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Synthesis and Biological Activity of Aminoglycosides and 1,4-Naphthoquinone Derivatives

Marina Fosso Yatchang

SYNTHESIS AND BIOLOGICAL ACTIVITY OF AMINOGLYCOSIDES AND 1,4-NAPHTHOQUINONE DERIVATIVES

by

Marina Fosso Yatchang

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in

Chemistry

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UTAH STATE UNIVERSITY
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ABSTRACT

Synthesis and Biological Activity of Aminoglycosides

and 1,4-Naphthoquinone Derivatives

by

Marina Fosso Yatchang, Doctor of Philosophy

Utah State University, 2012

Major Professor: Dr. Cheng-Wei Tom Chang
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Aminoglycosides, such as streptomycin, kanamycin and neomycin, are a group of naturally occurring antibiotics that structurally consist of various amino-modified sugars. They have long been used clinically for their broad-spectrum activity against Gram-negative and Gram-positive bacteria. However, the incidence of bacterial resistance has considerably hampered their clinical efficacy, forcing researchers to explore new applications of aminoglycosides.

An aminoglycoside belonging to the class of pyrankancin was identified as the lead compound in the treatment of spinal muscular atrophy, an infantile disease caused by nonsense mutations. To further investigate its therapeutic capabilities, additional batches of this lead compound were prepared and its mode of action study revealed an unprecedented SMNΔ7 read-through event.

In addition, the chemical derivation of kanamycin B was examined in the aim of developing potential agro fungicides. Indeed, a library of kanamycin B analogs was synthesized to investigate the length of the alkyl chain and its position in kanamycin B that will confer to this latter an optimum antifungal activity. Results of this study revealed that the attachment of an octyl group at the *O*-4´´ position of the core structure of the classical aminoglycoside kanamycin B converts this obsolete drug into a broad-spectrum fungicide. Another interesting finding was the simultaneous loss of antibacterial activity usually observed in aminoglycosides. This was essential as it paves the way for the development of a new class of aminoglycoside-based fungicides suitable for use in crop disease application.

Molecules with naphthoquinone scaffolds are also of great interest due to their important biological and pharmaceutical applications. Three synthetic protocols were examined to optimize the production of the 1,4-naphthoquinone derivatives and to conveniently synthesize a library of novel cationic anthraquinone analogs. The antibacterial activities of these compounds were evaluated and they were found to display much higher levels of activities against Gram-positive than Gram-negative bacteria. In addition, with double alkyl chains of various lengths (C_2 –C_{12}) at N-1 and N-3 positions, a synergistic effect of the alkyl groups was observed, suggesting the importance of overall lipophilicity in the activity of this class of compounds against Gram-positive bacteria.

(287 pages)

PUBLIC ABSTRACT

Synthesis and Biological Activity of Aminoglycosides

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Marina Fosso Yatchang, Doctor of Philosophy

Utah State University, 2012

The research described in this dissertation is at the interface of organic chemistry and biology, and it aimed at designing and synthesizing biologically active molecules for the possible development of therapeutic agents.

Spinal muscular atrophy is an incurable disease that affects 1 in every 6000 babies, making it the leading genetic cause of infant mortality. While no treatment is available, efforts are being taken to solve this issue. Part of the work outlined in this dissertation was carried out in collaboration with researchers from the University of Missouri to investigate a potential therapeutic for this disease.

In addition, the continuous outbreak of diseases caused by bacteria demands for new and improved antibiotics that could help eradicate those pathogens. My research thus allowed me to discover molecules with interesting activity against bacteria for the possible development of potential antibacterial agents.

Finally, my research also allowed me to develop potential agro fungicides, which are still very much needed nowadays. Many crop diseases are due to fungal infections,

which globally cause enormous economic losses. The use of fungicides is still the main strategy to control these diseases. However, current agro fungicides show some limitations. This is illustrated with Fusarium head blight (FHB), a destructive and costly disease of wheat, barley and other small grains, whose economic losses in the Central United States alone were estimated to $2.7 billion.

DEDICATION

I would like to dedicate this work to my mother, KOUAKEP JOSETTE, for every single sacrifice she has ever made in her life for my well-being.

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First and foremost, I would like to express my profound gratitude to my supervisor, Dr. Cheng-Wei Tom Chang, for giving me the opportunity to conduct my doctoral research in his laboratory. He taught me how to work hard and think critically. His guidance, patience, and support throughout my program have been invaluable sources of motivation.

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I would also like to thank Sanjib Shrestha and Yukie Kawasaki for testing the biological activities of my compounds. At the end, this collaboration turned into great friendship. I will not forget Dr. John Lawson who gave me the opportunity to work in his company and improve my organic synthetic skills. He has also been so understanding during the time I was writing my dissertation.

I would like to thank all my friends in the U.S.A., Cameroon, and elsewhere, who have been supportive. Colette Tasha, Grace Kengne, and Hermine Mbouguela: I have always known you would be there for me anytime I needed you. Eric and Christabel Tanifum, "Auntie Ste" Marystella Beh, Joyce Mumah, Brenda and Alvin Lailam, Yannick Bidias, Alem, and Omar and Susie Arrieta, we sure had our good share of fun times. My AFSA (African Students Association) family at USU, you have helped me stay connected with my roots while in the United States, rendering this sojourn pleasant.

Special thanks go to Eric and Christabel Tanifum who have welcomed me in their family without knowing who I was. I will never say it enough but you guys have a special place in my heart.

To my "nounours" Yannick Bidias, you are certainly the one who has experienced my ups and downs during my doctoral program. You offered me your shoulder to cry on when nothing was going on well, and you were there to share every single moment of happiness I had. You are my best friend and I could not think of a better person to share my life with.

Last but not least, I must acknowledge the support of my mother, my sister Fosso Seukep Valerie, and my brothers Gangnang Fosso Aristide, Fosso Djatend Anaclet, and Fosso Kamsu Ghislain. Thank you all for always believing in me!

Marina Fosso Yatchang

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LIST OF ABBREVIATIONS

2-DOS: 2-deoxystreptamine

Ac: acetyl

Ac_2O: acetic anhydride

ACOH: acetic acid

APCI: atmospheric pressure chemical ionization

Bn: benzyl

BnBr: benzyl bromide

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DMAP: 4-(dimethylamino)pyridine

DMF: dimethyformamide

DMSO: dimethyl sulfoxide

ESI: electrospray ionization

FAB: fast atom bombardment

FHB: fusarium head blight

G-: gram negative

G+: gram positive

HTB: hexadecyltrimethylammonium bromide

MALDI: matrix-assisted laser desorption/ionization

MIC: minimum inhibitory concentration

NBS: *N*-bromosuccinimide

NIS: *N*-iodosuccinimide

PBS: phosphate buffer saline

r.t.: room temperature

ROS: reactive oxygen species

SMA: spinal muscular atrophy

SMN: survival motor neuron

S_N2: bimolecular nucleophilic substitution

TBAI: tetrabutylammonium iodide

TBAHS: tetrabutyl ammonium hydrogen sulfate

TEA: triethylamine

Tf_2O: trifluoromethanesulfonyl acid anhydride

TfOH: trifluoromethanesulfonic acid

TFA: trifluoroacetic acid

THF: tetrahydrofuran

TMSOTf: trimethylsilyl trifluoromethanesulfonate

Tr: trityl or triphenylmethyl

Ts: tosyl

TsOH: *p*-toluene sulfonic acid

TsCl: toluenesulfonyl chloride

VPA: valproic acid

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CHAPTER I

GENERAL INTRODUCTION

Between 1940 and 2004, a staggering 335 infectious diseases have been discovered.[1] And with an estimated three new diseases being identified every couple of years, this number is constantly increasing.[2] Furthermore, diseases that were once treatable are resurging as a threat for a significant portion of the population. Through mutation or genetic exchange, infectious agents are able to develop resistance against available drugs and evolve into new deadly strains.

This alarming prevalence of drug-resistant microorganisms, together with the continuous emergence of infectious diseases, has enabled these pathogens to be two steps ahead of humans and contributed to ranking infectious diseases among the leading causes of mortality in the world.[3]

In addition to these emerging infectious diseases, which are caused by external factors (bacteria, viruses, and fungi), abnormalities in an individual's genome could also result in disorders called genetic diseases. Genetic diseases can either be inherited from the parents, or they could result from developed mutations or changes on the DNA. Changes that occur on a single gene give rise to Mendelian or single-gene disorders; meanwhile, multifactorial genetic diseases are caused by mutations in several genes, often coupled with environmental factors.

Spinal muscular atrophy (SMA) is an example of Mendelian disorders. It is caused by the homozygous loss of the *Survival Motor Neuron 1* (*SMN1*) gene.[4] It is an incurable neuromuscular disease characterized by the death of motor neurons present in

the anterior horn of the spinal cord.[5,6] It manifests itself by the progressive weakness and degeneration of the muscles.[7] Four types of SMA exist and they are categorized based upon the disease severity and the age of onset:[8]

- Type I or Werdnig-Hoffman disease is the most severe form of SMA and manifests itself in the first months of life (0-6 months),
- Type II or Dubowitz disease is the intermediate form with an age of onset between 6 and 18 months,
- Type III or Kugelberg-Welander disease manifests after 18 months (juvenile form),
- Type IV or adult-onset form appears after 35 years.

With an incidence of one in every 5,000 – 10,000 births, SMA is the leading genetic cause of infant mortality.[9,10]

In light of these observations, the need to develop new and improved drugs that will help treat these diseases and alleviate this global threat becomes obvious. And what better place than nature to find the inspiration! This is clearly evidenced by the number of approved and clinical-trial drugs derived from natural products.[11,12] For example, 26% of the new drugs approved by the Food and Drug Administration (FDA) in 2009-2010 were derived from nature.[13]

Aminoglycosides and naphthoquinones are two abundant, naturally occurring classes of compounds that have significant pharmacological properties. Anthracyclines, which can be viewed as 1,4-naphthoquinone derivatives, and aminoglycosides have even

been categorized as "drug-productive scaffolds".[13] It thus becomes apparent why we have directed our efforts toward these two classes of compounds.

I.1. Aminoglycosides

I.1.1. Classification and traditional mode of action of aminoglycosides

Streptomycin (Figure 1) was the first aminoglycoside to be discovered. Isolated from the actinobacterium *Streptomyces griseus* in 1944,[14] it was the first antibiotic effective in the treatment of tuberculosis. Since then, the broad-spectrum of activity of aminoglycosides against both Gram-negative and Gram-positive bacteria has stimulated multitude interests.

Aminoglycosides are a group of naturally occurring antibiotics that structurally consist of various amino-modified sugars. 2-Deoxystreptamine (2-DOS) has been found to play a pivotal role in the biological activity of aminoglycosides,[15,16] resulting in its derivatives being among the most studied aminoglycosides. This includes the two major classes of neomycin and kanamycin (Figure 2). Members of the neomycin class can be viewed as 4,5-disubstituted 2-deoxystreptamines, while the kanamycin class encompasses the 4,6-disubstituted 2-deoxystreptamines.

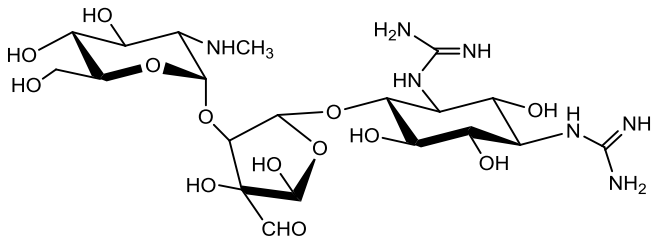
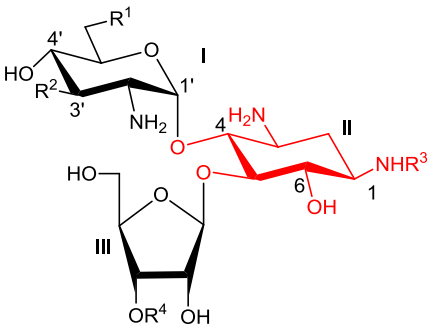
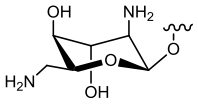
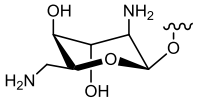
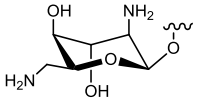
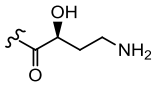


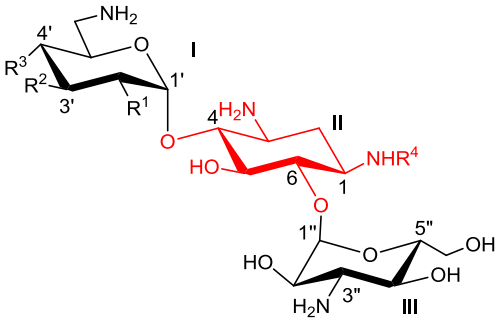
Figure 1: Structure of streptomycin.

4, 5-disubstituted 2-deoxystreptamines – Neomycin class



	R^1	R^2	R^3	R^4
Neomycin B	NH_2	OH	H	
Paromomycin I	OH	OH	H	
Lividomycin B	OH	H	H	
Butirosin B	NH_2	OH		H
Ribostamycin	NH_2	OH	H	H

4, 6-disubstituted 2-deoxystreptamines – Kanamycin class



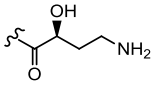
	R^1	R^2	R^3	R^4
Kanamycin A	OH	OH	OH	H
Kanamycin B	OH	NH_2	OH	H
Dibekacin	NH_2	H	H	H
Arbekacin	NH_2	H	H	

Figure 2: Structures of 2-deoxystreptamine (2-DOS) aminoglycosides

Aminoglycosides are well known for their traditional role of antibacterial agents. Their mode of action has been extensively studied. They have been found to exert their bactericidal action by selectively binding to the A-site (aminoacyl site) decoding region of the 16S ribosomal RNA (rRNA) of bacteria.[17,18] During the protein synthesis, binding of the correct tRNA to the mRNA causes conformational changes of two adenine residues (A1492 and A1493) in16S rRNA, allowing them to contact with the mRNA-tRNA codon-anticodon hybrid.[19] Since mispairing of codon and anticodon cannot induce this conformational change, this "proof-reading" process helps to ensure translational fidelity. However, the binding of the aminoglycosides at the decoding region impacts the conformational changes of A1492 and A1493.[20,21] As a result, discrimination between cognate and near-cognate tRNA is reduced in the presence of aminoglycosides, enabling codon misreading.[22] Misfolded proteins are then produced, some of which are incorporated in the bacterial membrane, leading to the loss of membrane integrity and increased permeability for the antibiotics. As a consequence, aminoglycosides accumulate rapidly in the cytoplasm and saturate all ribosomes, resulting in cell death (Figure 3).[23-25]

Despite these noticeable advantages, the nephrotoxicity and ototoxicity associated with aminoglycosides have considerably hampered their clinical usefulness.[26]

Aminoglycosides have also suffered from the emergence of drug-resistant bacteria. Over fifty aminoglycoside-deactivating enzymes have been identified.[24, 27-30] They act by modifying the structures of aminoglycoside antibiotics. This could be accomplished either through phosphorylation of a hydroxyl group (aminoglycoside

phosphoryltransferases, APH), adenylation of a hydroxyl group (aminoglycoside adenylyltransferases, AAD or ANT), or acetylation of an amino group (aminoglycoside acetyltransferases, AAC). Other mechanisms of resistance include the decrease of drug uptake into bacteria and the alteration of the ribosomal binding sites.

All these phenomena have rendered these once-before-acclaimed drugs obsolete, resulting in a growing interest in the development of new and modified aminoglycosides, with improved antibacterial activity.[24,31] Despite all the efforts invested, a huge gap is still to be filled. This has thus forced other research groups to explore new applications of aminoglycosides.

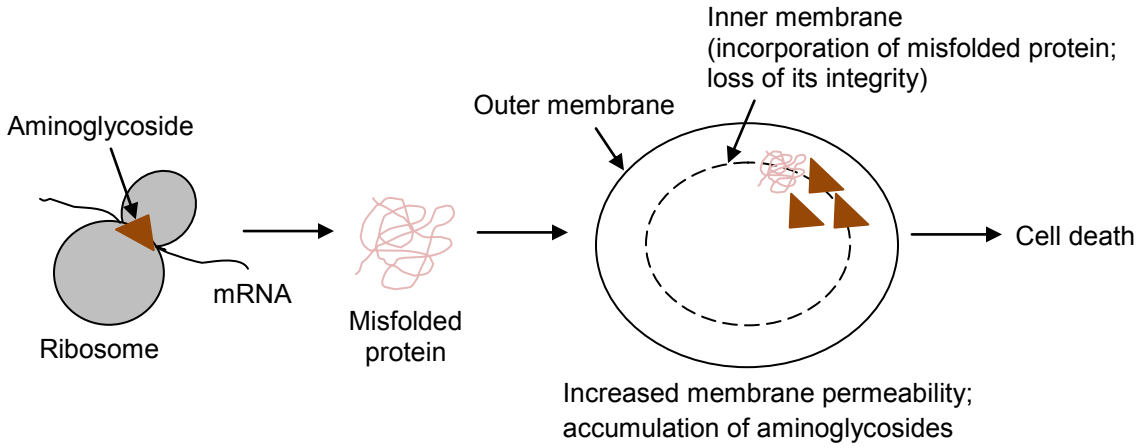


Figure 3: Bactericidal action of aminoglycosides
(Adapted from Kohanski, 2010 [Ref. 25])

I.1.2. Aminoglycosides in the treatment of genetic diseases

The selective binding of aminoglycoside antibiotics toward bacterial ribosome is crucial for their therapeutic use, and this is largely achieved through critical interactions

of the drug with nucleotides of the rRNA that are not similar in bacteria and human.[32] For example, studies have demonstrated that A1408 and G1491 of the bacterial decoding site determine the selectivity of aminoglycosides.[33,34] Eukaryotic cytoplasmic ribosomes are insensitive to aminoglycosides because a guanine residue is found at position 1408 and an adenine residue at position 1491 of 16S rRNA, which are all not able to interact with aminoglycosides.

However, it was found that certain aminoglycosides can bind to the small subunit of bacterial and eukaryotic ribosomes, especially at sites where nucleotides that are conserved between bacteria and eukaryotes are involved.[35] For example, apramycin and geneticin (Figure 4) are known to bind to the human decoding site.[32,36] This disadvantage turned out to be useful in the treatment of genetic diseases caused by nonsense mutations.

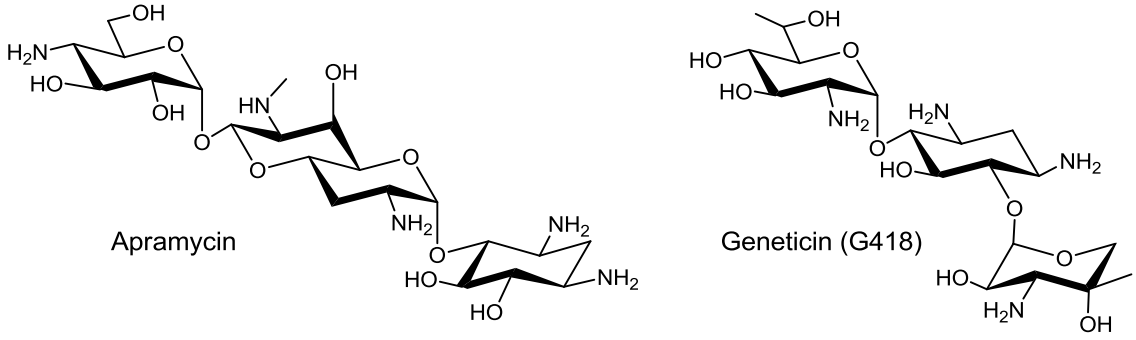


Figure 4: Structures of apramycin and geneticin (G418)

More than 1800 distinct heritable human diseases are caused by nonsense mutations,[37] during which a change in a single nucleotide in a DNA sequence converts a codon that specified an amino acid into a stop codon. As a result, protein translation prematurely terminates, leading to the production of non-functional shortened

proteins.[38,39] In 1985, Burke and Mogg[40] showed that aminoglycosides can suppress the effect of a nonsense mutation; by binding to the decoding site, aminoglycosides reduce the translation fidelity and allow a random amino acid to be incorporated at a premature-termination codon in mammalian cells. As a result, the protein translation can proceed through the natural stop codon (Figure 5).[41]

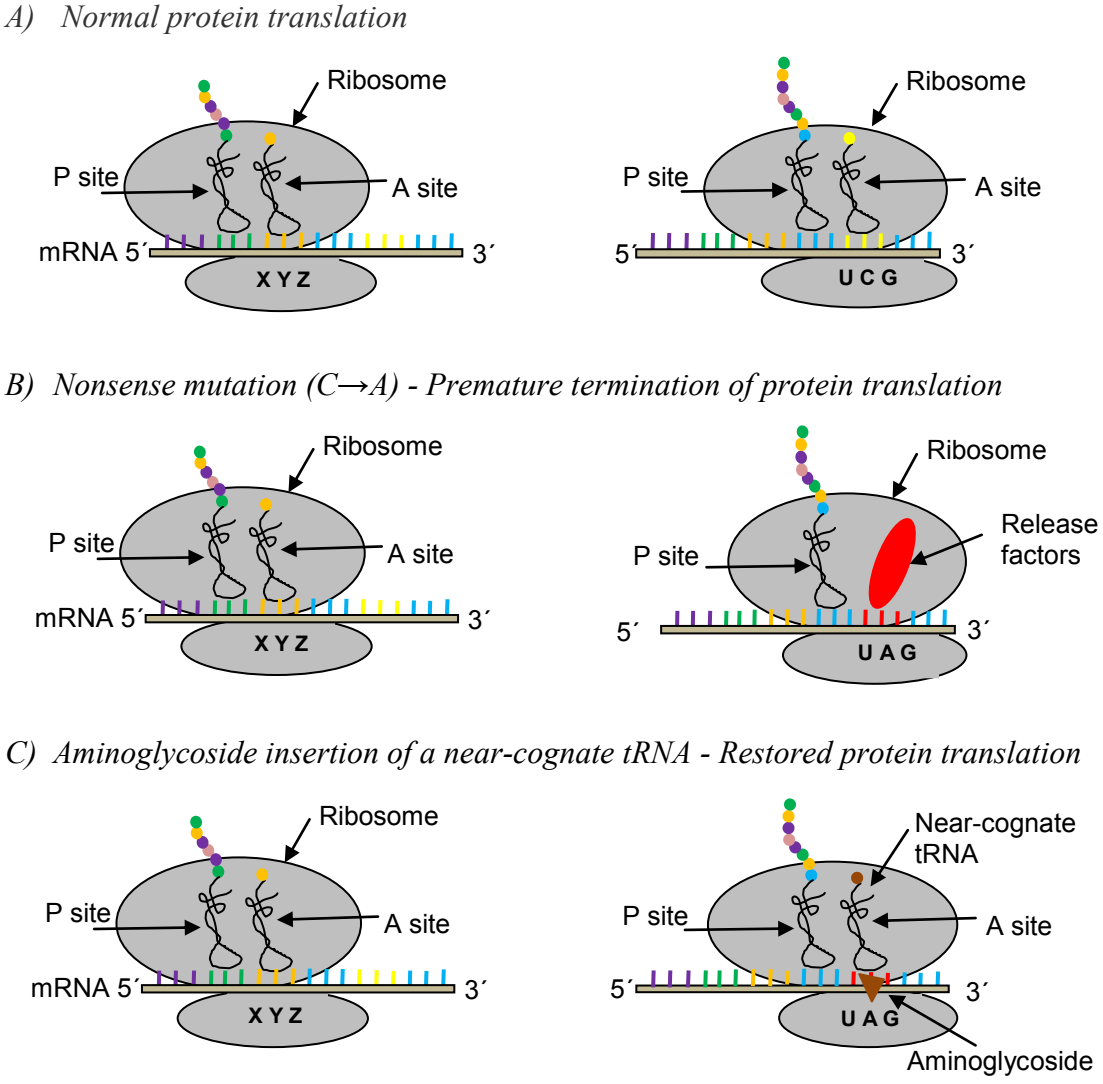


Figure 5: Suppression of nonsense mutation by aminoglycosides
(Adapted from Malik, 2010 [Ref. 41])

This concept has introduced novel research avenues in the field of aminoglycosides, allowing them to emerge as stop codon read-through inducers. This new ability was tested as a therapeutic approach for human genetic diseases, including spinal muscular atrophy.

I.1.3. Aminoglycosides as antifungal agents

Fungal infections are mainly responsible for the huge economic losses generated from crop and turf diseases. Current strategies to control these infections include the direct application of chemical fungicides.[42] However, their associated toxic side effects toward animals and humans oblige the growers to reduce their dependency on these antibiotics and seek for better alternatives. Unfortunately, while enormous efforts have been devoted to the development of new antibacterial, antiviral, and anticancer therapeutics, only a few new fungicides have been introduced since the mid-1980s.[43]

Fungi are eukaryotic organisms whose cells contain a nucleus enclosed within a distinct membrane. As in any eukaryote, anionic sphingolipids are found on the outer surface of fungal cell membranes. Therefore, cationic molecules such as aminoglycosides would be expected to interact with the fungal cell walls. As a matter of fact, it was recently reported that certain commercially aminoglycosides are inhibitory to plant pathogenic oomycetes.[44] However, the major drawback related to the use of aminoglycosides to combat crop diseases is their potential contribution to the propagation of bacterial resistant strains.[45,46] Therefore, the best aminoglycoside agrofungicide candidates will be those that completely lose their antibacterial capabilities while gaining some antifungal activities.

I.2. 1,4-Naphthoquinone derivatives

I.2.1. History and biological functions

1,4-naphthoquinone belongs to the broad class of compounds called quinones. 1,4-naphthoquinone derivatives are of particular interest because of their large occurrence as natural products.[47-51] They are found in various parts of plants such as leaves, flowers, roots, bark, and wood. In addition, they exhibit a wide range of interesting biological activities.[52-56] Molecules bearing naphthoquinone scaffold have also been employed as inhibitors against vitamin K dependent carboxylase,[57] protein kinase,[58] coenzyme Q,[59] and as growth stimulator for bifidobacteria.[60]

A representative class of 1,4-naphthoquinone derivatives is the group of fat-soluble compounds called vitamin K. This includes the naturally occurring vitamin K_1, or phylloquinone, required for blood coagulation, and vitamin K_2, or menaquinone, which is of vital importance for bone health (Figure 6). A synthetic form of vitamin K is vitamin K_3 or menadione (Figure 6), which is often used as a quinone model for in vivo studies.

Menadione has been shown to undergo both redox cycling and arylation reactions. This is mainly due to the two carbonyl groups, which give the ability to 1,4-naphthoquinone derivatives to accept one and/or two electrons.[61] 1,4-naphthoquinone derivatives can accept an electron to form the semiquinone radicals upon catalysis by flavoenzymes such as NADPH-cytochrome P-450 reductase (Figure 7).[52,62,63] The semiquinone radicals can be further reduced to hydroquinones. In aerobic conditions, reactive oxygen species (ROS) are produced by transfer of electrons to oxygen. ROS is

commonly used to refer to superoxide, hydroxyl radical, and hydrogen peroxide, which are all known to break DNA strands.[64-66]

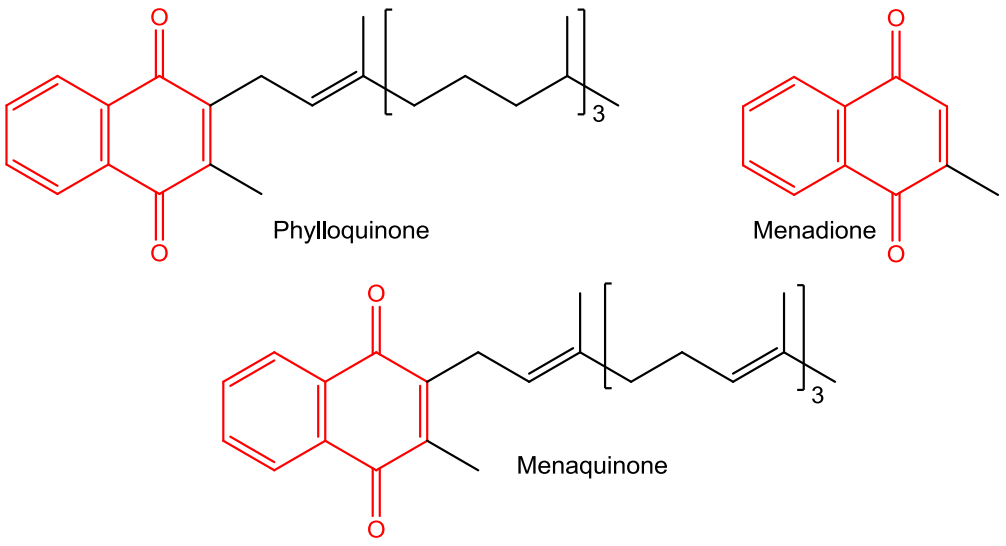


Figure 6: Structures of vitamin K_1 (phylloquinone), vitamin K_2 (menaquinone), and vitamin K_3 (menadione)

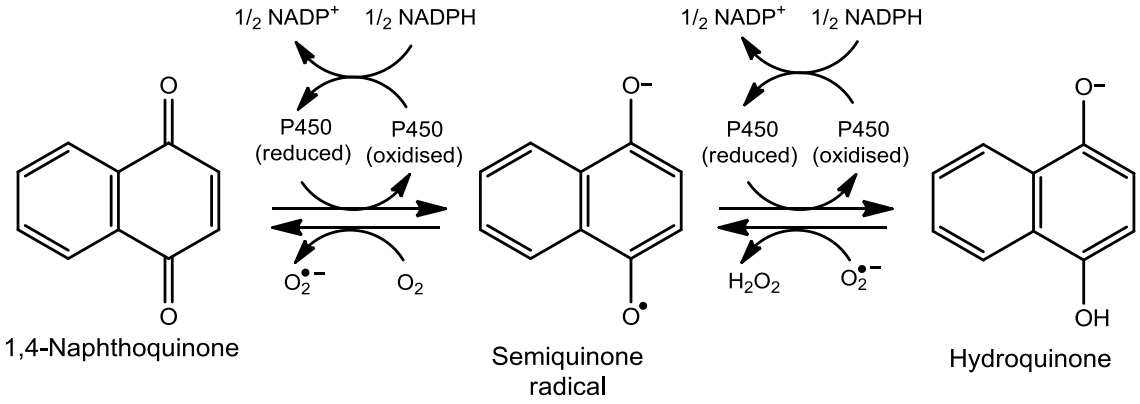


Figure 7: 1,4-Napthoquinone derivatives as redox cyclers

In addition, 1,4-naphthoquinone derivatives can undergo arylation reactions. They contain electrophilic α,β-unsaturated carbonyl groups, which can react with nucleophilic moieties of proteins, such as thiolate groups, and form covalent bonds. This usually results in the inactivation and loss of protein function.[67]

I.2.2. 1,4-Naphthoquinone derivatives as antibacterial agents

Various 1,4-naphthoquinone derivatives with antibacterial activity are known (Figure 8). This includes plumagin, juglone and lawsone, which are naturally occurring naphthoquinones of plant origin.[68] Alkannin, shikonin, and their derivatives are other natural naphthoquinone products whose antimicrobial activity has been widely investigated.[69] Pleosporone was isolated from a pleosporalean ascomycete.[70]

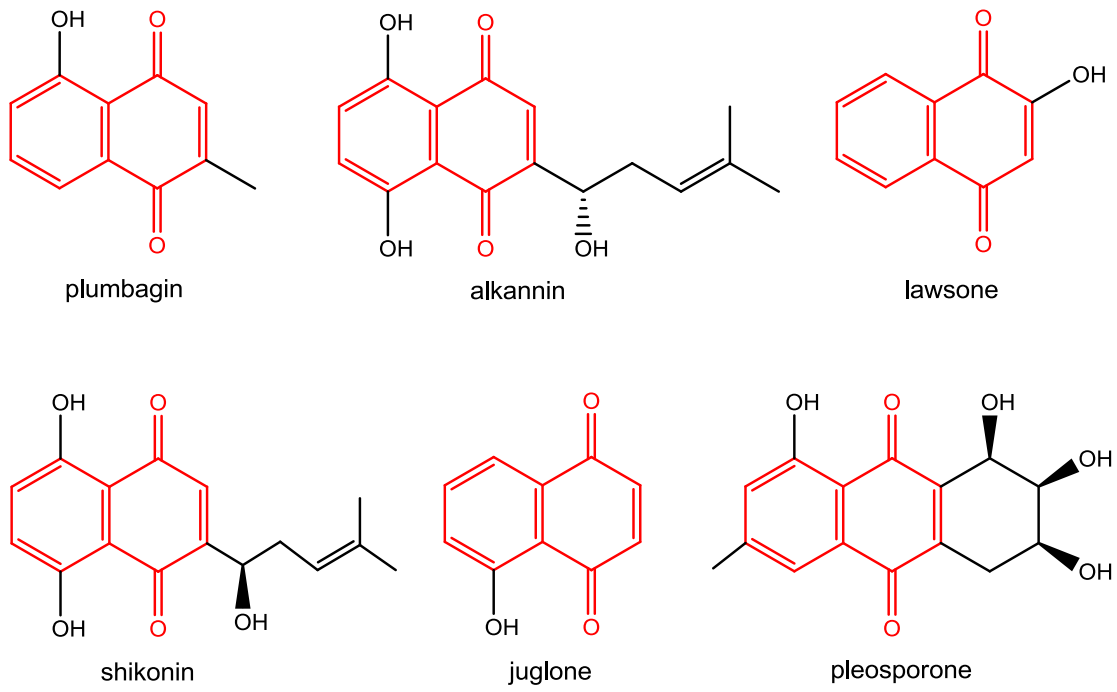


Figure 8: Structures of antibacterial 1,4-naphthoquinone derivatives

1,4-naphthoquinone derivatives can exert their antibacterial activity by decoupling of oxidative phosphorylation, a process essential for ATP synthesis. Because of their ability to accept electrons, they can compete with electron carriers such as coenzyme Q and uncouple the electron transport chain.[71]

In addition, 1,4-naphthoquinone derivatives are known to inhibit the growth of Gram-positive bacteria such as *Staphylococcus aureus*, *Enterococcus faecium*, and *Bacillus subtillus*. However, they are ineffective against Gram-negative bacteria such as *Escherichia coli* and *Salmonella typhimurium*.[69]

I.3. Research summary

The aim of this research was to synthesize biologically active molecules. First of all, new therapeutic potentials of antibiotic aminoglycosides were investigated. A pyranmycin compound, an aminoglycoside, was re-synthesized and its mode of action in the treatment of spinal muscular atrophy was studied (chapter II). In addition, synthesis of various kanamycin B analogs revealed that a simple alkylation can convert this well-known antibacterial into an antifungal agent with potential use in agriculture (chapter III). Finally, a library of cationic 1,4-naphthoquinone derivatives was developed and their antibacterial activity studied (chapter IV).

CHAPTER II

AMINOGLYCOSIDES AS THERAPEUTICS FOR SPINAL MUSCULAR ATROPHY[a]

II.1. Rationale

Spinal muscular atrophy (SMA) is an autosomal recessive disease. SMA patients carry a pair of defective chromosomes 5 that both lack the *Survival Motor Neuron-1 (SMN1)* gene on the long (q) arm, at position 13.2.[72] *SMN1* produces full-length transcripts that translate into high levels of the survival motor neuron (SMN) protein, essential for the maintenance of motor neurons (specialized nerve cells that control muscle movement). *SMN2*, a nearly identical gene to *SMN1* also found at locus 5q13.2,[4] exhibits a critical C to T nucleotide variation within the 5′ end of exon 7.[73] This causes *SMN2*-derived transcripts to undergo alternative splicing at the junction of intron 6 and exon 7.[74,75] As a result, 90% of the *SMN2*-derived transcripts lack the exon 7 and will therefore code a truncated and unstable SMNΔ7 protein; only 10% will produce a fully functional SMN protein.[4,76] Therefore, in the absence of *SMN1*, *SMN2* alone cannot produce enough SMN protein for the maintenance of motor neurons. However, an increase in the number of *SMN2* copies will result in more *SMN2*-derived SMN protein, and thus reduce the severity of SMA.

Dr. Christian Lorson and co-workers (Department of Veterinary Pathobiology, Bond Life Sciences Center, University of Missouri) have previously reported the ability

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[a] Part of this chapter was coauthored by Virginia B Mattis, Marina Y Fosso, Cheng-Wei Chang and Christian L Lorson. Reproduced with kind permission from *BMC Neurosc*. **2009**, *10*:142.

of two aminoglycosides, tobramycin and amikacin (Figure 9), to elevate the SMN protein levels in SMA cells.[77] By employing the capacity of aminoglycosides to read-through ribosomes past stop codons (see chapter I for more details), tobramycin and amikacin enable the incorporation of missing sequences at the C-terminus of SMNΔ7 protein, thereby restoring the stability and the functionality of this novel SMN protein.

In light of these results, through collaboration with Dr. Lorson, our libraries of previously synthesized aminoglycosides were screened to identify **TC007** (Figure 9) as the lead in the treatment of spinal muscular atrophy.[78] Therefore, my goal was to prepare more **TC007** in order to study its mode of action in the treatment of spinal muscular atrophy.

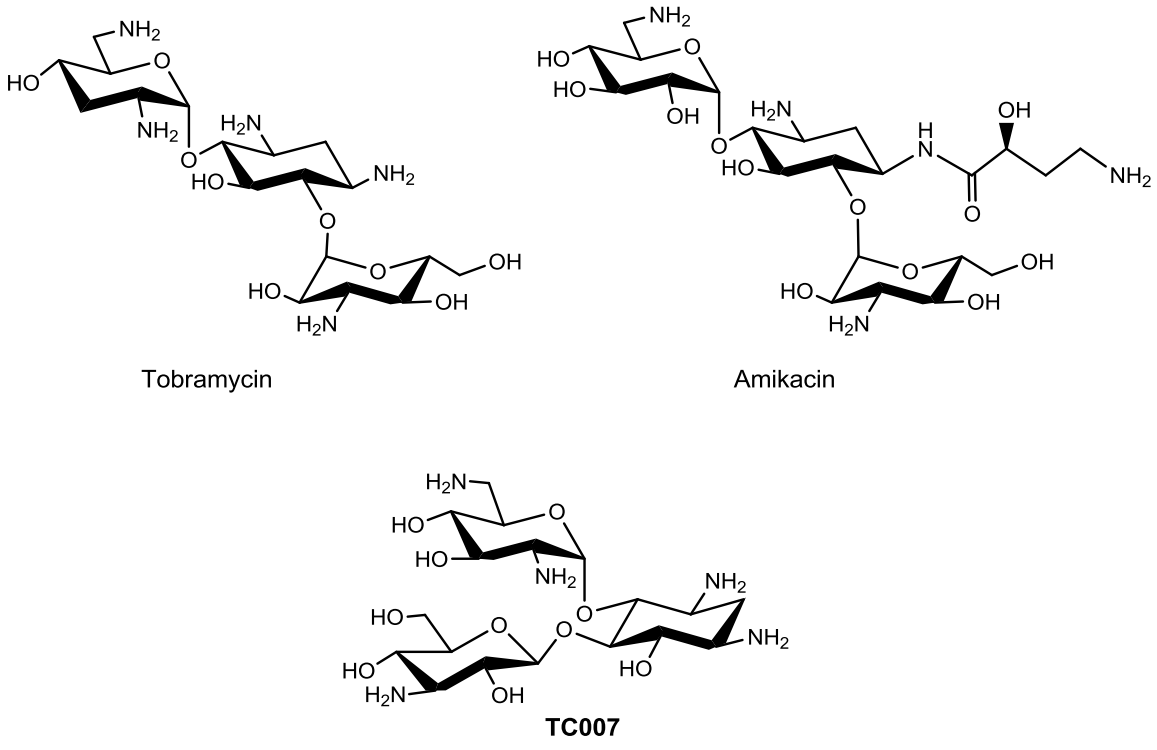


Figure 9: Structures of tobramycin, amikacin, and **TC007**

II. 2. Results and discussion

II.2.1. Synthesis of **TC007**

TC007 belongs to the class of pyranmycin compounds. These are neomycin analogs and they result from the replacement of the neobiosamine core (rings III and IV) of neomycin with a pyranose (Figure 10).[79] It has been previously demonstrated that the glycosidic bond of a furanose is more prone to acid cleavage than that of a pyranose.[80] Pyranmycin could therefore survive harsh acidic conditions that will otherwise degrade neomycin.[81]

Following the protocol previously described by Dr. Ravi Rai,[79] the synthesis of **TC007** will start from the commercially available neomycin B. Conversion of the amino groups into azido groups followed by benzylation afforded compound **1**[82] (Scheme 1). Cleavage of the glycosidic bond between rings II and III was accomplished by refluxing **1** in the presence of copper (II) chloride, and this gave the known neamine derivative **2**.[82] The free hydroxyl group at the 5-position is required for the final compound to be a 4,5-disubstituted 2-deoxystreptamine, thus an analog of neomycin.

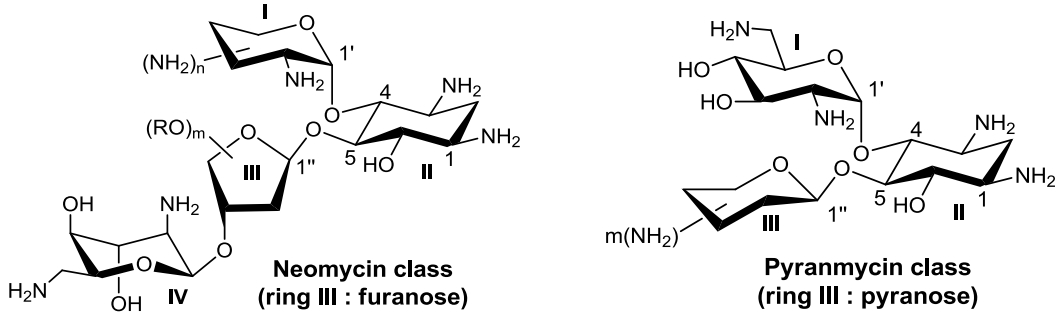
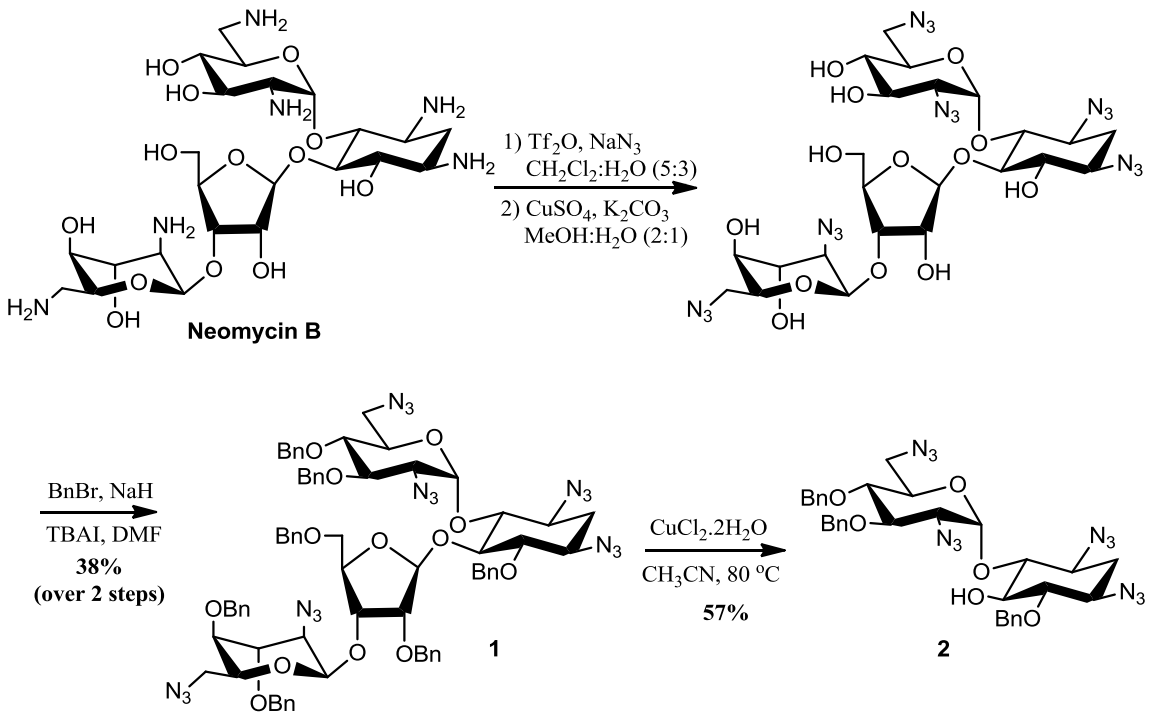


Figure 10: Structures of neomycin and pyranmycin

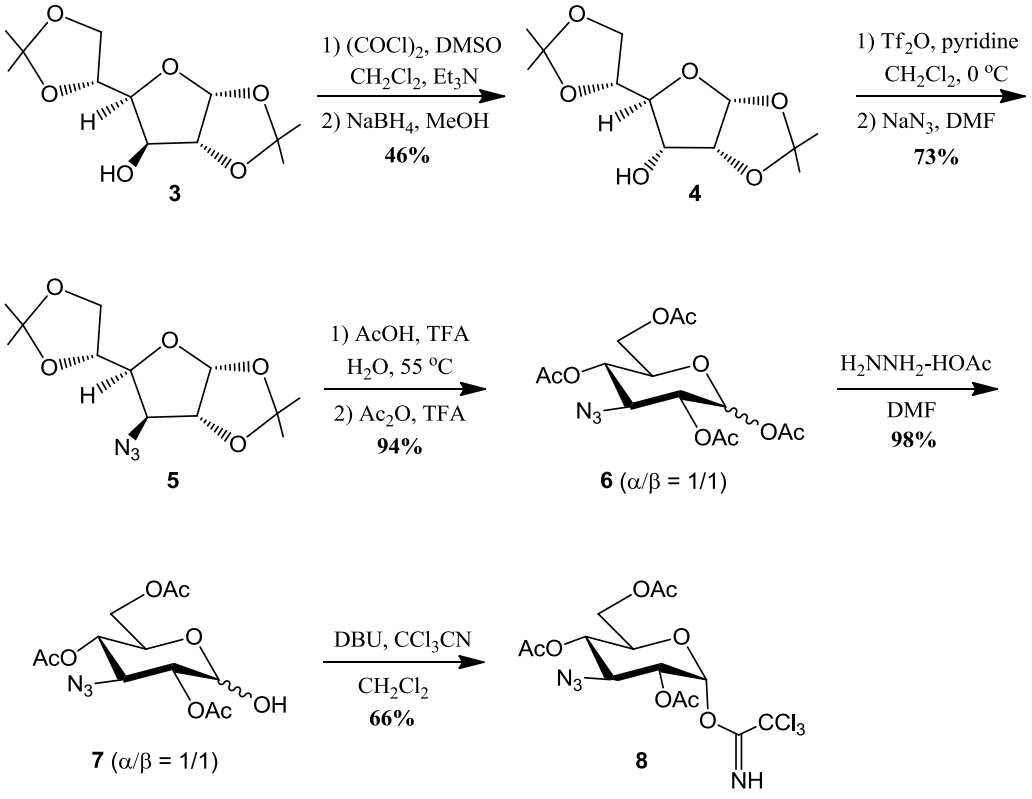


Scheme 1: Synthesis of the neamine derivative acceptor **2**

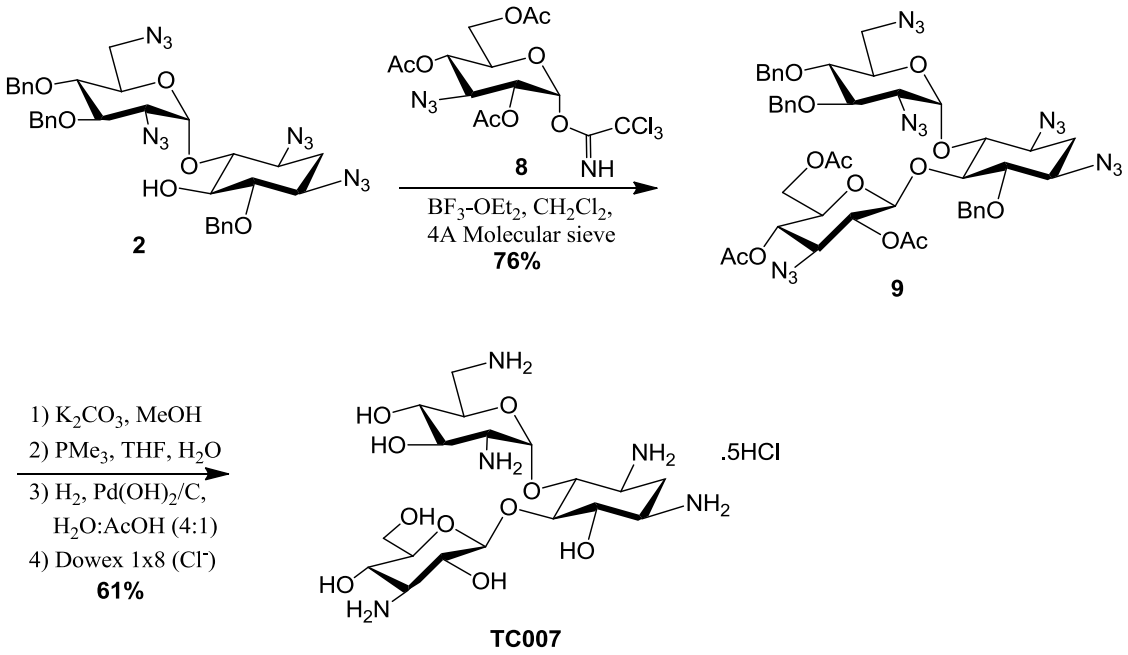
The synthesis of the glycosyl donor **8** started from the commercially available diacetone-D-glucose **3** (Scheme 2). Swern oxidation of **3** and reduction of the corresponding ketone with $NaBH_4$ gave the epimer alcohol **4**.[83] Triflation, which converts the free hydroxyl group into the better triflate leaving group, and S_N2 azido substitution afforded compound **5**.[84] Acid-catalyzed hydrolysis, followed by acetylation, provided the tetraacetyl pyranose **6**.[85] Treatment with hydrazine acetate selectively hydrolyzed the acetyl group at the anomeric position to give **7**,[86] whose free hydroxyl group was then activated in the presence of trichloroacetonitrile to afford our glycosyl donor **8**.[87]

With the neamine acceptor **2** and the glycosyl donor **8** on hand, we were ready to embark on the synthesis of **TC007** (Scheme 3). Glycosylation of **2** and **8** in the presence of the Lewis acid BF_3-OEt_2 provided compound **9.**[87] The acetyl group present at C-2 of

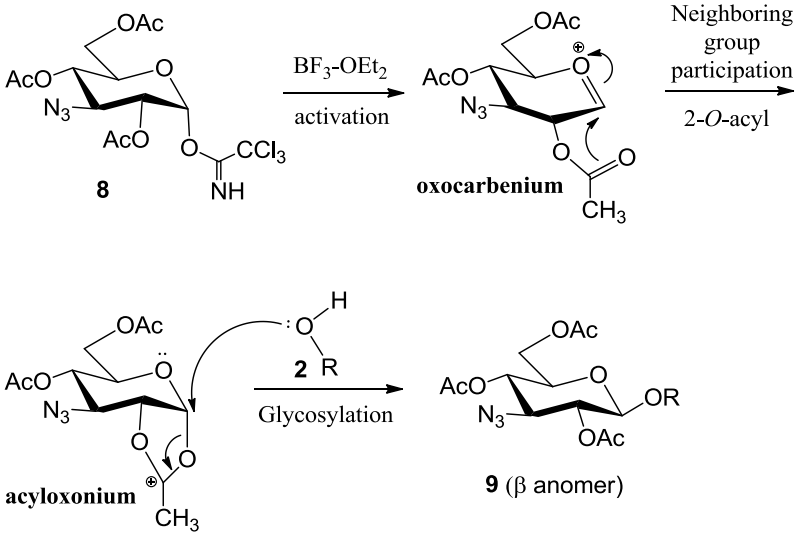
the glycosyl donor **8** controls the formation of the β-glycosidic bond in **9** (Scheme 4)**.** Indeed, as the donor **8** gets activated in the presence of BF_3-OEt_2, an oxocarbenium intermediate is formed, which in the presence of a 2-*O*-acyl group will give an acyloxonium intermediate. Therefore, the attack by a nucleophile (acceptor **2**) can only happen from the open top face, resulting in the formation of the β-anomer in **9**. The acetyl groups in compound **9** will then be hydrolyzed using K_2CO_3 in methanol. Staudinger reduction of the azide, followed by hydrogenolysis and ion-exchange, provide **TC007** as a chloride salt.



Scheme 2: Synthesis of the glycosyl donor **8**



Scheme 3: Synthesis of **TC007**



Scheme 4: Formation of the β-glycosidic bond in compound **9**

II.2.2. Mode of action of **TC007** in the treatment of spinal muscular atrophy

SMN proteins localize in nuclear bodies known as gems.[88] Gem numbers have been frequently used as a biomarker for total cellular SMN protein levels in SMA patient fibroblasts.[77,89-93] In a low throughput cell-based screen, **TC007** and other aminoglycosides were found to elevate SMN and gem numbers in SMA type I fibroblasts.[78] Patient fibroblasts treated for 48 h in 100 μg/mL of aminoglycoside-media showed a higher amount of SMN nuclear gems (Figure 11).[78] **TC007** was found to be even more effective than valproic acid (VPA), a previously identified histone deacetylase inhibitor compound known to increase SMN expression by stimulating the SMN2 promoter and SMN exon 7 inclusion.

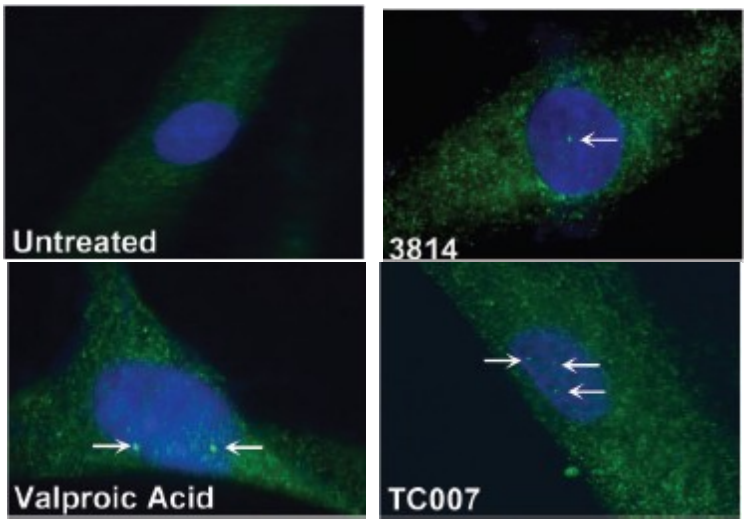


Figure 11: Increase in SMN-positive gems (white arrows) after treatment with **TC007**[78]

TC007 was found to induce SMN protein levels by a novel SMNΔ7 read-through event. Experiments carried out in Dr. Lorson's laboratory revealed that **TC007** causes the

ribosome to incorporate a tyrosine into the first stop codon of SMNΔ7 exon 8 and read-through until the second stop, 16 nucleotides downstream (Figure 12).[78] This allows the translational machinery to elongate the truncated protein by additional five amino acids, length which has been demonstrated sufficient to restore more functionality to the protein. This SMN read-through protein, while in the low level, enters into an SMN complex with the existing full-length protein, resulting into a small increase in SMN-functional (SMN-Fl) protein after treatment.

Animal model experiments performed in Dr. Lorson's laboratory have revealed that **TC007** can actually lessen the severity of SMA.[94] As a result, subcutaneous administration of **TC007** was found to increase myofiber size and gross motor function in SMA mice (Figure 13).[95]

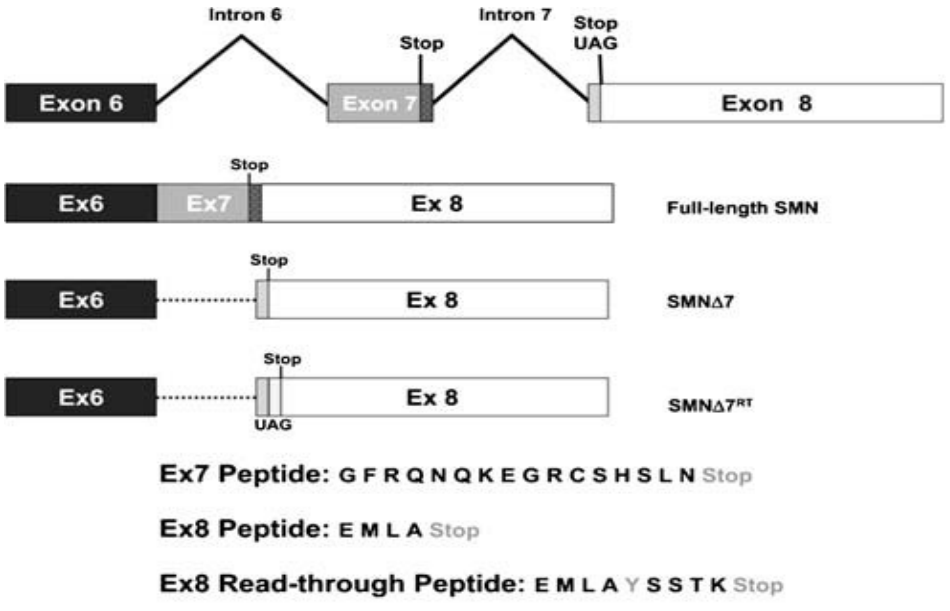


Figure 12: Schematic of SMN C-termini[78]

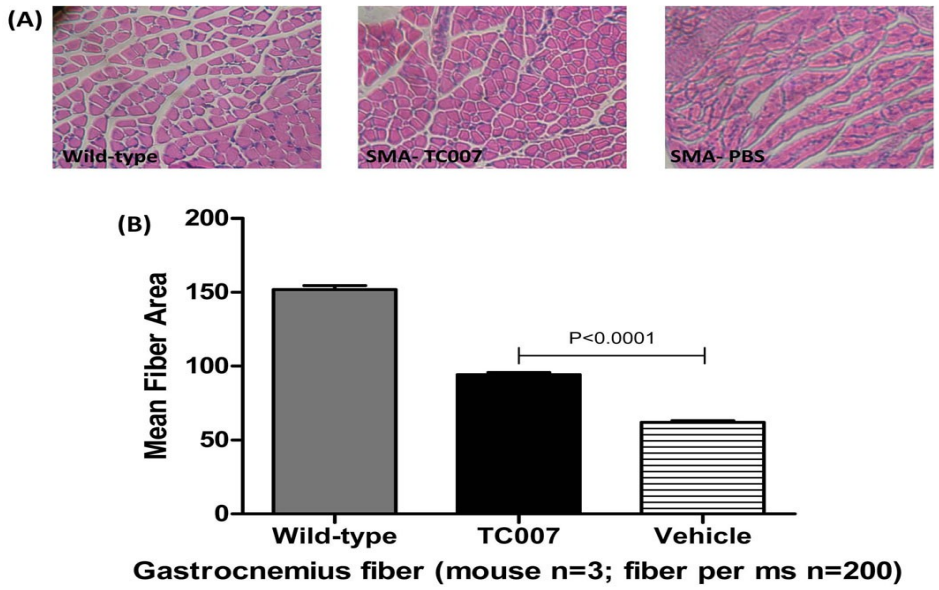


Figure 13: Increase in muscle fiber size of **TC007**-treated mice[95]

II. 3. Conclusion

The bioactivity screening of a library of previously synthesized aminoglycosides has identified **TC007** as the lead compound in the treatment of spinal muscular atrophy. To further investigate its mode of action, more **TC007** was synthesized from neomycin B. The use of copper (II) chloride in the cleavage of the glycosidic bond between rings II and III of neomycin B was found to be slightly more effective than the previously used MeOH/HCl mixture.

TC007 was found to act through an unprecedented SMNΔ7 read-through event. **TC007** triggers the insertion of an amino acid such as tyrosine, in the premature stop codon and allows the ribosome to read-through until the following natural stop codon. This elongates the truncated SMNΔ7 protein by an additional five amino acids, enabling

it to regain functionality. These findings could lead to the development of novel therapeutic approaches for the treatment of spinal muscular atrophy.

CHAPTER III

STRUCTURAL OPTIMIZATION OF ANTIFUNGAL KANAMYCIN B ANALOGS[b]

III.1. Rationale

A recent report has demonstrated that aminoglycosides, including neomycin, paromomycin, ribostamycin, and streptomycin (Figures 1 and 2), can manifest modest to excellent antifungal activity against a panel of pathogenic fungi.[44] However, all these aminoglycosides are clinically used antibiotics for the treatment of human bacterial pathogens. Therefore, if any of them happened to be involved in plant disease management, microbial resistance could easily be extended to human, leading to an increase of human illnesses and possibly death. This phenomenon has previously been observed with farm animals, when the overuse of in-feed antibiotics in livestock resulted in the detection of a large number of drug-resistant bacteria in human.[96]

In addition, among the two most commonly used classes of aminoglycosides, neomycin and kanamycin, this study limited itself to the neomycin class of aminoglycosides (neomycin, paromomycin, and ribostamycin). No representative member of the kanamycin class was included.

To solve both issues, we decided to investigate the antifungal activity of some kanamycin class aminoglycosides. In addition, these aminoglycosides needed to be inactive against bacteria in order to be the ideal antifungal agent candidates.

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[b] Part of this chapter was coauthored by Chang, C.-W. T.; Fosso, M.; Kawasaki, Y.; Shrestha, S.; Bensaci, M.; Wang, J.; Evans, C. K.; Takemoto, J. Y. Reproduced with kind permission from *J. Antibiot*. **2010**, 6*3*, 667-672.

Kanamycin B (Figure 2) is a naturally occurring antibacterial aminoglycoside. As the prototypal model of the kanamycin class of aminoglycosides, its antibiotic efficacy has been excessively used. The net result was the high prevalence of resistant bacteria and thus the loss of its clinical attractiveness. In the effort to restore its antibacterial activity, our group has been involved in the development of new strategies to derivatize this class of compounds and had previously synthesized a library of kanamycin B analogs.[97-99] Screening of this library of analogs uncovered few compounds that inhibited the growth of fungi and yeasts. One compound, **FG08**, displayed broad spectrum fungicidal activity coupled with the loss of antibacterial activity. Therefore, more **FG08** had to be prepared to investigate its mechanism of action. In addition, other kanamycin B analogs would be synthesized in the aim of developing potential antifungal agents.

III. 2. Results and discussion

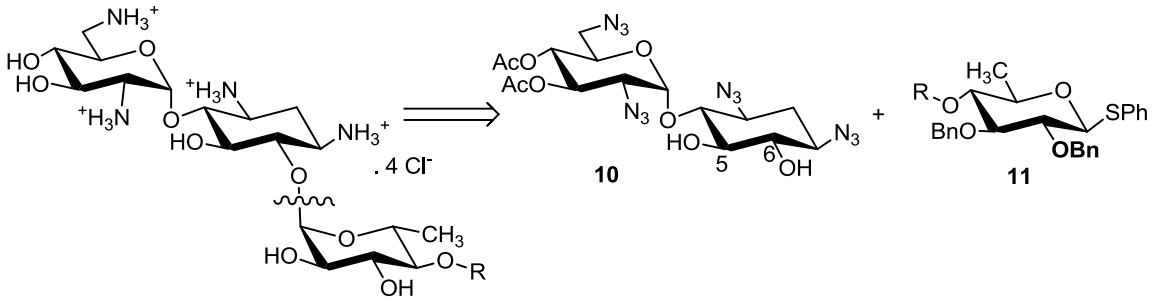
III.2.1. Investigation of the optimum chain length

The surprising antifungal activity of **FG08** was attributed to the attachment of a long (C8) alkyl chain. To investigate the chain length that will confer the optimum antifungal activity, two other kanamycin B analogs were synthesized: **FG01**, with a shorter (C4) alkyl chain, and **FG02**, with a longer (C12) alkyl chain.

a) Retrosynthetic analysis of **FG01**, **FG02** and **FG08**

FG01, **FG02**, and **FG08** are all kanamycin B analogs and thus share a pseudo-disaccharide core (neamine) substituted at the 6-position. Their syntheses could therefore start from the neamine derivative **10**[97] and the phenylthioglycosyl donor **11** (Scheme 5).

Unlike the β-glycosidic bond, there is no general and stereospecific protocol for the formation of the α-glycosidic bond. However, a 2-*O*-Bn group does not favor the formation of the acyloxonium intermediate required for β-selectivity. Therefore, the phenylthioglycoside **11** will enable the formation of the α-glycosidic bond between rings II and III due to the anomeric effect. Indeed, upon activation by NIS and TMSOTf, **11** is converted into an oxocarbenium intermediate (Scheme 6). Nucleophilic attack by the acceptor **10** can occur from the top face to give the β-anomer, or from the bottom face to give the α-anomer. Because of the orbital overlap, the β-anomer is less favored than the α-anomer. Therefore, the α-anomer will be obtained as the major product. In addition, since **10** has two free hydroxyl groups, steric hindrance will prevent 5-OH from acting as the nucleophile, allowing glycosylation to happen only at the 6-position.



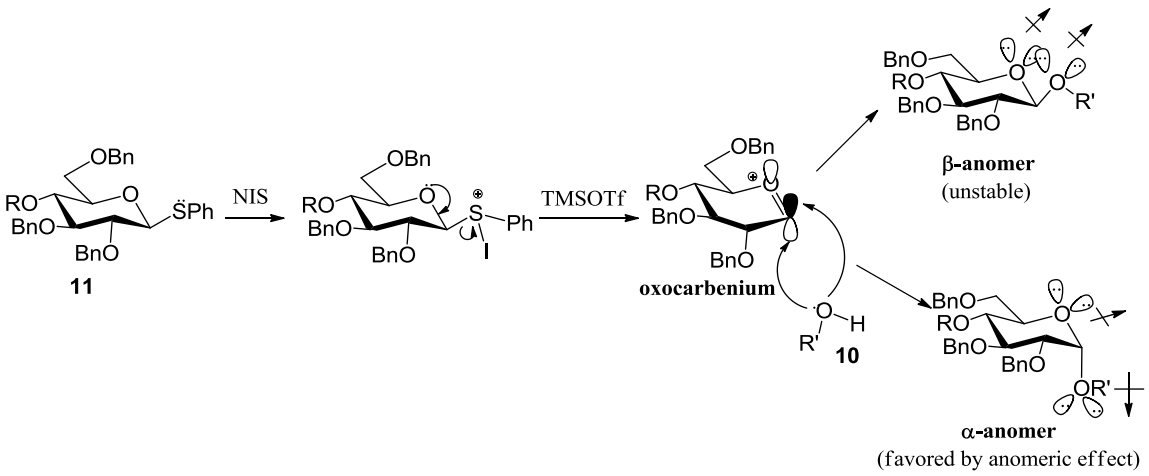
FG01 (R = C_4H_9), **FG02** (R = $C_{12}H_{25}$)
FG08 (R = C_8H_{17})

Scheme 5: Retrosynthetic analysis of **FG01**, **FG02,** and **FG08**

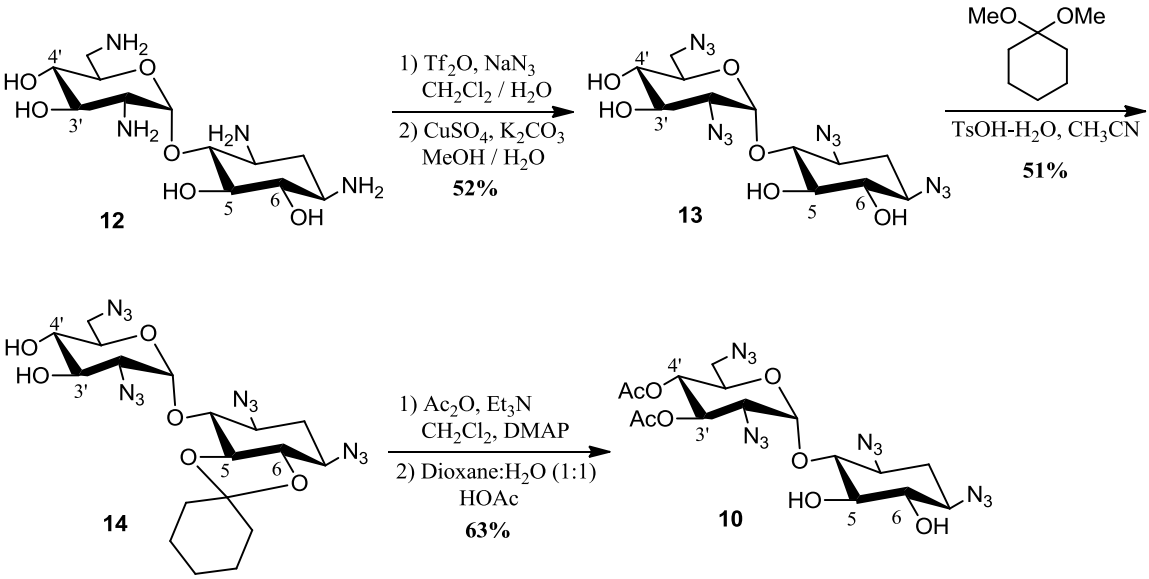
b) Syntheses of **FG01**, **FG02** and **FG08**

Starting from neamine **12**,[100] conversion of the amino groups to azido groups gave **13**[101] (Scheme 7). Regioselective protection of the 1,2-diol at positions 5 and 6 gave **14**.[97]

Acetylation of the hydroxyl groups at positions 3´ and 4´, and acid cleavage of the cyclohexylidene protecting group afforded the neamine derivative **10**.

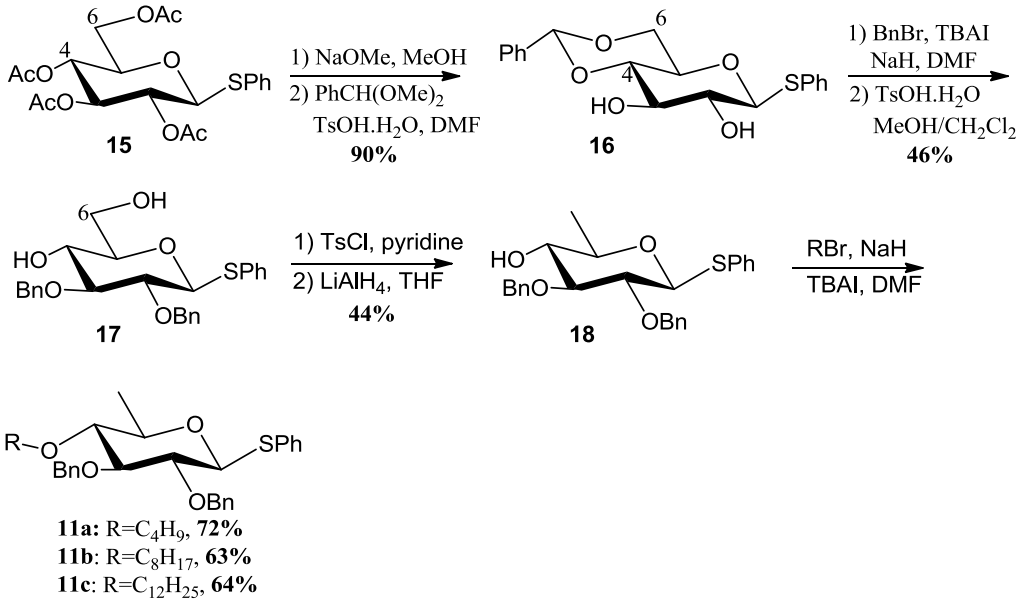


Scheme 6: Anomeric effect



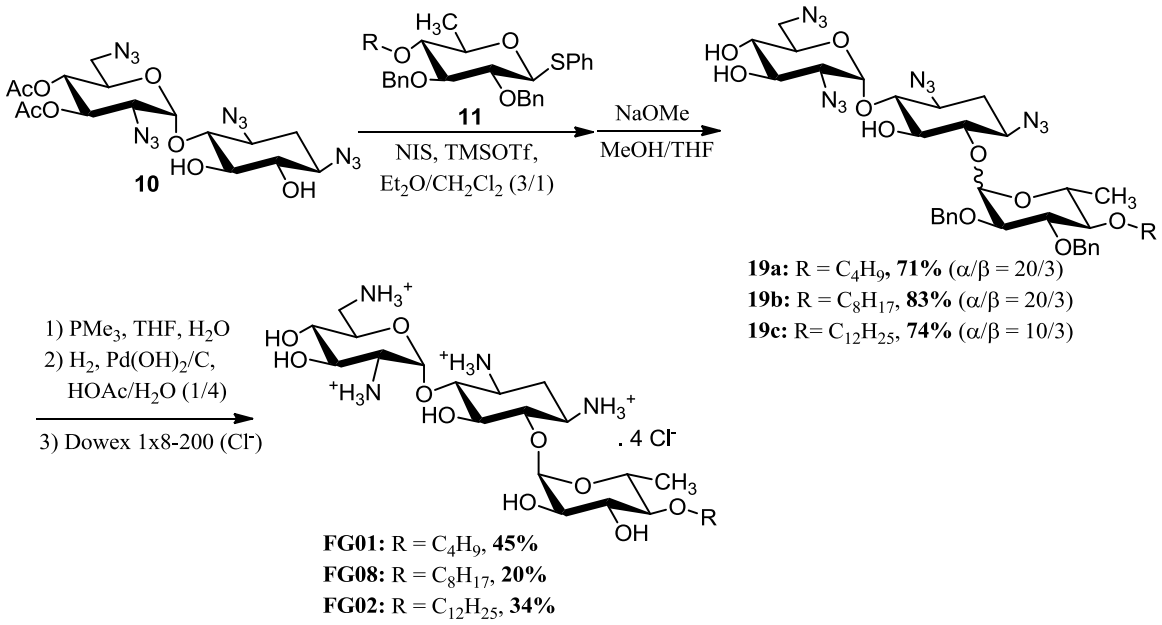
Scheme 7: Synthesis of the neamine derivative acceptor **10**

The synthesis of the glycosyl donors started from the known compound **15**[102] (Scheme 8). Acetonolysis, followed by regioselective protection of the hydroxyl groups at positions 4 and 6 afforded **16**.[102] Benzylation and acid cleavage of the benzylidene protecting group gave **17**,[102] as a 1,3-diol. Selective tosylation of the primary alcohol and reduction with $LiAlH_4$ gave **18**.[103] Alkylation using *n*-butyl bromide, *n*-octyl bromide, and *n*-dodecyl bromide gave the glycosyl donors **11a**, **11b**, and **11c**, respectively.



Scheme 8: Synthesis of the glycosyl donors **11a, 11b,** and **11c**

With the neamine acceptor **10** and the glycosyl donors **11a**, **11b**, and **11c** on hand, we were ready to embark on the synthesis of **FG01**, **FG02**, and **FG08** (Scheme 9). Glycosylation in the presence of NIS and TMSOTf followed by acetonolysis using NaOMe in MeOH/THF mixture afforded **19**. Staudinger reduction of the azide into an amine, hydrogenation, and ion-exchange provided **FG01**, **FG02**, and **FG08** as chloride salts.



Scheme 9: Synthesis of **FG01**, **FG02**, and **FG08**

c) The C8 alkyl chain confers optimum antifungal activity

Through collaboration with Dr. Jon Takemoto (Department of Biology, Utah State University), the effectiveness of each of the **FG** compounds was evaluated. The synthesized kanamycin B analogs were tested against *Rhodotorula piliminae* (Figure 14).[104] From the disk diffusion growth inhibitory assay, **FG08** gave a larger zone of inhibition and thus is more active than **FG01** and **FG02** against *R. piliminae*.

Further alkyl chain lengths were not investigated because from a similar study of alkyl chain length vs. aminoglycoside bioactivity,[105] it was reported that compounds with C7 and C10 alkyl chains showed reduced activities compared to the parent compound. Therefore, we reasoned that the C8 alkyl chain will still be the best at conferring an optimal antifungal activity.

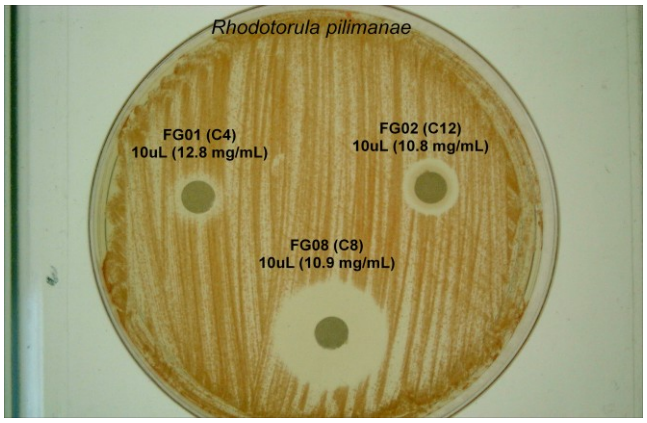


Figure 14: Disk diffusion inhibitory assay of **FG01**, **FG02**, and **FG08**

Based on these results, more emphasis was directed toward the antimicrobial activity of **FG08**. Microbroth dilution assays performed in Dr. Takemoto's laboratory revealed that **FG08** exhibits little to no activity against Gram-positive and Gram-negative bacteria (Table 1). Its MIC values against both types of bacteria were at least 125-fold higher than shown by kanamycin B (Table 1).

In addition, **FG08** was found to inhibit the growth of a wide range of yeasts, oomycetes, and true fungi with MICs ranging between 3.9 and 31.3 μg/mL (Table 1).[104] On the other hand, kanamycin B was not active against those same microbes.

In light of these results, the ability of **FG08** to control Fusarium head blight (FHB) was evaluated.

Table 1: Minimal inhibitory concentrations (MICs) of **FG08** and kanamycin B[104]

	MIC (μg/mL)	
Organism	**FG08**	Kanamycin B[a]
Bacteria		
Escherichia coli TG1[b]	125-250	1.95
*Staphylococcus aureus (*ATCC 25923)[c]	250	<0.98
Pseudomonas aeruginosa (ATCC 27853)[b]	250	1.95
Enterococcus faecalis (ATCC 29212)[c]	125-250	<0.98
Klebsiella pneumoniae (ATCC 138883)[b]	250	1.95
Klebsiella pneumoniae (ATCC 700603)[b]	250	1.95
Fungi		
Rhodotorula pilimanae (ATCC 26423*)*	7.8	>250
Candida albicans (ATCC 10231)	31.3	>250
Saccharomyces cerevisias W303	3.9	>250
Fusarium graminearum B-4-5A	31.3	>250
Fusarium oxysporum	7.8	>250
Ulocladium spp.	7.8	ND[d]
Pythium irregular	15.6	ND
Pythium ultimum	15.6	ND
Phytophthora parasitica	15.6	ND
Rhizopus stolonifer	31.3	ND
Cladosporium cladosporioides	31.3	ND
Curvularia brachyspora	31.3	ND
Bortrytis cinerea	31.3	ND
Phoma spp.	31.3	ND

[a]Microboth dilution assays were performed at least twice, and each in triplate
[b]Gram-negative bacteria
[c]Gram-positive bacteria
[d]Not determined

III.2.2. Antifungal activity of **FG08** against *Fusarium graminearum*

F. graminearum is the causative agent of Fusarium head blight (FHB) and affects wheat, barley, and maize. With economic losses averaging $3 billion annually, FHB is among the most serious plant disease the U.S. has encountered.[106] Efforts to eradicate this crop disease have not been successful yet. Therefore, the development of a fungicide that will inhibit *F. graminearum* is much awaited.

a) Green house experiments

FG08 was investigated for its ability to control FHB of wheat.[104] Leaf infection assays performed by Yukie Kawasaki, a graduate student in Dr. Takemoto's laboratory, revealed the ability of **FG08** to suppress in *planta F. graminearum* infection at its in vitro MIC value. When FHB-susceptible wheat leaves were inoculated with 10 μL of a mixture of **FG08** (30 μg/mL) and suspensions of *F. graminearum* macronidia, not only was mycelial growth prevented (Figure 15, upper panel), but a 5-fold decrease in leaf lesions was also observed (Figure 15, middle panel, white bars). At 180 μg/mL, **FG08** was found to be phytotoxic (Figure 15, lower panel).

In addition, **FG08** reduced the rate of FHB infection on cultivar Apogee (a rapidly maturing and FHB-susceptible variety of wheat) spikelet florets. Inoculation of **FG08**-pretreated spikelet florets with *F. graminearum* did not result in any of the FHB symptoms (chlorosis and curled spikes) that were noticeable within 4 days on non-pretreated spikelet florets (Figure 16). Therefore, the attachment of the octyl group triggered the loss of the antibacterial activity of **FG08**, while instantly imparting to it a fungicidal activity. This definitely suggested a different mode of action of **FG08**.

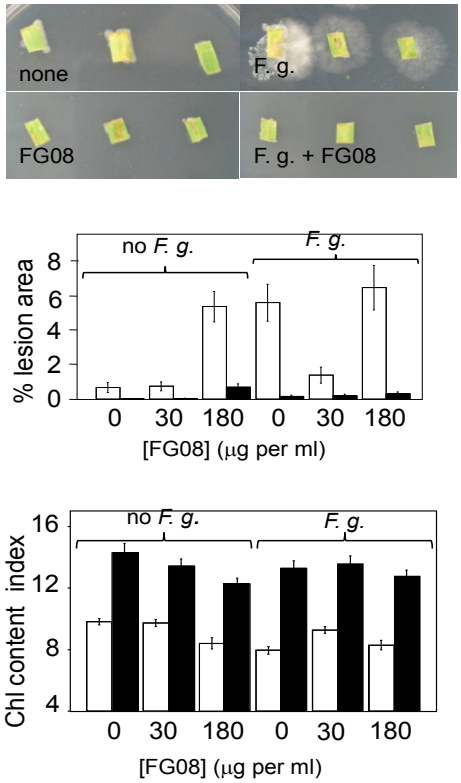


Figure 15: **FG08** suppression of wheat leaf infection after exposure to *F. graminearum*[104]

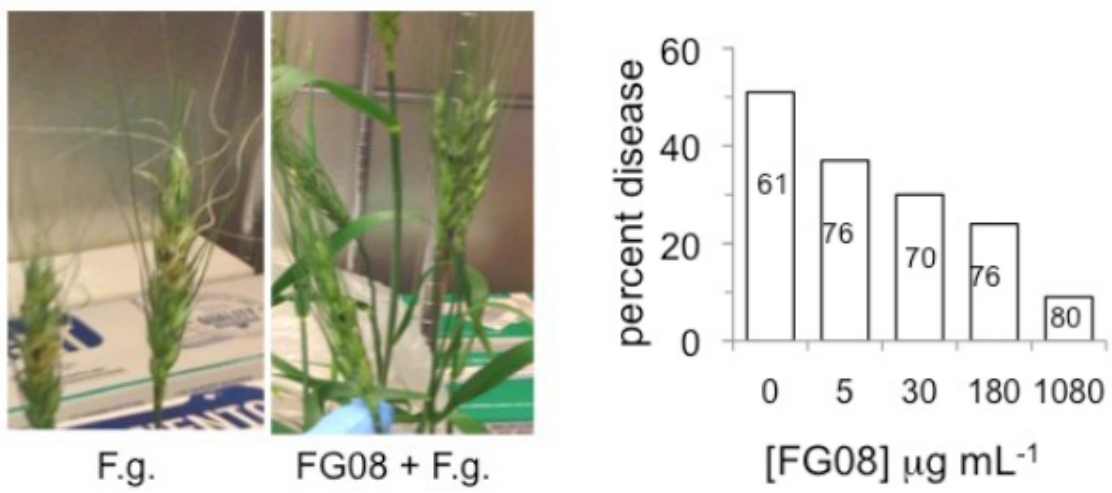


Figure 16: **FG08** suppression of FHB disease in wheat spikelet florets[104]

b) Mechanism of action of **FG08**

Aminoglycosides are known to kill bacteria by binding to the ribosome and inhibiting protein synthesis. However, studies with fluorescent dye SYTOX green demonstrated that **FG08** exerts its antifungal activity by perturbation of the membrane function.[104] Upon binding with nucleic acids, SYTOX green will fluoresce when excited at 450-490 nm. Unless the cell membrane is compromised, the dye does not have the ability to cross the membrane. When Mr. Sanjib Shrestha, a graduate student in Dr. Takemoto's laboratory, performed the dye permeation experiment, it was found that **FG08** rapidly influenced the dye permeability of *C. albicans* cells and *F. graminaerum* hyphae (10 minutes). In addition, **FG08** increased the membrane permeability of *C. albicans* 12 times better than kanamycin B. Also, **FG08** did not lyse more than 20% of erythrocytes at a concentration 10-fold higher than its fungal MIC. This suggests that **FG08** does not act as a surface-active agent that non-specifically disrupts membranes.

Aminoglycosides are polycationic at physiological conditions. They can then aggregate on the fungal cell membrane by electrostatic interaction with the anionic sphingolipids. Then, the lipophilic alkyl chain found on **FG08** enabled it to insert itself into the membrane bilayer of the fungi and eventually form pores. Therefore, the C8 alkyl chain found in **FG08** confers to it amphipatic properties.

III.2.3. Optimization of **FG08**

In light of the impressive antifungal activity of **FG08**, we decided to improve on its synthesis by preparing **FG03**. **FG03** differs from **FG08** by the hydroxyl group present at the 6´´ position (Figure 17).

a) Synthesis of **FG03**

Starting from the 1,3-diol **17**,[102] tritylation selectively protects the primary alcohol, leaving a free hydroxyl group at position 4 (Scheme 10). Alkylation of the 4-OH, followed by the acid-catalysed removal of the trityl group revealed the 6-OH in compound **20**. Benzylation afforded the thiophenyl donor **21**. Glycosylation of **2** and **21**, followed by acetonolysis, gave **22**. Staudinger reduction of the azide into amine, hydrogenation, and ion-exchange provided **FG03** as a chloride salt.

b) Antimicrobial activities of **FG03**

While maintaining its non-antibacterial activity, **FG03** was also found to be effective against a number of fungi (Table 2). In addition, it was even more active than **FG08** against *F. graminearum*.

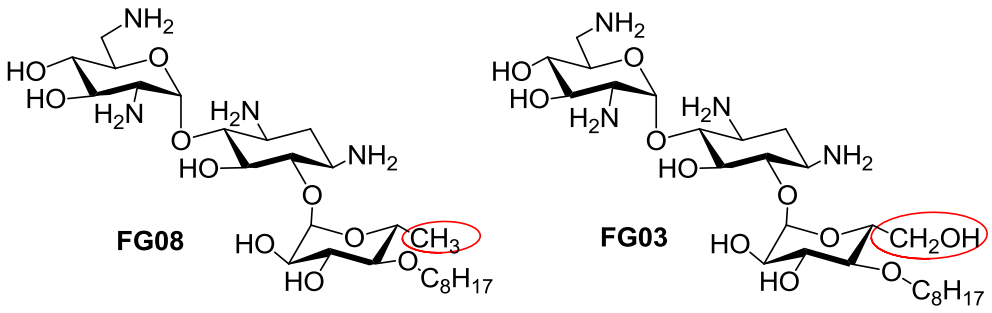
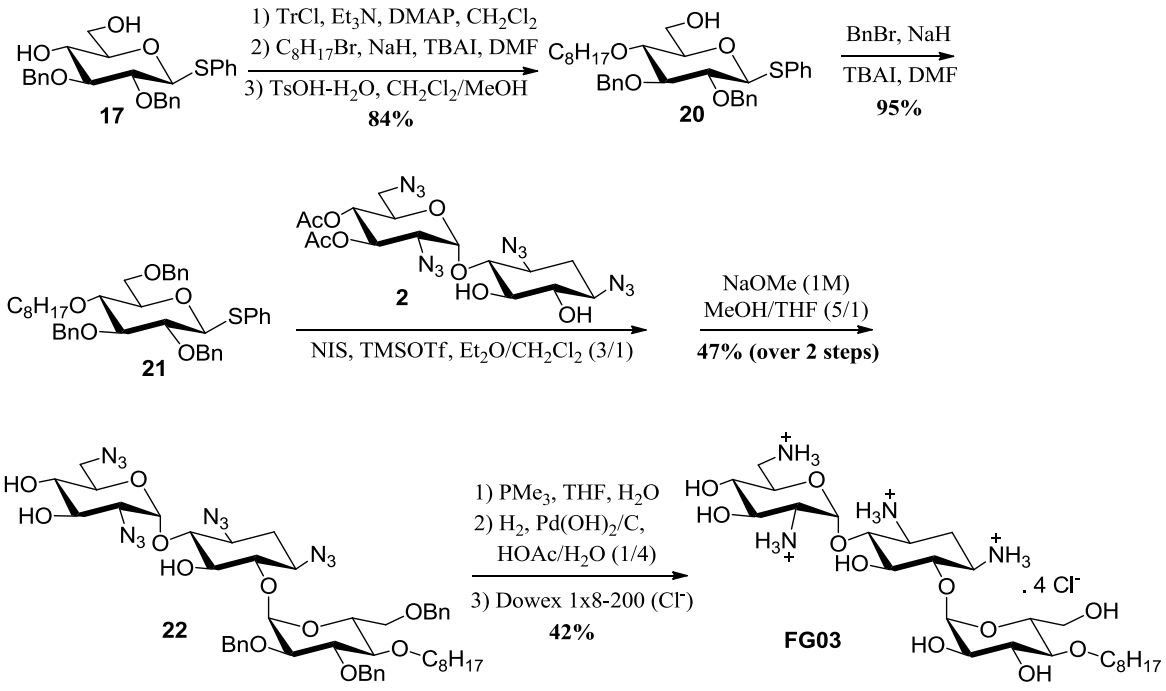


Figure 17: Structures of **FG08** and **FG03**



Scheme 10: Synthesis of **FG03**

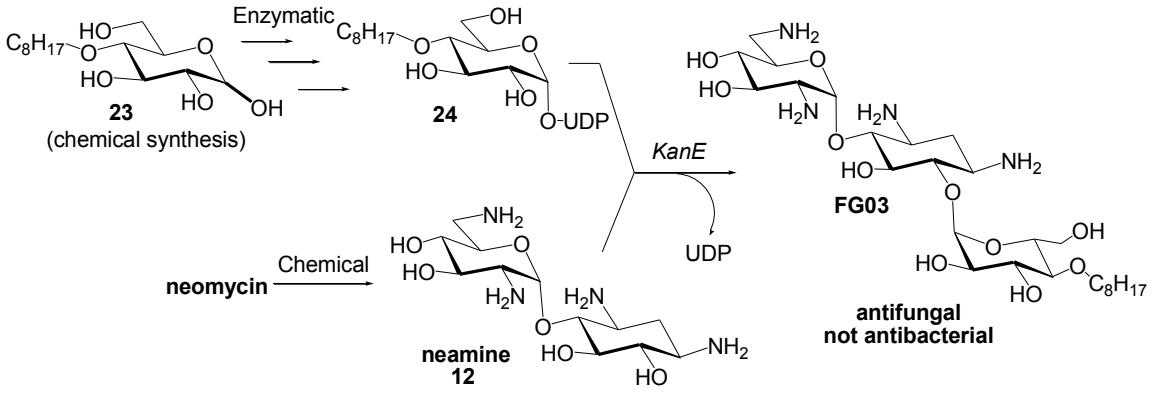
Table 2: MIC values of **FG08** and **FG03**[a]

	MIC (μg/mL)	
Organism	**FG08**	**FG03**
Bacteria		
Escherichia coli TG1[b]	125-250	>500
*Staphylococcus aureus (*ATCC25923)[c]	250	ND[d]
Filamentous fungi		
Fusarium graminearum B-4-5A	31.3	7.8
Pythium ultimum	15.6	62.5
Curvularia brachyspora	31.3	31.3
Bortrytis cinerea	31.3	31.3
Yeasts		
Rhodotorula pilimanae (ATCC26423*)*	7.8	62.5
Candida albicans (ATCC10231)	31.3	62.5

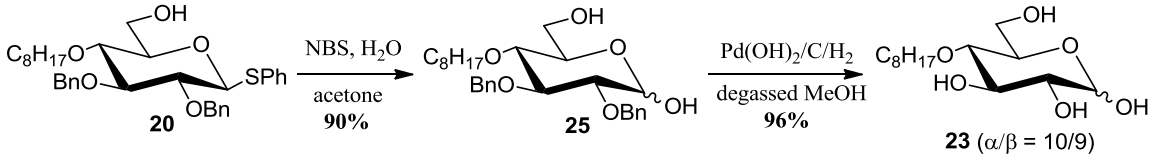
[a] Data obtained by Sanjib Shrestha
[b] Gram-negative bacteria
[c] Gram-positive bacteria
[d] Not determined

The scale-up synthesis of **FG03** by a chemoenzymatic approach was attempted in Dr. Takemoto's laboratory (Scheme 11). Although unsuccessful, this approach required 4-*O*-octyl-D-glucopyranoside **23** and neamine **12**, both chemically synthesized in our laboratory.

The synthesis of **23** started from compound **20**. Treatment with *N*-bromosuccinimide gave **35**, whose hydrogenation provided **23** (Scheme 12).



Scheme 11: Proposed chemo-enzymatic synthesis of **FG03**



Scheme 12: Synthesis of compound **23**

III.2.4. Alkyl group mapping

From the promising results of **FG03** and **FG08**, which both have a linear C8 alkyl chain at the *O*-4′′ position, we decided to explore the effect of an octyl group at other positions, by synthesizing kanamycin B analogs **FG05**, **FG06**, **FG07**, **FG09**, **FG10**, and **FG11**.

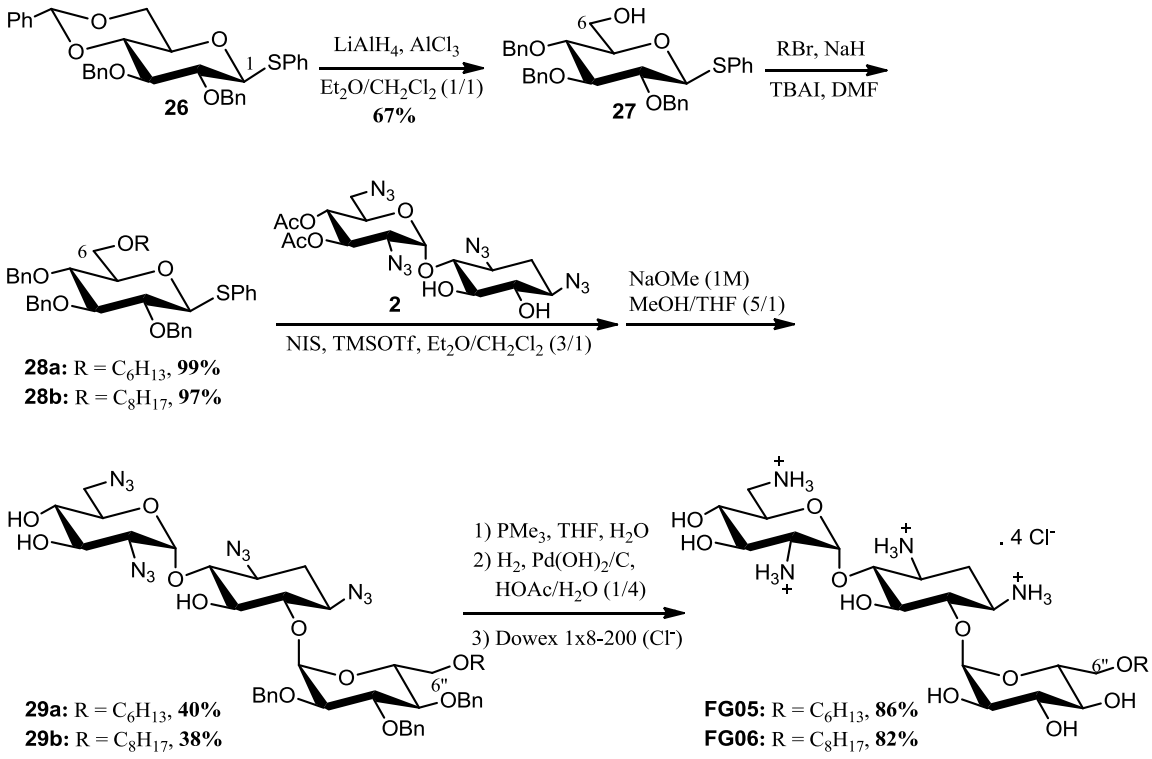
a) Synthesis of **FG05** and **FG06** (alkylation at *O*-6′′ position)

The synthesis started with the regioselective ring opening of the known compound **26**[107] to obtain **27**[108] with a free hydroxyl group at the 6-position (Scheme 13). Alkylation using *n*-hexyl bromide and *n*-octyl bromide provided the thiophenyl donors **28a** and **28b**, respectively. Glycosylation followed by acetonolysis gave **29a** and **29b**. Staudinger reaction, hydrogenation, and ion-exchange afforded **FG05** and **FG06**, with C6 and C8 alkyl chain at the *O*-6′′ position, respectively.

b) Synthesis of **FG07** (Alkylation at *O*-3′′ position)

The synthesis started with the alkylation of diacetone-D-glucose **3** (Scheme 14). This gave the known compound **30**,[109] whose acid-catalysed hydrolysis and acetylation provided **31**. Treatment of **31** with thiophenol in the presence of BF_3-OEt_2 gave **32**. Through neighboring group participation (see Scheme 4), the acetyl group present at position 2 in **32** will favor the formation of a β-anomer after glycosylation. However, a 2-*O*-Bn will provide the required α-glycosidic bond (see Scheme 6). Thus acetonolysis of **32**, followed by benzylation, afforded the thiophenyl donor **33**, with a 2-*O*-Bn. Glycosylation of **2** and **33** in the presence of NIS and TMSOTf, followed by acetonolysis,

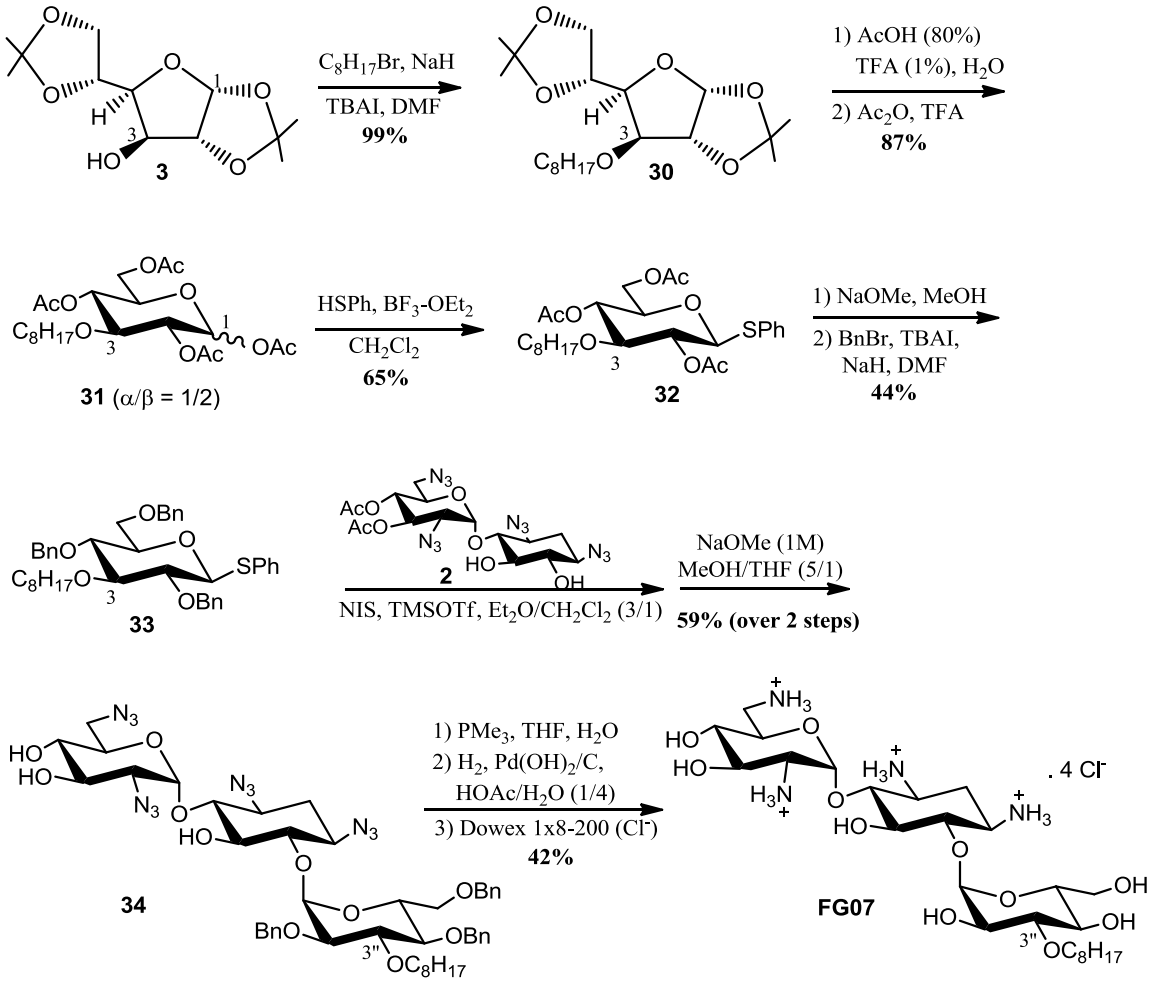
gave **34**. Staudinger reaction, hydrogenation, and ion-exchange afforded **FG07**, which has a C8 alkyl chain at the 3´´ position.



