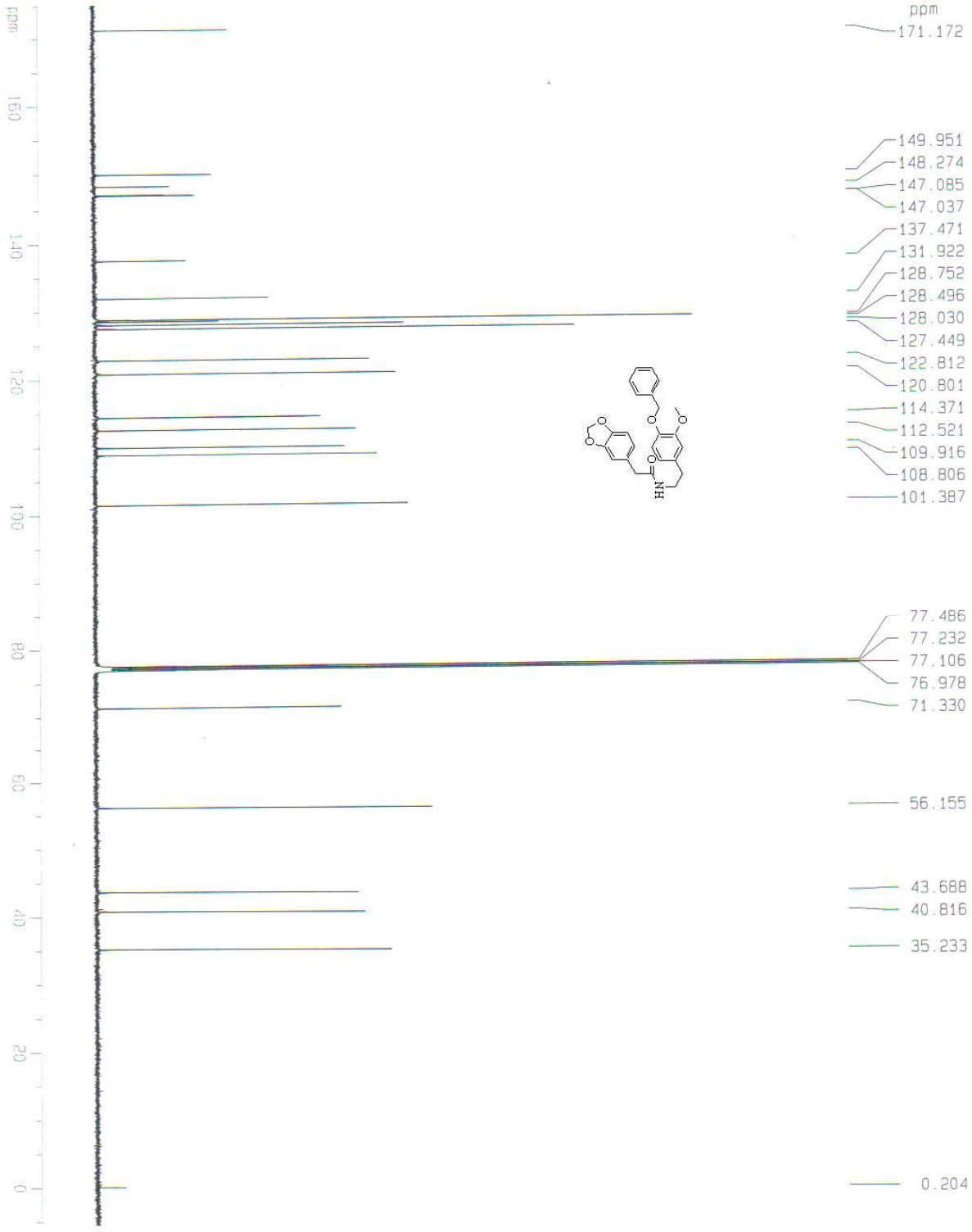
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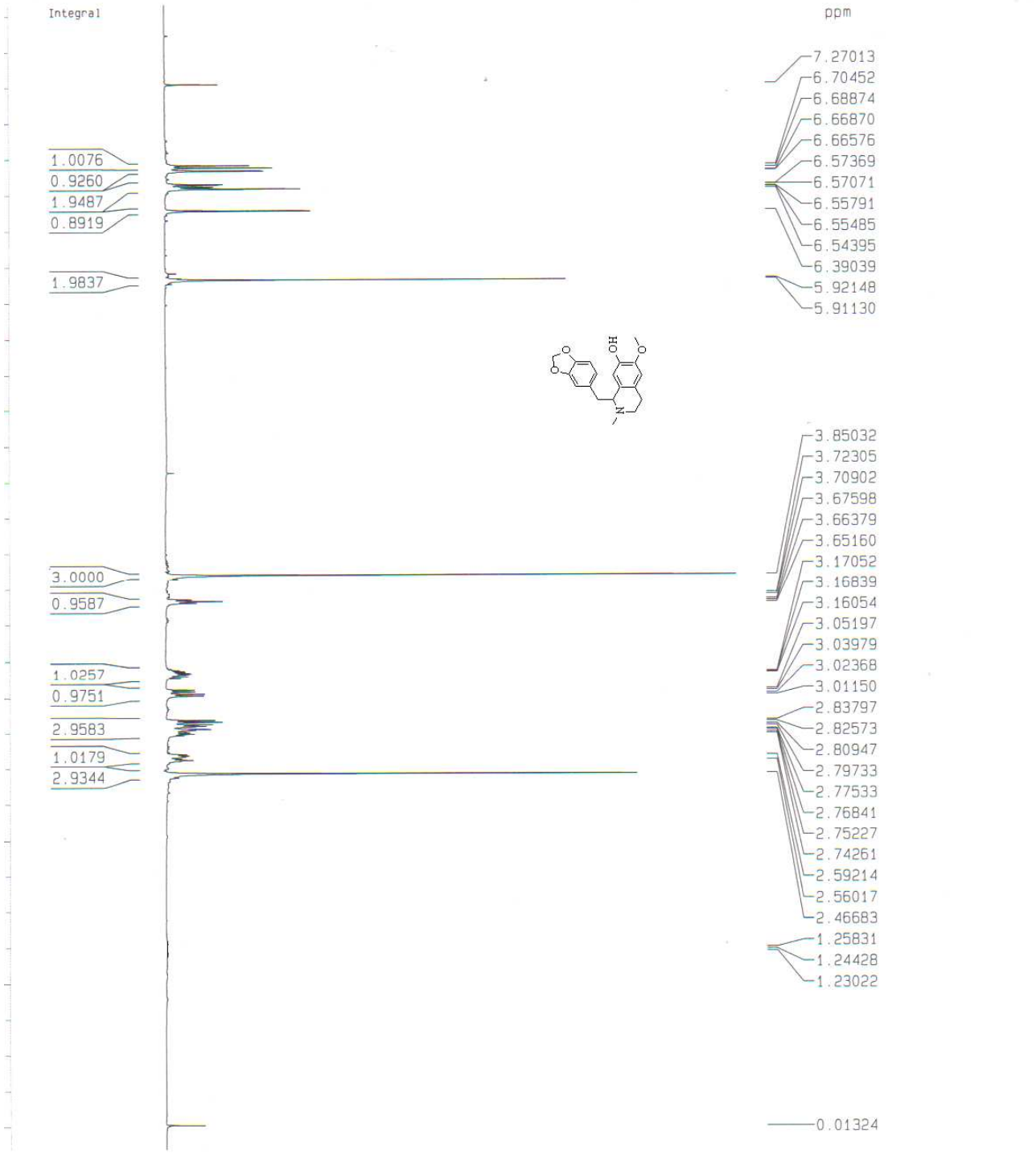
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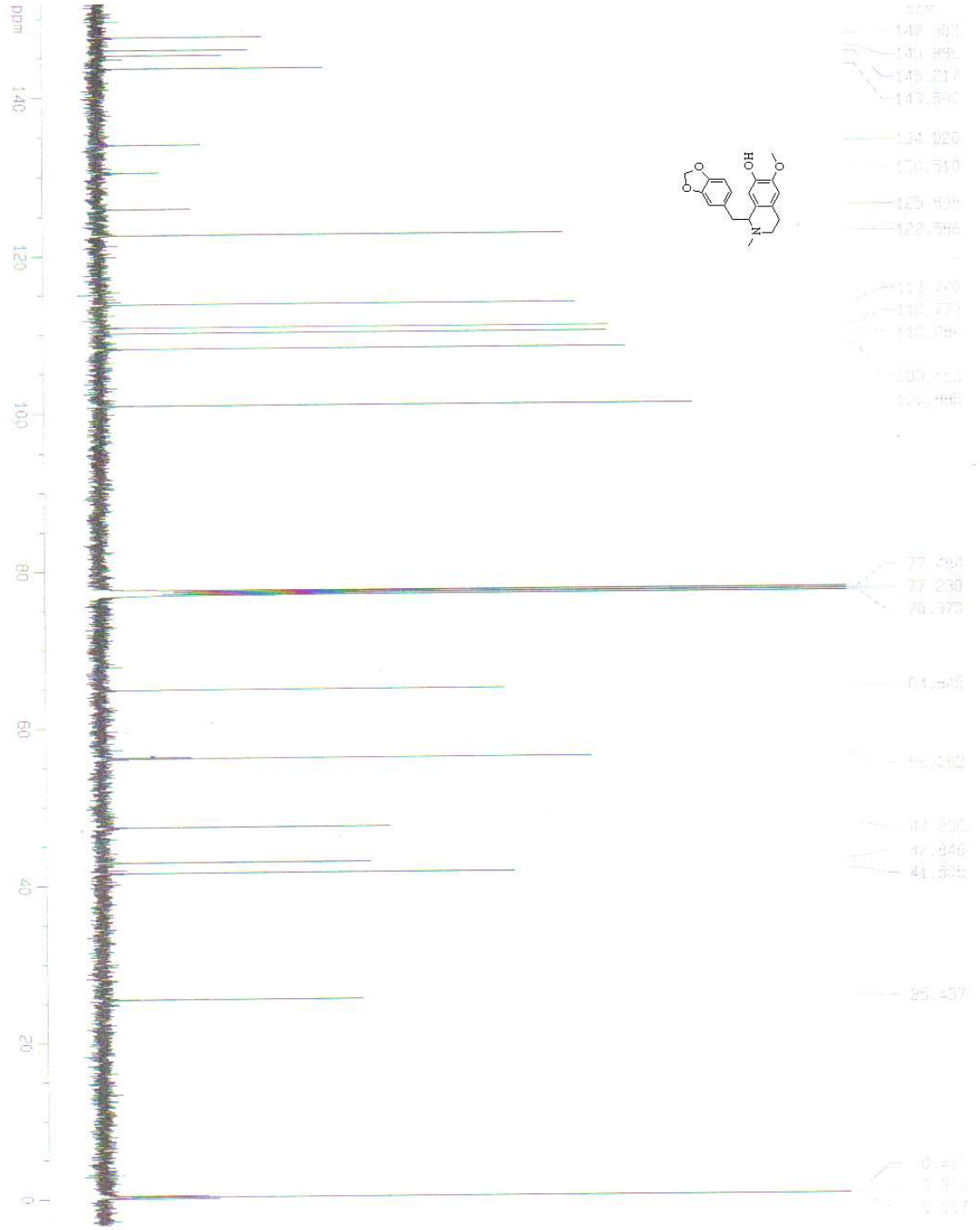
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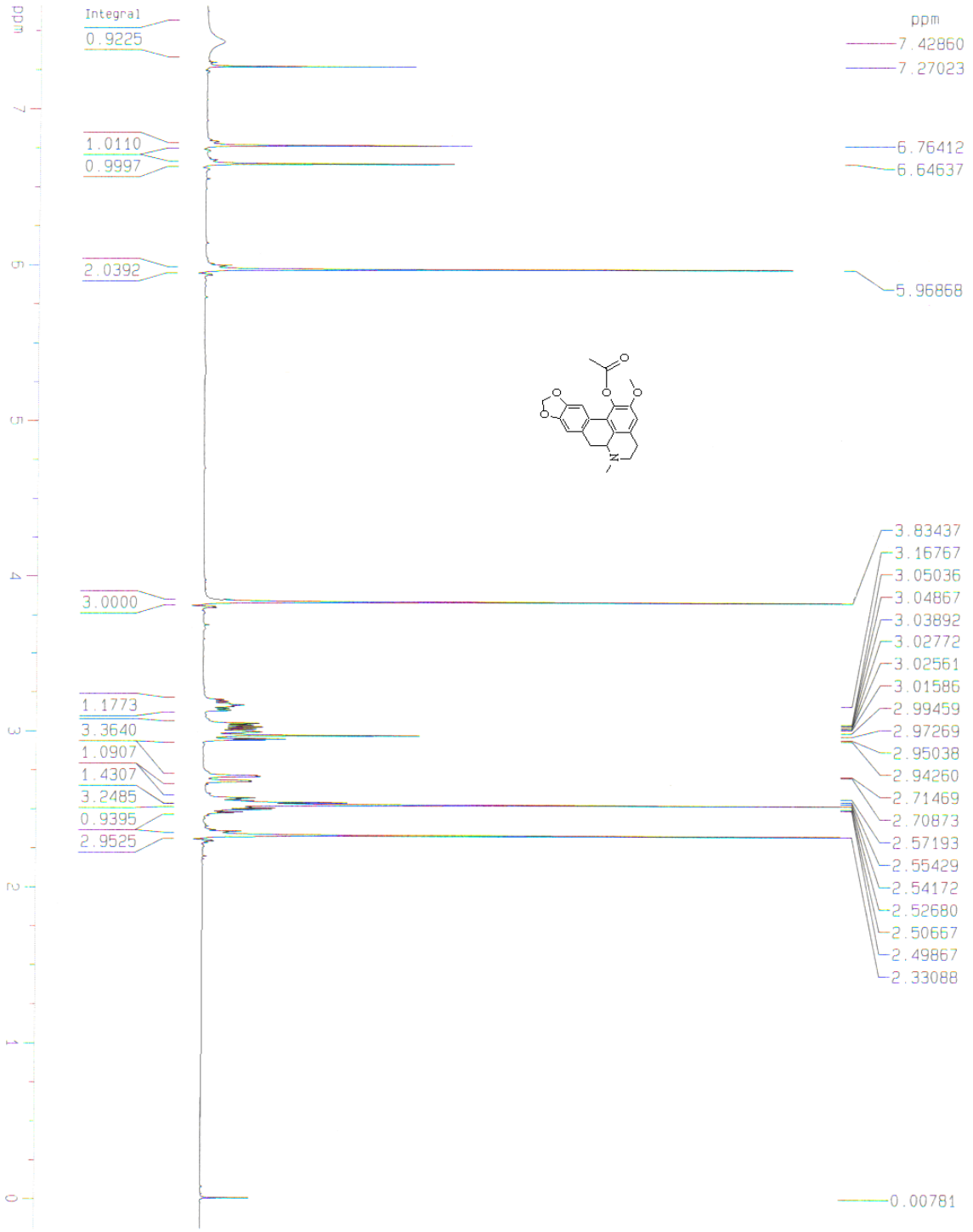
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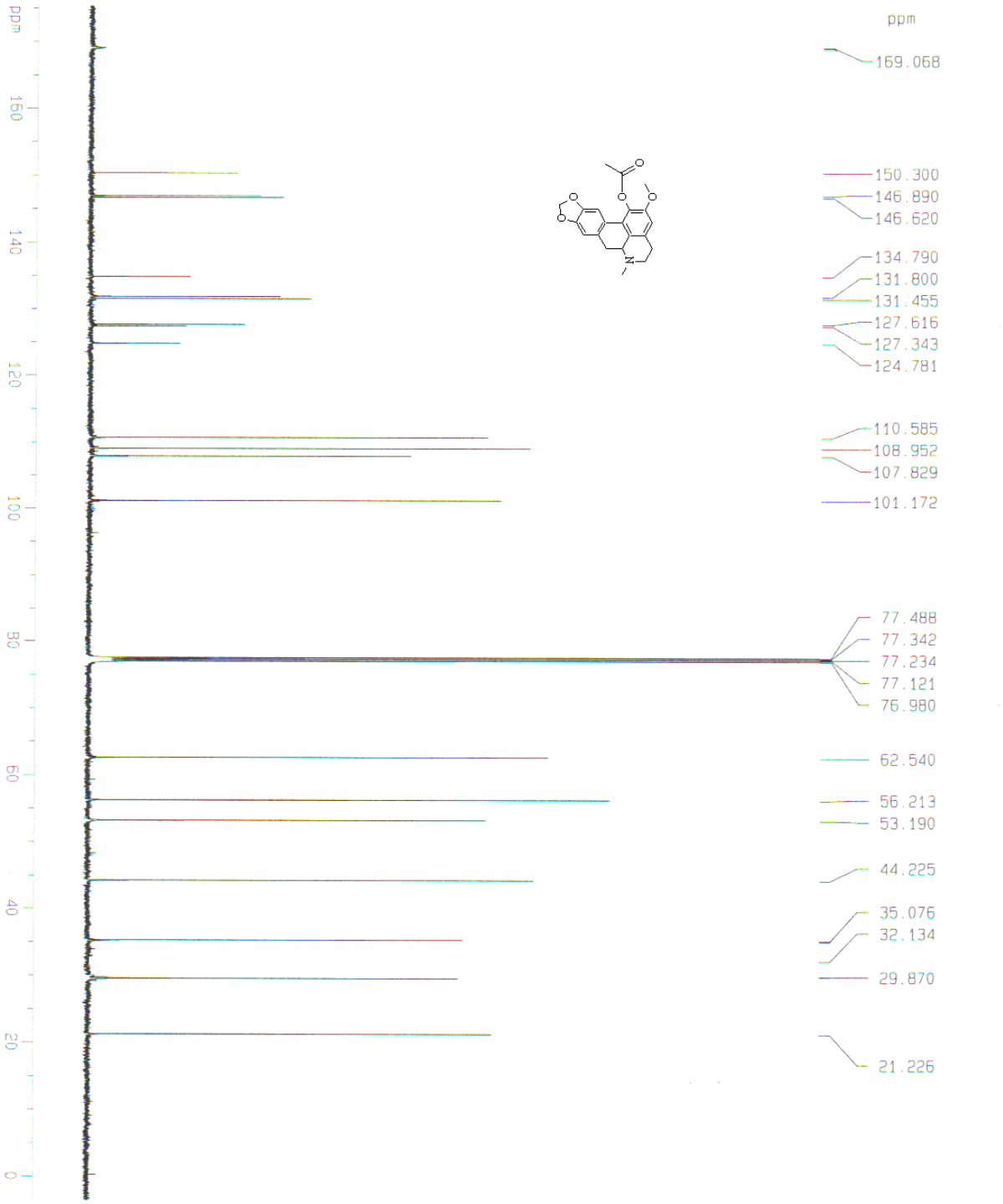
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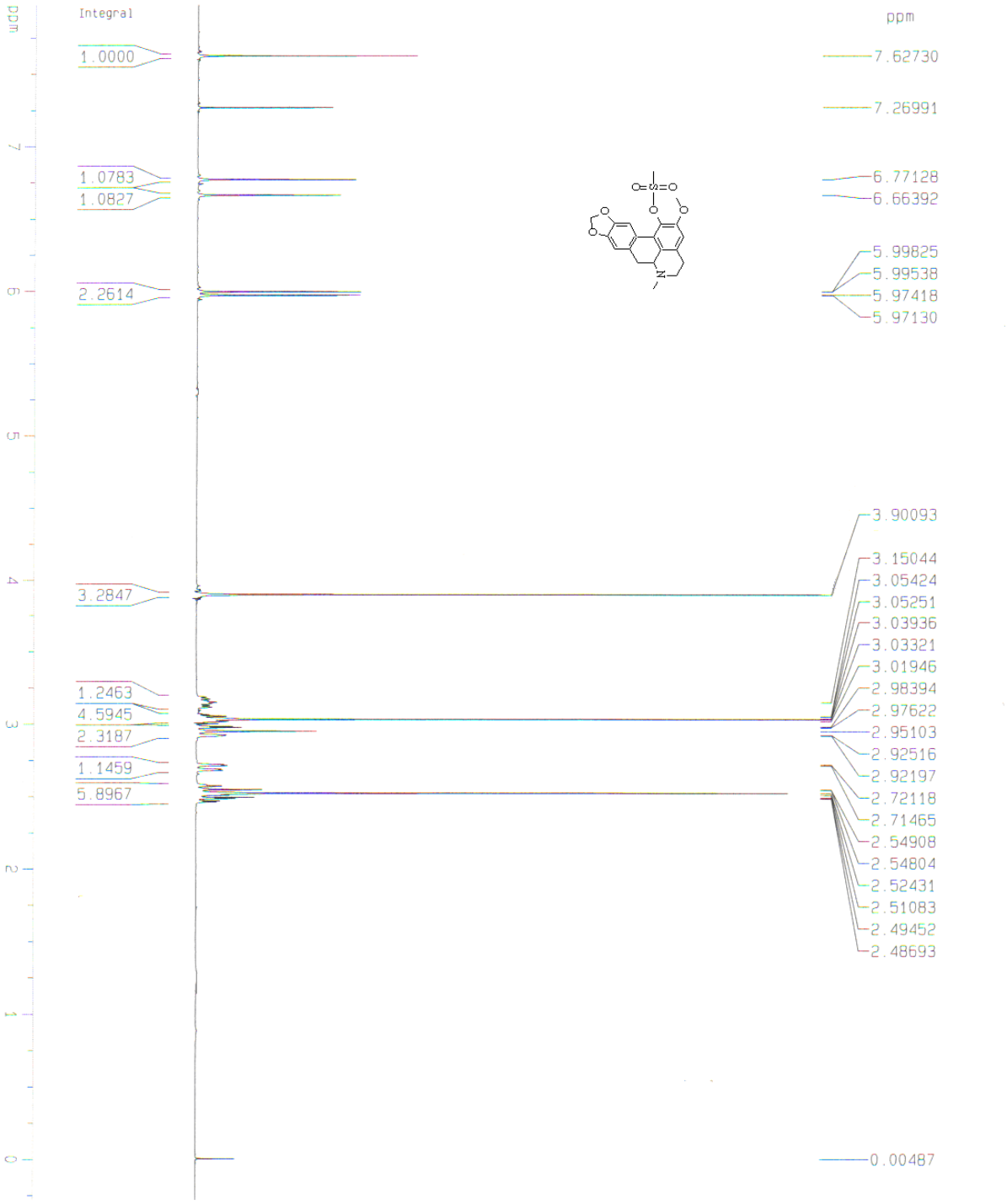
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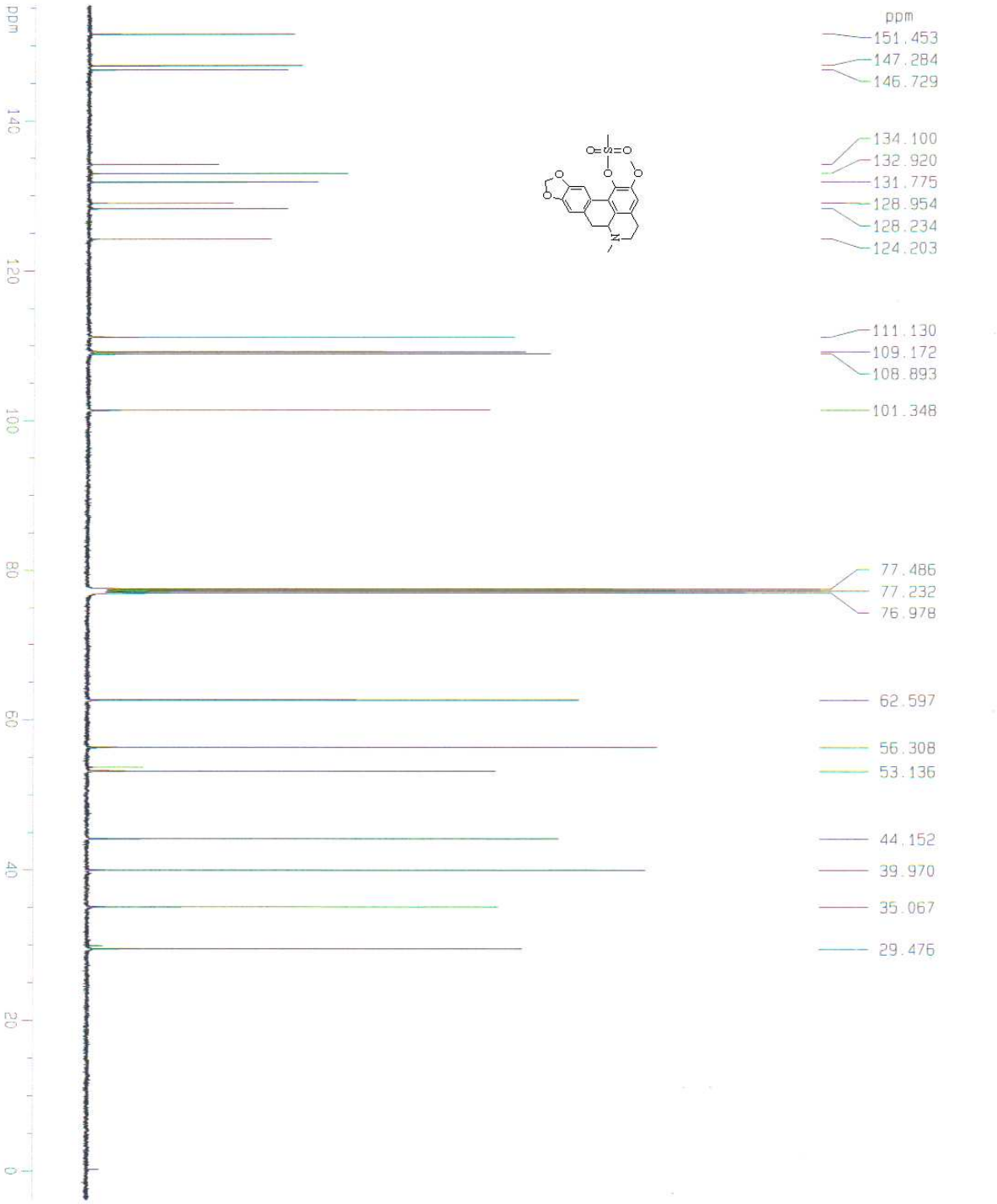
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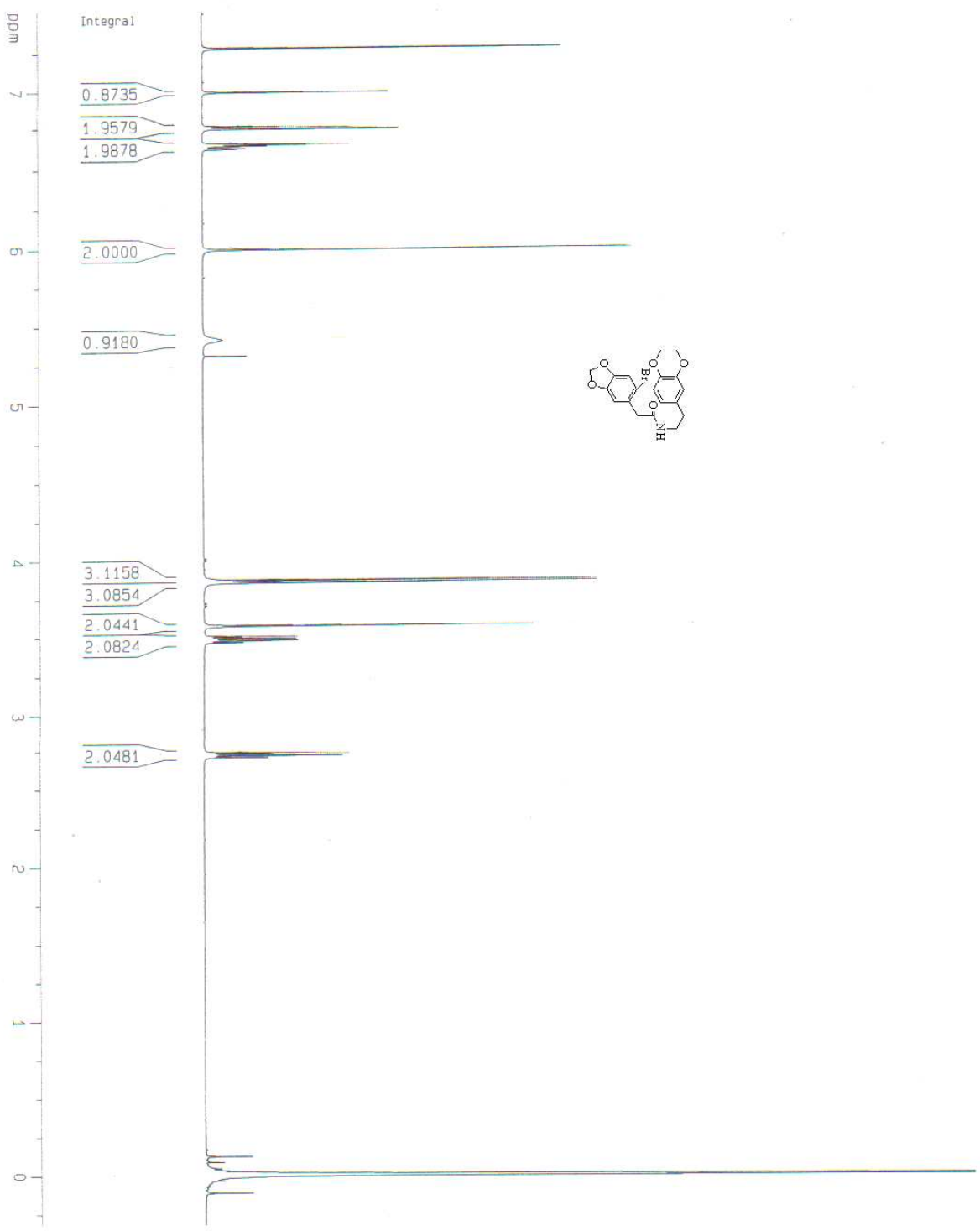
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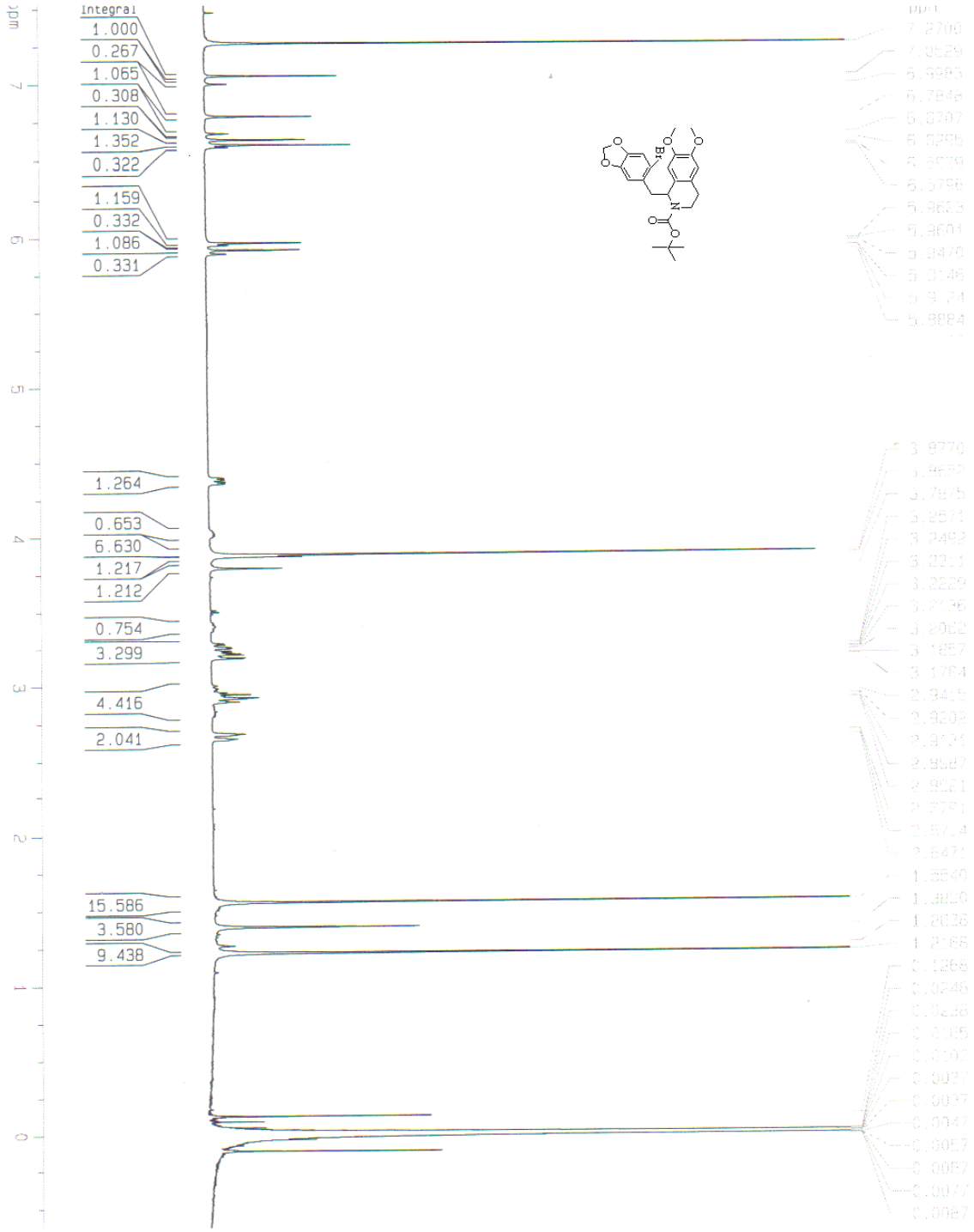
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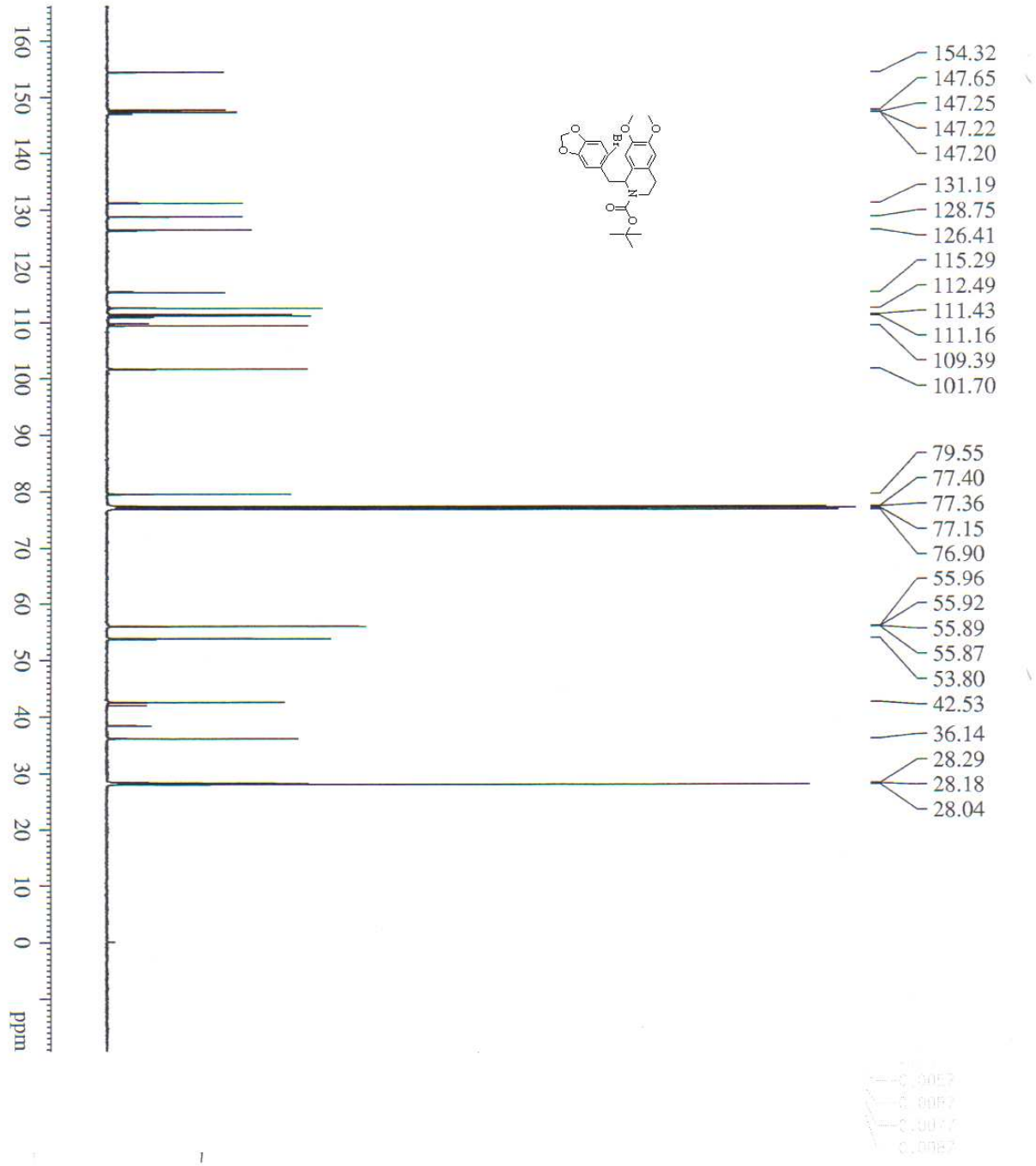
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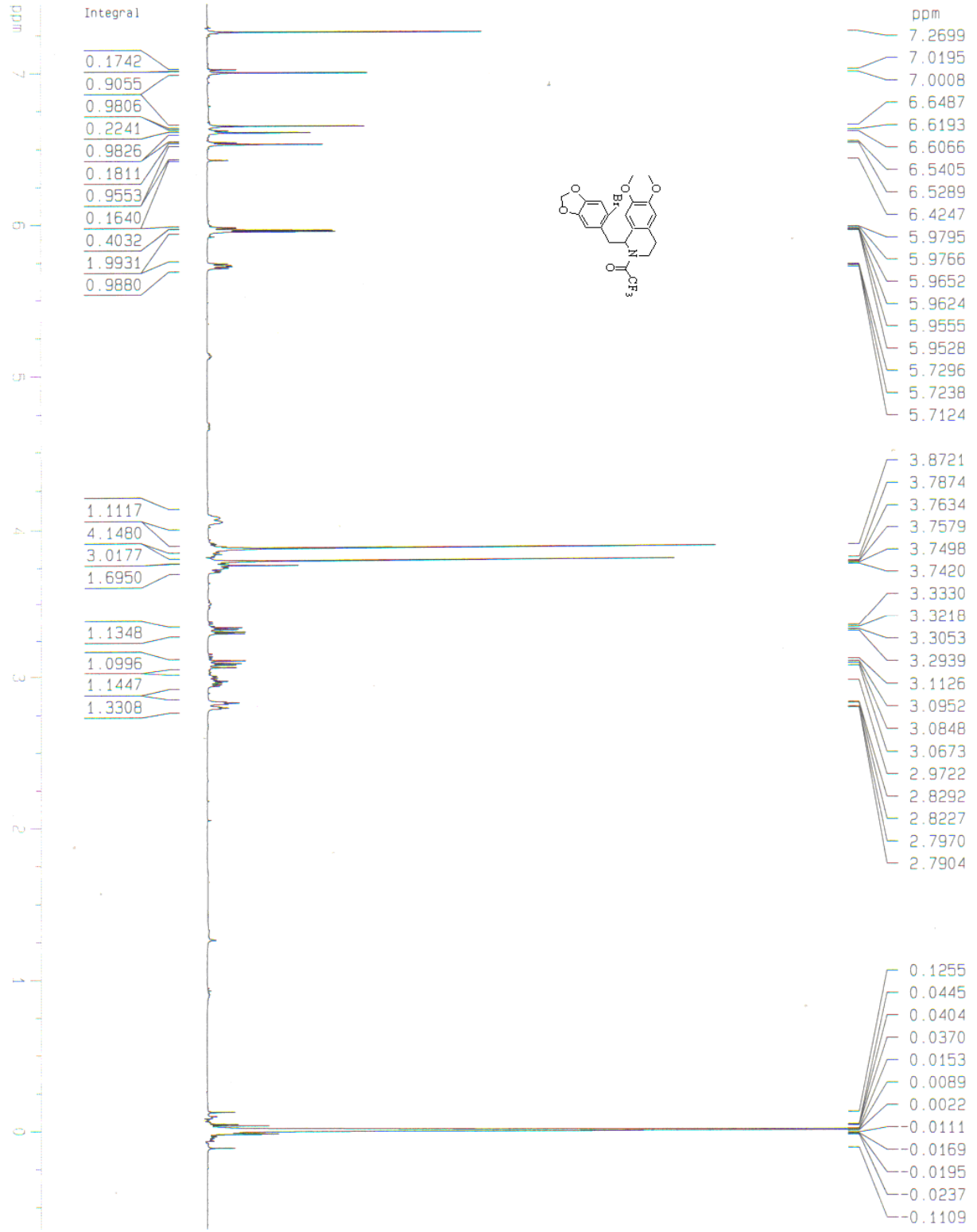
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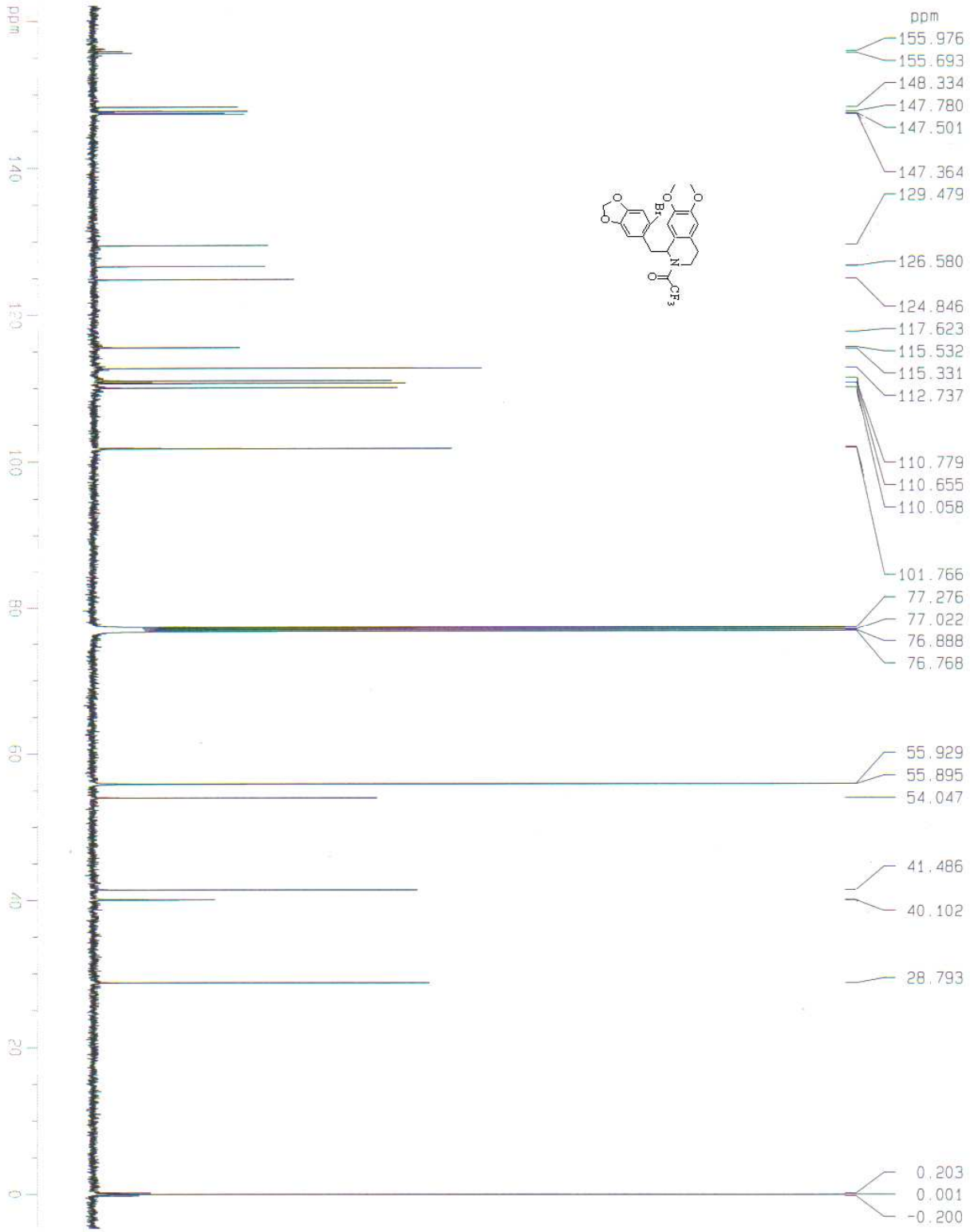
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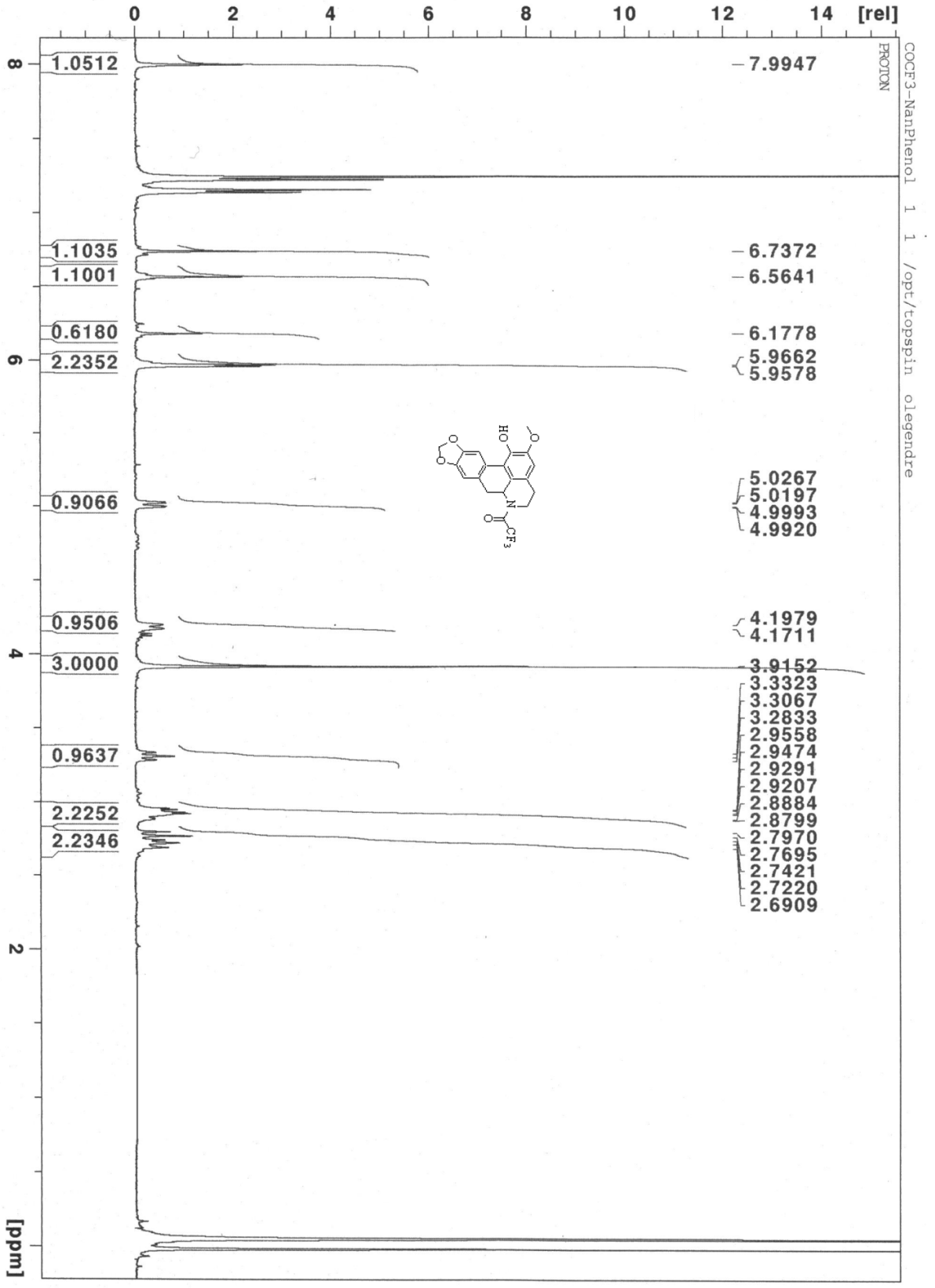
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6
4
2
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0.9637
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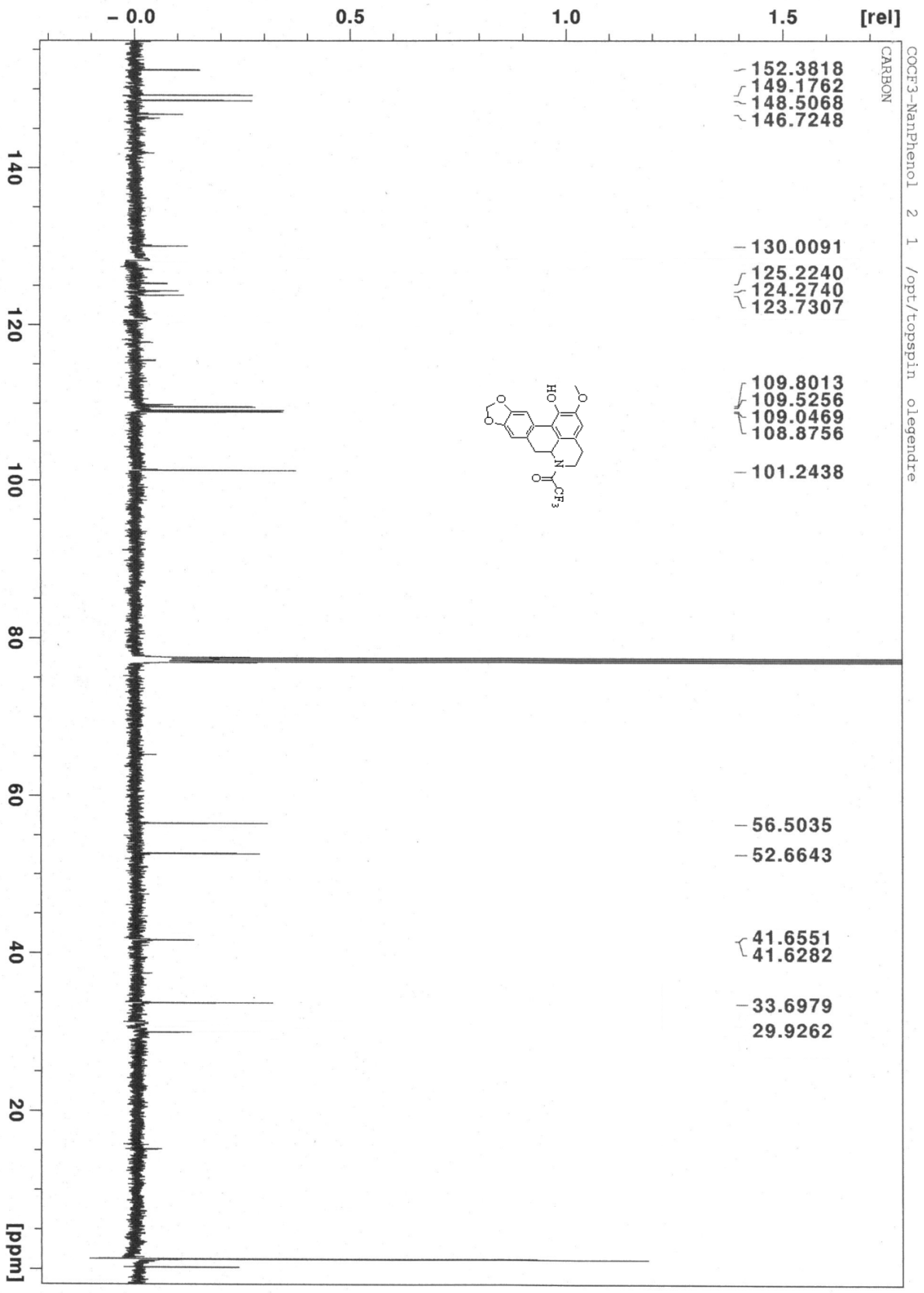
2.2346
7.9947
6.7372
6.5641
6.1778
5.9662
5.9578
5.0267
5.0197
4.9993
4.9920
4.1979
4.1711
3.9152
3.3323
3.3067
3.2833
2.9558
2.9474
2.9291
2.9207
2.8884
2.8799
2.7970
2.7695
2.7421
2.7220
2.6909
HO
O
O
O
N
O
CF3
PROTON
COCF3-NanPhenol 1 1 /opt/topspin olegendre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1.5
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COCF3-NanPhenol 2 1 /opt/topspin olegendre
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146.7248
130.0091
125.2240
124.2740
123.7307
109.8013
109.5256
109.0469
108.8756
101.2438
56.5035
52.6643
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29.9262
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40
20
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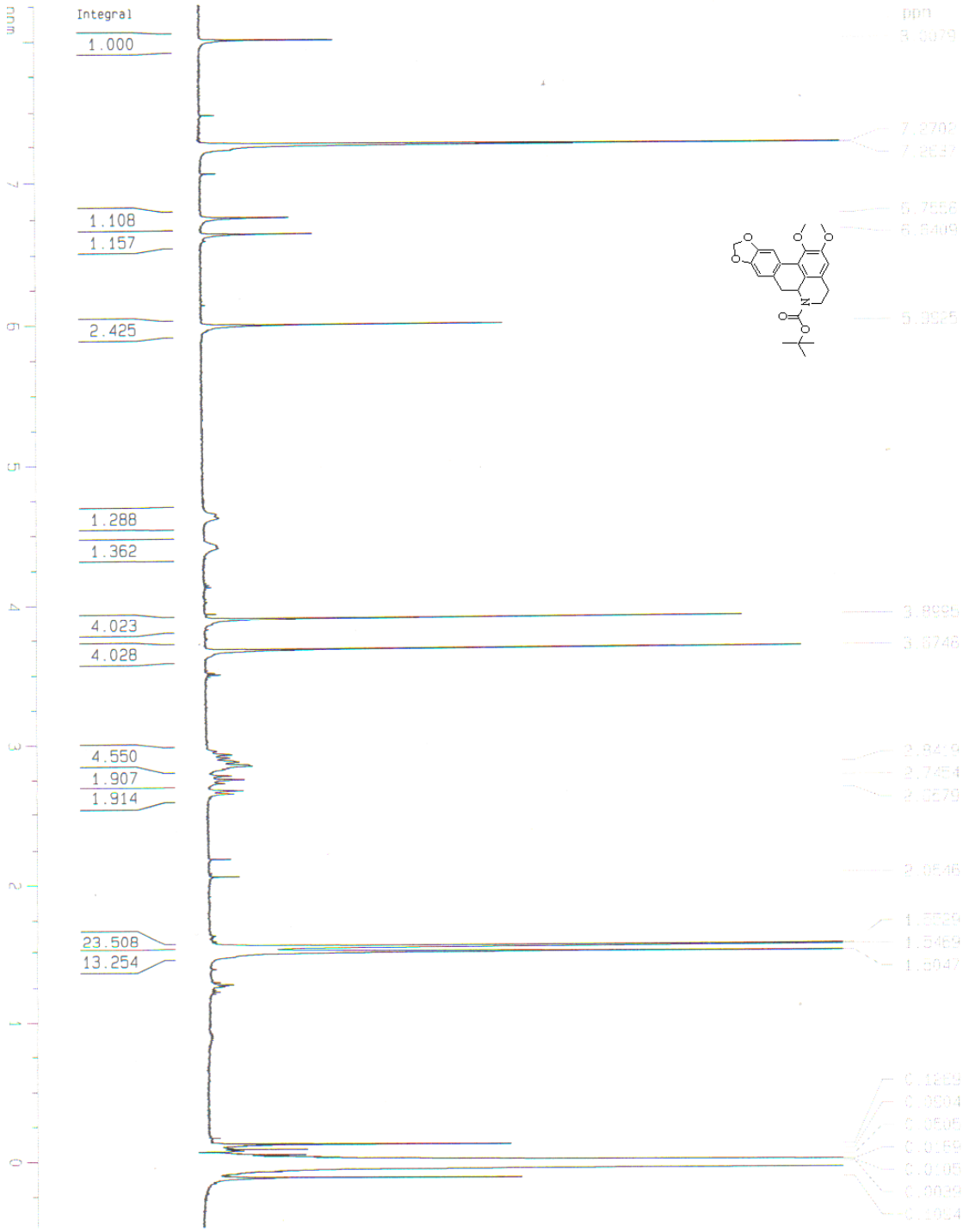
HO
O
N
CF3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4.550
1.907
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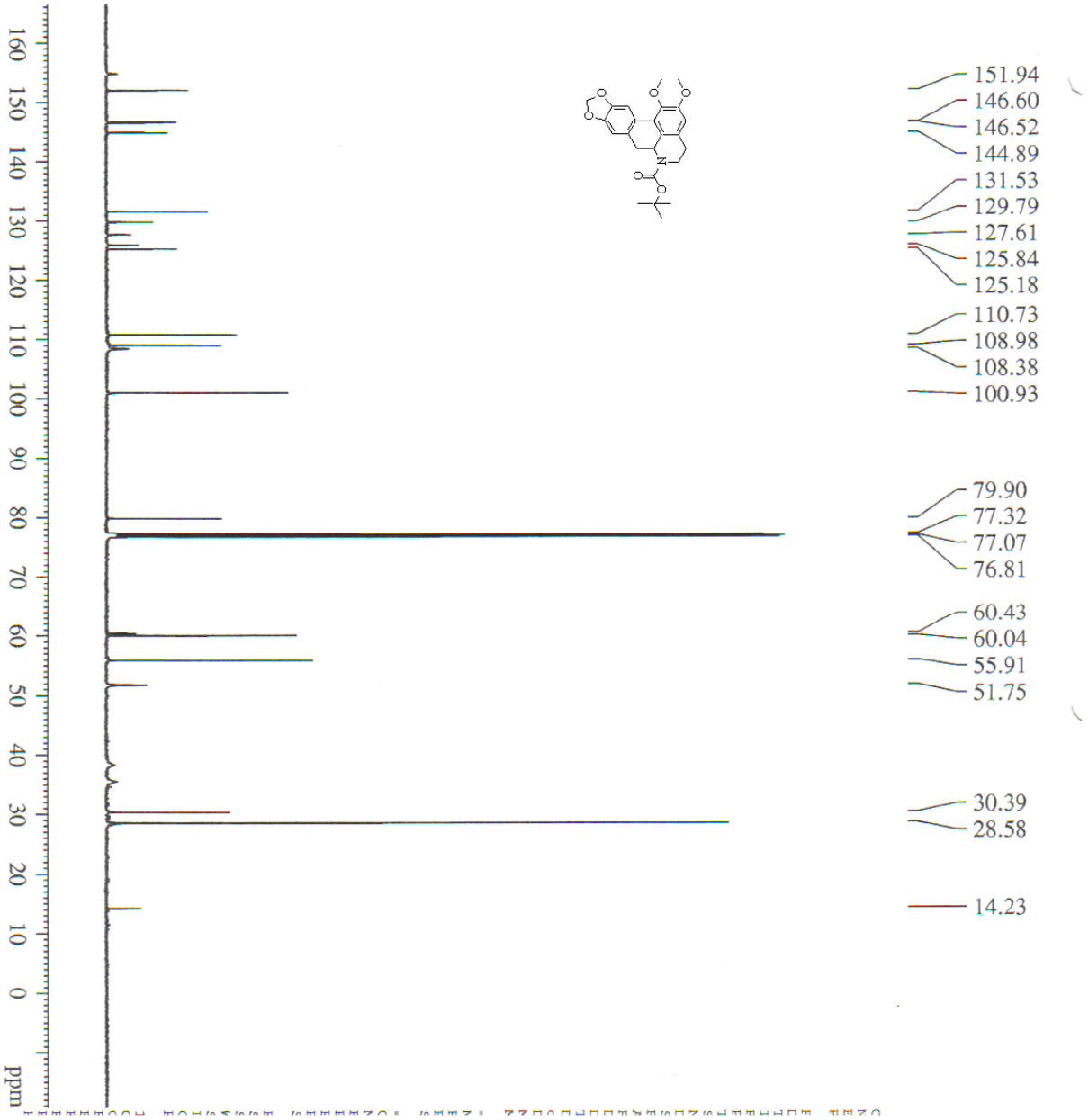
23.508
13.254
ppm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140
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120
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100
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80
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60
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40
30
20
10
0
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146.52
144.89
131.53
129.79
127.61
125.84
125.18
110.73
108.98
108.38
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77.07
76.81
60.43
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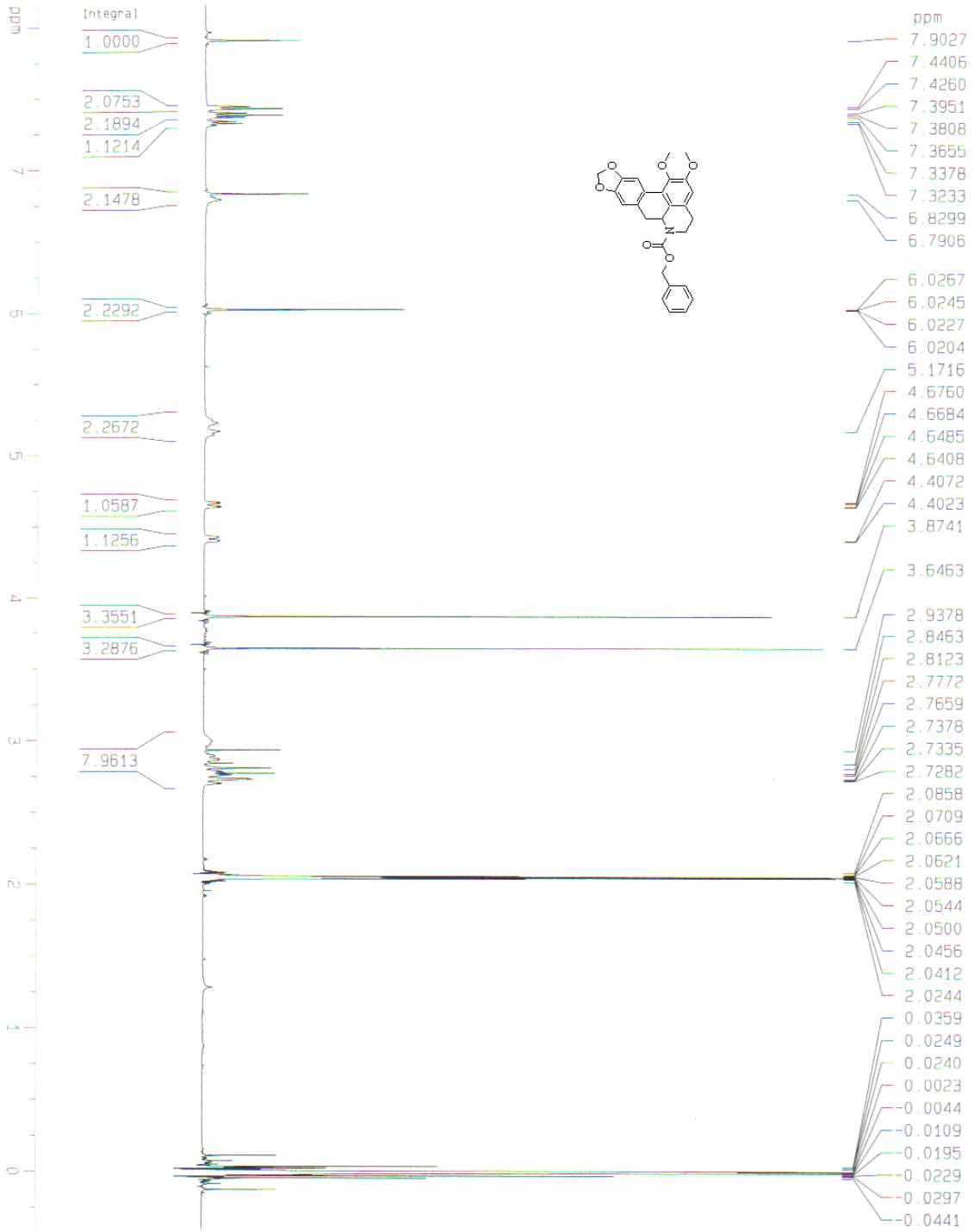
55.91
51.75
30.39
28.58
14.23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3.2876
7.9613
ppm
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7.4260
7.3951
7.3808
7.3655
7.3378
7.3233
6.8299
6.7906
6.0267
6.0245
6.0227
6.0204
5.1716
4.6760
4.6684
4.6485
4.6408
4.4072
4.4023
3.8741
3.6463
2.9378
2.8463
2.8123
2.7772
2.7659
2.7378
2.7335
2.7282
2.0858
2.0709
2.0666
2.0621
2.0588
2.0544
2.0500
2.0456
2.0412
2.0244
0.0359
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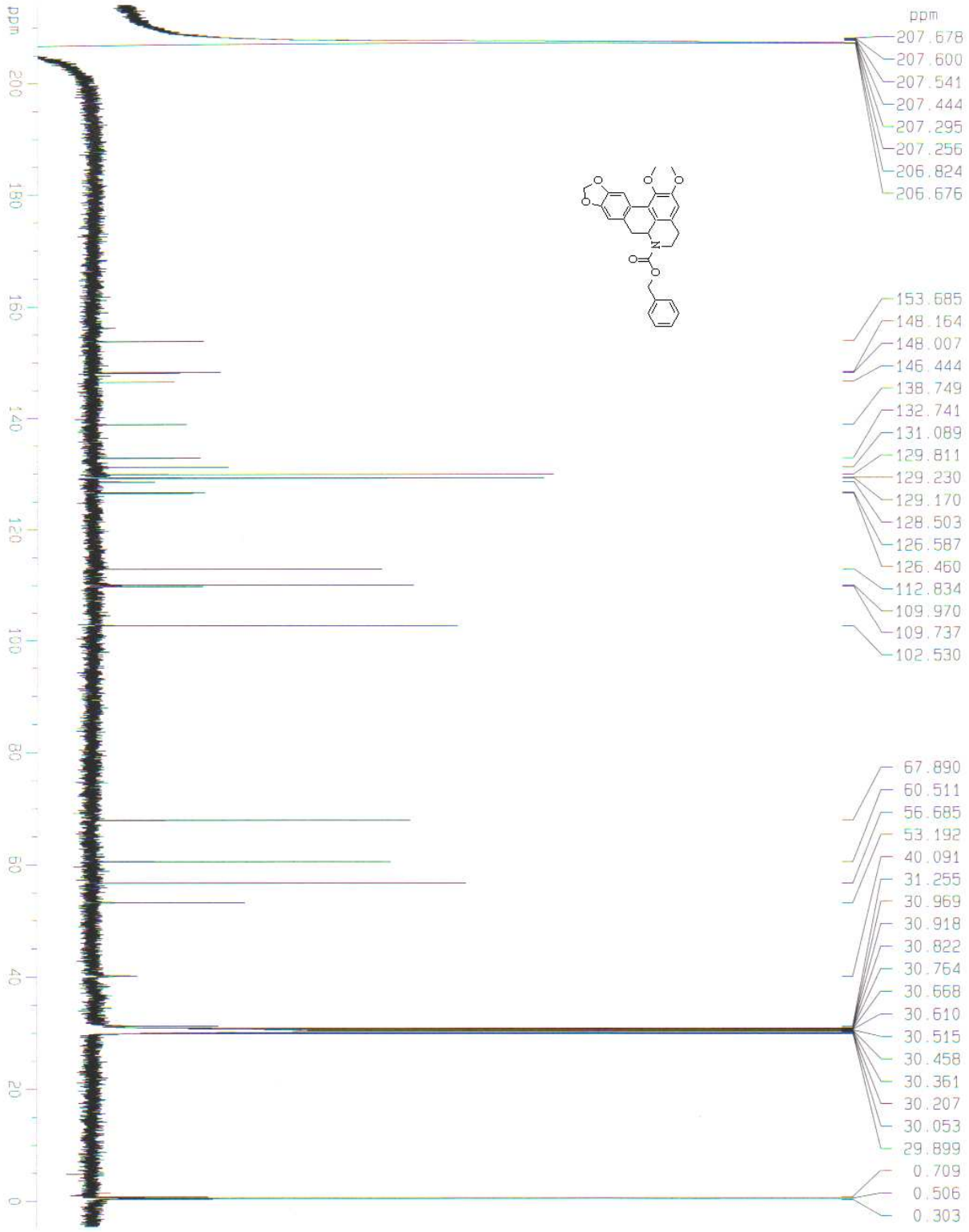
-0.0441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153.685
148.164
148.007
146.444
138.749
132.741
131.089
129.811
129.230
129.170
128.503
126.587
126.460
112.834
109.970
109.737
102.530
67.890
60.511
56.685
53.192
40.091
31.255
30.969
30.918
30.822
30.764
30.668
30.610
30.515
30.458
30.361
30.207
30.053
29.899
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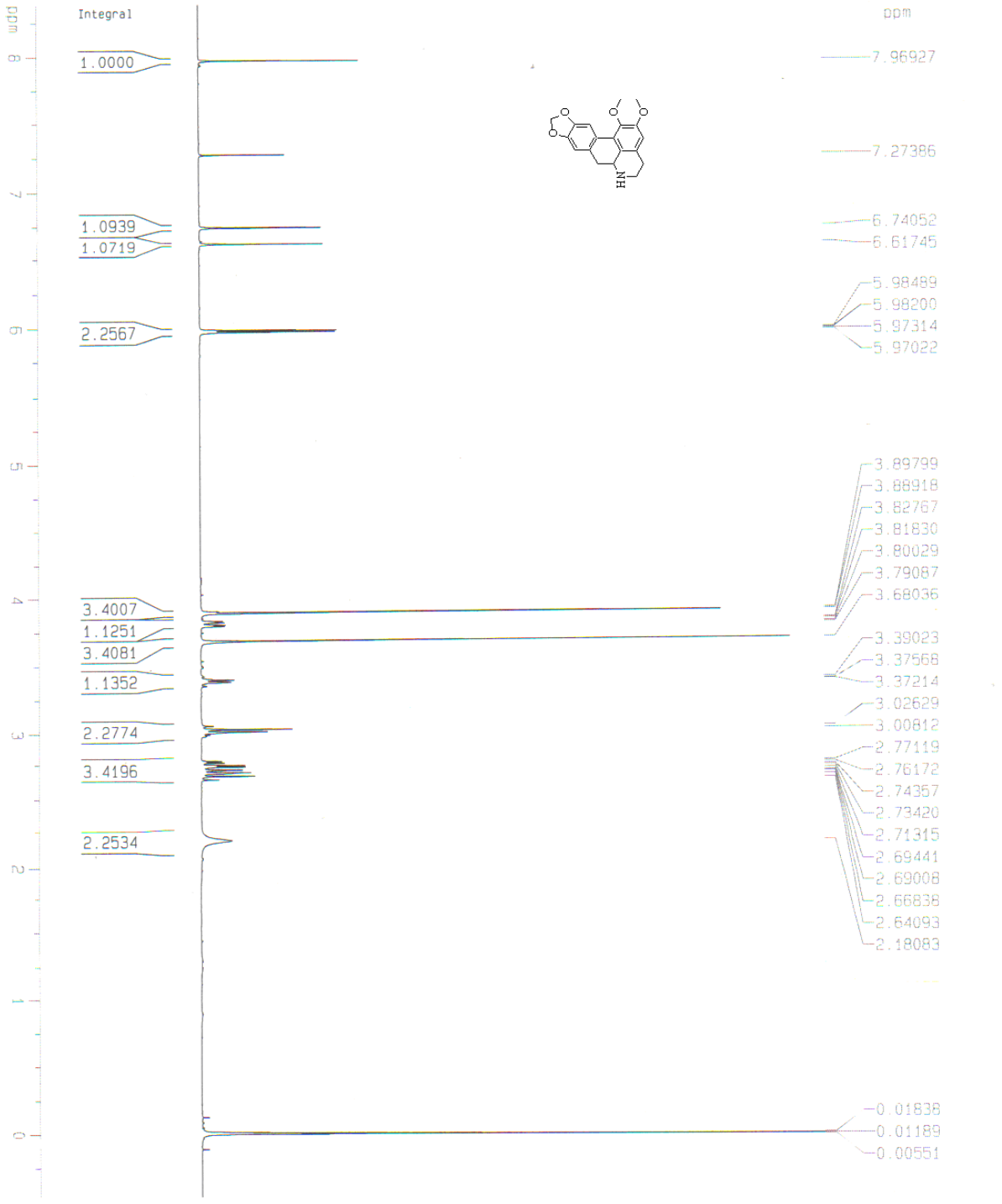
0.506
0.303