Scheme 13: Synthesis of **FG05** and **FG06**

c) Synthesis of **FG09** (alkylation at *O*-2´´ position)

The synthesis of **FG09** started from the known compound **35**[110] (Scheme 15). Alkylation of the 2-OH gave **36**, which upon treatment with $Ac_2O/AcOH/H_2SO_4$ provided **37**. Reaction with thiophenol in the presence of BF_3-OEt_2 gave **38**. Acetonolysis, followed by benzylation gave **39**. Glycosylation of **2** and **39** in the presence of NIS and TMSOTf, followed by acetonolysis provided **40**. Staudinger reaction, hydrogenation, and ion-exchange gave **FG09** with the C8 alkyl chain at position 2´´.

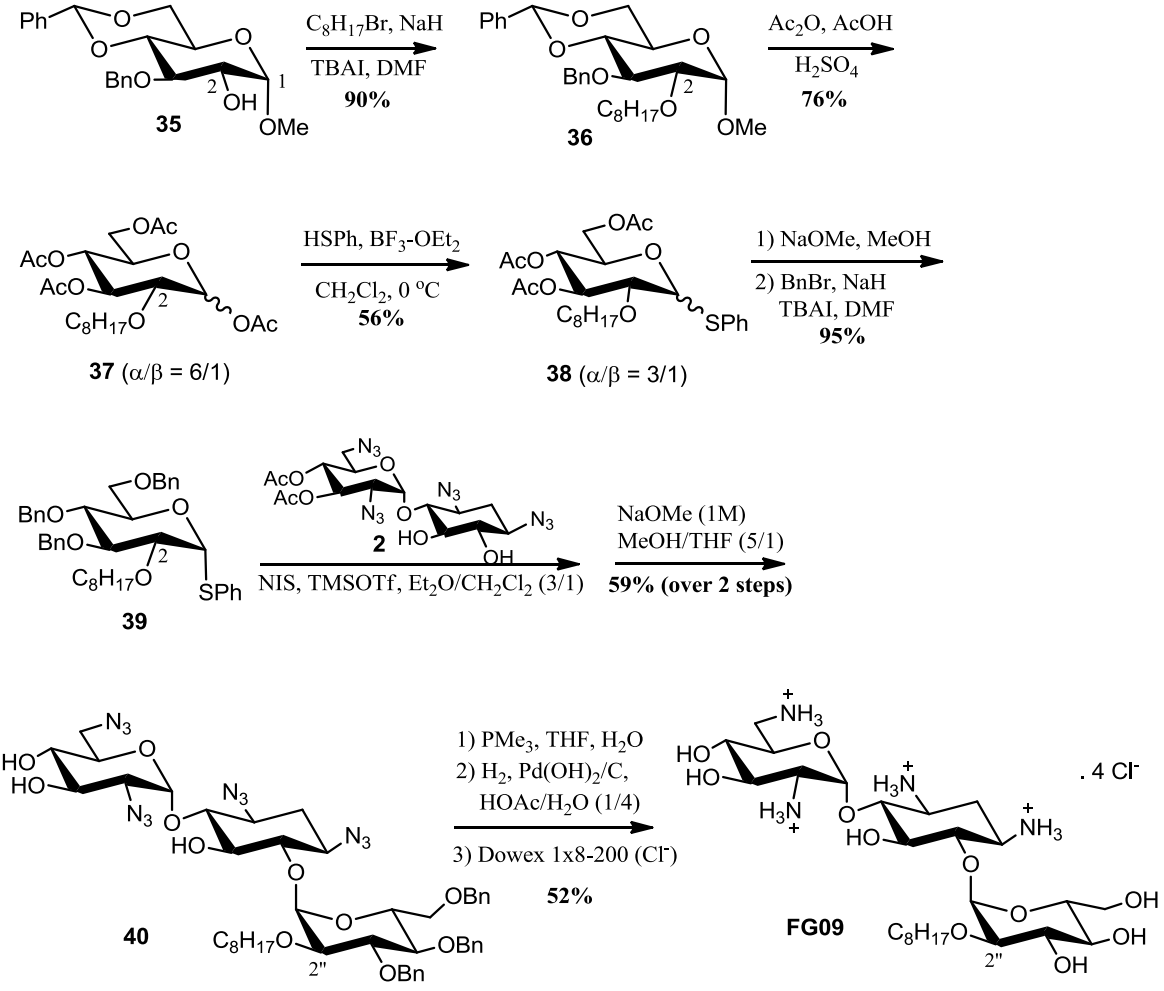


Scheme 14: Synthesis of **FG07**

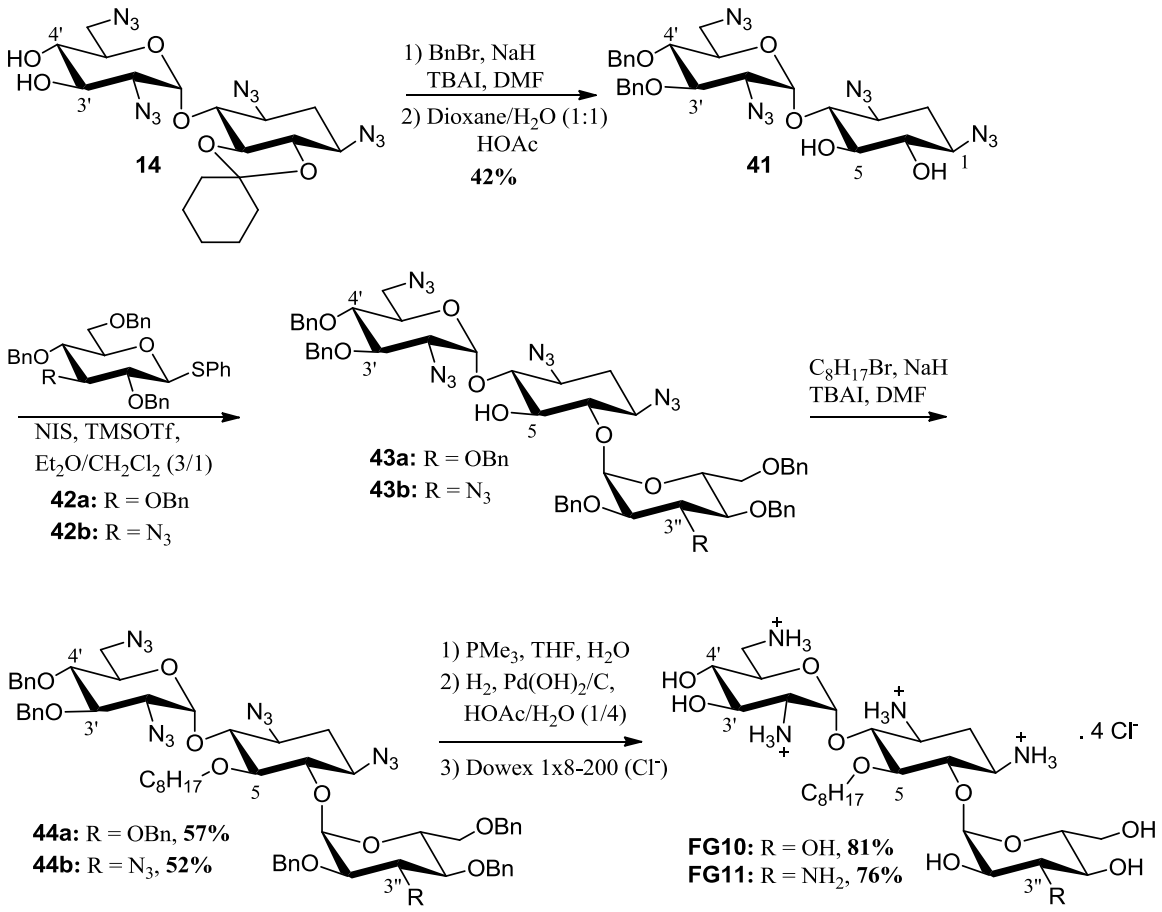
d) Synthesis of **FG10** and **FG11** (alkylation at *O*-5 position)

Benzylation at the 3′ and 4′ positions of the neamine derivative 14,[97] followed by the acid-catalyzed cleavage of the cyclohexylidene protecting group gave the glycosyl acceptor **41**[98] (Scheme 16). Glycosylation of **41** with the known thiophenyl donors **42a**[111] and **42b**[112] gave the compounds **43a** and **43b**, respectively. Both compounds have a free hydroxyl group at position 5 which will be alkylated to provide **44a** and **44b**, respectively. Staudinger reaction, hydrogenation, and ion-exchange afforded **FG10** and

FG11, respectively, with the C8 alkyl chain at *O*-5 position. **FG10** has a free hydroxyl (OH) group at position 3´´, while **FG11** has an amino (NH_2) group at position 3´´'. **FG10** is thus an analog of **FG08** and **FG11** looks more to kanamycin B.



Scheme 15: Synthesis of **FG09**

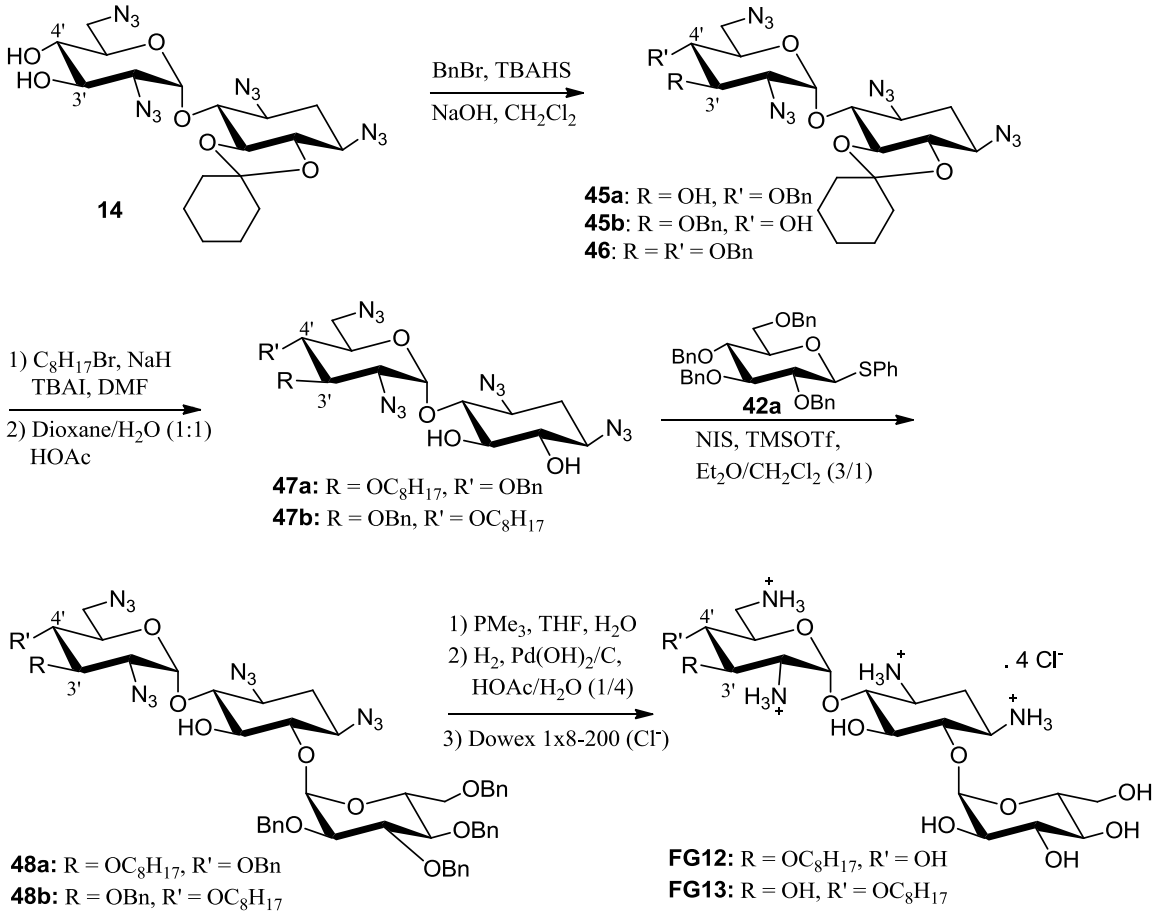


Scheme 16: Synthesis of **FG10** and **FG11**

e) Synthesis of **FG12** and **FG13** (alkylation at *O*-3′ and *O*-4′ positions, respectively)

The neamine derivative **14**[97] has two free hydroxyl groups at position 3′ and 4′. Selective benzylation of **14** afforded a mixture of regioisomers (**45a** and **45b**), along with the dibenzylated compound **46** (Scheme 17). The regioisomer **45a** has a Bn group at the 4′ position while the regioisomer **45b** has the Bn group at the 3′ position. Attempts to separate **45a** and **45b** were unsuccessful. That mixture of **45a** and **45b** was then used as so. Alkylation of the free hydroxyl group in each regioisomer, followed by the acid-

cleavage of the cyclohexylidene protecting group gave compounds **47a** and **47b** as an inseparable mixture. Glycosylation of the acceptors **47a** and **47b** with the donor **42a** afforded **48a** and **48b**, which upon Staudinger reduction, hydrogenolysis, and ion exchange gave a mixture of **FG12** and **FG13**.



Scheme 17: Synthesis of **FG12** and **FG13**

f) Alkylation at *O*-4´´position confers optimum antifungal activity

The effectiveness of the **FG** compounds was evaluated. The synthesized kanamycin B analogs were tested against the fungus *F. graminearum*. Microbroth

dilution assays performed in Dr. Takemoto's laboratory revealed that **FG08** and **FG03**, which both have an octyl group at the *O*-4´´ position, were the most active (Table 3). Indeed, **FG08** and **FG03** were found to inhibit the growth of *F. graminearum* at the minimum concentration of 7.8 µg/mL.

Table 3: MIC values of **FG** compounds against *F. graminearum*[a]

Alkylation site	Compound	MIC
O-2"	**FG09**	20
O-3"	**FG07**	62.5
O-4"	**FG03** (6"-OH)	7.8
O-4"	**FG08** (6"-H)	7.8
O-6"	**FG05**	125
O-6"	**FG06**	31.3
O-5	**FG10** (3"-OH)	<500
O-5	**FG11** (3"-NH_2)	31.3
O-3' & *O*-4'	**FG12** & **FG13**	≤500

[a] Data obtained by Yukie Kawasaki

On the other hand, the mixture of **FG12** and **FG13** showed no activity against *F. graminearum*. Since each compound constituted 50% of the mixture, we can therefore conclude that any of them, by itself, would be inactive against fungi.

From the MIC values, it is therefore obvious that a linear C8 alkyl chain imparts optimum antifungal activity when it is attached at the *O*-4´´ position.

III.3. Conclusion

The presence of a linear C8 alkyl chain was found to induce an antibacterial to antifungal transformation to kanamycin B. Indeed, **FG08**, which has a linear C8 alkyl chain at the *O*-4´´ position, displayed impressive antifungal activity against a wide range

of crop disease pathogens (fungi). **FG03**, which also has a linear C8 alkyl chain at the *O*-4′′ position, was synthesized with the intention to scale up the synthesis of **FG08** by a chemo-enzymatic approach, but this route turned out unsuccessful.

By employing glycodiversification, various sites in kanamycin B have successfully been alkylated to give new analogs. The antifungal activity results indicate the importance of the *O*-4′′ position. Indeed, **FG08** and **FG03,** which are both alkylated at the *O*-4′′ position, were the most potent antifungal agents.

In light of all these results, a structure-activity relationship can be drawn: attachment of a C8 alkyl chain at the *O*-4′′ position of kanamycin B converts this obsolete drug into a potent agro fungicide, with simultaneous loss of antibacterial activity.

CHAPTER IV

SYNTHESIS AND ANTIBACTERIAL STUDY OF CATIONIC 1,4-NAPHTHOQUINONE DERIVATIVES[c]

IV.1. Rationale

With the growing rate of bacterial infections and antibiotic-resistance, there have been continuous calls for new antibacterial agents and natural products usually provide resourceful scaffolds. 1,4-naphthoquinone derivatives are ubiquitous in nature[47-51] and display a wide range of biological activities.[52-56] Our group has thus recently invested some efforts in the development of interesting molecules derived from 1,4-naphthoquinone.[113-115] We have synthesized a class of 1-alkyl-1*H*-naphtho[2,3-*d*][1,2,3] triazole-4,9-diones.[114] These heterocyclic compounds combine two pharmacologically important moieties (1,4-naphthoquinone and 1,2,3-triazole), and were thus expected to exhibit unique biological activities. However, their poor solubility in aqueous media rendered them unavailable for biological testing. Nevertheless, methylation helped to solve this issue and led us to the discovery of a new series of anthraquinone analogs.[115] Many of these anthraquinone analogs happened to exhibit impressive antibacterial activity, notably against G+ bacteria, which might somewhat be related to the alkyl chain length at N-1 position.

The aim of this project was therefore to optimize the production of 1-alkyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-diones. In addition, we decided to synthesize a library of 1,3-dialkyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3] triazol-3-ium chloride

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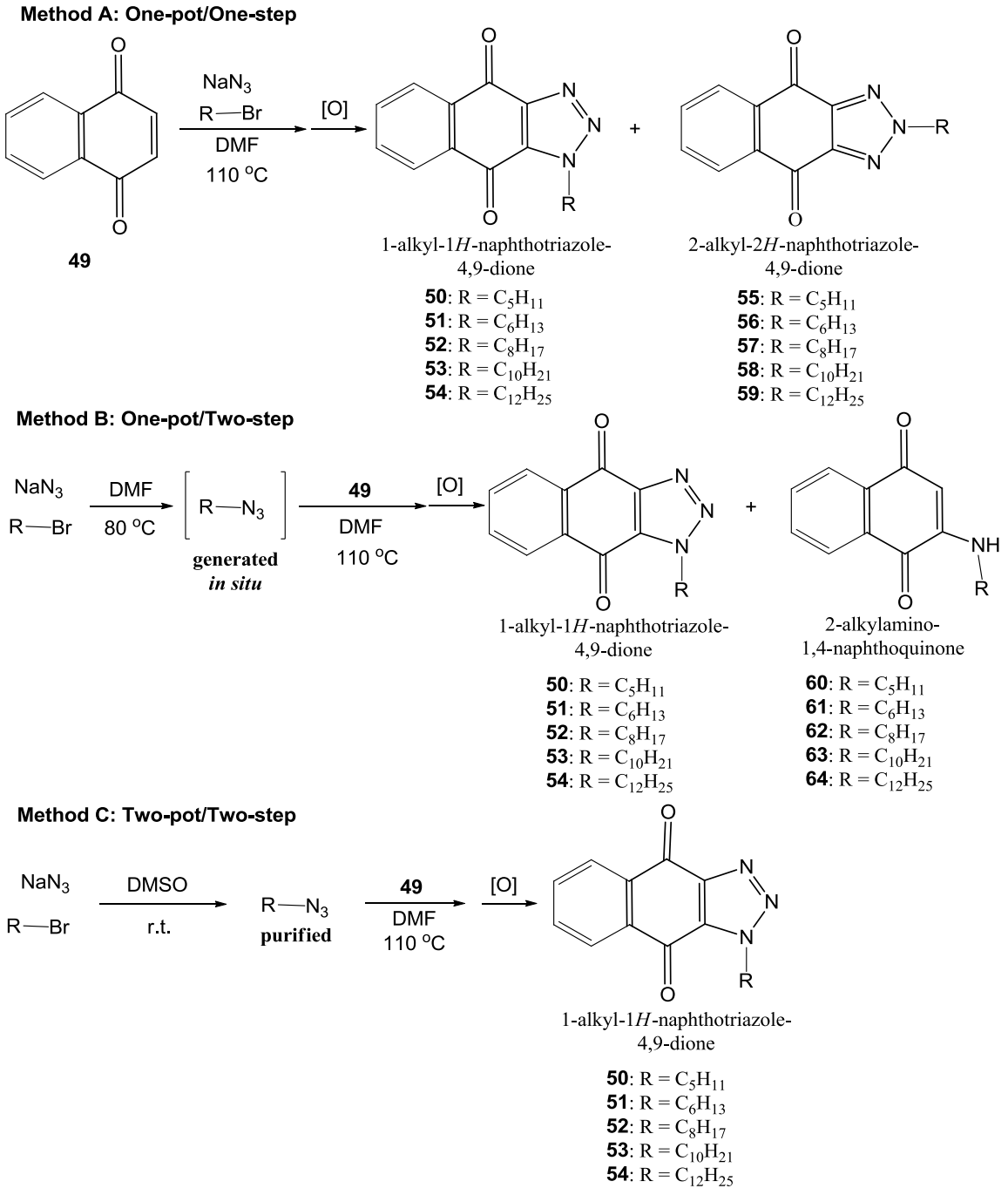
salts, which are cationic 1,4-naphthoquinone derivatives. The study of their antibacterial activity will enable us to elucidate the structure-activity relationship that will result from the incorporation of various alkyl chains at both N-1 and N-3 positions.

IV.2. Results and discussion

IV.2.1. Optimization of the production of 1-alkyl-1*H*-naphtho[2,3-*d*]1,2,3]triazole-4,9-diones

The reaction between 1,4-naphthoquinone and azido compounds has been known to occur either via a [2+3] cycloaddition,[915,116-118] or through a Michael addition and/or oxidation process.[118,119] Our group has recently reported the synthesis of 1-alkyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-diones.[114] This involves a thermodynamically-controlled cycloaddition of 1,4-naphthoquinone **49** with alkyl azides, followed by an oxidation. Interestingly, this simple but versatile reaction was found to provide structurally diverse molecules, depending on the order of addition of the different reagents or the reaction conditions.

For example, a one-pot/one-step [3+2] cycloaddition in which **49**, sodium azide, and alkyl bromides were allowed to react in DMF provided our expected products **50-54** (Scheme 18, Method A).[114] This method also afforded the byproducts 2-alkyl-2*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-diones **55-59**. Although this protocol provided a one-pot divergent synthesis of both classes of compounds in a unique and simple fashion, difficulty in separating them arose. Indeed, they displayed almost identical R*f* values on TLC plate rendering it very difficult to scale up this protocol.



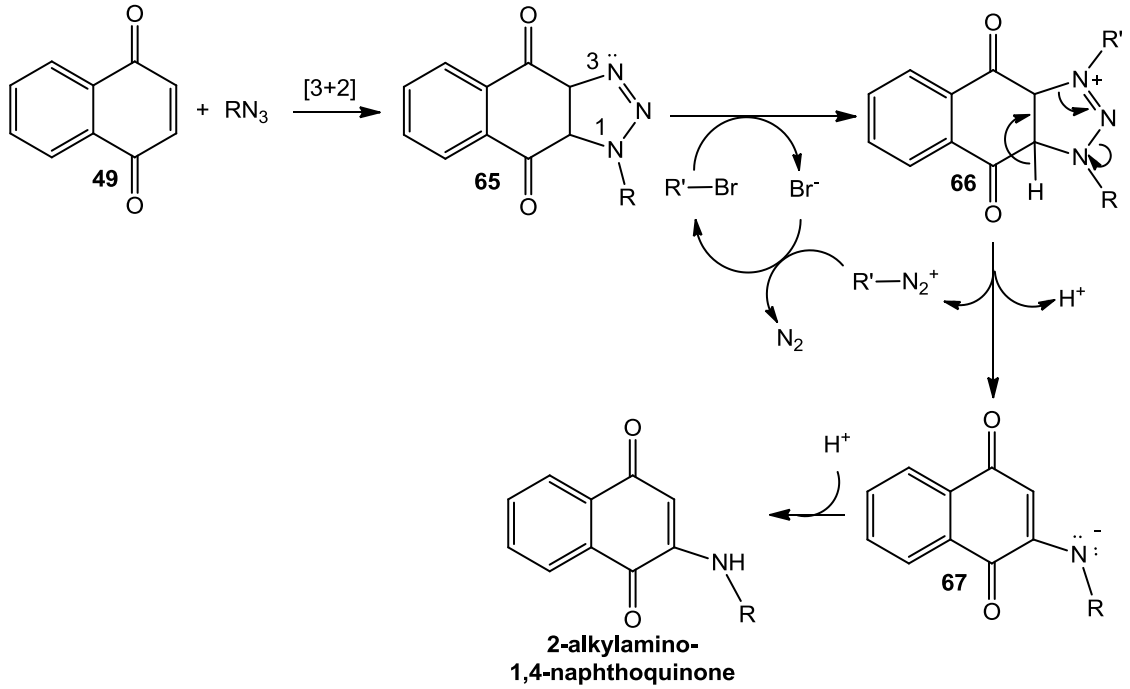
Scheme 18: Protocols for the preparation of compounds **50-54**

To circumvent this problem, we decided to approach the synthesis of compounds **50-54** in a one-pot/two-step fashion: the alkyl azides are first prepared *in situ* by reaction of sodium azide and alkyl bromides, before being allowed to react with 1,4-naphthoquinone **49** (Scheme 18, Method B). To our surprise, this also gave the byproducts 2-alkylamino-1,4-naphthoquinones **60-64**. Even though this class of compounds has been extensively studied for their pharmacological activities (antimycobaterial agents[120] and inhibitors of coenzyme Q[57]), it was important to understand their formation.

We suggested that the formation of 2-alkylamino-1,4-naphthoquinones **60-64** results from the presence of an excess amount of alkyl bromides in the reacting vessel (Scheme 19). Following the initial cycloaddition of **49** with the alkyl azide, it is possible to have an S_N^2 nucleophilic substitution via N-3 of the triazoline adduct **65** toward the alkyl bromide. The unstable molecule **66** can undergo decomposition to give the intermediate species **67**. Re-protonation of **67** affords the byproduct 2-alkylamino-1,4-naphthoquinone. In this proposed mechanism, the remaining alkyl bromide from the previous step can actually function as a *catalyst* that facilitates the formation of 2-alkylamino-1,4-naphthoquinone.

In light of these results, we expected that a third alternative, a two-pot/two-step synthesis, whereby the alkyl azides were prepared separately and allowed to react with **49** in another reacting vessel, would only provide our desired compounds **50-54** (Scheme 18, Method C). As expected, Method C generated only **50-54** with yields comparable to the other two methods (Table 4). More importantly, purification of compounds **50-54**

produced in Method C was much easier as they could be isolated by precipitation in diethyl ether, avoiding the use of a column chromatography.



Scheme 19: Mechanistic explanation for the formation of compounds **60-64**

Table 4: Comparison of the different methods for the preparation of compounds **50-54**

	Alkyl bromides	1-alkyl-1*H*-naphtho[2,3-*d*] [1,2,3] triazole-4,9-dione	Yield (%) Method A[a]	Method B[b]	Method C
1	*n*-pentyl bromide	**50**[a]	41	53	40
2	*n*-hexyl bromide	**51**	n.a.	66	49
3	*n*-octyl bromide	**52**[a]	52	63	62
4	*n*-decyl bromide	**53**[a]	64	33	54
5	*n*-dodecyl bromide	**54**[a]	68	49	68

[a]: Ref. 114 [b]: obtained as inseparable mixtures of 1-alkyl-1*H*-naphtho[2,3-*d*] [1,2,3] triazole-4,9-dione and 2-alkylamino-1,4-naphthoquinone.The yields of **50-54** are estimated from the integral ratio of the ^{1}H NMR.

IV.2.2. Synthesis of novel cationic 1,4-naphthoquinone derivatives

Our initial class of cationic 1,4-naphthoquinone derivatives was obtained by methylation at the N-3 position of the triazole motif of compounds **50-54.**[115] In order to investigate the effect of the chain length at N-3 position, we synthesized analogs with various chain lengths at both nitrogen atoms (N-1 and N-3) using alkyl triflates (ROTf) prepared *in situ* from the corresponding alcohol (**a-f)** (Scheme 20). After alkylation, the TfO^- anion was exchanged with Cl^- anion using ion-exchange resin to yield our library of cationic 1,4-naphthoquinone derivatives. This protocol enabled the parallel synthesis of 24 novel 1,3-dialkyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride salts.

IV.2.3. Antibacterial study

Similarly to the series of previously synthesized cationic anthraquinone analogs,[115] each member of our library bears the structural scaffolds of naphthoquinone, cation and lypophilic alkyl chain, and was therefore expected to show similar biological activity.

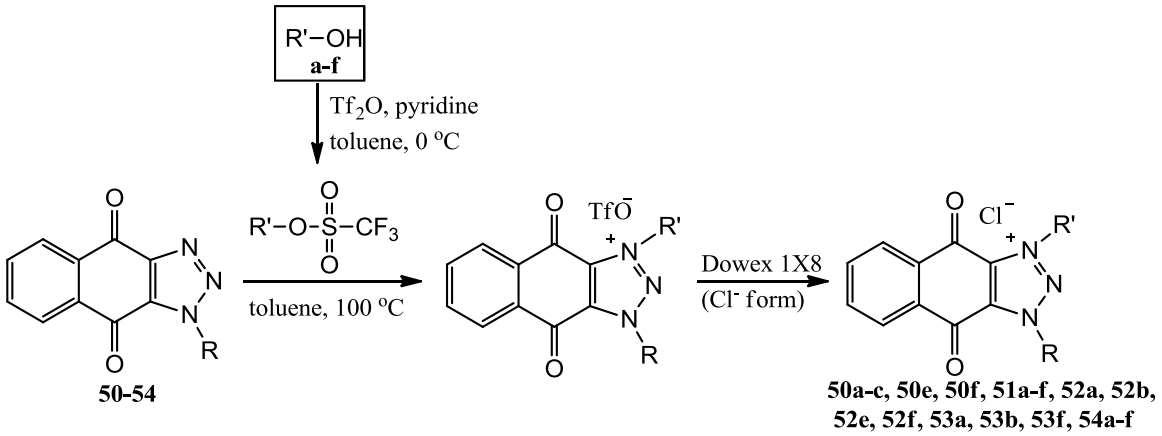
The 1,3-dialkyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*] [1,2,3]triazol-3-ium chloride salts were tested against *E. coli* (ATCC 25922, G-) and *S. aureus* (ATCC 25923, G+) using neomycin, kanamycin, vancomycin, amikacin and hexadecyltrimethylammonium bromide (HTB) as the controls. The MIC values determined in standard fashion using serial 2-fold dilutions are listed in Table 5. The results show that these cationic compounds are more active against G+ bacteria than G-

bacteria, which is consistent with the antibacterial profile of naphthoquinone[63] and cationic antiseptic agents such as HTB and cetrimonium bromide.[121]

For cationic 1,4-naphthoquinone derivatives with a methyl group at N-3 position, we had previously observed that the antibacterial activity against *S. aureus* slightly increased with the number of carbon atoms in the alkyl group at N-1, reaching a maximum with the octyl group and then decreasing as the chain length was extended to 16 carbons.[115]

The presence of a different alkyl group at N-3 was however found to have a profound influence on antibacterial activity (Figure 18a). In general, compounds with MIC values below or equal to 1 μg/mL against *S. aureus* were obtained when the total number of carbon atoms of the alkyl groups on both nitrogen atoms was between 9 and 16. This synergistic effect of alkyl group suggests that overall lipophilicity is an important factor in the antibacterial activity. In fact, antiseptic agents with lipophilic alkyl chains have been noted for their ability to disrupt the bacterial membrane of *S. aureus*.[122] It should also be noted that those cationic antiseptic agents generally have a C_{12} or longer hydrophobic tail length. This new library therefore combines shorter-chain and longer-chain compounds.

On the other hand, no general trend could be deduced from the MIC values based on the chain length against *E. coli* suggesting that lipophilicity might not be a prerequisite for the antibacterial activity of this library against G- bacteria (Figure 18b).



1-alkyl-1*H*-naphtho-triazole-4,9-diones	R	Alcohol	R'	Product	Yield (%)
50	C_5H_{11}	**a**	C_2H_5	**50a**	80
		b	C_4H_9	**50b**	53
		c	C_5H_{11}	**50c**	64
		e	C_8H_{17}	**50e**	74
		f	$C_{10}H_{21}$	**50f**	58
51	C_6H_{13}	**a**	C_2H_5	**51a**	82
		b	C_4H_9	**51b**	95
		c	C_5H_{11}	**51c**	62
		d	C_6H_{13}	**51d**	90
		e	C_8H_{17}	**51e**	88
		f	$C_{10}H_{21}$	**51f**	39
52	C_8H_{17}	**a**	C_2H_5	**52a**	51
		b	C_4H_9	**52b**	99
		e	C_8H_{17}	**52e**	29
		f	$C_{10}H_{21}$	**52f**	81
53	$C_{10}H_{21}$	**a**	C_2H_5	**53a**	99
		b	C_4H_9	**53b**	87
		f	$C_{10}H_{21}$	**53f**	93
54	$C_{12}H_{25}$	**a**	C_2H_5	**54a**	99
		b	C_4H_9	**54b**	93
		c	C_5H_{11}	**54c**	99
		d	C_6H_{13}	**54d**	88
		e	C_8H_{17}	**54e**	52
		f	$C_{10}H_{21}$	**54f**	99

Scheme 20: Synthesis of cationic 1,4-naphthoquinone derivatives

Table 5: MIC values of cationic 1,4-naphthoquinone derivatives (μg/mL)

Compound	R	R'	*E.coli*	*S. aureus*
Neomycin B	-	-	8	1
Kanamycin	-	-	4	1-2
Vancomycin	-	-	64-125	0.5
Amikacin	-	-	0.125	0.5
HTB	-	-	1	0.5-1
68[a]	C_5H_{11}	CH_3	8-16	2
50a	C_5H_{11}	C_2H_5	≥250	2-4
50b	C_5H_{11}	C_4H_9	≥250	0.5
50c	C_5H_{11}	C_5H_{11}	≥250	1
50e	C_5H_{11}	C_8H_{17}	32-64	0.125
50f	C_5H_{11}	$C_{10}H_{21}$	8-16	1-2
69[b]	C_6H_{13}	CH_3	125-250	1-2
51a	C_6H_{13}	C_2H_5	125-250	1
51b	C_6H_{13}	C_4H_9	125-250	1
51c	C_6H_{13}	C_5H_{11}	125	1-2
51d	C_6H_{13}	C_6H_{13}	32-64	0.5-1
51e	C_6H_{13}	C_8H_{17}	4-8	0.5-1
51f	C_6H_{13}	$C_{10}H_{21}$	2	0.25-0.5
70[a]	C_8H_{17}	CH_3	16-32	0.032-0.064
52a	C_8H_{17}	C_2H_5	≥250	0.25-0.5
52b	C_8H_{17}	C_4H_9	64	1-2
52e	C_8H_{17}	C_8H_{17}	≥250	2-4
52f	C_8H_{17}	$C_{10}H_{21}$	32-64	1-2
71[a]	$C_{10}H_{21}$	CH_3	32	0.032
53a	$C_{10}H_{21}$	C_2H_5	≥250	0.125-0.25
53b	$C_{10}H_{21}$	C_4H_9	64-125	0.25
53f	$C_{10}H_{21}$	$C_{10}H_{21}$	125-250	16-32
72[a]	$C_{12}H_{25}$	CH_3	16-32	0.064-0.125
54a	$C_{12}H_{25}$	C_2H_5	32	0.125
54b	$C_{12}H_{25}$	C_4H_9	≥250	0.5-1
54c	$C_{12}H_{25}$	C_5H_{11}	125-250	0.25-0.5
54d	$C_{12}H_{25}$	C_6H_{13}	125	0.5-1
54e	$C_{12}H_{25}$	C_8H_{17}	125-250	2-4
54f	$C_{12}H_{25}$	$C_{10}H_{21}$	>250	16-32

[a]: Ref. 115; [b]: Compound **69** was synthesized according to the protocol described in reference 115.

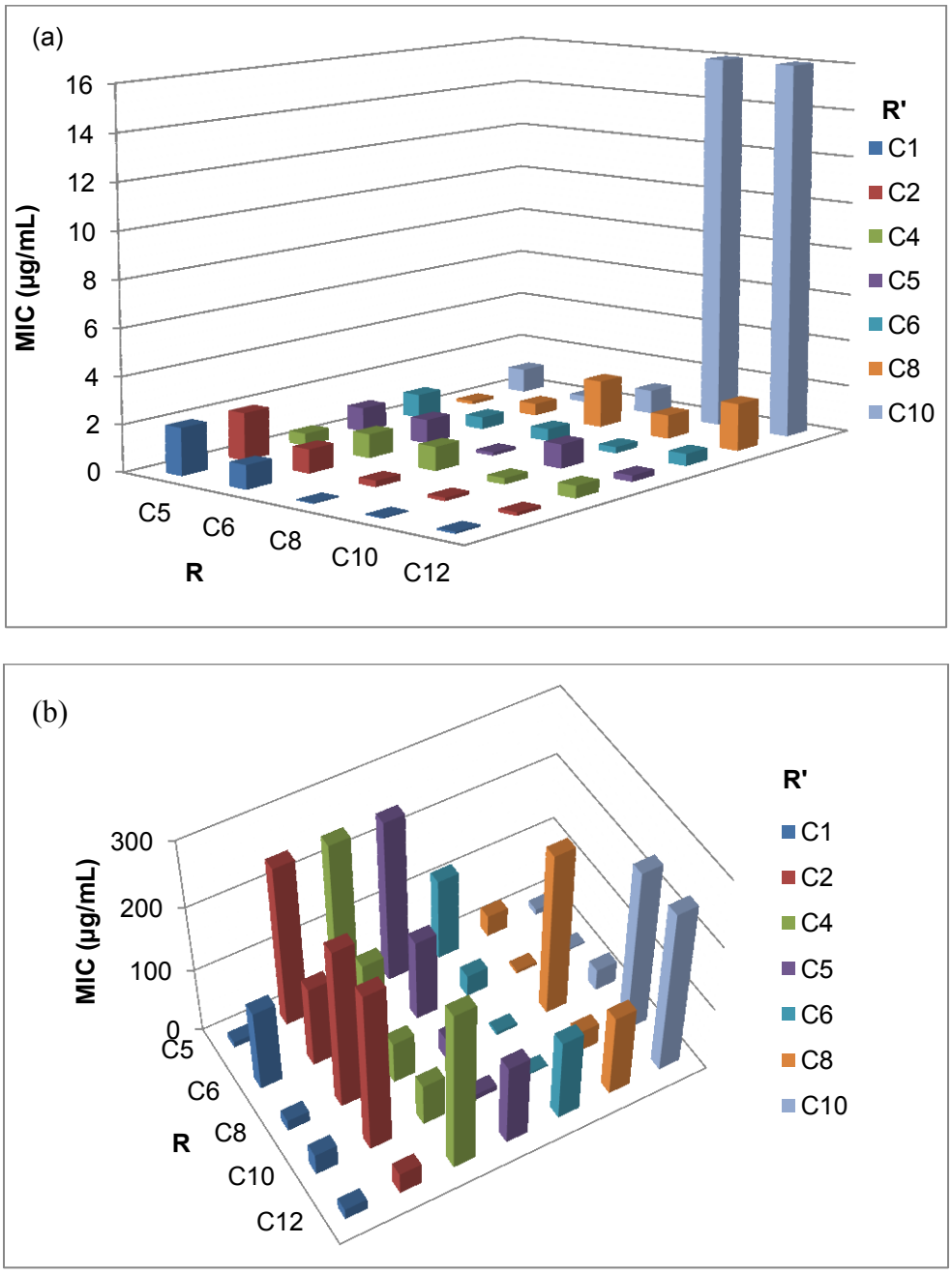


Figure 18: Effect of the alkyl chain length on the MIC values of the cationic 1,4-naphthoquinone derivatives against (a) *S. aureus* and (b) *E. coli*

IV.3. Conclusion

We have developed a new and improved protocol for the synthesis of 1-alkyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-diones. To further investigate the effect of alkyl substitution at N-3 position, we constructed a library of 4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride salts and tested them against a representative G+ and G- bacterium. When the total number of carbon atoms of the alkyl groups at both N-1 and N-3 ranged between 9 and 16, these cationic 1,4-naphthoquinone derivatives will exhibit nanomolar-level antibacterial activity against *S. aureus*, suggesting a synergistic effect of the alkyl group. However, they showed little or no activity against *E. coli*.

CHAPTER V

CONCLUSIONS AND SIGNIFICANCE

Aminoglycosides and 1,4-naphthoquinone derivatives are two classes of naturally occurring compounds that have long attracted interest due their important biological and pharmaceutical applications, earning them the title of "drug-productive scaffolds."

Aminoglycosides are clinically used antibiotics with a broad-spectrum of activity against Gram-negative and Gram-positive bacteria. However, the continuous emergence of bacterial resistance has seriously hampered their efficacy. While many efforts have been devoted to reviving their antibacterial activity, novel avenues have also been explored in the field of aminoglycosides. Their ability to bind to the ribosome has been exploited in the development of new therapeutic approaches to treat genetic diseases caused by premature nonsense mutations. Our laboratory has previously synthesized libraries of aminoglycosides and the bioactive screening of these libraries has enabled the identification of a lead compound, **TC007**, in the treatment of spinal muscular atrophy. By slightly modifying the original protocol, more **TC007** was prepared and it was found to restore the functionality of the truncated and unstable SMNΔ7 protein by allowing the incorporation of a near-cognate amino acid at the premature stop codon.

Another screening of our libraries of aminoglycosides has revealed **FG08**, a kanamycin B analog, as a potential antifungal agent with application in agriculture. **FG08** was found to inhibit the growth of several pathogenic fungi that are responsible for a large number of crop diseases. In particular, **FG08** was found to suppress Fusarium head blight, a crop disease that has incurred huge economic losses to the U.S. government.

More interesting, unlike other antibiotics used in plant disease control, **FG08** did not show any activity against bacteria. As a result, **FG08** will unlikely contribute to the transfer of bacterial resistance. The main chemical feature of **FG08** that enabled it to "switch" from an antibacterial agent (kanamycin) to a fungicide was found to be the C8 alkyl chain present at *O*-4′′position. Novel kanamycin B analogs were then synthesized to investigate the alkyl chain length and the position of its attachment that will confer optimum fungicidal activity. First, two different alkyl groups (*n*-butyl and *n*-dodecyl) were inserted at the *O*-4′′position of ring III, which was later on attached by regio- and stereoselective glycosylation at the *O*-6 position of neamine. Second, an *n*-octyl group was introduced at various positions of ring I (*O*-2′′, *O*-3′′, *O*-4′′, and *O*-6′′), ring II (*O*-5), and ring III (*O*-3′ and *O*-4′) to afford seven additional kanamycin B analogs. A bioactive screening of these analogs allowed us to draw a SAR for the optimization of kanamycin B analogs as potential agro fungicides.

Finally, a protocol was developed to improve the production of 1-alkyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-diones and a library of cationic 1,4-naphthoquinone derivatives was synthesized. Unlike the previously reported one-pot/one-step [3+2] cycloaddition that gives an inseparable mixture of 1-alkyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-diones and its byproduct,[115] a two-pot/two-step method provided only the desired compound upon precipitation in diethyl ether, avoiding the use of a column chromatography. This enabled the facile synthesis of a library of cationic 1,4-naphthoquinone derivatives whose several members were found to exhibit antibacterial activity in the nanomolar range. More importantly, these compounds were more active

against Gram-positive bacteria than Gram-negative. They could be of great importance when antibiotics with narrow-spectrum activity are required. For example, *Clostrodium difficile* is a Gram positive bacterium responsible for clodistrium difficile infection (CDI), which is a severe inflammation of the colon. CDI is usually observed following surgery, when the gut flora has been eradicated by the use of antibiotics. The human body lacking the ability to defend itself, invasion of *C. difficile* is now inevitable, unless a drug with specific activity against Gram-positive bacteria is used.

This research has therefore contributed to the investigation of new applications of aminoglycosides, and developed novel cationic 1,4-naphthoquinone derivatives. However, more work is still to be done to get as close as possible to the development of a new drug. With the finding of the conversion of the antibacterial kanamycin B to an agro fungicide as a result of the attachment of a C8 alkyl chain at the 4´´ position, an appropriate 4-*O*-octyl glucopyranose derivative needs to be developed for a facile chemoenzymatic synthesis of **FG08** or **FG03**. In addition, novel cationic 1,4-naphthoquinone derivatives with aryl groups at N-1 position could be synthesized.

CHAPTER VI

EXPERIMENTAL SECTION

Chemical reagents and chromatography solvents were purchased from Aldrich Chemical Co. or Acros Chemical Co. and were used without purification unless otherwise noted. Dichloromethane was freshly distilled from calcium hydride. Pyridine and triethylamine were stored over 4 Å molecular sieves. Column chromatographic purifications were carried out on silica gel 230x450 mesh, Sorbent Tech. Analytical TLC was performed on Sorbent Technologies silica gel glass TLC plates. Visualization was accomplished with UV light (254 nm) followed by staining with diluted sulfuric acid (5% in methanol) solution and heating.

Proton magnetic resonance spectra were recorded using JEOL 300 or Bruker ARX 400 spectrometers. Chemical shifts were reported as parts per million (ppm) downfield from tetramethylsilane in δ unit and coupling constants were given in cycles per seconds (Hz). Signal multiplicities were indicated by s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). ^{13}C NMR spectra were obtained using JEOL 300 at 75 MHz, or Bruker ARX 400 at 100 MHz. Routine ^{13}C NMR spectra were fully decoupled by broad-band WALTZ decoupling. All NMR spectra were at ambient temperature. High-resolution fast-atom bombardment (HRFAB), high-resolution MALDI, chemical ionization (CI), atmospheric pressure chemical ionization (APCI) or electrospray ionization (ESI) were provided by the Mass Spectrometry Facilities, University of California, Riverside.

General Procedure for Aminoglycoside Treatment of SMA (performed in Dr. Lorson's laboratory). 3,813 SMA type I patient fibroblasts cells were plated on cover slips and grown in Dulbeccos's modified Eagle's medium (DMEM) containing 10% (v/v) fetal bovine serum and antibiotics for 24 h. Cells were washed three times with phosphate-buffered saline (PBS) and re-fed with DMEM containing the aminoglycoside diluted to the indicated concentration. In prolonged experiments, the medium containing freshly diluted aminoglycoside was changed every 24 h for the indicated duration (up to 96 h). For cells used in Western blot analysis, cells were plated at ~80% confluence in six-well dishes and treated for 48 h. Fresh drug-containing media was replaced every 24 h, diluted to 100 μg/mL. Cells were initially identified by DAPI staining, not by the presence or the absence of SMN and gems. Only after obtaining a field of view, the SMN/FTIC channel was observed. The DAPI field was done randomly across a large number of treated cells, providing an unbiased assessment of gem numbers throughout the cell population.

General Procedure for Mice and TC007 Treatment (performed in Dr. Lorson's laboratory). All animal experiments were carried out in accordance with protocols approved by the Animal Care and Use Committee of the University of Missouri. Mice were genotyped and litters excluded. **TC007** was initially resuspended in distilled water, further diluted in PBS, and administered by subcutaneous injection (10 μL/gram of body weight) on post-natal days 2 through 15. PBS (vehicle) was injected as a negative control. To assess gross motor function, righting reflex was measured starting at post-natal day 5.

General Procedure for MIC Determination. A solution of selected bacteria was inoculated in the Trypticase Soy broth at 35 ^{o}C for 1-2 h. The bacteria concentration was found and diluted with broth, if necessary, to an absorption value of 0.08 to 0.1 at 625 nm. The adjusted inoculated medium (100 μL) was diluted with 10 mL of broth and then applied to a 96-well microtiter plate (50 μL). A series of solutions (50 μL each in 2-fold dilution) of the tested compounds was added to the testing wells. The 96-well plate was incubated at 35 ^{o}C for 12-18 h. The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound needed to inhibit the growth of bacteria. The MIC results are repeated at least three times.

General Procedure for Leaf Infection Assay (performed by Ms. Yukie Kawasaki, a graduate student of Dr. Jon Takemoto. All the figures/data related to leaf infection assay remain her sole propriety). Suspensions of *F. graminearum* macronidia ($2.0x10^{4}$ mL^{-1}) were prepared in sterile solution of 0.25% (wt vol^{-1}) agar and 0.20% (by volume) of Tween 20 and mixed with equal volumes of aminoglycoside made in the same solution.

FHB Disease Suppression (performed by Ms. Yukie Kawasaki, a graduate student of Dr. Jon Takemoto. All the figures/data related to FHB disease suppression remain her sole propriety). Rapid-maturing cultivar Apogee was grown for 5-6 weeks in a greenhouse to the flowering stage. Florets (one per spikelet) were treated with a solution of aminoglycoside at the indicated concentration, and then inoculated with suspension of *F. graminearum* macroconidia (10 μL, 10^{5} conidia mL^{-1}). After 4 days, the spikelets were visually inspected for disease symptoms (chlorosis, spikelet curling, and dehydration).

General Procedure for *O*-Alkylation of Sugars. To a solution of starting material in anhydrous DMF, alkyl bromide (2.0 equivalents), NaH (2.0 equivalents), and catalytic amount of TBAI were added. The reaction was stirred overnight. When complete, the reaction was quenched by addition of MeOH (5 mL) and was slowly poured into a mixture of ice and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with 1 N aqueous HCl, water, saturated aqueous $NaHCO_3$ and brine, and then dried over solid Na_2SO_4. After removal of the solvent and purification with gradient column chromatography (hexane:EtOAc = 100:0 to 60:40), the product was obtained.

General Procedure for the Glycosylation using Thiophenyl donor, and Hydrolysis. A solution of glycosyl donor, neamine derivative (1.2 equivalents), and activated powder 4 Å molecular sieve was stirred at room temperature for 2 h in 12 mL of a mixed anhydrous solution Et_2O:CH_2Cl_2 = 3:1. The mixture was cooled to -70 ^oC and *N*-iodosuccinimide (1.2 equivalents) was quickly added. After the temperature has warmed up to -40 ^oC, trifluoromethanesulfonic acid (0.15 equivalents) was added. The solution was stirred at low temperature till the complete consumption of the glycosyl donor. The reaction mixture was quenched by addition of solid $NaHCO_3$, $Na_2S_2O_3$, and Na_2SO_4. After being stirred for 15 minutes, the reaction mixture was filtered through celite. The residue was washed thoroughly with EtOAc. After removal of the solvents, the crude product was purified with gradient column chromatography. The glycosylated compounds were often mixed with inseparable impurities, and were therefore fully characterized after hydrolysis. The glycosylated product was dissolved in THF (1 mL)

and MeOH (5 mL), and 1M NaOMe in MeOH (0.5 mL) was added. The mixture was stirred at room temperature until TLC analysis indicated completion of the reaction (about 30 minutes). The reaction was neutralized with Amberlite IR-120 (H^+), and filtered through celite. After removal of the solvents, the crude product was purified with gradient column chromatography (Hexane:EtOAc = 100:0 to 50:50) to afford the expected product.

General Procedure for Cycloaddition of 1,4-Naphthoquinone

Method A. is described in ref 114.

Method B. A solution of NaN_3 (~0.1 g) and alkyl bromide (2 equivalents) in DMF (10 mL) was stirred at 80 ^oC for one day in a sealed vial. Then naphthoquinone (2 equivalents) was added and the mixture was heated for another day at 110 ^oC. The solvent was evaporated and the crude product was purified by column chromatography (eluted from hexane:EtOAc = 100:0 to 50:50) to afford a mixture containing both 1-alkyl-1*H*-naphtho[2,3-*d*]triazole-4,9-diones and 2-alkylamino-1,4-naphthoquinones. The 2-alkylamino-1,4-naphthoquinones were recovered after N-3 alkylation.

Method C. A solution of alkyl azide (~0.3 g), which was obtained using the method described in reference 124, and naphthoquinone (2 equivalents) in DMF (10 mL) was stirred at 110 ˚C overnight in a sealed vial. The solvent was evaporated and cold diethyl ether (50 mL) was added. The solid that precipitated was collected by filtration through a Hirsh funnel and washed with more diethyl ether to afford the expected product as a pale brown solid.

General Procedure for N-3 Alkylation. The alcohol (2 equivalents) and pyridine (4 equivalents) were dissolved in anhydrous toluene (10 mL) and cooled in an ice-water bath before Tf_2O (4 equivalents) was slowly added. The mixture was stirred at 0 ^oC for 2 h and the triazole (0.11 g, 1 equivalent) was then added. This mixture was then refluxed at 110 ^oC for 6-8 h. After completion of the reaction, the solvent was removed and the crude product was purified by column chromatography (eluted with 300 mL Hexane:EtOAC = 50:50, 200 mL pure EtOAc, and finally 100 mL EtOAc:MeOH = 80:20) to afford the expected product, which was then eluted through a small column packed with Dowex 1x8 (Cl^-) resin for ion exchange.

Hexaazido-hepta-*O*-benzyl Neomycin (1).[82] NaN_3 (54.8 g, 842.2 mmol) was first dissolved with distilled water (75 mL) in a 1L round-bottomed flask. Dichloromethane (125 mL) was then added and the flask was transferred in an ice-water bath. Tf_2O (28.4 mL, 168.5 mmol) was slowly added and the mixture was stirred at low temperature. Two hours later, the reaction mixture was transferred into a 1L separatory funnel and a saturated aqueous $NaHCO_3$ solution was added. The funnel was shaken to release CO_2 gas and the CH_2Cl_2 phase was separated. The aqueous phase was extracted with an additional 75 mL CH_2Cl_2. The organic layers were then combined and washed with saturated $NaHCO_3$ solution until no more gas was produced. This freshly prepared dichloromethane solution of triflic azide was slowly added to a mixture of neomycin trisulfate (10.0 g, 14.04 mmol), $CuSO_4.5H_2O$ (0.35 g, 1.40 mmol), K_2CO_3 (15.5 g, 112.3 mmol) in H_2O (150 mL) and MeOH (300 mL). The mixture was stirred at room temperature overnight until TLC analysis showed complete reaction. The solvent was

then removed under reduced pressure, and the residue was redissolved in EtOAc. The filtrate obtained following filtration through a celite bed was subsequently extracted with 1N aqueous HCl, saturated aqueous $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure to provide a greenish crude product. After being dried under vacuum pump for a few hours, the crude product (14.07 g, 18.3 mmol) was dissolved in DMF (100 mL), and BnBr (32.8 mL, 274.1 mmol) and a catalytic amount of TBAI were added. The mixture was then transferred in an ice-water bath and NaH (11.0 g, 274.1 mmol) was slowly added. When TLC analysis performed the following day indicated completion, the reaction was quenched with MeOH (20 mL) and poured over ice. The mixture was diluted with EtOAc, extracted with 1N aqueous HCl, saturated aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4, filtered, and concentrated. Purification of the crude product by gradient column chromatography (hexane:EtOAc = 100:0 to 50:50) provided **1** (7.44 g, 5.3 mmol, 38% from neomycin sulfate).

1,3,2′,6′-Tetraazido-6,3′,4′-tri-*O*-benzyl Neamine (2).[82] Compound **1** (7.44 g, 5.3 mmol) was dissolved in CH_3CN (100 mL) and $CuCl_2.2H_2O$ (1.81 g, 10.6 mmol) was added. The mixture was stirred at 80 ^oC overnight until TLC analysis showed completion of the reaction. The solvent was then removed under reduced pressure. The residue obtained was redissolved in EtOAc and filtered through a celite bed. The filtrate was then extracted with water and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by gradient column chromatography (hexane:EtOAc = 100:0 to 20:80) provided **2** (2.10 g, 3.0 mmol, 57%).

1,2:5,6-Di-*O*-isopropylidene-α-D-allofuranose (4).[83] To a sealed round-bottomed flask containing anhydrous CH_2Cl_2 (400 mL) at -78 ^oC, oxalyl chloride (5.03 mL, 57.6 mmol) and anhydrous DMSO (8.2 mL, 115.3 mmol) were added dropwise. When the temperature warmed up to -65 ^oC, a solution of diacetone-D-glucose **3** in anhydrous CH_2Cl_2 (100 mL) was added, and the reaction was allowed to stir until the temperature reaches -45 ^oC. At that moment, anhydrous Et_3N (32.3 mL, 230.6 mmol) was added and the reaction mixture was stirred until room temperature. The mixture was diluted with CH_2Cl_2 and washed with 1N aqueous HCl, pH 7 buffer (3 times), and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product obtained was then dissolved in anhydrous MeOH and the solution was cooled down to 0 ^oC. $NaBH_4$ (4.36 g, 115.3 mmol) was then slowly added and the reaction was allowed to stir overnight till room temperature. The reaction was quenched by adding HCl dropwise until the solution reaches pH 8. Removal of the solvents gave a syrup-like residue that was diluted with EtOAc. Filtration through layers of silica gel and celite provided a solution that was concentrated and purified by gradient column chromatography (hexane:EtOAc = 100:0 to 40:60) to afford **4** (4.62 g, 17.7 mmol, 46%).

3-Azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-glucopyranose (5).[84] To a solution of **4** (4.59 g, 17.6 mmol) in anhydrous CH_2Cl_2 (100 mL), pyridine (4.2 mL, 51.1 mmol) was added and the mixture was cooled down to 0 ^oC in an ice-water bath. Tf_2O (7.5 mL, 44.1 mmol) was then added dropwise and the reaction was allowed to stir for 2 h, during which time the temperature reached 20 ^oC. The reaction mixture was diluted with CH_2Cl_2 and washed with water, saturated aqueous $NaHCO_3$ (twice), and brine. The

organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude triflate was added to a solution of NaN_3 (3.44 g, 52.9 mmol) in DMF (50 mL) and the reaction was stirred at room temperature overnight until TLC analysis confirmed completion of the reaction. The solvent was then removed to afford a residue that was dissolved in EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. Purification by gradient column chromatography (hexane:EtOAc = 100:0 to 20:80) provided **5** (3.68 g, 12.9 mmol, 73%).

1,2,4,6-Tetra-*O*-acetyl-3-azido-3-deoxy-D-glucopyranose (6).[85] A solution of **5** (4.40 g, 15.4 mmol) in 150 mL of a mixed solution of AcOH/TFA/H_2O (80/1/19) was stirred at 55 ^oC overnight. When TLC analysis indicated completion of the reaction, the solvents were removed. After being dried *in vacuo* for a few hours, the crude product was dissolved in Ac_2O (50 mL) and TFA (5 mL), and the mixture was stirred at room temperature overnight. Solid $NaHCO_3$ was then added to neutralize the excess acid. EtOAc was added to dilute the solution and the organic layer was washed with water, saturated aqueous $NaHCO_3$ (3 times), and brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated. Purification by gradient column chromatography (hexane:EtOAc = 100:0 to 40:60) provided **6** (5.42 g, 14.5 mmol, 94%) as a mixture of α/β anomers in a 1/1 ratio.

2,4,6-Tri-*O*-acetyl-3-azido-3-deoxy-D-glucopyranose (7).[86] To a solution of **6** (0.37 g, 0.99 mmol) in anhydrous DMF (5 mL) was added hydrazine acetate (0.11 g, 1.2 mmol). The reaction mixture was stirred at room temperature for 6 h when TLC analysis indicated completion of the reaction. The reaction mixture was then filtered through a

short column packed with layers of silica gel and celite. The column was eluted thoroughly with EtOAc. After removal of the solvents, the crude product was purified by gradient column chromatography (hexane:EtOAc = 100:0 to 0:100) to afford **7** (0.32 g, 0.97 mmol, 98%) as a mixture of α/β anomers in a 1/1 ratio.

3-Azido-2,4,6-tri-O-acetyl-3-deoxy-α-D-glucopyranosyl trichloroacetimidate (8).[87] To a solution of **7** (0.66 g, 2.0 mmol) and trichloroacetonitrile (1.0 mL, 10.0 mmol) in anhydrous CH_2Cl_2, DBU (0.08 mL, 0.50 mmol) was added dropwise. The solution was stirred at room temperature until TLC analysis indicated completion of the reaction, sometimes as fast as 10 minutes. Then charcoal was added to the reaction mixture. This was then filtered through a short column packed with celite and the column was thoroughly eluted with EtOAc. After removal of the solvents, the crude product was loaded in a column that has been pretreated with triethylamine. Purification by gradient column chromatography (hexane:EtOAc = 100:0 to 50:50) provided **8** (0.63 g, 1.3 mmol, 66%). This was kept in the fridge until needed to prevent it from degrading at room temperature.

5-*O*-(3′′-Azido-2′′,4′′,6′′-tri-*O*-acetyl-3-deoxy-β-D-glucopyranosyl)-1,3,2′,6′-tetrazido-6,3′,4′-tri-*O*-benzyl neamine (9).[87] A solution of neamine derivative **2** (0.20 g, 0.29 mmol), glycosyl trichloroacetimidate **8** (0.16 g, 0.34 mmol), and activated powder 4 Å molecular sieve was stirred in anhydrous diethyl ether (10 mL) at room temperature for 2 h, then cooled to -50 ^{o}C. BF_3-OEt_2 (0.05 mL) was then added. The solution was stirred till the complete consumption of **2**. The reaction mixture was quenched by the addition of powder $NaHCO_3$. After being stirred for 15 minutes, the reaction mixture was filtered

through celite. The residue was washed thoroughly with EtOAc. After removal of the solvents, the crude product was purified with gradient column chromatography (hexane:EtOAc = 100:0 to 50:50) to afford **9** (0.22 g, 0.22 mmol, 76%).

5-*O*-(3-Amino-3-deoxy-β-D-glucopyranosyl)neamine (TC007).[87] A solution of **9** (0.33 g, 0.33 mmol) and K_2CO_3 (0.41 g, 2.94 mmol) was stirred in MeOH (10 mL) at room temperature overnight until TLC analysis indicated completion of the reaction. The solvent was removed, and the reaction mixture was diluted with EtOAc and filtered through a short column packed with layers of silica gel and celite. The column was eluted with EtOAc and MeOH. After removal of the solvents, the crude product was dissolved in THF (5 mL) and the solution was transferred in a reaction flask equipped with a reflux condenser. Then H_2O (0.6 mL) and PMe_3 (1M in THF, 1.36 mL, 1.36 mmol) were added. The reaction mixture was stirred at 50 ^oC for 2 h until completion of the reaction. Removal of the solvents afforded a crude product that was dissolved in 5 mL of degassed AcOH/H_2O (1/4). Then a catalytic amount of $Pd(OH)_2/C$ (20% Degussa type) was added and the reaction mixture was further degassed. The reaction mixture was then stirred at room temperature under atmospheric H_2 pressure for one day. The reaction mixture was then filtered through celite. The residue was washed with water, and the combined solutions were concentrated, affording a crude product that was eluted through an ion-exchange column packed with Dowex 1X8 resin (Cl^- form). Removal of the solvents afforded **TC007** as a chloride salt (136.3 mg, 0.20 mmol, 61% over 4 steps).

1,3,2′,6′-Tetraazidoneamine (13).[101] NaN_3 (50.0 g, 768.9 mmol) was first dissolved with distilled water (46 mL) in a 1L round-bottomed flask. Dichloromethane

(77 mL) was then added and the flask was transferred in an ice-water bath. Tf_2O (26.0 mL, 153.8 mmol) was slowly added and the mixture was stirred at low temperature. Two hours later, the reaction mixture was transferred into a 1L separatory funnel and saturated aqueous $NaHCO_3$ was added. The funnel was shaken to release CO_2 gas and then the CH_2Cl_2 phase was separated. The aqueous phase was extracted with an additional 75 mL CH_2Cl_2. The organic layers were then combined and washed with saturated aqueous $NaHCO_3$ solution until no more gas was produced. (Even though an explosion never happened whenever I had to prepare triflic azide, extra precaution should be taken throughout its synthesis as it is known to be very explosive).This freshly prepared dichloromethane solution of triflic azide was slowly added to a mixture of neamine hydrochloride **12** (9.0 g, 19.2 mmol), $CuSO_4.5H_2O$ (0.48 g, 1.92 mmol), and K_2CO_3 (21.2 g, 153.8 mmol) in H_2O (150 mL) and MeOH (300 mL). The mixture was stirred at room temperature overnight until TLC analysis showed complete reaction. The solvent was then removed under reduced pressure, and the residue was redissolved in EtOAc. The filtrate obtained following filtration through a celite bed was subsequently extracted with 1N aqueous HCl, saturated aqueous $NaHCO_3$, water and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. Purification with gradient column chromatography (hexane:EtOAc = 100:0 to 0:100) afforded **13** (4.26 g, 10.0 mmol, 52%).

1,3,2′,6′-Tetraazido-5,6-*O*-cyclohexylideneneamine (14).[97] To a solution of **13** (7.95 g, 18.6 mmol) and *p*-toluenesulfonic acid monohydrate (1.77 g, 9.32 mmol) in anhydrous CH_3CN (100 mL), cyclohexanone dimethyl ketal (12.8 mL, 83.9 mmol) was added, and the mixture was stirred overnight at room temperature. The reaction mixture

was quenched by addition of Et_3N (2.6 mL) and was concentrated. The residue obtained was redissolved in EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated. Purification with column chromatography provided **14** (4.8 g, 9.5 mmol, 51%).

1,3,2′,6′-Tetraazido-3′,4′-di-*O*-acetylneamine (10).[97] To a solution of **14** (3.20 g, 6.32 mmol) in anhydrous CH_2Cl_2 (50 mL), Et_3N (6.2 mL, 44.3 mmol) and DMAP (0.31 g, 2.53 mmol) were slowly added, followed by Ac_2O (3.0 mL, 32.6 mmol). The reaction was stirred at room temperature for 3 h. When complete, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with 1N aqueous HCl, water, saturated aqueous $NaHCO_3$, brine, and dried over solid Na_2SO_4. After removal of the solvent, a brownish, oily crude product was obtained, to which 80 mL of a mixed solution of dioxane:H_2O = 1:1 was added, followed by 50 mL glacial acetic acid. The resulting mixture was refluxed at 60~65^oC overnight. When complete, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with 1N aqueous HCl, water, saturated aqueous $NaHCO_3$, brine, and dried over solid Na_2SO_4. After removal of the solvent followed by purification with a gradient column chromatography (hexane:EtOAc = 100:0 to 40:60), **10** was obtained (2.03 g, 4.0 mmol, 63%).

Phenyl 4,6-*O*-(phenylmethylene)-1-thio-β-D-glucopyranoside (16).[102] To a solution of **15** (10.0 g, 22.7 mmol) in anhydrous MeOH (300 mL), 5 mL of a 1M solution of NaOMe in MeOH was added and the mixture was stirred at room temperature for 2 h. When complete, the reaction was quenched by adding Amberlite IR 120 H^+ resin to the

mixture, followed by filtration through celite and concentration of the filtrate. The crude product obtained was diluted in anhydrous DMF (50 mL), and $TsOH.H_2O$ (2.23 g, 11.7 mmol) and benzaldehyde dimethyl acetal (3.53 mL, 23.4 mmol) were added. The reaction flask was then attached to a rotavapor and rotated at 60 ^oC for 1 h. The temperature of the water bath was then raised to 100 ^oC and most of the DMF was removed. The reaction mixture was cooled down to room temperature and saturated aqueous $NaHCO_3$ (60 mL) was added. Lots of white precipitates were formed. The solution was then stirred at 90 ^oC and cooled down again to room temperature. The solids were filtered through a Buchner funnel, washed with plenty of water, and dried under reduced pressure to give **16** (7.4 g, 20.4 mmol, 90%).

Phenyl 2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside (17).[102] To a solution of **16** (2.24 g, 6.2 mmol) in DMF (40 mL), BnBr (3.0 mL, 24.9 mmol) and a catalytic amount of TBAI were added. The mixture was then transferred in an ice-water bath and NaH (1.00 g, 24.9 mmol) was slowly added. When TLC analysis performed the following day indicated completion, the reaction was quenched with MeOH (5 mL) and poured over ice. The mixture was diluted with EtOAc. The organic layer was washed with 1N aqueous HCl, saturated aqueous $NaHCO_3$, water and brine, dried over Na_2SO_4, filtered, and concentrated. The obtained crude product was dissolved in 30 mL of a mixed solution of $MeOH:H_2O$ = 1:1, and *p*-toluenesulfonic acid monohydrate (0.59 g, 3.1 mmol) was added. The reaction mixture was stirred at room temperature overnight. When complete, the reaction was quenched by addition of Et_3N (1.3 mL) and concentrated. The residue obtained was redissolved in EtOAc, washed with water and brine, dried over

Na_2SO_4, and concentrated. Purification with gradient column chromatography (hexane:EtOAc = 100:0 to 50:50) provided **17** (1.29 g, 2.9 mmol, 46%).

Phenyl 2,3-di-*O*-benzyl-6-deoxy-1-thio-β-D-glucopyranoside (18).[103] To a solution of **17** (5.13 g, 11.3 mmol) in anhydrous pyridine was slowly added TsCl (2.59 g, 13.6 mmol) at 0 ^oC. The reaction mixture was stirred overnight allowing the reaction to warm to room temperature. After completion of the reaction, the reaction mixture was extracted with EtOAc. The combined organic layer was washed with aqueous 1 N HCl (3 times), saturated aqueous $NaHCO_3$, and brine, and dried over Na_2SO_4. After removal of the solvent, the tosylated crude product was dissolved in anhydrous THF (100 mL) and $LiAlH_4$ (0.99 g, 26.0 mmol) was added. The reaction was stirred at room temperature overnight and then refluxed for 2 h. When complete, the reaction mixture was quenched by slow addition to ice then filtered through celite. The filtered residue was eluted with more EtOAc. The combined organic layers were washed with 1 N HCl, water, saturated aqueous $NaHCO_3$ and brine, and dried over Na_2SO_4. Removal of the solvent followed by purification with gradient column chromatography (hexane: EtOAc = 90:10 to 40:60) afforded **18** (2.17 g, 4.97 mmol, 44%).

Phenyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-*n*-butyl-1-thio-β-D-glucopyranoside (11a). Please refer to the general procedure for *O*-alkylation of sugars. Compound **11a** was obtained with 72% yield. ^1H NMR ($CDCl_3$, 400 MHz) δ 7.2 - 7.8 (m, 15H), 5.01 (d, J = 10.3 Hz, 1H), 4.9 - 5.0 (m, 2H), 4.85 (d, J = 10.3 Hz, 1H), 4.77 (d, J = 9.8 Hz, 1H, H-1), 3.9 (m, 1H, H-4), 3.7 (m, 2H), 3.57 (dd, J = 9.0, 9.5 Hz, 1H, H-2), 3.4 - 3.5 (m, 1H, H-5), 3.13 (t, J = 9.2 Hz, 1H, H-3), 1.6 - 1.7 (m, 2H), 1.48 (d, J = 6.1 Hz, 3H, H-6), 1.4 -

1.6 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.9, 138.5, 134.3, 132.2 (2 carbons), 129.2 (2 carbons), 128.7 (4 carbons), 128.5 (2 carbons), 128.1 (3 carbons), 128.0, 127.7, 87.7, 86.2, 84.1, 81.5, 76.1 (2 carbons), 75.8, 73.6, 32.9, 19.7, 18.5, 14.3; ESI/APCI calcd for $C_{30}H_{36}O_4SNa$ ($[M+Na]^+$) *m/z* 515.2232; measured *m/z* 515.2231.

Phenyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-*n*-octyl-1-thio-β-D-glucopyranoside (11b).[103] Please refer to the general procedure for *O*-alkylation of sugars. Compound **11b** was obtained with 63% yield.

Phenyl 2,3-di-*O*-benzyl-6-deoxy-4-*O*-*n*-dodecyl-1-thio-β-D-glucopyranoside (**11c**). Please refer to the general procedure for *O*-alkylation of sugars. Compound **11c** was obtained with 64% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.3 - 7.7 (m, 15H), 5.0 (m, 3H), 4.83 (d, J = 10.3 Hz, 1H), 4.74 (d, J = 9.7 Hz, 1H, H-1), 3.9 (m, 1H, H-4), 3.7 (m, 2H), 3.4 - 3.6 (m, 2H), 3.12 (t, J = 9.2 Hz, 1H, H-3), 1.6 - 1.7 (m, 2H), 1.46 (d, J = 6.1 Hz, 3H, H-6), 1.4 (m, 18H), 0.99 (t, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.9, 138.5, 134.3, 132.1 (2 carbons), 129.2 (2 carbons), 128.7 (4 carbons), 128.5 (2 carbons), 128.1 (3 carbons), 127.9, 127.7, 87.7, 86.8, 84.0, 81.4, 76.1 (2 carbons), 75.7, 73.9, 32.2, 30.8, 30.0 (2 carbons), 29.9 (2 carbons), 29.8, 29.7, 26.5, 23.0, 18.4, 14.5; ESI/APCI calcd for $C_{30}H_{36}O_4SNa$ ($[M+Na]^+$) *m/z* 627.3484; measured *m/z* 627.3478.

6-*O*-(2,3-Di-*O*-benzyl-6-deoxy-4-*O*-*n*-butyl-D-glucopyranosyl)-1,3,2′,6′-tetraazidoneamine (19a). Please refer to the general procedure for glycosylation using thiophenyl donor, and hydrolysis. Compound **19a** was obtained with 71% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2 - 7.4 (m, 10H), 5.69 (d, J = 3.8 Hz, 1H, H-1′), 4.92 (d, J = 3.4

Hz, 1H, H-1´´), 4.6 - 4.9 (m, 4H), 4.2 (m, 1H), 3.8 - 4.0 (m, 4H), 2.9 - 3.6 (m, 12H), 2.3 (m, 1H), 1.3 - 1.6 (m, 5H), 1.24 (d, J = 6.2 Hz, 3H, H-6´´), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8, 138.2, 128.7, 128.5 (2 carbons), 128.4 (2 carbons), 128.2 (2 carbons), 128.0 (2 carbons), 127.7, 98.5, 98.2, 86.2, 83.6, 81.0, 79.8, 79.7, 75.9, 75.5, 73.7, 73.5, 71.6, 71.3, 71.1, 68.8, 63.2, 59.4, 59.1, 51.3, 32.6, 32.4, 19.4, 17.8, 14.0; ESI/APCI calcd for $C_{36}H_{48}N_{12}O_{10}Na^+$ ([M+Na]$^+$) *m/z* 831.3509; measured *m/z* 831.3500.

6-*O*-(2,3-Di-*O*-benzyl-6-deoxy-4-*O*-*n*-octyl-α-D-glucopyranosyl)-1,3,2´,6´-tetraazidoneamine (19b).[103] Please refer to the general procedure for glycosylation using thiophenyl donor, and hydrolysis. Compound **19b** was obtained with 83% yield.

6-*O*-(2,3-Di-*O*-benzyl-6-deoxy-4-*O*-*n*-dodecyl-α-D-glucopyranosyl)-1,3,2´,6´-tetraazidoneamine (19c). Please refer to the general procedure for glycosylation and hydrolysis. Compound **19c** was obtained with 74% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2 - 7.4 (m, 10H), 5.67 (d, J = 3.8 Hz, 1H, H-1´), 4.94 (d, J = 3.8 Hz, 1H, H-1´´), 4.6 - 4.9 (m, 4H), 4.2 (m, 1H), 3.8 - 4.0 (m, 4H), 2.9 - 3.6 (m, 12H), 2.3 (m, 1H), 1.5 - 1.6 (m, 2H), 1.33 (d, J = 6.2 Hz, 3H, H-6´´), 1.2 - 1.3 (m, 19H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8, 138.2, 128.6 (2 carbons), 128.5 (2 carbons), 128.1 (2 carbons), 128.0 (2 carbons), 127.8, 127.7, 98.4, 98.2, 85.9, 83.7, 81.0, 79.8, 79.7, 75.9, 75.7, 74.0, 73.5, 71.6, 71.3, 71.2, 68.7, 63.2, 59.4, 59.1, 51.3, 32.4, 32.0, 30.5, 29.8 (2 carbons), 29.7 (2 carbons), 29.6, 29.5, 26.2, 22.8, 17.8, 14.2; ESI/APCI calcd for $C_{44}H_{64}N_{12}O_{10}Na^+$ ([M+Na]$^+$) *m/z* 943.4761; measured *mze* 943.4751.

6-*O*-(6-Deoxy-4-*O*-*n*-butyl-α-D-glucopyranosyl)neamine (FG01). Please refer to the general procedure for the final synthesis of kanamycin B analogs. **FG01** was

obtained with 45% yield as a chloride salt. ^{1}H NMR (D_2O, 300 MHz) δ 5.84 (d, *J* = 4.1 Hz, 1H, H-1′), 4.84 (d, *J* = 3.1 Hz, 1H, H-1′′), 3.2 - 4.0 (m, 15H), 3.15 (dd, *J* = 6.9, 13.4 Hz, 1H), 2.89 (t, *J* = 9.3 Hz, 1H), 2.4 (m, 1H), 1.7 - 1.8 (m, 1H), 1.4 (m, 2H), 1.2 (m, 2H), 1.15 (d, *J* = 6.5 Hz, 3H, H-6′′), 0.73 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (D_2O, 75 MHz) δ 101.6, 95.8, 83.6, 83.0, 77.4, 74.1, 73.2, 72.5, 71.9, 70.6, 69.2, 68.21, 68.17, 53.4, 49.9, 48.3, 40.1, 31.4, 28.0, 18.6, 16.9, 13.1; ESI/APCI calcd for $C_{22}H_{45}N_4O_{10}^+$ ($[M+H]^+$) *m/z* 525.3130; measured *m/z* 525.3140.

6-*O*-(6-Deoxy-4-*O*-*n*-octyl-α-D-glucopyranosyl)neamine (FG08)[103] Please refer to the general procedure for the final synthesis of kanamycin B analogs. **FG08** was obtained with 20% yield as a chloride salt.

6-*O*-(6-Deoxy-4-*O*-*n*-dodecyl-α-D-glucopyranosyl)neamine (FG02). Please refer to the general procedure for the final synthesis of kanamycin B analogs. **FG02** was obtained with 34% yield as a chloride salt. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.84 (s, 1H, H-1′), 4.86 (s, 1H, H-1′′), 3.2 - 4.0 (m, 17H), 2.3 (m, 1H), 1.7 (m, 2H), 1.46 (d, *J* = 7.5 Hz, 3H, H-6′), 1.1 (m, 19H), 0.7 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 101.6, 95.9, 83.8, 83.6, 77.9, 74.1, 73.9, 72.7, 72.1, 70.8, 69.2, 68.5, 68.1, 53.6, 50.0, 48.4, 40.2, 31.7, 29.6, 29.3 (4 carbons), 29.1 (2 carbons), 28.6, 25.5, 22.4, 17.1, 13.8; ESI/APCI calcd for $C_{30}H_{61}N_4O_{10}^+$ ($[M+H]^+$) *m/z* 637.4382; measured *m/z* 37.4395.

Phenyl 2,3-di-*O*-benzyl-4-*O*-*n*-octyl-1-thio-β-D-glucopyranoside (20). To a solution of **17** (1.80 g, 3.98 mmol) in anhydrous CH_2Cl_2 were added TrCl (1.77 g, 6.36 mmol), Et_3N (1.12 mL, 7.95 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred overnight at room temperature. When complete, the reaction was

quenched by addition of MeOH (5 mL). Then the mixture was washed with water, saturated aqueous $NaHCO_3$, and brine, dried over Na_2SO_4 and concentrated. The tritylated crude product was then dissolved in anhydrous DMF, and octyl bromide (1.7 mL, 9.79 mmol), NaH (0.39 g, 9.79 mmol) and a catalytic amount of TBAI were added. The reaction was stirred overnight. When complete, the reaction was quenched by addition of MeOH (5 mL) and was slowly poured into a mixture of ice and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water, saturated aqueous $NaHCO_3$ and brine, and then dried over Na_2SO_4. After removal of the solvent, the obtained crude product was dissolved in 50 mL of a mixed solution of CH_2Cl_2:MeOH = 1:1 and *p*-toluenesulfonic acid monohydrate (0.61 g, 3.20 mmol) was added. The resulting mixture was stirred at room temperature overnight. When complete, the reaction mixture was quenched with Et_3N (1.35 mL) and extracted with EtOAc. The organic layer was washed with 1N aqueous HCl, water, saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. After removal of the solvent and purification with a gradient column chromatography (hexane:EtOAc = 100:0 to 40:60), **20** was obtained as a white solid (1.84 g, 3.26 mmol, 84%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5 (m, 2H), 7.2 – 7.4 (m, 13H), 4.88 (d, *J* = 10.3 Hz, 1H), 4.85 (s, 1H), 4.84 (s, 1H), 4.74 (d, *J* = 10.3 Hz, 1H), 4.70 (d, *J* = 10.0 Hz, 1H), 3.9 (m, 1H), 3.5 – 3.8 (m, 4H), 3.43 (t, *J* = 9.6 Hz, 1H), 3.3 (m, 2H), 1.94 (t, *J* = 6.9 Hz, 1H, OH), 1.5 (m, 2H), 1.2 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.5, 138.0, 133.5, 131.9 (2 carbons), 129.1 (2 carbons), 128.5 (4 carbons), 128.3 (2 carbons), 128.0, 127.9, 127.82 (2 carbons), 127.75,

87.5, 86.5, 81.0, 79.5, 78.2, 75.9, 75.6, 73.6, 62.3, 31.9, 30.5, 29.6, 29.3, 26.2, 22.7, 14.2; ESI/APCI calcd for $C_{34}H_{44}O_5SNa$ ($[M+Na]^+$) *m/z* 587.2802; measured *m/z* 587.2803.

Phenyl 2,3,6-tri-*O*-benzyl-4-*O*-*n*-octyl-1-thio-β-D-glucopyranoside (21). To a solution of **20** (1.15 g, 2.04 mmol) in DMF (40 mL) were added BnBr (0.49 mL, 4.07 mmol) and a catalytic amount of TBAI. The mixture was then transferred in an ice-water bath and NaH (0.16 g, 4.07 mmol) was slowly added. When TLC analysis performed the following day indicated completion, the reaction was quenched with MeOH (2 mL) and poured over ice. The mixture was extracted with EtOAc. The organic layer was washed with 1N aqueous HCl, saturated aqueous $NaHCO_3$, water and brine, and then dried over Na_2SO_4. After removal of the solvent and purification with a gradient column chromatography (hexane:EtOAc = 100:0 to 50:50), **21** was obtained (1.26 g, 1.92 mmol, 95%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.6 (m, 2H), 7.2 – 7.4 (m, 18H), 4.9 (m, 3H), 4.6 – 4.8 (m, 4H), 3.7 – 3.9 (m, 3H), 3.4 – 3.7 (m, 5H), 1.5 (m, 2H), 1.3 (m, 10H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.6, 138.5, 138.2, 134.0, 132.0 (2 carbons), 129.2 (2 carbons), 128.5 (4 carbons), 128.4 (2 carbons), 128.3 (2 carbons), 127.9 (2 carbons), 127.8, 127.7 (3 carbons), 127.6, 127.5, 87.5, 86.8, 80.8, 79.4, 78.2, 75.9, 75.6, 73.5, 73.4, 69.2, 32.0, 30.5, 29.6, 29.4, 26.3, 22.8, 14.3; ESI/APCI calcd for $C_{41}H_{50}O_5SNa$ ($[M+Na]^+$) *m/z* 677.3271; measured *m/z* 677.3280.

6-*O*-(2,3,6-Tri-*O*-benzyl-4-*O*-*n*-octyl-α-D-glucopyranosyl)-1,3,2′,6′-tetraazidoneamine (22). Please refer to the general procedure for glycosylation and hydrolysis. Compound **22** was obtained with 47% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2 – 7.4 (m, 15H), 5.63 (d, *J* = 3.4 Hz, 1H, H-1′), 5.02 (d, *J* = 3.8 Hz, 1H, H-1′′), 4.92

(d, *J* = 11.0 Hz, 1H), 4.75 (d, *J* = 12.4 Hz, 1H), 4.72 (m, 2H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.51 (d, *J* = 12.4 Hz, 1H), 4.1 – 4.2 (m, 1H), 4.0 – 4.1 (m, 1H), 3.96 (d, *J* = 10.3 Hz, 1H), 3.89 (d, *J* = 10.0 Hz, 1H), 3.2 – 3.8 (m, 18H), 2.31 (ddd, *J* = 13.1, 4.5, 4.1 Hz, 1H, H-2eq), 1.51 (ddd, *J* = 13.0, 12.4, 12.4 Hz, 1H, H-2ax), 1.4 – 1.5 (m, 2H), 1.2 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8, 138.1, 137.8, 128.55 (2 carbons), 128.49 (2 carbons), 128.4 (2 carbons), 128.13 (2 carbons), 128.06 (2 carbons), 128.0 (3 carbons), 127.9, 127.7, 98.6, 98.2, 86.3, 86.1, 81.4, 79.6, 78.0, 75.9, 75.7, 73.7, 73.5 (2 carbons), 71.6 (2 carbons), 71.4, 71.1, 68.5, 62.9, 59.6, 59.2, 51.3, 32.4, 31.9, 30.4, 29.6, 29.3, 26.2, 22.8, 14.2; ESI/APCI calcd for $C_{47}H_{62}N_{12}O_{11}Na$ ($[M+Na]^+$) *m/z* 993.4553; measured *m/z* 993.4563.

6-*O*-(4-*O*-*n*-Octyl-D-glucopyranosyl)neamine (FG03). Please refer to the general procedure for the final synthesis of kanamycin B analogs. **FG03** was obtained with 42% yield as a chloride salt. ^{1}H NMR (D_2O, 300 MHz) (chloride salt) δ 5.81 (d, *J* = 3.8 Hz, 1H, H-1′), 4.93 (d, *J* = 3.8 Hz, 1H, H-1′′), 3.3 - 4.0 (m, 17H), 3.1 – 3.2 (m, 2H), 2.4 (m, 1H), 1.7 - 1.9 (m, 1H), 1.4 – 1.5 (m, 2H), 1.1 - 1.2 (m, 10H), 0.71 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (D_2O, 100 MHz) (chloride salt) δ 101.7, 96.1, 83.8, 77.8, 77.6, 74.3, 73.7, 72.9, 72.3, 71.8, 70.9, 69.4, 68.4, 60.4, 53.7, 49.9, 48.5, 40.3, 31.3, 29.4, 28.7, 28.6, 28.2, 25.4, 22.2, 13.7; ESI/APCI calcd for $C_{26}H_{53}N_4O_{11}^+$ ($[M+H]^+$) *m/z* 597.3705; measured *m/z* 597.3708.

2,3-Di-*O*-benzyl-4-*O*-*n*-octyl-D-glucopyranose (25). Compound **20** (0.90 g, 1.59 mmol) was dissolved in a mixture of acetone (35 mL) and CH_2Cl_2 (10 mL). Distilled water (3.44 mL, 191.2 mmol) was added and the mixture was cooled down to 0 ^{o}C. *N*-

bromosuccinimide (0.68 g, 3.82 mmol) was added and the reaction mixture was stirred overnight till room temperature. When complete, the solvent was evaporated and the residue was redissolved in EtOAc. The organic layer was washed with water and brine, and dried over Na_2SO_4. After removal of the solvent, purification by gradient column chromatography (Hexane:EtOAc = 100:0 to 0:100) afforded **25** (0.68 g, 1.44 mmol, 90%) as a mixture of α/β anomers in a 1/1 ratio. ^{1}H NMR (α-anomer) ($CDCl_3$, 300 MHz) δ 7.2 – 7.4 (m, 10H), 5.16 (dd, *J* = 3.1, 3.1 Hz, 1H, H-1), 4.6 - 4.9 (m, 4H), 3.3 - 4.0 (m, 7H), 3.17 (d, *J* = 2.4 Hz, 1H), 2.28 (dd, *J* = 7.2, 5.8 Hz, 1H), 1.94 (dd, *J* = 7.9, 4.8 Hz, 1H), 1.5 (m, 2H), 1.2 (m, 10H), 0.87 (t , *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.7, 137.9, 128.6, 128.5 (3 carbons), 128.2, 128. 1 (2 carbons), 128.0, 127.9, 127.7, 91.4, 83.1, 80.0, 78.0, 75.6, 75.0, 73.5, 71.2, 62.0, 31.9, 30.5, 29.6, 29.4, 26.2, 22.7, 14.2; ESI/APCI calcd for $C_{28}H_{40}O_6Na$ ($[M+Na]^+$) *m/z* 495.2717; measured *m/z* 495.2720.

4-*O*-*n*-Octyl-D-glucopyranose (23). Compound **25** (0.20 g, 0.42 mmol) was dissolved in a degassed mixture MeOH:H_2O (1:1) and a catalytic amount of $Pd(OH)_2$/C was added. The vial was then sealed and freed of air before H_2 balloon was loaded. The reaction was stirred overnight under H_2 atmosphere. The reaction was filtered through a short column packed with celite and eluted with water. Removal of the solvent afforded **23** as a mixture of α/β anomers in a 10/9 ratio. (0.12 g, 0.41 mmol, 96%). ^{1}H NMR (α-anomer) (CD_3OD, 300 MHz) δ 5.07 (d, *J* = 3.8 Hz, 1H, H-1), 3.0 – 4.0 (m, 8H), 1.5 – 1.6 (m, 2H), 1.3 (m, 10 H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 92.6, 78.3, 76.0, 73.8, 72.7, 71.0, 61.1, 31.2, 30.2, 29.5, 29.3, 26.0, 22.5, 13.3; ESI/APCI calcd for $C_{14}H_{28}O_6Na$ ($[M+Na]^+$) *m/z* 315.1778; measured *m/z* 315.1780.

Phenyl 2,3,4-tri-*O*-benzyl-1-thio-β-D-glucopyranoside (27).[108] **26** (2.00 g, 3.70 mmol) was dissolved in 40 mL of a mixed solution of anhydrous Et_2O:CH_2Cl_2 (1:1) and $LiAlH_4$ (0.66 g, 17.4 mmol) was slowly added. The mixture was then gently heated. Then a solution of $AlCl_3$ (1.97 g, 14.8 mmol) in anhydrous CH_2Cl_2 (20 mL) was added to the hot reaction mixture over a 1 h period. The combined solutions were then refluxed at 40 ^oC. Two hours later, the reaction was complete as confirmed by TLC analysis. The reaction was quenched by transferring it to flask containing ice and EtOAc. The organic layer was washed with 1 N HCl, water, saturated aqueous $NaHCO_3$, and brine, and dried over Na_2SO_4. Removal of the solvent gave a crude product that was recrystallized in diethyl ether and hexane to give **27** (1.34g, 2.47 mmol, 67%).

Phenyl 2,3,4-tri-*O*-benzyl-6-*O*-*n*-hexyl-1-thio-β-D-glucopyranoside (28a). Please refer to the general procedure for *O*-alkylation of sugars. Compound **28a** was obtained with 99% yield. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.6 – 7.7 (m, 2H), 7.2 – 7.5 (m, 18H), 4.9 – 5.0 (m, 4H), 4.77 (d, J = 10.0 Hz, 1H), 4.70 (d, J = 10.0 Hz, 2H), 3.6 – 3.8 (m, 4H), 3.4 – 3.6 (m, 4H), 1.6 (m, 2H), 1.2 – 1.5 (m, 6H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.6, 138.3, 138.2, 134.1, 132.0 (2 carbons), 129.0 (2 carbons), 128.60 (5 carbons), 128.57 (2 carbons), 128.4 (2 carbons), 128.03 (2 carbons), 127.97 (3 carbons), 127.9, 127.5, 87.6, 86.9, 81.0, 79.3, 78.0, 76.0, 75.6, 75.2, 71.9, 69.7, 31.9, 30.0, 26.0, 22.3, 14.3; ESI/APCI calcd for $C_{39}H_{46}O_5S$ Na ($[M+Na]^+$) *m/z* 649.2958, measured *m/z* 649.2971.

Phenyl 2,3,4-tri-*O*-benzyl-6-*O*-*n*-octyl-1-thio-β-D-glucopyranoside (28b). Please refer to the general procedure for *O*-alkylation of sugars. Compound **28b** was

obtained with 97% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.6 – 7.7 (m, 2H), 7.2 – 7.5 (m, 18H), 4.9 – 5.0 (m, 4H), 4.79 (d, *J* = 10.3 Hz, 1H), 4.71 (d, *J* = 10.0 Hz, 2H), 3.7 – 3.8 (m, 4H), 3.4 – 3.6 (m, 4H), 1.6 (m, 2H), 1.2 – 1.5 (m, 10H), 0.94 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.6, 138.4, 138.2, 134.2, 132.0 (2 carbons), 129.0 (2 carbons), 128.63 (5 carbons), 128.64 (2 carbons), 128.4 (2 carbons), 128.1 (2 carbons), 128.0 (3 carbons), 127.9, 127.5, 87.7, 86.9, 81.0, 79.4, 78.0, 76.0, 75.6, 75.2, 71.9, 69.8, 32.1, 30.1, 29.7, 29.5, 26.4, 22.9, 14.3; ESI/APCI calcd for $C_{41}H_{50}O_5SNa$ ($[M+Na]^+$) *m/z* 677.3271, measured *m/z* 677.3280.

6-*O*-(2,3,4-Tri-*O*-benzyl-6-*O*-*n*-hexyl-α-D-glucopyranosyl)-1,3,2′,6′-tetraazidoneamine (29a). Please refer to the general procedure for glycosylation and hydrolysis. Compound **29a** was obtained with 40% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2 - 7.4 (m, 15H), 5.69 (d, *J* = 3.8 Hz, 1H, H-1'), 5.05 (d, *J* = 3.8 Hz, 1H, H-1''), 4.97 (d, *J* = 11.0 Hz, 1H), 4.88 (d, *J* = 10.7 Hz, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.75 (s, 1H), 4.74 (s, 1H), 4.59 (d, *J* = 10.7 Hz, 1H), 4.48 (d, *J* = 2.4 Hz, 1H), 4.1 – 4.2 (m, 1H), 3.9 – 4.1 (m, 3H), 3.1 – 3.7 (m, 15H), 2.97 (d, *J* = 3.4 Hz, 1H), 2.92 (d, *J* = 4.1 Hz, 1H), 2.32 (ddd, *J* = 13.1, 4.5, 4.1 Hz, 1H, H-2eq), 1.6 (m, 2H), 1.50 (ddd, *J* = 13.1, 12.7, 12.7 Hz, 1H, H-2ax), 1.2 – 1.4 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8, 138.16, 138.07, 128.61 (2 carbons), 128.58 (2 carbons), 128.51 (2 carbons), 128.16 (2 carbons), 128.10 (4 carbons), 128.04 (2 carbons), 127.8, 98.6, 98.2, 85.9, 81.5, 79.7, 79.6, 75.8 (2 carbons), 75.4, 73.5, 71.9 (2 carbons), 71.7, 71.6, 71.4, 71.1, 69.1, 63.0, 59.6, 59.2, 51.3, 32.4, 31.7, 29.4, 25.8, 22.7, 14.2 ; ESI/APCI calcd for $C_{47}H_{62}N_{12}O_{11}Na$ ($[M+Na]^+$) *m/z* 965.4240; measured *m/z* 965.4255.

6-*O*-(2,3,4-Tri-*O*-benzyl-6-*O*-*n*-octyl-α-D-glucopyranosyl)-1,3,2′,6′-tetraazidoneamine (29b). Please refer to the general procedure for glycosylation and hydrolysis. Compound **29b** was obtained with 38% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2 - 7.4 (m, 15H), 5.69 (d, *J* = 3.8 Hz, 1H, H-1'), 5.05 (d, *J* = 3.8 Hz, 1H, H-1''), 4.97 (d, *J* = 11.0 Hz, 1H), 4.88 (d, *J* = 10.7 Hz, 1H), 4.82 (d, *J* = 11.0 Hz, 1H), 4.75 (s, 1H), 4.74 (s, 1H), 4.59 (d, *J* = 10.7 Hz, 1H), 4.48 (d, *J* = 2.4 Hz, 1H), 4.1 – 4.2 (m, 1H), 3.9 – 4.1 (m, 3H), 3.1 – 3.7 (m, 15H), 2.97 (d, *J* = 3.4 Hz, 1H), 2.92 (d, *J* = 4.1 Hz, 1H), 2.32 (ddd, *J* = 13.1, 4.5, 4.1 Hz, 1H, H-2eq), 1.6 (m, 2H), 1.50 (ddd, *J* = 13.1, 12.7, 12.7 Hz, 1H, H-2ax), 1.2 – 1.4 (m, 6H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.9, 138.3, 138.2, 128.7 (4 carbons), 128.6 (2 carbons), 128.23 (6 carbons), 128.22 (2 carbons), 127.9, 98.7, 98.3, 85.8, 81.6, 79.8 (2 carbons), 77.7, 75.9 (2 carbons), 75.5, 73.6, 72.0, 71.8, 71.7, 71.6, 71.3, 69.2, 63.2, 59.7, 59.3, 51.4, 32.5, 32.1, 29.7, 29.6, 29.5, 26.3, 22.9, 14.3 ; ESI/APCI calcd for $C_{47}H_{62}N_{12}O_{11}Na$ ($[M+Na]^+$) *m/z* 993.4611; measured *m/z* 993.4578.

6-*O*-(6-*O*-*n*-Hexyl-D-glucopyranosyl)neamine (FG05). Please refer to the general procedure for the final synthesis of kanamycin B analogs. **FG05** was obtained with 86% yield as a chloride salt. ^{1}H NMR (D_2O, 300 MHz) (chloride salt) δ 5.85 (d, *J* = 4.1 Hz, 1H, H-1′), 4.89 (d, *J* = 3.5 Hz, 1H, H-1′′), 3.2 - 4.0 (m, 18H), 3.1 (m, 1H), 2.4 (m, 1H), 1.8 (m, 1H), 1.3 – 1.5 (m, 2H), 1.0 - 1.2 (m, 6H), 0.69 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (D_2O, 100 MHz) (chloride salt) δ 101.9, 95.5, 83.8, 77.0, 74.3, 72.9, 72.11, 72.07, 71.7, 70.8, 69.4, 69.3, 68.8, 68.4, 53.6, 49.9, 48.4, 40.4, 31.1, 28.6, 28.1, 25.0, 22.1, 13.6; ESI/APCI calcd for $C_{24}H_{49}N_4O_{11}$ ($[M+H]^+$) *m/z* 569.3392; measured *m/z* 569.3408.

6-*O*-(6-*O*-*n*-Octyl-D-glucopyranosyl)neamine (FG06). Please refer to the general procedure for the final synthesis of kanamycin B analogs. **FG06** was obtained with 82% yield as a chloride salt. ^{1}H NMR (D_2O, 300 MHz) (chloride salt) δ 5.92 (d, *J* = 4.1 Hz, 1H, H-1′), 4.95 (d, *J* = 3.8 Hz, 1H, H-1′′), 3.3 - 4.0 (m, 18H), 3.2 (m, 1H), 2.4 – 2.5 (m, 1H), 1.9 (m, 1H), 1.4 – 1.5 (m, 2H), 1.1 - 1.2 (m, 10H), 0.74 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (D_2O, 100 MHz) (chloride salt) δ 102.0, 95.6, 83.8, 76.9, 74.3, 72.9, 72.2, 72.1, 71.8, 70.9, 69.5, 69.3, 68.8, 68.4, 53.7, 49.9, 48.6, 40.4, 31.3, 28.8, 28.7, 28.6, 28.0, 25.4, 22.2, 13.7; ESI/APCI calcd for $C_{26}H_{53}N_4O_{11}$ ($[M+H]^+$) *m/z* 597.3705; measured *m/z* 597.3708.

1,2:5,6-Di-*O*-isopropylidene-3-*O*-n-octyl-α-D-glucopyranose (30).[109] Please refer to the general procedure for *O*-alkylation of sugars. Compound **30** was obtained with 99% yield.

1,2,4,6-Tetra-*O*-acetyl-3-*O*-*n*-octyl-D-glucopyranose (31). Please refer to the synthesis of **6**. Compound **31** was obtained with 87% yield as a mixture of α/β anomers in the ratio 1/2. ^{1}H NMR ($CDCl_3$, 300 MHz) (α and β anomers) δ 6.27 (d, *J* = 3. 8 Hz,1H, H-1α), 5.62 (d, *J* = 8.3 Hz, 1H, H-1β), 4.9 – 5.5.1 (m, 4H), 3.9 – 4.2 (m, 4H), 3.4 – 3.8 (m, 8H), 2.0 – 2.1 (m, 24H), 1.1 – 1.3 (m, 24H), 0.86 (t, *J* = 6.9 Hz, 6H).

Phenyl 2,4,6-tri-*O*-acetyl-3-*O*-*n*-octyl-1-thio-β-D-glucopyranoside (32). A solution of **31** (4.04 g, 8.77 mmol) and thiophenol (3.4 mL, 33.3 mmol) in anhydrous CH_2Cl_2 (50 mL) was cooled down to 0 ^oC and BF_3-OEt_2 was slowly added. The reaction was stirred for 2 days till completion. Solid $NaHCO_3$, Na_2SO_4 and some few drops of water were then added and the mixture was stirred for 1 h. The solution was then filtered

through a Fritz funnel and the collected solids were washed with EtOAc. After removal of the solvents, purification by gradient column chromatography afforded **32** (2.91 g, 5.70 mmol, 65%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.4 (m, 2H), 7.1 – 7.2 (m, 3H), 4.89 (dd, *J* = 9.6, 9.6 Hz, 1H, H-2), 4.88 (dd, *J* = 9.6, 9.6 Hz, 1H, H-4), 4.56 (d, *J* = 10.3 Hz, 1H, H-1), 3.9 – 4.1 (m, 3H), 3.5 – 3.6 (m, 1H), 3.4 – 3.5 (m, 2H), 2.03 (s, 3H), 2.00 (s, 3H), 1.95 (s, 3H), 1.3 – 1.4 (m, 2H), 1.1 – 1.2 (m, 10H), 0.77 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 169.4, 169.2, 132.9, 132.5 (2 carbons), 129.0 (2 carbons), 128.1, 86.2, 81.9, 76.1, 72.9, 71.5, 69.8, 62.7, 31.9, 30.4, 29.5, 29.4, 26.1, 22.7, 21.1, 20.9, 20.8, 14.2 ; ESI/APCI calcd for $C_{26}H_{38}O_8SNa$ ($[M+Na]^+$) *m/z* 533.2180; measured *m/z* 533.2187.

Phenyl 2,3,6-tri-*O*-benzyl-4-*O*-*n*-octyl-1-thio-β-D-glucopyranoside (33). To a solution of **32** (2.91 g, 5.70 mmol) in anhydrous MeOH (40 mL), 0.5 mL of a 1M solution of NaOMe in MeOH was added and the mixture was stirred at room temperature for 1 h. When complete, the reaction was quenched by adding amberlite IR 120 H^+ resin to the mixture, followed by filtration through celite and concentration of the filtrate. The obtained crude product was dissolved in DMF (40 mL), and BnBr (10.0 mL, 84.0 mmol) and a catalytic amount of TBAI were added. The mixture was then transferred in an ice-water bath and NaH (3.36 g, 84.0 mmol) was slowly added. When TLC analysis performed the following day indicated completion, the reaction was quenched with MeOH (5 mL) and poured over ice. The mixture was diluted with EtOAc, extracted with 1N aqueous HCl, saturated aqueous $NaHCO_3$, water and brine, and dried over Na_2SO_4. After removal of the solvents, purification by gradient column chromatography

(Hexane:EtOAc = 100:0 to 50:50) gave **33** (2.00 g, 3.05 mmol, 44%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2 – 7.8 (m, 20H), 5.0 (m, 2H), 4.86 (d, *J* = 10.3 Hz, 1H), 4.6 – 4.8 (m, 4H), 3.8 – 4.0 (m, 4H), 3.5 – 3.7 (m, 4H), 1.7 – 1.8 (m, 2H), 1.3 - 1.5 (m, 10H), 1.01 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.7, 138.65, 138.55, 134.3, 132.3 (2 carbons), 129.2 (2 carbons), 128.75 (4 carbons),128.67 (2 carbons), 128.5 (2 carbons), 128.3 (2 carbons), 128.1 (2 carbons), 128.0 (2 carbons), 127.9, 127.7, 87.7, 87.1, 81.2, 79.4, 78.1, 75.7, 75.3, 74.4, 73.7, 69.4, 32.2, 31.0, 29.9, 29.6, 26.7, 23.0, 14.5 ; ESI/APCI calcd for $C_{41}H_{50}O_5SNa$ ($[M+Na]^+$) *m/z* 677.3271; measured *m/z* 677.3270.

6-*O*-(2,4,6-Tri-*O*-benzyl-3-*O*-*n*-octyl-α-D-glucopyranosyl)-1,3,2′,6′-tetraazidoneamine (34). Please refer to the general procedure for glycosylation and hydrolysis. Compound **34** was obtained with 59% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.1 – 7.5 (m, 15H), 5.60 (d, *J* = 3.8 Hz, 1H, H-1′), 5.02 (d, *J* = 3.8 Hz, 1H, H-1′′), 4.83 (d, *J* = 10.7 Hz, 1H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.61 (d, *J* = 12.4 Hz, 1H), 4.54 (s, 1H), 4.53 (s, 1H), 4.49 (d, *J* = 12.4 Hz, 1H), 4.45 d, *J* = 10.7 Hz, 1H), 4.0 – 4.1 (m, 2H), 3.0 – 4.0 (m, 18H), 2.30 (ddd, *J* =13.1, 4.5, 4.1 Hz, 1H, H-2eq), 1.6 – 1.7 (m, 2H), 1.49 (ddd, *J* = 12.7, 12.7, 12.7 Hz, 1H, H-2ax), 1.2 -1.4 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.4, 138.1, 137.9, 128.7 (6 carbons), 128.32 (2 carbons), 128.25 (2 carbons), 128.1 (4 carbons), 128.0, 98.7, 98.4, 85.8, 81.5, 79.9, 79.6, 77.8, 75.9, 75.4, 74.0, 73.6 (2 carbons), 71.7, 71.5 (2 carbons), 71.3, 68.5, 63.0, 59.7, 59.3, 51.4, 32.5,32.1,30.9, 29.8, 29.5, 26.5, 22.9, 14.3 ; ESI/APCI calcd for $C_{47}H_{62}N_{12}O_{11}Na$ ($[M+Na]^+$) *m/z* 993.4553; measured *m/z* 993.4564.

6-*O*-(3-*O*-*n*-Octyl-D-glucopyranosyl)neamine (FG07). Please refer to the general procedure for the final synthesis of kanamycin B analogs. **FG07** was obtained with 42% yield as a chloride salt. ^{1}H NMR (D_2O, 300 MHz) (chloride salt) δ 5.81 (d, *J* = 4.1 Hz, 1H, H-1′), 4.93 (d, *J* = 4.0 Hz, 1H, H-1′′), 3.3 - 4.0 (m, 18H), 3.16 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.42 (ddd, J = 12.4, 4.1, 4.1 Hz, 1H, H-2eq), 1.87 (ddd, J = 12.7, 12.4, 12.4 Hz, 1H, H-2ax), 1.4 – 1.5 (m, 2H), 1.0 - 1.3 (m, 10H), 0.71 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (D_2O, 100 MHz) (chloride salt) δ 101.8, 96.2, 83.8, 81.3, 77.7, 74.2, 73.4, 73.2, 71.3, 70.8, 69.4, 68.9, 68.4, 60.5, 53.6, 49.9, 48.4, 40.3, 31.3, 29.5, 28.7, 28.6, 28.1, 25.3, 22.2, 13.6; ESI/APCI calcd for $C_{26}H_{53}N_4O_{11}$ ($[M+H]^+$) *m/z* 597.3705; measured *m/z* 597.3720.

Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-*O*-*n*-octyl-α-D-glucopyranoside (36). Please refer to the general procedure for *O*-alkylation of sugars. Compound **36** was obtained with 90% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5 (m, 2H), 7.2 – 7.4 (m, 8H), 5.58 (s, 1H), 4.89 (d , *J* = 11.3 Hz, 1H), 4.84 (d, *J* = 3.8 Hz, 1H, H-1), 4.82 (d, *J* = 11.3 Hz, 1H), 4.30 (dd, *J* = 9.6, 4.1 Hz, 1H, H-2), 3.98 (dd, *J* = 9.3, 8.9 Hz, 1H, H-4), 3.6 – 3.9 (m, 6H), 3.46 (s, 3H), 1.6 – 1.7 (m, 2H), 1.2 – 1.4 (m, 10H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.0, 137.7, 129.1, 128.5 (2 carbons), 128.4 (2 carbons), 128.2 (2 carbons), 127.7, 126.3 (2 carbons), 101.5, 99.2, 82.2, 80.7, 78.6, 75.5, 72.4, 69.3, 62.6, 55.2, 32.1, 30.3, 29.7, 29.5, 26.2, 22.9, 14.4 ; ESI/APCI calcd for $C_{29}H_{40}O_6Na$ ($[M+Na]^+$) *m/z* 507.2717; measured *m/z* 507.2723.

1,3,4,6-Tetra-*O*-acetyl-2-*O*-n-octyl-D-glucopyranose (37). Please refer to the synthesis of **6.** Compound **37** was obtained with 76% yield as a mixture of α/β anomers in a 6/1 ratio**.** ^{1}H NMR (α-anomer) ($CDCl_3$, 300 MHz) δ 6.25 (d, *J* = 3.8 Hz, 1H, H-1), 5.21

(dd, *J* = 10.0, 9.6 Hz, 1H, H-4), 4.94 (dd, *J* = 10.3, 9.6 Hz, 1H, H-3), 4.17 (dd, *J* = 13.0, 4.1 Hz, 1H), 3.9 – 4.0 (m, 2H), 3.4 – 3.6 (m, 2H), 3.3 (m, 1H), 2.05 (s, 3H), 1.95 (s, 3H), 1.92 (s, 3H), 1.91 (s, 3H), 1.3 – 1.4 (m, 2H), 1.1 (m, 10H), 0.75 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5, 170.1, 169.7, 169.0, 89.3, 76.7, 71.6 (2 carbons), 69.8, 68.1, 61.7, 31.9, 29.8, 29.3 (2 carbons), 25.9, 22.7, 21.0, 20.8, 20.72, 20.66, 14.1 ; ESI/APCI calcd for $C_{22}H_{36}O_{10}Na$ ($[M+Na]^+$) *m/z* 483.2201; measured *m/z* 483.2192.

Phenyl 3,4,6-tri-*O*-acetyl-2-*O*-*n*-octyl-1-thio-D-glucopyranoside (38). Please refer to the synthesis of **32.** Compound **38** was obtained with 56% yield as a mixture of α/β anomers in a 3/1 ratio.^{1}H NMR (α-anomer) ($CDCl_3$, 300 MHz) δ 7.5 (m, 2H), 7.3 (m, 3H), 5.77 (d, *J* = 5.5 Hz, 1H, H-1), 5.30 (dd, *J* = 9.6, 9.6 Hz, 1H, H-4), 5.01 (dd, *J* = 10.3, 9.3 Hz, 1H, H-3), 4.54 (ddd, *J* = 10.3, 5.2, 2.1 Hz, 1H, H-5), 4.29 (dd, *J* = 12.0, 5.2 Hz, 1H, H-6), 3.99 (dd, *J* = 12.4, 2.1 Hz, 1H, H-6´), 3.6 – 3.8 (m, 2H), 3.3 – 3.5 (m, 1H), 2.04 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.5 (m, 2H), 1.2 – 1.4 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H).

Phenyl 3,4,6-tri-*O*-benzyl-2-*O*-*n*-octyl-1-thio-α-D-glucopyranoside (39). Please refer to the synthesis of **33.** Compound **39** was obtained with 95% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5 – 7.7 (m, 2H), 7.2 -7.5 (m, 18H), 5.86 (d, *J* = 4.8 Hz, 1H, H-1), 5.10 (d, *J* = 11.0 Hz, 1H), 4.95 (d, *J* = 10.7 Hz, 1H), 4.87 (d, *J* = 10.7 Hz, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.59 (d, *J* = 11.0 Hz, 1H), 4.50 (d, *J* = 12.1 Hz, 1H), 3.5 – 4.0 (m, 8H), 1.6 – 1.8 (m, 2H), 1.3 – 1.5 (m, 10H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.2, 138.6, 138.3, 135.1, 132.0, 131.8 (2 carbons), 129.2 (2 carbons), 128.7 (5 carbons), 128.3 (3 carbons), 128.2 (3 carbons), 128.0 (2 carbons), 127.9, 127.3, 87.2,

82.8, 81.0, 77.2, 76.0, 75.4, 73.7, 71.5, 70.7, 68.9, 32.2, 30.4, 29.8, 29.6, 26.5, 23.0, 14.5 ; ESI/APCI calcd for $C_{41}H_{50}O_5NaS$ ($[M+Na]^+$) *m/z* 677.3271; measured *m/z* 677.3277.

6-*O*-(3,4,6-Tri-*O*-benzyl-2-*O*-*n*-octyl-α-D-glucopyranosyl)-1,3,2′,6′-tetraazidoneamine (40). Please refer to the general procedure for glycosylation and hydrolysis. Compound **40** was obtained with 59% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.1 – 7.5 (m, 15H), 5.60 (d, *J* = 3.8 Hz, 1H, H-1′), 5.02 (d, *J* = 3.8 Hz, 1H, H-1′′), 4.83 (d, *J* = 10.7 Hz, 1H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 1H), 4.61 (d, *J* = 12.4 Hz, 1H), 4.54 (s, 1H), 4.53 (s, 1H), 4.49 (d, *J* = 12.4 Hz, 1H), 4.45 d, *J* = 10.7 Hz, 1H), 4.0 – 4.1 (m, 2H), 3.0 – 4.0 (m, 18H), 2.30 (ddd, *J* =13.1, 4.5, 4.1 Hz, 1H, H-2eq), 1.6 – 1.7 (m, 2H), 1.49 (ddd, *J* = 12.7, 12.7, 12.7 Hz, 1H, H-2ax), 1.2 -1.4 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.4, 138.1, 137.9, 128.7 (6 carbons), 128.32 (2 carbons), 128.25 (2 carbons), 128.1 (4 carbons), 128.0, 98.7, 98.4, 85.8, 81.5, 79.9, 79.6, 77.8, 75.9, 75.4, 74.0, 73.6 (2 carbons), 71.7, 71.5 (2 carbons), 71.3, 68.5, 63.0, 59.7, 59.3, 51.4, 32.5,32.1,30.9, 29.8, 29.5, 26.5, 22.9, 14.3 ; ESI/APCI calcd for $C_{47}H_{62}N_{12}O_{11}Na$ ($[M+Na]^+$) *m/z* 993.4553; measured *m/z* 993.4564.

6-*O*-(2-*O*-*n*-Octyl-D-glucopyranosyl)neamine (FG09). Please refer to the general procedure for the final synthesis of kanamycin B analogs. **FG09** was obtained with 52% yield as a chloride salt. ^{1}H NMR (D_2O, 300 MHz) (chloride salt) δ 5.81 (d, *J* = 3.8 Hz, 1H, H-1′), 5.06 (d, *J* = 3.4 Hz, 1H, H-1′′), 3.0 - 4.0 (m, 19H), 2.4 (m, 1H), 1.4 – 1.5 (m, 3H), 1.1 - 1.2 (m, 10H), 0.72 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (D_2O, 100 MHz) (chloride salt) δ 100.3, 96.4, 83.9, 80.1, 78.0, 74.4, 73.3, 73.2, 72.7, 70.8, 69.5, 69.4,

68.4, 60.7, 53.7, 49.8, 48.4, 40.3, 31.3, 29.3, 28.7, 28.5, 28.0, 25.1, 22.2, 13.6; ESI/APCI calcd for $C_{26}H_{53}N_4O_{11}$ ($[M+H]^+$) *m/z* 597.3705; measured *m/z* 597.3701.

3′,4′-Di-*O*-benzyl-1,3,2′,6′-Tetraazidoneamine (41)[98]. To a solution of **14** (3.60 g, 7.11 mmol) in DMF (40 mL) were added BnBr (3.40 mL, 28.5 mmol) and a catalytic amount of TBAI. The mixture was then transferred in an ice-water bath and NaH (1.14 g, 28.5 mmol) was slowly added. When TLC analysis performed the following day indicated completion, the reaction was quenched with MeOH (2 mL) and poured over ice. The mixture was extracted with EtOAc. The organic layer was washed with 1N aqueous HCl, saturated aqueous $NaHCO_3$, water and brine, and dried over Na_2SO_4. After removal of the solvent, a brownish crude product was obtained, to which 80 mL of mixed solution of dioxane: H_2O = 1:1 was added, followed by 35 mL glacial acetic acid. The resulting mixture was refluxed at 60~65 ^oC overnight. When complete, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with 1N aqueous HCl, water, saturated aqueous $NaHCO_3$, brine, and dried over Na_2SO_4. After removal of the solvent followed by purification with a gradient column chromatography (pure hexane to hexane: EtOAc = 40:60), **41** was obtained (2.03 g, 6.62 mmol, 42%).

6-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-3′,4′-*O*-dibenzyl-1,3,2′,6′-tetraazidoneamine (43a). A solution of **41** (0.20 g, 0.33 mmol), **42a** (0.25 g, 0.40 mmol), and activated powder 4 Å molecular sieve was stirred at room temperature for 2 h in 12 mL of a mixed anhydrous solution Et_2O:CH_2Cl_2 = 3:1. The mixture was cooled to -70 ^oC and *N*-iodosuccinimide (0.09 g, 0.40 mmol) was quickly added. After the

temperature has warmed up to -40 ^{o}C, trifluoromethanesulfonic acid (0.05 mL) was added. The solution was stirred at low temperature till the complete consumption of the glycosyl donor. The reaction mixture was quenched by addition of solid $NaHCO_3$, $Na_2S_2O_3$ and Na_2SO_4. After being stirred for 15 minutes, the reaction mixture was filtered through celite. The residue was washed thoroughly with EtOAc. After removal of the solvents, the crude product was purified with gradient column chromatography (Hexane:EtOAc = 100:0 to 50:50) to afford **43a**. Because it was mixed with inseparable impurities, it was used as so in the next step.

6-*O*-(3-Azido-3-deoxy-2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)-3′,4′-*O*-dibenzyl-1,3,2′,6′-tetraazidoneamine (43b). Please refer to the synthesis of **43a.** Compound **43b** was also obtained mixed with inseparable impurities and was then used as so in the next step.

6-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-3′,4′-*O*-dibenzyl-5-*O*-n-octyl-1,3,2′,6′-tetraazidoneamine (44a). Please refer to the general procedure for *O*-alkylation of sugars. Compound **44a** was obtained with 57% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2 -7.5 (m, 30H), 5.72 (d, *J* = 3.4 Hz, 1H, H-1′), 5.62 (d, *J* = 3.8 Hz, 1H, H-1′′), 4.8 – 5.0 (m, 8H), 4.67 (d, *J* = 11.3 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 11.3 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.32 (d, *J* = 9.6 Hz, 1H), 4.15 (d, *J* = 10.0 Hz, 1H), 4.04 (dd, *J* = 10.3, 8.9 Hz, 1H), 3.9 – 4.0 (m, 1H), 3.3 – 3.8 (m, 15H), 2.4 (m, 1H), 1.5 – 1.7 (m, 3H), 1.0 - 1.4 (m, 10H), 0.86 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.8, 138.7, 138.1 (2 carbons), 137.83, 137.77, 128.64 (3 carbons), 128.57 (3 carbons), 128.49 (4 carbons), 128.25 (3 carbons), 128.20 (4 carbons), 128.1 (3 carbons), 128. 0 (3

carbons), 127.9 (2 carbons), 127.8, 127.7, 127.6 (2 carbons), 127.5, 97.5, 96.0, 83.3, 82.1, 80.2, 79.5, 78.8, 77.7, 77.5, 76.1, 75.8, 75.7, 75.5, 75.2, 75.1, 73.5, 73.4, 71.1, 70.2, 68.5, 63.5, 60.6, 60.5, 59.3, 32.1, 31.9, 30.2, 29.7, 29.6, 26.1, 22.8, 14.2; ESI/APCI calcd for $C_{68}H_{80}N_{12}O_{11}Na$ ($[M+Na]^+$) *m/z* 1263.5962; measured *m/z* 1263.5961.

6-*O*-(3-Azido-3-deoxy-2,4,6-tri-*O*-benzyl-α-D-glucopyranosyl)-3′,4′-*O*-dibenzyl-5-*O*-n-octyl-1,3,2′,6′-tetraazidoneamine (44b). Please refer to the general procedure for *O*-alkylation of sugars. Compound **44b** was obtained with 52% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2 -7.5 (m, 25H), 5.70 (d, *J* = 3.5 Hz, 1H, H-1′), 5.58 (d, *J* = 3.8 Hz, 1H, H-1′′), 4.92 (d, *J* = 11.3 Hz, 1H), 4.91 (s, 2H), 4.82 (d, *J* = 12.0 Hz, 1H), 4.80 (d, *J* = 10.6 Hz, 1H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 11.3 Hz, 1H), 4.64 (d, *J* = 12.0 Hz, 1H), 4.47 (d, *J* = 12.0 Hz, 1H), 4.3 (m, 1H), 4.11 (d, *J* = 10.0 Hz, 1H), 4.02 (dd, *J* = 10.3, 8.9 Hz, 1H), 3.3 – 3.9 (m, 17H), 2.3 – 2.4 (m, 1H), 1.4 – 1.7 (m, 3H), 1.0 – 1.3 (m, 10H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 138.2, 138.0, 137.9, 137.8, 137.6, 128.8 (5 carbons), 128.7 (2 carbons), 128.43 (2 carbons), 128.40 (2 carbons), 128.3 (5 carbons), 128.2 (2 carbons), 128.04 (4 carbons), 128.00 (2 carbons), 127.9, 97.6, 95.2, 83.3, 80.3, 78.9, 77.5, 76.5 (2 carbons), 76.3, 75.8, 75.5, 75.3, 75.1, 73.8, 73.1, 71.2, 69.9, 68.3, 65.8, 63.6, 60.5, 59.3, 51.2, 32.1, 32.0, 30.3, 29.7, 29.6, 26.0, 22.9, 14.3; ESI/APCI calcd for $C_{61}H_{73}N_{15}O_{10}Na$ ($[M+Na]^+$) *m/z* 1198.5557; measured *m/z* 1198.5527.

6-*O*-(α-D-Glucopyranosyl)-5-*O*-*n*-octylneamine (FG10). Please refer to the general procedure for the final synthesis of kanamycin B analogs. **FG10** was obtained with 81% yield as a chloride salt. ^{1}H NMR (D_2O, 300 MHz) (chloride salt) δ 5.59 (d, *J* =

3.8 Hz, 1H, H-1′), 5.01 (d, *J* = 3.4 Hz, 1H, H-1′′), 3.0 - 4.0 (m, 19H), 2.4 (m, 1H), 1.9 (m, 1H), 1.4 – 1.5 (m, 3H), 1.1 - 1.2 (m, 10H), 0.72 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (D_2O, 100 MHz) (chloride salt) δ 102.1, 93.1, 81.7, 80.7, 73.7, 73.31, 73.30, 72.8, 72.2, 71.3, 69.9, 68.6, 68.4, 59.9, 53.1, 50.2, 48.7, 40.0, 31.2, 29.4, 29.0, 28.5, 28.2, 25.2, 22.2, 13.6; ESI/APCI calcd for $C_{26}H_{53}N_4O_{11}$ ($[M+H]^+$) *m/z*; measured *m/z*.

6-*O*-(3-Amino-3-deoxy-α-D-glucopyranosyl)-5-*O*-*n*-octylneamine (FG11). Please refer to the general procedure for the final synthesis of kanamycin B analogs. **FG11** was obtained with 28% yield as a chloride salt. ^{1}H NMR (D_2O, 300 MHz) (chloride salt) δ 5.61 (d, *J* = 3.5 Hz, 1H, H-1′), 5.08 (d, *J* = 3.5 Hz, 1H, H-1′′), 3.0 - 4.2 (m, 19H), 2.4 (m, 1H), 1.9 (m, 1H), 1.4 – 1.5 (m, 2H), 1.1 - 1.2 (m, 10H), 0.72 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (D_2O, 100 MHz) (chloride salt) δ 101.3, 93.0, 82.0, 81.1, 73.7, 73.2, 71.8, 71.1, 69.6, 68.7, 68.2, 64.9, 59.3, 54.9, 53.0, 49.0, 48.7, 39.9, 31.2, 29.4, 29.0, 28.6, 27.9, 25.3, 22.2, 13.6; ESI/APCI calcd for $C_{26}H_{54}N_5O_{10}$ ($[M+H]^+$) *m/z* 596.3865; measured *m/z* 596. 3865.

4′-*O*-benzyl-5,6-*O*-benzylidene-1,3,2′,6′-Tetraazidoneamine (45a). To a solution of **14** (3.72 g, 7. 35 mmol) in CH_2Cl_2 (25 mL) was added TBAHS (0.75 g, 2.21 mmol), followed by BnBr (0.97 mL, 8.09 mmol) and NaOH (25 mL, 1N aqueous solution). The mixture was refluxed at 60 ^{o}C overnight. When complete, CH_2Cl_2 was removed from the reaction mixture using a rotavapor and the obtained solution was extracted with EtOAc. The organic layer was then washed with 1 N aqueous HCl, water and brine, and then dried over solid Na_2SO_4. After removal of the solvent and purification with gradient column chromatography (hexane:EtOAc = 100:0 to 40:60), the product **45a**

was obtained mixed with its regioisomer **45b** in a 1/1 ratio (1.97 g, 3.31 mmol, 45%). ^{1}H NMR ($CDCl_3$, 300 MHz) (mixture of **45a** and **45b**) δ 7.3 – 7.4 (m, 10H), 5.56 (d, *J* = 3.4 Hz, 1H), 5.52 (d, *J* = 3.8 Hz, 1H), 4.96 (d, *J* = 11.3 Hz, 1H), 4.85 (d, *J* = 11.7 Hz, 1H), 4.70 (d, *J* = 11.7 Hz, 2H), 4.0 - 4.1 (m, 4H), 3.7 – 3.9 (m, 2H), 3.3 – 3.7 (m, 13H), 3.23 (dd, *J* = 10.7, 3.8 Hz, 1H), 2.81 (d, *J* = 3.8 Hz, 1H), 2.50 (d, *J* = 3.8 Hz, 1H), 2.2 -2.4 (m, 2H), 1.3 – 1.8 (m, 24H).

3′-*O*-benzyl-5,6-*O*-benzylidene-1,3,2′,6′-Tetraazidoneamine (45b). Please refer to the synthesis of compound **45a.**

4′-*O*-benzyl-3′-*O*-*n*-octyl-1,3,2′,6′-Tetraazidoneamine (47a). To a solution of a mixture of **45a** and **45b** (1.22 g, 2.04 mmol) in anhydrous DMF (50 mL), *n*-octyl bromide (1.42 mL, 8.18 mmol), NaH (0.33 g, 8.18 mmol), and a catalytic amount of TBAI were added. The reaction was stirred at room temperature overnight. When complete, the reaction was quenched by addition of MeOH (5 mL) and was slowly poured into a mixture of ice and EtOAc. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with 1 N aqueous HCl, water, saturated aqueous $NaHCO_3$ and brine, and then dried over solid Na_2SO_4. After removal of the solvent, a brownish, oily crude product was obtained, to which 70 mL of a mixed solution of dioxane:H_2O = 1:1 was added, followed by 50 mL glacial acetic acid. The resulting mixture was refluxed at 60 ^oC overnight. When complete, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with 1N aqueous HCl, water, saturated aqueous $NaHCO_3$, brine, and dried over solid Na_2SO_4. After removal of the solvent followed by purification with a gradient

column chromatography (hexane:EtOAc = 100:0 to 40:60), a mixture of **47a** and **47b** was obtained in a 10/7 ratio (0.92 g, 1.46 mmol, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz) (mixture of **47a** and **47b**) δ 7.3 – 7.4 (m, 10H), 5.12 (d, *J* = 3.7 Hz, 1H), 5.11 (d, *J* = 3.4 Hz, 1H), 4.89 (d, *J* = 10.7 Hz, 1H), 4.87 (d, *J* = 10.3 Hz, 1H), 4.83 (d, *J* = 10.3 Hz, 1H), 4.63 (d, *J* = 1.0 Hz, 1H), 4.0 - 4.2 (m, 4H), 3.7 – 3.9 (m, 5H), 3.3 – 3.6 (m, 16H), 3.2 – 3.3 (m, 4H), 2.8 (m, 1H), 2.3 (m, 2H), 1.4 – 1.7 (m, 6H), 1.2 (m, 20H), 0.87 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 137.8 (2 carbons), 128.8 (4 carbons), 128.32, 128.27, 128. 16 (2 carbons), 128.09 (2 carbons), 99.7 (2 carbons), 84.3 (2 carbons), 81.2 (2 carbons), 80.9 (2 carbons), 79.1, 78.7 (2 carbons), 76.1, 75.8, 75.5, 74.2, 73.9, 71.7, 71.5, 64.4 (2 carbons), 59.9 (2 carbons), 59.0 (2 carbons), 51.1 (2 carbons), 32.2 (2 carbons), 32.0 (2 carbons), 30.6 (2 carbons), 29.7 (2 carbons), 29.4 (2 carbons), 26.3 (2 carbons), 22.8 (2 carbons), 14.3 (2 carbons); ESI/APCI calcd for $C_{27}H_{40}N_{12}O_6Na$ ($[M+Na]^+$) *m/z* 651.3086; measured *m/z* 651.3105.

3′-*O*-benzyl-4′-*O*-*n*-octyl-1,3,2′,6′-Tetraazidoneamine (47b). Please refer to the synthesis of compound **47a.**

6-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-4′-*O*-benzyl-3′-*O*-*n*-octyl-1,3,2′,6′-tetraazidoneamine (48a). A solution of the mixture of **47a** and **47b** (0.20 g, 0.32 mmol), **42a** (0.24 g, 0.38 mmol), and activated powder 4 Å molecular sieve was stirred at room temperature for 2 h in 12 mL of a mixed anhydrous solution Et_2O:CH_2Cl_2 = 3:1. The mixture was cooled to -70 ^{o}C and *N*-iodosuccinimide (0.09 g, 0.38 mmol) was quickly added. After the temperature has warmed up to -40 ^{o}C, trifluoromethanesulfonic acid (0.05 mL) was added. The solution was stirred at low temperature till the complete

consumption of the glycosyl donor. The reaction mixture was quenched by addition of solid $NaHCO_3$, $Na_2S_2O_3$ and Na_2SO_4. After being stirred for 15 minutes, the reaction mixture was filtered through celite. The residue was washed thoroughly with EtOAc. After removal of the solvents, the crude product was purified with gradient column chromatography (Hexane:EtOAc = 100:0 to 50:50) to afford a mixture of **48a and 48b**, obtained together with some inseparable impurities that prevented a full characterization.

6-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-3′-*O*-benzyl-4′-*O*-*n*-octyl-1,3,2′,6′-tetraazidoneamine (48b). Please refer to the synthesis of **48a**.

6-*O*-(α-D-Glucopyranosyl)-3′-*O*-*n*-octylneamine (FG12). Please refer to the general procedure for the final synthesis of kanamycin B analogs. An inseparable mixture of **FG12** and **FG13** was obtained in 35% yield as chloride salts. The spectral information of only one of them (**FG12** or **FG13**) is reported as follows: ^{1}H NMR (D_2O, 300 MHz) (chloride salt) δ 5.79 (d, J = 3.8 Hz, 1H), 4.95 (d, J = 3.1 Hz, 1H), 3.3 - 4.0 (m, 19H), 2.4 (m, 1H), 1.7 - 1.9 (m, 1H), 1.4 – 1.5 (m, 2H), 1.1 - 1.2 (m, 10H), 0.71 (t, J = 6.9 Hz, 3H); ^{13}C NMR (D_2O, 100 MHz) (chloride salt) 101.8, 96.1, 84.0, 79.2, 77.6, 74.3, 73.0, 72.9 (2 carbons), 71.7, 69.8, 69.3 (2 carbons), 60.6, 52.9, 49.9, 48.4, 40.1, 31.3, 29.5, 28.7, 28.5, 25.3, 25.2, 22.2, 13.6; ESI/APCI calcd for $C_{26}H_{53}N_4O_{11}$ ($[M+H]^+$) *m/z* 597.3705; measured *m/z* 597.3716.

6-*O*-(α-D-Glucopyranosyl)-4′-*O*-*n*-octylneamine (FG13). Please refer to the synthesis of **FG12.**

1-Pentyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione (50).[114] Please refer to the general procedure for cycloaddition of 1,4-naphthoquinone, Method C. Compound **50** was obtained in 40% yield.

1-Hexyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione (51). Please refer to the general procedure for cycloaddition of 1,4-naphthoquinone , Method C. Compound **51** was obtained in 49% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.3 – 8.4 (m, 1H), 8.2 – 8.3 (m, 1H), 7.8 – 7.9 (m, 2H), 4.85 (t, *J* = 7.2 Hz, 2H), 2.0 (m, 2H), 1.2 - 1.4 (m, 6H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 177.1, 175.7, 145.8, 135.4, 134.5, 133.7 133.5, 133.1, 128.1, 127.6, 50.9, 31.3, 30.2, 26.2, 22.6, 14.1; ESI/APCI calcd for $C_{16}H_{18}N_3O_2^+$ ($[M+H]^+$) *m/z* 284.1394; measured *m/z* 284.1390.

1-Octyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione (52).[114] Please refer to the general procedure for cycloaddition of 1,4-naphthoquinone, Method C. Compound **52** was obtained in 62% yield.

1-Decyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione (53).[114] Please refer to the general procedure for cycloaddition of 1,4-naphthoquinone, Method C. Compound **50** was obtained in 54% yield.

1-Dodecyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione (54).[114] Please refer to the general procedure for cycloaddition of 1,4-naphthoquinone, Method C. Compound **50** was obtained in 68% yield.

2-Pentylamino-1,4-naphthoquinone (60).[57] Please refer to the general procedure for cycloaddition of 1,4-naphthoquinone, Method B. Compound **60** was obtained in 29% yield (estimated from the integral ratio of ^{1}H NMR).

2-Hexylamino-1,4-naphthoquinone (61). Please refer to the general procedure for cycloaddition of 1,4-naphthoquinone, Method B. Compound **61** was obtained in 18% yield (estimated from the integral ratio of ^{1}H NMR). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.0 – 8.1 (m, 2H), 7.7 (m, 1H), 7.6 (m, 1H), 5.87 (br s, 1H), 5.72 (s, 1H), 3.16 (q, *J* = 7.2 Hz, 2H), 1.7 (m, 2H), 1.2 -1.5 (m, 6H), 0.90 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.1, 182.1, 148.2, 134.9, 133.9, 132.1, 130.7, 126.45, 126.39, 100.9, 42.8, 31.6, 28.4, 26.9, 22.7, 14.2. ESI/APCI calcd for $C_{16}H_{20}NO_2^+$ ($[M+H]^+$) *m/z* 258.1489; measured *m/z* 258.1492.

2-Octylamino-1,4-naphthoquinone (62).[120] Please refer to the general procedure for cycloaddition of 1,4-naphthoquinone, Method B. Compound **62** was obtained in 11% yield (estimated from the integral ratio of ^{1}H NMR).

2-Decylamino-1,4-naphthoquinone (63). Please refer to the general procedure for cycloaddition of 1,4-naphthoquinone, Method B. Compound **63** was obtained in 3% yield (estimated from the integral ratio of ^{1}H NMR). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.0 – 8.1 (m, 2H), 7.7 (m, 1H), 7.6 (m, 1H), 5.88 (br s, 1H), 5.73 (s, 1H), 3.16 (q, *J* = 7.2 Hz, 2H), 1.7 (m, 2H), 1.2 -1.4 (m, 14H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 183.1, 182.2, 148.2, 135.0, 133.9, 132.1, 130.7, 126.5, 126.4, 100.9, 42.8, 32.1, 29.9, 29.7 (2 carbons), 29.5, 28.5, 27.2, 22.9, 14.3 ESI/APCI calcd for $C_{20}H_{28}NO_2^+$ ($[M+H]^+$) *m/z* 314.2115; measured *m/z* 314.2112.

2-Dodecylamino-1,4-naphthoquinone (64).[123] Please refer to the general procedure for cycloaddition of 1,4-naphthoquinone, Method B. Compound **64** was obtained in 4% yield (estimated from the integral ratio of ^{1}H NMR).

3-Ethyl-1-pentyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (50a). Please refer to the general procedure for N-3 alkylation. Compound **50a** was obtained in 80% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.36 (dd, *J* = 8.9, 2.7 Hz, 2H), 8.04 (dd, *J* = 9.3, 2.4 Hz, 2H), 5.12 (q, *J* = 7.2 Hz, 2H), 5.06 (t, *J* = 7.2 Hz, 2H), 2.1 – 2.2 (m, 2H), 1.74 (t, *J* = 7.2 Hz, 3H), 1.4 - 1.5 (m, 4H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 171.2, 171.1, 134.4 (2 carbons), 134.31, 134.30, 131.2 (2 carbons), 126.3 (2 carbons), 52.8, 48.6, 26.9, 26.5, 20.3, 11.4, 11.3; ESI/APCI calcd for $C_{17}H_{20}N_3O_2^+$ ($[M]^+$) *m/z* 298.1550; measured *m/z* 298.1543.

3-Butyl-1-pentyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (50b). Please refer to the general procedure for N-3 alkylation. Compound **50b** was obtained in 53% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.35 (dd, *J* = 9.3, 2.4 Hz, 2H), 8.02 (dd, *J* = 9.3, 2.4 Hz, 2H), 5.07 (t, *J* = 7.2 Hz, 2H), 5.06 (t, *J* = 7.2 Hz, 2H), 2.1 (m, 4H), 1.4 - 1.6 (m, 6H), 1.03 (t, *J* = 7.2 Hz, 3H), 0.95 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.7 (2 carbons), 135.9 (4 carbons), 132.8 (2 carbons), 127.8 (2 carbons), 54.3, 54.1, 30.6, 28.4, 28.1, 21.8, 19.3, 12.9, 12.4; ESI/APCI calcd for $C_{19}H_{24}N_3O_2^+$ ($[M]^+$) *m/z* 326.1863; measured *m/z* 326.1856.

1,3-Dipentyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (50c). Please refer to the general procedure for N-3 alkylation. Compound **50c** was obtained in 64% yield. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.38 (dd, *J* = 9.0, 2.5 Hz, 2H), 8.05 (dd, *J* = 9.0, 2.4 Hz, 2H), 5.08 (t, *J* = 7.2 Hz, 4 H), 2.1 (m, 4 H), 1.2 - 1.6 (m, 8H), 0.98 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.7 (2 carbons), 135.9 (4 carbons), 132.8 (2 carbons), 127.9 (2 carbons), 54.3 (2 carbons), 28.4 (2 carbons), 28.1

(2carbons), 22.2 (2 carbons), 21.8 (2 carbons), 12.9 (2 carbons); ESI/APCI calcd for $C_{20}H_{26}N_3O_2^+$ ($[M]^+$) *m/z* 340.2020; measured *m/z* 340.2028.

3-Octyl-1-pentyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (50e). Please refer to the general procedure for N-3 alkylation. Compound **50e** was obtained in 74% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.37 (dd, *J* = 9.3, 2.4 Hz, 2H), 8.04 (dd, *J* = 8.9, 2.4 Hz, 2H), 5.07 (t, *J* = 7.2 Hz, 4 H), 2.1 (m, 4 H), 1.3 - 1.5 (m, 14H), 0.96 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.7 (2 carbons), 136.0 (2 carbons), 135.9 (2 carbons), 132.8 (2 carbons), 127.9 (2 carbons), 54.3 (2 carbons), 31.7, 29.0, 28.7 (2 carbons), 28.4, 28.1, 26.0, 22.5, 21.8, 13.2, 12.9; ESI/APCI calcd for $C_{23}H_{32}N_3O_2^+$ ($[M]^+$) *m/z* 382.2489; measured m/z 382.2497.

3-Decyl-1-pentyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (50f). Please refer to the general procedure for N-3 alkylation. Compound **50f** was obtained in 58% yield. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.4 (m, 2H), 8.1 (m, 2H), 5.10 (t, *J* = 7.2 Hz, 4H), 2.1 (m, 4H), 1.2 – 1.6 (m, 18H), 0.8 – 1.0 (m, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.7 (2 carbons), 136.0 (2 carbons), 135.9 (2 carbons), 132.7 (2 carbons), 127.9 (2 carbons), 54.3 (2 carbons), 31.8, 29.4, 29.2 (2 carbons), 28.7 (2 carbons), 28.5, 28.1, 26.0, 22.5, 21.8, 13.2, 12.9; ESI/APCI calcd for $C_{25}H_{36}N_3O_2^+$ ($[M]^+$) *m/z* 410.2802; measured *m/z* 410.2813.

3-Ethyl-1-hexyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (51a). Please refer to the general procedure for N-3 alkylation. Compound **51a** was obtained in 82% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.37 (dd, *J* = 8.9, 2.1 Hz, 2H), 8.04 (dd, *J* = 8.9, 2.7 Hz, 2H), 5.13 (q, *J* = 7.2 Hz, 2H), 5.07 (t, *J* = 7.6 Hz, 2H), 2.1

(m, 2H), 1.73 (t, J = 7.2 Hz, 3H), 1.3 - 1.5 (m, 6H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.73, 172.66, 135.9 (2 carbons), 135.8 (2 carbons), 132.8 (2 carbons), 127.9 (2 carbons), 54.3, 50.2, 31.0, 28.7, 25.7, 22.2, 13.1, 13.0; ESI/APCI calcd for $C_{18}H_{22}N_3O_2^+$ ($[M]^+$) *m/z* 312.1707; measured *m/z* 312.1710.

3-Butyl-1-hexyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (51b). Please refer to the general procedure for N-3 alkylation. Compound **51b** was obtained in 95% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.34 (dd, J = 8.9, 2.4 Hz, 2H), 8.01 (dd, J = 8.9, 2.8 Hz, 2H), 5.05 (t, J = 7.2 Hz, 2H), 5.04 (t, J = 7.2 Hz, 2H), 2.1 (m, 4H), 1.2 - 1.6 (m, 8H), 1.02 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.8 (2 carbons), 135.9 (4 carbons), 132.8 (2 carbons), 127.8 (2 carbons), 54.3, 54.1, 30.9, 30.6, 28.6, 25.7, 22.2, 19.3, 13.1, 12.4; ESI/APCI calcd for $C_{20}H_{26}N_3O_2^+$ ($[M]^+$) *m/z* 340.2020; measured *m/z* 340.2025.

1-Hexyl-3-pentyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (51c). Please refer to the general procedure for N-3 alkylation. Compound **51c** was obtained in 62% yield. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.38 (dd, J = 9.1, 2.4 Hz, 2H), 8.05 (dd, J = 9.1, 2.4 Hz, 2H), 5.08 (t, J = 7.3 Hz, 4H), 2.1 (m, 4H), 1.2 – 1.6 (m, 10 H), 0.9 (m, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.2 (2 carbons), 136.0 (4 carbons), 132.8 (2 carbons), 127.9 (2 carbons), 54.3 (2 carbons), 31.0, 28.7, 28.4, 28.1, 25.7, 22.2, 21.8, 13.1, 12.9; ESI/APCI calce for $C_{21}H_{28}N_3O_2^+$ ($[M]^+$) *m/z* 354.2176; measured *m/z* 354.2178.

1,3-Dihexyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (51d). Please refer to the general procedure for N-3 alkylation. Compound **51d**

was obtained in 90% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.34 (dd, *J* = 8.9, 2.7 Hz, 2H), 8.01 (dd, *J* = 9.3, 2.4 Hz, 2H), 5.05 (t, *J* = 7.2 Hz, 4H), 2.1 (m, 4H), 1.3 - 1.6 (m, 12H), 0.92 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.8 (2 carbons), 135.9 (4 carbons), 132.8 (2 carbons), 127.8 (2 carbons), 54.3 (2 carbons), 30.9 (2 carbons), 28.6 (2 carbons), 25.7 (2 carbons), 22.2 (2 carbons), 13.0 (2 carbons); ESI/APCI calcd for $C_{22}H_{30}N_3O_2^+$ ($[M]^+$) *m/z* 368.2333; measured *m/z* 368.2340.

1-Hexyl-3-octyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (51e). Please refer to the general procedure for N-3 alkylation. Compound **51e** was obtained in 88% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.35 (dd, *J* = 9.3, 2.4 Hz, 2H), 8.02 (dd, *J* = 8.9, 2.4 Hz, 2H), 5.05 (t, *J* = 7.2 Hz, 4H), 2.1 (m, 4H), 1.3 - 1.6 (m, 16H), 0.9 (m, 6H); ^{13}C NMR (CD_3OD, 75 MHz) δ 172.6 (2 carbons), 135.8 (4 carbons), 132.7 (2 carbons), 127.7 (2 carbons), 54.2 (2 carbons), 31.6, 30.8, 28.8, 28.6, 28.53, 28.52, 25.9, 25.6, 22.4, 22.1, 13.1, 13.0; ESI/APCI calcd for $C_{24}H_{34}N_3O_2^+$ ($[M]^+$) *m/z* 396.2646; measured *m/z* 396.2650.

3-Decyl-1-hexyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (51f). Please refer to the general procedure for N-3 alkylation. Compound **51f** was obtained in 39% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.37 (dd, *J* = 8.9, 2.4 Hz, 2H), 8.04 (dd, *J* = 8.9, 2.0 Hz, 2H), 5.08 (t, *J* = 7.2 Hz, 4H), 2.1 (m, 4H), 1.2 – 1.6 (m, 20H), 0.9 (m, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.7 (2 carbons), 136.1 (2 carbons), 135.9 (2 carbons), 132.7 (2 carbons), 127.9 (2 carbons), 54.4 (2 carbons), 31.8, 31.0, 29.4, 29.3, 29.2, 28.7 (3 carbons), 26.0, 25.7, 22.5, 22.3, 13.2, 13.1; ESI/APCI calcd for $C_{26}H_{38}N_3O_2^+$ ($[M^+]$) *m/z* 424.2959; measured *m/z* 424.2962.

3-Ethyl-1-octyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (52a).[124] Please refer to the general procedure for N-3 alkylation. Compound **52a** was obtained with 51% yield.

3-Butyl-1-octyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (52b). Please refer to the general procedure for N-3 alkylation. Compound **52b** was obtained in 99% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.35 (dd, *J* = 8.9, 2.8 Hz, 2H), 8.02 (dd, *J* = 8.9, 2.4 Hz, 2H), 5.0 - 5.1 (m, 4H), 2.1 (m, 4H), 1.2 – 1.6 (m, 12H), 1.03 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.8 (2 carbons), 135. 9 (4 carbons), 132.8 (2 carbons), 127.8 (2 carbons), 54.3, 54.1, 31.7, 30.6, 28.9, 28.71, 28.65, 26.0, 22.5, 19.3, 13.2, 12.5; ESI/APCI calcd for $C_{22}H_{30}N_3O_2^+$ ($[M]^+$) *m/z* 368.2333; measured *m/z* 368.2337.

1,3-Dioctyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (52e). Please refer to the general procedure for N-3 alkylation. Compound **52e** was obtained in 29% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.38 (dd, *J* = 8.9, 2.4 Hz, 2H), 8.05 (dd, *J* = 8.9, 2.7 Hz, 2H), 5.10 (t, *J* = 7.2 Hz, 4H), 2.1 (m, 4H), 1.2 – 1.6 (m, H), 0.89 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.6 (2 carbons), 136.1 (2 carbons), 135.9 (2 carbons), 132.7 (2 carbons), 127.9 (2 carbons), 54.4 (2 carbons), 31.7 (2 carbons), 30.0 (2 carbons), 28.9 (2 carbons), 28.7 (2 carbons), 26.0 (2 carbons), 22.5 (2 carbons), 13.2 (2 carbons); ESI/APCI calcd for $C_{26}H_{38}N_3O_2^+$ ($[M]^+$) *m/z* 424.2959; measured *m/z* 424.2960.

3-Decyl-1-octyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (52f). Please refer to the general procedure for N-3 alkylation. Compound **52f**

was obtained in 81% yield. ^{1}H NMR (CD_3OD, 400 MHz) δ 8.40 (dd, *J* = 9.2, 2.4 Hz, 2H), 8.06 (dd, *J* = 9.0, 2.5 Hz, 2H), 5.10 (t, *J* = 7.2 Hz, 4H), 2.1 (m, 4H), 1.2 – 1.6 (m, 24H), 0.9 (m, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.7 (2 carbons), 136.0 (2 carbons), 135.9 (2 carbons), 132.8 (2 carbons), 127.9 (2 carbons), 54.4 (2 carbons), 31.8, 31.7, 29.4, 29.3, 29.2, 28.9, 28.7 (4 carbons), 26.0 (2 carbons), 22.52, 22.49, 13.2 (2 carbons); ESI/APCI calcd for $C_{22}H_{30}N_3O_2^+$ ($[M]^+$) *m/z* 452.3280; measured *m/z* 452.3272.

3-Ethyl-1-decyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (53a). Please refer to the general procedure for N-3 alkylation. Compound **53a** was obtained in 99% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.32 (dd, *J* = 9.3, 2.4 Hz, 2H), 8.00 (dd, *J* = 8.9, 2.4 Hz, 2H), 5.08 (q, *J* = 7.2 Hz, 2H), 5.01 (t, *J* = 7.6 Hz, 2H), 2.1 (m, 2H), 1.72 (t, *J* = 7.2 Hz, 3H), 1.2 - 1.5 (m, 14H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.9, 172.8, 135.9 (2 carbons), 132.8 (2 carbons), 127.8 (4 carbons), 54.3, 50.2, 31.8, 29.4, 29.2 (2 carbons), 28.7, 28.6, 26.0, 22.5, 13.3, 12.9; ESI/APCI calcd for $C_{18}H_{22}N_3O_2^+$ ($[M]^+$) *m/z* 368.2333; measured *m/z* 368.2342.

3-Butyl-1-decyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (53b). Please refer to the general procedure for N-3 alkylation. Compound **53b** was obtained in 87% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.35 (dd, *J* = 8.9, 2.4 Hz, 2H), 8.02 (dd, *J* = 9.3, 2.4 Hz, 2H), 5.07 (t, *J* = 7.2 Hz, 2H), 5.06 (t, *J* = 7.2 Hz, 2H), 2.1 (m, 4H), 1.2 - 1.6 (m, 16H), 1.03 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.8 (2 carbons), 135.9 (4 carbons), 132.8 (2 carbons), 127.8 (2 carbons), 54.3, 54.1, 31.8, 30.6, 29.4, 29.22, 29.20, 28.73, 28.65, 26.0, 22.5, 19.3, 13.2, 12.4; ESI/APCI calcd for $C_{24}H_{34}N_3O_2^+$ ($[M]^+$) *m/z* 396.2646; measured *m/z* 396.2651.

1,3-Didecyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (53f). Please refer to the general procedure for N-3 alkylation. Compound **53f** was obtained in 93% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.35 (dd, *J* = 9.3, 2.4 Hz, 2H), 8.02 (dd, *J* = 9.3, 2.4 Hz, 2H), 5.06 (t, *J* = 7.2 Hz, 4H), 2.1 (m, 4H), 1.2 - 1.5 (m, 28H), 0.88 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.7 (2 carbons), 135.9 (4 carbons), 132.8 (2 carbons), 127.9 (2 carbons), 54.3 (2 carbons), 31.8 (2 carbons), 29.4 (2 carbons), 29.3 (2 carbons), 29.2 (2 carbons), 28.8 (2 carbons), 28.6 (2 carbons), 26.0 (2 carbons), 22.5 (2 carbons), 13.3 (2 carbons); ESI/APCI calcd for $C_{30}H_{46}N_3O_2^+$ ($[M]^+$) *m/z* 480.3585; measured *m/z* 480.3588.

1-Dodecyl-3-ethyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (54a). Please refer to the general procedure for N-3 alkylation. Compound **54a** was obtained in 99% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.35 (dd, *J* = 8.9, 2.4 Hz, 2H), 8.02 (dd, *J* = 8.6, 2.4 Hz, 2H), 5.11 (q, *J* = 7.2 Hz, 2H), 5.04 (t, *J* = 7.2 Hz, 2H), 2.1 (m, 2H), 1.73 (t, *J* = 7.2 Hz, 3H), 1.2 - 1.5 (m, 18H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.8, 172.7, 135.9 (4 carbons), 132.8 (2 carbons), 127.8 (2 carbons), 54.3, 50.2, 31.9, 29.5 (2 carbons), 29.4, 29.3, 29.2, 28.8, 28.7, 26.0, 22.5, 13.2, 12.9; ESI/APCI calcd for $C_{24}H_{34}N_3O_2^+$ ($[M]^+$) *m/z* 396.2646; measured *m/z* 396.2639.

3-Butyl-1-dodecyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (54b). Please refer to the general procedure for N-3 alkylation. Compound **54b** was obtained in 93% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.33 (dd, *J* = 9.3, 2.4 Hz, 2H), 8.00 (dd, *J* = 8.9, 2.4 Hz, 2H), 5.04 (t, *J* = 7.2 Hz, 2H), 5.03 (t, *J* = 7.2 Hz, 2H), 2.1 (m, 4H), 1.2 - 1.6 (m, 20H), 1.01 (t, *J* = 7.2 Hz, 3H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR

(CD_3OD, 100 MHz) δ 172.8 (2 carbons), 135.9 (2 carbons), 135.8 (2 carbons), 132.8 (2 carbons), 127.8 (2 carbons), 54.3, 54.1, 31.9, 30.5, 29.5 (2 carbons), 29.4, 29.3, 29.2, 28.7, 28.6, 26.0, 22.5, 19.3, 13.2, 12.5; ESI/APCI calcd for $C_{26}H_{38}N_3O_2^+$ ($[M]^+$) *m/z* 424.2959; measured *m/z* 424.2958.

1-Dodecyl-3-pentyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (54c). Please refer to the general procedure for N-3 alkylation. Compound **54c** was obtained in 99% yield. ^1H NMR (CD_3OD, 300 MHz) δ 8.36 (dd, *J* = 9.3, 2.4 Hz, 2H), 8.02 (dd, *J* = 8.9, 2.4 Hz, 2H), 5.07 (t, *J* = 7.2 Hz, 4 H), 2.1 (m, 4 H), 1.2 - 1.6 (m, 22H), 0.95 (t, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.7 (2 carbons), 136.0 (2 carbons), 135.9 (2 carbons), 132.8 (2 carbons), 127.9 (2 carbons), 54.3 (2 carbons), 31.9, 29.5 (2 carbons), 29.4, 29.3 (2 carbons), 28.74, 28.69, 28.4, 28.1, 26.0, 22.5, 21.8, 13.2, 12.9; ESI/APCI calcd for $C_{27}H_{40}N_3O_2^+$ ($[M]^+$) *m/z* 438.3128; measured *m/z* 438.3122.

1-Dodecyl-3-hexyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (54d). Please refer to the general procedure for N-3 alkylation. Compound **54d** was obtained in 88% yield. ^1H NMR (CD_3OD, 300 MHz) δ 8.35 (dd, *J* = 9.3, 2.4 Hz, 2H), 8.02 (dd, *J* = 9.3, 2.4 Hz, 2H), 5.06 (t, *J* = 7.2 Hz, 4H), 2.1 (m, 4H), 1.2 - 1.6 (m, 24H), 0.8 – 1.0 (m, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.7 (2 carbons), 136.0 (2 carbons), 135.9 (2 carbons), 132.8 (2 carbons), 127.9 (2 carbons), 54.4 (2 carbons), 31.9, 31.0, 29.5 (2 carbons), 29.4, 29.3 (2 carbons), 28.8, 28.7 (2 carbons), 26.0, 25.7, 22.5, 22.3, 13.2, 13.1; ESI/APCI Calcd for $C_{28}H_{42}N_3O_2^+$ ($[M]^+$) *m/z* 452.3273; measured *m/z* 452.3273.

1-Dodecyl-3-octyl-4,9-dioxo-4,9-dihydro-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (54e). Please refer to the general procedure for N-3 alkylation. Compound **54e** was obtained in 52% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.37 (dd, *J* = 9.3, 2.4 Hz, 2H), 8.05 (dd, *J* = 9.3, 2.4 Hz, 2H), 5.09 (t, *J* = 7.2 Hz, 4 H), 2.1 (m, 4 H), 1.2 - 1.5 (m, 28H), 0.9 (m, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.6 (2 carbons), 136.1 (2 carbons), 135.9 (2 carbons), 132.7 (2 carbons), 127.9 (2 carbons), 54.4 (2 carbons), 31.9, 31.7, 29.5 (2 carbons), 29.4, 29.3 (2 carbons), 29.0, 28.8 (4 carbons), 26.0 (2 carbons), 22.52, 22.48, 13.2 (2 carbons); ESI/APCI calcd for $C_{30}H_{46}N_3O_2^+$ ($[M]^+$) *m/z* 480.3585; measured *m/z* 480.3580.

3-Decyl-1-dodecyl-4,9-dioxo-4,9-dihydro 1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (54f). Please refer to the general procedure for N-3 alkylation. Compound **54f** was obtained in 99% yield. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.36 (dd, *J* = 8.9, 2.4 Hz, 2H), 8.03 (dd, *J* = 8.9, 2.4 Hz, 2H), 5.07 (t, *J* = 7.2 Hz, 4 H), 2.1 – 2.2 (m, 4 H), 1.2 - 1.5 (m, 32H), 0.88 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.7 (2 carbons), 136.0 (4 carbons), 132.8 (2 carbons), 127.9 (2 carbons), 54.4 (2 carbons), 31.9 (2 carbons), 29.4 (2 carbons), 29.3 (4 carbons), 28.8 (2 carbons), 28.7 (2 carbons), 26.0 (2 carbons), 22.5 (2 carbons), 13.2 (2 carbons); ESI/APCI calcd for $C_{32}H_{50}N_3O_2^+$ ($[M]^+$) *m/z* 508.3898; measured *m/z* 508.3896.

3-Methyl-1-hexyl-1*H*-naphtho[2,3-*d*][1,2,3]triazol-3-ium chloride (69). Compound **69** was synthesized according to the protocol described in reference 115. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.3 – 8.4 (m, 2H), 8.0 (m, 2H), 5.04 (t, *J* = 7.2 Hz, 2H), 4.68 (s, 3H), 2.1 (m, 2H), 1.3 - 1.6 (m, 6H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (CD_3OD, 100

MHz) δ 172.72, 172.65, 136.2, 136.0 (2 carbons), 135.6, 132.9, 132.7, 127.9, 127.8, 54.3, 39.8, 31.0, 28.8, 25.7, 22.2, 13.1; ESI/APCI calcd for $C_{17}H_{20}N_3O_2^+$ ($[M]^+$) *m/z* 298.1550; measured *m/z* 298.1560.

REFERENCES

1. Jones, K. E.; Patel, N. G.; Levy, M. A.; Storeygard, A.; Balk, D.; Gittleman, J. L.; Daszak, P. *Nature* **2008**, *451*, 990-993.
2. "Emergence of infectious diseases in the 21st century" http://www.gideononline.com/2008/03/05/emergence-of-infectious-diseases-in-the-21st-century/
3. WHO report on infectious diseases, 1999 http://www.who.int/infectious-disease-report/pages/textonly.html
4. Lefebvre, S.; Burglen, L.; Reboullet, S.; Clermont, O.; Burlet, P.; Viollet, L.; Benichou, B.; Cruaud, C.; Millasseau, P.; Zeviani, M.; Paslier, D. L.; Frezal, J.; Cohen, D.; Weissenbach, J.; Munnich, A.; Melki, J. *Cell* **1995**, *80*, 155-165.
5. Iannaconne, S. T.; Smith, S. A.; Simard, L. R. *Curr. Neurol. Neurosci. Rep.* **2004**, *4*, 74-80.
6. Roe, A. M.; Shur, N. *Am. J. Med. Genet. C Semin. Med. Genet*. **2007**, *145C*, 77-86.
7. Crawford, T. O.; Pardo, C. A. *Neurobiol. Dis*. **1996**, *3*, 97-110.
8. Zerres, K.; Rudnik-Schnebrn, S. *Arch. Neurol*. **1995**, *52*, 518-523.
9. (a) Pearn, J. *Lancet*. **1980**, *1*, 919-922. (b) Ogino, S.; Leonard, D. G.; Rennert, H.; Ewens, W. J.; Wilson, R. B. *Am. J. Med. Genet*. **2002**, *110*, 301-307. (c) Ogino, S.; Wilson, R. B. *Expert Rev. Mol. Diagn.* **2004**, *4*, 15-29. (d) Lunn, M. R.; Wang, C. H. *Lancet*. **2008**, *371*, 2120-2133.
10. Simic, G. *Acta Neuropathol*. **2008**, *116*, 223-234.

11. Newman, D. J.; Cragg, G. M. *J. Nat. Prod*. **2007**, *70*, 461-477.

12. Butler, M.S. *Nat. Prod. Rep*. **2008**, *25*, 475-516.

13. Zhu, F.; Qin, C.; Tao, L.; Liu, X.; Shi, Z.; Ma, X.; Jia, J.; Tan, Y.; Cui, C.; Lin, J.; Tan, C.; Jiang, Y.; Chen, Y. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 12943-12948.

14. Schatz, A.; Waksman, S. A. *Proc. Soc. Exp. Biol. Med*. **1944**, *55*, 244-248.

15. Busscher, G. F.; Rutjes, F. P. J. T.; van Delft, F. L. *Chem. Rev*. **2005**, *105*, 775-792.

16. Hermann, T. *Curr. Opin. Struct. Biol*. **2005**, *15*, 355-366.

17. Moazed, D.; Noller, H. F. *Nature* **1987**, *327*, 389-394.

18. Fourmy, D.; Recht, M. I.; Blanchard, S. C.; Puglisi, J. D. *Science* **1996**, *274*, 1367-1371.

19. Yoshizawa, S.; Fourmy, D.; Puglisi, J. D. *Science* **1999**, *285*, 1722-1725.

20. Ogle, J. M.; Ramakrishnan, V. *Annu. Rev. Biochem.* **2005**, *74*, 129-177.

21. Shandrick, S.; Zhao, Q.; Han, Q.; Ayida, B. K.; Takahashi, M.; Winters, G. C.; Simonsen, K. B.; Vourloumis, D.; Hermann, T. *Angew. Chem. Int. Ed. Engl.* **2004**, *43*, 3177-3182.

22. Ogle, J. M.; Brodersen, D. E.; Clemons, Jr., W. M.; Tarry, M. J.; Carter, A. P.; Ramakrishnan, V. *Science* **2001**, *292*, 897-902.

23. Kondo, S. *Jpn. J. Antibiot*. **1994**, *47*, 561-574.

24. Vakulenko, S. B.; Mobashery, S. *Clin. Microbiol. Rev*. **2003**, *16*, 430-450.

25. Kohanski, M. A.; Dwyer, D. J.; Collins, J. J. *Nat. Rev. Microbiol*. **2010**, *8*, 423-425.

26. Zembower, T. R.; Noskin, G. A.; Potstelnick, M. J.; Nguyen, C.; Peterson, L. R. *Int. J. Antimicrob. Agents* **1998**, *10*, 95-105.

27. Mingeot-Leclercq, M.-P.; Glupczynski, Y.; Tulkens, P. M. *Antimicrob. Agents Chemother*. **1997**, *43*, 727-737.

28. Kotra, L. P.; Haddad, J.; Mobashery, S. *Antimicrob. Agents Chemother*. **2000**, *44*, 3249-3256.

29. Wright, G. D. *Curr. Opin. Microbiol*. **1999**, *2*, 499-503.

30. Neonakis, I.; Gikas, A.; Scoulica, E.; Manios, A.; Georgiladakis, A.; Tselentis, Y. *Int. J. Antimicrob. Ag.* **2003**, *22*, 526-531.

31. Hermann, T.; Tor, T. *Expert Opin. Ther. Patents* **2005**, *15*, 49-62.

32. Hermann, T. *Cell. Mol. Life. Sci*. **2007**, *64*, 1841-1852.

33. Recht, M. I.; Douthwaite, S.; Puglisi, J. D. *EMBO J*. **1999**, *18*, 3133-3138.

34. Francois, B.; Russell, R. J.; Murray, J. B.; Aboul-ela, F.; Masquida, B.; Vicens, Q.; Westhof, E. *Nucleic Acids Res*. **2005**, *33*, 5677-5690.

35. Böttger, E. C.; Springer, B.; Prammananan, T.; Kidan, Y.; Sander, P. *EMBO Rep.* **2001**, *2*, 318-323.

36. Griffey, R. H.; Hofstadler, S. A.; Sannes-Lowery, K. A.; Ecker, D. J.; Crooke, S. T. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 10129-10133.

37. Pokrovskaya, V.; Nudelman, I.; Kandasamy, J.; Baasov, T. *Methods Enzymol*. **2010**, *478*, 437-462.

38. Kellermayer, R. *Eur. J. Med. Genet*. **2006**, *49*, 445-450.

39. Zingman, L. V.; Park, S.; Olson, T. M.; Alekseev, A. E.; Terzic, A. *Clin. Pharmacol. Ther.* **2007**, *81*, 99-103.

40. Burke, J. K.; Mogg, A. E. *Nucleic Acids Res.* **1985**, *13*, 6265-6272.

41. Malik, V.; Rodino-Kaplac, L.R.; Viollet, L.; Mendell, J. R. *Ther. Adv. Neurol. Disord*. **2010**, *3*, 379-389.

42. Knight, S. C.; Anthony, V. M.; Brady, A. M.; Greenland, A. J.; Heaney, S. P.; Murray, D. C.; Powell, K. A.; Schulz, M. A.; Spinks, C. A.; Worthington, P. A.; Youle, D. *Ann. Rev. Phytopathol*. **1997**, *35*, 349-372.

43. Gianessi, L. P.; Reigner, N. *The value of fungicides in U.S. crop production*; Technical Report for CropLife Foundation - Crop Protection Research Institute: Washington, DC, 2005.

44. Lee, H. B.; Kim, Y.; Kim, J. C.; Choi, G. J.; park, S.-H.; Kim, C.-J.; Jung, H. S. *J. Appl. Microbiol*. **2005**, *99*, 836-843.

45. Allen, H. K.; Donato, J.; Wang, H. H.; Cloud-Hansen, K. A.; Davies, J.; Handelsman, J. *Nat. Rev. Microbiol.* **2010**, *8*, 251-259.

46. McManus, P. S.; Stockwell, V. O.; Sundin, G. W.; Jones, A. L. *Ann. Rev. Phytopathol.* **2003**, *40*, 443-465.

47. Pinto, A. V.; de Castro, S. L. *Molecules* **2009**, *14*, 4570-4590.

48. Abdelmohsen, K.; Patak, P.; von Montfort, C.; Melchheier, I., Sies, H.; Klotz, L. O. *Methods Enzymol*. **2004**, *378*, 258-272.

49. Shearer, M. J.; Newman P. *Throm. Haemost*. **2008**, *100*, 530-547.

50. Michaelakis, A.; Strongilos, A. T.; Bouzas, E. A.; Koliopoulos, G.; Couladouros, E. A. *Parasitol. Res.* **2009**, *104*, 657-662.

51. Riffel, A.; Medina, L. F.; Stefani, V.; Santos, R. C. *Braz. J. Med. Biol. Res*. **2002**, *35*, 811-818.

52. Verma, R. P. *Anticancer Agents Med. Chem*. **2006**, *6*, 489-499 and references herein.

53. Cunha, A. S.; Lima, E. L. S.; Pinto, A. C.; Esteves-Souza, A.; Echevarria, A.; Camara, C. A.; Vargas, M. D.; Torres, J. C. *J. Braz. Chem. Soc*. **2006**, *17*, 439-442.

54. Krishnan, P.; Bastow, K. F. *Cancer Chemother. Pharmacol*. **2001**, *47*, 187-198.

55. Fournet, A.; Angelo, A.; Muñoz, V.; Roblot, F.; Hocquemiller, R.; Cavé, A. *J. Ethnopharmacol*. **1992**, *37*, 159-162.

56. Esteves-Souza, A.; Figueiredo, D. V.; Esteves, A.; Câmara, C. A.; Vargas, M. D.; Pinto, A. C.; Echevarria, A. *Braz. J. Med. Biol. Res.* **2007**, *40*, 1399-1402.

57. Dhaon, M. K.; Lehrman, S. R.; Rich, D. H.; Engelke, J. A.; Suttie, J. W. *J. Med. Chem*. **1984**, *27*, 1196-1201.

58. Brauers, G.; Edrada, R. A.; Ebel, R.; Proksch, P.; Wray, V.; Berg, A.; Gräfe, U.; Schächtele, C.; Totzke, F.; Finkenzeller, G.; Marme, D.; Kraus, J.; Münchbach, M.; Michel, M.; Bringmann, G.; Schaumann, K. *J. Nat. Prod*. **2000**, *63*, 739-745.

59. Porter, T. H.; Skelton, F. S.; Bowman, C. M.; Folkers, K. *J. Med. Chem*. **1972**, *15*, 504-506.

60. Yamazaki, S.; Iwasa, K.; Kano, K.; Ikeda, T.; Taketomo, N.; Kaneko, T. *J. Agric. Food Chem*. **2000**, *48*, 5643-5648.

61. O'Brien, P. J. *Chem. Biol. Interact*. **1991**, *80*, 1-41.

62. Kumagai, Y.; Shinkai, Y.; Miura, T.; Cho, A. K. *Ann. Rev. Pharmacol. Toxicol*. **2012**, *52*, 221-247.

63. Medentsev, A. G.; Akimenko, V. K. *Phytochem.* **1998**, *47*, 935-959.

64. Silvermann, R. B. *The organic chemistry of drug design and drug action*; Academic Press: New York, 1992.

65. Tewey, K. M.; Chen, G. L.; Nelson, E. M.; Liu, L. F.; *J. Biol. Chem.* **1984**, *259*, 9182-9187.

66. Lown, J. W.; Sim, S.-K.; Majumdar, K. C.; Chang, R.-Y. *Biochem. Biophys. Res. Commun*. **1977**, *76*, 705-710.

67. Cowan, M. M. *Clin. Microbiol. Rev.* 1**999**, *2*, 564-582.

68. Didry, N.; Pinkas, M.; Dubreil, L. *Ann. Pharma. Fr*. **1986**, *44*, 73-78.

69. Papageorgiou, V. P.; Assimopoulou, A. N.; Couladouros, E. A.; Hepworth, D.; Nicolaou, K. C. *Angew. Chem. Int. Ed.* **1999**, *38*, 270-300.

70. Zhang, C.; Ondeyka, J. G.; Zink, D. L.; Basilio, A.; Vicente, F.; Collado, J.; Platas, G.; Huber, J.; Dorso, K.; Motyl, M.; Byrne, K.; Singh, S. B. *Bioorg. Med. Chem.* **2009**, *17*, 2162-2166.

71. Holmes, H. L.; Currie, D. J.; Maltman, J. R.; Silver, R. F.; Lough, C. E. *Biochem. Biophys. Res. Commun.* **1997**, *239*, 186-190.

72. Brzustowicz, L. M.; Lehner, T.; Castilla, L.H.; Penchaszaden, G. K.; Wilhelmsen, K. C.; Daniels, R.; Davies, K. E.; Leppert, M.; Ziter, F.; Wood, D.; Dubowitz, V.; Zerres, K.; Hausmanowa-Petrusewicz, I.; Ott, J.; Munsat, T. L.; Gilliam, T. C. *Nature* **1990**, *344*, 540-541.

73. Monani, U. R.; Lorson, C. L.; Parsons, D. W.; Prior, T. W.; Androphy, E. J.; Burghes, A. H. M.; McPherson, J. D. *Hum. Mol. Genet*. **1999**, *8*, 1177-1183.

74. Lorson, C. L.; Hahnen, E.; Androphy, E. J.; Wirth, B. *Proc. Natl. Acad. Sci. USA* **1999**, *96*, 6307-6311.

75. Cartegni, L.; Krainer, A. R. *Nat. Genet.* **2002**, *30*, 377-384.

76. Novelli, G.; Calza, L.; Amicucci, P.; Giardino, L.; Pozza, M.; Silani, V.; Pizzuti, A.; Gennarelli, M.; Piombo, G.; Capon, F.; Dallapiccola, B. *Biochem. Mol. Med.* **1997**, *61*, 102-106.

77. Wolstencroft, E. C.; Mattis, V.; Bajer, A. A.; Young, P. J.; Lorson, C. L. *Hum. Mol. Genet*. **2005**, *14*, 1199-1210.

78. Mattis, V. B.; Rai, R.; Wang, J.; Chang, C.-W. T.; Coady, T.; Lorson, C. L. *Hum. Genet.* **2006**, *120*, 589-601.

79. Rai, R. *Design and Synthesis of Novel Aminoglycosides with Activity against Modifying Bacteria.* Ph.D. Thesis, Utah State University, 2006.

80. (a) Cohen, M. L. *Science* **1992**, 257, 1050-1055; (b) Neu, H. C. *Science* **1992**, 257, 1064-1072.

81. Hooper, I. R. *Aminoglycoside Antibiotics*; Springer-Verlag: New York, 1982.

82. Greenberg, W. A.; Priestley, E. S.; Sears, P. S.; Alper, P. B.; Rosenbohm, C.; Hendrix, M.; Hung, S.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 6527-6541.

83. Christensen, S. M.; Hansen, H. F.; Koch, T. *Org. Process Res. Dev*. **2004**, *8*, 777-780.

84. Knapp, S.; Gore, V. K. *Org. Lett*. **2000**, *2*, 1391-1393.

85. Suhara, Y.; Yamaguchi, Y.; Collins, B.; Schnaar, R. L.; Yanagishita, M.; Hildreth, J. E. K.; Shimida, I.; Ichikawa, Y. *Bioorg. Med. Chem*. **2002**, *10*, 1999-2013.

86. Danac, R.; Ball, L.; Gurr, S. J.; Fairbanks, A. J. *Carbohydr. Res*. **2008**, *343*, 1012-1022.

87. Chang, C.-W. T.; Hui, Y.; Elchert, B.; Wang, J.; Li, J.; Rai, R. *Org. Lett*. **2002**, *4*, 4603-4606.

88. Liu, Q.; Dreyfuss, G. *EMBO J*. **1996**, *15*, 3555-3565.

89. Andreassi, C.; Jarecki, J.; Zhou, J.; Coovert, D. D.; Monanai, U. R.; Chen, X.; Whutney, M.; Pollok, B.; Zhang, M.; Androphy, E.; Burghes, A. H. *Hum. Mol. Genet*. **2001**, *10*, 2841-2849.

90. Andreassi, C.; Angelozzi, C.; Tiziano, F. D.; Vitali, T.; De Vincenzi, E.; Boninsegna, A.; Villanova, M.; Bertini, E.; Pini, A.; Neri, G.; Brahe, C. *Eur. J. Hum. Genet*. **2004**, *12*, 59-65.

91. Jarecki, J.; Chen, X.; Bernardino, A.; Coovert, D. D.; Whitney, M.; Burghes, A.; Stack, J.; Pollok, B. A. *Hum. Mol. Genet*. **2005**, *14*, 2003-2018.

92. Lunn, M. R.; Root, D. E.; Martino, A.M.; Flaherty, S. P.; Kelley, B. P.; Coovert, D. D.; Burghes, A. H.; Man, N. T.; Morris, G. E.; Zhou, J.; Androphy, E. J.; Sumner, C. J.; Stockwell, B. R. *Chem. Biol*. **2004**, *11*, 1489-1893.

93. Sumner, C. J.; Huynh, T. N.; Markowitz, J. A.; Perhac, J. S.; Hill, B.; Coovert, D. D.; Schussler, K.; Chen, X.; Jarecki, J.; Burghes, A. H.; Taylor, J. P.; Fischbeck, K. H. *Ann. Neurol.* **2003**, *54*, 647-654.

94. Mattis, V. B.; Ebert, A. D.; Fosso, M. Y.; Chang, C.-W.; Lorson, C. L. *Hum. Mol. Genet.* **2009**, *18*, 3906-3913.

95. Mattis, V. B.; Fosso, M. Y.; Chang, C.-W.; Lorson, C. L. *BMC Neurosc.* **2009**, *10*:142.

96. (a) Ferber, D. *Science* **2000**, *288*, 792-794. (b) Article from Animal and Plant Health Inspection Service (APHIS), http://www.aphis.usda.gov:80/vs/ceah/cei/antiresist.intrbkgd.pdf. (c) "Prevalence of Salmonella spp. And Escherichia coli on U.S. Livestock Operations" http://www.aphis.usda.gov:80/vs/ceah/cei/antiresist.epdemiol.pdf. (d) "Epidemiology of antimicrobial drug resistance in Salmonella spp., Escherichia coli and other selected pathogens of livestock" http://www.aphis.usda.gov:80/vs/ceah/cei/antiresist/epdemiol.pdf

97. Li, J.; Wang, J.; Czyryca, P. G.; Chang, H.; Orsak, T. W.; Evanson, R.; Chang, C.-W. T. *Org. Lett.* **2004**, *6*, 1381-1384.

98. Li, J.; Chen, H.-N.; Chang, H.; Wang, J.; Chang, C.-W. T. *Org. Lett.* **2005**, *7*, 3061-3064.

99. Wang, J.; Li, J.; Chen, H.-N.; Chang, H.; Tanifum, C. T.; Liu, H.-H.; Czyryca, P. G.; Chang, C.-W. T. *J. Med. Chem.* **2005**, *48*, 6271-6285.

100. Leach, B. E.; Teeters, C. M. *J. Am. Chem. Soc*. **1951**, *73*, 2794-2797.

101. Chou, C.-H.; Wu, C.-S.; Chen, C.-H.; Lu, L.-D.; Kulkarni, S. S.; Wong, C.-H.; Hung, S.-C. *Org. Lett*. **2004**, *6*, 585-588.

102. Blom, P.; Ruttens, B.; van Hoof, S.; Hubrecht, I.; van der Eycken, J. *J. Org. Chem.* **2005**, *70*, 10109-10112.

103. Wang, J. Design, Synthesis, and Structure Activity Relationship Study of Novel Pyranmycins, Kanamycin Analogs and Trehalose Derivatives. Ph.D. Thesis, Utah State University, 2006.

104. Chang, C.-W. T.; Fosso, M.; Kawasaki, Y.; Shrestha, S.; Bensaci, M. F.; Wang, J.; Evans, C. K.; Takemoto, J. Y. *J. Antibiot.* **2010**, *63*, 667-672.

105. Zhang, J.; Chiang, F.-I.; Wu. L.; Czyryca, P. G.; Li, D.; Chang, C.-W. T. *J. Med. Chem.* **2008**, *51*, 7563-7573.

106. Windels, C. E. *Phytopathol*. **2000**, *90*, 17-21.

107. Nicolaou, K. C.; Randall, J. L.; Furst, G. T. *J. Am. Chem. Soc.* **1985**, *107*, 5556-5558.

108. He, X.; Chan, T. H. *Synthesis* **2006**, *10*, 1645-1651.

109. Huestis, M. P.; Aish, G. A.; Hui, J. P. M. Soo, E. C.; Jakeman, D. L. *Org. Biomol. Chem*. **2008**, *6*, 477-484.

110. Franais, A.; Urban, D.; Beau, J.-M. *Angew. Chem. Int. Ed.* **2007**, *46*, 8662-8665.

111. Dinkelar, J.; de Jong, A. R.; van Meer, R.; Somers, M.; Lodder, G.; Overkleeft, H. S.; Codee, J. D. C.; van der Marcl, G. A. *J. Org. Chem*. **2009**, *74*, 4982-4991.

112. Greenberg, W. A.; Priestley, E.s.; Sears, P. S.; Alper, P. B.; Rosenbohm, Hendrix, M.; Hung, S.-C.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 6527-6541.

113. Zhang, J.; Chang, C.-W. T. *J. Org. Chem*. **2009**, 7*4*, 685-695.

114. Zhang, J.; Chang, C.-W. T. *J. Org. Chem*. **2009**, *74*, 4414-4417.

115. Zhang, J.; Redman, N.; Litke, A. P.; Zeng, J.; Zhan, J., Chan, K. Y.; Chang, C.-W. T. *Bioorg. Med. Chem*. **2011**, *19*, 498-503.

116. Schultz, A. G.; McMahon, W. G. *J. Org. Chem.* **1984**, *49*, 1676-1678.

117. Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 71-77.

118. Couladouros, E. A.; Plyta, Z. F.; Haroutounian, S. A. *J. Org. Chem.* **1997**, *62*, 6-10.

119. a) del Corral, J. M. M.; Castro, M. A.; Gordaliza, M.; Martin, M. L.; Gualberto, S. A.; Gamito, A. M.; Cuevasc, C.; Feliciano, A. S. *Bioorg. Med. Chem*. **2005**, *13*, 631-644. c) Parker, K. A.; Sworin, M. E. *J. Org. Chem.* **1981**, *46*, 3218-3223.

120. Mital, A.; Sonawane, M.; Bindal, S.; Mahlavat, S.; Negi, V. *Der Pharma Chemica* **2010**, *2*, 63-73.

121. For examples: (a) Thorsteinsson, T.; Másson, M.; Kristinsson, K. G.; Hjálmarsdottir, M. A.; Hilmarsson, H.; Loftsson, T. *J. Med. Chem*. **2003**, *46*, 4173-4181. (b) Maeda, S.; Kita, T.; Meguro, K. *J. Med. Chem*. **2009**, *52*, 597-600.

(c) Kanazawa, A.; Ikeda, T.; Endo, T. *Antimicrob. Agents Chemother*. **1994**, *38*, 945-952.

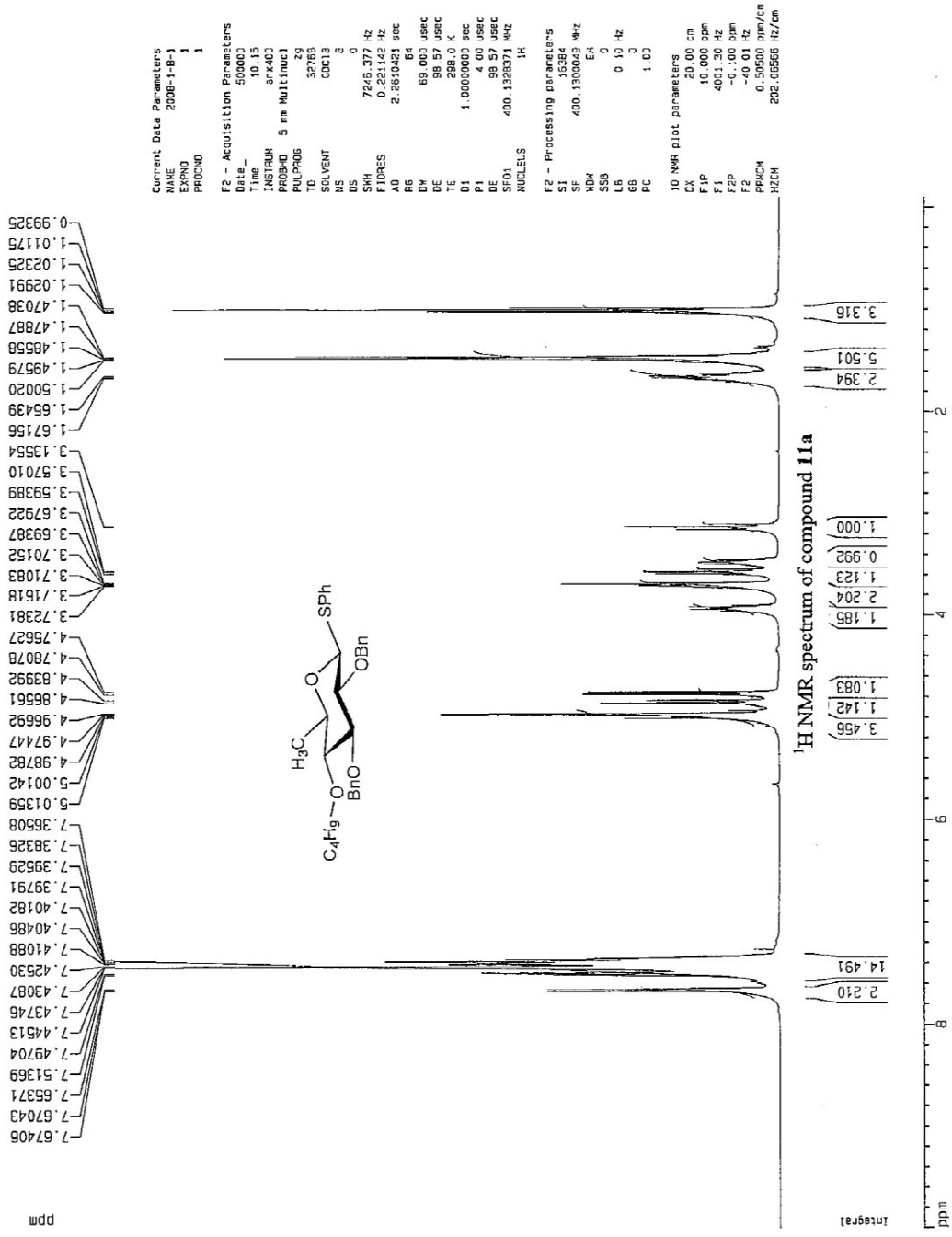
122. Ioannou, C. J.; Hanlon, G. W.; Denyer, S. P. *Antimicrob. Agents Chemother*. **2007**, *51*, 296-306.

123. Alvarez, S. G.; Alvarez, M. T. *Synthesis* **1997**, *1997*, 413-414.

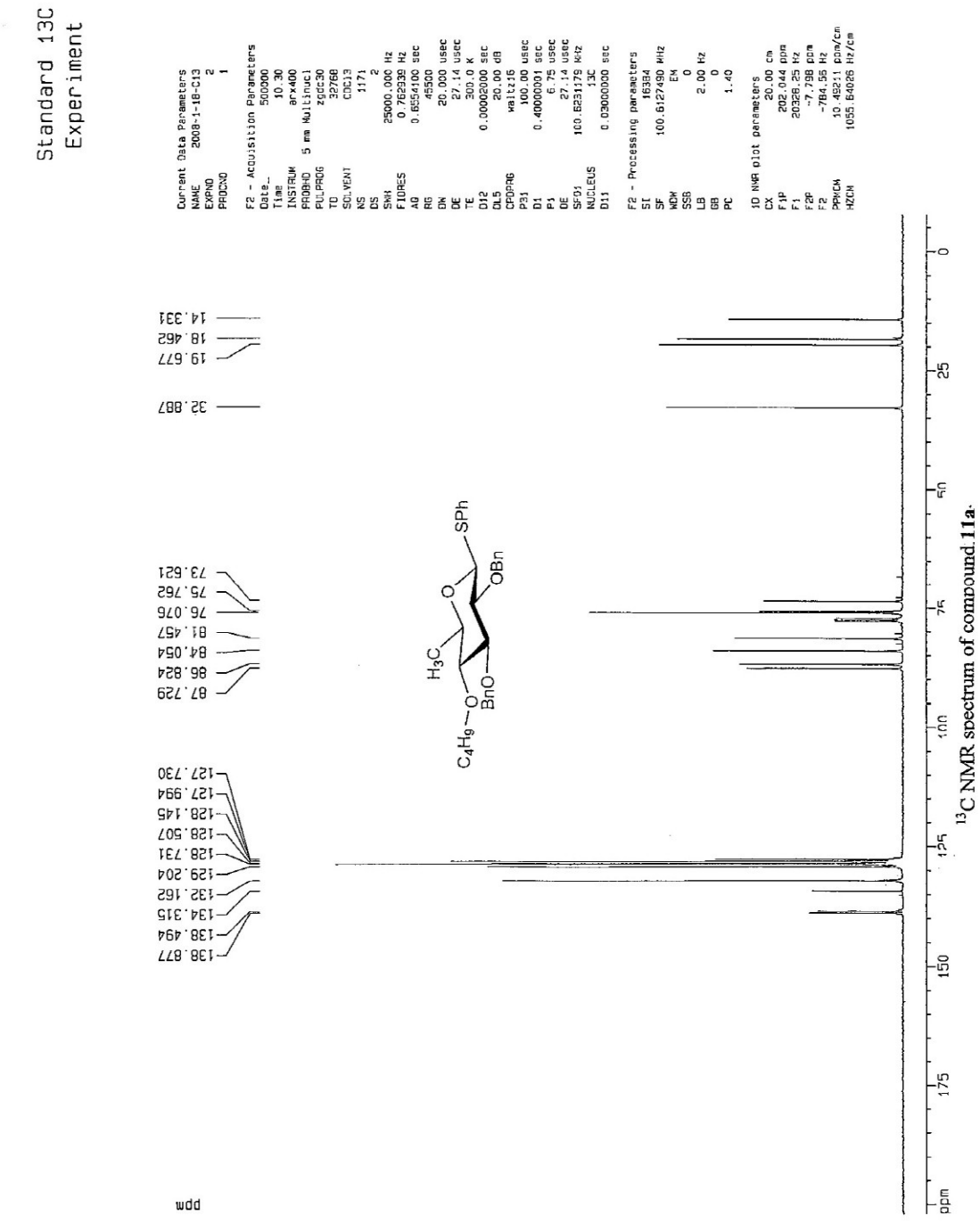
124. Chan, K. Y.; Zhang, J.; Chang, C.-W. T. *Bioorg. Med. Chem. Lett*. **2011**, *21*, 6353-6356.