Integral
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2.2567
3.4007
1.1251
3.4081
1.1352
2.2774
3.4196
2.2534
7.96927
7.27386
6.74052
6.61745
5.98489
5.98200
5.97314
5.97022
3.89799
3.88918
3.82767
3.81830
3.80029
3.79087
3.68036
3.39023
3.37568
3.37214
3.02629
3.00812
2.77119
2.76172
2.74357
2.73420
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2.69008
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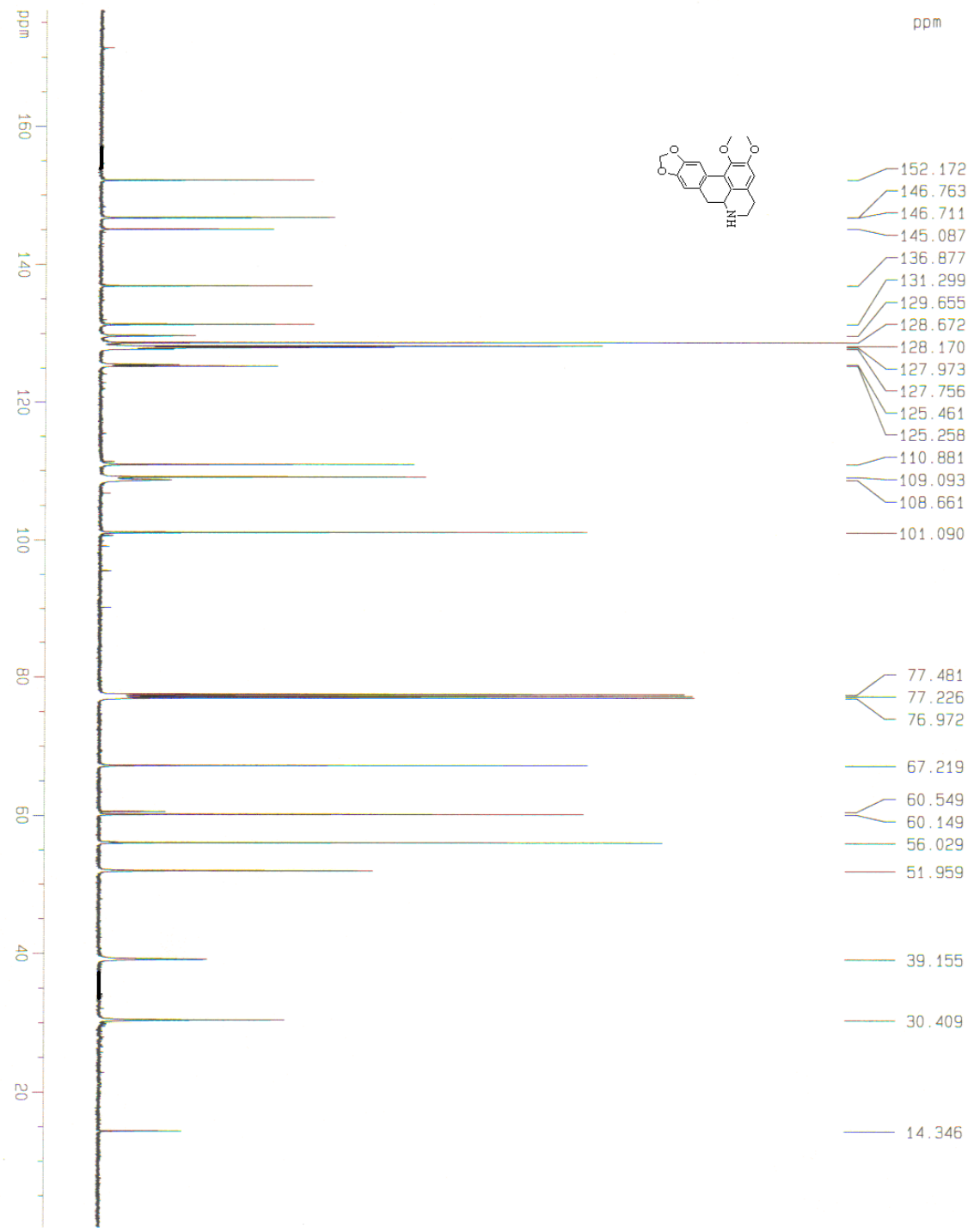
0.01189
0.00551
HN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140
120
100
80
60
40
20
ppm
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129.655
128.672
128.170
127.973
127.756
125.461
125.258
110.881
109.093
108.661
101.090
77.481
77.226
76.972
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56.029
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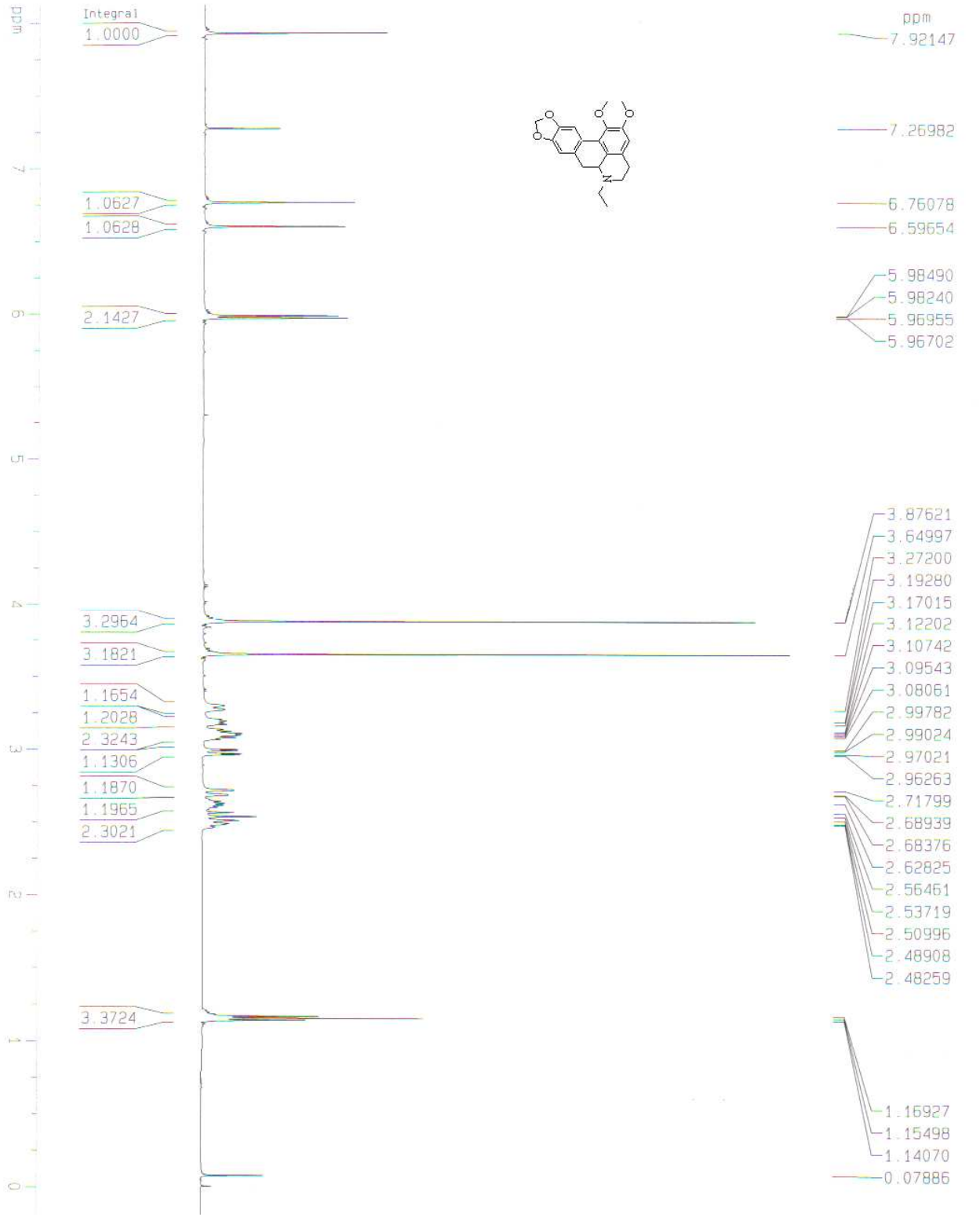
30.409
14.346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1.2028
2.3243
1.1306
1.1870
1.1965
2.3021
3.3724
7.92147
7.26982
6.76078
6.59654
5.98490
5.98240
5.96955
5.96702
3.87621
3.64997
3.27200
3.19280
3.17015
3.12202
3.10742
3.09543
3.08061
2.99782
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2.97021
2.96263
2.71799
2.68939
2.68376
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2.53719
2.50996
2.48908
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1.16927
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1.14070
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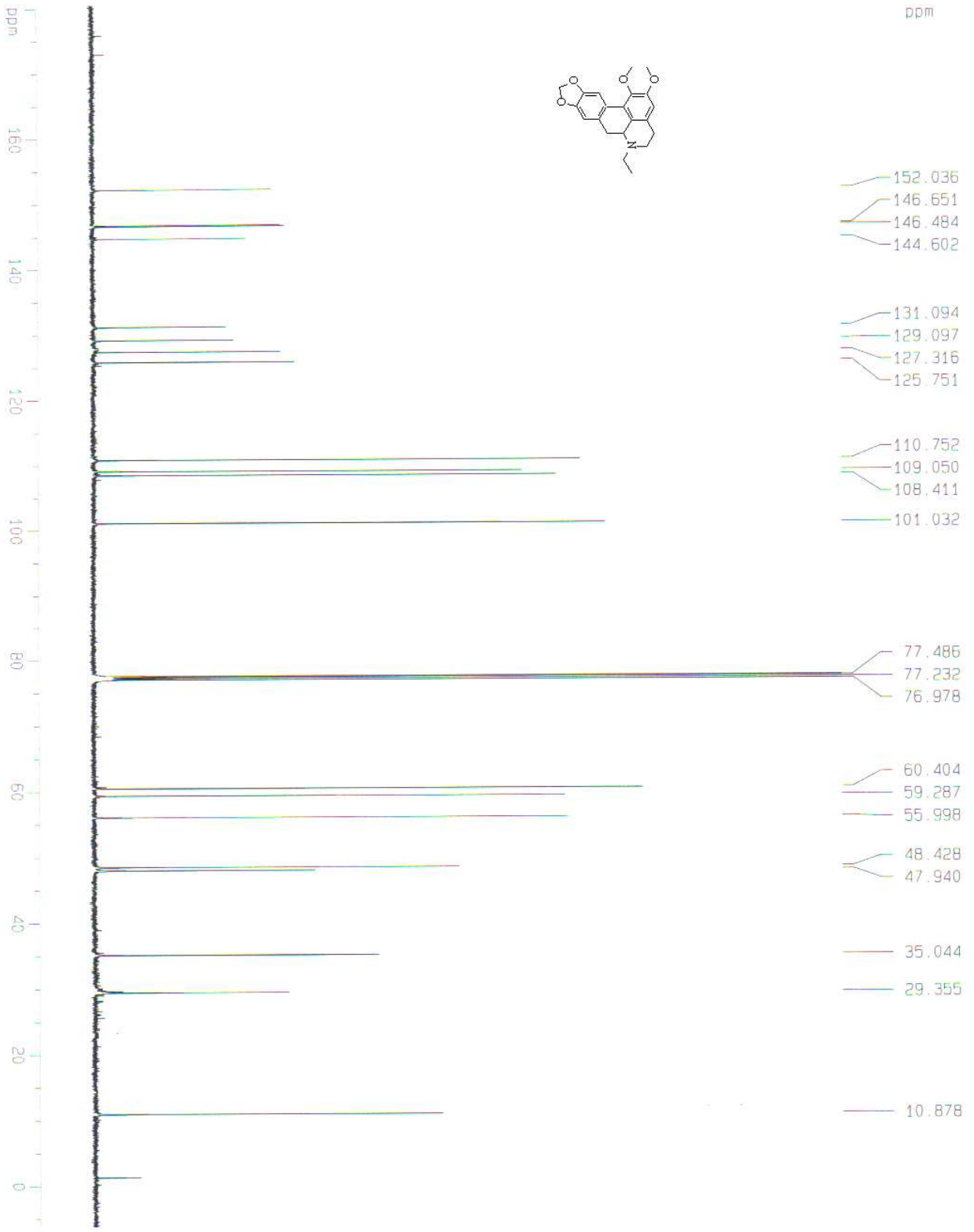
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20
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127.316
125.751
110.752
109.050
108.411
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29.355
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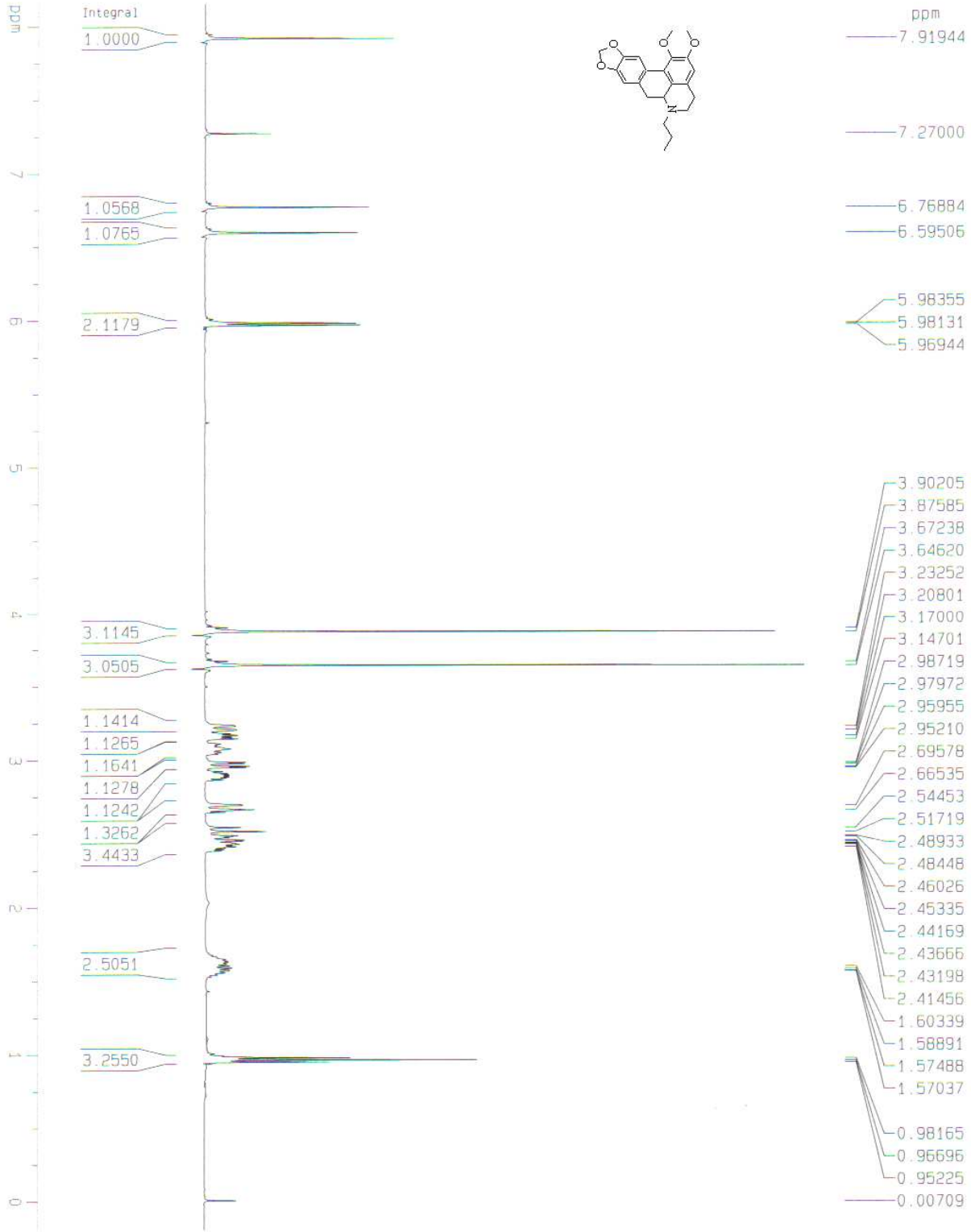
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1.1265
1.1641
1.1278
1.1242
1.3262
3.4433
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3.2550
ppm
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6.59506
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3.90205
3.87585
3.67238
3.64620
3.23252
3.20801
3.17000
3.14701
2.98719
2.97972
2.95955
2.95210
2.69578
2.66535
2.54453
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2.48933
2.48448
2.46026
2.45335
2.44169
2.43666
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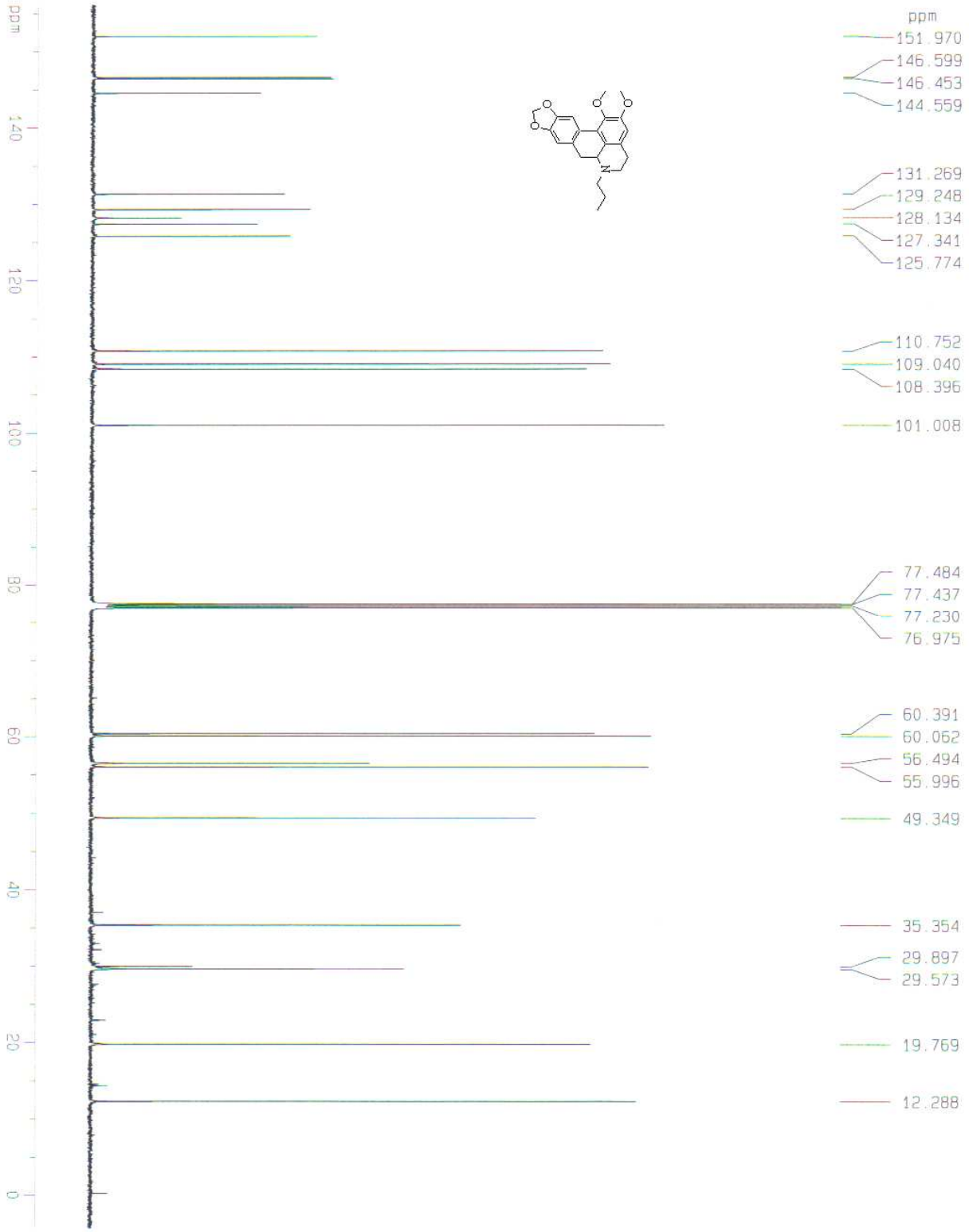
0.00709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120
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80
60
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127.341
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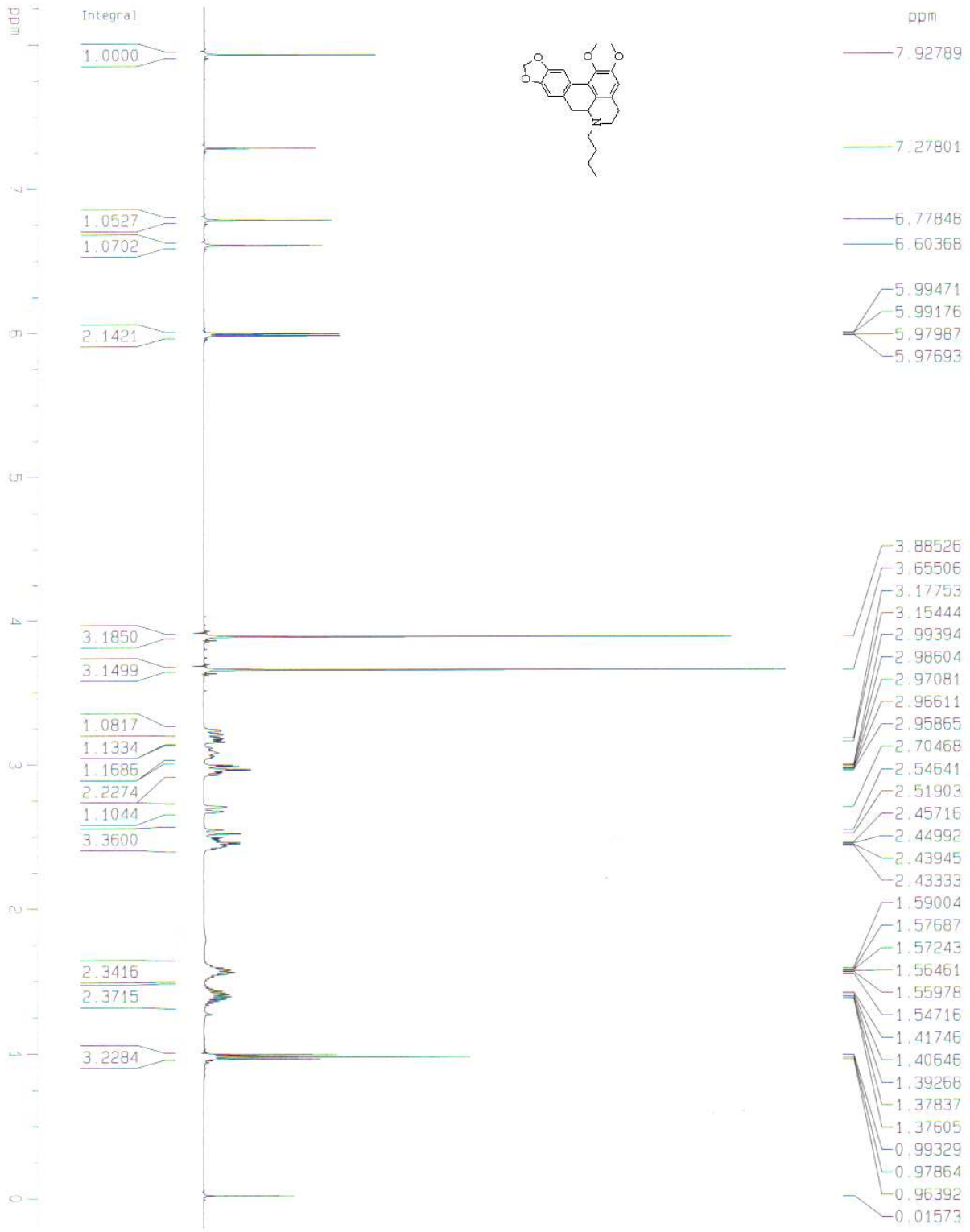
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1.1044
3.3600
2.3416
2.3715
3.2284
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6.77848
6.60368
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5.99176
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5.97693
3.88526
3.65506
3.17753
3.15444
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2.97081
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2.95865
2.70468
2.54641
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2.45716
2.44992
2.43945
2.43333
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1.57243
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1.55978
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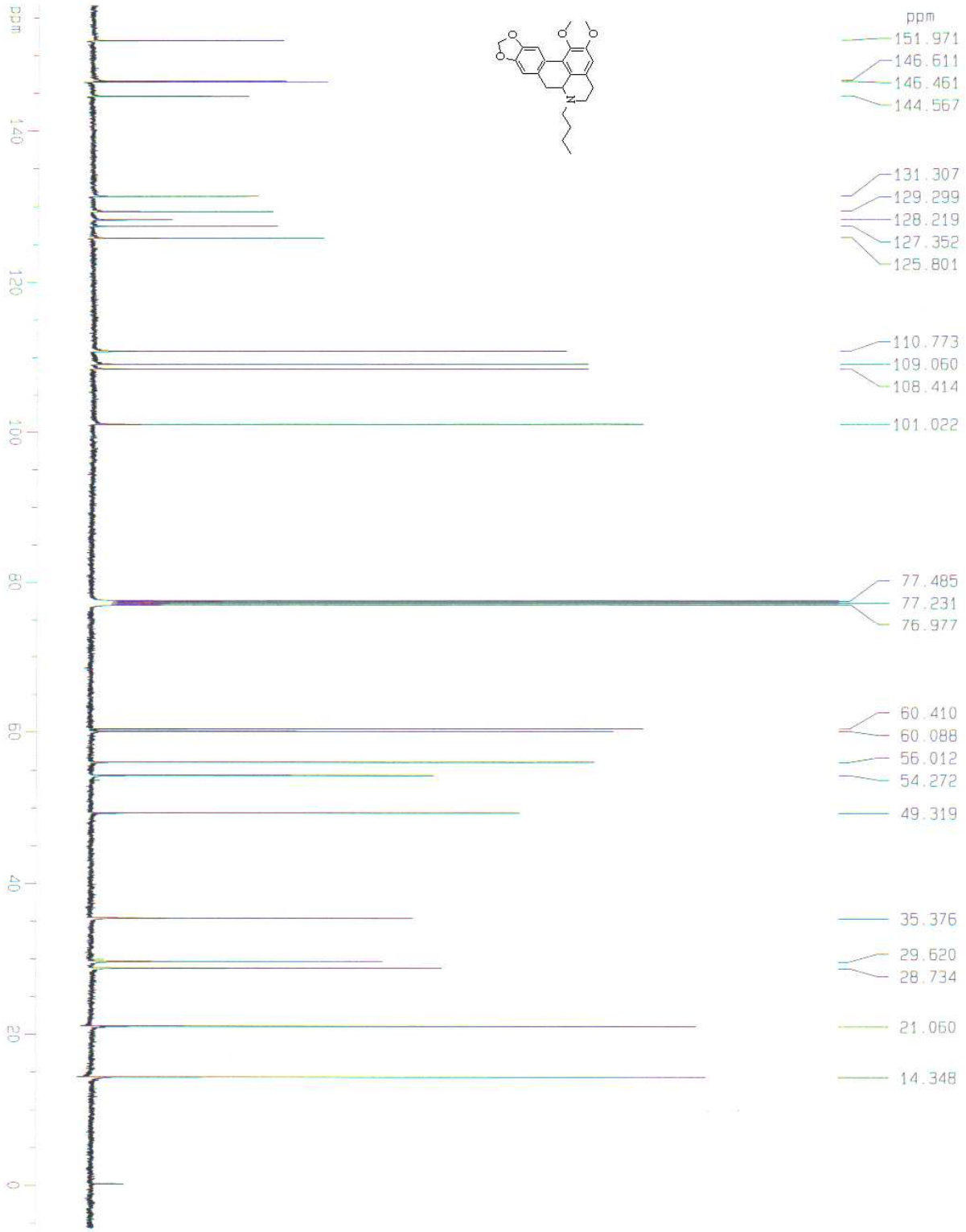
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101.022
77.485
77.231
76.977
60.410
60.088
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29.620
28.734
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60
40
20
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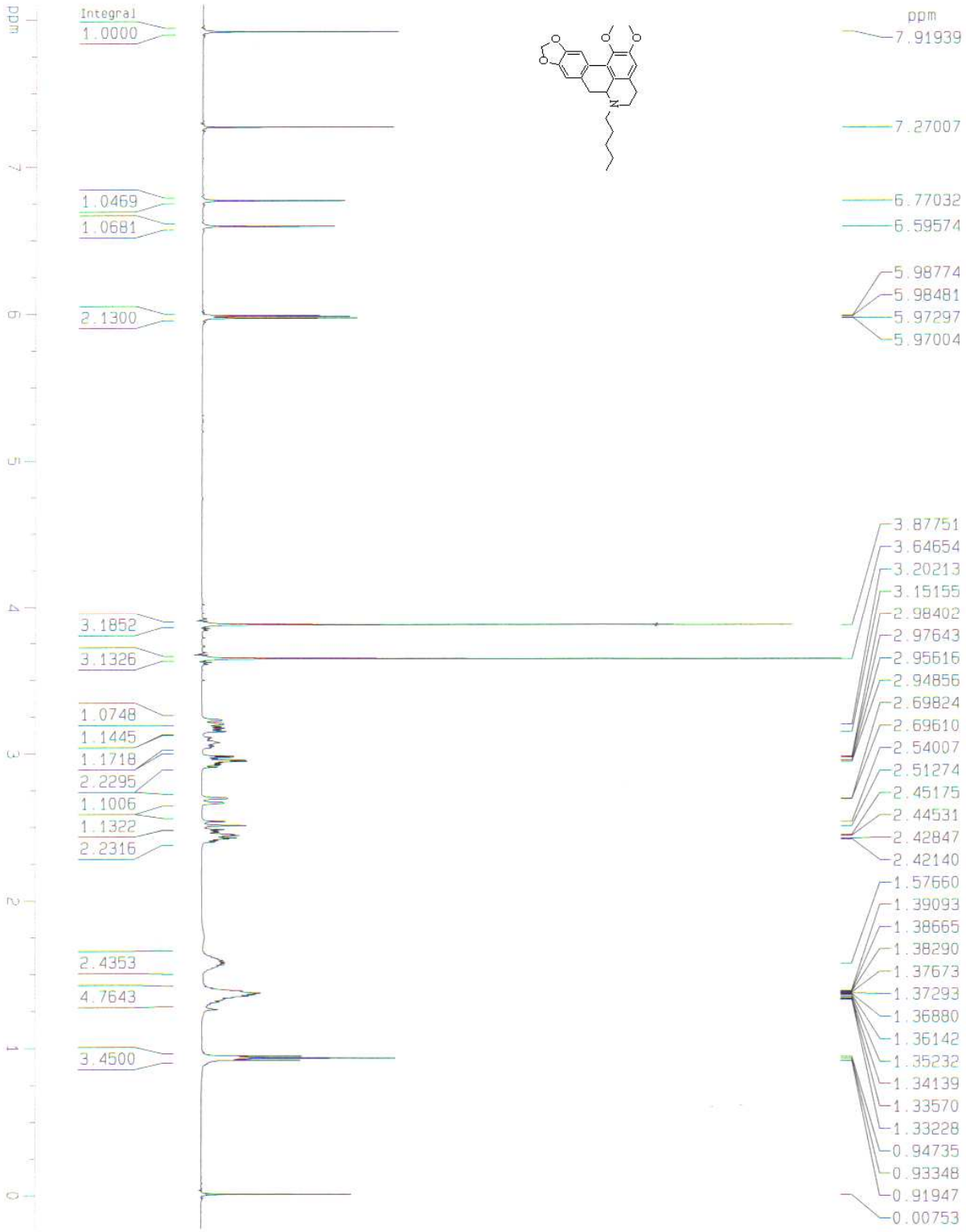
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3.4500
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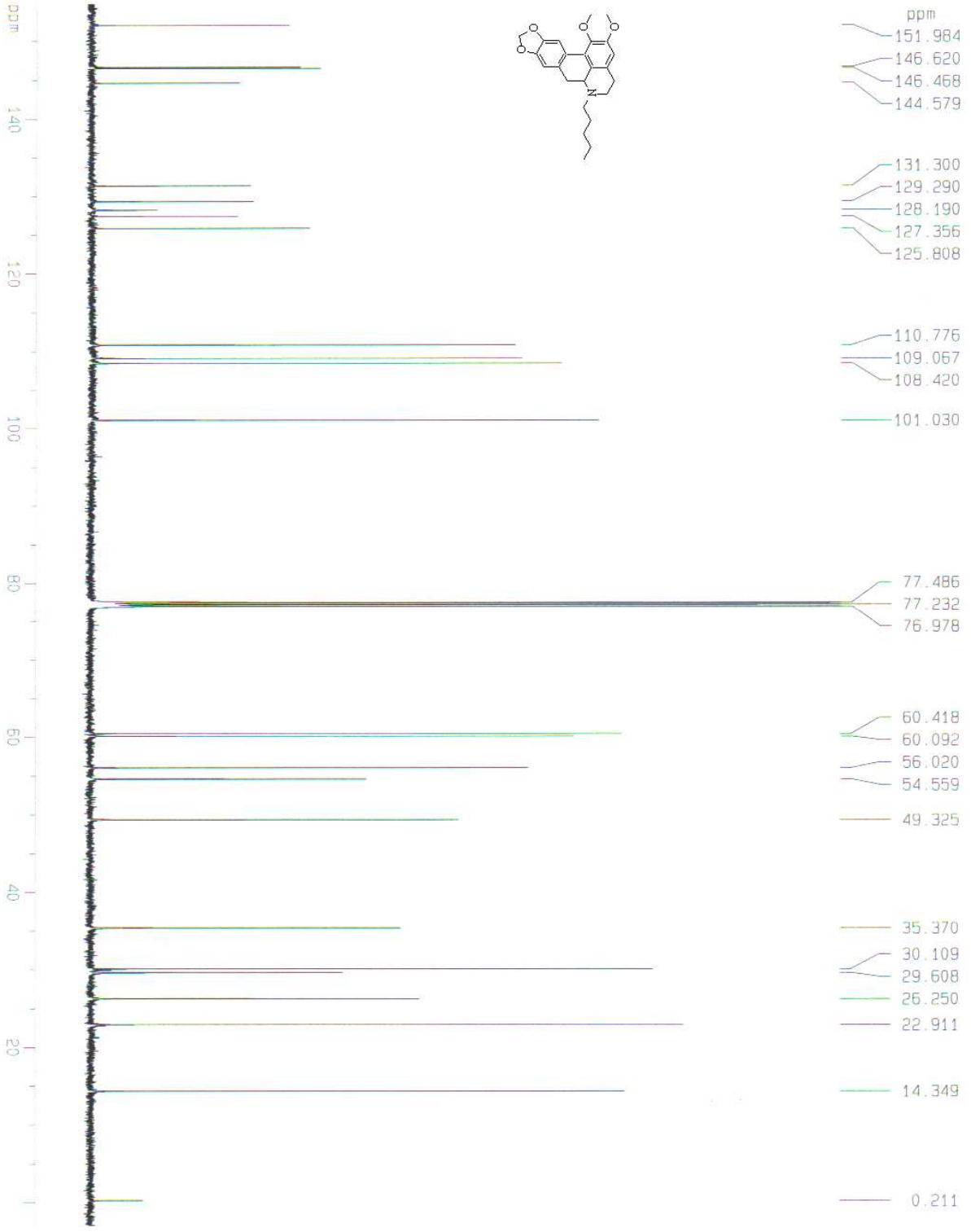
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77.232
76.978
60.418
60.092
56.020
54.559
49.325
35.370
30.109
29.608
26.250
22.911
14.349
0.211
ppm
140
120
100
80
60
40
20


ppm
Integral
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3.2727
3.2053
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1.1181
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2.1990
ppm
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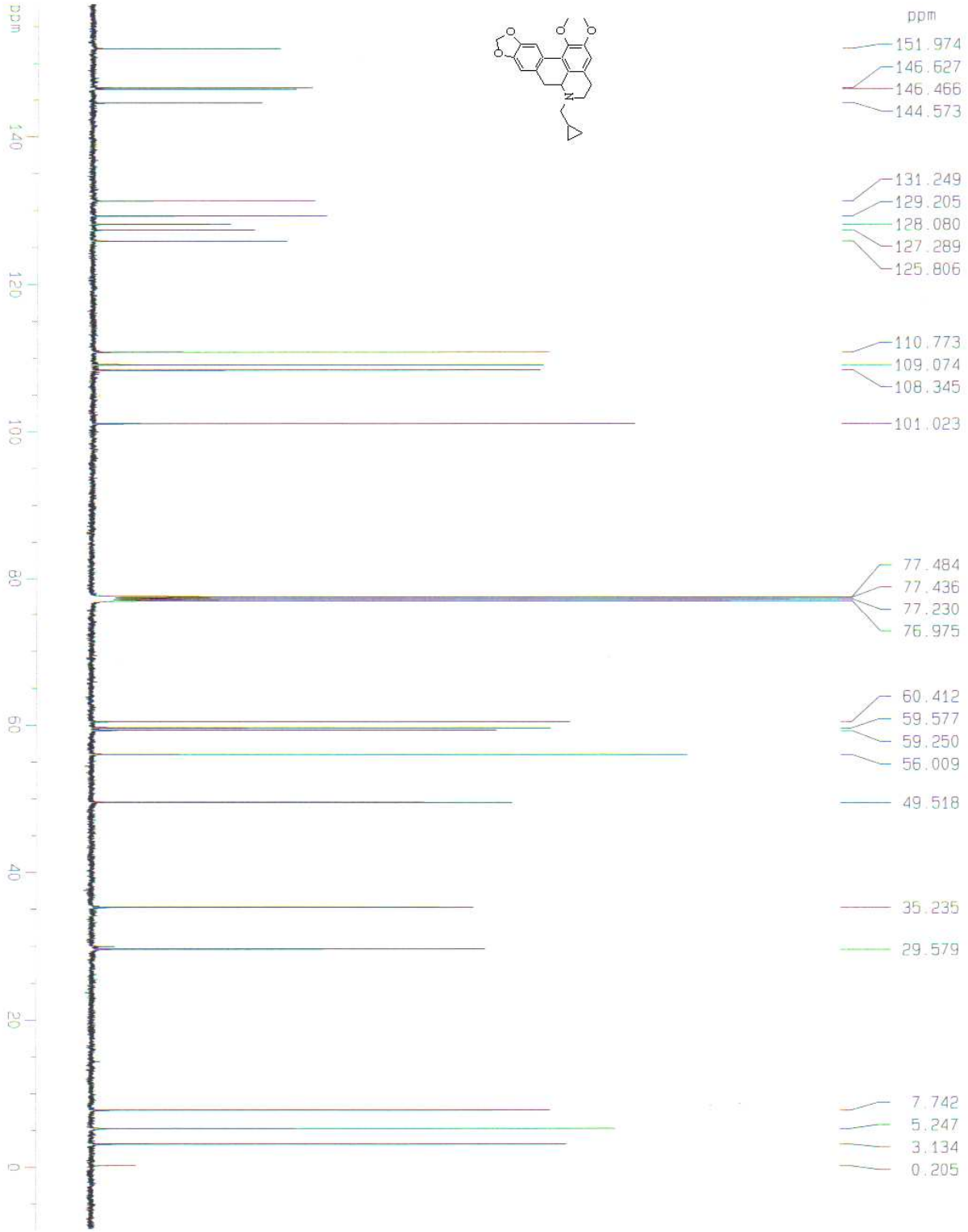
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77.484
77.436
77.230
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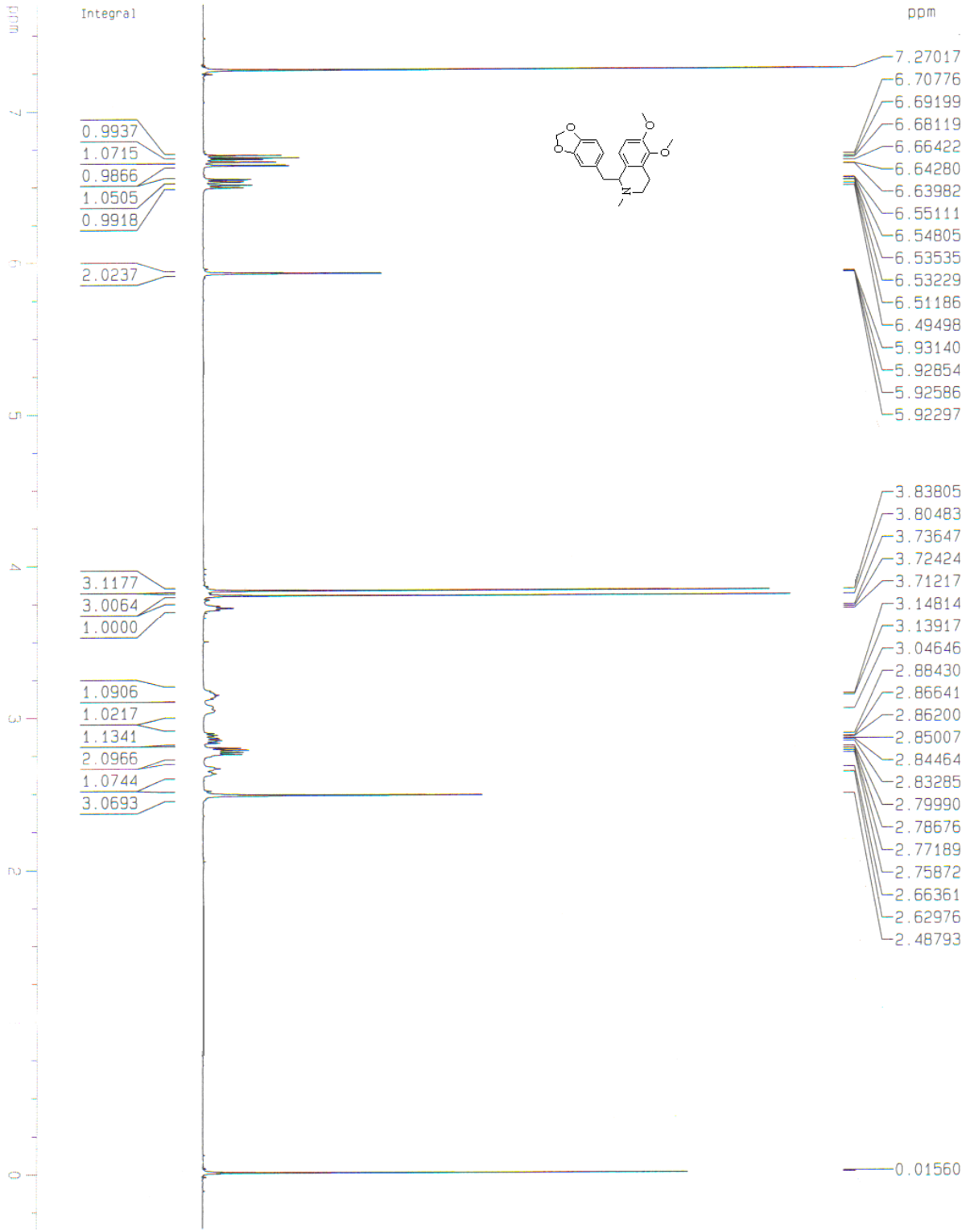
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1.0906
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1.1341
2.0966
1.0744
3.0693
7.27017
6.70776
6.69199
6.68119
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6.63982
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6.53535
6.53229
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6.49498
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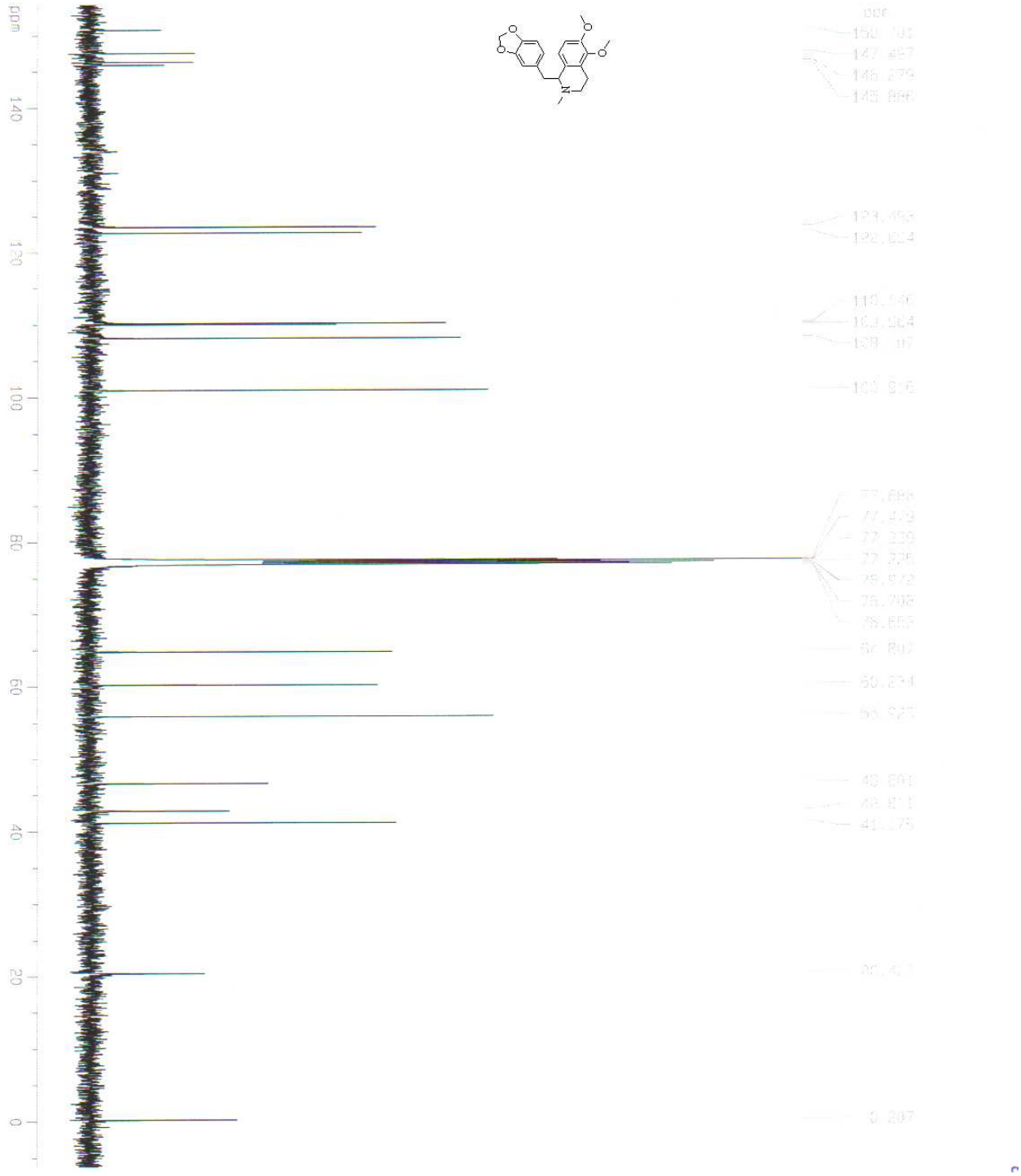

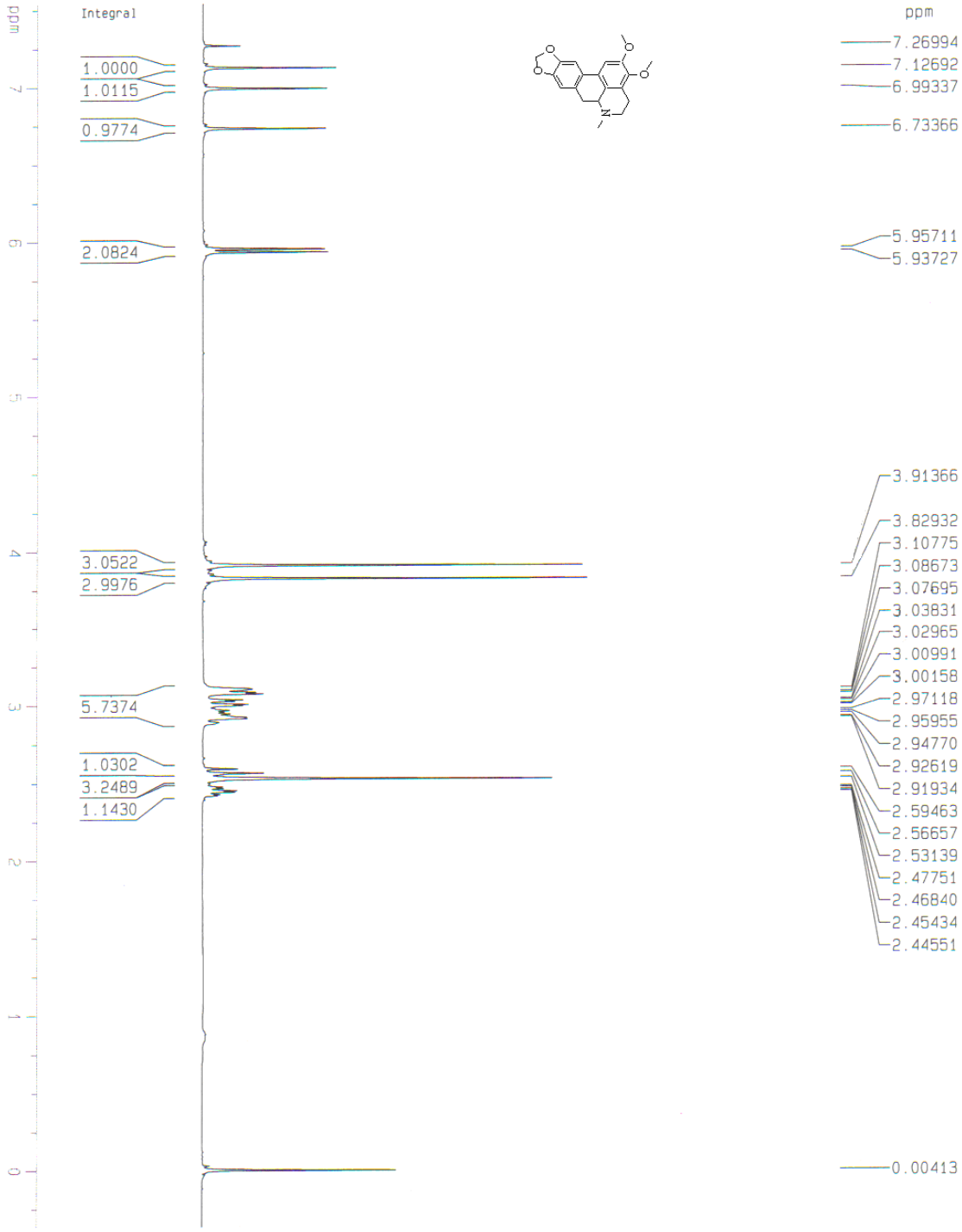
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ppm
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7.12692
6.99337
6.73366
5.95711
5.93727
3.91366
3.82932
3.10775
3.08673
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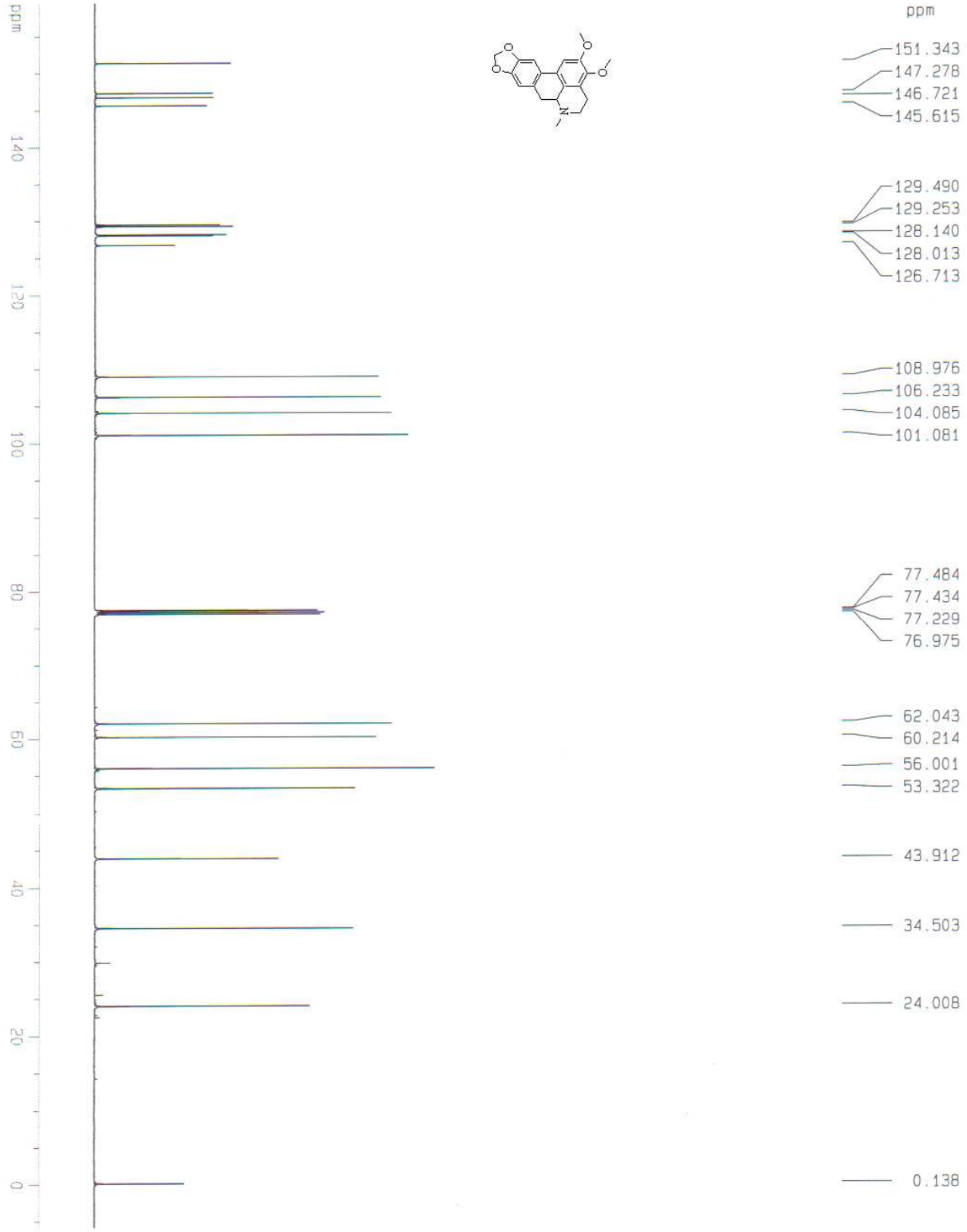
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147.278
146.721
145.615
129.490
129.253
128.140
128.013
126.713
108.976
106.233
104.085
101.081
77.484
77.434
77.229
76.975
62.043
60.214
56.001
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43.912
34.503
24.008
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60
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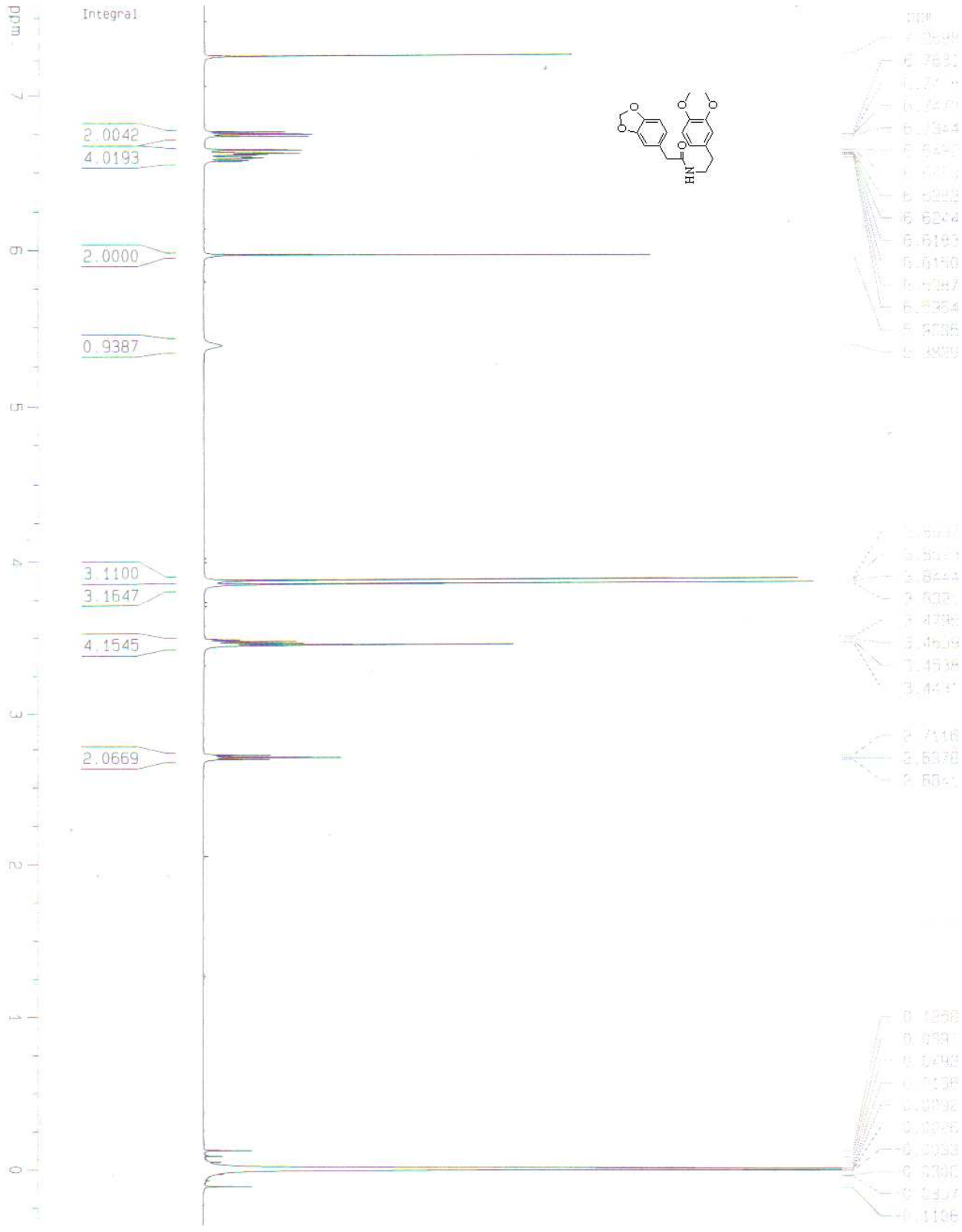
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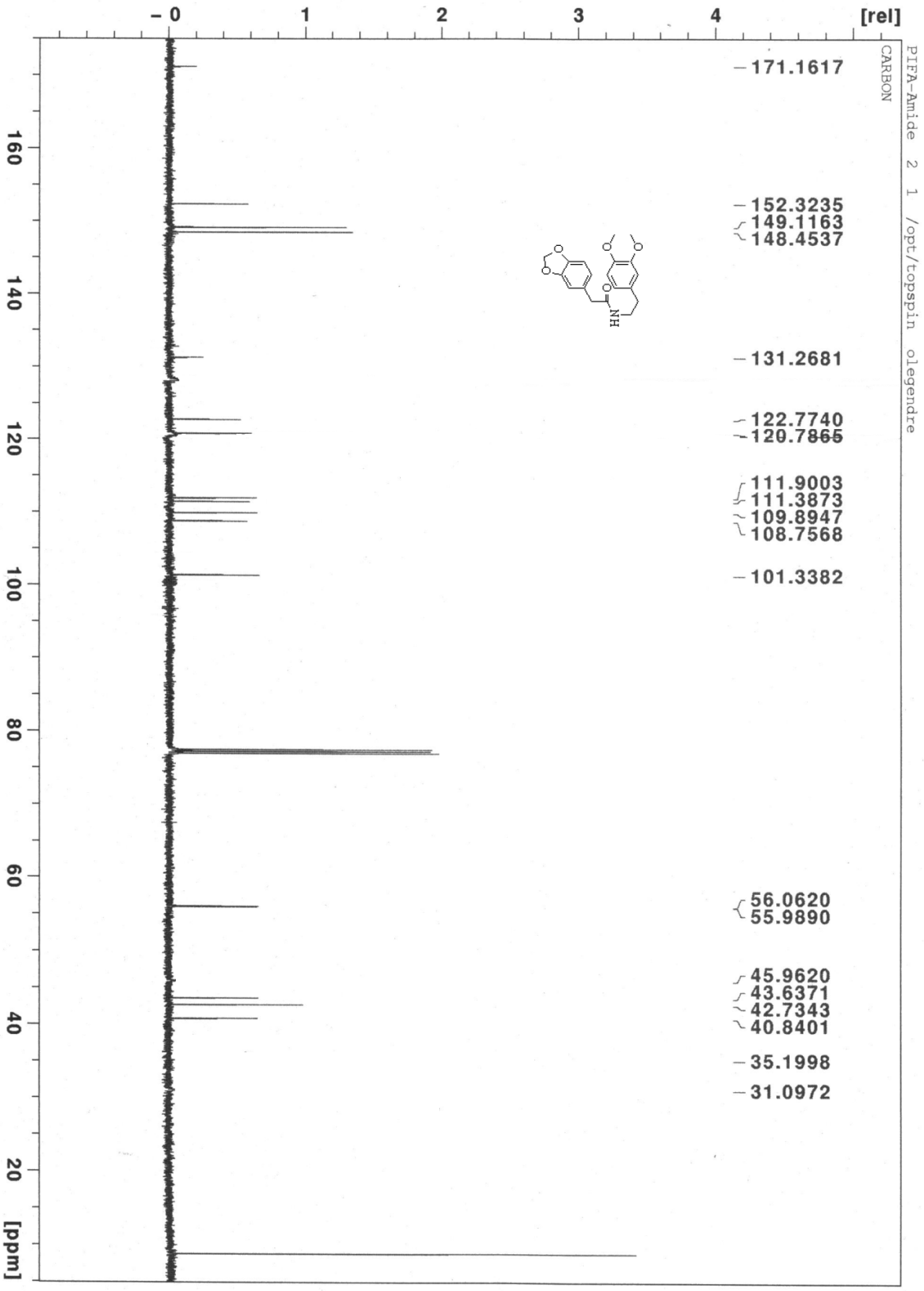
2.0000
0.9387
3.1100
3.1647
4.1545
2.0669
HN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3
4
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140
120
100
80
60
40
20
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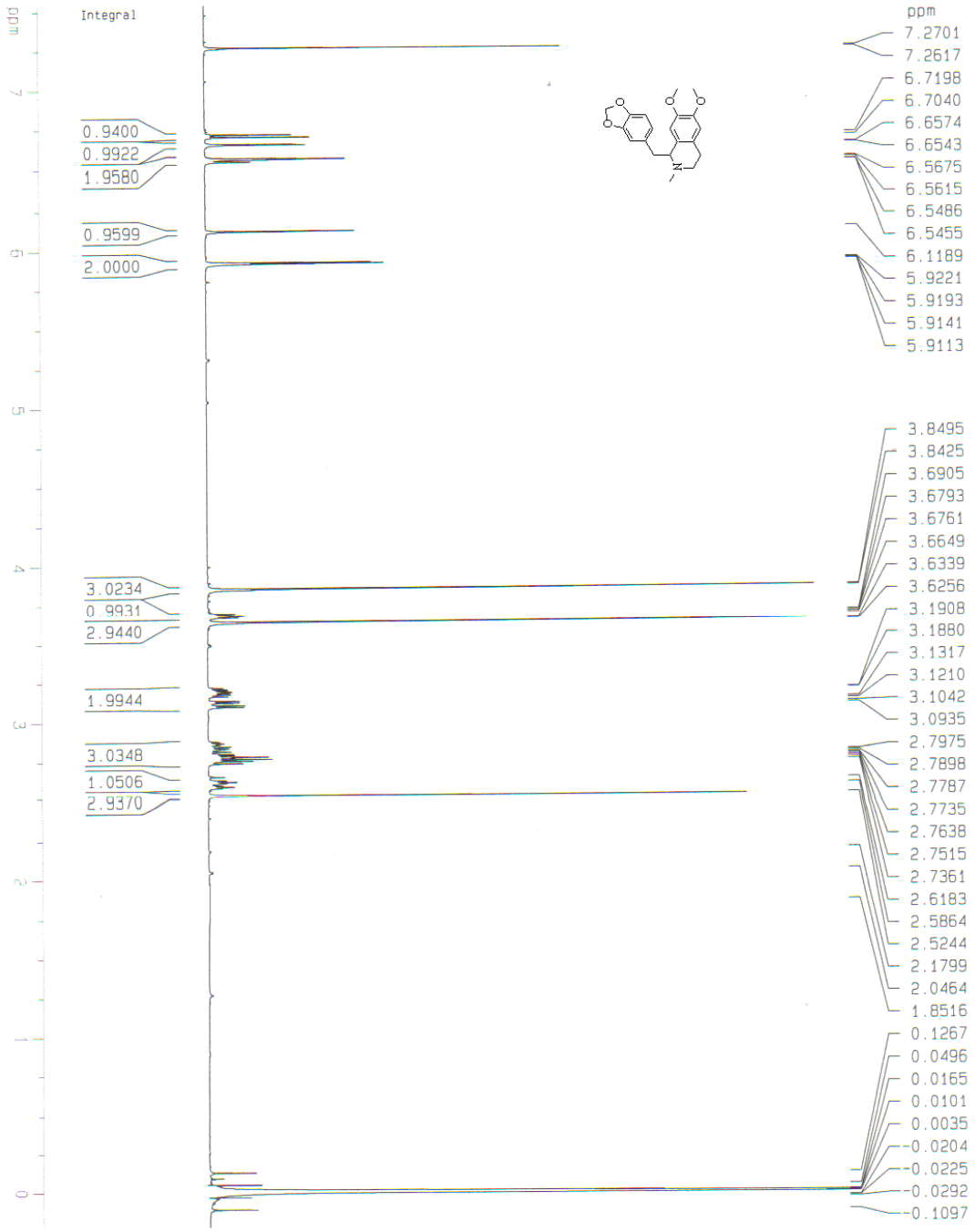
152.3235
149.1163
148.4537
131.2681
122.7740
120.7865
111.9003
111.3873
109.8947
108.7568
101.3382
56.0620
55.9890
45.9620
43.6371
42.7343
40.8401
35.1998
31.0972
NH
CARBON
PIFA-Amide 2 1 /opt/topspin olegendre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ppm
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0.9599
2.0000
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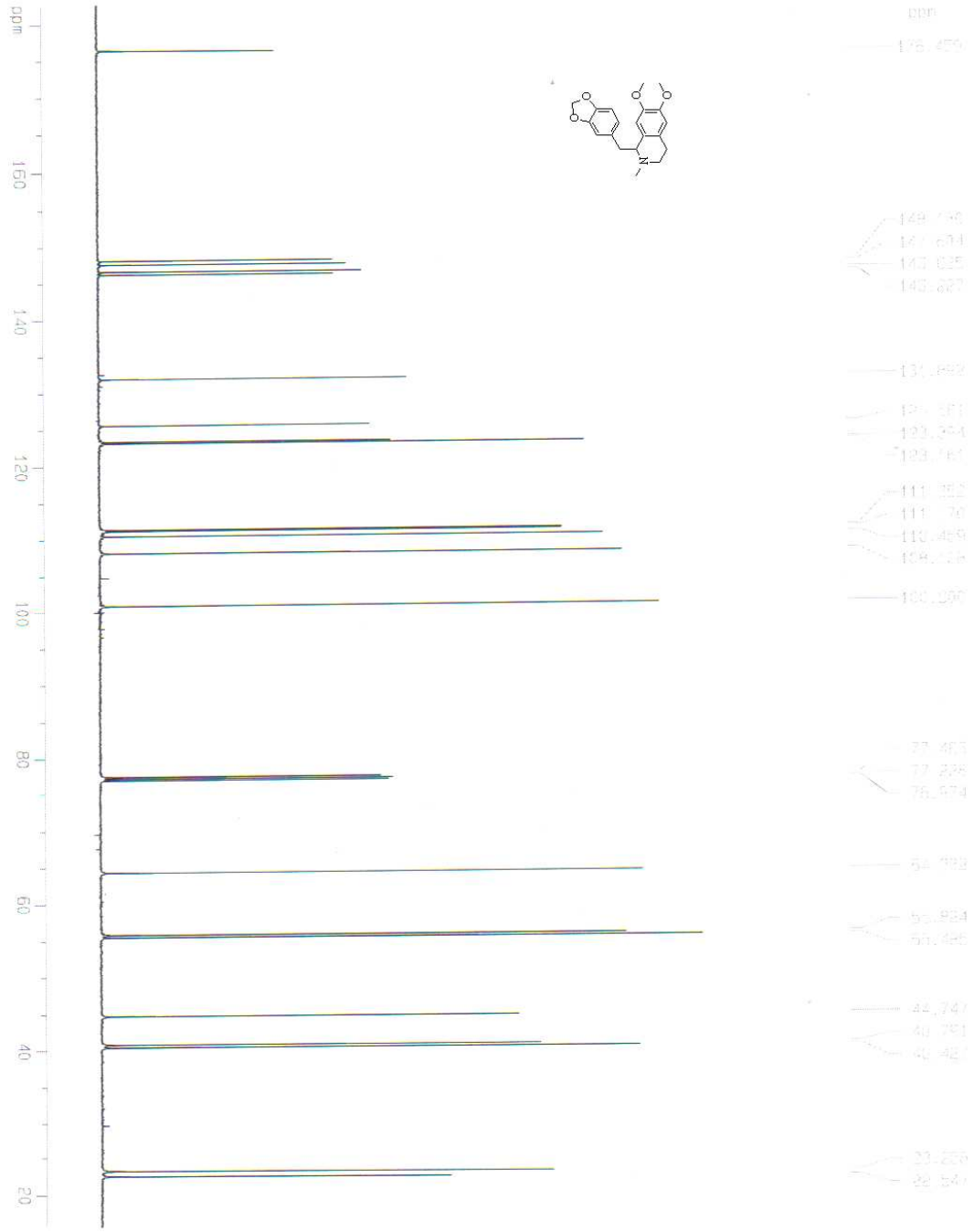
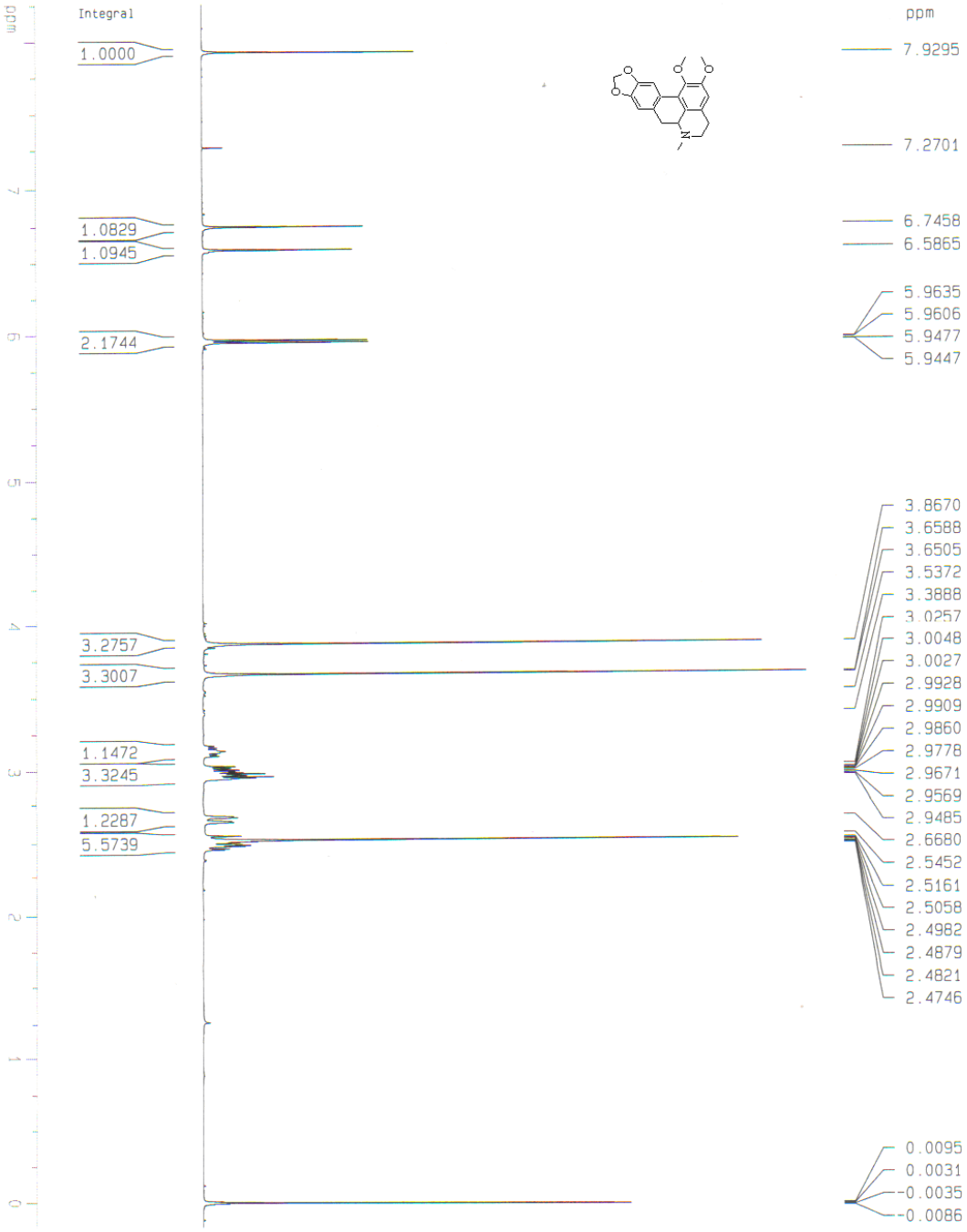
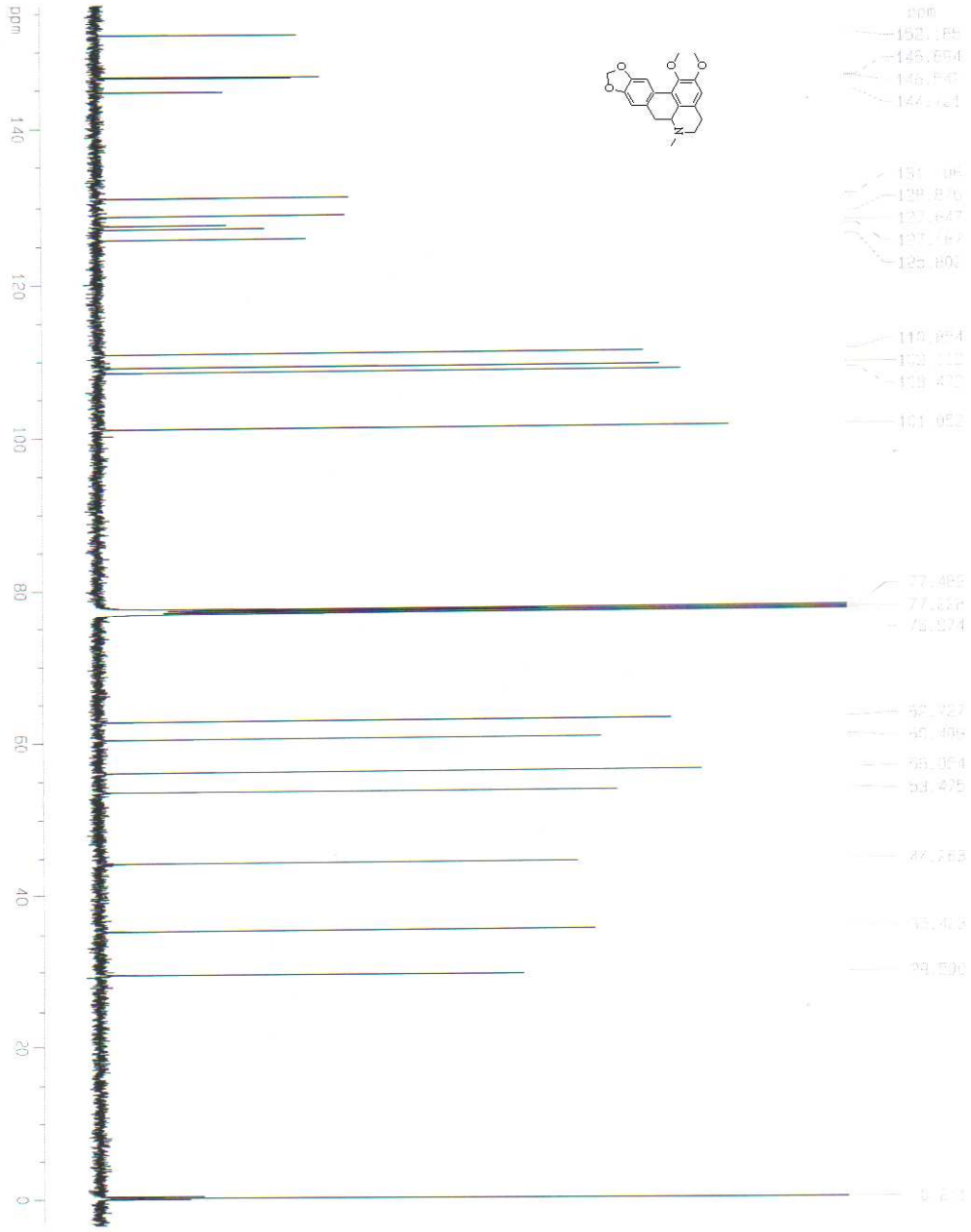
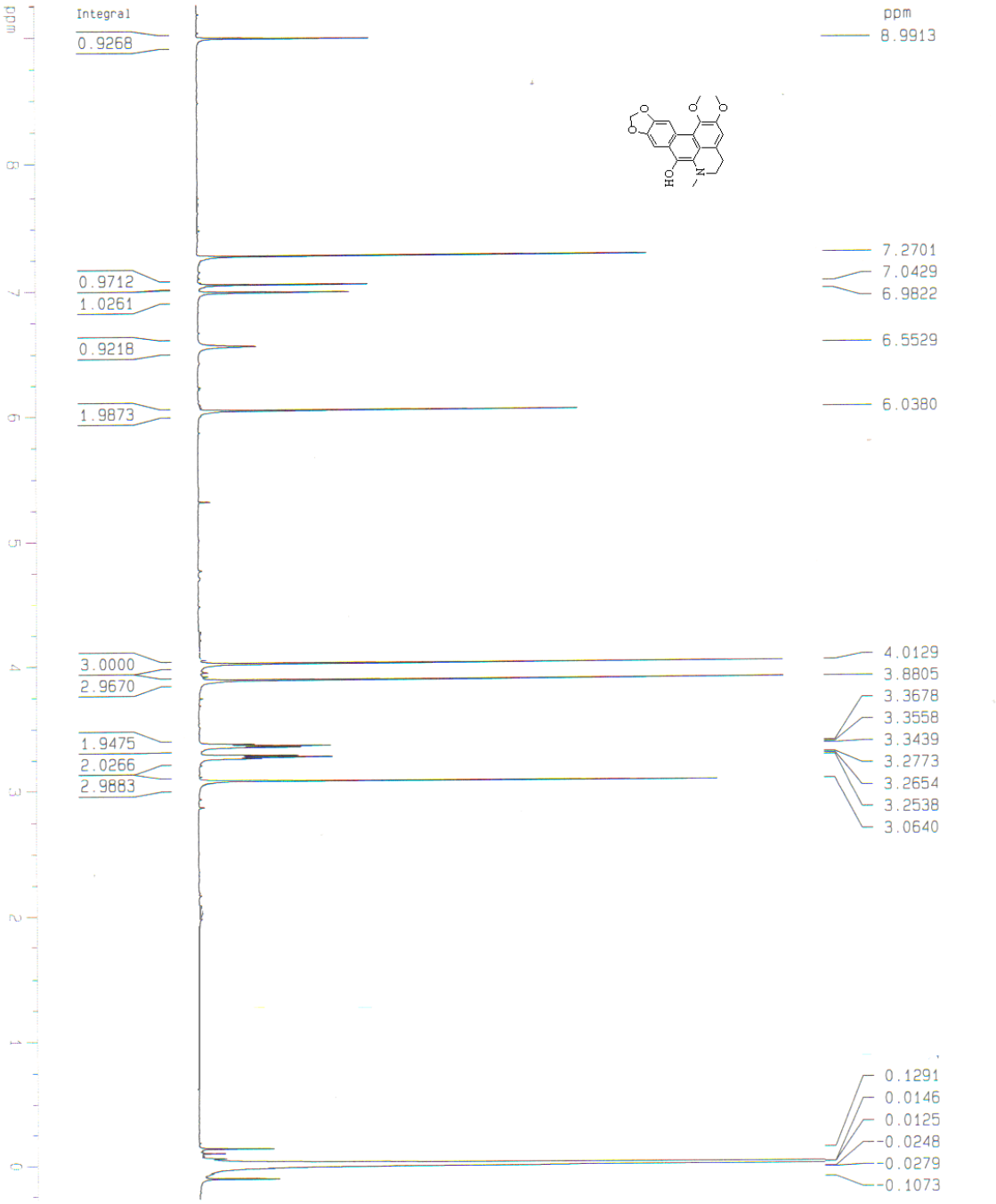
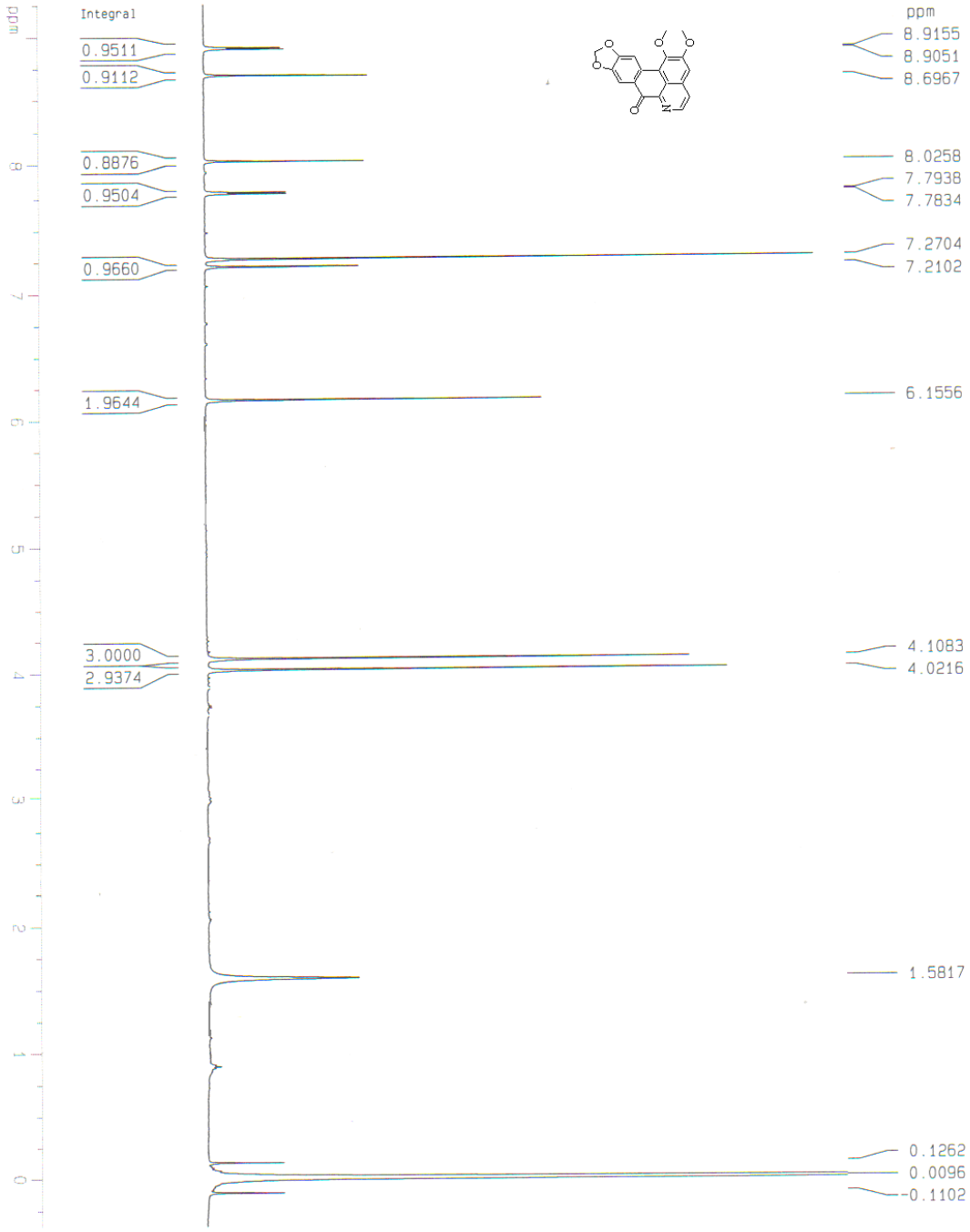
2.9440
1.9944
3.0348
1.0506
2.9370
7.2701
7.2617
6.7198
6.7040
6.6574
6.6543
6.5675
6.5615
6.5486
6.5455
6.1189
5.9221
5.9193
5.9141
5.9113
3.8495
3.8425
3.6905
3.6793
3.6761
3.6649
3.6339
3.6256
3.1908
3.1880
3.1317
3.1210
3.1042
3.0935
2.7975
2.7898
2.7787
2.7735
2.7638
2.7515
2.7361
2.6183
2.5864
2.5244
2.1799
2.0464
1.8516
0.1267
0.0496
0.0165
0.0101
0.0035
-0.0204
-0.0225
-0.0292
-0.1097