APPENDICES

Appendix A. ^{1}H NMR and ^{13}C NMR Spectra for Selected Compounds



^{1}H NMR spectrum of compound **11a**



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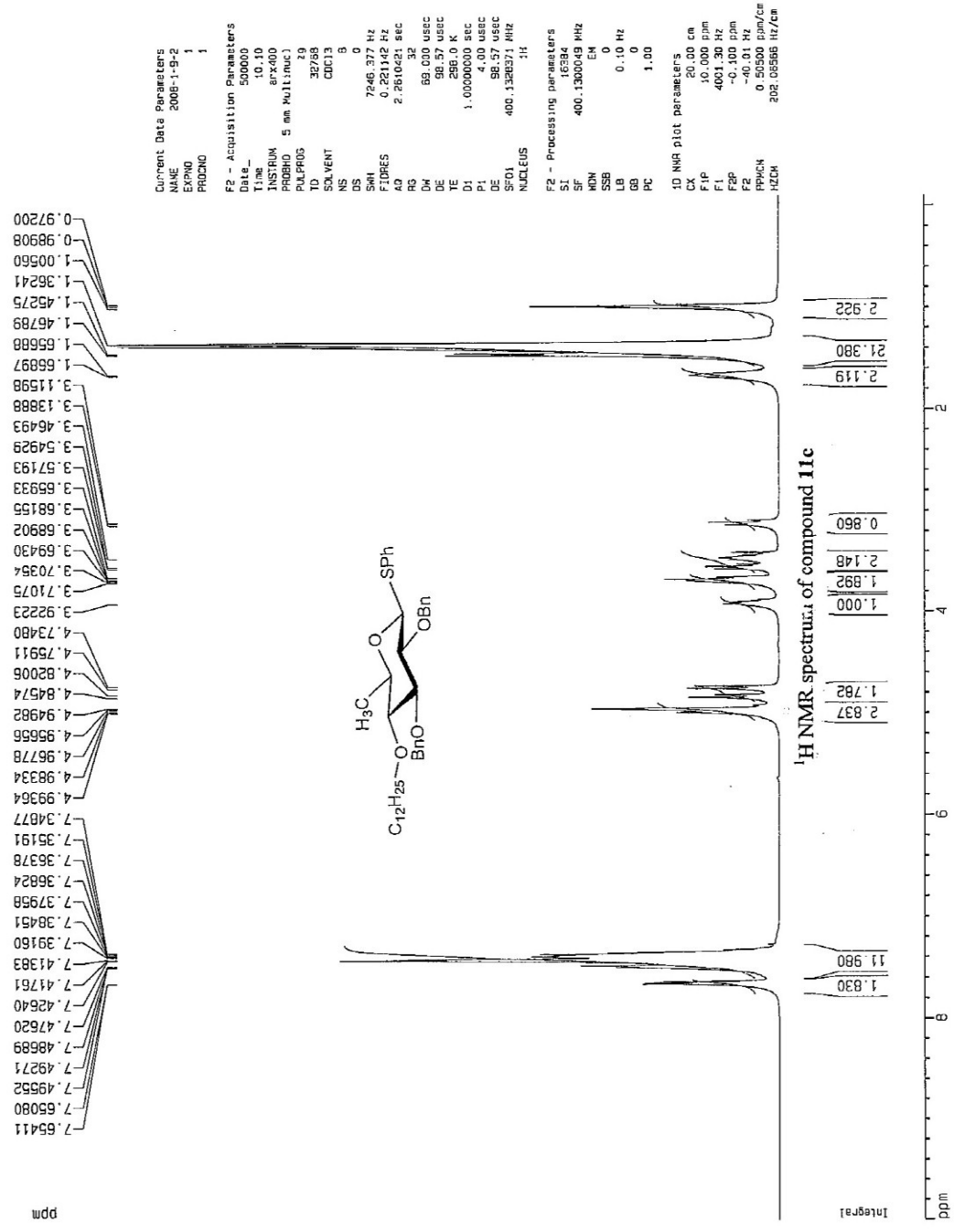
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PROCNO 1
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PULPROG zg
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SWH 7246.377 Hz
FIDRES 0.221142 Hz
AQ 2.2610421 sec
RG 32
DW 69.000 usec
DE 98.57 usec
TE 298.0 K
D1 1.00000000 sec
P1 4.00 usec
DE 98.57 usec
SFO1 400.1320371 MHz
NUCLEUS 1H
F2 - Processing parameters
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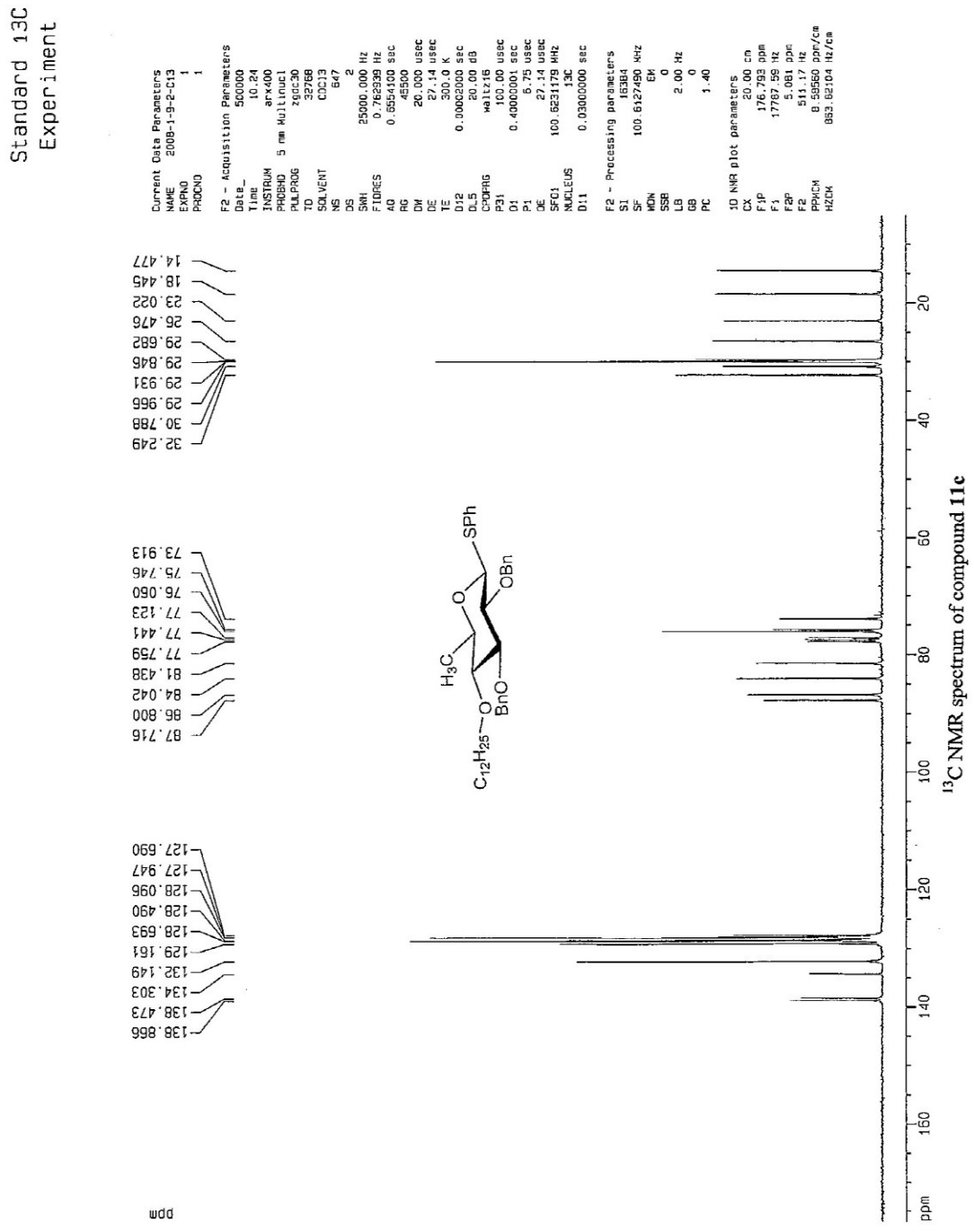
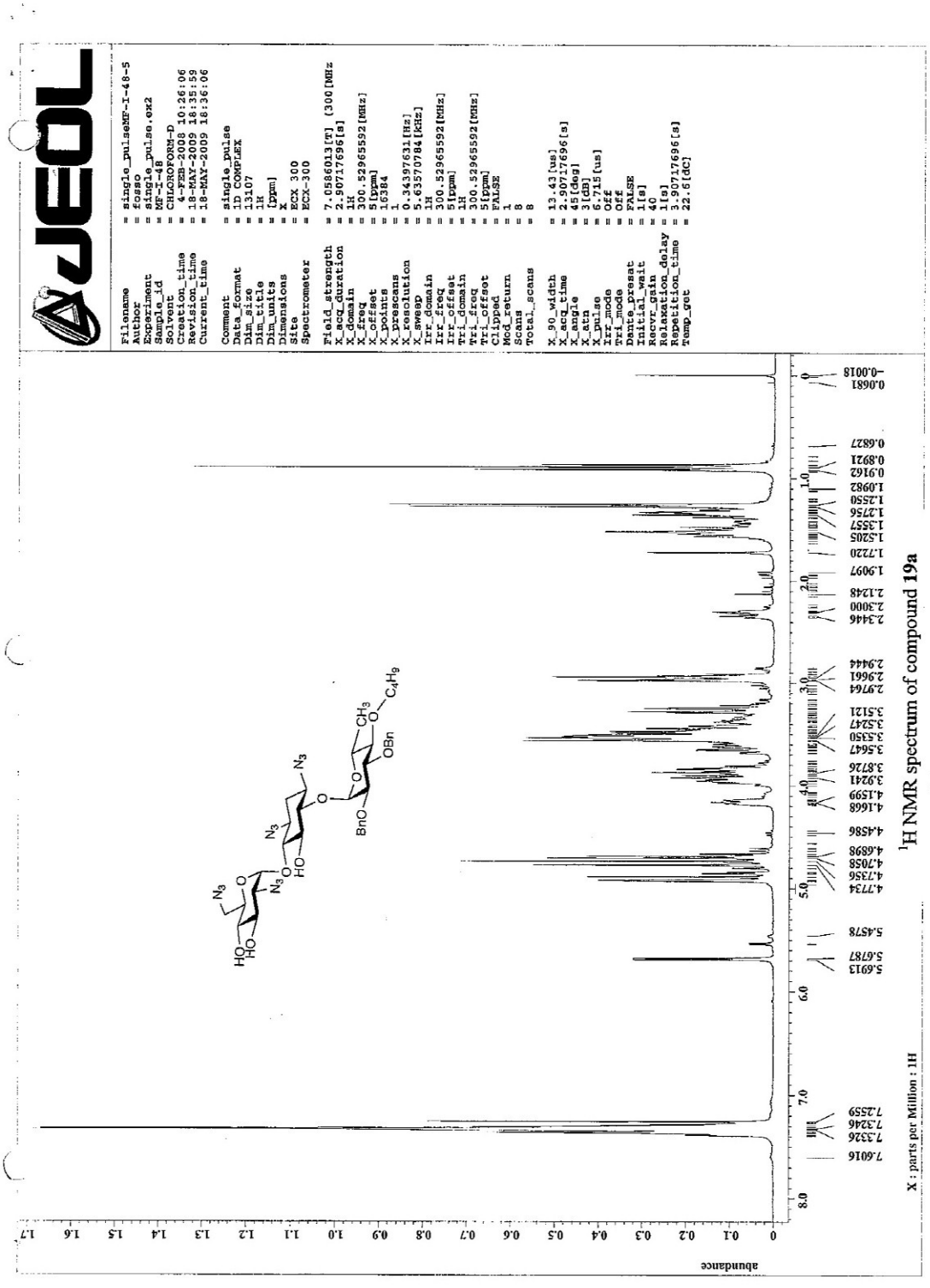
SF 400.1300049 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
CY 10.000 ppm
F1 4001.30 Hz
F1P -0.100 ppm
F2P -40.01 Hz
F2 0.50500 ppm/cm
PPMCM 202.08566 Hz/cm
SPh
OBn
O
H3C
O
BnO
C12H25
ppm
Integral
1H NMR spectrum of compound 11c



^{13}C NMR spectrum of compound **11e**



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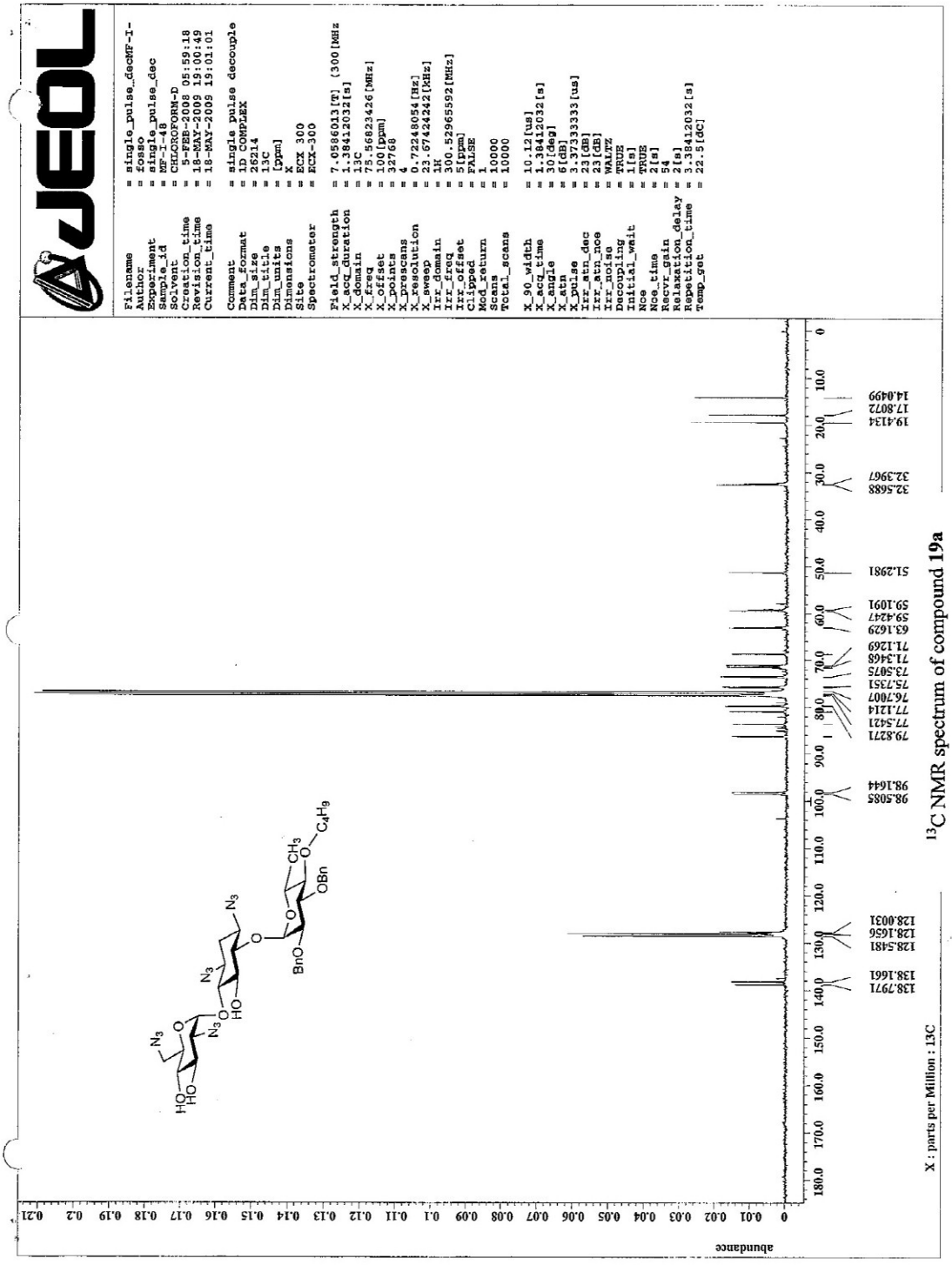

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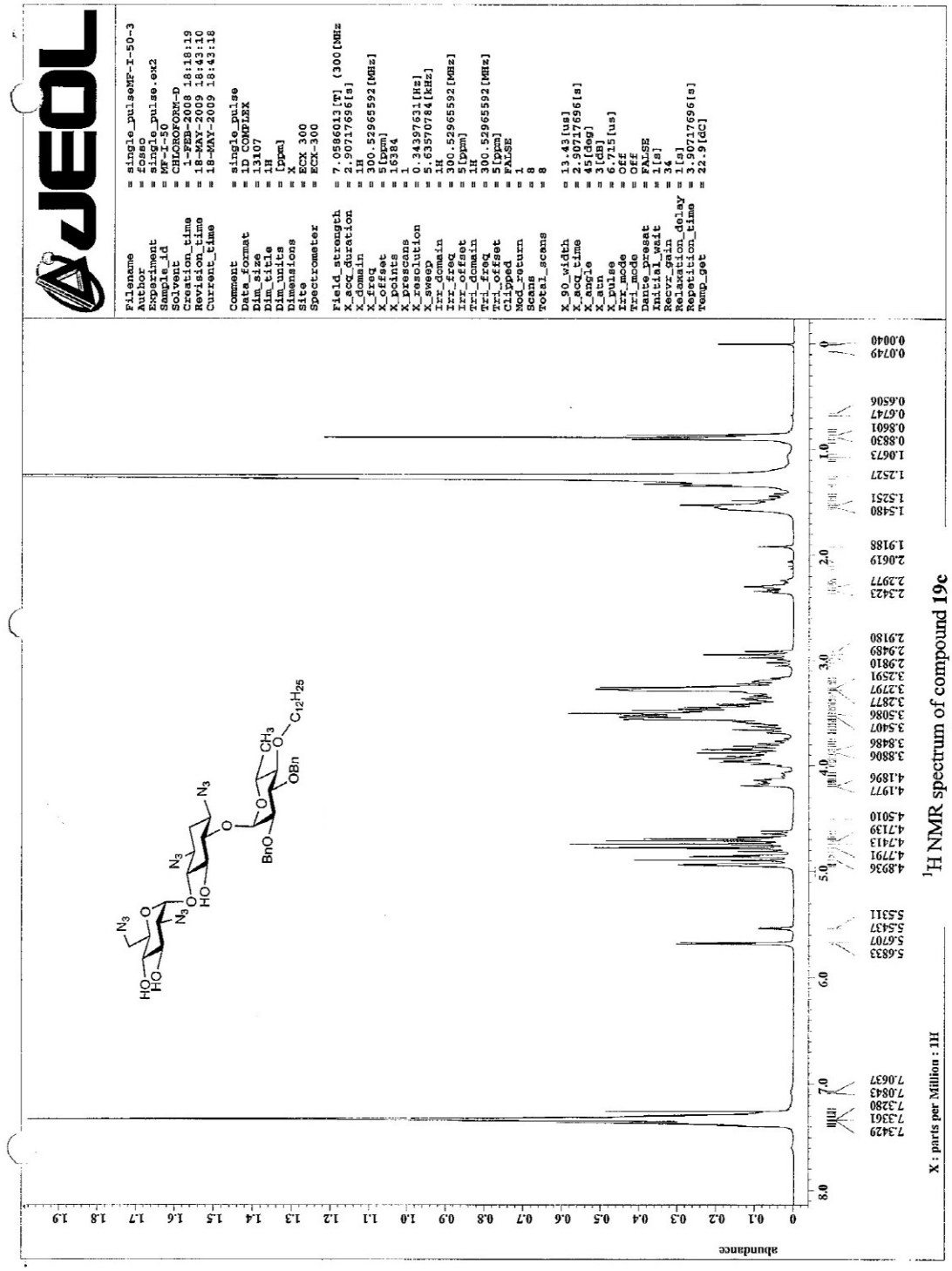

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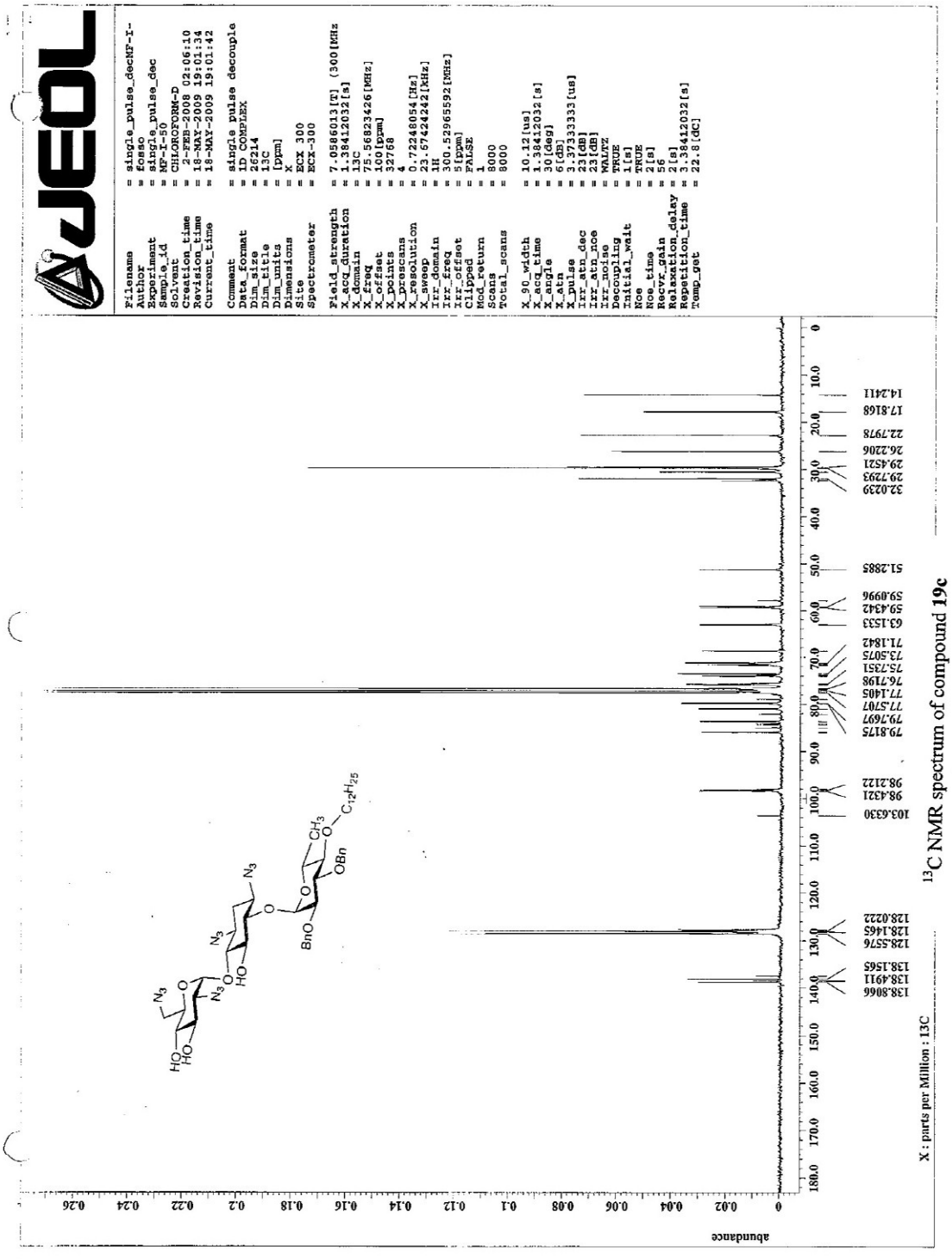

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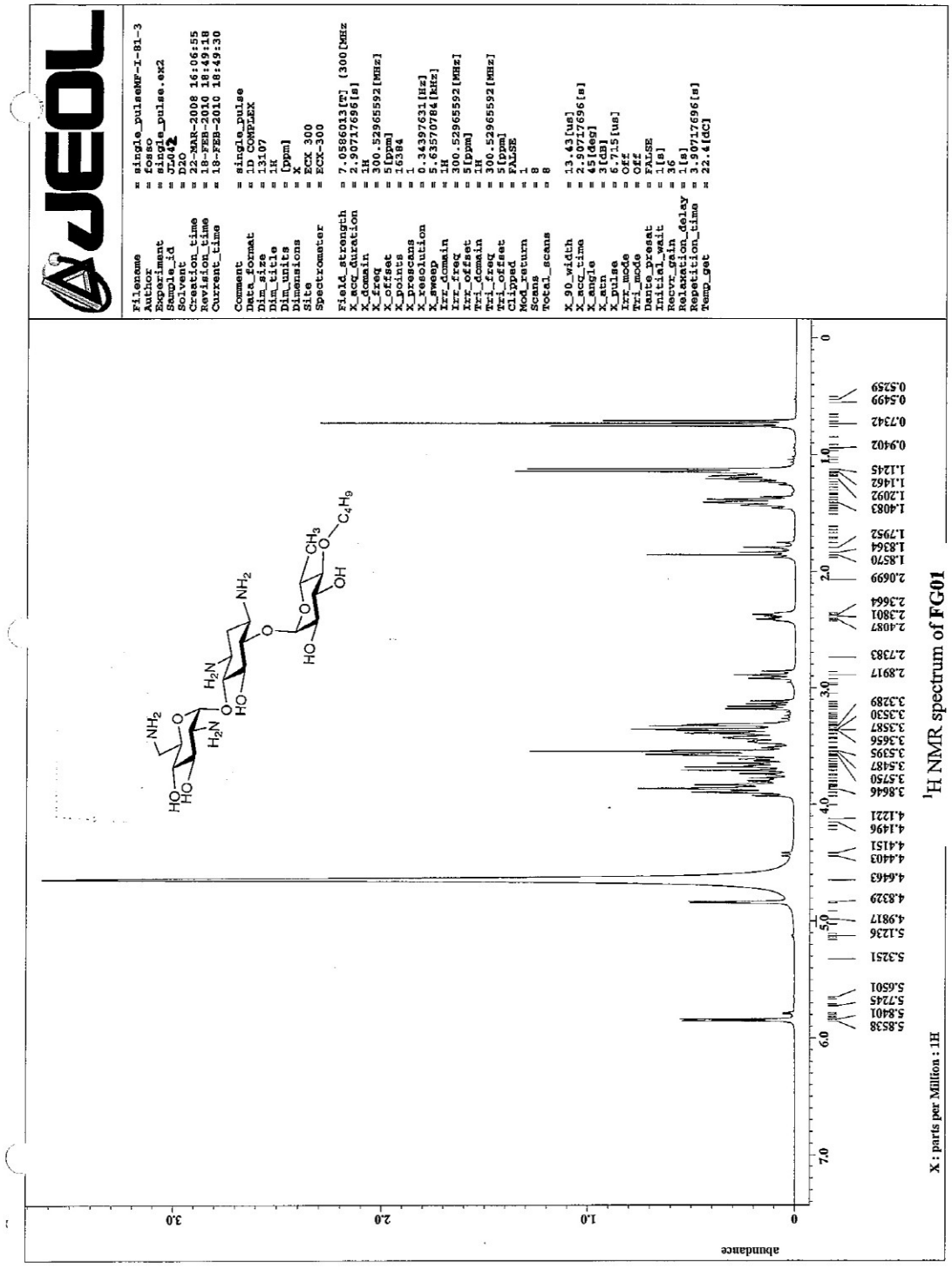
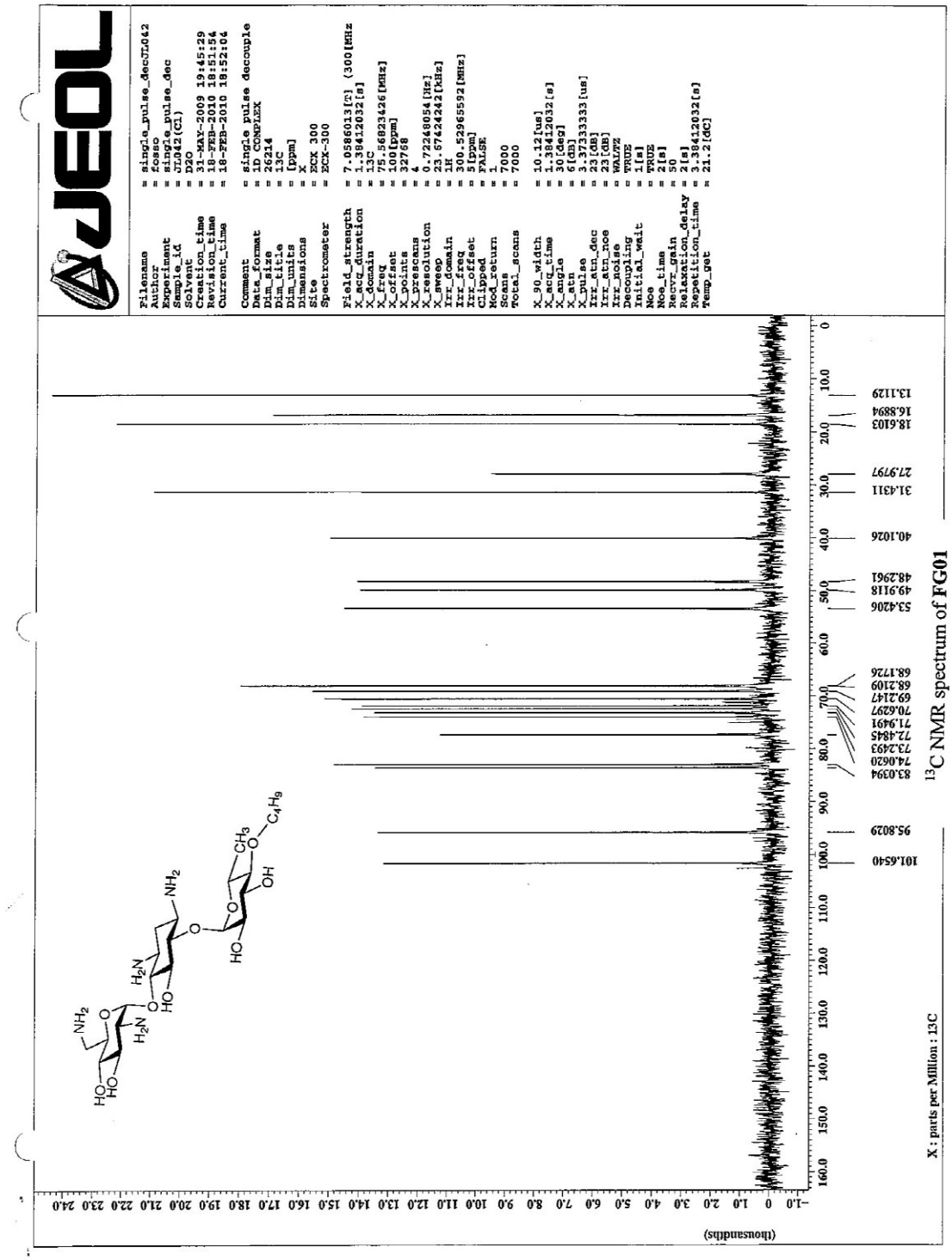


^{1}H NMR spectrum of **FG01**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83.0394
74.0620
73.2493
72.4845
71.9491
70.6297
69.2147
68.2109
68.1726
53.4206
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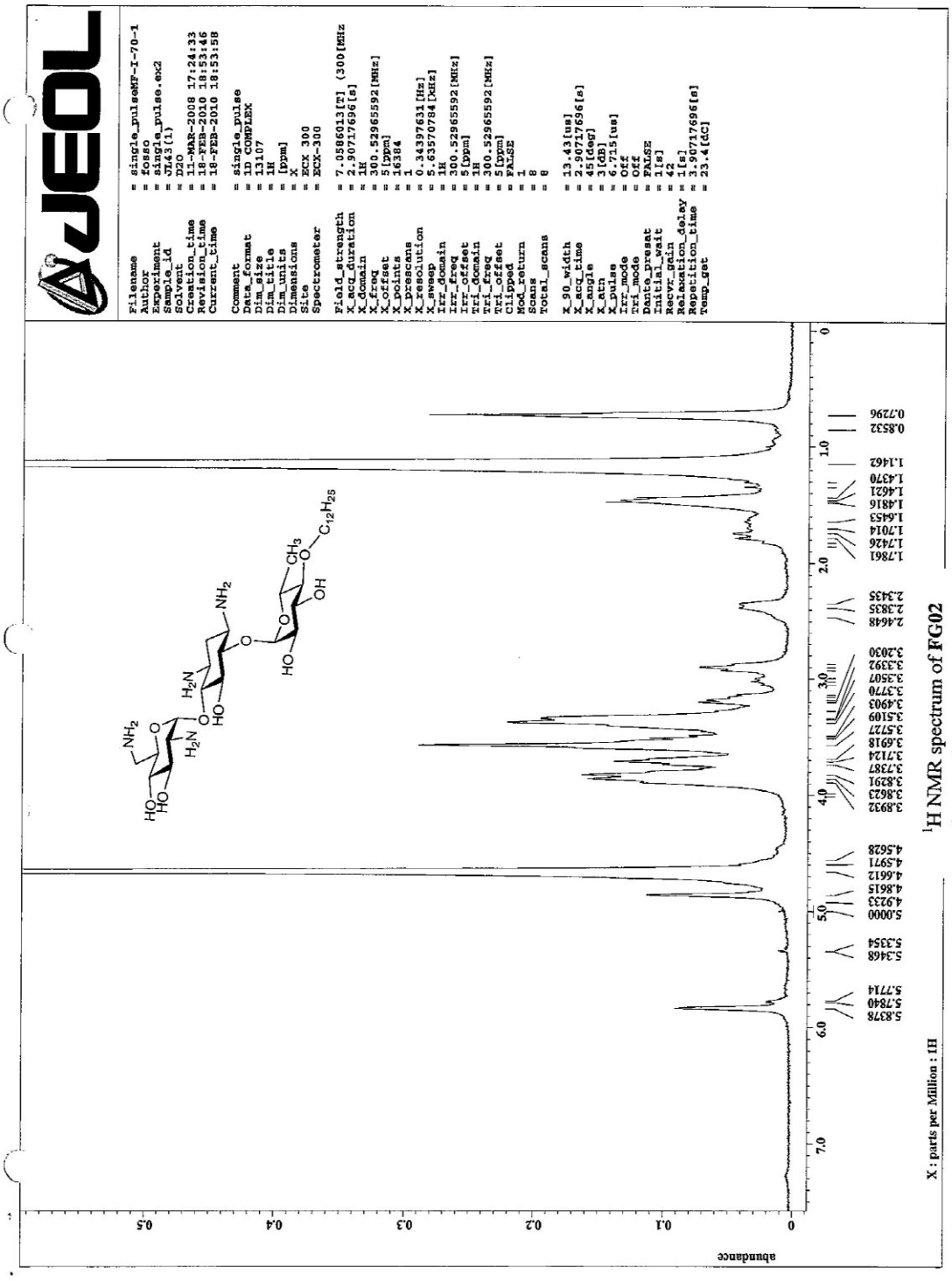
^{13}C NMR spectrum of FG01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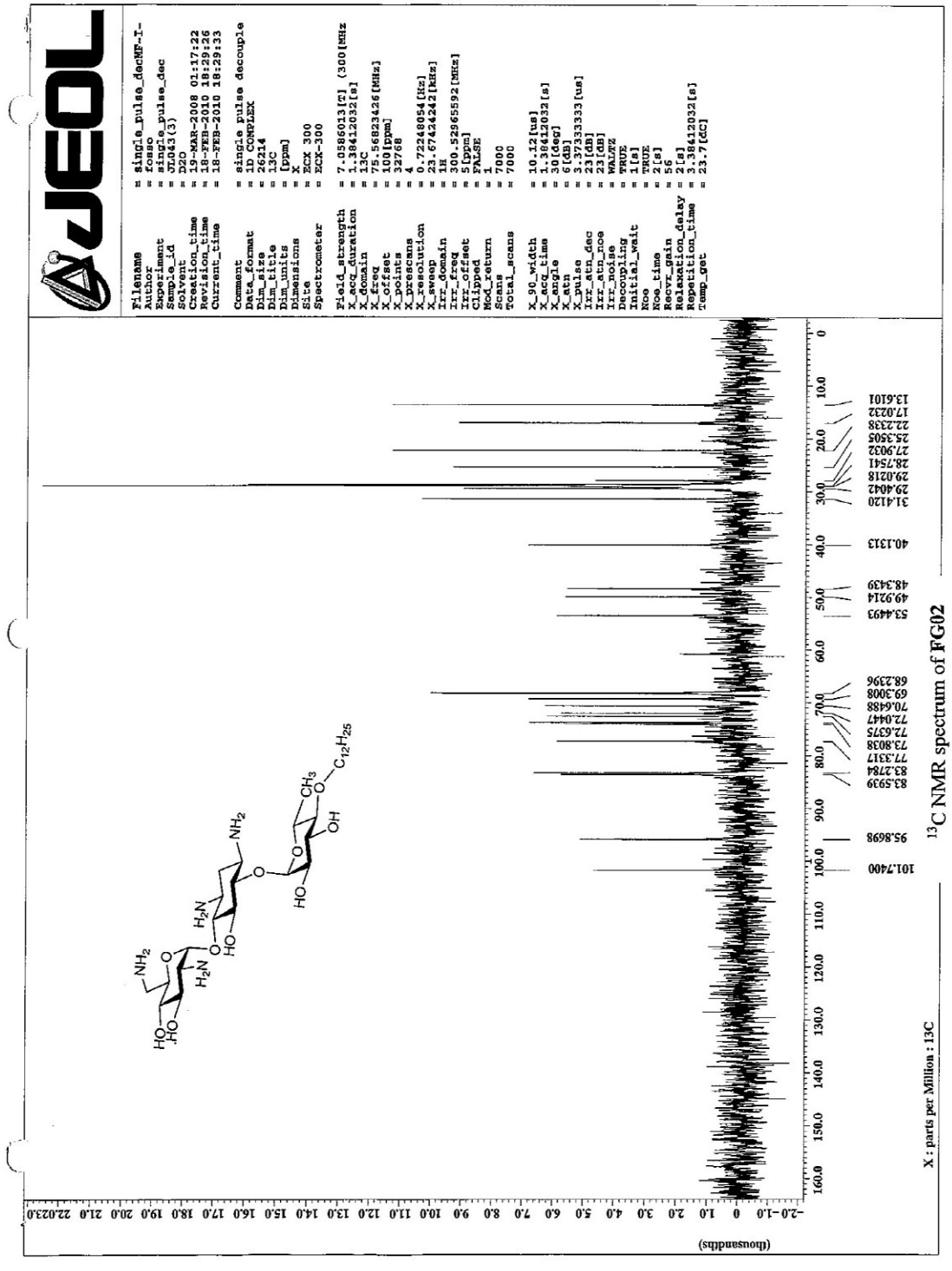

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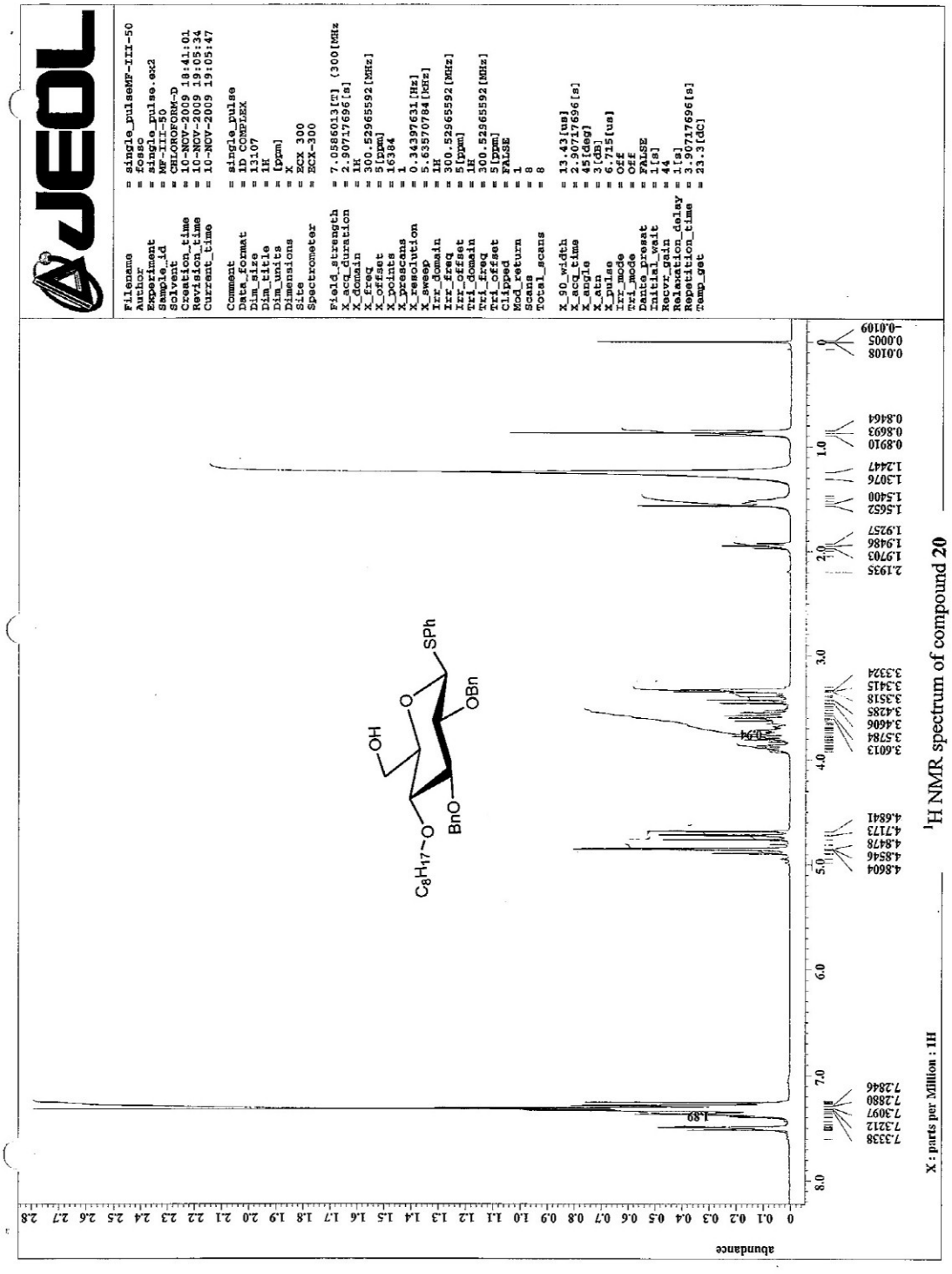

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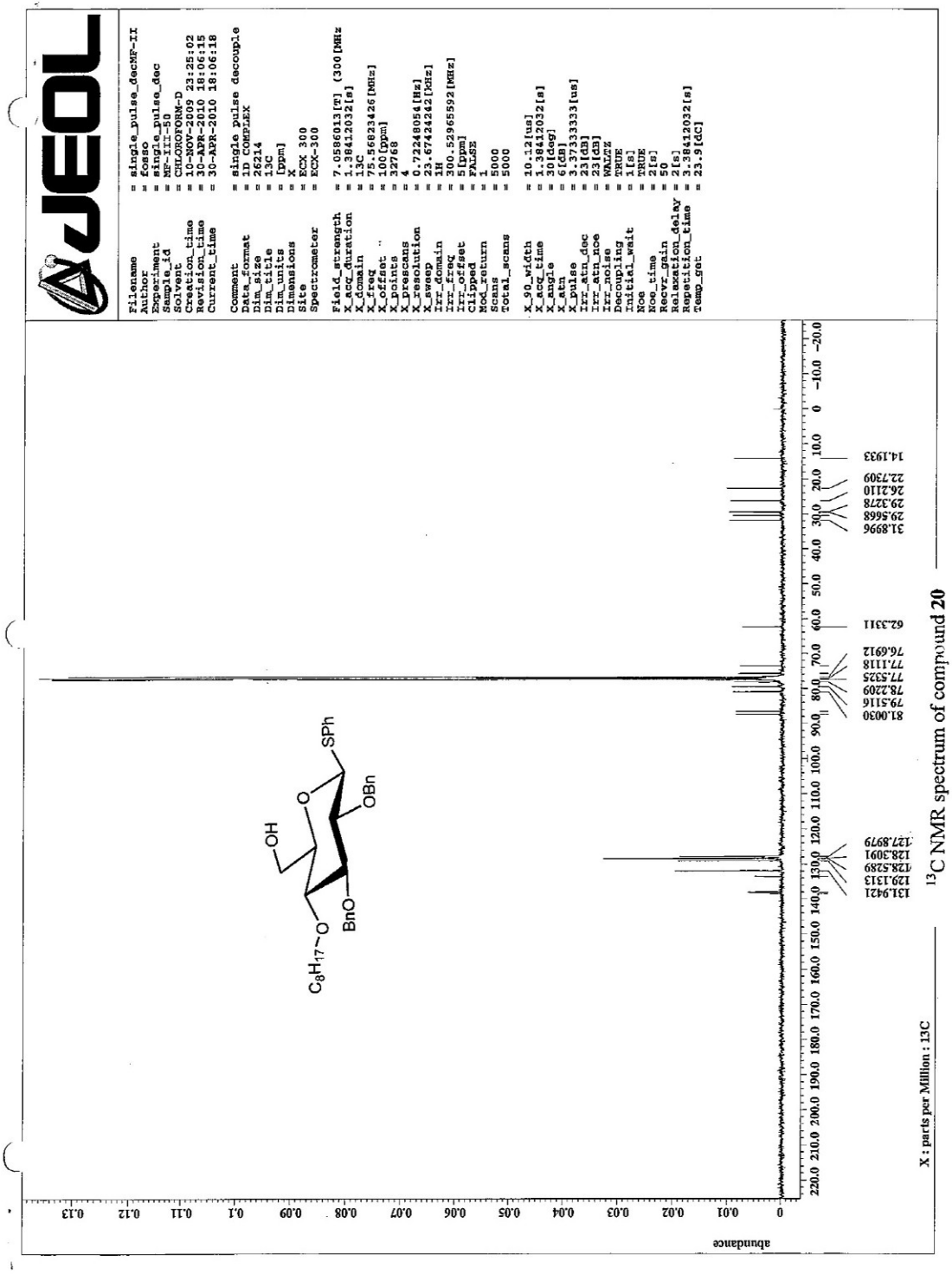

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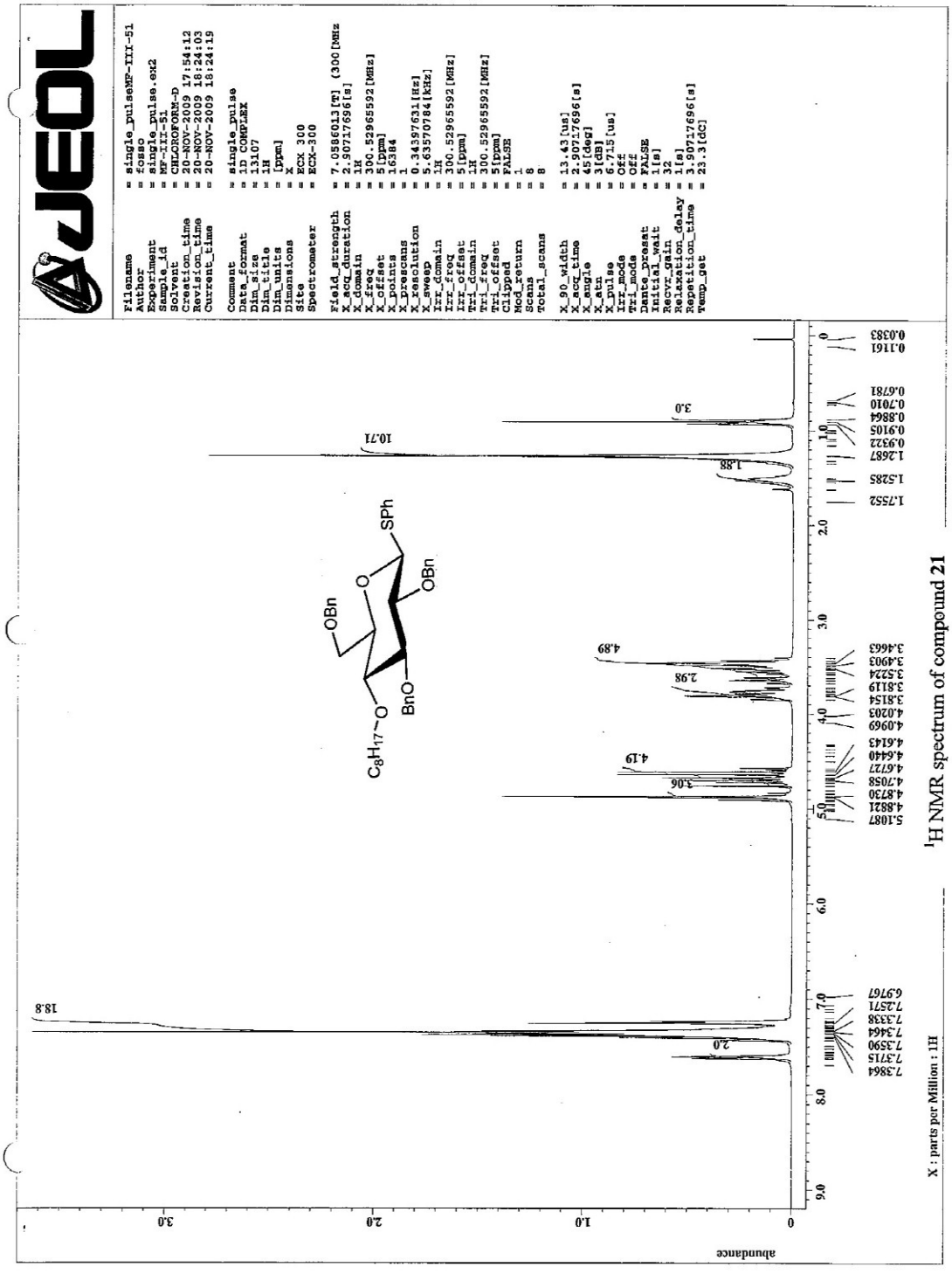

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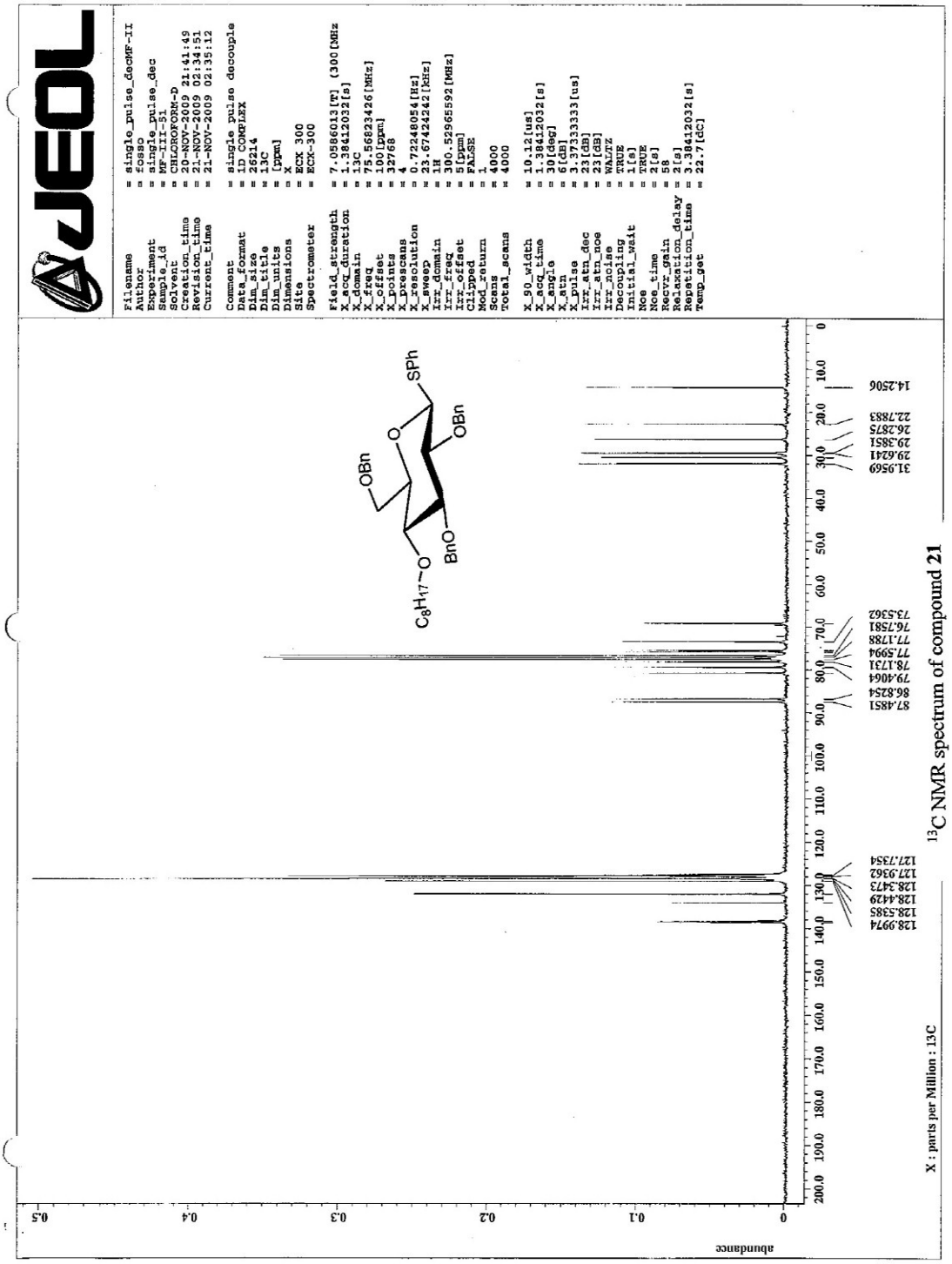
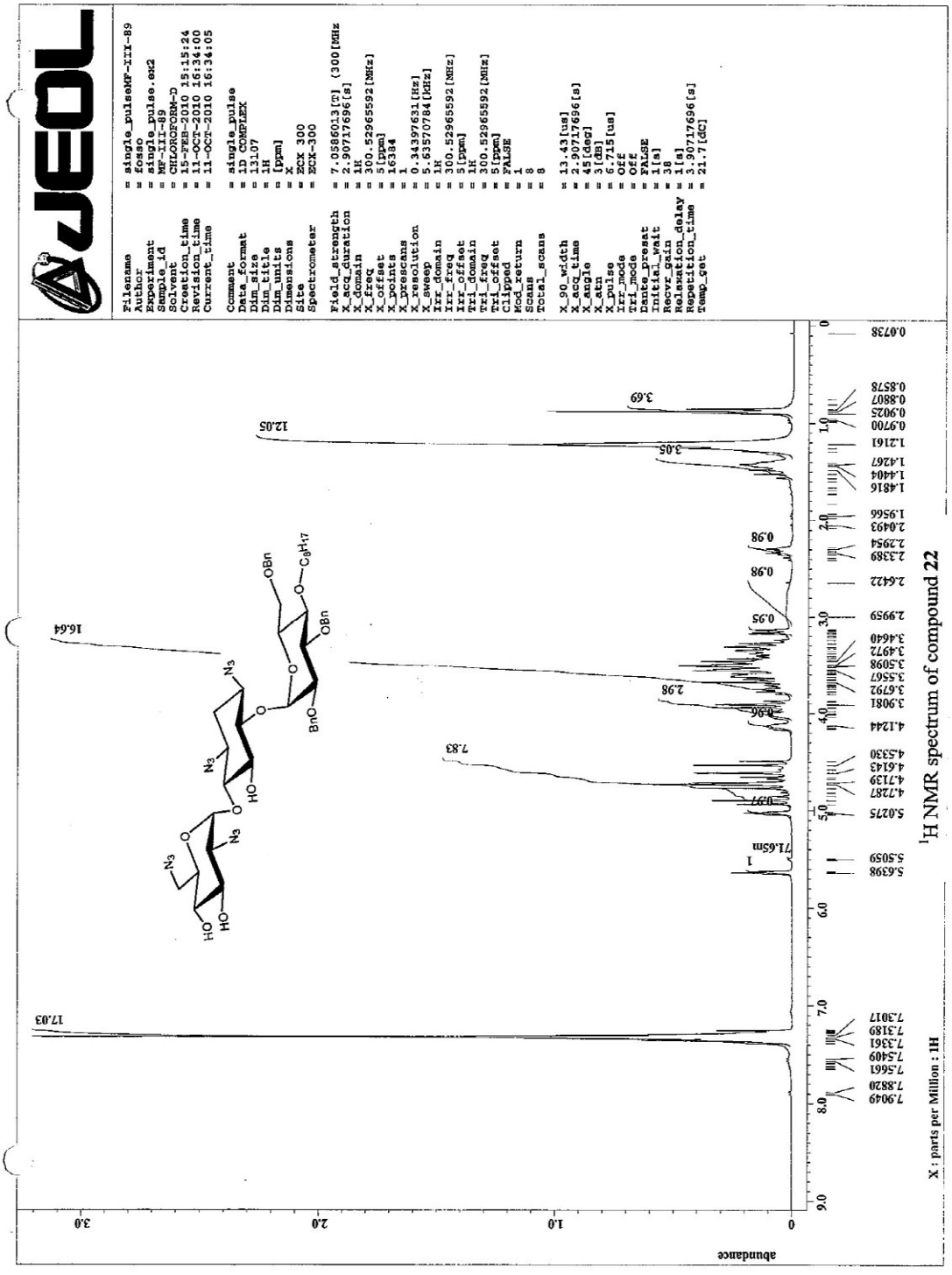


^{13}C NMR spectrum of compound **21**



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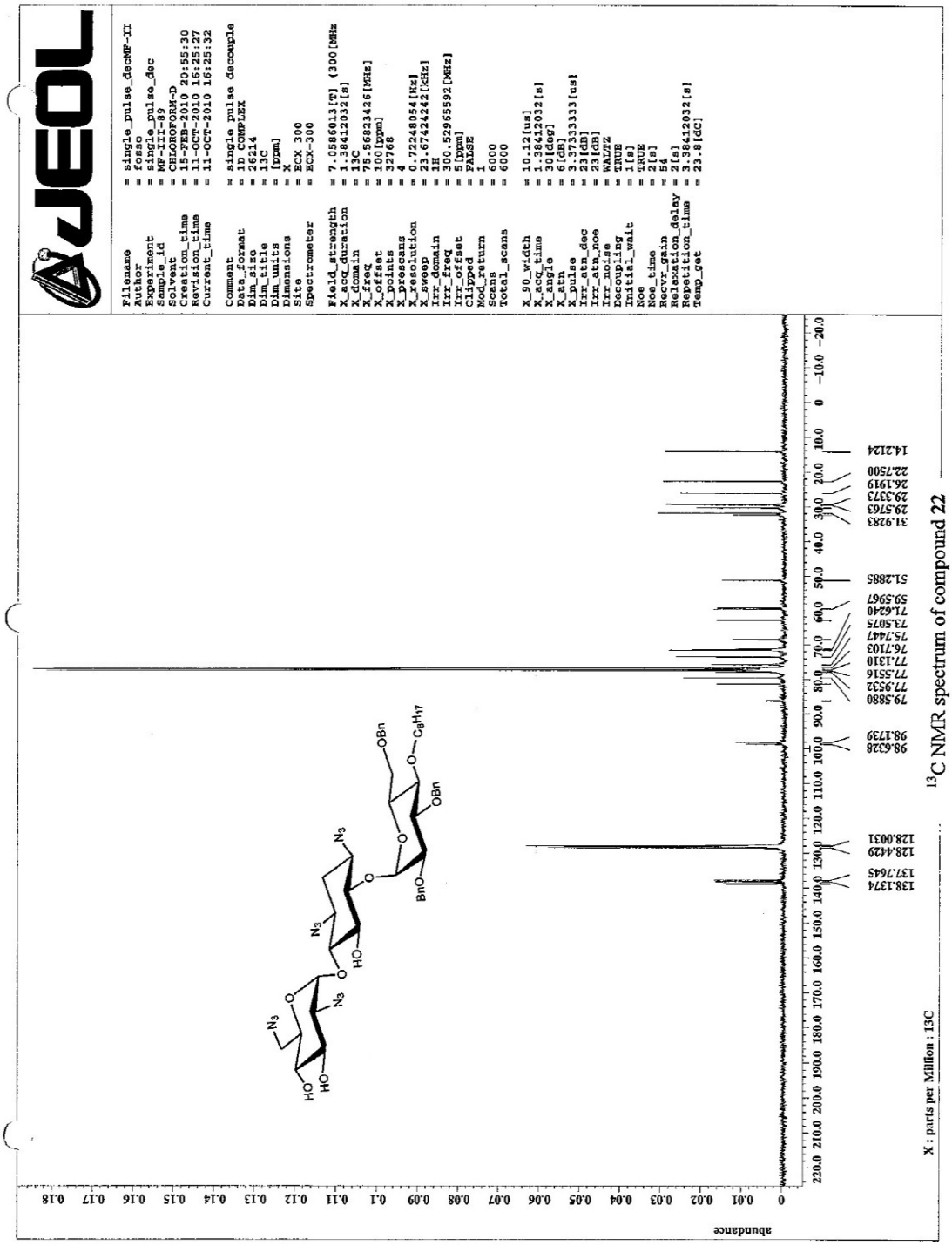
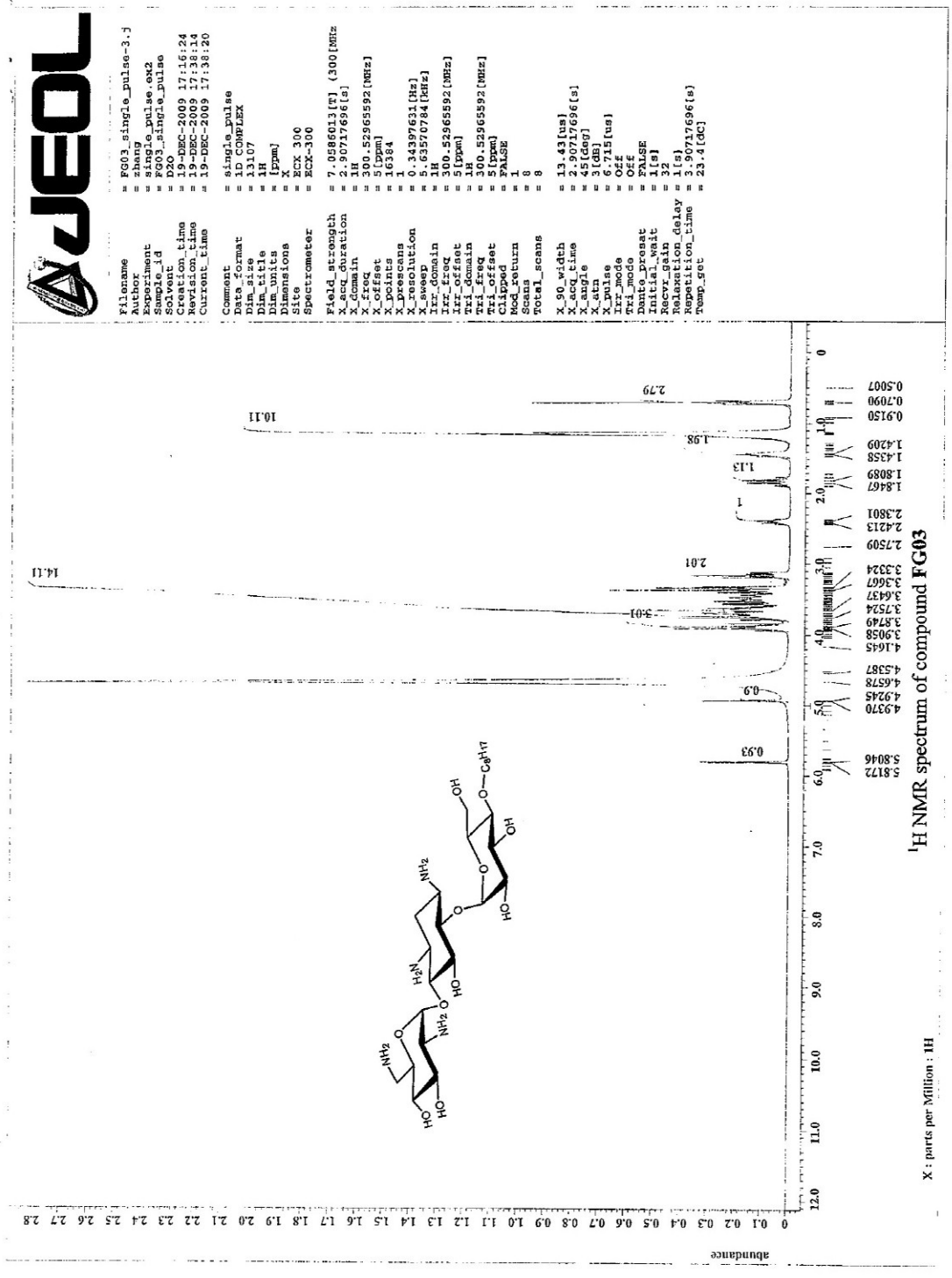
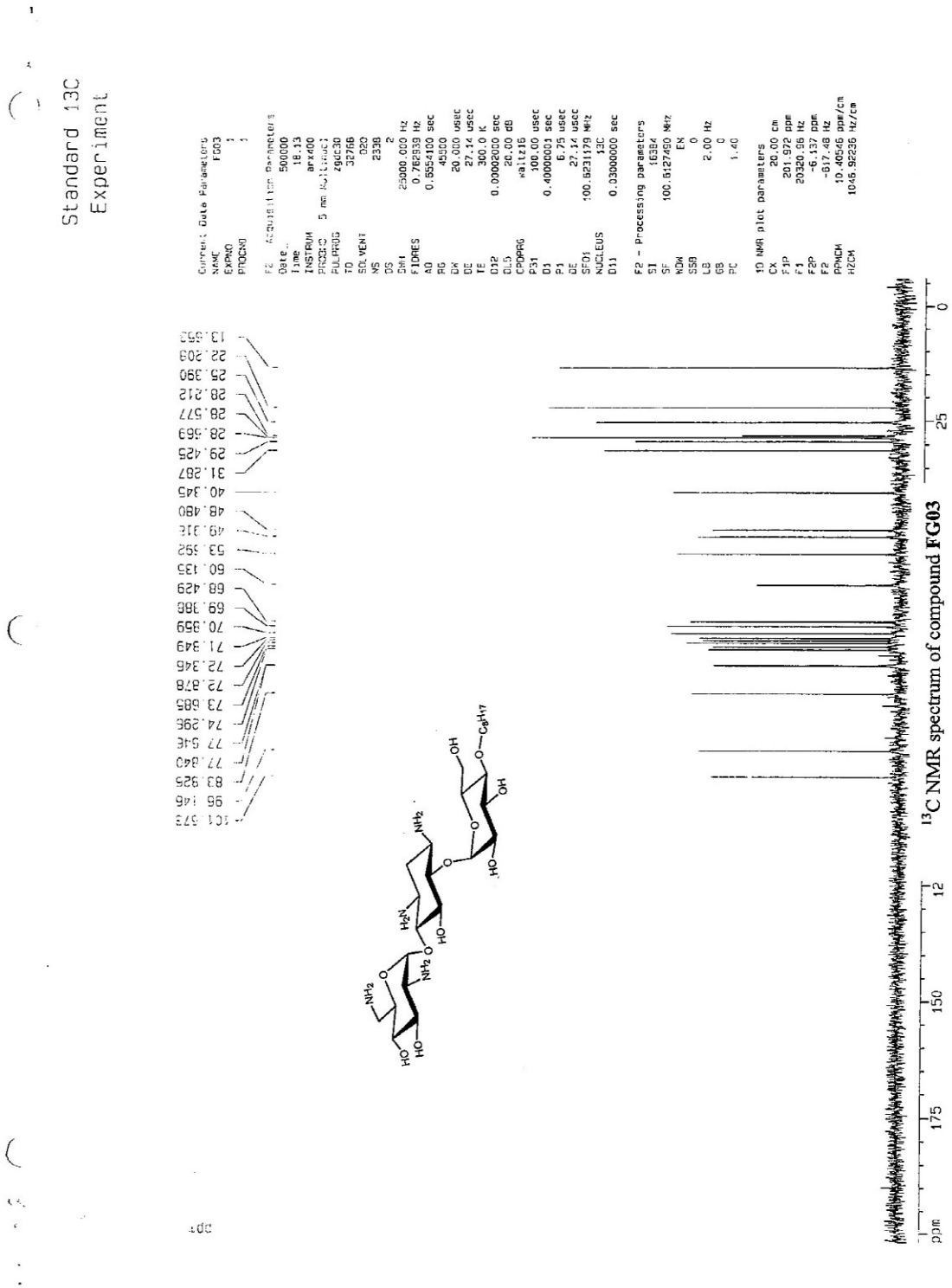


^{13}C NMR spectrum of compound **22**



^{1}H NMR spectrum of compound **FG03**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TD 32768
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FIDRES 0.762939 Hz
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RG 45900
DW 20.000 usec
DE 27.14 usec
TE 300.0 K
D12 0.00002000 sec
D16 20.00 dB
CPDPRG waltz16
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DE 27.14 usec
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HZCM 1046.92236 Hz/cm
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25.390
28.212
28.577
28.669
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31.287
40.345
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53.592
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68.429
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72.878
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74.296
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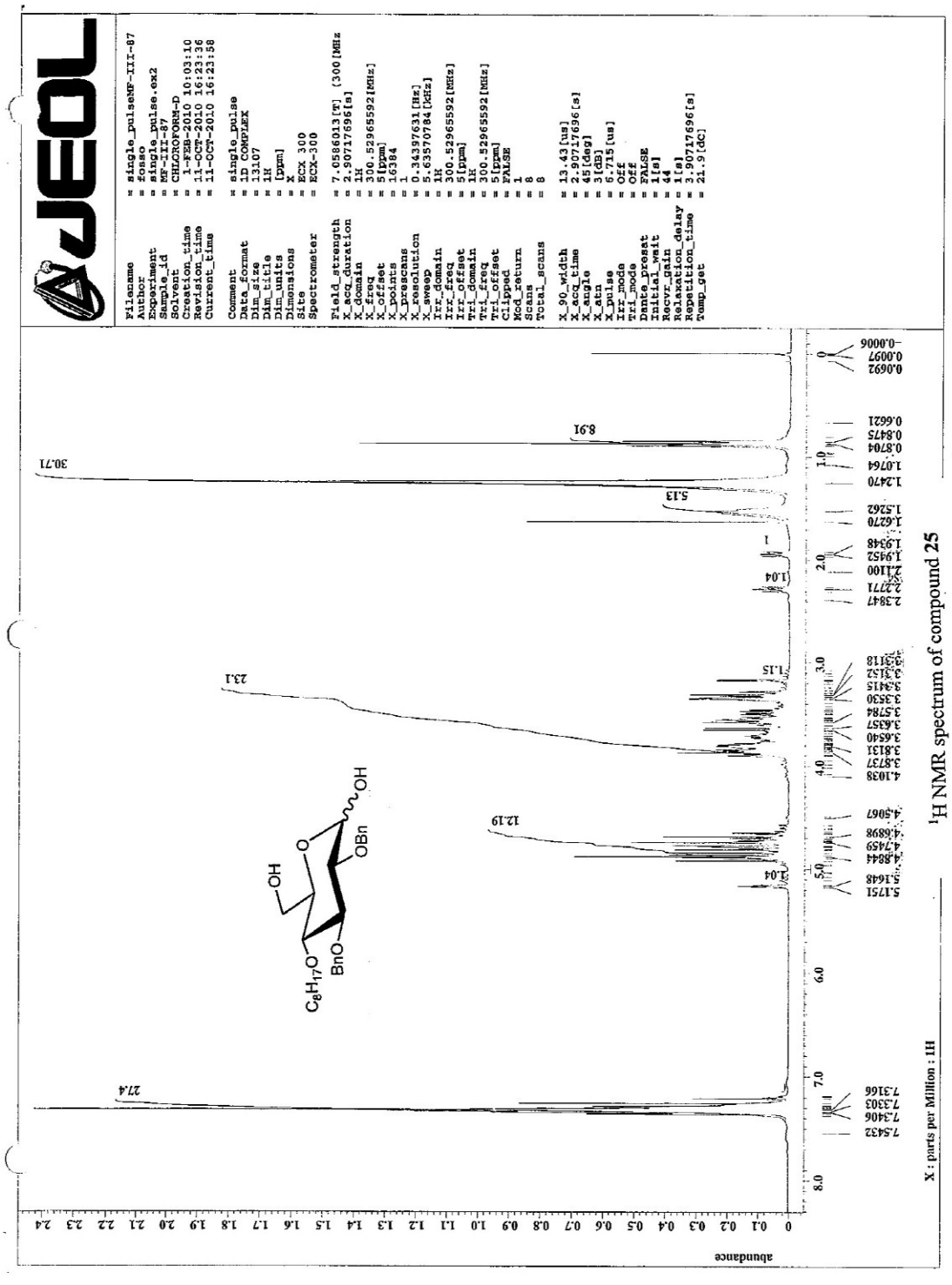
^{13}C NMR spectrum of compound **FG03**



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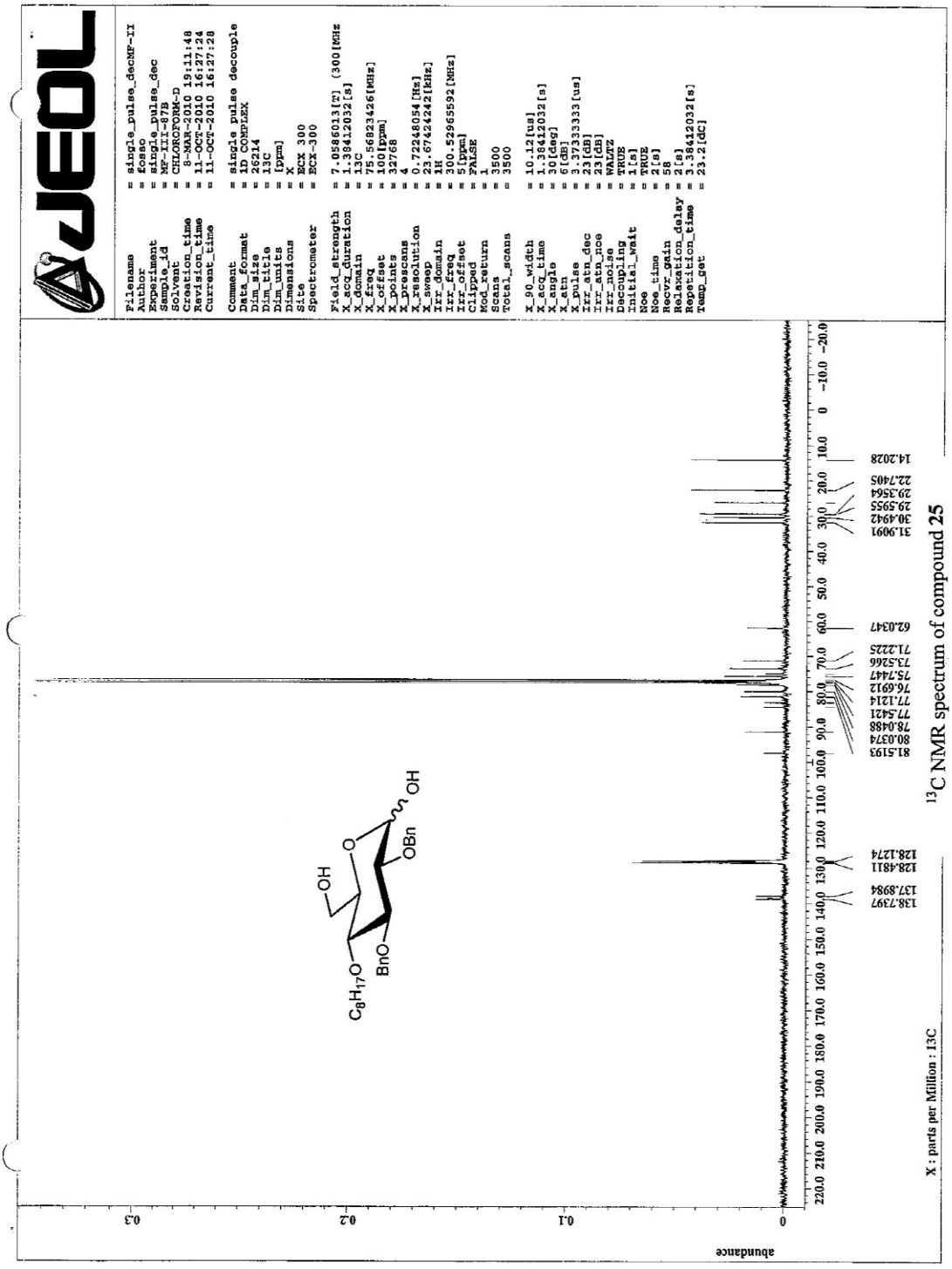

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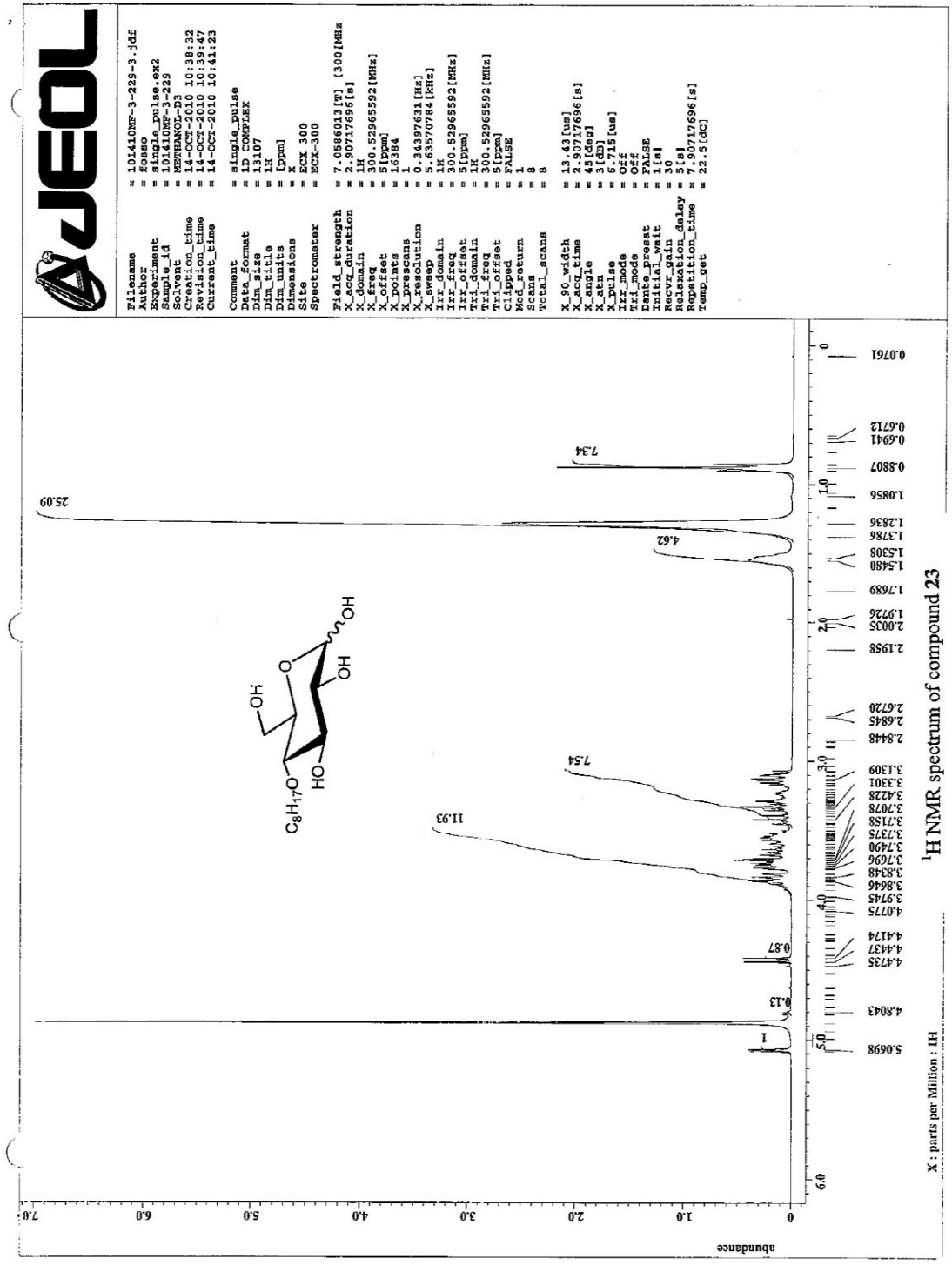
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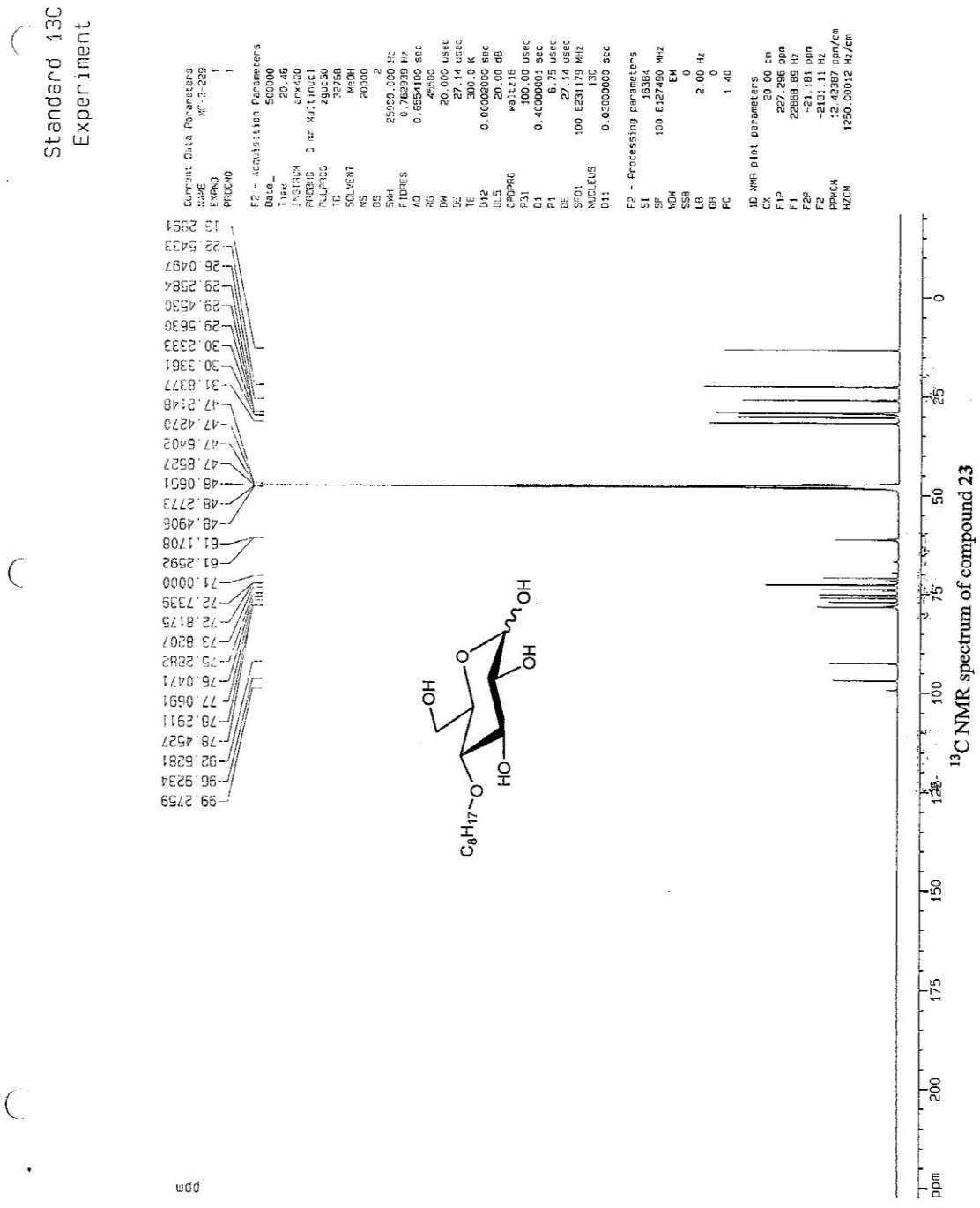
OH
HO
OH
O
HO
$C_8H_{17}O$
^{1}H NMR spectrum of compound 23



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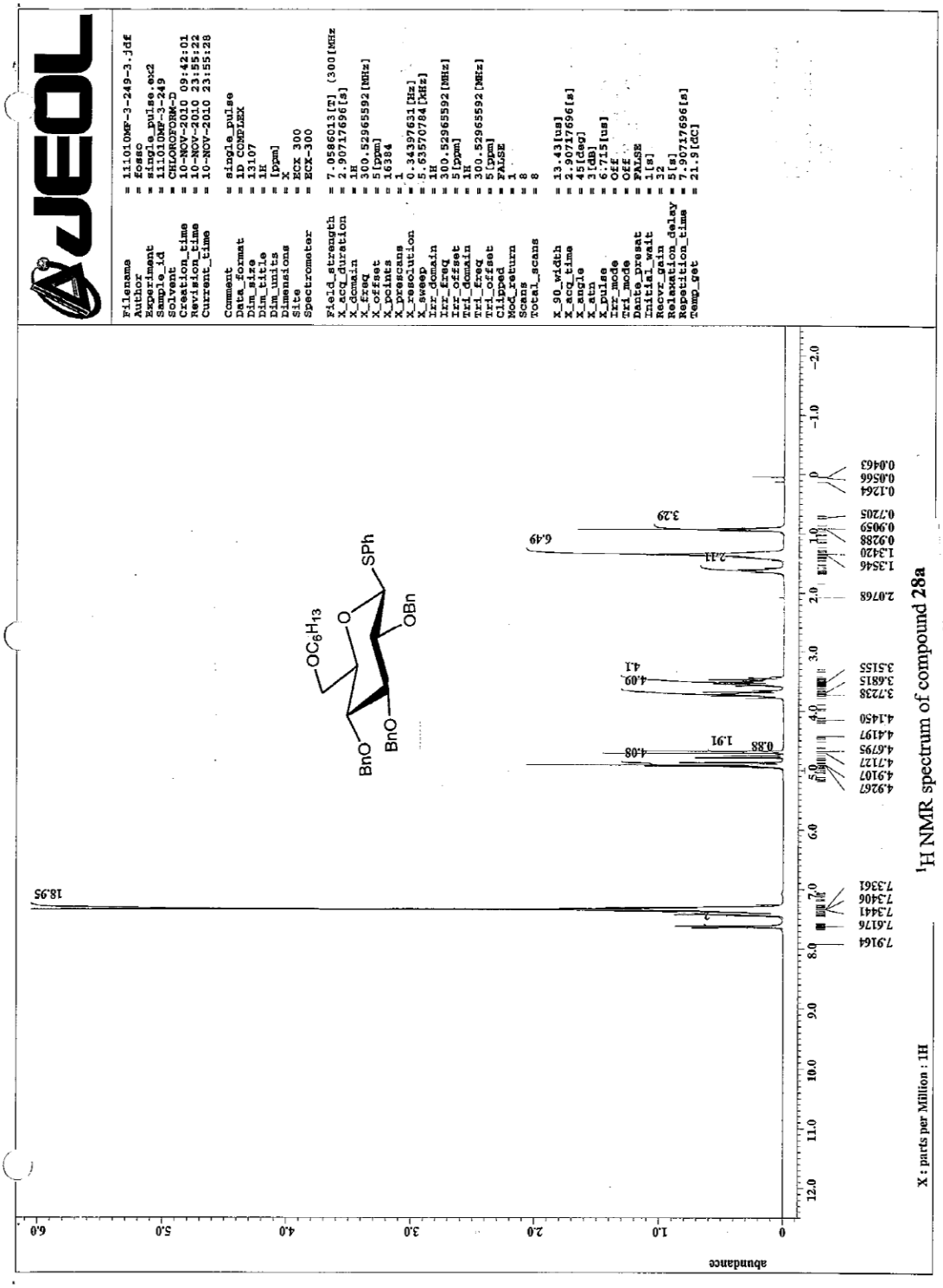

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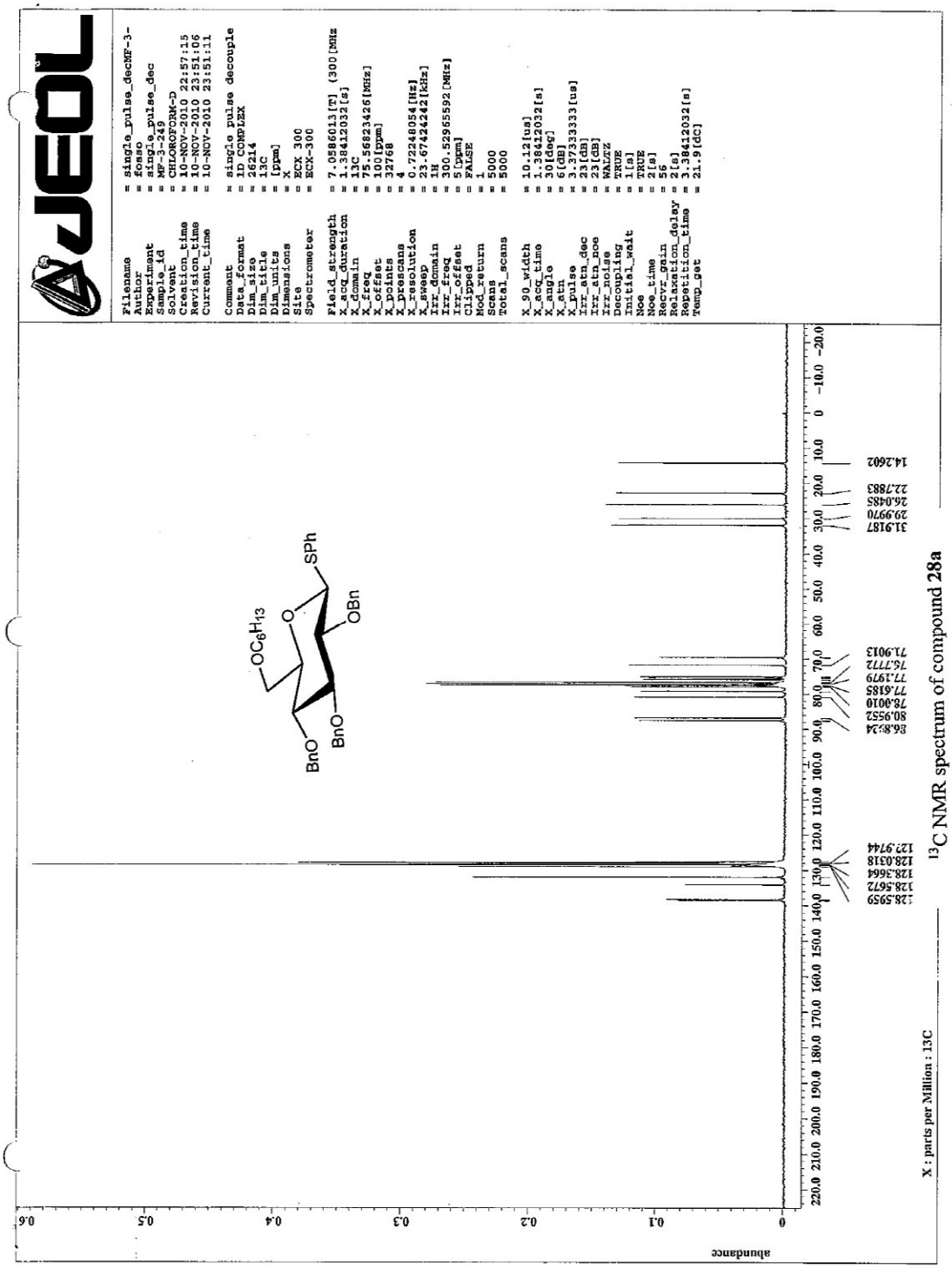

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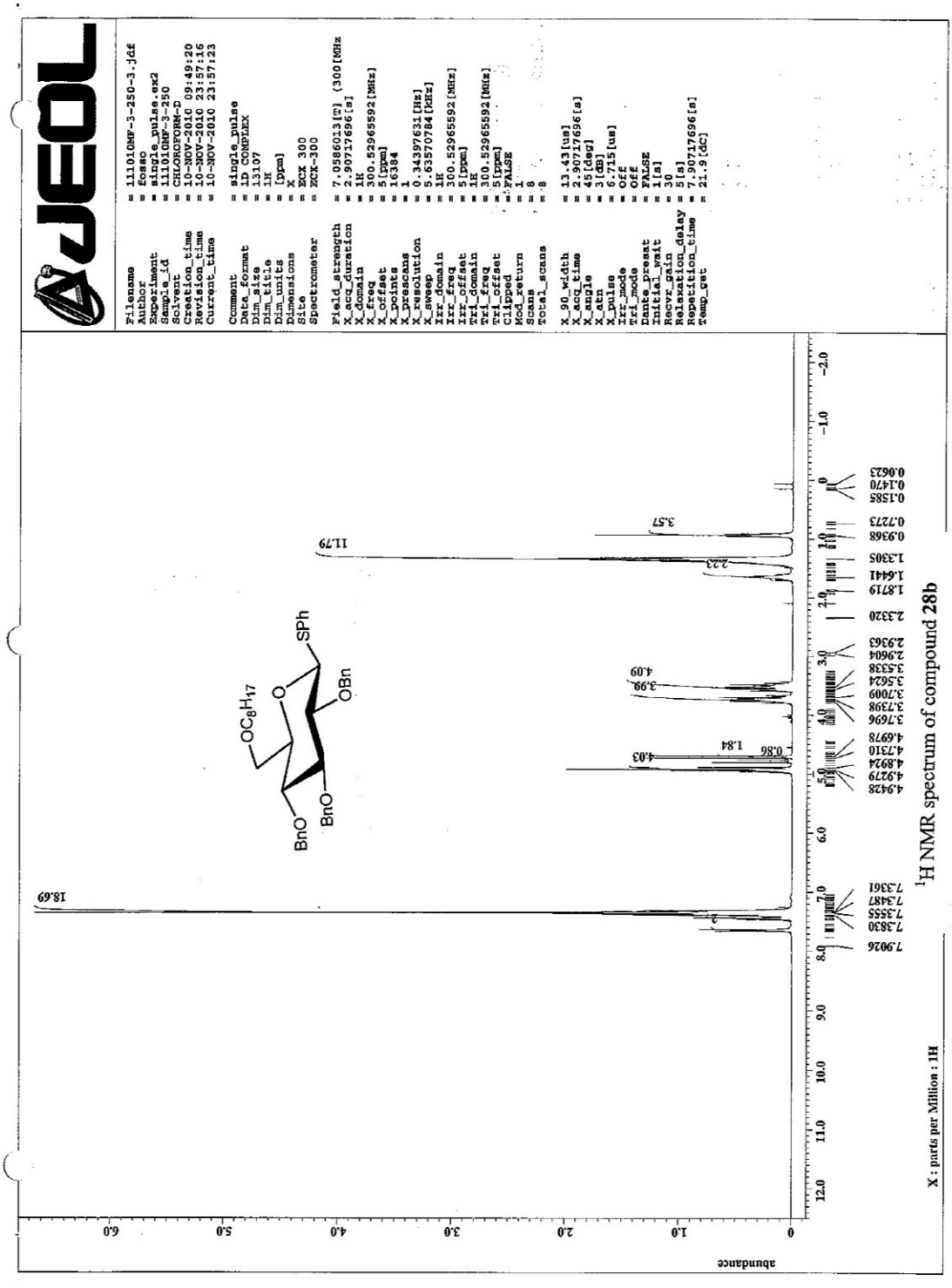
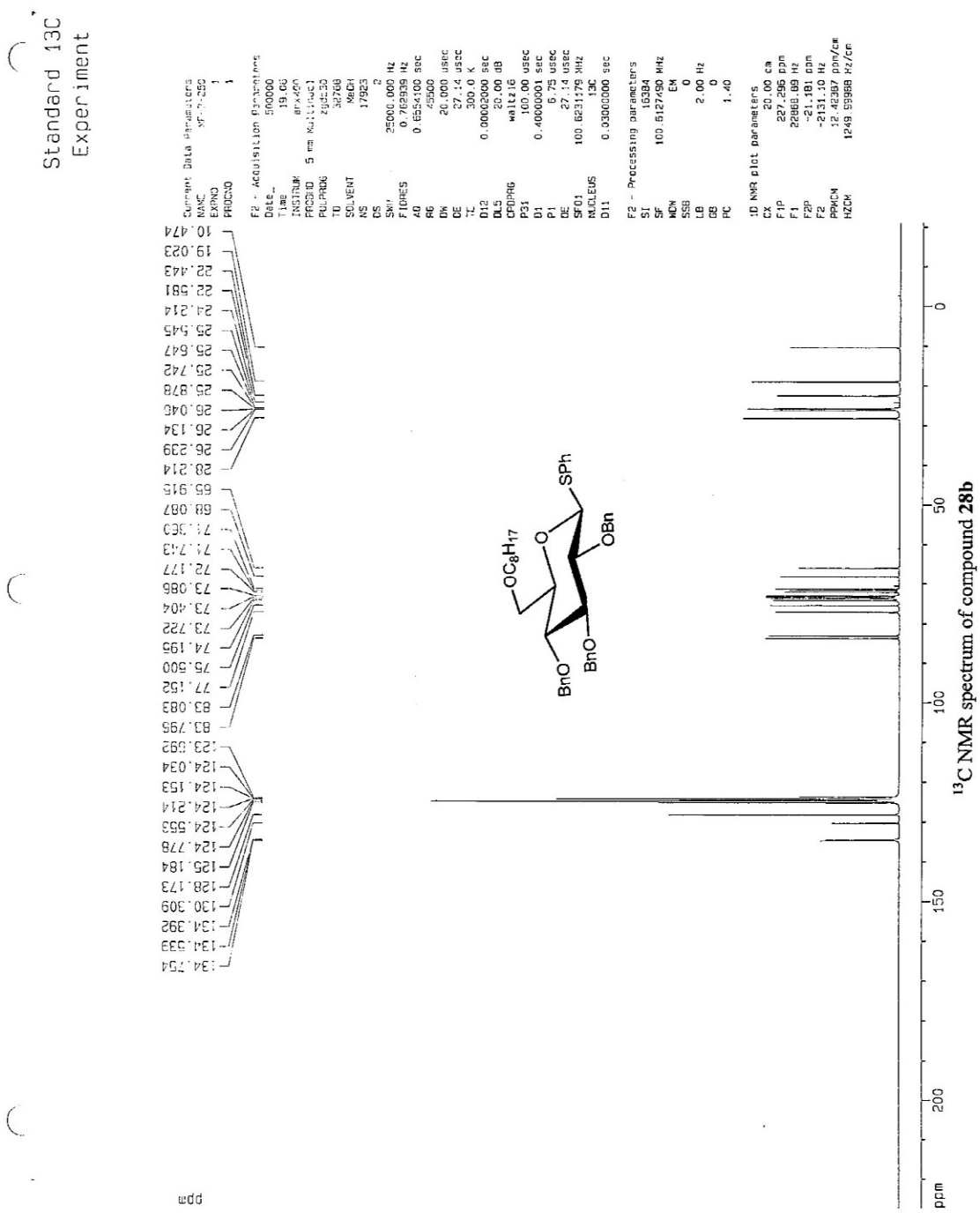
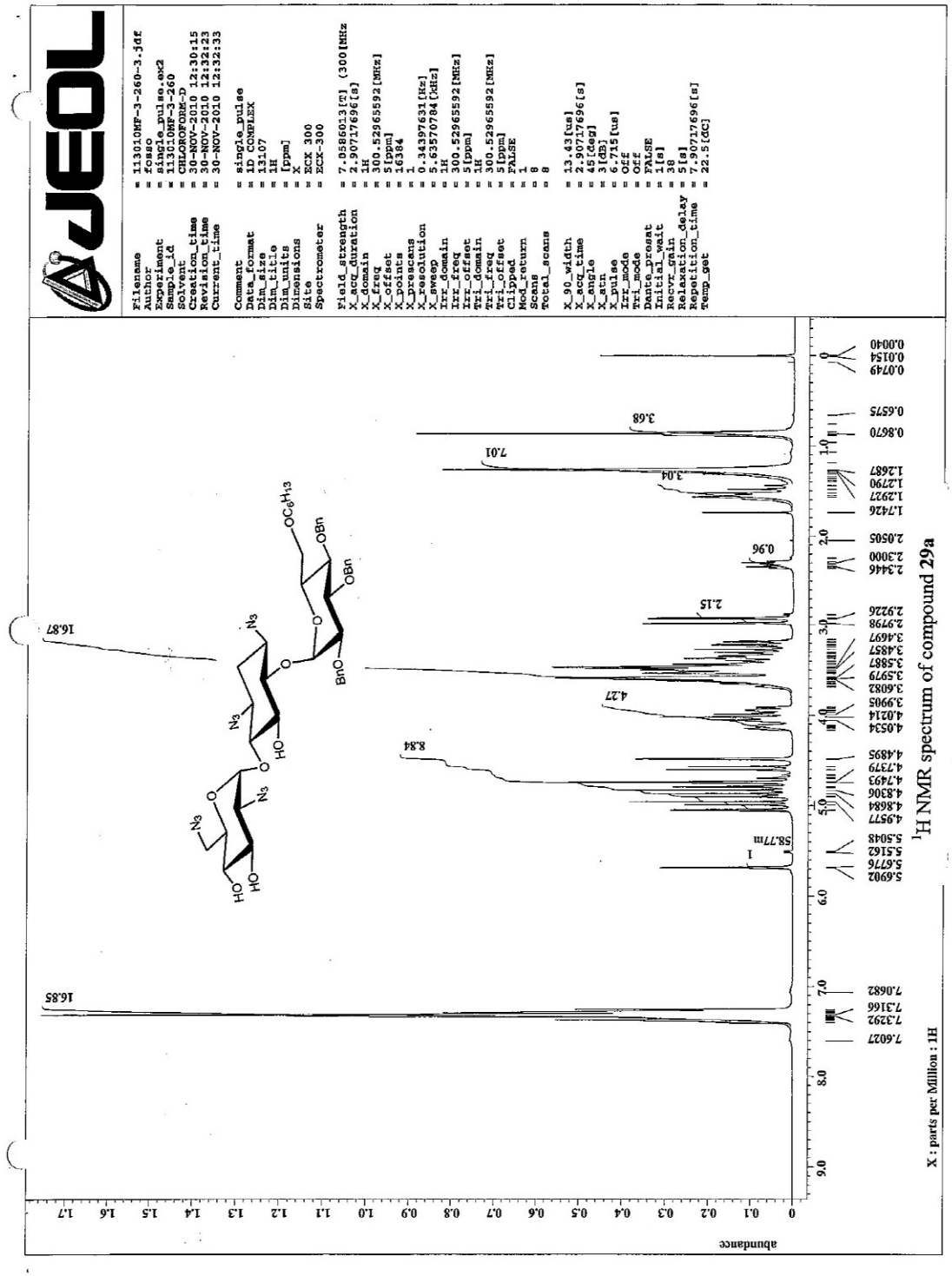


^{1}H NMR spectrum of compound **28b**



^{13}C NMR spectrum of compound **28b**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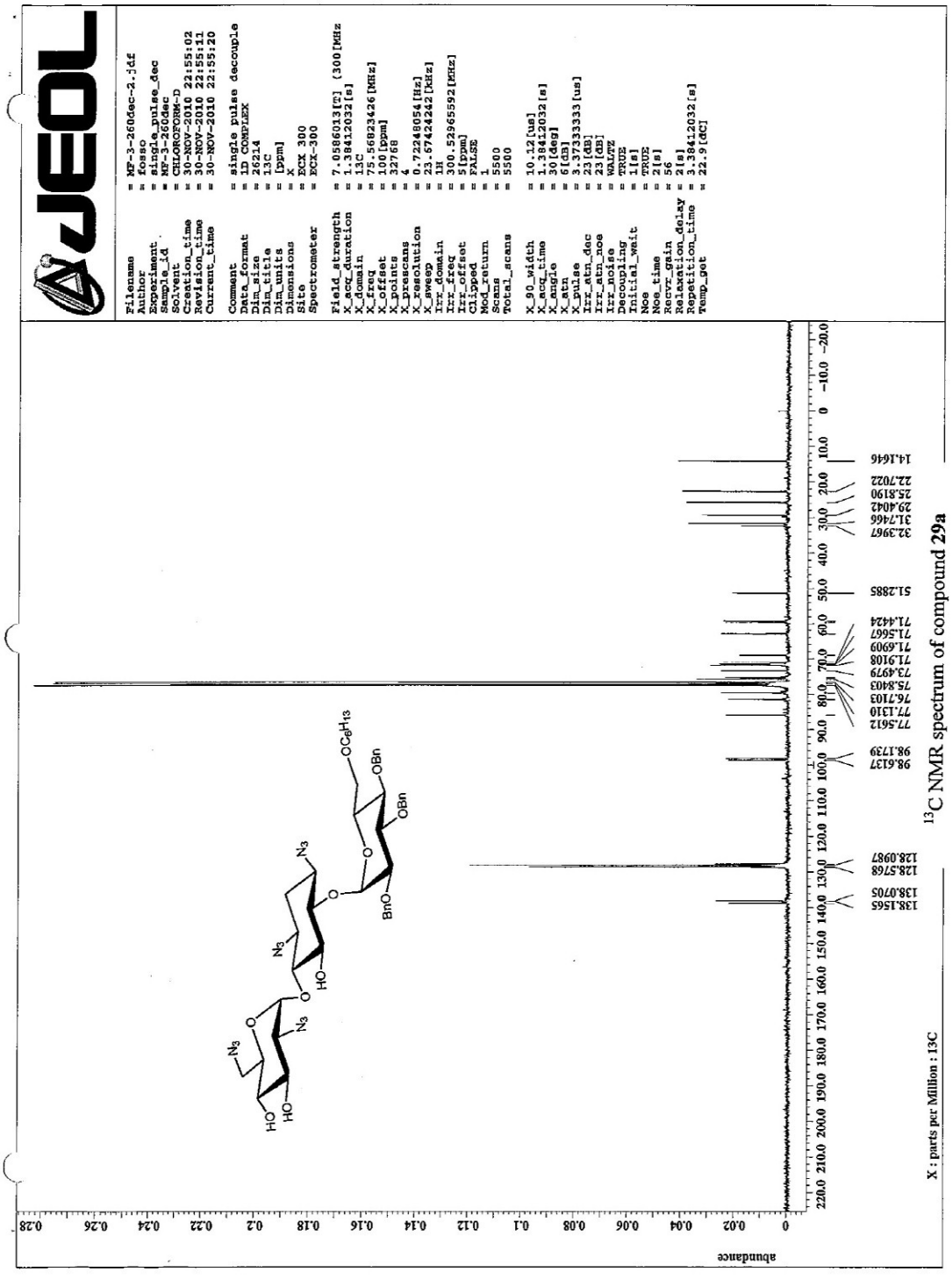
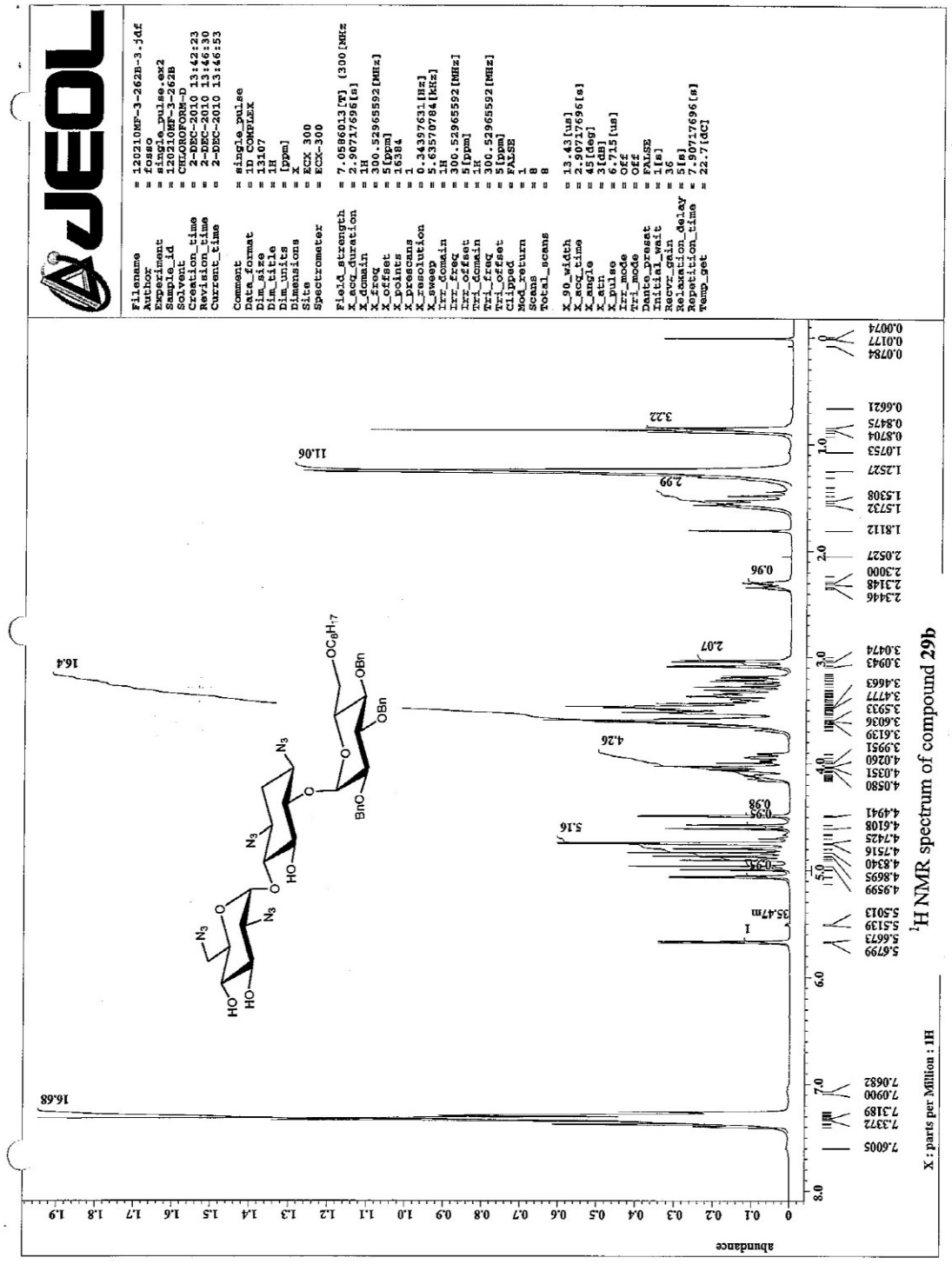
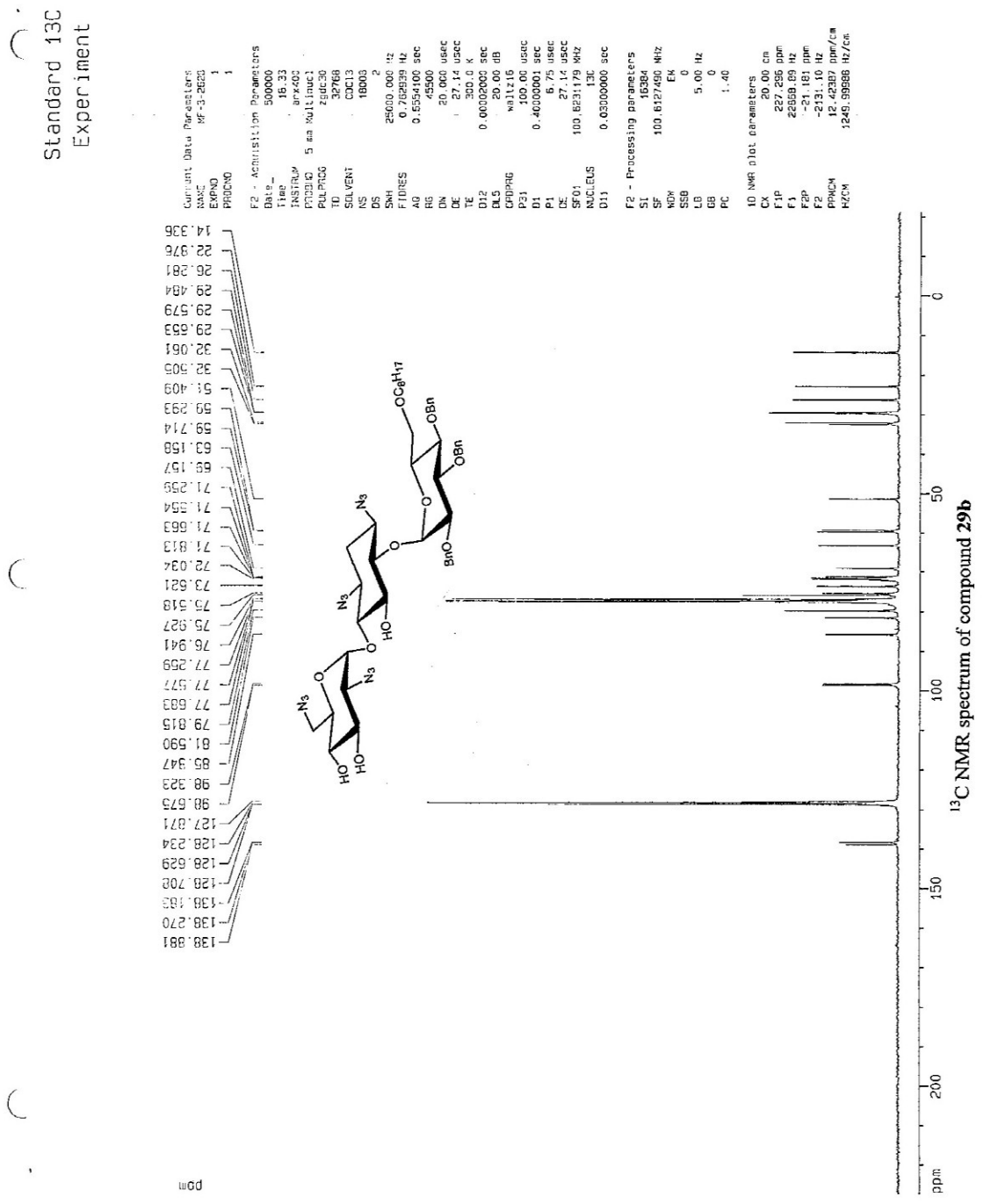
X_sweep = 5.63570784[kHz]
Irr_domain = 1H
Irr_freq = 300.52965592[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 300.52965592[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 8
Total_scans = 8
X_90_width = 13.43[us]
X_acq_time = 2.90717696[s]
X_angle = 45[deg]
X_atn = 3[dB]
X_pulse = 6.715[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recyc_grain = 38
Relaxation_delay = 5[s]
Repetition_time = 7.90717696[s]
Temp_get = 22.5[dC]
16.87
16.85
8.84
7.01
4.27
3.68
3.04
2.15
0.96
abundance
X : parts per Million : 1H
^{1}H NMR spectrum of compound **29a**

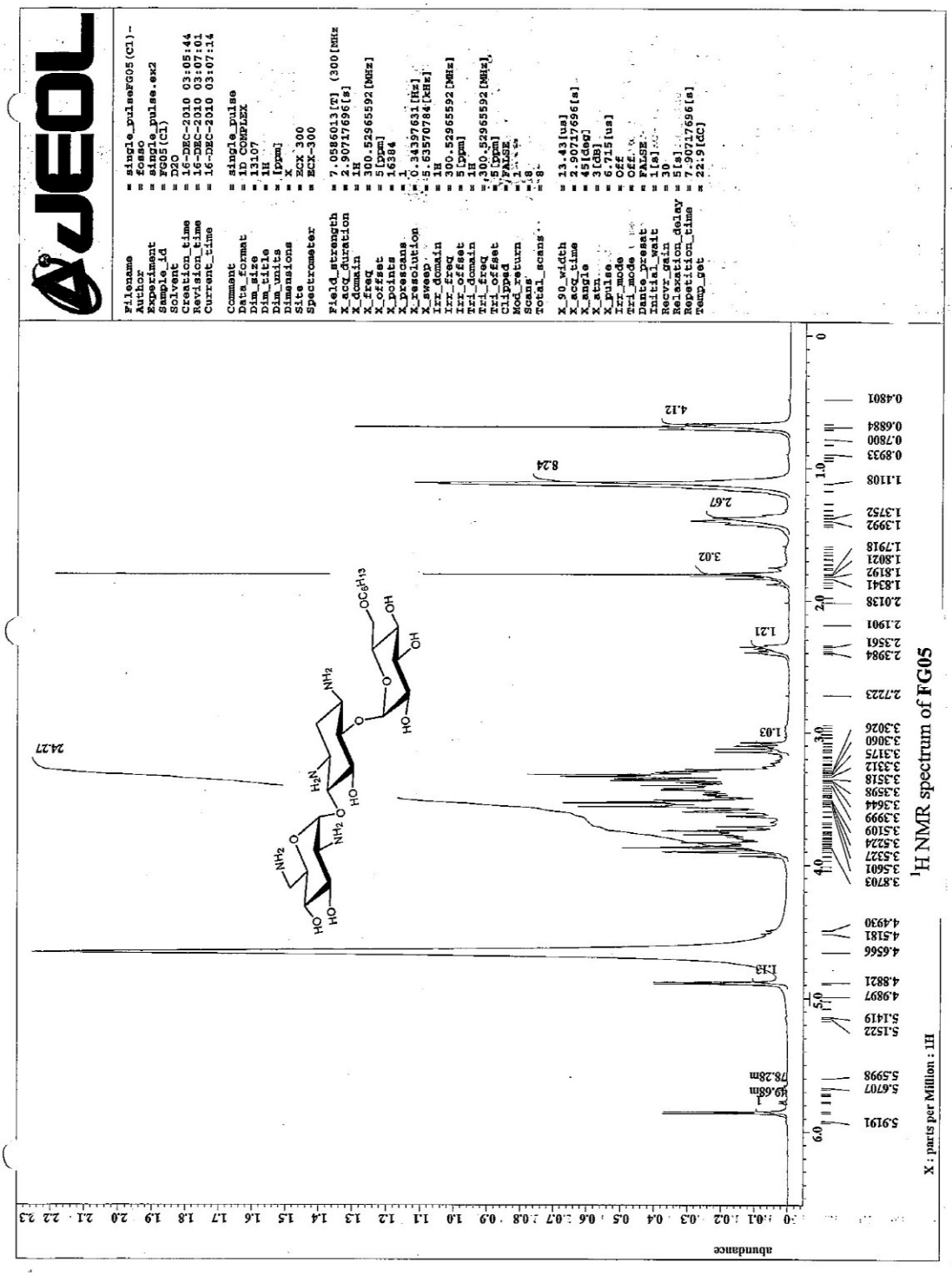

JEOL
Filename = MF-3-260dec-2.jdf
Author = fonso
Experiment = single_pulse_dec
Sample_id = MF-3-260dec
Solvent = CHLOROFORM-D
Creation_time = 30-NOV-2010 22:55:02
Revision_time = 30-NOV-2010 22:55:11
Current_time = 30-NOV-2010 22:55:20
Comment = single pulse decouple
Data_format = 1D COMPLEX
Dim_size = 26214
Dim_title = 13C
Dim_units = [ppm]
Dimensions = X
Site = ECX 300
Spectrometer = ECX-300
Field_strength = 7.0586013[T] (300[MHz
X_acq_duration = 1.384120320[s]
X_domain = 13C
X_freq = 75.56823426[MHz]
X_offset = 100[ppm]
X_points = 32768
X_prescans = 4
X_resolution = 0.72248054[Hz]
X_sweep = 23.67424242[kHz]
Irr_domain = 1H
Irr_freq = 300.52965592[MHz]
Irr_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 5500
Total_scans = 5500
X_90_width = 10.12[us]
X_acq_time = 1.384120320[s]
X_angle = 30[deg]
X_atn = 6[dB]
X_pulse = 3.37333333[us]
Irr_atn_dec = 23[dB]
Irr_atn_noe = 23[dB]
Irr_mode = WALTZ2
Decoupler = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Recvr_gain = 56
Relaxation_delay = 2[s]
Repetition_time = 3.384120320[s]
Temp_get = 22.9[dC]
abundance
X : parts per Million : 13C
14.1646
22.7022
25.8190
29.4042
31.7466
32.3967
51.2885
71.4424
71.5667
71.6909
71.9108
73.4979
75.8403
76.7103
77.1310
77.5612
98.1739
98.6137
128.0987
128.5768
138.0705
138.1565
^{13}C NMR spectrum of compound **29a**



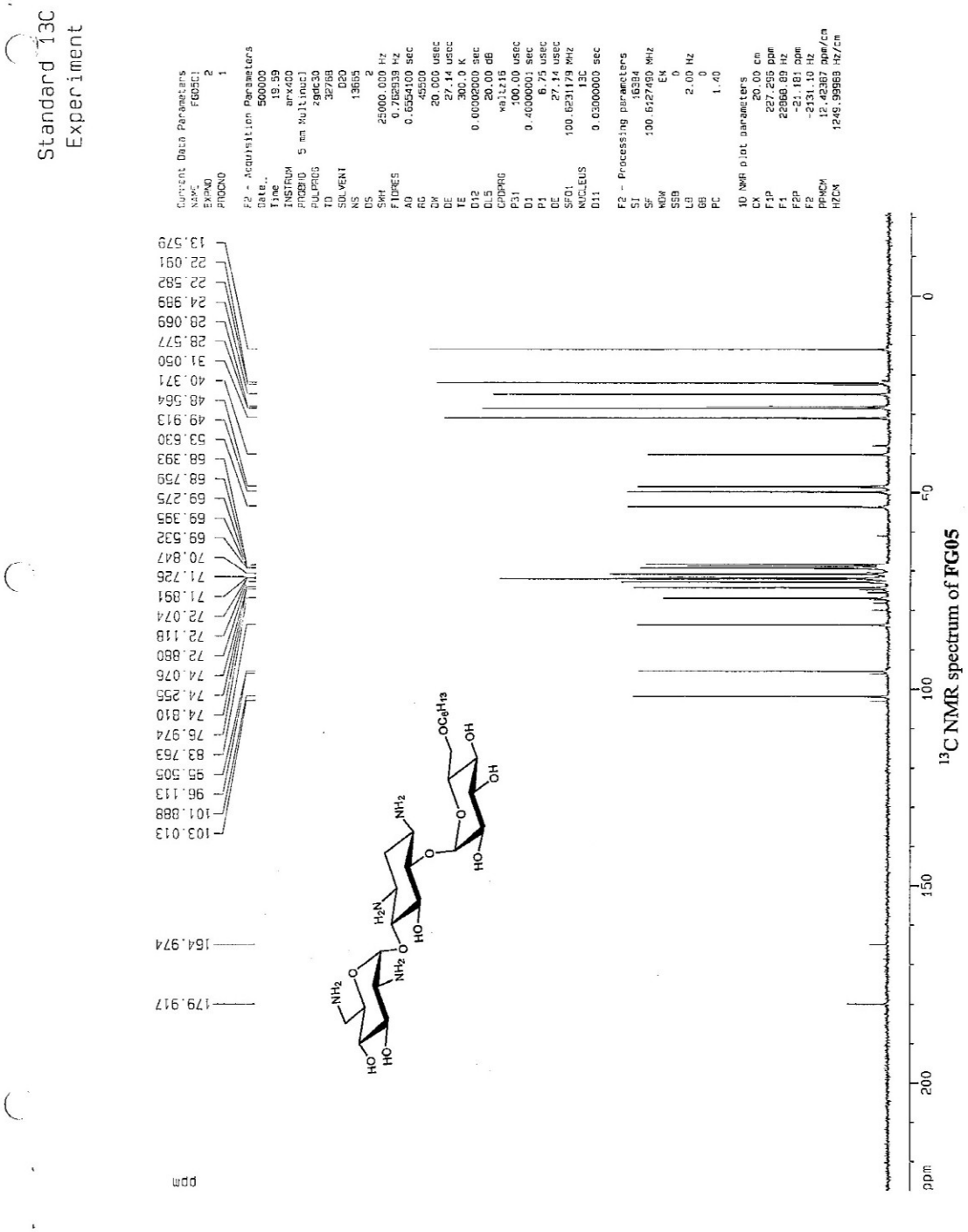
^{1}H NMR spectrum of compound **29b**

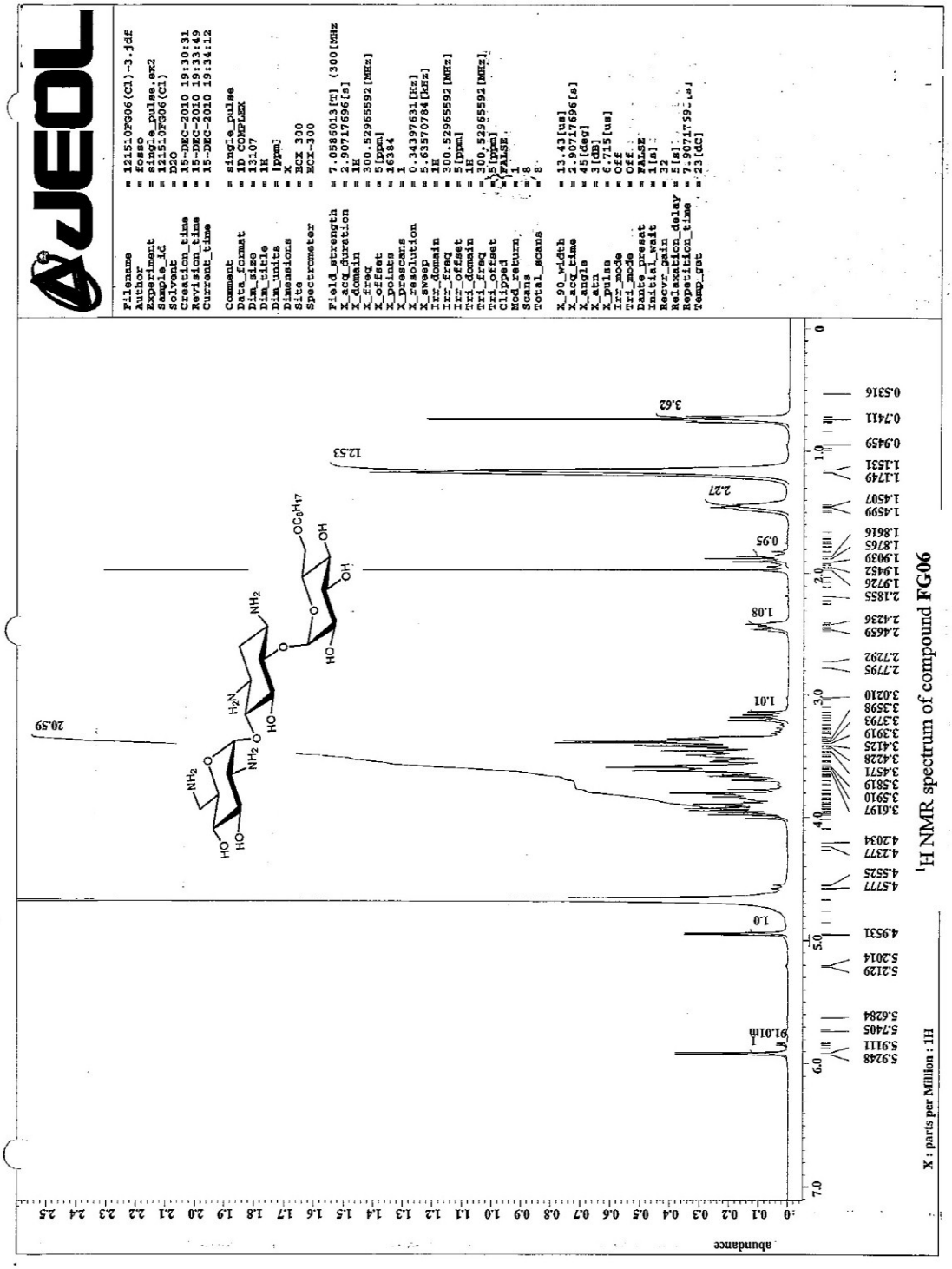


^{13}C NMR spectrum of compound **29b**

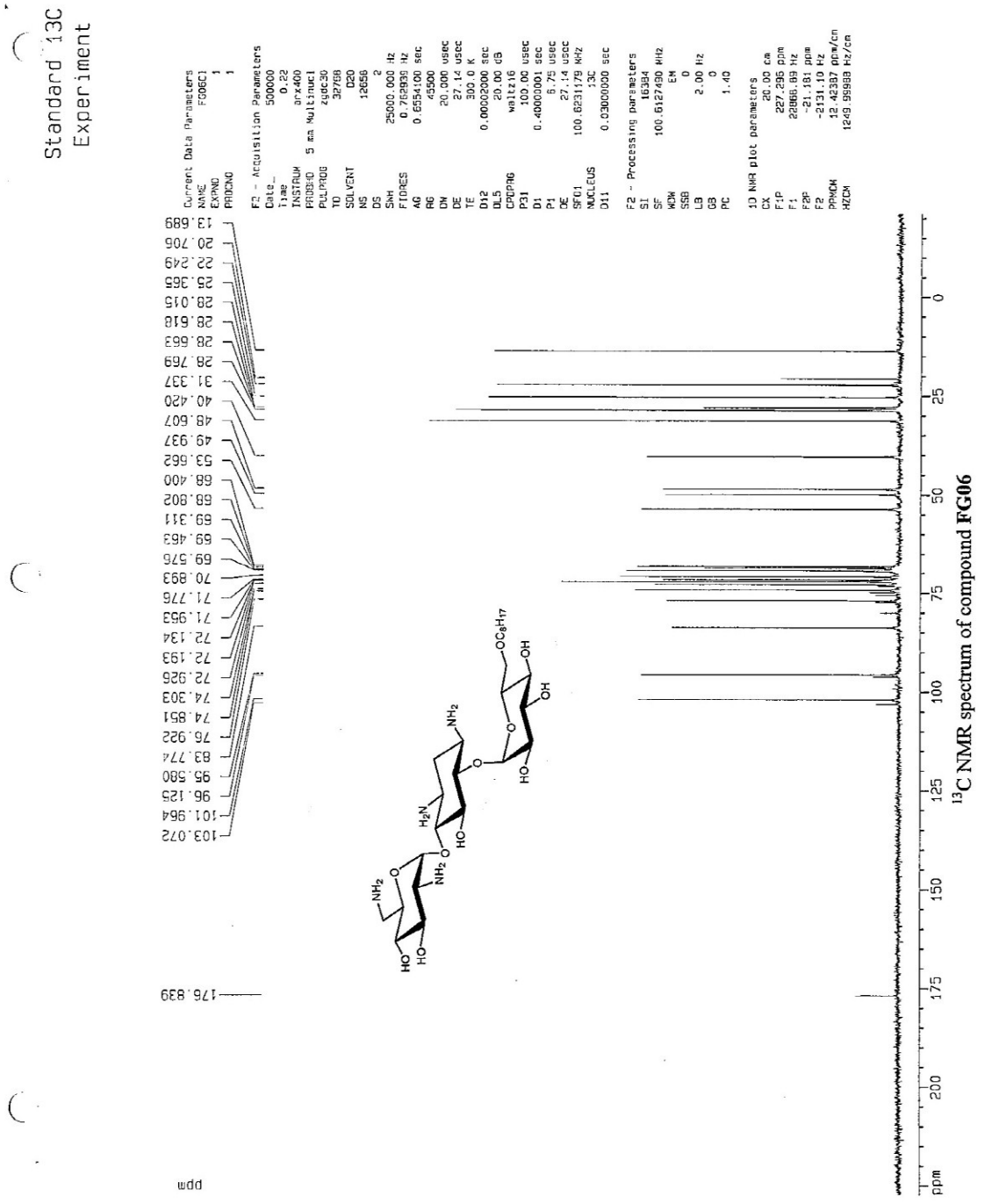


^{1}H NMR spectrum of **FG05**

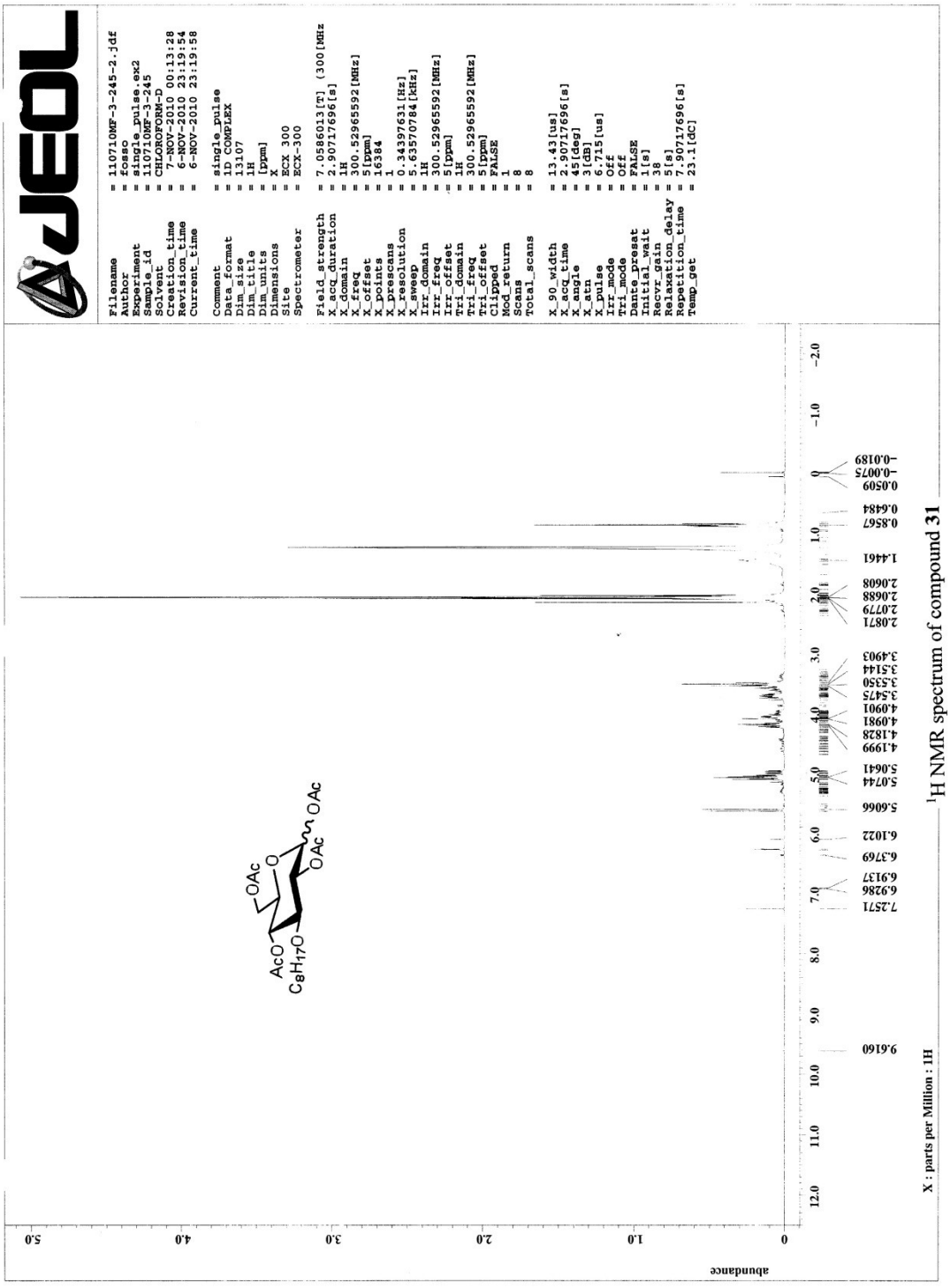

Standard 13C
Experiment
Current Data Parameters
NAME FG05C1
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 500000
Time 19.59
INSTRUM spx400
PROBHD 5 mm Multinucl
PULPROG zgdc30
TD 32768
SOLVENT D20
NS 13665
DS 2
SWH 25000.000 Hz
FIDRES 0.762939 Hz
AQ 0.6554100 sec
RG 45500
DW 20.000 usec
DE 27.14 usec
TE 300.0 K
D12 0.00002000 sec
DL5 20.00 dB
CPDPRG waltz16
P31 100.00 usec
D1 0.40000001 sec
P1 6.75 usec
DE 27.14 usec
SFO1 100.6231179 MHz
NUCLEUS 13C
D11 0.03000000 sec
F2 - Processing parameters
SI 16384
SF 100.6127400 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 227.255 ppm
F1 22868.89 Hz
F2P -21.181 ppm
F2 -2131.10 Hz
PPMCM 12.42367 ppm/cm
HZCM 1249.99968 Hz/cm
ppm
13.579
22.091
22.582
24.989
28.069
28.577
31.050
40.371
48.564
49.913
53.630
68.393
68.759
69.275
69.335
69.532
70.847
71.226
71.091
72.074
72.118
72.880
74.076
74.255
74.810
76.974
83.763
95.505
96.113
101.088
103.013
164.974
179.917
NH2
HO
HO
O
NH2
O
H2N
HO
O
NH2
HO
O
OC8H13
OH
OH
HO
0
50
100
150
200
ppm
13C NMR spectrum of FG05



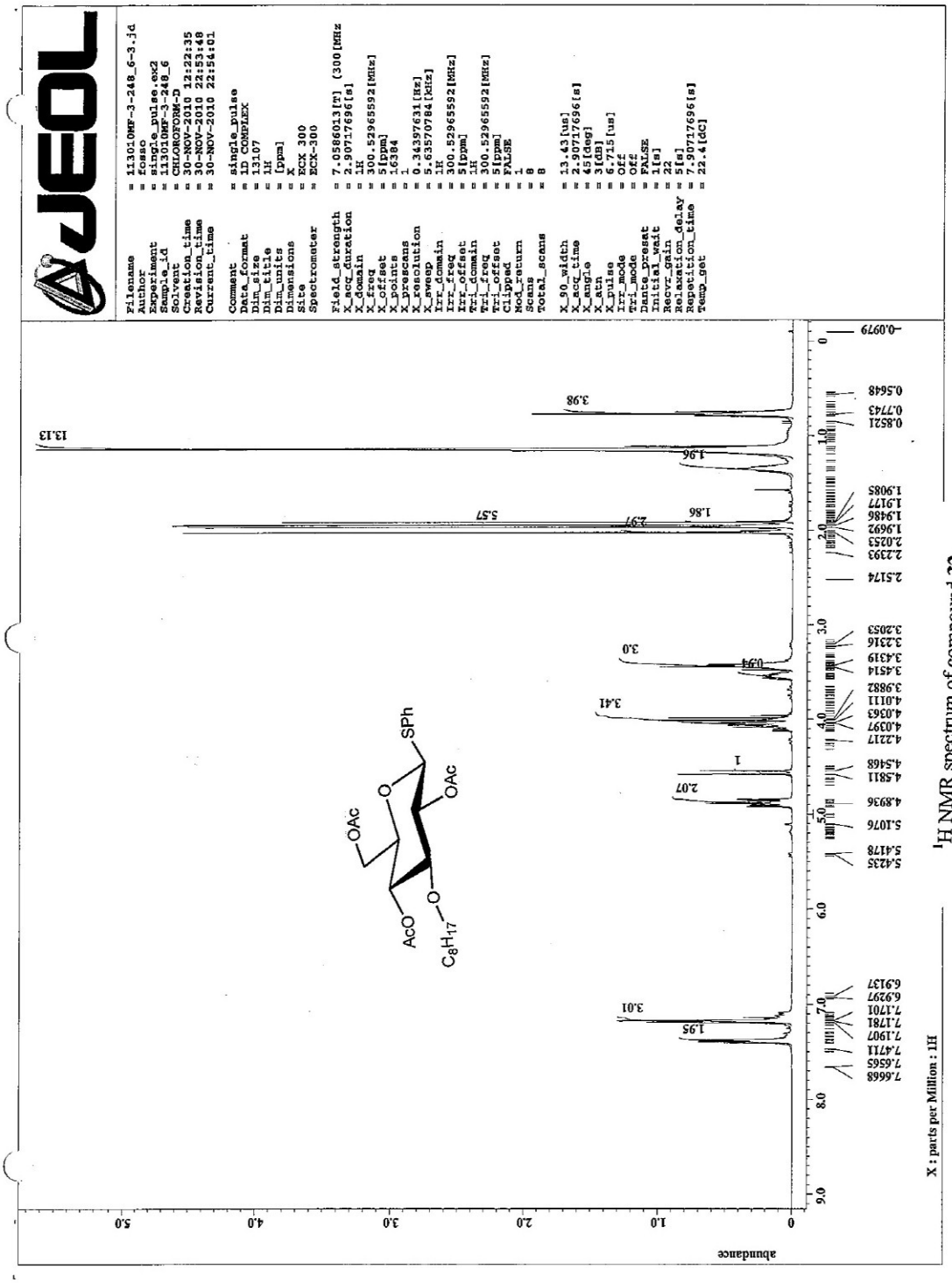
^{1}H NMR spectrum of compound **FG06**



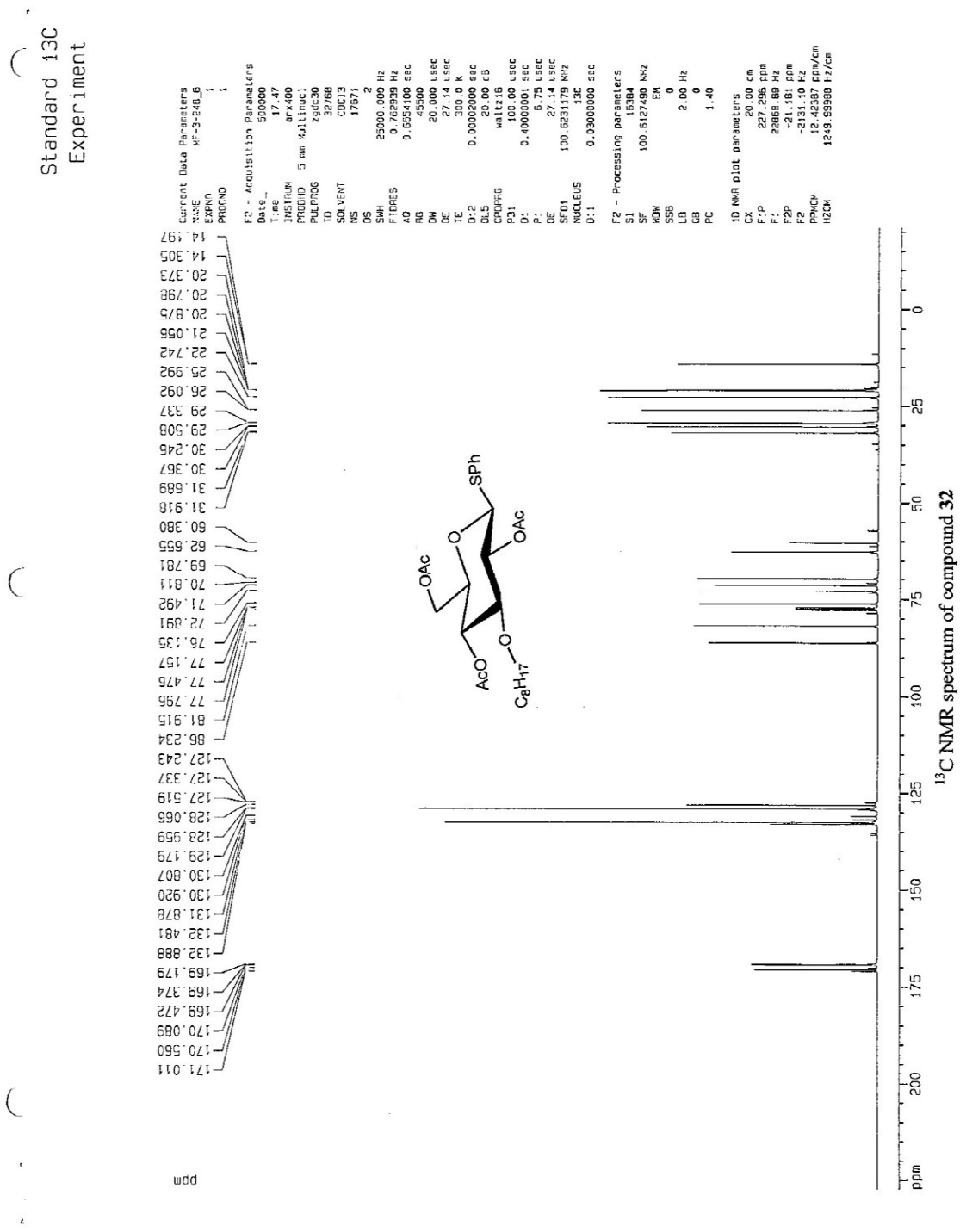
^{13}C NMR spectrum of compound **FG06**



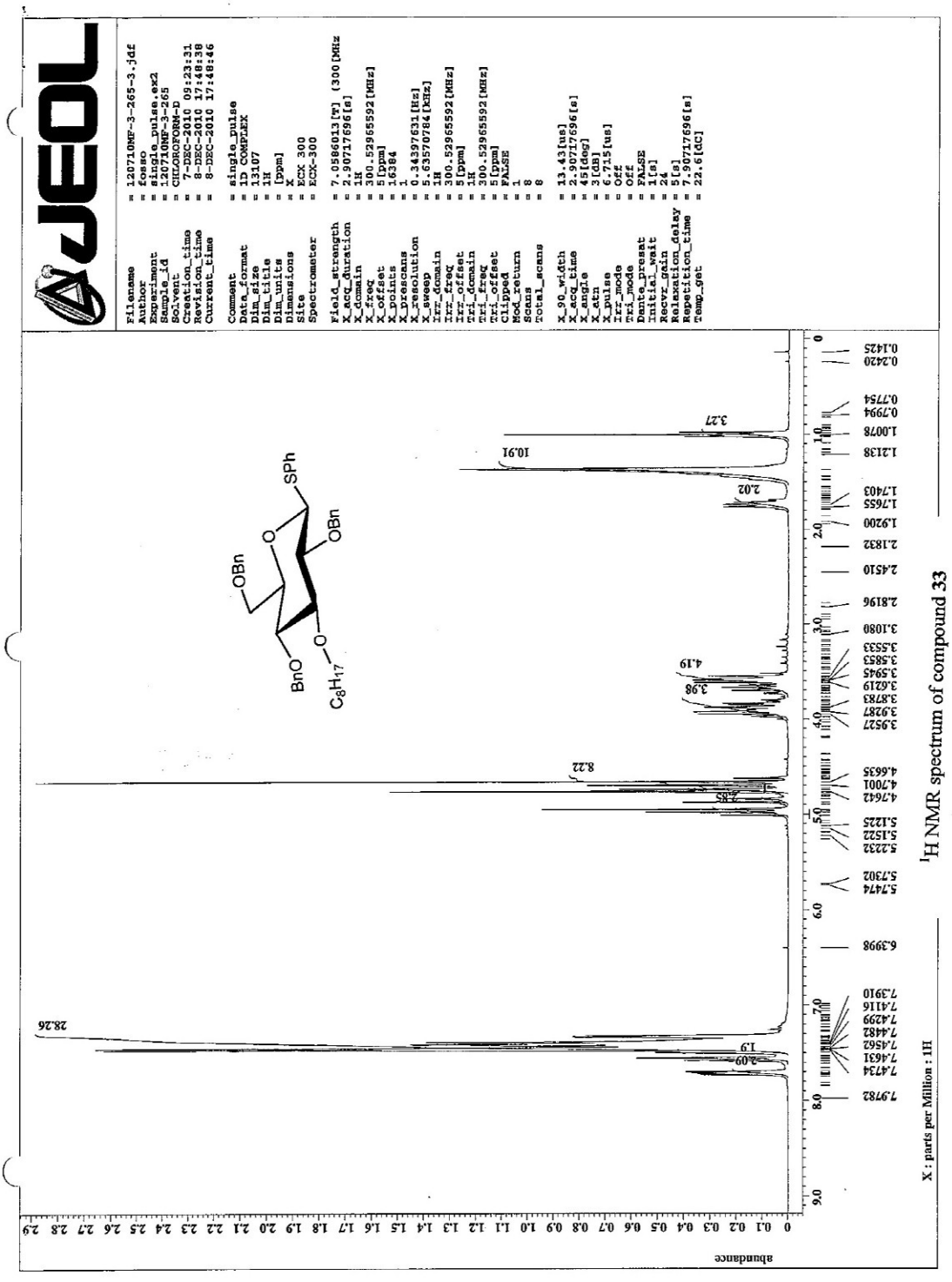
^{1}H NMR spectrum of compound **31**



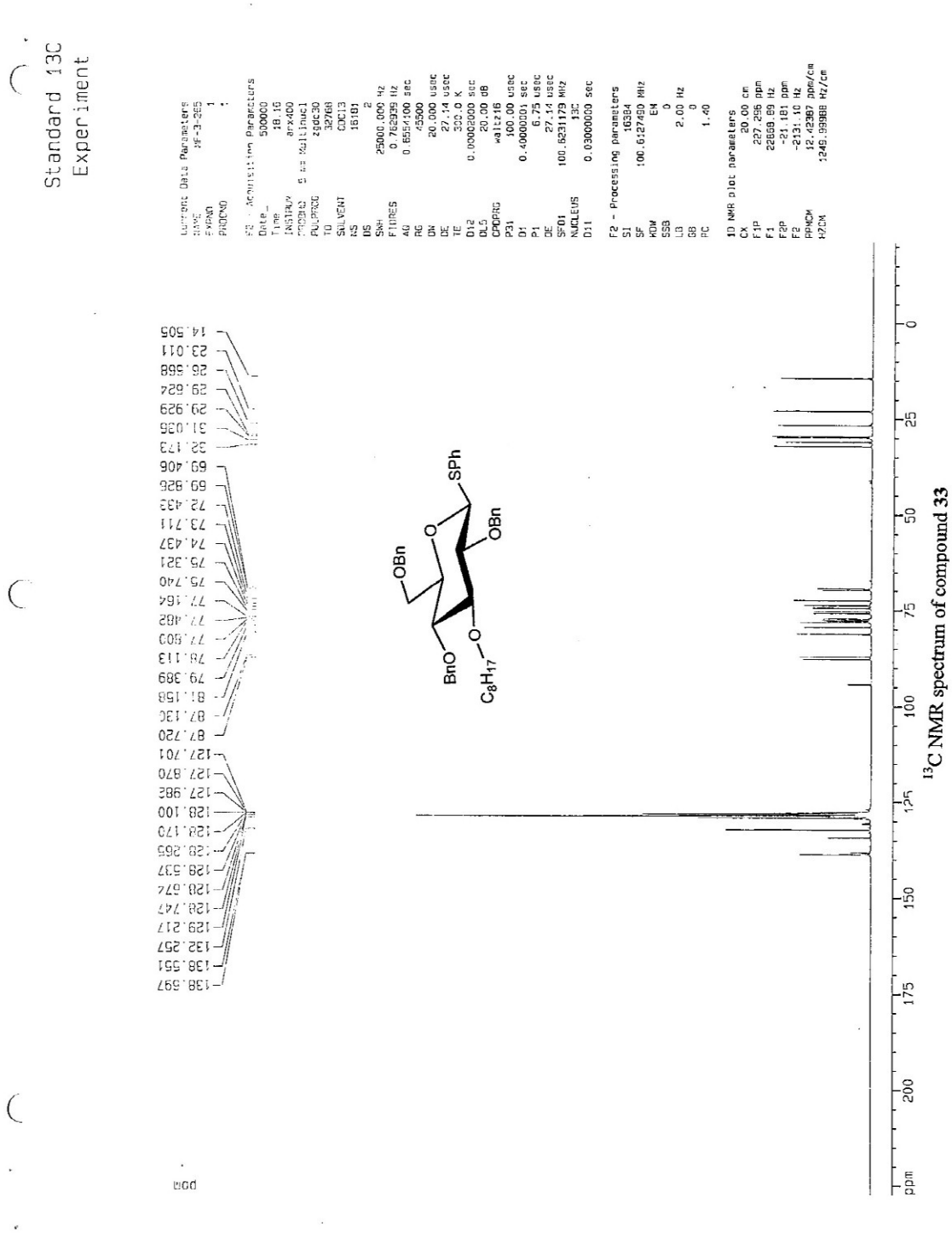
^{1}H NMR spectrum of compound **32**



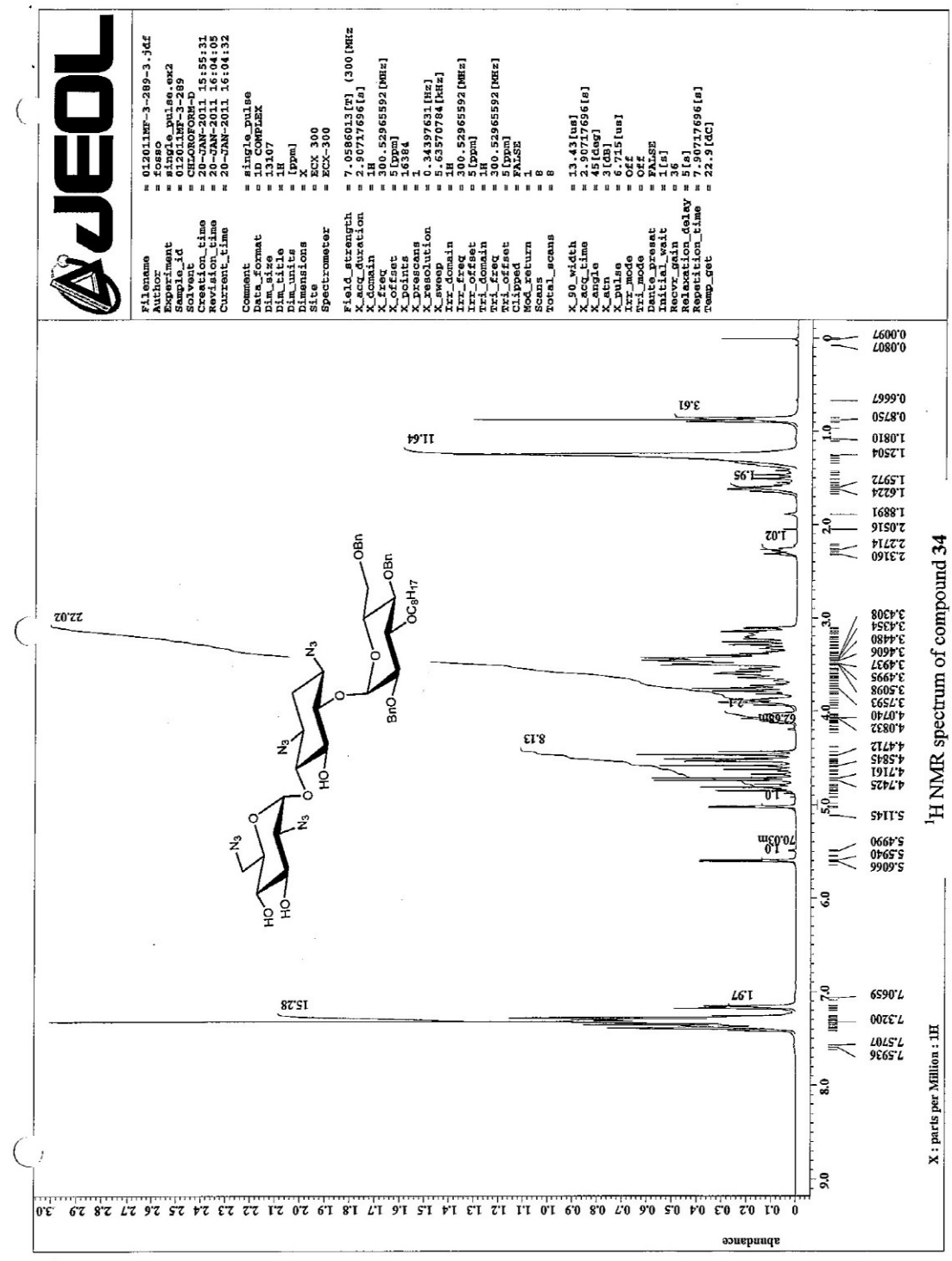
^{13}C NMR spectrum of compound **32**

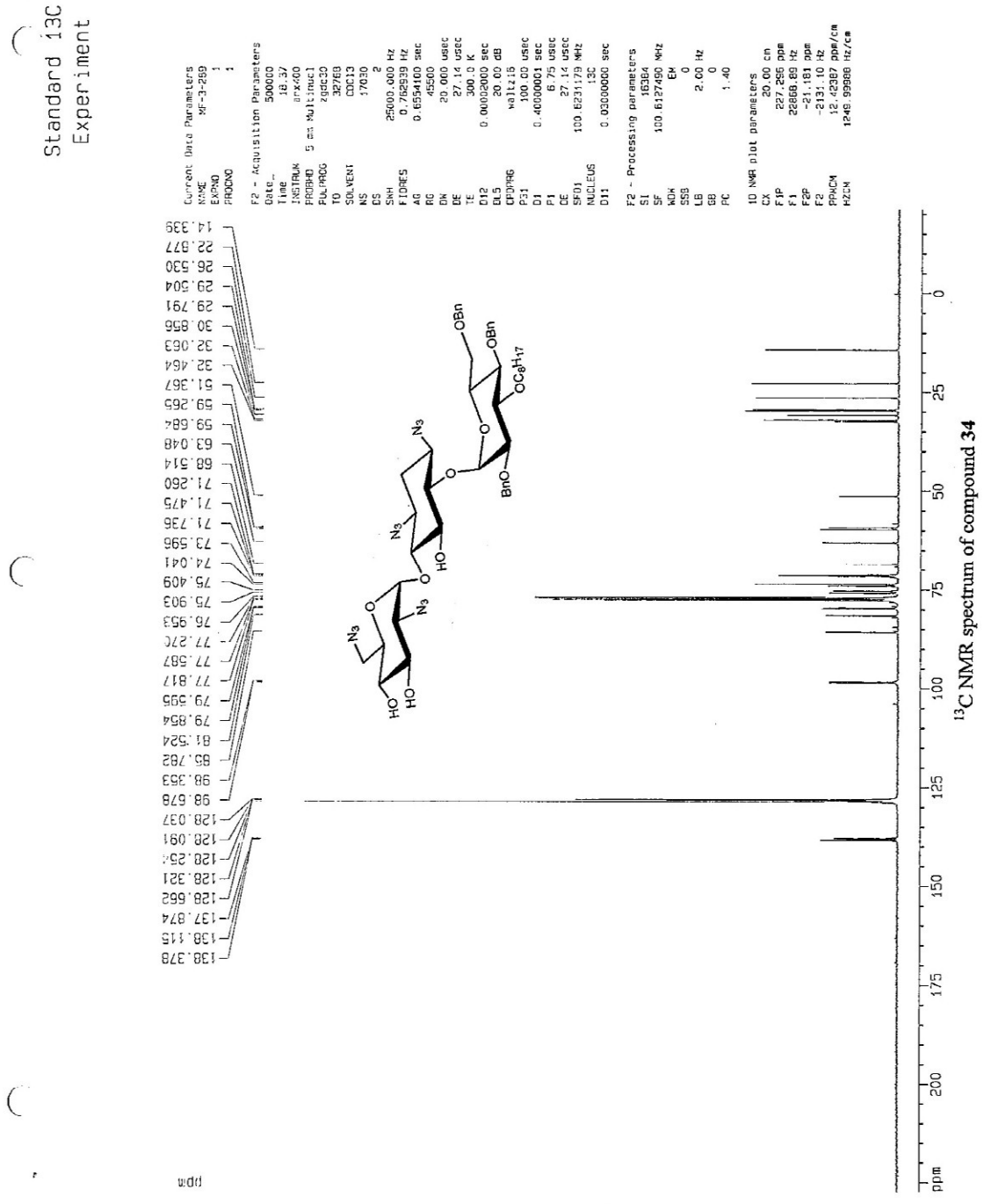


^{1}H NMR spectrum of compound **33**

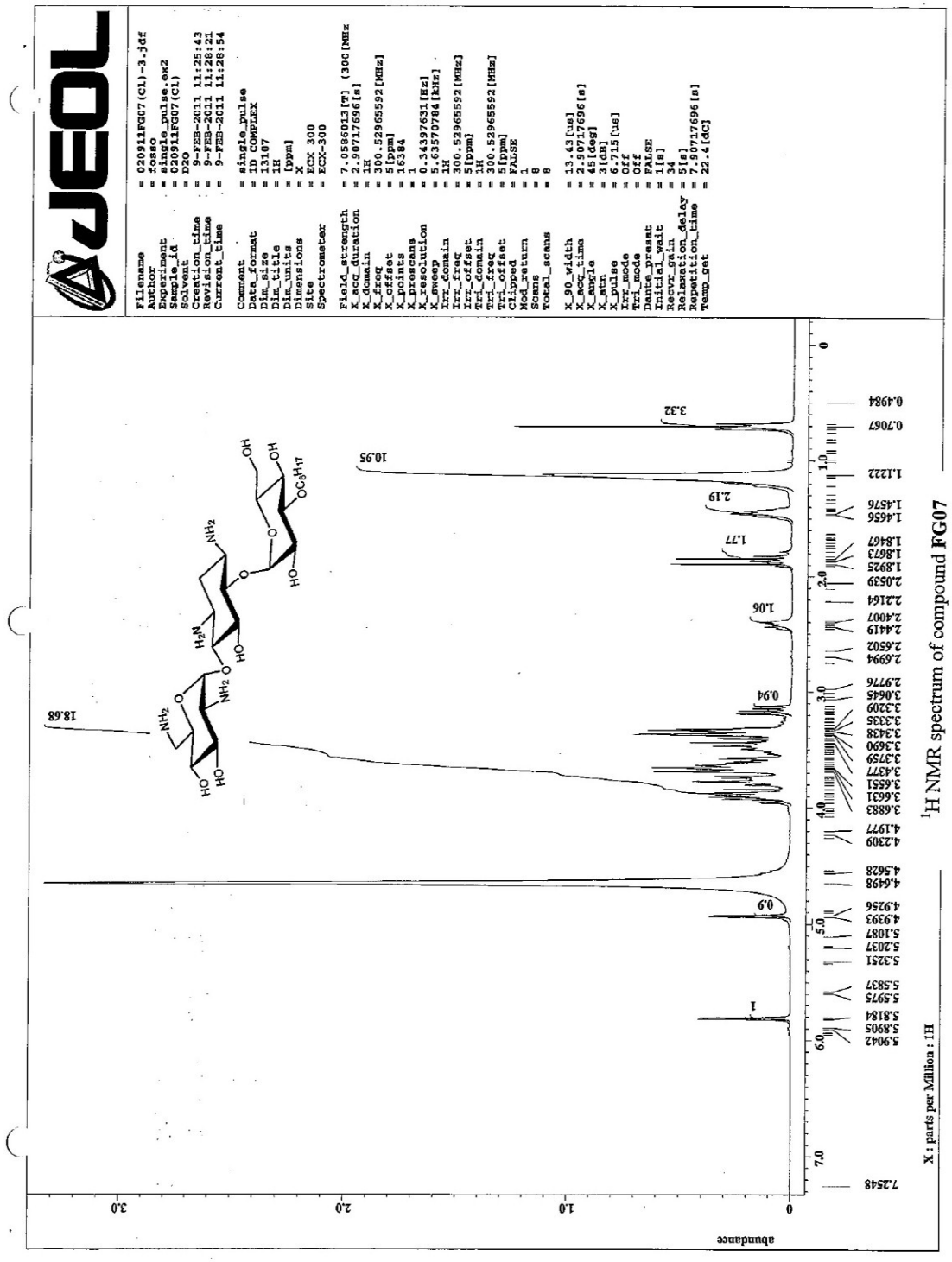


^{13}C NMR spectrum of compound **33**

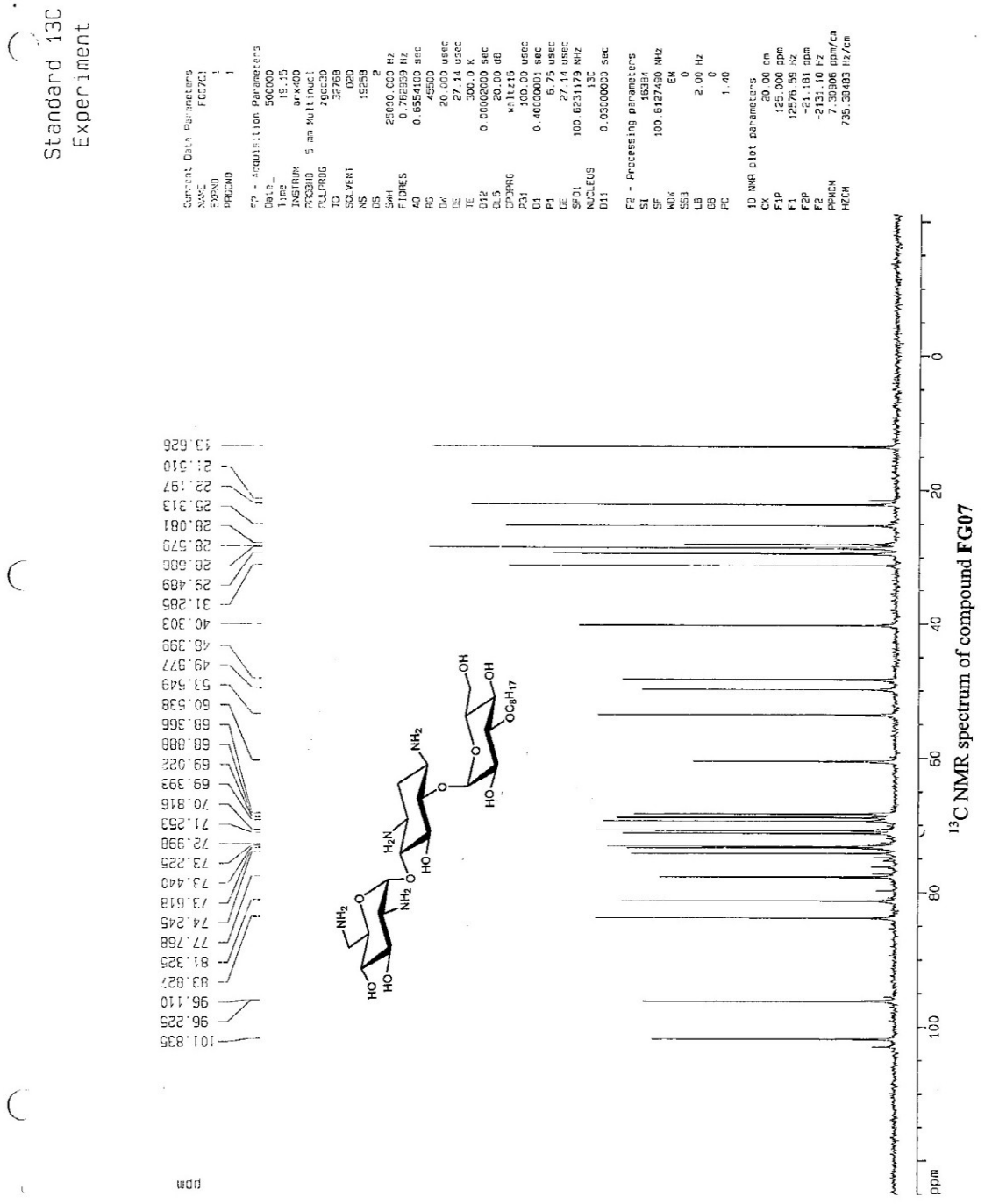

JEOL
Filename = 012011MF-3-289-3.jdf
Author = fosso
Experiment = single_pulse.ex2
Sample_id = 012011MF-3-289
Solvent = CHLOROFORM-D
Creation_time = 20-JAN-2011 15:55:31
Revision_time = 20-JAN-2011 16:04:05
Current_time = 20-JAN-2011 16:04:32
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECX 300
Spectrometer = ECX-300
Field_strength = 7.05860131[T] (300[MHz
X_acq_duration = 2.90717696[s]
X_domain = 1H
X_freq = 300.52965592[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.34397631[Hz]
X_sweep = 5.63570784[kHz]
Irr_domain = 1H
Irr_freq = 300.52965592[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 300.52965592[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 8
Total_scans = 8
X_90_width = 13.43[us]
X_acq_time = 2.90717696[s]
X_angle = 45[deg]
X_atn = 3[dB]
X_pulse = 6.715[us]
Irr_mode = Off
Tri_mode = Off
Dante_preset = FALSE
Initial_wait = 1[s]
Recyc_gain = 36
Relaxation_delay = 5[s]
Repetition_time = 7.90717696[s]
Temp_get = 22.9[dC]
22.02
15.28
11.64
8.13
3.61
2.21
1.97
1.95
1.02
1.0
70.03m
92.08m
abundance
X : parts per Million : 1H
^{1}H NMR spectrum of compound **34**



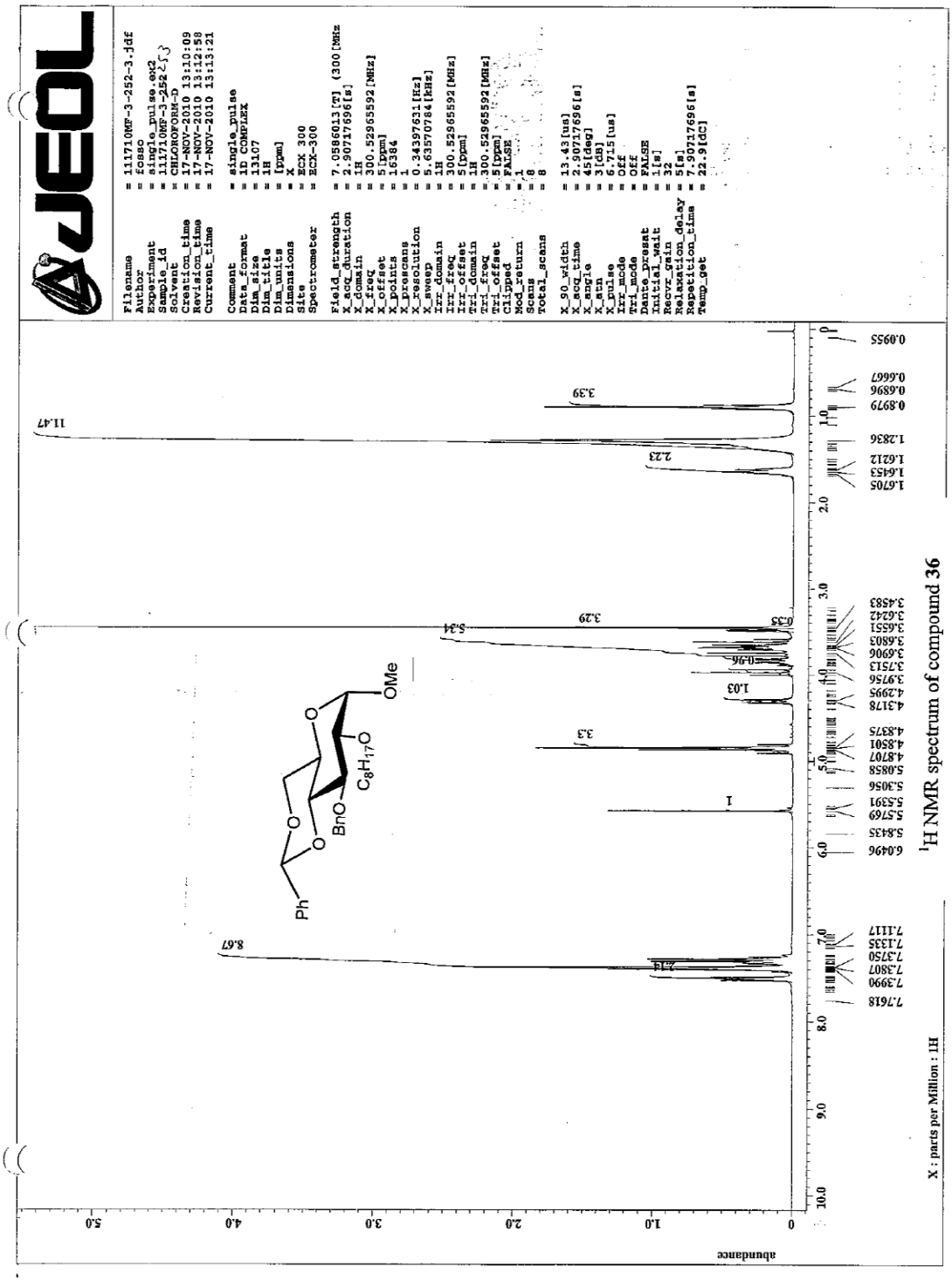
^{13}C NMR spectrum of compound **34**



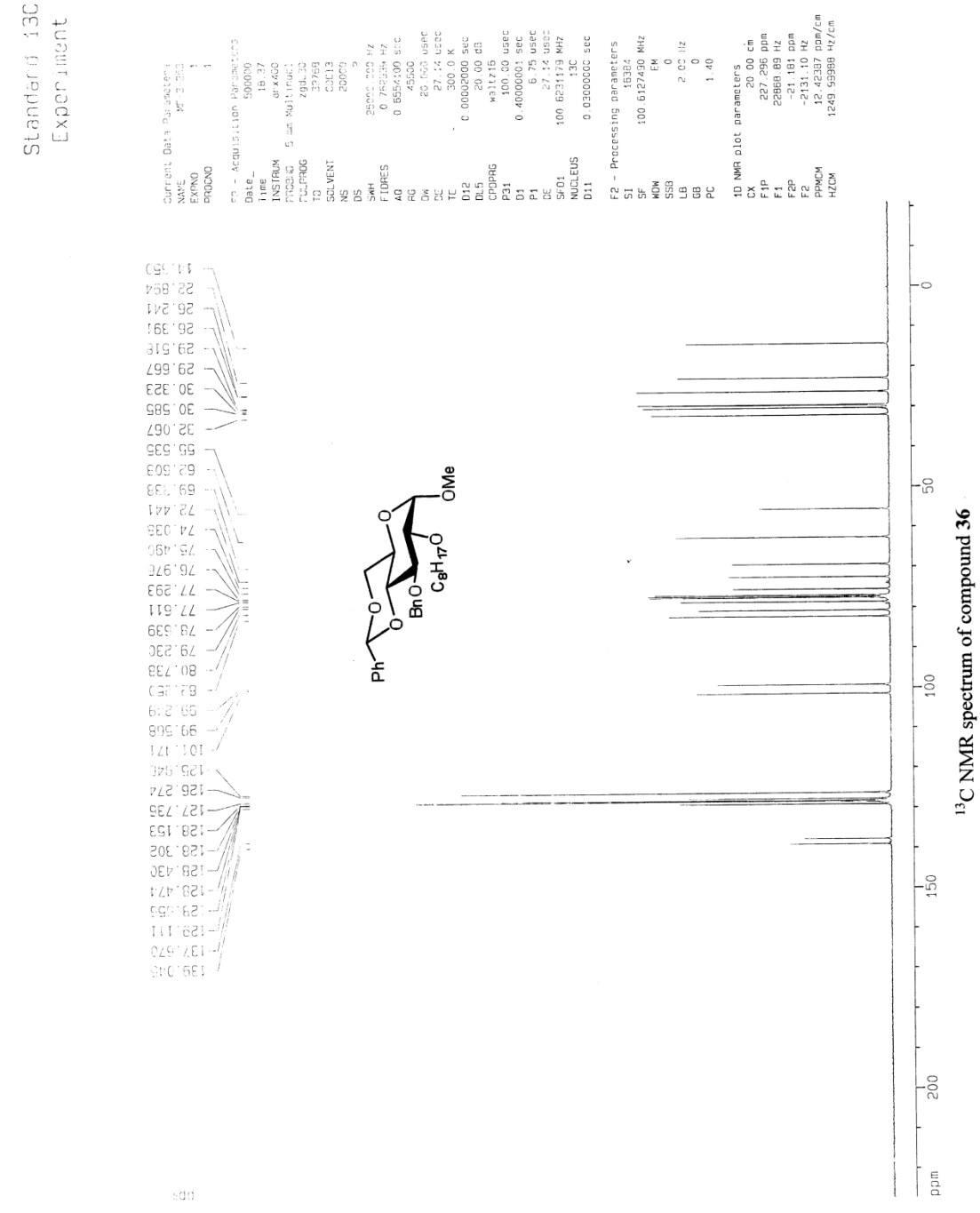
^{1}H NMR spectrum of compound **FG07**



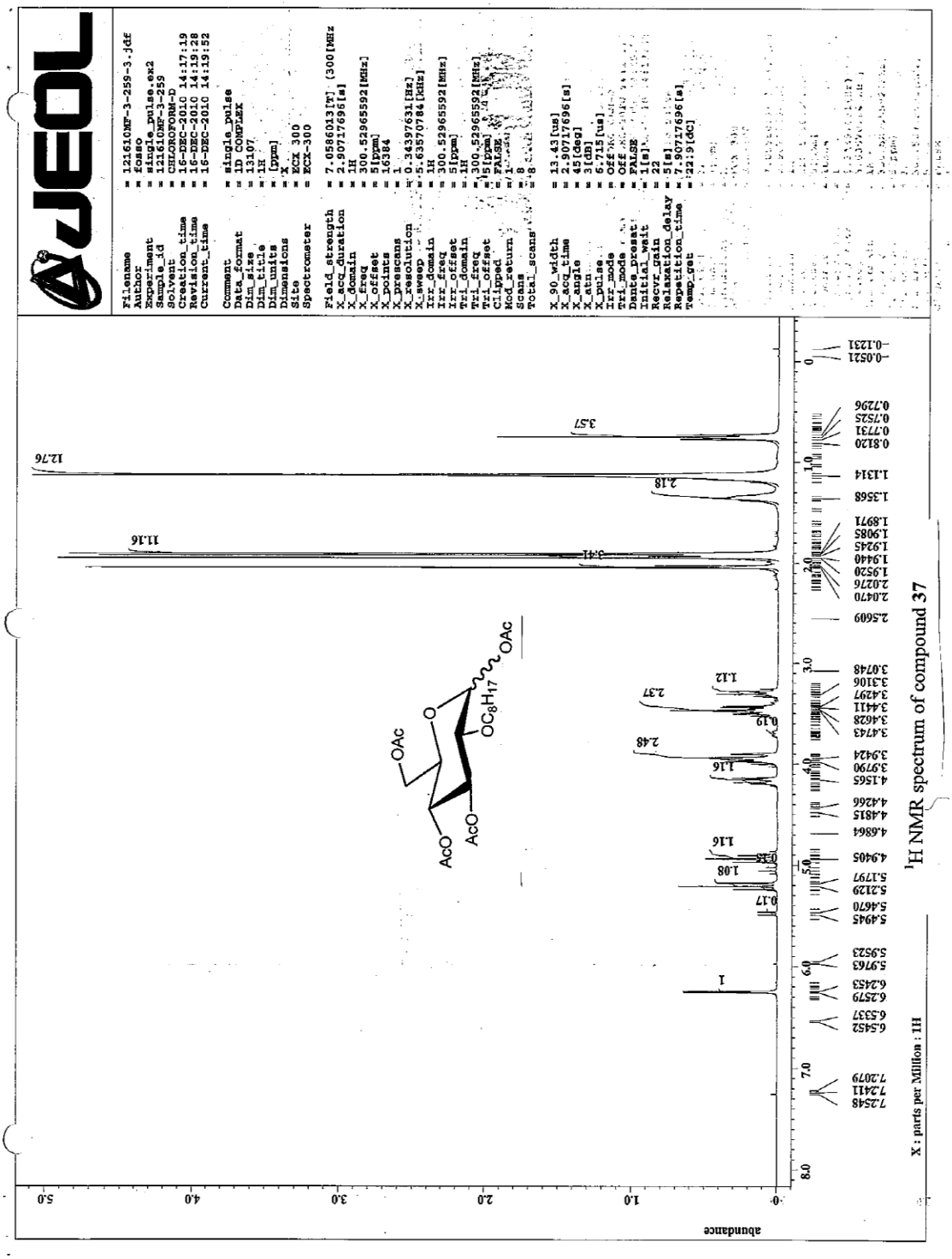
^{13}C NMR spectrum of compound **FG07**



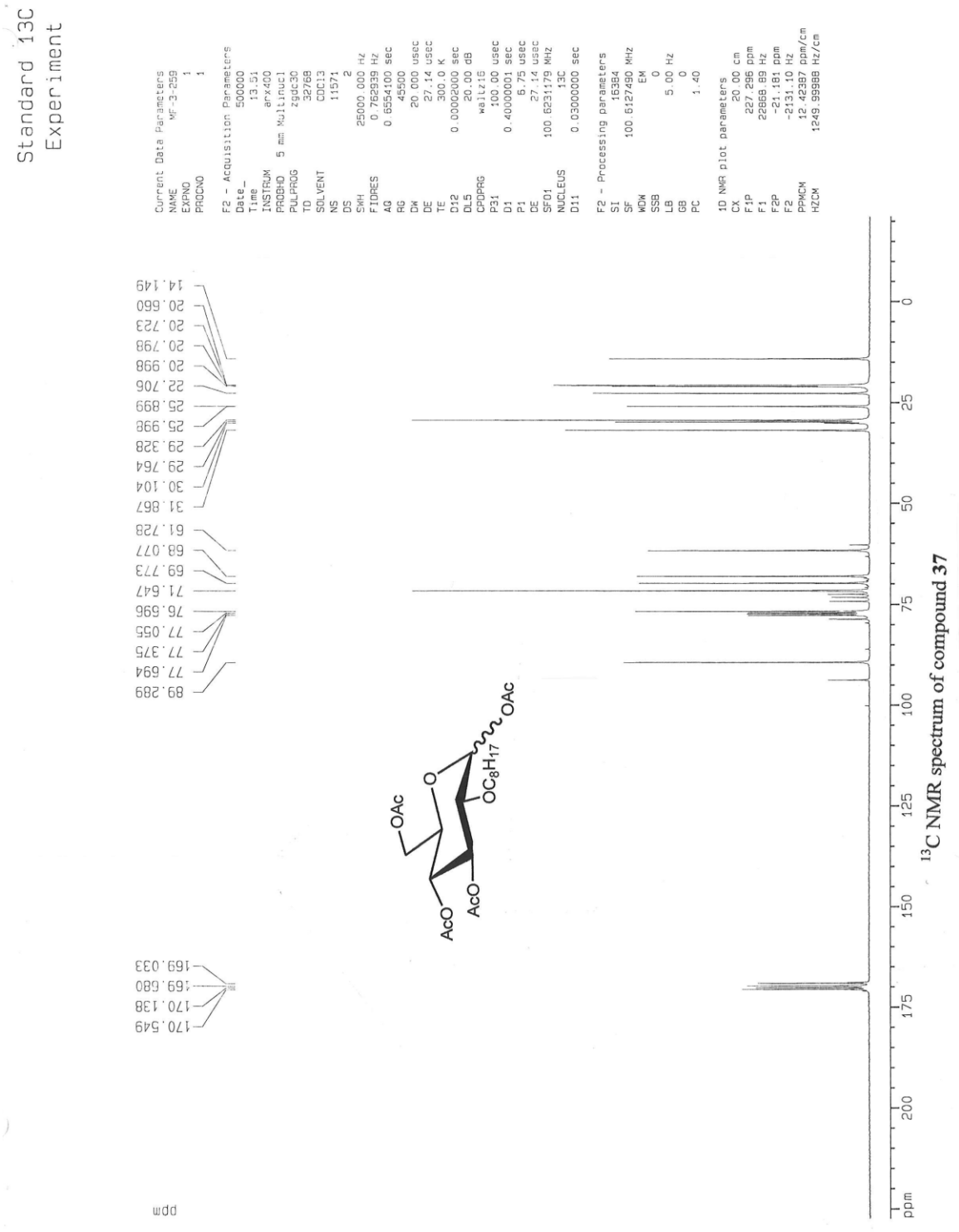
^{1}H NMR spectrum of compound **36**



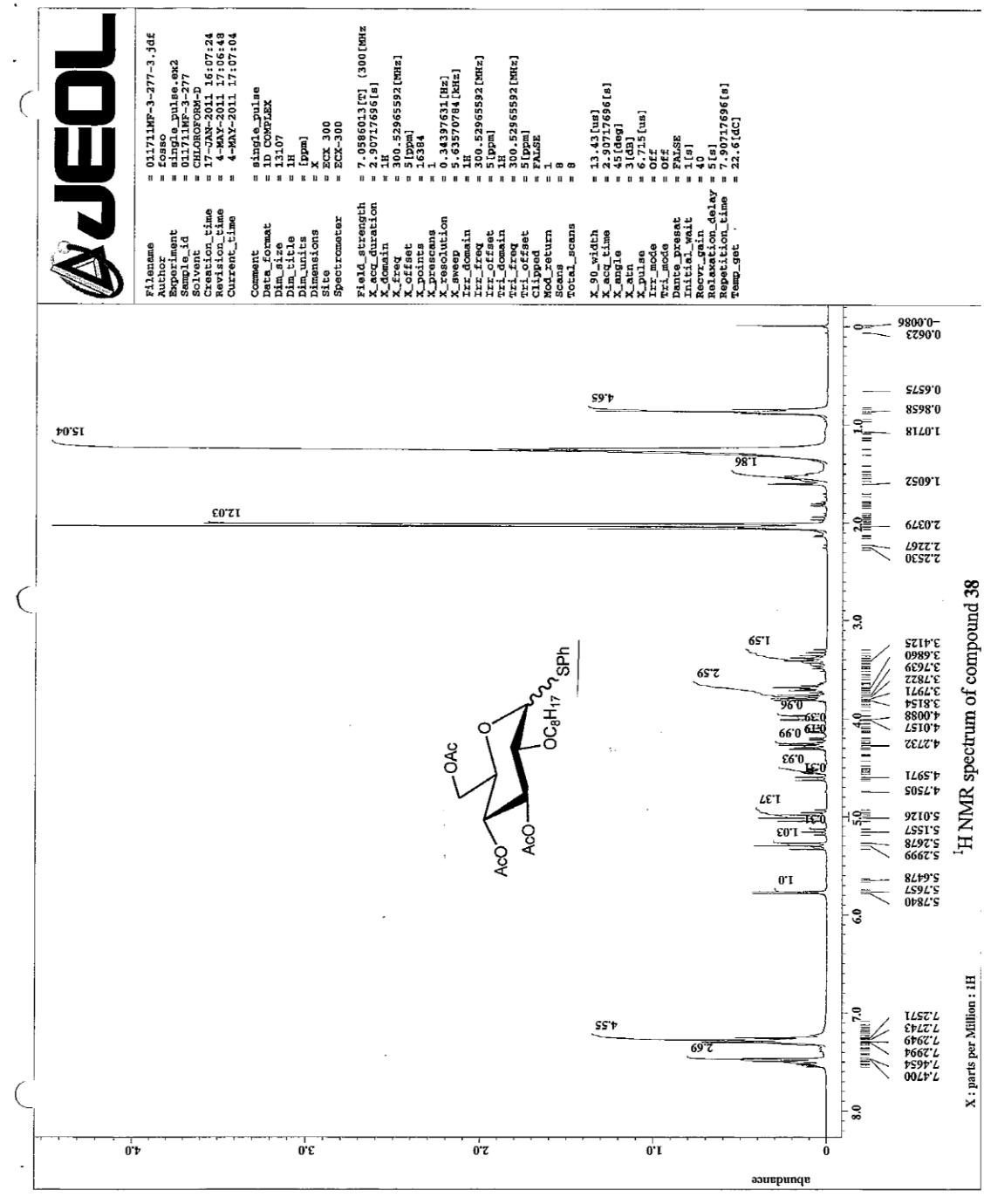
^{13}C NMR spectrum of compound **36**

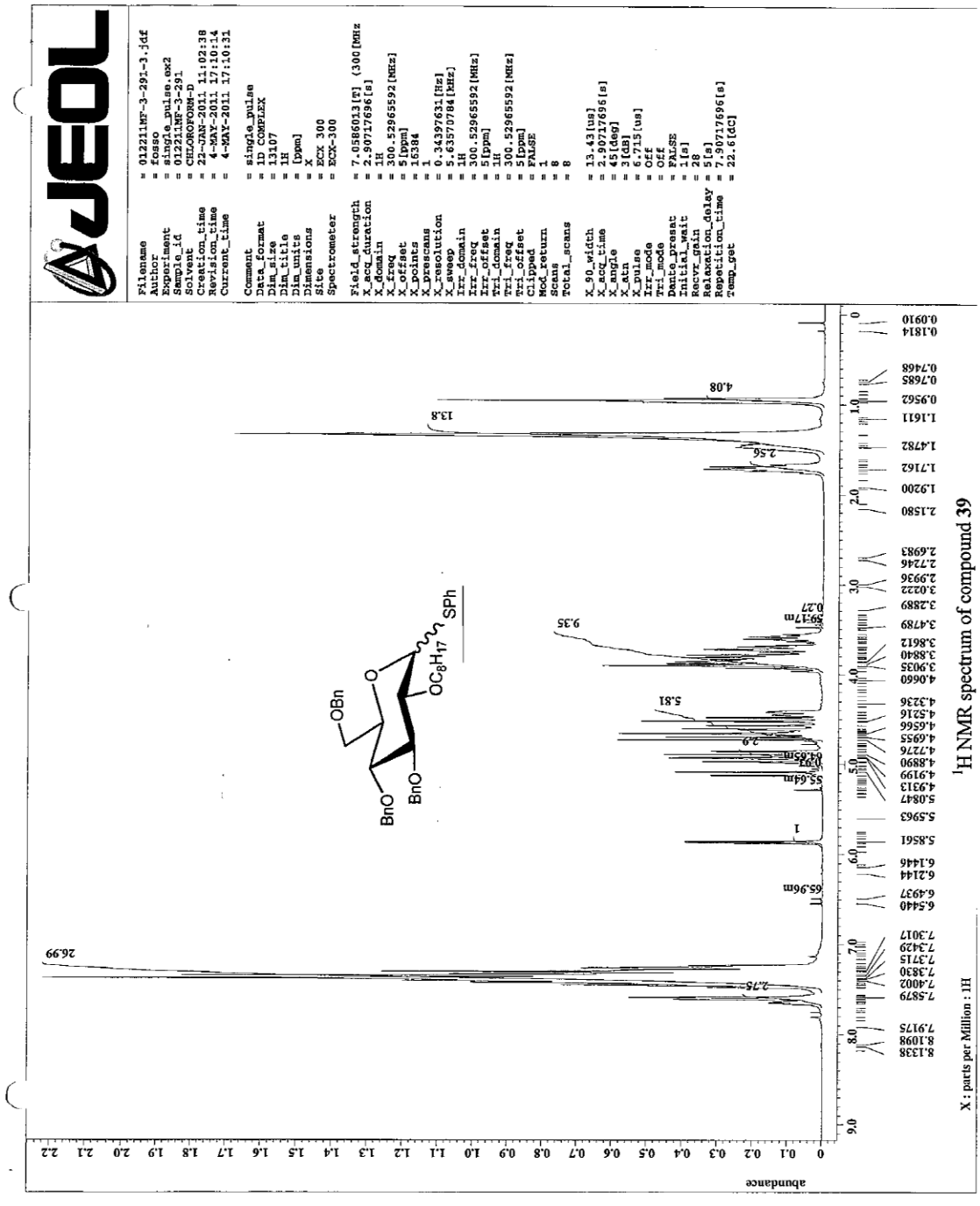


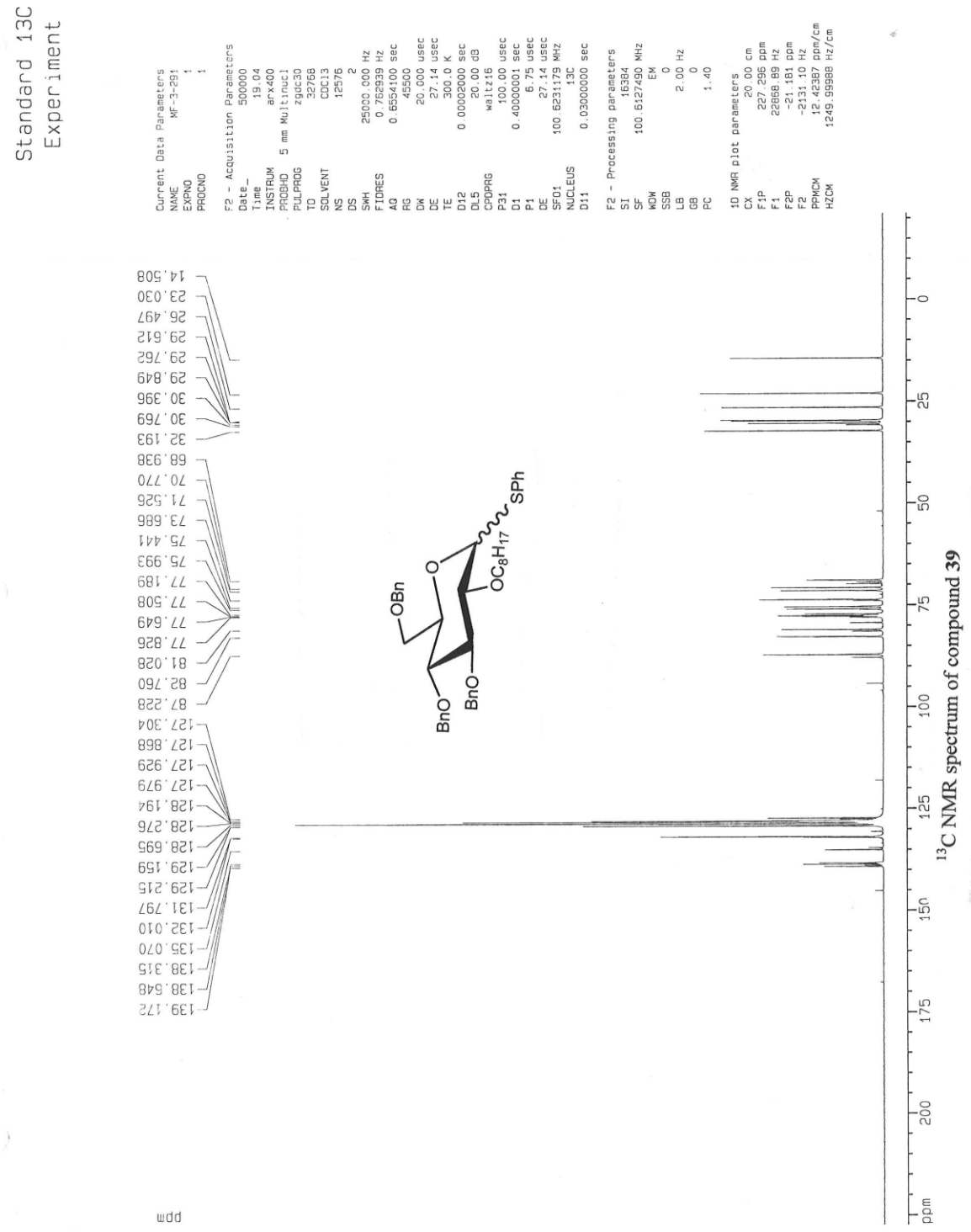
^{1}H NMR spectrum of compound **37**



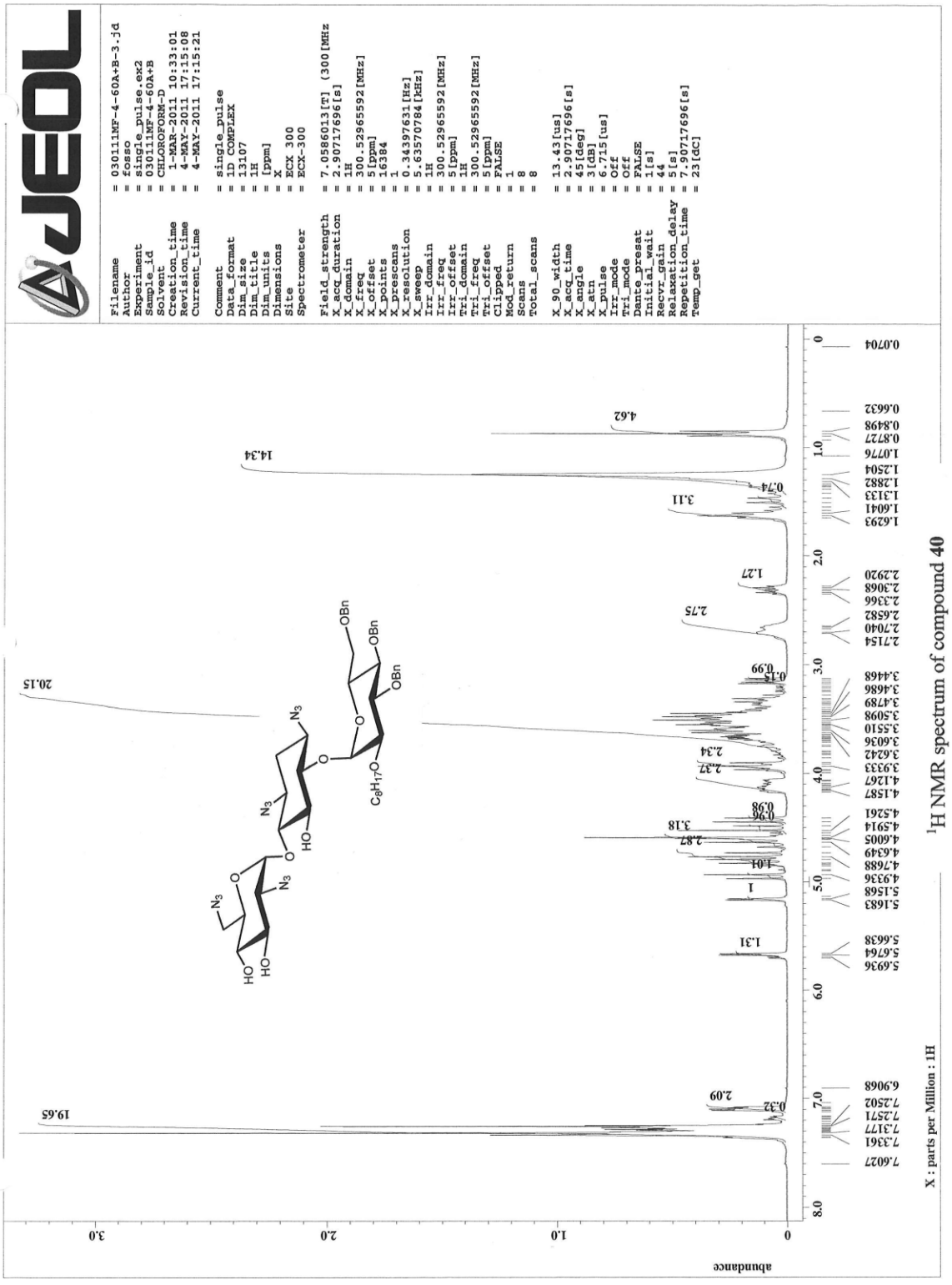
^{13}C NMR spectrum of compound **37**

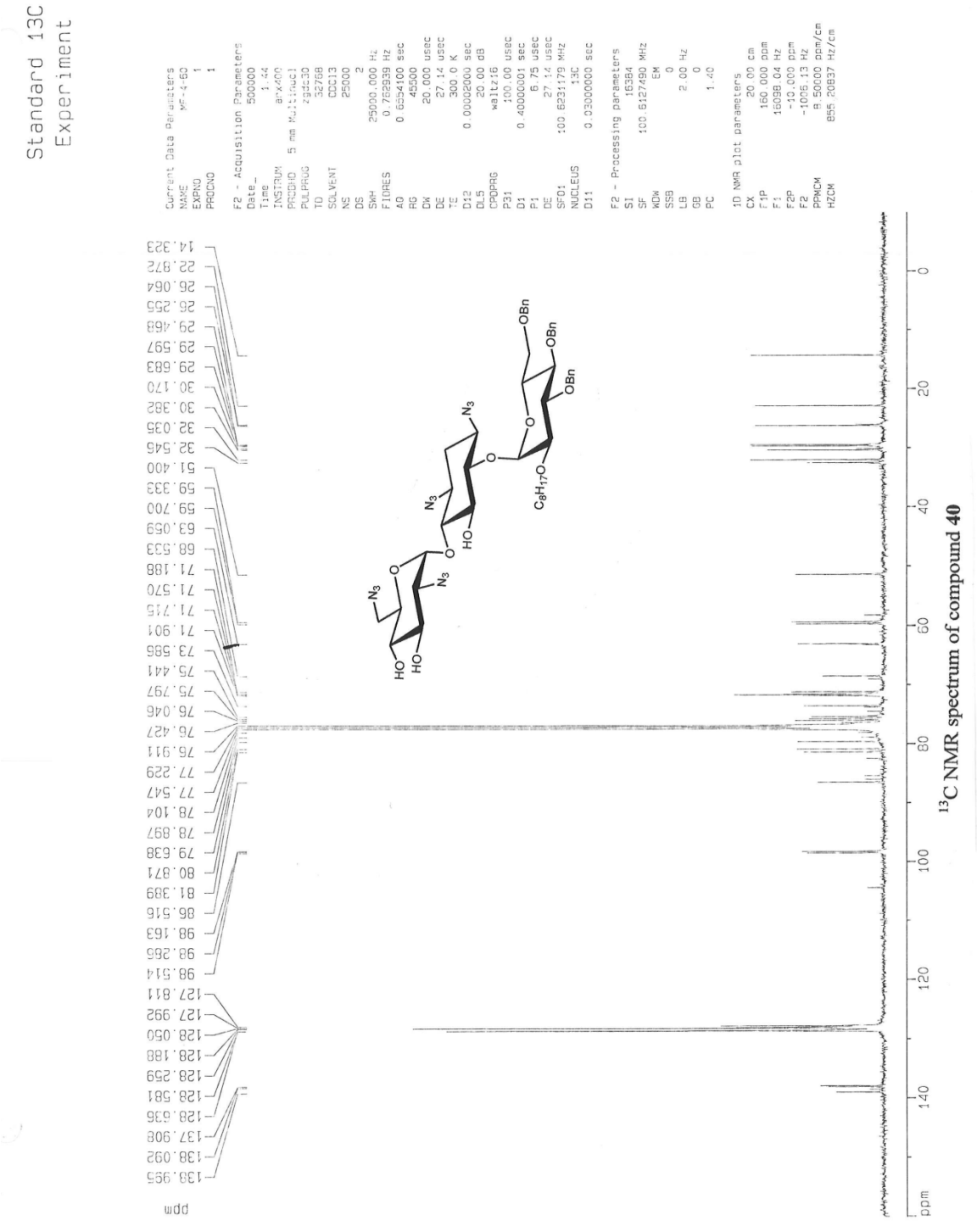

JEOL
Filename = 011711MF-3-277-3.jdf
Author = fosso
Experiment = single_pulse.ex2
Sample_id = 011711MF-3-277
Solvent = CHLOROFORM-D
Creation_time = 17-JAN-2011 16:07:24
Revision_time = 4-MAY-2011 17:06:48
Current_time = 4-MAY-2011 17:07:04
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
File = ECX 300
Spectrometer = ECX-300
Field_strength = 7.0586013[T] (300[MHz
X_acq_duration = 2.90717696[s]
X_domain = 1H
X_freq = 300.52965592[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.34397631[Hz]
X_sweep = 5.63570784[kHz]
Irr_domain = 1H
Irr_freq = 300.52965592[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 300.52965592[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 8
Total_scans = 8
X_90_width = 13.43[us]
X_acq_time = 2.90717696[s]
X_angle = 45[deg]
X_atn = 3[dB]
X_pulse = 6.715[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 40
Relaxation_delay = 5[s]
Repetition_time = 7.90717696[s]
Temp_get = 22.6[dC]
abundance
X : parts per Million : 1H
OAc
AcO
AcO
OC8H17
SPh
^{1}H NMR spectrum of compound 38