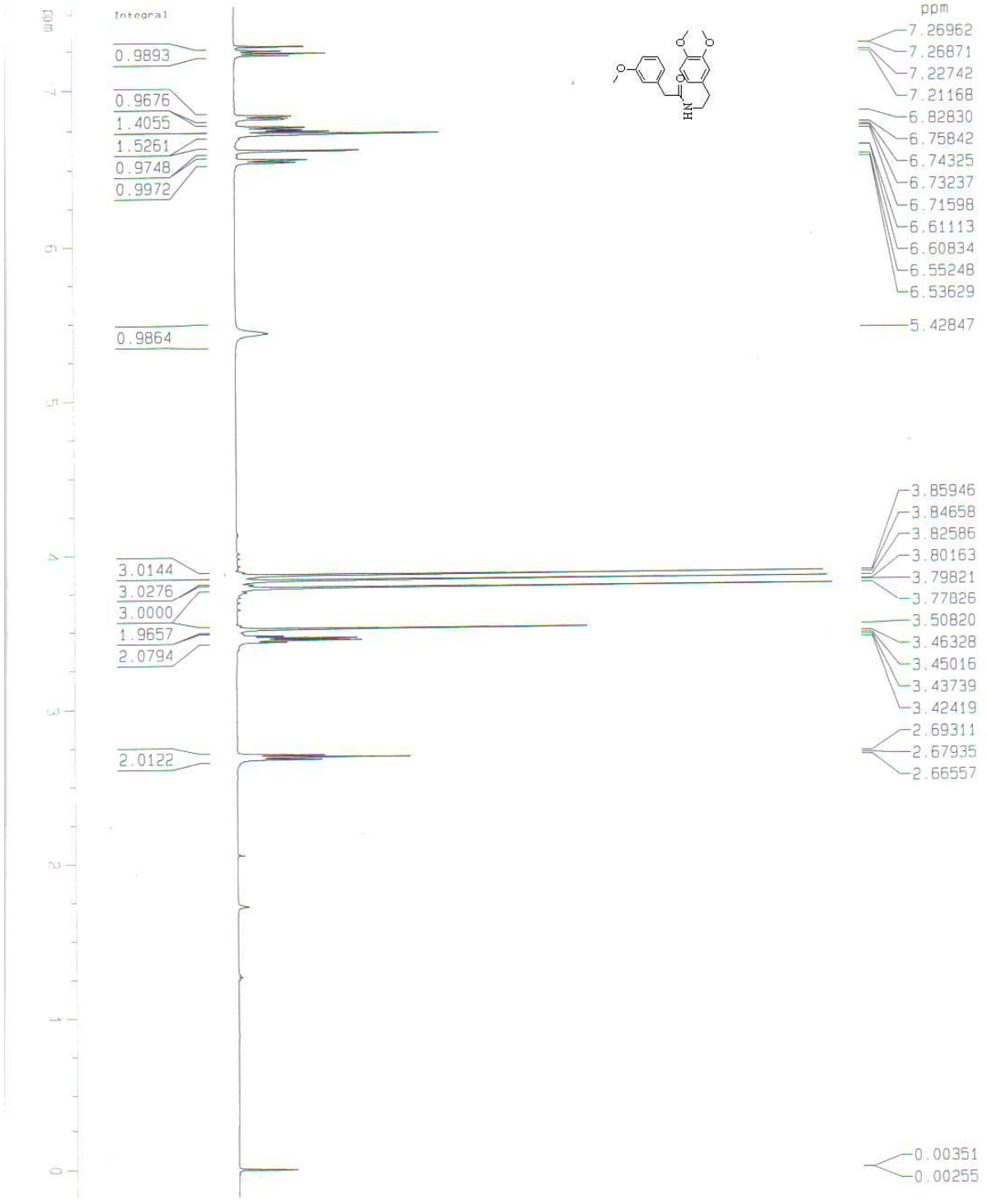


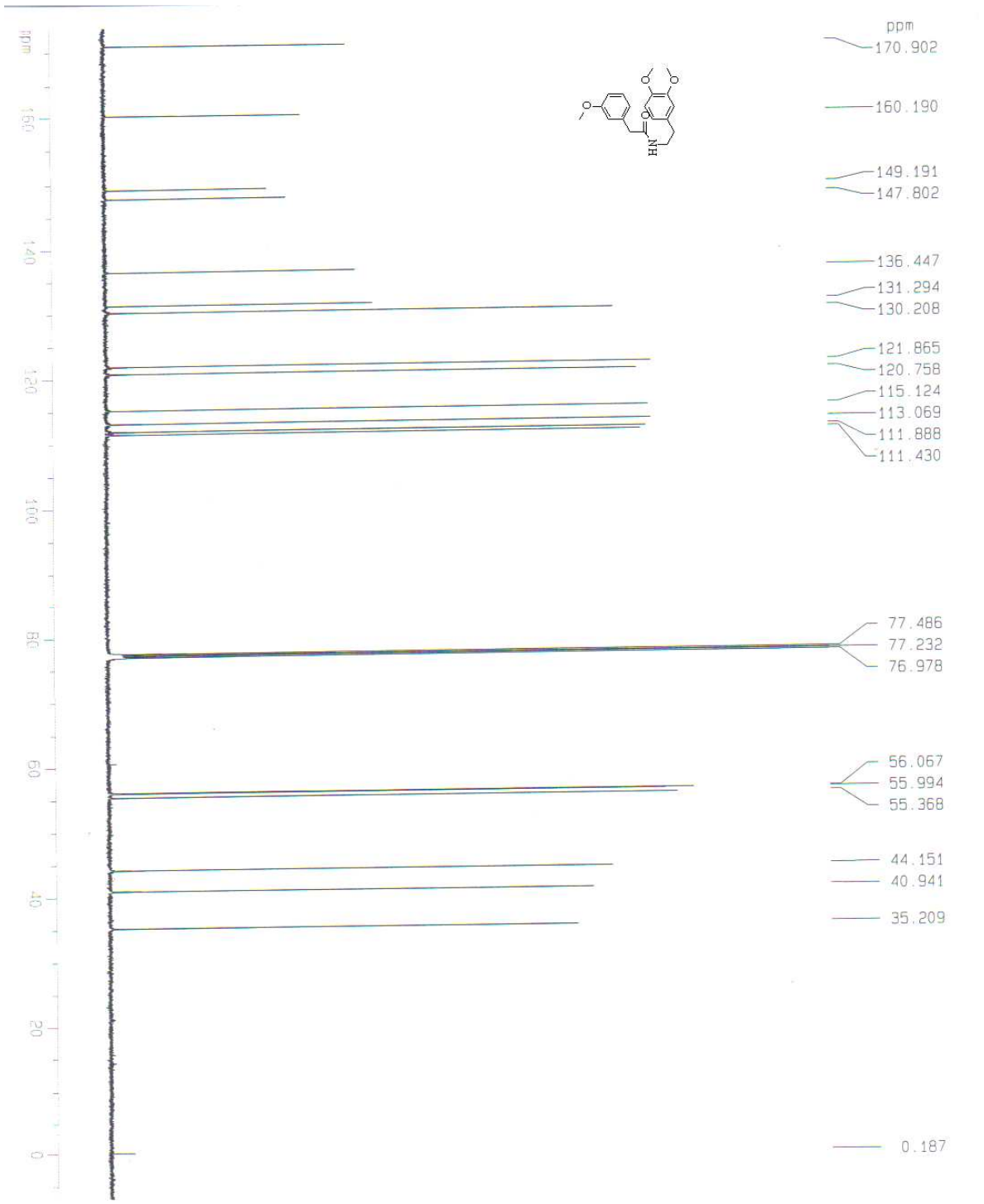

Integral
1.0000
1.0829
1.0945
2.1744
3.2757
3.3007
1.1472
3.3245
1.2287
5.5739
ppm
7.9295
7.2701
6.7458
6.5865
5.9635
5.9606
5.9477
5.9447
3.8670
3.6588
3.6505
3.5372
3.3888
3.0257
3.0048
3.0027
2.9928
2.9909
2.9860
2.9778
2.9671
2.9569
2.9485
2.6680
2.5452
2.5161
2.5058
2.4982
2.4879
2.4821
2.4746
0.0095
0.0031
-0.0035
-0.0086




Integral
0.9268
0.9712
1.0261
0.9218
1.9873
3.0000
2.9670
1.9475
2.0266
2.9883
ppm
8.9913
7.2701
7.0429
6.9822
6.5529
6.0380
4.0129
3.8805
3.3678
3.3558
3.3439
3.2773
3.2654
3.2538
3.0640
0.1291
0.0146
0.0125
-0.0248
-0.0279
-0.1073
HO
N


Integral
0.9511
0.9112
0.8876
0.9504
0.9660
1.9644
3.0000
2.9374
ppm
8.9155
8.9051
8.6967
8.0258
7.7938
7.7834
7.2704
7.2102
6.1556
4.1083
4.0216
1.5817
0.1262
0.0096
-0.1102


Integral
0.9893
0.9676
1.4055
1.5261
0.9748
0.9972
0.9864
3.0144
3.0276
3.0000
1.9657
2.0794
2.0122
ppm
7.26962
7.26871
7.22742
7.21168
6.82830
6.75842
6.74325
6.73237
6.71598
6.61113
6.60834
6.55248
6.53629
5.42847
3.85946
3.84658
3.82586
3.80163
3.79821
3.77826
3.50820
3.46328
3.45016
3.43739
3.42419
2.69311
2.67935
2.66557
0.00351
0.00255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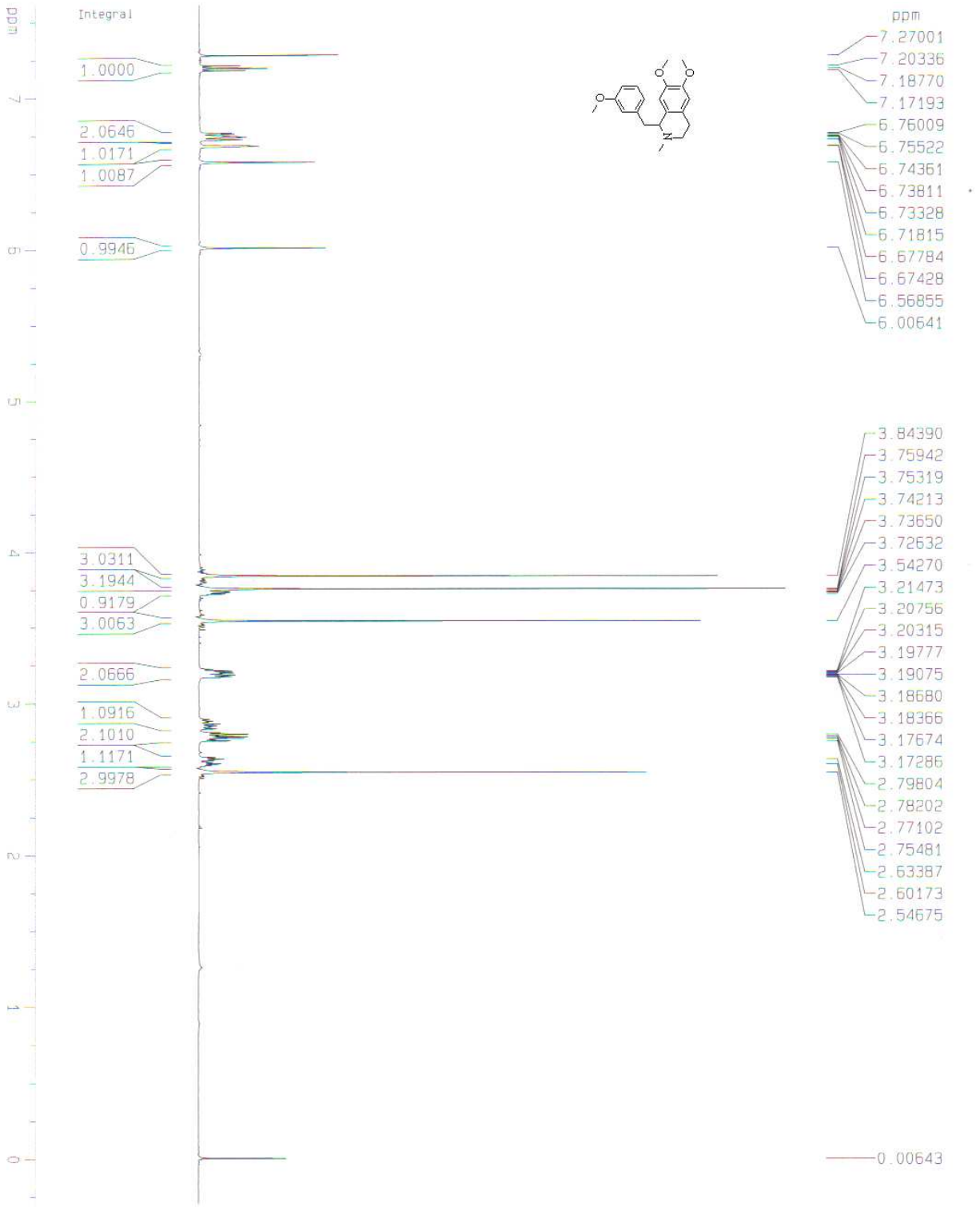
149.191
147.802
136.447
131.294
130.208
121.865
120.758
115.124
113.069
111.888
111.430
77.486
77.232
76.978
56.067
55.994
55.368
44.151
40.941
35.209
0.187
NH


Integral
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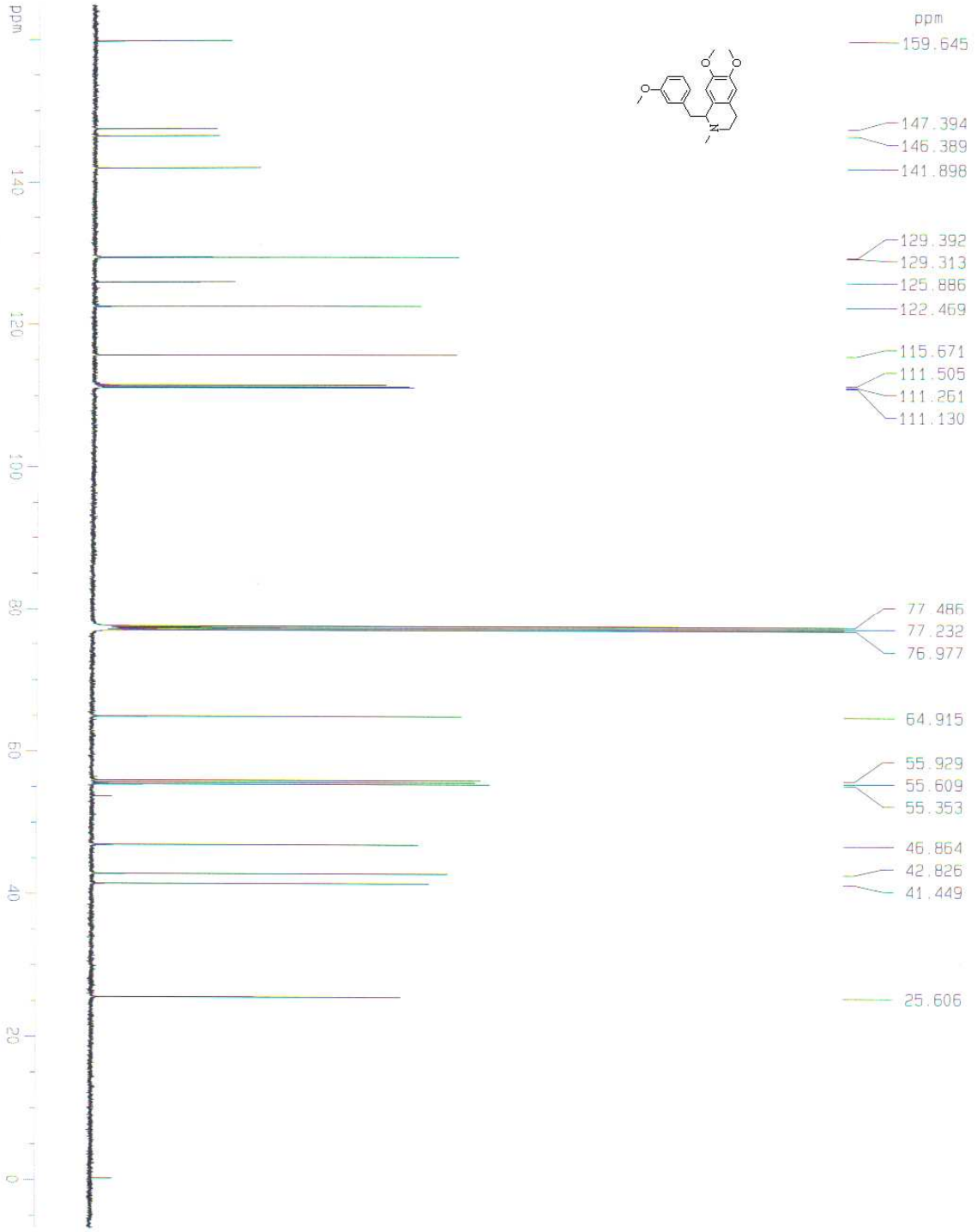
1.0171
1.0087
0.9946
3.0311
3.1944
0.9179
3.0063
2.0666
1.0916
2.1010
1.1171
2.9978
ppm
7.27001
7.20336
7.18770
7.17193
6.76009
6.75522
6.74361
6.73811
6.73328
6.71815
6.67784
6.67428
6.56855
6.00641
3.84390
3.75942
3.75319
3.74213
3.73650
3.72632
3.54270
3.21473
3.20756
3.20315
3.19777
3.19075
3.18680
3.18366
3.17674
3.17286
2.79804
2.78202
2.77102
2.75481
2.63387
2.60173
2.54675
0.00643


ppm
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146.389
141.898
129.392
129.313
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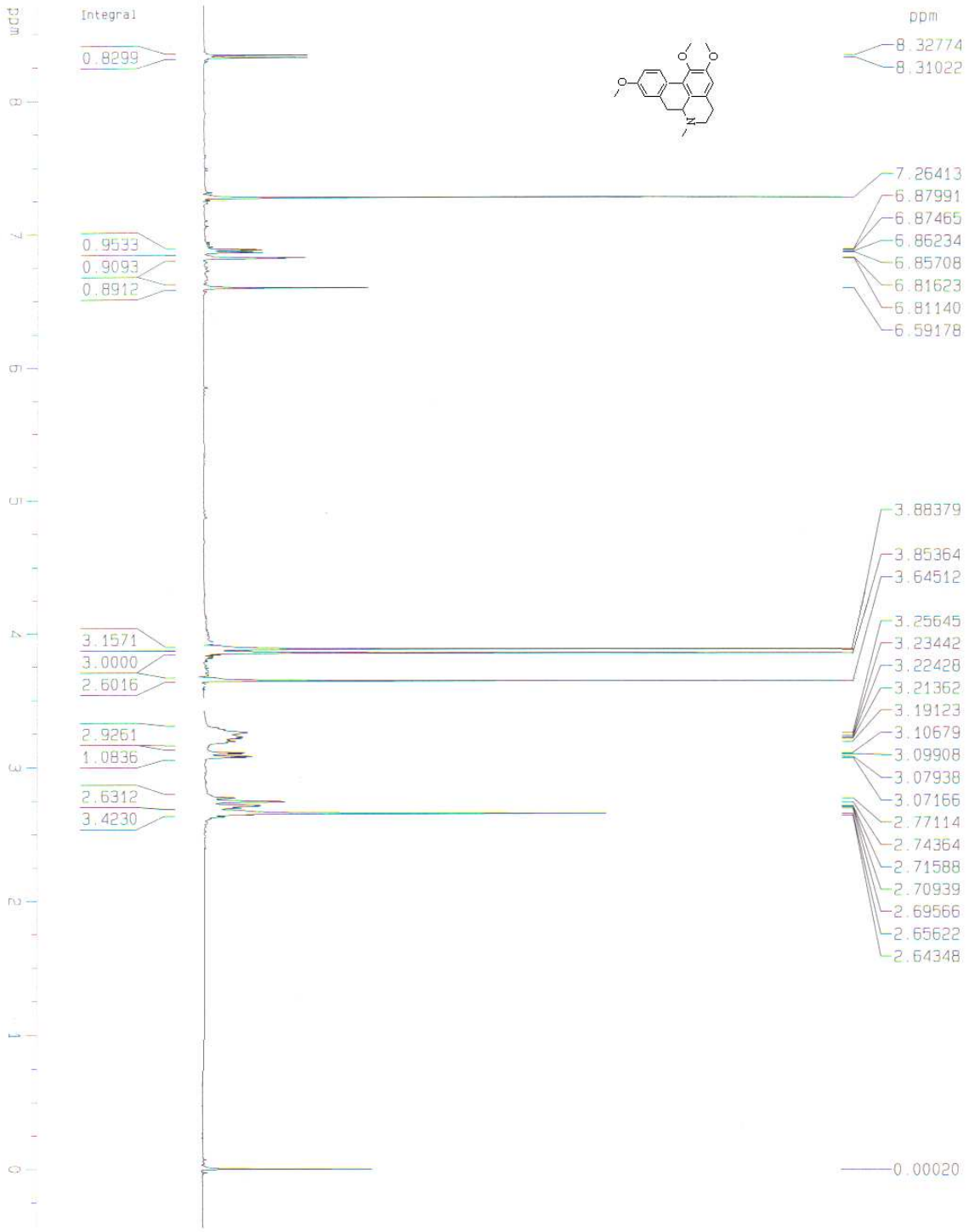
122.469
115.671
111.505
111.261
111.130
77.486
77.232
76.977
64.915
55.929
55.609
55.353
46.864
42.826
41.449
25.606
ppm
140
120
100
80
60
40
20
0


ppm
Integral
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0.9093
0.8912
3.1571
3.0000
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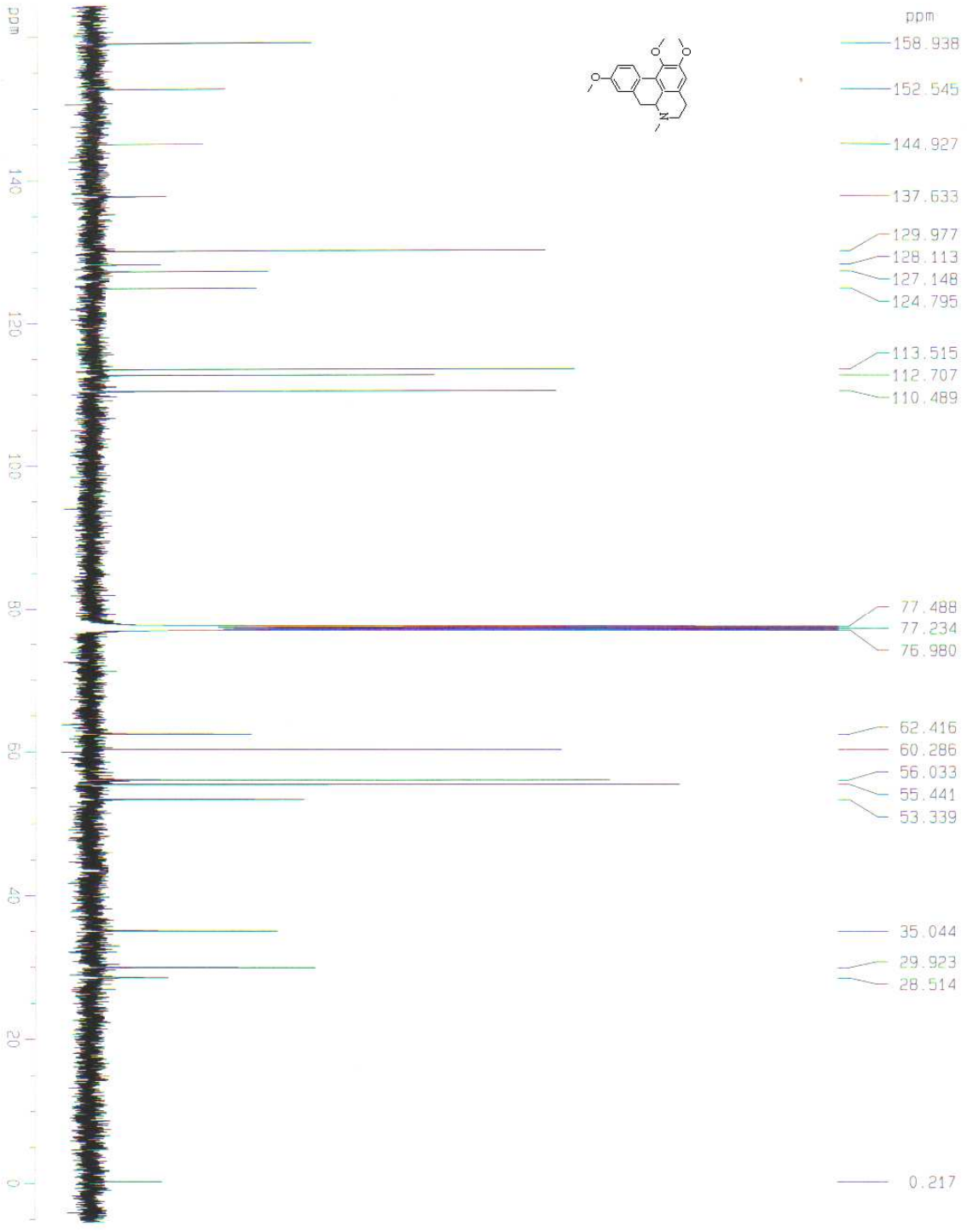
2.9261
1.0836
2.6312
3.4230
ppm
8.32774
8.31022
7.26413
6.87991
6.87465
6.86234
6.85708
6.81623
6.81140
6.59178
3.88379
3.85364
3.64512
3.25645
3.23442
3.22428
3.21362
3.19123
3.10679
3.09908
3.07938
3.07166
2.77114
2.74364
2.71588
2.70939
2.69566
2.65622
2.64348
0.00020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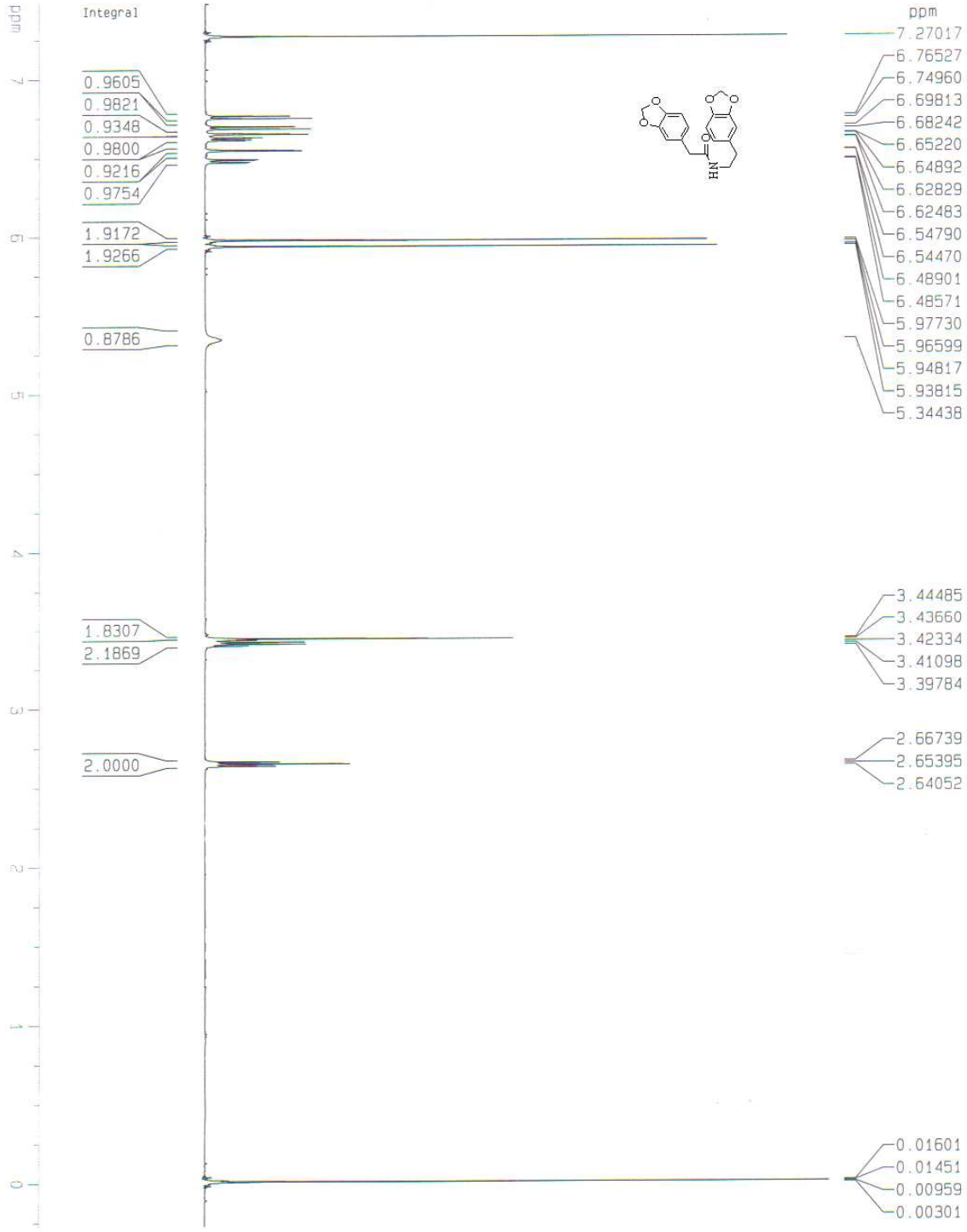
129.977
128.113
127.148
124.795
113.515
112.707
110.489
77.488
77.234
76.980
62.416
60.286
56.033
55.441
53.339
35.044
29.923
28.514
0.217
ppm
140
120
100
80
60
40
20
0


Integral
ppm
0.9605
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0.9348
0.9800
0.9216
0.9754
1.9172
1.9266
0.8786
1.8307
2.1869
2.0000
7.27017
6.76527
6.74960
6.69813
6.68242
6.65220
6.64892
6.62829
6.62483
6.54790
6.54470
6.48901
6.48571
5.97730
5.96599
5.94817
5.93815
5.34438
3.44485
3.43660
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3.41098
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2.66739
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2.64052
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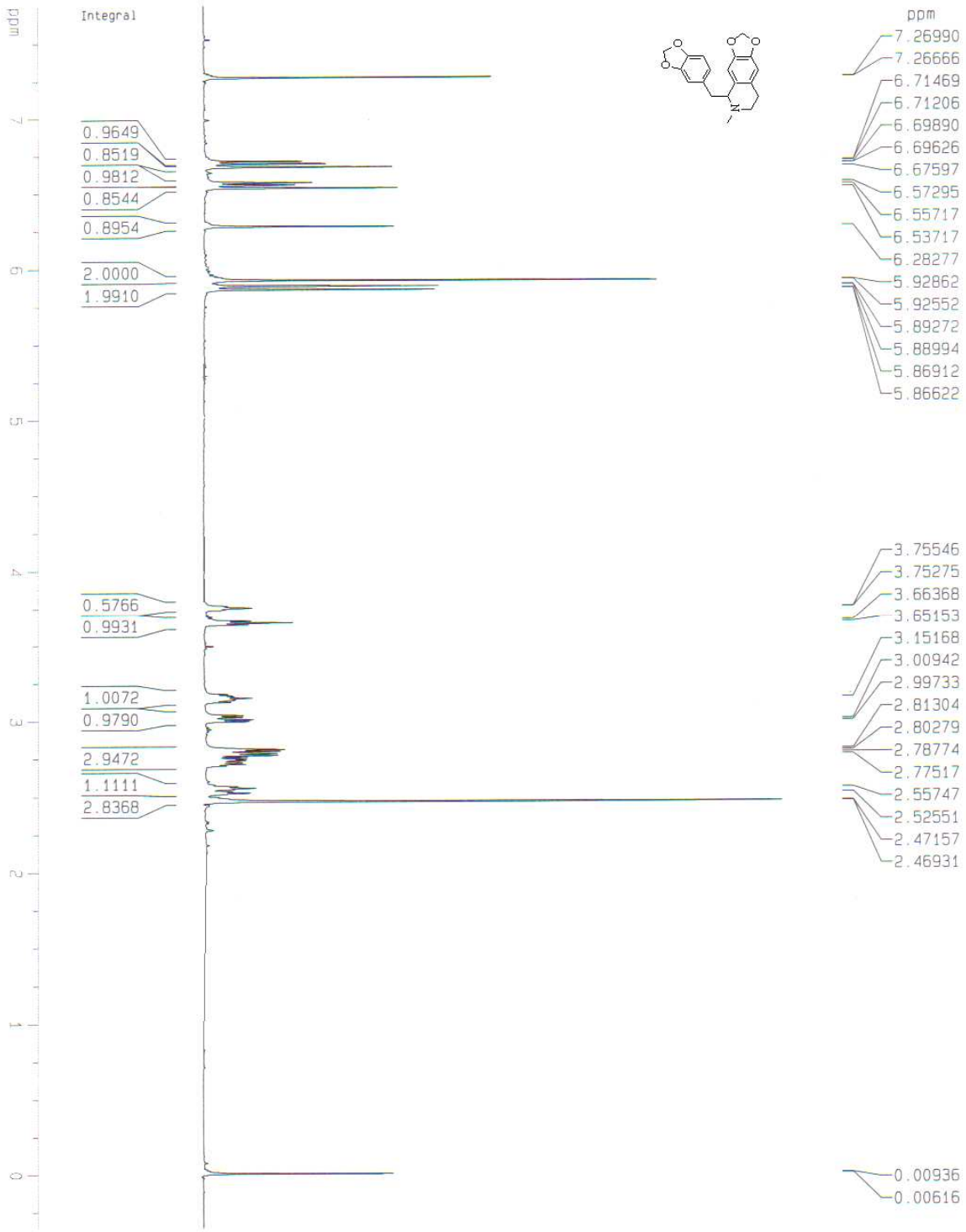
0.00959
0.00301
NH


Integral
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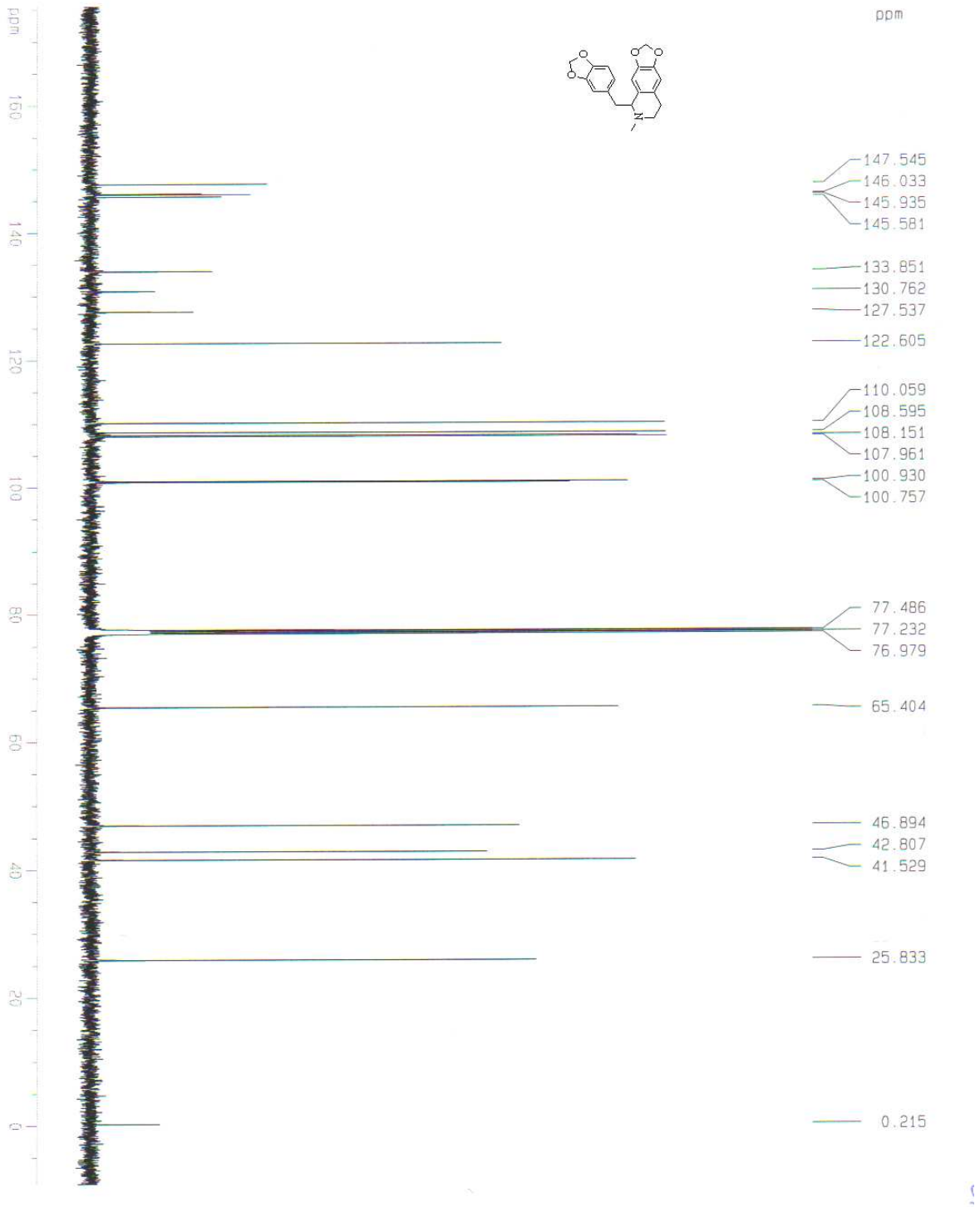
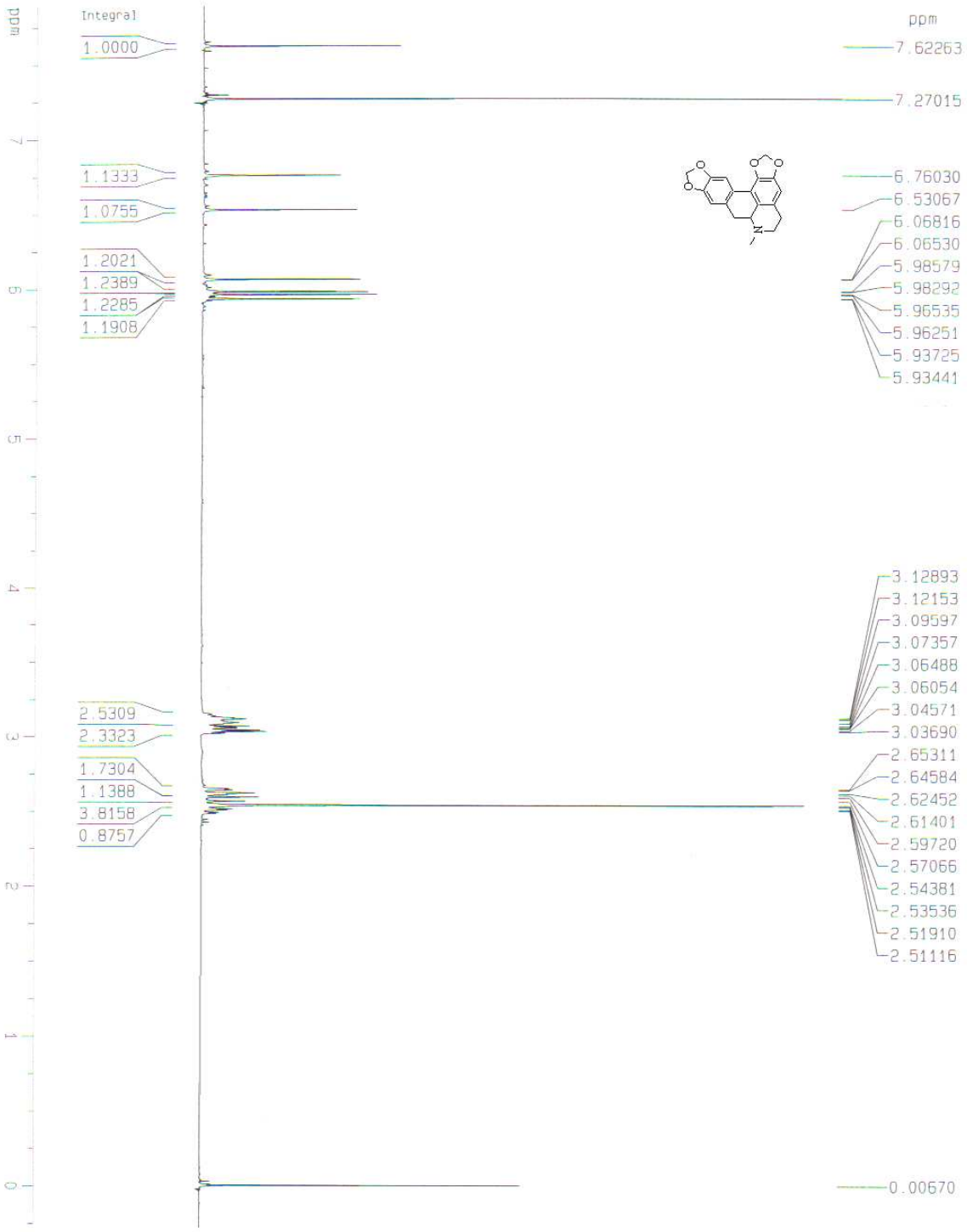
0.9812
0.8544
0.8954
2.0000
1.9910
0.5766
0.9931
1.0072
0.9790
2.9472
1.1111
2.8368
ppm
7.26990
7.26666
6.71469
6.71206
6.69890
6.69626
6.67597
6.57295
6.55717
6.53717
6.28277
5.92862
5.92552
5.89272
5.88994
5.86912
5.86622
3.75546
3.75275
3.66368
3.65153
3.15168
3.00942
2.99733
2.81304
2.80279
2.78774
2.77517
2.55747
2.52551
2.47157
2.46931
0.00936
0.00616


ppm
160
140
120
100
80
60
40
20
0
ppm
147.545
146.033
145.935
145.581
133.851
130.762
127.537
122.605
110.059
108.595
108.151
107.961
100.930
100.757
77.486
77.232
76.979
65.404
46.894
42.807
41.529
25.833
0.215


Integral
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1.2021
1.2389
1.2285
1.1908
2.5309
2.3323
1.7304
1.1388
3.8158
0.8757
ppm
7.62263
7.27015
6.76030
6.53067
6.06816
6.06530
5.98579
5.98292
5.96535
5.96251
5.93725
5.93441
3.12893
3.12153
3.09597
3.07357
3.06488
3.06054
3.04571
3.03690
2.65311
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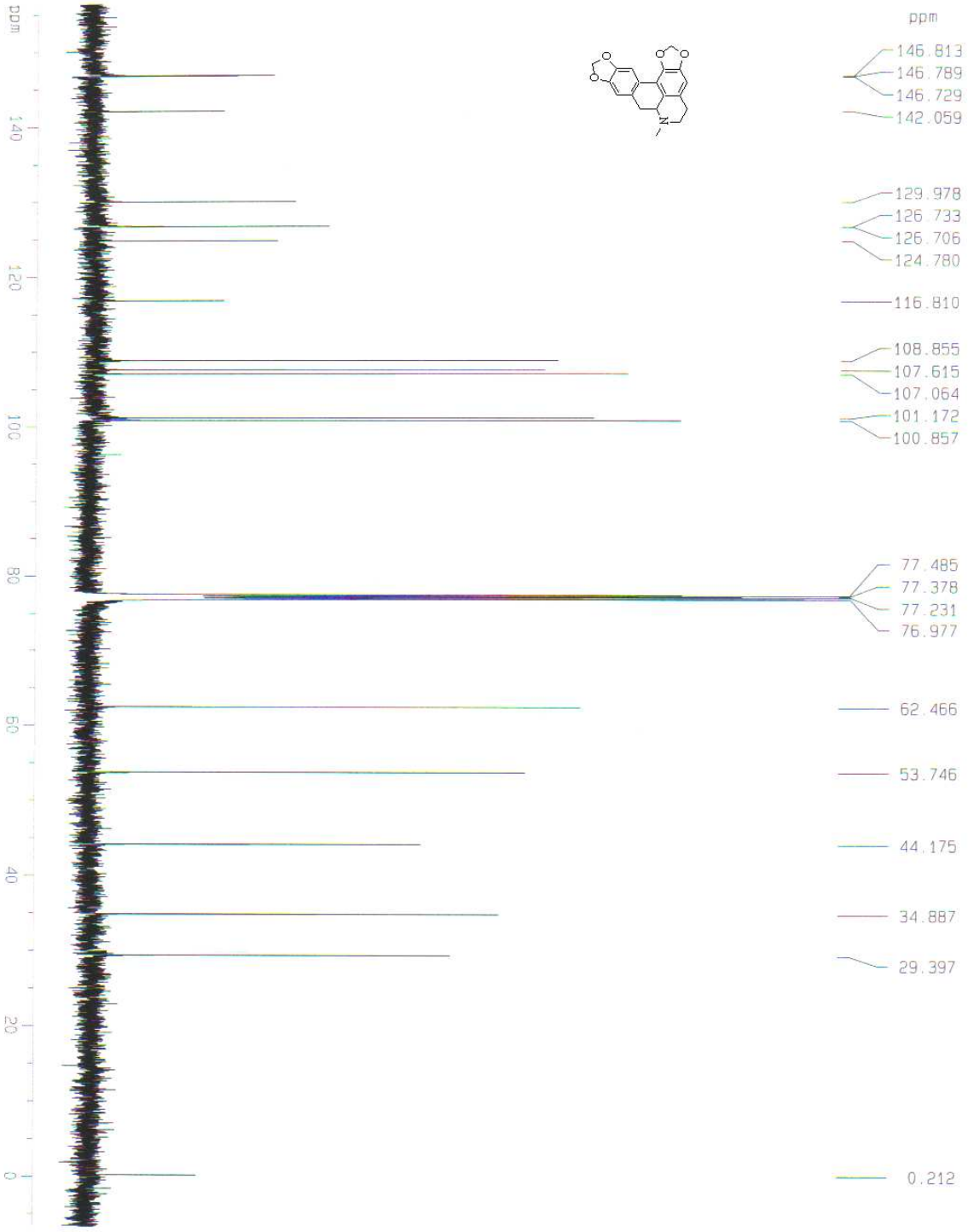
2.61401
2.59720
2.57066
2.54381
2.53536
2.51910
2.51116
0.00670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126.706
124.780
116.810
108.855
107.615
107.064
101.172
100.857
77.485
77.378
77.231
76.977
62.466
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44.175
34.887
29.397
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ppm
140
120
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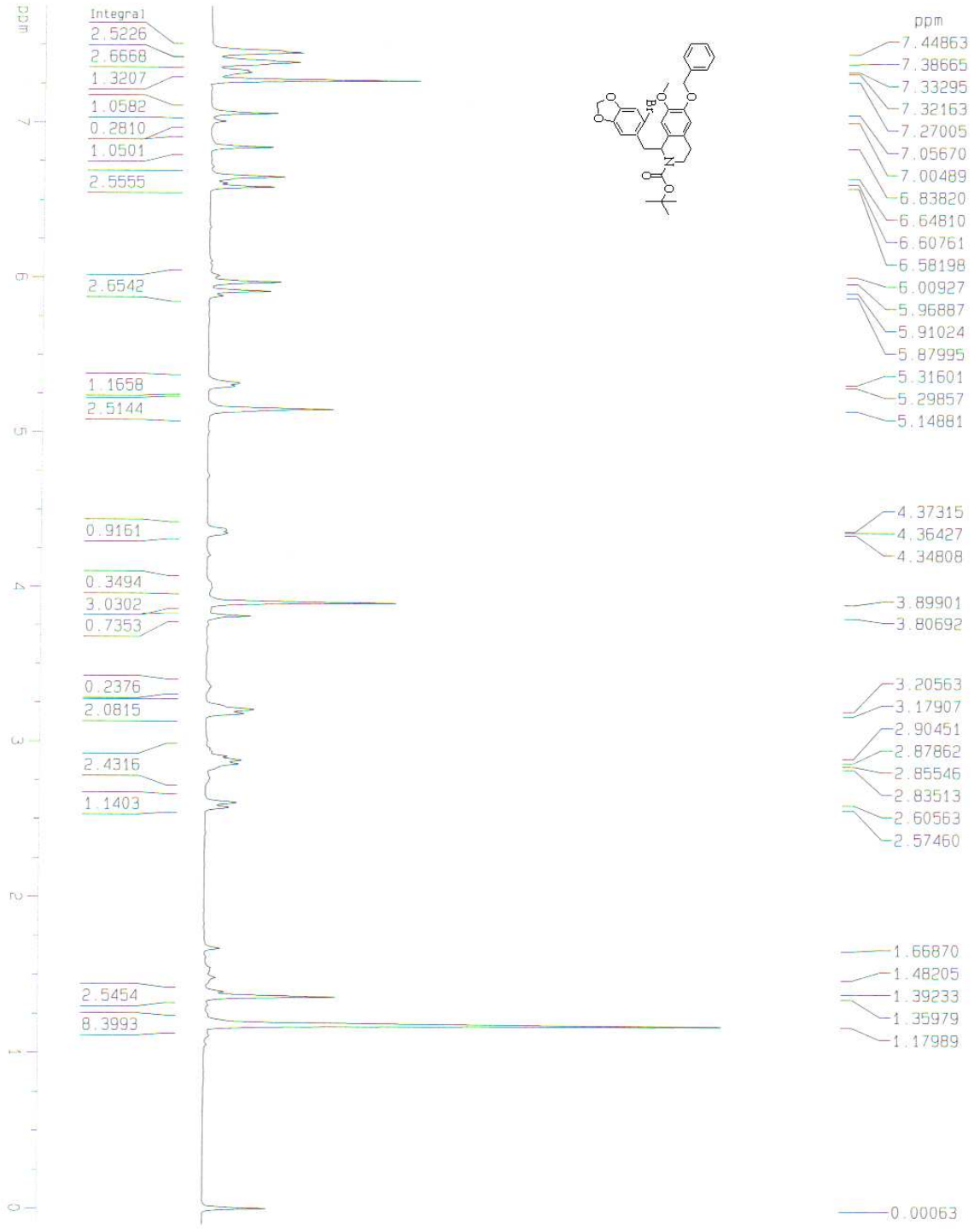
80
60
40
20
0


Integral
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2.6668
1.3207
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0.2810
1.0501
2.5555
2.6542
1.1658
2.5144
0.9161
0.3494
3.0302
0.7353
0.2376
2.0815
2.4316
1.1403
2.5454
8.3993
ppm
7.44863
7.38665
7.33295
7.32163
7.27005
7.05670
7.00489
6.83820
6.64810
6.60761
6.58198
6.00927
5.96887
5.91024
5.87995
5.31601
5.29857
5.14881
4.37315
4.36427
4.34808
3.89901
3.80692
3.20563
3.17907
2.90451
2.87862
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2.60563
2.57460
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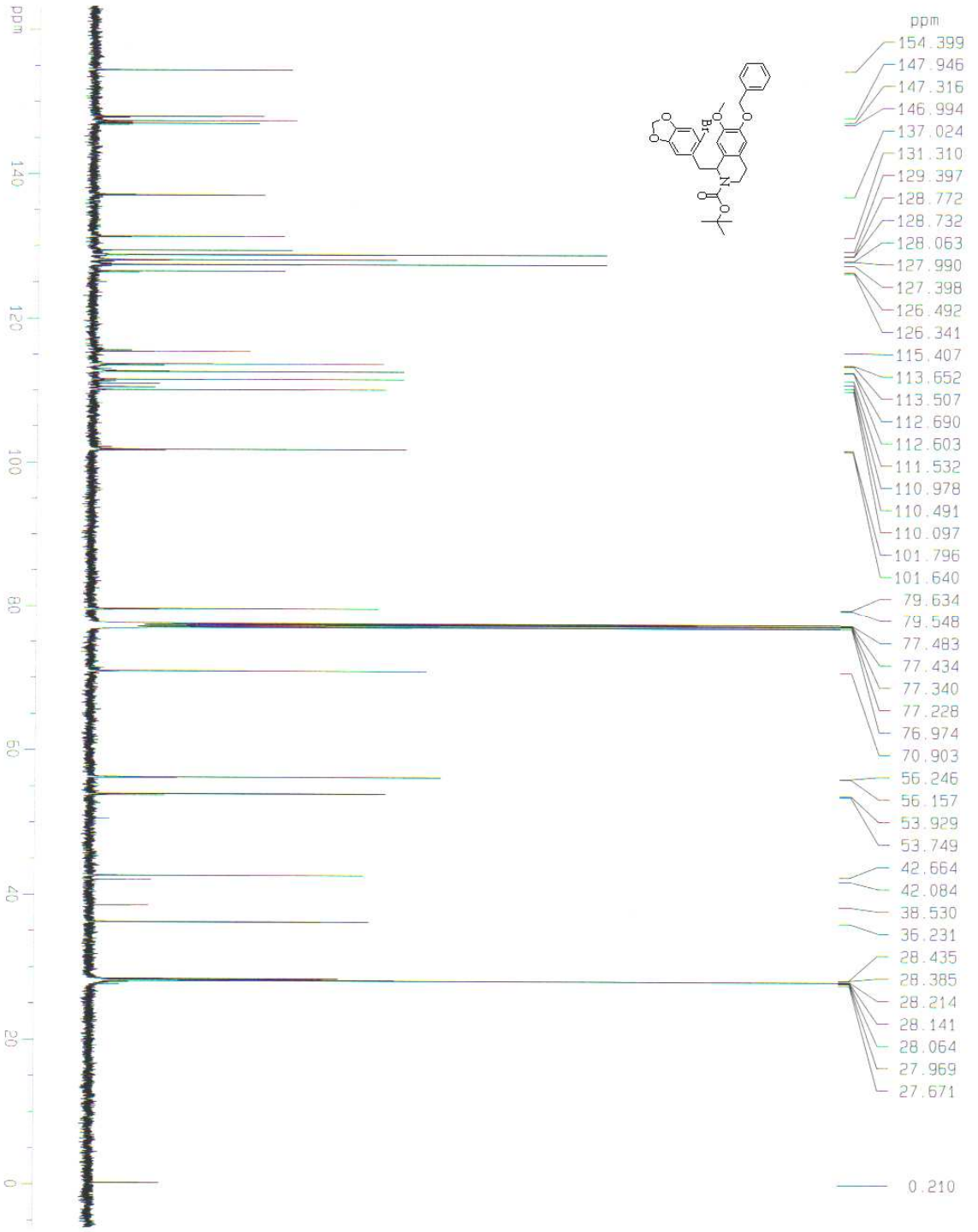
1.39233
1.35979
1.17989
0.00063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137.024
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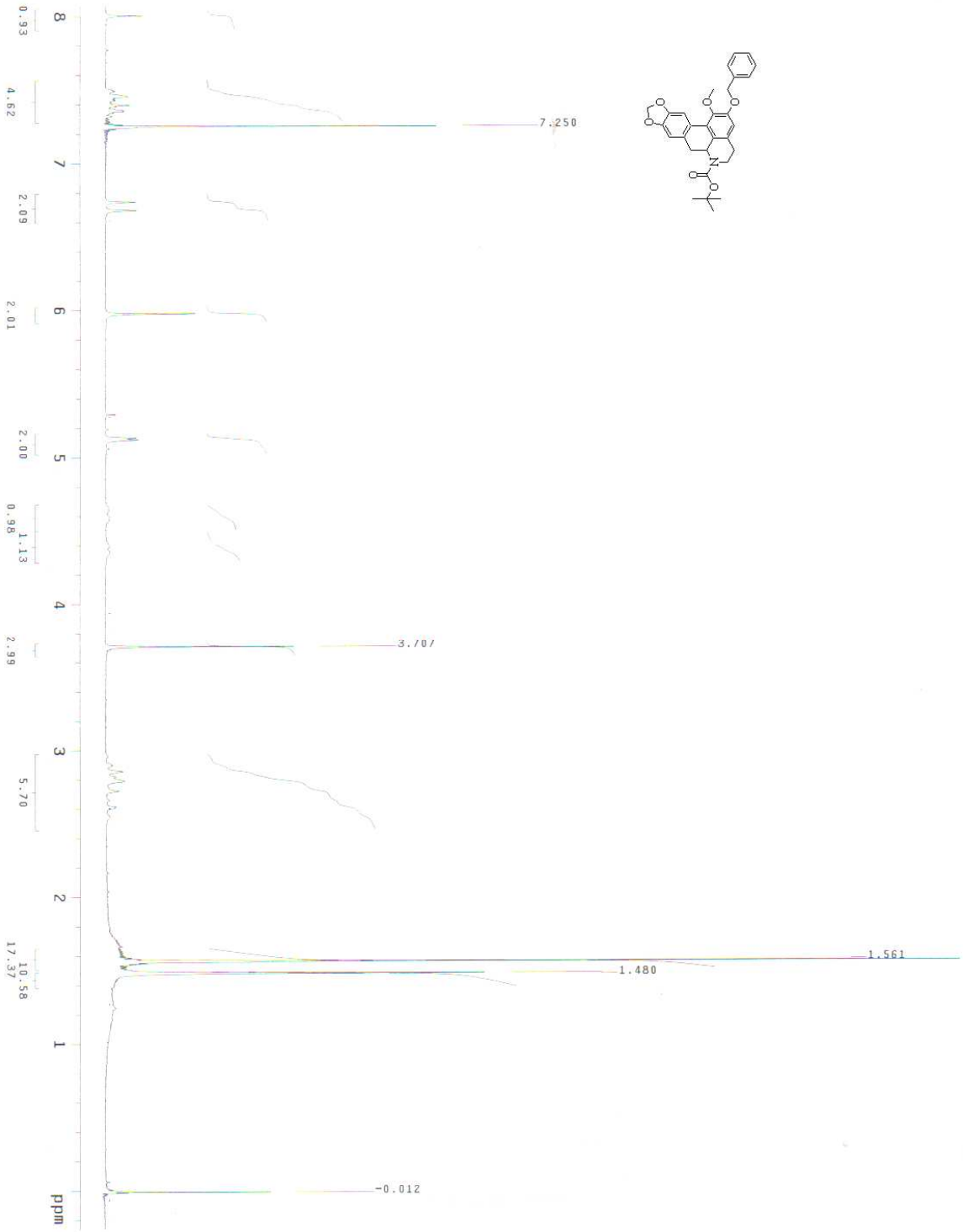
128.772
128.732
128.063
127.990
127.398
126.492
126.341
115.407
113.652
113.507
112.690
112.603
111.532
110.978
110.491
110.097
101.796
101.640
79.634
79.548
77.483
77.434
77.340
77.228
76.974
70.903
56.246
56.157
53.929
53.749
42.664
42.084
38.530
36.231
28.435
28.385
28.214
28.141
28.064
27.969
27.671
0.210
ppm
140
120
100
80
60
40
20
0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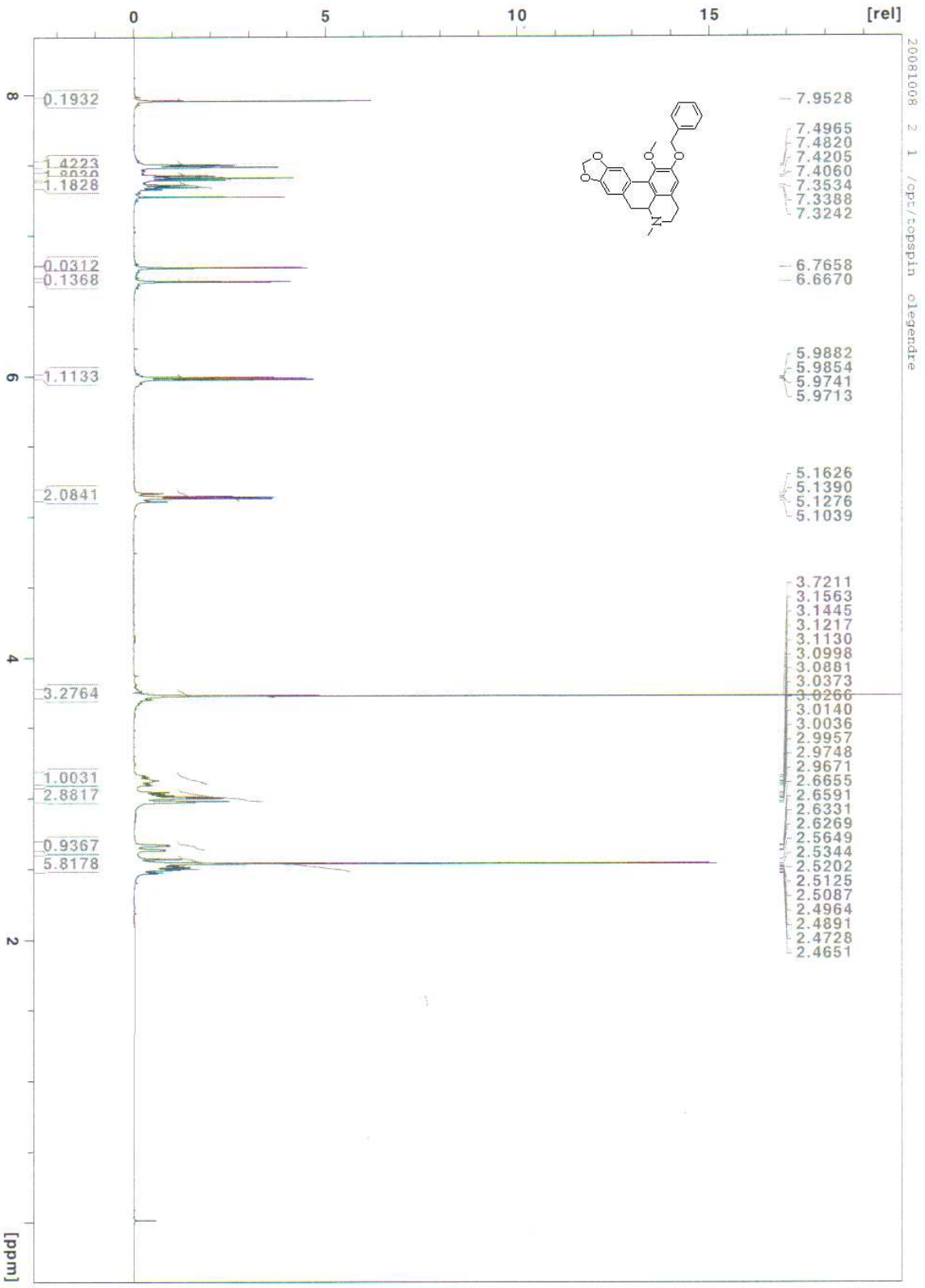
1.561
1.480
-0.012
ppm