JEOL
Filename = 012211MF-3-291-3.jdf
Author = fosso
Experiment = single_pulse.ex2
Sample_id = 012211MF-3-291
Solvent = CHLOROFORM-D
Creation_time = 22-JAN-2011 11:02:38
Revision_time = 4-MAY-2011 17:10:14
Current_time = 4-MAY-2011 17:10:31
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECX 300
Spectrometer = ECX-300
Field_strength = 7.0586013[T] (300[MHz
X_acq_duration = 2.90717696[s]
X_domain = 1H
X_freq = 300.52965592[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.34397631[Hz]
X_sweep = 5.63570784[kHz]
Irr_domain = 1H
Irr_freq = 300.52965592[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 300.52965592[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 8
Total_scans = 8
X_90_width = 13.43[us]
X_acq_time = 2.90717696[s]
X_angle = 45[deg]
X_atn = 6.71[dB]
X_pulse = 6.715[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recyc_gain = 28
Relaxation_delay = 5[s]
Repetition_time = 7.90717696[s]
Temp_get = 22.6[dC]
OBn
BnO
BnO
O
OC_8H_{17}
SPh
26.99
2.75
65.96m
1
55.64m
2.9
5.81
9.35
2.56
13.8
4.08
abundance
X : parts per Million : 1H
^{1}H NMR spectrum of compound 39

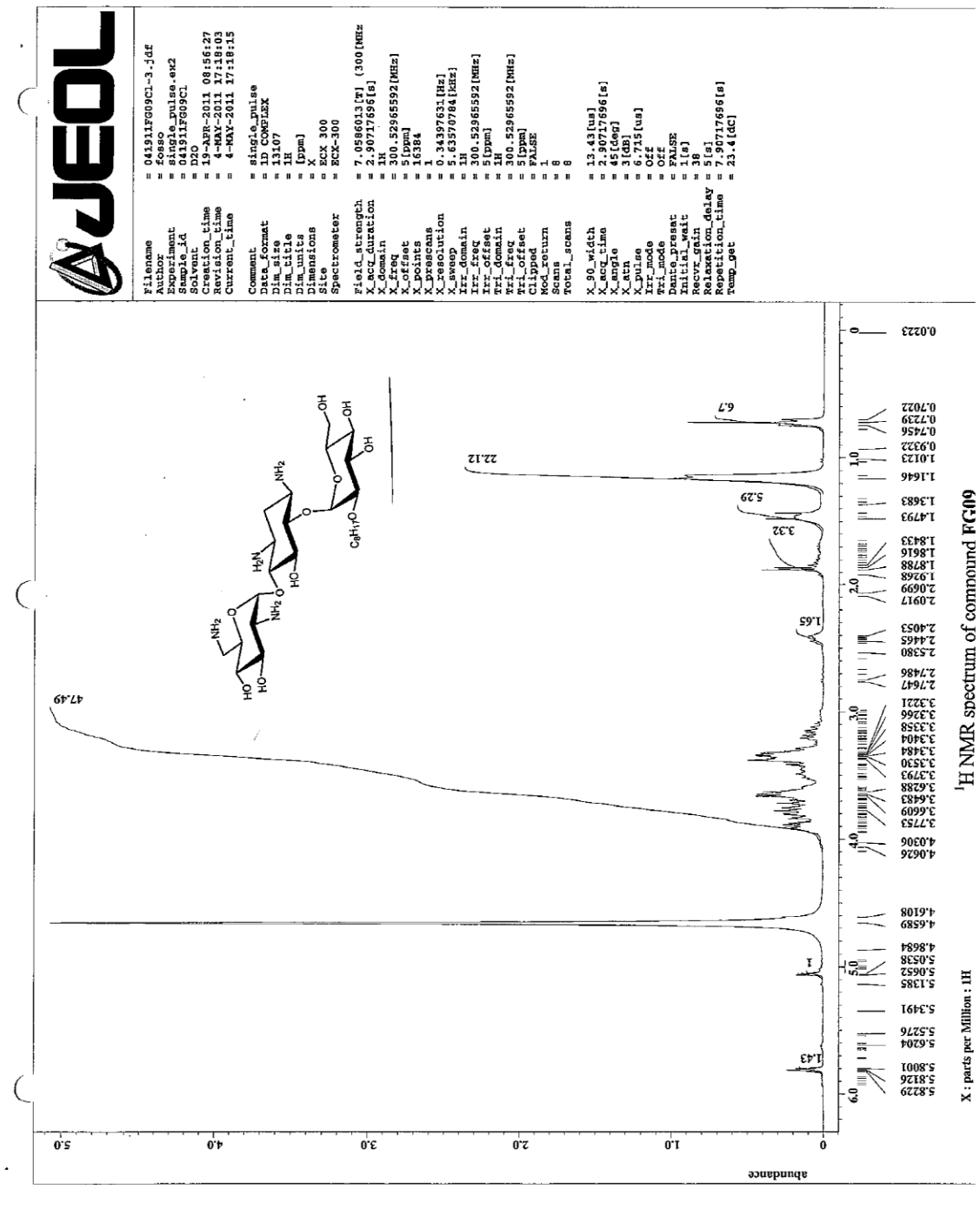


^{13}C NMR spectrum of compound **39**


JEOL
Filename = 030111MF-4-60A+B-3.jd
Author = fosso
Experiment = single_pulse.ex2
Sample_id = 030111MF-4-60A+B
Solvent = CHLOROFORM-D
Creation_time = 1-MAR-2011 10:33:01
Revision_time = 4-MAY-2011 17:15:08
Current_time = 4-MAY-2011 17:15:21
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = 1H
Dim_units = [ppm]
Dimensions = X
Site = ECX 300
Spectrometer = ECX-300
Field_strength = 7.0586013[T] (300[MHz
X_acq_duration = 2.90717696[s]
X_domain = 1H
X_freq = 300.52965592[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.34397631[Hz]
X_sweep = 5.63570784[kHz]
Irr_domain = 1H
Irr_freq = 300.52965592[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 300.52965592[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 8
Total_scans = 8
X_90_width = 13.43[us]
X_acq_time = 2.90717696[s]
X_angle = 45[deg]
X_atn = 3[dB]
X_pulse = 6.715[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 44
Relaxation_delay = 5[s]
Repetition_time = 7.90717696[s]
Temp_get = 23[dC]
abundance
X : parts per Million : 1H
19.65
20.15
14.34
4.62
3.11
2.75
2.37
2.34
2.09
1.31
1.27
1.01
0.99
0.98
0.96
0.74
0.32
3.18
2.87
0.75
OBn
OBn
OBn
N3
N3
N3
HO
HO
HO
O
O
O
C8H17O
7.6027
7.3361
7.3177
7.2571
7.2502
6.9068
5.6936
5.6764
5.6638
5.1683
5.1568
4.9336
4.7688
4.6349
4.6005
4.5914
4.5261
4.1587
4.1267
3.9333
3.6242
3.6036
3.5510
3.5098
3.4789
3.4686
3.4468
2.7154
2.7040
2.6582
2.3366
2.3068
2.2920
1.6293
1.6041
1.3133
1.2882
1.2504
1.0776
0.8727
0.8498
0.6632
0.0704
1H NMR spectrum of compound 40



^{13}C NMR spectrum of compound **40**

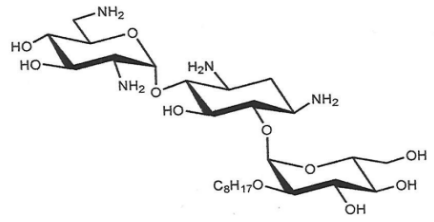


^{1}H NMR spectrum of comound **FG09**

Standard 13C
Experiment

ppm

102.560
100.294
96.383
96.215
83.887
81.293
80.096
78.697
78.017
77.849
75.186
75.300
75.225
74.354
73.641
73.291
73.193
72.729
70.792
69.586
69.494
69.403
68.406
61.018
60.741
60.651
53.654
49.796
48.640
48.398
40.264
31.264
29.335
29.274
28.729
28.663
28.615
28.548
28.155
28.013
25.210
25.140
22.182
13.597

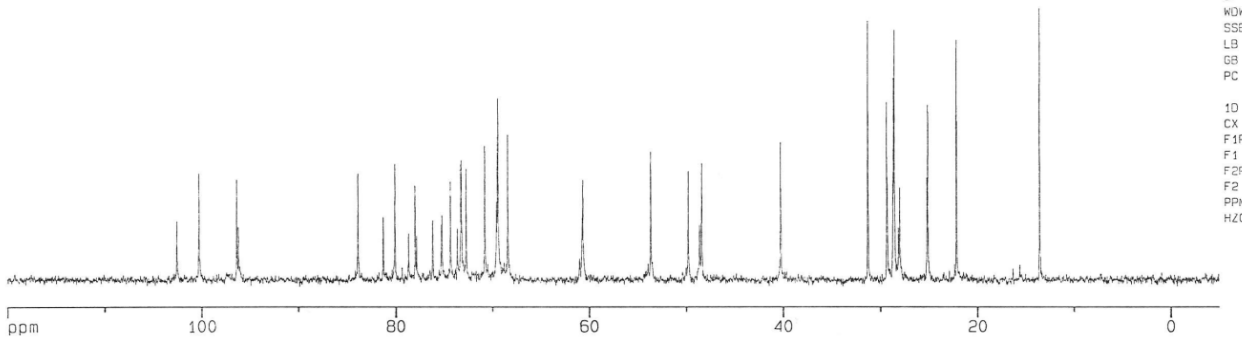


Current Data Parameters
NAME FG09C1
EXPNO 3
PROCNO 1

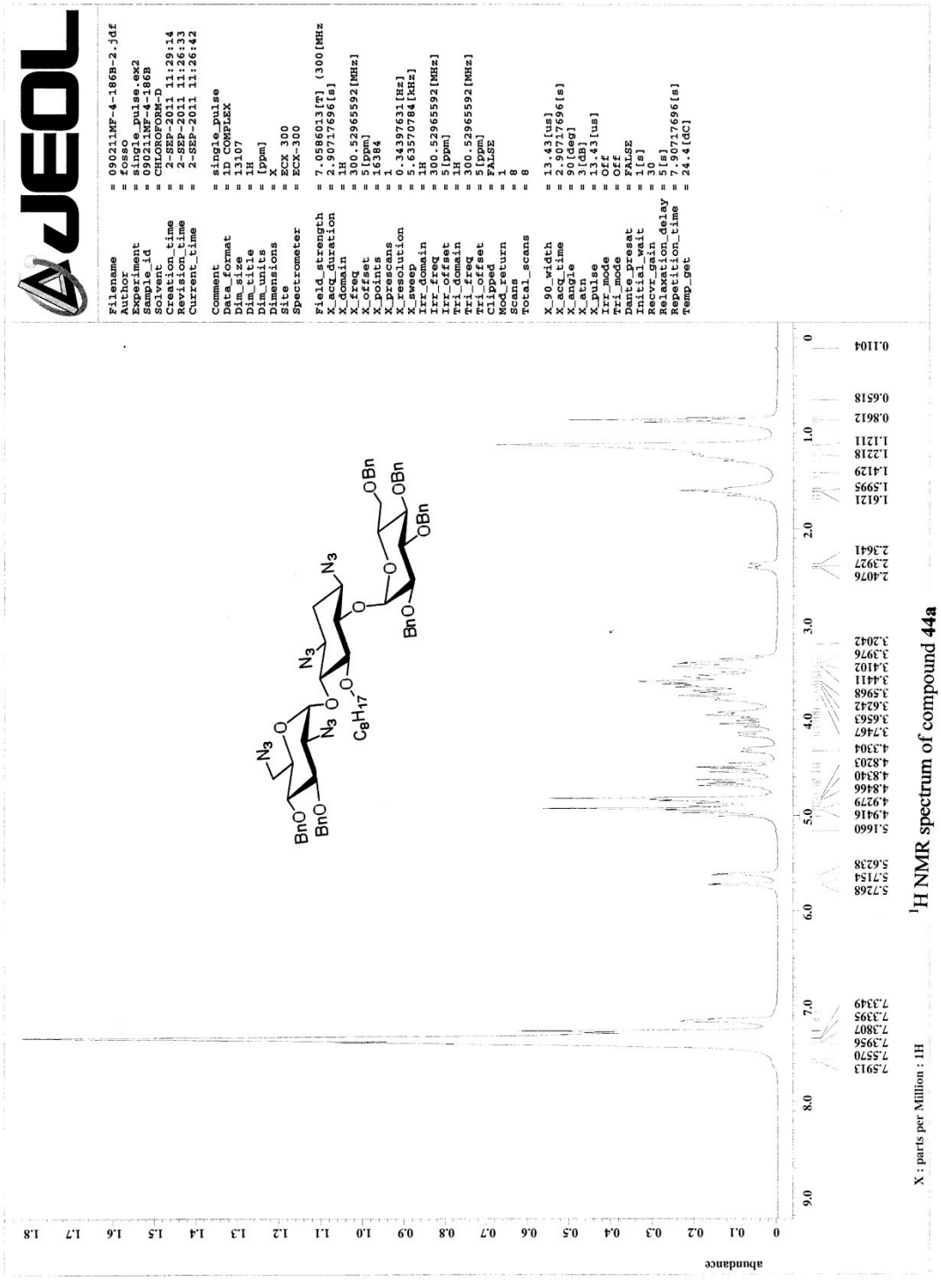
F2 - Acquisition Parameters
Date_ 500000
Time 20.58
INSTRUM drx400
PROBHD 5 mm Multinucl
PULPROG zgdc30
TD 32768
SOLVENT D2O
NS 20000
DS 2
SWH 25000.000 Hz
FIDRES 0.762939 Hz
AQ 0.6554100 sec
RG 45500
DW 20.000 usec
DE 27.14 usec
TE 300.0 K
D12 0.00002000 sec
DL5 20.00 dB
CPDPRG waltz16
P31 100.00 usec
D1 0.40000001 sec
P1 6.75 usec
DE 27.14 usec
SF01 100.6231179 MHz
NUCLEUS 13C
D11 0.03000000 sec

F2 - Processing parameters
SI 16384
SF 100.6127490 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40

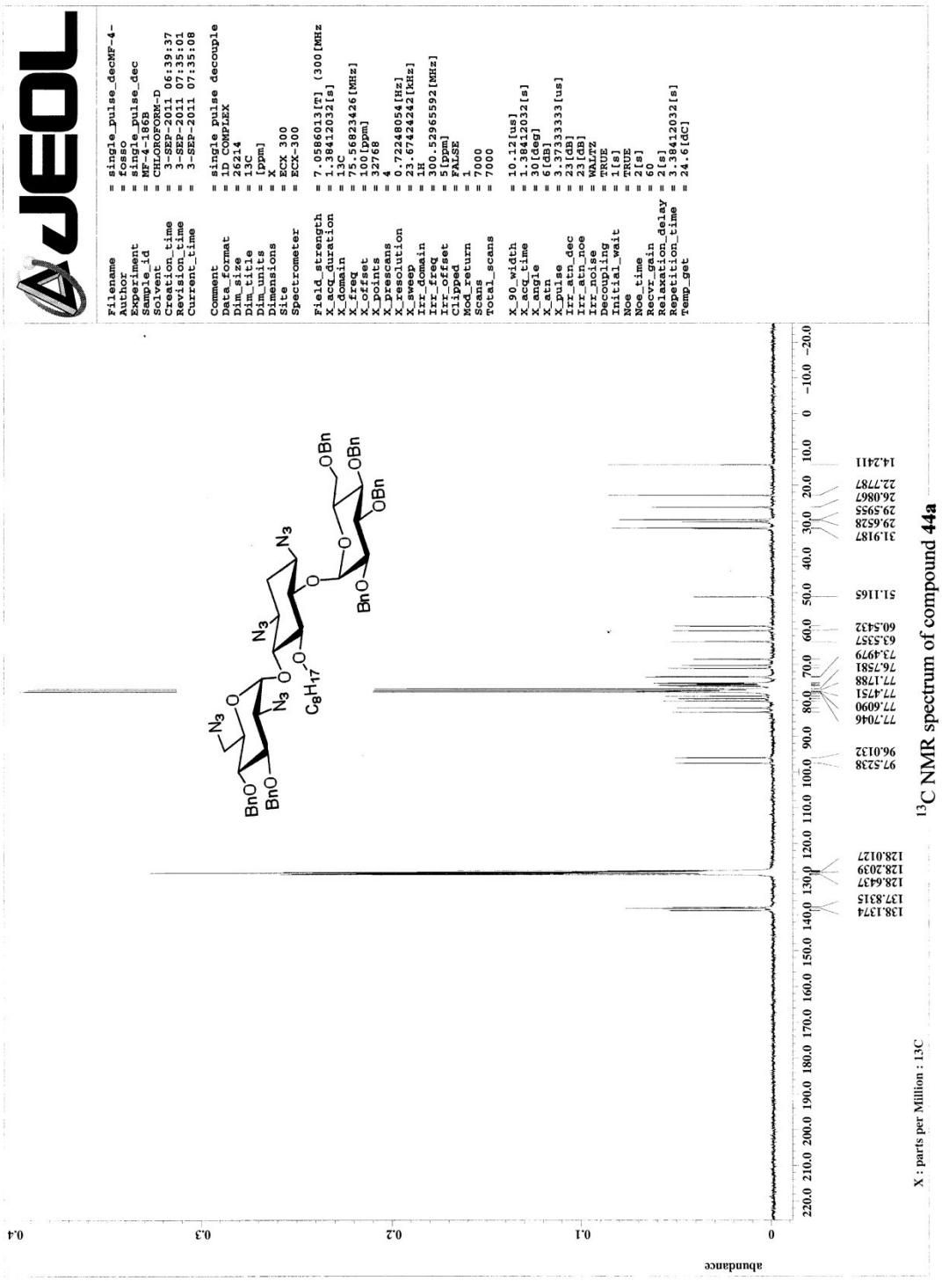
1D NMR plot parameters
CX 20.00 cm
F1P 120.000 ppm
F1 12073.53 Hz
F2P -5.000 ppm
F2 -503.06 Hz
PPMCM 6.25000 ppm/cm
HZCM 628.82965 Hz/cm



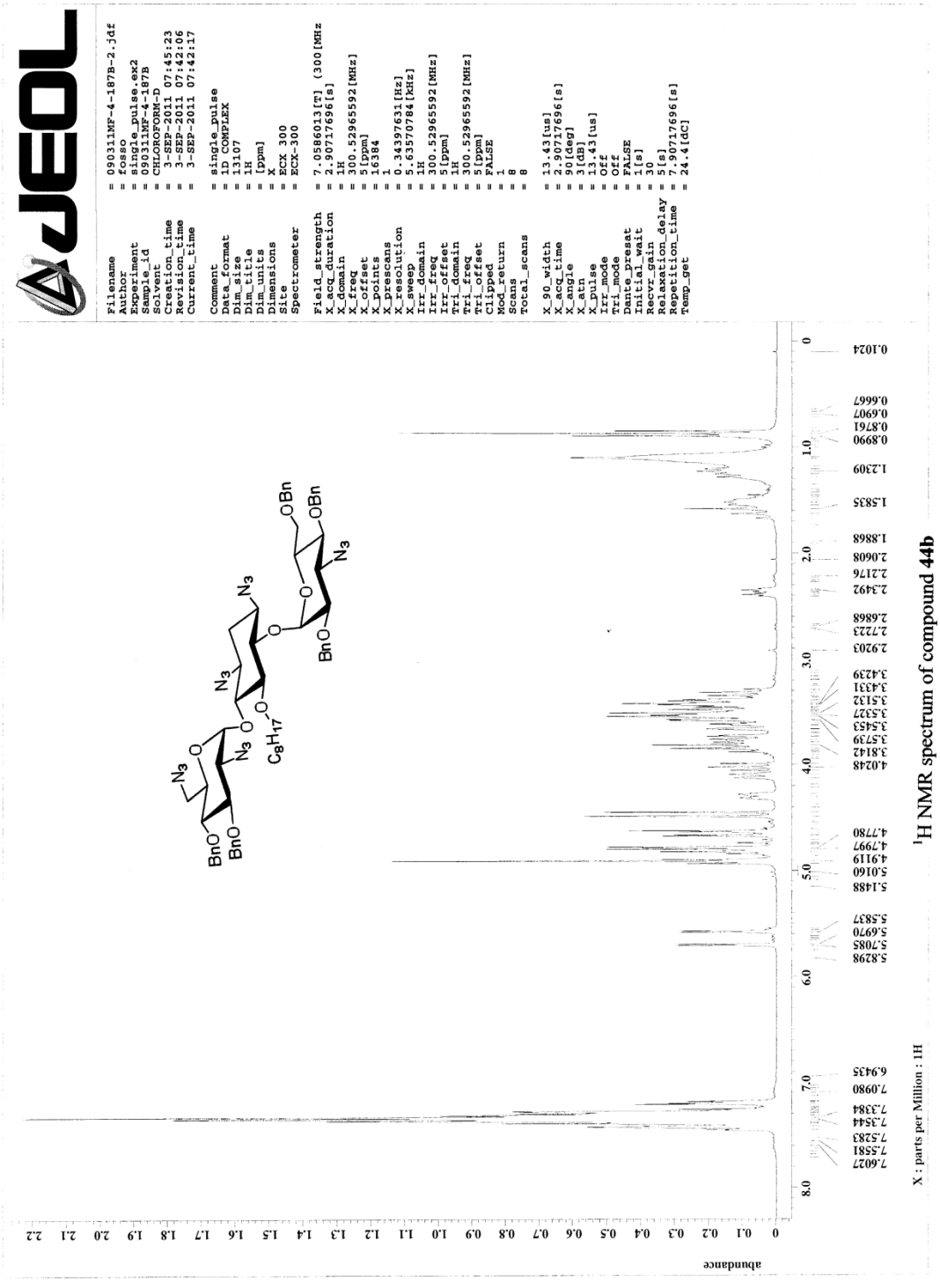
^{13}C NMR spectrum of compound **FG09**



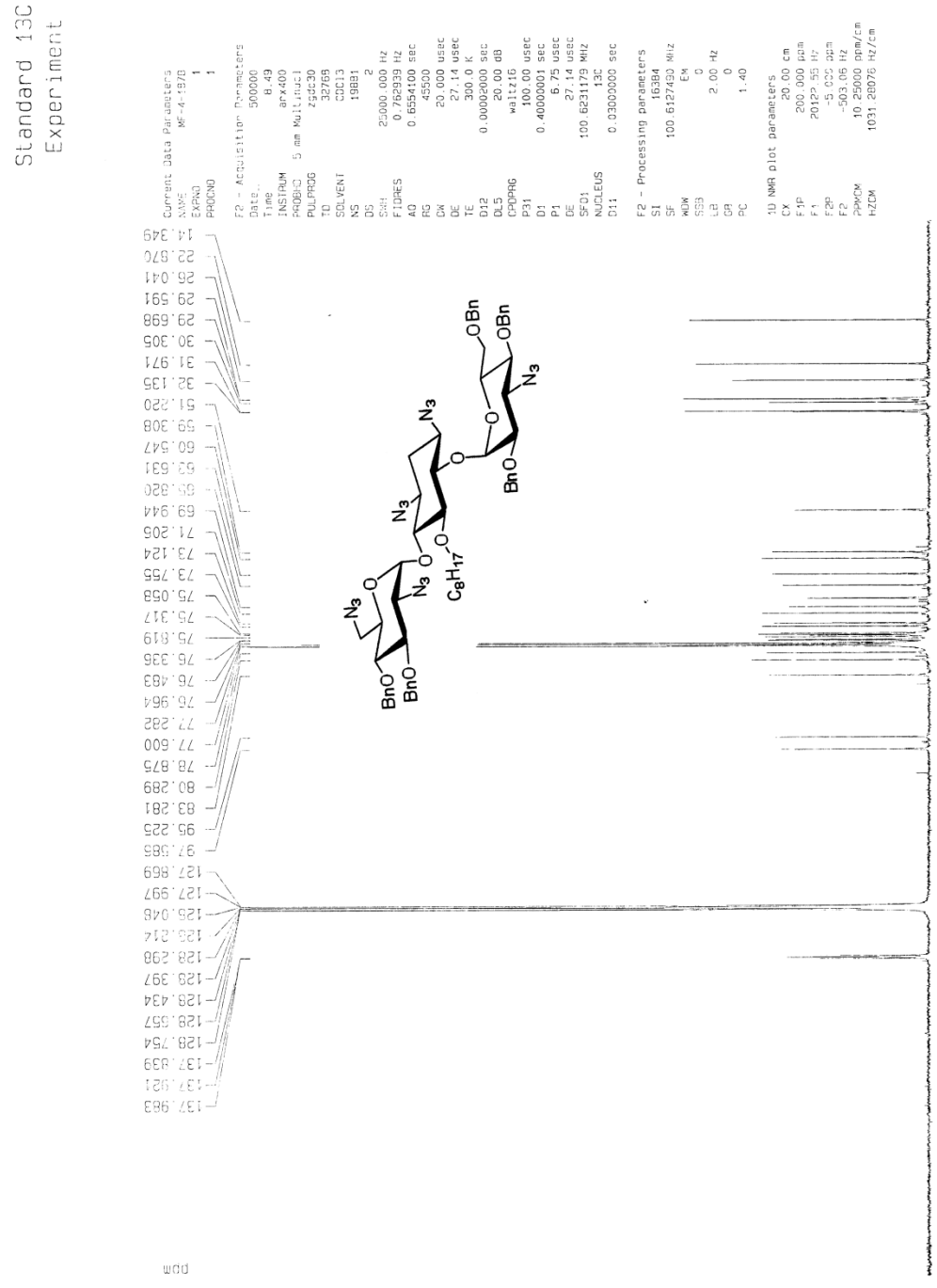
^{1}H NMR spectrum of compound **44a**



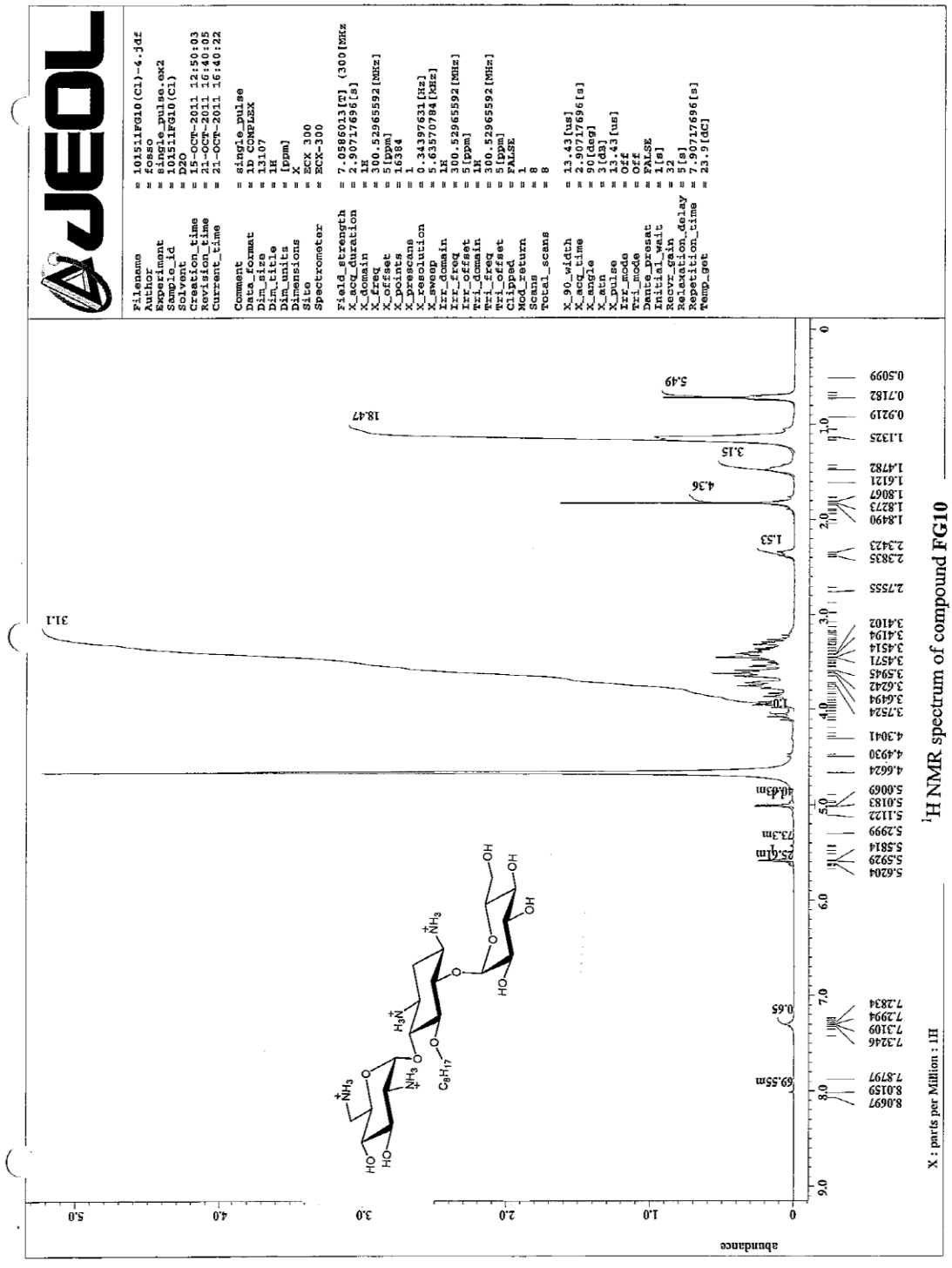
^{13}C NMR spectrum of compound **44a**



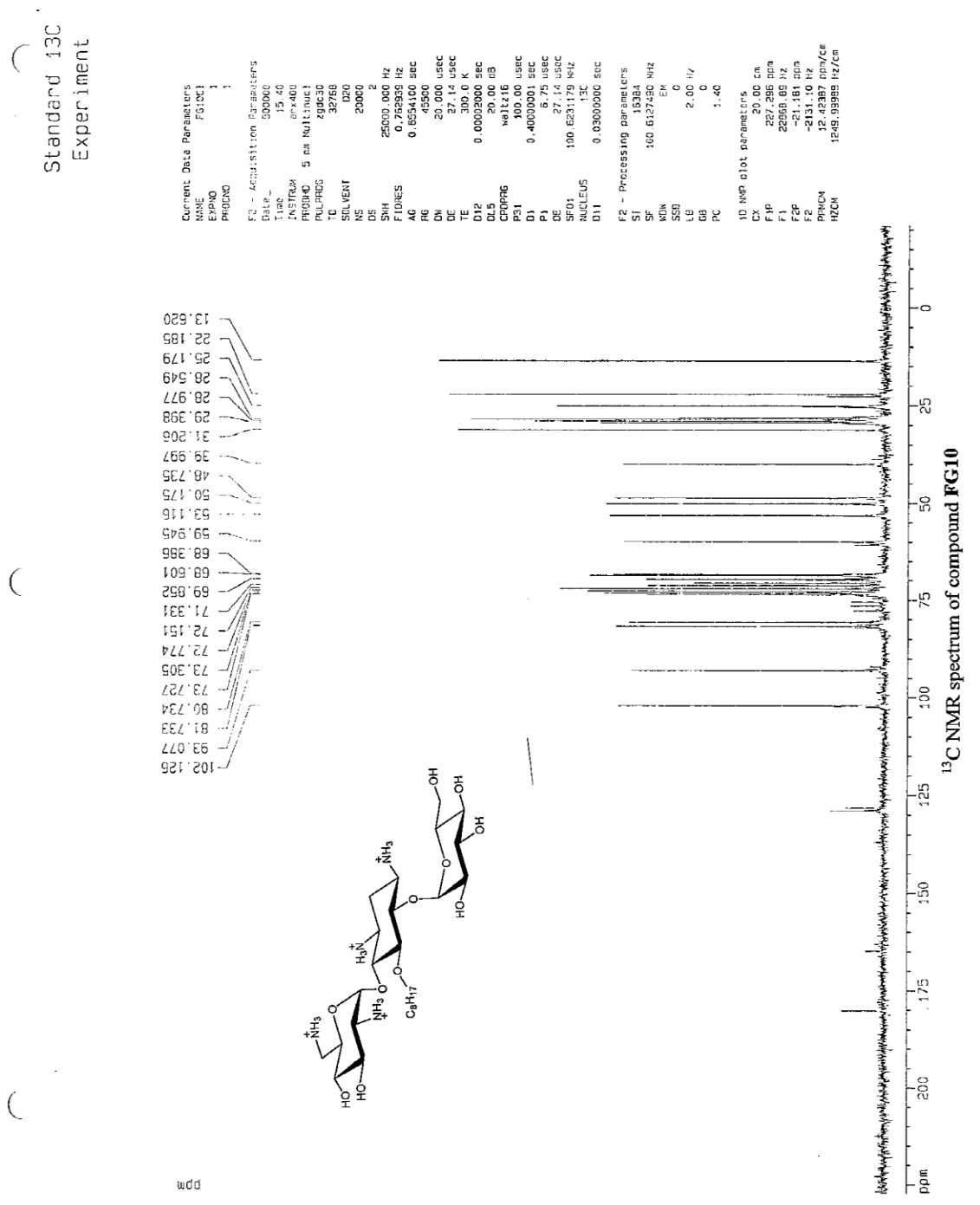
^{1}H NMR spectrum of compound **44b**



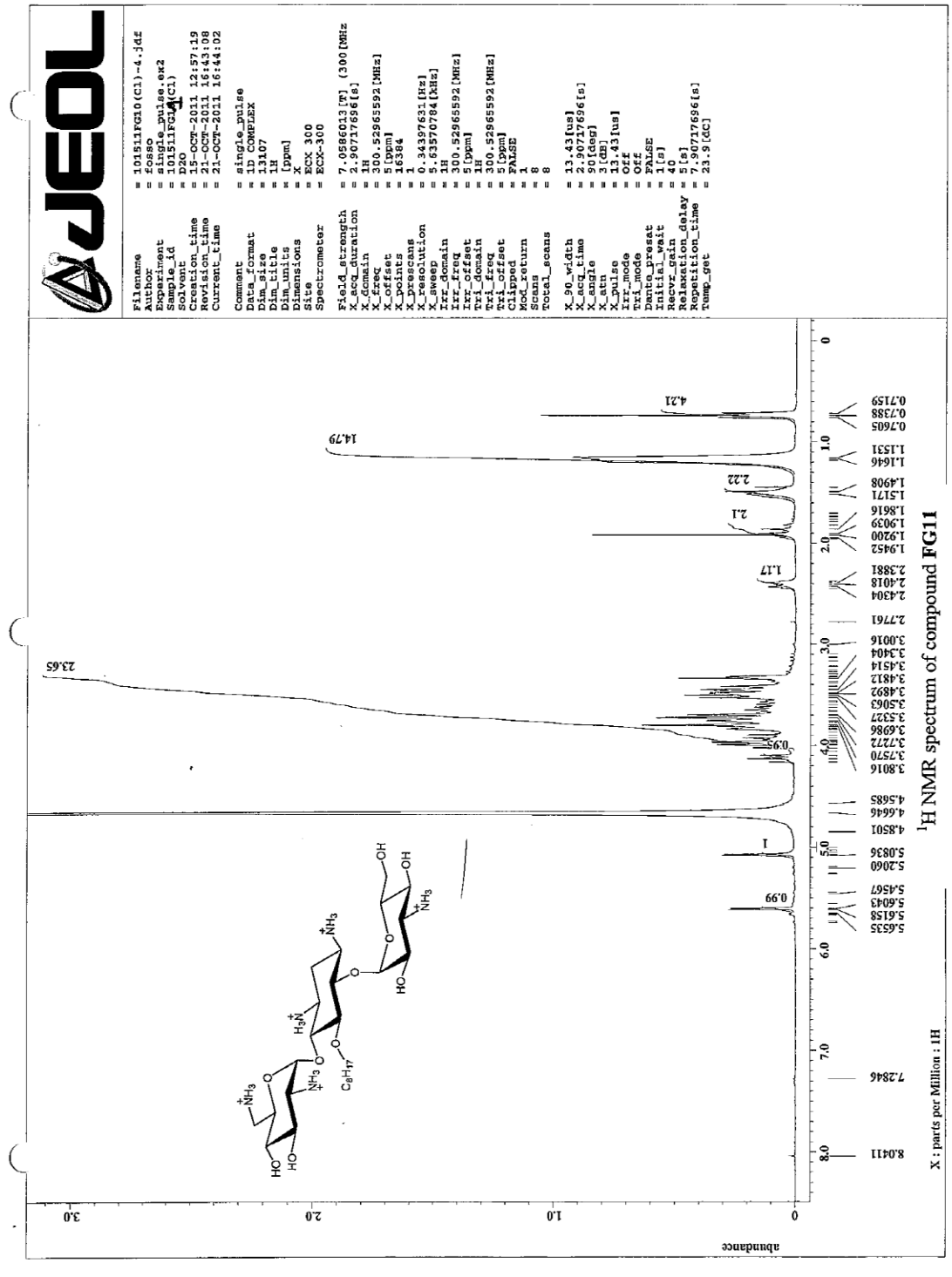
^{13}C NMR spectrum of compound **44b**



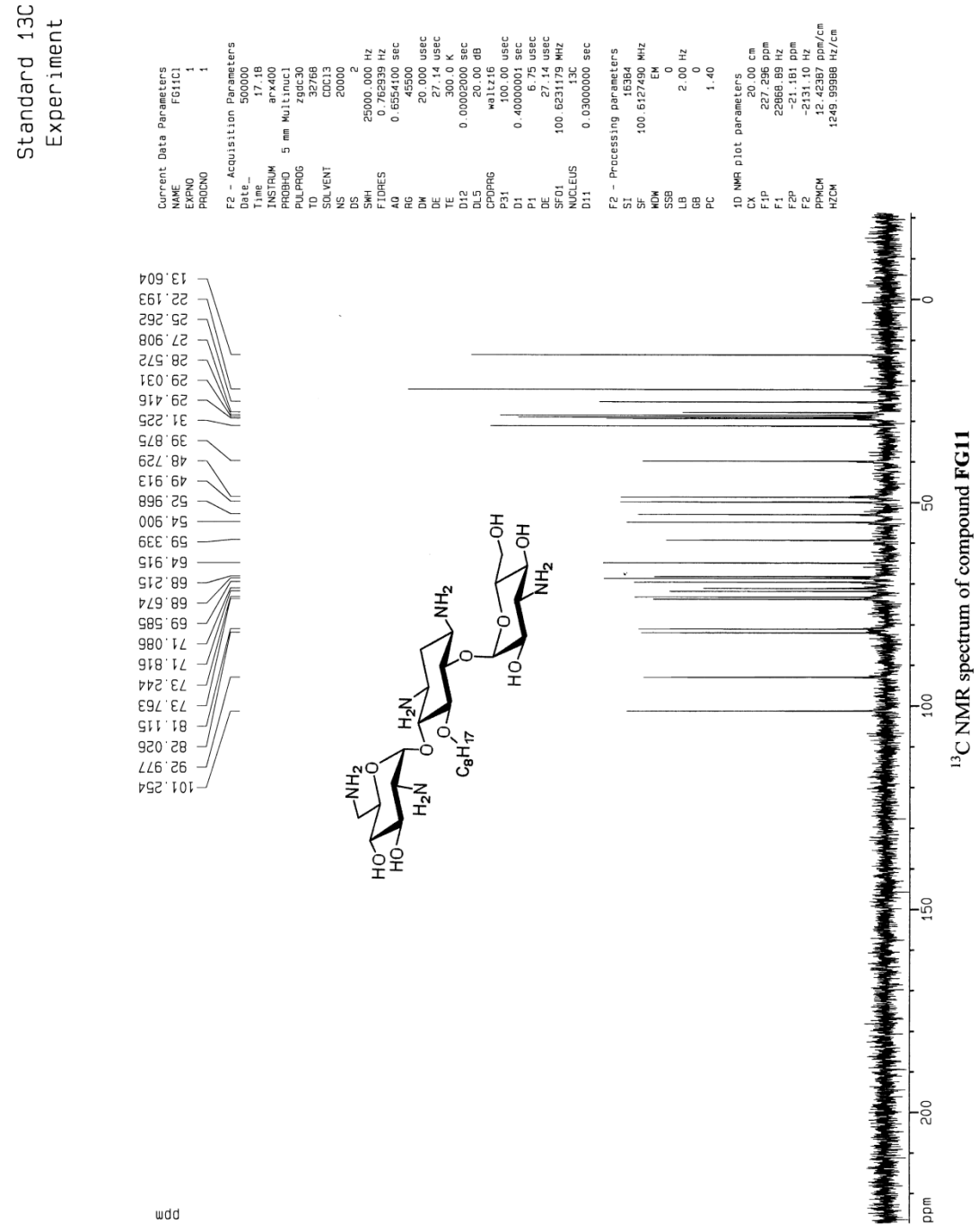
^{1}H NMR spectrum of compound **FG10**



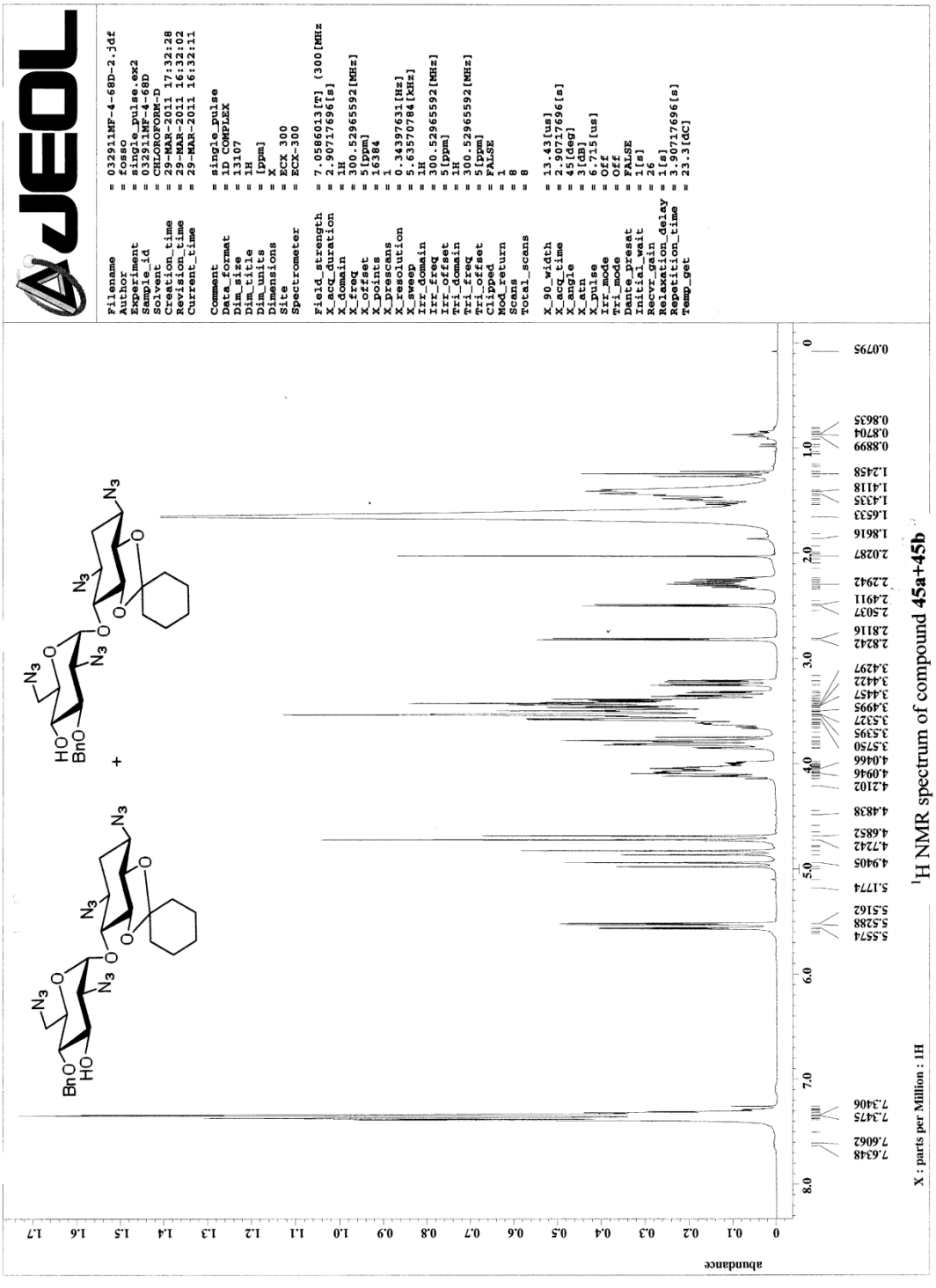
^{13}C NMR spectrum of compound **FG10**



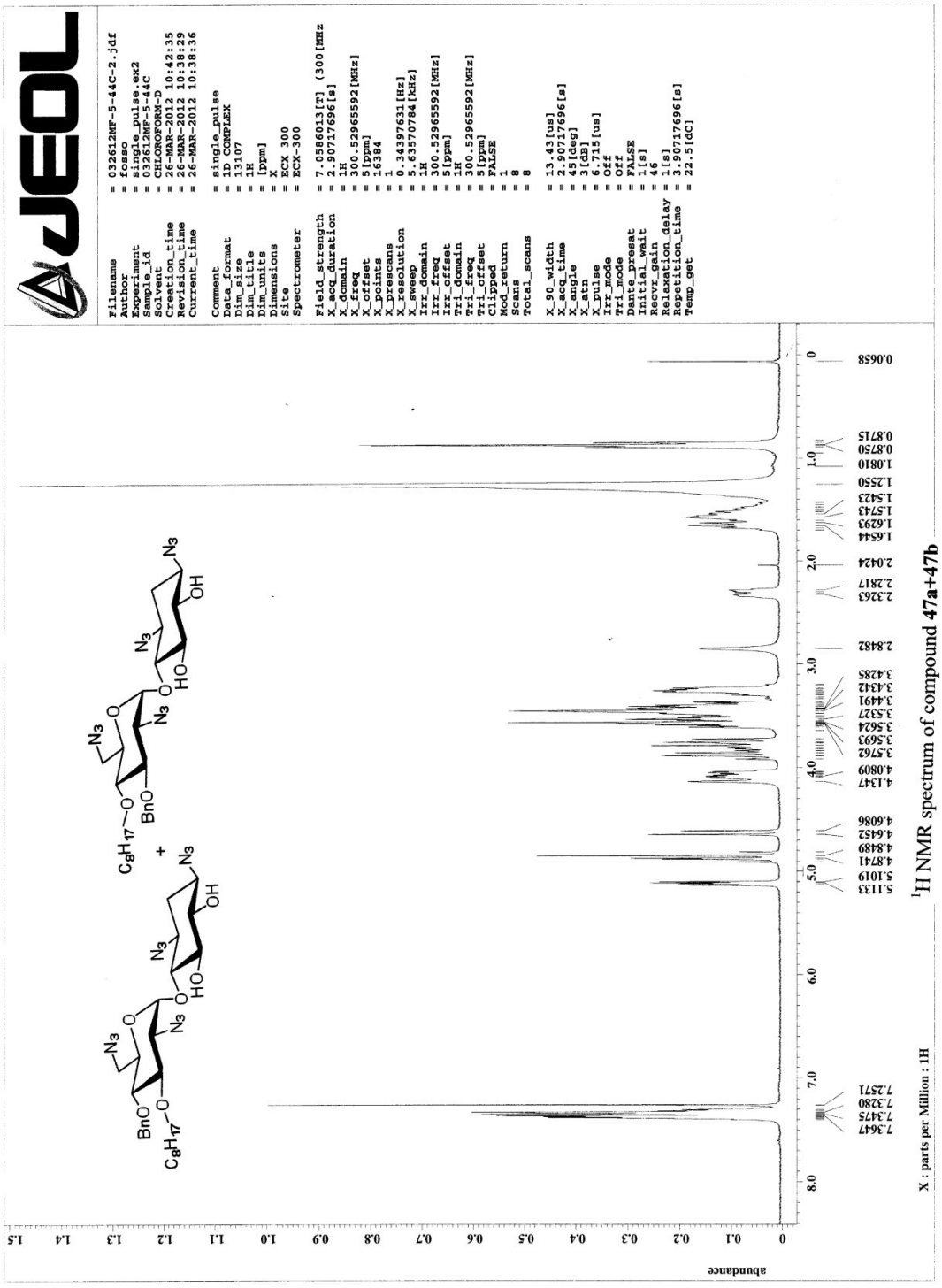
^{1}H NMR spectrum of compound **FG11**



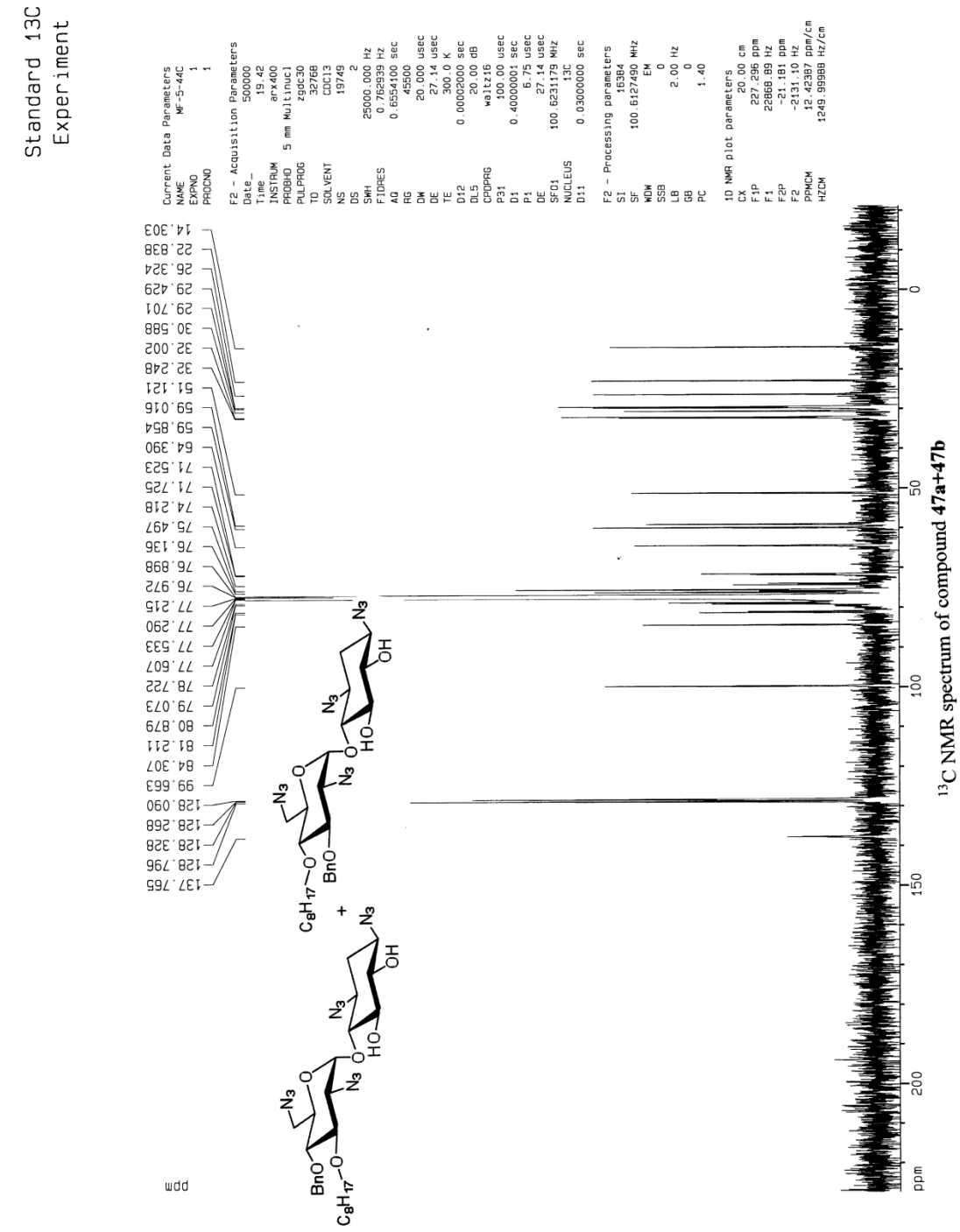
^{13}C NMR spectrum of compound **FG11**



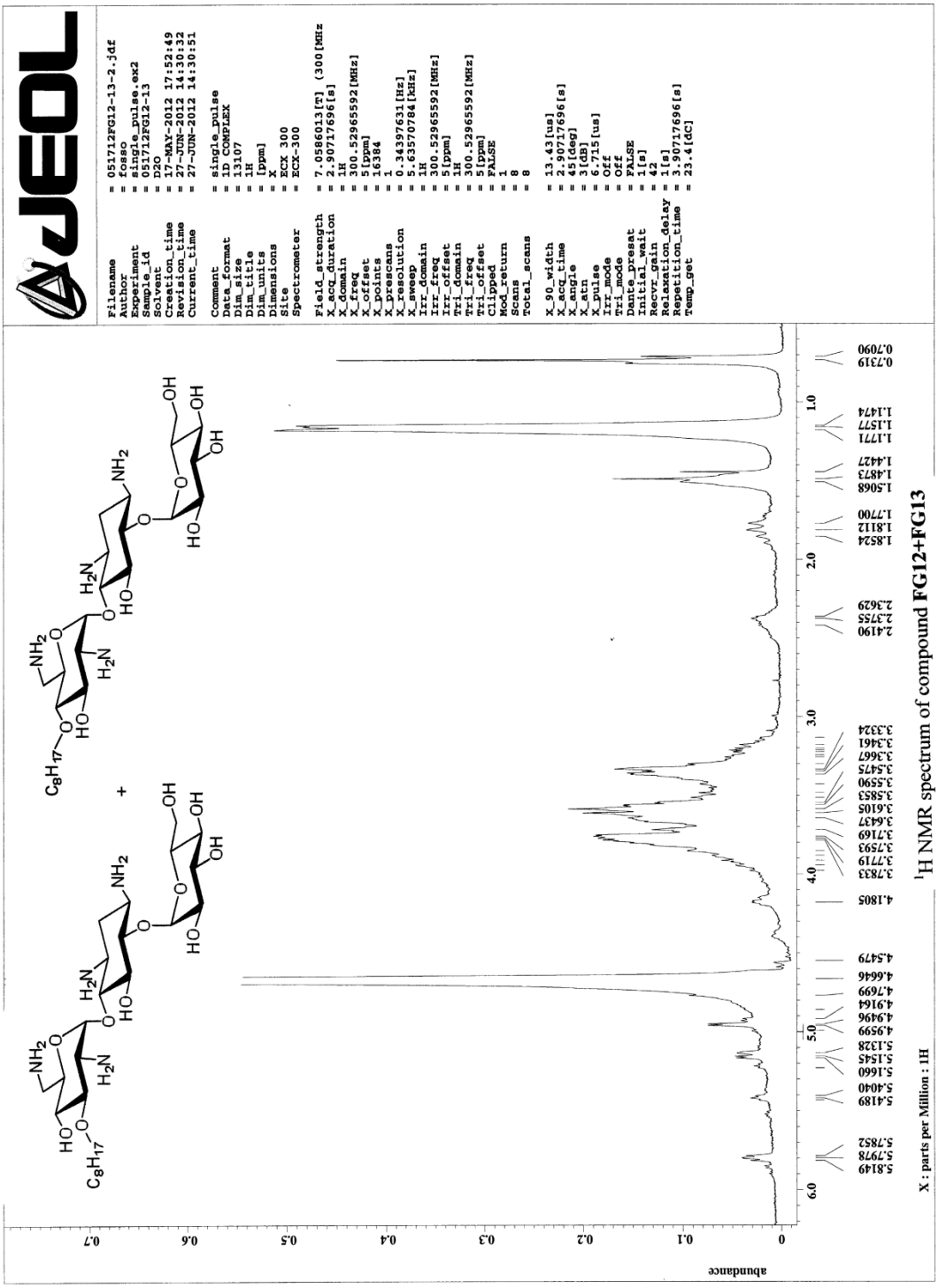
^{1}H NMR spectrum of compound **45a+45b**



^{1}H NMR spectrum of compound **47a+47b**



^{13}C NMR spectrum of compound **47a+47b**


JEOL
Filename = 051712FG12-13-2.jdf
Author = fosso
Experiment = single_pulse.ex2
Sample_id = 051712FG12-13
Solvent = D2O
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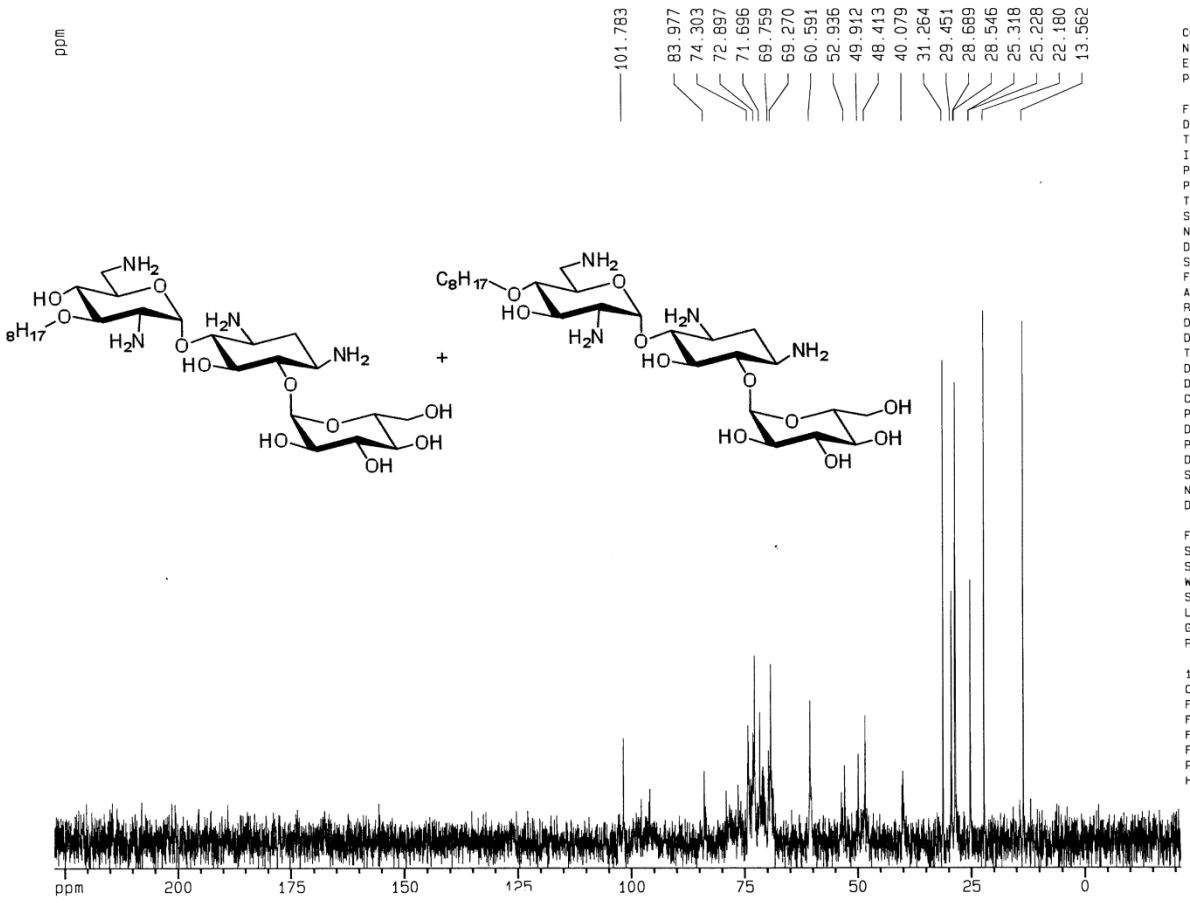
Revision_time = 27-JUN-2012 14:30:32
Current_time = 27-JUN-2012 14:30:51
Comment = single_pulse
Data_format = 1D COMPLEX
Dim_size = 13107
Dim_title = H
Dim_units = [ppm]
Dimensions = X
Site = ECX 300
Spectrometer = ECX-300
Field_strength = 7.0586013[T] (300[MHz
X_acq_duration = 2.90717696[s]
X_domain = 1H
X_freq = 300.52965592[MHz]
X_offset = 5[ppm]
X_points = 16384
X_prescans = 1
X_resolution = 0.34397631[Hz]
X_sweep = 5.63570784[kHz]
Irr_domain = 1H
Irr_freq = 300.52965592[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 300.52965592[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Mod_return = 1
Scans = 8
Total_scans = 8
X_90_width = 13.43[us]
X_acq_time = 2.90717696[s]
X_angle = 45[deg]
X_atn = 31.03
X_pulse = 6.715[us]
Irr_mode = Off
Tri_mode = Off
Dante_presat = FALSE
Initial_wait = 1[s]
Recvr_gain = 42
Relaxation_delay = 1[s]
Repetition_time = 3.90717696[s]
Temp_get = 23.4[dC]
abundance
X : parts per Million : 1H
^{1}H NMR spectrum of compound FG12+FG13

Standard 13C
Experiment



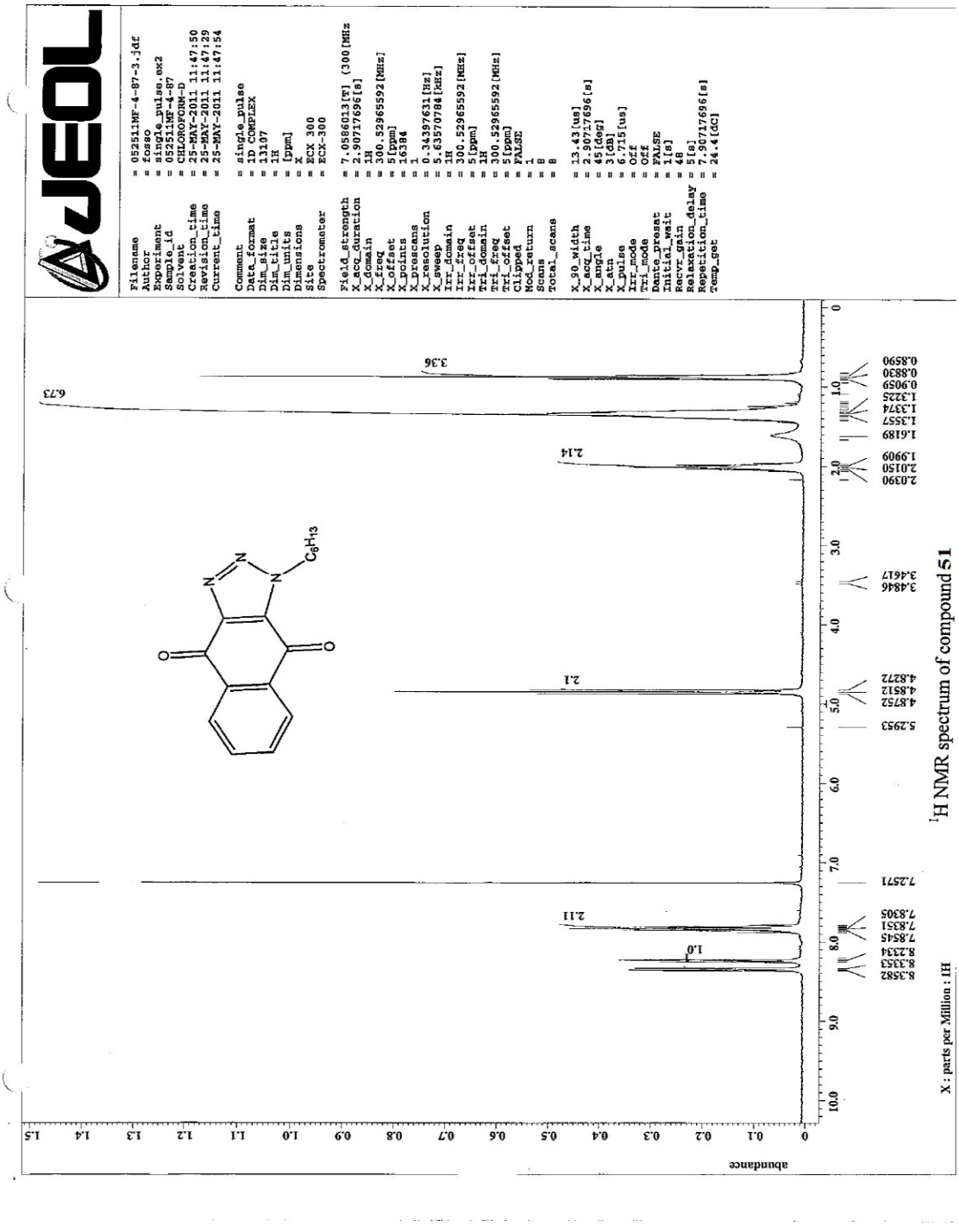
Current Data Parameters
NAME FG12,13
EXPNO 1
PROCNO 1

F2 - Acquisition Parameters
Date_ 500000
Time 21.28
INSTRUM arx400
PROBHD 5 mm Multinucl
PULPROG zgdc30
TD 32768
SOLVENT D2O
NS 20000
DS 2
SWH 25000.000 Hz
FIDRES 0.762939 Hz
AQ 0.6554100 sec
RG 45500
DW 20.000 usec
DE 27.14 usec
TE 300.0 K
D12 0.00002000 sec
DL5 20.00 dB
CPDPRG waltz16
P31 100.00 usec
D1 0.40000001 sec
P1 6.75 usec
DE 27.14 usec
SFO1 100.6231179 MHz
NUCLEUS 13C
D11 0.03000000 sec

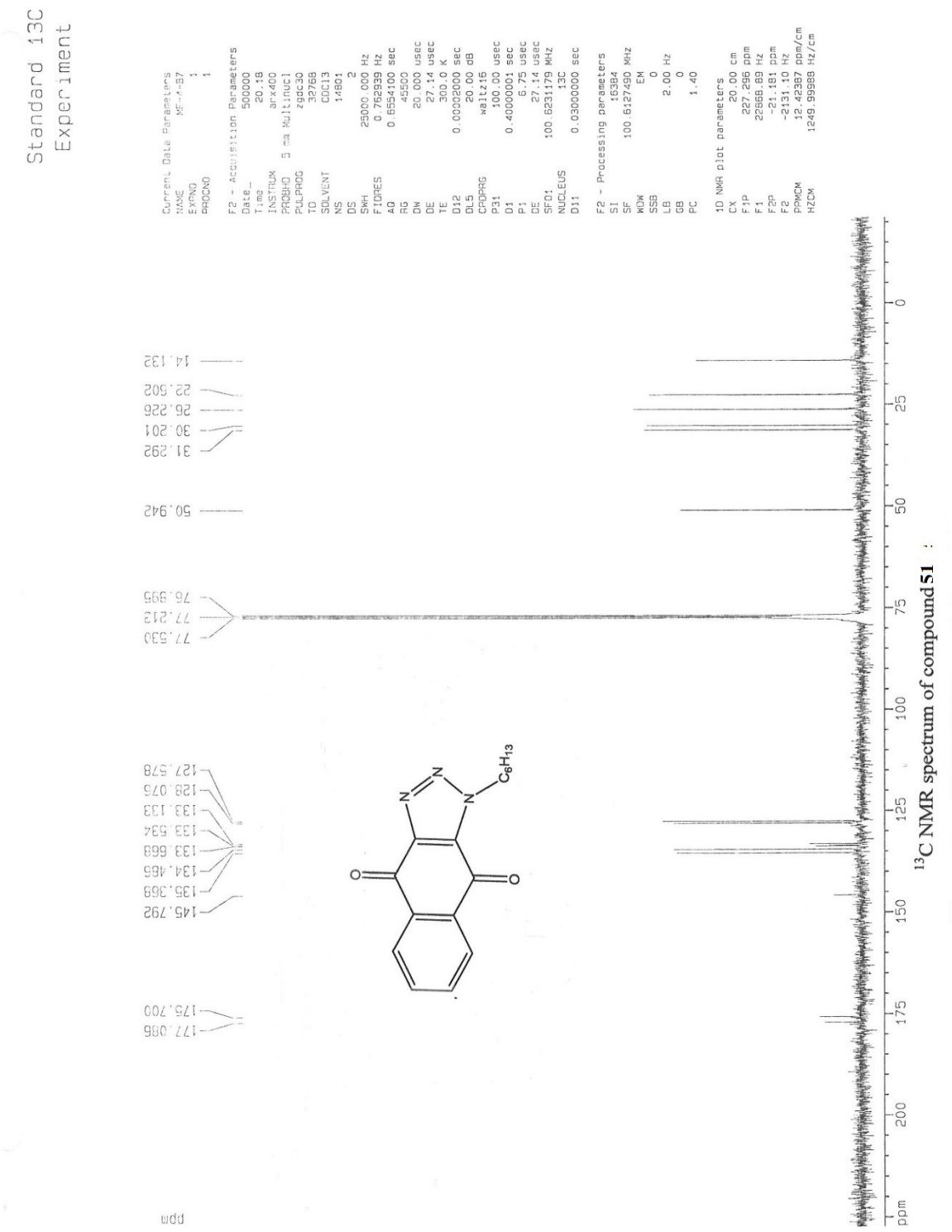
F2 - Processing parameters
SI 16384
SF 100.6127490 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40

1D NMR plot parameters
CX 20.00 cm
F1P 227.296 ppm
F1 22868.89 Hz
F2P -21.181 ppm
F2 -2131.10 Hz
PPMCM 12.42387 ppm/cm
HZCM 1249.99988 Hz/cm

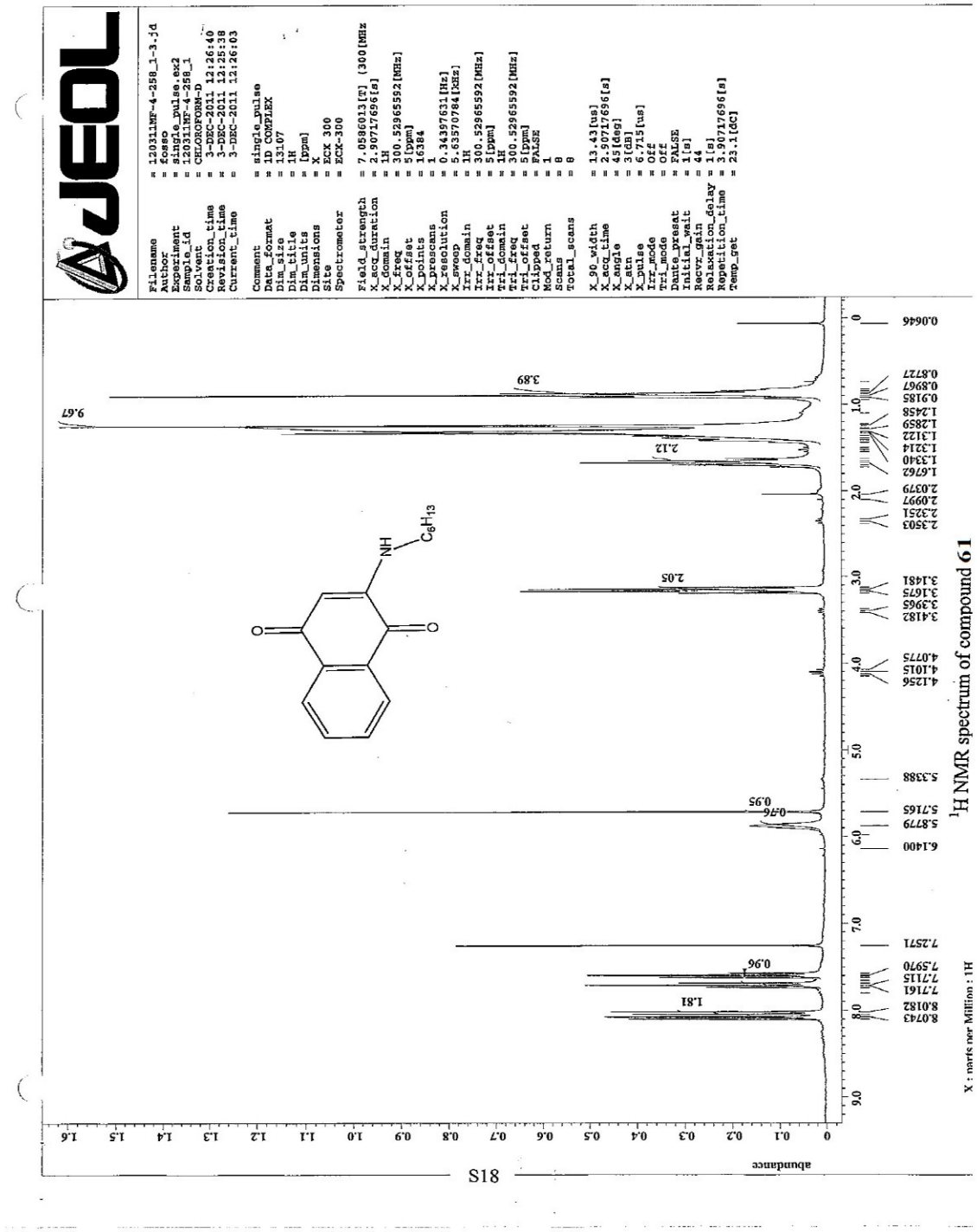
^{13}C NMR spectrum of compound **FG12+FG13**