0
5
10
15
[rel]
8
6
4
2
[ppm]
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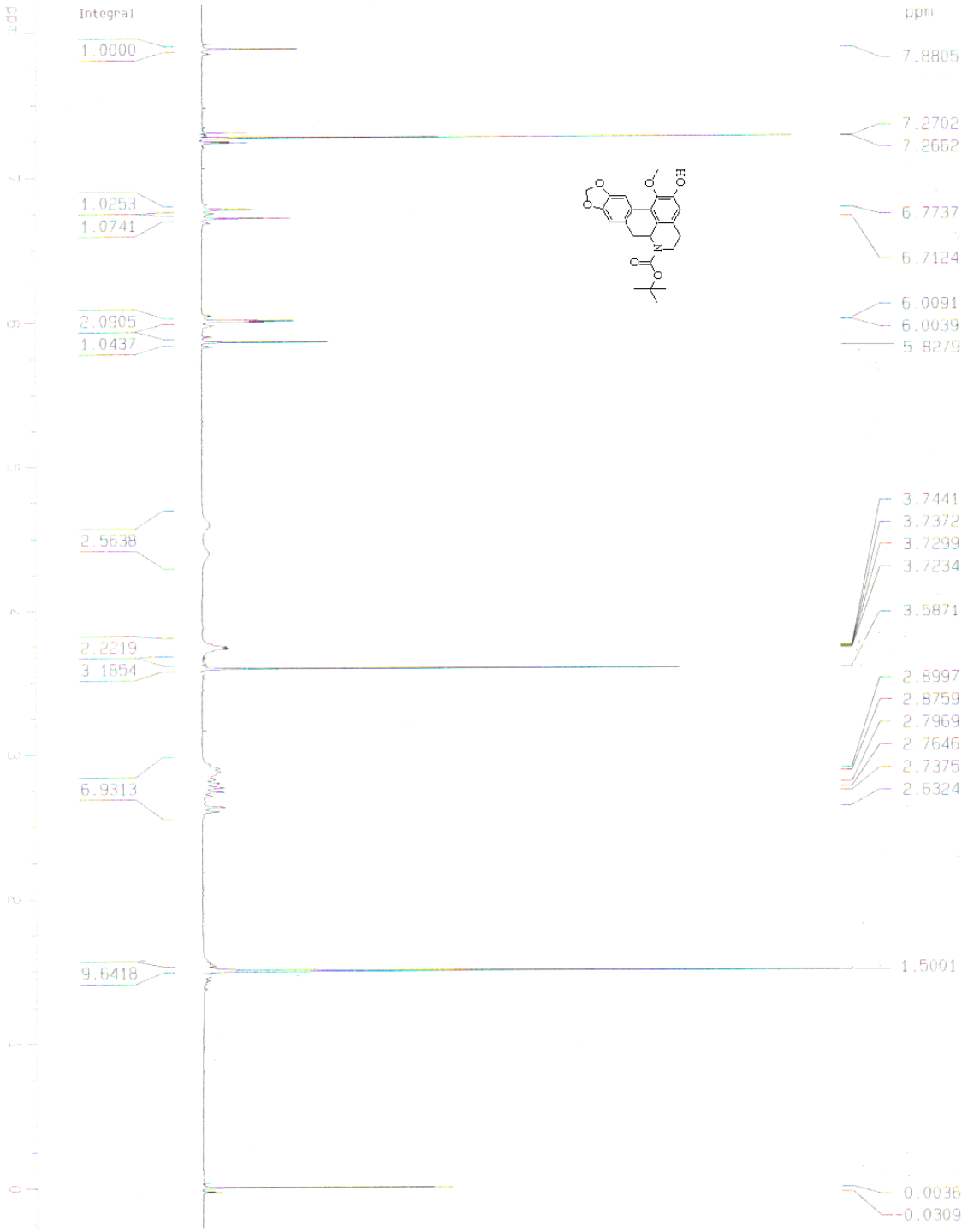
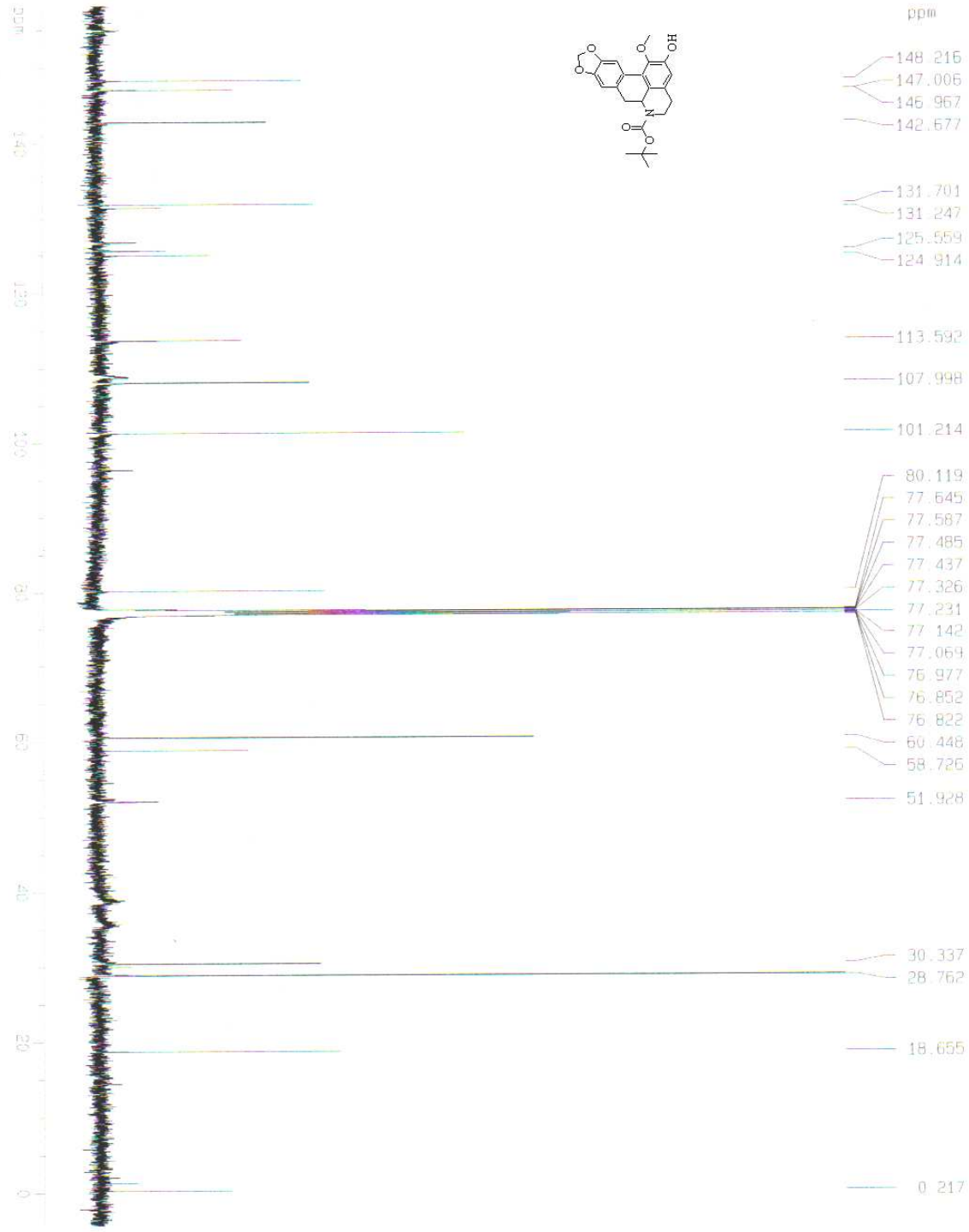
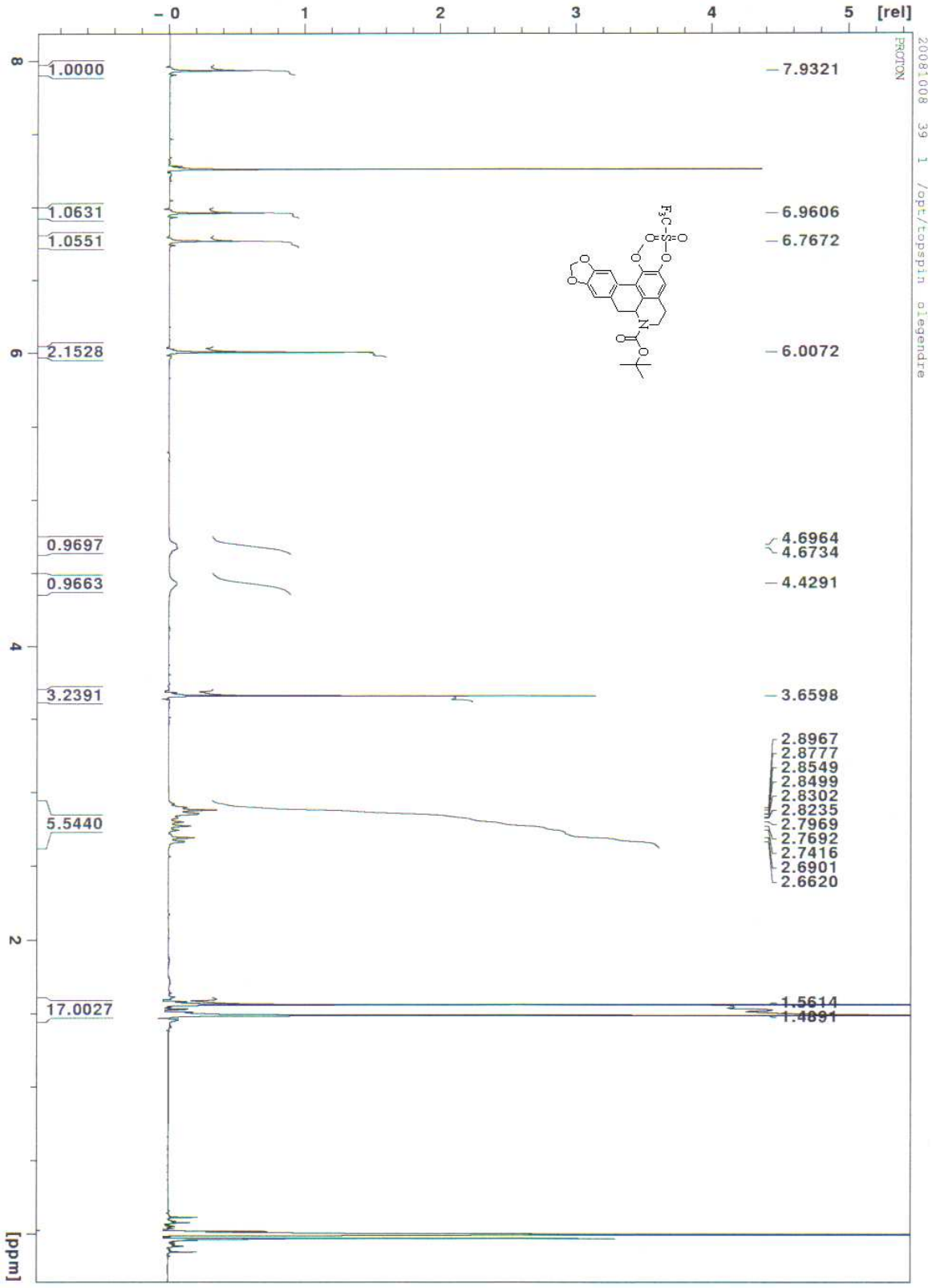
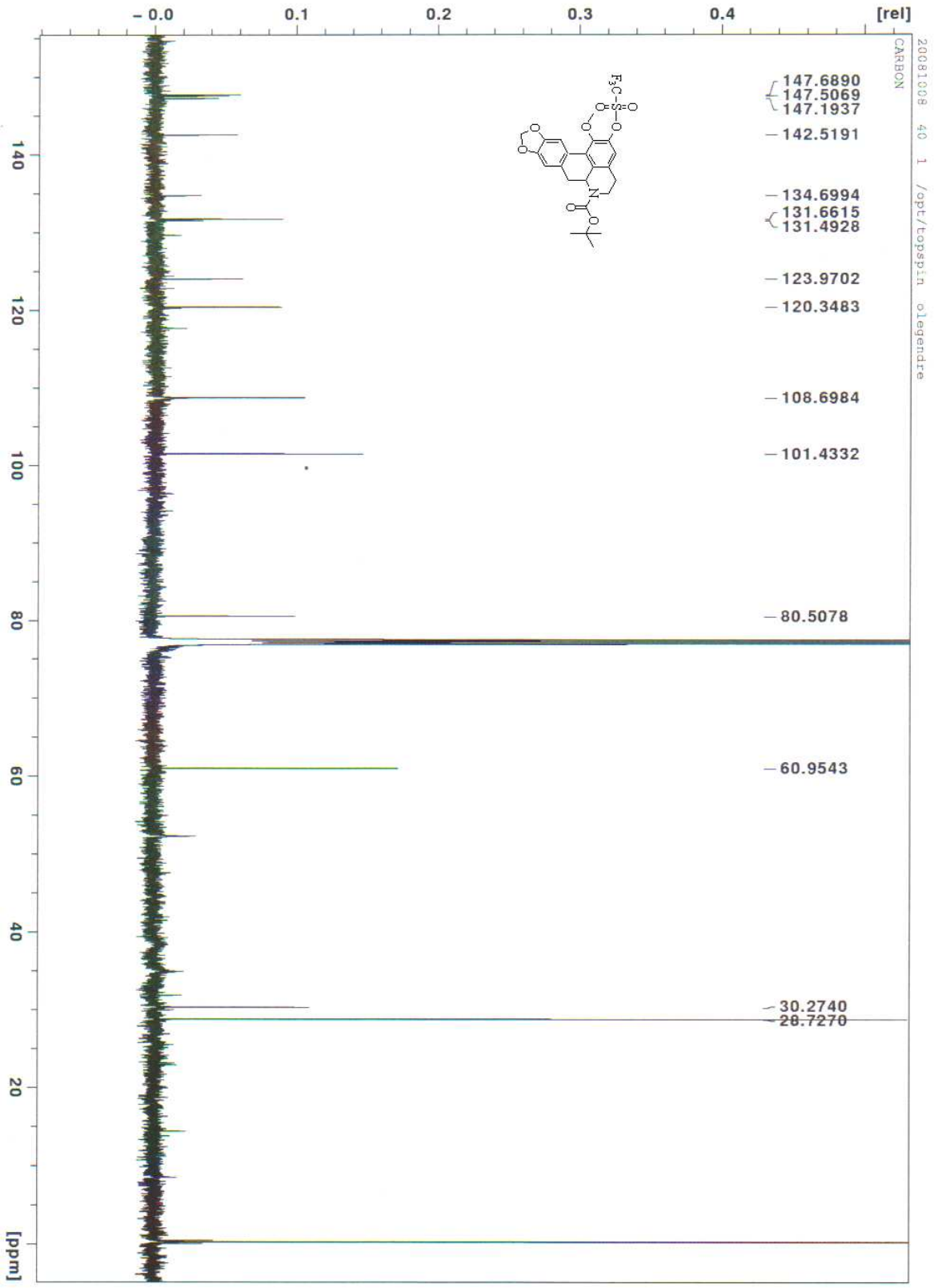
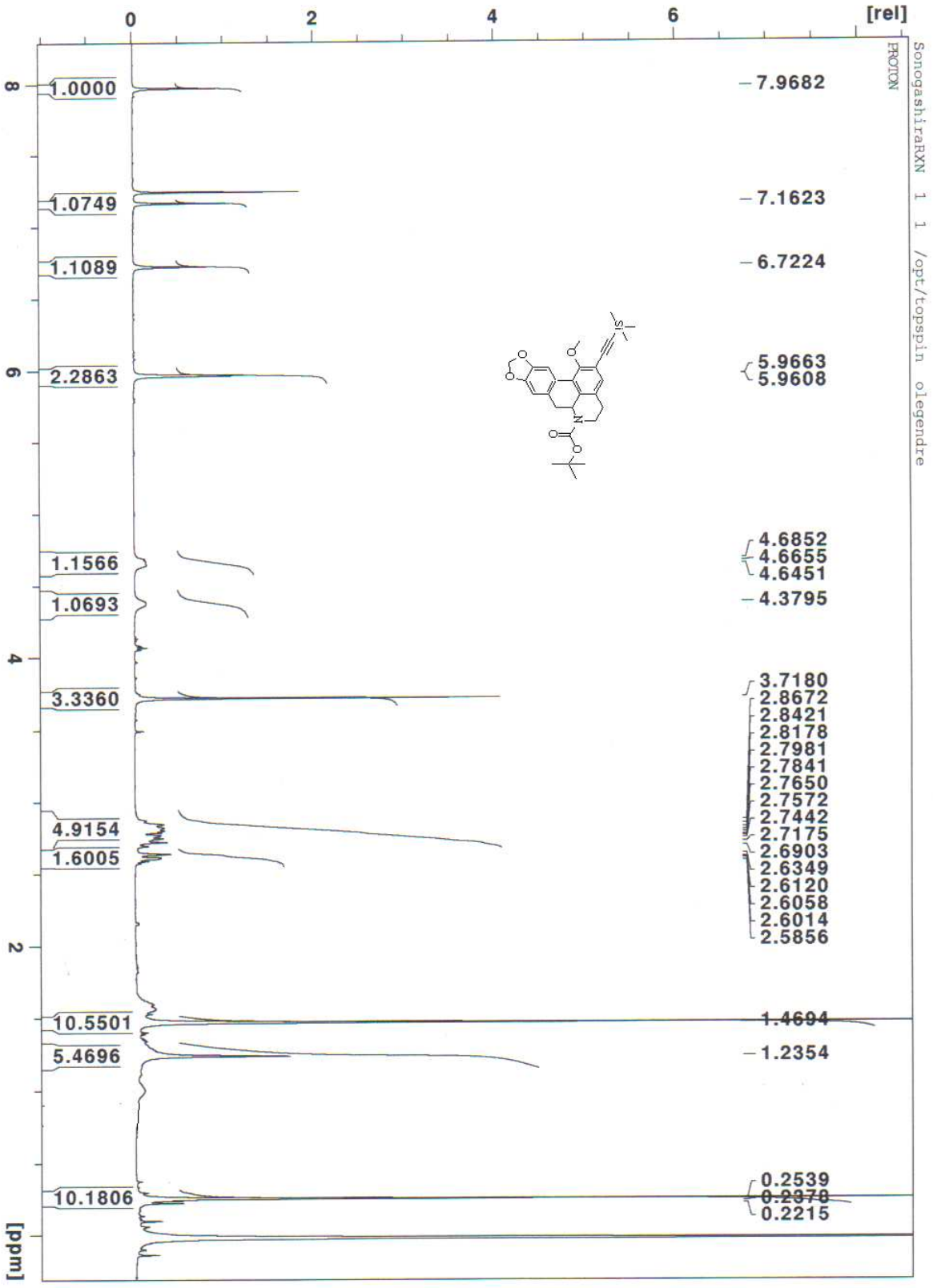
1.4223
1.1828
0.0312
0.1368
1.1133
2.0841
3.2764
1.0031
2.8817
0.9367
5.8178
7.9528
7.4965
7.4820
7.4205
7.4060
7.3534
7.3388
7.3242
6.7658
6.6670
5.9882
5.9854
5.9741
5.9713
5.1626
5.1390
5.1276
5.1039
3.7211
3.1563
3.1445
3.1217
3.1130
3.0998
3.0881
3.0373
3.0266
3.0140
3.0036
2.9957
2.9748
2.9671
2.6655
2.6591
2.6331
2.6269
2.5649
2.5344
2.5202
2.5125
2.5087
2.4964
2.4891
2.4728
2.4651
20081008 2 1 /dpx/copspin olegendre

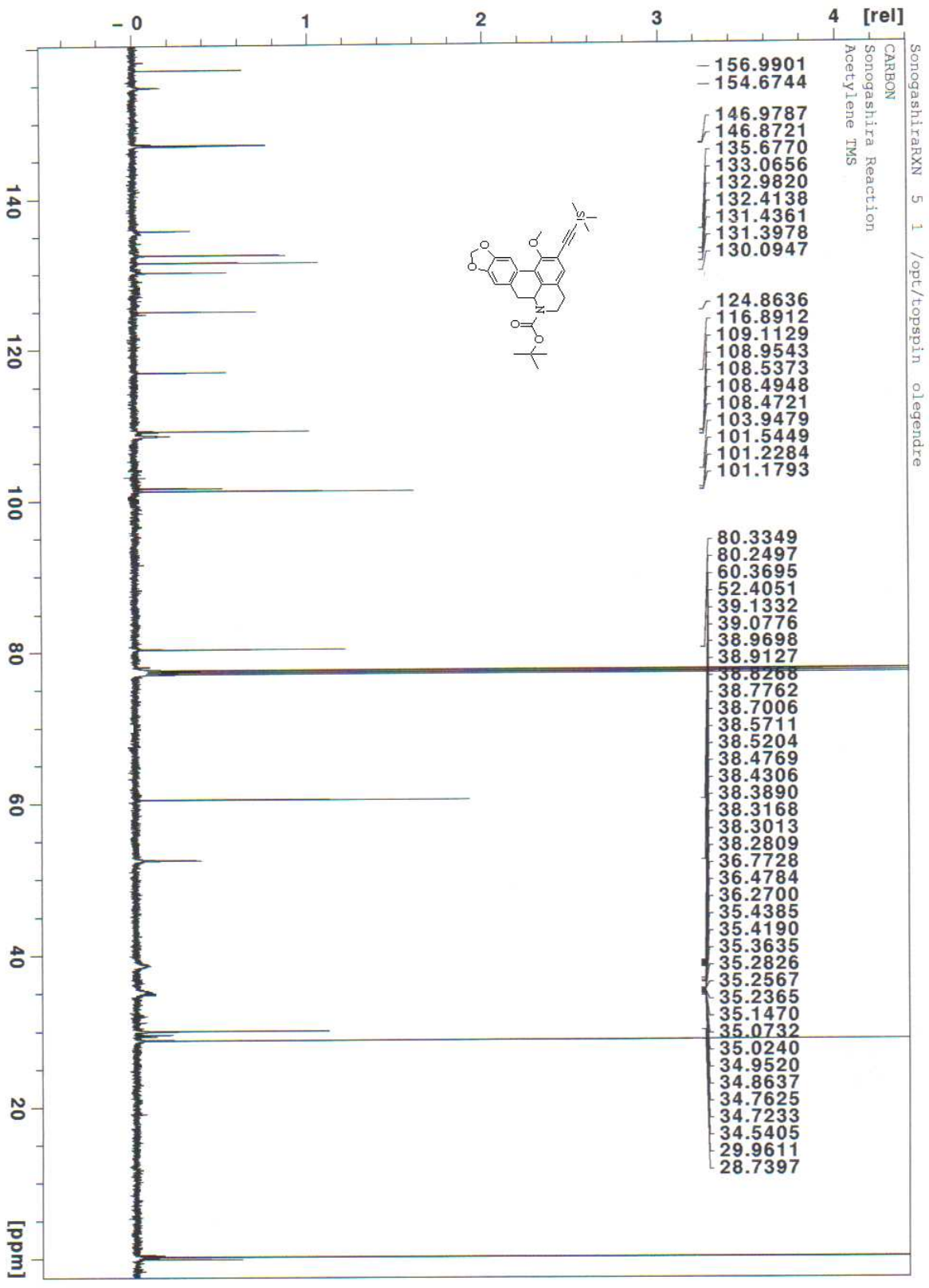

Integral
1.0000
1.0253
1.0741
2.0905
1.0437
2.5638
2.2219
3.1854
6.9313
9.6418
ppm
7.8805
7.2702
7.2662
6.7737
6.7124
6.0091
6.0039
5.8279
3.7441
3.7372
3.7299
3.7234
3.5871
2.8997
2.8759
2.7969
2.7646
2.7375
2.6324
1.5001
0.0036
-0.0309
HO
O
O
O
N
O
O

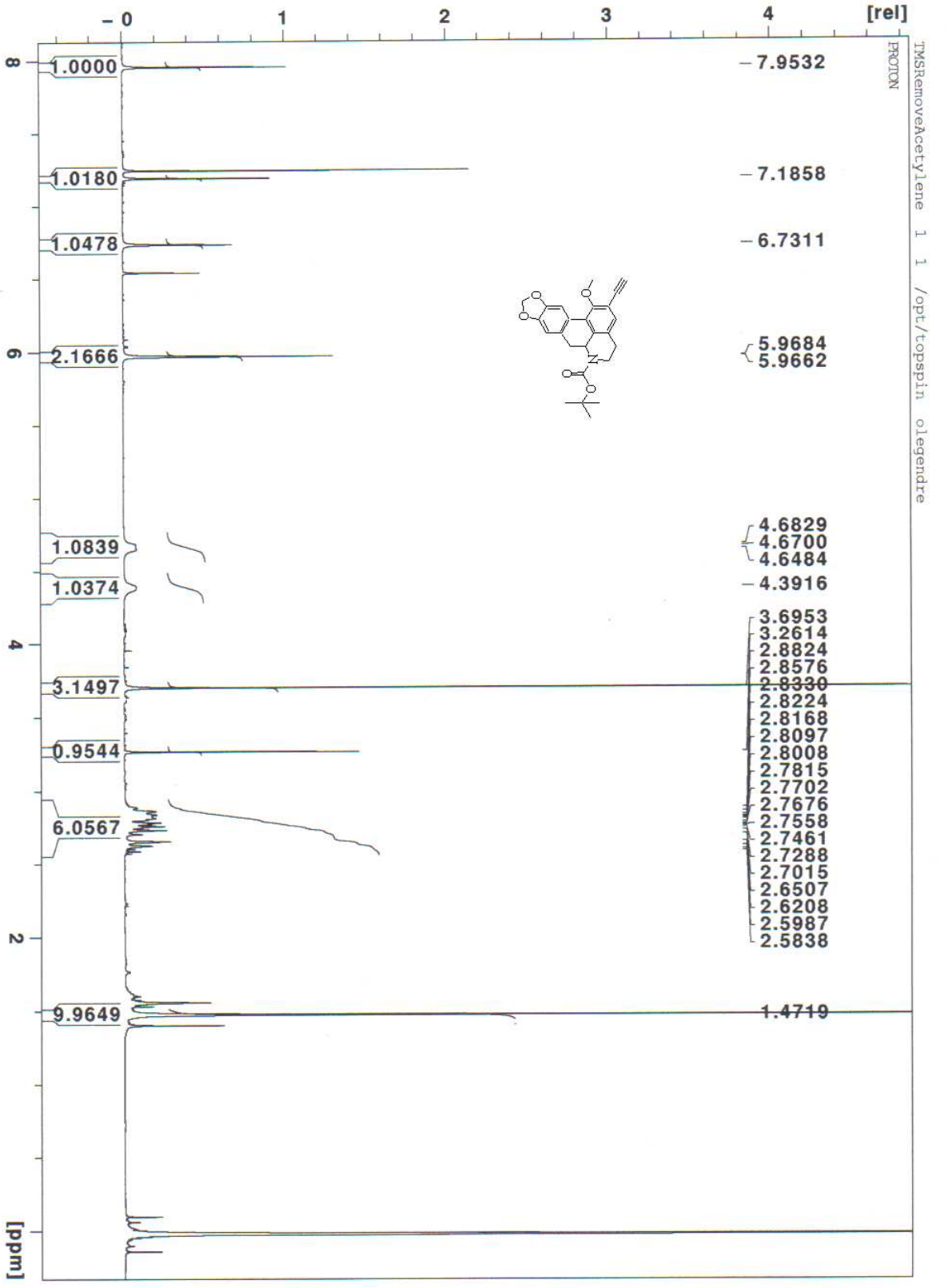

ppm
148.216
147.006
146.967
142.677
131.701
131.247
125.559
124.914
113.592
107.998
101.214
80.119
77.645
77.587
77.485
77.437
77.326
77.231
77.142
77.069
76.977
76.852
76.822
60.448
58.726
51.928
30.337
28.762
18.655
0.217

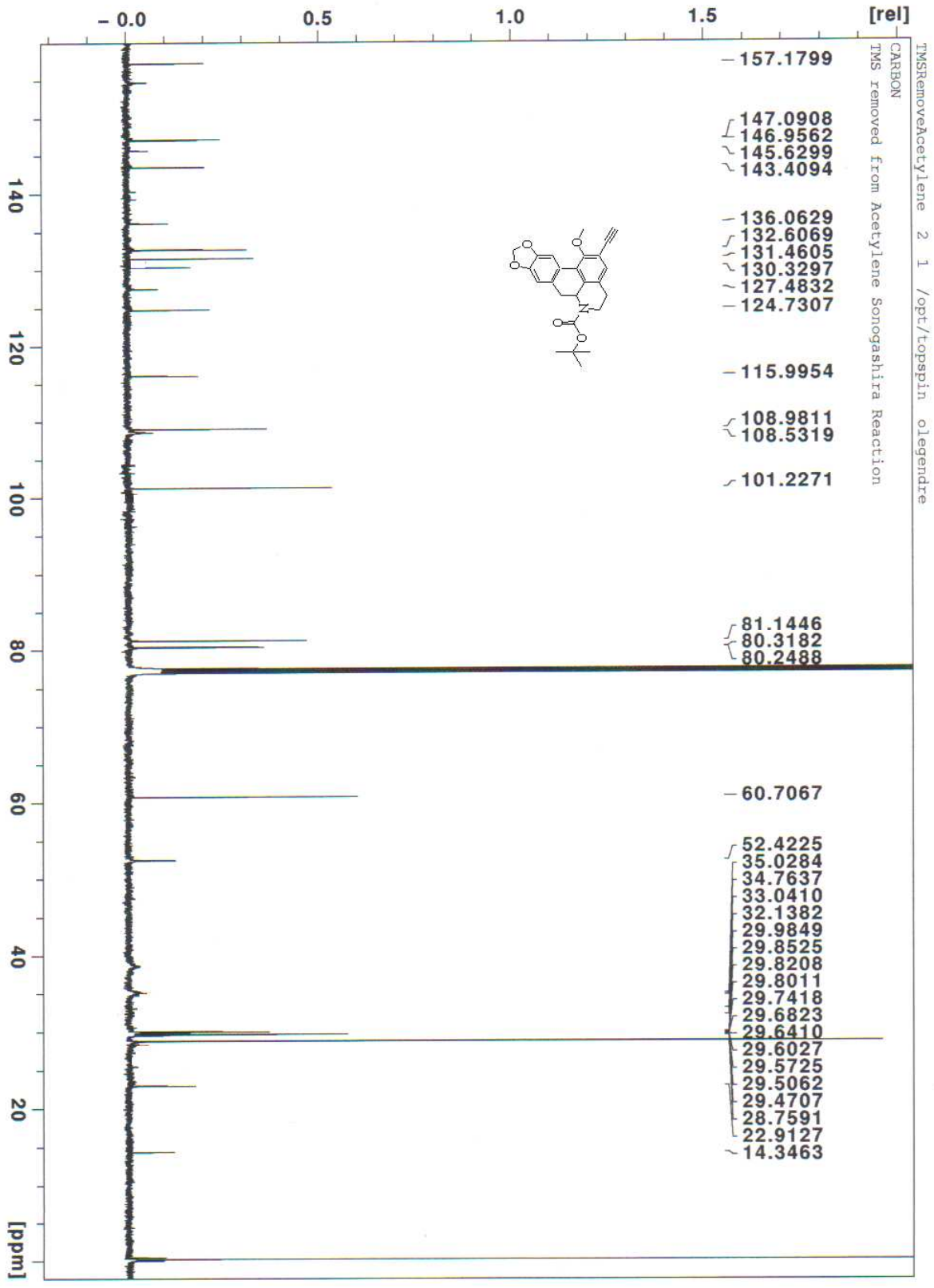

– 0
1
2
3
4
5
[rel]
8
6
4
2
[ppm]
1.0000
1.0631
1.0551
2.1528
0.9697
0.9663
3.2391
5.5440
17.0027
7.9321
6.9606
6.7672
6.0072
4.6964
4.6734
4.4291
3.6598
2.8967
2.8777
2.8549
2.8499
2.8302
2.8235
2.7969
2.7692
2.7416
2.6901
2.6620
1.5614
1.4891
PROTON
20081008 39 1 /opt/topspin oiegendre

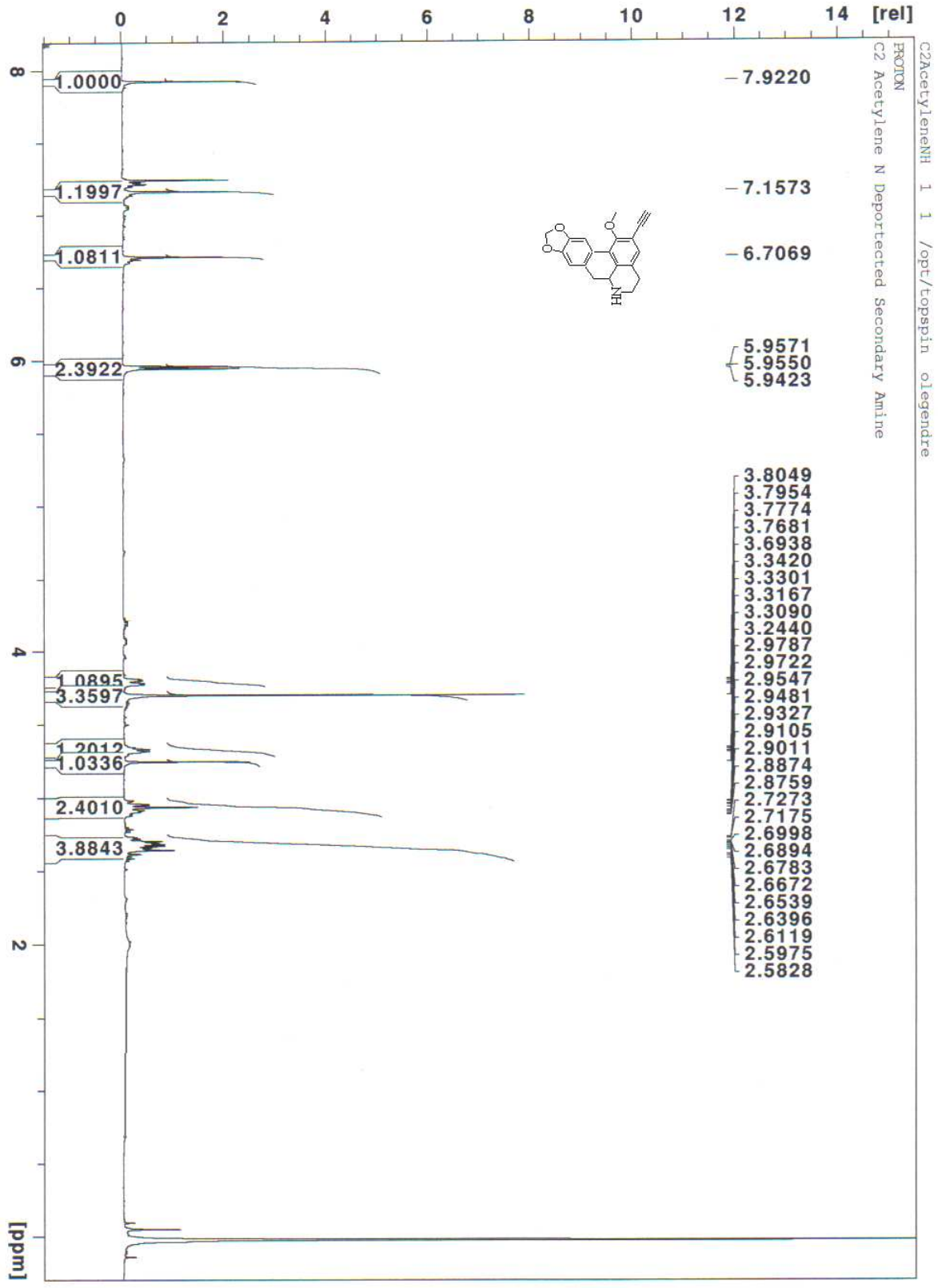

– 0.0
0.1
0.2
0.3
0.4
[rel]
CARBON
20081008 40 1 /opt/topspin olegendre
147.6890
147.5069
147.1937
142.5191
134.6994
131.6615
131.4928
123.9702
120.3483
108.6984
101.4332
80.5078
60.9543
30.2740
28.7270
140
120
100
80
60
40
20
[ppm]

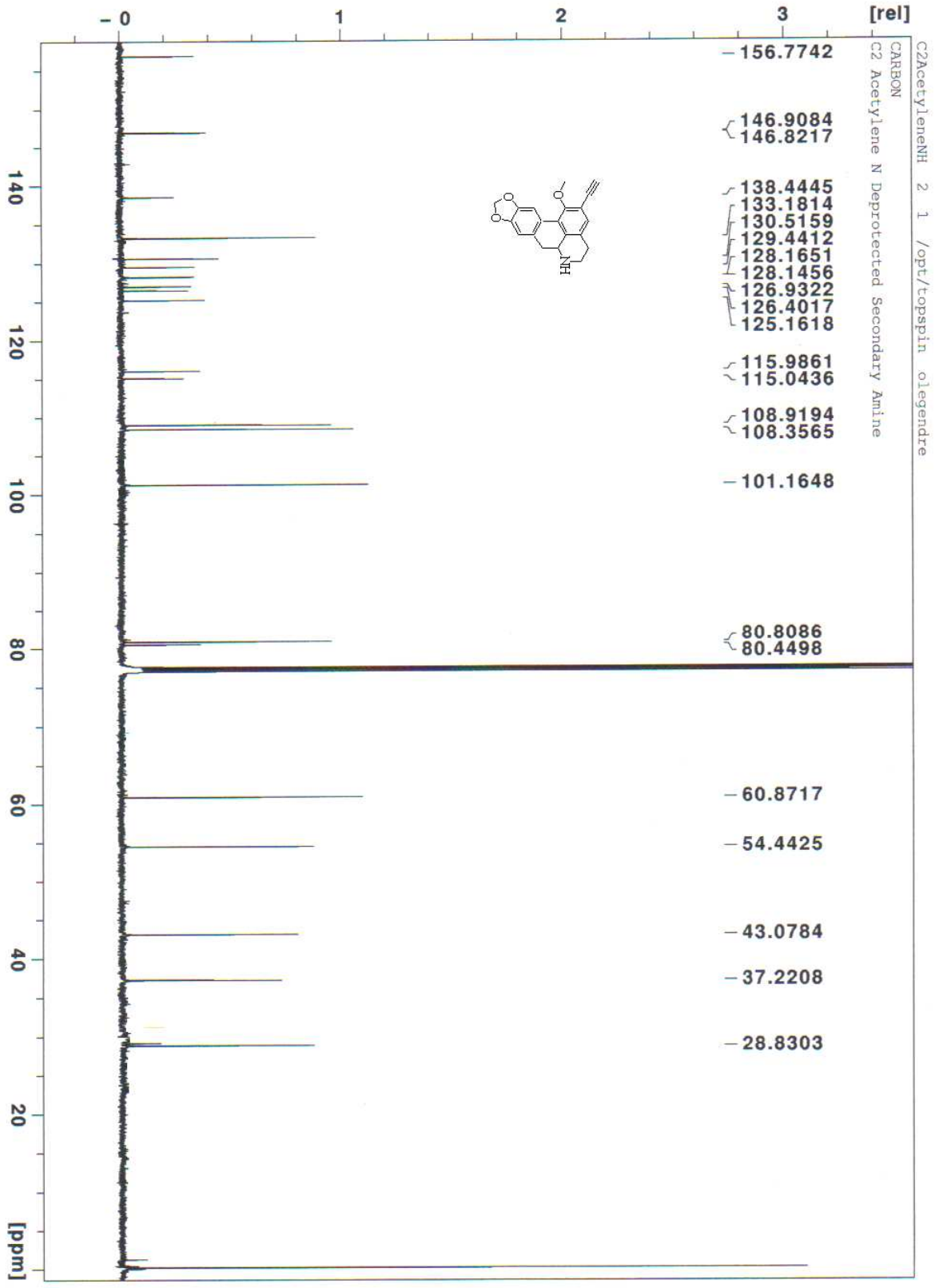

0
2
4
6
[rel]
8
6
4
2
[ppm]
PROTON
SonogashiraRXN 1 1 /opt/topspin olegendre
1.0000
1.0749
1.1089
2.2863
1.1566
1.0693
3.3360
4.9154
1.6005
10.5501
5.4696
10.1806
7.9682
7.1623
6.7224
5.9663
5.9608
4.6852
4.6655
4.6451
4.3795
3.7180
2.8672
2.8421
2.8178
2.7981
2.7841
2.7650
2.7572
2.7442
2.7175
2.6903
2.6349
2.6120
2.6058
2.6014
2.5856
1.4694
1.2354
0.2539
0.2378
0.2215

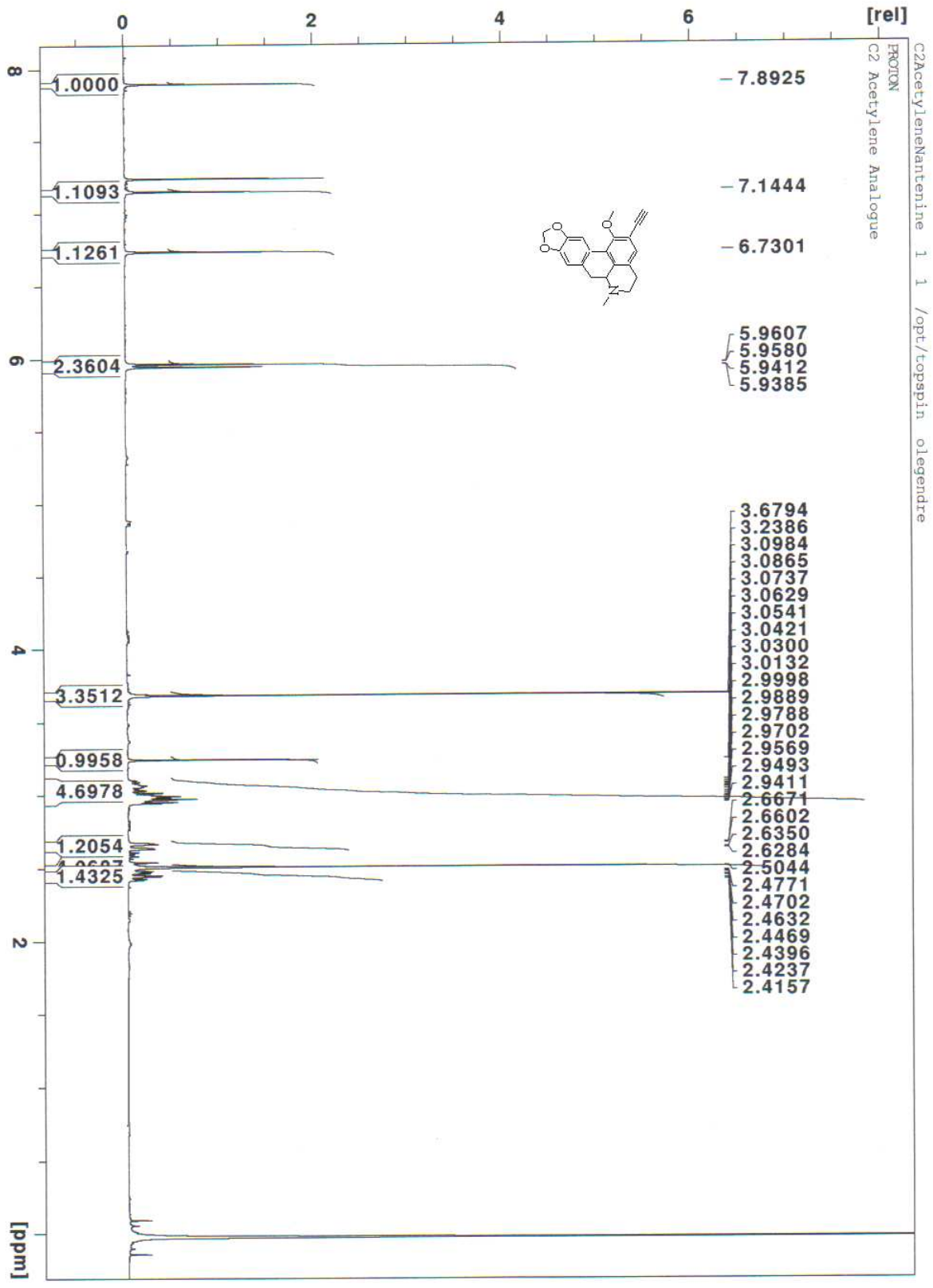

SonogashiraRXN 5 1 /opt/topspin olegendre
CARBON
Sonogashira Reaction
Acetylene TMS
156.9901
154.6744
146.9787
146.8721
135.6770
133.0656
132.9820
132.4138
131.4361
131.3978
130.0947
124.8636
116.8912
109.1129
108.9543
108.5373
108.4948
108.4721
103.9479
101.5449
101.2284
101.1793
80.3349
80.2497
60.3695
52.4051
39.1332
39.0776
38.9698
38.9127
38.8268
38.7762
38.7006
38.5711
38.5204
38.4769
38.4306
38.3890
38.3168
38.3013
38.2809
36.7728
36.4784
36.2700
35.4385
35.4190
35.3635
35.2826
35.2567
35.2365
35.1470
35.0732
35.0240
34.9520
34.8637
34.7625
34.7233
34.5405
29.9611
28.7397
[rel]
[ppm]

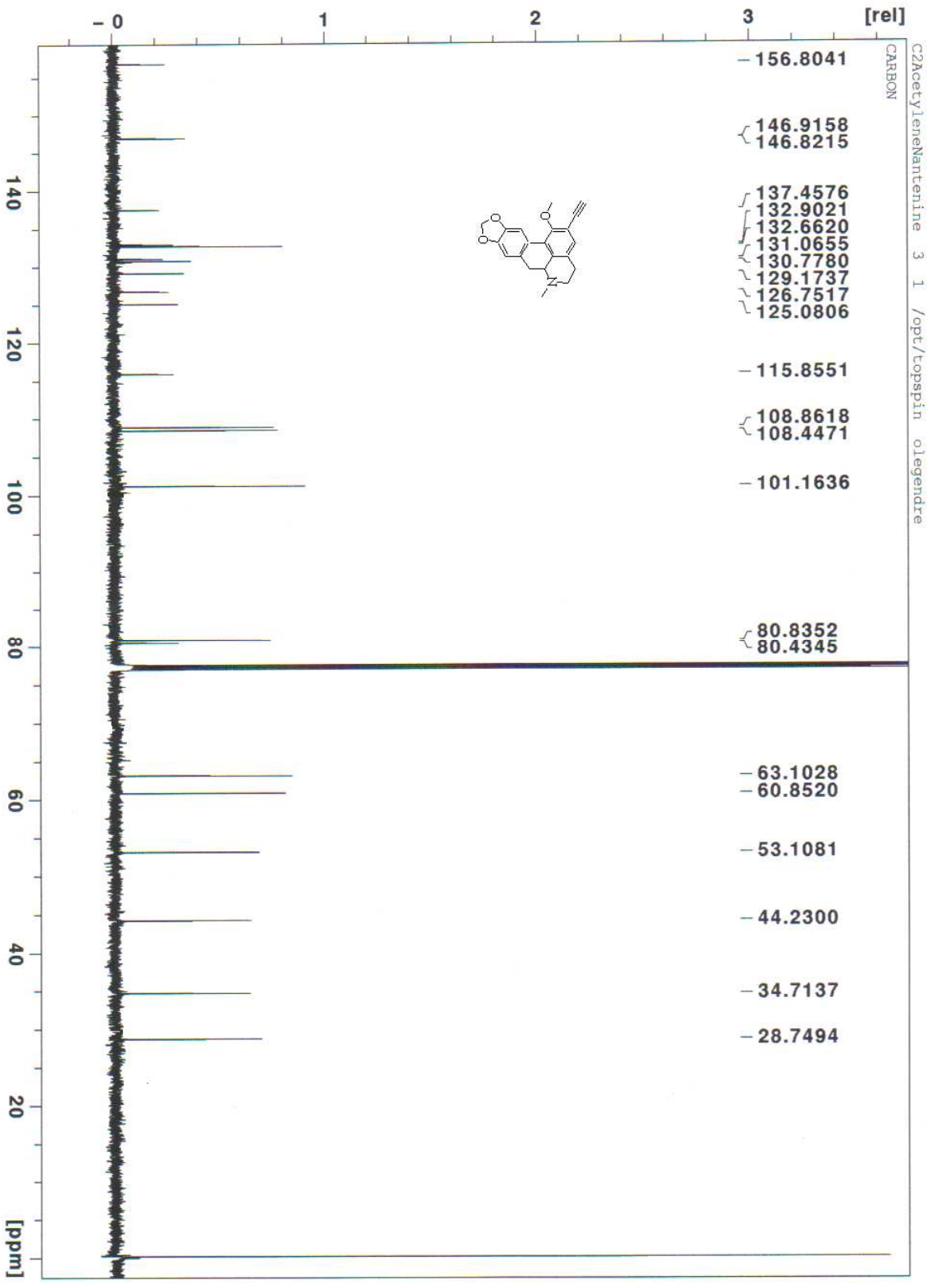

– 0
1
2
3
4
[rel]
8
6
4
2
[ppm]
1.0000
1.0180
1.0478
2.1666
1.0839
1.0374
3.1497
0.9544
6.0567
9.9649
– 7.9532
– 7.1858
– 6.7311
5.9684
5.9662
4.6829
4.6700
4.6484
– 4.3916
3.6953
3.2614
2.8824
2.8576
2.8330
2.8224
2.8168
2.8097
2.8008
2.7815
2.7702
2.7676
2.7558
2.7461
2.7288
2.7015
2.6507
2.6208
2.5987
2.5838
1.4719
PROTON
TMSRemoveAcetylene 1 1 /opt/topspin olegendre

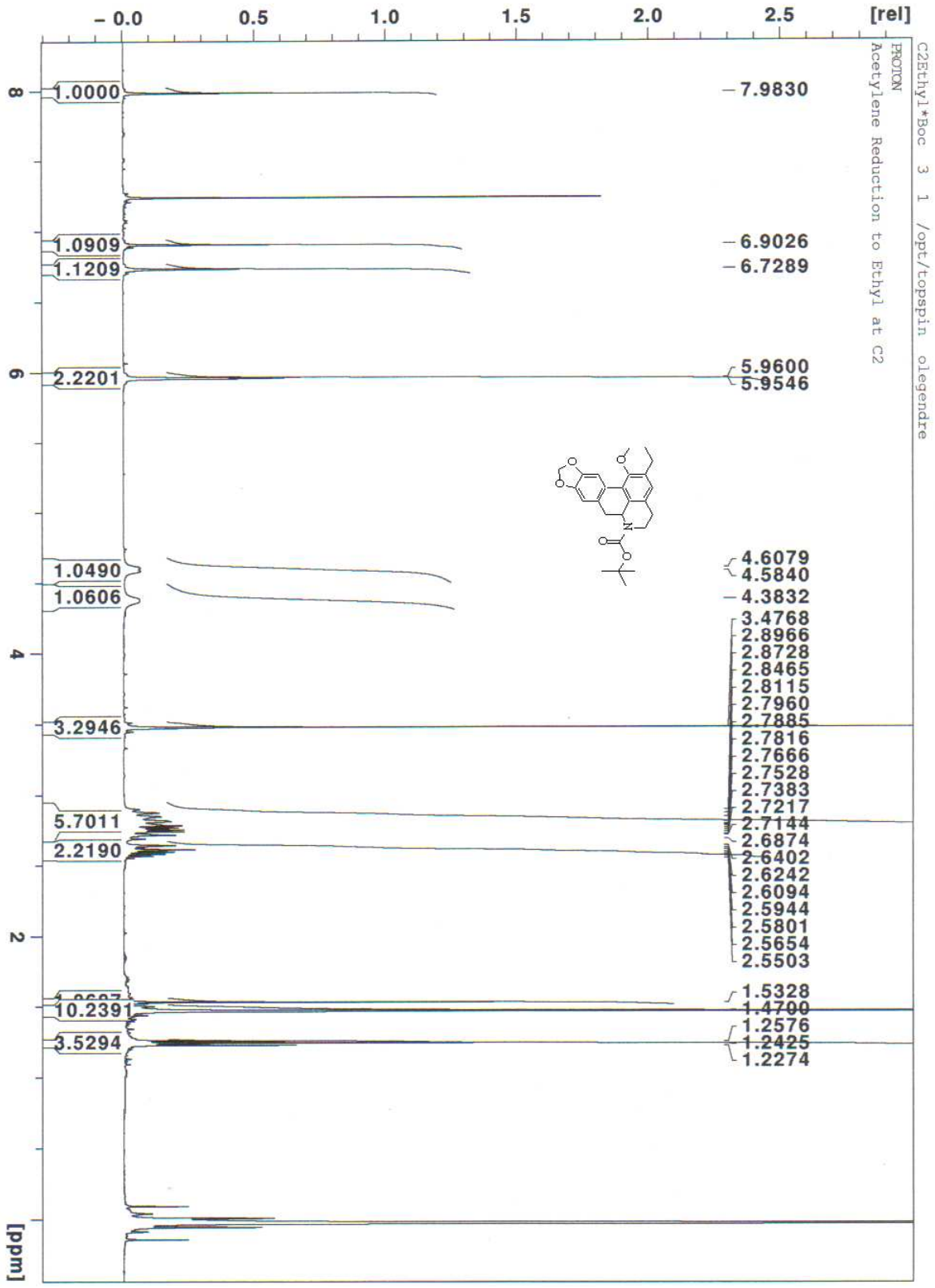

– 0.0
0.5
1.0
1.5
[rel]
TMSRemoveAcetylene 2 1 /opt/topspin olegendre
CARBON
TMS removed from Acetylene Sonogashira Reaction
157.1799
147.0908
146.9562
145.6299
143.4094
136.0629
132.6069
131.4605
130.3297
127.4832
124.7307
115.9954
108.9811
108.5319
101.2271
81.1446
80.3182
80.2488
60.7067
52.4225
35.0284
34.7637
33.0410
32.1382
29.9849
29.8525
29.8208
29.8011
29.7418
29.6823
29.6410
29.6027
29.5725
29.5062
29.4707
28.7591
22.9127
14.3463
140
120
100
80
60
40
20
[ppm]

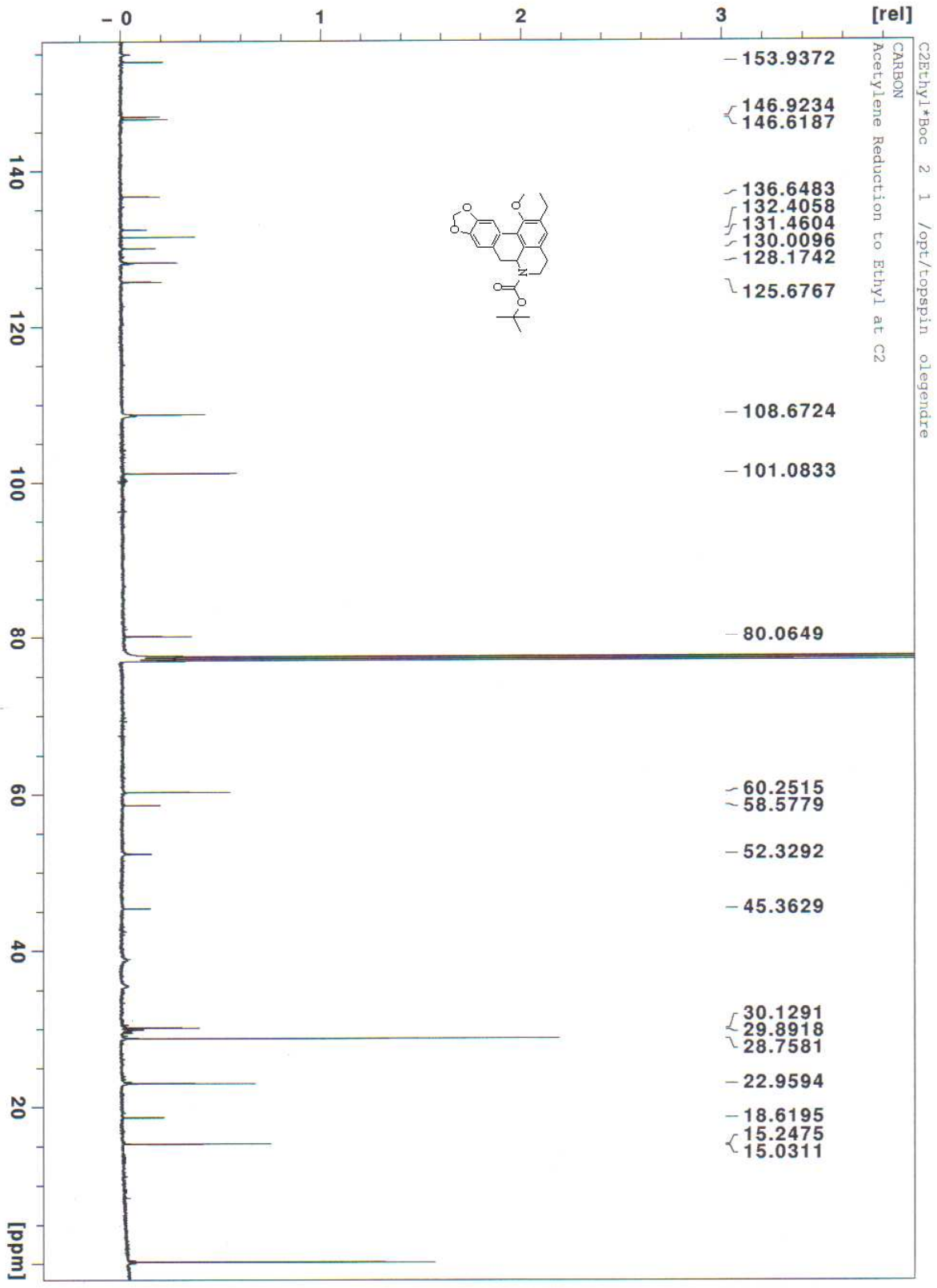

0
2
4
6
8
10
12
14
[rel]
8
6
4
2
[ppm]
1.0000
1.1997
1.0811
2.3922
1.0895
3.3597
1.2012
1.0336
2.4010
3.8843
7.9220
7.1573
6.7069
5.9571
5.9550
5.9423
3.8049
3.7954
3.7774
3.7681
3.6938
3.3420
3.3301
3.3167
3.3090
3.2440
2.9787
2.9722
2.9547
2.9481
2.9327
2.9105
2.9011
2.8874
2.8759
2.7273
2.7175
2.6998
2.6894
2.6783
2.6672
2.6539
2.6396
2.6119
2.5975
2.5828
PROTON
C2 Acetylene N Deportected Secondary Amine
C2AcetyleneNH 1 1 /opt/topspin olegendre

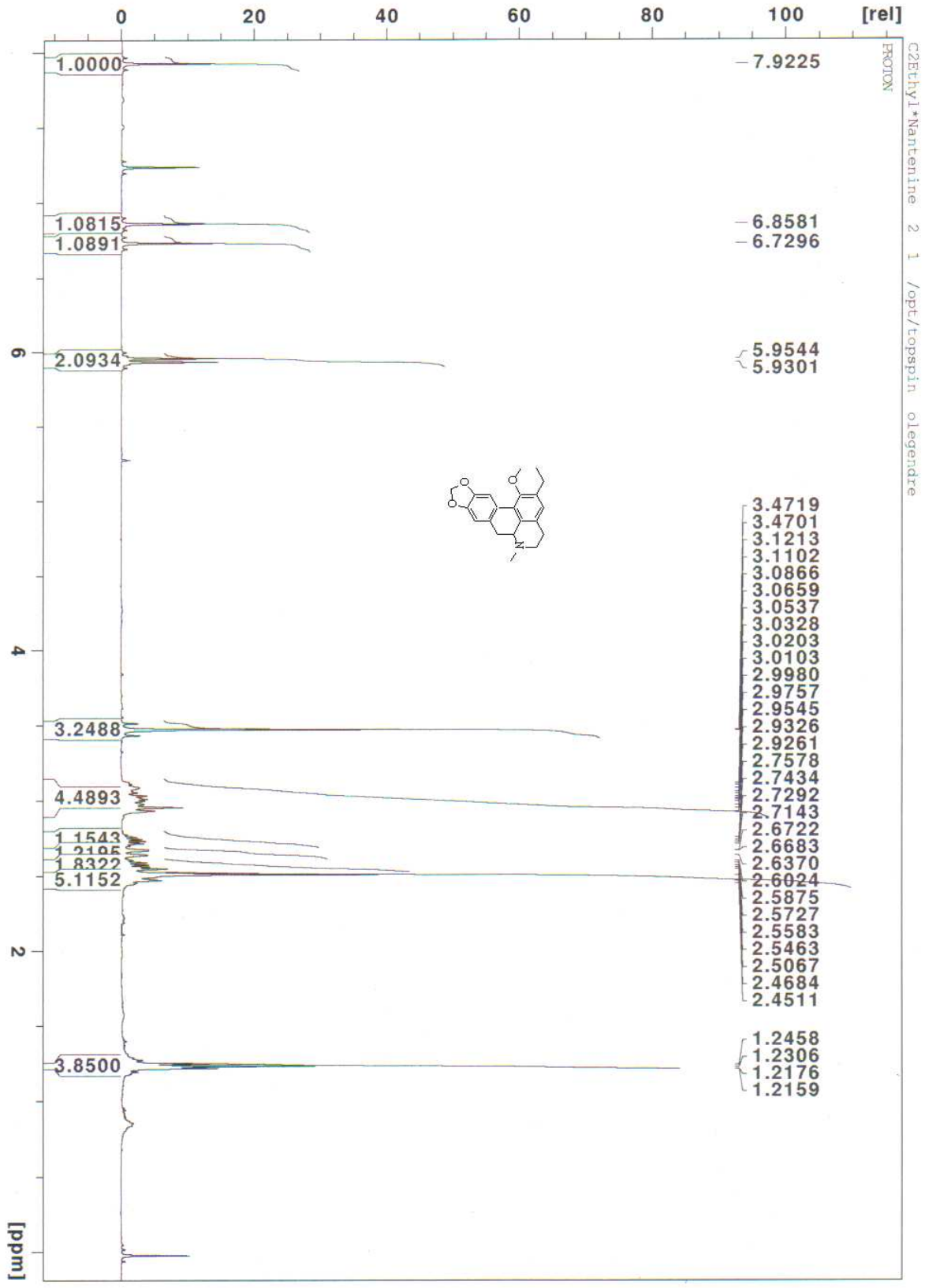

C2AcetyleneNH 2 1 /opt/topspin olegendre
CARBON
C2 Acetylene N Deprotected Secondary Amine
156.7742
146.9084
146.8217
138.4445
133.1814
130.5159
129.4412
128.1651
128.1456
126.9322
126.4017
125.1618
115.9861
115.0436
108.9194
108.3565
101.1648
80.8086
80.4498
60.8717
54.4425
43.0784
37.2208
28.8303
NH
0
1
2
3
[rel]
140
120
100
80
60
40
20
[ppm]

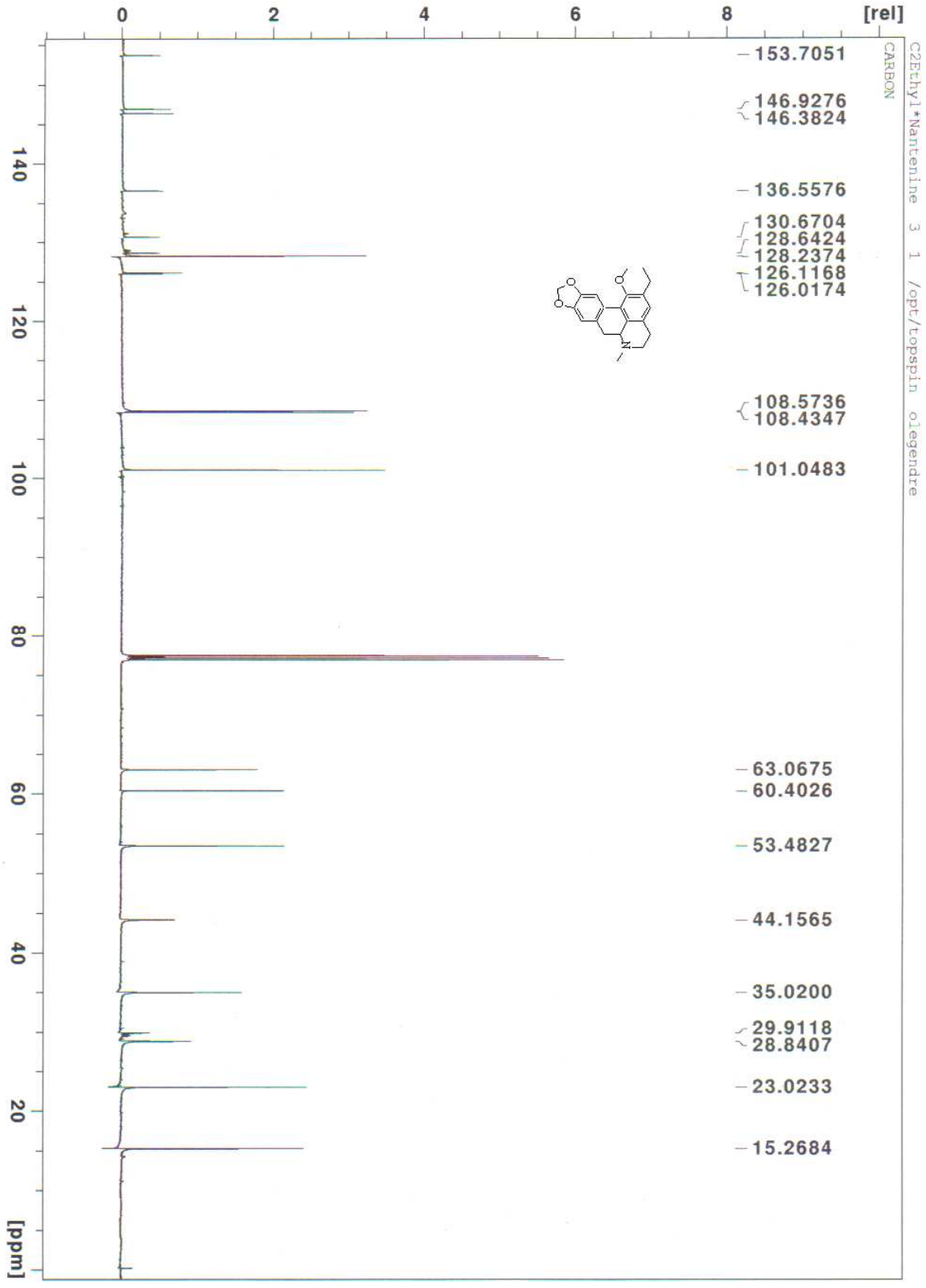

0
2
4
6
[rel]
8
6
4
2
[ppm]
1.0000
1.1093
1.1261
2.3604
3.3512
0.9958
4.6978
1.2054
1.4325
7.8925
7.1444
6.7301
5.9607
5.9580
5.9412
5.9385
3.6794
3.2386
3.0984
3.0865
3.0737
3.0629
3.0541
3.0421
3.0300
3.0132
2.9998
2.9889
2.9788
2.9702
2.9569
2.9493
2.9411
2.6671
2.6602
2.6350
2.6284
2.5044
2.4771
2.4702
2.4632
2.4469
2.4396
2.4237
2.4157
PROTON
C2 Acetylene Analogue
C2AcetyleneNantenine 1 1 /opt/topspin olegendre

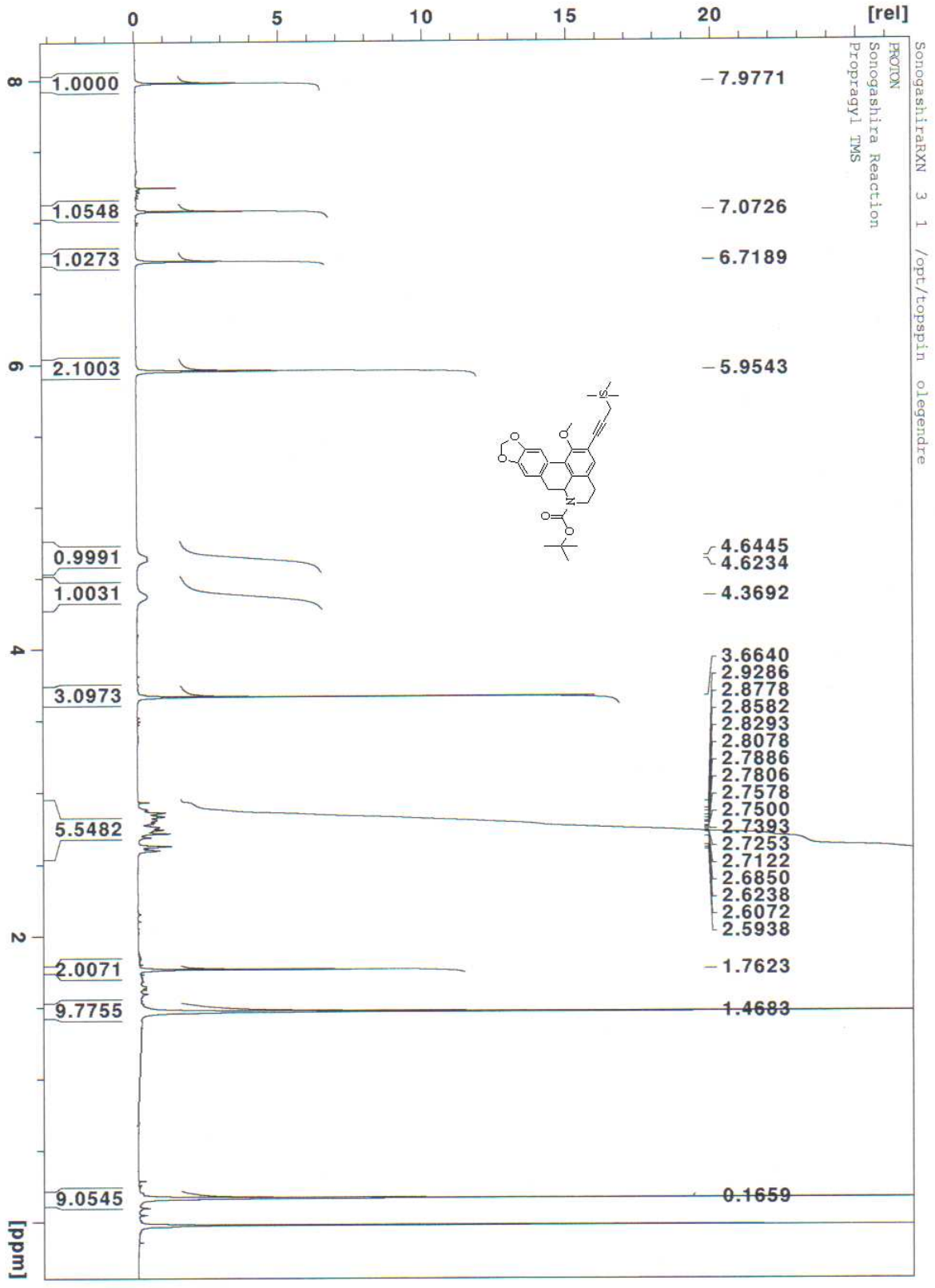

– 0
1
2
3
[rel]
CARBON
C2AcetyleneNantenine 3 1 /opt/topspin olegendre
156.8041
146.9158
146.8215
137.4576
132.9021
132.6620
131.0655
130.7780
129.1737
126.7517
125.0806
115.8551
108.8618
108.4471
101.1636
80.8352
80.4345
63.1028
60.8520
53.1081
44.2300
34.7137
28.7494
140
120
100
80
60
40
20
[ppm]

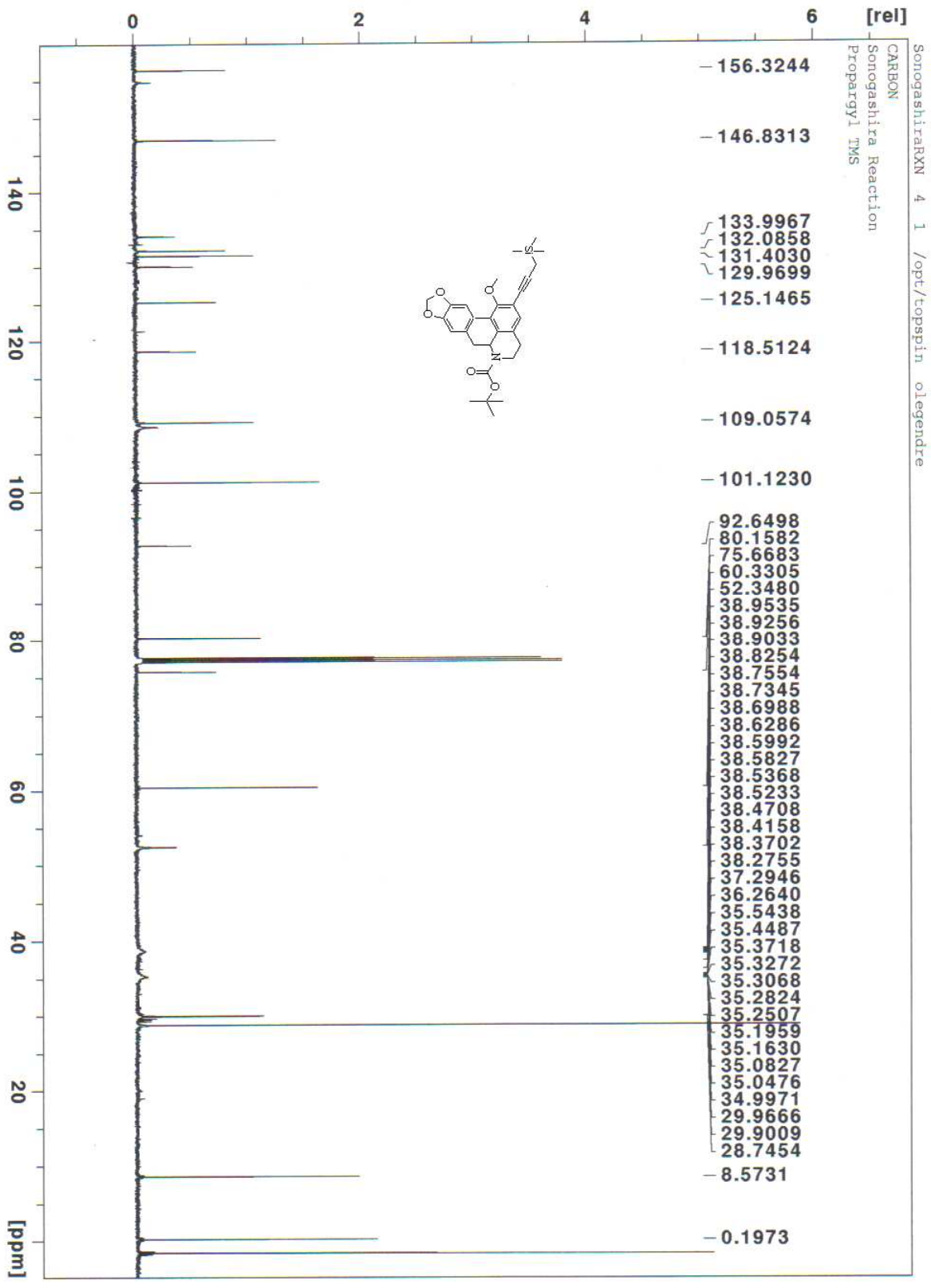

– 0.0
0.5
1.0
1.5
2.0
2.5
[rel]
C2Ethyl*Boc 3 1 /opt/topspin olegendre
PROTON
Acetylene Reduction to Ethyl at C2
8
6
4
2
[ppm]
1.0000
1.0909
1.1209
2.2201
1.0490
1.0606
3.2946
5.7011
2.2190
10.2391
3.5294
7.9830
6.9026
6.7289
5.9600
5.9546
4.6079
4.5840
4.3832
3.4768
2.8966
2.8728
2.8465
2.8115
2.7960
2.7885
2.7816
2.7666
2.7528
2.7383
2.7217
2.7144
2.6874
2.6402
2.6242
2.6094
2.5944
2.5801
2.5654
2.5503
1.5328
1.4700
1.2576
1.2425
1.2274

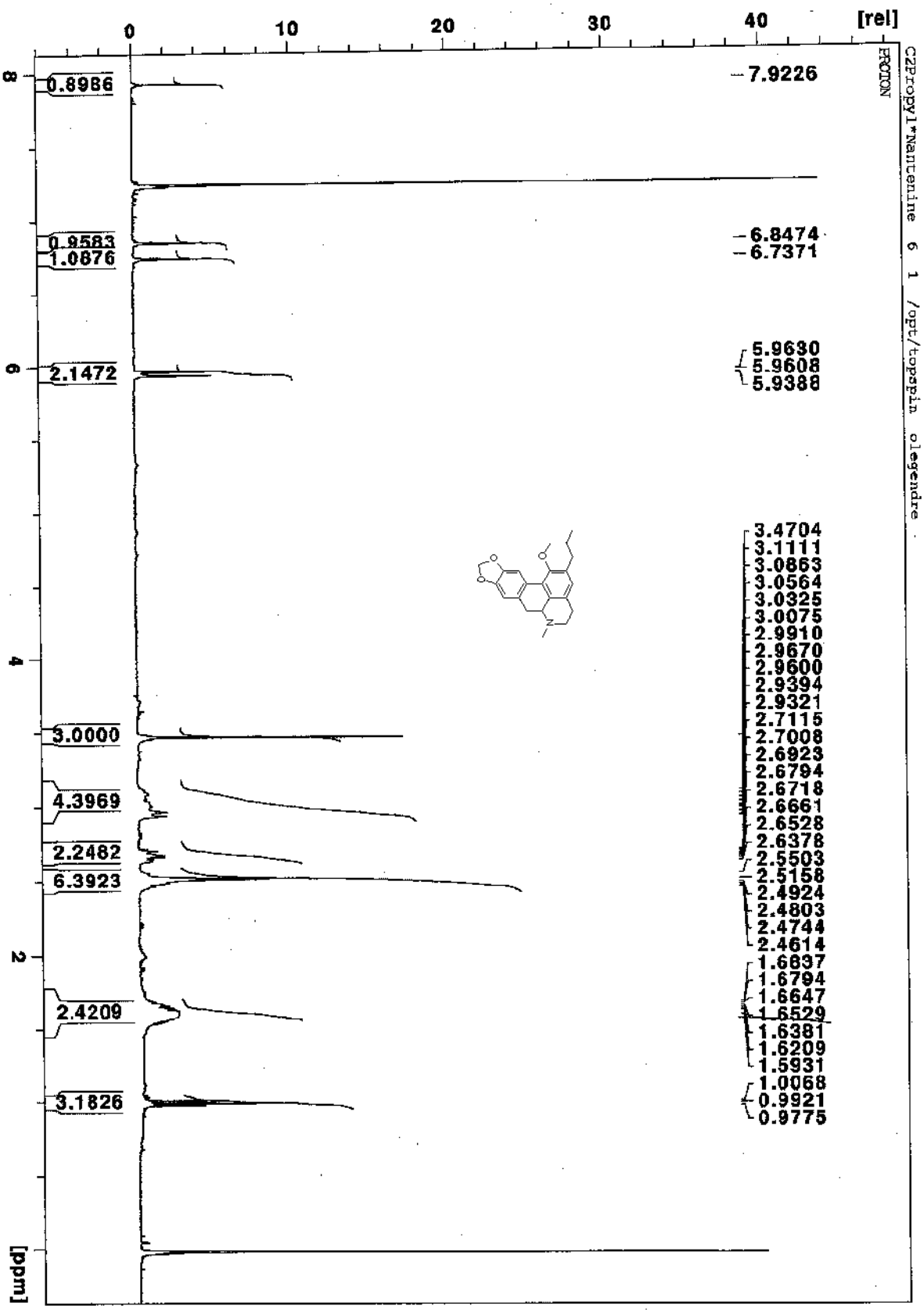

– 0
1
2
3
[rel]
C2Ethyl*Boc 2 1 /opt/topspin olegendre
CARBON
Acetylene Reduction to Ethyl at C2
153.9372
146.9234
146.6187
136.6483
132.4058
131.4604
130.0096
128.1742
125.6767
108.6724
101.0833
80.0649
60.2515
58.5779
52.3292
45.3629
30.1291
29.8918
28.7581
22.9594
18.6195
15.2475
15.0311
140
120
100
80
60
40
20
[ppm]


0
20
40
60
80
100
[rel]
1.0000
1.0815
1.0891
2.0934
3.2488
4.4893
1.1543
1.2195
1.8322
5.1152
3.8500
7.9225
6.8581
6.7296
5.9544
5.9301
3.4719
3.4701
3.1213
3.1102
3.0866
3.0659
3.0537
3.0328
3.0203
3.0103
2.9980
2.9757
2.9545
2.9326
2.9261
2.7578
2.7434
2.7292
2.7143
2.6722
2.6683
2.6370
2.6024
2.5875
2.5727
2.5583
2.5463
2.5067
2.4684
2.4511
1.2458
1.2306
1.2176
1.2159
6
4
2
[ppm]
C2Ethyl*Nantenine 2 1 /opt/topspin olegendre
PROTON


0
2
4
6
8
[rel]
140
120
100
80
60
40
20
[ppm]
153.7051
146.9276
146.3824
136.5576
130.6704
128.6424
128.2374
126.1168
126.0174
108.5736
108.4347
101.0483
63.0675
60.4026
53.4827
44.1565
35.0200
29.9118
28.8407
23.0233
15.2684
CARBON
C2Ethyl*Nantenine 3 1 /opt/topspin oiegendre


0
5
10
15
20
[rel]
PROTON
Sonogashira Reaction
Propragyl TMS
SonogashiraRXN 3 1 /opt/topspin olegendre
8
6
4
2
[ppm]
1.0000
1.0548
1.0273
2.1003
0.9991
1.0031
3.0973
5.5482
2.0071
9.7755
9.0545
7.9771
7.0726
6.7189
5.9543
4.6445
4.6234
4.3692
3.6640
2.9286
2.8778
2.8582
2.8293
2.8078
2.7886
2.7806
2.7578
2.7500
2.7393
2.7253
2.7122
2.6850
2.6238
2.6072
2.5938
1.7623
1.4683
0.1659


SonogashiraRXN 4 1 /opt/topspin olegendre
CARBON
Sonogashira Reaction
Propargyl TMS
[rel]
0
2
4
6
[ppm]
140
120
100
80
60
40
20
156.3244
146.8313
133.9967
132.0858
131.4030
129.9699
125.1465
118.5124
109.0574
101.1230
92.6498
80.1582
75.6683
60.3305
52.3480
38.9535
38.9256
38.9033
38.8254
38.7554
38.7345
38.6988
38.6286
38.5992
38.5827
38.5368
38.5233
38.4708
38.4158
38.3702
38.2755
37.2946
36.2640
35.5438
35.4487
35.3718
35.3272
35.3068
35.2824
35.2507
35.1959
35.1630
35.0827
35.0476
34.9971
29.9666
29.9009
28.7454
8.5731
0.1973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6
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4.3969
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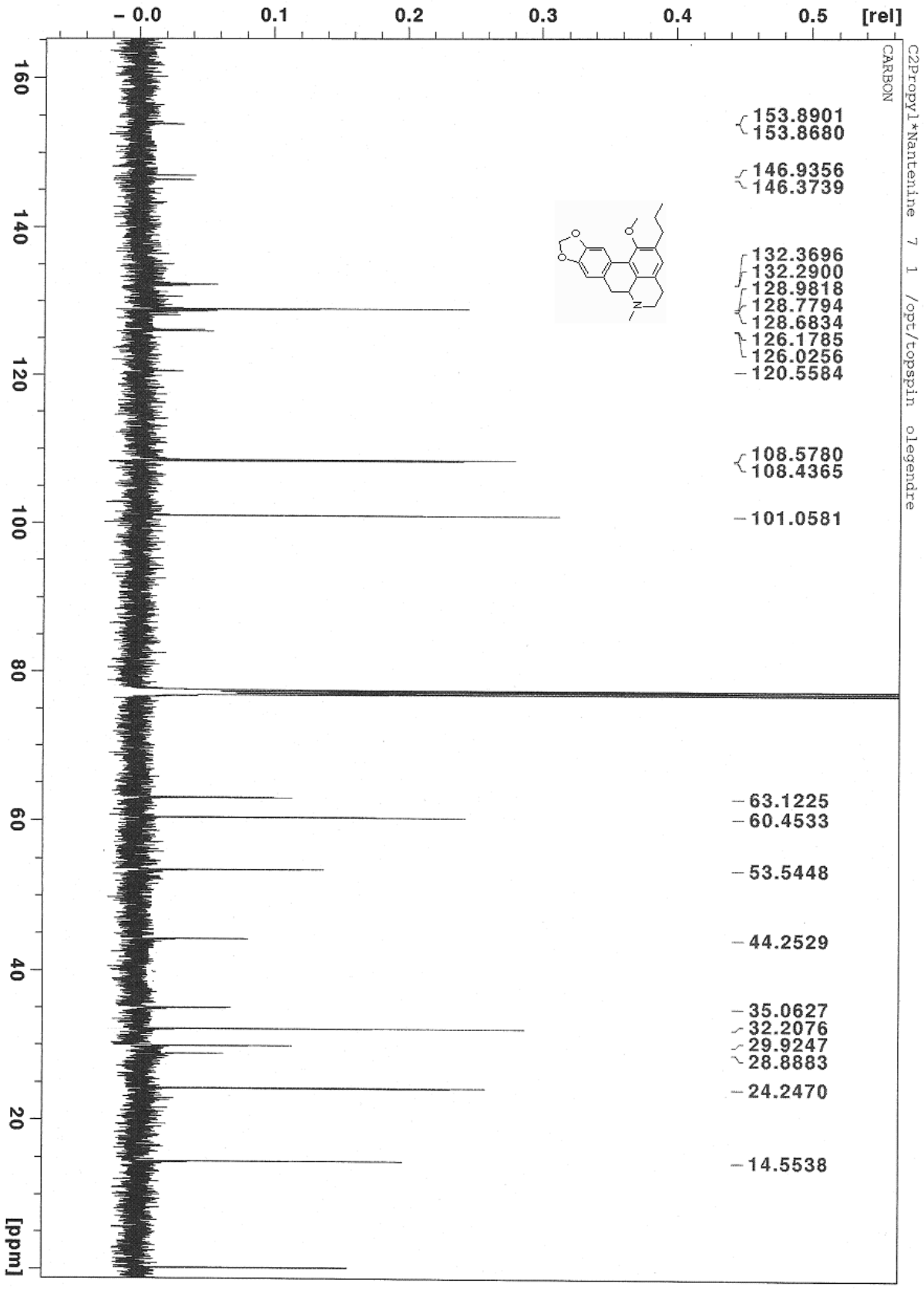
6.3923
2.4209
3.1826
7.9226
6.8474
6.7371
5.9630
5.9608
5.9388
3.4704
3.1111
3.0863
3.0564
3.0325
3.0075
2.9910
2.9670
2.9600
2.9394
2.9321
2.7115
2.7008
2.6923
2.6794
2.6718
2.6661
2.6528
2.6378
2.5503
2.5158
2.4924
2.4803
2.4744
2.4614
1.6837
1.6794
1.6647
1.6529
1.6381
1.6209
1.5931
1.0068
0.9921
0.9775
PROTON
CZPropyl*Nantenine 6 1 /opt/topspin olegendre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0.3
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0.5
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140
120
100
80
60
40
20
[ppm]
CARBON
C2Propyl*Nantenine 7 1 /opt/topspin olegendre
153.8901
153.8680
146.9356
146.3739
132.3696
132.2900
128.9818
128.7794
128.6834
126.1785
126.0256
120.5584
108.5780
108.4365
101.0581
63.1225
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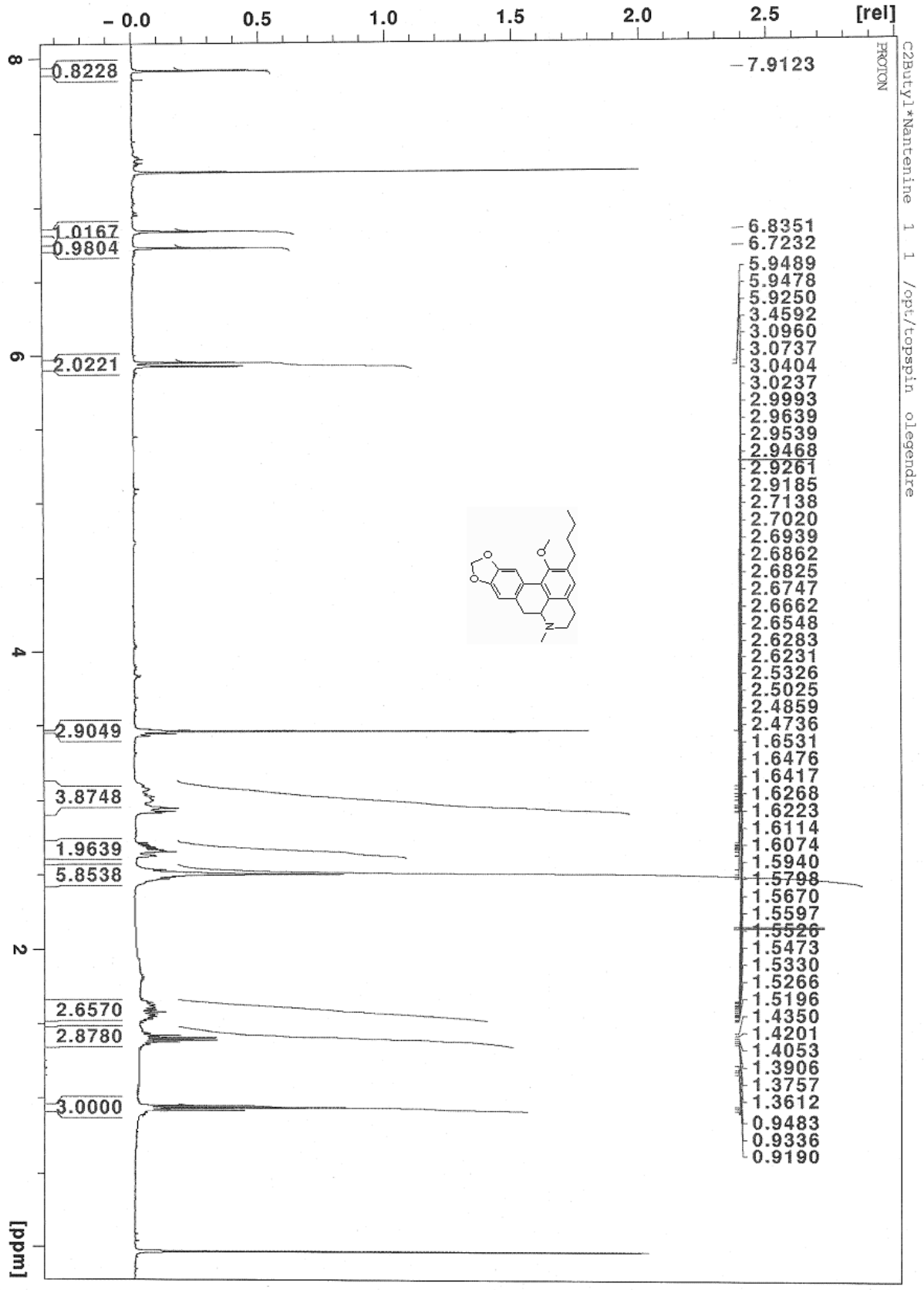
53.5448
44.2529
35.0627
32.2076
29.9247
28.8883
24.2470
14.5538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2
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0.9804
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3.8748
1.9639
5.8538
2.6570
2.8780
3.0000
7.9123
6.8351
6.7232
5.9489
5.9478
5.9250
3.4592
3.0960
3.0737
3.0404
3.0237
2.9993
2.9639
2.9539
2.9468
2.9261
2.9185
2.7138
2.7020
2.6939
2.6862
2.6825
2.6747
2.6662
2.6548
2.6283
2.6231
2.5326
2.5025
2.4859
2.4736
1.6531
1.6476
1.6417
1.6268
1.6223
1.6114
1.6074
1.5940
1.5798
1.5670
1.5597
1.5526
1.5473
1.5330
1.5266
1.5196
1.4350
1.4201
1.4053
1.3906
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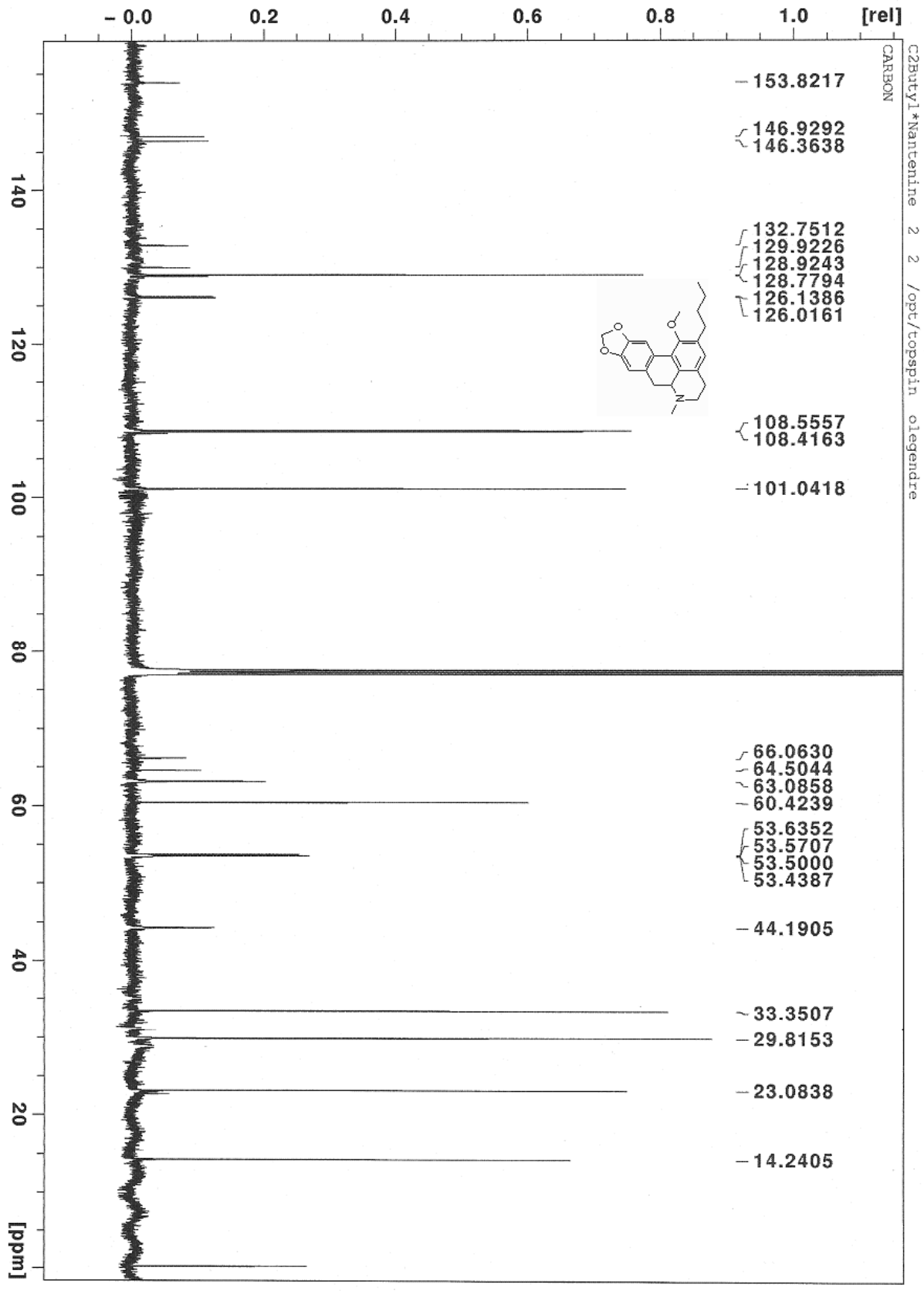
1.3612
0.9483
0.9336
0.9190
PROTON
C2Butyl*Nantenine 1 1 /opt/topspin olegendre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0.4
0.6
0.8
1.0
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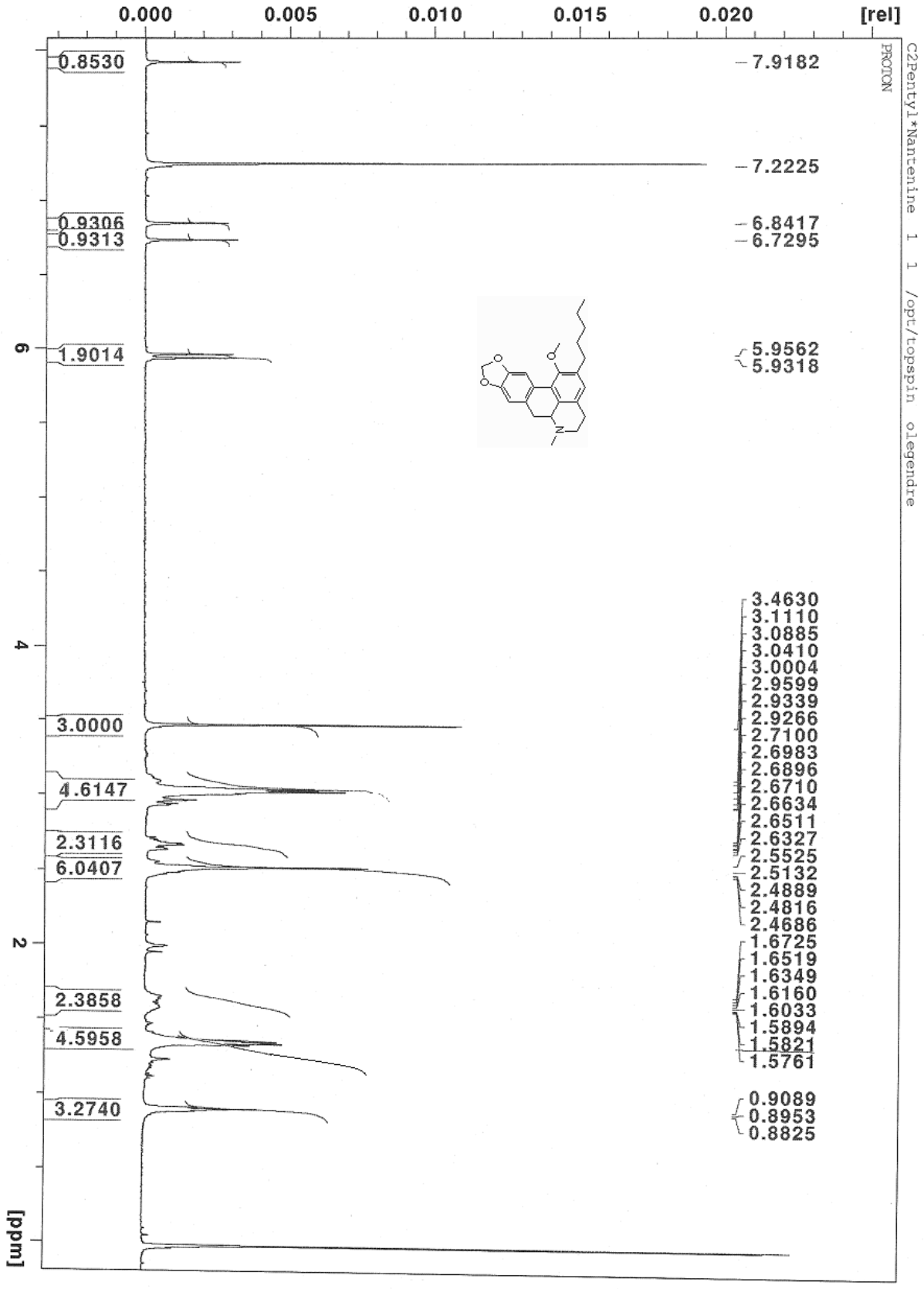
C2Butyl*Nantenine 2 2 /opt/topspin olegendre
153.8217
146.9292
146.3638
132.7512
129.9226
128.9243
128.7794
126.1386
126.0161
108.5557
108.4163
101.0418
66.0630
64.5044
63.0858
60.4239
53.6352
53.5707
53.5000
53.4387
44.1905
33.3507
29.8153
23.0838
14.2405
140
120
100
80
60
40
20
[ppm]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0.020
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C2Pentyl*Nantenine 1 1 /opt/topspin olegendre
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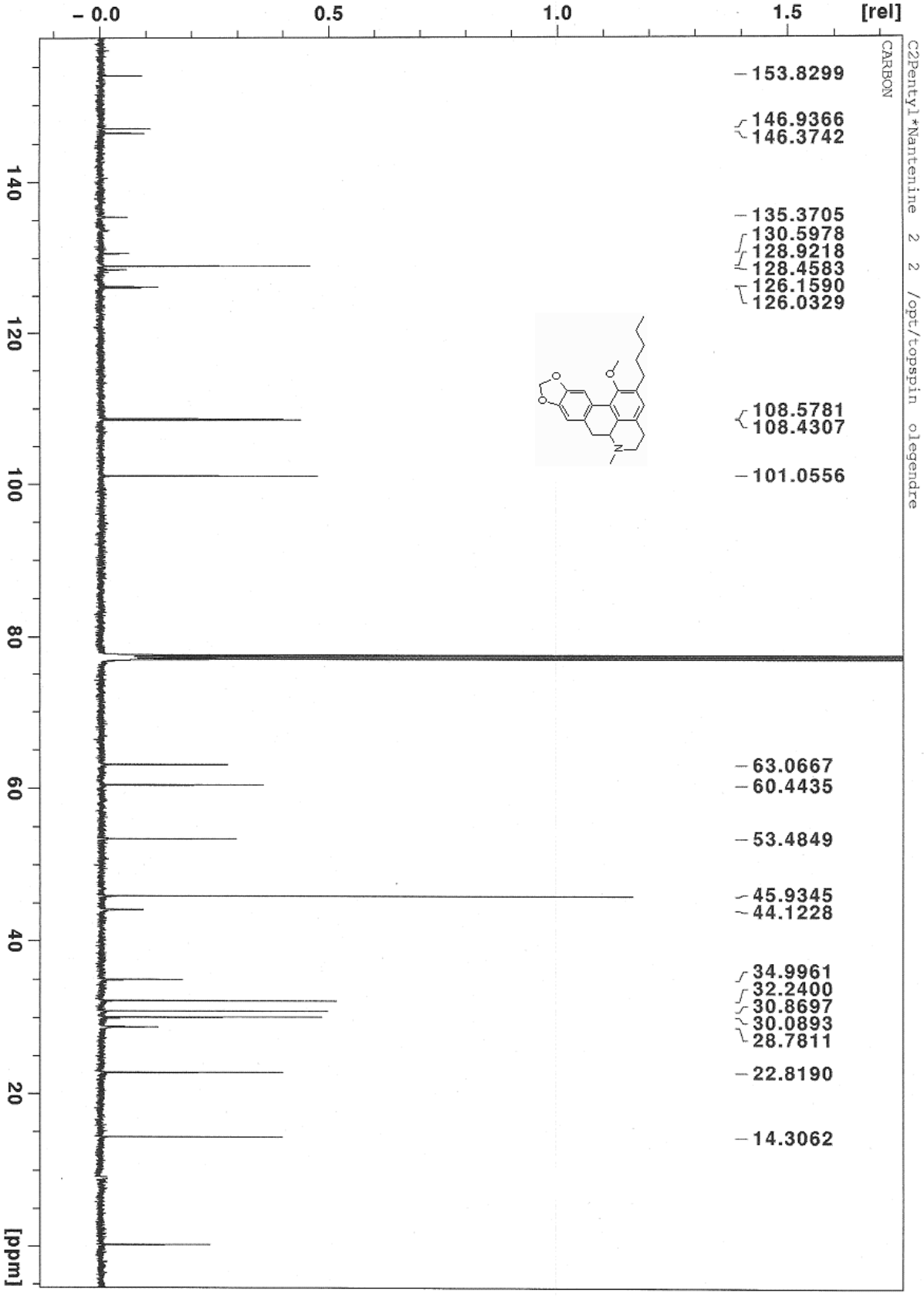
0.9313
1.9014
3.0000
4.6147
2.3116
6.0407
2.3858
4.5958
3.2740
7.9182
7.2225
6.8417
6.7295
5.9562
5.9318
3.4630
3.1110
3.0885
3.0410
3.0004
2.9599
2.9339
2.9266
2.7100
2.6983
2.6896
2.6710
2.6634
2.6511
2.6327
2.5525
2.5132
2.4889
2.4816
2.4686
1.6725
1.6519
1.6349
1.6160
1.6033
1.5894
1.5821
1.5761
0.9089
0.8953
0.8825
6
4
2
[ppm]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0.5
1.0
1.5
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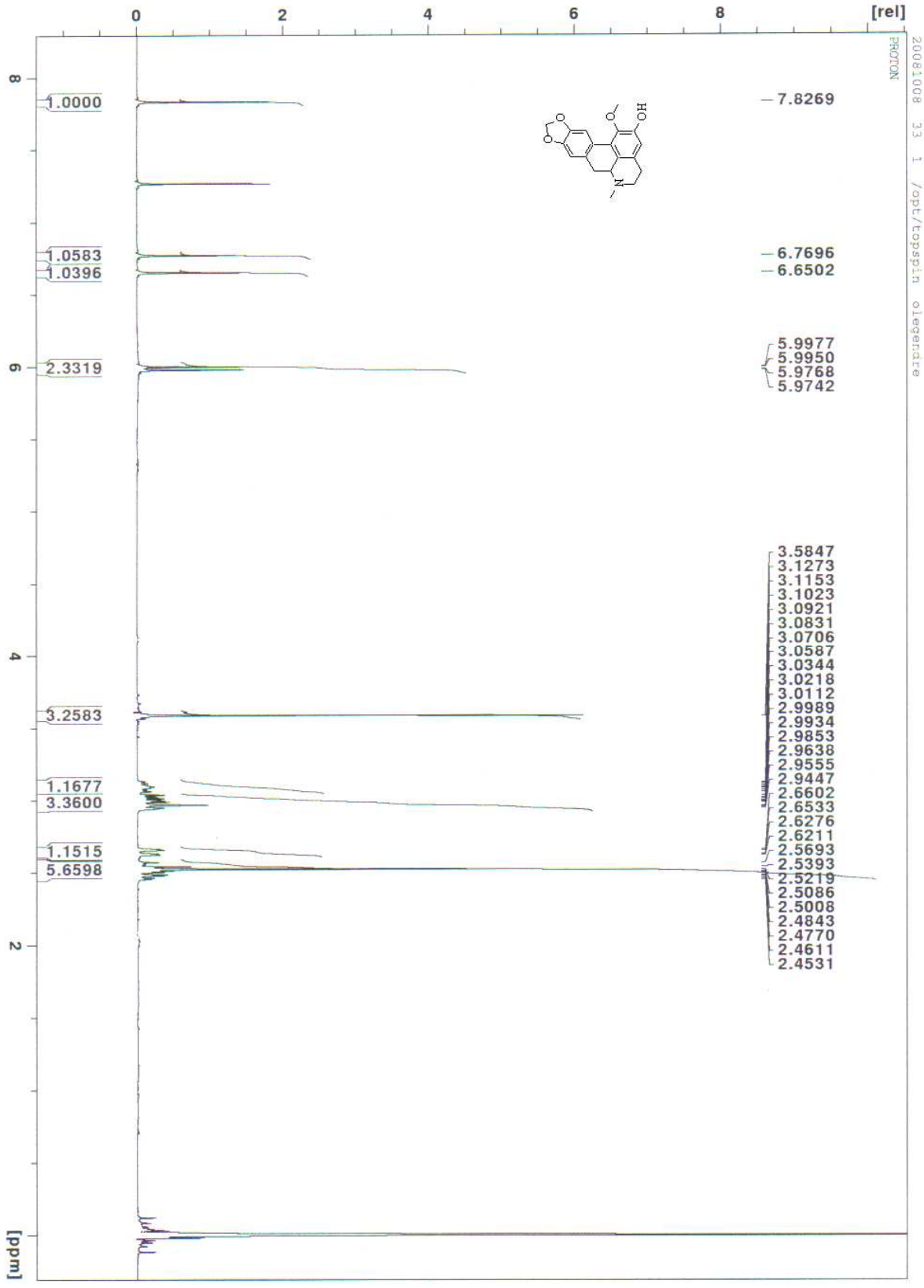
CARBON
C2Pentyl*Nantenine 2 2 /opt/topspin olegendre
153.8299
146.9366
146.3742
135.3705
130.5978
128.9218
128.4583
126.1590
126.0329
108.5781
108.4307
101.0556
63.0667
60.4435
53.4849
45.9345
44.1228
34.9961
32.2400
30.8697
30.0893
28.7811
22.8190
14.3062
140
120
100
80
60
40
20
[ppm]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4
6
8
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8
6
4
2
[ppm]
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20081008 33 1 /opt/topspin olegenare
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1.0583
1.0396
2.3319
3.2583
1.1677
3.3600
1.1515
5.6598
7.8269
6.7696
6.6502
5.9977
5.9950
5.9768
5.9742
3.5847
3.1273
3.1153
3.1023
3.0921
3.0831
3.0706
3.0587
3.0344
3.0218
3.0112
2.9989
2.9934
2.9853
2.9638
2.9555
2.9447
2.6602
2.6533
2.6276
2.6211
2.5693
2.5393
2.5219
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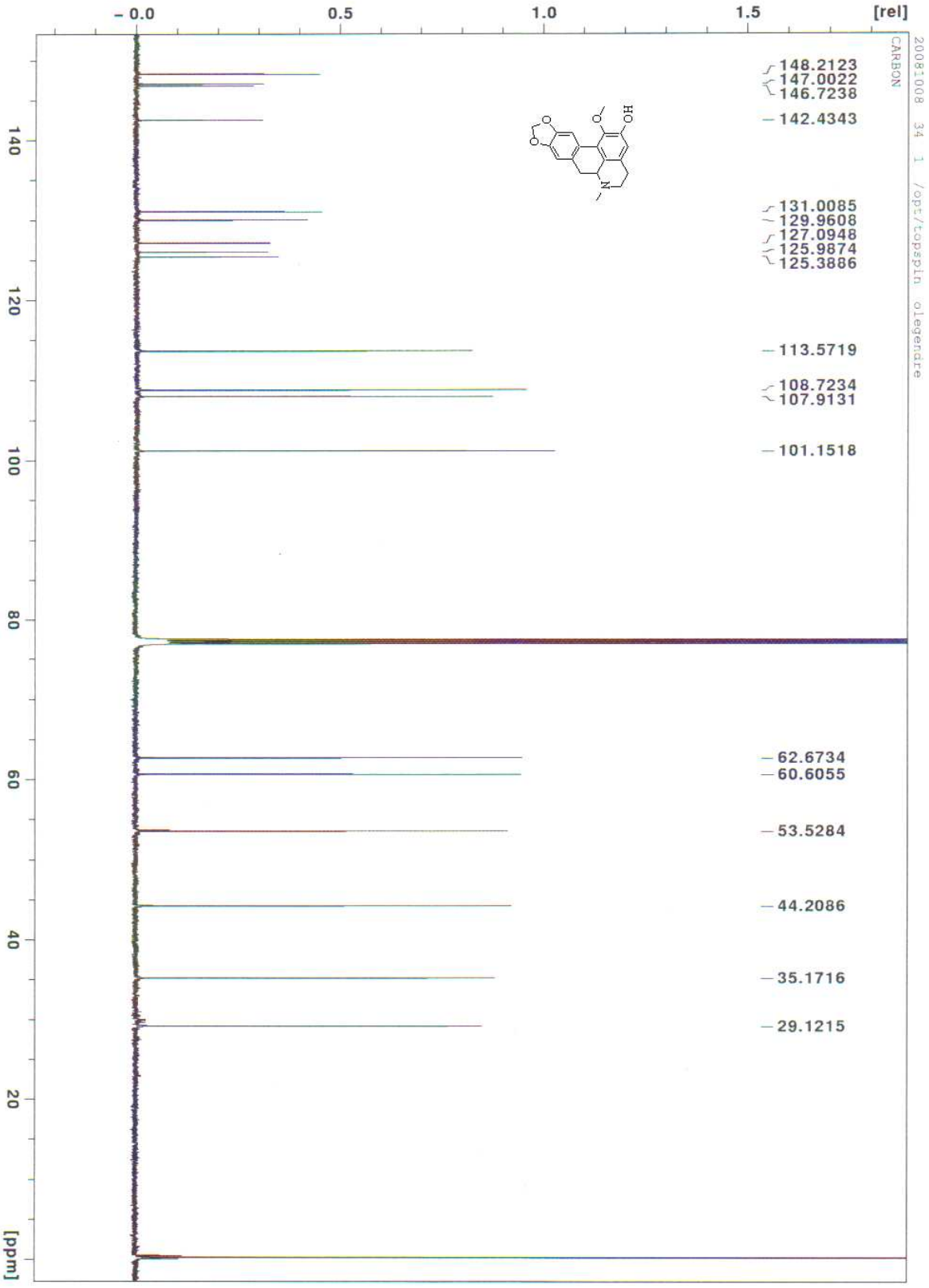
2.5008
2.4843
2.4770
2.4611
2.4531
HO
O
O
O
N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1.5
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20081008 34 1 /opt/topspin olegendre
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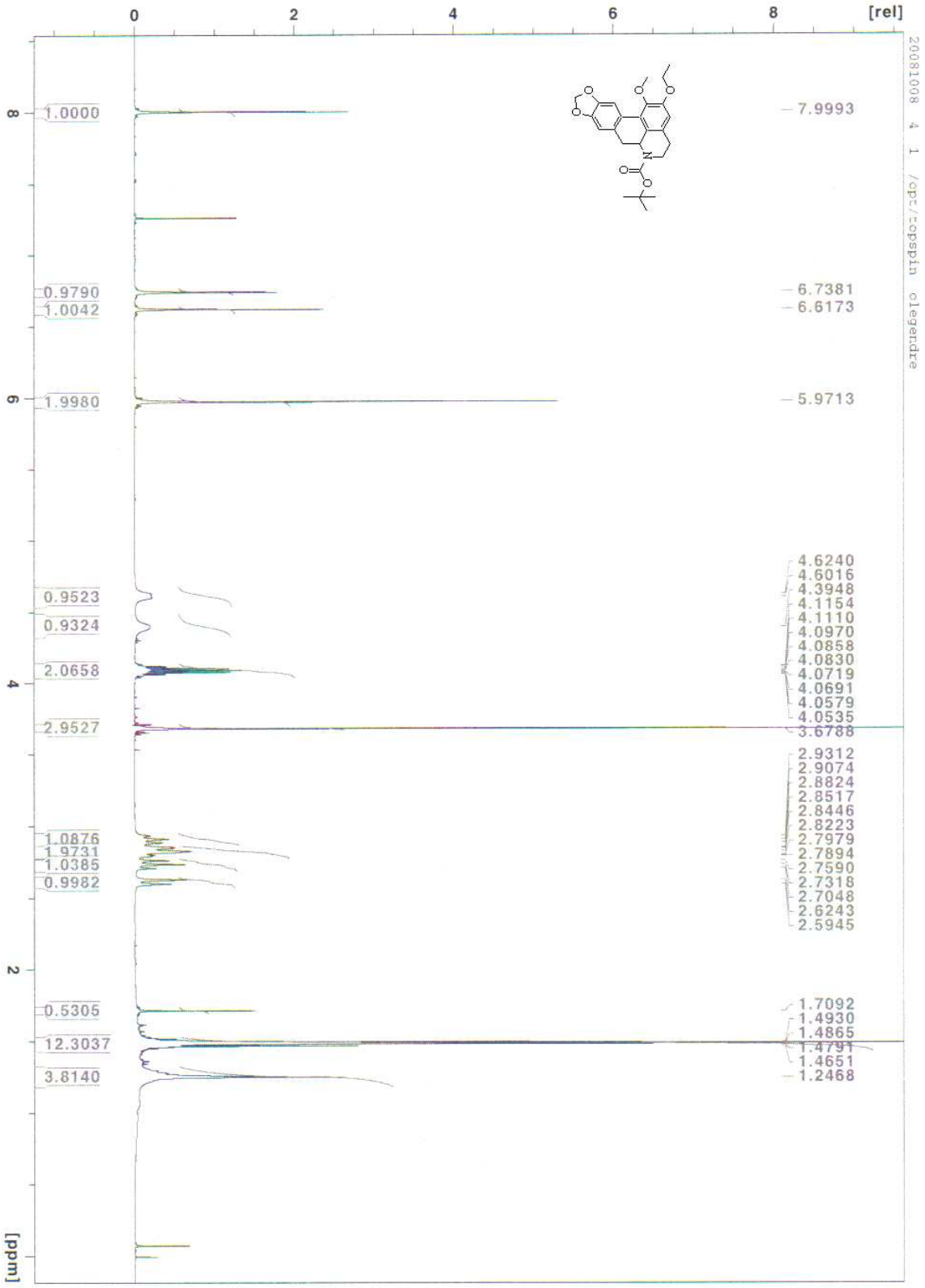
142.4343
131.0085
129.9608
127.0948
125.9874
125.3886
113.5719
108.7234
107.9131
101.1518
62.6734
60.6055
53.5284
44.2086
35.1716
29.1215
140
120
100
80
60
40
20
[ppm]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2
4
6
8
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8
6
4
2
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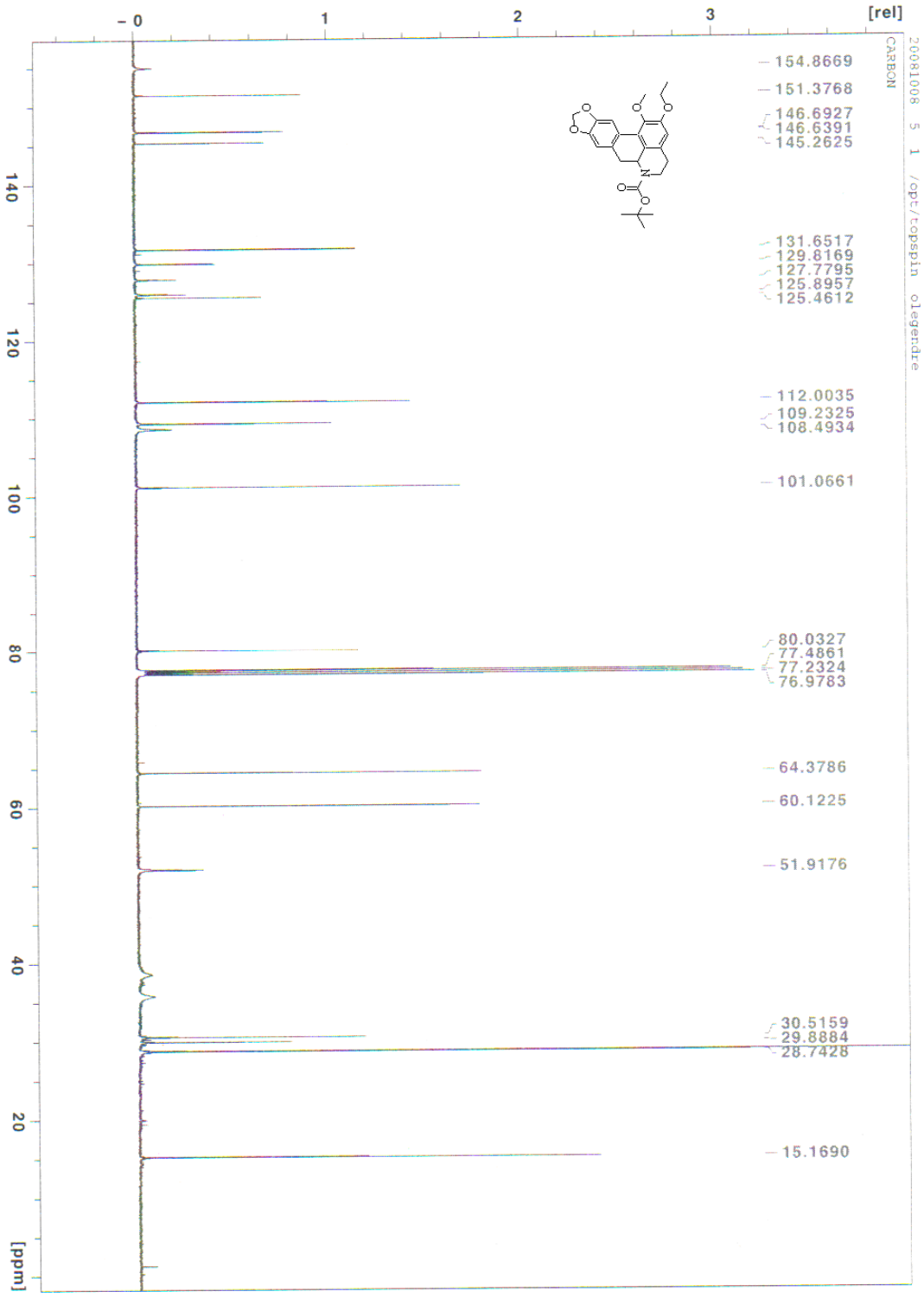
1.0042
1.9980
0.9523
0.9324
2.0658
2.9527
1.0876
1.9731
1.0385
0.9982
0.5305
12.3037
3.8140
7.9993
6.7381
6.6173
5.9713
4.6240
4.6016
4.3948
4.1154
4.1110
4.0970
4.0858
4.0830
4.0719
4.0691
4.0579
4.0535
3.6788
2.9312
2.9074
2.8824
2.8517
2.8446
2.8223
2.7979
2.7894
2.7590
2.7318
2.7048
2.6243
2.5945
1.7092
1.4930
1.4865
1.4791
1.4651
1.2468
20081008 4 1 /opt/topspin clegendre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1
2
3
[rel]
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20081008 5 1 /opt/topspin olegendre
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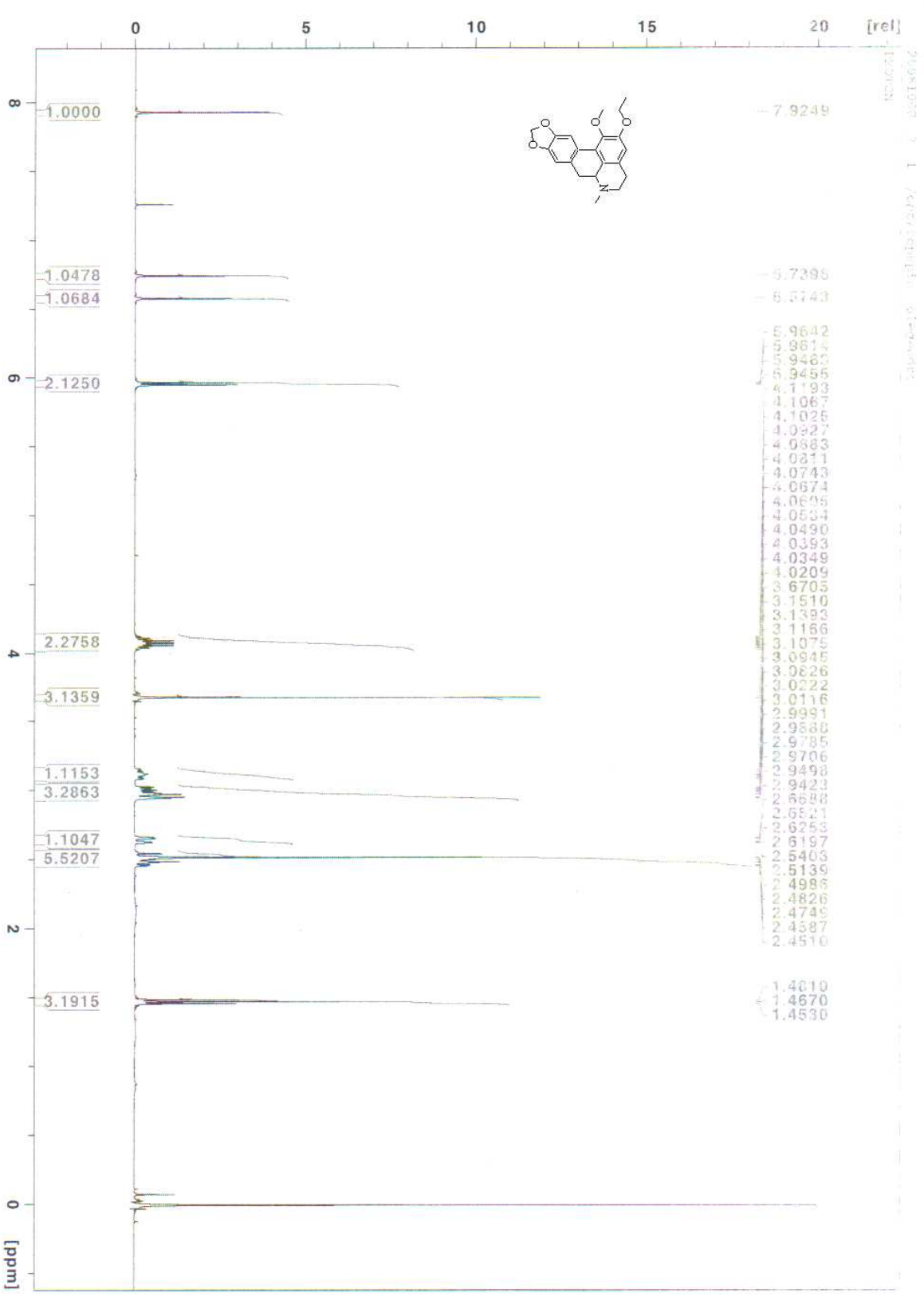
146.6927
146.6391
145.2625
131.6517
129.8169
127.7795
125.8957
125.4612
112.0035
109.2325
108.4934
101.0661
80.0327
77.4861
77.2324
76.9783
64.3786
60.1225
51.9176
30.5159
29.8884
28.7428
15.1690
140
120
100
80
60
40
20
[ppm]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10
15
20
[rel]
8
6
4
2
0
[ppm]
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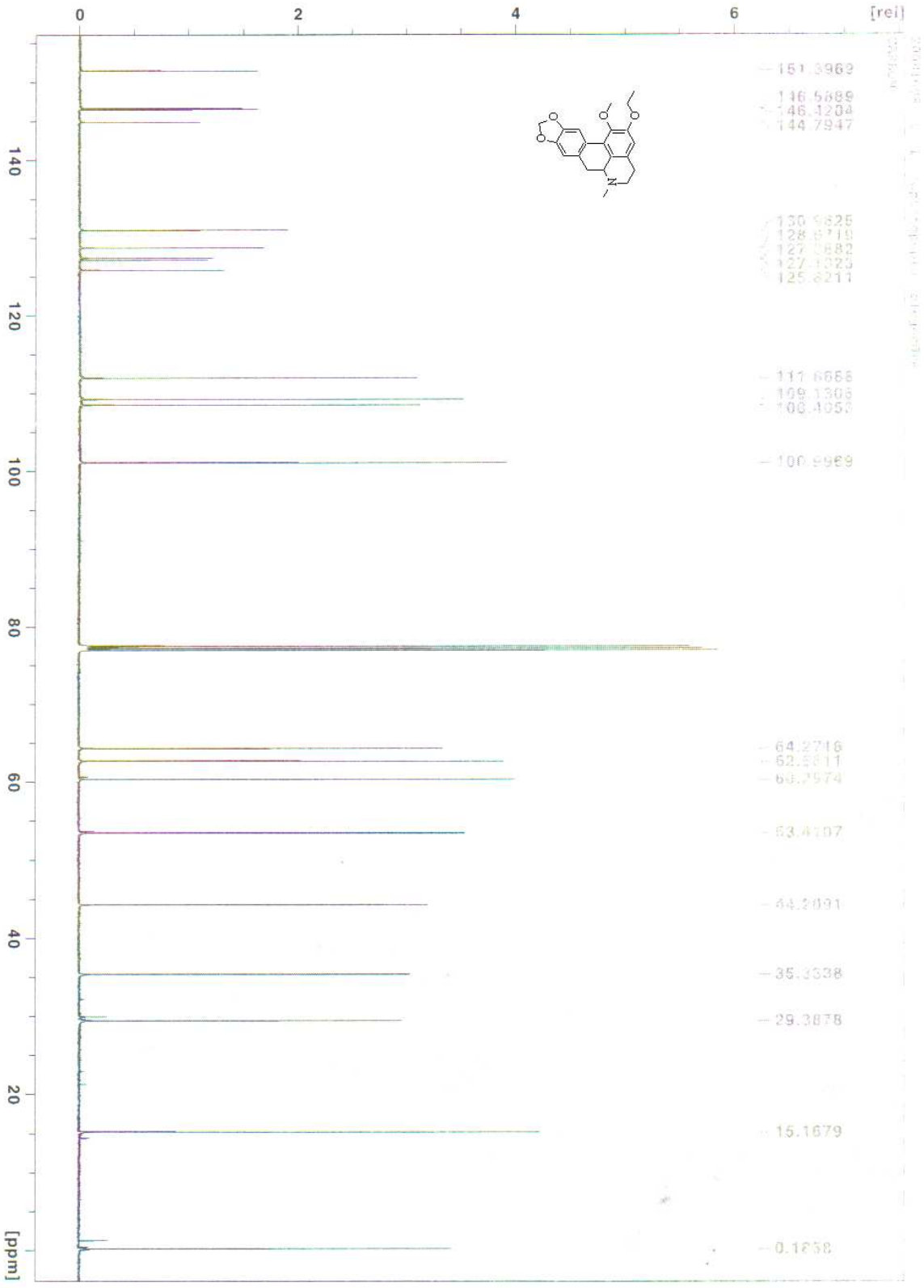
2.2758
3.1359
1.1153
3.2863
1.1047
5.5207
3.1915
7.9249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2
4
6
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120
100
80
60
40
20
[ppm]
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146.4204
144.7947
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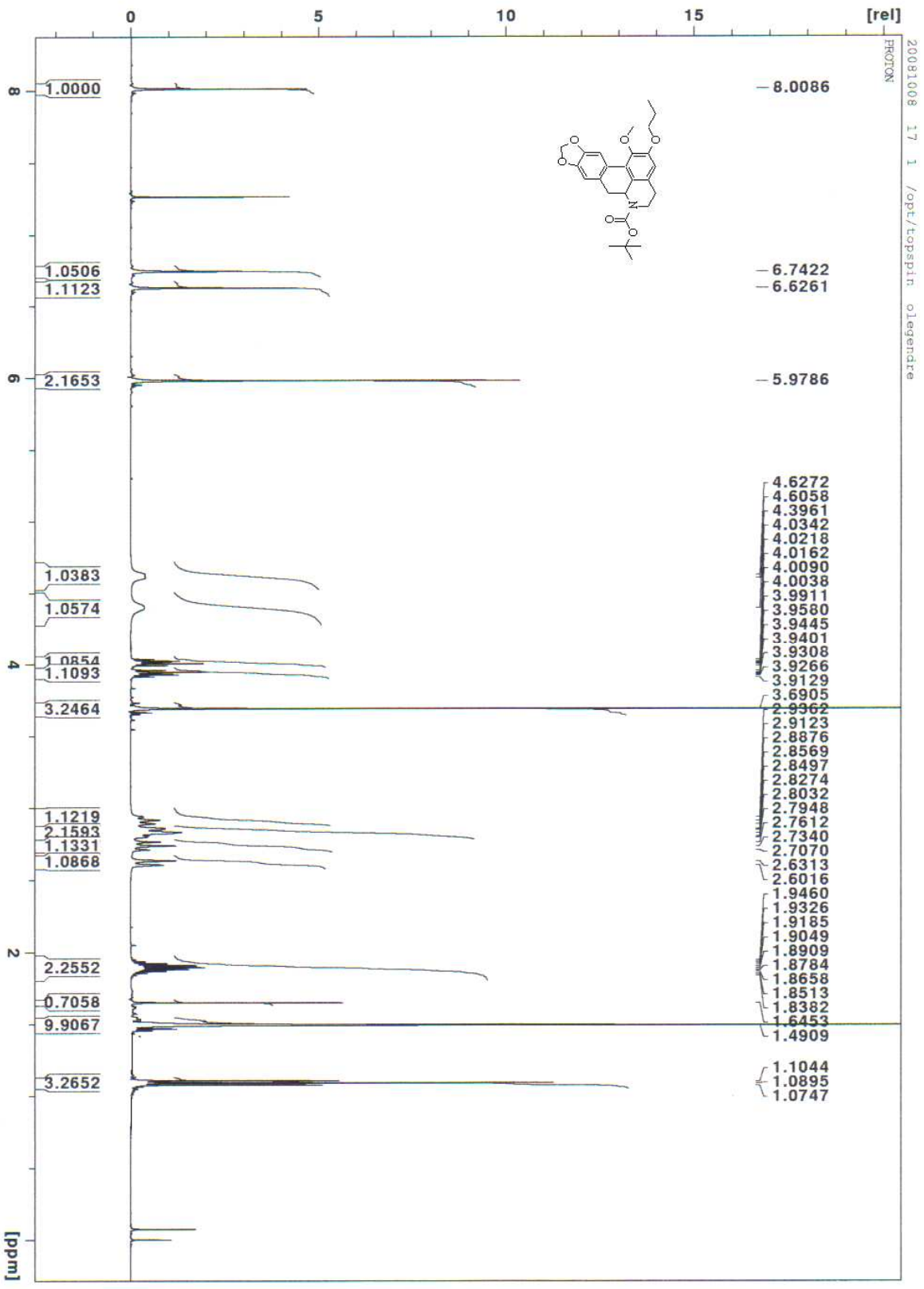
128.6719
127.5882
127.1025
125.8211
111.6666
109.1305
100.4053
100.9989
64.2716
62.5611
60.7974
53.4107
44.2091
35.3338
29.3878
15.1679
0.1658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10
15
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20081008 17 1 /opt/topspin olegendre
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6
4
2
[ppm]
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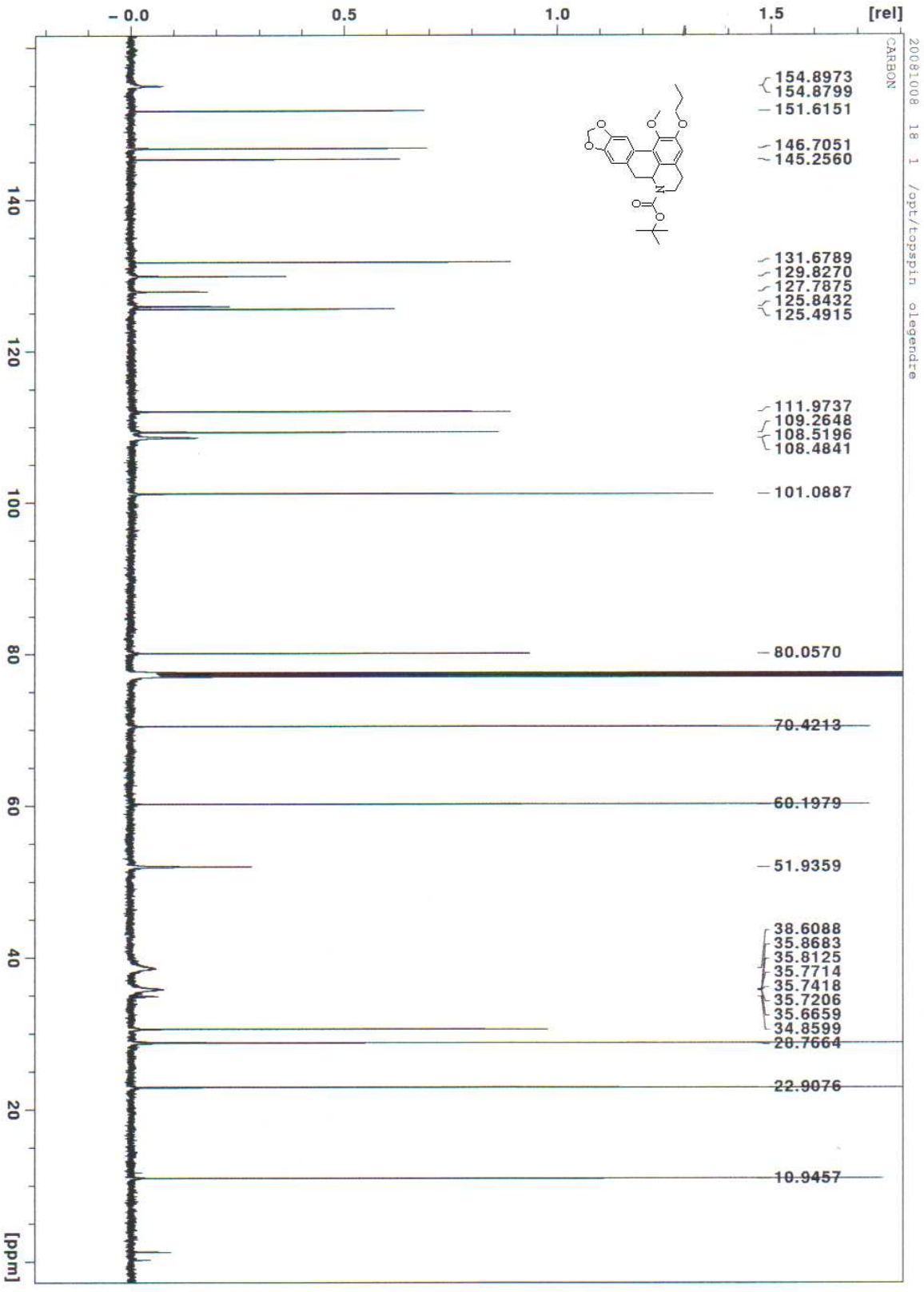
1.0383
1.0574
1.0854
1.1093
3.2464
1.1219
2.1593
1.1331
1.0868
2.2552
0.7058
9.9067
3.2652
8.0086
6.7422
6.6261
5.9786
4.6272
4.6058
4.3961
4.0342
4.0218
4.0162
4.0090
4.0038
3.9911
3.9580
3.9445
3.9401
3.9308
3.9266
3.9129
3.6905
2.9962
2.9123
2.8876
2.8569
2.8497
2.8274
2.8032
2.7948
2.7612
2.7340
2.7070
2.6313
2.6016
1.9460
1.9326
1.9185
1.9049
1.8909
1.8784
1.8658
1.8513
1.8382
1.6453
1.4909
1.1044
1.0895
1.0747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0.5
1.0
1.5
[rel]
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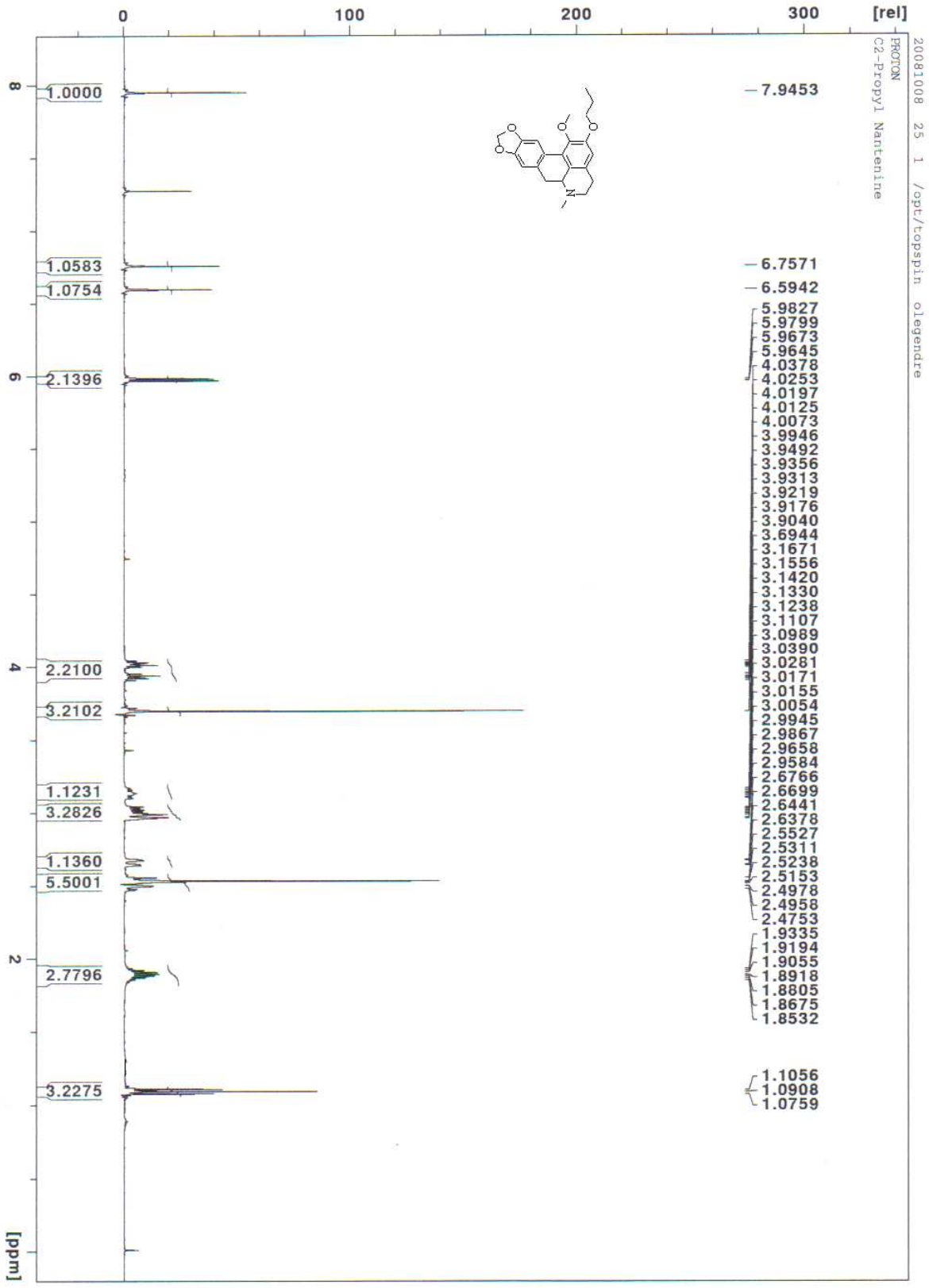
20081008 18 1 /opt/topspin olegendre
154.8973
154.8799
151.6151
146.7051
145.2560
131.6789
129.8270
127.7875
125.8432
125.4915
111.9737
109.2648
108.5196
108.4841
101.0887
80.0570
70.4213
60.1979
51.9359
38.6088
35.8683
35.8125
35.7714
35.7418
35.7206
35.6659
34.8599
28.7664
22.9076
10.9457
140
120
100
80
60
40
20
[ppm]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100
200
300
[rel]
8
6
4
2
[ppm]
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1.0754
2.1396
2.2100
3.2102
1.1231
3.2826
1.1360
5.5001
2.7796
3.2275
7.9453
6.7571
6.5942
5.9827
5.9799
5.9673
5.9645
4.0378
4.0253
4.0197
4.0125
4.0073
3.9946
3.9492
3.9356
3.9313
3.9219
3.9176
3.9040
3.6944
3.1671
3.1556
3.1420
3.1330
3.1238
3.1107
3.0989
3.0390
3.0281
3.0171
3.0155
3.0054
2.9945
2.9867
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2.9584
2.6766
2.6699
2.6441
2.6378
2.5527
2.5311
2.5238
2.5153
2.4978
2.4958
2.4753
1.9335
1.9194
1.9055
1.8918
1.8805
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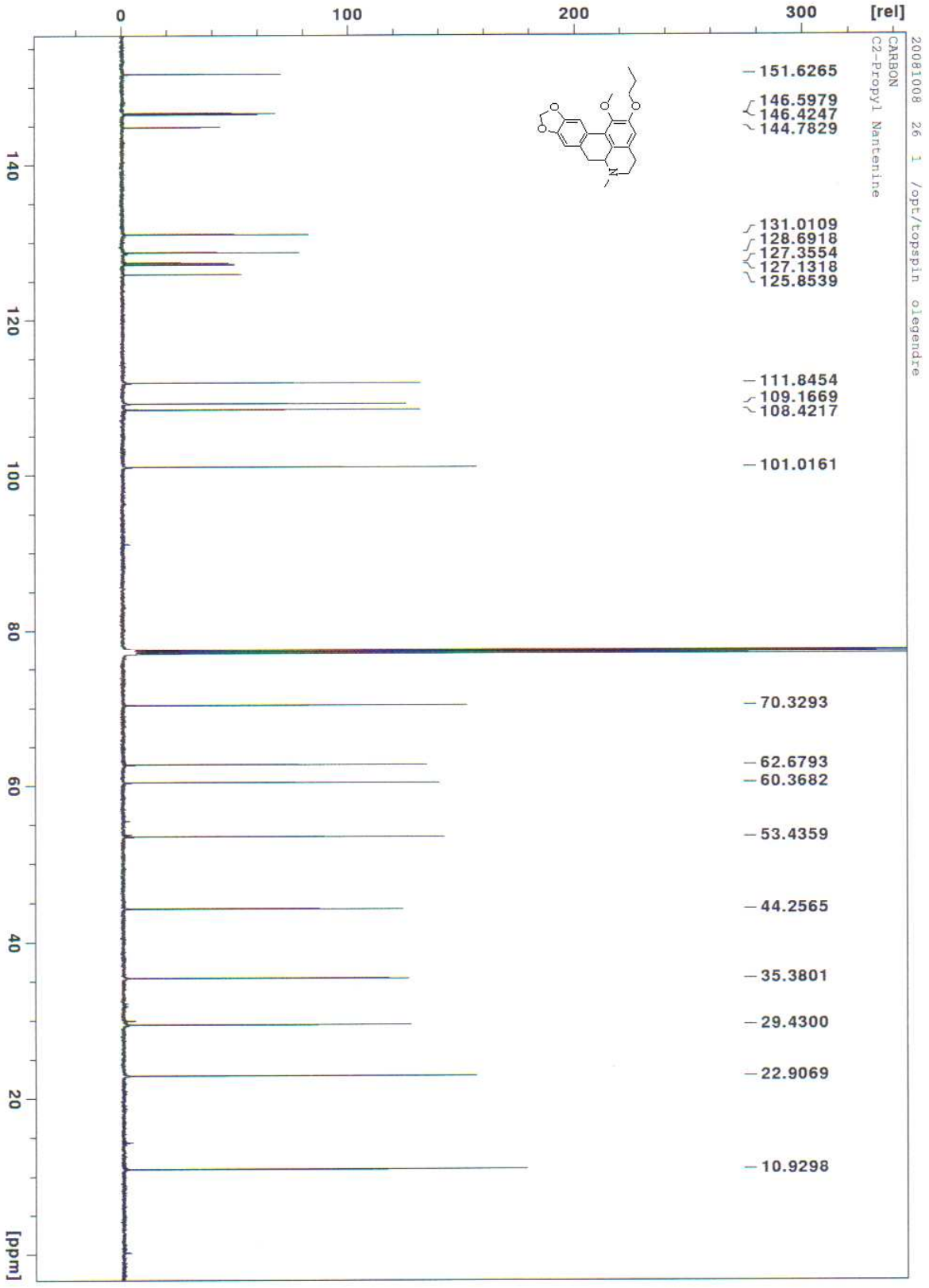
1.1056
1.0908
1.0759
PROTON
C2-Propyl Nantenine
20081008 25 1 /opt/topspin olegendre


0
100
200
300
[rel]
140
120
100
80
60
40
20
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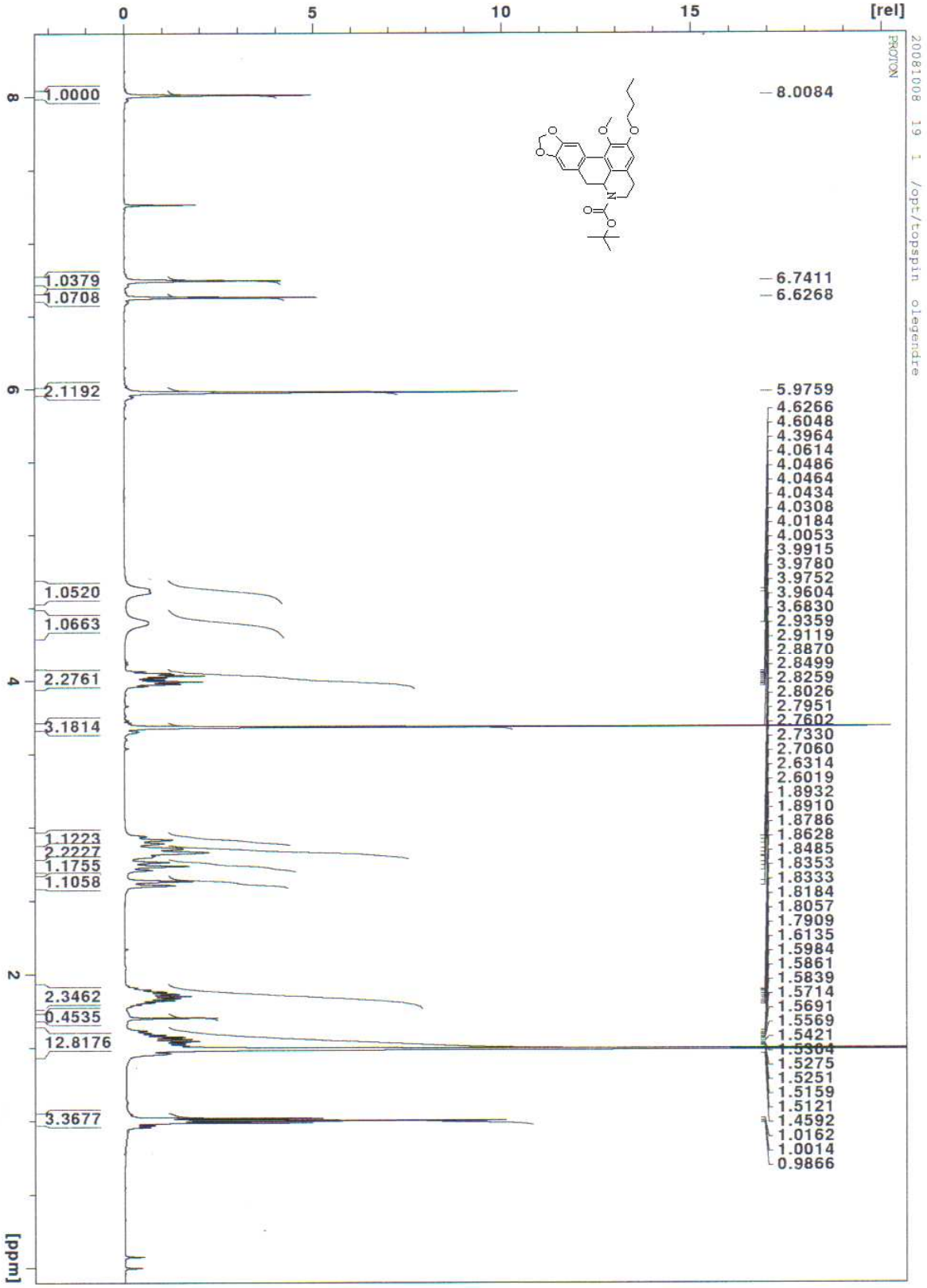
146.5979
146.4247
144.7829
131.0109
128.6918
127.3554
127.1318
125.8539
111.8454
109.1669
108.4217
101.0161
70.3293
62.6793
60.3682
53.4359
44.2565
35.3801
29.4300
22.9069
10.9298
CARBON
C2-Propyl Nantenine
20081008 26 1 /opt/topspin olegendre


0
5
10
15
[rel]
PROTON
20081008 19 1 /opt/topspin olegendre
8
6
4
2
[ppm]
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1.0708
2.1192
1.0520
1.0663
2.2761
3.1814
1.1223
2.2227
1.1755
1.1058
2.3462
0.4535
12.8176
3.3677
8.0084
6.7411
6.6268
5.9759
4.6266
4.6048
4.3964
4.0614
4.0486
4.0464
4.0434
4.0308
4.0184
4.0053
3.9915
3.9780
3.9752
3.9604
3.6830
2.9359
2.9119
2.8870
2.8499
2.8259
2.8026
2.7951
2.7602
2.7330
2.7060
2.6314
2.6019
1.8932
1.8910
1.8786
1.8628
1.8485
1.8353
1.8333
1.8184
1.8057
1.7909
1.6135
1.5984
1.5861
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1.5691
1.5569
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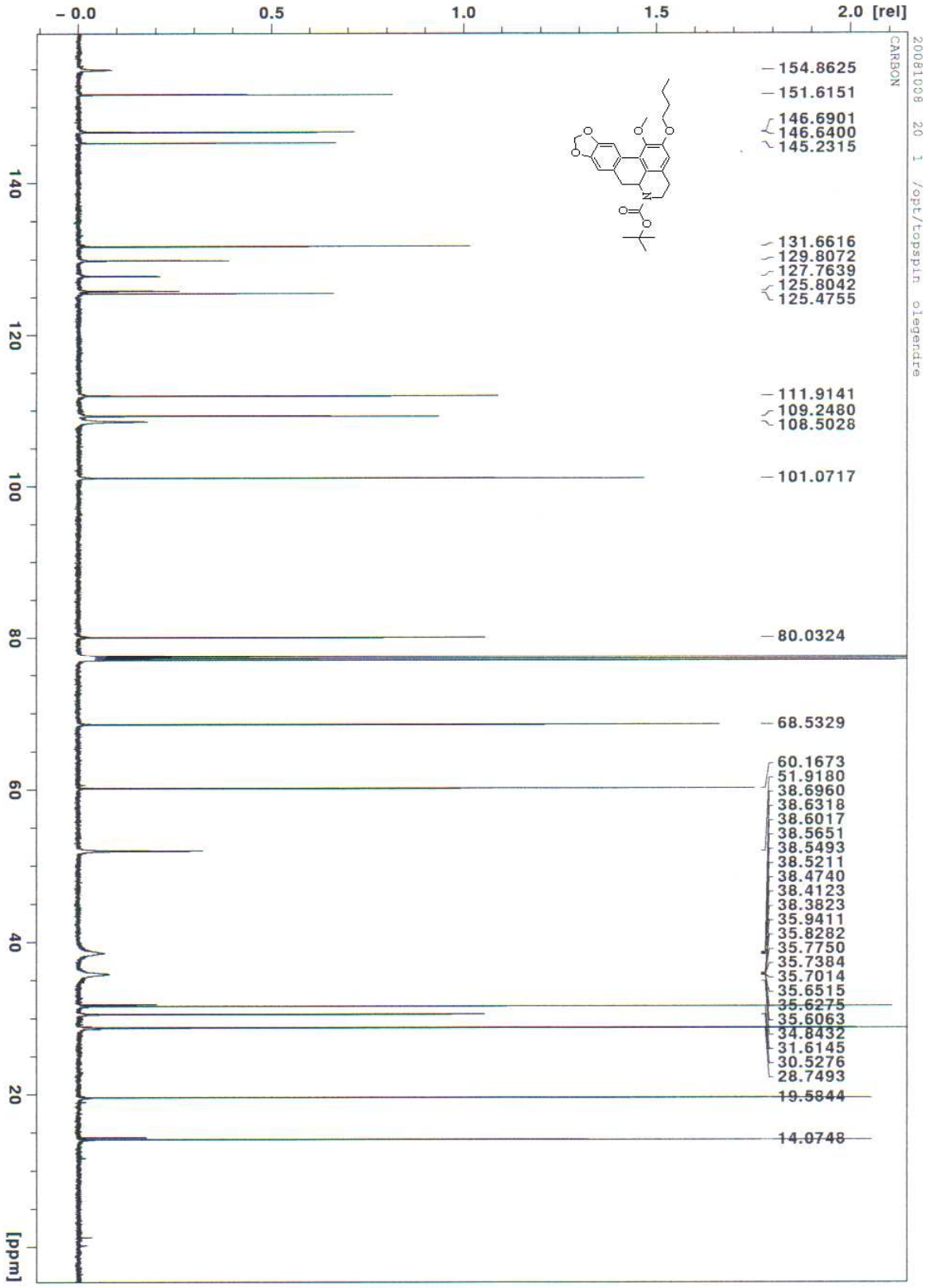
1.4592
1.0162
1.0014
0.9866