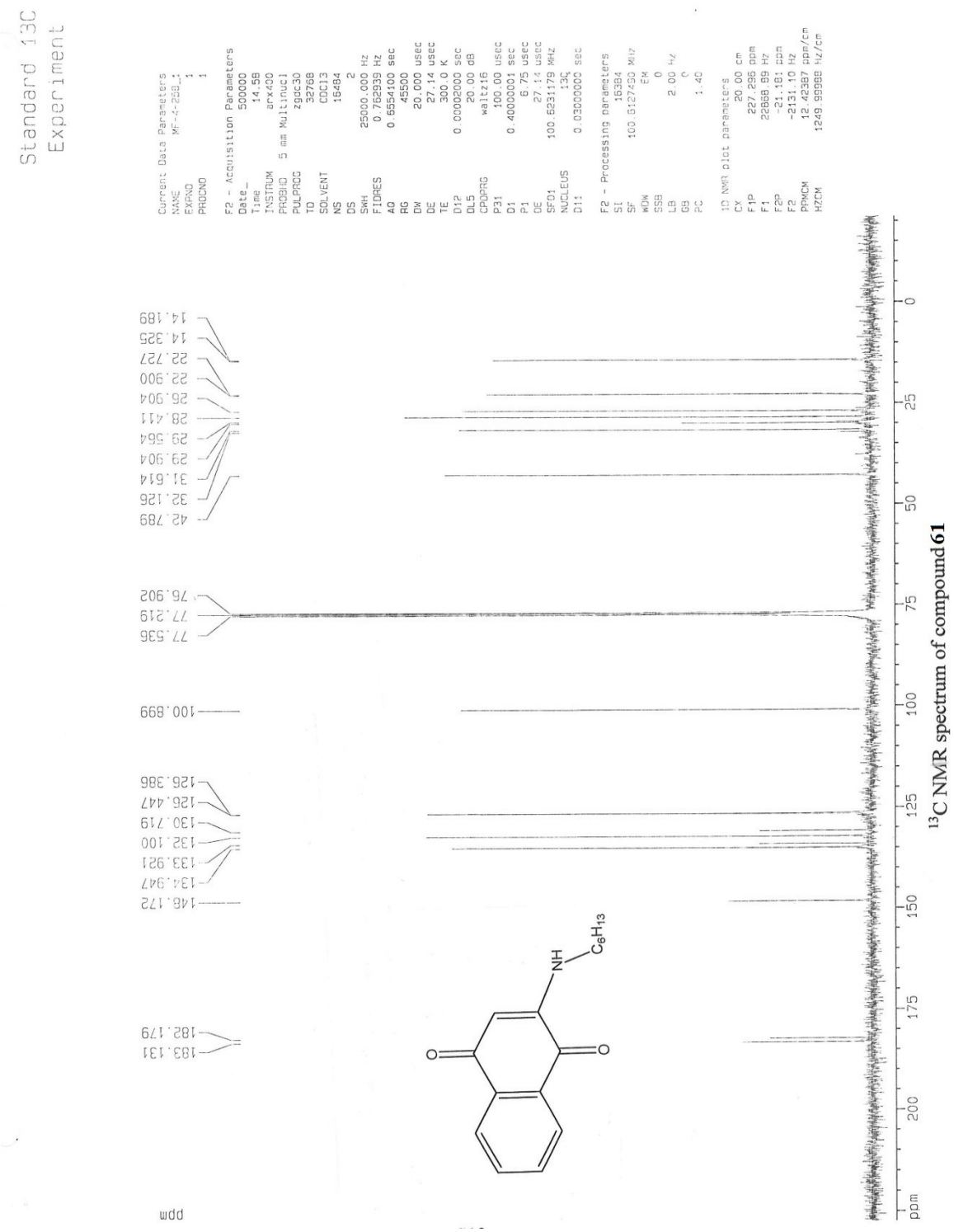
^{1}H NMR spectrum of compound **51**



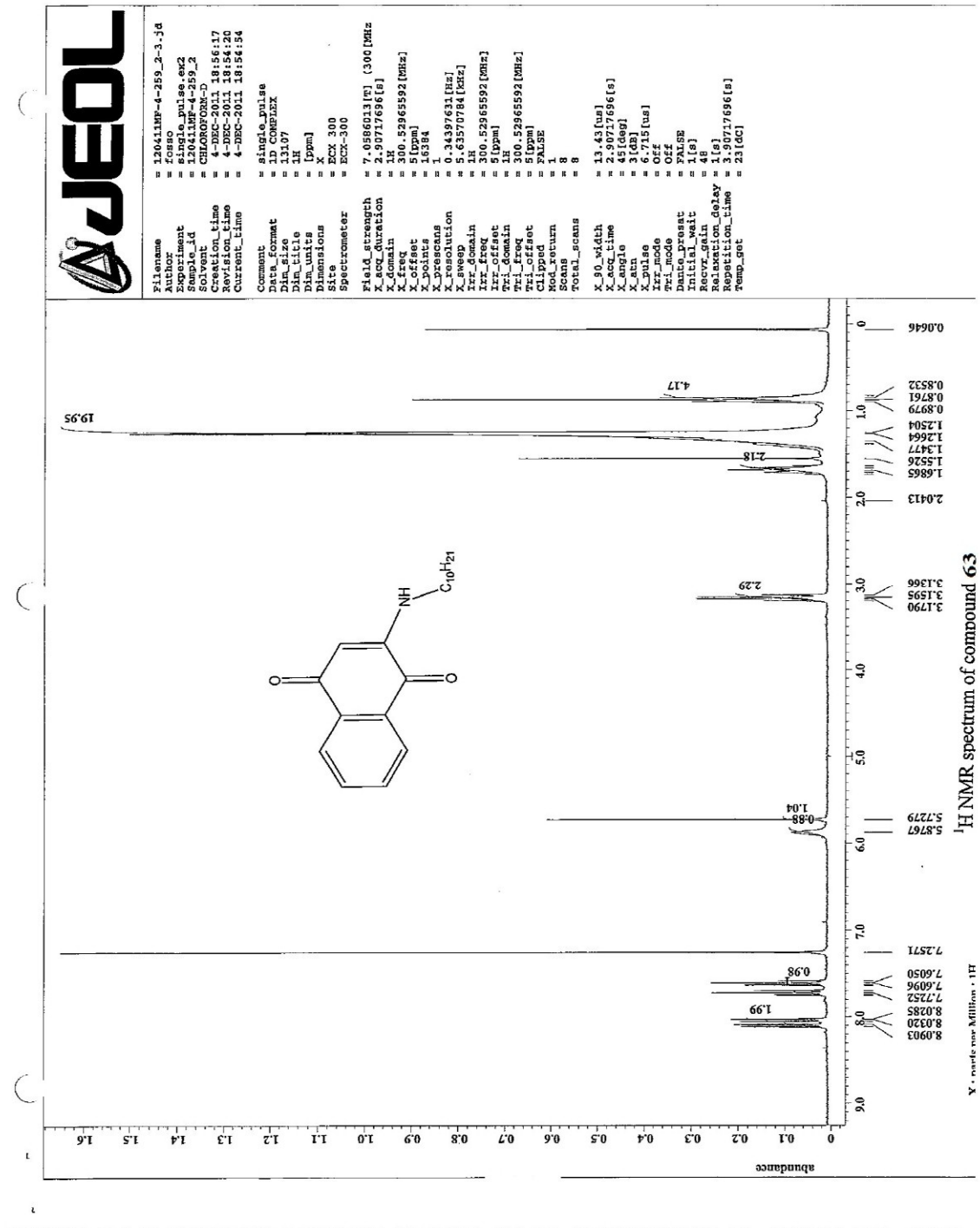
^{13}C NMR spectrum of compound **51**



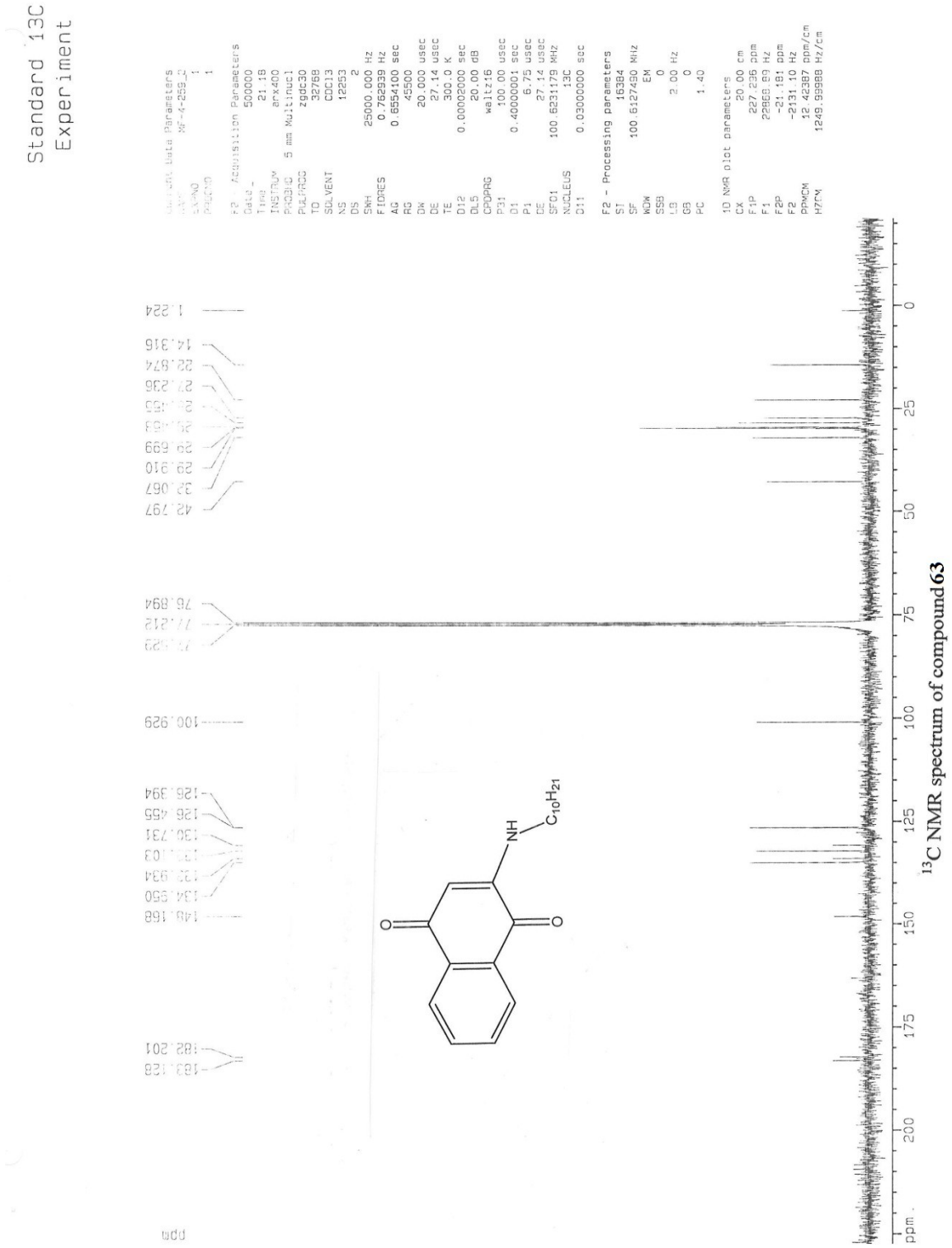
^{1}H NMR spectrum of compound **61**



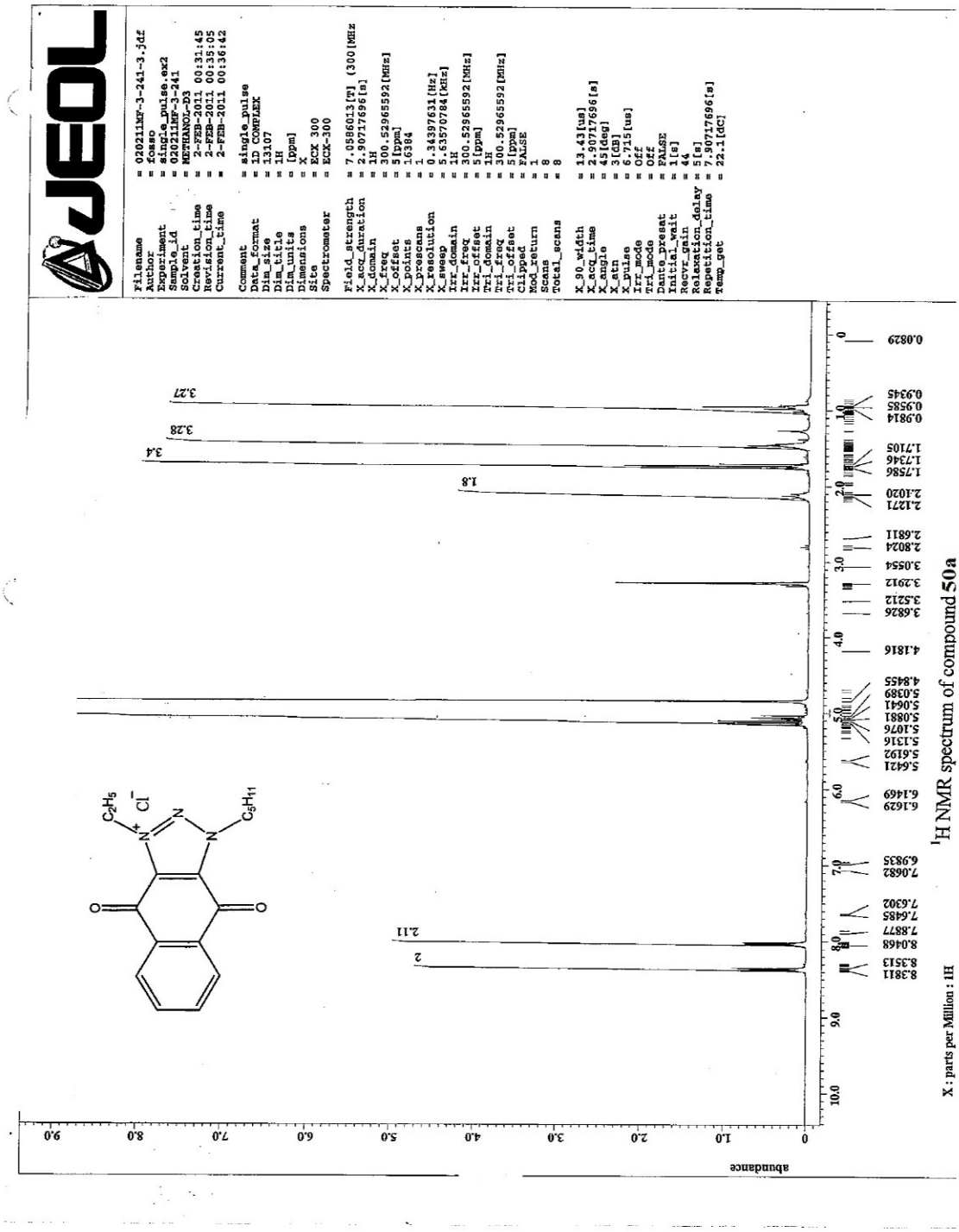
^{13}C NMR spectrum of compound **61**



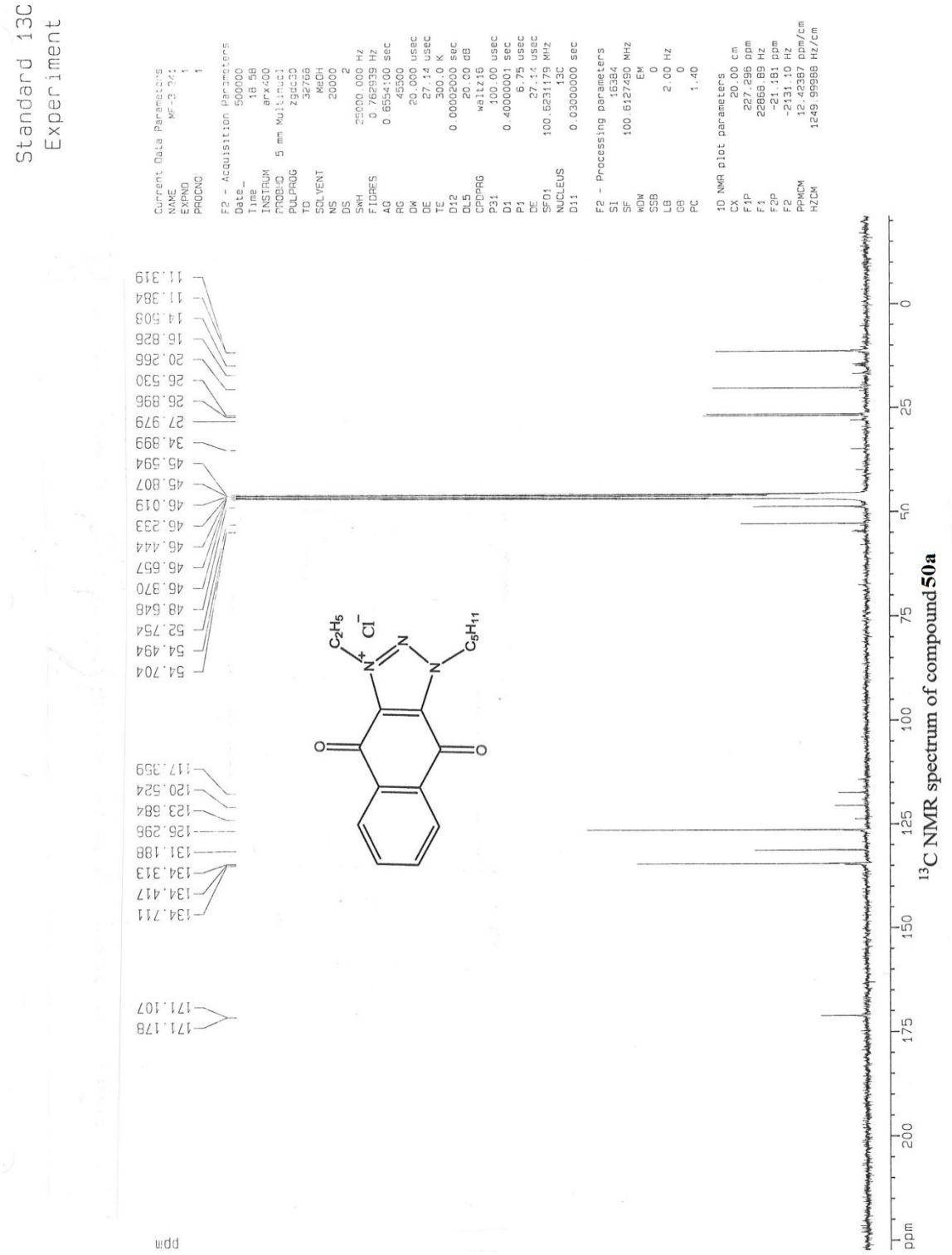
^{1}H NMR spectrum of compound **63**



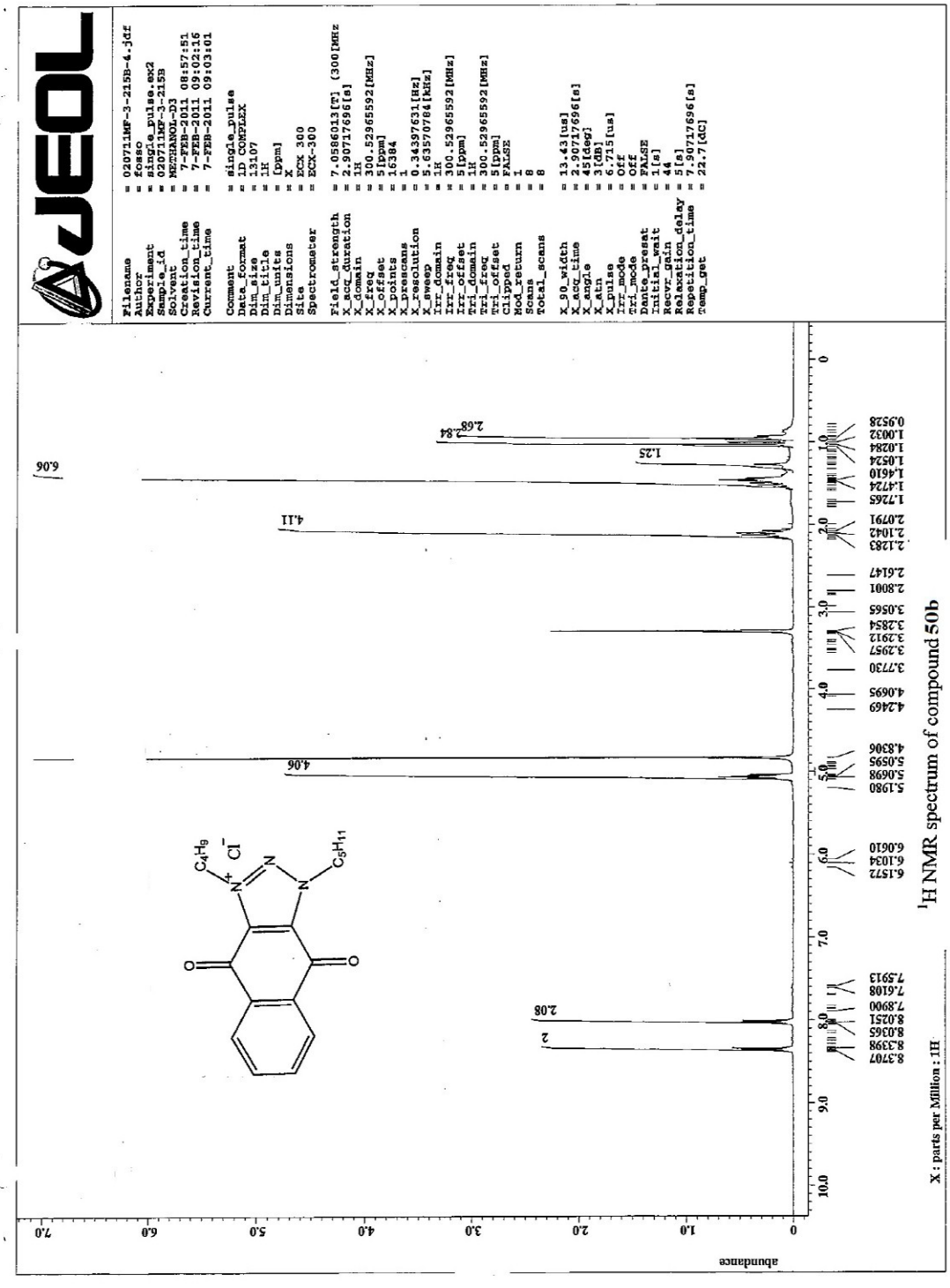
^{13}C NMR spectrum of compound **63**



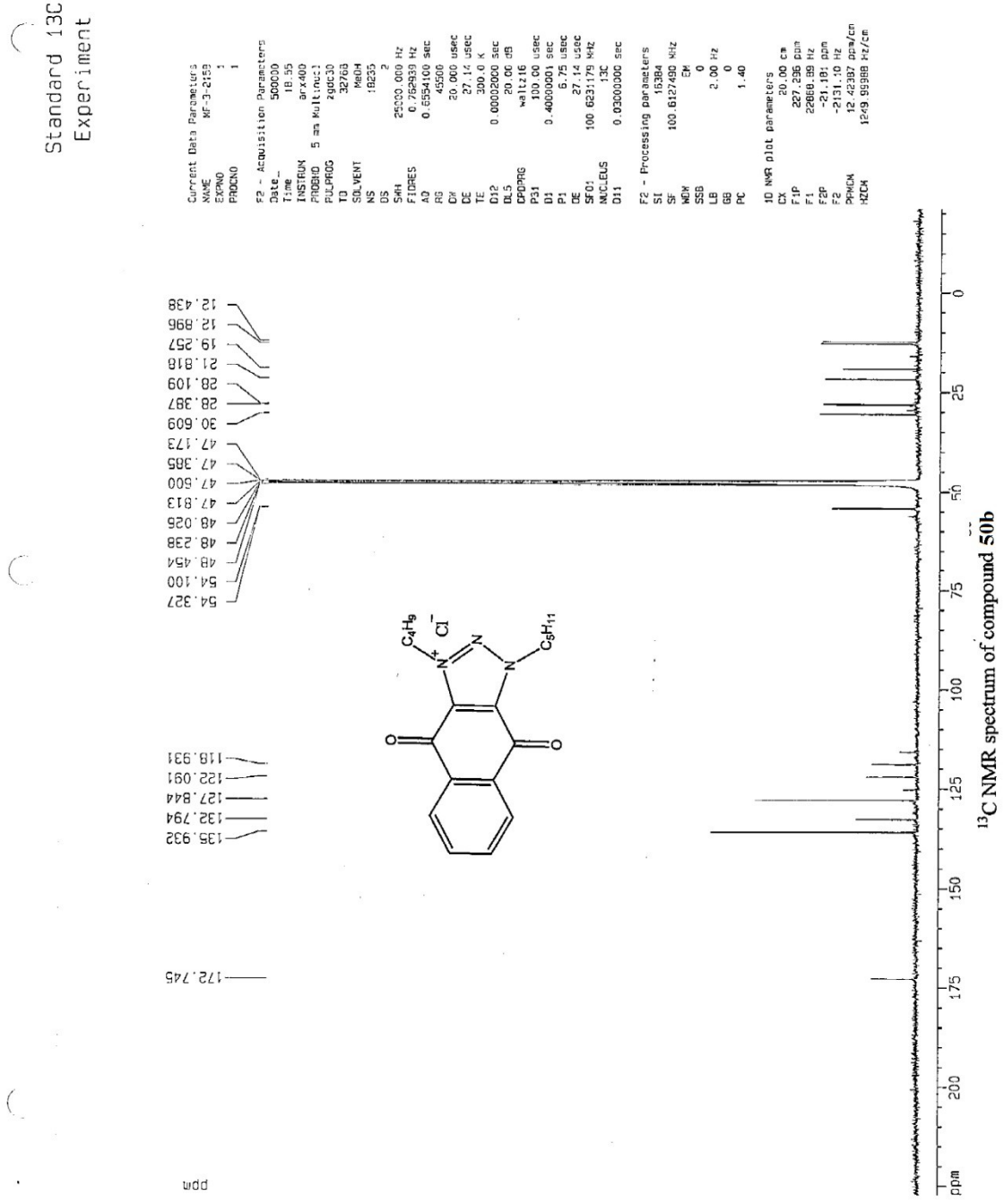
^{1}H NMR spectrum of compound **50a**



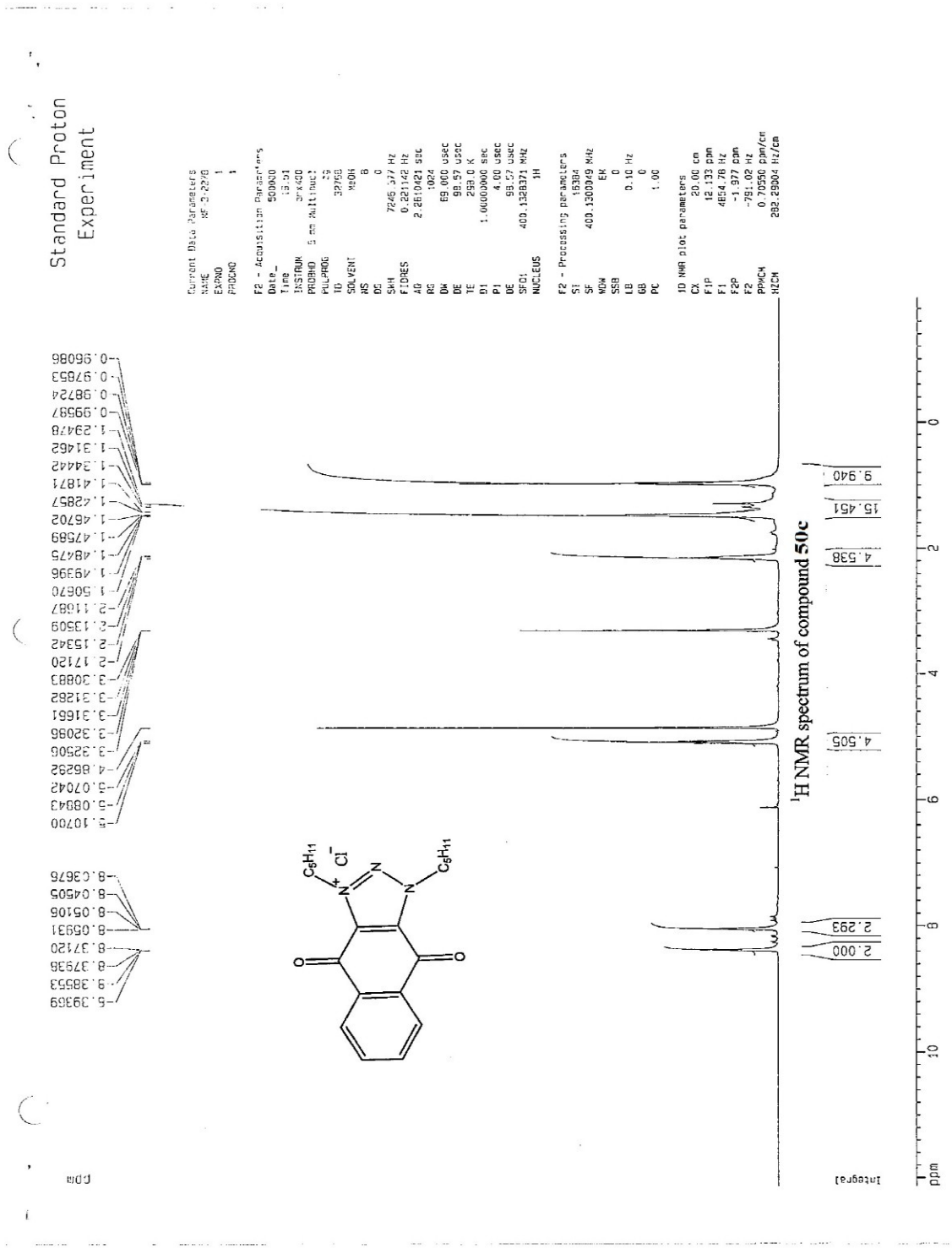
^{13}C NMR spectrum of compound **50a**

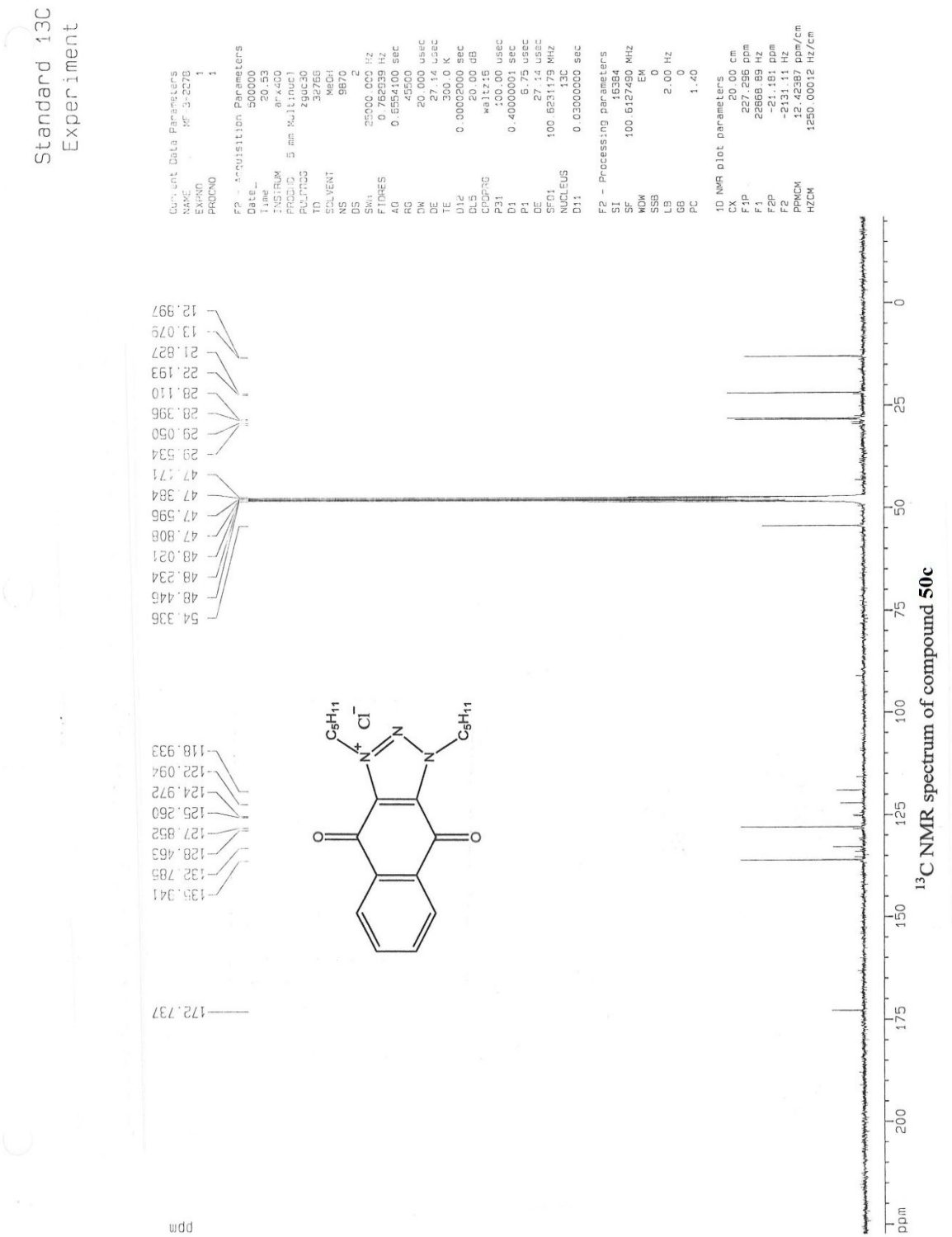


^{1}H NMR spectrum of compound **50b**

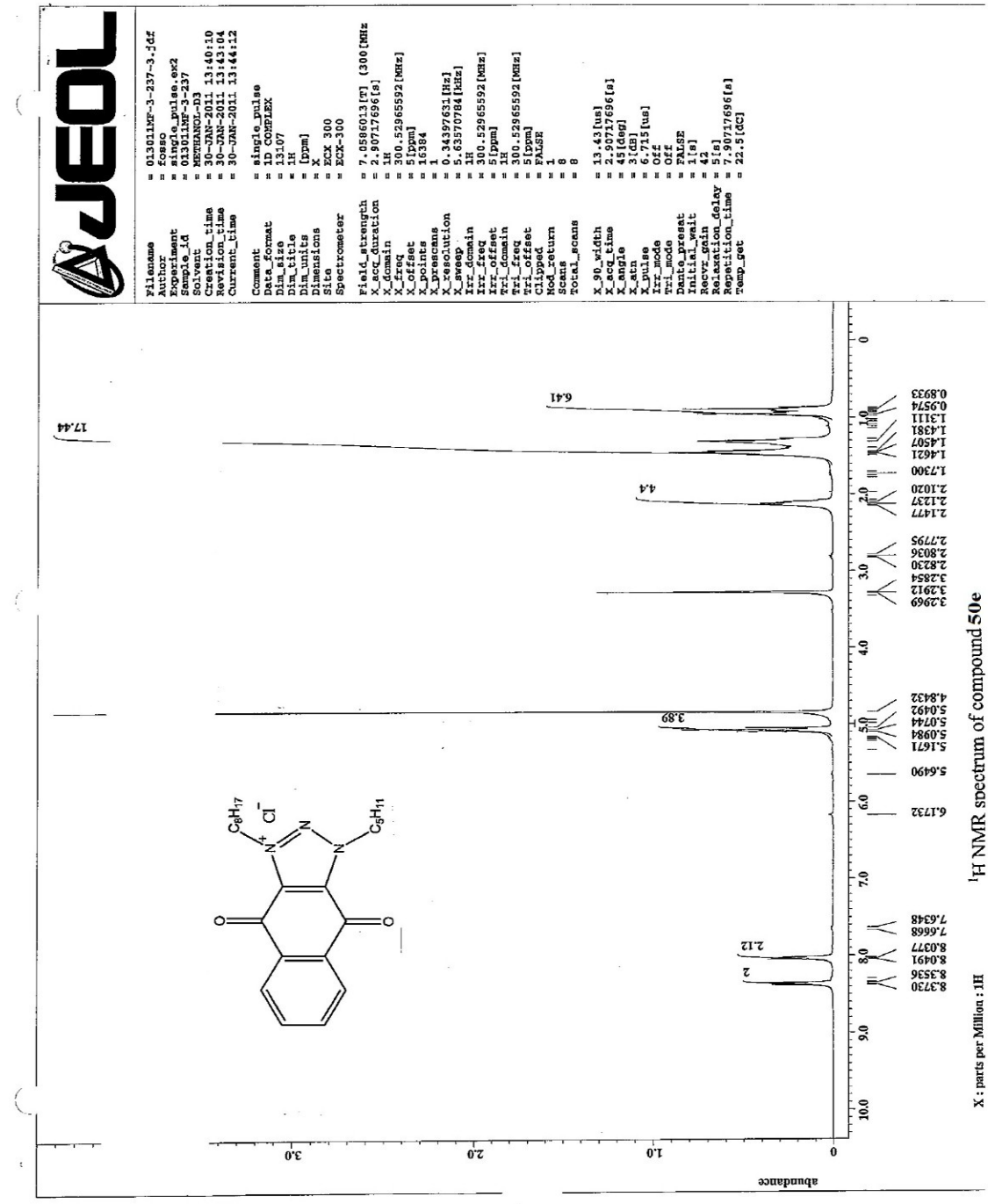


^{13}C NMR spectrum of compound **50b**

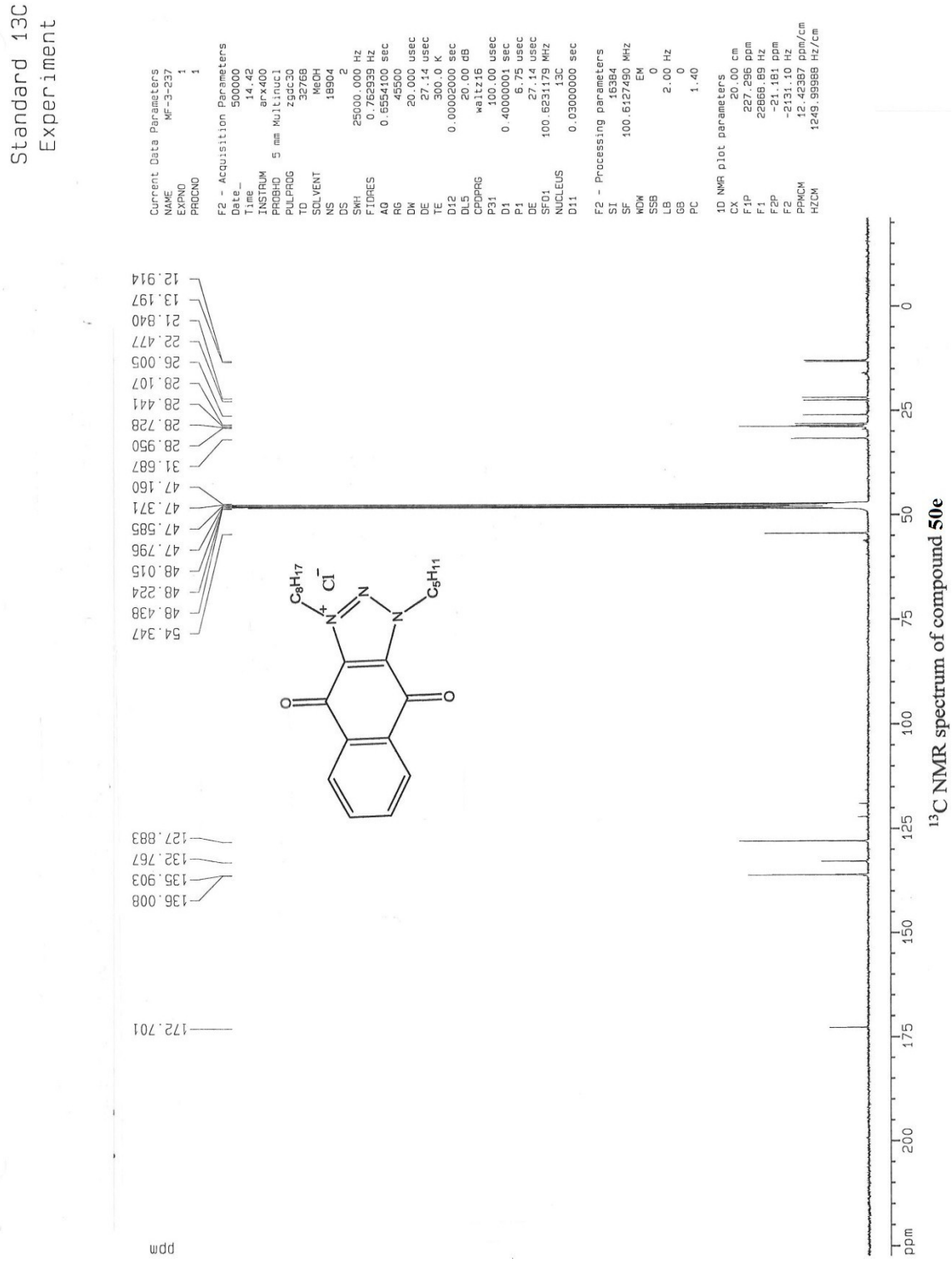

Standard Proton
Experiment
Current Data Parameters
NAME
EXPNO
PROCNO
F2 - Acquisition Parameters
Date_
Time
INSTRUM
PROBHD
PULPROG
TD
SOLVENT
NS
DS
SWH
FIDRES
AQ
RG
DW
DE
TE
D1
P1
DE
SFO1
NUCLEUS
F2 - Processing parameters
SI
SF
WDW
SSB
LB
GB
PC
1D NMR plot parameters
CX
F1P
F1
F2P
F2
PPMCM
HZCM
7246.377 Hz
0.221142 Hz
2.2610421 sec
1024
69.000 usec
6.00 usec
298.0 K
1.00000000 sec
4.00 usec
6.00 usec
400.1328371 MHz
1H
400.1300049 MHz
0.10 Hz
1.00
20.00 cm
12.133 ppm
4854.76 Hz
-1.977 ppm
-791.02 Hz
0.70550 ppm/cm
282.29004 Hz/cm
^{1}H NMR spectrum of compound **50c**
9.940
15.451
4.538
4.505
2.000
2.293
Integral
ppm



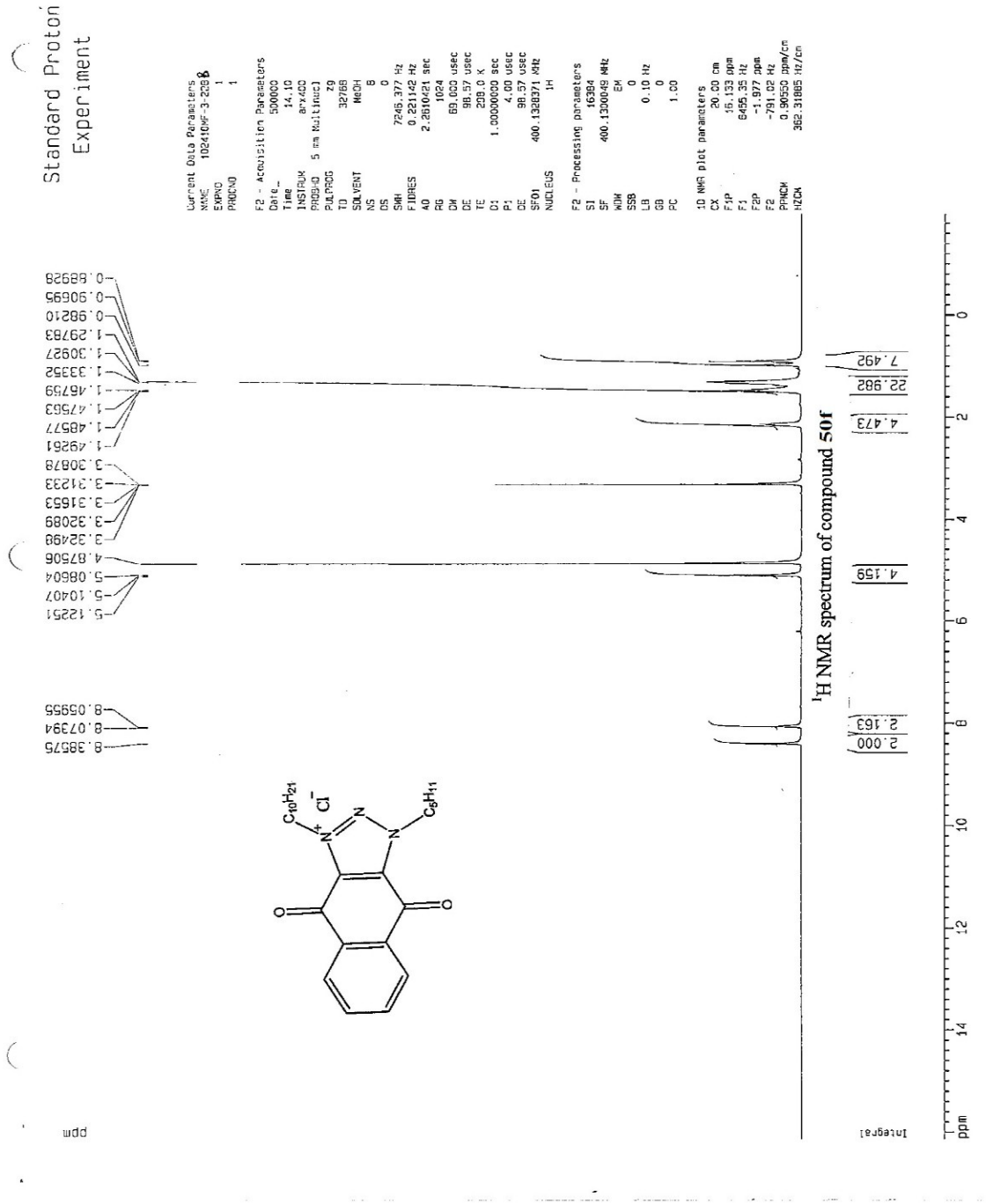
^{13}C NMR spectrum of compound **50c**

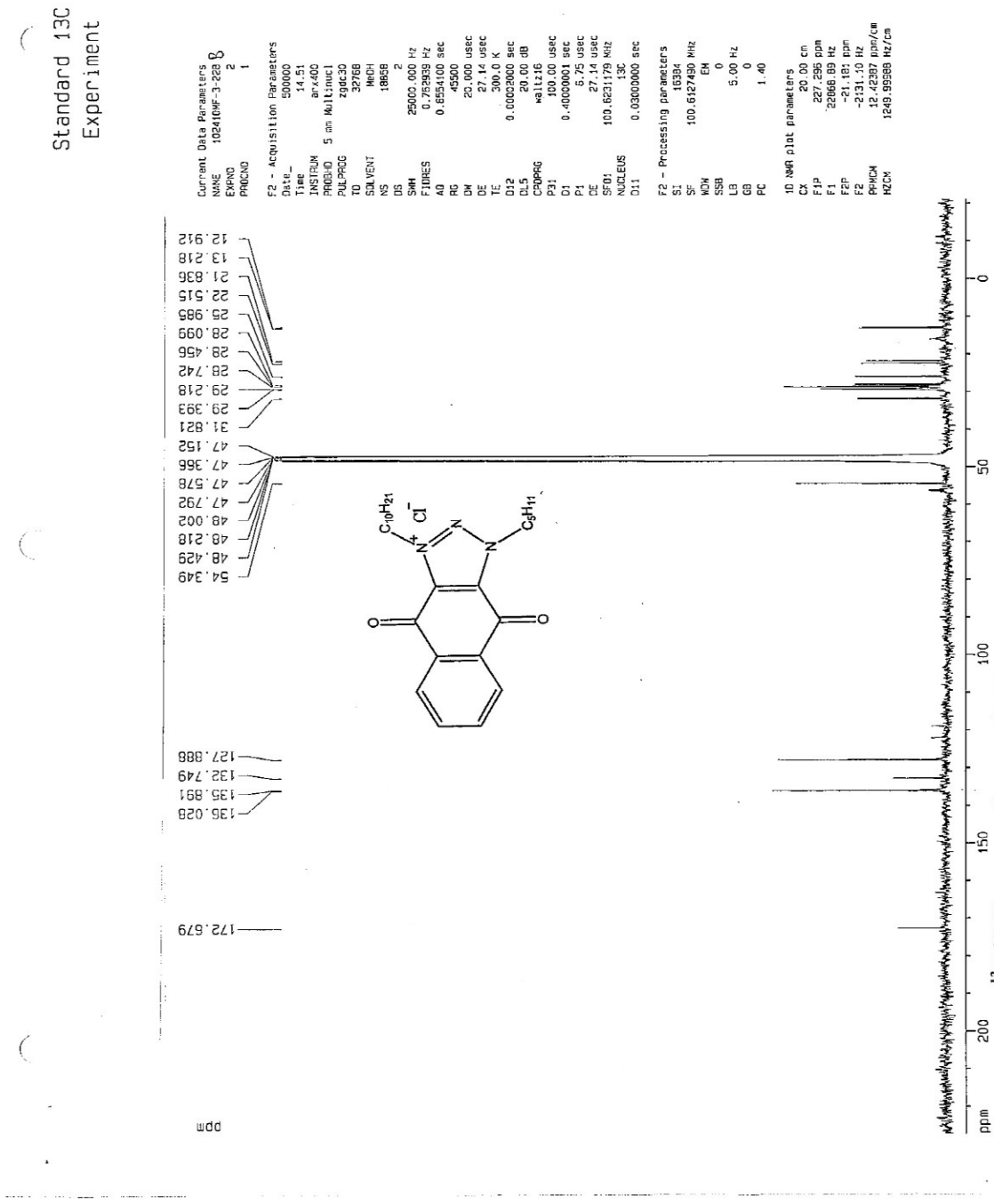


^{1}H NMR spectrum of compound **50e**

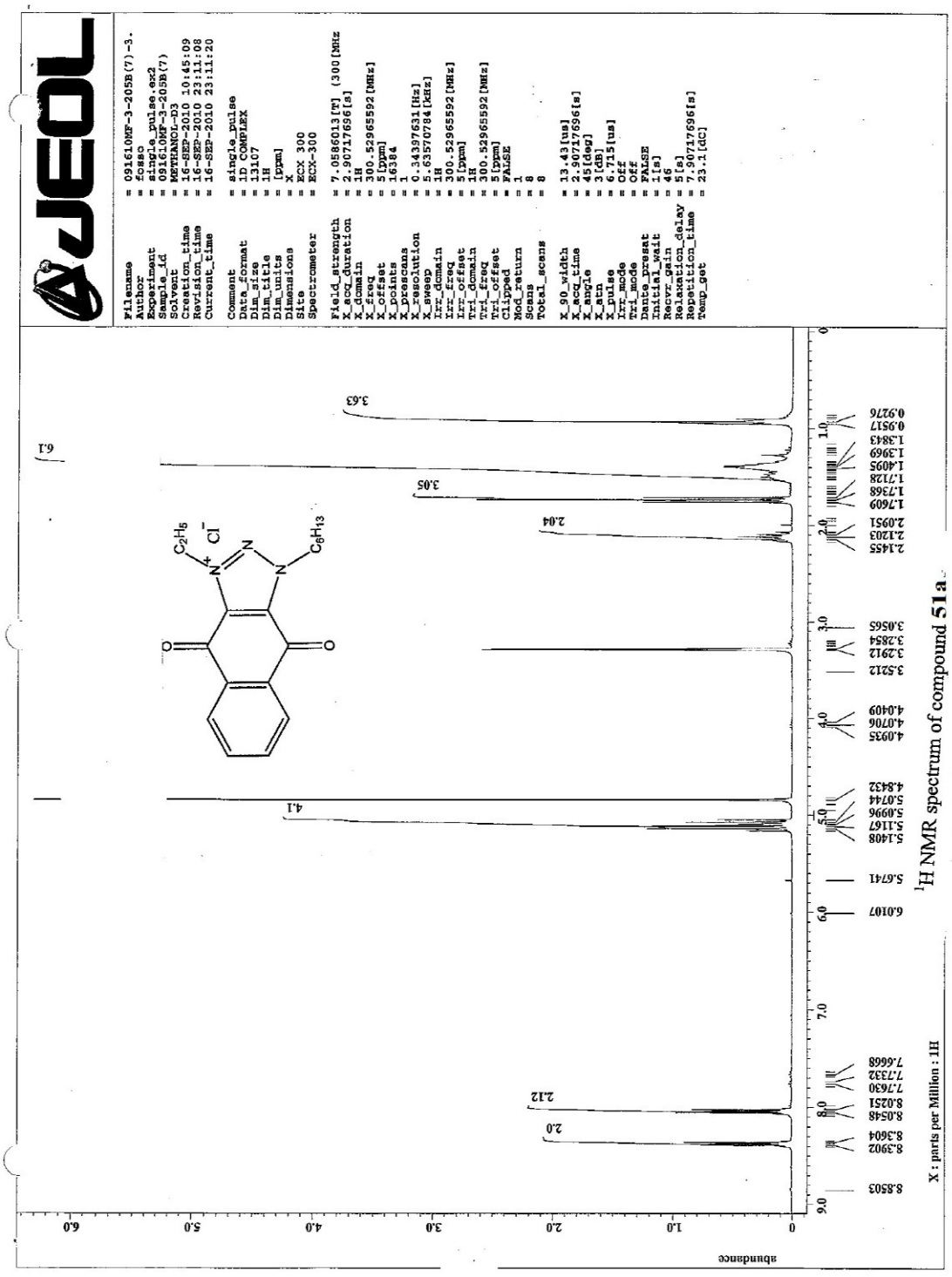


^{13}C NMR spectrum of compound **50e**

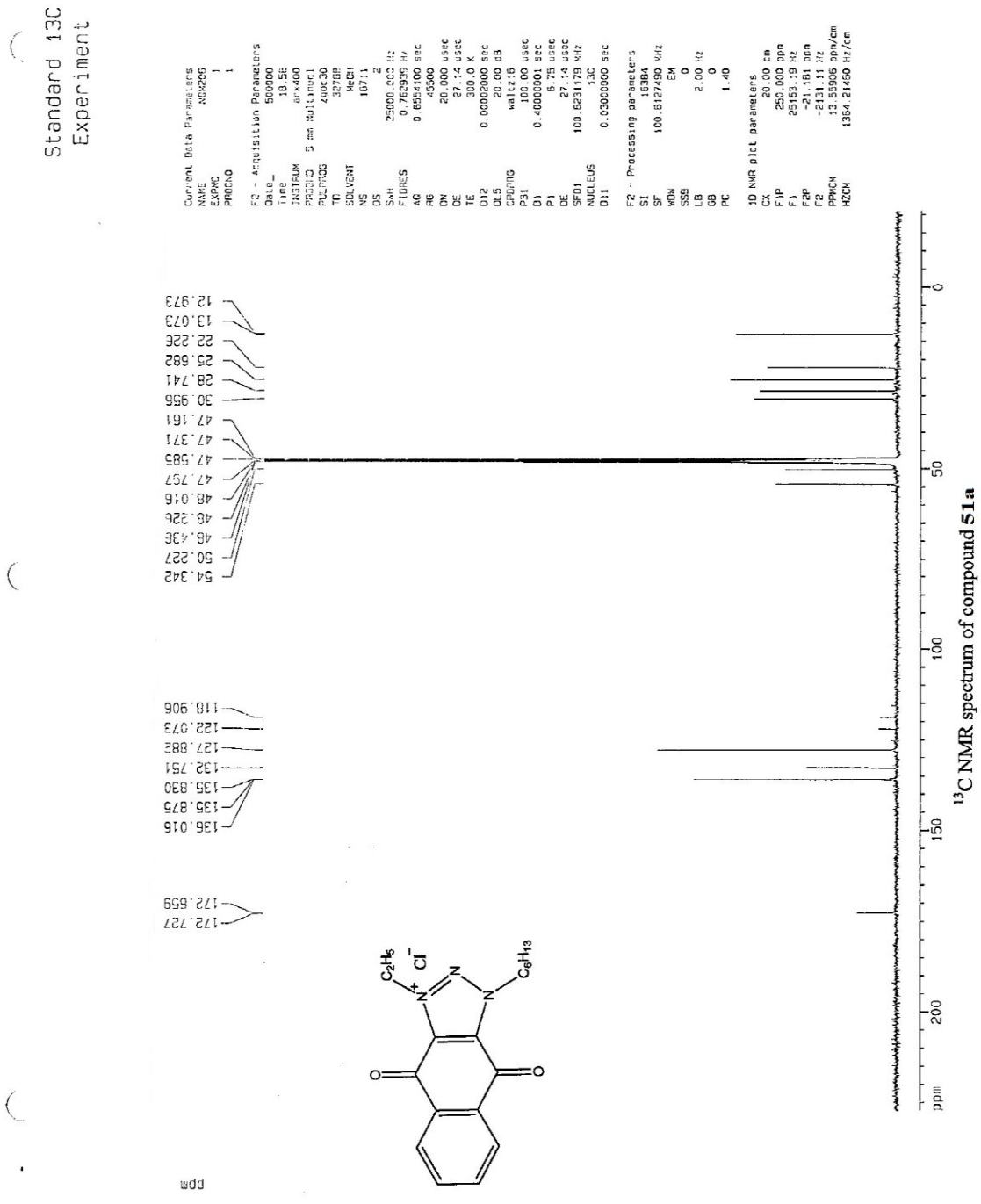

Standard Proton Experiment
Current Data Parameters
NAME 10241DWF-3-20B
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 500000
Time 14.10
INSTRUM arx400
PROBHD 5 mm Multinucl
PULPROG zg
TD 32768
SOLVENT MeOH
NS 8
DS 0
SWH 7245.377 Hz
FIDRES 0.221142 Hz
AQ 2.2610421 sec
RG 1024
DW 69.000 usec
DE 98.57 usec
TE 298.0 K
D1 1.00000000 sec
P1 4.00 usec
DE 98.57 usec
SFO1 400.1328371 MHz
NUCLEUS 1H
F2 - Processing parameters
SI 16384
SF 400.1300049 MHz
WDW EM
SSB 0
LB 0.10 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 16.133 ppm
F1 6455.35 Hz
F2P -1.977 ppm
F2 -791.02 Hz
PPMCM 0.90550 ppm/cm
HZCM 362.31885 Hz/cm
8.38575
8.07394
8.05955
5.12251
5.10407
5.08604
4.87506
3.32498
3.32089
3.31653
3.31233
3.30878
1.49261
1.48577
1.47563
1.46759
1.33352
1.30927
1.29783
0.98210
0.90695
0.88928
2.000
2.163
4.159
4.473
22.982
7.492
ppm
Integral
^{1}H NMR spectrum of compound **50f**



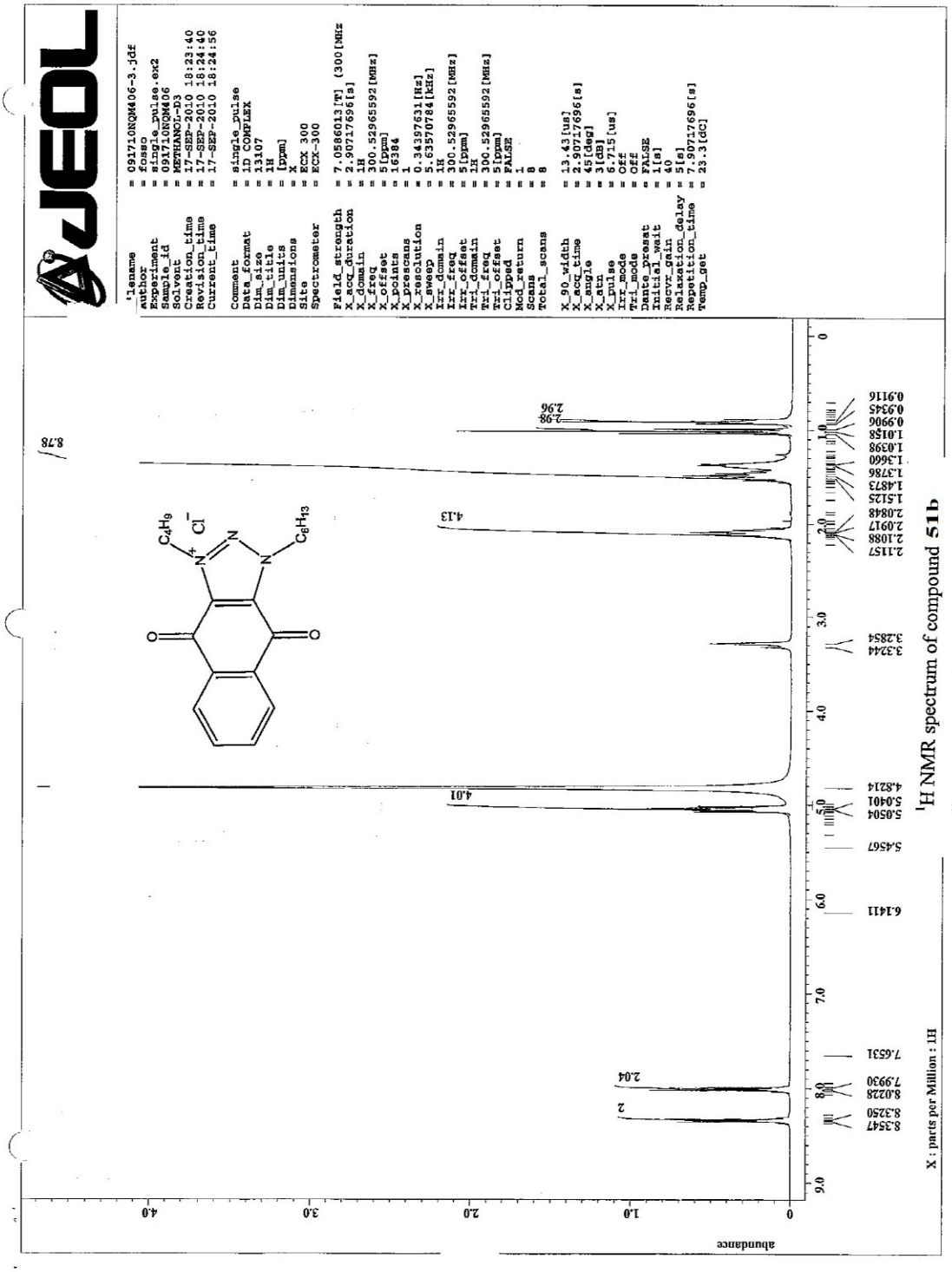
^{13}C NMR spectrum of compound **50f**



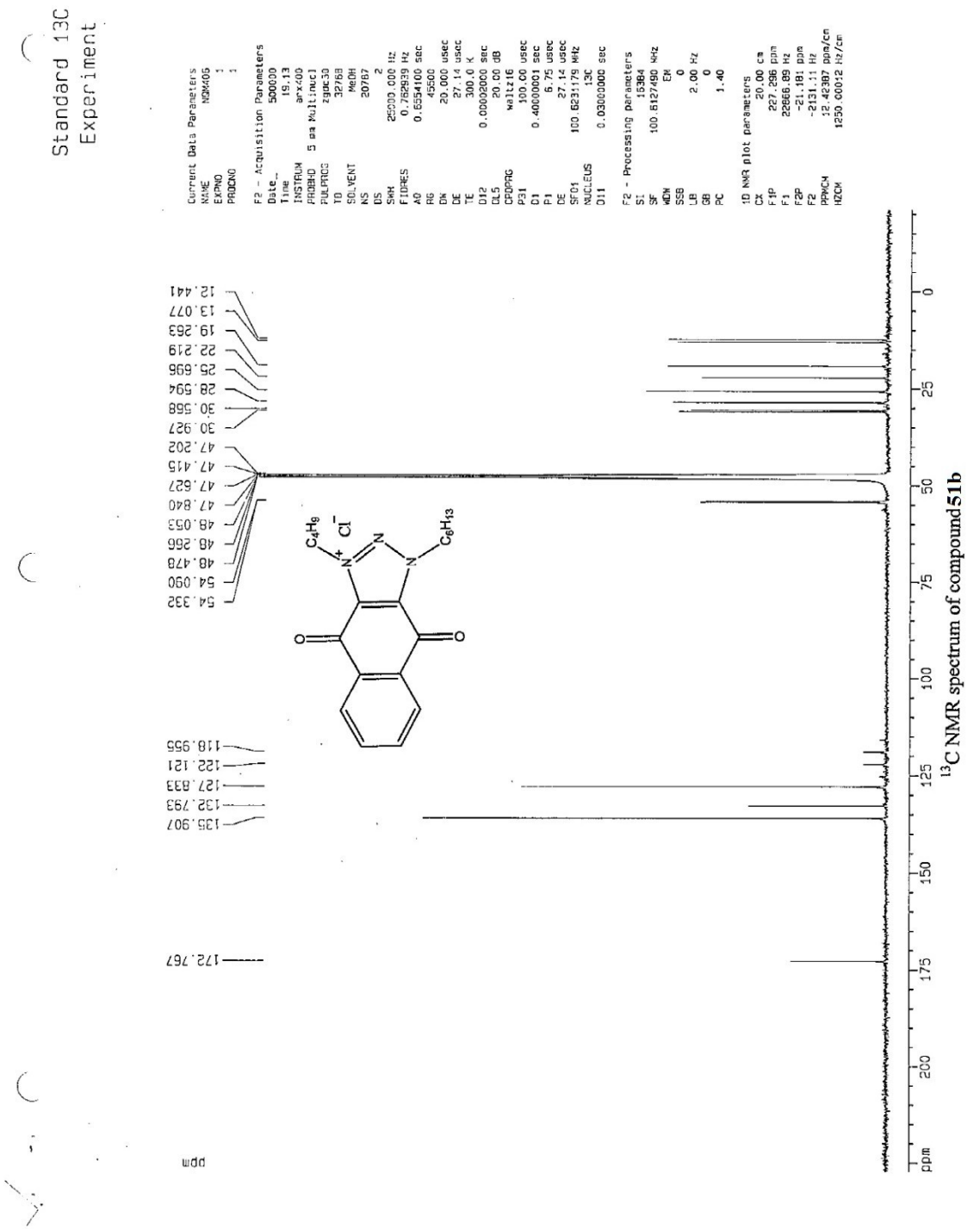
^1H NMR spectrum of compound **51a**



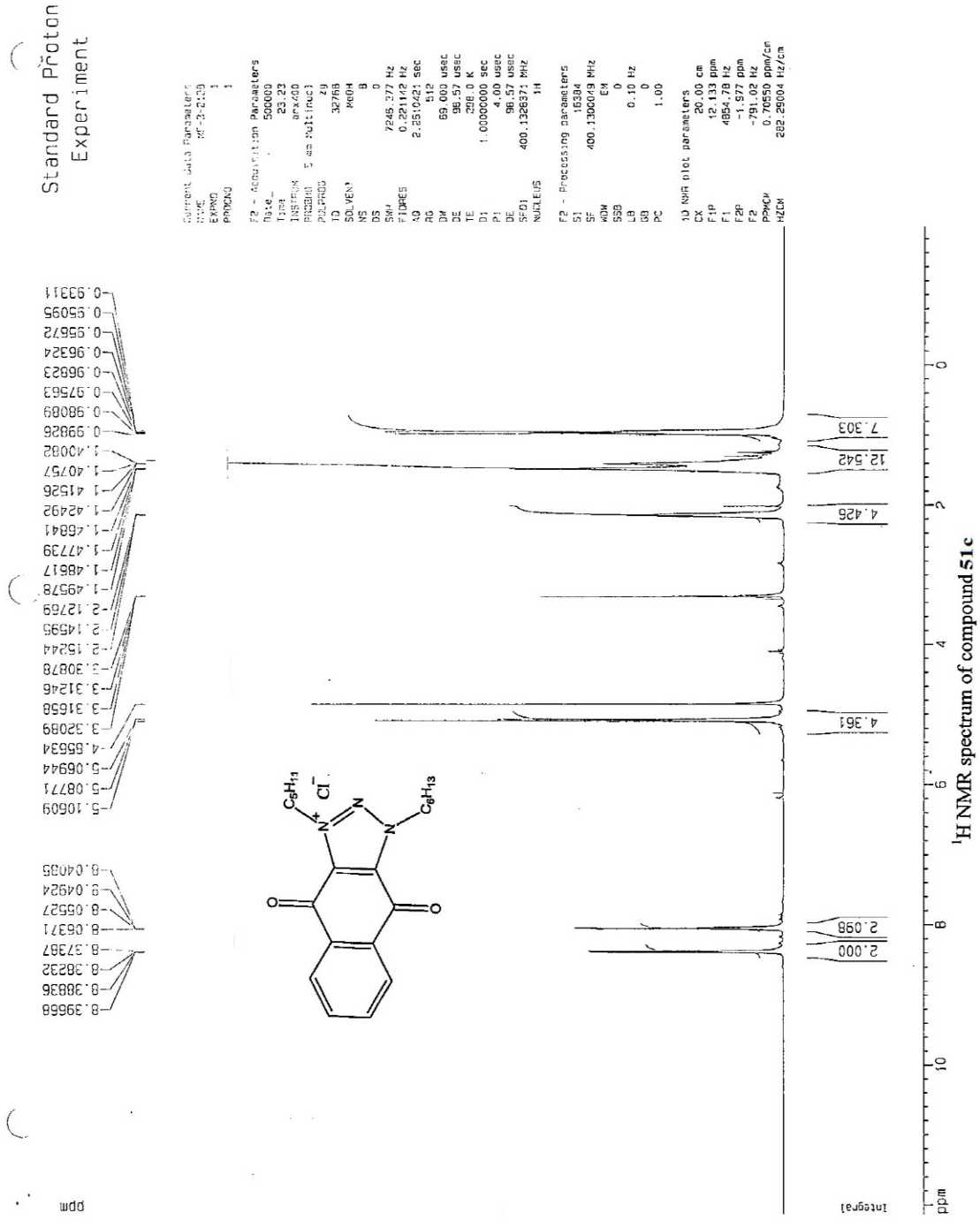
^{13}C NMR spectrum of compound **51a**



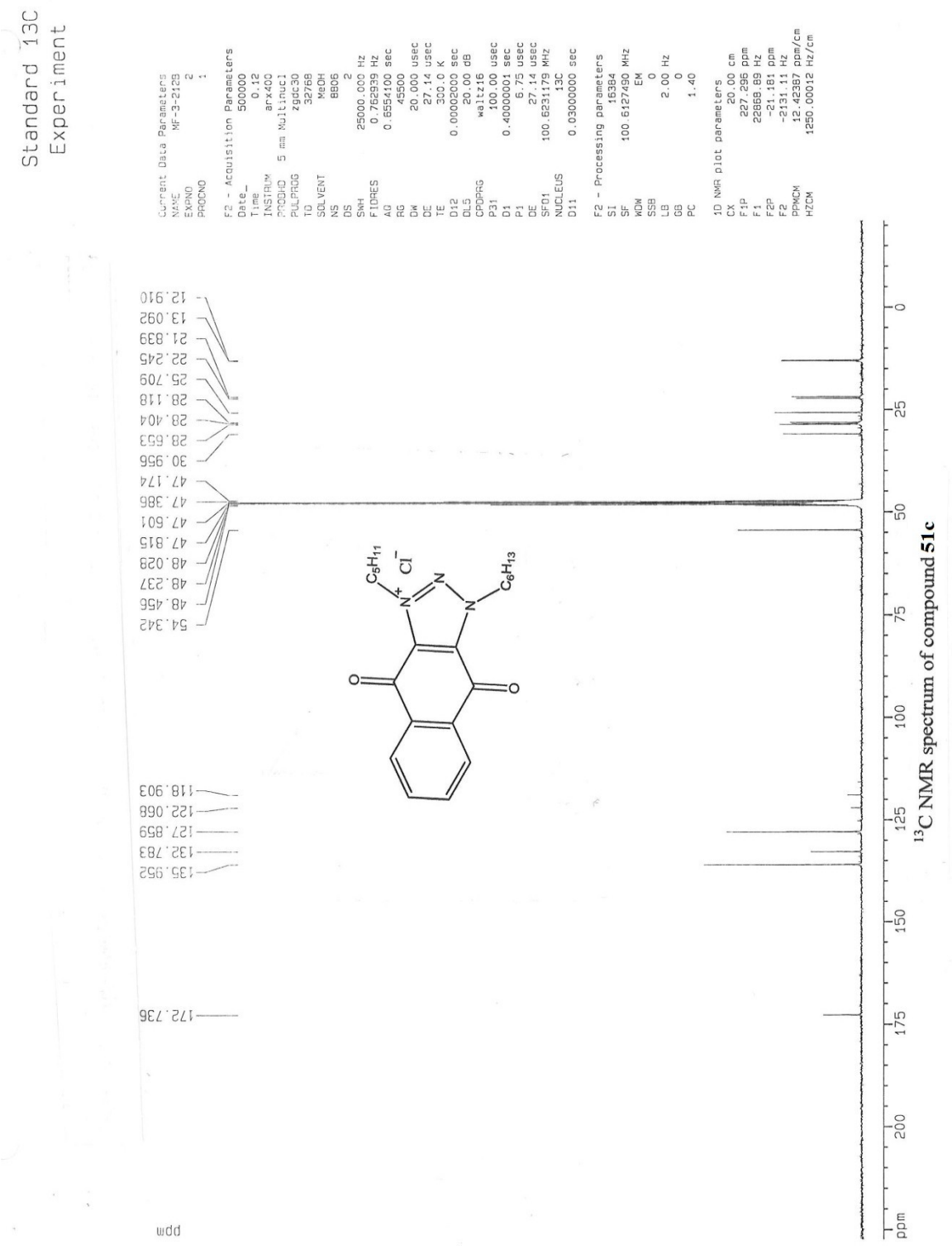
^{1}H NMR spectrum of compound **51b**



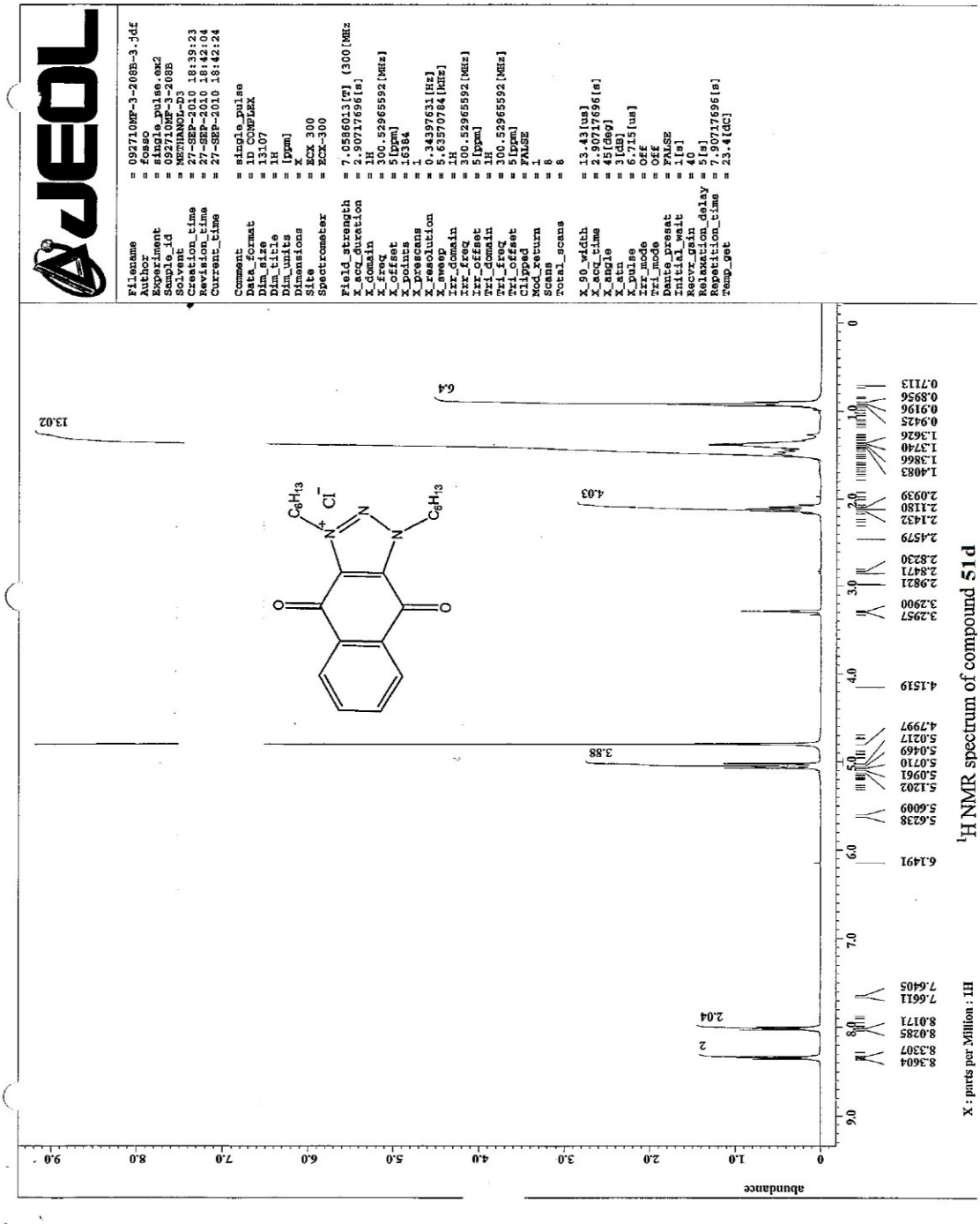
^{13}C NMR spectrum of compound **51b**



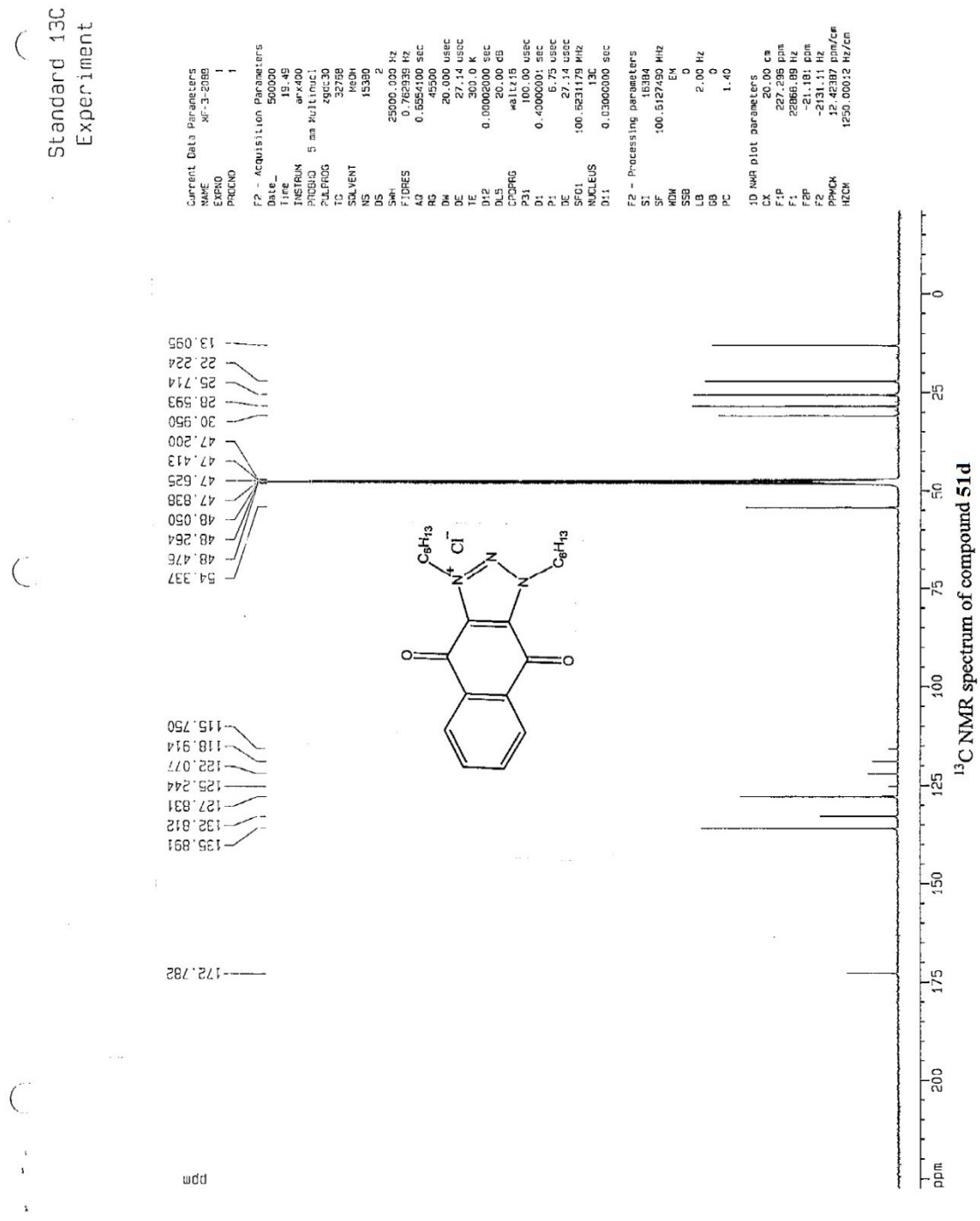
^{1}H NMR spectrum of compound **51c**



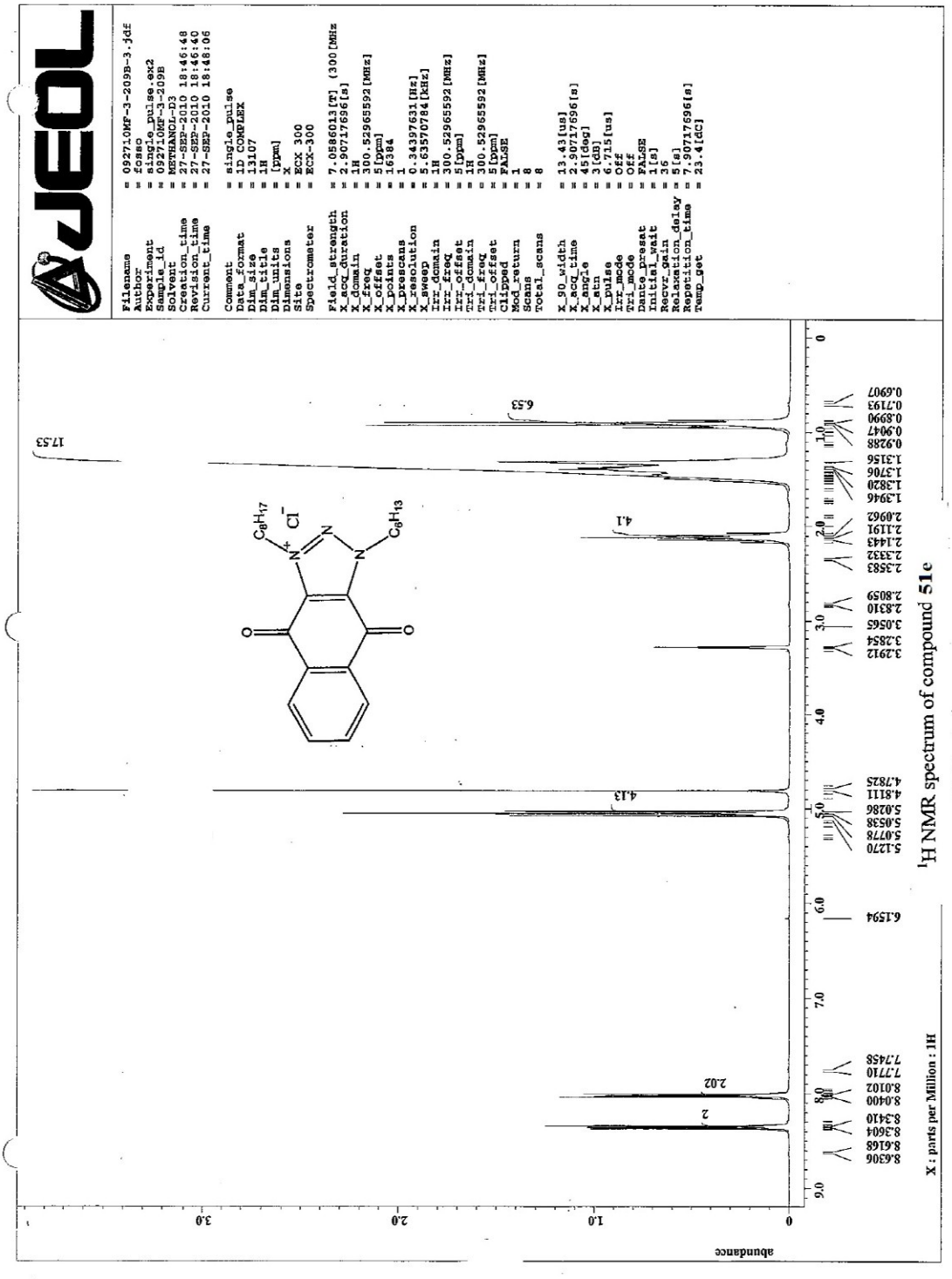
^{13}C NMR spectrum of compound **51c**



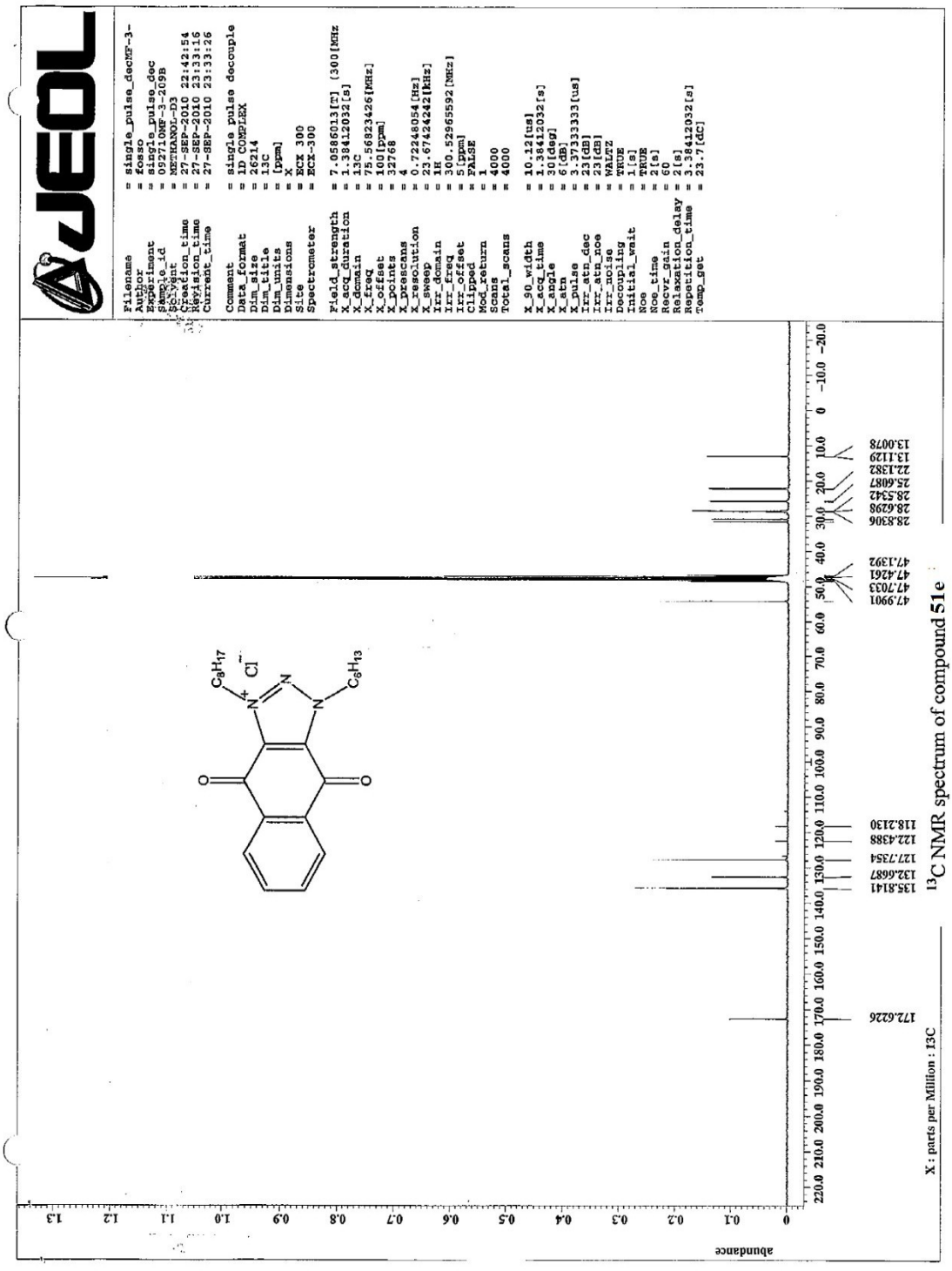
^{1}H NMR spectrum of compound **51d**



^{13}C NMR spectrum of compound **51d**



^{1}H NMR spectrum of compound **51e**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Author = fosso
Experiment = single_pulse_dec
sample_id = 092710MF-3-209B
Solvent = METHANOL-D3
Creation_time = 27-SEP-2010 22:42:54
Revision_time = 27-SEP-2010 23:33:16
Current_time = 27-SEP-2010 23:33:26
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Dim_title = 13C
Dim_units = [ppm]
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Spectrometer = ECX-300
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X_domain = 13C
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X_offset = 100[ppm]
X_points = 32768
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X_sweep = 23.67424242[kHz]
Irr_domain = 1H
Irr_freq = 300.52965592[MHz]
Irr_offset = 5[ppm]
Clipped = PULSE
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X_atn = 6[dB]
X_pulse = 3.37333333[us]
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Irr_atn_noe = 23[dB]
Irr_noise = WALTZ
Decoupling = TRUE
Initial_wait = 1[s]
Noe = TRUE
Noe_time = 2[s]
Rec_gain = 0
Relaxation_delay = 2[s]
Repetition_time = 3.38412032[s]
Temp_get = 23.7[dC]
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X : parts per Million : 13C
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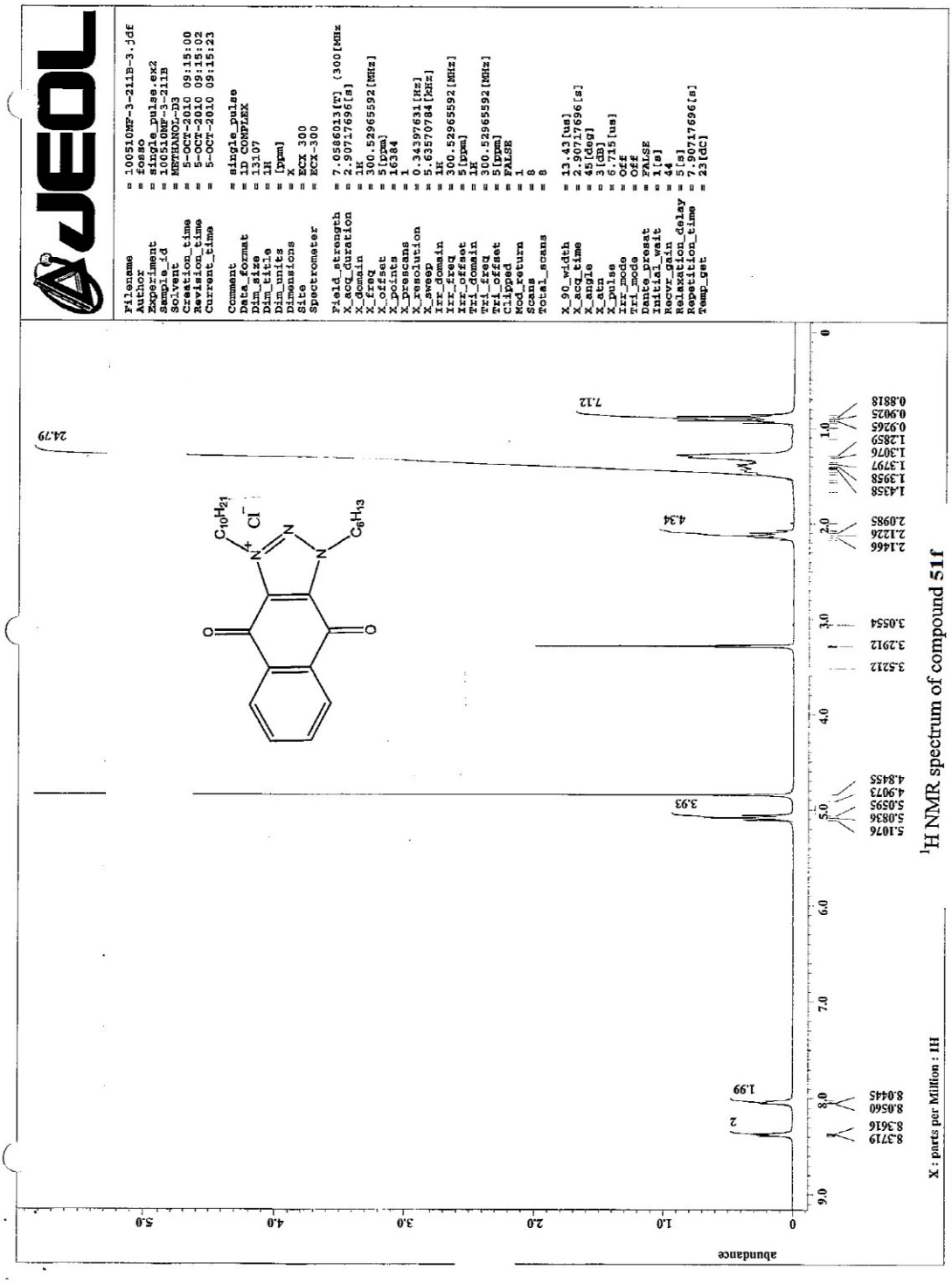
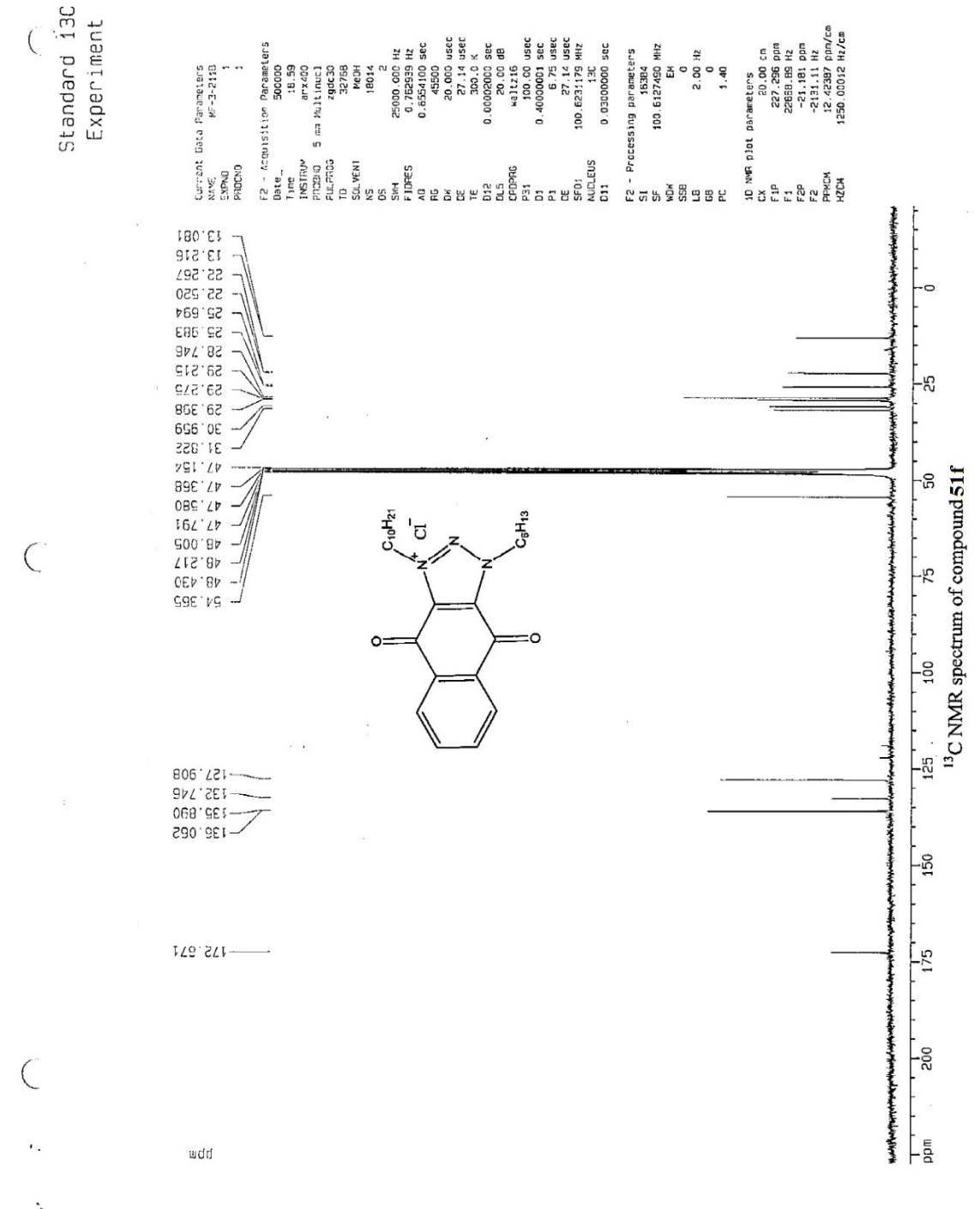
135.8141
132.6687
127.7354
122.4388
118.2130
47.9901
47.7033
47.4261
47.1392
28.8306
28.6298
28.5342
25.6087
22.1382
13.1129
13.0078
^{13}C NMR spectrum of compound **51e**



^{1}H NMR spectrum of compound **51f**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PROCNO 1
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Time_ 15.59
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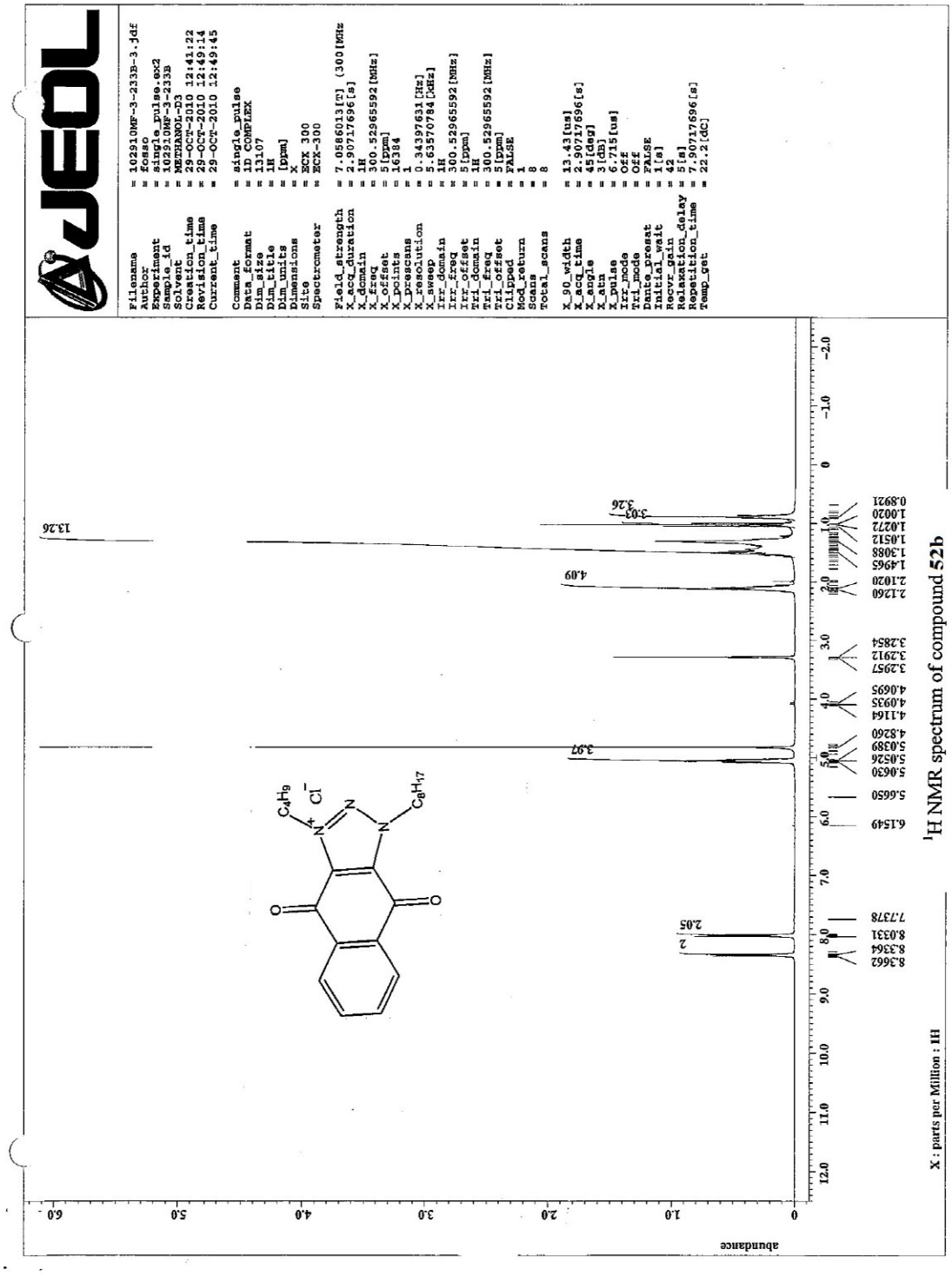
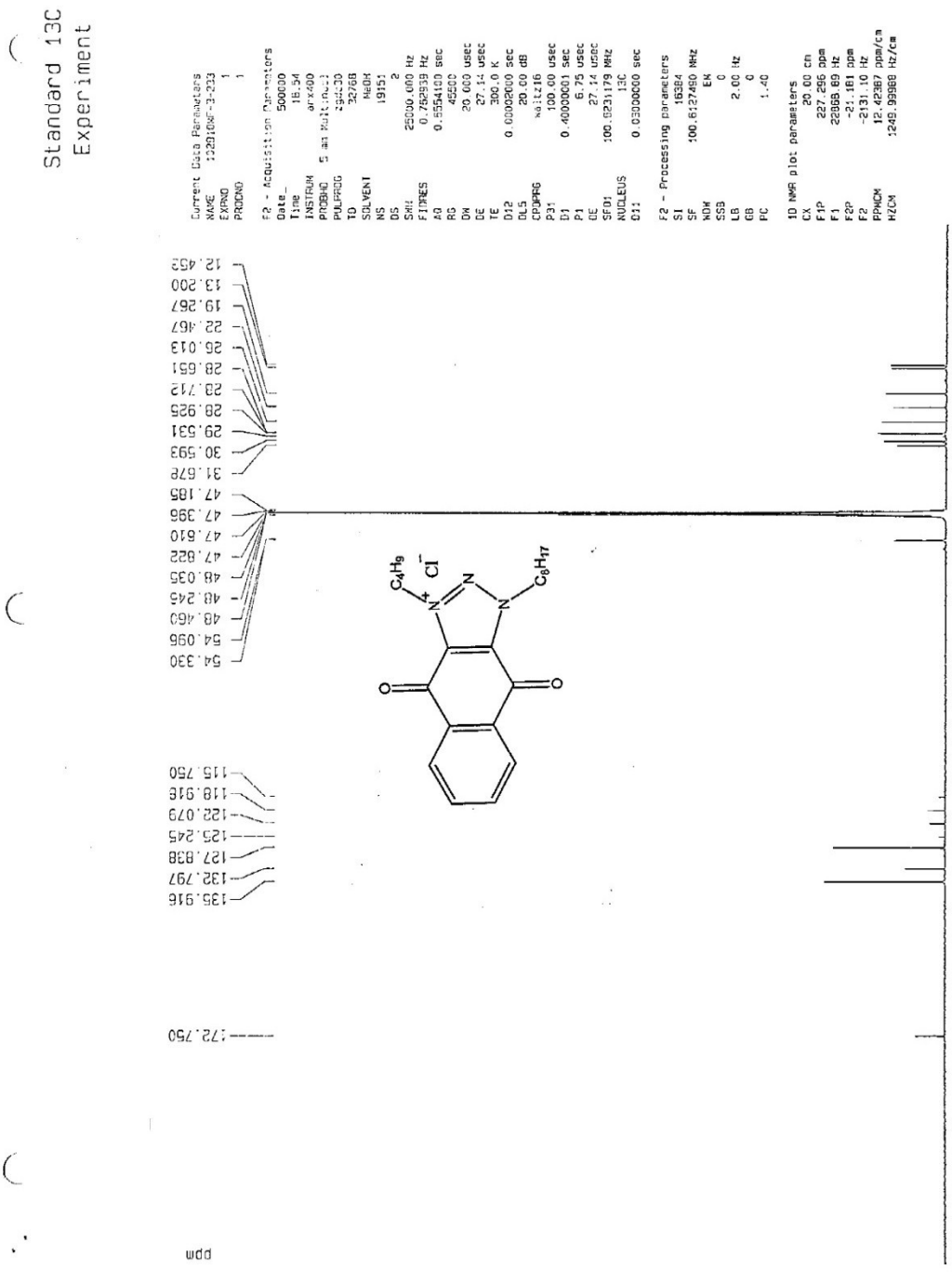
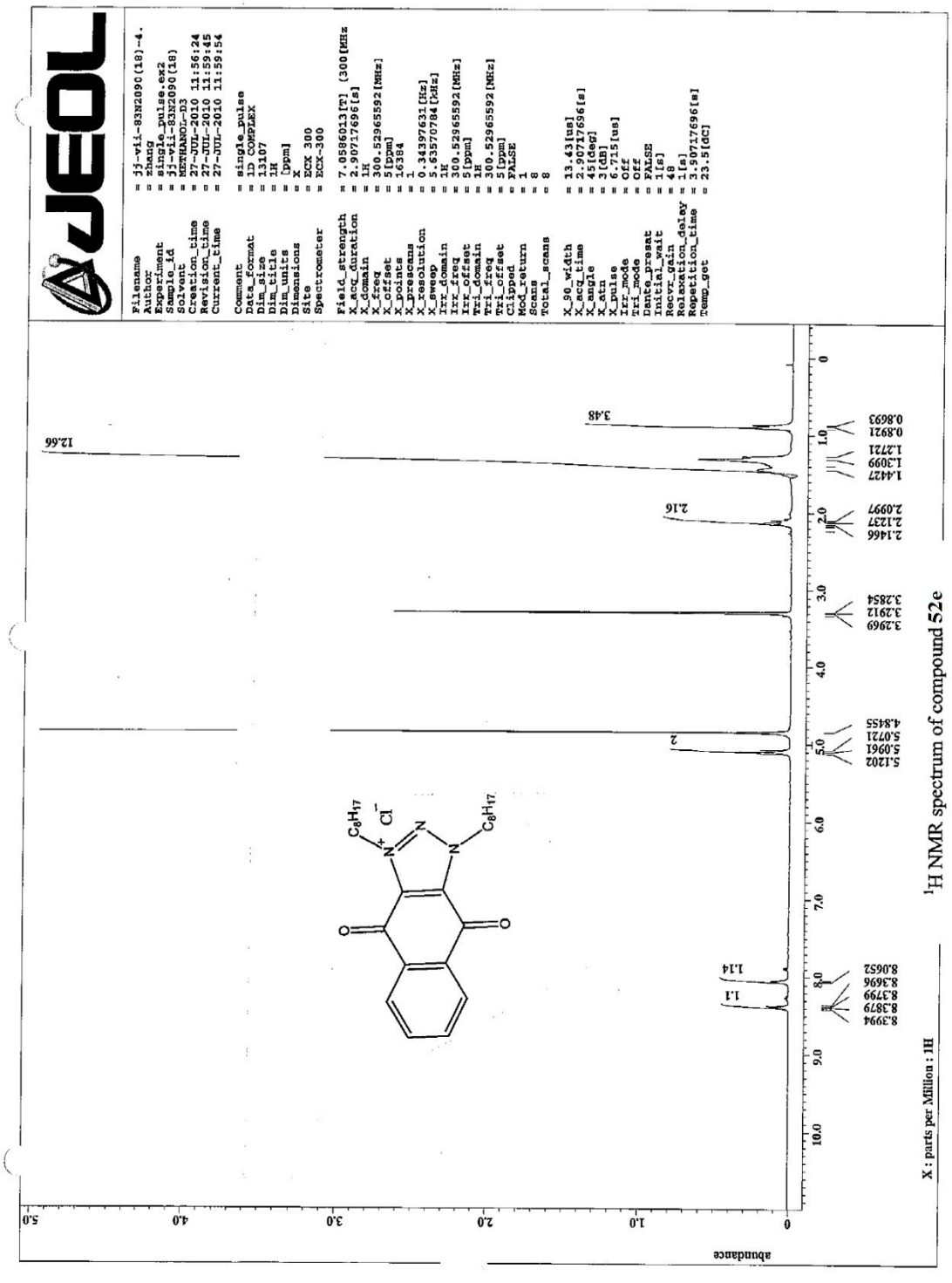
PROBHD 5 mm Multinucl
PULPROG zgdc30
TD 32768
SOLVENT MeOH
NS 18014
DS 2
SWH 25000.000 Hz
FIDRES 0.762939 Hz
AQ 0.6554100 sec
RG 45500
DW 20.000 usec
DE 27.14 usec
TE 300.0 K
D12 0.00002000 sec
DL5 20.00 dB
CPDPRG waltz16
P31 100.00 usec
D1 0.40000001 sec
P1 6.75 usec
DE 27.14 usec
SFO1 100.6231179 MHz
NUCLEUS 13C
D11 0.03000000 sec
F2 - Processing parameters
SI 16384
SF 100.6127490 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 227.296 ppm
F1 22868.89 Hz
F2P -21.181 ppm
F2 -2131.11 Hz
PPMCM 12.42387 ppm/cm
HZCM 1250.00012 Hz/cm
13.081
13.216
22.267
22.520
25.694
25.983
28.746
29.215
29.275
29.358
30.959
31.822
47.154
47.368
47.580
47.791
48.005
48.217
48.430
54.365
127.908
132.746
135.890
136.062
172.671
ppm
ppm
^{13}C NMR spectrum of compound **51f**