– 0.0
0.5
1.0
1.5
2.0 [rel]
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20081008 20 1 /opt/topspin olegendre
154.8625
151.6151
146.6901
146.6400
145.2315
131.6616
129.8072
127.7639
125.8042
125.4755
111.9141
109.2480
108.5028
101.0717
80.0324
68.5329
60.1673
51.9180
38.6960
38.6318
38.6017
38.5651
38.5493
38.5211
38.4740
38.4123
38.3823
35.9411
35.8282
35.7750
35.7384
35.7014
35.6515
35.6275
35.6063
34.8432
31.6145
30.5276
28.7493
19.5844
14.0748
140
120
100
80
60
40
20
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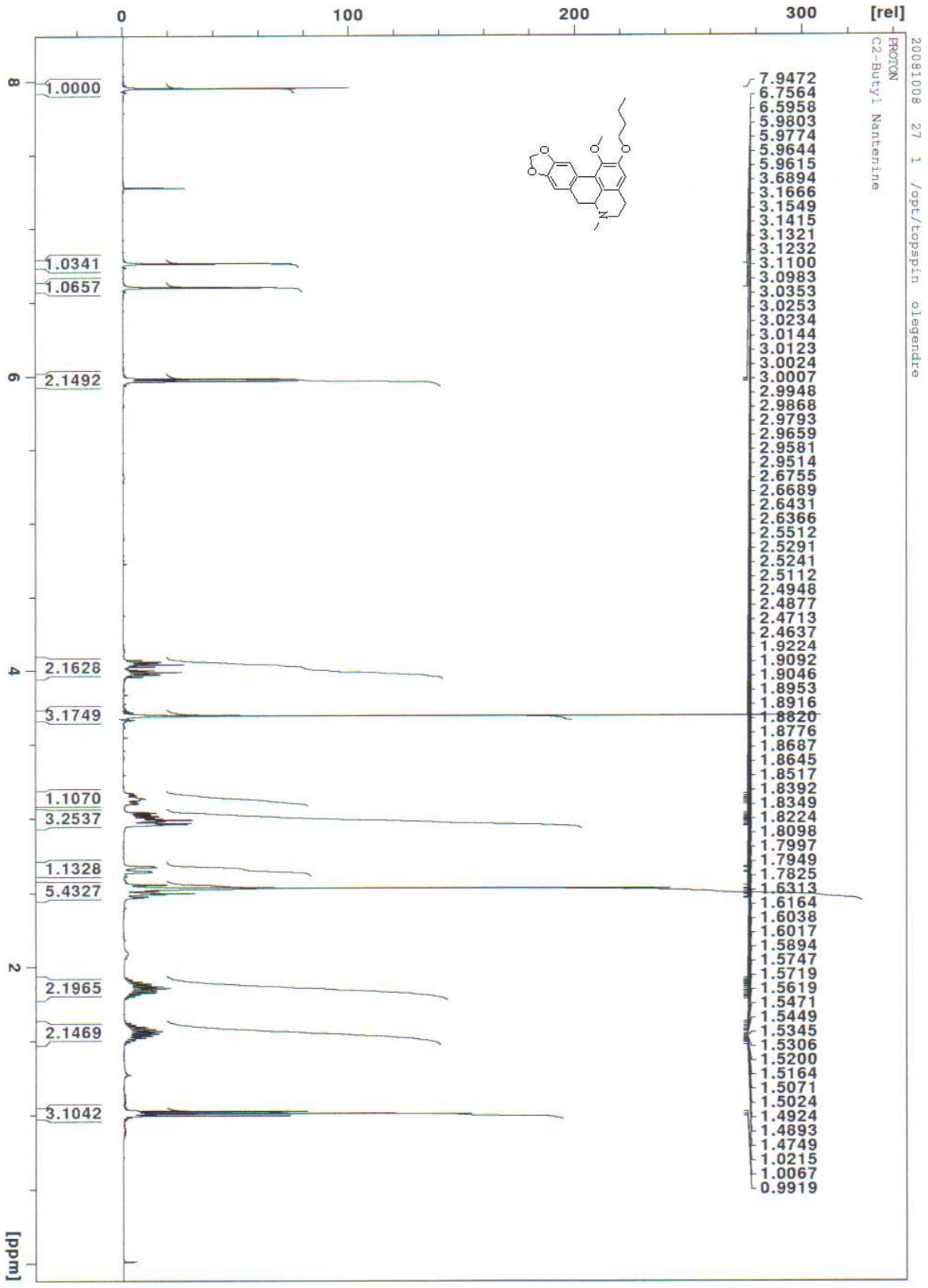
0
100
200
300
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20081008 27 1 /opt/topspin olegendre
PROTON
C2-Butyl Nantenine
8
6
4
2
[ppm]
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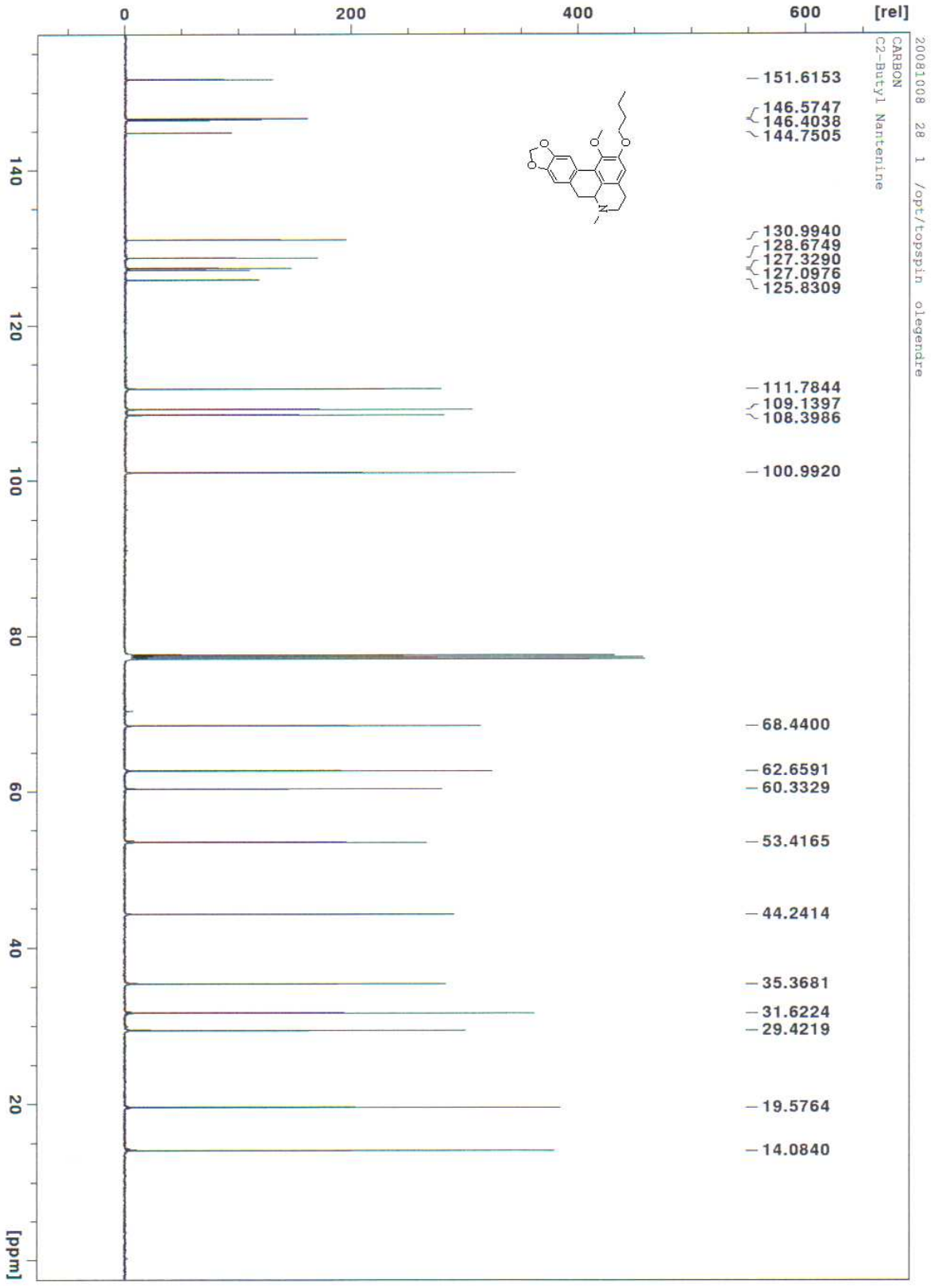
1.0341
1.0657
2.1492
2.1628
3.1749
1.1070
3.2537
1.1328
5.4327
2.1965
2.1469
3.1042
7.9472
6.7564
6.5958
5.9803
5.9774
5.9644
5.9615
3.6894
3.1666
3.1549
3.1415
3.1321
3.1232
3.1100
3.0983
3.0353
3.0253
3.0234
3.0144
3.0123
3.0024
3.0007
2.9948
2.9868
2.9793
2.9659
2.9581
2.9514
2.6755
2.6689
2.6431
2.6366
2.5512
2.5291
2.5241
2.5112
2.4948
2.4877
2.4713
2.4637
1.9224
1.9092
1.9046
1.8953
1.8916
1.8820
1.8776
1.8687
1.8645
1.8517
1.8392
1.8349
1.8224
1.8098
1.7997
1.7949
1.7825
1.6313
1.6164
1.6038
1.6017
1.5894
1.5747
1.5719
1.5619
1.5471
1.5449
1.5345
1.5306
1.5200
1.5164
1.5071
1.5024
1.4924
1.4893
1.4749
1.0215
1.0067
0.9919


0
200
400
600
[rel]
CARBON
C2-Butyl Nantenine
20081008 28 1 /opt/topspin olegendre
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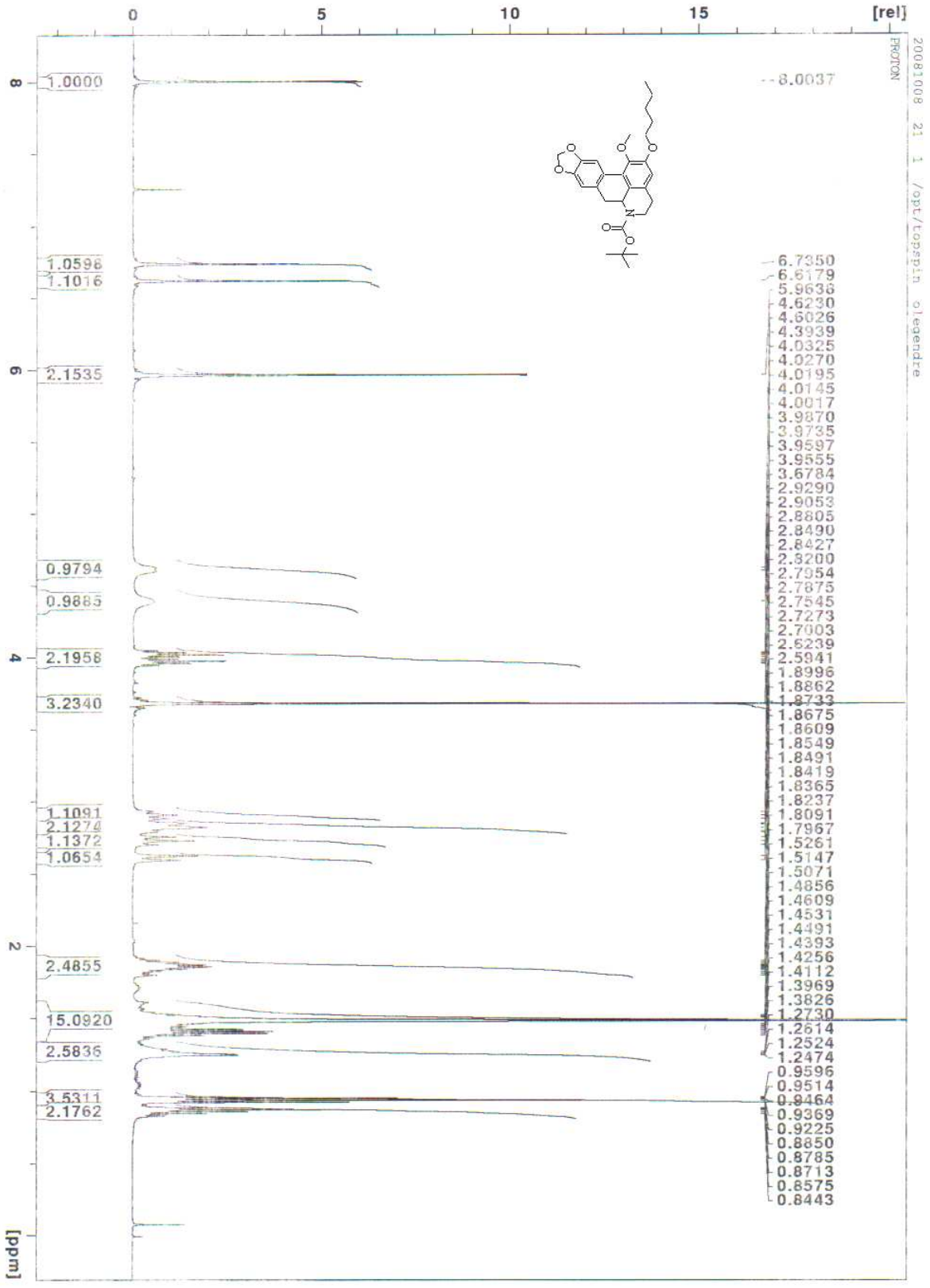
146.4038
144.7505
130.9940
128.6749
127.3290
127.0976
125.8309
111.7844
109.1397
108.3986
100.9920
68.4400
62.6591
60.3329
53.4165
44.2414
35.3681
31.6224
29.4219
19.5764
14.0840
140
120
100
80
60
40
20
[ppm]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5
10
15
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20081008 21 1 /opt/topspin olegendre
8
6
4
2
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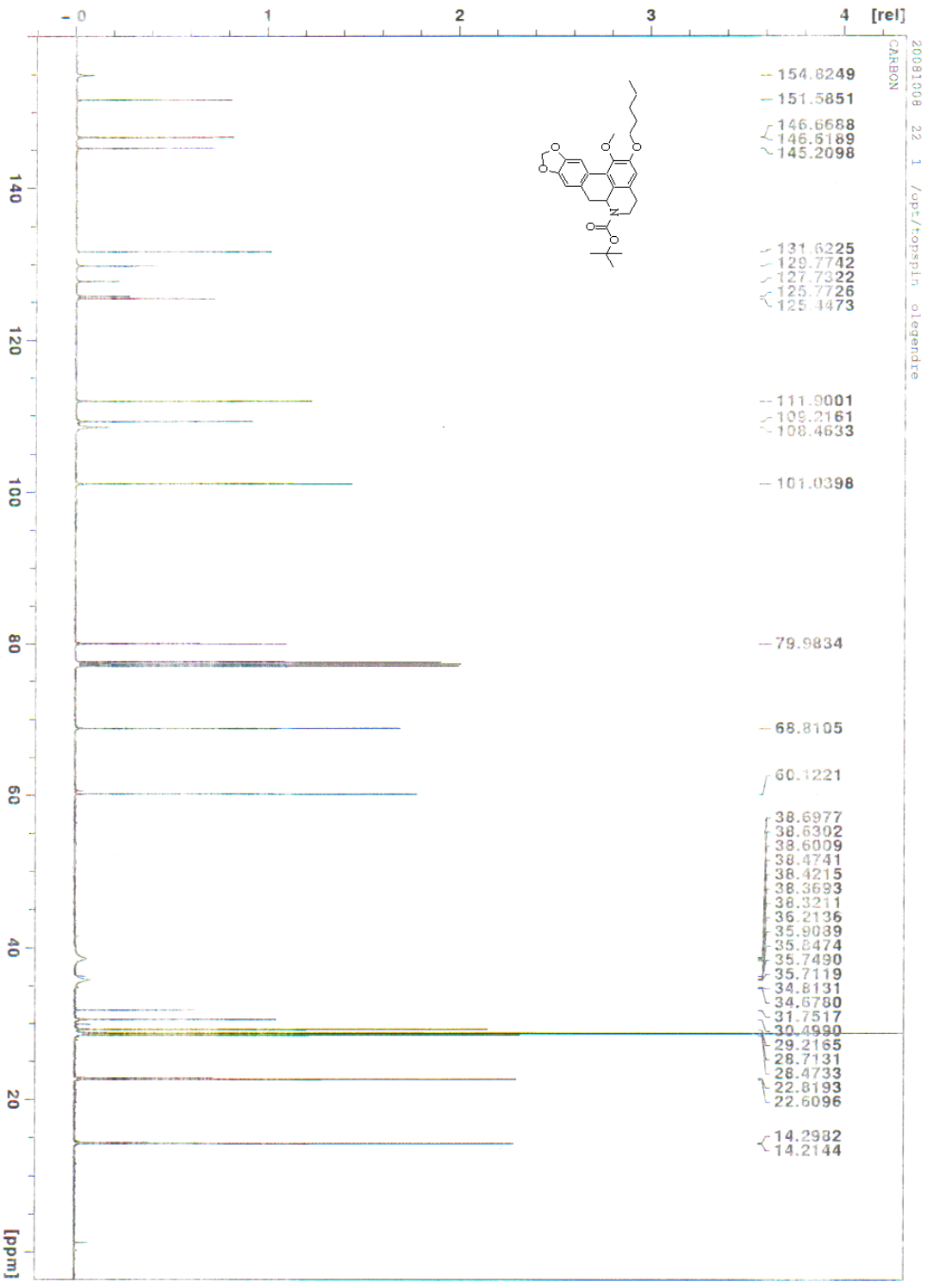
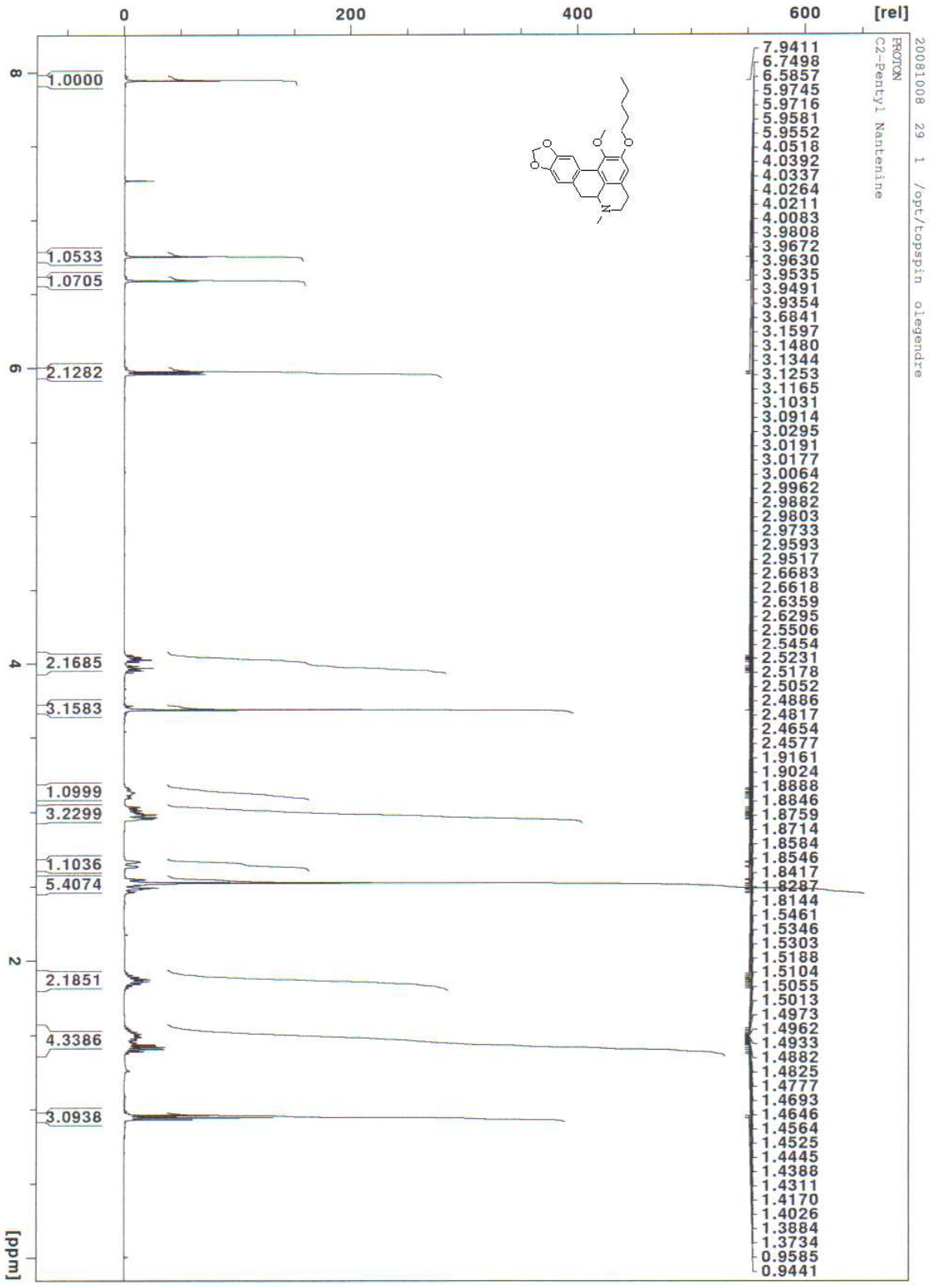
8.0037
1.0598
1.1016
2.1535
0.9794
0.9885
2.1958
3.2340
1.1091
2.1274
1.1372
1.0654
2.4855
15.0920
2.5836
3.5311
2.1762
6.7350
6.6179
5.9636
4.6230
4.6026
4.3939
4.0325
4.0270
4.0195
4.0145
4.0017
3.9870
3.9735
3.9597
3.9555
3.6784
2.9290
2.9053
2.8805
2.8490
2.8427
2.8200
2.7954
2.7875
2.7545
2.7273
2.7003
2.6239
2.5941
1.8996
1.8862
1.8733
1.8675
1.8609
1.8549
1.8491
1.8419
1.8365
1.8237
1.8091
1.7967
1.5261
1.5147
1.5071
1.4856
1.4609
1.4531
1.4491
1.4393
1.4256
1.4112
1.3969
1.3826
1.2730
1.2614
1.2524
1.2474
0.9596
0.9514
0.9464
0.9369
0.9225
0.8850
0.8785
0.8713
0.8575
0.8443


0
1
2
3
4
[rel]
CARBON
20081008 22 1 /opt/topspin olegendre
154.8249
151.5851
146.6688
146.5189
145.2098
131.6225
129.7742
127.7322
125.7726
125.4473
111.9001
109.2161
108.4633
101.0398
79.9834
68.8105
60.1221
38.6977
38.6302
38.6009
38.4741
38.4215
38.3693
38.3211
36.2136
35.9089
35.8474
35.7490
35.7119
34.8131
34.6780
31.7517
30.4990
29.2165
28.7131
28.4733
22.8193
22.6096
14.2982
14.2144
140
120
100
80
60
40
20
[ppm]


0
200
400
600
[rel]
8
6
4
2
[ppm]
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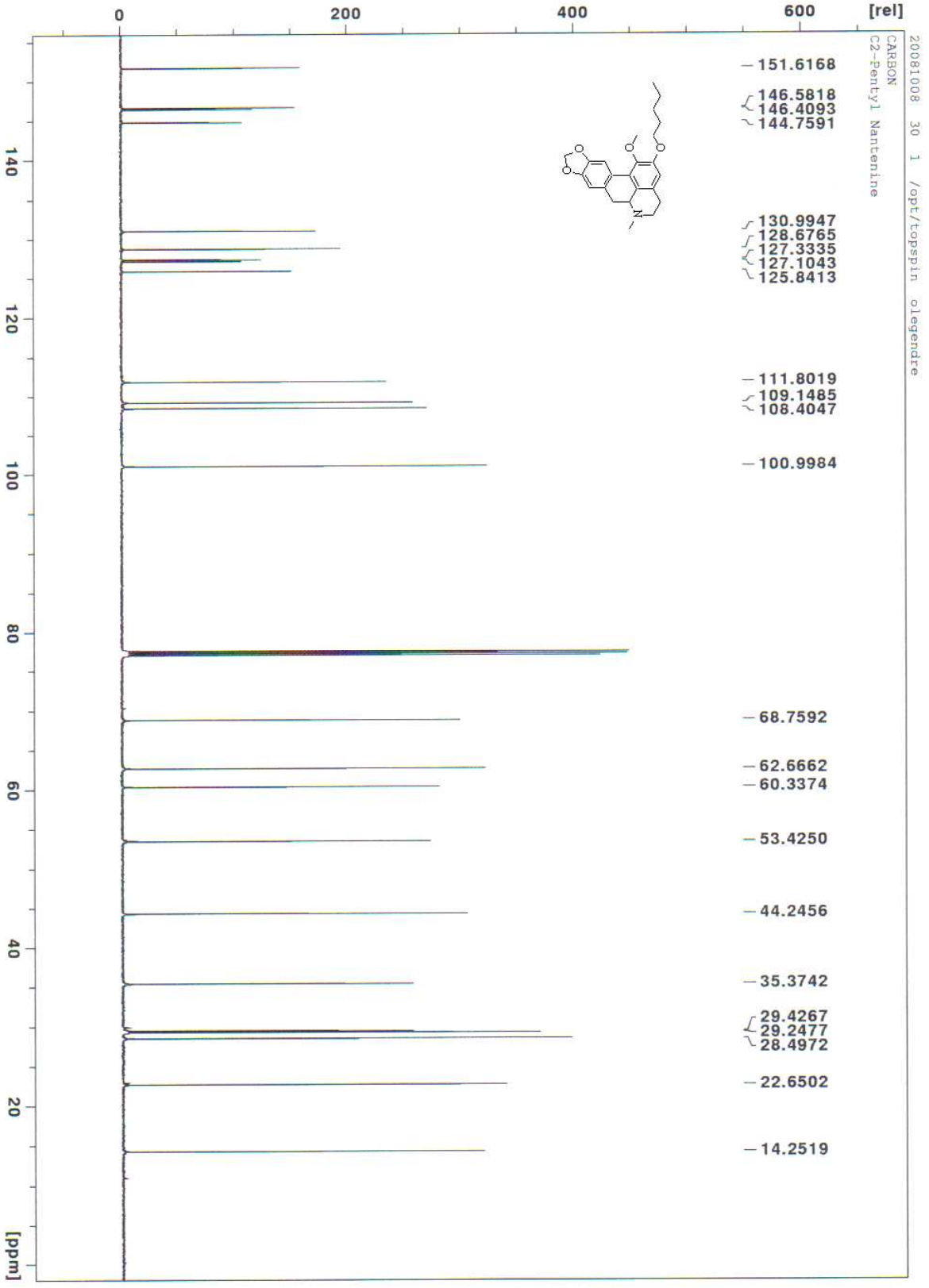
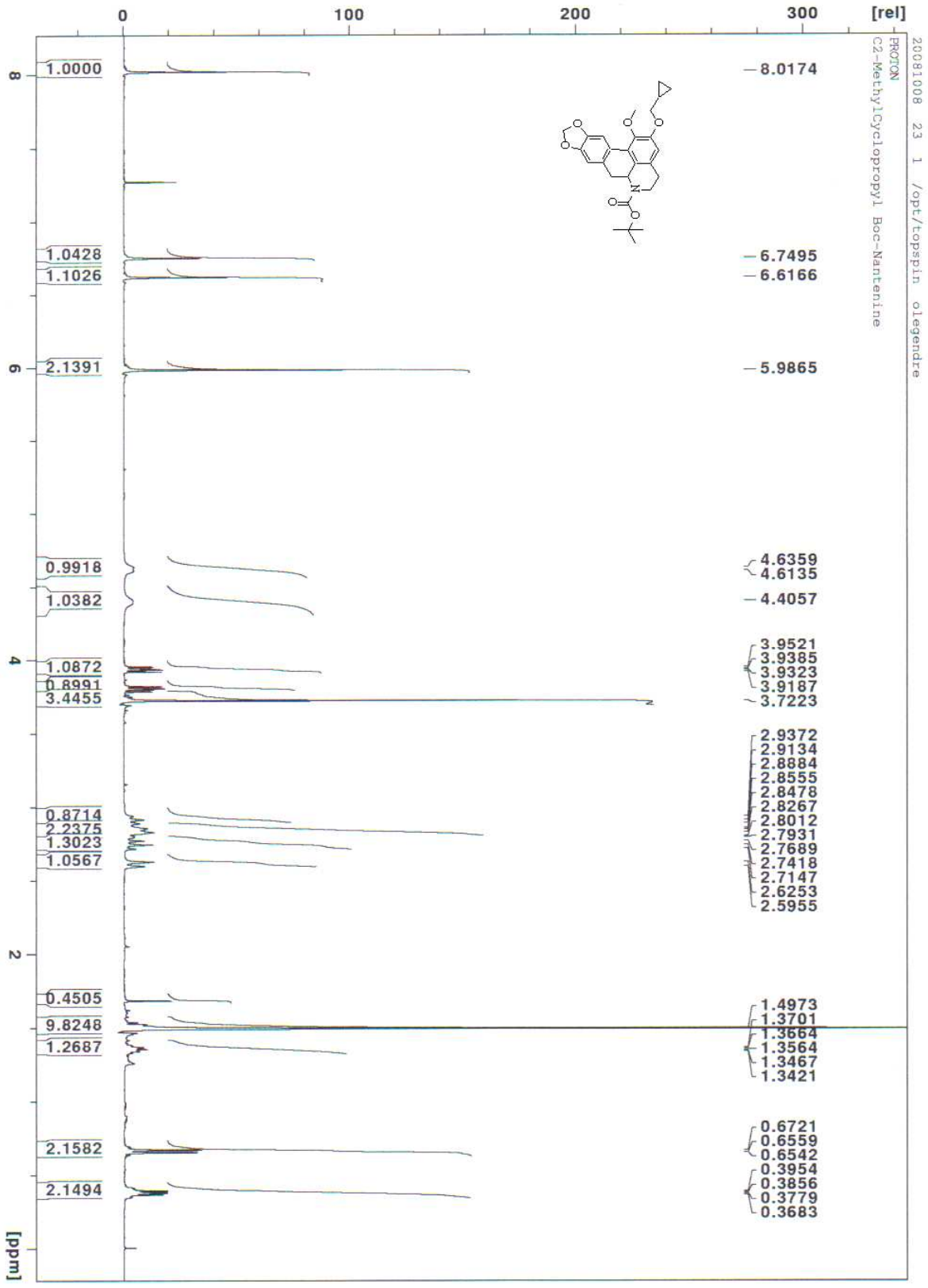
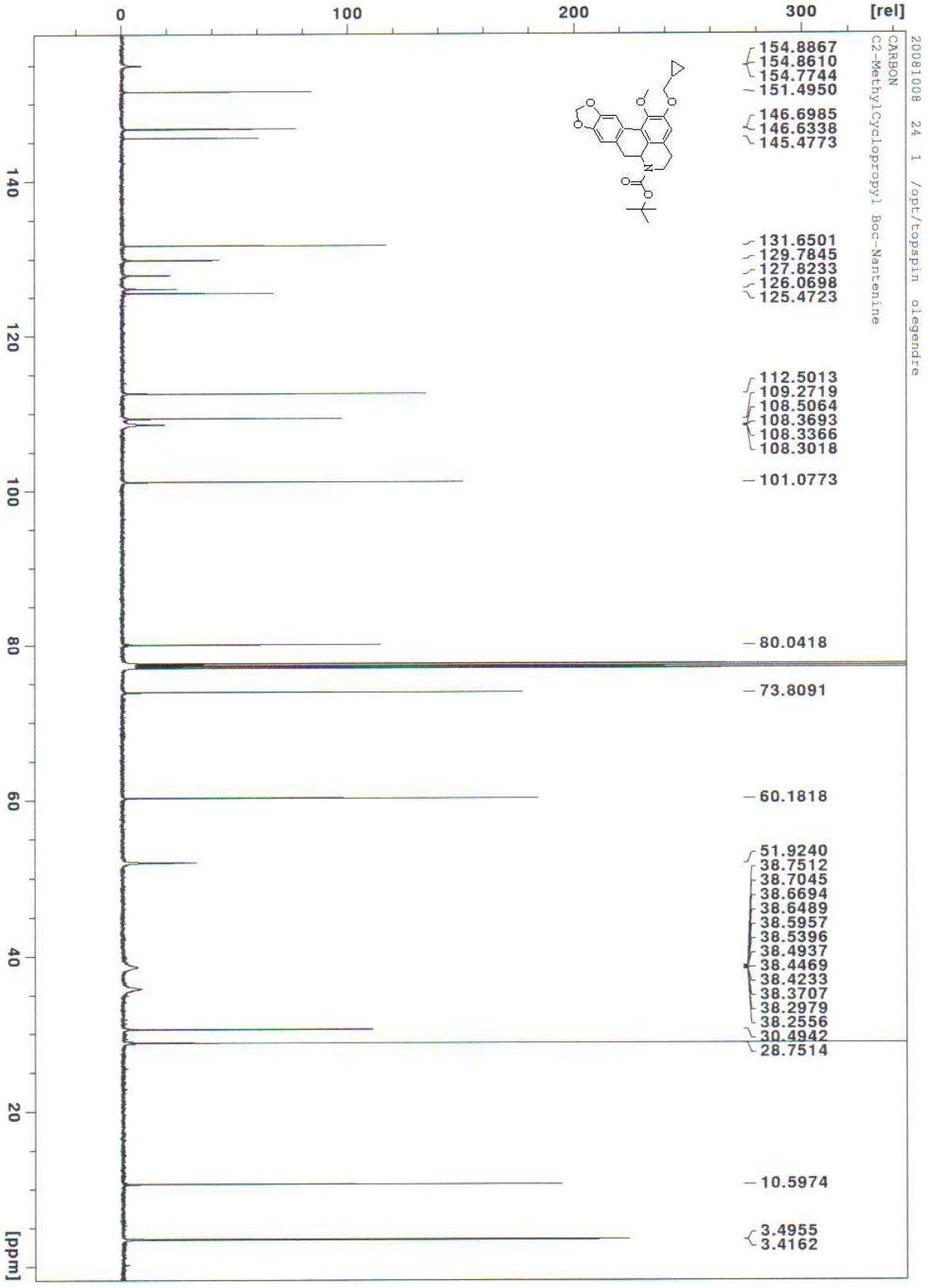
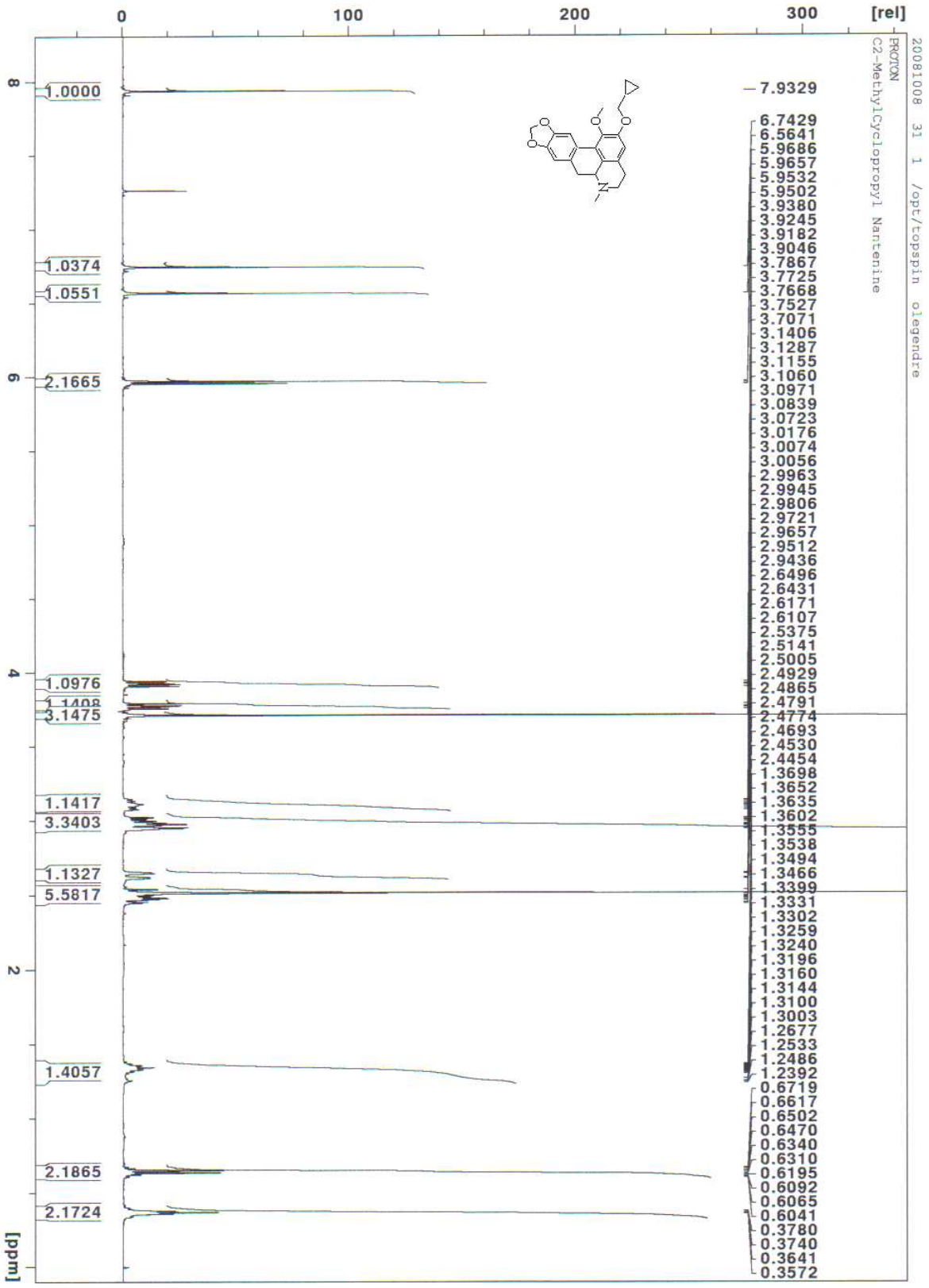
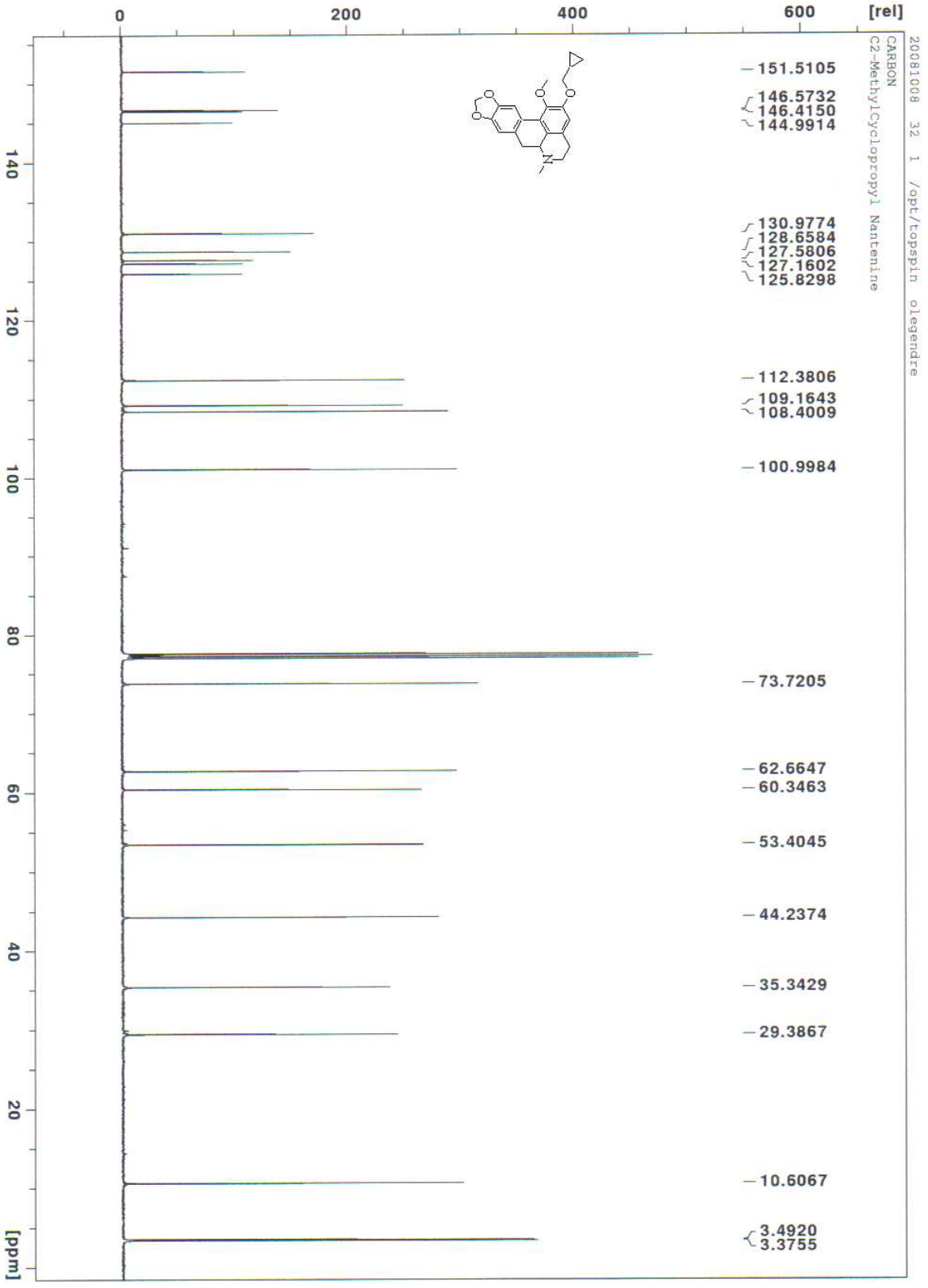
1.0533
1.0705
2.1282
2.1685
3.1583
1.0999
3.2299
1.1036
5.4074
2.1851
4.3386
3.0938
7.9411
6.7498
6.5857
5.9745
5.9716
5.9581
5.9552
4.0518
4.0392
4.0337
4.0264
4.0211
4.0083
3.9808
3.9672
3.9630
3.9535
3.9491
3.9354
3.6841
3.1597
3.1480
3.1344
3.1253
3.1165
3.1031
3.0914
3.0295
3.0191
3.0177
3.0064
2.9962
2.9882
2.9803
2.9733
2.9593
2.9517
2.6683
2.6618
2.6359
2.6295
2.5506
2.5454
2.5231
2.5178
2.5052
2.4886
2.4817
2.4654
2.4577
1.9161
1.9024
1.8888
1.8846
1.8759
1.8714
1.8584
1.8546
1.8417
1.8287
1.8144
1.5461
1.5346
1.5303
1.5188
1.5104
1.5055
1.5013
1.4973
1.4962
1.4933
1.4882
1.4825
1.4777
1.4693
1.4646
1.4564
1.4525
1.4445
1.4388
1.4311
1.4170
1.4026
1.3884
1.3734
0.9585
0.9441
PROTON
C2-Pentyl Nantenine
20081008 29 1 /opt/topspin olegendre


0
200
400
600
[rel]
140
120
100
80
60
40
20
[ppm]
151.6168
146.5818
146.4093
144.7591
130.9947
128.6765
127.3335
127.1043
125.8413
111.8019
109.1485
108.4047
100.9984
68.7592
62.6662
60.3374
53.4250
44.2456
35.3742
29.4267
29.2477
28.4972
22.6502
14.2519
CARBON
C2-Pentyl Nantenine
20081008 30 1 /opt/topspin olegendre

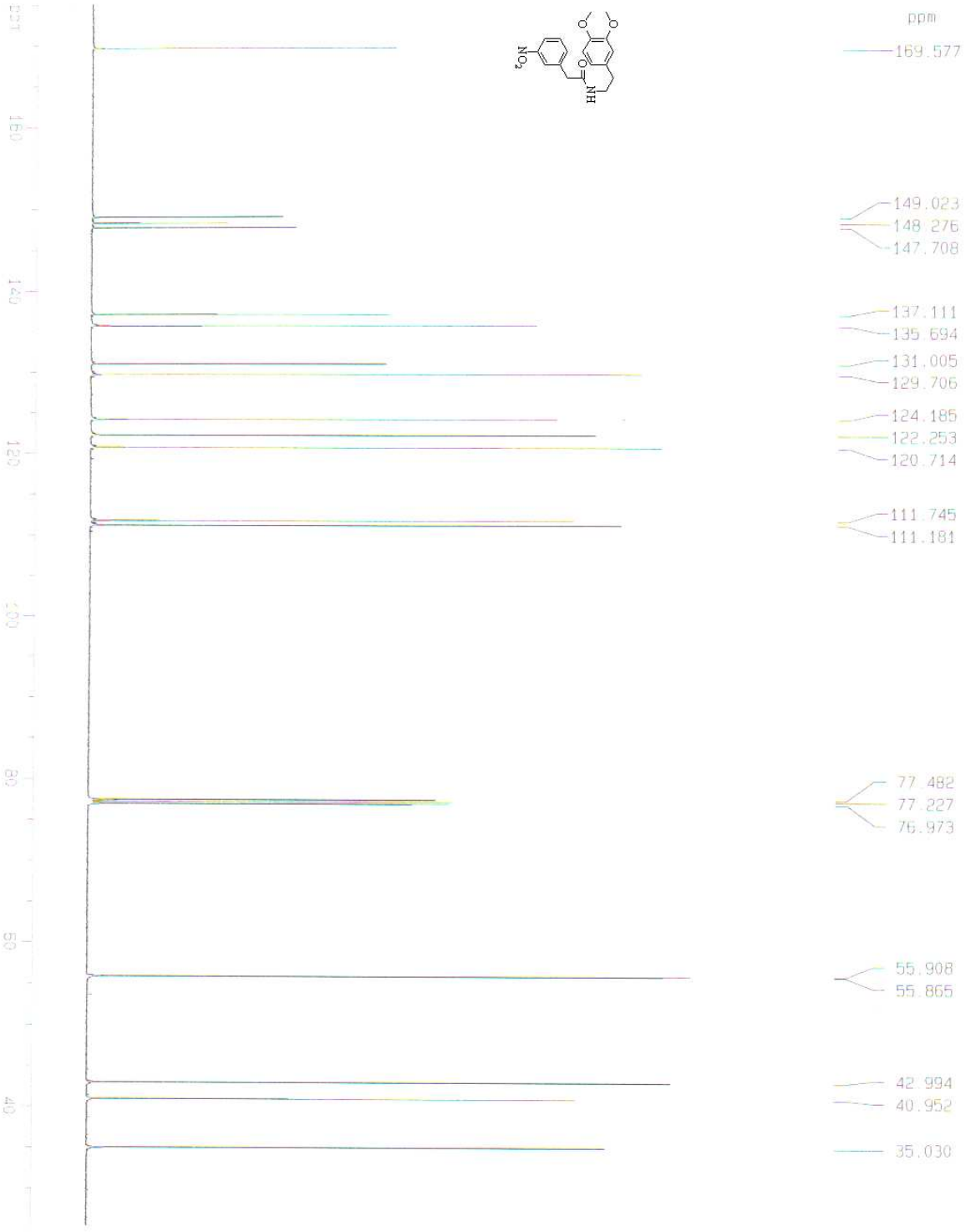

0
100
200
300
[rel]
8
6
4
2
[ppm]
PROTON
C2-MethylCyclopropyl Boc-Nantenine
20081008 23 1 /opt/topspin olegendre
1.0000
1.0428
1.1026
2.1391
0.9918
1.0382
1.0872
0.8991
3.4455
0.8714
2.2375
1.3023
1.0567
0.4505
9.8248
1.2687
2.1582
2.1494
8.0174
6.7495
6.6166
5.9865
4.6359
4.6135
4.4057
3.9521
3.9385
3.9323
3.9187
3.7223
2.9372
2.9134
2.8884
2.8555
2.8478
2.8267
2.8012
2.7931
2.7689
2.7418
2.7147
2.6253
2.5955
1.4973
1.3701
1.3664
1.3564
1.3467
1.3421
0.6721
0.6559
0.6542
0.3954
0.3856
0.3779
0.3683


0
100
200
300
[rel]
140
120
100
80
60
40
20
[ppm]
CARBON
C2-MethylCyclopropyl Boc-Nantenine
20081008 24 1 /opt/topspin olegendre
154.8867
154.8610
154.7744
151.4950
146.6985
146.6338
145.4773
131.6501
129.7845
127.8233
126.0698
125.4723
112.5013
109.2719
108.5064
108.3693
108.3366
108.3018
101.0773
80.0418
73.8091
60.1818
51.9240
38.7512
38.7045
38.6694
38.6489
38.5957
38.5396
38.4937
38.4469
38.4233
38.3707
38.2979
38.2556
30.4942
28.7514
10.5974
3.4955
3.4162


0
100
200
300
[rel]
PROTON
C2-MethylCyclopropyl Nantenine
20081008 31 1 /opt/topspin olegendre
8
6
4
2
[ppm]
1.0000
1.0374
1.0551
2.1665
1.0976
3.1475
1.1417
3.3403
1.1327
5.5817
1.4057
2.1865
2.1724
7.9329
6.7429
6.5641
5.9686
5.9657
5.9532
5.9502
3.9380
3.9245
3.9182
3.9046
3.7867
3.7725
3.7668
3.7527
3.7071
3.1406
3.1287
3.1155
3.1060
3.0971
3.0839
3.0723
3.0176
3.0074
3.0056
2.9963
2.9945
2.9806
2.9721
2.9657
2.9512
2.9436
2.6496
2.6431
2.6171
2.6107
2.5375
2.5141
2.5005
2.4929
2.4865
2.4791
2.4774
2.4693
2.4530
2.4454
1.3698
1.3652
1.3635
1.3602
1.3555
1.3538
1.3494
1.3466
1.3399
1.3331
1.3302
1.3259
1.3240
1.3196
1.3160
1.3144
1.3100
1.3003
1.2677
1.2533
1.2486
1.2392
0.6719
0.6617
0.6502
0.6470
0.6340
0.6310
0.6195
0.6092
0.6065
0.6041
0.3780
0.3740
0.3641
0.3572


0
200
400
600
[rel]
140
120
100
80
60
40
20
[ppm]
151.5105
146.5732
146.4150
144.9914
130.9774
128.6584
127.5806
127.1602
125.8298
112.3806
109.1643
108.4009
100.9984
73.7205
62.6647
60.3463
53.4045
44.2374
35.3429
29.3867
10.6067
3.4920
3.3755
CARBON
C2-Methylcyclopropyl Nantenine
20081008 32 1 /opt/topspin olegendre


Integral
1.9542
0.9932
1.0216
1.0414
1.0141
1.0206
1.0000
3.1517
2.9945
2.0061
2.0636
2.0539
ppm
8.08736
8.07115
8.06933
8.06067
8.05730
8.05375
7.57257
7.55727
7.47501
7.45917
7.44350
6.71733
6.70106
6.63388
6.63000
6.59666
6.59274
6.58046
5.94393
3.80884
3.78895
3.56140
3.49240
3.47854
3.46659
3.45286
2.72737
2.71345
2.69949


ppm
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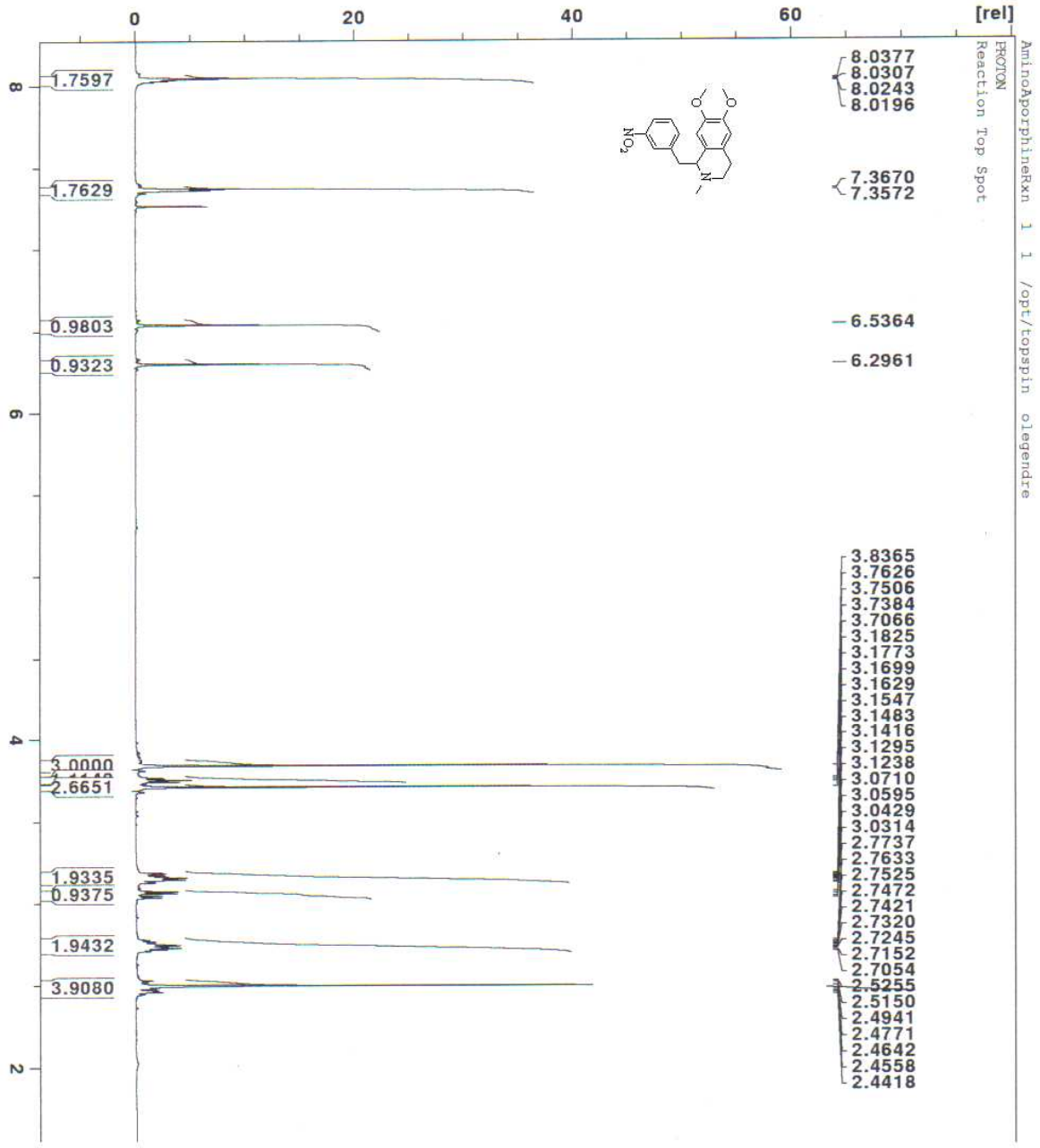
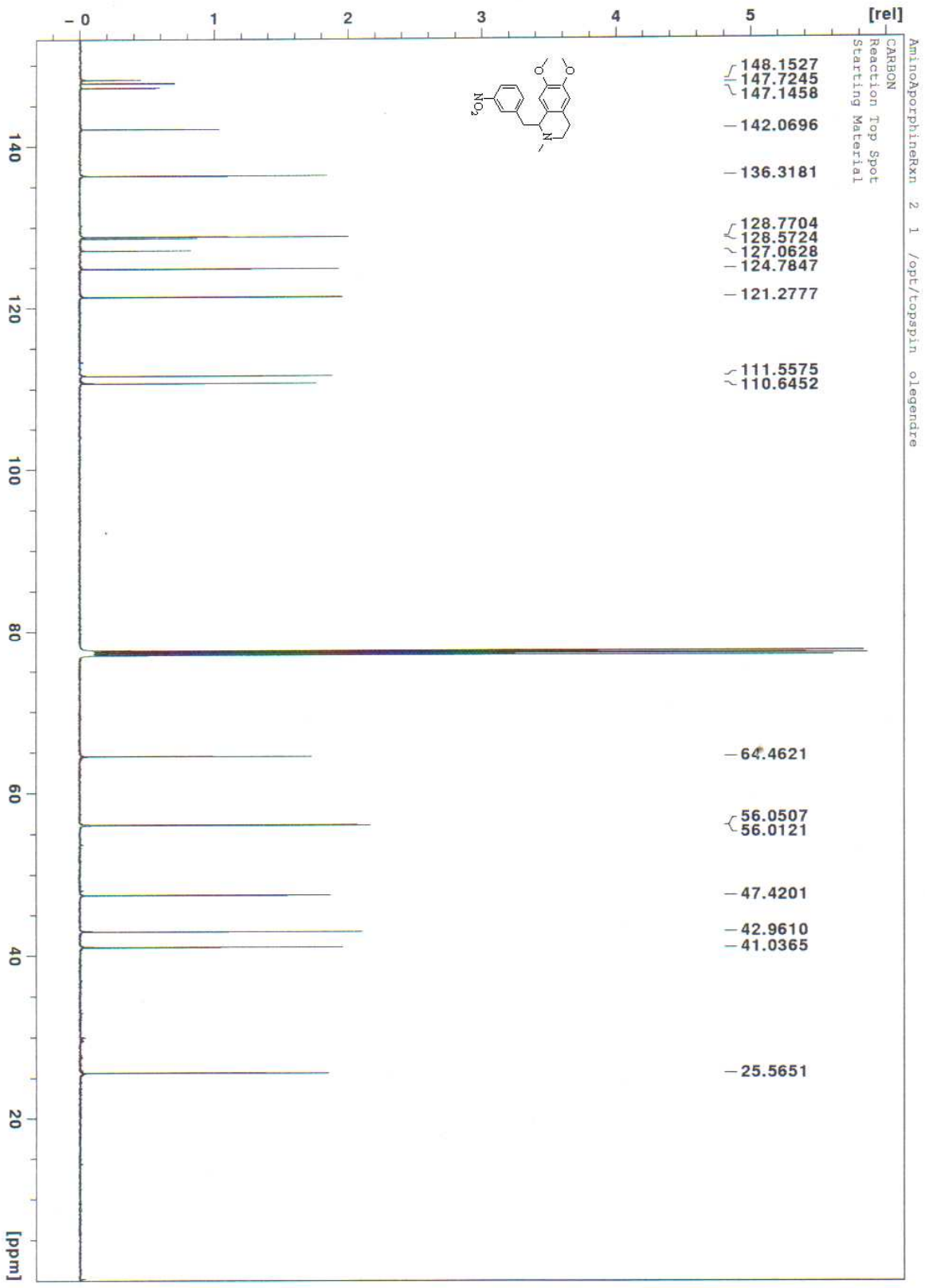
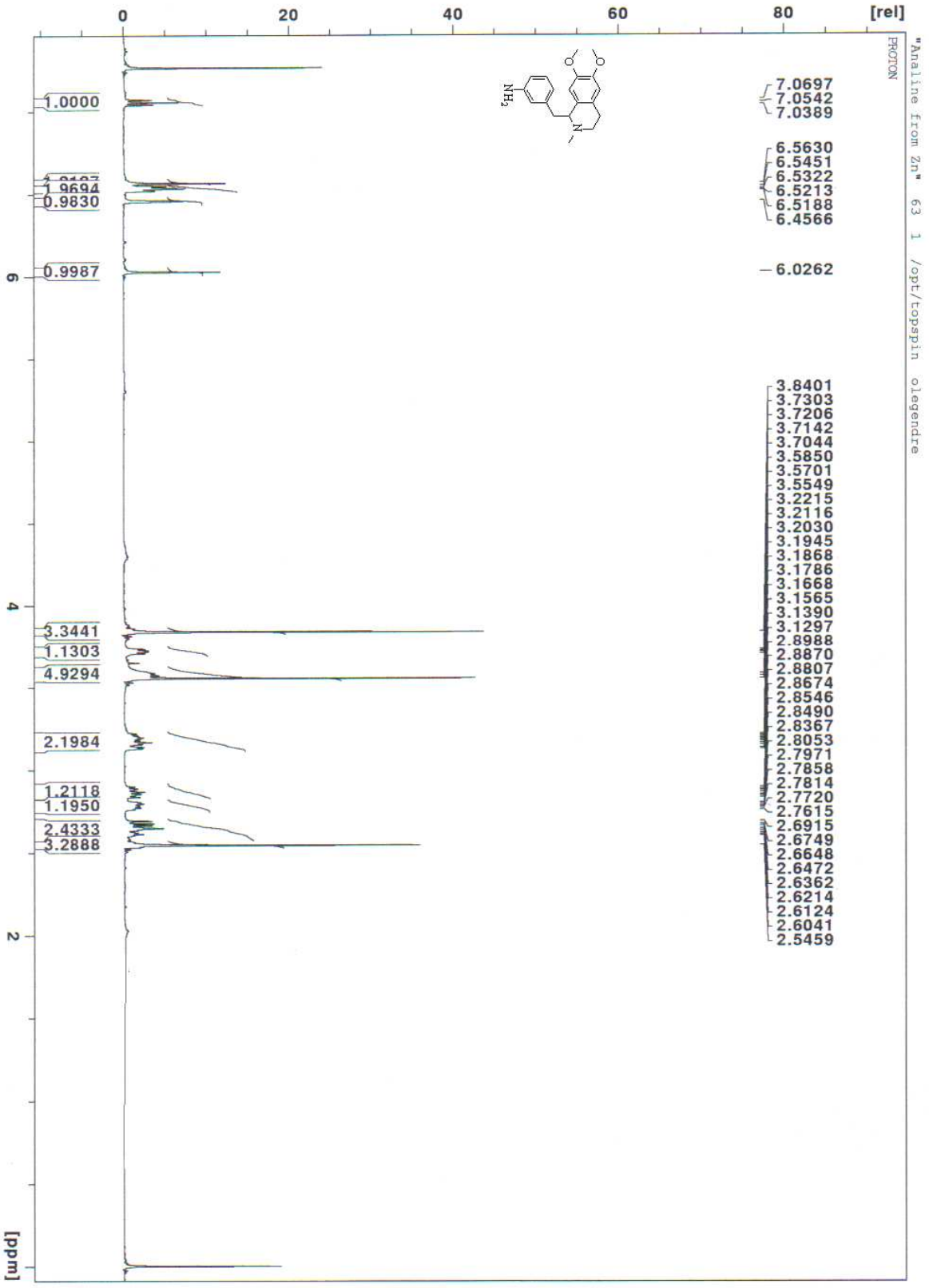
148.276
147.708
137.111
135.694
131.005
129.706
124.185
122.253
120.714
111.745
111.181
77.482
77.227
76.973
55.908
55.865
42.994
40.952
35.030


0
20
40
60
[rel]
8
6
4
2
1.7597
1.7629
0.9803
0.9323
3.0000
2.6651
1.9335
0.9375
1.9432
3.9080
8.0377
8.0307
8.0243
8.0196
7.3670
7.3572
6.5364
6.2961
3.8365
3.7626
3.7506
3.7384
3.7066
3.1825
3.1773
3.1699
3.1629
3.1547
3.1483
3.1416
3.1295
3.1238
3.0710
3.0595
3.0429
3.0314
2.7737
2.7633
2.7525
2.7472
2.7421
2.7320
2.7245
2.7152
2.7054
2.5255
2.5150
2.4941
2.4771
2.4642
2.4558
2.4418
PROTON
Reaction Top Spot
AminoAporphineRxn 1 1 /opt/topspin olegendre


[rel]
[ppm]
148.1527
147.7245
147.1458
142.0696
136.3181
128.7704
128.5724
127.0628
124.7847
121.2777
111.5575
110.6452
64.4621
56.0507
56.0121
47.4201
42.9610
41.0365
25.5651
CARBON
Reaction Top Spot
Starting Material
AminoAporphineRxn 2 1 /opt/topspin olegendre


0
20
40
60
80
[rel]
PROTON
"Analine from Zn" 63 1 /opt/topspin o.legendre
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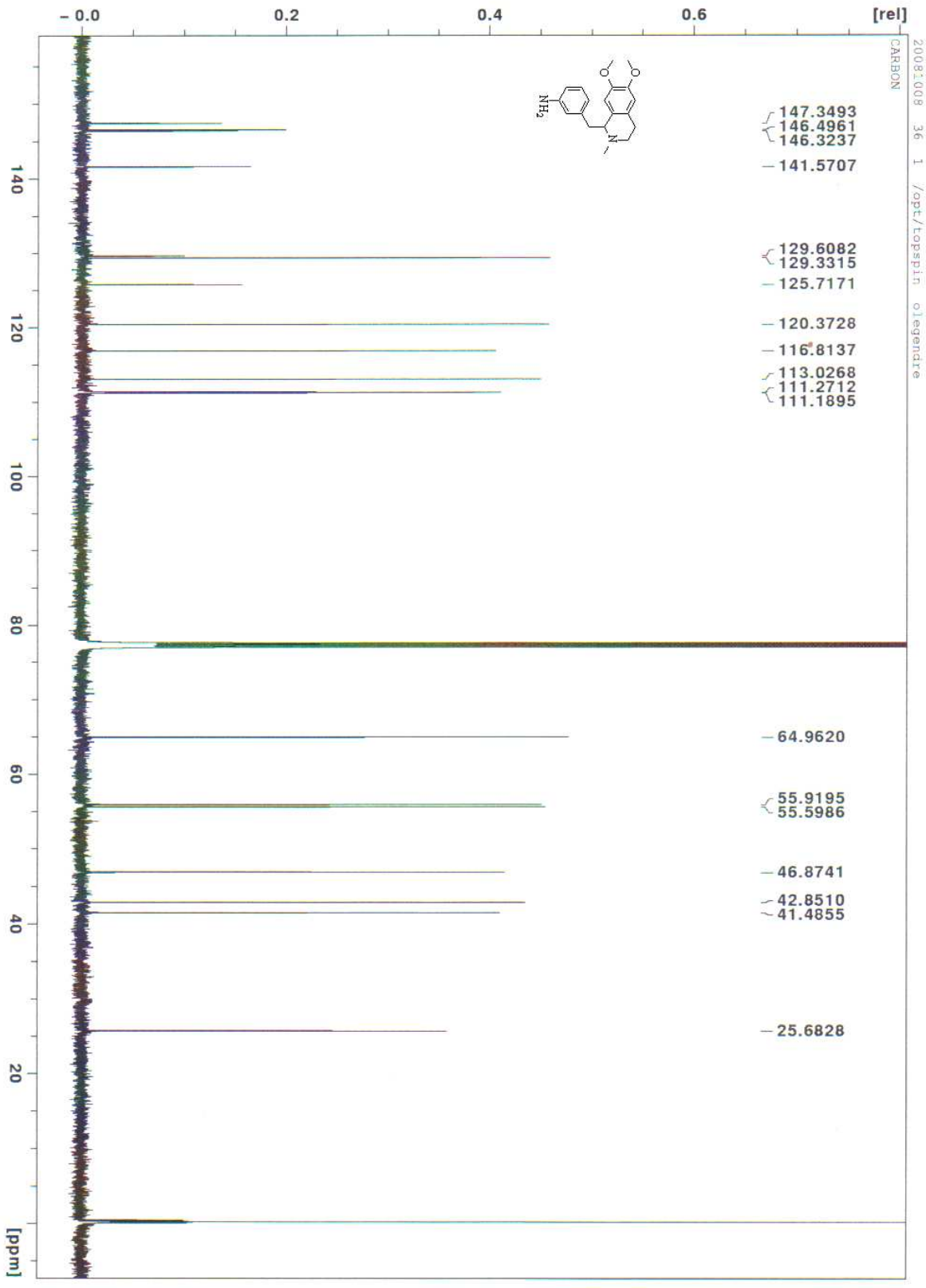
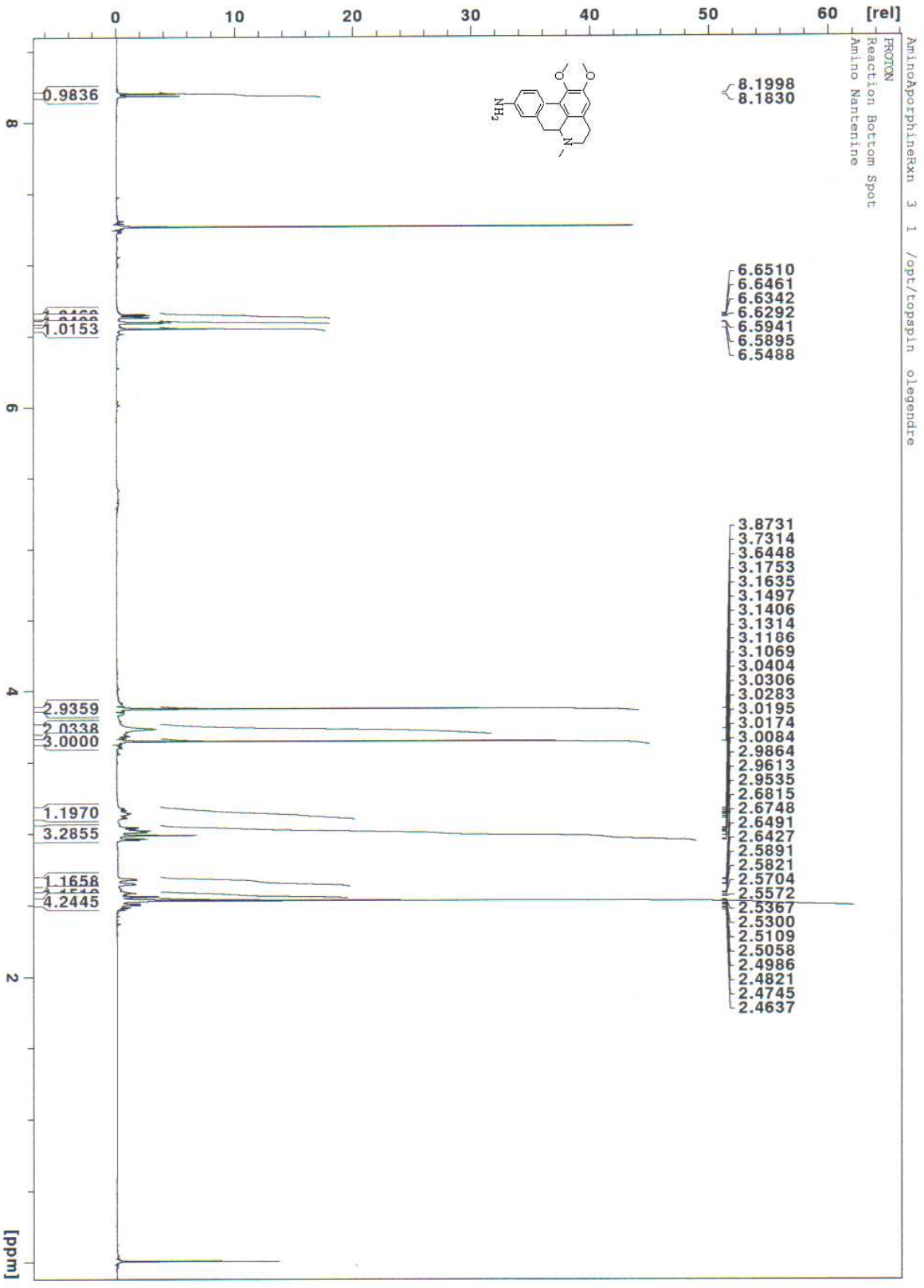
0.9987
3.3441
1.1303
4.9294
2.1984
1.2118
1.1950
2.4333
3.2888
7.0697
7.0542
7.0389
6.5630
6.5451
6.5322
6.5213
6.5188
6.4566
6.0262
3.8401
3.7303
3.7206
3.7142
3.7044
3.5850
3.5701
3.5549
3.2215
3.2116
3.2030
3.1945
3.1868
3.1786
3.1668
3.1565
3.1390
3.1297
2.8988
2.8870
2.8807
2.8674
2.8546
2.8490
2.8367
2.8053
2.7971
2.7858
2.7814
2.7720
2.7615
2.6915
2.6749
2.6648
2.6472
2.6362
2.6214
2.6124
2.6041
2.5459
6
4
2
[ppm]


– 0.0
0.2
0.4
0.6
[rel]
CARBON
20081008 36 1 /opt/topspin olegendre
147.3493
146.4961
146.3237
141.5707
129.6082
129.3315
125.7171
120.3728
116.8137
113.0268
111.2712
111.1895
64.9620
55.9195
55.5986
46.8741
42.8510
41.4855
25.6828
140
120
100
80
60
40
20
[ppm]


0
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40
50
60
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8
6
4
2
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Reaction Bottom Spot
Amino Nantenine
AminoAporphineRxn 3 1 /opt/topspin olegendre
0.9836
1.0153
2.9359
2.0338
3.0000
1.1970
3.2855
1.1658
4.2445
8.1998
8.1830
6.6510
6.6461
6.6342
6.6292
6.5941
6.5895
6.5488
3.8731
3.7314
3.6448
3.1753
3.1635
3.1497
3.1406
3.1314
3.1186
3.1069
3.0404
3.0306
3.0283
3.0195
3.0174
3.0084
2.9864
2.9613
2.9535
2.6815
2.6748
2.6491
2.6427
2.5891
2.5821
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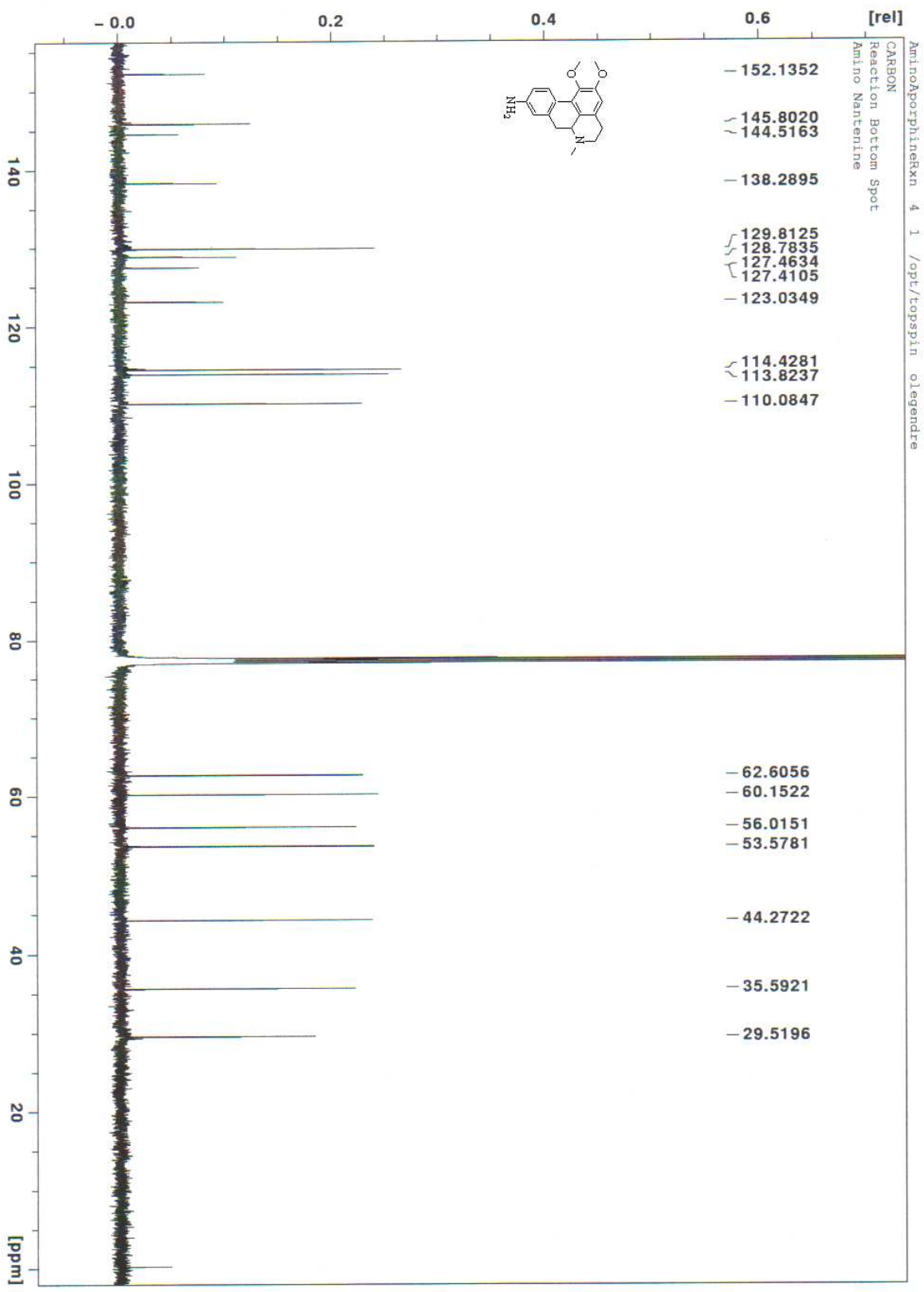
2.5058
2.4986
2.4821
2.4745
2.4637