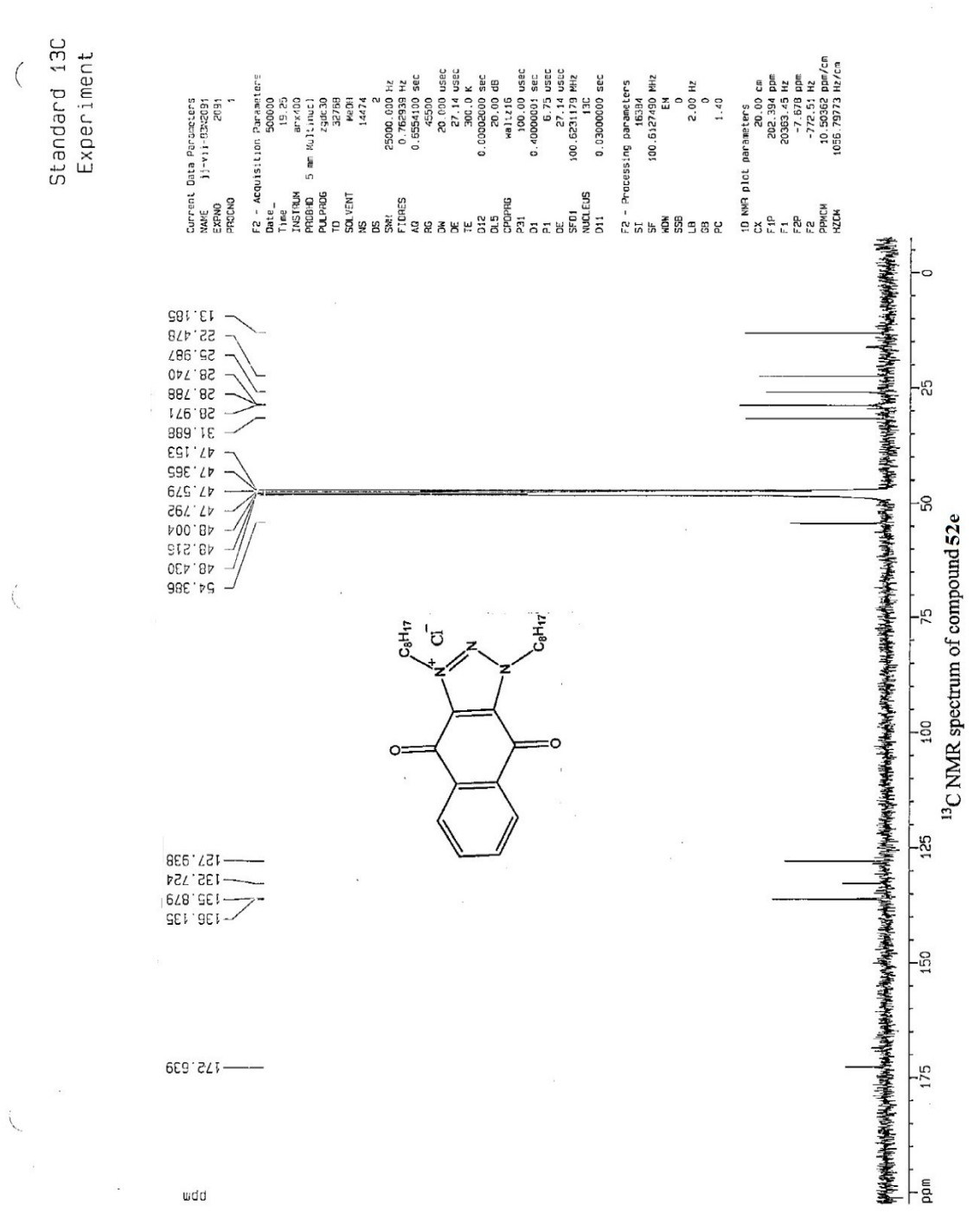
^{1}H NMR spectrum of compound **52b**



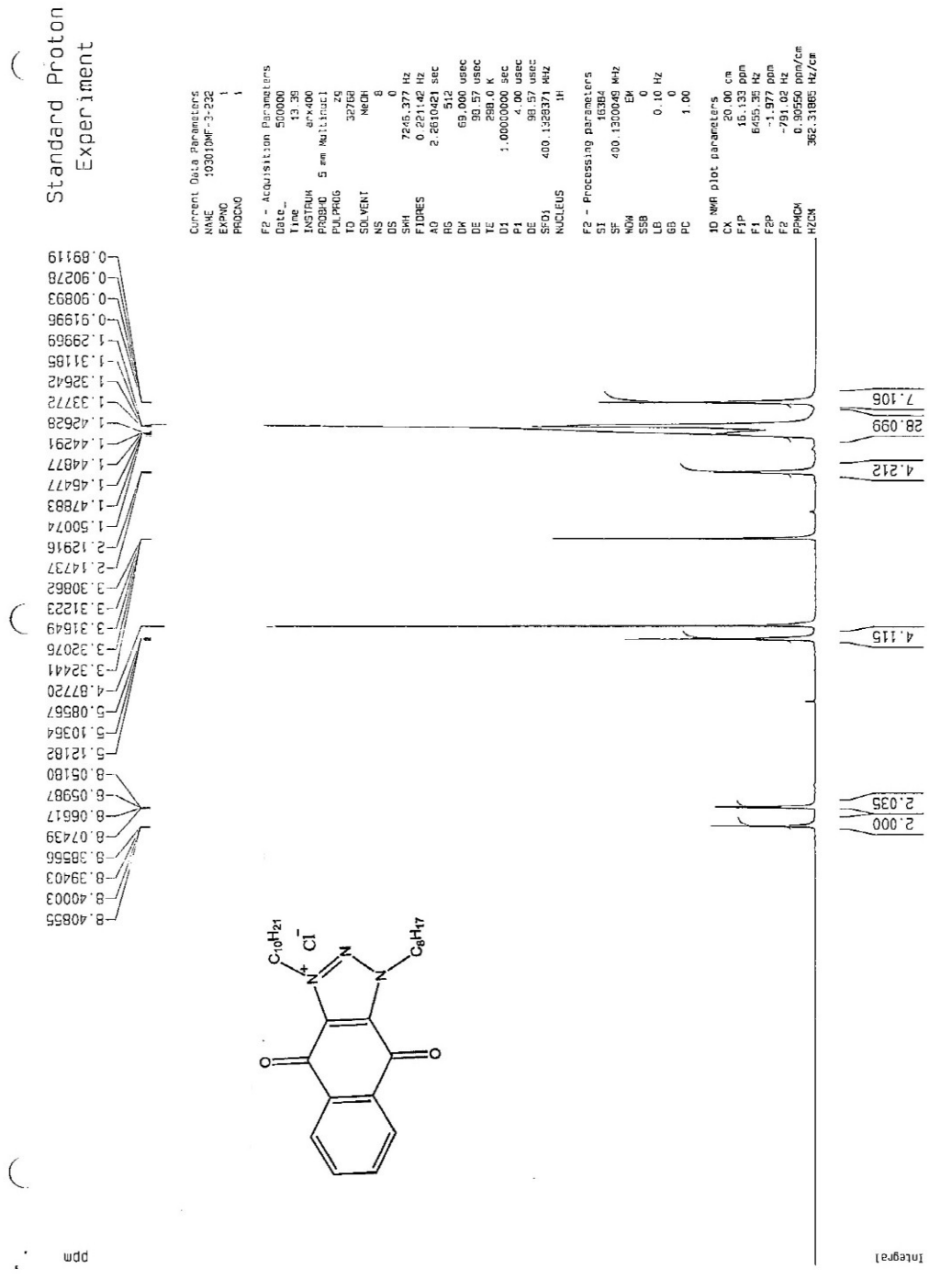
^{13}C NMR spectrum of compound **52b**



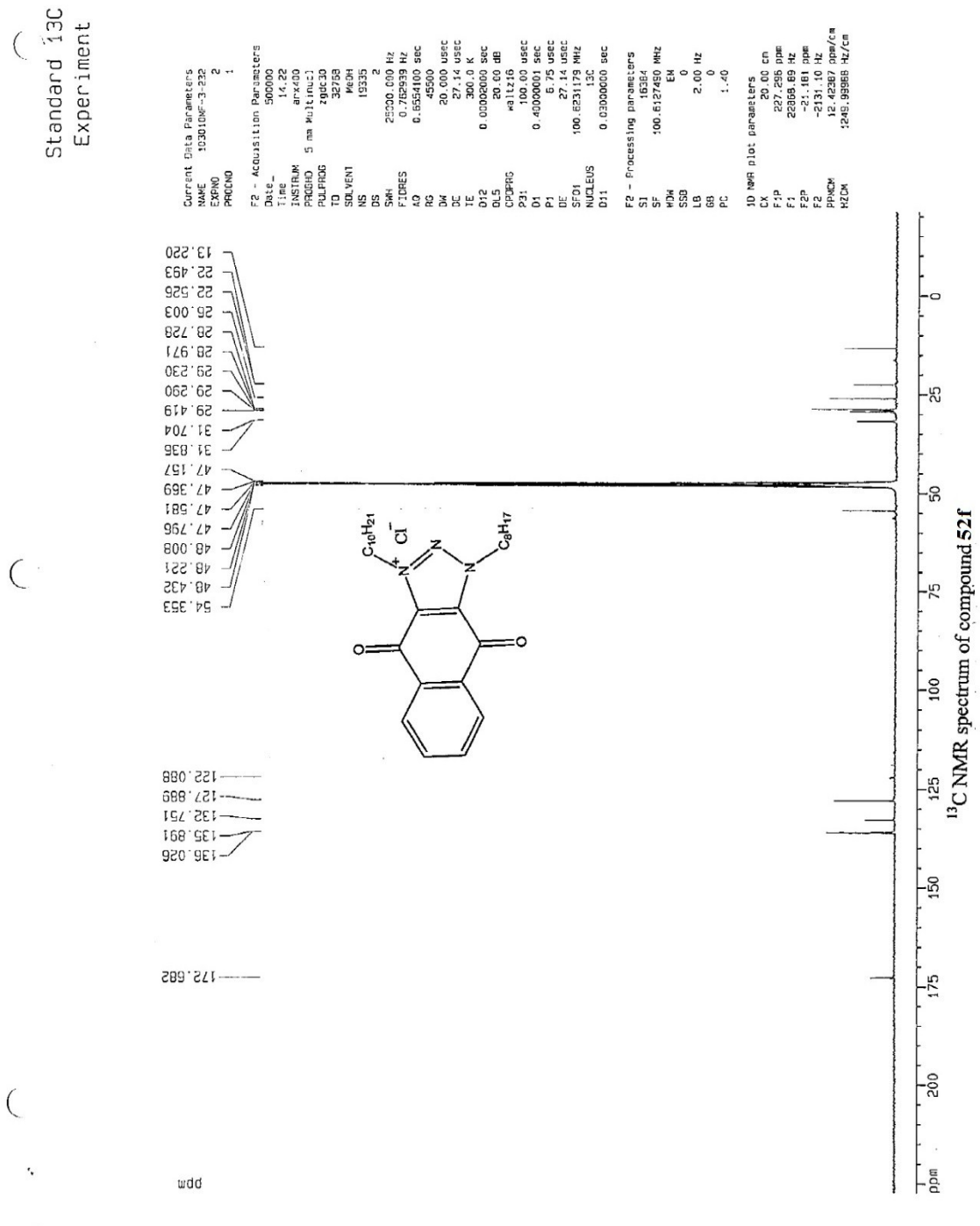
^{1}H NMR spectrum of compound **52e**



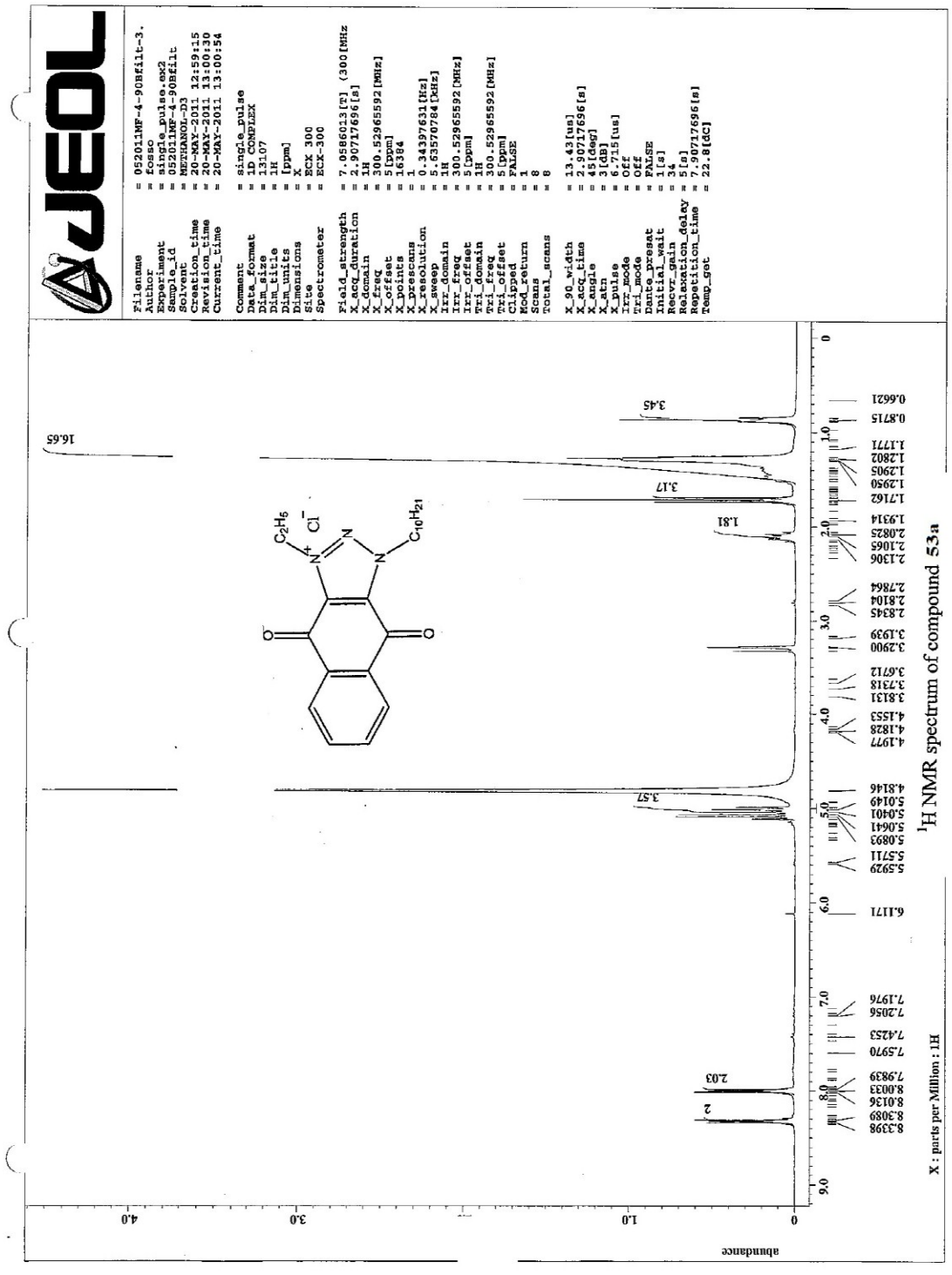
^{13}C NMR spectrum of compound **52e**



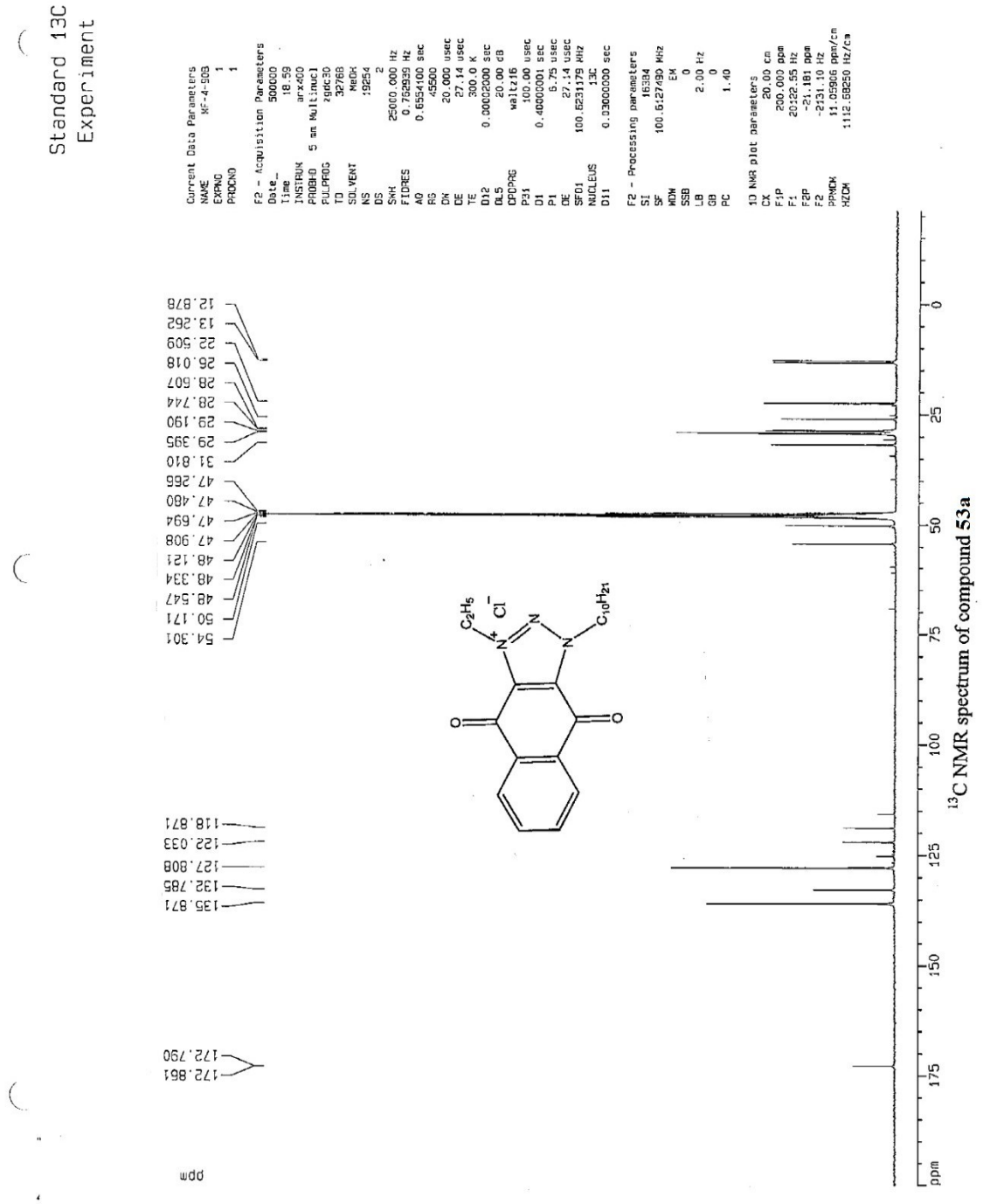
^{1}H NMR spectrum of compound **52f**



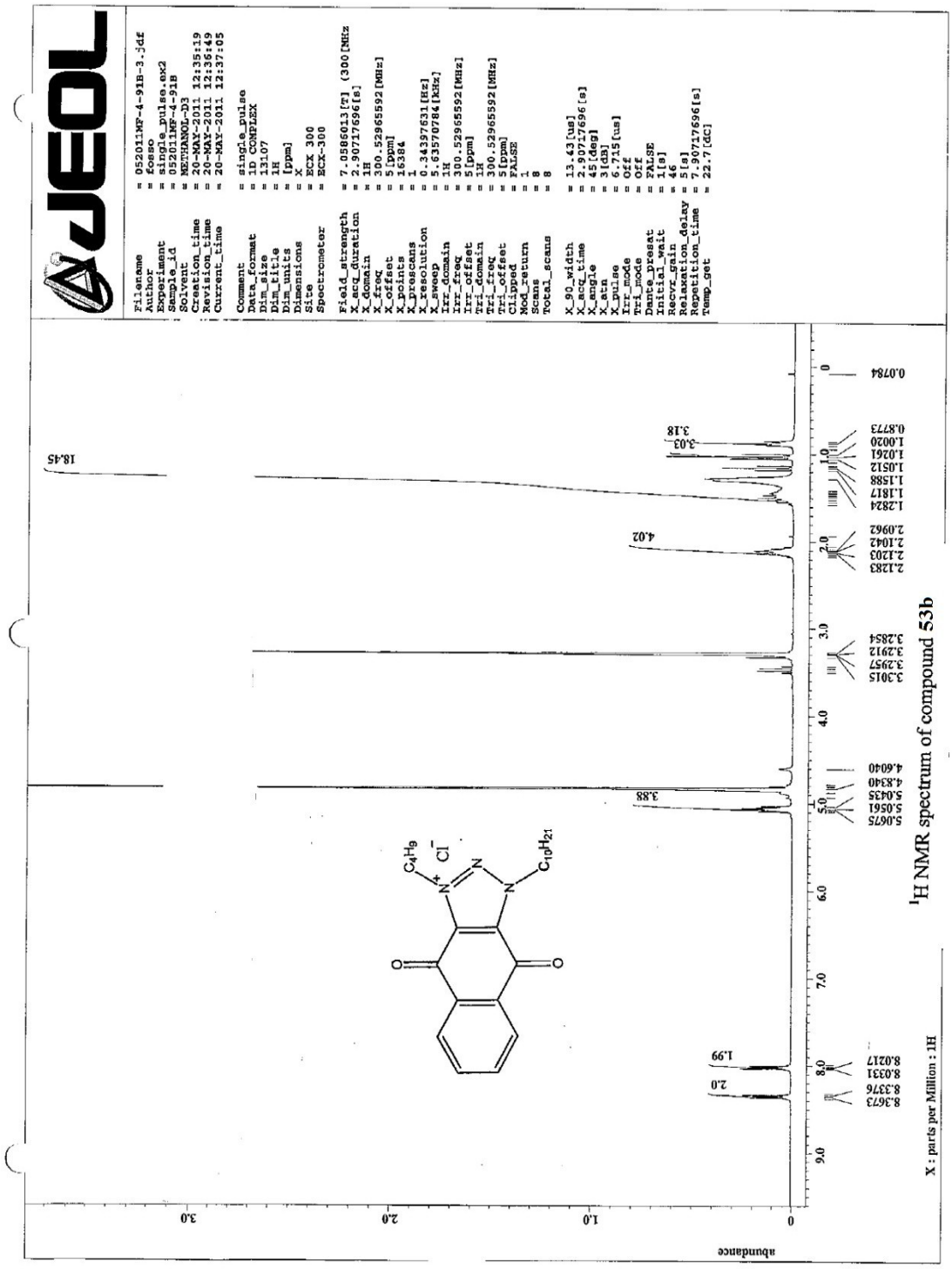
^{13}C NMR spectrum of compound **52f**



^{1}H NMR spectrum of compound **53a**



^{13}C NMR spectrum of compound **53a**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Filename = 052011MF-4-91B-3.3df
Author = foeso
Experiment = single_pulse.ex2
Sample_id = 052011MF-4-91B
Solvent = METHANOL-D3
Creation_time = 20-MAY-2011 12:35:19
Revision_time = 20-MAY-2011 12:36:49
Current_time = 20-MAY-2011 12:37:05
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Dim_units = [ppm]
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X_domain = 1H
X_freq = 300.52965592[MHz]
X_offset = 5.[ppm]
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X_resolution = 0.34397631[Hz]
X_sweep = 5.63570784[kHz]
Irr_domain = 1H
Irr_freq = 300.52965592[MHz]
Irr_offset = 5[ppm]
Tri_domain = 1H
Tri_freq = 300.52965592[MHz]
Tri_offset = 5[ppm]
Clipped = FALSE
Num_return = 1
Scans = 8
Total_scans = 8
X_90_width = 13.43[us]
X_acq_time = 2.90717696[s]
X_angle = 45[deg]
X_atn = 3[dB]
X_pulse = 6.715[us]
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Tri_mode = Off
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Initial_wait = 1[s]
Recvr_gain = 46
Relaxation_delay = 5[s]
Repetition_time = 7.90717696[s]
Temp_get = 22.7[dC]
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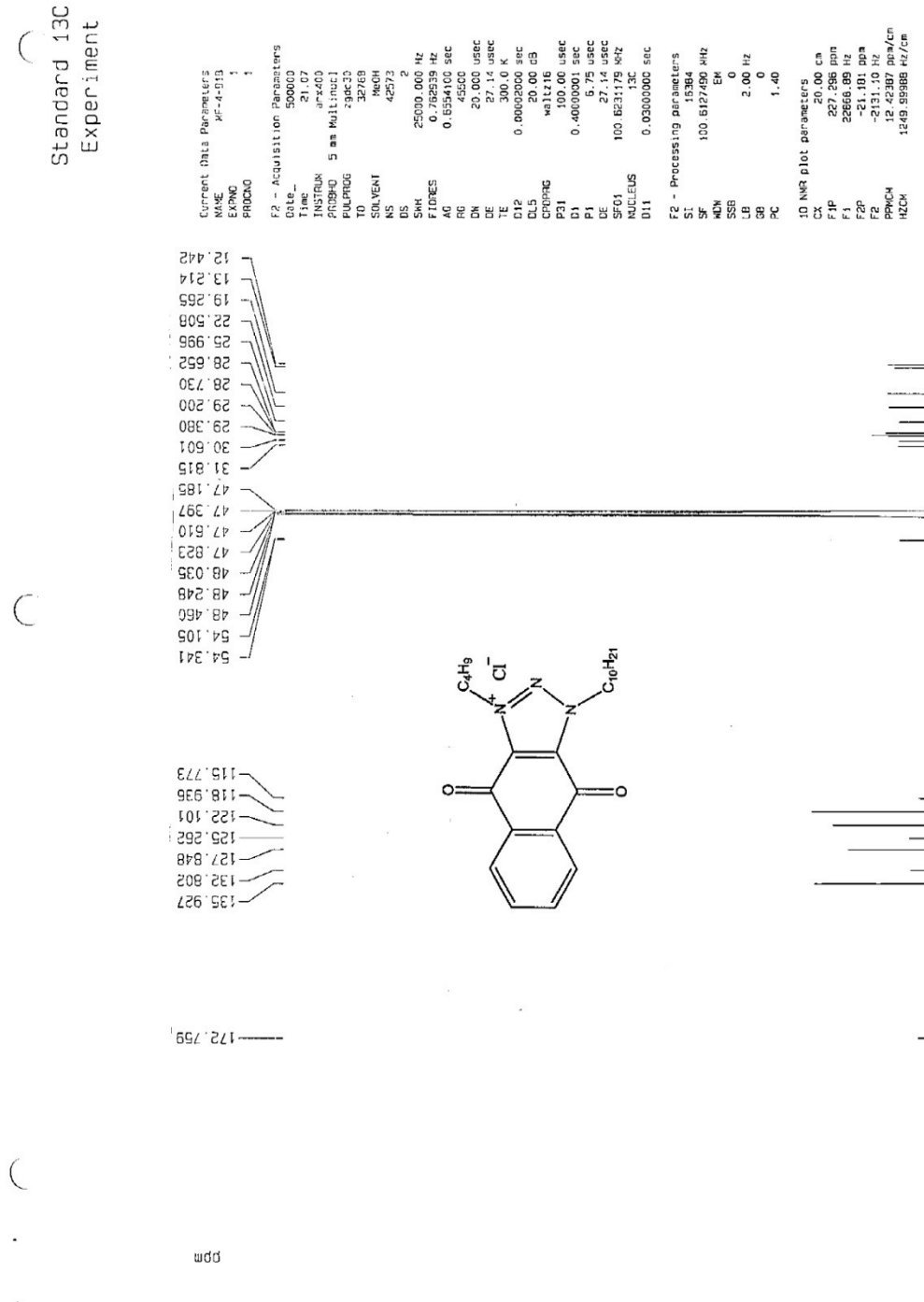
4.02
3.88
3.18
3.03
1.99
2.0
8.3673
8.3376
8.0331
8.0217
5.0675
5.0561
5.0435
4.8340
4.6040
3.3015
3.2957
3.2912
3.2854
2.1283
2.1203
2.1042
2.0962
1.2824
1.1817
1.1588
1.0512
1.0261
1.0020
0.8773
0.0784
abundance
X : parts per Million : 1H
^{1}H NMR spectrum of compound **53b**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Current Data Parameters
NAME MF-4-019
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 500603
Time 21.07
INSTRUM spx400
PROBHD 5 mm Multinucl
PULPROG zgdc30
TD 32768
SOLVENT MeOH
NS 42573
DS 2
SWH 25000.000 Hz
FIDRES 0.762939 Hz
AQ 0.65544100 sec
RG 45600
DW 20.000 usec
DE 27.14 usec
TE 300.0 K
D12 0.00002000 sec
DL5 20.00 dB
CPDPRG waltz16
P31 100.00 usec
D1 0.40000001 sec
P1 6.75 usec
DE 27.14 usec
SFO1 100.6231179 MHz
NUCLEUS 13C
D11 0.03000000 sec
F2 - Processing parameters
SI 15384
SF 100.6127490 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 227.296 ppm
F1 22868.89 Hz
F2P -21.101 ppm
F2 -2131.10 Hz
PPMCM 12.42307 ppm/cm
HZCM 1249.99988 Hz/cm
172.759
135.927
132.802
127.848
125.262
122.101
118.936
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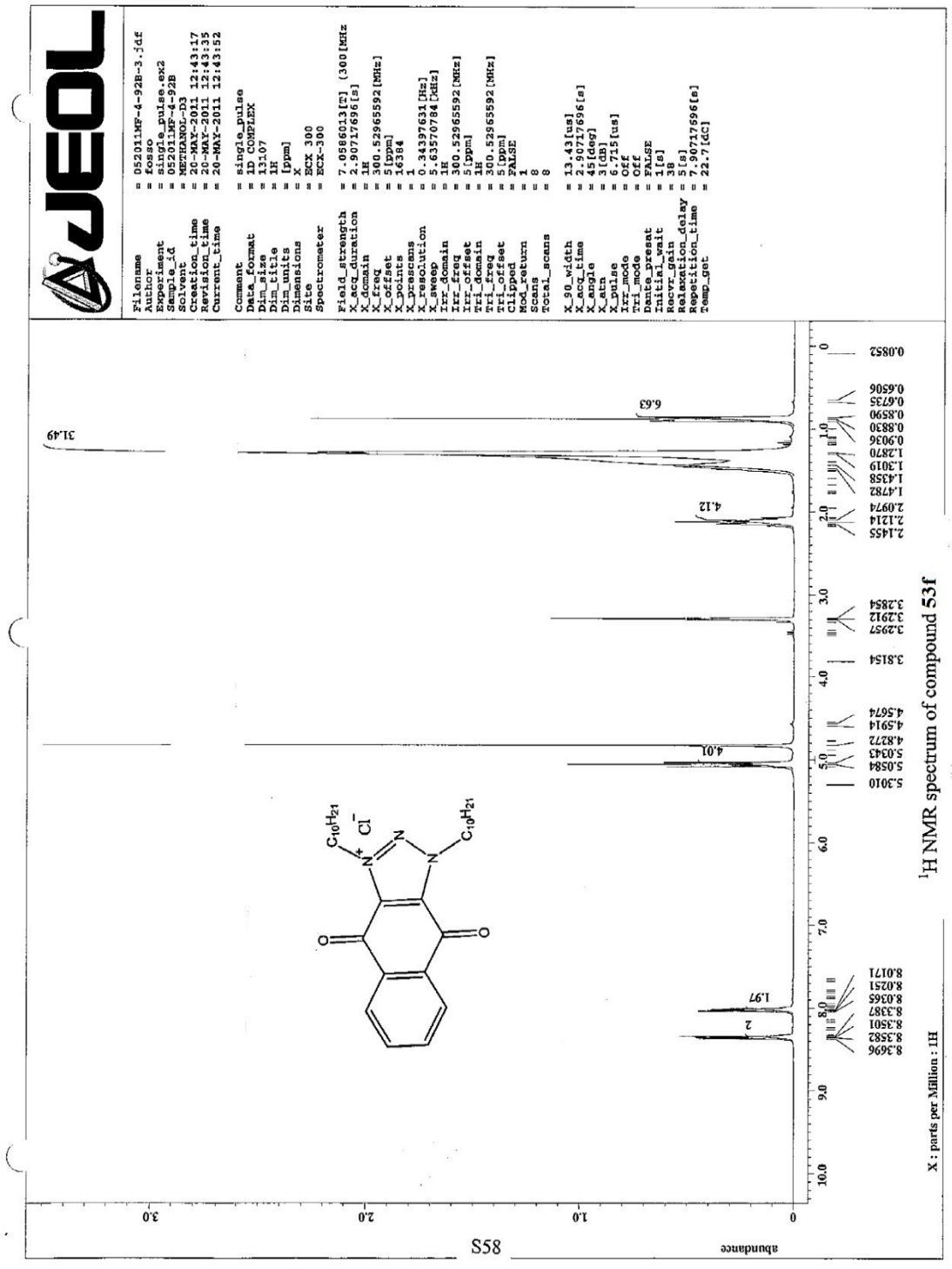
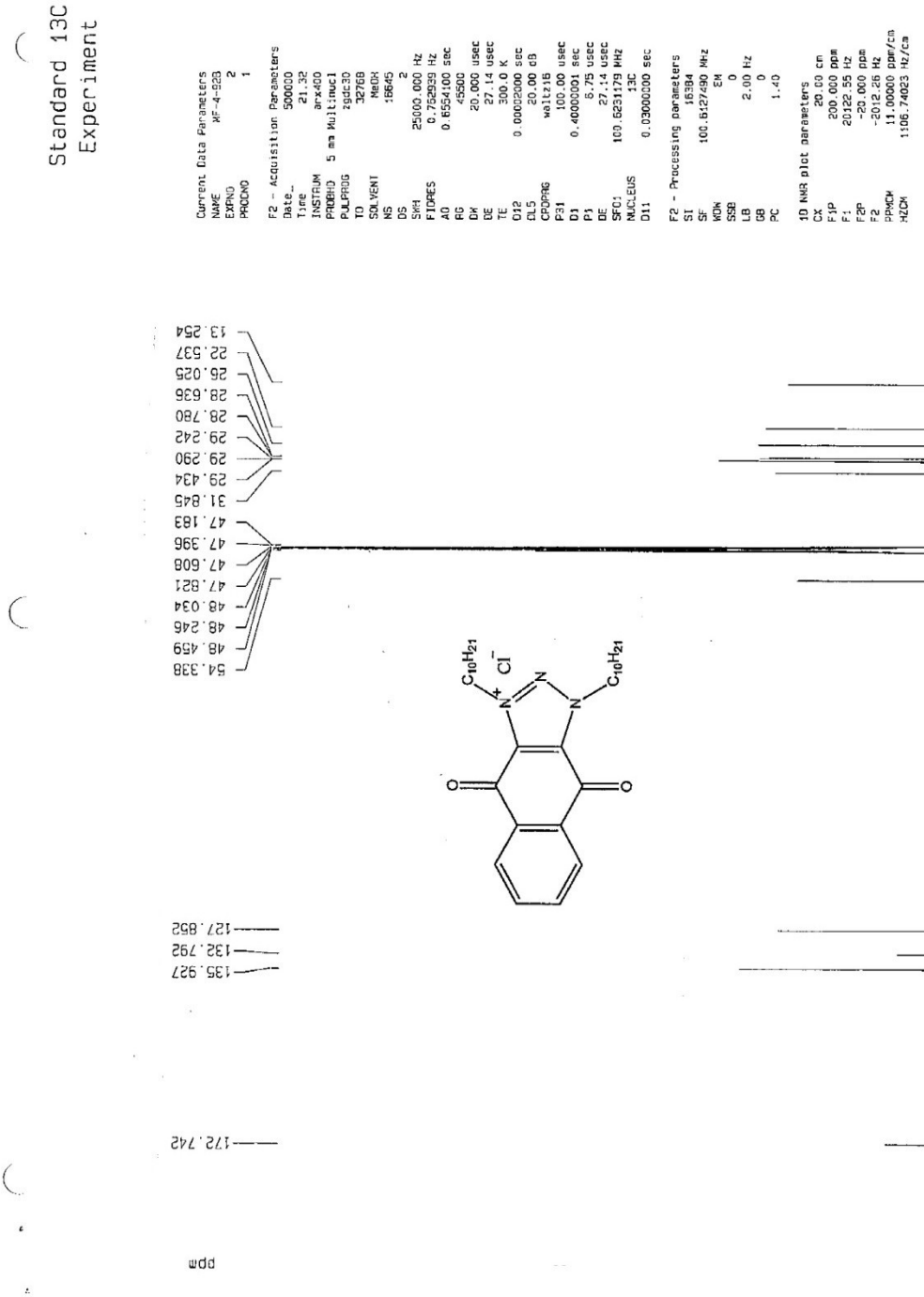
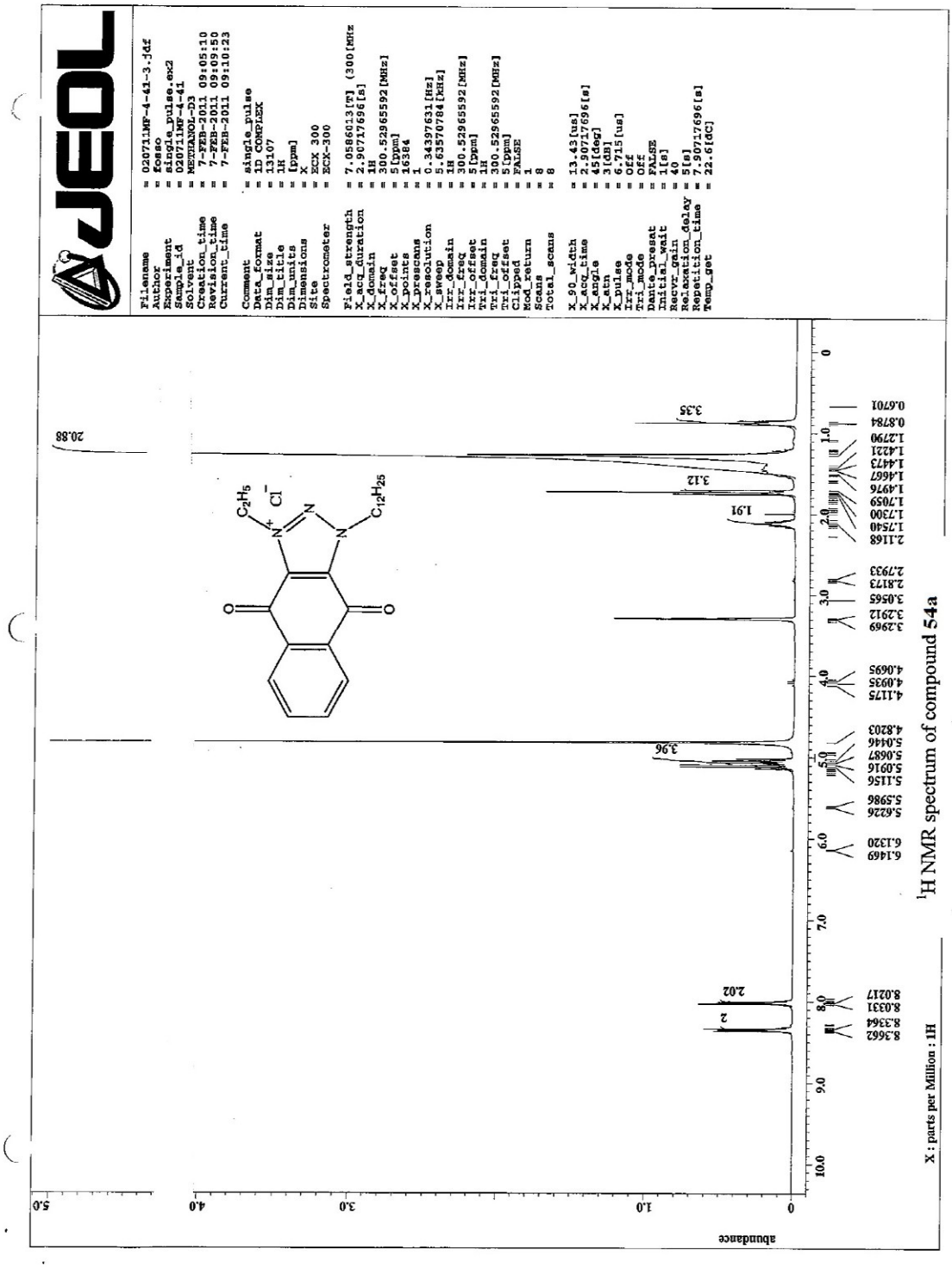
54.105
48.460
48.248
48.035
47.823
47.610
47.397
47.185
31.815
30.601
29.380
29.200
28.730
28.652
25.996
22.508
19.265
13.214
12.442
ppm
200
175
150
125
100
75
50
25
0
C_4H_9
Cl^-
$C_{10}H_{21}$
^{13}C NMR spectrum of compound **53b**



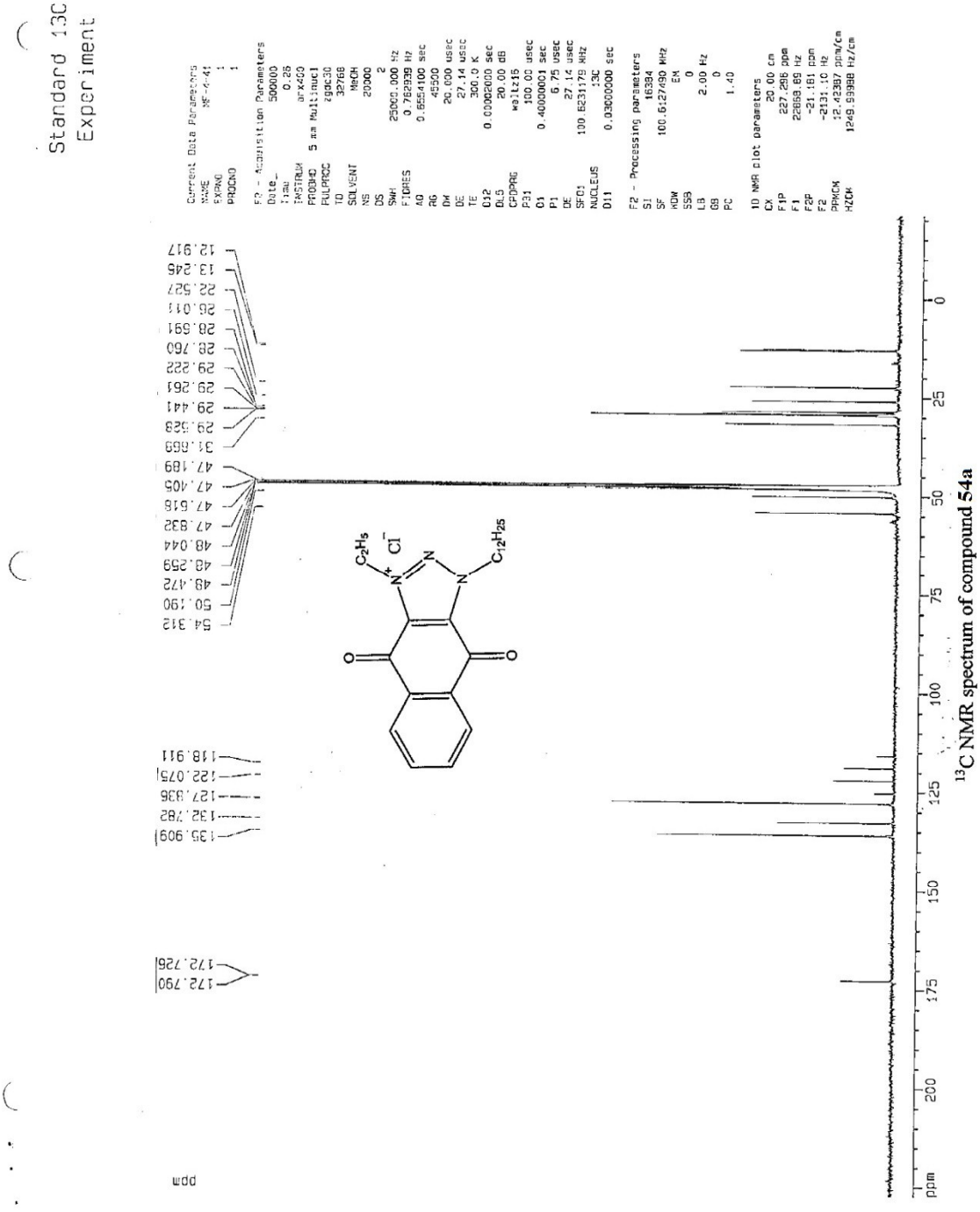
^{1}H NMR spectrum of compound **53f**



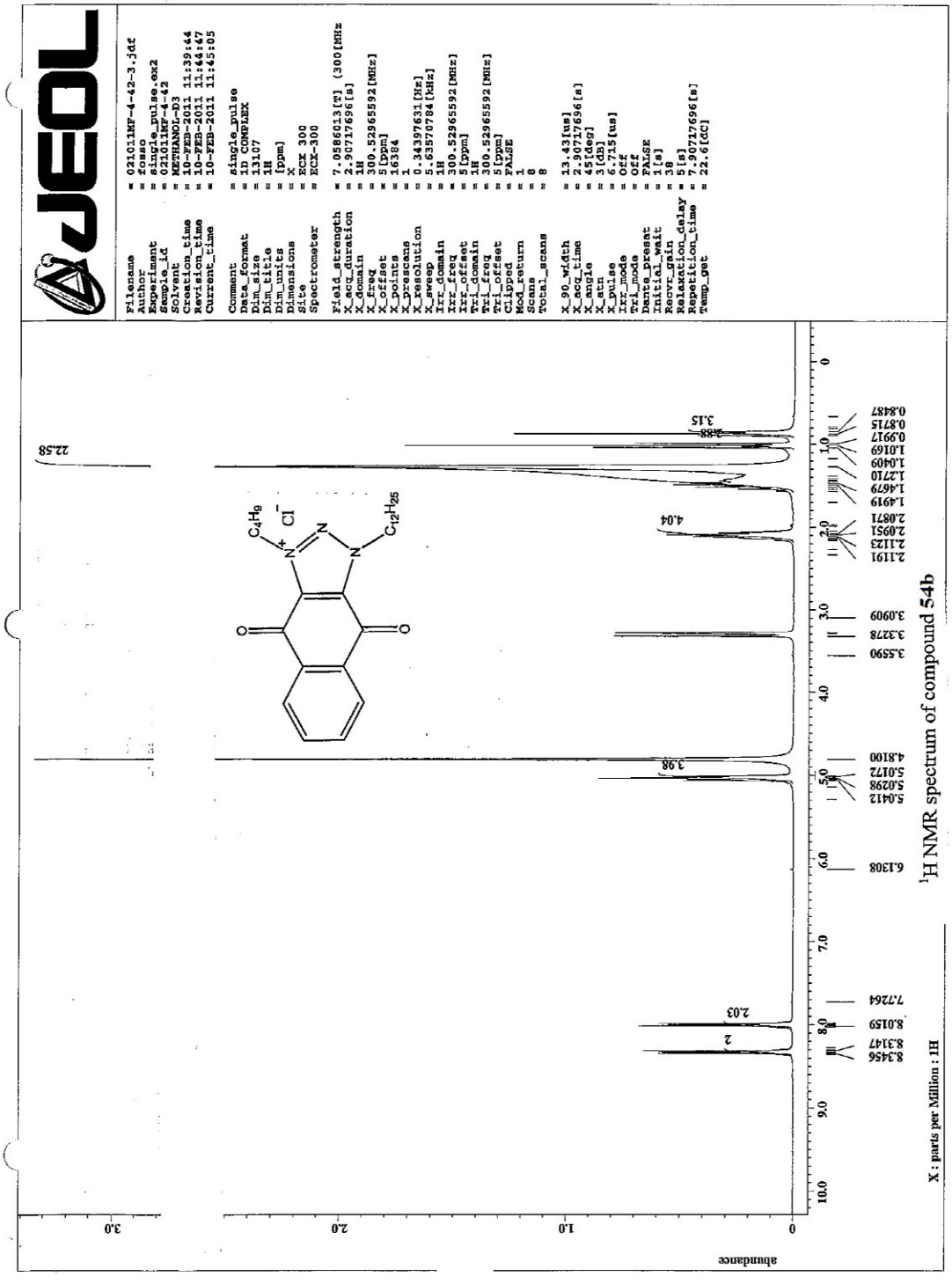
^{13}C NMR spectrum of compound **53f**



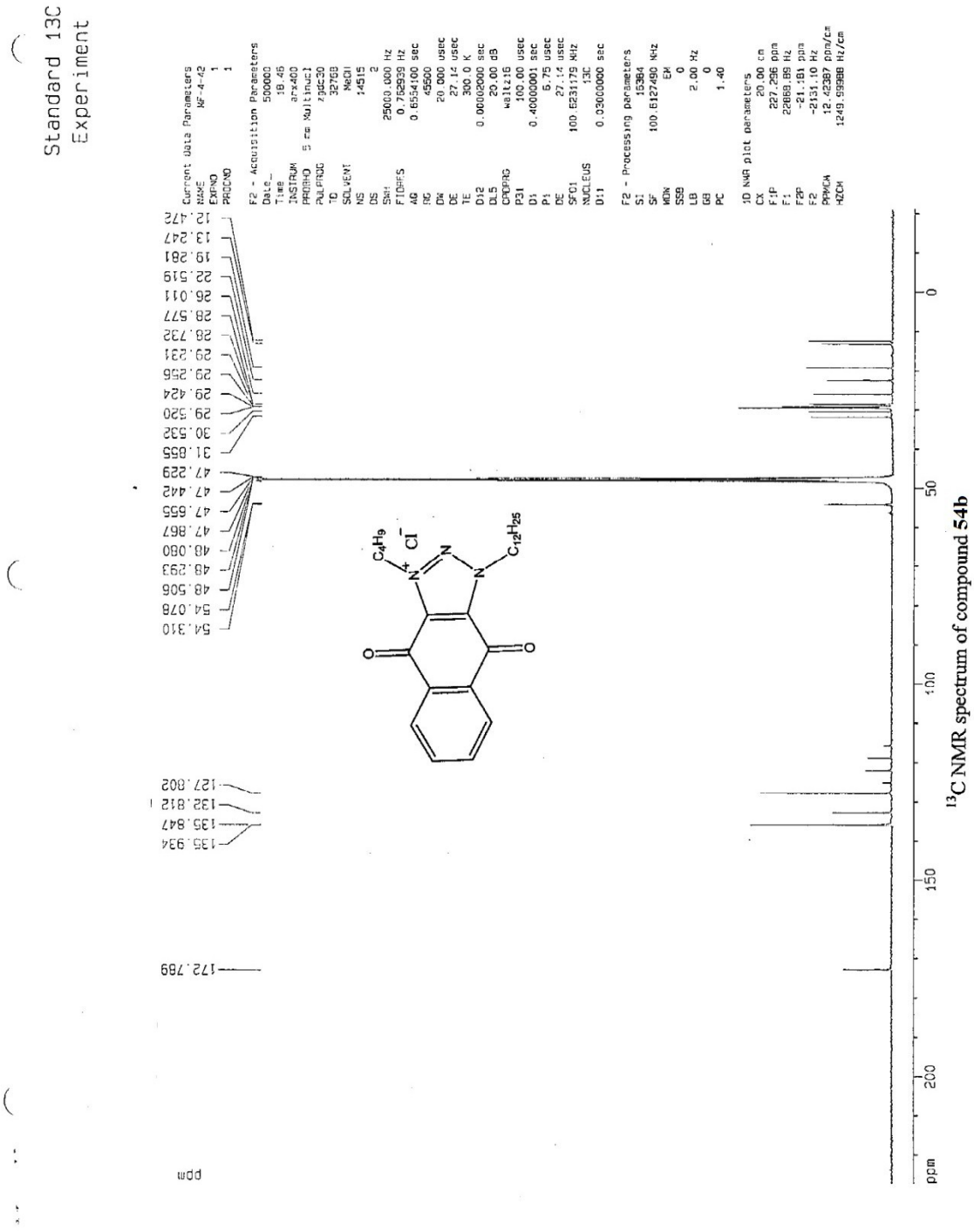
^{1}H NMR spectrum of compound **54a**



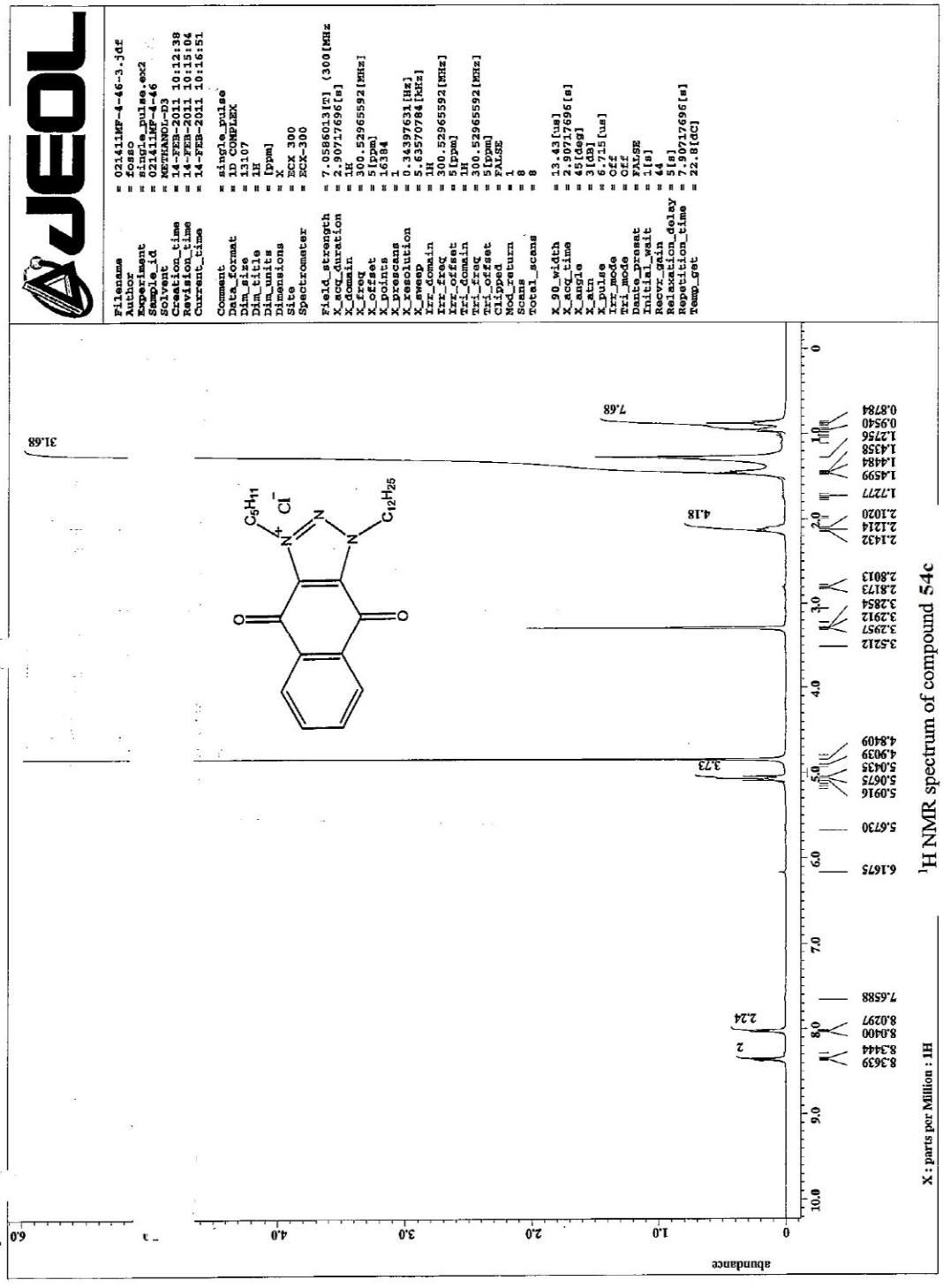
^{13}C NMR spectrum of compound **54a**



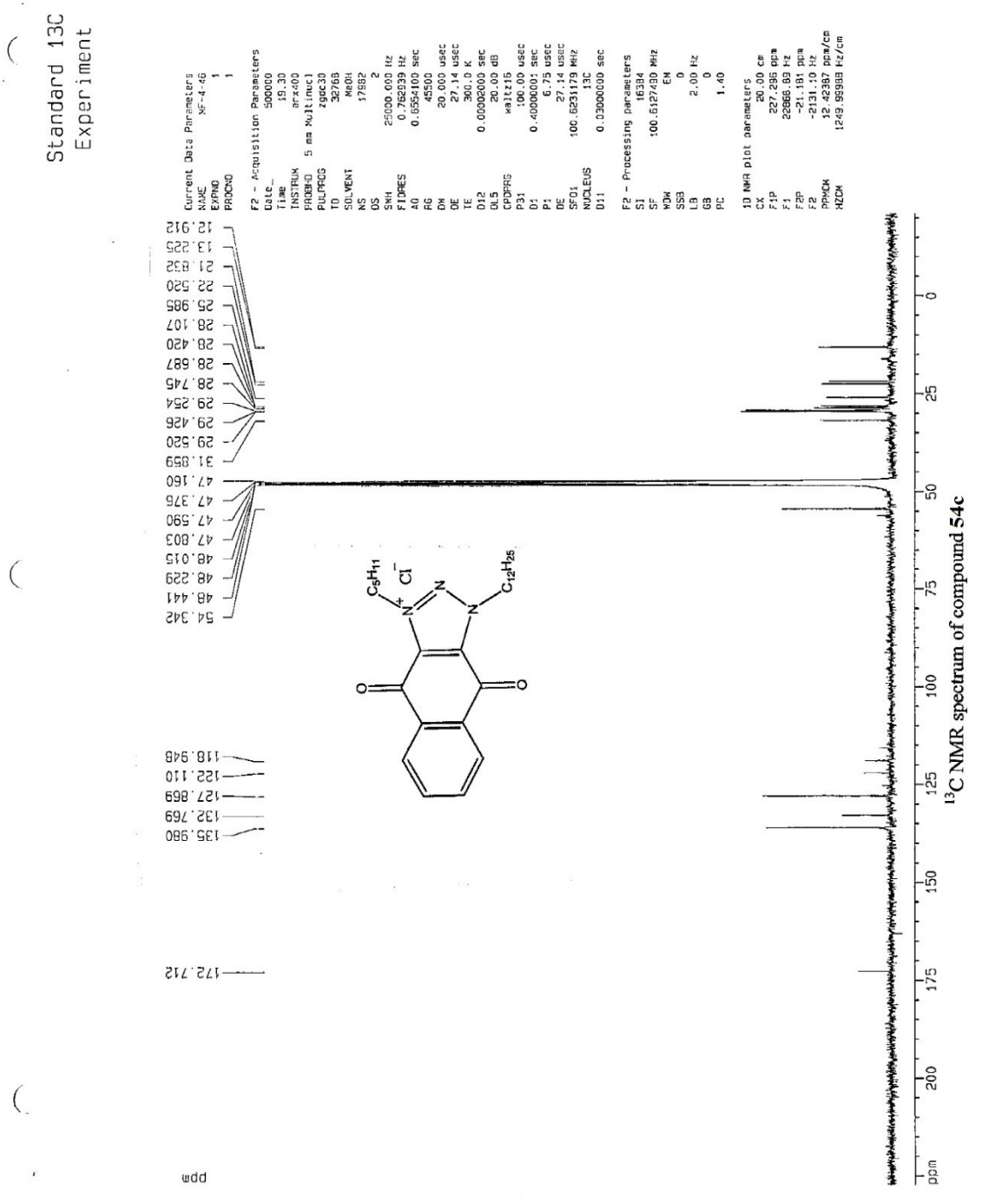
^{1}H NMR spectrum of compound **54b**



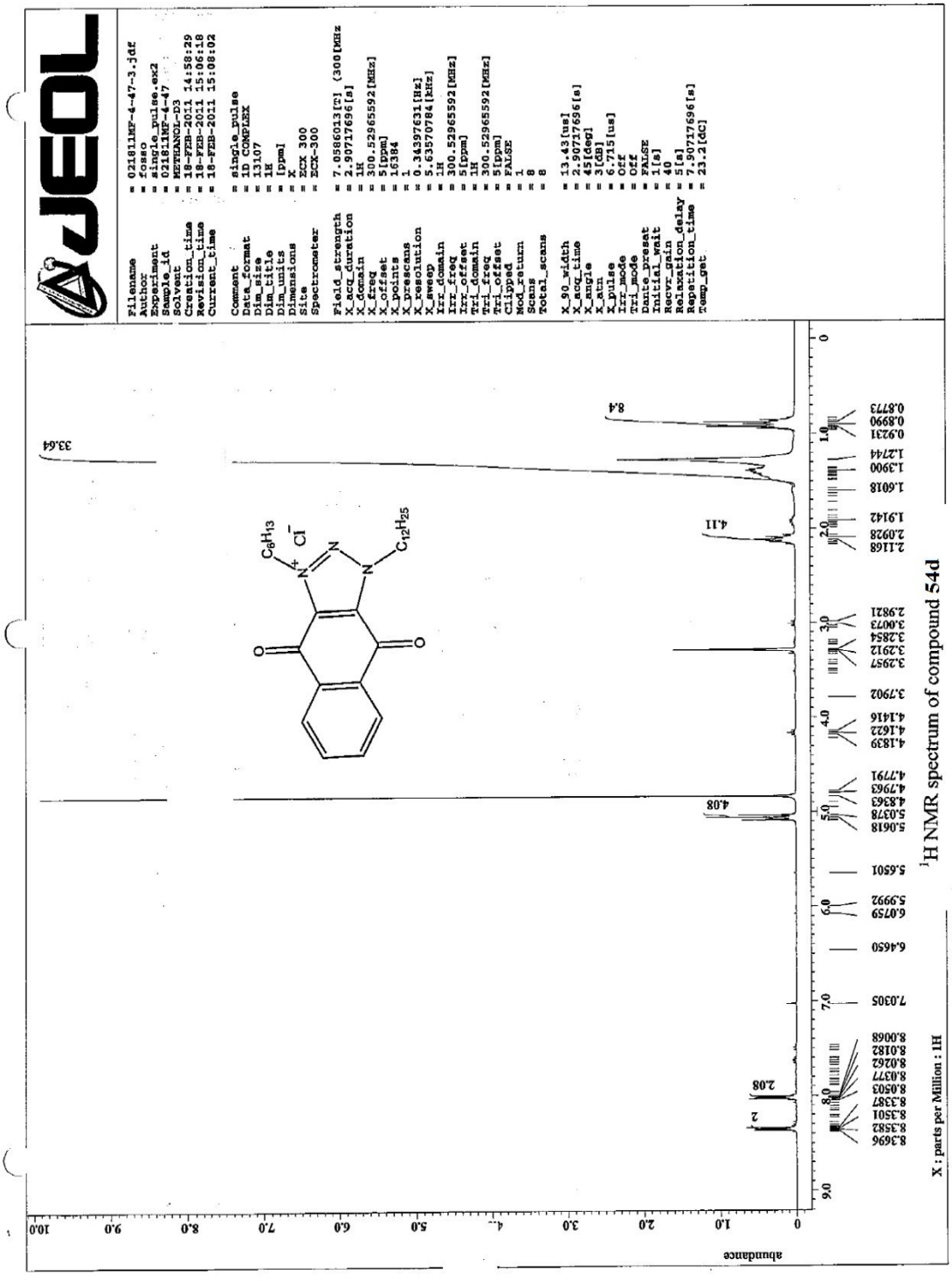
^{13}C NMR spectrum of compound **54b**



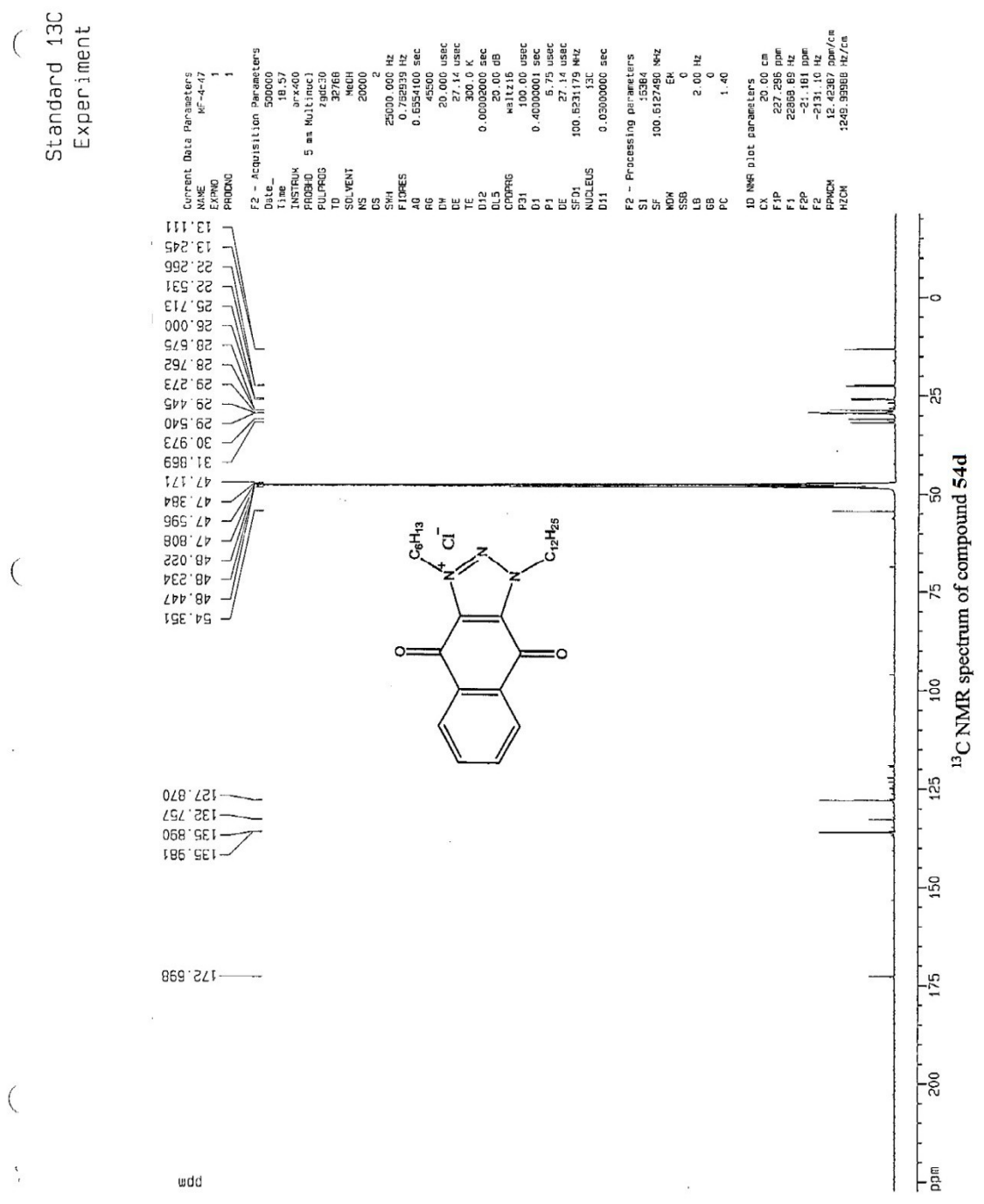
^{1}H NMR spectrum of compound **54c**



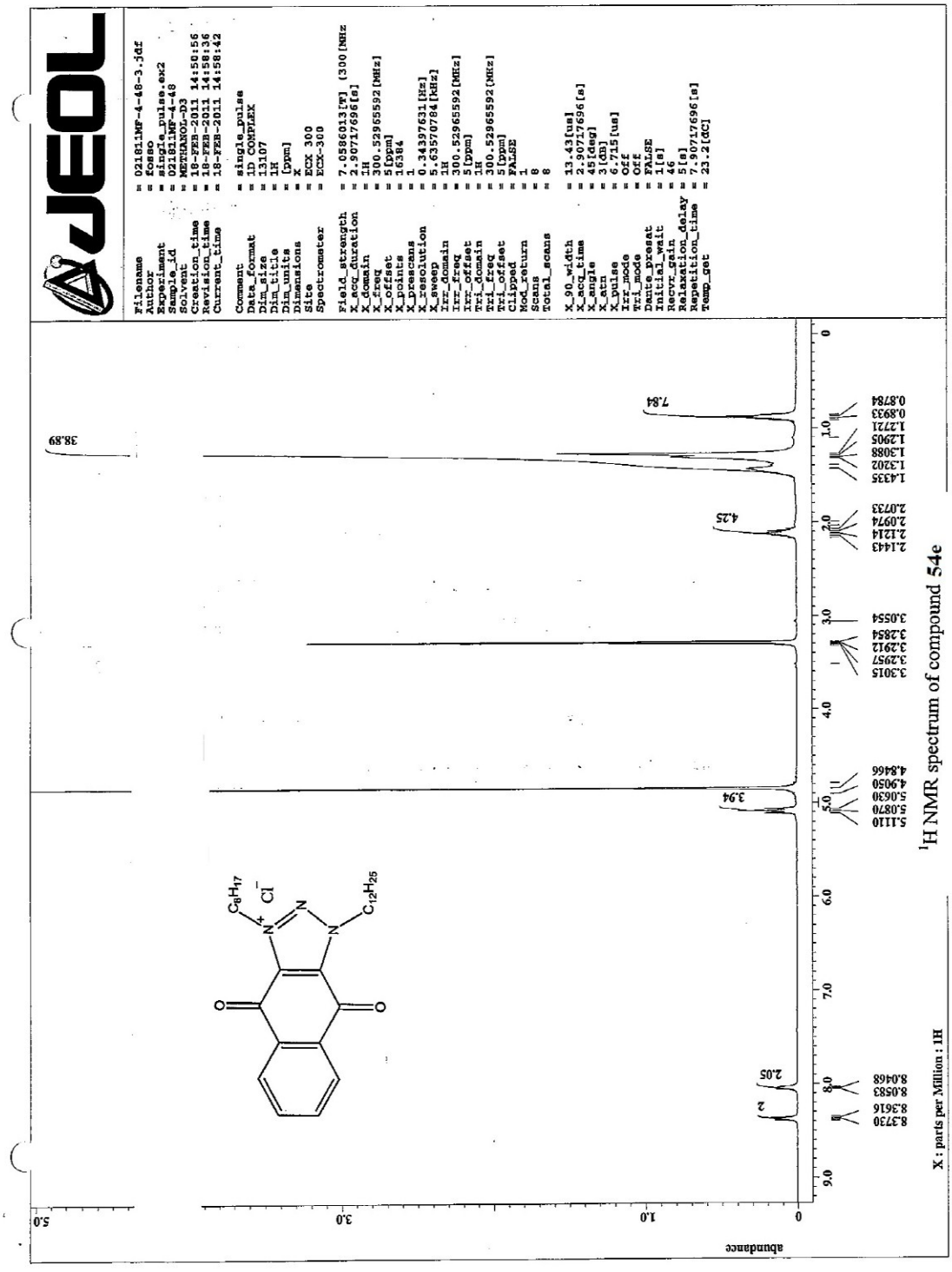
^{13}C NMR spectrum of compound **54c**



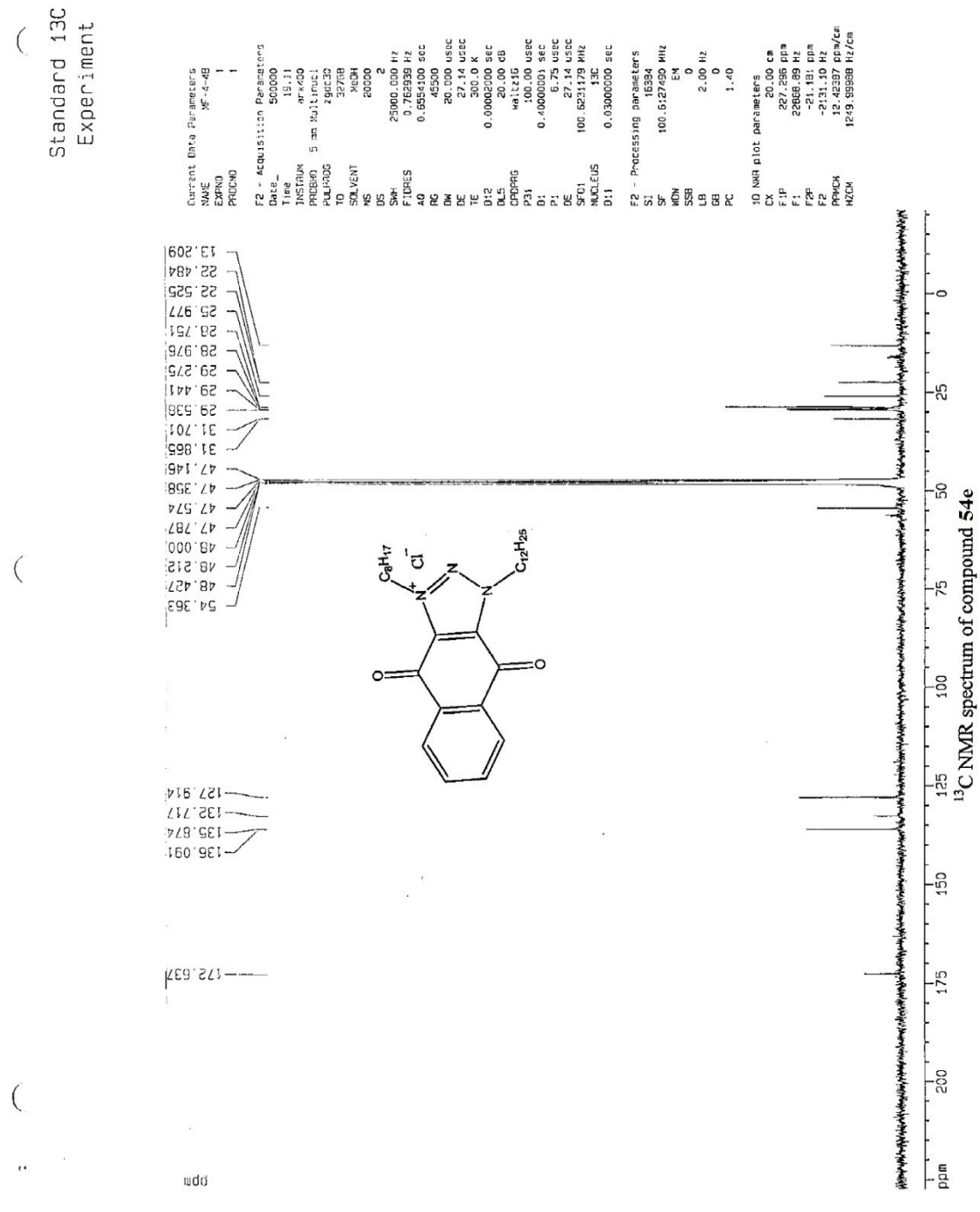
^{1}H NMR spectrum of compound **54d**



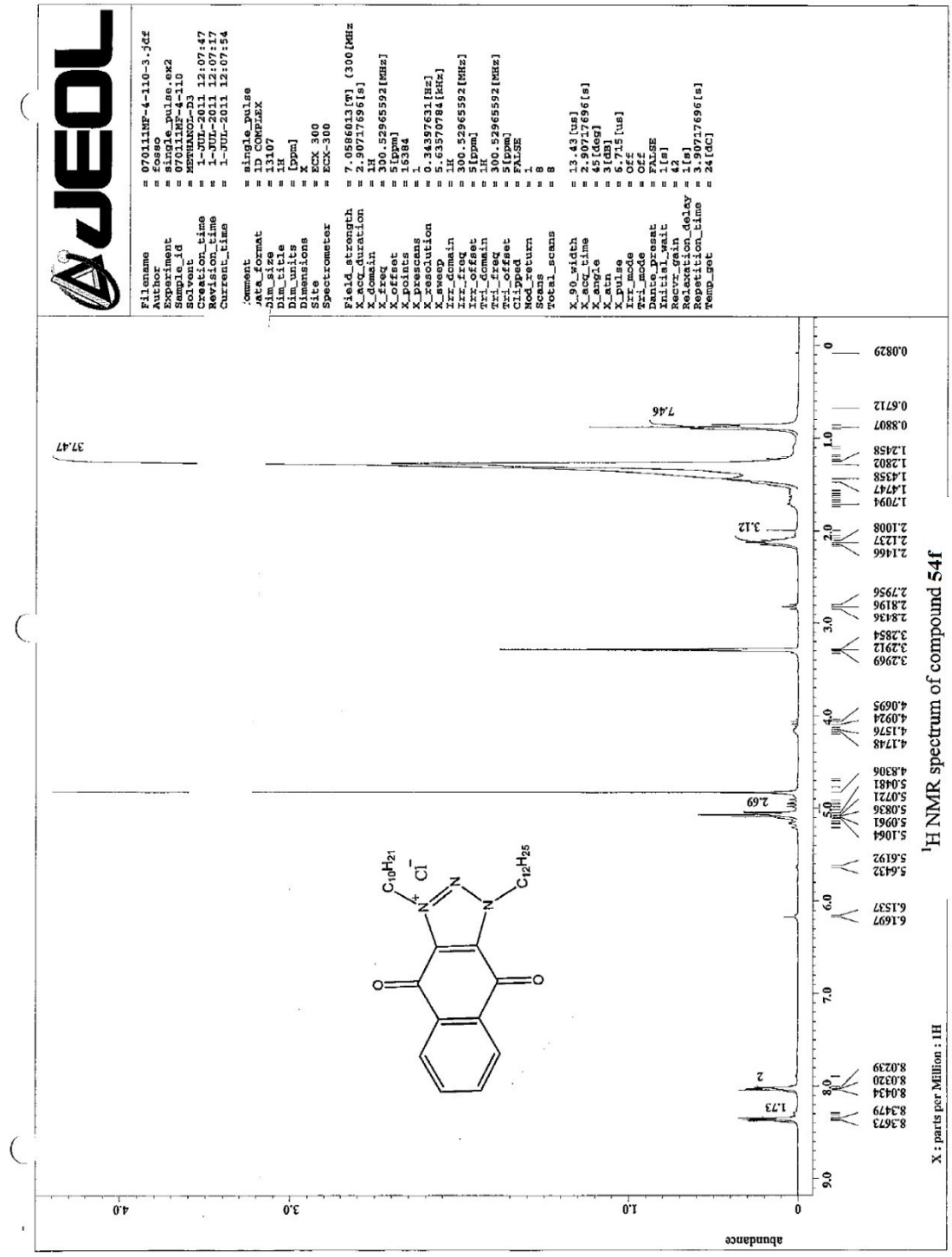
^{13}C NMR spectrum of compound **54d**



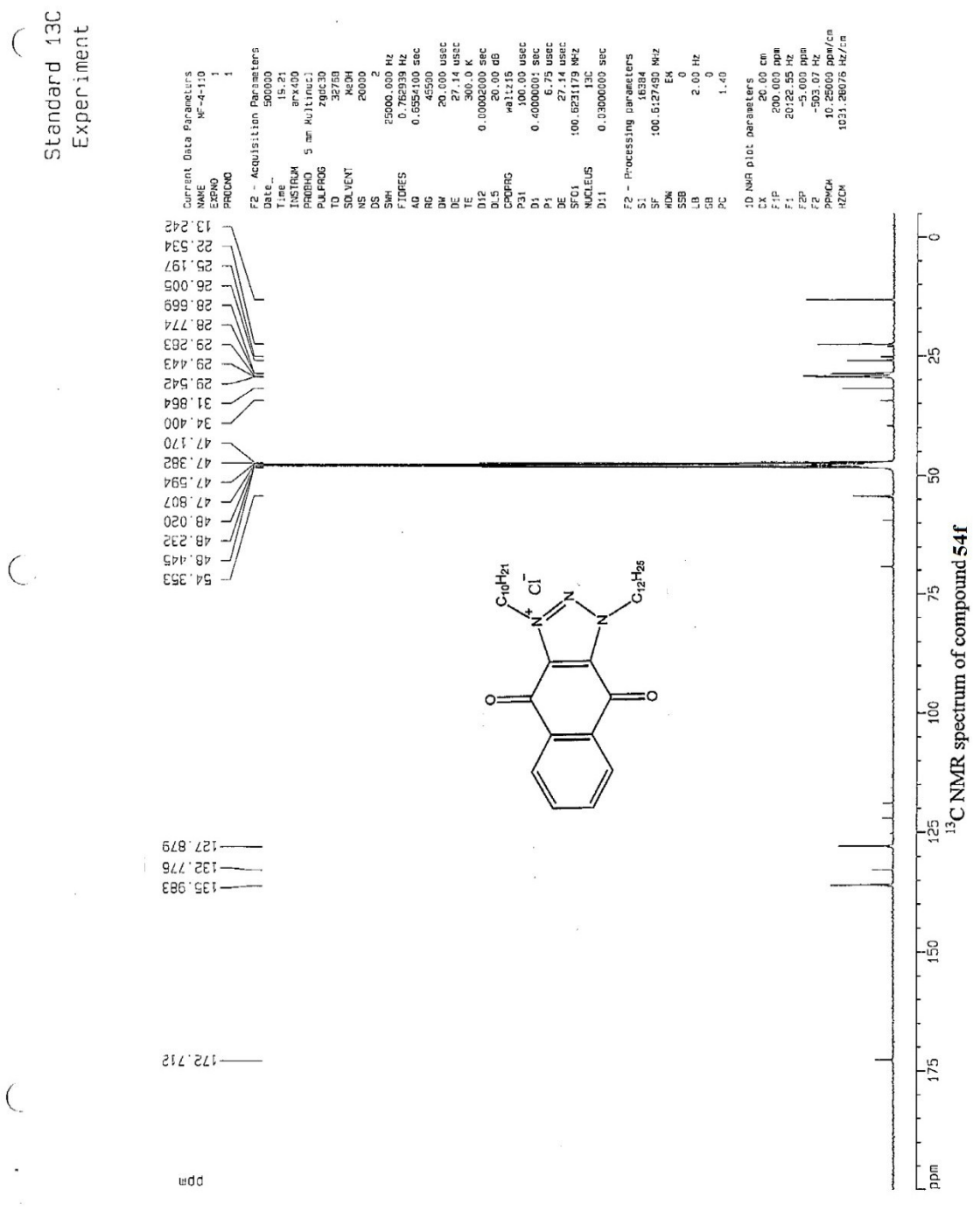
^{1}H NMR spectrum of compound **54e**



^{13}C NMR spectrum of compound **54e**



^{1}H NMR spectrum of compound **54f**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Experiment
Current Data Parameters
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PROCNO 1
F2 - Acquisition Parameters
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Time_ 15.21
INSTRUM av400
PROBHD 5 mm Multinucl
PULPROG zgdc30
TD 32768
SOLVENT MeOH
NS 20000
DS 2
SWH 25000.000 Hz
FIDRES 0.762939 Hz
AQ 0.6554100 sec
RG 45500
DW 20.000 usec
DE 27.14 usec
TE 300.0 K
D12 0.00002000 sec
DL5 20.00 dB
CPDPRG waltz15
P31 100.00 usec
D1 0.40000001 sec
P1 6.75 usec
DE 27.14 usec
SFO1 100.6231179 MHz
NUCLEUS 13C
D11 0.03000000 sec
F2 - Processing parameters
SI 16384
SF 100.6127490 MHz
WDW EM
SSB 0
LB 2.00 Hz
GB 0
PC 1.40
1D NMR plot parameters
CX 20.00 cm
F1P 200.000 ppm
F1 20122.55 Hz
F2P -5.000 ppm
F2 -503.07 Hz
PPMCM 10.25000 ppm/cm
HZCM 1031.26076 Hz/cm
13.242
22.534
25.197
26.005
28.669
28.774
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34.400
47.170
47.382
47.594
47.807
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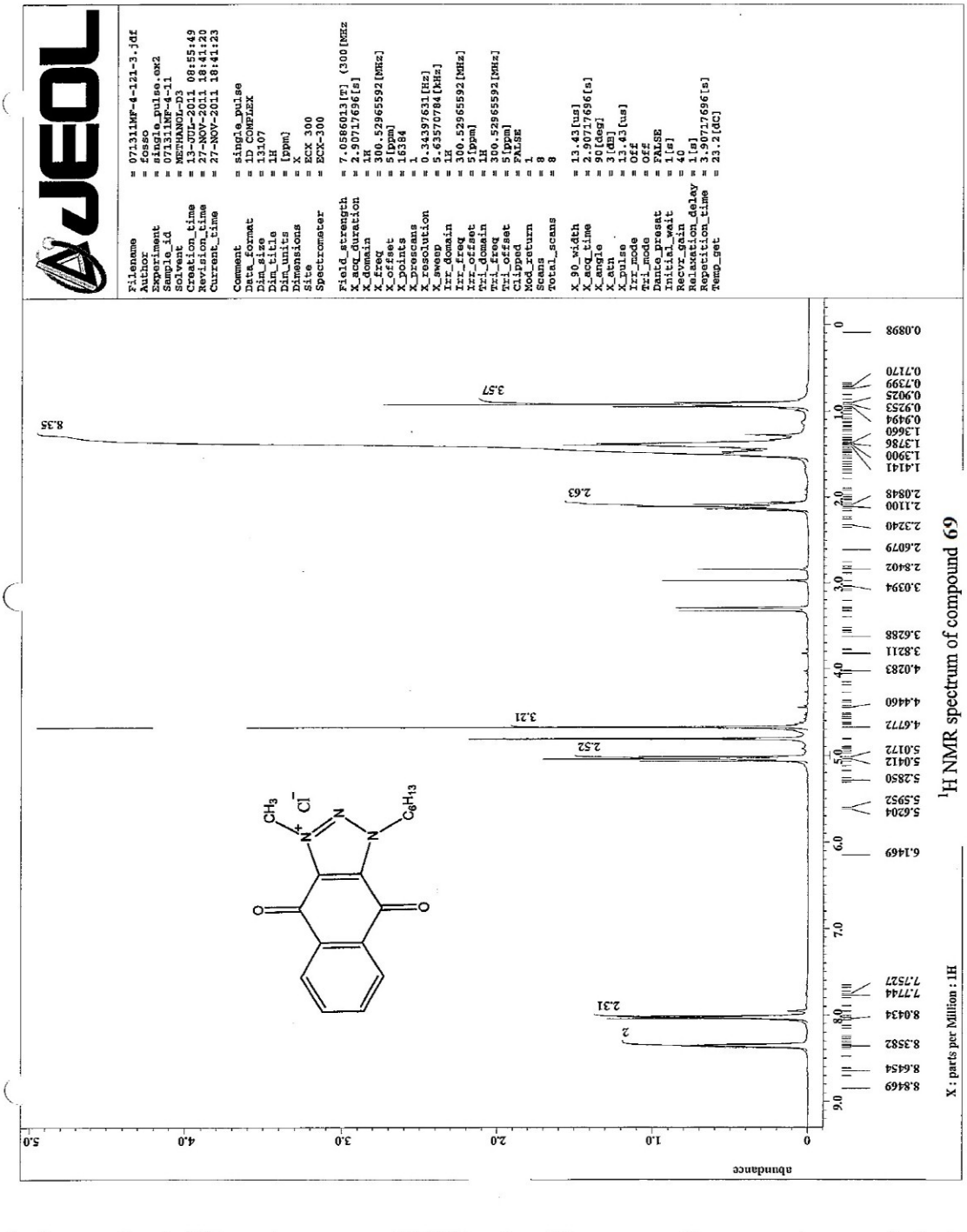
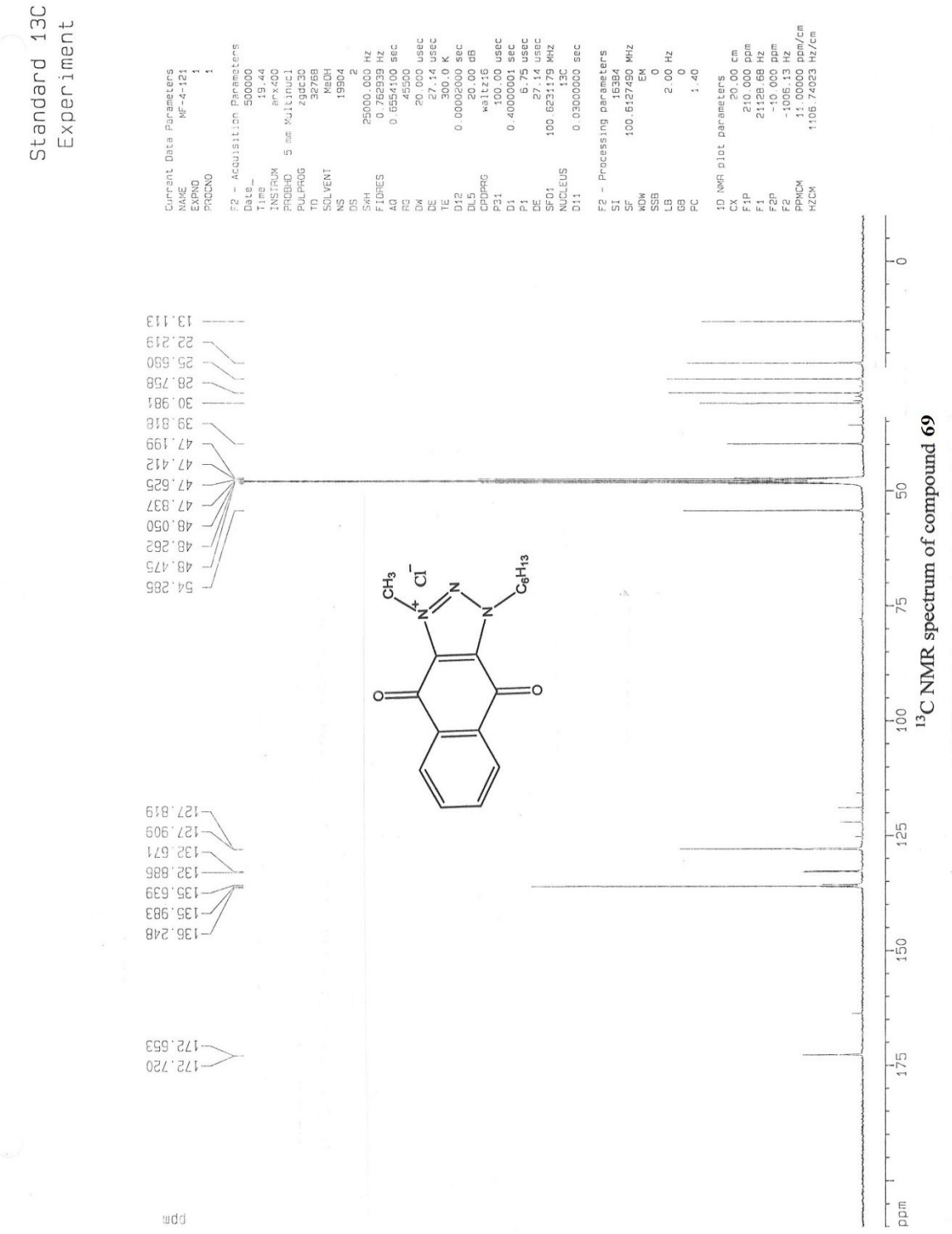
ppm
^{13}C NMR spectrum of compound **54f**



^{1}H NMR spectrum of compound **69**



^{13}C NMR spectrum of compound **69**

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Permission Letter

June 20, 2012

Marina Fosso Yatchang
Utah State University
Department of Chemistry and Biochemistry
0300 Old Main Hill
Logan, UT 84321-0300

Dear Dr. Mattis:

I am in the process of preparing my dissertation in the Department of Chemistry and Biochemistry at Utah State University. I hope to complete in the summer of 2012.

I am requesting your permission to include the following paper we co-authored in my doctoral dissertation:

Virginia B Mattis, Marina Y Fosso, Cheng-Wei Chang and Christian L Lorson "Subcutaneous administration of TC007 reduces disease severity in an animal model of SMA" *BMC Neurosc.* **2009**, *10*:142.

Please indicate your approval by signing in the space provided, attaching any other form or instruction necessary to confirm permission.

Thank you for your cooperation,

Marina Fosso Yatchang

I hereby give permission to Marina Fosso Yatchang to reprint the following publication in part or in full in her doctoral dissertation:

Virginia B Mattis, Marina Y Fosso, Cheng-Wei Chang and Christian L Lorson "Subcutaneous administration of TC007 reduces disease severity in an animal model of SMA" *BMC Neurosc.* **2009**, *10*:142.

Signed Virginia B Mattis Date 6/20/12

Permission Letter

June 20, 2012

Marina Fosso Yatchang
Utah State University
Department of Chemistry and Biochemistry
0300 Old Main Hill
Logan, UT 84321-0300

Dear Dr. Lorson:

I am in the process of preparing my dissertation in the Department of Chemistry and Biochemistry at Utah State University. I hope to complete in the summer of 2012.

I am requesting your permission to include the following paper we co-authored in my doctoral dissertation:

Virginia B Mattis, Marina Y Fosso, Cheng-Wei Chang and Christian L Lorson "Subcutaneous administration of TC007 reduces disease severity in an animal model of SMA" *BMC Neurosc.* **2009**, *10*:142.

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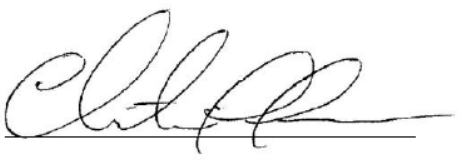
Signed  Date June 25, 2012

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June 20, 2012

Marina Fosso Yatchang
Utah State University
Department of Chemistry and Biochemistry
0300 Old Main Hill
Logan, UT 84321-0300

Dear Ms. Kawasaki:

I am in the process of preparing my dissertation in the Department of Chemistry and Biochemistry at Utah State University. I hope to complete in the summer of 2012.

I am requesting your permission to include the following paper we co-authored in my doctoral dissertation:

Chang, C.-W. T.; Fosso, M.; Kawasaki, Y.; Shrestha, S.; Bensaci, M. F.; Wang, J.; Evans, C. K.; Takemoto, J. Y. "Antibacterial to antifungal conversion of neamine aminoglycosides through alkyl modification. Strategy for reviving old drugs into agrofungicides" *J. Antibiot.* **2010**, *63*, 667-672.

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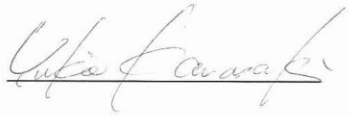
Signed  Date 6/20/12

Permission Letter

June 20, 2012

Marina Fosso Yatchang
Utah State University
Department of Chemistry and Biochemistry
0300 Old Main Hill
Logan, UT 84321-0300

Dear Mr. Shrestha:

I am in the process of preparing my dissertation in the Department of Chemistry and Biochemistry at Utah State University. I hope to complete in the summer of 2012.

I am requesting your permission to include the following paper we co-authored in my doctoral dissertation:

Chang, C.-W. T.; Fosso, M.; Kawasaki, Y.; Shrestha, S.; Bensaci, M. F.; Wang, J.; Evans, C. K.; Takemoto, J. Y. "Antibacterial to antifungal conversion of neamine aminoglycosides through alkyl modification. Strategy for reviving old drugs into agrofungicides" *J. Antibiot*. **2010**, *63*, 667-672.

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Signed  Date 06/20/12

Permission Letter

June 20, 2012

Marina Fosso Yatchang
Utah State University
Department of Chemistry and Biochemistry
0300 Old Main Hill
Logan, UT 84321-0300

Dear Dr. Bensaci:

I am in the process of preparing my dissertation in the Department of Chemistry and Biochemistry at Utah State University. I hope to complete in the summer of 2012.

I am requesting your permission to include the following paper we co-authored in my doctoral dissertation:

Chang, C.-W. T.; Fosso, M.; Kawasaki, Y.; Shrestha, S.; Bensaci, M. F.; Wang, J.; Evans, C. K.; Takemoto, J. Y. "Antibacterial to antifungal conversion of neamine aminoglycosides through alkyl modification. Strategy for reviving old drugs into agrofungicides" *J. Antibiot.* **2010**, *63*, 667-672.

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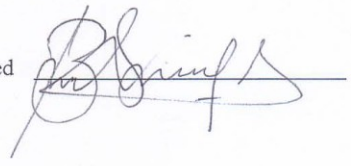
Signed  Date 6/21/2012

Permission Letter

June 20, 2012

Marina Fosso Yatchang
Utah State University
Department of Chemistry and Biochemistry
0300 Old Main Hill
Logan, UT 84321-0300

Dear Dr. Wang:

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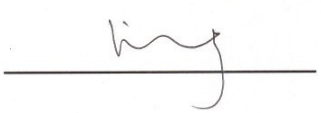
Signed  Date 06/24/2012

Permission Letter

June 20, 2012

Marina Fosso Yatchang
Utah State University
Department of Chemistry and Biochemistry
0300 Old Main Hill
Logan, UT 84321-0300

Dear Dr. Evans:

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Signed C. Kent Evans Date 6/23/2012

CURRICULUM VITAE

Marina FOSSO YATCHANG

Department of Chemistry and Biochemistry
Utah State University
0300 Old Main Hill
Logan, UT 84322-0300
marina.fosso@aggiemail.usu.edu
(435) 512-6778

CAREER OBJECTIVE

To obtain a research position in a competitive institution that will allow me to apply my extensive knowledge in multi-step synthesis of bioactive molecules. Research interests include: organic synthesis, drug discovery, library synthesis, and methodology development.

EDUCATION

Ph.D., Chemistry May 2012
Utah State University (USU) Logan, Utah
Dissertation: Synthesis and Biological Activity of
Aminoglycosides and 1,4-Naphthoquinone Derivatives"
Advisor: Dr. Tom C.-W. Chang

B.S., Chemistry (First Class Honors) July 2005
University of Buea (UB) Buea, Cameroon

RESEARCH EXPERIENCE

Research Intern October 2011-August 2012
Phoenix Pharmalabs, Inc Logan, UT

- Synthesized four new opioids as potential non-addictive treatments of pain
- Isolated enantiomers from racemic mixtures by column chromatography and diastereoisomeric crystallization

Graduate Research Assistant December 2007-May 2012
Utah State University Logan, UT

- Performed the synthesis of a carbohydrate, which was investigated as a potential therapeutic of the infantile genetic disease spinal muscular atrophy
- Explored methods for chemical derivation of the natural product kanamycin B for the development of antifungal agents, with complete loss of antibacterial activity. Results from this work provided general criteria for the design of good agro fungicide candidates

- Developed a methodology for the facile synthesis of libraries of novel antibacterial and anticancer 1,4-naphthoquinone derivatives
- Purified and characterized organic compounds by TLC, column chromatography, recrystallization, NMR (^{1}H, ^{13}C, COSY, HETCOR) spectroscopy, UV-visible, IR, and mass spectrometry

TEACHING EXPERIENCE

Teaching Assistant August 2007-December 2011
Utah State University Logan, UT

- Supervised and instructed 24 students in each of three sections of General and Organic chemistry laboratories for seven semesters. Classes taught include:
  - Chemistry Principles Lab I (CHEM 1215)
  - Chemistry Principles Lab II (CHEM 1225)
  - Organic Chemistry Lab I (CHEM 2315)
  - Organic Chemistry Lab II (CHEM 2325)
- Emphasized keeping complete and accurate scientific notes
- Substituted for major professor to teach General Chemistry II (CHEM 1120) Principles of Organic Chemistry (CHEM 2300)

AWARDS, FELLOWSHIP AND HONORS

- Outstanding Graduate Student in Chemistry, USU 2012
- Dr. Dinesh and Kalpana Patel Doctoral Graduate Fellowship, USU 2011-2012
- Center for Women and Gender Graduate Student Research Grant, USU 2011
- Graduate Student Senate Travel Award, USU 2010
- Teaching Instructor Certificate, USU 2007
- Top Graduating Student in Chemistry, UB 2005
- The Thomas and Janice Huang's Scholarship (Outstanding Student), UB 2004
- Minister of Higher Education Scientific Women Award, UB 2003-2005
- Dean's List Awards, UB 2003-2005

PUBLICATIONS

- **Fosso, M. Y**.; Nziko, V. P. N.; Chang, C.-W. T. "Chemical Synthesis of *N*-Aryl Glycosides" *J. Carbohydr. Chem*. Just accepted

- **Fosso, M. Y**.; Chan, K. Y.; Gregory, R.; Chang, C.-W. T. "Library synthesis and antibacterial study of cationic anthraquinones." *ACS Comb. Sci*. **2012**, *14*, 231

- Chang, C.-W. T.; **Fosso, M. Y.;** Kawasaki, Y.; Shrestha, S.; Bensaci, M. J.; Wang, J.; Evans, C. K.; Takemoto, J. Y. "Antibacterial to antifungal conversion of neamine aminoglycosides through alkyl modification. Strategy for reviving old drugs into agrofungicides**."** *J. Antibiot.* **2010**, 63, 667

- Mattis, V. B.; **Fosso, M. Y.;** Chang, C.-W.; Lorson, C. L. "Subcutaneous administration of TC007 reduces disease severity in an animal model of SMA." *BMC Neurosci*. **2009**, *10*, 142

- Mattis, V. B.; Ebert, A. D.; **Fosso, M. Y.**; Chang, C.-W. T.; Lorson, C. L. "Delivery of a read-through inducing compound, TC007, lessens the severity of a SMA animal model." *Hum. Mol. Genet.* **2009**, *18*, 3906

PRESENTATIONS

- **Marina Fosso**. Synthetic chemistry of aminoglycolipids. Bioproducts Summit – USU Commercial Enterprises & Synthetic Bioproducts Center. July 19, 2012, Logan, UT (oral)

- **Marina Fosso**, Yukie Kawasaki, Sanjib Shrestha, Jon Takemoto and Tom Chang. Synthesis and antifungal activity of kanamycin B analogs. Gordon Research Conference "Carbohydrates", June 19-24 2011, Waterville, ME (poster)

- **Marina Fosso**, Yukie Kawasaki, Sanjib Shrestha, Jon Takemoto and Tom Chang. Synthesis and structural optimization of antifungal kanamycin B analogs. 240th ACS National Meeting & Exposition, August 22-26 2010, Boston, MA (poster)

- **Marina Fosso**, Tom Chang, Jon Takemoto, Mekki Bensaci and Yukie Kawasaki, Synthesis of new kanamycin B analogs with surprising antifungal activity Joint 63rd Northwest/ 21st Rocky Mountain (NORM/RMRM), June 17 2008, Park City, UT (poster)

PROFESSIONAL AFFILIATIONS

Memberships

- American Chemical Society 2010-present
- Golden Key International Honor Society 2009-present

Leadership/Service

- Senior graduate student 2008-2011
  - Supervised seven new graduate/undergraduate researchers, training them to perform standard operating procedures and chemical experiments
  - Mentored two high school students during their summer internship in the Chemistry and Biochemistry department at USU, providing them with work directions
  - Managed the laboratory in the absence of the major professor
- Vice-president AFSA (African Students Association), 2009-2010
  - Assisted in the organization of the club's events to showcase the African culture, attracting more than 300 students

- Volunteer 2008-2009
  - Helped packaging Christmas gifts for kids in the hospitals

SKILLS

Languages: English (fluent), French (native)

Computer skills: Microsoft (Word, Excel, PowerPoint), Chemdraw, Scifinder, Chemsketch, Discovery Studio, PyMol

REFERENCES

Dr. Cheng-Wei Tom Chang
Associate Professor
Utah State University
Department of Chemistry and Biochemistry
0300 Old Main Hill
Logan, UT 84322-0300
(435) 797 3545
tom.chang@usu.edu
Ph.D. Advisor

Dr. Alvan C. Hengge
Professor and Department Head
Utah State University
Department of Chemistry and Biochemistry
0300 Old Main Hill
Logan, UT 84322-0300
(435) 797 3442
alvan.hengge@usu.edu
Ph.D. Supervisory Committee Member

Dr. Bradley S. Davidson
Associate Professor
Utah State University
Department of Chemistry and Biochemistry
0300 Old Main Hill
Logan, UT 84322-0300
(435) 797 1638
brad.davidson@usu.edu
Ph.D. Supervisory Committee Member

Dr. John A. Lawson
CEO
Phoenix Pharmalabs, Inc.
525 West 465 North, Suite 150
Logan, UT 84332-5604
(435) 213-9361
jalawson3@comcast.net
Internship Supervisor