– 0.0
0.2
0.4
0.6
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AminoAporphineRxn 4 1 /opt/topspin olegendre
CARBON
Reaction Bottom Spot
Amino Nantenine
152.1352
145.8020
144.5163
138.2895
129.8125
128.7835
127.4634
127.4105
123.0349
114.4281
113.8237
110.0847
62.6056
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56.0151
53.5781
44.2722
35.5921
29.5196
140
120
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40
20
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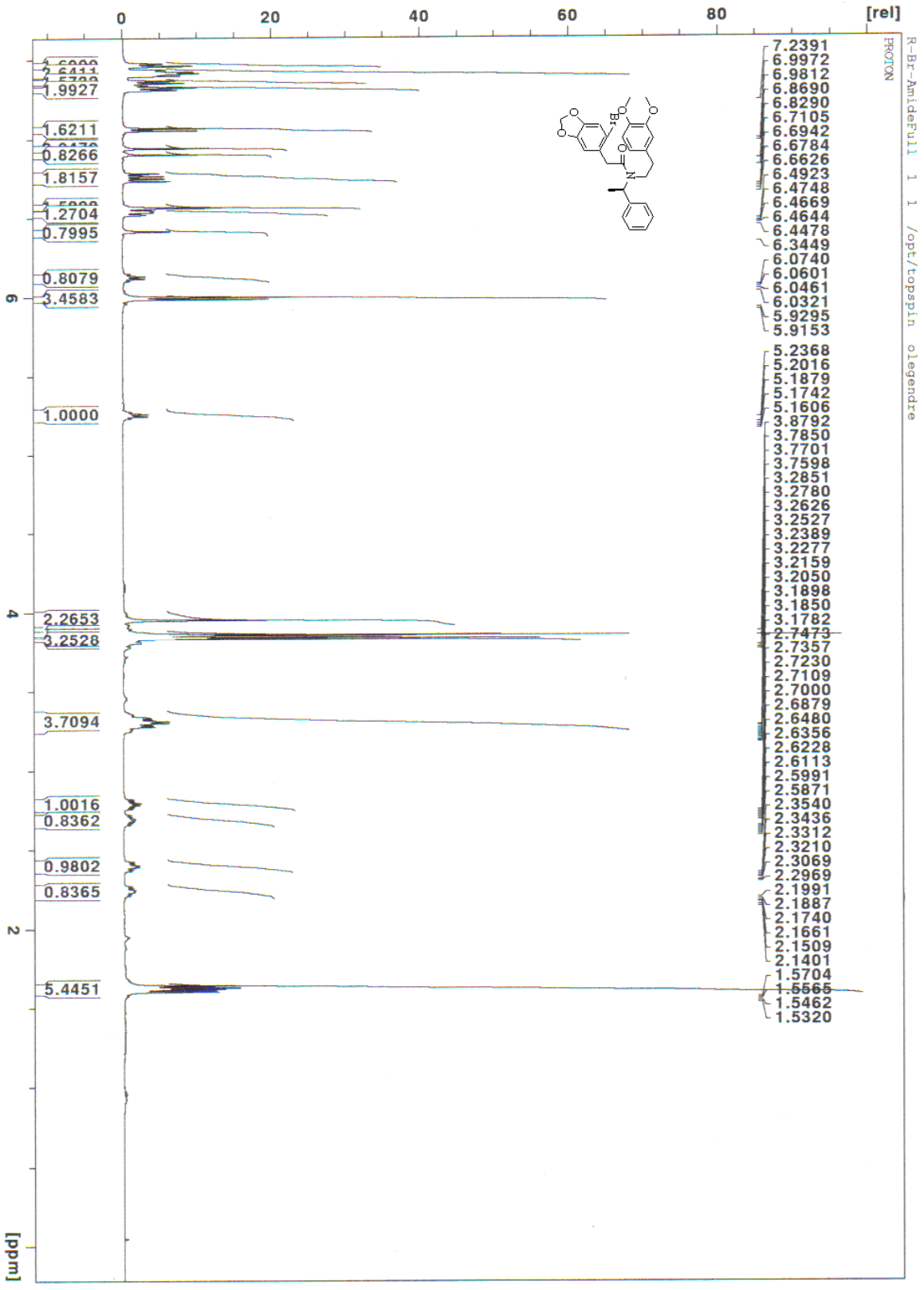
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R-Br-AmideFull 1 1 /opt/topspin olegendre
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0.8079
3.4583
1.0000
2.2653
3.2528
3.7094
1.0016
0.8362
0.9802
0.8365
5.4451
7.2391
6.9972
6.9812
6.8690
6.8290
6.7105
6.6942
6.6784
6.6626
6.4923
6.4748
6.4669
6.4644
6.4478
6.3449
6.0740
6.0601
6.0461
6.0321
5.9295
5.9153
5.2368
5.2016
5.1879
5.1742
5.1606
3.8792
3.7850
3.7701
3.7598
3.2851
3.2780
3.2626
3.2527
3.2389
3.2277
3.2159
3.2050
3.1898
3.1850
3.1782
2.7473
2.7357
2.7230
2.7109
2.7000
2.6879
2.6480
2.6356
2.6228
2.6113
2.5991
2.5871
2.3540
2.3436
2.3312
2.3210
2.3069
2.2969
2.1991
2.1887
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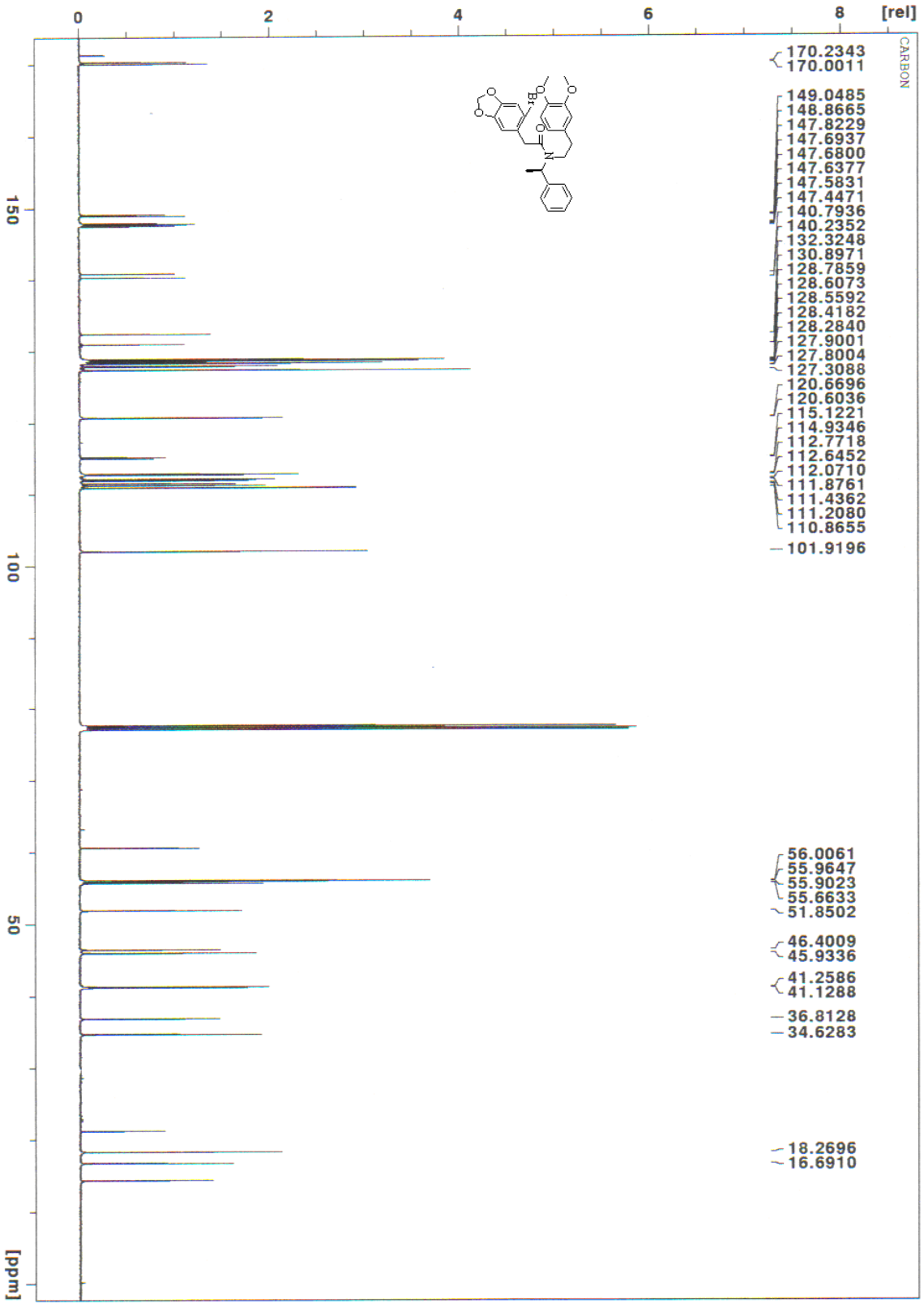
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8
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147.4471
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140.2352
132.3248
130.8971
128.7859
128.6073
128.5592
128.4182
128.2840
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127.8004
127.3088
120.6696
120.6036
115.1221
114.9346
112.7718
112.6452
112.0710
111.8761
111.4362
111.2080
110.8655
101.9196
56.0061
55.9647
55.9023
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41.1288
36.8128
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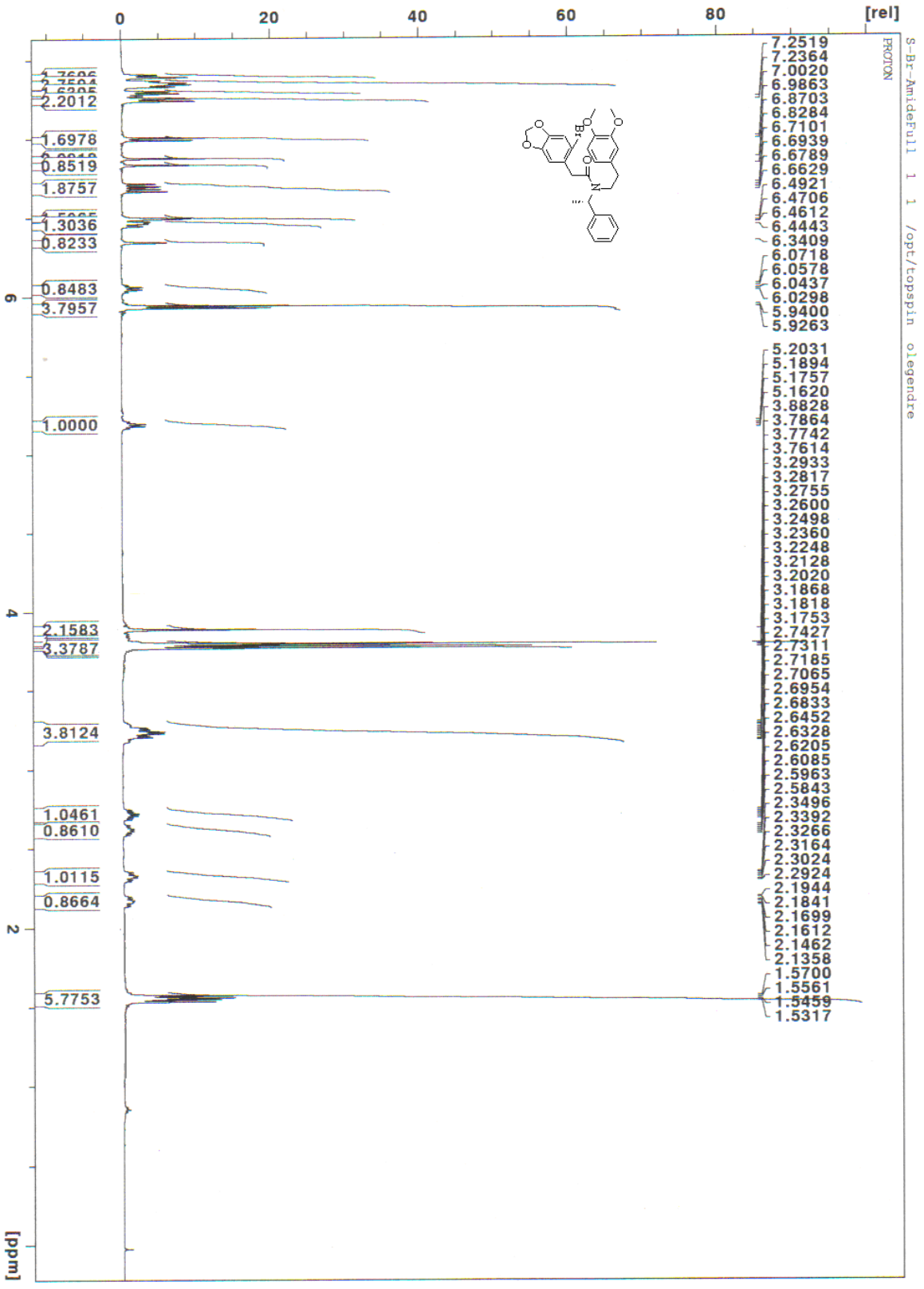
18.2696
16.6910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6.8703
6.8284
6.7101
6.6939
6.6789
6.6629
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6.4706
6.4612
6.4443
6.3409
6.0718
6.0578
6.0437
6.0298
5.9400
5.9263
5.2031
5.1894
5.1757
5.1620
3.8828
3.7864
3.7742
3.7614
3.2933
3.2817
3.2755
3.2600
3.2498
3.2360
3.2248
3.2128
3.2020
3.1868
3.1818
3.1753
2.7427
2.7311
2.7185
2.7065
2.6954
2.6833
2.6452
2.6328
2.6205
2.6085
2.5963
2.5843
2.3496
2.3392
2.3266
2.3164
2.3024
2.2924
2.1944
2.1841
2.1699
2.1612
2.1462
2.1358
1.5700
1.5561
1.5459
1.5317
2.2012
1.6978
0.8519
1.8757
1.3036
0.8233
0.8483
3.7957
1.0000
2.1583
3.3787
3.8124
1.0461
0.8610
1.0115
0.8664
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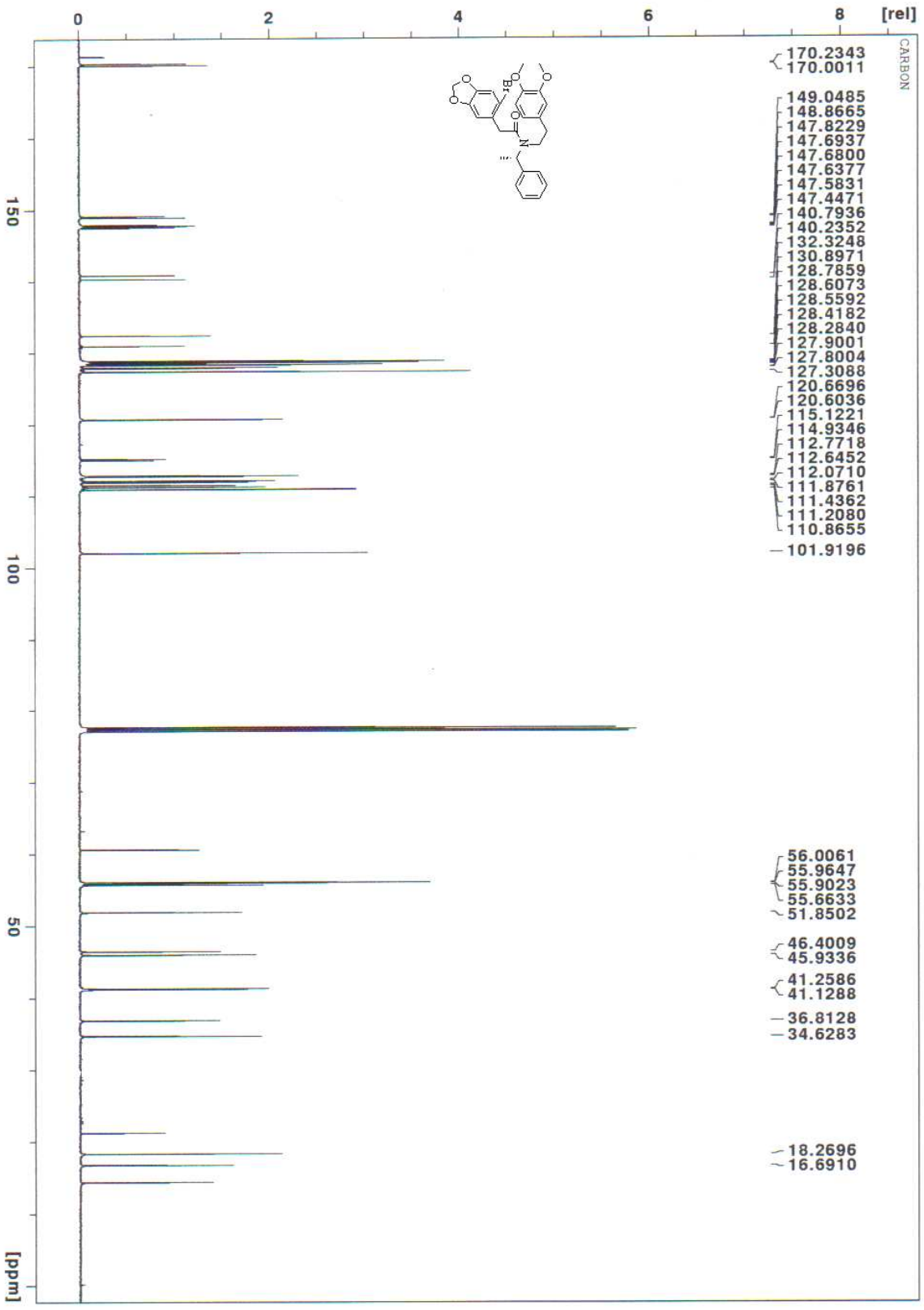
6
4
2
[ppm]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4
6
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100
50
[ppm]
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170.0011
149.0485
148.8665
147.8229
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147.6800
147.6377
147.5831
147.4471
140.7936
140.2352
132.3248
130.8971
128.7859
128.6073
128.5592
128.4182
128.2840
127.9001
127.8004
127.3088
120.6696
120.6036
115.1221
114.9346
112.7718
112.6452
112.0710
111.8761
111.4362
111.2080
110.8655
101.9196
56.0061
55.9647
55.9023
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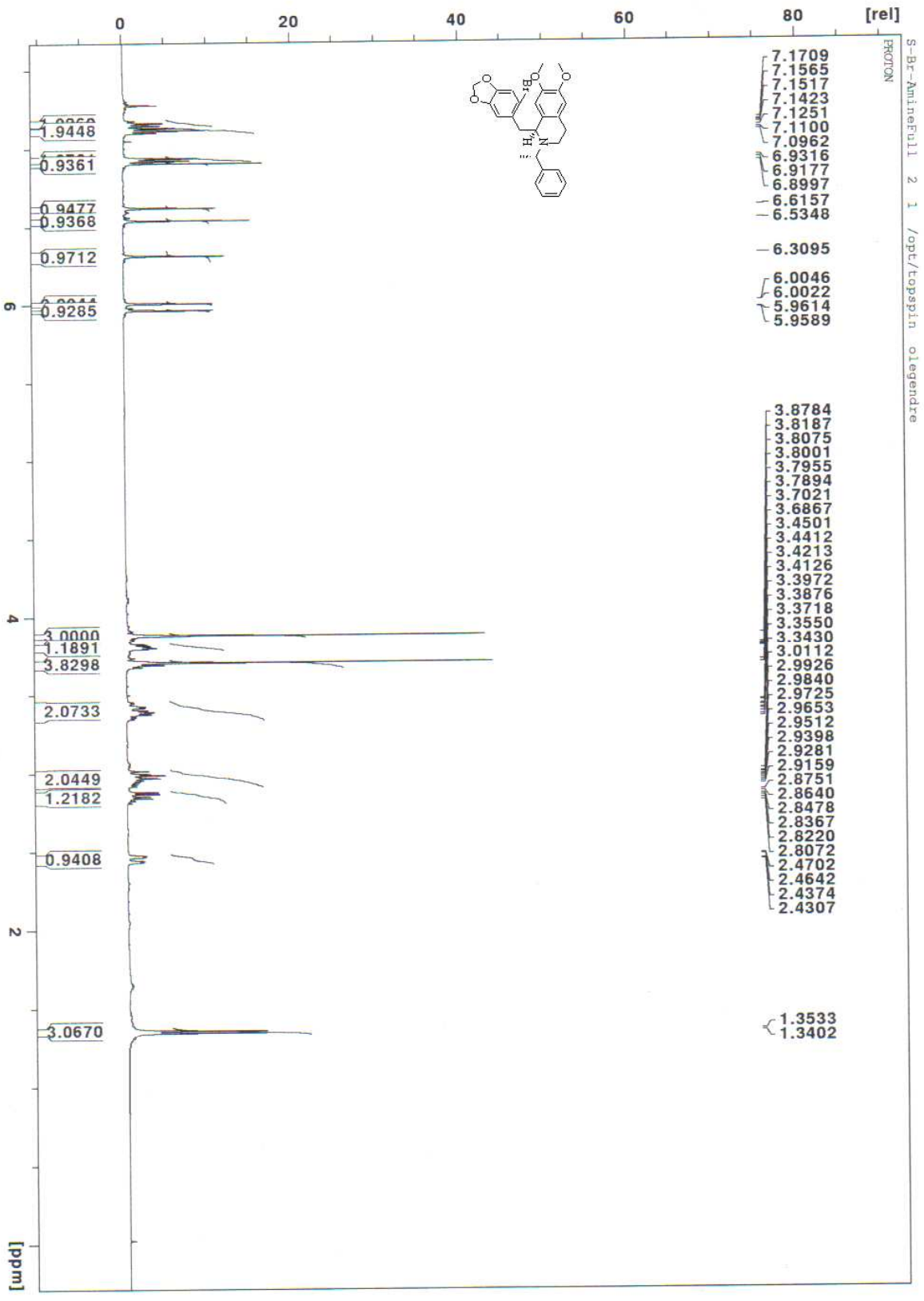
51.8502
46.4009
45.9336
41.2586
41.1288
36.8128
34.6283
18.2696
16.6910


0
20
40
60
80
[rel]
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S-Br-AmineFull 2 1 /opt/topspin olegendre
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7.1517
7.1423
7.1251
7.1100
7.0962
6.9316
6.9177
6.8997
6.6157
6.5348
6.3095
6.0046
6.0022
5.9614
5.9589
3.8784
3.8187
3.8075
3.8001
3.7955
3.7894
3.7021
3.6867
3.4501
3.4412
3.4213
3.4126
3.3972
3.3876
3.3718
3.3550
3.3430
3.0112
2.9926
2.9840
2.9725
2.9653
2.9512
2.9398
2.9281
2.9159
2.8751
2.8640
2.8478
2.8367
2.8220
2.8072
2.4702
2.4642
2.4374
2.4307
1.3533
1.3402
1.9448
0.9361
0.9477
0.9368
0.9712
0.9285
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2.0449
1.2182
0.9408
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6
4
2
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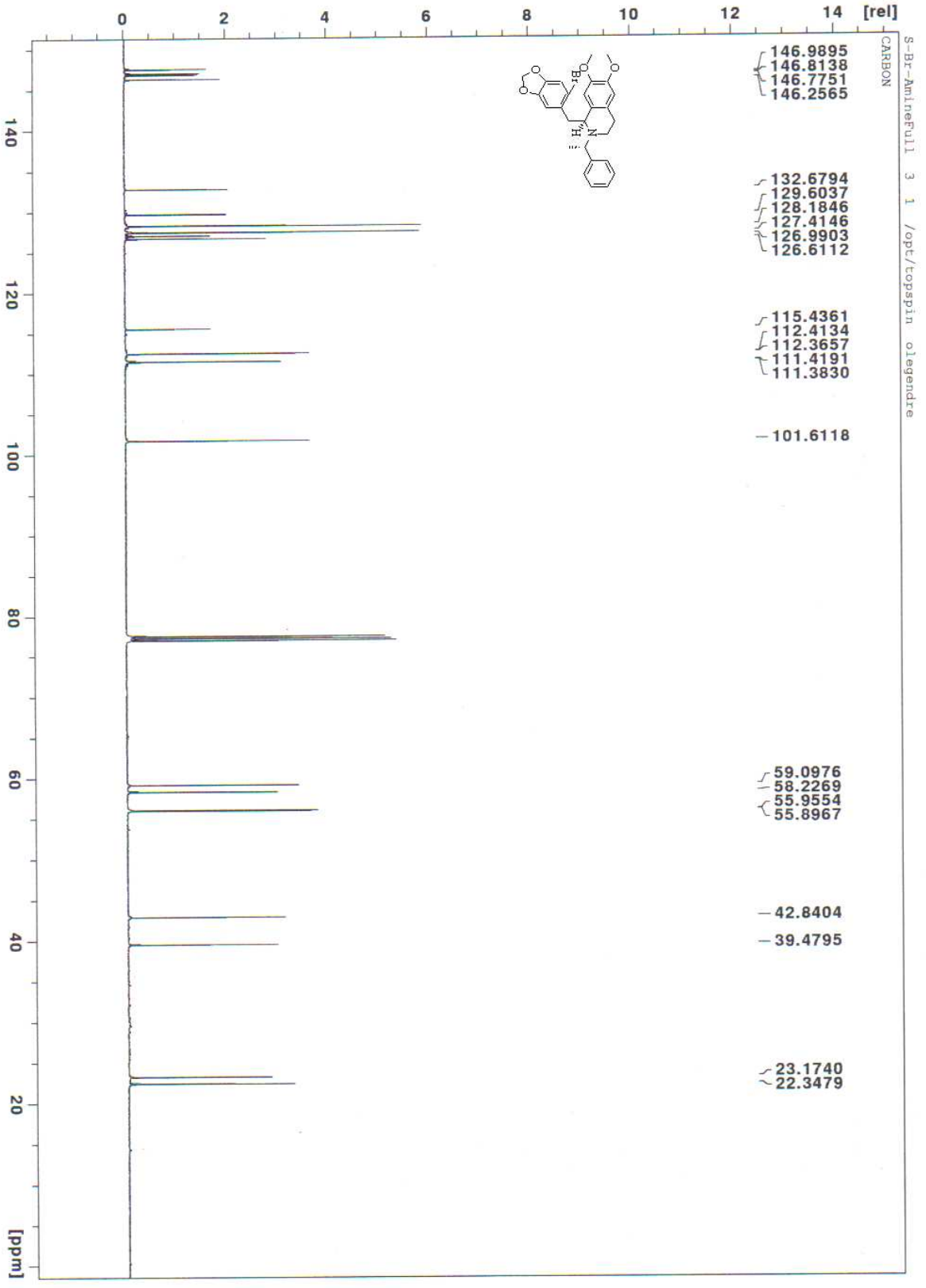
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2
4
6
8
10
12
14
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140
120
100
80
60
40
20
[ppm]
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S-Br-AmineFull 3 1 /opt/topspin olegendre
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146.2565
132.6794
129.6037
128.1846
127.4146
126.9903
126.6112
115.4361
112.4134
112.3657
111.4191
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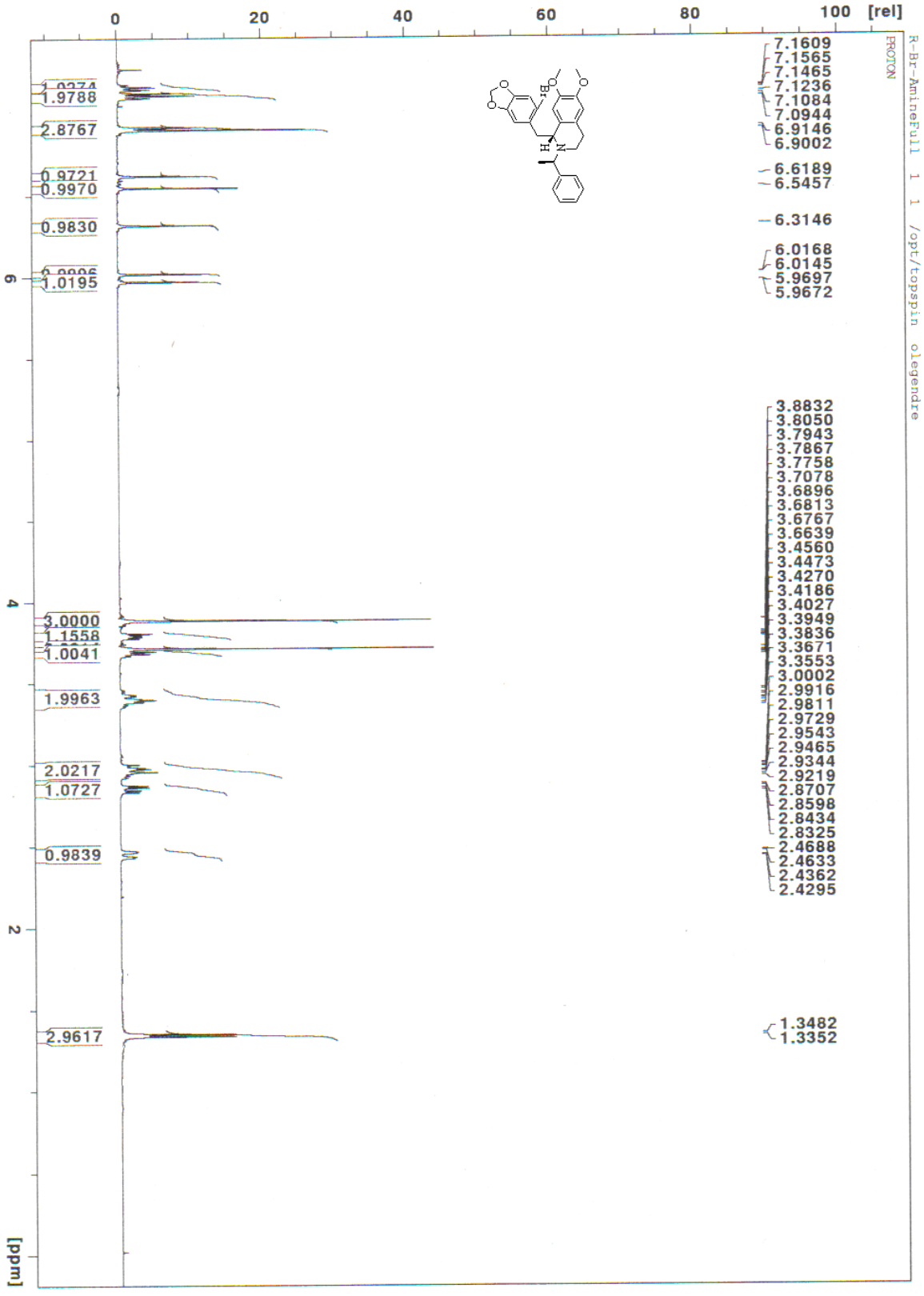
58.2269
55.9554
55.8967
42.8404
39.4795
23.1740
22.3479


0
20
40
60
80
100
[rel]
PROTON
R-Br-AmineFull 1 1 /opt/topspin olegendre
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7.1565
7.1465
7.1236
7.1084
7.0944
6.9146
6.9002
6.6189
6.5457
6.3146
6.0168
6.0145
5.9697
5.9672
3.8832
3.8050
3.7943
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3.7758
3.7078
3.6896
3.6813
3.6767
3.6639
3.4560
3.4473
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3.4186
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3.3553
3.0002
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2.9811
2.9729
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2.9465
2.9344
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2.8707
2.8598
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2.8325
2.4688
2.4633
2.4362
2.4295
1.3482
1.3352
1.9788
2.8767
0.9721
0.9970
0.9830
1.0195
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1.0041
1.9963
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1.0727
0.9839
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6
4
2
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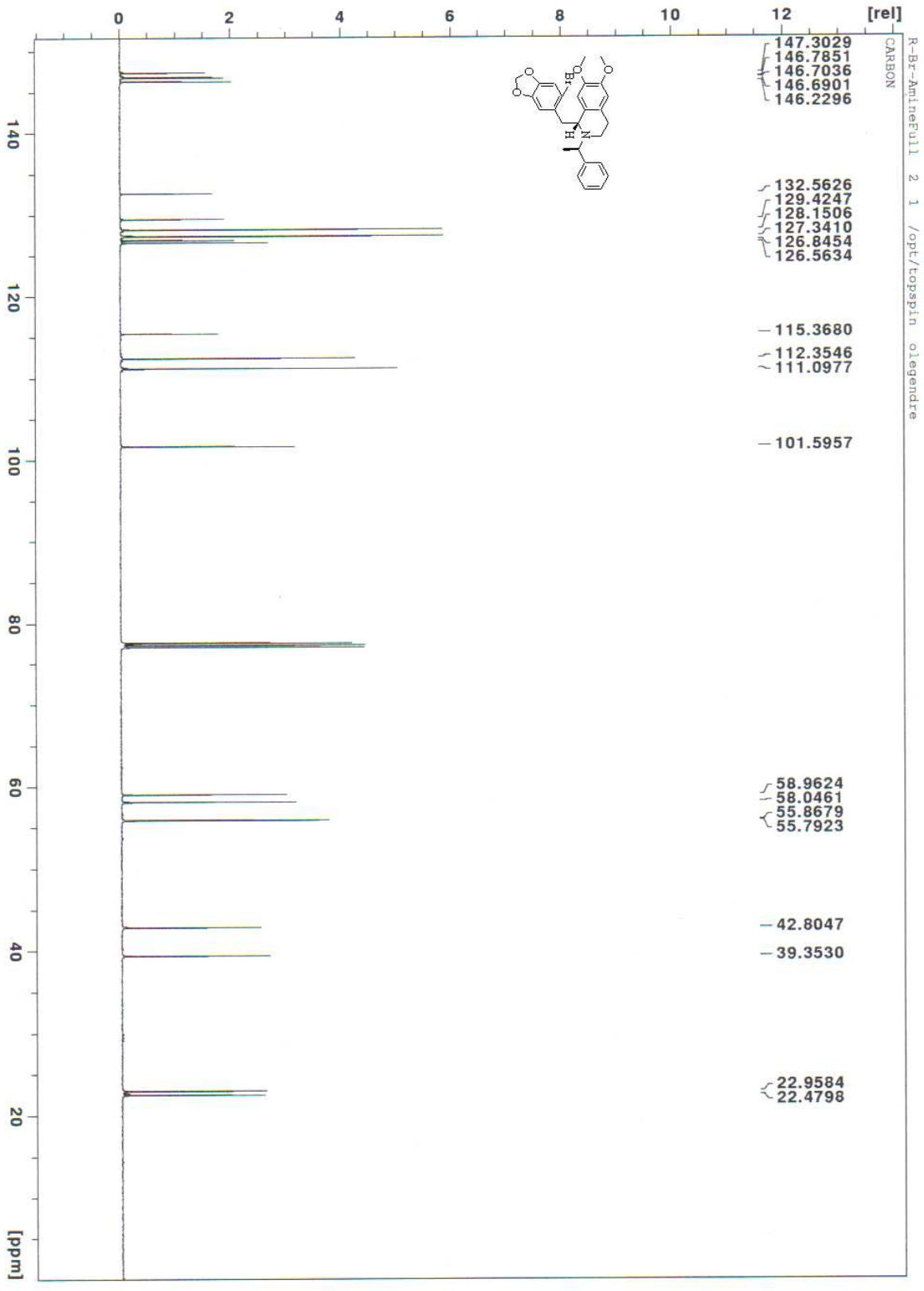
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4
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8
10
12
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60
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20
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146.2296
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115.3680
112.3546
111.0977
101.5957
58.9624
58.0461
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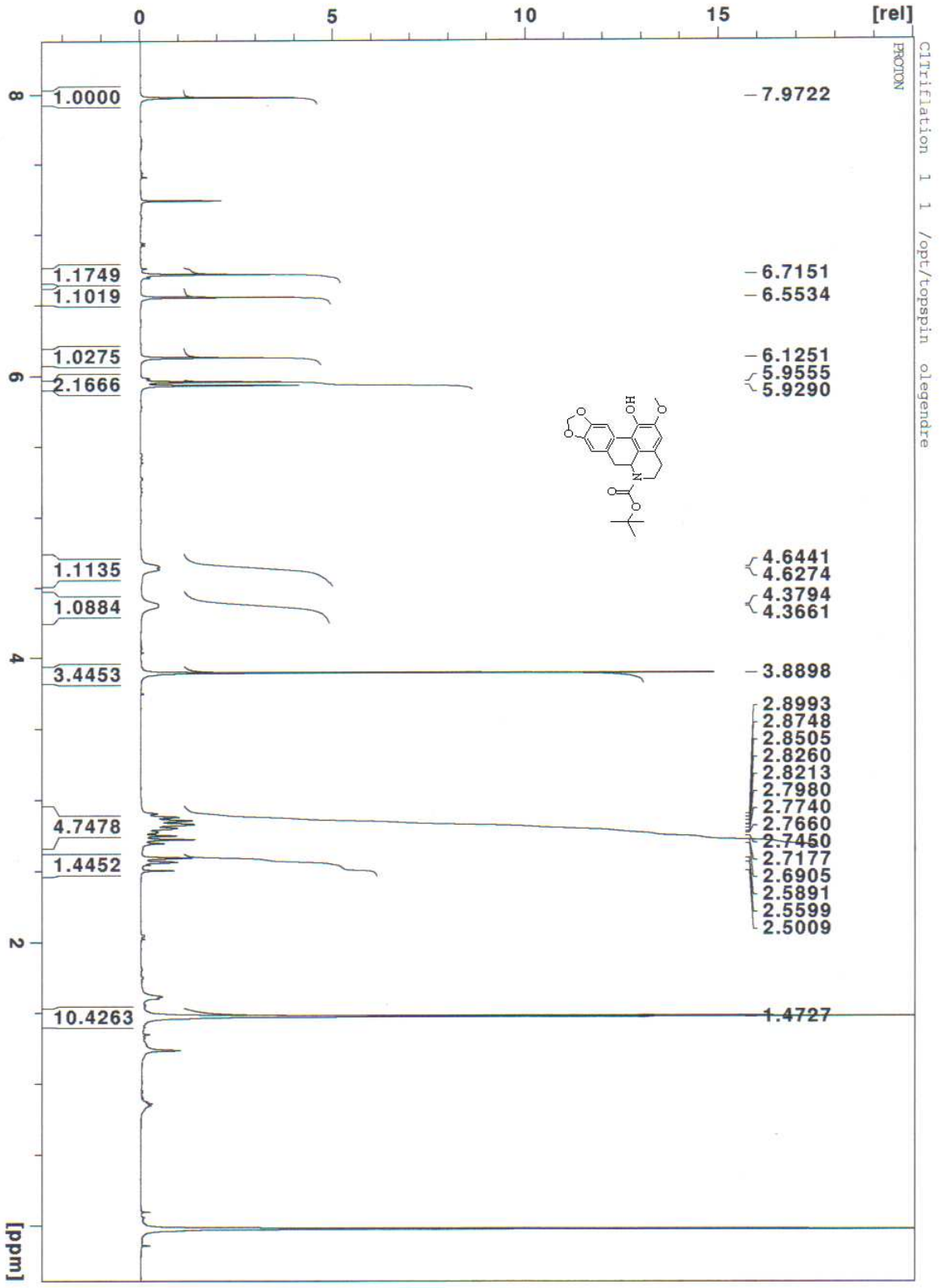
42.8047
39.3530
22.9584
22.4798
CARBON
R-Br-AmineFull 2 1 /opt/topspin olegendre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C1Trifilation 1 1 /opt/topspin olegendre
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4
2
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1.1135
1.0884
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1.4452
10.4263
7.9722
6.7151
6.5534
6.1251
5.9555
5.9290
4.6441
4.6274
4.3794
4.3661
3.8898
2.8993
2.8748
2.8505
2.8260
2.8213
2.7980
2.7740
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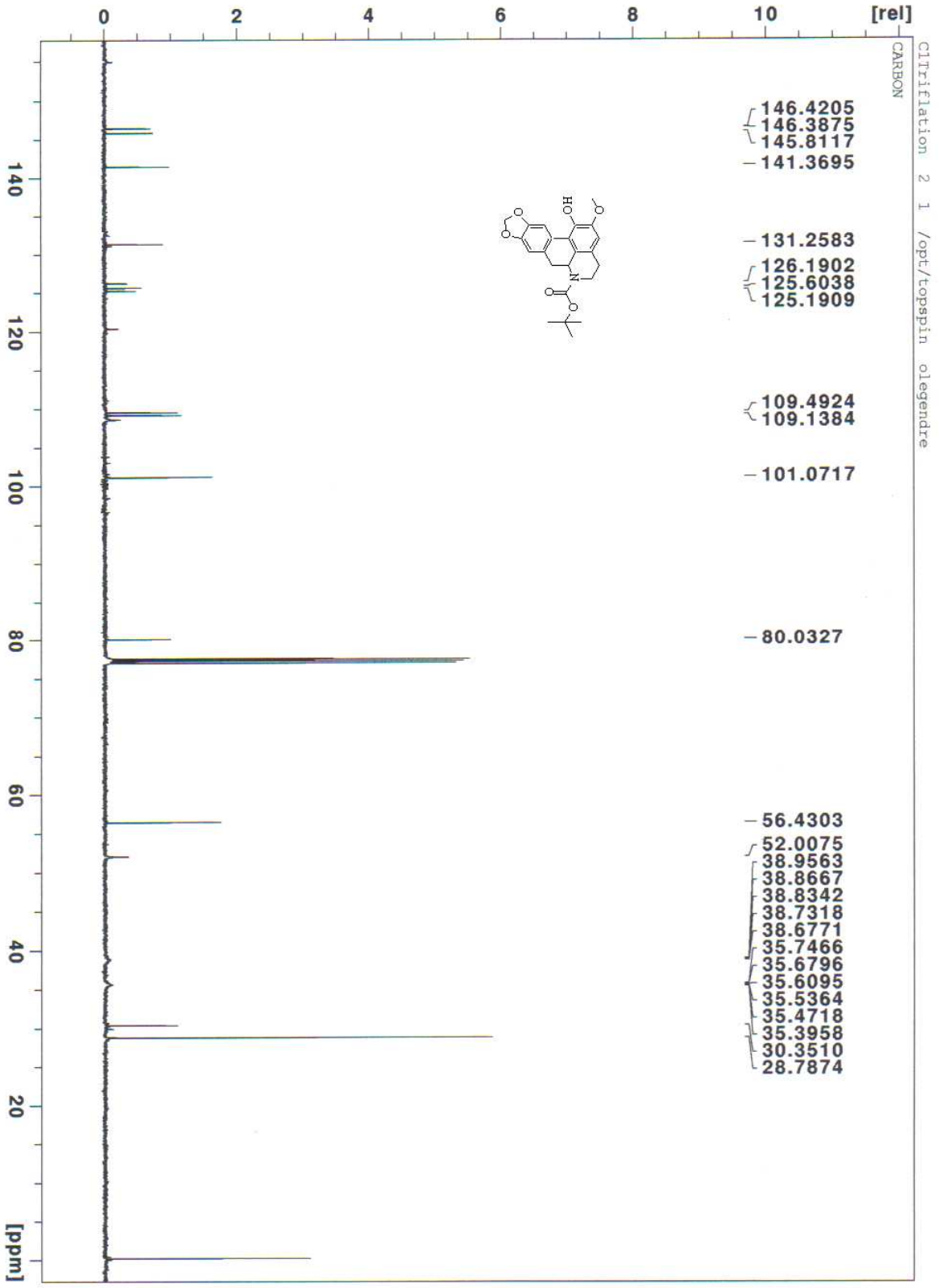
1.4727
HO
O
N
O
O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4
6
8
10
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145.8117
141.3695
131.2583
126.1902
125.6038
125.1909
109.4924
109.1384
101.0717
80.0327
56.4303
52.0075
38.9563
38.8667
38.8342
38.7318
38.6771
35.7466
35.6796
35.6095
35.5364
35.4718
35.3958
30.3510
28.7874
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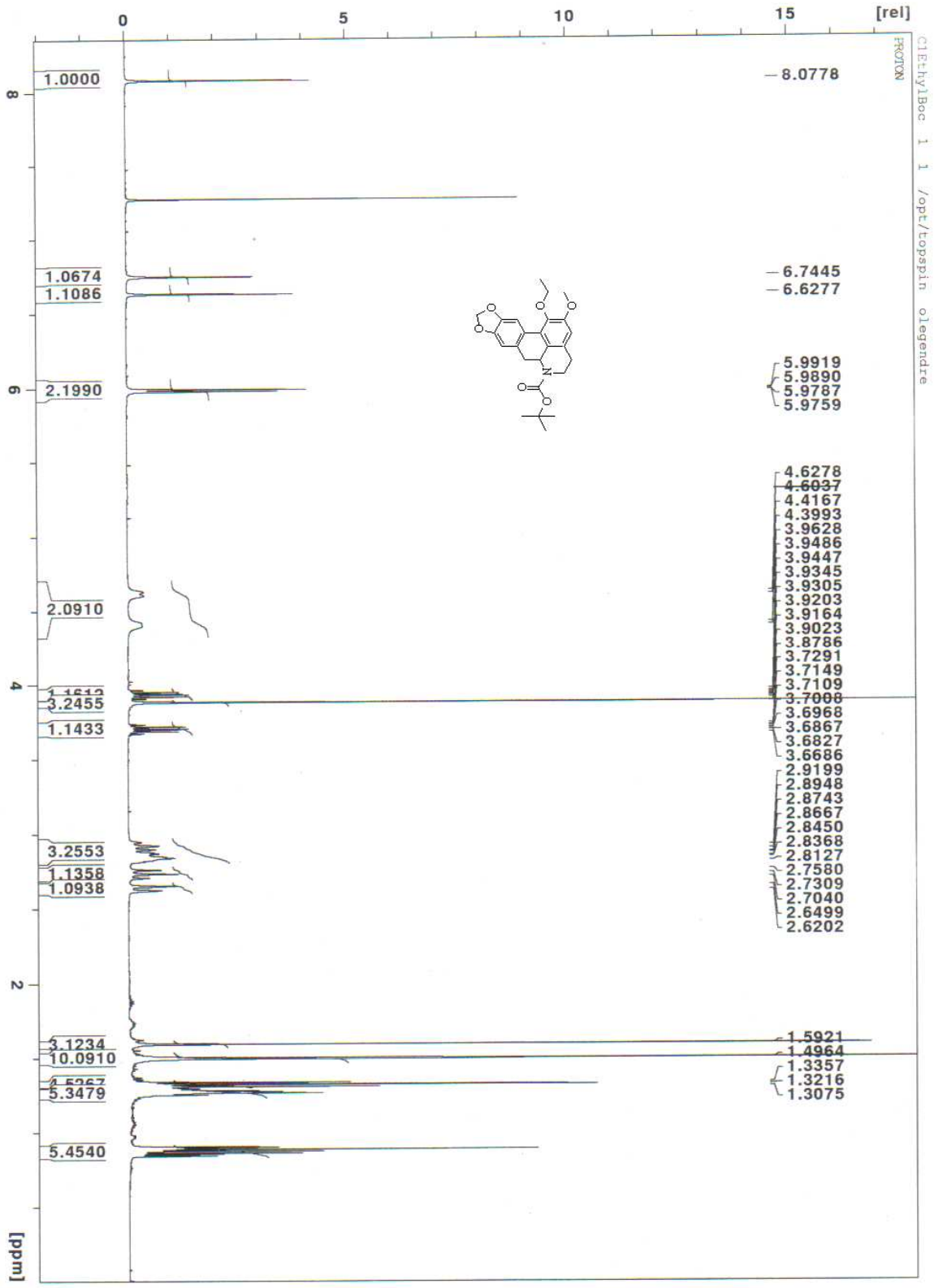
120
100
80
60
40
20
[ppm]


0
5
10
15
[rel]
[ppm]
8
6
4
2
C1EthylBoc 1 1 /opt/topspin olegendre
PROTON
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1.0674
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2.1990
2.0910
3.2455
1.1433
3.2553
1.1358
1.0938
3.1234
10.0910
5.3479
5.4540
8.0778
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5.9759
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4.3993
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3.9486
3.9447
3.9345
3.9305
3.9203
3.9164
3.9023
3.8786
3.7291
3.7149
3.7109
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3.6867
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3.6686
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2.8743
2.8667
2.8450
2.8368
2.8127
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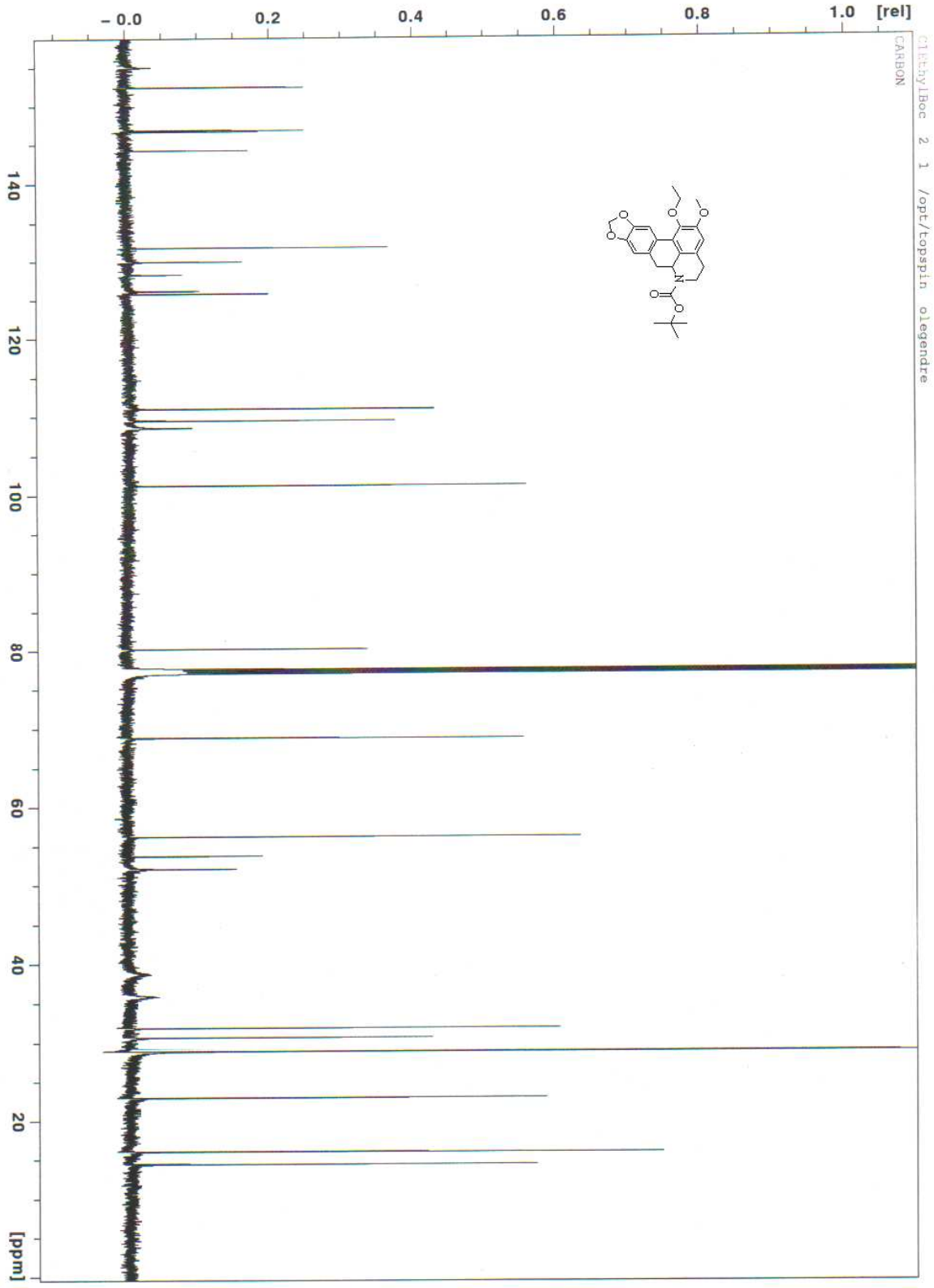
1.3075


– 0.0
0.2
0.4
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0.8
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[rel]
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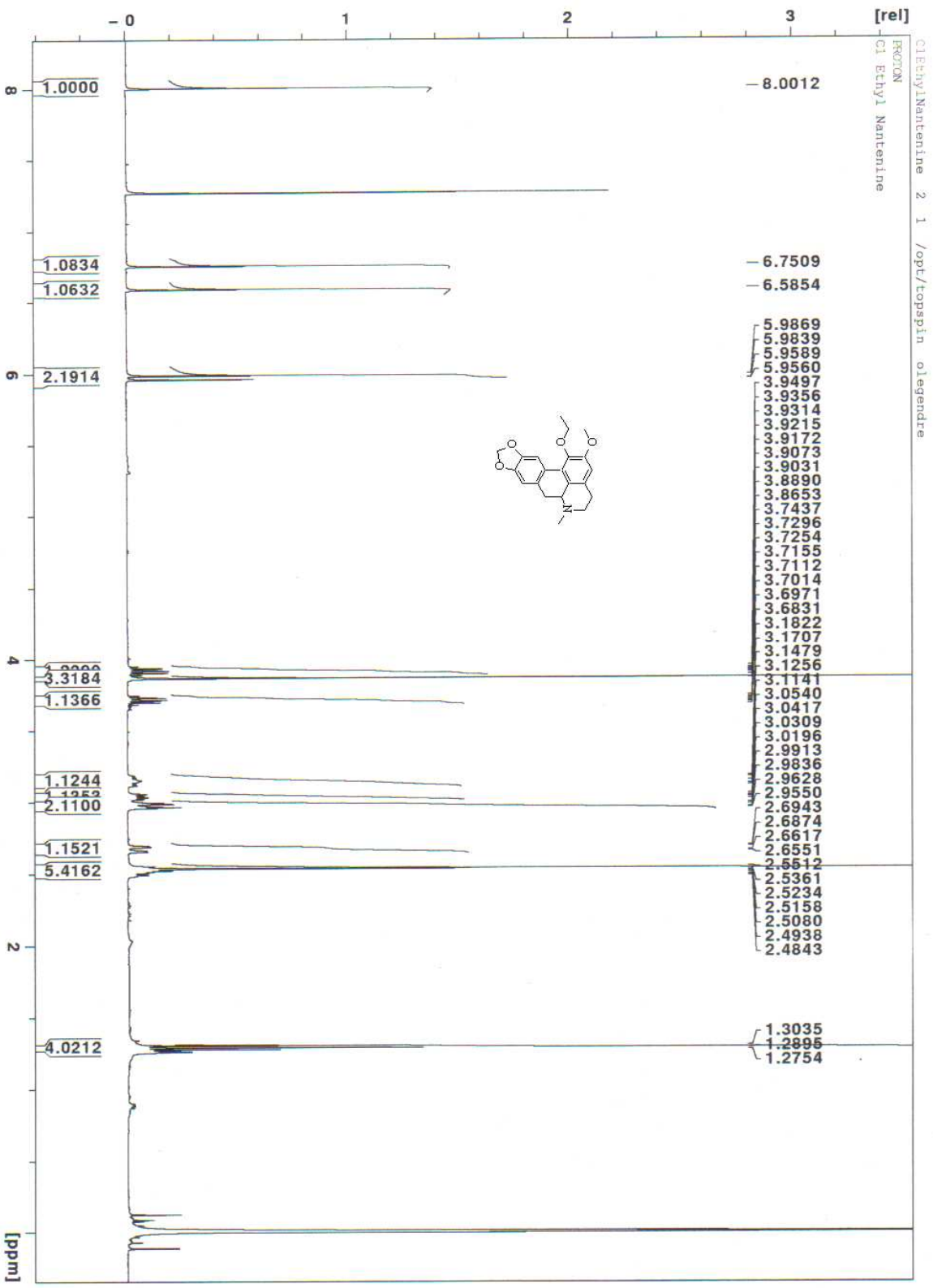
/opt/topspin olegendre
140
120
100
80
60
40
20
[ppm]


[rel]
[ppm]
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C1 Ethyl Nantenine
C1EthylNantenine 2 1 /opt/topspin olegendre
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6.5854
2.1914
5.9869
5.9839
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5.9560
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3.9314
3.9215
3.9172
3.9073
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3.8890
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3.7437
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3.7112
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3.1707
3.1479
3.1256
3.1141
1.1366
3.0540
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2.9550
2.1100
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1.1521
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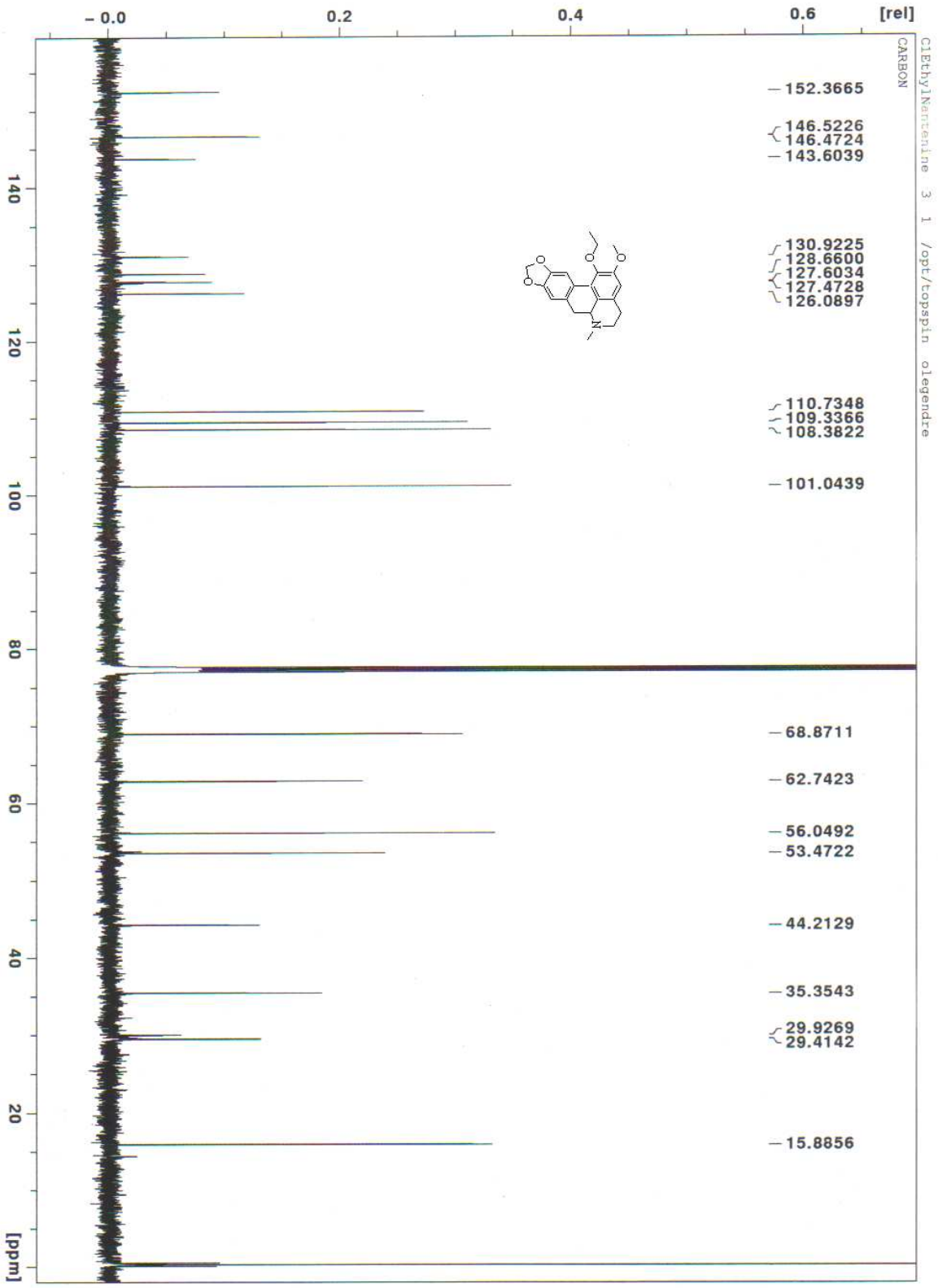
1.2895
1.2754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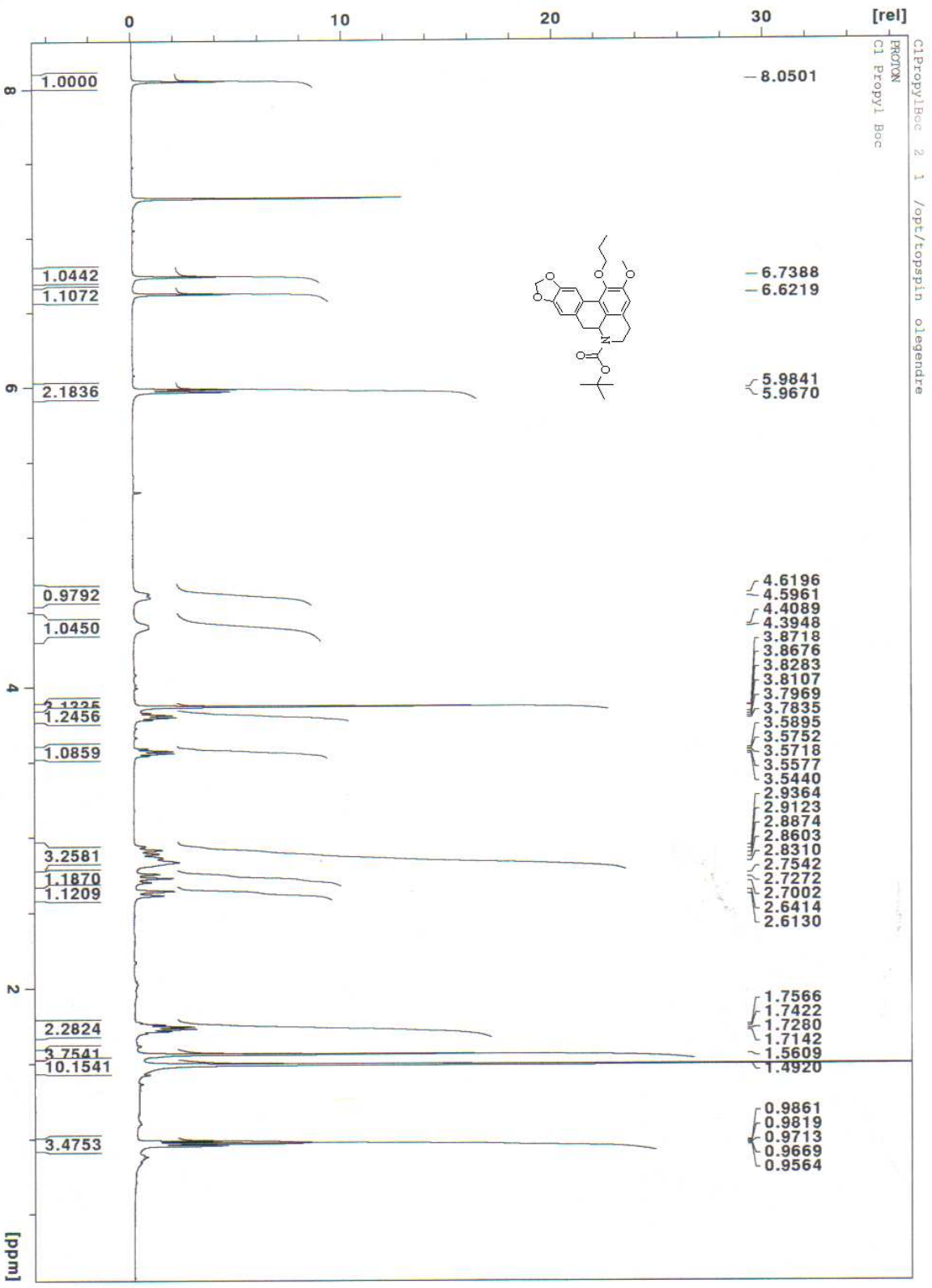
0.2
0.4
0.6
[rel]
CARBON
C1EthylNarceine 3 1 /opt/topspin olegendre
152.3665
146.5226
146.4724
143.6039
130.9225
128.6600
127.6034
127.4728
126.0897
110.7348
109.3366
108.3822
101.0439
68.8711
62.7423
56.0492
53.4722
44.2129
35.3543
29.9269
29.4142
15.8856
140
120
100
80
60
40
20
[ppm]


0
10
20
30
[rel]
[ppm]
8
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4
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1.0442
1.1072
2.1836
0.9792
1.0450
1.2456
1.0859
3.2581
1.1870
1.1209
2.2824
10.1541
3.4753
8.0501
6.7388
6.6219
5.9841
5.9670
4.6196
4.5961
4.4089
4.3948
3.8718
3.8676
3.8283
3.8107
3.7969
3.7835
3.5895
3.5752
3.5718
3.5577
3.5440
2.9364
2.9123
2.8874
2.8603
2.8310
2.7542
2.7272
2.7002
2.6414
2.6130
1.7566
1.7422
1.7280
1.7142
1.5609
1.4920
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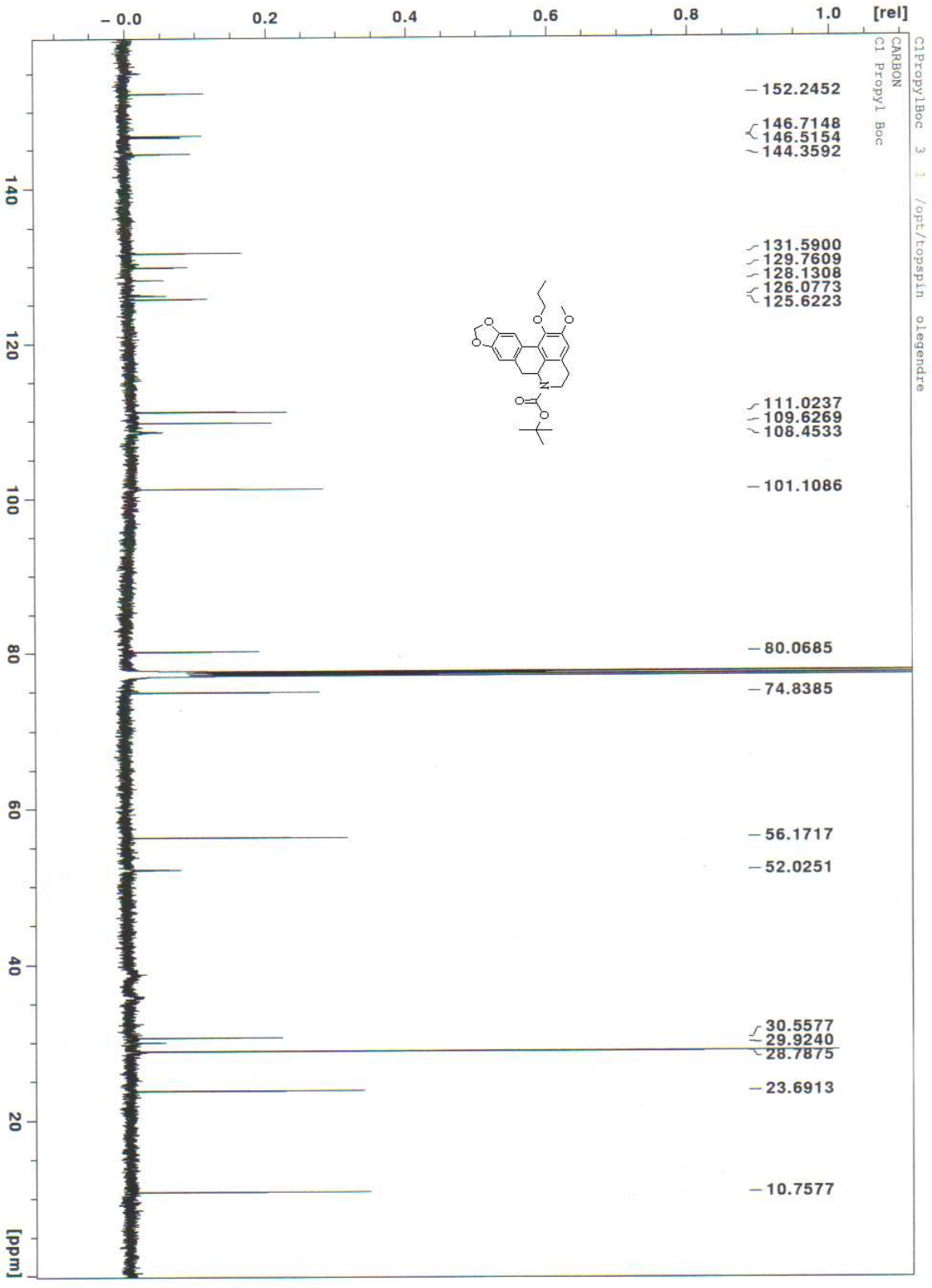
ClPropylBoc 2 1 /opt/topspin olegendre
PROTON
Cl Propyl Boc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0.4
0.6
0.8
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CARBON
C1 Propyl Boc
152.2452
146.7148
146.5154
144.3592
131.5900
129.7609
128.1308
126.0773
125.6223
111.0237
109.6269
108.4533
101.1086
80.0685
74.8385
56.1717
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29.9240
28.7875
23.6913
10.7577
140
120
100
80
60
40
20
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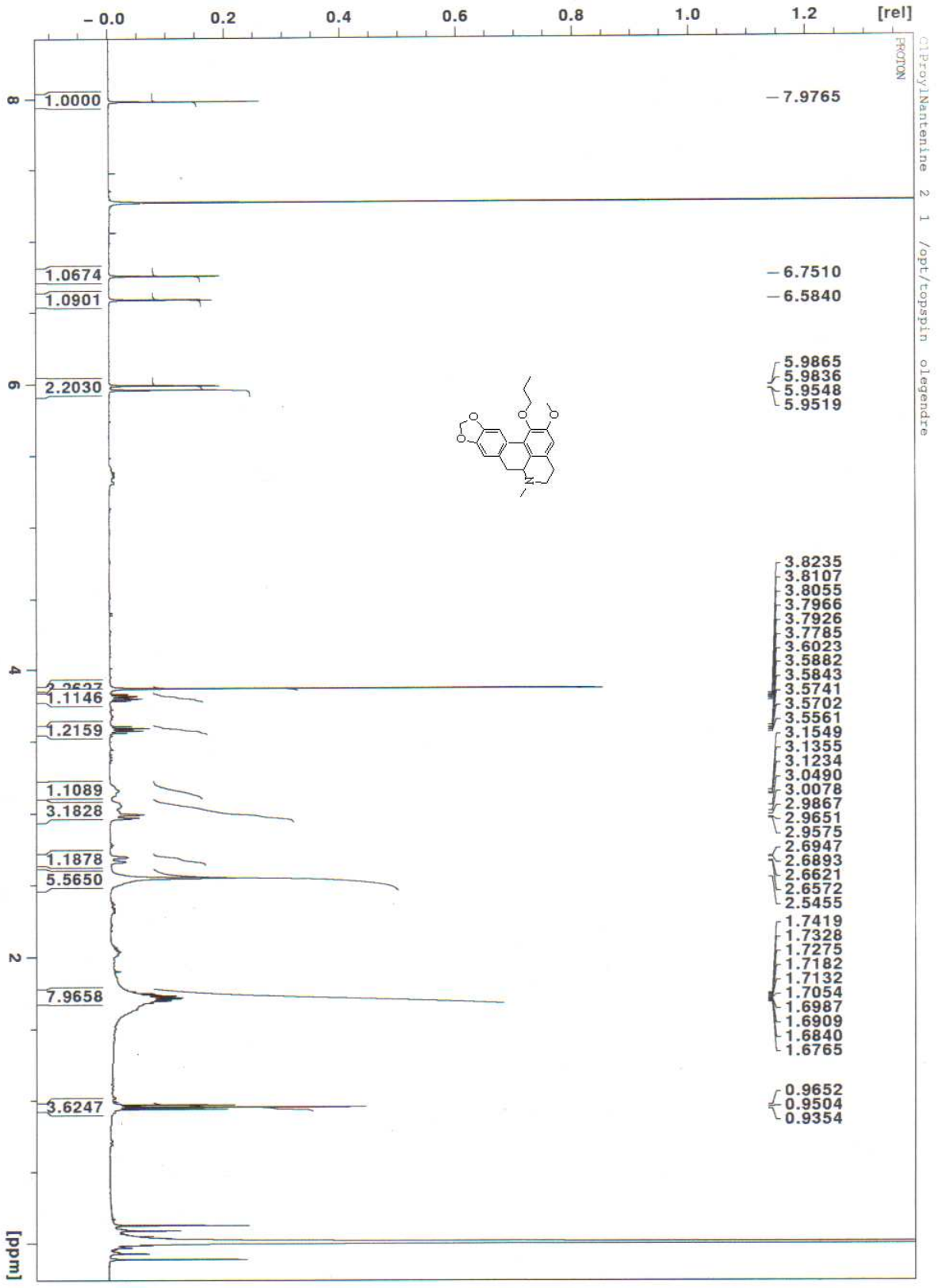
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0.4
0.6
0.8
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C1ProylNantenine 2 1 /opt/topspin olegendre
8
6
4
2
[ppm]
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1.0674
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1.1146
1.2159
1.1089
3.1828
1.1878
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3.6247
7.9765
6.7510
6.5840
5.9865
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5.9548
5.9519
3.8235
3.8107
3.8055
3.7966
3.7926
3.7785
3.6023
3.5882
3.5843
3.5741
3.5702
3.5561
3.1549
3.1355
3.1234
3.0490
3.0078
2.9867
2.9651
2.9575
2.6947
2.6893
2.6621
2.6572
2.5455
1.7419
1.7328
1.7275
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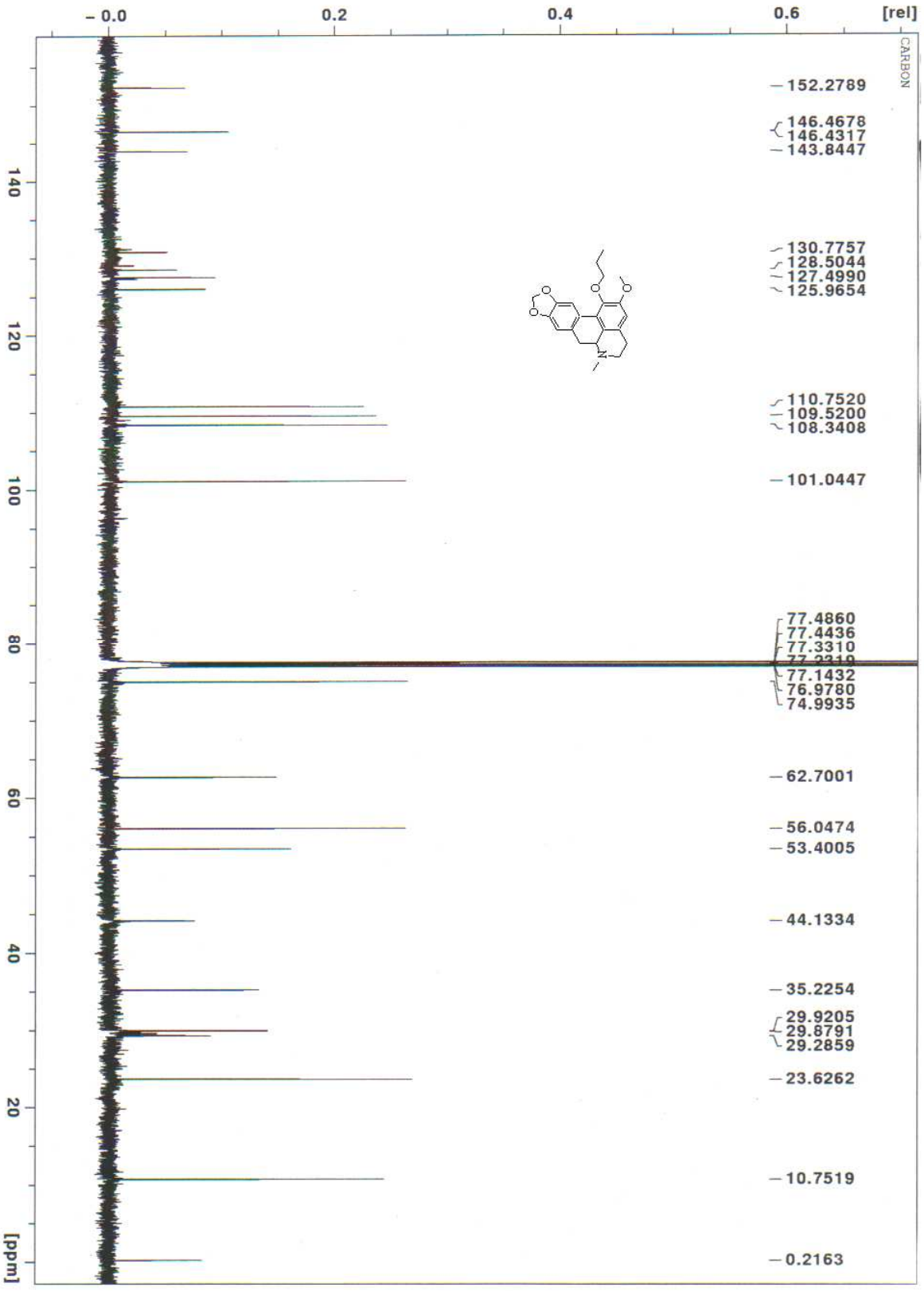
0.9354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0.4
0.6
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CARBON
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128.5044
127.4990
125.9654
110.7520
109.5200
108.3408
101.0447
77.4860
77.4436
77.3310
77.1432
76.9780
74.9935
62.7001
56.0474
53.4005
44.1334
35.2254
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29.8791
29.2859
23.6262
10.7519
0.2163
140
120
100
80
60
40
20
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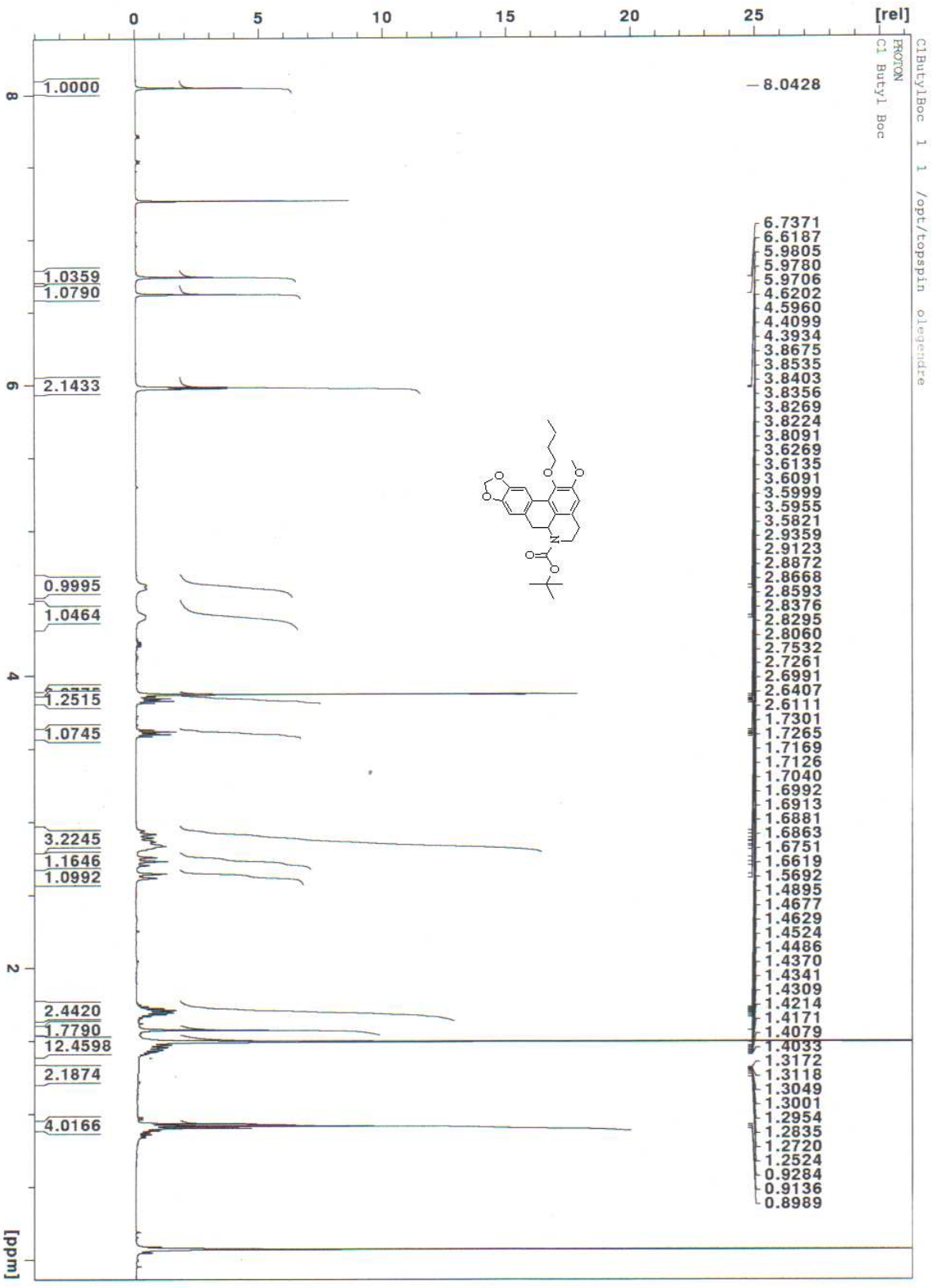
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2.4420
1.7790
12.4598
2.1874
4.0166
8.0428
6.7371
6.6187
5.9805
5.9780
5.9706
4.6202
4.5960
4.4099
4.3934
3.8675
3.8535
3.8403
3.8356
3.8269
3.8224
3.8091
3.6269
3.6135
3.6091
3.5999
3.5955
3.5821
2.9359
2.9123
2.8872
2.8668
2.8593
2.8376
2.8295
2.8060
2.7532
2.7261
2.6991
2.6407
2.6111
1.7301
1.7265
1.7169
1.7126
1.7040
1.6992
1.6913
1.6881
1.6863
1.6751
1.6619
1.5692
1.4895
1.4677
1.4629
1.4524
1.4486
1.4370
1.4341
1.4309
1.4214
1.4171
1.4079
1.4033
1.3172
1.3118
1.3049
1.3001
1.2954
1.2835
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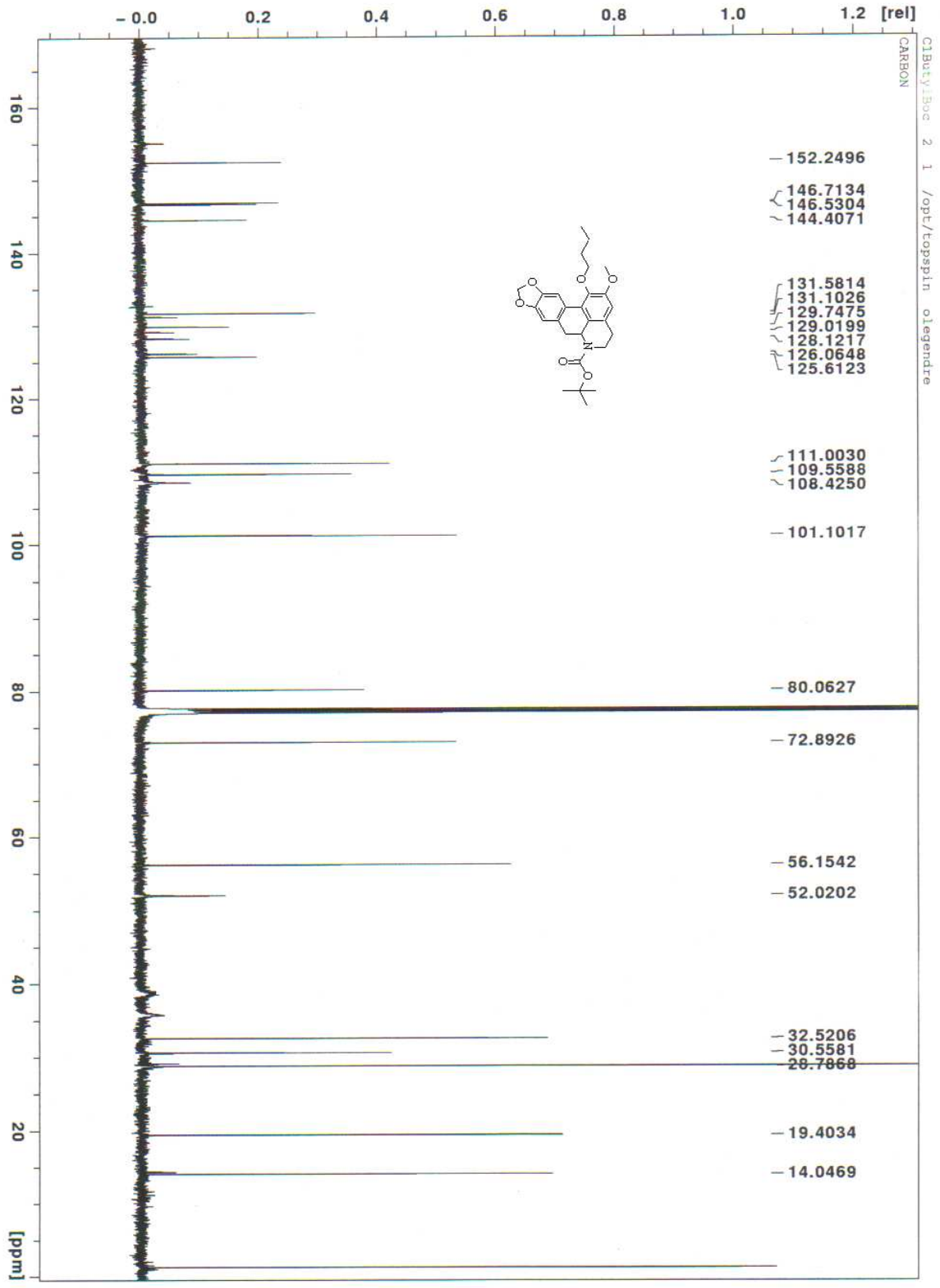
PROTON
C1 Butyl Boc
C1ButylBoc 1 1 /opt/topspin olegendre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0.2
0.4
0.6
0.8
1.0
1.2
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CARBON
C1Butyl5oc 2 1 /opt/topspin olegendre
160
140
120
100
80
60
40
20
[ppm]
152.2496
146.7134
146.5304
144.4071
131.5814
131.1026
129.7475
129.0199
128.1217
126.0648
125.6123
111.0030
109.5588
108.4250
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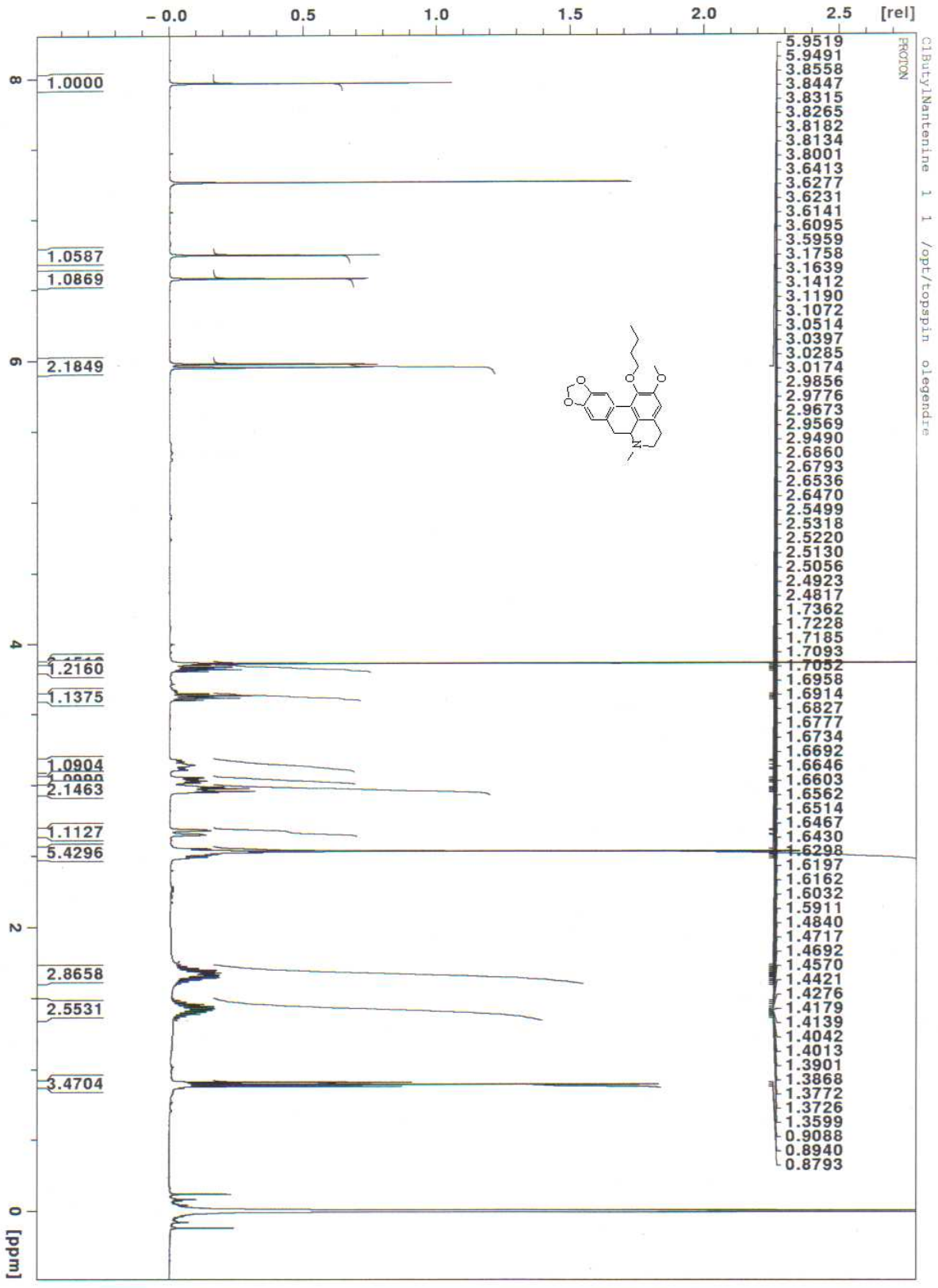
32.5206
30.5581
28.7868
19.4034
14.0469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1.5
2.0
2.5
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8
6
4
2
0
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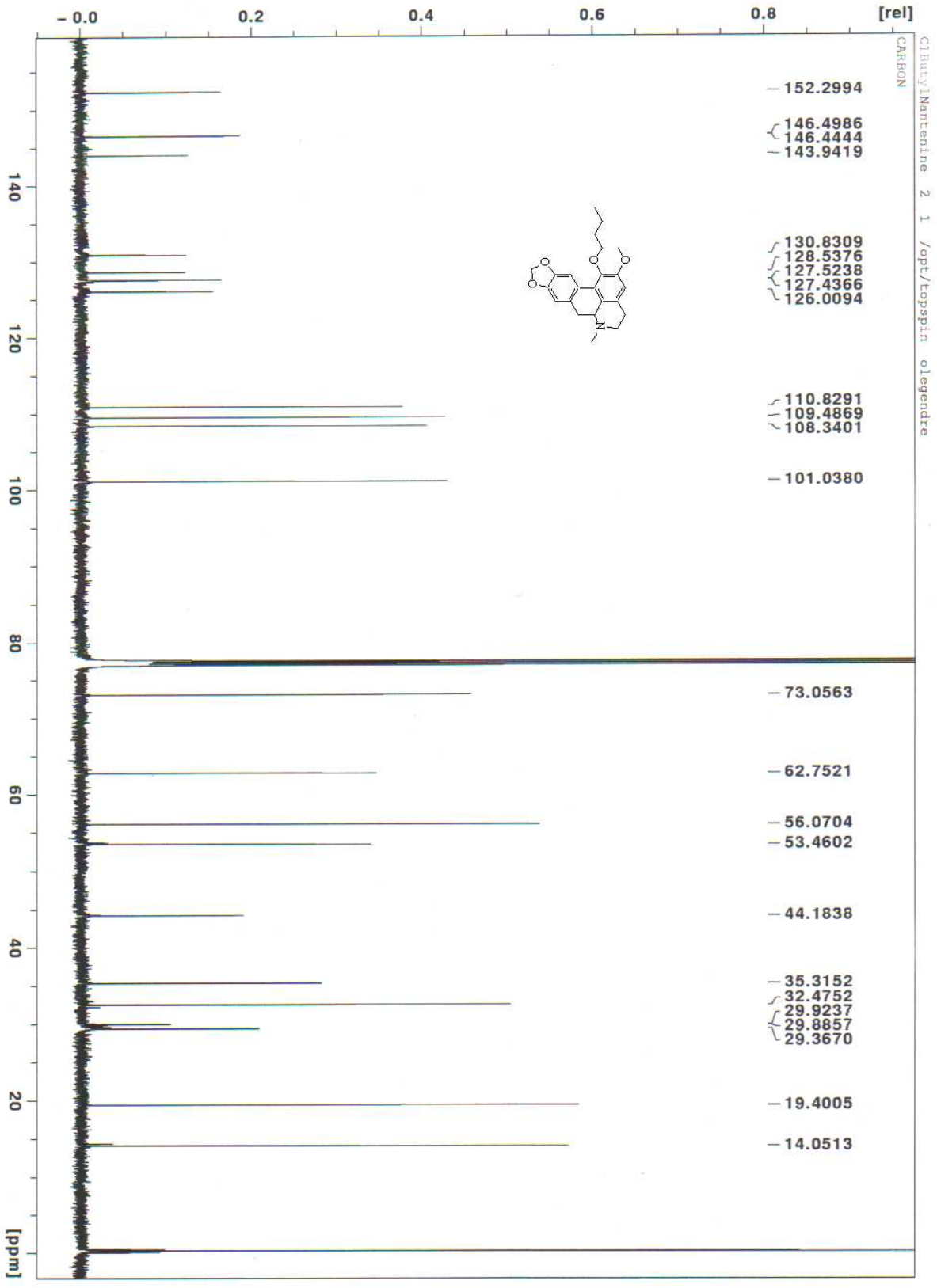
1.0904
2.1463
1.1127
5.4296
2.8658
2.5531
3.4704
5.9519
5.9491
3.8558
3.8447
3.8315
3.8265
3.8182
3.8134
3.8001
3.6413
3.6277
3.6231
3.6141
3.6095
3.5959
3.1758
3.1639
3.1412
3.1190
3.1072
3.0514
3.0397
3.0285
3.0174
2.9856
2.9776
2.9673
2.9569
2.9490
2.6860
2.6793
2.6536
2.6470
2.5499
2.5318
2.5220
2.5130
2.5056
2.4923
2.4817
1.7362
1.7228
1.7185
1.7093
1.7052
1.6958
1.6914
1.6827
1.6777
1.6734
1.6692
1.6646
1.6603
1.6562
1.6514
1.6467
1.6430
1.6298
1.6197
1.6162
1.6032
1.5911
1.4840
1.4717
1.4692
1.4570
1.4421
1.4276
1.4179
1.4139
1.4042
1.4013
1.3901
1.3868
1.3772
1.3726
1.3599
0.9088
0.8940
0.8793
PROTON
C1ButylNantenine 1 1 /opt/topspin olegendre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0.2
0.4
0.6
0.8
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C1butylNanteniine 2 1 /opt/topspin olegendre
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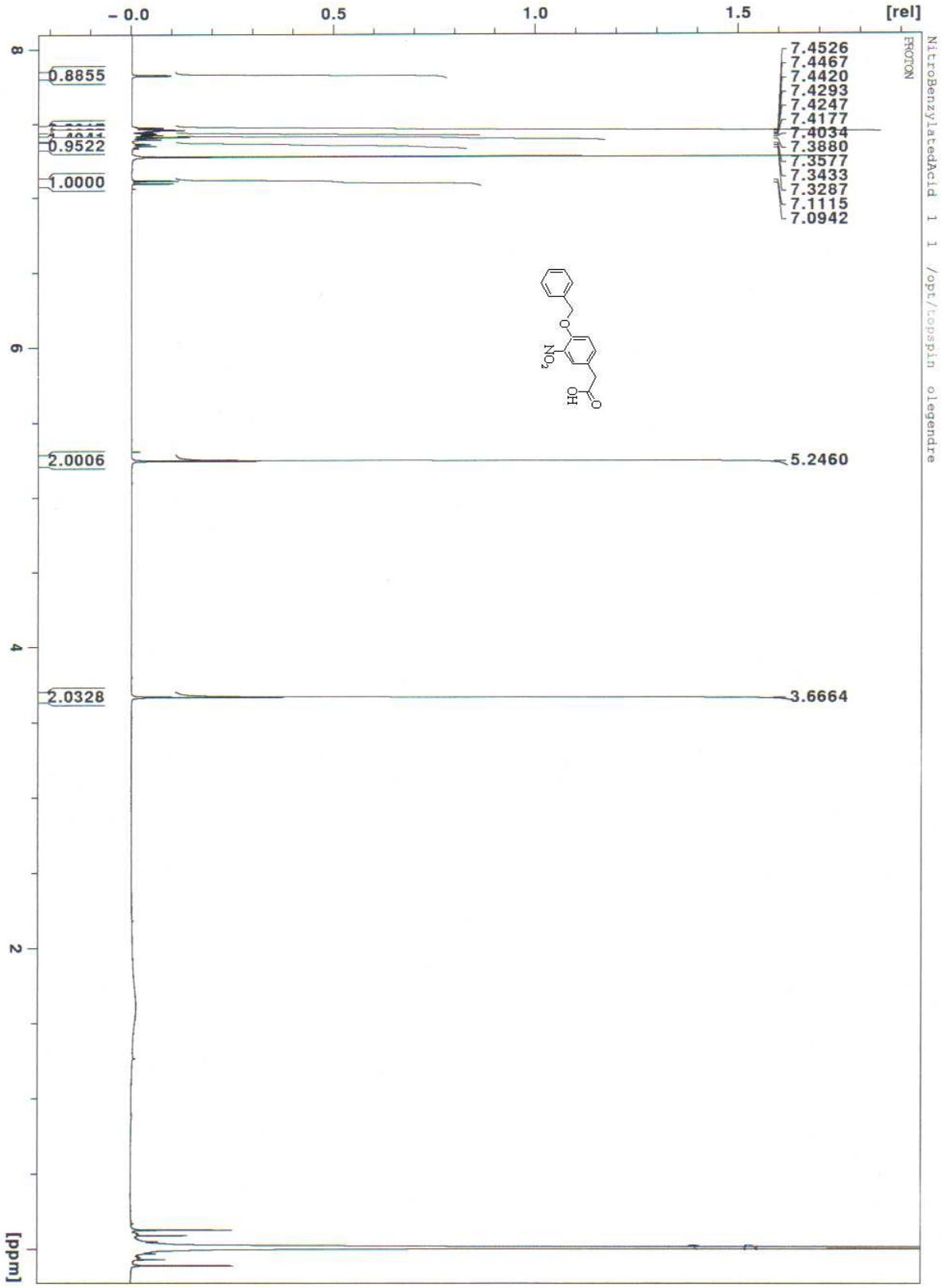
146.4986
146.4444
143.9419
130.8309
128.5376
127.5238
127.4366
126.0094
110.8291
109.4869
108.3401
101.0380
73.0563
62.7521
56.0704
53.4602
44.1838
35.3152
32.4752
29.9237
29.8857
29.3670
19.4005
14.0513
140
120
100
80
60
40
20
[ppm]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0.5
1.0
1.5
[rel]
8
6
4
2
[ppm]
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0.9522
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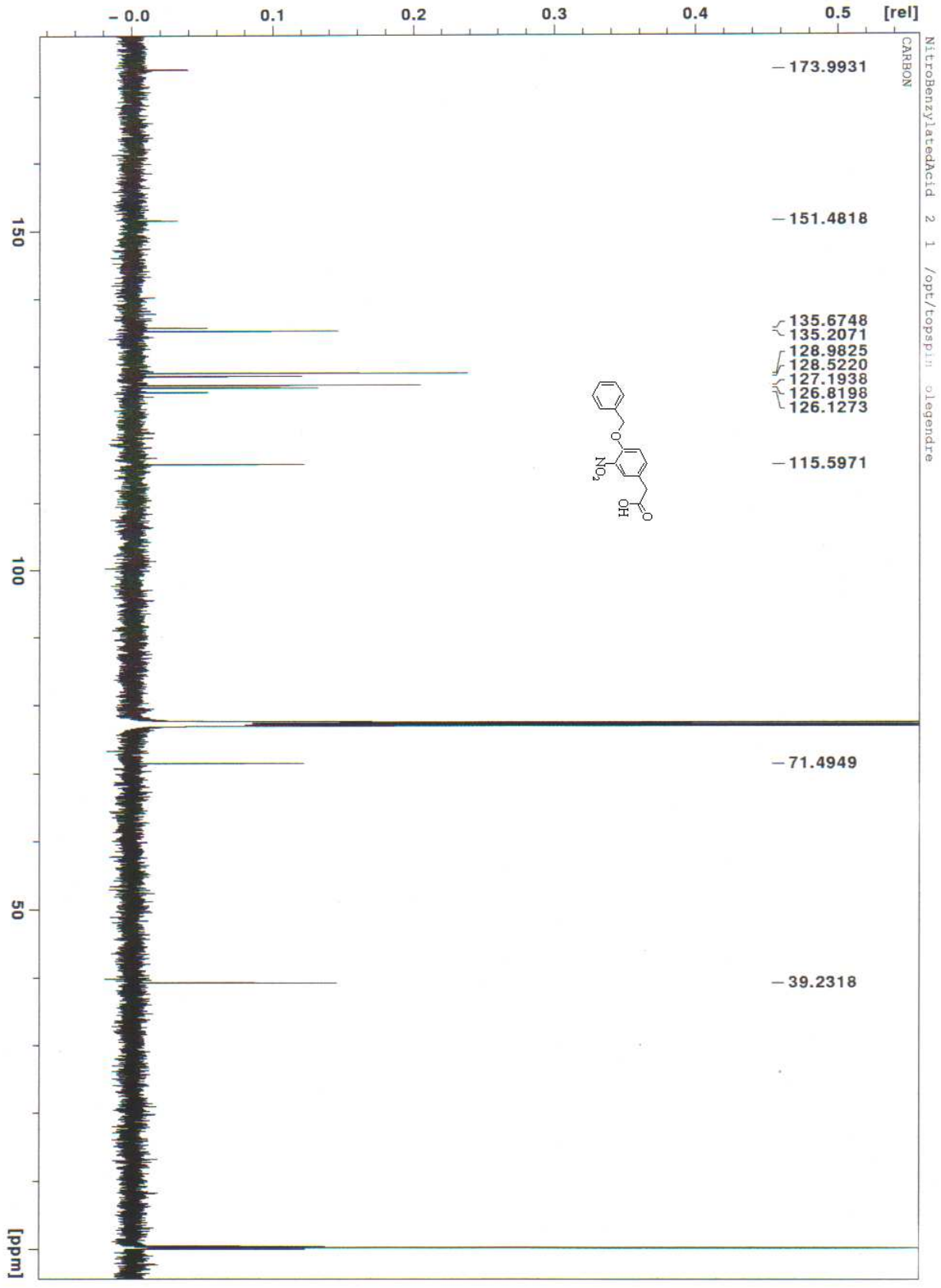
2.0006
2.0328
7.4526
7.4467
7.4420
7.4293
7.4247
7.4177
7.4034
7.3880
7.3577
7.3433
7.3287
7.1115
7.0942
5.2460
3.6664
PROTON
NitroBenzylatedAcid 1 1 /opt/topspin olegendre


– 0.0
0.1
0.2
0.3
0.4
0.5
[rel]
CARBON
NitroBenzylatedAcid 2 1 /opt/topspin olegendre
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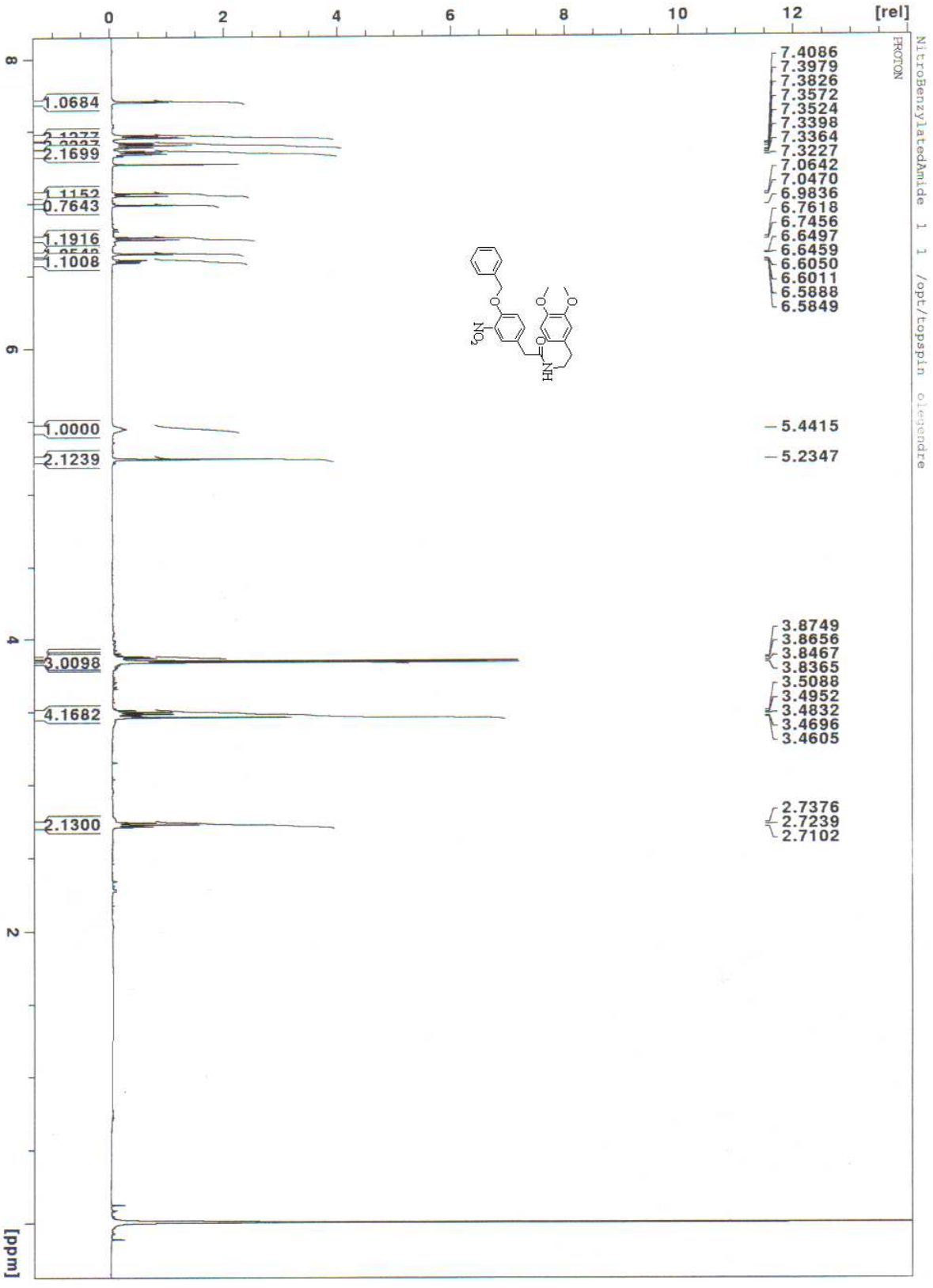
151.4818
135.6748
135.2071
128.9825
128.5220
127.1938
126.8198
126.1273
115.5971
71.4949
39.2318
150
100
50
[ppm]
NO2
OH
O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2
4
6
8
10
12
[rel]
8
6
4
2
[ppm]
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NitroBenzylatedAmide 1 1 /opt/topspin olegendre
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2.1699
0.7643
1.1916
1.1008
1.0000
2.1239
3.0098
4.1682
2.1300
7.4086
7.3979
7.3826
7.3572
7.3524
7.3398
7.3364
7.3227
7.0642
7.0470
6.9836
6.7618
6.7456
6.6497
6.6459
6.6050
6.6011
6.5888
6.5849
5.4415
5.2347
3.8749
3.8656
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3.5088
3.4952
3.4832
3.4696
3.4605
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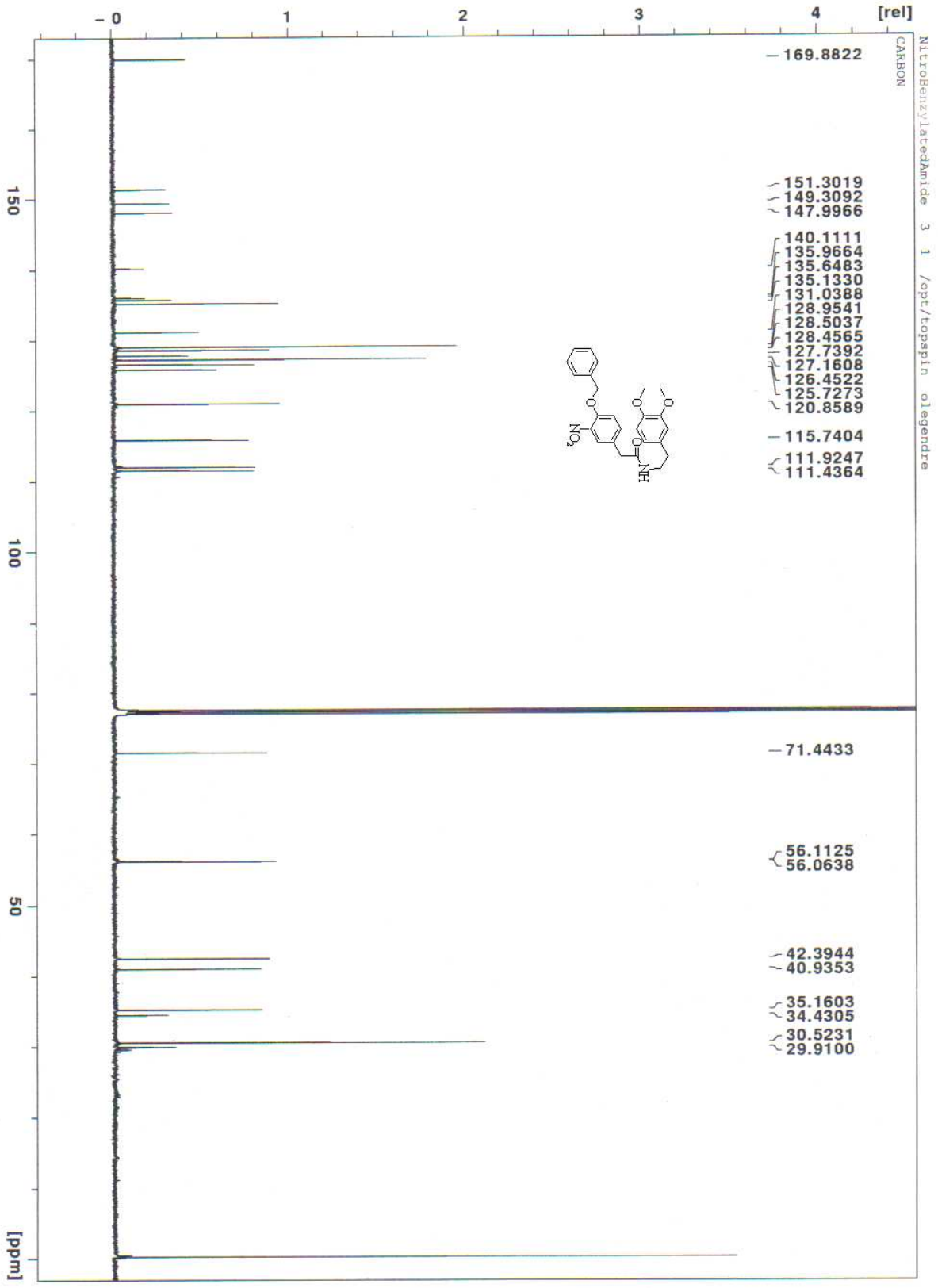
2.7239
2.7102


0
1
2
3
4
[rel]
150
100
50
[ppm]
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NitroBenzylatedAmide 3 1 /opt/topspin olegendre
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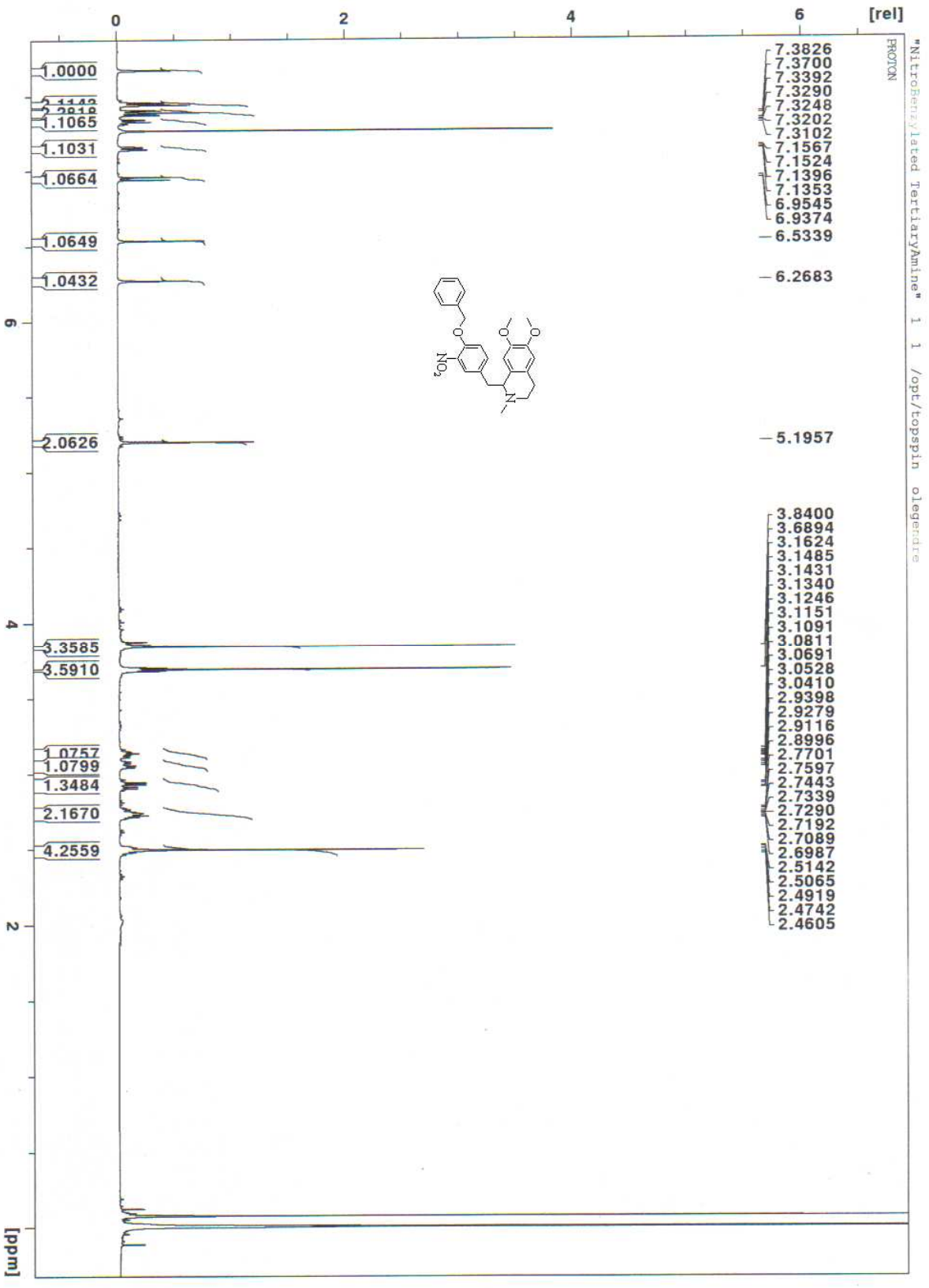
151.3019
149.3092
147.9966
140.1111
135.9664
135.6483
135.1330
131.0388
128.9541
128.5037
128.4565
127.7392
127.1608
126.4522
125.7273
120.8589
115.7404
111.9247
111.4364
71.4433
56.1125
56.0638
42.3944
40.9353
35.1603
34.4305
30.5231
29.9100


0
2
4
6
[rel]
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"NitroBenzylated TertiaryAmine" 1 1 /opt/topspin olegendre
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1.0664
1.0649
1.0432
2.0626
3.3585
3.5910
1.0757
1.0799
1.3484
2.1670
4.2559
7.3826
7.3700
7.3392
7.3290
7.3248
7.3202
7.3102
7.1567
7.1524
7.1396
7.1353
6.9545
6.9374
6.5339
6.2683
5.1957
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3.6894
3.1624
3.1485
3.1431
3.1340
3.1246
3.1151
3.1091
3.0811
3.0691
3.0528
3.0410
2.9398
2.9279
2.9116
2.8996
2.7701
2.7597
2.7443
2.7339
2.7290
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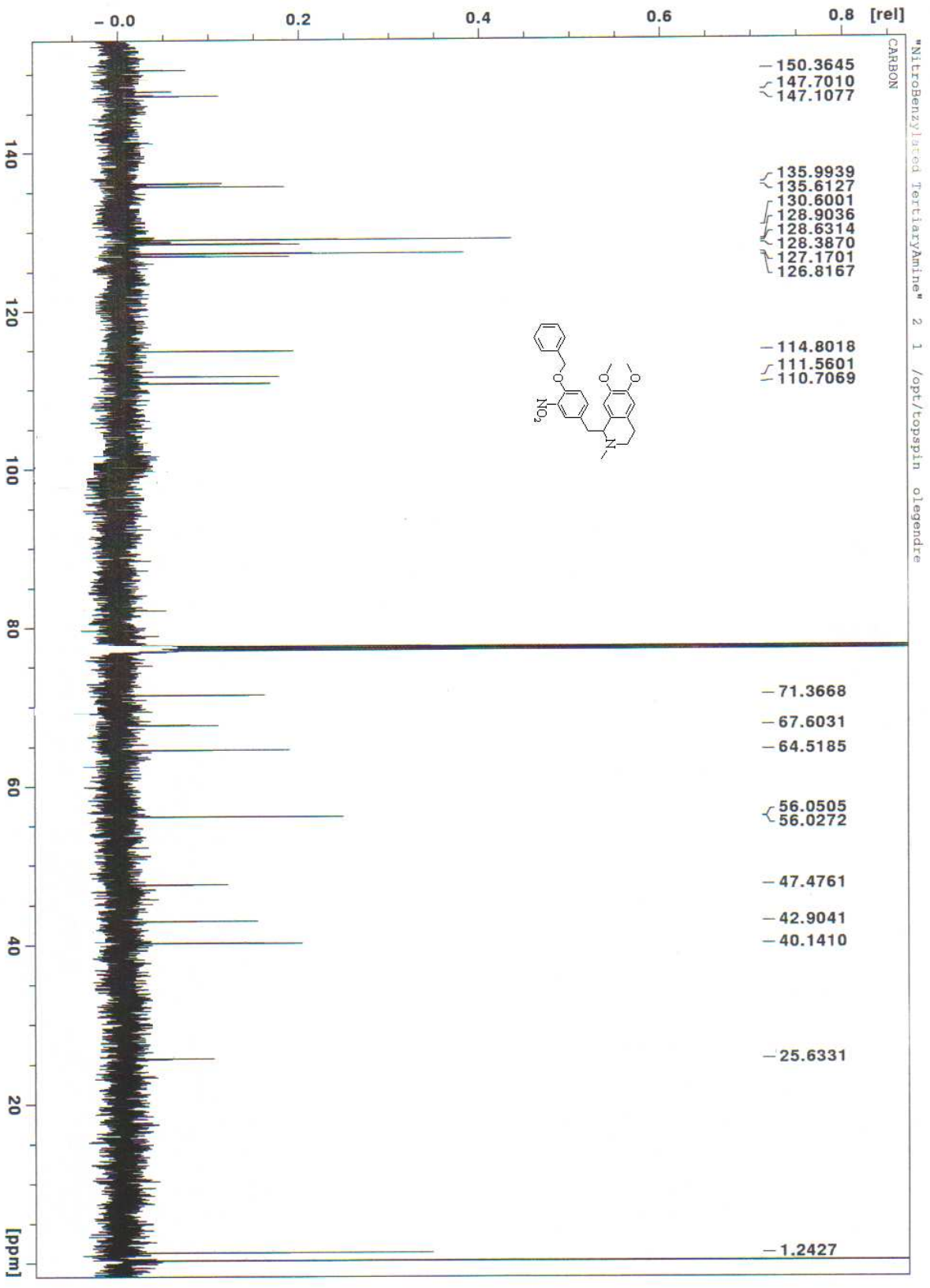
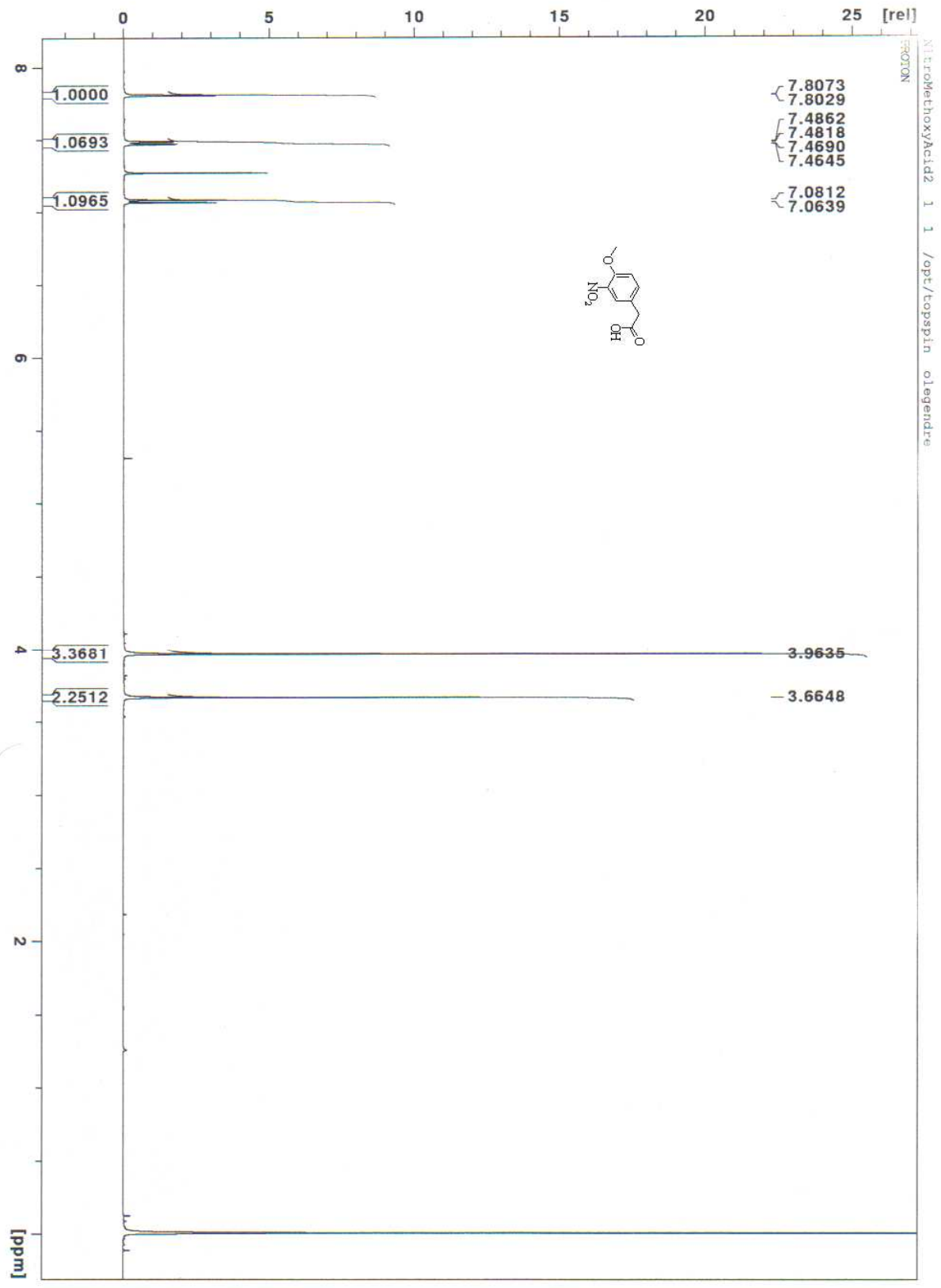
2.7089
2.6987
2.5142
2.5065
2.4919
2.4742
2.4605
6
4
2
[ppm]


– 0.0
0.2
0.4
0.6
0.8 [rel]
CARBON
"NitroBenzylated TertiaryAmine" 2 1 /opt/topspin olegendre
150.3645
147.7010
147.1077
135.9939
135.6127
130.6001
128.9036
128.6314
128.3870
127.1701
126.8167
114.8018
111.5601
110.7069
71.3668
67.6031
64.5185
56.0505
56.0272
47.4761
42.9041
40.1410
25.6331
1.2427
140
120
100
80
60
40
20
[ppm]


0
5
10
15
20
25
[rel]
8
6
4
2
[ppm]
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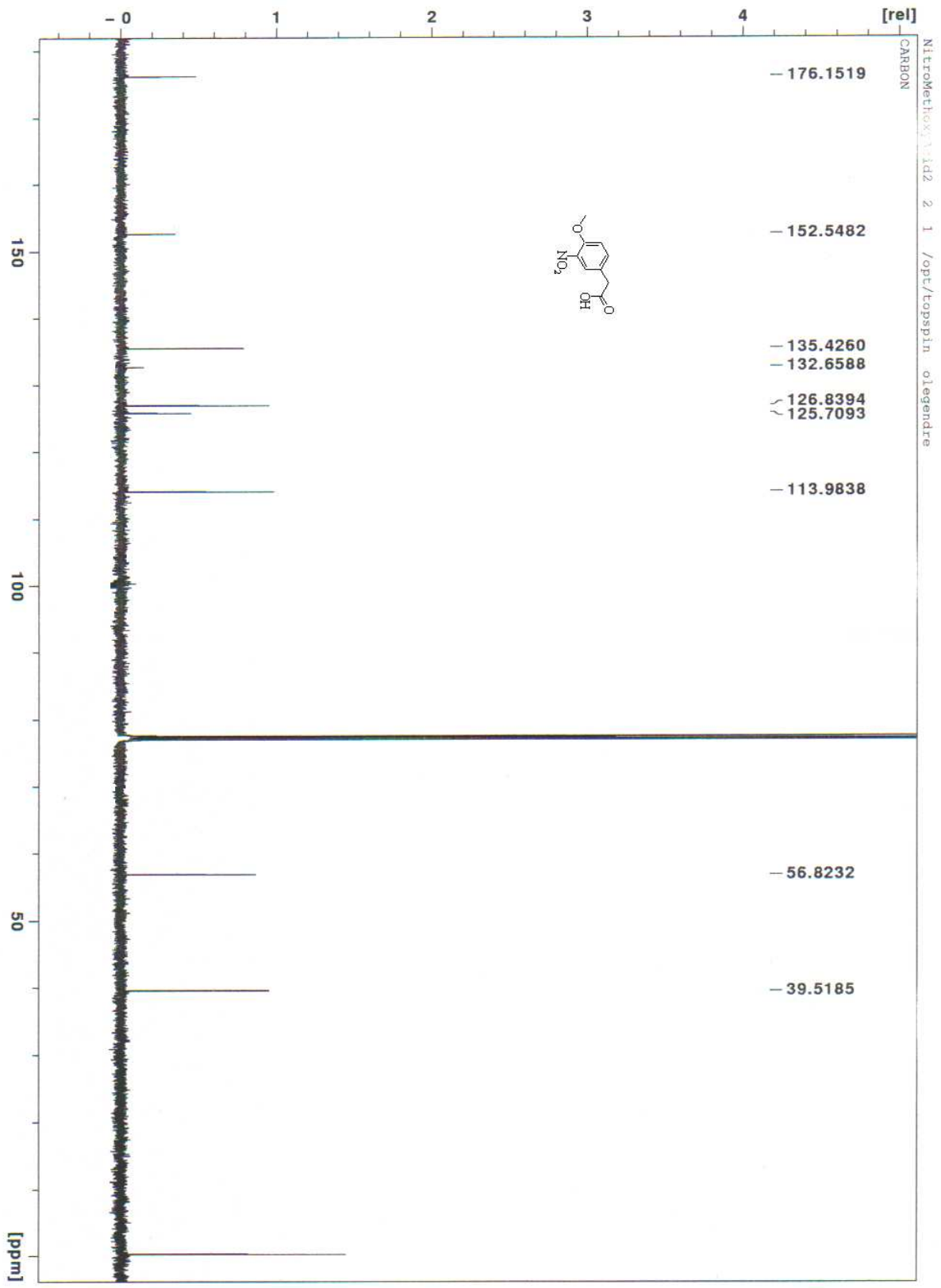
1.0965
3.3681
2.2512
7.8073
7.8029
7.4862
7.4818
7.4690
7.4645
7.0812
7.0639
3.9635
3.6648
NitroMethoxyAcid2 1 1 /opt/topspin olegendre
PROTON


– 0
1
2
3
4
[rel]
CARBON
NitroMethoxyAcid2 2 1 /opt/topspin oiegendre
176.1519
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135.4260
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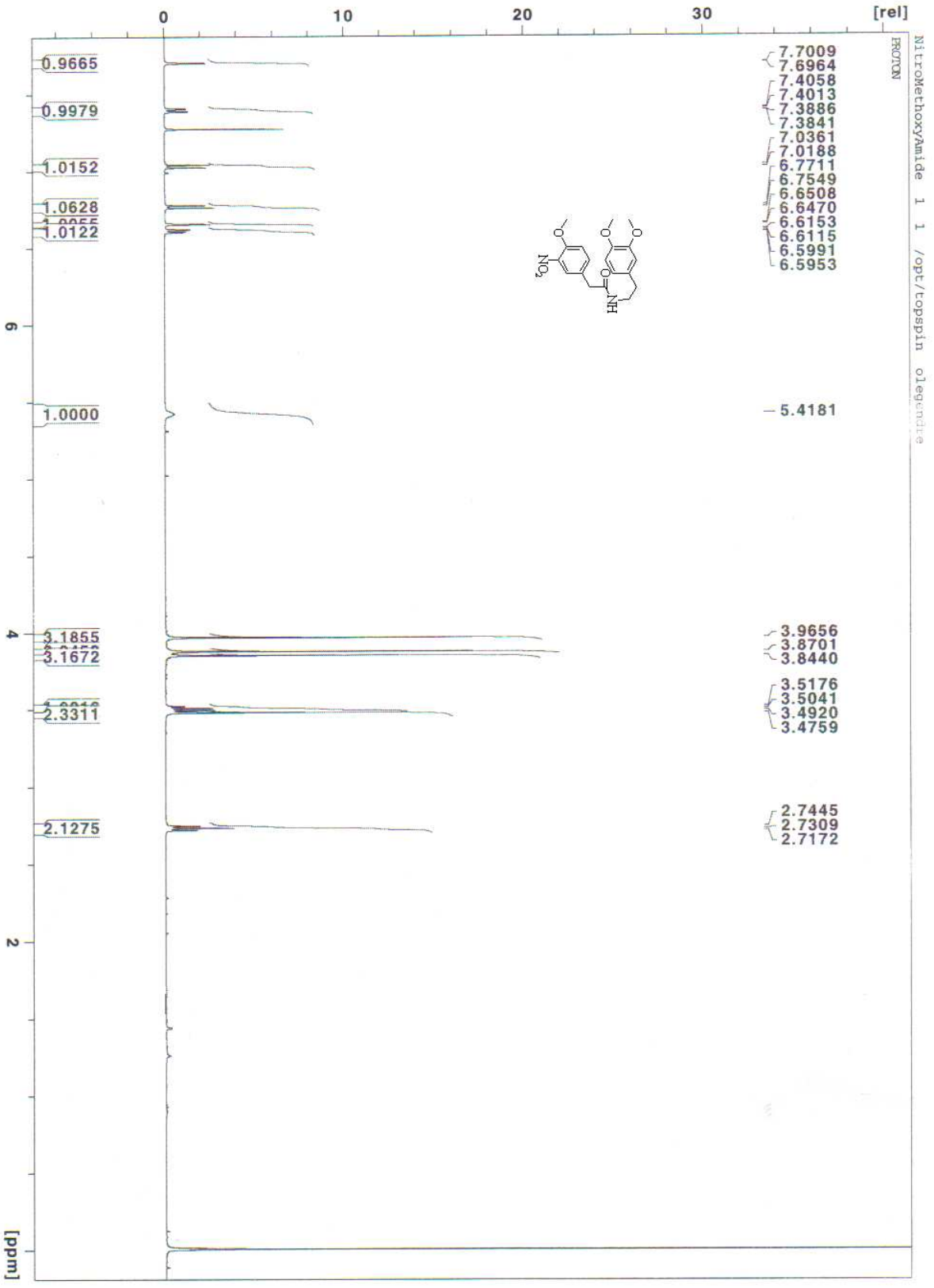
125.7093
113.9838
56.8232
39.5185
150
100
50
[ppm]
NO2
OH
O


0
10
20
30
[rel]
PROTON
NitroMethoxyAmide 1 1 /opt/topspin oleg-nmr
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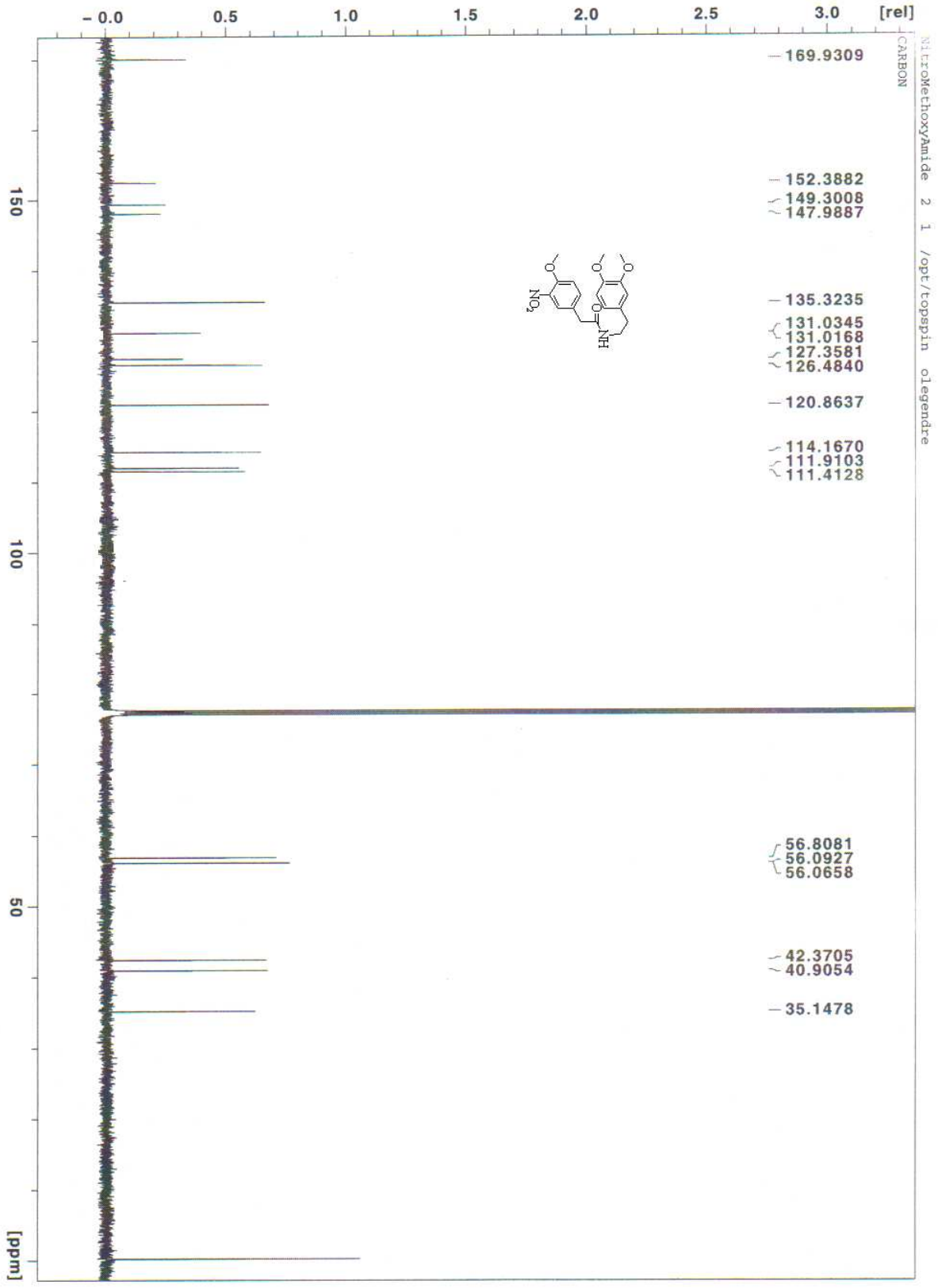
1.0628
1.0122
1.0000
3.1855
3.1672
2.3311
2.1275
7.7009
7.6964
7.4058
7.4013
7.3886
7.3841
7.0361
7.0188
6.7711
6.7549
6.6508
6.6470
6.6153
6.6115
6.5991
6.5953
5.4181
3.9656
3.8701
3.8440
3.5176
3.5041
3.4920
3.4759
2.7445
2.7309
2.7172
NO2
O
NH
6
4
2
[ppm]


0.0
0.5
1.0
1.5
2.0
2.5
3.0
[rel]
CARBON
NitroMethoxyAmide 2 1 /opt/topspin olegendre
169.9309
152.3882
149.3008
147.9887
135.3235
131.0345
131.0168
127.3581
126.4840
120.8637
114.1670
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56.8081
56.0927
56.0658
42.3705
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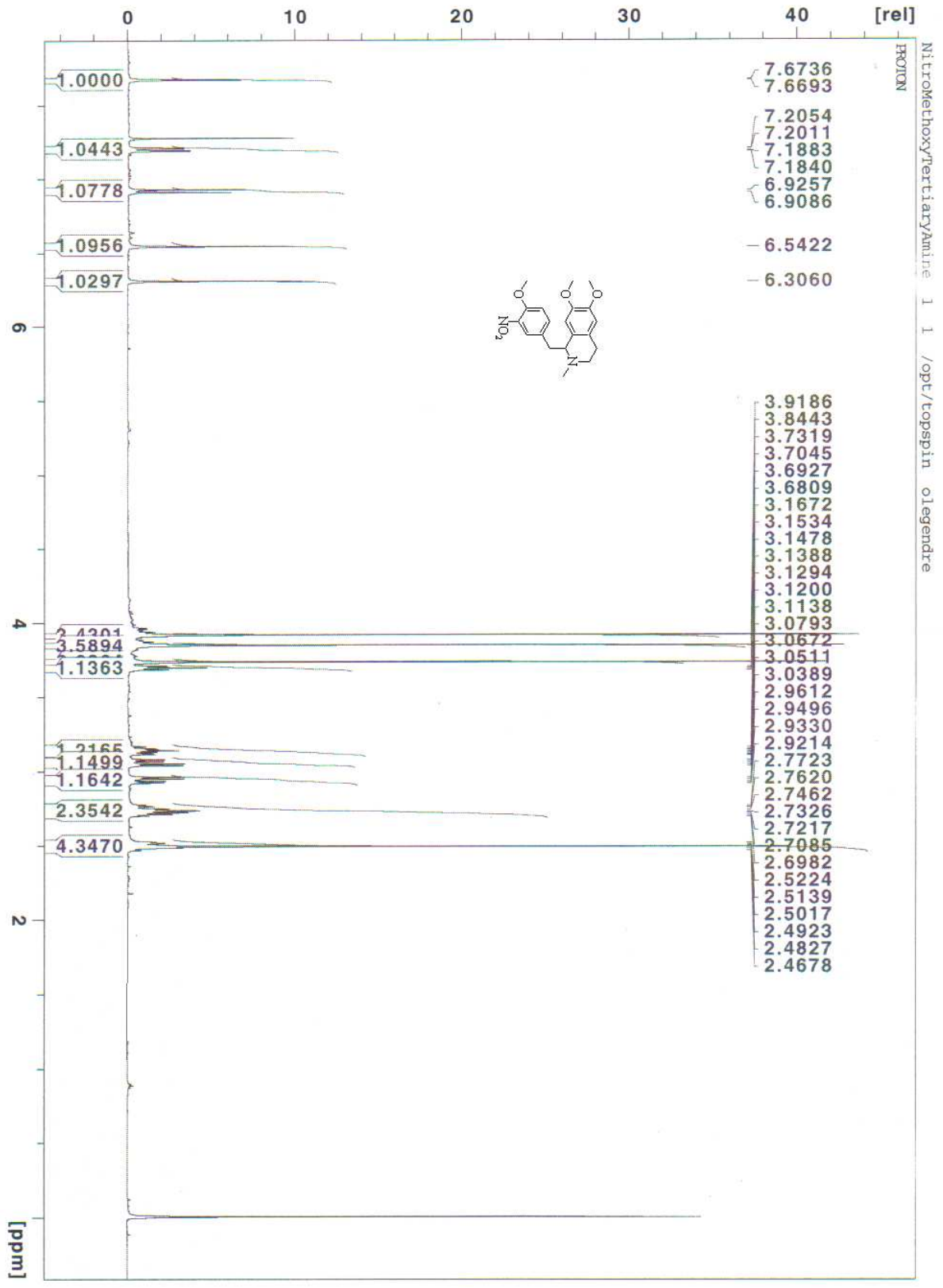
35.1478
150
100
50
[ppm]


0
10
20
30
40
[rel]
6
4
2
[ppm]
PROTON
NitroMethoxyTertiaryAmine 1 1 /opt/topspin olegendre
1.0000
1.0443
1.0778
1.0956
1.0297
3.5894
1.1363
1.1499
1.1642
2.3542
4.3470
7.6736
7.6693
7.2054
7.2011
7.1883
7.1840
6.9257
6.9086
6.5422
6.3060
3.9186
3.8443
3.7319
3.7045
3.6927
3.6809
3.1672
3.1534
3.1478
3.1388
3.1294
3.1200
3.1138
3.0793
3.0672
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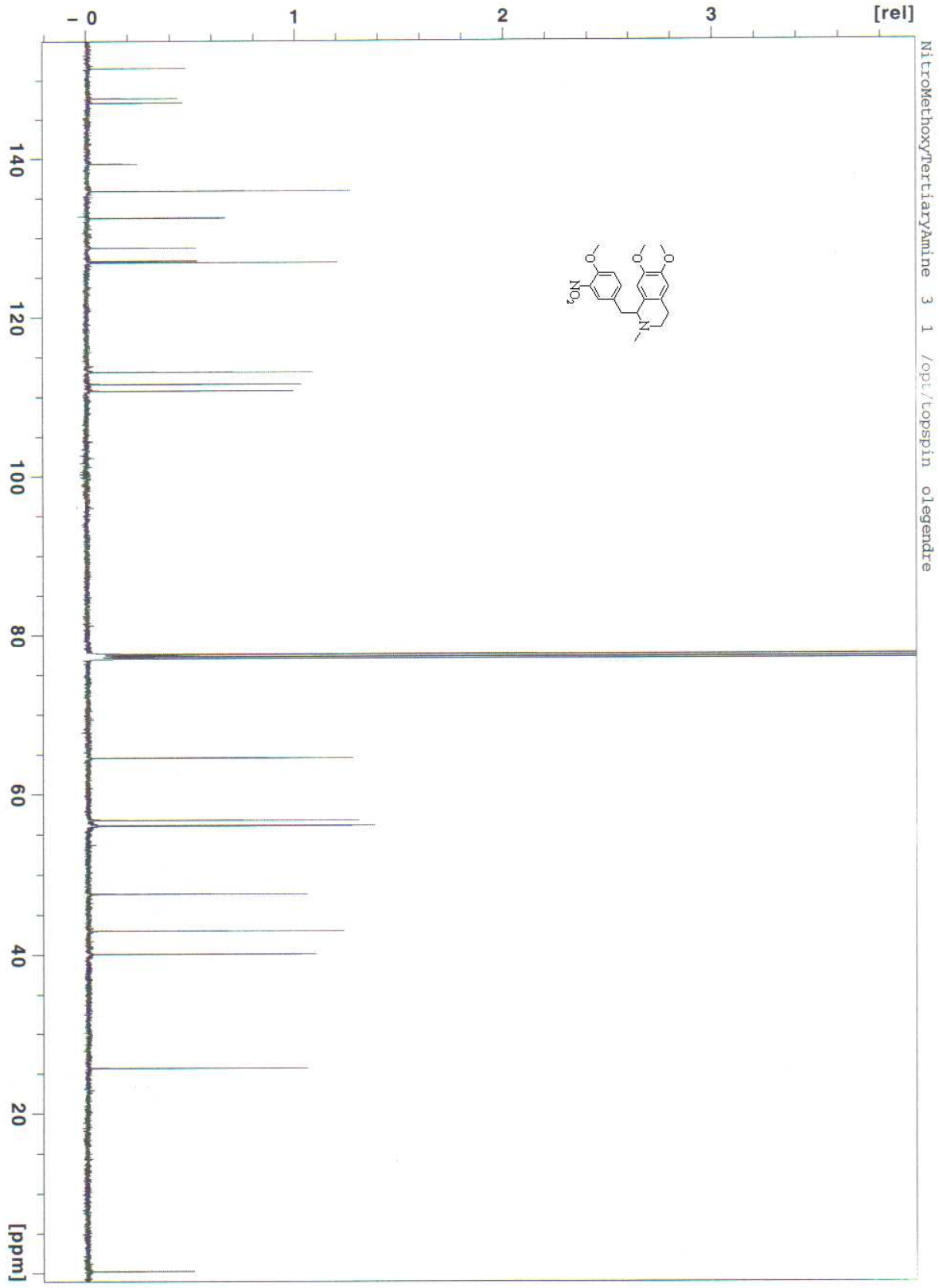
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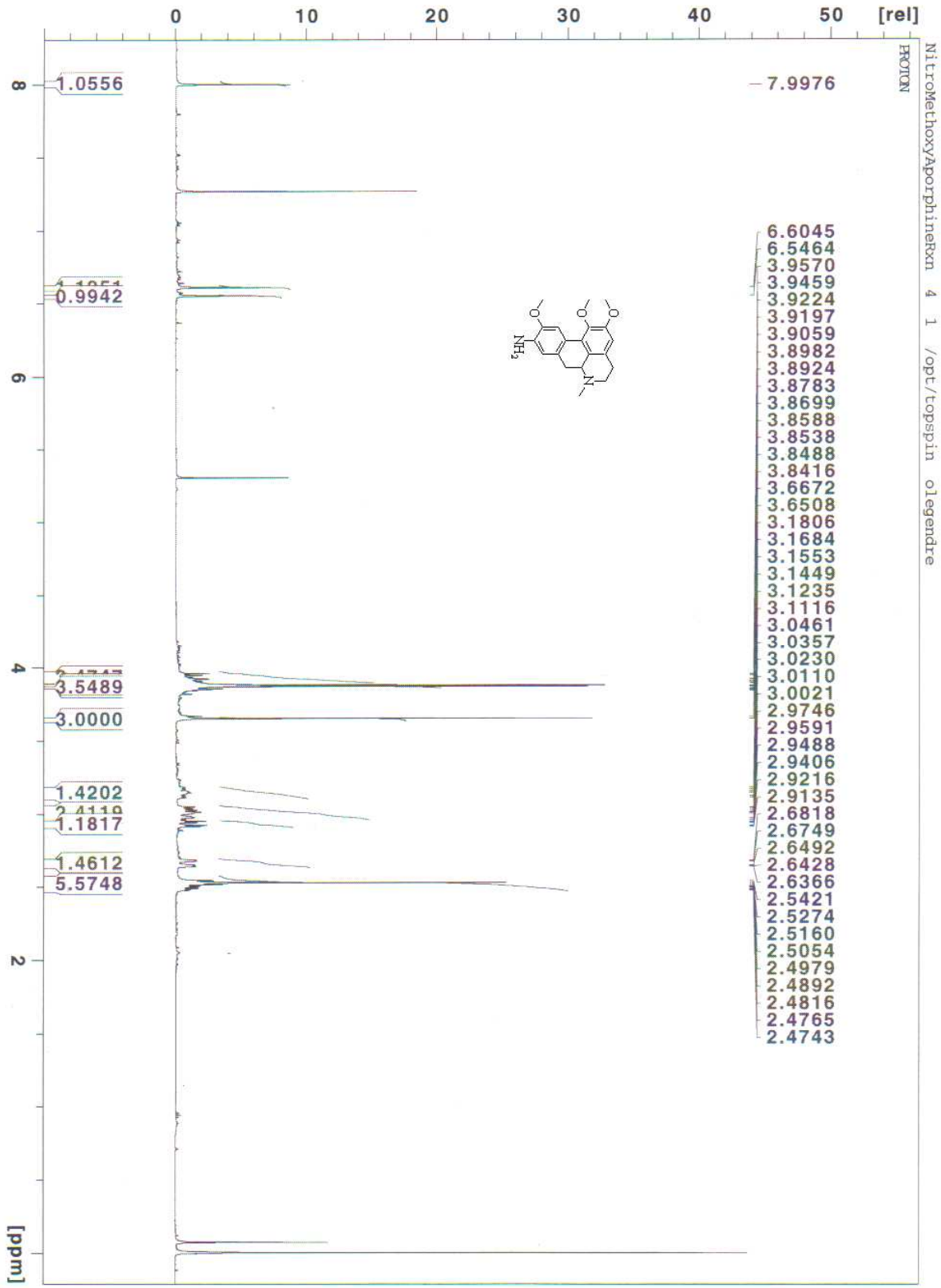
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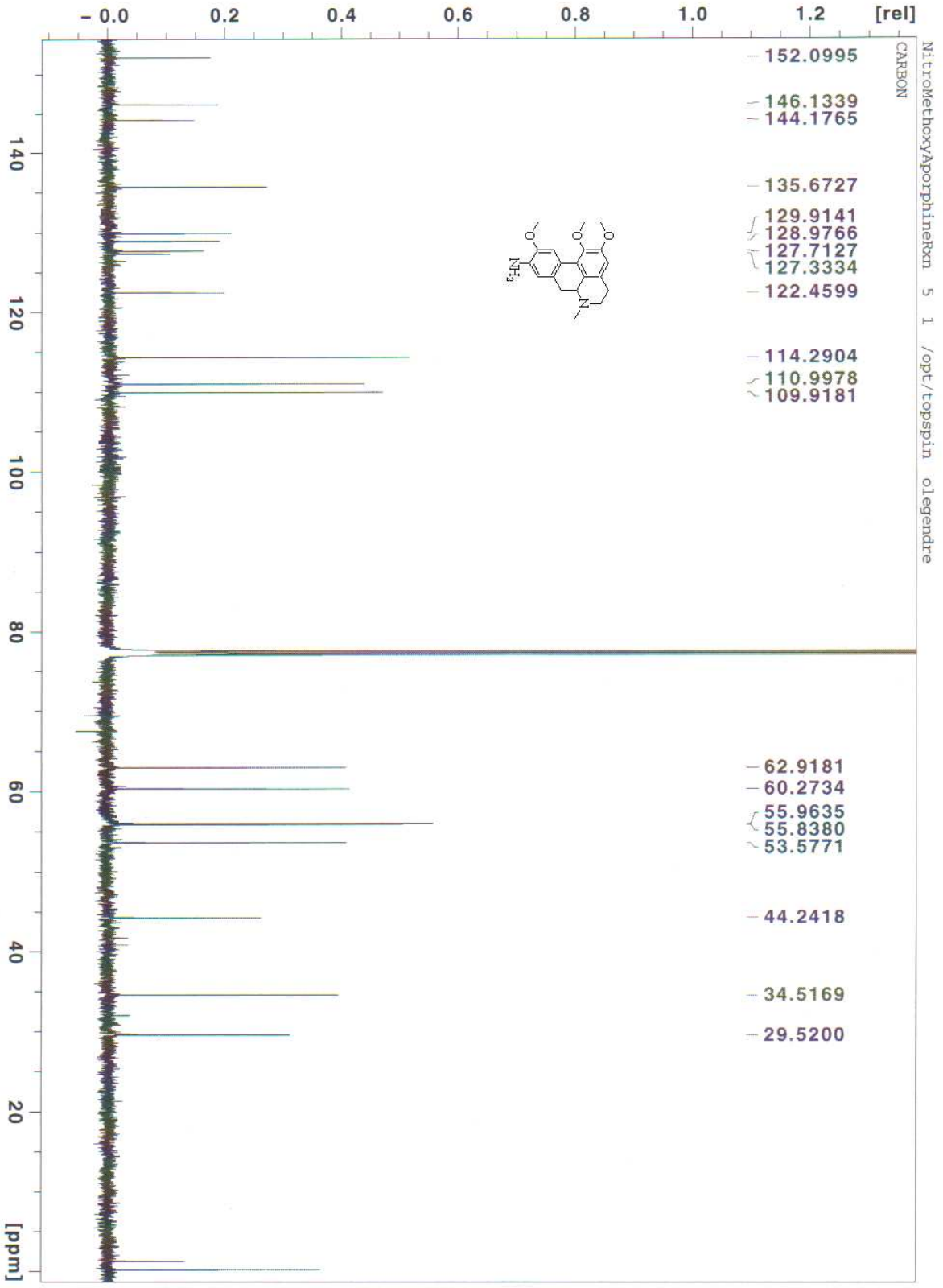
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